Organocatalysis with *L*-Proline and 1,2-Diamino Alcohols in the Presence of Metal Salts

Dissertation

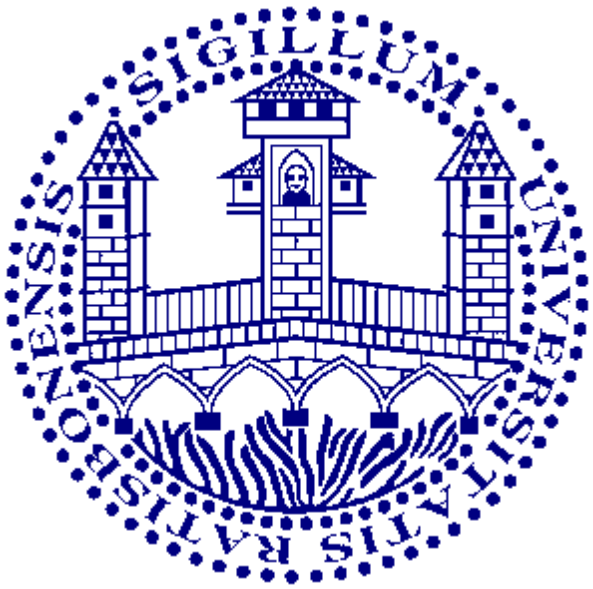
Zur Erlangung des Doktorgrades

Dr. rer. nat.

an der Fakultät für

- Chemie und Pharmazie -

der Universität Regensburg



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Regensburg 2015

Diese Arbeit wurde angeleitet von:	Prof. Dr. Oliver Reiser
Promotionsgesuch eingereicht am:	09.11.2015
Promotionskolloquium am:	09.12.2015
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Die vorliegende Arbeit wurde unter Leitung von Herrn Prof. Dr. Oliver Reiser im Zeitraum von Oktober 2011 bis Juni 2015 am Institut für Organische Chemie der Universität Regensburg angefertigt.

Besonders bedanken möchte ich mich bei Herrn Prof. Dr. Oliver Reiser für die Aufnahme in seinen Arbeitskreis, die Überlassung des interessanten Themas, die anregenden Diskussionen und die stete Unterstützung.

Meiner Familie

Table of Contents

A Introduction

1. Organocatalysis – The Beginning of a Great Success Story

Asymmetric synthesis is a method for the preparation of chemical compounds which aims to bias the synthesis in favor of producing one stereoisomer over another stereoisomer. Therefore, asymmetric synthesis is a wide field in organic chemistry which can be achieved *via* different methods. The most applied techniques are the use of catalysts from the chiral pool, reactions mediated by chiral auxiliaries, (kinetic) *racemic* resolutions or asymmetric catalysis (Figure 1).[1] The latter is the most important area in sustainable chemistry. Therefore, the development of new and more efficient methods with the ulterior motive of waste avoidance, higher atom economy, energy saving and generating high stereoselectivity is of great interest in the field of organic chemistry. The modern asymmetric catalysis is based on three big pillars, namely enzyme catalysis, organometallic catalysis and organocatalysis (Figure 1).[2]

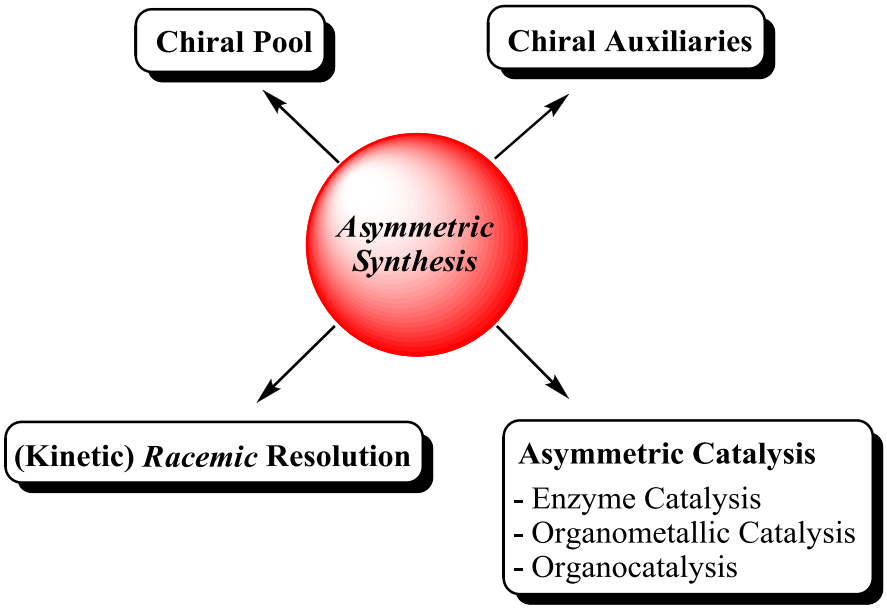
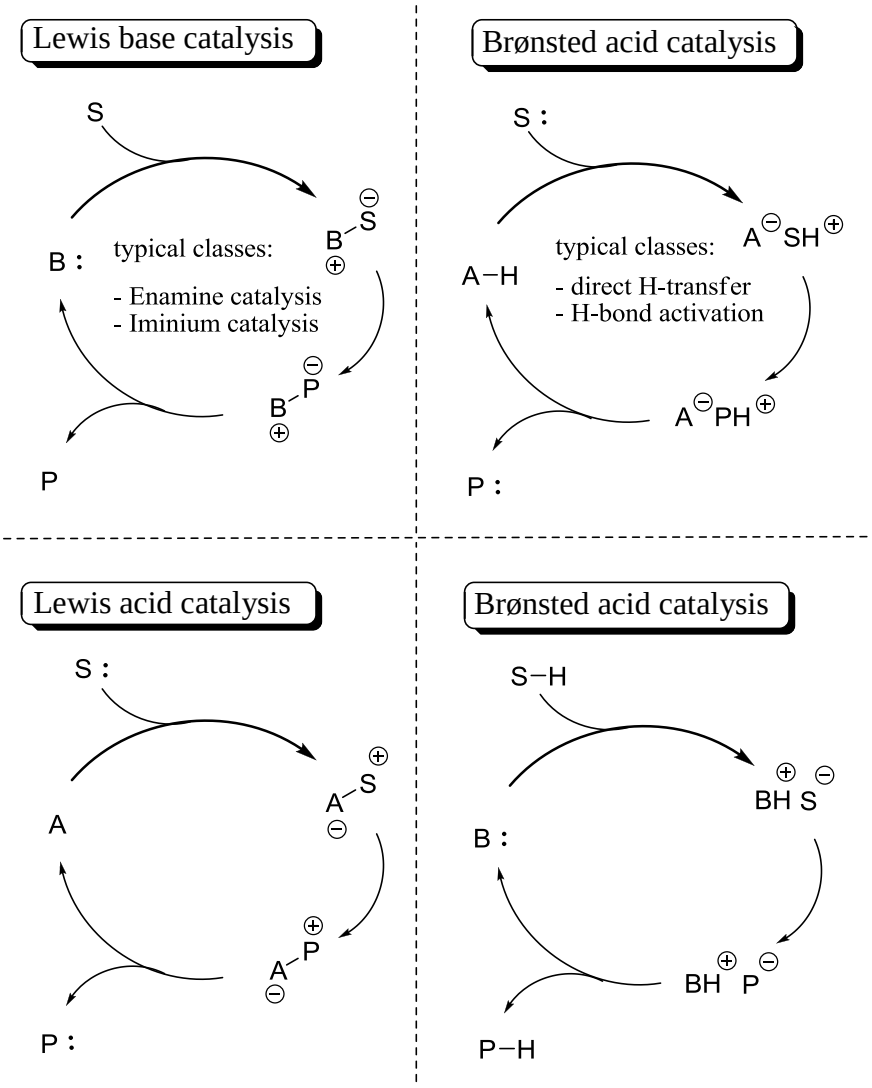


Figure 1. The most important methodes in asymmetric synthesis.

Enzyme catalysis is highly selective but often requires special reaction conditions (*e.g.* water as solvent) and is limited to certain substrates. Metal catalysis is highly selective but, at the same time, very air or moisture sensitive and the products often contain traces of metals, which in pharmaceutical production is undesirable. Among them, organocatalysis is one of the todays most chosen methods for generating high stereoselectivities in C-C-bond forming reactions, due to its robustness, low costs, non-toxicity and easy feasibility.

Moreover, it is suitable to many organic transformations including aldol reactions, Diels-Alder reactions, epoxidations, cyclopropanations, alkylations, oxidations and reductions.

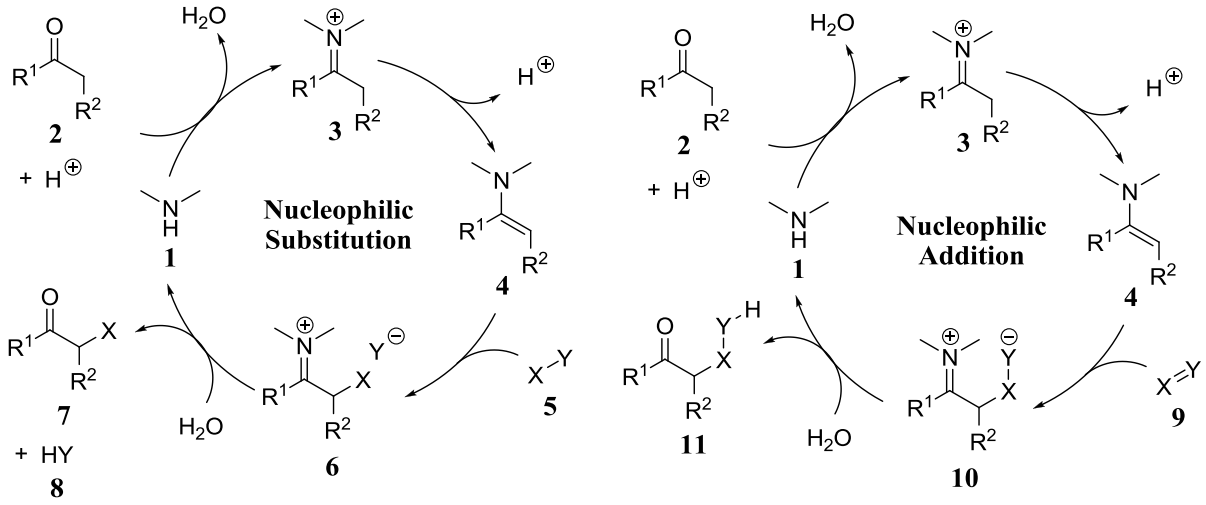


Scheme 1. Catalytic cycles for the main activation pathways in organocatalysis.[2-3]

Generally, there are four different types of organocatalysts, Lewis bases and acids, and Brønsted bases and acids. Organocatalysis is ruled by Lewis base catalysis such as amines (*e.g. L*-proline (**14**)) and carbenes. Brønsted acid catalysis has become the second big field in organocatalysis and takes place over a direct hydrogen transfer or H-bond activation. The counterparts, Lewis base and Brønsted base catalysis, are only seldom used in organocatalysis (Scheme 1).[2-3] In the following, the most important activation modes and catalysts will be briefly introduced.

2. Asymmetric Enamine Catalysis

The asymmetric enamine catalysis has become the most important field of organocatalysis in the last years, due to its high atom and step economy. The reactivity is based on the enamine formation which lowers the LUMO (lowest unoccupied molecule orbital) energy, leading to an increased C-H acidity. The enamine catalysis could proceed over two pathways, either a nucleophilic substitution by reaction of **4** with a single bond containing electrophile **5** (*e.g.* alkyl halides) or *via* a nucleophilic addition by reaction of **4** with a double bond containing electrophile **9** (*e.g.* aldehydes, imines, Michael acceptors) (Scheme 2).[4]

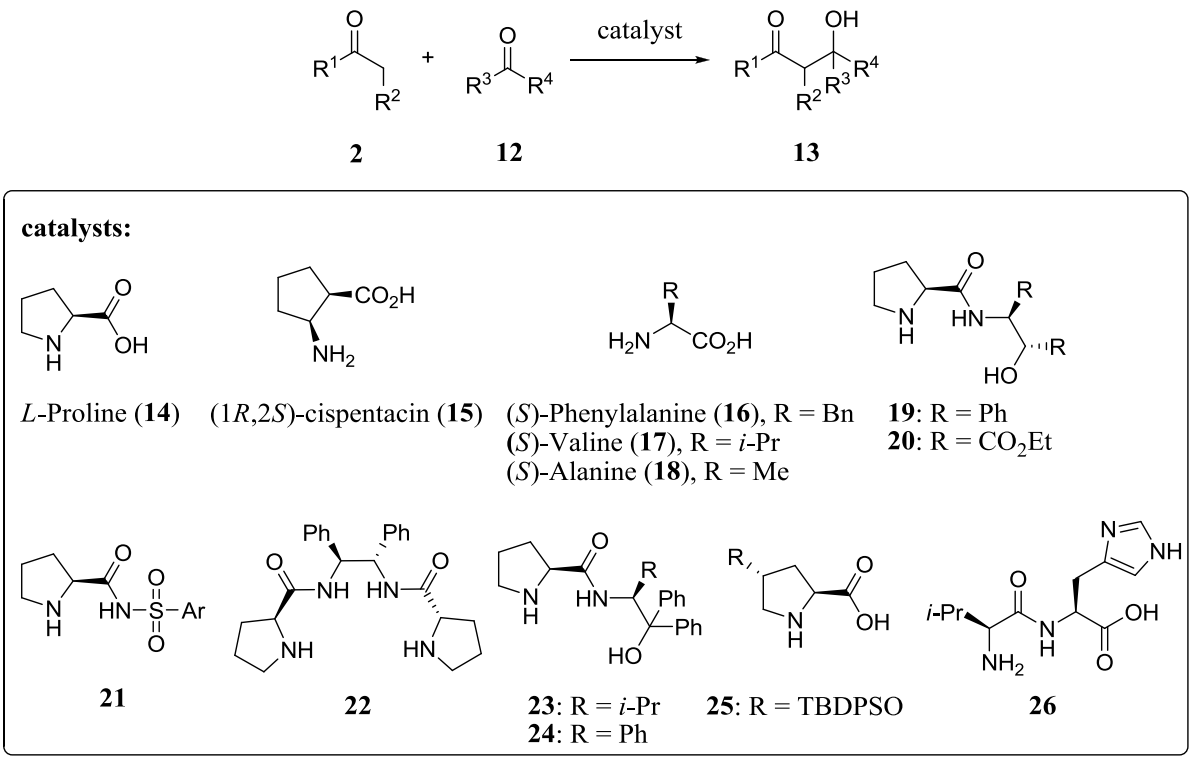


Scheme 2. Enamine catalysis by the example of a nucleophilic substitution (left) and addition (right).[4]

In the following, the most important catalytic structures based on this activation mode are presented.

2.1 Asymmetric Aldol Reactions

Aldolases, nature's catalyst for direct asymmetric aldolizations of unmodified carbonyl compounds are using primary amino groups as Lewis base (*e.g.* class I aldolases). Inspired by this model, many organocatalysts with an amino acid motif were developed for the aldol reaction, mainly based on *L*-proline (**14**). Moreover, also primary amino acids, dipeptides or *L*-proline-based catalysts were utilized (Scheme 3).[4] Therefore, aldol reactions are one of the best investigated C-C bond forming reactions.



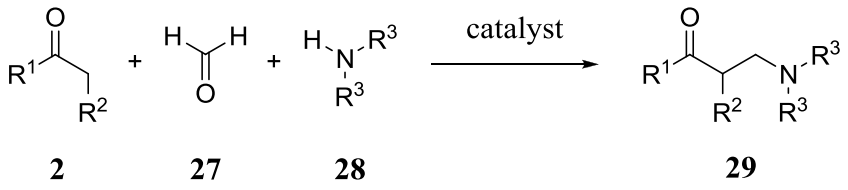
Scheme 3. Examples of organocatalysts for various aldol reactions.

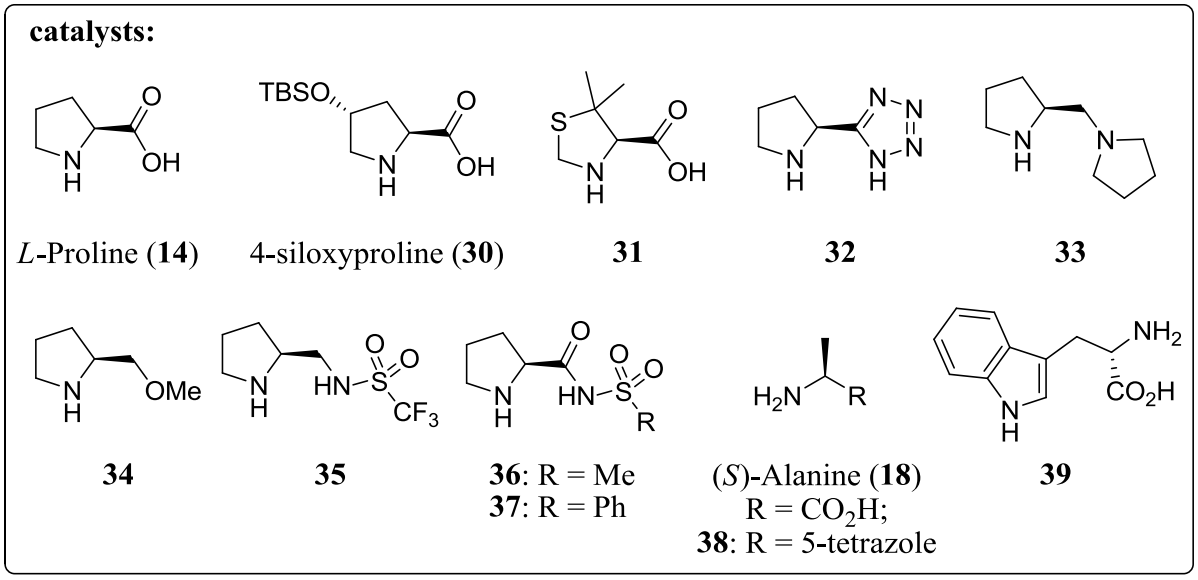
In the 1970s, Hajos-Parrish-Eder-Sauer-Wiechert discovered the first aminocatalytic asymmetric aldol reaction, namely an *intramoleculare L*-proline (**14**) catalyzed 6-enolendo aldolization of di- and triketones.[5] Further studies revealed that also primary amines (*e.g.* (1*R*, 2*S*)-cispentacin (**15**) or (*S*)-phenylalanine (**16**)) were prone to catalyze these *intramolecular* cyclizations even with higher enantioselectivities than those obtained with *L*-proline (**14**).[6] The first amine-catalyzed asymmetric direct *intermolecular* aldol reaction was found by List *et al.*, namely an *L*-proline (**14**) catalyzed, asymmetric direct aldol reaction of acetone (**130**) with different aromatic aldehydes.[7] However, in this case primary amines turned out to be inferior catalysts compared to *L*-proline (**14**).[4] Even in the presence of water, an aldol reaction of cyclic ketones to electron-deficient aldehydes was practicable catalyzed by primary amines (*e.g.* (*S*)-valine (**17**) and (*S*)-alanine (**18**)) reported by Cordova and co workers in 2005.[8] The first investigations in the field of *L*-proline-derived amino alcohol amides (*e.g.* **19** and **20**) were done by Gong *et al.* and showed increased stereoselectivities, but slightly lower yields compared to *L*-proline (**14**).[9] The *L*-proline-derived *N*-acylsulfonamide catalysts **21** generate superior results compared to *L*-proline (**14**) as the sole catalyst and were developed Berkessel and co-workers.[10] Moreover, Zhao *et al.* reported an aldol reaction in which they used the C_2-symmetric ligand **22**.[11] Outstanding entantioselectivities were obtained by the application of *L*-proline-based amides **23** and **24** in

direct aldol reactions of acetone (**130**) and various aldehydes by Singh and co-workers.[12] Furthermore, even in the presence of water a direct aldol reaction of ketones and aldehydes was feasible by the use of *trans*-4-silyloxy-proline (**25**), discoverd by Hayashi and co-workers.[13] Moreover, Tsogoeva *et al.* showed the good applicability of dipeptides, containing primary α-amino acids (*e.g.* **26**), as catalyst for the asymmetric direct aldol reaction.[14] These manifold examples show the great potential of mainly secondary, but also primary amines to catalyze various aldol reactions with excellent outcome.

2.2 Asymmetric Mannich Reactions

The Mannich reaction is a beneficial three component reaction between two carbonyl compounds and an amine (ammonia, primary or secondary) which give rise to β-amino-carbonyl compounds that are core structures in a great number of drugs and natural products, thus making it to an indispensable tool for organic chemists.[4] The first organocatalyzed Mannich reaction between different ketones, *p*-anisidine and aldehydes catalyzed by *L*-proline (**14**) was discovered by List *et al.* in 2000.[7a, 15] From that moment on, the interest of many researches was raised to develop new organocatalysts for highly stereoselective three component Mannich reactions, mostly based on *L*-proline structures (Scheme 4). In 2004, Hayashi *et al.* showed, that 4-siloxyproline (**30**) was applicable as catalyst in the asymmetric Mannich reaction to a broader scope of substrates compared to *L*-proline (**14**), however with identical results.[16] The DMTC catalyst (**31**) was the first time used by Barbas and co-workers in the reaction of acetone (**130**) with different preformed aldimines.[17] Due to its better solubility in different organic solvents, the pyrrolidine-based tetrazole catalyst **32** was applied to this reaction as well.[18] Jørgensen *et al.* studied the preparation of asymmetric quaternary carbons derived from the reaction of ketimines and unmodified aldehydes using catalyst **33**.[19] In 2002, the methoxypyrrolidine catalyst **34** was applied by Barbas and co-workers in the transformation of unmodified aldehydes and *N*-PMP-protected α-amino ethyl glyoxylates.[20] The proline-derived pyrrolidinesulfonamide **35** was developed for the reaction of ketones with α-imino esters by Wang *et al.*.[21] Ley and co-workers applied the sulfonamide catalysts **36** and **37** to various Mannich reactions.[22]



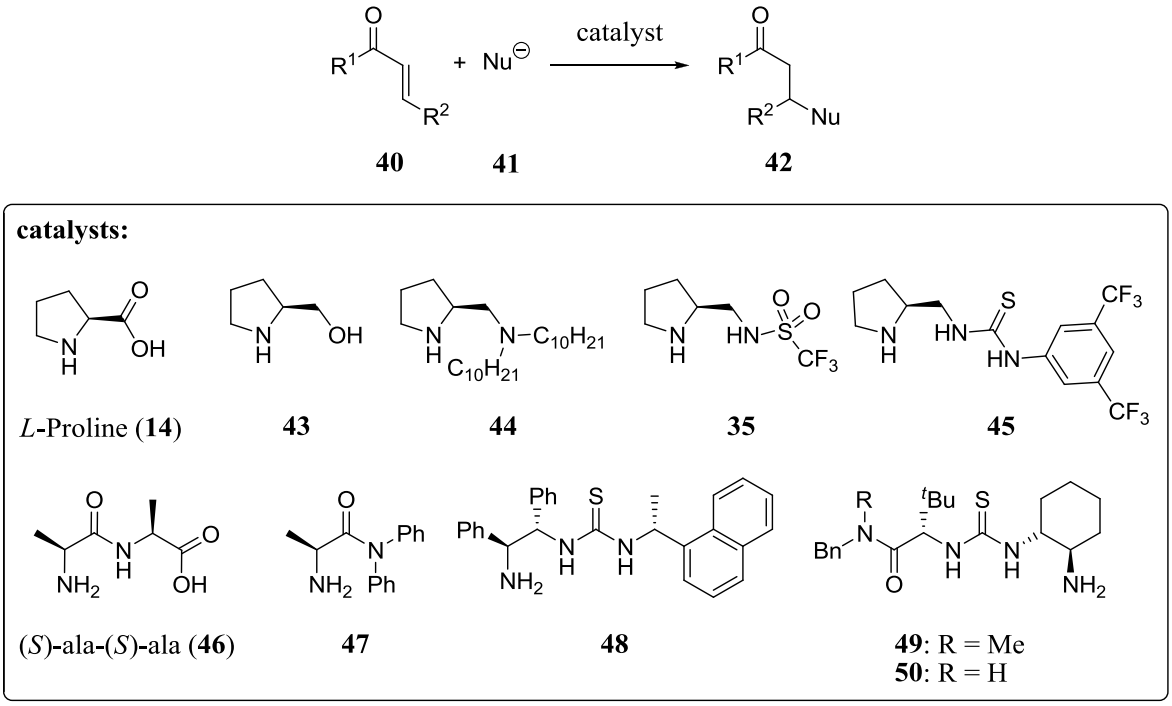


Scheme 4. Examples of organocatalysts for Mannich reactions.

Furthermore, not only secondary amines were utilized in the Mannich reaction also primary amino acids like (*S*)-alanine (**18**) and (*S*)-tryptophan (**39**) and alanine-based tetrazole (**38**) were used as catalysts.[23] In summary, these examples demonstrate the high applicability of secondary but also primary amine catalysts to diverse asymmetric Mannich reactions.

2.3 Asymmetric Michael Reactions

The asymmetric Michael addition has become an indispensable tool in organic chemistry for generating stereogenic centers. Thus, great effort was spent in developing new and especially atom economic strategies for such transformations. For this purpose, possible methodes are enamine-catalyzed enantioselective additions. The pioneering work in this field was done by Stork *et al.* which paved the way for a manifold potpourri of different approaches in this direction.[4, 24] In Scheme 5, a few examples of organocatalysts which were applied to the asymmetric Michael addition are summarized.



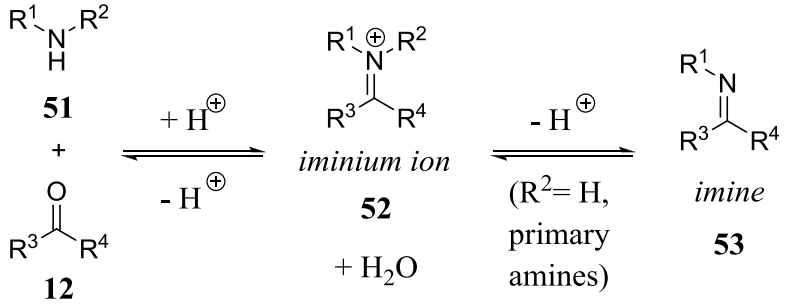
Scheme 5. Examples of organocatalysts used in asymmetric Michael reactions.

The first examples of *L*-proline (**14**) catalyzed asymmetric Michael additions were reported by Yamada and co-workers in 1969.[25] Since then many other examples, *intramolecular*[26] or *intermolecular*[15a, 22, 27], were published in which *L*-proline (**14**) was utilized as catalyst. Moreover, *L*-prolinol (**43**)[28], *L*-proline-derived diamines **44**[29] and pyrrolidine sulfonamide **35**[30] were as well applied to this reaction. Furthermore, bifunctional catalysts like the *L*-proline-derived thiourea catalyst **45** were used in the asymmetric Michael addition of cyclohexanone to nitroolefins.[31] On the other hand, also primary amines found their application in asymmetric Michael additions of ketones and aldehydes to nitroolefins, especially dipeptides like **46**[32] or amino amides like **47**[33]. Another class of primary amine catalysts are bifunctional primary amine-derived chiral thiourea structures like **48**[34], **49**[35] and **50**[35b], revealing a great potential compared to secondary amine, proline-based chiral thioureas because of their outstanding activity and reactivity. In summary, so far a great number of primary and secondary amines were used as organocatalysts in the asymmetric Michael addition to generate the products in high yields and stereoselectivities.

All in all, the three presented reaction types are the most important applications in asymmetric enamine catalysis. Beside them, there are also the asymmetric α- and γ-functionalization of carbonyl compounds, which are not covered here (for further information see reference [4]).

3. Iminium Catalysis

In 1864 Schiff[36] discovered the condensation reaction of aldehydes and ketones **12** with primary amines **51** in which the starting materials and the products are in equilibrium (Scheme 6).[37] The position of the equilibrium is strongly depending on the pK_a value because the primary amine-derived imines **53** are basic thus they are present as iminium ions **52** in acidic solution.[38]



Scheme 6. Formation of iminium ions **52** and imines **53**, if the starting material is a primary amine.

However, by the reaction of secondary amines **51** with aldehydes and ketones **12** only iminium ions **52** can be formed. These latter discoveries were the basis for extensive studies of small organic molecules which were able to catalyze organic reactions especially stereoselective ones *via* iminium activation. As a consequence of the iminium salt formation **52**, the electrophilicity compared to the corresponding aldehyde or ketone **12** is increased, which makes the compound more suitable against a nucleophilic attack.[39] This concept, in modern terms, was described by MacMillan and co-workers in 2000 and was named "LUMO-lowering catalysis".[40] This was the motivation for many working groups to devote great effort in the development of new synthesis strategies based on iminium-catalyzed processes. In the following, a brief summary of the most important iminium catalyzed transformations and the used organocatalysts is given.

3.1 Cycloadditions

The first organocatalytic cycloaddition was reported by MacMillan and co-workers in 2000. They applied the imidazolidinone catalyst **54** to the Diels-Alder reaction between activated enals and dienes *via* iminium ion formation.[40] Moreover, they used this catalyst for a dipolar cycloaddition between Crotonaldehyde and different nitrones.[41]

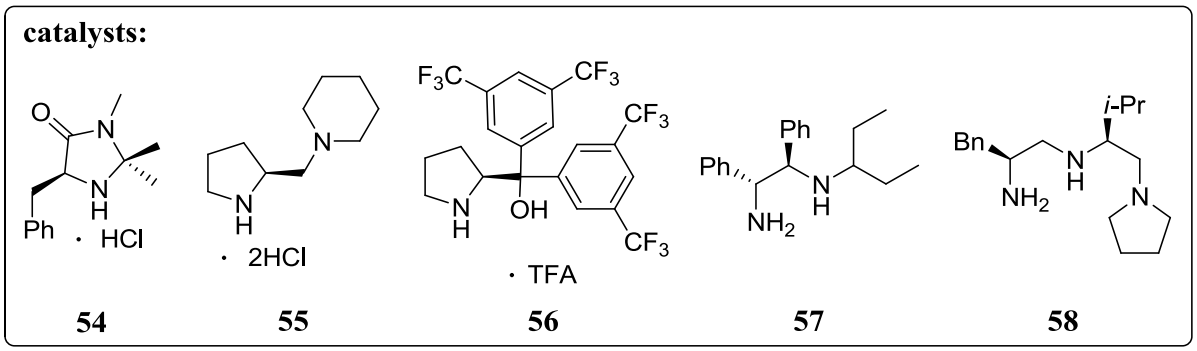


Figure 2. Examples of organocatalysts used for cycloadditions.

Karlsson and Högberg utilized catalyst **55** to the [3+2]-addition of cyclic aldehydes and different nitrones with much better results than obtained with imidazolidinone **54**.[42] Catalyst **57** was used in a [3+2]-addition between enals and cyclic azomethine imines by Chen and co-workers in 2006.[43] The primary amines **57**[44] and **58**[45] were both utilized in the Diels-Alder reaction with an excellent outcome.

3.2 Conjugated Additions

Conjugated additions are important reactions in organic chemistry, which give access to a great diversity of carbonyl compounds depending on the used nucleophile. Over time, many C-, H-, S-, N- and O-nucleophiles were tested for such addition reactions.[39] In the following a small selection of different organocatalysts used for this approach are shown (Figure 3).The first *L*-proline (**14**) catalyzed conjugated addition of nitroalkanes to cycloalkenones was reported by Hannessian and Pham in 2000.[46] Before this discovery Yamaguchi *et al.* utilized the *L*-proline salts **59**[47] and **60**[47d, 48] to the asymmetric Michael addition of malonates or nitroalkanes to α,β-unsaturated aldehydes. The chiral imidazolidinone **61** was applied to a Friedl-Crafts alkylation by MacMillan *et al.*[49] and moreover, was used as catalyst in the key step of a total synthesis of various alkaloids by Banwell and co-workers[50]. The pyrrolidin-based tetrazole **32** was used in the asymmetric addition of nitroalkanes to enones by Ley *et al.*.[51] Moreover, the pyrrolidine-derived catalyst **62** was widely used in diverse asymmetric conjugated additions of malonates[52], thiols[53] or hydroxylamines[54] to α,β-unsaturated carbonyl compounds.

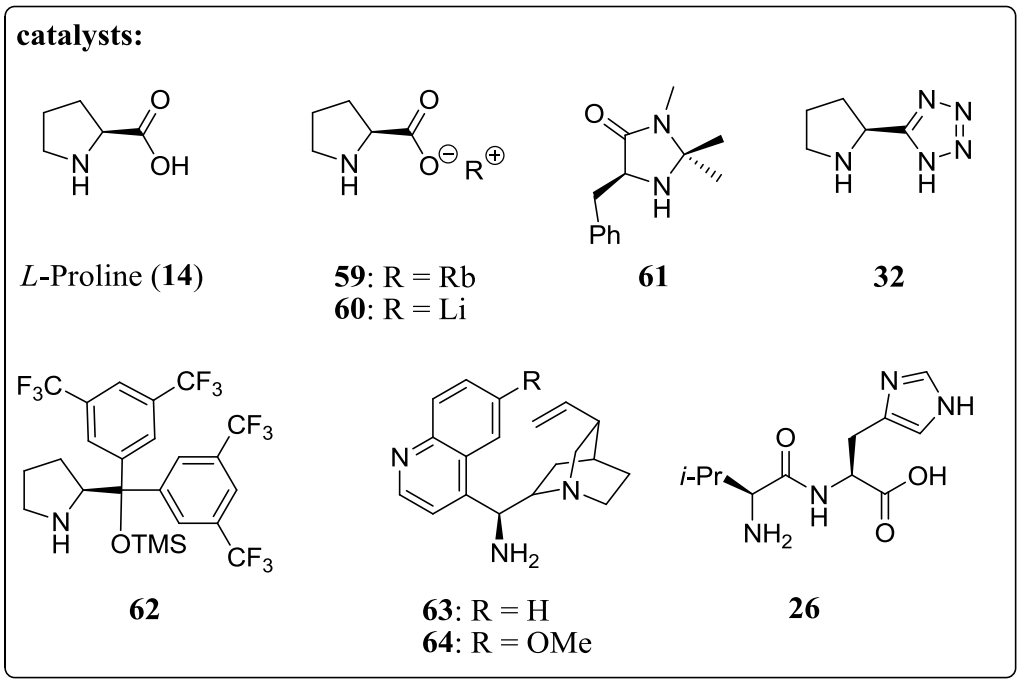


Figure 3. Examples of organocatalysts used for conjugated additions.

However, besides secondary also primary amines were applied. The quinine based catalysts **63** and **64** were utilized to a broad scope of asymmetric conjugated additions, most often in the additions of different nucleophiles, like 1,3-dicarbonylcompounds[55], dicyanoalkanes[56] and indols[57] to α,β-unsaturated ketones. Tsogoeva *et al.* studied the histidine-based dipeptide **26** in the addition of nitroalkanes to cyclohexanone.[58]

There are many other activation modes that proceeding *via* iminium catalysis. All of them leading to C-C-double bonds or C-N-double bonds either in the product or in the transitions state (for more detailed information see reference [39]).

In conclusion, iminium catalysis has grown to an often used and well established part of organocatalysis. However, the high catalyst loadings required (up to 20-30 mol%) are a certain drawback, thus there is still room for improvement in terms of developing faster and more selective catalysts.

4. Brønsted Acid Catalysis

The field of Brønsted acid catalysis is currently becoming an important pillar of organocatalysis. This type of activation could be divided into two categories. On the one hand hydrogen-bonding catalysts like thiourea **66** and TADDOL derivatives **67** and on the other hand stronger Brønsted acid catalysts like BINOL derivatives **68** and phosphoric acids **69** (Figure 4).[59]

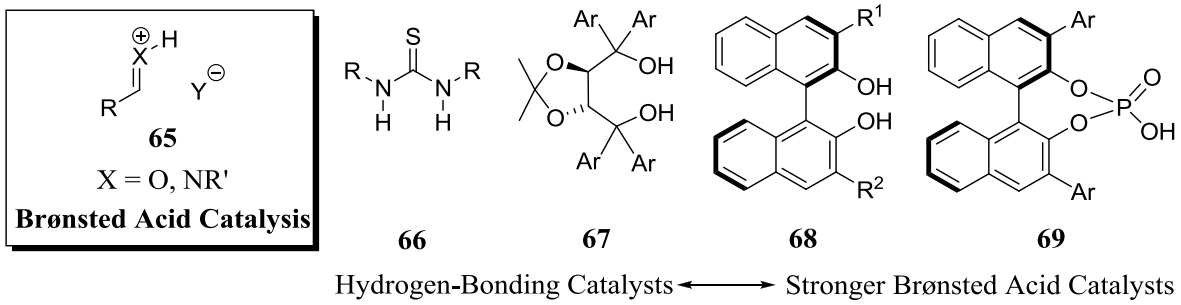


Figure 4. Chiral Brønsted acids.

The binaphthol derivatives **68** were utilized to large variety of reactions including the enantioselective Morita-Baylis-Hillman [60] as well as the enantioselective aza-Morita-Baylis-Hillman[61], the Mannich[62] and the Diels-Alder reaction[63]. Moreover, different BINOL-derived phosphoric acids **69** were applied to miscellaneous reactions like Mannich type reactions[64], aza-Friedel-Crafts alkylations[65], Strecker[66] and aza-Diels-Alder reactions[67] and transfer hydrogenations with Hantzsch ester as hydride source[68].

On the other hand, there are also examples of Brønsted acids catalyzing reactions *via* hydrogen bonding (Figure 5). Even though, *L*-proline (**14**) is usually considered to belong to the group of enamine catalysts it is also possible to assign it to the group of hydrogen bonding catalysts because of its carboxylic acid moiety which could additionally activate the substrate *via* H-bonding. This concept was first presumed by Barbas *et al.* in the *L*-proline (**14**) catalyzed asymmetric aldol reaction[7b] and later Wu and co-workers achieved improved results by installing a dual H-bond donor instead of the carboxylic acid in catalyst **19**.[9a] This concept of hydrogen bonding was also assumed in the *L*-proline (**14**) catalyzed Mannich reactions.[69] A better soluble alternative to *L*-proline (**14**) in Mannich reactions is the tetrazole catalyst **32**.[22, 27f] Furthermore, Diels-Alder reactions[70] as well as hetero Diels-Alder reactions[71] are known to be catalyzed over hydrogen-bonding interactions with the TADDOL-derived catalyst **70**.

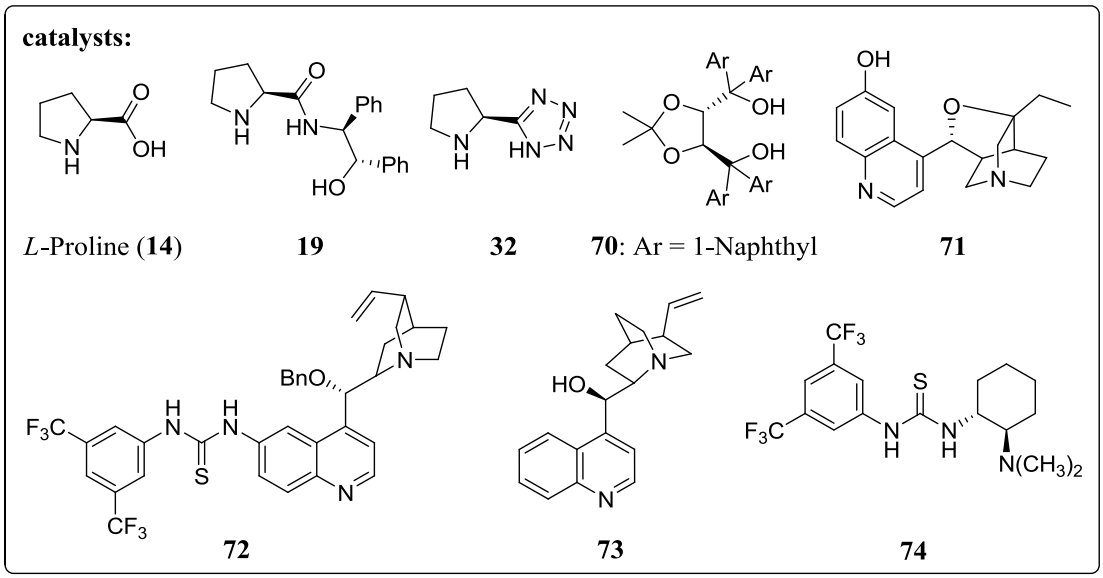


Figure 5. Brønsted acids acting as organocatalysts in different reactions.

The quinidine catalyst **71** was found to catalyze Baylis-Hillman[72] as well as aza-Baylis Hillman reactions[73] in excellent yield and stereoselectivity, which is referred to the H-bonding ability of the hydroxy group. Hiemstra *et al.* discovered that the cinchona alkaloid derivative **72** served as outstanding catalyst for the enantioselective Henry reaction.[74] Cinchona alkaloid **73** was used in a Friedel-Crafts addition of indole to ethyl trifluoropyruvate and thereby the necessity of the hydroxyl group for the formation of hydrogen-bonding was proofed.[75] Moreover, catalyst **73**[76] and the tertiary amine-thiourea derivative **74**[77] were both utilized in the Michael addition.

These examples reflecting only a small section of the great diversity of H-bond donor catalysts developed during the last years.

5. Brønsted Base Catalysis

The Brønsted base catalysis is a hardly classifiable field, due to the fact that many organocatalyst are bifunctional. Thus, an urea catalyst that bears an amine could be seen either as Brønsted base catalyst or as an H-bonding donor catalyst.[2] Typical examples of Brønsted base catalysts are displayed in Figure 6.

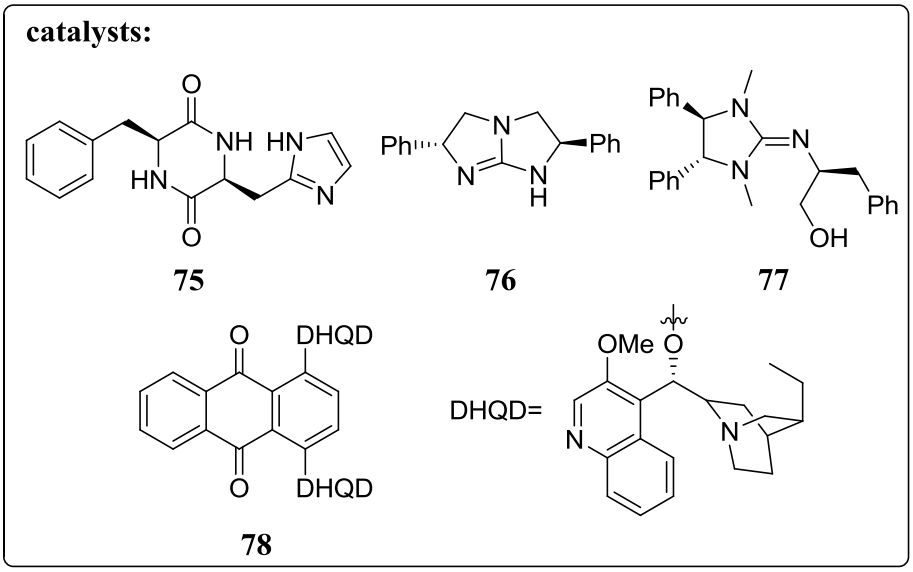


Figure 6. Organic Brønsted bases for organocatalysis.

Typical reactions in this field are hydrocyanation reactions like the cyanohydrin synthesis and the Strecker reaction.[3] The cyclopeptide **75**, for example, was used in a HCN addition reaction to various aldehydes.[78] Moreover, Corey and Grogan studied the Strecker reaction using a chiral C_2-symmetric guanidine **76**.[79] Furthermore, Isobe *et al.* reported a Michael reaction of a prochiral glycine derivative catalyzed by the modified guanidine **77**.[80] Deng and co-workers applied the modified cinchona alkaloid **78** as catalyst to the desymmetrization of cyclic *meso*-anhydrides.[81] The latter mentioned desymmetrization of meso compounds has developed to a powerful tool in asymmetric synthesis and especially in Brønsted base organocatalysis in the last few years (for a detailed review see reference [82]). In conclusion, these different examples make clear that Brønsted base catalysts is a fast growing and important sector of organocatalysis.

6. Lewis Acid Catalysis

Lewis acid catalysis is a small and often neglected but important activation mode in organocatalysis. The main focus of research was laid on Lewis base (enamine/iminium catalysis) and Brønsted acid catalysis although it can develop to an equal powerful tool.[83] By taking a closer look, it gets obvious that a big part of Lewis acid organocatalysts can also be seen as phase-transfer catalysts[3] and often these catalysts bear a positively charged center that is prone to activate the substrate.[84] Figure 7 displays a few examples of Lewis acid organocatalysts.

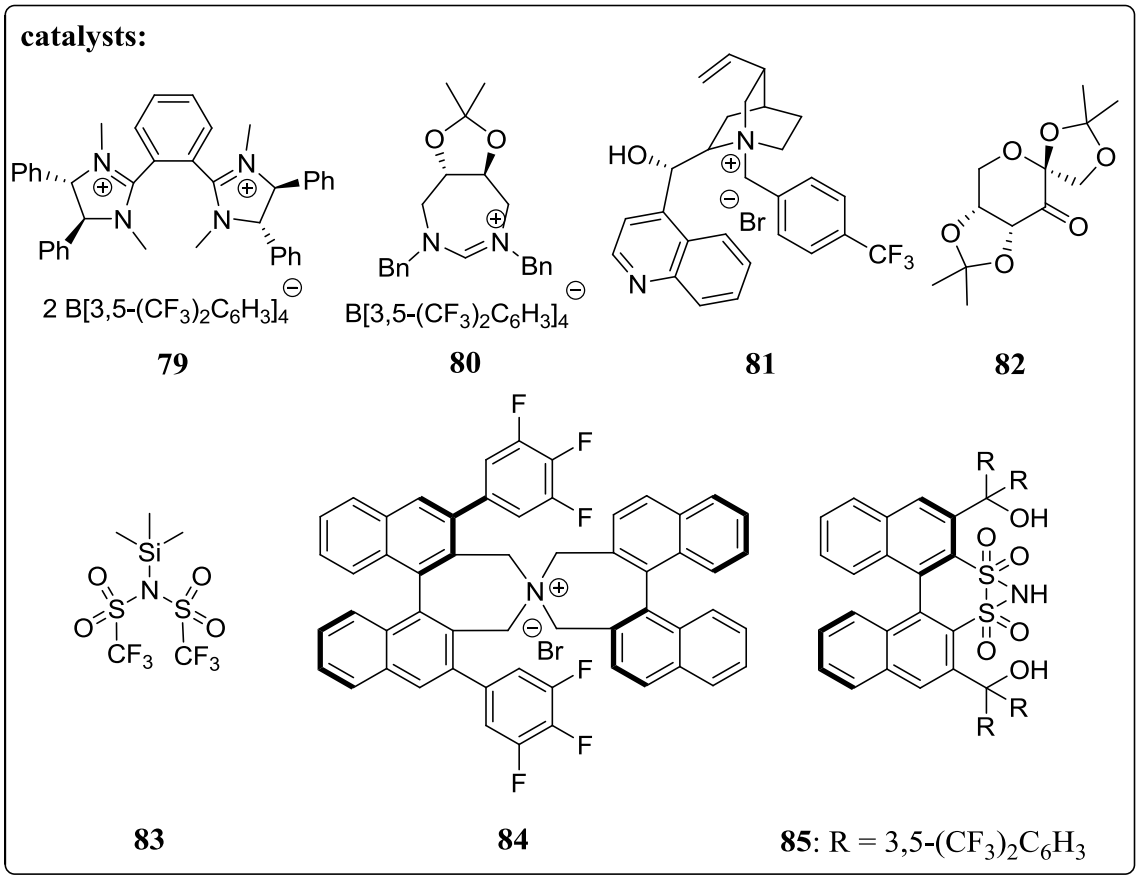


Figure 7. Examples of Lewis acid organocatalysts.

Wilhelm *et al.* used the bis-imidazolinium salt **79** in a Diels-Alder reaction and obtained the product in excellent *endo*:*exo*-selectivity with good yield. Moreover, they applied catalyst **79** and **80** in the ring opening reaction of cyclohexene epoxide with outstanding results.[84] Aryl cinchoninium salt **81** was one of the first examples of an Lewis acid organocatalyst developed by Dolling and co-workers in 1984.[85] It was applied to an α-alkylation of indanone under phase-transfer catalytic conditions. Another example that shows a great applicability of Lewis acid organocatalysts to various C-C-bond forming reactions is the C_2-symmetric chiral spiro

ammonium salt catalyst **84**. It was utilized to α-alkylations[86], aldol[87] and Michael reactions[88]. On the other hand, also uncharged molecules are known that serve as Lewis acid catalysts. One important class are the *in situ* formed chiral dioxiranes generated from chiral ketone catalysts and Oxone (potassium peroxomonosulfate).[89] Shi *et al.* used the *D*-fructose derived ketone catalyst **82** for an enantioselective epoxidation of various olefines.[90] Furthermore, the imide **83** was found to be an excellent catalyst for the Friedel-Crafts alkylation[91] and different cycloaddition reactions[92]. The BINOL-derived disulfonimide **85** was developed by List and co-workers and was applied to the Mukaiyama aldol reaction to obtain outstanding results.[83] These manifold examples show the great potential of Lewis acid catalysis especially in the field of phase-transfer catalysis.

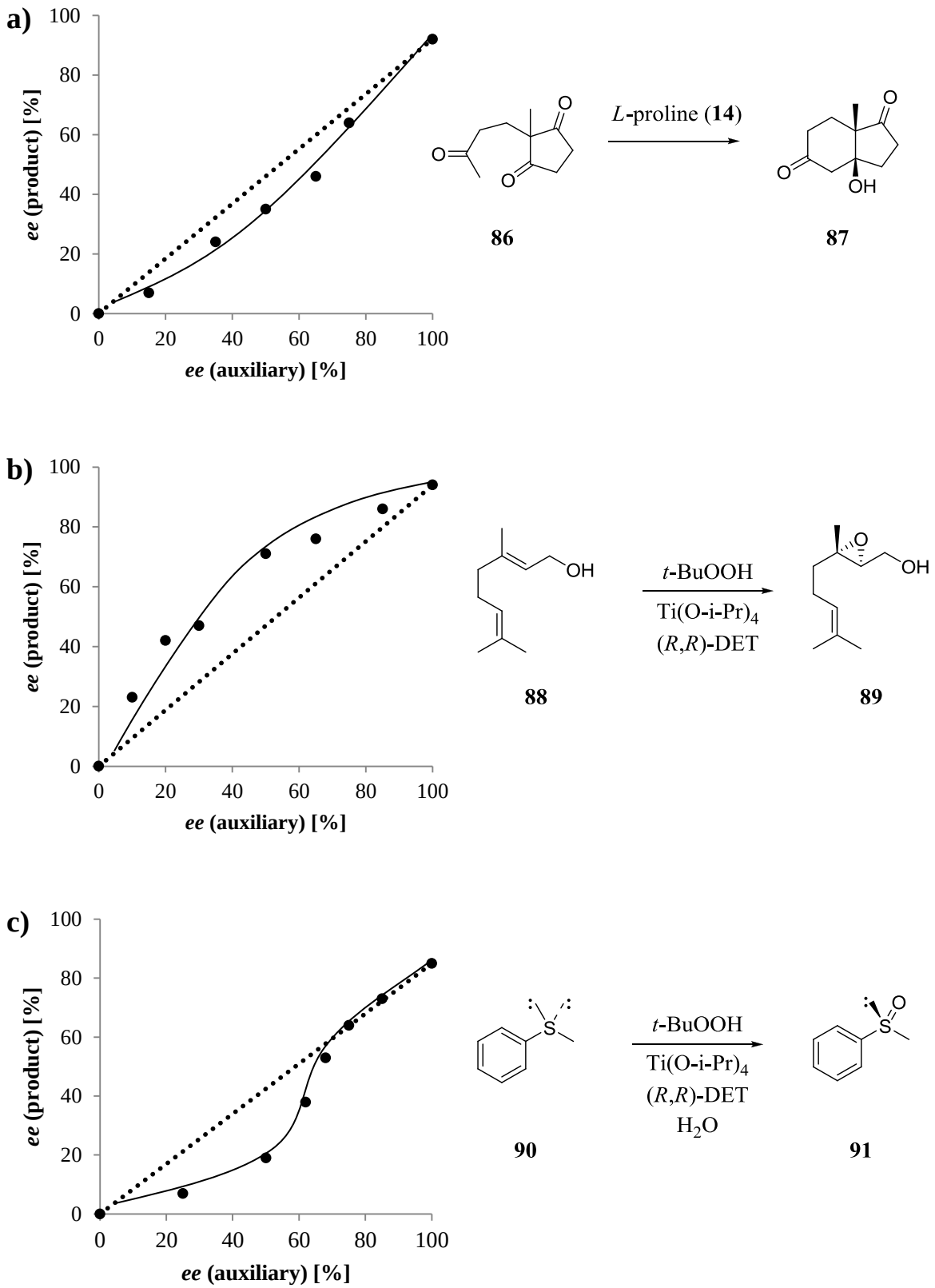
All in all, the literature examples presented above demonstrate the broad applicability of organocatalysts to many reactions. Moreover, it seems obvious that from such an easy modifiable and robust class of catalysts creative ideas for developing new and powerful catalysts could arise in the future. In the present thesis, attempts for the optimization and investigation of an *L*-proline/Co(II)-catalyzed aldol reaction, as well as the subsequent application of this complex to other reactions were done. Moreover, easy accessible 1,2-diamio alcohols were utilized to various organic transformations to show their broad applicability. The results are presented in the following.

B Organocatalysis of *L*-Proline in the Presence of Metal Salts

1. Introduction

1.1 The Nonlinear Effect (NLE) - From the Discovery to Present Research

An important aim for organic chemists has always been the development of reactions and strategies that induce a high level of stereoselectivity in the desired target molecule.[93] The discovery of chirality dates back to the year 1848, when Luis Pasteur examined the ammonium sodium salt of tartaric acid and thereby recognized that it rotates the plane of polarized light in two different ways depending on its origin.[93b, 94] Moreover, he realized that a *racemic* mixture of compounds has no effect on the rotation of polarized light and is therefore optical inactive. Thus, a linear correlation between the *enantiomeric excess* (*ee*) and the optical purity was concluded making the use of polarimetry for determining the *ee* the method of choice. Nevertheless, further investigations lead to the finding of a deviation of this linear correlation, which was explained by the nature and composition of the present mixture and its enantiomeric purity, as pure enantiomers compared to *racemic* mixtures can have a different chemical rate and thus generating a different product distribution. The pioneering work in this field was done by Horeau *et al.*[95] who were the first to notice this phenomenon of the not exact linear correlation between specific rotation and enantiomeric excess.[94b, 94c, 96] Further work in this area was done by Wynberg and Feringa[97], who examined the non-ideal behavior of a mixture of enantiomers in solution and pointed out that diastereoselective reactions are influenced by the *ee* of the substrate. The reason for this is that in a *racemic* mixture interactions between the two enantiomers could develop that are not possible in an enantiopure system. As a consequence these mixtures differ in their influence on reactivity and stereoinduction.[93b, 94b, 94c, 96] In 1986 Kagan *et al.* explained, for the first time, the quantitative aspects of the nonlinear correlation between the *ee* of the auxiliary (ee_{aux}) and the *ee* of the product (ee_{prod}), proved by three examples from asymmetric catalysis (Scheme 7).[93b, 93c, 94b, 94c, 96, 98] They coined it “nonlinear effect” (NLE), whereas over time and further investigations terms like *chiral/asymmetric amplification*, *chiral multiplication* or *asymmetric depletion* occurred.[93b, 93c, 96, 98b, 99]



Scheme 7. Examples of the first NLEs in literature; **a)** (−)-NLE in the Hajos-Parrish-Wiechert reaction of **86** to **87** catalyzed by (*L*)-proline (**14**); **b)** (+)-NLE in the Sharpless epoxidation of geraniol (**88**); **c)** (−)-NLE until 70% (from then on linearity was resumed) in the asymmetric oxidation of sulfide **90** with a chiral titanium reagent.[93b, 93c, 94b, 94c, 96, 98]

Diagram **a)** in Scheme 7 shows the *intramolecular* asymmetric aldolization of triketone **86** catalyzed by *L*-proline (**14**) for which a small negative nonlinear effect [(-)-NLE)] was assumed. However, more recent studies by List *et al.* disproved this assumption.[100] A positive nonlinear effect [(+)-NLE] was noticed in the Sharpless epoxidation of geraniol (**88**) [diagram **b)**, Scheme 7]. Furthermore, the asymmetric sulfoxidation of **90** generated a (-)-NLE, until 70% *ee* were reached, from then on linearity was resumed till a maximum of 85% *ee* [diagram **c)**, Scheme 7].[94b, 98a]

The correlation of the *ee* value of the product in an asymmetric reaction with the *ee* value of the chiral auxiliary could easily be done if the latter are acting independently from each other. For this case equation (1) can be applied in which the *ee* of the product correlates in a linear way with the *ee* of the auxiliary. The maximum *ee* value of the product (ee_{max}) is obtained by carrying out the catalysis with the enantiopure chiral catalyst or auxiliary.[93c, 94b, 96a]

$$ee_{prod}(\%) = (ee_{max} \times ee_{aux}) \times 100 \quad (1)$$

After transforming equation (1) into equation (2), it is possible to specify ee_{prod} by using the linear relationship given in equation (2)

$$ee_{max}(\%) = (ee_{prod} \div ee_{aux}) \times 100 \quad (2)$$

If ee_{prod} is plotted versus ee_{aux} as displayed in Figure 8 in the case described above a linear correlation should occur (blue line, Figure 8). However, there also might occurr a positive nonlinear effect (red line, Figure 8) or a negative nonlinear effect (green line, Figure 8). It should be mentioned that the curves in Figure 8 correspond to an ideal case and are not generalizable, since there are known literature examples of a combination of linear and nonlinear effects, *e.g.* in the asymmetric sulfoxidation described above (Scheme 7).[98a]

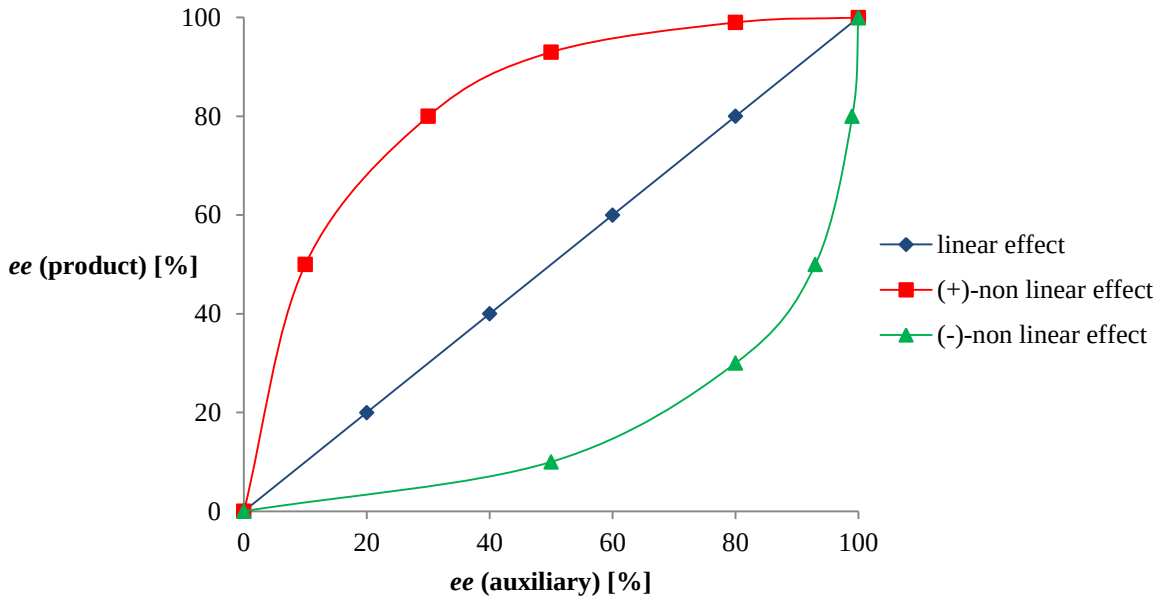
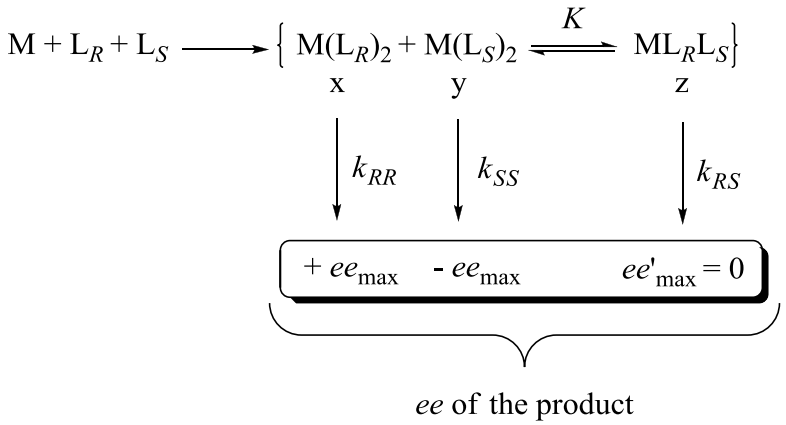


Figure 8 General graph displaying the three cases of a linear (blue line) correlation and a positive (red line) or a negative (green line) nonlinear correlation between ee_{prod} and ee_{aux}.

This nonlinear phenomenon can appear, if the catalyst contains two or more chiral ligands that are not enantiomerically pure, because in this scenario homochiral or heterochiral catalytic species are formed, which differ in their reaction rate and stereoinduction. Therefore, the linear relationship expressed in equation (1) and (2) is no longer valid, requiring their adjustment by introducing correction factors. Many theoretical models to describe such non-linear effects were established in the last two decades. The simplest situation is encountered when two enantiomeric chiral ligands (L_R and L_S) are attached to a metal center (M) to generate ML_2 complexes as reactive species. Owing to this situation it is possible to get three different species, two homochiral ones [$M(L_R)_2$ and $M(L_S)_2$] and one hetero- or *meso*chiral one (ML_RL_S). Scheme 8 illustrates the case for a dynamic equilibrium between the three complexes $M(L_R)_2$, $M(L_S)_2$ and ML_RL_S and a fast exchange of the ligands (L_R and L_S) at the metal (M).



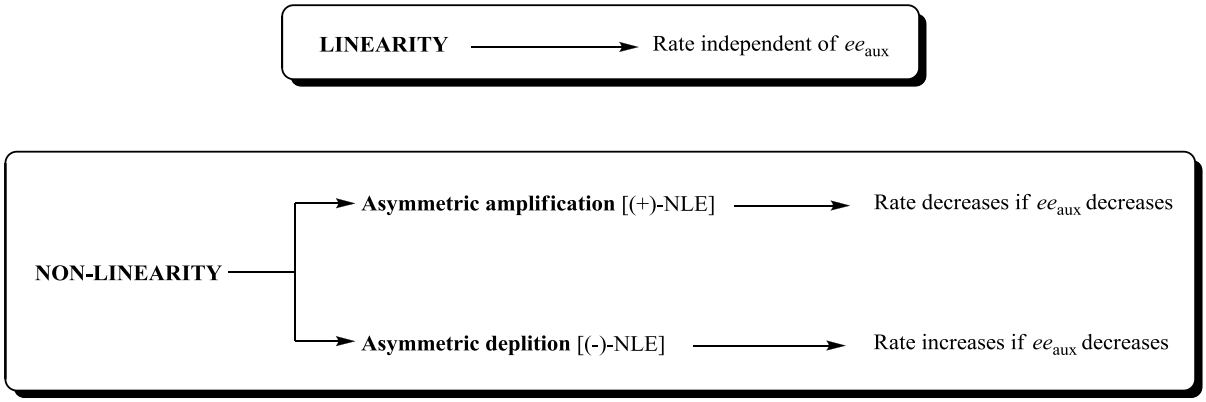
Scheme 8. Overview of the ML_2 model system.[101]

In this model system the two homochiral complexes are forming the two opposite enantiomeric products, whereas the heterochiral species is forming exclusively the *racemic* product with respect to their relative reactivity (g = k_{RS}/k_{RR} or k_{RS}/k_{SS}) and their relative concentrations [β = z/(x+y)][93c, 102] (Scheme 8).[101] With these assumptions, it is now possible to formulate equation (3), which expresses the ee_{prod} as a function of ee_{aux} (red and green curve, Figure 8) [101]

$$ee_{prod}(\%) = \left[(ee_{max} \times ee_{aux}) \times \frac{1+\beta}{1+g\beta}\right] \times 100 \qquad (3)$$

The values for g and ee_{max} are fixed for a certain system and β can be calculated with the help of the equilibrium constant *K* between the heterochiral and homochiral complexes.[101] The requirement for equation (3) to be valid is that all ligand (L_R and L_S) is converted into one of the three metal complexes [$M(L_R)_2$, $M(L_S)_2$ or ML_RL_S] or that the external ligand is enantiopure and therefore maintains the initial value of ee_{aux}. Thus, three different cases may occur. When β = 0 (no *meso* catalyst is forming) or g = 1 (reactivities of *meso* and homochiral catalysts are identical) equation (3) is simplified to equation (2) and a linear correlation between ee_{prod} and ee_{aux} (blue curve, Figure 8, page 19) is obtained. When g > 1 a negative nonlinear effect is observed which at the same time means that the *meso* complex is more reactive than the homochiral one (green curve, Figure 8, page 19). If g < 1 the reversed case is true. The homochiral complex is more reactive compared to the *meso* complex, hence leading to a positive nonlinear effect (red curve, Figure 8, page 19). As one might expect, the biggest deviation from linearity in a positive NLE is obtained when g = 0 meaning that the *meso* complex is catalytic inactive.[96a] By reaching the thermodynamic equilibrium, the highest positive NLEs can be achieved if the equilibrium constant *K* is large and g is small which, in other words, means the reaction takes place very slowly and the concentration of the *meso*

complex is high.[96a] Blackmond *et al.* investigated the NLE with regard to kinetic aspects, because this point of view was often neglected by other groups.[96b] Based on the assumption that the value of *K* is fixed, there are two cases for non-linearity (summarized in Scheme 9). When an asymmetric amplification [(+)-NLE] is present the reaction rate is decreases if the ee_{aux} decreases. In contrast, if there is an asymmetric depletion [(−)-NLE] the reaction rate increases if the ee_{aux} decreases. Therefore, it is necessary to decide whether the product should be formed in a big amount but with low *ee* value (high reactivity) or in small quantities but with high enantiomeric purity (low reactivity).[96b, 98b]



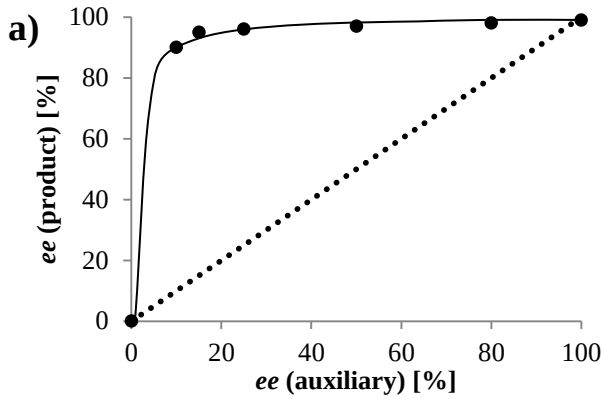
Scheme 9. Relations between reaction rates and the presence or absence of nonlinear effects.[98b]

For systems with more than two ligands (ML_3, ML_4...ML_n,) or for the, so-called reservoir effect, in which the catalytic active species is partially transferred into a catalytic inactive species also theoretical models were investigated, but in the course of this work it is not further focused on these models. For more detailed information of these models see the publications of Kagan *et al.*.[93b, 94b, 98b, 101]

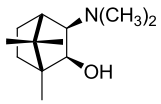
Since the discovery and the detailed investigation of the NLE by Kagan *et al.* many reactions catalyzed by a combination of a metal and two or more chiral ligands were examined under the focus of asymmetric amplification. One important example in homogeneous asymmetric catalysis is the asymmetric addition of organozinc compounds to aldehydes, which was intensively analyzed under the aspects of this effect by many working groups, *inter alia* Oguni *et al.*[93c, 103], Noyori *et al.*[93c, 102, 104], Bolm *et al.*[93c, 105] and also Kellog *et al.*[93c, 106]. Scheme 10 shows the asymmetric addition of diethylzinc (**93**) to benzaldehyde (**92**) catalyzed by different ligands **95**-**103** which show either a (+)-NLE or a (−)-NLE.[93c, 102-106]

92 **93** **94**

a)



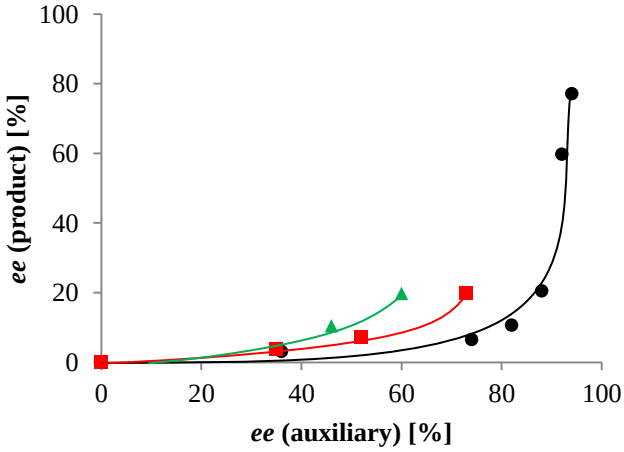
Chiral Catalyst



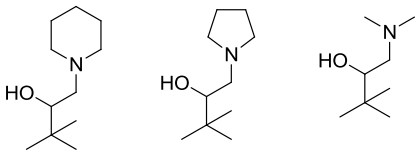
95

Noyori *et al.*

b) ● catalyst 96 ■ catalyst 97 ▲ catalyst 98



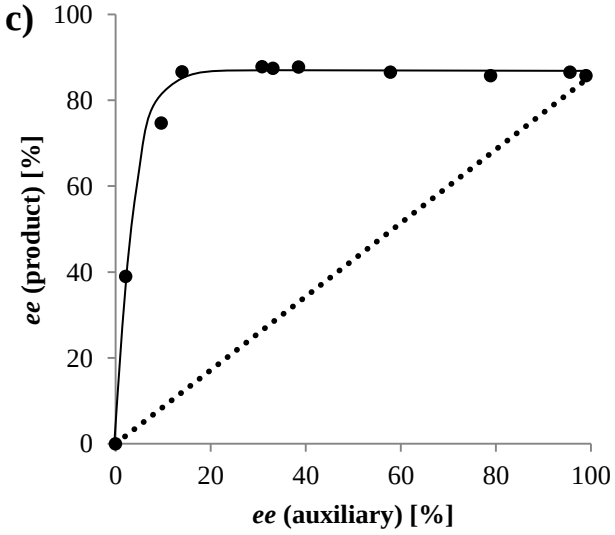
Chiral Catalyst



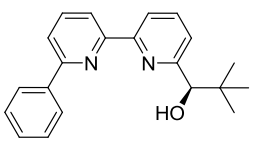
96 **97** **98**

Oguni *et al.*

c)

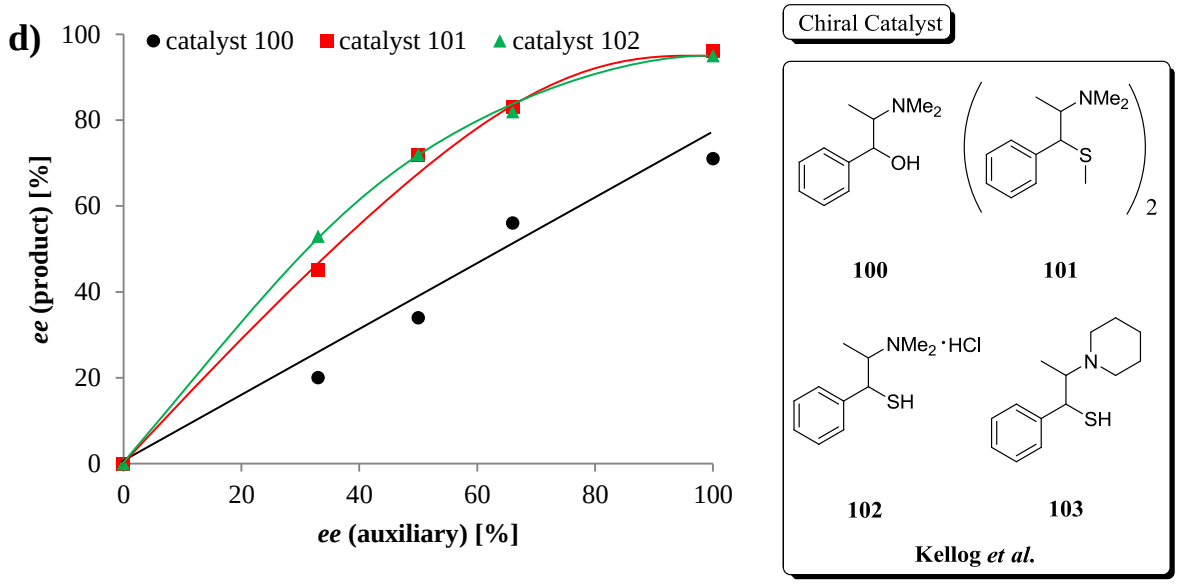


Chiral Catalyst



99

Bolm *et al.*

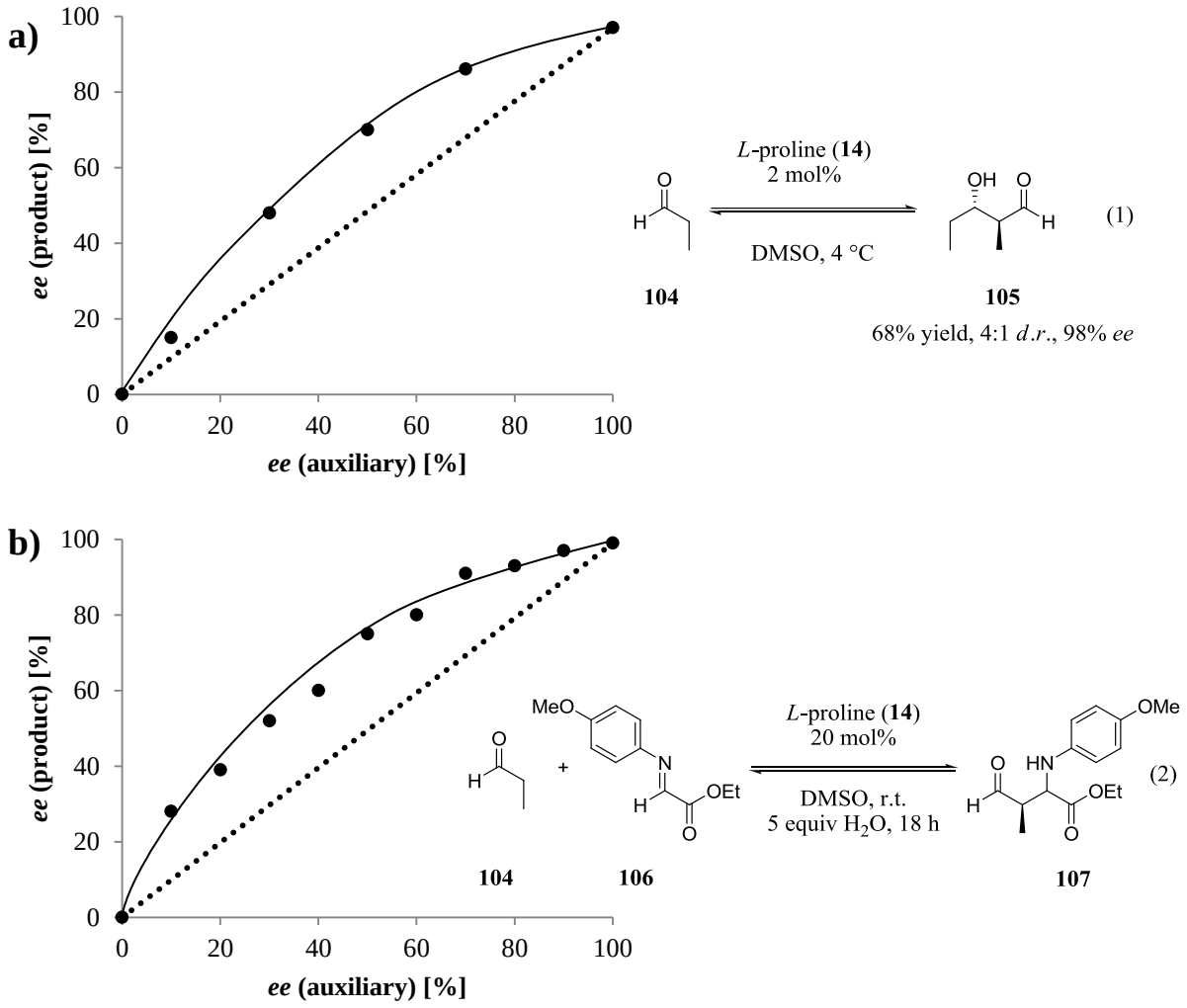


Scheme 10. First examples of asymmetric amplifications in the asymmetric addition of Et_2Zn (**93**) to benzaldehyde (**92**); the graphs on the left side show the correlation between the *ee* of product (**94**) and the *ee* of the auxiliary, investigated for the catalyst **a) 95** by Noyori *et al.*[104a]; **b) 96-98** by Oguni *et al.*[103]; **c) 99** by Bolm *et al.*[105]; **d) 100-103** by Kellog *et al.*[106].

In the course of the years, many other homogeneous organometallic catalyzed reactions with NLEs were found, *e.g.* conjugated additions of organometal compounds to enones, allylation of aldehydes, cyanide addition to carbonyl groups, C-alkylations, epoxide openings and rearrangements, enantioselective oxidations, reductions and Diels-Alder reactions.[93c] Nevertheless, here no closer look is taken on these reactions because they did not deal with the reactions which are investigated in this work. For an overview of these reactions see the review of Kagan *et al.*.[93c] Two, so far not mentioned homogeneous organometallic catalyzed reactions are aldol and Mannich reactions, respectively. As part of this work the NLE for the direct asymmetric aldol reaction between cyclohexanone (**150**) and *p*-nitrobenzaldehyde (**149**) catalyzed by a combination of *L*-proline (**14**) and $CoCl_2$ was analyzed. Therefore, some examples of aldol additions with respect to asymmetric amplification are presented in detail on the next few pages.

Another big field besides homogeneous organometallic catalysis is represented by homogeneous organocatalysis, which was intensively investigated in terms of NLEs. As mentioned before, the Robinson Annulation was the first reaction in this field which showed a NLE and was investigated by Kagan, Agami and co-workers (Scheme 7, page 17).[98a] However, List and co-workers reexamined the reaction and observed no deviation from linearity between the *ee* of the auxiliary and the *ee* of the product. Therefore, they made the assumption that only one *L*-proline (**14**) molecule is involved in the transition state of the reaction and not two like postulated by Agami and Kagan a long time.[98a, 100] The only

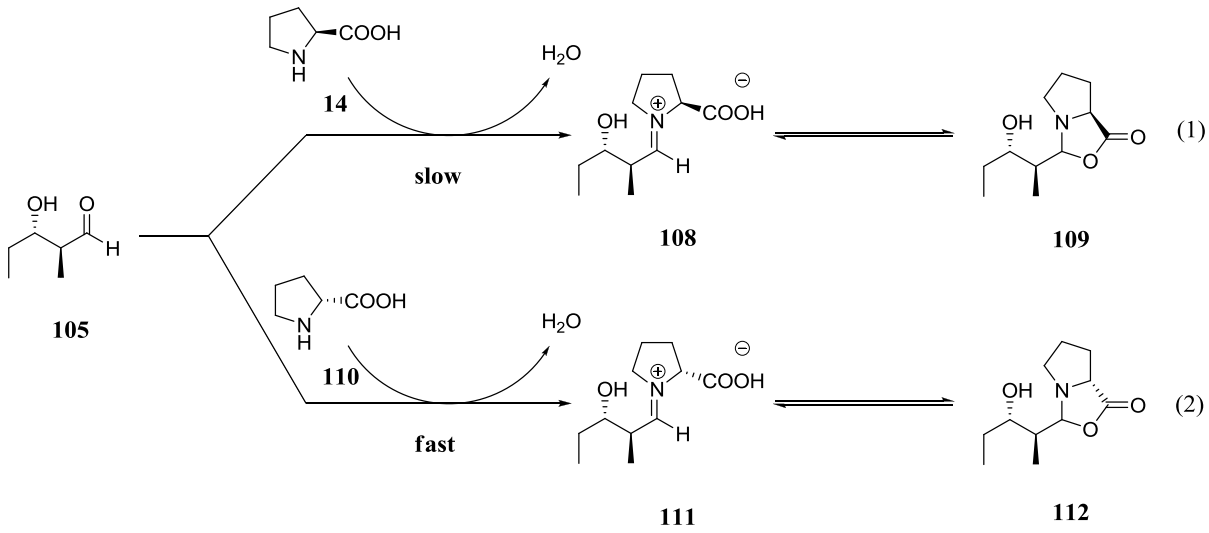
examples of an asymmetric amplification in *L*-proline (**14**) catalyzed reactions are shown in Scheme 11.



Scheme 11. The only two literature known *L*-proline (**14**) catalyzed reactions showing an asymmetric amplification; the graphs on the left side show the correlation between the *ee* of the product and the *ee* of the auxiliary; **a)** self aldol addition of propionaldehyde (**104**) [Eq. (1)]; **b)** Mannich type reaction between propionaldehyde (**104**) and *N*-protected α–amino glyoxylate **106** [Eq. (2)].[93c, 107]

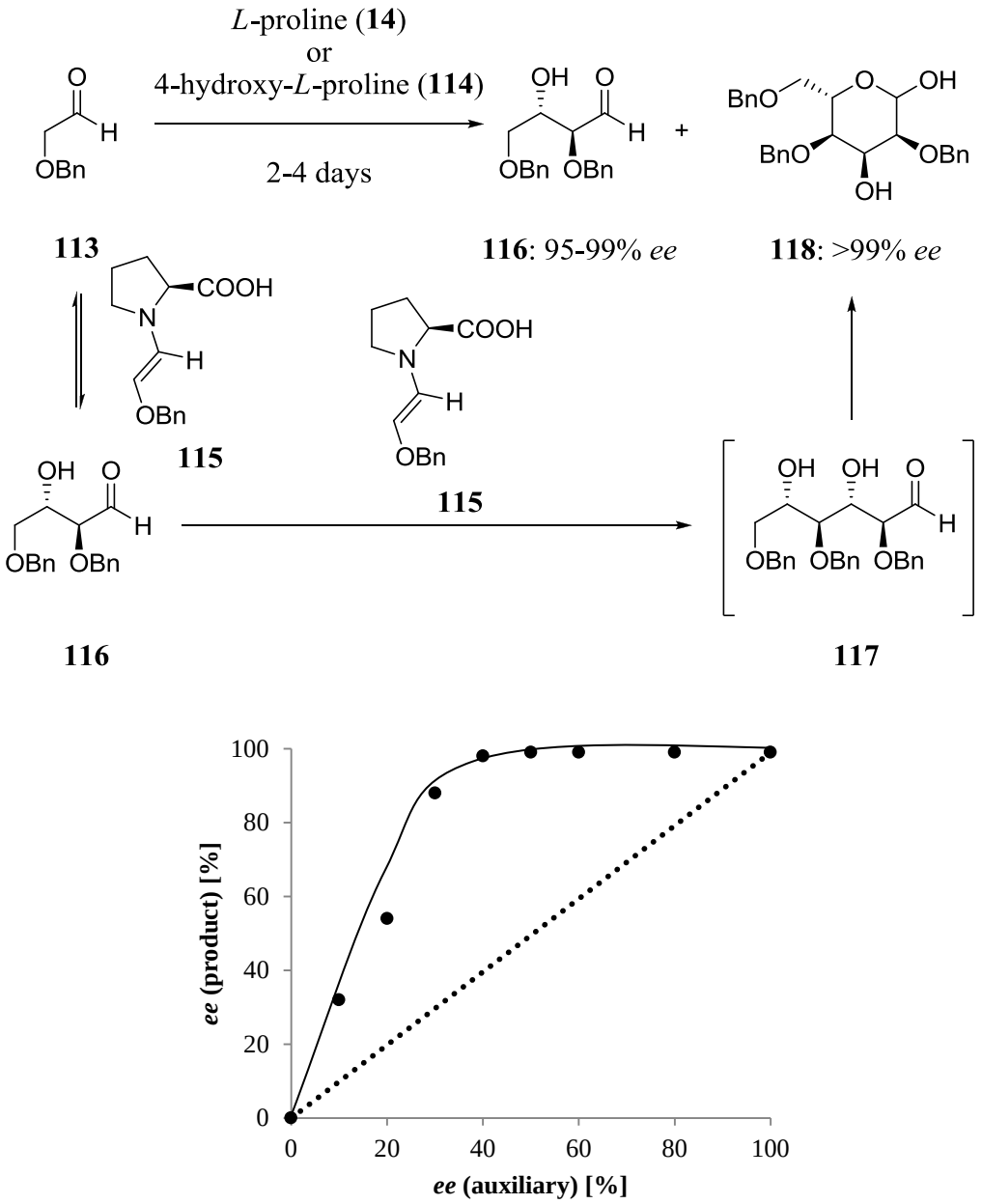
Equation (1) in Scheme 11 shows the asymmetric formation of the aldol addition product **105** catalyzed by *L*-proline (**14**), whereby a significant asymmetric amplification was noticed by Cordova *et al.*.[107a] Since only one *L*-proline (**14**) molecule is involved in the catalytic process, the (+)-NLE must be caused by the product **105** itself. It is hypothesized that the amplification is based on the fact of different rates of reactivity of *L*- (**14**) or *R*-proline (**110**) with the sugar precursor **105**. Therefore, the latter is "auto"-kinetically resolved leading to an enrichment of the free amino acid in the next catalytic cycle and hence to a positive nonlinear effect (Scheme 12).[93c, 107a] Equation (2) in Scheme 11 displays the Mannich type reaction of propionaldehyde (**104**) with the *N*-protected α-amino glyoxylate **106**. The studies of

Cordova *et al.* on this reaction also revealed an asymmetric amplification. Based on earlier mechanistic studies on Mannich type reactions it was supposed that also here only one proline molecule is involved in the formation of amino acid derivative **107**.[15b, 108] Based on these facts it is proposed that the amino acid **107** is probably reacting at different rates with the *L*- (**14**) or *R*-proline (**110**) and therefore "auto"-kinetically resolves the amino acid catalyst by forming oxazolidine structures which are leading to an (+)-NLE in the next catalytic cycle.[93c, 107b] This is in accordance with the explanation given for the aldol reaction of propionaldehyde (**104**) (see Eq. (1), Scheme 11 and Scheme 12).[107b]



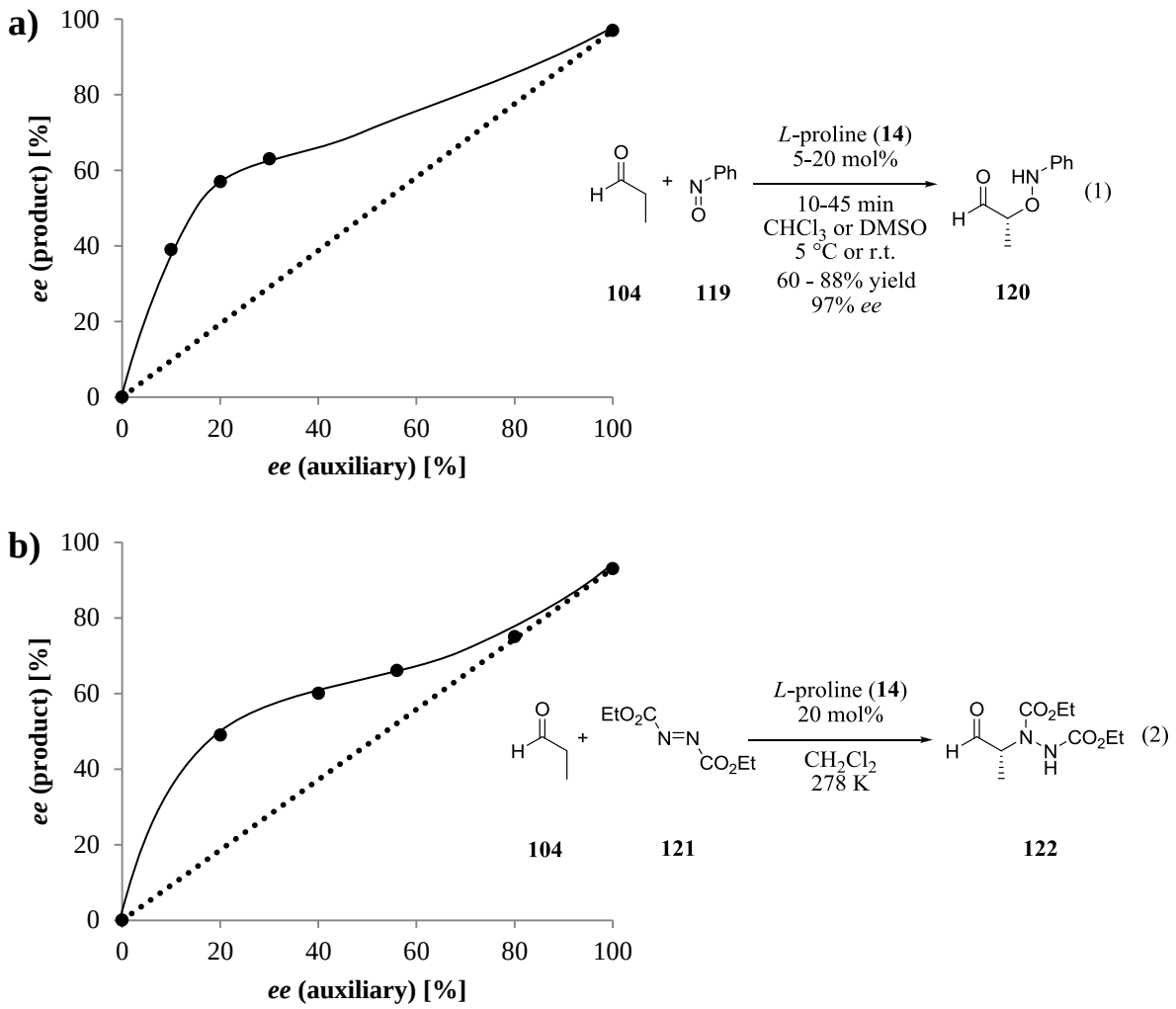
Scheme 12. Different reaction rates of *L*- (**14**) and *R*-proline (**110**) with sugar **105**.[93c, 107a]

Close related with these findings is the discovery of a positive nonlinear effect in the neogenesis of carbonhydrates catalyzed by *L*-proline (**14**) or 4-hydroxy-*L*-proline (**114**), respectively, by Cordova *et al.* (Scheme 13).[109] The reaction proceeds in the following way: First a self aldol addition takes place forming erythrose **116**, followed by the addition of erythrose **116** to a second enamine **115** leading to the allose intermediate **117**, which subsequently is transformed to the more stable hexose **118**. The latter step is also the rate-determing one. Hence, the interaction between non-enantiomerically pure proline and the tetrose **116** was given as explanation for the asymmetric amplification in the aldol addition.[109]



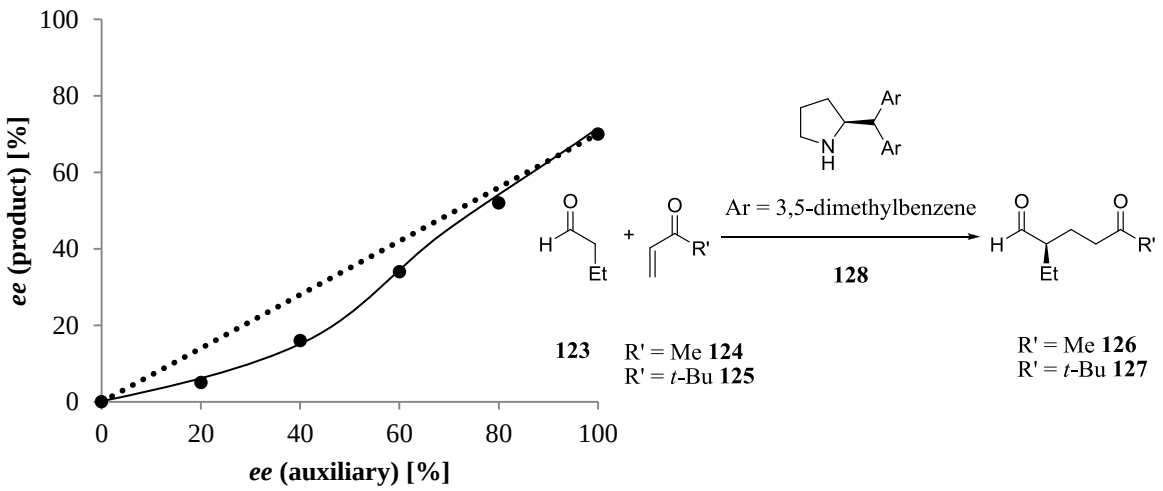
Scheme 13. *L*-proline (**14**) catalyzed asymmetric one-step synthesis of allose **118** and the observed NLE.[109]

Blackmond *et al.* examined the two reactions shown in Scheme 14, the *L*-proline (**14**) catalyzed *a*-aminoxylation [Eq. (1)][110] and the *α*-amination [(Eq. (2)][111] of propionaldehyde (**104**).



Scheme 14. The graphs on the left side show the correlation between the *ee* of the product and the *ee* of the auxiliary; **a)** asymmetric amplification of the *L*-proline (**14**) catalyzed α-aminoxylation of propionaldehyde (**104**) [Eq. (1)]; **b)** asymmetric amplification of the *L*-proline (**14**) catalyzed α-amination of propionealdehyde (**104**) [Eq. (2)].[110-111]

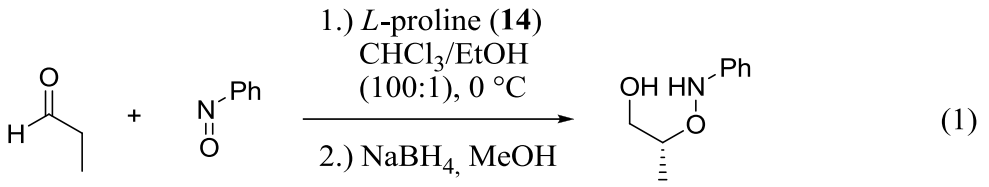
In both reactions an abnormal increase in the reaction rate and (+)-NLE was found probably, due to the formation of a proline adduct with product **120** or **122**, which in the further course of the reaction acts as a superior catalyst compared to *L*-proline (**14**). Thus, the asymmetric amplification is explained by kinetic resolution of proline by the reaction with product **120** or **122**, respectively, which can be seen as a selectivity-enhancing autoinductive process.[110-111] In conclusion these are the only examples where *L*-proline (**14**) shows a nonlinear effect. However, one further case is described in literature where a catalyst **118** similar to *L*-proline (**14**) is leading to asymmetric amplification, which was discovered by Jørgensen and co-workers (Scheme 15).[93c, 112]



Scheme 15. Nonlinear effect in the asymmetric enantioselctive Michael addition of aldehyde **123** to vinyl ketone **124** catalyzed by the chiral amine **128**.[93c, 112]

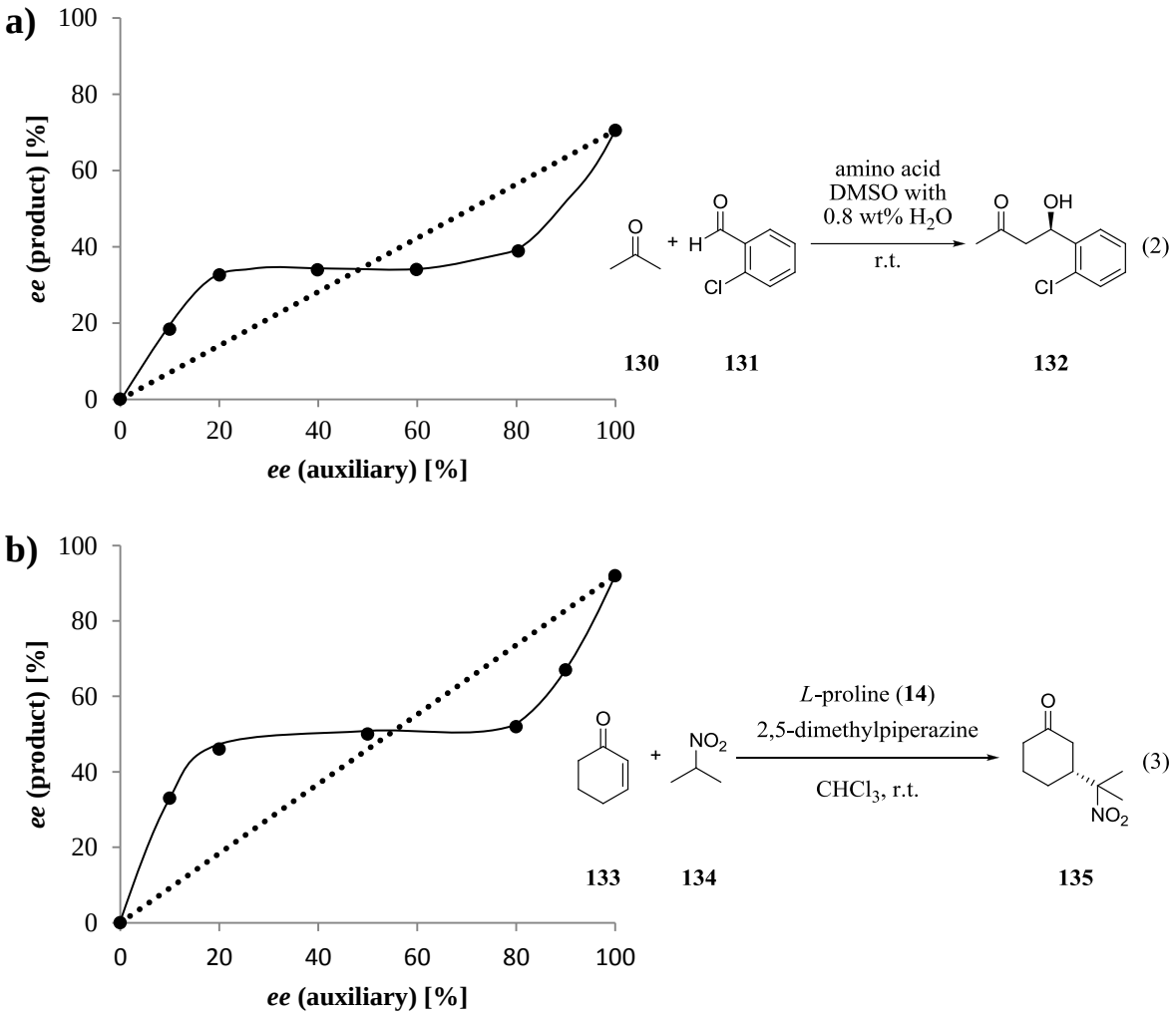
The reaction of aldehyde **123** with the 1,4-unsaturated ketones **124** or **125** catalyzed by the proline derivative **128** give rise to two different outcomes, by using different ratios of the *L*- and the *D*-form of catalyst **128**. In the case of enone **124**, a (−)-NLE could be noticed, whereas, in the case of enone **125**, this effect was not appearing. Therefore, Jørgensen *et al.* argued that a second molecule of the chiral amine **128** has to take part in the catalytic cycle owing to the (-)-NLE. The missing of an asymmetric amplification in the second case was explained by the sterically more demanding *t*-Bu-group of **125** in comparison to the Me-group of **124**, which makes formation of the iminium ion more challenging.[93c, 112]

A special consideration of nonlinear effects is based on the partial solubility of the catalytic species during the reaction which is linked with a reservoir effect. More precisely, one has to differentiate if the effect is caused by the different solubility of homo- and heterochiral complexes formed during the catalysis or if it is due to the different solubility of the catalyst itself due to aggregation effects in solution.



104 **119** **129**

I) 93%, 96% *ee*
II) 90%, 19% *ee*



Scheme 16. Eq. (1): (+)- NLE in the α-aminoxylation of propionaldehyde (**104**) catalyzed by *L*-proline (**14**);[93c, 113] **a)** NLE in the asymmetric aldol reaction between aceton (**130**) and 2-chlorobenzaldehyde (**131**) [Eq. (2)];[93c, 114] **b)** NLE in the catalytic conjugated addition of 2-nitropropane (**134**) to cyclohexenone (**133**) [Eq. (3)].[46]

The latter effect was intensively studied by Hayashi *et al.* in the α-aminoxylation of propionaldehyde (**104**) catalyzed with non-enantiopure proline prepared from solid proline with only 10% *ee*. They obtained the product in 90% yield but only 19% *ee* [Scheme 16, Eq. (1), II)], whereas when the precipitate was filtered off a yield of 93% and an *ee* of 96%

was generated [Scheme 16, Eq. (1), I)].[93c, 113] These results were based on the fact that it is possible to obtain a very high *ee* value of proline in solution by using a solid mixture of proline with a low *ee* value and dissolve it in a mixture of $CHCl_3$ and EtOH (100:1). This is explained by the different stability in the solid state of the heterochiral catalyst (linked by two strong hydrogenbonds) compared to the homochiral catalyst (linked only over weak hydrogen bonds), which primarily influences the solubility. Therefore, the homochiral catalyst is better soluble and hence is enriched in the solution and leading to a higher *ee* value as predicted by the *ee* value of the solid mixture.[115] The lower *ee* value obtained in the unfiltered case compared to the filtered solution [Scheme 16, Eq. (1), I) *vs.* II)] was explained in the following way: in the course of the reaction the formed product **129** acts as a polarized solvent and therefore brings *D*- (**110**) and *L*-proline (**14**) in the organic phase which in consequence decreases the *ee* value of proline in solution.

Moreover, also Blackmond and co-workers found a nonlinear effect due to the different solubility of non-enantiopure proline above their solubility limit in the aldol addition of acetone (**130**) and 2-chlorobenzaldehyde (**131**) in DMSO catalyzed by *L*-proline (**14**) [Scheme 16, Eq. (2)]. Because the solids which are formed consisting of a *racemic* compound (crystals L/D = 1:1) and an enantiopure solid of the excess enantiomer, leading to an accumulation of only one enantiomere in the solution. All in all, the NLE in this reaction is owing to the selective crystallization of the *racemic* part of the non-enantiopure chiral auxiliary [Scheme 16, graph **a)**].[93c, 114] Such a crystallization effect is also shown for a conjugated addition of 2-nitropropane (**134**) to cyclohexenone (**133**) catalyzed by a combination of *L*-proline (**14**) and 2,5-dimethylpiperazine in $CHCl_3$ [Scheme 16, Eq. (3)]. There, Hanessian and co-workers obtained a (+)-NLE for the use of *L*-proline (**14**) with an *ee* under 20%, whereas by the use of *L*-proline (**14**) with an *ee* over 80% they got an (−)-NLE [Scheme 16, diagram **b)**].[46, 93c]

In summery this short overview highlighted the different prerequisites why NLEs may occur in organocatalysis and furthermore, presents some adequate theoretical models for their description. Moreover, it was shown that the study of the ee_{aux} as a function of ee_{prod} is an easy and simple method to gain a better mechanistic inside in various enantioselective reactions. Thus, in the further course of this thesis the NLE in the (*L*-proline)$_2$/Co(II)-catalyzed aldol reaction was investigated.

1.2 4-Substituted *L*-Proline Derivatives

Considering the high demand for asymmetric, enantioselective reactions in organic synthesis it is getting clear that there is great need for the development of catalytic procedures which are, at the same time, easy to carry out and robust against external influences like air or moisture. In organocatalysis these two main criteria are met by the application of small organic molecules as catalysts for enantioselective reactions. In the last decade, enormous effort was put in the investigation and development of such catalytic systems, mainly by chiral secondary amines. Among them especially *L*-proline (**14**) attracted great attention due to its low costs, non-toxicity and natural abundancy, therefore it is likely used for the synthesis of pharmacological compounds. Recently, primary amines started to arouse attention in this area, albeit their unfavorable imine-enamine equilibria,[116] which is going to be discussed later. Owing to its bifunctional character, proline (**14**) is prone to various activation modes in catalysis (Figure 9).

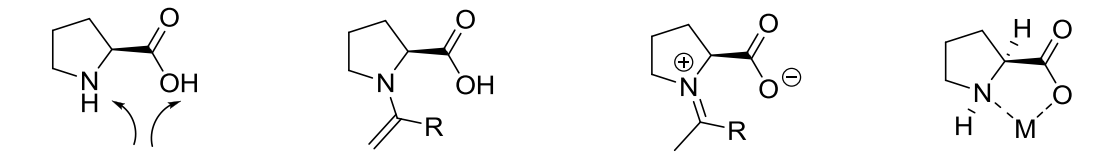


Figure 9. Modes of action in proline-catalysis.[7e]

Besides the activation modes by an enamine- **136** and an iminium-intermediate **137** proline can act as bidentate ligand for metals to form highly active metal complexes **138**. Compared to primary amino acids the secondary amine *L*-proline (**14**) exhibits unique properties, namely its increased pK_a value which enhances its applicability as Lewis-base-type catalyst. Moreover, it could also function as general Brønsted co-catalyst which is referred to the presence of the carboxylate.[7e]

The main focus of this part of the work lies on the development and application of combinations of different metal salts and *L*-proline (**14**) for organocatalyzed C-C bond forming reactions with the ulterior motive to improve their efficiency and selectivity. The first literature known attempts in this direction were made by the use of different amino acids, proline (**14**) and its derivatives in combination with zinc[117] or rubidium[47b-d, 118]. During their investigation on the aldol reaction of *p*-nitrobenzaldehyde (**149**) and acetone (**130**) Darbre and

co-workers proved that a complex of (*L*-proline)$_2$Zn provides superior results in terms of yield (quantitative) and *ee* (56%) compared to other (amino acid)$_2$Zn complexes.[117d] In further studies Penhoat *et al.* showed that the use of proline/$ZnCl_2$ in a mixture of DMSO/H_2O (4:1) leads to outstanding results in reference to *ee* (> 99%) and *diastereomeric ratio* (16:1).[117i] Furthermore, various metal prolinates were reported as capable catalysts for Michael additions. The pioneering work in this direction was done by Yamaguchi *et al.*.[47-48, 118] Other examples were reported by Furukawa and co-workers and Oro *et al.*[119] who were applying an *in situ* formed Ru(II)-*L*-proline complex to a Noyori-typ asymmetric transfer hydrogenation.

Inspired by these examples the goal was to develop a new kind of catalytic system using *L*-proline and its derivatives in combination with a metal salt to quantify their impact on catalytic activity and stereoselectivity. As model system the protocol for the application of an *in situ* formed, *L*-Proline/$CoCl_2$-complex (2:1 ratio) which shows superior diastereo- and enantioselectivity compared to sole *L*-proline (**14**) as catalyst for direct asymmetric aldol reactions which was developed in the Reiser group.[120] Furthermore, other suitable applications for this system should be found in the further course of this work. However, the investigation was started preparing various *L*-proline derivatives, which could be applied to the model system.

Recognizing the positive effect of metal(II) salts, especially Co(II)[120-121] and Zn(II)[117d-g, 117i, 117j, 122], in combination with *L*-proline (**14**) in aldol reactions and in other C-C bond forming reactions, the idea was to apply different *L*-proline derivatives (cf. **139** and **140** in Figure 10) to study their influence on the catalytic effectivity. To avoid the destruction or the blocking of the two coordination sites the modification has to take place at the backbone of the *L*-proline (**14**) skeleton. Thus, the modelling could take place at four positions. However, 2- and 5-substituted *L*-proline derivatives are known to greatly impair the catalytic efficiency, whereas 3-substituted ones show only a negligible impact on the catalytic activity and stereoselectivity.[123] As the starting point for the synthesis of the *L*-proline derivatives (2*S*,4*R*)-4-hydroxypyrrolidine-2-carboxylic acid (**114**) was chosen as an inexpensive and commercially available structure. This molecule shows improved reactivity and selectivity in the aldol reaction between acetone and *p*-nitrobenzaldehyde (**149**) in DMSO compared to *L*-proline (**14**) and different amino acids, which was shown by Barbas *et al.*.[17a] Furthermore, 4-substituted *L*-proline derivatives are superior compared to *L*-proline (**14**) because of their extended solubility in different organic solvents, whereas *L*-proline (**14**) catalyzed reactions often require the use of strong polar organic solvents such as DMSO.[124]

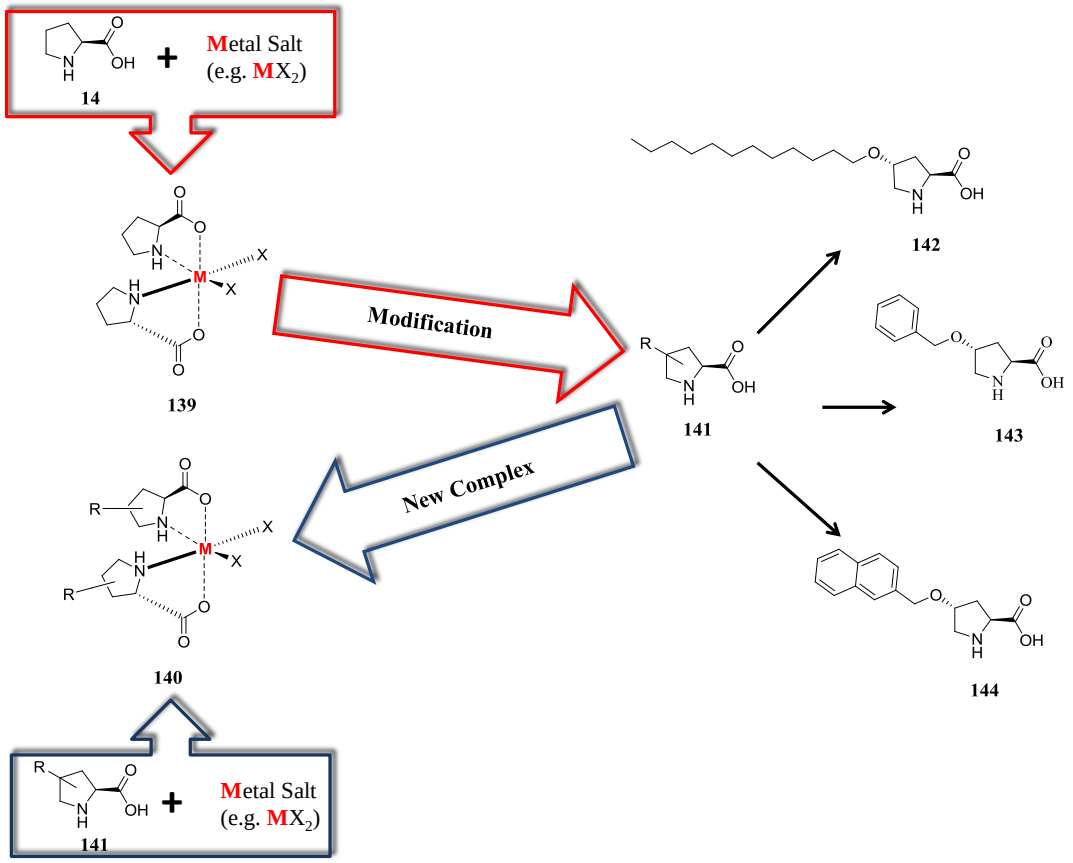


Figure 10. General concept of the formation of new complexes **140** of different 4-substituted *L*-proline derivatives **142**, **143** and **144** in combination with metal(II) salts based on the concept of the *L*-proline/$CoCl_2$-complex **139** described by Reiser *et al.*.[120]

Finally, three, already literature known[123-125], 4-substiuted *L*-proline derivatives **142**, **143** and **144** were chosen. Compared to *L*-proline (**14**) they should show an extended solubility in different organic solvents but also in water (amphiphilic character) due to their bulky and non-polar residue at the 4-position. Moreover, the correlation between their structure and their capability as chiral inductors should be investigated. Furthermore, it should be examined if combining them with different metal(II) salts, especially $CoCl_2 \cdot 6H_2O$, leads, similar to *L*-proline (**14**), to a catalytic active species **140**.[120] Figure 11 presents an overview of the chosen 4-substituted *L*-proline derivatives **142**, **143** and **144**. They were all synthesized starting from the simple and commercially available (2*S*,4*R*)-4-hydroxyproline (**114**) in more or less straight forward way.

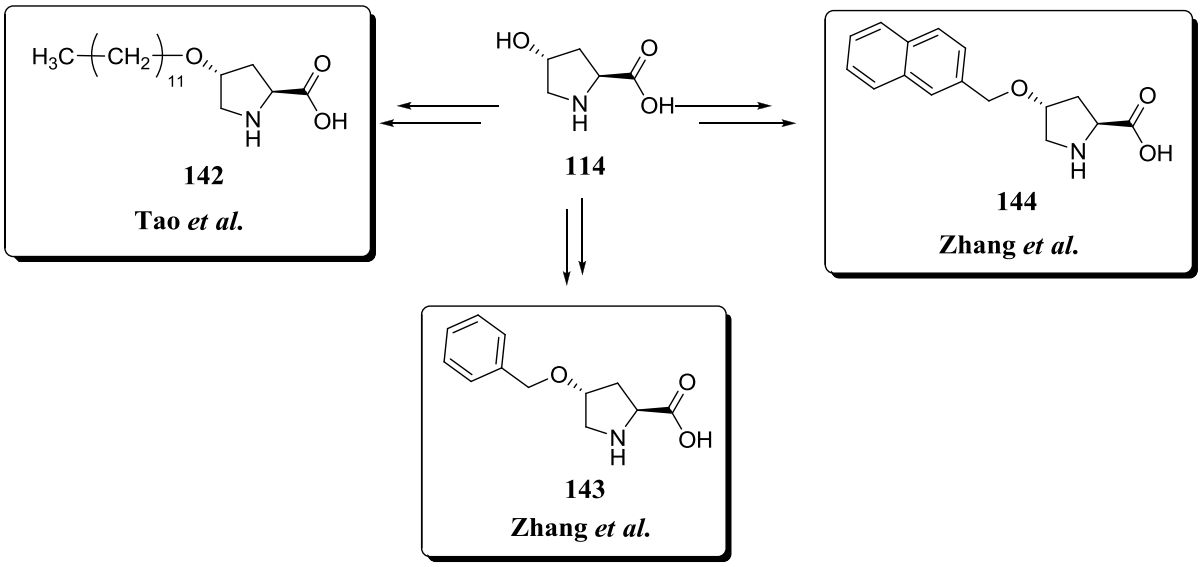
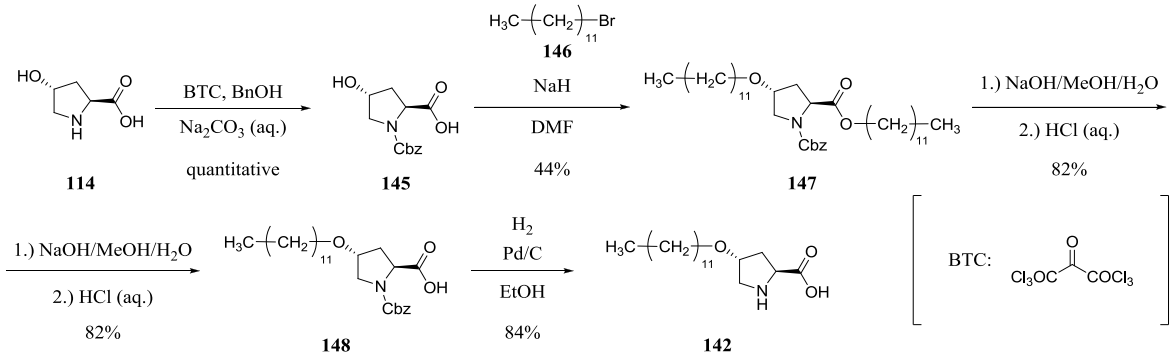


Figure 11. Overview of the chosen 4-substituted *L*-proline derivatives **142**, **143** and **144**.[123-125]

Due to their similarity to *L*-proline (**14**) all three of them were used and studied in regard to their ability to catalyze direct asymmetric aldol reactions with simple ketones, like cyclohexane (**150**) or acetone (**130**) and aldehydes like *p*-nitrobenzaldehyde (**149**) in water or under neat conditions. The only publications in literature one could find in terms of this purpose were reported by Zhang and co-workers[123, 125] and Tao *et al.*[124] who both applied these *L*-proline derivatives (**142**-**144**) to the aldol reaction between acetone (**130**) and various aldehydes. Another point worthwhile to mention, is that these derivatives were never applied to other catalytic reactions like Michael addition or Baylis-Hillman reaction, which are well known to be catalyze by *L*-proline (**14**) in a good fashion.

1.3 Synthesis and Applications of the 4-Substituted *L*-Proline Derivatives 142-144

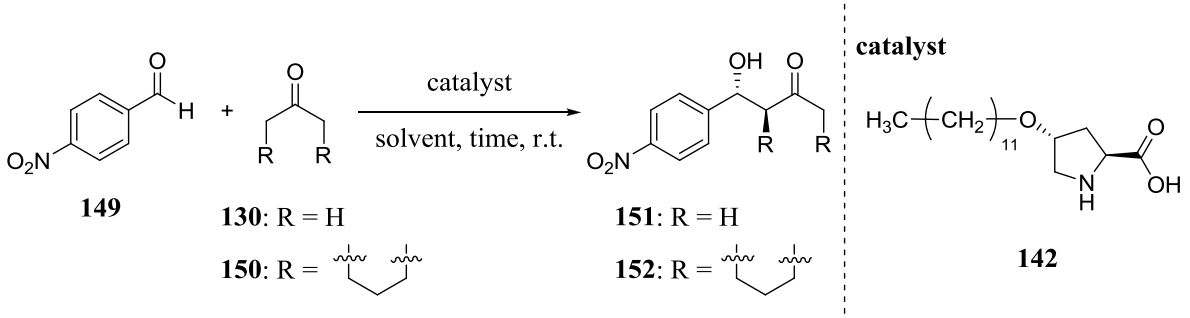
The only literature example where *L*-proline derivative **142** was used in catalysis is displayed in Table 1. Tao *et al.*[126] applied (2*S*,4*R*)-4-(dodecyloxy)pyrrolidine-2-carboxylic acid (**142**) to the aldol reaction between *p*-nitrobenzaldehyde (**149**) and cyclohexanone (**150**) or acetone (**130**). They highlighted the advantages over *L*-proline (**14**) in catalysis which in their opinion is the better solubility in most organic solvents and water owing to its amphiphilic character. Moreover, they noted that *L*-proline (**14**) requires an additional surfactant for reactions in water, whereas for catalyst **142** reactions in water are feasible without additives because of its long hydrophobic chain, acting similar to a surfactant.[124, 127] The synthesis over 5 steps is straight forward due to easy accessible starting material (2*S*,4*R*)-4-hydroxypyrrolidine-2-carboxylic acid (**114**) (Scheme 17).[124]



Scheme 17. Synthesis of (2*S*,4*R*)-4-(dodecyloxy)pyrrolidine-2-carboxylic acid (**142**) starting from commercially available (2*S*,4*R*)-4-hydroxypyrrolidine-2-carboxylic acid (**114**).[124]

In order to avoid side reactions, the first thing was to protect the secondary amine of **114** by a combination of BTC (bis(trichloromethyl)carbonate) and benzylhydroxide to get **145**, followed by the coupling between the hydroxy groups of **145** and dodecylbromid (**146**) using sodium hydride. The coupling product **147** was immediately converted to the carbon acid **148** by stirring it in a mixture of sodium hydroxide, methanol and water. Finally, the secondary amine of **148** was deprotected by a palladium catalyzed hydrogenation in ethanol to afford catalyst **142** in 30% overall yield. With catalyst **142** at hand, Tao and co-workers investigated its impact on the aldol reaction between *p*-nitrobenzaldehyde (**149**) and cyclohexanone (**150**) or acetone (**130**) (Table 1).[124]

Table 1. Aldol reaction between *p*-nitrobenzaldehyde (**149**) and cyclohexanone (**150**) or acetone (**130**) catalyzed by (2*S*,4*R*)-4-(dodecyloxy)pyrrolidine-2-carboxylic acid (**142**).[124]

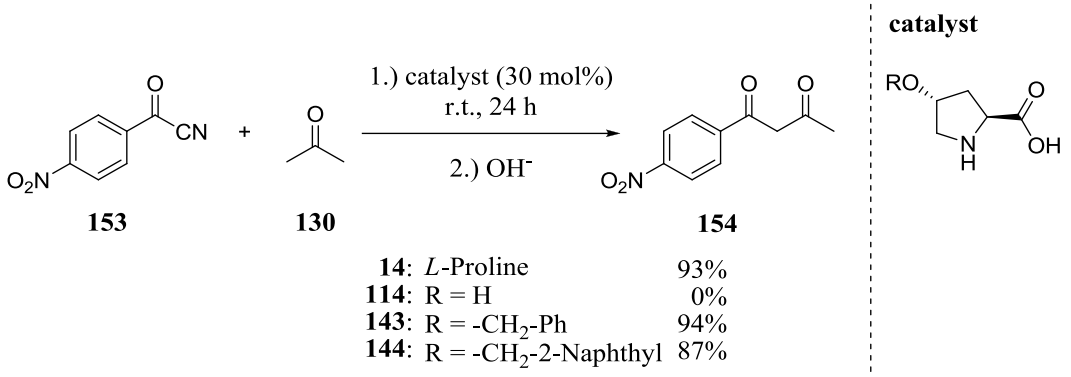


entry	ketone	cat. [mol%]	solvent	time [h]	*d.r.* (*anti*/*syn*) [c]	*ee* [%] [d]	yield [%] [e]
1[a]	acetone (**130**)	20	neat	36	-	77 (*R*)	78
2[a]	acetone (**130**)	5	neat	36	-	79 (*R*)	82
3[a]	acetone (**130**)	20	H_2O	24	-	18 (*S*)	48
4[b]	cyclohexanone (**150**)	5	neat	36	98:2	69 (*R*)	98
5[b]	cyclohexanone (**150**)	5	H_2O	48	97:3	98 (*R*)	92

[a]: 0.33 mmol of **149** (50 mg), 6.8 mmol of **130** (0.5 mL), H_2O (6.1 mL per mmol aldehyde); **[b]**: 0.33 mmol of **149** (50 mg), 3.9 mmol of **150** (0.4 mL), H_2O (0.6 mL per mmol aldehyde); **[c]**: Isolated or determined by chiral HPLC analysis; **[d]**: Determined by chiral HPLC analysis; **[e]**: Isolated yield.

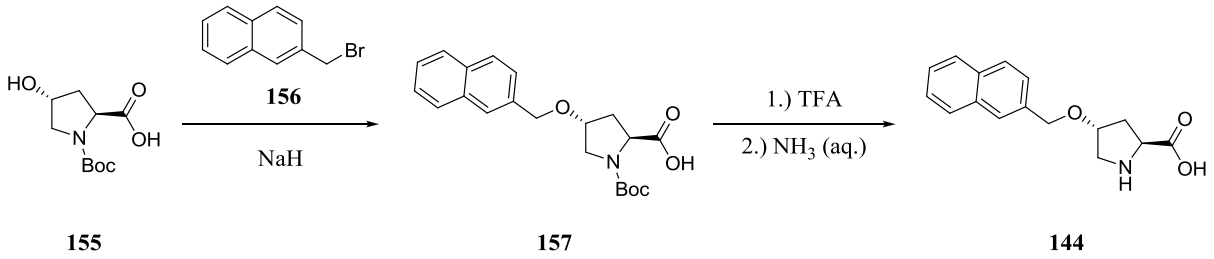
First of all, Tao *et al*. obtained superior results with catalyst **142** compared to *L*-proline (**14**) which they explained by the higher lipophilicity owing to the additional alkyl moiety. Acetone (**130**) was utilized either under neat conditions or with water as solvent (entries 1-3). With 5 mol% catalyst loading and under neat conditions they got the best results (entry 2), however in water they received inferior results (entry 3), whereas, with cyclohexanone (**150**) as ketone source water was the superior solvent compared to neat conditions (entries 4-5). Indeed, this indicates that there is an effect of the amount of used water and in addition also an influence of the used ketone. They concluded that cyclohexanone (**150**), due to stronger hydrophobic interactions, compared to acetone (**130**) (lower hydrophobicity) is able to assemble with aldehyde (**150**) and catalyst **142** in the presence of water, thus, the transition state is kept away from the water phase and the reaction proceeds in the aggregated organic phase leading to higher yields and enantioselectivities.[124, 127a, 127b, 128]

The only two reports in regard to catalyst **143** and **144** were published by Zhang and co-workers. In the first publication they applied **143** and **144** to an asymmetric aldol-type reaction between acyl cyanide **153** and acetone (**130**) in order to investigate the impact of electronic effects on the reactivity (Scheme 18).[125]



Scheme 18. Aldol reaction of acyl cyanide **153** with acetone (**130**).[125]

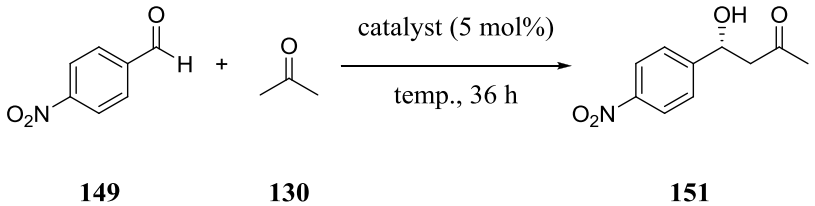
By using *L*-proline (**14**) (93% yield), catalyst **143** (94% yield) or catalyst **144** (87% yield) the obtained results almost stayed at a similar high level, however, 4-hydroxy-*L*-proline (**114**) (0% yield) showed no catalytic activity. Moreover, they made no statements about the synthesis of **143** and **144**. In the second publication Zhang *et al.*[123] wanted to develop an *L*-proline (**14**) based catalyst for direct asymmetric aldol reactions without the requirement for polar solvents like DMSO or DMF. They chose (2*S*,4*R*)-4-(naphthalen-2-ylmethoxy)pyrrolidine-2-carboxylic acid (**144**) owing to its assumed higher solubility compared to *L*-proline (**14**). They synthesized **144** over three steps (Scheme 19).



Scheme 19. Synthesis of (2*S*,4*R*)-4-(naphthalen-2-ylmethoxy)pyrrolidine-2-carboxylic acid (**144**) starting from commercially available Boc-protected (2*S*,4*R*)-4-hydroxypyrrolidine-2-carboxylic acid (**155**).[123]

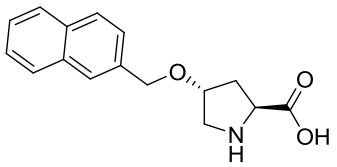
Starting from Boc-protected (2*S*,4*R*)-4-hydroxypyrrolidine-2-carboxylic acid (**155**) which subsequently was converted with naphthylbromide (**156**) and NaH to yield **157**. Subsequently, **157** was deprotected with TFA and NH_3 (*aq.*) to get the free secondary amine **144**. Surprisingly they did not give yields for the single synthesis steps. With **144** at hand, they started their study regarding the catalytic activity in the aldol reaction of acetone (**130**) with *p*-nitrobenzaldehyde (**149**) (Table 2).

Table 2. Aldol reaction between *p*-nitrobenzaldehyde (**149**) and acetone (**130**) catalyzed by (2*S*,4*R*)-4-(naphthalen-2-ylmethoxy)pyrrolidine-2-carboxylic acid (**144**).[123]



149 **130** **151**

catalyst



144

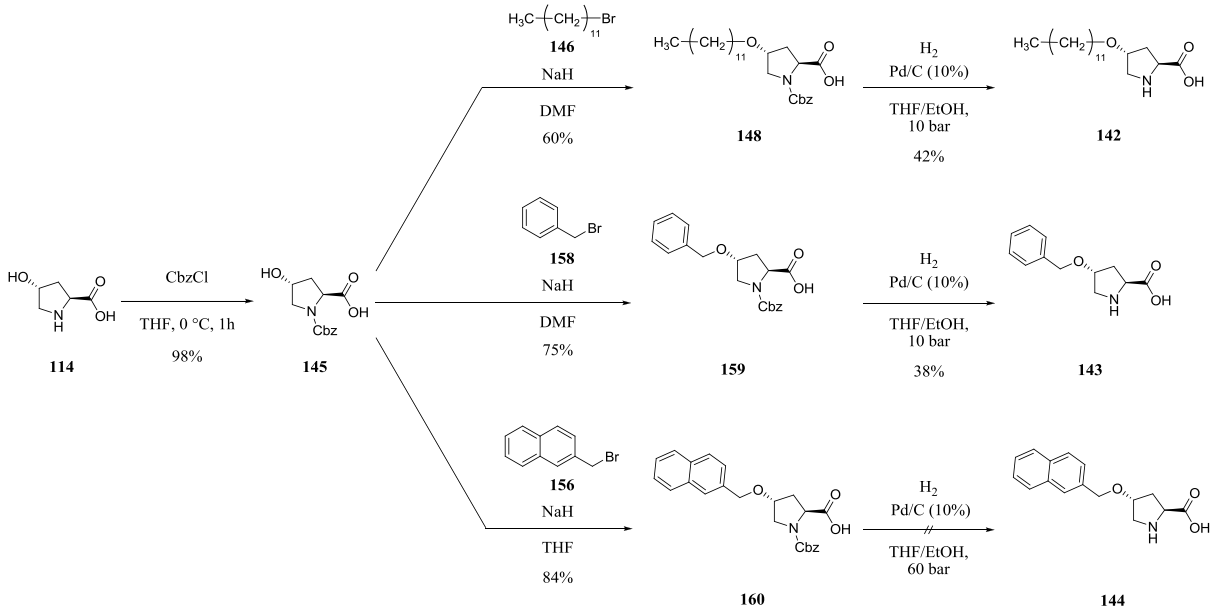
entry	temp. [°C]	*ee* [%] [a]	yield [%] [b]
1	25	78 (*R*)	65
2	0	77 (*R*)	46
3	- 25	86 (*R*)	41

[a]: Determined by chiral HPLC analysis; **[b]**: Isolated yield.

As one can see they only used 5mol% catalyst and the reaction was carried out in an excess of acetone (**130**) which at the same time served as reagent. Furthermore, they examined the influence of temperature on the reaction showing the expectable results, which means at low temperatures (entry 3) the *ee* is increased to 86% (*R*) at the costs of yield, whereas at 25 °C (entry 1) it is the other way around, there the yield is increased to 64% but the *ee* is slightly decreased to 78% (*R*). All in all, (2*S*,4*R*)-4-(naphthalen-2-ylmethoxy)pyrrolidine-2-carboxylic acid (**144**) proved to be an efficient catalyst for the asymmetric aldol reaction between acetone (**130**) and different aldehydes.

2. Synthesis of Catalysts 142-144

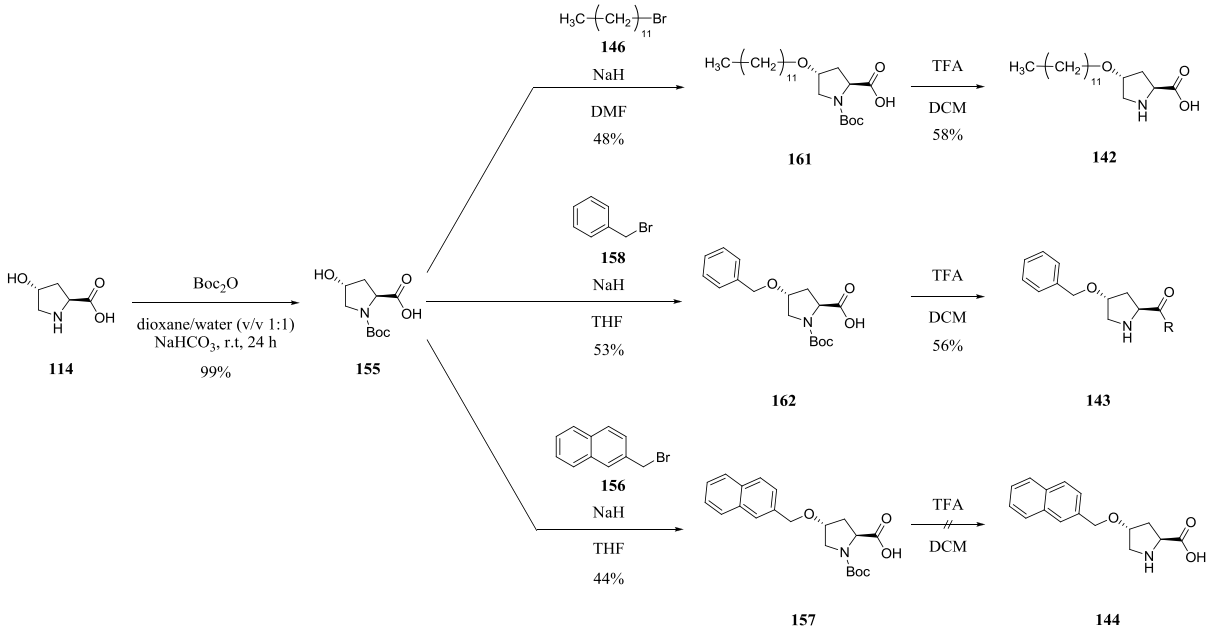
The synthesis of *L*-proline derivatives**142**, **143** and **144** is displayed in Scheme 20. Starting point of the synthesis was the Cbz-protection of the secondary amine of 4-hydroxy-*L*-proline (**114**) to prevent unwanted side reactions which might occur as a result of the higher nucleophilicity of the secondary amine compared to the hydroxyl group.[129] The second step was the coupling of the Cbz-protected 4-hydroxy-*L*-proline (**145**) with the nonpolar residues, namely dodecyl-[124] (**146**), naphthyl-[130] (**156**) and benzylbromide[131] (**158**), with the help of NaH which furnished **148**, **159** and **160** in reasonable yields.



Scheme 20. Synthesis of the 4-substituted *L*-proline derivatives **142**, **143** and **144** *via* the Cbz-protected 4-hydroxy-*L*-proline (**145**).

The last obstacle was the regeneration of the free secondary amine by a deprotection of the Cbz-group *via* hydrogenation catalyzed by palladium on active charcoal.[124] By using 10 mol% Pd on active charcoal and EtOH as solvent at ambient pressure, only unreacted starting material could be recovered. Screening of different solvents (*e.g.* EtOH, MeOH, THF/EtOH *etc.*), catalyst loadings (from 3 mol% up to 20 mol%) and hydrogen pressures (1 to 60 bar) identified THF/EtOH at 10 bar H_2-pressure with a catalyst loading of 8.5 mol% and 2 mol% as best conditions yielding the deprotected proline derivatives **142** and **143** with 42% and 38% yield, respectively. Surprisingly, this methodology did not apply for **160**. Even harsher conditions, *e.g.* $Pd(OH)_2$ on active charcoal or the addition of a catalytic amount of acetic acid which should support the cleavage of the Cbz-group proved to be unsuccessful. As consequence Boc was used as protecting group due to its applicability to secondary amines

and its easy cleavage by using TFA or HCl which also was applied in literature for protecting the secondary amine of 4-hydroxy-*L*-proline (**114**).[132] The new synthesis route and its results are displayed in Scheme 21.



Scheme 21. Synthesis of the 4-substituted *L*-proline derivatives **142**, **143** and **144** *via* the Boc-protected 4-hydroxy-*L*-proline (**155**).

The protection of 4-hydroxy-*L*-proline (**114**) was carried out by reacting it with Boc_2O to yield **155** in almost quantitative yield.[132d] Subsequently the Boc-protected *L*-proline **155** was coupled with the three nonpolar residues which slightly decreases the yields of the coupling products **157**, **161** and **162** (see second step, Scheme 21) compared to **148**, **159** and **160** (see second step, Scheme 20, page 39). The final deprotection was first performed using a mixture of TFA in DCM, which is the common procedure for this type of reaction. Again this procedure worked out well in the cases of Boc-protected dodecyl-*L*-proline **161** and Boc-protected benzyl-*L*-proline **162**, which gave **142** in 58% and **143** in 56% yield. However, the *L*-proline derativative **144** could not be obtained even by applying 6N HCl (*aq.*) to **157**.

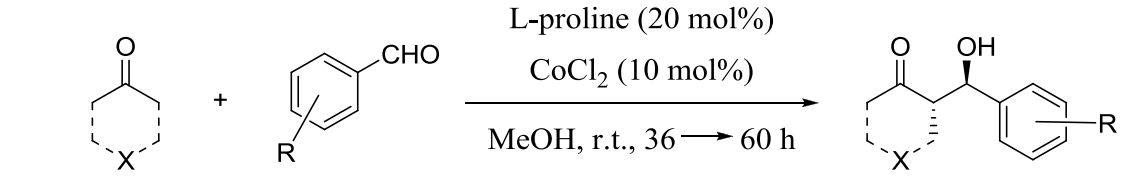
In conclusion, both strategies led to (2*S*,4*R*)-4-(dodecyloxy)pyrrolidine-2-carboxylic acid (**145**) in an overall yield of 25% (in the case of Cbz-protection, Scheme 20, page 39) or 28% (in the case of Boc-protection, Scheme 21, page 40), respectively, over three steps. In addition, (2*S*,4*R*)-4-(benzyloxy)pyrrolidine-2-carboxylic acid (**146**) could be obtained in an overall yield of 28% (in the case of Cbz-protection, Scheme 20, page 39) or 29% (in the case of Boc-protection, Scheme 21, page 40), respectively. Unfortunately, the formation of (2*S*,4*R*)-4-(naphthalen-2-ylmethoxy)pyrrolidine-2-carboxylic acid (**147**) was not possible,

although, the in Scheme 20 (page 39) presented pathway was already published and performed by Zhang and co-workers.[123] Having the two catalysts at hand, they were investigated on their catalytic activity at the model system developed by Reiser *et al.*.[120] In the further course of this thesis the catalysts **142** and **143** were also applied to other *L*-proline catalyzed reactions like the Michael addition or the Baylis-Hillman reaction.

3. *L*-Proline/Metal – complexes as Catalysts in Asymmetric Aldol Reactions

3.1 Introduction

In 2011 Reiser and co-workers developed a *L*-proline/$CoCl_2$-system (2:1) for the aldol reaction between both cyclic and acyclic ketones in combination with aromatic and aliphatic aldehydes (Scheme 22).[120]



130: acetone
150: X = CH_2
163: X = O
164: X = $CH(CH_3)$

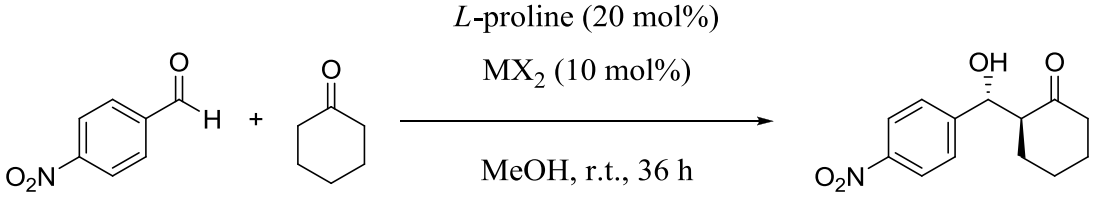
165

166: acetone aldol
167: X = CH_2
168: X = O
169: X = $CH(CH_3)$

Scheme 22. *L*-proline/$CoCl_2$ (2:1) catalyzed direct aldol reaction.[120]

With this system good to excellent yields (up to 93%) and compared to the use of *L*-proline (**14**) significant improvements in terms of stereoselectivity (*anti*/*syn* 45:1 and *ee* values > 99%) were obtained. One particular example is shown in Table 3. Here, the use of well-established starting materials allows a facial comparison to other catalytic systems and makes this reaction a perfect model system. The model system using *p*-nitrobenzaldehyde (**149**) and cyclohexanone (**150**) yields the aldol addition product **152** in *anti*-configuration with good to high *ee* depending on the solvent and the co-catalyst used.

Table 3. Results of the *L*-proline/$CoCl_2$-catalyzed highly diastereo- and enantioselective direct aldol reaction of *p*-nitrobenzaldehyde (**149**) and cyclohexanone (**150**).[120]

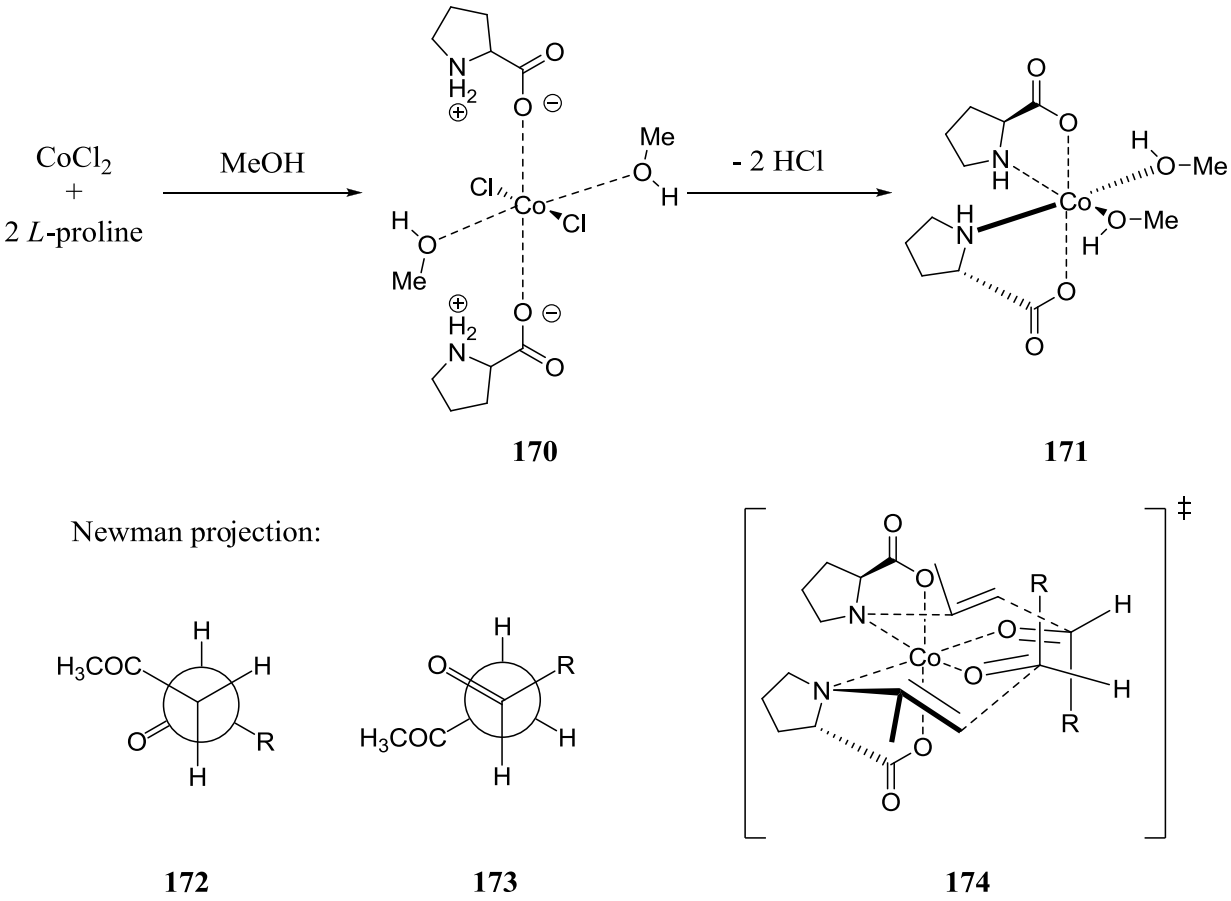


149 **150** **152**

entry [a]	MX_2	solvent	*d.r.* (*anti*/*syn*) [b]	*ee* [%] [c]	yield [%] [d]
1	-	DMSO	1.7:1	89	89
2	-	MeOH	3:1	58	69
3	$CoCl_2$	MeOH	10:1	98	91

[a]: 1 mmol of **149** (151 mg), 3 mmol of **150** (310 µL), 20 mol% *L*-proline (23 mg), 10 mol% $CoCl_2$ (13 mg), MeOH (dist.) (0.10 mL per mmol of aldehyde); **[b]**: Determined from the ^{1}H-NMR spectrum of the crude reaction mixture; **[c]**: Determined by chiral HPLC analysis of the combined, isolated *anti*- and *syn*-product; **[d]**: Combined, isolated yield of *anti*- and *syn*-product.

In entry 1 the results of the reaction carried out in DMSO and without the use of $CoCl_2$ are shown which led to a *diasteromeric ratio* of 1.7:1 (*anti*/*syn*) with an *ee* and a yield of 89%. By changing the solvent to MeOH the results were drastically impaired (entry 2), however, by addition of $CoCl_2$ the reaction gives rise to superior results especially in regard to stereoselectivity but also in conversion (entry 3). In this case, a *diasteromeric ratio* of 10:1 (*anti*/*syn*), an *ee* of 98% and a yield of 91% was obtained. These observations clearly indicate the presence of an *L*-proline/$CoCl_2$-complex, however, by the addition of other metal(II) salts like $MnCl_2$, $FeCl_2$, $MgCl_2$, $CuCl_2$, $ZnCl_2$ and $NiCl_2$ the results were inferior compared to $CoCl_2$. Thus, an *in situ* chelation of *L*-proline (**14**) to $CoCl_2$ (2:1) was proposed to promote the aldol reaction by Reiser *et al.* (Scheme 23)[120], based on literature examples investigating the structural behavior of amino acids in combination with metals, mainly with copper(II)[133] but also with nickel (II)[133f] and iridium (III)[134]. Furthermore, 2:1 complexes of metals and either amino acids[135] or amino based ligands[136] are literature known to catalyze aldol reactions. Especially a combination of *L*-proline (**14**) and zink[117d-g, 117i, 117j, 122] was often used for these purposes, but also combinations of *L*-proline (**14**) with rubidium[47b-d, 118] and *L*-proline (**14**) derivatives with cobalt[121] were employed to organocatalytic reactions.



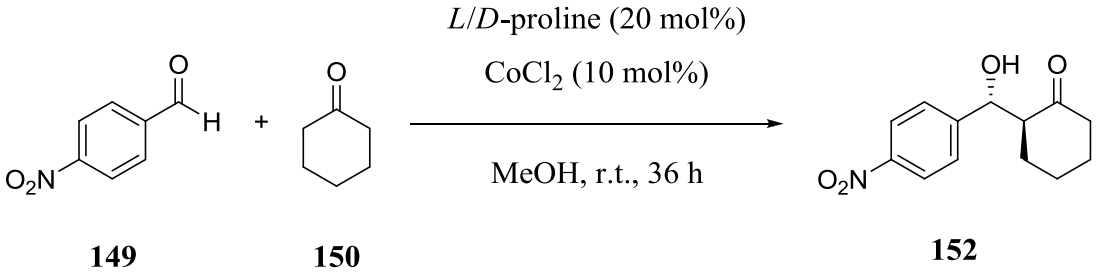
Scheme 23. Proposed mechanism of the formation of the catalytic active species **171**.[120]

The first step was supposed to be the coordination of two *L*-proline (**14**) molecules through their carboxylate groups to cobalt(II), giving complex **170**. Subsequently, HCl is cleaved of, supported by the measured decrease of pH value to 4-6. However, this decrease is only noticeable by adding the substrates to the reaction mixture leading to species **171**. The reaction is assumed to take place over a Zimmerman-Traxler-type transition state **174**. Owing to its C_2-symmetry and the availability of both coordination sites it is giving rise to the same stereoisomers of the aldol product. On the left hand side are shown the two Newman projections **172** and **173** for both coordination sites.

3.2 Investigation of the NLE (nonlinear effect)

In continuation of the previous work it was investigated whether in this transformation a NLE can be observer. The NLE is based on different ML_2 or ML_n model systems and on the partial solubility of the different catalysts in solution.[93c] Since the mechanism of the *L*-proline/$CoCl_2$ (2:1) catalyzed asymmetric aldol reaction is proposed to run over a six-membered Zimmermann-Traxler type transition state which is formed by chelation of two *L*-proline (**14**) molecules to Co(II)[120] and therefore is prone to exhibit a nonlinear effect it was investigated under this point of view. Its transition state complex can probably lead to an asymmetric amplification as a result of the formation of a homochiral catalytic complex [(L-proline)$_2$Co(II) or (D-proline)$_2$Co(II)] and a heterochiral catalytic complex [(L-proline)(D-proline)Co(II)] described by the ML_2 model. Another conceivable possibility for a NLE can be the reservoir effect (described in chapter 1.1, page 17 f.) where under the chosen reaction conditions the solubility of the heterochiral complex is worse compared to the homochiral complex which should thus enhance the *ee* value of the homochiral complex in solution. For the investigation of this effect different ratios of *L*- (**14**) and *D*-proline (**110**) in a quantity of 20 mol% were applied to the $CoCl_2$-catalyzed aldol reaction between *p*-nitrobenzaldehyde (**149**) and cyclohexanone (**150**) while all other conditions stayed constant (Table 4).[120]

Table 4. Investigation of the nonlinear effect in the *L*-proline/$CoCl_2$ (2:1) catalyzed aldol reaction between *p*-nitrobenzaldehyde (**149**) and cyclohexanone (**150**).



149 **150** **152**

entry [a]	L/D-proline	*ee* (auxiliary) [%]	*ee* [%] [b]	*d.r.* (*anti*/*syn*) [c]	yield [%] [d]
1	1:1	0	0.4	10.1:1	86
2	2:1	33	31	11.5:1	78
3	3:1	50	43	8.1:1	80
4	4.7:1	65	57	6.7:1	84
5	9:1	80	68	5.3:1	84
6	1:0	100	90	6.7:1	87

[a]: 1 mmol of **149** (151 mg), 3 mmol of **150** (310 µL), 20 mol% *L*/*D*-proline (23 mg), 10 mol% $CoCl_2$ (13 mg), MeOH (dist.) (0.1 mL per mmol aldehyde); **[b]**: Determined by chiral HPLC analysis of the combined, isolated *anti*- and *syn*-product; **[c]**: Determined from the ^{1}H-NMR spectrum of the crude reaction mixture; **[d]**: Combined, isolated yield of *anti*- and *syn*-product.

Different ratios of *L*- (**14**) and *D*-proline (**110**) from a *racemic* mixture of proline (entry 1) up to enantiomeric pure *L*-proline (**14**) (entry 6) were used. In all cases, the product was formed in similar yields, whereas the *diasteromeric ratio* (*anti*/*syn*) decreased by raising the amount of *L*-proline (**14**) from values of around 10:1 to ratios of 5:1. In addition, a linear correlation between the *ee* of the auxiliary, in this case *L*-proline (**14**), and the *ee* of the product **152** was observed. This linearity becomes even clearer if the *ee* of the product (ee_{prod}) is plotted as a function of the *ee* of the auxiliary (ee_{aux}) (Figure 12).

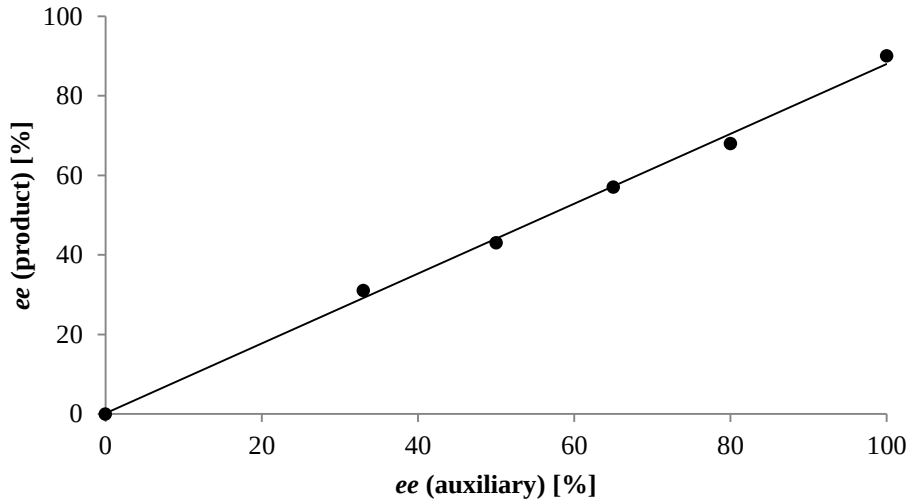


Figure 12. Plot of the *ee* of the product (ee_{prod}) against the *ee* of the auxiliary (ee_{aux}).

Based on the linearity of this catalytic system a few interpretations are possible. The first prediction involves the absence of a heterochiral metal/proline complex [(*L*-proline)(*D*-proline)Co(II)], thus the reaction only is catalyzed by the two homochiral metal/proline complexes [(*L*-proline)$_2$Co(II) or (*D*-proline)$_2$Co(II)] which, therefore, would lead to a linear correlation, due to the fact that the two complexes producing the opposite enantiomers of product **152** as shown in chapter 1.1 (see Scheme 8, page 20). Nevertheless, there is also the possibility of the presence of heterochiral complex with the assumption that it exhibits the same reaction rate as the homo chiral complex which as well results in a linear correlation.

In summary, the formation of only homochiral, or homochiral and additional heterochiral complexes which show the same reactivity is the most likely conclusion, since the positive influence of the metal was already shown. Until now the role of Co(II) is not finally clarified, because it could act as both, metal center for building up the (*L*-proline)$_2$/Co(II)-complex or as simple Lewis acid to activate the aldehyde for a nucleophilic attack. However, since there are (*L*-proline)$_2$/Zn(II)-complexes[137] and also a (*L*-proline)$_2$/Co(II)(H$_2$O)$_2$-complex[138] literature known, the formation of a complex with Co(II) and MeOH seems to be the most logical consequence.

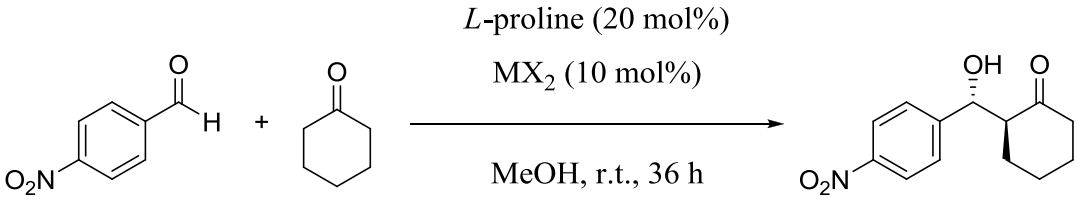
3.3 Screening of Various Metals in the *L*-Proline (14) Catalyzed Aldol Reaction

In early days many attempts were done to characterize the structure and coordination sphere of different amino acid/metal-complexes by various analytical methods, *e.g.* Raman Spectroscopy[139], IR vibrational studies[139-140], powder diffusion reflection[137a, 140e, 140h], crystallographic measurements[133g, 134, 137, 140h, 141], magnetic susceptibility[140b, 140e, 140h], thermal analysis[137a, 140e, 140h], electronic spectra[133h, 140e, 140h, 142], circular dichroism spectroscopy[133h, 143], potentiometric methods[133a, 133c, 133f, 144] or NMR studies[133j, 140b, 145]. These investigations mostly focus on transition metals of group 8 to 12, especially Ni(II)[133f, 139-140, 140d-g, 143b, 144a, 146], Zn(II)[137b, 140a, 140d, 140e, 144b], Cu(II)[133, 139-140, 140c-g, 141-143, 144a, 144b, 146b, 147], Co(II)[133d, 137a, 139a, 140a-e, 144a, 145], Fe(II)[140e], Ir (III)[134], Cd(II)[140d, 140e, 140h], Pt(II)[140d, 140f, 140g] and Pd(II)[140d, 140f, 140g], but also Pb(II)[140e] were examined. Furthermore, a broad range of simple amino acids and their slightly functionalized analogues, like glycine[133i, 139a, 140f], lysine[133i], alanine[133i], serine[133i, 140g], tyrosine[133i], phenylalanine[133i], glutamine[133i], glutamic acid[133i], cysteine[133i], tryptophan[133i], arginine[133i], leucine[140d], proline[133e, 134, 137, 141, 144a, 144c, 145, 148], histidine[133b, 133g, 133j], threonine[133g] were tested in combination with the latter listed metals in these publications, whereby their attention lies on the structural characterization of the complexes and not on their applications in catalysis. Moreover, a plausible fact that all these literature examples have in common, is regardless what amino acids were used, always the same tendency in terms of binding strength between metal and amino acid was observed, which are decreasing in the following order: Pt(II) > Pd(II)> Cu(II) > Zn(II) > Cd(II) > Ni(II) > Co(II).[140d-f, 144a, 146b, 147] Besides structural investigation Zhuchkova *et al.* additionally examined the behavior of Cu(II)-*N*-alkyl-α-amino acid complexes in solution (MeOH, H_2O or in $CHCl_3$).[133e] In their opinion, two complexes with different coordination numbers were forming. On the one hand, a complex with coordination number four and on the other hand an octahedral complex with coordination number six with two apical bonded solvent molecules. They argued that the solvent molecules in the apical position, namely MeOH or H_2O, are capable to stabilize the complex in contrast to $CHCl_3$ leading to no additional stabilization. Hence, this showed that the right choice of the solvent is an important factor for the formation of the amino acid/metal-complex.

Based on the former described solvent stabilizing effects of MeOH it was of great interest to screen various metal salts in the model reaction in order to study their influence on the

catalytic activity and stereoselectivity (Table 5). All reactions were carried out under inert gas and anhydrous conditions.

Table 5. Screening of different metal salts in the aldol reaction between *p*-nitrobenzaldehyde (**149**) and cylohexanone (**150**).



149 **150** **152**

entry [a]	MX_2	*d.r.* (*anti*/*syn*) [b]	*ee* [%] [c]	yield [%] [d]
1 [e]	-	3:1	69	58
2 [e]	$CoCl_2$	10:1	98	91
3	$CoCl_2$	6.7:1	89	91
4	NiI_2	9:1	96	86
5	$NiBr_2$	5.7:1	89	89
6	K_2PtCl_4	3.8:1	55	85
7	$PdBr_2$	7.3:1	90	93
8	$PdCl_2$	7.3:1	91	79
9	$RuCl_3$	9:1	93	83

[a]: All reactions were carried out under inert gas and anhydrouse condition; 1 mmol of **149** (151 mg), 3 mmol of **150** (310 µL), 20 mol% *L*-proline (23 mg), 10 mol% metal, MeOH (dist.) (0.1 mL per mmol aldehyde); **[b]**: Determined from the ^{1}H-NMR spectrum of the crude reaction mixture; **[c]**: Determined by chiral HPLC analysis of the combined, isolated *anti*- and *syn*-product; **[d]**: Combined, isolated yield of *anti*- and *syn*-product; **[e]**: Results of Reiser *et al.*, see reference [120].

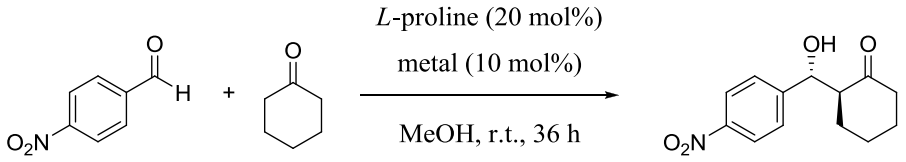
Comparison of the reactivity with just *L*-proline (**14**) as catalyst (entry 1) and in the presence of various metals (entries 2-9) revealed that in all latter cases better yields were obtained. Moreover, the *diastereomeric ratio* (*anti*/*syn*) and also the *ee* were significantly increased compared to the use of *L*-proline (**14**) as the sole catalyst. Notably, K_2PtCl_4 impairs the

outcome in terms of *ee* (entry 6), but the overall best results, with 96% *ee* and 86% yield, were achieved by the use of NiI_2 as metal source (entry 4). All in all, this screening showed the ability of various metal salts to significantly improve the catalytic activity towards the use of *L*-proline (**14**) alone. At this state however, the results obtained using $CoCl_2$ (entry 3) did not exactly match with the results obtained by Reiser *et al.*[120] (entry 2). Based on this fact and on the requirement to carry out the reaction under inert gas and anhydrouse conditions, it was further focused on the optimization of this catalytic process in respect to the simplification of the set up and as well the conditions.

3.4 Optimization of the *L*-Proline/$CoCl_2$ (2:1) Catalyzed Aldol Reaction

Since there are many parameters known influencing the performance of the aldol reaction the focal point of the investigation was to initially find the optimal conditions. Based on the model system various influencing parameters like solvent, metal source or conditions were screened (Table 6).

Table 6. Screening of different reaction conditions in the aldol reaction between *p*-nitrobenzaldehyde (**149**) and cyclohexanone (**150**).



149 **150** **152**

entry [a]	metal	conditions	*d.r.* (*anti*/*syn*) [b]	*ee* [%] [c]	yield [%] [d]
1[e]	$CoCl_2$	dry, inert atmosphere conditions	10:1	98	91
2	$CoCl_2$	inert gas, flame dried glasware, MeOH (abs.)	6.7:1	89	91
3	$CoCl_2$	inert gas, flame dried glasware, MeOH (dist.; tech.)	9:1	91	93
4	$CoCl_2$	inert gas, flame dried glasware, MeOH (*p.A.*)	6.7:1	89	93
5	$CoCl_2 \cdot 6H_2O$	inert gas, flame dried glasware, MeOH (dist.; tech.)	8.1:1	93	93
6	$CoCl_2 \cdot 6H_2O$	inert gas, MeOH (dist.; tech.)	11.5:1	94	96
7	$CoCl_2 \cdot 6H_2O$	MeOH (dist.; tech.)	11.5:1	96	94
8	$CoCl_2 \cdot 6H_2O$	MeOH (undist.; tech.)	11.5:1	97	93
9	$CoCl_2$	MeOH (dist.; tech.)/H_2O (V = 100 µL) (v/v 99:1)	4.9:1	88	93
10	$CoCl_2 \cdot 6H_2O$	MeOH (dist.; tech.)/H_2O (V = 100 µL) (v/v 99:1)	7.3:1	94	95

[a]: 1 mmol of **149** (151 mg), 3 mmol of **150** (310 µL), 20 mol% *L*-proline (23 mg), 10 mol% metal, MeOH (0.1 mL per mmol aldehyde); **[b]**: Determined from the ^{1}H-NMR spectrum of the crude reaction mixture; **[c]**: Determined by chiral HPLC analysis of the worked up reaction mixture; **[d]**: Combined yield of *anti*- and *syn*-product determined by using an internal standard (triphenylmethane) in the crude reaction mixture; **[e]**: Results of Reiser *et al.*, see reference [120].

In order to have reference values entry 1 is showing the achieved literature findings of Reiser *et al.*.[120] There, dry and inert atmosphere conditions were reported under which excellent results with regard to yield and stereoselectivity were obtained. Entry 2 shows the attempt to reproduce these results, however inferior selectivities were observed. Thus, in particular, the influence of external parameters, like moisture or oxygen, and internal

parameters, such as solvent quality and the applied Co(II)-source, were investigated. By comparing entries 2-4, in which anhydrous $CoCl_2$ serving as metal source and the external parameters were maintained, the best results were achieved by the use of distilled MeOH[*] (entry 3), thus it was obvious that this solvent was chosen in the further course of the screening. As next logical consequence the cobalt-source was replaced by cobalt(II) chloride hexahydrate leading to a slightly improved *ee* value (entry 5). This shows that water positively influences the outcome of the reaction as the amount of water coming from the hexahydrate cannot be underestimated, since it corresponds to 0.6 mmol (60 mol%). Based on these findings the reaction was carried out under no precautions to exclude moisture (entry 6) and in addition air (entry 7), resulting in a slightly improved outcome with regard to stereoselectivity. Moreover, in entry 8 undistilled MeOH[†] was used and, indeed, in this case the best results, *i.e.* 93% yield, 97% *ee* and a *diastereomeric ratio* of 11.5:1 (*anti*/*syn*) were obtained. In order to see the influence of additional water on the reaction the experiments in entry 9 and 10 were performed. In both cases 1 μL water was added which corresponds to amount of substance of 0.06 mmol (6 mol%). However, there neither a positive nor a negative effect was seen (Comparing entry 5 *vs.* 10 and entry 3 *vs.* 9).

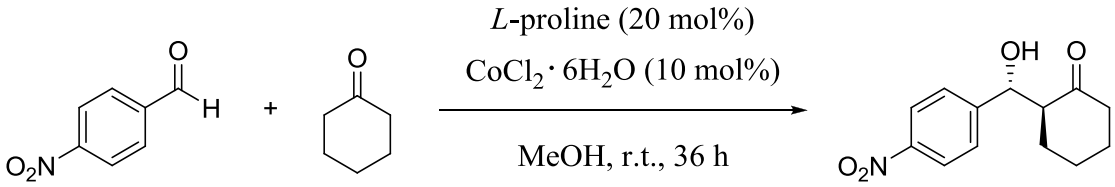
In summary, an optimized, robust and more easy workable protocol for the *L*-proline/Co(II)-catalyzed aldol reaction between *p*-nitrobenzaldehyde (**149**) and cyclohexanone (**150**) with no necessity of working under dry and inert atmosphere was developed. With this result at hand, the focus was further laid on developing an easy practicable big scale approach to circumvent the need for special equipment and reaction conditions.

[*] MeOH (technical grade) was distilled at 75 °C and used without further purification.
[†] MeOH (technical grade) was used without further purification.

3.5 Upscaling with simplified equipment

Inspired by the easy feasibility of the new developed protocol it was another aim to investigate the applicability of bigger scale approaches. Therefore, the reaction was carried out on a 5 mmol and a 20 mmol scale (Table 7).

Table 7. Results of the upscaling of the aldol reaction between *p*-nitrobenzaldehyde (**149**) and cyclohexanone (**150**).



149 **150** **152**

entry [a]	scale	*d.r.* (*anti*/*syn*) [b]	*ee* [%] [c]	yield [%] [d]
1	1 mmol	11.5:1	97	92
2	5 mmol	10.1:1	97	88
3	20 mmol	11.5:1	97	87

[a]: 1 equiv. of **149**, 3 equiv. of **150**, 20 mol% *L*-proline, 10 mol% $CoCl_2 \cdot 6H_2O$, MeOH (0.1 mL per mmol aldehyde); **[b]**: Determined from the ^{1}H-NMR spectrum of the crude reaction mixture; **[c]**: Determined by chiral HPLC analysis of the combined, isolated *anti*- and *syn*-product; **[d]**: Combined, isolated yield of *anti*- and *syn*-product.

As Table 7 indicates, the reaction was also suitable for making bigger amounts of aldol product **152** without loss of stereoselectivity and as well owing to the simplified reaction setup requiring no inert and dry atmosphere techniques. This reveals the possibility to perform the reaction in snap-on vials (Figure 13) instead of Schlenk flasks which made its handling much easier by delivering the same results like displayed in Table 7.

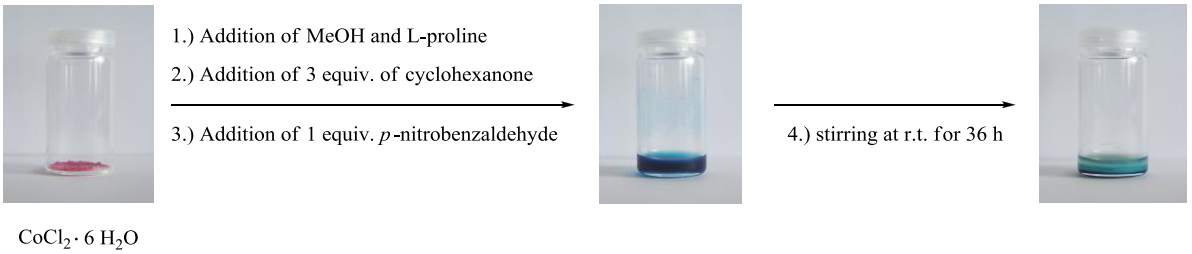


Figure 13. Performance of the aldol reaction between *p*-nitrobenzaldehyde (**149**) and cyclohexanone (**150**) in snap-on vials catalyzed by a combination of *L*-proline/$CoCl_2 \cdot 6H_2O$ (2:1).

3.6 Evaluation of 4-Substitued *L*-Proline Derivatives in the Aldol Reaction

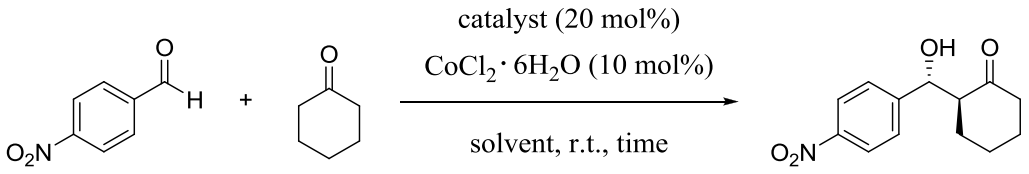
Cyclohexanone (150) as ketone source

Having determined the optimized reaction conditions for the *L*-proline/Co(II)-catalyzed aldol reaction, the 4-substituted *L*-proline derivatives **142** and **143** were also tested under these conditions to study their impact on the reactivity and stereoinduction. Sole catalyst **142** without any additional metal was already investigated by Tao *et al.*[126] in the asymmetric aldol reaction. They found, that water can influence both, the reactivity and enantioselectivity which was explained by solubility effects. Based on this result, the role of water was also investigated in the model system (Table 8). As entry 2 reveals, water in combination with $CoCl_2 \cdot 6H_2O$ and *L*-proline (**14**) positively influenced the *diastereomeric ratio*, whereas the *ee* value stayed constant and furthermore the yield drastically decreased despite prolonged reaction time compared to the optimized conditions in MeOH. Applying the optimized reaction conditions with MeOH as solvent (entries 1, 3, 5, 7), the best *diastereomeric ratio* of 14.3:1 (*anti*/*syn*) was obtained with catalyst **143** (entry 5), whereas the *ee* value in all cases remained the same. The lowest yield was obtained with catalyst **114** (entry 3), whereby with catalyst **142** (entry 7) similar results to the use of *L*-proline (**14**) (entry 1) were achieved. By comparing the results obtained under aqueous conditions (entries 2, 4, 6, 9) with the results obtained with MeOH as solvent (entries 1, 3, 5, 7), it is obvious that the *diastereomeric ratio* is increased up to a ratio of 20:1 in these cases. Moreover, *L*-proline (**14**) (entry 2) and 4-hydroxy-*L*-proline (**114**) (entry 4) showed a drastically decrease in reactivity even with a prolonged reaction time, however *L*-proline derivative **142** (entry 9) gave the same yield and derivative **143** (entry 6) even gave a superior yield within a shortened reaction time of 24 h compared to the results with the use of MeOH as solvent. To finally examine the influence of cobalt(II) under both conditions, *i.e.* performing the reaction in methanol and water, respectively, one reaction was carried out with (entry 7 and 9) or without (entry 8 and 10) metal. In the case of MeOH, additional $CoCl_2 \cdot 6H_2O$ clearly had a positive impact on stereoselectivity and reactivity, however in the case of water the additional metal showed no effect. This trend was also observable with the other catalysts[‡] and might be explained with the high solubility of $CoCl_2 \cdot 6H_2O$ in water and the in comparison limited solubility of catalysts **14**, **114**, **142** and **143** in water, hence leading to no *in situ* formation of a

[‡] For detailed screening with catalysts **14**, **114**, **142** and **143** in water see Table 49, page 164 in the experimental part.

(*L*-proline)$_2$/Co(II)-complex. Therefore, the reaction is just catalyzed by *L*-proline (**14**) or its derivatives **114**, **142** or **143**.

Table 8. Screening of the 4-substituted *L*-proline derivatives **114**, **142** and **143** in the *L*-proline/Co(II)-catalyzed highly diastereo- and enantioselective direct aldol reaction between *p*-nitrobenzaldehyde (**149**) and cyclohexanone (**150**).

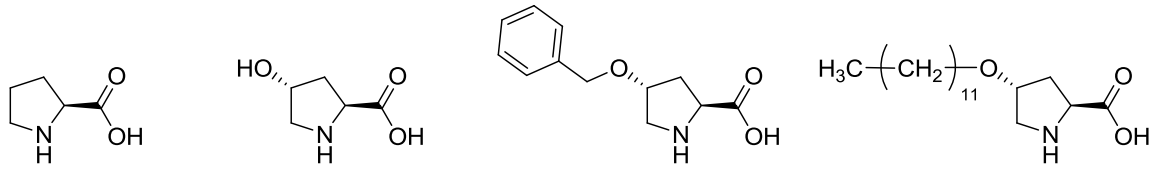


149 **150** **152**

entry [a]	catalyst	time [h]	solvent	*d.r.* (*anti*/*syn*) [b]	*ee* [%] [c]	yield [%] [d]
1	**14**/$CoCl_2 \cdot 6H_2O$	40	MeOH	11.5:1	97	92
2		95	H_2O	14:1	97	39
3	**114**/$CoCl_2 \cdot 6H_2O$	40	MeOH	7.7:1	96	44
4		95	H_2O	20:1	96	15
5	**143**/$CoCl_2 \cdot 6H_2O$	40	MeOH	14.3:1	95	77
6		24	H_2O	20:1	99	93
7	**142**/$CoCl_2 \cdot 6H_2O$	40	MeOH	8:1	96	91
8	**142**			3.6:1	89	84
9	**142**/$CoCl_2 \cdot 6H_2O$	24	H_2O	20:1	98	91
10	**142**			20:1	98	90

[a]: 1 mmol of **149** (151 mg), 3 mmol of **150** (310 µL), 20 mol% catalyst, 10 mol% $CoCl_2 \cdot 6H_2O$ (24 mg), solvent (0.1 mL per mmol aldehyde); **[b]**: Determined from the ^{1}H-NMR spectrum of the crude reaction mixture; **[c]**: Determined by chiral HPLC analysis of the combined, isolated *anti*- and *syn*-product; **[d]**: Combined, isolated yield of *anti*- and *syn*-product.

catalysts:

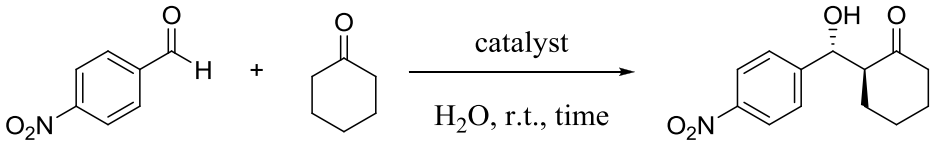


14 **114** **143** **142**

By comparing the results with the literature values of Tao and co-workers[124] (yield = 92%, *ee* = 98%, *d.r.* (*anti*/*syn*) = 97:3), it became obvious, that both systems

(with and without $CoCl_2.6H_2O$) lead to the same yield and *ee*, however, in the above cases (Table 8, entries 9-10) the reaction was performed at a catalyst loading of 20 mol%. Therefore, the influence of the catalyst loading of **142** on the stereoselectivity and reactivity in the model system without additional $CoCl_2 \cdot 6H_2O$ and in the presence of water was investigated (Table 9).

Table 9. Screening of different catalyst loadings of (2*S*,4*R*)-4-(dodecyloxy)pyrrolidine-2-carboxylic acid (**142**) in the asymmetric aldol reaction between *p*-nitrobenzaldehyde (**149**) and cyclohexanone (**150**) in the presence of water.

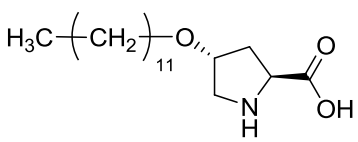


149 **150** **152**

entry [a]	catalyst [mol%]	time [h]	*d.r.* (*anti*/*syn*) [b]	*ee* [%] [c]	yield [%] [d]
1	20	22	20:1	98	90
2	5	25	29:1	99	91
3	1	25	29:1	> 99	91
4	0.5	48	25:1	> 99	58
5	0.1	48	29:1	99	36

[a]: 1 mmol of **149** (151 mg), 3 mmol of **150** (310 µL), H_2O (0.1 mL per mmol aldehyde); **[b]**: Determined from the ^{1}H-NMR spectrum of the crude reaction mixture; **[c]**: Determined by chiral HPLC analysis of the combined, isolated *anti*- and *syn*-product; **[d]**: Combined, isolated yield of *anti*- and *syn*-product.

catalyst:



142

The screening revealed that catalyst **142** is able to perform the reaction effectively up to a concentration limit of 1 mol% (entry 3). However, while the reactivity decreased drastically at even lower catalyst concentrations, the stereoselectivity stayed at a similar high level (entries 4 and 5). This trend is displayed in Figure 14, where the yield (blue curve) and the *ee* of the product (red curve) is plotted against the applied amount of catalyst **142**.

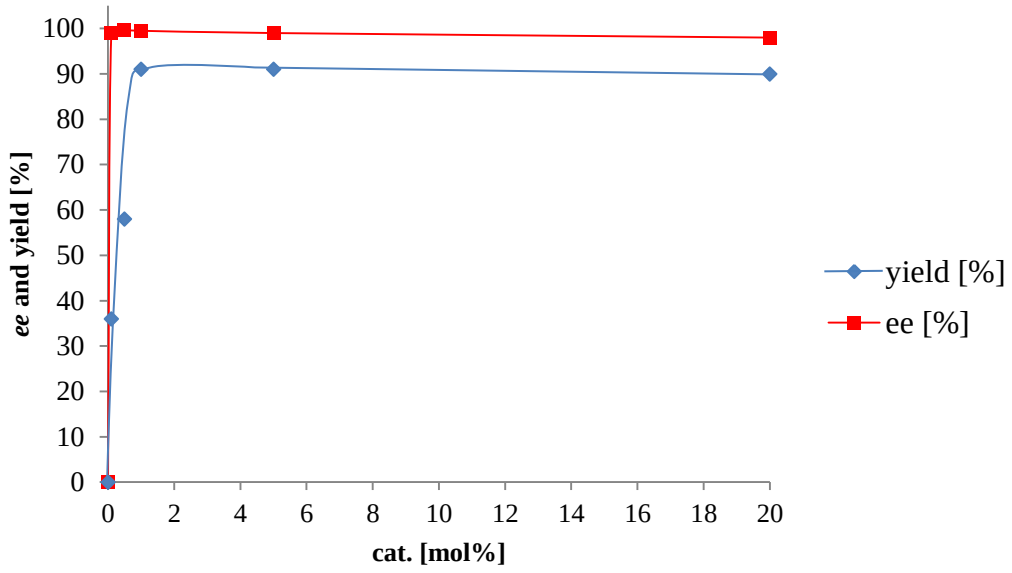
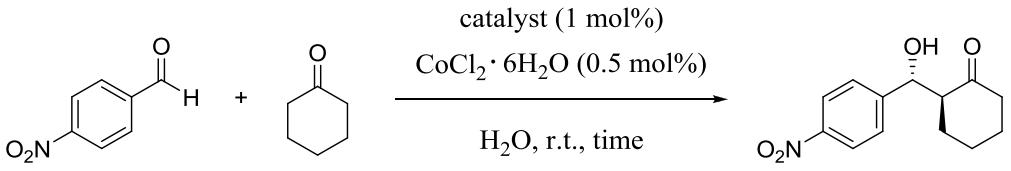


Figure 14. Plot of the *ee* or yield of the product against the amount of used catalyst **142**.

Nevertheless, a small trend in terms of stereoselecitvity was recognizable by using less amount of catalyst **142**. In entries 2 and 3 the *diastereomeric ratio* was increased up to 29:1 (*anti*/*syn*) compared to entries 1 in which only a *diastereomeric ratio* of 20:1 (*anti*/*syn*) was achieved and furthermore the *ee* was slightly elevated from 98% up to > 99%. To quantify the influence of additional $CoCl_2 \cdot 6H_2O$ and only 1 mol% of catalyst in the presence of water catalysts **14**, **114**, **142** and **143** were subsequently subjected to the optimized conditions (Table 10).

Table 10. Application of catalysts **14**, **114**, **142** and **143** to the asymmetric aldol reaction with 1 mol% catalyst and 0.5 mol% $CoCl_2 \cdot 6H_2O$ in the presence of water.

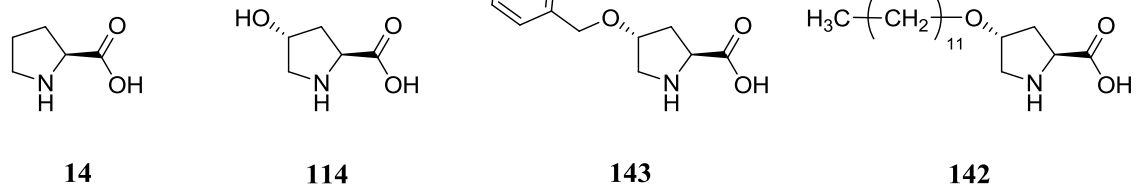


149 **150** **152**

entry [a]	catalyst	time [h]	*d.r.* (*anti*/*syn*) [b]	*ee* [%] [c]	yield [%] [d]
1	**14**	141	14.3:1	19	16
2	**14**/$CoCl_2 \cdot 6H_2O$	141	n.d.	n.d.	traces
3	**114**/$CoCl_2 \cdot 6H_2O$	141	n.d.	n.d.	traces
4	**143**/$CoCl_2 \cdot 6H_2O$	30	29:1	99	85
5	**142**/$CoCl_2 \cdot 6H_2O$	30	29:1	> 99	93

[a]: 1 mmol of **149** (151 mg), 3 mmol of **150** (310 µL), 1 mol% catalyst, 0.5 mol% $CoCl_2 \cdot 6H_2O$ (1 mg) , H_2O (0.1 mL per mmol aldehyde); **[b]**: Determined from the ^{1}H-NMR spectrum of the crude reaction mixture; **[c]**: Determined by chiral HPLC analysis of the combined, isolated *anti*- and *syn*-product; **[d]**: Combined, isolated yield of *anti*- and *syn*-product. **n.d.** = not determined.

catalysts:



14 **114** **143** **142**

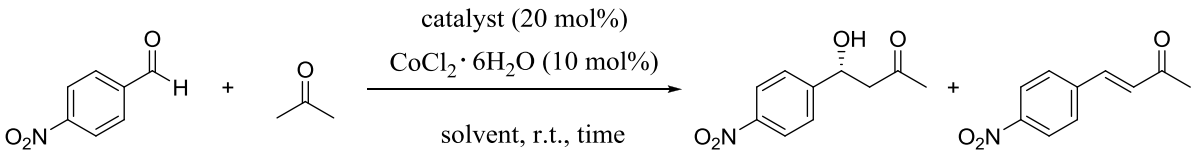
The key message of Table 10 is that $CoCl_2 \cdot 6H_2O$ only shows an influence in the case of *L*-proline (**14**), there the additional metal impairs the results (entry 1 *vs.* 2). However, in all other cases $CoCl_2 \cdot 6H_2O$ showed no effect on the outcome of the reaction. Nevertheless, catalyst **142** (entry 5) and **143** (entry 4) showed excellent results with regard to stereoselectivity and reactivity, regardless whether metal was applied or not. [§]

[§] For a detailed screening of catalysts **14**, **114**, **142** and **143** in water without metal see Table 50, page 165 in the experimental part.

Acetone (130) as ketone source

Interestingly, Tao *et al.*[126] also reported an influence of the ketone source on the reactivity with catalyst **142**. This was explained by the different solubility behavior of cyclohexanone (**150**) and acetone (**130**). Consistently, the protocol for the asymmetric aldol reaction between acetone (**130**) and *p*-nitrobenzaldehyde (**149**), which was developed by the Reiser group, was chosen as starting point for the investigation.[120] Furthermore, based on the good results obtained with water and cyclohexanone (**150**) as ketone source, the effect of water was also investigated (Table 11). The results of Reiser and co-workers with the combination of *L*-proline (**14**) and $CoCl_2$ under the optimized reaction conditions with MeOH as solvent are shown in entry 1. By applying catalyst **14** and **114** in combination with $CoCl_2 \cdot 6H_2O$ and MeOH as solvent (entries 2 and 5) the yield was drastically decreased down to 24% or 16%, respectively. However, with catalyst **142** and **143** the combined yield is improved up to 39% (entries 8 and 11). Interestingly, with the use of catalyst **114**, **142** and **143** (entries 5, 8, 11) also by-product **175** was additionally obtained. Moreover, with catalyst **142** and **143** the degree of stereoselectivity (entries 8 and 11) was comparable to the results obtained with $CoCl_2$ (entry 1). When the solvent was switched to water (entries 3, 6, 9, 12), a massive loss in both stereoselectivity and reactivity despite prolonged reaction times compared to MeOH as solvent was observed. Furthermore, the absence of $CoCl_2 \cdot 6H_2O$ showed no effect on reactivity (entries 4, 7, 10, 13).

Table 11. Screening of catalysts **14**, **114**, **142** and **143** in the asymmetric aldol reaction between *p*-nitrobenzaldehyde (**149**) and acetone (**130**).

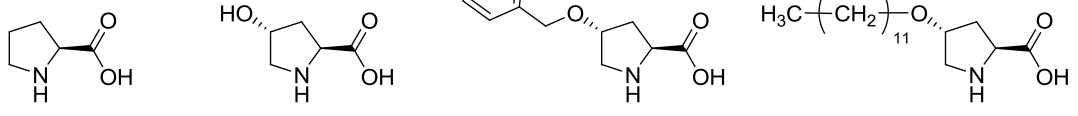


149 **130** **151** **175**

entry [a]	catalyst	time [h]	solvent	*ee* [%] [b]	yield 151 [%] [c]	yield 175 [%] [c]
1 [d]	**14**/$CoCl_2$	36	MeOH	54	73	-
2	**14**/$CoCl_2 \cdot 6H_2O$	40	MeOH	36	24	-
3		140	H_2O	4	traces	-
4	**14**	140	H_2O	2	6	-
5	**114**/$CoCl_2 \cdot 6H_2O$	40	MeOH	49	10	6
6		140	H_2O	-	-	-
7	**114**	140	H_2O	n.d.	5	-
8	**143**/$CoCl_2 \cdot 6H_2O$	40	MeOH	48	19	15
9		140	H_2O	n.d.	7	traces
10	**143**	140	H_2O	n.d.	traces	-
11	**142**/$CoCl_2 \cdot 6H_2O$	40	MeOH	54	20	19
12		140	H_2O	n.d.	10	4
13	**142**	140	H_2O	n.d.	4	-

[a]: 1 mmol of **149** (151 mg), 4.1 mmol of **130** (300 µL), 20 mol% catalyst, 10 mol% $CoCl_2$ $6H_2O$ (24 mg), solvent (c = 0.83 mol/L); **[b]**: Determined by chiral HPLC analysis; **[c]**: Isolated yield; **[d]**: Results of Reiser *et al.*, see reference [120]; **n.d.** = not determined.

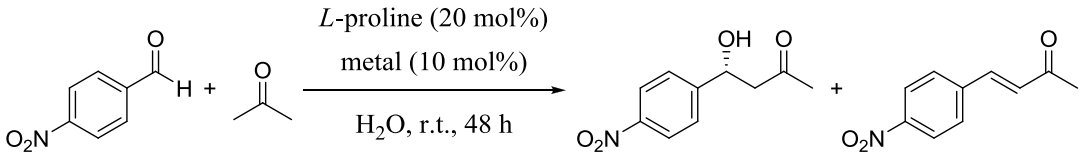
catalysts:



14 **114** **143** **142**

Based on these results and taking into account that the amount of water drastically influences the reactivity and stereoinduction it was therefore of great interest to investigate this parameter by screening different ratios of acetone (**130**)/water-mixtures in the aldol reaction catalyzed by *L*-proline (**14**) to find the optimal ratio (Table 12).

Table 12. Screening of different acetone (**130**)/water-mixtures in the asymmetric aldol reaction between acetone (**130**) and *p*-nitrobenzaldehyde (**149**) catalyzed by *L*-proline (**14**).



149 **130** **151** **175**

entry [a]	H_2O/acetone [ml/ml], [mmol/mmol]	metal	*ee* [%] [b]	yield 151 [%] [c]	yield 175 [%] [c]
1	1.20/1.25, 66.7/17.0	$CoCl_2 \cdot 6H_2O$	16	7	-
2		-	- 4	87	3
3	0.50/1.25, 27.8/17.0	$CoCl_2 \cdot 6H_2O$	37	4	-
4		-	2	91	5
5	0.31/1.25, 17.0/17.0	$CoCl_2 \cdot 6H_2O$	53	15	-
6		-	6	82	3
7	0.10/1.25, 5.6/17.0	$CoCl_2 \cdot 6H_2O$	68	20	-
8		-	37	88	10
9	0/1.25, 0/17.0	$CoCl_2 \cdot 6H_2O$	65	33	-
10		-	71	70	5

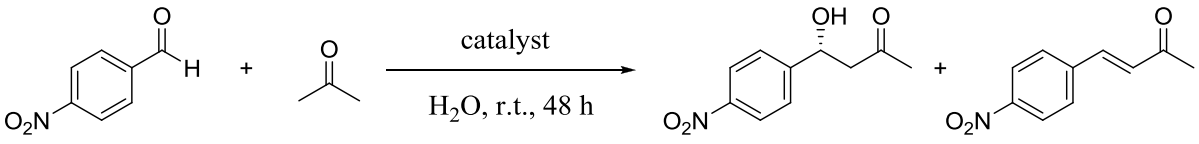
{a]: 1 mmol of **149** (151mg), amount of **130** (see table), 20 mol% *L*-proline (23 mg), 10 mol% $CoCl_2 \cdot 6H_2O$ (24 mg), H_2O (see table); **[b]**: Determined by chiral HPLC analysis; **[c]**: Isolated yield.

In the case of additional $CoCl_2 \cdot 6H_2O$ the best yields (up to 33%) and stereoselectivites (*ee* up to 68%) were obtained by the use of 5.6 mmol water or no water (entries 7 and 9). Moreover, by increasing the amount of water the results were inferior (entries 1, 3, 5). However, in the absence of $CoCl_2 \cdot 6H_2O$ the yield was significantly increased (up to 91%), whereas the best stereoselctivity was received without water (*ee* up to 71%). Interestingly, in the case of additional metal the formation of small quantities of by-product **175** was observed. To summarize, in both cases the optimal conditions are the application of 5.6 mmol of water or even no water (entries 7-10), however by higher aliquots of water the results are strongly impaired.

With these optimized conditions at hand, *L*-proline derivatives **142** and **143** were subsequently evaluated as catalysts in the aldol reaction. Based on the excellent results in the

case of cyclohexanone (**150**), the catalyst loading was reduced to 5 or even 1 mol% (Table 13).

Table 13. Aldol reaction between acetone (**130**) and *p*-nitrobenzaldehyde (**149**) under aqueous conditions catalyzed by *L*-proline derivatives **142** and **143**.

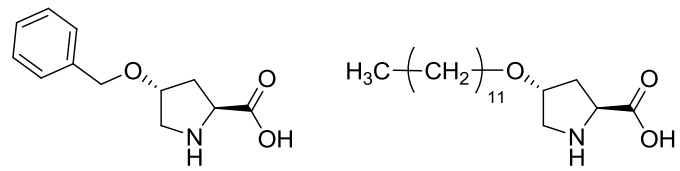


149 **130** **151** **175**

entry [a]	catalyst	solvent	*ee* [%] [b]	yield 151 [%] [c]	yield 175 [%] [c]
1	**143** (1 mol%)	neat	80	14	3
2		H_2O	79	41	-
3	**143** (5 mol%)	H_2O	65	42	42
4	**142** (1 mol%)	neat	76	15	-
5		H_2O	80	31	-

[a]: 1 mmol of **149** (151 mg), 17 mmol of **130** (1.25 mL), catalyst, H_2O (c = 10 mol/L); **[b]**: Determined by chiral HPLC analysis; **[c]**: Isolated yield.

catalysts:



143 **142**

With catalyst **142** a poor reactivity (up to 31%), caused by its low solubility in acetone (**130**), and a good stereoselectivity (up to 80%) was obtained (entries 4-5). Moreover, catalyst **143** showed the same trend, however, with better results. Under neat conditions the yield was low (14%), but the stereoselectivity reached 80% (entry 1) and by performing the reaction in water (entry 2) the *ee* stayed at the same level, whereas the yield improved to 41%. Surprisingly, by the use of 5 mol% catalyst, 42% elimination product **175** was additionally obtained and the *ee* was slightly decreased to 65% (entry 3).

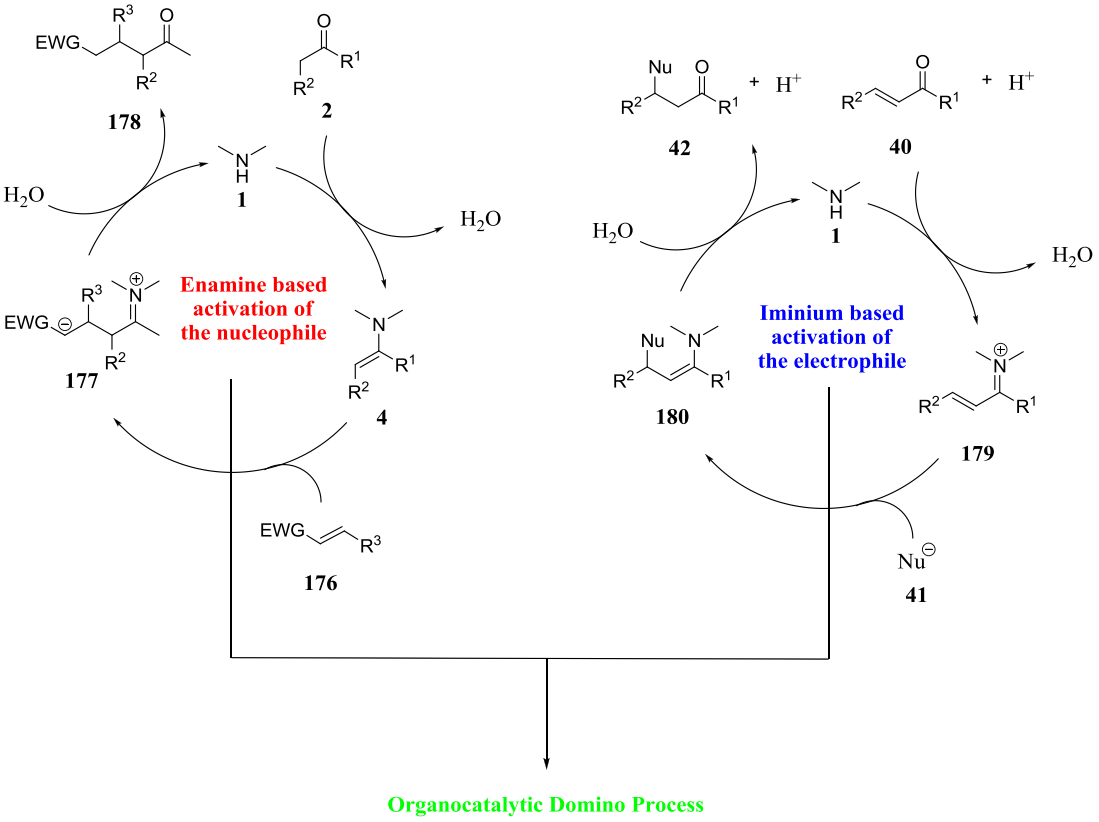
3.7 Summary

In summary, an improved and simplified protocol for the *L*-proline/Co(II)-catalyzed asymmetric aldol reaction was developed requiring no dry and inert atmosphere techniques. In the further course of this study the absence of a NLE and as well the feasibility of larger scale approaches was proofed. Moreover, two 4-substituted *L*-proline derivatives **142** and **143** were synthesized and subsequently investigated on their influence on the *L*-proline/Co(II)-catalyzed asymmetric aldol reaction with cyclohexanone (**150**) and acetone (**130**) as ketone source and furthermore the impact of MeOH and water was examined. In MeOH catalysts **142** and **143** showed no improvement compared to *L*-proline (**14**), however in the case of water the results were superior but additional $CoCl_2 \cdot 6H_2O$ revealed no effect under these conditions. By changing the ketone source to acetone (**130**) the results in MeOH were poor, however in a small amount of water and additional metal, catalysts **14**, **142** and **143** showed improved results, whereby without $CoCl_2 \cdot 6H_2O$ the outcome was even superior.

4. *L*-Proline/Metal-Complexes as Catalysts in Michael Additions

4.1 Introduction

One of the most important fields in organic chemistry is the asymmetric carbon-carbon and carbon-heteroatom bond formation. The conjugated addition of nucleophiles to electron-deficient olefins, namely, the Michael addition is considered as one of the most prominent example in this area. Hence, the development of highly stereoselective versions attracted the attention of scientists since long.[149] Today, a broad variety of methods for stereoselective Michael additions are known including organocatalysis.[149b, 150] In organocatalysis, three activation modes are known (Scheme 24).



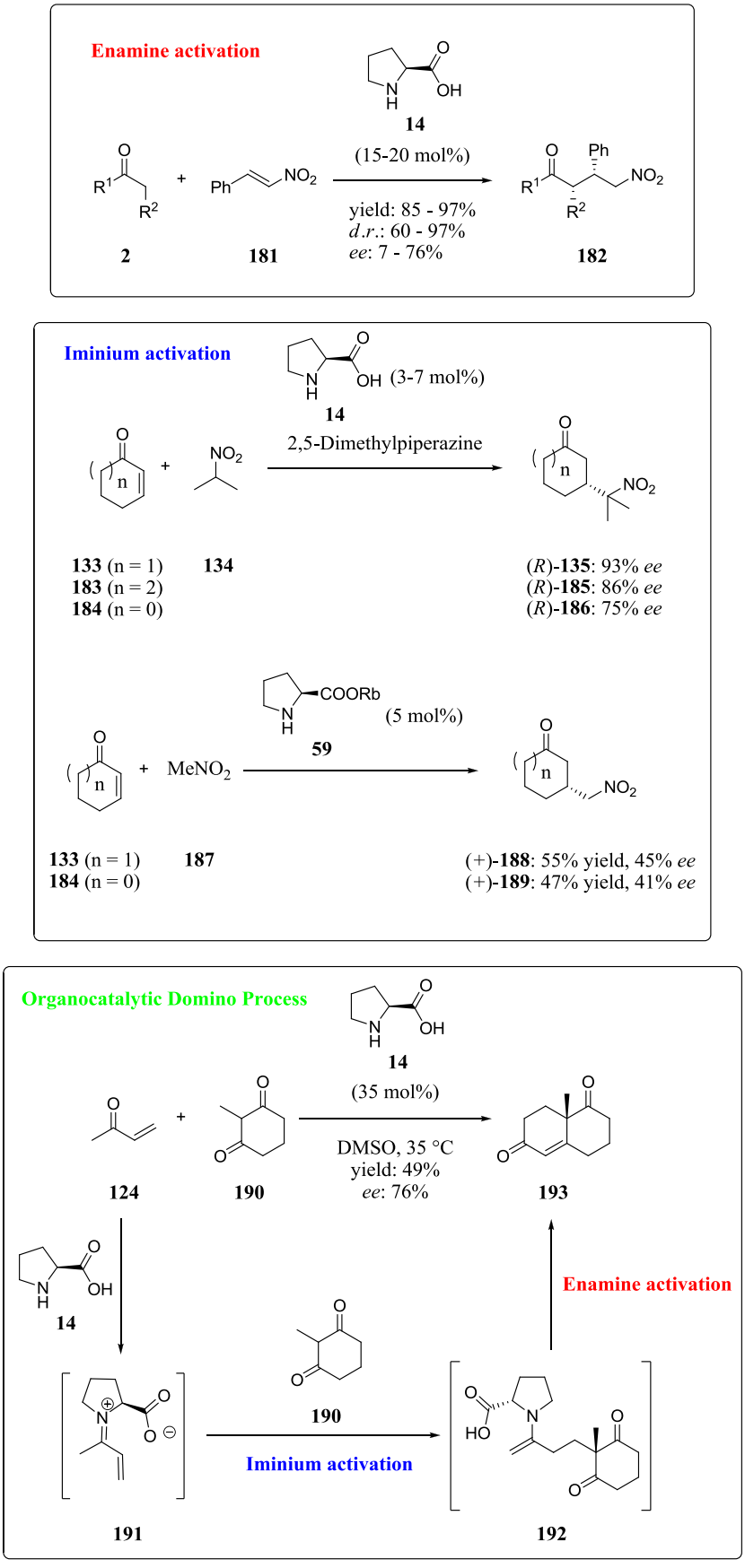
Scheme 24. Proposed catalytic cycle for the amine catalyzed Michael addition *via* iminum activation or *via* enamine activation and the combination of both.[27a, 150a]

The enamine-type activation mode always runs *via* the enamine **4** which is formed by the reaction of an enolizable carbonyl compound **2** and a chiral primary or secondary amine **1** (*e.g. L*-proline (**14**) or *L*-proline derivatives are used). Subsequently, the enamine **4** is adding to an electron deficient olefin **176** (*e.g.* EWG = NO_2), which after hydrolysis furnishes product **178** and the regenerated catalyst **1**.[7e, 150a, 151] The second activation mode strongly differs from the enamine based mode, because in this case, the electrophile **40** and not the

nucleophile is activated *via* an iminium ion intermediate **179**, which in the further course of the reaction is attacked by a nucleophile **41** to give enamine **180**. After hydrolysis the product **42** and the amine **1** is released, which then is available for a second catalytic cycle. The iminium intermediate **179** is mainly responsible for the generation of enantioselectivity and its formation is often provided by the addition of Brønsted acids as co-catalyst.[150a] The third type of activation is a combination of both types leading to the so called "organocatalytic domino process".[150a, 152] In Scheme 25 a few examples of *L*-proline (**14**) catalyzed Michael reactions using the three different activation modes are presented.

The first investigations of the enamine based mechanism were independently made by Barbas[17a], List[27a] and Enders[153] who reported the first *L*-proline (**14**) catalyzed addition of different ketones **2** to *trans*-*β*-nitrostyrene (**181**), which opened the field for further studies. In most cases, the use of modified *L*-prolines (*e.g. N*-alkyl-2,2'-bipyrrolidine derivatives[154], *N*-terminal prolyl-peptides[155], homo proline tetrazole[156]) gave superior results compared to *L*-proline (**14**).[149b] This way, good to excellent yields (85-97%) and diastereoselectivities (60-97%) were achieved, however the enantioselectivities (7-76%) only reaching moderate degrees. The results attained by the use of acetone (**130**) as ketone source were even inferior compared to their cyclic analogues. In these cases only *ee* values of 0 to 12% were obtained.[17a, 27a, 149b, 153]

The second activation mode takes place *via* an iminium transition state. In both depicted reactions, a variety of cyclic enones (**133**, **183**-**184**) were converted to various 4-substituted cyclic ketones (**135**, **185**-**186**, **188**-**189**) with different nitro alkanes (**134**, **187**). The pioneering work in this field was done by Hanessian and Pham[46, 150a], who investigated the *L*-proline (**14**) catalyzed Michael addition and found, that an additional base is required, which acts as co-catalyst. They also used different modified *L*-proline derivatives for this transformation.[157] Further efforts in this direction were made by Tsogoeva *et al.*.[158] In the second example, no additional base is required since the reaction is catalyzed by a Rb-*L*-proline salt (**59**) and requires no additional base. This catalytic system was first discovered and further studied by Yamaguchi *et al.*.[47b, 47c, 150a, 157]



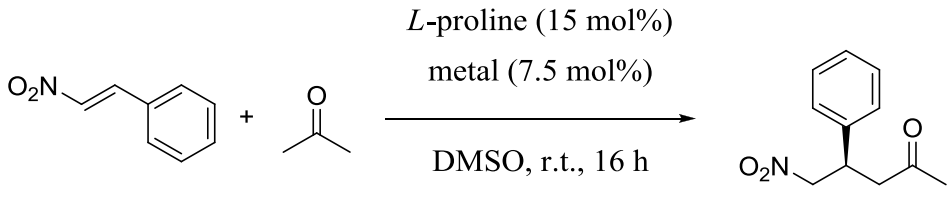
Scheme 25. Literature examples in regard to the three different activation modes of the Michael addition catalyzed by *L*-proline (**14**).

Finally, the last activation mode is running *via* a combination of both reaction pathways, the so called organocatalytic domino process. The first literature evidence of this type of reaction was furnished by Bui and Barbas[159] who noticed that *L*-proline (**14**) was able to perform the Robinson annulation between MVK (**124**) and 1,3 cyclohexandione (**190**) over a initiating Michael reaction in a stereoselective way.

4.2 *L*-Proline/Metal-Complexes as Novel Catalysts in the Michael Addition

Owing to the promising results obtained in the aldol reaction catalyzed by an *in situ* formed *L*-proline/Co(II)-complex, this protocol was investigated for other similar reactions, *e.g.* the Michael addition of acetone (**130**) to *trans*-*β*-nitrostyrene (**181**). This approach is rationalized by the similar activation mode of the aldol reaction and the Michael addition. Both reactions proceed *via* a enamine based mechanism, in which the ketone is activated by an enamine transition state that subsequently gets attacked by a nucleophilic center.[27a] To see the influence of the applied catalyst on stereoselectivity and reactivity, a literature-known Michael addition developed by List and co-workers[27a] for which only moderate degree of enantioselectivity was reported, was chosen as model system (Table 14, entry 1). By reproducing the reaction similar results were obtained (Table 14, entry 2). First, the impact of different metal salts on the outcome of the reaction especially in regard to stereoselectivity but also in regard to reactivity was investigated (Table 14). The results without additional metal yielded 82% and 4% *ee* (entry 2) and served as benchmark experiment in the further course of the study. When looking at entries 3-10, the additional metals revealed no influence on stereoselectivity, however, an effect on reactivity was recognizable. The yield was in the range of 60% to 94%. The worst results were obtained with $FeCl_3 \cdot 6H_2O$ (entry 9), whereas the best results were achieved by $La(OTf)_3$ (entry 10) [$Ln(OTf)_3$ (Ln =La, Pr, Nd, Sm, Eu, Gd, Dy, Ho, Er, Tm, Yb, Lu)[160] are known to catalyze the Michael reaction of silyl enolates with *α,β*-unsaturated ketones well)] and NiI_2 (entry 4) (also known to catalyze different Michael additions in combination with various Ligands, for examples see review of Krause and Hoffmann-Röder[149a]). In all other cases moderate to good degrees of reactivity were accomplished.

Table 14. Screening of different metal salts in the Michael addition of acetone (**130**) to *trans*-*β*-nitrostyrene (**181**) catalyzed by *L*-proline (**14**).



181 **130** **194**

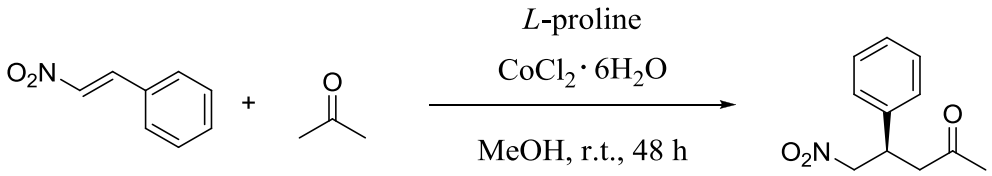
entry [a]	metal	*ee* [%] [b]	yield [%] [c]
1 [d]	-	7	97
2	-	4	82
3	$CoCl_2 \cdot 6H_2O$	4	86
4	NiI_2	3	91
5	$ZnCl_2$	3	78
6	$PbCl_2$	3	83
7	$YbCl_3 \cdot 6H_2O$	3	87
8	$Sc(OTf)_3$	5	86
9	$FeCl_3 \cdot 6H_2O$	5	60
10	$La(OTf)_3$	6	94

[a]: 1 mmol of **181** (149 mg), 27.2 mmol of **130** (2 mL), 15 mol% *L*-proline (17 mg), 7.5 mol% metal, DMSO (c = 0.125 mol/L); **[b]**: Determined by chiral HPLC analysis; **[c]**: Isolated yield; **[d]**: Results of List *et al.*, see reference [27a].

These slightly improved results might be explained by a combination of two activation modes, namely the activation of acetone (**130**) through an enamine transition state formed by *L*-proline (**14**) or an enone transtition state formed by the Lewis acid, respectively, and an additional Lewis acid activation of *trans*-*β*-nitrostyrene (**181**). Nevertheless, these results raise the question if there is taking place a complex formation of metal and *L*-proline (**14**) in this reaction at all.

Based on the postulation that MeOH is facilitating the *L*-proline/Co(II)-complex formation it was considered to apply the catalytic system to the protocol of Enders and co-workers, because there they used MeOH as solvent. (Table 15) [153]

Table 15. Screening of additional $CoCl_2 \cdot 6H_2O$ in the Michael addition of acetone (**130**) to *trans*-*β*-nitrostyrene (**181**) catalyzed by *L*-proline (**14**) in MeOH.



181 **130** **194**

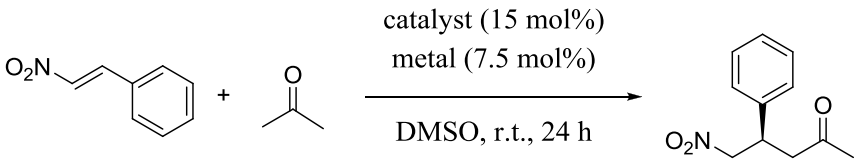
entry [a]	*L*-proline	$CoCl_2 \cdot 6H_2O$	MeOH	*ee* [%] [b]	yield [%] [c]
1 [d]		-		12	93
2	0.2 equiv.	-	5 mL (c = 0.2 mol/L)	20	36
3		10 mol%		16	5
4 [d]		-		20	90
5	1.5 equiv.	-	0.5 mL (c =2 mol/L)	18	92
6		75 mol%		2	10

[a]: 1.0 mmol of **181** (149 mg), 10 mmol of **130** (0.74 mL), *L*-proline (see table), $CoCl_2 \cdot 6H_2O$, MeOH (see table); **[b]**: Determined by chiral HPLC analysis; **[c]**: Isolated yield; **[d]**: Results of Enders *et al.*, see reference [153].

The results obtained by Enders *et al.* were excellent in terms of yield (93%), but only generated a poor stereoselectivity (12% *ee*) (entry 1). By reproducing the literature, the results were drastically impaired (entry 2), and moreover the use of $CoCl_2 \cdot 6H_2O$ (entry 3) only resulted in a further decrease of stereoselectivity and reactivity. In entry 5 1.5 equivalents of *L*-proline (**14**) and a more concentrated reaction solution were used which led to much better results in terms of yield but did not improve the stereoselectivity (conditions also used by Enders and co-workers[153], entry 4). However, with 75 mol% $CoCl_2 \cdot 6H_2O$, 10% yield and a decreased *ee* value were achieved (entry 6). This makes clear that the additional metal reduces the catalytic activity in this case, thus no further experiments under these conditions were carried out.

Nevertheless, based on the knowledge that 4-substituted *L*-proline derivatives **142** and **143** were never applied to the asymmetric Michael addition it was of great interest to investigate their impact on the enantio- and diastereoselectivity in this transformation (Table 16). Moreover, the effect of additional $La(OTf)_3$ and $CoCl_2 \cdot 6H_2O$ should be studied, due to their positive effect in the *L*-proline (**14**) catalyzed Michael addition (see Table 14, page 69). By considering the results in Table 16, it gets clear that the additional metal showed no influence on the *ee* in all of the case, in contrast, the reactivity was influenced. The application of $CoCl_2 \cdot 6H_2O$ had no positive impact on the yield (entries 2, 5, 8, 11), however, $La(OTf)_3$ slightly improved the yield (entries 3, 6, 9, 12) compared to the results without metal (entries 1, 4, 7, 10). These facts give rise to two conclusions. First, lanthanum coordinates to the nitro group of *trans*-*β*-nitrostyrene (**181**) and, therefore, activates it against a nucleophilic attack or second, it additionally is activating acetone (**130**) as Lewis acid. The best overall results were obtained with *L*-proline derivative **143** (entries 7-9). There, superior *ee* values and yields compared to *L*-proline (**14**) and its derivatives **114** and **142** were achieved. Moreover, derivatives **142** (entries 10-12) and **114** (entries 4-6) showed an increased stereoinduction in contrast to *L*-proline (**14**) (entries 1-3).

Table 16. Application of 4-substituted *L*-proline derivatives **114**, **142** and **143** to the Michael addition of acetone (**130**) to *trans*-*β*-nitrostyrene (**181**).

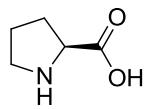


181 **130** **194**

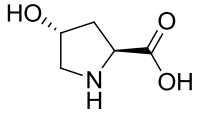
entry [a]	catalyst	metal	*ee* [%] [b]	yield [%] [c]
1		-	4	82
2	**14**	$CoCl_2 \cdot 6H_2O$	4	86
3		$La(OTf)_3$	6	94
4		-	11	73
5	**114**	$CoCl_2 \cdot 6H_2O$	12	65
6		$La(OTf)_3$	10	88
7		-	14	89
8	**143**	$CoCl_2 \cdot 6H_2O$	13	85
9		$La(OTf)_3$	8	90
10		-	11	59
11	**142**	$CoCl_2 \cdot 6H_2O$	9	41
12		$La(OTf)_3$	12	62

[a]: 1 mmol of **181** (149 mg), 27.2 mmol of **130** (2 mL), 15 mol% catalyst, 7.5 mol% metal, DMSO (c = 0.125 mol/L); **[b]**: Determined by chiral HPLC analysis; **[c]**: Isolated yield.

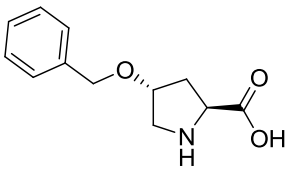
catalysts:



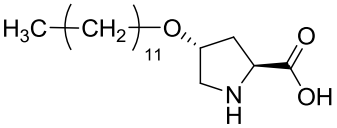
14



114



143



142

4.3 Summary

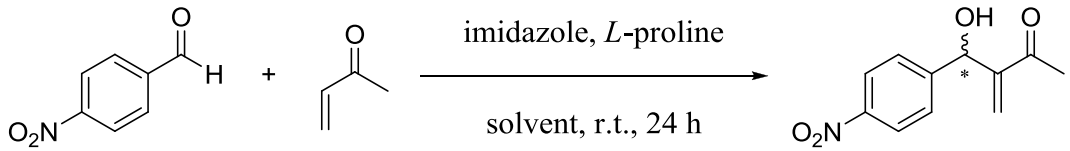
In summary, a novel catalytic system using *L*-proline (**14**) and its derivatives **114**, **142** and **143** in combination with metal salts was evaluated and quantified under the aspect of its effect on the reactivity and stereoselectivity in the asymmetric Michael addition. The screening of various metals revealed no effect on stereoselectivity, however the reactivity was improved by the use of $La(OTf)_3$. Moreover, *L*-proline derivatives **114**, **142** and **143** showed an increased stereoinduction compared to *L*-proline (**14**) and especially catalyst **143** also gave similar yields. In conclusion, these results clearly demonstrated the applicability of the 4-substituted *L*-proline derivatives **114**, **142** and **143** in the Michael addition leading, beside *L*-proline (**14**), to competitive results.

5. *L*-Proline/Metal -Complexes as Catalysts in the Baylis-Hillman Reaction

5.1 Introduction

L-proline (**14**) has proven to be a remarkably efficient catalyst for organocatalytic transformations and therefore has been applied to a broad scope of transformations.[150b] One of these transformations is the asymmetric Baylis-Hillman reaction and the asymmetric Morita-Baylis-Hillman reaction, which in the course of the years was intensively studied under the application of an enormous number of different catalytic systems mainly based on organic molecules like quinidine derived chiral amines,[161] different Lewis bases,[162] combinations of Lewis bases and metals acting as Lewis acids,[163] *L*-proline derived secondary amines[164] and combinations of Lewis bases and urea-type organocatalysts.[165] Furthermore, combinations of Lewis bases and *L*-proline (**14**) as co-catalyst were used in this context, too.[161, 166] Moreover, to some extent excellent conversions were obtained, but the stereoselectivity only reached a moderate degree in most cases (up to 69% *ee* for *p*-nitrobenzaldehyde (**149**) and MVK (**124**)[166f]; up to 83% *ee* for *o*-nitrobenzaldehyde and MVK (**124**)[166a, 166b]). The first, literature-known discovery that *L*-proline (**14**) in combination with imidazole (**196**) was able to catalyze the Baylis-Hillman reaction between MVK (**124**) and *p*-nitrobenzaldehyde (**149**) in excellent yield but with no stereoinduction was made by Shi *et al.* in 2002.[167] Further studies in this direction were done by Tomkins *et al*. in 2007 who published an important solvent effect in this regard (Table 17).[168]

Table 17. Literature results obtained by Shi *et al.*[167] and Tomkins *et al.*[168] in the Baylis-Hillman reaction of *p*-nitrobenzaldehyde (**149**) and methyl vinyl ketone (MVK) (**124**) catalyzed by a combination of imidazole (**196**) and *L*-proline (**14**).

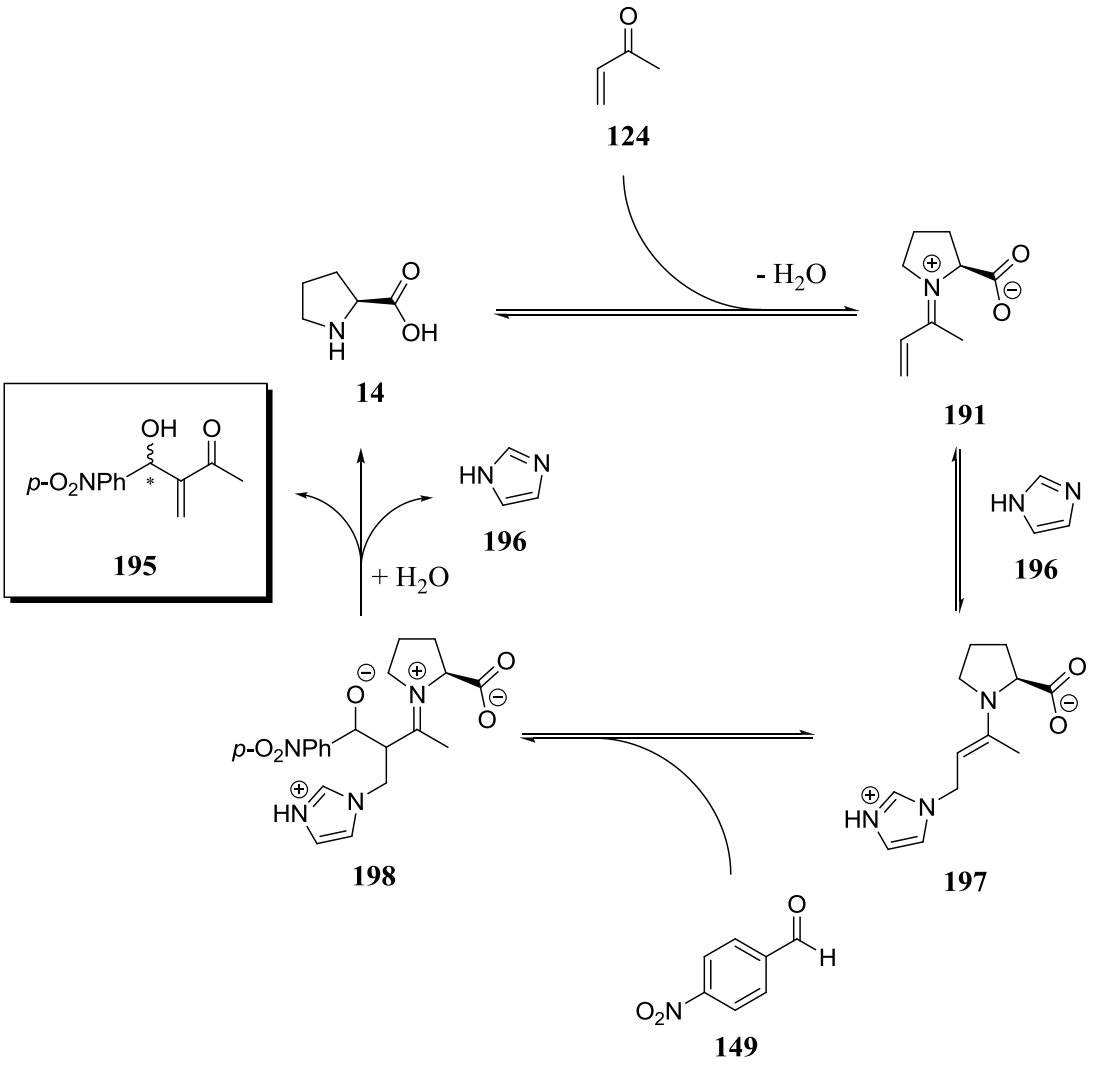


149 **124** **195**

entry	solvent	imidazole, *L*-proline	*ee* [%] [a]	yield [%] [b]
1 [c]	DMF	30 mol%	*rac.*	54
2 [d]				91
3 [c]	DMF/H_2O (v/v 9:1)	10 mol%	*rac.*	80

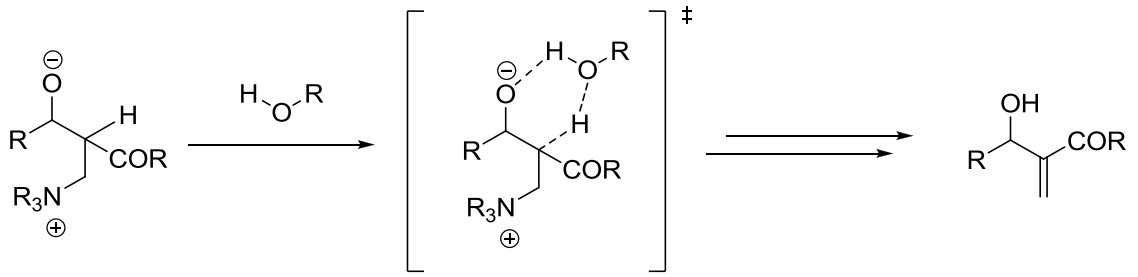
[a]: Determined by chiral HPLC analysis; **[b]**: Isolated yield; **[c]**: Results of Tomkinson *et al.*, see reference [168]; **[d]**: Results of Shi *et al*., see reference [167].

When one compares the results of Tomkinson *et al*. with the results of Shi *et al*. under the same conditions, they surprisingly differ significantly. Both used 30 mol% *L*-proline (**14**) in combination with imidazole (**196**) and DMF as solvent, but the yield varies from 54% (entry 1) to 91% (entry 2), which Tomkins *et al*. assumed is due to the water contaminated DMF which was presumably used by the group of Shi. Therefore, they carried out the reaction with different mixtures of DMF and water and achieved the best results by a ratio of 9:1 and 10 mol% of both catalysts (entry 3). Moreover, as Table 17 reveals only racemic product mixtures were obtained under these conditions. Shi *et al.* proposed following mechanism displayed in Scheme 26.[167]



Scheme 26. Proposed mechanism for the *L*-proline (**14**)/imidazole (**196**)-catalyzed Baylis-Hillman reaction.[166c, 167]

The first step is the iminium ion formation **191** by the reaction of MVK (**124**) with *L*-proline (**14**). Subsequently, this α,β-unsaturated system **191** is attacked by imidazole (**196**) to obtain enamine **197**, which then reacts with *p*-nitrobenzaldehyde (**149**) to give **198**. After the elimination of imidazole (**196**) through hydrolysis of the iminium ion **198**, the Baylis-Hillman adduct **195** is obtained. Furthermore, Aggarwal *et al.* considered that, if a protic species is present in the reaction, in the form of either solvent or product **201**, the reaction is running over intermediate **200** involving a proton-transfer reaction, which accelerates the product formation **201** (Scheme 27).[166c, 169]



199 **200** **201**

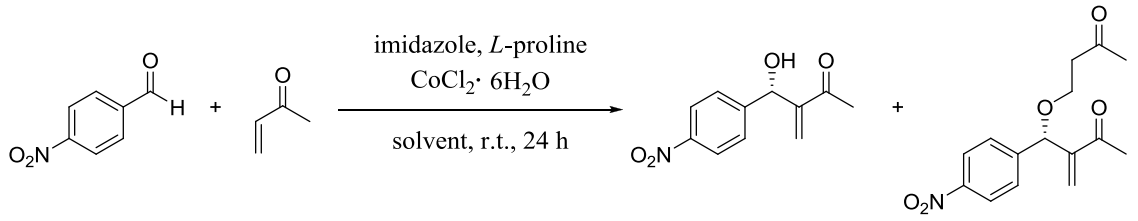
Scheme 27. Proposed influence of protic solvents on the Baylis-Hillman reaction.[166c, 169]

Nevertheless, there are also literature reports giving examples of enantioselective, *intramolecular* Baylis-Hillman reactions.[170] Moreover, enantioselective *intermolecular* Baylis-Hillman reactions catalyzed by a combination of *L*-proline (**14**) and a peptide instead of imidazole (**196**)[166d] or by a combination of *L*-proline (**14**) and a chiral tertiary amine are also known.[166a, 166b]

5.2 *L*-Proline/Metal-Complexes as Novel Catalysts in the Baylis-Hillman Reaction

Inspired by these results and the absence of stereoinduction by applying *L*-proline (**14**) in combination with imidazole (**196**) to the Baylis-Hillman reaction between MVK (**124**) and *p*-nitrobenzaldehyde (**149**), this transformation was chosen as model system for investigating the impact of *L*-proline (**14**) and the 4-substitited *L*-proline derivatives **114**, **142** and **143** on their catalytic activity and especially stereoselectivity in this reaction. Furthermore, the outcome in the presence of additional $CoCl_2 \cdot 6H_2O$ should be quantified. However, the starting point for the study was finding the optimal reaction conditions without additives (Table 18).

Table 18. Screening to find the optimal conditions in the Baylis-Hillman reaction of *p*-nitrobenzaldehyde **149** and methyl vinyl ketone (MVK) (**124**) catalyzed by a combination of *L*-proline (**14**) and imidazole (**196**) without (entries 1-4) and with (entries 5) $CoCl_2 \cdot 6H_2O$.



149 **124** **195** **202**

entry [a]	solvent	imidazole, *L*-proline	$CoCl_2 \cdot 6H_2O$	*ee* 195 [%] [b]	yield 195 [%] [c]	yield 202 [%] [c]
1 [d]	DMF/H_2O (v/v 9:1)	30 mol%	-	*rac.*	80	-
2	DMF	10 mol%	-	*rac.*	36	traces
3	DMF	30 mol%	-	*rac.*	38	8
4	DMF/H_2O (v/v 9:1)	30 mol%	-	*rac.*	68	traces
5	DMF/H_2O (v/v 9:1)	30 mol%	15 mol%	14	39	traces

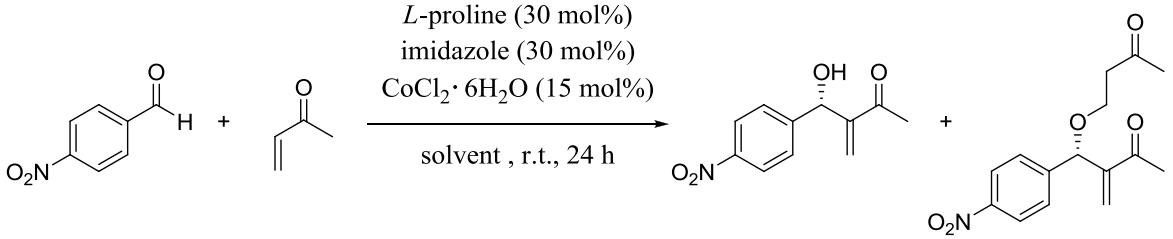
[a]: 1 mmol of **149** (151 mg), 3 mmol of **124** (253 µL), solvent (c = 1 mol/L); **[b]**: Determined by chiral HPLC analysis; **[c]**: Isolated yield; **[d]**: Results of Tomkinson *et al.*, see reference [168].

The first intriguing observation one could make when looking at Table 18 is the formation of side product **202** beside the formation of main product **195**, however in very small quantities. The finding of the Michael addition product **202**, through a side reaction of **195** with MVK (**124**), was already described by Shi *et al.*[171] which was obtained by the application of DMAP as Lewis base and DCM as solvent. However, the initial step was to find the optimal reaction conditions without metal. By comparing entries 2-4 the best results indeed were achieved by using 0.1 mL water and 0.9 mL DMF (entry 4) as figured out by Tomkinson *et al.* (entry 1).[168] Moreover, in accordance to the observations made by Shi[167] and Tomkinson[168] the products showed no stereoinduction in these cases. Based on these findings, 30 mol% *L*-proline (**14**) and imidazole (**196**), respectively, and a DMF/water-mixture in a volume ratio of 9:1 were chosen for further approaches. In order to see the effect of additional $CoCl_2 \cdot 6H_2O$ these conditions were simply extended by the use of 15 mol% metal owing to the presumed 2:1 stoichiometry of the (*L*-proline)$_2$/Co(II)-complex. When $CoCl_2 \cdot 6H_2O$ was utilized a decreased yield of 39% and an increased *ee* of 14% were obtained (entry 5). However, this might be explained by the fact that $CoCl_2$ is known to be able forming complexes with imidazole (**196**) and water.[172] Moreover, cobalt(II) diformate dimethylformamide-[173] and hexakis(*N*,*N*-dimethylformamide-κ*O*)-cobalt(II) bis(perchlorate)-complexes[174] are known, which might negatively influence the sensitive organocatalytic

system. Based on these facts the lowered reactivity is somehow getting clearer. Considering the mechanism (Scheme 26, page 76) imidazole (**196**) is a crucial factor for the activation of the enamine **191** for a nucleophilic attack, but owing to the presumed complexation of imidazole (**196**) by Co(II) it is therefore unavailable for the activation and hence the reactivity is limited to a certain degree. However, $CoCl_2 \cdot 6H_2O$ also showed a positive effect, namely in terms of stereoselectivity (entry 4 *vs.* 5), leading to the conclusion that there also must be an interaction between cobalt(II) and *L*-proline (**14**) increasing the stereoinduction. This indicates to a simultaneous formation of a (*L*-proline)$_2$/Co(II)-complex and imidazole/Co(II)-complex. Another scenario one could imagine is the possibility that cobalt is acting as Lewis acid and activates the α,β-unsaturated ketone by coordination to the carbonyl function which in consequence stands in competition to the predicted enamine based mechanism (Scheme 26, page 76). This explanation is based on the studies of Shi *et al.* who developed a $TiCl_4$ and amine-promoted Baylis-Hillman reaction where they describing the role of $TiCl_4$ as Lewis acid activating the a α,β-unsaturated ketone through coordination to the carbonyl function.[175] All in all, these facts clearly demonstrate that the Baylis-Hillman reaction is influenced by many factors, thus making it difficult to find the optimal reaction conditions.

As mentioned before the solvent also seemed to play an important role due to its ability to coordinate metal ions (in the case of DMF) and as well due to the acceleration of the proton transfer in the product formation (see Scheme 27, page 77). Therefore, various solvents were screened to investigate their effect on the Baylis-Hillman reaction (Table 19).

Table 19. Screening of different solvents in the Baylis-Hillamn reaction of *p*-nitrobenzaldehyde (**149**) and MVK (**124**) catalyzed by a combination of *L*-proline (**14**), imidazole (**196**) and $CoCl_2 \cdot 6H_2O$.



149 **124** **195** **202**

entry [a]	solvent	*ee* 195 [%]	conversion [%] [b]	yield 195 [%]	yield 202 [%]
1	MeOH		n.d.	24 [c]	4 [c]
2	DMSO		n.d.	16 [c]	5 [c]
3	DMF/MeOH (v/v 9:1)		n.d.	26 [c]	9 [c]
4	MeOH/H_2O (v/v 9:1)		n.d.	41 [b]	
5	THF		89	38 [b]	
6	Et_2O		99	38 [b]	
7	$CHCl_3$	*rac.*	83	28 [b]	
8	MeCN		83	35 [b]	
9	Toluene		78	6 [b]	traces [b]
10	DMSO		100	26 [b]	
11	H_2O		92	13 [b]	
12	1,4-Dioxane		48	5 [b]	
13	DCM		78	36 [b]	

[a]: 1 mmol of **149** (151 mg), 3 mmol of **124** (253 µL), 30 mol% *L*-proline (35 mg), 30 mol% imidazole (20 mg), 15 mol% of $CoCl_2$ $6H_2O$ (36 mg), solvent (c = 1 mol/L); **[b]**: Determined by ^{1}H-NMR of the crude reaction mixture using an internal standard (1,4 Dimethoxybenzol); **[c]**: isolated yield; **n.d.** = not determined.

As Table 19 reveals, the use of these solvents led to moderate yields. Comparable results to the initially used DMF/H_2O-mixture (v/v 9:1) were obtained with MeOH/H_2O (v/v 9:1) (entry 4), THF (entry 5), Et_2O (entry 6), MeCN (entry 8) and DCM (entry 13). However, in all cases only a *racemic* product **195** was generated, hence the initial conditions with DMF/H_2O (v/v 9:1) were maintained for further experiments. Interestingly, one thing worth mentioning is that, in most cases, the reaction reaches full conversion leading to the question what happened with the rest of the starting material. One possibility which indeed should be considered is the high reactivity of MVK (**124**) and thus its affinity to polymerize which in

the course of the reaction might lead to polymerized side products involving *p*-nitrobenzaldehyde (**149**). Based on the low solubility of these molecules in $CDCl_3$, they are beyond the detection limit of NMR spectroscopy and hence should show no signals in the NMR spectra. This possibly explains the almost vanished peaks of *p*-nitrobenzaldehyde (**149**) in the crude NMR, although only a low amount of product **195** and no other peaks of potential side products were visible. Moreover, the observed color change from a light yellow, clear solution at the beginning of the reaction to a brown to black, turbid suspension after 24 h also suggests that a polymerization took place. A second explanation might be the slow decomposition of product **195** in the course of the reaction. To verify these presumptions a kinetic measurement was carried out (Figure 15). On the left side in Figure 15 is displayed the Baylis-Hillman reaction of *p*-nitrobenzaldehyde (**149**) and MVK (**124**) catalyzed by *L*-proline (**14**) and imidazole (**196**) and on right side it is catalyzed by a combination of *L*-proline (**14**), imidazole (**196**) and additional $CoCl_2 \cdot 6H_2O$.

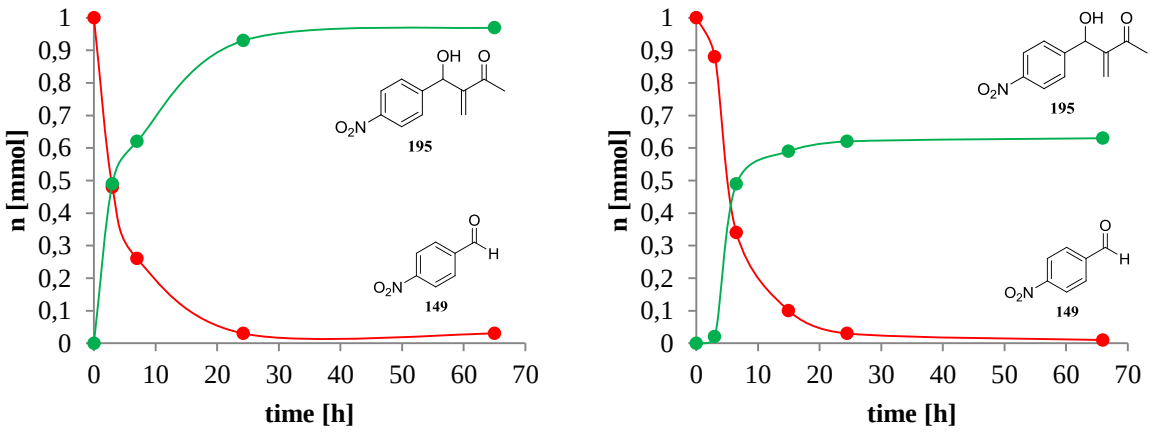


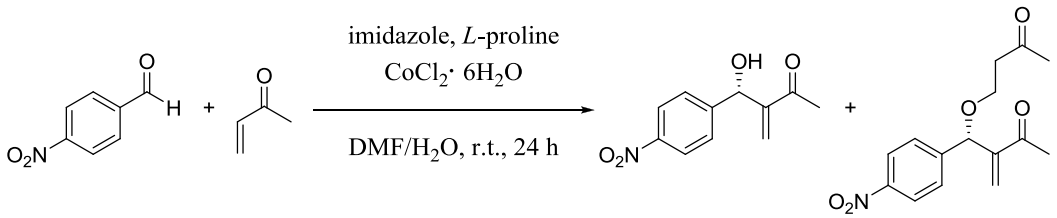
Figure 15. Kinetic measurement of the Baylis-Hillman reaction between *p*-nitrobenzaldehyde (**149**) and MVK (**124**). The left diagram shows the reaction carried out with *L*-proline (**14**) and imidazole (**196**). The right diagram shows the reaction carried out with a combination of *L*-proline (**14**), imidazole (**196**) and $CoCl_2 \cdot 6H_2O$.[**]

In both cases no decomposition of product was observed in the course of the reaction, even though two things are remarkable. First, the obtained yield by using additional $CoCl_2 \cdot 6H_2O$ is significantly lower, possible reasons for this observation were already discussed on page 78 *ff.* in this chapter. A second observation is the retarded product formation after 3 h in the case of additional $CoCl_2 \cdot 6H_2O$ (Figure 15, right diagram). In conclusion, there presumably is a formation of either an (*L*-proline)$_2$/Co(II)-complex or an *L*-proline/imidazole-complex which hinders the reaction. Besides, the *ee* is not significantly influenced in the case of additional

[**] For experimental data and conditions see Table 51 on page 169 and Table 52 on page 170 in the experimental part.

metal and constantly stays at the same level over time, however after 66 h the *ee* slightly goes down from 12% to 9%.[**] To get further insight in the reaction mechanism some benchmark reactions were performed (Table 20).

Table 20. Benchmark reactions in the *L*-proline (**14**) and imidazole (**196**) catalyzed Baylis-Hillman reaction of *p*-nitrobenzaldehyde (**149**) and MVK. (**124**).



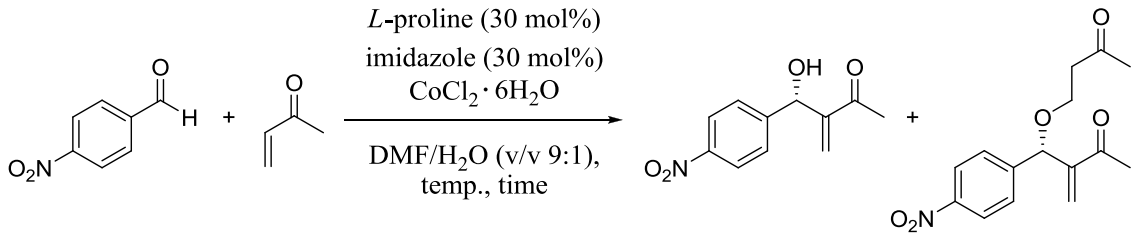
149 **124** **195** **202**

entry [a]	*L*-proline	imidazole	$CoCl_2 \cdot 6H_2O$	*ee* 195 [%] [b]	conversion [%] [c]	yield 195 [%] [c]	yield 202 [%] [c]
1	30 mol%	30 mol%	-	*rac.*	99	79	traces
2	30 mol%	30 mol%	15 mol%	13	98	42	traces
3	30 mol%	-	-	n.d.	14	8	0
4	30 mol%	-	15 mol%	n.d.	14	5	0
5	-	-	15 mol%	-	4	0	0
6	-	30 mol%	-	-	99	40	0
7	-	30 mol%	15 mol%	-	95	65	0

[a]: 1 mmol of **149** (151 mg), 3 mmol of **124** (253 µL), 30 mol% *L*-proline (35 mg), 30 mol% imidazole (20 mg), 15 mol% of $CoCl_2 \cdot 6H_2O$ (36 mg), DMF/H_2O (v/v 9:1) (c = 1 mol/L); **[b]**: Determined by chiral HPLC analysis; **[c]**: Determined by ^{1}H-NMR of the crude reaction mixture using an internal standard (1,4 Dimethoxybenzol); **n.d.** = not determined.

The results in entry 1 and 2 clearly indicate that $CoCl_2 \cdot 6H_2O$ has a negative effect on reactivity, however leading to an increased *ee* value. This disclosed the question how the single components influence the reactivity and stereoselectivity. In all cases where imidazole (**196**) was left out the obtained conversion and yield was almost zero, showing that it is an essential component in this reaction (entries 3-5). By the application of imidazole (**196**) as sole catalyst full conversion and a yield of 40% was obtained (entry 6) and moreover by combining it with $CoCl_2 \cdot 6H_2O$, in addition, an increased reactivity was observed (entry 7), which reveals an positive effect of the metal. However, the exact role of $CoCl_2 \cdot 6H_2O$ finally could not be elucidated. To receive more information on its influence, different amounts of $CoCl_2 \cdot 6H_2O$ were applied to the Baylis-Hillman reaction (Table 21).

Table 21. Screening of different amounts of $CoCl_2 \cdot 6H_2O$ in the Baylis-Hillman reaction between *p*-nitrobenzaldehyde (**149**) and MVK (**124**).



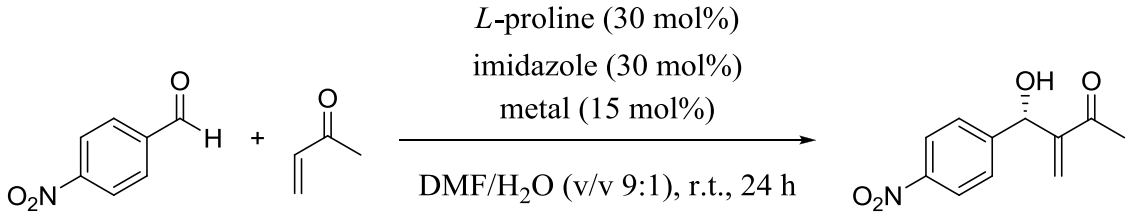
149 **124** **195** **202**

entry [a]	$CoCl_2 \cdot 6H_2O$	time [h]	temp. [°C]	*ee* 195 [%] [b]	yield 195 [%] [c]	yield 202 [%] [c]
1	30 mol%			*rac.*	17	4
2	15 mol%			14	39	traces
3	5 mol%	28	25	*rac.*	51	6
4	1 mol%			*rac.*	23	11
5 [d]	15 mol%			*rac.*	29	traces
6	15 mol%	7	50	5	36	traces

[a]: 1 mmol of **149** (151 mg), 3 mmol of **124** (253 µL), 30 mol% *L*-proline (35 mg), 30 mol% imidazole (20 mg), DMF/H_2O (v/v 9:1) (c = 1 mol/L); **[b]**: Determined by chiral HPLC analysis; **[c]**: Isolated yield; **[d]**: reaction was carried out without solvent.

From entries 1 and 2 can be concluded that 30 mol% metal impairs the reactivity and the stereoselectivity possibly owing to the complexation of imidazole (**196**) to cobalt(II), which in consequence is not available for the reaction. Therefore, the yield should be improved by lowering the amount of metal which is in accordance with the results obtained by the use of 15 and 5 mol% of catalyst (entry 2-3). However, 1 mol% metal should logically lead to a further increased yield, but this was not the case (entry 4). There only an increased formation of by-product **202** was observable, possibly due to the ability of $CoCl_2 \cdot 6H_2O$ to activate the Michael system of MVK (**124**) for a nucleophilic attack of the alcohol group ending up in the formation of **202**. However, it is unclear why this effect is not visible in the other cases, whereby a trend to an increased by-product formation is noticeable (entries 1-4). The use of solvent free conditions (entry 5) and furthermore the application of higher temperatures showed no improvement (entry 6). The best overall *ee* value was achieved in the case of *L*-proline/$CoCl_2 \cdot 6H_2O$ in a 2:1 ratio, indicating to the formation of a (*L*-proline)$_2$/Co(II)-complex during the reaction. In the course of this investigation also $ZnCl_2$, $PbCl_2$, $Sc(OTf)_3$, $SnCl_2 \cdot 2H_2O$, $La(OTf)_3$ and $YCl_3 \cdot 6H_2O$ were screened (Table 22).

Table 22. Screening of different metals in the Baylis-Hillman reaction between *p*-nitrobenzaldehyde (**149**) and MVK (**124**).



149 **124** **195**

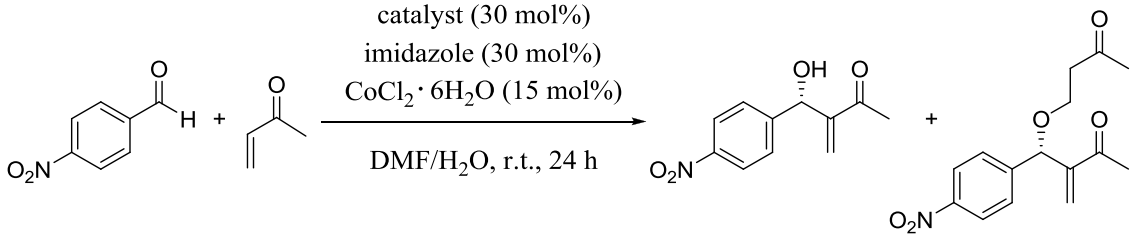
entry [a]	metal	*ee* [%] [b]	conversion [%] [c]	yield [%] [c]
1	$ZnCl_2$	5	98	79
2	$La(OTf)_3$		99	28
3	$SnCl_2 \cdot 2H_2O$		35	7
4	$YCl_3 \cdot 6H_2O$	*rac.*	95	68
5	$Sc(OTf)_3$		95	70
6	$PbCl_2$		91	87

[a]: 1 mmol of **149** (151 mg), 3 mmol of **124** (253 µL), 30 mol% *L*-proline (35 mg), 30 mol% imidazole (20 mg), DMF/H_2O (v/v 9:1) (c = 1 mol/L); **[b]**: Determined by chiral HPLC analysis; **[c]**: Determined by ^{1}H-NMR of the crude reaction mixture using an internal standard (1,4 Dimethoxybenzol).

With the use of $ZnCl_2$ 79% yield and 5 *ee* were obtained (entry 1). In all other cases no stereoinduction was observable (entries 2-6). However, with $PbCl_2$ an increased yield of 87% was obtained (entry 6). Nevertheless, the application of $CoCl_2 \cdot 6H_2O$ delivers the best results in terms of stereoselectivity.

Based on the knowledge that the 4-substituted *L*-proline derivatives **142** and **143** never have been utilized in the Baylis-Hillman reaction, their impact on the reaction was investigated. Furthermore, the influence of additional $CoCl_2 \cdot 6H_2O$ was quantified (Table 23).

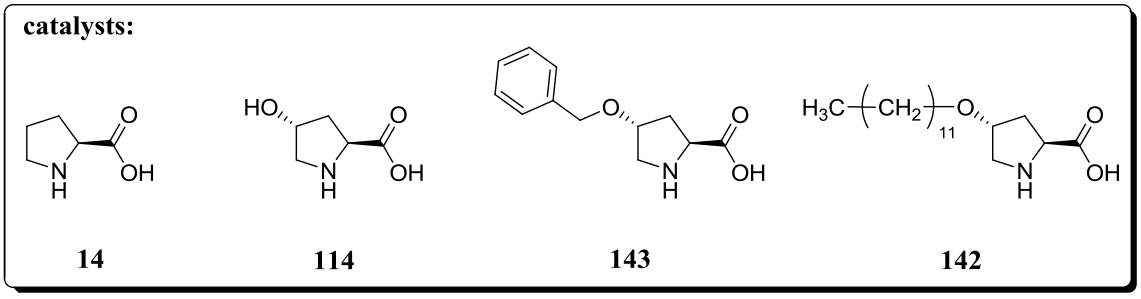
Table 23. Applying the the 4-substituted *L*-proline derivatives **114**, **142** and **143** to the Baylis-Hillman reaction of *p*-nitrobenzaldehyde (**149**) and MVK (**124**).



149 **124** **195** **202**

entry [a]	catalyst	metal	*ee* 195 [%] [b]	conversion [%] [c]	yield 195 [%] [c]	yield 202 [%] [c]
1	**14**	$CoCl_2 \cdot 6H_2O$	12	86	42	traces
2		-	*rac.*	99	79	
3	**114**	$CoCl_2 \cdot 6H_2O$	7	99	44	traces
4		-	*rac.*	99	98	
5	**143**	$CoCl_2 \cdot 6H_2O$	17	90	22	traces
6		-	*rac.*	98	94	
7	**142**	$CoCl_2 \cdot 6H_2O$	17	90	32	traces
8		-	*rac.*	100	99	

[a]: 0.5 mmol of **149** (76 mg), 1.5 mmol of **124** (127 µL), 30 mol% catalyst, 30 mol% imidazole (10 mg), 15 mol% $CoCl_2 \cdot 6H_2O$ (18 mg), DMF/H_2O (v/v = 9:1) (c = 1 mol/L); **[b]**: Determined by chiral HPLC analysis; **[c]**: Determined by ^{1}H-NMR of the crude reaction mixture using an internal standard (1,4 Dimethoxybenzol).



By the use of *L*-proline (**14**) and 4-substituted *L*-proline derivatives **114**, **142** and **143** in combination with $CoCl_2 \cdot 6H_2O$ yields in the range of 40% were obtained (entries 1, 3, 5, 7), however without additional metal the yield was drastically improved up to 99% (entries 2, 4, 6, 8). Despite the decreased yield, $CoCl_2 \cdot 6H_2O$ also showed a positive effect, namely on the *ee* which was slightly increased from a *racemic* level up to 17%, demonstrating the ability of the additional metal to weakly induce chirality in the product. The results might be explained by the fact that the catalyst acts as chiral surfactant and, therefore, is assembling with MVK (**124**) and the aldehyde in water through hydrophobic interactions. Thus, the

reaction proceeded efficiently in the aggregated organic phase[126] to obtain the Baylis-Hillman product **195** in high yield but low enantioselectivity. The slightly increased *ee* at the costs of a drastically decreased yield by the use of additional metal forced the decision to carry out no further efforts in this direction.

5.3 Summary

In summary, a novel catalytic system using *L*-proline (**14**) and its derivatives **114**, **142** and **143** in combination with metal salts should be developed and quantified under the aspect of its effect on the reactivity and stereoselectivity in the Baylis-Hillman reaction. The additional metal led to a drastically decreased reactivity but a slightly enhanced stereoinduction, which in consequence speaks for the *in situ* formation of a (*L*-proline)$_2$/Co(II)-complex during the reaction. The application of *L*-proline derivatives **114**, **142** and **143** without additional metal gave *racemic* product mixtures, however the reactivity was significantly improved up to 99% compared to *L*-proline (**14**).

C Organocatalysis of Azabox Ligands in the Presence of $CoCl_2 \cdot 6H_2O$

1. Introduction

1.1 The Discovery of Box Ligands as Versatile Applicable Structure in Catalysis

Bis(oxazoline) ligands **206** are suitable to coordinate a broad variety of different metals, and thus are able to induce a high order of stereoselectivity in different reactions. Therefore, they belong to one of the most successful groups of ligands in enantioselective synthesis. These ligands consist of two identical oxazoline rings which are linked *via* a carbon atom at the 2-position with two identical substituents different from hydrogen.[176] Variations can be obtained by introducing various moieties at the 4-position of the oxazoline rings. It is also important to point out that the pioneering studies in this area were done by Brunner *et al.*[177] who were the first to combine oxazoline ligands **203** with different metals and to apply the complexes in asymmetric catalysis. Related structures to the bis(oxazolines) **206** are represented by the semicorrin **204**[178] and the aza-semicorrin structure **205**[179] which both were developed by Pfaltz and co-workers in the late eighties and early nineties, to serve as ligands in enantioselective synthesis. Simultaneously, Evans *et al.*[180] and Masanume and co-workers[181] utilized different bis(oxazoline) ligands **206** in combination with copper for the asymmetric cyclopropanation of olefins with excellent results in terms of stereoselectivity.

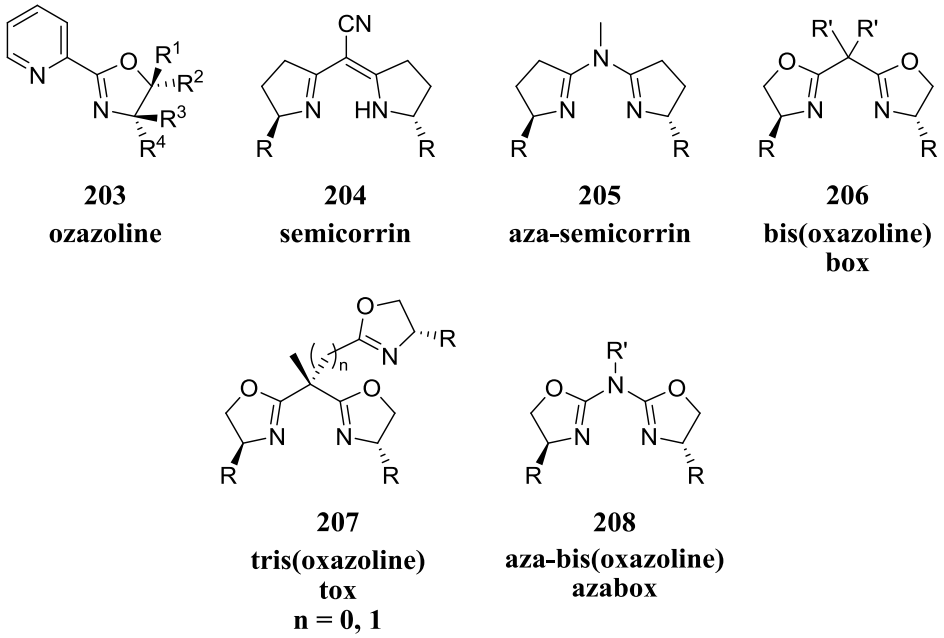
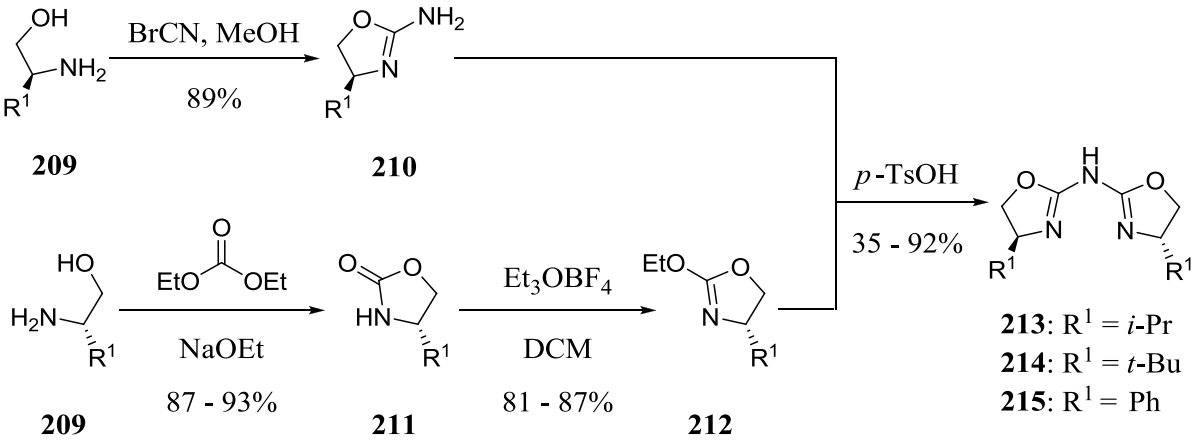


Figure 16. General structure of different *N*-containing bi- and tridentate ligands for catalysis.

Initiated by these encouraging results, bisoxazolines **206** were applied to a wide field of different catalytic transformations, in combination with various metals, for example aziridination reactions, aldol reactions, Michael and Mukaiyama-Michael reactions, allylic substitution reactions, radical reactions, Diels-Alder reactions, hetero Diels-Alder reactions and 1,3-dipolar cycloaddition reactions, to mention only a few.[176] Moreover, a slight modification of the ligands was introduced by Tang *et al.*[182] and Gade *et al.*[183] who installed a third coordination site at the bis(oxazoline) **206** to give tris(oxazoline) structure **207**. A further modification of bis(oxazolines) **206** was done by Reiser *et al.* by linking two oxazoline rings not *via* a carbon atom but *via* a nitrogen atom giving rise to aza-box structures **208**. A decisive advantage compared to the bis(oxazoline) ligands **206** is the center nitrogen atom which could serve as additional coordination site for various metals and also offers the possibility to control its Lewis acidity by functionalization with different electron withdrawing or electron donating groups.[184] The synthesis is straight forward and was optimized by Reiser and co-workers (Scheme 28).[185]



Scheme 28. Improved synthesis of aza-bis(oxazoline) ligands **213-215** starting from simple 1,2-diamino alcohol **209**.

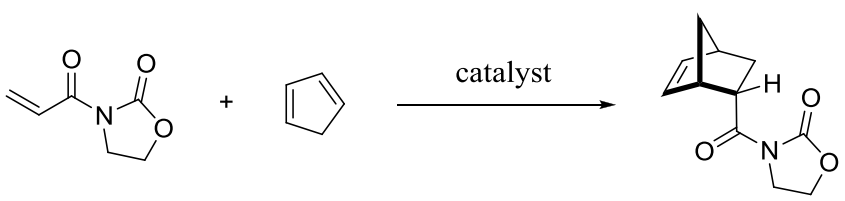
The synthesis starts from chiral 1,2-amino alcohol **209** which offer a convenient possibility to prepare enantiomerically pure oxazolines **210** and **212** from the chiral pool. Amino oxazoline **210** is obtained by reaction of amino alcohol **209** with *in situ* formed cyanogen bromide in one step with excellent yields. 2-Ethoxy oxazoline **212** is accessible by treating **209** with diethylcarbonate to yield oxazolidinone **211**, which subsequently is alkylated by the usage of Meerwein's reagent to furnish **212** in excellent yields over two steps. The final step, the coupling of **210** and **212**, proceeds by acid catalysis to give **213-215** in reasonable yield. The functionalization of the central nitrogen atom of **213-215** is carried out by deprotonation of the nitrogen atom with *n*-butyl lithium and trapping of the lithiated species with an

electrophile. These derivatives have found application as ligands in different stereoselective reactions including asymmetric benzoylations[186], reductions of α,β-unsaturated carbonyl compounds[187] and enantioselective Henry reactions[188].

1.2 Azabox/$CoCl_2 \cdot 6H_2O$ as Powerful Catalyst

Box ligands **206** and azabox ligands **208** are able to coordinate many metals, but they are used most commonly with copper(I)- or copper(II)-salts.[176, 186, 188-189] However, also cobalt-salts, with different counter ions, were applied to enantioselective catalysis in combination with box **206** and azabox ligands **208**. The first example is a Diels Alder reaction of amide **216** and cyclopentadiene **217**, which is catalyzed by a combination of box ligand and different metal salts (**219**-**222**) (Table 24). This reaction was studied by Evans *et al.* in 1999.[190]

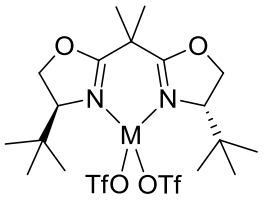
Table 24. Diels Alder reaction of amide **216** with cyclopentadien **217** catalyzed by a combination of box ligand and different metal salts (**219**-**222**).[190]



216 **217** **218**

entry	catalyst	*endo*/*exo*	*endo ee* [%]	yield [%]
1	**219**	98:2	98	86
2	**220**	90:10	50	85
3	**221**	95:5	38	85
4	**222**	90:10	40	75

catalyst:

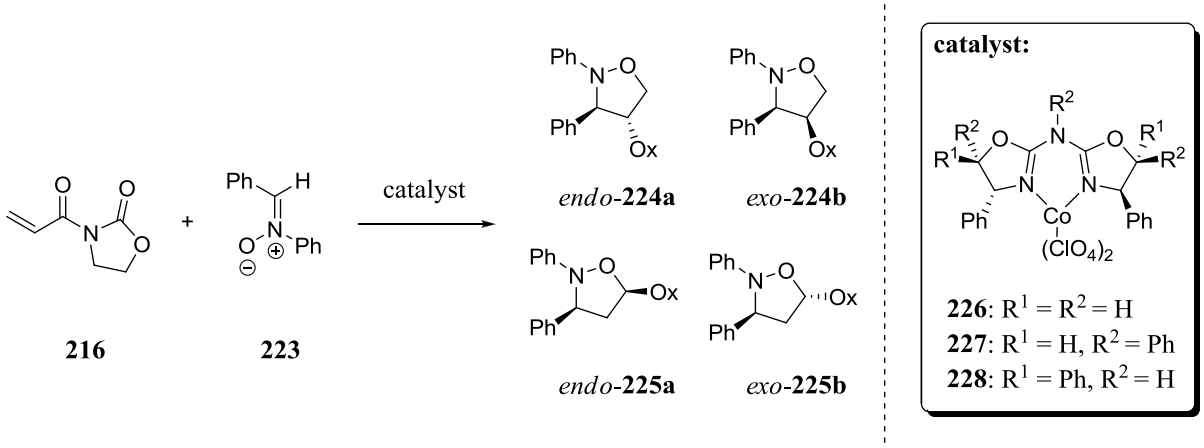


219 (M = Cu)
220 (M = Co)
221 (M = Zn)
222 (M = Ni)

The best metal/ligand combination is represented by box ligand and copper(II)triflate **219** giving a 98:2 *endo*/*exo* ratio, 98% *ee* of *endo* product and 86% yield. But also with cobalt(II)triflate a remarkable stereoinduction was achieved with a 90:10 *endo*/*exo* ratio, 50% *ee* of *endo* product and 85% yield.

Desimoni and co-workers investigated the 1,3 dipolar cycloaddition between acryloyloxazolidinone **216** and diphenylnitrone **223** catalyzed by a combination of different metals and azabox ligands (Table 25).[191]

Table 25. 1,3 dipolar cycloaddition between acryloyloxazolidinone **216** and diphenylnitrone **223** catalyzed by a combination of different metals and azabox ligands (**226**-**228**).[191]

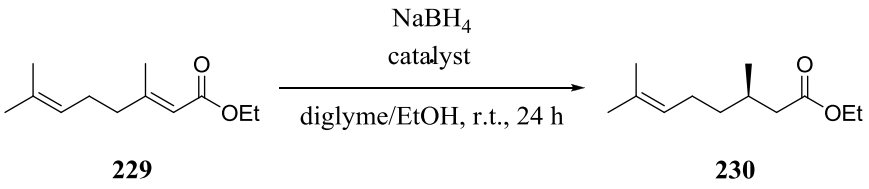


entry	catalyst	[224a+b]:[225a+b]	[224a:224b]	*endo* 224a *ee* [%] (config.)	*exo* 224b *ee* [%]	yield [%]
1	**226**	95:5	90:10	47 (3'*R*, 4'*S*)	40	quant.
2	**227**	91:9	44:56	68 (3'*S*, 4'*R*)	33	quant.
3	**228**	>98:<2	16:84	79 (3'*S*, 4'*R*)	-92	quant.

They also screened other metals *i.e.* Mg, Mn, Ni, Cu and Zn and took a closer look on the combination of three azabox ligands and cobalt(II)perchlorate (**226**-**228**), which gave excellent results in terms of reactivity and stereoselectivity. Furthermore, they were able to show that the counter ion of the metal and also the moieties at the azabox ligand play a crucial role in the stereoinductive process of product formation.

Moreover, enantioselective conjugated reductions of α,β-unsaturated carbonyl compounds employing various cobalt(II)-aza-bis(oxazoline)-complexes were carried out by Reiser *et al.* in 2005.[187] In this case $CoCl_2 \cdot 6H_2O$ was used as cobalt(II)-source (Table 26).

Table 26. Enantioselective conjugated reduction of α,β-unsaturated carbonyl compound **229** mediated by different cobalt(II)-aza-bis(oxazoline)-complexes **231**-**234**.[187]

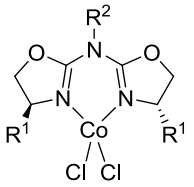


229 **230**

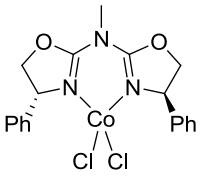
entry [a]	catalyst	*ee* [%] [b]	yield [%] [c]
1	**231**	0	12
2	**232**	96 (*S*)	82
3	**233**	-	0
4	**234**	96 (*R*)	86

[a]: 0.5 mmol of **229** (98 mg), 1.25 mmol of $NaBH_4$ (47 mg), 2.8 mol% azabox ligand, 2.5 mol% $CoCl_2 \cdot 6H_2O$ (6 mg), diglyme/EtOH (v/v = 1:1) (c = 0.25 mol/L); **[b]**: Determined by chiral HPLC analysis **[c]**: Isolated yield.

catalyst:



231: R^1 = *i*-Pr, R^2 = H
232: R^1 = *i*-Pr, R^2 = Me
233: R^1 = *t*-Bu, R^2 = Me

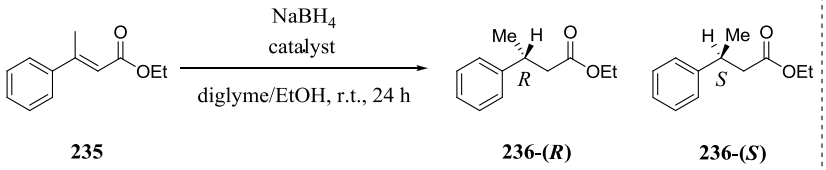


234

By comparing entries 1 and 3 in Table 26 it is getting clear that complexes **231** and **233** show only moderate to none catalytic efficiency on the reduction of ester **229**. However, way better results were achieved with the catalysts **232** and **234** which gave 82% and 86% yield, respectively and *ee*s' of 96% in each case (entries 2 and 4). This observation shows the huge impact of the moieties on the oxazoline rings and their configuration at the chiral center on the outcome of the reaction.

A similar investigation was done by Fraile *et al.* in 2010 who also examined an enantioselective conjugated reduction of ester **235** with $NaBH_4$ as reductant catalyzed by various azabox ligands in combination with cobalt(II) (**232**-**234**, **237**-**239**) (Table 27). In addition they also examined the recyclability of the catalysts.[192]

Table 27. Enantioselective conjugated reduction of ester **235** mediated by $NaBH_4$ and a combination of box and azabox ligands, respectively, and cobalt(II) (**232**-**234**, **237**-**239**).[192]

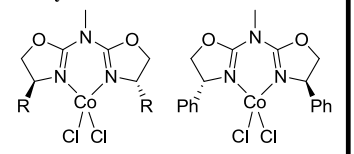


235 **236-(*R*)** **236-(*S*)**

entry [a]	catalyst	*ee* [%] [b]	yield [%] [c]
1	**232**	72 (*R*)	83
2	**233**	14 (*R*)	22
3	**234**	91 (*S*)	82
4	**237**	8 (*S*)	14
5	**238**	27 (*R*)	21

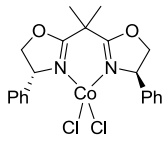
[a]: 1.0 mmol of **235**, 2.5 mmol of $NaBH_4$ (47 mg), 2.8 mol% ligand, 2.5 mol% $CoCl_2$, diglyme/EtOH (v/v = 1:1) (c = 0.25 mol/L); **[b]**: Determined by gas chromatography (*β*-cyclodex column); **[c]**: Determined by gas chromatography.

catalyst:

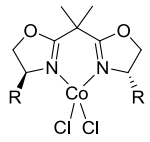


232: R = *i*-Pr
233: R = *t*-Bu

234



237



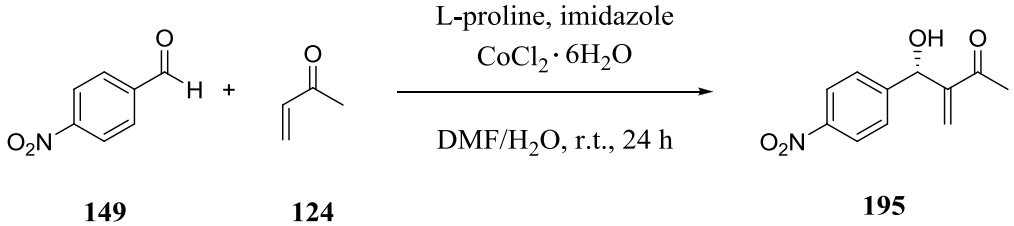
238: R = *i*-Pr
239: R = *t*-Bu

They examined different box (**237**-**239**) and azabox ligands (**232**-**234**) in combination with $CoCl_2$. The best results were obtained using azabox catalyst **234** giving **236**-(*R*) in excellent yield and enantioselectivity (entry 3). Almost identical results were achieved by utilizing **232** yielding the opposite enantiomere **236**-(*S*) in good stereoselectivity and yield (entry 1). This observation is in accordance with the results obtained by Reiser *et al.* and elucidates that the choice of the right ligand is crucial for the catalytic efficiency. These are the only combinations of cobalt(II) and box or azabox ligands applied in catalysis so far.

2. Azabox/$CoCl_2 \cdot 6H_2O$ as Catalyst in the Baylis-Hillman Reaction

In the previous described investigation of the Baylis-Hillman reaction in chapter B (5.2 *L*-Proline/Metal-Complexes as Novel Catalysts in the Baylis-Hillman Reaction) a few benchmark experiments were performed, which revealed some interesting findings in regard to the influence of the single catalytic components on the reaction. These results are summarized in Table 28.

Table 28. Benchmark reactions in the *L*-proline (**14**) and imidazole (**196**) catalyzed Baylis-Hillman reaction of *p*-nitrobenzaldehyde (**149**) and MVK. (**124**).



149 **124** **195**

entry [a]	*L*-Proline	imidazole	$CoCl_2 \cdot 6H_2O$	*ee* [%] [b]	conversion [%] [c]	yield [%] [c]
1	30 mol%	30 mol%	-	*rac.*	99	79
2	30 mol%	30 mol%	15 mol%	13	98	42
3	30 mol%	-	-	n.d.	14	8
4	30 mol%	-	15 mol%	n.d.	14	5
5	-	-	15 mol%	-	4	0
6	-	30 mol%	-	-	99	40
7	-	30 mol%	15 mol%	-	95	65

[a]: 1 mmol of **149** (151 mg), 3 mmol of **124** (253 µL), 30 mol% *L*-Proline (35 mg), 30 mol% imidazole (20 mg), 15 mol% of $CoCl_2 \cdot 6H_2O$ (36 mg), DMF/H_2O (v/v 9:1) (c = 1 mol/L); **[b]**: Determined by chiral HPLC analysis; **[c]**: Determined by ^{1}H-NMR of the crude reaction mixture using an internal standard (1,4 Dimethoxybenzol); **n.d.** = not determined.

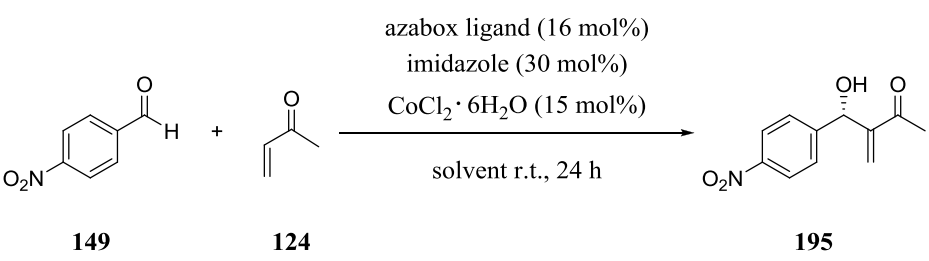
The experiments in which imidazole (**196**) was used (entries 1, 2, 6-7) showed complete conversion and the best yields. However, not only imidazole (**196**) has an impact but also $CoCl_2 \cdot 6H_2O$ is influencing the reaction to some extent when comparing entries 6 and 7. Presumably, owing to its Lewis acidity, cobalt(II) is suitable to coordinate the carbonyl oxygen atom of MVK (**124**), thus increasing the activation of the α,β-unsaturated π-system, complementary to the activation through imidazole (**196**), for an nucleophilic attack to *p*-nitrobenzaldehyde (**149**).[††] This led to the idea that a combination of $CoCl_2 \cdot 6H_2O$ and a chiral ligand could generate an enhancement in both, reactivity and stereoselectivity in the Baylis-Hillman reaction.

Due to the fact that the Reiser group has put great effort in the development of new catalysts based on azabox ligands for different applications in asymmetric catalysis, the idea was to combine these ligands with Co(II) salts. Based on the knowledge that the combination of

[††] For the mechanism of the Baylis-Hillman reaction and the role of imidazole see chapter B (5.1 Introduction), Scheme 26, page 76.

azabox ligands with $CoCl_2 \cdot 6H_2O$ in asymmetric catalysis has been successful in a few cases, the aim was to develop a protocol for a stereoselective Baylis-Hillman reaction catalyzed by a combination of azabox ligands and $CoCl_2 \cdot 6H_2O$. Therefore, first the reaction conditions used by Reiser *et al.*[187] in the conjugated enantioselective reduction of α,β-unsaturated ketones were transferred to the Baylis-Hillman reaction (Table 29).

Table 29. Application of a combination of $CoCl_2 \cdot 6H_2O$ and azabox ligands to the Baylis-Hillman reaction based on the results of Reiser *et al.*.[187]

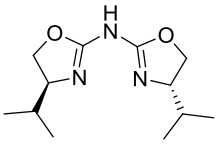


149 **124** **195**

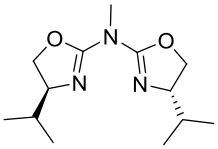
entry [a]	solvent	azabox ligand	*ee* [%] [b]	yield [%] [c]
1	DMF/H_2O (v/v = 9:1)	**213**	*rac.*	74
2	diglyme/EtOH (v/v = 1:1)	**213**	*rac.*	58
3	EtOH	**213**	*rac.*	54
4	MeOH	**213**	- 8	37
5	diglyme/EtOH (v/v = 1:1)	**240**	*rac.*	62
6	diglyme/EtOH (v/v = 1:1)	**241**	*rac.*	60

[a]: 1.0 mmol of **149** (151 mg), 3.0 mmol of **124** (253 µL), 16 mol% azabox ligand, 30 mol% imidazole (20 mg), 15 mol% $CoCl_2 \cdot 6H_2O$ (36 mg), solvent (c = 1 mol/L); **[b]**: Determined by chiral HPLC analysis **[c]**: Determined by ^{1}H-NMR of the crude reaction mixture using an internal standard (1,4 Dimethoxybenzol).

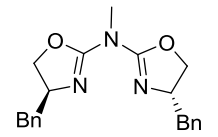
azabox ligands:



213



240

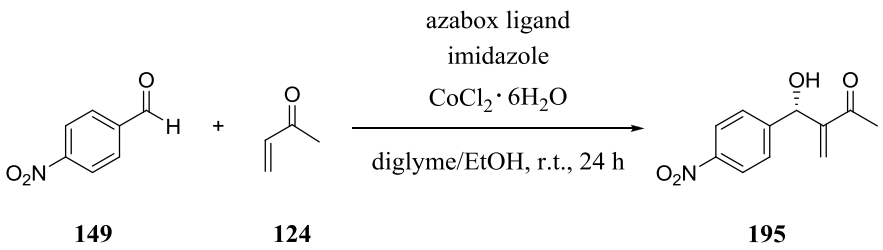


241

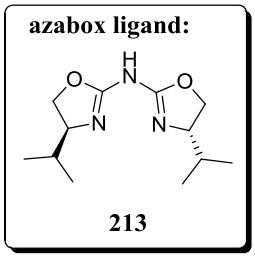
For the screening three different azabox ligands were used, namely ligand **213**, with (*S*,*S*)- configured *i*-Pr moieties and a secondary amine in the C_2-center of symmetry, as well ligands **240** and **241** with a methylated amine functionality in the C_2-center of symmetry. Ligands **240** and **241** exhibit (*S*,*S*)-configured *i*-Pr and benzyl moieties, respectively, at the oxazoline rings. As can be seen in entries 1-4, different solvents and solvent combinations were tested for the catalytic system. Moreover, the amount of cobalt(II)-salt was slightly reduced (15 mol%) compared to the amount of azabox ligands (16 mol%) to achieve full complexation of the metal. The initially used amount of 30 mol% imidazole was maintained as used in the *L*-proline (**14**)/imidazole (**196**) catalyzed Baylis-Hillman reaction in chapter B. The best yield of 74% was obtained with a mixture of DMF/water 9:1 (entry 1). With regard to stereoselectivity only a small effect was observable by the use of MeOH (entry 3) which is

reflected in an *ee* of 8%, whereas in all other cases only *racemic* product mixtures were obtained. Owing to the mentioned influence of the moieties at the oxazoline rings, two other azabox ligands were tested in this reaction, namely catalyst **240** (entry 5) and **241** (entry 6). What is intriguing by comparing entries 2, 5 and 6 is the fact that in all cases reasonable yields were obtained, however enantioselectivities were low. This presumably is caused by the weak Lewis acid coordination of the azabox/Co(II)-complex to the MVK (**124**). To get a deeper insight into the mechanism a few benchmark reactions were carried out (Table 30).

Table 30. Benchmark reactions of the Baylis-Hillman reaction catalyzed by a $CoCl_2 \cdot 6H_2O$ in combination with azabox ligand **213**.



149 **124** **195**



213

entry [a]	$CoCl_2 \cdot 6H_2O$	azabox ligand	imidazole	*ee* [%] [b]	yield [%] [c]
1	-	-	30 mol%	-	49
2	-	**213**	30 mol%	*rac.*	29
3	15 mol%	-	30 mol%	-	17
4	15 mol%	**213**	-	n.d.	0
5	15 mol%	**213**	30 mol%	*rac.*	58

[a]: 1.0 mmol of **149** (151 mg), 3.0 mmol of **124** (253 µL), 16 mol% azabox ligand, 30 mol% imidazole (20 mg), 15 mol% $CoCl_2 \cdot 6H_2O$ (36 mg), diglyme/EtOH (v/v = 1:1) (c = 1 mol/L); **[b]**: Determined by chiral HPLC analysis **[c]**: Determined by ^{1}H-NMR of the crude reaction mixture using an internal standard (1,4 Dimethoxybenzol); **n.d.** = not determined.

As one can see by looking at Table 30, one catalytic species was left out in every test reaction. Entry 1 elucidates that also imidazole alone is able to generate a certain amount of product **195**. Withtout the use of imidazole (**196**) (entry 4) no product was formed during the reaction wich revealed the importance of imdiazol (**196**) in the catalytic process. A combination of imidazole (**196**) and $CoCl_2 \cdot 6H_2O$ (entry 3) led to a decreased yield of 17% compared to pure imidazole (**196**), for which 49% yield was accomplished. This supports the assumption of a complex formation of imidazole (**196**) and $CoCl_2 \cdot 6H_2O$ already described in chapter B (page 77 f.) resulting in a highly decreased catalytic activity. A combination of azabox ligand **213** and imidazole (**196**) gave 29% yield (entry 2). The best results in terms of reactivity were achieved by using all three components together (entry 5), however, without any

stereoinduction. In the latter case the improved yield is probably due to the fact that the monodentated imidazole (**196**) is available as catalyst, because $CoCl_2 \cdot 6H_2O$ is completly bound by the bidentate azabox ligand **213**. The low enantioselectivity might be explained by the weak Lewis acid coordination of the azabox/Co(II)-complex through only one binding site to the MVK (**124**). This lead to the assumption that a substrate with two binding sites (*e.g.* a 1,3-dicarbonyl function) should improve the coordination of the azabox/Co(II)-complex to the substrate and therefore induce a higher stereoinduction.

3. Summary and Outlook

In summary, a new protocol for the Baylis-Hillman reaction of MVK (**124**) and *p*-nitrobenzaldehyde (**149**) catalyzed by a combination of imidazole (**196**), azabox ligands and Co(II) should be developed. However, no stereoinduction with moderate yields were obtained in this transformation. These results were not fully understood so far and further experiments have to be carried out to elucidate possible reasons for the low catalytic activity of the imidazole (**196**) and azabox/Co(II) combination.

D 1,2-Diamino Alcohols – Synthesis and Applications in Catalysis

1. Introduction

1.1 Primary Amines – Often Underestimated Catalysts with Unique Properties

Since the remarkable discovery of small organic molecules, mainly amino acids, like alanine, glycine or especially proline to catalyze different carbon-carbon bond forming transformations in a chiral fashion, *e.g*. aldol reactions or Michael additions, it was of enormous interest for a great number of chemists to push research forward in this promising field. The advantages of amino acids in C–C bond forming procedures are huge compared to other methodologies, *e.g*. metal catalysis, due to their easy accessibility, their robustness against external influences like air or moisture, as well their environmental friendliness and versatile applicability. Currently, one of the most successful catalysts in this area is *L*-proline (**14**), which is utilized in a wide range of various asymmetric reactions.[150b] Based on the heavily employed chiral, secondary amines, primary amines were neglected over years, which in big parts was due to their disadvantageous imine-enamine equilibria.[116] However, primary amino acids were already studied in early reports of the 1970s in the *intramolecular* Hajos-Parrish-Eder-Sauer-Wiechert reaction[5, 193] yielding the product in almost the same range like *L*-proline (**14**), even so the big potential of these promising catalysts passed unnoticed, till the early years of the 21th century. Recently, primary amines again attracted great attention as a new class of catalyst for stereoselective, organocatalytic reactions, because of their primary amine function which more likely than the secondary pyrrolidine moiety of proline has shown an unique and undiscovered reactivity and stereoselectivity in various asymmetric reactions.[194] Catalytic reactions with primary amines can be divided in two big groups of activation modes, on the one hand the iminium catalysis and on the other hand the enamine catalysis.[151a] The term iminium catalysis refers to the lowering of the LUMO energy, leading to an increased electrophilicity and acidity, whereas enamine catalysis ends up in the formation of a nucleophilic enamine species which causes an enhancement of the HOMO energy.[151a] Generally speaking, aldehydes and ketones are activated *via* enamine formation, whereby α,β-unsaturated carbonyl compounds are activated by iminium-ion formation.[116] The iminium activation displays a big field of organocatalysis including well-known reactions, like Friedel-Crafts alkylations[57], Michael additions of α,α-dicyanoalkanes[56] or cyclic 1,3-dicarbonyls[55, 195] to α,β-unsaturated ketones, [4+2] cycloadditions[45, 196], [2+2] reactions[197], 1,3-dipolar cycloadditions[198],

transfer hydrogenations[199], as well as aza-Michael additions[58]. Also enamine catalysis, is a huge part of organocatalytic transfomations catalyzed by different primary amines, including Michael additions of aldehydes and ketones to nitro olefins[32-35, 200], Mannich reactions[23, 201], α-amination of aromatic ketones[202] and especially aldol reactions[8b, 14, 23b, 203]. In these reactions various primary amines were used, some examples are displayed in Figure 17.

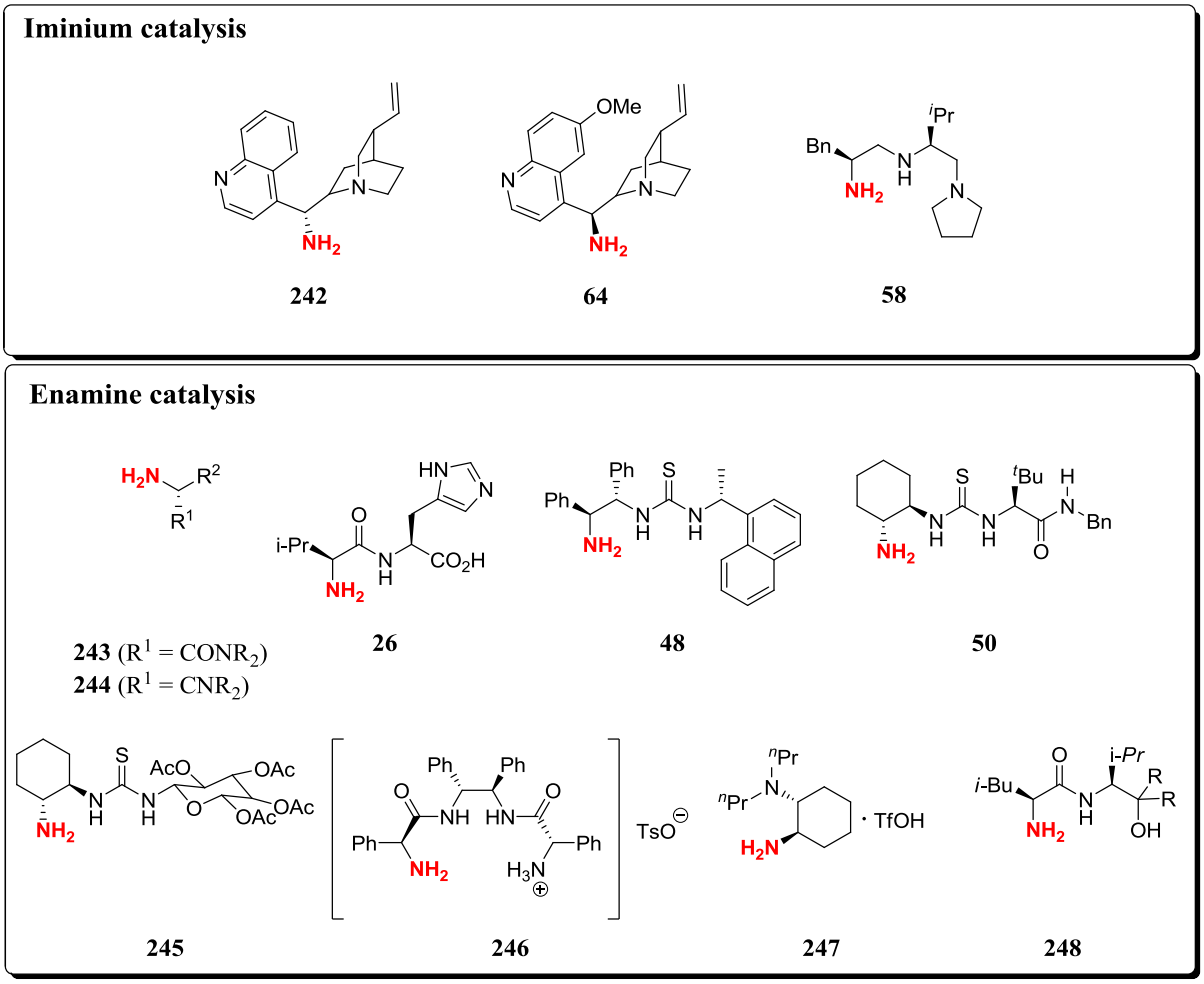
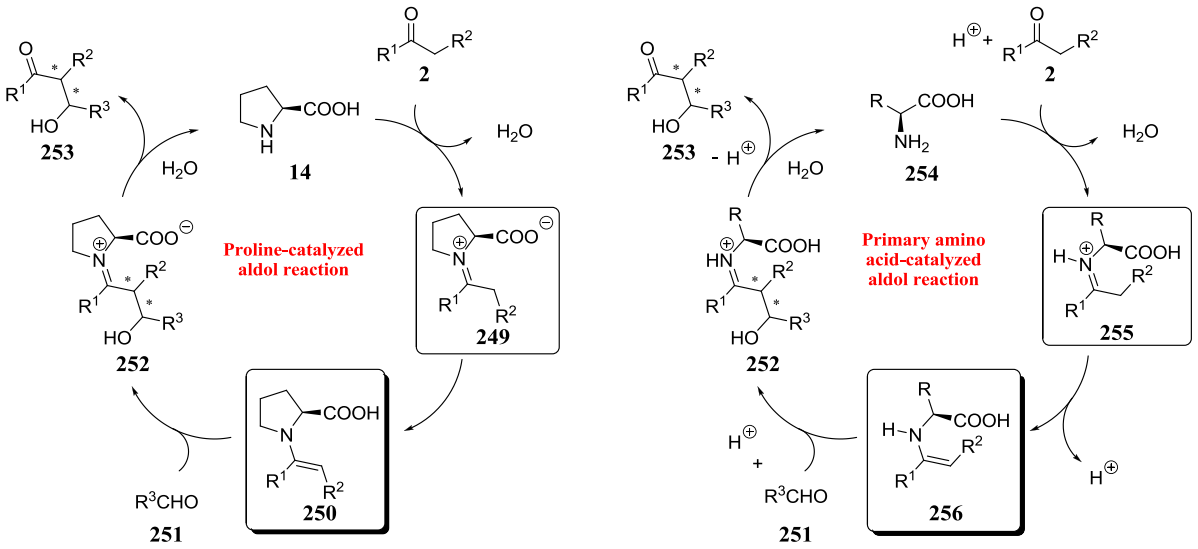


Figure 17. Selected examples of primary amines which were applied in organocatalysis.[116]

By looking at Figure 17 it quickly becomes clear that there is a wide range of primary chiral amines which were used in organocatalytic transformations to date, most of them based on naturally occurring compounds like different cinchonine structures **64** and **242**. Another big class is presented by triamines **58**, dipeptides like **26**, or as well 1,2-amide alcohols **248**. Moreover, different primary amino acids **243** and **244** are prone for organocatalysis and thus were often used. Furthermore, chiral primary amine-thiourea structures like **48, 50** and **245** also found their application in this field. However, also exceptional examples like the primary cation salt **246** or triflate-containing simple chiral primary amine catalyst **247** were also utilized in this type of reactions. These examples revealing primary amino acids to be a

powerful but underestimated tool in asymmetric organic synthesis, and therefore it seemed worthwhile to work out the small but significant differences of primary and secondary amine catalysis. As example the general aldol reaction between ketone **2** and aldehyde **251**, on the left hand catalyzed by *L*-proline (**14**) and on the right hand catalyzed by an simple primary amino acid **254**, was chosen (Scheme 29).[194]



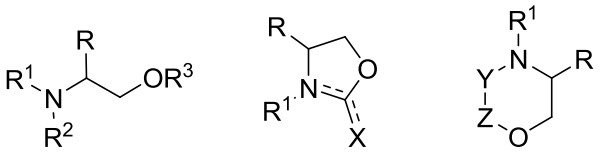
Scheme 29. *L*-Proline (**14**) and primary amino acid **254** promoted *intermoleculare* aldol reactions *via* the enamine mechanism.[194]

The advantage of a secondary amine like *L*-proline (**14**) over a primary amine **254** in catalysis was long attributed to the more stable enamine-intermediate **250** which is stabilized by hyperconjugation. In the case of the primary amine-catalyzed reaction, the iminium ion **255** is mainly formed and the tautomerization to the enamine **256** is the major problem. Recently, some progress was made in the mechanistic clarification and the optimization of primary amine-catalyzed aldol reactions by different working groups. It was found, that *e.g.* a small amount of water facilitates the formation of the required enamine **256** and therefore improves the reactivity and stereoselectivity of the aldol reaction.[203a, 204] Beside these points, the hydrogen derived from the primary amino group in the enamine **256** which is missing in the enamine **250** was assumed to presumably lead to an increased control in the enamine formation to attain a unique reactivity and selectivity surpassing earlier results with *L*-proline (**14**). Moreover, primary amino acid catalysis are ready available and provide a big structural flexibility for the design of a broad variety of chiral organocatalysts. This is reflected in the great number of publications on primary amino acid catalyzed aldol or Mannich reactions.[194] Thus, primary amino acid catalysis opens up new and promising ways

for developing novel and privileged organocatalysts in respect to both reactivity and stereoselectivity.

1.2 Acyclic 1,2-Amino Alcohols as Versatile Structural Motive in Catalysis

A big class of well-established ligands and catalysts in the area of primary, asymmetric amino catalysis are 1,2-amino alcohols (Figure 18). They found application as chiral auxiliaries and were used as ligands in various stereoselective transformations in both cyclic (**259**-**260**) and acyclic (**258**) variants.[205]



258 **259** **260**

Figure 18. Auxiliary systems based on amino alcohols.[189]

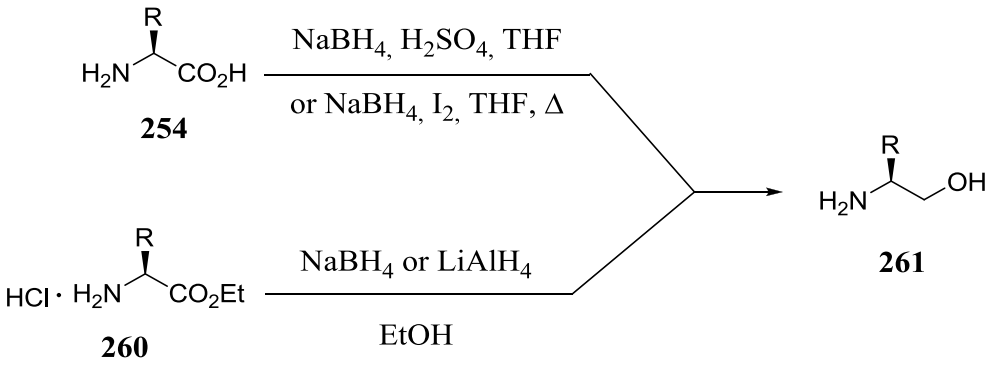
The additional alcohol function, which can serve as potential coordination site over hydrogen bonding, presumably may affect the reactivity and the stereoselectivity of a reaction. Moreover, they are easy accessible over the synthesis starting from epoxides or natural occurring amino acids which already contain the stereochemical information, thus an additional stereoinducing step can be circumvented. In principal, these derivatives are obtained from carbohydrates or amino acids.[189] All in all, these facts make 1,2-diamino alcohols an outstanding scaffold for new and easy fine-tunable catalysts.

1.3 1,2-Amino Alcohols – Easy Accessible Structures

There are two possible ways to synthesize chiral 1,2-amino alcohols. First, this goal can be achieved by the application of stereoinducing reactions during the preparation steps or second, the chiral starting materials like natural α-amino acids are employed. Based on the great variety, only the most important literature known synthesis strategies for acyclic, chiral 1,2-amino alcohols (**258**) are going to be presented in the following pages.[205]

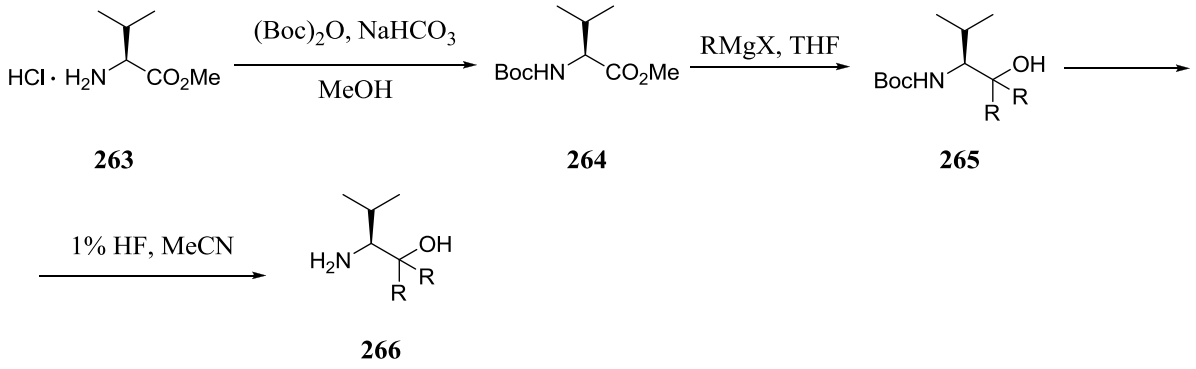
Synthesis Starting from Amino Acids

A straight forward way to get easy access to a large number of different acyclic 1,2-amino alcohols **261** is the use of readily available amino acids **254** or **260** and subsequently reducing their carboxylic acid function (Scheme 30).



Scheme 30. Synthesis of chiral 1,2-amino alcohols **261** by reducing different amino acids (**254** and **260**).

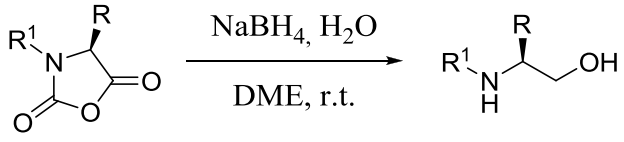
In the upper case in Scheme 30 a combination of sodium borohydride and sulfuric acid[206] or iodine[207], respectively, was used to reduce amino acids **254** to the corresponding 1,2-amino alcohols **261**, whereas in the lower example amino ester hydrochlorides **260** were reduced with $LiAlH_4$[208] or $NaBH_4$[209] to get the corresponding 1,2-amino alcohols **261** in excellent yields. Nevertheless, other reducing agents were also utilized, *e.g.* $LiAlH_4$[210], borane-methyl sulfide in the presence of boron trifluoride etherate[211] or lithium borohydride in the presence of trimethylsilyl chloride[212], to mention only a few. Another class of 1,2-amino alcohols are the more unusual double alkylated β-amino alcohols **266** which for instance can easily be obtained by a 3 step synthesis starting from hydrochloric *L*-valinate (**263**) (Scheme 31).[213]



263 **264** **265** **266**

Scheme 31. Synthesis of *β*-amino alcohols **266** starting from hydrochloric *L*-valinate (**263**).[213]

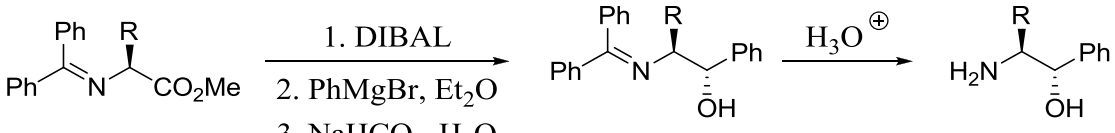
Another possibility to get access to *β*-amino alcohols **268** is the reduction of *N*-protected *N*-carboxyanhydrides **267** with $NaBH_4$ (Scheme 32).[214]



267 **268**

Scheme 32. Synthesis of *β*-amino alcohols **268** by reduction of *N*-protected *N*-carboxyanhydrides **267**.[214]

Yet another feasible approach is the conversion of *α*-amino esters to their corresponding imines (Scheme 33). In this specific example imine **269** was generated from benzophenone. Owing to the iminium functionality it is now possible to reduce the ester group to the aldehyde and subsequently react it with a Grignard reagent to form iminium **270**, which in the next step can be transferred to the 1,2-amino alcohol **271** through acid catalyzed cleavage of the benzophenone.[215]

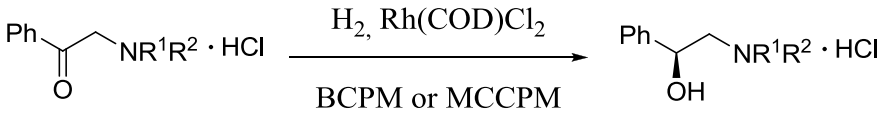


269 **270** **271**

Scheme 33. Reduction of imine **269** to imine **270** followed by acid catalyzed formation of 1,2-amino alcohol **271**.[215]

Synthesis Starting from other α-Amino Carbonyl Compounds

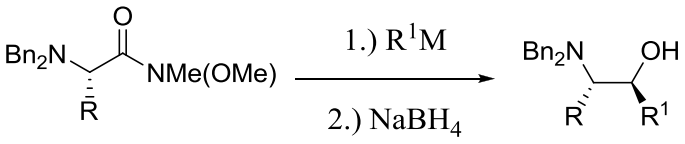
This method is based on the potential of α-carbonyl compounds to be reduced in a highly selective fashion as demonstrated for example in Scheme 34.[216]



272 **273**

Scheme 34. Stereoselective reduction of α-amino carbonyl compounds **272** to α-amino alcohols **273**.[216]

Furthermore, reductions of α-amino ketones **274** and amides **274** with $NaBH_4$ giving the corresponding 1,2-amino alcohols **275** in good stereoselectivities (Scheme 35).[217]

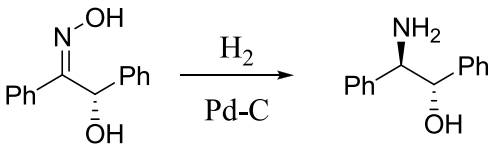


274 **275**

Scheme 35. Reduction of α-amino ketones **274** and amides **274** with $NaBH_4$ and different organometallic compounds to the corresponding 1,2-amino alcohols **275**.[217]

A variation is given by the application of different counterions in the reducing agent, *e.g.* by the use of $LiAlH_4$[218] and especially in combination with lithium iodide[219] *syn* selectivity is observed, whereas by the utilization of titanium[220] *anti* selectivity is observed.

Synthesis Starting from Alkoxy Carbonyl Compounds



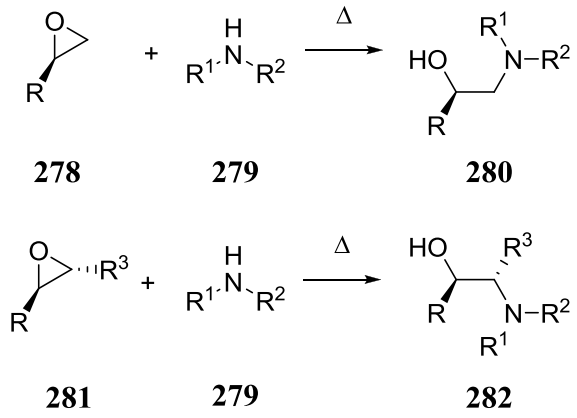
276 **277**

Scheme 36. Reduction of oxime derivative **276** to yield 1,2-amino alcohol **277**.[221]

Another suitable synthesis strategy giving rise to 1,2-amino alcohols **277** is the reduction of oxime derivatives **276** with hydrogen and palladium on active charcoal (Scheme 36).[221]

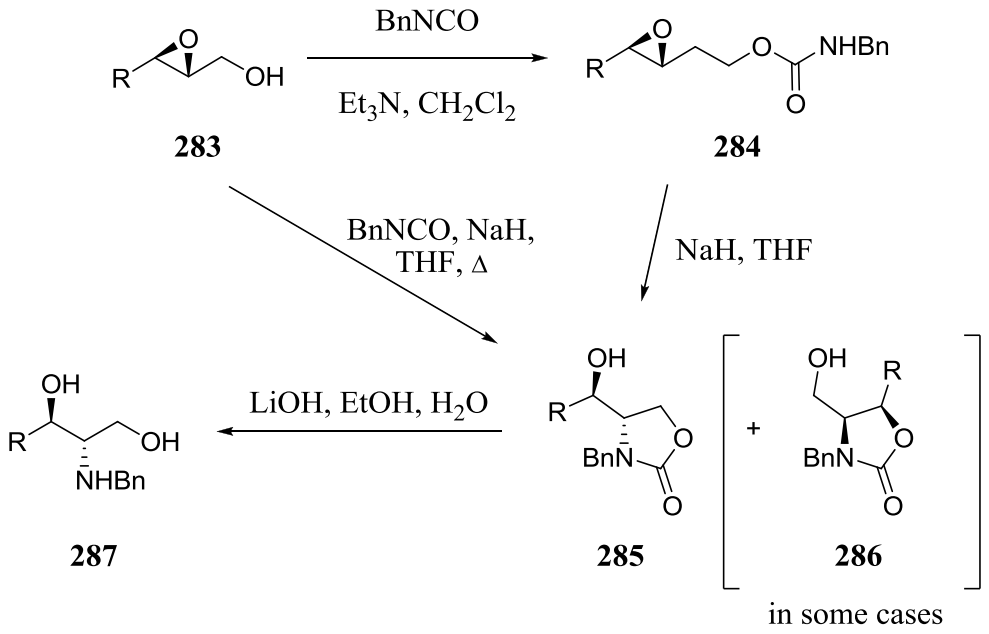
Synthesis Starting from Epoxides

Epoxides are the most utilized substance class for the preparation of 1,2-amino alcohols by reacting them with different nucleophiles.[222] A requirement for this method is the stereoselective synthesis of symmetrical or unsymmetrical epoxides through well precedented methodes. The nucleophilic attack in most cases takes place at the sterically less hindered site of the epoxide and is accompanied by inversion of the stereocenter by the use of primary and secondary amines[223] (Scheme 37) and their group I and II metal salts[202b, 223c, 224], whereas group IV and V amine compounds show the opposite trend by adding to the more hindered site of the epoxide.[225] The regioselectivity in unsymmetrical epoxides can also be controlled through reagent choice.[226]



Scheme 37. Reaction of symmetrical (**281**) and unsymmetrical (**278**) epoxides with primary and secondary amines (**279**) to obtain 1,2-amino alcohols (**280**, **282**).

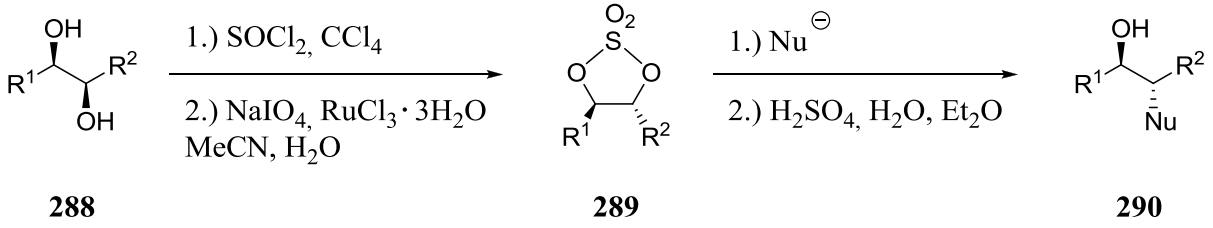
Moreover, there are more complex ring opening protocolls known in literature (Scheme 38). In this case, epoxides **283**, derived from allylic alcohols**,** are converted in an one-pot transformation first to the oxazolidinones **285** which subsequently are opened with LiOH to obtain the desired 2-amino 1,3-diols **287**.[227]



Scheme 38. One-pot transformation of epoxides **283** to the 2-amino 1,3-diols **287**.[227]

Synthesis Starting from Cyclic Sulfates

A further methodology, similar to the use of epoxides, is the application of 1,2-cyclic sulfates **289** for the synthesis of various 1,2-amino alcohols **290** (Scheme 39).

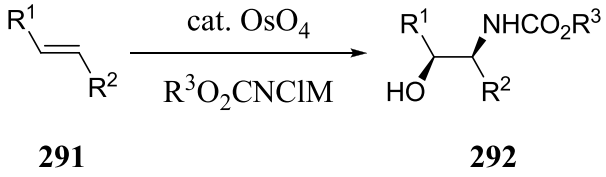


Scheme 39. Preparation of 1,2-amino alcohols **290** starting from 1,2-diols **288** *via* 1,2-cyclic sulfates **289**.[228]

The starting point of the synthesis are various 1,2-diols **288** which are transformed to the corresponding sulfates **289** by treating them with thionyl chloride and subsequent oxidation[229] of the sulfur, catalyzed by ruthenium chloride.[230] Followed by the ring opening with different nucleophiles, like azide and amines.[205, 228]

Synthesis via Other Methods

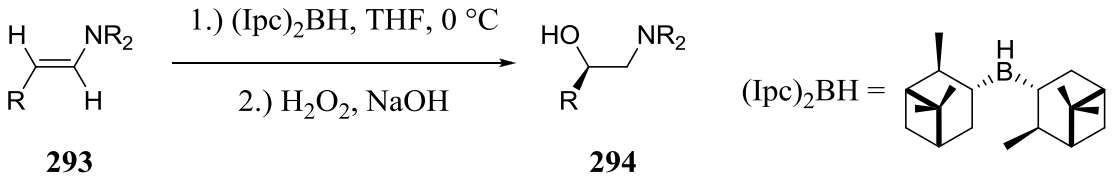
1,2-amino alcohols **292** could also be obtained *via* oxyamination of alkenes **291** (Scheme 40).[205, 231]



291 **292**

Scheme 40. Access to 1,2-amino alcohols **292** *via* oxyamination of alkenes **291**.[205, 231]

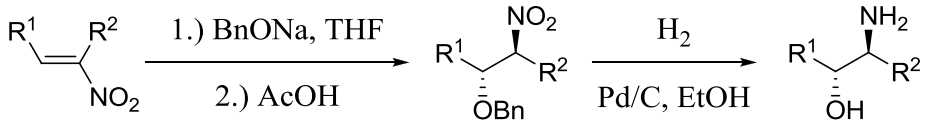
Moreover, various *β*-amino alcohols **294** in moderate enantioselectivity are accessible by hydroboration of aldehyde enamines **293** (Scheme 41).[232]



293 **294**

Scheme 41. Synthesis of *β*-amino alcohols **294** *via* hydroboration of aldehyde enamines **293**.[232]

Another elegant method for the preparation of *syn* 1,2-amino alcohols **297** is shown in Scheme 42.[233] The first step is the Michael addition of an alkoxide to the nitroolefin **295** to get compound **296**, which subsequently is reduced to the desired *syn* 1,2-amino alcohol **297**.



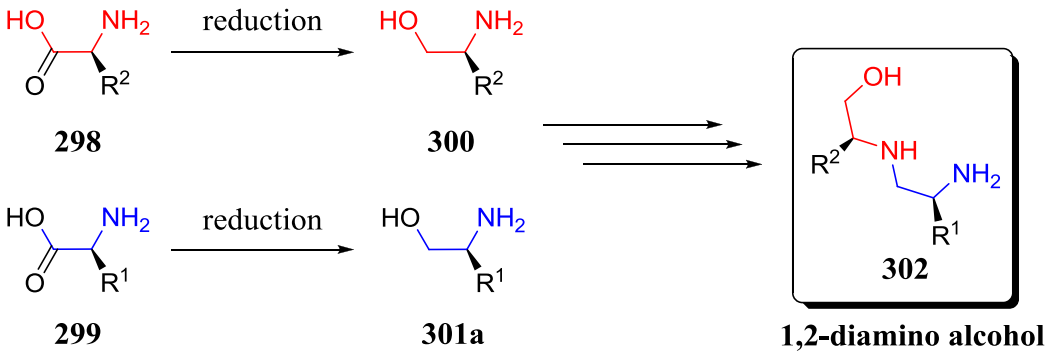
295 **296** **297**

Scheme 42. Synthesis route for *syn* 1,2-amino alcohols **297** starting from nitroalkenes **295**.[233]

2. Novel Synthesis Strategy for 1,2-Diamino Alcohols

2.1 Library of 9 novel 1,2-Diamino Alcohols

As chapter 1.3 reveals, there is an enormous pool of different and simple strategies to obtain 1,2-amino alcohols in every conceivable kind of stereochemistry and variations of moieties. This versatile adaptability shows why it is a perfect basic structure for developing novel ligands or catalysts for asymmetric organic transformations. Therefore, the concept was to develop new and easy tunable 1,2-amino alcohols which subsequently should be investigated for their impact in different catalytic processes. The first steps in this direction, including the synthesis strategy and the selection of the catalytic core structure itself, were done by Vinh Ngoc Huynh of the Reiser group. The idea was to maintain the structure of 1,2-amino alcohols and to extend them by an additional amine functionality to get easy access to the 1,2-diamino alcohols like **302** (Scheme 43).

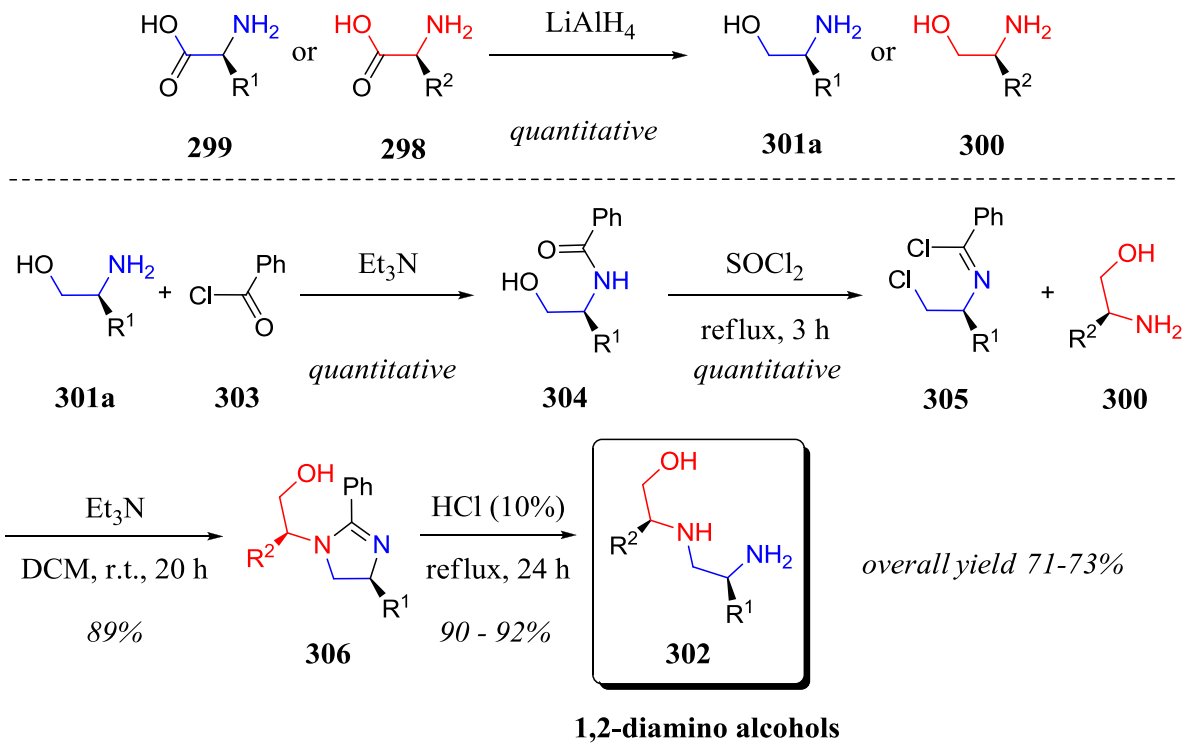


Scheme 43. Novel synthesis strategy for 1,2-diamino alcohols **302** by coupling of two 1,2-amino alcohols **300** and **301a** which are easy accessible by reduction of the corresponding amino acids **298** and **299**.

This introduction of an additional amino function can give rise to new catalytic properties and an enhanced reactivity and selectivity compared to the already known 1,2-amino alcohols. The additional amino group might act as an extra binding site for metals or substrates *via* hydrogen bonding or even enamine or iminium formation. The chosen synthesis route starting from natural occurring amino acids **298** and **299** also leaves open the possibility for further fine-tuning approaches on the 1,2-diamino alcohols **302** in a later stage of the synthesis, namely the modification of the primary and secondary amines or even the primary alcohol by attaching electron donating, electron withdrawing or bulky residues.

Scheme 44 shows the novel synthesis route developed by Vinh Ngoc Huynh to receive different 1,2-diamino alcohols **302** in an overall yield of 71-73% over 5 steps depending on the chosen amino alcohols **300** and **301a**. The amino alcohols **300** and **301a** can easily be

obtained in quantitative yield through reduction of the corresponding amino acids **298** and **299** with sodium borohydride. The next step is the benzyl protection of the primary amine function of **301a** to get the protected 1,2-amino alcohol **304** in quantitative yield. Subsequently, the alcohol and the amide moiety of **304** is chlorinated with the help of thionyl chloride to furnish **305** in quantitative yield, which subsequently is coupled with a second 1,2-amino alcohol **300** leading to the imidazole structure **306** in 89% yield. The ring-opening of the imidazole give rise to the desired 1,2-diamino alcohols **302** in excellent yields of 90-92%.



Scheme 44. Synthesis route of novel 1,2-diamino alcohols **302**.‡‡

In conclusion, this 5 step synthesis giving access to a library of nine novel 1,2-diamino alcohols **308**-**316** in an excellent overall yield of 71-73% (Figure 19).

‡‡ This synthesis strategy was developed by Vinh Ngoc Huynh of the Reiser goup.

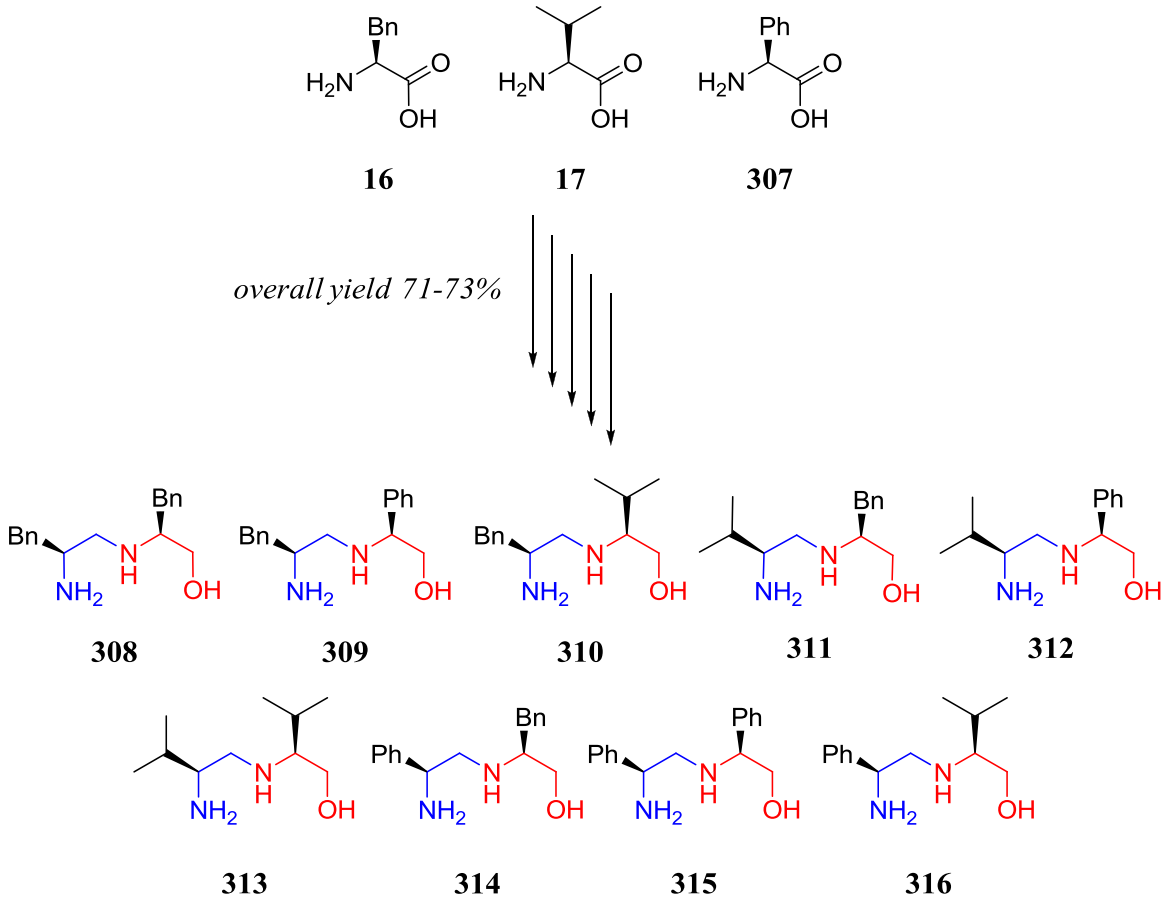
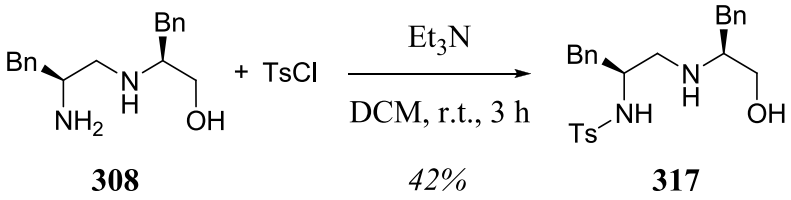


Figure 19. Library of nine 1,2-diamino alcohols **308-316** synthesized starting from the essential amino acids *L*-phenylalanine **16** or *L*-valine **17** and from the easy obtainable *L*-phenylglycine **307**.

With this small library at hand the task was to extend the functionalization not only at the backbone of the 1,2-diamino alcohols but also at the functional groups responsible for the coordination and reactivity. It was assumed that the moieties at the backbone of the 1,2-diamino alcohols did not have this much impact on reactivity and stereoinduction because they are only able to influence the outcome owing to their bulkiness, but not in respect to their electron distribution as it is the case for the amine and alcohol moieties. 1,2-diamino alcohol **308** was chosen as an model demonstrating the simple way to fine-tune these structures and subsequently applying them to catalysis.

2.2 Fine-Tuning Approaches on 1,2-Diamino Alcohol 308

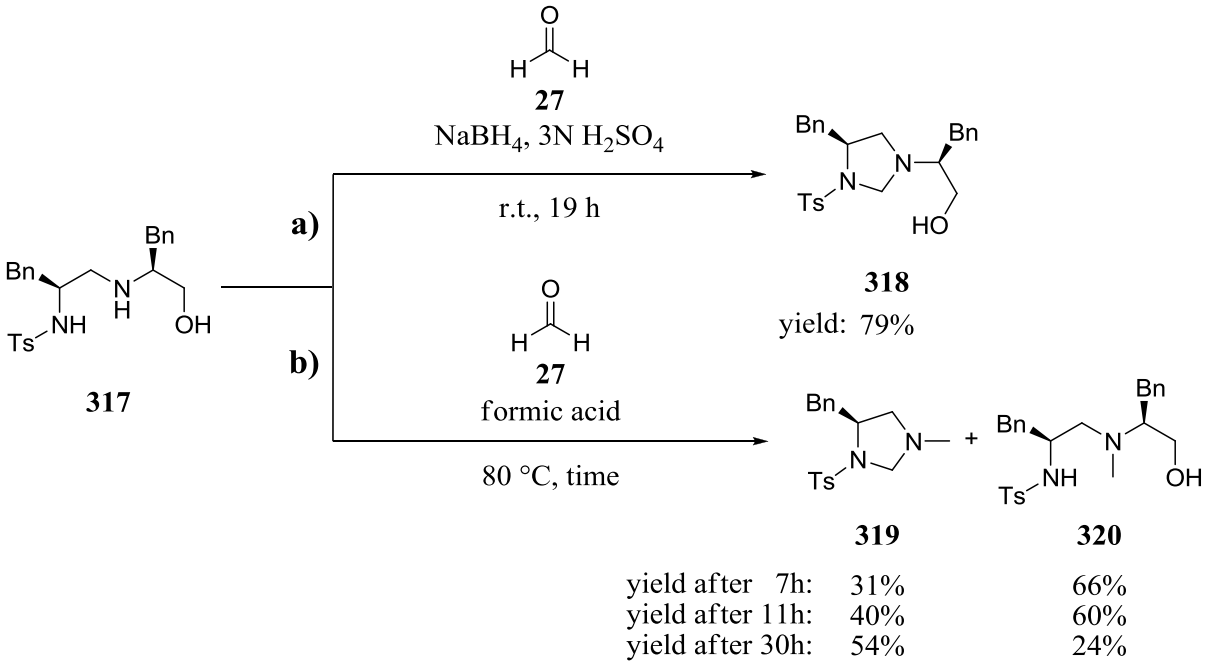
The 1,2-diamino alcohol **308** was chosen as starting point for this investigation and moreover taken this compound as a representative example should demonstrate a general way to fine-tune these structures. The first position which was chosen to be modified was the primary amine, due to its highest nucleophilicity and the lowest steric hindrance. It has been decided to carry out a tosylation at this position (Scheme 45). The assumed effect of this modification should lay in the increased acidity compared to the unmodified primary amine, which might lead to more facial coordination of various metals, while also increasing bulkiness at this center, which might improve the stereoinduction.



308 *42%* **317**

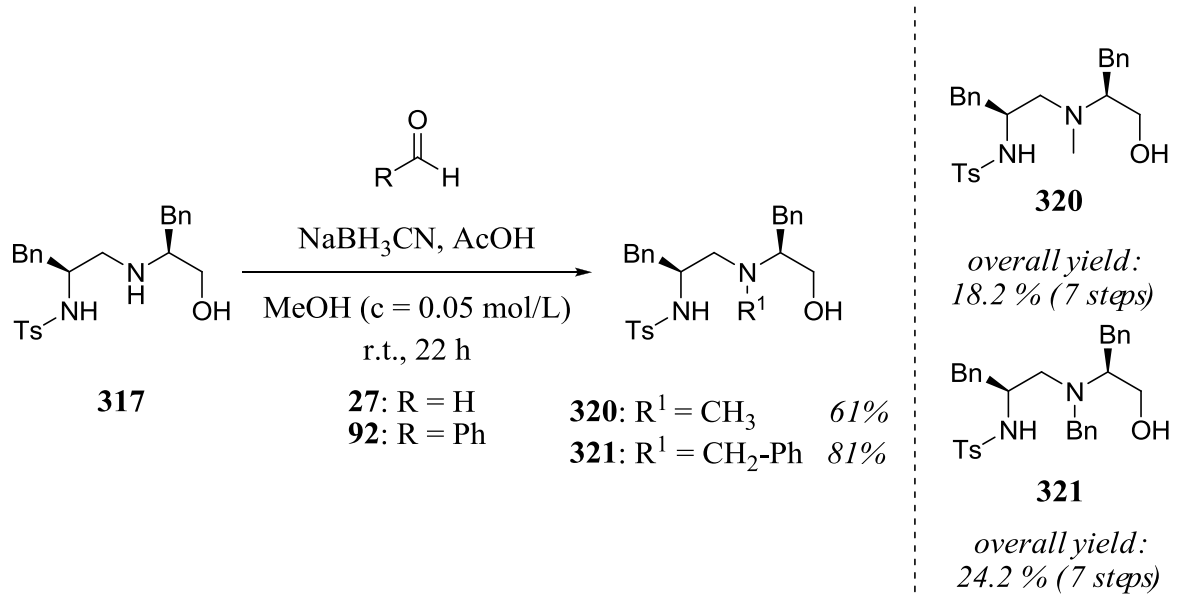
Scheme 45. Tosylation of the primary amine function of 1,2-diamino alcohol **308** based on the protocol of Xiao *et al.*.[234]

A protocol by Xiao *et al.* who tosylated a primary 1,2-diamine under these conditions was followed [234]. By treating **308** with tosyl chloride and triethylamine the desired product was obtained in 42% yield. With the tosylated 1,2-diamino alcohol **317** at hand, the secondary amine was functionalized next. This opens up the possibility to convert the secondary amine of **317** into a tertiary amine by treating it with different electrophiles. The decision was made in favor of attaching a methyl or a benzyl group to the secondary amine. Through those modifications, the Lewis basicity of the nitrogen atom should be significantly enhanced, which might lead to an increased reactivity and selectivity. The first attempts by treating **317** with methyl iodide[235] or ethyl bromide[236], respectively, in combination with potassium carbonate were unsuccessful. Only complex product mixtures were obtained. Furthermore, in regard to the results of Blumberg *et al.*[237] by using a combination of formaldehyde (*aq.*), 3N sulfuric acid (*aq.*) and $NaBH_4$ as reductant, this approach ended in the undesired formation of (*S*)-2-((*S*)-4-benzyl-3-tosylimidazolidin-1-yl)-3-phenylpropan-1-ol (**318**) [Scheme 46, pathway **a)**].



Scheme 46. Attempts to obtain the desired product **320**; **a)** Application of fromaldehyde (*aq.*) in combination with 3N H_2SO_4 (*aq.*) and $NaBH_4$ as reductant ended in the undesired formation of imidazolidinone **318**;[237] **b)** Esweiler-Clark procedure which ended in the hardly seperable mixture of **319** and **320**.[238]

Moreover, the Eschweiler-Clark procedure in which **317** is reacted with formaldehyde (*aq.*) and formic acid gave a, *via* flash column chromatography, hardly seperabel mixture of **319** and the desired product **320** [Scheme 46, pathway **b)**][238]. In additon should be noted, that the longer the reaction time the higher the yield of the side product **319** gets. The last attempt is shown in Scheme 47 and was accomplished by reacting **317** with either formaldehyde (*aq.*) solution or benzaldehyde, respectively, acetic acid and $NaBH_3CN$ as reductant instead of the previously used 3N sulfuric acid (*aq.*)/$NaBH_4$ combination [Scheme 46, pathway **a)**].



Scheme 47. Additional modification of tosylated 1,2-diamino alcohol **317** by converting the secondary amine to a tertiary one (**320** and **321**).

Indeed in this case the reaction worked out well and yielded the methylated and benzylated products **320** and **321** in 61% and 81%, respectively. This protocol was also used to methylate and benzylate the secondary amine of a functionalized *L*-proline amide in quantitative yield by Silverman and co-workers.[239] On the right hand side in Scheme 47 the overall yield in both cases starting from the amino acid precursor till the final product is shown.

2.3 Summary and Outlook

In summary, a novel synthesis of nine different 1,2-diamino alcohols (**308**-**316**) in an easy and straight forward way was developed in the Reiser group which opens up ways for further modifications and fine-tuning approaches in a late stage of the synthesis. The facial synthesis of three novel functionalized 1,2-diamino alcohol derivatives **317**, **320** and **321** was demonstrated. These structures offer a high potential for serving as ligands in asymmetric metal catalysis and also as organocatalysts. The task was now to find suitable applications for these structures in organic synthesis.

3. 1,2-Diamino Alcohols as Versatile Structure in Organic Synthesis - Application as Catalysts or Ligands

3.1 Introduction

1,2-Diamino alcohols have an enormous potential to serve as ligands for various metal catalyzed reactions (*e.g.* addition of diethylzinc (**92**) to various aldehydes or Henry-type reactions) or also as organocatalysts. Unlike the well investigated and closely related 1,2-amino alcohols, 1,2-diamino alcohols have rarely been applied in such reactions. Furthermore, a review by Shao *et al.*[116] additionally points out the ability of primary amino acids to catalyze a great number of organic transformations like Friedel-Crafts alkylations, Michael additions, aldol reactions and Mannich reactions through iminium or enamine transition states. The primary amine in the novel developed 1,2-diamino alcohols therefore also could show a similar reactivity. All in all, there is an enormous scope of potentially feasible applications for this scaffold which in the course of this work should be investigated.

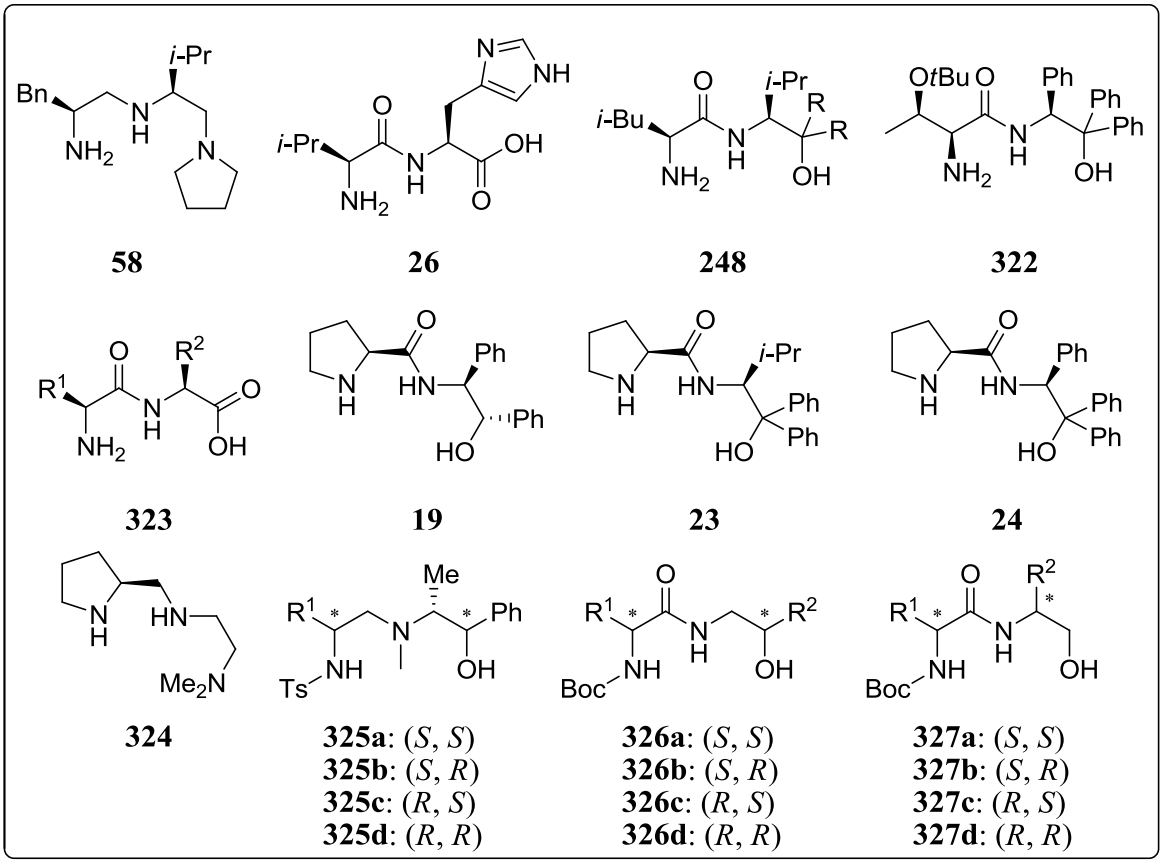


Figure 20. Known structures related to 1,2-diamino alcohols.

Carefully analyzing the literature for similar structures only revealed a hand full of examples exhibiting a more or less related core structure (Figure 20). Nevertheless, they slightly differ

in their structure. Catalysts **26**, **58** and **324** are for instance based on triamines and amid structures and hence missing the primary alcohol function. Triamine **58** in combination with a $C_6F_5SO_3H$ ammonium salt was used by Nakano *et al.*[45] in an enantioselective Diels-Alder reaction of diens and acrolein. Compound **26** and a diamine co-catalyst were utilized by Tsogoeva and co-workers[58] in an asymmetric conjugated addition of 2-nitropropane (**134**) to cyclohex-2-en-1-on (**133**). Whereas, proline based triamine **324** was used by Panday *et al.* in a Michael addition of cyclic ketones to *trans*-*β*-nitrostyrene (**181**).

Compared to the 1,2-diamino alcohols (**308**-**316**), structures **248, 322**-**323** only differ in the amide function with the exception of **323** which in addition bears a carboxylic acid group instead of the primary alcohol. Gong and co-workers[203g] used the primary amine **248** derived from *L*-valine in an asymmetric aldol reaction of hydroxyacetone to acyclic ketones and aldehydes. The threonine-based compound **322** developed by Barbas *et al.*[240] found its application in an aldol reaction of dihydroxyacetone with various aldehydes in brine. Moreover, the dipeptide structures **323** developed by Cordova and co-workers[32] were found to deliver good results in the asymmetric Michael addition of ketones to nitro olefins.

Structures **19, 23**-**24** are based on *L*-proline (**14**) and, therefore containing a secondary instead of a primary amine and an amide group instead of the secondary amine. Catalysts **23** and **24** were utilized in aldol reactions of ketones and aldehydes in aqueous medium by Singh *et al.*.[241] A similar observation was made by Wu and co-workers[9a] in 2003 who discovered that amino alcohol **19** catalyzed the aldol reaction of acetone with various aldehydes reasonably well.

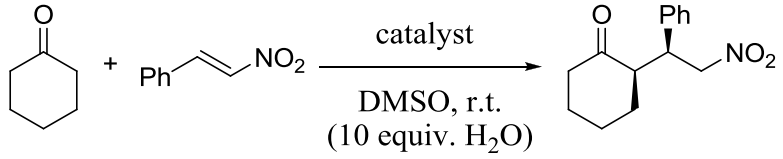
In contrast to the 1,2-diamino alcohols (**308**-**316**), the structures **325**-**327** are all protected at the primary amine and in addition **325** is methylated at the secondary amine and **326** and **327** bearing an amide function instead of the secondary amine. These three compounds were applied as ligands, whereby sulfonamide **325** was used in an enantioselective addition of diethylzinc (**92**) to aldehydes by Lu and co-workers[242] and **326a**-**d** and **327a**-**d** were applied to a ruthenium catalyzed reduction of ketones by Adolfsson *et al.*[243]

3.2 1,2-Diamino Alcohols as Catalysts in the Michael Addition

3.2.1 Introduction and Application

The Michael addition is a powerful tool in organic synthesis to generate C-C bonds in a stereoselective fashion and hence is one of the most established and well examined reactions in organocatalysis.[149a, 150a] Nevertheless, there is still room for improvement in both stereoselectivity and reactivity.

Table 31. Michael addition of cyclohexanone (**150**) to *trans*-*β*-nitrostyrene (**181**) catalyzed by small peptides **330**-**333** and dipeptides **46** and **329**.[32-33]

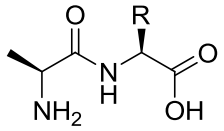


150 **181** **329**

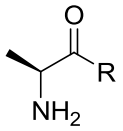
entry [a]	catalyst	time [h]	*d.r.* (*syn*/*anti*) [%] [b]	*ee* [%] [c]	yield [%] [d]
1	**329**	28	17:1	78	58
2	**46**		12:1	84	55
3	**330**		20:1	59	60
4	**331**	16	14:1	46	62
5	**332**		17:1	57	33
6	**333**		14:1	51	25

[a]: 0.75 mmol of **150**, 0.25 mmol of **181**, 30 mol% catalyst, solvent (c = 0.25 mol/L), 2.5 mmol H_2O; **[b]**: Determined from the ^{1}H-NMR spectrum of the crude reaction mixture; **[c]**: Determined by chiral HPLC analysis; **[d]**: isolated yield.

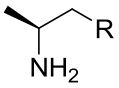
catalyst:



329: R = H
46: R = Me



330: R = pyrrolidine
331: R = morpholine

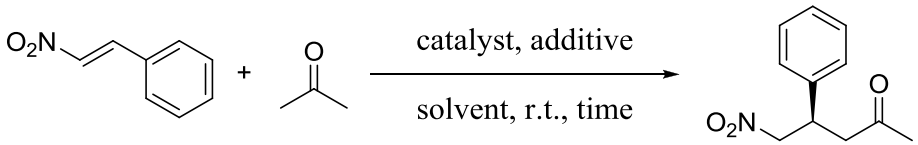


332: R = pyrrolidine
333: R = morpholine

For instance, Cordova *et al.* applied small peptides and dipeptides to the Michael addition of cyclic and acyclic ketones to various aryl-nitroolefins. Table 31 shows a specific example of

Cordova and co-workers of the Michael addition between cyclohexanone (**150**) and *trans*-β-nitrostyrene (**181**) catalyzed by small peptides **330**-**333** and the dipeptides **46** and **329**.[32-33] In the course of time other primary amines, *e.g.* primary amines containing an additional thiourea moiety[34-35, 200b-d] (see Figure 17, page 98, **48**, **50** and **245**) or primary amines based on cinchona alkaloid structures[200a] (see Figure 17, page 98, **64**), showed a slightly improved reactivity and stereoselectivity compared to the peptides **46**, **329**-**333**. It was argued that this improvement was due to the thiourea moiety, which is able to activate the nitroolefin **181** for a nucleophilic attack through hydrogen bonding, whereas the ketone **150** is assumed to be activated for enamine formation through the primary amine of the catalyst. Another fact worth mentioning is the greatly improved yield by the application of an acid co-catalyst in combination with water. It was presumed that the Brønsted acid in combination with water may facilitate the formation and regeneration of the catalyst by protonation.[33]

Table 32. Literature examples of 1,2-diamine (**33**, **35**, **109**) and 1,2-amino amide (**108**) catalyzed nitro Michael addition of *trans*-β-nitrostyrene (**181**) and acetone (**130**).[244]

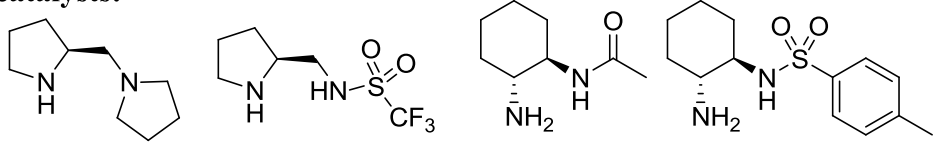


181 **130** **194**

entry	catalyst	additive	time [h]	solvent	*ee* [%] [a]	yield [%] [b]
1 [c]	**33**	-	72	THF	35 (*R*)	81
2 [d]	**35**	-	10	neat	55 (*R*)	96
3 [e]	**334**	PHCOOH	72	Et_2O	60 (*R*)	60
4 [e]	**335**	PHCOOH	72	Et_2O	61 (*R*)	62

[a]: Determined by chiral HPLC analysis; **[b]**: isolated yield; **[c]**: Results of Barbas *et al.*, see reference [245b]; **[d]**: Reaction was carried out at 0 °C; Results of Sun *et al.*, see reference [245a]; **[e]**: Results of Yan *et al.*, see reference [245c].

catalysts:



33 **35** **334** **335**

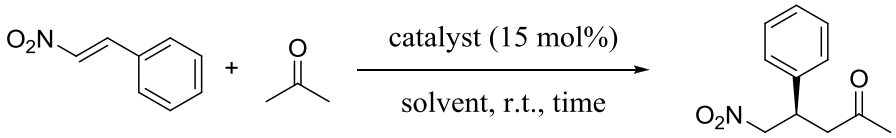
Based on these results and the high similarity of the 1,2-diamino alcohols to these catalytic structures, they were applied to the Michael addition between *trans*-β-nitrostyrenes (**181**) and

acetone (**130**) as ketone source, because it was rarely used in combination with these type of peptide catalysts and it, moreover, led only to disappointing results in catalysis performance.[245] For comparison purpose, in Table 32 are shown the best literature results of the most similar 1,2-diamino and 1,2-amino amide catalysts (**33**, **35**, **334** and **335**) compared to the catalysts (**308**, **317** and **336**) used in this work.[244] The best *ee* value of 61% in this transformation was obtained with the tosylated diamine catalyst **335** (entry 4), whereas the best yield of 96% was obtained with diamine **35** (entry 2). These results give still room for improvement, especially in the case of stereoselectivity. A point that makes the catalysts **308**, **317** (1,2-diamino alcohols) and **336** (1,2-aminoamide alcohol) superior compared to the peptides (**330**-**333**) and dipeptides (**46**, **329**) used by Cordova and co-workers and the above shown 1,2-diamines and 1,2-amino amid (**33**, **35**, **334**-**335**) is the additional alcohol group bearing a great potential to serve as Brønsted acid as well as extra binding site to generate a stronger coordination of the substrates and furthermore to improve the alignment in the transition state.

Based on these considerations the first screening with catalysts **308**, **317** and **336**[§§] was carried out (Table 33). In entries 1-8 different solvents in combination with 1,2-diamino alcohol **308** were screened and it turned out that neat conditions were the optimum, which gave 81% yield and 12% *ee* (entry 3), whereas the best results in terms of stereoselectivity were obtained in $CHCl_3$, generating an increased *ee* of 20% but a decreased yield of 64% (entry 2). Thus, in further catalyst screenings $CHCl_3$, DMSO or neat conditions were chosen as solvent. Despite prolonged reaction times, amide **336** gave only disappointing results (entries 9-11). The only fact worthwhile mentioning is the inversed stereochemistry in the product which changed from (*R*)- to (*S*)-configuration (entries 10-11). Tosylated catalyst **317** showed no catalytic activity in the Michael addition (entries 12-13). These results indicate that the primary amine function is an essential factor in the structure of 1,2-diamino alcohols in order to catalyze this kind of reaction.

[§§] Synthesised and provided by Vinh Ngoc Huynh of the Reiser group.

Table 33. Screening of 1,2-diamino alcohols **308** and **317** and amide **336** in the Michael addition of acetone (**130**) to *trans*-*β*-nitrostyrene (**181**).

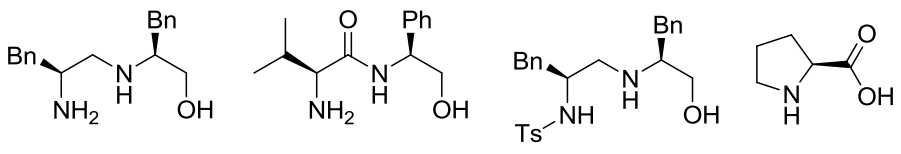


181 **130** **194**

entry [a]	catalyst	time [h]	solvent	*ee* [%] [b]	yield [%] [c]
1			DMSO	1 (*R*)	56
2			$CHCl_3$	20 (*R*)	64
3			-	12 (*R*)	81
4	**308**	28	MeOH	5 (*R*)	42
5			DCM	17 (*R*)	61
6			THF	10 (*R*)	70
7			Toluene	12 (*R*)	51
8			Et_2O	7 (*R*)	58
9			DMSO	-	0
10	**336**	139	$CHCl_3$	15 (*S*)	12
11			-	13 (*S*)	12
12	**317**	168	$CHCl_3$	-	0
13			-	-	0
14	**14**	146	DMSO	7 (*R*)	97
15			$CHCl_3$	0	8
16		16	-	7 (*R*)	14

[a]: 0.5 mmol of **181** (75 mg), 13.6 mmol of **130** (1 mL, 27.2 equiv.), 15 mol% catalyst, solvent (c = 0.125 mol/L); **[b]**: Determined by chiral HPLC analysis; **[c]**: isolated yield.

catalysts:

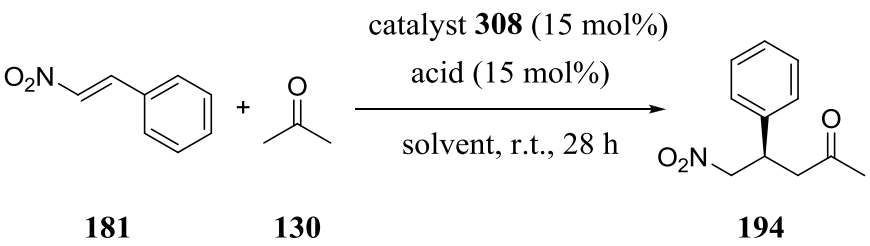


308 **336** **317** **14**

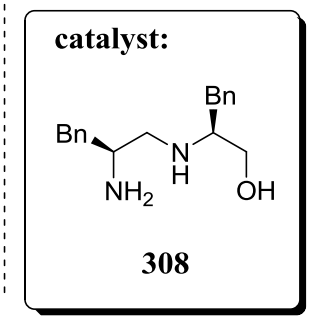
For comparison, benchmark experiments with *L*-proline (**14**) as catalyst were performed (entries 14-16), because Cordova *et al.* never applied his catalysts to acetone (**130**) as ketone source. In the cases of $CHCl_3$ and neat conditions where the 1,2-diamino alcohol generated the best results (entries 2 and 3), *L*-proline (**14**), however, only showed an impaired outcome (entries 15-16). Only with DMSO as solvent, where the results in the case of catalyst **308** were rather poor (entry 1), a comparable outcome in regard to reactivity was obtained but with a lowered *ee* of 7% (entry 16). These results demonstrate the high potential of 1,2-diamino alcohol **308** to achieve good results in the Michael addition between acetone (**130**) and *trans*-*β*-nitrostyrene (**181**) in a great number of solvents compared to *L*-proline (**14**) which is limited to DMSO. However, regarding comparable structures known from literature (Table 32) the results with catalyst **308** were inferior. For Example the tosylated amine **335** gave 62% yield and 61% *ee* (Table 32, entry 4) in comparison with the results obtained with 1,2-diamino alcohol **308**, the stereoselectivity was inferior, but the reactivity was at the same level or even higher.

It is a well-known fact that in some cases Brønsted acid co-catalysts lead to superior results in various Michael additions, which was reported by many working groups[150a, 154, 246] and is also shown in Table 32 (entries 3 and 4) in which benzoic acid is used as additive [244a]. In addition they found, that a 1:1 acid/catalyst-ratio is the optimal choice, whereas by deviating from this ratio the reactivity was significantly reduced. Based on these findings the application of different Brønsted acids was quantified on their effect on the reactivity and stereoselectivity of the Michael addition (Table 34).

Table 34. Screening of different Brønsted acids as co-catalysts in the Michael addition of acetone (**130**) to *trans*-*β*-nitrostyrene (**181**) catalyzed by 1,2-diamino alcohol **308**.



181 **130** **194**



308

entry [a]	acid (pK_a)	solvent	*ee* [%] [b]	yield [%] [c]
1	-	-	12 (*R*)	81
2		$CHCl_3$	20 (*R*)	64
3	TFA (0.23)	-	12 (*R*)	28
4		$CHCl_3$	25 (*R*)	38
5 [d]		-	12 (*R*)	34
6 [d]		$CHCl_3$	28 (*R*)	58
7	*p*-TSA (0.7)	-	27 (*R*)	12
8 [e]		$CHCl_3$	30 (*R*)	16
9	PhCOOH (4.02)	-	17 (*R*)	22
10	AcOH (4.76)	-	14 (*R*)	30

[a]: 0.5 mmol of **181** (75 mg), 13.6 mmol of **130** (1 mL, 27.2 equiv.), 15 mol% catalyst, 15 mol% additive, solvent (c = 0.125 mol/L); **[b]**: determined by chiral HPLC analysis; **[c]**: isolated yield; **[d]**: 48 h reaction time and only 10 mol% additive was used; **[e]**: 48 h reaction time.

Based on the results in Table 33 (page 118), the reactions were carried out either under neat conditions or with $CHCl_3$ as solvent and 1,2-diamino alcohol **308** as catalyst. For the screening 4 different Brønsted acids were used, namely trifluoroacetic acid, *p*-toluenesulfonic acid, benzoic acid and acetic acid which are in a pK_a range of 0.23 to 4.76. The results in terms of reactivity obtained with the four acid co-catalysts (entries 3, 7, 9-10) were inferior compared to the yield without additive (entry 1) however, the stereoselectivity was slightly increased. If the reaction was carried out in $CHCl_3$ instead of neat conditions, the catalyst showed an enhanced performance in terms of both selectivity and reactivity

(entry 3 *vs.* 4; entry 10 *vs.* 11). By applying a catalyst/acid-ratio of 1.5:1 instead of 1:1 (entries 5-6) it gets clear that a decreased acid amount implicates no effect on the outcome under neat conditions (entry 3 *vs.*5). However, by the use of $CHCl_3$ as solvent an increased reactivity was observed (entry 4 *vs.* 6). These results might occur due to the lowered amount of acid thus a certain quantity of unprotonated catalyst is available for catalyzing the reaction. This thought is also supported by the fact that almost the same results were obtained by carrying out the reaction without acid additive (entry 2 *vs.* 6).

3.2.2 Summary and Outlook

In summary, the 1,2-diamino alcohol **308** was successfully applied for the first time to the Michael addition of *trans*-*β*-nitrostyrene (**181**) to acetone (**130**) with good results. Compared to *L*-proline (**14**), which is restricted to DMSO and in addition giving lower *ee* values, the 1,2-diamino alcohol **308** is utilizable in combination with various solvents leading to good results. Nevertheless, the stereoselectivity and as well the reactivity is inferior compared to the best, literature known 1,2-diamino catalysts (**33**, **35**, **335**) and 1,2-amino amid (**334**) catalysts (see Table 32, entries 1-4). Moreover, the influence of different acid co-catalysts was investigated without improved results. Future prospects might be the application of other 1,2-diamino alcohols to investigate their impact on stereoselectivity and reactivity. Other promising attempts are the utilization of various Michael donors to *trans*-*β*-nitrostyrene (**181**), like 1,3-dicarbonylcompounds or cyclic ketones, which already gave good results with 1,2-amino alcohols as catalysts.[150a] Furthermore, 1,2-diamino alcohols serving as ligands in a copper(II)-catalyzed Michael addition of diethylzinc (**92**) to different cycloalkenones also might be a feasible application.[149a]

3.3 1,2-Diamino Alcohols as Catalysts in the Aldol Addition

3.3.1 Introduction and Application

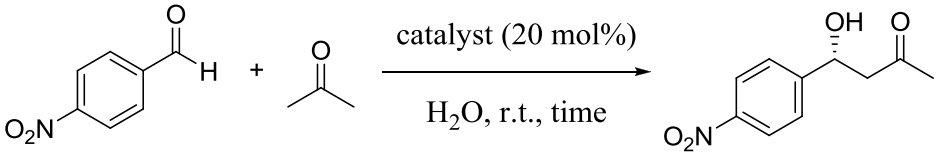
Introduction

The aldol reaction is one of the most applied methods in organic synthesis for generating C–C bonds. Therefore, an enormous effort was put in the development of new strategies. *L*-proline (**14**) is one of the most used and investigated catalysts in this sector, because it is easily accessible and low priced owing to its high abundance in nature. Hence, an enormous number of different *L*-proline derivatives were developed in the last twenty years. However, the use of primary amino acids, like *L*-valine or *L*-glycin, was neglected due to their unfavored enamine formation which was argued to be essential for a smooth proceeding of the reaction. Nevertheless, primary amino acids of this kind can be superior to *L*-proline (**14**) giving rise to new and undiscovered selectivity and reactivity.[116, 247] Thus, the attention was more and more shifted to the promising utilization of primary amino acids to the aldol reaction in the course of the last years, which is reflected by the increasing numbers of publications in this research field.[116, 194] Furthermore, a small number of 1,2-amido alcohols were also applied to the aldol reaction between acetone (**130**) or hydroxyacetone (**338**) and various 4-substituted benzaldehydes. Gong *et al.*[9b, 203g], Singh and co-workers[241, 248], Wu *et. al.*[9a] and also Barbas and co-workers[240] for example applied various *L*-proline and primary amine based 1,2-amido alcohols (see Figure 20, page 113, structures **248**, **322** or **19**, **23**, **24**, respectively) to the aldol reaction of acyclic ketones and 4-substituted benzaldehydes to achieve excellent reactivity and selectivity.

Acetone (130) as ketone source

A small amount of water is facilitating the essential enamine formation in primary amine catalyzed aldol reactions.[194] Singh *et al.*[241] also came to the same conclusion that water is supporting the enamine formation through the agglomeration of organic molecules by excluding water which forcing the equilibrium toward the enamine formation. Therefore, the reactions were carried out in the presence of water (2.8 equiv.). Based on these promising facts, the 1,2-diamino alcohols **308** and **317** and the 1,2-amido alcohol **336** were applied to the aldol reaction between acetone (**130**) and *p*-nitrobenzaldehyde (**149**) serving as model system (Table 35).

Table 35. Application of 1,2-diamino alcohols **308** and **317** and amide **336** to the aldol reaction between *p*-nitrobenzaldehyde (**149**) and acetone (**130**) in the presence of water.

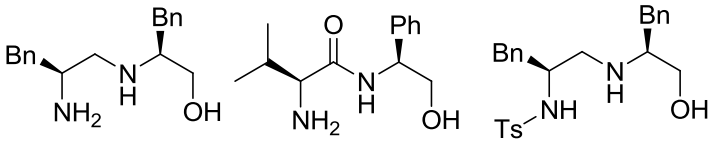


149 **130** **151**

entry [a]	catalyst	time [h]	*ee* [%] [b]	yield [%] [c]
1	**308**	48	4 (*R*)	52
2	**336**	48	35 (*R*)	74
3	**317**	121	-	0

[a]: 0.5 mmol of **149** (76 mg), 8.6 mmol of **130** (0.63 mL, 17.2 equiv.), 20 mol% catalyst, 20 mol% metal, 20 mol% additive, H_2O (V = 50 µL); **[b]**: determined by chiral HPLC analysis; **[c]**: isolated yield.

catalyst:

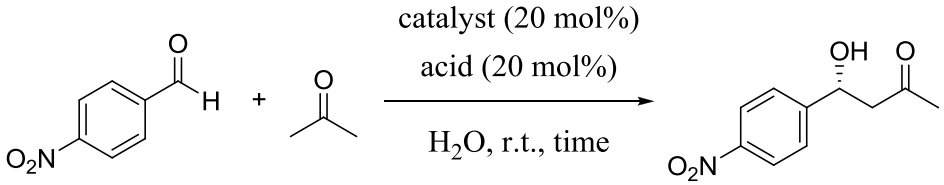


308 **336** **317**

By the use of primary amines **308** and **336** (entries 1-2) the reaction proceeds reasonably well in 52% and 74% yield, respectively. However, the application of tosylated catalyst **317** in the aldol reaction led to no product formation (entry 3) revealing that the primary amine plays a crucial role in the process of product formation. When catalyst **308** was applied an *ee* value of 4% was achieved (entry 1), whereas with amide **336** the *ee* was significantly increased to 35% (entry 2). This clearly suggests that the amide function might be responsible for the big difference in the *ee* value, probably owing to its higher acidity compared to the secondary amine in **308** leading to an improved coordination of the substrate through hydrogen bonding. As earlier publications already have shown, different acid co-catalysts were able to accelerate the aldol reaction and in addition the stereoselectivity was raised in some cases.[249] However, this parameter is very sensitive and is dependent on the solvent and also on the pK_a of the Brønsted acid. If the milieu is too acidic, the catalyst gets inactive by protonation of the amine, thus the enamine formation is suppressed. Based on these facts several Brønsted acid

co-catalysts with different pK_a values were screened to quantify their influence on the aldol reaction (Table 36).

Table 36. Screening of various acid co-catalyst in the aldol reaction of *p*-nitrobenzaldehyde (**149**) and acetone (**130**) catalyzed by 1,2-diamino alcohol **308** and amide **336**.

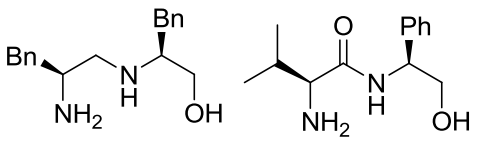


149 **130** **151**

entry [a]	catalyst	acid (pK_a)	time [h]	*ee* [%] [b]	yield [%] [c]
1	**308**	-	48	4 (*R*)	52
2	**336**			35 (*R*)	74
3	**308**	TFA (0.23)	24	23 (*R*)	84
4	**336**			32 (*R*)	18
5		AcOH (4.76)		2 (*R*)	52
6		PhCOOH (4.02)		5 (*R*)	56
7	**308**	*p*-TSA (0.7)	24	3 (*R*)	74
8		$MeSO_3H$ (-1.9)		17 (*R*)	90
9 [d]				10 (*R*)	8
10	-	TFA (0.23)	144	-	0

[a]: 0.5 mmol of **149** (76 mg), 8.6 mmol of **130** (0.63 mL, 17.2 equiv.), 20 mol% catalyst, 20 mol% metal, 20 mol% additive, H_2O (V = 50 µL); **[b]**: determined by chiral HPLC analysis; **[c]**: isolated yield; **[d]**: 40 mol% of $MeSO_3H$ was used.

catalyst:



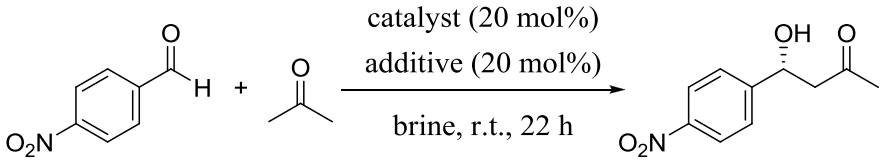
308 **336**

1,2-diamino alcohol **308** and amide **336** in combination with five different Brønsted acids with a pK_a range of -1.9 to +4.76 were applied to the aldol reaction. It became obvious that in the case of amid **336** the catalytic activity is severely decreased by the addition of a strong acid (entry 2 *vs.* 4), however, in the case of 1,2-diamino alcohol **308** the reactivity is enhanced (entry 1 *vs.* 3). In the latter case, the *ee* was increased from almost *racemic* to 23% and the yield was also improved from 52% to 84%. This is due to the fact that in the case of catalyst **336** the primary amine function is completely protonated, whereas in **308** the stronger basic secondary amine is preferably protonated, thus the iminium/enamine formation is not restricted in this case and, hence, 1,2-amino alcohol **308** was used for further studies. Then, different acid co-catalysts were utilized to the reaction to get an idea of how the pK_a of the acid influences the reactivity and selectivity (entries 5-8). In the cases of acetic acid (entry 5) and benzoic acid (entry 6) which have an pK_a value around 4, only moderate to none improvement in selectivity or reactivity was observed. However, by the use of *p*-toluenesulfonic acid (entry 7) and sulfonic acid (entry 8) a significant increase of reactivity (up to 90% yield) and stereoselectivity (up to 17% *ee*) was obtained. These findings demonstrate that the pK_a value of the acid additive has to be around 0 to promote the reaction. Subsequently, the amount of acid additive was increased from 20 to 40 mol% (entry 9) leading to an almost complete deactivation of the catalyst. To exclude the possibility that only acid alone is able to catalyze the reaction, TFA was used as the sole catalyst showing no activity (entry 10).

All in all, it was possible to apply TFA and sulfonic acid in combination with 1,2-diamino alcohol **308** to the aldol reaction between acetone (**130**) and *p*-nitrobenzaldehyde (**149**) to achieve improved results in terms of reactivity and also stereoselectivity compared to the use of 1,2-diamino alcohol **308** as sole catalyst. However, amide **336** showed superior results without acid additive.

Based on the publication of Da *et al.*[249a] who applied a primary amine organocatalyst in combination with 2,4-dinitrophenol as acid co-catalyst (1:1 ratio) to the asymmetric aldol reaction of acetone (**130**) to *p*-nitrobenzaldehyde (**149**) in brine to yield the aldol addition product in 82% and 96% *ee* (Table 37, entry 1) and the promising results obtained in water and with acid co-catalyst (see Table 36, page 124), it was a logical deduction to transfer this protocol to 1,2-diamino alcohol **308** (Table 37).

Table 37. Asymmetric aldol reaction of *p*-nitrobenzaldehyde (**149**) and acetone (**130**) in brine catalyzed by a combination of 2,4-dinitrophenol and 1,2-diamino alcohol **308**.

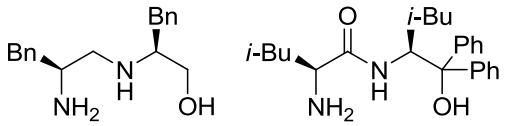


149 **130** **151**

entry [a]	catalyst	additive	*ee* [%] [b]	yield [%] [c]
1 [d]	**337**	2,4-dinitrophenol	96	82
2		-	*rac.*	22
3 [e]	**308**	2,4-dinitrophenol	31	66
4		2,4-dinitrophenol	16	86

[a]: 0.5 mmol of **149** (76 mg), 8.6 mmol of **130** (0.63 mL, 17.2 equiv.), 20 mol% 2,4-dinitrophenol (18 mg), 20 mol% catalyst (28 mg), brine (c = 0.17 mol/L); **[b]**: determined by chiral HPLC analysis; **[c]**: isolated yield; **[d]**: Results of Da *et al*., see reference [249a]; **[e]**: Reaction was carried out without solvent.

catalyst:



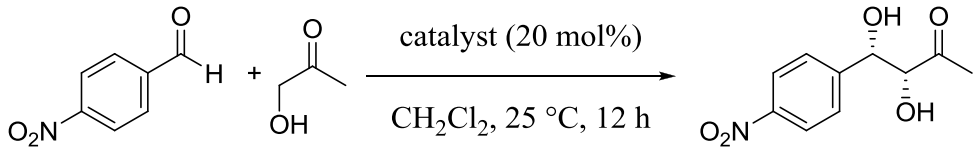
308 **337**

When 1,2-diamino alcohol **308** was utilized to the aldol reaction in brine only poor results with a *racemic* product in 22% yield were obtained (entry 2), which is in accordance with the results of the aldol reaction in the presence of water. In this case 54% yield and 4% *ee* were achieved (see entry 1, Table 36, page 123). By applying 2,4-nitrophenole and neat conditions to the reaction 66% yield and 31% *ee* were received (entry 3). With brine as solvent the yield was lifted up to 86% but the *ee* was reduced to 16% (entry 4). This finding led to the conclusion that brine impairs the hydrogen bonding interactions between the substrates and the catalyst which causes an increased stereoselectivity, thus no further efforts in this direction were conducted.

Hydroxyacetone (338) as ketone source

In order to investigate whether 1,2-diamino alcohols could be applied to other substrates than acetone (**130**), hydroxyacetone (**338**) was chosen as ketone source based on the publication of Gong *et al.*[203g] in 2007 where various amino alcohols derived from *L*-leucine (see Figure 20, page 113, structure **248**) were examined as catalysts in aldol reactions leading to excellent results in regard of stereoselectivity and reactivity (Table 38).

Table 38. Literature results of Gong *et al.* in the aldole reaction between hydroxyacetone (**338**) and *p*-nitrobenzaldehyde (**149**) catalyzed by *L*-leucine derived amino alcohols **340a-c** and **248a-b**.[203g]

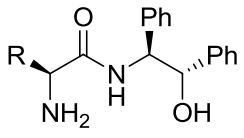


149 **338** **339**

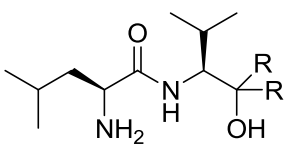
entry [a]	catalyst	d.r. (syn/anti) [b]	*ee* [%] [c]	yield [%] [d]
1	**340a**	4:1	67	89
2	**340b**	4:1	61	77
3	**340c**	4:1	71	91
4	**248a**	5:1	86	95
5	**248b**	7:1	89	99

[a]: 0.3 mmol of **149** (45 mg), 3 mmol of **338** (206 µL, 10 equiv.), 20 mol% catalyst, CH_2Cl_2 (c = 0.3 mol/L); **[b]**: Determined from the ^{1}H-NMR spectrum of the crude reaction mixtuer; **[c]**: Determined by chiral HPLC analysis; **[d]**: Combined isolated yield of *syn*- and *anti*-product.

catalyst:



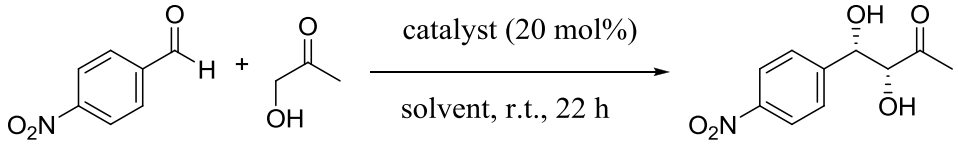
340a: R = Bn
340b: R = *i*-Pr
340c: R = *i*-Bu



248a: R = Ph
248b: R = 3,5-$(CF_3)_2C_6H_3$

Therefore, 1,2-diamino alcohols **308** and **317** and the *L*-valine based amide **336** were applied to the aldol reaction between hydroxyacetone (**338**) and *p*-nitrobenzadehyde (**149**) (Table 39).

Table 39. Asymmetric aldol reaction of *p*-nitrobenzaldehyde (**149**) and hydroxyacetone (**338**) catylazed by 1,2-diamino alcohols **308** and **317** and 1,2-amido alcohol **336**.

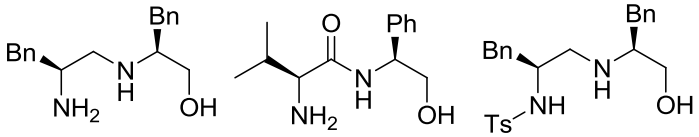


149 **338** **339**

entry [a]	catalyst	solvent	*d.r.* (*syn*/*anti*) [b]	*ee* (*syn*) [%] [c]	*ee* (*anti*) [%] [c]	yield [%] [d]
1	**308**		2.3:1	- 11	+ 23	92
2	**336**	CH_2Cl_2	2.3:1	- 56	+ 3	92
3	**317**		1:2.6	n.d.	n.d.	traces
4		*p*-xylene	1.8:1	- 26	+41	60
5	**308**	toluene	1.9:1	- 27	+35	66
6		THF	1:2.0	- 15	+23	62

[a]: 0.5 mmol of **149** (76 mg), 5 mmol of **338** (343 µL, 10 equiv.), 20 mol% catalyst, solvent (c = 0.3 mol/L); **[b]**: Determined from the ^{1}H-NMR spectrum of the crude reaction mixture; **[c]**: Determined by chiral HPLC analysis; **[d]**: Combined isolated yield of *syn*- and *anti*-product.

catalyst:



308 **336** **317**

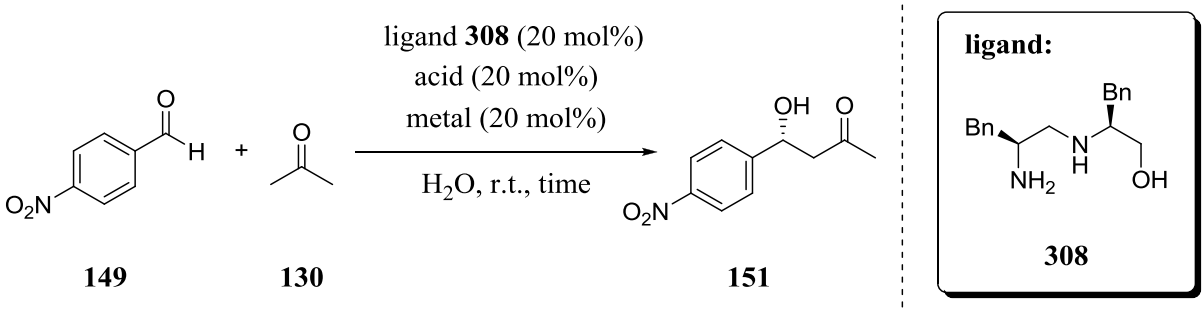
Under these conditions the catalysts **308** and **336** (entries 1-2) which contain a primary amine function gave superior results compared to tosylated catalyst **317** (entry 3). The same trend was already observed in the aldol reaction between acetone (**130**) and *p*-nitrobenzaldehyde (**149**) (see Table 35, page 123) and also in the Michael addition of acetone (**130**) to *trans*-*β*-nitrostyrene (**181**) (see Table 33, page 118). In both cases a *diastereomeric ratio* of 2.3:1 (*syn*/*anti*) was obtained (entries 1-2). 1,2-diamino alcohol **308** gave the *syn*-product in 11% *ee* and the *anti*-product in 23% *ee* in 92% combined yield (entry 1). The amide **336** generated the *syn*-product in 56% *ee* and the *anti*-product in 3% *ee* in also 92% combined yield (entry 2). A remarkable fact is that amide **336** generated a better *ee* in terms of *syn*-product, whereas the 1,2-diamino alcohol **308** produced a better *ee* in

regard to the *anti*-product. This led to the conclusion that other interactions of the less basic amide function of **336** with the substrate causing this discrepancy in stereoselectivity. In entries 4-6 different solvents were screened in combination with catalyst **308**, whereby *p*-xylene gave the best results in terms of stereoselectivity. There the *syn*-product was obtained in 26% *ee* and the *anti*-product in 41% *ee* in 60% combined yield (entry 4). However, by changing the solvent the stereoselectivity is improved at costs of the reactivity. All in all, by comparing these results with the results obtained by Gong and co-workers, which were superior, it seemed not worthwhile to put further effort in this direction.

1,2-Diamino Alcohol 308 as Ligand

The knowledge of aldol reactions which are catalyzed by various Lewis acids in combination with different chirality inducing ligands[250] led to the idea to apply 1,2-diamino alcohol **308** in combination with $Cu(OAc)_2$ or $ZnCl_2$ to the model reaction of acetone (**130**) and *p*-nitrobenzaldehyde (**149**) (Table 40).

Table 40. Screening of different metal salts as additives in the aldol reaction of acetone (**130**) and *p*-nitrobenzaldehyde (**149**) catalyzed by 1,2-diamino alcohol **308**.



entry [a]	metal	acid	time [h]	*ee* [%] [b]	yield [%] [c]
1	-	-	48	4 (*R*)	52
2	-	TFA	24	23 (*R*)	84
3	$Cu(OAc)_2 \cdot H_2O$	-	24	11 (*R*)	84
4		TFA		15 (*R*)	91
5	$ZnCl_2$	-	21	2 (*S*)	86
6		TFA		18 (*R*)	88

[a]: 0.5 mmol of **149** (76 mg), 8.6 mmol of **130** (0.63 mL, 17.2 equiv), 20 mol% catalyst, 20 mol% metal, 20 mol% additive, H_2O (V = 50 µL); **[b]**: determined by chiral HPLC analysis; **[c]**: isolated yield.

By the use of additional metal (entry 3 and 5) the reactivity in both cases was noticeable increased compared to the use without metal (entry 1), however the stereoselectivity in the case of $ZnCl_2$ (entry 5) was not improved, whereby with $Cu(OAc)_2 \cdot H_2O$ (entry 3) it was slightly elevated. This indicates that zinc(II) is not coordinated to the ligand **308** and, therefore, only acts as Lewis acid which results in a higher yield but no improvement in stereoselectivity (entry 1 *vs.* 5). In the case of copper(II) a slightly increased *ee* was observed (entry 1 *vs.* 3). To further improve the selectivity TFA was added to the reaction (entries 4 and 6), however only in the case of $ZnCl_2$ the stereoselectivity was slightly improved. Based on these results no further efforts were put in this direction.

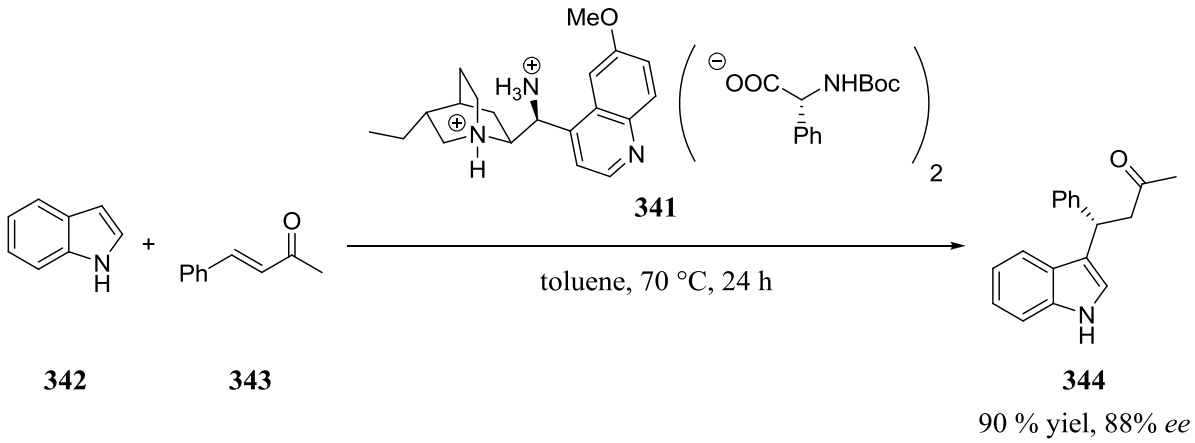
3.3.2 Summary

In summary, a protocol for the application of 1,2-diamino alcohol **308** and 1,2-amido alcohol **336** as catalysts in the aldol reaction of acetone (**130**) or hydroxyacetone (**338**) to *p*-nitrobenzaldehyde (**149**) in the presence of water and Brønsted acids as co-catalysts was developed. Moreover, the application of **308** and **336** as ligands for the Lewis acid catalyzed asymmetric aldol reaction was investigated. However, the synthetic result can not compete with established literature catalysts.

3.4 1,2-Diamino Alcohols as Catalysts in the Asymmetric Friedel-Crafts Alkylation

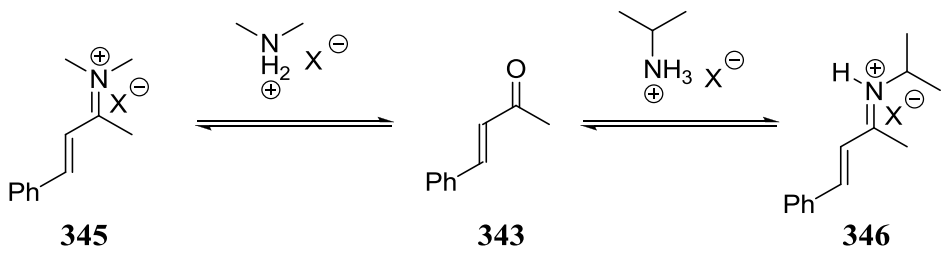
3.4.1 Introduction and Application

The Friedel-Crafts alkylation got more attention over the past few years.[251] With it various chiral indole derivatives, which represent a preferred structural motive in medicinal chemistry, can be synthesized. Effective asymmetric variants therefore are consequently highly desirable. One of these new strategies was developed by Melchiorre *et al.*[57b] who applied a primary amine salt to the Friedel-Crafts alkylation of indoles with α,β-unsaturated ketones. The exact catalyst **341** is a combination of a cinchonine derived primary amine cation and a Boc-protected phenylglycin anion. By applying the optimized conditions to the Friedel-Crafts alkylation between indole (**342**) and phenylbutenone (**343**) the product was obtained in 90% yield and 88% *ee*, which was the first addition of such kind (Scheme 48).



Scheme 48. Organocatalytic asymmetric Friedel-Crafts alkylation of indole (**342**) with phenylbutenone (**343**) catalyzed by **341**.[57b]

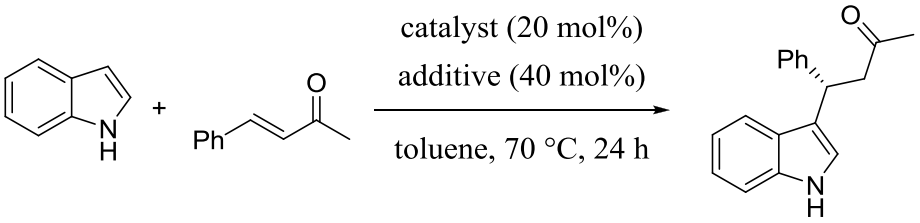
Inter alia Melchiorre and co-workers argued that the reaction is proceeding through an iminium ion activation of enone **343** making it accessible for a nucleophilic attack by the indole (**342**) (Scheme 49).[56-57]



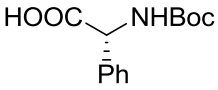
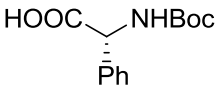
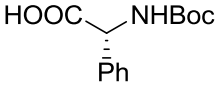
Scheme 49. Iminium ion formation of enone **343** *via* a primary (**346**) or a secondary amine salt (**345**).[56-57]

Moreover, it was argued that the iminium formation between a α,β-unsaturated ketone like **343** and a secondary amine is relatively unfavoured due to its steric hinderance. Thus this reaction bears a great potential for the application of 1,2-diamino alcohols as catalyst owing to their less bulky primary amine function which is expected to facilitate the iminium ion formation **346**. Therefore, the protocol was carried over to the primary amines **308**, **336** and the tosylated catalyst **317** (Table 41).

Table 41. Friedel-Crafts alkylation of indole (**342**) with phenylbutenone (**343**) catalyzed by a combination of Boc-protected phenylglycin with different primary amines **308** and **336** and the tosylated amine **317**.

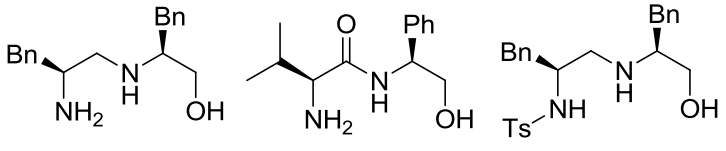


342 **343** **344**

entry [a]	catalyst	additive	*ee* [%] [b]	yield [%] [c]
1	**308**	TFA	15	48
2	**308**		65	50
3	**336**		29	66
4	**317**		16	8

[a]: 0.6 mmol of **342** (70 mg), 0.5 mmol of **343** (73 mg), 20 mol% catalyst, 40 mol% additive, toluene (c = 0.25 mol/L); **[b]**: Determined by chiral HPLC analysis; **[c]**: isolated yield.

catalyst:



308 **336** **317**

In accordance with the results obtained by Melchiorre *et al.*, the application of Boc-protected phenlyglycin (entrie 2) as acid co-catalyst is superior compared to TFA (entry 1) with respect to stereoselectivity. The yield remained at the same level in both cases. Owing to the

improved results obtained with Boc-protected phenylglycin the other reactions were also performed with this additive. By combining amide **336** with the amino acid co-catalyst the yield was enhanced to 66%, however, the *ee* was lowered to 29% (entry 3). Finally the tosylated amine **317** was applied to the Friedel-Crafts alkylation. Due to its blocked primary amine function, which was suspected to be essential for the fast formation of the iminium ion and consequently the smooth processing of the catalysis, the synthetic results deteriorated (entry 4). This fact is supported by the finding that proline which also lacks a primary amine function shows no catalytic activity in this type of transformation.[57b]

3.4.2 Summary and Outlook

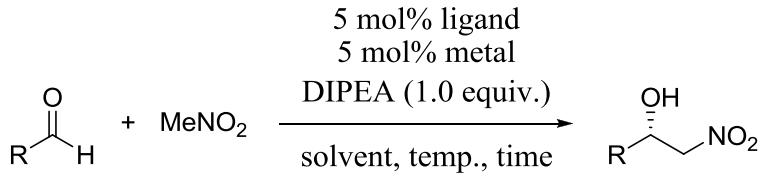
In summary, these results demonstrating the ability of 1,2-diamino alcohol **308** to catalyze the Friedel-Crafts alkylation of indole (**342**) to phenlybutenone (**343**) with a good outcome. In order to improve the results one could think about extending the scope by applying 1,2-diamino alcohols with different residues at the two chiral centers to perhaps generate a better alignment of the substrates in the transition state or to facilitate the interaction between catalyst and co-catalyst. Furthermore, the application of other chalcones might lead to improved results.

3.5 1,2-Diamino Alcohols as Ligands in the Henry Reaction

3.5.1. Introduction and Application

In the course of this work, the aim was to find suitable applications for the small library of 1,2-diamino alcohols (**308**-**316**) (see Figure 19, page 109). In the previous chapters these compounds were investigated for their potential as organocatalyst. The possibility to utilize them as chiral C_1-symmetric ligands in varies metal catalyzed reactions was neglected so far. A promising attempt with prospect of success is given by the well investigated Henry reaction which represents an excellent method for the enantioselective preparation of carbon-carbon bonds.[252] Based on these facts a tremendous effort was undertaken to develop powerful catalytic strategies based either on metal- or organocatalysis with the ulterior motive to generate high stereoselectivity. A big role in these investigations was played by copper due to its low costs and low toxicity it was the metal of choice in most cases. Copper was mainly combined with C_2-symmetric chiral ligands, like different amino alcohols[253] or bis(oxazoline) ligands[254], however the application of C_1-symmetric ligands in combination with copper in this direction are surprisingly rare.[255] Due to their much more simple tunable electronic and steric characteristics this is surprising. Nevertheless, in 2011 Gong and co-workers[256] published two papers in this direction. They used various C_1-symmetric bornylamine based dinitrogen ligands **350**-**353** or primary and secondary C_1-symmetric diamine based ligands with camphor **355**-**357** or menthone **354** moieties to the copper(II)-catalyzed Henry reaction between cyclic **92** and acyclic **345** aldehydes and nitromethane (**187**). Outstanding results in both reactivity and stereoselectivity were achieved (Table 42).

Table 42. Asymmetric copper(II)-catalyzed Henry (nitroaldol) reactions between cyclic **92** and acyclic **347** aldehydes and nitromethane (**187**) catalyzed by various C_1-symmetric bornylamine based dinitrogen ligands **350**-**353** or primary and secondary C_1-symmetric diamine based ligands with camphor **355**-**357** or menthone **354** moieties.[256]



92: R = Ph
347: R = *i*-Pr

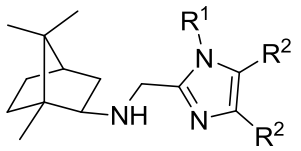
187

348: R = Ph
349: R = *i*-Pr

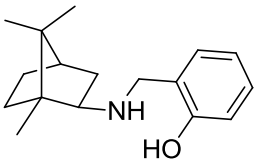
entry [a]	ligand	metal	ketone	product	*ee* [%] [b]	yield [%] [c]
1[d]	**350**				92	95
2[d]	**351**				90	80
3[d]	**352**	$CuCl_2 \cdot 2\ H_2O$	**92**	**348**	86	85
4[d]	**353**				- 48	78
5[e]	**354**				n.d.	trace
6[f]	**355**				91	65
7[f]	**356**	$Cu(OAc)_2 \cdot H_2O$	**347**	**349**	16	68
8[f]	**357**				61	63

[a]: 0.5 mmol of **92** (51 µL), **347** (54 µL), 5 mmol of **187** (268 µL), 0.5 mmol DIPEA (85 µL), 5 mol% ligand, 5 mol% metal; **[b]**: Determined by chiral HPLC analysis; **[c]**: Isolated yield; **[d]**: Recation conditions: THF (c = 0.25 mol/L), - 20 °C, 15 h; **[e]**: Reaction conditions: THF (c = 0.25 mol/L), - 20 °C, 40 h; **[f]**: Reaction conditions: EtOH (c = 0.25 mol/L), 4 °C, 10 h.

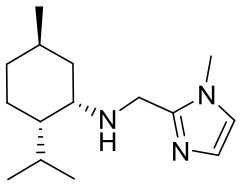
ligands:



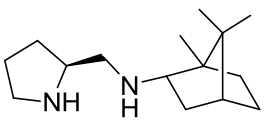
350: R^1 = Me, R^2 = H
351: R^1 = Bn, R^2 = H
352: R^1 = Me, R^2 = Me



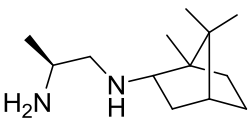
353



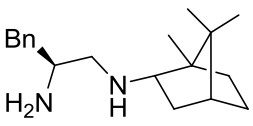
354



355



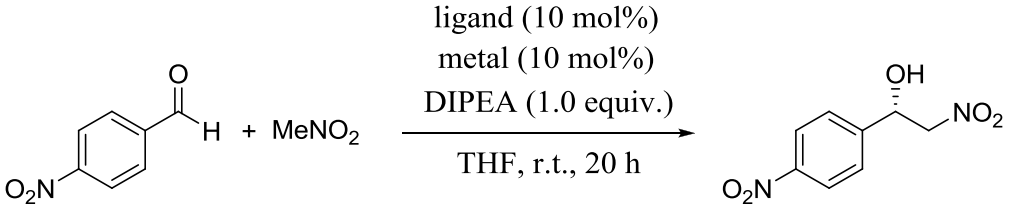
356



357

Overall, only a handful literature reports of the application of amino alcohols to the Henry reaction are known to date[257], although amino alcohols are known to be prone to coordinate various copper salts[258], thus it was decided to apply the 1,2-diamino alcohols as ligands to the copper catalyzed Henry reaction. Finally, the Henry reaction between *p*-nitrobenzaldehyde (**149**) and nitromethane (**187**) catalyzed by 5 mol% of copper salt in combination with 5 mol% ligand and 1 equiv. DIPEA developed by Gong *et al.*[256] was chosen as model reaction (Table 43).

Table 43. Asymmetric Henry reaction between *p*-nitrobenzaldehyde (**149**) and nitromethane (**187**) catalyzed by a combination of metal(II) salts and ligands **308**, **317** and **336**.

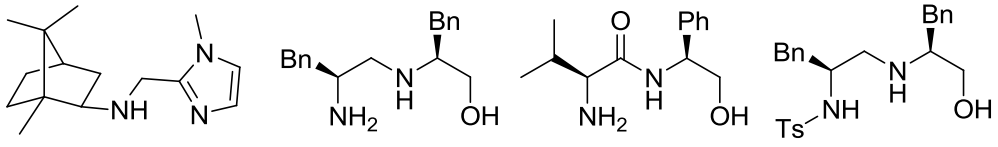


149 **187** **358**

entry [a]	ligand	metal	*ee* [%] [b]	yield [%] [c]
1 [d]	**350**	$CuCl_2 \cdot H_2O$	94	93
2	**308**		*rac.*	88
3	**336**	$Cu(OAc)_2 \cdot H_2O$	*rac.*	80
4	**317**		*rac.*	84
5	**308**	$ZnCl_2$	*rac.*	70

[a]: 0.5 mmol of **149** (76 mg), 5 mmol of **187** (268 µL), 0.5 mmol DIPEA (85 µL), 10 mol% Ligand, 10 mol% metal, THF (c = 0.25 mol/L); **[b]**: Determined by chiral HPLC analysis; **[c]**: isolated yield; **[d]**: Results of Gong *et al.*, see reference [256b], reaction conditions: 30 h, - 40 °C.

ligand:

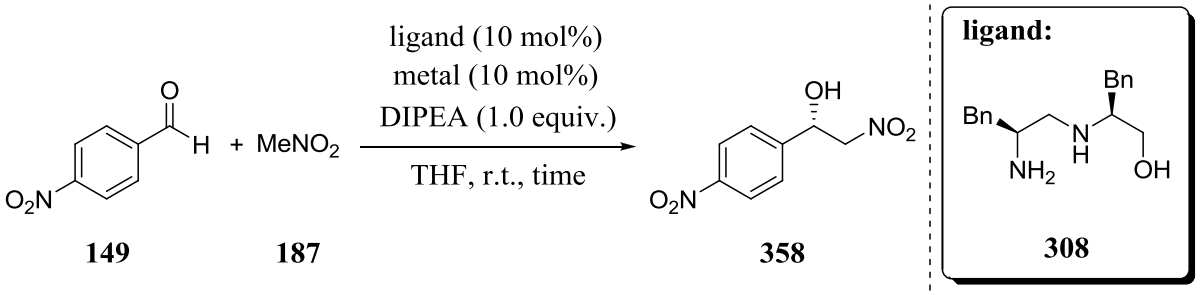


350 **308** **336** **317**

Entry 1 shows the literature results of ligand **350** obtained by Gong *et al.*[256b]. In entries 2-4 the three ligands **308**, **317** and **336** were utilized to the Henry reaction. The best results were

achieved with 1,2-diamino alcohol **308** with 88% yield of a *racemic* product (entry 1). Surprisingly, the reactivity with the ligands **317** and **336** was only slightly inferior compared to ligand **308**, whereby also no stereoinduction was observable. These findings may led to the assumption that the ligand might not coordinate to the copper(II), hence the reaction is only catalyzed by $Cu(OAc)_2 \cdot H_2O$ acting as Lewis acid. Moreover, $ZnCl_2$ was applied to the Henry reaction, however no improvement was noticeable. In order to get a deeper understanding of potential reasons for the absent stereoinduction a few benchmark experiments were carried out (Table 44).

Table 44. Benchmark experiments in the Henry reaction.



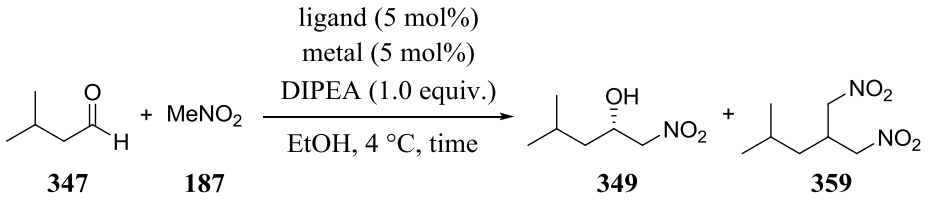
entry [a]	base	ligand	metal	time [h]	*ee* [%] [b]	yield [%] [c]
1	DIPEA	**308**	$Cu(OAc)_2 \cdot H_2O$	18	*rac.*	88
2	DIPEA	-	-	26	n.d.	80
3	DIPEA	**308**	-	47	*rac.*	74
4	DIPEA	-	$Cu(OAc)_2 \cdot H_2O$	25	n.d.	94
5	-	-	$Cu(OAc)_2 \cdot H_2O$	45	n.d.	60
6	-	**308**	-	44	33	16
7	-	**308**	$Cu(OAc)_2 \cdot H_2O$	24	*rac.*	84

[a]: 0.5 mmol of **149** (76 mg), 5 mmol of **187** (268 µL), 0.5 mmol DIPEA (85 µL), 10 mol% Ligand, 10 mol% metal, THF (c = 0.25 mol/L); **[b]**: Determined by chiral HPLC analysis; **[c]**: isolated yield; **n.d.** = not determined.

For the benchmark experiments ligand **308** was chosen, owing to its slightly better performance. Entry 1 shows the results when all components considered crucial were present in the reaction. In the following experiments one or two catalytic species were left out. DIPEA alone gave the product **358** in 80% yield (entry 2). A combination of DIPEA and ligand **308** yielded **358** in 74%, however without stereoinduction (entry 3). By leaving out ligand **308**, 94% yield was obtained (entry 4), which is in accordance with the presumption

that the ligand is not taking part in the catalytic cycle. Furthermore, a plausible argument is the much faster coordination or activation, respectively, of the aldehyde by copper acting as Lewis acid compared to the coordination of copper to the ligand. In entries 5-7 DIPEA was left out. Surprisingly, $Cu(OAc)_2 \cdot H_2O$ as the sole catalyst also produced a yield of 60%, which, indeed, confirmed the assumption that copper acts as Lewis acid activating the aldehyde for a nucleophilic attack, which perhaps stands in competition to the much slower coordination to the ligand (entry 5). Interestingly, ligand **308** alone is catalyzing the reaction and gave 16% yield and an *ee* value of 33% (entry 6), which revealed the stereoselective catalytic ability of the ligand itself, however, at a very slow reaction rate. This is a hint explaining the bad results in regard of stereoselectivity by combination of all catalysts, thus the reaction is faster catalyzed by copper and DIPEA compared to the ligand. When $Cu(OAc)_2 \cdot H_2O$ and ligand **308** were used in combination, a *racemic* product at a satisfying yield of 84% was obtained (entry 7). Based on these findings it was a logical consequence to change the substrate from the highly reactive *p*-nitrobenzaldehyde (**149**) to the less reactive isovaleraldehyde (**347**) (Table 45). This should lower the reaction rate and therefore improve the slow stereoinducing step in the Henry reaction. The chosen model reaction was also investigated by Gong and co-workers[256a] in 2011 to quantify the influence of various *L*-proline based dinitrogen ligands in combination with different copper salts.

Table 45. Asymmetric Henry reaction between isovaleraldehyde (**347**) and nitromethane (**187**) catalyzed by a combination of various copper salts and ligand **308**.

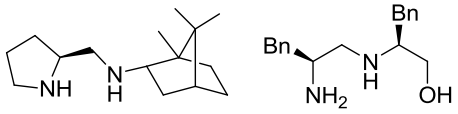


347 **187** **349** **359**

entry [a]	ligand	metal	time [h]	*ee* [%] [b]	yield of 349 [%] [c]	yield of 359 [%] [c]
1 [d]	**355**	$Cu(OAc)_2 \cdot H_2O$	10	91	65	16
2			23		63	0
3	**308**	$Cu(OAc)_2 \cdot H_2O$	51	*rac.*	60	8
4 [e]			23		68	12
5		$CuCl_2 \cdot 2H_2O$			54	0
6		Cu(OAc)			28	2
7	**308**	CuBr	23	*rac.*	42	0
8		CuI			53	0

[a]: 0.5 mmol of **347** (54 µL), 5 mmol of **187** (268 µL), 0.5 mmol DIPEA (85 µL), 5 mol% Ligand, 5 mol% metal, EtOH (c = 0.25 mol/L); **[b]**: Determined by chiral HPLC analysis; **[c]**: isolated yield; **[d]**: Results of Gong *et al.*, see reference [256a]; **[e]**: 25 °C instead of 4 °C were applied.

ligands:



355 **308**

In entry 1 are displayed the literature results of Gong *et al.*[256a] for comparison purposes. In entries 2-4 the external parameters like temperature and reaction time were examined. $Cu(OAc)_2 \cdot H_2O$ was chosen as metal source in these three experiments. Surprisingly, by prolonging the reaction time from 23 h (entry 1) to 51 h (entry 2) at 4 °C the formation of main product **349** stays at the same level, however, 8% by-product **359** was formed in the latter case. Therefore, in the further course of the screening a reaction time of 23 h was applied. The increase of temperature from 4 °C to r.t. led to a slightly improved yield of 68% of **349**, however, at the same time it results in the formation of by-product **359** (entry 3). Interestingly, the change in temperature showed no influence on the stereoinduction – the product was *racemic* in all cases. For further investigations 23 h and 4 °C were chosen as

model conditions. In order to achieve better stereoinduction which might be owing to the poor coordination of copper(II) to the ligand a series of copper(II)- as well as copper(I)-salts with different counter ions were tested in the reaction (entries 5-8). The best results with 53% yield and a *racemic* product were obtained by CuI (entry 7), however, the results were inferior compared to the use of $Cu(OAc)_2 \cdot H_2O$ (entry 1).

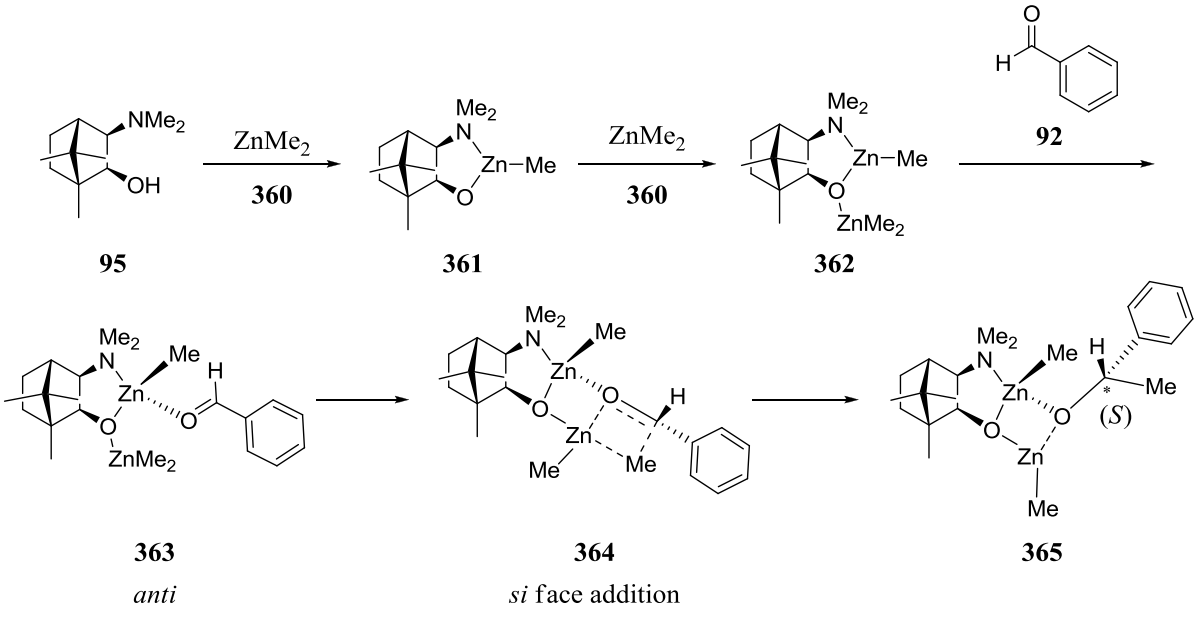
3.5.2 Summary and Outlook

In summary, 1,2-diamino alcohols were utilized as ligands in the copper catalyzed Henry reaction of nitromethane (**187**) and different aldehydes with good yields, however, without stereoinduction. A future prospect can be the application of more oxophilic metals to achieve a better coordination to the substrates and to the used ligands **308**, **317** and **336**.

3.6 1,2-Diamino Alcohols as Ligands in the Enantioselective Addition of Diethylzinc to Aldehydes

3.6.1 Introduction and Application

Oguni and Omi made the outstanding discovery that a combination of (*S*)-leucinol[259] or amino alcohols[260] and various metals catalyze the addition of diethylzinc (**92**) to benzaldehyde (**93**) in moderate stereoselectivities. Moreover, worth mentioning is the finding of the first highly enantioselective addition of dialkylzinc to aldehydes catalyzed by (−)-3-*exo*-(dimethylamino)isoborneol by Noyori *et al.*[261] in 1986. These two milestones paved the way for a countless number of studies in this field making that transformation to one of the most well investigated ones in organic chemistry. In the further course of time it was figured out that different chiral ligands not only control the stereochemistry but also accelerating the organozinc addition. The most important structural motive are amino alcohols but also amines, amino thiols, disulfides, diselenides, diols (*e.g.* TADDOL and BINOL ligands), sulfonamide and phosphoramide complexes were applied to this type of reaction.[262] Mechanistic studies revealed that the reaction between benzaldehyde (**92**) and dimethylzinc (**360**) catalyzed by (−)-DAIB **95** needs two equivalents dimethylzinc (**360**) to proceed well.[104b, 263] In Scheme 50 the proposed mechanism is displayed.



Scheme 50. Proposed mechanism for the catalytic dimethylzinc (**360**) addition to benzaldehyde (**92**).[104b, 263]

The first step is the addition of dimethylzinc (**360**) to the amino alcohol **95** leading to complex **361** which subsequently coordinates a second dimethylzinc (**360**) by its Lewis basic alkoxy oxygen atom giving **362**. Then, benzaldehyde (**92**) coordinates to **362** which generates the

anti-complex **363** that in the further course is transformed to the transition state **364** where a methyl migrates to the *si* face of the aldehyde to form **365**, which directly reacts with dimethylzinc (**360**) to dissociate the product and regenerate **95**.[262]

As mentioned before, a big number of various acyclic 1,2-amino alcohols **366**-**376**[196b, 213, 264] and sulfonamide ligands **377**-**384**[265] were applied to the asymmetric addition of dialkylzinc to aldehydes and ketones (Figure 21).

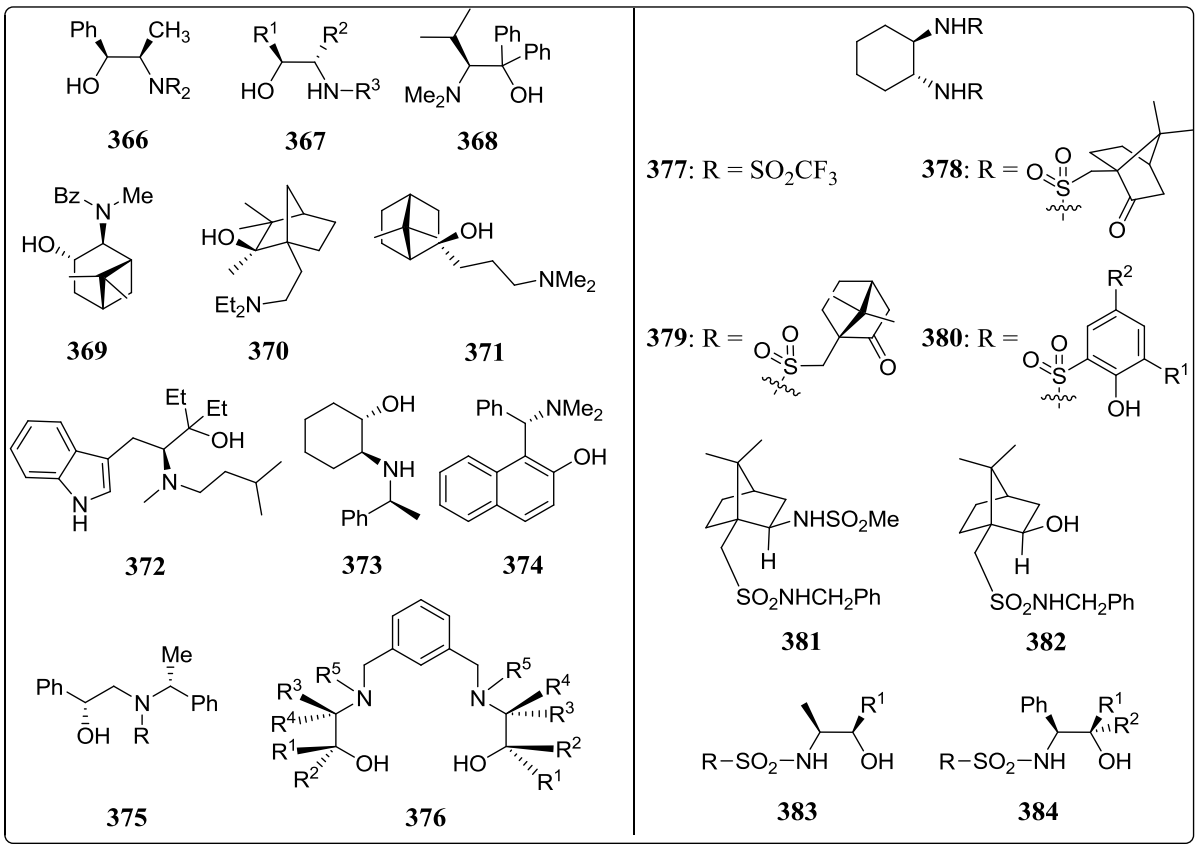
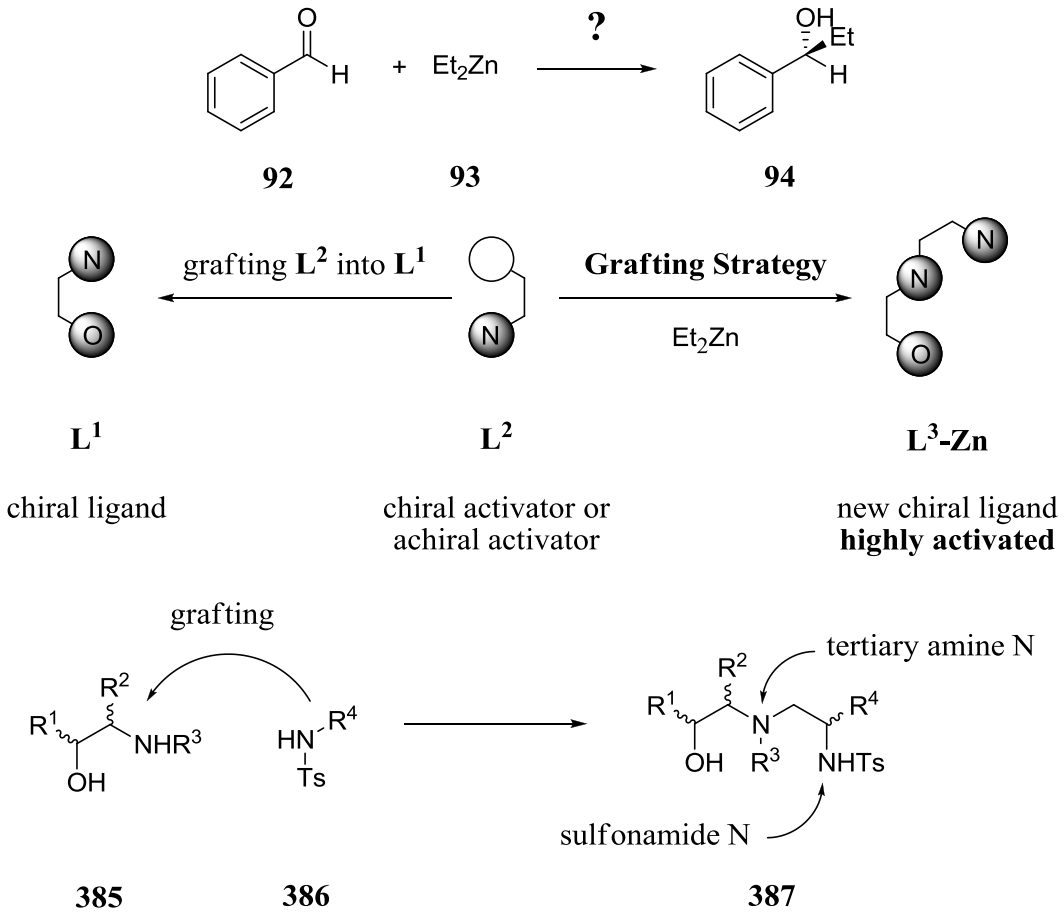


Figure 21. Examples of amino alcohols **366**-**376** and sulfonamides **377**-**384** which were used as ligands in the asymmetric addition of dialkylzinc to aldehydes and ketones.[262]

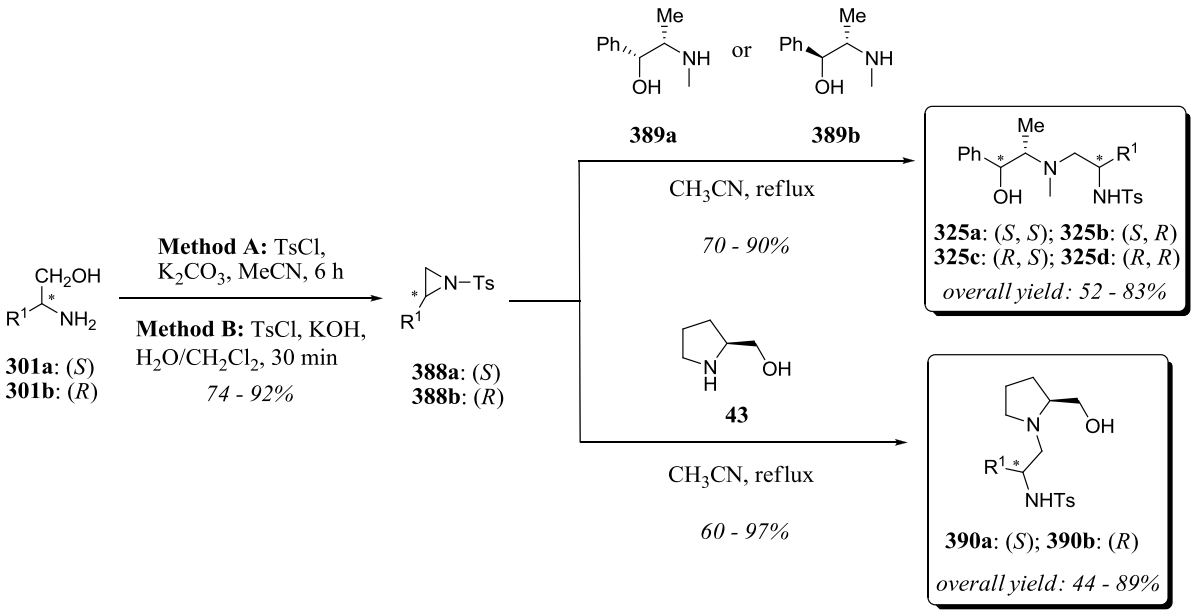
The 1,2-amino alcohols on the left in Figure 21 were excellent ligands in the asymmetric addition of dialkylzinc to aldehydes and ketones yielding outstanding results, whereas the sulfonamides alone showing rather poor results in this reaction.[242, 266] However, also a combination of titanium salts with sulfonamide ligands gave inferior results compared to amino alcohols.[267] Therefore, Lu *et al.*[242] came up with the idea to develop a novel ligand system for the addition of diarylzinc to aldehydes based on a sulfonamide ligand without the necessity of an additional titanium additive, which should be achieved by the so-called grafting strategy. This strategy consists of the combination of 1,2-amino alcohols with sulfonamides in one single molecule (Scheme 51). This concept is based on many literature

reports where a chiral ligand $\mathbf{L^1}$ in combination with another chiral or achiral ligand $\mathbf{L^2}$ as an activator lead to superior results in many stereoselective reactions.[246d, 268]



Scheme 51. Design of novel sulfonamide-amine alcohol ligands by Lu *et al.*.[242]

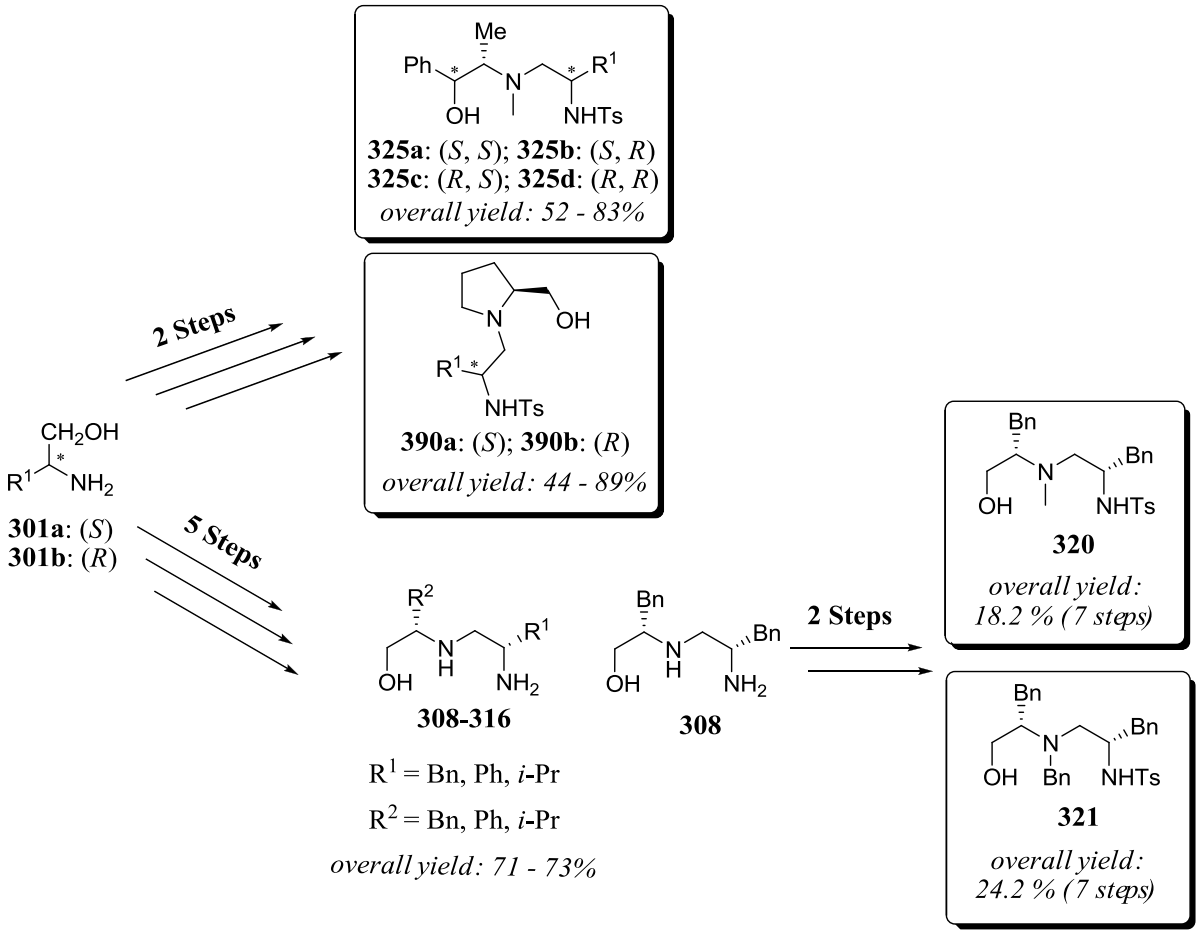
Therefore, Lu and co-workers designed a ligand $\mathbf{L^3}$**-Zn** which owns the advantages of both the amino alcohols and the sulfonamides in one molecule. With this at hand, they predicted improved results compared to the use of each catalyst alone and in addition they avoide the use of moisture sensitive $Ti(O^iPr)_4$. They choose sulfonamides **386** as activators and amino alcohols **385** as chiral ligands to get easy access to the new ligands **387** which are closely related to the 1,2-diamino alcohols (**308-316**) developed by Reiser *et al.*. Moreover, they evolved an easy and simple 2 step synthesis strategy starting from amino alcohols (**301a-b**) (Scheme 52).



Scheme 52. Synthesis of sulfonamide-amine alcohols **325a-d** and **390a-b** developed by Lu *et al.*.[242]

These amino alcohols (**301a-b**) were transferred to the corresponding toyslated aziridines (**388a-b**) and subsequently opened again by reacting them either with the chiral resources (-)-ephedrine (**389a**) and (+)-pseudoephedrine (**389b**) or with *L*-prolinol (**43**). This protocol gave the corresponding acyclic ligands **325a-d** and the prolinol based ligands **390a-b** in enantiopure forms in moderate to excellent overall yields. All in all, this synthesis route is a simple and elegant method to obtain such sulfonamide-amine alcohols **325a-d** and **390a-b**.

In Scheme 53 a comparison of the two synthesis routes is given. The above one, leading to sulfonamide-amino alcohols **325a-d** and **390a-b**, was developed by Lu and co-workers and the below one, leading to sulfonamide-amino alcohols **320** and **321**, was developed by Reiser *et al.*.



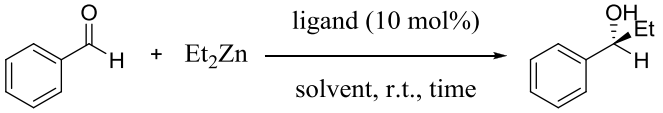
Scheme 53. Comparison of the synthesis of sulfonamide-amine alcohols of Lu and co-workers (**325a-d** and **390a-b**) and the strategy developed by Reiser *et al.* (**320** and **321**).

When looking at Scheme 53 it is immediately noticeable that the synthesis of Lu *et al*. is much shorter than the one of Reiser *et al.*. In both cases the starting point is the easy accessible amino alcohol **301a-b** which in the case of Lu and co-workers is giving rise to the desired products **325a-d** and **390a-b** within two steps in moderate to excellent overall yields, whereas in the case of Reiser *et al.* it takes 7 steps to get the target structures **320** and **321**. However, a closer look on the first method reveals disadvantages compared to the route of Reiser and co-workers. In the latter case, for instance, more possibilities for modifications in a later stage of the synthesis are available. Starting from amino alcohols **308**-**316** there is the possibility to subsequently varying the two amino functions by installing different electron pulling or pushing moieties, whereas in the synthesis of Lu *et al.* one is restricted to the methylated amines **325a-d** or the prolinol based amines **390a-b**. In conclusion, both synthesis routes bearing its individual advantages, the one of Lu *et al.* is much shorter (2 steps) and gives rise to the desired sulfonamide-amine alcohols **325a-d** and **390a-b** in a much better overall yield. However, the route of Reiser and co-workers is much more flexible if one wants to fine tune and adept the ligand structure to a certain problem by changing the moieties in a

later stage of the synthesis. For a more detailed overview of the synthesis by Reiser *et al.* see chapter D on page 107.

Based on the structurally familiarity of the 1,2-diamino alcohols developed in the Reiser group to the sulfonamide-amine alcohols **325a-d** and **390a-b** developed by Lu *et al.* the idea was to apply them in the asymmetric addition of diethylzinc (**93**) to benzaldehyde (**92**) to quantify their impact on the reactivity and stereoselectivity (Table 46). Lu and co-workes obtained the best results by the application of ligand **391** and **394**. In these cases (*S*)-**94** was yielded in 91% and 92% *ee* (entry 1) and (*R*)-**94** was yielded in 86% and >99% *ee* (entry 4). However, they got slightly inferior results in terms of stereoselectivity by utilizing ligand **392** (entry 2) to the reaction. Moreover, in the case of **393** the stereoselectivity was even worse (entry 3). This might be caused by the change of the stereocenter next to the alcohol group from (*R*)- to (*S*)-configuration. In this study five different ligands were utilized to the asymmetric addition of diethylzinc (**93**) to benzaldehyde (**92)**. The 1,2-diamino alcohol **308** containing a primary and a secondary amine and an alcohol group as potential binding sites. Ligand **336** carries an amide function instead of the secondary amine increasing the Lewis acidity at this position and is furnished with different residues at the backbone of the structure, which due to their different sterically demand should give rise to another stereoselectivity in the product. Structures **317, 320**-**321** are tosylated at the primary amine which should lead to a higher acidity at this position compared to the primary amine. And ligand **320** and **321** in addition are methylated or benzylated, respectively, at the secondary amine with the purpose to induce a higher Lewis basicity at this position to see its influence on the reactivity and stereoslectivity. The five different ligands were screened under the conditions of Lu and co-workers (entries 5-9). The results of ligand **308**, **317** and **336** with free secondary amine functionalities showed inferior results (entries 5-7) compared to the ligands **320** and **321** (entries 8-9) with tertiary amines at the core. This led to the conclusion that the Lewis acidity or basicity of the secondary amine is a crucial factor for a well working ligand/catalyst system. The trend appeared to be as following: the more basic the amine is the better the coordination to the zinc gets and at the same time the higher the reactivity and stereoselectivity becomes (increased Lewis basicity of the secondary amine in the row of **336** < **308** ≈ **317** < **320** < **321**). Therefore, the best results were obtained with ligand **321**, namely 61% yield and 75% *ee* (entry 9).

Table 46. Screening of the 1,2-diamino alcohols **308** and **317**, **320**-**321** and the amide **336** in the asymmetric addition of diethylzinc (**93**) to benzaldehyde (**92**).

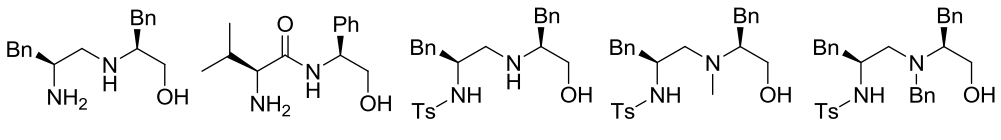


92 **93** **94**

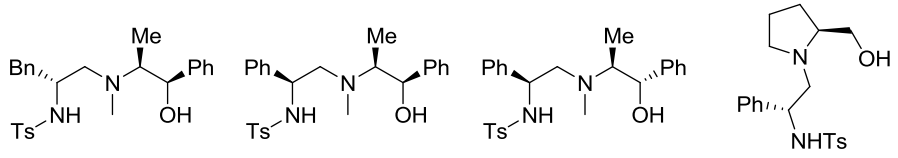
entry [a]	ligand	solvent	time	*ee* [%] [b]	yield [%] [c]
1 [d]	**391**	hexane	24 h	92 (*S*)	91
2 [d]	**392**			81 (*S*)	99
3 [d]	**393**			26 (*S*)	61
4 [d]	**394**			>99 (*R*)	86
5	**308**	hexane	24 h	14 (*R*)	44
6	**336**			3 (*S*)	30
7	**317**			16 (*R*)	22
8	**320**			63 (*R*)	46
9	**321**			75 (*R*)	61
10	**321**	hexane	44 h	57 (*R*)	66
11 [e]	**321**			65 (*R*)	40
12	**308**	toluene	24 h	18 (*R*)	6
13	**317**			n.d.	no product
14	**320**			40 (*R*)	8
15	**321**			50 (*R*)	12

[a]: 0.5 mmol of **92** (51 µL), 1.1 mmol of **93** (1.0 M in hexane) (1.1 mL), 10 mol% ligand, hexane or toluene (c = 0.125 mol/L); **[b]**: Determined by chiral HPLC analysis; **[c]**: Isolated yield; **[d]**: Results of Lu *et al.*, see reference [242]; **[e]**: 3 equiv. of **93** were used.

ligands:



308 **336** **317** **320** **321**



391 **392** **393** **394**

Compared to the results obtained by Lu *et al.* (entries 1-4) the yield and stereoselectivity is slightly impaired, which might be due to the sterically more demanding benzyl moiety next to the tertiary amine of **321** compared to the smaller methyl moiety of ligands **391**-**393** of Lu and co-workers. Moreover, neither a prolonged reaction time from 24 h to 44 h (entry 10) nor the use of 3 equiv. of diethylzinc (**93**) (entry 11) instead of 2.2 equiv. improved the outcome. Furthermore, the solvent was changed from hexane to toluene because some literature reports claimed that this lifts up the reactivity in such transformation. However, the results were inferior (entries 12-15) compared to the ones obtained with hexane as solvent (entries 5-9), whereas the same trend as in hexane was observable as ligands **320** (entry 14) and **321** (entry 15) again delivered the best results.

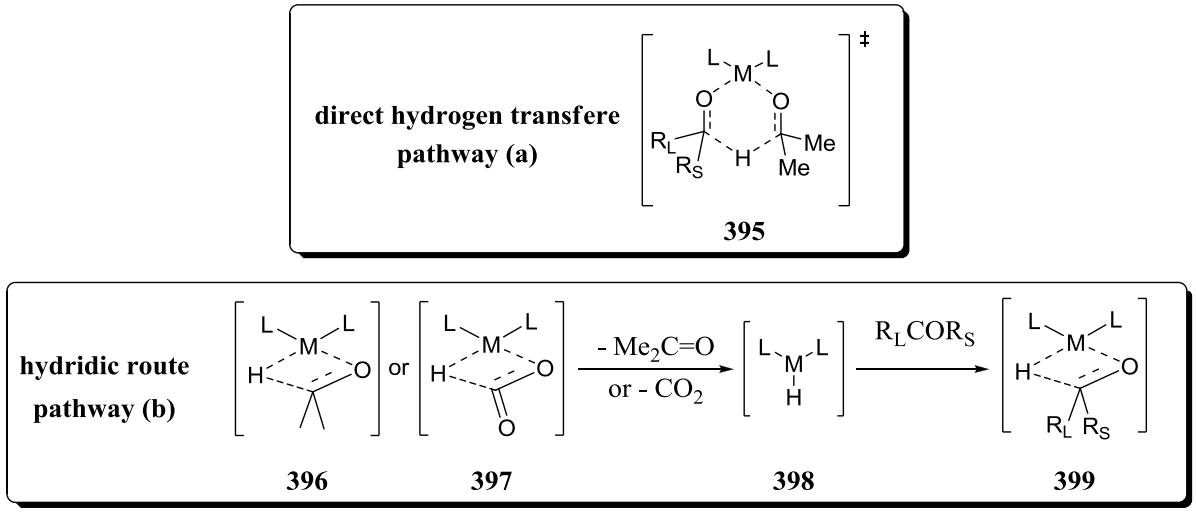
3.6.2 Summary and Outlook

All in all, this application is a further example of the broad applicability of 1,2-diamino alcohols in organic transformations as ligands as well as catalysts. Especially, in this example the benefit of flexibility and adaptability by functionalization with different moieties is evident. Three further points for improvement are thinkable. First, the alkylation of the secondary amine with even more electron pulling residues might further increase the Lewis basicity at this position to probably give superior results. Second, the utilization of other 1,2-diamino alcohols (**308**-**316**, see Figure 19, page 109) with different moieties at the two chiral centers and third, the application of additional $Ti(O^iPr)_4$ because it is known to improve the reactivity and stereoselectivity in this transformation.

3.7 1,2-Diamino Alcohols as Ligands in the Ruthenium-Catalyzed Enantioselective Transfer Hydrogenation of Ketones

3.7.1 Introduction and Application

Transfer hydrogenations reach high enantioselectivities in diverse transformations. *E.g.* oxidoreductases such as horse liver alcohol dehydrogenase catalyze the transfer hydrogenation of carbonyl compounds to alcohols using cofactors like NADH or NADPH, are one among many elegant and high efficient methods in nature's potpourri of fascinating processes. Thus, it got an ulterior motive beneath organic chemists to develop widely applicable and highly efficient asymmetric reductions of different carbonyl compounds to get easy access to a broad scope of chiral alcohols.[269] These methods bear some tremendous benefits compared to earlier developed procedures utilizing oxazaborolidine- and BINAP-Ru(II) complex catalysts, including an easy feasibility, the use of non-hazardous reagents like *i*-PrOH as hydrogen source instead of molecular hydrogen and most important the increased reactivity and stereoselectivity.[269-270] There are two pathways how the hydrogenation of ketones takes place: **(a)** by a direct hydrogen transfer or **(b)** *via* a hydridic route (Scheme 54).



Scheme 54. Two possible pathways of the transfer hydrogenation of ketones: **(a)** direct hydrogen transfer and **(b)** hydridic route.[269-270]

Pathway **(a)** includes a six-membered cyclic transition state **395** consisting of the hydride source (*i*-PrOH) and the ketone, related to the mechanism of the Meerwein-Ponndorf-Verley (MPV) reduction.[271] In contrast, pathway **(b)** proceeds stepwise and is presumed running over the metal hydride **399** which is generated by cleaving off

acetone or CO_2 form the complexes **396** or **397**, respectively. The hydride transfer step takes place in complex **399**. A mentionable side note that in general main group metals are following mainly pathway **(a)** (direct hydrogen transfer)[271a, 271b], whereas transition metal complexes are preferentially following pathway **(b)** (hydridic route).[269] In order to increase the reactivity and stereoselectivity of the enantioselective transfer hydrogenation of ketones many ligands were developed in the past few years (mainly based on rhodium, iridium or ruthenium metals). In Figure 22 are shown a few examples of ligands which were used in the asymmetric transfer hydrogenation of acetophenone (**406**).

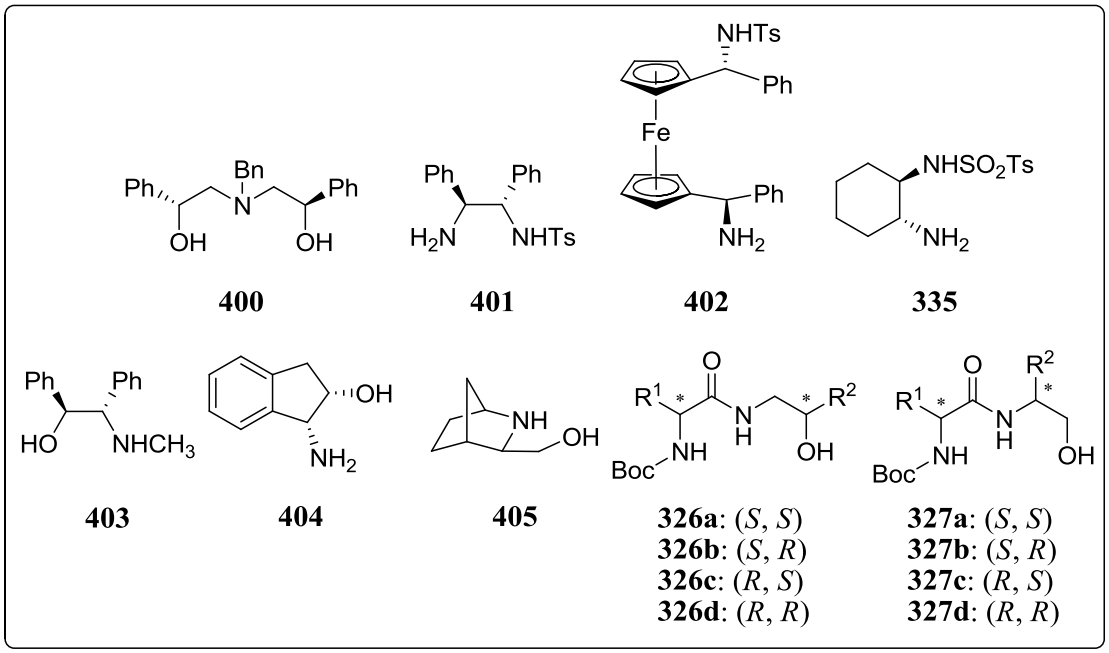
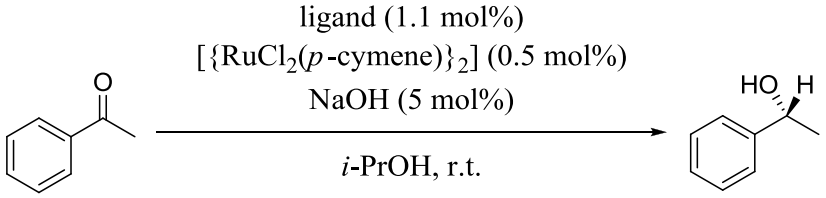


Figure 22. Ligands used in asymmetric transfer hydrogenation of acetophenone (**406**).

The trident ligand **400** in combination with Sm(III) was used by Evans *et al.*[272] in an asymmetric reduction of aromatic ketones in propan-2-ol to yield the products in excellent enantioselectivities. Moreover, a big group and presumably the most important one is represented by the monotosylated 1,2-diamines **335**, **401**-**402** and 1,2-amine alcohols **403**-**405**. The pioneering work in this field was done by Noyori and co-workers who applied ligand **401** to the Ru(II)-catalyzed transfer hydrogenations to achieve outstanding results in both reactivity and enantioselectivity.[269, 273] Furthermore, Knochel and co-workers used monoarylsulfonylated ligands **335** and **402** in asymmetric reductions with almost identical results as Noyori.[274] β-amino alcohols **403**-**405** are a third group that show a big potential in catalyzing transfer hydrogenations in combination with Ru(II).[269, 270b, 275] Furthermore, Adolfsson *et al.* synthesized a library of different readily available dipeptide analogous **326a-d** and **327a-d** and successfully applied them to the enantioselective transfer

hydrogenation of various ketones.[243] Based on these promising results and the similarity of the 1,2-diamino alcohols (**308**-**316**) developed in the Reiser group to the pseudo dipeptides **326a-d** and **327a-d**, they were applied as ligands in the enantioselective transfer hydrogenation of acetophenone (**406**). Thus, following the precedent set by Adolfsson and co-workers, the first experiments were carried out using the same conditions as they did. They used 2-propanol as hydrogen source, which is easy handable, non-toxic and inexpensive. Nevertheless, there are also certain drawbacks the most undesired one is for sure the reversibility of the reaction under these conditions, thus in order to minimize the unfavorable back reaction the substrate concentration has to be kept low during the reaction. $[RuCl_2(\eta^6\text{-arene})]_2$ is used as metal source, which by heating in the presence of base, usually NaOH or KOH, *in situ* forms a chiral Ru complex with the ligand.[269, 276] With this conditions at hand the first test reactions with the 1,2-diamino alcohols **308**, **317**, **320**-**321** and the amido alcohol **336** were carried out (Table 47). Adolfsson and co-workers obtained the best results with the Boc-protected peptide ligands **408** and **409** (entries 1-2).[243] The best results in terms of conversion were achieved by the use of ligand **308** which yielded (*S*)-**407** in 90% and 18% *ee* (entry 3). However, the best results in terms of stereoselectivity were obtained with ligand **321** which gave (*R*)-**407** in 57% *ee* after 2 h (entry 7). In order to increase the yield in this case the reaction time was prolonged to 23 h (entry 8), but only the *ee* of (*R*)-**407** was drastically decreased to 8%. Moreover, ligand **308** (entry 3) is exclusively giving rise to excess (*S*)-**407**, whereas in all other cases (entries 4-8) (*R*)-**407** was the major enantiomer. Compared to the results of Adolfsson *et al.* (entries 1-2), ligands **308**, **317**, **320**-**321** and **336** gave inferior results (entries 3-8). This led to the assumption that the reactivity and stereoselectivity is strongly depending on the nature of the primary and secondary amine, owing to the fact that ligand **308** is the only one with two unmodified amine functionalities, whereas in ligand **336** the amide function instead of the secondary amine is present and ligands **317**, **320**-**321** are tosylated at the primary amine and in addition the secondary amine is alkylated. Both modifications are influencing the Lewis acidity or basicity at these positions which in consequence might have a weakening effect on the coordination ability of the ligand to the ruthenium leading to an unfavorable ligand-Ru-complex that delivers inferior results in the reaction.

Table 47. Application of 1,2-diamino alcohols **308**, **317**, **320**-**321** and amide **336** as ligands in the enantioselective transfer hydrogenation of acetophenone (**406**).[243]

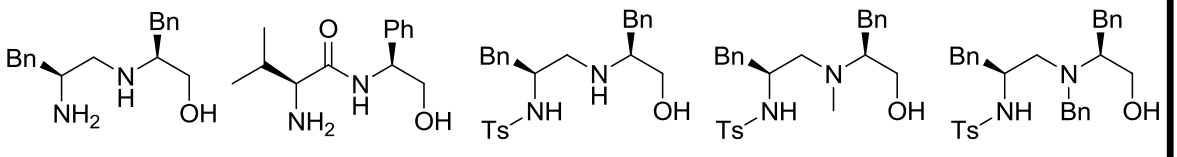


406 **407**

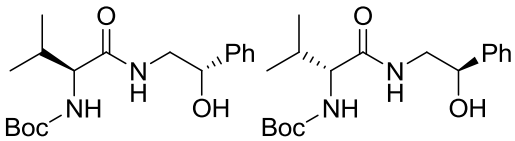
entry [a]	ligand	time [h]	*ee* [%] [b]	conversion [%] [b]	yield [%] [b]
1 [c]	**407**	2	93 (*S*)	91	n.d.
2 [c]	**408**		93 (*R*)	92	n.d.
3	**308**	2	18 (*S*)	93	90
4	**336**	4	6 (*R*)	4	0.7
5	**317**	2	23 (*R*)	17	15
6	**320**	2	2 (*R*)	9	4
7	**321**	2	57 (*R*)	5	4
8	**321**	23	8 (*R*)	8	3

[a]: 2 mmol of **406** (233 μL), 1.1 mol% ligand, 0.5 mol% Ru-salt (6 mg), 5 mol% NaOH (4 mg), 10 mL *i*-PrOH (c = 0.2 mol/L); **[b]**: Determined by chiral GC analysis using dodecane as internal standard; **[c]**: Results of Adolfsson *et al.*, see references [243]; **n.d.** = not determined.

ligands:

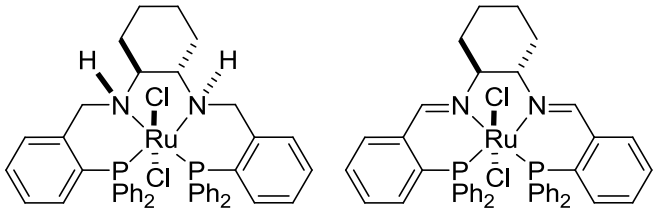


308 **336** **317** **320** **321**



408 **409**

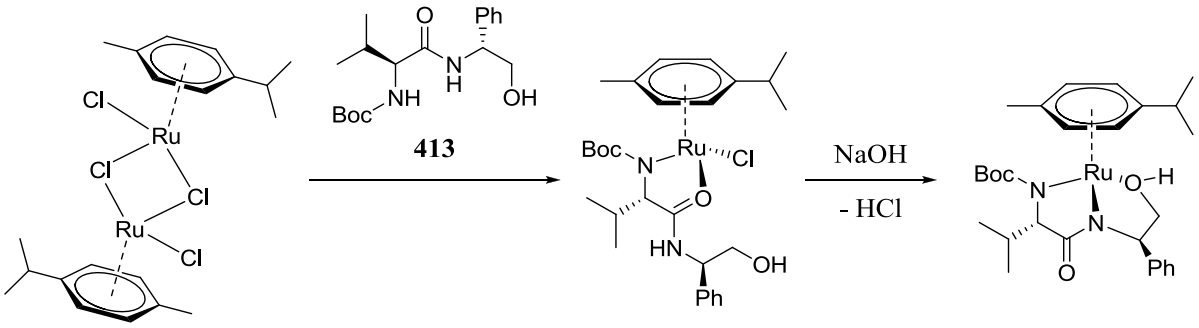
Furthermore, Noyori and co-workers compared almost similar diphosphine/diamine ligand **410** with a diphosphine/diimine ligand **411** which only differ in the lack of the H atoms at the imine positions causing a drastic loss of reactivity in the catalysis (Figure 23).[269]



(*S*,*S*)-**410** (*S*,*S*)-**411**

Figure 23. Comparison of diphosphine/diamine ligand **410** and diphosphine/diimine ligand **411** in the catalytic reduction of acetophenone (**406**).

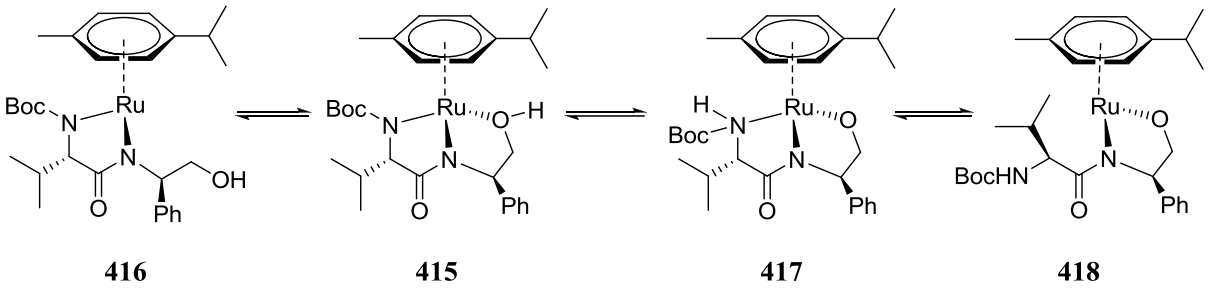
Additionally, Adolfsson *et al.* made some statements about a possible mechanism of their pseudo dipeptide analogous based on ligand **413** (Scheme 55).[243a]



412 [{$RuCl_2$(*p*-cymene)}$_2$] **413** **414** **415**

Scheme 55. Proposed route for the formation of the pre-catalyst **415** by Adolfsson *et al.*.[243a]

The initial step is the formation of complex **414** by coordination of the Boc-protected amine and the amide oxygen to the ruthenium. Then, the amide proton is cleaved of by addition of base leading to complex **415** where the alcohol group is believed to be crucial for the generation of a stabilized 18-electron complex. Furthermore, it was argued that there takes place a simultaneous transfer of a hydride and a proton between the hydrogen donor/substrate and the ruthenium complex giving rise to the 16-electron complexes **416** or **418** which in the further course could form the active ruthenium hydride (Scheme 56).



Scheme 56. Postulated pre-catalyst equilibrium.[243a]

It was assumed that the formation of complex **416** strongly depends on the acidity of the proton at the *N*-terminus, which is mainly influenced by the sort of protecting group. A tosylated *N*-terminus, for example, would lead to a more acidic proton compared to the Boc-protected one, and also a free *N*-terminus should favor the formation of **416** owing to the increased coordinating ability of the primary amine, thus, in both cases, a low reactivity is observed. This was a hint that the reaction presumably proceeding over the 16-electron complex **418** which means that the alcohol functionality is an important structural motive for the high reactivity and stereoselectivity.

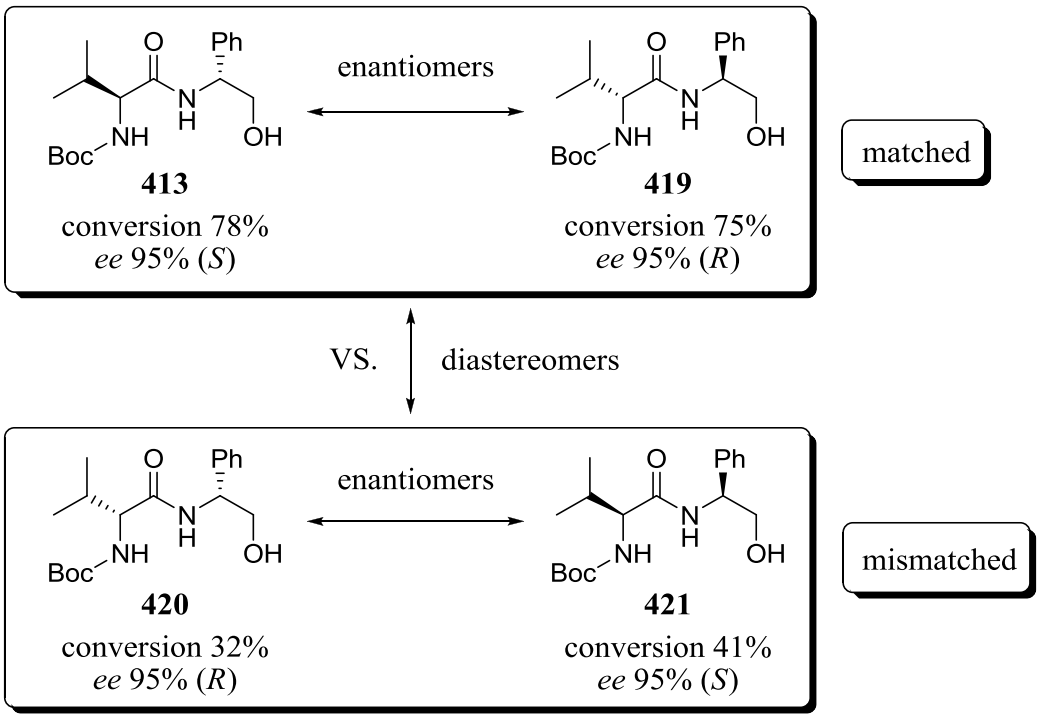


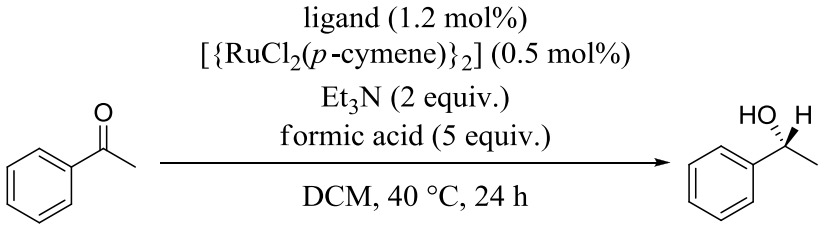
Figure 24. Matched/Mismatched scenario by comparing the 4 stereoisomers **413** and **419-421** in the enantioselective transfer hydrogenation of acetophenone (**406**).

Adolfsson and co-workers[243] discovered a second essential factor for the smooth proceeding of the reaction, namely the orientation of the moieties at the two chiral centers and their steric hindrance. By comparing the results of the four stereoisomers **413** and **419-421** in the

enantioselective hydrogenation of acetophenone (**406**) it is becoming obvious that there is a matched/mismatched situation (Figure 24). When looking at the results obtained with the ligands **413** and **419** which are enantiomers to each other, they showed a high reactivity and stereoselectivity which suggested a matched scenario. The (*L*)-amino acid based ligand **413** gave the product in (*S*) configuration, whereas the (*R*)-amino acid based ligand **419** gave the product in (*R*) configuration. However, ligands **420** and **421** produced almost the same results, but a decreased reactivity compared to the other two diastereomers which points to a mismatched case.

A second approach was done by changing the conditions from the system consisting of *i*-PrOH and NaOH to the system of acetic acid and triethylamine, which was already successfully applied by Noyori *et al.* to the enantioselective transfer hydrogenation of various aromatic ketones catalyzed by a ruthenium complex with a tosylated diamine as ligand.[269, 273b] This system bears the advantage that the reaction is irreversible in contrast to the use of *i*-PrOH, thus in principle a conversion of 100% is possibly.[269] Encouraged by these promising results the 1,2-diamino alcohols **308**, **317**, **320**-**321** and the amide **336** were applied to the transfer hydrogenation under these conditions (Table 48).

Table 48. Application of 1,2-diamino alcohols **308**, **317, 320**-**321** and amide **336** as ligands to the enantioselective transfer hydrogenation of acetophenone (**406**).

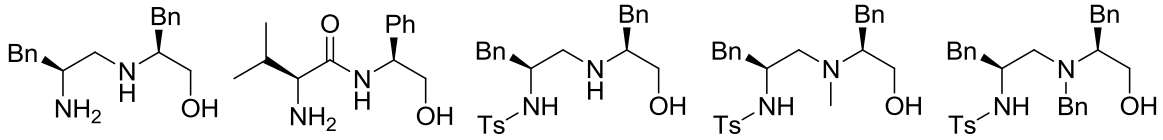


406 **407**

entry[a]	ligand	*ee* [%] [b]	conversion [%] [b]	yield [%] [b]
1	**308**	1 (*R*)	16	11
2	**336**	5 (*R*)	26	19
3	**317**	1 (*R*)	13	5
4	**320**	1 (*R*)	16	9
5	**321**	1 (*R*)	16	10

[a]: 1.25 mmol of **406** (146 µL), 6.25 mmol acetic acid (236 µL), 2.5 mmol Et_3N (347 µL), 1.2 mol% ligand, 0.5 mol% Ru-salt (3 mg), 1mL DCM (c = 1.25 mol/L); **[b]**: Determined by chiral GC analysis using dodecane as inetrnal standard.

ligands:



308 **336** **317** **320** **321**

The best results were obtained by the amide **336** which produced 19% yield and 5% *ee*, whereas the 1,2-diamino alcohols **308** and **317**, **320**-**321** gave inferior results (entry 1 and 3-5) leading to the conclusion that these conditions are not suitable for these ligands.

3.7.2 Summary and Outlook

In summary, the tosylated 1,2-diamino alcohols **308** and **317**, **320**-**321** and the amide **336** were applied to the transfer hydrogenation of acetophenone (**406**) under various conditions. However, only 1,2-diamino alcohol **308** in combination with *i*-PrOH as hydrogen source showed good results in reactivity. Moreover, the acidity of the proton at the tosylated amine

was probably found to be the reason for the inferior reactivity, thus the installation of other protecting groups like the Boc- or Cbz-group might lead to an increased reactivity and selectivity. Furthermore, based on the knowledge of a matched/mismatched catalyst situation, there is the possibility to attach different residues at the backbone of the ligands to perhaps create a matched case leading to an increase of reactivity and selectivity

4. Summary and Outlook

In this chapter a new and straight forward synthesis strategy starting from easy accessible amino alcohols giving rise to a library of nine new and unknown 1,2-diamino alcohol derivatives (**308**-**316**) was presented. Furthermore, this method paves the way for manifold modifications at various positions of the catalyst in a late stage of the synthesis making it enormous adaptable to suddenly occurring problems in catalysis. In the further course, the wide scope of asymmetric reactions and transformations that could be performed with these 1,2-diamino alcohols (**308**-**316**), which in general are able to serve as organocatalysts or as ligands, was demonstrated. They were applied to the Michael addition, the aldol reaction, the asymmetric Friedel-Crafts alkylation, the Henry reaction, the enantioselective addition of diethylzinc (**92**) to aldehydes or ruthenium-catalyzed enantioselective transfer hydrogenation of ketones. In conclusion, 1,2-diamino alcohols offer outstanding features and advantages owing to their simple and adaptable synthesis and their versatile applicability in different organic reactions. However, in most cases the synthetic results of the 1,2-diamino alcohol catalysts could not compete with established literature catalysts.

E Summary

Chapter A gives an overview on the most common activation modes used in organocatalysis. In addition, for every activation mode selected examples of most commonly used organocatalysts are described.

After summarizing the nonlinear effect (NLE) and 4-subsitiuted *L*-proline derivatives as well as their application in organocatalysis, *chapter B* describes the synthesis of two 4-substituted *L*-proline derivatives. In the further course, the investigation and optimization of a newly developed (4-substituted-)*L*-proline/metal catalyzed asymmetric aldol reaction is outlined, including the investigation of the NLE and an upscaling procedure. Moreover, the application of (4-substituted-)*L*-proline/metal-complexes to other *L*-proline catalyzed reactions like the Michael addition or the Baylis-Hillman reaction was examined.

After a short introduction on the history and application of box ligands in asymmetric catalysis, especially a combination of aza-box and $CoCl_2 \cdot 6H_2O$, *chapter C* describes the development of a catalytic system based on the combination of different aza-box ligands and $CoCl_2 \cdot 6H_2O$ and its application in the asymmetric Baylis-Hillman reaction.

In *chapter D,* a short introduction summarizes the utilization of primary amines and acyclic 1,2-amino alcohols in organocatalysis. Moreover, the most common synthesis strategies for acyclic 1,2-amino alcohols are briefly described. A novel synthesis strategy for the preparation of a library of nine different 1,2-diamino alcohols and their subsequent modification is shown. In addition, the structures were applied to a great number of asymmetric reactions either as catalysts or as ligands, including the Michael addition, the aldol reaction, the Friedl-Crafts alkylation, the Henry reaction, the enantioselective addition of diethylzinc to aldehydes and the ruthenium-catalyzed enantioselective transfer hydrogenation of ketones.

F Experimental Part

1. Instruments and General Techniques

1.1 Solvents and Chemicals

The used commercially available chemicals where purchased in high quality and where used without further purification. Absolute THF, Et_2O and CH_2Cl_2 were taken from a MB-SPS solvent purification system. Other absolute solvents were prepared by established laboratory procedures. EtOAc, hexanes (petroleum ether, PE (60/40)) and DCM were distilled prior to use for column chromatography. Reactions with moisture and oxygen sensitive reagents were carried out in flame dried glassware under an atmosphere of predried nitrogen.

1.2 NMR-Spectrometry

^{1}H-NMR spectra were recorded on BRUKER Avance 300 (300 MHz) and BRUKER Avance III 400 "Nanobay" (400 MHz) Spectrometer. The chemical shifts were reported in δ parts per million (ppm) relative to chloroforme-d_1 ($CDCl_3$, 7.26 ppm), dichloromethane-d_2 (CD_2Cl_2, 5.32 ppm), methanol-d_3 (CD_3OH, 3.34 ppm), dimethylsulfoxid-d_6 (C_2D_6SO, 2.50 ppm). Spectra were evaluated in 1st order and coupling constants (*J*) are reported in Hertz (Hz). Splitting patterns for the spin multiplicity in the spectra are given as follows: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, dd = doublet of a doublet, ddd = doublet of a doublet of a doublet, dt = doublet of a triplet, m = multiplet. Integration is determined as the relative number of atoms.

^{13}C-NMR spectra were recorded on BRUKER Avance 300 (75 MHz) and BRUKER Avance III 400 "Nanobay" (100 MHz) Spectrometer. The chemical shifts were reported in δ parts per million (ppm) relative to chloroforme-d_1 ($CDCl_3$, 77.0 ppm), dichloromethane-d_2 (CD_2Cl_2, 53.84 ppm), methanol-d_3 (CD_3OH, 49.0 ppm), dimethylsulfoxid-d_6 (C_2D_6SO, 39.52 ppm). Multiplicities of the signals were assigned with DEPT 135 and are stated as: + = primary or tertiary carbon (positive intensity in DEPT 135), − = secondary carbon (negative intensity in DEPT 135), Cq = quaternary carbon (zero intensity in DEPT).

1.3 Mass spectrometry (MS)

Mass spectrometry was performed by the central analytical department of the University of Regensburg on Finnigan MAT 95, ThermoQuest Finnigan TSQ 7000, Agilent Q-TOF 6540 UHD and Finnigan MAT SSQ 710 A.

1.4 Elemental microanalysis

Elemental microanalysis was measured on a Vario EL III or Mikro-Rapid CHN (Heraeus) by the central analytical department of the University of Regensburg.

4.1.5 X-Ray Structure Analysis

Analysis of single crystals was performed on an Agilent Technologies SuperNova, Agilent Technologies Gemini R Ultra or Stoe IPDS by the X-Ray crystallographic department of the University of Regensburg.

1.6 Infrared Spectroscopy (IR)

Infrared spectroscopy in form of ATR-IR spectroscopy was carried out on a Biorad Excalibur FTS 3000 Spectrometer, equipped with a Specac Golden Gate Diamond Single Reflection ATR-System.

1.7 Optical Rotations

Optical rotations were determined in a Perkin Elmer 241 polarimeter at 589 nm wavelength (sodium-*d*-line) in a 1.0 dm measuring cell.

1.8 Chromatography

Thin Layer Chromatography (TLC) was performed with TLC precoated aluminum sheets (Merck silica gel 60 F 254, d = 0.2 mm). Visualization was accomplished by UV light (λ = 254 nm or 366 nm), staining with vanillin (1.25 g Vanillin, 8 mL conc. sulfuric acid, 25 mL conc. acetic acid, 215 mL methanol), ninhydrin (300 mg ninhydrin, 5 mL conc. acetic acid, 35 mL isopropyl alcohol) or potassium permanganate (1.5 g of $KMnO_4$, 10 g K_2CO_3, 1.25 mL 10% NaOH in 200 mL water).

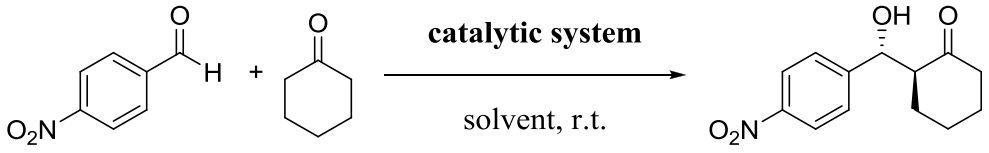
Column Chromatography was performed with silica gel (Merck, Geduran 60, 0.063-0.200 mm particle size) and flash silica gel 60 (Merck, 0.040-0.063 mm particle size).

Gas Chromatography (GC) was performed on a Fisons GC 8000 using a flame ionization detector.

High Performance Liquid Chromatography (HPLC) Analytical HPLC was performed on a Varian 920-LC with DAD. Phenomenex Lux Cellulose-1 and Cellulose-2, Chiralcel OD-H and OJ-H, and Chiralpak AS-H served as chiral stationary phase, and mixtures of *n*-heptan and *i*-PrOH were used for eluation.

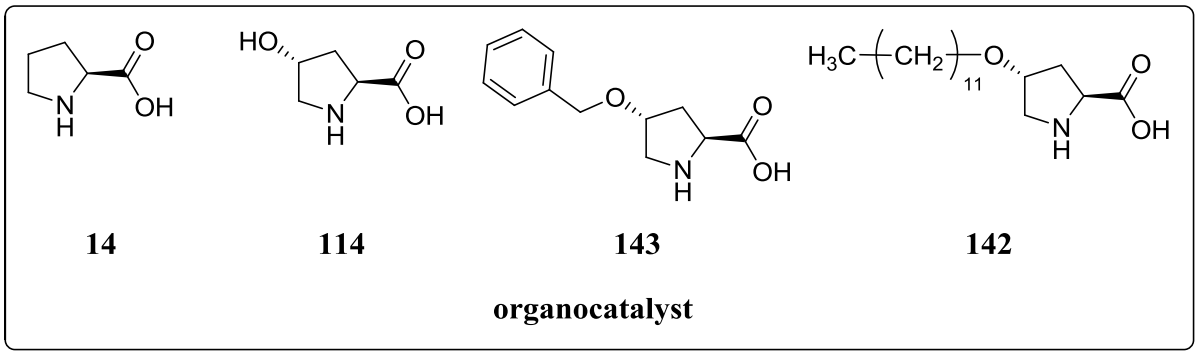
2. Synthesis of Compounds

General procedure for the organocatalyzed aldol reactions between *p*-nitrobenzaldehyde (149) and cyclohexanone (150) under ambient conditions (GP-1):



149 **150** **152**

catalytic system: Combination of **organocatalyst** and **metal salt**.



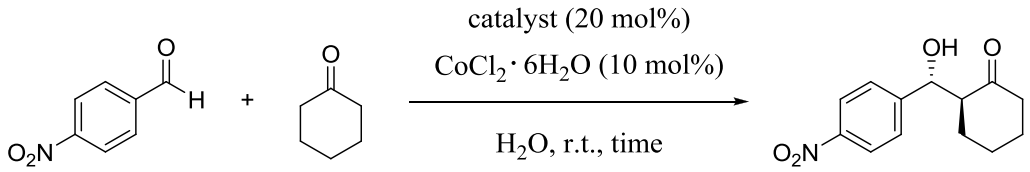
14 **114** **143** **142**

organocatalyst

+ **metal salt**

The **catalytic system** (**organocatalyst** and **metal** in a 2:1 molar ratio or only **organocatalyst**) was dissolved in the specified amount of solvent and the mixture was stirred at r.t. for 15 min. Subsequently cyclohexanone (**150**) (3 equiv.) and aldehyde (**149**) (1 equiv.) were added and the mixture was stirred at r.t. for the indicated time. The reaction was monitored by TLC until full consumption of *p*-nitrobenzaldehyde (**149**) was observed. The reaction mixture was quenched with NH_4Cl (sat.) and extracted with EA (3x). The combined organic layers were evaporated under reduced pressure to obtain the crude product (*diasteriomeric ratio* was determined by ^{1}H-NMR of the crude product). The crude product was purified *via* flash column chromatography (silica, PE/EA = 3:1) and the enantiomeric excess (*ee*) was analyzed by chiral HPLC.

Table 49. Detailed screening of *L*-proline (**14**) and the 4-substituted *L*-proline derivatives **114**, **142** and **143** in the direct aldol reaction between *p*-nitrobenzaldehyde (**149**) and cyclohexanone (**150**) in water.

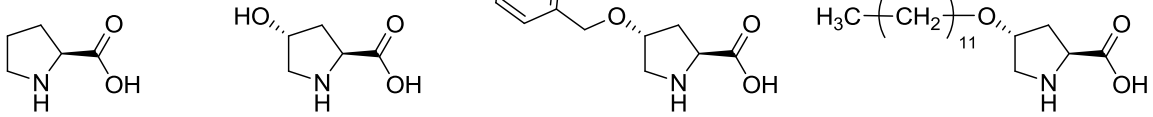


149 **150** **152**

entry [a]	catalyst	time [h]	*d.r.* (*anti*/*syn*) [b]	*ee* [%] [c]	yield [%] [d]
1	**14**	95	11:1	97	46
2	**14**/$CoCl_2 \cdot 6H_2O$		14:1	97	39
3	**114**	95	12.5:1	96	49
4	**114**/$CoCl_2 \cdot 6H_2O$		20:1	96	15
5	**142**	24	20:1	97	90
6	**143**/$CoCl_2 \cdot 6H_2O$		20:1	99	93
7	**142**	24	20:1	98	90
8	**142**/$CoCl_2 \cdot 6H_2O$		20:1	98	91

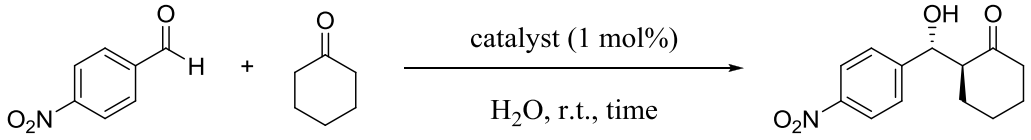
[a]: 1 mmol of **149** (151 mg), 3 mmol of **150** (310 µL), 20 mol% catalyst, 10 mol% $CoCl_2 \cdot 6H_2O$ (24 mg), solvent (0.1 mL per mmol aldehyde); **[b]**: Determined from the ^{1}H-NMR spectrum of the crude reaction mixture; **[c]**: Determined by chiral HPLC analysis of the combined, isolated *anti*- and *syn*-product; **[d]**: Combined, isolated yield of *anti*- and *syn*-product.

catalysts:



14 **114** **143** **142**

Table 50. Detailed screening of *L*-proline (**14**) and the 4-substituted *L*-proline derivatives **114**, **142** and **143** in the direct aldol reaction between *p*-nitrobenzaldehyde (**149**) and cyclohexanone (**150**) in water.

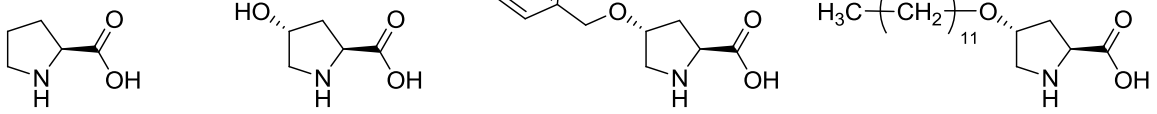


149 **150** **152**

entry [a]	catalyst	time [h]	*d.r.* (*anti*/*syn*) [b]	*ee* [%] [c]	yield [%] [d]
1	**14**	141	14.3:1	19	16
2	**114**		n.d.	n.d.	traces
3	**143**	30	26:1	99	87
4	**142**		29:1	> 99	91

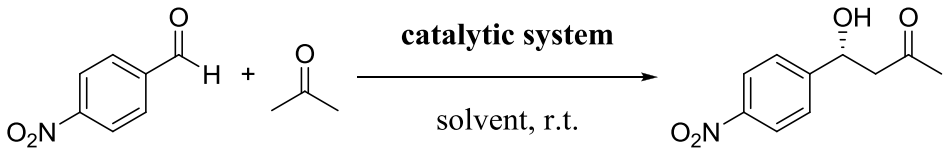
[a]: 1 mmol of **149** (151 mg), 3 mmol of **150** (310 µL), 1 mol% catalyst, H_2O (0.1 mL per mmol aldehyde); **[b]**: Determined from the ^{1}H-NMR spectrum of the crude reaction mixture; **[c]**: Determined by chiral HPLC analysis of the combined, isolated *anti*- and *syn*-product; **[d]**: Combined, isolated yield of *anti*- and *syn*-product; **n.d.** = not determined.

catalysts:



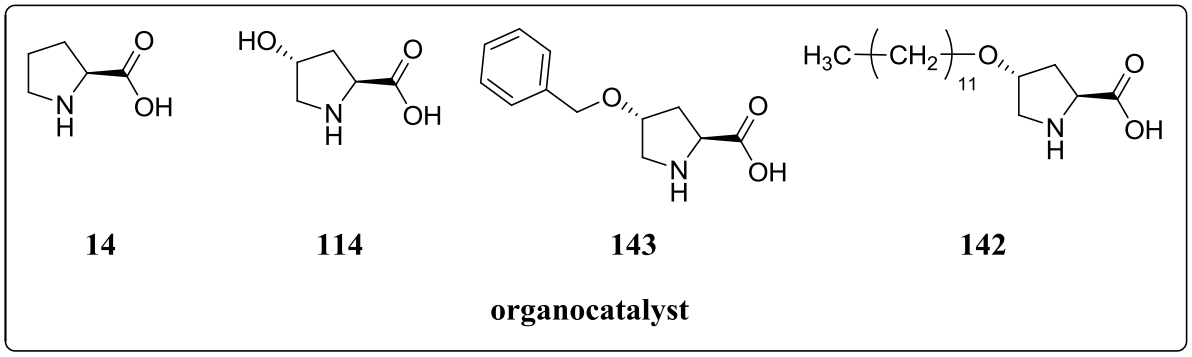
14 **114** **143** **142**

General procedure for the organocatalyzed aldol reactions between *p*-nitrobenzaldehyde (149) and acetone (130) under ambient conditions (GP-2):



149 **130** **151**

catalytic system: Combination of **organocatalyst** and **metal salt**.



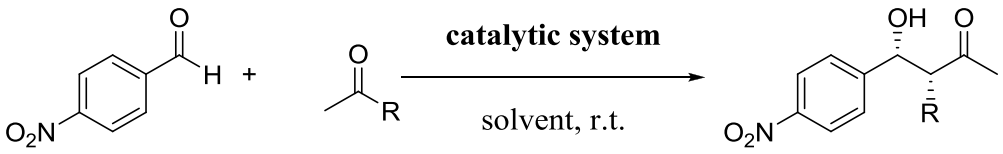
14 **114** **143** **142**

organocatalyst

+ metal salt

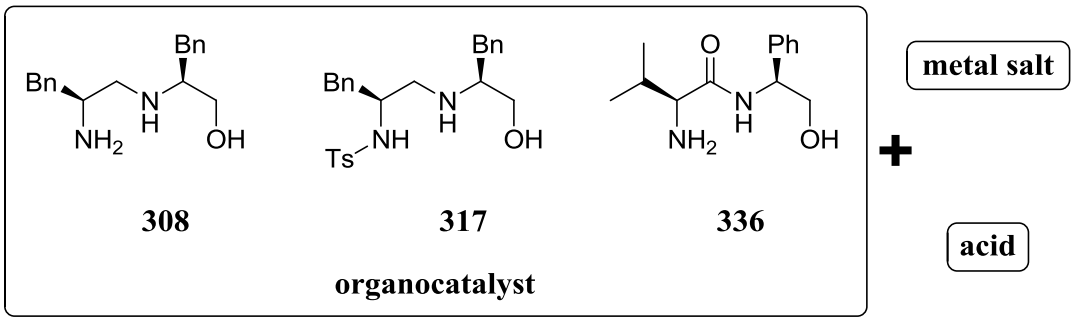
The **catalytic system** was dissolved (**organocatalyst** and **metal salt** in a 2:1 molar ratio or only **organocatalyst**) were dissolved in the specified amount of solvent and the mixture was stirred at r.t. for 15 min. Subsequently, acetone (**130**) and *p*-nitrobenzaldehyde (**149**) (1 equiv.) were added and the mixture was stirred at r.t. for the indicated time. The reaction was monitored by TLC until full consumption of the *p*-nitrobenzaldehyde (**149**) was observed. The reaction mixture was quenched with NH_4Cl (sat.) and extracted with EA (3x). The combined organic layers were evaporated under reduced pressure to obtain the crude product. The crude product was purified *via* flash column chromatography (silica, PE/EA = 2:1) and the enantiomeric excess (*ee*) was analyzed by chiral HPLC.

General procedure for the organocatalyzed aldol reactions between *p*-nitrobenzaldehyde (149) and acetone (130) under ambient conditions (GP-3):



149 **130**: R = CH_3 **151**: R = H
338: R = CH_2-OH **339**: R = OH

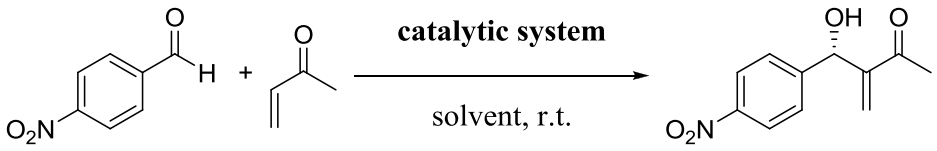
catalytic system: Combination of **organocatalyst**, **metal salt** and **acid**.



308 **317** **336**

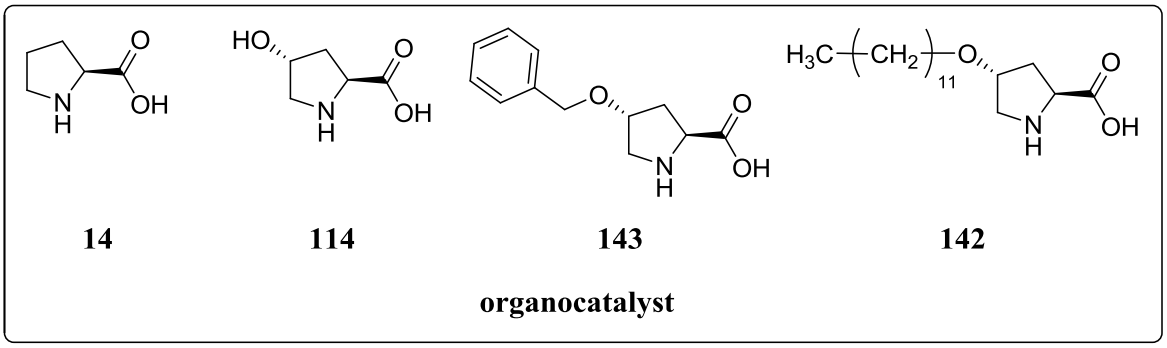
The **organocatalyst** and **metal salt** (1:1 molar ratio) were dissolved in the specified amount of solvent and the mixture was stirred at r.t. for 15 min. Subsequently **acid** was added (when stated) and the mixture was stirred at r.t. for another 15 min. Then acetone (**130**) or hydroxyacetone (**338**) and *p*-nitrobenzaldehyde (**149**) (1 equiv.) were added and the mixture was stirred at r.t. for the indicated time. The reaction was monitored by TLC until full consumption of the *p*-nitrobenzaldehyde (**149**) was observed. The reaction mixture was quenched with NH_4Cl (sat.) and extracted with DCM (3x). The combined organic layers were washed with water (1x) (in the case of acetone (**130**) as ketone source) or NaCl (sat.) (3x) (in the case of hydroxyacetone (**338**) as ketone source) and evaporated under reduced pressure to obtain the crude product. The residue was purified by flash column chromatography (silica, for **151** PE/EA = 2:1; for **339** PE/EA = 2:1 to PE/EA 0:1) and the enantiomeric excess (*ee*) was analyzed by chiral HPLC.

General procedure for the organocatalyzed Baylis-Hillman reactions between *p*-nitrobenzaldehyde (149) and MVK (124) under ambient conditions (GP-4):



149 **124** **195**

catalytic system: Combination of **organocatalyst**, **metal salt** and **imidazole**.



14 **114** **143** **142**

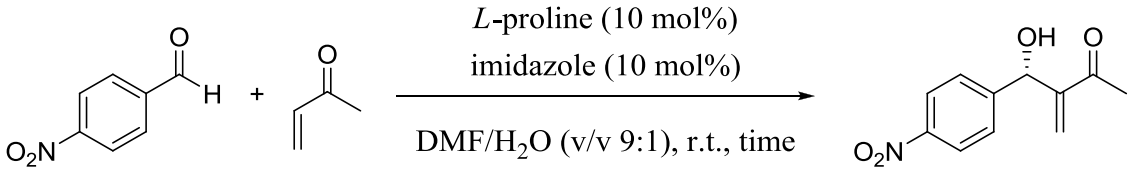
organocatalyst

+

metal salt **imidazole**

The **metal salt** was dissolved in the specified amount of solvent and subsequently the **organocatalyst** was added (molare ratio 1:2) and the mixture was stirred at r.t. for 15 min.. Subsequently **imidazole** (**196**) was added and the mixture was stirred at r.t. for another 15 min.. Then *p*-nitrobenzaldehyde (**149**) (1 equiv.) and MVK (**124**) (3 equiv.) were added and the mixture was stirred at r.t. for the indicated time. The reaction was monitored by TLC until full consumption of the *p*-nitrobenzaldehyde (**149**) was observed. The reaction mixture was quenched with $NaHCO_3$ (sat.) and NH_4Cl (sat.) and extracted with DCM (3x). The combined organic layers were washed with water (1x) and evaporated under reduced pressure to obtain the crude product. The residue was purified by flash column chromatography (silica, PE/EA = 3:1) and the enantiomeric excess (*ee*) was analyzed by chiral HPLC.

Table 51. Kinetic measurement of the *L*-proline (**14**)/imidazole (**196**) catalyzed Baylis-Hillman reaction of *p*-nitrobenzaldehyde (**149**) and MVK (**124**).

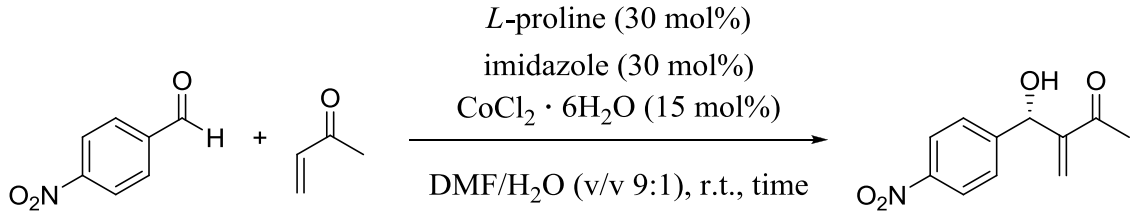


149 **124** **195**

entry [a]	time [h]	ee [%] [b]	n (149) [mmol] [c]	n (195) [mmol] [c]
1	0		1	0
2	3		0.48	0.49
3	7	rac.	0.26	0.62
4	24.25		0.03	0.93
5	65		0.03	0.93

[a]: 1 mmol of **149** (151 mg), 3 mmol of **124** (253 µL), 10 mol% *L*-proline (12 mg), 10 mol% imidazole (7 mg), DMF/H_2O (v/v 9:1) (c = 1 mol/L); **[b]:** Determined by chiral HPLC analysis; **[c]:** Isolated yield.

Table 52. Kinetic measurement of the *L*-proline (**14**)/imidazole (**196**)/$CoCl_2$·6H2O catalyzed Baylis-Hillman reaction of *p*-nitrobenzaldehyde (**149**) and MVK (**124**).

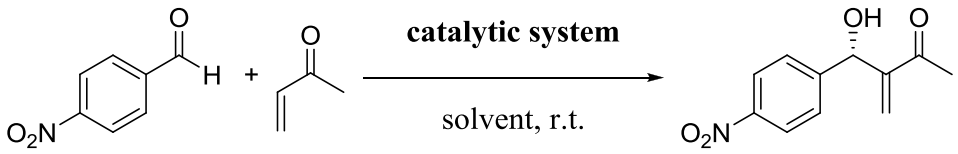


149 **124** **195**

entry [a]	**time [h]**	**ee [%]** [b]	**n (149) [mmol]** [b]	**n (195) [mmol]** [b]
1	0	rac.	1	0
2	3		0.88	0.02
3	6.5	14	0.34	0.49
4	15	13	0.10	0.59
5	24.5	12	0.03	0.62
6	66	9	0.01	0.63

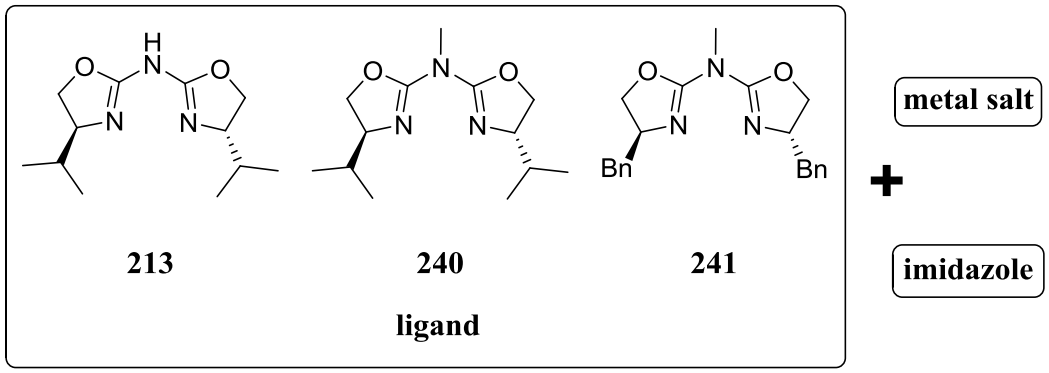
[a]: 1 mmol of **149** (151 mg), 3 mmol of **124** (253 µL), 30 mol% *L*-proline (35 mg), 30 mol% imidazole (20 mg), 15 mol% $CoCl_2$ $6H_2O$ (36 mg), (DMF/H_2O (v/v 9:1) (c = 1 mol/L); **[b]**: Determined by chiral HPLC analysis; **[c]**: Isolated yield.

General procedure for the organocatalyzed Baylis-Hillman reactions between and *p*-nitrobenzaldehyde (149) and MVK (124) under ambient conditions (GP-5):



149 **124** **195**

catalytic system: Combination of **ligand**, **metal salt** and **imidazole**.

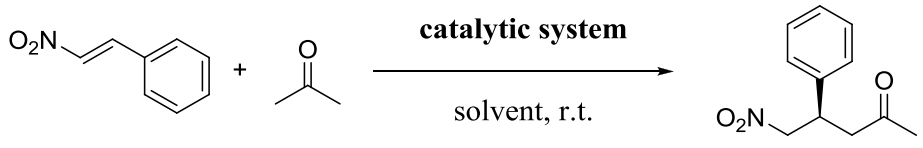


213 **240** **241**

ligand

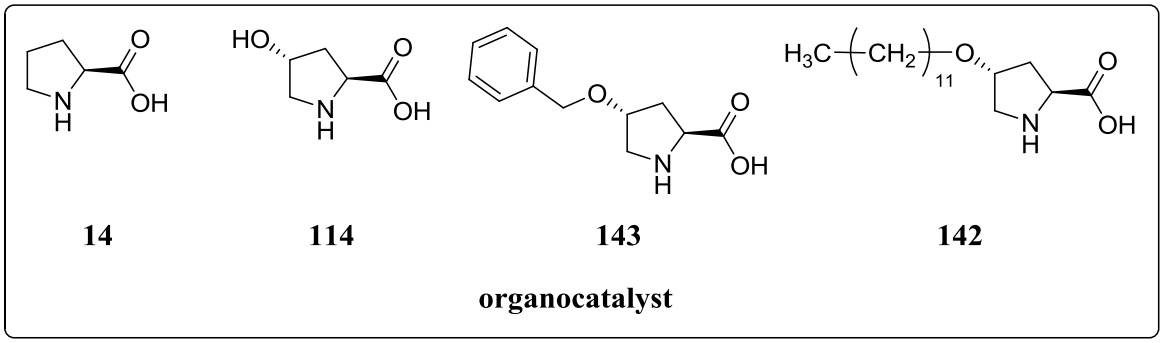
The **metal salt** was dissolved in the specified amount of solvent and subsequently the **ligand** was added and the mixture was stirred at r.t. for 15 min. Subsequently **imidazole** (**196**) was added and the mixture was stirred at r.t. for another 15 min.. Then *p*-nitrobenzaldehyde (**149**) (1 equiv.) and MVK (**124**) (3 equiv.) were added and the mixture was stirred at r.t. for the indicated time. The reaction was monitored by TLC until full consumption of the *p*-nitrobenzaldehyde (**149**) was observed. The reaction mixture was quenched with $NaHCO_3$ (sat.) and NH_4Cl (sat.) and extracted with DCM (3x). The combined organic layers were washed with water (1x) and evaporated under reduced pressure to obtain the crude product. The residue was purified by flash column chromatography (silica, PE/EA = 3:1) and the enantiomeric excess (*ee*) was analyzed by chiral HPLC.

General procedure for the organocatalyzed Nitro-Michael additions between *trans*-β-nitrostyrene (181) and acetone (130) under ambient conditions (GP-6):



181 **130** **194**

catalytic system: Combination of **organocatalyst** and **metal salt**.



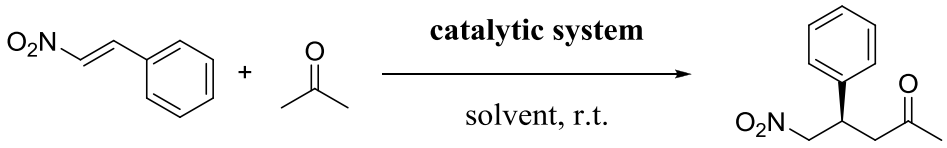
14 **114** **143** **142**

organocatalyst

+ metal salt

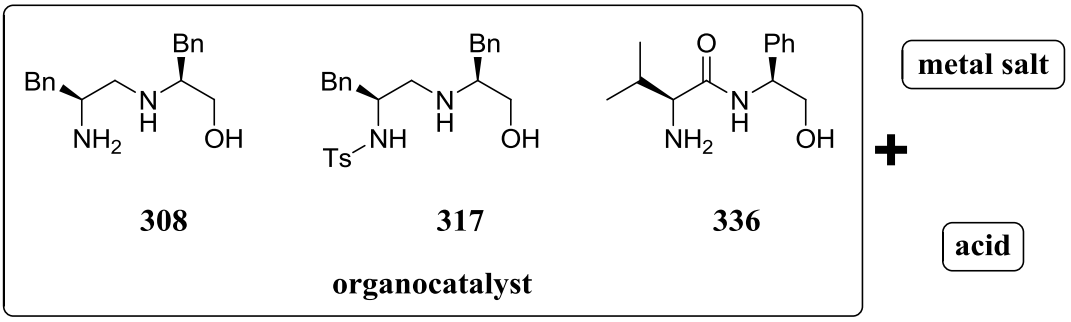
A mixture of **organocatalyst** and **metal salt** (molar ratio 2:1) was dissolved in the specified amount of solvent and the mixture was stirred at r.t. for 15 min. Then acetone (**130**) and *trans*-β-nitrostyrene (**181**) (1 equiv.) were added and the mixture was stirred at r.t. for the indicated time. The reaction was monitored by TLC until full consumption of the *trans*-β-nitrostyrene (**181**) was observed. The reaction mixture was quenched with NH_4Cl (sat.) and extracted with EA (3x). The combined organic layers were washed with water (1x) and evaporated under reduced pressure to obtain the crude product. The residue was purified by flash column chromatography (silica, PE/EA = 2:1) and the enantiomeric excess (*ee*) was analyzed by chiral HPLC.

General procedure for the organocatalyzed Nitro-Michael addition between *trans*-β-nitrostyrene (181) and acetone (130) under ambient conditions (GP-7):



181 **130** **194**

catalytic system: Combination of **organocatalyst**, **metal** and **acid**.

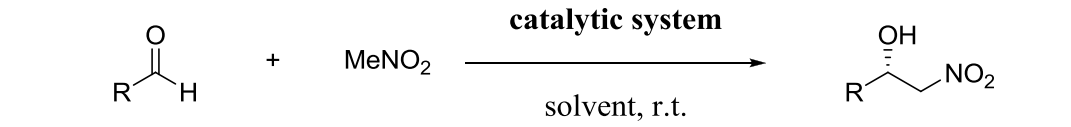


308 **317** **336**

organocatalyst

A mixture of **organocatalyst** and **metal salt** (molar ratio 1:1) or a mixture of **organocatalyst** and **acid** was dissolved in the specified amount of solvent and the mixture was stirred at r.t. for 15 min. Then acetone (**130**) and *trans*-β-nitrostyrene (**181**) (1 equiv.) were added and the mixture was stirred at r.t. for the indicated time. The reaction was monitored by TLC until full consumption of the *trans*-β-nitrostyrene (**181**) was observed. The reaction mixture was quenched with NH_4Cl (sat.) and extracted with EA (3x). The combined organic layers were washed with water (1x) and evaporated under reduced pressure to obtain the crude product. The residue was purified by flash column chromatography (silica, PE/EA = 2:1) and the enantiomeric excess (*ee*) was analyzed by chiral HPLC.

General procedure for the metal catalyzed nitroaldol (Henry) reactions between aldehydes (149 and 347) and nitromethane (187) under ambient conditions (GP-8):

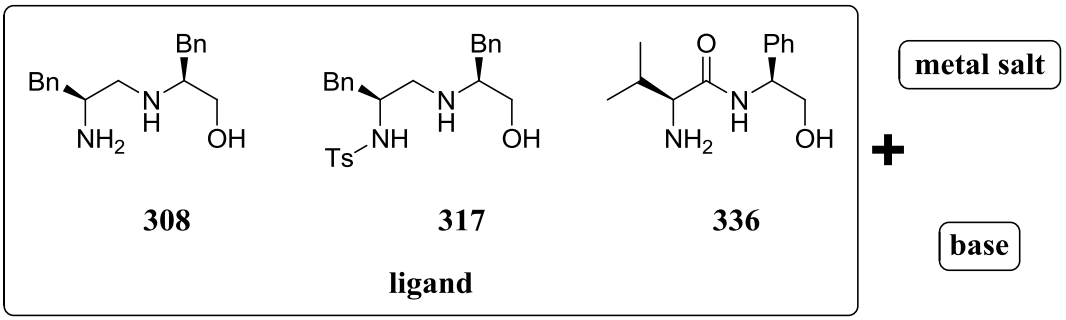


149: R = 4-nitrophenyl
347: R = *i*-Pr

187

358: R = 4-nitrophenyl
349: R = *i*-Pr

catalytic system: Combination of **ligand**, **metal salt** and **base**.

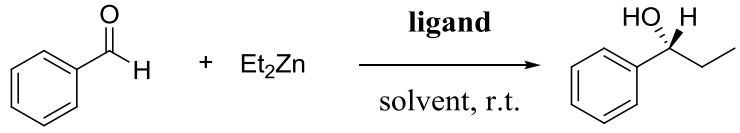


308 **317** **336**

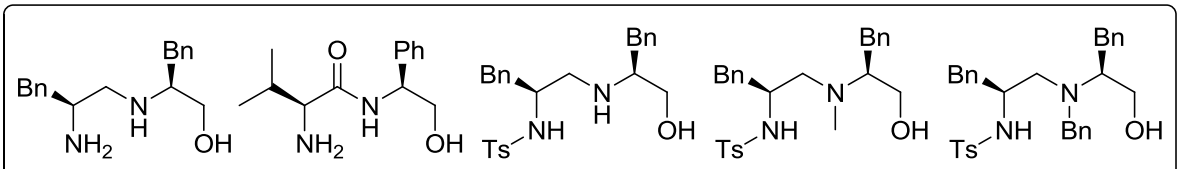
ligand

Ligand and **metal salt** (molar ratio 1:1) were dissolved in the indicated solvent and stirred at r.t. for 15 min. The aldehyde (**149**, **347**) (1 equiv.), nitromethane (**187**) and **base** were added successively to the resulting solution and cooled to the indicated temperature. The reaction was monitored by TLC until full consumption of the aldehyde (**149**, **347**) was observed. After the indicated time the reaction was quenched with HCl (aq.) (3M), and the mixture was concentrated and directly purified by flash column chromatography (silica, for **358** PE/EA = 3:1 to PE/EA = 0:1; for **349** PE/EA = 9:1 and PE/EA = 0:1). The enantiomeric excess (*ee*) was analyzed by chiral HPLC.

General procedure for the enantioselective addition of diethylzinc (93) to benzaldehyde (92) under ambient conditions (GP-9)[242]:



92 **93** **94**

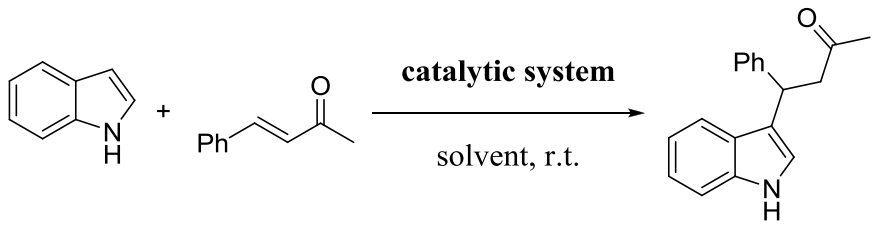


308 **336** **317** **320** **321**

ligand

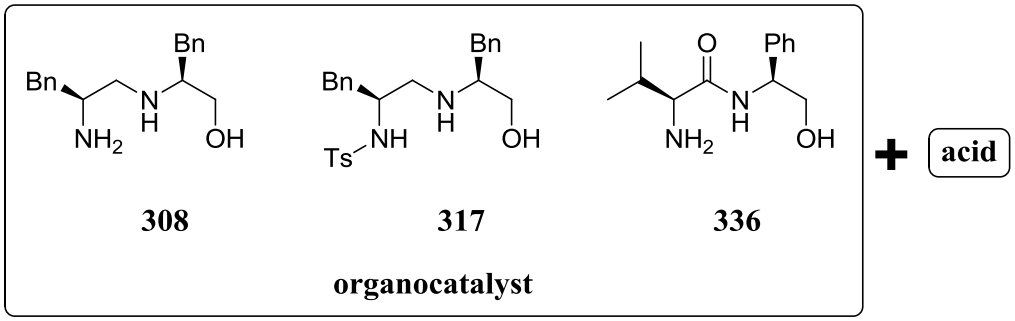
The reaction was carried out under flame dried glassware and under protective gas. The **ligand** was dissolved in the specified solvent and cooled to 0 °C and a solution of Et_2Zn (**93**) (1.0 M in hexanes) (2.2 equiv.) was added slowly (dropwise). The mixture was stirred for 30 min. at 0°C, then benzaldehyde (**92**) was added and the reaction was stirred for the indicated time and temperature. The reaction mixture was quenched with 1N HCl (*aq.*) at 0 °C. Subsequently the mixture was extracted with EA (3x). The combined organic phases were washed with brine (1x) and the solvent was evaporated under reduced pressure. The crude product was purified *via* flash column chromatography (silica, PE/EA 2:1 to PE/EA 0:1). The enantiomeric excess (*ee*) was analyzed by chiral HPLC.

General procedure for the organocatalytic asymmetric Friedel-Crafts alkylation of indole (342) with (*E*)-4-phenylbut-3-en-2-one (343) (GP-10)[57b]:



342 **343** **344**

catalytic system: Combination of **organocatalyst** and **acid**

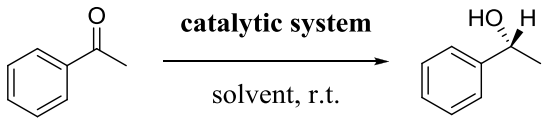


308 **317** **336**

organocatalyst

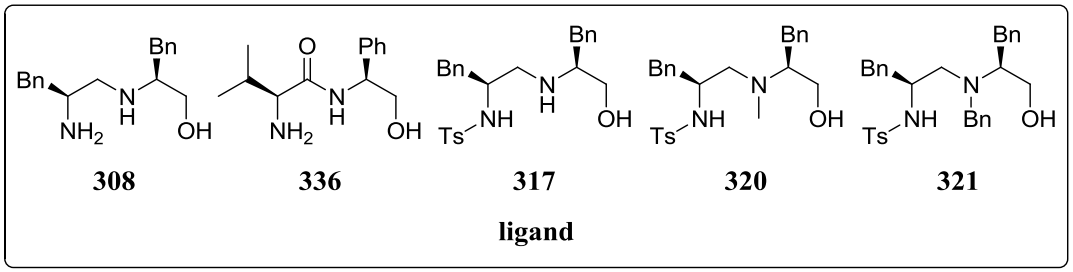
The **catalyst** was dissolved in the specified solvent and **acid** was added (molar ratio 1:2), then the solution was stirred at r.t. for 5 min.. After addition of α,β-unsaturated ketone (**343**) (1 equiv.), the mixture was stirred at the indicated temperature for 10 min.. Subsequently, indole (**342**) (1.2 equiv.) was added in one portion and the mixture was stirred for the indicated time and temperature. The crude mixture was directly loaded on flash column and purified (silica, PE/EA = 6:1 to PE/EA = 0:1). The enantiomeric excess (*ee*) was analyzed by chiral HPLC.

General procedure for the asymmetric transfer hydrogenation of acetophenone (406) (GP-11)[243a, 277]:



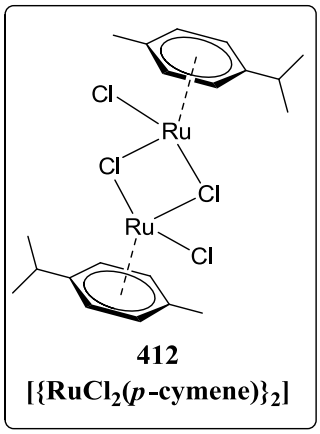
406 **407**

catalytic system: Combination of **ligand, [{RuCl$_2$(*p*-cymene)}$_2$]** and **additive**.



308 **336** **317** **320** **321**

ligand

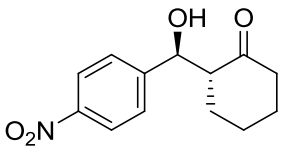


412
[{RuCl$_2$(*p*-cymene)}$_2$]

+ **additive**

The reaction was carried out under flame dried glassware and under protective gas. The **ligand**, **[{RuCl$_2$(*p*-cymene)}$_2$]** (**412**) and **additive** (NaOH in the case of *i*-propanol as solvent) were dissolved in the indicated amount of solvent. Subsequently, the solution was degased by freez-pump-thaw (3x) and was stirred at the indicated temperature and time to preform the catalyst (for DCM: 1 h at 40 °C; for *i*-propanol: 15 min. at r.t.). Then ketone (**406**) (1 equiv.) was added, followed by formic acid and Et_3N (only when DCM was used as solvent). Subsequently, an exact amount of *n*-dodecane as GC standard was added. The solution was degased by freez-pump-thaw (3x) and the mixture was stirred at the specified temperature and time. For determining the yield and *ee*, an aliquot (V ≈ 0.2 mL) of the reaction mixture was taken and filtered through a short plug of flash silica gel (rinsed with 3 mL Et_2O). The Et_2O was removed under vacuum (T (water bath) = 60 °C, p = 850 mbar) and the sample was analyzed by chiral GC using *n*-dodecane as internal standard.

(*R*)-2-((*S*)-hydroxy(4-nitrophenyl)methyl)cyclohexanone (152 (*anti*))



152 (*anti*)

$\mathbf{R_f}$ = 0.23 (PE/EA = 2:1)

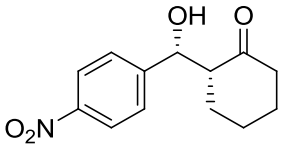
^{1}H-NMR (300 MHz, $CDCl_3$): δ_H (ppm) = 8.25 – 8.17 (m, 2H), 7.55 – 7.46 (m, 2H), 4.89 (d, *J* = 8.3 Hz, 1H), 3.98 (bs, 1H), 2.65 – 2.54 (m, 1H), 2.54 – 2.44 (m, 1H), 2.43 – 2.30 (m, 1H), 2.17 – 2.06 (m, 1H), 1.88 – 1.77 (m, 1H), 1.76 – 1.62 (m, 1H), 1.62 – 1.47 (m, 2H), 1.46 – 1.23 (m, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ_C (ppm) = 214.80, 148.37, 147.56, 127.89, 123.58, 74.01, 57.18, 42.69, 30.76, 27.65, 24.69.

Anal. chiral HPLC (Daicel Chiralcel OD-H, *i*-PrOH - *n*-hexane (10:90, v/v), UV 268 nm, flow rate 0.5 ml/min) t_r = 35.54 min (major, *anti*); t_r = 50.96 min (minor, *anti*).

(Daicel Chiralpak AS-H, *i*-PrOH - *n*-heptan (5:95, v/v), UV 266 nm, flow rate 1.0 mL/min) t_r = 68.50 min (major, *anti*), t_r = 80.84 min (minor, *anti*).

(*R*)-2-((*R*)-hydroxy(4-nitrophenyl)methyl)cyclohexanone (152 (*syn*))



152 (*syn*)

$\mathbf{R_f}$ = 0.33 (PE/EA = 2:1)

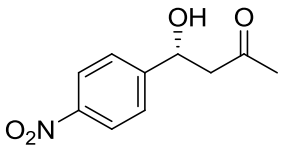
^{1}H-NMR (300 MHz, $CDCl_3$): δ_H (ppm) = 8.24 – 8.16 (m, 2H), 7.53 – 7.45 (m, 2H), 5.48 (s, 1H), 3.18 (bs, 1H), 2.68 – 2.58 (m, 1H), 2.54 – 2.44 (m, 1H),2.44 – 2.29 (m, 1H), 2.18 – 2.05 (m, 1H), 1.91 – 1.78 (m, 1H), 1.77 – 1.69 (m, 1H), 1.68 – 1.56 (m, 2H), 1.56 – 1.34 (m, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ_C (ppm) = 214.13, 149.07, 147.04, 126.61, 123.47, 70.12, 56.79, 42.63, 27.87, 25.91, 24.78.

Anal. chiral HPLC (Daicel Chiralcel OD-H, *i*-PrOH - *n*-hexane (10:90, v/v), UV 268 nm, flowrate 0.5 ml/min) t_r = 29.44 min (major, *anti*); t_r = 33.77 min (minor, *anti*).

(Daicel Chiralpak AS-H, *i*-PrOH - *n*-heptan (5:95, v/v), UV 266 nm, flow rate 1.0 mL/min) t_r = 58.33 min (minor, *syn*), t_r = 89.68 min (major, *syn*).

(*R*)-4-hydroxy-4-(4-nitrophenyl)butan-2-one (151)



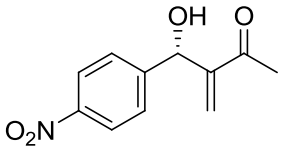
151

R_f = 0.16 (PE/EA = 2:1)

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H (ppm) = 8.16 – 8.9 (m, 2H), 7.53 – 7.46 (m, 2H), 5.26 – 5.18 (m, 1H), 3.85 (bs, 1H), 2.83 (d, *J* = 6.1 Hz, 1H), 2.18 (s, 3H).

Anal. chiral HPLC (Daicel Chiralpak AS-H, *i*-PrOH- *n*-heptane (30:70, v/v), UV 254 nm, flowrate 0.5 ml/min) t_r = 23,55 min (major), t_r = 28.65 min (minor).

(*S*)-3-(hydroxy(4-nitrophenyl)methyl)but-3-en-2-one (195)



195

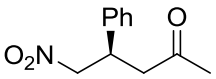
R_f = 0.19 (PE/EA = 2:1)

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H (ppm) = 8.21 – 8.16 (m, 2H), 7.58 – 7.52 (m, 2H), 6.26 (s, 1H), 6.04 (s, 1H), 5.67 (s, 1H), 2.35 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ_C (ppm) = 200.11, 149.03, 148.99, 147.31, 127.80, 127.29, 123.99, 72.14, 26.37.

Anal. chiral HPLC (Phenomenex Lux Cellulose-2, *i*-PrOH- *n*-heptane (10:90, v/v), UV 254 nm, flowrate 1.0 ml/min) t_r = 19.74 min (minor), t_r = 22.92 min (major).

(*R*)-5-nitro-4-phenylpentan-2-one (194)



194

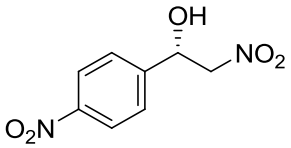
R_f = 0.35 (PE/EA = 2:1)

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H (ppm) = 7.37 – 7.18 (m, 5H), 4.69 (dd, *J* = 12.3, 6.8 Hz, 1H), 4.59 (dd, *J* = 12.3, 7.8 Hz, 1H), 4.07 – 3.93 (m, 1H), 2.91 (d, *J* = 7.0 Hz, 2H), 2.11 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ_C (ppm) = 205.53, 138.93, 129.22, 128.06, 127.52, 79.59, 46.26, 39.17, 30.55.

Anal. chiral HPLC (Chiralpak AS-H, *i*-PrOH- *n*-heptane (20:80, v/v), UV 215 nm, flowrate 0.5 mL/min) t_r = 43.88 min (minor), t_r = 38.05 min (major).

(*S*)-2-nitro-1-(4-nitrophenyl)ethanol (358)



358

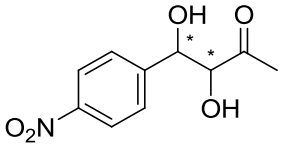
R_f = 0.13 (PE/EA = 3:1)

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H (ppm) = 8.25 – 8.17 (m, 2H), 7.66 – 7.57 (m, 2H), 5.66 – 5.54 (m, 1H), 4.66 – 4.53 (m, 2H), 3.54 (bs, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ_C (ppm) = 148.00, 145.29, 127.03, 124.16, 80.68, 70.00.

Anal. chiral HPLC (Phenomenex Lux Cellulose-2, *i*-PrOH- *n*-heptane (30:70, v/v), UV 215 nm, flowrate 0.5 mL/min) t_r = 16.60 min (minor), t_r = 19.34 min (major).

3,4-dihydroxy-4-(4-nitrophenyl)butan-2-one (339)



339

R_f (*syn*) = 0.47 (PE/EA = 0:1)

R_f (*anti*) = 0.37 (PE/EA = 0:1)

^{1}H-NMR (*syn*) (300 MHz, $CDCl_3$): δ_H (ppm) = 8.24 – 8.10 (m, 2H), 7.61 – 7.53 (m, 2H), 5.21 (d, *J* = 2.1 Hz, 1H), 4.38 (d, *J* = 2.5 Hz, 1H), 2.33 (s, 3H).

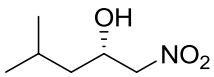
^{1}H-NMR (*anti*) (300 MHz, $CDCl_3$): δ_H (ppm) = 8.24 – 8.10 (m, 2H), 7.61 – 7.53 (m, 2H), 5.05 (d, *J* = 4.5 Hz, 1H), 4.43 (d, *J* = 4.5 Hz, 1H), 1.98 (s, 3H).

^{13}C-NMR (*syn*) (75 MHz, $CDCl_3$): δ_C (ppm) = 207.44, 147.54, 146.83, 127.15, 123.61, 80.16, 72.89, 26.09.

^{13}C-NMR (*anti*) (75 MHz, $CDCl_3$): δ_C (ppm) = 207.97, 147.69, 147.44, 127.37, 123.61, 80.74, 74.35, 27.84.

Anal. chiral HPLC (Chiralpak AS-H, *i*-PrOH- *n*-heptane (10:90, v/v), UV 254 nm, flowrate 1.0 mL/min) t_r = 41.41 min (major, *anti*), t_r = 48.09 min (minor, *anti*), t_r = 58.06 min (minor, *syn*), t_r = 62.24 min (major, *syn*).

(*S*)-4-methyl-1-nitropentan-2-ol (349)



349

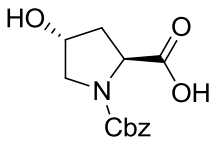
R_f = 0.14 (PE/EA = 6:1)

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H (ppm) = 4.38 – 4.23 (m, 3H), 1.85 – 1.66 (m, 1H), 1.51 – 1.35 (m, 1H), 1.22 – 1.10 (m, 1H), 0.93 – 0.84 (m, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ_C (ppm) = 81.1, 67.0, 42.4, 24.3, 23.1, 21.7.

Anal. chiral HPLC (Daicel Chiralcel OJ-H, *i*-PrOH- *n*-heptane (1:99, v/v), UV 215 nm, flowrate 1.0 mL/min) t_r = 27.40 min (major), t_r = 30.13 min (minor).

(2*S*,4*R*)-1-((benzyloxy)carbonyl)-4-hydroxypyrrolidine-2-carboxylic acid (145)



145

A procedure from literature [129] was modified as follows:

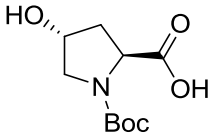
A solution of *trans*-4-hydroxy-*L*-proline (**114**) (5.00 g, 38.1 mmol) in 30 mL THF (p.A.) and 100 mL $NaHCO_3$ (sat.) at 0 °C was treated by dropwise addition of benzyl chloroformate dissolved in 30 mL THF (p.A.). The solution was stirred at r.t. for 20 h. The pH was maintained at 1 by the addition of 2N HCl (*aq*.) and the reaction mixture was extracted with EA (3 x 80 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (silica, PE/EA = 2:1 to DCM/MeOH = 8:2) to yield **145** as (9.95 g, 37.5 mmol, 98%) a colorless oil.

R_f = 0.55 (DCM/MeOH = 8:2)

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H (ppm) = 7.38 – 7.12 (m, 5H), 5.17 – 4.88 (m, 2H), 4.54 – 4.37 (m, 1H), 4.40 – 4.24 (m, 1H), 3.87 – 3.20 (m, 2H), 2.44 – 1.84 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$) (2 conformational isomers): δ_C (ppm) =176.32 and 175.98, 155.87 and 155.16, 136.07 and 136.01, 128.53 and 128.46, 128.16 and 127.98, 127.77 and 127.51, 69.76 and 69.05, 67.64 and 67.56, 58.26 and 57.76, 54.77 and 54.32, 38.72 and 38.00.

(2*S*,4*R*)-1-(tert-butoxycarbonyl)-4-hydroxypyrrolidine-2-carboxylic acid (155)



155

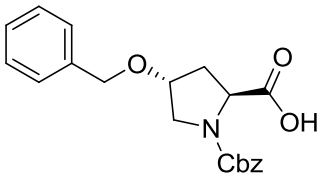
A procedure from literature [132d] was modified as follows:

To a solution of *trans*-4-hydroxy-*L*-proline (**114**) (10.0 g, 76.3 mmol, 1 equiv.) in 100 mL dioxane/H_2O (v/v = 1:1) and 201 mL $NaHCO_3$ (sat.) at 0 °C solid Boc_2O (33.3 g, 152.6 mmol, 2 equiv.) was added in portions over 10 min.. The solution was stirred at r.t. for 20 h. The crude mixture was extracted with diethylether (2 x 150 mL). The diethylether phase was treated with isopropylamine (6.25 mL, 76.3 mmol, 1 equiv.). The pH of the water phase was maintained at 3 by addition of 1N HCl (*aq*.) and the reaction mixture was extracted with EA (4 x 150 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to obtain **155** as sticky, colorless oil (17.4 g, 75.4 mmol, 99%).

^{1}H-NMR (300 MHz, CD_6SO) (2 conformational isomers): δ_H (ppm) = 12.52 (bs, 1H), 4.16 – 4.03 (m, 1H), 3.42 – 3.30 (m, 2H), 3.26 and 3.22 (bs, 1H), 3.20 (m, 2H), 2.17 – 2.02 (m, 1H), 1.95 – 1.80 (m, 1H), 1.39 and 1.34 (s, 9H) .

^{13}C-NMR (75 MHz, CD_6SO) (2 conformational isomers): δ_C (ppm) =174.37 and 173.87, 153.76 and 153.22, 146.21, 85.61, 78.77, 68.50 and 67.80, 57.70 and 57.46, 54.67 and 54.36, 28.11 and 27.91, 26.87.

(2*S*,4*R*)-4-(benzyloxy)-1-((benzyloxy)carbonyl)pyrrolidine-2-carboxylic acid (159)



159

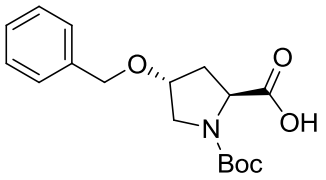
A procedure from the literature [131] was modified as follows:

The reaction was carried out under flame dried glassware and under protective gas. Cbz-proline **145** (5.25 g, 19.81 mmol, 1 equiv.) was dissolved in 95 mL THF (abs.) and cooled to 0 °C. NaH (60 wt. % in mineral oil) (1.66 g, 41.60 mmol, 2.1 equiv.) was added in portions to the solution and the mixture was stirred at r.t. for 30 min.. Subsequently, benzyl bromide (**158**) (7.11 g, 41.60 mmol, 2.1 equiv.) was added slowly (dropwise) and the reaction was stirred at r.t. for 20 h and then refluxed for additional 5 h. Afterwards the reaction was quenched with 10 mL H_2O and THF was removed under reduced pressure. The crude was taken back in 40 mL 1N HCl (*aq.*) and the aqueous layer was extracted with Et_2O (3 x 70 mL). The combined organic layers were reduced in vacuum and the crude product was purified by flash column chromatography (silica, PE/EA = 3:1, DCM/ MeOH = 8:2) to obtain **159** (5.28 g, 14.86 mmol, 75%) as a pale oil.

$\mathbf{R_f}$ = 0.02 (PE/EA = 1:1)

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H (ppm) = 11.47 (bs, 1H), 7.43 – 7.21 (m, 10H), 4.25 – 4.10 (m, 2H), 4.64 – 4.43 (m, 3H), 4.27 – 4.16 (m, 1H), 3.93 – 3.60 (m, 2H), 2.60 – 2.36 (m, 1H), 2.33 – 2.12 (m, 1H).

(2*S*,4*R*)-4-(benzyloxy)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid (162)



162

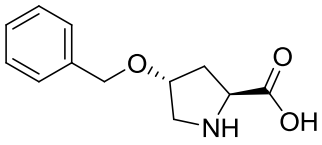
Compound **162** was prepared as follows [131], [278]:

The reaction was carried out under flame dried glassware and under protective gas. NaH (60 wt. % dispersion in mineral oil) (1.39 g, 34.7 mmol, 1.8 equiv.) was dissolved in 50 mL THF (abs.) and cooled to 0 °C. The Boc-protected proline **155** (4.39 g, 19.0 mmol, 1.0 equiv.) was dissolved in 50 mL THF (abs.) and slowly added to the cooled solution (dropwise). Subsequently, the mixture was stirred at r.t. for 30 min. and the benzyl bromide (**158**) (4.12 mL, 34.7 mmol, 1.8 equiv.) was added slowly. The mixture was stirred at r.t. for 20 h and then refluxed for additional 5 h. The mixture was quenched with 10 mL H_2O. Then THF was removed under reduced pressure. The crude was taken back in 50 mL 1N HCl (*aq.*) and the aqueous layer was extracted with diethylether (3 x 75 mL) and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica, PE/EA 2:1 to DCM/ MeOH 8:2) to obtain **162** (3.24 g, 10.1 mmol, 53%) as a pale, yellow oil.

$\mathbf{R_f}$ = 0.25 (DCM/MeOH = 8:2)

^{1}H-NMR (300 MHz, $CDCl_3$) (2 conformational isomers): δ_H (ppm) = 9.40 (bs, 1H), 7.40 – 7.20 (m, 5H), 4.60 – 4.30 (m, 3H), 4.20 (bs, 1H), 3.80 – 3.45 (m, 2H), 2.55 – 2.00 (m, 2H), 1.45 and 1.41 (s, 9H).

(2*S*,4*R*)-4-(benzyloxy)pyrrolidine-2-carboxylic acid (143)



143

Method A: Compound **143** was prepared as follows [130]:

(2*S*,4*R*)-4-(benzyloxy)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid (**162**) (3.24 g, 10.1 mmol, 1.0 equiv.) was dissolved in 5 mL DCM (c = 2.0 mol/L). Subsequently TFA (5.00 mL, 65.5 mmol, 6.6 equiv.) was added and the reaction mixture was stirred for 3 h. The solvent was evaporated under HV with the help of a cooling trap. The crude product was purified by flash column chromatography (silica, PE/EA = 1:1 to DCM/MeOH 8:2) to yield **143** (1.26 g, 5.69 mmol, 56%) as a white solid.

Method B: Compound **143** was prepared as follows [126]:

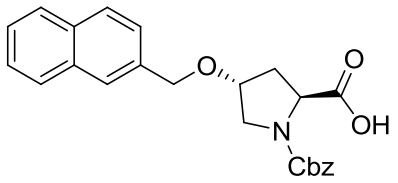
(2*S*,4*R*)-4-(benzyloxy)-1-((benzyloxy)carbonyl)pyrrolidine-2-carboxylic acid (**159**) (802 mg, 2.26 mmol, 1 equiv.) was dissolved in 23 mL THF/EtOH (c = 0.1 mol/L; v/v 1:1). Subsequently, Pd/C (10 wt. %) (53 mg, 0.05mmol, 2 mol% of Pd) was added and the mixture was stirred at r.t. and 5 bar H_2-pressure for 16 h in an autoclave. The crude reaction mixture was filtered through a short plug of celite (rinsed with MeOH). The solvent was removed under reduced pressure and the crude product was purified *via* flash column chromatography (silica, PE/EA = 2:1, DCM/MeOH = 8:2) to yield **143** (191.2 mg, 0.86 mmol, 38%) as a white solid.

$\mathbf{R_f}$ = 0.07 (DCM/MeOH = 8:2)

^{1}H-NMR (300 MHz, CD_6SO): δ_H (ppm) = 7.41 – 7.23 (m, 5H), 4.48 (s, 2H), 4.23 – 4.15 (m, 1H), 3.81 – 3.70 (m, 1H), 3.32 – 3.14 (m, 2H), 2.35 – 2.23 (m, 1H), 1.97 – 1.84 (m, 1H).

^{13}C-NMR (75 MHz, CD_6SO): δ_C (ppm) =168.81, 137.88, 128.15, 127.62, 127.44, 77.38, 69.75, 59.54, 49.71, 34.75.

(2*S*,4*R*)-1-((benzyloxy)carbonyl)-4-(naphthalen-2-ylmethoxy)pyrrolidine-2-carboxylic acid (160)



160

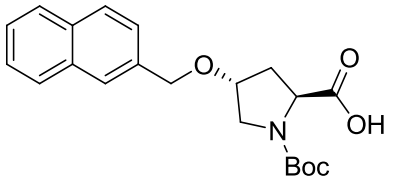
Compound **160** was prepared as follows [130]:

The reaction was carried out under flame dried glassware and under protective gas. To a solution of Cbz-proline **145** (3.68 g, 13.89 mmol, 1 equiv.) in 30 mL THF (abs.) NaH (60 wt. % dispersion in mineral oil) (1.22 g, 30.60 mmol, 2.2 equiv.) was added in portions at 0 °C (causion!!! H_2-evolution). The mixture was stirred at r.t. for 45 min. and subsequently a solution of 2-(bromomethyl)naphthalene (**156**) (6.75 g, 30.6 mmol, 2.2 equiv.) in 20 mL THF (abs.) was slowly added. The mixture was stirred at r.t. for 20 h and then an additional amount of 20 mL THF (abs.) was added and the mixture was refluxed for 4 h. Afterwards the reaction was carefully quenched with 50 mL H_2O and extracted with Et_2O (2 x 50 mL). The aqueous layer was acidified with 6N HCl (*aq.*) (pH ≈ 1-2) and extracted with DCM (3 x 50 mL). The combined organic layers were concentrated under reduced pressure and the product was purified by flash column chromatography (silica, DCM/MeOH = 8:2) to yield **160** (4,73 g, 11.67 mmol, 84%) as a pale, yellow oil.

$\mathbf{R_f}$ = 0.58 (DCM/MeOH = 8:2)

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H (ppm) = 9.22 (bs, 1H), 7.90– 7.75 (m, 4H), 7.55 – 7.27 (m, 8H), 5.24– 5.15 (m, 2H), 4.72 – 4.56 (m, 3H), 4.29 – 4.19 (m, 1H), 4.00 – 3.60 (m, 2H), 2.61 – 2.43 (m, 1H), 2.32 – 2.15 (m, 1H).

(2*S*,4*R*)-1-(tert-butoxycarbonyl)-4-(naphthalen-2-ylmethoxy)pyrrolidine-2-carboxylic acid (157)



157

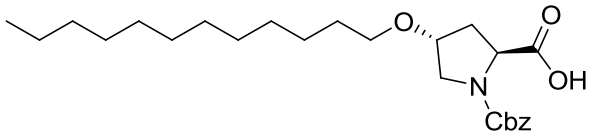
A procedure was adapted from the literature [130], [123] as follows:

The reaction was carried out under flame dried glassware and under protective gas. NaH (60 wt. % dispersion in mineral oil) (0.61 g, 15.3 mmol, 1.8 equiv.) was dissolved in 18 mL THF (abs.) and cooled to 0 °C. Boc-*cis*-4-hydroxy-*L*-proline (**155**) (2.25 g, 8.48 mmol, 1 equiv.) was dissolved in 18 mL THF (abs.) and added dropwise to the cooled solution (*via* droppingfunnel). The mixture was stirred at r.t. for 45 min. and a solution of 2-(bromomethyl)naphthalene (**156**) (3.37 g, 15.3 mmol, 1.8 equiv.) in 24 mL THF (abs.) was added dropwise. The mixture was refluxed for 4 h. The reaction mixture was quenched with 30 mL H_2O and extracted with Et_2O (4 x 25 mL). The aqueous layer was acidified with 6N HCl (*aq*.) (pH ≈ 1-2) and extracted with DCM (3 x 25 mL). The combined organic layers were reduced in *vacuo*. The product was purified *via* flash column chromatography (silica, PE/EA = 2:1 to DCM/MeOH = 8:2) to yield **157** (1.50 g, 3.69 mmol, 44%) as a yellow, viscous oil.

$\mathbf{R_f}$ = 0.06 (PE/EA = 0:1)

^{1}H-NMR (300 MHz, CD_6SO): δ_H (ppm) = 7.86– 7.76 (m, 4H), 7.52 – 7.41 (m, 3H), 5.44 – 5.21 (m, 2H), 4.68 – 4.36 (m, 2H), 4.23 – 4.15 (m, 1H), 3.65 – 3.23 (m, 2H), 2.36 – 2.19 (m, 1H), 2.08 – 1.99 (m, 1H).

(2*S*,4*R*)-1-((benzyloxy)carbonyl)-4-(dodecyloxy)pyrrolidine-2-carboxylic acid (148)



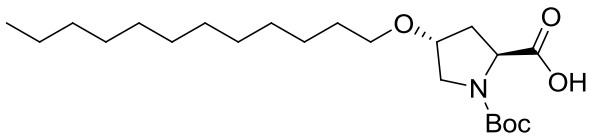
148

A procedure from the literature [126] was modified as follows:

The reaction was carried out under flame dried glassware and under protective gas. Cbz-proline **145** (5.16 g, 19.47 mmol, 1 equiv.) was dissolved in 40 mL DMF (abs.), cooled down to 0 °C and NaH (60 wt. % dispersion in mineral oil) (1.95 g, 48.66 mmol, 2.5 equiv.) was added in small portions. The mixture was stirred at 0 °C for 30 min. and 1-bromododecan (**146**) (13.1 g, 52.56 mmol, 2.7 equiv.) was added dropwise (over 30 min.). Afterwards the mixture was let come to r.t. and stirred for another 17 h. Subsequently the reaction was quenched with 6N HCl (*aq.*) (pH ≈ 2) followed by extraction with Et_2O (3 x 60 mL). The combined organic layers were concentrated in vacuum to afford the crude product which was purified *via* flash column chromatography (silica, PE/EA = 3:1, DCM/MeOH = 8:2) to yield **148** (5.10 g, 11.76 mmol, 60%) as a pale, yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H (ppm) = 8.83 (bs, 1H), 7.40– 7.23 (m, 5H), 7.52 – 7.41 (m, 3H), 5.23 – 5.06 (m, 2H), 4.55 – 4.40 (m, 1H), 4.10 – 4.00 (m, 1H), 3.75 – 3.54 (m, 2H), 3.44 – 3.27 (m, 2H), 2.47 – 2.07 (m, 2H), 1.58 – 1.45 (m, 2H), 1.34 – 1.18 (m, 18H), 0.91 – 0.83 (m, 3H).

(2*S*,4*R*)-1-(tert-butoxycarbonyl)-4-(dodecyloxy)pyrrolidine-2-carboxylic acid (161)



161

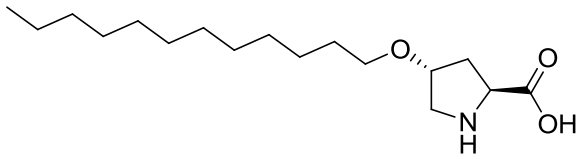
Compound **161** was prepared as follows [126]:

The reaction was carried out under flame dried glassware and under protective gas. Boc-*cis*-4-hydroxy-*L*-proline (**155**) (4.00 g, 17.3 mmol, 1 equiv.) was dissolved in 39 mL

DMF (abs.) (c = 0.5 mol/L) and cooled down to 0 °C. Subsequently, NaH (60 wt. % dispersion in mineral oil) (1.51 g, 37.8 mmol, 2.2 equiv.) was added in small portions (over 10 min.). After stirring the mixture for 30 min. 1-bromododecan (**146**) (1.50 g, 40.8 mmol, 2.4 equiv.) was added dropwise to the reaction mixture (over 30 min.) and stirred at r.t. for 20 h. The reaction mixture was acidified with 6N HCl (*aq.*) (to pH ~ 2) followed by extraction with Et_2O (3 x 20 mL). The organic layer was washed with 1N HCl (*aq.*) (4 x 30 mL). The solvent was evaporated under reduced pressure and the remaining DMF was removed under high vacuum at 60 °C. The product was purified *via* flash column chromatography (silica, PE/EA = 3:1 to DCM/MeOH = 8:2) to yield **161** (3.34 g, 8.36 mmol, 48%) as a pale, yellow, viscous oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H (ppm) = 6.65 bs, 1H), 4.45 – 3.95 (m, 2H), 3.72 – 3.32 (m, 4H), 2.42 – 1.90 (m, 2H), 1.66 – 1.45 (m, 2H), 1.44 – 1.32 (m, 9H), 1.31 – 1.14 (m, 18H), 0.88 – 0.78 (m, 3H).

(2*S*,4*R*)-4-(dodecyloxy)pyrrolidine-2-carboxylic acid (142)



142

Method A: Compound **142** was prepared as follows [126]:

The Boc-protected *L*-proline **161** (3.34 g, 8.36 mmol, 1 equiv.) was dissolved in 4.2 mL DCM (c = 2.0 mol/L). Then TFA (4.2 mL, 54.8 mmol, 6.6 equiv.) was slowly added and the mixture was stirred vigorously at r.t. for 4 h (until TLC showed full conversion of the starting material). Subsequently, the solvent and TFA was removed under high vacuum. The crude product was purified by flash column chromatography (silica, PE/EA = 1:1 to DCM/MeOH = 8:2) to yield **142** (1.46 g, 4.87 mmol, 58%) as white solid.

Method B: Compound **142** was prepared as follows [126]:

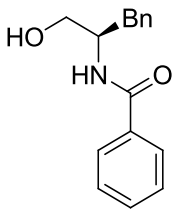
The Cbz-protected *L*-proline **148** (2,82 g, 6.5 mmol, 1 equiv.) was dissolved in 23 mL THF/EtOH (c = 0.5 mol/L; v/v 1:1). Subsequently, Pd/C (10 wt. %) (586 mg, 0.55mmol, 8.5 mol% of Pd) was added and the mixture was stirred at r.t. and 10 bar H_2-pressure for 24 h in

an autoclave. The crude reaction mixture was filtered through a short plug of celite (rinsed with MeOH). The solvent was removed under reduced pressure and the crude product was purified *via* flash column chromatography (silica, PE/EA = 2:1, DCM/MeOH = 8:2) to yield **142** (818.7 mg, 2.73 mmol, 42%) as white solid.

$\mathbf{R_f}$ = 0.15 (DCM/MeOH = 8:2)

^{1}H-NMR (300 MHz, CD_6SO): δ_H (ppm) = 4.70– 4.52 (m, 1H), 4.28 – 4.06 (m, 2H),3.65 – 3.45 (m, 1H), 3.42 – 3.20 (m, 2H), 2.60 – 2.33 (m, 1H), 2,16 – 1.95 (m, 1H), 1.72 – 1.40 (m, 2H), 1.35 – 1.18 (m, 18H), 0.90 – 0.81 (m, 3H).

***N*-(1-hydroxy-3-phenylpropan-2-yl)benzamide (422)**



422

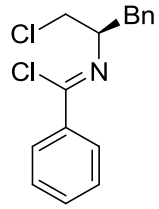
Compound **422** was prepared as follows [279], [280]:

Benzoyl chloride (**71**) (17.1 mL, 147.5 mmol, 1.5 equiv.) was added dropwise to a solution of *L*-Phenylglycinol (14.9 g, 98.3 mmol, 1 equiv.) in 246 mL MeOH (c = 0.4 mol/L) at r.t.. The solution was stirred for 24 h and MeOH was evaporated under reduced pressure. The residue was filtered and washed with ice cold DCM, H_2O and 1N HCl (*aq.*) to get the product **422** (25.0 g, 97.7 mmol, 100%) as white solid.

^{1}H-NMR (300 MHz, CD_6SO): δ_H (ppm) = 8.19 (d, *J* = 8.4 Hz, 1H), 7.84 – 7.74 (m, 2H), 7.55 – 7.38 (m, 3H), 7.30 – 7.09 (m, 5H), 4.24 – 4.09 (m, 1H), 3.56– 3.37 (m, 2H), 3.32 – 3.14 (m, 2H), 2.96 (dd, *J* = 13.7 Hz, 5.2 Hz, 1H), 2.79 (dd, *J* = 13.7 Hz, 9.1 Hz, 1H).

^{13}C-NMR (75 MHz, CD_6SO): δ_C (ppm) = 166.01, 139.51, 134.76, 131.02, 129.11, 128.16, 128.13, 127.25, 125.90, 62.92, 53.30, 36.50.

(*R*,*Z*)-*N*-(1-chloro-3-phenylpropan-2-yl)benzimidoyl chloride (423)

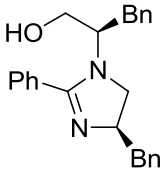


423

Compound **423** was prepared according to the procedure developed by Vinh Ngoc Huynh as follows:

The reaction was carried out under flame dried glassware and under protective gas. Thionyl chloride (26.3 mL, 362 mmol, 6 equiv.) was added dropwise to the Bz-*L*-Phenylglycinol (15.4 g, 60.3 mmol, 1 equiv.) (attention: exothermic reaction!). The reaction mixture was refluxed for 3 h and subsequently thionyl chloride was distilled of and the product was used without further purification.

(*R*)-2-((*R*)-4-benzyl-2-phenyl-4,5-dihydro-1*H*-imidazol-1-yl)-3-phenylpropan-1-ol (424)



424

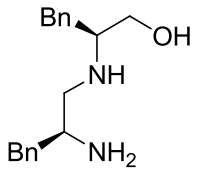
Compound **424** was prepared according to the procedure developed by Vinh Ngoc Huynh as follows:

The reaction was carried out under flame dried glassware and under protective gas. *L*-Phenylglycinol (9.11 g, 60.3 mmol, 1 equiv.) was dissolved in 134 mL DCM (abs.) (c = 0.45 mol/L). Subsequently Et_3N (abs.) (25.1 mL, 180.9 mmol, 3equiv.) was added dropwise at r.t. and stirred for 30 min.. Then the solution was cooled to 0 °C and the chloride **423** (17.62 g, 60.3 mmol, 1 equiv.) dissolved in 134 mL DCM (abs.) (c = 0.45 mol/L) was added dropwise to the *L*-Phenylglycinol solution. The solution was stirred at r.t. for 21 h. Then the reaction mixture was extracted with H_2O (1 x 150 mL) and 2N NaOH (*aq.*) until pH = 14 is reached.

The combined aqueous layers were extracted with DCM (3 x 150 mL). The combined organic layers were evaporated under reduced pressure to get the crude product which was further used without purification.

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H (ppm) = 7.36 – 6.79 (m, 15H), 4.54 – 4.39 (m, 1H), 3.70 – 3.48 (m, 2H), 3.39– 3.20 (m, 3H), 3.03 – 2.87 (m, 2H), 2.52 – 2.46 (m, 2H).

(*S*)-2-(((*S*)-2-amino-3-phenfylpropyl)amino)-3-phenylpropan-1-ol (308)



308

Compound **308** was prepared according to the procedure developed by Vinh Ngoc Huynh as follows:

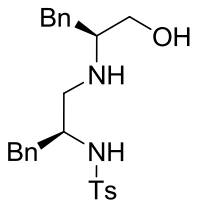
Imidazole **424** (19.88 g, 53.7 mmol, 1 equiv.) was dissolved in 537 mL HCl (*aq*.) (w = 10%) and refluxed for 24 h. Then the mixture was quenched with 6N NaOH (*aq*.) solution until pH = 14 is reached. The mixture was extracted with DCM (3 x 300 mL) and the combined organic layers were evaporated under reduced pressure to get the crude product which subsequently was purified by flash column chromatography (silica, DCM/MeOH 19:1 to DCM/MeOH 8:2) to yield **308** (7.33 g, 25.8 mmol, 48%) as a pale, white, viscous oil.

$\mathbf{R_f}$ = 0.06 (DCM/MeOH = 9:1)

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H (ppm) = 7.33 – 7.14 (m, 10H), 3.62 (dd, *J* = 10.8 Hz, 3.8 Hz, 2H), 3.39 (dd, *J* = 10.9 Hz, 7.2 Hz, 2H), 3.16 – 3.05 (m, 2H), 2.77 dd, *J* = 13.5 Hz, 5.3 Hz 2H), 2.51 (dd, *J* = 13.5 Hz, 8.7 Hz, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ_C (ppm) = 138.82, 138.44, 129.25, 129.22, 128.61, 128.54, 126.50, 126.34, 63.05, 60.66, 52.72, 51.63, 41.79, 38.05.

_N_-((_S_)-1-(((_S_)-1-hydroxy-3-phenylpropan-2-yl)amino)-3-phenylpropan-2-yl)-4-methylbenzenesulfonamide (317)



317

A procedure was adapted from the literature [234] as follows:

To a solution of 1,2-diamino alcohol **308** (2.29 g, 8.04 mmol, 1 equiv.) and Et_3N (1.23 mL, 8.84 mmol, 1.1 equiv.) in 80 mL DCM (c = 0.2 mol/L), tosyl chloride (1.53 g, 8.04 mmol, 1.0 equiv.) was added and the mixture was stirred at r.t. for 3 h. Upon completion of the reaction the crude mixture was concentrated up under reduced pressure and subsequently was purified *via* flash column chromatography (silica, PE/EA 1:1 to DCM/MeOH 9:1) to yield the product **317** (1.51 g, 3.44 mmol, 43%) as a pale, clear, viscous oil.

$\mathbf{R_f}$ = 0.32 (DCM/MeOH = 9:1)

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H (ppm) = 7.73 – 7.64 (m, 2H), 7.32 – 7.14 (m, 8H), 6.94 – 6.84 (m, 2H), 3.55 – 3.38 (m, 2H), 3.32 – 3.23 (m, 1H), 2.78 – 2.48 (m, 7H), 2.40 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ_C (ppm) = 143.27 (Cq), 138.57 (Cq), 137.98 (Cq), 137.22 (Cq), 129.69 (+, CH), 129.22 (+, CH), 129.17 (+, CH), 128.57 (+, CH), 128.53 (+, CH), 127.03 (+, CH), 126.52 (+, CH), 126.40 (+, CH), 62.96 (-, CH_2), 60.44 (+, CH), 55.08 (+, CH), 48.96 (-, CH_2), 39.37 (-, CH_2), 37.87 (-, CH_2), 21.53 (+, CH_3).

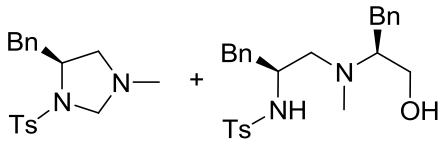
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = - 9.10 [°·mL·dm^{-1}·g^{-1}] (c = 1.0g/100mL, $CHCl_3$).

IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3290, 3028, 2927, 2872, 1599, 1495, 1454, 1410, 1326, 1154, 1087, 1031, 964, 813, 747, 699, 663, 547, 420.

LRMS (ESI): m/z = 439.2 $[M+H]^+$, 877.4 $[2M+H]^+$.

HRMS (ESI): m/z = 439.2053 $[M+H]^+$; calc. for $[C_{25}H_{31}N_2O_3S]^+$ = 439.205.

(*S*)-4-benzyl-1-methyl-3-tosylimidazolidine (319) and *N*-((*S*)-1-(((*S*)-1-hydroxy-3-phenylpropan-2-yl)(methyl)amino)-3-phenylpropan-2-yl)-4-methylbenzenesulfonamide (320)



319 **320**

A procedure was adapted from the literature [238] as follows:

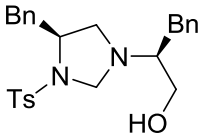
To a solution of 1,2-diamino alcohol **317** (110 mg, 0.25 mmol, 1 equiv.) dissolved in less as possible DCM was added formic acid (493 µL, 13.1 mmol, 52.3 equiv.) at 0°C. Subsequently, formaldehyde (37 wt. % in H_2O) (440 µL, 5.8 mmol, 23.0 equiv.) was added dropwise at 0°C. The mixture was warmed to r.t. and then refluxed (80 °C) for 11h. When the reaction mixture was at r.t. it was diluted with DCM (5 mL) and brought to pH 13 with the help of 50% NaOH (*aq.*). The solution was extracted with DCM (3x10 mL). The combined organic layers were concentrated up under reduced pressure and subsequently the crude product was purified *via* flash column chromatography (silica, PE/EA3:1 to DCM/MeOH 8:2) to yield the product **319** (33 mg, 0.10 mmol, 40%) and **320** (68 mg, 0.15 mmol, 60%) as inseperable mixture.

$\mathbf{R_f}$ = 0.47 (EA)

^{1}H-NMR (319) (300 MHz, $CDCl_3$): δ_H (ppm) = 7.81 – 7.76 (m, 2H), 7.35 – 7.19 (m, 7H), 4.02 (d, *J* = 7.1 Hz, 1H), 3.88 (d, *J* = 7.1 Hz, 1H), 3.36 (dd, *J* = 13.4 Hz, 3.6 Hz, 1H), 2.83 (dd, *J* = 13.4 Hz, 10.2 Hz, 1H), 2.58 – 2.44 (m, 2H), 2.43 (s, 3H), 2.07 (s, 3H).

^{1}H-NMR (320) (300 MHz, $CDCl_3$): see below

(*S*)-2-((*S*)-4-benzyl-3-tosylimidazolidin-1-yl)-3-phenylpropan-1-ol (318)



318

Following a procedure reported in the literature [239]:

The 1,2-diamino alcohol **317** (101 mg, 0.23 mmol, 1 equiv.) was dissolved in THF (3.9 mL, c = 0.06 mol/L) and subsequently $NaBH_4$ was added (44 mg, 1.15mmol, 5 equiv.). The resultant suspension was added dropwise into a freshly prepared mixture of formaldehyde (37 wt. % in H_2O) (178 µL, 2.31 mmol, 10.0 equiv.) and 3N H_2SO_4 (*aq.*) under vigorus stirring at 0 °C. After the addition the mixture was warmed to r.t. and stirred for additional 19 h. The reaction mixture was quenched with saturated NaOH (*aq.*) and then the mixture was partitioned between EA (1x10 mL) and water (1x10 mL). The organic layer was washed with brine (1x10 mL). After removal of the solvent in *vacuo* the residue was purified by flash column chromatography (silica, PE/EA = 3:1 to PE/EA 0:1) to obtain the product **318** (82 mg, 0.18 mmol, 79%).

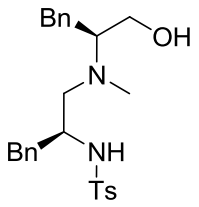
$\mathbf{R_f}$ = 0.49 (PE/EA 1:1)

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H (ppm) = 7.81 – 7.76 (m, 2H), 7.38 – 7.20 (m, 10H), 7.08 – 7.03 (m, 2H), 4.26 (d, *J* = 6.9 Hz, 1H), 3.96 (d, J = 6.9 Hz, 1H), 3.29 (dd, *J* = 13.4 Hz, 3.7 Hz, 2H), 3.18 – 3.09 (m, 1H), 2.91 (dd, *J* = 13.4 Hz, 9.5 Hz, 1H), 2.74 – 2.47 (m, 5H), 2.46 – 2.39 (m, 1H), 2.44 (s, 3H), 2.42 -2.36 (m, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ_C (ppm) = 144.21, 138.06, 137.45, 134.28, 129.94, 129.55, 129.14, 128.69, 128.66, 127.81, 126.82, 126.59, 66.63, 62.18, 60.39, 60.19, 53.64, 41.47, 33.59, 21.66.

LRMS (ESI): m/z = 451.2 $[M+H]^+$

_N_-((_S_)-1-(((_S_)-1-hydroxy-3-phenylpropan-2-yl)(methyl)amino)-3-phenylpropan-2-yl)-4-methylbenzenesulfonamide (320)



320

Following a procedure reported in the literature [239]:

To a solution of 1,2-diamino alcohol **317** (441.7 mg, 1.01 mmol, 1 equiv.) in MeOH (20.2 mL, c = 0.05 mol/L) at 0 °C were added formaldehyde (37 wt. % in H_2O) (778 µL, 10.07 mmol, 10 equiv.), $NaBH_3CN$ (316.1 mg, 5.03 mmol, 5 equiv.), and AcOH (115 µL, 2.01 mmol, 2 equiv.). The reaction mixture was stirred at r.t. for 24 h. Then the solvent was evaporated under reduced pressure and the residue was dissolved in 5% $NaHCO_3$ (*aq.*) (1 x 20 mL) and extracted with EA (3 x 20 mL). The combined organic layers were evaporated in *vacuo* and the residue was purified by flash column chromatography (silica, PE/EA = 1:1 to PE/EA 0:1) to obtain the product **320** (279.5 mg, 0.62 mmol, 61%) as white, crystalline solid.

$\mathbf{R}_f$ = 0.55 (EA)

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H (ppm) = 7.57 – 7.60 (m, 2H), 7.37 – 7.11 (m, 9H), 7.10 – 6.94 (m, 4H), 3.47 – 3.29 (m, 3H), 3.01 – 2.88 (m, 1H), 2.85 – 2.63 (m, 3H), 2.60 – 2.48 (m, 1H), 2.46 – 2.39 (m, 1H), 2.38 (s, 3H), 2.31 -2.21 (m, 1H), 2.08 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ_C (ppm) = 143.18 (Cq), 139.13 (Cq), 137.50 (Cq), 137.14 (Cq), 129.60 (+, CH), 129.48 (+, CH), 128.92 (+, CH), 128.62 (+, CH), 128.57 (+, CH), 127.34 (+, CH), 126.54 (+, CH), 126.26 (+, CH), 66.58 (+, CH), 60.92 (-, CH_2), 55.80 (-, CH_2), 53.25 (+, CH), 39.76 (-, CH_2), 37.35 (+, CH_3), 31.89 (-, CH_2), 21.61 (+, CH_3).

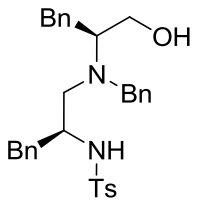
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = + 6.96 [°·mL·dm^{-1}·g^{-1}] (c = 1.0g/100mL, $CHCl_3$).

IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3477, 3275, 3028, 2923, 2854, 2360, 2200, 1600, 1495, 1495, 1454, 1404, 1322, 1222, 1156, 1089, 1030, 1026, 967, 813, 744, 699, 665, 574, 550, 501, 432, 417.

LRMS (ESI): m/z = 453.2 $[M+H]^+$, 927.4 $[2M+Na]^+$.

HRMS (ESI): m/z = 453.2213 $[M+H]^+$; calc. for $[C_{26}H_{32}N_2O_3S]^+$ = 453.2134.

_N_-((_S_)-1-(benzyl((_S_)-1-hydroxy-3-phenylpropan-2-yl)amino)-3-phenylpropan-2-yl)-4-methylbenzenesulfonamide (321)



321

Following a procedure reported in the literature [239]:

To a solution of 1,2-diamino alcohol **317** (200.0 mg, 0.46 mmol, 1 equiv.) in MeOH (9.2 mL, c = 0.05 mol/L) at 0 °C were added benzaldehyde (465 µL, 4.60 mmol, 10 equiv.), $NaBH_3CN$ (144.5 mg, 2.3 mmol, 5 equiv.), and AcOH (53 µL, 0.92 mmol, 2 equiv.). The reaction mixture was stirred at r.t. for 24 h. Then the solvent was evaporated under reduced pressure and the residue was dissolved in 5% $NaHCO_3$ (1 x 10 mL) and extracted with EA (3 x 10 mL). The combined organic layers were evaporated in *vacuo* and the residue was purified by flash column chromatography (silica, PE/EA = 6:1, PE/EA = 3:1, PE/EA = 2:1, PE/EA = 1:1) to yield product **321** (184.3 mg, 0.35 mmol, 76%) as white, crystalline solid.

$\mathbf{R_f}$ = 0.40 (PE/EA = 1:1)

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H (ppm) = 7.75 – 7.64 (m, 2H), 7.41 – 7.10 (m, 14H), 7.02 – 6.95 (m, 2H), 6.90 – 6.82 (m, 2H), 5.33 (bs, 1H), 3.78 (d, *J* = 13.3 Hz, 1H), 3.54 – 3.32 (m, 4H), 3.03 – 3.72 (m, 4H), 2.71 – 2.51 (m, 3H), 240 (s, 3H), 2.33 – 2.20 (m, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ_C (ppm) = 143.26 (Cq), 139.07 (Cq), 138.71 (Cq), 137.61 (Cq), 137.42 (Cq), 129.68 (+, CH), 129.30 (+, CH), 128.94 (+, CH), 128.65 (+, CH), 128.61 (+, CH), 128.52 (+, CH), 127.45 (+, CH), 127.22 (+, CH), 126.51 (+, CH), 126.16 (+, CH), 62.99 (+, CH), 60.85 (-, CH_2), 54.60 (-, CH_2), 53.99 (+, CH), 53.09 (-, CH_2), 39.78 (-, CH_2), 31.78 (-, CH_2), 21.60 (+, CH_3).

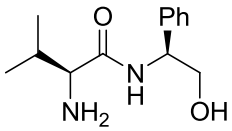
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = - 5.23 [°·mL·dm^{-1}·g^{-1}] (c = 1.0g/100mL, $CHCl_3$).

IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3303, 3029, 2932, 2921, 2858, 2258, 2051, 1981, 1603, 1496, 1454, 1323, 1302, 1157, 1092, 1031, 971, 815, 738, 700, 667, 636, 580, 550, 505, 498, 472, 464, 454, 447, 433, 421, 412, 407.

LRMS (ESI): m/z = 529.3 $[M+H]^+$.

HRMS (ESI): m/z = 529.2526 $[M+H]^+$; calc. for $[C_{32}H_{36}N_2O_3S]^+$ = 529.2447.

(*S*)-2-amino-*N*-((*S*)-2-hydroxy-1-phenylethyl)-3-methylbutanamide (336)



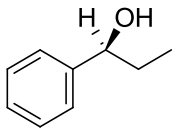
336

Following compound was synthesized and characterized by Vinh Ngoc Huynh (publishing in progress).

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H (ppm) = 8.09 (d, *J* = 6.8 Hz, 1H), 7.41 – 7.27 (m, 5H), 5.06 (dd, *J* = 12.3 Hz, 5.6 Hz, 1H), 3.95 – 3.81 (m, 2H), 3.33 (d, *J* = 3.9 Hz, 1H) 6H), 2.40 – 2.05 (m, 4H), – 2.27 (m, 1H), 0.98 (d, *J* = 7.0 Hz, 3H), 0.79 (d, *J* = 6.9 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ_C (ppm) = 175.13, 139.01, 128.89, 127.87, 126.72, 67.20, 60.06, 56.14, 30.73, 19.73, 16.08.

(*S*)-1-phenylpropan-1-ol (94)



94

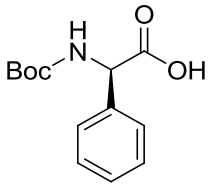
R_f = 0.28 (PE/EA = 6:1)

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H (ppm) = 7.39 – 7.24 (m, 5H), 4.58 (t, *J* = 6.6 Hz, 1H), 2.16 (bs, 1H), 1.91 – 1.66 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ_C (ppm) = 144.61, 128.41, 127.51, 126.01, 76.03, 31.89, 10.18.

Anal. chiral HPLC (Phenomenex Lux Cellulose-1, *i*-PrOH- *n*-heptane (5:95, v/v), UV 215 nm, flowrate 0.5 mL/min) t_r = 18.72 min (major), t_r = 20.40 min (minor).

(*R*)-2-((tert-butoxycarbonyl)amino)-2-phenylacetic acid (425)



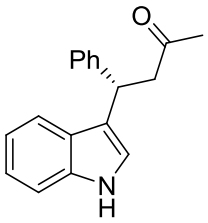
425

Following the procedure [281] for compound **425**, (*R*)-2-amino-2-phenylacetic acid (3.02 g, 20 mmol, 1 equiv.), Boc_2O (6.55 g, 30 mmol, 1.5 equiv.), dioxane/water (v/v = 2:1) (60 mL), $NaHCO_3$ (1.68 g, 20 mmol, 1 equiv.) yielded **425** (5.03 g, 20 mmol, quantitative) as a white, crystalline solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H (ppm) = 11.58 (bs, 1H), 8.20 (d, *J* = 5.2 Hz, 1H), 7.50 – 7.24 (m, 5H), 5.15 (d, *J* = 5.2 Hz, 1H), 1.22 (s, 9H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ_C (ppm) = 173.41, 157.09, 138.39, 128.46, 128.00, 127.22, 81.71, 58.88, 27.99.

(*S*)-4-(1*H*-indol-3-yl)-4-phenylbutan-2-one (344)



344

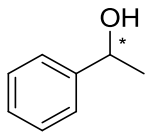
R_f = 0.25 (PE/EA = 2:1)

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H (ppm) = 8.11 (bs, 1H), 7.48 – 7.43 (m, 2H), 7.37 – 7.27 (m, 5H), 7.23 – 7.14 (m, 2H), 7.08 – 7.14 (m, 1H), 6.98 – 6.94 (m, 1H), 4.86 (t, *J* = 6.6 Hz, 1H), 3.28 (dd, *J* = 16.1 Hz, 1H), 3.18 (dd, *J* = 16.1 Hz, 1H), 2.10 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ_C (ppm) = 207.75, 143.95, 136.58, 128.51, 127.72, 126.53, 126.41, 122.21, 121.37, 119.45, 118.84, 111.17, 50.36, 38.40, 30.41.

Anal. chiral HPLC (Chiralpak AS-H, *i*-PrOH- *n*-heptane (20:80, v/v), UV 215 nm, flowrate 0.5 mL/min) t_r = 27.14 min (minor), t_r = 32.57 min (major).

1-Phenylethanol (407)



407

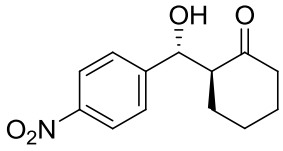
^{1}H-NMR (300 MHz, $CDCl_3$): δ_H (ppm) = 7.41 – 7.24 (m, 5H), 7.37 – 7.27 (m, 5H), 4.90 (q, *J* = 6.5 Hz, 1H), 2.01 (bs, 1H), 1.50 (d, *J* = 6.5 Hz, 1H).

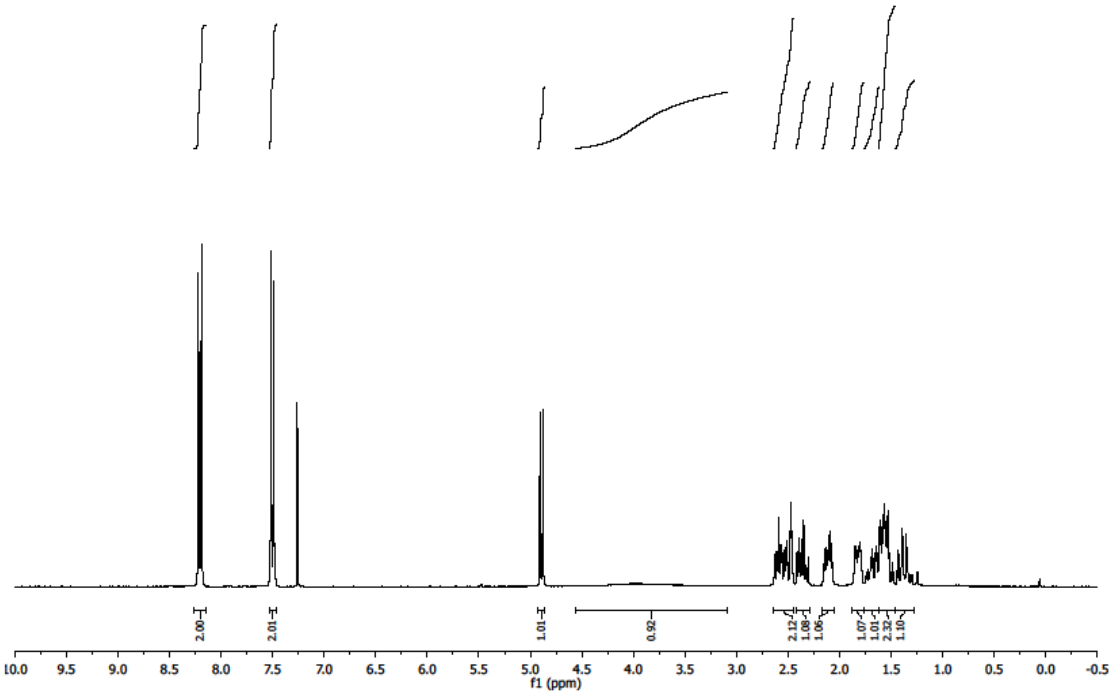
^{13}C-NMR (75 MHz, $CDCl_3$): δ_C (ppm) = 145.82, 128.53, 127.51, 125.41, 70.44, 25.18.

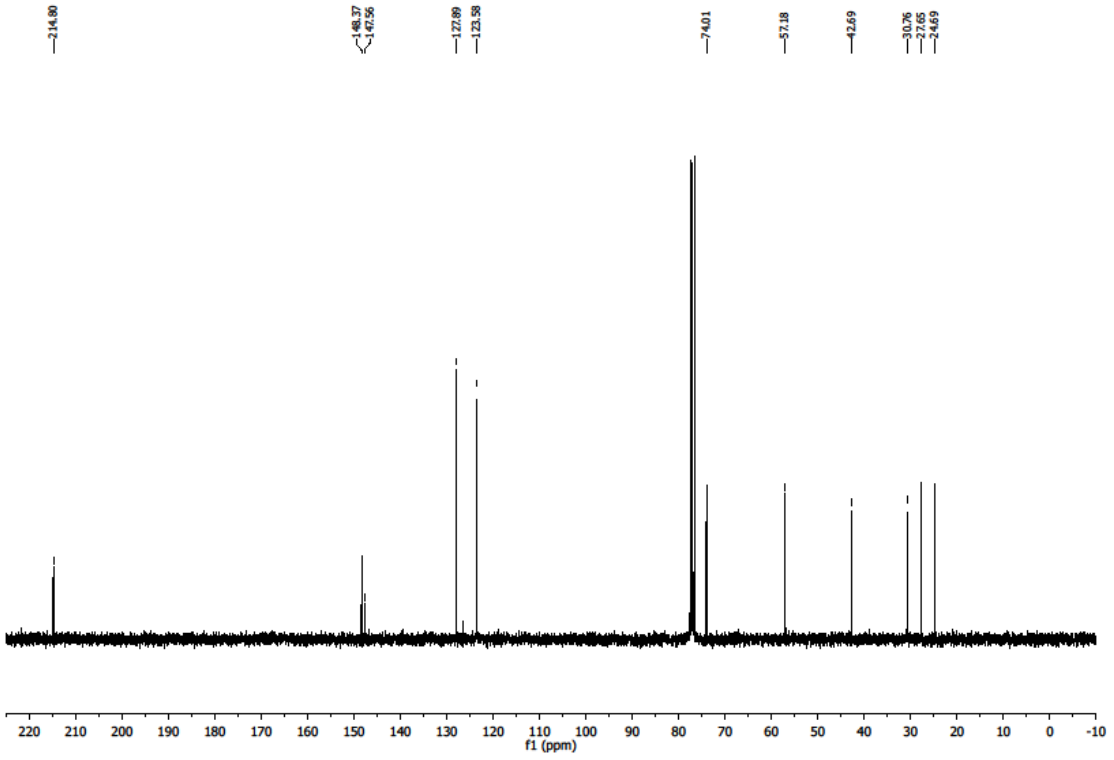
Anal. chiral GC (Chiralpak AS-H, isothermal T = 125 °C) t_r = 7.90 min (major), t_r = 8.52 min (minor).

3. Spectra

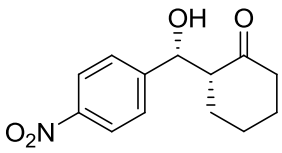
(*S*)-2-((*R*)-hydroxy(4-nitrophenyl)methyl)cyclohexanone (152 (*anti*)):

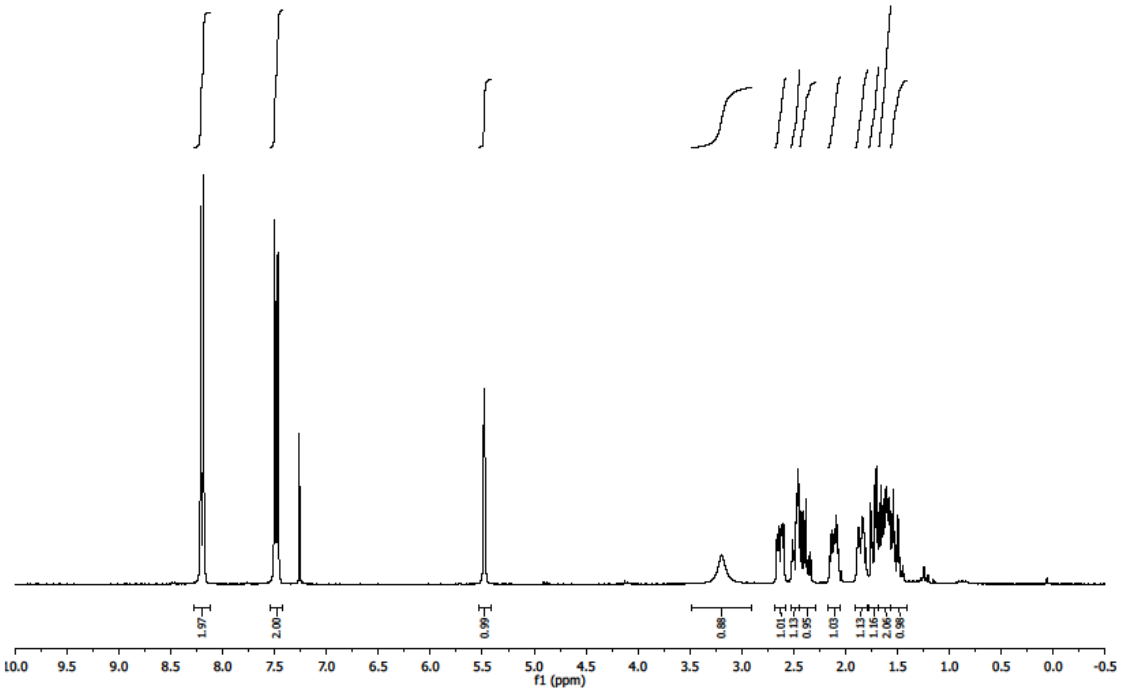


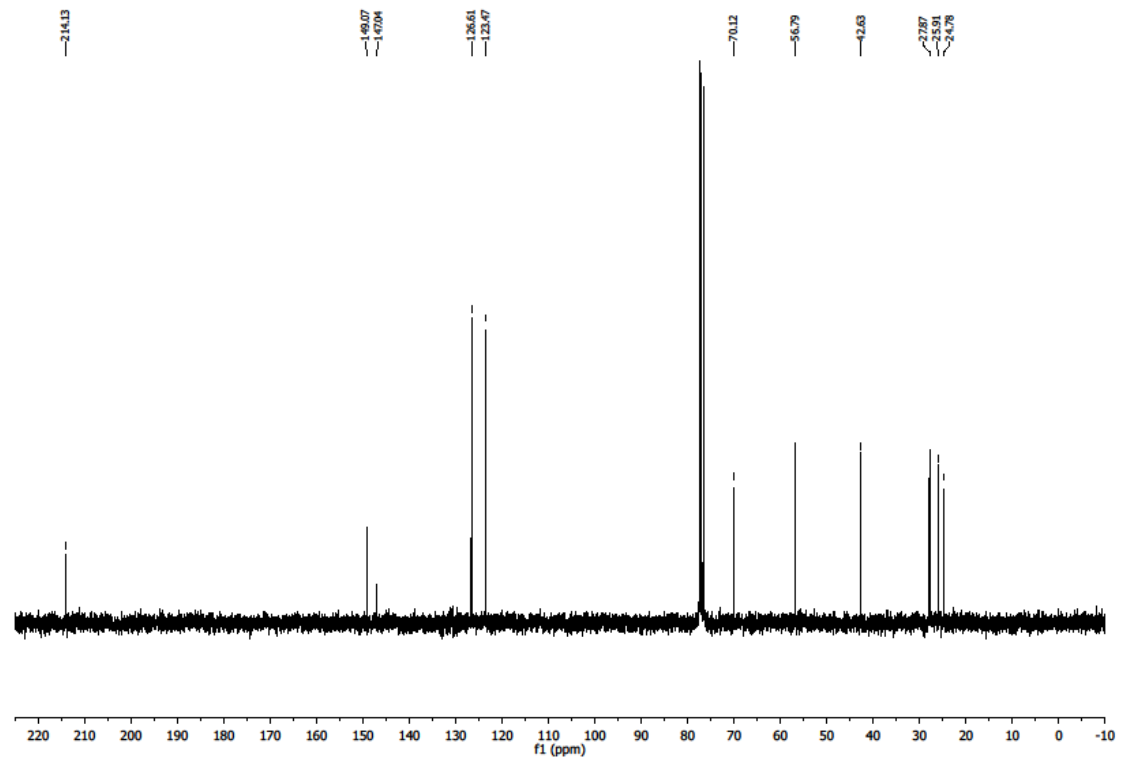




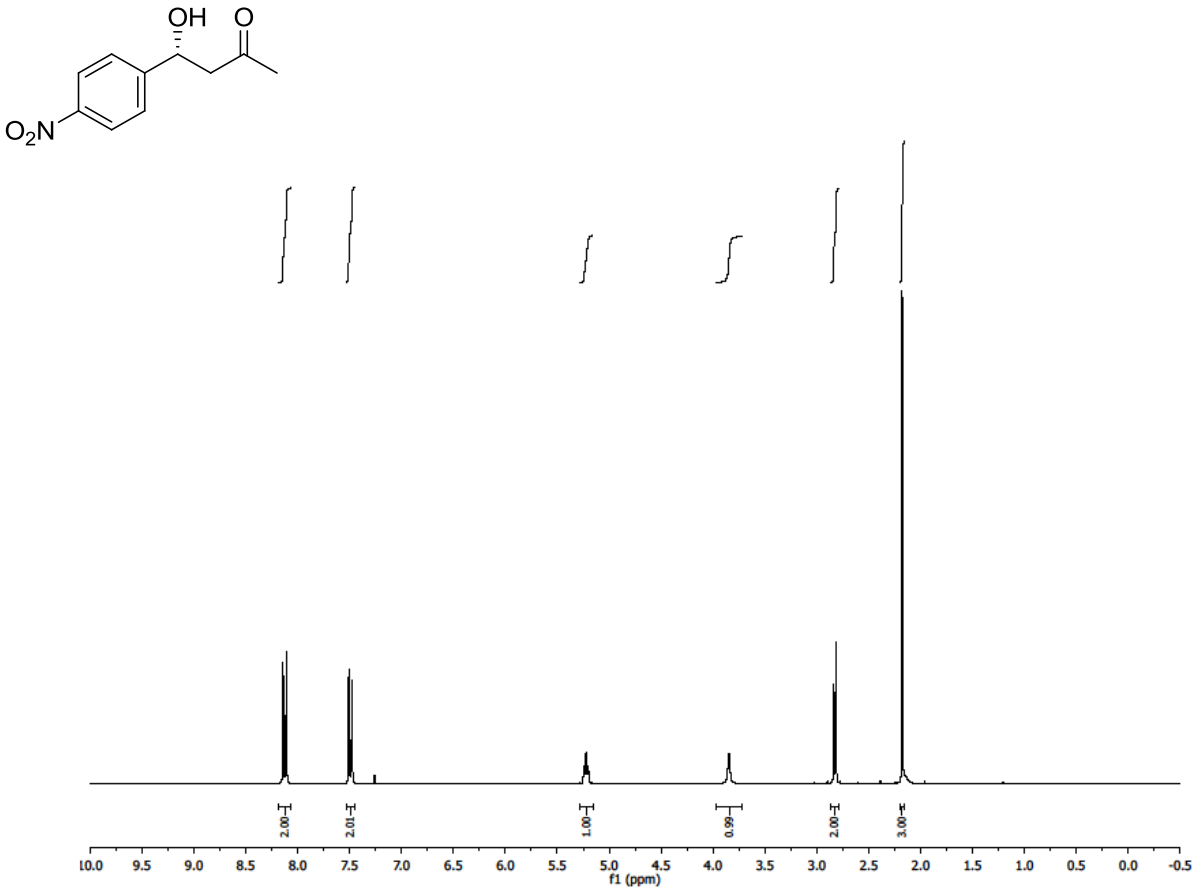
(*R*)-2-((*R*)-hydroxy(4-nitrophenyl)methyl)cyclohexanone (152 (*syn*)):



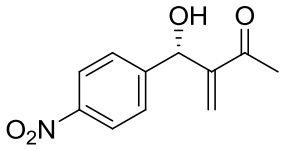


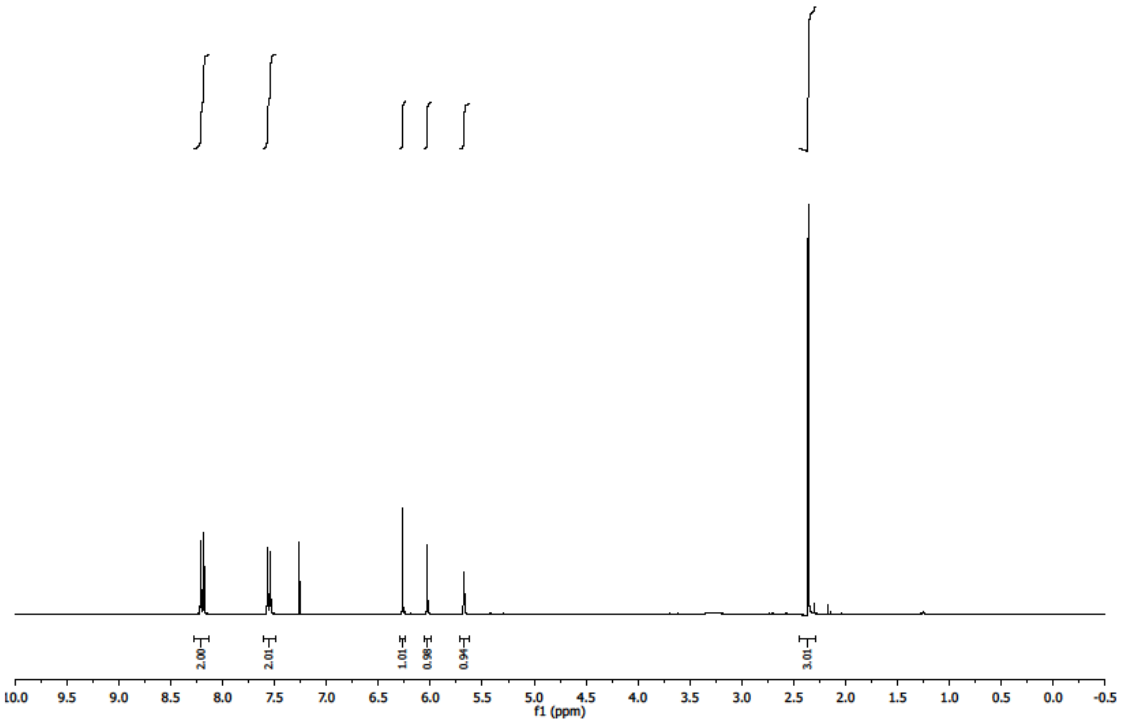


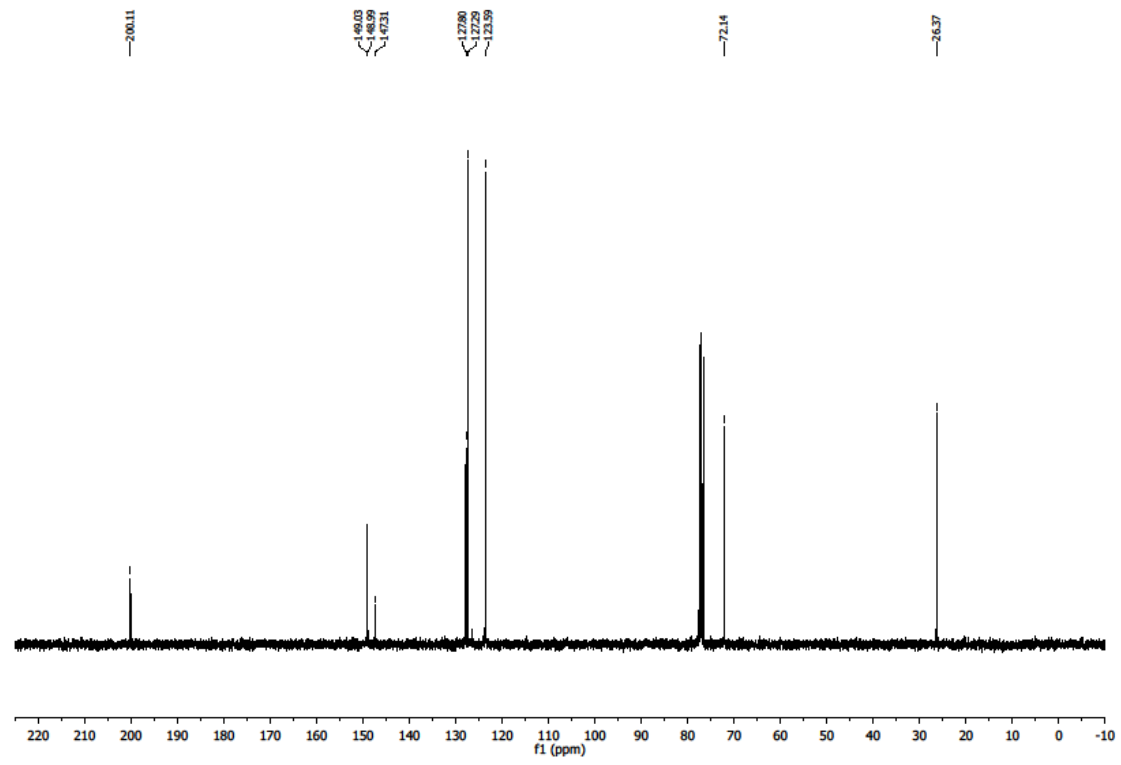
(*R*)-4-hydroxy-4-(4-nitrophenyl)butan-2-one (151):



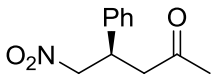
(*S*)-2-(hydroxy(4-nitrophenyl)methyl)pent-1-en-3-one (195):

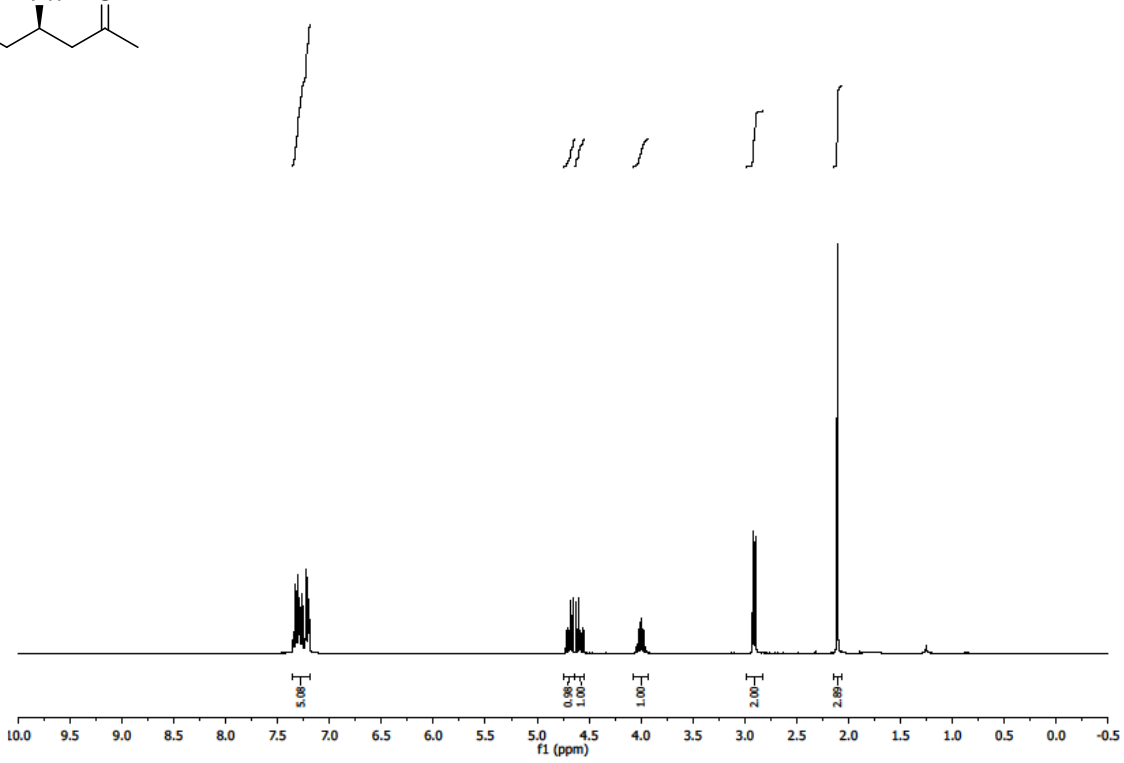


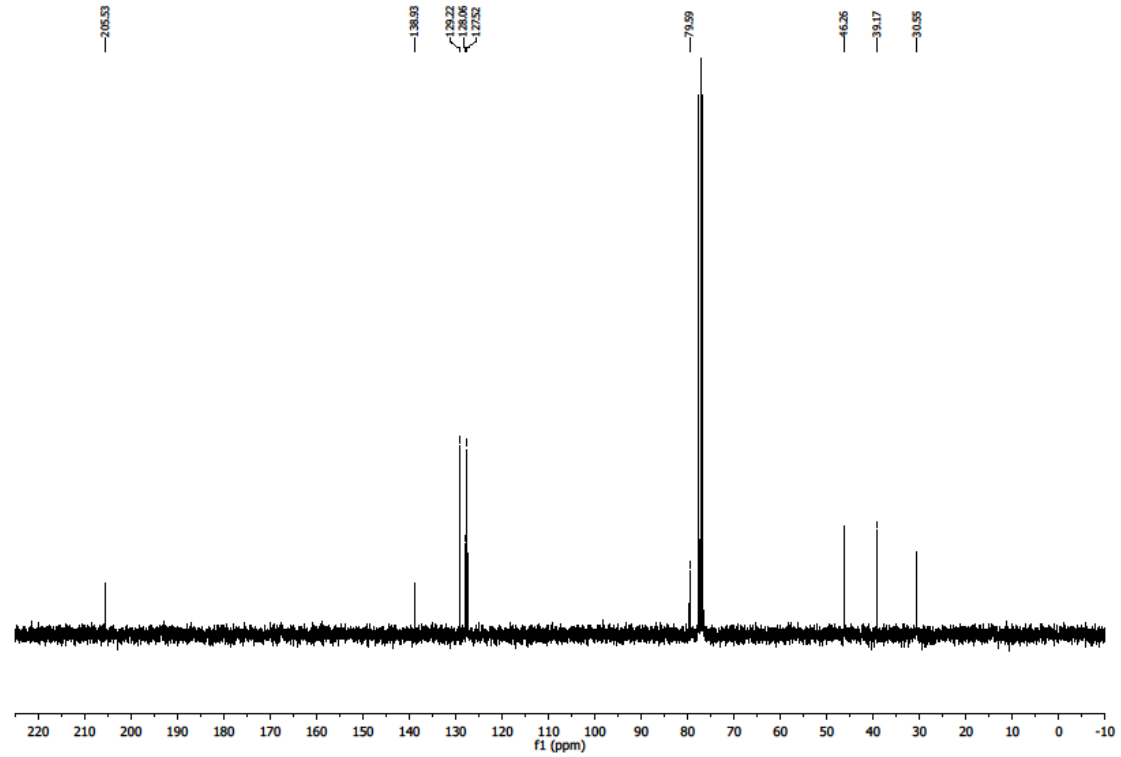




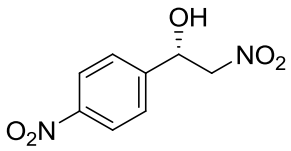
(*R*)-5-nitro-4-phenylpentan-2-one (194):

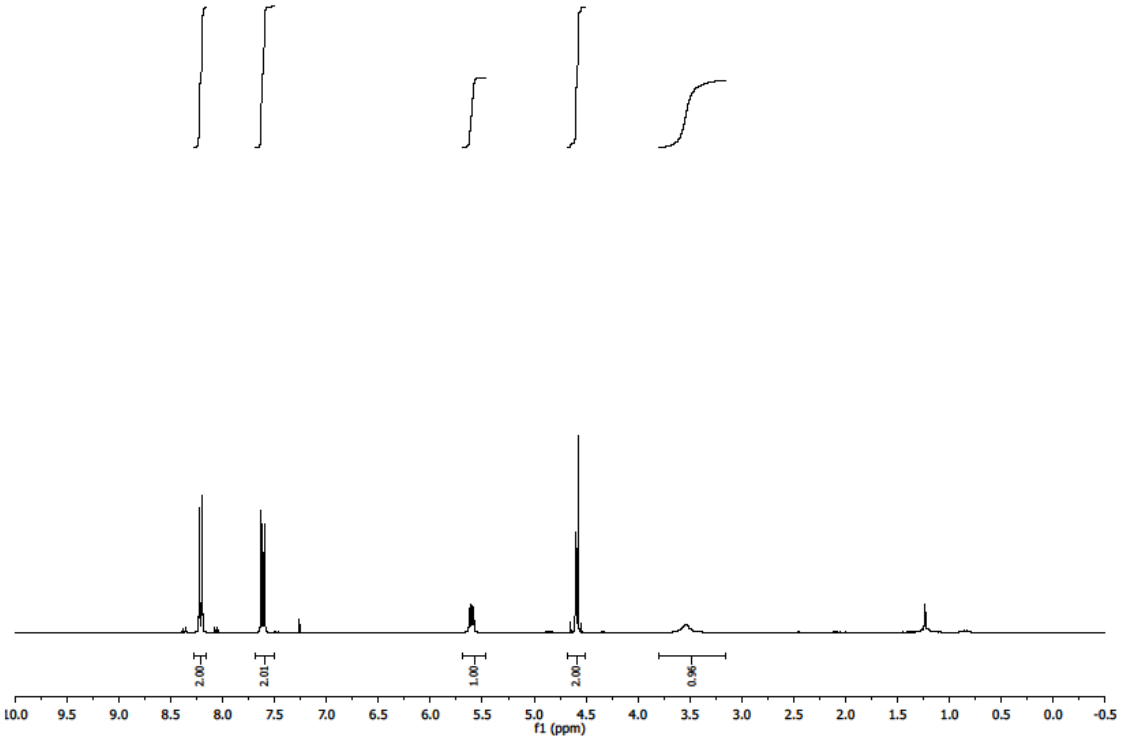


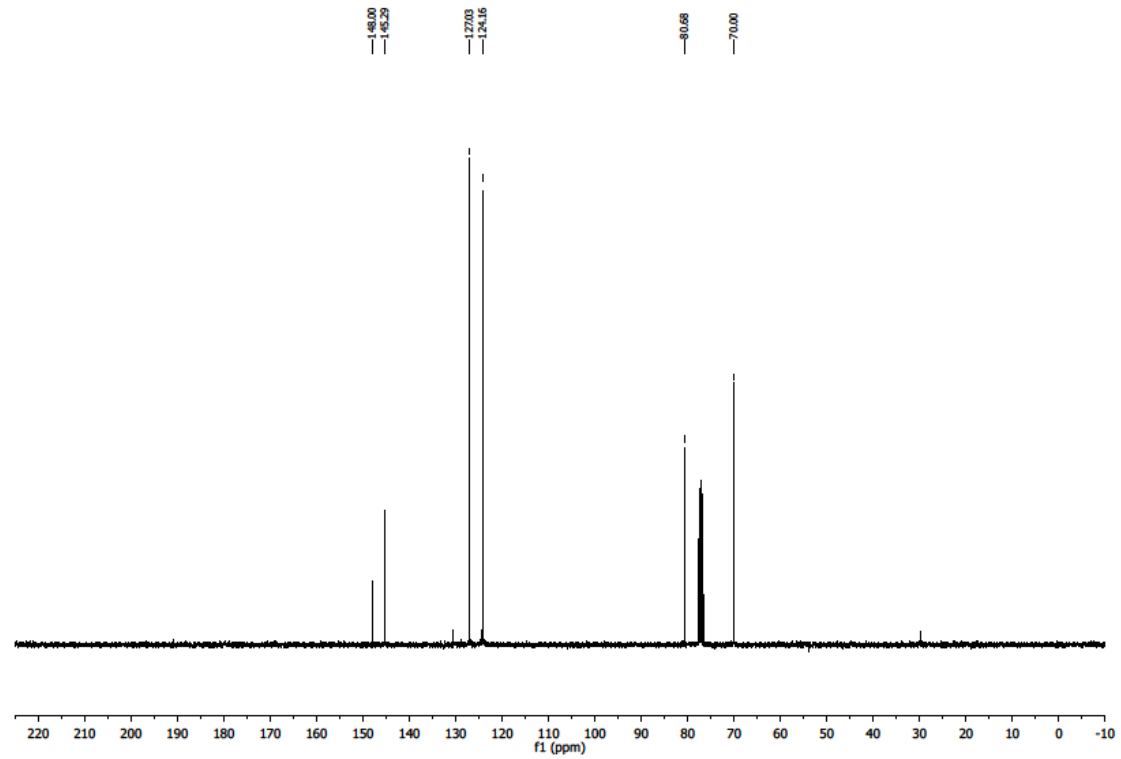




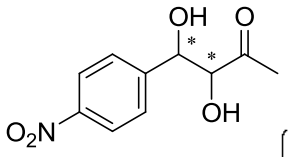
(*R*)-2-nitro-1-(4-nitrophenyl)ethanol (358):

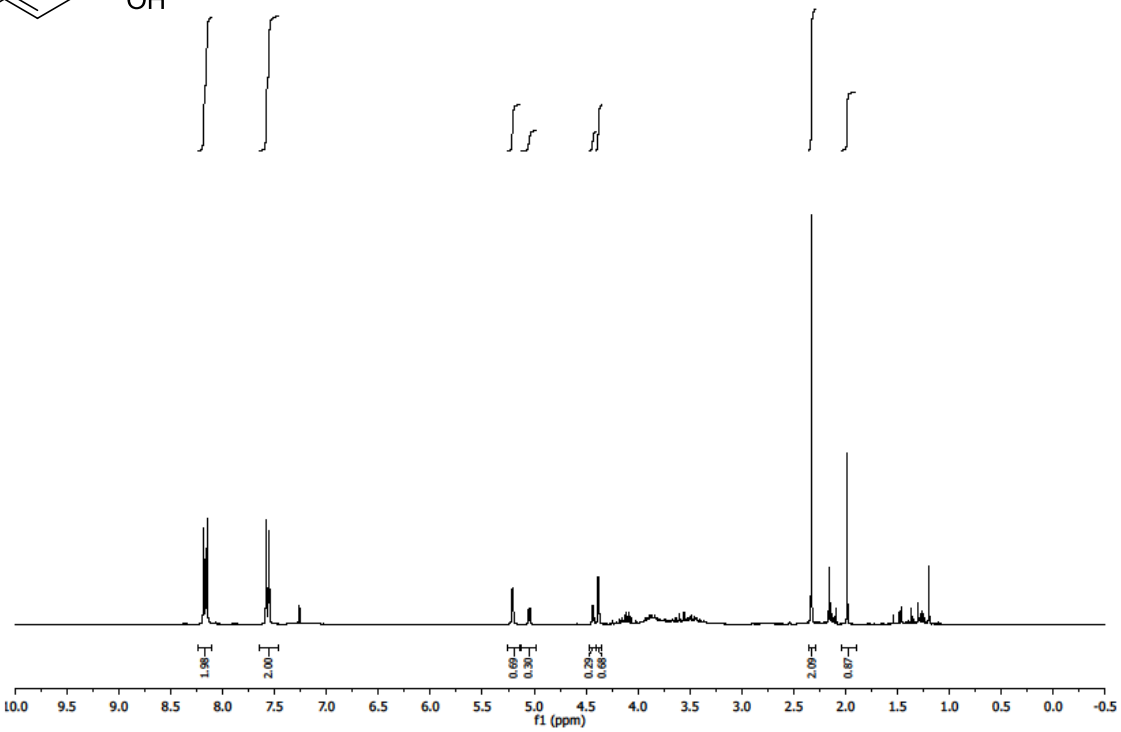


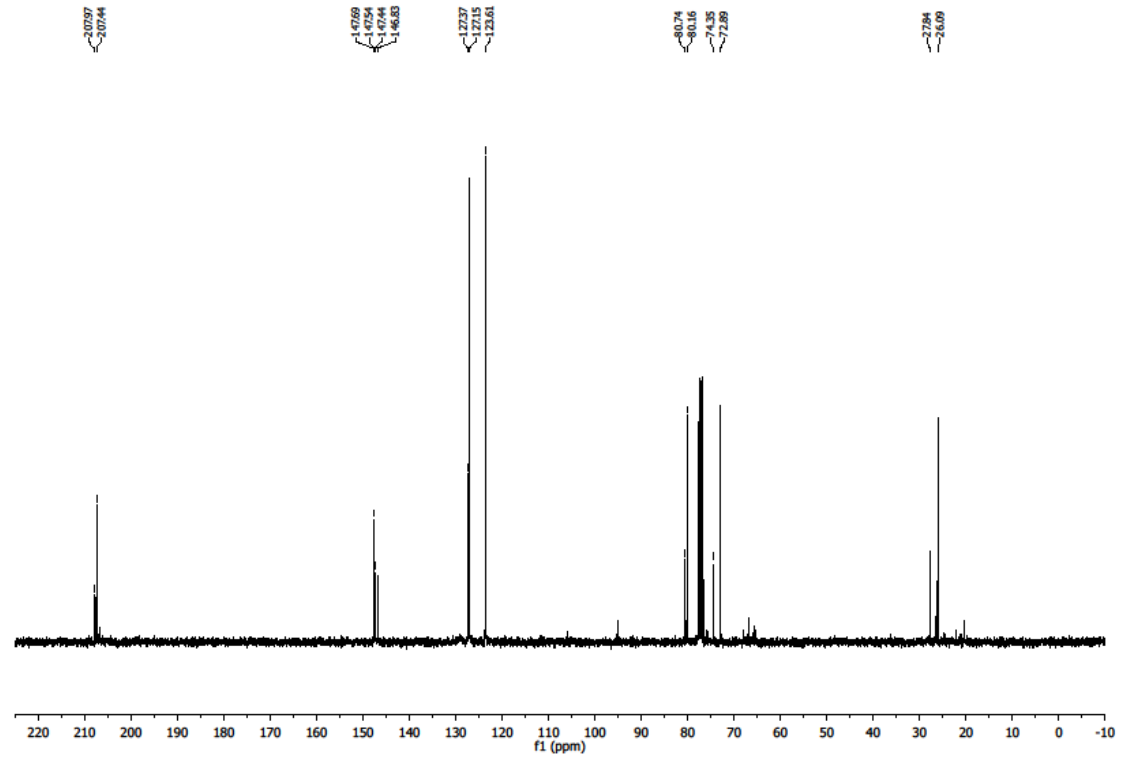




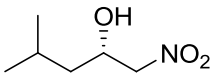
3,4-dihydroxy-4-(4-nitrophenyl)butan-2-one (339):

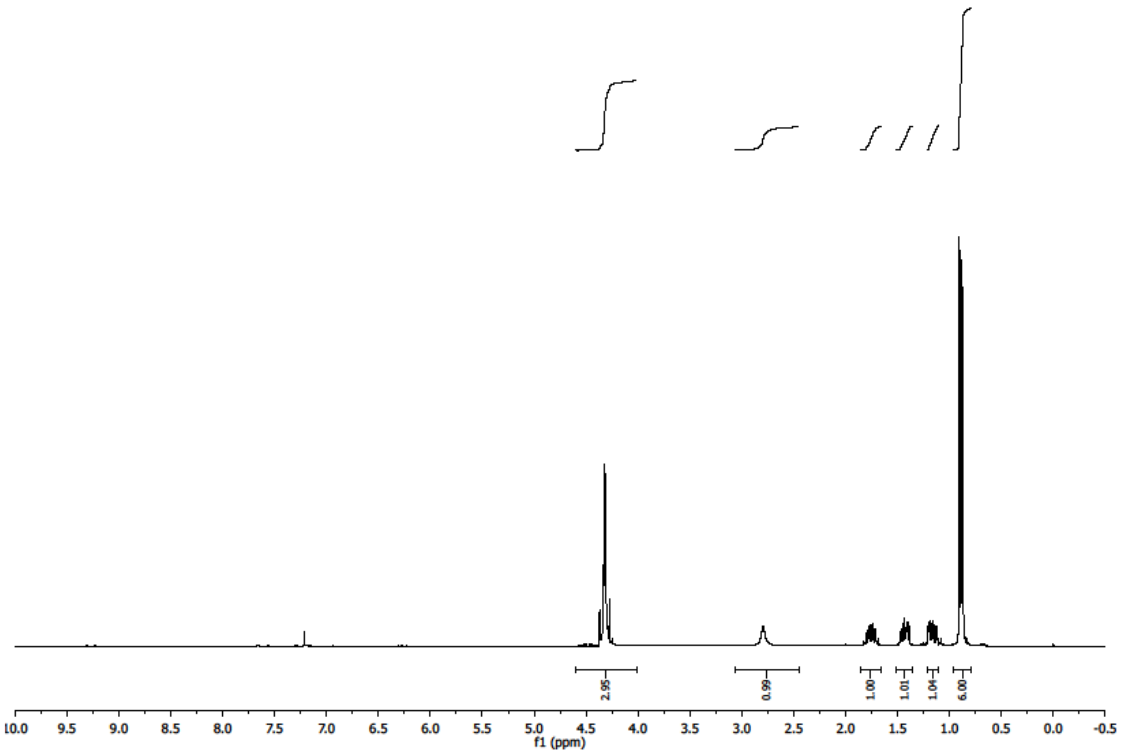


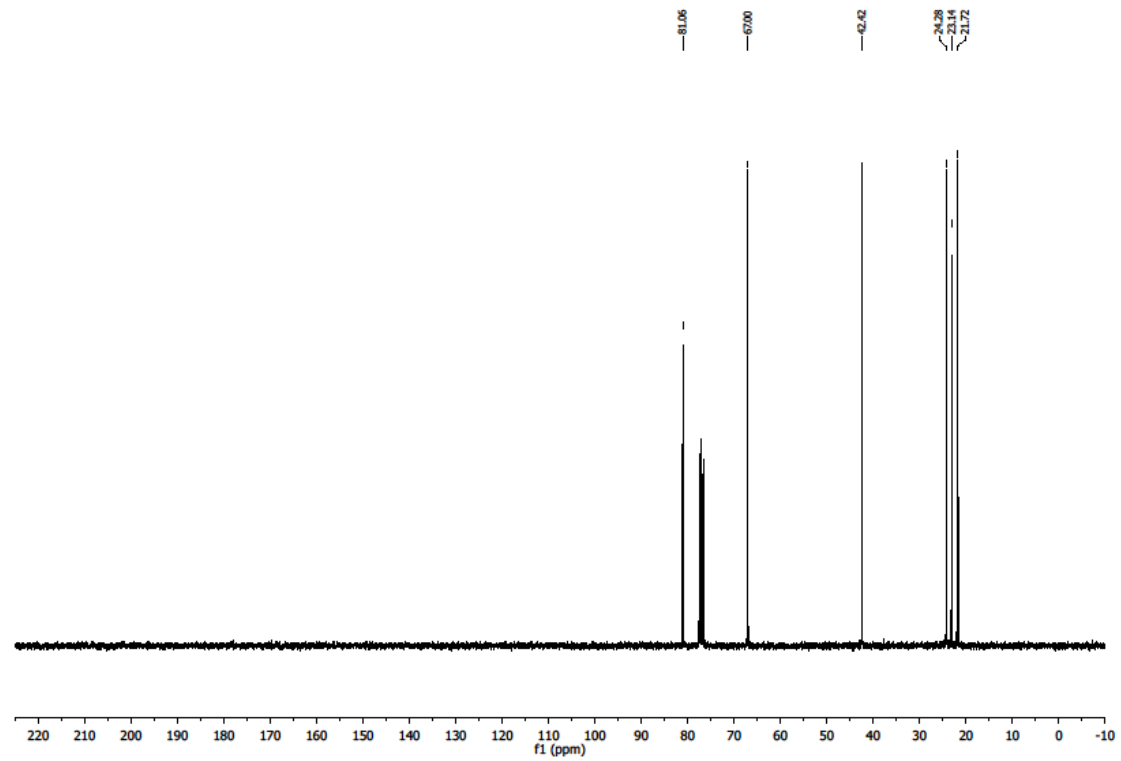




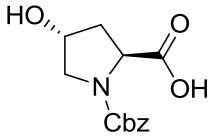
(*S*)-4-methyl-1-nitropentan-2-ol (349):

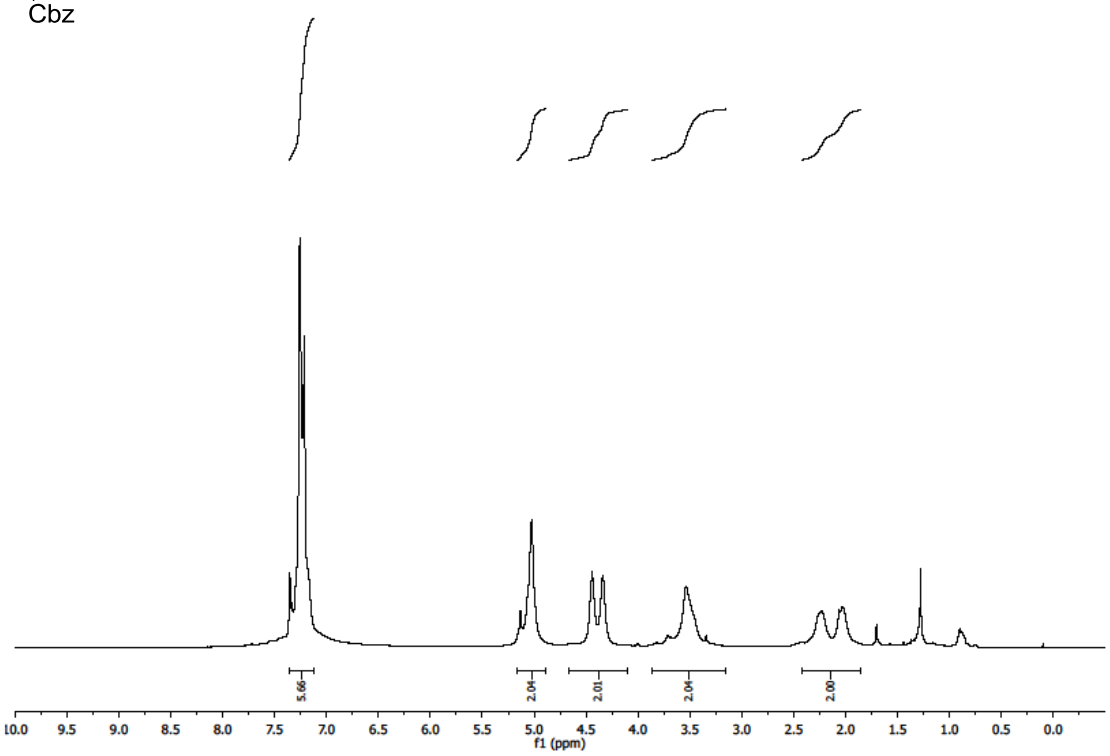


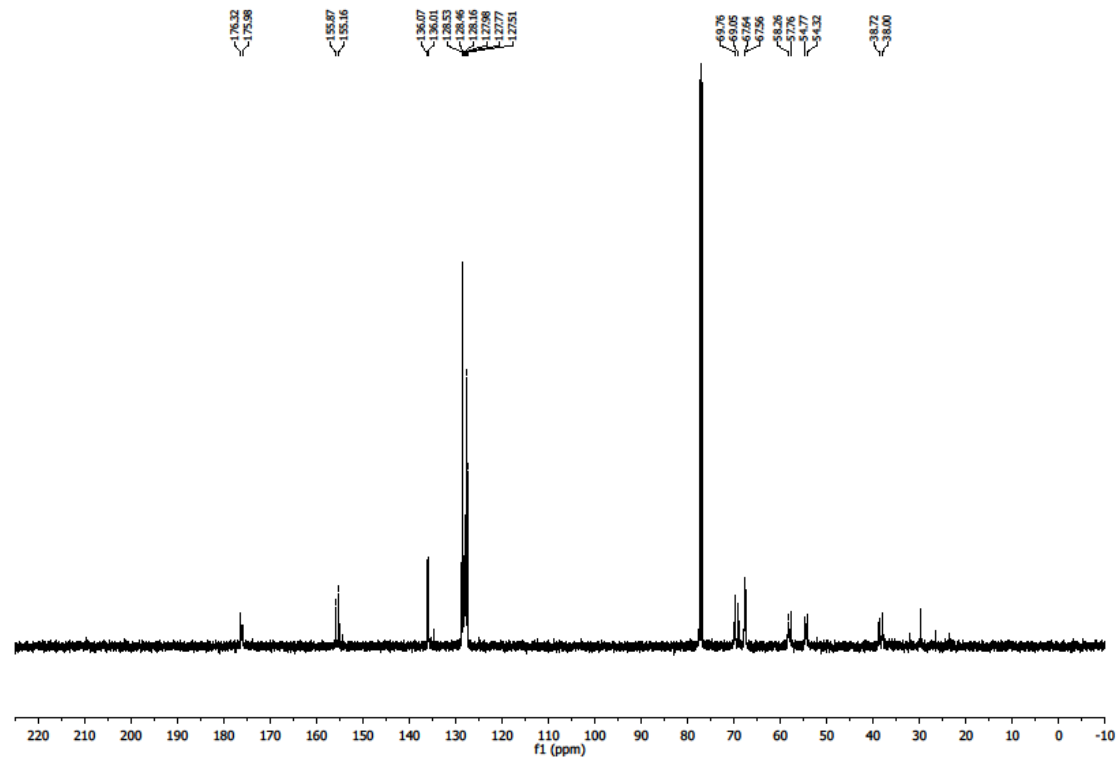




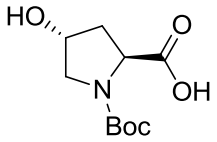
(2*S*,4*R*)-1-((benzyloxy)carbonyl)-4-hydroxypyrrolidine-2-carboxylic acid (145):

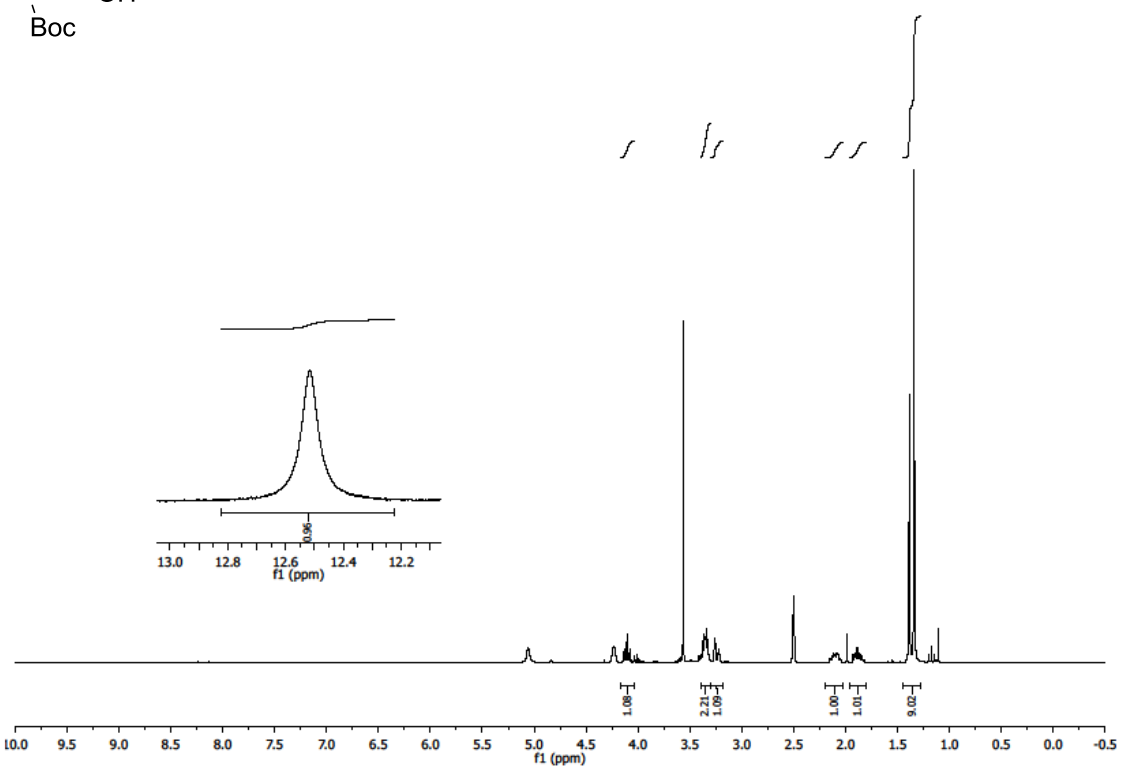


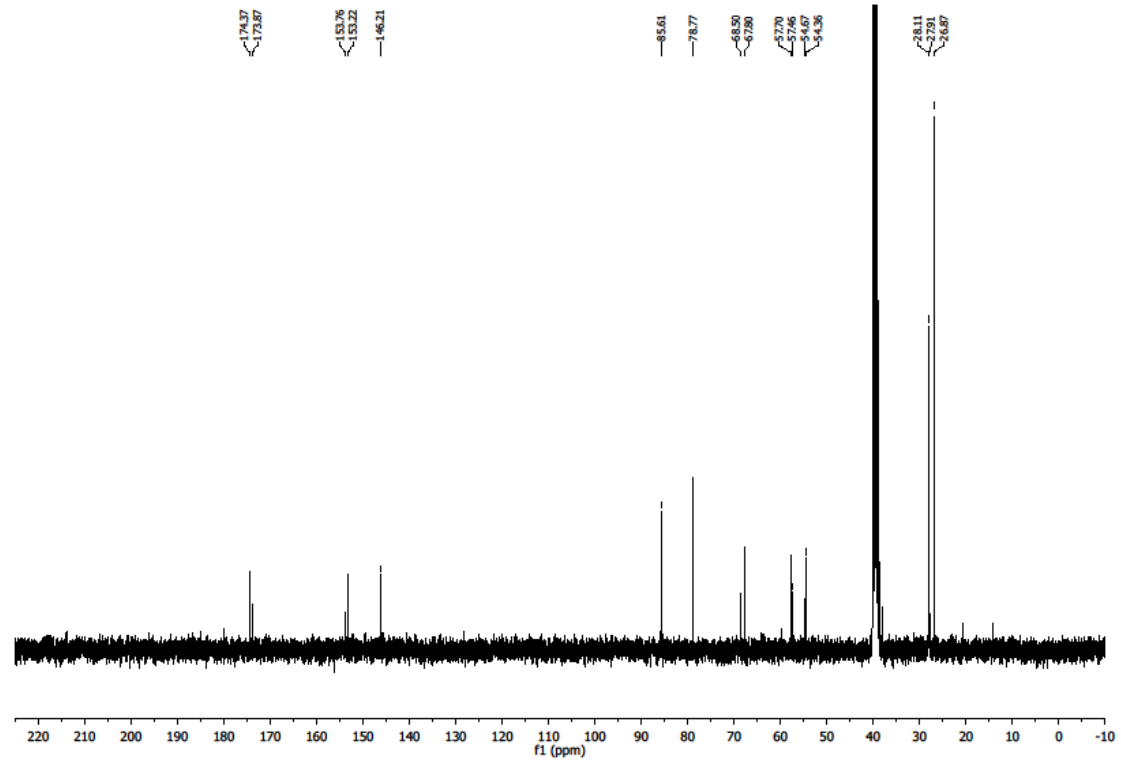




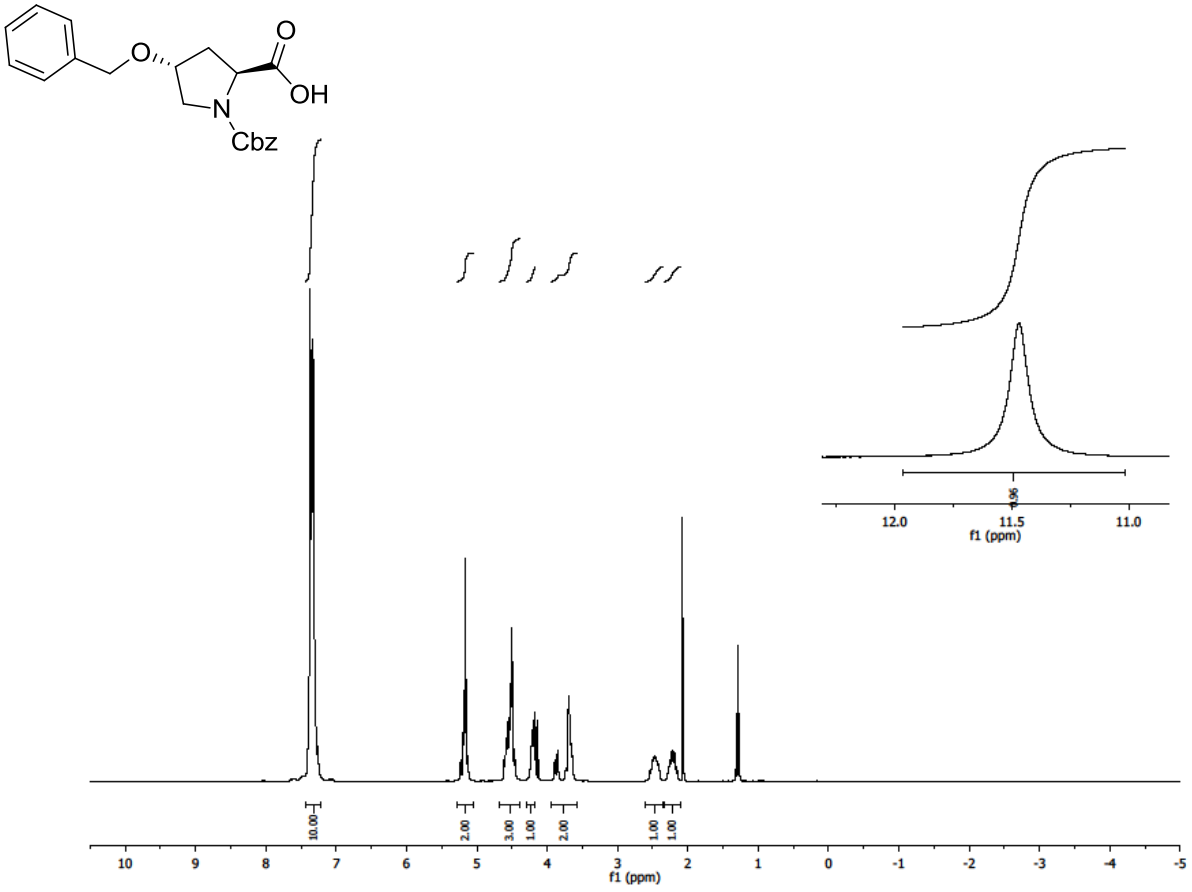
(2*S*,4*R*)-1-(tert-butoxycarbonyl)-4-hydroxypyrrolidine-2-carboxylic acid (155):



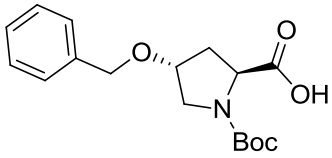


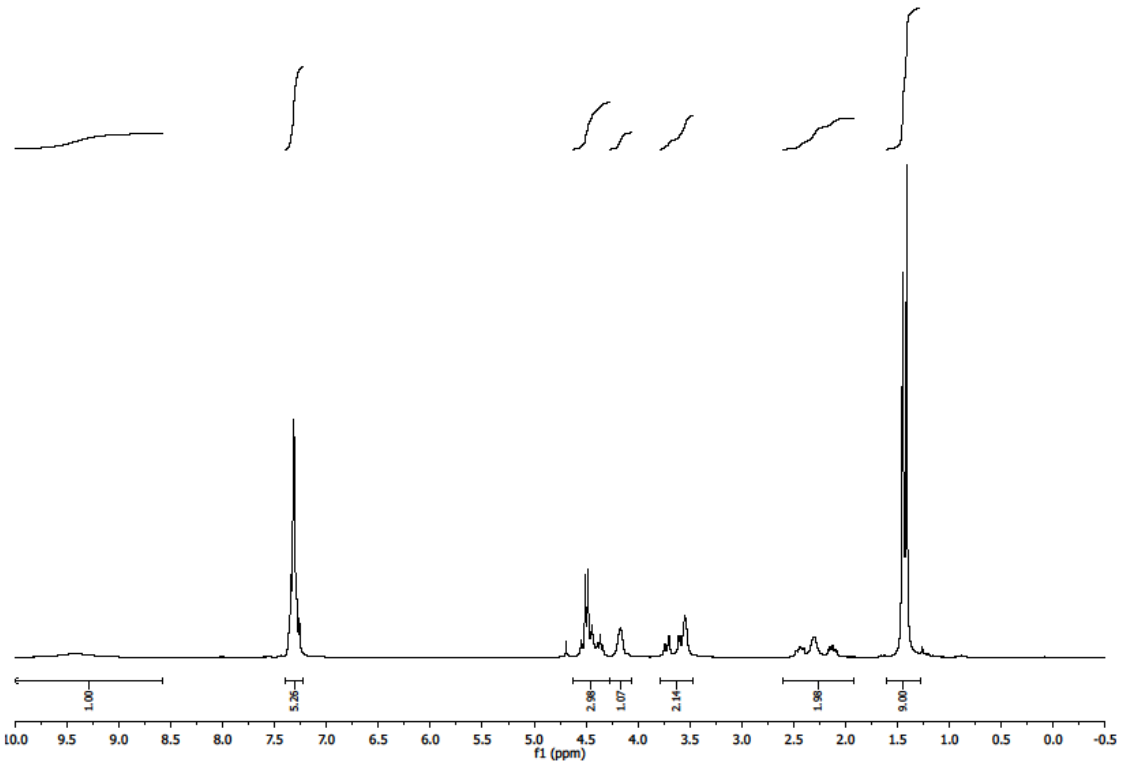


(2*S*,4*R*)-4-(benzyloxy)-1-((benzyloxy)carbonyl)pyrrolidine-2-carboxylic acid (159):

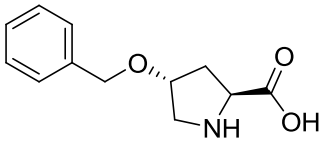


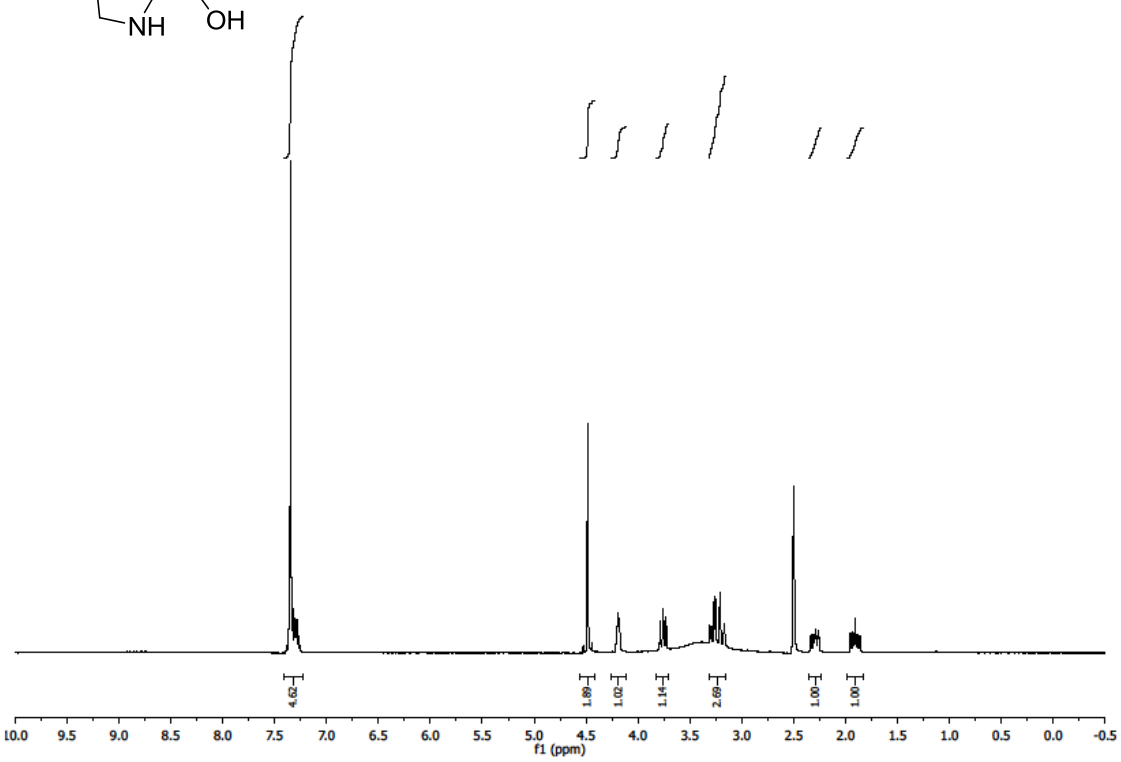
(2*S*,4*R*)-4-(benzyloxy)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid (162):

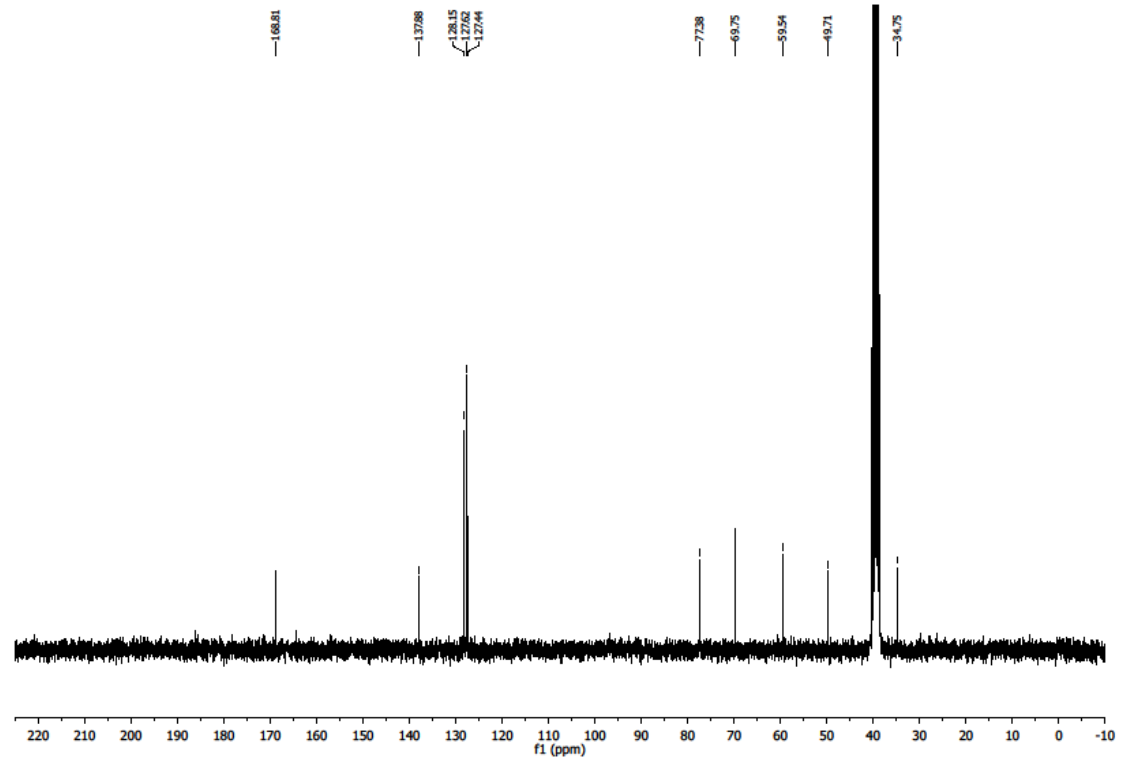




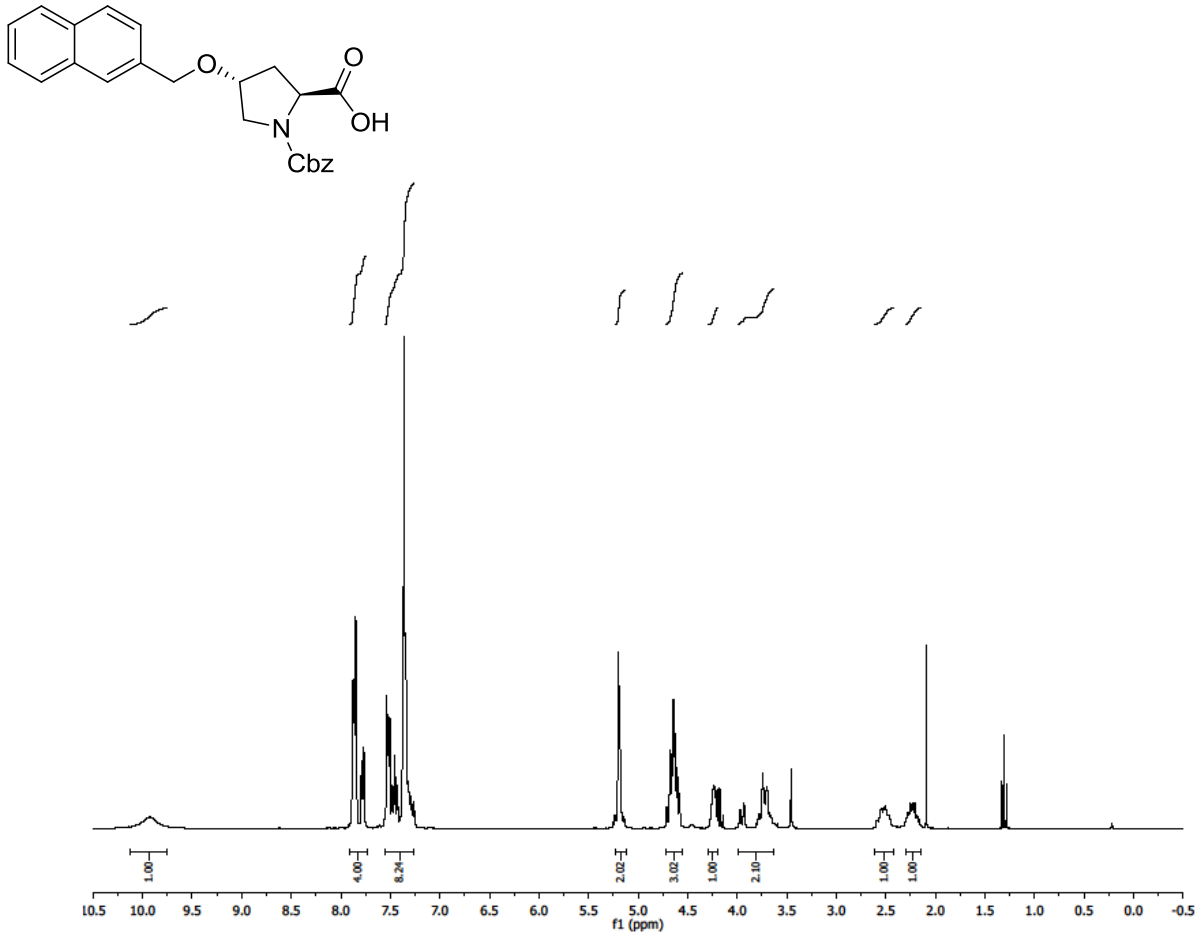
(2*S*,4*R*)-4-(benzyloxy)pyrrolidine-2-carboxylic acid (143):



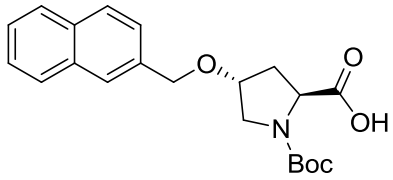


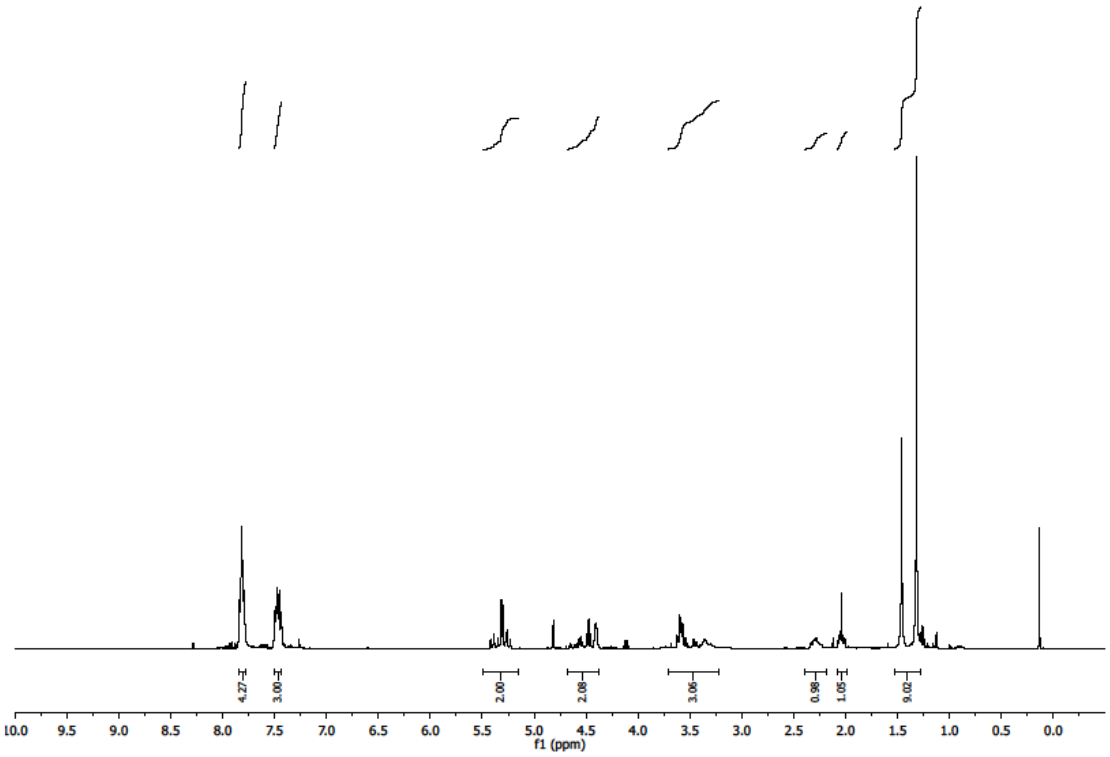


(2*S*,4*R*)-1-((benzyloxy)carbonyl)-4-(naphthalen-2-ylmethoxy)pyrrolidine-2-carboxylic acid (160):

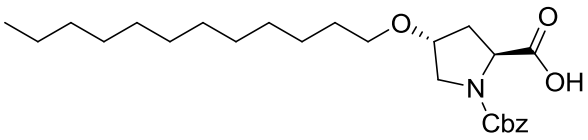


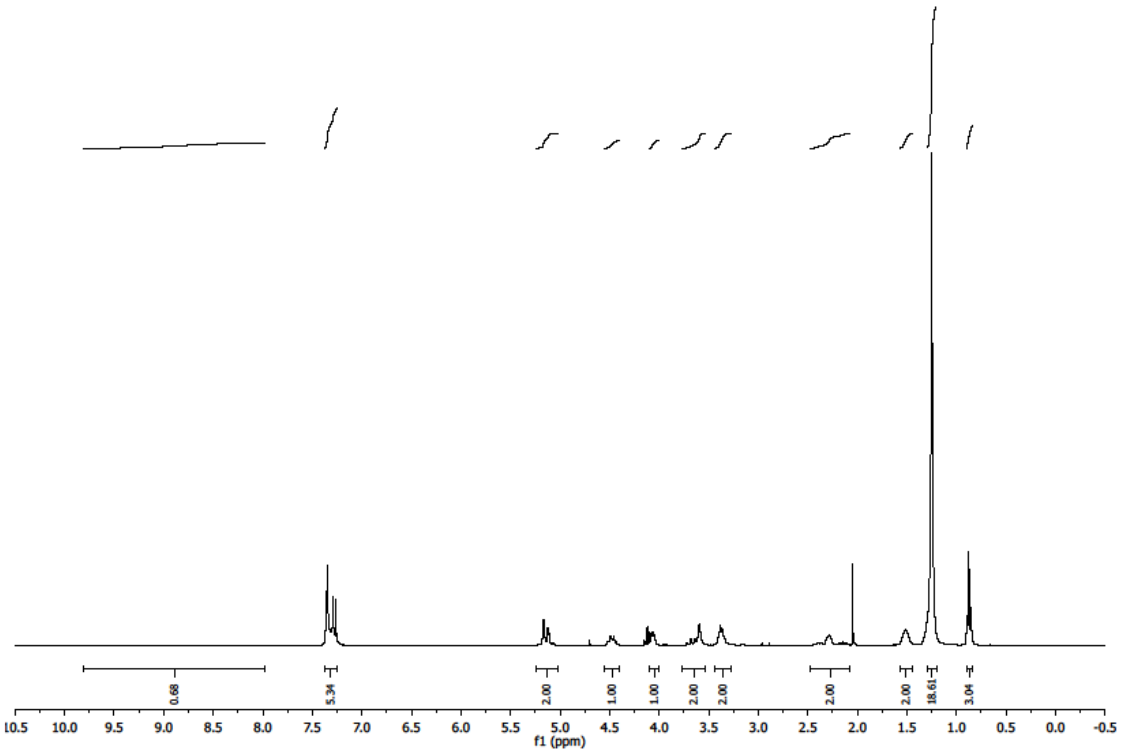
(2*S*,4*R*)-1-(tert-butoxycarbonyl)-4-(naphthalen-2-ylmethoxy)pyrrolidine-2-carboxylic acid (157):



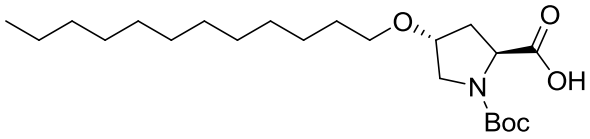


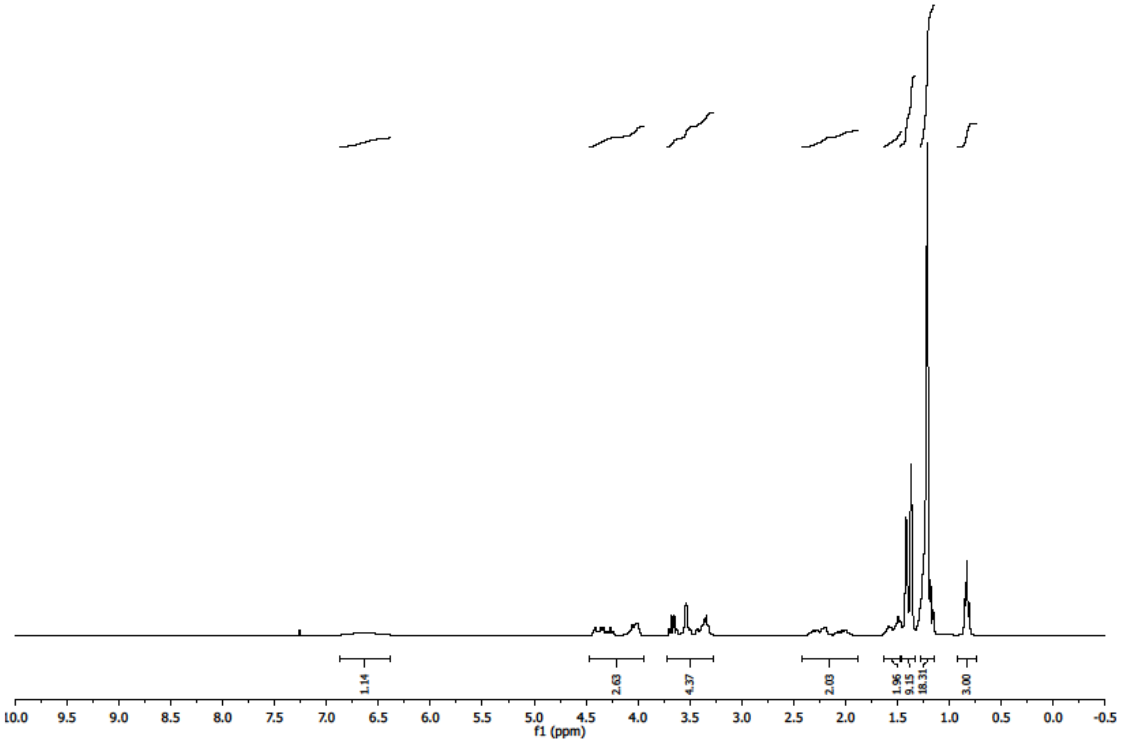
(2*S*,4*R*)-1-((benzyloxy)carbonyl)-4-(dodecyloxy)pyrrolidine-2-carboxylic acid (148):



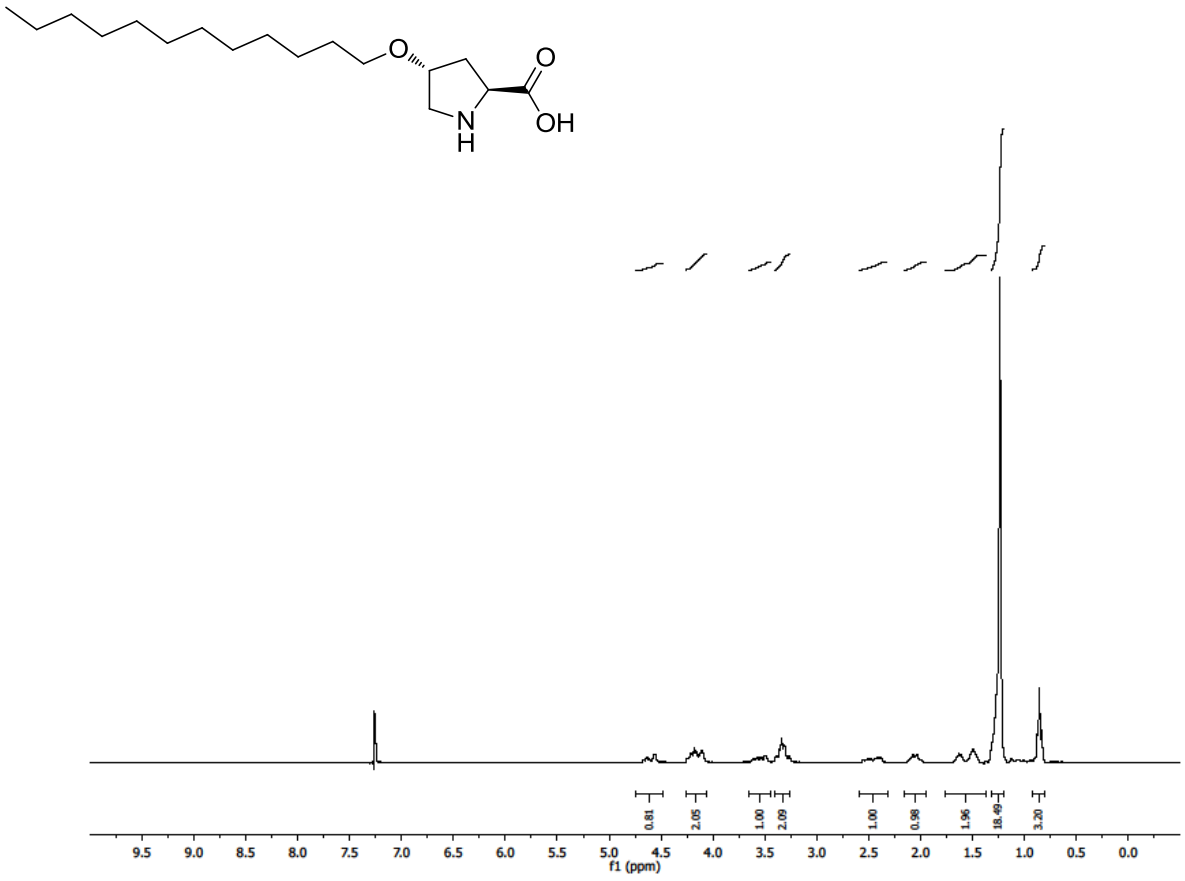


(2*S*,4*R*)-1-(tert-butoxycarbonyl)-4-(dodecyloxy)pyrrolidine-2-carboxylic acid (161):

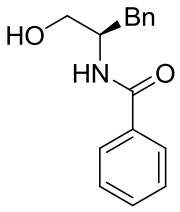


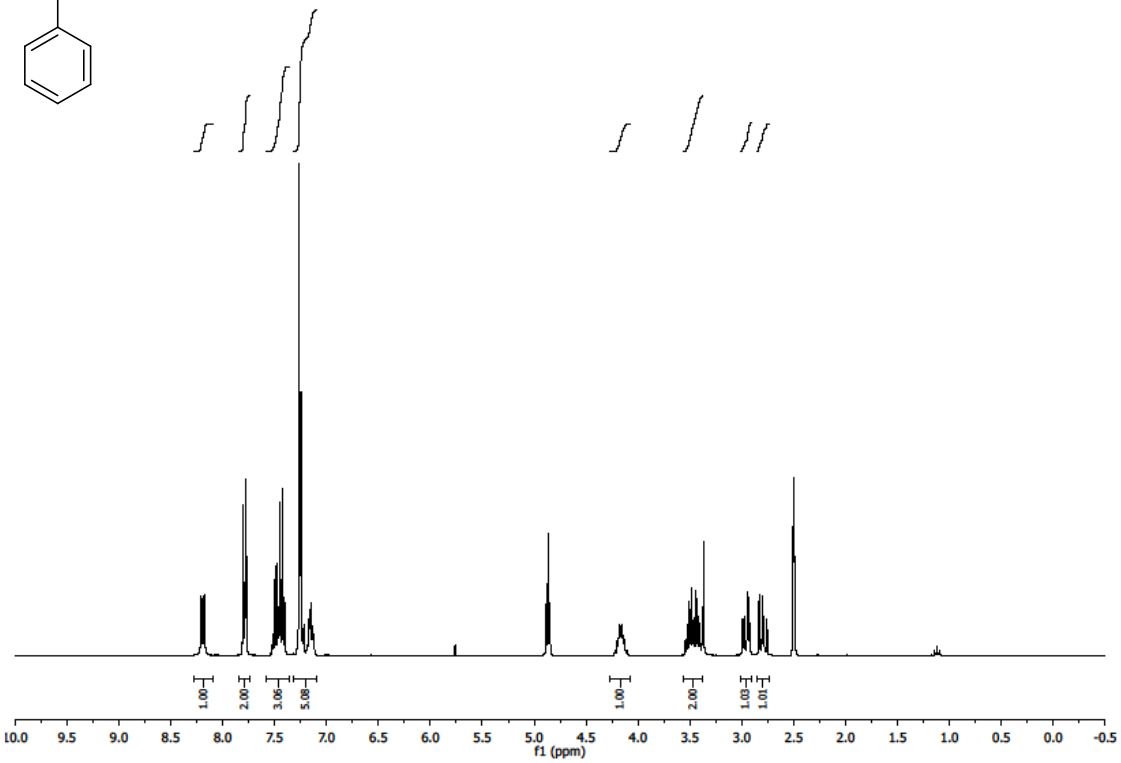


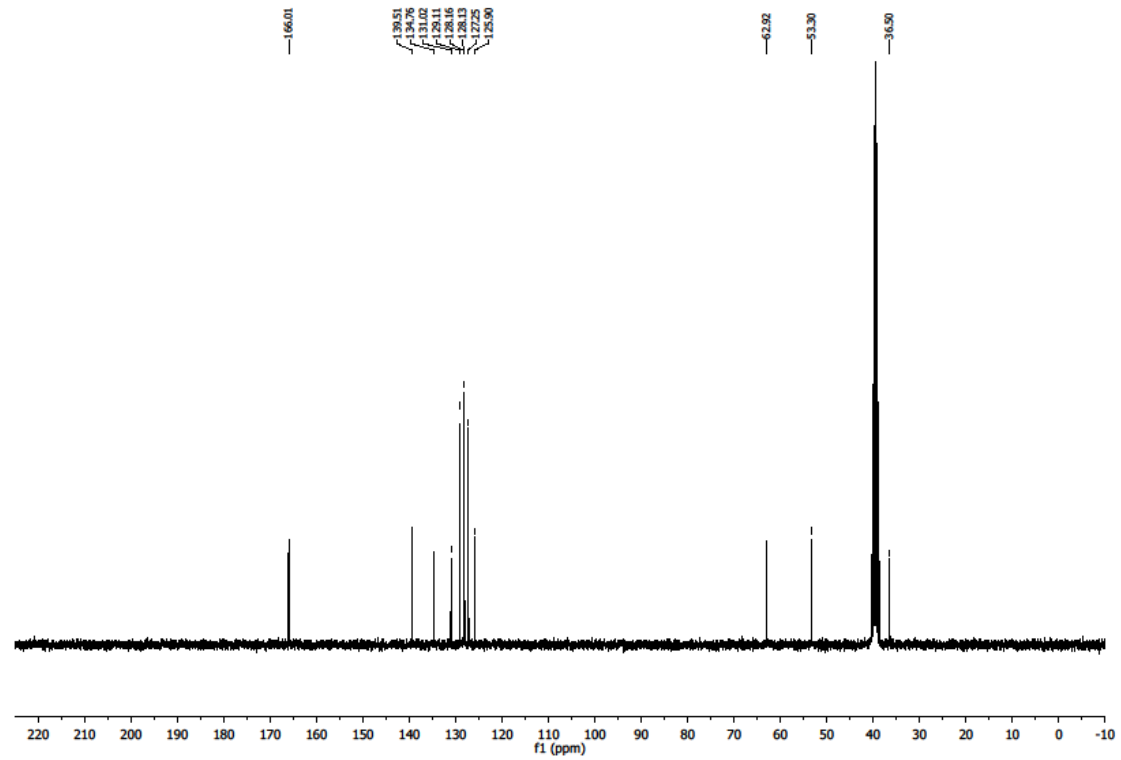
(2*S*,4*R*)-4-(dodecyloxy)pyrrolidine-2-carboxylic acid (142):



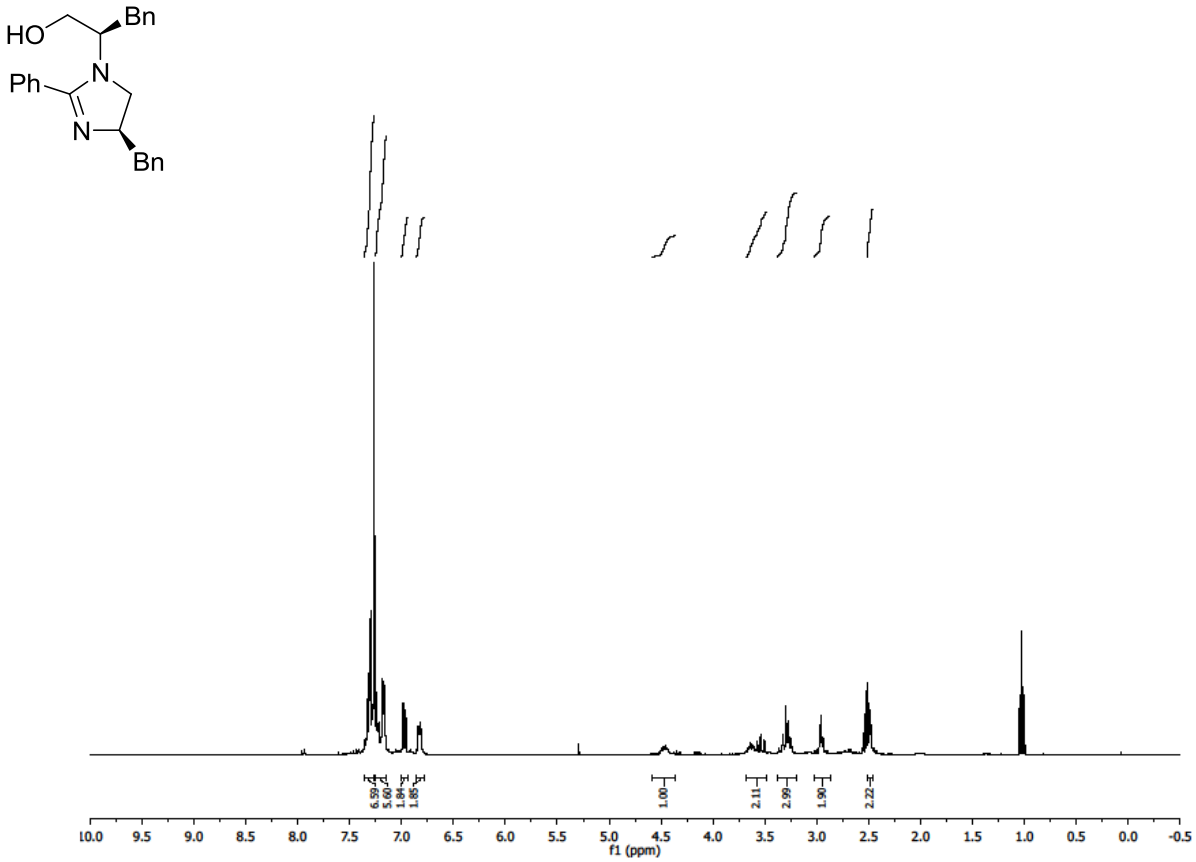
***N*-(1-hydroxy-3-phenylpropan-2-yl)benzamide (422):**



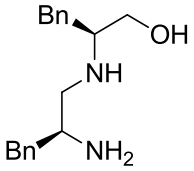


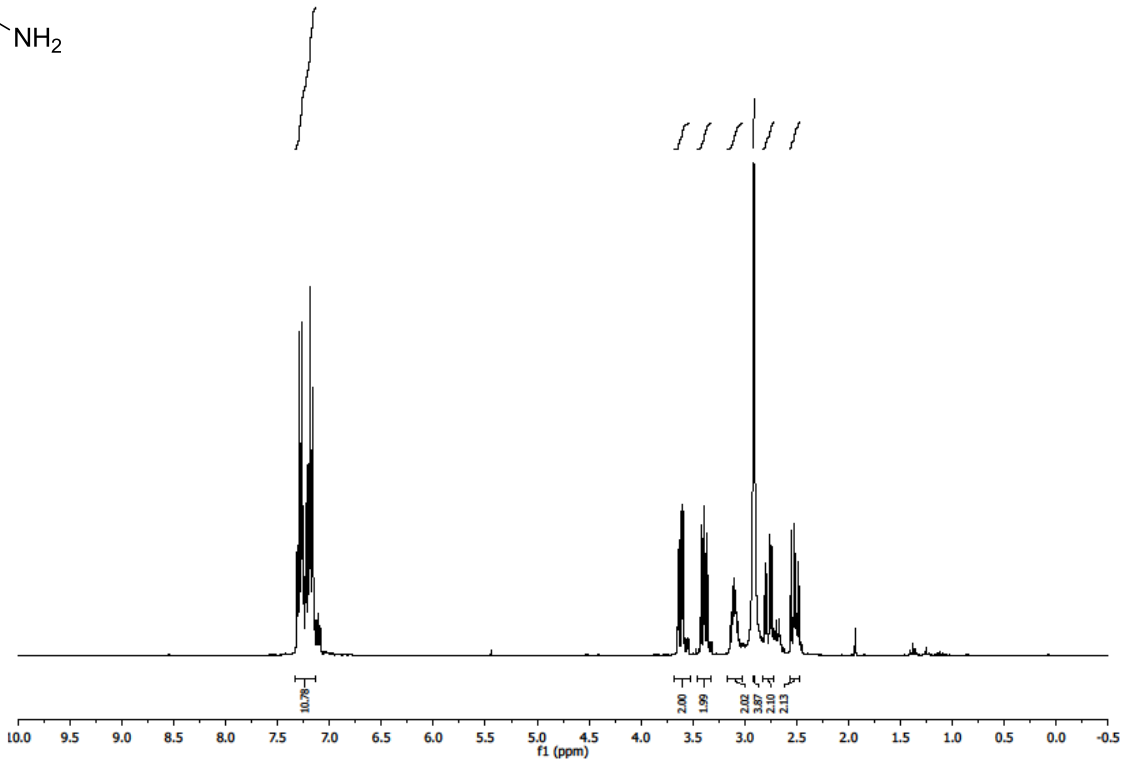


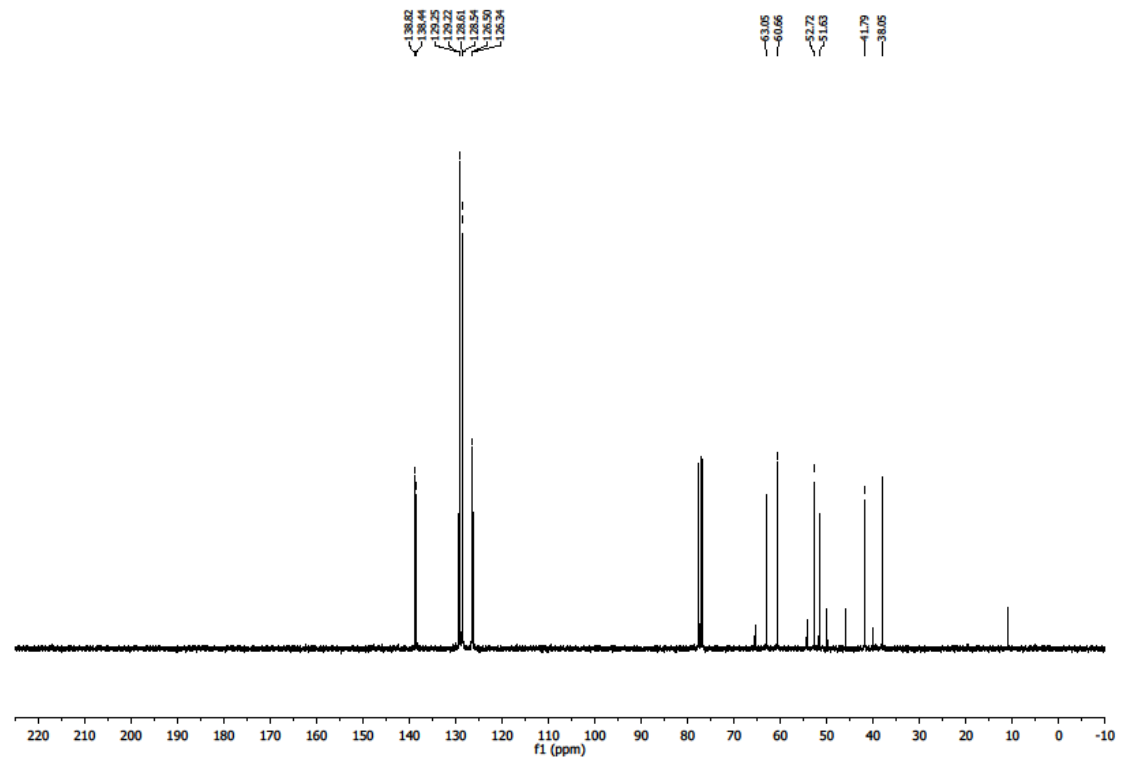
(*R*)-2-((*R*)-4-benzyl-2-phenyl-4,5-dihydro-1*H*-imidazol-1-yl)-3-phenylpropan-1-ol (424):



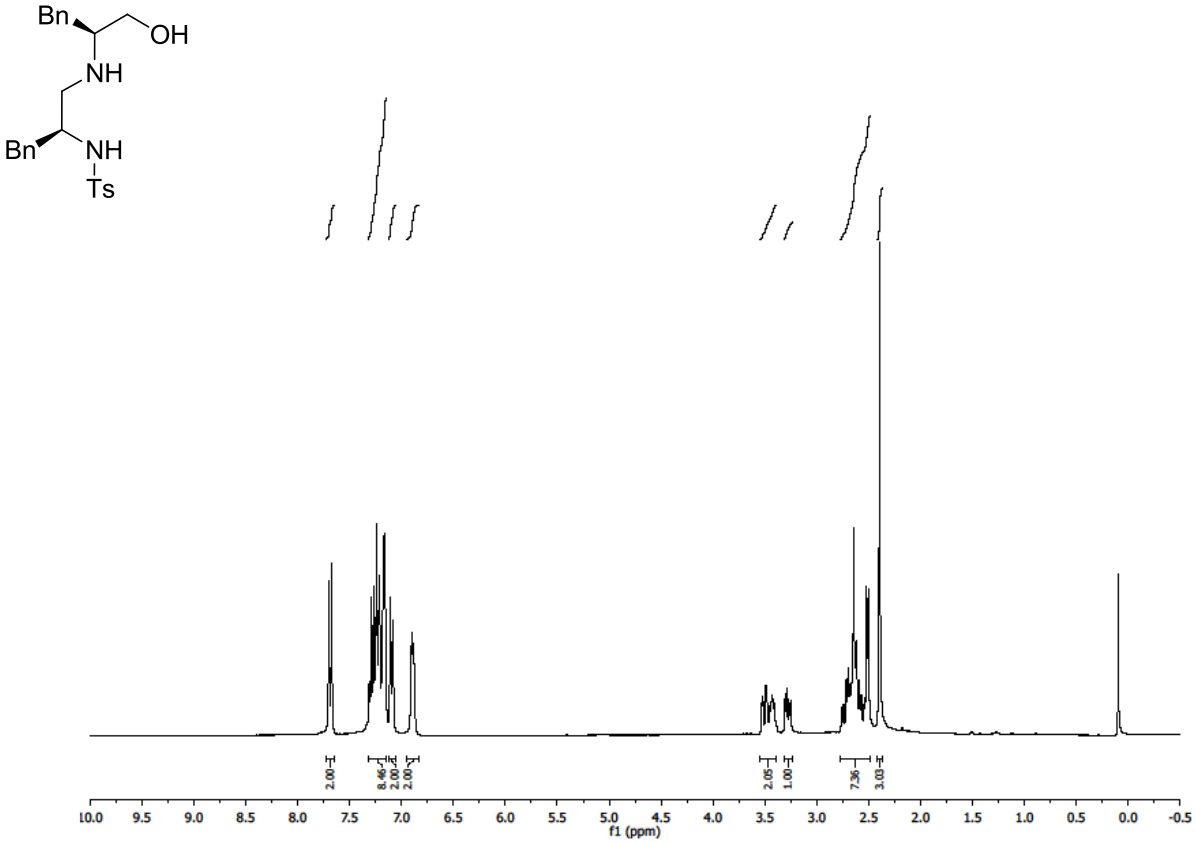
(*S*)-2-(((*S*)-2-amino-3-phenfylpropyl)amino)-3-phenylpropan-1-ol (308):

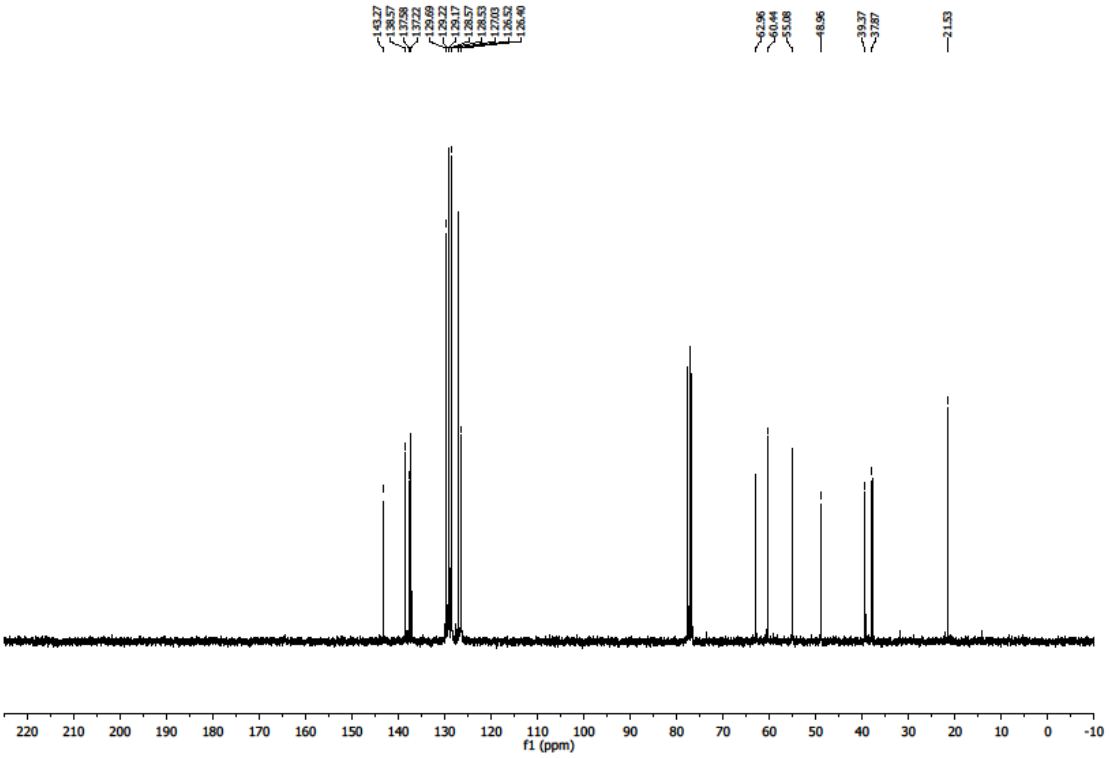


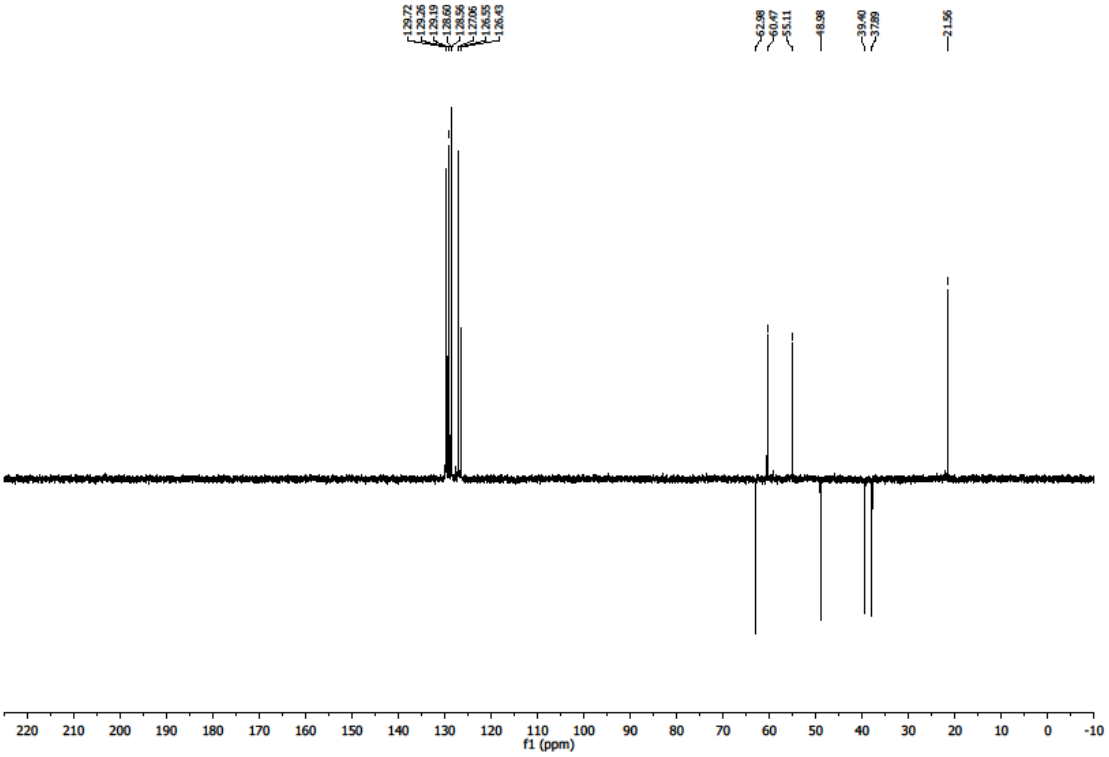




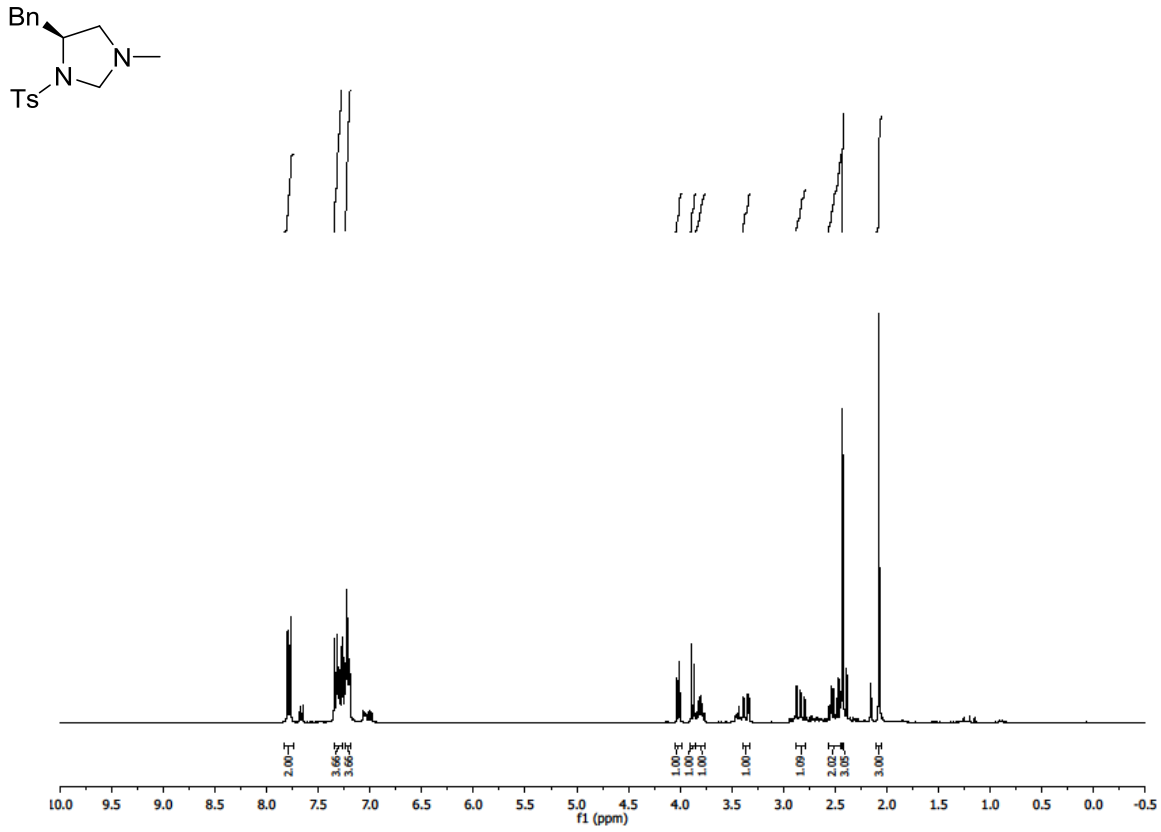
***N*-((*S*)-1-(((*S*)-1-hydroxy-3-phenylpropan-2-yl)amino)-3-phenylpropan-2-yl)-4-methylbenzenesulfonamide (317):**



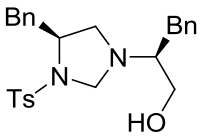

143.27
138.57
137.58
137.22
129.69
129.22
129.17
128.57
128.53
127.03
126.52
126.40
62.96
62.44
55.08
48.96
39.37
37.87
21.53
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

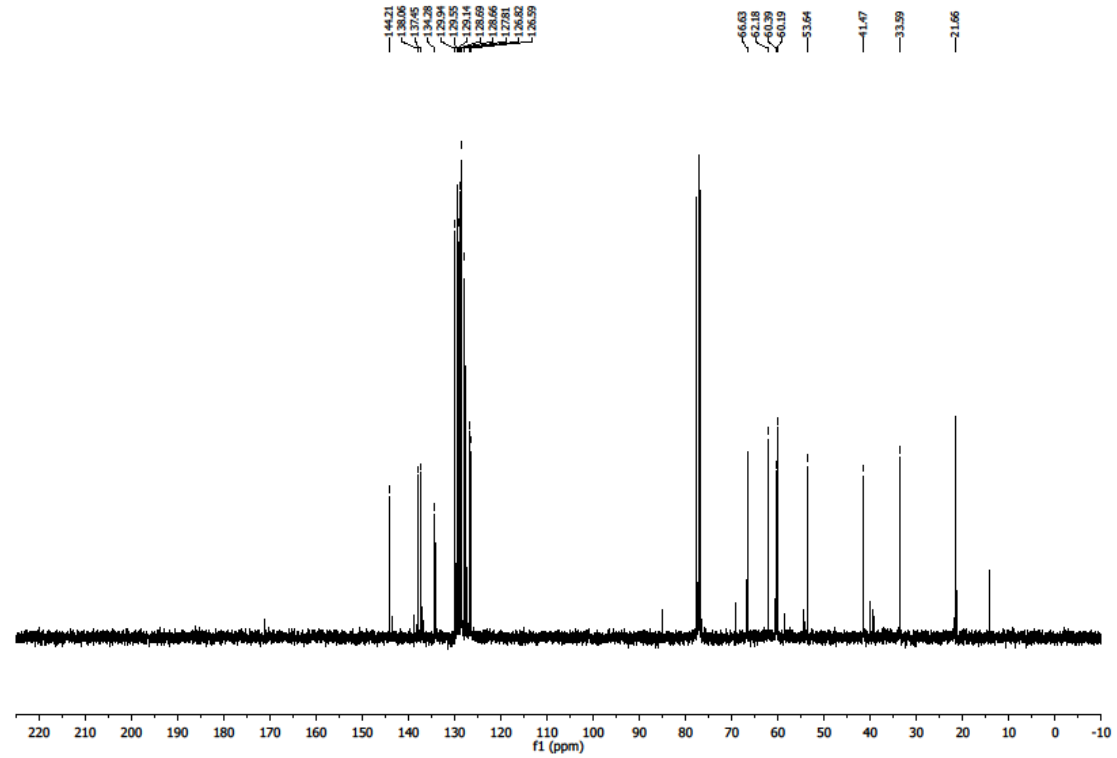

129.72
129.26
129.19
128.60
128.56
127.06
126.55
126.43
62.98
62.47
55.11
48.98
39.40
37.89
21.56
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

(*S*)-4-benzyl-1-methyl-3-tosylimidazolidine (319):

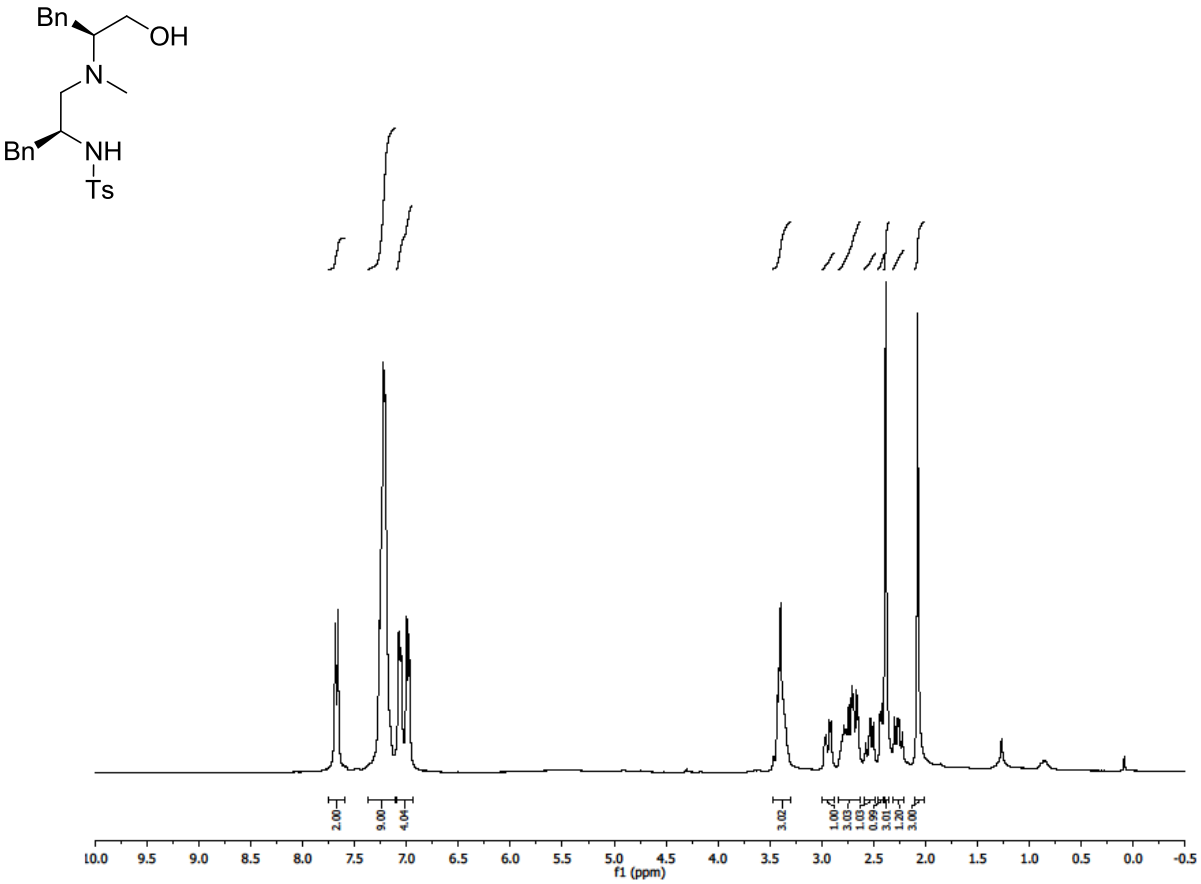


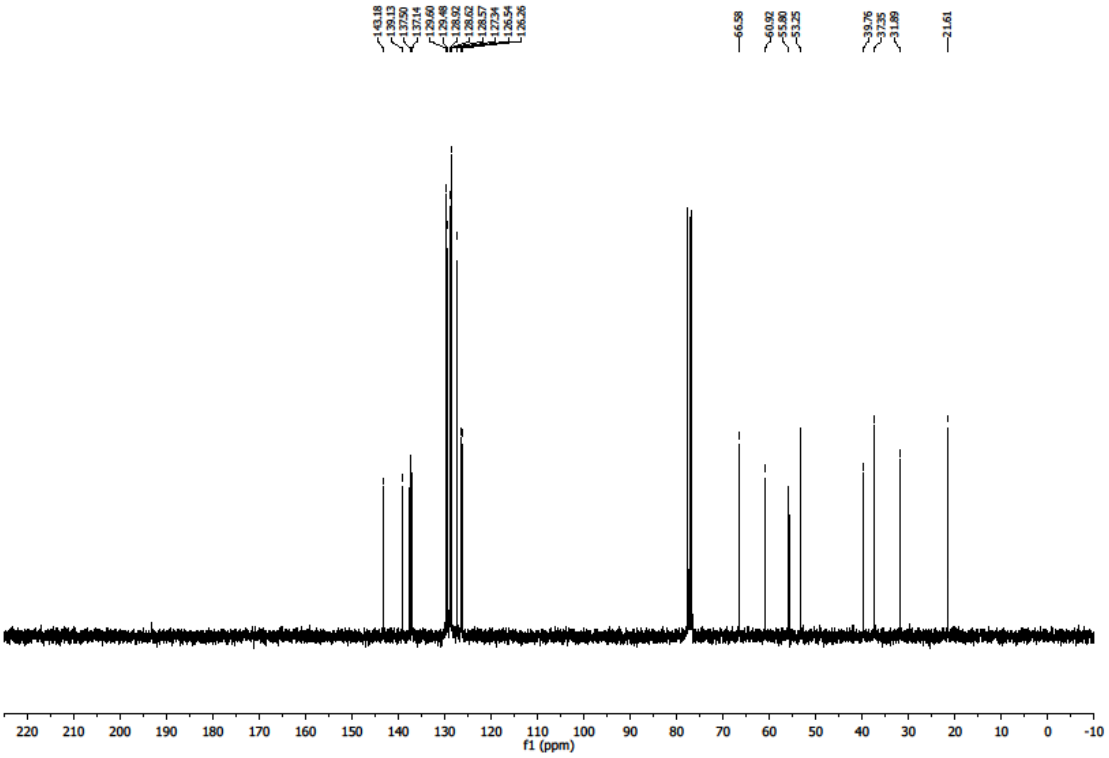
(*S*)-2-((*S*)-4-benzyl-3-tosylimidazolidin-1-yl)-3-phenylpropan-1-ol (318):

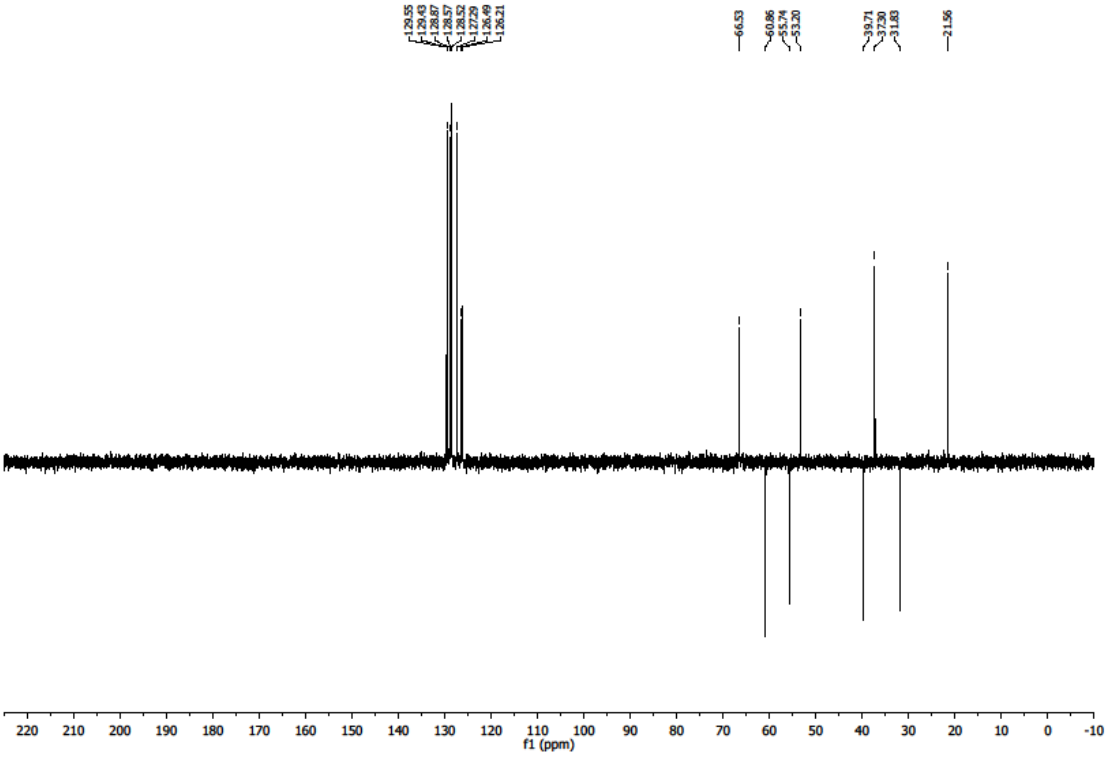




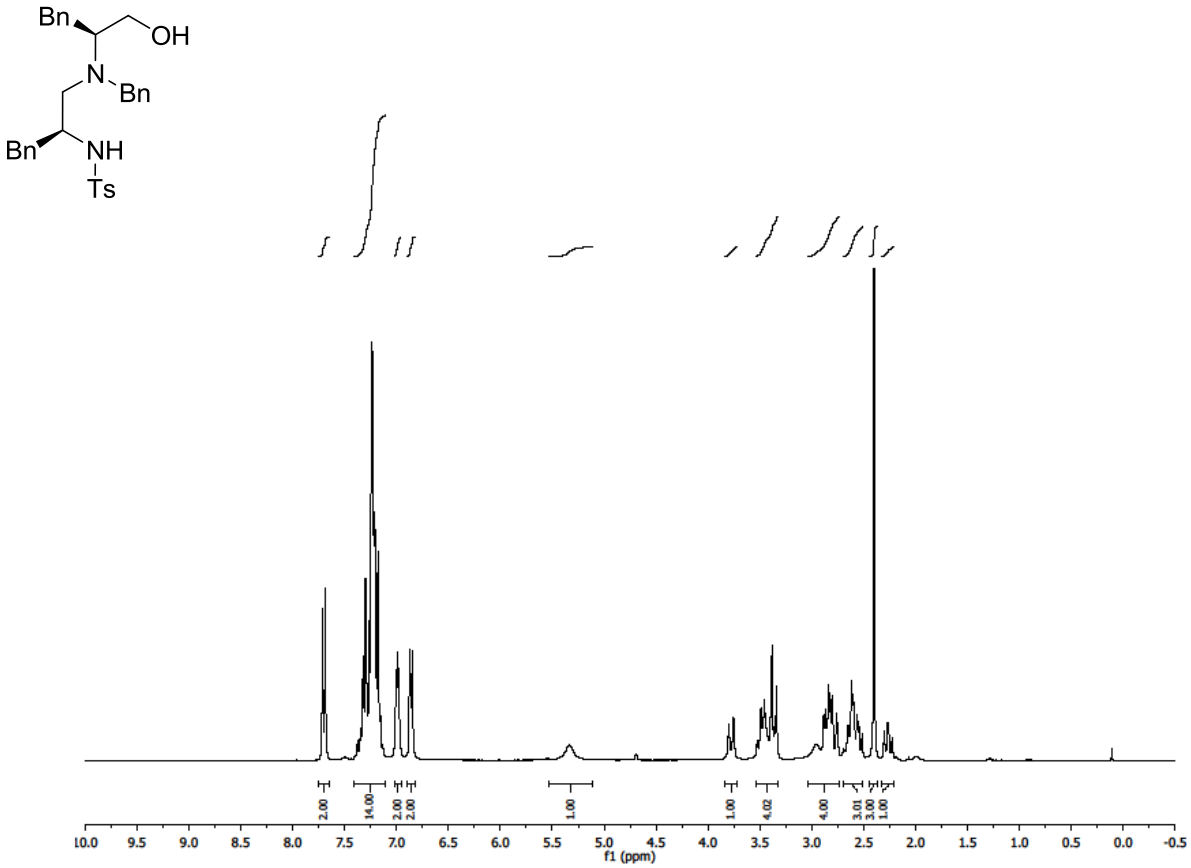
***N*-((*S*)-1-(((*S*)-1-hydroxy-3-phenylpropan-2-yl)amino)-3-phenylpropan-2-yl)-4-methylbenzenesulfonamide (320):**

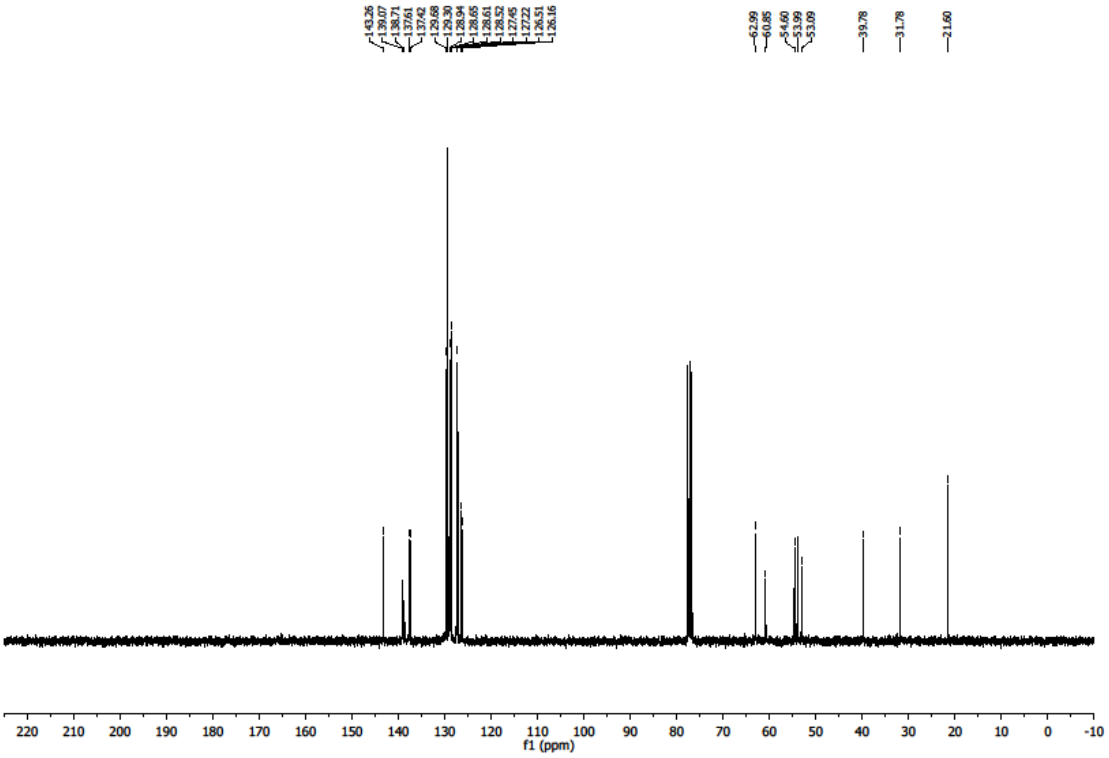


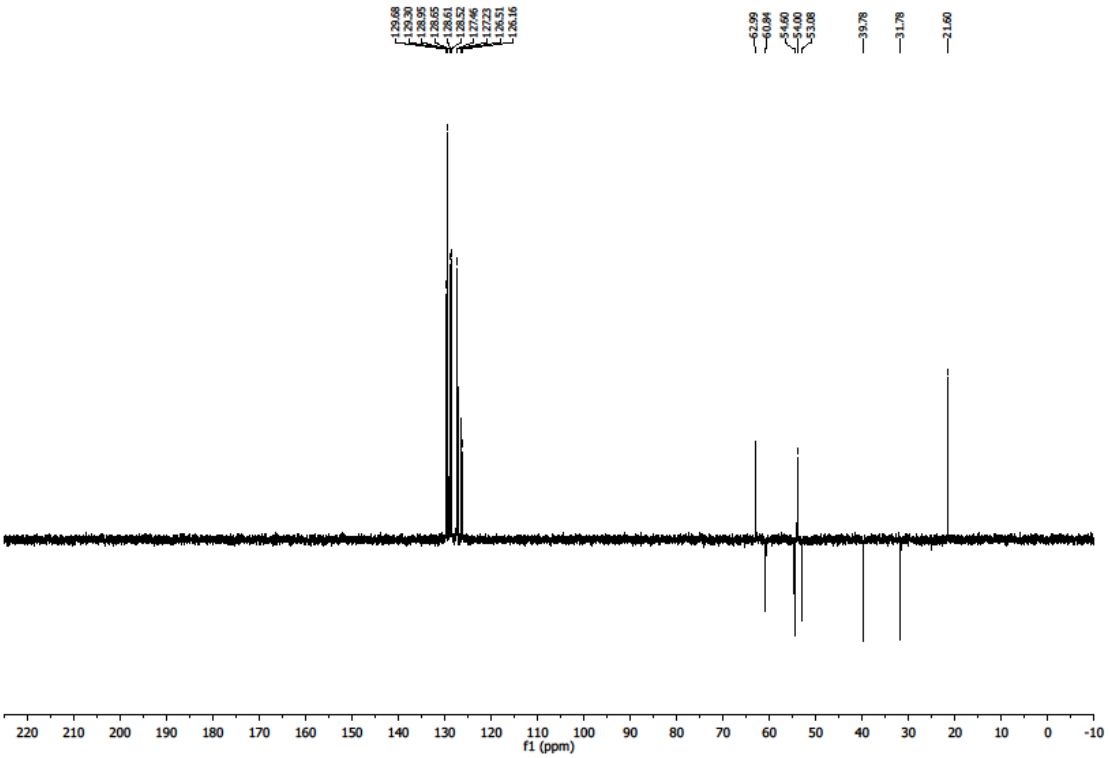

143.18
139.13
137.50
137.14
129.60
129.48
128.92
128.62
128.57
127.24
126.54
126.26
66.58
60.92
55.80
53.25
39.76
37.35
31.89
21.61
f1 (ppm)


129.55
129.43
128.87
128.57
128.52
127.29
126.49
126.21
66.53
60.86
55.74
53.20
39.71
37.30
31.83
21.56
f1 (ppm)

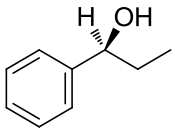
***N*-((*S*)-1-(benzyl((*S*)-1-hydroxy-3-phenylpropan-2-yl)amino)-3-phenylpropan-2-yl)-4-methylbenzenesulfonamide (321):**

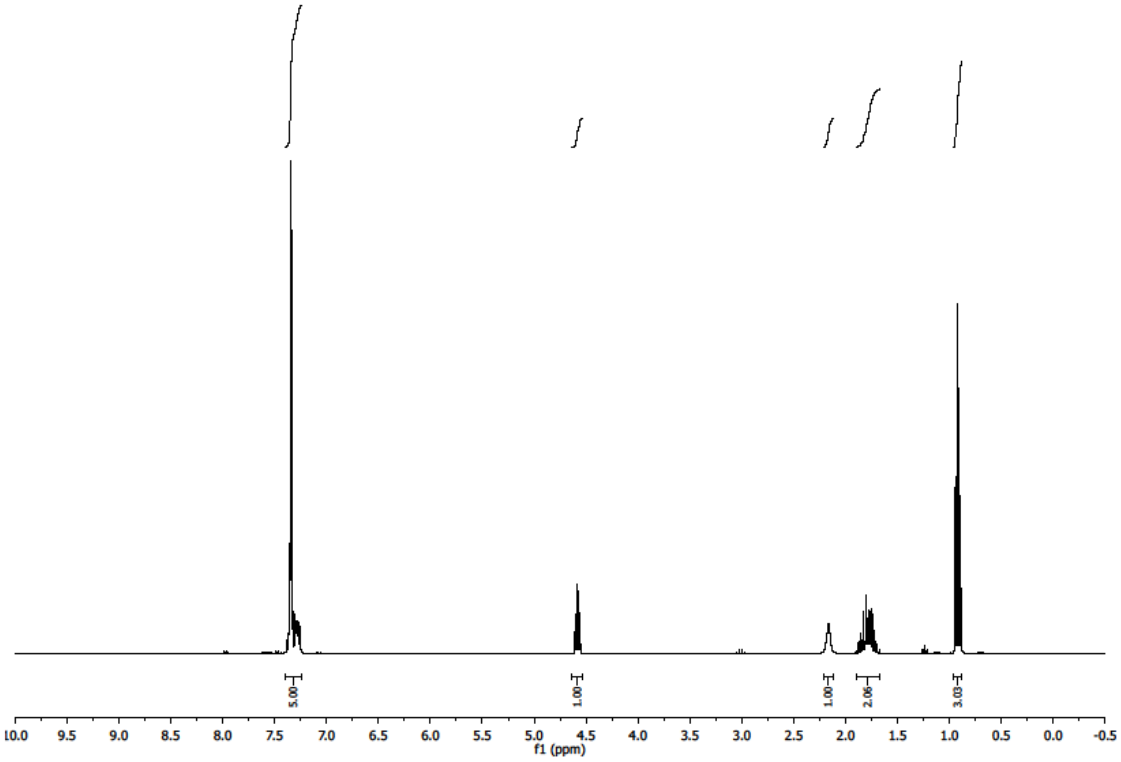


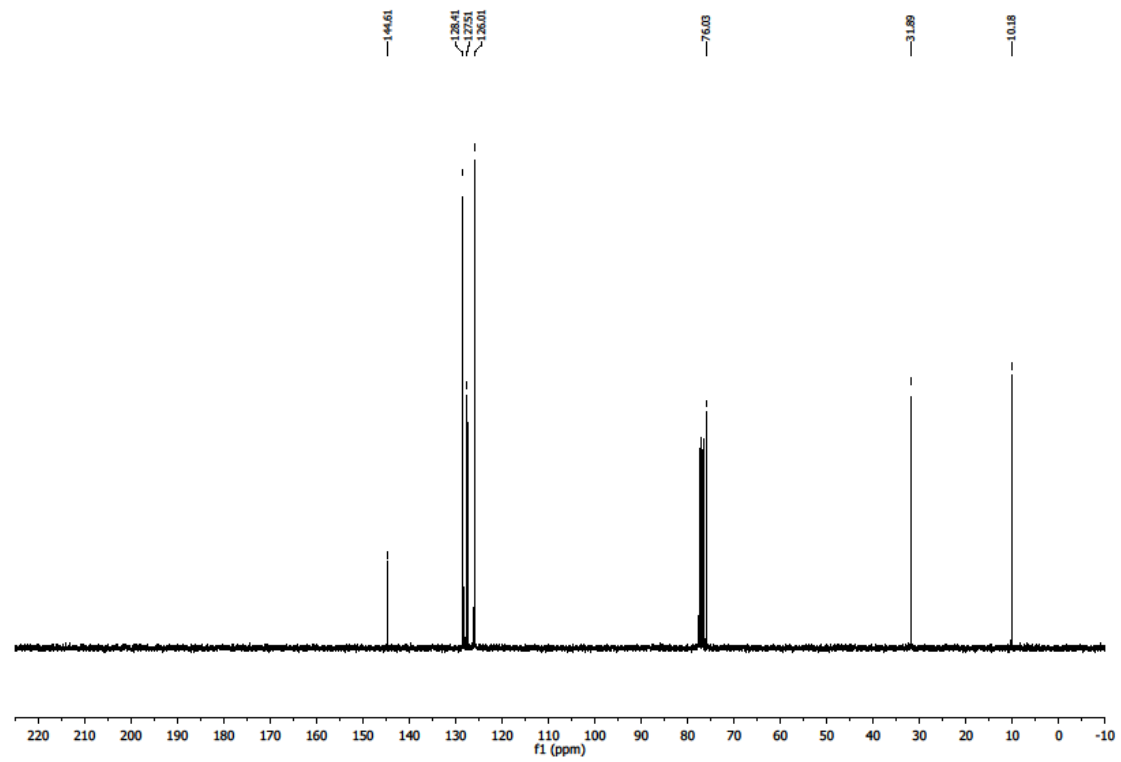

143.26
139.07
138.71
137.61
137.42
129.68
129.30
128.94
128.65
128.61
128.52
127.45
127.22
126.51
126.16
62.99
60.85
54.60
53.99
53.09
39.78
31.78
21.60
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


129.68
129.30
128.95
128.65
128.61
128.52
127.46
127.23
126.51
126.16
62.99
60.84
54.60
54.00
53.08
39.78
31.78
21.60
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

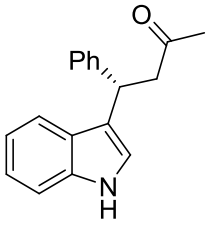
(*S*)-1-phenylpropan-1-ol (94):

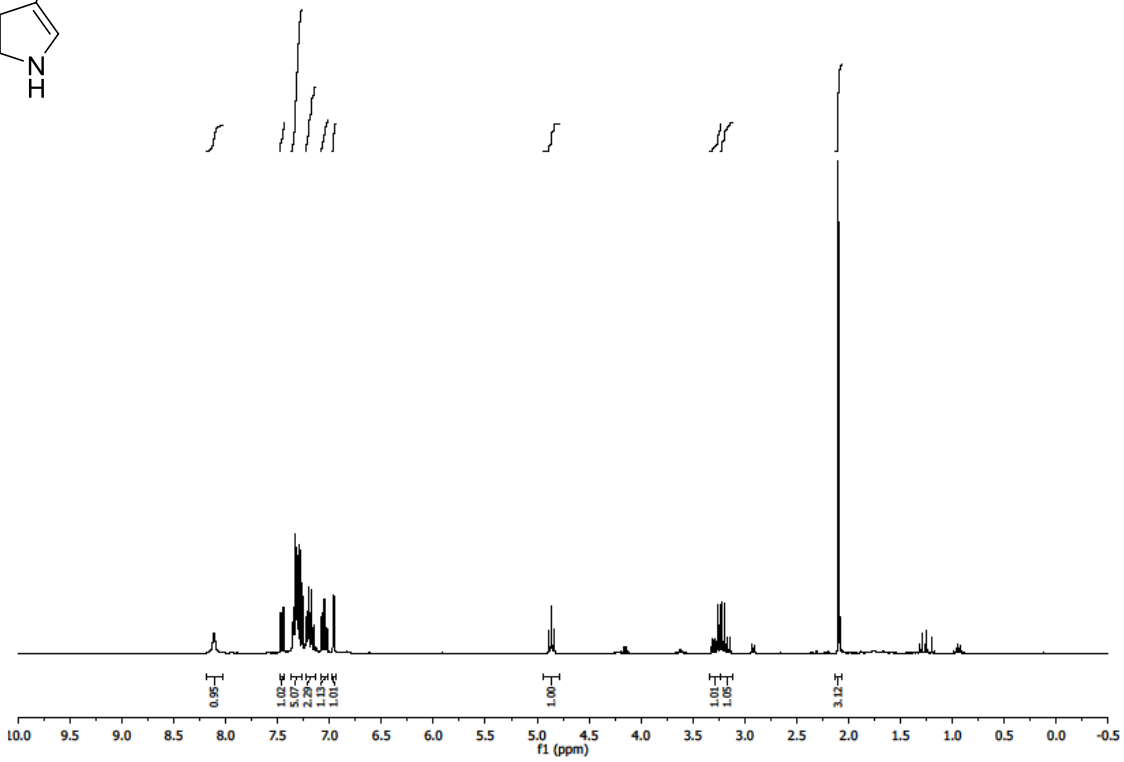


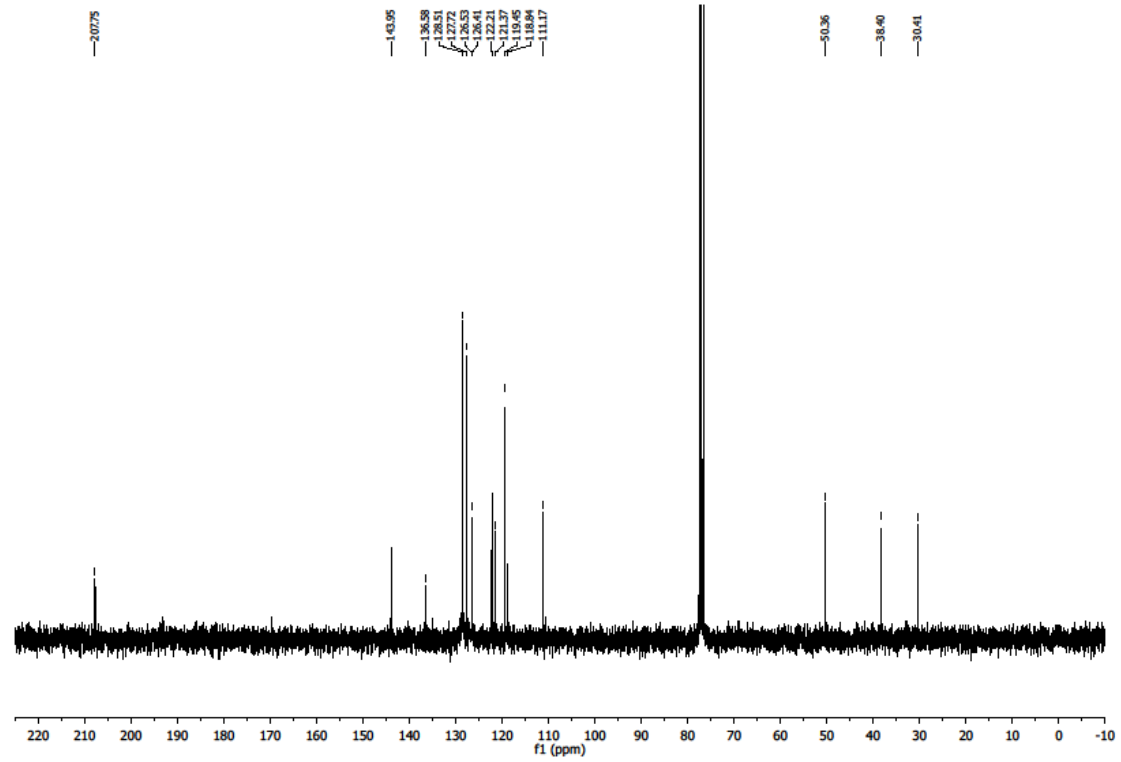




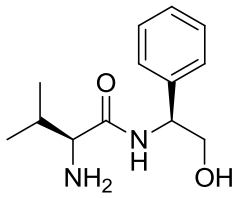
(*S*)-4-(1*H*-indol-3-yl)-4-phenylbutan-2-one (344):

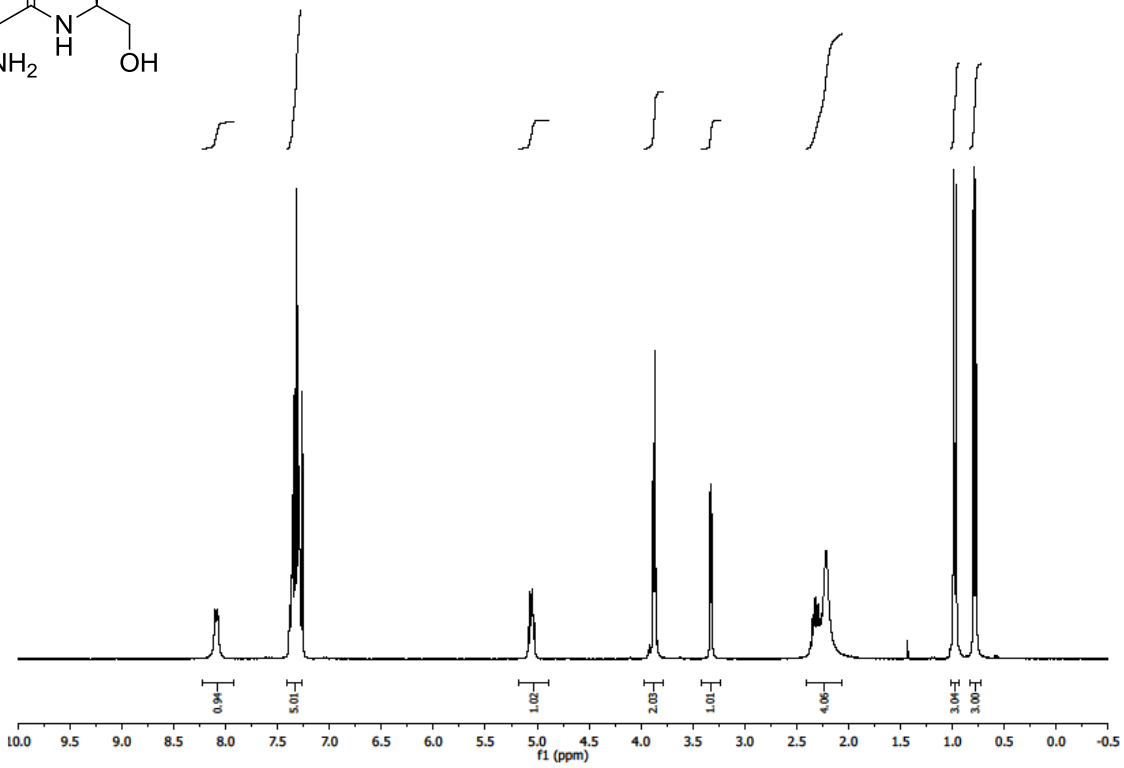


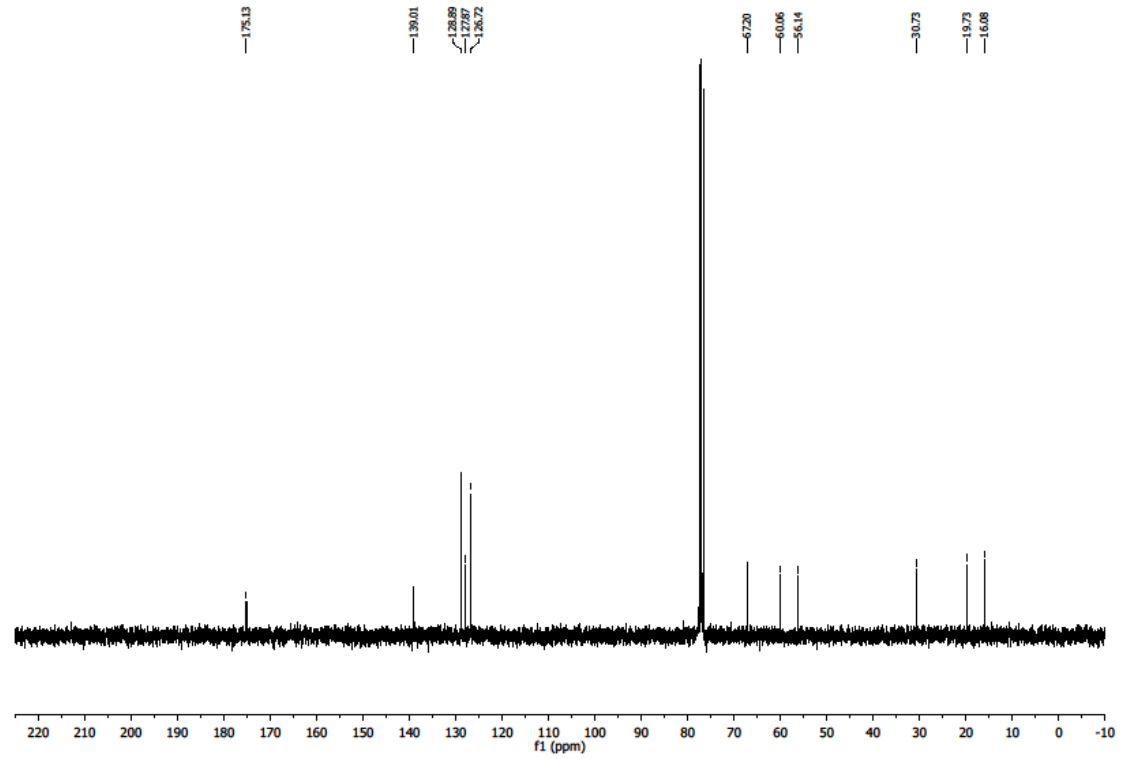




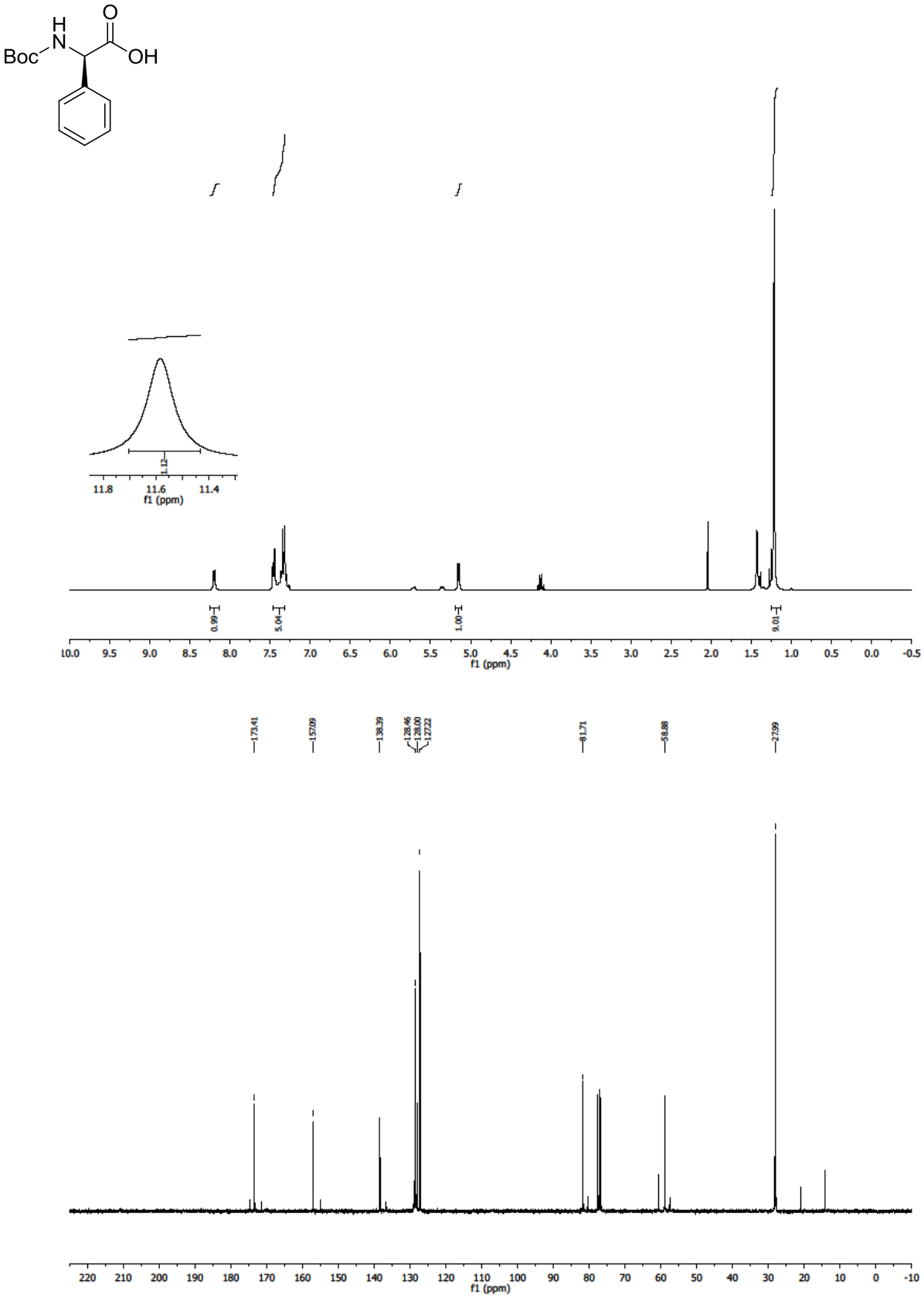
(*S*)-2-amino-*N*-((*S*)-2-hydroxy-1-phenylethyl)-3-methylbutanamide (336):



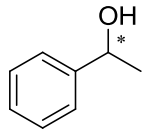


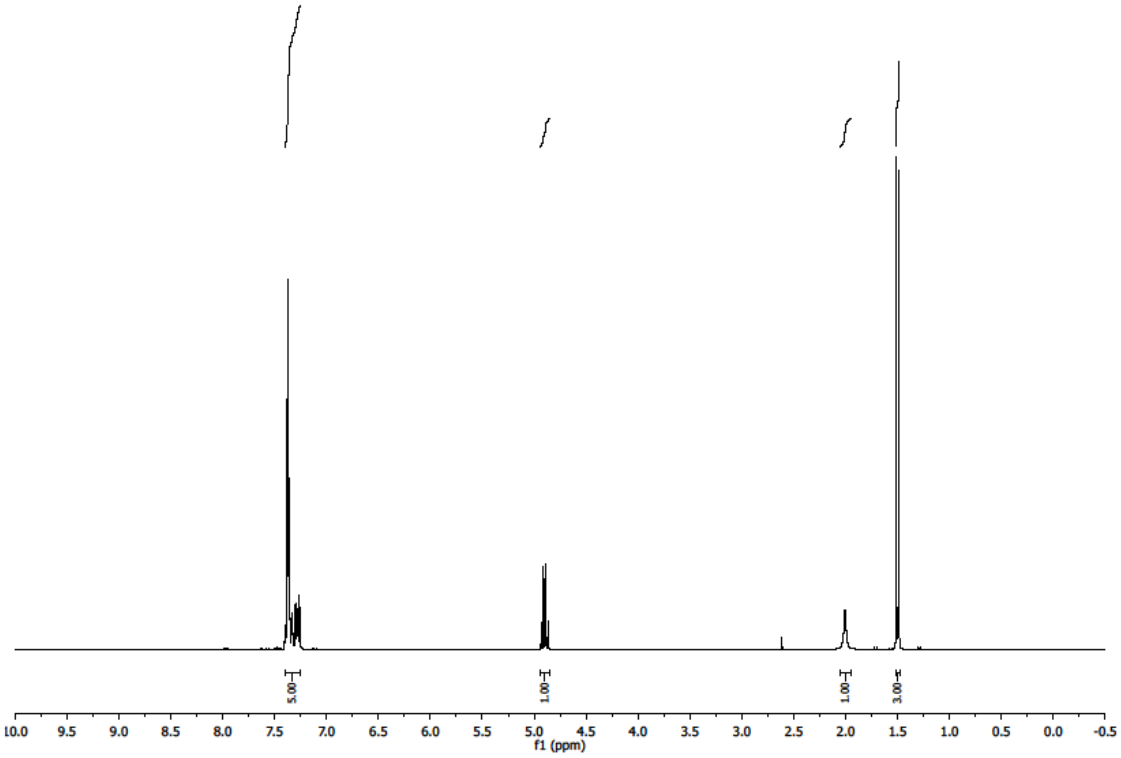


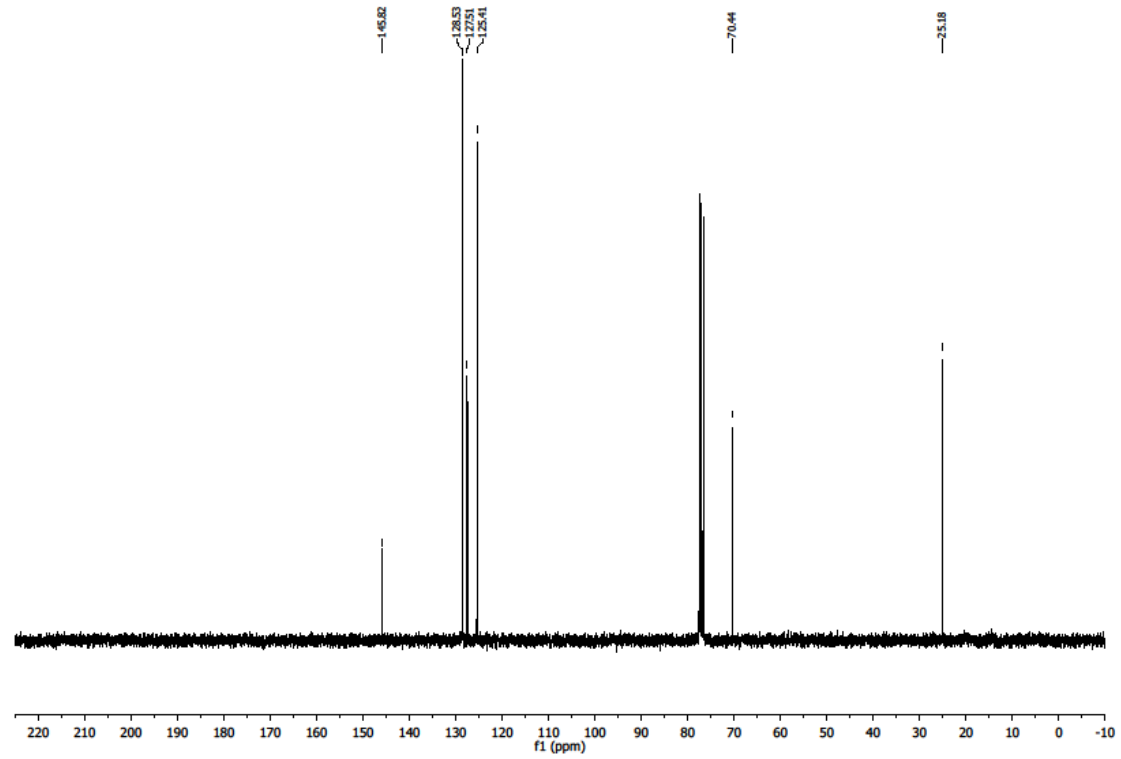
(*R*)-2-((tert-butoxycarbonyl)amino)-2-phenylacetic acid (425):



1-Phenylethanol (407):







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H Appendix

1. Curriculum Vitae

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Education

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	Major Subject:	Organic Chemistry
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I Acknowledgment – Danksagung

Zu Beginn möchte ich ganz herzlich meinem Doktorvater Prof. Dr. Oliver Reiser für die Aufnahme in seinen Arbeitskreis und die Überlassung des interessanten Themas danken. Desweitern möchte ich mich auch für die stete Hilfestellung, Unterstützung und die zahlreichen Anregungen und Ideen in Bezug auf meine Arbeit bedanken. Auch für die Ermöglichung an der Teilnahme an diversen Konferenzen und die dabei erhaltene finanzielle Unterstützung gilt ihm mein großer Dank.

Ein großes Dankeschön gilt auch meinen Laborkollegen Dr. Ludwig Pilsl, Dr. Daniel Rackl, Sabine Möhle, Silvia Panzeri und Thomas Föll für die Unterstützung in chemischen Fragen sowie für die äußerst angenehme Arbeitsatmosphäre.

Für die Unterstützung und Erleichterung der Laborarbeit möchte ich mich ganz herzlich bei Roxane Harteis, Brigitte Eichenseer, Klaus Döring, Georg Adolin und Peter Kreitmeier bedanken. Mein besonderer Dank gilt hierbei Helena Konkel, die sich mit diversen HPLC Proben von mir herumschlagen musste. Vielen Dank auch an die Sekretärinnen Young Rothermund, Hedwig Ohli und Antje Weigert.

Für die HPLC Messungen möchte ich mich bei Rudolf Vasold vom Arbeitskreis König bedanken.

Der zentralen Analytik der Universität Regensburg danke ich für die Messung vieler Proben. Hervorheben möchte ich hierbei Josef Kiermaier und Wolfgang Söller, die mir bei der Auswertung und Interpretation zahlreicher Massenspektren halfen. Bedanken möchte ich mich auch bei der NMR-Abteilung der Universität Regensburg und insbesondere bei Fritz Kastner, für die Messungen unzähliger Proben und die bereitwillige Hilfestellung in diversen Fachfragen.

Meinen ehemaligen Forschungspraktikanten Peter Braun, Matthias Gnahn, Christiane Jung und Martin Mayer danke ich für ihre engagierte Mitarbeit.

Ein ebenfalls großer Dank gilt Vinh Ngoc Huynh, der mich während der Bearbeitung des Projekts der 1,2-Diamino Alkohole mit zahlreichen Diskussionen und Tipps unterstützte. Zudem versorgte er mich stets mit neuen Katalysatoren und Hilfestellung zu deren Synthese.

Für das Korrekturlesen dieser Arbeit bedanke ich mich herzlich bei Dr. Matthias Knorn, Dr. Daniel Rackl und Dr. Carina Koch.

Dem ganzen Arbeitskreis Reiser mit all seinen Mitgliedern danke ich für die familiäre und entspannte Atmosphäre.

Meiner Freundin Rini möchte ich für die unendlich Unterstützung und die Geduld während der Anfertigung dieser Arbeit danken.

Und zu guter Letzt möchte ich meiner Familie von ganzem Herzen danken ohne deren Unterstützung ich nie bis zu diesem Punkt gekommen wäre. Vielen Dank!

J Declaration

Herewith I declare that this present thesis is a presentation of my original work prepared single-handed. Wherever contributions from other are involved all of them are marked clearly, with reference to the literature, license, and acknowledgement of collaborative research.

Okun Andreas

Regensburg, 09.11.2015