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Synthesis and Organocatalyzed Enantioselective Transfer-Hydrogenation of β-Amino Nitroolefins

Tesi di laurea sperimentale

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Abstract

The importance of the β-amino nitroalkanes is due to their high versatility allowing a straightforward entry to a variety of nitrogen-containing chiral building blocks; furthermore obtaining them in enantiopure form allows their use in the synthesis of biologically active compounds or their utilization as chiral ligands for different uses. In this work, a reaction for obtaining enantiopure β-amino nitroalkanes through asymmetric organocatalysis has been developed. The synthetic strategy adopted for the obtainment of these compounds was based on an asymmetric reduction of β-amino nitroolefins in a transfer hydrogenation reaction, involving an Hantzsch ester as hydrogen source and a chiral thiourea as organic catalyst. After the optimization of the reaction conditions over the β-acyl-amino nitrostyrene, we tested the reaction generality over other aromatic compound and for Boc protected substrate both aromatic and aliphatic. A scale-up of the reaction was also performed.

Riassunto

L'importanza dei β-ammino nitroalcani è dovuta alla loro elevata versatilità in quanto consentono un accesso diretto a diversi building blocks contenenti azoto; inoltre il loro ottenimento in forma enantiopura consente di utilizzarli nella sintesi di composti biologicamente attivi o di essere usati come leganti chirali per svariati usi. Nel mio lavoro di tesi magistrale ho sviluppato una reazione per l'ottenimento di β-ammino nitroalcani enantiopuri attraverso la tecnica dell'organo-catalisi asimmetrica. La strategia adottata per l'ottenimento di questi composti è stata quella della riduzione di β-ammino nitroolefine attraverso una reazione di transfer hydrogenation, utilizzando un estere di Hantzsch come fonte di idrogeno ed una tiourea chirale come organo-catalizzatore. In seguito all'ottimizzazione delle condizioni di reazione fatta sul β-acil-ammino nitro-stirene si è studiata la generalità della reazione per altri substrati aromatici e per substrati Boc protetti sia aromatici che alifatici. Si è inoltre provato uno scale-up della reazione.

Table of contents

1. Introduction

1.1 β-Amino Nitroalkanes: useful synthetic building blocks

Enantiomerically pure β-amino nitroalkanes are versatile intermediates in organic synthesis, because the two nitrogenated functions are present in different oxidation states, thus giving access to further transformations with complete chemoselectivity. β-nitroamines can easily be converted into a variety of useful compounds[1] such as α-amino acids[2] and 1,2-diamines.[3]

α-amino acids: Amino acids are biologically important organic compounds containing amine ($-NH_2$) and carboxylic acid (-COOH) functional groups, usually along with a side-chain specific to each amino acid. In biochemistry, amino acids having both the amine and the carboxylic acid groups attached to the first (alpha-) carbon atom have particular importance. They are known as α-amino acids (generic formula $H_2NCHRCOOH$ in most cases, where R is an organic substituent known as a "side-chain"). They include the 23 proteinogenic ("protein-building") amino acids, which combine into peptide chains ("polypeptides") to form the building-blocks of a vast array of proteins. These are all *L*-stereoisomers. Because of their biological significance, amino acids are important in nutrition and are commonly used in nutritional supplements, fertilizers, and food technology. Industrial uses include the production of drugs, biodegradable plastics, and chiral catalysts. α-Amino acids can be easily obtained from β-amino nitroalkanes through the Nef reaction using a buffered permanganate solutions (pH=11) that can oxidise primary nitroalkanes into alkanoic acids without affecting other functions such as esters, amides, primary alcohols and acetals.[2]

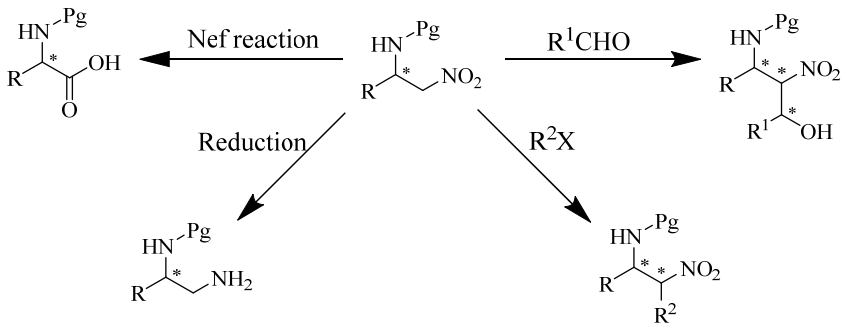
1,2-diamines: compounds incorporating the 1,2-diamine functionality are currently the topic of studies conducted in several fields. For instance, in recent years several synthetic diamine derivatives have been employed as medicinal agents, in particular in chemotherapy (e.g. platinum 1,2-diamino complexes). Chiral, enantiomerically pure 1,2-diamines (or vicinal diamines) and their derivatives are also used increasingly in stereoselective organic synthesis, for example as chiral auxiliaries, or as metal ligands in catalytic asymmetric synthesis. For these reasons, the development of synthetic methods for the preparation of aliphatic 1,2-diamines in diastereomerically and enantiomerically pure form[3] is an important task. 1,2-Diamines can be obtained by reducing the nitro

group of β-amino nitroalkanes; there are several procedures for the reduction of nitro compounds to amines; one of this methods, applicable to the reduction of both aromatic and aliphatic nitro compounds, concern the use of ammonium formate in the presence of Pd/C.[1]

β-amino nitroalkanes are also precursors of other interesting compounds like **monoamines**,[4] **α-aminocarbonyls** and **glycosamines**;[5]

Moreover, the alkylation of β-amino nitroalkanes with alkyl halides and the Henry reaction with aldehydes enable the facile preparation of a myriad of structurally diverse and complex molecules bearing two or three stereocenters (Scheme 1).

The most convenient way to obtain these useful enantiomerically pure building block is to use enantioselective catalysis as a synthetic tool.



Scheme 1. Conversion of β-amino nitroalkanes into other compounds.

Many of the described compounds are key structural element and they are present in biologically active molecules and pharmaceuticals (Figure 1) such as

Clopidogrel [6] (an oral thienopyridine-class antiplatelet agent used to inhibit blood clots in coronary artery disease, peripheral vascular disease, cerebrovascular disease, and to prevent myocardial infarction and stroke);

Oseltamivir[7] (marketed under the trade name Tamiflu, an antiviral medication used to treat influenza A and influenza B (flu), and to prevent flu after exposure);

Asimadoline [8] (acts as a peripherally selective κ-opioid receptor (KOR) agonist, and has been researched as a possible treatment for irritable bowel syndrome, with reasonable efficacy seen in clinical trials.);

CP-690,550 [9] (a drug of the janus kinase (JAK) inhibitor class; marketed as Xeljanz and Jakvinus, it is currently approved for the treatment of rheumatoid arthritis (RA) in the

United States and other countries. It has demonstrated effectiveness in the treatment of psoriasis. It is being studied for treatment of inflammatory bowel disease, and other immunological diseases, as well as for the prevention of organ transplant rejection.);

Valsartan[10] (trade name Diovan, is an angiotensin II receptor antagonist, that is selective for the type I (AT_1) angiotensin receptor. Valsartan is mainly used for treatment of high blood pressure, congestive heart failure, and to increase the chances of living longer after a heart attack.)

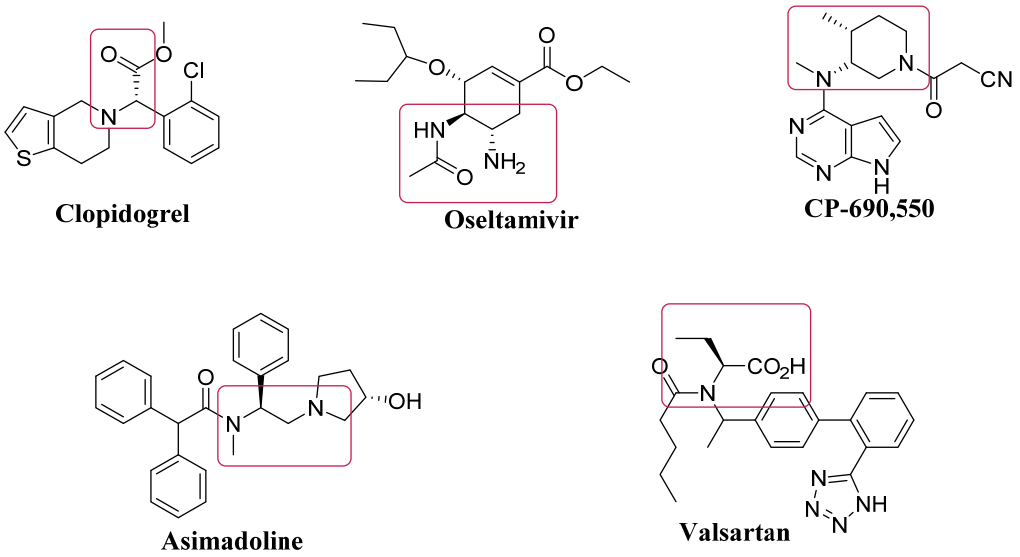


Figure 1. key structural elements in chiral pharmaceuticals.

1.2 Enantioselective/Asymmetric Catalysis

The enantioselective production of compounds is a central theme in current research. The broad utility of synthetic chiral molecules as single-enantiomer has made asymmetric catalysis a prominent area of investigation.

Until few years ago, it was generally accepted that transition-metal complexes and enzymes were the two main classes of very efficient asymmetric catalysts. A change in perception has occurred during the last few years, when several reports confirmed that relatively simple organic molecules could be highly effective enantioselective catalysts of a variety of fundamentally important transformations. Organocatalyst not only have ease of manipulation and a green advantage, but also can be very efficient catalysts. This rediscovery has initiated an explosive growth of research activities in organocatalysis, both in industry and in academia.

Thus, the use of pure organic catalysts turned out to be an additional efficient tool for the synthesis of chiral building blocks besides the well-established asymmetric metal-complex-catalysed syntheses and biocatalysis.

The organocatalysts can be classified by means of their interactions with the substrate or "*mode of action*" as covalent or noncovalent catalysts (Figure 2).

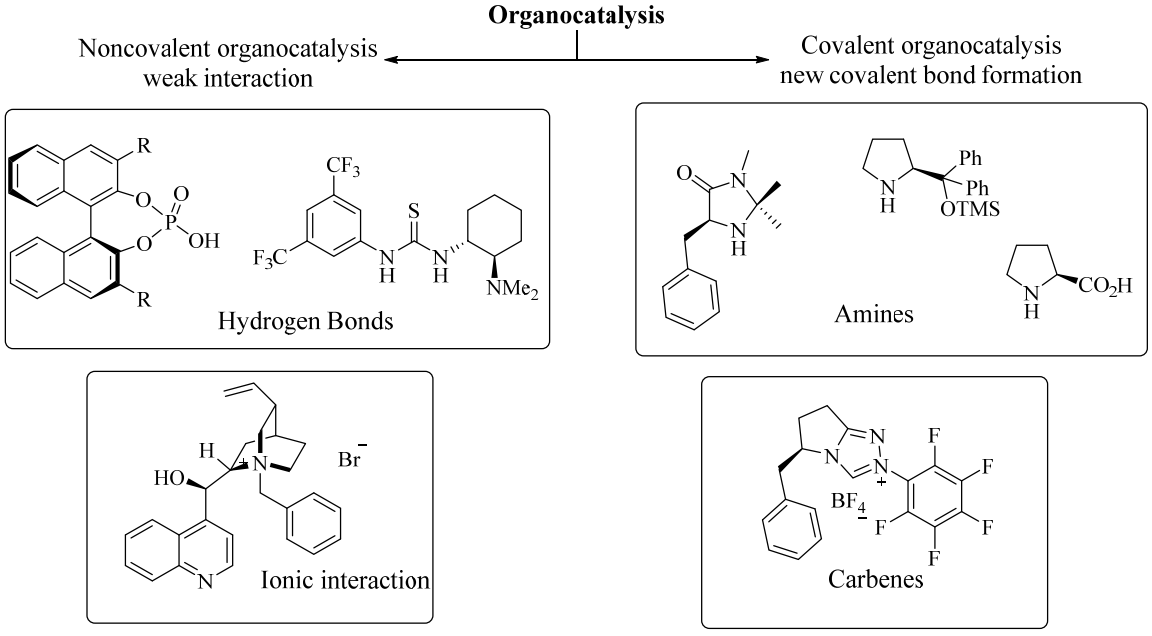


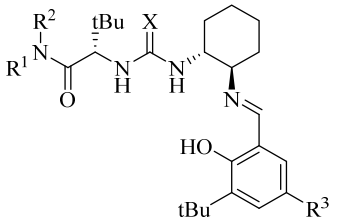
Figure 2. General classification of the activation mode of representative classes of molecules in organocatalysis.

In covalent organocatalysis, a new covalent bond between the catalysts and the substrate is formed as in the case of aminocatalysis and carbenes, leading to a strong interaction between the substrate and the reagent in the reaction. In the case of noncovalent interactions between the substrate and the catalyst, the activation of the substrate occurs *via* weak binding exemplified by hydrogen bonding or ionic interaction as in the case of phase transfer catalysis.[11]

1.2.1. **Hydrogen Bonding Catalysis**

This ubiquitous interaction is one of the central forces in Nature; the unusual and complex properties of bulk water, the ability of proteins to fold into stable three-dimensional structures, the fidelity of DNA base pairing, and the binding of ligands to receptors are among the manifestations of this ubiquitous noncovalent interaction. Hydrogen bonds are feeble and quite easy to break, however when acting together they become much stronger and lean each other; this phenomenon is called “cooperativity”. Hydrogen bonding to an electrophile serves to decrease the electron density of this species, activating it toward nucleophilic attack. This principle is employed frequently by Nature's catalysts, enzymes, for the acceleration of a wide range of chemical processes. Recently, organic chemists have begun to appreciate the potential offered by hydrogen bonding as a mechanism for electrophile activation in small molecule, synthetic catalyst systems. In particular, chiral hydrogen bond donors have emerged as a broadly applicable class of catalysts for enantioselective synthesis.[12]

The discovery that Schiff bases **a–c** (Figure 3) catalyze asymmetric hydrocyanation reactions of a wide variety of imine substrates[13] revealed for the first time that chiral urea and thiourea derivatives are capable of mediating highly enantioselective transformations.



a: R^1= Bn, R^2= H, R^3=OCH_3, X= S
b: R^1= Bn, R^2= H, R^3=OCOtBu, X= O
c: R^1= R^2= CH_3, R^3=OCOtBu, X= S

Figure 3. Urea and thiourea Schiff bases.

These compounds had been designed originally as potential ligands for Lewis acidic metals, afterwards a higher enantioselectivity was observed in the absence of metal additives. Several factors may contribute to the special behavior of these species. The presence of electron-withdrawing groups serves to decrease the pK_a of the N-H bonds, increasing their H-bond donating ability. The choice of urea or thiourea provides a method for altering H-bond-donating ability, while variation of the nitrogen substituents permits a high degree of fine-tuning of catalyst steric and electronic properties. Their structures also lend themselves readily to the preparation of bifunctional catalysts, using amine coupling partners incorporating additional acidic or basic groups. This approach has resulted in further expansion of the scope of this catalyst class.[13]

Since 2001 research groups worldwide (e.g., Jacobsen, Nagaswa, Takemoto, Ricci, Connon) have realized the potential of **thiourea** derivatives and developed various achiral/chiral mono- and bifunctional derivatives (Figure 4) incorporating the electron-poor 3,5-bis(trifluoromethyl)phenyl substrate-"anchor" functionality. A broad variety of monofuctional and chiral double hydrogen-bonding (thio)urea organocatalysts have been developed to accelerate various synthetically useful organic transformations employing H-bond accepting substrates, e.g., carbonyl compounds, imines, nitroalkenes as the starting materials. The research towards the design and implementations of these catalysts in organic synthesis is still in the focus of interest.[14]

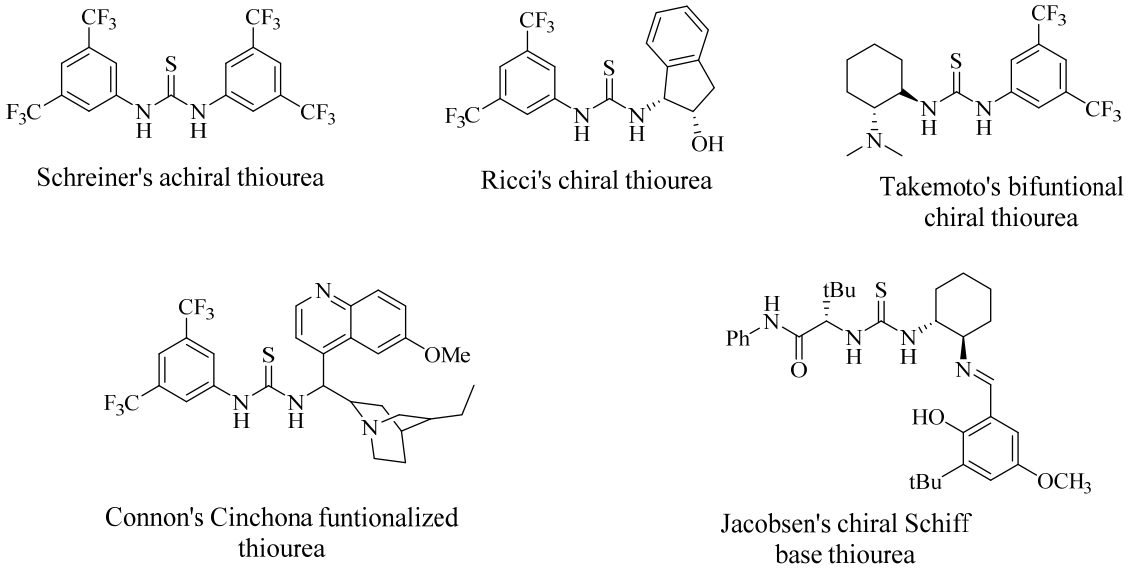


Figure 4. Structures of various thiourea derivatives.

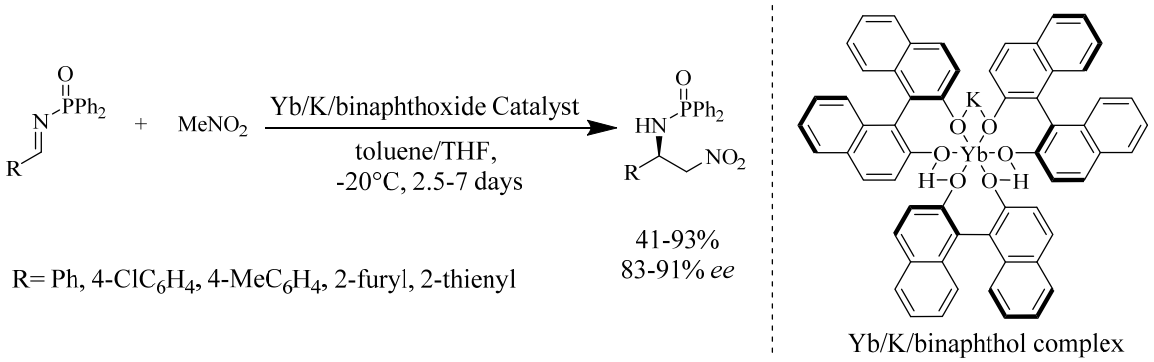
1.3. Different Routes to Chiral β -Amino Nitroalkanes

To date, the preparation of chiral β-amino nitroalkanes can be performed with different asymmetric reactions.

1.3.1. **Aza-Henry (or Nitro-Mannich) Asymmetric Reaction**

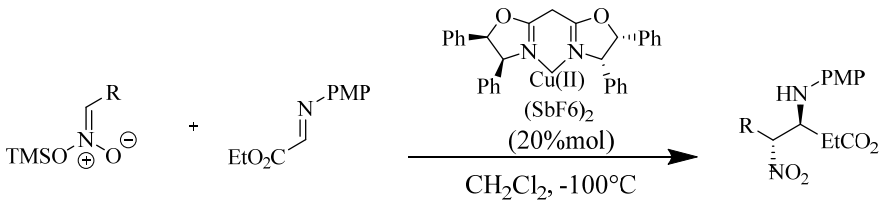
The aza-Henry (nitro-Mannich) reaction,[15] that is, nucleophilic addition of nitroalkanes to imines, is a useful carbon-carbon bond-forming process in organic chemistry. Although this reaction has been known for over a century, real interest from the synthetic community only began around the turn of the century and has since received considerable attention. This resulted in rapid development of a wide range of novel methodologies. Interest in the nitro-Mannich reaction arises from the value of the synthetically versatile β-Amino Nitroalkanes products.

The first example of an asymmetric direct metal-catalyzed nitro-Mannich reaction was reported by Shibasaki et al. in 1999.[16] They used the Yb/K heterobimetallic complex, which contains both Lewis-acidic and Brønsted-basic sites, for reaction between nitromethane and a variety of N-phosphinoyl-aryl imines (Scheme 2). The catalyst successfully promoted nitro- Mannich reaction in good enantioselectivities; however, the catalyst failed to promote reaction of higher homologues of nitromethane, such as nitroethane.



Scheme 2. Aza-Henry Reactions Catalyzed by Yb/K/binaphthoxide Catalyst.

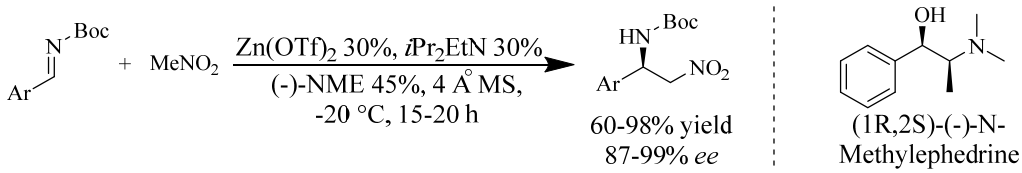
In 2001, Jørgensen published the first asymmetric nitro-Mannich reactions of TMS-nitronates with ethylglyoxylate-*N*-PMP-imine[17] (Scheme 3). They used Cu(II)−cis-DiPh-BOX catalyst to achieve excellent yields and enantio- and diastereoselectivities.



R= Et: 94%, 25:1 dr, 95% *ee*
R= ^{n}pentyl: 99%, 39:1 dr, 83% *ee*

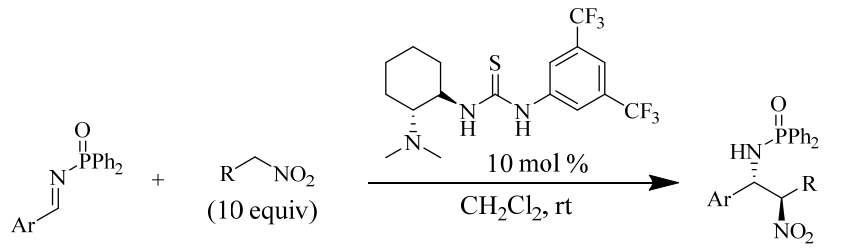
Scheme 3. Asymmetric Lewis-Acid-Catalyzed indirect Nitro-Mannich Reaction.

In 2006 Palomo also described the use of complexes of ZnII and *N*-methylephedrine as catalysts of the reaction of nitromethane and *N*-Boc aryl imines,[18] thus providing a new entry to give N-Boc β-nitroamines in generally with good yields and with high levels of stereocontrol.



Scheme 4. Enantioselective Aza-Henry Assisted by Zn^{II} and N-Methylephedrine (MS = molecular sieves).

Several drawbacks of the reactions catalyzed or promoted by metal salts may lie in the cost and the toxicity of the metal species. The first asymmetric organocatalyzed nitro-Mannich reaction was reported by the group of Takemoto in 2004.[19] The group applied Takemoto's bifunctional thiourea catalyst, to the reaction of nitromethane and a range of N-phosphinoyl-aryl imines (Scheme 5). The reactions were high yielding but only gave moderate enantioselectivities. Only a single diastereoselective example was given using nitroethane to form the product in a modest 3:1 dr in favor of the *anti* diastereomer.

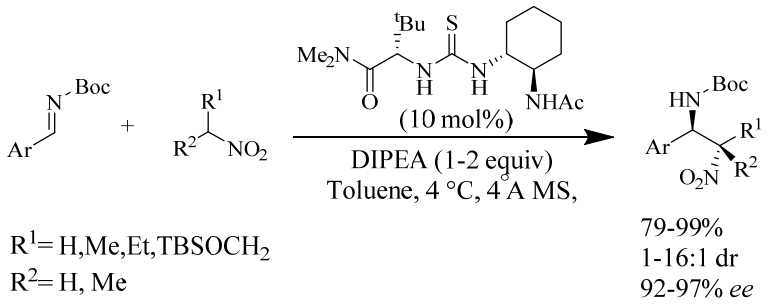


R = H,Me
Ar = Ph, 4-ClC_6H_4, 4-MeC_6H_4, 2-furyl, 2-thienyl, 2-naphthyl, 2-pyridyl, CH=CHPh

57-91%
3:1 dr (anti)
63-76% *ee*

Scheme 5. First Asymmetric Organocatalytic Aza-Henry Reaction.

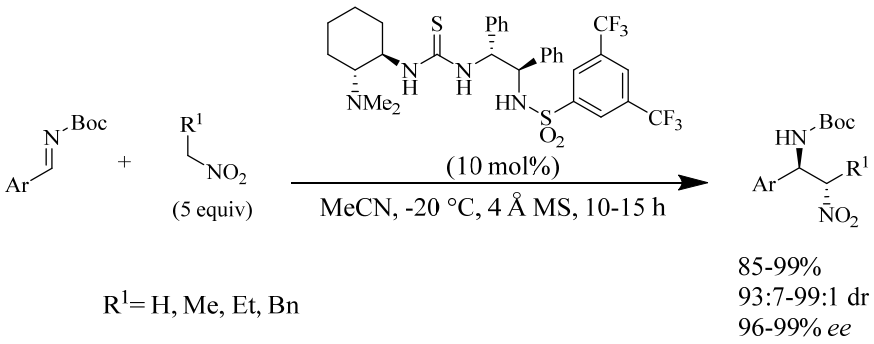
In 2005, Jacobsen et al. found a new thiourea catalyst that promoted the addition of a range of nitroalkanes to N-Boc-aryl-imines, affording both excellent yields and enantioselectivities (Scheme 6).[20]



Scheme 6. Jacbsen's Thiourea-Catalyzed Aza-Henry Reactions (DIPEA = *N*,*N*-Diisopropylethylamine).

Since the reports by Takemoto[19] and Jacobsen[20] on the application of thiourea-based organocatalysts to asymmetric nitro-Mannich reactions, there have been a large number of publications from other groups demonstrating the use of thioureas bearing various chiral scaffolds. These include catalyst-derived structures including from cinchona alkaloids, [21] chiral sulfonamides,[22] glycosides,[23] and steroids.

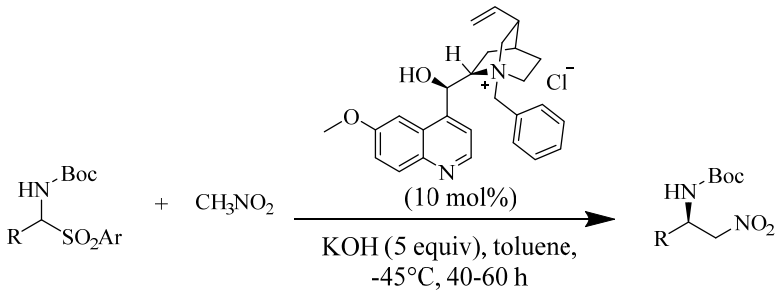
One of the most efficient organocatalytic nitro-Mannich protocols reported to date was presented by C. Wang et al. in 2008.[24] They used a chiral thiourea to catalyze the nitro-Mannich reaction between a range of N-Boc-aryl-imines and a number of nitroalkanes (Scheme 7). Near quantitative yields were obtained in the majority of cases, accompanied by exceptional stereoselectivities.



Scheme 7. Wang's Thiourea Catalyzed Aza-Michael Reactions.

The β-amino-alkyl nitroalkanes are difficult to obtain with the Aza-Henry reaction since the N-carbamoyl imines derived from aliphatic enolizable aldehydes readily tautomerize to the corresponding ene carbamate. To overcome these drawbacks, in 2005, Bernardi et al. developed a new approach to the asymmetric addition of nitromethane to N-

carbamoyl imines generated in situ from α-amido sulfones[25] (scheme 8); the reaction is catalyzed by a simple quininium salt (a chiral phase transfer catalyst), which first promotes the formation of the imines, and then activates the nucleophile for asymmetric addition. This method allows the use of N-carbamoyl imines derived from enolizable aldehydes in a catalytic asymmetric aza-Henry reaction, thus extending the generality of this asymmetric transformation.



R = aryl: 70-98% yield, 84-95% *ee*
R = alkyl: 84-95% yield, 92-98% *ee*

Scheme 8. Phase-Transfer-Catalyzed Aza-Henry Reaction Using Imines Generated In Situ.

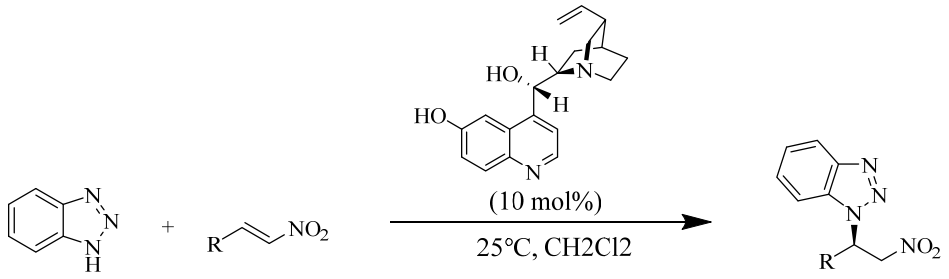
1.3.2. **Aza-Michael Asymmetric Reaction**

Consisting in the conjugate addition of nitrogen-based nucleophiles to Michael acceptors, the Aza-Michael reaction is an efficient C-N bond forming reactions of significant interest in organic chemistry. Considering that stereogenic centers containing C-N bonds are present in many important biomolecules, in recent years the development of efficient stereoselective Aza-Michael[26] has attracted considerable attention. In particular, the addition of ammonia equivalents to nitroalkenes gives rise to the synthetically interesting β-amino nitro functionality.

The first example of asymmetric Aza-Michael was published by Jørgensen et al. in 1996.[27] The reaction is catalysed by titanium complexes such as TiX_2–TADDOLate and $TiCl_2$–BINOLate and good conversions with enantiomeric excesses up to 42% were obtained with the application of 10 mol% of the catalyst.

Since then, a number of chiral catalyst systems for this reaction have been developed.

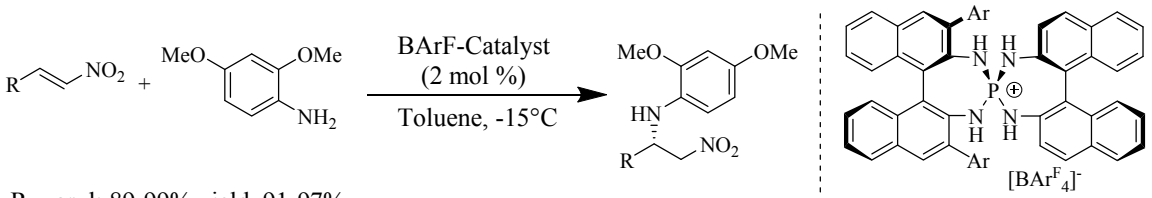
The first asymmetric organocatalytic aza-Michael addition to nitroalkenes was demonstrated in 2006 by Wang et al.,[28] employing aromatic heterocyclic benzotriazoles as nitrogen centered nucleophiles; the process is promoted by a cinchona alkaloid derivative to give Michael adducts in moderate to high enantioselectivities. However, the synthetic applicability of the products are limited.



R = aryl: 64-90% yield, 67-94% *ee*
R = alkyl: 67-83% yield, 57-68% *ee*

Sheme 9. First Asymmetric Organocatalytic Aza-Michael Reaction.

In 2009, Ooi et al.[29] reported the aza-Michael addition of 2,4-dimethoxyaniline to nitroalkenes in excellent yields and enantioselectivities by Brønsted-acid catalysis using chiral arylaminophosphonium barfates. A minor drawback is that 2.5 equivalents of CAN (cerium ammonium nitrate) were required for deprotection to afford the primary amine.

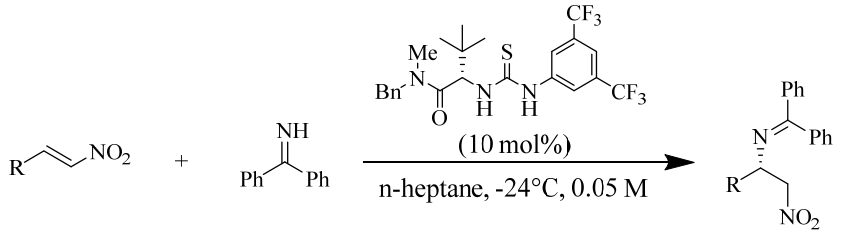


R = aryl: 89-99% yield, 91-97% *ee*
R = alkyl: 93-98% yield, 86-87% *ee*

BArF-Catalyst

Scheme 10. Aza-Michael Reaction Catalized by Chiral Arylaminophosphonium Barfates Catalyst (Ar = 3,4,5-F_3-C_6H_2; BArF = (3,5-$(CF_3)_2$-$C_6H_3)_4B^-$).

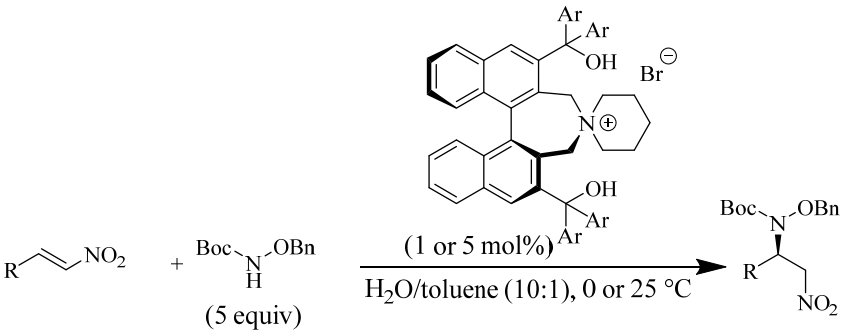
In 2010, Jorgensen et al. [30] reported the formal addition of ammonia to nitroalkenes affording optically active β-amino nitro compounds in high yields and enantioselectivities. The approach is based on a thiourea-catalyzed aza-Michael reaction, by which benzophenone imine serves as a masked ammonia equivalent, which is released by one pot hydrolysis.



R = aryl: 79-88% yield, 81-92% *ee*
R = alkyl: 85-95% yield, 78-89% *ee*

Scheme11. Jacbsen Type Thiourea Catalyzed Aza-Michael Reaction.

In 2011 Maruoka et al.[31] developed a highly efficient catalytic asymmetric amination of nitroolefins under neutral phase-transfer conditions with the influence of a chiral bifunctional tetraalkylammonium bromide in biphasic solvent.



R = aryl: 62-94% yield, 90-95% *ee*
R = alkyl: 95-99% yield, 77-83% *ee*

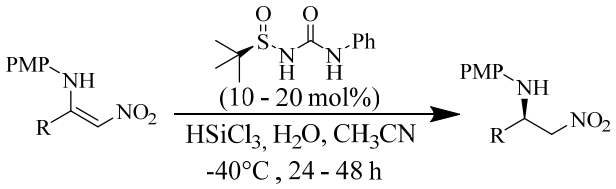
Ar = 3,5-[3,5-$(CF_3)_2C_6H_3$]$_2C_6H_3$

Scheme 12. Asymmetric Neutral Amination Catalyzed by Chiral Ammonium Salts.

1.3.3. **Asymmetric Reduction of β-Amino nitroolefins**

The asymmetric catalytic reduction of β-amino nitroolefins constitutes a complementary straightforward pathway to form chiral β-amino nitroalkanes, owing to the easy availability of starting materials.

In this context, in 2012, J. Sun et al.[32] reported the asymmetric hydrosilylation of β-*p*-methoxyphenylamino nitroolefins using 10 to 20 mol % of a simple *N*-sulfinyl urea as a bifunctional catalyst and 3 equivalent of trichlorosilane (a reagent not very easy to handle due to its volatility, toxicity and corrosivity) (Scheme 13). β-Amino nitroalkanes with good to high enantioselectivities (79-97% *ee*) were obtained.

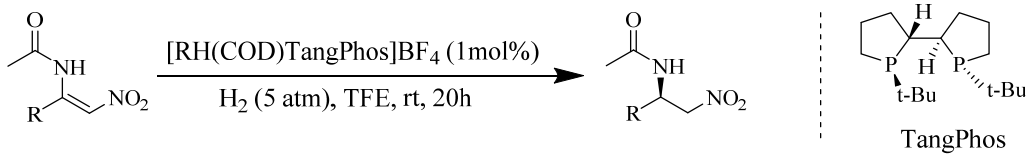


R = aryl: 82-99% yield, 79-97% *ee*
R = alkyl: 96-97% yield, 82-90% *ee*

Scheme 13. Asymmetric hydrosilylation of β-*p*-methoxyphenylamino nitroolefins (PMP= p-methoxyphenyl).

More recently, enantioselective metal catalysed asymmetric hydrogenations[13] of β-acylamino nitroolefins have been developed.

In 2013, Wang and Zhang[33] used a Rh–Tangphos complex achieving high enantioselectivities for β-aryl β-amino nitroalkenes (up to 93% *ee*) but rather poor enantioselectivity for alkyl substrates (only 18–22% *ee*) (Scheme 14).

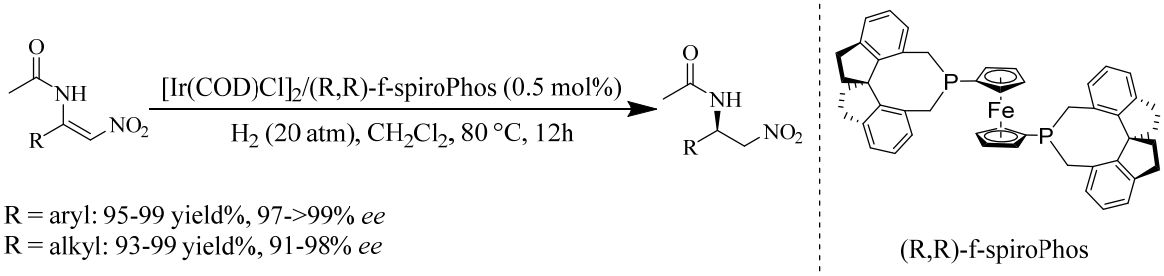


R = aryl: 93-98% yield, 81-93% *ee*
R = alkyl: 67-96% yield, 18-22% *ee*

Scheme 14. Asymmetric Hydrogenation of β-Acylamino Nitroalkenes with Rh Complex (COD= 1,5-cyclooctadiene).

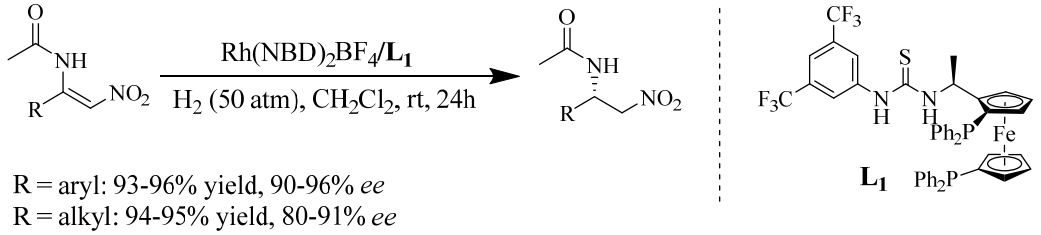
Afterward, in 2014 Hou et al.[34] reported an highly efficient enantioselective hydrogenation of β-acylamino nitroolefins successfully accomplished employing an Ir-spiroPhos complex in 20 atm H_2 and 80 °C condition; very high yields and excellent

enantioselectivities were achieved with both aryl and alkyl β-amino nitroalkenes (Scheme 15).



Scheme 15. Asymmetric Hydrogenation of B-Acylamino Nitroalkenes with Ir Complex.

Very recently, Hu, Dong and Zhang[35] developed the highly efficient asymmetric hydrogenation of β-amino nitroolefins catalyzed by rhodium/bis(phosphine)-thiourea L1 complex with excellent enantioselectivities (in *S* enantiomer) and yields (up to 96% *ee*, 96% yield, >99% conversion, TON up to 1000) (Scheme 16).



Scheme 16. Asymmetric Hydrogenation of B-Acylamino Nitroalkenes with Rh/Bis(Phosphine)-Thiourea Complex (NBD= 2,5-norbornadiene).

2. Aim of the project

My apprenticeship activity was based on the development of an organocatalyzed enantioselctive reduction of β-amino nitroolefins in a transfer hydrogenation reaction, a reaction in which the hydrogen source is a molecule different from H_2. As we have seen in the previous paragraph, the different types of reaction for the reduction of β-amino nitroolefins that have been proposed to date, are based on the utilization of metal complex catalysts[33-35] or a hydrosilylation reaction as reported by J. Sun et al.[32] The choice of operating with a transfer hydrogenation reaction is in line with the organocatalysis principles; indeed, this method avoids hazardous high pressures of H_2 gas with the relative experimental setups.

In Nature, transfer hydrogenation processes are very frequent, and are typically mediated by the dihydropyridine-containing cofactor NADH (nicotinamide adenine dinucleotide) or by its phosphate analogue NADPH, associated with enzymes. Aromatisation to the corresponding pyridine (NAD+ or NADP+) is the thermodynamic driving force promoting the hydride transfer. Analogous to Nature's NADH, Hantzsch esters (HE) (Fig. 7) have been shown to serve the role of small molecule NADH analogues given that the dihydropyridine system participates in hydride delivery with electrophilic π-systems in a variety of non-catalytic processes. Also due to their rapid synthetic access, HE have served as a powerful platform for the development of a large number of reductive organocatalytic processes in the last few years, and perhaps represent the most successful and broadly applied example of a bioinspired catalytic manifold.[36]

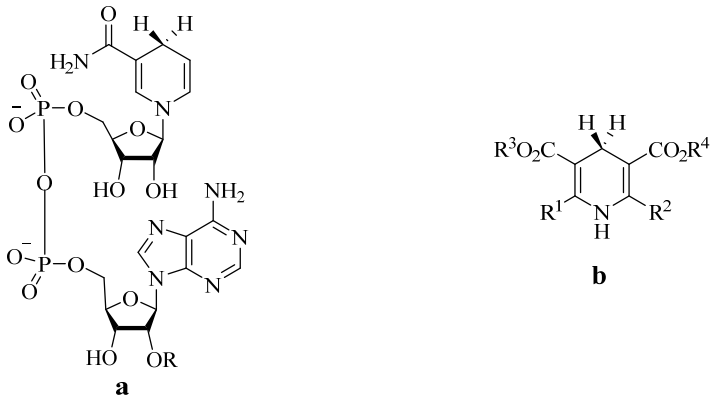
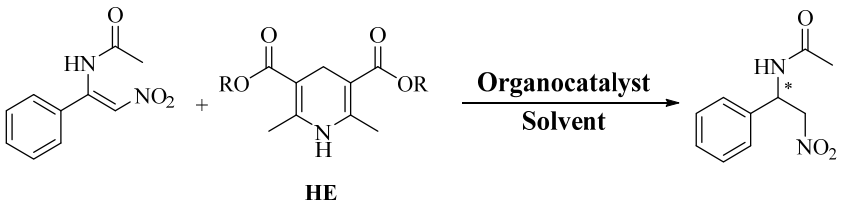


Figure 7. a) NADH: R= H; NADPH: R= PO_3^{2-}. **b**) Hantzsch ester structure.

Following the previous experience of the research group in this field,[37] we decided to use the Hantzsch ester as hydrogen source for the development of an organocatalytic enantioselective reduction of β-amino nitroalkenes.

Discover a metal-free catalyst able to perform the reaction of asymmetric reduction with a good conversion and good enantioselectivity is the first target of this project. The organocatalyst considered are thioreas for their capacity to activate the nitro compounds. The model reaction taken into consideration, as for the previous analogous work utilizing metal complexes,[33-35] is the reaction of the reduction of (Z)-*N*-(2-nitro-1-phenylvinil)acetamide (Scheme 17).



Scheme 17. Model reaction taken into consideration for the asymmetric reduction reaction.

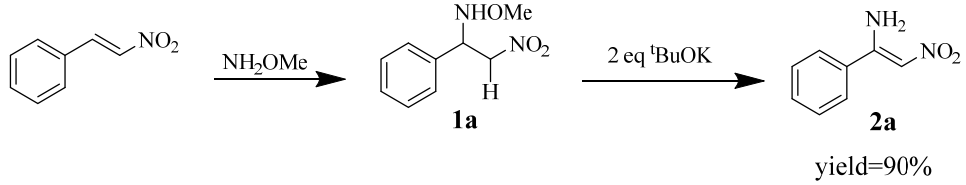
After finding a catalyst with a promising reactivity, the targets will be:

- Optimizing the reaction conditions to reach the best conversion and enantioselection for this reaction. Among the parameters that we could change there are: temperature, reaction time, R substituent of HE, solvent, catalyst load.
- Test the reaction with a different protecting group, such as *tert*-butyloxycarbonyl (Boc) as it is considered one of the most useful protecting group and the most widely used in synthetic organic chemistry when it is required to protect primary or secondary amines. This utility is mainly due to the easiness of its introduction and removal and to its orthogonality with many other protecting groups.[38]
- Study the generality of the reaction introducing substituents of different nature over the aromatic ring of the nitroalkene.
- Test the reaction with aliphatic nitroolefins, since this kind of nitrolefins represent challenging substrates.
- Conducting the reaction with a substrate having an α-substituent with respect to the nitro group, for achieving the formation of two stereo centers.
- Determining the absolute configuration of the obtained stereocenter.

3. Results and Discussion

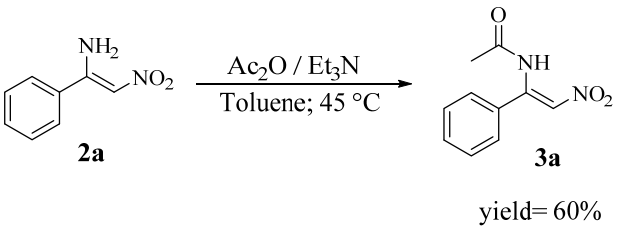
3.1. Synthesis of (*Z*)-*N*-(2-nitro-1-phenylvinyl)acetamide

We started from the synthesis of the (*Z*)-*N*-(2-nitro-1-phenylvinyl)acetamide; to obtain this compound we proceeded with the amination of β-nitrostyrene with methoxylamine in dimethylformamide (DMF); the addition of the methoxylamine to nitrostyrene provided the intermediate **1a** in quantitative yield, and the subsequent treatment of **1a** with two equivalent of base (potassium *tert*-butoxide) furnished product **2a** (Scheme 18).



Scheme 18. Amination of Nitrostyrene.

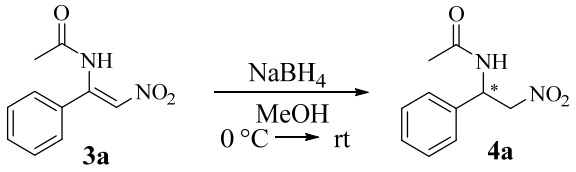
Next, we protected the amino moiety with an acetyl group by treating **2a** with acetic anhydride in the presence of triethylamine. The reaction was conducted in toluene at 45°C overnight (Scheme 19) and the pure β-acetylamino nitroolefin **3a** was obtained after column chromatography.



Scheme 19. Protection of the amino group.

3.2. Synthesis of Racemic Product 4a

With the β-acetylamino nitrostyrene **3a** in hand, we started with the preparation of the racemic product **4a** by reducing the olefin's double bound with sodium borohydride ($NaBH_4$) in methanol (MeOH) (Scheme 20). The racemic mixture was injected in a chiral stationary phase HPLC to separate the two enantiomers, in order to have a reference to measure the enantiomeric excess (*ee*) of the asymmetric reaction.

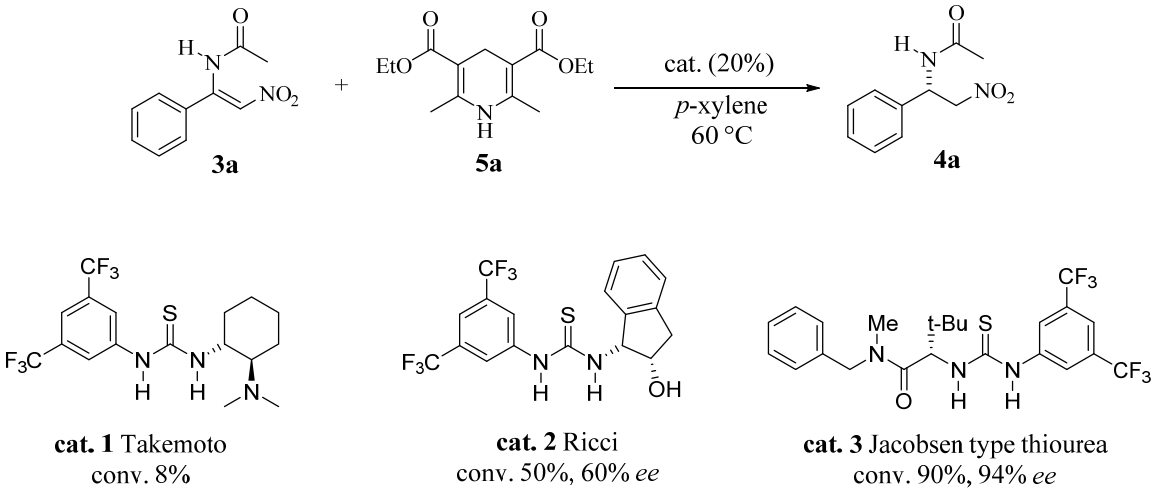


Scheme 20. Racemic Reduction of the Compund **3a**.

3.3. Optimization of the reaction conditions

We started to test the transfer hydrogenation of **3a** with Hantzsch ester **5a** as hydrogen donor with three different chiral thioureas in *p*-xylene at 60 °C (Scheme 21).

Takemoto's catalyst (**cat 1)**, Ricci's catalyst (**cat 2)** and a Jacobsen type thiourea (**cat 3**), afforded product **4a** in a 8%, 50% and 90% conversion respectively (Scheme 21) and with an enantiomeric excess (*ee*) of 60% and 94% respectively (the *ee* of the reaction with **cat 1** was not determined because of the low conversion).

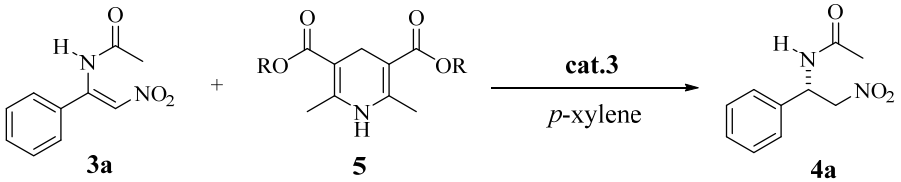


Scheme 21. Chiral Thioureas Tested for the Enantioselective Transfer Hydrogenation.

Satisfied with the result obtained with the **cat. 3**, we started to study this reaction with the aim of optimizing the reaction conditions in term of conversion and enantiomeric excess. All the reactions have been performed in a screw cap round bottom vial to prevent the oxidation of the Hantzsch ester. We have observed that opening the vial and sampling the mixture with the aim of checking the conversion, stopped the reaction probably for the complete oxidation of the HE. For this reason, all the test reactions performed for evaluating the conversion and the *ee* at different conditions were performed without opening the vials till the end.

We observed that the use of the Hantzsch ester **5b** with *tert*-butyl substituents at the ester functionality afforded better result in term of conversion with respect to **5a**. A catalyst loading of 5 mol% was also well tolerated (compare entries 1-3 in table 1). Moreover increasing the temperature to 60 °C (entries 4,5) the possibility of using a 5 mol% of catalyst was confirmed with a promising 80% of conversion. Extending the reaction time to 14 h (entry 6), the conversion reached 90% yet with a small erosion of the *ee*. Next the concentration of the reaction mixture was increased to 0.3M (entry 7), obtaining a complete conversion of **3a** and a very high *ee*. A further decrease of the catalyst loading (compare entries 7, 8 and 9) gave a slight lower enantioselectivity of the product **4a**.

Table 1. Optimization of the Reaction Conditions in the Asymmetric Reduction of **3a**.[a)]



R = Et **5a**
R = *t*-Bu **5b**

Entry	HE (eq)	Cat.3 (mol%)	p-Xylene (M)	T (°C)	t (h)	Conv. (%)[b)]	*ee* (%)[c)]
1	**5b** (1.15)	15	(0.1M)	r.t.	4:10	66	/
2	**5a** (1.15)	10	(0.1M)	60	3:40	37	/
3	**5b** (1.1)	5	(0.1M)	60	2:15	70	/
4	**5b** (1.15)	10	(0.1M)	r.t.	5:30	85	98
5	**5b** (1.15)	5	(0.1M)	60	5:30	80	98
6	**5b** (1.2)	5	(0.1M)	60	14	90	92
7	**5b** (1.2)	5	(0.3M)	60	14	100	97
8	**5b** (1.2)	2.5	(0.3M)	60	14	96	90
9	**5b** (1.2)	1	(0.3M)	60	14	94	90

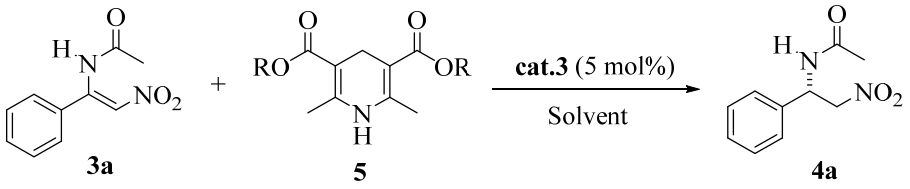
[a)] Reactions performed over 0.05 mmol of **3a** [b)] Determined on the crude mixture by ^{1}H NMR analysis. [c)] Determined by chiral stationary phase HPLC.

Next a solvent screening was performed as reported in Table 2. Both toluene and benzotrifluoride furnished excellent results at 60°C (compare entries 1-3). DCM was tested both at 40 °C and at r.t. affording **4a** with a good conversions but a lower *ee* (entries 4,5). All the aromatic solvents were tested at r.t. achieving in the all the case a

single enantiomer of **4a** (the second enantiomer was not visible in HPLC) but with a slightly lower conversions (entries 6-10).

To conclude the screening reactions we performed three parallel tests in *p*-xilene, toluene and benzotrifluoride at 40°C for 14h (entries 11-13) and perfect results were obtained (conversion >99%, *ee* >99%). So we decided to go on with toluene as the solvent since is the less expensive and we adopted the conditions of entry 12 for the following reactions.

Table 2. Optimization of the Reaction Conditions in the Asymmetric Reduction of 3a.[a)]



R = Et **5a**
R = *t*-Bu **5b**

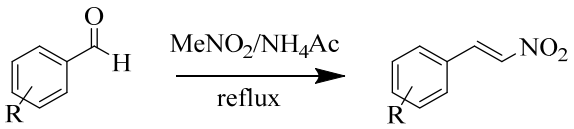
Entry	HE (1.2eq)	Solvent (0.3M)	T (°C)	t (h)	Conv. (%)[b)]	*ee* (%)[c)]
1	**5b**	p-Xylene	60	14	>99	97
2	**5b**	Toluene	60	14	>99	97
3	**5b**	Benzotrifluoride	60	14	>99	97
4	**5b**	DCM	40	14	>99	96
5	**5b**	DCM	r.t.	14	97	96
6	**5b**	*p*-Xylene	r.t.	14	93	99
7	**5b**	Benzotrifluoride	r.t.	14	91	>99
8	**5b**	*p*-Xylene	r.t.	18	97	>99
9	**5b**	Toluene	r.t.	18	97	>99
10	**5b**	Benzotrifluoride	r.t.	18	97	>99
11	**5b**	*p*-Xylene	40	14	>99	>99
12	**5b**	Toluene	40	14	>99	>99
13	**5b**	Benzotrifluoride	40	14	>99	>99

[a)] Reactions performed over 0.05 mmol of **3a** [b)] Determined on the crude mixture by ^{1}H NMR analysis. [c)] Determined by chiral stationary phase HPLC.

3.4. Scope of the Reaction

3.4.1. **Aromatic Rings substituted β-acetylamino Nitroolefins**

With the optimized reaction condition in hand, we started to study the scope of the reaction. Different protected β-amino nitroolefins bearing aromatic rings substituted with either electron releasing and electron withdrawing groups have been synthesized starting from the corresponding nitroolefins in turn obtained from the related aldehydes and nitromethane. The synthetic sequence (Henry reaction with a subsequent dehydration) was performed in the presence of ammonium acetate and using nitromethane as solvent (Scheme 22).



Scheme 22. General synthesis for substituted β-nitrostyrenes.

After five hours of reflux, solvent extraction and purification (by recrystallization from ethanol or column chromatography), the nitroolefins have been obtained; subsequently this nitroolefins were aminated and protected following the methodology previously described for the amination and the acetyl protection of the nitrostyrene. The obtained β-acetylamino aromatic nitroolefins are reported in figure 8.

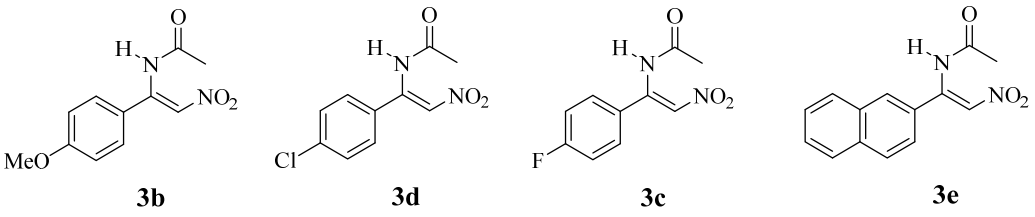


Figure 8. Aromatic Rings substituted β-acetylamino Nitroolefins.

The transfer hydrogenation reaction was achieved with substrates **3b-3e**, using the optimized condition affording the corresponding β-acetylamino nitroalkanes **4b-4e** with excellent results, 89->99% conversion and 97->99% *ee* (Table 3).

Table 3. Scope of the Reaction with Aromatic β-Acetylamino Nitroolefins.[a)]

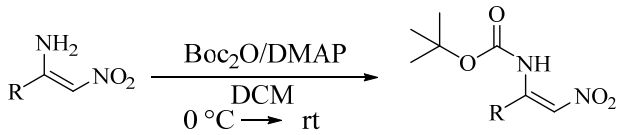
Entry	3	Conv. (%)[b)]	Yield (%)[c)]	*ee* (%)[d)]
1	**a**	>99	97	>99
2	**b**	89	81	>99
3	**c**	>99	90	96
4	**d**	>99	94	97
5	**e**	99	91	98

[a)] Conditions: **3** (0.15 mmol), **cat.3** (0.075 mmol, 5 mol%), **5b** (0.18 mmol), 40 °C, 14 h. [b)] Determined on the crude mixture by ^{1}H NMR analysis. [c)] Pure product **4**, isolated by chromatography on silica gel. [d)] Determined by chiral stationary phase HPLC.

3.4.2. *Tert*-Butyloxycarbonyl Protected β-Amino Nitroolefins

Established the robustness of the transfer hydrogenation involving aromatic β-acetylamino nitroolefins, Hantzsch ester **5b** and **cat 3**, we decided to try the reaction over Boc-protected β-amino nitroolefins.

Boc-protect β-amino nitroolefins were obtained by reaction with 1.2 equivalents of di-*t*-butyl dicarbonate in the presence of 0.05 equivalents of dimethylamino pyridine (DMAP) (Scheme 23).



Scheme 23. Boc-Protection of General β-Amino Nitroolefins.

The reaction with the Boc-protected nitroolefins **3f** (figure 9) was accomplished with the optimized conditions, and we obtained a lower conversion (70%) compared to the analogous acetylated substrate, so we increased both the reaction time and the temperature.

We decided to maintain the temperature at 40°C and to use a longer reaction time, paying attention to saturate the reaction's vial with nitrogen; in fact in some tests the Hantzsch ester resulted completely oxidized, probably due to the atmospheric oxygen. The reaction in this re-optimized conditions afforded the product **4f** in 95% conversion (90% yield) and complete enantioselection (entry 1 table 4).

The transfer hydrogenation of **3f** could also be performed on a larger scale (2 mmol, Table 4, entry 2) although with a small erosion in the yield (compare entries 1 and 2).

With the aim of enlarging the scope of the transfer hydrogenation, we synthesized a large series of Boc protected β-amino nitroolefins bearing both aromatic and aliphatic substituents.

The aromatic nitroolefins were synthesized from the related aldehydes, using the methodology previously reported in scheme 22. Amination and Boc protection led to the various *tert*-butyloxycarbonyl aromatic β-amino nitroolefins (figure 9, product **3g-3l**). Among this, substrates with a methyl group placed in the *ortho*, *metha* and *para* position of the aromatic ring **(3j,k,l)** have been synthetized to evaluate the influence of the substitution pattern on the benzene ring; a heteroaromatic one has been also synthesized (**3i**).

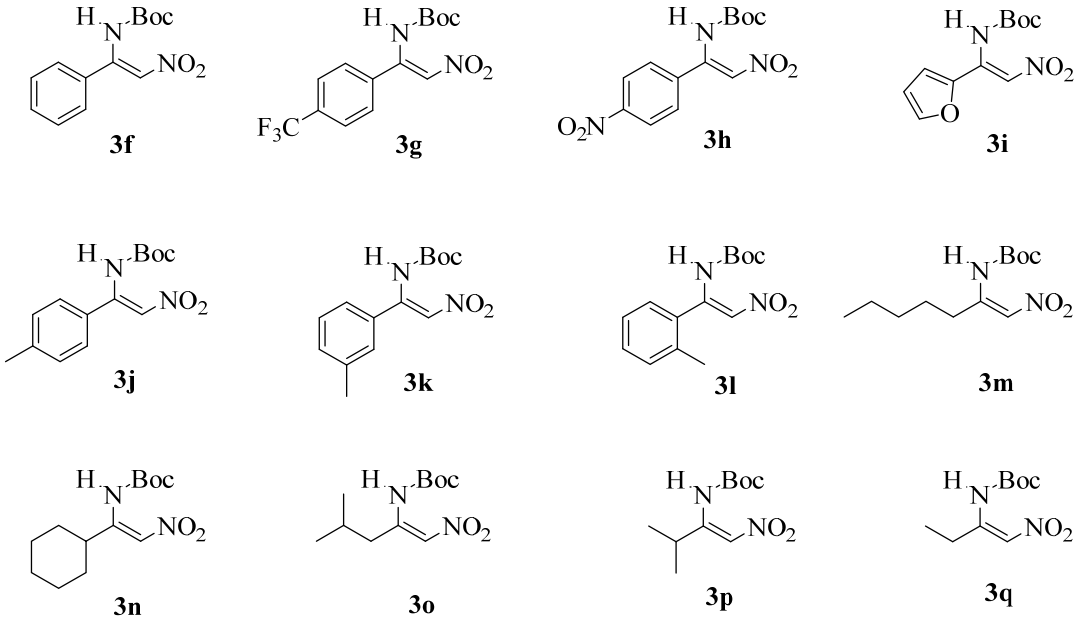
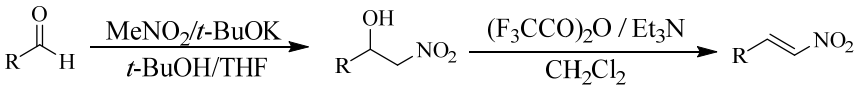


Figure 9. *N*-Boc β-amino Nitroolefins.

To obtain the various aliphatic nitroolefins we started from the related aldehydes and nitromethane in the presence of potassium *tert*-butoxide; the β-nitroalcohols, obtained from the Henry reaction, were reacted in the presence of trifluoroacetic anhydride with the subsequent addition of triethylamine to afford the related β-aliphatic nitroolefins (Scheme 24).



R= aliphatic

Scheme 24. Synthesis β Aliphatic Nitroolefins

After common work-up and purification operation, the β-aliphatic nitroolefins were aminated and Boc protected, following the same procedures of the aromatic ones, affording the nitroolefins **3m-q** shown in figure 9.

Compounds **3g-3l** were reacted under the optimized conditions for the substrate **3f**, (Hantzsch ester **5b** as hydrogen donor in toluene at 40 °C for 18 hours) and the obtained results are reported in table 4.

We observed that also using Boc as protecting group, the aromatic substrates with either electron donating or electron withdrawing substituents over the aromatic rings, as well as the heteroaromatic substrate **3i**, were well tolerated, affording the corresponding *N*-Boc adducts **4g-j** with very good conversions, yields and enantioselectivities, see the entries 3-6. The reaction of derivative **3h** (entry 4) was conducted at 20°C instead of 40°C, in this way we enhanced the *ee* from 93 to 96 without compromising the conversion value.

Table 4. Scope of the Reaction with Aromatic *N*-Boc β-amino Nitroolefins..[a)]

Entry	3	Conv. (%)[b)]	Yield (%)[c)]	ee (%)[d)]
1	**f**	95	90	>99
2[e)]	**f**	/	86	>99
3	**g**	97	86	>99
4[f)]	**h**	95	93	96
5	**i**	75	71	>99
6	**j**	93	86	97
7	**k**	95	75	>99
8	**l**	50	40	98

[a)] Conditions: **3** (0.15 mmol), **cat.3** (0.075 mmol, 5 mol%), **5b** (0.18 mmol), 40 °C, 18 h. [b)] Determined on the crude mixture by ^{1}H NMR analysis. [c)] Pure product **4**, isolated by chromatography on silica gel. [d)] Determined by chiral stationary phase HPLC. [e)] On a 2.0 mmol scale. [f)] Reaction performed at 20 °C.

Derivatives **4j–l** could be obtained in 86–40% yields and with very good enantioselectivities (entries 6-8). Yields followed the order *para>meta>ortho*, indicating

a (not dramatic) sensitivity of the reaction to steric factors. Enantioselectivities remained always very high.

Regarding the β-aliphatic nitroolefins, we started to test their reactivity in the optimized reaction conditions (table 2, entry 10); since we obtained poor conversions, respect to the aromatic substrates, with both **3m** and **3n** nitroolefins, we tried to change some reaction parameters such as: time and temperature, catalytic load and **5b** equivalents. For both **3m** and **3n**, we reached the best conversion by reacting them at 60°C for 24 hours, with the same catalytic load, solvent and HE equivalents used for the aromatic nitroolefins.. We decided to react all the aliphatic nitroolenfins in the latter found condition, obtaining the excellent results shown in the table 5.

Table 5. Scope of the Reaction with Aliphatic *N*-Boc β-amino Nitroolefins..[a)]

Entry	3	Conv. (%)[b)]	Yield (%)[c)]	*ee* (%)[d)]
1	**m**	91	91	98
2	**n**	99	88	98
3	**o**	89	60	96
4	**p**	>99	91	93
5	**q**	97	92	97

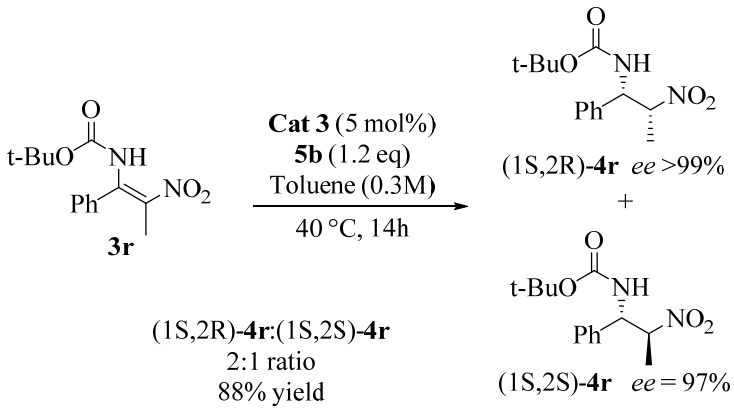
[a)] Conditions: **3** (0.15 mmol), **cat.3** (0.075 mmol, 5 mol%), **5b** (0.18 mmol), 60 °C, 24 h. [b)] Determined on the crude mixture by ^{1}H NMR analysis. [c)] Pure product **4**, isolated by chromatography on silica gel. [d)] Determined by chiral stationary phase HPLC.

3.4.3. **Reaction with *α*-substituted β-Amino Nitroolefin**

One of our initial aims was to synthesize an α-substituted substrate, that allow the possibility of forming two stereo centers in the H-transfer reaction and to evaluate the diastereoselectivity of the process. Accordingly, we synthetized the analogous *α*-methylated of the substrate **3f**.

We reacted benzaldehyde with the nitroethane, and after the usual procedure of amination, ad Boc protection product **3r** was obtained in about 40% yield.

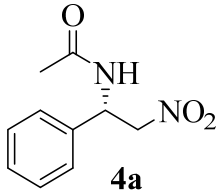
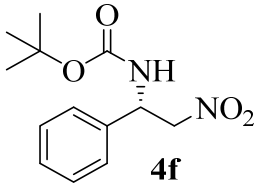
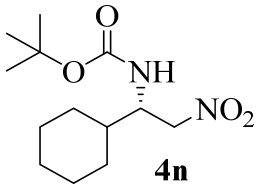
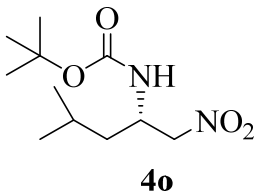
Next the *tert*-butyl (*Z*)-(2-nitro-1-phenylprop-1-en-1-yl)carbamate **3r** was subjected to the optimized reaction conditions affording a mixture of two nearly enantiopure diasteroisomers (1*S*,2*R*)-**4r** and (1*S*,2*S*)-**4r** in a 2:1 ratio with complete conversion (88% yield) (Scheme 25).



Scheme 25. Transfer hydrogenation with the α-substituted substrate **3r**.

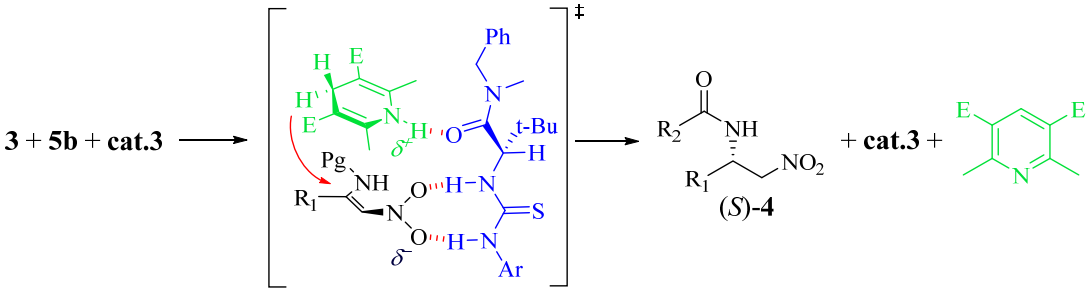
3.5. Determination of the Absolute Configuration of the β-amino Nitroalkanes

The absolute configuration of products **4** was determined to be *S* by comparison with literature data (CSP-HPLC retention time and optical rotation $[\alpha]_D$ value) for compound **4a**,[39] **4f**,[30,40] **4n**[30,40] and **4o**[40] (Table 6).

 **4a**	$[\alpha]_D^{25}$ +73 (c 1, CH_2Cl_2); Lit $[\alpha]_D^{20}$ = -69.20 (c = 0.5, CH_2Cl_2), 99% *ee* (*R*)
 **4f**	$[\alpha]_D^{25}$ +29 (c 1, CH_2Cl_2); Lit $[\alpha]_D^{25}$ = -20.1(c 1.0, $CHCl_3$), 91% *ee* (*R*)
 **4n**	$[\alpha]_D^{25}$ -15.5 (c 1, CH_2Cl_2); Lit $[\alpha]_D^{25}$ = +24 (c 1.0, $CHCl_3$), 98% *ee* (*R*)
 **4o**	$[\alpha]_D^{25}$ -40 (c 1, CH_2Cl_2); Lit $[\alpha]_D^{25}$ = +26.4 (c 1.0, $CHCl_3$), 97 % *ee* (*R*)

3.6. Proposed mechanism for the Transfer Hydrogenation

Extensive mechanistic studies of the role of chiral thiourea catalysts related to **cat.3**, using kinetic, spectroscopic and computational work, have previously been performed, establishing its more stable conformations and mode of action.[41] Building upon these studies and in line with the research group previous hypothesis[37] and related calculation results,[42] a tentative reaction model for the transfer hydrogenation reaction of β-amino nitroalkenes can be reasonably put forward (Scheme 26). This model implies the stabilization of the transition state of the reaction by coordination of the nitro group of nitroalkenes by the thiourea moiety, while the amide oxygen coordinates the Hantzsch ester at its NH proton, positively charged during the hydride-transfer step. Subsequent irreversible proton transfer step leads to the (*S*)-adducts **4** and the pyridine derivative with concomitant catalyst release.



Schem 26. Proposed Reaction Model.

The very high enantioselectivities obtained with the **cat.3** with both the present β-amino- and the previously reported[37] β-trifluoromethyl nitroolefins remarks the reliability of this model and the good geometrical fit between the electrostatically complementary functionalities of the catalyst and a transition state leading to (*S*)-products.

Moreover, the results reported in Scheme 25 suggest that the addition of the hydride at the carbon in β to the nitro group occurs with high enantioselectivity when the substrate is bound to the catalyst, while the addition of the proton occurs without any stereocontrol. The two diastereomers at the stereogenic centre α-to the nitro group are in fact generated in nearly equimolar amounts.

4. Conclusion

In summary, we have developed a highly enantioselective organocatalytic transfer hydrogenation of β-acylamino and β-*t*-butyloxycarbonylamino nitroolefins **3** with a simple thiourea catalyst and Hantzsch esters as hydrogen source for the direct access to enantiomerically pure β-amino nitroalkanes.

To reach this achievement we firstly identified **cat.3** and HE **5b** as the most promising catalyst and hydrogen source for the substrate **3a**, then we optimized the reaction conditions until reaching a complete conversion and enantioselection with 5 mol% of catalyst, 1.2 equivalents of **5b**, toluene as solvent, temperature of 40 °C in 14 hours of reaction. Excellent results were obtained for all the tested β-acylamino nitroolefins.

After observing a promising reactivity with the Boc protected substrate **3f**, a wide range of both aliphatic and aromatic Boc protected substrates have been synthetized. The reaction conditions were adjusted for both types of substrates; also in these cases the nitroalkanes products **4** have been obtained with good yields and excellent *ee's*. Furthermore, with the substrate **3r** we observed that the reaction did not furnish substantial diastereoselection in the formation of the second stereocentre. A scale up of the reaction has been successful completed utilizing 2 millimoles of the substrate **3f**, obtaining the nitroalkane **4f** with 86% yield and total enantioselection.

This optimized methodology represent a valid alternative to the previously developed reduction of the β-amino nitroolefins affording the various nitroalkanes **4** with excellent results.

5. Experimental Section

5.1. General Methods

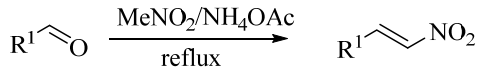
^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Varian AS 400 spectrometer. Chemical shifts (δ) are reported in ppm relative to residual solvent signals for ^{1}H and ^{13}C NMR,[43] and using $CF_3C_6H_5$ as external reference calibrated at -63.72 ppm for ^{19}F NMR. ^{13}C NMR spectra were acquired with ^{1}H broad band decoupled mode. Data are reported either as: s = singlet, d = doublet, dd= double doublet, t = triplet, q = quartet, m = multiplet, br = broad, coupling constant(s) in Hz, integration. Mass spectra were recorded on a micromass LCT spectrometer using electrospray (ESI) ionisation techniques or by use of electronic impact ionization (EI^+). Optical rotations were measured on a Perkin-Elmer 241 polarimeter provided with a sodium lamp and are reported as follows: $[\alpha]^{T(°C)}_{\lambda}$ (c = g/100 mL, solvent). The enantiomeric excess (*ee*) of the products was determined by chiral stationary phase HPLC (Daicel Chiralpak AD-H and AS columns or Chiralcel OJ-H and OD columns see below for further details), using a UV detector operating at 254 nm. Chromatographic purifications were performed using 70-230 mesh silica.

5.2. Materials

Analytical grade solvents and commercially available reagents were used as received, unless otherwise stated. Hantzsch ester **2a**[44] and chiral thioureas **3a,c**[45] were prepared as reported in the literature. *β*-Aryl substituted nitroolefines[46] and *β*-alkyl substituted nitroolefines[47] were prepared from the corresponding freshly distilled aldehydes following literature procedures as described at page S2. (*E*)-(2-nitroprop-1-en-1-yl)benzene was prepared following literature procedure.[48]

5.3. Procedures to Obtain the Protected *β*-Amino Nitroolefins

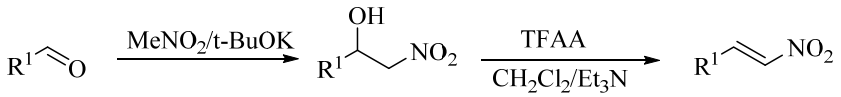
5.3.1. **Typical rocedure for the preparation of *β*-Aryl substituted nitroolefins**[46]



R^1 = Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-FC_6H_4, 2-Naphthyl,
4-$F_3CC_6H_4$, 4-$NO_2C_6H_4$,4-MeC_6H_4, 3-MeC_6H_4, 2-MeC_6H_4

A stirred solution of the appropriate aldehyde (10 mmol) and ammonium acetate (190 mg, 2.5 mmol) in nitromethane (50 mL) was heated at reflux for 5 h. The obtained solution was poured into water and extracted with diethyl ether (3 × 50 mL). The extract was washed with brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by recrystallization from ethanol or by silica gel column chromatography (hexanes/EtOAc, 20/1).

5.3.2. **Typical procedure for the preparation of *β*-Alkyl substituted nitroolefins**[47]



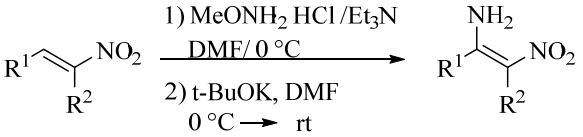
R^1 = n-Pent, i-Bu, c-Hex, i-Pr, Et

Potassium *tert*-butoxide (0.336 g, 3.0 mmol, 0.1 equiv) was added to a stirred solution of the appropriate aldehyde (30.0 mmol), nitromethane (2.44 mL, 45 mmol, 1.5 equiv), THF (7.5 mL), and *tert*-butanol (7.5 mL) at 0 °C. The stirred mixture was allowed to warm to room temperature over 2 h and stirred an additional 10 h. The mixture was poured into water (100 mL) and extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with brine (1 × 50 mL), dried over $MgSO_4$, filtered through a pad of Celite, and concentrated *in vacuo*. The resulting *β*-nitro alcohol was used for the next step without further purification.

Trifluoroacetic anhydride (4.2 mL, 30 mmol, 1 equiv) was added to a solution *β*-nitro alcohol in dichloromethane (30 mL) at -10 °C. The resulting solution was allowed to stir for 2 min, and then triethylamine (8.4 mL, 60 mmol, 2 equiv) was slowly added dropwise over 5 min and the reaction mixture was stirred for an additional 1 h at -10 °C. The

resulting mixture was poured into dichloromethane (100 mL) and washed with saturated aqueous NH_4Cl solution (50 mL). The aqueous layer was back-extracted with dichloromethane (2 × 50 mL), and the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The light yellow oil was purified by silica gel column chromatography (hexanes/EtOAc, 20/1) to afford the *β*-nitro alkene. The obtained spectroscopic data were in accordance with those previously published.[47]

5.3.3. **General procedure for the synthesis of *β*-amino nitroolefins**[49]

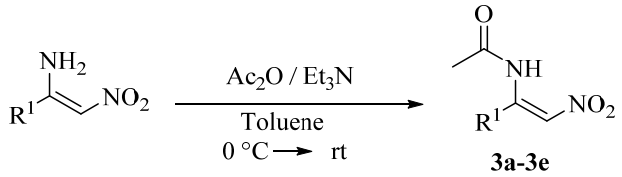


R^1 = Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-FC_6H_4, 2-Naphthyl, n-Pent, i-Bu, c-Hex, i-Pr, 2-furyl, 4-$CF_3C_6H_4$, 4-$NO_2C_6H_4$, 4-MeC_6H_4, 3-MeC_6H_4, 2-MeC_6H_4

R^2= H, Me

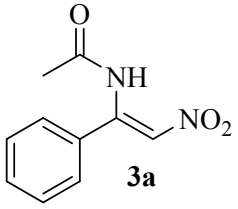
Triethylamine (0.7 mL, 5.0 mmol) was added to a solution of methoxylamine-HCl (0.42 g, 5.0 mmol) in dimethylformamide (8 mL) at 0 °C. *β*-Nitroalkene (5.0 mmol) was then added and the resulting suspension was stirred at 0°C for 15 min and at rt for 5 min. The precipitate was removed by filtration and washed with a small amount of DMF. The combined filtrate was transferred into an addition funnel and was added dropwise to a potassium *tert*-butoxide (1.12 g, 10 mmol) solution in DMF (12 mL) at 0 °C. The cooling bath was then removed and the reaction mixture was stirred for 30 min at rt. The reaction was quenched with saturated aq. NH_4Cl (30 mL). The solvents were distilled *in vacuo* and the residue was dissolved in CH_2Cl_2. The obtained organic phase was washed with water and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (CH_2Cl_2/ethyl acetate 6:1) to afford the desired *β*-amino nitroolefin. The obtained spectroscopic data were in accordance with those previously published.[49]

5.3.4. **General procedure for the synthesis of *β*-acylamino nitroolefins**[50]



A stirred solution of *β*-amino nitrolefin (3.0 mmol) in toluene (10 mL) was cooled at 0 °C and triethylamine (1.7 ml, 12.0 mmol, 4.0 equiv) followed by Ac_2O (0.85 mL, 9.0 mmol, 3.0 equiv) were added. The cooling bath was then removed and the solution was stirred at 45 °C overnight. The mixture was then concentrated under vacuum and the residue was purified by chromatography on silica gel (petroleum ether/ethyl acetate, 80:20 to 50:50 or CH_2Cl_2/ethyl acetate 90:10) to afford the desired *β*-acylamino nitroolefin as a solid. The obtained spectroscopic data were in accord with those previously published.[50]

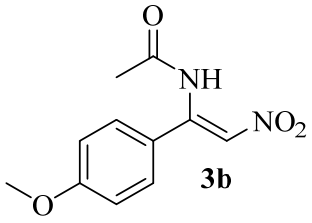
(*Z*)-*N*-(2-nitro-1-phenylvinyl)acetamide (3a)



3a

Light yellow solid; Yield: 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.82 (s, 1H), 7.54-7.38 (m, 5H), 6.70 (s, 1H), 2.25 (s, 3H).

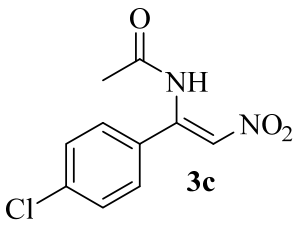
(*Z*)-*N*-(1-(4-methoxyphenyl)-2-nitrovinyl)acetamide (3b)



3b

Light yellow solid; Yield: 38%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.79 (s, 1H), 7.36-7.34 (m, 2H), 6.95-6.92 (m, 2H), 6.73 (s, 1H), 3.85 (s, 3H), 2.26 (s, 3H).

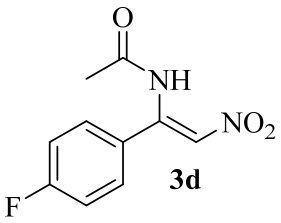
(*Z*)-*N*-(1-(4-chlorophenyl)-2-nitrovinyl)acetamide (3c)



3c

Light yellow solid; Yield: 60%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.79 (s, 1H), 7.42-7.39 (m, 2H), 7.34-7.31 (m, 2H), 6.67 (s, 1H), 2.27 (s, 3H).

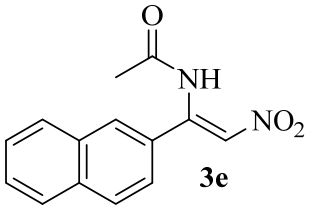
(*Z*)-*N*-(1-(4-fluorophenyl)-2-nitrovinyl)acetamide (3d)



3d

Light yellow solid; Yield: 48%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.80 (s, 1H), 7.40-7.37 (m, 2H), 7.14-7.10 (m, 2H), 6.67 (s, 1H), 2.26 (s, 3H).

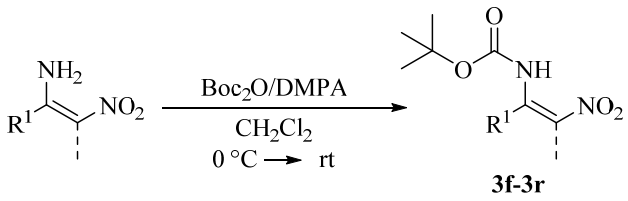
(*Z*)-*N*-(1-(naphthalen-2-yl)-2-nitrovinyl)acetamide (3e)



3e

Light yellow solid; Yield: 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.90 (s, 1H), 7.89-7.85 (m, 4H), 7.59-7.52 (m, 2H), 7.42 (dd, J = 8.5, 1.8 Hz, 1H), 6.82 (s, 1H), 2.28 (s, 3H).

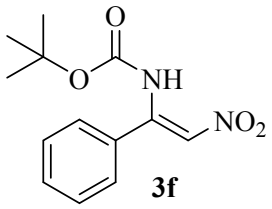
5.3.5. **General procedure for the synthesis of *β-t*-butyloxycarbonylamino nitroolefins**



3f-3r

A stirred solution of *β*-amino nitroolefin (3.0 mmol) in CH_2Cl_2 (5 mL) was cooled at 0 °C and di-*t*-butyl dicarbonate (0.78 g, 3.6 mmol, 1.2 equiv) followed by 4-dimethylamino pyridine (DMAP) (18 mg, 0.15 mmol, 0.05 equiv) were added. The cooling bath was then removed and the solution was stirred at rt for 15 min. The reaction was then quenched with water and extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered concentrated *in vacuo* and the residue was purified by chromatography on silica gel (CH_2Cl_2/petroleum ether 3:1) to afford the desired *β-t*-butyloxycarbonylamino nitroolefin.

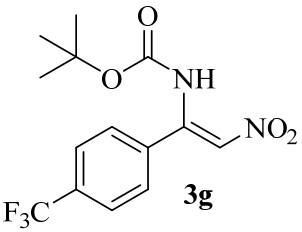
***tert*-Butyl (*Z*)-(2-nitro-1-phenylvinyl)carbamate (3f)**



3f

Yield: 85%; pale yellow solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.29 (s, 1H), 7.54-7.37 (m, 5H), 6.63 (s, 1H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.7, 150.0, 132.0, 130.8, 128.3, 127.6, 119.4, 83.1, 27.7; ESI MS(-) m/z: 263 (M^+-1); ESI MS(+) m/z: 287 (M^++Na).

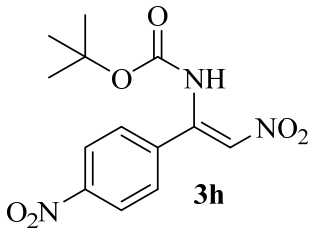
***tert*-butyl (*Z*)-(2-nitro-1-(4-(trifluoromethyl)phenyl)vinyl)carbamate (3g)**



3g

Yield: 80%; pale yellow solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.29 (s, 1H), 7.70 (br d, J = 8.1 Hz, 2H), 7.53 (br d, J = 8.1 Hz, 2H), 6.59 (s, 1H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.0, 148.9, 135.7, 132.6 (q, J = 32.9 Hz), 128.1, 125.5 (q, J = 3.8 Hz), 123.4 (q, J = 273 Hz), 119.95, 83.8, 27.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -62.95 (s, 3F); ESI MS(+) m/z: 355 (M^++Na).

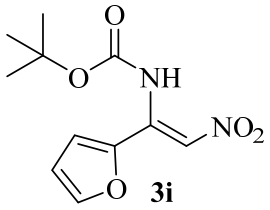
***tert*-butyl (*Z*)-(2-nitro-1-(4-nitrophenyl)vinyl)carbamate (3h)**



3h

Yield: 75%; pale yellow solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.27 (s, 1H), 8.28 (br d, J = 8.9 Hz, 2H), 7.59 (br d, J = 8.9 Hz, 2H), 6.60 (s, 1H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.0, 149.0, 147.9, 138.4, 128.75, 123.6, 120.0, 84.0, 27.8; ESI MS(+) m/z: 332 (M^++Na)

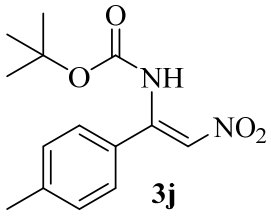
***tert*-butyl (*Z*)-(1-(furan-2-yl)-2-nitrovinyl)carbamate (3i)**



3i

Yield: 80%; pale yellow solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.98 (s, 1H), 7.60 (dd, J_1 = 1.8, J_2 = 0.8 Hz, 1H), 7.03 (s, 1H), 6.96 (dd, J_1 = 3.5, J_2 = 0.8 Hz, 1H), 6.56 (dd, J_1 = 3.5, J_2 = 1.8 Hz, 1H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.2, 145.9, 144.2, 138.8, 118.4, 116.7, 112.4, 83.2, 27.8; ESI MS(+) m/z: 277 (M^++Na).

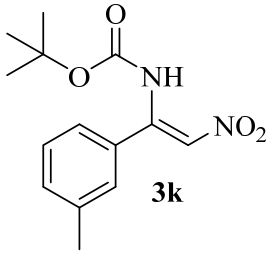
***tert*-butyl (*Z*)-(2-nitro-1-(*p*-tolyl)vinyl)carbamate (3j)**



3j

Yield: 84%; pale yellow solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.30 (s, 1H), 7.30 (br d, J = 8.4 Hz, 2H), 7.24 (br d, J = 8.4 Hz, 2H), 6.64 (s, 1H), 2.41 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.0, 150.2, 141.5, 129.2, 129.0, 127.7, 119.3, 83.1, 27.8, 21.5; ESI MS(+) m/z: 301 (M^++Na).

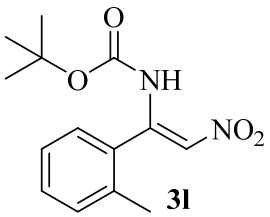
***tert*-butyl (*Z*)-(2-nitro-1-(*m*-tolyl)vinyl)carbamate (3k)**



3k

Yield: 72%; pale yellow solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.26 (s, 1H), 7.34-7.30 (m, 2H), 7.23-7.18 (m, 2H), 6.63 (s, 1H), 2.39 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.9, 150.1, 138.2, 132.0, 131.7, 128.3, 128.1, 124.8, 119.4, 83.1, 27.7, 21.3; ESI MS(+) m/z: 301 (M^++Na).

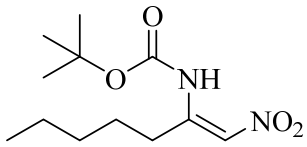
***tert*-butyl (*Z*)-(2-nitro-1-(*o*-tolyl)vinyl)carbamate (3l)**



3l

Yield: 70%; pale yellow solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.59 (s, 1H), 7.37 (td, J_1 = 7.4, J_2 = 1.5 Hz, 1H), 7.29-7.15 (m, 3H), 6.47 (s, 1H), 2.30 (s, 3H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.6, 149.5, 135.8, 131.6, 130.0, 127.65, 125.8, 118.55, 83.1, 27.6, 19.2; ESI MS(+) m/z: 301 (M^++Na).

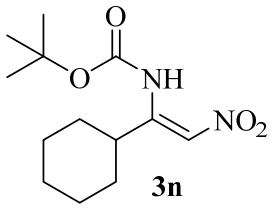
***tert*-butyl (*Z*)-(1-nitrohept-1-en-2-yl)carbamate (3m)**



3m

Yield: 85%; pale yellow solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.69 (s, 1H), 6.53 (s, 1H), 2.74-2.66 (m, 2H), 1.64-1.53 (m, 2H), 1.51 (s, 9H), 1.39-1.31 (m, 4H), 0.93-0.86 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.2, 150.1, 116.8, 82.95, 31.3, 31.2, 28.1, 27.9, 22.2, 13.8; ESI MS(+) m/z: 281 (M^++Na).

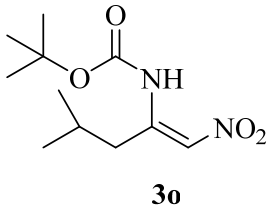
***tert*-butyl (*Z*)-(1-cyclohexyl-2-nitrovinyl)carbamate (3n)**



3n

Yield: 82%; pale yellow solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.84 (s, 1H), 6.62 (s, 1H), 3.62 (tt, J_1 = 11.6, J_2 = 2.8 Hz, 1H), 1.99-1.89 (m, 2H), 1.89-1.70 (m, 3H), 1.51 (s, 9H), 1.46-1.3 (m, 2H), 1.29-1.09 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.0, 150.2, 115.8, 82.8, 37.6, 32.0, 28.0, 26.2, 25.85; ESI MS(+) m/z: 253 (M^++Na).

***tert*-butyl (*Z*)-(4-methyl-1-nitropent-1-en-2-yl)carbamate (3o)**

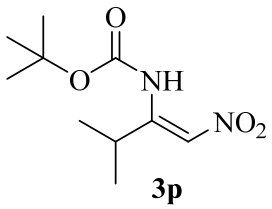


3o

Yield: 80%; pale yellow solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.67 (s, 1H), 6.49 (s, 1H), 2.56 (d, J = 7.0 Hz, 2H), 2.06-1.92 (m, 1H), 1.51 (s, 9H), 0.98 (d, J = 6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.8, 150.2, 117.6, 82.9,

39.85, 27.9, 27.7, 22.2; ESI MS(+) m/z: 267 (M^++Na).

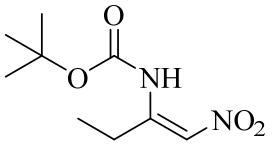
***tert*-butyl (*Z*)-(3-methyl-1-nitrobut-1-en-2-yl)carbamate (3p)**



3p

Yield: 89%; pale yellow solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.83 (s, 1H), 6.64 (s, 1H), 4.04-3.89 (m, 1H), 1.51 (s, 9H), 1.19 (d, *J* = 9.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.1, 150.2, 115.5, 82.9, 28.0, 27.8, 21.2; ESI MS(+) m/z: 253 (M^++Na).

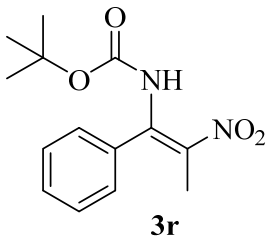
***tert*-butyl (*Z*)-(1-nitrobut-1-en-2-yl)carbamate (3q)**



3q

Yield: 50%; pale yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.68 (s, 1H), 6.54 (s, 1H), 2.77 (q, *J* = 7.4 Hz, 2H), 1.50 (s, 9H), 1.20 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.2, 150.1, 116.4, 82.95, 28.0, 24.75, 12.6; ESI MS(+) m/z: 239 (M^++Na).

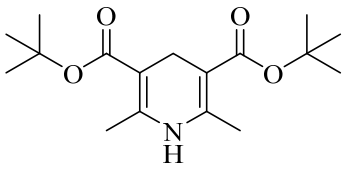
***tert*-butyl (*Z*)-(2-nitro-1-phenylprop-1-en-1-yl)carbamate (3r)**



3r

Yield: 68%; pale yellow solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.79 (s, 1H), 7.60-7.42 (m, 3H), 7.30-7.25 (m, 2H), 1.93 (s, 3H), 1.32 (s, 9H); ESI MS(+) m/z: 301 (M^++Na).

5.4. Procedure for the Synthesis of Hantzsch ester 5b[51]

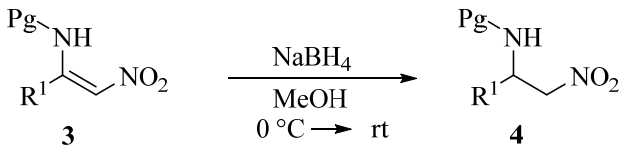


5b

A solution of paraformaldehyde (0.75 g, 25 mmol), *tert*-butyl acetoacetate (8.25 mL, 50 mmol), aqueous NH_4OH (15 mL of a 5 M solution, 75 mmol) in EtOH (20 mL) was heated at reflux (oil bath at 85°C) for 2 h. The mixture was then cooled to rt, poured into ice-water (75 mL) and extracted with Et_2O (100 mL). The ether phase was washed successively with 10% aqueous solution of NaOH (50 mL), water (50 mL), 5% aqueous solution of HCl (50 mL) and water (50 mL). The ether solution was dried over $MgSO_4$ and filtered. The solvent was removed *in vacuum* to afford a yellow solid. The crude product was crystallized with MeOH (about 6-8 mL). To avoid oxidation of the dihydropyridine to the corresponding pyridine derivative, the solubilization of the crude product with MeOH must be quick and the recrystallization must be carry out under nitrogen atmosphere for not longer than 2 h. The title compound **5b** was obtained as a pale yellow solid in a 32% yield. The reaction can be performed using a double amount of reagents using about 15 mL of MeOH for the crystallization affording **5b** in 30% yield

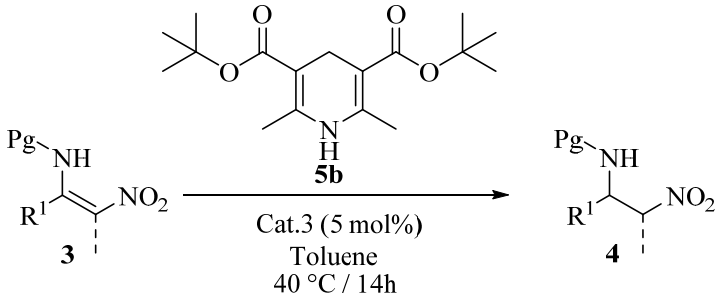
^1H NMR ($CDCl_3$, 400 MHz): δ = 4.96 (br s, 1H), 3.18 (s, 2H), 2.15 (s, 6H), 1.48 (s, 18H).

5.5. General procedure for the synthesis of racemic *β*-amino nitroalkanes 4



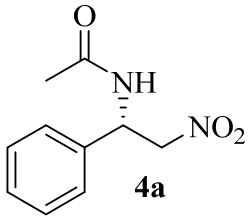
A stirred solution of **3** (0.1 mmol) in MeOH (0.5 mL, 0.2M) was cooled at 0 °C and $NaBH_4$ (0.2 mmol, 8 mg, 2 equiv) was added in one portion. The cooling bath was then removed and the solution was stirred at rt for 15 min. The reaction was then quenched with saturated aq. NH_4Cl (1 mL) and extracted with CH_2Cl_2 (2 x 3 ml). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The obtained product was purified by chromatography on silica gel (CH_2Cl_2/petroleum ether 3:1) if necessary or directly injected in CSP HPLC.

5.6. General Procedure for the Asymmetric Transfer Hydrogenation



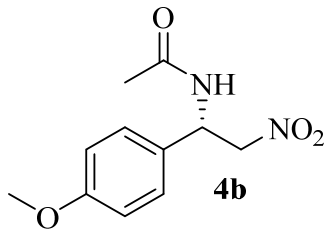
In a screw cap round bottom vial, to a stirred solution of **3** (0.15 mmol) in toluene (510 μL, 0.3 M), catalyst **3** (3.9 mg, 0.0075 mmol, 0.05 equiv) and Hantzsch ester **5b** (56 mg, 0.18 mmol, 1.2 equiv) were added. The vial was saturated with nitrogen and closed with the cap. The reaction mixture was stirred for 14 h at 40 °C (Pg = Ac) or for 18 h at 40 °C (Pg = Boc, R_1 = Aromatic) or for 24 h at 60 °C (Pg = Boc, R_1 = Aliphatic). The resulting mixture was purified by column chromatography to afford product **4**.

(*S*)-*N*-(2-nitro-1-phenylethyl)acetamide (4a)



The title compound **4a** was prepared according to the general procedure and purified by silica gel chromatography (eluent ethyl acetate/petroleum ether 4:1). White solid; Yield 97%. The enantiomeric excess was determined by CSP HPLC analysis using a Daicel Chiralcel OJH column; *n*-hexane/2-propanol 9:1; 0.75 mL/min; λ = 254 nm; t_R (major) = 35.3 min; t_R (minor) = 42.8 min; *ee* >99%. $[\alpha]_D^{25}$ +73 (c 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.64 (d, J = 8.7 Hz, 1H), 7.40-7.33 (m, 3H), 7.32-7.26 (m, 2H), 5.62-5.54 (m, 1H), 4.93 (dd, J_1 = 5.3, J_2 = 13.1 Hz, 1H), 4.76 (dd, J_1 = 9.6, J_2 = 13.1 Hz, 1H), 1.85 (s, 3H); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42-7.28 (m, 5H), 6.33 (brs, 1H), 5.72-5.64 (m, 1H), 4.92 (dd, J_1 = 13.0, J_2 = 6.4 Hz, 1H), 4.74 (dd, J_1 = 13.0, J_2 = 5.6 Hz, 1H), 2.05 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 169.4, 138.6, 129.1, 128.4, 127.6, 78.9, 51.1, 23.0; ESI MS(+) m/z: 231 (M^++Na).

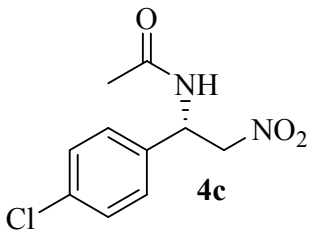
(*S*)-*N*-(1-(4-methoxyphenyl)-2-nitroethyl)acetamide (4b)



4b

The title compound **4b** was prepared according to the general procedure and purified by silica gel chromatography (eluent ethyl acetate/petroleum ether 4:1). White solid; Yield 91%. The enantiomeric excess was determined by CSP HPLC analysis using a Daicel Chiralcel OJH column; *n*-hexane/2-propanol 9:1; 0.75 mL/min, λ = 254 nm; t_R (major) = 68.3 min; t_R (minor) = 82.3 min; *ee* >99%. $[\alpha]_D^{25}$ +80 (c 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.54 (d, *J* = 8.7 Hz, 1H), 7.29 (br d, *J* = 8.7 Hz, 2H), 6.90 (br d, *J* = 8.7 Hz, 2H), 5.49 (m, 1H), 4.86 (dd, J_1 = 5.6, J_2 = 12.9 Hz, 1H), 4.75 (dd, J_1 = 9.3, J_2 = 12.9 Hz, 1H), 3.71 (s, 3H), 1.82 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 169.2, 159.3, 130.5, 128.7, 114.5, 79.0, 55.6, 50.6, 23.0; ESI MS(+) m/z: 261 (M^++Na).

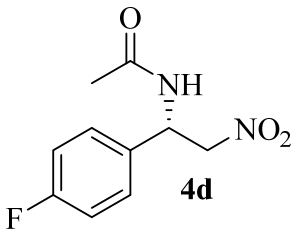
(*S*)-*N*-(1-(4-chlorophenyl)-2-nitroethyl)acetamide (4c)



4c

The title compound **4c** was prepared according to the general procedure and purified by silica gel chromatography (eluent ethyl acetate/petroleum ether 2.5:1). White solid; Yield 90%. The enantiomeric excess was determined by CSP HPLC analysis using a Daicel Chiralpak ADH column; *n*-hexane/2-propanol 8:2; 0.75 mL/min, λ = 254 nm; t_R (major) = 5.8 min; t_R (minor) = 9.1 min; *ee* 97%. $[\alpha]_D^{25}$ +70 (c 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, Acetone-d_6) δ: 7.91 (br d, *J* = 7.2 Hz, 1H), 7.50 (br d, *J* = 8.5 Hz, 2H), 7.41 (br d, *J* = 8.5 Hz, 2H), 5.76-5.72 (br dd, J_1 = J_2 = 7.5 Hz, 1H), 4.99-4.90 (m, 2H), 1.93 (s, 3H); ^{13}C NMR (100 MHz, Acetone-d_6) δ: 169.0, 137.2, 133.4, 128.8, 128.7, 78.0, 50.7, 21.9; ESI MS(+) m/z: 265 (M^++Na).

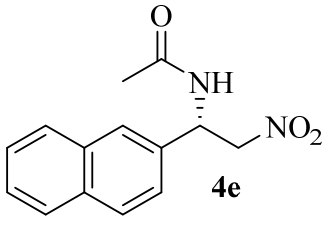
(*S*)-*N*-(1-(4-fluorophenyl)-2-nitroethyl)acetamide (4d)



4d

The title compound **4d** was prepared according to the general procedure and purified by silica gel chromatography (eluent ethyl acetate/petroleum ether 2.5:1). White solid; Yield 94%. The enantiomeric excess was determined by CSP HPLC analysis using a Daicel Chiralpak ADH column; *n*-hexane/2-propanol 9:1; 0.75 mL/min, λ = 254 nm; t_R (major) = 10.7 min; t_R (minor) = 18.6 min; *ee* 97%. $[\alpha]_D^{25}$ +54.5 (c 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33-7.27 (m, 2H), 7.11-7.02 (m, 2H), 6.45 (br d, J = 7.3 Hz, 1H), 5.64 (br dd, J_1 = 13.5, J_2 = 6.2 Hz, 1H), 4.89 (dd, J_1 = 13.0, J_2 = 6.6 Hz, 1H), 4.70 (dd, J_1 = 13.0, J_2 = 5.5 Hz, 1H), 2.05 (s, 3H); ^{13}C NMR (101 MHz, Acetone-d_6) δ: 168.9, 167.4 (d, J = 244 Hz), 134.3 (d, J = 3.7 Hz), 129.1 (d, J= 8.1 Hz), 115.4 (d, J = 21 Hz), 78.2, 50.6, 21.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -115.77 (br s, 1F); ESI MS(+) m/z: 249 (M^++Na)

(*S*)-*N*-(1-(naphthalen-2-yl)-2-nitroethyl)acetamide (4e)

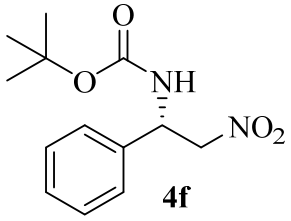


4e

The title compound **4e** was prepared according to the general procedure and purified by silica gel chromatography (eluent ethyl acetate/petroleum ether 2.5:1). White solid; Yield 91%. The enantiomeric excess was determined by CSP HPLC analysis using a Daicel Chiralpak ADH column; *n*-hexane/2-propanol 9:1; 0.75 mL/min, λ = 254 nm; t_R (major) = 14.25 min; t_R (minor) = 24.8 min; *ee* 99%. $[\alpha]_D^{25}$ +112 (c 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, Acetone-d_6) δ: 8.01 (br d, J = 8.3 Hz, 1H), 7.98 (br s, 1H), 7.92 (br d, J = 8.6 Hz, 1H), 7.91-7.88 (m, 2H), 7.62 (br d, J_1 = 8.6, J_2 = 1.9 Hz, 1H), 7.55-7.50 (m, 2H), 5.95 (br d, J_1 = 8.0, J_2 = 7.3 Hz, 1H), 5.05 (d, J = 7.2 Hz,

2H), 1.96 (s, 3H); ^{13}C NMR (100 MHz, Acetone-d_6) δ: 169.1, 135.6, 133.3, 133.1, 128.6, 127.9, 127.6, 126.4, 126.3, 125.95, 124.85, 78.3, 51.5, 22.0; ESI MS(+) m/z: 281 (M^++Na).

***tert*-Butyl (*S*)-(2-nitro-1-phenylethyl)carbamate (4f)**



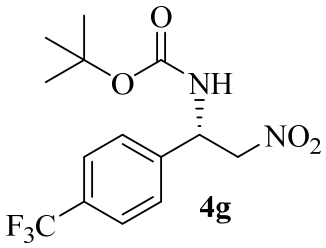
4f

The title compound **4f** was prepared according to the general procedure and purified by silica gel chromatography (eluent CH_2Cl_2/petroleum ether 6:1). White solid; Yield 90%. The enantiomeric excess was determined by CSP HPLC analysis using a Daicel Chiralcel OJH column; *n*-hexane/2-propanol 9:1; 0.75 mL/min, λ = 254 nm; t_R (major) = 22.6 min; t_R (minor) = 25.7 min; *ee* >99%.

The same procedure was repeated using 2.0 mmol (532 mg) of **1f** giving product **4f** in 86% yield and >99%. *ee*.

$[\alpha]_D^{25}$ +29 (c 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42-7.28 (m, 5H), 5.44-5.32 (m, 1H), 5.28 (br s, 1H), 4.91-4.79 (m, 1H), 4.7 (dd, J_1 = 12.6, J_2 = 5.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.8, 136.9, 129.2, 128.7, 126.4, 80.7, 78.9, 52.9, 28.3; MS(+) m/z: 289 (M^++Na).

***tert*-butyl (*S*)-(2-nitro-1-(4-(trifluoromethyl)phenyl)ethyl)carbamate (4g)**

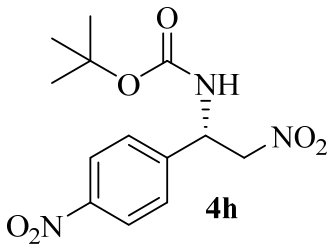


4g

The title compound **4g** was prepared according to the general procedure and purified by silica gel chromatography (eluent CH_2Cl_2/petroleum ether 6:1). White solid; Yield 86%. The enantiomeric excess was determined by CSP HPLC analysis using a Daicel Chiralpak ADH column; *n*-hexane/2-propanol 9:1; 0.75 mL/min, λ = 254 nm; t_R (major) = 13.8 min; t_R (minor) = 21.1 min; *ee* >99%. $[\alpha]_D^{25}$ +18.5 (c 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.65 (br d, *J* = 8.4 Hz, 2H), 7.45 (br d, *J* = 8.4 Hz, 2H), 5.52 (br s, 1H), 5.44 (br s, 1H), 4.86 (br

s, 1H), 4.79-4.69 (br m, 1H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.7, 141.0, 130.0 (q, J = 33 Hz), 126.8, 126.1 (q, J = 3.7 Hz), 123.7 (q, J = 273 Hz), 81.1, 78.5, 52.3, 28.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -62.8; ESI MS(+) m/z: 357 (M^++Na).

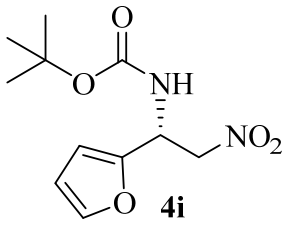
***tert*-butyl (*S*)-(2-nitro-1-(4-nitrophenyl)ethyl)carbamate (4h)**



4h

The title compound **4h** was prepared according to the general procedure and purified by silica gel chromatography (eluent CH_2Cl_2/petroleum ether 5:1). White solid; Yield 93%. The enantiomeric excess was determined by CSP HPLC analysis using a Daicel Chiralpak ADH column; *n*-hexane/2-propanol 9:1; 1.0 mL/min; λ = 254 nm; t_R (major) = 26.6 min; t_R (minor) = 57.6 min; *ee* 96%. $[\alpha]_D^{25}$ +22.5 (c 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.24 (br d, J = 8.9 Hz, 2H), 7.53 (br d, J = 8.9 Hz, 2H), 5.64 (br s, 1H), 5.49 (br s, 1H), 4.89 (br s, 1H), 4.83-4.72 (br m, 1H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.6, 147.9, 144.2, 127.4, 124.35, 81.3, 78.3, 52.1, 28.3; ESI MS(+) m/z: 334 (M^++Na).

***tert*-butyl (*S*)-(1-(furan-2-yl)-2-nitroethyl)carbamate (4i)**

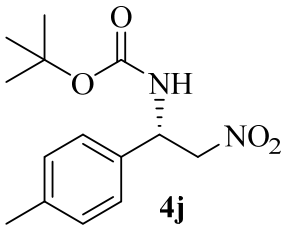


4i

The title compound **4i** was prepared according to the general procedure and purified by silica gel chromatography (eluent petroleum ether/ethyl acetate 3.5:1). White solid; Yield 71%. The enantiomeric excess was determined by CSP HPLC analysis using a Daicel Chiralcel OJH column; *n*-hexane/2-propanol 9:1; 0.75 mL/min, λ = 254 nm; t_R (major) = 20.8 min; t_R (minor) = 26.2 min; *ee* >99%. $[\alpha]_D^{25}$ +36.4 (c 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37 (dd, J_1 = 1.9, J_2 =0.8 Hz, 1H), 6.34 (dd, J_1 = 3.3, J_2 =1.9 Hz, 1H), 6.31 (d t, J_1 = 3.3, J_2

=0.8 Hz, 1H), 5.51-5.41 (m, 1H), 5.30 (br s, 1H), 4.90-4.80 (m, 1H), 4.72 (dd, J_1 = 13.0, J_2 =5.7 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.6, 149.4, 143.0, 110.8, 107.8, 80.9, 76.55, 47.2, 28.3; ESI MS(+) m/z: 279 (M^++Na).

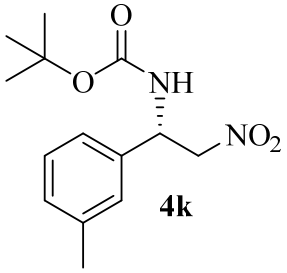
***tert*-butyl (*Z*)-(2-nitro-1-(*p*-tolyl)vinyl)carbamate (4j)**



4j

The title compound **4j** was prepared according to the general procedure and purified by silica gel chromatography (eluent petroleum ether/ethyl acetate 7:1). White solid; Yield 86%. The enantiomeric excess was determined by CSP HPLC analysis using a Daicel Chiralcel OJH column; *n*-hexane/2-propanol 9:1; 0.75 mL/min, λ = 254 nm; t_R (major) = 17.2 min; t_R (minor) = 23.4 min; *ee* 97%. $[\alpha]_D^{25}$ +35.7 (c 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.21-7.15 (m, 4H), 7.38-7.25 (m, 2H), 4.82 (br s, 1H), 4.67 (br dd, J_1 = 12.3, J_2 =5.2 Hz, 1H), 2.33 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.75, 138.5, 133.9, 129.9, 126.1, 80.6, 78.9, 52.6, 28.2, 21.1; ESI MS(+) m/z: 303 (M^++Na).

***tert*-butyl (*S*)-(2-nitro-1-(*m*-tolyl)ethyl)carbamate (4k)**

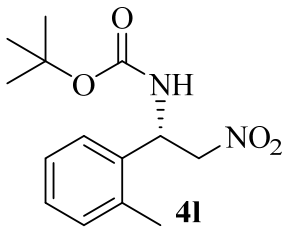


4k

The title compound **4k** was prepared according to the general procedure and purified by silica gel chromatography (eluent petroleum ether/ethyl acetate 7:1). White solid; Yield 75%. The enantiomeric excess was determined by CSP HPLC analysis using a Daicel Chiralpak AS column; *n*-hexane/2-propanol 9:1; 1.0 mL/min, λ = 254 nm; t_R (major) = 10.6 min; t_R (minor) = 15.7 min; *ee* >99%. $[\alpha]_D^{25}$ +31.6 (c 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29-7.23 (m, 1H), 7.16-7.07 (m, 3H), 5.38-5.24 (m, 2H), 4.82 (br s, 1H), 4.68 ((br dd, J_1 = 12.4, J_2 =5.5 Hz, 1H), 2.35 (s, 3H), 1.44 (s, 9H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ: 154.7, 138.95, 136.8, 129.4, 129.0, 127.1, 123.25, 80.6, 78.9, 52.8, 28.2, 21.4; ESI MS(+) m/z: 303 (M^++Na).

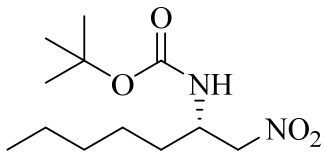
***tert*-butyl (*S*)-(2-nitro-1-(*o*-tolyl)ethyl)carbamate (4l)**



4l

The title compound **4l** was prepared according to the general procedure and purified by silica gel chromatography (eluent petroleum ether/ethyl acetate 7:1). White solid; Yield 40% (conversion 50%). The enantiomeric excess was determined by CSP HPLC analysis using a Daicel Chiralcel OJH column; *n*-hexane/2-propanol 9:1; 0.75 mL/min, λ = 254 nm; t_R (major) = 28.3 min; t_R (minor) = 19.0 min; *ee* 98% or Daicel Chiralcel OD column; *n*-hexane/2-propanol 9:1; 1.0 mL/min, λ = 254 nm; t_R (major) = 43.8 min; t_R (minor) = 21.5 min. $[\alpha]_D^{25}$ +43.5 (c 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.25-7.19 (m, 4H), 5.65 (br dd, $J_1 = J_2$ = 6.9 Hz, 1H), 5.11 (br d, J = 7.5 Hz, 1H), 4.76 (br s, 1H), 4.71-4.62 (m, 1H), 2.45 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.5, 135.9, 135.2, 131.3, 128.6, 126.8, 124.9, 80.6, 77.9, 49.31, 28.2, 19.1; ESI MS(+) m/z: 303 (M^++Na).

***tert*-butyl (*S*)-(1-nitroheptan-2-yl)carbamate (4m)**

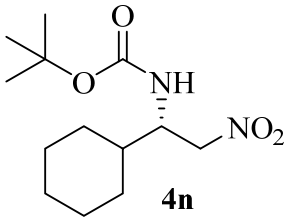


4m

The title compound **4m** was prepared according to the general procedure and purified by silica gel chromatography (eluent petroleum ether/ethyl acetate 7:1). White solid; Yield 91%. The enantiomeric excess was determined by CSP HPLC analysis using a Daicel Chiralpak ADH column; *n*-hexane/2-propanol 95:5; 0.75 mL/min, λ = 254 nm; t_R (major) = 13.4 min; t_R (minor) = 12.5 min; *ee* 98%. $[\alpha]_D^{25}$ -28.6 (c 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.82 (br d, J = 7.5 Hz, 1 H), 4.52 (br

d, J = 4.7 Hz, 2H), 4.15-4.03 (m, 1H), 1.61-1.50 (m, 2H), 1.44 (s, 9H), 1.41-1.23 (m, 6H), 0.88 (br t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.1, 80.1, 78.3, 49.2, 31.7, 31.4, 28.25, 25.5, 22.4, 13.8; MS(+) m/z: 283 (M^++Na).

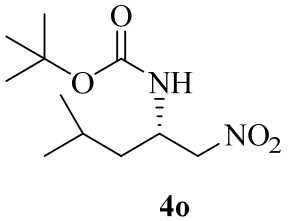
***tert*-butyl (*S*)-(1-cyclohexyl-2-nitroethyl)carbamate (4n)**



4n

The title compound **4n** was prepared according to the general procedure and purified by silica gel chromatography (eluent petroleum ether/ethyl acetate 8:1). White solid; Yield 88%. The enantiomeric excess was determined by CSP HPLC analysis using a Daicel Chiralpak ADH column; *n*-hexane/2-propanol 95:5; 0.75 mL/min, λ = 254 nm; t_R (major) = 19.2 min; t_R (minor) = 14.1 min; *ee* 98%. $[\alpha]_D^{25}$ -15.5 (c 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.87 (br d, J = 9.2 Hz, 1H), 4.62-4.48 (m, 2H), 4.00-3.90 (br s, 1H), 1.85-1.47 (m, 6H), 1.43 (s, 9H), 1.30-0.93 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.3, 80.0, 76.7, 53.9, 39.4, 29.8, 29.0, 28.25, 25.9, 25.7; ESI MS(+) m/z: 295 (M^++Na).

***tert*-butyl (*S*)-(4-methyl-1-nitropentan-2-yl)carbamate 4(o)**

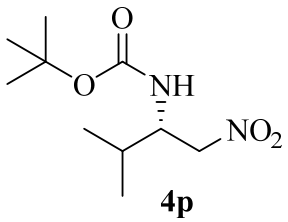


4o

The title compound **4o** was prepared according to the general procedure and purified by silica gel chromatography (eluent CH_2Cl_2/petroleum ether 6:1). White solid; Yield 60%. The enantiomeric excess was determined by CSP HPLC analysis using a Daicel Chiralpak ADH column; *n*-hexane/2-propanol 95:5; 0.75 mL/min; λ = 254 nm. t_R (major) = 15.3 min; t_R (minor) = 12.3 min; *ee* 96%. $[\alpha]_D^{25}$ -40 (c 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.79 (br s, 1H), 4.53 (br d, 2H), 4.26-4.13

(m, 1H), 1.80-1.64 (m, 1H), 1.59-1.30 (m, 2H), 1.46 (s, 9H), 0.96 (d, J = 6.6 Hz, 3H), 0.95 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ:155.0, 80.2, 78.7, 47.4, 40.6, 28.3, 24.8, 22.8, 21.9; ESI MS(+) m/z: 269 (M^++Na).

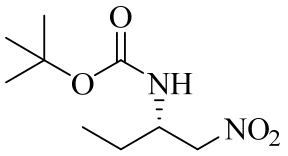
***tert*-butyl (*S*)-(3-methyl-1-nitrobutan-2-yl)carbamate (4p)**



4p

The title compound **4p** was prepared according to the general procedure and purified by silica gel chromatography (eluent petroleum ether/ethyl acetate 6:1). White solid; Yield 91%. The enantiomeric excess was determined by CSP HPLC analysis using a Daicel Chiralpak ADH column; *n*-hexane/2-propanol 95:5; 0.75 mL/min, λ = 254 nm; t_R (major) = 21.7 min; t_R (minor) = 13.6 min; *ee* 93%. $[\alpha]_D^{25}$ -21.5 (c 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.86 (br d, J = 8.2 Hz, 1H), 4.61-4.49 (m, 2H), 4.01-3.91 (br s, 1H), 1.95-1.83 (m, 1H), 1.44 (s, 9H), 1.01 (d, J_1 = 6.8, 3H), 0.99 (d, J_1 = 6.8, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.25, 80.1, 76.96, 54.7, 30.0, 28.3, 19.4, 18.55; ESI MS(+) m/z: 255 (M^++Na).

***tert*-butyl (*S*)-(1-nitrobutan-2-yl)carbamate (4q)**

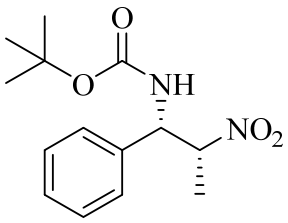


4q

The title compound **4q** was prepared according to the general procedure and purified by silica gel chromatography (eluent CH_2Cl_2/petroleum ether 6:1). White solid; Yield 92%. The enantiomeric excess was determined by CSP HPLC analysis using a Daicel Chiralpak ADH column; *n*-hexane/2-propanol 95:5; 0.75 mL/min, λ = 234 nm; t_R (major) = 16.5 min; t_R (minor) = 14.0 min; *ee* 97%. $[\alpha]_D^{25}$ -21.5 (c 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.81 (br s, 1H), 4.60-4.48 (m, 2H), 4.09-3.96 (m, 1H), 1.68-1.54 (m, 2H), 1.44 (s, 9H), 1.00 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.1,

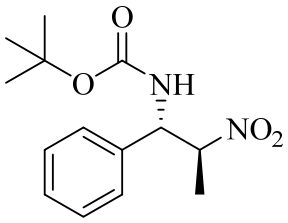
80.1, 78.0, 50.6, 28.2, 25.0, 10.4; ESI MS(+) m/z: 241 (M^++Na).

***tert*-butyl (1*S*,2*R*)-2-nitro-1-phenylpropylcarbamate and tert-butyl (1*S*,2*S*)-2-nitro-1-phenylpropylcarbamate (4r)**



(1S,2R)-**4r** *ee* >99%

+



(1S,2S)-**4r** *ee* = 97%

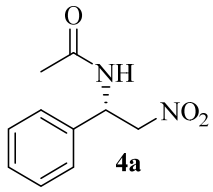
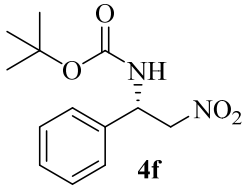
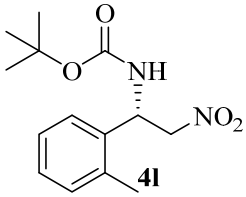
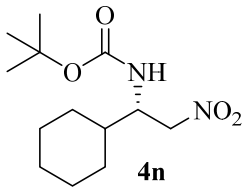
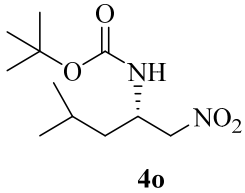
A 2:1 mixture of (1*S*,2*R*)-**4r** and (1*S*,2*S*)-**4r** was obtained following the general procedure and was purified by silica gel chromatography (eluent CH_2Cl_2/petroleum ether 5:1). White solid; Yield 88%. The enantiomeric excess was determined by CSP HPLC analysis using a Daicel Chiralpak ADH column; *n*-hexane/2-propanol 95:5; 1.0 mL/min, λ = 254 nm; (1*S*,2*R*)-**4r**: t_R (major) = 19.9 min; t_R (minor) = 22.8 min; (1*S*,2*S*)-**4r**: t_R (major) = 33.6 min; t_R (minor) = 26.86 min. The relative and the absolute configurations were determined by comparison with literature data. [52]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40-720 (m, $5H_{maj}$+$5H_{min}$), 5.60 (br s, $1H_{min}$), 5.35 (br s, $1H_{maj}$), 5.20 (dd, J_1 = 9.0, J_2 = 5.8 Hz, $1H_{maj}$), 5.11 (brs, $1H_{min}$), 4.93 (br m, $1H_{maj}$+$1H_{min}$), 1.54 (brs, $3H_{min}$), 1.53 (d, J = 6.9 Hz, $3H_{maj}$), 1.43-1.42 (br s, $9H_{maj}$+$9H_{min}$).

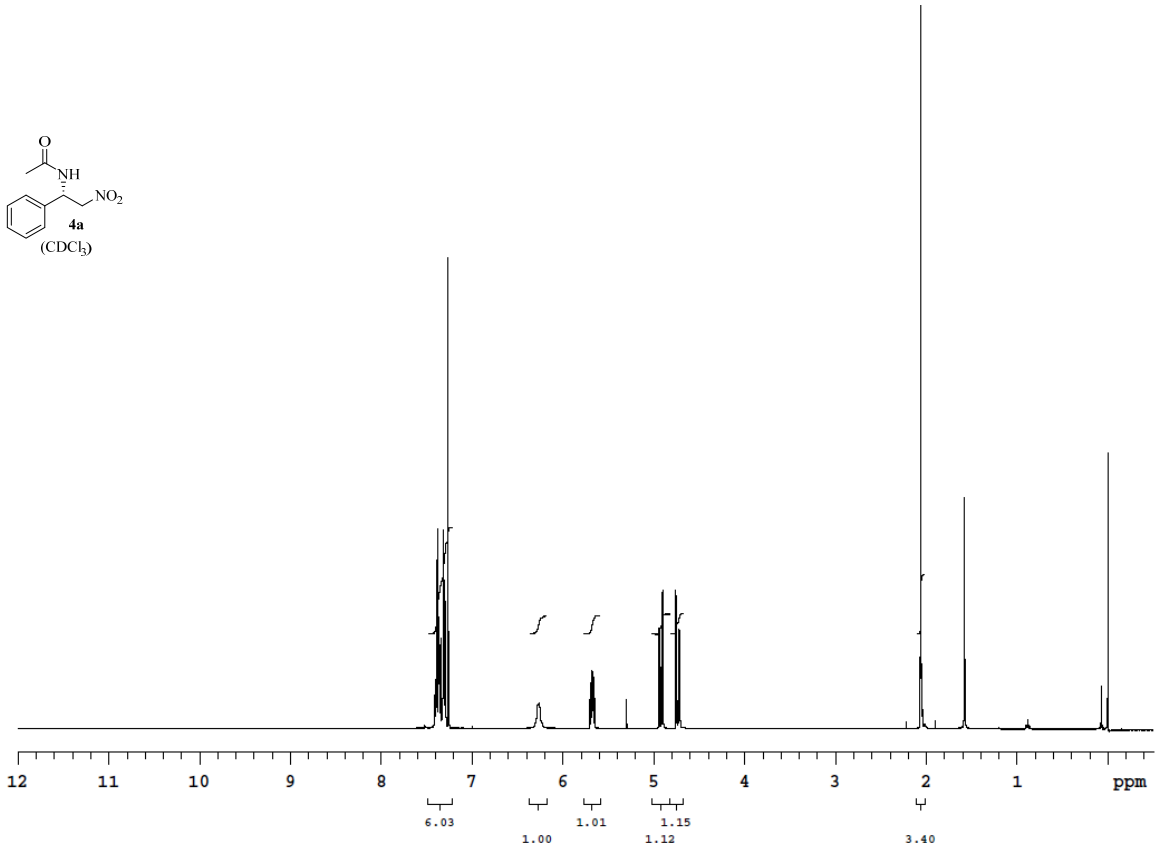
The obtained spectroscopic data were in accordance with those previously published.[52,53,54]

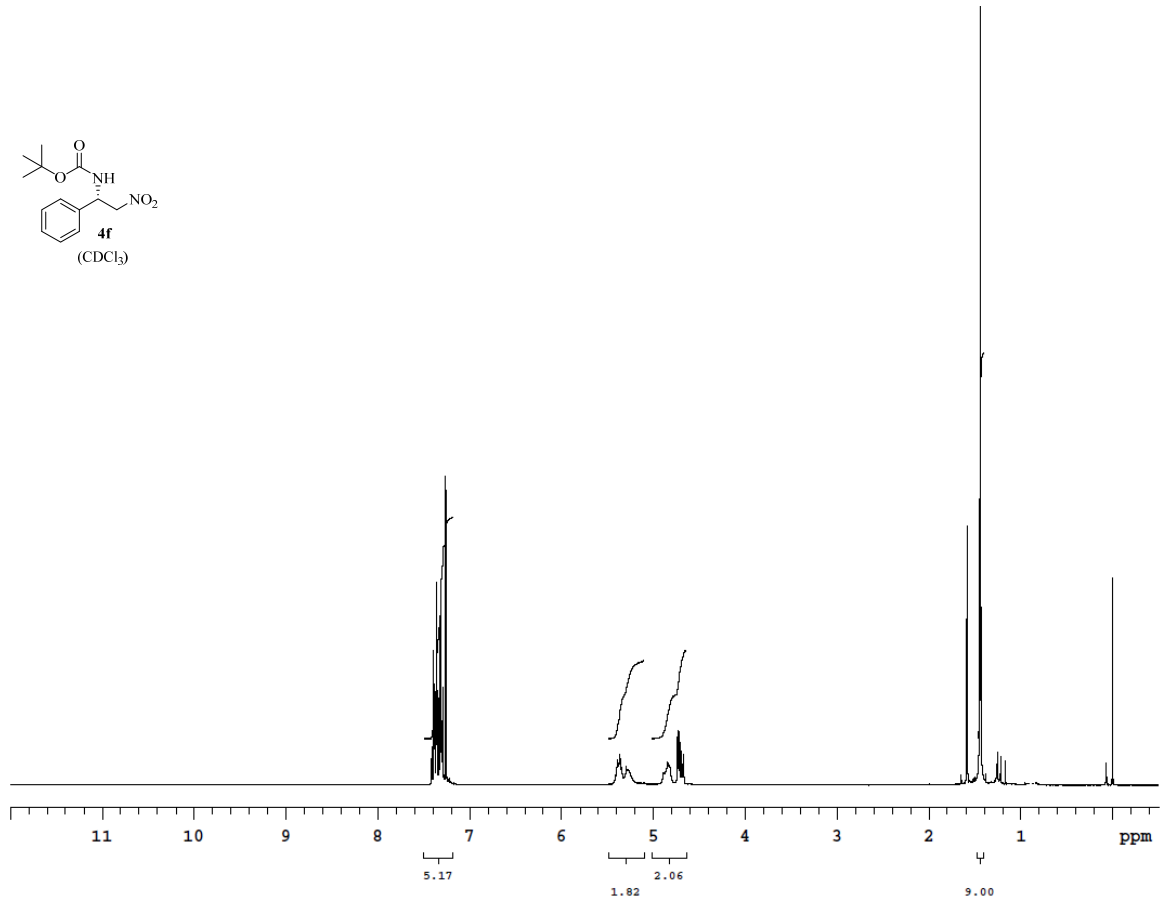
5.7. Determination of the absolute configuration of the *β*-amino nitroalkanes

The absolute configuration of products **4** was determined to be *S* by comparison with literature data (CSP-HPLC retention time and optical rotation $[\alpha]_D$ value) for compound **4a,**[39] **4f**,40[30,40] **4l**,[55] **4n**[30,40] and **4o**[40]**.**

 **4a**	$[\alpha]_D^{25}$ +73 (c 1.0, CH_2Cl_2); Lit $[\alpha]_D^{20}$ = -69.20 (c = 0.5, CH_2Cl_2), 99% *ee* (*R*)
 **4f**	$[\alpha]_D^{25}$ +29 (c 1.0, CH_2Cl_2); Lit $[\alpha]_D^{25}$ = -20.1(c 1.0, $CHCl_3$), 91% *ee* (*R*)
 **4l**	$[\alpha]_D^{25}$ +43.5 (c 1.0, CH_2Cl_2); Lit $[\alpha]_D^{25}$ = - 47.0 (c 0.5, $CHCl_3$); 99% *ee* (*R*)
 **4n**	$[\alpha]_D^{25}$ -15.5 (c 1.0, CH_2Cl_2); Lit $[\alpha]_D^{25}$ = +24 (c 1.0, $CHCl_3$), 98% *ee* (*R*)
 **4o**	$[\alpha]_D^{25}$ -40 (c 1.0, CH_2Cl_2); Lit $[\alpha]_D^{25}$ = +26.4 (c 1.0, $CHCl_3$), 97 % *ee* (*R*)

5.8. ^{1}H-NMR spectra of products 4a and 4f





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