NOVEL ORGANOCATALYSTS WITH PYRROLIDINE AND BRÖNSTED ACIDS FOR ALDOL REACTION AND OTHER REACTIONS

DISSERTATION

ZUR ERLANGUNG DES GRADES

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Curiosity is more important than knowledge itself.

Interest is even more important than pure curiosity.

----Confucius

This thesis is dedicated to my family.

ABSTRACT

This dissertation describes the development of several novel organocatalysts. At first novel imidazolidinone derivatives, which have a carboxylic group at the 5-position, have been synthesized and tested. Secondly, several novel proline amide derivatives have been synthesized and tested with aldol reactions and Mannich reactions. The best enantioselectivity (ee over 98%) has been obtained from the reactions catalyzed by the novel *N*-trifluoromethylsulfonyl-*L*-proline amide in both reactions. Besides this, it could generally been concluded from the results that the acidity of the catalysts plays a very important role in selectivity.

Based on this conclusion, several novel proline imidazole derivatives, which combine diverse Brönsted acids, have been designed and synthesized by a novel route. In the tests, high enantioselectivity (ee over 98%) has been obtained by several of these catalysts. In tests with the same catalyst and different acids, it could be proved that the acidity of the catalysts mainly determine the selectivity of reactions. A value of the pk_a of the added acid solution, with which the reactions exhibit high selectivity, could be given. Several other reactions have been tested with these catalysts.

Besides, novel peptidic organocatalysts have been designed and tested in aldol reactions. Novel BINOL catalysts with imidazole functionalities have also been synthesized and tested. But the results showed that the catalytic activity of the other novel catalysts is much higher than BINOL derived phosphoric acid derivatives.

CITATION

Part of this dissertation has already been published:

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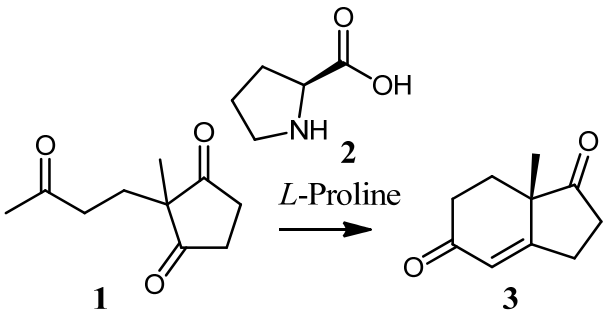
I. Introduction

1.1 Historical background

In organic chemistry, the term of organocatalysis refers to a form of catalysis, whereby the rate of a chemical reaction is increased by small organic compound referred to as an "organocatalyst" consisting of carbon, hydrogen, sulfur and other nonmetal elements found in organic compounds.[1,2,3,4,5,6] The term organic catalyst can retrospect to the year 1927, in which the chemist Langenbeck published a paper with the title "Über organische Katalysatoren, I. Isatin und seine Derivative als Katalysatoren der Dehydrierung von Amino-säuren".[7] The first example of organocatalysts for asymmetric reaction was reported by Bredig and Fiske in 1912 for the addition of HCN to benzaldehyde.[8]

The first use of an amino acids as an organocatalyst was reported by Fischer and Marschall with alanin in 1931.[9] However, the breakthrough of aldol reaction catalyzed by an amino acid in asymmetric synthesis was obtained forty years later by Hajos and Parrish[10]. In their report, *L*-proline was used as catalyst for the intramolecular aldol addition to produce important bicyclic intermediates for natural product synthesis. However, further research with *L*-proline has been paid attention only thirty years later.



Scheme 1. *L*-proline as organocatalyst for the intramolecular asymmetric aldol addition

In 2001, List reported that *L*-proline could also catalyze intermolecular aldol reaction and give, for instance with acetone as a starting material, the product 4-hydroxy-5,5-dimethylhexan-2-one with very high selectivity (ee>99%).[11] In the same year, Macmillan introduced

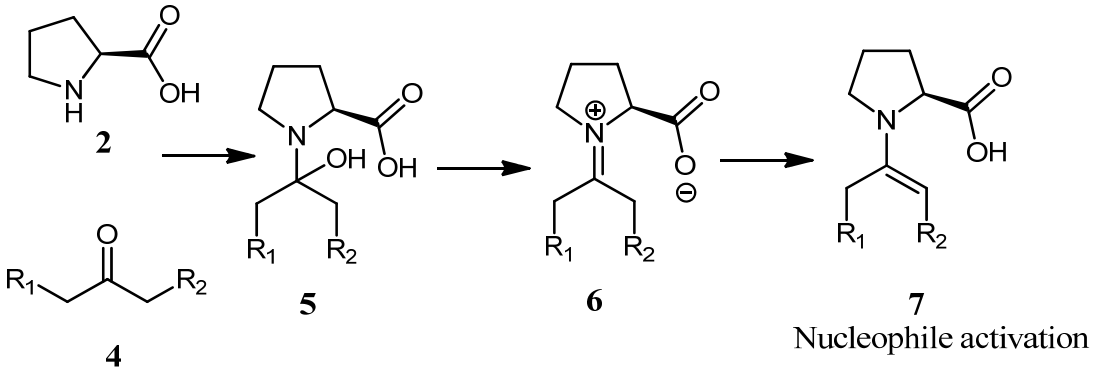
imidazolidinone derivatives as efficient catalysts.[12] Since then, organocatalysis has obtained great popularity from chemists interested in synthetic methodology.

It is clear by now that organocatalysis has become one of the pillars of modern asymmetric catalysis besides biocatalysis and metal catalysis.[13] Compared with organocatalysts, it has been realized that there are some serious disadvantages of metal catalysts. Generally, metal catalysts are often expensive and some of them are very sensitive to oxygen and/or moisture and must be applied under absolutely dry reaction conditions with exclusion of oxygen. Besides this, the metal from the catalysts can also pollute the environment, because most of the applied metals are toxic. So, considering the environment and the safety of the product, metal catalysts are obviously not the best choice.

In nature, catalysis can be carried out without any metal. It has been estimated that only one quarter to one third of all proteins that are active as catalysts require metals to carry out their functions.[14] In the last decade, it has been realized that catalytically active small organic molecules have many advantages. Among these advantages, the most important is that the rigorous condition - the absence of water and oxygen free conditions - is not necessary for the reactions with organocatalysts. In some reactions, good selectivity can be obtained even when the organic solvent is wet and sometimes water is used as a solvent. Besides this, the variation of efficient control by different functional groups and activation modes is another advantage compared to other kinds of catalysts. Several different activation modes have been developed by different groups in recent years. In the following, the classification of organocatalytic reactions will be discussed by activation mode.

1.2 Classification of organocatalysts by activation mode

1.2.1 Enamine and iminium organocatalysis



Scheme 2. The enamine activation mode with *L*-proline

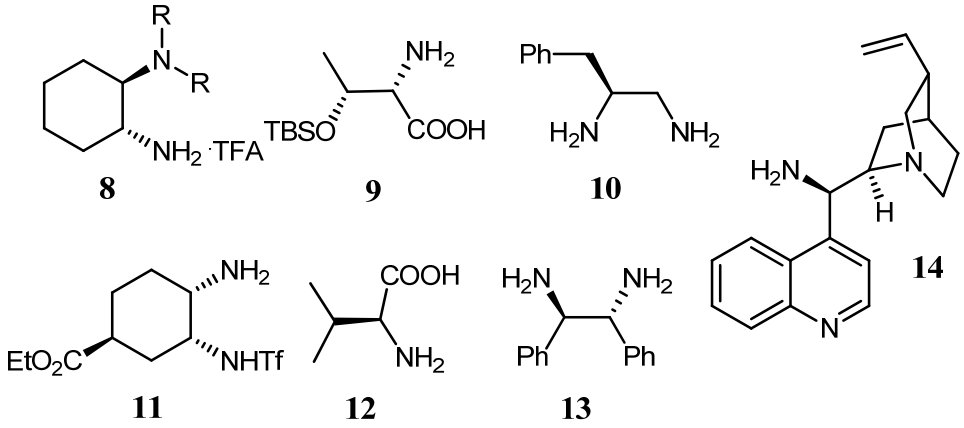
Achiral secondary and primary amine catalysts have been used in organic synthesis for a long time. As early as in the eighteen century, Knoevenagel found that primary secondary amines and their salts could catalyze the condensation between ketoesters or malonates and aldehydes or ketones.[15] For a long time, however, after the research of Knoevenagel, amine catalysts did not obtain more attention from chemists. In 1930, Kuhn and Hoffer reported that secondary amines could also catalyze the self- and cross-aldol condensations of aldehydes besides Knoevenagel condensation.[16] In 1931, Fischer and Marshall reported that primary amino acids could catalyze the aldol addition and the condensation of acetaldehyde.[9] In 1937, Langenbeck and Sauerbier showed that piperidinium acetate could catalyze the hydration of crotonaldehyde.[17]

The first asymmetric catalysis with a secondary amine is the Hajos-Parrish-Eder-Sauer-Wiechert Reaction. This reaction was reported by Eder, Sauer and Wiechert in 1971[18] and by Hajos and Parrish in 1974[19], respectively. In the report of Hajos and Parrish, an enol mechanism was proposed. In 1978, Eschenmoser reported the crystalline enamine of ketone and piperidine, which proved to be very important for the mechanism research.[20] In 1981, the Nobel laureate (1965 in chemistry) Robert B. Woodward, reported the first stereocontrolled asymmetric chemical synthesis of erythromycin A[21], in which proline was used as a very efficient catalyst for the synthesis of a chiral intermediate. In 1990s, Yamaguchi and Taguchi

reported proline derivatives as catalysts in enantioselective Michael additions and suggested iminium ion activation as the catalytic principle. [22]

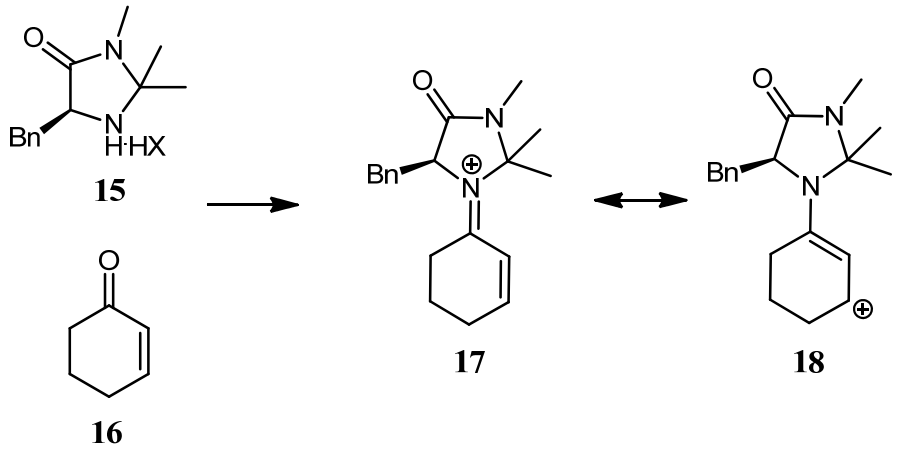
However, the complete catalytic cycle of proline was not clearly illustrated until the last decade. Then the enamine activation mode was given by List for *L*-proline catalysis of the aldol reaction[23]. In aldol reactions with proline as catalyst, an aldehyde or a ketone reacts with the secondary amine of proline (Scheme 2). After H_2O is eliminated, the iminum/enamine is produced. The double bond of the enamine is activated by the pair of free electrons of the nitrogen atom to give a nucleophile which can attack the electrophilic carbonyl group of the reaction partner.

Considering the bad solubility of proline in organic solvents, a great deal of catalysts with enamine activation mode based on proline has been designed after *L*-proline. In the newly designed catalysts, the main work was contributed to increase the hydrophobicity of catalysts to improve solubility in organic solvents, modification of the carboxylic acid to a variety of other hydrogen-bonding groups and adding steric bulk and further stereo centers to enhance the enantioselectivity. This activation mode has been also used with other chiral scaffolds besides proline (scheme 3).



Scheme 3. Other catalysts with enamine activation mode

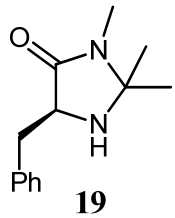
The catalysts with enamine activation mode have been widely used in various reactions: inter- and intramolecular-aldol reactions, Mannich reactions[24], Michael addition[25], and reactions for the introduction of α-substituents to the carbonyl group [26].



Scheme 4. The iminium activation mode

Another activation mode with secondary amines is the iminium activation mode, which was given by Macmillan[12]. This activation mode is also called LUMO activation, because the catalyst lowers the energy of the lowest unoccupied molecular orbitals of an enal or enone. This iminium activation is similar to the activation of carbonyl groups by a Lewis acid which lowers the LUMO of α, β-unsaturated carbonyl compound. The catalysts from Macmillan react firstly with a substrate to give an iminum intermediate by resonance, the β position of the former carbonyl group is thus activated as a good electrophile, actually as the LUMO energy is lowered giving a more reactive intermediate than the α, β-unsaturated carbonyl compound.

The Macmillan catalyst is synthesized from *S*-phenylalanine in two steps. Firstly, *S*-phenylalanine is amidated with methylamine, followed by condensation with acetone or another ketone to give an *N*, *N*-acetal. With the first generation catalyst, good yields and high enantioselectivities can be obtained, however the reaction is done mostly at low temperature (-30 °C). After the modification by introducing more steric hindrance to the first generation catalyst, a second generation catalyst was designed which afforded higher levels of efficiency and enantioselectivity at room temperature. Besides this work, other structural variations of Macmillan catalysts have also been synthesized and tested (scheme 5).



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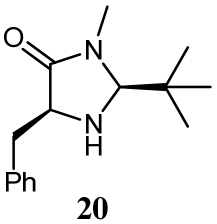
The first generation of Macmillan catalyst



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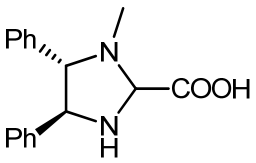
The second generation of Macmillan catalyst



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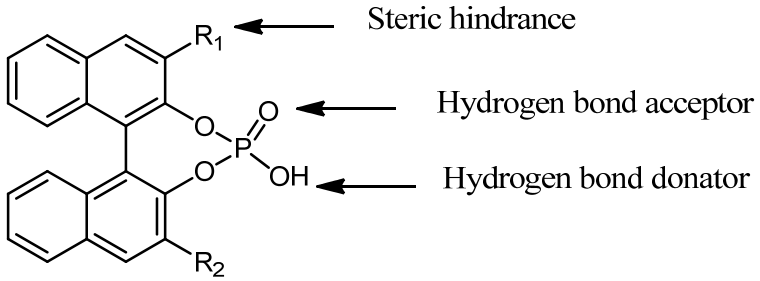
other stuctures of Macmillan catalyst

Scheme 5. Different Macmillan catalysts

This activation mode has been used for the Diels-Alder reaction[27], indole addition[28] , nitrone cycloaddition[29], [2+1] cycloaddition[30], Friedel-Crafts reaction of pyrrole[12], hydrogenation reactions[31], etc.

1.2.2 Organocatalysis with Lewis and Brönsted acid

1.2.2.1 Chiral Brönsted acids with BINOL



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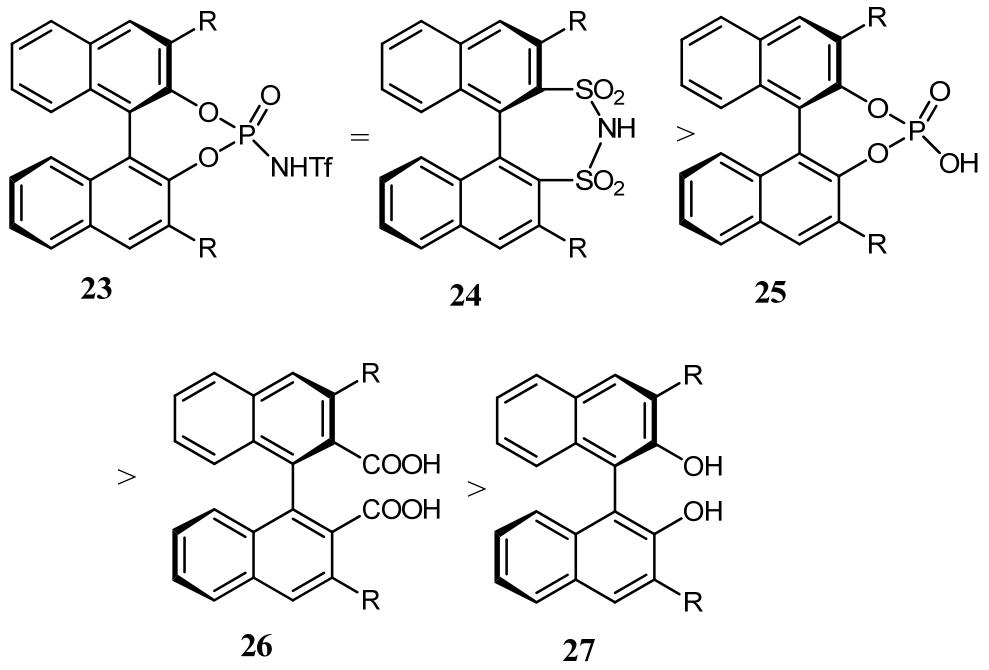
Scheme 6. The activation mode of chiral phosphoric acid with BINOL

In asymmetric Brönsted acid activation, chiral phosphoric acid with BINOL is the most common catalyst. Before introduced in organocatalysis, the chiral scaffold of *S*- or *R*-BINOL has been used quite widely in organometal catalysis.[32] In 2004, the group of T. Akiyama reported the application of chiral BINOL-derived phosphoric acids as efficient Brönsted acid catalysts in Mannich-type reactions.[33] One month later in the same year, the group of Terada reported other chiral BINOL derived phosphoric acids also for Mannich-type reactions.[34] Continuous research in the field has made great development in recent years and a lot of modification has been done to the structure.

The modification focused on two aspects. As it is well known, the key role performed by the phosphoric acids in reactions is to activate the electrophile by protonation to form an intermediary ion pair composed of the protonated electrophile and a chiral phosphate counterion. For the efficiency of the catalyst in this activation step, a fine-tuning of the acidity of the catalyst is necessary. So, one aspect is to modify the phosphoric acid group, for instance by changing into other acid groups, such as the sulfonamide groups. Stronger acidic groups have been introduced in the structure of the catalysts (scheme 7).[35] Here, it has to be pointed out that the phosphoryl oxygen in phosphoric acid group is very important in some reactions, as it can act as a hydrogen bonding acceptor, which is sometimes essential for high stereo selectivity, so the phosphoryl oxygen remains in all the modifications of phosphoric acid group.



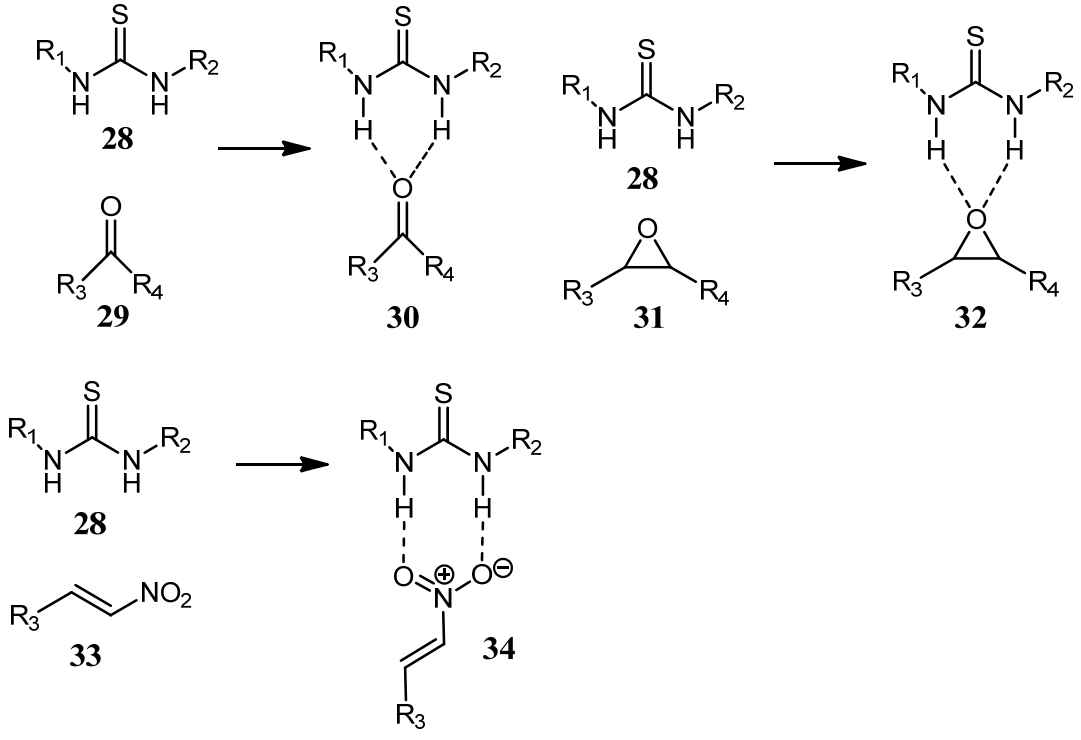
Scheme 7. BINOL derived acid catalysts in pH decreasing order

Another aspect is usually to do modification at the 3 and 3' positions of the rigid BINOL scaffold with sterically demanding aryl groups and with diverse electronic properties, eventually. These big substituents are shielding the active site of the catalyst - the acidic proton. The rigid BINOL scaffold and the aryl moieties at the 3 and 3' are responsible for the control of stereochemical induction in reactions. So, the modification of aryl moieties can change the

selectivity of catalysts.

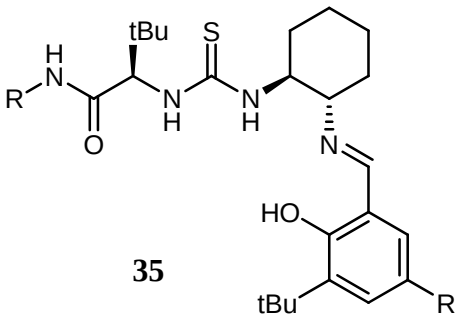
For these kinds of catalysts, the rigid BINOL scaffold is a big advantage, however the modification of position 3 and 3' in BINOL normally takes too many steps. The common way to do this modification is firstly to protect the OH group with a methyl group. Then a bromide or another good leaving group is introduced at the 3 and 3' position. The wanted substituent will be incorporated at the 3 and 3' position under metal catalysis. After deprotection of the OH functions, the phosphoric acid can be introduced in several steps. Totally, such simple modification from BINOL needs 10 steps under metal catalysis.[36] Compared with other catalysts like proline catalysts, the modification of BINOL is difficult and a disadvantage of the system. Some methods have been tried to modify the synthesis. But still the synthetic routes are normally very long and the overall yield is not high. Besides this, the bad solubility in organic and aqueous solvents is another problem. Nevertheless, these catalysts have often been used for Mannich type reactions[37] , aldol type reactions[35], Friedel-Crafts type reactions[38], Diels-Alder and related cycloadditions[39] and rearrangements [40].

1.2.2.2 Thiourea or urea based organocatalysis



Scheme 8. Activation by thiourea or urea systems

Catalysts based on thiourea or urea were developed by Jacobsen in 1998.[41] In this paper, the catalyst with urea was combined with a metal to catalyze the Strecker reaction. In 2002, the Schreiner group used urea and thiourea as Lewis acid through double hydrogen bonding to control carbonyl groups.[42] In the meanwhile, such double hydrogen bonding activation mode has been used for controlling reactions with carbonyl groups, nitro groups and epoxides. In the transition state, the carbonyl group or nitro group is fixed by double hydrogen bonding and controlled in the planar state which leads to high selectivity in the reaction. Thiourea catalysts have been synthesized from the amines with carbon disulfide, to give isothiocyanate derivatives which react with another amine to the thiourea product. In the process of the synthesis, there are still some problems. One is that H_2S gas is produced in the synthesis of isothiocyanate. Another is that thiourea is also a nucleophile, which can react with the isothiocyanate intermediate. In the last ten years, a great amount of catalysts based on thiourea (urea) have been reported by many groups (scheme 9), as they proved to have a lot of advantages.



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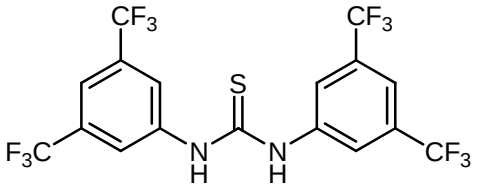
Chiral schiff base thiourea catalyst by Jacobsen



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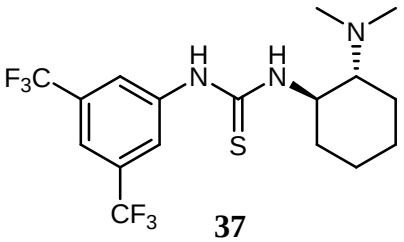
Chiral lewis acid thiourea catalyst by Schreiner



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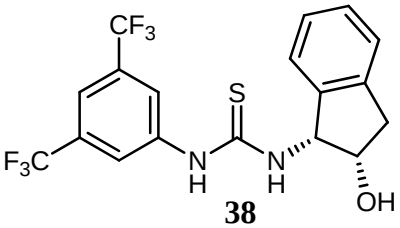
Bifunctional chiral thiourea catalyst byTakemoto



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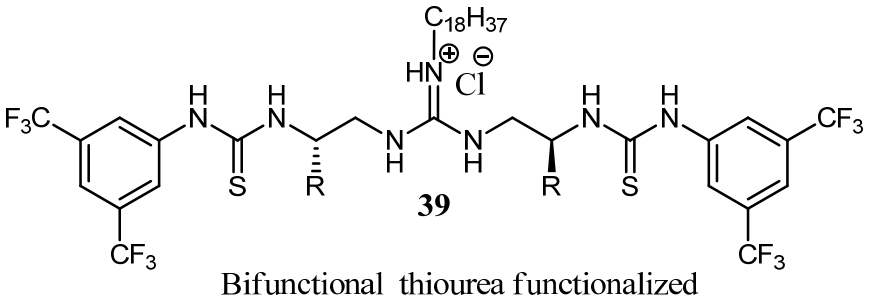
Chiral thiourea catalyst with additional hydroxy group by Ricci



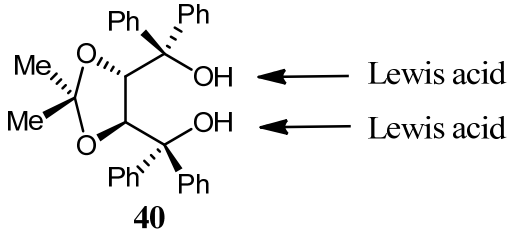
Bifunctional thiourea functionalized guanidine catalyst by Nagasawa

Scheme 9. Different thiourea catalysts

Many functionalities can be activated and controlled as thiourea and urea have specific binding "recognition" to several substrates. In addition, the catalysis is performed under mild conditions, so even acid-sensitive substrates can be used in the reaction with thiourea (urea) as catalyst.

Such a hydrogen bond activation mode has been used for the following reactions: Michael addition[43], Aza-Henry reaction[44], Strecker reaction[45], Baylis-Hillman reactions[46]. Double hydrogen bonding of thiourea can also be used to control other functional groups such as imides[47] or cyanides[48].

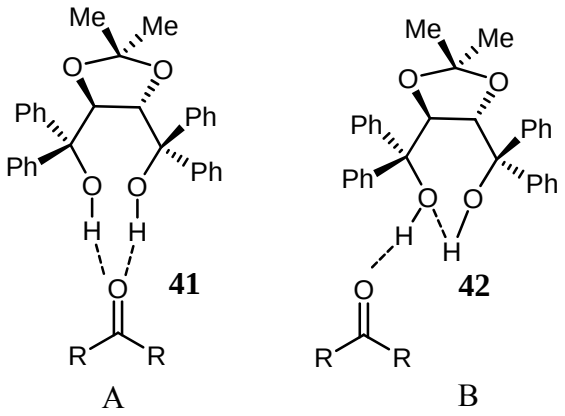
1.2.2.3 DIOL organocatalysis



Scheme 10. The activation sites of DIOL

Diol catalysts are another hydrogen bond catalyst besides thiourea (urea) and phosphoric acid systems. TADDOL and its derivatives are the primary structures of diol catalysts. The TADDOLs have been used as metal chiral auxiliaries for over one hundred years.[49] They have also been used as enantiodifferentiating reagents. The consideration of initial design of TADDOL mainly focused on the least expensive chiral starting material - tartaric acid which is available from natural sources in both enantiomeric forms. The TADDOL as organocatalyst

was firstly reported by Rawal in 2003 for Hetero-Diels-Alder cycloaddition reactions[50]. In the reaction, the carbonyl compounds and imines can be activated by decreasing the LUMO energy with TADDOLs by the double hydrogen bonding interaction with the carbonyl oxygen atom or imine nitrogen atom. The activated carbonyl compounds and imines can react with carbon nucleophiles to produce the corresponding alcohols and amines with excellent stereoselectivities. Moreover, the ether functional groups in the structure can be easily substituted, giving access to a variety of derivatives.



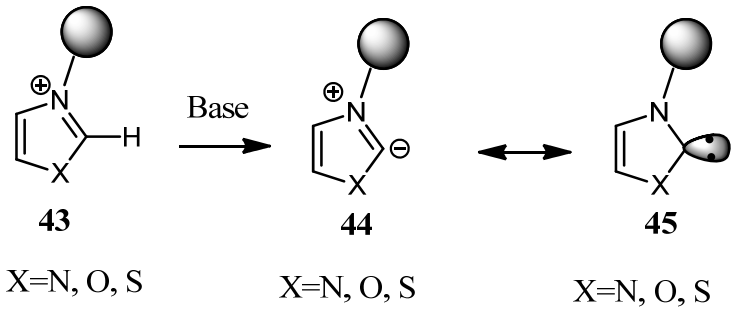
Scheme 11. Proposed hydrogen bond interactions with a carbonyl group

Two hydrogen bond interactions between TADDOL and a carbonyl group have been proposed (scheme 11). Until now, it is still difficult to determine which is more reasonable. These catalysts have been used for Diels-Alder and related cycloadditions [50].

Another diol catalyst is 1,8-biphenylene diol which was firstly reported by Hine and co-workers in the opening of phenyl glycidyl ether by diethylamine.[51] After this, the Kelly group applied this kind of catalyst also for acceleration of Diels-Alder cycloadditions.[52] Several years later, Maruoka and co-workers have done a great work with this type of catalyst to promote aldol reactions[53], Michael additions and Claisen rearrangements[54].

1.2.3 Organocatalysis with Lewis and Brönsted base

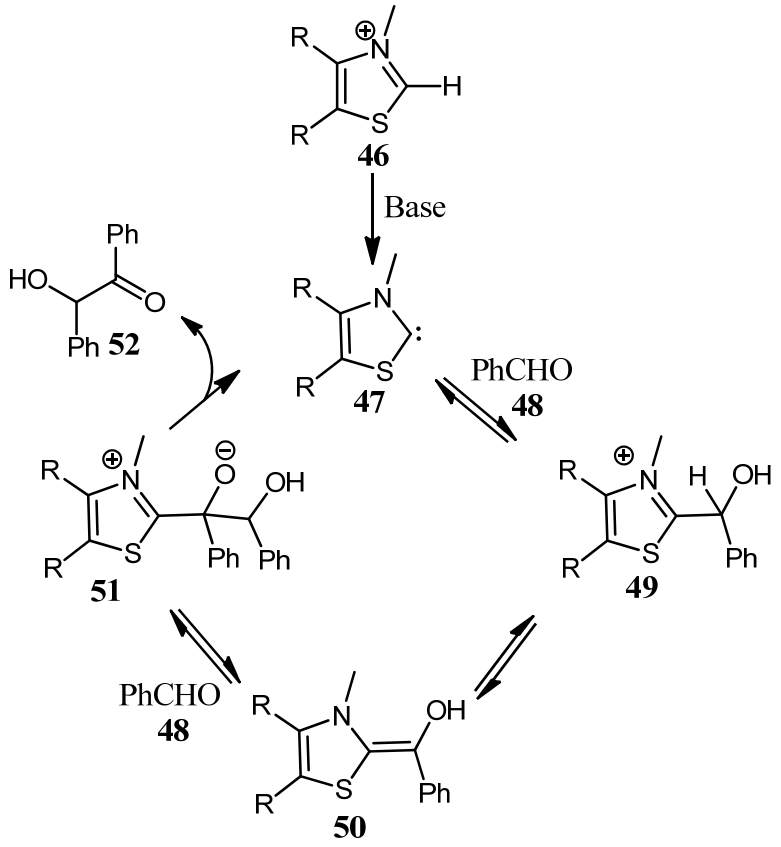
1.2.3.1 Nucleophilic Heterocyclic Carbene Catalysis



Scheme 12. Nucleophilic Heterocyclic Carbene Catalysis

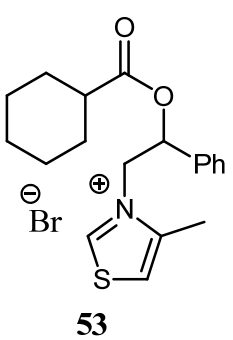
In organocatalysis, carbenes were introduced into transition-metal catalysis in 1995.[55] The Herrmann group reported that *N*-heterocyclic carbenes (NHC) can be applied as ligands in transition metal palladium catalysis for Heck reactions. Since then, the *N*-heterocyclic carbene has been introduced in a lot of transition-metal catalysis. It has become one of the most important ligands for organometal catalysis because *N*-heterocyclic carbenes are strong σ-donor ligands, even more electron-rich than the already electron-rich trialkylphosphines and the shape of the carbene ligands can be modified in a wide range, allowing the design and adjustment of the NHC for a variety of different applications [56]

Carbenes have been used much earlier as organocatalysts than they were introduced into organometal catalysis. Thiazoliums salt-derived *N*-heterocyclic carbene have been well-known in catalysis of a number of important biochemical reactions.[57] As early as 1943, Ugai found thiamine in the presence of a base catalyzed the benzoin reaction.[58] Much research has been done to determine the actual catalytically active species of these reactions. Some years later, it was found that the activity of the natural thiamine is based on its thiazolium unit. However, the mechanism of thiamine catalysis of benzoin reaction was still unknown until R. Breslow proposed the catalytic cycle of the benzoin condensation in 1958.[59]



Scheme 13. The proposed catalytic cycle of the benzoin condensation by R. Breslow

In the proposed catalytic cycle, after deprotonation the intermediate of thiazol-2-ylidene is formed as the actual catalyst which adds to an aldehyde molecule to generate an active hydroxy-enamine-type intermediate. This intermediate works as a nucleophilic reagent after losing another hydrogen. Reaction between this nucleophilic reagent and an electrophilic substrate (a second aldehyde) yields the product.



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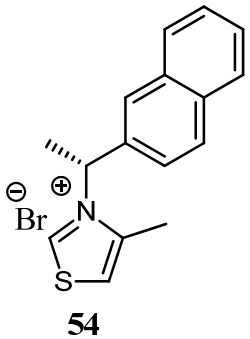
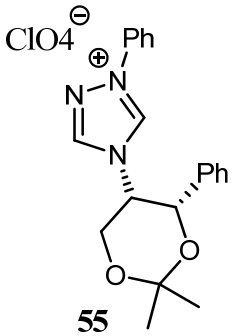
1966
Sheehan, J



54

1974
Sheehan, J



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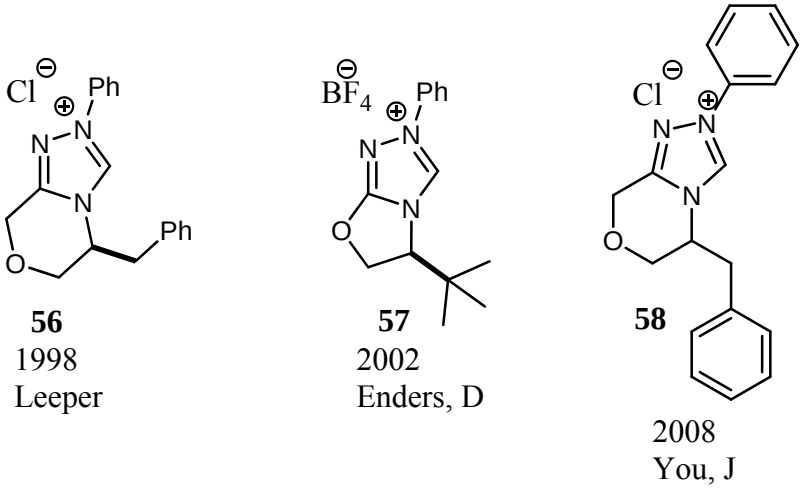
1996
Enders,D



56
1998
Leeper

57
2002
Enders, D

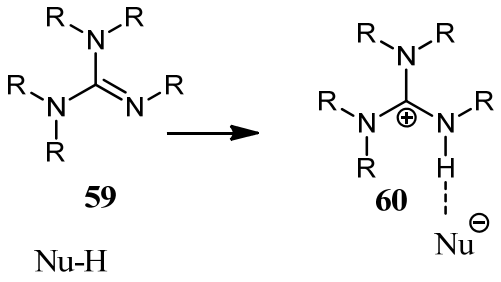
58
2008
You, J

Scheme 14. Some stable carbenes as catalysts

In the catalytic cycle proposed by Breslow, the intermediate formation of thiazol-2-ylidene stands for a class of highly reactive reagents which bear a divalent carbon atom as the character. A number of stable *N*-heterocyclic carbenes, which have similar structure like thiazolium, have been isolated and characterized by different groups.[60] The *N*-heterocyclic carbene usually has a five-membered ring of an aromatic heterocycle. The sp^2 lone pair acts as an electron donor, while the empty *p*-orbital works as an electron acceptor. In a great development, *N*-heterocyclic carbenes have become an important class of organocatalysts, and several stable carbenes have been developed as catalyst for asymmetric synthesis (scheme 14).

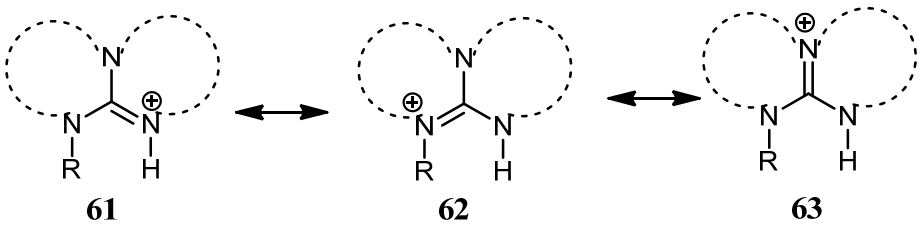
During recent years, there has been an increased interest in such *N*-heterocyclic carbenes, owing to its special properties. One is that nitrogen heterocycles such as imidazole, imidazoline, tetrazole, thiazole can change the electronic and steric properties of *N*-heterocyclic carbenes. Different structures are affecting the activity of the catalyst and also the selectivity of the reaction. Another property is that substitution in 1- and 3-positions of the *N*-heterocyclic carbenes can be easily reached, which will give a lot of possibilities for design and adjustment for a variety of different applications. Many reactions have been developed with *N*-heterocyclic carbenes as organocatalysts, for instance the benzoin condensation[61] and the Stetter reaction[62].

1.2.3.2 Guanidine catalysis



Scheme 15. The guanidine activation mode

Guanidines have a common functional group with the general structure $(RRN)_2C=N-R$. In the protonated form, the guanidinium ion has a positive charge and is a highly stable cation in aqueous solution due to the efficient resonance stabilization of the charge.

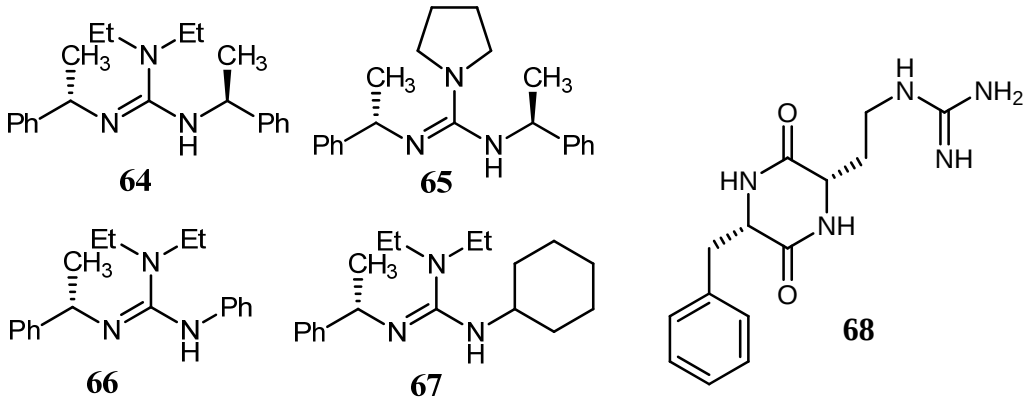


Scheme 16. The resonance of guanidinium

Compared with other active nitrogen analogues, the guanidines have been very slowly developed in coordination chemistry, because due to the high basicity of guanidine and its substituted derivatives they readily form guanidinium cations in aqueous media. In the structure of the guanidinium cations, it is obvious that the positive charge has lowered availability of the nitrogen lone pairs, so the guanidinium cations have negligible ability to behave as Lewis bases. In the last century, the coordination of deprotonated guanidines to metals in organometal catalysts has received more attention and this has been greatly developed in coordination chemistry. [63]

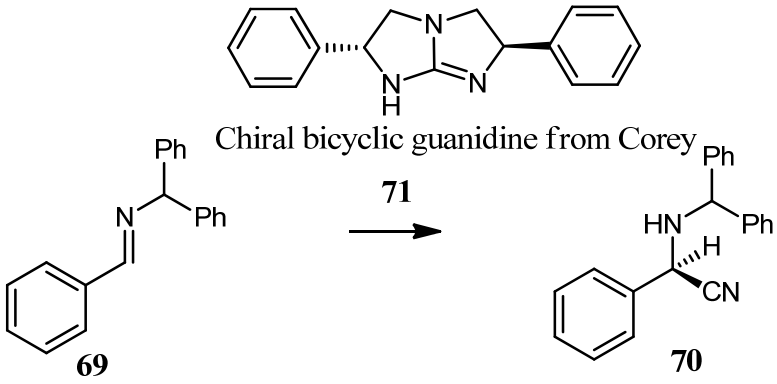
The use of guanidines as strong basic catalysts was reported by Davis in 1992.[64] In that paper, Davis reported that the nitronate anions which have electronic similarity with the carboxylates can be deprotonated to give a reaction with electrophiles to build new C-C bonds. In the paper, even a crystalline complex of nitromethylbenzene and bicyclic guanidine catalyst was obtained

and described.



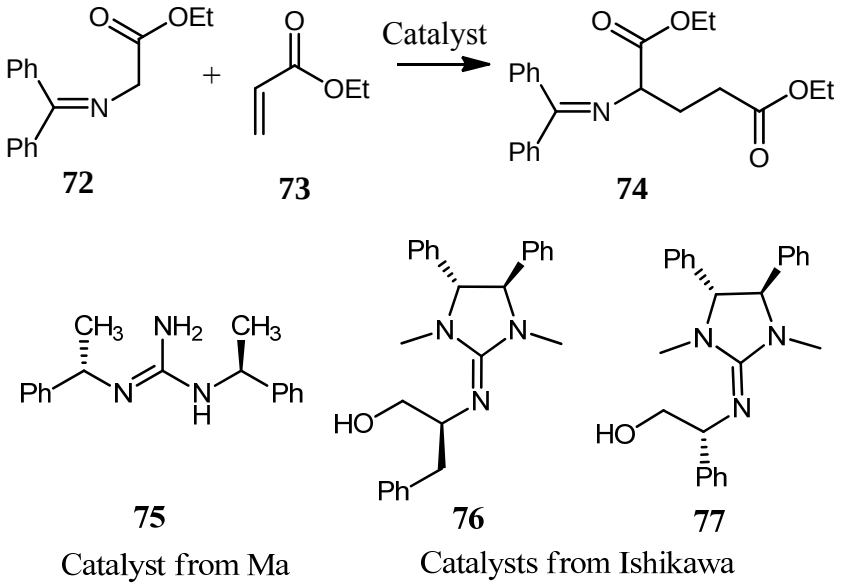
Scheme 17. Different guanidine catalysts

Guanidines have been introduced as organocatalysts for asymmetric synthesis in 1994 by Chinchilla.[65] Chinchilla synthesized a series of chiral guanidine systems as catalysts for the addition of nitromethane to aldehydes, but the reaction showed no good selectivity. The highest selectivity (ee 54%) was obtained at very low temperature. Shortly after the report of Chinchilla, Lipton reported the use of a cyclic dipeptide with guanidine as the key functional group in a catalyst for the asymmetric synthesis Strecker amino acid in 1996.[66] In the paper, Lipton pointed out that in the previous research, the same dipeptide with imidazole substitution failed to afford any asymmetric induction in the mechanistically similar Strecker synthesis, probably due to the weak basicity of imidazole in the side chain. Based on this result guanidine was chosen by Lipton to take the place of imidazole. High yields (98%) at low temperatures and very high enantioselectivities (ee 99%) for aromatic imines have been obtained.

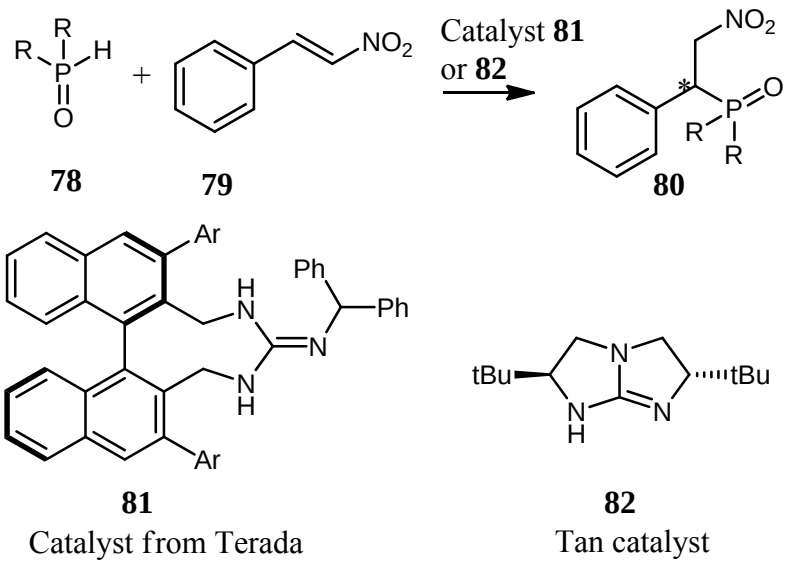


Scheme 18. Corey catalyst for the asymmetric Strecker reaction

In 1999, Corey developed a chiral bicyclic guanidine catalyst to promote the asymmetric Strecker reaction.[67] In the paper, a possible mechanistic basis for the observed stereoselectivity was proposed, relying on π-π-interaction with the benzene rings. In the same year, the group of Ma reported that chiral guanidine catalysts could be used to catalyze the addition of glycine derivatives to acrylates.[68] His mechanistic proposal was that the catalyst gets a proton from the activated glycine derivative and then controls the ester group. In the reaction, the selectivity was only moderate. Two years later, Ishikawa reported a structurally modified guanidine as a catalyst for the addition of glycine derivatives to acrylates.[69] The selectivity of this catalyst was very high (ee 97%). The Ph substituent in the five-membered ring plays an important role in increasing the selectivity. The guaninidine structure has also been combined with another chiral scaffold - BINOL - by Terada.[70] This system has been used to catalyze the Michael addition of dicarbonyl compounds to nitro-olefins. More specifically, 3,5-di-tert-butylphenyl substitution on the 3,3'-position of the binaphthol backbone provided overall best yields and selectivity. The selectivities of the product is determined by the binaphthol backbone, whose effect is similar to chiral phosphoric acid modified BINOL derivatives.



Scheme 19. Addition of glycine derivatives to acrylates with catalysts from Ma and Ishikawa



Scheme 20. Addition of P (O)-H to nitroalkene

Compared with the research on the catalysis of C-C bond, the contribution on the phosphorus-carbon bond formation is late and not pronounced.[71] In recent years, chiral compounds containing P-C bonds have played important synthetic roles.[72] However, only a few methods to get asymmetric formation of P-C bonds have been described. Among these methods, the direct addition of P (O)-H bonds (dialkyl phosphites or dialkyl phosphine oxides [R_2 P (O) H]) to activated alkenes is one of the most convenient routes to generate P-C bonds with a new chiral center. In order to catalyze this addition, some new catalysts have been reported. Among them, Tan and his co-workers reported a bicyclic guanidine catalyst for the asymmetric addition of phosphine oxides to nitro-olefins.[73] In the report, the author achieved a chiral amino-phosphine with a pronounced selectivity and high yield. This bicyclic guanidine catalyst was also reported by Tan for the asymmetric addition of nitroalkanes to α,β-unsaturated ketones and the addition of malonates to nitroalkene, but only moderate selectivities could be obtained. The first asymmetric Diels-Alder addition of anthrone to maleimides has been reported also by Tan with the same bicyclic guanidine catalyst. Considering the facility of the modification of guanidine, this kind of catalyst could have a great potential for a wide range of reactions.

II. Objective

From the introduction, it can be found that many organocatalysts express their selectivities mostly by hydrogen bonding, but the development of organocatalysts with hydrogen bonding in different chiral scaffolds is still in demand.

The detailed objectives of this thesis can be summarized as follows:

1. As has been referred to in the discussion of the activation modes, the development of organocatalysts based on imidazolidinone has been greatly developed by Macmillan and his coworker. In the activation mode, the iminium has been regarded as the electrophile, which will be attacked the nucleophile. However, there is no other report in an attempt to guide the nucleophile in the reaction. In this thesis, it should be tried to synthesize some analogs of imidazolidinone with a carboxyl group in the side chain, which could improve the selectivity by hydrogen bonding with the electrophile and to examine whether there is a common characteristic in structure between imidazolidinone and proline.

2. In the enamine activation mode, diverse catalysts based on proline have been reported. In those reports, it has been shown that factors such as substituents, acidity, hydrophobicity, steric bulk, can affect the selectivity. However, there is no report which factor is more important to the selectivity. Facing these factors, a series of *L*-prolinamide derivatives should be synthesized by a novel route and evaluated in different reactions.

3. Based on the hypothesis that the acidity of the catalyst plays an important role, we have focused on increasing the acidity of the organocatalysts in order to get higher yield with lower catalyst loading and less excess of the nucleophile. However, until now the modification has only focused on the introduction of electron-withdrawing groups. The limit of increasing the acidity in such a way is obvious. So, new methods to increase the acidity of the catalysts should be searched for.

4. Peptides have been used in organocatalysts for a long time. Since the sulfonamide group was introduced into organocatalysts, there is no report to combine a sulfonamide to a

peptide. Therefore, such new peptides should be synthesized and applied as catalysts.

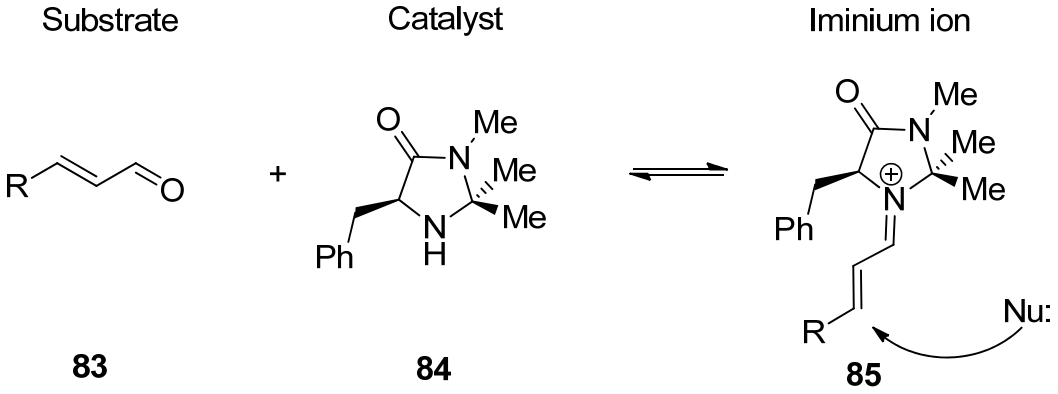
5. As BINOL derivatives have been widely used as chiral scaffolds for catalysts it should be found out if they can also serve as the basis for new organocatalysts.

III. Results & Discussions

3.1 New imidazolidinone derivatives as organocatalysts

3.1.1 The design of imidazolidinone derivatives

As we have pointed out in the discussion of the iminium activation, the imidazolidinone compounds as catalysts in a reaction react firstly with the α,β-unsaturated aldehydes or enone to get activated iminium intermediates.[74]

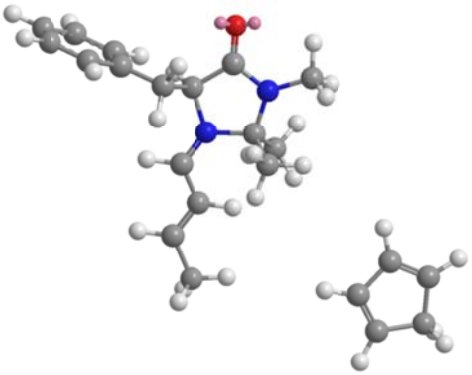


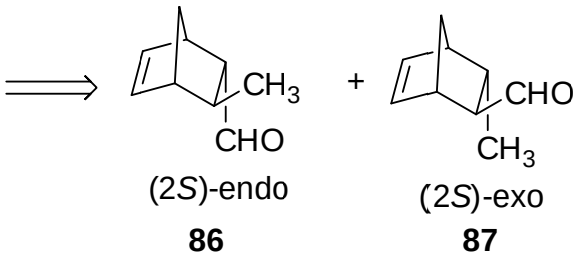
Scheme 21. The iminium activation mode with an α, β-unsaturated aldehyde

In the activation mode, the steric effect plays an important role for the high selectivity. The benzyl group works as a sterically demanding group which hinders the nucleophile to attack the electrophile from the *si*-face leading to faster attack to the electrophile from the sterically less hindered *re*-face.[74]

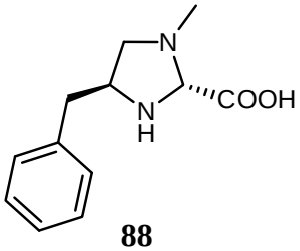
Steric hindrance has been recognized quite widely in the imidazolidinone series. Only a few substituents have been used other than the benzyl group, which has become one of the standard groups for imidazolidinone catalysts. Surprisingly, there has been no report of using hydrogen bonding of a carboxyl group in the 5-position of the imidazolidinone system - in analogy to the well-known activation effect of the

carboxyl functionality in proline.





Scheme 22. Diene attacking the dienophile from the *re*-face



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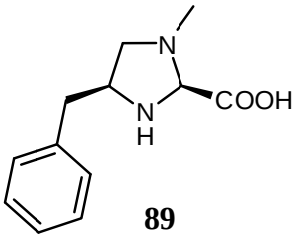

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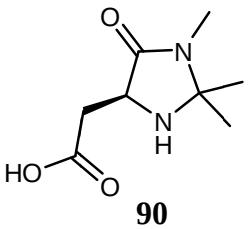
Scheme 23. Imidazolidinone catalysts from Jørgensen.

In 2002, however, Jørgensen reported novel imidazolidinone catalysts with a carboxylic acid group which is connected with the carbon between two nitrogen atoms.[75] In this report, the hydrogen bond of the carboxylic group was used to recognize the nitro group. As the direct connection of a carboxylic acid function to the ring next to the amide carbonyl function to get a proline analogue did not seem to be meaningful, as such a 1,3-dicarbonyl compound will be too acidic to maintain the absolute configuration at that center, we designed systems which have the carboxylic acid in the β position, namely compound **90**-**92**.



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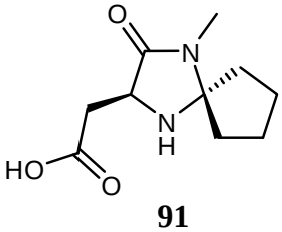

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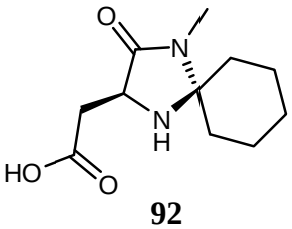

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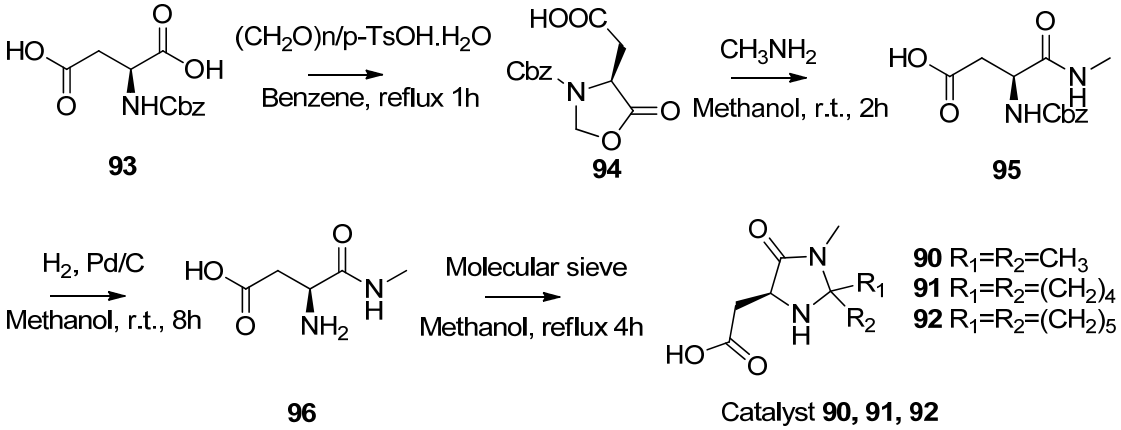
Scheme 24. Designed novel imidazolidinone catalysts

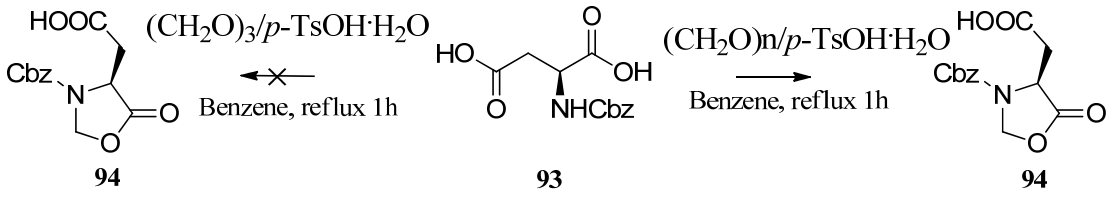
3.1.2 The synthesis of new imidazolidinone derivatives

The synthesis of imidazolidinone systems has been reported by Macmillan.[74] In the report, (*S*)-phenylalanine methyl ester hydrochloride has been used as the starting material. However, there is no report to synthesize the imidazolidinone with a carboxylic group in the side chain. So we developed a new route for the synthesis of catalyst **90-92**.



Scheme 25. The synthesis of catalyst **90-92**

N-Benzyloxycarbonyl-(*L*)-aspartic acid was chosen as starting material for the synthesis of such a system. The synthesis of the known compound **94** has been reported.[76] *N*-Benzyloxycarbonyl-(*L*)-aspartic acid was reacted with paraformaldehyde with *p*-TSA as catalyst in benzene at reflux with water removal by a dean-stark trap. For the synthesis of compound **94**, 1,3,5-trioxane has also been reported instead of formaldehyde.[77] However, the reaction with 1,3,5-trioxane as reagent did not work in our hand. The reaction was tried several times but no product was detected in the reaction. The difference of the generation of formaldehyde from paraformaldehyde and



Scheme 26. The attempts to synthesize compound **94**

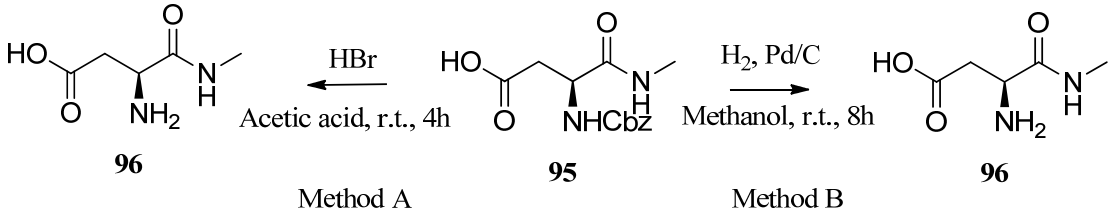
1,3,5-trioxane is known.[78,79] 1,3,5-Trioxane is such a stable cyclic trimer of formaldehyde that it decomposes to generate three molecules of formaldehyde only under strong acidic solutions or at its boiling point of 114.5 °C. Paraformaldehyde can be depolymerized to formaldehyde under much milder conditions by acid or heat.

Table 1. The character of 1,3,5- trioxane and paraformaldehyde

Formaldehyde resource	Boiling point	Melting point	Decompose condition
1,3,5- trioxane	114.5 °C	64 °C	strong acid solution
paraformaldehyde	no	120 °C	heating or acid solution

In the reaction, in order to remove the produced water in the reaction, benzene was used as the reaction solvent. The *p*-TSA was added only in catalytic amount to the reaction mixture and the reaction had not enough acidity for the decomposition of 1,3,5-trioxane but worked well with paraformaldehyde to give compound **94**.

With compound **94**, an excess of a methylamine solution in methanol was used to open the five-membered ring. After the reaction was completed, the excess methylamine was removed under vacuum with a jet pump and diluted hydrochloride. When the free methylamine has been removed, diluted hydrochloride acid was added to produce the free carboxylic acid, which precipitates as a white solid in the clear solution. When the mixture was cream like, the addition was stopped and the mixture was filtered to remove water, hydrochloride acid and the amine salt.

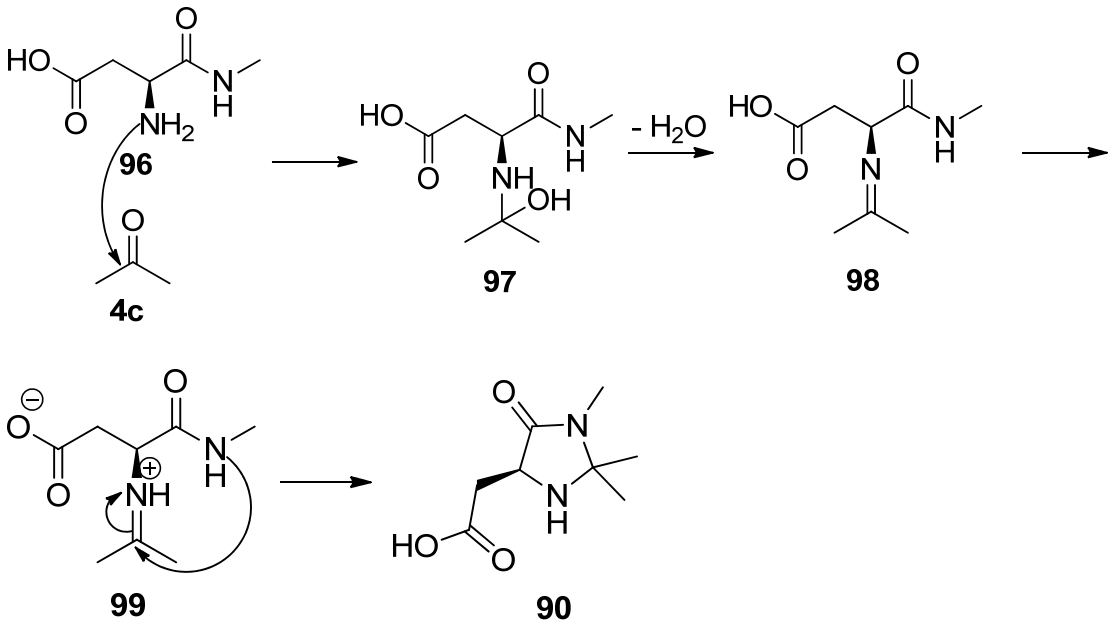


Scheme 27. Two methods for the deprotection of Cbz

The Cbz deprotection has been successfully done by two methods. Method A uses HBr in acetic acid. With this method, the product is the HBr salt. Before the next step or after the next step, the HBr will have to be removed in order to get the target product. In

method B a hydrogenation with Pd/C under hydrogen atmosphere is used. Compound **96** can be obtained in very high yield with both of these methods.

For the synthesis of imidazolidinones, a general method exists in the reaction of an amino acid amide with a carbonyl compound with *p*-TSA as catalyst. The acid will be helpful in the activation of the carbonyl group in the production of an imine. It will also protonate the nitrogen atom of the imine and increase its activity as an electrophile. In our case, it is not necessary to have *p*-TSA as catalyst because the material already has an acidic group in the molecule. So we only added molecular sieves to remove the produced water in the reaction. With this method, the reactions with cyclohexanone and cyclopentanone were also successful.



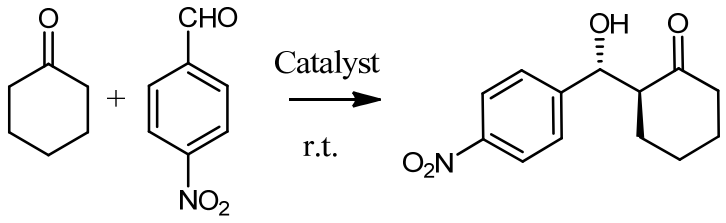
Scheme 28. The proposed mechanisms of ring formation

3.1.3 The tests with imidazolidinone organocatalysts

After we got the target compounds, tests for their catalytic activity have been done. Considering the character of a carboxylic group which has very good recognization for a carbonyl group, the aldol reaction was chosen for tests. In the test reactions we chose cyclohexanone and *p*-nitrobenzaldehyde as the reagents. The reactions were firstly

performed in DMSO with catalysts **90-92**.

Table 2. Screening of organocatalysts for the aldol reaction[a].



4a **48a** **100a**

Entry	Catalyst	Solvent	Catalyst [mol%]	Time [h]	Yield [%][b]	anti /syn[c]	ee[%] (major)[d]
1	90	DMSO	30	24	24	53/47	0
2	91	DMSO	30	24	28	62/38	0
3	92	DMSO	30	24	34	64/36	1
4[e]	90	DCM	30	24	22	60/40	0
5[e]	91	DCM	30	24	20	60/40	4
6[e]	92	DCM	30	24	25	62/38	3
7[f]	90	MeOH	30	24	30	56/44	10
8[f]	91	MeOH	30	24	22	58/42	17
9[f]	92	MeOH	30	24	24	66/40	19
10[g]	90	H_2O	30	24	12	56/44	27
11[g]	91	H_2O	30	24	12	58/42	33
12[g]	92	H_2O	30	24	14	59/41	33

[a] The reaction was performed with **90-92** (0.15 mmol), **4a** (0.51 mL, 5.0 mmol) and **48a** (76 mg, 0.5 mmol), DMSO (1 mL) at room temperature.

[b] Combined yields of isolated diastereomers.

[c] Determined by ^{1}H NMR of the crude product.

[d] Determined by chiral-phase HPLC analysis of the major product.

[e] The reaction was performed with 1ml DCM as solvent.

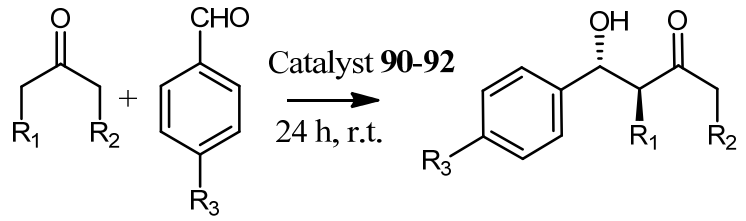
[f] The reaction was performed with 1ml methanol as solvent.

[g] The reaction was performed with 1ml H_2O as solvent.

From the results in Table 2, it can be found that the catalysts **90-92** gave higher

enantioselectivity for the products in methanol and H_2O than in DCM and DMSO.

Table 3. Direct aldol reaction of aldehydes and ketones catalyzed by catalysts **90-92**[a]



4 **48** **100a-104a**

Entry	R_1	R_2	R_3	Catalyst	Product	Yield [%][b]	anti / syn[c]	ee[%] (major)[d]
1	-$(CH_2)_3$-		NO_2	**90**	**100a**	12	56/44	27
2	-$(CH_2)_3$-		NO_2	**91**	**100a**	12	58/42	33
3	-$(CH_2)_3$-		NO_2	**92**	**100a**	14	59/41	33
4	-$(CH_2)_2$-		NO_2	**90**	**101a**	12	51/49	18
5	-$(CH_2)_2$-		NO_2	**91**	**101a**	14	51/49	38
6	-$(CH_2)_2$-		NO_2	**92**	**101a**	17	55/46	37
7	H	H	NO_2	**90**	**102a**	trace	ND	ND
8	H	H	NO_2	**91**	**102a**	trace	ND	ND
9	H	H	NO_2	**92**	**102a**	trace	ND	ND
10	-$(CH_2)_3$-		Cl	**90**	**103a**	trace	ND	ND
11	-$(CH_2)_3$-		Cl	**91**	**103a**	trace	ND	ND
12	-$(CH_2)_3$-		Cl	**92**	**103a**	8	67/33	33
13	-$(CH_2)_3$-		OCH_3	**90**	**104a**	trace	ND	ND
14	-$(CH_2)_3$-		OCH_3	**91**	**104a**	trace	ND	ND
15	-$(CH_2)_3$-		OCH_3	**92**	**104a**	7	62/34	24

[a] The reaction was performed with **90-92**(0.15 mmol), **4** (5.0 mmol) and **48** (0.5 mmol), H_2O (1 mL), and at room temperature.

[b] Combined yields of isolated diastereomers.

[c] Determined by ^1H NMR of the crude product.

[d] Determined by chiral-phase HPLC analysis of the major product.

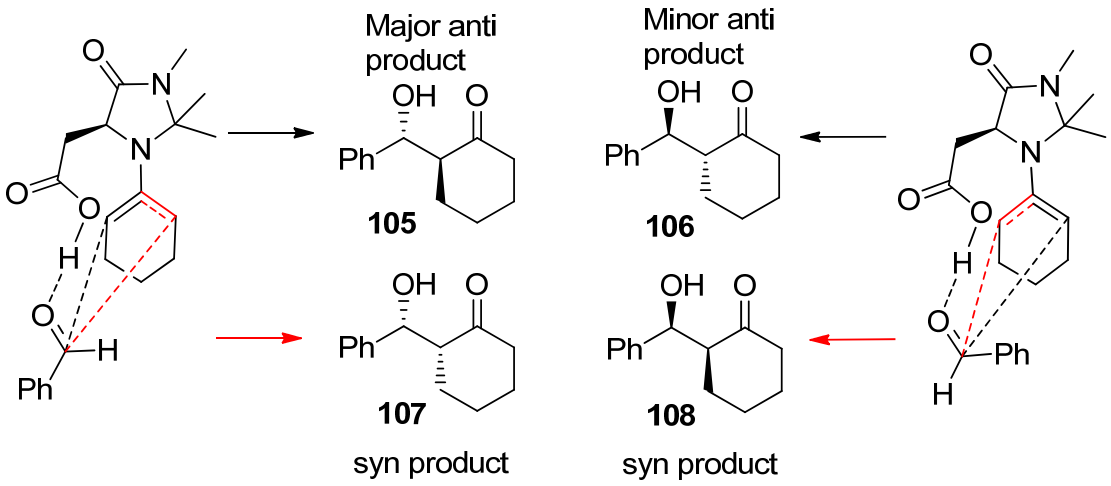
The best enantiomeric excess (ee) (33 %), however, has been obtained by **91** and **92** in

water. (entries 11 and 12, Table 2), but the yield was very low in the reactions with water as solvent. (entries 10, 11 and 12, Table 2). It can also be seen that there is no big difference in selectivity between catalysts **90-92** in different solvents. After screening the different solvents, other ketones and aldehydes have been tested in the test reactions.

From the results in Table 3, it can be found that the selectivity of reactions with **90-92** is not good at all with different ketones and aldehydes. With cyclohexanone the selectivity is a little better than acetone. The yield is very low when the aldehyde is substituted with Cl or OCH_3 at the para position of the benzene ring because these two aldehyedes have less activity than *p*-nitro benzaldehyde.

The low diastereoselectivity from these catalysts can be explained with two possible transition states with regard to the position of the enamine: as predicted in scheme 29 the less sterically hindered transition state leads to the anti product, the other one to the syn product. There is also no big bulky group on the carbon which is between the two nitrogen atoms, as in the case of Macmillan's second generation catalyst.

The lower selectivity of the anti product can be explained by the fact that the hydrogen bond of the carboxylic acid in the side chain is far away from the NH, so the reacting aldehyde controlled by this hydrogen bond will be too far from the enamine to give a tight transition state. So the selectivity is not high.



Scheme 29. The transition state and products with catalyst **90**

3.1.4 Conclusion

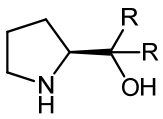
In conclusion, we have synthesized three new imidazolidinone derivatives and tested them for their use as organocatalysts for aldol reaction. However the selectivity of the reaction is not high, which has been explained with the possible stereo structures of the transition state.

3.2 New proline sulfonamide and imide derivatives as organocatalysts

3.2.1 The design of proline amide derivatives

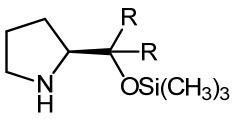
In the introduction, it has been pointed out that proline is one of the earliest used organocatalysts in industry. Compared with other catalysts, the low cost of proline and the high selectivity in aldol reactions are the obvious advantages. However, there are still several disadvantages such as low solubility in organic solvent, long reaction time, and the necessity of a large excess of reagent. These disadvantages continue to motivate chemists to do further search for new catalysts.

As referred[80], great effort has been made to the modification of proline in order to get higher selectivity and higher yields (Scheme 30). Among these modifications, increasing acidity, hydrophobicity and steric hindrance have doubtless attracted the main attention. In this section, we will focus on increasing the acidity of organocatalysts based on proline. It is believed that the proton of carboxylic acid plays an important role in recognizing the carbonyl group and leads to the high selectivity of the product (Scheme 31). As reported in the literature[81], a theoretical study has pointed out that the acidity of proline amides can affect the enantioselectivity of the reaction. However, until now there is no practical report about the effect of acidity of such proline derivatives. So we decided to do further research on proline derivatives with the same or similar substituents but different acidity.



R= Bn, Ph.

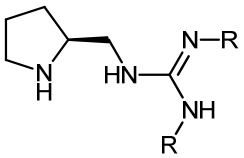
109



R= Bn, Ph, H.

110

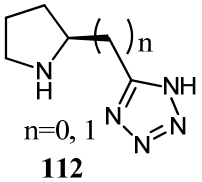
Prolinol derivatives



R= H, CH_3.

111

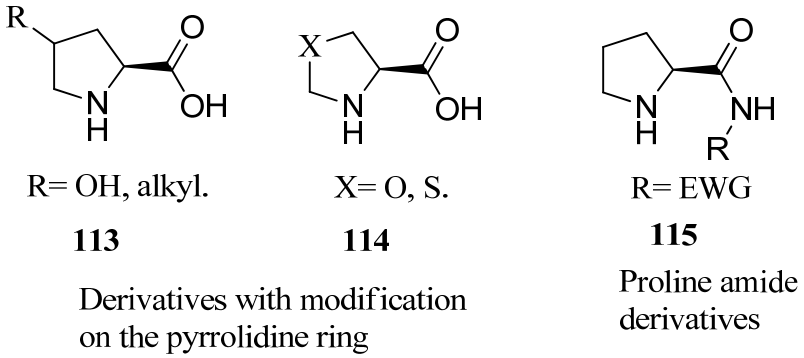
(*S*)-5-(Pyrrolidin-2-yl) guanidine derivatives



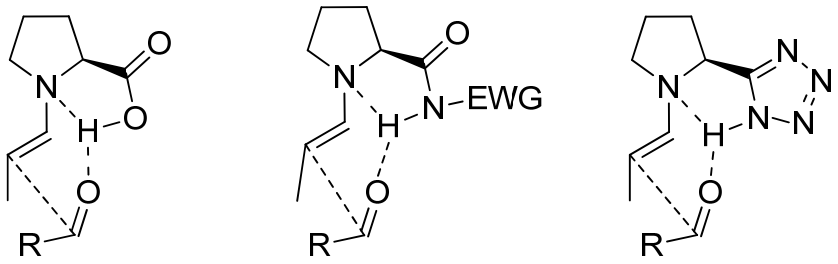
n=0, 1

112

(*S*)-5-(Pyrrolidin-2-yl)-1H-tetrazole



Scheme 30. Organocatalysts based on proline



Scheme 31. The critical role of the proton of different organocatalysts in the transition state

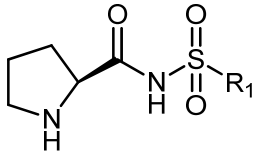
Compared to the known derivatives from proline and prolinol derivatives[82], proline amide derivatives provide more opportunities in acidity modification. Proline amide is obviously a good substrate for modification of the acidity by simple modification of the substituent. In the amide derivatives, the sulfonamide and the carboxylic amide have a great similarity in structure compared with other functional group and the acidities of these compounds can be modified in a wide range, as can be seen in the following Table, where the calculated pK_a of several amide and sulfonamide functionalities are shown. (The calculation is made by ACD Lab ACD/pK_a DB Version 6.0)

Table 4. Calculated acidity of amide and sulfonamide functions

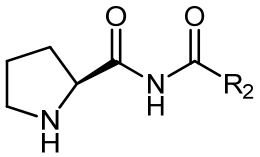
	CH_3CONH_2	$C_6H_5CONH_2$	CF_3CONH_2	$CH_3SO_2NH_2$	$C_6H_5SO_2NH_2$	$CF_3SO_2NH_2$
pK_a	16.60	16.00	12.33	10.86	10.08	6.37

In the report of Berkessel[83], proline derived sulfonamides were synthesized and utilized

as efficient organocatalysts for aldol reaction. In their synthesis, DCC was used for connecting proline and the corresponding sulfonamides. One year later, proline trifluroacetamide was reported by Wang[84] for the same reaction. The compound was synthesized by reaction of Boc-*L*-proline amide with trifluoroacetic anhydride at 0 ^{o}C, followed by removal of the protection group with trifluoroacetic acid in dichloromethane. But in this case the aldol reaction was followed by aldol condensation: possibly the reaction conditions were too acidic. In order to get more information on the influence of acidity we designed the following proline amide derivatives.



116a R_1= $C_6H_4CH_3$
116b R_1= CH_3
116c R_1= CF_3



117a R_2= CF_3
117b R_2= CCl_3
117c R_2= $C(CH_3)_3$
117d R_2= C_6H_5

Scheme 32. The designed *L*-proline sulfonamide and imide catalysts

3.2.2 The synthesis of new proline amide derivatives

The synthesis of proline sulfonamide derivatives followed the route of Berkessel with DCC and DMAP. The imide derivatives were firstly synthesized following the Wang operation. The Boc-*L*-proline amide, which is the starting material in the report for the synthesis of proline imide derivatives, was prepared following the process of Yamamoto[85]. When following the report of Wang, the Boc-*L*-proline amide reacted with trifluoroacetic anhydride at 0 ^{o}C and the wanted intermediate was obtained. However, there were some problems in repeating Boc deprotection in our hand. In Wang's report, a solution of trifluoroacetic acid (14 mL) in 48 mL of dichloromethane was added dropwise in 45 min into a stirring mixture of (*S*)-*tert*-butyl 2-(2,2,2-trifluoroacetyl carbamoyl)pyrrolidine-1-carboxylate (1.15 g, 3.70 mmol) and 28 mL of dichloromethane at room temperature. The solution was stirred for 2 h at room temperature, and the volatiles were removed under reduced pressure. The

remaining viscous product was treated with ethyl ether (3×20 mL) to provide a white solid in 57% yield (441 mg, 2.10 mmol). Following exactly this operation, even with the same amount of reagent in the reaction several times, the target deprotection product could not be got in our hand. From the ^{1}H NMR of our deprotected product, the pyrrolidine ring is correct. However, in the ^{13}C NMR, we cannot find obvious quartet peaks of CF_3 like the report. In our analysis, the peak of ^{19}F changed to -74.2 ppm from -76.4 of starting material. However, the ^{19}F was not given in the report.

After several attempts, the process and the NMR-analysis in the report was carefully checked. Then we found that after removal of Boc in trifluoroacetic acid, the free secondary amine of the product should still be a salt with one equivalent of trifluoroacetic acid. In order to get the target product, the trifluoroacetic acid should be removed after deprotection. However, this process was not reported without any reason. In the ^{13}C NMR, the quartet peaks of CF_3 can be regarded as existing, but the carbonyl group, which should be around 170 - 174 ppm, does not occur. Based on these analyses, this method seems to be unsuitable to get the target imide compound.

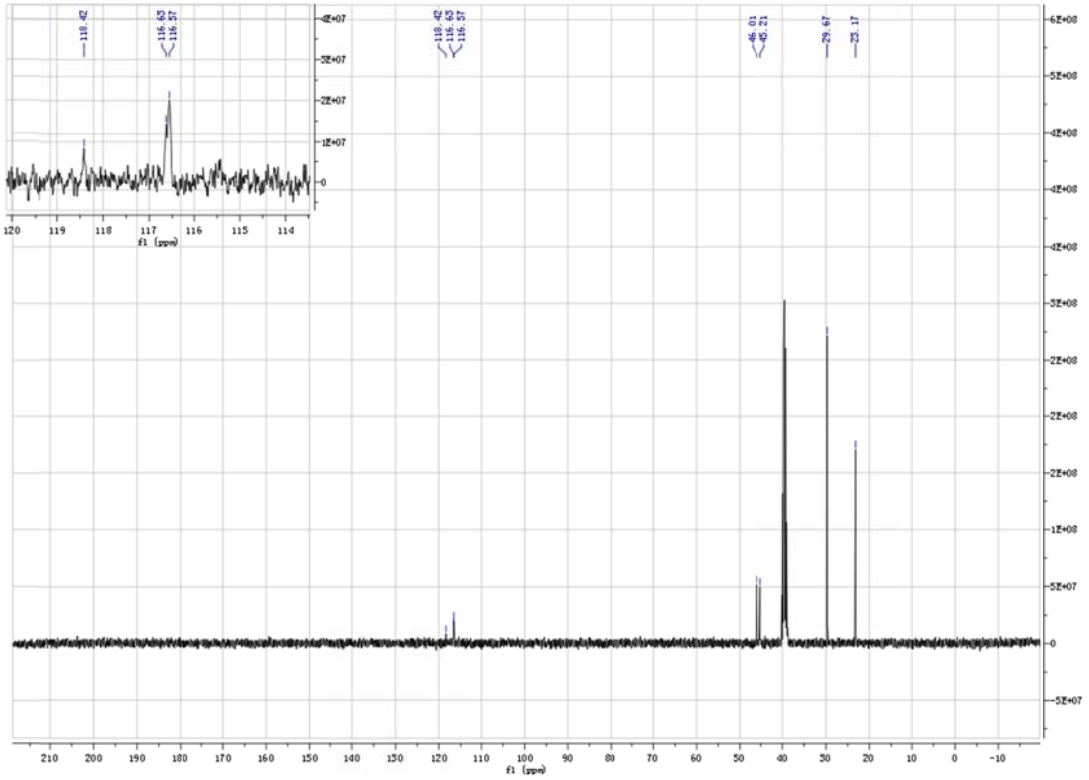
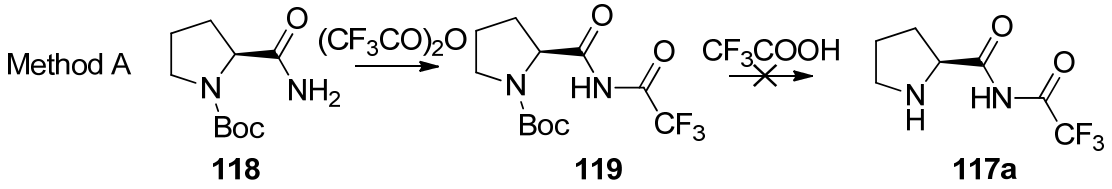
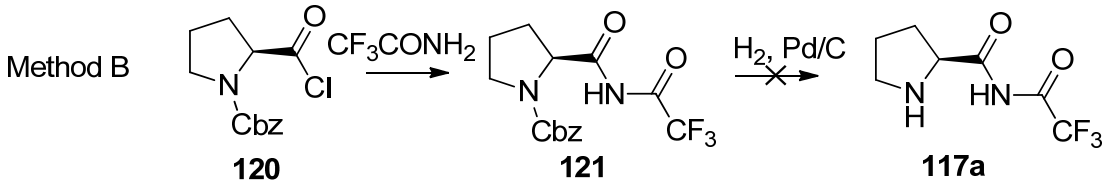


Figure 1. The ^{13}C NMR of the product after Boc removal



Scheme 33. Wang's synthesis of imide

So, we tried another alternative method for the synthesis of the target compound. As a possible reason for the failure could be the difficult deprotection of the Boc group with strong acid, the Cbz protection group was used in the following reaction. In order to get good acylating reactivity, the Cbz-proline was transformed into its acyl chloride to react easily with 2,2,2-trifluoroacetamide. The acyl chloride of Cbz-*L*-proline was obtained by PCl_5 following the operation from the literature.[86] The intermediate **121** was quantitatively obtained according to the analysis by H, C and F-NMR. The peak of ^{19}F is -76.1 ppm. The quartet peaks of C in CF_3 occur at 119.8, 116.9, 114.1, 111.2 ppm.



Scheme 34. The synthesis of proline derived imide with Cbz-*L*-proline

However, the deprotection of Cbz group with trifluoroacetic acid or with HBr in acetic acid could not be achieved. The deprotection was tried under normal hydrogenation condition with H_2, Pd/C. In the ^{13}C NMR of the product, the peaks of Cbz and CF_3 group disappear completely, showing that the imide has been further reduced to the free amide. Such a reaction has been described in the literature. [87]

From the results, it can be realized that the two classically protected proline derivatives are not suitable to give the desired target compound in the deprotection step. So, the proline should be not protected by Cbz or Boc which has to be deprotected by strong acid or H_2, however the secondary amine without protection would lead to the reaction with the carboxylic acid of another proline. Based on this experience, *L*-proline

N-carboxyanhydride **122** has been taken into consideration, as it has already been successfully used for the protection and activation of proline.

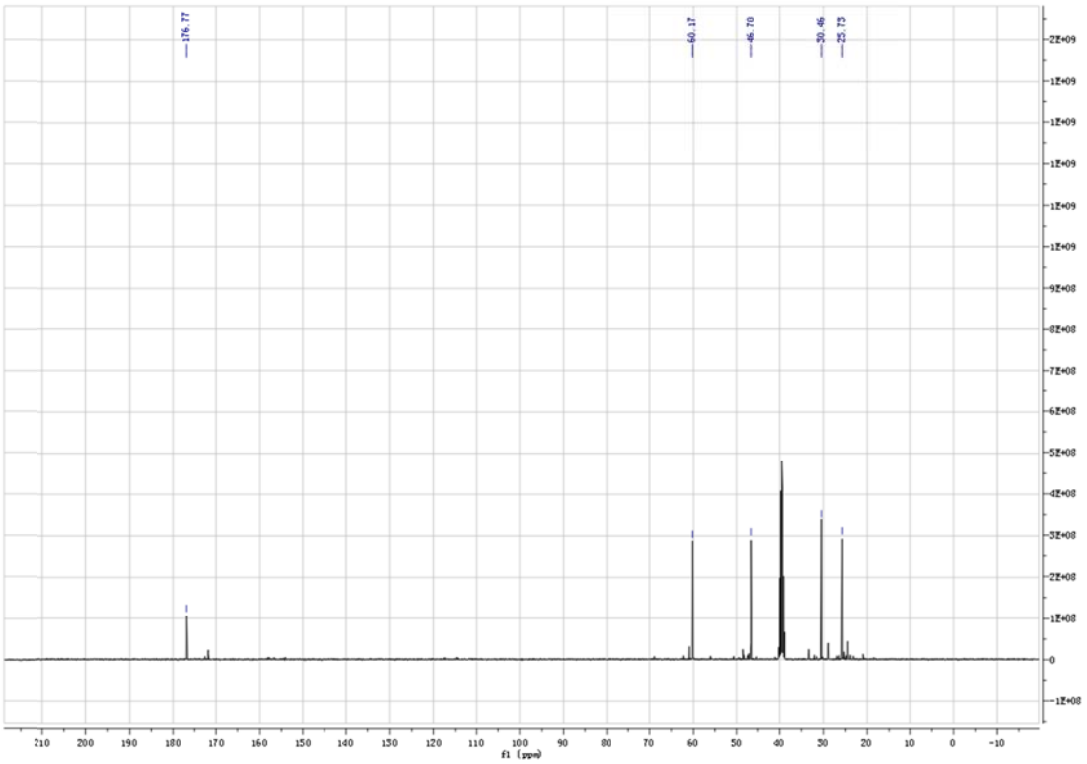
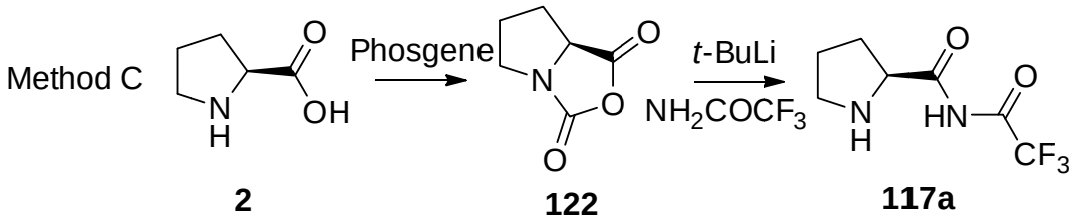


Figure 2. ^{13}C NMR spectrum of the Cbz deprotection product with H_2, Pd/C



Scheme 35. Synthesis of imide starting from *L*-proline *N*-carboxyanhydride

It was known that secondary amines react with the anhydride leading, even in methanol, to the free amide with release of CO_2. There are several reports on the preparation of proline *N*-carboxyanhydride.[88] We followed the operation with phosgene as reagent, which led to the proline *N*-carboxyanhydride quantitatively.

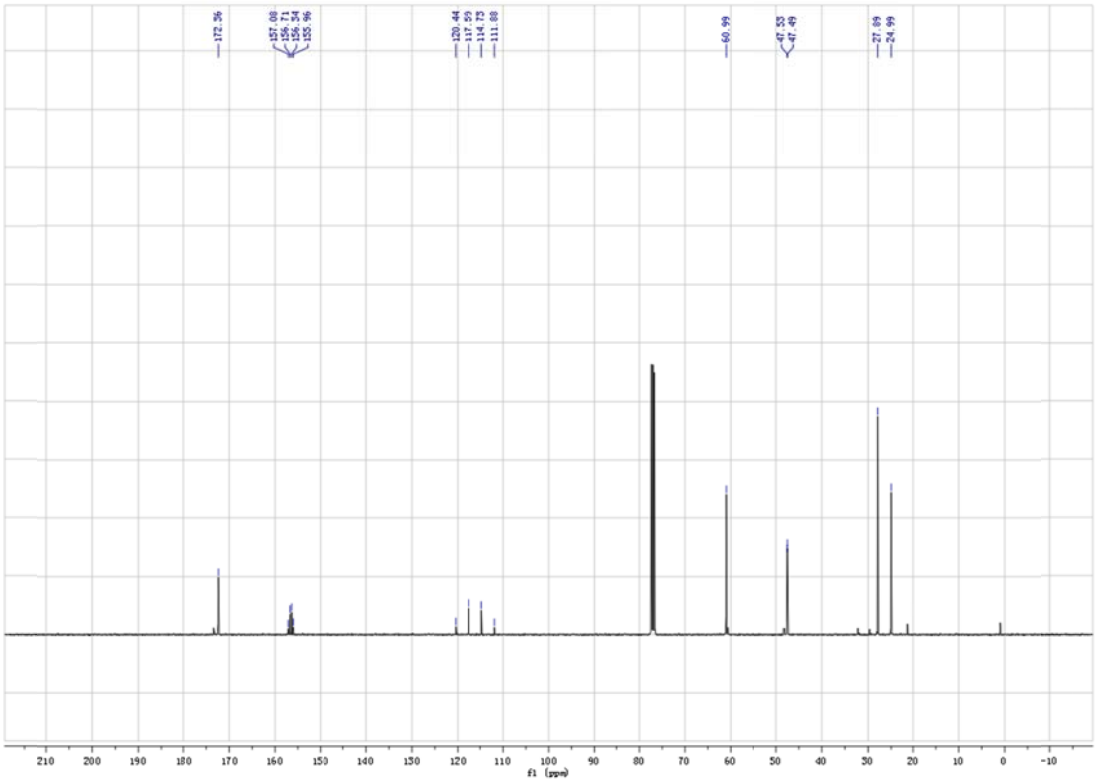
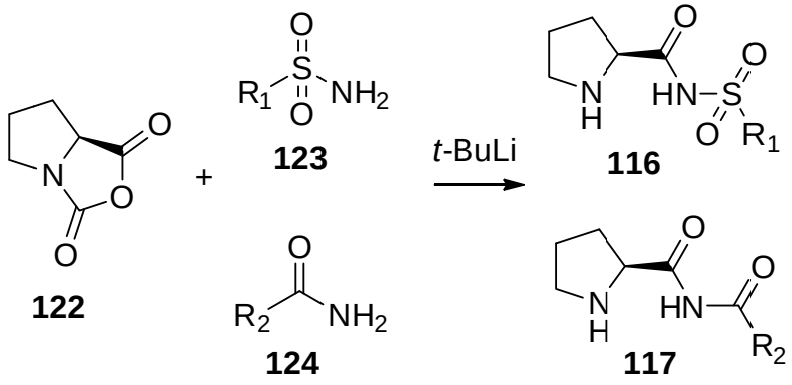


Figure 3. ^{13}C NMR of *N*-(trifluoroacetyl)-*L*-proline amide

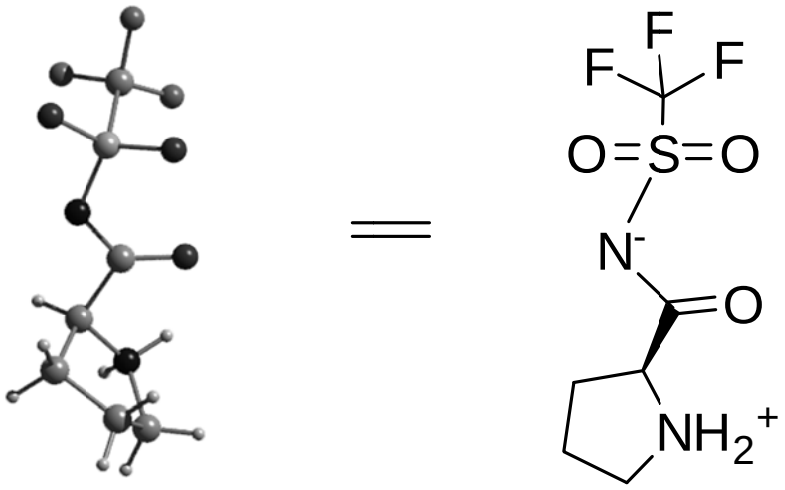
The solution was directly used without further purification for the next step. In order to activate the nucleophile, *t*-BuLi has been used to deprotonate the trifluoromethyl amide in THF at -78 ^{o}C. After the reaction, the desired target compound was obtained in 45% yield. Besides a correct mass spectrum, NMR analysis confirmed the structure: there are quartet peaks of CF_3 in 120.4, 117.5, 114.7, 111.8 ppm in ^{13}C NMR and there is a single peak in -72.8 ppm for the fluorine atoms in ^{19}F NMR.



Scheme 36. The imide and sulfonamide synthesis starting from proline anhydride

After the easy preparation of *N*-(trifluoroacetyl)-*L*-proline amide by this new route, this method was used for the synthesis of other imides, and also proline sulfonamide derivatives could be successfully obtained by this method.

The crystalline *N*-trifluoromethylsulfonyl-*L*-proline amide has been analyzed by X-Ray. The result is shown in scheme 37. The pyrrolidine function is protonated whereas the trifluoromethylsulfonylamide group is deprotonated due to the high acidity of trifluoromethylsulfonyl amide group. This is consistent with the results of Berkessel for other related sulfonamides [83].



Scheme 37. X-Ray structure of *N*-trifluoromethylsulfonyl-*L*-proline amide

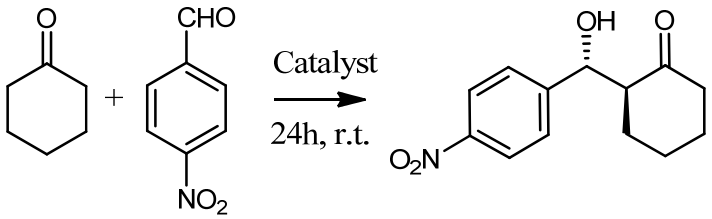
3.2.3 The tests with proline amide organocatalysts

For testing the catalytic activity of the *L*-proline amide derivatives, we used the standard model aldol reaction with 4-nitrobenzaldehyde and cyclohexanone in DMSO (Table 5). As in the known examples the main product is the anti isomer with 2*R*, 1'*S*-configuration.[89] The results obviously showed that the catalysts with sulfonamide structure gave much better yield and selectivity than the catalysts with carboxyl imide structure (Table 5). With *N*-(trifluoroacetyl)-*L*-proline amide, we also observed the aldol condensation product as Wang[84] reported, but as the main product we isolated the unsaturated condensation product. In the other cases aldol condensation reaction did not occur under the described conditions at room temperature. With

N-(trichloroacetyl)-*L*-proline amide, there was only very low selectivity observed in the reaction. (entry 5, Table 5) and the reactions with *N*-pivaloyl-*L*-proline amide and *N*-benzoyl-*L*-proline amide gave almost no product. After some TFA was added to the reaction, nearly racemic product was observed. It can be supposed that the acidity of the side chain is very important for both the yield and selectivity. When the additional acid is added, the free acid can catalyze the reaction leading to a racemic product

In accordance with our expectation, the most acidic proline amide - *N*-trifluoromethylsulfonyl-*L*-proline amide - proved to be the best catalyst in the model reaction in DMSO, but unexpectedly gave even better results in dichloromethane (DCM) and water (entries 10 and 11, Table 5). Whereas in DCM the reaction phase is still homogeneous, in pure water a two phases system is observed, but this has no significant effect on the reactivity and selectivity. With *N*-trifluoromethylsulfonyl-*L*-proline amide the anti/syn ratio of 96/4 in both solvents was the highest of all tested catalysts and with 92 % ee in DCM and 93 % ee on water the best enantioselectivity was detected (entries 10 and 11, Table 5). The catalyst *N*-(2,2,2-trifluoroacetyl)-*L*-proline amide has also been used in the reaction with DCM and water as solvent, however the selectivity and yield of the reactions were not greatly increased.

Table 5. Screening of organocatalysts for the aldol reaction[a].



4a **48a** **100a**

Entry	Catalyst	Solvent	Catalyst [mol%]	Yield [%][b]	anti /syn[c]	ee[%] (major)[d]
1	**116a**	DMSO	30	58	88/12	82
2	**116b**	DMSO	30	54	73/37	61
3	**116c**	DMSO	30	64	94/6	85

Entry	Catalyst	Solvent	Catalyst [mol%]	Yield [%][b]	anti /syn[c]	ee[%] (major)[d]
4	**117a**	DMSO	30	33	58/42	20
5	**117b**	DMSO	30	22	56/44	13
6	**117c**	DMSO	30	Trace	ND	ND
7	**117d**	DMSO	30	Trace	ND	ND
8[e]	**117c**	DMSO	30	14	55/45	4
9[e]	**117d**	DMSO	30	12	56/44	5
10[f]	**116c**	DCM	30	58	96/4	92
11[g]	**116c**	H_2O	30	64	96/4	93
12[f]	**117a**	DCM	30	18	55/45	23
13[g]	**117a**	H_2O	30	13	56/44	24

[a] The reaction was performed with **116** or **117** (0.15 mmol), **4a** (0.51 mL, 5.0 mmol) and **48a** (76 mg, 0.5 mmol), DMSO (1 mL), and at room temperature.

[b] Combined yields of isolated diastereomers.

[c] Determined by ^{1}H NMR of the crude product.

[d] Determined by chiral-phase HPLC analysis of the major product.

[e] The reaction is with 10 mol% TFA.

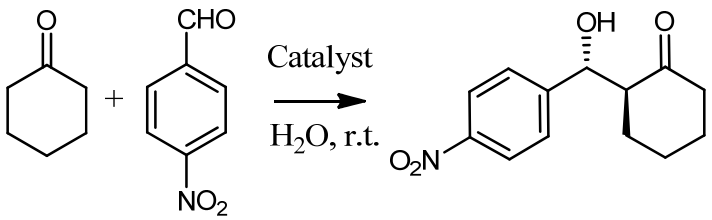
[f] The reaction was performed with 1mL DCM as solvent.

[g] The reaction was performed with 1mL H_2O as solvent.

With these promising results for the trifluoromethylsulfonamide derivative **116c** of proline as an effective catalyst for the aldol reaction on water, the influence of catalyst loading, the water volume, the amount of ketone and the reaction time were studied. We tested 30, 20, 10 and 5 mol% catalyst loading in water under the standard conditions in the model reaction. As expected the reaction rate is obviously affected by the loading amount (Table 6), the medial rate was observed with 30 mol% of catalyst leading after 24h to a high yield of 64% (entry 1, Table 6), whereas the reaction with 10 mol% loading gave 63% yield compared to 60% with 5 mol% loading after 72h (entries 3 and 5, Table 6), showing that higher catalyst loading or longer reaction time will raise the yield. The reaction with 5 mol% catalyst resulted only in a little lower enantioselectivity (96%) than with 10 mol% (entry 7, Table 6). After this, we tested the dependence of the reaction from water volume, and found that the result is similar

between 110 equiv. and 55 equiv. water. Decreasing the excess of ketone had only little influence on selectivity. With 10 mol% catalyst, the highest enantiomeric excess (99%) was reached with 10 equiv. as well as with 2 equiv. of ketone (entries 5 and 13, Table 6). Therefore it should be pointed out that a decrease in the catalyst loading had no significant impact on the enantioselectivity and large excess of ketone is not necessary for high yield and selectivity. As a reference, *N*-(2,2,2-trifluoroacetyl)-*L*-proline amide was also introduced in the test. The reactions with *N*-(2,2,2-trifluoroacetyl)-*L*-proline amide gave low yield with catalyst amount decreasing. With 10 mol%, the reaction gave only trace product, while the reaction with *N*-trifluoromethylsulfonyl-*L*-proline amide gave yield over 60%, proving again that the acidity of the catalyst is important for the yield and selectivity.

Table 6. Screening of conditions for the aldol reaction [a]



4a **48a** **100a**

Entry	Catalyst	Catalyst [mol%]	Time [h]	Yield [%][b]	anti /syn[c]	ee[%] (major)[d]
1	**116c**	30	24	64	96/4	93
2	**117a**	30	24	13	56/44	24
3	**116c**	20	48	63	91/9	94
4	**117a**	20	48	8	52/48	22
5	**116c**	10	72	60	96/4	99
6	**117a**	10	72	Trace	ND	ND
7	**116c**	5	72	48	90/10	96
8	**117a**	5	72	Trace	ND	ND
9[e]	**116c**	10	72	77	95/5	97
10	**117a**	10	72	Trace	ND	ND
11[f]	**116c**	10	72	67	97/3	98

Entry	Catalyst	Catalyst [mol%]	Time [h]	Yield [%][b]	anti /syn[c]	ee[%] (major)[d]
12	**117a**	10	72	Trace	ND	ND
13[g]	**116c**	10	72	64	97/3	99
14	**117a**	10	72	Trace	ND	ND

[a] The reaction was performed with **116c** or **117a**, **4a** (0.51 mL, 5.0 mmol) and **48a** (76 mg, 0.5 mmol), water (1 mL), and at room temperature.

[b] Combined yields of isolated diastereomers.

[c] Determined by ^{1}H NMR of the crude product.

[d] Determined by chiral-phase HPLC analysis of the major product.

[e] Reaction in 0.5mL water.

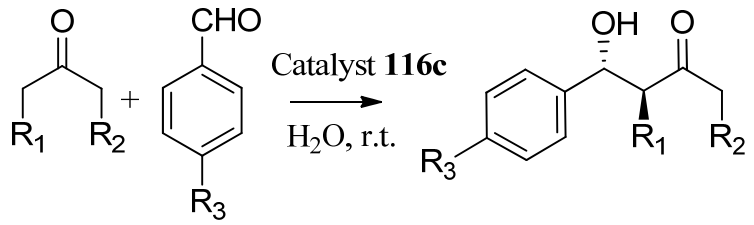
[f] Reaction in 0.5mL water with 2.5mmol cyclohexanone.

[g] Reaction in 0.5mL water with 1mmol cyclohexanone.

Getting the highest enantioselectivity in the reaction on water with 10 mol% loading of *N*-trifluoromethylsulfonyl-*L*-proline amide, we further studied the aldol reaction with different ketones and aldehydes under these conditions. We found out that the enantioselectivity for cyclopentanone and acetone is also high but lower than for cyclohexanone (Table 7). For different aromatic aldehydes, the *p*-chloro and *p*-methoxy substitution reduced the aldehyde activity - as expected - giving lower yield, the selectivity, however, was not affected.

Finally we elaborated a procedure for catalyst recycling utilizing another advantage of the trifluoromethyl group. After reaction, diethyl ether (10 mL) and water (5 mL) was added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with ether (2×10 mL). Then, the aqueous layers were collected, and water was removed by lyophilization. The remaining is the pure catalyst as revealed by NMR analysis. The recycling rate can easily reach over 90%, higher than other catalysts [90]. The activity of recycled **116c** exhibited almost no change in the test (entries 6 and 7, Table 7).

Table 7. Direct aldol reaction of substituted benzaldehydes with ketones catalyzed by organocatalyst **116c**[a]



4 **48** **100a-104a**

Entry	R_1	R_2	R_3	Product	Yield [%][b]	anti /syn[c]	ee[%] (major)[d]
1	-$(CH_2)_3$-		NO_2	**100a**	64	97/3	99
2	-$(CH_2)_2$-		NO_2	**101a**	54	97/3	94
3	H	H	NO_2	**102a**	55		86
4	-$(CH_2)_3$-		Cl	**103a**	43	99/1	97
5	-$(CH_2)_3$-		OCH_3	**104a**	42	97//3	91
6[e]	-$(CH_2)_3$-		NO_2	**100a**	58	98/2	98
7[f]	-$(CH_2)_3$-		NO_2	**100a**	61	97/3	98

[a] The reaction was performed with **116c** (10 mol%), **4** (1.0 mmol) and **48** (0.5 mmol), water (0.5 mL), and at room temperature for 72h.

[b] Combined yields of isolated diastereomers.

[c] Determined by ^{1}H NMR of the crude product.

[d] Determined by chiral-phase HPLC analysis of the major product.

[e] The reaction was performed with **116c (**10 mol%**)** recycled after use in entry 1, compounds **4**, **48** and water with the same moleratio with entry 1 .

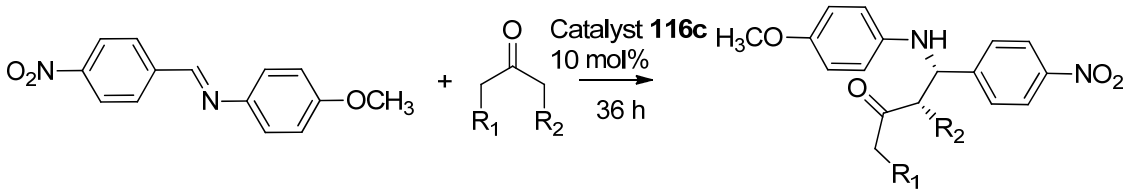
[f] The reaction was performed with **116c (**10 mol%**)** recycled after use in entry 6, compounds **4**, **48** and water with the same mole ratio with entry 1.

After aldol reaction, Mannich reaction was also tested. Firstly, the different racemic products of the Mannich reaction were synthesized with the method reported.[91] After the analysis of synthesized racemic products with our chiral HPLC, only two racemic products can be separated. So, only two Mannich products were utilized in the following process. In the test, the catalyst *N*-(trifluoromethyl) sulfonyl-*L*-proline amide

was used. The Mannich reaction was done firstly in DMSO.

From the results in Table 8, it can be found that the selectivity is low and the product **126a** is nearly racemic. However, the diastereoselectivity is very high (89/11). (entry1, Table 8) The selectivity of product **126b** is much higher than **126a** under the corresponding conditions. The highest selectivity of the product is 98% ee which is

Table 8. Mannich reaction with ketones catalyzed by catalyst **116c** [a]



125 **4** **126**

Entry	R_1	R_2	Catalyst	Solvent	Product	Yield [%][b]	syn/ anti [c]	ee[%] (major)[d]
1	-$(CH_2)_3$-		**116c**	DMSO	**126a**	64	89/11	5
2	H	H	**116c**	DMSO	**126b**	68		98
3[e]	-$(CH_2)_3$-		**116c**	DCM	**126a**	58	64/36	0
4[f]	H	H	**116c**	DCM	**126b**	61		94
5	-$(CH_2)_3$-		**116c**	H_2O	**126a**	89	79/21	0
6	H	H	**116c**	H_2O	**126b**	93		0
7[g]	-$(CH_2)_3$-		*L*-proline	DMSO	**126a**	55	90/10	5
8[g]	H	H	*L*-proline	DMSO	**126b**	60		87

[a] The reaction was performed with **116c** (0.15 mmol), **4** (5.0 mmol) and **125** (0.128g, 0.5 mmol), DMSO (1 mL), and at room temperature.

[b] Combined yields of isolated diastereomers.

[c] Determined by ^{1}H NMR of the crude product.

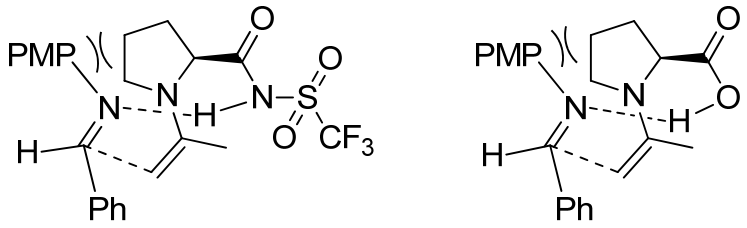
[d] Determined by chiral-phase HPLC analysis of the major product

[e] The reaction was performed with 1mL DCM as solvent.

[f] The reaction was performed with 1mL H_2O as solvent.

[g] The reaction was performed with *L*-proline (0.15 mmol), **4** (5.0 mmol) and **125** (0.128g, 0.5 mmol), DMSO (1 mL), and at room temperature.

much higher than *L*-proline under the same condition (87% ee). (entries 2 and 8, Table 8) From the screening of the reaction conditions, it can be found that the selectivity of product formation is going down in water, in which the same catalyst gave higher selectivity for aldol reaction. The possible transition state has been given in the report by List[92]. The selectivity is governed by steric hindrance. The enamine attack of the imine from *re*-face would result in unfavorable steric interactions between the pyrrolidine and the aromatic ring.



Scheme 38. The transition state of Mannich reaction with catalyst **116c** and *L*-proline

3.2.4 Conclusion

In conclusion, a simple way has been developed to synthesize proline imide and sulfonimide derivatives from *L*-proline-NCA. By this route we have prepared a novel proline trifluoromethylsulfonimide derivative, which turned out to be an efficient organocatalyst for asymmetric aldol reactions on water. Compared with other prolinamide-based catalysts, better yields (77%) and higher enantioselectivities (up to 99% ee) were obtained by using 10 mol% of the catalyst in water. Besides this, a simple recycling procedure of this catalyst could be established with a recovering rate higher than 90%. As has been found for other prolinamide-based catalysts this catalyst can be expected to be well suited for other organocatalytic reactions like Mannich reactions. When testing with Mannich reaction, we found that proline trifluoromethylsulfonimide derivative is also a very good catalyst. High selectivity (98% ee) and yield (93%) of Mannich product have been obtained. The results are better than those from *L*-proline.

Comparing these proline amide catalysts, it can be found that the catalyst with strong electron with-drawing groups can give better yield and higher selectivity in aldol

reactions. Comparing the results from different sulfonamide proline derivatives it can be found that other factors such as bulky groups play less important roles in selectivity than the acidity of catalysts. This is extremely obvious on comparing the results from proline sulfonamide derivatives and proline imide derivatives.

3.3 Novel proline imidazole derivatives as organocatalysts

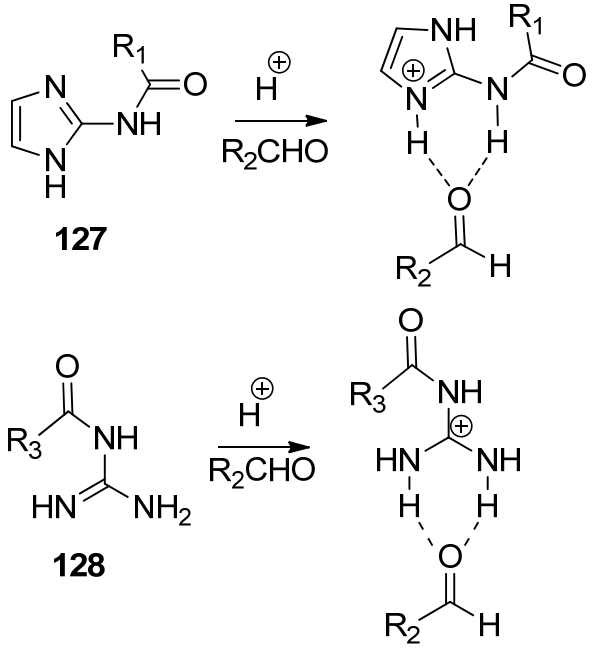
3.3.1 The design of imidazole derivatives

Based on the results of the last section, it can be assumed that the acidity of the catalyst plays a very important role in yield and selectivity. Unfortunately the yield with our new catalyst is only moderate. Therefore further modification is necessary to improve the yield and keep the high selectivity. In order to solve this problem, the activation mode for proline catalysis through enamine intermediate formation has been taken in consideration. In the catalytic cycle, the proton from the carboxyl group plays a crucial role in the rate-determining step.[93] So, the modification of the acid group might be of value. The method to increase the acidity of our catalysts by different electron-withdrawing groups is not a good choice because of some disadvantages. The obvious one is the limitation in the electron-withdrawing ability of different substituents. As we know, CF_3 is already one of the strongest electron-withdrawing groups. Furthermore, the substitution of CF_3 by other groups is possible but the synthesis of such compounds might be more difficult.

After intense search, imidazole systems have drawn our attention, as imidazole has a bifunctional structure with Brönsted acid (acidic proton on *N*-1) and Brönsted base (imine) sites and is incorporated in many important biological molecules.[94] The imidazole ring is an aromatic system which when protonated leads to a symmetric system with a possible hydrogen bond which may have a better chance in controlling and activating carbonyl groups than other catalysts with amide or protonated amine functions.

Imidazole systems as organocatalysts have been introduced for a long time. There are a number of reports where an imidazole ring in a *N*-heterocyclic carbene (NHC) can catalyze various reactions.[95] Besides this, an imidazole ring has been introduced to

other chiral scaffolds as organocatalysts.[96, 97, 98] However, the most widely adopted approach is to introduce chiral substituent(s) to imidazole, which lead to adducts with complicated structure and/or chemically labile bond. In the past it was often difficult to build the linkage between the imidazole and the chiral scaffold.[96] This strategy has limited the application of imidazole in organocatalyst, resulting in imidazole only working as a confined moiety for aldol reaction. So, 2-aminoimidazole derivatives were chosen, because the amide bond can be easily built to connect imidazole with the chiral scaffold and the proton of the amide can also help to activate the oxygen of a carbonyl by hydrogen bonding (Scheme 39).

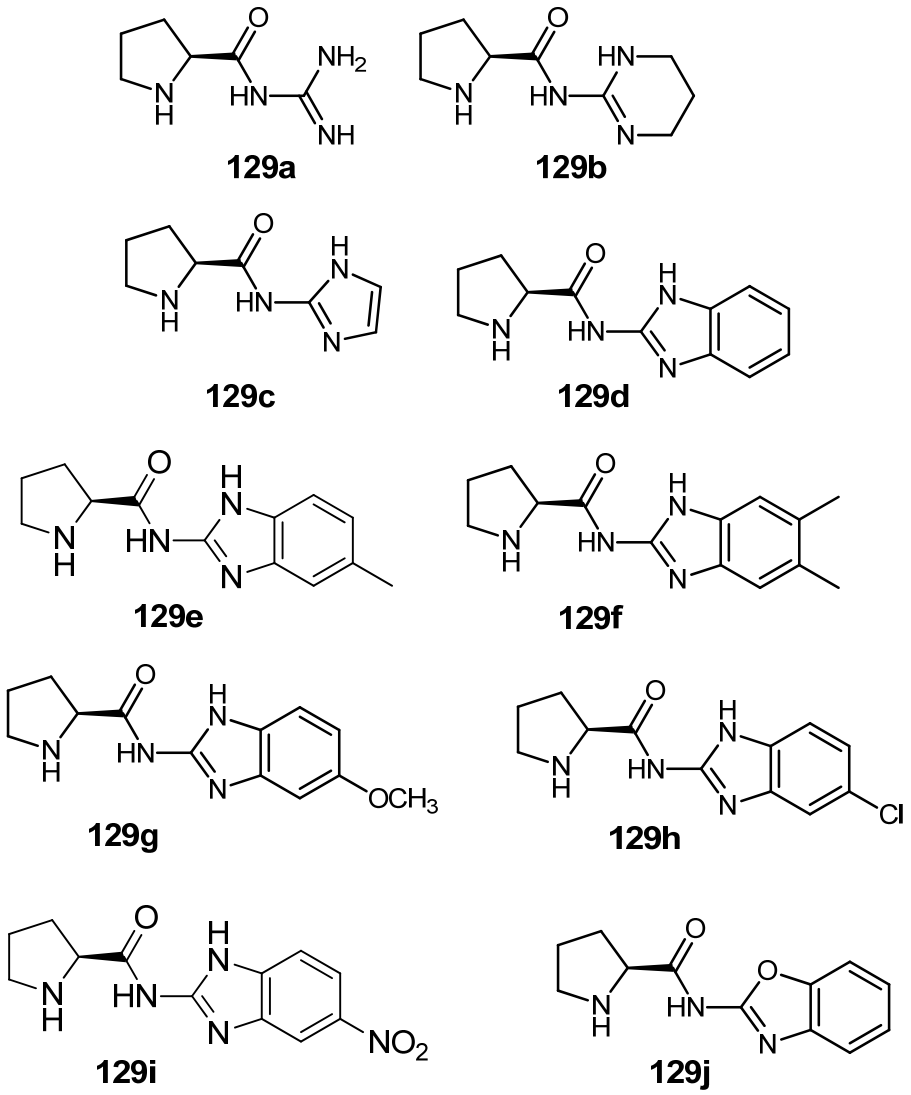


Scheme 39. The proposed imidazolium and guanidinium activation mode

So, based on this, a series of imidazole and guanidine derivatives have been designed as new organocatalysts. Three guanidine derivatives have been considered with different steric hindrance at the nitrogen atom of guanidine. Another seven imidazole derivatives have been chosen with different substituents. Several derivatives with electron with-drawing groups, with electron donating groups or without substituents on the benzene ring have been designed to research the effect. Another derivative with benzo[*d*]oxazol-2-amine, which has a similar structure as 2-aminoimidazole, has been chosen for comparison (Scheme 40).

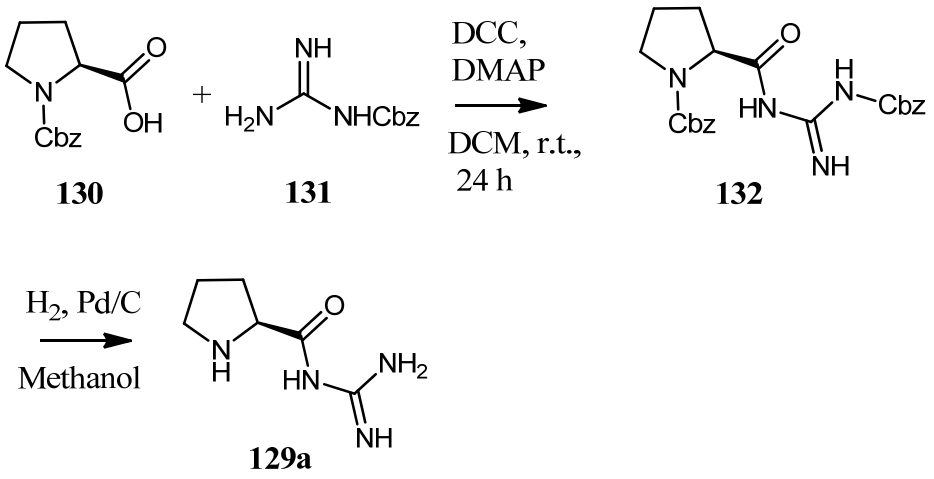
3.3.2 The synthesis of imidazole and guanidine derivatives

When searching for syntheses for the designed systems, it was found that in the literature there were not many reports about these compounds. Only after we had synthesized the imidazole compounds, the synthesis of derivatives of a proline derived with imidazole was reported.[99]



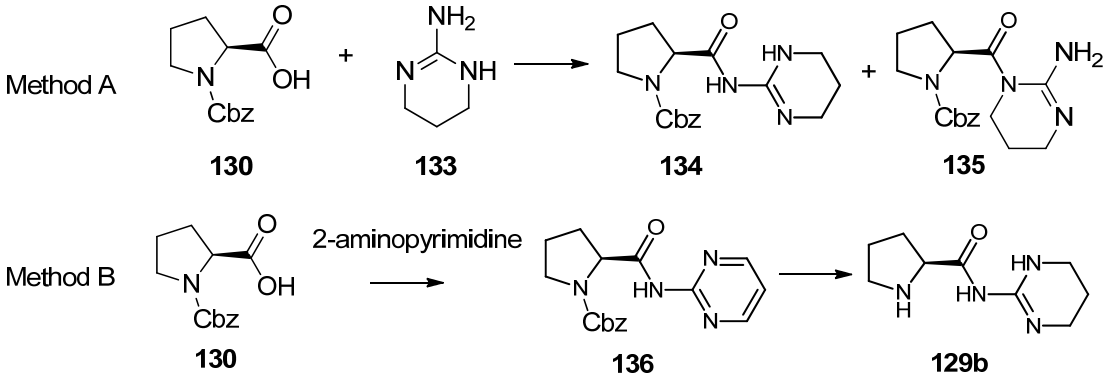
Scheme 40. The synthesized imidazole and guanidine systems

The synthesis of guanidine derivatives was planned in a straightforward manner starting from protected proline.



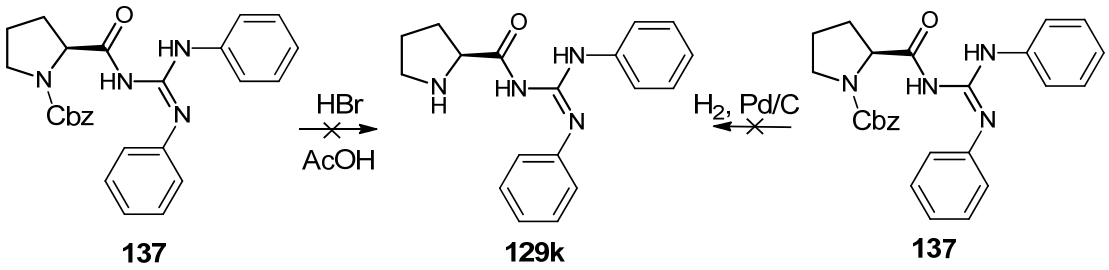
Scheme 41. The synthesis of guanidine proline derivatives

Considering the protection group according with Cbz-*L*-proline, Cbz was chosen as the protection group of guanidine. Besides this, the deprotection of Cbz with H_2 is operated in neutral condition, not in trifluoroacetic acid. *N*-Cbz-Guanidine was synthesized from guanidine hydrochloride according to a literature method. To guanidine hydrochloride (1 equiv.), which was dissolved in aqueous sodium hydroxide (2 equiv.), benzyl chloroformate (1 equiv.), which was dissolved in 1,4-dioxane, was added dropwise to the guanidine solution with vigorous stirring at 0 ^{o}C. The product was isolated as a white solid in 88% yield. After this, *N*-Cbz-Guanidine and *N*-carbobenzyloxy-*L*-proline, DCC, DMAP reacted in dry DCM for 24 hours. Then the protection group was removed by H_2, Pd/C. The target product could be obtained after purification in 90% yield.



Scheme 42. Possible routes to (*S*)-*N*-(1,4,5,6-tetrahydropyrimidin-2-yl) pyrrolidine-2-carboxamide

For the synthesis of (*S*)-*N*-(1,4,5,6-tetrahydropyrimidin-2-yl) pyrrolidine-2-carboxamide, two routes have been considered (Scheme 42). In the first route, the 1,4,5,6 -tetrahydropyrimidine-2-amine should directly be introduced, however Cbz-*L*-proline could react with two amine sites (NH_2 and NH). As the selectivity seemed to be a problem, this method was not acceptable. Therefore, 2-amino-pyrimidine was reacted with Cbz-*L*-proline, followed by reduction of the pyrimidine. In fact, it was found that the 2-amino-pyrimidine can be reduced with H_2, Pd/C with catalytic amount acid at room temperature. Under these conditions, the Cbz protection group of the proline can be removed also.



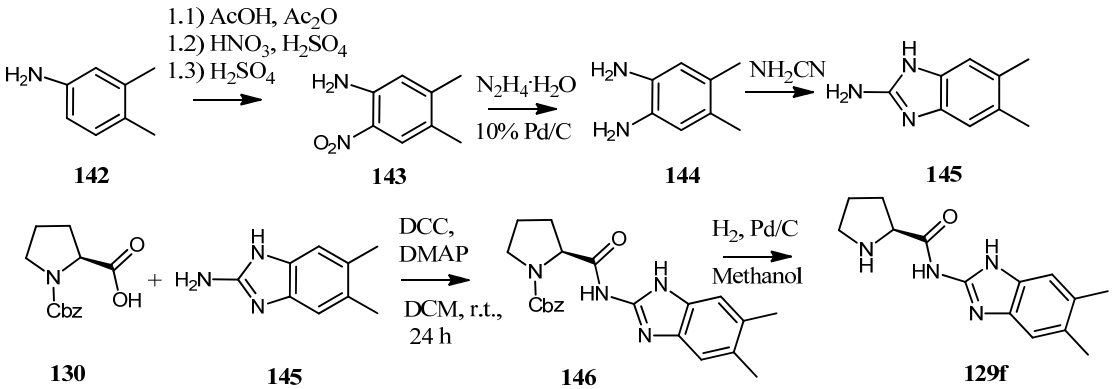
Scheme 43. The synthesis of (*S*)-*N*-(*N,N*'-diphenylcarbamimidoyl)pyrrolidine-2-carboxamide by Cbz deprotection.

In the synthesis of (*S*)-*N*-(*N, N*'-diphenylcarbamimidoyl) pyrrolidine-2-carboxamide, difficulties in the deprotection step occurred. The reaction between Cbz-*L*-proline and 1, 2-diphenylguanidine went well by coupling with DCC and DMAP. The product has been confirmed by NMR and MS. When the deprotection with H_2, Pd/C was tried, the phenyl groups at the guanidine could not be found from the ^{1}H NMR. It looks as if the phenyl group has also been removed by H_2.When using another method for the deprotection of the Cbz group with HBr in AcOH, also no target product could be found. So, the synthetic route was changed starting with proline *N*-carboxyanhydride and 1,2-diphenylguanidine. However, after the reaction in -78 ^{o}C no target product could be detected in the NMR and LCMS analysis. Therefore this structure was abandoned.

2-Aminoimidazole and 2-aminobenzimidazole are commercially available and the

reaction with Cbz-*L*-proline followed the same operation as with the proline guanidine derivatives. However the other derivatives had to be synthesized first. 5-Methyl-1*H*-benzo[*d*]imidazol-2-amine was prepared according to a method of Krommer by the reaction of benzene-1,2-diamine with cyanamide.[100]

The intermediate 5, 6-dimethyl-1*H*-benzo[*d*]imidazol-2-amine was synthesized from 3, and 4-dimethylaniline. Firstly, 3, 4-dimethylaniline was acylated with acetic anhydride under acidic conditions for protection. Mild nitration conditions with 65 % nitric acid, and 98% sulphuric acid have been used to reduce the formation of side products [101]. After the nitration, the removal of the acetyl group was done by hot sulphuric acid to yield the 4, 5-dimethyl-2-nitroaniline. For the reduction of the nitro group, several methods have been reported, such as $SnCl_2$, with H_2 at high pressure or with Fe. We used another method with $N_2H_4 \cdot H_2O$, Pd/C to reduce the nitro group.



Scheme 44. The synthesis of *N*-(5,6-dimethyl-1*H*-benzimidazol-2-yl)-*L*-prolinamide

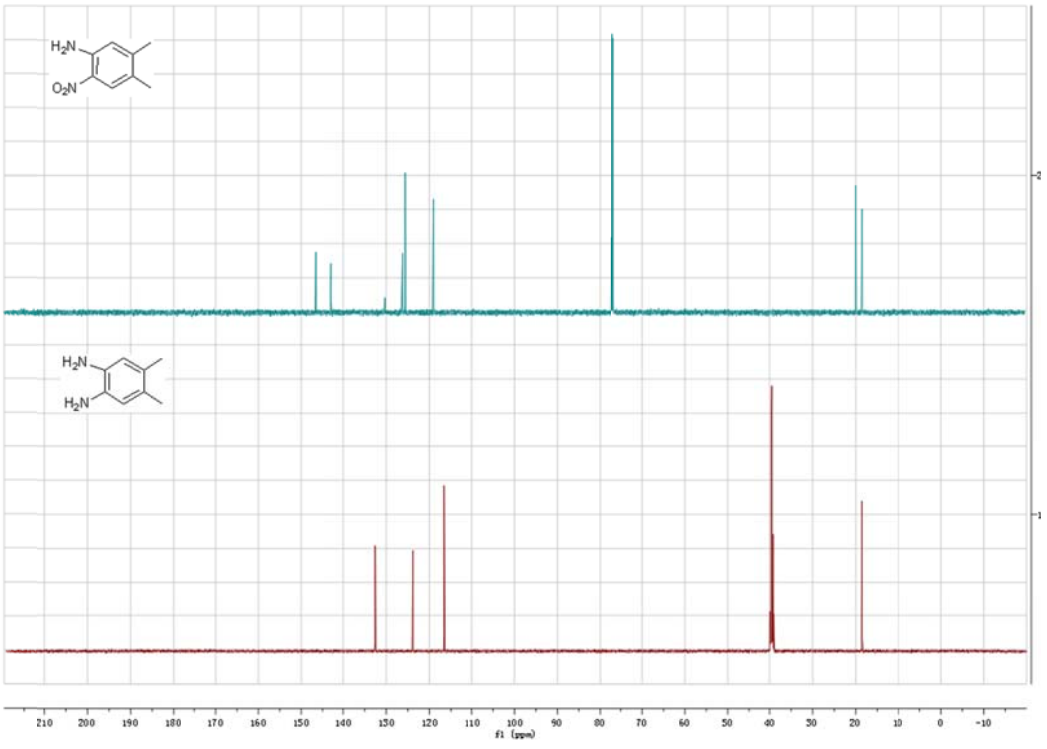
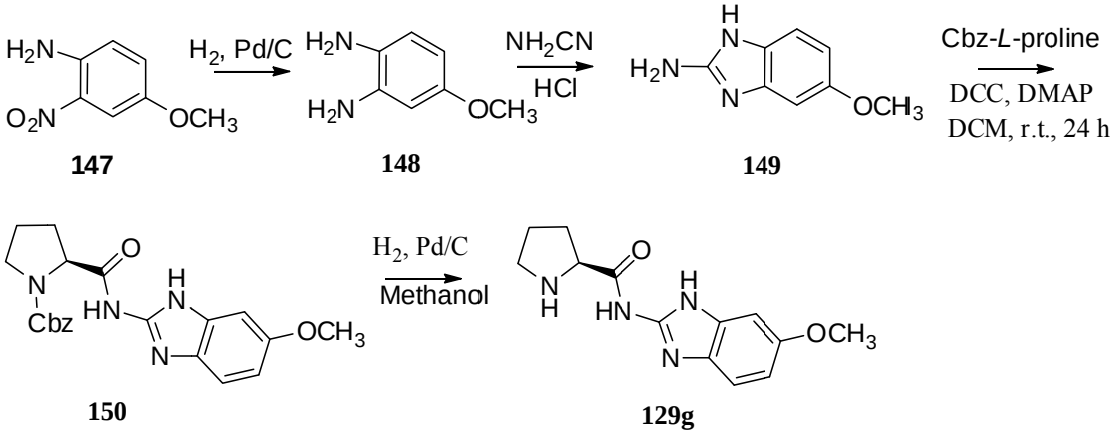


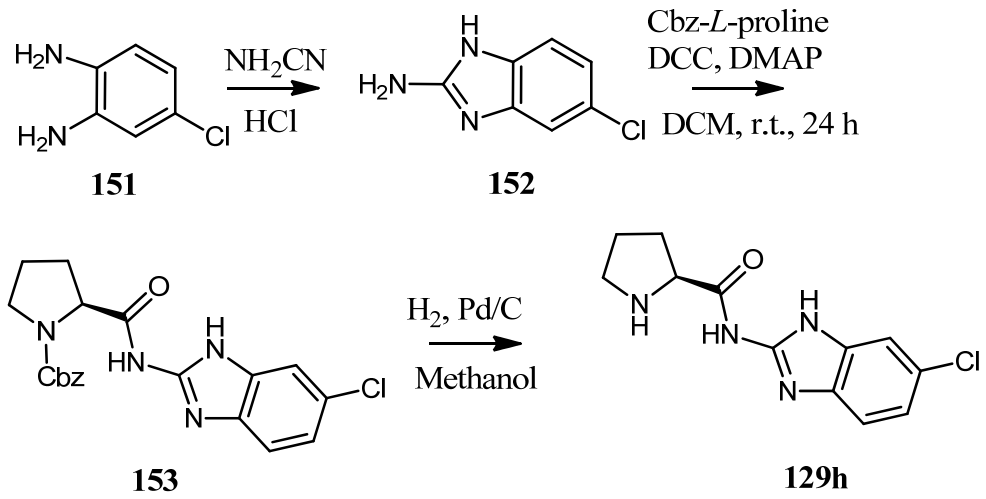
Figure 4. The ^{13}C NMR of **143** and **144**



Scheme 45. The synthesis of *N*-(5-methoxy-1*H*-benzimidazol-2-yl)-*L*-prolinamide

The intermediate 5-methoxy-1*H*-benzo[*d*]imidazol-2-amine is synthesized from 4-methoxy-2-nitroaniline. Following earlier research, the reduction of 4-methoxy-2-nitroaniline to 4-methoxybenzene-1,2-diamine was performed with H_2, Pd/C in methanol.[102] After this, the product was reacted with cyanamide leading to the corresponding 2-aminoimidazole derivative.

The yield of this reaction is lower than with the methyl substituted imidazole derivatives in this step. The same reaction sequence could be successfully followed for



Scheme 46. The synthesis of *N*-(5-chloro-1*H*-benzimidazol-2-yl)-*L*-prolinamide

the synthesis of 5-chloro-1*H*-benzo[*d*]imidazol-2-amine starting with 4-chlorobenzene -1,2-diamine. The reaction with Cbz-*L*-proline and the deprotection were done like for the other derivatives.

The synthesis of intermediate 5-nitro-1*H*-benzo[*d*]imidazol-2-amine was going on with 4-nitrobenzene-1,2-diamine and cyanamide. The coupling with Cbz-*L*-proline was done with DCC and DMAP. However, there were some problems with the Cbz deprotection. When we tested the deprotection with H_2, Pd/C at room temperature, after the reaction and purification, the analysis of ^{13}C NMR revealed that the product was not the target product, because the carbon at position 11 should be at about 140 ppm, not as observed at 125.3 ppm. The carbon peak had moved to higher field indicating that the nitro group has been reduced by H_2, Pd/C to the amine. After the detailed analysis with NMR, the product was also checked with LCMS. A peak at 246.1(M+ H^+) confirmed that the product from H_2 reduction is the amine product. However, in this compound there are two amine groups, complications may occur when using it for organocatalysis.[103] Therefore this structure will not be included in the tests.

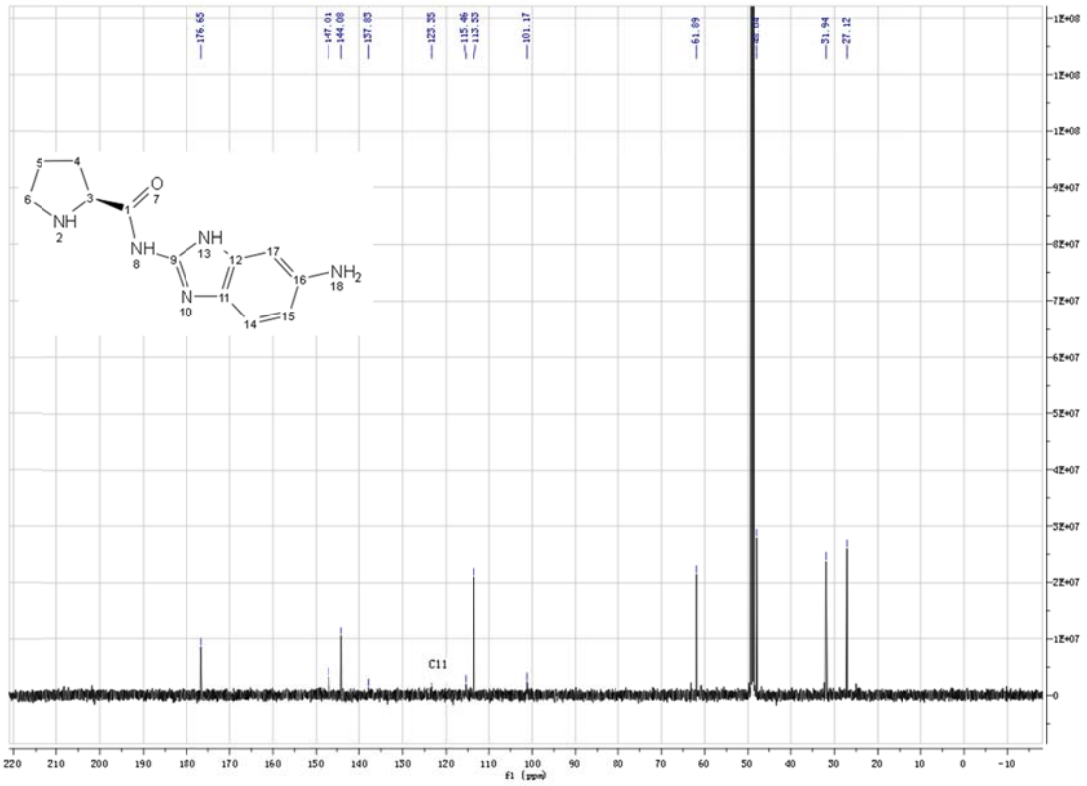
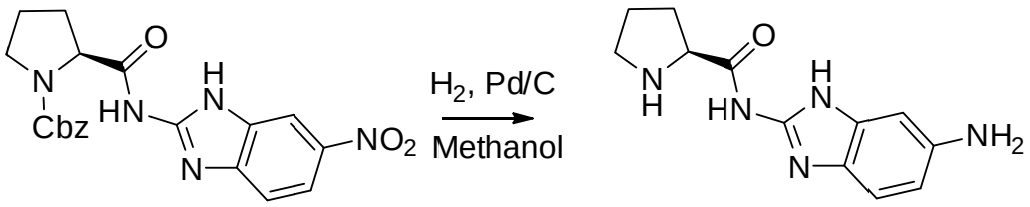


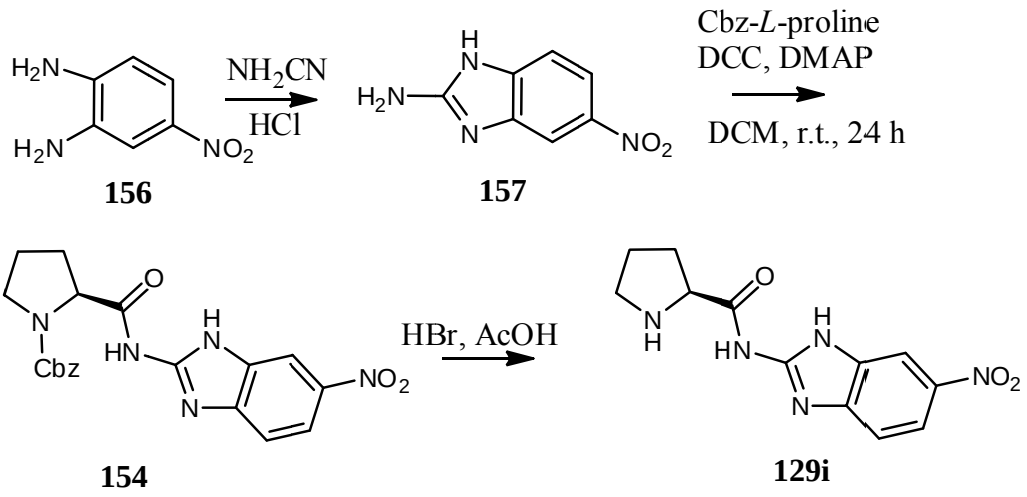
Figure 5. The ^{13}C NMR of *N*-(5-amino-1*H*-benzimidazol-2-yl)-*L*-prolinamide



154 **155**

Scheme 47. Cbz deprotection and NO_2 reduction with H_2

In order to get the wanted product, another Cbz deprotection method was considered as a better choice. On treatment with HBr in acetic acid, however , after deprotection the free secondary amine of pyrrolidine will combine with excess of HBr or acetic acid and the imidazole will also be protonated. In order to get the free amine compound, two equivalents of $NaHCO_3$ solution were used to wash the DCM solution of the product. After purification, the analysis of the product with NMR and MS confirmed it as the target compound.



Scheme 48. The synthesis *N*-(5-nitro-1*H*-benzimidazol-2-yl)-*L*-prolinamide

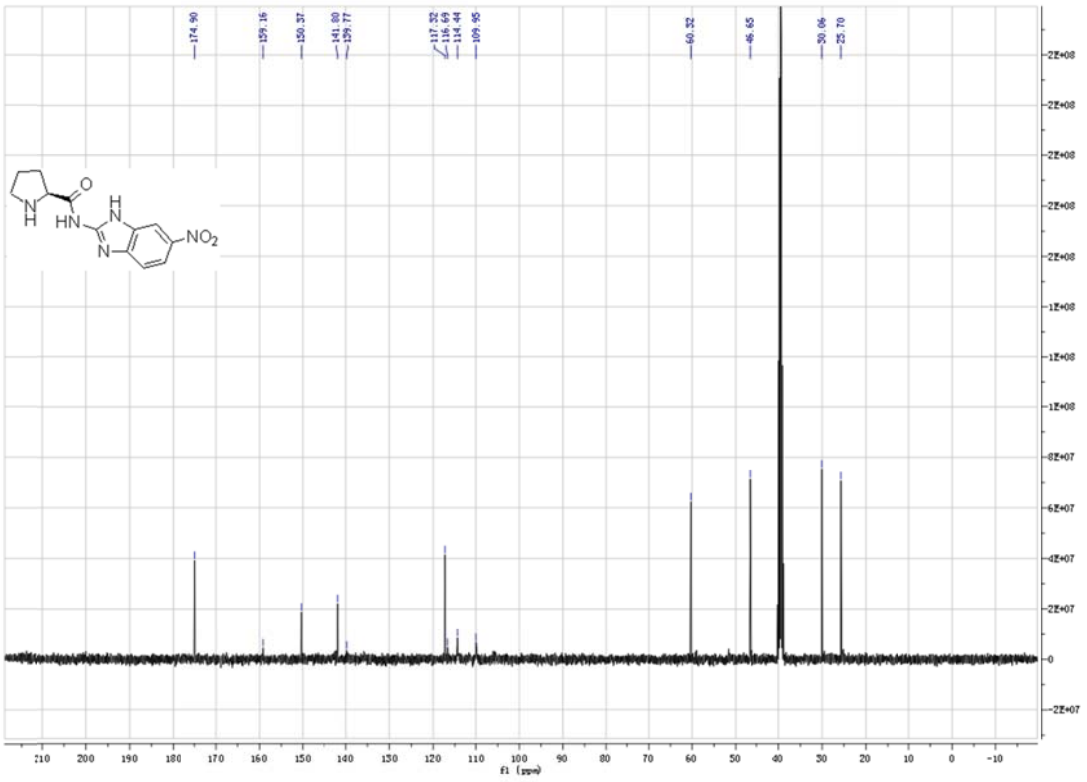
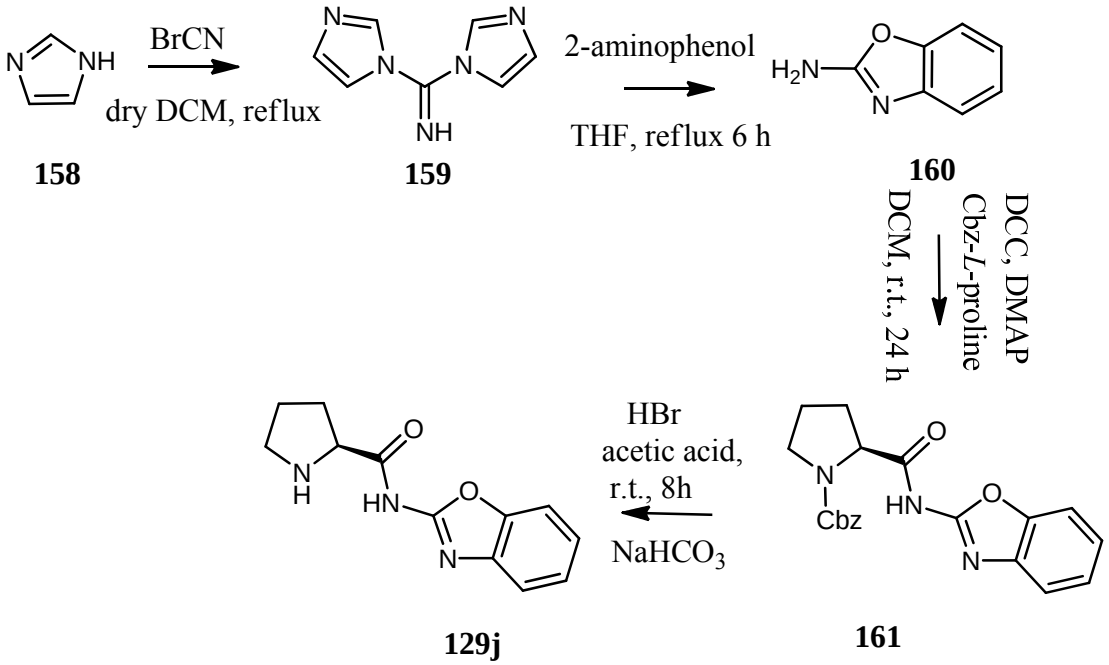


Figure 6. The ^{13}C NMR of *N*-(5-nitro-1*H*-benzimidazol-2-yl)-*L*-prolinamide

In order to obtain 2-aminobenzoxazole, the methods for the synthesis of this compound have been collected and analyzed. There are several methods starting with 2-aminophenol and reacting it with cyanogen bromide[104] or with 1,1'-carbonimidoylbis-1*H*-imidazole[105]. Using 1,3-benzoxazole as starting material and reacting it with hydroxylamine hydrochloride[106] is another method. Considering the

commercial availability and the simple operation, we chose the following route with 1, 1'-carbonimidoylbis-1*H*-imidazole.



Scheme 49. The synthesis of *N*-1,3-benzoxazol-2-yl-*L*-prolinamide

The synthesis of 1,1'-carbonimidoylbis-1*H*-imidazole has been reported many times. We followed the operation of Wu[107] with cyanogen bromide. The imidazole and cyanogen bromide was refluxed in dry DCM for 30 min. Then the mixture was filtrated and the main part of DCM was removed with vacuum. Then the left solution was put in a refrigerator at -20 ^{o}C for two days and the formed crystals were separated by filtration. The analysis with NMR confirmed that it was the wanted product which was collected for the next step.

The following reaction was done in dry THF under N_2 atmosphere under reflux for 6 h. After work up and purification, the product was confirmed by NMR and MS. The coupling reaction between benzo[*d*]oxazol-2-amine and Cbz-*L*-proline was successfully done with DCC and DMAP in dry DCM at room temperature for 24 h. Deprotection could be done with H_2, Pd/C in dry methanol at room temperature for 8 h. After purification, the product was confirmed by NMR and MS.

3.3.3 The tests with organocatalysts of imidazole derivatives

3.3.3.1 In intermolecular aldol reactions

The tests of the different catalysts were done firstly in intermolecular aldol reactions. 4-Nitrobenzaldehyde and cyclohexanone in DMSO were utilized to evaluate the catalysts **129a-129j** (Table 9). The reaction with catalysts **129a- 129j** without added acid gave good yield (40%-87%) but low selectivity (less than 78%) (entries 1-10, Table 9). Especially the catalysts containing guanidine and oxazole gave extreme low selectivity (less than 10 %) (entries 1,2, 10, Table 9). An explanation may be that these catalysts have not the right basicity. When the basicity of the functional group is very weak, then the combination to the added proton is weak and the most part of the catalysis will be done by the free acid. On the other hand, when the functional group is a very strong base which can hold the proton firmly, the activity of the proton will become weak with less tendency to bind to carbonyl group, so that there will be no contribution to increase the selectivity of the product. From the results without extra addition of acid, it can be seen that the reactions with weak acid catalysts give low selectivity in the aldol reaction.

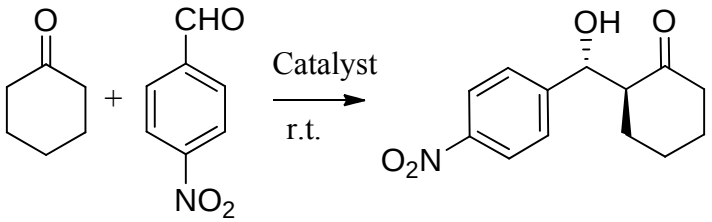
When the same catalysts were applied with added acid even with weak acids like acetic acid, good selectivities of the products have been obtained in the aldol reaction. Catalysts **129c-129h** gave obviously much higher selectivity than without added acid, with enantisoselectivities between 71%-75% ee (entries 13-18, Table 9). Among these catalysts, it can be seen that the substitution of the benzene ring has very little effect on the selectivity of the reaction, even when the substituents on benzene are not symmetric. This result is rather unexpected.

In Table 9 with acetic acid, there are also some unexpected results. The catalyst **129j** containing oxazole exhibited very weak selectivity. Considering the acidity of oxazole, it's pk_a of conjugate acid is 0.8 [108] which is much stronger than imidazole's conjugate

acid (7.05)[109]. The catalyst **129j** should give much higher selectivity than the catalysts with imidazole residues. However, the product was almost racemic (entry 19, Table 9). Obviously the oxazole system as a very weak base has less attraction to the proton, leading to catalysis by the free added acid giving no selectivity. The result from **129i** with acetic acid is also not as usual. With acid the catalyst **129i** gave similar low selectivity, but without acid the selectivity is higher than in the other cases. Probably because the NO_2-group increases the acidity of the system very much, leading to better hydrogen bonding with a carbonyl group.

From the observed selectivity of the catalyzed reactions on addition of acetic acid, it can be seen that the added acetic acid raises the selectivity and the yield but the selectivity is only acceptable not very good. By adding stronger acids, especially trifluoroacetic acid much better results could be obtained with **129a, 129b** and **129i, 129j** as can be expected and can be explained by the discussion above. The catalysts **129c-129h** gave excellent results, indeed with enantioselectivities (ee) over 90% (entries 23-28, Table 9). The yields of most of these reactions were also very high, between 88-93%.

Table 9. Screening added acids and catalysts loading for aldol reaction[a]



4a **48a** **100a**

Entry	Acid	Catalyst	Catalyst [mol%]	Reaction time [h]	Yield [%][b]	anti/syn[c]	ee[%] (major)[d]
1	No	**129a**	10%	48	60	64/36	3
2	No	**129b**	10%	48	63	71/29	5
3	No	**129c**	10%	48	75	65/35	44
4	No	**129d**	10%	48	80	68/32	48
5	No	**129e**	10%	48	83	67/33	55

Entry	Acid	Catalyst	Catalyst [mol%]	Reaction time [h]	Yield [%][b]	anti/syn[c]	ee[%] (major)[d]
6	No	**129f**	10%	48	83	66/34	46
7	No	**129g**	10%	48	87	65/35	45
8	No	**129h**	10%	48	84	63/37	50
9	No	**129i**	10%	48	80	74/26	78
10	No	**129j**	10%	48	40	51/49	3
11	AcOH	**129a**	10%	24	66	45/55	5
12	AcOH	**129b**	10%	24	70	68/32	7
13	AcOH	**129c**	10%	24	77	80/20	71
14	AcOH	**129d**	10%	24	78	83/17	72
15	AcOH	**129e**	10%	24	80	84/16	74
16	AcOH	**129f**	10%	24	83	85/15	75
17	AcOH	**129g**	10%	24	82	84/16	74
18	AcOH	**129h**	10%	24	81	88/12	75
19	AcOH	**129i**	10%	24	83	77/23	0
20	AcOH	**129j**	10%	24	45	55/43	5
21	CF_3COOH	**129a**	10%	24	80	48/52	6
22	CF_3COOH	**129b**	10%	24	83	70/30	5
23	CF_3COOH	**129c**	10%	24	88	78/22	91
24	CF_3COOH	**129d**	10%	24	92	91/9	94
25	CF_3COOH	**129e**	10%	24	90	90/10	92
26	CF_3COOH	**129f**	10%	24	93	92/8	92
27	CF_3COOH	**129g**	10%	24	91	92//8	95
28	CF_3COOH	**129h**	10%	24	92	90/10	93
29	CF_3COOH	**129i**	10%	24	87	81/19	0
30	CF_3COOH	**129j**	10%	24	44	56/44	2

[a] The reaction was performed with catalysts **129a-129j**,with or without same equivalent added acid, **4a** (0.10 mL, 1.0 mmol) and **48a** (151 mg, 1.0 mmol), solvent (DMSO, 0.5 mL) at room temperature.

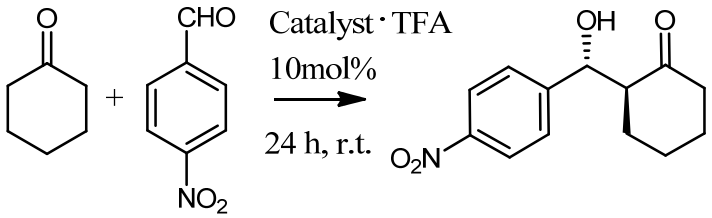
[b] Combined yields of isolated diastereomers.

[c] Determined by ^1H NMR of the crude product.

[d] Determined by chiral-phase HPLC analysis of the anti product.

Summarizing the results in Table 9, it can be concluded that the weak activity of the protonated amine group in **129a**, **129b** gives less control in fixation of the carbonyl group, so that the selectivity of reactions with these catalysts is very low. On the other hand, it has been proven that catalysts with an imidazole functions (except **129i**) are very good catalysts when strong acids are added in equal molar amount.

Table 10. Screening of organocatalysts for the aldol reaction [a]



4a **48a** **100a**

Entry	Catalyst	Solvent	Yield [%][b]	anti/syn[c]	ee[%](anti)[d]
1	**129c**	DMSO	88	78/22	91
2	**129d**	DMSO	92	91/9	94
3	**129e**	DMSO	90	90/10	92
4	**129f**	DMSO	93	92/8	92
5	**129g**	DMSO	93	89/11	94
6	**129h**	DMSO	94	90/10	92
7	**129c**	DCM	93	88/12	82
8	**129d**	DCM	94	76/24	86
9	**129e**	DCM	92	78/22	87
10	**129f**	DCM	94	84/16	88
11	**129g**	DCM	95	80/20	88
12	**129h**	DCM	92	77/23	83
13	**129c**	THF	95	77/23	72
14	**129d**	THF	94	81/19	67
15	**129e**	THF	94	83/17	69
16	**129f**	THF	93	78/22	72
17	**129g**	THF	91	85/15	65

Entry	Catalyst	Solvent	Yield [%][b]	anti/syn[c]	ee[%](anti)[d]
18	**129h**	THF	93	80/20	69
19	**129c**	EtOAc	96	70/30	77
20	**129d**	EtOAc	96	83/17	78
21	**129e**	EtOAc	95	88/12	79
22	**129f**	EtOAc	96	78/22	83
23	**129g**	EtOAc	94	75/25	72
24	**129h**	EtOAc	94	82/18	81
25	**129c**	MeOH	90	90/10	94
26	**129d**	MeOH	92	95/5	92
27	**129e**	MeOH	89	88/12	92
28	**129f**	MeOH	91	94/6	90
29	**129g**	MeOH	92	90/10	92
30	**129h**	MeOH	90	93/7	93
31	**129c**	H_2O	78	92/8	96
32	**129d**	H_2O	85	96/4	98
33	**129e**	H_2O	78	90/10	94
34	**129f**	H_2O	80	94/6	96
35	**129g**	H_2O	81	91/9	96
36	**129h**	H_2O	82	95/5	93
37	**129c**[e]	H_2O/EtOAc	71	94/6	94
38	**129d**[e]	H_2O/EtOAc	85	96/4	98

[a] The reaction was performed with **129c-129h** (0.1 mmol), TFA (0.1 mmol), **4a** (0.51 mL, 5.0 mmol) and **48a** (151 mg, 1.0 mmol), solvent (0.5 mL) at room temperature.
[b] Combined yields of isolated diastereomers.
[c] Determined by ^{1}H NMR of the crude product.
[d] Determined by chiral-phase HPLC analysis of the anti product.
[e] The solvent is 0.25 mL H_2O and 0.25 mL EtOAc.

Based on the promising results with trifluoroacetic acid, further research has been done in the following tests. In order to increase the selectivity, the solvents for the reactions have been screened. Besides the reaction in DMSO, we used other solvents like DCM,

THF, EtOAc, MeOH and also water with catalysts **129c-129h**. Water is widely used as a solvent for organocatalysis for its special properties, but there is still a debate on its role.[110] It has been reported that the selectivity of reactions in water is higher than that in organic solvents.[111] The results show that in organic solvents, where the reaction is in a homogeneous phase, always higher yields are obtained than in heterogeneous reactions with water (Table 10). The yields of reactions with catalyst **129c** and **129d** in organic solvents are always above 88%, whereas with water only moderate yields are reached.

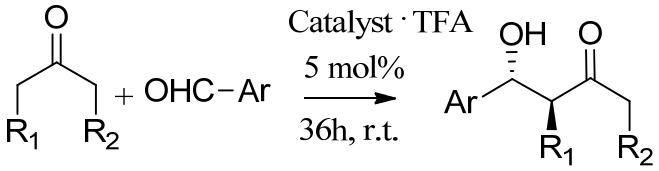
Even more importantly, it was found that the solvent has a significant effect in diastereoselectivity. The anti/syn-ratio of the reaction product with **129c** in DMSO, DCM, THF, EtOAc was much lower than the obtained 90/10 and 92/8 in methanol and water (entries 1, 7, 13, 19, 25, 31, Table 10). **129d** and other catalysts gave similar results as **129c**. We suspect that the added acid not entirely dissociates in aprotic solvent like in protic solvent. When the acid is not firmly attached to imidazole, the hydrogen bonding of imidazolium salt is not active like in protic solvent and a weak hydrogen bonding lowers selectivity. However, the reaction rate-determining step is not the C-C bond-forming step[93], so the yield is obviously not affected by different solvents.

As the enantioselectivity of the reaction with **129c** and **129d** in protic solvents (94%, 92% in methanol and 96%, 98% in water) (entries 25, 26, 31, 32, Table 10) was generally better than in aprotic solvents and considering the advantages of water, we chose water as the solvent for further studies. In the reactions above, the ketone was applied in excess as usual, being also a co-solvent. But surprisingly we found that using cheap and biodegradable ethyl acetate as a co-solvent, excess ketone was not necessary to obtain good yields and selectivity. With 1 equivalent of cyclohexanone **129c** gave 71% yield and 94% ee (entry 37, Table 10). **129d** gave even better results (85% yield and 98% ee) (entry 38, Table 10).

Finally, the optimized conditions and low catalysts loading (5 mol%) were used to test

different aldehydes and ketones. Firstly, different substituted benzaldehydes were investigated and it was found that regarding selectivity electron poor and electron rich substituted systems gave similar results, only the yields were lower with 4-chloro-and 4-methoxybenzaldehyde compared to the nitro substituted benzaldehydes. After testing different aldehydes, different ketones namely cyclopentanone and acetone, were also investigated. Notably, in comparison to cyclohexanone, the selectivities in the reactions with the five-membered ketone and also with acetone decreased (entries 31-42, Table 11).

Table 11. The aldol reaction with various keones and aldehydes[a]



4 **48** **100a-106a**

Entry	Aldehyde Ar	Ketone R_3, R_4	Catalyst	Yield of product [%][b]		anti/syn[c]	ee[%] (major)[d]
1	*p*-$NO_2C_6H_4$	-$(CH_2)_3$-	**129c**	**100a**	80	98/2	96
2	*p*-$NO_2C_6H_4$	-$(CH_2)_3$-	**129d**	**100a**	83	98/2	98
3	*p*-$NO_2C_6H_4$	-$(CH_2)_3$-	**129e**	**100a**	81	97/3	98
4	*p*-$NO_2C_6H_4$	-$(CH_2)_3$-	**129f**	**100a**	86	96/4	97
5	*p*-$NO_2C_6H_4$	-$(CH_2)_3$-	**129g**	**100a**	83	97/3	97
6	*p*-$NO_2C_6H_4$	-$(CH_2)_3$-	**129h**	**100a**	78	98/2	97
7	*o*-$NO_2C_6H_4$	-$(CH_2)_3$-	**129c**	**105a**	78	94/6	94
8	*o*-$NO_2C_6H_4$	-$(CH_2)_3$-	**129d**	**105a**	81	95/5	96
9	*o*-$NO_2C_6H_4$	-$(CH_2)_3$-	**129e**	**105a**	86	96/4	96
10	*o*-$NO_2C_6H_4$	-$(CH_2)_3$-	**129f**	**105a**	82	95/5	87
11	*o*-$NO_2C_6H_4$	-$(CH_2)_3$-	**129g**	**105a**	79	97/3	95
12	*o*-$NO_2C_6H_4$	-$(CH_2)_3$-	**129h**	**105a**	84	96/4	95
13	*m*-$NO_2C_6H_4$	-$(CH_2)_3$-	**129c**	**106a**	84	96/4	96
14	*m*-$NO_2C_6H_4$	-$(CH_2)_3$-	**129d**	**106a**	80	95/5	97
15	*m*-$NO_2C_6H_4$	-$(CH_2)_3$-	**129e**	**106a**	81	96/4	93

Entry	Aldehyde Ar	Ketone R_3, R_4	Catalyst	Yield of product [%][b]		anti/syn[c]	ee[%] (major)[d]
16	*m*-$NO_2C_6H_4$	-$(CH_2)_3$-	**129f**	**106a**	88	95/5	97
17	*m*-$NO_2C_6H_4$	-$(CH_2)_3$-	**129g**	**106a**	83	96/4	95
18	*m*-$NO_2C_6H_4$	-$(CH_2)_3$-	**129h**	**106a**	85	97/3	97
19	*p*-ClC_6H_4	-$(CH_2)_3$-	**129c**	**103a**	65	98/2	97
20	*p*-ClC_6H_4	-$(CH_2)_3$-	**129d**	**103a**	63	99/1	97
21	*p*-ClC_6H_4	-$(CH_2)_3$-	**129e**	**103a**	68	97/3	98
22	*p*-ClC_6H_4	-$(CH_2)_3$-	**129f**	**103a**	66	98/2	95
23	*p*-ClC_6H_4	-$(CH_2)_3$-	**129g**	**103a**	60	97/3	96
24	*p*-ClC_6H_4	-$(CH_2)_3$-	**129h**	**103a**	63	98/2	95
25	*p*-$CH_3OC_6H_4$	-$(CH_2)_3$-	**129c**	**104a**	48	96/4	97
26	*p*-$CH_3OC_6H_4$	-$(CH_2)_3$-	**129d**	**104a**	58	97/3	96
27	*p*-$CH_3OC_6H_4$	-$(CH_2)_3$-	**129e**	**104a**	53	95/5	97
28	*p*-$CH_3OC_6H_4$	-$(CH_2)_3$-	**129f**	**104a**	50	96/4	96
29	*p*-$CH_3OC_6H_4$	-$(CH_2)_3$-	**129g**	**104a**	59	97/3	97
30	*p*-$CH_3OC_6H_4$	-$(CH_2)_3$-	**129h**	**104a**	55	98/2	94
31	*p*-$NO_2C_6H_4$	-$(CH_2)_2$-	**129c**	**101a**	86	56/44	90
32	*p*-$NO_2C_6H_4$	-$(CH_2)_2$-	**129d**	**101a**	84	60/40	91
33	*p*-$NO_2C_6H_4$	-$(CH_2)_2$-	**129e**	**101a**	78	63/37	92
34	*p*-$NO_2C_6H_4$	-$(CH_2)_2$-	**129f**	**101a**	84	60/40	94
35	*p*-$NO_2C_6H_4$	-$(CH_2)_2$-	**129g**	**101a**	81	64/36	92
36	*p*-$NO_2C_6H_4$	-$(CH_2)_2$-	**129h**	**101a**	86	65/35	93
37	*p*-$NO_2C_6H_4$	H, H	**129c**	**102a**	50		84
38	*p*-$NO_2C_6H_4$	H, H	**129d**	**102a**	60		84
39	*p*-$NO_2C_6H_4$	H, H	**129e**	**102a**	57		80
40	*p*-$NO_2C_6H_4$	H, H	**129f**	**102a**	65		81
41	*p*-$NO_2C_6H_4$	H, H	**129g**	**102a**	59		79
42	*p*-$NO_2C_6H_4$	H, H	**129h**	**102a**	64		82

[a] The reaction was performed with **129d-129h** (0.05 mmol), TFA (0.05 mmol), **4** (1.0 mmol) and **48** (1.0 mmol), solvent (0.25 mL H_2O and 0.25 mL EtOAc) at room temperature.

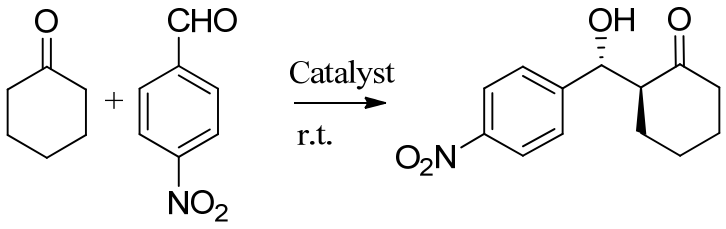
[b] Combined yields of isolated diastereomers.

[c] Determined by ^{1}H NMR of the crude product.

[d] Determined by chiral-phase HPLC analysis of the anti product.

After testing the catalysts with different acids, solvents, aldehydes and ketones, it was realized that the added acid plays an important role in determining the selectivity of product. So in the following, more added acids and different acid loading were examined. Considering the similar results from **129c-129h**, the catalysts **129c, 129d and 129e** have been taken for the following tests.

Table 12. The test with different added acids and catalysts loading [a]



4a **48a** **100a**

Entry	Added acid	Catalyst	Catalyst [mol%]	Reaction time [h]	Yield [%][b]	anti/syn[c]	ee[%] (major)[d]
1	4-Hydroxy-benzoic acid	**129c**	10	24	63	75/25	53
2		**129d**	10	24	60	77/23	53
3		**129e**	10	24	61	76/24	54
4	Succinic acid	**129c**	5	24	62	85/15	68
5		**129d**	5	24	65	85/15	69
6		**129e**	5	24	63	84/16	69
7	AcOH	**129c**	10	24	78	84/16	74
8		**129d**	10	24	76	83/17	73
9		**129e**	10	24	80	85/15	72
10	CF_3COOH	**129c**	10	24	71	94/6	94
11		**129d**	10	24	85	96/4	98
12		**129e**	10	24	78	95/5	96
13	CF_3SO_2OH	**129c**	10	18	89	86/14	96

Entry	Added acid	Catalyst	Catalyst [mol%]	Reaction time [h]	Yield [%][b]	anti/syn[c]	ee[%] (major)[d]
14		**129d**	10	18	88	88/12	97
15		**129e**	10	18	84	85/15	98
16		**129c**	10	18	74	83/17	78
17	HCl	**129d**	10	18	69	84/16	82
18		**129e**	10	18	70	81/19	80
19		**129d**	5	36	83	98/2	98
20	CF_3COOH	**129d**	2.5	48	80	90/10	95
21		**129d**	1	72	80	87/13	95

[a]The reaction was performed with **129c**-**129e**, added acid, **4a** (0.10 mL, 1.0 mmol) and **48a** (151 mg, 1.0 mmol), solvent (0.25 mL H_2O and 0.25 mL EtOAc) at room temperature.

[b] Combined yields of isolated diastereomers.

[c] Determined by ^1H NMR of the crude product.

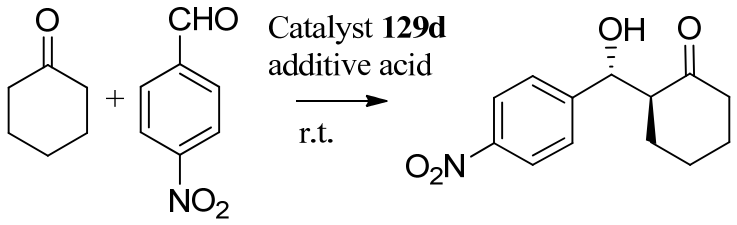
[d] Determined by chiral-phase HPLC analysis of the anti product.

In the search with different acids, it can be found again that the same catalyst can give different selectivity with different added acid and the selectivity is generally raised up when the added acid becomes stronger in acidity. However, there is an exception: The catalysts on addition with HCl did not lead to higher selectivity. Compared with trifluoroacetic acid and trifluoromethanesulfonic acid, the selectivity of the reaction with HCl is only 78%, 82%, 80% respectively (entries 16, 17, 18, Table 12). In these reactions, quite a few condensation products have been detected after the reaction. It can be supposed that the aldol addition product has been obtained and the anti product is the main product like those with the other strong acids. However, HCl is a too strong acid and can catalyze the elimination of water to give the aldol condensation product.

In order to find the relationship between pH of water phase and reaction selectivity, the pH of reactions from Table 12 was researched in the following. The solution with acid in water has been made and the pH of acid solution has been measured with Mettler DL25. This machine has been corrected with Buffer pH 4.01± 0.02 and pH 7.00.

In experiments, it has been found that the mixture with 4-hydroxybenzoic acid and water is suspension and therefor it has not been taken in the pH measurement.

Table 13. The pH of different added acids solution and corresponding selectivity [a]



4a **48a** **100a**

	5 mol% Succinic acid [b]	10 mol% AcOH[c]	1 mol% TFA[d]	2.5 mol% TFA[e]	5 mol% TFA[f]	10 mol% TFA[g]	10 mol% TFSA [h]	10 mol% HCl [i]
pH	2.438	2.536	1.439	1.130	0.905	0.687	0.579	0.544
ee[%][j]	68	74	95	95	98	98	97	82

[a] The reaction was performed with **129d**, **4a** (0.50 mL, 5.0 mmol) and **48a** (151 mg, 1.0 mmol), solvent (0.25 mL added acid solution and 0.25 mL EtOAc) at room temperature.

[b] The solution is made with 10 mL water and 0.236g (2 mmol) succinic acid.

[c] The solution is made with 10 mL water and 0.228 mL (4 mmol) AcOH.

[d] The solution is made with 10 mL water and 0.029 mL (0.4 mmol) TFA.

[e] The solution is made with 10 mL water and 0.074 mL (1 mmol) TFA.

[f] The solution is made with 10 mL water and 0.148 mL (2 mmol) TFA.

[g] The solution is made with 10 mL water and 0.297 mL (4 mmol) TFA.

[h] The solution is made with 10 mL water and 0.353 mL (4 mmol) TFSA.

[I] The solution is made with 10 mL water and 0. 338 mL (4 mmol) Con. HCl.

[g] The enantioselectivity is for the major product.

From the Figure 7, it is obvious that the pH for high selectivity of product is mainly between 0.5-1.5. When the pH of the solution is lower than 0.5, it can be predicted that the selectivity of aldol addition product will decrease because of the condensation of addition product. When the pH of solution is higher than 1.5, the selectivity is going down. It should be pointed out that with the same amount of catalyst (10 mol%), the added acid is stronger and the selectivity of the product is higher.

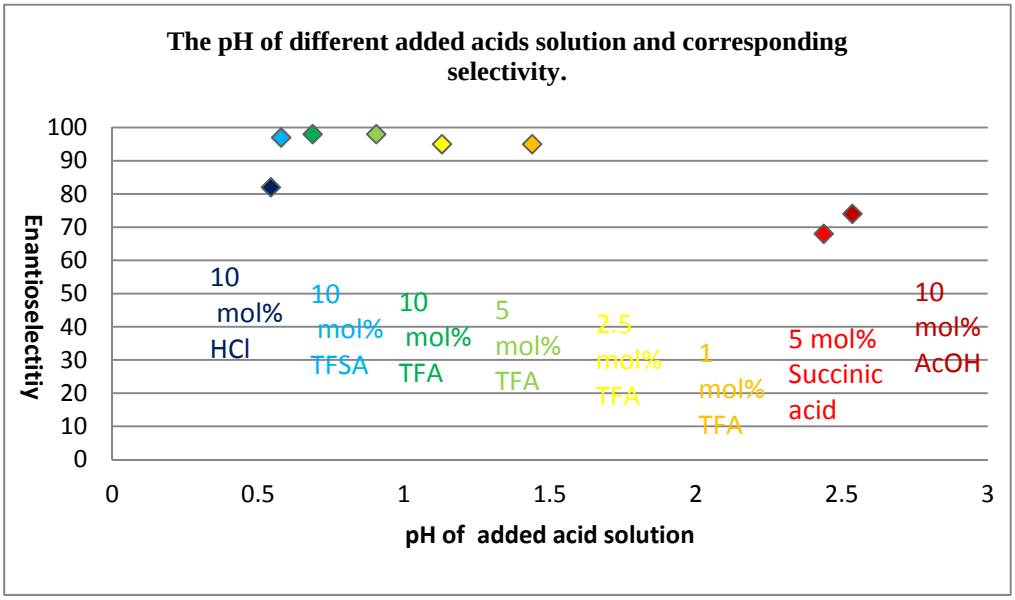
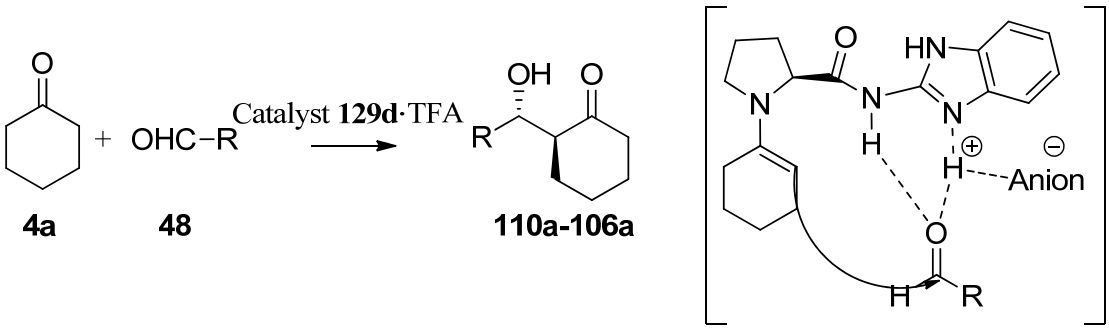


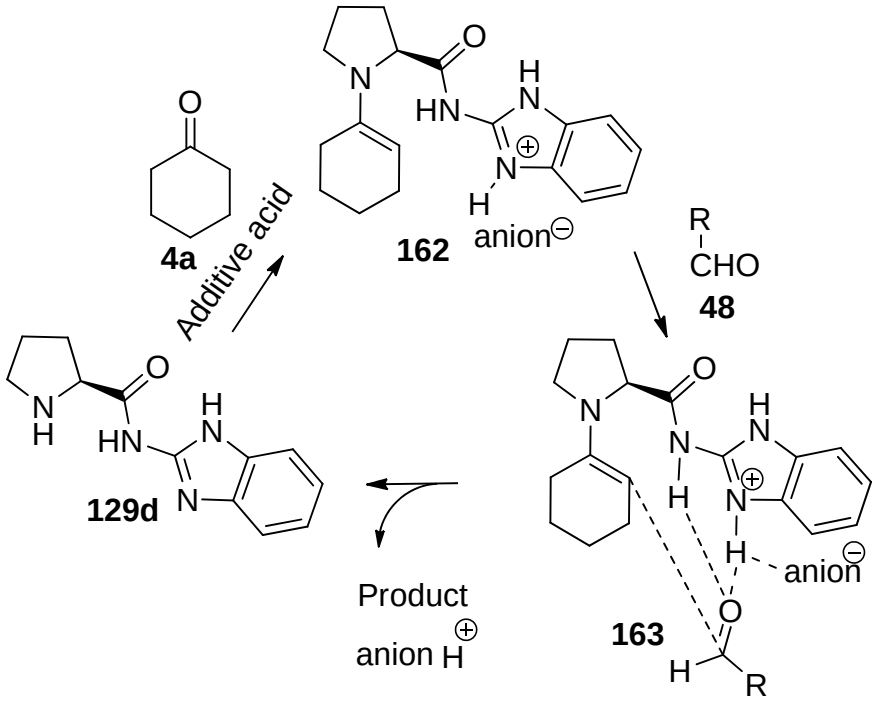
Figure 7. The pH of added acid solution and corresponding selectivity

After these results were obtained, further analysis has been done. From the results with TFSA and HCl in Figure 7, it can be seen that there is a big difference in selectivity of product with similar pH. Based on this, it can be concluded that the selectivity of product is also dependent on the anion, probably due to different transition states.



Scheme 50. The proposed transition state with catalyst **129d**

The catalytic cycle with catalyst **129d** has been also proposed as shown below:

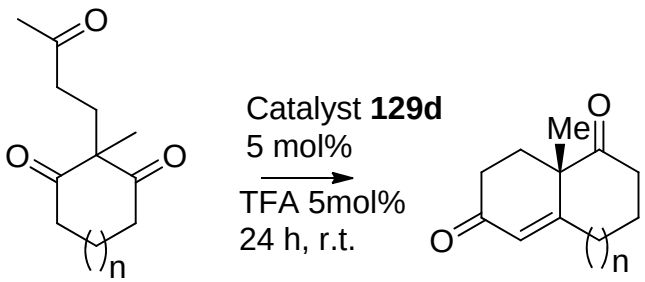


Scheme 51. The proposed catalytic cycle with catalyst **129d**

3.3.3.2 In intramolecular aldol reaction

From the series of tests with catalyst **129a-129j** in intermolecular aldol reactions, it has been found that the catalysts **129c-129h** are highly efficient organocatalysts. It has also been proved that the added acid plays a very important role in the selectivity of reactions, even the determining role for obtaining high selectivity. On further research, it has been found that not only the proton but also the anion can influence the selectivity of the reaction. Catalyst **129d** with TFA was chosen to do tests in an intramolecular aldol reaction after it had been proven to be the best catalytic system in intermolecular aldol reactions. The best known intramolecular aldol reaction is the Hajos-Parrish-Eder- Sauer-Wiechert process for the synthesis of compound **3**[19,18] , which is a valuable intermediate for steroid synthesis. Compounds **1** and **1a**[112] were treated in different solvents with 5 mol% of catalyst **129d** and TFA. Aldol addition and condensation was accomplished in 24 h at room temperature in one step. The enantioselectivity was highest (ee 73%) in the reaction in water (entry 4, Table 14), even better than the reported value of ee using *L*-proline as catalyst. This is a very interesting result which needs further research.

Table 14. Intramolecular aldol reaction catalyzed by catalyst **129d** [a]



1(n=0), **1a**(n=1)

3(n=0), **3a**(n=1)

Entry	n	Product	Solvent	Yield [%][b]	ee[%](major)[c]
1	1	**3a**	THF	95	65
2	1	**3a**	DMSO	96	67
3	1	**3a**	Methanol	97	71
4	1	**3a**	H_2O	93	73
5	0	**3**	H_2O	91	86

[a] The reaction was performed with **129d** (0.05 mmol), TFA (0.05 mmol), **1** or **1a** (1.0 mmol) and solvent (0.5 mL) at room temperature.

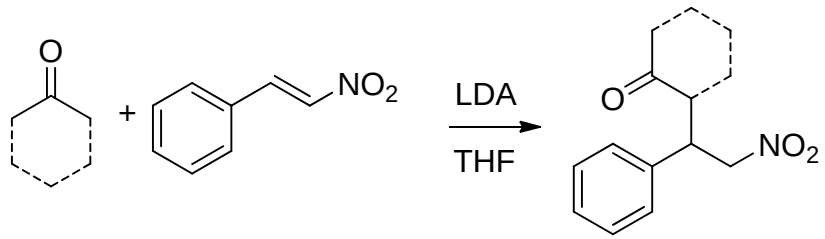
[b] Yield after purification.

[c] Determined by chiral-phase HPLC analysis.

3.3.3.3 Michael addition between ketones and nitro olefins

Considering the previous research, it can be concluded that the hydrogen bonding of the catalysts plays the dominating role in the aldol reaction. Michael additions between ketones and nitro olefins have been reported many times to give high stereoselectivities with organocatalysts. Considering our catalysts based on proline and imidazole, they also could coordinate with the nitro group of nitro olefins by hydrogen bonding and may lead to high selectivity in Michael reactions with ketones. The racemic products had to be synthesized to separate them on our chiral column because there is no report about the condition for separation with IA chiral column. These racemic products were synthesized according to the report of Schneider [113]. The reaction was done with LDA at -78 ^{o}C. The method with sodium hydroxide in

methanol was also tried for the synthesis of the racemic products, however, it did not work in our hand. After the racemic products have been obtained and confirmed by NMR, the separation of these products with chiral column IA was tested. However, their separation with this column was not good, only the product from acetone could be separated. So in the following tests, only acetone has been used as nucleophile. However, it is known that the reaction of acetone has much lower selectivity than that of cyclic ketones.[114]

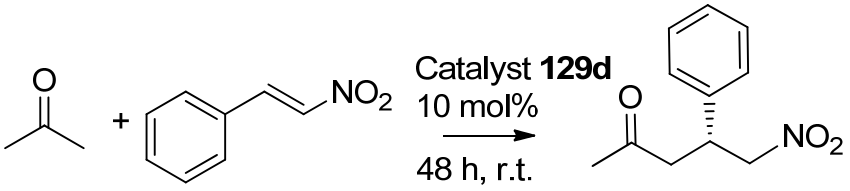


4 **79** **164**

Scheme 52. Michael addition of ketones to (*E*)-(2-nitroethenyl)benzene

In previous reports, THF was used very often as solvent for Michael additions. 2-Fluorobenzoic acid and benzoic acid were chosen as acid additives in many reports[115]. In our work with aldol reactions, TFA had always turned out to be the best additive. So in the following tests, TFA, 2-fluorobenzoic acid and benzoic acid have been chosen as acid additives. Moreover, different solvents and different temperatures have been tested.

Table 15. Michael addition of acetone to nitro-olefin by catalyst **129d**[a]



4c **79** **164a**

Entry	Acid	Solvent	Reaction temperature	Yield [%][b]	ee[%] (major)[c]
1	TFA	THF	-10 °C	trace	ND
2	TFA	THF	r.t.	22	18
3	TFA	Methanol	r.t.	17	3

4	TFA	EtOAc	r.t.	21	2
Entry	Acid	Solvent	Reaction temperature	Yield [%][b]	ee[%] (major)[c]
5[d]	TFA	EtOAc	r.t.	8	3
6	TFA	H_2O	r.t.	10	0
7	TFA	Toluene	r.t.	34	27
8	2-fluoro benzoic acid	Toluene	r.t.	30	23
9	benzoic acid	THF	-10 °C	trace	ND
10	benzoic acid	THF	r.t.	21	6
11	No acid	THF	r.t.	18	2
12	No acid	Methanol	r.t.	13	3

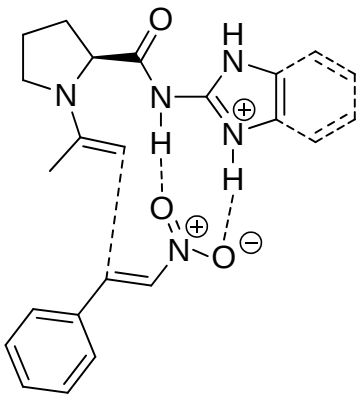
[a] The reaction was performed with **129d** (0.023g, 0.1 mmol), acetone (0.58 g, 1.0 mmol) and(*E*)-(2-nitroethenyl)benzene (149 mg, 1.0 mmol), solvent (0.5 mL).

[b] Yield of isolated product.

[c] Determined by chiral-phase HPLC analysis of product.

[d] The solvent is 0.25 mL water and 0.25 mL EtOAc.

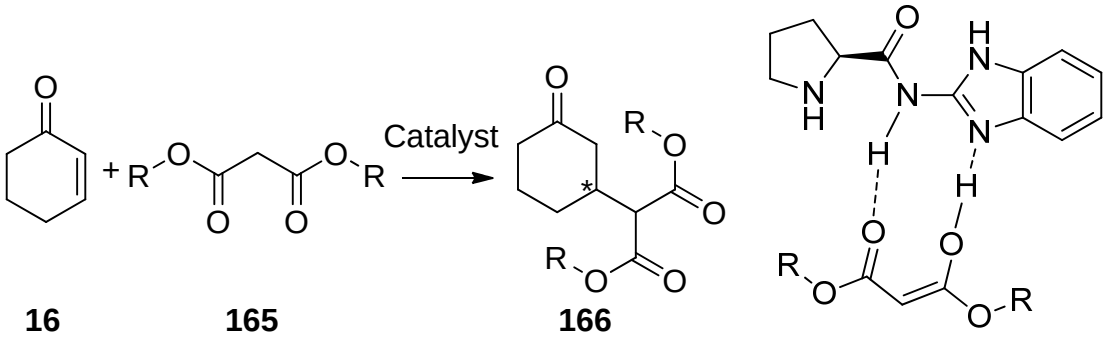
From the tests, it can be found that the added acid plays a less important role in the selectivity of the reactions than in aldol reactions. However, the reactions with TFA in different solvents gave different selectivities. It seems from the preliminary results that the selectivity of the reaction with catalyst **129d** is more dependent from solvents than from added acid. As reported by List in the case with proline as a catalyst, the Michael reaction of nitro olefins with acetone is not a good example. Much higher selectivities have been obtained with cyclohexanone.[116] However, there was no separation on our chiral HPLC with the product from cyclohexanone. So, further research with catalyst **129d** for Michael additions with (*E*)-(2- nitroethenyl)benzene could not be done.



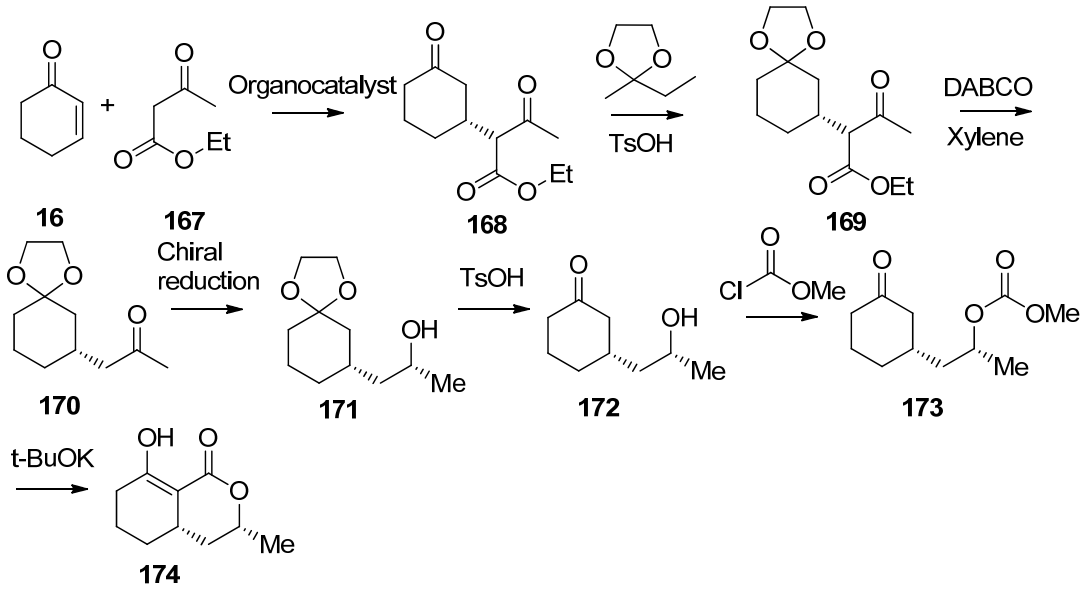
Scheme 53. The transition state of Michael addition between acetone and nitro olefins

3.3.3.4 Michael addition between 2-cyclohexen-1-one and malonate esters

It has been reported that *L*-proline can catalyze Michael addition between 2-cyclohexen-1-one and malonate esters. The selectivity of the products is very high.[117,118] A new route for the synthesis of (+) ramulosin could be envisioned using this as a key reaction in 7 steps (scheme 55). Most other reports need at least 10 steps.[119] Considering our catalyst based on *L*-proline and the imidazole structure containing Lewis base, we tried to test the Michael addition between 2-cyclohexen-1-one and malonate esters with catalyst **129d** (scheme 54).



Scheme 54. Michael addition of 2-cyclohexen-1-one to malonate esters and the proposed binding mode of malonate esters with catalyst **129d**



Scheme 55. The proposed route for synthesis of (+) ramulosin

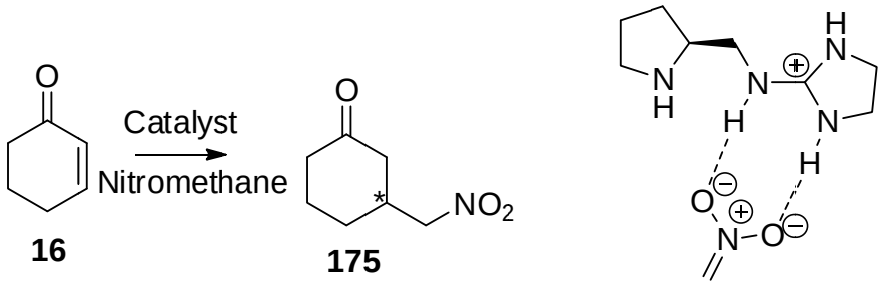
Before we tested the reaction with catalyst **129d**, the racemic products had to be synthesized because there was also no report about the separation with IA chiral column. After we got the racemic products with diethyl malonate and dimethyl malonate, it was found that the products could not be separated with our IA and OD – HPLC-columns, also not with our chiral GC. So further research had to be stopped and given up.

3.3.3.5 Michael addition between 2-cyclohexen-1-one and nitroalkane

After the tests with malonate esters, another Michael addition between 2-cyclohexen-1-one and nitroalkane has also been considered. As reported, the nitro group can be controlled by guanidine functional groups.[120] Considering the similarity of imidazole and guanidine, our catalyst has also been tested with this kind of reaction.

Firstly, the racemic products were synthesized for the analysis of our chiral column using nitromethane as solvent and TBD (1,5,7-Triazabicyclo[4.4.0] dec-5-ene)[121] as catalyst. However, there was no target product. After analysis of the main product by ^{1}H NMR, it has been found that there are two more hydrogen at 4.42 ppm than expected for the target product. Therefore it was supposed that a double addition had been taken

place to form 1, 3-bis(nitromethyl)cyclohexanol which was confirmed by ^{13}C NMR. In ^{13}C NMR, there was no signal for a carbonyl group, instead a signal at 70 ppm was found which should be the quaternary carbon atom. All other signals were in accord with the presumed structure.

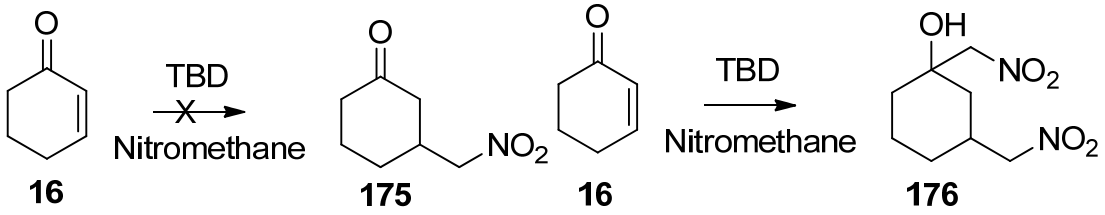


Scheme 56. Michael addition of 2-cyclohexen-1-one to nitroalkane and guanidine derivatives controlling nitro group by hydrogen bond

Figure 8. The ^{1}H NMR of product **176** obtained by TBD as catalyst

In order to solve this problem, another base TMG (1,1,3,3-Tetramethylguanidine)[122] which is a weaker base than TBD, and 1 equiv. nitromethane was used in this reaction, but again without success. So, it had to be realized that both the catalysts TBD and

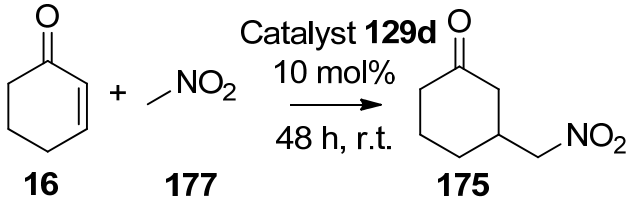
TMG are too strong for the selective addition of nitroalkane to 2-cyclohexen-1-one, and the carbonyl group had also been attacked by nitroalkane and there was no target product. So, a weak basic catalyst should be better for obtaining the target product.



Scheme 57. The reaction between nitromethane and 2-cyclohexen-1-one with catalyst TBD

Then another catalyst KF/alumina[122] was taken for the synthesis. The target products 3-(nitromethyl)cyclohexanone,3-(1-nitroethyl)cyclohexanone and 3-(2-nitropropan-2-yl)cyclohexanene could finally be synthesized using this catalyst. However only 3-(nitromethyl)cyclohexanone can be separated by chiral IA column. So, only nitromethane has been used in the test reactions with our catalyst.

Table 16. Michael addition of nitromethane to 2-cyclohexen-1-one by catalyst **129d** [a]



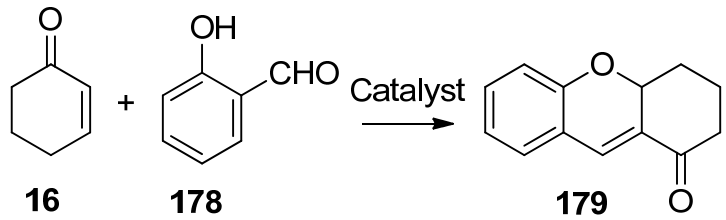
Entry	Solvent	Additive	Yield [%][b]	ee[%] (major)[c]
1	Toluene	NO	53	44
2	DCM	NO	44	40
3	THF	NO	45	32
4	$CHCl_3$	NO	40	38
5	EtOAc	NO	21	28
6	DMSO	NO	trace	ND
7	H_2O	NO	10	19
8	DCM	2,5-dimethylpiperazine[d]	48	47

[a] The reaction was performed with **129d (**0.023g, 0.1 mmol), 2-cyclohexen-1-one (0.096 g, 1.0 mmol) and nitromethane (0.54 g, 10.0 mmol), solvent (2 mL).
[b] Yield of isolated product.
[c] Determined by chiral-phase HPLC analysis of product.
[d] 2, 5-Dimethylpiperazine (0.1 mmol) was added.

From the reaction, it can be found that the selectivity of the reaction is generally going up when the polarity of solvents is decreasing. The yield of reaction is also going up with the decreasing of solvents polarity. In the report of Ley[123], it has been found that 5-pyrrolidin-2-yltetrazole is a good organocatalyst for the asymmetric conjugate addition of nitroalkanes to enones and the addition of the base 2,5-dimethyl piperazine can increase the yield and selectivity. So, here the addition of 2, 5-dimethylpiperazine was also tried in the reaction. The selectivity of the reaction is a little bit higher (7 %) but not seriously. The yield is nearly the same. Comparing this catalyst with other efficient catalysts[123], there were disappointing results and the way to improve the selectivity and yield was not clear. So, further research on addition of nitroalkanes to enones was not continued.

3.3.3.6 Domino reactions

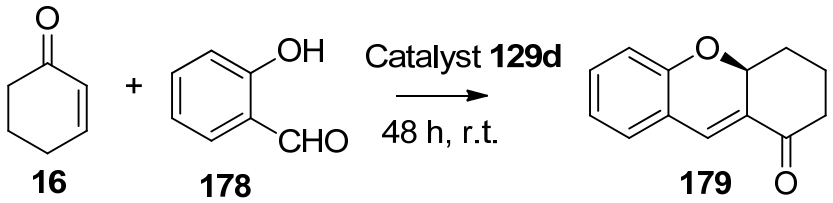
Tetrahydroxanthenone units have been widely found in nature products, such as diversonol[124], beticolins[125], simaomicins[126], phomoxan-thones[127] and rugulotrosins [128]. Only a few stereo selective syntheses of natural products containing tetrahydroxanthenone units have been reported.[129] The synthesis of this tetrahydroxanthenone core with domino Michael addition-aldol reaction has been reported in 2006.[130] In the report, salicylic aldehyde and 2-cyclohexen-1-one were used as starting material. However, the selectivity of the reaction was very low. Considering our catalysts with an imidazole substructure, it could be a good catalyst for this reaction. The pyrrolidine can react and activate 2-cyclohexen-1-one; meanwhile the imidazole substructure can coordinate to the aldehyde by hydrogen bonding.



Scheme 58. Domino Michael-aldol reaction of 2-cyclohexen-1-one and salicylic aldehyde

Firstly the racemic product was synthesized using imidazole as the catalyst. After the confirmation of its structure with NMR, the analysis with a chiral column revealed that the racemic product can be successfully separated with the IA chiral column. The tests were done in the following way as can be seen in Table 17.

Table 17. Domino Michael addition-aldol reaction by catalyst **129d**[a]



Entry	Solvent	Yield [%][b]	ee[%] (major)[c]
1	Toluene	trace	ND
2	DCM	trace	ND
3	THF	trace	ND
4	$CHCl_3$	trace	ND
5	EtOAc	trace	ND
6	DMSO	trace	ND
7	H_2O	trace	ND
8	H_2O[d]	15	2

[a] The reaction was performed with **129d (**0.023g, 0.1 mmol), 2-cyclohexen-1-one (0. 96 g, 10.0 mmol) and salicylic aldehyde (0.121 g, 1.0 mmol), solvent (1 mL).

[b] Yield of isolated product.

[c] Determined by chiral-phase HPLC analysis of product.

[d] The reaction was performed with **129d (**0.023g, 0.1 mmol), TFA (0.1 mmol),

2-cyclohexen-1-one (0. 96 g, 10.0 mmol) and salicylic aldehyde (0.121 g, 1.0 mmol), solvent (1 mL).

From the results of the reactions, it can be found that there is very little product formation in the reaction in different solvents without added acids. In the reaction some new spots were detected by TLC, however they were not the wanted products. When the reaction was done with addition of TFA, the yield was also not high (entry 8, Table 17). From the analysis of GC, it can be found that the main peaks are starting materials. Besides this, the peak of mass 200 (target product) is much bigger than mass 218(the addition product). It can be suggested that the addition product can quickly undergo the next step and the reaction determining step is in the first stage - the addition of the phenolic OH group to 2-cyclohexen-1-one. Considering the low yield, the reaction was not continued further.

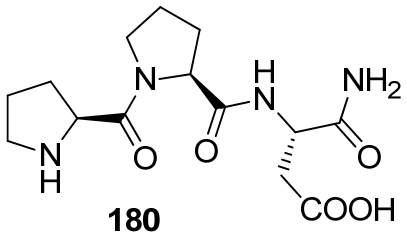
3.3.4 Conclusion

In conclusion, we have found a series of new catalysts based on imidazole containing *L*-proline derivatives. These catalysts with added acids exhibited high selectivity and activity in aldol reaction. In order to understand the role of added acids, an extensive examination has been done with aqueous solutions of the same added acid of different pH. By these experiments, the most efficient pH of additive solution could be evaluated. In these tests, it has also been found that the counter ion of the added acid plays an important role in determining the selectivity of the reaction. Besides, different Michael additions reactions and Michael-aldol domino reactions have been tested with catalyst **129d**. However, either the observed selectivities were not satisfying or the stereoselectivities could not be determined because separation of the products was not possible with the available chiral columns.

3.4 Peptide based organocatalysts with sulfonamide groups

3.4.1 The design of peptide derivatives

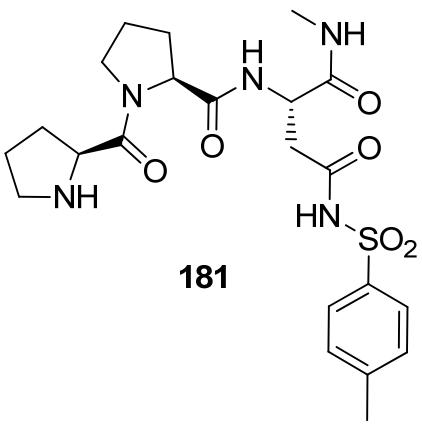
Peptides have been used in organocatalysis for a long time.[131] One of the peptide catalysts from Wennemers group has very high selectivity (90% ee) and yield (98%) in aldol reactions.[132] Especially the finding that the catalyst loading is only 1 mol% has found great attraction in the field.



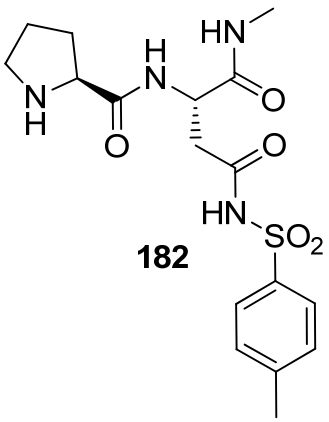
180

Scheme 59. The peptide catalyst of Wennemers

Based on our previous research that proline sulfonamide derivatives gave much better results in selectivity and yield than proline, it was obvious to combine the sulfonamide with peptides and test such systems as organocatalysts.



181

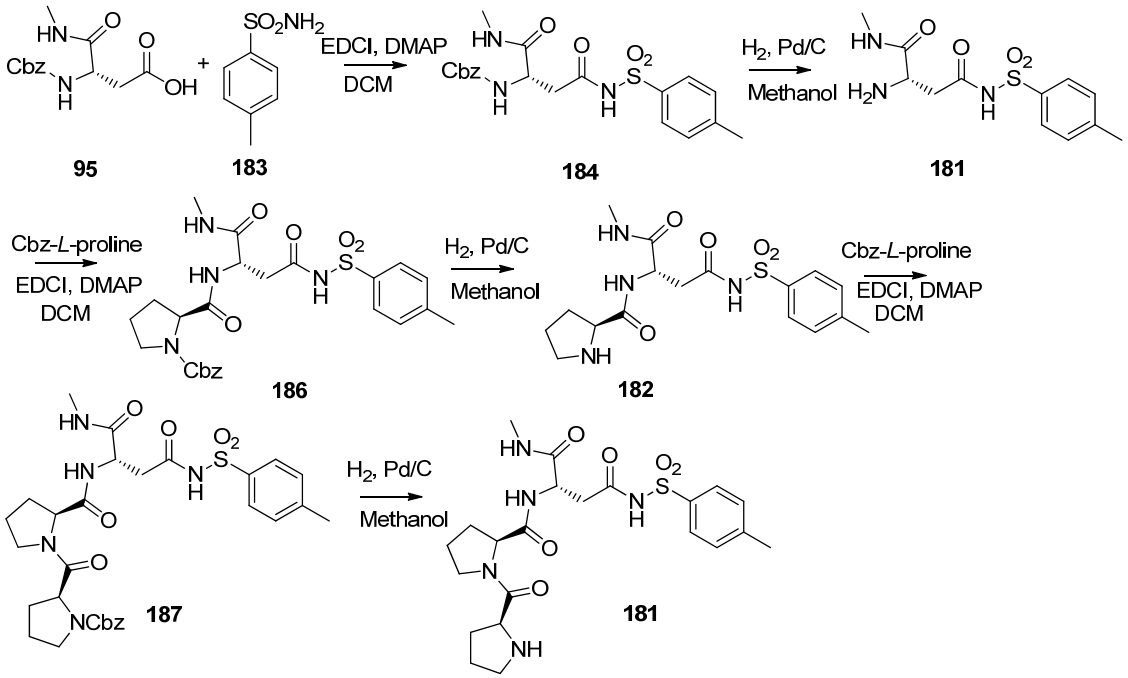


182

Scheme 60. The designed peptide catalysts with sulfonamide functionalities

In a first attempt a substitution of the carboxyl group by a sulfonimide function was tested for its catalytic activity in aldol reactions.

3.4.2 The synthesis of peptide derivatives



Scheme 61. The synthetic route for the designed catalysts

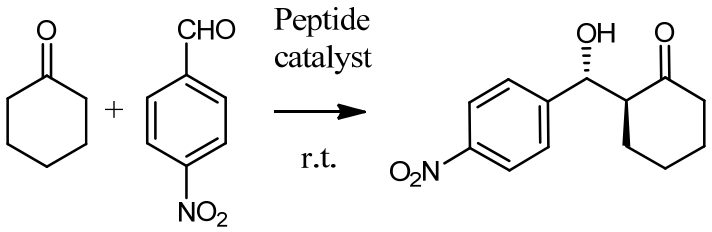
The synthesis started with compound **95**, which had been used as an intermediate in the preparation of the imidazolidinone catalysts, and its condensation with *p*-toluenesulfonamide to give **184**. After Cbz-deprotection, Cbz-protected proline was connected to **185** in the usual way, leading after deprotection to the first system which should be tested. The Wennemers peptide analogue **181** could be obtained after the introduction of another proline group in the same manner. The synthesis of these products is easier than that of other peptides[132], since the sulfonamide works like a stabilizing protection group.

3.4.3 The tests with peptide organocatalysts

With the two synthesized peptide systems tests have been done for evaluating their catalytic activity in the standard model aldol reaction with 4-nitrobenzaldehyde and cyclohexanone in DMSO (Table 18). As in our previous results, the main product is the anti isomer with 2*R*, 1'*S*-configuration. However, the peptides with sulfonamide structure gave only medium yield and selectivity. With these two catalysts, it was

found that the selectivity of the product is not good in water and only a little bit better in MeOH. When TFA was added to help to activate the aldehyde, the yield is a little bit higher but the selectivity is going down, probably by direct acid catalyzed reaction with TFA leading to racemic product so that the selectivity is lower than without acid. As there was no big improvement in selectivity after the screening of solvents and acids, it had to be realized that the modification of the structure may have created some problems.

Table 18. Direct aldol reaction of 4-nitrobenzaldehyde and cyclohexanone catalyzed by peptide [a]



4a **48a** **100a**

Entry	Catalyst	Solvent	Yield [%][b]	anti / syn[c]	ee [%](major)[d]
1	**181**	H_2O	50	68/32	37
2	**182**	H_2O	54	57/43	17
3	**181**	H_2O[e]	55	55/45	23
4	**182**	H_2O[e]	58	56/44	11
5	**181**	Methanol	54	72/28	44
6	**182**	Methanol	55	77/23	31
7	**181**	DMSO	54	53/47	19
8	**182**	DMSO	55	52/48	11

[a] The reaction was performed with **181** or **182** (0.1 mmol), cyclohexanone (0.98 g, 10.0 mmol) and 4-nitrobenzaldehyde (0.151 g, 1.0 mmol), solvent (1 mL) and at room temperature.

[b] Combined yields of isolated diastereomers.

[c] Determined by ^{1}H NMR of the crude product.

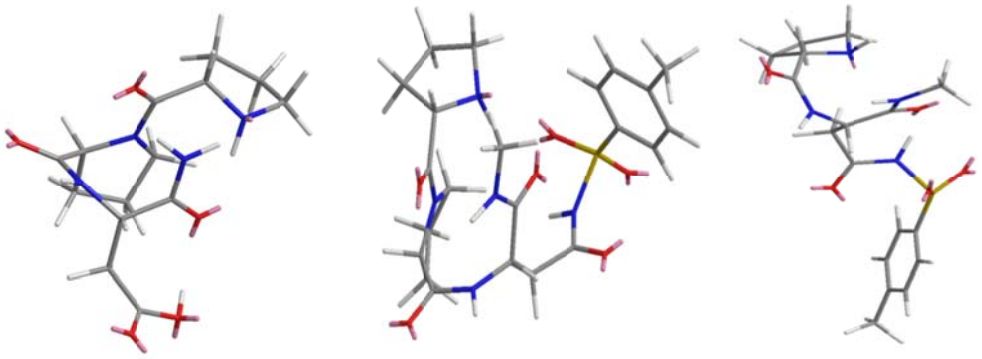
[d] Determined by chiral-phase HPLC analysis of the major product

[e] The reactin is with 10 mol%TFA

[f] The reaction was performed with 1mL DCM as solvent.

[g] The reaction was performed with 1mL H_2O as solvent.

Therefore, the structures of the catalysts were carefully examined by molecular modeling. The design of Wennemers catalyst has been intensely discussed.[132] In the lowest energy structure of Wennemers catalyst, the secondary amine of pyrrolidine and the carboxylic acid in the side chain are very close. This proximity can be assumed to be crucial for the observed catalysis.[132] However, in the lowest energy structure of our systems, the NH group, which takes the place of carboxylic acid in our catalyst **181**, is far away from the secondary amine of pyrrolidine because of the Ph group. The CH_3 group may also contribute some hindrance for catalyst **181 and 182**. (The lowest energy structure is calculated by chem. 3D pro).



Wennemers catalyst **180** Catalyst **181** Catalyst **182**

Scheme 62. The lowest energy structure of Wennemers catalyst and our two catalysts

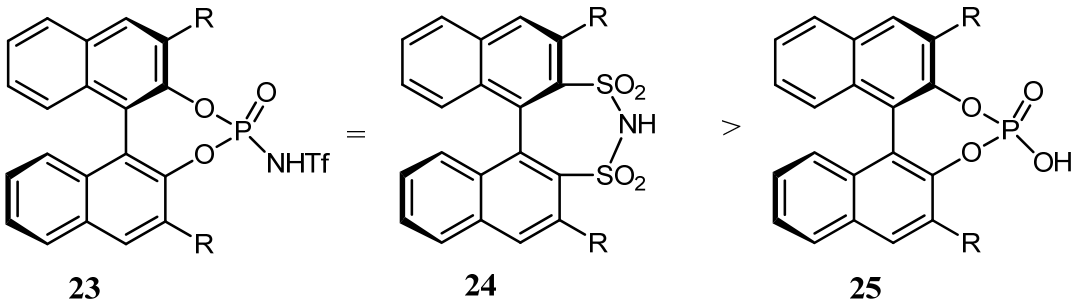
3.3.4 Conclusion

In conclusion, two new peptides have been synthesized and tested as organocatalysts for aldol reaction. However, the systems with the sulfonamide functionalities had no improvement in yield and selectivity in the model reaction probably due to too little steric hindrance.

3.5 BINOL derivatives as Organocatalysts

3.5.1 The design of BINOL derivatives

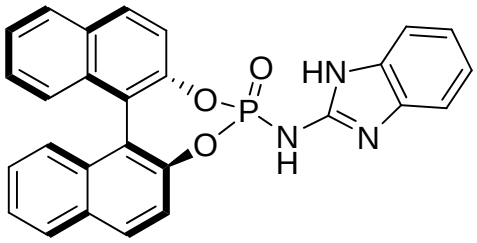
In this chapter, our attempts for the synthesis of BINOL derivatives for organocatalysts are described. As referred in the introduction, BINOL is a very good chiral scaffold. A lot of organocatalysts have been obtained, which are based on BINOL.[133] Among these catalysts chiral Brönsted acids obviously take the main part. [133] Since chiral Brönsted acids have been introduced as organocatalysts, two aspects for modifications have been followed. The first aspect is to increase the steric hindrance at the 3 and 3' position, the second to increase the acidity of the catalyst, namely by changing the phosphoric acid to a trifluoromethylsulfonamide or sulfonamide function.



23 **24** **25**

Scheme 63. The modification of chiral Brönsted acids based on BINOL

In our previous research, it has been found that the introduction of imidazolium groups lead to strong acidity. The catalysts containing this functional group and *L*-proline substructures gave very high selectivity and yield especially in aldol reactions. Considering the contribution in increasing the acidity of chiral Brönsted acids catalysts, the imidazolium functional group should be introduced into chiral Brönsted acids catalyst. More interesting until now, there was no report on the incorporation of an imidazolium group to chiral BINOL derived phosphoric acids. So, the amide of the (*S*)-BINOL based phosphorous acid **25** with aminobenzimidazole was chosen as a test candidate. The (*S*)-BINOL has been chose as chiral scaffold.

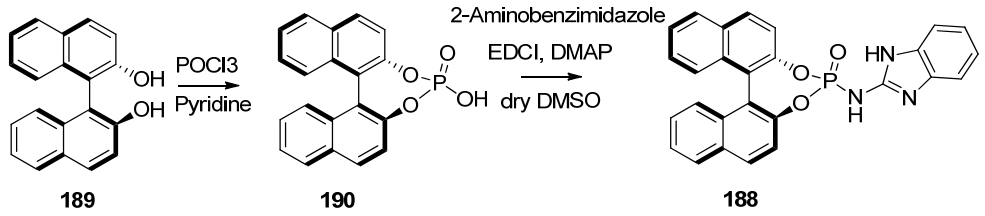


188

Scheme 64. The new (*S*)-BINOL derivative

3.5.2 The synthesis of BINOL derivatives

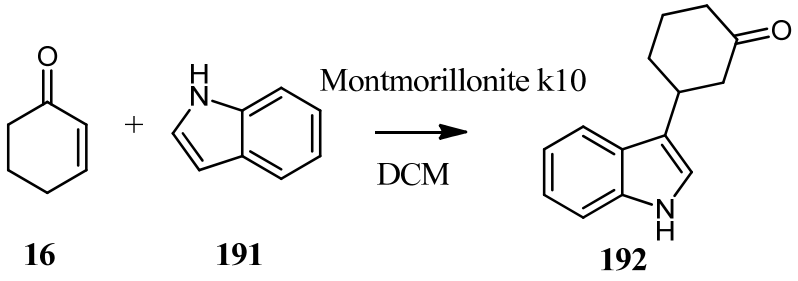
Considering the complexity of synthesizing BINOL derivatives which have substituents at 3 and 3' position, we decided to begin the synthesis without any substituent at (*S*)-BINOL. Firstly, we tried to synthesize (*S*)-(+)-1,1'-Binaphthyl-2,2'-diylhydrogenphosphate, following a report in the literature.[134] After the pure product has been obtained, it was condensed with 2-aminobenzimidazole in dry DMSO with the help of EDCI and DMAP. The mixture was stirred at room temperature for 24 h. After the reaction, DCM and HCl solution were added to work up. The organic phase was dried with Na_2SO_4 and the crude product was purified by flash silica gel chromatography with methanol and DCM. In the reaction mixture, a new spot could be observed. However, the product after purification on the column proved to be starting material in ^{1}HNMR and ^{13}CNMR. So there are two possibilities. The first one is that the target product is cleaved on treatment with HCl solution. The second one is that the target product is cleaved on the column. So in the work up no acid was used, only water washing. After the removal of the main part of DCM, the mixture became a suspension and a filtration had to be done. The filtrate cake was collected and the NMR of the crude product proved to be correct. However, again with LC-MS the expected mass could not be detected. Only two compounds could be found, although the TLC had shown only one peak before the LC-MS measurement. So it is supposed that the compound is cleaved in the analytical step.



Scheme 65. The synthesis of (*S*)-BINOL imidazole derivatives

3.5.3 The tests with organocatalysts of BINOL derivatives

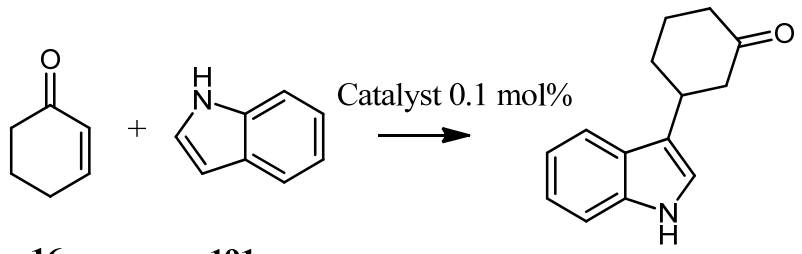
After the catalyst has been obtained, the synthesis of racemic product of the planned reactions had to be done. For chiral Brönsted acids, one of the common test reactions is a Friedel-Crafts reaction between indole and α, β-unsaturated ketone which can be activated by acids.[135] In the literature report, the selectivity of the product from the addition of indole and cyclic enones is very low. So, the reaction with cyclohex-2-enone has been chosen. The racemic product has been obtained following the published procedure.[136] Indole was added to cyclohex-2-enone in DCM. After montmorillonite k10 was added to mixture, the reaction was refluxed for 2 h. Then the mixture was filtrated, the filtrate was concentrated with vacuum. After the purification by flash silica gel chromatography, the racemic product could be obtained and confirmed by NMR. Then racemic product was separated by IA column chromatograph.



Scheme 66. The synthesis of racemic Friedel-Crafts product

The test has been done with our catalyst **188** and with the catalyst **190** for comparison.

Table 19. Direct aldol reaction of indole with cyclohex-2-enone catalyzed by Brönsted acid [a]



16 **191** **192**

Entry	Catalyst	Solvent	Yield [%][b]	ee[%] (major)[c]
1	**190**	DMSO	23	0
2	**188**	DMSO	54	2
3	**190**	DCM	28	0
4	**188**	DCM	55	1

[a] The reaction was performed with **190** or **188** (0.001 mmol), cyclohex-2-enone (0.096 g, 1.0 mmol) and indole (0.14 g, 1.2 mmol), solvent (0.5 mL), and at room temperature.

[b] Yield of isolated product.

[c] Determined by chiral-phase HPLC analysis of product.

From the results, it can be seen that there is no big difference in selectivity between catalysts **190** and **188**. As we expected, the yield in the reaction with **188** is much higher than with **190**. So the catalyst **188** has much higher efficiency than catalyst **190**. The attempt to introduce 2-aminobenzimidazole is very promising. It can be expected that the BINOL catalyst with 2-aminobenzimidazole will have high yield and high selectivity, if big bulky groups are introduced at 3 and 3' position in BINOL scaffold like in other effective organocatalysts. Further research introducing bulky groups is undergoing now.

3.5.4 Conclusion

In conclusion, we have designed and synthesized a new efficient Brönsted acid organocatalyst based on our previous research. Compared with the published

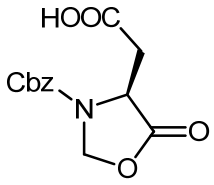
examples, this catalyst gives much higher yield and similar selectivity. In a successful attempt the introduction of 2-aminobenzimidazole onto a BINOL-scaffold could be achieved. If the same bulky group can be introduced at the 3 and 3'- of BINOL like in other organocatalysts, also higher yield and selectivity can be expected.

IV. Experimental Section

4.1 The synthesis of organocatalysts

4.1.1 The synthesis of imidazolidinone derivatives

(*S*)-2-(3-(Benzyloxycarbonyl)-5-oxooxazolidin-4-yl) acetic acid (94)



94

A mixture containing *N*-benzyloxycarbonyl-*L*-aspartic acid (2.67 g, 10 mmol), paraformaldehyde (0.6 g, 20 mmol) and *p*-TsOH·H_2O (0.12 g, 0.6 mmol) in benzene (75 ml) was heated at reflux for 60 min with removal of water with a Dean-Stark trap. EtOAc (20 ml) was added, the solution was washed with 0.3 M aq. K_2CO_3 (1 ml) and H_2O (3×2 ml) and dried with Na_2SO_4. After this, the solvent was removed by evaporation and colorless syrup (2.54 g, 91.0% yield) was obtained.

$[\alpha]_D^{20}$ = +137.4 (c = 6.75, $CHCl_3$).

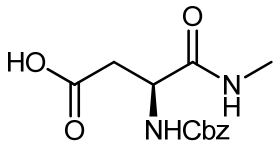
^{1}H NMR (400 MHz, $CHCl_3$-d) δ = 10.09 (1H, s), 7.51 (5H, m), 5.60 (1H, s), 5.30 (1H, s), 5.21 (2H, m), 5.56 (1H, s), 3.69 (1H, m), 3.00 (1H, d, J = 18 Hz).

^{13}C NMR (400 MHz, $CHCl_3$-d) δ = 173.9, 171.6, 152.7, 135.0, 128.5, 128.4, 128.1, 78.2, 67.9, 51.3, 33.9.

HRMS (ESI) *m/z* calculated for $[M+Na]^+$ 302.0641, found 302.0635.

TLC (Acetone / DCM = 1:6), R_f = 0.4.

(*S*)-3-(Benzyloxycarbonylamino)-4-(methylamino)-4-oxobutanoic acid (95)



95

(*S*)-2-(3-(Benzyloxycarbonyl)-5-oxooxazolidin-4-yl) acetic acid (5.58 g, 20 mmol) was dissolved in methanol (10 ml) and methylamine (0.1 mol, 12.5 ml, 8 mol/l in methanol) was added. The mixture was stirred at room temperature for 8 h, and the solvent removed by evaporation. The residue was dissolved in H_2O (10 ml) and the solution was justified to pH 2 with HCl (1 mol/L). The white insoluble product was filtered and the filter cake was washed with water. After drying, product (1.32 g 79.9% yield) was collected.

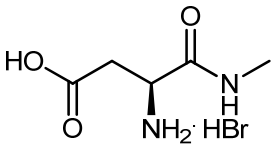
^{1}H NMR (400 MHz, DMSO-d6) δ = 7.31 (5H, m), 5.03 (2H, dd, J = 12.6 Hz, J = 9.1 Hz), 4.25 (1H, m), 2.86 (1H, dd, J = 11.10 Hz, J = 5.36 Hz), 2.63 (3H, d, J = 4.53 Hz), 2.41 (1H, m).

^{13}C NMR (400 MHz, DMSO-d6) δ = 171.8, 171.0, 155.8, 136.9, 128.3, 127.8, 127.7, 65.5, 51.5, 36.5, 25.8.

HRMS (ESI-neg) *m/z* calculated for $[M-H]^+$ 279.0981, found 279.0986.

TLC (Methanol / DCM = 1:6), R_f = 0.4.

(*S*)-3-Amino-4-(methylamino)-4-oxobutanoic acid (96)



96

(*S*)-3-(Benzyloxycarbonylamino)-4-(methylamino)-4-oxobutanoic acid (1.12 g, 4 mmol) was dissolved in acetic acid (10 ml) and HBr (2.94 ml, 33% in acetic acid) was dropwise added. The reaction was stirred at room temperature for 5 h and was poured then onto diethyl ether (60 ml). The precipitate was filtered and washed with ether. After drying, a white product (0.83 g, 92.4% yield) was afforded.

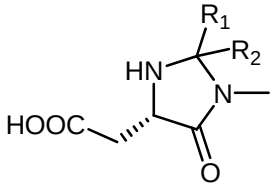
$[\alpha]_D^{20}$ = +16.8 (c = 1.35, H_2O).

^{1}H NMR (400 MHz, H_2O-d2) δ = 4.29 (1H, m), 2.99 (2H, m), 2.76 (3H,s).

^{13}C NMR (400 MHz, H_2O-d2) δ = 175.0, 171.0, 51.9, 37.1, 28.3.

HRMS (ESI-neg) *m/z* calculated for $[M-H]^+$ 224.9875, found 224.9880.

The general procedures for the synthesis of compound 90-92.

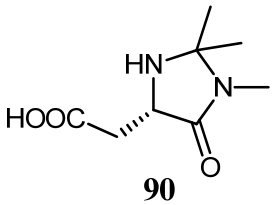


90-92

Method A

To a solution of (*S*)-3-amino-4-(methylamino)-4-oxobutanoic acid salt (2.43 g, 10.8 mmol) in methanol (20 ml) was added dry Et_3N (1.5 ml, 10.8 mmol) at room temperature. The reaction was stirred at room temperature for 2 h. Then the solvent was removed by vacuum. Benzene (60 ml) was added to the residue, ketone (30.24 mmol, 3.0 equiv) and *p*-TSA anhydrous (0.185 g, 1.08 mmol) were added and refluxed overnight. Then the solvent was removed by evaporation. The purification was done by flash silica gel chromatography.

(*S*)-2-(1, 2, 2-Trimethyl-5-oxoimidazolidin-4-yl) acetic acid (90)



90

Flash silica gel chromatography (MeOH / DCM = 1:6) gave white product (1.46 g, 73% yield)

$[\alpha]_D^{20}$ = +8.6 (c = 0.50, $CHCl_3$).

^{1}H NMR (400 MHz, DMSO-d6) δ = 3.90 (1H, m), 2.79 (3H, s), 2.70 (1H, m), 2.55 (1H, dd, *J* = 9.2 Hz, *J* = 8.7 Hz), 1.42 (3H, s), 1.35 (3H, s).

^{13}C NMR (400 MHz, DMSO-d6) δ = 174.3, 170.1, 77.6, 56.2, 36.7, 27.2, 25.5, 24.5.

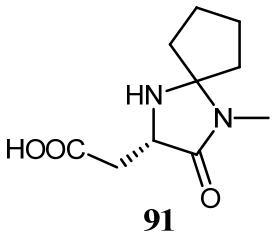
HRMS (ESI) *m/z* calculated for $[M+H]^+$ 187.1083, found 187.1077.

Flash silica gel chromatography (Methanol / DCM = 1:6), R_f = 0.5.

Method B

A mixture of (*S*)-3-amino-4-(methylamino)-4-oxobutanoic acid (1.46 g, 10 mmol), ketone (30 mmol, 3.0 equiv), 4 A molecular sieves (6.0 g) and dry ethanol 30.0 mL was heated to reflux for 20 h. The mixture was cooled down to room temperature and then filtered through Celite, and the filtrate was concentrated in vacuum. The purification was made by Flash silica gel chromatography.

(*S*)-2-(4-Methyl-3-oxo-1,4-diazaspiro [4.4] nonan-2-yl)acetic acid (91) (with Method B)



91

Flash silica gel chromatography (MeOH / DCM = 1:5) gave white product (1.69 g, 80% yield).

$[\alpha]_D^{20}$ = +3.4 (c = 1.00, $CHCl_3$).

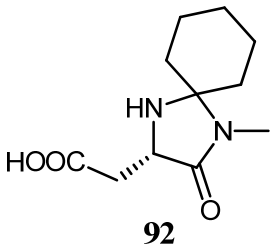
^{1}H NMR (400 MHz, $CHCl_3$-d) δ = 4.00 (1H, m), 2.86-2.88 (1H, m), 2.80 (3H, s), 2.70-2.60 (1H, m), 2.20-1.65 (8H, m).

^{13}C NMR (400 MHz, $CHCl_3$-d) δ = 175.5, 172.2, 86.2, 55.1, 35.9, 33.9, 25.4, 24.0, 23.9.

HRMS (ESI) *m/z* calculated for $[M+H]^+$ 213.1239, found 213.1234.

Flash silica gel chromatography (Methanol / DCM = 1:5), R_f = 0.5.

(*S*)-2-(4-Methyl-3-oxo-1, 4-diazaspiro [4.5] decan-2-yl) acetic acid (92) (with Method B)



92

Flash silica gel chromatography (MeOH / DCM = 1:5) gave white product (1.98g, 88% yield).

$[\alpha]_D^{20}$ = +25.1 (c = 1.50, CH_3Cl).

^{1}H NMR (400 MHz, $CHCl_3$-d) δ = 4.00 (1H, m), 2.90-2.83 (1H, m), 2.80 (3H, s), 2.66-2.55 (1H, m), 1.70-1.50 (10H, m).

^{13}C NMR (400 MHz, $CHCl_3$-d) δ = 174.2, 172.3, 78.0, 62.2, 40.3, 36.0, 32.4, 25.3, 24.5, 22.4, 21.8.

HRMS (ESI) *m/z* calculated for $[M+H]^+$ 227.1396, found 227.1390.

Flash silica gel chromatography (Methanol / DCM = 1:5), $R_{f=}$ 0.6.

4.1.2 The synthesis of *L*-proline amide derivatives

The general procedures for the synthesis of proline *N*-sulfonylamide and imide catalysts

Method A

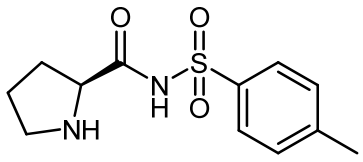
Under a dry Argon atmosphere, to a stirred solution of Cbz-*L*-proline (2.37 g, 11 mmol) in DCM (25 mL) the corresponding amide (10 mmol), DMAP (366 mg, 3 mmol) and DCC (2.47 g, 12 mmol), respectively, were added. The resulting mixture was stirred at room temperature for 24 h. Then the mixture was filtered, and washed with DCM (10 mL). The filtrate was washed with saturated brine (2×10 mL), dried with Na_2SO_4 and concentrated in vacuum. The crude product was purified by flash silica gel chromatography (MeOH / DCM). Deprotection was performed by 10% Pd/C in methanol. The mixture was stirred at room temperature for 14 hours under an atmosphere of hydrogen. The reaction was filtered through Celite and the filtrate concentrated in vacuum. The crude product was purified by flash silica gel chromatography to give the corresponding deprotection product.

Method B

Proline *N*-carboxyanhydride was synthesized starting from *L*-proline according to the following procedure. A dry 250 mL three-necked flask, fitted with a stirrer, nitrogen inlet tube, 50mL pressure- equalized addition funnel and a Teflon-coated thermocouple probe, containing dry THF (60 mL) is charged with *L*-proline (6.0 g, 52.1 mmol). To the cooled (15-20 °C) suspension, phosgene (32.4 mL, 62.5 mmol, 1.93 M in toluene) is added, via a pressure-equalized addition funnel, over a 0.5-1.0 hour period maintaining a temperature of 15-20 °C. The reaction mixture is then aged for 0.5-0.75 hour at 30-40 °C. The reaction mixture should become homogeneous as the proline reacts with the phosgene to afford the intermediate *N*-carbamoyl chloride. Once homogeneous, the reaction mixture is aged an additional 0.5 hour, then concentrated under reduced pressure (15-20 °C, 20 mBar) to a volume of 8 mL. Dry tetrahydrofuran (60 mL) is added to the mixture and it is cooled to 0-5°C. Dry triethylamine (7.26 mL, 52.1 mmol) is added over 0.25 hour. The mixture is aged for 0.5 hour at 0-5 °C, then filtered through an enclosed, 200 mL, medium-frit Schlenk funnel under an atmosphere of nitrogen (with careful exclusion of moisture). The triethylammonium hydrochloride cake is washed with dry tetrahydrofuran (3×10 mL). The filtrate was used immediately.

A solution of the corresponding amide (6.8 mmol) in THF (50 ml) was cooled to -78 °C, *t*-BuLi (8.5 ml, 13.6 mmol) was added, and the mixture was stirred for 10 min. A solution of proline *N*-carboxyanhydride (6.8 mmol) in THF (10 ml) was added, and the reaction was completed by stirring at -78 °C for 1 h. The mixture was warmed to room temperature, and the solvent was removed. The mixture was added 50 ml ethyl acetate and it was washed with saturated solution of NH_4Cl (8 ml). The layers were separated, and the aqueous layer was extracted again with EtOAc (2×50 ml). The combined organic layers were dried with Na_2SO_4 and concentrated in vacuum. The product was purified by flash silica gel chromatography.

_N_-Toluenesulfonyl-_L_-proline amide (116 a) with Method A and B



116a

Yield 51%

$[\alpha]_D^{20}$ = 9.1 (c = 1.00, MeOH).

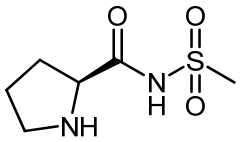
^{1}H NMR (400 MHz, MeOH-d4) δ = 7.81 (2H, d, *J* = 8.4 Hz), 7.41 (2H, d, *J* = 8.1 Hz), 4.15 (1H, t, *J* = 12.0 Hz), 3.35 (1H, m), 3.34-3.30 (2H, m), 2.45 (3H, s), 1.88-2.08 (3H, m).

^{13}C NMR (400 MHz, MeOH-d4) δ = 168.4, 146.7, 137.1, 130.7, 129.3, 61.5, 47.3, 30.3, 24.7, 21.5.

HRMS (ESI) *m/z* calculated for $[M+H]^+$ 269.0960, found 269.0954.

Flash silica gel chromatography (Hexane / EtOAc = 1:1), R_f = 0.4.

_N_-methanesulfonyl-_L_-proline amide (116b) with Method A and B



116b

Yield 38%

$[\alpha]_D^{20}$ = −2.3 (c = 0.60, MeOH).

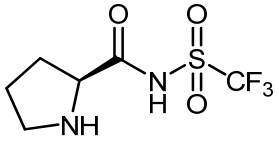
^{1}H NMR (400 MHz, MeOH-d4) δ = 3.82 (1H, t, *J* = 8.2 Hz), 3.50-3.33 (2H, m), 3.01 (3H, s), 2.40 (1H, m), 2.16 (1H, m), 2.07-2.00 (2H, m).

^{13}C NMR (400 MHz, MeOH-d4) δ = 175.2, 63.6, 47.3, 40.5, 30.7, 24.9.

HRMS (ESI) *m/z* calculated for $[M+H]^+$ 193.0647, found 193.0641.

Flash silica gel chromatography (Hexane / EtOAc = 1:1), R_f = 0.2.

_N_-Trifluoromethylsulfonyl-_L_-proline amide (116 c) with method A and method B



116c

Yield 47%

$[\alpha]_D^{20}$ = −18.4 (c = 1.00, MeOH).

^{1}H NMR (400 MHz, DMSO-d6) δ = 9.73 (1H, s), 8.26 (1H, s), 3.98 (1H, t, J = 7.3 Hz), 3.28-3.0 (2H, m), 2.38-2.23 (1H, m), 1.98-1.72 (3H, m).

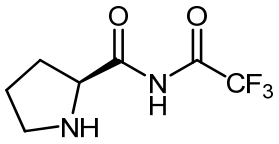
^{13}C NMR (400 MHz, DMSO-d6) δ = 172.8, 125.0, 121.8, 118.5, 115.3, 61.9, 45.3, 29.1, 23.2.

^{19}F NMR (400 MHz, DMSO-d6) δ = 77.504.

HRMS (ESI) *m/z* calculated for $[M+H]^+$ 247.0364, found 247.0359.

Flash silica gel chromatography (Hexane / EtOAc = 1:1), R_f = 0.2.

_N_-(2, 2, 2-Trifluoroacetyl)-_L_-proline amide (117a) with method B



117a

Yield 45%

$[\alpha]_D^{20}$ = -65.5 (c = 1.00, MeOH).

^{1}H NMR (400 MHz, $CHCl_3$-d) δ = 6.61 (1H, s), 6.03 (1H, s), 4.57-4.55 (1H, t, J = 3.4 Hz), 3.69-3.82 (2H, m), 3.34-3.30 (2H, m), 2.00-2.30 (4H, m).

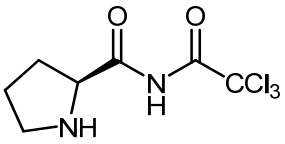
^{13}C NMR (400 MHz, $CHCl_3$-d) δ = 172.3, 156.7, 156.3, 120.4, 117.5, 114.7, 111.8, 129.3, 60.9, 47.5, 27.8, 24.9.

^{19}F NMR (400 MHz, $CHCl_3$-d) δ = 72.841.

HRMS (ESI) *m/z* calculated for $[M+Na]^+$ 233.0514, found 233.0508.

Flash silica gel chromatography (Hexane / EtOAc = 1:1), R_f = 0.2.

_N_-(2, 2, 2-Trichloroacetyl)-_L_-proline amide (117b) with method B



117b

Yield 30%

$[\alpha]_D^{20}$ = -36.8 (c = 1.00, MeOH).

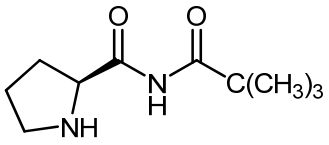
^{1}H NMR (400 MHz, $CHCl_3$-d) δ = 6.53 (1H, s), 6.16 (1H, s), 4.56 (1H, s), 4.05 (1H, m) 3.96 (1H, m), 2.19-2.13 (3H, m), 1.98 (1H, m).

^{13}C NMR (400 MHz, $CHCl_3$-d) δ = 173.1, 159.7, 99.9, 62.9, 50.2, 28.2, 25.7.

HRMS (ESI) *m/z* calculated for $[M+Na]^+$ 280.9627, found 280.9622.

Flash silica gel chromatography (Hexane / EtOAc = 1:1), R_f = 0.2.

N-Pivaloyl-*L*-proline amide (117c) with method B



117c

Yield 47%

$[\alpha]_D^{20}$ = -10.1 (c = 1.00, MeOH).

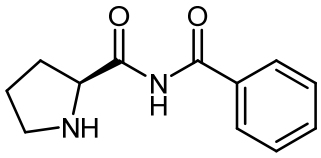
^{1}H NMR (400 MHz, $CHCl_3$-d) δ = 6.70 (1H, s), 5.89 (1H, s), 4.57-4.54 (1H, m), 3.70-3.68 (1H, m), 2.14-2.10 (2H, m), 1.93-1.92 (2H, m).

^{13}C NMR (400 MHz, $CHCl_3$-d) δ = 177.5, 174.9, 61.4, 48.2, 38.9, 27.3.

HRMS (ESI) *m/z* calculated for $[M+H]^+$ 199.1447, found 199.1441.

Flash silica gel chromatography (Hexane / EtOAc = 1:1), R_f = 0.2.

N-Benzoyl-*L*-proline amide (117d) with method B



117d

Yield 53%

$[\alpha]_D^{20}$ = -98.0 (c = 1.00, MeOH).

^{1}H NMR (400 MHz, $CHCl_3$-d) δ = 7.50 (2H, d), 7.40 (3H, m), 7.10 (1H, s), 6.10 (1H, s), 4.70 (1H, m), 3.50-3.40 (2H, m), 2.30-2.25 (1H, m), 2.11-2.08 (1H, m), 1.98-1.75 (2H, m).

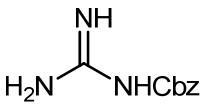
^{13}C NMR (400 MHz, $CHCl_3$-d) δ = 173.9, 170.5, 136.0, 130.1, 128.1, 127.0, 59.6, 45.0, 28.0, 25.2.

HRMS (ESI) *m/z* calculated for $[M+Na]^+$ 241.0953, 241.0947.

Flash silica gel chromatography (Hexane / EtOAc = 1:1), R_f = 0.3.

4.1.3 The synthesis of imidazole derivatives

_N_-Cbz-Guanidine(131)



131

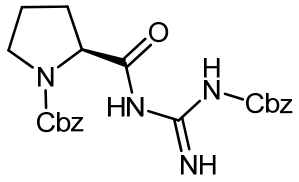
Guanidine hydrochloride (7.5 g, 78.5 mmol) was dissolved in aqueous 4N NaOH (40 mL) and cooled to 0℃. Benzyl chloroformate (11.2 ml, 78.5 mmol) was dissolved in 1, 4-dioxane (80 mL) and was added dropwise to the guanidine solution with vigorous stirring. The reaction was allowed to react for 18 h at room temperature after which the solvents were removed under reduced pressure. The crude product was suspended in 20 mL H_2O, filtered and washed with cold water (20 ml). Then the white solid was washed with cold diethyl ether (20 mL) subsequently dried in a desiccator. The product was isolated as a white solid (13.30 g, 88% yield).

^{1}H NMR (400 MHz, DMSO-d6) δ = 7.35 (5H, m), 4.86 (2H, s).

^{13}C NMR (400 MHz, DMSO-d4) δ = 163.2, 163.0, 138.1, 128.1, 127.3, 127.2, 64.7.

LC/MS $[M+H]^+$ caculated 194.1, found 194.1

(*S*)-Benzyl 2-(*N*-(benzyloxycarbonyl) carbamimidoylcarbamoyl) pyrrolidine-1-carboxylate(132)



132

To a solution of *N*-carbobenzyloxy-*L*-proline (2.49 g, 10.0 mmol, 1.0 equiv.) and *N*-Cbz-guanidine (2.213g, 11 mmol, 1.1 equiv.) in CH_2Cl_2 (30.0 mL) *N*, *N'*-dicyclohexyl- carbodiimide(2.26 g, 11.0 mmol, 1.1 eq) and 4-dimethylamino pyridine(1.34g, 11 mmol) were added at 0 ^oC under N_2 atmosphere. The reaction mixture was stirred for 30 minutes at 0 ^oC, then stirred at room temperature for 24 hours. The reaction mixture was fast filtrated through silica gel pad (SiO_2 15 g) to remove dicyclohexyl urea. Further purification was through flash silica gel chromatography.

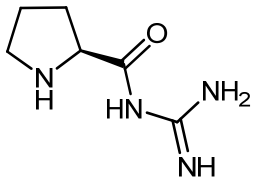
^1H NMR (400 MHz, $CHCl_3$-d) δ = 7.42-7.20 (10H, m), 5.23-5.15 (1H, m), 5.15-5.14 (2H, d, J = 2.55 Hz), 5.14-4.99 (1H, m), 4.45-4.32 (2H, m), 3.72-3.41 (2H, m), 2.32-1.99 (2H, m), 1.99-1.82 (2H, m).

^{13}C NMR (400 MHz, $CHCl_3$-d) δ = 171.7, 158.6, 155.9, 146.9, 136.0, 128.4, 128.4, 128.1, 128.0, 128.0, 67.6, 67.1, 61.8, 47.3, 29.3, 24.4.

HRMS (ESI) *m/z* calculated for $[M+H]^+$ 425.1825, found 425.1819.

Flash silica gel chromatography (Methanol / DCM = 1:15), R_f = 0.8.

(*S*)-*N*-Carbamimidoylpyrrolidine-2-carboxamide (129a)



129a

To a solution of **132** (2.12 g, 5 mmol) in MeOH (20 mL) was added 10% Pd/C. The mixture was stirred at room temperature for 14 hours under an atmosphere of hydrogen. The reaction was filtered through Celite and the filtrate concentrated in vacuum. The crude product was purified by flash column chromatography (MeOH / DCM = 1: 4) to give the product (0.69g, 90% yield).

$[\alpha]_D^{20}$ = -3.0 (c = 0.40, MeOH).

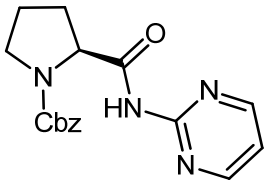
^1H NMR (400 MHz, DMSO-d_6) δ = 8.50-7.91 (1H, br), 7.72-7.50 (1H, br), 3.90-3.82 (1H, t, J = 8.6 Hz), 3.51-3.30 (3H, m), 3.20-3.10 (1H, m), 2.08-1.80 (3H, m), 1.56-1.48 (1H, m).

^{13}C NMR (400 MHz, DMSO-d_6) δ = 189.0, 177.3, 66.9, 47.9, 27.2, 26.4.

HRMS (ESI) *m/z* calculated for $[M+H]^+$ 157.1089, found 157.1084.

Flash silica gel chromatography (Methanol / DCM = 1:4), R_f = 0.2.

(*S*)-Benzyl 2-(pyrimidin-2-ylcarbamoyl) pyrrolidine-1-carboxylate (136)



136

To a solution of *N*-carbobenzyloxy-*L*-proline (2.49 g, 10.0 mmol, 1.0 equiv.) and pyrimidin-2-amine (1.04g, 11 mmol, 1.1 equiv.) in CH_2Cl_2 (30.0 mL) N,N'-dicyclohexyl- carbodiimide(2.26 g, 11. mmol, 1.1 equiv.) and 4-dimethylamino pyridine(1.34g, 11 mmol) were added at 0 ^oC under N_2 atmosphere. The reaction mixture was stirred for 30 minutes at 0 ^oC, then stirred at room temperature for 24 hours. The reaction mixture was filtrated through silica gel pad (SiO_2 15 g) to remove dicyclohexyl urea. Further purification was through flash silica gel chromatography. The target product (2.37 g, 73% yield) was obtained as a white solid.

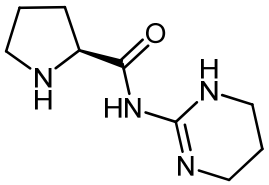
^1H NMR (400 MHz, $CHCl_3$-d) δ = 8.50-7.91 (1H, br), 8.60 (2H, d, J = 4.85 Hz), 7.50-7.10 (5H, m), 7.00 (1H, S), 5.10 (2H, m), 4.95-4.85 (1H, S), 3.70-3.40 (2H, m), 2.40-1.90 (4H, m).

^{13}C NMR (400 MHz, $CHCl_3$-d) δ = 158.1, 136.1, 128.2, 127.8, 127.6, 116.3, 67.2, 61.1, 46.9, 28.0, 24.1.

HRMS (ESI) *m/z* calculated for $[M+Na]^+$ 349.1277, found 349.1271.

Flash silica gel chromatography (Methanol / DCM = 1:10), R_f = 0.8.

(*S*)-*N*-(1,4,5,6-Tetrahydropyrimidin-2-yl) pyrrolidine-2-carboxamide (129b)



129b

To a solution of **136** (1.63 g, 5 mmol) in MeOH (20 mL) was added 10% Pd/C. Then 2 drops of concentrated HCl was added to the solution. The mixture was stirred at room temperature for 14 hours under an atmosphere of hydrogen. Then excess of Na_2CO_3 was added to the solution. Then the reaction mixture was filtered through Celite and the filtrate concentrated in vacuum. The crude product was purified by flash silica gel chromatography (MeOH / DCM = 1:4) to give the product (0.891g, 91% yield).

$[\alpha]_D^{20}$ = -1.5 (c = 1.00, MeOH).

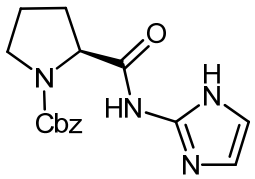
^{1}H NMR (400 MHz, MeOH-d4) δ = 4.18-4.14 (1H, m), 3.54-3.48 (2H, m), 3.44-3.36 (2H, m), 3.10-3.00 (2H, m), 2.20-2.10 (3H, m), 2.08-1.98 (2H, m), 1.65-1.58 (1H, m).

^{13}C NMR (400 MHz, MeOH-d4) δ = 191.9, 176.9, 69.3, 49.2, 40.5, 37.7, 29.1, 28.7, 27.8.

HRMS (ESI) *m/z* calculated for $[M+H]^+$ 197.1402, found 197.1397.

Flash silica gel chromatography (Methanol / DCM = 1:4), R_f = 0.2.

(*S*)-Benzyl 2-(1*H*-imidazol-2-ylcarbamoyl)pyrrolidine-1-carboxylate (138)



138

To a solution of *N*-carbobenzyloxy-*L*-proline (2.49 g, 10.0 mmol, 1.0 equiv.) and 2-aminoimidazole sulfate(2.36 g, 11 mmol, 1.1 equiv.) in CH_2Cl_2 (30.0 mL) N,N'-dicyclohexylcarbodiimide(2.26 g, 11. mmol, 1.1 equiv.) and 4-dimethylamino pyridine(2.68g, 22 mmol,) were added at 0 ^oC under N_2 atmosphere. The reaction mixture was stirred for 30 minutes at 0 ^oC, then at room temperature for 24 hours. The reaction mixture was filtrated through silica gel pad (SiO_2 15 g) to remove dicyclohexyl urea. Further purification was through flash silica gel chromatography. The target product (2.4g, 78% yield)was obtained as a white solid.

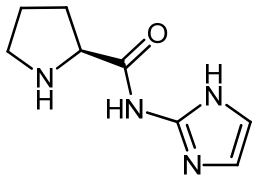
^{1}H NMR (400 MHz, $CHCl_3$-d) δ = 7.46-7.08 (5H, m), 6.82 (2H, s), 5.21-4.92 (2H, m), 4.53-4.43 (1H, dd, *J* = 3.62 Hz), 3.73-3.50 (2H, m), 2.42-2.22 (1H, m), 2.19-1.82 (3H, m).

^{13}C NMR (400 MHz, $CHCl_3$-d) δ =173.6, 156.9, 142.6, 140.4, 129.3, 128.9, 128.7, 119.2, 108.2, 68.3, 61.6, 40.1, 32.4, 24.6.

HRMS (ESI) *m/z* calculated for $[M+H]^+$ 315.1457, found 315.1452.

Flash silica gel chromatography (Methanol / DCM = 1:15), R_f = 0.6.

_N_-1_H_-Imidazol-2-yl-_L_-prolinamide (129c)



129c

To a solution of **138** (1.57 g, 5 mmol) in MeOH (20 mL) was added 10% Pd/C. The mixture was stirred at room temperature for 14 hours under an atmosphere of hydrogen. The reaction was filtered through Celite and the filtrate concentrated in vacuum. The crude product was purified by flash silica gel chromatography (MeOH / DCM =1: 4) to give the product (0.74 g, 82% yield).

$[\alpha]_D^{20}$ = -48.6 (c = 0.53, MeOH).

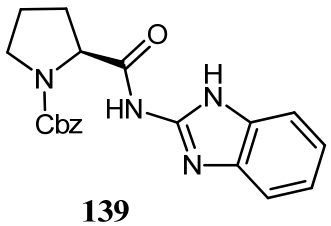
^{1}H NMR (400 MHz, MeOH-d4) δ = 6.72-6.68 (2H, d, *J* = 1.82Hz), 3.60-3.50 (1H, m), 3.00-2.90 (2H, m), 2.18-2.08 (1H, m), 1.90-1.75 (1H, m), 1.72-1.65 (2H, m).

^{13}C NMR (400 MHz, MeOH -d4) δ = 175.6, 142.8, 118.9, 118.9, 61.7, 47.9, 31.8, 26.9.

HRMS (ESI) *m/z* calculated for $[M+H]^+$ 181. 1089, found 181.1084.

Flash silica gel chromatography (Methanol / DCM = 1:4), R_f = 0.3.

(_S_)-Benzyl 2-(1_H_-benzo [_d_] imidazol-2-ylcarbamoyl) pyrrolidine-1-carboxylate (139)



139

To a solution of *N*-carbobenzyloxy-*L*-proline (2.49 g, 10.0 mmol, 1.0 equiv.) and

2-amino-1*H*-benzimidazole (1.46 g, 11 mmol, 1.1 equiv.) in CH_2Cl_2 (30.0 mL) *N*, *N*'-dicyclohexylcarbodiimide(2.26 g, 11. mmol, 1.1 equiv.) and 4-dimethylamino pyridine (2.68g, 22 mmol) were added at 0 ^oC under N_2 atmosphere. The reaction mixture was stirred for 30 minutes at 0 ^oC, then at room temperature for 24 hours. The reaction mixture was filtrated through silica gel pad (SiO_2 15 g) to remove dicyclohexyl urea. Further purification was through flash silica gel chromatography.

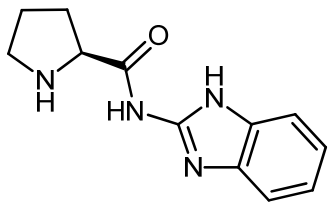
^{1}H NMR (600 MHz, $CHCl_3$-d) δ = 7.4 89 (2H, s), 7.41-7.35 (3H, m), 7.28-7.22 (3H, m), 6.99 (1H, s), 5.29-5.27 (1H, d, J = 12.2 Hz), 5.17-5.06 (1H, m), 4.77-4.74 (2H, d, J = 17.6 Hz), 3.74-3.55 (2H, m), 2.18-2.12 (2H, m), 2.10-2.01 (1H, m), 1.90-1.89 (1H, m).

^{13}C NMR (600 MHz, $CHCl_3$-d) δ = 173.9, 173.2, 155.4, 154.2, 147.5, 147.4, 136.3, 135.8, 128.4, 128.3, 128.0, 128.0, 127.8, 127.7, 122.4, 122.2, 67.3, 60.7, 60.2, 47.3, 46.9, 31.4, 29.8, 24.4,23.6.

HRMS (ESI) *m/z* calculated for $[M+H]^+$ 365. 1614, found 365.1608.

Flash silica gel chromatography (Methanol / DCM = 1:15), R_f = 0.8.

_N_-1_H_-Benzimidazol-2-yl-_L_-prolinamide (129d)



129d

To a solution of **139** (1.82 g, 5 mmol) in MeOH (20 mL) was added 10% Pd/C. The mixture was stirred at room temperature for 14 hours under an atmosphere of hydrogen. The reaction was filtered through Celite and the filtrate concentrated in vacuum. The crude product was purified by flash column chromatography (MeOH / DCM = 1: 4) to give the product (1.04 g, 91% yield) as a white solid.

$[\alpha]_D^{20}$ = -50.8 (c = 0.46, MeOH).

^{1}H NMR (600 MHz, $CHCl_3$-d) δ = 7.55-7.35 (2H, m), 7.25-7.20 (2H, m), 4.00-3.95 (1H, t, J = 4.5 Hz), 3.15-2.95 (2H, m), 2.33-2.22 (1H, m), 2.12-2.02 (1H, m), 1.82-1.74 (2H, m).

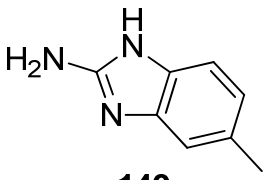
^{13}C NMR (600 MHz, $CHCl_3$-d) δ = 175.8, 146.2, 129.0, 128.5, 122.0, 114.5, 114.2,

60.4, 47.2, 30.8, 26.1.

HRMS (ESI) *m/z* calculated for $[M+H]^+$ 231. 1246, found 231.1240.

Flash silica gel chromatography (Methanol / DCM = 1:4), $R_f = 0.5$.

5-Methyl-1*H*-benzo[*d*]imidazol-2-amine (140)



140

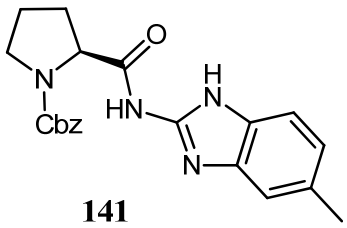
Compound 140 was synthesized with the method from Weiss [100].

^{1}H NMR (600 MHz, MeOH-d4) δ = 6.96 (1H, d, J = 7.56 Hz), 6.90 (1H, s), 6.71 (1H, d, J = 7.89 Hz), 2.27 (3H, s).

^{13}C NMR (600 MHz, $CHCl_3$-d) δ = 154.5, 129.8, 121.1, 112.0, 111.1, 20.9.

LC/MS $[M+ H]^+$ calculated 148.08, found148.08.

(*S*)-Benzyl 2-(5-methyl-1*H*-benzo [*d*] imidazol-2-ylcarbamoyl) pyrrolidine-1-carboxylate (141)



141

To a solution of *N*-carbobenzyloxy-*L*-proline (2.49 g, 10.0 mmol, 1.0 equiv.) and 6-methyl-1*H*-benzo [*d*]imidazol-2-amine (1.61 g, 11 mmol, 1.1 equiv.) in CH_2Cl_2 (30.0 mL) *N*, *N*'-dicyclohexylcarbodiimide (2.26 g, 11. mmol, 1.1 equiv.) and 4-dimethyl-amino pyridine(1.34g, 11 mmol, 1.1 equiv.) were added at 0 ^oC under N_2 atmosphere. The reaction mixture was stirred for 30 minutes at 0 ^oC, then at room temperature for 24 hours. The reaction mixture was filtrated through silica gel pad (SiO_2 15 g) to remove dicyclohexyl urea. Further purification was through flash silica gel chromatography.

^{1}H NMR (600 MHz, $CHCl_3$-d) δ = 7.42-7.31 (4H, m), 7.27 (1H, s), 7.21 (1H, s),

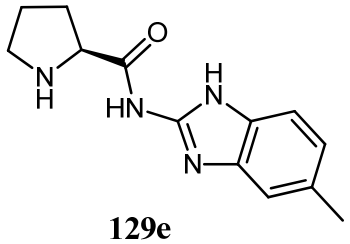
7.06-7.02 (2H, m), 5.30-5.21 (1H, m), 5.18-5.04 (1H, m), 4.75-4.70 (1H, s), 3.72-3.55 (2H, m), 2.47 (3H, s), 2.30-2.20 (3H, m), 1.98-1.80 (1H, m).

^{13}C NMR (600 MHz, $CHCl_3$-d) δ = 172.9, 155.7, 147.0, 137.1, 135.9, 132.2, 132.1, 128.4, 128.2, 128.1, 128.0, 123.8, 123.8, 123.7, 117.7, 67.5, 67.5, 60.8, 60.4, 47.4, 47.0, 29.5, 29.2, 24.5, 23.7, 21.6.

HRMS (ESI) *m/z* calculated for $[M+H]^+$ 379. 1770, found 379.1765.

Flash silica gel chromatography (Methanol / DCM = 1:15), R_f = 0.8.

_N_-(5-Methyl-1_H_-benzimidazol-2-yl)-_L_-prolinamide (129e)



129e

To a solution of **141** (1.89g, 5 mmol) in MeOH (20 mL) was added 10% Pd/C. The mixture was stirred at room temperature for 14 hours under an atmosphere of hydrogen. The reaction was filtered through Celite and the filtrate concentrated in vacuum. The crude product was purified by flash column chromatography to give the corresponding deprotection product.

$[\alpha]_D^{20}$ = - 66.4(c = 1.00, MeOH).

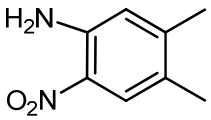
^{1}H NMR (600 MHz, $CHCl_3$-d) δ = 7.32-7.30 (1H, d, J = 8.15 Hz), 7.24 (1H, s), 6.93-6.92 (1H, d, J = 8.17 Hz), 3.95-3.91 (1H, m), 2.99-2.98 (2H, m), 2.37 (3H, s), 2.16-2.10 (1H, m), 1.89-1.82 (1H, m), 1.75-1.70 (2H, m).

^{13}C NMR (600 MHz, $CHCl_3$-d) δ = 175.7, 147.2, 134.3, 132.4, 132.1, 123.6, 113.5, 113.3, 60.6, 46.8, 30.6, 25.7, 21.5.

HRMS (ESI) *m/z* calculated for $[M+H]^+$ 245. 1402, found 245.1397.

Flash silica gel chromatography (Methanol / DCM = 1:4), R_f = 0.5.

4,5-Dimethyl-2-nitroaniline (143)



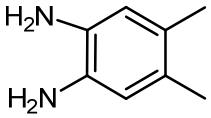
143

3,4-Dimethylaniline (20.0 g, 165 mmol) was dissolved in acetic acid (25 mL) and acetic anhydride (25 mL, 27 g, 0.26 mol, 1.6 equiv.) was added. The reaction mixture was heated to reflux for 15 min, and then added dropwise to water (300 mL) with ice and the white precipitate was filtered off using a Büchner funnel. A mixture of 65% nitric (95 mL, 1.36 mol, 8.2 equiv.) and acetic acid (35 mL) was cooled to 10-15 °C. The filtration cake from the previous step was dissolved in acetic acid (50 mL) and the solution was added dropwise to the mixture of acids. Once the addition was complete, the reaction mixture was stirred for additional 60 min at 10-20 °C. The reaction mixture was poured into water (ca. 1 L) and the resulting yellow precipitate was filtered off using a Büchner funnel, and washed well with water. The filtration cake was dissolved in concentrated sulphuric acid (125 mL) and heated to ca. 90 °C for 20 min. The reaction mixture was allowed to cool to ambient temperature, added dropwise to ice (ca. 200 g), the resulting orange precipitate was filtered off using a Büchner funnel and dried. The product (17.0 g, 61.5% yield) was obtained.

^{1}H NMR (600 MHz, $CHCl_3$-d) δ = 7.87 (1H, s), 6.62 (1H, s), 5.56 (2H, br) 2.24 (3H, s), 2.19 (3H, s).

^{13}C NMR (600 MHz, $CHCl_3$-d) δ = 146.5, 142.8, 130.3, 126.2, 125.6, 119.0, 20.0, 18.5.

4,5-Dimethylbenzene-1, 2-diamine (144)



144

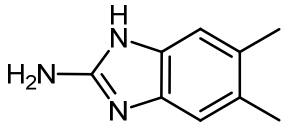
4,5-Dimethyl-2-nitroaniline (16.6 g, 10 mmol) was dissolved in ethanol (450 mL) and Pd/C (10%) (0.75g) was added. The mixture was dropwise added $N_2H_4 \cdot H_2O$ (30 mL, 5 equiv.) at N_2 atmosphere. After the addition, the reaction mixture was stirred at room temperature for another 30 min. Then the reaction mixture was heated to 80 °C for 14 hours. The reaction mixture was filtrate with celite. Ethanol and water was removed by

vacuum. The product (12.2 g, 90.0% yield) was obtained as white solid which became dark quickly.

^{1}H NMR (600 MHz, DMSO-d6) δ = 6.32 (2H, s), 2.00 (6H, s).

^{13}C NMR (600 MHz, DMSO-d6) δ = 132.61, 123.8, 116.6, 18.5.

5, 6-Dimethyl-1*H*-benzo[*d*]imidazol-2-amine (145)



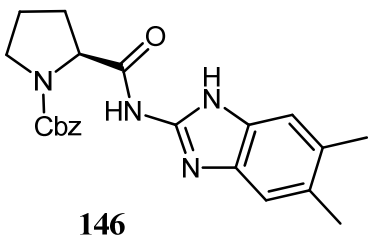
145

To a solution of 4, 5-dimethylbenzene-1,2-diamine (2.72 g, 20 mmol) and con. HCl (1.7mL, 20 mmol), a cyanamide solution (in 50% water) (2mL) was added and the mixture was heated at 100 ^{o}C for 10 hours. NaOH solution (0.83g in 1.7 mL H_2O) was dropped to the reaction mixture. When no more ammonia was produced, the reaction mixture was poured on ice (5 g). The resulting brown precipitate was filtrated off using a Büchner funnel and washed well with cold water. The precipitate was dried to give product (1.94 g, 60% yield).

^{1}H NMR (400 MHz, DMSO-d6 / CHCl3-d = 1: 10) δ = 6.95 (2H, s), 2.21 (6H, s).

^{13}C NMR (400 MHz, DMSO-d6 / CHCl3-d = 1: 10) δ = 153.8, 133.3, 127.2, 112.8, 19.4.

(*S*)-Benzyl-2-(5, 6-dimethyl-1*H*-benzo[*d*]imidazol-2-ylcarbamoyl) pyrrolidine-1-carboxylate (146)



146

To a solution of *N*-carbobenzyloxy-*L*-proline (2.49 g, 10.0 mmol, 1.0 equiv.) and 5, 6-dimethyl-1*H*-benzo[*d*]imidazol-2-amine (1.77 g, 11 mmol, 1.1 equiv.) in CH_2Cl_2 (30.0 mL) *N*, *N*'-dicyclohexylcarbodiimide(2.26 g, 11. mmol, 1.1 equiv.) and

4-dimethylamino pyridine(1.34g, 11 mmol, 1.1 equiv.) were added at 0 ^{o}C under N_2 atmosphere. The reaction mixture was stirred for 30 minutes at 0 ^{o}C, then at room temperature for 24 hours. The reaction mixture was filtrated through silica gel pad (SiO_2 15 g) to remove dicyclohexyl urea. Further purification was through flash silica gel chromatography.

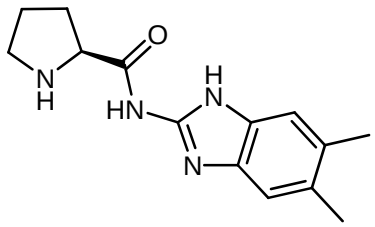
^{1}H NMR (600 MHz, $CHCl_3$-d) δ = 7.46-7.32 (3H, m), 7.28-7.24 (2H, m), 7.24-7.20 (1H, m), 7.06-7.00 (1H, m), 5.80-5.60 (1H, m), 5.20-5.00 (1H, m), 4.70-4.60 (1H, m), 3.90-3.75 (2H, m), 2.40-2.32 (6H, d, J = 12.2 Hz), 2.35-2.25 (2H, m), 2.20 (1H, m), 1.95-1.80 (1H, m).

^{13}C NMR (600 MHz, $CHCl_3$-d) δ = 173.3, 155.5, 146. 8, 146.7, 136.3, 136.0, 131.3, 131.2, 128.4, 128.3, 128.1, 128.0, 127.8, 127.7, 127.6, 127.4, 67.3, 67.2, 60.9, 60.5, 47.3, 46.9, 31.5, 29.9, 24.4, 23.7.

HRMS (ESI) *m/z* calculated for $[M+H]^+$ 393.1927, found 393.1921.

Flash silica gel chromatography (Methanol / DCM = 1:20), R_f = 0.7.

_N_-(5,6-Dimethyl-1_H_-benzimidazol-2-yl)-_L_-prolinamide (129f)



129f

To a solution of **146** (1.96 g, 5 mmol) in MeOH (20 mL) was added 10% Pd/C. The mixture was stirred at room temperature for 14 hours under an atmosphere of hydrogen. The reaction was filtered through Celite and the filtrate concentrated in vacuum. The crude product was purified by flash silica gel chromatography. The product (1.09 g, 84% yield) was obtained as a white solid.

$[\alpha]_D^{25}$ = -68.0 (c = 1.02, $CHCl_3$).

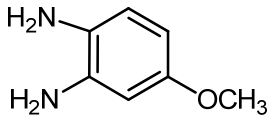
^{1}H NMR (600 MHz, MeOH-d4) δ = 7.24 (2H, s), 3.50-3.45 (1H, dd, J = 3.15 Hz, J = 7.25 Hz), 3.20 (1H, m), 2.80 (1H, m), 2.60 (1H, m), 2.30 (6H, s), 2.20 (1H, m), 2.00 (1H, m), 1.70 (2H, m).

^{13}C NMR (600 MHz, MeOH-d4) δ = 176.6, 147.9, 134.3, 132.2, 114.9, 62.1, 47.9, 31.7, 26.8, 20.2.

HRMS (ESI) *m/z* calculated for $[M+H]^+$ 259. 1559, found 259.1553.

Flash silica gel chromatography (Methanol / DCM = 1:4), R_f = 0.5.

4-Methoxybenzene-1,2-diamine (148)



148

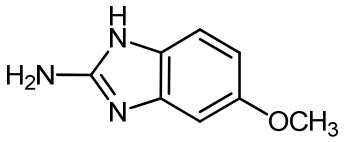
To a solution of 2-nitro-4-methoxyaniline (4.1 g, 24.4 mmol) in methanol (45 mL) was added 10% Pd/C (0.48 g) in small portions and the solution was stirred at hydrogen atmosphere for 18 h at room temperature. The reaction mixture was filtered through Celite, washed with EtOH, and solvent was evaporated in vacuum to give a white solid (3.10 g, 93% yield), which was carried to the next step without further purification.

^{1}H NMR (400 MHz, $CHCl_3$-d) δ = 6.65 (1H, d, *J* = 8.41 Hz), 6.35 (1H, d, *J* = 2.74 Hz), 6.29-6.27 (1H, dd, *J* = 2.73 Hz, *J* = 5.64 Hz), 3.74 (3H, s).

^{13}C NMR (400 MHz, $CHCl_3$-d) δ = 154.5, 137.0, 127.2, 118.2, 104.0, 102.9, 55.4.

TLC (Acetone / DCM = 1: 3), R_f = 0.3.

5-Methoxy-1*H*-benzo[*d*]imidazol-2-amine (149)



149

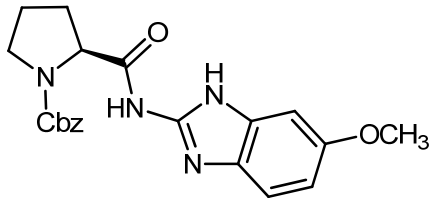
To a solution of 4-methoxybenzene-1, 2-diamine (3.1 g, 22.46 mmol) and con. HCl (1.9mL, 22.8 mmol), a cyanamide solution (in 50% water) (2.25mL) was added and the mixture was heated at 100 ^{o}C for 10 hours. NaOH solution (0.923g in 1.88 mL H_2O) was dropped to the reaction mixture. Until no ammonia was produced, the reaction mixture was poured to ice (10 g). The resulting brown precipitate was filtrated off using

a Büchner funnel and washed well with cold water. The precipitate was dried and the product (2.28 g, 62% yield) was obtained as dark solid.

^{1}H NMR (400 MHz, DMSO-d6) δ = 7.00 (1H, d, J = 8.42 Hz), 6.70 (1H, d, J = 2.42 Hz), 6.50 (1H, dd, J =2.43 Hz, J = 6.00 Hz), 3.70 (3H, s).

^{13}C NMR (400 MHz, DMSO-d6) δ = 159.7, 154.9, 139.3, 131.2, 111.0, 106.3, 97.5, 95.4.

(*S*)-Benzyl 2-(6-methoxy-1*H*-benzo[*d*]imidazol-2-ylcarbamoyl) pyrrolidine-1-carboxylate (150)



150

To a solution of *N*-carbobenzyloxy-*L*-proline (2.49 g, 10.0 mmol, 1.0 equiv.) and 5-methoxy-1*H*-benzo[*d*]imidazol-2-amine (1.79 g, 11 mmol, 1.1 equiv.) in CH_2Cl_2 (30.0 mL) N, N'-dicyclohexylcarbodiimide(2.26 g, 11. mmol, 1.1 equiv.) and 4-dimethylamino pyridine(1.34g, 11 mmol, 1.1 equiv.) were added at 0 ^oC under N_2 atmosphere. The reaction mixture was stirred for 30 minutes at 0 ^oC, then at room temperature for 24 hours. The reaction mixture was filtrated through silica gel pad (SiO_2 15 g) to remove dicyclohexyl urea. Further purification was through flash silica gel chromatography.

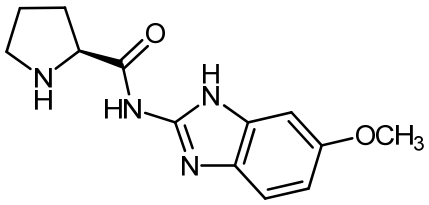
^{1}H NMR (400 MHz, $CHCl_3$-d) δ = 7.50-7.30 (4H, m), 7.20-6.80 (4H, m), 5.15-5.05 (2H, m), 4.60-4.40 (1H, m), 3.84 (3H, d, J = 7.80 Hz), 3.72-3.48 (2H, m), 2.38-2.20 (1H, m), 2.10-1.75 (3H, m).

^{13}C NMR (400 MHz, $CHCl_3$-d) δ = 179.3, 156.6, 154.5, 146.6, 136.7, 128.3, 128.0, 127.7, 127.4, 111.9, 66.5, 59.4, 55.7, 46.8, 30.8, 23.3.

HRMS (ESI) *m/z* calculated for $[M+H]^+$ 395.1719, found 395.1714.

Flash silica gel chromatography (Methanol / DCM = 1:10), R_f = 0.8.

_N_-(5-Methoxy-1_H_-benzimidazol-2-yl)-_L_-prolinamide (129g)



129g

To a solution of **150** (1.97 g, 5 mmol) in MeOH (20 mL) was added 10% Pd/C. The mixture was stirred at room temperature for 14 hours under an atmosphere of hydrogen. The reaction was filtered through Celite and the filtrate concentrated in vacuum. The crude product was purified by flash column chromatography to give the deprotection product (1.14 g, 88% yield).

$[\alpha]_D^{20}$ = -81.5 (c = 1.10, MeOH).

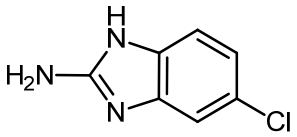
^{1}H NMR (400 MHz, MeOH-d4) δ = 6.90-7.30 (1H, d, J = 7.76 Hz), 6.54-6.52 (1H, d, J = 2.37 Hz), 6.35 (1H, dd, J = 2.39 Hz, J = 7.46 Hz), 3.50 (1H, m), 3.38 (3H, s), 2.60 (2H, m), 1.75 (1H, m), 1.50 (1H, m), 1.35 (2H, m).

^{13}C NMR (400 MHz, MeOH-d4) δ = 176.4, 157.7, 148.0, 115.3, 112.1, 108.8, 98.6, 62.0, 56.2, 47.9, 31.8, 26.9.

HRMS (ESI) *m/z* calculated for $[M+H]^+$ 261.1352, found 261.1352.

Flash silica gel chromatography (Methanol / DCM = 1:4), R_f = 0.5.

5-Chloro-1_H_-benzo[_d_]imidazol-2-amine (152)



152

To a solution of 4-chlorobenzene-1,2-diamine (5.68 g, 40.0 mmol) and con. HCl (3.4 mL, 40.8 mmol), cyanamide solution (in 50% water) (4.00 mL) was added and the mixture was heated at 100 ^oC for 10 hours. NaOH solution (1.69g in 3.4 mL H_2O) was dropped to the reaction mixture. When no more ammonia was produced, the reaction

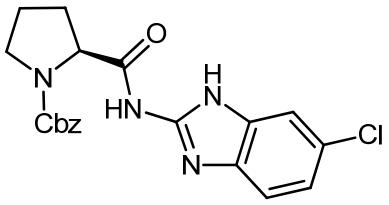
mixture was poured to ice (10 g). The resulting brown precipitate was filtrated off using a Büchner funnel and washed well with cold water. The precipitate was dried to give the product (4.08 g, 60% yield) as a white solid.

$[\alpha]_D^{25}$ = -18.2 (c = 1.02, MeOH).

^{1}H NMR (400 MHz, DMSO-d6 / $CHCl_3$-d = 2:1) δ = 6.90 (1H, d, J = 2.00 Hz), 6.86 (1H, d, J = 8.32 Hz), 6.68 (1H, dd, J = 2.02 Hz, J = 6.29 Hz).

^{13}C NMR (400 MHz, DMSO-d6 / $CHCl_3$-d = 2:1) δ = 160.7, 144.6, 141.0, 129.7, 124.4, 117.1, 116.8.

(*S*)-Benzyl 2-(6-chloro-1*H*-benzo[*d*]imidazol-2-ylcarbamoyl) pyrrolidine-1-carboxylate (153)



153

To a solution of *N*-carbobenzyloxy-*L*-proline (2.49 g, 10.0 mmol, 1.0 equiv.) and 5-chloro-1*H*-benzo[*d*]imidazole-2-amine (1.83 g, 11 mmol, 1.1 equiv.) in CH_2Cl_2 (30.0 mL) *N*, *N*'-dicyclohexylcarbodiimide(2.26 g, 11. mmol, 1.1 equiv.) and 4-dimethylamino pyridine(1.34g, 11 mmol, 1.1 equiv.) were added at 0 ^oC under N_2 atmosphere. The reaction mixture was stirred for 30 minutes at 0 ^oC, then at room temperature for 24 hours. The reaction mixture was filtrated through silica gel pad (SiO_2 15 g) to remove dicyclohexyl urea. Further purification was through flash silica gel chromatography.

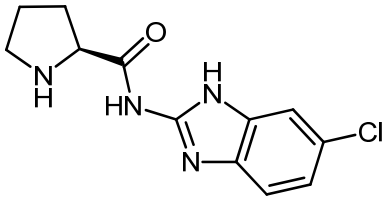
^{1}H NMR (400 MHz, $CHCl_3$-d) δ = 7.50-7.30 (5H, m), 7.20 (2H, m), 7.00 (1H, s), 5.30-5.25 (1H, m), 5.10 (1H, m), 4.60 (1H, m), 3.64 (2H, m), 2.28 (1H, m), 2.18-1.90 (2H, m).

^{13}C NMR (400 MHz, $CHCl_3$-d) δ = 172.8, 155.9, 147.7, 136.1, 135.8, 128.5, 128.1, 128.0, 127.8, 122.8, 114.6, 114.2, 67.6, 60.8, 47.0, 29.2, 24.5.

HRMS (ESI) *m/z* calculated for $[M+H]^+$ 399.1224, found 399.1218.

Flash silica gel chromatography (Methanol / DCM = 1:10), R_f = 0.7.

_N_-(5-Chloro-1_H_-benzimidazol-2-yl)-_L_-prolinamide (129h)



129h

To a solution of (*S*)-benzyl 2-(6-chloro-1*H*-benzo[*d*]imidazol-2-ylcarbamoyl) pyrrolidine-1-carboxylate (1.99 g, 5 mmol) in AcOH (15 mL) was added 33% HBr in glacial AcOH (3.7 mL) and the resulting mixture was stirred at room temperature for 4 hours. Then the reaction was poured into ether (100 mL). The white precipitate was filtered and then dissolved in H_2O (5 mL) with $NaHCO_3$(5 mmol, 0.42 g). The solution was extracted with EtOAc (3×10 mL), the organic layers were combined and dried with $NaSO_4$. After removal EtOAc by evaporation, the deprotection product (0.79 g, 60% yield) was obtained.

$[\alpha]_D^{25}$ = -18.2 (c = 1.02, MeOH).

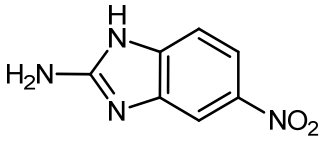
^{1}H NMR (400 MHz, $CHCl_3$-d) δ = 7.50 (1H, s), 7.40 (1H, d, *J* = 8.10 Hz), 7.18 (1H, dd, *J* = 1.98 Hz, *J* = 6.54 Hz), 3.50 (1H, dd, *J* = 2.82 Hz, *J* = 7.73 Hz), 3.22 (1H, m), 2.90 (1H, m), 2.60 (1H, m), 2.25-2.12 (1H, m), 2.10-2.02 (1H, m), 1.90-1.70 (2H, m).

^{13}C NMR (400 MHz, $CHCl_3$-d) δ = 176.6, 146.8, 140.4, 140.2, 136.4, 127.5, 122.5, 114.9, 114.4, 64.0, 50.7, 31.5, 24.7.

HRMS (ESI) *m/z* calculated for $[M+H]^+$ 265.0856, found 265.0851.

TLC (Methanol / DCM = 1:4), R_f = 0.5.

5-Nitro-1_H_-benzo[_d_]imidazol-2-amine (157)



157

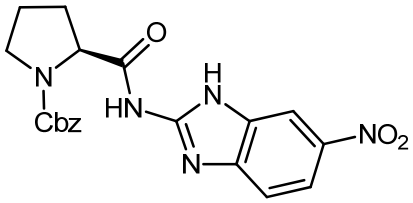
To a solution of 4-nitrobenzene-1,2-diamine (3.06 g, 20.0 mmol) and con. HCl (1.66

mL, 20.0 mmol), a cyanamide solution (in 50% water) (1.84 mL) was added and the mixture was heated at 100 ℃ for 10 hours. Then a NaOH solution (0.83g in 1.66 mL H_2O) was dropped to the reaction mixture. when no more ammonia was produced, the reaction mixture was poured to ice (10 g). The resulting brown precipitate was filtrated off using a Büchner funnel and washed well with cold water. The precipitate was dried to give product (2.31 g, 65% yield).

^{1}H NMR (400 MHz, DMSO-d6) δ = 7.90 (1H, dd, J = 2.27 Hz, J = 6.37 Hz), 7.68 (1H, d, J = 2.26 Hz), 7.06 (1H, d, J = 8.63 Hz).

^{13}C NMR (400 MHz, DMSO-d6) δ = 155.4, 141.2, 135.6, 129.7, 117.7, 108.0, 103.6.

(*S*)-Benzyl-2-(6-nitro-1*H*-benzo[*d*]imidazol-2-ylcarbamoyl) pyrrolidine-1-carboxylate (154)



154

To a solution of *N*-carbobenzyloxy-*L*-proline (2.49 g, 10.0 mmol, 1.0 equiv.) and 5-nitro-1*H*-benzo[*d*]imidazole-2-amine (1.96 g, 11 mmol, 1.1 equiv.) in CH_2Cl_2 (30.0 mL) *N*, *N*'-dicyclohexylcarbodiimide(2.26 g, 11. mmol, 1.1 equiv.) and 4-dimethylamino pyridine(1.34g, 11 mmol, 1.1 equiv.) were added at 0 ^oC under N_2 atmosphere. The reaction mixture was stirred for 30 minutes at 0 ^oC, then stirred at room temperature for 24 hours. The reaction mixture was filtrated through silica gel pad (SiO_2 15 g) to remove dicyclohexyl urea. Further purification was through flash silica gel chromatography.

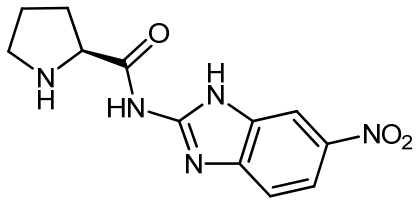
^{1}H NMR (400 MHz, DMSO-d6) δ = 8. 37 (1H, m), 8.07 (1H, m), 7.60 (1H, m), 7.40-7.00 (5H, m), 5.10-4.95 (2H, m), 4.50 (1H, m), 3.54 (2H, m), 2.30 (1H, m), 2.05-1.85 (3H, m).

^{13}C NMR (400 MHz, DMSO-d6) δ = 172.0, 154.0, 153.4, 136.8, 136.5, 128.3, 127.9, 127.7, 127.5, 127.4, 126.9, 66.0, 59.9, 59.4, 47.1, 46.5, 30.9, 29.9, 24.0, 23.1.

HRMS (ESI) *m/z* calculated for $[M+H]^+$ 410.1464, found 410.1459.

Flash silica gel chromatography (Methanol / DCM = 1:10), R_f = 0.7.

N-(5-Nitro-1*H*-benzimidazol-2-yl)-*L*-prolinamide (129i)



129i

To a solution of (*S*)-benzyl 2-(6-nitro-1*H*-benzo[*d*]imidazol-2-ylcarbamoyl)pyrrolidine -1-carboxylate (2.04 g, 5 mmol) in AcOH (15 mL) 33% HBr in glacial AcOH (3.7 mL) was added and the resulting mixture was stirred at room temperature for 4 hours. Then the reaction was poured into ether (100 mL). The white precipitate was filtered and then dissolved in H_2O (5 mL) with $NaHCO_3$(5 mmol, 0.42 g). The solution was extracted with EtOAc (3×10 mL), the organic layer was conbined together and dried with $NaSO_4$. After removal EtOAc by evaporation, the deprotection product (0.87 g, 63% yield) was obtained as orange solid.

$[\alpha]_D^{20}$ = -49.9 (c = 1.15, DMSO).

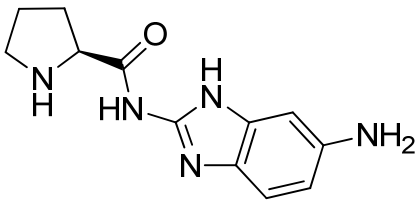
^{1}H NMR (400 MHz, DMSO-d6) δ = 8. 31 (1H, d, *J* = 2.26 Hz), 8.03 (1H, dd, *J* = 2.34 Hz, *J* = 6.48 Hz), 7.57 (1H, d, *J* = 8.83 Hz), 4.05 (1H, m), 3.00 (2H, m), 2.10 (1H, m), 1.85 (1H, m), 1.70 (2H, m).

^{13}C NMR (400 MHz, DMSO-d6) δ = 174.9, 150.1, 150.3, 141.7, 117.3, 116.9, 114.4, 109.9, 60.3, 46.6, 126.9, 66.0, 59.9, 59.4, 47.1, 46.5, 30.0, 25.7.

HRMS (ESI) *m/z* calculated for $[M+H]^+$ 276.1097, found 276.1091.

TLC (Methanol / DCM = 1:4), R_f = 0.4.

N-(5-Amino-1*H*-benzimidazol-2-yl)-*L*-prolinamide (155)



155

To a solution of **154** (2.04 g, 5 mmol) in MeOH (20 mL) was added 10% Pd/C. The mixture was stirred at room temperature for 14 hours under an atmosphere of hydrogen. The reaction was filtered through Celite and the filtrate concentrated in vacuum. The crude product was purified by flash column chromatography to give the deprotection product (1.14 g, 88% yield).

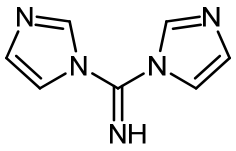
^{1}H NMR (400 MHz, MeOH-d4) δ = 7.24 (1H, d, J = 8.68 Hz), 6.87 (1H, d, J = 1.76 Hz), 6.35 (1H, dd, J = 2.18 Hz, J = 8.45 Hz), 3.89 (1H, m), 3.00 (2H, m), 2.25 (1H, m), 1.95 (1H, m), 1.80 (2H, m).

^{13}C NMR (400 MHz, MeOH -d4) δ = 176.6, 147.0, 144.0, 137.8, 123.3, 115.4, 113.5, 101.1, 61.8, 48.0, 31.9, 27.1.

HRMS (ESI) *m/z* calculated for $[M+H]^+$ 246.1355, found 246.1365.

Flash silica gel chromatography (Methanol / DCM = 1:4), R_f = 0.4.

Di (imidazole-1-yl) methanimine (159)



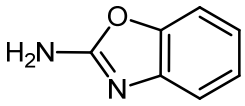
159

To a solution of imidazole (6.8 g, 100 mmol) in 500 mL of dichloromethane cyanogen bromide (3.7 g, 33 mmol) was added and the mixture heated at reflux temperature for 30 min. The mixture was cooled to room temperature, the white precipitate removed by filtration, and the filtrate concentrated to 50 mL and cooled to 0 °C for 2 days. The crystallized solid was filtered and washed with cold dichloromethane and dried to give product (5.20 g, 97.8 % yield) as a white solid.

^{1}H NMR (400 MHz, DMSO-d6) δ = 8. 10 (1H, s), 7.56 (1H, s), 7.30 (1H, s), 7.10 (1H, s).

^{13}C NMR (400 MHz, DMSO-d6) δ = 140.4, 137.3, 129.6, 118.9.

Benzo[*d*]oxazol-2-amine (160)



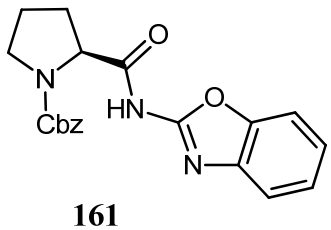
160

A solution containing di (imidazole-1-yl) methanimine 43 (805mg, 5.0 mmol) and 2-aminophenol (545 mg, 5.0 mmol) in anhydrous THF (25 mL) was allowed to reflux under nitrogen overnight. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (100 mL), and washed successively with water, saturated aqueous NH_4Cl solution and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuum to afford the crude product. Further purification by flash silica gel chromatography gave the desired product (0.56g, 84% yield) as a white solid.

^{1}H NMR (400 MHz, $CHCl_3$-d) δ = 7. 36 (1H, d, J = 7.87 Hz), 7.29 (1H, d, J = 7.83 Hz), 7.20 (1H, m), 7.09 (1H, m).

^{13}C NMR (400 MHz, $CHCl_3$-d) δ = 162.0, 148.4, 142.4, 123.9, 121.2, 116.2, 108.9.

(*S*)-Benzyl 2-(benzo[*d*]oxazol-2-ylcarbamoyl)pyrrolidine-1-carboxylate(161)



161

To a solution of *N*-carbobenzyloxy-*L*-proline (2.49 g, 10.0 mmol, 1.0 equiv.) and 44 (1.47 g, 11 mmol, 1.1 equiv.) in CH_2Cl_2 (30.0 mL) *N*, *N*'-dicyclohexylcarbodiimide (2.26 g, 11. mmol, 1.1 equiv.) and 4-dimethylamino pyridine(1.34g, 11 mmol, 1.1 equiv.) were added at 0 ^oC under N_2 atmosphere. The reaction mixture was stirred for 30 minutes at 0 ^oC, then stirred at room temperature for 24 hours. The reaction mixture was filtrated through silica gel pad (SiO_2 15 g) to remove dicyclohexyl urea. Further purification was through flash silica gel chromatography.

^{1}H NMR (400 MHz, $CHCl_3$-d) δ = 7. 60 (1H, d, J = 7.35 Hz), 7.45 (1H, d, J = 7.68 Hz), 7.40-7.20 (7H, m), 7.40-7.00 (5H, m), 5.30 (2H, m), 4.60 (1H, m), 3.54 (2H, m), 2.30 (1H, m), 2.50 (1H, m), 2.20-2.00 (3H, m).

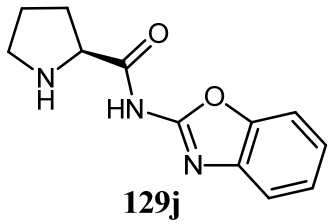
^{13}C NMR (400 MHz, $CHCl_3$-d) δ = 172.1, 157.0, 154.6, 147.7, 140.1, 135.9, 128.5,

128.2, 127.9, 124.6, 123.7, 118.6, 110.0, 67.9, 60.3, 47.1, 33.6, 24.8.

HRMS (ESI) *m/z* calculated for $[M+Na]^+$ 388.1273, found 388.1268.

Flash silica gel chromatography (Methanol / DCM = 1:10), R_f = 0.6.

_N_-1,3-Benzoxazol-2-yl-_L_-prolinamide (129j)



129j

To a solution of **161** (1.82g, 5 mmol) in MeOH (20 mL) was added 10% Pd/C. The mixture was stirred at room temperature for 14 hours under an atmosphere of hydrogen. The reaction was filtered through Celite and the filtrate concentrated in vacuum. The crude product was purified by flash column chromatography to give the deprotection product (1.02g, 89% yield).

$[\alpha]_D^{20}$ = -253.5 (c = 1.20, DMSO).

^{1}H NMR (400 MHz, DMSO-d6) δ = 7. 40 (1H, m), 7.00 (1H, m), 6.87 (1H, d, J = 7.78 Hz), 6.80 (1H, t, J = 7.51 Hz, J = 7.31 Hz), 4.00 (1H, m), 3.35 (2H, m), 2.00 (3H, m), 1.60 (1H, m).

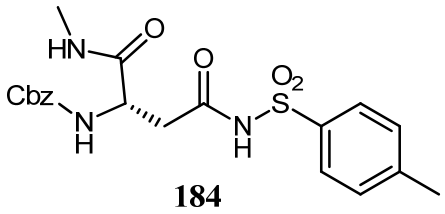
^{13}C NMR (400 MHz, DMSO-d6) δ = 172.2, 151.8, 149.6, 142.9, 126.0, 124.9, 119.0, 116.9, 66.7, 48.6, 27.3, 26.4.

HRMS (ESI) *m/z* calculated for $[M+H]^+$ 232.1086, found 232.1086.

Flash silica gel chromatography (Methanol / DCM = 1:4), R_f = 0.3.

4.1.4 The synthesis of peptidic organocatalysts

(_S_)-Benzyl(1-(methylamino)-4-(4-methylphenylsulfonamido)-1,4-dioxobutan-2-yl) carbamate (184)



184

To a stirred solution of (*S*)-3-(benzyloxycarbonylamino)-4-(methylamino)-oxo butanoic acid (2.80 g, 10 mmol) in DCM (25 mL) were added 4-methylbenzene-sulfonamide (1.71 g, 10 mmol), DMAP (1.22g, 10 mmol) and EDCI (1.55 g, 10 mmol) respectively. The resulting mixture was stirred at room temperature for 24 h. Then the mixture was washed with HCl solution (15 mL, 1 mol/L) and saturated brine (2×10 mL). The organic phase was dried with Na_2SO_4 and concentrated in vacuum. The crude product was purified by flash column chromatography (DCM / MeOH). The pure compound (3.8 g, 88% yield) was obtained as a white solid.

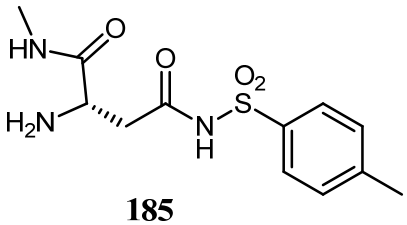
^{1}H NMR (400 MHz, $CHCl_3$-d) δ = 7.90-7.84 (2H, d, J = 8.10 Hz), 7.34-7.30 (5H, m), 7.26-7.10 (2H, d, J = 7.97 Hz), 5.08 (2H, s), 4.58 (1H, s), 2.92-2.86 (1H, m), 2.80-2.72 (1H, m), 2.70 (3H, d, J = 3.75 Hz), 2.40 (3H, s).

^{13}C NMR (400 MHz, $CHCl_3$-d) δ = 175.0, 171.6, 156.3, 135.8, 129.4, 128.5, 128.2, 128.0, 127.9, 67.3, 51.5, 38.4, 26.4, 21.5.

HRMS (ESI) *m/z* calculated for $[M+Na]^+$ 456.1205, found 456.1200.

Flash silica gel chromatography (Methanol / DCM = 1:6), R_f = 0.7.

(*S*)-2-Amino-N^1-methyl-N^4-tosylsuccinamide (185)



185

To a solution of **184** (2.17 g, 5 mmol) in MeOH (20 mL) was added 10% Pd/C. The mixture was stirred at room temperature for 14 hours under an atmosphere of hydrogen. The reaction was filtered through Celite and the filtrate concentrated in vacuum. The crude product was purified by flash column chromatography (Methanol / DCM = 1:6) to give the product (1.3 g, 86.9% yield).

$[\alpha]_D^{20}$ = +1.8 (c = 1.80, MeOH).

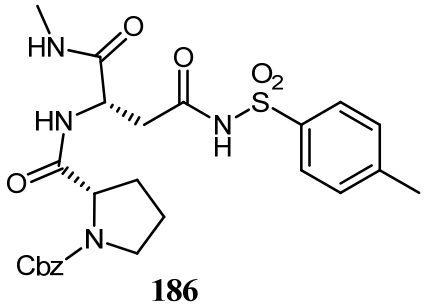
^{1}H NMR (400 MHz, MeOH-d4) δ = 7.80 (2H, d, J = 8.07 Hz), 7.26 (2H, d, J = 8.06 Hz), 3.35 (1H, m), 2.70 (2H, d, J = 6.60 Hz), 2.40 (3H, s), 1.90 (3H,s).

^{13}C NMR (400 MHz, MeOH-d4) δ = 179.8, 177.4, 142.9, 142.3, 129.7, 127.9, 45.4, 38.4, 26.2, 24.2, 21.2.

HRMS (ESI-neg) *m/z* calculated for $[M-H]^+$ 298.0862, found 298.0867.

Flash silica gel chromatography (Methanol / DCM = 1:6), R_f = 0.7.

(*S*)-Benzyl-2-((*S*)-1-(methylamino)-4-(4-methylphenylsulfonamido)-1,4-dioxobutan- 2-ylcarbamoyl) pyrrolidine-1-carboxylate (186)



186

DMAP (1.22 g, 10 mmol) and EDCI (1.55 g, 10 mmol) were added to a stirred solution of Cbz-*L*-proline (2.37 g, 11 mmol) and compound **185** (2.99 g, 10 mmol) in DCM (25 mL). The mixture was stirred at room temperature for 24 h. Afterwards the mixture was washed with diluted HCl solution (15 mL, 1 mol/L). Then the organic phase was washed with saturated brine (2×10 mL), dried with Na_2SO_4 and concentrated in vacuum. The crude product was purified by flash column chromatography (Acetone / DCM). The target product (4.61 g, 87% yield) was obtained as a white solid.

$[\alpha]_D^{20}$ = −56.1 (c = 1.50, MeOH).

^{1}H NMR (400 MHz, $CHCl_3$-d) δ = 7.89 (2H, d, J = 7.94 Hz), 7.53 (1H, d, J = 7.61 Hz), 7.40 (3H, m), 7.35-7.30 (2H, m), 7.27 (2H, d, J = 7.79 Hz), 5.20 (2H, m), 4.76 (1H, m), 4.30 (1H, m), 3.65 (1H, m), 3.50 (1H, m), 3.00 (1H, dd, J = 6.2 Hz, J = 5.07Hz), 2.73-2.70 (1H, dd, J = 4.83 Hz, J = 4.81 Hz), 2.70-2.65 (3H, d, J = 4.23 Hz), 2.58 (1H, s), 2.42 (3H,s), 2.20 (1H, m), 2.05 (1H, m), 1.89 (2H, m).

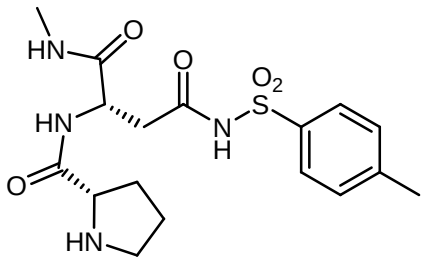
^{13}C NMR (400 MHz, $CHCl_3$-d) δ = 172.1, 170.8, 169.3, 153.9, 136.1, 129.4, 128.6,

128.1, 127.5, 67.6, 61.4, 53.4, 47.1, 33.3, 29.9, 26.5, 24.5, 21.6.

HRMS (ESI-neg) *m/z* calculated for $[M-H]^+$ 529.1757, found 529.1762.

Flash silica gel chromatography (Acetone / DCM = 1:4), $R_f = 0.5$.

(*S*)-*N*^{1}-Methyl-2-((*S*)-pyrrolidine-2-carboxamido)-*N*^{4}-tosylsuccinamide (182)



182

To a solution of **186** (2.65 g, 5 mmol) in MeOH (20 mL) was added 10% Pd/C. The mixture was stirred at room temperature for 14 hours under an atmosphere of hydrogen. The reaction was filtered through Celite and the filtrate concentrated in vacuum. The crude product was purified by flash column chromatography (Methanol / DCM) to give the product (1.8 g, 91% yield).

$[\alpha]_D^{20} = -26.9$ (c = 1.20, MeOH).

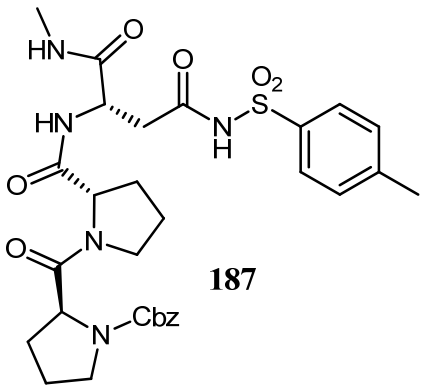
^{1}H NMR (400 MHz, $CHCl_3$-d) δ = 7.75 (2H, d, J = 7.52 Hz), 7.19-7.15 (2H, d, J = 7.31 Hz), 4.80 (1H, s), 4.60 (1H, s), 3.47 (2H, s), 2.57 (2H, s), 2.60 (3H, s), 2.36 (1H, s), 2.34 (3H, s), 2.02 (1H, s), 1.90 (2H, s).

^{13}C NMR (400 MHz, $CHCl_3$-d) δ = 171.6, 170.9, 170.5, 139.4, 129.1, 126.7, 126.6, 60.1, 50.7, 45.8, 45.5, 34.6, 29.7, 26.2, 24.3, 21.3.

HRMS (ESI-neg) *m/z* calculated for $[M-H]^+$ 395.1389, found 395.1395.

Flash silica gel chromatography (Methanol / DCM = 1:4), $R_f = 0.2$.

(*S*)-Benzyl-2-((*S*)-2-((*S*)-1-(methylamino)-4-(4-methylphenylsulfonamido)-1,4-dio xo butan-2-ylcarbamoyl) pyrrolidine-1-carbonyl) pyrrolidine-1-carboxylate (187)



187

DMAP (1.22 g, 10 mmol) and EDCI (1.55 g, 10 mmol) were respectively added to a stirred solution of Cbz-*L*-proline (2.37 g, 11 mmol) and compound **182** (3.96 g, 10 mmol) in DCM (40 mL). The resulting mixture was stirred at room temperature for 24 h. After reaction, the mixture was washed with HCl solution (15 mL, 1 mol/L). Then the organic phase was washed with saturated brine (2×10 mL), dried with Na_2SO_4 and concentrated in vacuum. The crude product was purified by flash column chromatography (MeOH / DCM). The target product (5.61 g, 89.6% yield) was obtained as white solid.

$[\alpha]_D^{20} = -69.5$ (c = 1.05, MeOH).

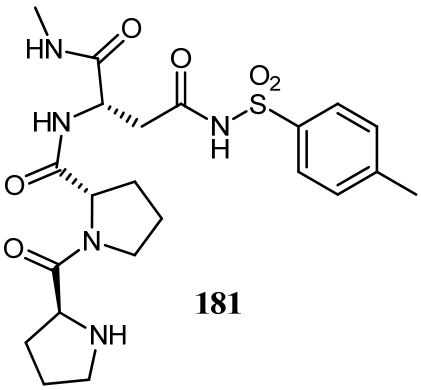
^{1}H NMR (400 MHz, DMSO-d6) δ = 7.75 (2H, dd, J = 2.60 Hz, J = 5.69 Hz), 7.40-7.35 (7H, m), 5.08 (2H, m), 4.50 (1H, m), 4.35 (1H, m), 4.15 (1H, m), 3.52 (4H, m), 2.67 (2H, m), 2.50 (3H, d, J = 4.57 Hz), 2.36 (1H, s), 1.93-1.70 (6H, m).

^{13}C NMR (400 MHz, DMSO-d6) δ = 173.9, 173.5, 171.0, 169.6, 153.4, 136.9, 136.6, 129.2, 128.3, 128.2, 127.7, 127.3, 126.9, 66.0, 65.8, 60.0, 57.1, 48.9, 48.8, 37.1, 30.6, 29.6, 25.7, 24.5, 24.3, 20.9.

HRMS (ESI) *m/z* calculated for $[M+Na]^+$ 650.2261, found 650.2255.

Flash silica gel chromatography (Methanol / DCM = 1:4), R_f = 0.8.

(*S*)-*N*^{1}-Methyl-2-((*S*)-1-((*S*)-pyrrolidine-2-carbonyl)pyrrolidine-2-carboxamido)-*N*^{4}-tosylsuccinamide (181)



181

To a solution of **187** (3.15 g, 5 mmol) in MeOH (30 mL) was added 10% Pd/C. The mixture was stirred at room temperature for 14 hours under an atmosphere of hydrogen. The reaction was filtered through Celite and the filtrate concentrated in vacuum. The crude product was purified by flash column chromatography (Methanol / DCM) to give the product (2.3 g, 93% yield).

$[\alpha]_D^{20} = -77.9$ (c = 1.25, MeOH).

^{1}H NMR (400 MHz, MeOH-d4) δ = 7.80 (1H, d, J = 1.26 Hz), 7.76 (1H, d, J = 1.25 Hz), 7.30 (1H, s), 7.27 (1H, s), 4.55 (1H, dd, J = 3.70 Hz, J = 6.29 Hz), 4.52-4.40 (2H, m), 3.75-3.45 (4H, m), 2.73 (1H, d, J = 5.78 Hz), 2.62-2.50 (2H, m), 2.40 (3H, s), 2.38-1.90 (8H, m).

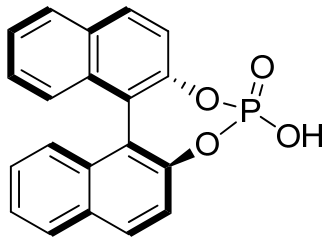
^{13}C NMR (400 MHz, MeOH-d4) δ = 178.6, 173.9, 173.2, 170.3, 143.1, 142.0, 129.8, 127.9, 62.3, 61.1, 52.5, 50.8, 46.1, 32.7, 30.1, 29.8, 26.4, 25.3, 23.4, 21.3.

HRMS (ESI) *m/z* calculated for $[M+H]^+$ 494.2073, found 494.2068.

Flash silica gel chromatography (Methanol / DCM = 1:4), R_f = 0.2.

4.1.5 The synthesis of BINOL Brönsted acid derivatives

(*S*)-(-)-1,1'-Binaphthyl-2,2'-diyl hydrogenphosphate (190)



190

(S)-BINOL (1.43g, 5.0 mmol) was dissolved in 5mL pyridine. $POCl_3$ (0.47 mL,

5.0mmol) was dropwise added to the mixture under nitrogen. The reaction was stirred at room temperature for 8 h. Afterwards, 10mL of water were added to the reactions. Then the mixture was stirred for 30 minutes and DCM (20 mL) was added. After separation, the organic phase was washed with 1 mol/L HCl solution (3×10 mL). The organic phases were dried over with Na_2SO_4 and concentrated in vacuum. The crude product was purified by flash column chromatography to give product (1.26 g, 73% yield) as a white solid.

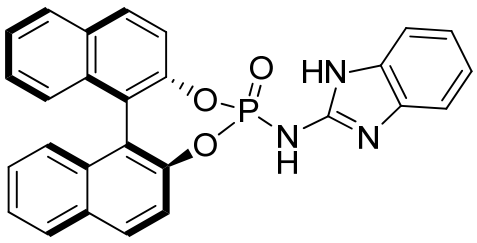
^{1}H NMR (400 MHz, DMSO-d6) δ = 8.19 (2H, d, J = 8. 86 Hz), 8.10 (2H, d, J = 8.19 Hz), 7.58 (2H, d, J = 8.84 Hz), 7.52 (2H, t, J = 7.32 Hz), 7.37 (2H, t, J = 7.55 Hz), 7.24 (2H, d, J = 8.65 Hz).

^{13}C NMR (400 MHz, DMSO-d6) δ = 147.5, 147.4, 131.5, 130.9, 130.9, 128.5, 126.7, 126.0, 125.4, 121.1, 120.9.

^{31}P NMR (400 MHz, DMSO-d6) δ = 2.58.

Flash silica gel chromatography (Methanol / DCM = 1:4), R_f = 0.4.

(4*S*, 11b*S*)-4-((1*H*-benzo[*d*]imidazol-2-yl)amino)dinaphtho[2,1-d:1',2'-f][1,3,2] dioxaphosphepine 4-oxide (188)



188

To a solution of compound **186** (3.48 g, 10.0 mmol, 1.0 equiv.) and 2-aminobenzimidazole (1.47 g, 11 mmol, 1.1 equiv.) in dry DMSO (30.0 mL), EDCI(1.7 g, 11. mmol, 1.1 equiv.) and 4-dimethylamino pyridine(1.34g, 11 mmol, 1.1 equiv.) were added at 0 ^{o}C under N_2 atmosphere. The reaction mixture was stirred for 30 minutes at 0 ^{o}C, then stirred at room temperature for 24 hours. The reaction mixture was washed with water, and then the organic phase was concentrated in vacuum until a large amount of white suspension occurred. The mixture was filtrated and washed with cold DCM several times. Then dry filtrate cake (2.1 g, 45% yield)

was collected.

^{1}H NMR (400 MHz, DMSO-d6) δ = 8.07 (2H, d, J = 8. 81 Hz), 8. 30 (2H, d, J = 8.14 Hz), 7.53 (2H, d, J = 8.47 Hz), 7.46 (2H, t, J = 7.14 Hz), 7.32 (2H, t, J = 8.12 Hz), 7.25 (2H, d, J = 8.49 Hz), 7.17 (2H, q, J = 3.26 Hz, J = 5.66 Hz), 7.96 (2H, q, J = 3.15 Hz, J = 5.77 Hz).

^{13}C NMR (400 MHz, DMSO-d6) δ = 153.1, 149.5, 134.2, 131.8, 130.5, 130.0, 128.4, 126.2, 126.0, 124.6, 122.4, 121.6, 120.7, 111.2.

^{31}P NMR (400 MHz, DMSO-d6) δ = 4.68.

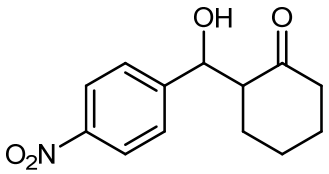
TLC (Methanol / DCM = 1:5), R_f = 0.5.

4.2 The synthesis of racemic products

4.2.1 The synthesis racemic products of the aldol reaction

The aldehyde (20 mmol) was dissolved in ketone (0.2 mol) cooled in an ice bath, and 3.0 mL of 0.2 mol/L aqueous sodium hydroxide was dropwise added. The mixture was stirred at 0°C for 4 h, after which the excess ketone was removed by vacuum at room temperature. 50 mL water and 50 mL ether were added. The organic layer was separated. The water layer was extracted with 25 mL ether. The organic layers were combined and dried over Na_2SO_4. The crude product was purified by flash silica gel chromatography (Ethyl acetate / Cyclohexane).

2-[Hydroxy-(4-nitrophenyl)-methyl]-cyclohexan-1-one (racemic) (100)



100

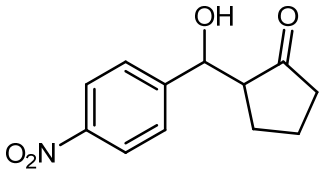
^{1}H NMR (400 MHz, $CHCl_3$-d) δ = 8.45-8.40 (2H, m), 7.55-7.50 (2H, m), 5.55 (1H, s, syn), 4.80 (1H, d, J = 1 Hz), 4.10 (1H, s, syn), 3.40 (1H, s, anti), 2.70-2.60 (1H, m),

2.60-2.70 (1H, m), 2.45-2.30 (1H, m), 2.15-2.10 (1H, m), 1.80-1.70 (1H, m), 178-1.54 (4H, m), 1.48-1.35 (1H, m).

^{13}C NMR (400 MHz, $CHCl_3$-d) δ = 214.6, 213.9, 149.0, 148.3, 127.8, 126.5, 123.5, 123.4, 73.9, 70.0, 57.1, 56.7, 42.6, 42.5, 30.7, 27.8, 27.6, 25.8, 24.7, 24.6.

HPLC (Chiralpac IA, Heptan / Ethanol = 70:30, flow rate 1 mL/min, λ = 209-300 nm): *t*R = 11.55 (*syn*), 31.68 (*syn*), 24.24 (*anti*), 26.93 (*anti*).

2-[Hydroxy-(4-nitrophenyl)-methyl]-cyclopentan-1-one (racemic)(101)



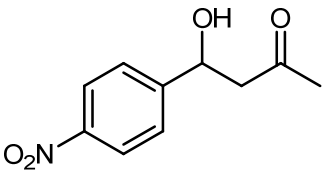
101

^{1}H NMR (400 MHz, $CHCl_3$-d) δ = 8.18-8.22 (2H, m), 7.54-7.50 (2H, m), 5.42-5.40 (1H, d, *J* = 2.8 Hz, syn), 4.80-4.60 (1H, d, *J* = 9.0 Hz, anti), 2.60-2.40 (2H, m), 2.20-1.80 (2H, m), 1.80-1.70 (2H, m).

^{13}C NMR (400 MHz, $CHCl_3$-d) δ = 150.2, 148.6, 127.3, 126.3, 123.6, 123.5, 74.2, 70.3, 56.0, 55.0, 38.8, 38.5, 26.7, 22.3, 20.3.

HPLC (Chiralpac IA, Heptan / Ethanol = 70:30, flow rate 1 mL/min, λ = 209-300 nm): *t*R = 10.35 (*syn*), 17.49 (*syn*), 13.68 (*anti*), 23.12 (*anti*).

4-Hydroxy-4-(4-nitrophenyl) butan-2-one (racemic)(102)



102

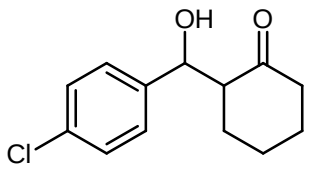
^{1}H NMR (400 MHz, $CHCl_3$-d) δ = 8.18 (2H, d, *J* = 8.8 Hz), 7.54 (2H, d, *J* = 8.8 Hz), 5.28 (1H, q, *J* = 6.1Hz), 3.79 (1H, br), 2.87 (2H, d, *J* = 6.1 Hz), 2.23 (3H, s);

^{13}C NMR (400 MHz, $CHCl_3$-d) δ = 208.6, 150.1, 147.3, 126.4, 123.7, 68.8, 51.4, 30.5.

HPLC (Ciracel OJ-H, Heptan / 2-Propanol = 80:20, flow rate 1 mL/min, λ = 209-300

nm): *t*R = 14.21, 15.87.

2-(Hydroxy-*p*-chlorophenylmethyl) cyclohexan-1-one (racemic)(103)



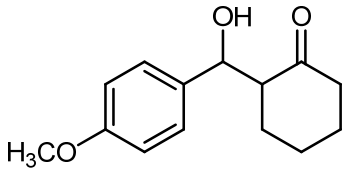
103

^{1}H NMR (400 MHz, $CHCl_3$-d) δ = 7.35-7.32 (2H, m), 7.30-7.22 (2H, m), 5.40 (1H, m, anti), 4.70 (1H, dd, *J* = 2.1 Hz), 2.61 (1H, m), 2.51 (1H, m), 2.41 (1H, m), 2.11 (1H, m), 1.82 (1H, m), 1.72 (1H, m), 1.57 (2H, m), 1.31 (1H, m).

^{13}C NMR (400 MHz, $CHCl_3$-d) δ = 215.1, 139.5, 133.5, 128.5, 128.3, 74.1, 57.3, 42.6, 30.7, 27.6, 24.6.

HPLC (Chiralpac IA, Heptan / Ethanol = 85:15, flow rate 0.8 mL/min, λ = 209-300 nm): *t*R = 11.63 (*syn*), 21.20 (*syn*), 19.84 (*anti*), 25.01(*anti*).

2-(Hydroxy-*p*-methoxyphenylmethyl) cyclohexan-1-one (racemic)(104)



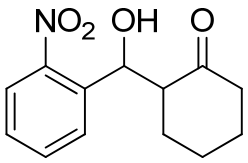
104

^{1}H NMR (400 MHz, $CHCl_3$-d) δ = 7.28-7.22 (2H, m), 6.90 (2H, d, *J* = 8.7 Hz), 5.33 (1H, m, anti), 4.77-4.74 (1H, dd, *J* = 1.7 Hz, syn), 3.93 (1H, d, *J* = 2.42 Hz, syn), 3.81 (3H, s), 3.01 (1H, d, *J* = 2.9 Hz, anti), 2.41 (1H, m), 2.50-2.30 (2H, m), 1.90-1.50 (4H, m), 1.30-1.20 (1H, m).

^{13}C NMR (400 MHz, $CHCl_3$-d) δ = 215.5, 214.7, 159.2, 158.5, 133.6, 133.1, 128.1, 126.8, 113.7, 113.5, 74.2, 70.3, 57.4, 57.2, 55.2, 42.6, 30.8, 27.9, 27.7, 26.1, 24.8, 24.6.

HPLC (Chiralpac IA, Heptan / Ethanol = 70:30, flow rate 1 mL/min, λ = 209-300 nm): *t*R = 8.69 (*syn*), 11.39 (*syn*), 10.08 (*anti*), 13.12 (*anti*).

2-(Hydroxy(2-nitrophenyl)methyl)cyclohexanone(racemic)(105)



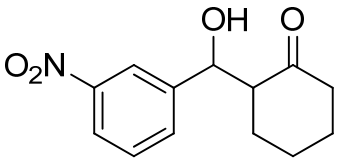
105

^{1}H NMR (400 MHz, $CHCl_3$-d) δ = 8.00 (1H, d, J = 7.94 Hz), 7.86 (1H, d, J = 7.07 Hz), 7.69 (1H, m), 7.45 (1H, m), 5.98 (1H, d, J = 1.09 Hz, syn), 5.46 (1H, d, J = 7.11 Hz, anti), 2.90 (1H, m), 2.49 (2H, m), 2.12 (1H, m), 1.85 (2H, m), 1.70 (2H, m), 1.60 (1H, m).

^{13}C NMR (400 MHz, $CHCl_3$-d) δ = 214.8, 213.9, 148.7, 147.1, 136.5, 136.9, 133.0, 133.0, 128.9, 129.6, 128.3, 127.8, 124.0, 124.6, 69.7, 66.6, 57.2, 54.8, 42.7, 42.5, 31.0, 27.9, 27.7, 26.4, 24.9, 24.8.

HPLC (Chiralpac IA, Heptan / Ethanol = 70:30, flow rate 1 mL/min, λ = 209-300 nm): *t*R = 6.45 (*syn*), 11.09 (*syn*), 9.60 (*anti*), 11.49 (*anti*).

2-(Hydroxy(3-nitrophenyl)methyl)cyclohexanone (racemic)(106)



106

^{1}H NMR (400 MHz, $CHCl_3$-d) δ = 8.22 (1H, s), 8.10 (1H, m), 7.65 (1H, m), 7.50 (1H, m), 5.48 (1H, m, syn), 4.90 (1H, m, anti), 4.16 (1H, d, J = 2.73 Hz, syn), 3.34 (1H, d, J = 3.05 Hz, anti), 2.70 (1H, m), 2.45 (2H, m), 2.10 (1H, m), 1.72 (1H, m), 1.70-1.50 (4H, m).

^{13}C NMR (400 MHz, $CHCl_3$-d) δ = 214.7, 213.8, 148.1, 143.9, 143.2, 133.1, 131.8, 129.1, 129.00, 122.6, 121.8, 121.8, 120.7, 73.7, 69.7, 56.9, 56.6, 42.4, 42.4, 30.5, 27.6, 27.5, 25.7, 24.5, 24.4.

HPLC (Chiralpac IA, Heptan / Ethanol = 70:30, flow rate 1 mL/min, λ = 209-300 nm): *t*R = 9.44 (*syn*), 14.88 (*syn*), 10.87 (*anti*), 20.21 (*anti*).

4.2.2 The synthesis of racemic products of the Hajos-Parrish-Eder-Sauer-Wiechert reaction

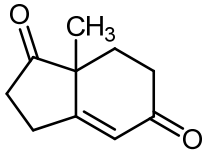
General procedure:

Et_3N (2 ml) was added to a stirred solution of the corresponding 1, 3-diketone (2.0 mmol) at 0 °C. The solution was allowed to stir for 30 min before the addition of methyl vinyl ketone (3.0 mmol). After the addition of vinyl ketone, the reaction mixture was stirred for 24 hours at room temperature. Triethylamine and excess methyl vinyl ketone was removed in vacuum. The residue was purified by flash column chromatography.

Racemic proline (0.1g, 0.9 mmol) was added to a stirred solution of triketone (3.0 mmol) in anhydrous DMF (2 ml) at room temperature. After 48 hours, the reaction mixture was added saturated aq. NH_4Cl, followed by extraction with EtOAc. The organic solution was dried with Na_2SO_4 and concentrated in vacuum. The remaining starting material was removed by flash silica gel chromatography.

The residue was then dissolved in toluene and treated with *p*-TSA (0.1 equiv.). The mixture was heated at reflux under Dean-Stark conditions for 5 h before being allowed to cool to room temperature. Addition of saturated aq. $NaHCO_3$ solution, followed by extraction with two portions of EtOAc gave an organic solution which was dried over MgSO4, filtered and concentrated in vacuum. The product was purified by flash silica gel chromatography.

7a-Methyl-2,3,7,7a-tetrahydro-1*H*-indene-1,5(6*H*)-dione (racemic)(3)



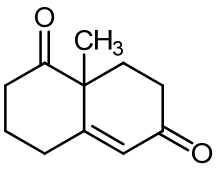
3

^{1}H NMR (400 MHz, $CHCl_3$-d) δ = 5.98 (1H, s), 3.00 (1H, m), 2.75 (2H, m), 2.55 (1H, m), 2.45 (2H, m), 2.10 (1H, m), 1.75 (1H, m), 1.30 (3H, s).

^{13}C NMR (400 MHz, $CHCl_3$-d) δ = 216.4, 198.0, 169.6, 123.8, 48.6, 35.8, 32.8, 29.1, 26.7, 20.5.

HPLC (Chiralpac IA, Heptan / Ethanol = 90:10, flow rate 1 mL/min, λ = 209-300 nm): *t*R = 18.24, 19.49.

8a-Methyl-3,4,8,8a-tetrahydronaphthalene-1,6(2*H*,7*H*)-dione (racemic)(3a)



3a

^{1}H NMR (400M, $CHCl_3$-d) δ = 5.85 (1H, s), 2.78-2.71 (2H, m), 2.55-2.45 (4H, m), 2.18-2.08 (3H, m), 1.75-1.66 (1H, m), 1.45 (3H, s).

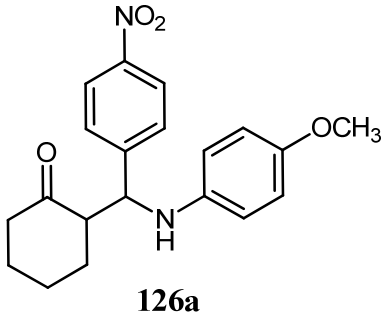
^{13}C NMR (400M, $CHCl_3$-d) δ = 210.9, 198.2, 165.7, 125.7, 50.5, 37.5, 33.5, 31.6, 29.6, 23.2, 22.8.

HPLC (Chiralpac IA, Heptan / Ethanol = 90:10, flow rate 1 mL/min, λ = 209-300 nm): *t*R = 16.93, 20.56.

4.2.3 The synthesis of racemic products of the Mannich reaction

4-Nitroaniline (0.138 g, 1 mmol) was dissolved in methanol (5 mL). The freshly distilled 4-methoxybenzaldehyde (0.136 g, 1mmol) was added to the solution at room temperature. The reaction was stirred for 1 hour. Then the solvent was removed in vacuum. The residue was dissolved in 95% ethanol (3 ml), and the corresponding ketone (1.1 mmol) was dropped to the mixture. A solution of 10 mol % HCl (0.041 ml) was added. The mixture was stirred at room temperature for another 18 hours. The reaction was worked up by adding saturated NH_4Cl solution and extracted with EtOAc. The organic layer was dried with Na_2SO_4. The product was purified by flash silica gel chromatography.

2-((4-Methoxyphenylamino)(4-nitrophenyl)methyl)cyclohexanone(racemic) (126a)



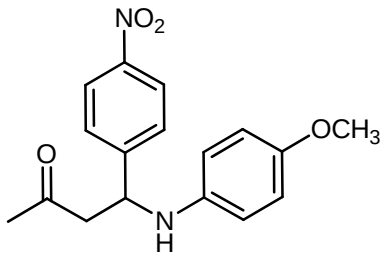
126a

^{1}H NMR (400M, $CHCl_3$-d) δ = 8.10 (2H, d, J = 8.51 Hz), 7.50 (2H, d, J = 8.67 Hz), 6.66 (2H, d, J = 8.76 Hz), 6.46 (2H, d, J = 7.64 Hz), 4.79 (1H, d, J = 4.26 Hz, syn), 4.64 (1H, d, J = 5.86 Hz, anti), 3.30 (3H, s), 2.70 (1H, m), 2.40 (2H, m), 2.00 (3H, m), 1.60 (3H, m).

^{13}C NMR (400M, $CHCl_3$-d) δ = 211.7, 210.6, 152.8, 152.7, 149.7, 149.5, 147.1, 147.0, 140.5, 140.1, 128.5, 128.4, 123.6,123.5, 115.6, 115.4, 114.8, 114.7, 59.0, 58.2, 56.7, 56.2, 55.6, 55.5, 42.3, 42.2, 27.6, 27.0, 24.9, 24.3.

HPLC (Chiralpac IA, Heptan / Ethanol = 70:30, flow rate 1 mL/min, λ = 209-300 nm): *t*R = 19.79 (*syn*), 22.53 (*syn*), 24.96 (*anti*), 28.32 (*anti*).

4-(4-Methoxyphenylamino)-4-(4-nitrophenyl) butan-2-one (racemic)(126b)



126b

^{1}H NMR (400M, $CHCl_3$-d) δ = 8.19 (2H, d, J = 8.80 Hz), 7.58 (2H, d, J = 8.66 Hz), 6.71 (2H, d, J = 8.97 Hz), 6.51 (2H, d, J = 8.93 Hz), 4.90 (1H, t, J = 6.26 Hz), 3.70 (1H, s), 3.00 (2H, m), 2.17 (3H, s).

^{13}C NMR (400M, $CHCl_3$-d) δ = 205.9, 153.1, 150.3, 147.2, 139.6, 127.5, 124.0, 115.7,

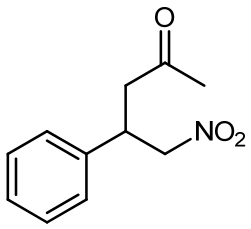
114.8, 55.6, 55.0, 50.4, 30.6.

HPLC (Ciracel OD, Heptan / Ethanol = 80:20, flow rate 0.8 mL/min, λ = 209-300 nm): *t*R = 20.96, 25.41.

4.2.4 The synthesis of racemic Michael addition products

LDA was freshly prepared from diisopropylamine (3.197 mmol) and n-BuLi (3.197 mmol, 2.0 mL, 1.6 M in hexanes. [113] To The solution of LDA in THF (10 mL) at -78 ^{o}C was added dropwise a solution of the ketone (3.045 mmol) in THF (1 mL) over 10 min at the same temperature. After stirring the mixture for 1 h, a solution of the (E)-(2-nitrovinyl) benzene (3.0 mmol) in THF (15 mL) was added over 2 min. The resulting mixture was stirred for 5 min at -78 ^{o}C and immediately quenched with acetic acid (12.0 mmol) in THF (5 mL). After warming to room temperature, the mixture was poured into water (30 mL) and extracted with DCM (4 x 30 mL). The combined organic layers were washed with 5% aqueous $NaHCO_3$ solution (40 mL), water (40 mL), and brine (40 mL), dried with $MgSO_4$, and concentrated. The crude product was purified by flash silica gel chromatography.

5-Nitro-4-phenylpentan-2-one (racemic)(164a)



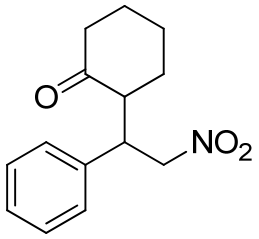
164a

^{1}H NMR (400M, $CHCl_3$-d) δ = 7.30 (5H, m), 4.65 (2H, m), 4.00 (1H, m), 2.90 (2H, d, *J* = 7.02 Hz), 2.17 (3H, s).

^{13}C NMR (400M, $CHCl_3$-d) δ = 205.3, 138.8, 128.9, 127.7, 127.2, 79.3, 46.0, 38.9, 30.2.

HPLC (Chiralpac IA, Heptan / Ethanol = 90:10, flow rate 0.8 mL/min, λ = 209-300 nm): *t*R = 16.61, 18.03.

2-(2-Nitro-1-phenylethyl) cyclohexanone (racemic)(164b)

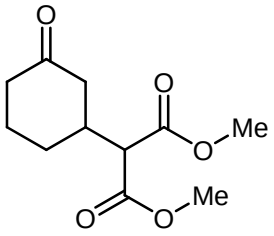


164b

^{1}H NMR (400M, $CHCl_3$-d) δ = 7.35 (2H, m), 7.28 (2H, m), 7.20 (1H, m), 4.20 (1H, m), 4.66 (1H, m), 3.75 (1H, m), 2.70 (1H, m), 2.50 (1H, m), 2.40 (1H, m), 2.10 (1H, m), 1.75 (4H, m), 1.38 (1H, m).

^{13}C NMR (400M, $CHCl_3$-d) δ = 211.8, 137.7, 128.9, 128.7, 128.1, 78.8, 43.9, 42.6, 33.1, 28.4, 24.9.

Diethyl 2-(3-oxocyclohexyl) malonate (racemic)(166a)



166a

This racemic product was obtained with NaH as reported in the literature[137].

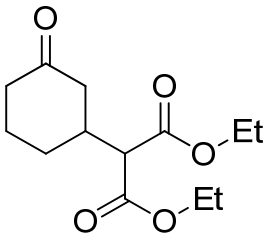
Dimethyl malonate (4.79g, 36 mmol) was slowing dropped to a mixture of cyclohex-2-enone (1.2 g, 12.1 mmol) and NaH (0.32g, 13.3 mmol) in dry diethyl ether. After the addition, the reaction was stirred at room temperature for 3 h. After the reaction, another 50 ml diethyl ether was added, followed by a HCl solution (1 mol/L) until the pH of the water phase is 3.0. After the extraction, the organic phase was dried and the solvent was removed by vacuum. The crude product was purified by flash silica gel chromatography.

^{1}H NMR (400M, $CHCl_3$-d) δ = 3.66 (3H, s), 3.60 (3H, s), 3.25 (2H, d, J = 7.07 Hz), 2.50 (1H, m), 2.30 (2H, m), 2.20 (2H, m), 2.00 (1H, m), 1.90 (1H, m), 1.60 (1H, m), 1.48 (1H, m).

^{13}C NMR (400M, $CHCl_3$-d) δ = 209.2, 167.9, 167.8, 56.2, 52, 2, 44.8, 40.7, 37.7, 28.5, 24.2.

HPLC (Chiralpac IA, Heptan / Ethanol = 70:30, flow rate 1 mL/min, λ = 209-300 nm): *t*R = 3.68, 7.84.

Diethyl 2-(3-oxocyclohexyl)malonate (racemic)(166b)



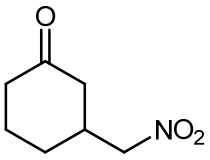
166b

Diethyl malonate (5.96g, 36 mmol) was slowing dropped to a mixture of cyclohex-2-enone (1.2 g, 12.1 mmol) and NaH (0.32g, 13.3mmol) in dry diethyl ether. After the addition, the reaction was stirred at room temperature for 3 h. After the reaction, another 50 ml diethyl ether was added , followed by a HCl solution (1 mol/L) until the pH of the water phase is 3.0. After the extraction, the organic phase was dried and the solvent was removed by vacuum. The crude product was purified by flash silica gel chromatography.

^{1}H NMR (400M, $CHCl_3$-d) δ = 4.20 (4H, m), 3.20 (1H, d, J = 7.94 Hz), 2.50 (1H, m), 2.30 (2H, m), 2.20 (2H, m), 2.00 (1H, m), 1.90 (1H, m), 1.60 (1H, m), 1.48 (1H, m), 1.20 (6H, td, J = 1.88 Hz, J = 7.11 Hz).

^{13}C NMR (400M, $CHCl_3$-d) δ = 209.2, 167.6, 167.5, 61.2, 56.6, 44.8, 40.7, 37.7, 28.5, 24.3, 13.8.

3-(Nitromethyl) cyclohexanone (racemic)(175)



175

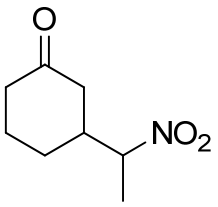
The solid base catalyst was alumina-supported potassium fluoride (KF/alumina) which was obtained following the operation in a literature[138] . Nitromethane (0.61 g, 10 mmol) and cyclohex-2-enone (0.72 g, 7.5 mmol) were dropped to a suspension of KF/alumina (5 g) in 40 mL dry THF. The reaction was stirred at room temperature for 18 h. After the reaction, the mixture was filtrated. The solvent was removed by vacuum. The crude product was purified by flash column chromatography.

^{1}H NMR (400M, $CHCl_3$-d) δ = 4.40 (2H, m), 2.60 (1H, m), 2.50 (2H, m), 2.30 (2H, m), 2.10 (2H, m), 2.00 (1H, m), 1.75 (1H, m), 1.51 (1H, m).

^{13}C NMR (400M, $CHCl_3$-d) δ = 207.9, 79.9, 44.3, 40.7, 37.1, 28.1, 24.1.

HPLC (Ciracel OD, Heptan / Ethanol = 80:20, flow rate 0.8 mL/min, λ = 209-300 nm): *t*R = 27.33, 32.24.

3-(1-Nitroethyl) cyclohexanone (racemic)(175a)



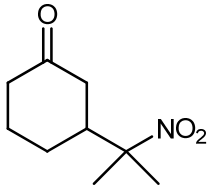
175a

The nitroethane (0.75 g, 10 mmol) and cyclohex-2-enone (0.72 g, 7.5 mmol) were dropped to a suspension KF/alumina (5 g) in 40 mL dry THF. The reaction was stirred at room temperature for 18 h. After the reaction, the mixture was filtrated and the solvent was removed by vacuum. The crude product was purified by flash column chromatography.

^{1}H NMR (400M, $CHCl_3$-d) δ = 4.50 (1H, m), 2.30 (3H, m), 2.10 (1H, m), 1.78 (1H, m), 1.65 (2H, m), 1.50 (5H, m).

^{13}C NMR (400M, $CHCl_3$-d) δ = 208.6, 208.4, 86.8, 86.7, 43.4, 42.9, 42.2, 42.0, 40.6, 40.5, 27.2, 26.6, 24.1, 23.9, 15.9, 15.9.

3-(2-Nitropropan-2-yl) cyclohexanone (racemic)(175b)



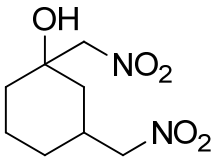
175b

2-Nitropropane (0.89 g, 10 mmol) and cyclohex-2-enone (0.72 g, 7.5 mmol) were dropped to a suspension KF/alumina (5 g) in 40 mL dry THF. The reaction was stirred at room temperature for 18 h. After the reaction, the mixture was filtrated. The solvent was removed by vacuum. The crude product was purified by flash silica gel chromatography.

^{1}H NMR (400M, $CHCl_3$-d) δ = 2.40 (3H, m), 2.25 (1H, m), 2.20 (2H, m), 1.80 (1H, m), 1.65 (1H, m), 1.57 (3H, s), 1.56 (3H, s), 1.40 (1H, m).

^{13}C NMR (400M, $CHCl_3$-d) δ = 208.8, 90.6, 46.5, 42.6, 40.7, 26.0, 24.3, 23.5, 22.5.

1, 3-Bis(nitromethyl)cyclohexanol (176)



176

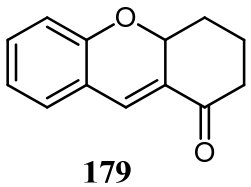
Nitromethane (3 g, 50 mmol) and cyclohex-2-enone (0.96 g, 10 mmol) were stirred at 0 ^{o}C. Then TMG (0.23g, 2mmol) or TBD (0.417g, 3mmol) was slowly dropped to the mixture. The reaction was stirred 12 h. After the reaction, diethyl ether (20 mL) and HCl (2 mol/L, 5 mL) were added to the reaction. After the extraction, the organic phase was collected and dried with $NaSO_4$. The solvents were removed by vacuum. The crude product was purified by flash column chromatography (acetone / cyclohexane = 1:3).

^{1}H NMR (400M, $CHCl_3$-d) δ = 4.43 (2H, s), 4.41 (2H, d, J = 1.2 Hz), 2.62 (2H, m), 1.75 (5H, m), 1.55 (1H, m), 1.37 (1H, m), 1.24 (1H, m)

^{13}C NMR (400M, $CHCl_3$-d) δ = 85.3, 80.9, 70.3, 37.7, 33.7, 31.8, 28.8, 19.8.

4.2.5 The synthesis of Domino reaction racemic product

2, 3, 4, 4a-Tetrahydro-1*H*-xanthen-1-one (racemic)(179)



179

Salicylic aldehyde (1.22g, 10.0 mmol), cyclohexanone (0.96 g, 10.0 mmol) and imidazole (0.68 10.00 mmol) are added to a previously degassed mixture of dioxane (5.0 mL) and water (5.0 mL,). The resulting slurry is stirred for 48 h and extracted with ethyl acetate (20 mL). The organic phase is dried with sodium sulfate, the solvent stripped of. The residue obtained is purified by flash column chromatography (ethyl acetate / cyclohexane = 1:6).

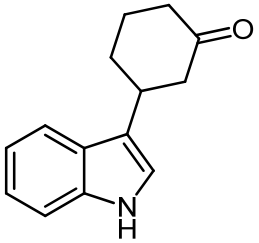
^{1}H NMR (400M, $CHCl_3$-d) δ = 7.45 (1H, d, J = 2.33 Hz), 7.25 (2H, m), 6.97 (1H, td, J = 7.50 Hz, J = 1. 09 Hz), 6.90 (1H, d, J = 8.17 Hz), 5.02 (1H, m), 2.52 (1H, m), 2.50 (1H, m), 2.48 (1H, m), 2.20 (1H, m), 2.00 (1H, m), 1.75 (1H, m).

^{13}C NMR (400M, $CHCl_3$-d) δ = 197.4, 155.8, 132.0, 131.4, 130.4, 129.7, 122.1, 116.0, 74.6, 38.8, 29.6, 17.9.

HPLC (Ciracel OD, Heptan / 2-isopropanol = 90:10, flow rate 0.8 mL/min, λ = 209-300 nm): *t*R = 49.70, 50.13.

4.2.6 The synthesis of racemic product of the Friedel-Crafts reaction

3-(1*H*-Indol-3-yl) cyclohexanone (racemic)(192)



192

Indole (1.16g, 1.mol) was added to a solution of cyclohex-2-enone (0.6g, 8.6mmol) in dichloromethane (50 mL). After montmorillonite k10 (0.68 g) was added to the solution, the mixture was stirred at reflux for 2 h. The colour of the clay turned light brown and the reaction was followed to completion. After the reaction, the mixture was filtrated and the filtrate was concentrated in vacuum. The crude product has been purified by flash silica gel chromatography with ethyl acetate and cyclohexane (1:4).

^{1}H NMR (400M, MeOH-d4) δ = 7.78 (1H, d, J = 7.94 Hz), 7.35 (1H, d, J = 8.19 Hz), 7.10 (1H, t, J = 7.43 Hz), 7.15 (1H, t, J = 7.56 Hz), 7.00 (1H, s), 3.32 (1H, m), 2.62 (2H, m), 2.43 (2H, m), 2.18 (1H, m), 2.00 (1H, m), 1.92 (1H, m), 1.75 (1H, m).

^{13}C NMR (400M, MeOH-d4) δ = 214.7, 138.2, 127.4, 122.4, 121.6, 119.6, 112.3, 42.1, 37.5, 32.9, 27.9, 26.0.

HPLC (Chiralpac IA, Heptan / Ethanol = 85:15, flow rate 1 mL/min, λ = 209-300 nm): tR = 8.69, 11.47.

Appendix

X-Ray data

Table 1 Crystal data and structure refinement for exp_851

Identification code	exp_851
Empirical formula	$C_6H_9F_3NO_3S$
Formula weight	232.20
Temperature/K	676(2)
Crystal system	monoclinic
Space group	$P2_1$
a/Å	10.5021(4)
b/Å	8.9388(3)
c/Å	11.4888(4)
α/°	90.00
β/°	115.183(5)
γ/°	90.00
Volume/Å^3	976.01(6)
Z	4
ρ_{calc}mg/mm^3	1.580
m/mm^{-1}	3.317
F(000)	476.0
Crystal size/mm^3	? × ? × ?
2Θ range for data collection	8.5 to 122.24°
Index ranges	-11 ≤ h ≤ 11, -10 ≤ k ≤ 6, -10 ≤ l ≤ 13
Reflections collected	2404

Independent reflections	1934[R(int) = 0.0239]
Data/restraints/parameters	1934/1/271
Goodness-of-fit on F^2	1.059
Final R indexes [I>=2σ (I)]	R_1 = 0.0381, wR_2 = 0.1022
Final R indexes [all data]	R_1 = 0.0411, wR_2 = 0.1041
Largest diff. peak/hole / e $Å^{-3}$	0.65/-0.45
Flack parameter	0.05(3)

Table 2 Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for exp_851. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
S1	7172.5(10)	8324.9(13)	8062.6(9)	21.9(3)
O1	6741(3)	9832(4)	8156(3)	26.3(7)
O2	7403(3)	7921(4)	6962(3)	30.0(8)
C1	8964(5)	8227(7)	9382(4)	31.9(11)
F1	9818(3)	9090(4)	9115(3)	50.7(9)
F2	9476(3)	6849(4)	9521(3)	50.8(9)
F3	8984(3)	8671(5)	10486(3)	54.7(11)
N1	6268(4)	7059(5)	8304(4)	25.1(9)
C2	5718(5)	7341(6)	9162(4)	23.8(11)
O3	6030(3)	8310(4)	9974(3)	27.4(7)
C3	4550(5)	6222(6)	9007(4)	21.8(10)
N2	4078(4)	6510(5)	10049(3)	22.7(9)
C4	2729(5)	7361(7)	9455(4)	33.5(12)
C5	2019(5)	6681(8)	8129(4)	36.7(13)
C6	3237(5)	6493(7)	7740(4)	32.2(12)

S2	7050.1(11)	5771.9(14)	3554.6(10)	24.9(3)
O4	7634(4)	4461(4)	4311(3)	36.1(9)
O5	6537(3)	5648(5)	2194(3)	34.0(8)
C7	8571(6)	7028(8)	4029(5)	42.4(14)
F4	8291(4)	8251(5)	3393(5)	84.6(15)
F5	9580(4)	6345(6)	3810(4)	78.0(14)
F6	9122(4)	7246(7)	5282(4)	90.4(16)
N3	6068(4)	6537(4)	4107(3)	22.3(9)
C8	5193(5)	7698(6)	3478(4)	22.7(10)
O6	5016(3)	8313(4)	2466(3)	28.1(7)
C9	4357(5)	8230(6)	4224(4)	23.5(10)
N4	3593(4)	9650(5)	3620(4)	23.5(9)
C10	2056(5)	9287(6)	2816(5)	28.6(12)
C11	1977(5)	7602(6)	2818(5)	28.3(11)
C12	3185(5)	7121(6)	4078(4)	28.2(11)

Table 3 Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for exp_851. The Anisotropic displacement factor exponent takes the form:
$-2\pi^2[h^2a^{*2}U_{11}+...+2hka \times b \times U_{12}]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
S1	26.3(5)	19.6(7)	23.2(5)	0.1(5)	13.8(4)	-1.3(5)
O1	35.3(17)	16.4(19)	34.3(17)	4.0(15)	21.6(14)	1.6(16)
O2	36.5(17)	30(2)	30.3(16)	-4.1(15)	20.5(14)	-6.1(16)
C1	35(3)	21(3)	36(2)	-8(3)	12(2)	-6(3)
F1	32.9(15)	43(2)	75(2)	-9.5(18)	21.7(15)	-11.7(15)
F2	40.1(17)	23(2)	68(2)	0.6(16)	2.6(15)	7.7(15)

F3	38.8(16)	83(3)	32.9(16)	-17.2(18)	5.8(12)	3.0(18)
N1	33(2)	19(2)	31(2)	1.3(18)	20.7(17)	-2.1(19)
C2	36(2)	17(3)	20(2)	2(2)	14.5(19)	2(2)
O3	38.7(17)	20.3(18)	28.3(15)	-2.6(18)	19.1(13)	-2.0(17)
C3	32(2)	16(3)	24(2)	-0.2(19)	17.9(19)	-1(2)
N2	29.5(19)	21(2)	22.0(17)	1.7(18)	15.6(15)	-0.3(18)
C4	34(2)	36(3)	33(2)	3(2)	17(2)	11(3)
C5	31(2)	47(4)	31(2)	4(3)	12(2)	0(3)
C6	43(3)	31(3)	25(2)	-3(2)	17(2)	-9(2)
S2	29.9(5)	23.0(7)	26.8(5)	4.2(5)	16.9(4)	3.2(6)
O4	51.1(19)	29(2)	38.1(18)	14.3(17)	28.7(17)	17.2(19)
O5	37.7(17)	38(2)	31.1(16)	2.0(18)	19.6(14)	11(2)
C7	36(3)	49(4)	48(3)	9(3)	23(2)	-4(3)
F4	51(2)	42(2)	151(4)	38(3)	33(2)	-9(2)
F5	49(2)	85(4)	125(3)	28(3)	61(2)	12(2)
F6	54(2)	144(5)	67(2)	-27(3)	20.0(18)	-48(3)
N3	29.0(19)	19(2)	23.2(18)	-2.0(18)	15.0(16)	0.6(18)
C8	31(2)	21(3)	19(2)	-1(2)	13.1(18)	-3(2)
O6	38.4(17)	23.7(19)	28.9(16)	3.4(17)	20.8(13)	1.9(18)
C9	32(2)	20(3)	22.4(19)	2(2)	15.0(17)	8(2)
N4	35(2)	16(2)	26.6(18)	4.5(18)	19.9(16)	5.7(19)
C10	33(2)	28(3)	26(2)	0(2)	13(2)	5(2)
C11	30(2)	26(3)	34(2)	-4(2)	18(2)	-5(2)
C12	44(3)	19(3)	33(2)	4(2)	28(2)	5(3)

Table 4 Bond Lengths for exp_851.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
S1	O1	1.440(4)	S2	O4	1.432(4)
S1	O2	1.431(3)	S2	O5	1.424(3)
S1	C1	1.849(5)	S2	C7	1.835(6)
S1	N1	1.577(4)	S2	N3	1.579(4)
C1	F1	1.314(6)	C7	F4	1.278(8)
C1	F2	1.326(7)	C7	F5	1.336(7)
C1	F3	1.321(6)	C7	F6	1.318(7)
N1	C2	1.360(6)	N3	C8	1.370(6)
C2	O3	1.212(6)	C8	O6	1.226(6)
C2	C3	1.533(7)	C8	C9	1.540(6)
C3	N2	1.500(5)	C9	N4	1.504(6)
C3	C6	1.539(6)	C9	C12	1.533(7)
N2	C4	1.493(6)	N4	C10	1.514(6)
C4	C5	1.509(7)	C10	C11	1.509(8)
C5	C6	1.534(7)	C11	C12	1.526(7)

Table 5 Bond Angles for exp_851.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
O1	S1	C1	103.1(2)	O4	S2	C7	103.1(3)
O1	S1	N1	115.2(2)	O4	S2	N3	107.2(2)
O2	S1	O1	118.6(2)	O5	S2	O4	117.8(2)
O2	S1	C1	102.5(2)	O5	S2	C7	104.4(2)
O2	S1	N1	108.4(2)	O5	S2	N3	117.92(19)
N1	S1	C1	107.5(2)	N3	S2	C7	104.5(3)
F1	C1	S1	109.8(3)	F4	C7	S2	113.2(4)

F1	C1	F2	106.9(4)	F4	C7	F5	106.9(5)
F1	C1	F3	108.3(4)	F4	C7	F6	112.6(6)
F2	C1	S1	111.2(3)	F5	C7	S2	108.9(5)
F3	C1	S1	111.6(3)	F6	C7	S2	109.7(4)
F3	C1	F2	108.9(4)	F6	C7	F5	105.0(5)
C2	N1	S1	117.9(4)	C8	N3	S2	121.5(3)
N1	C2	C3	111.1(4)	N3	C8	C9	110.7(4)
O3	C2	N1	129.1(5)	O6	C8	N3	129.5(4)
O3	C2	C3	119.8(4)	O6	C8	C9	119.8(4)
C2	C3	C6	110.9(4)	N4	C9	C8	108.8(4)
N2	C3	C2	108.4(4)	N4	C9	C12	104.4(3)
N2	C3	C6	105.1(4)	C12	C9	C8	111.2(4)
C4	N2	C3	107.1(3)	C9	N4	C10	108.8(4)
N2	C4	C5	102.8(4)	C11	C10	N4	104.9(4)
C4	C5	C6	102.9(4)	C10	C11	C12	105.0(4)
C5	C6	C3	105.3(4)	C11	C12	C9	103.0(4)

Table 6 Hydrogen Atom Coordinates ($Å \times 10^4$) and Isotropic Displacement Parameters ($Å^2 \times 10^3$) for exp_851.

Atom	*x*	*Y*	*z*	U(eq)
H3	4892	5171	9051	26
H2A	3943	5620	10384	27
H2B	4745	7057	10703	27
H4A	2903	8443	9408	40
H4B	2157	7218	9944	40
H5A	1286	7356	7529	44
H5B	1587	5704	8155	44

H6A	3353	7406	7307	39
H6B	3066	5632	7151	39
H9	4997	8392	5152	28
H4C	3978	10064	3109	28
H4D	3676	10329	4249	28
H10A	1460	9732	3201	34
H10B	1743	9673	1929	34
H11A	2093	7178	2072	34
H11B	1062	7268	2782	34
H12A	3475	6079	4026	34
H12B	2919	7204	4806	34

[RSC Journal Format]

Experimental

Single crystals of $C_6H_9F_3No_3S$ **[exp_851]** were **[]**. A suitable crystal was selected and **[]** on a diffractometer. The crystal was kept at 676(2) K during data collection. Using Olex2 [1], the structure was solved with the ShelXS [2] structure solution program using Direct Methods and refined with the ShelXL [3] refinement package using Least Squares minimisation.

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2. ?
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Crystal structure determination of [exp_851]

Crystal Data. $C_6H_9F_3No_3S$, M =232.20, monoclinic, a = 10.5021(4) Å, b = 8.9388(3) Å, c = 11.4888(4) Å, β = 115.183(5)°, V = 976.01(6) Å^3, T = 676(2), space group $P2_1$ (no. 4), Z = 4, μ(CuKα) = 3.317, 2404 reflections measured, 1934 unique (R_{int} = 0.0239) which were used in all calculations. The final wR_2 was 0.1041 (all data) and R_1 was 0.0381 (>2sigma(I)).

Appendix

This report has been created with Olex2, compiled on Nov 1 2011 20:42:30. Please let us know if there are any errors or if you would like to have additional featrues.

Abbreviations

δ	Chemical shift
$[\alpha]_D$	Specific optical rotation
Ac	Acetyl
aq.	Aqueous
Boc	*tert*-butyl-oxycarbonyl
BINOL	1,1'-Bi-2-naphthol
Bu	Butyl
c	Concentration
Cbz	Carboxybenzyl
d	Days
DABCO	1,4-Diazabicyclo[2.2.2]octane
DCC	Dicyclohexylcarbodiimide
DCU	Dicyclohexylurea
DCM	Dichloromethane
DMAP	4-(Dimethylamino)-pyridine
DMF	Dimethylformamide
DMSO	Dimethyl
EDCI	*N*-(3-Dimethylaminopropyl)-*N*'-ethylcarbodiimide-hydrochloride
ee	Enantiomeric excess
equiv.	Equivalents
ESI	electrospray ionization
Et	Ethyl
GC	Gas chromatography
h	Hours
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
J	NMR coupling constant
LUMO	lowest unoccupied molecular orbital
M	Molar

Me	Methyl
MS	mass spectroscopy
N	Normality
NMR	nuclear magnetic resonance
Ph	Phenyl
R_f	retention factor
r.t.	room temperature
TADDOL	α, α, α′, α′-Tetraaryl-1, 3-dioxolan-4, 5-di- methanol
t-Bu	*tert*-Butyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	thin layer chromatography
TMS	Tetramethylsilane
p-TSA	*p*-Toluenesulfonic acid
TFSA	Trifluoromethanesulfonic acid
*t*R	retention time

Reference:

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