# Bifunctional Thiourea-Based Organocatalysts for Asymmetric C-C Bond Formation Reactions: Strecker, Nitro-Michael, Mannich

DISSERTATION

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.

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*Für meine Eltern, meine Oma und meine Schwester Reseda*

„The mind is not a vessel to be filled but a fire to be kindled."

*Plutarch*

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# A. Introduction

**Abstract:** In this section some historical aspects of organocatalysts (cinchona alkaloids and amino acids) and their successful applications on important C-C bond forming asymmetric Michael and Mannich reactions are presented. The interesting art of hydrogen bonding, namely, the formation of double hydrogen bonds between organic molecules is also described.

## 1. Organocatalysis

### 1.1 Asymmetric Organocatalysis and Some Historical Moments

"Organocatalysis is the field wherein small organic molecules efficiently and selectively catalyze organic transformations."

***David W. C. MacMillan***

"Organocatalysis is the catalysis of a reaction with an organic small molecule. By accepted convention, organic small molecule means a molecule without a metal, and not a macromolecule like protein, nucleic acid, or polymer."

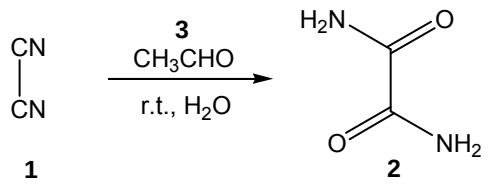
***K. N. Houk***

"Organocatalysis is catalytic reactions mediated by small organic molecule in absence of metals or metal ions."

***Carlos F. Barbas, III***

These utterances are quite correct. In organic chemistry, the term *Organocatalysis* can be interpreted as the chemical processes in which the small metal free molecules are active and catalyse organic reactions.

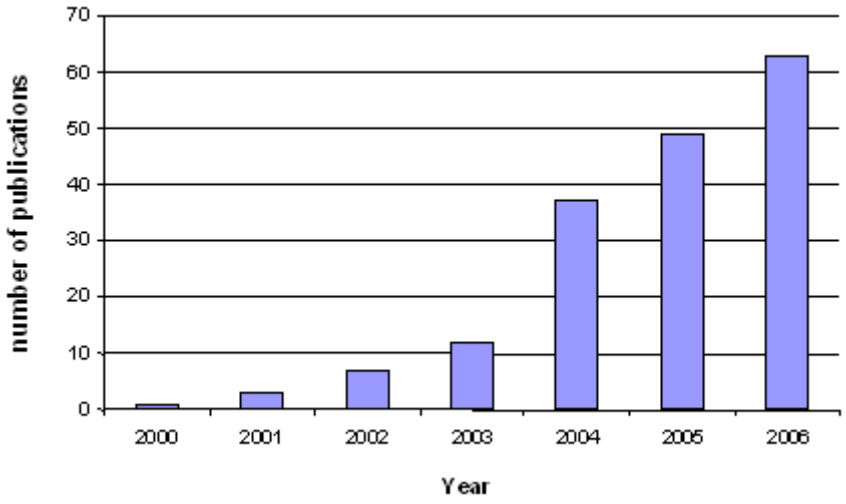
If we look back on the history of organocatalysis we can find that the first organocatalytic reaction without any metal was discovered in 1859 by German chemist Justus von Liebig. He was the first chemist who observed and presented the oxamide-synthesis from cyanogen (**1**) and water in the presence of acetaldehyde (**3**) under mild conditions[1] (eq 1).




(1)

Justus von Liebig's discovery can be recognized as the beginning of an epoch of organocatalysis. Diagram 1 which was generated from *SciFinder* clearly demonstrates an annual increase of scientific publications including keyword "Organocatalysis" from 2000 to 2006.

**Diagram 1.** Annual publications containing a keyword "Organocatalysis"




In modern organic chemistry, especially in pharmacology, the use of metal containing catalysts is less appropriate because of their hazardous properties. Furthermore, in practice the catalysts containing transition metals are in many cases less stable under air, moisture sensitive, very toxic, normally expensive and difficult to handle. A high toxicity does not allow the use of such catalysts in large amounts because it acts contrary to the principles of green chemistry to some extent. It is important to note that the principles of green chemistry are essential ones which must be adhered to as far as possible by every man living on this planet in order to protect the world's environment. The transition metals may build up in biological systems and become a significant health hazard.

Some metals are required by our body in small amounts, but can be toxic in larger quantities. Metals can enter the body with food, water, air, or by absorption through the skin. Therefore, handling and utilization of catalysts containing transition metals has to be done carefully.

In order to solve these problems, a complete discontinuance in the use of the metal containing catalysts can be proposed. But today the realization of this suggestion is not possible due to a big popularity of metal-containing catalysts. Perhaps, in the future it will be possible. Relatively new and promising ways for the realization this idea is the development and application of competitive non-metal catalysts. It should be noted that chemists of the whole world have been developing organic catalysts for more than 30 years.

It is known the reactions leading to the generation of chiral molecules are normally completed with the formation of racemic mixtures. In most cases only one of the enantiomer is important. Occasionally, the resolution of racemic mixtures is a difficult task. Classical separation methods are founded on the physical properties of molecules. They contain as crystallization from organic or inorganic solvents and chromatographic resolution on chiral columns. Both methods are expensive and slow. However, separation by crystallization became wide spread as an effective and powerful method among chemists.

A relatively new and effective way to enantiomerically pure compounds is so-called *asymmetric organocatalysis*. This method is founded in chemical and also physical properties of molecules. In comparison to biocatalysis promoted by enzymes, the asymmetric organocatalysis operates with small chiral organic catalysts without any metal. In asymmetric transformations performed by enzymes and small organocatalysts the analogy may be observed. Enzymes as well as man-made or nature-made (as proline) small organocatalysts act via direct contact with substrates. Electrostatic, Van der Waals and intermolecular hydrogen bonding with substrates are the main types of interaction in enzyme catalyzed reactions. On the other hand, in addition to these interaction types the formation of covalent bonds is typical for organocatalysts. The ability to take part in covalent and non-covalent bonding with substrates is responsible for catalytic activity of organocatalysts. Organocatalysts may contain such functional pairs as Lewis base/acid and Bronsted base/acid within one molecule. Even the combination Lewis(base or acid) + Bronsted(base or acid) is possible. Stereocontrolled synthesis is a widely distributed method in organic chemistry to date.

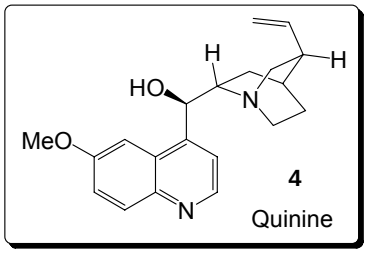
Today many chemists of the whole world do believe in the usefulness of isolated natural compounds and draw as promising organocatalysts in the different directions of asymmetric organocatalysis.

### *1.1.1 Cinchona Alkaloids as Organocatalysts.*

Today the popularity of cinchona alkaloids as organocatalysts has no borders. Why are they so popular? An answer to this question is clear: they are commercially available, relatively inexpensive, stable under mild conditions, can be easily modified in order to improve a catalytic efficiency and in many cases they are recoverable.

Additionally, first cinchona alkaloid known as *Quinine* (**4**) (Figure 1) was isolated from the bark of the South American cinchona tree in 1817 by French researchers Pierre Joseph Pelletier and Joseph B. Caventou[2]. From the 17th century quinine was the first effective remedy for *falciparum malaria*. It is interesting to mention that the quinine and its derivatives were recognized as antimalarial agents and used until 1940s! Today medicinal properties of cinchona alkaloids and their derivatives are well known[3].

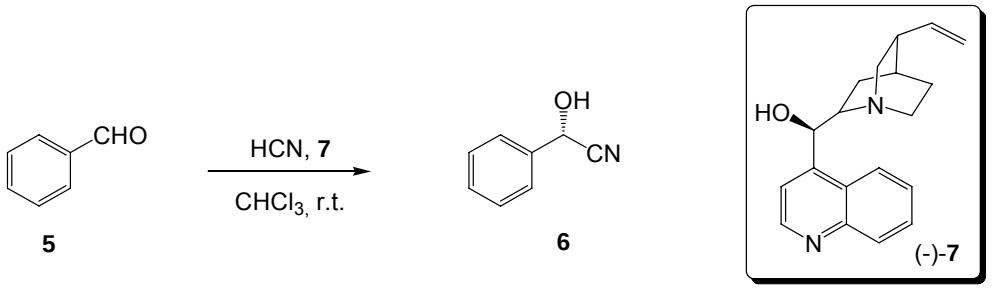
**Figure 1.**




**4**
Quinine

In 1912 two scientists Bredig and Fiske reported the first asymmetric addition reaction of hydrogen cyanide to the benzaldehyde catalysed by natural cinchona alkaloid (-)-Cinchonidine (-)-**7**. The reaction was performed with a low enantioselectivity (*ee* ~ 9%) (Scheme 1).[4]

**Scheme 1.**

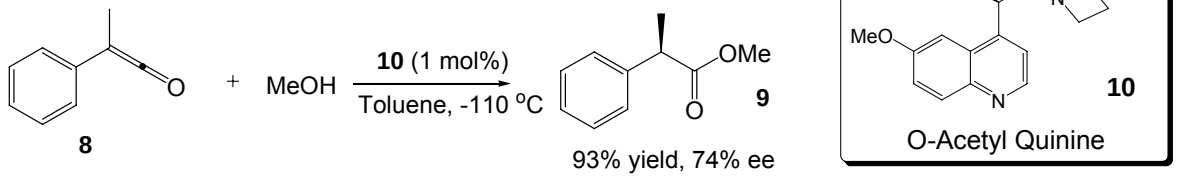



**5** **6**

However, cinchona alkaloids did not receive proper attention as asymmetric organocatalysts until 1960's. In 1960 the studies performed by Pracejus permitted him to reveal that quinine acylated on the *C9* hydroxyl group **10** acts like a high enantioselective organocatalyst in addition reaction of methanol to phenylmethylketene (**7**) to give optically

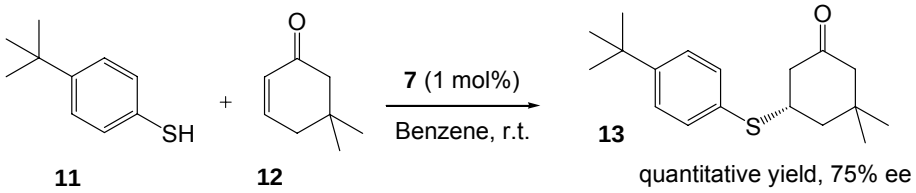
active methyl phenylpropionate (**9**)[5] (Scheme 2). Amazingly, only 1 mol% of **10** can promote the reaction with a good enantioselectivity and yield.

**Scheme 2.** Enantioselective addition of methanol to phenylmethylketene




In 1981 a detailed investigation of the mechanism of asymmetric Michael-addition of aromatic thiols to conjugated cycloalkenones catalyzed by four diastereomeric pairs quinine, quinidine, cinchonine and cinchonidine (**7**) was published by Wynberg (Scheme 3).[6] He fortuitously discovered that cinchonidine (**7**) is a good asymmetric catalyst which gives the enantioselectivity up to 75% and nearly quantitative yield.

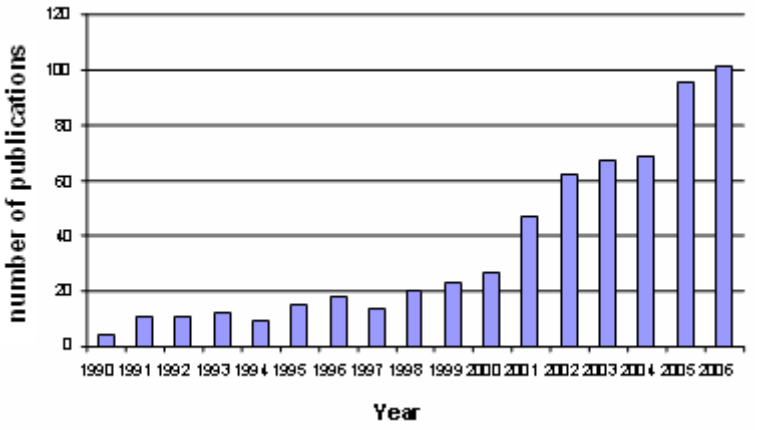
**Scheme 3.** Enantioselective Michael-addition




Future investigations performed by Wynberg revealed some interesting applications and properties of cinchona alkaloids[7].

The results obtained in the workgroups of Pracejus (1960) and Wynberg (1981) quickly made the cinchona alkaloids very popular in area of asymmetric organocatalysis. For instance, as shown on Diagram 2, the use of natural cinchona alkaloids and their derivatives as organocatalysts increased from 1990 to 2006 and is still increasing.

**Diagram 2.** Annual increasing of publications containing a keyword "Cinchona catalysts"

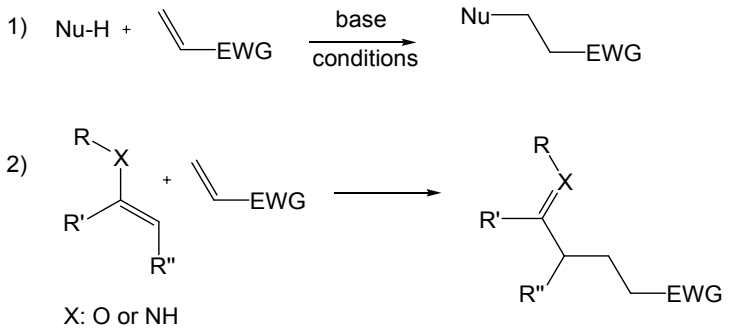



Today many important reactions in organic chemistry can be stereoselectively catalyzed by cinchona alkaloids and derivatives. Some examples of highly stereoselctive Michael and Mannich reactions catalyzed by cinchona alkaloids are presented below. The successful applications of natural cinchona alkaloids and their derivatives as effective asymmetric organocatalysts in period from 1960s to 2001s is sufficiently well described.[8]

### *1.1.2 Michael-reaction Catalyzed by Cinchona Alkaloids*

The Michael-addition reaction is base-catalyzed nucleophilic addition of any molecule which represents an anion or nucleophilic enough substrate (enols, enamines etc.) to the *α, β* unsaturated compounds (Figure 2). Michael-addition is an important and simple carbon–carbon bond forming reaction in organic chemistry. Furthermore, many asymmetric transformations performed in total synthesis of natural compounds include some key steps in which the Michael-addition reaction plays partially an important role. For instance, in the total synthesis of (-)-Strychnine performed by Shibasaki the asymmetric Michael reaction was an important step[9]. In addition, the Strychnine is a very toxic compound used as a pesticide, particularly for killing of small rodents.

**Figure 2.** Michael-addition



Asymmetric versions of Michael-addition reaction catalyzed by cinchona alkaloids are not abundant in organocatalysis. Only limited examples are known to date.

Wang et al. reported the synthesis of *N*-heterocycles catalysed by cinchona alkaloid derivative **15** with good enantioselectivities (up to 94%) and good yields (up to 90%) (Scheme 4).[10] This is an interesting example of high-enantioselective Michael-addition of benzotriazole (**14**) to the variety of nitroolefins.

**Scheme 4**. Enantioselective Michael-addition of benzotriazole to nitroolefins

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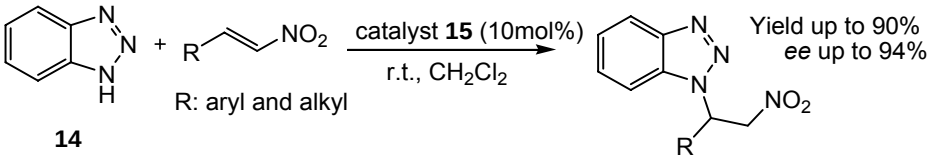
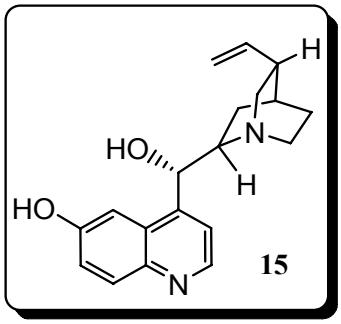
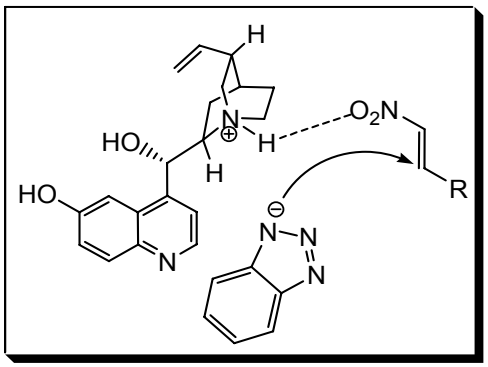



In this reaction the first step probably produces the benzotriazole anions via deprotonation of **14** by strong organic base quinuclidine of catalyst **15**. Then the generated anion attacks a double bond of coordinated nitroolefin (Figure 3). It is typical for Michael-addition reaction.

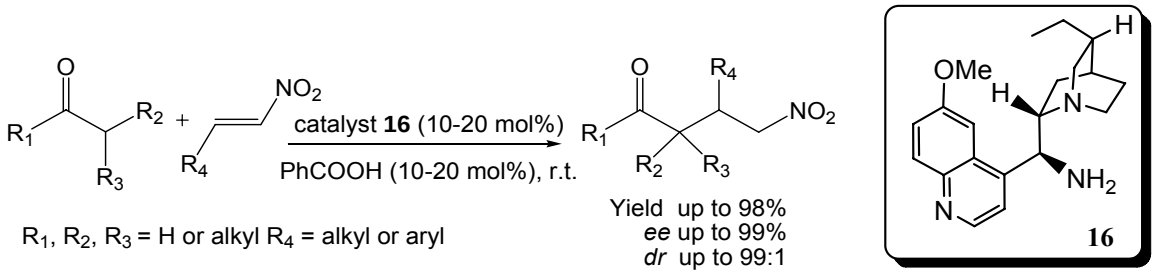
**Figure 3.** Probable mechanism



In addition, the triazole containing compounds such as fluconazole, itraconazole, voriconazole and posaconazole are antifungal drugs and as a consequence, present a big interest in medicinal chemistry.

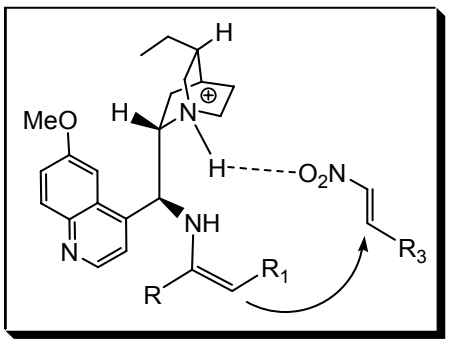
High stereoselective (*ee* up to 99%) Michael-addition of ketones and aldehydes to the *α, β* unsaturated nitroolefins catalyzed by cinchona alkaloid derivative **16** in the presence of acidic cocatalyst was performed by Connon (Scheme 5)[11].

**Scheme 5**. Enantioselective Michael-addition of ketones and aldehydes to the *α, β* unsaturated nitroolefins




The authors proposed that first the ketone was activated by the reaction with the primary amine moiety of **16** that lead to the formation of an active enamine. In the next step the generated enamine attacked the double bond of coordinated nitroolefin to give Michael product (Figure 4). It is possible, that the nitroolefin coordinated to the catalyst due to hydrogen bonding interaction with the protonated quinuclidine nitrogen atom.

**Figure 4.** Proposed mechanism



It is not an overstatement to say that today asymmetric version of Michael reaction is one of the most popular reaction in organic chemistry.

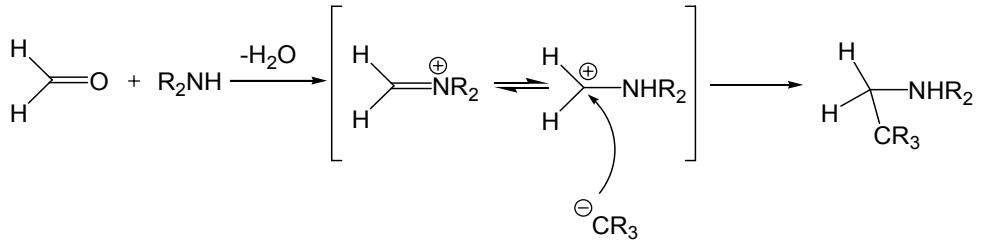
Other widely used C-C bond forming reaction in organic chemistry is the Mannich reaction. The Mannich reaction also like Michael-addition reaction is popular in organic

chemistry. Some asymmetric versions of Mannich reaction catalyzed by cinchona alkaloids are presented below.

### *1.1.3 Mannich Reaction Catalyzed by Cinchona Alkaloids*

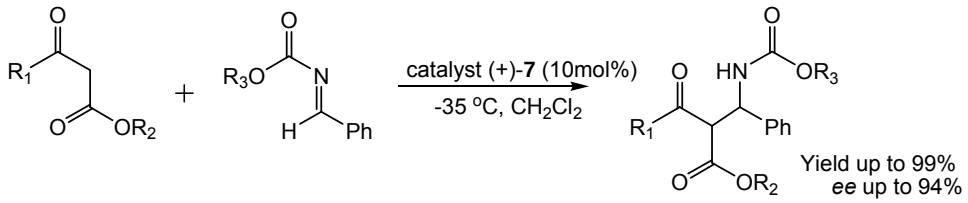
Mannich reaction is an organic one in which a carbanion or nucleophilic part of any molecule reacts with a pre-aggregated iminium cation; normally, iminium cation initiated by the condensation of primary or secondary amine with the carbonyl compounds (Figure 5). The Mannich reaction can be interpreted as a three-component reaction. Furthermore, the Mannich-type reaction is also widely distributed in asymmetric organic synthesis. Mannich-type reaction is an organic reaction which represents an addition of nuclephilic molecules to the *C=N* double bond of pre-synthesized imines.

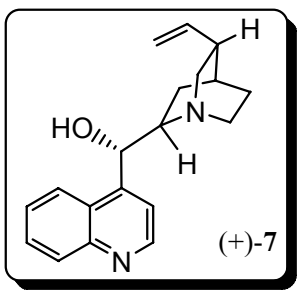
**Figure 5.** Mannich reaction




The enantioselective direct Mannich reaction between *β*-keto esters and acyl aryl imines catalyzed by the natural cinchona alkaloid cinchonine (+)-**7** was performed by Schaus [12a] (Scheme 6).

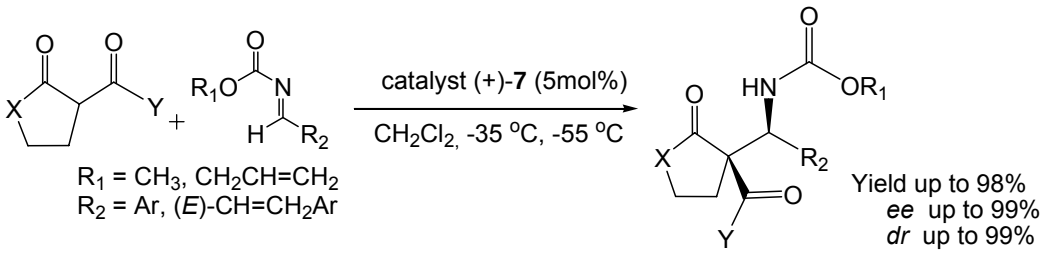
**Scheme 6**. Asymmetric Mannich Reaction of *β*-Keto Esters



The mechanism is probably the same as shown in Figure 3 (see above). In the same group cinchonine (+)-**7** was also found to be active and highly enantioselective in the Mannich addition of 1,3-dicarbonyls to different acyl imines (Scheme 7)[12b].

**Scheme 7.**



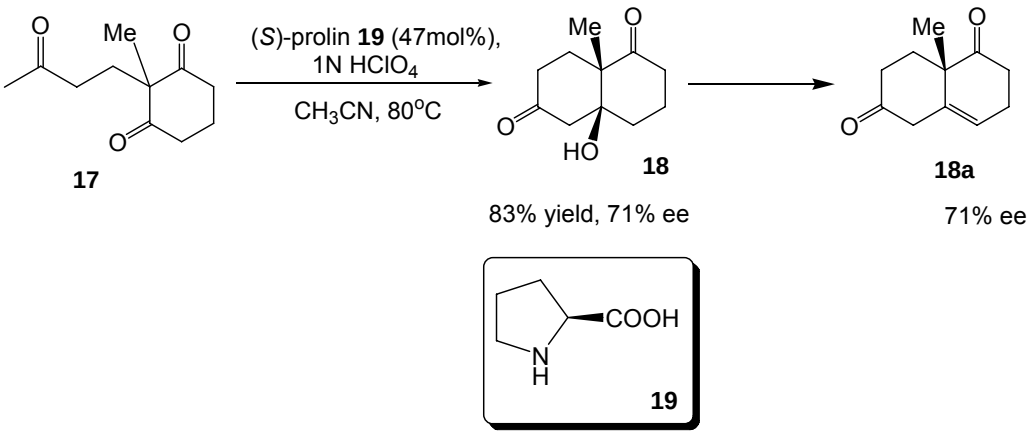

Cinchona alkaloids are known as chiral basic organocatalysts due to the high availability of the nitrogen lone pair of quinuclidine ring. For instance, the basicity of the quinuclidine nitrogen is $10^3$ higher than that of the quinoline nitrogen within one molecule. Without any question, the quinuclidine part of chinchona alkaloids is responsible for the catalytic action in base-catalyzed reactions.

## 1.2 Proline Derivatives as an Effective Organocatalysts in Asymmetric Organocatalysis

One of the other classes of natural compounds is amino acids. Amino acids like cinchona alkaloids are found to be good asymmetric organo-catalysts in organic chemistry. Various simple amino acids and their derivatives are known as effective organocatalysts in the different asymmetric transformations. Asymmetric aldol reaction[13-24], Diels-Alder reaction[25], Michael reaction[26-34], Mannich reaction[34-39] and many other asymmetric C-C bond-forming reactions promoted by amino acid derivatives are already described[52]. It is interesting to note that the amino acid *proline* is the most popular organocatalyst in different asymmetric transformations[40].

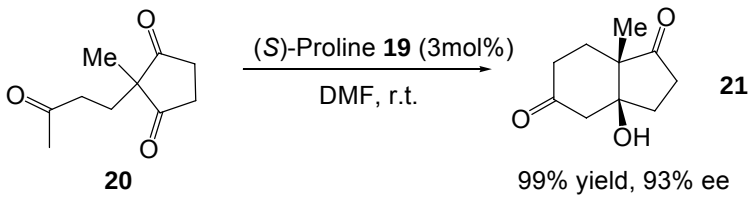
In 1971 Eder, Sauer and Wiechert[41] demonstrated the first highly enantioselective intramolecular cyclization reaction of cyclic ketones in the presence of catalytic amount of natural amino acid (*S*)-proline (**19**) (Scheme 8).

**Scheme 8.** Eder, Sauer and Wiechert experiment




In 1974 Hajos and Parrish reported independently from Eder, Sauer and Wiechert the same activity of (S)-proline (**19**) in analogous reaction under mild conditions (Scheme 9)[42]. The stereoselectivity and yields were sufficiently better.

**Scheme 9.** Hajos and Parrish experiment



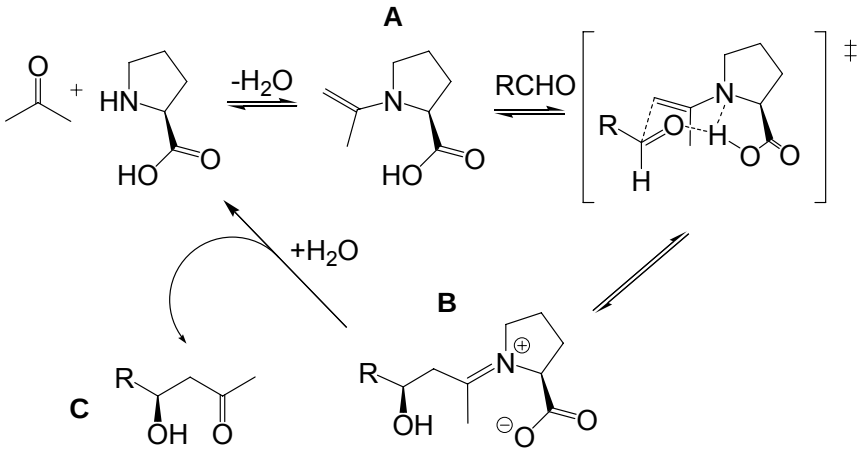

This reaction in modern organic chemistry is called *Hajos-Parrish-Eder-Sauer-Wiechert reaction* (Schemes 9 and 10). Additionally, this reaction is an important transformation and represents one of the two steps in *Robinson annulation reaction*. This reaction is a short way to the so-called *Wieland-Miescher ketone*[43] **18a** (Scheme 8) which proved to be particularly indispensable for the construction a variety of biologically active compounds such as sequiterpenoids, diterpenes and steroids.

In 2000, List et al. reported a first direct intermolecular aldol reaction between acetone and a variety of aldehydes promoted by (*S*)-proline[44]. The authors drew attention to some advantages of proline over metal catalyzed aldol reactions[45] and concluded that: 1) Proline is nontoxic, therefore it does not contradict to green chemistry's principles; 2) Proline is relatively chip reagent; 3) The reactions can be carried out at room temperature and do not require inert atmosphere; 4) Proline can be easy modify in order to improve a catalytic activity;

5) Proline is water soluble and therefore can by readily removed by aqueous extraction from reaction mixture; additionally, the reaction mechanism is relatively simple and can be easy understood.

List et al. assumed that proline-catalyzed direct aldol-reaction between acetone and a variety of aldehydes occured via *enamine mechanism* as shown on Scheme 10.[44]

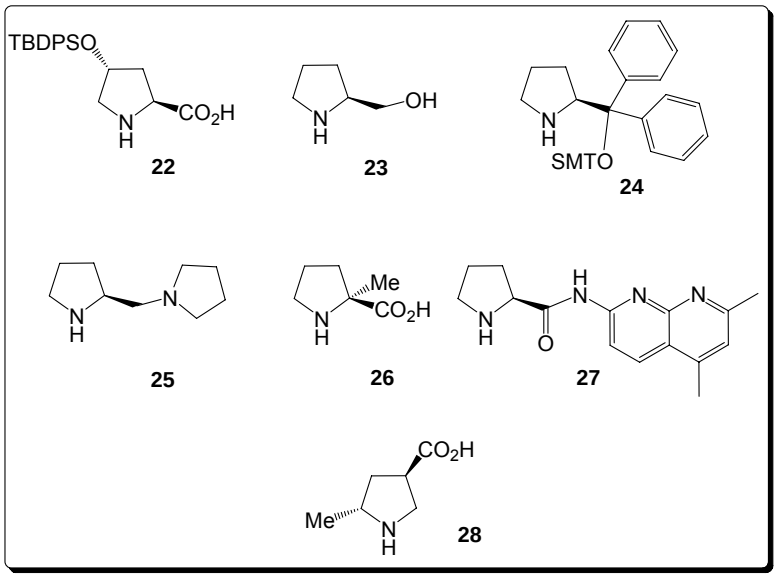
**Scheme 10.** Proposed Enamine Mechanism




This reaction mechanism is generally accepted. At first the condensation reaction between carbonyl compound and secondary amine leads to the formation of active enamine intermediate **A**. Then the enamine readily reacts with coordinated molecule of aldehyde to give the iminium-aldol intermediate **B**. At the last step intermediate **B** after hydrolysis gives desired product **C** and free catalyst. Transition state in this process represents metal-free version of the so-called *Zimmermann-Traxler-Model*[46].

Barbas et al. investigated some proline-like catalysts on Robinson annulation reaction and suggested that organic catalysts containing a secondary amine of the pyrrolidine-type and a carboxylate functionality are the most efficient catalysts[47]. The catalysts constructed from pyrrolidine ring moiety became a rapid expansion in asymmetric organocatalysis. Secondary amine catalysis was found to be attractive in a broad area of asymmetric catalysis. On Figure 6 are shown some interesting chiral catalysts built from pyrrolidine ring.

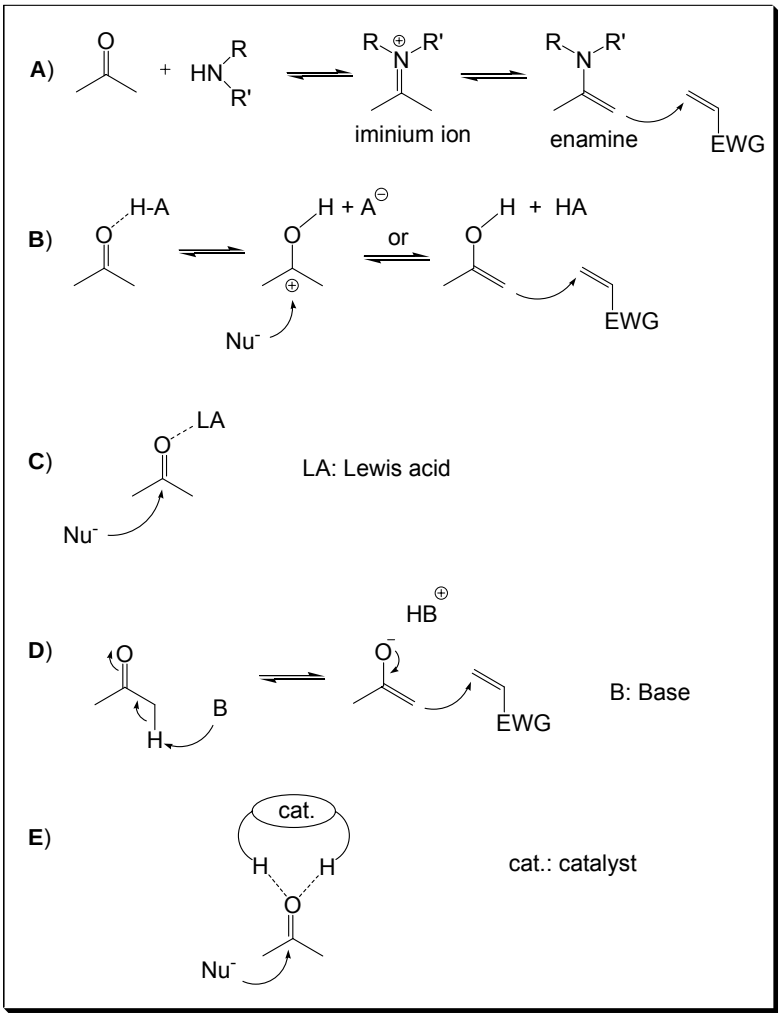
**Figure 6.** Asymmetric Organic Catalysts Based On Pyrrolidine Ring




Catalyst **22** promoted high enantioselective aldol reactions between aldehydes and variety of ketones under mild conditions[14]. Only 1 mol% of catalyst **22** was enough to promote the reaction in water without any organic solvent. Furthermore, **22** can be easily prepared from commercially available *trans*-hydroxyproline. The (*S*)-prolinol (**23**) can catalyze aldol reactions between fluoroacetone and variety of aldehydes to give fluoroaldol products which can be used as a building blocks in the synthesis of pharmacologically active compounds.[15] The pyrrolidine derivative **24** was found to be an excellent catalyst in organocatalytic asymmetric epoxidation of *α,β*-unsaturated aldehydes with peroxides[48a] and in Michael-addition of aldehydes to maleimides.[48b] The fully basic catalyst **25** in combination with trifluoroacetic acid is active in Michael-additon of *α,α*-disubstituted aldehydes to *β*-nitrostyrenes.[28] High enantioselective intramolecular *α*-alkylation of aldehydes was successfully performed in the presence of catalytic amounts of the proline derivative **26**[49]. Interesting results with the catalyst **27** in asymmetric Michael-addition of ketones to nitroolefins was obtained[50]. The increase of enantioselectivity was detected by the combination of **27** with achiral hydrogen-bonding pyridinone additives. The catalyst **28** demonstrated amazingly good enantioselectivity >99% in direct asymmetric *anti*-Mannich-type reaction performed under mild conditions.[51] Moreover, some other amino acids can also be active in asymmetric organic reactions. For example, (*S*)-alanine acts as an excellent catalyst in asymmetric direct intermolecular aldol reaction.[52a] The (*S*)-phenylalanine and (*S*)-leucine are also active in three-component Mannich reaction with good enantioselectivities.[52b] Last examples represent primary amine catalyzed reactions.

Activation pathways of carbonyl compounds can be interpreted as follows in Scheme 11.

**Scheme 11.** Activation Pathways for Carbonyl Compounds




Ways **A** and **B** are typical for reactions catalyzed by amino acids. Normally, types **A** and **B** are combinated. Way **C** is typical for metal catalyzed reactions. The way **D** very often occurs in cinchona alkaloid catalyzed transformations. And the last pathway **E** represents the unusual activation's art following via the formation of double hydrogen bonds between catalyst and carbonyl compound. Way **E** is typical by urea or thiourea catalyzed reactions. Urea/thiourea-based compounds which are able to form the double hydrogen bonds to substrates became wide spread in asymmetric organocatalysis as effective catalysts.

The formation of double hydrogen bonds between organic catalyst and substrates was found to be an interesting and attractive way of the activation of proton acceptor substrates such as carbonyl compounds or imine-like compounds without any proton transfer.

# 2. Evolution to the Thioureacatalysts

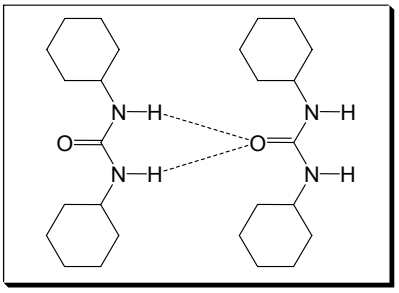
## 2.1 Some Historical Moments

As was already shown above the cinchona alkaloids, amino acids and their derivatives are excellent asymmetric catalysts in different important reactions and their catalytic activity is already very well known. Evolution of asymmetric organocatalysis began in 19th century. The earlier fortuitously discovered catalytic properties of cinchona alkaloids and amino acid proline that gave a stimulus to investigate the natural compounds as promising and effective organocatalysts.

Today, chemists of the whole world can control the direction of every asymmetric reaction. No wonder that chemists have a big interest in the mechanism of organocatalysis. The mechanism of reactions promoted by cinchona alkaloids and amino acids is sufficiently well investigated.

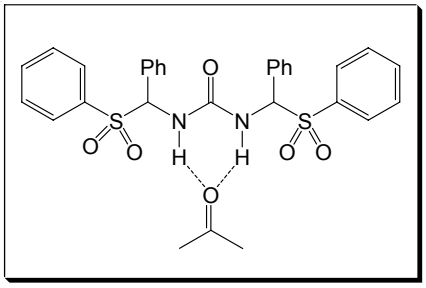
The interesting and relatively new art of organocatalysts is small molecules derived from urea or thiourea moieties. The urea/thiourea catalysts are famous as molecules able to form double hydrogen bonds with the substrates thereby activating or coordinating the substrates or even these both functions act in a synergetic manner. Already in the beginning of 1970's Coiro et al. observed and presented the molecules of *N,N′*-Dicyclohexylurea that were able to pack in crystal and form the intermolecular double hydrogen bonds as shown on Figure 7.[53]

**Figure 7.** Double hydrogen bonds between molecules of *N,N′*-Dicyclohexylurea



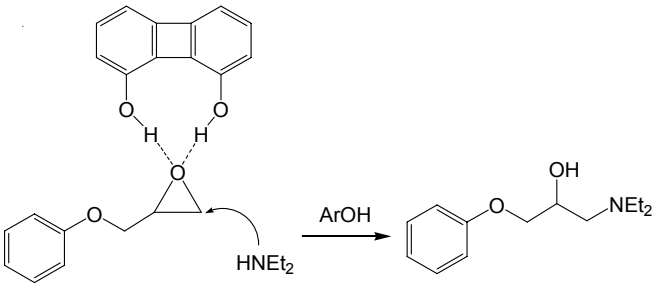

In 1976 Tel et al. investigated and reported that in crystals of *N,N′*-[Bis-(α-tosylbenzyl)]urea which was crystallised from acetone at -20 $^{o}$C, the molecules of acetone can be detected near all urea molecules[54]. It was found that acetone molecules form double hydrogen bonds with both *NH* groups of *N,N′*-[Bis-(α-tosylbenzyl)]urea (Figure 8).

**Figure 8.** Double hydrogen bonds between acetone and *N,N′*-[Bis-(α-tosylbenzyl)]urea




The first organocatalytic experiments where the formation of double hydrogen bonds between catalyst and substrates plays an important role were performed by Hine et al. (1985). He demonstrated that molecules of 1,8-biphenylenediol are active and can catalyse a reaction of phenylglycidyl ether with diethylamine[55] (Scheme 12).

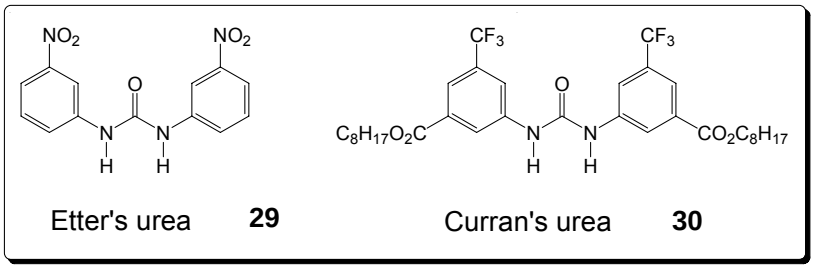
**Scheme 12.** Reaction of phenylglycidyl ether with diethylamine catalyzed by 1,8-biphenylenediol




Some crystallographic studies over the structures of 1,8-biphenylenediol derivatives permitted the revelation of clearly formed double hydrogen bonds with a variety of proton acceptors[55c]. The 1,8-biphenylenediol derivatives did not become a wide spread occurrence in organocatalysis, perhaps due to their complicated synthesis in comparison to urea/thiourea derivatives.

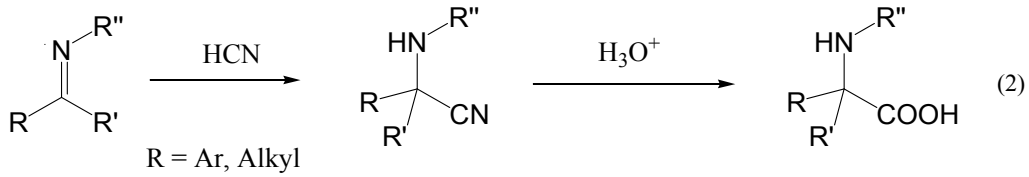
Many crystallographic experiments in which urea derivative **29** formed double hydrogen bonds with different proton acceptors in crystals were performed by Etter[56] (Figure 9). Curran et al. modified the Etter's urea derivative **29** to the new urea derivative **30**: urea **30** was a sufficiently good catalyst in allylation reaction of seleno sulfoxides[57].

**Figure 9.** Urea derivatives




### *2.1.1 Enantioselcetive Strecker Reaction Catalyzed by Thioureacatalysts*

*Strecker synthesis* is one of the most important and short synthetical way to the α-amino acids in organic chemistry. The classic variant of this reaction represents the condensation of aldehydes or ketones with primary or secondary amine (even with $NH_3$) to give imines (Schiff base). Such imines then react with $CN^-$ anion (generated by *KCN* or *HCH*) to give α-aminonitriles, which are subsequently hydrolyzed to the desired amino acid (eq. 2).

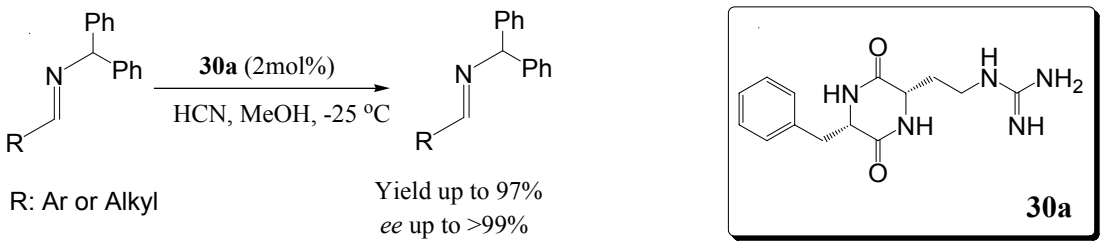



(2)

R = Ar, Alkyl
R' = Ar, Alkyl or H
R" = Ar, Alkyl or H

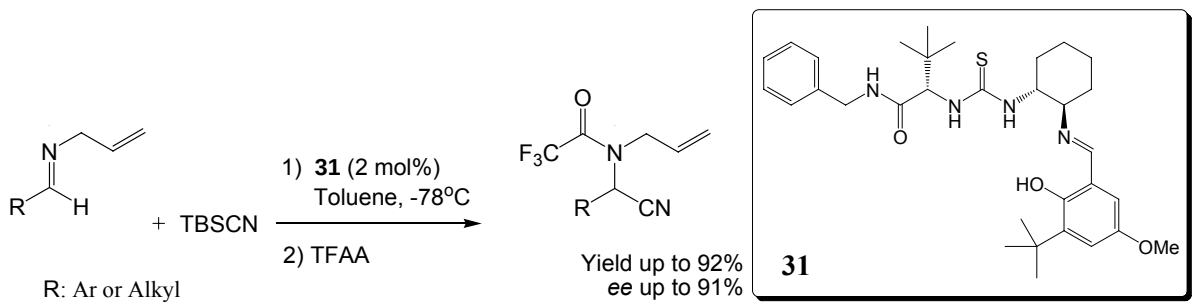
In 1996 the first asymmetric organocatalytic version of the Strecker synthesis was reported by Lipton et al.[63]. He investigated the stereoselective addition of *HCN* to variety of imines catalyzed by synthetically obtained diketopiperazine-based organocatalyst **30a** (Scheme 13). Catalyst **30a** was found to be extremely enantioselective in this reaction (ee up to >99%).

**Scheme 13.** Asymmetric addition of HCN to imines catalyzed by **30a**



The first application of chiral thiourea organocatalysts for enantioselective Strecker reaction of *HCN* with imines was reported by Jacobsen et al. in 1998[58]. He demonstrated that thiourea-based derivative **31** can stereoselectively catalyze this reaction (Scheme 14).

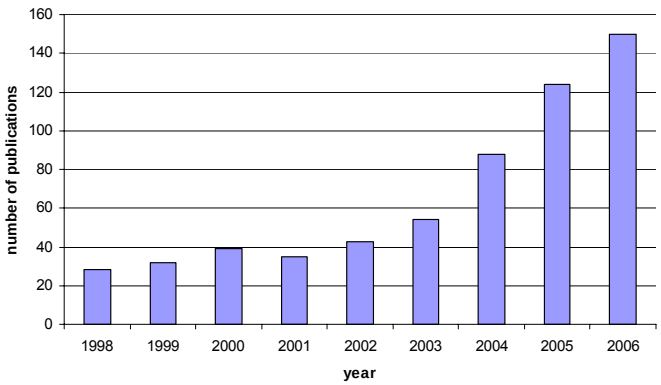
**Scheme 14.** Strecker synthesis catalyzed by thiourea derivative **31**




During the last ten years many chiral urea and thiourea derived catalysts were developed for the different enantioselective reactions. In addition, the thiourea derivatives are more popular in this field than urea derivative. Possibly the formation of stronger intermolecular hydrogen bonds (in comparison to thiourea analogues) between two molecules of urea leads to the decreasing of "free *NH*" groups which are responsible for the activation and coordination of substrates. Such interactions between urea molecules are well-known and described in literature [53, 59].

At the moment natural compounds containing the thiourea moiety are not known. Therefore, thiourea catalysts can be interpreted as molecules which were fully modelled and synthesized by chemist and represent a new generation of organocatalysts. The annual interest to thiourea catalysts is still increasing due to their important advantages and effectivity (Diagram 3).

**Diagram 3.** Annual increasing of publications containing a keyword "Thiourea catalysts"



The advantages of thiourea catalysts can be considered as follows:

a) Relatively simple and inexpensive synthesis;
b) Non-toxic and metal-free derivatives;
c) No inert atmosphere is necessary by handling and tolerant to water;
d) Thiourea derivatives are stable and can be stored for several months at room temperature;
e) Thiourea-based catalysts can be recovered from reaction mixture and used repeatedly;
f) The small amount of catalyst is enough to catalyse a reaction cycle.

# 3. Purpose of this Doctoral Thesis

At the beginning of our study according to already described properties of organic catalysts based on urea/thiourea molecules we have posed a goal to synthesise the new thiourea catalysts with improved properties. A variety of new thiourea-based organocatalysts were synthesized in our laboratory and tested on different important C-C bond forming reactions.

More detailed the aim of this doctoral thesis can be summarized as follows:

- Development of efficient organocatalyst based on thiourea molecules for the asymmetric Strecker reaction

- Development and application of new thiourea-based organocatalysts for asymmetric Michael-addition reaction of ketones to the nitroolefins

- Development and application of thiourea catalysts for the Mannich-type addition of different ketones to the α-hydrazonoesters.

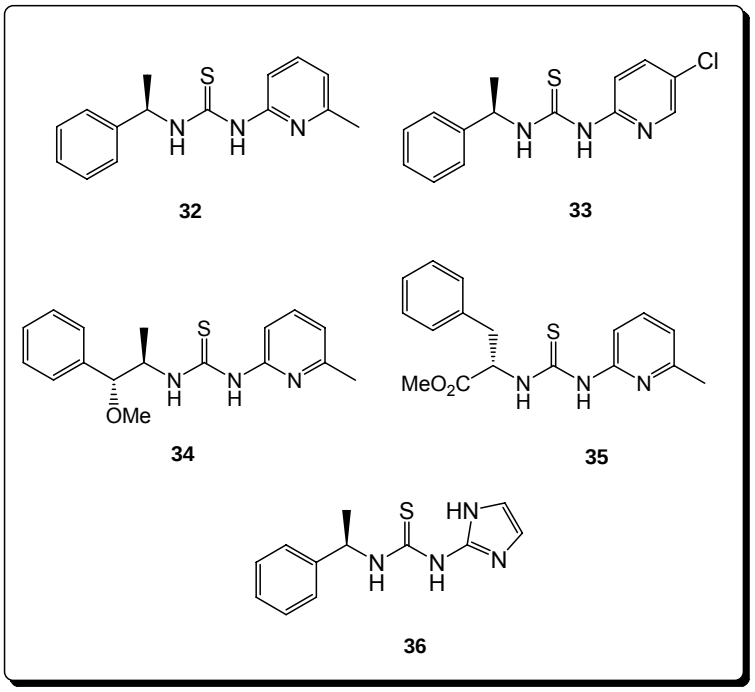
# B. Main part

## 1. Development and Application of Thioureacatalysts for the Asymmetric Strecker Reaction

### 1.1 Introduction

Chiral catalysts containing both an acidic and a basic/nucleophilic structural unit are of growing importance in the development of asymmetric catalysis.[60,61] Recently, several enantioselective bifunctional organic catalysts have been identified.[62] Among them are chiral organic catalysts for the Strecker synthesis, including a guanidine-bearing diketopiperazine,[63] a $C_2$-symmetric guanidine catalyst[64] and the chiral peptide-like catalysts described by Jacobsen, which possess both acidic (urea and/or thiourea moiety) as well as basic functionality (Schiff base).[58,65–67] Furthermore, the use of chiral bifunctional thiourea-based organocatalysts in the enantioselective Michael-addition,[68] the Aza-Henry,[69] Baylis–Hillman,[70,71] Acyl-Pictet-Spengler[72] and Nitro-Mannich[73] reactions as well as for the dynamic kinetic resolution of azalactones[74] has been recently reported. There are many known compounds displaying important biological activity containing both a thiourea moiety as well as a pyridine residue.[74–79] For instance, chiral α-methyl benzyl pyridyl thiourea compounds **32** and **33** (Figure 10) were reported by Uckun and co-workers to be non-nucleoside inhibitors (NNI) of the reverse transcriptase enzyme of the human immunodeficiency virus (HIV).[80–83] These structures incorporate both the acidic and the basic/nucleophilic bifunctionality of interest with respect to potential enantioselective bifunctional organocatalysts. This prompted us to apply these pyridine based thiourea compounds, as well as the novel thiourea derivatives **34**–**36** (Figure 10), synthesised in our laboratory, as catalysts for C–C bond formation reactions.

**Figure 10.** Thiourea catalysts

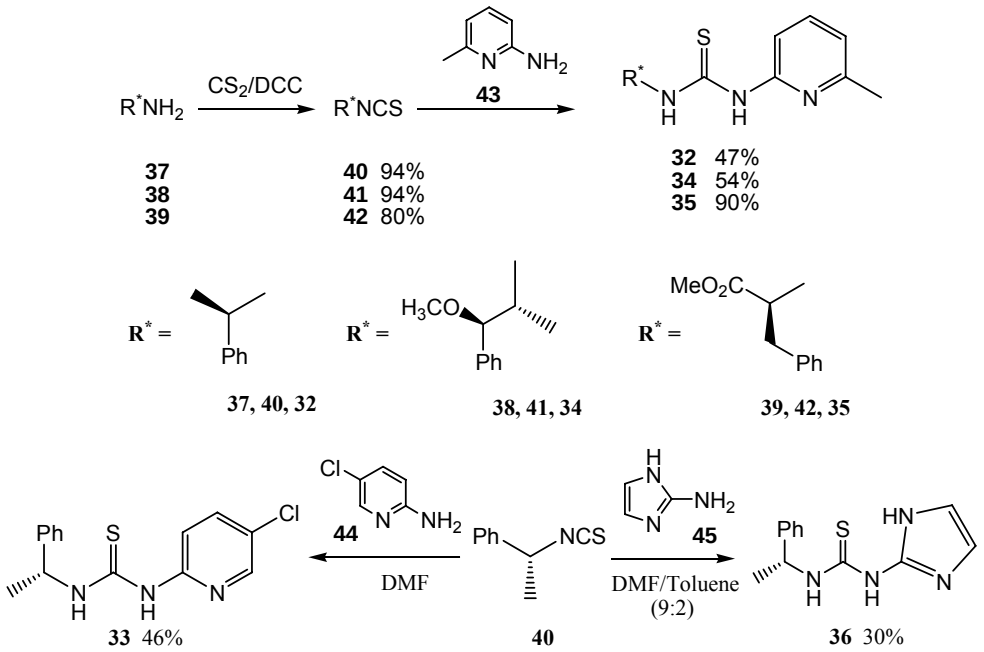



In particular, we were interested in the Strecker synthesis,[84, 85] which provides synthetically useful building blocks and has many important applications both in natural product synthesis as well as in the industrial preparation of pharmaceuticals and agrochemicals.

## 1.2 Results and Discussion

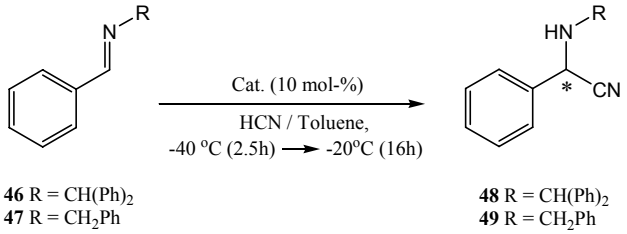
The syntheses of the thiourea compounds were accomplished by known methods[86, 87] as summarized in Scheme 15. Three different amines: (*R*)-(+)-1-phenylethylamine (**37**), (1*R*,2*S*)-(-)-2-amino-1-methoxy-1-phenylpropane (**38**) and (*S*)-phenylalanine methyl ester (**39**) were employed for the synthesis of chiral isothiocyanates **40–42**. Subsequent treatment of these chiral isothiocyanates with 2-amino-6-methylpyridine (**43**) and 2-amino-5-chloropyridine (**44**) gave the target pyridyl thioureas **32–35**.

**Scheme 15.** Syntheses of the thiourea compounds




The addition of hydrogen cyanide to aldimines **46** and **47** (Scheme 16) was employed to determine the catalytic activity of the pyridyl thiourea derivatives **32–35** (Figure 10) and thus their potential as bifunctional organocatalysts.

**Scheme 16.** The addition of hydrogen cyanide to aldimines




Aldimines **46** and **47** were selected as the substrates of choice to enable an effective comparison with earlier investigations in the literature.[64, 67] All reactions were performed as solutions in toluene with 10 mol % of the appropriate catalyst and were stirred for 2.5 h at -40 °C and subsequently for a further 16 h at -20 °C. Low conversions (up to 25%) and enantioselectivities (up to 14%) were observed in all cases (entries 1–4, Table 1).

In searching for ways to improve the catalyst activity, we were drawn to the strategy of base variation. Therefore, we continued our investigation with an examination of the catalytic efficacy of some available organic bases (entries 5–8, Table 1).

**Table 1.** Strecker reactions catalyzed by thiourea derivatives **32**–**36**

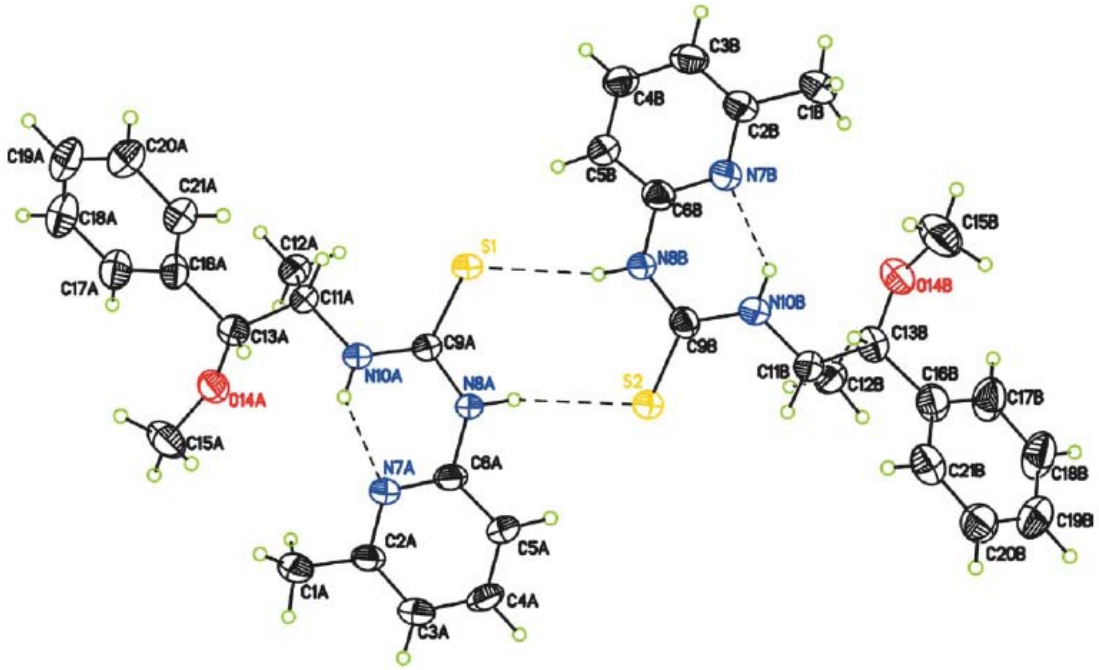
| Entry | Catalyst (10 mol%) | Substrate | 2.5 h at -40 °C<br>16 h at -20 °C | |
|---|---|---|---|---|
| | | | Conversion [%][a] | ee [%][a] |
| 1 | **32** | **46** | 17 | 14 |
| 2 | **33** | **46** | 25 | 12 |
| 3 | **34** | **46** | 9 | 6 |
| 4 | **35** | **46** | 9 | 4 |
| 5 | Pyridine | **46** | 5 | - |
| 6 | Pyrrolidine | **46** | 11 | - |
| 7 | $Et_3N$ | **46** | 6 | - |
| 8 | Imidazole | **46** | 32 | - |
| 9 | Biotine | **46** | 10 | 4 |
| 10 | Biotine[b] + Imidazole[b] | **46** | 37 | 4 |
| 11 | **36** | **46** | 85 | 6 |
| 12 | **36** | **47** | 100 | 7 |

[a] Determined by HPLC after 16 h of reaction at -20 °C. Reported conversions and *ee* values are the average of 2 runs.
[b] 10 mol % of co-catalyst.

We found that use of imidazole as a base generally gave a better conversion (32%, entry 8) than pyridine (5%, entry 5), pyrrolidine (11%, entry 6) or $Et_3N$ (6%, entry 7). From this observation we concluded that the more basic additive is favourable and responsible for the better conversion. For instance, the pKa value of imidazole base is 6.95 and for pyridine is 5.25. Thus, in the chiral thiourea **36** (Scheme 13), the methylpyridyl group of **32** was replaced by an imidazolyl substituent. Intriguingly, whereas imidazole and/or biotin alone, as well as their mixture gave the Strecker product from the substrate **46** in only 32%, 10% and 37% yields, respectively (entries 8–10). High conversion was observed with substrates **46** and **47** under the same conditions in the presence of imidazolyl thiourea catalyst **36** (85% and 100%, respectively, entries 11 and 12, Table 1), which represented up to 76% improvement in the conversion of imine **46** over the corresponding pyridyl thiourea based catalysts **32–35** (entries 1–4). These results indicate that for a high conversion the catalyst should possess both an imidazole group and a urea/thiourea moiety in the same molecule. More probably, the basic group and the thiourea reaction centre act in a synergistic manner within the catalyst. The enantioselectivities obtained with imidazolyl thiourea **36**, however, proved to be in the same range as those observed with pyridyl thioureas **32–35**.

The X-ray crystal structure of the new thiourea derivative **34** (chiral methylpyridyl thiourea) sheds light on the cause of the low chiral induction observed in the Strecker reaction using bifunctional catalysts **32–36** (Figure 11).

**Figure 11.** X-ray crystal structure of two molecules of compound **34**; thermal ellipsoids are shown at 50% probability level




As already reported by Vachal and Jacobsen,[67] Schreiner and Wittkopp,[88] ureas and thioureas are able to provide two hydrogen bonds to bind the *H*-bond acceptors (carbonyl or imine groups). It appears likely that a bridged structure, in which the imine forms hydrogen-bonds to both thiourea hydrogen atoms simultaneously, is important for catalyst activity and selectivity.[67] The X-ray structure[89] of methylpyridyl thiourea **34** shows, however, that an intramolecular hydrogen bond is formed between the thiourea $N_{10}$–*H* group and the basic nitrogen atom ($N_7$) of the pyridyl group as well as an intermolecular hydrogen bond from $N_8$–*H* to the sulfur of a crystallographic independent second molecule leading to a dimer. There are two of these nearly identical dimers in the asymmetric unit (Figure 11). Furthermore, such intramolecular interaction is possible for **36**. As was already mentioned above the availability of basic nitrogen atom as well as free thiourea *NH* groups in catalyst are responsible for catalytic activity. As can be seen from X-Ray analysis for **34** (Figure 11) the nitrogen atom of pyridine ring is partially deactivated because of intramoleculare hydrogen bonding. The better reaction conversion by using **36** can be explained according to Figure 12.

We proposed that in the case of imidazolyl thiourea **36**, there the favourable intramolecular formation of hydrogen bond between *N-H* group of imidazole moiety and sulfure within one molecule takes place (Figure 12). Such transformation, possibly, makes the nitrogen atom of imidazole ring more available thus the formation of the cyanide complex and the following attack of $CN^-$ onto the C=N bond of imine is possible (Figure 13).

**Figure 12.** Possible intramolecular transformations for imidazolyl thiourea **36**

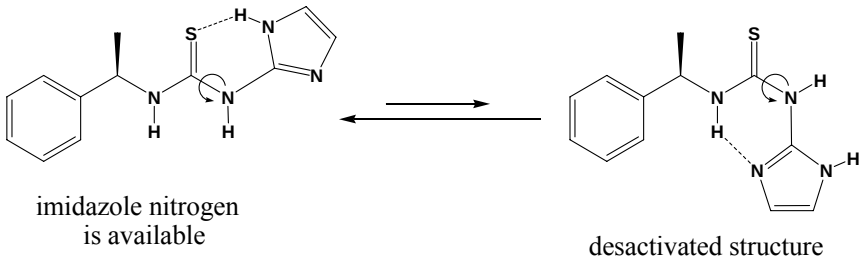
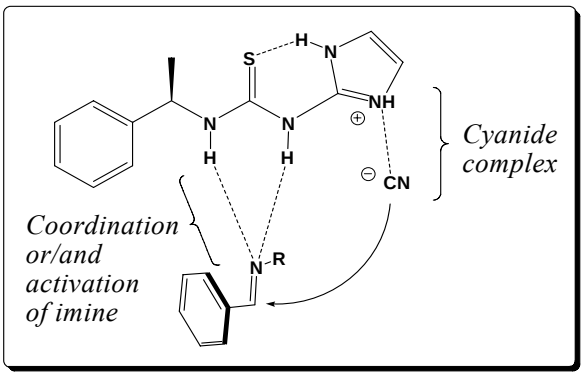



**Figure 13.** Proposed transition state




However, as a result, the imine substrate cannot be placed in a bridging mode between the two thiourea hydrogen atoms, which might serve to explain the low enantioselectivities obtained with catalyst **34**, as well as with all the other thiourea derivatives presented here (since structural similarities are evident). These observations are consistent with the postulation that H-bonding interactions are central to reaction selectivity.[67]

Based on these results and the observation that imidazole as a base is essential for catalyst activity, we targeted imidazolyl thiourea derivative **36** as a candidate that might be further modified to improve catalyst enantioselectivity.

## 1.3 Summary

- The examination of the catalytic potential of the pyridyl thiourea derivatives **32**–**35**, as well as an X-ray analysis of the new compound **34** proved that the formation of H-bonding interactions between imine substrates and the thiourea moiety of the catalysts is crucial for good yields and enantioselectivities.

- It was determined that the substitution of an imidazolyl moiety for a pyridyl group (derivative **36**) resulted in a much more active catalyst.

- The results presented herein indicate that the combination of an imidazolyl group with suitable chiral aliphatic or aromatic substituents leads to substantial improvements in the catalytic activity of the thiourea catalyst.

Further design, synthesis and application of new improved bifunctional organocatalysts for the Strecker and nitro-Michael reaction are described and discussed in the next chapter.

# 2. Development and Application of new Thioureacatalysts for the Asymmetric Strecker and nitro-Michael reactions.

## 2.1 Introduction

The continually increasing number of contributions to the field of asymmetric synthesis with chiral bifunctional catalysts undoubtedly confirms the importance of this area of research for chemists.[58, 60] A large amount of results from Jacobsen's laboratory clearly demonstrated peptide-like thiourea based molecules to be excellent bifunctional chiral catalysts for the asymmetric Strecker synthesis,[58, 66, 67] enantioselective hydrophosphonylation of imines,[90] Acyl-Pictet–Spengler[72] and nitro-Mannich[73] reactions. Furthermore, examples of enantioselective Michael-addition,[68, 91–95] Aza-Henry,[68] Baylis–Hillman[69,70] reactions and dynamic kinetic resolution of azlactones[74] have recently been reported in which chiral bifunctional organocatalysts have been employed. However, the design and development of new, effective and easily accessible bifunctional chiral organic catalysts continues to be a major challenge.

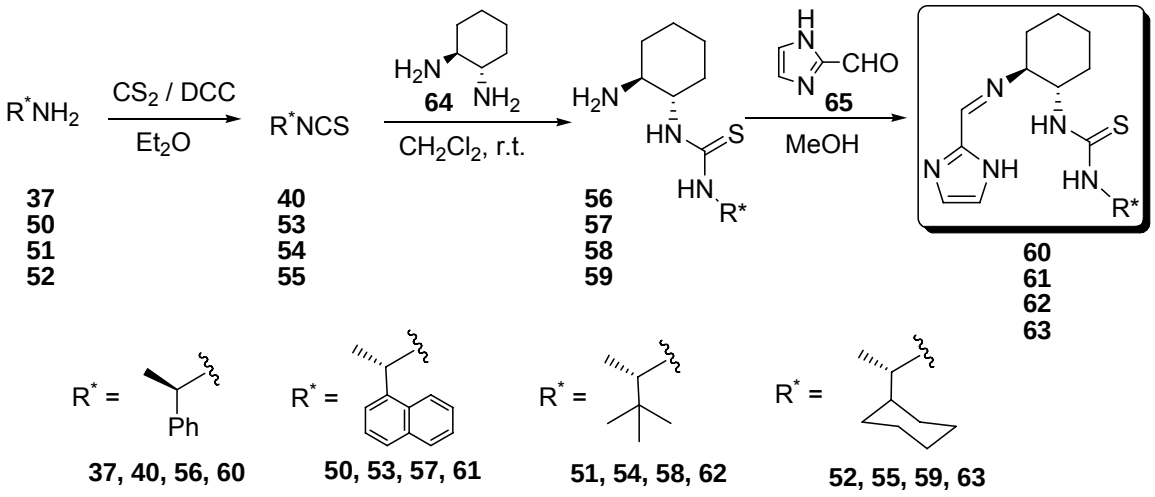
Based on our previous results and the observation[96] described in Chapter 1 that imidazole as a base is essential for thiourea catalytic activity, we describe here the syntheses and application of some novel chiral imidazole-based thiourea catalysts for C–C bond formation reactions. Initially, these bifunctional organocatalysts were tested in the asymmetric Strecker reaction.[84] Furthermore, the high potential of these bifunctional organocatalysts for conjugate addition reactions, for example in the Michael-addition of acetone to β-nitrostyrene, is demonstrated.

## 2.2 Results and Discussion

### *2.2.1 Strecker Reaction*

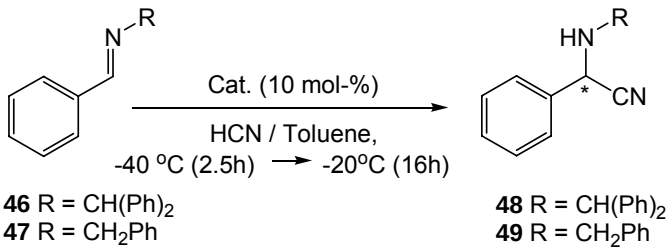
Our investigation began with the preparation of novel thiourea compounds **60**–**63** from four different chiral amines: (*R*)-(+)-1-phenylethylamine (**37**), (*S*)-1-(2-naphthyl) ethylamine (**50**), (*S*)-3,3-dimethyl-2-aminobutane (**51**) and (*S*)-1-cyclohexylethylamine (**52**) by known methods[67,86,87] as summarised in Scheme 17. These derivatives were then examined for their ability to catalyze the enantioselective Strecker reaction.

**Scheme 17.** The synthesis of novel thiourea compounds **60**–**63**




As a model transformation we studied the addition of hydrogen cyanide to aldimines **47** and **46** in the presence of 0.1 equiv. of the appropriate thiourea derivative, with the reaction proceeding for 2.5 h at –40 °C and subsequently for a further 16 h at –20 °C (Scheme 18). The results obtained show that the nature of the substrate influences both the reaction rate and enantioselectivity to a large extent.

**Scheme 18.** The addition of hydrogen cyanide to aldimines



Notably, catalysts **60–63** afforded low to moderate conversions (up to 47%) and enantioselectivities (up to 39% *ee*) with substrate **47** over 2.5 h at –40 °C (entries 1, 3, 5, 7 of Table 2). Better enantioselectivities (up to 68% *ee*), but worse conversions (up to 24%) were observed under the same reaction conditions with the aldimine substrate **46**. Nevertheless, the enantioselectivity obtained is much better than obtained by using of imidazolyl thiourea **36** and pyridyl thioureas **32–35** (Table 1) at the same conditions described in Chapter 1.

**Table 2.** Strecker reactions catalyzed by thiourea derivatives **60–63** and compounds **66** and **67**

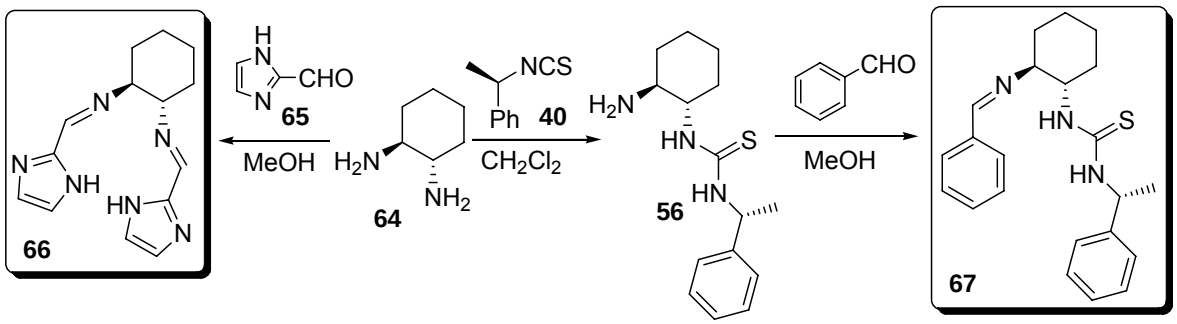
| Entry | Catalyst | Substrate | 2.5 h at -40 °C | | 16 h at -20 °C | |
|---|---|---|---|---|---|---|
| | | | conv (%)[a] | ee (%)[a] | conv (%)[a] | ee (%)[a] |
| 1 | **60** | **47** | 27 | 22 | 96 | 12 |
| 2 | **60** | **46** | 24 | 63 | 73 | 24 |
| 3 | **61** | **47** | 14 | 39 | 93 | 17 |
| 4 | **61** | **46** | 2 | - | 12 | 15 |
| 5 | **62** | **47** | 47 | 24 | 100 | 10 |
| 6 | **62** | **46** | 17 | 68 | 71 | 20 |
| 7 | **63** | **47** | 16 | 13 | 99 | 5 |
| 8 | **63** | **46** | 0 | - | 47 | 2 |
| 9 | **66** | **47** | 8 | 2 | 74 | 3 |
| 10 | **67** | **47** | 20 | 2 | 97 | 4 |
| 11 | **67** | **46** | 0 | - | 10 | 4 |
| 12 | none | **46** | 0 | - | 5 | - |
| 13 | none | **47** | 6 | - | 54 | - |
| 14 | **60** | **47** | - | - | 50[b] | 31[b] |

[a] Determined by HPLC after 16 h of reaction at -20 °C. Reported conversions and *ee* values are the average of 2 runs.
[b] Reaction was carried out at –78 °C for 120 h.

The bulkier *N*-benzhydryl subunit present in substrate **46** seems to have a beneficial effect on the enantioselectivity (entries 2 and 6 of Table 2). A longer reaction time (16 h at –20 °C) provided high conversions with the aldimine substrate **47** (93–100%, entries 1, 3, 5, 7 of Table 2) and low to good conversions with the bulkier substrate **46** (12–73%, entries 2, 4, 6, 8 of Table 2). At the same time, the enantiomeric excess values of all products were reduced during the course of the reaction, indicating that racemization of the product takes place under the reaction conditions. The contribution of the thiourea and imidazole subunits to the activity of the catalyst was then investigated. Replacing the thiourea moiety of **60** with an imidazole ring (compound **66**, Scheme 17) led to a reduction in the conversion of aldimine **47** from 96% to 74%, as well as a corresponding reduction in enantiomeric excess of the product from 12% to 3% (Table 2, entry 1 vs. entry 9).

Whereas thiourea derivative **67**, which has no imidazole moiety (prepared according to Scheme 19), provides a comparatively high conversion of substrate **47** to that generated by catalyst **60** (Table 2, entry 10 vs. entry 1), only 10% conversion and 4% *ee* were observed with catalyst **67** for substrate **46** (Table 2, Entry 11 vs. Entry 2).

**Scheme 19.** Preparation of new compounds **66** and **67**



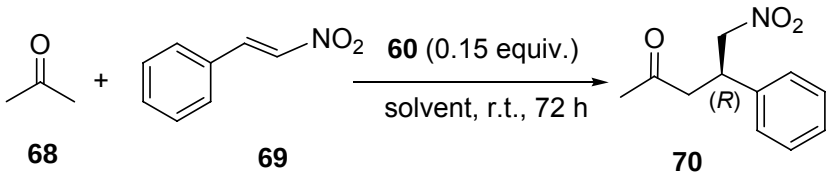

This represents a 63% reduction in the conversion and a 20% reduction in the *ee* value compared to the imidazole-based chiral thiourea **60**. These results indicate that for a high conversion the catalyst should possess both an imidazole group and a thiourea moiety. In order to explain the low enantioselectivities observed we examined the reaction of aldimine substrates **47** and **46** in the absence of catalyst under the standard reaction conditions (–20 °C, 16 h). The rate of the noncatalysed racemic reaction was found to be very low for the *N*-benzhydryl imine **46** but significant for the *N*-benzyl benzaldehyde imine **47** (5% and 54% conversion, respectively (entries 12, 13 in Table 2). Taking these results into consideration we speculated that complete suppression of the noncatalysed racemic reaction pathway might occur at a reduced temperature. Indeed, a slight enhancement in the *ee* value from 12% to 31% was observed when the conversion of **47** was carried out at –78 °C (Table 2, entry 1 vs. entry 14). Unfortunately, this improved enantioselectivity was paid for by a much lower reaction rate (50% conversion in 120 h).

### *2.2.2 Nitro-Michael-addition of Acetone to trans-β-nitrostyrene*

The novel thiourea derivatives **60**–**63** subsequently proved to be effective catalysts in the nitro-Michael reaction. The addition of acetone to *trans*-β-nitrostyrene was chosen as a model reaction to determine the catalytic activity of the thiourea compounds. Barbas and co-workers were the first to report the organocatalytic version of this reaction.

Using (*L*)-proline as the catalyst in DMSO[97] they were only able to isolate the product in the racemic form. As a result, considerable effort has been directed towards the development of a catalytic asymmetric version of this reaction over the past several years, though only low enantioselectivities (up to 31% *ee*) have been obtained at the beginning of our study.[98–100] The best results to date have been achieved very recently using a homo-proline tetrazole catalyst in the addition of acetone to *trans*-β-nitrostyrene with up to 42% *ee*.[95b] We first screened a range of solvents for the reaction catalysed by the novel bifunctional organocatalyst **60** (Table 3, entries 1–5).

**Table 3.** Michael-addition of acetone **68** to *trans*-β-nitrostyrene **69** in different solvents




**68** **69** **70**

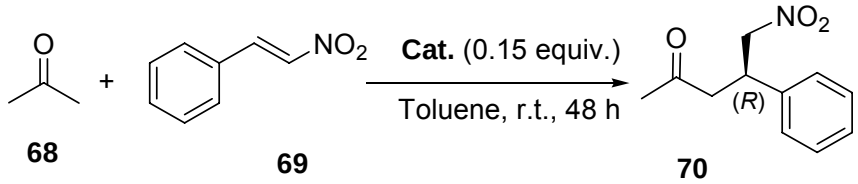
| Entry | Solvent | Conversion [%][a] | *ee* [%][b] |
|---|---|---|---|
| 1 | Toluene | 89 | 87 |
| 2 | $CH_2Cl_2$ | 58 | 86 |
| 3 | $CHCl_3$ | 86 | 85 |
| 4 | Acetone | 48 | 79 |
| 5 | MeOH | 39 | 56 |

[a] Determined by $^1$H NMR of crude mixture.
[b] Enantioselectivities were determined by chiral HPLC analysis (Daicel Chiralpak AS) in comparison with authentic racemic material.

The optimum result was observed in nonpolar toluene, providing high conversion (89%) and very good enantioselectivity (87% *ee*) (Table 3, entry 1). This represents a 45% improvement in the *ee* value over the reported homo-proline tetrazole catalyst.[95b] Interestingly, the results in $CH_2Cl_2$ and $CHCl_3$ resemble those in toluene, with the sole exception of the reduced conversion achieved in $CH_2Cl_2$ (Table 3, entries 2, 3). In more polar solvents (acetone, MeOH) the adduct was obtained with lower conversions and enantioselectivities, since these solvents might inhibit the hydrogen-bonding interaction between *trans*-β-nitrostyrene and the thiourea moiety of **60** (Table 3, entries 4, 5).

It is necessary to note that the thiourea analogue of compound **60** gave a lower conversion (78%) and enantioselectivity (72% *ee*) in toluene with respect to thiourea **60**, which is in agreement with results reported in the literature (the interaction in the catalyst-substrate complex is stronger for thiourea than for urea).[67] When the bifunctional thioureas **61**–**63** with the *S*-configuration in the naphthyl-, *tert*-butyl- and cyclohexylethylamine moieties were studied as catalysts in the same reaction, we found that the Michael product was formed with slightly reduced enantioselectivities (73–77% *ee*, entries 2–4 of Table 4).

**Table 4.** Michael-addition of acetone to *trans*-β-nitrostyrene




**68** **69** **70**

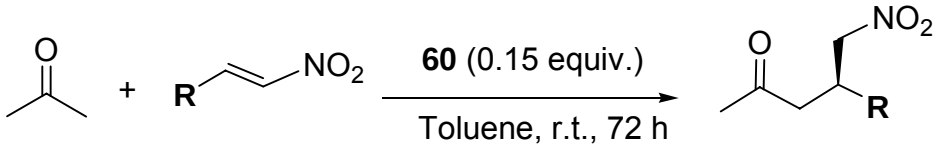
| Entry | Catalyst | Yield [%][a] | *ee* [%][b] (R) |
|---|---|---|---|
| 1 | **60** | 55[c] | 87[c] |
| 2 | **61** | 49 | 73 |
| 3 | **62** | 60 | 73 |
| 4 | **63** | 61 | 77 |
| 5 | imidazole | - | - |
| 6 | **66** | - | - |
| 7 | **67** | - | - |

[a] Yield of isolated product after column chromatography on $SiO_2$.
[b] Enantioselectivities were determined by chiral HPLC analysis (Daicel Chiralpak AS) in comparison with authentic racemic material.
[c] Yield and % *ee* were determined after 40 h.

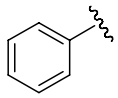
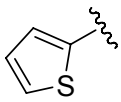
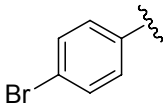
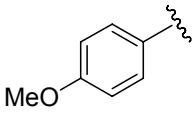
The stereoselectivity of this reaction was shown to be dependent on the presence of a suitable combination of the absolute configurations of the stereogenic centres in the catalyst molecule. The similarity of the results using the thiourea catalysts **61**–**63** is also noteworthy, suggesting that the functionality attached to the thiourea moiety has little effect on the outcome of this reaction. In order to gain an insight into the mechanism of catalysis, imidazole alone as well as compounds **66** and **67** were tested as catalysts. Whereas thioureas **60**–**63** gave the Michael product in up to 61% yield (entries 1–4), no reaction was observed in the presence of either imidazole, or compounds **66** and **67** (entries 5–7, Table 4). These experiments show that neither the imidazole ring nor the thiourea moiety are able to facilitate the Michael-addition on their own, and thus the prerequisite for successful conversion to product is that the catalyst

possess both functionalities. Both of these groups most probably act in a synergistic manner within the catalyst. Once the optimal catalyst and solvent conditions were established, various nitroolefins were then evaluated as substrates (Table 5).

**Table 5.** Michael-addition of acetone to nitroolefins under optimised conditions.



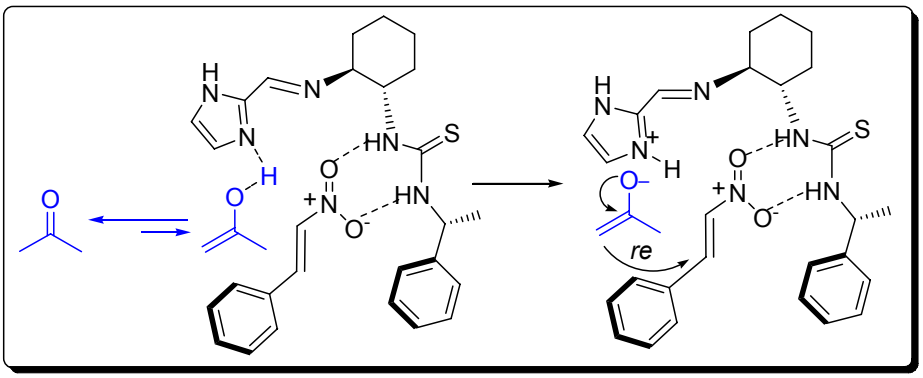

**68** **70-73**

| Entry | Substrate (R) | Yield [%][a] | ee, [%][b] |
|---|---|---|---|
| 1 |  **70** | 55[c] | 87[c] |
| 2 |  **71** | 57 | 84 |
| 3 |  **72** | 62 | 83 |
| 4 |  **73** | 46 | 86 |

[a] Yield of isolated product after column chromatography on $SiO_2$.
[b] Enantioselectivities were determined by chiral HPLC analysis (Daicel Chiralpak AS) in comparison with authentic racemic material.
[c] Yield and % *ee* were determined after 40 h.

The introduction of electron-withdrawing or electron-donating groups in the aromatic ring of the nitroolefins did not affect the enantioselectivities (83–87% *ee*, Table 5, entries 1–4) or the yields (46–62%) significantly. Although further studies are needed to firmly elucidate the reaction mechanism of this Michael-addition, we postulate the sequence shown in Figure 14. Acetone in the enol/enolate form is stabilised by the imidazole group and attacks the nitrostyrene molecule enantioselectively from one face of the double bond.

**Figure 14.** Proposed transition state




According to obtained results and the proposed model, the *Re* approach is favoured for acetone. The nitrostyrene substrate is held in place by hydrogen bonding between the nitro group and the thiourea moiety. The hydrogen bonding strength is evidently affected by the solvent polarity and this is consistent with the observed range of conversions and enantioselectivities found in the various solvents investigated (Table 3).

## 2.3 Summary

- The novel imidazole-based chiral thiourea derivatives **60**–**63** have been synthesized and shown to catalyse the nitro-Michael reaction with much higher stereoselectivity than the Strecker synthesis

- In the case studied (addition of acetone to *trans*-β-nitrostyrene) novel catalysts **60**–**63** gave superior results in terms of enantioselectivity (up to 87% *ee*) than the known proline derivatives described in the literature.

# 3. Michael-Addition of Acetone to Nitroolefins Promoted by a Chiral Primary Amine-Thiourea Catalyst: A Joint Experimental-Theoretical Study

## 3.1 Introduction

Among the numerous asymmetric carbon-carbon bond formation reactions the conjugate Michael-addition plays a particularly important role.[101] Without question, one of the more elegant and economically most attractive ways to introduce chirality into a Michael acceptor is through chiral organic catalysts.[62a, 102] Employing nitroolefins as Michael acceptors opens the way to synthetically very useful C-C and C-X (X = N, O) bond-forming reactions.[103, 104] In particular, the Michael reaction of ketones with nitroolefins represents a convenient access to γ-nitroketones which are valuable building blocks in organic synthesis.[104] Considerable effort has been directed towards the development of an organocatalytic asymmetric version of this Michael-addition over the recent years. [95, 97-100, 105]Although many improvements to this reaction have been made, poor to moderate enantioselectivities resulted when acetone was used as substrate.[95, 97-100, 105]

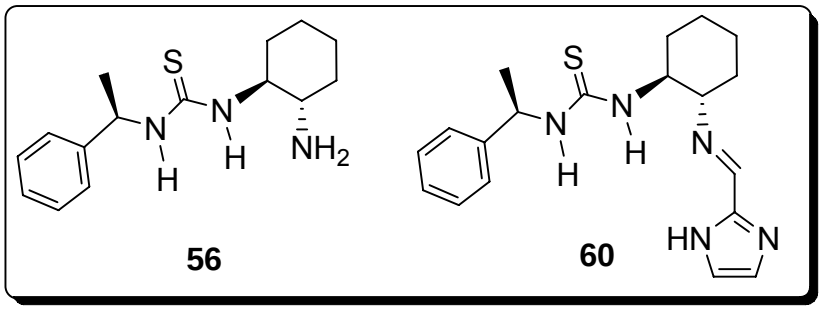
A successful design of a general chiral organic catalyst for the Michael reaction of ketones with nitroolefins with high enantioselectivity is still a challenging task. For the solution of this problem, computational chemistry has proven to be a valuable tool: semiempirical, wave-function based quantum-chemical and density functional methods (DFT-calculations) can predict reaction pathways, product ratios and even enantioselectivities.[106] While it is nowadays possible to tackle realistic problems with remarkably accurate computational methods, the search for transition state structures in reactive processes still remains a challenge due to the high flexibility of these structures, in particular when more than two reactants are present, as is naturally the case in homogeneous catalytic processes.

Organic catalysts which possess both an acidic and basic/nucleophilic moiety have received a broad interest in asymmetric synthesis during the last years.[62b, 107]

Several enantioselective urea and thiourea based bifunctional organic catalysts have been identified.[59, 66-74, 90-95] Examples of asymmetric Michael-addition, [68, 91-95] also Strecker synthesis,[66, 67, 96] enantioselective hydrophosphonylation of imines,[90] Acyl-Pictet-Spengler,[72] Nitro-Mannich[73] reactions, Aza-Henry, [69] Baylis-Hillman[70, 71] reactions and dynamic kinetic resolution of azlactones[74] have been reported in which the chiral bifunctional organocatalysts have successfully been employed.

As was already shown above in Chapter 2 a new bifunctional organocatalyst **60** (Figure 15), bearing both a thiourea moiety and an imidazole group on a chiral scaffold, catalyzed the addition of acetone to *trans*-β-nitrostyrene and gave adduct in 87% *ee* and with 55% yield (Table 6). Notably, this enantioselctivity is superior to those generated by the proline and/or homo-proline tetrazole catalysts described in the literature.[95, 97-100, 105]

**Figure 15.** Thiourea-based bifunctional organocatalysts



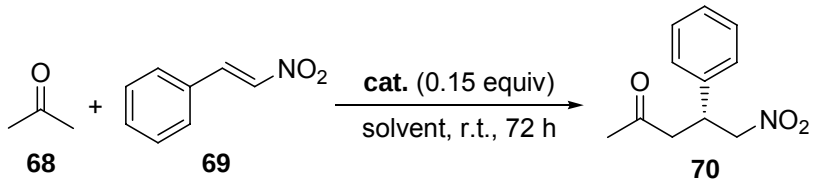

Considering the fact that secondary and primary amines with ketones reversibly form enamines,[61a] which can further react with electrophiles, we anticipate that the substitution of the imidazolyl moiety in **60** by an amino group might result in a simpler but more active catalyst **56**, which might be able to activate both ketones through enamine formation and nitroolefins by double hydrogen bonding to a thiourea moiety.

In this part is described the ability of new chiral bifunctional organic catalyst **56**, that possess both a thiourea moiety and a primary amine group as a base, in performing asymmetric nitro-Michael addition reaction, accompanied by a quantum-chemical calculation of the stereoselectivity. Preliminary exploratory experiments revealed that thiourea catalyst **56** (0.15 equiv) promoted the addition of acetone to *trans*-β-nitrostyrene at room temperature in toluene with results (55%, 86% *ee* (***R***)) comparable to those provided with catalyst **60** (55%, 87% *ee* (***R***) [108]).

## 3.2 Results and Discussion

We chose thiourea **56** as a good catalyst candidate for a further optimisation of the reaction conditions. A range of solvents for the addition of acetone to *trans*-β-nitrostyrene catalysed by **56** was screened (Table 6). The use of $CH_2Cl_2$, $CHCl_3$, $CH_3COCH_3$, MeOH and DMSO as solvents led, in general, to a decrease in the reaction rate with respect to toluene (Table 6, entry 1 vs. entries 2-6).

**Table 6.** Solvent screen for the conjugate addition of acetone (**68**) to *trans*-β-nitrostyrene (**69**) catalyzed by chiral thiourea-amine **56**



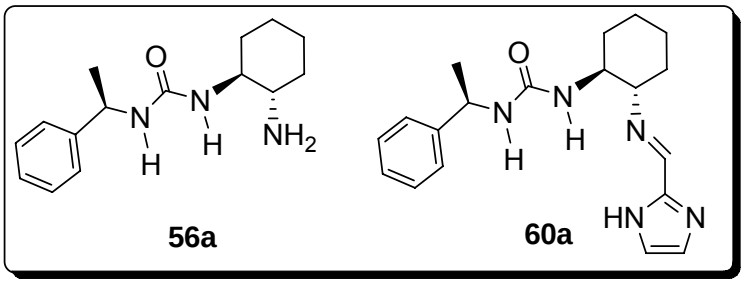

**68** **69** **70**

| Entry | Catalyst | Solvent | Conv.[%][a] | ee [%][b] |
|---|---|---|---|---|
| 1 | **56** | Toluene | 100 | 86.0 |
| 2 | **56** | $CH_2Cl_2$ | 56 | 81.0 |
| 3 | **56** | $CHCl_3$ | 51 | 84.0 |
| 4 | **56** | Acetone | 22 | 62.0 |
| 5 | **56** | MeOH | 50 | 50.0 |
| 6 | **56** | DMSO | 80 | 14.0 |
| 7 | **56a** | Toluene | 77 | 76.0 |
| 8 | **60a** | Toluene | 83 | 72.5 |

[a] Determined by $^1$H NMR of crude reaction mixture.
[b] Enantioselectivities were determined by chiral HPLC analysis (Daicel Chiralpak AS) in comparison with authentic racemic material.

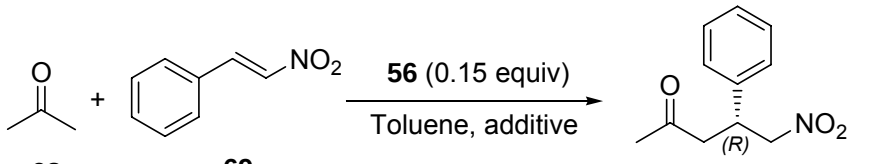
Much lower *ee* values were observed in acetone and MeOH (62% and 50% *ee*, respectively, entries 4 and 5) relative to that in toluene (86% *ee*, entry 1). Furthermore, the use of DMSO as solvent significantly decreased the enantioselectivity (14% *ee*, Table 6, entry 6). These observations are consistent with the fact that the hydrogen bonding strength is affected by the solvent;[109] the effect of replacing DMSO by non-polar toluene increases the double hydrogen bonding interaction between the nitro group of *trans*-β-nitrostyrene and the thiourea moiety of catalyst **56**. Toluene, thus, remained the solvent of choice. Urea derivatives **56a** and **60a** (Figure 16) were found to be less active than thioureas **56** and **60** (Table 6, entries 7 and 8). In practice **56a** and **60a** were synthesized in a same manner like **56** and **60**.

**Figure 16.** New urea derivatives **56a** and **60a**

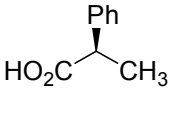
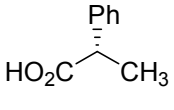



Screening several achiral and chiral additives allowed us to further improve the yields and enantioselectivities. It is interesting to note that the reaction rate was increased to a different extent, depending on the nature of the additive used (Table 7).

**Table 7.** Asymmetric addition of acetone (**68**) to *trans*-β-nitrostyrene (**69**) in toluene catalyzed by **56** in the presence of different additives




**68** **69** **70**

| Entry | Additive | T[°C] | t [h] | Yield [%][a] | ee [%][b] |
|---|---|---|---|---|---|
| 1 | - | rt | 72 | 55.0 | 86.0 |
| 2 | PhCOOH (0.15 eq) | rt | 20 | 71.0 | 89.5 |
| 3 |  (0.15 eq) | rt | 12 | 81.0 | 88.5 |
| 4 |  (0.15 eq) | rt | 12 | 75.0 | 89.0 |
| 5 | $NH_4Cl$ (1eq); $H_2O$ (1eq) | rt | 18 | 59.0 | 84.0 |
| 6 | $H_2O$ (1eq) | rt | 47 | 59.0 | 85.0 |
| 7 | $H_2O$ (2eq) | rt | 32 | 78.0 | 86.0 |
| **8** | **$H_2O$ (2eq); AcOH (0.15 eq)** | **rt** | **16** | **85.5** | **86.0** |
| 9 | $H_2O$ (2eq); AcOH (0.15 eq) | 40 | 7 | 80.0 | 86.0 |
| 10 | $H_2O$ (2eq); AcOH (0.15 eq) | 60 | 3 | 63.0 | 82.0 |

[a] Yield of isolated product after column chromatography on $SiO_2$; [b] Enantioselectivities were determined by chiral HPLC analysis (Daicel Chiralpak AS) in comparison with authentic racemic material.

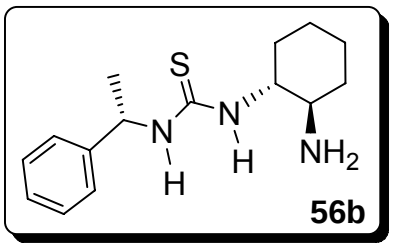
When PhCOOH[100] was studied, we found that the product was formed in 20 h with 71% yield and 89.5% *ee*.

The use of (*R*)-(-)- and (*S*)-(+)-2-phenylpropionic acids as chiral additives provided the adduct **70** already in 12 hours with 81%, 88.5% *ee* and 75%, 89% *ee*, respectively (Table 7, entries 3 and 4). Addition of $NH_4Cl/H_2O$[100] only slightly improved the yield (entry 5). We then tested $H_2O$ alone (1equiv. and 2equiv.) and noted that 2 equiv of $H_2O$ gave much better results than 1 equiv (Table 7, entry 7 vs. entry 6).

Moreover, the use of $H_2O$ (2 equiv) and AcOH (0.15 equiv) as an additive gave the product **70** in 85.5% yield with 86% *ee* (***R***) in 16 hours. Raising the reaction temperature in the presence of additive $AcOH/H_2O$ led to reduced reaction times (up to 3 h) but lower yields as well as enantioselectivities was observed (entries 9 and 10 vs. entry 8, Table 7). Thus, $AcOH/H_2O$ used at room temperature was found to be the most promising additive system regarding the yield and enantioselectivity.

Additionally, pseudoenantiomeric catalyst **56b** (Figure 17) showed a similar activity as **56** with the difference that predominant formation of (***S***) enantiomer of **70** was observed.

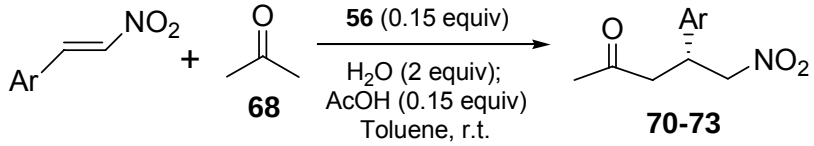
**Figure 17.** Pseudoenantiomeric catalyst **56b**

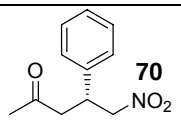
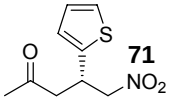
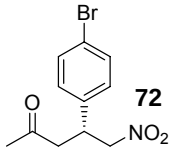
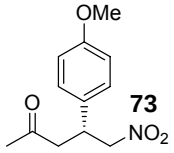



With optimal reaction conditions established, several aromatic olefins were then evaluated as substrates (Table 8).

The introduction of electron-withdrawing or electron-donating groups in the aromatic ring of the nitroolefins slightly affected enantioselectivities (84-92% *ee* (***R***)) and yields (85.5-93%, Table 8, entries 1-4). Notably, in general, much better reaction rates, higher yields and enantioselectivities were achieved by the thiourea-amine **56** relative to that by thiourea-imidazole catalyst **60**.[108] Additionally, we also tested the urea analog **56a** and determined that this catalyst less active than **56** and gave the target product in 22% of yield and 70% of enantioselectivity under same conditions as for entry 1 in Table 7.

**Table 8.** Catalytic asymmetric Michael-addition of acetone to different aromatic nitroolefines under optimised conditions




| Entry | Product | Time [h] | Yield [%][a] | ee [%][b] |
|---|---|---|---|---|
| 1 |  **70** | 16 | 85.5 | 86.0 |
| 2 |  **71** | 25 | 87.0 | 92.0 |
| 3 |  **72** | 15 | 93.0 | 84.0 |
| 4 |  **73** | 71 | 87.0 | 87.0 |

[a] Yield of isolated product after column chromatography on $SiO_2$.
[b] Enantioselectivities were determined by chiral HPLC analysis (Daicel Chiralpak AS) in comparison with authentic racemic material.

### *3.2.1 Computational Study for the Michael-Addition of Acetone to trans-β-nitrostyrene*

To explain the predominant production of ***R*** adducts, we have computationally determined the first order saddle points ("transition state structures") for the formation of both ***R*** and ***S*** enantiomers (Figures 18 and 19). In the quantum-chemical calculations the Gaussian 03 program package[110] was employed throughout. The DFT variant B3LYP[111] with Becke's exchange functional[112] and the Lee, Yang and Parr correlation functional[113] was used in conjunction with the 6-31G(d) basis set (567 cGTOs) to fully optimize the structures.

Eigenvalues of Hessian matrices at the relevant stationary points on the potential energy surfaces were calculated to verify their nature; the geometries of the first order saddle points were identified using the intrinsic reaction coordinate (IRC) method.[114] At the B3LYP/6-31G(d) geometries, we carried out B3LYP/6-31G(d,p) single point calculations in order to assess the influence of hydrogen polarization functions. The calculations are carried out for the isolated systems without explicit consideration of solvent effects. This is a reasonable assumption because toluene might not influence the reaction because of its polarity.

**Figure 18**. Transition state structure leading to the **R** enantiomer

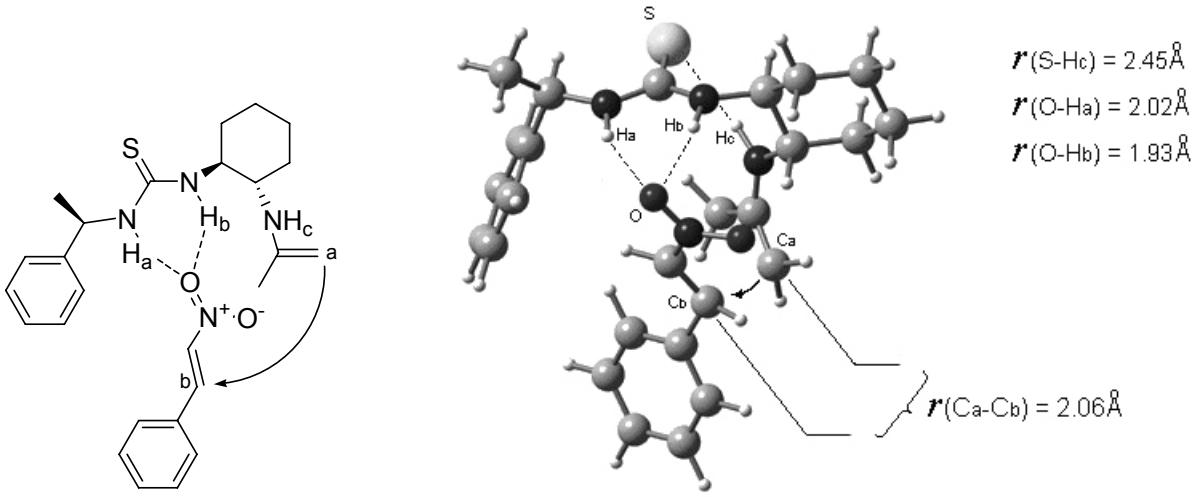
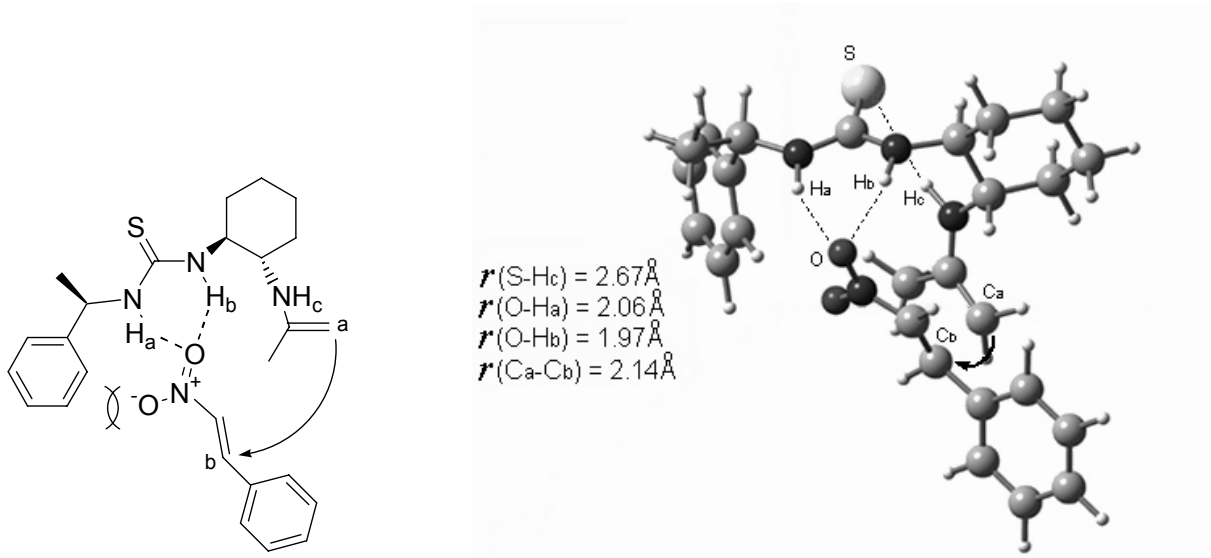



**Figure 19.** Transition state structure leading to the **S** enantiomer



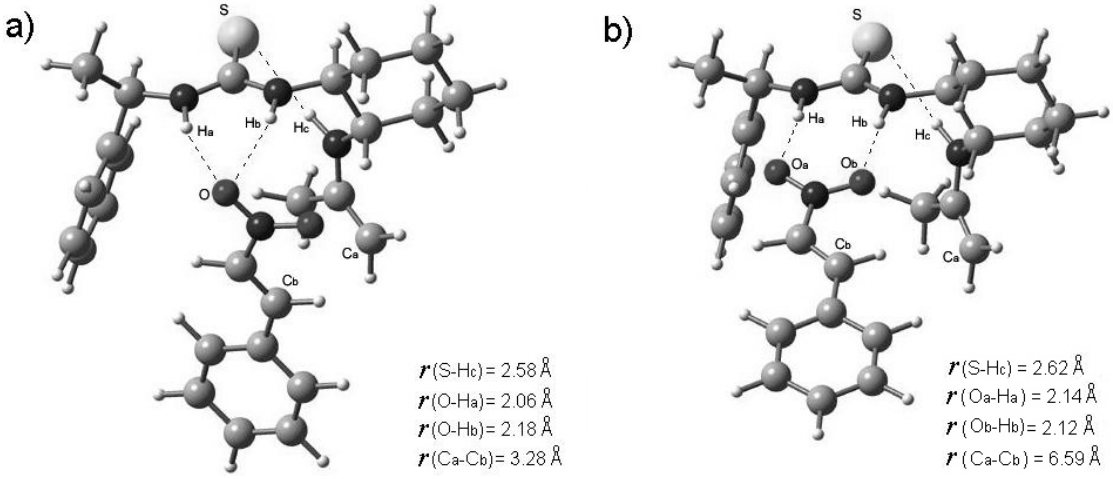
In the transition state (TS) structures leading to both the (***R***) and (***S***) enantiomers, the arrangement of the oxygen atoms of the nitrostyrene nitro group relative to the hydrogen atoms of the thiourea moiety is clearly nonplanar (Figures 18 and 19). Furthermore, catalyst **56** shows additional structure stabilization due to the formation of an intramolecular hydrogen bond between the sulfur atom and hydrogen atom $H_c$ (Figures 18 and 19). Compared to the TS leading to (***R***)-enantiomer, the two distances between the nitro group oxygen atom and the two thiourea hydrogens are larger by 0.04 Å in the TS leading to (***S***)-enantiomer, and the distances $C_a \cdots C_b$ and $S \cdots H_c$ are longer by 0.08 Å and 0.22 Å, respectively. The $H_a \cdots O \cdots H_b$ angles in both structures differ only by 0.4º. In summary, the (***R***) TS is more compact and the second nitro group oxygen points towards the reactive center. In the (***S***) TS, this oxygen atom points away from that center and undergoes a repulsive interaction with the phenyl ring of the catalyst.

On the basis of the Curtin-Hammett principle and according to the calculated Gibbs free energies (calculated within the standard harmonic-oscillator rigid-rotor model) of the transition states, theoretical *ee* values were determined to be 69 and 71 % for 6-31G(d) and 6-31G(d,p) basis sets respectively, which is in good agreement with the experimental value (86% *ee*). Here, the *ee* is defined as ([*R*]-[*S*])/([*R*]+[*S*]) and [*R*]/[*S*] is obtained as the ratio of the rate constants at $T$ = 295 $^{o}$K, $k_R/k_S = \exp((G^{\neq}_S - G^{\neq}_R)/RT)$. The good agreement between experimental and theoretical results is to a large extent due to error cancellation because only the difference of the free energies enters the calculation and the absolute barriers (which are defined as the energetic differences between the saddle point structures and the intermolecular complexes between enamine and nitrostyrene) are not important.

Our results give clear evidence that only one oxygen atom of the nitro group is bound to the thiourea moiety, in juxtaposition to a working hypothesis of Takemoto et al. that assumes a bonding of both oxygens and that was quoted in several papers by this group.[68, 91] The possible intermolecular complex structure with two oxygens bound to the thiourea unit is calculated and shown in Figure 20 (a), along with the pre-complex pertinent to the transition state for the (***R***)-enantiomer. The structure from Figure 20 (b) will not lead to Michael reaction for sterical reasons. The nitrostyrene-thiourea unit is planar and the attack of the enamine group is not possible. Furthermore, the complex bound by two oxygens is energetically less stable by 4.7 kJ mol$^{-1}$. We note that Takemoto's experimental verification of this hypothetical structure by $^{1}$H-NMR[91a] is not acceptable as these experimental data also allow for a structure according to our computational results.

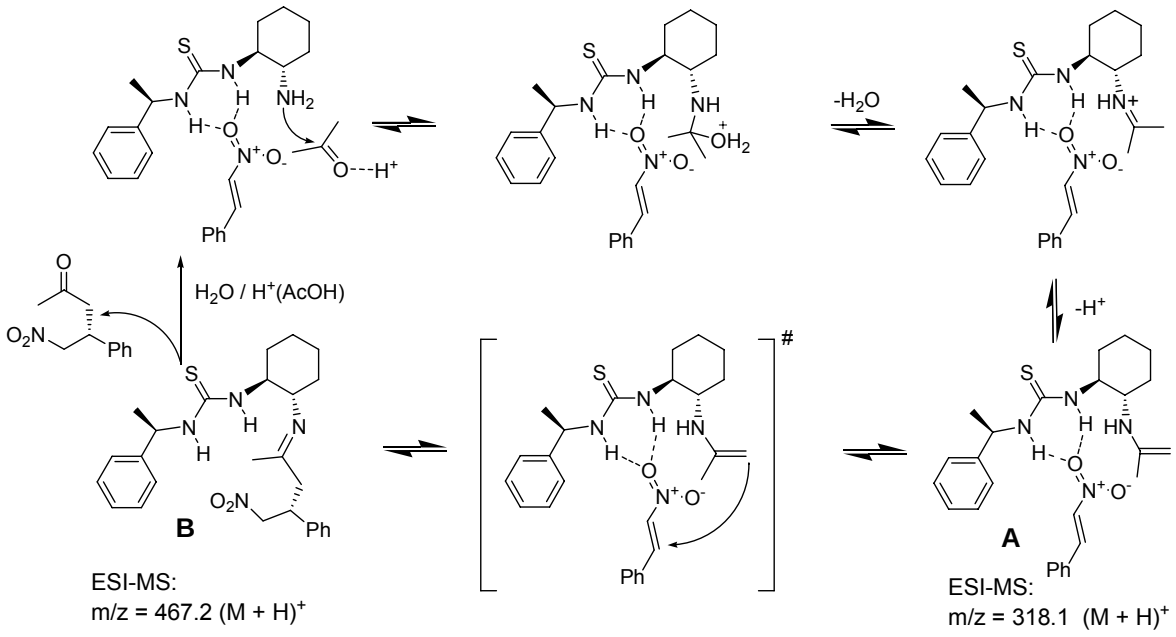
Due to the good agreement of our calculated *ee* value, that is quite a sensitive parameter, with the experimental we are confident that the transition state structures reported in this work are reliable. In addition, from a more intuitive point of view, six-membered TSs (this work) is preferred over eight-membered structures (Takemoto).

**Figure 20.** Calculated complexes



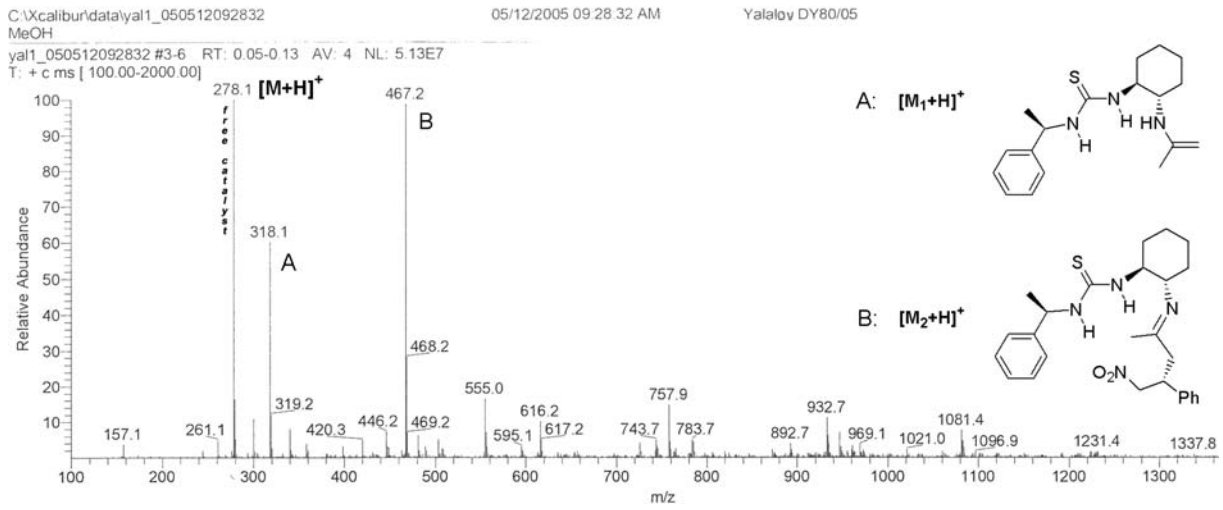

Based on obtained results we proposed a plausible reaction mechanism for chiral thioureaamine **56** catalyses (Scheme 20). According to Scheme 20, the formation of the acetone enamine occurs following the formation of an iminium ion intermediate, supported by acid additive (AcOH). This *C*-nucleophile attacks the *trans*-β-nitrostyrene activated by double hydrogen bonding with thiourea moiety to give the intermediate **B**.

**Scheme 20.** Plausible multistep chiral thiourea-amine **56** catalyses



The existence of the intermediates **A** and **B** in the reaction mixture was confirmed using ESI-MS method. On ESI-MS spectra the signals for both molecular ions **A** and **B** can be clearly detected (Figure 21). At the last step the regeneration of the catalyst through hydrolysis of the imine **B** is facilitated by water.

**Figure 21.** ESI-MS spectra of reaction mixture. Addition of acetone to *trans*-β-nitrostyrene catalysed by **56**



## 3.3 Summary

- A highly enantioselective organocatalytic Michael-addition of acetone to aromatic nitroolefins has been described. The new thiourea catalyst **56** shows high enantioselectivities (84-92% ee) and yields (up to 93%) in the presented reaction

- We have calculated and analyzed the transition state geometries for formation of (***R***) and (***S***) enantiomers. Our results give clear evidence that only one oxygen atom of the nitro group is bound to the thiourea moiety of the thiourea-amine catalyst **56**

- The theoretical and experimental enantiomeric excess values show good agreement, rendering the computations a very efficient tool for predicting the *ee* values in similar reactions with slightly modified catalysts, the efficiency and selectivity of which may be considerably improved in this way.

# 4. Direct Mannich-type Reaction of Ketones with α-Hydrazonoesters Promoted by a Chiral Primary Amine-Thiourea Catalyst

## 4.1 Introduction

The results obtained in Chapter 3 demonstrated that the primary amine-thiourea **56** acts as an excellent catalyst for Michael-addition of ketones to the variety of nitroolefins, which accompanied with high enantioselectivities (up to 92%) and yields (up to 93%). In this chapter another unexpected and intriguing properties of thioureacatalyst **56** are presented. We found that this bifunctional organocatalyst **56** is active and highly enantioselective for Mannich-type addition of ketones to the different α-hydrazonoesters.

The Mannich (also Mannich-type) reaction, or more general the α-amino alkylation of carbonyl compounds, is one of the eminent preparative C-C bond-formig reactions in organic chemistry. The products, *β*-amino ketones (Mannich bases) and their derivatives afford a variety of interesting applications. Among them the preparation of agents for medicine has still great value.

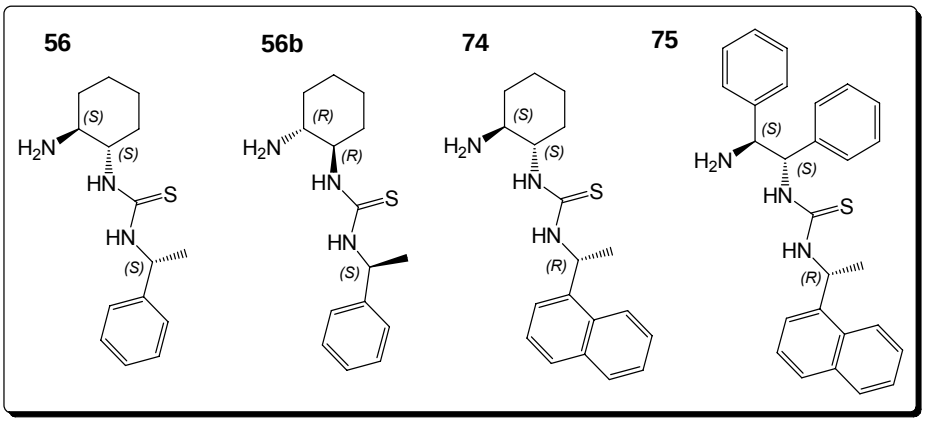
Without questions, last few years many variations of chiral bifunctional thiourea catalysts which possess both an acidic and basic/nucleophilic moiety have attracted broad interest and were employed by chemists for variety asymmetric transformations.[62b, 65-74, 90-96, 107, 115]

In asymmetric organocatalysis the primary amine catalyzed transformations in comparison with the number of secondary amine catalyzed reactions is limited. However, during our study the use of organic catalysts containing primary amine function in asymmetric Michael-addition, anti-Mannich and aldol reactions was found promissing.[116-121] According to our previous results described in Chapter 3, we have targeted the thioureacatalyst **56** as a possible candidate for an asymmetric Mannich reaction. During our study we found that catalyst **56** is active and high enantioselective in Mannich-type reaction of ketones with different α-hydrazonoesters (Figure 23, see below). Mannich-type reaction leads to the functionalized compounds that could be converted into different amine derivatives. Furthermore, productive preparation of amine derivatives through reductive cleavage of an *N*-*N* bond of corresponding hydrazines using $SmI_2$ is reported.[122-125] The intriguing and interesting results obtained with **56** are described below.

## 4.2 Results and Discussion

Besides **56** and **56b** we also tested new bifunctional asymmetric thioureacatalysts **74** and **75**, which were found to be active in Michael-addition reaction of cyclic ketones to nitroolefins recently performed in our laboratory (Figure 22).[116a]

**Figure 22.** Bifunctional thiourea-catalyst bearing primary amine moiety



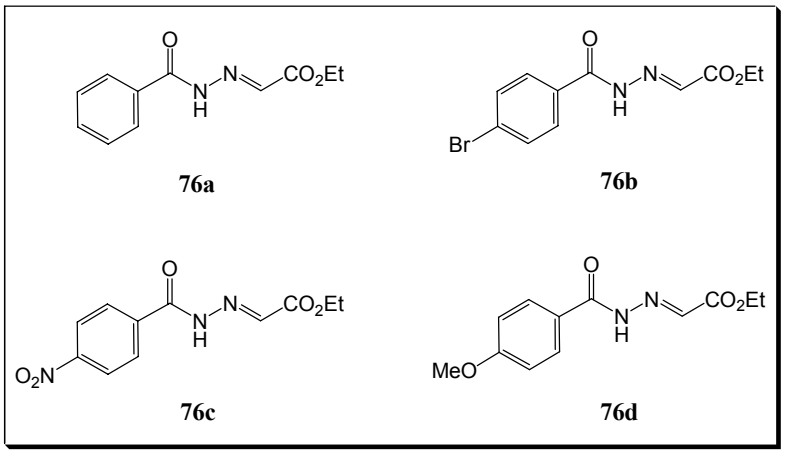

As a first example we chose Mannich-type addition of acetone to *N*-PMP-protected α-imino ethyl glyoxylate catalyzed by 15mol% of **56**, **74** and **75** (Table 9, entry 1-3). Additionally, *N*-PMP-protected α-imino ethyl glyoxylate is an interesting imine derivative in asymmetric Mannich reactions.[121, 126-128]

To our disappointment these catalysts showed worse results. However, the catalyst **56** gave the product in 47% yield and in 45% enantioselectivity (Table 9, entry 1).

As a second example, we chose a reaction between acetone and α-hydrazono ester **76a** (Figure 23). Remarkably, use of the catalyst **56** under mild conditions gave excellent enantioselectivity >99% and moderate yield 50% (Table 9, entry 7). No wonder that we were impressed by this result and directed our attention to the investigation of this problem.

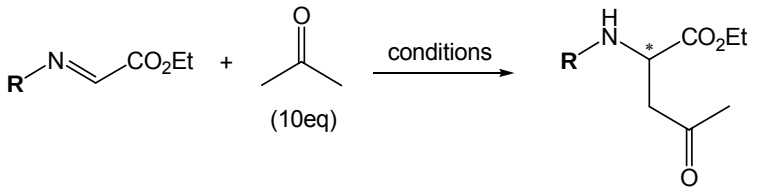
In addition to already known α-hydrazono esters **76a** and **76d**, we also synthesized new *para* substituted α-hydrazono esters **76b** and **76c** (Figure 23). In practice **76a**-**76d** are stable compounds and can be stored for several months at room temperature. Furthermore, the **76a** and **76d** are known α-hydrazono esters which in recent years were successfully used by Kobayashi for many interesting asymmetric transformations[122, 129].

**Figure 23.** α-Hydrazono esters




To evaluate the catalytic efficiency of the chiral thioureas the reaction of acetone and α-hydrazono esters was performed in different solvents in the presence of each of these catalysts **56**, **74** and **75** (Table 9).

**Table 9.** Optimization of the Mannich-type reaction's conditions




| Entry | R | Catalyst, mol% | solvent | T[°C] | Time [h] | Yield[a] [%] | ee [%] | Abs. Config. |
|---|---|---|---|---|---|---|---|---|
| 1 | -PMP | **56**, 15 | toluene | rt | 24[d] | 47 | 45 | S[b] |
| 2 | -PMP | **74**, 15 | toluene | rt | 24[d] | 29 | 0 | - |
| 3 | -PMP | **75**, 15 | toluene | rt | 24[d] | 45 | 6 | S |
| 4 | -NBz | **56**, 5 | DMSO | rt | 48[c] | 0 | 0 | - |
| 5 | -NBz | **56**, 5 | $CH_2Cl_2$ | rt | 48[c] | 10 | >99 | R |
| 6 | -NBz | **56**, 5 | toluene | rt | 48[c] | 20 | >99 | R |
| 7 | -NBz | **56**, 15 | toluene | rt | 24[d] | 50 | >99 | R |
| 8 | -NBz | **56**, 15 | **acetone** | rt | 60[c] | 15 | >99 | R |
| 9 | -NBz | **56**, 15 | toluene | 40-45 | 24[d] | 43 | 95 | R |
| 10 | -NBz | **74**, 15 | toluene | rt | 24[d] | 40 | 86 | R |
| 11 | -NBz | **75**, 15 | toluene | rt | 24[d] | 21 | 58 | R |

[a] Isolated product; [b] The stereochemistry was determined in comparison with literature data[122]; [c] After 24 hrs only traces of product was observed; [d] 24 hrs. was chosen as a limit of the reaction time

Initial screening studies identified toluene as the optimal solvent for the reaction. Toluene was also demonstrated as a more appropriate solvent in Chapter 2 and 3 for Michael-addition reaction of ketones with *trans*-β-nitroolefins[116, 117]. The lower yields as well as enantioselectivities were obtained by raising the temperature (Table 9, entries 7 and 9).

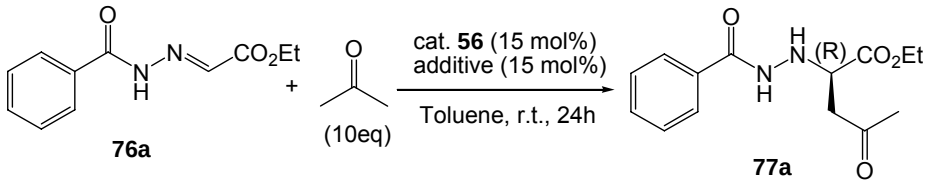
The use of chiral thioureas **74** and **75** gave the product only in 86% and 58% of *ee* and moderate yields 40 % and 21%, respectively (Table 9, entries 10 and 11). Screening of several achiral and chiral additives clearly demonstrated that:

- In the presence of all additives no change in enantiomeric excess was observed (Table 10, entries 2-8);

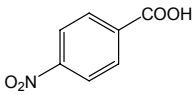
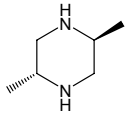
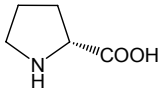
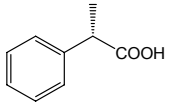
- In the presence of water or acidic additives the decrease of yield without any change of *ee* was clearly detected (Table 10, entries 2-5, 7,8);

- In the presence of *trans*-2,5-dimethylpiperazine as a basic additive no change of yield and enantiomeric excess was observed (Table 10, entry 6 vs. Table 9, entry 7).

**Table 10.** Asymmetric addition of acetone to the **76a** catalyzed by **56** in the presence of different additives




**76a** **77a**

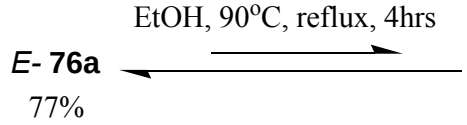
| Entry | **Additive** [15mol%] | **Yield**[a] [%] | **ee** [%] |
|---|---|---|---|
| 1 | - | 50 | >99 |
| 2 |  | 7 | >99 |
| 3 | $H_2O$ | 32 | >99 |
| 4 | AcOH | 8 | >99 |
| 5 | AcOH/$H_2O$, 1/1 | 9 | >99 |
| 6 |  | 48 | >99 |
| 7 |  | 19 | >99 |
| 8 |  | 9 | >99 |

[a] Isolated product

With the optimal catalyst and reaction conditions several ketones were added to the α-hydrazono esters. The results are summarized in Table 11 and Table 12. The coupling of several ketones with **76a** gave interesting results.

Not surprisingly, that the use of pseudoenantiomeric catalyst **56b** (Figure 22) in reaction leads to the formation of (**S**) enantiomer (Table 11, entry 2).

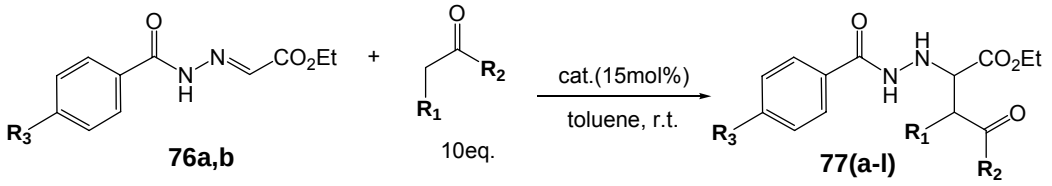
It's important to note, that α-hydrazono ester **76a** with *Z* configuration was also employed in Mannich-type reaction**.** *Z*-**76a** can be easily isolated by flash chromatography after reaction between benzoylhydrazine and ethyl glyoxylate or prepared from *E*-**76a** by the refluxing in ethanol for 4hrs (eq. 3).




(3)

*Z*-**76a** can be used during few days. After few weeks the inversion of *Z*-**76a** to *E*-**76a** was observed. Remarkably, the partial formation of *Z*-**76a** during the reaction between *E*-**76a** and different ketones was also observed. If *Z*-**76a** was employed as a starting material the reaction completed with a lower yield and *ee* values (Table 11, entry 3; Table 11, entry 4). For the future investigation only (*E*) isomer of α-hydrazono esters was used as a starting material. The enantioselectivities obtained were excellent for essentially all the ketones explored and even for the branched or sterically hindered ketones, which gave values of *ee* up to ≥99% (Table 11).

**Table 11.** Mannich-type addition of aliphatic ketones to the α-hydrazono esters catalysed by bifunctional thiourea catalysts



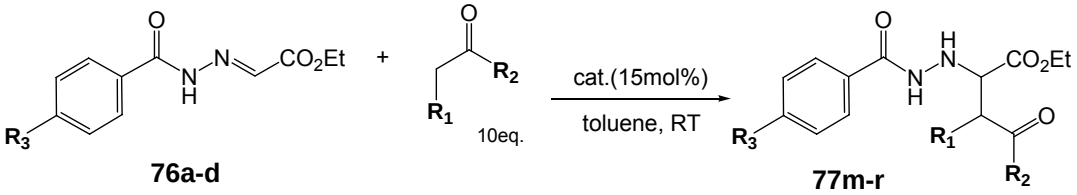

| Entry | Product | $R_1$ | $R_2$ | $R_3$ | catalyst [15mol%] | Time[h] | Yield[a] [%] | ee [%] | de[%] | Abs. Config. |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | **77a** | H | Me | H | **56** | 37[b] | 50 and 10% of **77a'**[h] | >99 | - | R |
| 2 | **77a** | H | Me | H | **56b** | 37[b] | 53 and 10% of **77a'**[h] | >99 | - | S |
| 3 | **77a**[c] | H | Me | H | **56** | 60[g] | 40 | 98 | - | R |
| 4 | **77b**[d] | H | Et | H | **56** | 40[b] | 50 | >99 | - | R |
| 5 | **77c**[d] | Me | Me | H | **56** | 40[b] | 36 | >99 **syn** and **anti** | 40(**anti**) | - |
| 6 | **77d** | Me | Et | H | **56** | 55[b] | 82 | 90/99, **syn/anti** | 72(**anti**) | - |
| 7 | **77e**[e] | H | $CH_2$(Et) | H | **56** | 55[b] | 74 | >99 **syn** and **anti** | - | R |
| 8 | **77f**[e, f] | Et | Me | H | **56** | 55[b] | 6 | >99 **syn** and **anti** | 29 | - |
| 9 | **77g** | H | $CH(Me)_2$ | H | **56** | 60[g] | 54 | >99 | - | R |
| 10 | **77h** | H | $CH_2CH(Me)_2$ | H | **56** | 60[g] | 27 | >99 | - | R |
| 11 | **77i** | H | cyclo-$C_6H_{11}$ | H | **56** | 60[g] | 45 | 97 | - | R |
| 12 | **77j** | H | Ph | H | **56** | 60[g] | trace | n.d. | - | R |
| 13 | **77k** | $NO_2$ | Ph | H | **56** | 60[g] | 0 | n.d. | - | - |
| 14 | **77l** | H | Me | Br | **56** | 37[b] | 45 | >99 | - | R |

[a] Isolated product; [b] Conversion of hydrazone is 100%; [c] *Z*-**76a** was used; [d] General yield is 86%, regioselectivity ratio (**77b**/**77c**) = 58/42; [e] General yield is 80%, regioselectivity ratio (**77e**/**77f**) = 93/7; [f] Stereochemistry was not determined; [g] 60 hrs. was chosen as a limit of the reaction time; [h] byproduct (see Experimental Part, page 79)

A decrease of the yield of target products was observed in case of the use branched ketones. To our disappointment, in all cases the diastereoselectivity of the reaction was still low. Only the reaction between diethylketone and α-hydrazono ester **76a** completed with a sufficiently good diastereoselectivity (*de* ~72%) (Table 11, entry 6). Furthermore, the use of nonsymmetric ketones such as methylethylketone and methylpropylketone introduced the problem of regioselectivity. Predominant formation of the kinetic product by using of methylethylketone was observed (Table 11, entry 4 vs entry 5, *rr*(**77b**/**77c** = 58/42). The formation of the kinetic product with better regioselectivity was observed in case of methylpropylketone (Table 11, entry 7 *vs* entry 8, *rr*(**77e**/**77f** = 93/7).

Much more intriguing is the addition of cyclic ketones such as cyclohexan to the α-hydrazono esters (Table 12). The involvement of cyclic ketones in the reaction process gave good yields up to 89% (Table 12, entry 7) and enantioselectivity up to 96% (Table 12, entry 3) in a short reaction time.

**Table 12.** The addition of cyclic ketones to the α-hydrazono esters

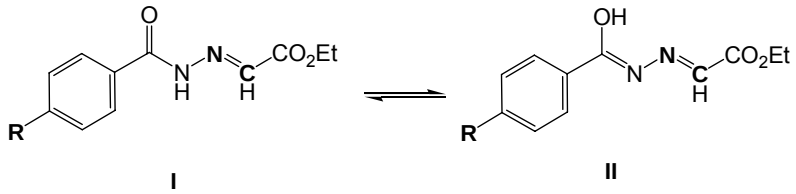



| Entry | Product | $R_1$ | $R_2$ | $R_3$ | cat [15mol%] | Time [h] | Yield[a] [%] | ee [%] | de[%] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **77m**[b] | -$(CH_2)_5$- | | H | **56** | 60 | 24 | 65/81 | 8 |
| 2 | **77n** | -$(CH_2$-S-$(CH_2)_2)$- | | H | **56** | 50[c] | 88 | 92/82, **syn/anti** | 19 (**syn**) |
| 3 | **77o** | -$(CH_2)_4$- | | H | **56** | 17[c] | 87 | 96/94, **syn/anti** | 8 (**syn**) |
| 4 | **77o**[d] | -$(CH_2)_4$- | | H | **56** | 60 | 50 | 84/87, **syn/anti** | 7 (**syn**) |
| 5 | **77o** | -$(CH_2)_4$- | | H | **74** | 34[c] | 80 | 95/94, **syn/anti** | 8 (**syn**) |
| 6 | **77o** | -$(CH_2)_4$- | | H | **75** | 60 | 15 | n.d. | n.d. |
| 7 | **77p** | -$(CH_2)_4$- | | Br | **56** | 7[c] | 89 | 94/92, **syn/anti** | 8 (**syn**) |
| 8 | **77q** | -$(CH_2)_4$- | | $NO_2$ | **56** | 6,5[c] | 85 | 95/90, **syn/anti** | 8 (**syn**) |
| 9 | **77r** | -$(CH_2)_4$- | | OMe | **56** | 44[c] | 83 | 93/92, **syn/anti** | 9 (**syn**) |

[a] Isolated product
[b] Stereochemistry was not determined
[c] Conversion of hydrazone is 100%
[d] *Z*-**76a** was used

The introduction of electron withdrawing substituents in the *para* position of aromatic ring leads to the increasing of reaction's rate, at the same time the electron donating groups act vice versa (Table 12, entry 3 *vs.* 7-9). We may only assume that the molecules of α-hydrazono esters exist in two tautomeric forms **I** and **II** (Scheme 21).

**Scheme 21.** Probable tautomerism in molecules of α-hydrazono esters




**R:** H, $NO_2$, Br, OMe

Probably, the tautomeric form **II** is susceptible to mesomeric effect in molecular sceletone. This effect can lead to the activation or deactivation (depending on the substitute's nature) of *C=N* bond (marked on Scheme 21). And as a result the more and less active *C=N* bond react differently with activated ketones. In addition to this supposition we detected that in $H^1$ NMR spectra for (*E*) form of **76a** (measured in DMSO-$d_6$) the signal from $NH_b$ group can be detected nearly at 12.25 ppm (Figure 24) and for (*Z*) form of **76a** nearly at 13.14 ppm respectively (Figure 25). Normally, this area of *ppm* is typical for signals of active protons like in enols. This observation partially confirms the possibility of form **II** (Scheme 21). Such transformations, probably, are responsible for observed results in the addition of cyclohexanone to the different *para*-substituted α-hydrazono esters (Table 12, entries 3, 7-9).

**Figure 24.** $H^1$NMR spectra for the *E* configuration of **76a** measured in DMSO-*d6* at 300MHz

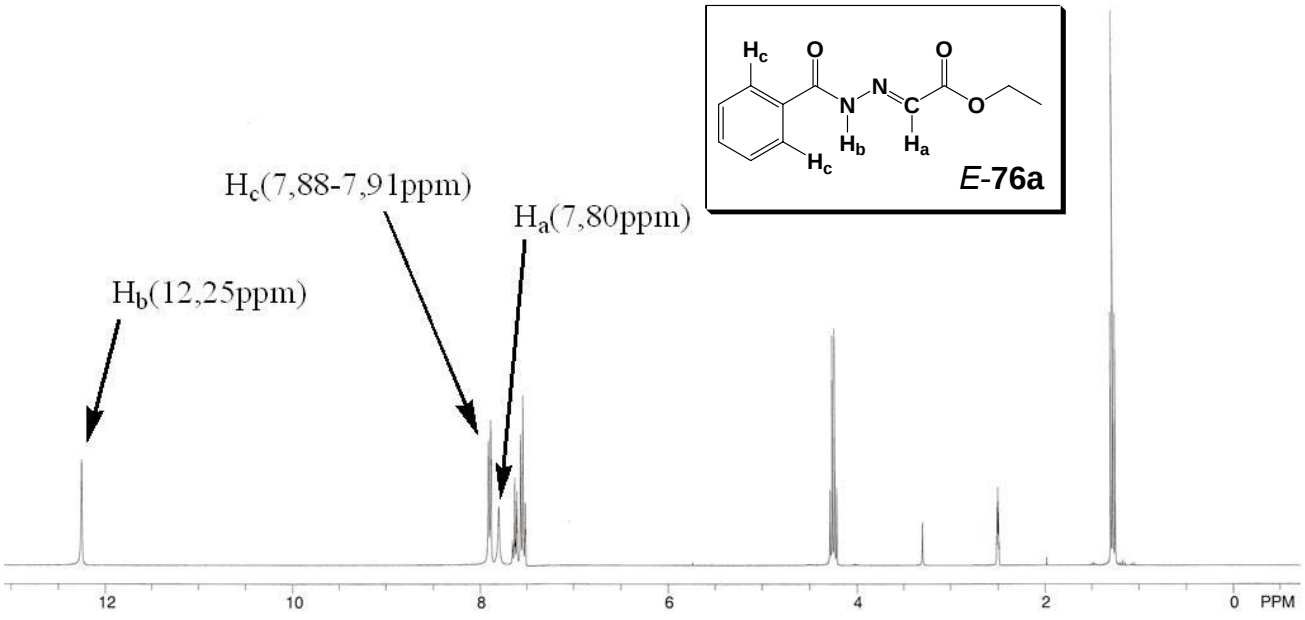
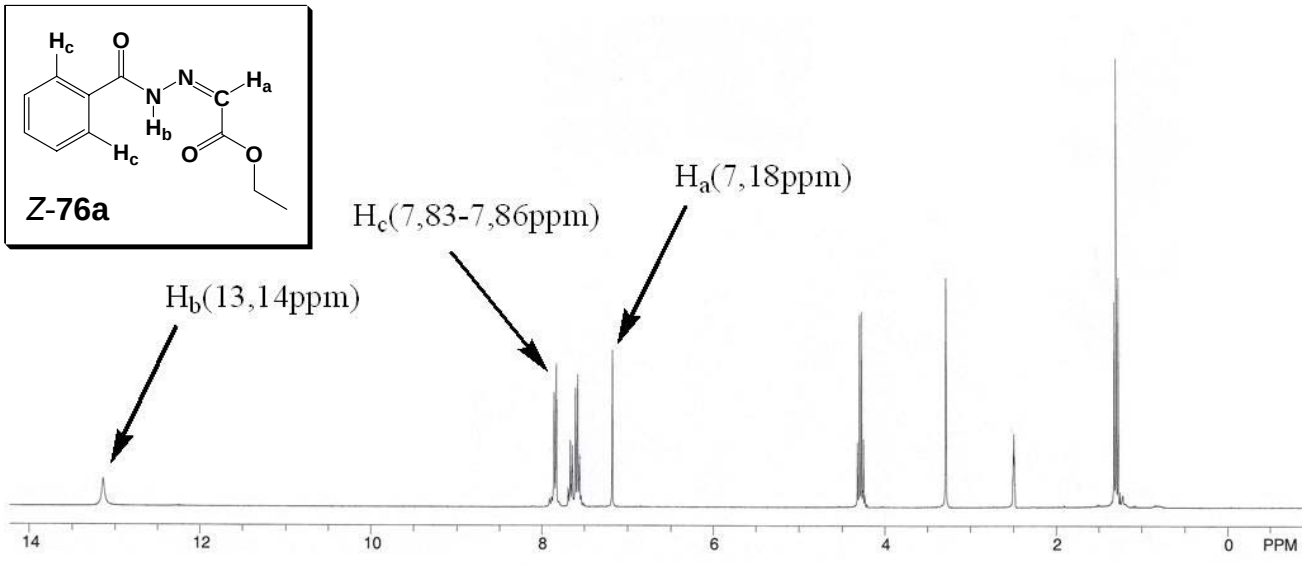
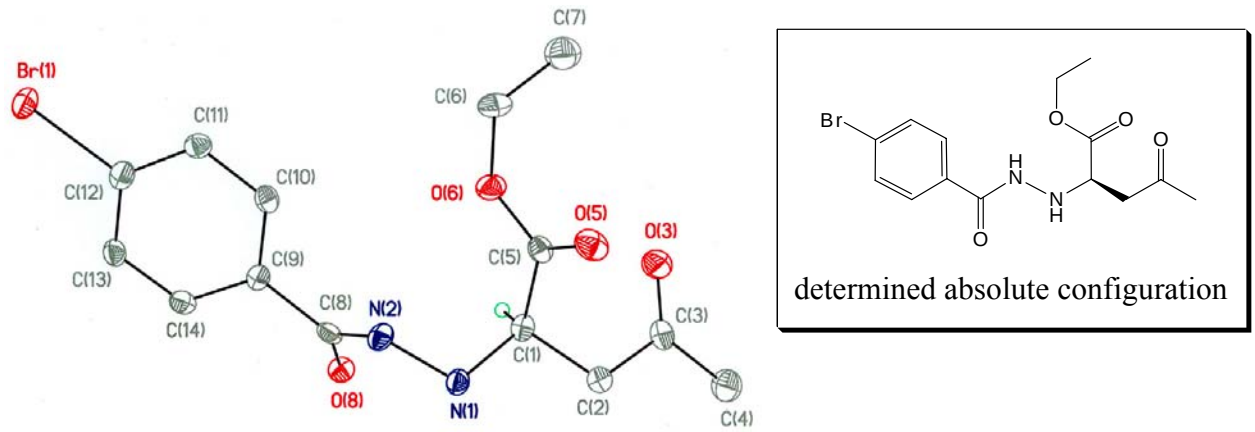


**Figure 25.** $H^1$NMR spectra for the *Z* form of **76a** measured in DMSO-*d6* at 300MHz



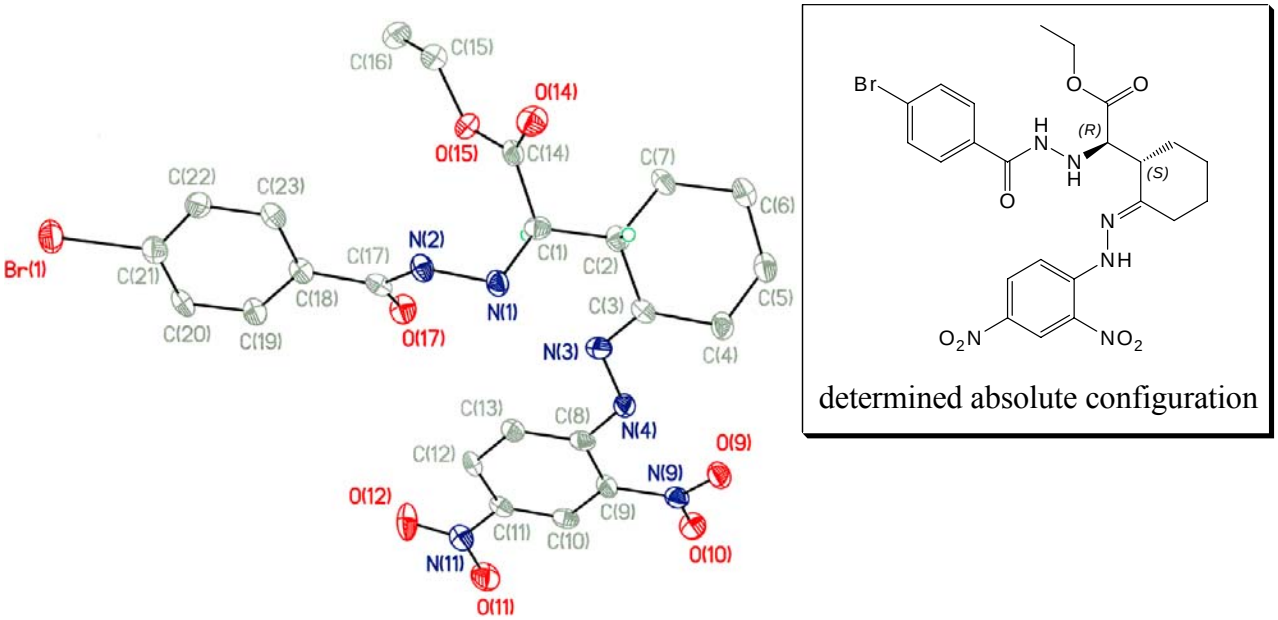

Absolute configurations of new compounds **77a-k** (Table 11) were determined accordingly with the performed X-ray crystallographic analysis of the compound **77l** (Table 11, entry 14). The Mannich product **77l** was successfully crystallized from ethyl acetate/n-hexane at room temperature and was obtained in form of needle-like crystals analysed by X-Ray crystallography. The X-Ray structure of **77l** is shown on Figure 26.

**Figure 26.** The X-Ray structure of **77l**

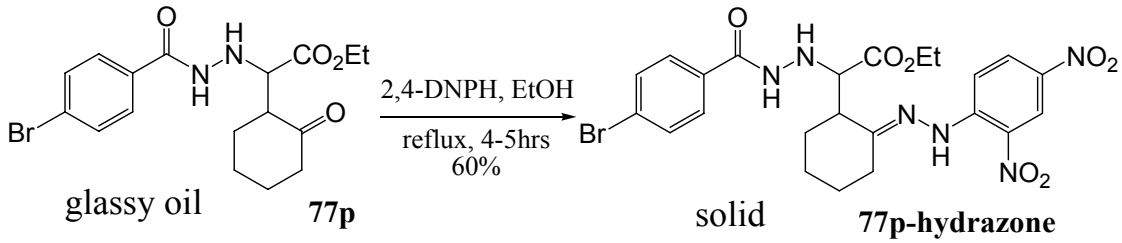


Furthermore, the absolute configurations of new compounds **77m-o**, **77q** and **77r** (Table 12) were also determined analogously by X-ray crystallographic analysis of compound **77p-hydrazone** (Figure 27). The Mannich product **77p** represents an oil-like compound and can't be crystallized. In order to solve this problem the **77p** was converted into solid compound **77p-hydrazone** which was crystallized and analyzed by X-ray crystallography (Scheme 22) (see also Experimental Part, page 85).

**Figure 27.** The X-Ray structure of **77p-hydrazone**




**Scheme 22.** Synthesis of **77p-hydrazone**



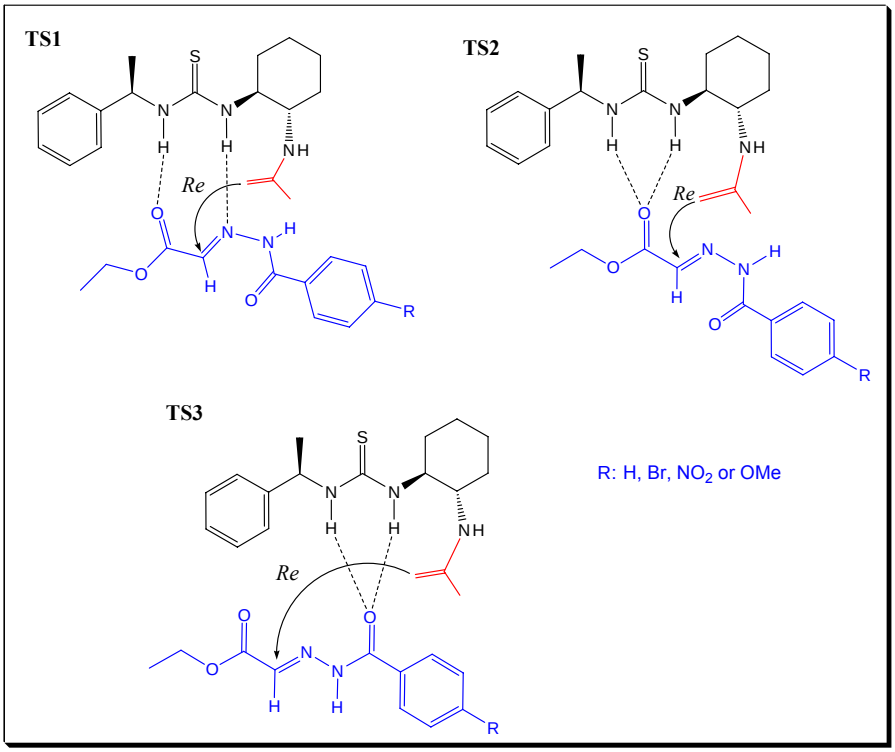

In accordance with performed X-Ray analysis some informative observations can be made:

- the high enantioselective (*ee* ~ 100%) reaction of non-cyclic ketones with α-hydrazono ester **76a** catalyzed by **56** leads to the predominant formation of (***R***) enantiomer. It means that the *Re* attack of *C=N* bond (of α-hydrazono esters) is favourable;

- the *Re* attack of *C=N* bond is also predominant in reaction between cyclic ketones and different α-hydrazono esters catalyzed by **56**

Although the Mannich-type reaction is simple in execution and uses readily available reagents, the elucidation of its mechanism is complicated. It is a known fact that ketones can be activated by the formation of enamines[105c, 116, 117, 123, 130-133] with primary or secondary amine moiety of catalysts or by the formation of enol form [61a, 100, 107a, 108] which can be stabilized by Lewis base moiety of catalyst. In previous Chapter 3, it was demonstrated[116b, 117] that the enamine mechanism is in good agreement with theoretical investigations (Michael-addition of ketones to the different nitroolefins). Therefore, we chose the enamine mechanism as an appropriate variant for Mannich-type addition of ketones to the α-hydrazono esters performed in this study. Without any question the complicated skeleton of α-hydrazono esters with different functional groups within one molecule gives wide scope in complexation with molecules of thiourea catalyst (for instance with **56**). We know that *Re* attack of *C=N* bond is favourable and accordingly to this we proposed enamine mechanisms leading to the formation of (**R**) enantiomer (Scheme 23). It is probable that in transition states leading to (**S**) enantiomer the strong intermolecular interaction between two bulky phenyl rings of catalyst **56** and α-hydrazono esters takes place.

**Scheme 23.** Proposed enamine transition states leading to the formation of **R** enantiomer



## 4.3 Summary

- The chiral thiourea-amine **56** was found to be excellent organocatalyst in Mannich-type addition of different ketones to α-hydrazono esters

- We investigated and presented the Mannich-type addition of different non-cyclic ketones to the α-hydrazono esters with excellent enantioselectivities (>99%) and good yields (up to 82%)

- We demonstrated the Mannich-type addition of cyclic ketones to the different α-hydrazono esters with good enantioselectivities (up to 96%) and good yields (up to 89%)

- The absolute configurations of new compounds were determined by the X-Ray crystallographic analysis

# C. Conclusions

Many C-C bond forming organic reactions lead to the formation of one or more chiral centres in molecule. Therefore, it emerges the problem of enantiopurity of products. Normally, only one enantiomer is important for living creatures. Furthermore, in pharmacology the enantiopurity of synthetical remedies is rigorous criterion. Two enantiomers act differently on living organisms. One enantiomer can be harmless and at the same time the second one can be toxic and do much harm. As well known, Nature ideally constructed the mechanism for the synthesis of chiral molecules. For the selective synthesis of enantiopure compounds, Nature uses complicated molecular systems (e.g. enzymes in biological cells) as organocatalysts. The chemists learned to use the isolated natural compounds as active organic catalysts in the asymmetric synthesis. As was already mentioned above, the cinchona alkaloids became a big popularity in asymmetric organocatalysis. Some years later amino acids (for example proline) were also found to be excellent organocatalysts.

In general the evolution of organocatalysts in organic chemistry can be summarized in three stages as follows:

- The use of isolated natural compounds (for example cinchona alkaloids and amino acids) as organocatalysts;

- Development and use of modificated natural compounds with improved catalytical activity;

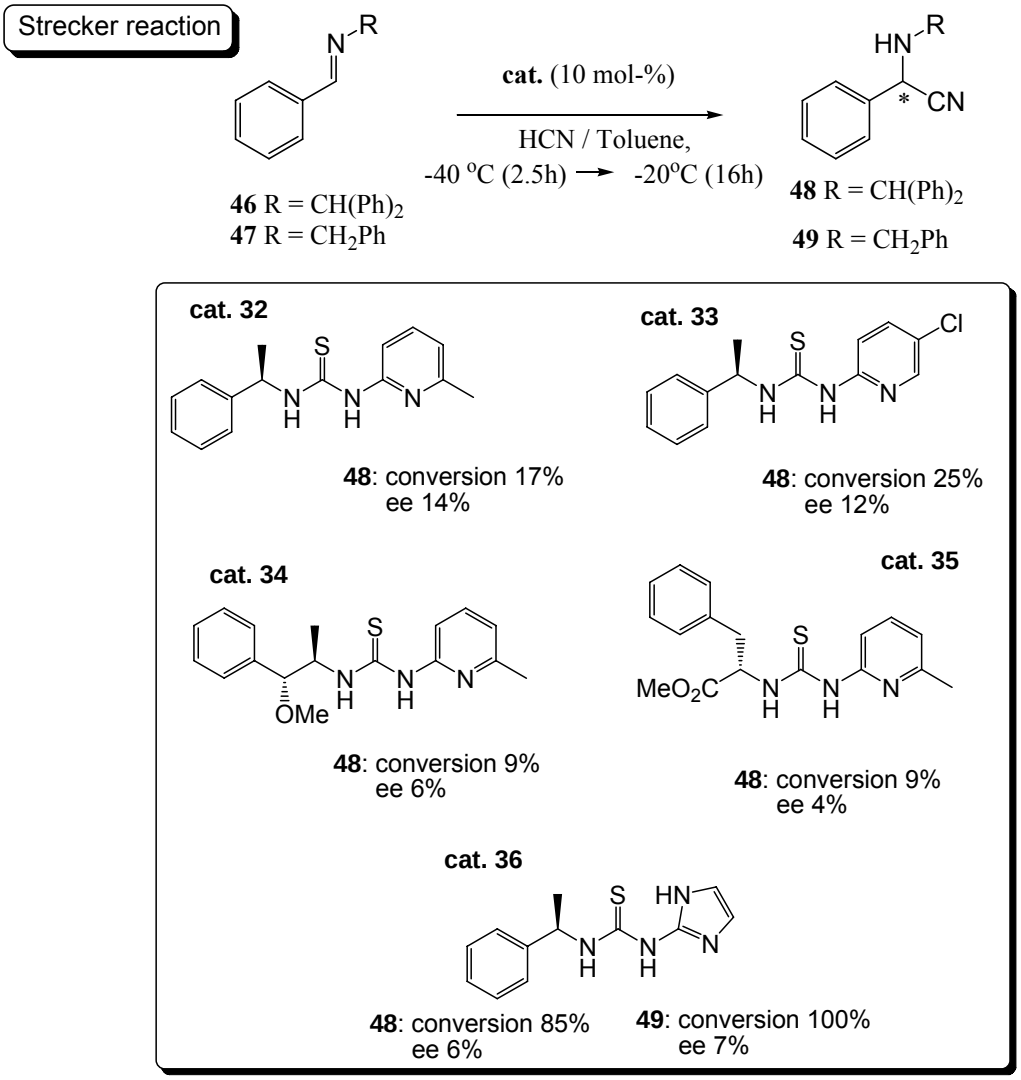
- Creation of artificial molecules (smaller and simpler than molecular structure of enzymes) which are able to catalyse enantioselective reactions.

The thiourea derivatives can be recognized as the man-made artificial molecules which are found to be good organocatalysts in different asymmetric transformations in the last decade. At the beginning of our study (2004) we were good informed about all catalytical properties of urea and thiourea-based organocatalysts already published in the literature. As a main goal of our study we chose the synthesis and application of new thiourea-based organocatalysts with improved catalytical properties.

During our study the thiourea-based catalysts we had synthesized found to be good to excellent in different asymmetric transformations such as Strecker-reaction, Michael-addtion and Mannich-reaction.

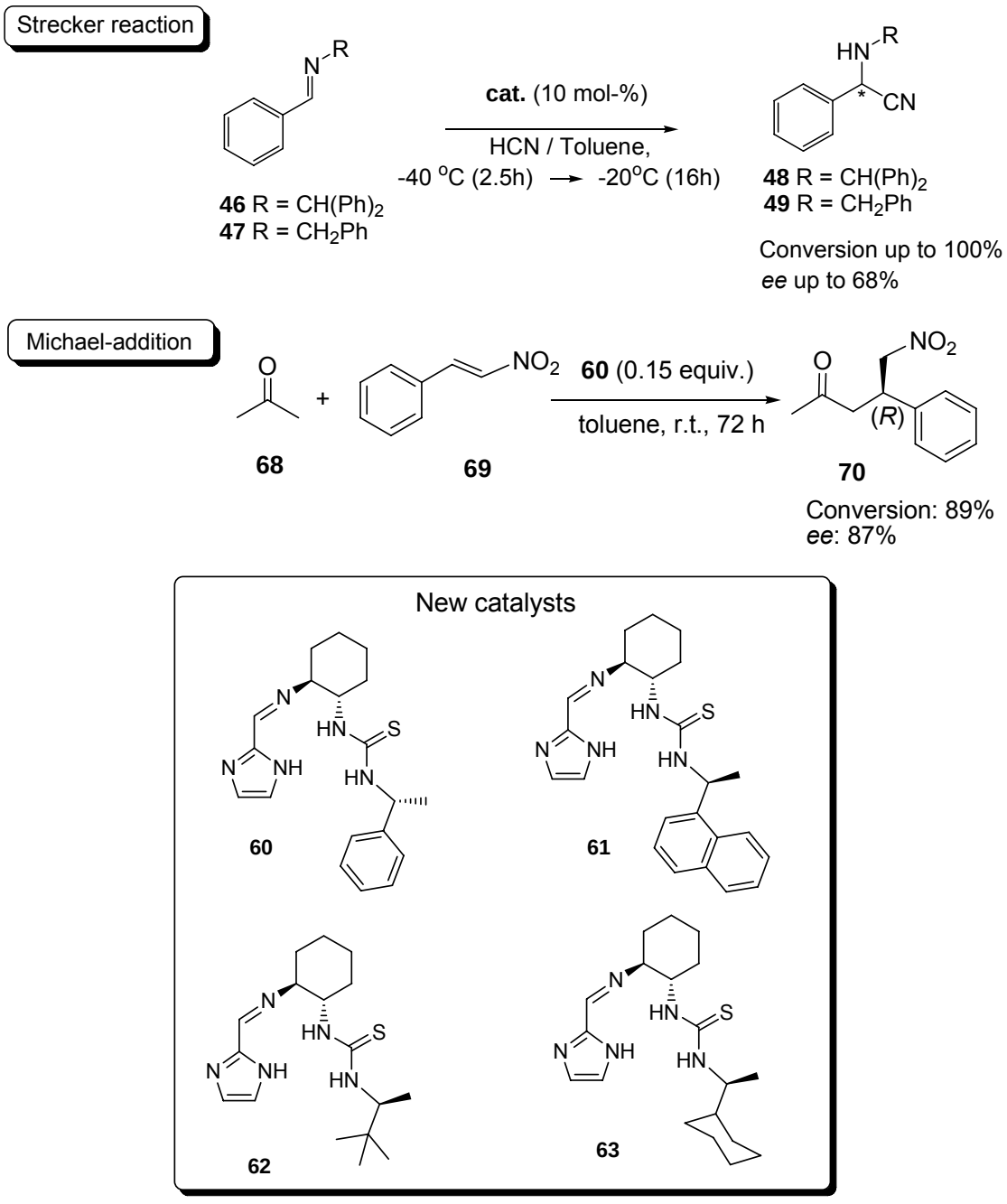
The results obtained in our laboratory during the study can be summarized as follows:

I) In **Chapter 1** the potential of novel and known pyridyl thiourea derivatives as bifunctional organic catalysts in the asymmetric Strecker synthesis was presented. It was shown that incorporation of the imidazolyl moiety in place of a pyridyl group results in a new thiourea derivative that displays a much higher catalytic activity (catalysts **32** *vs*. catalysts **36**).



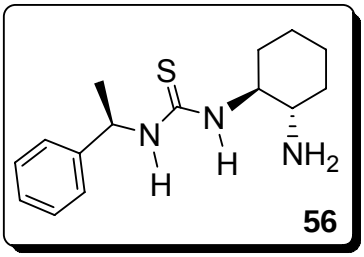

II) In **Chapter 2** novel bifunctional organocatalysts bearing both a thiourea moiety and an imidazole group on a chiral scaffold **60**-**63** were synthesized and applied to the Strecker synthesis and nitro-Michael reaction.

The addition of acetone to nitroolefins (Michael-addition) in the presence of these novel bifunctional organocatalysts gave enantioselectivities (up to 87% *ee*) that are superior to those generated by the proline and/or homo-proline tetrazole catalysts described in the literature.

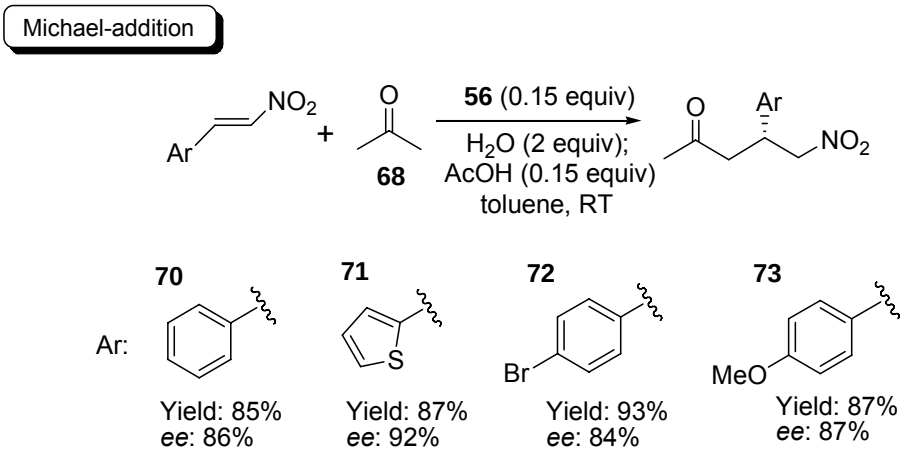



III) The enantiopurity of optically active products is one of the main targets in modern asymmetric organocatalysis. Without any questions, the use of cheap catalysts is more attractive and practicable for both academia and pharmaceutical industry.

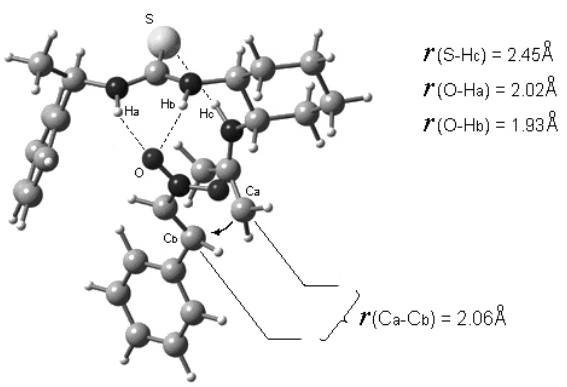
We presented the new relatively cheap thiourea-catalyst **56** which was synthesized in one stage from commercially available educts.



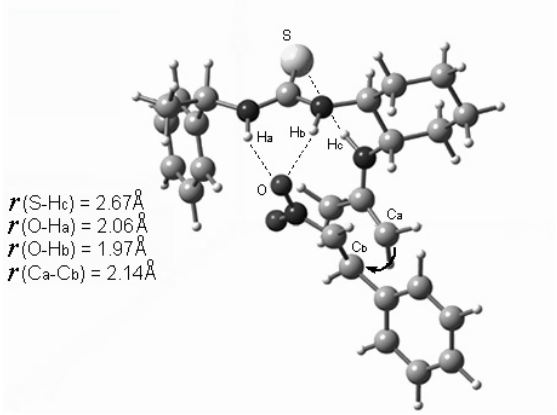

In **Chapter 3** a highly enantioselective (up to 92% *ee*) organocatalytic nitro-Michael addition of acetone to different nitroolefins catalyzed by thiourea-catalyst **56** in the presence of co-catalysts was described.




The transition state (TS) geometries for formation of **R** and **S** enantiomers of **70** in this Michael-addition were calculated and analyzed. It was shown, that only one oxygen atom of the nitro group is bound to the thiourea moiety, in contradiction to the literature known working hypothesis that assumes a bonding of both oxygens. The theoretical and experimental enantiomeric excess values show good agreement, rendering the computations a very efficient tool for predicting the *ee* values in similar reactions.

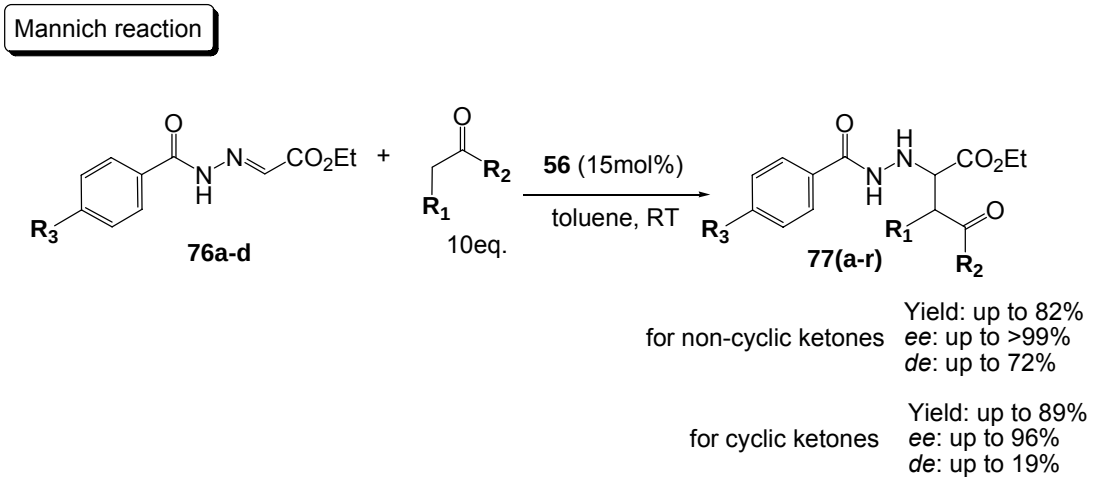



TS leading to the **R** enantiomer




TS leading to the **S** enantiomer

IV) In the last **Chapter 4** it was demonstrated that thiourea derivative **56** acts as an excellent asymmetric organic catalyst for the Mannich-type addition of several ketones to the different α-hydrazono esters **76a-d** with high enantioselectivities (*ee* >99%), moderate diastereoselectivity (*de* up to 72%) and good yields (up to 89%).



# D. Experimental part

## 1. General Remarks

Reagents obtained from commercial sources were used without further purification. All reactions were carried out under an inert atmosphere even if water was used as a solvent or additive. All solvents were purified by standard procedures and were distilled prior to use.

Analytical TLC chromatography was performed on precoated aluminium silica gel ALUGRAM® SIL G/$UV_{254}$ plates (Macherey-Nagel GmbH&Co.) and preparative TLC was performed on precoated silica gel SIL G-50 $UV_{254}$ glass plates (Macherey-Nagel GmbH&Co). All TLC plates were visualized under ultraviolet light (254nm) and(or) developed by treatment with the molybdenephosphoric acid solution following by heating. Flash chromatography was performed using silica gel Merck 60 (particle size 0.040-0.063 mm).

NMR spectra were recorded with *Varian Unity 300* and *Mercury 300*. For the characterization of the observed signal multiplicities the following abbreviations were applied: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, as well as br = broad.

Electron ionization mass spectras (EI-MS) were measured with a *Finnigan MAT 95: Alpha AXP DEC station 3000-300LX*; Electrospray ionization mass spectras (ESI-MS) were recorded with a *LCQ Finnigan* spectrometer. High-resolution mass spectras (HRMS) were measured with a *Bruker APEX IV 7T FT-ICR* instrument.

X-Ray structures were measured with a *Siemens SMART 6000 area* detector system.

For the optical rotation measurements a *Perkin-Elmer 241* polarimeter was used.

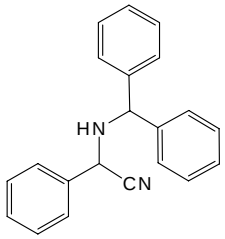
The enantiomeric excess of products was determined by chiral HPLC analysis (using chiral columns AD, OD and IA) in comparison with authentic racemic material. For the HPLC measurements as an eluents n-hexane, isopropanol and dichloromethane were used which commercially available from *ACROS* and *VWR International*. HPLC measurement were performed using *Jasco* enginery: Pump *PU-2080* for analytical chiral columns (OD, AD, IA) and *PU-2087* for preparative chiral IA column, mixing chamber *LG – 1580-04*, multiwave detector *MD 2010 Plus*, automatic switchover *LC – Net II/ADC*, automatic probechanger *AS – 2055*. *Jasco* enginery was promoted by *Borwin PDA HSS 200* and *Borwin Chromatography* software.

# 2. Experimental Procedures for the Compounds Described in Chapter 1

## General procedure for the catalytic asymmetric addition of hydrogen cyanide to substituted imines 46 and 47:

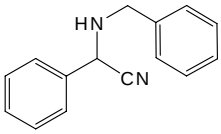
A solution of hydrogen cyanide (1.5 mmol) in dry toluene (1.5 ml) was added in one batch to a suspension of catalyst (10 mol-%) and an aldimine (**46** or **47**, 1 mmol) in dry toluene (3.5 ml) under an argon atmosphere at -40 °C. The mixture was then stirred at -40 °C for 2.5 hours and subsequently at -20 °C for a further 16 hours. The crude reaction mixture was analysed by HPLC using a Daicel Chiralpak AS 250 column at 22 °C (n-hexane/2-propanol = 90:10, flow rate 1 ml/min, $\lambda$ = 210 nm; amino nitrile **48**: $t_{R1}$(major) = 8.9 min, $t_{R2}$(minor) = 14.4 min. amino nitrile **49**: $t_{R1}$(major) = 9.8 min, $t_{R2}$(minor) = 8.7 min).

**(Benzhydrylamino)(phenyl)acetonitrile (48):**



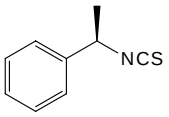

$^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 7.2-7.6 (m, 15H), 5.25 (s, 1H), 4.60 (s, 1H), 2.15 (d, 1H). EI-MS (70 eV): *m/z* (%) = 298.2(2), 221.1(48), 182.1(58), 167.1(67), 116.0(100), 77.0(18), 51.0(6).

**(Benzylamino)(phenyl)acetonitrile (49):**



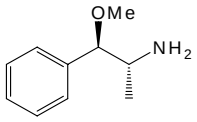

$^1$H NMR (DMSO-$d_6$, 300 MHz): $\delta$ = 7.56-7.23 (m, 10H), 5.0 (d, 1H, NH), 3.89-3.75 (m, 2H), 3.62-3.57 (m, 1H). EI-MS (70 eV): *m/z* (%) = 222.1(5), 116.0 (70), 91.0(91), 77.0(62), 65.0(56), 51.0(100).

**(*R*)-1-Phenylethylisothiocyanate (40):**



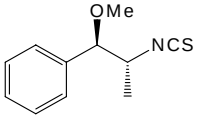

To a solution of (*R*)-1-phenylethylamine (**37**) (0.42 ml, 3.3 mmol) in dry ether (4.2 ml) at -10 C$^{o}$ were added $CS_2$ (1.26 ml) and DCC (680 mg, 3.3 mmol). The reaction mixture was allowed to warm slowly to room temperature over a period of 3 h and was then stirred for a further 12 h at room temperature. The thiourea which precipitated was removed by filtration and the solvent was subsequently removed under vacuum. The residue was taken up in ether and more of the thiourea was able to be removed by filtration. Evaporation of the solvent and rapid filtration on silica gel (with n-hexane) gave product **40** as a colourless liquid. Yield = 94%. $^{1}$H NMR ($CDCl_3$, 300 MHz): δ 7.28-7.40 (m, 5H), 4.87-4.93 (q, 1H, *J* = 6.8 Hz), 1.69 (d, 3H, *J* = 6.8 Hz). $^{13}$C NMR ($CDCl_3$, 200 MHz): δ 140.11, 128.84, 128.14, 125.35, 56.98, 24.90. $[\alpha]^{20}_{D}$ = -4.2$^{o}$ (*c* 1, Acetone).

**(1*S*,2*R*)-2-methoxy-1-methyl-2-phenylethylamine (38):**




Prepared according to the literature, see ref.[5] A solution of (*L*)-(-)-Norephedrine 5g (33 mmol) in dry THF (10,45 ml) was added dropwise to a suspension of "oil free" sodium hydride (from 1,42 g (47,25 mmol of 80% NaH in paraffin) in THF (41,80 ml) at 0$^{o}$C. After stirring at room temperature for 1 h, the mixture was treated dropwise with methyliodide 2,3 ml (34.65mmol) and then heated under reflux for 1 – 2 h. The reaction mixture was then cooled to room temperature and then methanol was added to destroy the excess of NaH. The mixture was poured into water (100 ml), the aqueous solution was saturated with NaCl then extracted with ether. Then combined extracts were dried and concentrated. The residue was purified by column chromatography on silica gel (ethanol/ethyl acetat, 2:1, $R_f$ – broad 0.4-0.5) to give **38** as a yellowish oil. Yield = 25%. $^{1}$H NMR (DMSO-$d_6$, 300 MHz): δ 7.25-7.36 (m, 5H), 3.87 (d, 1H, *J* = 5.7 Hz), 3.13 (s, 3H), 2.90-2.94 (m, 1H), 0.92 (d, 3H, *J* = 6.6 Hz). $^{13}$C NMR (DMSO-$d_6$, 75.5 MHz): δ 139.59, 127.88, 127.33, 127.22, 88.62, 56.39, 51.26, 18.97. ESI-MS calcd. for $[M]^{+}$ $C_{10}H_{15}NO$ 165.33; found 166.0 $[M+H]^{+}$. $[\alpha]^{20}_{D}$ = -89.0$^{o}$ (*c* 1, Acetone)

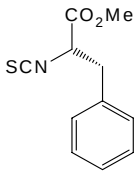
**[(1*R*,2*S*)-2-isothiocyanato-1-methoxypropyl]benzene (41):**




$CS_2$ (2,3 ml) and DCC (1,24 g, 6 mmol) were added at –10 $^{o}$C to a solution of **38:** (1g, 6 mmol) in dry ether (7,8 ml). The reaction mixture was allowed to warm up slowly to room temperature during 3 h and stirred for further 12 h at room temperature. The precipitated urea was filtered off and the solvent removed under

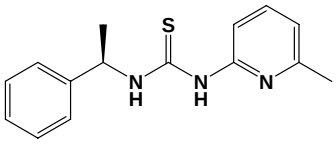
reduced pressure. Purification by column chromatography on silica gel (n-hexane/ethyl acetate, 3:0.25, $R_f$ - 0.5) gave the isothiocyanate **41** as a yellowish solid. Yield = 94%. $^1$H NMR (DMSO-$d_6$, 300 MHz): δ 7.32-7.42 (m, 5H), 4.35 (d, 1H, *J* = 4.8Hz), 4.25-4.27 (m, 1H), 3.22 (s, 3H), 1.17 (d, 3H, *J* = 6.3Hz). $^{13}$C NMR (DMSO-$d_6$, 50.3 MHz): δ 136.76, 128.15, 127.33, 84.11, 57.20, 56.54, 16.88. $[\alpha]^{20}_D$ = -100.0$^o$ (*c* 1, Acetone).

**Methyl *N*-(thioxomethylene)-(*S*)-phenylalaninate (42):**



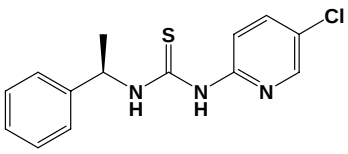

This compound was prepared from (*S*)-phenylalanine methyl ester (**39**) in a manner analogous to that used for **40** with the difference that the reaction was carried out in dry DMF. Reaction time - 14h Purification by column chromatography on silica gel (ethyl acetate/n-hexane, 1.4:5, $R_f$ - 0.75) gave **42** as a colourless liquid. Yield = 80%.. $^1$H NMR (DMSO-$d_6$, 300 MHz): δ 7.22–7.34 (m, 5H), 5.09–5.13 (m, 1H), 3.74 (s, 3H), 3.08–3.27 (m, 2H). $^{13}$C NMR (DMSO-$d_6$, 75.5 MHz): δ 167.92, 135.32, 129.22, 128.37, 127.15, 60.04, 52.94, 38.17. EI-MS m/z (rel intensity) 221.1 ($M^+$, 9.5), 162.1 (100), 128.1 (20), 91.1 (72). $[\alpha]^{20}_D$ = -60.0 (*c* 1, toluene).

***N*-(6-methylpyridin-2-yl)-*N*'-[(1*R*)-1-phenylethyl]thiourea (32):**



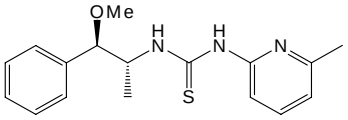

(*R*)-1-Phenylethylisothiocyanate (**40**) (350 mg, 2.14 mmol) was added to a stirred solution of 2-amino-6-methylpyridine (**43**) (231 mg, 2.14 mmol) in ethanol (10.7 ml). The reaction mixture was heated to reflux for 5 h. The solvent was removed under reduced pressure and the residue was allowed to cool. The precipitate formed was filtered off and washed with ethanol. Further purification by flash chromatography on silica gel (n-hexane/ethyl acetat, 3:0.5, $R_f$ - 0.3) gave **32** as a white solid. Yield= 47%. $^1$H NMR ($CDCl_3$, 300 MHz): δ 12.42-12.44 (d, NH, *J* = 6.4 Hz), 8.13 (br, NH), 7.23-7.58 (m, 6H), 6.76-6.78 (d, 1H, *J* = 7.2 Hz), 6.43-6.46 (d, 1H, *J* = 7.5 Hz), 5.54-5.63 (m, 1H), 2.40 (s, 3H), 1.64-1.67 (d, 3H, *J* = 7.2Hz). $^{13}$C NMR ($CDCl_3$, 50 MHz): δ 178.50, 154.87, 152.96, 142.93, 138.89, 128.59, 127.23, 126.26, 117.08, 108.92, 55.08, 23.74, 22.47. EI-MS m/z (rel intensity) 271.2 ($M^+$, 100), 151.1 (33), 120.1 (53), 109.1 (42), 92.1 (25); the exact molecular mass m/z = 271.1143 ± 2 ppm ($M^+$) was confirmed by HRMS (EI, 70 eV). $[\alpha]^{20}_D$= -134.8$^o$ (*c* 0.25, $CHCl_3$).

**_N_-(5-chloropyridin-2-yl)-_N'_-[(1_R_)-1-phenylethyl]thiourea (33):**



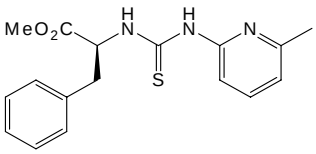
This compound was prepared from (*R*)-1-phenylethylisothiocyanate (**40**) and 2-amino-5-chloropyridine (**44**) in a manner analogous to that used for **32** with the difference that the reaction was carried out in DMF and the reaction mixture was stirred at 65° C for 5 days. Purification by column chromatography on silica gel (ethyl acetate/n-hexane, 1.5:5, $R_f$ - 0.54) gave **33** as a colourless solid. Yield = 46%. $^1$H NMR (DMSO-$d_6$, 300 MHz): δ 11.74-11.77 (d, NH, *J* = 8.3Hz), 10.72 (br, NH), 8.32-8.34 (m, 1H), 7.87-7.91 (dd, 1H, $J_1$ = 2.6Hz, $J_2$ = 2.6Hz), 7.22-7.39 (m, 6H), 5.53-5.62 (m, 1H), 1.53-1.55 (d, 3H, *J* = 6.8Hz). ESI-MS calcd. for $[M]^+$ $C_{14}H_{14}ClN_3S$ 291.0; found 292.1 $[M+H]^+$, 314.1 $[M+Na]^+$, 604.8 $[2M+Na]^+$. $[\alpha]^{20}_D$ = -189.0° (*c* 0.5, $CHCl_3$).

**_N_-[(1_S_,2_R_)-2-methoxy-1-methyl-2-phenylethyl]-_N'_-(6-methylpyridin-2-yl)thiourea (34):**



To a solution 2-amino-6-methylpyridine **43** (0.96 mmol) in toluene (2,5 ml) was added **41** (0.96 mmol) in toluene (2.5 ml). The reaction mixture was stirred at 60° C for 4 days. The reaction mixture was cooled to room temperature. The solvent was evaporated, the residue was purified by column chromatography on silica gel (n-hexane/ethyl acetat, 3:0.7, $R_f$ - 0.5) to give **34** as a white solid. Yield = 54%. $^1$H NMR (DMSO-$d_6$, 300 MHz): δ 12.17-12.20 (d, NH, *J* = 7.2 Hz), 10.44 (br, NH), 7.62-7.68 (m, 1H), 7.28-7.43 (m, 5H), 6.95-6.98 (d, 1H, *J* = 8.3 Hz), 6.89-6.92 (d, 1H, *J* = 7.5 Hz), 4.57-4.61 (m, 1H), 3.31 (s, 3H), 2.43 (s, 3H), 1.02-1.05 (d, 3H, *J* = 6.8Hz). $^{13}$C NMR (DMSO-$d_6$, 75.5 MHz): δ 178.42, 154.31, 153.25, 139.02, 138.60, 128.26, 127.44, 126.40, 116.72, 109.28, 84.12, 57.32, 55.44, 23.37, 12.99. Anal. Calcd for $C_{17}H_{21}N_3OS$: C 64.73, H 6.71, N 13.32; found: C 64.84, H 6.46, N 13.78. HRMS: calcd. for $C_{17}H_{21}N_3OS$ $[M]^+$ 315.1405; found 315.1405 $[M]^+$. $[\alpha]^{20}_D$ = -11.5° (*c* 0.4, $CHCl_3$).

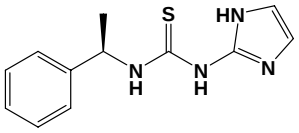
**Methyl _N_-{[(6-methylpyridin-2-yl)amino]carbonothioyl}-(_S_)-phenylalaninate (35):**



This compound was prepared from isothiocyanate **42** and 2-amino-6-methylpyridine (**43**) in a manner analogous to **32**. Reaction time - 48h. Purification by column chromatography on silica gel (n-hexane/ethyl acetat, 3:1, $R_f$ - 0.65) gave **35** as a white solid. Yield = 90%. $^1$H NMR ($CDCl_3$, 300 MHz): δ 12.54-12.56 (d, NH, *J* = 7.9 Hz), 8.88 (br, NH), 7.45-7.50 (t, 1H, *J* = 7.9 Hz), 7.11-7.24 (m, 5H), 6.72-6.75 (d, 1H, *J* = 7.5 Hz), 6.57-6.60 (d, 1H, *J* = 8.3),

5.49-5.55 (m, 1H), 3.71 (s, 3H), 3.25-3.40 (m, 2H), 2.19 (s, 3H). $^{13}$C NMR ($CDCl_3$, 50.3 MHz): δ 178.98, 171.45, 155.47, 152.47, 138.82, 136.01, 129.38, 128.30, 126.86, 117.36, 108.54, 59.47, 52.18, 37.81, 23.44. ESI-MS: calcd. for $C_{17}H_{19}N_3O_2S$ $[M]^+$ 329.1; found 352.1 $[M+Na]^+$, 680.8 $[2M+Na]^+$. $[\alpha]^{20}_D$ = -1.8° (*c* 1, $CHCl_3$).

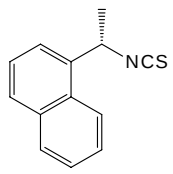
***N*-(1*H*-imidazol-2-yl)-*N*'-[(1*R*)-phenylethyl]thiourea (36):**



This compound was prepared from (*R*)-1-phenylethylisothiocyanate (**40**) and 2-aminoimidazole (**45**) in a manner analogous to that used for **32** with the difference that the reaction was carried out in a 9:2 mixture of DMF:Toluene and that the reaction mixture was stirred at 60 °C for 20 h. The desired product **36** was obtained as a colourless solid in 30% yield. $^1$H NMR (DMSO-d6, 300MHz): δ 11.26 (br, NH), 10.6 (br, 2H, 2xNH), 7.22-7.40 (m, 5H), 6.78 (br, 2H of imidazole), 5.50-5.60 (m, 1H), 1.52 (d, 3H, *J* = 6.9 Hz). $^{13}$C NMR (DMSO-d6, 150.8 MHz) δ 176.27, 143.22, 142.85, 128.41, 126.87, 125.93, 53.31, 22.25. ESI-MS (positive ion): m/z 247.1 $[M+H]^+$, 269.1 $[M+Na]^+$: ESI-MS (negative ion): m/z 245.2 $[M-H]^-$; EI-MS m/z (rel intensity) 246.2 ($M^+$, 100), 126.0 (38), 120.1 (30), 105.1 (83), 84.0 (52), 83.0 (72), 77.0 (32); the exact molecular mass m/z = 246.0939 ± 2 ppm ($M^+$) was confirmed by HRMS (EI, 70 eV). $[\alpha]^{20}_D$ = -238.0 (*c* 0.2, CHCl3).

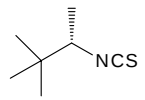
# 3. Experimental Procedures for the compounds Described in Chapters 2 and 3

**1-[(1*S*)-1-isothiocyanatoethyl]naphthalene (53):**



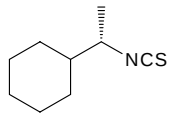
This compound was prepared in 51% yield as a white solid, by analogy with the above described procedure for **40**, starting from (*S*)-1-(2-naphthyl)ethylamine (**50**). $^1$H NMR (300 MHz, DMSO-$d_6$): δ 7.91-7.99 (m, 4H), 7.53-7.56 (m, 3H), 5.42 (q, 1H, *J* = 6.9 Hz), 1.71 (d, 3H, *J* = 6.6 Hz). $^{13}$C NMR (75.5 MHz, DMSO-$d_6$): δ 137.47, 132.60, 132.45, 128.60, 127.80, 127.48, 126.49, 126.32, 124.20, 123.53, 56.51, 23.86. $[\alpha]^{20}_D$ = +24.9 (*c* 0.095, $CHCl_3$).

**(3*S*)-3-isothiocyanato-2,2-dimethylbutane (54):**



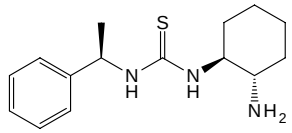

This compound was prepared from (*S*)-3,3-dimethyl-2-aminobutane (**51**) in a manner analogous to **40** and was obtained as a colourless liquid in 80% yield. $^{1}$H NMR (300 MHz, DMSO-$d_6$): δ 3.76 (q, 1H, *J* = 6.6 Hz), 1.26 (d, 3H, *J* = 6.9 Hz), 0.93 (s, 9H). $^{13}$C NMR (75.5 MHz, DMSO-$d_6$): δ 62.73, 35.20, 25.33, 16.25. $[\alpha]^{20}_{D}$ = +36.9 (*c* 0.85, $CHCl_3$).

**[(1*S*)-1-isothiocyanatoethyl]cyclohexane (55):**



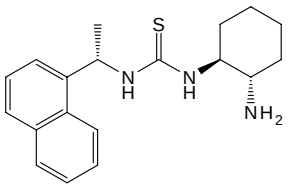

This compound was prepared from (*S*)-1-cyclohexylethylamine (**52**) in a manner analogous to **40** and was isolated as a colourless liquid in 66% yield. $^{1}$H NMR (300 MHz, DMSO-$d_6$): δ 3.81 (m, 1H), 1.62-1.76 (m, 5H), 1.42-1.52 (m, 1H), 1.29 (d, 3H, *J* = 6.6 Hz), 0.96-1.26 (m, 5H). $^{13}$C NMR (75.5 MHz, DMSO-$d_6$): δ 58.39, 42.83, 28.93, 27.39, 25.63, 25.27, 25.16, 18.45. $[\alpha]^{20}_{D}$ = +53.5 (*c* 0.095, $CHCl_3$).

***N*-[(1*S*,2*S*)-2-aminocyclohexyl]-*N*'-[(1*R*)-1-phenylethyl]thiourea (56):**



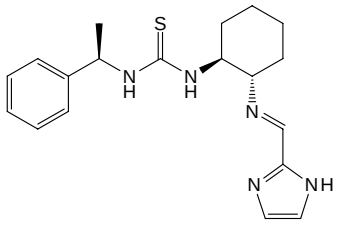

(*R*)-1-Phenylethylisothiocyanate (**40**) (1.28 g, 8.75 mmol) was added over a period of 1 h to a stirred solution of (*S*,*S*)-1,2-Diaminocyclohexane (**64**) (1 g, 8.75 mmol) in dry dichloromethane (17 mL). The reaction mixture was stirred for a further 2 h at room temperature. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on $SiO_2$ (ethyl acetate/ethanol, 3:1, $R_f$ - broad 0.1-0.7) to give **56** as a yellowish solid in 61% yield. $^{1}$H NMR (300 MHz, DMSO-$d_6$): δ 7.17-7.35 (m, 5H), 5.42-5.49 (m, 1H), 3.68-3.69 (m, 1H), 2.41-2.49 (m, 1H), 1.94-1.99 (m, 1H), 1.76-1.83 (m, 1H), 1.54-1.62 (m, 2H), 1.41 (d, 3H, *J* = 6.9 Hz), 0.99-1.26 (m, 4H). $^{13}$C NMR (75.5 MHz, DMSO-$d_6$): δ 181.57, 144.39, 128.12, 126.48, 125.97, 59.43, 54.20, 52.21, 34.40, 31.37, 24.42, 24.29, 22.30. ESI-MS (positive ion): *m/z* = 278.1 $[M + H]^+$, 554.9 $[2M + H]^+$. ESI-MS (negative ion): *m/z* = 276.1 $[M - H]^-$. HRMS: calcd. for $C_{15}H_{23}N_3S$ $[M]^+$ 277.16127; found 278.16866 $[M + H]^+$. $[\alpha]^{20}_{D}$ = -85.0 (*c* 1, $CHCl_3$).

***N*-[(1*S*,2*S*)-2-aminocyclohexyl]-*N*'-[(1*S*)-1-(1-naphthyl)ethyl]thiourea (57):**



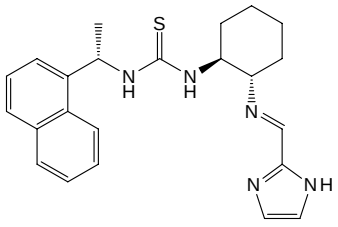
This compound was prepared in 50% yield (as a yellowish solid) by analogy with the above procedure, starting from **53**. $^{1}$H NMR (300 MHz, DMSO-$d_6$): δ 7.80-7.89 (m, 4H), 7.44-7.52 (m, 3H), 5.61-5.63 (m, 1H), 3.76-3.77 (m, 1H), 2.50-2.54 (m, 1H), 1.98-2.00 (m, 1H), 1.80-1.83 (m, 1H), 1.51-1.61 (m, 2H), 1.51 (d, 3H, *J* = 6.6 Hz), 1.15-1.22 (m, 4H). $^{13}$C NMR (75.5 MHz, DMSO-$d_6$): δ 181.65, 141.99, 132.78, 131.95, 127.72, 127.54, 127.33, 125.96, 125.46, 124.95, 123.99, 59.17, 33.91, 31.27, 24.37, 24.21, 22.23. ESI-MS (positive ion): *m/z* = 328.1 $[M + H]^+$, 655.0 $[2M+H]^+$.

***N*-((1*S*,2*S*)-2-{[(1*E*)-1*H*-imidazol-2-ylmethylidene]amino}cyclohexyl)-*N*'-[(1*R*)-1-phenylethyl]thiourea (60):**



To a solution of **56** (899 mg, 3.24 mmol) in anhydrous methanol (50 mL) at room temperature under argon were added $Na_2SO_4$ (2 g) and imidazole-2-carboxaldehyde (**65**) (3.24 mmol). The reaction mixture was stirred for 2 h at room temperature. Sodium sulfate filtered off and washed with anhydrous methanol (3 x 20 mL). The methanol was evaporated in *vacuo* to afford product **60** in a quantitative yield as a white solid. $^{1}$H NMR (300 MHz, DMSO-$d_6$): δ 8.20 (s, 1H), 7.68 (br, NH), 7.25 (br, NH), 7.10-7.20 (m, 5H), 7.11 (s, 2H), 5.36-5.37 (m, 1H), 4.16 (m, 1H), 3.13-3.21 (m, 1H), 2.17-2.20 (m, 1H), 1.55-1.71 (m, 4H), 1.39 (d, 3H, *J* = 6.9 Hz), 1.2-1.41(m, 2H), 1.11-1.32 (m, 1H). $^{13}$C NMR (75.5 MHz, DMSO-$d_6$): δ 181.2, 152.24, 145.04, 144.37, 127.98, 126.22, 125.94, 125.81, 72.47, 56.51, 51.85, 48.50, 33.45, 31.17, 24.21, 23.65, 22.03. ESI-MS (positive ion): *m/z* = 356.1 $[M + H]^+$, 710.9 $[2M + H]^+$. HRMS: calcd. for $C_{19}H_{25}N_5S$ $[M]^+$ 355.18307; found 356.19032 $[M + H]^+$. $[\alpha]^{20}_D$ = +98.2 (*c* 0.44, $CHCl_3$).

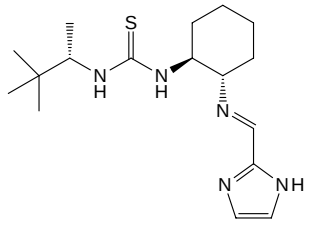
***N*-((1*S*,2*S*)-2-{[(1*E*)-1*H*-imidazol-2-ylmethylidene]amino}cyclohexyl)-*N*'-[(1*S*)-1-(1-naphthyl)ethyl]thiourea (61):**



This compound was prepared from **57** by the same procedure as described above for **60**, to give **61** as a white solid in a quantitative yield. $^{1}$H NMR (300 MHz, DMSO-$d_6$): δ 8.18 (s, 1H), 7.72-7.91 (m, 4H), 7.39-7.56 (m, 3H), 7.08 (s, 2H), 5.49-5.59 (m, 1H), 4.12-4.18 (m, 1H), 3.14-3.20 (m, 1H), 2.21-2.24 (m, 1H), 1.46-1.79 (m, 4H),

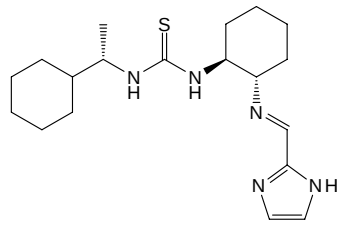
1.39 (d, 3H, *J* = 6.9 Hz), 1.20-1.39 (m, 2H), 1.05-1.19 (m, 1H). $^{13}$C NMR (75.5 MHz, DMSO-$d_6$): δ 181.30, 152.82, 145.90, 142.01, 132.78, 131.91, 127.68, 127.56, 127.31, 125.92, 125.42, 125.02, 123.93, 72.25, 56.71, 52.25, 33.54, 31.02, 24.15, 23.70, 22.07. ESI-MS (positive ion): *m/z* = 406.1 $[M + H]^+$, 428.2 $[M + Na]^+$, 810.8 $[2M + H]^+$, 832.8 $[2M + Na]^+$. HRMS: calcd. for $C_{23}H_{27}N_5S$ $[M]^+$ 405.19872; found 406.20621 $[M + H]^+$. $[\alpha]^{20}_D$ = +70.3 (*c* 0.65, $CH_3OH$).

**_N_-((1_S_,2_S_)-2-{[(1_E_)-1_H_-imidazol-2-ylmethylidene]amino}cyclohexyl)-_N_'-[(1_S_)-1,2,2-trimethylpropyl]thiourea (62):**



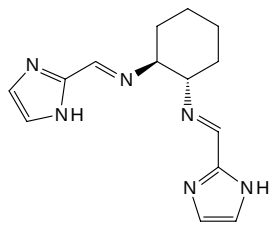
This compound was prepared from **58** (2.20 g, 8.56 mmol) by the same procedure as described above for **60**, to give **62** in a quantitative yield as a white solid. $^1$H NMR (300 MHz, DMSO-$d_6$): δ 12.6 (br, NH), 8.18 (s, 1H), 7.13 (s, NH), 7.12 (s, 2H), 6.92-6.96 (d, NH, *J* = 9.4 Hz), 4.12-4.21 (m, 2H), 3.14-3.21 (m, 1H), 2.26-2.31 (m, 1H), 1.58-1.74 (m, 4H), 1.26-1.40 (m, 2H), 1.00-1.12 (m, 1H), 0.83 (d, 3H, *J* = 6.9 Hz), 0.79 (s, 9H). $^{13}$C NMR (75.5 MHz, DMSO-$d_6$): δ 151.54, 144.33, 72.52, 56.59, 56.37, 45.49, 34.31, 33.53, 31.16, 26.18, 24.14, 23.68, 15.38, 8.45. ESI-MS (positive ion): m/z = 336.2 $[M + H]^+$, 358.2 $[M + Na]^+$, 670.9 $[2M + H]^+$, 692.9 $[2M + Na]^+$. HRMS: calcd. for $C_{17}H_{29}N_5S$ $[M]^+$ 335.21437; found 336.22170 $[M + H]^+$. $[\alpha]^{20}_D$ = +151.8 (*c* 0.38, $CH_3OH$).

**_N_-[(1_S_)-1-cyclohexylethyl]-_N_'-((1_S_,2_S_)-2-{[(1_E_)-1_H_-imidazol-2-ylmethylidene] amino}cyclohexyl)thiourea (63):**



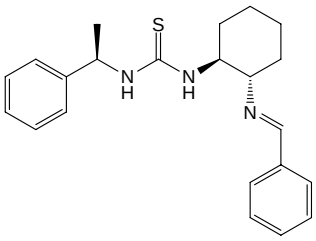
This compound was prepared from **59** in a manner analogous to **60** and was isolated in a quantitative yield as a yellowish solid. $^1$H NMR (300 MHz, DMSO-$d_6$): δ 12.6 (br, NH), 8.17 (s, 1H), 7.12 (s, 2H), 6.9-7.0 (m, 2H, 2xNH), 4.2 (m, 1H), 3.95 (m, 1H), 3.2 (m, 1H), 2.23 (m, 1H), 1.42-1.8 (m, 10H), 1.19-1.4 (m, 3H), 0.98-1.18 (m, 4H), 0.89 (d, 3H, *J* = 6.9 Hz), 0.8-0.98 (m, 1H). $^{13}$C NMR (75.5 MHz, DMSO-$d_6$): δ 151.64, 144.36, 72.40, 52.75, 42.45, 33.61, 31.16, 28.79, 28.38, 25.89, 25.57, 24.20, 23.74, 17.19. ESI-MS (positive ion): *m/z* = 384.4 $[M + Na]^+$. ESI-MS (negative ion): *m/z* = 360.1 $[M - H]^-$. HRMS: calcd. for $C_{19}H_{31}N_5S$ $[M]^+$ 361.23002; found 362.23741 $[M + H]^+$. $[\alpha]^{20}_D$ = +126.0 (*c* 0.96, $CH_3OH$).

**(1*S*,2*S*)-*N*,*N*'-bis[(1*E*)-1*H*-imidazol-2-ylmethylidene]cyclohexane-1,2-diamine (66):**



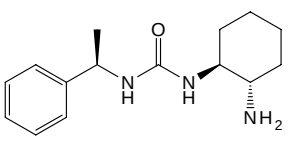
This compound was prepared from (*S*,*S*)-1,2-Diaminocyclohexane (**64**) (300 mg, 2.63 mmol) and imidazole-2-carboxaldehyde (**65**) (505 mg, 5.26 mmol) by the same procedure as described above for **60**, to give **66** in quantitative yield as a white solid. $^{1}$H NMR (300 MHz, DMSO-$d_6$): δ 8.04 (s, 2H), 7.03 (s, 4H), 3.30-3.39 (m, 2H), 1.39-1.81 (m, 8H). $^{13}$C NMR (75.5 MHz, DMSO-$d_6$): δ 150.86, 144.12, 123.72, 72.48, 32.37, 23.55. ESI-MS (positive ion): m/z = 271.2 $[M + H]^+$, 293.2 $[M + Na]^+$. ESI-MS (negative ion): m/z = 269.2 $[M - H]^-$. HRMS: calcd. for $C_{14}H_{18}N_6$ $[M]^+$ 270.15929; found 271.16666 $[M + H]^+$. $[\alpha]^{20}_D$ = +393.6 (*c* 0.41, $CH_3OH$).

***N*-[(1*R*)-1-phenylethyl]-*N*'-((1*S*,2*S*)-2-{[(1*E*)-phenylmethylidene]amino}cyclohexyl) thiourea (67):**



This compound was prepared from **56** (400 mg, 1.44 mmol) and benzaldehyd 0.147 (ml, 1.44 mmol) in a manner analogous to that used for **60** with the difference that the reaction mixture was stirred at 40-45 $^{o}$C for 5 hours. The desired product **67** was obtained in a quantitative yield as a white solid. $^{1}$H NMR (300 MHz, DMSO-$d_6$): δ 8.35 (s, 1H), 7.7 (m, 2H), 7.45 (m, 4H), 7.1-7.18 (m, 4H), 7.0 (br, 2H, 2xNH), 5.32-5.36 (m, 1H), 4.14-4.21 (m, 1H), 3.14-3.22 (m, 1H), 2.06-2.09 (m, 1H), 1.55-1.74 (m, 4H), 1.17-1.40 (m, 3H), 1.31 (d, 3H, *J* = 6.9Hz). $^{13}$C NMR (75.5 MHz, DMSO-$d_6$): δ 160.01, 144.77, 136.25, 130.26, 128.37, 127.84, 127.78, 126.30, 126.01, 125.71, 72.36, 56.27, 51.95, 48.38, 33.11, 31.15, 24.25, 23.61, 22.15. ESI-MS (positive ion): m/z = 366.2 $[M + H]^+$, 388.1 $[M + Na]^+$, 752.9 $[2M + Na]^+$. HRMS: calcd. for $C_{22}H_{27}N_3S$ $[M]^+$ 365.19257; found 366.20006 $[M + H]^+$. $[\alpha]^{20}_D$ = +59.3 (*c* 0.84, $CH_3OH$).

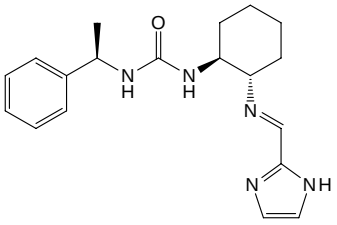
***N*-[(1*S*,2*S*)-2-aminocyclohexyl]-*N*'-[(1*R*)-1-phenylethyl]urea (56a):**



(*R*)-1-Phenylethylisocyanate (500 mg, 3.4 mmol) was added over a period of 1 h to a stirred solution of (*S*,*S*)-1,2-diaminocyclohexane (**64**) (388 mg, 3.4 mmol) in dry dichloromethane (17 mL). The reaction mixture was stirred for a further 2 h at room temperature. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on $SiO_2$ (ethyl acetate/ethanol, 2:1, $R_f$ - 0.26) to give **56a** as a white solid in

30% yield. $^{1}$H NMR (300 MHz, DMSO-$d_6$): δ 7.16-7.33 (m, 5H), 6.20-6.23 (d, NH, *J* = 7.9Hz), 5.54-5.67 (d, NH, *J* = 7.9Hz), 4.68-4.78 (m, 1H), 2.97-3.07 (m, 1H), 2.22-2.30 (m, 1H), 1.72-1.85 (m, 2H), 1.56-1.60 (m, 2H), 1.29-1.32 (d, 3H, *J* = 7.2Hz), 0.90-1.27 (m, 4H). $^{13}$C NMR (125.7 MHz, DMSO-$d_6$): δ 157.37, 145.78, 128.06, 126.25, 125.64, 55.56, 54.60, 48.44, 34.44, 32.48, 24.68, 24.37, 23.28. ESI-MS (positive ion): m/z = 262.1 $[M + H]^+$, 284.2 $[M + Na]^+$, 523.0 $[2M + H]^+$, 545.1 $[2M + Na]^+$.

***N*-((1*S*,2*S*)-2-{[(1*E*)-1*H*-imidazol-2-ylmethylidene]amino}cyclohexyl)-*N*'-[(1*R*)-1-phenylethyl]urea (60a):**

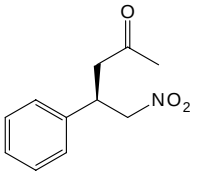


To a solution of (*R*)-1-Phenylethylisocyanate (193 mg, 0.74mmol) and $Na_2SO_4$ (2g) in methanol (14mL), 1H-imidazole-2-carbaldehyde (71 mg, 0.74mmol) was added and resulting mixture was stirred at room temperature for 5 hrs. The methanol was evaporated in *vacuo* to give product **60a** in a quantitative yield as a white solid. $^{1}$H NMR (DMSO-$d_6$, 300 MHz): δ 8.16 (s, 1H), 7.18 (s, 2H), 7.06-7.26 (m, 5H), 6.06-6.08 (d, NH, *J* = 8.1 Hz), 5.62-5.65 (d, 1H, *J* = 8.4 Hz), 4.58-4.67 (m, 1H), 3.47-3.58 (m, 1H), 2.96-3.04 (m, 1H), 1.95-2.00 (m, 1H), 1.56-1.75 (m, 4H), , 1.12-1.34 (m, 3H), 1.23-1.25 (d, 3H, *J* = 6.9 Hz). $^{13}$C NMR (DMSO-$d_6$, 75.5 MHz): δ 156.62, 151.39, 145.54, 144.53, 127.88, 125.97, 125.49, 73.26, 52.47, 48.12, 33.48, 32.59, 24.54, 23.73, 22.93. HRMS: calcd. for $C_{19}H_{25}N_2O$ $[M]^+$ 339.20591; found 340.21319 $[M+H]^+$. $[\alpha]^{20}_D = +86.0^o$ (*c* 0.45, $CH_3OH$).

## General procedure for the catalytic asymmetric Michael-addition of ketones to nitroolefins

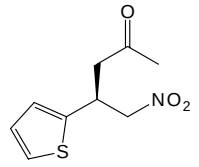
To a stirred solution of catalyst (0.15 equiv) in toluene (0.5 mL) and acetone (0.27 mL) at room temperature, was added water (2 equiv), acetic acid (0.15 equiv) and, after 2 minutes, nitroolefin (1 equiv). The reaction mixture was stirred at room temperature for the appropriate time. The solvent was evaporated and the residue was purified by preparative TLC or chromatography on $SiO_2$-column (n-hexane/ethyl acetate, 1:1) to afford the desired product. The enantiomeric excess of the Michael product was determined by chiral HPLC analysis (Daicel Chiralpak AS) in comparison with authentic racemic material.

**(4*R*)-5-nitro-4-phenylpentan-2-one (70):**



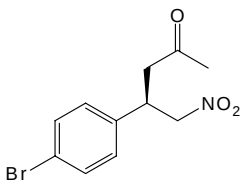
Reaction time – 16hrs. Purification by column chromatography on silica gel (n-hexane/ethyl acetat, 1:1, $R_f$ - 0.5) gave **70** as a white solid. Yield - 85%. $^1$H NMR (DMSO-$d_6$, 300 MHz): δ 7.22-7.31 (m, 5H), 4.72-4.89 (m, 2H), 3.81-3.87 (m, 1H), 2.91 (d, 2H, *J* = 7.2 Hz), 2.03 (s, 3H). $^{13}$C NMR (DMSO-$d_6$, 75.5 MHz): δ 205.79, 139.82, 128.37, 127.51, 127.08, 79.40, 45.60, 38.77, 29.91. ESI-MS (positive ion): *m/z* = 230.1 $[M+Na]^+$. HRMS: calcd. for $C_{11}H_{13}NO_3$ $[M]^+$ 207.08954; found 230.07878 $[M+Na]^+$. The product was analysed by HPLC using a *Daicel Chiralpak AS 250* column at 22 °C (n-hexane/2-propanol = 65:35, flow rate 1 ml/min, λ = 210 nm), (**S**)-enantiomer: $t_R$ = 12.5 min (major). (**R**)-enantiomer: $t_R$ = 15.1 min (minor).

**(4*S*)-5-nitro-4-thien-2-ylpentan-2-one (71):**



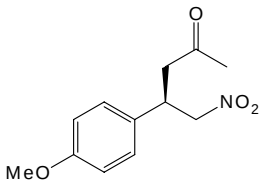
Reaction time – 25hrs. Purification by column chromatography on silica gel (n-hexane/ethyl acetat, 1:1, $R_f$ - 0.6) gave **71** as a dark solid. Yield - 85 %. $^1$H NMR (DMSO-$d_6$, 300 MHz): δ 7.37-7.39 (m, 1H), 6.93-6.99 (m, 2H), 4.70-4.91 (m, 2H), 4.10-4.19 (m, 1H), 2.97 (d, 2H, *J* = 7.2 Hz), 2.08 (s, 3H). $^{13}$C NMR (DMSO-$d_6$, 75.5 MHz): δ 205.47, 142.48, 126.81, 125.12, 124.68, 79.87, 46.29, 33.92, 29.90, 28.40. The exact molecular mass *m/z* = 213.0460 ± 2 ppm ($M^+$) was confirmed by HRMS (EI, 70 eV). The product was analysed by HPLC using a *Daicel Chiralpak AS 250* column at 22 °C (n-hexane/2-propanol = 65:35, flow rate 1 ml/min, λ = 210 nm), (**R**)-enantiomer: $t_R$ = 15.9 min (major). (**S**)-enantiomer: $t_R$ = 19.2 min (minor).

**(4*R*)-4-(4-bromophenyl)-5-nitropentan-2-one (72):**



Reaction time – 15hrs. Purification by column chromatography on silica gel (n-hexane/ethyl acetat, 1:1, $R_f$ - 0.5) gave **72** as a white solid. Yield - 93%. $^1$H NMR (DMSO-$d_6$, 300 MHz): δ 7.44-7.52 (m, 2H), 7.26-7.31 (m, 2H), 4.73-4.90 (m, 2H), 3.77-3,87 (m, 1H), 2.91 (d, 2H, *J* = 6.9 Hz), 2.04 (s, 3H). $^{13}$C NMR (DMSO-$d_6$, 75.5 MHz): δ 205.65, 139.34, 131.24, 129.91, 120.24, 79.09, 45.32, 38.21, 29.92. The exact molecular mass *m/z* = 285.0001 ± 2 ppm ($M^+$) was confirmed by HRMS (EI, 70 eV). The product was analysed by HPLC using a *Daicel Chiralpak AS 250* column at 22 °C (n-hexane/2-propanol = 65:35, flow rate 1 ml/min, λ = 210 nm), (**S**)-enantiomer: $t_R$ = 13.7 min (major). (**R**)-enantiomer: $t_R$ = 18.8 min (minor).

**(4*R*)-4-(4-methoxyphenyl)-5-nitropentan-2-one (73):**

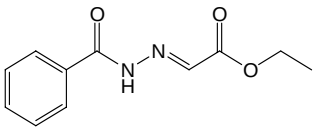


Reaction time – 71hrs. Purification by column chromatography on silica gel (n-hexane/ethyl acetat, 1:1, $R_f$ - 0.5) gave **73** as a yellowish solid. Yield – 87%. $^1$H NMR (DMSO-$d_6$, 300 MHz): δ 7.19-7.24 (m, 2H), 6.83-6.88 (m, 2H), 4.66-4.85 (m, 2H), 3.71-3.83 (m, 1H), 3.72 (s, 3H), 2.86 (d, 2H, *J* = 7.2 Hz), 2.02 (s, 3H). $^{13}$C NMR (DMSO-$d_6$, 75.5 MHz): δ 205.92, 158.24, 131.54, 128.60, 113.79, 79.66, 54.91, 45.76, 38.15, 29.99. The exact molecular mass *m/z* = 237.1001 ± 2 ppm ($M^+$) was confirmed by HRMS (EI, 70 eV). The product was analysed by HPLC using a *Daicel Chiralpak AS 250* column at 22 °C (n-hexane/2-propanol = 10:90, flow rate 1 ml/min, λ = 210 nm), (**S**)-enantiomer: $t_R$ = 10.4 min (major). (**R**)-enantiomer: $t_R$ = 16.5 min (minor).

# 4. Experimental Procedures for the Compounds Described in Chapter 4

## Synthesis of α-hydrazonoesters

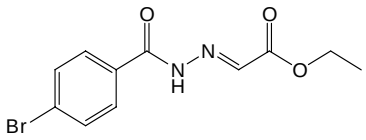
**Ethyl (2*E*)-(benzoylhydrazono)ethanoate (*E*-76a):**



To a solution of benzoylhydrazine (5g, 36,7mmol) in EtOH (50mL) was added a solution of ethyl glyoxylate (36,7mmol, 7,3mL (50% in Toluene)). After stirring at 80$^o$ C for 40 min, the reaction mixture was cooled to room temperature. The solvent was evaporated. The residue was purified by silica gel flash chromatography (ethyl acetate/n-hexane, 1:1, $R_f$ - 0.3) to afford the α-hydrazonoester *E*-**76a** in yield 80% as a white solid. $^1$H NMR (DMSO-$d_6$, 300 MHz): δ 12.20 (s, NH), 7.84-7.91 (m, 2H), 7.80 (s, 1H), 7.60-7.65 (m, 1H), 7.51-7.57 (m, 2H), 4.21-4.29 (q, 2H, *J* = 7.2 Hz), 1.24-1.31 (t, 3H, *J* = 6.6 Hz). $^{13}$C NMR (DMSO-$d_6$, 150.8 MHz): δ 162.93, 132.45, 132.27, 128.48, 127.89, 60.74, 13.97. ESI-MS: calcd. for $C_{11}H_{12}N_2O_3$ $[M]^+$ 220.2; found 243.0 $[M+Na]^+$, 462.8 $[2M+Na]^+$. **Ethyl (2*Z*)-(benzoylhydrazono)ethanoate (*Z*-76a):** (10% yield as a white solid). (Conditions for chromatography – ethyl acetate/n-hexane, 1:1, $R_f$ - 0.52). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ 13.14 (br, NH), 7.83-7.87 (m, 2H), 7.64-7.70 (m, 1H), 7.55-7.62 (m, 2H), 7.17 (s, 1H), 4.25-4.33 (q, 2H, *J* = 7.2 Hz), 1.28-1.32 (t, 3H, *J* = 6.9 Hz) ppm. $^{13}$C

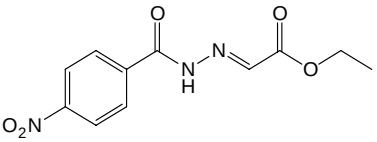
NMR (DMSO-$d_6$, 75.5 MHz): δ 161.62, 132.65, 131.92, 130.59, 128.94, 127.36, 61.49, 13.66. ESI-MS (positive ion): *m/z* = 243.0 $[M+Na]^+$, 462.8 $[2M+Na]^+$.

**Ethyl (2*E*)-[(4-bromobenzoyl)hydrazono]ethanoate (*E*-76b):**



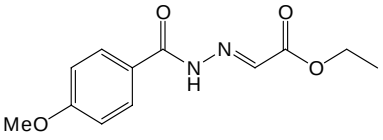
The acylhydrazone *E*-**76b** was prepared in the same manner as *E*-**76a.** Instead of benzoylhydrazine was used 4-Bromobenzoylhydrazine. Purification by flash chromatography (ethyl acetate/n-hexane/dichloromethane, 2:1:1, $R_f$ - 0.5) gave *E*-**76b** (75% yield) as a white solid. $^1$H NMR (DMSO-$d_6$, 300 MHz): δ 12.30 (br, NH), 7.74-7.85 (m, 4H), 7.77 (s, 1H), 4.21-4.28 (q, 2H, *J* = 7.2 Hz), 1.24-1.29 (t, 3H, *J* = 6.9 Hz). $^{13}$C NMR (DMSO-$d_6$, 150.8 MHz): δ 162.82, 131.50, 131.50, 129.91, 126.14, 60.78, 13.95. HRMS: calcd. for $C_{11}H_{11}BrN_2O_3$ $[M]^+$ 297.99530; found 299.00258 $[M+H]^+$, 320.98453 $[M+Na]^+$, 336.95846 $[M+K]^+$. **Ethyl (2*Z*)-[(4-bromobenzoyl)hydrazono]ethanoate (*Z*-76b):** (Yield 9% as a white solid). (Conditions for chromatography – ethyl acetate/n-hexane/dichloromethane, 2:1:1, $R_f$ - 0.58). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ 13.10 (br, NH) 7.73-7.88 (m, 4H), 7.19 (s, 1H), 4.25-4.32 (q, 2H, *J* = 7.2 Hz), 1.27-1.32 (t, 3H, *J* = 6.6 Hz). $^{13}$C NMR (DMSO-$d_6$, 75.6 MHz): δ 161.51, 131.97, 131.08, 129.50, 126.46, 61.53, 13.66. HRMS: calcd. for $C_{11}H_{11}BrN_2O_3$ $[M]^+$ 297.99530; found 299.00258 $[M+H]^+$, 320.98453 $[M+Na]^+$, 336.95846 $[M+K]^+$.

**Ethyl (2*E*)-[(4-nitrobenzoyl)hydrazono]ethanoate (*E*-76c):**



To a solution of 4-nitrobenzoylhydrazine (3g, 16,57mmol) in absolute EtOH (60mL) was added a solution of ethyl glyoxylate (16,57mmol, 3,29mL (50% in Toluene). After stirring at 80$^o$ C for 2 hrs, the reaction mixture was cooled to room temperature. Then after 5 hrs (necessary for the conversion of *Z* form to the *E* form) the solvent was evaporated to afford the α-hydrazonoester *E*-**76c**. Yield is nearly quantitative as a yellowish solid. $^1$H NMR (DMSO-$d_6$, 300 MHz): δ 12.51 (br, NH), 8.36-8.39 (m, 2H), 8.11-8.13 (m, 2H), 7.80 (br, H), 4.22-4.29 (q, 2H, *J* = 6.6 Hz), 1.25-1.30 (t, 3H, *J* = 6.9 Hz). $^{13}$C NMR (DMSO-$d_6$, 125.7 MHz): δ 162.95, 149.45, 138.52, 129.40, 123.56, 60.88, 13.94. HRMS: calcd. for $C_{11}H_{11}N_3O_5$ $[M]^+$; 265.06987; found 266.07715 $[M+H]^+$, 288.05909 $[M+Na]^+$.

**Ethyl (2*E*)-[(4-methoxybenzoyl)hydrazono]ethanoate (*E*-76d):**

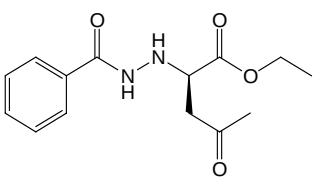


To a solution of 4-methoxybenzoylhydrazine (3g, 18mmol) in EtOH (24.5mL) was added a solution of ethyl glyoxylate (18mmol, 3,58mL (50% in Toluene). After stirring at 80° C for 30min, the reaction mixture was cooled to RT. The solvent was evaporated. The residue was purified by silica gel flash chromatography (petroleum ether/ethyl acetate, 1:3, $R_f$ - 0.45) to afford the α-hydrazonoester ***E*-76d** in yield 86% as a white solid. $^1$H NMR (DMSO-$d_6$, 300 MHz): δ 12.12 (br, NH), 7.88-7.91 (d, 2H, *J* = 8.7 Hz), 7.78 (s, 1H), 7.03-7.07 (d, 2H, *J* = 9 Hz), 4.18-4.26 (q, 2H, *J* = 6.9 Hz), 3.82 (s, 3H), 1.22-1.27 (t, 3H, *J* = 6.9 Hz). $^{13}$C NMR (DMSO-$d_6$, 75.4 MHz): δ 163.03, 162.48, 136.63, 130.04, 124.38, 113.76, 60.67, 55.40, 13.95. HRMS: calcd. for $C_{12}H_{14}N_2O_4$ $[M]^+$ 250.09536; found 251.10263 $[M+H]^+$, 273.08458 $[M+Na]^+$. **Ethyl (2*Z*)-[(4-methoxybenzoyl)hydrazono]ethanoate (*Z*-76d):** Yield 9% as a white solid. (Conditions for chromatography – petroleum ether/ethyl acetate, 1:3, $R_f$ - 0.6).

## A general procedure for the catalytic asymmetric Mannich-Type addition of ketones to the α-hydrazonoesters

To a stirred solution of catalyst (**56**, **56a**, **74** or **75**) (0.15 eq.) and corresponding α-hydrazonoester (1 eq.) in dry toluene (4ml per 1mmol of acylhydrazone) at room temperature the ketone (10 eq.) was added. The reaction mixture was stirred at room temperature under Ar atmosphere for the appropriate time (see Tables **11** and **12** in Main Part, pages 52-53). The solvent was evaporated. The residue was purified by silica gel flash chromatography to afford corresponding Mannich product. The enantiomeric and diastereomeric excess of the chiral products was determined by chiral HPLC analysis in comparison with authentic racemic material (see below).

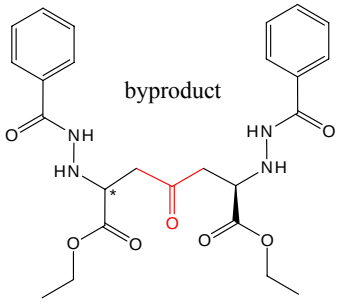
**Ethyl (2*R*)-2-(2-benzoylhydrazino)-4-oxopentanoate (77a):**



Yield 50% as a white solid. (Conditions for chromatography – ethyl acetate/n-hexane, 2:1, $R_f$ - 0.25). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ 9.97-10.00 (d, NH, *J* = 6.6 Hz), 7.77-7.80 (m, 2H), 7.42-7.55 (m, 3H),

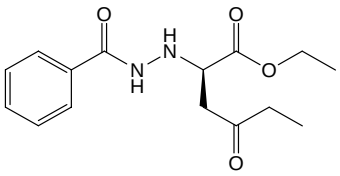
5.53-5.57 (t, NH, *J* = 6 Hz), 4.02-4.09 (q, 2H, *J* = 7.2 Hz), 3.87-3.93 (m, 1H), 2.79-2.98 (m, 2H), 2.13 (s, 3H), 1.11-1.16 (t, 3H, *J* = 7.2 Hz). $^{13}$C NMR (DMSO-$d_6$, 75.6 MHz): δ 205.64, 171.17, 165.63, 132.77, 131.26, 128.18, 127.01, 60.30, 58.16, 43.32, 20.61, 13.95. HRMS: calcd. for $C_{14}H_{18}N_2O_4$ $[M]^+$ 278.12666; found 279.13393 $[M+H]^+$, 301.11588 $[M+Na]^+$.

**Byproduct diethyl (2*R*)-2,6-bis(2-benzoylhydrazino)-4-oxoheptanedioate (77a'):**



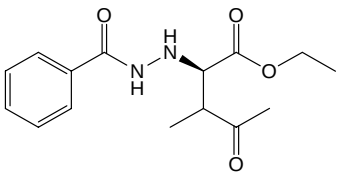

Yield = 10% (white solid). (Conditions for chromatography – ethyl acetate/n-hexane, 2:1, $R_f$ - 0.1). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ 10.00-10.02 (d, NH, *J* = 6.6 Hz), 7.77-7.80 (m, 2H), 7.42-7.56 (m, 3H), 5.56-5.60 (t, NH, *J* = 6 Hz), 4.01-4.08 (q, 2H, *J* = 7.5 Hz), 3.87-3.94 (m, 1H), 2.84-2.51 (m, 2H), 1.10-1.15 (t, 3H, *J* = 7.2 Hz). $^{13}$C NMR (DMSO-$d_6$, 150.8 MHz): δ 205.76, 171.59, 166.20, 133.30, 131.83, 128.74, 127.57, 60.89, 58.49, 43.36, 14.28. ESI-MS (positive ion): *m/z* = 521.2 $[M+Na]^+$, 1018.9 $[2M+Na]^+$.

**Ethyl (2*R*)-2-(2-benzoylhydrazino)-4-oxohexanoate (77b):**




Yield 50% as a white solid. (Conditions for chromatography – ethyl acetate/n-hexane/dichloromethane, 2:1:2, $R_f$ - 0.3). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ 9.97-9.99 (d, NH, *J* = 6.6 Hz), 7.76-7.79 (m, 2H), 7.43-7.53 (m, 3H), 5.53-5.57 (t, NH, *J* = 6 Hz), 4.02-4.09 (q, 2H, *J* = 7.2 Hz), 3.89-3.97 (m, 1H), 2.77-2.96 (m, 2H), 2.44-2.51 (q, 2H, *J* = 7.2 Hz), 1.11-1.16 (t, 3H, *J* = 7.2 Hz), 0.89-0.94 (t, 3H, *J* = 7.2 Hz). $^{13}$C NMR (DMSO-$d_6$, 125.7 MHz): δ 208.13, 171.21, 165.60, 132.76, 131.27, 128.19, 127.01, 60.29, 58.19, 42.19, 35.24, 13.77, 7.32. ESI-MS (positive ion): *m/z* = 315.2 $[M+Na]^+$.

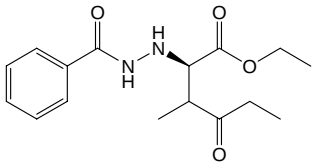
**Ethyl 2-(N`-benzoylhydrazino)-3-methyl-4-oxopentanoate (77c) (mixture of diastereomers):**




Yield 36% as a yellowish solid. (Conditions for chromatography – ethyl acetate/n-hexane/dichloromethane, 2:1:2, $R_f$ - 0.35). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ 10.06-10.08 (d, 0.1NH, *J* = 6.3 Hz), 9.90-9.92 (d, 0.56NH, *J* = 6 Hz), 7.74-7.79 (m, 2H), 7.42-7.63 (m, 3H), 5.55-5.59 (t, NH, *J* = 6 Hz), 3.99-4.09 (m, 2H), 3.84-3.89 (m, 0.23H), 3.71-3.76 (m, 0.73H), 2.99-3.08 (m, 0.69H), 2.85-2.95 (m, 0.21), 2.20 (s, 0.82H), 2.18 (s, 2.13H), 1.17-1.20 (d, 2.44H, *J* = 7.2 ), 1.11-1.16 (t, 0.89H, *J* = 7.2 Hz), 1.10-1.16 (t, 2H, *J* = 7.2 Hz), 1.01-1.03 (d, 0.71H, *J* = 7.5). $^{13}$C NMR (DMSO-$d_6$, 125.7 MHz): δ 209.37, 171.27, 165.61, 132.82, 131.24, 128.18,

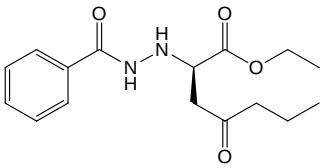
127.02, 63.69, 60.29, 46.65, 28.45, 13.74, 12.69. HRMS: calcd. for $C_{15}H_{20}N_2O_4$ $[M]^+$ 292.14231; found 293.14958 $[M+H]^+$, 315.13153 $[M+Na]^+$.

**Ethyl 2-(N`-benzoylhydrazino)-3-methyl-4-oxohexanoate (77d) (mixture of diastereomers):**



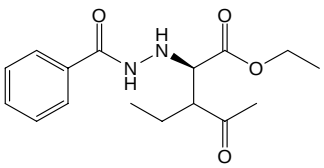
Yield 82% as a colourless dense oil. (Conditions for chromatography – ethyl acetate/n-hexane, 1:1, $R_f$ - 0.35). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ 10.06-10.08 (d, 0.01NH), 9.90-9.92 (d, 0.83NH, *J* = 6.4 Hz), 7.74-7.79 (m, 2H), 7.42-7.56 (m, 3H), 5.56-5.60 (t, NH, *J* = 6 Hz), 3.98-4.05 (m, 2H), 3.81-3.87 (m, 0.06H), 3.69-3.74 (m, 0.94H), 3.00-3.09 (m, 0.88H), 2.90-2.96 (m, 0.04H), 2.54-2.63 (m, 2H), 1.18-1.20 (d, 2.77H, *J* = 7.2 Hz), 1.08-1.13 (t, 3H, *J* = 7.2 Hz), 0.90-1.01 (d, 0.3H, *J* = 6.8 Hz), 0.89-0.94 (t, 3H, *J* = 7.2 Hz). $^{13}$C NMR (DMSO-$d_6$, 125.7 MHz): δ 212.00, 171.30, 165.59, 132.81, 131.24, 128.17, 127.03, 63.92, 60.26, 45.73, 33.68, 13.73, 13.22, 7.44. HRMS: calcd. for $C_{16}H_{22}N_2O_4$ $[M]^+$ 306.15796; found 307.16523 $[M+H]^+$, 329.14718 $[M+Na]^+$.

**Ethyl (2*R*)-2-(2-benzoylhydrazino)-4-oxoheptanoate (77e):**



Yield 74% as a white solid. (Conditions for chromatography – ethyl acetate/n-hexane, 2:1, $R_f$ - 0.4). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ 9.97-9.99 (d, NH, *J* = 6.3 Hz), 7.76-7.79 (m, 2H), 7.42-7.53 (m, 3H), 5.54-5.58 (t, NH, *J* = 6 Hz), 4.02-4.09 (q, 2H, *J* = 7.5 Hz), 3.90-3.92 (m, 1H), 2.77-2.96 (m, 2H), 2.41-2.45 (t, 2H, *J* = 6.9 Hz), 1.42-1.51 (m, 2H), 1.11-1.16 (t, 3H, *J* = 7.2 Hz), 0.81-0.9 (t, 3H, *J* = 7.5 Hz). $^{13}$C NMR (DMSO-$d_6$, 150.8 MHz): δ 207.90, 171.35, 165.67, 132.80, 131.43, 128.33, 127.13, 60.41, 58.15, 44.02, 42.57, 16.50, 13.89, 13.48. HRMS: calcd. for $C_{16}H_{22}N_2O_4$ $[M]^+$ 306.15796; found 307.16523 $[M+H]^+$, 329.14718 $[M+Na]^+$.

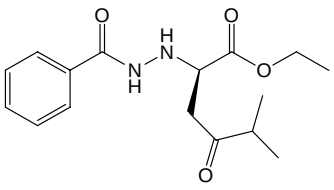
**Ethyl 2-(N`-benzoylhydrazino)-3-ethyl-4-oxopentanoate (77f) (mixture of diastereomers):**



Yield 6% as a dense yellowish oil. (Conditions for chromatography – ethyl acetate/n-hexane, 2:1, $R_f$ - 0.55). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ 10.07-10.09 (d, 0.24H, *J* = 6.6 Hz), 9.93-9.95 (d, 0.46H, *J* = 6.6 Hz), 7.75-7.78 (m, 2H), 7.42-7.56 (m, 3H), 5.55-5.65 (m, NH), 3.96-4.10 (m, 2H), 3.68-3.77 (m, 1H), 2.96-3.05 (m, 0.6H), 2.73-2.80 (m, 0.3H), 2.21 (s, 1.1H), 2.16 (s, 1.8H), 1.76-1.87 (m, 1H), 1.41-1.56 (m, 1H), 1.05-1.15 (m, 3H), 0.79-0.86 (m, 3H). $^{13}$C NMR (DMSO-$d_6$, 125.7 MHz): δ = 209.44, 171.42, 165.64, 132.86, 131.24, 128.19,

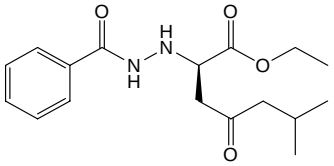
127.03, 61.88, 60.23, 52.86, 29.74, 20.22, 13.71, 10.46. HRMS: calcd. for $C_{16}H_{22}N_2O_4$ $[M]^+$ 306.15796; found 307.16523 $[M+H]^+$, 329.14718 $[M+Na]^+$.

**Ethyl (2*R*)-2-(2-benzoylhydrazino)-5-methyl-4-oxohexanoate (77g):**



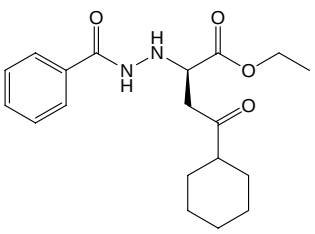
Yield 54% as a yellowish solid. (Conditions for chromatography – ethyl acetate/dichloromethane, 1:3, $R_f$ = 0.35 – 0.5). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ 9.98-10.00 (d, NH, *J* = 6.3 Hz), 7.76-7.80 (m, 2H), 7.42-7.52 (m, 3H), 5.56-5.60 (t, NH, *J* = 6 Hz), 4.01-4.08 (q, 2H, *J* = 7.2 Hz), 3.88-3.91 (m, 1H), 2.84-3.06 (m, 2H), 2.59-2.68 (m, 1H), 1.10-1.17 (t, 3H, *J* = 6.3 Hz), 1.01-1.03 (d, 3H, *J* = 7.2 Hz), 1.00-1.02 (d, 3H, *J* = 7.8 Hz). $^{13}$C NMR (DMSO-$d_6$, 150.8 MHz): δ 211.39, 171.34, 165.63, 132.81, 131.41, 128.33, 127.13, 60.38, 58.20, 40.48, 40.02, 17.88, 17.78, 13.89. HRMS: calcd. for $C_{16}H_{22}N_2O_4$ $[M]^+$ 306.15796; found 307.16523 $[M+H]^+$, 329.14718 $[M+Na]^+$.

**Ethyl (2*R*)-2-(2-benzoylhydrazino)-6-methyl-4-oxoheptanoate (77h):**



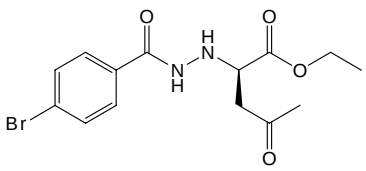
Yield 27% as a white solid. (Conditions for chromatography – ethyl acetate/n-hexane, 2:1, $R_f$ - 0.43). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ 9.98-10.00 (d, NH, *J* = 6.3 Hz), 7.77-7.80 (m, 2H), 7.42-7.53 (m, 3H), 5.54-5.58 (t, NH, *J* = 6 Hz), 4.01-4.09 (q, 2H, *J* = 7.5 Hz), 3.87-3.94 (m, 1H), 2.76-2.97 (m, 2H), 2.32-2.34 (d, 2H, *J* = 6.6 Hz), 1.99-2.05 (m, 1H), 1.11-1.15 (t, 3H, *J* = 7.2 Hz), 0.84-0.87 (d, 3H, *J* =9.6 Hz), 0.84-0.86 (d, 3H, *J* = 6.6 Hz). $^{13}$C NMR (DMSO-$d_6$, 125.7 MHz): δ = 207.63, 171.31, 165.65, 132.79, 131.41, 128.32, 127.12, 60.39, 58.09, 51.06, 42.99, 23.86, 22.30, 22.26, 13.87. ESI-MS (positive ion): *m/z* = 343.2 $[M+Na]^+$.

**Ethyl (2*R*)-2-(2-benzoylhydrazino)-4-cyclohexyl-4-oxobutanoate (77i):**



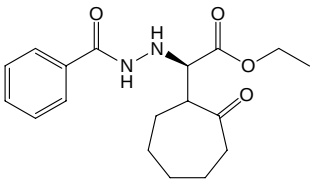
Yield 45% as a yellowish solid. (Conditions for chromatography – ethyl acetate/n-hexane/dichloromethane, 1:1:1, $R_f$ - 0.35). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ 9.97-10.00 (d, NH, *J* = 7.2 Hz), 7.77-7.80 (m, 2H), 7.43-7.53 (m, 3H), 5.55-5.59 (t, NH, *J* = 6.3 Hz), 4.01-4.08 (q, 2H, *J* = 7.2 Hz), 3.89-3.91 (m, 1H), 2.82-3.04 (m, 2H), 2.35-2.44 (m, 1H), 1.53-1.82 (m, 5H), 1.07-1.36 (m, 5H), 1.10-1.15 (t, 3H, *J* = 7.2 Hz). $^{13}$C NMR (DMSO-$d_6$, 125.7 MHz): δ 210.39, 171.19, 165.53, 132.77, 131.25, 128.19, 127.01, 60.23, 58.16, 49.52, 40.64, 27.75, 27.62, 25.35, 24.93, 24.89, 13.77. HRMS: calcd. for $C_{19}H_{26}N_2O_4$ $[M]^+$ 346.18926; found 347.19653 $[M+H]^+$, 369.17848 $[M+Na]^+$.

**Ethyl (2*R*)-2-[2-(4-bromobenzoyl)hydrazino]-4-oxopentanoate (77l):**



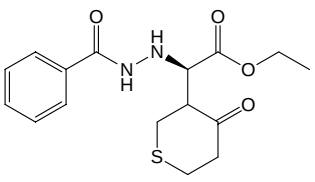
Yield 45% as a white solid. (Conditions for chromatography – ethyl acetate/n-hexane, 2:1, $R_f$ - 0.25). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ 10.08 (br, NH), 7.66-7.75 (m, 4H), 5.57 (br, NH), 4.01-4.08 (q, 2H, *J* = 6.9 Hz), 3.87-3.93 (m, 1H), 2.79-2.98 (m, 2H), 2.12 (s, 3H), 1.11-1.15 (t, 3H, *J* = 7.2 Hz). $^{13}$C NMR (DMSO-$d_6$, 150.8 MHz): δ 205.65, 171.15, 164.68, 131.89, 131.28, 129.14, 125.01, 60.32, 58.06, 43.32, 29.92, 13.78. HRMS: calcd. for $C_{14}H_{17}BrN_2O_4$ $[M]^+$ 356.03717; found 357.04445 $[M+H]^+$, 379.02639 $[M+Na]^+$, 395.00033 $[M+K]^+$.

**Ethyl (N`-benzoylhydrazino)(2-oxocycloheptyl)acetate (77m) (mixture of diastereomers):**



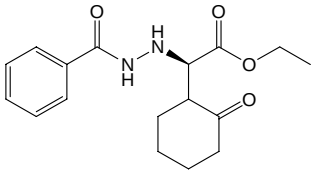
Yield 24% as a dense yellowish oil. (Conditions for chromatography – ethyl acetate/n-hexane, 1:2, $R_f$ - 0.34). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ 10.01-10.03 (d, 0.46NH, *J* = 6 Hz), 9.93-9.96 (d, 0.28NH *J* = 7.2 Hz), 7.74-7.81 (m, 2H), 7.43-7.53 (m, 3H), 5.62-5.66 (t, 0.35NH, *J* = 6.3 Hz) 5.46-5.50 (t, 0.48NH, *J* = 6 Hz), 4.05-4.15 (m, 0.83H), 3.93-4.02 (m, 1.23H), 3.93-3.97 (m, 0.43H), 3.56-3.60 (m, 0.55H), 3.05-3.12 (m, 0.56H), 2.77-2.85 (m, 0.35H), 2.30-2.58 (m, 2H), 1.23-1.92 (m, 8H), 1.14-1.19 (t, 1.46H, *J* = 7.2 Hz), 1.06-1.11 (t, 1.78H, *J* = 7.2 Hz). $^{13}$C NMR (DMSO-$d_6$, 150.8 MHz): δ 213.12, 171.15, 165.99, 133.24, 131.86, 128.77, 127.56, 65.05, 60.98, 53.06, 43.83, 29.65, 29.06, 26.27, 24.09, 14.37. HRMS: calcd. for $C_{18}H_{24}N_2O_4$ $[M]^+$ 332.17361; found 333.18088 $[M+H]^+$, 355.16283 $[M+Na]^+$.

**Ethyl (N`-benzoylhydrazino)(4-oxotetrahydro-2*H*-thiopyran-3-yl)acetate (77n) (mixture of diastereomers):**



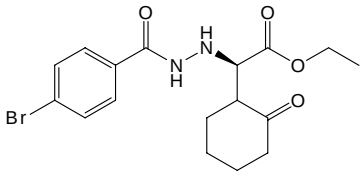
Yield 88% as a yellowish solid. (Conditions for chromatography – ethyl acetate/n-hexane, 2:1, $R_f$ - 0.52). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ 10.00-10.02 (d, 0.28H, *J* = 6 Hz), 9.93-9.95 (d, 0.54H, *J* = 6 Hz), 7.75-7.80 (m, 2H), 7.43-7.53 (m, 3H), 5.68-5.72 (t, 0.56H, *J* = 6.3 Hz), 5.54-5.58 (t, 0.28H, *J* = 6 Hz), 4.12-4.19 (m, 0.38H), 3.94-4.14 (m, 2H), 3.63-3.67 (dd, 0.51H, $J_1$ = 5.4 Hz, $J_2$ = 6 Hz), 3.36-3.42 (m, 0.52H), 2.88-3.24 (m, 4.33H), 2.55-2.79 (m, 2H), 1.12-1.17 (t, 1.3H, *J* = 5.7 Hz), 1.08-1.13 (t, 1.62H, *J* = 7.2 Hz) ppm. $^{13}$C NMR (DMSO-$d_6$, 125.7 MHz): δ 208.15, 170.87, 165.77, 132.90, 131.23, 128.18, 127.03, 61.53, 60.15, 52.95, 43.94, 32.16, 29.73, 13.68. HRMS: calcd. for $C_{16}H_{20}N_2SO_4$ $[M]^+$ 336.11438; found 337.12165 $[M+H]^+$, 359.10360 $[M+Na]^+$, 375.07754 $[M+K]^+$.

**Ethyl (N`-benzoylhydrazino)(2-oxocyclohexyl)acetate (77o) (mixture of diastereomers):**



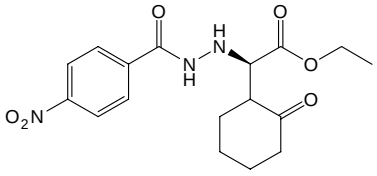
Yield 87% as a dense oil. (Conditions for chromatography – ethyl acetate/n-hexane/dichloromethane, 3:1:1, $R_f$ - 0.4). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ 9.91-9.93 (m, NH), 7.75-7.79 (m, 2H), 7.43-7.53 (m, 3H), 5.54-5.59 (m, NH), 3.95-4.11 (m, 2H), 3.94-3.96 (m, 0.41H), 3.51-3.56 (m, 0.54H), 2.89-2.96 (m, 1H), 1.49-2.47 (m, 8H), 1.11-1.16 (t, 1.23H, *J* = 7.2 Hz ), 1.07-1.12 (t, 1.57H, *J* = 7.2 Hz). $^{13}$C NMR (DMSO-$d_6$, 125.7 MHz): δ 210.25, 171.42, 165.43, 132.94, 131.15, 128.14, 127.02, 61.91, 60.18, 50.62, 41.44, 28.68, 26.29, 24.16, 13.73. HRMS: calcd. for $C_{17}H_{22}N_2O_4$ $[M]^+$ 318.15796; found 319.16523 $[M+H]^+$, 341.14718 $[M+Na]^+$.

**Ethyl [N`-(4-bromobenzoyl)hydrazino](2-oxocyclohexyl)acetate (77p) (mixture of diastereomers):**



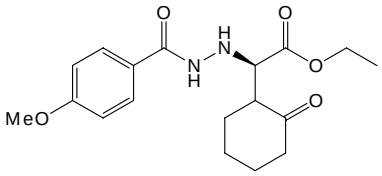
Yield 89% as a dense yellowish oil. (Conditions for chromatography – ethyl acetate/n-hexane/dichloromethane, 2:1:1, $R_f$ - 0.4). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ 10.03 (br, NH), 7.65-7.74 (m, 4H), 5.57-5.60 (m, NH), 3.92-4.11 (m, 2.5H), 3.51-3.56 (m, 0.51H), 2.81-2.97 (m, 1H), 2.18-2.46 (m, 3H), 1.43-2.05 (m, 5H), 1.11-1.16 (t, 1.20H, *J* = 7.2 Hz), 1.06-1.11 (t, 1.50H, *J* = 7.2 Hz). $^{13}$C NMR (DMSO-$d_6$, 125.7 MHz): δ 210.23, 171.37, 164.49, 132.03, 131.23, 129.13, 124.88, 61.82, 59.94, 50.59, 41.43, 30.05, 27.18, 24.15, 13.74. HRMS: calcd. for $C_{17}H_{21}BrN_2O_4$ $[M]^+$ 396.06847; found 397.07575 $[M+H]^+$, 419.05769 $[M+Na]^+$, 435.03163 $[M+K]^+$.

**Ethyl [N`-(4-nitrobenzoyl)hydrazino](2-oxocyclohexyl)acetate (77q) (mixture of diastereomers):**



Yield 85% as an orange solid. (Conditions for chromatography – ethyl acetate/dichloromethane, 1:1, $R_f$ – 0.34). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ 10.31 (br, NH), 8.29-8.33 (m, 2H), 7.97-8.03 (m, 2H), 5.68-5.71 (m, NH), 3.93-4.11 (m, 2.6H), 3.55-3.58 (m, 0.43H), 2.86-2.98 (m, 1H), 2.19-2.49 (m, 2H), 1.47-2.04 (m, 6H), 1.11-1.16 (t, 1.39H, *J* = 7.2 Hz), 1.07-1.12 (t, 1.40H, *J* = 7.2 Hz). $^{13}$C NMR (DMSO-$d_6$, 125.7 MHz): δ 209.63, 170.88, 163.64, 149.01, 138.54, 128.51, 123.45, 61.85, 60.28, 50.96, 41.45, 28.95, 26.40, 23.77, 13.87. HRMS: calcd. for $C_{17}H_{21}N_3O_6$ $[M]^+$ 363.14304 found 364.15031 $[M+H]^+$, 386.13226 $[M+Na]^+$.

**Ethyl [N`-(4-methoxybenzoyl)hydrazino](2-oxocyclohexyl)acetate (77r) (mixture of diastereomers):**



Yield 83% as a yellowish solid. (Conditions for chromatography – ethyl acetate/dichloromethane, 1:1, $R_f$ – 0.47). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ 9.77-9.82 (m, NH), 7.74-7.78 (m, 2H), 6.96-7.00 (m, 2H), 5.49-5.53 (m, NH), 3.92-4.11 (m, 2.3H), 3.80 (s, 3H), 3.48-3.53 (m, 0.5H), 2.80-2.96 (m, 1H), 2.22-2.46 (m, 2H), 1.47-2.05 (m, 6H), 1.06-1.16 (m, 3H). $^{13}$C NMR (DMSO-$d_6$, 125.7 MHz): δ 210.29, 171.50, 165.11, 161.58, 128.86, 125.09, 113.43, 62.01, 59.91, 55.25, 50.68, 41.47, 30.15, 27.23, 24.19, 13.75. HRMS: calcd. for $C_{18}H_{24}N_2O_5$ $[M]^+$ 348.16852 found 349.17580 $[M+H]^+$, 371.15774 $[M+Na]^+$.

## Determination of the Absolute configuration of **77p-hydrazone**

Initially, racemic mixture of compound **77p** (60mg) was separated by preparative HPLC on IA-column (n-hexane/2-propanol = 90:10, flow rate 18 ml/min). Then the separated oil-like products **B** (14mg) and **C** (9mg) (Diagram 3) were converted into solid products **B** and **C**, respectively (Scheme 22). Crystallization of product **B** from ethyl acetate/n-hexane was unsuccessful. However, crystallization of product **C** (**77p-hydrazone**) (8mg) under same conditions gave very good needle-like crystals which was analysed by X-Ray crystallography.

**Scheme 22.**

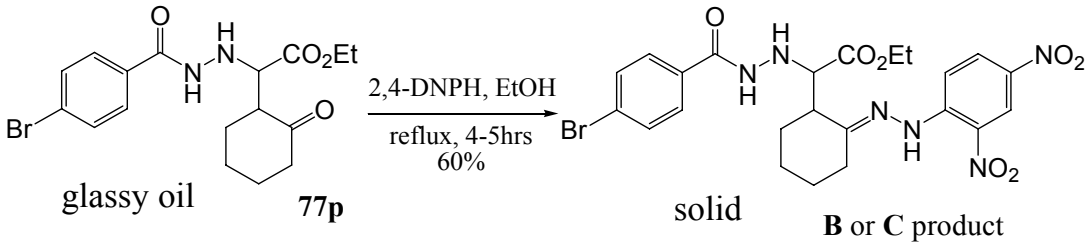
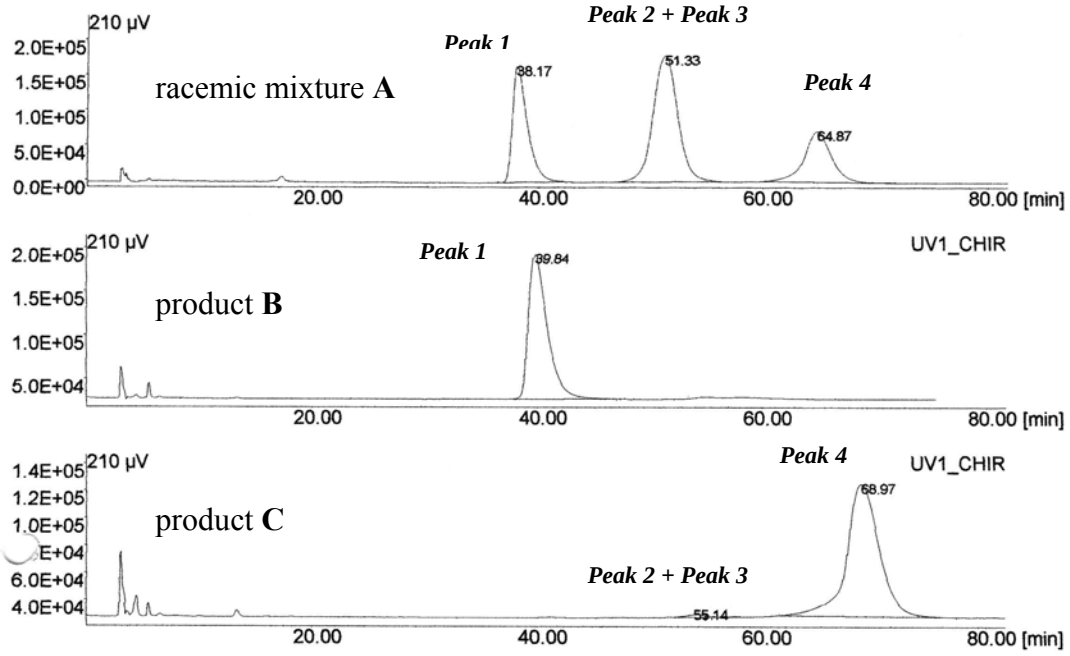
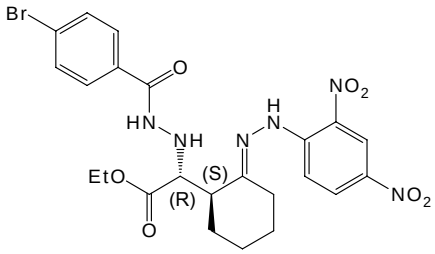



**Diagram 3.** HPLC measurements on analytical IA-column (n-hexane/2-propanol = 90:10, flow rate 1 ml/min, λ = 210nm)



**Ethyl (2*R*)-[2-(4-bromobenzoyl)hydrazino]{(1*S*,2*E*)-2-[(2,4-dinitrophenyl) hydrazono]cyclohexyl}ethanoate (77p-hydrazone):**




To a solution of **77p** 9 mg (0.023mmol) in 1mL of EtOH, 2,4-DNPH 7 mg (0.035mmol) was added. The resulting mixture refluxed at 90 $^{o}$C for 4-5 h (TLC control). The solvent was evaporated and residue was purified by silica gel flash chromatography (ethyl acetate/n-hexane, 1:1, $R_f$ - 0.4). Yield 60% as a yellow-orange solid. $^{1}$H NMR (DMSO-$d_6$, 300 MHz): δ 11.00 (br, NH), 10.14-10.16 (d, NH, *J* = 6.3 Hz), 8.85-8.86 (d, 1H, *J* = 2.7 Hz), 8.29-8.32 (m, 1H), 8.11-8.14 (m, 1H), 7.66-7.76 (m, 1H), 5.82-5.87 (t, NH, *J* = 6.9 Hz), 4.06-4.13 (q, 2H, *J* = 7.5 Hz), 4.05-4.10 (m, 1H), 2.95-2.97 (m, 1H), 2.74-2.78 (m, 1H), 2.33-2.35 (m, 1H), 1.60-1.98 (m 6H), 1.11-1.16 (t, 3H, *J* = 7.2 Hz). $^{13}$C NMR (DMSO-$d_6$, 125.7 MHz): δ 171.45, 164.01, 161.10, 144.86, 136.82, 131.95, 131.29, 129.62, 129.18, 129.08, 124.94, 122.89, 116.42, 62.88, 60.26, 45.68, 29.40, 26.24, 25.39, 23.44, 13.93. HRMS: calcd. for $C_{23}H_{25}BrN_6O_7$ $[M]^+$ 576.09681; found 577.10409 $[M+H]^+$.

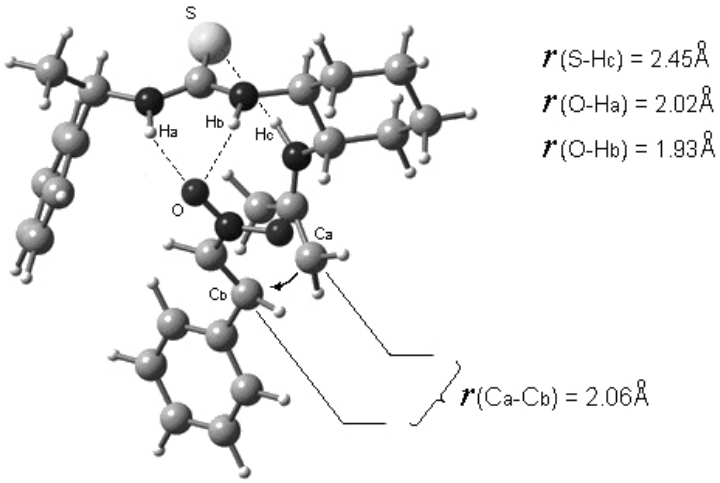
# 5. Molecular Geometries of Calculated Transition States for the Michael-addition of Acetone to the *trans*-β-nitrostyrene

**Gaussian Reference:**

**Gaussian 03** - Gaussian 03, Revision C.02, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V.G.Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A.Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, and J. A. Pople, Gaussian, Inc., Wallingford CT, 2004.

## Transition State structure for the formation of R isomer

(see Figure 18 in Main Part)




```
Stoichiometry    C26H34N4O2S
Framework group  C1[X(C26H34N4O2S)]
Standard orientation:
 ---------------------------------------------------------------------
```

| Center Number | Atomic Number | Atomic Type | Coordinates (Angstroms) X | Y | Z |
|---|---|---|---|---|---|
| 1 | 6 | C | 3.367605 | 0.114339 | -0.139752 |
| 2 | 6 | C | 2.658180 | -1.207091 | -0.523843 |
| 3 | 6 | C | 3.644002 | -2.169717 | -1.213791 |
| 4 | 6 | C | 4.835226 | -2.472690 | -0.292493 |
| 5 | 6 | C | 5.535355 | -1.181344 | 0.155327 |
| 6 | 6 | C | 4.547650 | -0.194835 | 0.796832 |
| 7 | 1 | H | 3.123304 | -3.094432 | -1.490359 |
| 8 | 1 | H | 2.287007 | -1.660918 | 0.403046 |
| 9 | 1 | H | 3.736900 | 0.602384 | -1.047535 |
| 10 | 1 | H | 4.477765 | -3.019283 | 0.591370 |
| 11 | 1 | H | 5.543663 | -3.133414 | -0.806780 |
| 12 | 1 | H | 6.340279 | -1.412118 | 0.863304 |
| 13 | 1 | H | 6.010421 | -0.705351 | -0.714671 |
| 14 | 1 | H | 4.153771 | -0.617029 | 1.732203 |
| 15 | 1 | H | 5.049249 | 0.745332 | 1.051833 |
| 16 | 1 | H | 3.997870 | -1.711323 | -2.148147 |
| 17 | 7 | N | 2.452825 | 1.048709 | 0.499799 |
| 18 | 1 | H | 2.164316 | 0.813198 | 1.455051 |
| 19 | 6 | C | 1.703330 | 1.988129 | -0.134388 |
| 20 | 16 | S | 1.917439 | 2.394839 | -1.787867 |
| 21 | 7 | N | 0.777752 | 2.570469 | 0.664041 |
| 22 | 1 | H | 0.588401 | 2.086487 | 1.544459 |
| 23 | 6 | C | -0.119445 | 3.665780 | 0.288624 |
| 24 | 1 | H | 0.279968 | 4.065823 | -0.644909 |
| 25 | 6 | H | -0.065261 | 4.761700 | 1.364320 |
| 26 | 1 | H | -0.718687 | 5.596212 | 1.088973 |
| 27 | 1 | H | -0.393900 | 4.387251 | 2.340827 |
| 28 | 1 | H | 0.958215 | 5.135272 | 1.469683 |
| 29 | 6 | C | -1.541638 | 3.177131 | 0.024642 |
| 30 | 6 | C | -2.088806 | 3.275606 | -1.260322 |
| 31 | 6 | C | -2.333862 | 2.642302 | 1.051831 |
| 32 | 6 | C | -3.398543 | 2.861586 | -1.514739 |
| 33 | 1 | H | -1.480424 | 3.677759 | -2.066083 |
| 34 | 6 | C | -3.641932 | 2.225071 | 0.800927 |
| 35 | 1 | H | -1.931076 | 2.548931 | 2.057957 |
| 36 | 6 | C | -4.180450 | 2.338086 | -0.484088 |
| 37 | 1 | H | -3.807550 | 2.952674 | -2.517784 |
| 38 | 1 | H | -4.242591 | 1.818086 | 1.610150 |
| 39 | 1 | H | -5.203769 | 2.025897 | -0.676676 |
| 40 | 6 | C | 0.413845 | -1.663561 | -1.535901 |
| 41 | 6 | C | 0.127047 | -2.793238 | -0.736915 |
| 42 | 1 | H | 0.951213 | -3.257182 | -0.206810 |
| 43 | 1 | H | -0.585518 | -3.494401 | -1.157964 |
| 44 | 6 | C | -0.575039 | -1.180361 | -2.564673 |
| 45 | 1 | H | -1.585585 | -1.512703 | -2.317639 |
| 46 | 1 | H | -0.567090 | -0.087767 | -2.642371 |
| 47 | 1 | H | -0.317931 | -1.589421 | -3.550222 |
| 48 | 8 | O | 0.702450 | 0.393149 | 2.648493 |
| 49 | 7 | N | 0.459855 | -0.765154 | 2.149635 |
| 50 | 8 | O | 1.285453 | -1.708029 | 2.309385 |
| 51 | 6 | C | -2.392116 | -2.496797 | 0.456148 |
| 52 | 6 | C | -3.232385 | -1.505711 | -0.079478 |
| 53 | 6 | C | -2.902380 | -3.799226 | 0.588851 |
| 54 | 6 | C | -4.536733 | -1.811793 | -0.466223 |
| 55 | 1 | H | -2.874783 | -0.487164 | -0.193572 |
| 56 | 6 | C | -4.207218 | -4.104582 | 0.205455 |
| 57 | 1 | H | -2.267910 | -4.577596 | 1.006941 |
| 58 | 6 | C | -5.030636 | -3.110516 | -0.326523 |
| 59 | 1 | H | -5.168746 | -1.028011 | -0.875213 |
| 60 | 1 | H | -4.581363 | -5.117734 | 0.325815 |

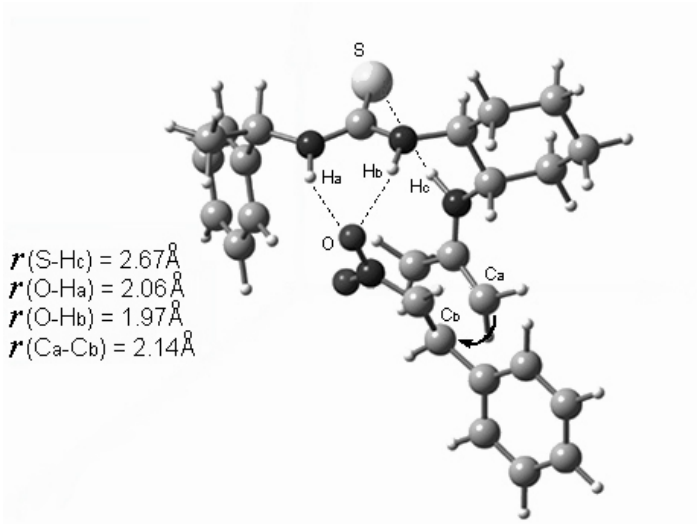
| | | | | | |
|---|---|---|---|---|---|
| 61 | 1 | H | -6.048091 | -3.344887 | -0.627270 |
| 62 | 6 | C | -0.678074 | -0.949364 | 1.424790 |
| 63 | 1 | H | 1.546188 | -0.021411 | -1.882975 |
| 64 | 1 | H | -1.266612 | -0.056772 | 1.277943 |
| 65 | 7 | N | 1.497848 | -0.912230 | -1.375198 |
| 66 | 6 | C | -0.995974 | -2.222090 | 0.894727 |
| 67 | 1 | H | -0.537603 | -3.038212 | 1.446279 |

Rotational constants (GHZ): 0.1466836 0.1125824 0.0789263
Standard basis: 6-31G(d) (6D, 7F)

E(RB+HF-LYP) = -1778.78984403 a.u.
1 imaginary frequencies ignored.
Zero-point vibrational energy 1498080.1 (Joules/Mol)
358.04973 (Kcal/Mol)
Zero-point correction= 0.570589 (Hartree/Particle)
Thermal correction to Energy= 0.601877
Thermal correction to Enthalpy= 0.602821
Thermal correction to Gibbs Free Energy= 0.506238
Sum of electronic and zero-point Energies= -1778.219255
Sum of electronic and thermal Energies= -1778.187967
Sum of electronic and thermal Enthalpies= -1778.187023
Sum of electronic and thermal Free Energies= -1778.283606

## Transition State structure for the formation of S isomer

(see Figure 19 in Main Part)




Stoichiometry C26H34N4O2S
Framework group C1[X(C26H34N4O2S)]
Standard orientation:

| Center Number | Atomic Number | Atomic Type | Coordinates (Angstroms) X | Y | Z |
|---|---|---|---|---|---|
| 1 | 6 | C | -0.037473 | 2.785852 | 0.057032 |
| 2 | 6 | C | 0.992041 | 1.964414 | -0.758146 |
| 3 | 6 | C | 1.748385 | 2.889404 | -1.729939 |
| 4 | 6 | C | 2.475463 | 3.997986 | -0.951651 |
| 5 | 6 | C | 1.509869 | 4.789699 | -0.056281 |
| 6 | 6 | C | 0.691888 | 3.869287 | 0.866227 |
| 7 | 1 | H | 2.459504 | 2.306394 | -2.327227 |
| 8 | 1 | H | 1.711150 | 1.523329 | -0.058428 |

| | | | | | |
|---|---|---|---|---|---|
| 9 | 1 | H | -0.720737 | 3.272918 | -0.645866 |
| 10 | 1 | H | 3.261786 | 3.545092 | -0.329634 |
| 11 | 1 | H | 2.984293 | 4.672051 | -1.651128 |
| 12 | 1 | H | 2.063523 | 5.522947 | 0.542548 |
| 13 | 1 | H | 0.818463 | 5.362012 | -0.690294 |
| 14 | 1 | H | 1.354070 | 3.394678 | 1.606360 |
| 15 | 1 | H | -0.049511 | 4.446449 | 1.429256 |
| 16 | 1 | H | 1.029057 | 3.329452 | -2.433749 |
| 17 | 7 | N | -0.873328 | 1.944097 | 0.895588 |
| 18 | 1 | H | -0.412303 | 1.420318 | 1.642094 |
| 19 | 6 | C | -2.124600 | 1.509741 | 0.544555 |
| 20 | 16 | S | -2.974391 | 2.125478 | -0.800826 |
| 21 | 7 | N | -2.623704 | 0.555670 | 1.360134 |
| 22 | 1 | H | -1.957670 | 0.092070 | 1.981592 |
| 23 | 6 | C | -3.989586 | 0.029849 | 1.307409 |
| 24 | 1 | H | -4.636338 | 0.873520 | 1.051112 |
| 25 | 6 | C | -4.357955 | -0.473999 | 2.713107 |
| 26 | 1 | H | -5.388389 | -0.841808 | 2.720764 |
| 27 | 1 | H | -3.706848 | -1.302554 | 3.016500 |
| 28 | 1 | H | -4.265463 | 0.330716 | 3.450774 |
| 29 | 6 | C | -4.211933 | -1.060416 | 0.261406 |
| 30 | 6 | C | -5.384697 | -1.052957 | -0.501844 |
| 31 | 6 | C | -3.304326 | -2.114527 | 0.096970 |
| 32 | 6 | C | -5.654305 | -2.078024 | -1.409674 |
| 33 | 1 | H | -6.086877 | -0.229339 | -0.393450 |
| 34 | 6 | C | -3.571066 | -3.137957 | -0.815462 |
| 35 | 1 | H | -2.378118 | -2.127164 | 0.663979 |
| 36 | 6 | C | -4.746661 | -3.126247 | -1.569140 |
| 37 | 1 | H | -6.568145 | -2.051868 | -1.998014 |
| 38 | 1 | H | -2.857038 | -3.949779 | -0.933088 |
| 39 | 1 | H | -4.951938 | -3.925012 | -2.277497 |
| 40 | 6 | C | 0.841562 | -0.326243 | -1.761991 |
| 41 | 6 | C | 2.192464 | -0.653004 | -1.540686 |
| 42 | 1 | H | 2.907821 | 0.149418 | -1.403640 |
| 43 | 1 | H | 2.572367 | -1.493539 | -2.111540 |
| 44 | 6 | C | -0.096048 | -1.312561 | -2.410112 |
| 45 | 1 | H | -0.185154 | -1.093940 | -3.482197 |
| 46 | 1 | H | 0.286082 | -2.329718 | -2.301878 |
| 47 | 1 | H | -1.095530 | -1.271626 | -1.967940 |
| 48 | 8 | O | -0.137729 | -1.746020 | 0.867171 |
| 49 | 7 | N | 0.539276 | -0.985305 | 1.603800 |
| 50 | 8 | O | -0.004271 | -0.294826 | 2.531530 |
| 51 | 6 | C | 3.980652 | -1.701527 | 0.311232 |
| 52 | 6 | C | 4.839497 | -0.667576 | 0.721532 |
| 53 | 6 | C | 4.551565 | -2.891969 | -0.166876 |
| 54 | 6 | C | 6.222166 | -0.826684 | 0.668861 |
| 55 | 1 | H | 4.423530 | 0.270836 | 1.078447 |
| 56 | 6 | C | 5.935408 | -3.053844 | -0.217139 |
| 57 | 1 | H | 3.900740 | -3.700998 | -0.490167 |
| 58 | 6 | C | 6.776069 | -2.021297 | 0.201049 |
| 59 | 1 | H | 6.869929 | -0.016364 | 0.992240 |
| 60 | 1 | H | 6.356180 | -3.986752 | -0.582149 |
| 61 | 1 | H | 7.854805 | -2.143870 | 0.160716 |
| 62 | 6 | C | 1.891189 | -0.868110 | 1.408426 |
| 63 | 1 | H | -0.692191 | 0.989100 | -1.588101 |
| 64 | 1 | H | 2.380037 | -0.163253 | 2.063961 |
| 65 | 7 | N | 0.307636 | 0.853257 | -1.428388 |
| 66 | 6 | C | 2.504075 | -1.581037 | 0.368684 |
| 67 | 1 | H | 1.954161 | -2.458129 | 0.046004 |

---

Rotational constants (GHZ): 0.1716137 0.0831420 0.0672950
Standard basis: 6-31G(d) (6D, 7F)

```
E(RB+HF-LYP) =  -1778.78734688 a.u.
 1 imaginary frequencies ignored.
Zero-point vibrational energy    1496144.0 (Joules/Mol)
                                 357.58699 (Kcal/Mol)
Zero-point correction=                           0.569851 (Hartree/Particle)
Thermal correction to Energy=                    0.601389
Thermal correction to Enthalpy=                  0.602333
Thermal correction to Gibbs Free Energy=         0.505324
Sum of electronic and zero-point Energies=          -1778.217496
Sum of electronic and thermal Energies=             -1778.185958
Sum of electronic and thermal Enthalpies=           -1778.185014
Sum of electronic and thermal Free Energies=        -1778.282023
```

# E. References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[89] Crystal data of 3: $C_{17}H_{21}N_3OS$, Mr = 315.43, crystal size 0.5x0.15x0.05 mm3, monoclinic, space group $P2_1$, $a$ = 9.863(2), $b$ = 23.217(2), $c$ = 15.423(2) A° , $\beta$ = 97.31(3)°, $V$ = 3503.0(9) A° $^3$, $T$ = 100(2) K, $Z$ = 8, $D_x$ = 1.196 Mg m$^{-3}$, $\mu$ = 1.675 mm$^{-1}$. A total of 47,774 reflections were collected, final $R_1$ ($I > 2\sigma$ ($I$)) = 0.0319, $wR_2$ (all data) = 0.0833 for 839 parameters and 9899 reflections, GOF = 1.025, $\theta$ = 2.89–59.56°. Absolute structure parameter = -0.005(8), maximum and minimum residual electron density 0.332 and -0.209 eA°$^{-3}$. Data were collected on a Bruker three-circle diffractometer (CuKa radiation, $k$ = 1.54178 A°) equipped with a *SMART 6000 area detector.* The structure was solved by using direct methods and refined by full-matrix least squares on $F^2$ for all data. All non-hydrogen atoms were refined anisotropically. H atoms at nitrogens were located in the difference Fourier map and refined isotropically with distance restraints. All other H atoms were placed at calculated positions and refined using a riding model. (G. M. Sheldrick, *SHELXS97* and *SHELXL97*, University of Göttingen, Germany, **1997**). Data were collected on a nonmerohedrally twinned crystal. The fractional contribution of the second twin domain was refined to 0.0609(6). CCDC-266193 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/data_request/cif (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; e-mail: deposit@ccdc.cam.ac.uk).

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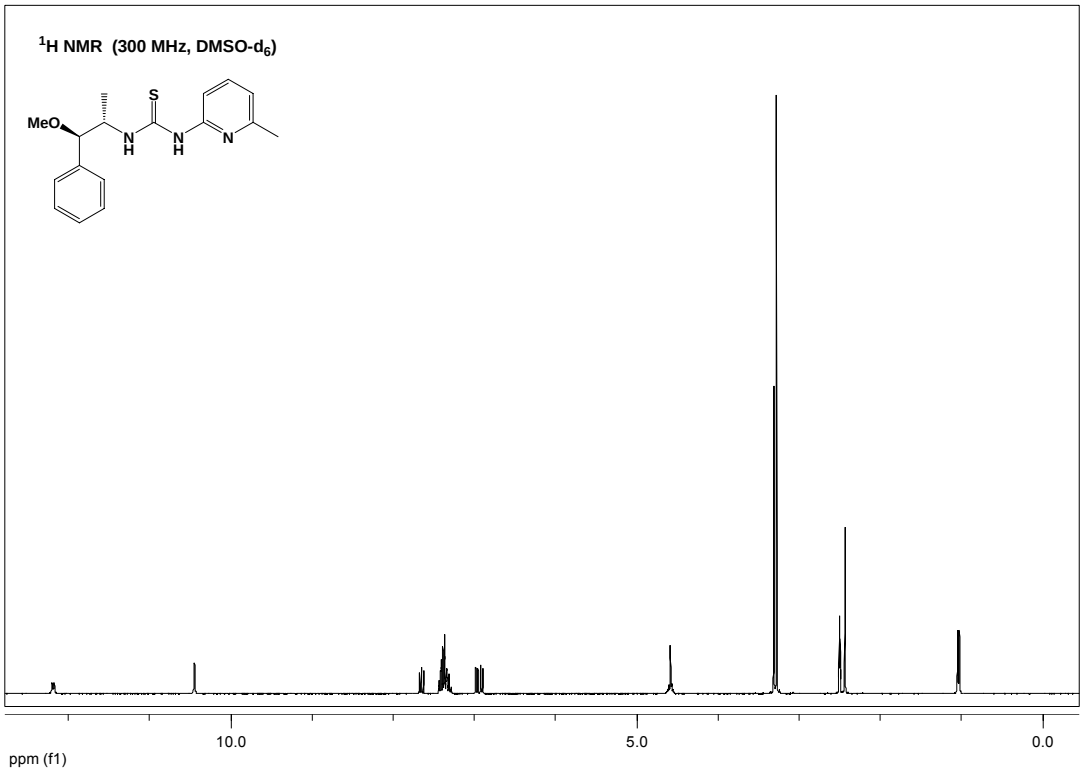
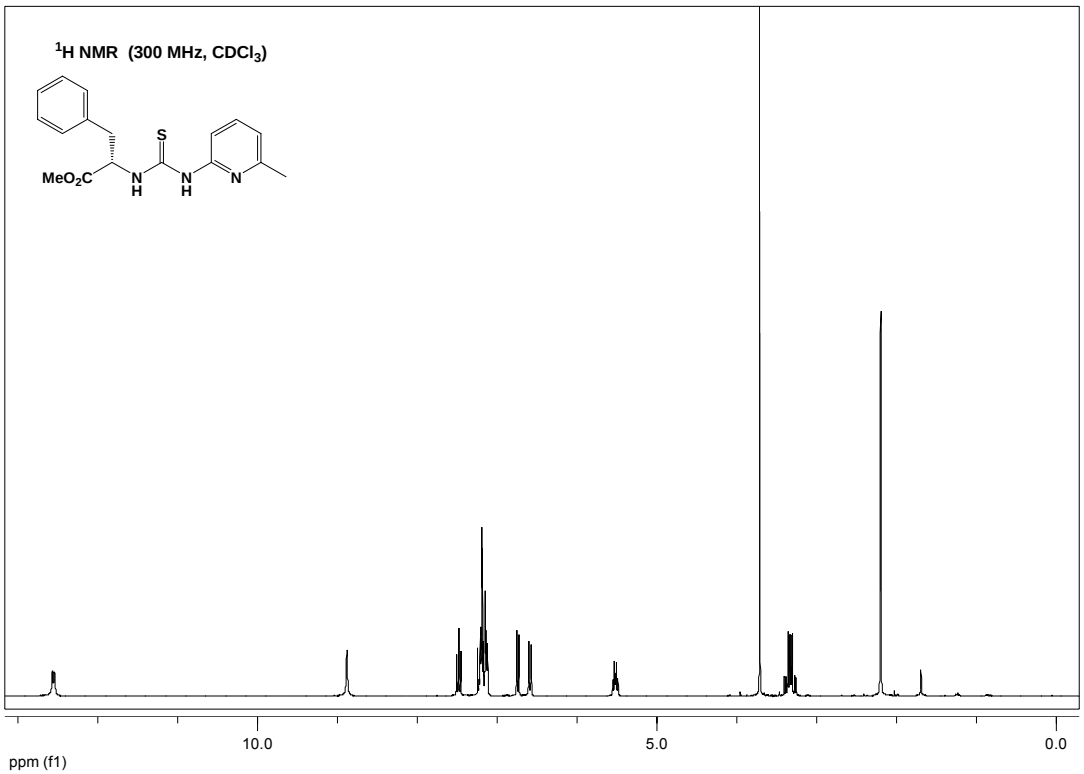
## F. Spectra

1. $^{1}$H NMR for new compounds
2. HPLC spectra of new compounds described in Chapter 4

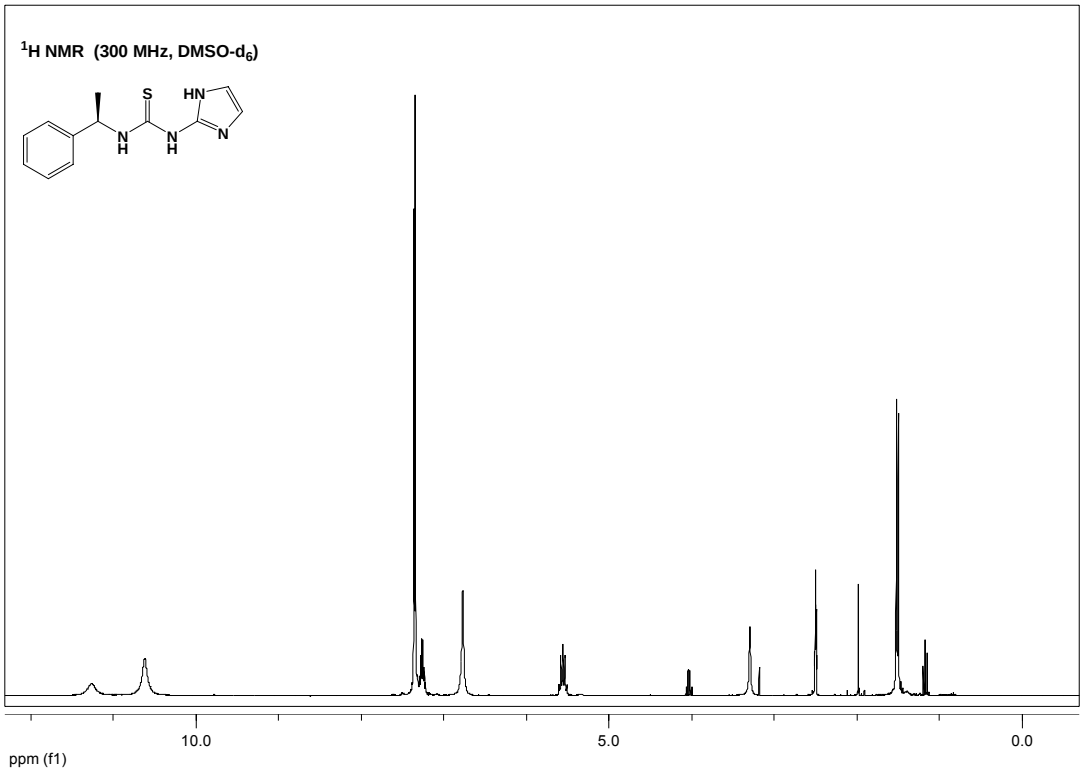
# 1. $^1$H NMR spectra for new compounds



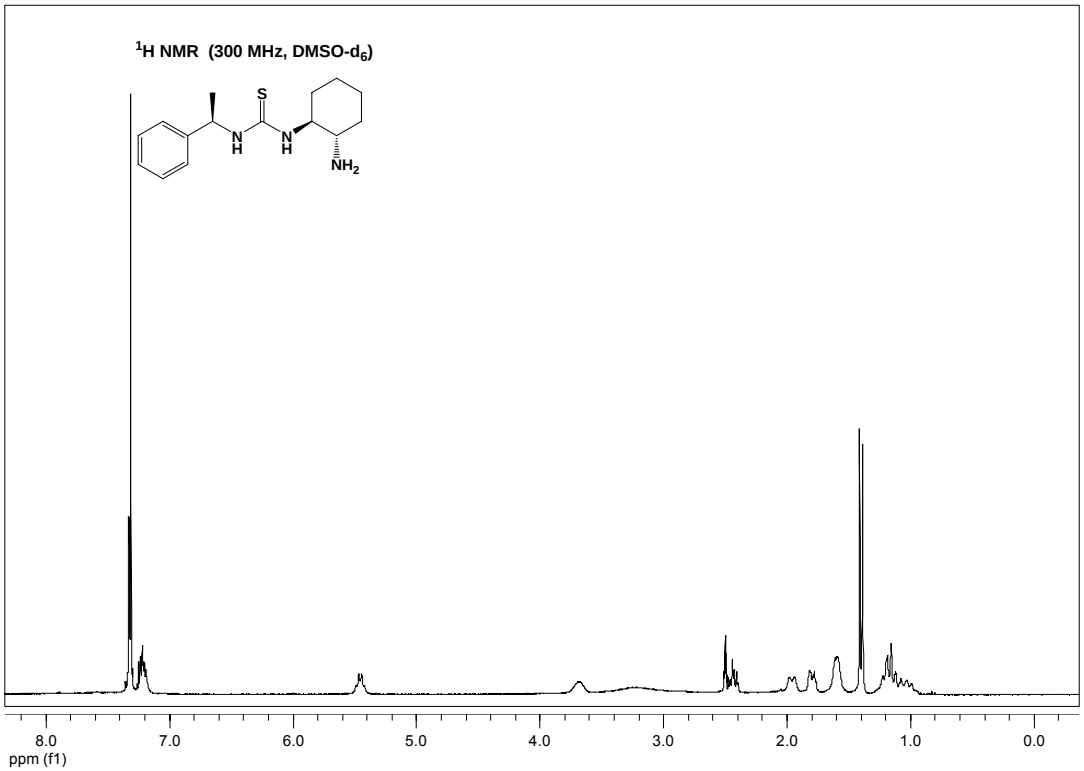

*N*-[(1*S*,2*R*)-2-methoxy-1-methyl-2-phenylethyl]-*N*'-(6-methylpyridin-2-yl)thiourea (**34**)



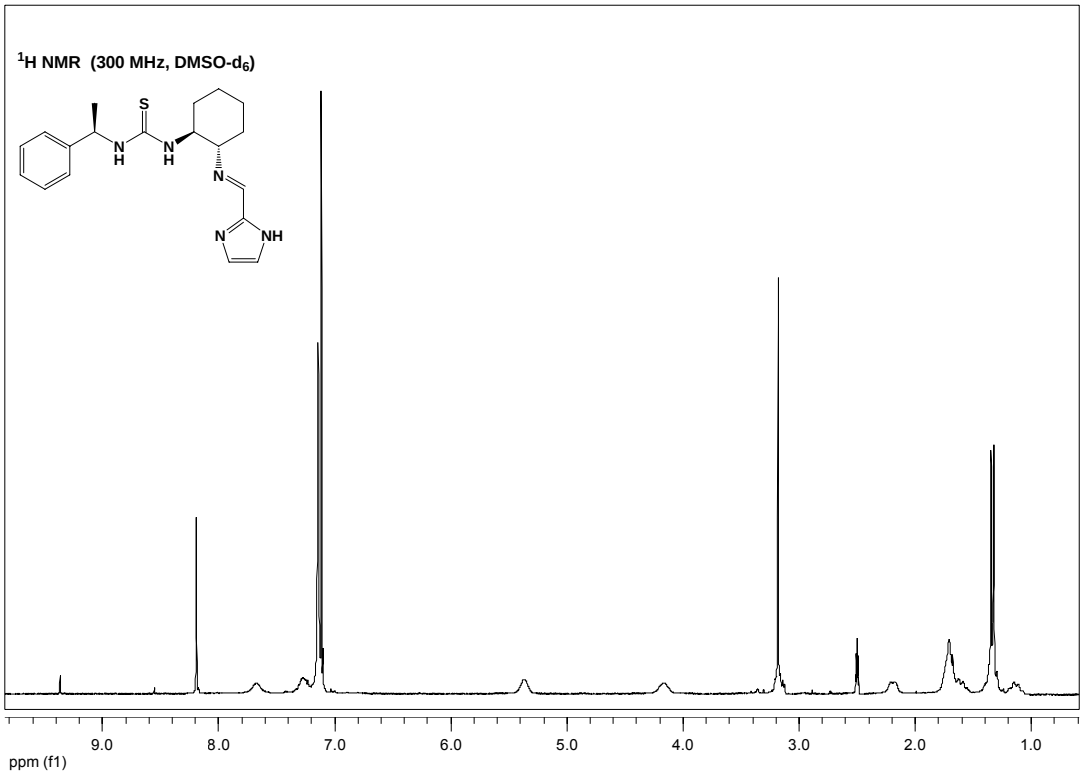

Methyl *N*-{[(6-methylpyridin-2-yl)amino]carbonothioyl}-(*S*)-phenylalaninate (**35**)



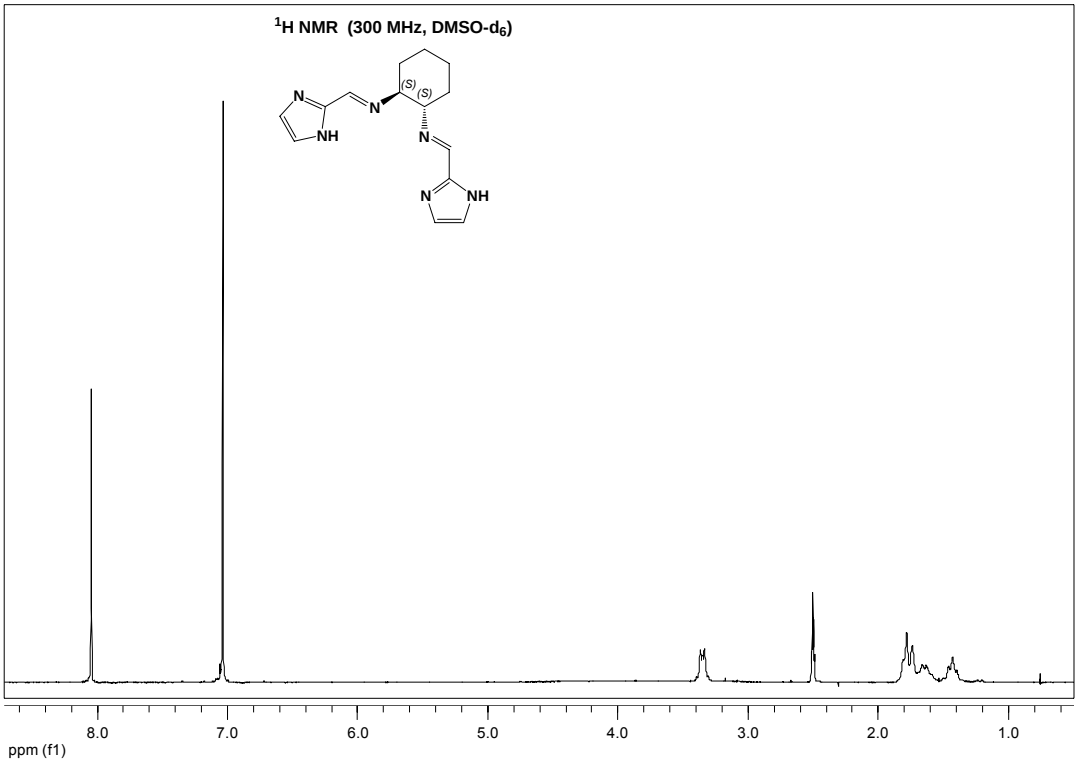

*N*-(1*H*-imidazol-2-yl)-*N*'-[(1*R*)-phenylethyl]thiourea (**36**)



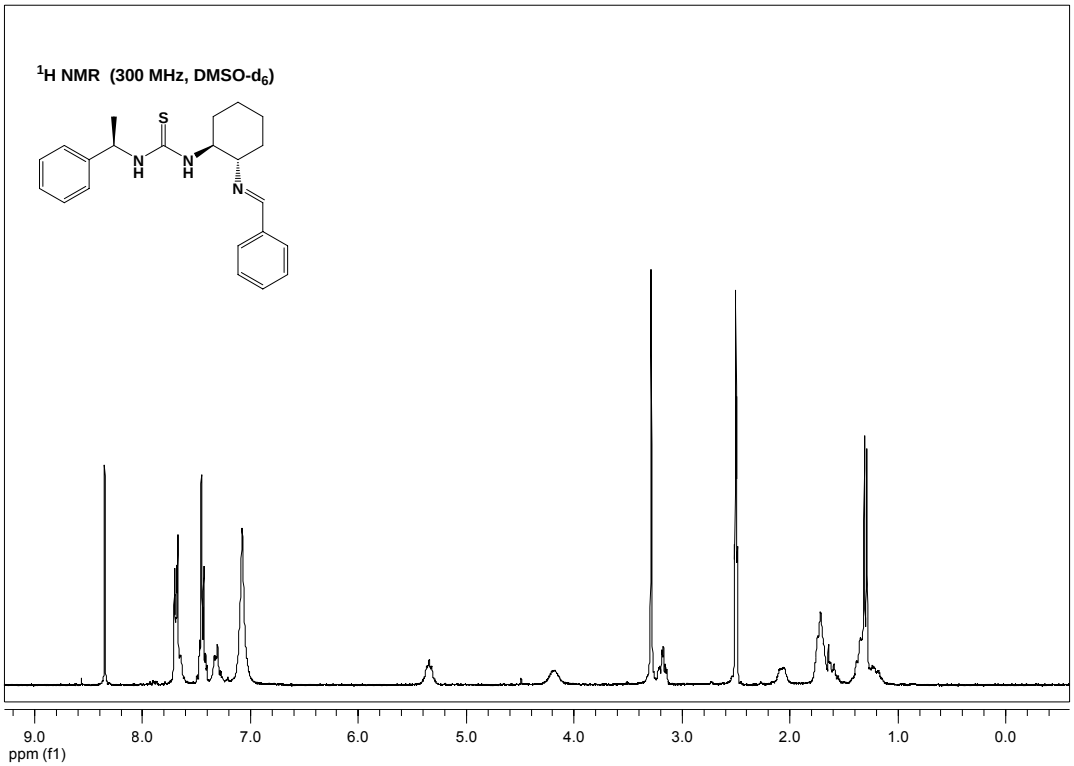

*N*-[(1*S*,2*S*)-2-aminocyclohexyl]-*N*'-[(1*R*)-1-phenylethyl]thiourea (**56**)



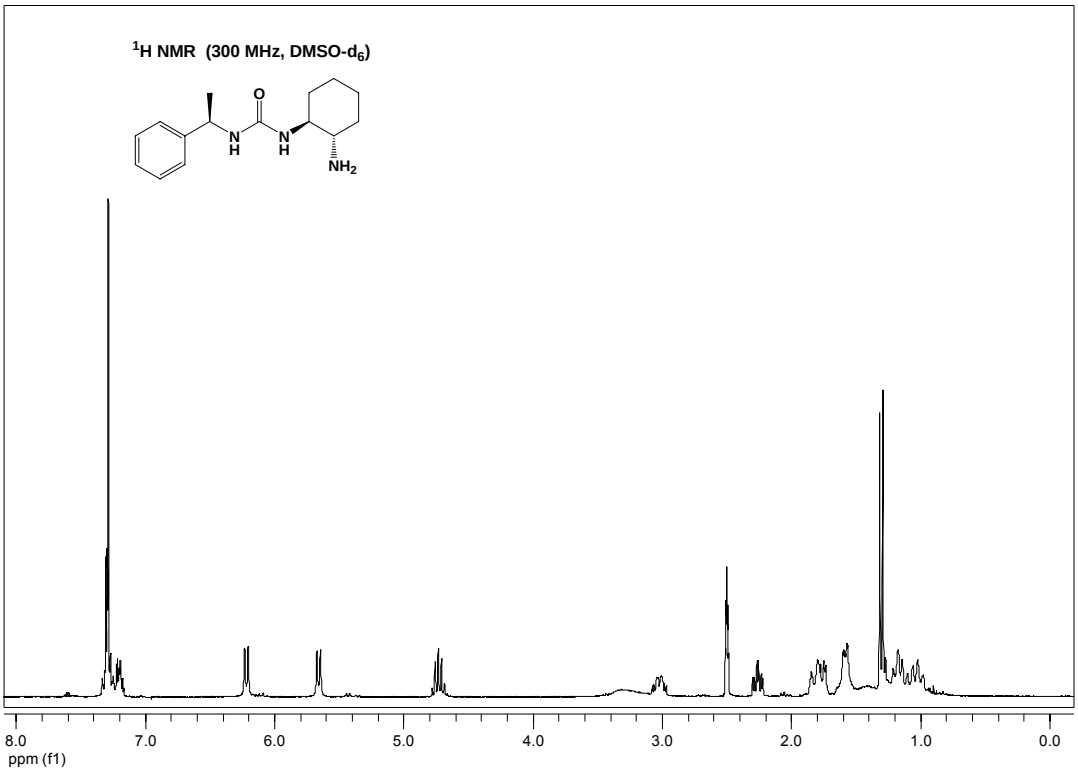

*N*-((1*S*,2*S*)-2-{[(1*E*)-1*H*-imidazol-2-ylmethylidene]amino}cyclohexyl)-*N*'-[(1*R*)-1-phenylethyl]thiourea (**60**)



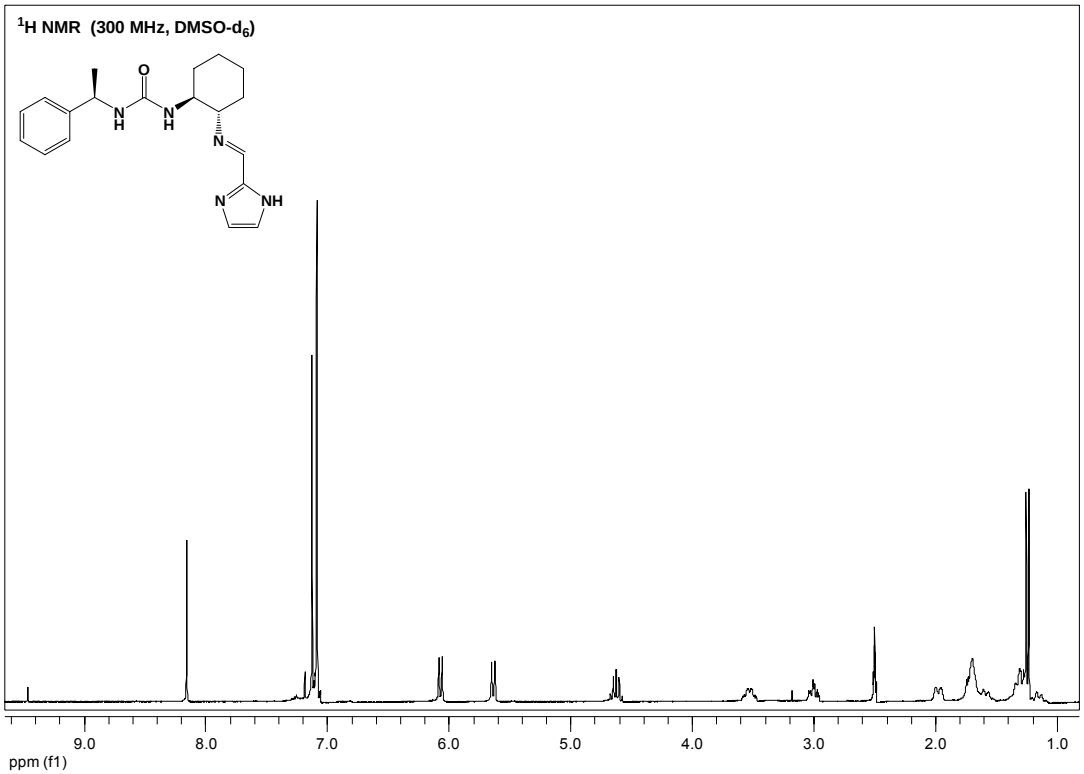

(1*S*,2*S*)-*N*,*N*'-bis[(1*E*)-1*H*-imidazol-2-ylmethylidene]cyclohexane-1,2-diamine (**66**)



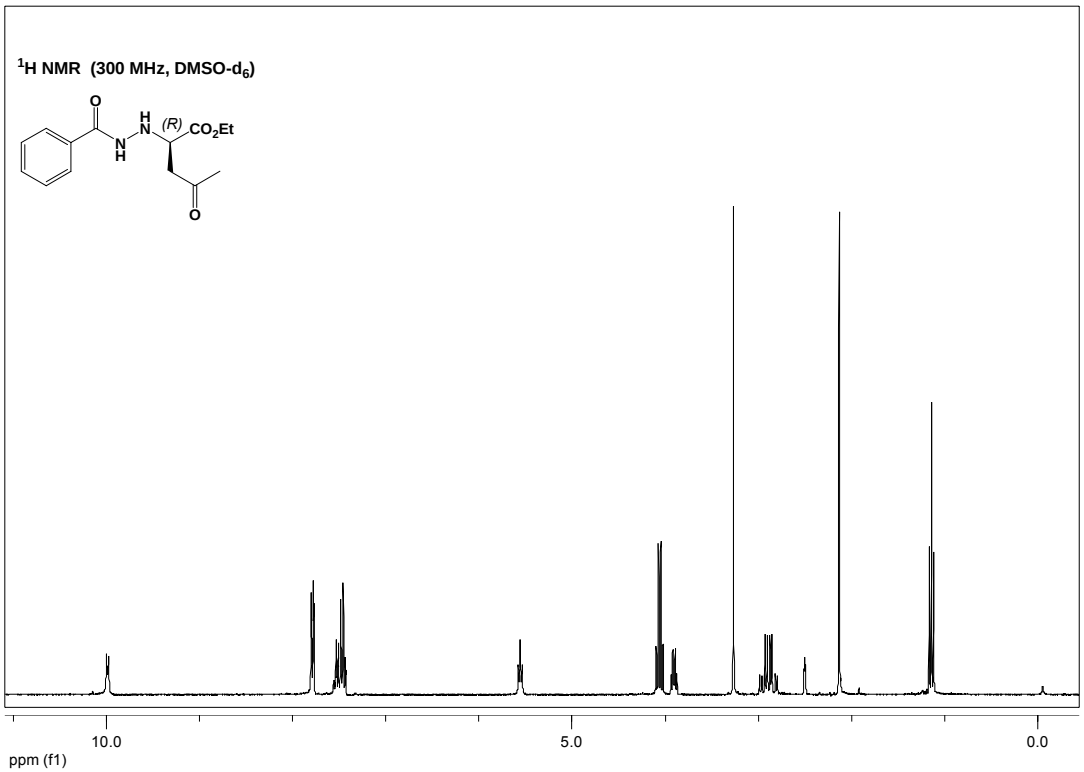

*N*-[(1*R*)-1-phenylethyl]-*N*'-((1*S*,2*S*)-2-{[(1*E*)-phenylmethylidene]amino}cyclohexyl) thiourea (**67**)



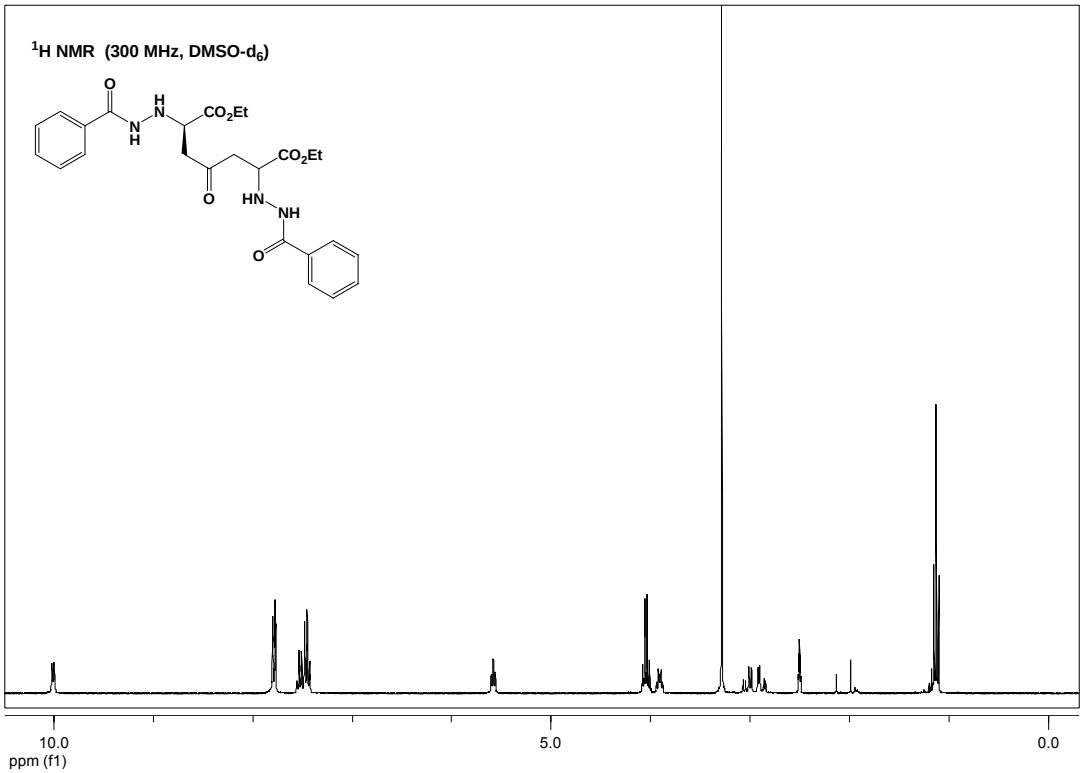

*N*-[(1*S*,2*S*)-2-aminocyclohexyl]-*N*'-[(1*R*)-1-phenylethyl]urea (**56a**)



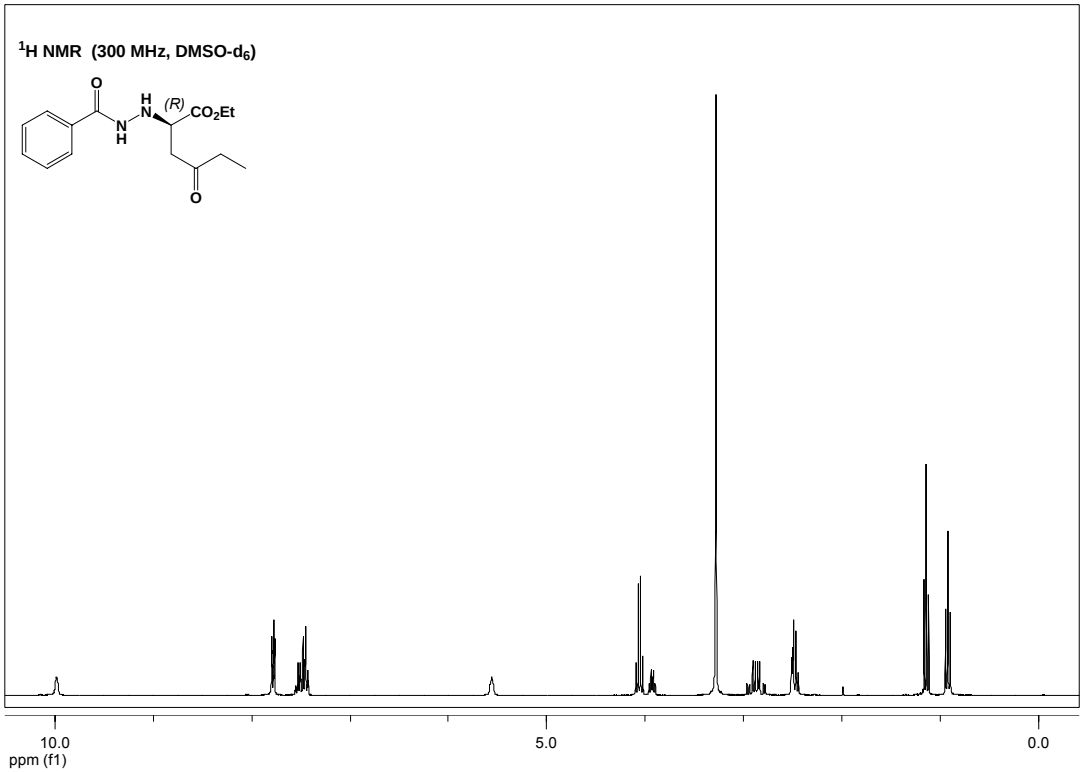

*N*-((1*S*,2*S*)-2-{[(1*E*)-1*H*-imidazol-2-ylmethylidene]amino}cyclohexyl)-*N*'-[(1*R*)-1-phenylethyl]urea (**60a**)



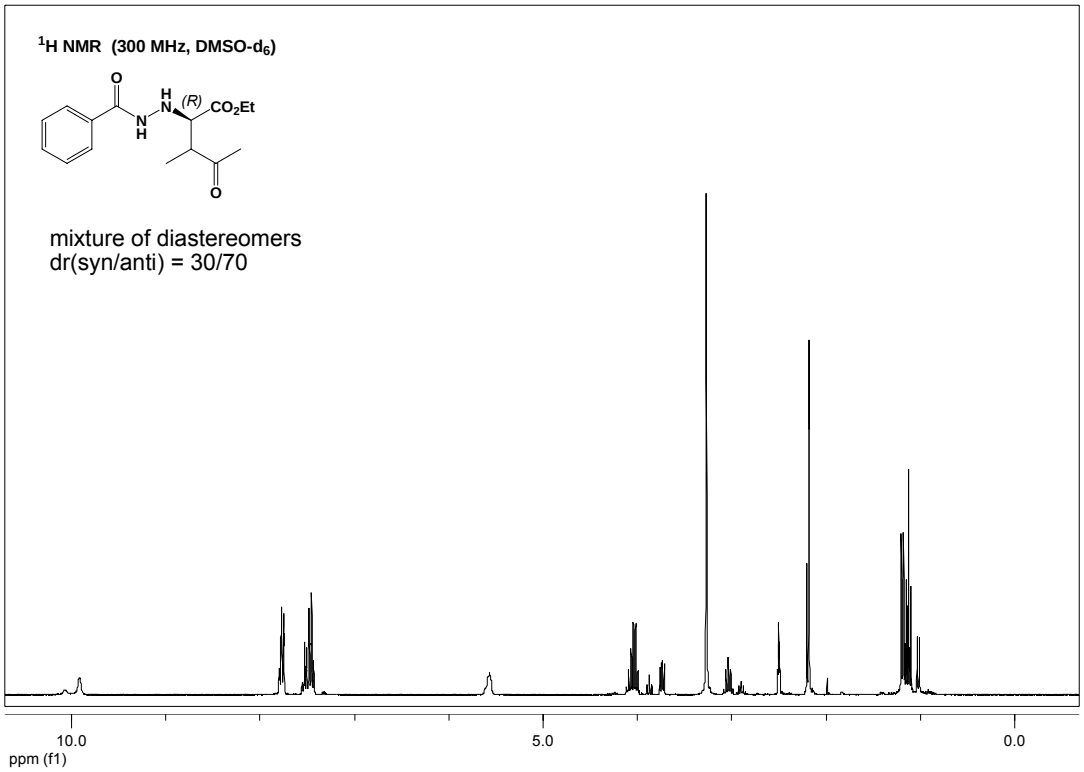

Ethyl (2*R*)-2-(2-benzoylhydrazino)-4-oxopentanoate (**77a**)



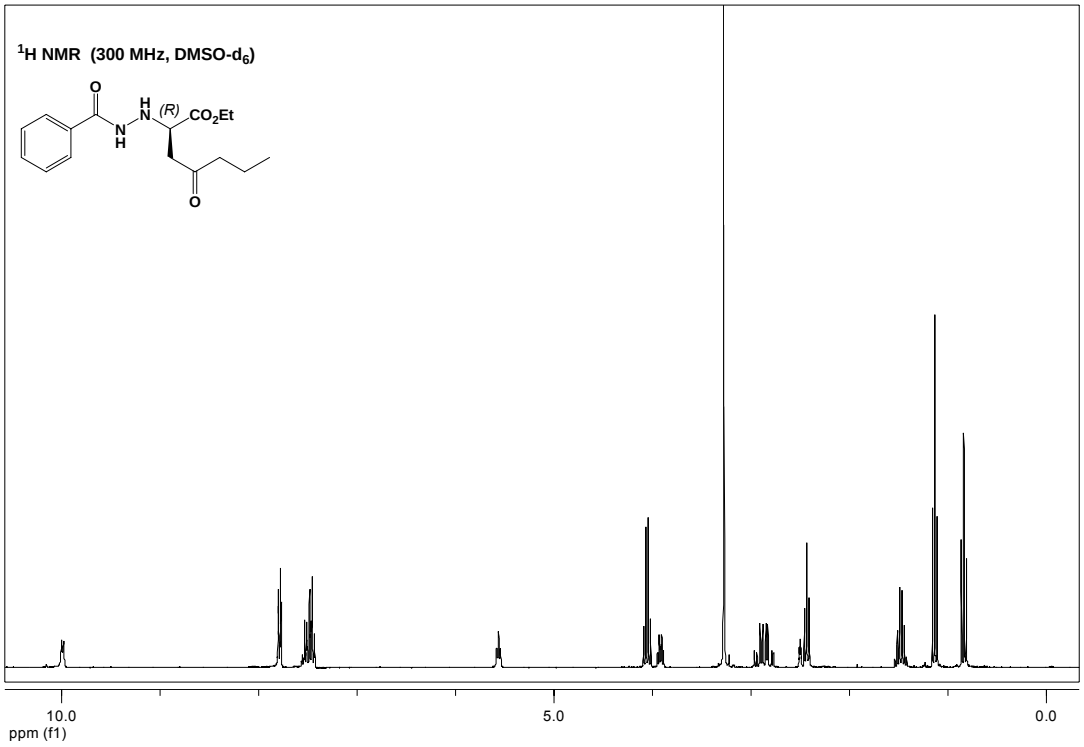

Diethyl (2*R*)-2,6-bis(2-benzoylhydrazino)-4-oxoheptanedioate (**77a'**)



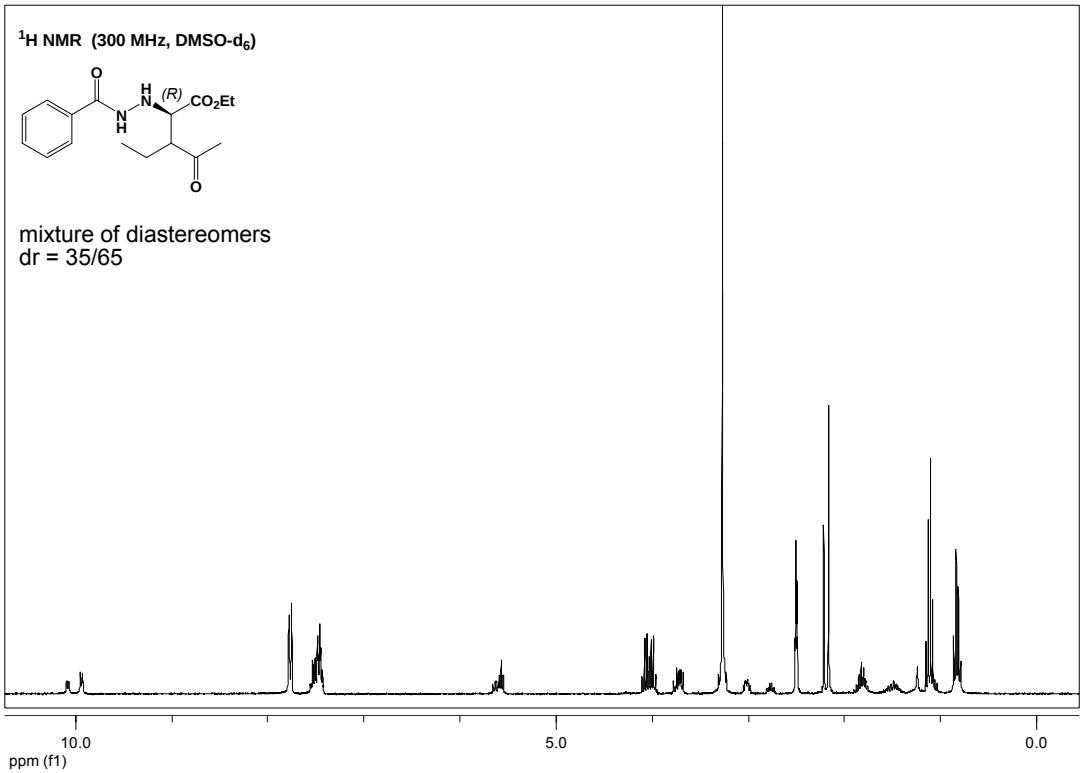

Ethyl (2*R*)-2-(2-benzoylhydrazino)-4-oxohexanoate (**77b**)



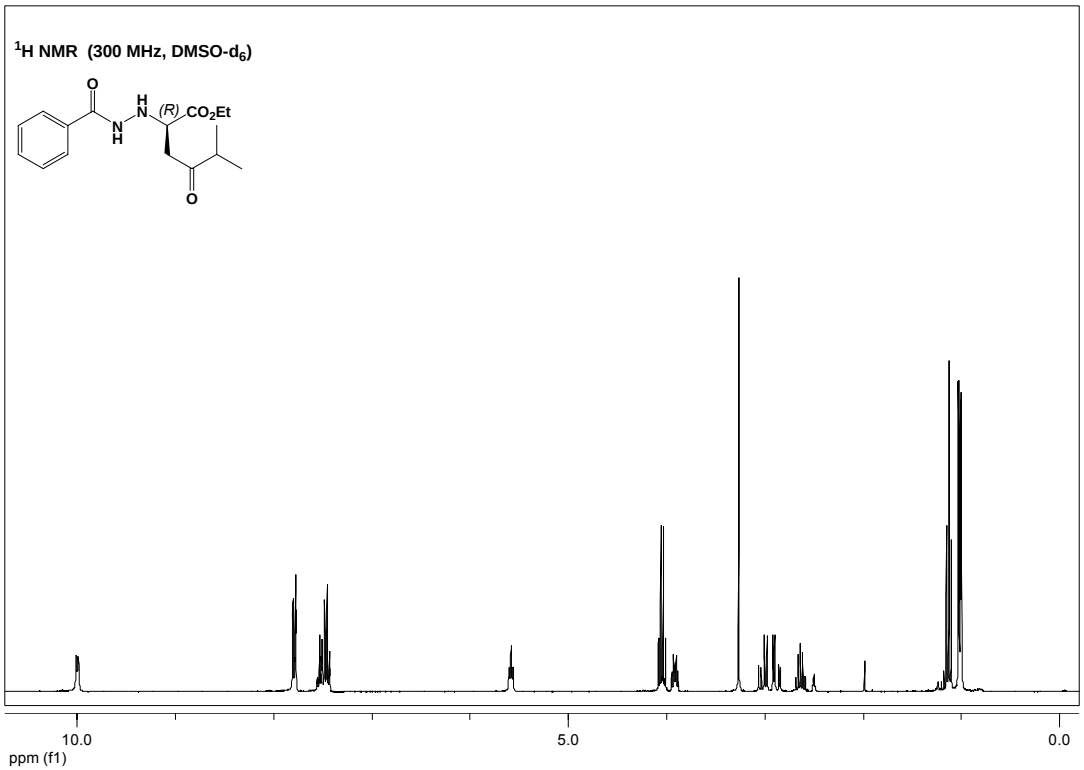

Ethyl 2-( N`-benzoylhydrazino)-3-methyl-4-oxopentanoate (**77c**)



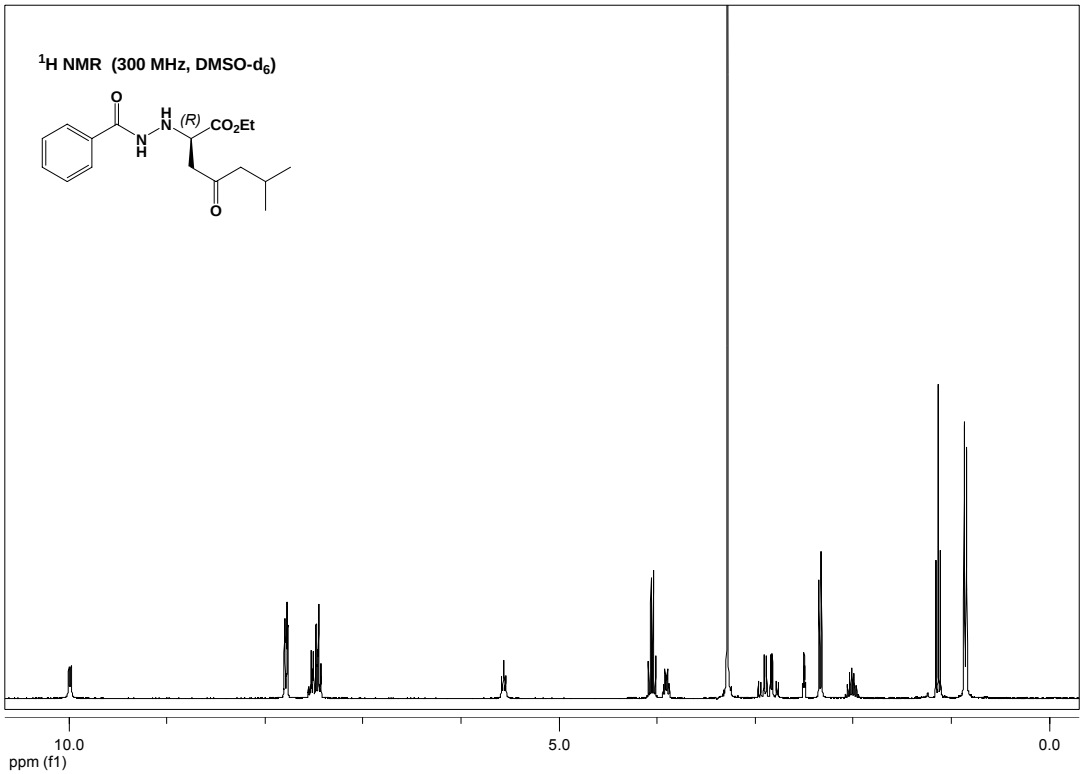

Ethyl (2*R*)-2-(2-benzoylhydrazino)-4-oxoheptanoate(**77e**)



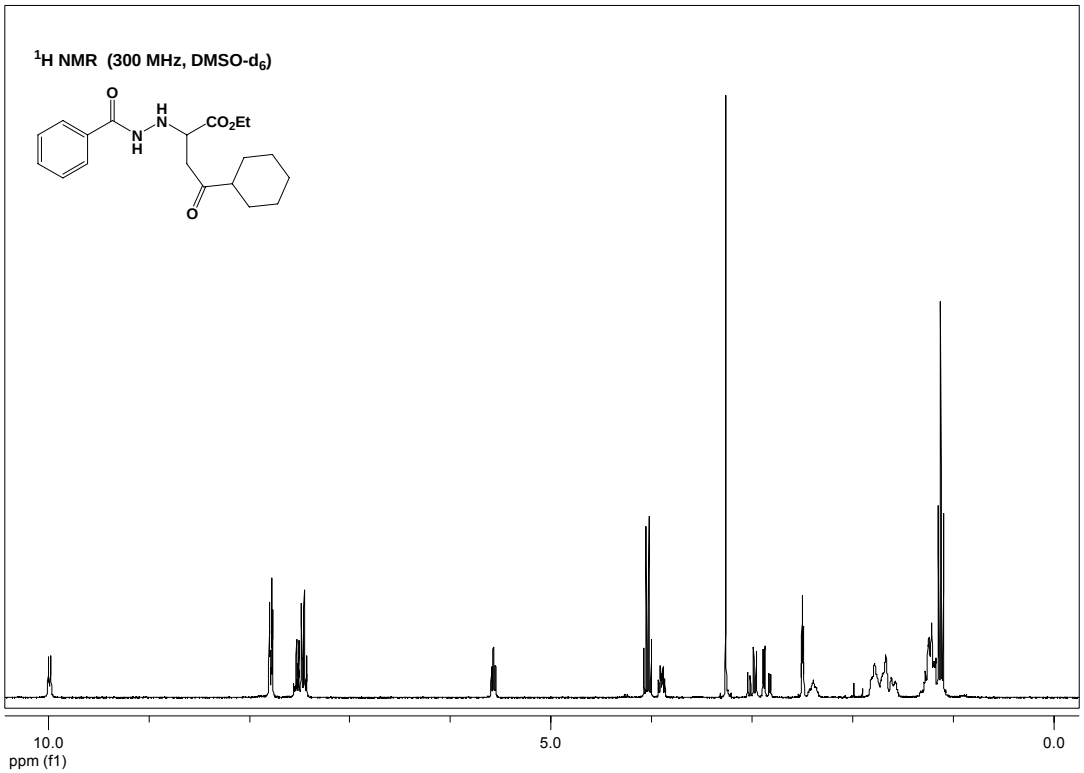

Ethyl 2-(N`-benzoylhydrazino)-3-ethyl-4-oxopentanoate (**77f**)



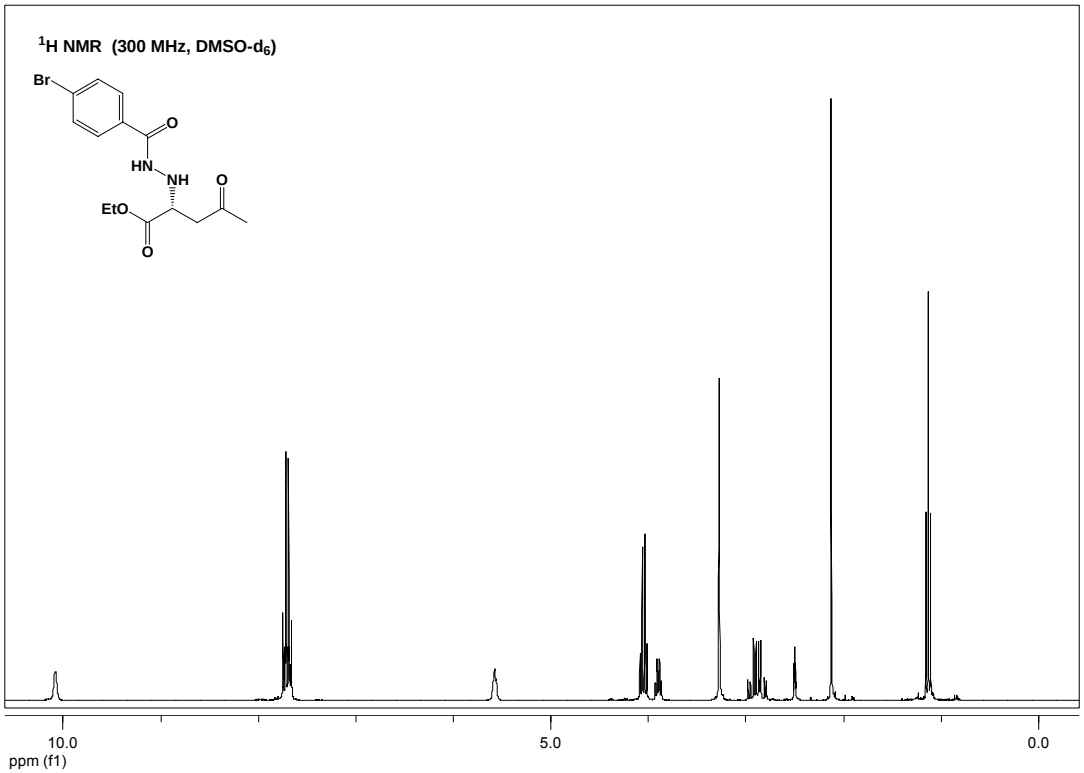

Ethyl (2*R*)-2-(2-benzoylhydrazino)-5-methyl-4-oxohexanoate (**77g**)



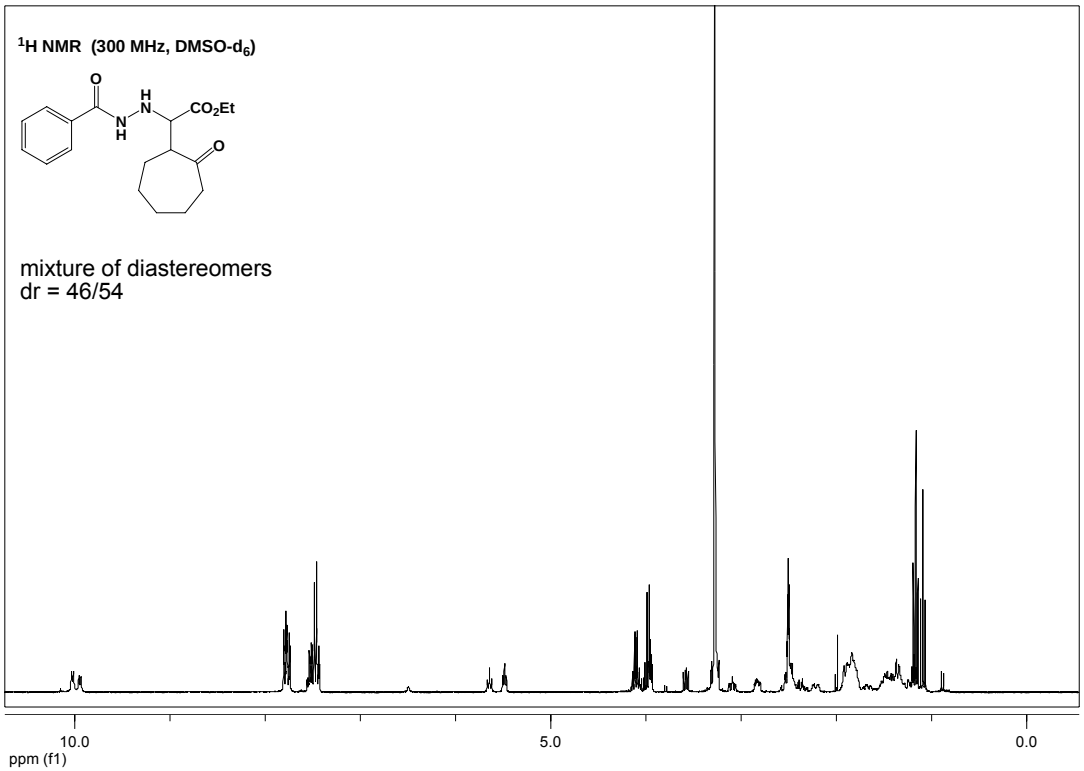

Ethyl (2*R*)-2-(2-benzoylhydrazino)-6-methyl-4-oxoheptanoate (**77h**)



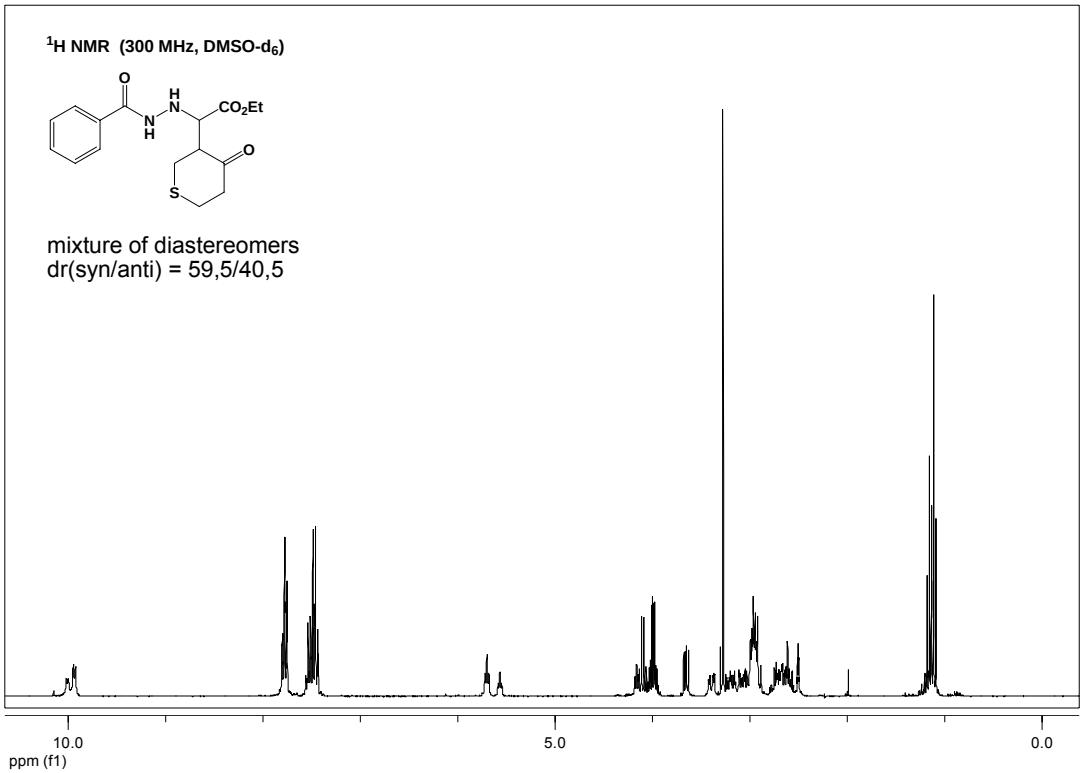

Ethyl (2*R*)-2-(2-benzoylhydrazino)-4-cyclohexyl-4-oxobutanoate (**77i**)



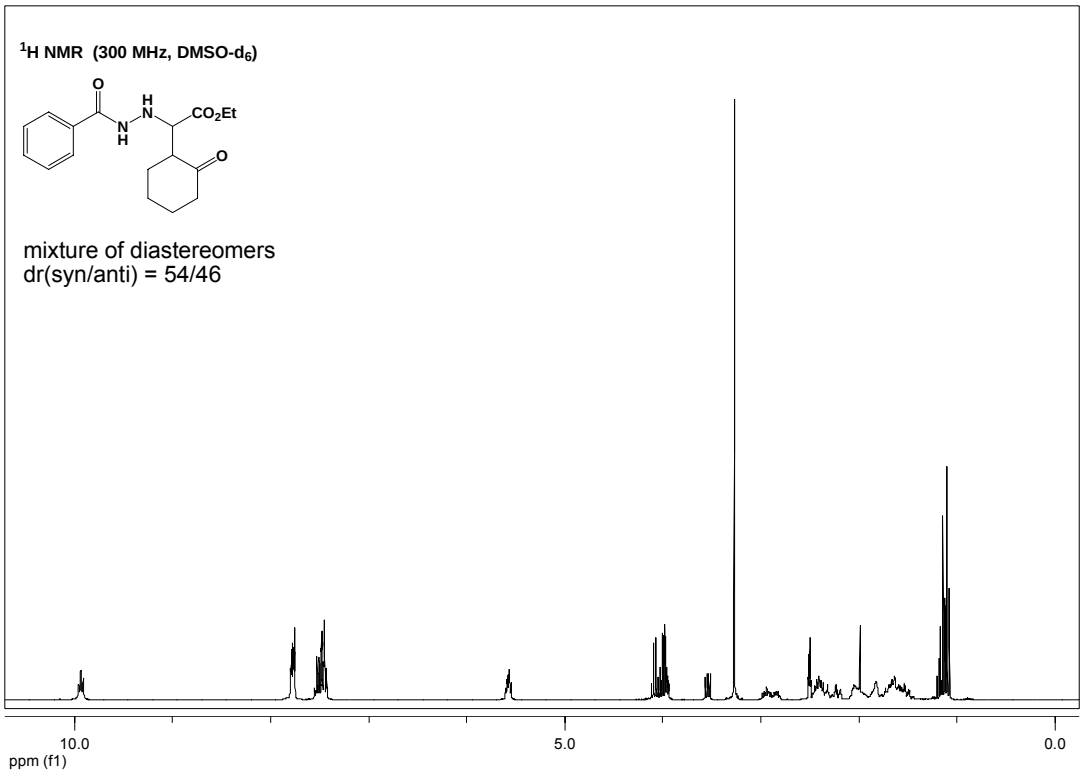

Ethyl (2*R*)-2-[2-(4-bromobenzoyl)hydrazino]-4-oxopentanoate (**77l**)



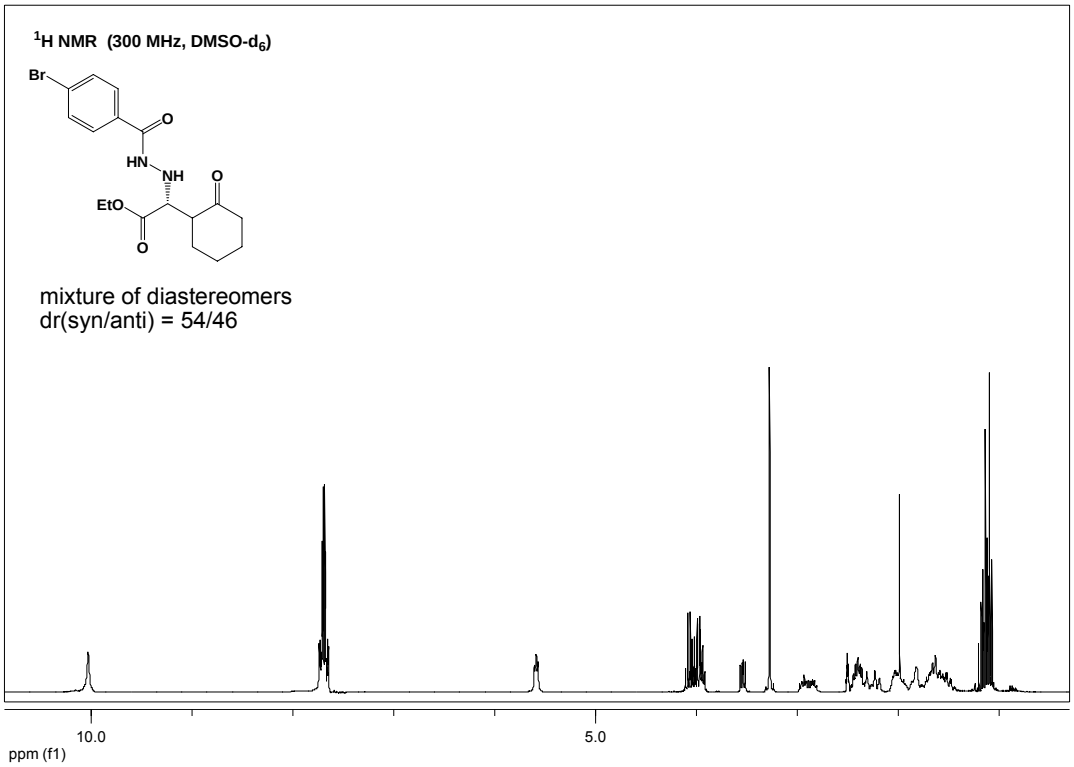

Ethyl (N`-benzoylhydrazino)(2-oxocycloheptyl)acetate (**77m**)



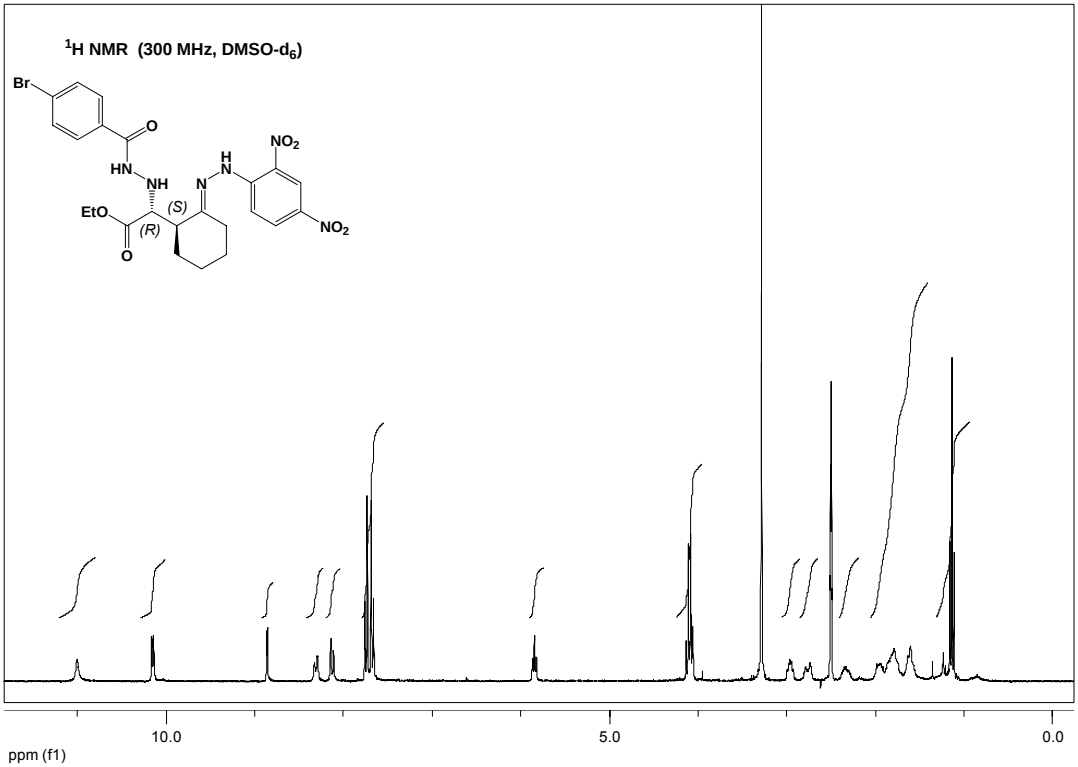

Ethyl (2-benzoylhydrazino)(4-oxotetrahydro-2*H*-thiopyran-3-yl)acetate (**77n**)



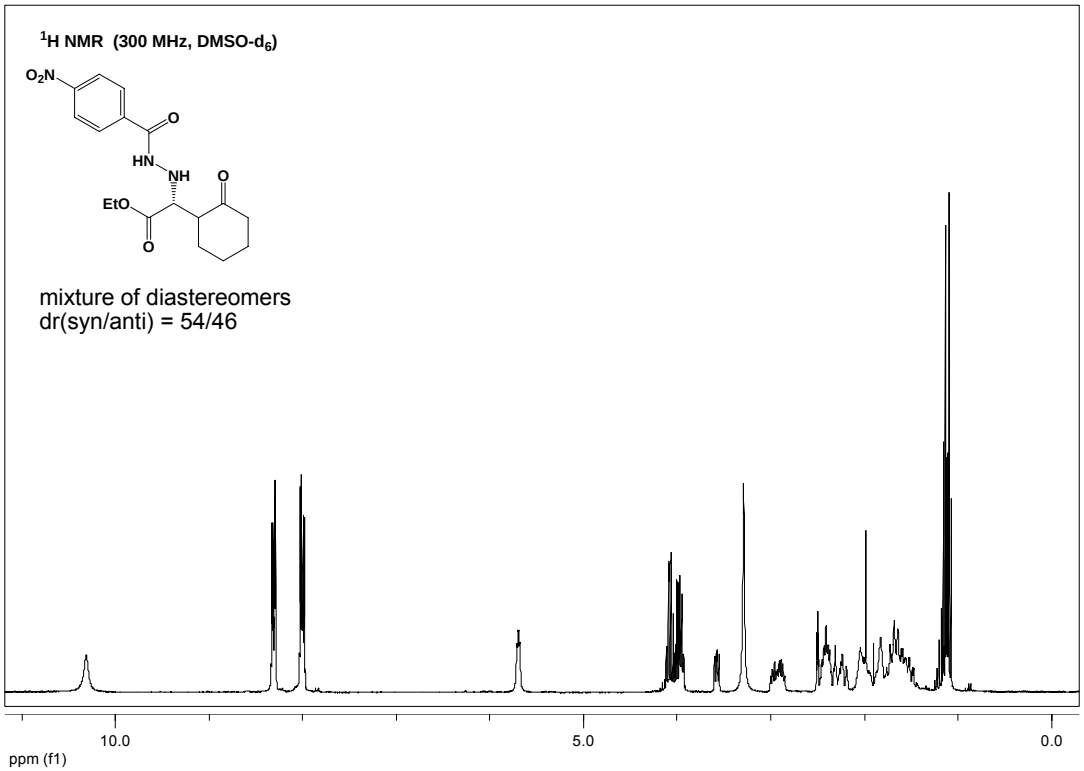

Ethyl (N`-benzoylhydrazino)(2-oxocyclohexyl)acetate (**77o**)



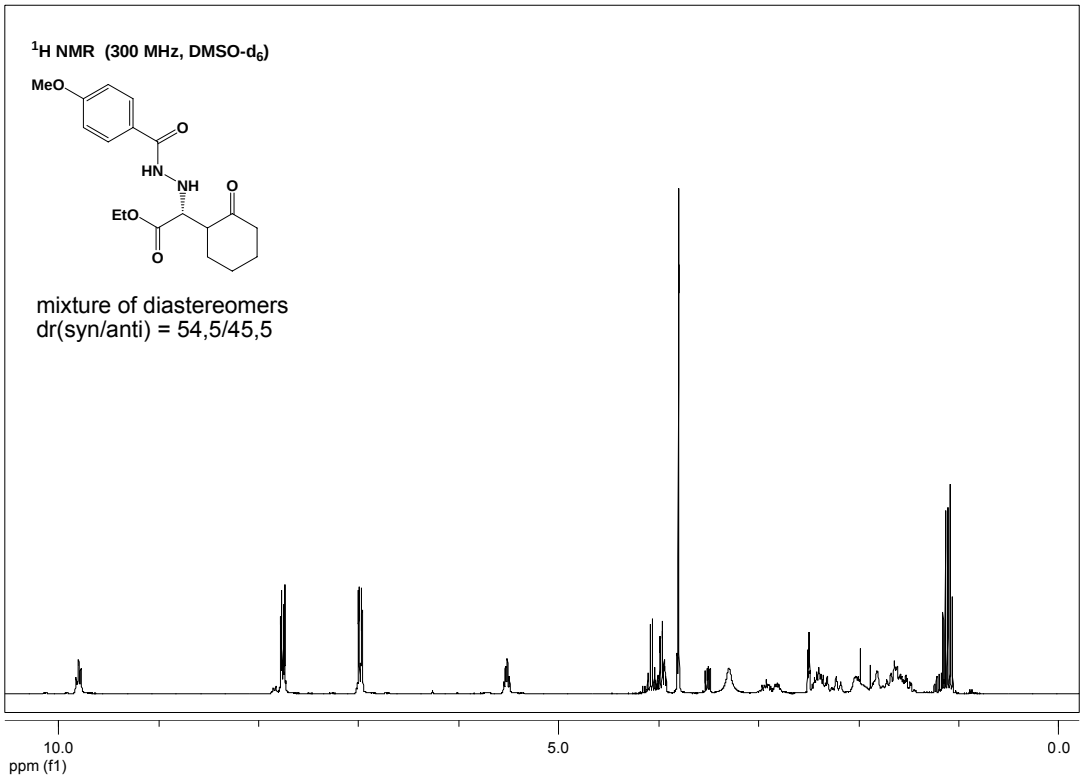

Ethyl [N`-(4-bromobenzoyl)hydrazino](2-oxocyclohexyl)acetate (**77p**)




Ethyl [N`-(4-bromobenzoyl)hydrazino]{(2*E*)-2-[(2,4-dinitrophenyl)hydrazono]cyclohexyl} acetate (**77p-hydrazone**)




Ethyl [N`-(4-nitrobenzoyl)hydrazino](2-oxocyclohexyl)acetate (**77q**)

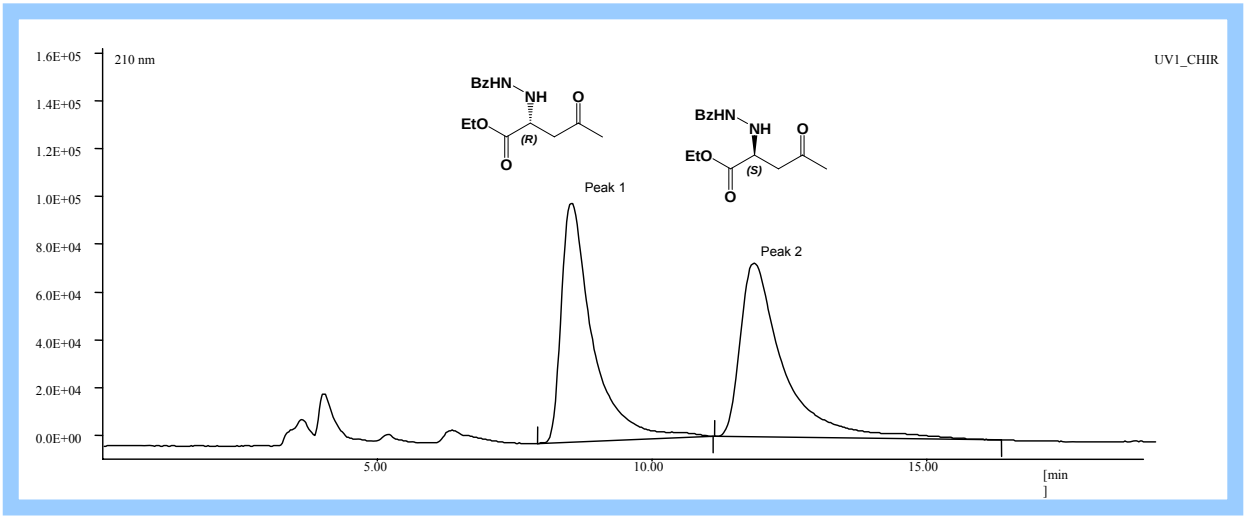



Ethyl [N`-(4-methoxybenzoyl)hydrazino](2-oxocyclohexyl)acetate (**77r**)

# 2. HPLC spectra for the new compounds described in Chapter 4

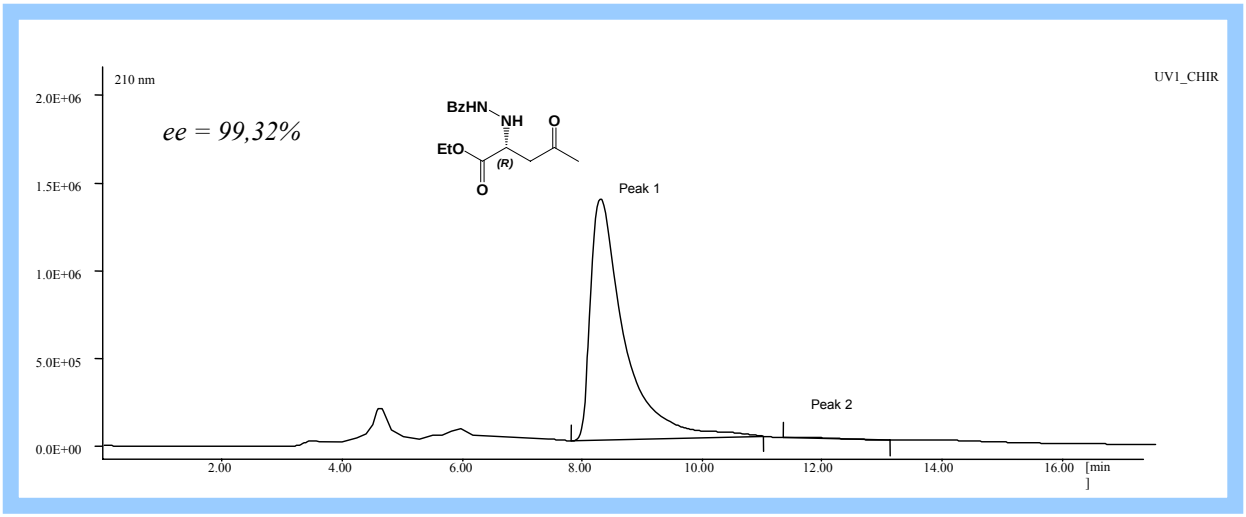
OD - column
n-hexane/2-propanol = 70/30, flow rate 1 ml/min, λ = 210nm:

Racemic mixture of **77a**




| # | Name | Rt | Area | %Area |
|---|---|---|---|---|
| 1 | Peak 1 | 8,43 | 3760448,500 | 49,621 |
| 2 | Peak 2 | 11,70 | 3817898,500 | 50,379 |

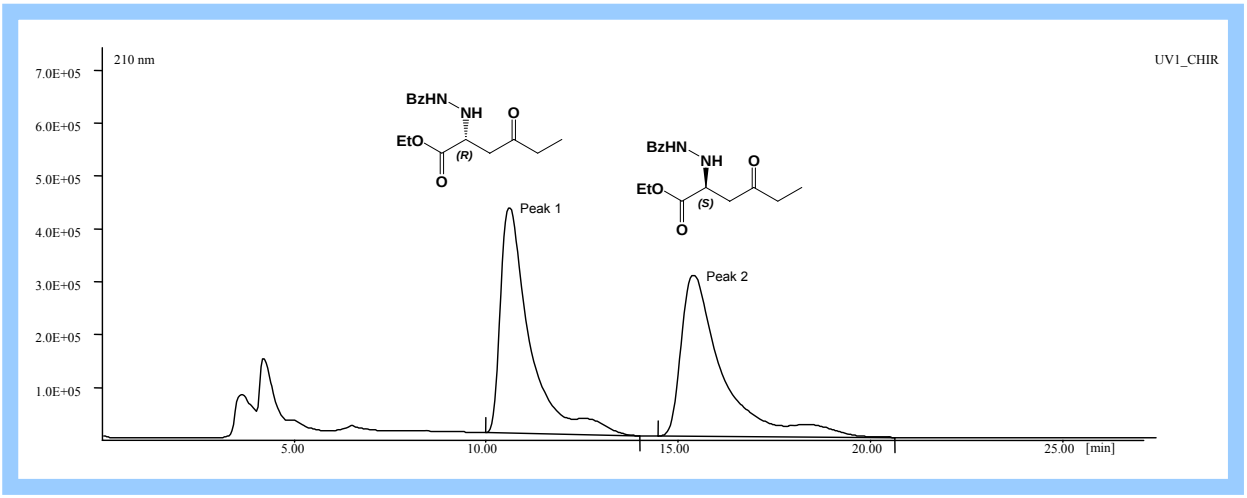
Product **77a** from Table 11 in Main Part




| # | Name | Rt | Area | %Area |
|---|---|---|---|---|
| 1 | Peak 1 | 8,20 | 51362563,500 | 99,658 |
| 2 | Peak 2 | 11,55 | 176295,000 | 0,342 |

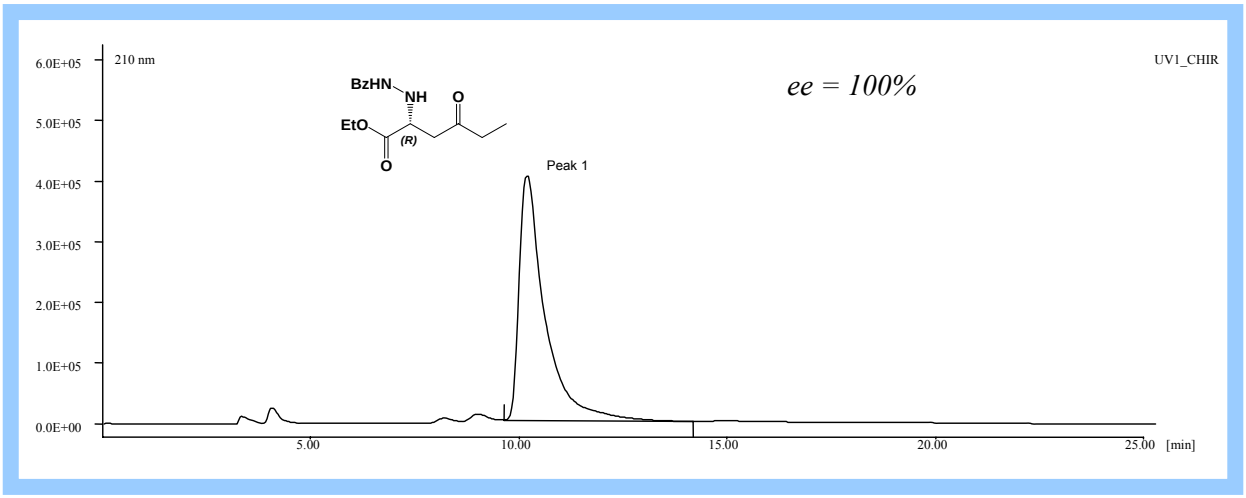
OD - column
n-hexane/2-propanol = 80/20, flow rate 1 ml/min, λ = 210nm:

Racemic mixture of **77b**




| # | Name | Rt | Area | %Area |
|---|---|---|---|---|
| 1 | Peak 1 | 10,46 | 21640837,50 | 49,52 |
| 2 | Peak 2 | 15,20 | 22056447,00 | 50,48 |

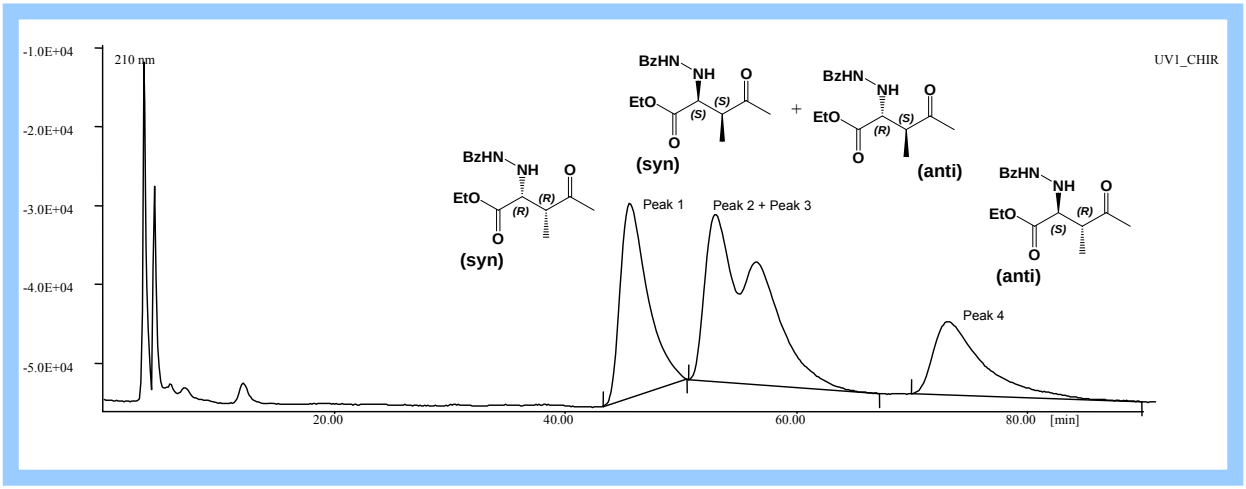
Product **77b** from Table 11 in Main Part




| # | Name | Rt | Area | %Area |
|---|---|---|---|---|
| 1 | Peak 1 | 10,07 | 16339308,000 | 100,000 |

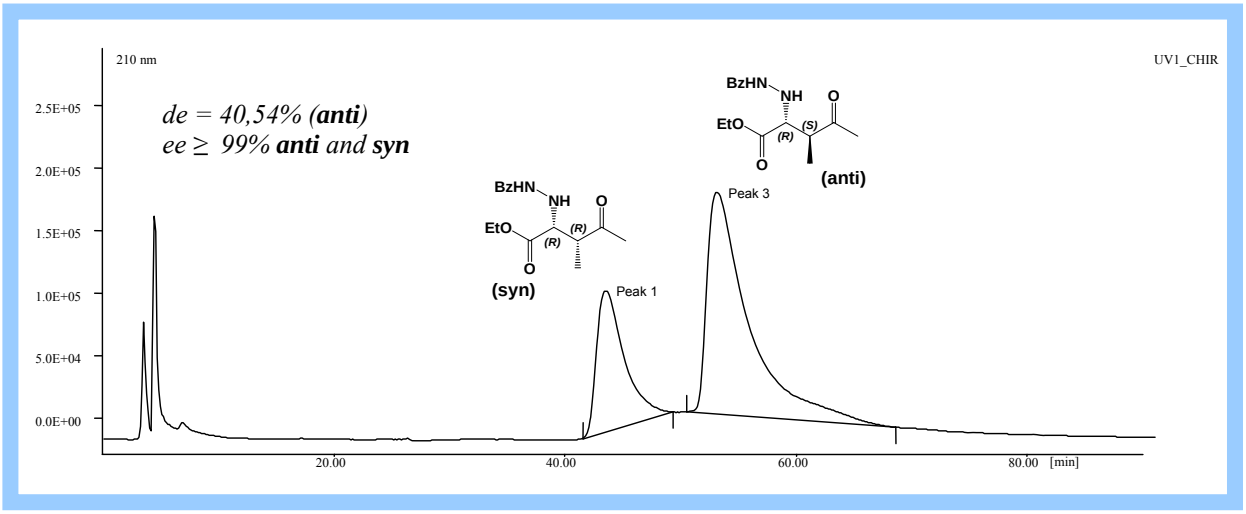
OD - column
n-hexane/2-propanol = 97/3, flow rate 1 ml/min, λ = 210nm:

Racemic mixture of **77c**




| # | Name | Rt | Area | %Area |
|---|---|---|---|---|
| 1 | Peak 1 | 45,03 | 4031405,75 | 29,41 |
| 2 | Peak 2 + Peak 3 | 52,38 | 6906652,99 | 50,38 |
| 3 | Peak 4 | 72,18 | 2771241,23 | 20,21 |

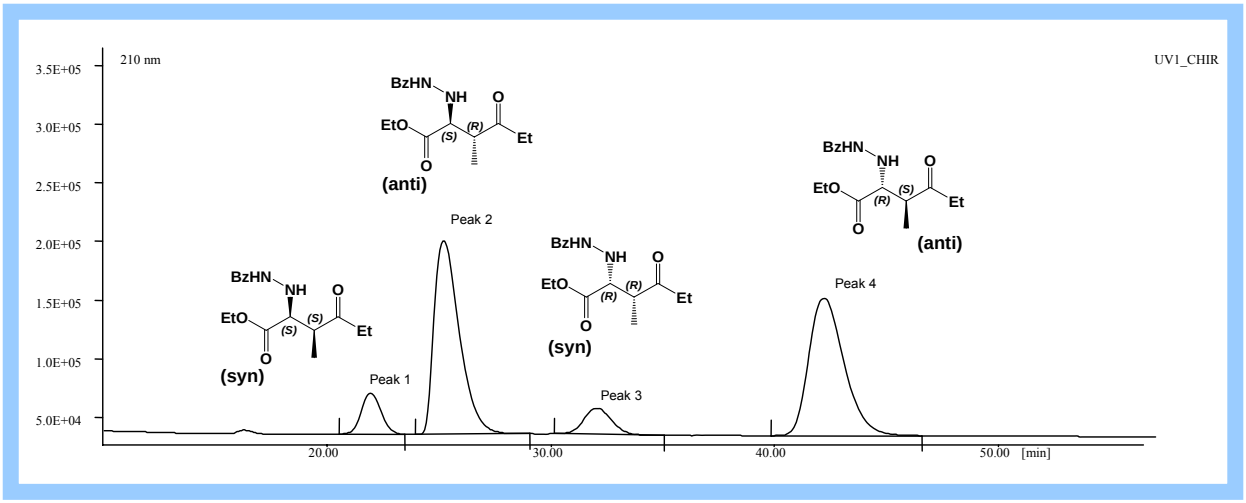
Product **77c** from Table 11 in Main Part




| # | Name | Rt | Area | %Area |
|---|---|---|---|---|
| 1 | Peak 1 | 42,98 | 18054547,00 | 29,73 |
| 2 | Peak 3 | 52,50 | 42683579,00 | 70,27 |

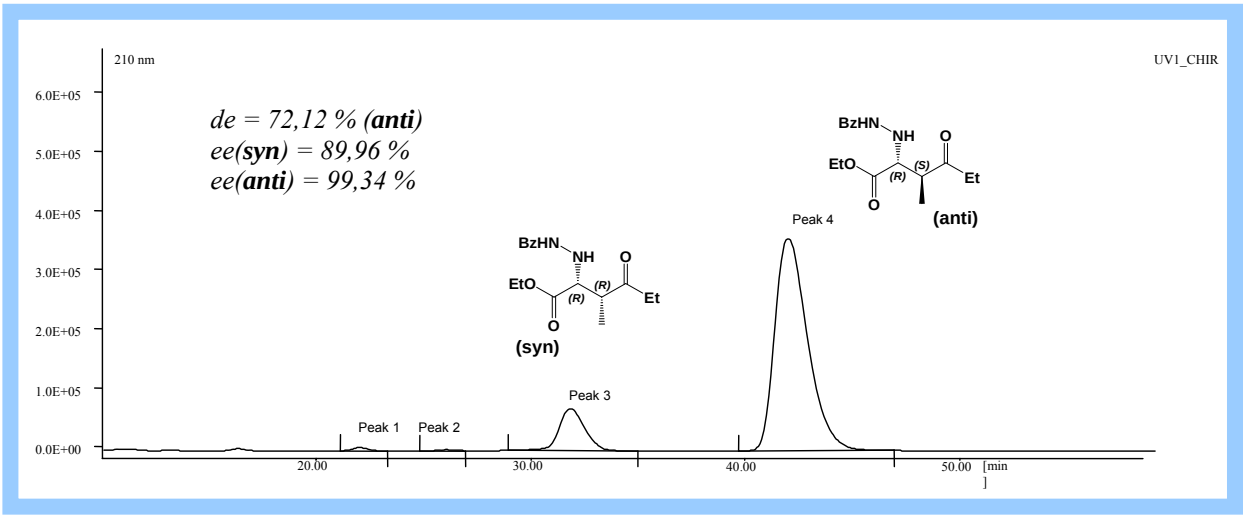
AD – column under Kobayashi`s conditions[125g]
n-hexane/2-propanol = 90/10, flow rate 0.8 ml/min, λ = 210nm:

Racemic mixture of **77d**




| # | Name | Rt | Area | %Area |
|---|---|---|---|---|
| 1 | Peak 1 | 21,79 | 1988461,00 | 7,07 |
| 2 | Peak 2 | 25,03 | 12185366,25 | 43,32 |
| 3 | Peak 3 | 31,74 | 1717578,75 | 6,11 |
| 4 | Peak 4 | 41,80 | 12235605,50 | 43,50 |

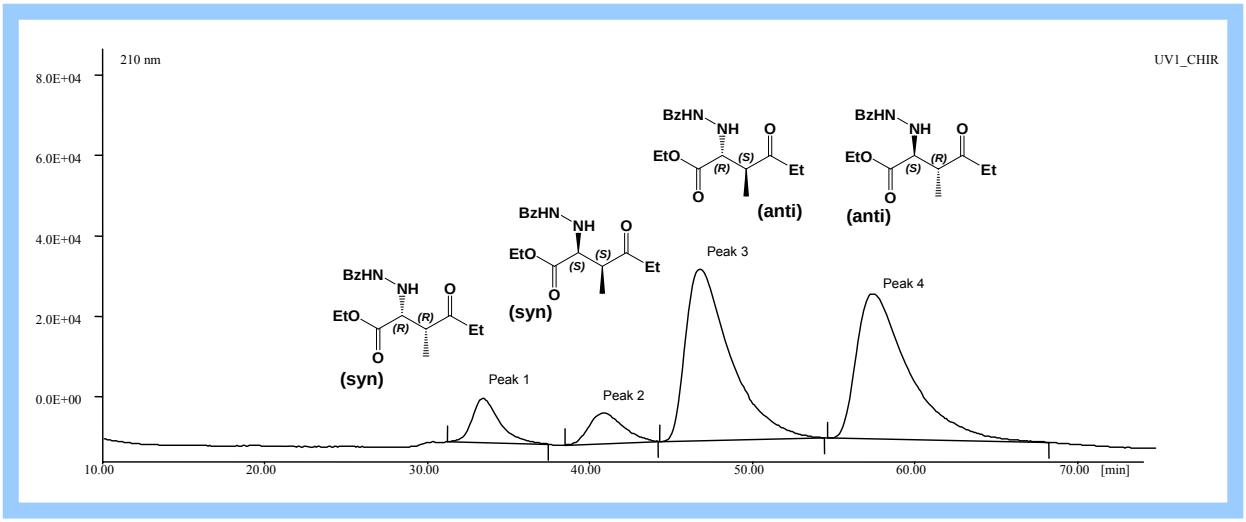
Product **77d** from Table 11 in Main Part




| # | Name | Rt | Area | %Area |
|---|---|---|---|---|
| 1 | Peak 1 | 21,83 | 299268,25 | 0,70 |
| 2 | Peak 2 | 25,86 | 118271,25 | 0,28 |
| 3 | Peak 3 | 31,57 | 5622541,50 | 13,24 |
| 4 | Peak 4 | 41,62 | 36415432,00 | 85,77 |

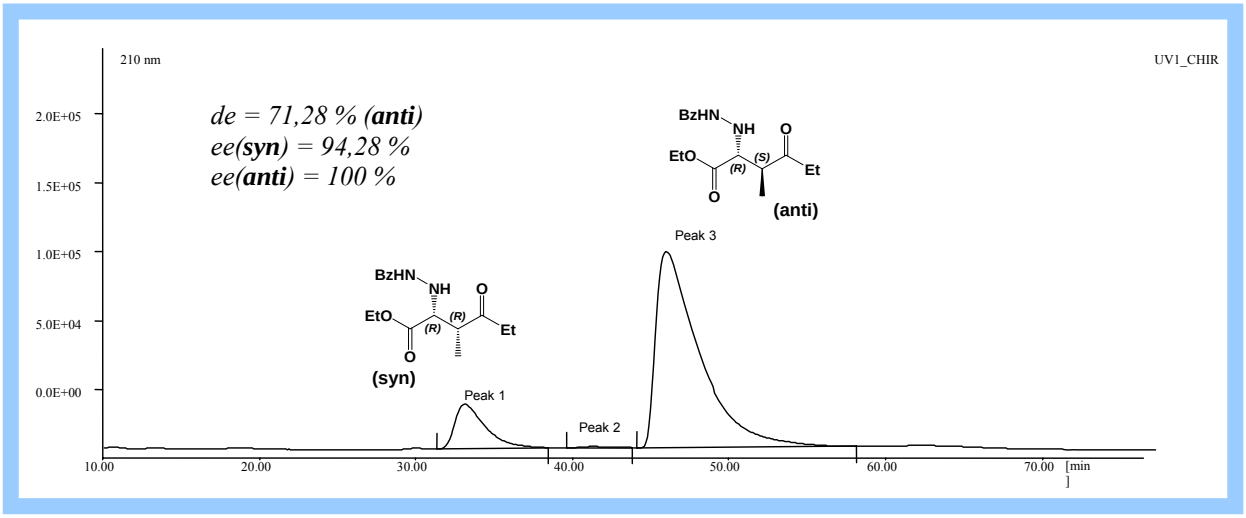
OD - column
n-hexane/2-propanol = 97/3, flow rate 1 ml/min, λ = 210nm:

Racemic mixture of **77d**




| # | Name | Rt | Area | %Area |
|---|---|---|---|---|
| 1 | Peak 1 | 33,15 | 1281035,00 | 7,03 |
| 2 | Peak 2 | 40,47 | 1094288,00 | 6,00 |
| 3 | Peak 3 | 46,30 | 7965653,50 | 43,68 |
| 4 | Peak 4 | 56,80 | 7893529,00 | 43,29 |

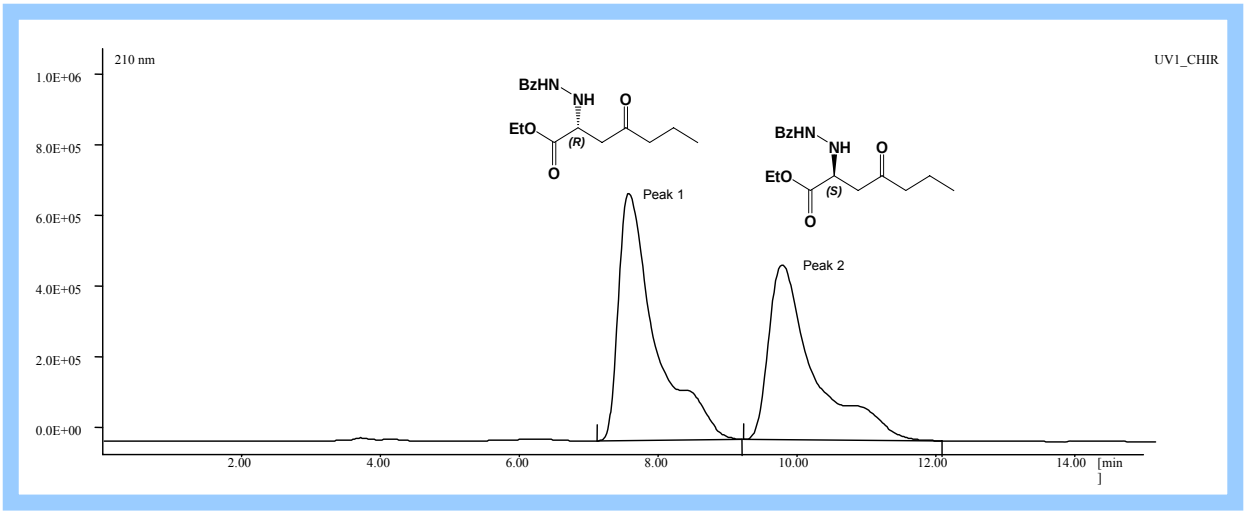
Product **77d** from Table 11 in Main Part




| # | Name | Rt | Area | %Area |
|---|---|---|---|---|
| 1 | Peak 1 | 32,85 | 4299922,50 | 13,79 |
| 2 | Peak 2 | 41,09 | 125458,00 | 0,40 |
| 3 | Peak 3 | 45,53 | 26749472,51 | 85,80 |

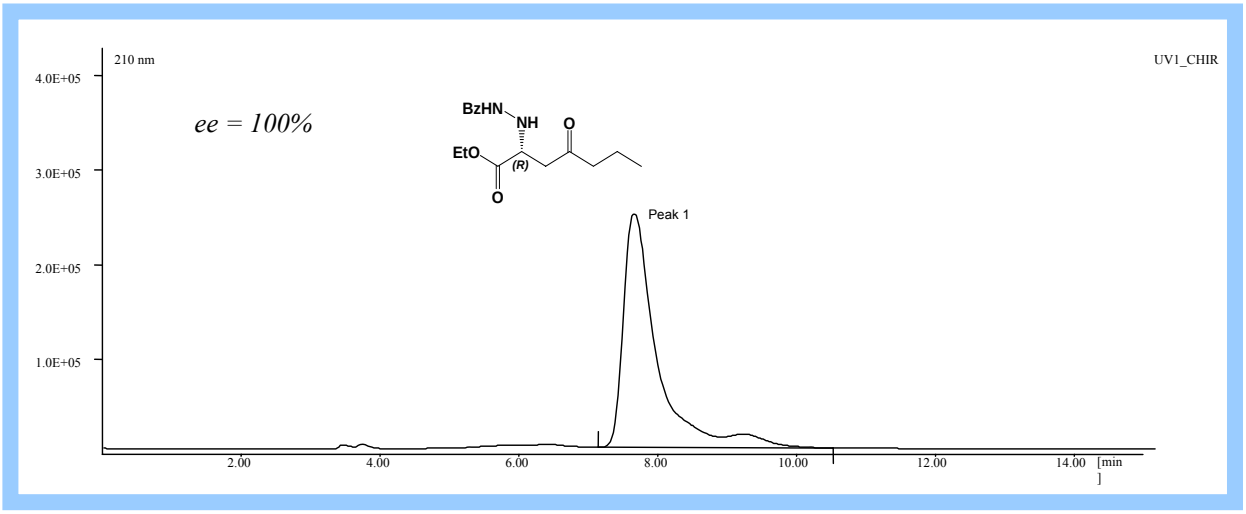
OD - column
n-hexane/2-propanol = 70/30, flow rate 1 ml/min, λ = 210nm:

Racemic mixture of **77e**




| # | Name | Rt | Area | %Area |
|---|---|---|---|---|
| 1 | Peak 1 | 7,49 | 24775605,50 | 53,20 |
| 2 | Peak 2 | 9,68 | 21791400,00 | 46,80 |

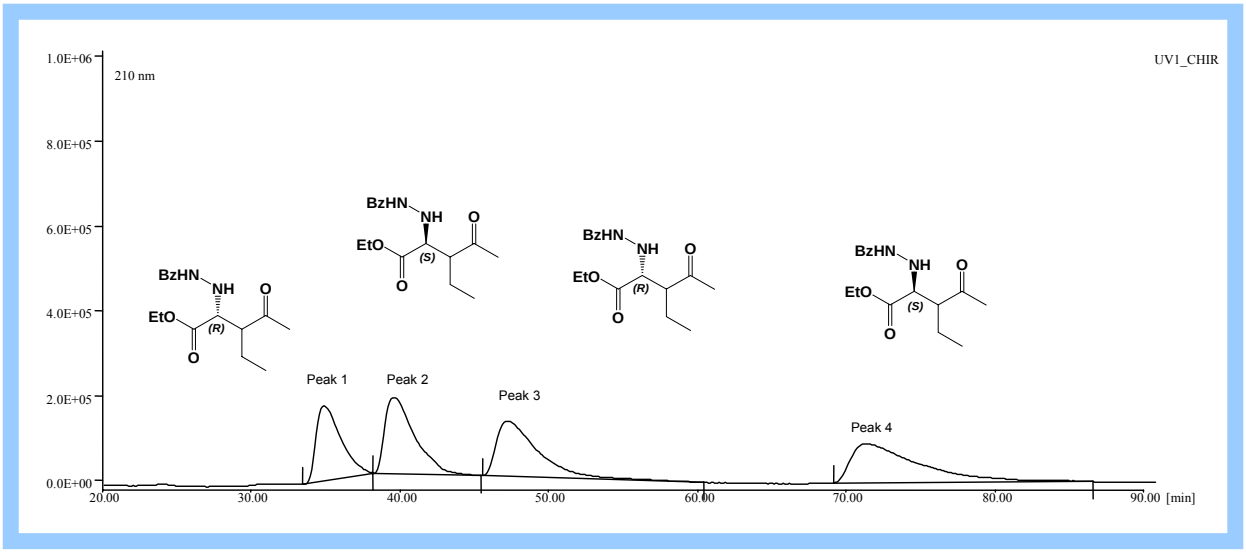
Product **77e** from Table 11 in Main Part




| # | Name | Rt | Area | %Area |
|---|---|---|---|---|
| 1 | Peak 1 | 7,57 | 7985765,00 | 100,00 |

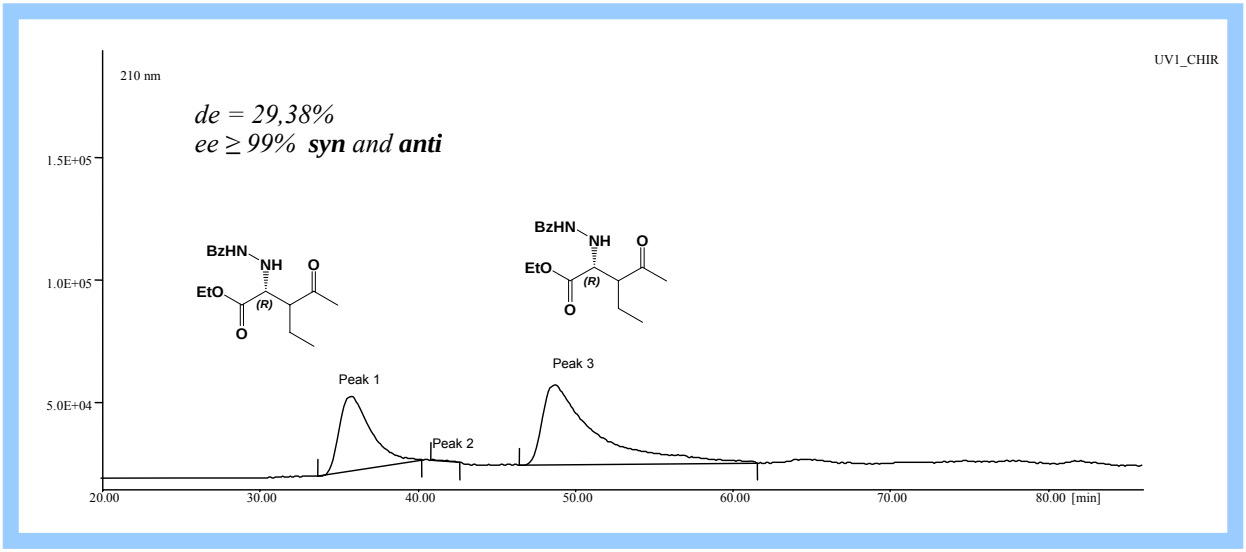
OD - column
n-hexane/2-propanol/TEA =97/3/0,1 ,flow rate 1 ml/min,λ= 210nm:

Racemic mixture of **77f**




| # | Name | Rt | Area | %Area |
|---|---|---|---|---|
| 1 | Peak 1 | 34,67 | 19383903,25 | 20,13 |
| 2 | Peak 2 | 39,28 | 23779322,00 | 24,70 |
| 3 | Peak 3 | 46,87 | 24325576,00 | 25,26 |
| 4 | Peak 4 | 70,82 | 28795748,00 | 29,91 |

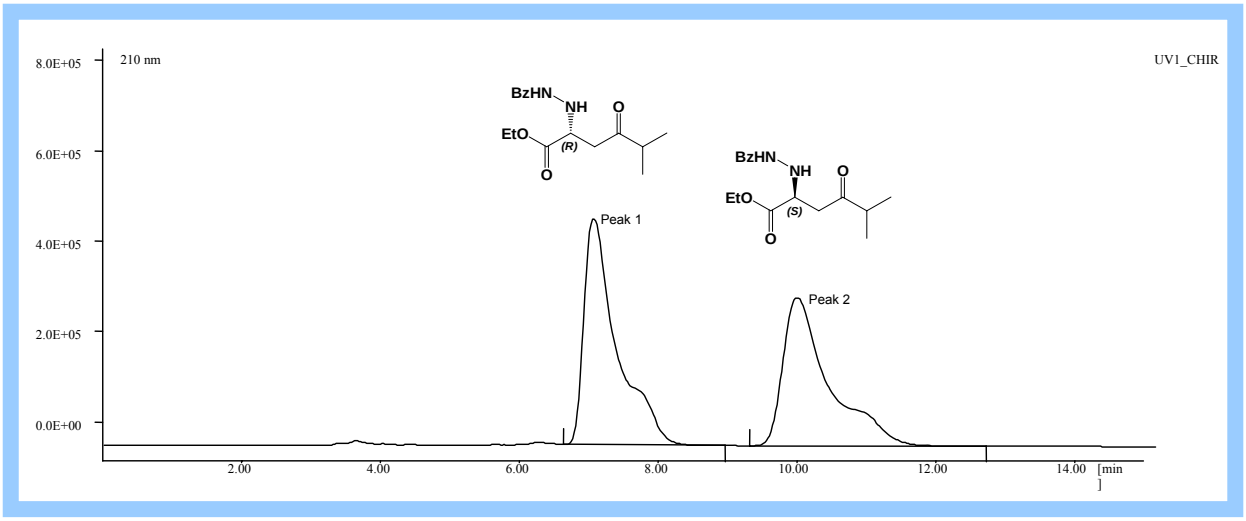
Product **77f** from Table 11 in Main Part




| # | Name | Rt | Area | %Area |
|---|---|---|---|---|
| 1 | Peak 1 | 35,51 | 4072034,50 | 35,21 |
| 2 | Peak 2 | 40,67 | 11916,00 | 0,10 |
| 3 | Peak 3 | 48,33 | 7482079,25 | 64,69 |

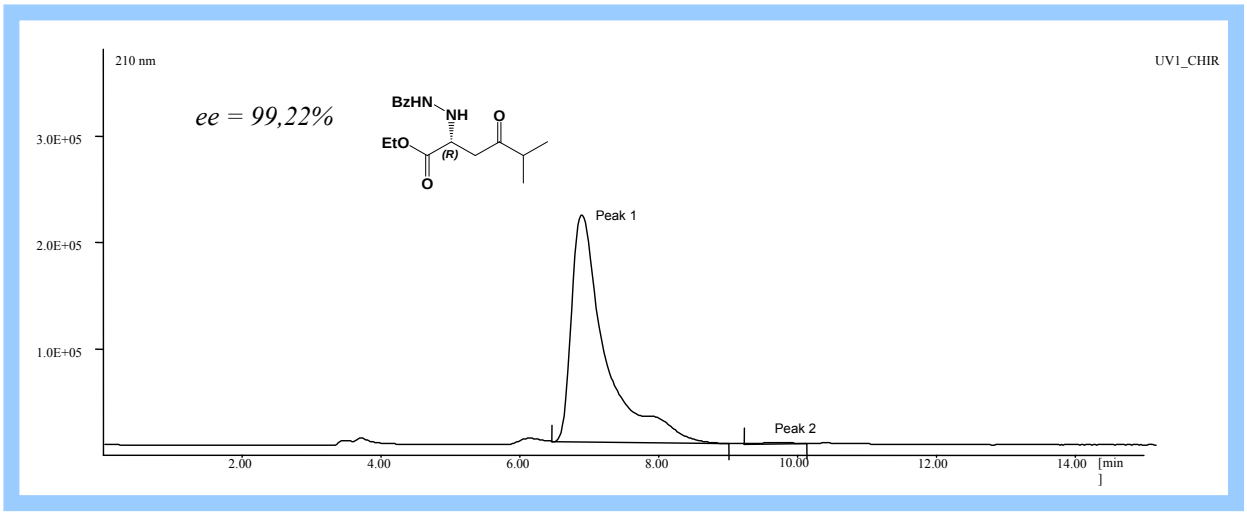
OD - column
n-hexane/2-propanol = 70/30, flow rate 1 ml/min, λ = 210nm:

Racemic mixture of **77g**




| # | Name | Rt | Area | %Area |
|---|---|---|---|---|
| 1 | Peak 1 | 6,99 | 15790449,75 | 52,04 |
| 2 | Peak 2 | 9,89 | 14553944,00 | 47,96 |

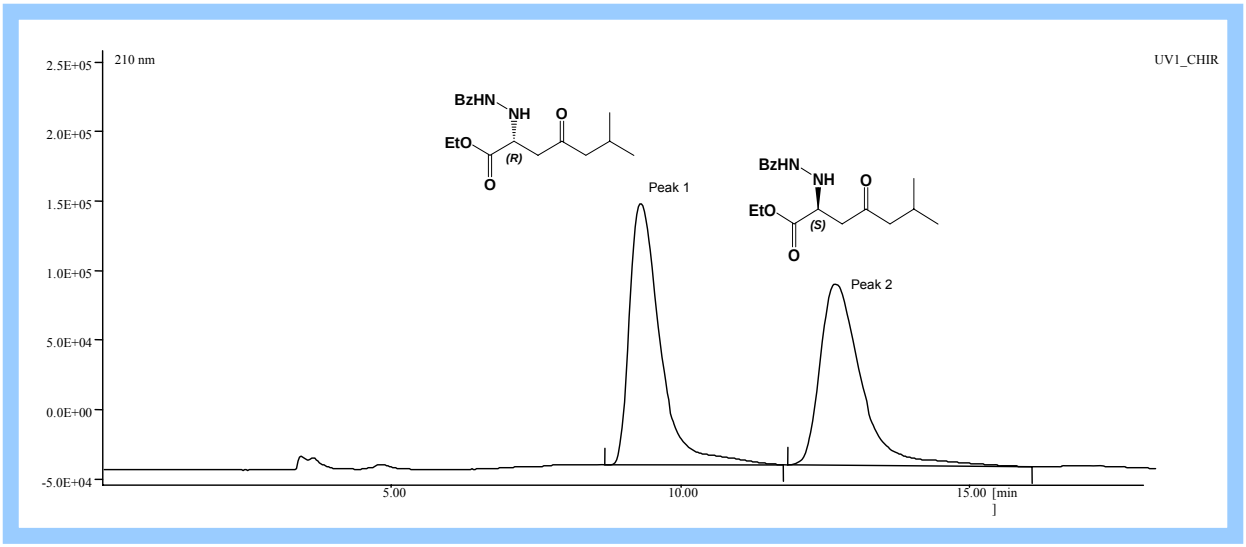
Product **77g** from Table 11 in Main Part




| # | Name | Rt | Area | %Area |
|---|---|---|---|---|
| 1 | Peak 1 | 6,81 | 6905922,50 | 99,61 |
| 2 | Peak 2 | 9,57 | 27145,50 | 0,39 |

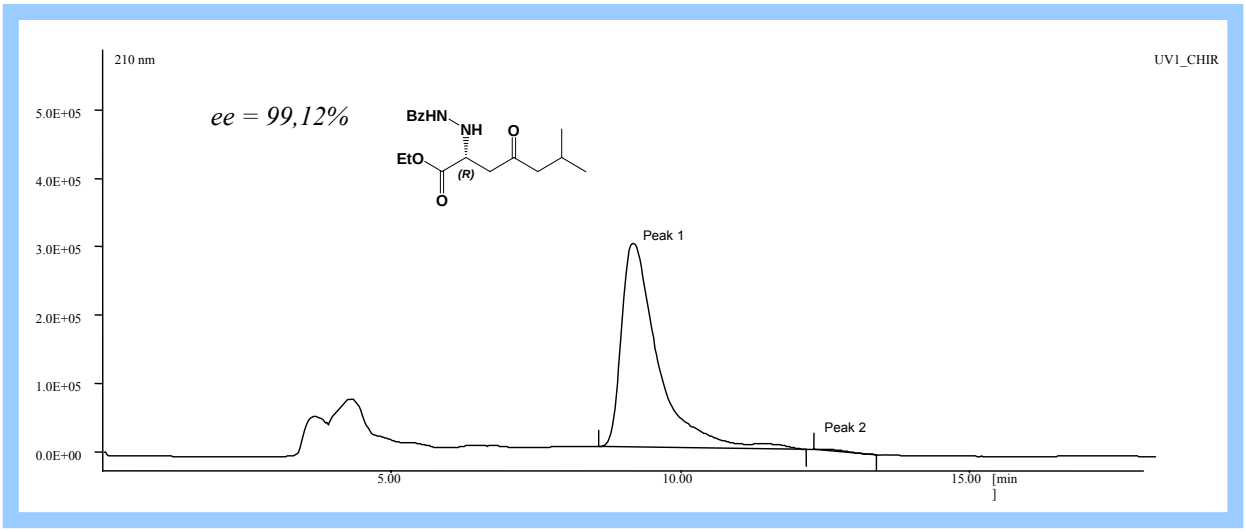
OD - column
n-hexane/2-propanol = 80/20, flow rate 1 ml/min, λ = 210nm:

Racemic mixture of **77h**




| # | Name | Rt | Area | %Area |
|---|---|---|---|---|
| 1 | Peak 1 | 9,19 | 6647179,00 | 51,74 |
| 2 | Peak 2 | 12,52 | 6200972,50 | 48,26 |

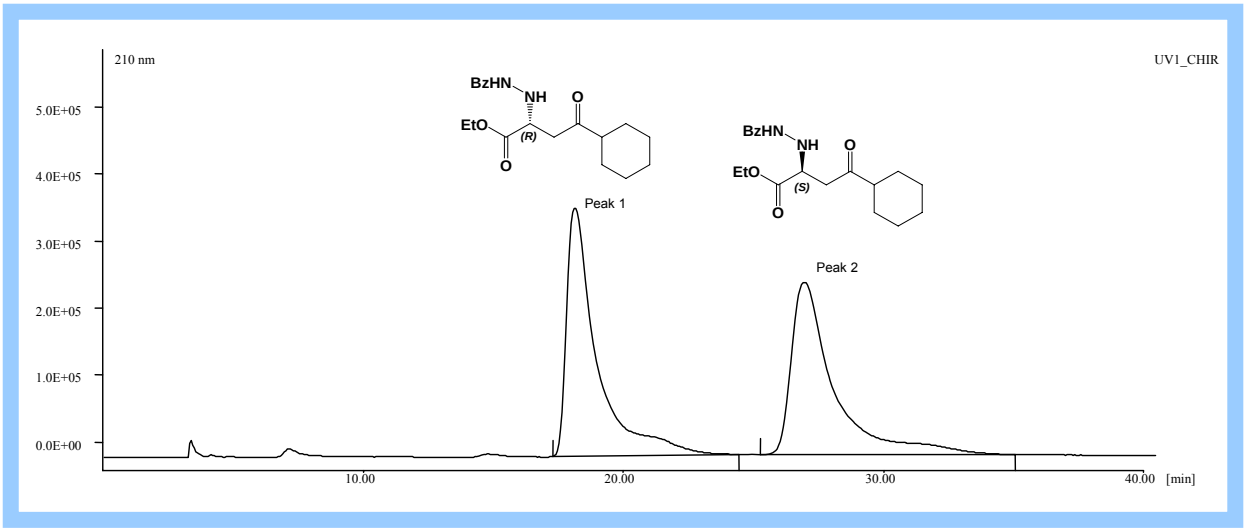
Product **77h** from Table 11 in Main Part




| # | Name | Rt | Area | %Area |
|---|---|---|---|---|
| 1 | Peak 1 | 9,07 | 12564359,25 | 99,56 |
| 2 | Peak 2 | 12,35 | 55547,25 | 0,44 |

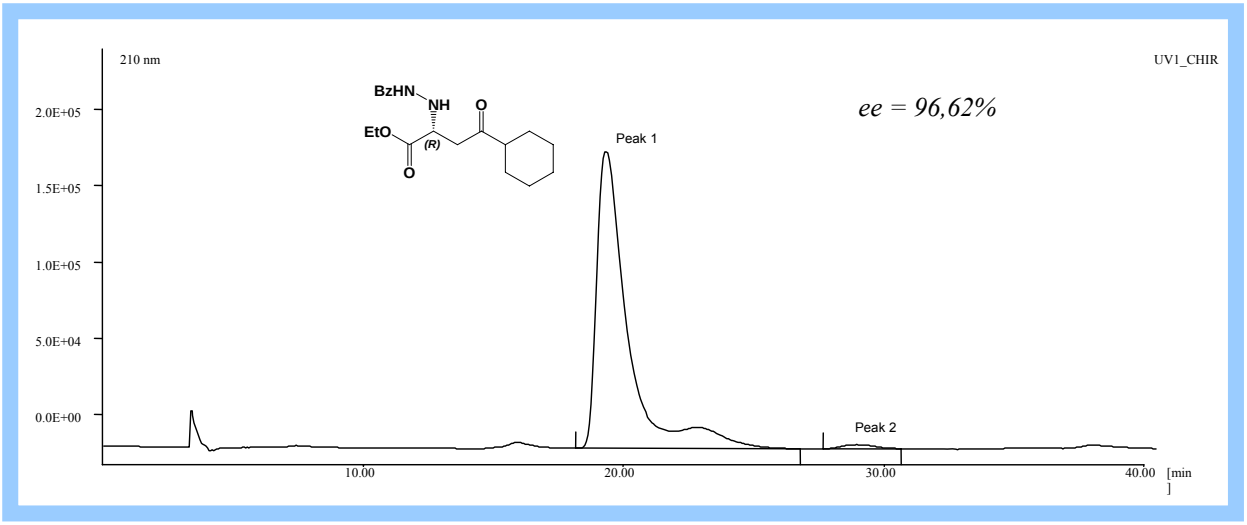
OD - column
n-hexane/2-propanol = 90/10, flow rate 1 ml/min, λ = 210nm:

Racemic mixture of **77i**




| # | Name | Rt | Area | %Area |
|---|---|---|---|---|
| 1 | Peak 1 | 17,91 | 28551449,50 | 50,46 |
| 2 | Peak 2 | 26,63 | 28029855,50 | 49,54 |

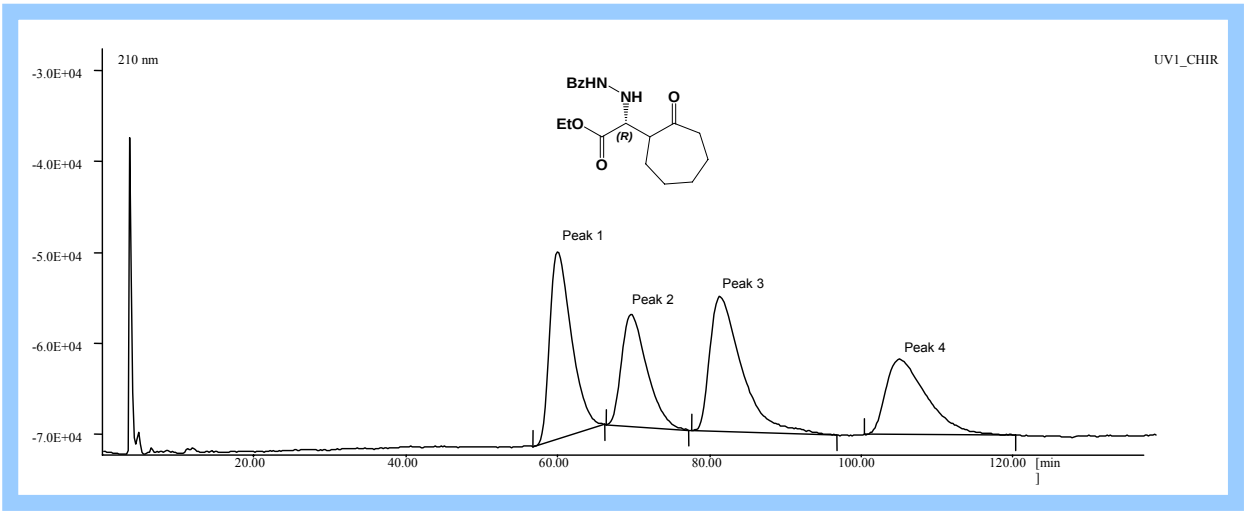
Product **77i** from Table 11 in Main Part




| # | Name | Rt | Area | %Area |
|---|---|---|---|---|
| 1 | Peak 1 | 19,10 | 15432128,50 | 98,31 |
| 2 | Peak 2 | 28,61 | 265924,00 | 1,69 |

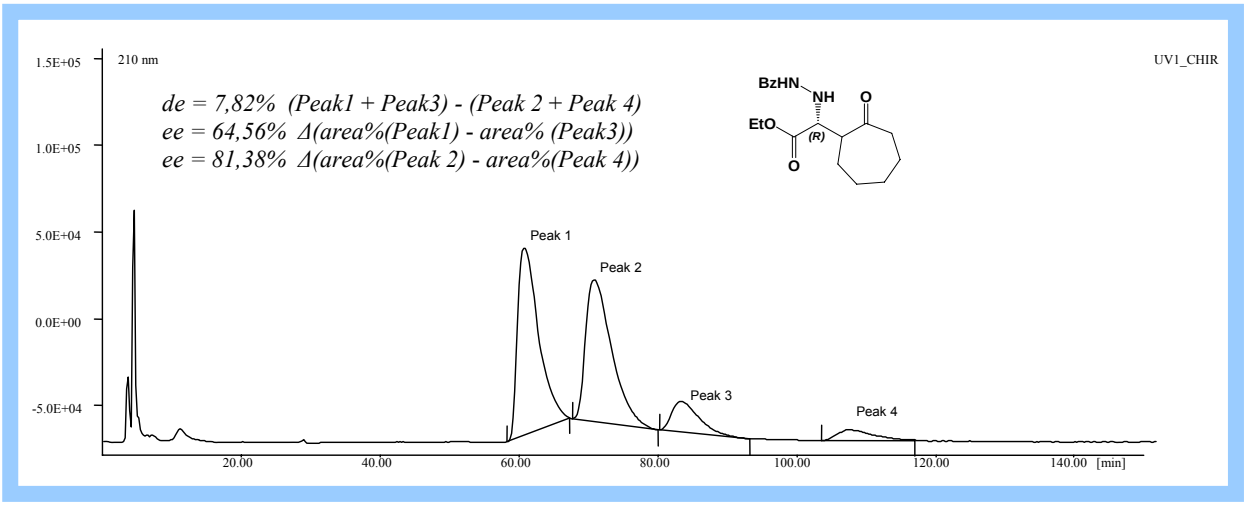
OD - column
n-hexane/2-propanol = 97/3, flow rate 1 ml/min, λ = 210nm:

Racemic mixture of **77m**




| # | Name | Rt | Area | %Area |
|---|---|---|---|---|
| 1 | Peak 1 | 59,29 | 4060806,992 | 28,927 |
| 2 | Peak 2 | 68,89 | 2864794,502 | 20,407 |
| 3 | Peak 3 | 80,43 | 4073250,015 | 29,016 |
| 4 | Peak 4 | 103,71 | 3039301,480 | 21,650 |

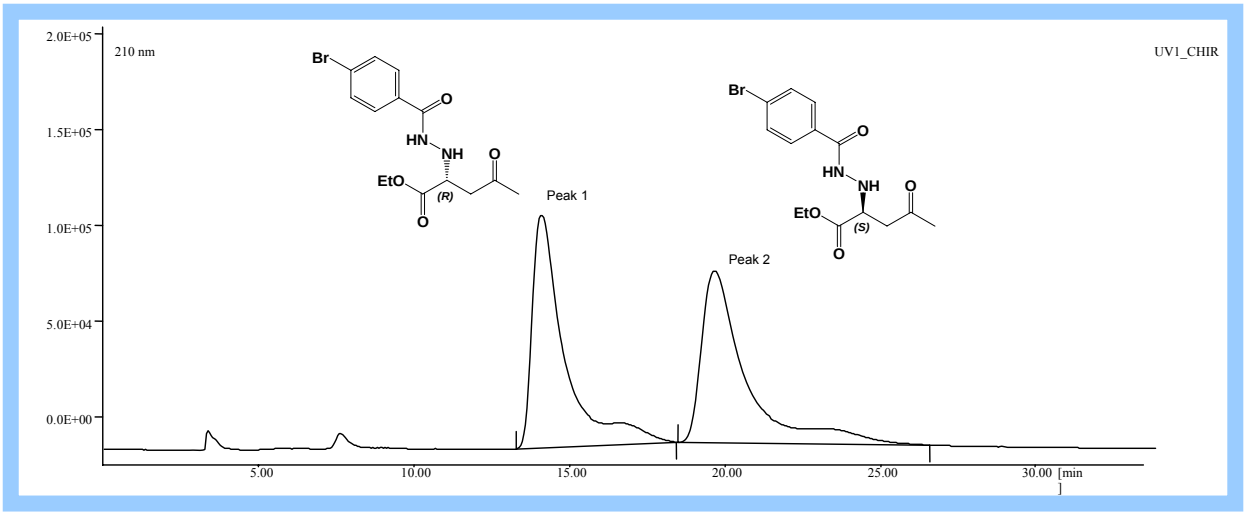
Product **77m** from Table 11 in Main Part




| # | Name | Rt | Area | %Area |
|---|---|---|---|---|
| 1 | Peak 1 | 59,99 | 22051050,50 | 44,36 |
| 2 | Peak 2 | 69,93 | 20764743,49 | 41,77 |
| 3 | Peak 3 | 82,37 | 4747594,99 | 9,55 |
| 4 | Peak 4 | 106,38 | 2148807,51 | 4,32 |

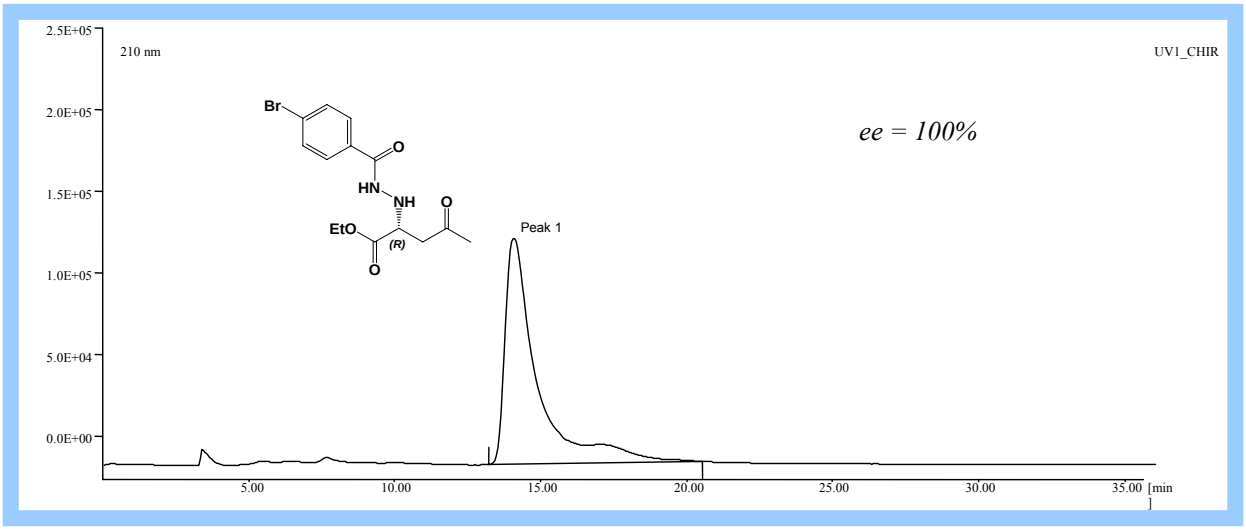
OD - column
n-hexane/2-propanol = 80:20, flow rate 1 ml/min, λ = 210nm:

Racemic mixture of **77l**




| # | Name | Rt | Area | %Area |
|---|---|---|---|---|
| 1 | Peak 1 | 13,93 | 8450858,50 | 49,71 |
| 2 | Peak 1 | 19,42 | 8550071,50 | 50,29 |

Product **77l** from Table 11 in Main Part

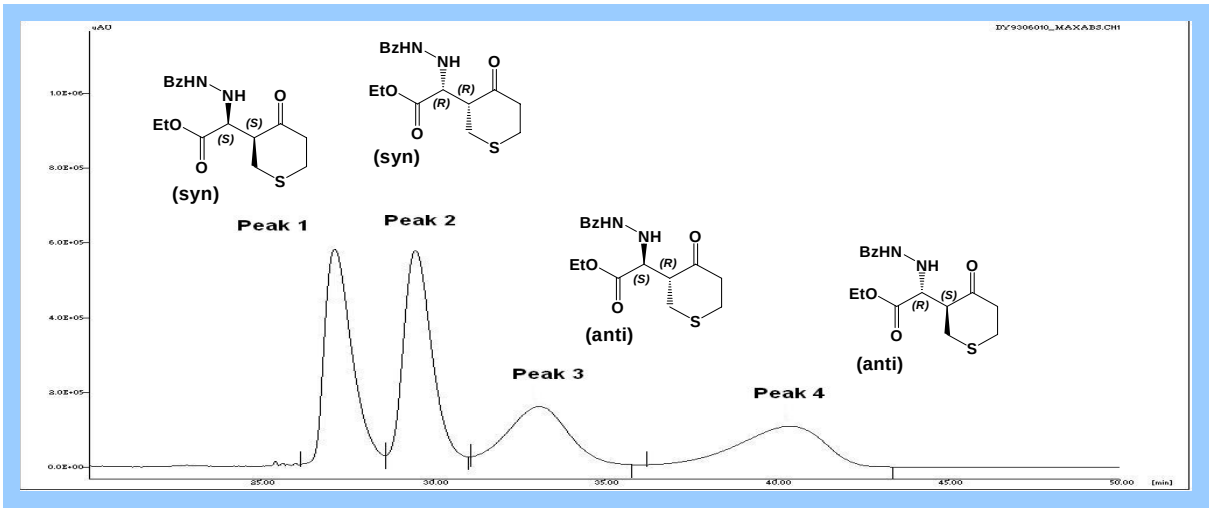



| # | Name | Rt | Area | %Area |
|---|---|---|---|---|
| 1 | Peak 1 | 13,90 | 10179321,00 | 100,00 |

# HPLC analysis on IA column

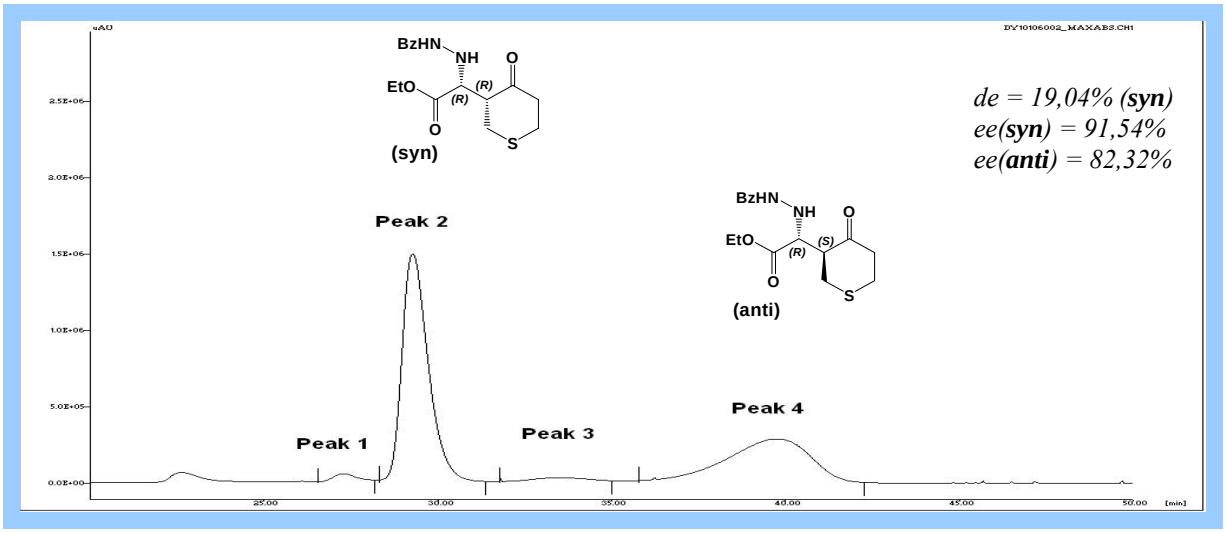
n-hexane/2-propanol = 75/25, flow rate 0.5 ml/min, λ = 210nm:

Racemic mixture of **77n**




| # | Name | Rt | Area | %Area |
|---|---|---|---|---|
| 1 | Peak 1 | 27,120 | 32042797 | 30,36 |
| 2 | Peak 2 | 29,467 | 33312840 | 31,56 |
| 3 | Peak 3 | 33,080 | 20832918 | 19,74 |
| 4 | Peak 4 | 40,373 | 19366235 | 18,35 |

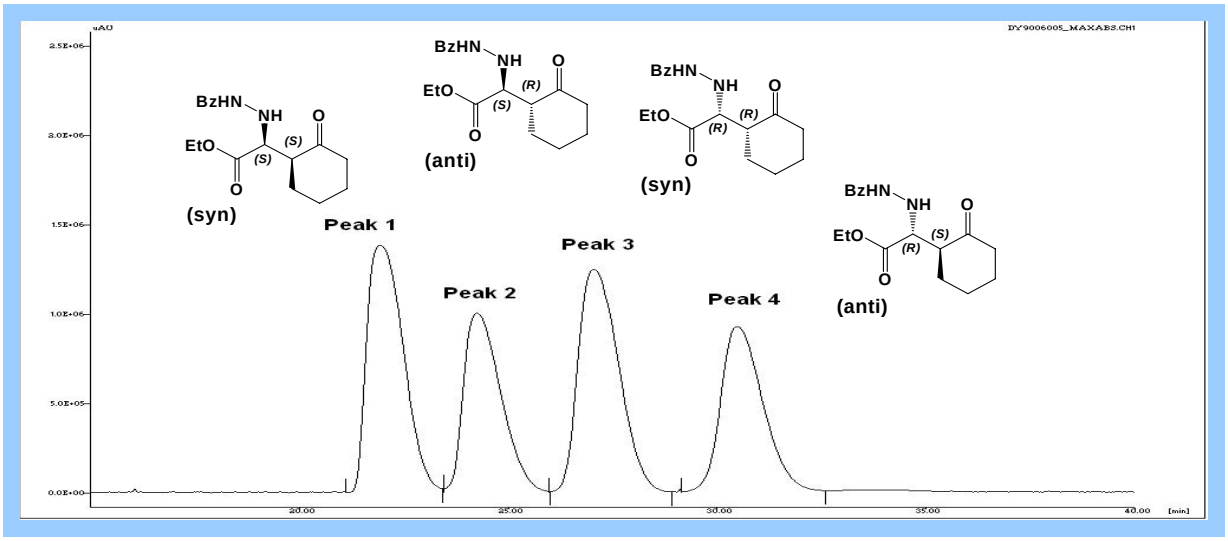
Product **77n** from Table 12 in Main Part




| # | Name | Rt | Area | %Area |
|---|---|---|---|---|
| 1 | Peak 1 | 27,253 | 3416257 | 2,52 |
| 2 | Peak 2 | 29,253 | 77195650 | 57,00 |
| 3 | Peak 3 | 33,493 | 4845874 | 3,58 |
| 4 | Peak 4 | 39,733 | 49973967 | 36,90 |

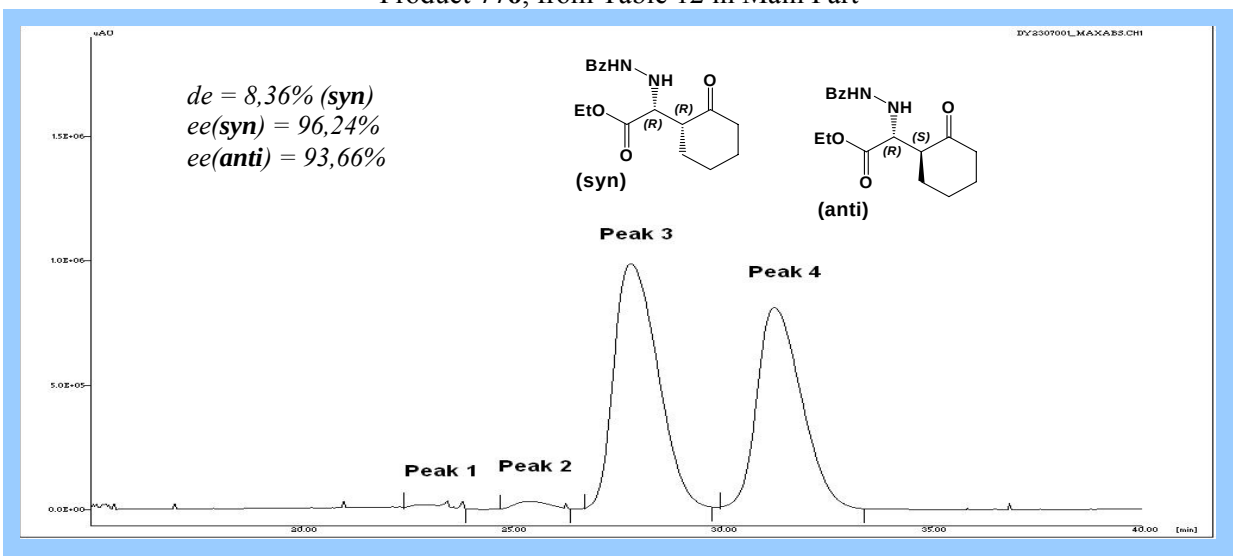
n-hexane/2-propanol/dichloromethane = 80/8/12, flow rate 0.5 ml/min, λ = 210nm:

Racemic mixture of **77o**




| # | Name | Rt | Area | %Area |
|---|---|---|---|---|
| 1 | Peak 1 | 21,920 | 82244068 | 28,34 |
| 2 | Peak 2 | 24,240 | 61116355 | 21,06 |
| 3 | Peak 3 | 27,053 | 82475029 | 28,42 |
| 4 | Peak 4 | 30,480 | 64405819 | 22,19 |

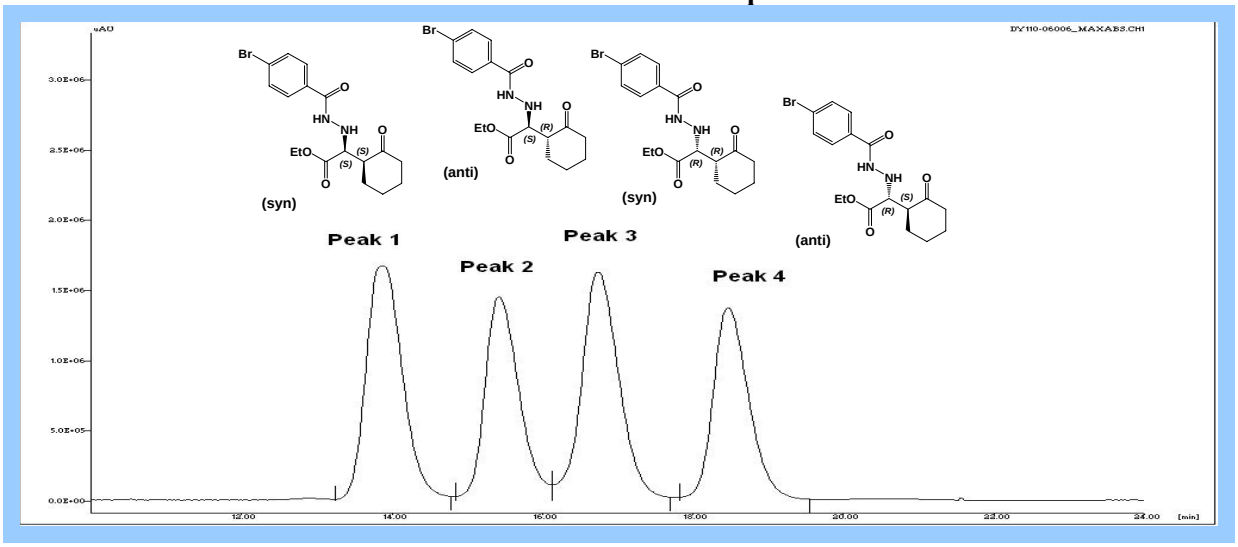
Product **77o**, from Table 12 in Main Part




| # | Name | Rt | Area | %Area |
|---|---|---|---|---|
| 1 | Peak 1 | 23,467 | 1358031 | 1,02 |
| 2 | Peak 2 | 25,413 | 1916323 | 1,45 |
| 3 | Peak 3 | 27,827 | 70464635 | 53,16 |
| 4 | Peak 4 | 31,227 | 58819916 | 44,37 |

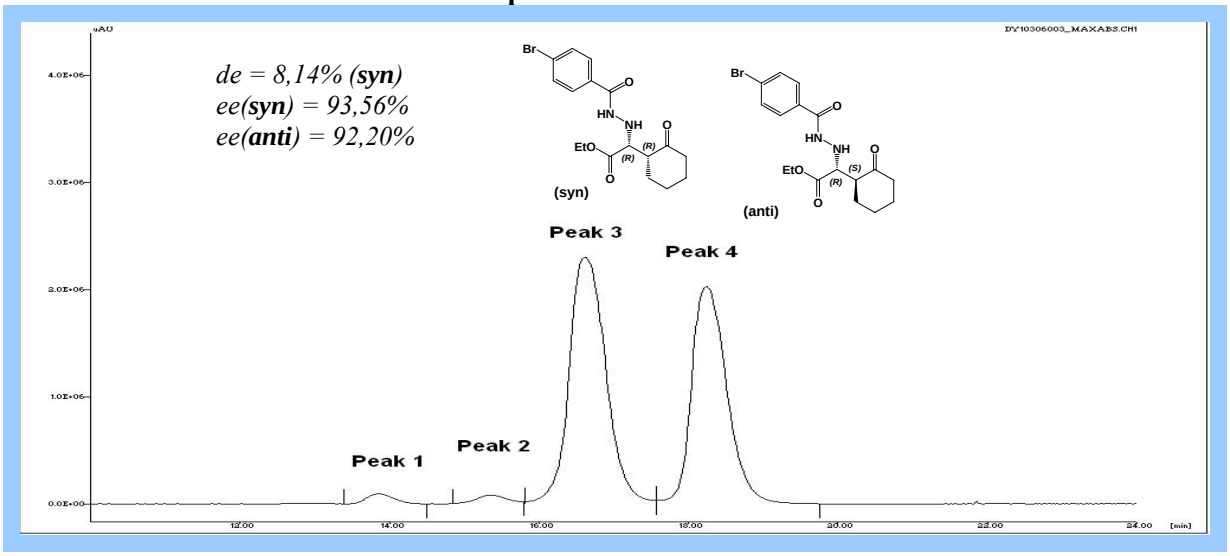
n-hexane/2-propanol/dichloromethane = 68/10/22, flow rate 0.5 ml/min, λ = 210nm:

Racemic mixture of **77p**




| # | Name | Rt | Area | %Area |
|---|---|---|---|---|
| 1 | Peak 1 | 13,867 | 55329150 | 27,65 |
| 2 | Peak 2 | 15,413 | 45100857 | 22,53 |
| 3 | Peak 3 | 16,733 | 55276012 | 27,62 |
| 4 | Peak 4 | 18,467 | 44434157 | 22,20 |

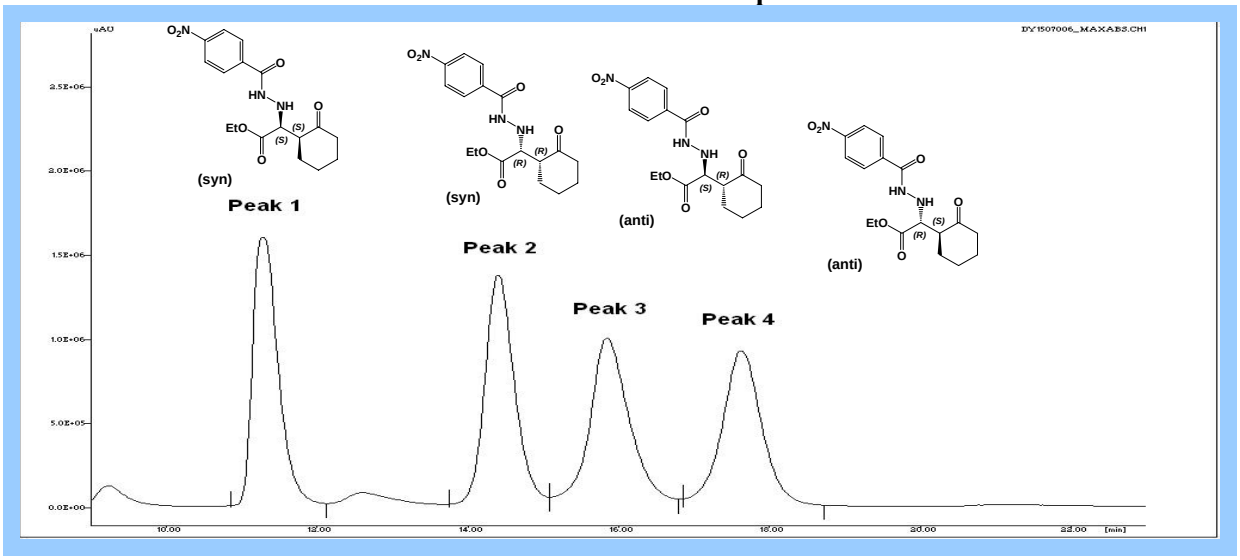
Product **77p** from Table 12 in Main Part




| # | Name | Rt | Area | %Area |
|---|---|---|---|---|
| 1 | Peak 1 | 13,840 | 2558570 | 1,74 |
| 2 | Peak 2 | 15,347 | 2633253 | 1,79 |
| 3 | Peak 3 | 16,600 | 76894793 | 52,33 |
| 4 | Peak 4 | 18,227 | 64845947 | 44,13 |

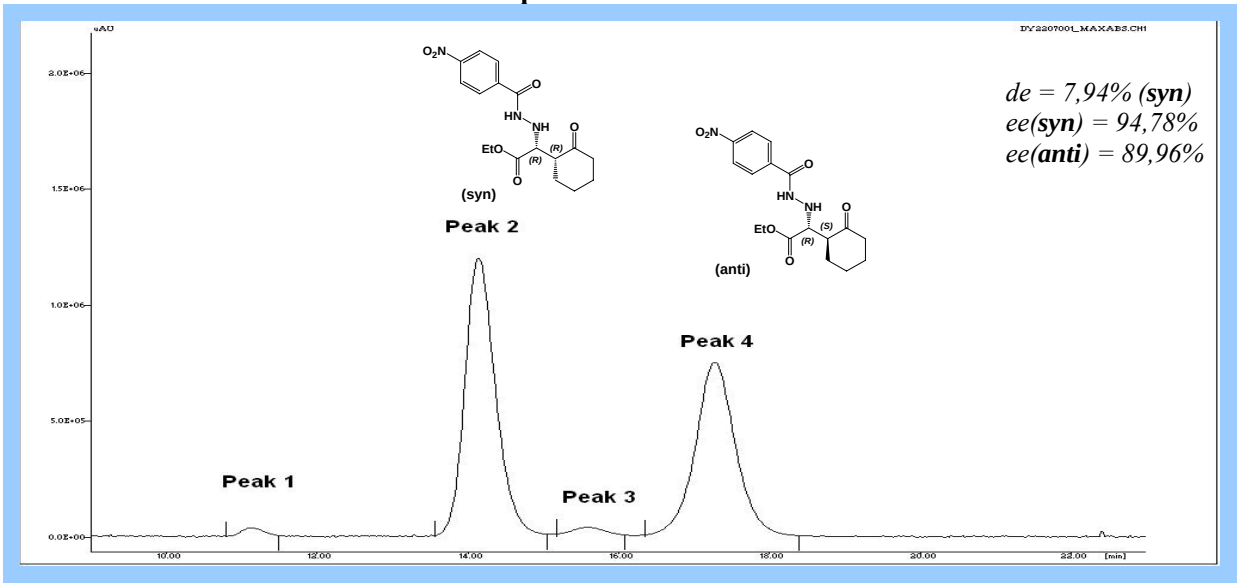
n-hexane/2-propanol/dichloromethane = 68/25/7, flow rate 0.8 ml/min, λ = 210nm:

Racemic mixture of **77q**




| # | Name | Rt | Area | %Area |
|---|---|---|---|---|
| 1 | Peak 1 | 11,267 | 36998249 | 25,37 |
| 2 | Peak 2 | 14,400 | 37282717 | 25,56 |
| 3 | Peak 3 | 15,840 | 37270076 | 25,56 |
| 4 | Peak 4 | 17,613 | 34285146 | 23,51 |

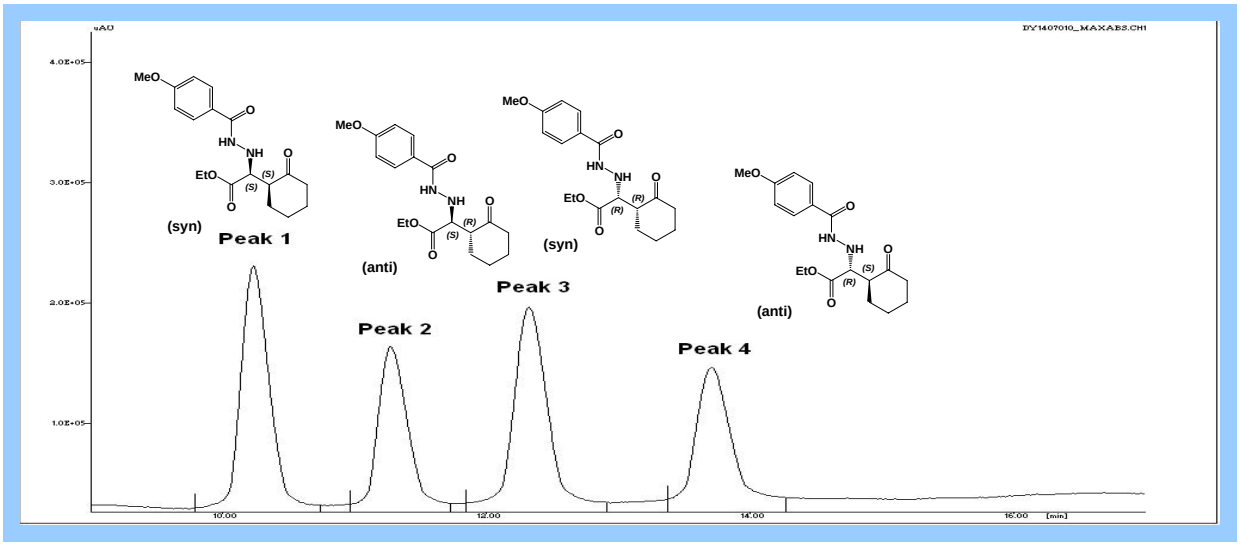
Product **77q** from Table 12 in Main Part




| # | Name | Rt | Area | %Area |
|---|---|---|---|---|
| 1 | Peak 1 | 11,120 | 892045 | 1,41 |
| 2 | Peak 2 | 14,133 | 33346844 | 52,56 |
| 3 | Peak 3 | 15,573 | 1466928 | 2,31 |
| 4 | Peak 4 | 17,267 | 27736465 | 43,72 |

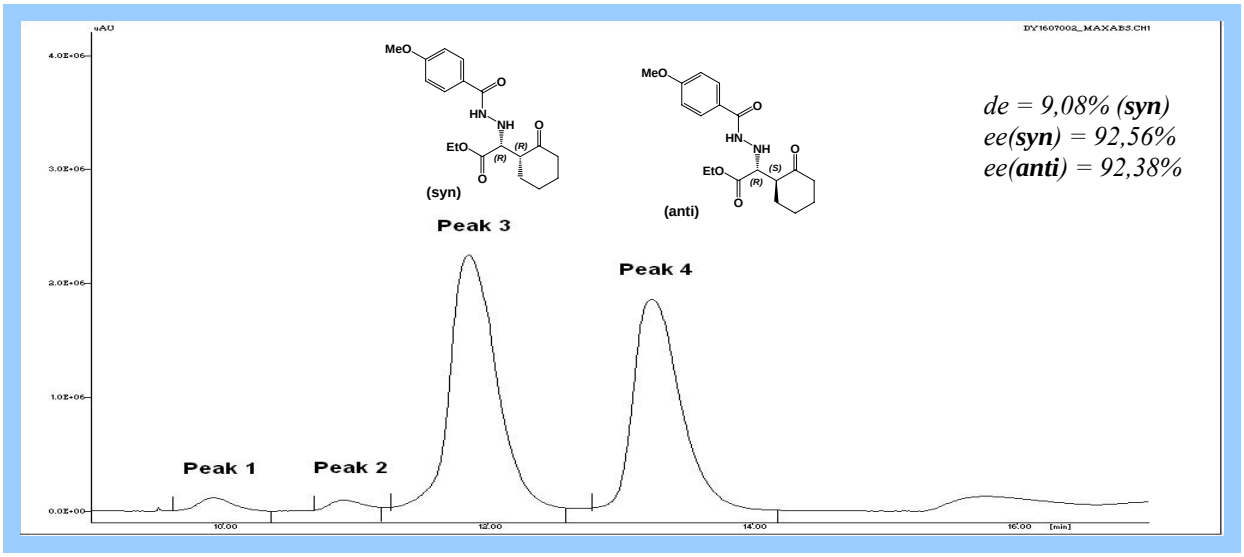
n-hexane/2-propanol/dichloromethane = 68/18/14, flow rate 0.8 ml/min, λ = 210nm:

Racemic mixture of **77r**




| # | Name | Rt | Area | %Area |
|---|---|---|---|---|
| 1 | Peak 1 | 10,227 | 4661930 | 27,66 |
| 2 | Peak 2 | 11,267 | 3445221 | 20,44 |
| 3 | Peak 3 | 12,320 | 4873696 | 28,92 |
| 4 | Peak 4 | 13,707 | 3873396 | 22,98 |

Product **77r** from Table 12 in Main Part




| # | Name | Rt | Area | %Area |
|---|---|---|---|---|
| 1 | Peak 1 | 9,920 | 2154512 | 2,03 |
| 2 | Peak 2 | 10,907 | 1837576 | 1,73 |
| 3 | Peak 3 | 11,853 | 55686288 | 52,51 |
| 4 | Peak 4 | 13,240 | 46379713 | 43,73 |

# G. Crystallographic Data

1. N-[(1S,2R)-2-methoxy-1-methyl-2-phenylethyl]-N'-(6-methylpyridin-2-yl) thiourea (**34**)
2. Ethyl 2-[N`-(4-bromobenzoyl)hydrazino]-4-oxopentanoate (**77l**)
3. Ethyl[N`-(4-bromobenzoyl)hydrazino]{(2E)-2-[(2,4-dinitrophenyl)hydrazono]cyclohexyl}acetate (**77p-hydrazone**)

1. N-[(1S,2R)-2-methoxy-1-methyl-2-phenylethyl]-

N'-(6-methylpyridin-2-yl) thiourea (**34**)

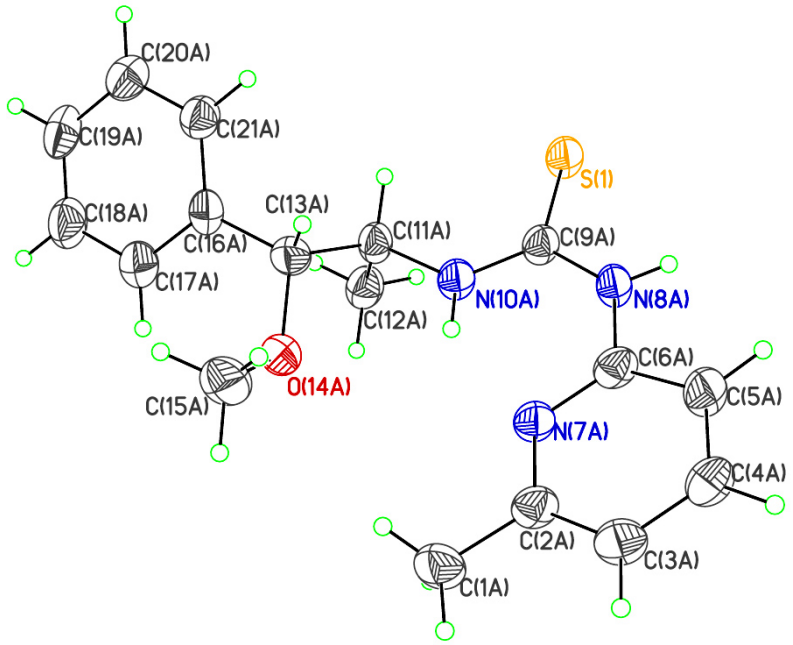



**Table 1.** Crystal data and structure refinement for **34**

| | | |
|---|---|---|
| Identification code | | |
| Empirical formula | $C_{17}H_{21}N_3OS$ | |
| Formula weight | 315.43 | |
| Temperature | 100(2) K | |
| Wavelength | 1.54178 Å | |
| Crystal system | Monoclinic | |
| Space group | P2(1) | |
| Unit cell dimensions | a = 9.863(2) Å | α= 90°. |
| | b = 23.217(2) Å | β= 97.31(3)°. |
| | c = 15.423(2) Å | γ = 90°. |
| Volume | 3503.0(9) $Å^3$ | |
| Z | 8 | |
| Density (calculated) | 1.196 $Mg/m^3$ | |
| Absorption coefficient | 1.675 $mm^{-1}$ | |
| F(000) | 1344 | |
| Crystal size | 0.50 x 0.15 x 0.05 $mm^3$ | |
| Theta range for data collection | 2.89 to 59.56°. | |
| Index ranges | -10<=h<=10, -25<=k<=25, 0<=l<=17 | |
| Reflections collected | 9899 | |
| Independent reflections | 9899 [R(int) = 0.0000] | |
| Completeness to theta = 59.56° | 97.4 % | |
| Absorption correction | Semi-empirical from equivalents | |
| Max. and min. transmission | 0.9209 and 0.4880 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 9899 / 13 / 839 | |
| Goodness-of-fit on $F^2$ | 1.025 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0319, wR2 = 0.0820 | |
| R indices (all data) | R1 = 0.0334, wR2 = 0.0833 | |
| Absolute structure parameter | -0.005(8) | |
| Extinction coefficient | 0.00098(10) | |
| Largest diff. peak and hole | 0.332 and -0.209 e.$Å^{-3}$ | |

**Table 2.** Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for **34**. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| S(1) | -10057(1) | 6388(1) | 1460(1) | 38(1) |
| S(2) | -6907(1) | 7680(1) | 1881(1) | 38(1) |
| S(3) | 2650(1) | 3763(1) | 3326(1) | 37(1) |
| S(4) | -201(1) | 5099(1) | 3560(1) | 41(1) |
| C(1A) | -4794(3) | 4817(1) | 232(2) | 49(1) |
| C(2A) | -4794(2) | 5370(1) | 739(2) | 37(1) |
| C(3A) | -3618(2) | 5672(1) | 1024(2) | 44(1) |
| C(4A) | -3716(2) | 6190(1) | 1467(2) | 46(1) |
| C(5A) | -4975(2) | 6387(1) | 1619(2) | 43(1) |
| C(6A) | -6120(2) | 6059(1) | 1301(2) | 36(1) |
| N(7A) | -6035(2) | 5560(1) | 880(1) | 34(1) |
| N(8A) | -7412(2) | 6267(1) | 1430(1) | 35(1) |
| C(9A) | -8658(2) | 6005(1) | 1279(1) | 33(1) |
| N(10A) | -8699(2) | 5466(1) | 998(1) | 34(1) |
| C(11A) | -9935(2) | 5116(1) | 839(2) | 34(1) |
| C(12A) | -10595(2) | 5180(1) | -103(2) | 41(1) |
| C(13A) | -9531(2) | 4494(1) | 1082(2) | 36(1) |
| O(14A) | -8558(2) | 4324(1) | 520(1) | 40(1) |
| C(15A) | -7698(3) | 3866(1) | 881(2) | 53(1) |
| C(16A) | -10775(2) | 4099(1) | 1018(2) | 38(1) |
| C(17A) | -11031(3) | 3693(1) | 359(2) | 47(1) |
| C(18A) | -12179(3) | 3340(1) | 324(2) | 53(1) |
| C(19A) | -13085(3) | 3400(1) | 927(2) | 51(1) |
| C(20A) | -12852(3) | 3809(1) | 1577(2) | 45(1) |
| C(21A) | -11695(2) | 4156(1) | 1621(2) | 40(1) |
| C(1B) | -12471(3) | 9404(1) | 2105(2) | 64(1) |
| C(2B) | -12359(3) | 8812(1) | 1724(2) | 46(1) |
| C(3B) | -13464(3) | 8511(1) | 1312(2) | 47(1) |
| C(4B) | -13260(2) | 7972(1) | 970(2) | 44(1) |
| C(5B) | -11965(2) | 7741(1) | 1038(2) | 40(1) |
| C(6B) | -10902(2) | 8068(1) | 1479(2) | 39(1) |
| N(7B) | -11074(2) | 8589(1) | 1807(1) | 42(1) |
| N(8B) | -9582(2) | 7828(1) | 1590(1) | 37(1) |
| C(9B) | -8362(2) | 8064(1) | 1923(1) | 35(1) |
| N(10B) | -8373(2) | 8593(1) | 2266(1) | 38(1) |
| C(11B) | -7158(2) | 8936(1) | 2543(2) | 38(1) |
| C(12B) | -6844(3) | 9320(1) | 1800(2) | 44(1) |
| C(13B) | -7396(2) | 9268(1) | 3377(2) | 43(1) |
| O(14B) | -8592(2) | 9611(1) | 3151(1) | 55(1) |
| C(15B) | -9195(4) | 9779(2) | 3905(2) | 82(1) |
| C(16B) | -6148(3) | 9626(1) | 3718(2) | 44(1) |
| C(17B) | -6015(3) | 10194(1) | 3476(2) | 58(1) |
| C(18B) | -4818(3) | 10490(1) | 3735(2) | 63(1) |
| C(19B) | -3748(3) | 10231(1) | 4246(2) | 59(1) |
| C(20B) | -3875(3) | 9663(1) | 4507(2) | 52(1) |
| C(21B) | -5075(3) | 9368(1) | 4238(2) | 46(1) |
| C(1C) | -3101(3) | 2098(1) | 3070(2) | 52(1) |
| C(2C) | -2867(2) | 2719(1) | 3311(2) | 39(1) |
| C(3C) | -3883(2) | 3072(1) | 3560(2) | 40(1) |
| C(4C) | -3561(2) | 3627(1) | 3830(2) | 39(1) |
| C(5C) | -2239(2) | 3829(1) | 3846(1) | 35(1) |
| C(6C) | -1285(2) | 3453(1) | 3546(1) | 35(1) |
| N(7C) | -1578(2) | 2915(1) | 3296(1) | 36(1) |
| N(8C) | 43(2) | 3656(1) | 3515(1) | 33(1) |
| C(9C) | 1150(2) | 3396(1) | 3233(1) | 33(1) |
| N(10C) | 993(2) | 2866(1) | 2917(1) | 37(1) |

| | | | | |
|---|---|---|---|---|
| C(11C) | 2095(2) | 2510(1) | 2665(2) | 37(1) |
| C(12C) | 2567(3) | 2084(1) | 3393(2) | 48(1) |
| C(13C) | 1614(2) | 2227(1) | 1785(2) | 38(1) |
| O(14C) | 466(2) | 1876(1) | 1902(1) | 46(1) |
| C(15C) | -398(3) | 1772(1) | 1101(2) | 64(1) |
| C(16C) | 2771(2) | 1893(1) | 1460(2) | 38(1) |
| C(17C) | 2913(3) | 1301(1) | 1579(2) | 46(1) |
| C(18C) | 4041(3) | 1017(1) | 1336(2) | 50(1) |
| C(19C) | 5033(3) | 1309(1) | 972(2) | 49(1) |
| C(20C) | 4897(3) | 1901(1) | 834(2) | 49(1) |
| C(21C) | 3771(3) | 2185(1) | 1082(2) | 44(1) |
| C(1D) | 5668(3) | 6626(1) | 4460(2) | 65(1) |
| C(2D) | 5402(2) | 6068(1) | 3986(2) | 44(1) |
| C(3D) | 6421(2) | 5741(1) | 3695(2) | 48(1) |
| C(4D) | 6072(2) | 5229(1) | 3259(2) | 42(1) |
| C(5D) | 4732(2) | 5049(1) | 3138(2) | 38(1) |
| C(6D) | 3775(2) | 5396(1) | 3480(1) | 35(1) |
| N(7D) | 4084(2) | 5899(1) | 3875(1) | 38(1) |
| N(8D) | 2423(2) | 5203(1) | 3423(1) | 34(1) |
| C(9D) | 1293(2) | 5469(1) | 3649(2) | 33(1) |
| N(10D) | 1417(2) | 6011(1) | 3933(1) | 34(1) |
| C(11D) | 274(2) | 6372(1) | 4116(2) | 34(1) |
| C(12D) | -34(3) | 6293(1) | 5047(2) | 43(1) |
| C(13D) | 619(2) | 6994(1) | 3898(2) | 36(1) |
| O(14D) | 1732(2) | 7162(1) | 4525(1) | 40(1) |
| C(15D) | 2470(3) | 7639(1) | 4240(2) | 60(1) |
| C(16D) | -637(2) | 7376(1) | 3882(2) | 39(1) |
| C(17D) | -793(3) | 7771(1) | 4535(2) | 57(1) |
| C(18D) | -1967(4) | 8105(1) | 4487(2) | 71(1) |
| C(19D) | -2987(3) | 8045(1) | 3806(2) | 62(1) |
| C(20D) | -2854(3) | 7652(1) | 3161(2) | 48(1) |
| C(21D) | -1674(2) | 7319(1) | 3198(2) | 41(1) |

**Table 3.** Bond lengths [Å] and angles [°] for **34**.

| | | | |
|---|---|---|---|
| S(1)-C(9A) | 1.694(2) | C(20A)-C(21A) | 1.391(3) |
| S(2)-C(9B) | 1.698(2) | C(1B)-C(2B) | 1.504(4) |
| S(3)-C(9C) | 1.697(2) | C(2B)-N(7B) | 1.360(3) |
| S(4)-C(9D) | 1.697(2) | C(2B)-C(3B) | 1.380(4) |
| C(1A)-C(2A) | 1.503(3) | C(3B)-C(4B) | 1.383(4) |
| C(2A)-N(7A) | 1.345(3) | C(4B)-C(5B) | 1.378(3) |
| C(2A)-C(3A) | 1.378(3) | C(5B)-C(6B) | 1.400(3) |
| C(3A)-C(4A) | 1.394(4) | C(6B)-N(7B) | 1.330(3) |
| C(4A)-C(5A) | 1.371(4) | C(6B)-N(8B) | 1.407(3) |
| C(5A)-C(6A) | 1.398(3) | N(8B)-C(9B) | 1.361(3) |
| C(6A)-N(7A) | 1.335(3) | C(9B)-N(10B) | 1.337(3) |
| C(6A)-N(8A) | 1.400(3) | N(10B)-C(11B) | 1.457(3) |
| N(8A)-C(9A) | 1.365(3) | C(11B)-C(12B) | 1.515(3) |
| C(9A)-N(10A) | 1.322(3) | C(11B)-C(13B) | 1.542(3) |
| N(10A)-C(11A) | 1.460(3) | C(13B)-O(14B) | 1.429(3) |
| C(11A)-C(12A) | 1.522(3) | C(13B)-C(16B) | 1.522(4) |
| C(11A)-C(13A) | 1.531(3) | O(14B)-C(15B) | 1.427(4) |
| C(13A)-O(14A) | 1.429(3) | C(16B)-C(21B) | 1.379(4) |
| C(13A)-C(16A) | 1.525(3) | C(16B)-C(17B) | 1.382(4) |
| O(14A)-C(15A) | 1.429(3) | C(17B)-C(18B) | 1.381(4) |
| C(16A)-C(17A) | 1.385(3) | C(18B)-C(19B) | 1.373(4) |
| C(16A)-C(21A) | 1.386(3) | C(19B)-C(20B) | 1.388(4) |
| C(17A)-C(18A) | 1.393(4) | C(20B)-C(21B) | 1.384(4) |
| C(18A)-C(19A) | 1.375(4) | C(1C)-C(2C) | 1.498(4) |
| C(19A)-C(20A) | 1.379(4) | C(2C)-N(7C) | 1.353(3) |

| | | | |
|---|---|---|---|
| C(2C)-C(3C) | 1.386(3) | C(15A)-O(14A)-C(13A) | 112.33(18) |
| C(3C)-C(4C) | 1.379(3) | C(17A)-C(16A)-C(21A) | 118.9(2) |
| C(4C)-C(5C) | 1.382(3) | C(17A)-C(16A)-C(13A) | 121.8(2) |
| C(5C)-C(6C) | 1.403(3) | C(21A)-C(16A)-C(13A) | 119.3(2) |
| C(6C)-N(7C) | 1.329(3) | C(16A)-C(17A)-C(18A) | 120.0(2) |
| C(6C)-N(8C) | 1.399(3) | C(19A)-C(18A)-C(17A) | 120.6(2) |
| N(8C)-C(9C) | 1.366(3) | C(18A)-C(19A)-C(20A) | 119.9(2) |
| C(9C)-N(10C) | 1.326(3) | C(19A)-C(20A)-C(21A) | 119.6(2) |
| N(10C)-C(11C) | 1.457(3) | C(16A)-C(21A)-C(20A) | 121.0(2) |
| C(11C)-C(12C) | 1.523(3) | N(7B)-C(2B)-C(3B) | 121.6(2) |
| C(11C)-C(13C) | 1.528(3) | N(7B)-C(2B)-C(1B) | 115.1(2) |
| C(13C)-O(14C) | 1.424(3) | C(3B)-C(2B)-C(1B) | 123.3(2) |
| C(13C)-C(16C) | 1.517(3) | C(2B)-C(3B)-C(4B) | 119.2(2) |
| O(14C)-C(15C) | 1.429(3) | C(5B)-C(4B)-C(3B) | 120.2(2) |
| C(16C)-C(21C) | 1.386(3) | C(4B)-C(5B)-C(6B) | 117.0(2) |
| C(16C)-C(17C) | 1.390(3) | N(7B)-C(6B)-C(5B) | 123.8(2) |
| C(17C)-C(18C) | 1.386(4) | N(7B)-C(6B)-N(8B) | 118.3(2) |
| C(18C)-C(19C) | 1.369(4) | C(5B)-C(6B)-N(8B) | 117.9(2) |
| C(19C)-C(20C) | 1.393(4) | C(6B)-N(7B)-C(2B) | 118.2(2) |
| C(20C)-C(21C) | 1.387(4) | C(9B)-N(8B)-C(6B) | 130.2(2) |
| C(1D)-C(2D) | 1.495(4) | N(10B)-C(9B)-N(8B) | 117.9(2) |
| C(2D)-N(7D) | 1.348(3) | N(10B)-C(9B)-S(2) | 123.11(18) |
| C(2D)-C(3D) | 1.380(4) | N(8B)-C(9B)-S(2) | 119.00(16) |
| C(3D)-C(4D) | 1.386(4) | C(9B)-N(10B)-C(11B) | 124.8(2) |
| C(4D)-C(5D) | 1.376(3) | N(10B)-C(11B)-C(12B) | 109.82(19) |
| C(5D)-C(6D) | 1.394(3) | N(10B)-C(11B)-C(13B) | 108.14(19) |
| C(6D)-N(7D) | 1.336(3) | C(12B)-C(11B)-C(13B) | 113.82(19) |
| C(6D)-N(8D) | 1.399(3) | O(14B)-C(13B)-C(16B) | 112.76(19) |
| N(8D)-C(9D) | 1.358(3) | O(14B)-C(13B)-C(11B) | 106.50(19) |
| C(9D)-N(10D) | 1.333(3) | C(16B)-C(13B)-C(11B) | 111.0(2) |
| N(10D)-C(11D) | 1.460(3) | C(15B)-O(14B)-C(13B) | 111.7(2) |
| C(11D)-C(12D) | 1.516(3) | C(21B)-C(16B)-C(17B) | 118.5(2) |
| C(11D)-C(13D) | 1.532(3) | C(21B)-C(16B)-C(13B) | 119.5(2) |
| C(13D)-O(14D) | 1.422(3) | C(17B)-C(16B)-C(13B) | 121.8(2) |
| C(13D)-C(16D) | 1.521(3) | C(18B)-C(17B)-C(16B) | 120.3(3) |
| O(14D)-C(15D) | 1.425(3) | C(19B)-C(18B)-C(17B) | 121.0(3) |
| C(16D)-C(21D) | 1.379(3) | C(18B)-C(19B)-C(20B) | 119.4(3) |
| C(16D)-C(17D) | 1.384(3) | C(21B)-C(20B)-C(19B) | 119.2(2) |
| C(17D)-C(18D) | 1.388(4) | C(16B)-C(21B)-C(20B) | 121.6(2) |
| C(18D)-C(19D) | 1.367(5) | N(7C)-C(2C)-C(3C) | 121.3(2) |
| C(19D)-C(20D) | 1.368(4) | N(7C)-C(2C)-C(1C) | 115.8(2) |
| C(20D)-C(21D) | 1.393(3) | C(3C)-C(2C)-C(1C) | 122.9(2) |
| N(7A)-C(2A)-C(3A) | 121.9(2) | C(4C)-C(3C)-C(2C) | 119.3(2) |
| N(7A)-C(2A)-C(1A) | 115.2(2) | C(3C)-C(4C)-C(5C) | 120.2(2) |
| C(3A)-C(2A)-C(1A) | 122.9(2) | C(4C)-C(5C)-C(6C) | 117.0(2) |
| C(2A)-C(3A)-C(4A) | 119.1(2) | N(7C)-C(6C)-N(8C) | 118.5(2) |
| C(5A)-C(4A)-C(3A) | 119.5(2) | N(7C)-C(6C)-C(5C) | 123.3(2) |
| C(4A)-C(5A)-C(6A) | 117.8(2) | N(8C)-C(6C)-C(5C) | 118.2(2) |
| N(7A)-C(6A)-C(5A) | 123.0(2) | C(6C)-N(7C)-C(2C) | 118.8(2) |
| N(7A)-C(6A)-N(8A) | 118.85(19) | C(9C)-N(8C)-C(6C) | 130.73(19) |
| C(5A)-C(6A)-N(8A) | 118.1(2) | N(10C)-C(9C)-N(8C) | 117.81(19) |
| C(6A)-N(7A)-C(2A) | 118.59(19) | N(10C)-C(9C)-S(3) | 123.84(17) |
| C(9A)-N(8A)-C(6A) | 129.68(19) | N(8C)-C(9C)-S(3) | 118.34(16) |
| N(10A)-C(9A)-N(8A) | 117.8(2) | C(9C)-N(10C)-C(11C) | 124.65(19) |
| N(10A)-C(9A)-S(1) | 124.00(17) | N(10C)-C(11C)-C(12C) | 109.88(19) |
| N(8A)-C(9A)-S(1) | 118.19(16) | N(10C)-C(11C)-C(13C) | 108.82(19) |
| C(9A)-N(10A)-C(11A) | 124.89(18) | C(12C)-C(11C)-C(13C) | 114.01(19) |
| N(10A)-C(11A)-C(12A) | 110.60(18) | O(14C)-C(13C)-C(16C) | 113.11(18) |
| N(10A)-C(11A)-C(13A) | 107.38(17) | O(14C)-C(13C)-C(11C) | 107.24(18) |
| C(12A)-C(11A)-C(13A) | 113.15(18) | C(16C)-C(13C)-C(11C) | 110.62(18) |
| O(14A)-C(13A)-C(16A) | 113.05(18) | C(13C)-O(14C)-C(15C) | 112.6(2) |
| O(14A)-C(13A)-C(11A) | 106.60(18) | C(21C)-C(16C)-C(17C) | 118.3(2) |
| C(16A)-C(13A)-C(11A) | 111.65(18) | C(21C)-C(16C)-C(13C) | 119.6(2) |

| | |
|---|---|
| C(17C)-C(16C)-C(13C)121.9(2) | N(10D)-C(9D)-S(4) 123.19(17) |
| C(18C)-C(17C)-C(16C)120.4(2) | N(8D)-C(9D)-S(4) 118.72(16) |
| C(19C)-C(18C)-C(17C)120.9(2) | C(9D)-N(10D)-C(11D) 124.32(19) |
| C(18C)-C(19C)-C(20C)119.5(2) | N(10D)-C(11D)-C(12D)111.44(19) |
| C(21C)-C(20C)-C(19C)119.5(2) | N(10D)-C(11D)-C(13D)107.50(17) |
| C(16C)-C(21C)-C(20C)121.3(2) | C(12D)-C(11D)-C(13D)113.47(19) |
| N(7D)-C(2D)-C(3D) 122.0(2) | O(14D)-C(13D)-C(16D)114.09(18) |
| N(7D)-C(2D)-C(1D) 114.9(2) | O(14D)-C(13D)-C(11D)106.45(18) |
| C(3D)-C(2D)-C(1D) 123.1(2) | C(16D)-C(13D)-C(11D)110.57(18) |
| C(2D)-C(3D)-C(4D) 118.9(2) | C(13D)-O(14D)-C(15D)112.57(18) |
| C(5D)-C(4D)-C(3D) 120.0(2) | C(21D)-C(16D)-C(17D)118.7(2) |
| C(4D)-C(5D)-C(6D) 117.3(2) | C(21D)-C(16D)-C(13D)118.6(2) |
| N(7D)-C(6D)-C(5D) 123.5(2) | C(17D)-C(16D)-C(13D)122.7(2) |
| N(7D)-C(6D)-N(8D) 118.0(2) | C(16D)-C(17D)-C(18D)120.1(3) |
| C(5D)-C(6D)-N(8D) 118.5(2) | C(19D)-C(18D)-C(17D)120.7(3) |
| C(6D)-N(7D)-C(2D) 118.2(2) | C(18D)-C(19D)-C(20D)119.9(3) |
| C(9D)-N(8D)-C(6D) 130.1(2) | C(19D)-C(20D)-C(21D)119.8(2) |
| N(10D)-C(9D)-N(8D) 118.1(2) | C(16D)-C(21D)-C(20D)120.8(2) |

**Table 4.** Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **34**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| S(1) | 23(1) | 34(1) | 59(1) | -6(1) | 8(1) | 0(1) |
| S(2) | 29(1) | 32(1) | 53(1) | -3(1) | 5(1) | 1(1) |
| S(3) | 24(1) | 34(1) | 54(1) | -2(1) | 4(1) | -1(1) |
| S(4) | 22(1) | 33(1) | 69(1) | -6(1) | 5(1) | -2(1) |
| C(1A) | 35(1) | 49(2) | 64(2) | -10(1) | 10(1) | 7(1) |
| C(2A) | 26(1) | 40(1) | 46(1) | 2(1) | 5(1) | 4(1) |
| C(3A) | 27(1) | 50(2) | 55(2) | -2(1) | 5(1) | 7(1) |
| C(4A) | 23(1) | 57(2) | 58(2) | -8(1) | 2(1) | -8(1) |
| C(5A) | 26(1) | 43(1) | 58(1) | -9(1) | 1(1) | -2(1) |
| C(6A) | 23(1) | 40(1) | 44(1) | 2(1) | 5(1) | 1(1) |
| N(7A) | 25(1) | 34(1) | 45(1) | -1(1) | 6(1) | 2(1) |
| N(8A) | 21(1) | 29(1) | 55(1) | -9(1) | 4(1) | 0(1) |
| C(9A) | 25(1) | 31(1) | 42(1) | 0(1) | 4(1) | -1(1) |
| N(10A) | 22(1) | 31(1) | 51(1) | -3(1) | 5(1) | 1(1) |
| C(11A) | 26(1) | 28(1) | 47(1) | -3(1) | 4(1) | -3(1) |
| C(12A) | 34(1) | 38(1) | 50(1) | 2(1) | 4(1) | -3(1) |
| C(13A) | 33(1) | 36(1) | 41(1) | -4(1) | 8(1) | 0(1) |
| O(14A) | 40(1) | 32(1) | 49(1) | 0(1) | 13(1) | 3(1) |
| C(15A) | 54(2) | 43(2) | 66(2) | 7(1) | 17(1) | 18(1) |
| C(16A) | 41(1) | 27(1) | 46(1) | 0(1) | 4(1) | -3(1) |
| C(17A) | 54(2) | 38(1) | 50(1) | -5(1) | 8(1) | -8(1) |
| C(18A) | 63(2) | 41(1) | 53(2) | -6(1) | 5(1) | -16(1) |
| C(19A) | 56(2) | 41(1) | 53(2) | 6(1) | -2(1) | -19(1) |
| C(20A) | 44(1) | 47(2) | 44(1) | 4(1) | 5(1) | -9(1) |
| C(21A) | 40(1) | 39(1) | 41(1) | -1(1) | 5(1) | -6(1) |
| C(1B) | 43(2) | 49(2) | 101(2) | -13(2) | 11(2) | 12(1) |
| C(2B) | 37(1) | 41(1) | 61(2) | -1(1) | 9(1) | 7(1) |
| C(3B) | 33(1) | 51(2) | 57(1) | 4(1) | 7(1) | 7(1) |
| C(4B) | 33(1) | 48(1) | 51(1) | 2(1) | 3(1) | 0(1) |
| C(5B) | 35(1) | 39(1) | 46(1) | -1(1) | 6(1) | -2(1) |
| C(6B) | 35(1) | 35(1) | 48(1) | 6(1) | 13(1) | 2(1) |
| N(7B) | 34(1) | 36(1) | 57(1) | -1(1) | 10(1) | 1(1) |
| N(8B) | 26(1) | 28(1) | 58(1) | -2(1) | 7(1) | 0(1) |
| C(9B) | 36(1) | 29(1) | 41(1) | 1(1) | 7(1) | 2(1) |
| N(10B) | 28(1) | 34(1) | 51(1) | -3(1) | 6(1) | 3(1) |
| C(11B) | 33(1) | 32(1) | 48(1) | -4(1) | 1(1) | 1(1) |

| | | | | | | |
|---|---|---|---|---|---|---|
| C(12B) | 37(1) | 41(1) | 51(1) | -1(1) | 1(1) | -5(1) |
| C(13B) | 44(2) | 33(1) | 51(1) | -4(1) | 6(1) | 3(1) |
| O(14B) | 48(1) | 48(1) | 68(1) | -16(1) | 3(1) | 12(1) |
| C(15B) | 66(2) | 89(3) | 91(2) | -40(2) | 15(2) | 21(2) |
| C(16B) | 51(2) | 37(1) | 42(1) | -4(1) | -2(1) | 5(1) |
| C(17B) | 68(2) | 36(1) | 63(2) | -2(1) | -18(1) | 2(1) |
| C(18B) | 78(2) | 38(2) | 67(2) | 0(1) | -13(2) | -12(1) |
| C(19B) | 56(2) | 59(2) | 57(2) | -14(1) | -8(1) | -8(1) |
| C(20B) | 53(2) | 54(2) | 45(1) | -9(1) | -4(1) | 7(1) |
| C(21B) | 58(2) | 38(1) | 42(1) | -1(1) | 6(1) | 9(1) |
| C(1C) | 34(1) | 44(2) | 77(2) | -6(1) | 2(1) | -8(1) |
| C(2C) | 28(1) | 40(1) | 49(1) | 3(1) | 0(1) | -4(1) |
| C(3C) | 26(1) | 44(1) | 50(1) | 4(1) | 1(1) | -2(1) |
| C(4C) | 29(1) | 43(1) | 45(1) | 1(1) | 6(1) | 5(1) |
| C(5C) | 28(1) | 35(1) | 43(1) | 1(1) | 4(1) | 3(1) |
| C(6C) | 26(1) | 37(1) | 42(1) | 2(1) | 0(1) | 3(1) |
| N(7C) | 26(1) | 35(1) | 47(1) | 0(1) | 0(1) | -1(1) |
| N(8C) | 22(1) | 25(1) | 53(1) | -5(1) | 4(1) | -1(1) |
| C(9C) | 28(1) | 31(1) | 38(1) | 0(1) | -1(1) | 1(1) |
| N(10C) | 23(1) | 35(1) | 52(1) | -4(1) | 4(1) | 1(1) |
| C(11C) | 31(1) | 33(1) | 47(1) | -3(1) | 7(1) | 3(1) |
| C(12C) | 44(2) | 49(2) | 49(1) | 2(1) | 4(1) | 13(1) |
| C(13C) | 33(1) | 31(1) | 49(1) | 1(1) | 2(1) | -2(1) |
| O(14C) | 34(1) | 42(1) | 63(1) | -9(1) | 4(1) | -6(1) |
| C(15C) | 46(2) | 62(2) | 78(2) | -22(2) | -10(1) | -4(1) |
| C(16C) | 38(1) | 34(1) | 43(1) | -3(1) | 3(1) | 0(1) |
| C(17C) | 45(2) | 36(1) | 58(2) | -1(1) | 11(1) | -1(1) |
| C(18C) | 51(2) | 33(1) | 67(2) | -4(1) | 10(1) | 3(1) |
| C(19C) | 45(2) | 46(2) | 56(2) | -9(1) | 10(1) | 4(1) |
| C(20C) | 48(2) | 47(2) | 54(2) | -4(1) | 13(1) | -2(1) |
| C(21C) | 47(2) | 35(1) | 50(1) | -1(1) | 10(1) | 1(1) |
| C(1D) | 41(2) | 76(2) | 82(2) | -33(2) | 18(1) | -25(1) |
| C(2D) | 27(1) | 50(2) | 54(2) | -6(1) | 5(1) | -10(1) |
| C(3D) | 25(1) | 55(2) | 64(2) | 2(1) | 6(1) | -6(1) |
| C(4D) | 22(1) | 43(1) | 63(2) | 0(1) | 9(1) | 7(1) |
| C(5D) | 29(1) | 34(1) | 52(1) | 2(1) | 8(1) | 4(1) |
| C(6D) | 26(1) | 44(1) | 37(1) | 4(1) | 3(1) | 1(1) |
| N(7D) | 27(1) | 41(1) | 47(1) | -5(1) | 4(1) | -5(1) |
| N(8D) | 19(1) | 29(1) | 55(1) | -4(1) | 4(1) | -2(1) |
| C(9D) | 27(1) | 29(1) | 43(1) | -2(1) | 4(1) | 2(1) |
| N(10D) | 21(1) | 32(1) | 49(1) | -3(1) | 3(1) | -3(1) |
| C(11D) | 25(1) | 30(1) | 46(1) | -3(1) | 5(1) | 3(1) |
| C(12D) | 37(1) | 42(1) | 53(1) | 1(1) | 12(1) | 1(1) |
| C(13D) | 34(1) | 33(1) | 39(1) | -4(1) | 3(1) | -1(1) |
| O(14D) | 40(1) | 33(1) | 44(1) | -2(1) | 1(1) | -9(1) |
| C(15D) | 70(2) | 50(2) | 56(2) | 0(1) | -1(1) | -29(2) |
| C(16D) | 47(1) | 31(1) | 40(1) | 1(1) | 8(1) | 4(1) |
| C(17D) | 72(2) | 49(2) | 47(1) | -8(1) | -4(1) | 21(1) |
| C(18D) | 98(2) | 58(2) | 54(2) | -14(1) | -1(2) | 40(2) |
| C(19D) | 69(2) | 59(2) | 59(2) | 2(1) | 12(1) | 33(2) |
| C(20D) | 46(2) | 46(1) | 52(1) | 5(1) | 6(1) | 10(1) |
| C(21D) | 42(1) | 35(1) | 45(1) | -2(1) | 10(1) | 4(1) |

**Table 5.** Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters (Å$^2$x $10^3$) for **34**.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(1A1) | -5217 | 4512 | 545 | 73 |
| H(1A2) | -3851 | 4709 | 168 | 73 |

| | | | | |
|---|---|---|---|---|
| H(1A3) | -5314 | 4870 | -348 | 73 |
| H(3A1) | -2752 | 5528 | 919 | 53 |
| H(4A1) | -2917 | 6406 | 1661 | 55 |
| H(5A1) | -5066 | 6734 | 1932 | 51 |
| H(8A) | -7410(20) | 6616(8) | 1583(13) | 22(5) |
| H(10A) | -7970(20) | 5330(11) | 872(16) | 38(7) |
| H(11A) | -10597 | 5252 | 1235 | 41 |
| H(12A) | -10830 | 5585 | -220 | 61 |
| H(12A) | -11427 | 4945 | -196 | 61 |
| H(12A) | -9954 | 5052 | -499 | 61 |
| H(13A) | -9073 | 4489 | 1699 | 43 |
| H(15A) | -7058 | 3760 | 471 | 80 |
| H(15A) | -8262 | 3531 | 986 | 80 |
| H(15A) | -7185 | 3991 | 1435 | 80 |
| H(17A) | -10424 | 3655 | -69 | 57 |
| H(18A) | -12338 | 3056 | -120 | 63 |
| H(19A) | -13870 | 3161 | 894 | 61 |
| H(20A) | -13476 | 3853 | 1994 | 54 |
| H(21A) | -11535 | 4437 | 2070 | 48 |
| H(1B1) | -12377 | 9378 | 2744 | 97 |
| H(1B2) | -13363 | 9570 | 1888 | 97 |
| H(1B3) | -11744 | 9650 | 1931 | 97 |
| H(3B1) | -14356 | 8673 | 1263 | 56 |
| H(4B1) | -14015 | 7761 | 688 | 53 |
| H(5B1) | -11800 | 7375 | 796 | 48 |
| H(8B) | -9550(30) | 7477(8) | 1478(17) | 49(8) |
| H(10B) | -9108(19) | 8764(9) | 2245(14) | 26(6) |
| H(11B) | -6370 | 8668 | 2694 | 46 |
| H(12B) | -6781 | 9085 | 1279 | 65 |
| H(12B) | -5973 | 9519 | 1968 | 65 |
| H(12B) | -7575 | 9605 | 1672 | 65 |
| H(13B) | -7578 | 8985 | 3837 | 52 |
| H(15B) | -10008 | 10014 | 3726 | 123 |
| H(15B) | -8534 | 10003 | 4296 | 123 |
| H(15B) | -9457 | 9434 | 4211 | 123 |
| H(17B) | -6749 | 10381 | 3129 | 70 |
| H(18B) | -4733 | 10879 | 3558 | 75 |
| H(19B) | -2928 | 10438 | 4420 | 70 |
| H(20B) | -3148 | 9479 | 4866 | 62 |
| H(21B) | -5162 | 8980 | 4415 | 55 |
| H(1C1) | -2542 | 1994 | 2612 | 78 |
| H(1C2) | -4069 | 2039 | 2854 | 78 |
| H(1C3) | -2846 | 1857 | 3586 | 78 |
| H(3C1) | -4792 | 2933 | 3544 | 48 |
| H(4C1) | -4248 | 3871 | 4006 | 47 |
| H(5C1) | -1988 | 4205 | 4050 | 42 |
| H(8C) | 180(20) | 4007(8) | 3603(14) | 29(6) |
| H(10C) | 230(20) | 2725(11) | 2910(16) | 42(7) |
| H(11C) | 2882 | 2768 | 2587 | 44 |
| H(12C) | 2804 | 2294 | 3943 | 71 |
| H(12C) | 3371 | 1875 | 3247 | 71 |
| H(12C) | 1830 | 1811 | 3456 | 71 |
| H(13C) | 1310 | 2535 | 1351 | 45 |
| H(15C) | -1113 | 1497 | 1203 | 96 |
| H(15C) | 147 | 1614 | 668 | 96 |
| H(15C) | -820 | 2135 | 882 | 96 |
| H(17C) | 2232 | 1091 | 1828 | 55 |
| H(18C) | 4127 | 612 | 1423 | 60 |
| H(19C) | 5808 | 1111 | 815 | 58 |
| H(20C) | 5570 | 2107 | 573 | 59 |
| H(21C) | 3684 | 2589 | 990 | 52 |
| H(1D1) | 5342 | 6602 | 5033 | 98 |
| H(1D2) | 5186 | 6937 | 4119 | 98 |

| | | | | |
|---|---|---|---|---|
| H(1D3) | 6652 | 6706 | 4539 | 98 |
| H(3D1) | 7346 | 5864 | 3791 | 57 |
| H(4D1) | 6758 | 5002 | 3044 | 51 |
| H(5D1) | 4470 | 4703 | 2833 | 46 |
| H(8D) | 2290(30) | 4849(8) | 3324(15) | 37(7) |
| H(10D) | 2208(19) | 6137(9) | 4013(14) | 25(6) |
| H(11D) | -553 | 6253 | 3712 | 40 |
| H(12D) | -252 | 5887 | 5142 | 65 |
| H(12D) | -815 | 6534 | 5145 | 65 |
| H(12D) | 767 | 6405 | 5454 | 65 |
| H(13D) | 928 | 7002 | 3306 | 43 |
| H(15D) | 3251 | 7725 | 4680 | 89 |
| H(15D) | 1868 | 7976 | 4162 | 89 |
| H(15D) | 2797 | 7544 | 3684 | 89 |
| H(17D) | -97 | 7813 | 5016 | 68 |
| H(18D) | -2062 | 8379 | 4933 | 85 |
| H(19D) | -3786 | 8276 | 3779 | 74 |
| H(20D) | -3566 | 7607 | 2690 | 58 |
| H(21D) | -1582 | 7049 | 2747 | 49 |

## 2. Ethyl 2-[N`-(4-bromobenzoyl)hydrazino]-4-oxopentanoate (**77l**)

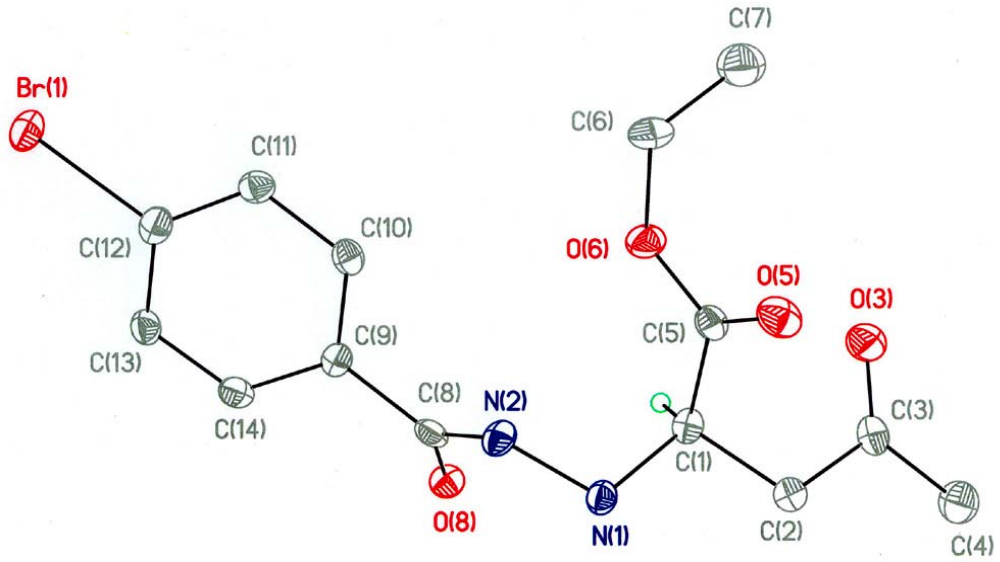



**Table 1.** Crystal data and structure refinement for **77l**

| | | |
|---|---|---|
| Identification code | | |
| Empirical formula | $C_{14}H_{17}BrN_2O_4$ | |
| Formula weight | 357.21 | |
| Temperature | 100(2) K | |
| Wavelength | 1.54178 Å | |
| Crystal system | Monoclinic | |
| Space group | P21 | |
| Unit cell dimensions | a = 10.198(2) Å | α= 90°. |
| | b = 6.5940(13) Å | β= 113.36(3)°. |
| | c = 11.994(2) Å | γ = 90°. |
| Volume | 740.4(3) $Å^3$ | |
| Z | 2 | |

| | |
|---|---|
| Density (calculated) | 1.602 $Mg/m^3$ |
| Absorption coefficient | 3.952 $mm^{-1}$ |
| F(000) | 364 |
| Crystal size | 0.20 x 0.04 x 0.04 $mm^3$ |
| Theta range for data collection | 4.01 to 59.12°. |
| Index ranges | -11<=h<=11, -7<=k<=7, -13<=l<=13 |
| Reflections collected | 9760 |
| Independent reflections | 2092 [R(int) = 0.0279] |
| Completeness to theta = 59.12° | 98.3 % |
| Absorption correction | Semi-empirical from equivalents |
| Max. and min. transmission | 0.8579 and 0.5053 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 2092 / 3 / 198 |
| Goodness-of-fit on $F^2$ | 1.061 |
| Final R indices [I>2sigma(I)] | R1 = 0.0170, wR2 = 0.0401 |
| R indices (all data) | R1 = 0.0179, wR2 = 0.0406 |
| Absolute structure parameter | -0.002(14) |
| Largest diff. peak and hole | 0.217 and -0.253 $e.Å^{-3}$ |

**Table 2.** Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for **77l**. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | | | | |
|---|---|---|---|---|
| Br(1) | -2317(1) | 1114(1) | 2333(1) | 25(1) |
| N(1) | 5637(2) | 6269(4) | 5834(1) | 16(1) |
| C(1) | 6048(2) | 6056(5) | 7169(2) | 16(1) |
| N(2) | 4272(2) | 5375(3) | 5166(2) | 17(1) |
| C(2) | 7490(2) | 7115(4) | 7821(2) | 20(1) |
| O(3) | 7367(1) | 6159(4) | 9689(1) | 28(1) |
| C(3) | 7963(2) | 7168(4) | 9184(2) | 22(1) |
| C(4) | 9179(3) | 8597(4) | 9858(2) | 31(1) |
| O(5) | 7127(2) | 2720(3) | 7705(1) | 24(1) |
| C(5) | 6109(2) | 3812(3) | 7520(2) | 17(1) |
| C(6) | 4701(2) | 1056(6) | 7733(2) | 26(1) |
| O(6) | 4844(2) | 3206(2) | 7507(1) | 23(1) |
| C(7) | 5191(3) | 651(4) | 9057(2) | 33(1) |
| C(8) | 3050(2) | 6444(4) | 4903(2) | 17(1) |
| O(8) | 3020(2) | 8275(2) | 5133(1) | 18(1) |
| C(9) | 1725(2) | 5180(3) | 4309(2) | 16(1) |
| C(10) | 1647(2) | 3225(3) | 4729(2) | 18(1) |
| C(11) | 436(2) | 2023(4) | 4157(2) | 18(1) |
| C(12) | -687(2) | 2803(4) | 3151(2) | 20(1) |
| C(13) | -651(2) | 4758(4) | 2722(2) | 19(1) |
| C(14) | 557(2) | 5958(5) | 3315(2) | 19(1) |

**Table 3.** Bond lengths [Å] and angles [°] for **77l**.

| | | | |
|---|---|---|---|
| Br(1)-C(12) | 1.916(2) | C(1)-C(2) | 1.533(3) |
| N(1)-N(2) | 1.430(3) | N(2)-C(8) | 1.356(3) |
| N(1)-C(1) | 1.492(2) | C(2)-C(3) | 1.510(3) |
| C(1)-C(5) | 1.533(4) | O(3)-C(3) | 1.213(3) |

| | | | |
|---|---|---|---|
| C(3)-C(4) | 1.511(4) | O(3)-C(3)-C(4) | 122.9(2) |
| O(5)-C(5) | 1.210(3) | C(2)-C(3)-C(4) | 115.82(19) |
| C(5)-O(6) | 1.345(3) | O(5)-C(5)-O(6) | 125.1(2) |
| C(6)-O(6) | 1.462(4) | O(5)-C(5)-C(1) | 124.30(19) |
| C(6)-C(7) | 1.487(3) | O(6)-C(5)-C(1) | 110.43(17) |
| C(8)-O(8) | 1.242(3) | O(6)-C(6)-C(7) | 110.8(2) |
| C(8)-C(9) | 1.505(3) | C(5)-O(6)-C(6) | 116.88(16) |
| C(9)-C(10) | 1.397(3) | O(8)-C(8)-N(2) | 123.76(19) |
| C(9)-C(14) | 1.406(3) | O(8)-C(8)-C(9) | 123.15(19) |
| C(10)-C(11) | 1.397(3) | N(2)-C(8)-C(9) | 113.1(2) |
| C(11)-C(12) | 1.391(3) | C(10)-C(9)-C(14) | 119.5(2) |
| C(12)-C(13) | 1.394(3) | C(10)-C(9)-C(8) | 120.56(19) |
| C(13)-C(14) | 1.398(3) | C(14)-C(9)-C(8) | 120.0(2) |
| N(2)-N(1)-C(1) | 111.08(16) | C(11)-C(10)-C(9) | 120.8(2) |
| N(1)-C(1)-C(5) | 110.4(2) | C(12)-C(11)-C(10) | 118.6(2) |
| N(1)-C(1)-C(2) | 108.00(17) | C(11)-C(12)-C(13) | 121.9(2) |
| C(5)-C(1)-C(2) | 111.90(18) | C(11)-C(12)-Br(1) | 118.53(17) |
| C(8)-N(2)-N(1) | 121.12(18) | C(13)-C(12)-Br(1) | 119.53(16) |
| C(3)-C(2)-C(1) | 113.14(17) | C(12)-C(13)-C(14) | 118.8(2) |
| O(3)-C(3)-C(2) | 121.3(2) | C(13)-C(14)-C(9) | 120.3(3) |

**Table 4.** Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **77l**.
The anisotropic displacement factor exponent takes the form:
$-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| Br(1) | 20(1) | 28(1) | 23(1) | -4(1) | 5(1) | -7(1) |
| N(1) | 13(1) | 17(1) | 17(1) | 0(1) | 4(1) | 0(1) |
| C(1) | 16(1) | 15(1) | 17(1) | -3(1) | 6(1) | 1(1) |
| N(2) | 17(1) | 13(1) | 21(1) | -3(1) | 6(1) | -2(1) |
| C(2) | 18(1) | 21(1) | 20(1) | 2(1) | 7(1) | 0(1) |
| O(3) | 30(1) | 33(1) | 21(1) | 2(1) | 10(1) | -4(1) |
| C(3) | 20(1) | 22(1) | 19(1) | 1(1) | 4(1) | 4(1) |
| C(4) | 33(1) | 31(2) | 24(1) | -4(1) | 5(1) | -8(1) |
| O(5) | 26(1) | 21(1) | 27(1) | 5(1) | 13(1) | 7(1) |
| C(5) | 19(1) | 19(1) | 14(1) | 0(1) | 6(1) | 1(1) |
| C(6) | 30(1) | 17(1) | 31(1) | 3(2) | 13(1) | -6(2) |
| O(6) | 20(1) | 16(1) | 31(1) | 5(1) | 10(1) | 1(1) |
| C(7) | 38(1) | 30(2) | 33(1) | 0(1) | 14(1) | -4(1) |
| C(8) | 22(1) | 19(2) | 12(1) | 4(1) | 8(1) | 0(1) |
| O(8) | 20(1) | 14(1) | 22(1) | -1(1) | 9(1) | 1(1) |
| C(9) | 15(1) | 17(1) | 15(1) | -3(1) | 7(1) | 0(1) |
| C(10) | 16(1) | 20(1) | 16(1) | 1(1) | 6(1) | 3(1) |
| C(11) | 19(1) | 19(1) | 19(1) | 0(1) | 10(1) | -1(1) |
| C(12) | 17(1) | 25(1) | 18(1) | -5(1) | 8(1) | -3(1) |
| C(13) | 15(1) | 24(1) | 16(1) | 2(1) | 4(1) | 1(1) |
| C(14) | 21(1) | 20(1) | 18(1) | 3(1) | 9(1) | 1(1) |

**Table 5.** Hydrogen coordinates ( $x\ 10^4$) and isotropic displacement parameters ($Å^2 x\ 10^3$) for **77l**.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| HN1 | 6220(20) | 5480(30) | 5630(20) | 24 |
| H(1) | 5315 | 6752 | 7392 | 19 |
| HN2 | 4230(30) | 4150(20) | 4880(20) | 21 |

| | | | | |
|---|---|---|---|---|
| H(2A) | 8224 | 6401 | 7622 | 24 |
| H(2B) | 7421 | 8522 | 7515 | 24 |
| H(4A) | 8826 | 9997 | 9738 | 47 |
| H(4B) | 9929 | 8450 | 9546 | 47 |
| H(4C) | 9569 | 8271 | 10726 | 47 |
| H(6A) | 5274 | 239 | 7397 | 31 |
| H(6B) | 3688 | 643 | 7315 | 31 |
| H(7A) | 6179 | 1116 | 9475 | 50 |
| H(7B) | 5141 | -808 | 9190 | 50 |
| H(7C) | 4576 | 1378 | 9376 | 50 |
| H(10) | 2427 | 2708 | 5411 | 21 |
| H(11) | 380 | 701 | 4449 | 22 |
| H(13) | -1434 | 5267 | 2039 | 23 |
| H(14) | 588 | 7305 | 3046 | 23 |

**Table 6.** Torsion angles [°] for **77l**

| | |
|---|---|
| N(2)-N(1)-C(1)-C(5) | 59.4(2) |
| N(2)-N(1)-C(1)-C(2) | -177.9(2) |
| C(1)-N(1)-N(2)-C(8) | 86.7(3) |
| N(1)-C(1)-C(2)-C(3) | 174.8(2) |
| C(5)-C(1)-C(2)-C(3) | -63.4(2) |
| C(1)-C(2)-C(3)-O(3) | 12.0(3) |
| C(1)-C(2)-C(3)-C(4) | -166.1(2) |
| N(1)-C(1)-C(5)-O(5) | 83.4(2) |
| C(2)-C(1)-C(5)-O(5) | -36.9(3) |
| N(1)-C(1)-C(5)-O(6) | -92.19(18) |
| C(2)-C(1)-C(5)-O(6) | 147.47(16) |
| O(5)-C(5)-O(6)-C(6) | -0.1(3) |
| C(1)-C(5)-O(6)-C(6) | 175.46(16) |
| C(7)-C(6)-O(6)-C(5) | 87.6(2) |
| N(1)-N(2)-C(8)-O(8) | 5.5(3) |
| N(1)-N(2)-C(8)-C(9) | -174.05(15) |
| O(8)-C(8)-C(9)-C(10) | -137.2(2) |
| N(2)-C(8)-C(9)-C(10) | 42.4(2) |
| O(8)-C(8)-C(9)-C(14) | 43.5(3) |
| N(2)-C(8)-C(9)-C(14) | -136.98(19) |
| C(14)-C(9)-C(10)-C(11) | 1.3(3) |
| C(8)-C(9)-C(10)-C(11) | -178.05(17) |
| C(9)-C(10)-C(11)-C(12) | 0.8(3) |
| C(10)-C(11)-C(12)-C(13) | -1.8(3) |
| C(10)-C(11)-C(12)-Br(1) | 177.76(14) |
| C(11)-C(12)-C(13)-C(14) | 0.7(3) |
| Br(1)-C(12)-C(13)-C(14) | -178.85(15) |
| C(12)-C(13)-C(14)-C(9) | 1.5(3) |
| C(10)-C(9)-C(14)-C(13) | -2.5(3) |
| C(8)-C(9)-C(14)-C(13) | 176.93(18) |

**Table 7.** Hydrogen bonds for **77l** [Å and °].

| D-H...A | d(D-H) | d(H...A) | d(D...A) | <(DHA) |
|---|---|---|---|---|
| N(1)-HN1...O(8)#1 | 0.895(10) | 2.028(12) | 2.895(3) | 163(2) |
| N(2)-HN2...N(1)#1 | 0.874(10) | 2.108(11) | 2.977(3) | 173(2) |

Symmetry transformations used to generate equivalent atoms:
#1 -x+1,y-1/2,-z+1

## 3. Ethyl[N`-(4-bromobenzoyl)hydrazino]-{(2*E*)-2-[(2,4-dinitrophenyl)hydrazono]cyclohexyl}acetate (**77p-hydrazone**)

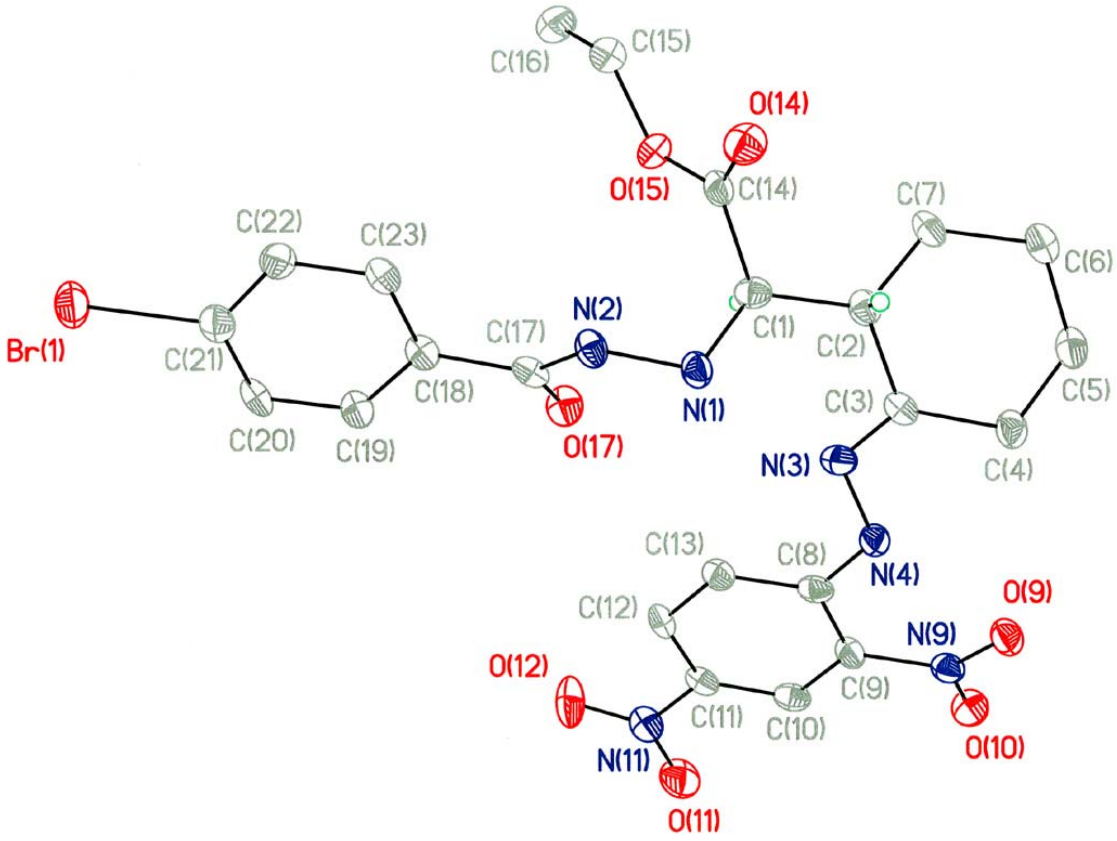



**Table 8.** Crystal data and structure refinement for **77p-hydrazone**.

| | | |
|---|---|---|
| Identification code | den3b | |
| Empirical formula | C23 H25 Br N6 O7 | |
| Formula weight | 577.40 | |
| Temperature | 100(2) K | |
| Wavelength | 1.54178 Å | |
| Crystal system | Triclinic | |
| Space group | P1 | |
| Unit cell dimensions | a = 4.8400(10) Å | α= 109.50(3)°. |
| | b = 11.143(2) Å | β= 91.00(3)°. |
| | c = 12.189(2) Å | γ = 98.23(3)°. |
| Volume | 611.8(2) $Å^3$ | |
| Z | 1 | |
| Density (calculated) | 1.567 $Mg/m^3$ | |
| Absorption coefficient | 2.787 $mm^{-1}$ | |
| F(000) | 296 | |
| Crystal size | 0.20 x 0.03 x 0.03 $mm^3$ | |
| Theta range for data collection | 3.86 to 58.57°. | |
| Index ranges | -5<=h<=5, -11<=k<=11, -13<=l<=13 | |
| Reflections collected | 2883 | |
| Independent reflections | 2883 [R(int) = 0.0000] | |
| Completeness to theta = 58.57° | 94.9 % | |
| Absorption correction | Semi-empirical from equivalents | |
| Max. and min. transmission | 0.9211 and 0.6056 | |

| | |
|---|---|
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 2883 / 6 / 347 |
| Goodness-of-fit on $F^2$ | 1.039 |
| Final R indices [I>2sigma(I)] | R1 = 0.0283, wR2 = 0.0695 |
| R indices (all data) | R1 = 0.0292, wR2 = 0.0701 |
| Absolute structure parameter | -0.001(14) |
| Largest diff. peak and hole | 0.534 and -0.373 e.Å$^{-3}$ |

**Table 9.** Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters (Å$^2$x $10^3$) for **77p-hydrazone**. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| Br(1) | 16667(1) | 9470(1) | 1945(1) | 34(1) |
| N(1) | 12075(6) | 4817(3) | 5846(3) | 21(1) |
| C(1) | 10048(7) | 3614(3) | 5262(3) | 21(1) |
| N(2) | 12930(6) | 5504(3) | 5093(3) | 21(1) |
| C(2) | 9917(7) | 2808(3) | 6049(3) | 21(1) |
| N(3) | 7797(6) | 4493(3) | 7357(2) | 22(1) |
| C(3) | 8807(7) | 3449(3) | 7223(3) | 21(1) |
| N(4) | 6429(6) | 4981(3) | 8364(3) | 22(1) |
| C(4) | 8753(7) | 2705(3) | 8048(3) | 24(1) |
| C(5) | 6945(8) | 1379(4) | 7482(3) | 26(1) |
| C(6) | 7975(8) | 673(4) | 6300(3) | 26(1) |
| C(7) | 8079(8) | 1477(4) | 5507(4) | 23(1) |
| C(8) | 5231(7) | 6048(4) | 8523(3) | 22(1) |
| O(9) | 3649(5) | 4780(3) | 10126(2) | 28(1) |
| C(9) | 3282(7) | 6437(4) | 9390(3) | 22(1) |
| N(9) | 2382(7) | 5681(3) | 10126(3) | 23(1) |
| O(10) | 367(5) | 5935(3) | 10707(2) | 29(1) |
| C(10) | 2045(7) | 7524(4) | 9534(3) | 22(1) |
| O(11) | -101(7) | 9709(3) | 9779(3) | 40(1) |
| N(11) | 1347(6) | 9357(3) | 8945(3) | 27(1) |
| C(11) | 2692(8) | 8226(3) | 8816(3) | 22(1) |
| O(12) | 1692(6) | 9878(3) | 8218(3) | 40(1) |
| C(12) | 4569(8) | 7890(4) | 7942(4) | 22(1) |
| C(13) | 5792(7) | 6800(4) | 7807(3) | 22(1) |
| O(14) | 13143(5) | 2338(3) | 3998(2) | 29(1) |
| C(14) | 11192(8) | 2931(4) | 4101(3) | 21(1) |
| O(15) | 9855(5) | 3105(2) | 3210(2) | 24(1) |
| C(15) | 10960(8) | 2599(4) | 2076(3) | 28(1) |
| C(16) | 8928(11) | 2711(5) | 1190(4) | 39(1) |
| O(17) | 8980(5) | 6409(2) | 5235(2) | 26(1) |
| C(17) | 11318(7) | 6301(3) | 4855(3) | 22(1) |
| C(18) | 12577(7) | 7032(3) | 4113(3) | 21(1) |
| C(19) | 11830(7) | 8224(4) | 4237(3) | 24(1) |
| C(20) | 13005(8) | 8959(4) | 3601(4) | 23(1) |
| C(21) | 14957(7) | 8469(4) | 2822(3) | 26(1) |
| C(22) | 15733(8) | 7288(4) | 2658(3) | 26(1) |
| C(23) | 14510(7) | 6568(4) | 3302(3) | 22(1) |

**Table 10.** Bond lengths [Å] and angles [°] for **77p-hydrazone**.

| | | | |
|---|---|---|---|
| Br(1)-C(21) | 1.907(4) | C(1)-C(2) | 1.514(5) |
| N(1)-N(2) | 1.410(4) | C(1)-C(14) | 1.522(5) |
| N(1)-C(1) | 1.493(5) | N(2)-C(17) | 1.358(5) |

| | | | |
|---|---|---|---|
| C(2)-C(3) | 1.517(5) | N(3)-C(3)-C(2) | 117.0(3) |
| C(2)-C(7) | 1.541(5) | C(4)-C(3)-C(2) | 115.1(3) |
| N(3)-C(3) | 1.287(5) | C(8)-N(4)-N(3) | 119.3(3) |
| N(3)-N(4) | 1.388(4) | C(3)-C(4)-C(5) | 109.4(3) |
| C(3)-C(4) | 1.500(5) | C(6)-C(5)-C(4) | 110.5(3) |
| N(4)-C(8) | 1.354(5) | C(7)-C(6)-C(5) | 111.3(3) |
| C(4)-C(5) | 1.535(5) | C(6)-C(7)-C(2) | 112.8(3) |
| C(5)-C(6) | 1.524(5) | N(4)-C(8)-C(13) | 120.9(3) |
| C(6)-C(7) | 1.519(6) | N(4)-C(8)-C(9) | 122.2(3) |
| C(8)-C(13) | 1.403(5) | C(13)-C(8)-C(9) | 116.9(3) |
| C(8)-C(9) | 1.429(5) | C(10)-C(9)-C(8) | 121.5(4) |
| O(9)-N(9) | 1.248(4) | C(10)-C(9)-N(9) | 116.5(3) |
| C(9)-C(10) | 1.388(5) | C(8)-C(9)-N(9) | 121.9(3) |
| C(9)-N(9) | 1.456(5) | O(10)-N(9)-O(9) | 122.3(3) |
| N(9)-O(10) | 1.226(4) | O(10)-N(9)-C(9) | 118.7(3) |
| C(10)-C(11) | 1.369(6) | O(9)-N(9)-C(9) | 119.0(3) |
| O(11)-N(11) | 1.231(4) | C(11)-C(10)-C(9) | 118.9(3) |
| N(11)-O(12) | 1.213(4) | O(12)-N(11)-O(11) | 124.0(3) |
| N(11)-C(11) | 1.463(5) | O(12)-N(11)-C(11) | 118.2(3) |
| C(11)-C(12) | 1.402(5) | O(11)-N(11)-C(11) | 117.8(3) |
| C(12)-C(13) | 1.389(6) | C(10)-C(11)-C(12) | 122.4(3) |
| O(14)-C(14) | 1.213(5) | C(10)-C(11)-N(11) | 119.2(3) |
| C(14)-O(15) | 1.338(5) | C(12)-C(11)-N(11) | 118.4(3) |
| O(15)-C(15) | 1.451(4) | C(13)-C(12)-C(11) | 118.1(4) |
| C(15)-C(16) | 1.496(7) | C(12)-C(13)-C(8) | 122.1(3) |
| O(17)-C(17) | 1.237(4) | O(14)-C(14)-O(15) | 123.9(3) |
| C(17)-C(18) | 1.491(5) | O(14)-C(14)-C(1) | 124.3(4) |
| C(18)-C(19) | 1.387(5) | O(15)-C(14)-C(1) | 111.8(3) |
| C(18)-C(23) | 1.396(5) | C(14)-O(15)-C(15) | 116.2(3) |
| C(19)-C(20) | 1.378(6) | O(15)-C(15)-C(16) | 107.3(3) |
| C(20)-C(21) | 1.388(6) | O(17)-C(17)-N(2) | 121.8(3) |
| C(21)-C(22) | 1.371(6) | O(17)-C(17)-C(18) | 123.0(3) |
| C(22)-C(23) | 1.382(6) | N(2)-C(17)-C(18) | 115.2(3) |
| N(2)-N(1)-C(1) | 113.3(3) | C(19)-C(18)-C(23) | 118.5(3) |
| N(1)-C(1)-C(2) | 107.5(3) | C(19)-C(18)-C(17) | 119.1(3) |
| N(1)-C(1)-C(14) | 106.7(3) | C(23)-C(18)-C(17) | 122.5(3) |
| C(2)-C(1)-C(14) | 111.3(3) | C(20)-C(19)-C(18) | 121.4(3) |
| C(17)-N(2)-N(1) | 121.2(3) | C(19)-C(20)-C(21) | 118.1(4) |
| C(1)-C(2)-C(3) | 113.4(3) | C(22)-C(21)-C(20) | 122.6(4) |
| C(1)-C(2)-C(7) | 113.2(3) | C(22)-C(21)-Br(1) | 118.1(3) |
| C(3)-C(2)-C(7) | 106.6(3) | C(20)-C(21)-Br(1) | 119.2(3) |
| C(3)-N(3)-N(4) | 117.0(3) | C(21)-C(22)-C(23) | 118.1(3) |
| N(3)-C(3)-C(4) | 127.6(3) | C(22)-C(23)-C(18) | 121.3(4) |

**Table 11.** Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **77p-hydrazone**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| Br(1) | 39(1) | 32(1) | 33(1) | 17(1) | 0(1) | -7(1) |
| N(1) | 20(2) | 19(2) | 24(2) | 9(1) | 2(1) | -1(1) |
| C(1) | 19(2) | 22(2) | 21(2) | 4(2) | 4(1) | 4(2) |
| N(2) | 16(2) | 19(2) | 29(2) | 10(1) | 5(1) | 2(1) |
| C(2) | 20(2) | 20(2) | 25(2) | 9(2) | 3(2) | 2(2) |
| N(3) | 20(2) | 20(2) | 21(2) | 2(1) | 4(1) | 1(1) |
| C(3) | 20(2) | 16(2) | 25(2) | 5(2) | 1(1) | 3(2) |
| N(4) | 27(2) | 19(2) | 22(2) | 8(1) | 7(1) | 7(1) |
| C(4) | 27(2) | 22(2) | 27(2) | 13(2) | 7(2) | 11(2) |
| C(5) | 26(2) | 25(2) | 33(2) | 16(2) | 7(2) | 7(2) |
| C(6) | 27(2) | 19(2) | 33(2) | 11(2) | 0(2) | 2(2) |

| | | | | | | |
|---|---|---|---|---|---|---|
| C(7) | 23(2) | 15(2) | 32(2) | 8(2) | 6(2) | 4(2) |
| C(8) | 18(2) | 19(2) | 21(2) | 1(2) | -1(1) | -3(2) |
| O(9) | 33(2) | 22(1) | 32(1) | 11(1) | 6(1) | 7(1) |
| C(9) | 22(2) | 16(2) | 25(2) | 7(2) | 3(2) | 1(2) |
| N(9) | 24(2) | 19(2) | 23(2) | 4(1) | 5(2) | 4(2) |
| O(10) | 26(1) | 32(2) | 31(1) | 11(1) | 11(1) | 7(1) |
| C(10) | 16(2) | 21(2) | 24(2) | 1(2) | 0(1) | 2(2) |
| O(11) | 48(2) | 30(2) | 44(2) | 10(2) | 12(2) | 17(2) |
| N(11) | 21(2) | 25(2) | 35(2) | 10(2) | 7(1) | 5(1) |
| C(11) | 21(2) | 15(2) | 26(2) | 2(2) | 2(2) | 3(2) |
| O(12) | 40(2) | 40(2) | 59(2) | 36(2) | 19(1) | 18(1) |
| C(12) | 23(2) | 15(2) | 30(2) | 11(2) | 0(2) | 0(2) |
| C(13) | 20(2) | 19(2) | 24(2) | 6(2) | 2(2) | 2(2) |
| O(14) | 27(1) | 33(2) | 30(1) | 11(1) | 7(1) | 11(1) |
| C(14) | 21(2) | 17(2) | 25(2) | 9(2) | 2(2) | -1(2) |
| O(15) | 29(1) | 26(2) | 19(1) | 9(1) | 5(1) | 4(1) |
| C(15) | 35(2) | 23(2) | 25(2) | 7(2) | 5(2) | 3(2) |
| C(16) | 64(3) | 33(2) | 23(2) | 10(2) | 7(2) | 13(2) |
| O(17) | 18(1) | 29(2) | 34(1) | 13(1) | 8(1) | 6(1) |
| C(17) | 22(2) | 15(2) | 25(2) | 3(2) | -2(2) | 2(1) |
| C(18) | 17(2) | 19(2) | 26(2) | 7(2) | 2(2) | 3(2) |
| C(19) | 23(2) | 21(2) | 29(2) | 10(2) | 3(2) | 3(2) |
| C(20) | 20(2) | 14(2) | 34(2) | 9(2) | -1(2) | 0(2) |
| C(21) | 26(2) | 25(2) | 23(2) | 8(2) | -8(2) | -6(2) |
| C(22) | 26(2) | 24(2) | 25(2) | 6(2) | 6(2) | 1(2) |
| C(23) | 22(2) | 17(2) | 28(2) | 8(2) | 0(2) | 4(2) |

**Table 12.** Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters (Å$^2$x $10^3$) for **77p-hydrazone**.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(1N1) | 11160(70) | 5330(30) | 6420(20) | 20(9) |
| H(1) | 8158 | 3826 | 5132 | 26 |
| H(1N2) | 14710(30) | 5660(40) | 4980(30) | 18(9) |
| H(2) | 11862 | 2663 | 6194 | 26 |
| H(1N4) | 5980(80) | 4550(30) | 8870(30) | 26(10) |
| H(4A) | 7973 | 3184 | 8783 | 29 |
| H(4B) | 10681 | 2598 | 8235 | 29 |
| H(5A) | 7026 | 861 | 7999 | 31 |
| H(5B) | 4973 | 1487 | 7379 | 31 |
| H(6A) | 9867 | 476 | 6414 | 31 |
| H(6B) | 6709 | -153 | 5925 | 31 |
| H(7A) | 6154 | 1599 | 5333 | 28 |
| H(7B) | 8820 | 1002 | 4761 | 28 |
| H(10) | 771 | 7777 | 10122 | 27 |
| H(12) | 4992 | 8394 | 7455 | 27 |
| H(13) | 7048 | 6556 | 7211 | 26 |
| H(15A) | 11175 | 1685 | 1907 | 34 |
| H(15B) | 12815 | 3098 | 2061 | 34 |
| H(16A) | 7140 | 2166 | 1177 | 59 |
| H(16B) | 9673 | 2430 | 419 | 59 |
| H(16C) | 8641 | 3611 | 1396 | 59 |
| H(19) | 10481 | 8541 | 4771 | 29 |
| H(20) | 12493 | 9777 | 3694 | 28 |
| H(22) | 17072 | 6974 | 2118 | 31 |
| H(23) | 14995 | 5741 | 3191 | 26 |

**Table 13.** Torsion angles [°] for **77p-hydrazone**.

| | |
|---|---|
| N(2)-N(1)-C(1)-C(2) | 165.1(3) |
| N(2)-N(1)-C(1)-C(14) | 45.7(4) |
| C(1)-N(1)-N(2)-C(17) | 81.4(4) |
| N(1)-C(1)-C(2)-C(3) | 63.2(3) |
| C(14)-C(1)-C(2)-C(3) | 179.6(3) |
| N(1)-C(1)-C(2)-C(7) | -175.2(3) |
| C(14)-C(1)-C(2)-C(7) | -58.7(4) |
| N(4)-N(3)-C(3)-C(4) | -1.8(5) |
| N(4)-N(3)-C(3)-C(2) | 171.2(3) |
| C(1)-C(2)-C(3)-N(3) | 8.5(4) |
| C(7)-C(2)-C(3)-N(3) | -116.7(3) |
| C(1)-C(2)-C(3)-C(4) | -177.6(3) |
| C(7)-C(2)-C(3)-C(4) | 57.1(4) |
| C(3)-N(3)-N(4)-C(8) | -177.3(3) |
| N(3)-C(3)-C(4)-C(5) | 114.7(4) |
| C(2)-C(3)-C(4)-C(5) | -58.5(4) |
| C(3)-C(4)-C(5)-C(6) | 54.8(4) |
| C(4)-C(5)-C(6)-C(7) | -55.2(4) |
| C(5)-C(6)-C(7)-C(2) | 56.7(4) |
| C(1)-C(2)-C(7)-C(6) | 179.7(3) |
| C(3)-C(2)-C(7)-C(6) | -54.9(4) |
| N(3)-N(4)-C(8)-C(13) | -12.1(5) |
| N(3)-N(4)-C(8)-C(9) | 165.7(3) |
| N(4)-C(8)-C(9)-C(10) | -179.2(3) |
| C(13)-C(8)-C(9)-C(10) | -1.3(5) |
| N(4)-C(8)-C(9)-N(9) | -2.5(5) |
| C(13)-C(8)-C(9)-N(9) | 175.5(3) |
| C(10)-C(9)-N(9)-O(10) | 9.4(5) |
| C(8)-C(9)-N(9)-O(10) | -167.5(3) |
| C(10)-C(9)-N(9)-O(9) | -172.0(3) |
| C(8)-C(9)-N(9)-O(9) | 11.1(5) |
| C(8)-C(9)-C(10)-C(11) | 0.8(5) |
| N(9)-C(9)-C(10)-C(11) | -176.1(3) |
| C(9)-C(10)-C(11)-C(12) | -0.3(5) |
| C(9)-C(10)-C(11)-N(11) | 178.6(3) |
| O(12)-N(11)-C(11)-C(10) | -171.6(3) |
| O(11)-N(11)-C(11)-C(10) | 7.4(5) |
| O(12)-N(11)-C(11)-C(12) | 7.3(5) |
| O(11)-N(11)-C(11)-C(12) | -173.7(3) |
| C(10)-C(11)-C(12)-C(13) | 0.2(5) |
| N(11)-C(11)-C(12)-C(13) | -178.6(3) |
| C(11)-C(12)-C(13)-C(8) | -0.8(6) |
| N(4)-C(8)-C(13)-C(12) | 179.3(3) |
| C(9)-C(8)-C(13)-C(12) | 1.3(5) |
| N(1)-C(1)-C(14)-O(14) | 75.5(5) |
| C(2)-C(1)-C(14)-O(14) | -41.4(5) |
| N(1)-C(1)-C(14)-O(15) | -102.0(3) |
| C(2)-C(1)-C(14)-O(15) | 141.0(3) |
| O(14)-C(14)-O(15)-C(15) | -3.3(5) |
| C(1)-C(14)-O(15)-C(15) | 174.2(3) |
| C(14)-O(15)-C(15)-C(16) | 171.4(3) |
| N(1)-N(2)-C(17)-O(17) | -3.7(5) |
| N(1)-N(2)-C(17)-C(18) | 175.9(3) |
| O(17)-C(17)-C(18)-C(19) | 28.4(5) |
| N(2)-C(17)-C(18)-C(19) | -151.3(3) |
| O(17)-C(17)-C(18)-C(23) | -152.3(3) |
| N(2)-C(17)-C(18)-C(23) | 28.1(5) |
| C(23)-C(18)-C(19)-C(20) | -1.6(5) |
| C(17)-C(18)-C(19)-C(20) | 177.8(3) |
| C(18)-C(19)-C(20)-C(21) | 0.4(5) |

| | |
|---|---|
| C(19)-C(20)-C(21)-C(22) | 0.5(5) |
| C(19)-C(20)-C(21)-Br(1) | -179.0(3) |
| C(20)-C(21)-C(22)-C(23) | -0.1(5) |
| Br(1)-C(21)-C(22)-C(23) | 179.4(3) |
| C(21)-C(22)-C(23)-C(18) | -1.1(5) |
| C(19)-C(18)-C(23)-C(22) | 2.0(5) |
| C(17)-C(18)-C(23)-C(22) | -177.4(3) |

**Table 14.** Hydrogen bonds for **77p-hydrazone** [Å and °].

| D-H...A | d(D-H) | d(H...A) | d(D...A) | <(DHA) |
|---|---|---|---|---|
| N(1)-H(1N1)...N(3) | 0.913(10) | 2.27(3) | 2.859(4) | 122(3) |
| N(2)-H(1N2)...O(17)#1 | 0.879(10) | 2.091(16) | 2.940(4) | 162(3) |
| N(4)-H(1N4)...O(9) | 0.910(10) | 1.89(3) | 2.610(4) | 135(3) |

Symmetry transformations used to generate equivalent atoms: #1 x+1,y,z

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Denis A. Yalalov

# Publications

1. S.-W. Wei, **D. A. Yalalov**, S. B. Tsogoeva, S. Schmatz. New highly enantioselective thiourea-based bifunctional organocatalysts for nitro-Michael addition reactions. *Catalysis Today*. **2007**, *121*, 151-157.

2. **D. A. Yalalov**, S. B. Tsogoeva, S. Schmatz. Chiral Thiourea-Based Bifunctional Organocatalysts in the Asymmetric Nitro-Michael Addition: A Joint Experimental-Theoretical Study. *Advanced Synthesis & Catalysis.* **2006**, *348,* 826.

3. S. B. Tsogoeva, **D. A. Yalalov**, M. J. Hateley, C. Weckbecker, K. Huthmacher. Asymmetric Organocatalysis with Novel Chiral Thiourea Derivatives: Bifunctional Catalysts for the Strecker and nitro-Michael Reactions. *Eur. J. Org. Chem.* **2005**, 4995-5000.

4. S. B. Tsogoeva, M. J. Hateley, **D. A. Yalalov**, K. Meindl, C. Weckbecker, K. Huthmacher. Thiourea-based Non-nucleoside Inhibitors of HIV Reverse Transcriptase as Bifunctional Organocatalysts in the Asymmetric Strecker Synthesis. *Bioorg. Med. Chem.* **2005**, *13*, 5680.

# Lebenslauf

Denis A. Yalalov

Ich wurde am 23. September 1981 als erstes von zwei Kindern des Piloten Albert Yalalov und der Grundschullehrerin Florida Yalalova in Ufa geboren. Von 01.09.1988 bis 19.06.1998 besuchte ich die allgemeinbildende Schule *N*129 in Ufa (UdSSR bzw. Russland). Von 01.09.1998 bis 06.19.2003 studierte ich Chemie an der Baschkirischen Staatlichen Universität in Ufa, wo ich am 19. Juni 2003 meine Diplomhauptprüfung vor der Staatlichen Prüfungskommission mit der Note „ausgezeichnet“ bestand. Von Juli 2003 bis Dezember 2003 arbeitete ich im Arbeitskreis von Prof. Dr. Ildus B. Abdrakhmanov als wissenschaftlicher Mitarbeiter am Institut für Organische Chemie des wissenschaftlichen Zentrums der Russischen Akademie der Wissenschaften in Ufa. Im Januar 2004 kam ich nach Deutschland und arbeitete bis Oktober 2004 als Gastwissenschaftler im Arbeitskreis von Prof. Dr. Svetlana B. Tsogoeva für die Firma Degussa. Von Oktober 2004 bis Februar 2005 arbeitete ich unter der Leitung von Prof. Dr. Svetlana B. Tsogoeva als Doktorand an meiner Dissertation mit dem Thema “Bifunctional Thiourea-Based Organocatalysts for Asymmetric C-C Bond Formation Reactions: Strecker, Nitro-Michael, Mannich” unter die Unterstützung von der Firma Degussa. Von März 2005 bis März 2007 setze ich meine Doktorarbeit mit Unterstützung der DFG (Schwerpunktprogramm 1179 „Organokatalyse”) unter der Leitung von Prof. Dr. Svetlana B. Tsogoeva und Prof. Dr. Stefan Schmatz fort. Von April 2007 bis Oktober 2007 setzte ich meine Doktorarbeit unter Leitung meiner Betreuer im Arbeitskreis von Prof. Dr. Dr. h. c. Lutz F. Tietze fort.

Ich besitze die russische Staatsangehörigkeit.