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Scuola di Dottorato in Scienze e Tecnologie Chimiche

Dipartimento di Chimica

PhD Course in Industrial Chemistry - XXXIII Cycle

Telescopic synthesis of functionalized chiral amines and development of a new chemodivergent transformation

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Abstract

The present thesis covers three different topics: the development of a novel chemodivergent transformation involving nitroalkanes (Figure 1a); the stereoselective, metal-free, catalytic synthesis of differently functionalized chiral 1,2-diamines in a two-step, continuous-flow process (Figure 1b); [1] and the telescopic continuous flow enantioselective synthesis of a fluorinated active pharmaceutical ingredient (API) precursor **A**[2] (Figure 1c).

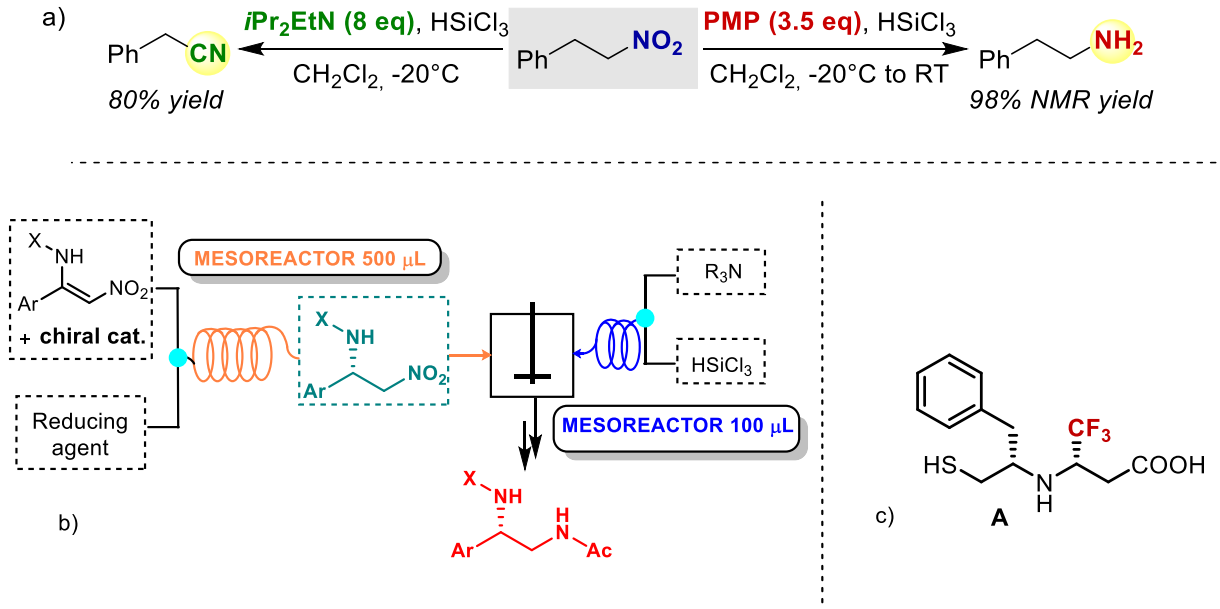


Figure 1

More in detail, a **General introduction** containing literature background regarding the use of trichlorosilane will be provided, since this versatile reagent was used for different purposes in all the three projects presented here. Subsequently, in **Chapter 1** we will focus on transformations of nitroalkanes, and we will present an unprecedented chemodivergent transformation, allowing to selectively obtain amines or nitriles starting from aliphatic nitro derivatives. Furthermore, we will report the application of this new synthetic methodology to chiral, optically active nitroalkanes, demonstrating the utility of the protocol that provides access to classes of compounds that are otherwise not easily accessed by classical methods in organic synthesis.

The following chapter will deal with synthetic applications of continuous flow processes for the telescopic synthesis of chiral amines. In particular, in **Chapter 2.1** a stereoselective, metal-free synthetic strategy for the preparation of trifluoromethylamine mimics of retro-thiorphan **A** (Figure 1) has been studied in batch and under continuous flow conditions, affording the target molecule in good yields and high diastereoselectivity. Crucial step is the catalytic stereoselective reduction of a fluorinated enamine with trichlorosilane as reducing agent in the presence of a chiral Lewis base.

Finally, in **Chapter 2.2**, we will focus on the development of a two-step, continuous-flow process for the stereoselective, metal-free, catalytic synthesis of chiral differently functionalized chiral 1,2-diamines. At first, the enantioselective organocatalytic reduction of aryl-substituted nitroenamines under continuous-flow conditions will be discussed. The chapter will include preliminary screening with a 10 µl microreactor, to establish the best reaction conditions, followed by a scaled-up in a 0.5 ml mesoreactor. Subsequently, the in-

flow nitro reduction will be studied, either by Raney-Ni catalyzed hydrogenation, and by a metal-free methodology based on the use of trichlorosilane. Preliminary attempts to obtain a continuous flow telescopic synthesis, avoiding the isolation of intermediates will be also discussed.

The **Appendix** included at the end of the present work, is related to the pharmaceutical industry, to briefly summarize the work performed during a two months traineeship spent in Flamma Innovation.

Introduction: Trichlorosilane, a versatile reagent for different transformations

Trichlorosilane ($HSiCl_3$) is a bulk chemical, widely used in the Silicon industry,[3] mostly to wash the pipeline to remove moisture, or as starting material for the production of ultrapure silicon. Its synthesis is quite simple and starts from very cheap starting materials such as silicon and HCl (Figure 2).

$$Si + 3\ HCl \xrightarrow{400°C} HSiCl_3 + H_2$$

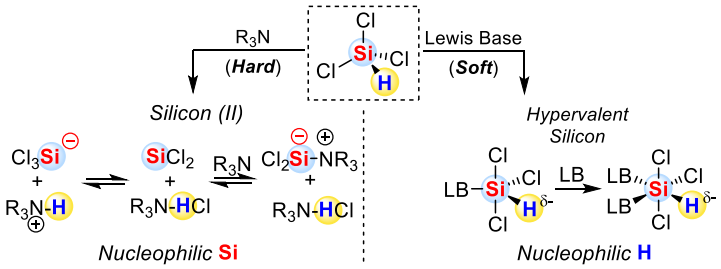
Figure 2

In the Siemens process, high-purity silicon rods are exposed to trichlorosilane at 1150°C, which gas decomposes and deposits additional silicon onto the electrically heated rods, enlarging them according to chemical reactions such as:[4]

$$2\ HSiCl_3 \longrightarrow Si + 2\ HCl + SiCl_4$$

$HSiCl_3$ is sensitive to moisture but can be easily handled adopting standard techniques for moisture sensitive compounds, like working under inert atmosphere and storage under nitrogen. When used in organic reactions, a standard work-up procedure, like quenching with an aqueous basic solution ($NaHCO_3$ or NaOH), produces non-toxic inorganic salts.

Trichlorosilane is a versatile reagent, able to undergo different activation pathways, and perform diverse reactions: it is a Lewis acid (LA), that in the presence of a Brønsted base, is able to form silicon (II) species, that as will be shown, can reduce the nitro group, while in the presence of a Lewis base (LB), is able to form hypervalent silicon species (Scheme 1), and transfer an hydride to reduce C=N or C=O double bonds.



Scheme 1

Both the silicon and the hydrogen atom of $HSiCl_3$ are acidic, but when LBs are involved in $HSiCl_3$ activation, and not strong Brønsted bases, they will preferentially interact with the silicon atom. On the other hand, a

Brønsted base such as an aliphatic tertiary amine will prefer to interact with the hydrogen atom.[5] As result, the H atom in $HSiCl_3$ seems to be a proton rather than a hydride, unless activated by LBs. Proof of this fact can be found in the ^{1}H-NMR chemical shift of $HSiCl_3$, which present a singlet a 6.1 ppm, chemical shift far to be assigned to a hydride.

To explain why $HSiCl_3$ reacts differently with a Brønsted or a LB, the Hard and Soft Bases and Acids principle (HSAB) should be considered. Indeed, while LBs can be categorized as soft compounds, tertiary amines present a harder character, that is why LBs preferentially interact with the soft silicon atom, while tertiary amines prefer to interact with the harder acidic site in the molecule, that is the proton. This behavior can be emphasized by the steric hindrance of the tertiary amine, as the hydrogen is less shielded than the silicon atom.

Stereoselective reduction of imines, mediated by trichlorosilane

As previously stated, the hydride character of $HSiCl_3$ could be rationalized using the "*hypervalent bonding analysis*". When trichlorosilane interacts with a LB, to form a new and more reactive adduct, the electron density of the LB is distributed on the ligand of the $HSiCl_3$ and, at the same time the positive charge on the silicon atom is increased, enhancing its LA character (Figure 3).

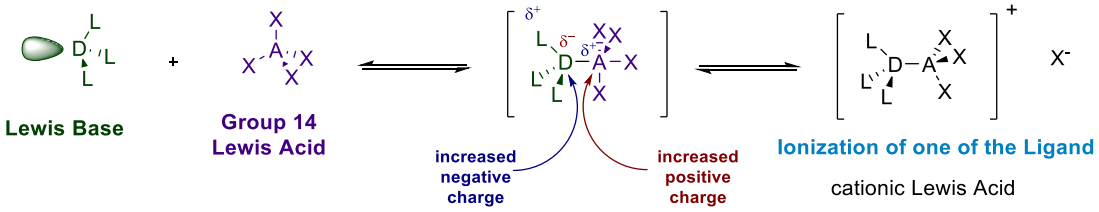


Figure 3

According to the hypervalent bonding analysis, the coordination of two LBs leads the silicon atom to the formation of hypervalent bonds (3-centers 4- electrons). The hybridization of the silicon atom changes from sp^3 to sp; notably the new molecular orbitals show a reduced electron density on the silicon and the increased presence of the electrons on the ligands (Figure 4).[6] The stronger is the LB, the stronger is the negative charge on the ligands, the more the hydrogen atom can act as a hydride and could be used for the reduction of C=N and C=O.

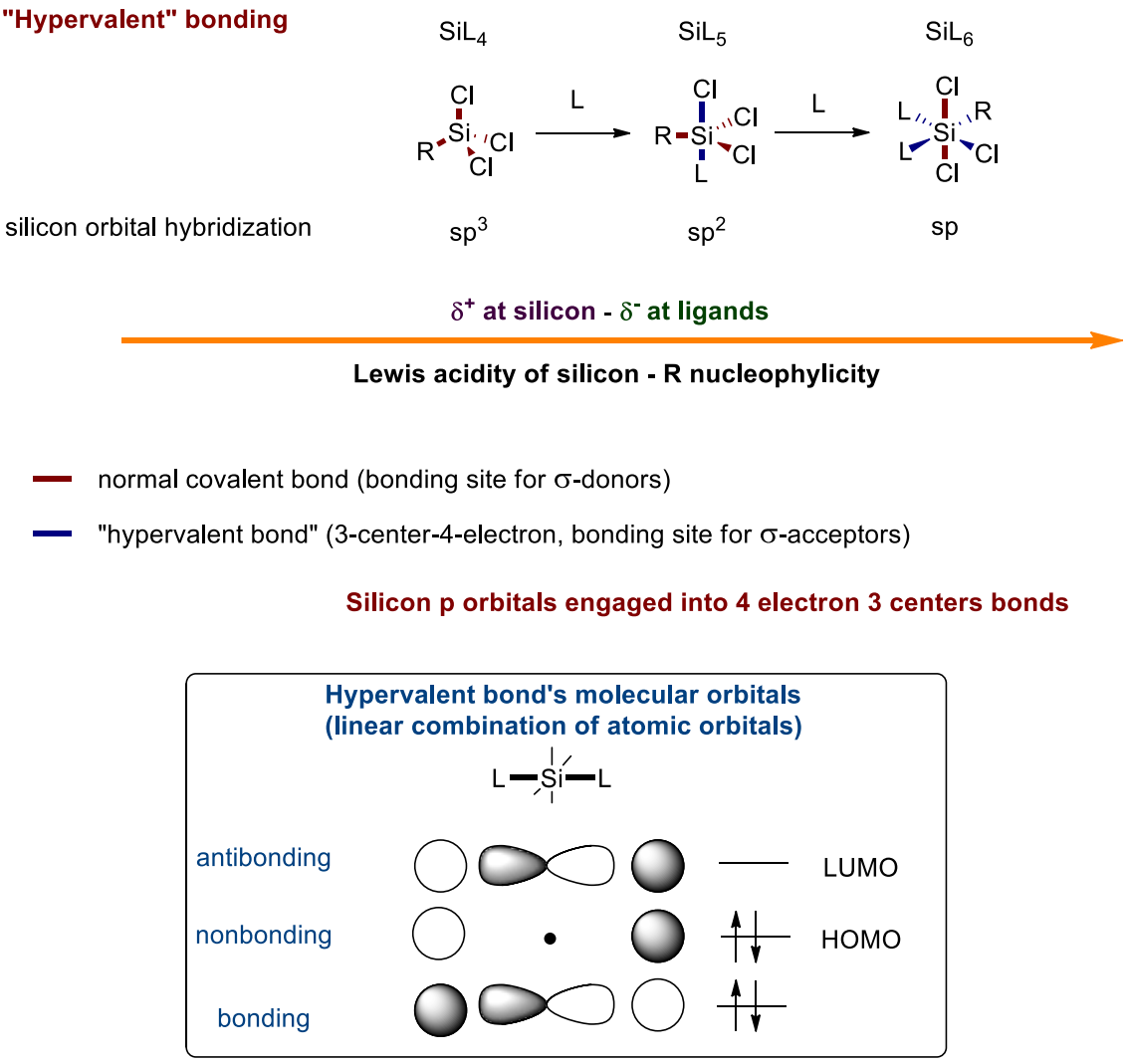
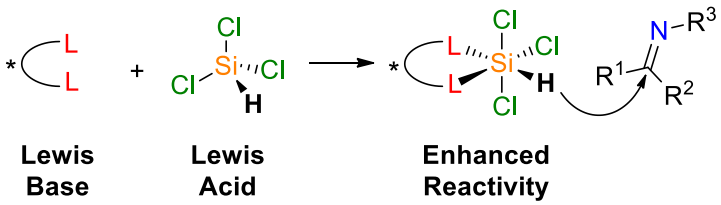


Figure 4

The nucleophilicity of silicon substituents allows the delivery of the hydride into an electrophilic substrate (C=O, C=N or Michael acceptors, Scheme 2), that could be also coordinated by the silicon atom, due to its increased Lewis acidity. Hence, using an enantiomerically pure LB for the activation of $HSiCl_3$, it could be possible to perform stereoselective reduction of C=N double bonds.



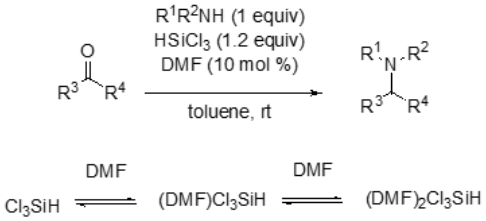
Scheme 2

Among all the methods for reduction by a non-metal hydride, the use of trichlorosilane combined with the presence of a Lewis base is particularly attractive, since trichlorosilane is a relatively inexpensive stoichiometric reducing agent. Moreover, the use of an enantiomerically pure Lewis base for activation of $HSiCl_3$ allows the enantioselective reduction of these functional groups.

Several examples of these classes are extensively reported in two reviews.[7,8] In this chapter, the development

of these chiral LBs will be analyzed, focusing the attention on the milestone events and more efficient examples.

In 1996, Kobayashi reported one of the first useful examples of trichlorosilane activation by a LB in the reductive amination of aldehydes and ketones catalyzed by DMF.[9] ^{29}Si NMR analysis allowed the identification of the hexacoordinate silicon species, demonstrating the important role of the LB in silicon activation (Scheme 3).

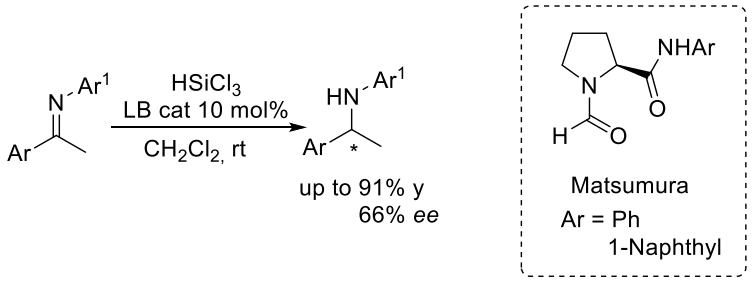


Scheme 3

Under these mild reaction conditions, imine derivatives containing functional groups such as an ester, nitro, nitrile or sulfone, could selectively react only at the C=N double bond. On the basis of this preliminary work, many other investigations followed, demonstrating that also secondary amines and heterocycles are compatible with the reductive elimination conditions. The use of $HSiCl_3$ as the reducing agent activated by a LB was then extended to many other substrates, including ketones, *N*-oxides, phosphine oxides and sulfoxides.[10,11][12][13,14]

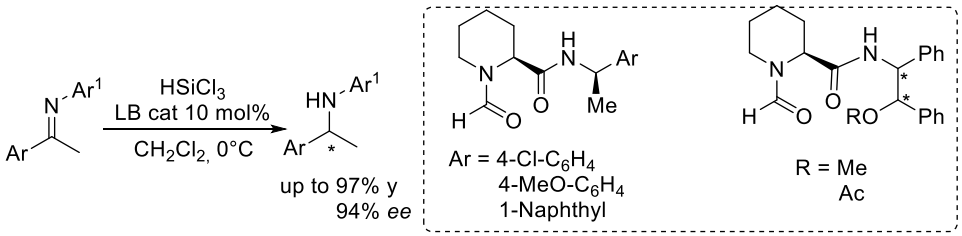
The use of chiral LBs in combination with $HSiCl_3$ was subsequently tested, providing the opportunity to control the stereochemical outcome of the process. This type of approach has been widely explored, leading to the development of many efficient catalysts.

The first example of an enantioselective, catalytic reduction with $HSiCl_3$ in the presence of a chiral LB, was reported in 1999 by Matsumura and co-workers who introduced *N*-formyl cyclic amines derived from proline as activators in the trichlorosilane mediated reduction of ketones[15] and imines (Scheme 4).[16]



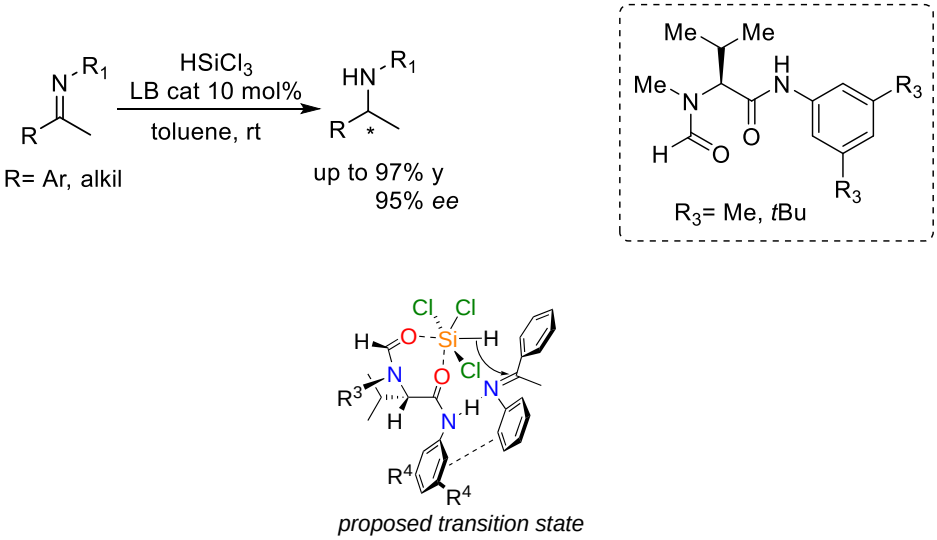
Scheme 4

Although with modest enantioselectivities, this work set the stage for the development of many *N*-formyl derived chiral catalysts, capable of delivering high yields and good enantioselectivities. Modification of the original Matsumura catalysts, by replacing of the proline core with a pipecolic acid or piperazine moiety and the introduction of a second stereocenter, provided an improvement of the enantioselectivity of the process (Scheme 5).[17–20]



Scheme 5

Malkov and coworkers disclosed an important breakthrough in 2004, when they developed the first highly selective catalyst derived from valine (Scheme 6).[21] Chiral amines were obtained in up to 95% *ee*.



Scheme 6

In the following years, Malkov and coworkers reported the syntheses of different substituted *N*-formyl amino acids bearing aromatic or aliphatic substituents.[22–27] The data collected by testing them in the stereoselective reduction of imines, helped rationalize the reaction mechanism, as well as the essential moieties in the catalyst to deliver high enantioselectivities: the *N*-methyl formamide group and the presence of an NH as part of the amide. Furthermore, arene-arene interactions between the catalyst and the substrate are invoked as stabilizing the transition state during the hydride transfer.[22,27,28] Interestingly, the absolute configuration of the product is primarily dominated by the nature of the amino acid side chain.

Generally speaking, low enantioselectivities were always observed with imines derived from pyridines, probably due to a competition in the coordination between the nitrogen of the catalyst and the pyridine moiety with trichlorosilane.

Subsequently, a novel class of chiral compounds was identified as very active in the reduction of imines promoted by trichlorosilane: *N*-picolinoyl derivatives (Figure 5).

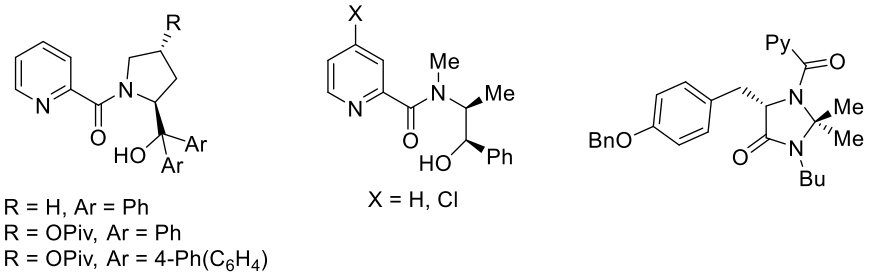
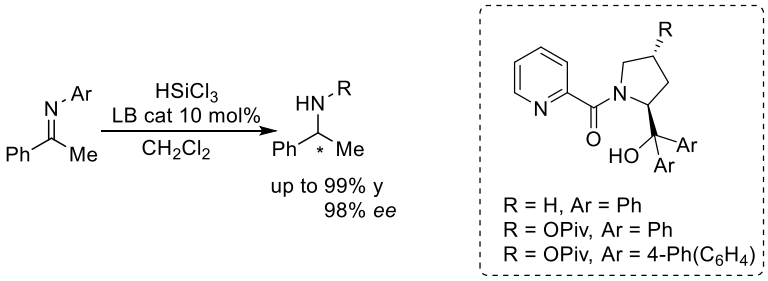


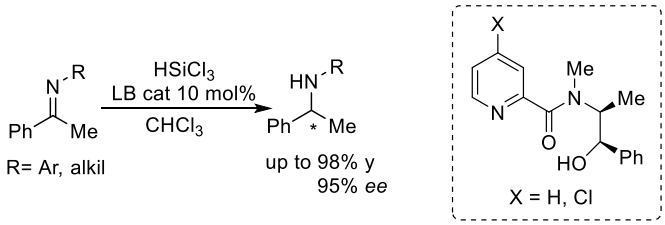
Figure 5

In 2006 Matsumura et al. reported the use of *N*-picolinoyl-(2*S*)-(diphenylhydroxymethyl) pyrrolidine as a catalyst for the reduction of aromatic imines to the corresponding amines mediated by trichlorosilane.[29,30] Various modification to the scaffold of the catalyst, lead to high enantioselectivities, up to 98% *ee* (Scheme 7).



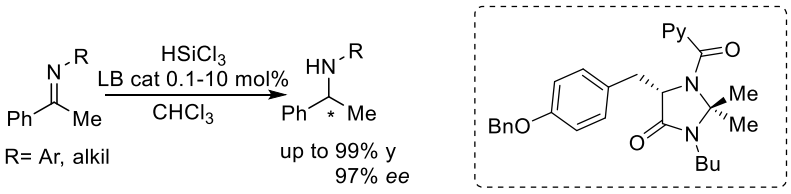
Scheme 7

Other catalysts, derived from the chiral scaffold of ephedrine,[31–33] were successfully tested for the stereoselective reduction of imines. The pyridine ring, the free hydroxyl group, and the *N*-methyl substitution in the amino alcohol portion represent key structural elements to ensure high stereocontrol. This catalyst provides high chemical and stereochemical efficiency with only 1 mol % loading; furthermore, reduction of N-alkyl imines can be performed with high enantioselectivity as well (Scheme 8).



Scheme 8

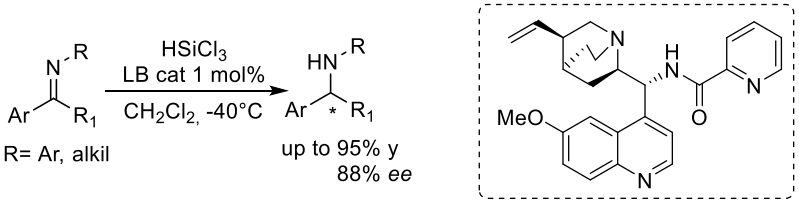
Benaglia et al. have developed an *N*-picolinoyl derivative based on an imidazolidinone core:[34] the catalyst showed remarkable activity in the reduction of *N*-aryl and *N*-alkyl substituted ketimines.[35] Products are obtained in higher than 90% yields and enantioselectivity ranging from 90 to 98% *ee*. Importantly, catalyst still works efficiently at 1 mol % loading without any erosion of stereoselectivity (Scheme 9). Furthermore at 0.1 mol % loading, chiral amines can be obtained in 92% yield and 90% *ee* at 0 °C, and in 80% yield and 97% *ee* at –20 °C. These results are quite impressive for an organocatalyst, being favorably comparable to organometallic catalysis.



Scheme 9

N-Picolinoyl derivatives have also found applications in the reduction of α-, β-, and γ-imino esters,[36,37] and β-enamino esters,[38,39] with good results.

In 2013 picolinamides based on the Cinchona alkaloids scaffold were developed by the Benaglia group in collaboration with the group of Professor Burke of the University of Évora.[40–42]



Scheme 10

Using the amide derivatives, it was possible to achieve high yields and *ee* up to 88%, working at -40°C with 1 mol % of catalyst loading (Scheme 10). The scope of the reaction included *N*-aryl alkyl- and arylketones, α-imino- and β-enaminoesters.

Other chiral LBs have been subsequently developed, based on oxazoline scaffold,[43,44] sulfonamides,[45] phosphoramides[46] and bisphosphine oxide derivatives (Figure 6).[47,48]

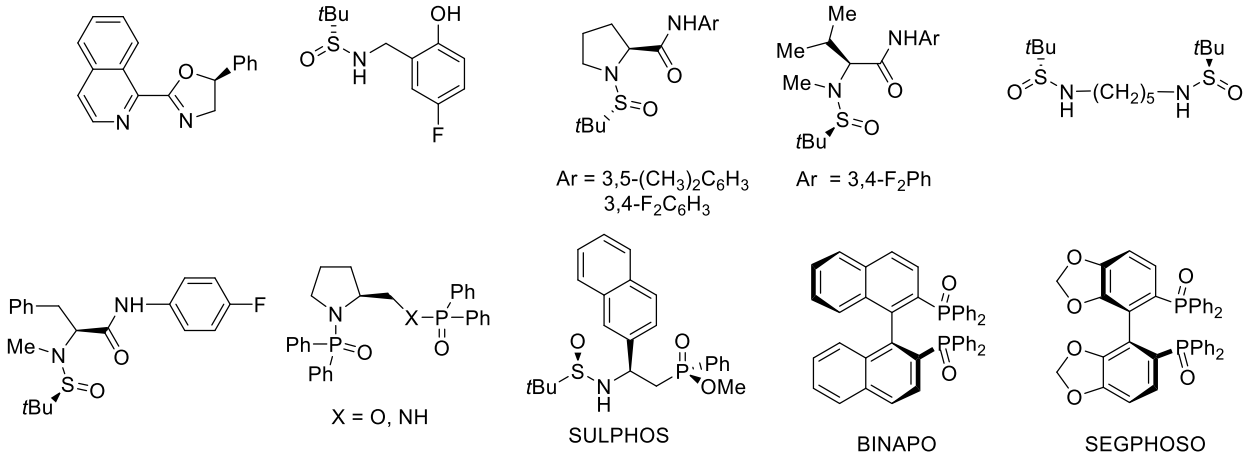
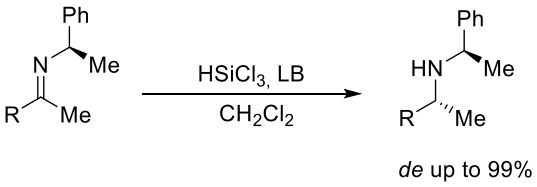


Figure 6

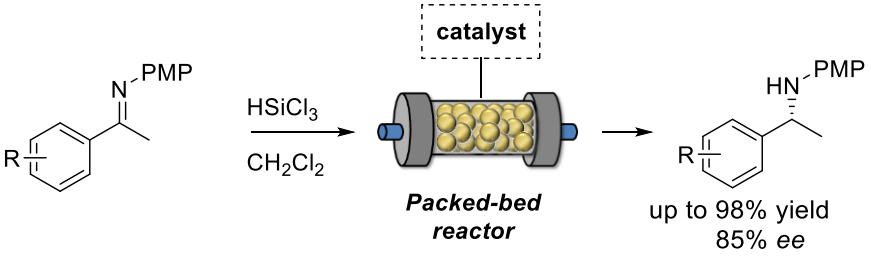
Another approach, for the synthesis of chiral amines via stereoselective reduction of imines mediated by trichlorosilane, can involve the use of chiral auxiliaries. In 2010 our group demonstrated that it was possible to achieve high diastereoselectivities in the reduction of ketoimines bearing a simple chiral residue, commercially available phenylethylamine, using $HSiCl_3$ in the presence of achiral DMF (yields up to 99%, *dr* up to 98:2, Scheme 11).



Scheme 11

Several of the previously reported catalyst were also tested as matching couples with chiral auxiliaries, or in more complex molecules presenting pre-existing stereocenters.

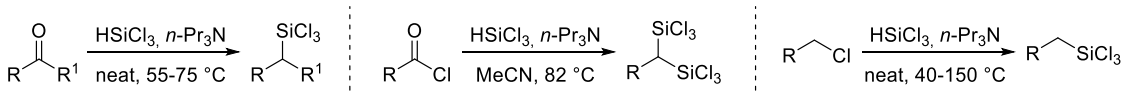
To address the problem of catalyst removal from reaction mixture, as well as catalyst recovery and recycle, some of the previously reported catalysts have been anchored onto different polymeric solid supports: simple filtration is needed to separate the catalyst from reaction medium (Scheme 12). Further improvement was achieved by preparing a packed bed reactor for the continuous flow synthesis of chiral amines,[49] which can be obtained in excellent yields and enantioselectivities.



Scheme 12

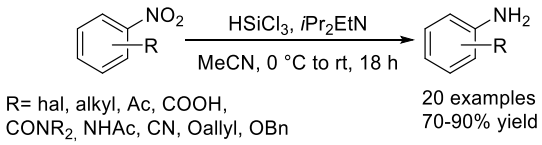
Trichlorosilane mediated reduction of nitroderivatives

Contrary to the interaction of a Lewis base with $HSiCl_3$ that leads to the formation of a more electrophilic hypercoordinate species, in the presence of a Brønsted base such as Et_3N or *i*$PrNEt_2$, a more nucleophilic silicon species is generated, which was demonstrated to be reactive towards carbonyls,[50] alkyl halides[51][52] and acid chlorides, typically under harsh reaction conditions (Scheme 13).[53]



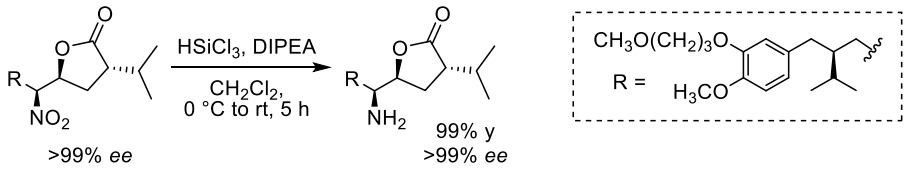
Scheme 13

Furthermore, in 2015, the group of Professor Benaglia successfully applied the combination of trichlorosilane whit *i*$PrNEt_2$ to the reduction of nitrobenzenes into anilines. In most cases, complete conversion of the nitro derivative into the corresponding amine was observed (Scheme 14). Nitriles, amides, ketones, alcohols and carboxylic acid moieties are compatible to reaction conditions, as are allylic and benzylic protecting groups. Moreover, halogenated nitro compounds can be converted to amines without any detectable traces of dehalogenated products. [54]



Scheme 14

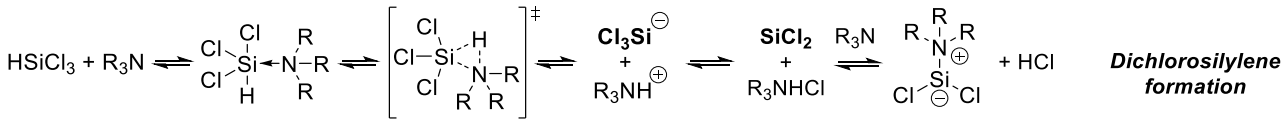
Due to very mild reaction conditions this method has found application in the total synthesis of Aliskiren, a product of the pharmaceutical industry, in which an enantiopure aliphatic nitro compound with four stereocenters (one of which directly bearing the nitro group, Scheme 15) is reduced to the corresponding aliphatic amine in 99% yield without eroding the stereochemical integrity of the four stereogenic centers.[55]



Scheme 15

$HSiCl_3$-mediated reduction of nitro-groups to amines has several positive features, being of general applicability, chemoselective, tolerant of many functional groups and respectful of the stereochemical integrity of the substrate. Moreover, the reduction protocol relies on the use of inexpensive and not hazardous chemicals, features a simple experimental procedure and is performed under mild conditions.

Mechanistic studies have provided some insight to the interaction of trichlorosilane with a Brønsted base. This type of interaction was already described in 1968.[50–53,56] Initially it was hypothesized that the combination of $HSiCl_3$ with a Brønsted base could lead to the formation of a R_3NH^+/Cl_3Si^- ion pair as illustrated in Scheme 16. However, Karsch proposed that this equilibrium may further evolve toward the formation of a dichlorosilylene species ($SiCl_2$) or one of its stabilized forms.[57]

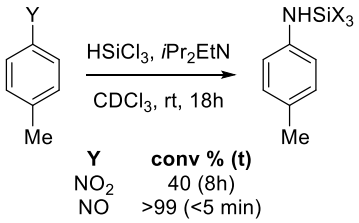


Scheme 16

On the basis of a screening of different bases, and of previous reports in the literature regarding the $HSiCl_3$ activation modes, all the three species, $SiCl_2$, $SiCl_3^-$ and the R_3N-stabilized $SiCl_2$ are plausible candidates for being the actual reducing agent. However, the known instability of $SiCl_2$ at temperatures above -50°C and several experiments aiming to a different generation of such a species reported in 2016,[5] suggested that $SiCl_2$'s ability to reduce the NO_2 group is considerably increased in the presence of tertiary amines. Even if these observations are not sufficient to exclude *a priori* the involvement of $SiCl_3^-$, further computational studies and competition experiments, strongly suggested the amine-stabilized dichlorosilylene to be the most probable reducing agent.

Furthermore, by monitoring by NMR the reduction of nitrobenzene in $CDCl_3$ (solvent in which the reaction is slow enough to be followed), no other reduction intermediates (nitroso- or hydroxylamine-compounds) were detected. This fact suggests that the first step (from nitro to nitroso) is rate determining. Also, the reduction of

nitrosotoluene was found to be complete in less than 5 minutes (that is much faster than nitrotoluene) (Scheme 17).



Scheme 17

Finally, the computation of a series of TSs in which different reducing species attack nitromethane (which was chosen as a benchmark substrate due to its small number of atoms), suggested that the reduction from a nitro to an amino group occur in three steps. At first, the Me_3N-$SiCl_2$ stabilized species is generated (–20.6 kcal/mol). Next, the interaction with the nitro aromatic compound allows the formation of the corresponding nitroso derivate (the addition of Me_3N-$SiCl_2$ to nitromethane occurs with an energy barrier of +15.8 kcal/mol). The transition state involves the addition of the negatively charged Si atom to the nitrogen of the nitro group. Once the Si-N bond is formed, a transient three-membered cycle involving the Si, N and O atoms is assembled, which through electron rearrangement forms Me_3N-$Si(O)Cl_2$ and nitrosomethane. This step, as already said, represents the rate determining step of the process. The second step involves a further reduction of the nitroso group (performed in analogy with the first step). This process is faster than the previous addition with an energy barrier of –12.9 kcal/mol (when considering the dissociated reagents as a zero-energy point). In the third and last step of the reduction, Me_3N-$SiCl_2$ attacks the cyclic intermediate by nucleophilic ring opening, breaking the N-O bond and leading to the formation of the silylated amine, which upon work-up generates the final amine product. The process has an energy barrier of –9.3 kcal/mol (Figure 7).

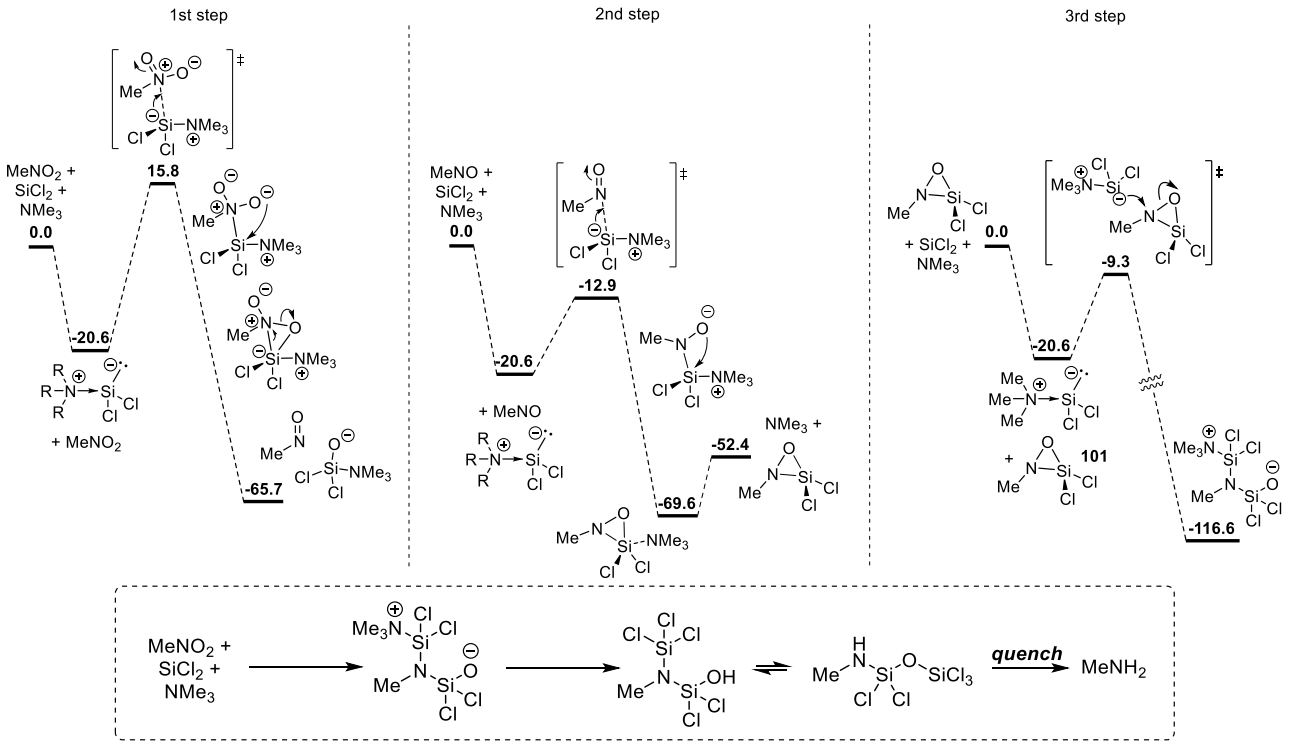


Figure 7

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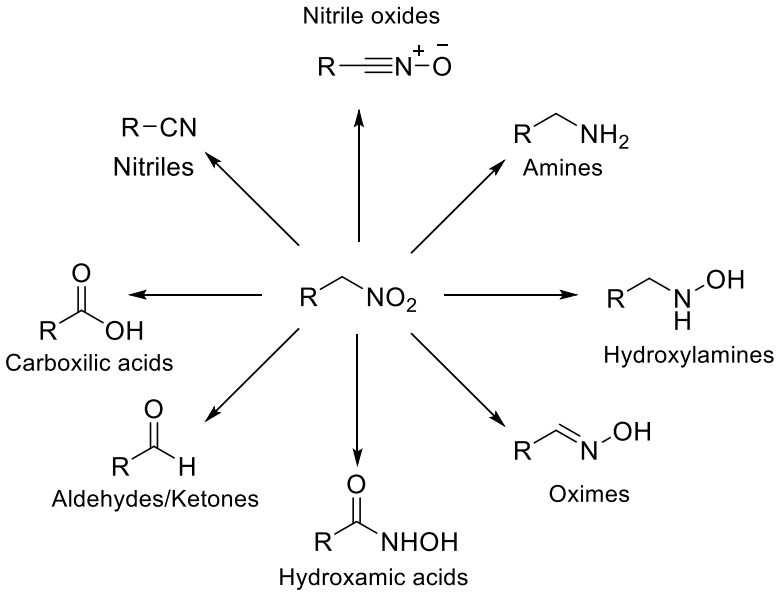
Chapter 1: introduction

Compounds that contains a nitro group are valuable and versatile molecules in organic synthesis, being widely available and possible precursors of a variety of diverse functionalities. Transformations that permit the interconversion between nitro and other functional groups,[1] such as the Nef reaction[2] or the reduction to give amines[3], are therefore of primary importance since they make possible the application of nitroalkanes as useful intermediates in synthesis. Historically nitro compounds, especially aromatic ones, has been used as important precursors of azo dyes and explosives; they are still used for that nowadays, in addition to be ideal starting materials for the construction of complex, polyfunctional molecules, which would be difficult to obtain by other known methods.[4]

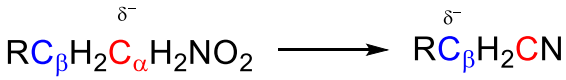
The nitro group, is one of the most electron-withdrawing group known,[4] and provides a very peculiar reactivity to the carbon chain: for nitroalkanes, a nucleophilic character in α-position (by making it prone to deprotonation), while for nitroalkenes, an electrophilic one in β-position. Furthermore, among Michael acceptors, nitroalkenes are very attractive: in Michael additions to nitroalkenes, the nitro group can serve as masked functionality to be further transformed after the addition has taken place, making it a very versatile functional group.



Scheme 1

Along with the already mentioned Nef reaction and reduction to an amino group, some examples of possible transformations that nitro containing molecules can undergo, are nucleophilic aromatic displacement,[4] the Henry reaction, and the dehydration into nitrile oxides, a class of reactive 1,3-dipolar reagents that form isoxazolines or isoxazoles by reaction with alkenes or alkynes respectively.[4] In addition, nitro compounds are also good precursors for other nitrogen containing derivatives, such as oximes, hydroxylamines, and imines (Scheme 1). These transformations are well established and routinely used in organic synthesis, while nitro compounds are less often used as precursors of nitriles:[4] in some cases, indirect conversion of nitro compounds into nitriles is achieved via dehydration of the corresponding oxime intermediate. The transformation of a primary nitroalkane into a nitrile permits the transfer of the nucleophilic character from C_α

to C_β, thus constituting an 'umpolung' case, similar to that involved in the conversion of nitro to carbonyl group (Scheme 2).

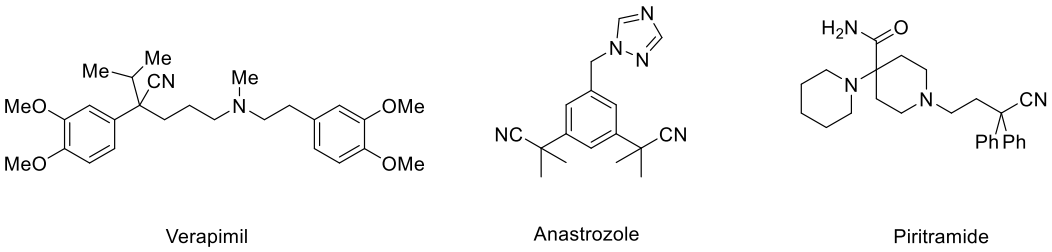


Scheme 2

In the following paragraph we will present a literature background relatively to the derivatization of nitroalkanes into nitriles and then focus on the metal-free reduction to give amines.

Transformation of nitroalkanes into nitriles: literature background

Due to their unique reactivity and activating ability, nitriles are important functional groups in organic synthesis.[5] Because of the electronegativity of the nitrogen atom, the CN bond is highly polar, resulting in high molecular dipole moments. The highly dipolar character of the nitrel group and its linearity have led to the development of a host of compounds possessing liquid crystal properties: several nitrile containing compounds are currently used in display technology, a field which has undergone extensive development in recent years. As well as being bulk chemicals, produced on a million-ton scale (e.g. for the polymer industry), [6] nitrile containing molecules can be found in the low-volume high-value product segments, such as the pharmaceutical one.[7] For instance, more than 30 nitrile-containing drugs have been approved for the treatment of depression, breast cancer, and Parkinson's disease, while 20 more are in clinical trials (Figure 1).[8,9]



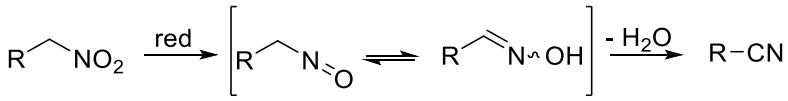
Verapimil Anastrozole Piritramide

Figure 1

The cyano group is highly reactive, as well as activating adjacent bonds especially α-CH bonds, and does not foster any steric hindrance. In general, the electrophilic cyano group is reactive toward nucleophiles, while aliphatic nitriles are also prone to base-catalyzed substitution reactions due to acidic hydrogens on the α-carbon atom: hydrogens in the α-position typically have pKa ~25, but the acidity increases if more than one cyano group is present. Nitriles are important synthetic precursors for the preparation of carboxylic acids, amides, aldehydes, ketones, amidines, amines, *N*-containing heterocycles, etc. or as directing groups for remote C−H activation through weak coordination.

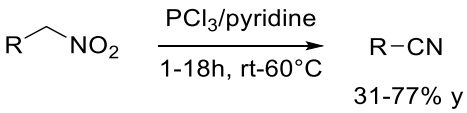
Reactions that forms C-CN bonds, includes mostly substitutions and rearrangements, often requiring the use of highly toxic and difficult to handle metal-cyanides. Cyanide-free synthesis of nitrile containing molecules is a valid and most of the time preferred alternative.[10] Construction of the cyano group by functional group transformation can come from a nitrogen-free starting material, such as an aldehyde, both in one step or with an intermediate nitrogen-containing derivative (e.g. an oxime). Additionally, ketones, carboxylic acids, acid

chlorides, and esters can be derivatized into nitriles. Direct dehydration of nitrogen containing functional group, like oximes or amides,[11] is a useful tool, and for both processes, a variety of reagents are now available; on the other hand, dehydration of other functionalities suffer from drawbacks such as harsh reaction conditions, traditionally requiring strongly acidic dehydrating reagents. Therefore, the development of a robust strategy for the synthesis of diverse functional-group-rich nitriles is highly desirable. As for the transformation of nitroalkanes into nitriles, the reaction requires both a reduction and a deoxygenation step; in many cases, an oxime intermediate is hypothesized in the reaction mechanism, eventually dehydrated in situ (Scheme 3).



Scheme 3

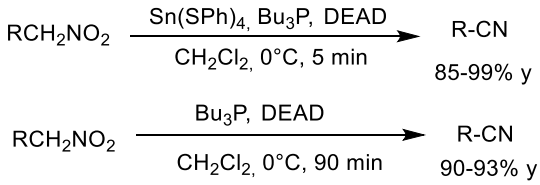
In 1977, a direct transformation of a variety of primary nitro alkanes into the corresponding nitriles was reported (Scheme 4). Before that, the transformation of a nitromethyl group into a nitrile, classically involved a Nef reaction leading to the corresponding aldehyde, followed by oxime formation with hydroxylamine and subsequent dehydration.[12] This sequence is long and often incompatible with other functional groups present in the starting molecule. Alternatively, direct conversions of primary nitro compounds into nitriles had been achieved by the reaction of alkali salts of nitromethyl compounds with diethyl phosphorochloridite[13] or by subjecting primary nitro compounds to Vilsmeier-Haack formylation conditions at temperatures above 100°C.[14]



Scheme 4

The method proved to be suitable for the preparation of both aryl and alkyl-nitriles, α,β-unsaturated nitriles and cyanohydrin acetates; on the other hand, due to quite harsh reaction conditions, it presented a limited tolerability to functional groups, although being innovative and revolutionary. More recently, also a mechanistic hypothesis was proposed, involving the formation of a nitrile-oxide intermediate.[15] Other phosphorous-based deoxygenating agent for nitroalkanes to give nitriles are P_2I_4[16] , $(Me_2N)_3P$[17] and PI_3.[18] . In view of a possible industrial applicability, it is important to consider that phosphorus containing waste, produced in the industry, usually causes eutrophication of aquatic ecosystems; stricter limitations for phosphorus containing industrial wastewater discharge have been set worldwide.[19,20]

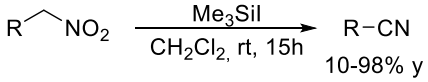
In 1990 a more convenient strategy was developed, starting from a primary nitro-group and using $Sn(SPh)_3^-$ (formed in situ by $Sn(SPh)_4$ and Bu_3P) as reducing agent and Bu_3P/DEAD (Diethyl azodicarboxylate) as dehydrating agent,[21] that allowed to obtain the corresponding nitriles in 5-10 minutes. Furthermore, the transformation could be performed also without the organostannane, in order to avoid traces of metals in the final product, just increasing reaction time up to 90 minutes, and with slightly lower yields (Scheme 5).



Scheme 5

Both methods lead to high yields in relatively short times and in mild reaction conditions. The main disadvantage of this approach, along with the limited scope due to low functional groups tolerance, is the toxicity of the reagents: DEAD is toxic, and classified as explosive, being sensitive to light and shock;[22] tributylphosphine is pyrophoric;[23] the tin complex is not commercially available, and must be synthetized, and furthermore organostannanes are generally speaking very toxic, and subjected to rigid protocols when used on large scale synthesis.

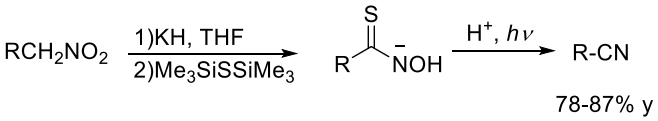
Previously, in 1983, iodiotrimethylsilane Me_3SiI was tested as deoxygenating agent for nitroalkanes,[24] since it had already proved to be suitable for the deoxygenation of sulfoxides and sulfonyl halides. The reaction resulted in the formation of corresponding nitrile via deoxygenation followed by in situ dehydration of the resulting oxime (Scheme 6).



Scheme 6

The method was feasible also for primary nitroalkanes and β-nitrostyrene derivatives, which also gave the corresponding nitrile. Exploiting the strong affinity of the silicon atom for oxygen and the reducing power of iodide (I^-), reaction can be run under mild conditions, at room temperature. In order to obtain high yield, the proton in α-position must be acidic: this is verified in the case of benzyl protons (e.g. α-nitrotoluene), while with compounds such as 1-nitrohexane the dehydration into nitrile is unfavored, so that the corresponding oxime is isolated.

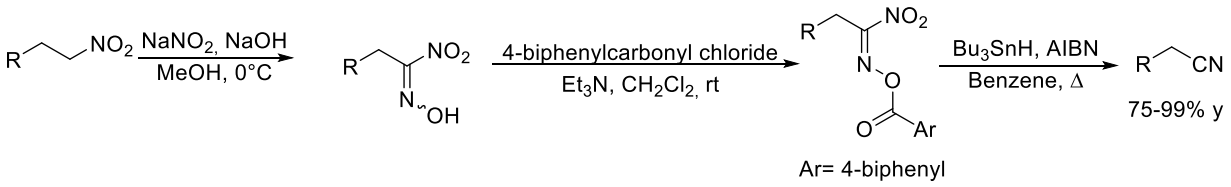
Disilanes are also effective for the conversion of nitro compounds into nitriles via an indirect method. A primary nitro compound is converted into a thiohydroxamic acid in the dark by using $Me_3SiSSiMe_3$ under alkaline conditions, followed by decomposition in the light to afford the corresponding nitrile in good yields (Scheme 7).[25]



Scheme 7

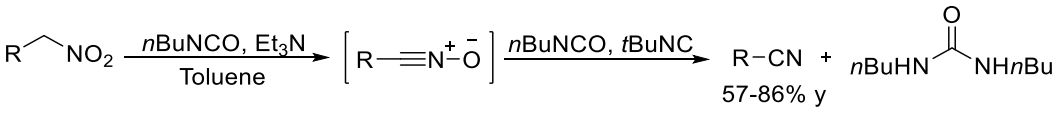
The first example involving a radical fragmentation, for the indirect conversion of nitro compounds into nitriles, was presented in 1996.[26] Starting from variously substituted nitroalkanes, the corresponding nitrolic acid was generated in alkaline conditions; alkyl and arylalkanenitrolic acid esters were then synthetized by reaction with 4-diphenylcarbonyl chloride and subsequently reacted with Bu_3SnH in the presence of catalytic amount of

AIBN to afford the corresponding nitrile in good yield, along with an equimolar amount of 4-diphenylcarboxylic acid (Scheme 8).



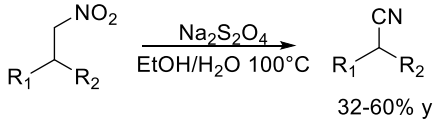
Scheme 8

A multicomponent reaction involving isocyanides (t-butylisocyanide, n-butylisocyanate) and a primary nitro compound, in the presence of triethylamine, was reported in 1997; the corresponding nitriles were isolated in 57-86% yield (Scheme 9).[27] The reaction involves the slow generation of the nitrile oxide, starting from a nitro alkane and *n*-BuNCO in the presence of Et_3N, followed by smooth reduction by *t*-BuNC, yielding the corresponding nitrile and an equimolar amount of *N,N*-di-*n*-butyl urea, as well as volatile byproducts (*t*-butylisocianide, *n*-butyl- and *t*-butylisocyanate) removed during workup (evaporation).



Scheme 9

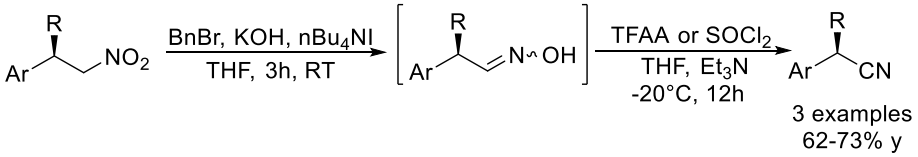
In 2014, the Unaleroglu's group in Ankara developed another method that doesn't require inert atmosphere and that could be performed in a mixture 1:1 of EtOH/H_2O (Scheme 10).[28]



Scheme 10

The main goal of the research was to realize a transformation that allowed the synthesis of a range of novel nitrile compounds. The method operates at high temperature, in a water-containing solvent system with sodium dithionite. Despite being an inexpensive and readily available reagent, the use of $Na_2S_2O_4$ on a large scale[29] has been reported to result in highly exothermic reactions.[30]

In 2005 the group of Czekelius and Carreira developed a synthetic method for the transformation of optically active aliphatic nitro derivatives into enantioenriched oximes.[31] The authors showed in three examples the possibility to further derivatize their products into nitriles by adding at the end of the reaction a dehydrating agent, avoiding also in this case racemization (Scheme 11). This is the only example present in literature where, starting from optically active nitro compounds, enantiomerically enriched nitriles are obtained. The use of optically active organonitro compounds as chiral building blocks would significantly benefit from the availability of methods for their conversion under mild conditions into other classes of chiral compounds.



Scheme 11

The advantages of this procedure are that the reaction can be performed at room temperature under air, inexpensive reagents are employed (BnBr, KOH, *n*Bu$_4$NI), and the use of heavy metals is avoided: this provides an environmentally friendly reaction. In many of the examples cited before, the reaction involved the use of inert atmosphere due to a certain sensitivity of reagents.

In the field of pharmaceutical, a great challenge is represented by the development of synthetic methods for the preparation of optically active nitriles, due to the increasing demand of the latter for drug synthesis.[32] For example, optically active 2-arylproprionitriles are very well known intermediates for the preparation of anti-inflammatory drugs such as ibuprofen, and all the others members of the so called “profen family” (Figure 2).[33]

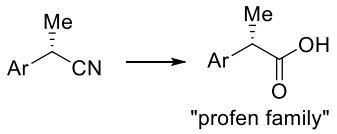


Figure 2

Several routes for the synthesis of enantiomerically pure nitriles are applied today: to introduce a cyano group, it’s possible to perform a stereoselective cyanation, either involving a chiral catalyst/additive or substrate-controlled (diastereoselective synthesis). Another option is functional group transformation of an already optically active substrate, without affecting the stereocenter, as in the previously reported example by Carreira.[31] If starting from racemic nitrile containing molecules, stereoselective functionalization (e.g. protonation or alkylation)[34,35] and deracemization[36,37] are interesting tools for this goal (Figure 3).

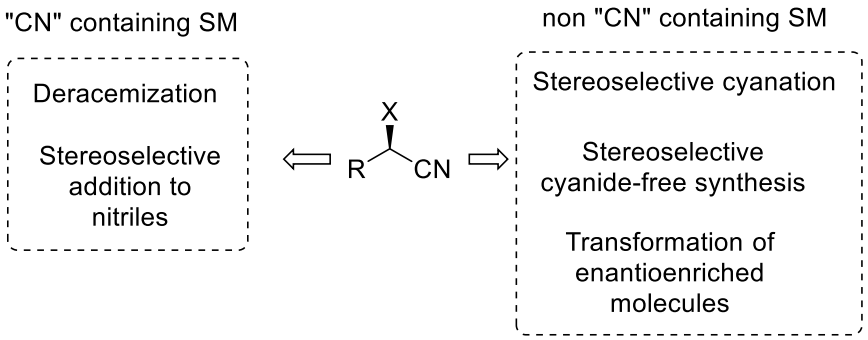
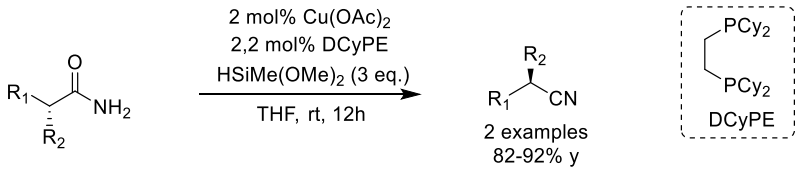


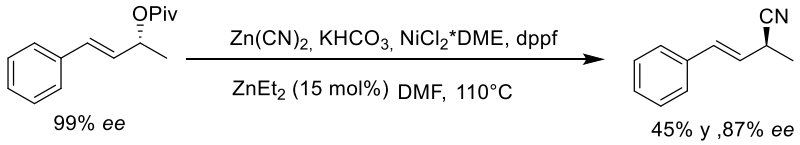
Figure 3

In 2018 the Buchwald group developed a strategy in which, starting from primary amides, through a copper catalyzed reaction at room temperature, nitriles were obtained in good yields. Furthermore, in the paper the methodology was successfully applied in two examples to chiral primary amides, yielding optically active nitriles without any loss in the enantiomeric excess of the starting material (Scheme 12).[38]



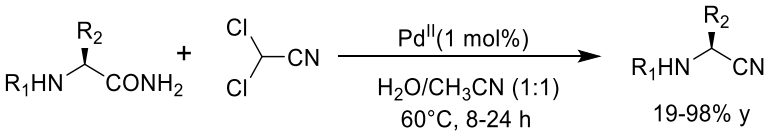
Scheme 12

Another contribution came by the Rosseaux group in Ontario: starting from allylic pivalate esters in a nickel catalyzed reaction, the nitrile was obtained with a small loss in the enantiomeric excess and inversion of configuration (Scheme 13).[39] This is the only example cited in the paper where racemization does not occur, and the mechanism for this reaction is still not clear.



Scheme 13

The most recent example, from 2019, involves the Pd catalyzed transfer dehydration of primary amides to nitriles under aqueous conditions, in the presence of a water acceptor, dichloroacetonitrile. The methodology was successfully applied to chiral α-aminonitriles, and also in this case, no racemization was observed (Scheme 14).[40]



Scheme 14

Several natural derived α-aminoacids were successfully tested in this protocol. The reaction can be run under air, with roughly the same results in terms of yield as the procedure run under inert atmosphere. The catalytic system proved to be compatible with the presence of various functional groups such as carbamates, hydroxyl groups, carboxylic acids, Boc-protected amines, Cbz-protected indoles and sulfoxides.

Efforts have been made in the development of synthetic routes toward enantiomerically pure α-amino nitriles or derivatives, in particular those being derived from *L*-proline, due to their application in the preparation of various active pharmaceutical molecules, such as Vildagliptin, NVP-DPP-728 and Saxagliptin (Figure 4). The Strecker reaction, involving the addition of cyano groups to imines, is a classical way to achieve α-aminonitriles, and several procedure are reported in the literature, with or without stereocontrol.[41–43]

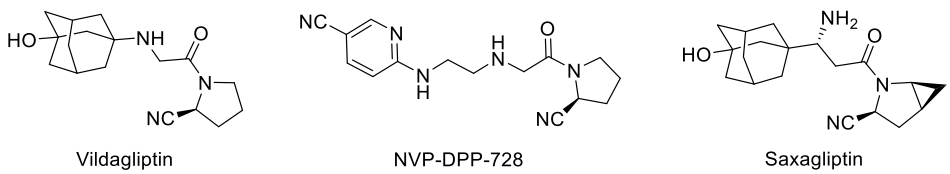
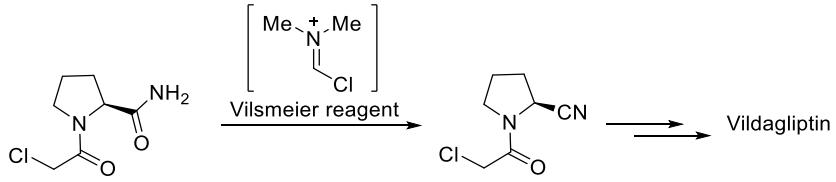


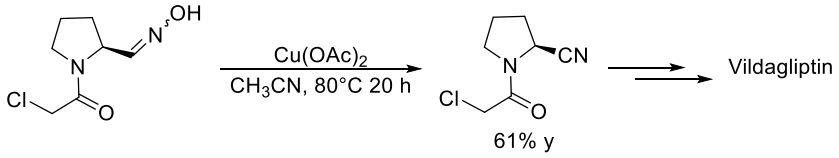
Figure 4

In the applied synthetic procedure by Novartis for the synthesis Vildagliptin, the Vilsmeier reagent is used for the “formal dehydration” step, without affecting the enantiopurity of the starting material (Scheme 15).[44] Due to its drawbacks, including being irritant, and having a high thermal energy of decomposition that leads to operational issues on larger scale, an alternative in flow synthesis of the advanced intermediate has been proposed,[45] in which the reagent is prepared (from DMF and $POCl_3$) and consumed in line, while the work-up is performed under classical batch conditions.



Scheme 15

A proposed alternative for the synthesis of enantiomerically pure *N*-acyl aminonitriles was achieved via a $Cu(OAc)_2$ catalyzed dehydration of aldoximes, obtained in two steps starting from natural aminoacids through condensation with hydroxylamine and the corresponding protected aldehyde (Scheme 16).[46] The overall process appears to be economical and sustainable, avoiding highly toxic cyanating agents, and proceeds in smooth conditions.



Scheme 16

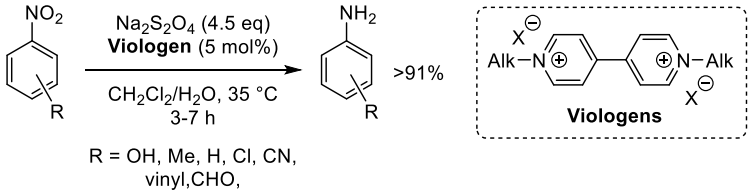
Metal-free reduction of the nitro group: literature background

Reduction of nitro-groups represents one of the most straightforward entries to aliphatic and aromatic amines.[4] Among the numerous available methodologies, reduction *via* hydrogenation, with classical and revisited protocols (Pd/C, PtO_2, Raney-Nickel or homogeneous transition metal catalysts),[47–49] or under transfer hydrogenation conditions[50,51] is largely employed. However, these protocols sometimes lack functional group compatibility, often requiring high pressure equipment, and may suffer from the use of hazardous reagents (e.g. hydrazine) or the presence of potentially toxic transition metals. Similar considerations can be made for the reductions with $SnCl_2$[52] or for metal dissolving reductions involving Zn, Fe, In or Sm,[53–56] which were reported to be poorly compatible with the presence of halogen atoms.[57] Efforts have been made to discover new methodologies that would avoid the use of metal catalysts, but only few new protocols have been reported so far.

Several research groups are involved in the field of metal-free methodologies for the reduction of nitro groups, as alternative to classical heavy metal-based protocols. In particular, several efforts have been made to develop methodologies that avoid also the use of hydrogen gas, but only few papers have been reported so far.

Firsts attempts arose from the observation by Bruce and Perez-Medina who, in the 1947,[58] showed that refluxing hydroiodic acid (57%) is a good nitro reducing agent. Toyokuni et al. have later revisited this

methodology.[59] Despite moderate to good yields were obtained in the reduction of simple aromatic nitro compounds, the very harsh reaction conditions, and the delivery of I_2 from the reaction environment, make this methodology unsuitable for the synthesis of valuable, functionalized molecules. In 1993,[60] Park showed that sodium dithionite ($Na_2S_2O_4$) is a single electron transfer reductant suitable for the mild transformation of several nitroarenes into the corresponding anilines. In particular, the reaction has been observed to be accelerated by Viologen (1,1'-dialkyl-4,4'-bipyridinium ions) via Electron Transfer Catalysis (Scheme 17). However, this methodology is still limited to the reduction of aromatic nitrogroups.

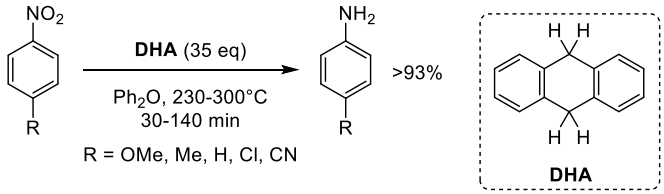


Scheme 17

Elemental sulfur (S_8) has been used as a nitro reducing agent in the presence of $NaHCO_3$ in DMF at 130°C. Seven different nitroarenes, also presenting CN, CO_2R and Cl substituents, have been selectively reduced in quite good yields.[61]

In 1995, Rüchardt discovered the ability of dihydroanthracene (DHA), xanthene and tetraline to act as reducing agents under harsh reaction conditions. When DHA is warmed up to 230-300°C a radical splitting occurs: the radical species are reductants able to react with unsaturated compounds (styrenes and fullerenes) and with nitrogroups.[62] This method has been applied to the reduction of five different nitroarenes in almost quantitative yields (Scheme 19); however, a large excess of DHA was required.

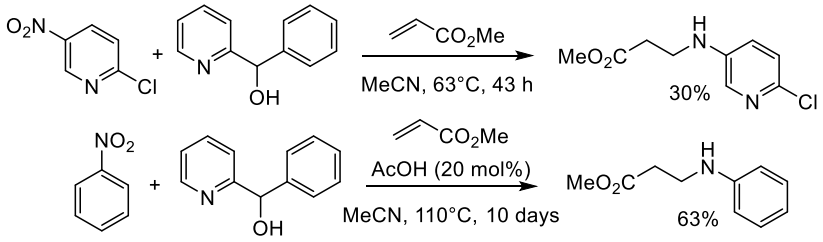
Scheme 18



Scheme 19

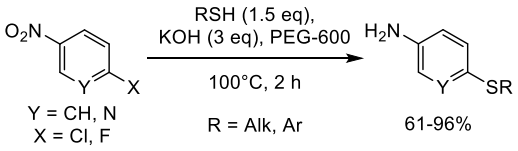
Hence, due to the use of great amount of DHA (that lead to the formation of difficultly removable organic byproducts, e.g. anthracene) and to the really high reaction temperatures, this methodology is useless from a synthetic perspective.

In 2008, Giomi et al. developed (2-pyridyl)phenyl methanol as a new reagent able to give transfer hydrogenation without giving side reactions (Scheme 20).[63] Performing the reduction with this new compound in the presence of methyl acrylate, the author obtained as final products the secondary amines. The major drawbacks of this methodology are the moderate yields (<68%), very long reaction times (from 2 to 10 days), and the great number of organic byproducts generated by the oxidation of the reductant.



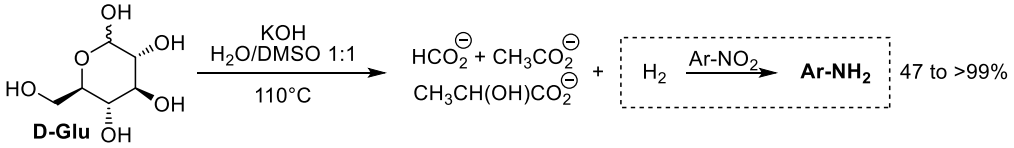
Scheme 20

Liu reported that thiols can be used as reducing species in order to promote the reduction of nitrocompounds to amine under basic conditions[64] (Scheme 21). Despite the intrinsic value of the obtained products (aminoaryl sulfides) and the possibility to reuse the reaction media (polyethylene glycol, PEG-600), it can be noted that the synthetic suitability of this method is very limited in scope. Indeed, the substrate nitroarene necessarily must be 2- or 4-substituted with a Cl or F atom, and no other functional groups have been reported to be compatible with the reaction conditions. Furthermore, the reduction of the nitrogroups in either the absence of the halogen atom on the aromatic ring or the sulfur substitution on the halogenated aniline, proceed sluggishly.



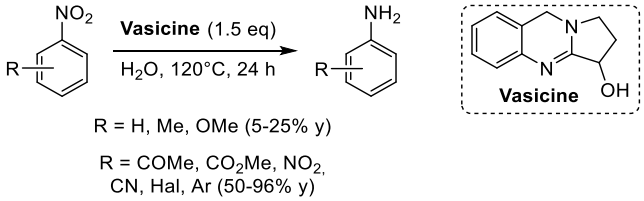
Scheme 21

Glucose has been reported to reduce nitro group to azoxy compounds. Starting from this observation, Kumar et al. developed a new methodology for the reduction of nitroarenes under basic conditions by heating *D*-glucose at 110°C in a 1:1 mixture of H_2O/DMSO.[65] This methodology is based on the delivery of H_2 by glucose degradation at high temperature (Scheme 22). However, even if the reaction occurs under harsh conditions, the authors were able to achieve the reduction of several nitro compounds in excellent yields and selectivity. In particular, CN, CHO, OMe, C=C, and halogen functionalities survived the reaction conditions providing the corresponding aniline without side reactions.



Scheme 22

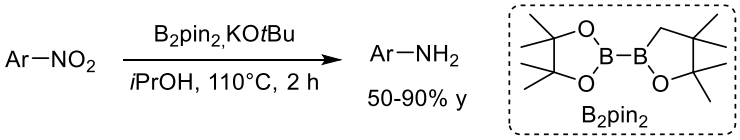
The same authors reported also Vasicine (Scheme 23), a natural alkaloid, to be able to perform transfer hydrogenation reactions in metal free conditions[66] leading to the reduction of several nitro groups in generally good yields and selectivity. In particular, despite several simple electronrich nitroarenes were reduced in very low yields (5-25%) due to the formation of considerable amount of undesired reduction intermediates (azo and azoxy compounds), nitroarenes bearing electronwithdrawing groups have been reduced with yields ranging between 60 and 96%. Notably, the reaction is performed in water even if at 120°C. However, during the reaction the reducing agent is oxidized to organic byproducts, thus a chromatographic purification of the desired product is needed. Furthermore, the extremely high cost of commercial Vasicine force one to directly extract it from *Adhatoda vasica* leaves.



Scheme 23

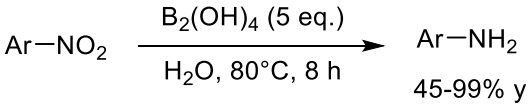
As previously mentioned, in the Introduction our group has reported in 2015 an unprecedented metal-free protocol for the reduction of nitro derivatives based on the use of $HSiCl_3$, an inexpensive and readily available compound, commonly used in the silicon industry, for the production of ultrapure silicon.[67] The methodology is extensively described in the introduction.

Another metal-free approach was reported in 2016 by the group of Wu, involving the use of Bis(pinacolate)diboron (B_2pin_2) and potassium *tert*-butylate, in isopropanol as hydrogen donor and solvent.[68] A series of nitro compounds containing various functional group sensitive to reduction were chemoselectively converted to the corresponding amine in good yields (Scheme 24). Although the reagents are commercially available and easy to use, the method is feasible only for aromatic nitro compounds, and unprotected hydroxy moieties are not tolerated.



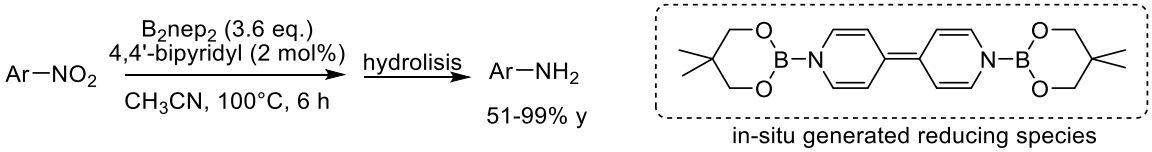
Scheme 24

Another boron-based reagent was subsequently reported for the reduction of nitroarenes to anilines, $B_2(OH)_4$.[69] Water was used in this case as hydrogen donor and solvent, making the methodology even more appealing. Unfortunately, no reaction was observed in the case of aliphatic nitro derivatives (Scheme 25). Mild conditions and a good functional group tolerance are the main advantages of this method.



Scheme 25

Finally, also Bis(neopentylglycolate)diboron was proposed as reducing agent for the synthesis of anilines starting from nitroarenes, in the presence of a catalytic amount of 4,4'bipyridyl.[70] *N,N*-diborylanilines are obtained, and hydrolysis is needed to complete the reaction and recover the desired aniline (Scheme 26).



Scheme 26

Protic functionalities such as OH, NH_2 and COOH are well tolerated; furthermore, several protecting group for hydroxy and amine moietis were successfully tested in this method.The reaction proceeds under air, and without need to further purify dry solvents. The authors exploited also the possibility to derivatize the obtained *N,N*-diborylanilines directly to ketimines, by reacting them in situ with a ketone.

Development of a New chemodivergent transformation: results and discussion

As already mentioned, our group has reported an unprecedented metal-free protocol for the reduction of nitro derivatives into amines based on the use of trichlorosilane ($HSiCl_3$),[71] an inexpensive and readily commercially available bulk chemical, widely used in the silicon industry.[72] Specifically, it was observed that nitro compounds could be reduced to the corresponding amines when reacted in the presence of $HSiCl_3$ and a tertiary amine under mild reaction conditions. A systematic screening of substrates revealed that this reduction protocol is applicable to both aryl and aliphatic nitro compounds and was successfully employed in the total synthesis of complex molecules.[73]

However, whit aliphatic nitro derivatives, the corresponding cyano derivative could be observed as a substantial reaction byproduct, in variable amounts, heavily depending on the experimental conditions, the nature and the stoichiometry of the base and the structural features of the aliphatic substrate. Our efforts were devoted to find optimized reaction conditions for the selective formation of both cyano and amine derivatives (Figure 5).

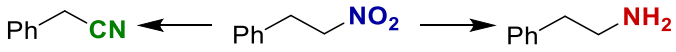
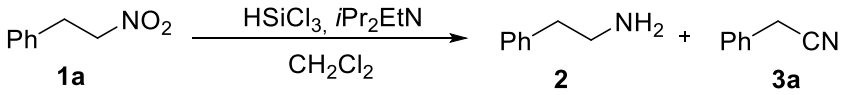


Figure 5

Optimization of reaction conditions

Our work started with the optimization of reaction conditions, using phenylnitroethane **1** as model substrate, in the presence of trichlorosilane ($HSiCl_3$) and a tertiary amine, diisopropylethylamine (iPr_2EtN), as base (Scheme 27).



Scheme 27

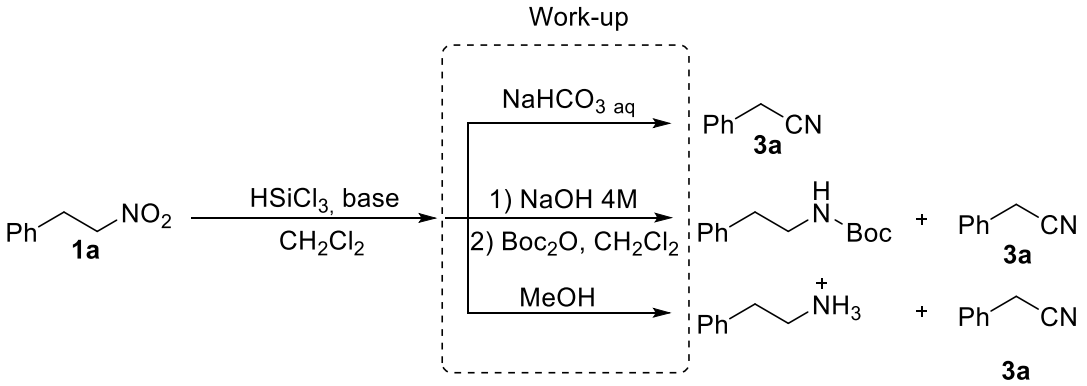
A first difficulty was encountered on the experimental setting of the reaction, in particular regarding the work-up. The classical work-up for this kind of reactions, where trichlorosilane is used, requires the quenching of the reagent by slow addition of an aqueous basic solution, at low temperature to control the exothermy, until basic pH is reached. Stirring of the biphasic mixture for 15 minutes is required to obtain a stabile basic solution, followed by extraction with an organic solvent.

Poor mass balance was encountered with this kind of work-up (as evaluated by GC in the presence of an internal standard), even changing the strength of the base or avoiding water (e.g. using a solid inorganic base). The best results were achieved by using 4M NaOH, allowing to achieve up to 79% of the total mass. The isolation of the aliphatic amine by column chromatography was still a challenging issue, and the isolated yield was always quite low.

To better understand the process, we performed the reaction in deuterated solvent (CD_2Cl_2), in the presence of an internal standard (trimethoxybenzene). We performed ^1H NMR at the end of reaction time, after quenching the mixture only with methanol (Scheme 28) (methanol allows the quenching of the excess of

trichlorosilane, leaving the two hydrochloride salts of the product and of the tertiary amine, which are very difficult to separate).

This test was done to exclude the formation of other byproducts and evaluate which was the nature of the missing mass. No other by-products where observed (not even the corresponding oxime), and all the missing mass belonged to the amine, since the yield of the nitrile was the same also after the aqueous workup, while the yield of the amine decreased. This result was predictable, since the amine is obtained in the silylated version at the end of the procedure, and we ascribed the loss to the difficulties in the cleavage of the N-Si bond as well as to the scarce lipophilicity of the aliphatic product.

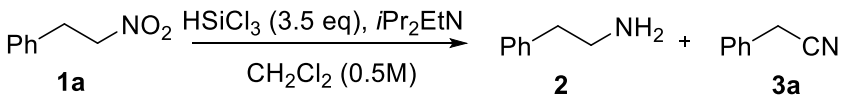


Scheme 28

Once established that, the subsequent screening of reaction conditions was performed by GC, calculating the yield over the amine as $[\text{yield NH}_2 = \frac{[\text{mmol } SM - (mmol\ CN + mmol\ unSM)]}{\text{mmol SM}} * 100\%]$; were SM is starting material, CN is the nitrile, unSM is unreacted starting material. In some cases (especially for the best results) the yield for the amine was also confirmed via ^{1}H NMR, as previously described.

As for the isolation of the amine, the best conditions were found to include an in situ Boc-protection: the reaction mixture was quenched with 1M NaOH solution in water, followed by addition of a Boc_2O solution in dichloromethane. The biphasic mixture was stirred overnight, and the amine was isolated in 50% yield over to steps (Scheme 28).

Once we established a reliable and reproducible experimental setup, we focused on optimizing reaction conditions: preliminary studies revealed that 3 equivalents of base are the minimum required to give a complete conversion of the starting nitro compound (entry 5, Table 1). Also, the temperature is a critical parameter, influencing both the reactivity and the selectivity of the system; it is indeed, necessary to keep the reaction temperature below -20°C during the exothermic addition of $HSiCl_3$.



Scheme 29

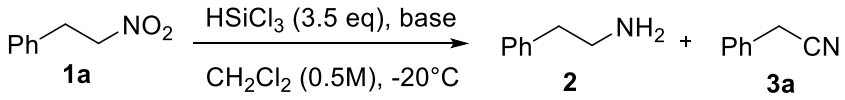
Table 1

Entry	T (°C)	*i*Pr$_2$EtN eq.	2 (y%)[1]	3a (y%)[2]	Conv. (%)
1	0	**0**	-	-	0
2	0	**0.5**	6.5	1	7.5
3	0	**1**	19.5	2.5	22
4	0	**2**	54	27	81
5	0	**3**	61	38	99
6	0	**5**	56	44	>99
7	**-40**	3	48	5	53
8	**-20**	3	68	18	86
9	**rt**	3	55	45	>99

1) calculated as difference between SM consumed and the amount of nitrile formed; 2) GC yield.

The role of the base proved to be crucial for the chemoselectivity of the reaction: in fact, increasing the equivalents of base, up to 8 equivalents, leads to a higher selectivity toward the nitrile, giving complete conversion of the starting material and up to 80% yield for the nitrile (Table 1Table 2, entry 3).

We then decided to test the influence of the steric hindrance of the base: in our hypothesis, a less hindered base could further increase the formation of the nitrile **3a**. Counterintuitively, using triethylamine (Et$_3$N) comparable results to *i*Pr$_2$EtN were obtained (entry 4-6, Table 2).



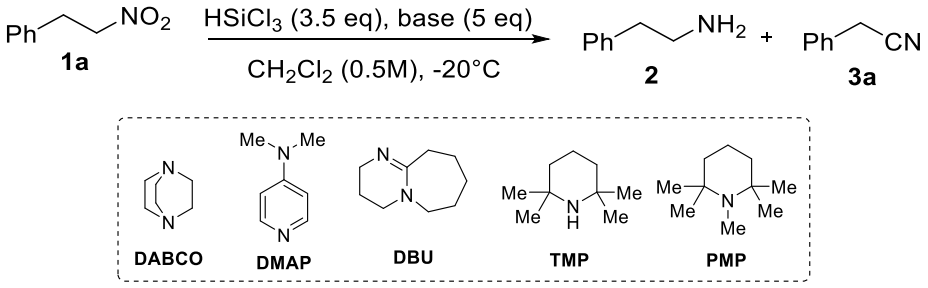
Scheme 30

Table 2

Entry	Base	Base eq.	2 (y%)[1]	3a (y%)[2]
1	*i*Pr$_2$EtN	3	68	18
2	*i*Pr$_2$EtN	5	56	44
3	***i*Pr$_2$EtN**	**8**	**17**	**80**
4	Et$_3$N	3	42	50
5	Et$_3$N	5	55	45
6	Et$_3$N	8	35	65

1) calculated as difference between SM consumed and the amount of nitrile formed; 2) GC yield.

In order to further improve the yield for the formation of the nitrile, we tested tertiary amines that were less effective in the reduction of nitrobenzenes, as demonstrated in a previous published paper,[71] hoping that they would have been less effective for the reduction of the nitro group, but not for its derivatization into nitrile.



Scheme 31

We decided to test *N,N*-dimethylaminopyridine (DMAP), 1,4-diazabicyclo[2.2.2]octane (DABCO) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as tertiary amines for our reaction conditions (Scheme 31).

Table 3

Entry	Base	Base eq.	2 (y%)[1]	3a (y%)[2]	Conv. (%)
1	DABCO	5	9	10	14
2	DBU	5	84.	16	>99
3	DMAP	5	n.d.	n.d.	4
4	TMP	3	50	40	90
5	PMP	3	40	-	40
6[3]	**PMP**	**3.5**	**98**[4]	**2**	**>99**

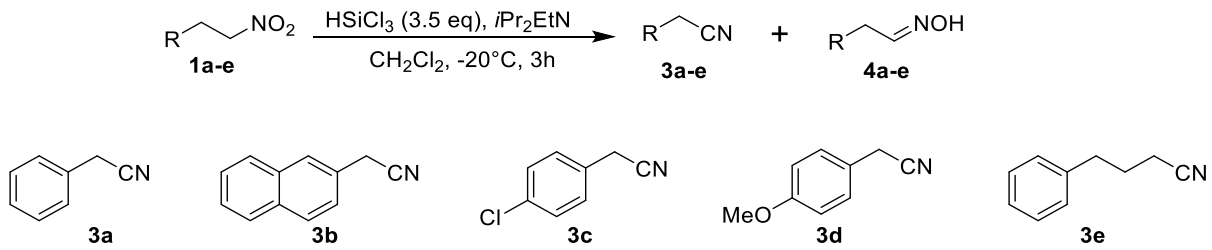
1) calculated as difference between SM consumed and the amount of nitrile formed; 2) GC yield; 3) reaction performed at room temperature after the addition of $HSiCl_3$ at -20°C; 4) ^1H NMR yield.

As shown in Table 3, the bases used proved less efficient than diisopropylethilamine in the transformation toward nitrile. DABCO and DMAP proved to be ineffective in the nitro-group conversion under our reaction conditions (entry 1 and 3). The use of the DBU led to a total conversion of the starting material but produced only a small amount of nitrile (entry 2). This result was indeed coherent with our hypothesis, since DBU can be considered a hindered base, and gave us good results over the formation of the amine. In order to maximize the yield, we decided to switch toward the use of hindered bases, like tetramethylpiperidine (TMP) and pentamethylpiperidine (PMP). Furthermore, we decided to decrease the number of equivalents to 3; with this condition, we were able to dramatically change the reaction outcome: using PMP, nitrile formation is almost completely inhibited in favor of the amine. In this case, to increase the conversion of the starting material, after the addition of trichlorosilane at -20°C, the temperature was raised to room temperature and the amine was obtained in 98% yield (entry 6).

To summarize, we were able to achieve up to 80% yield over the nitrile and up to 98% yield over the amine, just changing the steric hindrance and the amount of base used in our reaction. This is, at the best of our knowledge, the first example of a chemodivergent transformation that starting from an aliphatic nitro compound is able to give almost complete selectivity in the formation of the amine or the cyano derivative. While the reduction of nitro group to give amine is a very studied and well explored topic, the deoxygenation of nitroalkanes to give nitriles is a less common transformation, and we decided to focus on the isolation of this particular product.

Deoxygenation of nitroalkanes to nitriles

To further expand the applicability of the protocol, with the optimized condition in our hands, we decided to test different nitroalkanes, including compounds featuring aromatic rings (electron-rich and electron-deficient) and aliphatic chains (Scheme 32). For this set of experiment, we performed an aqueous basic work-up ($NaHCO_3$) and proceeded to the isolation of the desired product with chromatography. In all cases, the expected nitriles were isolated with moderate to good yields (Table 3).



Scheme 32

Table 4

Entry	Compound	R	3 (y%)[1]	4 (y%)[1]
1	**1a**	Ph	80	-
2	**1b**	Napht	70	30
3	**1c**	4-Cl-Ph	51	22
4[2]	**1c**	4-Cl-Ph	45	15
5	**1d**	4-OMe-Ph	66	11
6	**1e**	$PhCH_2CH_2$	50	23
7[2]	**1e**	$PhCH_2CH_2$	66	15

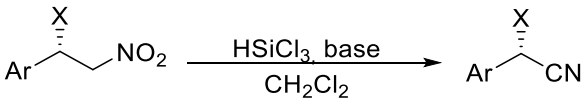
1) Isolated yield; 2) Et_3N was used (8 eq.)

The formation of the oxime as byproduct was observed, although in lower yield compared to the desired product (Scheme 32, Table 3). Based on this experimental observation, and on the previous results, we tried to rationalize a reaction mechanism, that will be presented later in this chapter.

Application of the synthetic method to optically active substrates

Our next goal was the implementation of such methodology for the deoxygenation of synthetically useful chiral nitroalkanes, hoping that when using optically active β-substituted nitroalkanes the stereochemical integrity of the compound would be preserved. This is particularly important since most of the substrates involve intermediates in which an acidic C-H bond is present on the stereocenter, made labile by the aryl and the cyano groups.

There has been intense activity in the development of catalytic, enantioselective methods for the preparation of chiral nitroalkanes.[74] In this context, the use of optically active organonitro compounds would significantly benefit from the availability of methods for their conversion into other functionalities under mild reaction conditions, compatible with the presence of a stereocenter: that would give access to other classes of optically active compounds (Scheme 33).

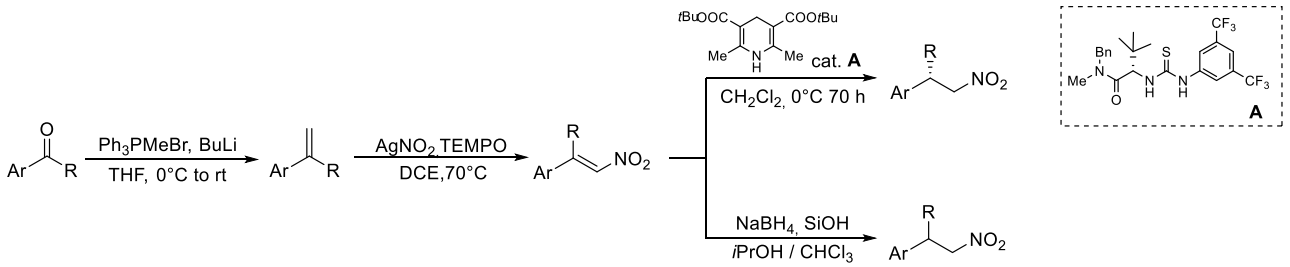


Scheme 33

Preliminary screening of the base showed that, in this case, the use of Et_3N gave better results in terms of yield toward the nitrile, compared to iPr_2EtN.

A possible explanation is that since in this case we are stressing the steric hinderance of the substrates, we can observe a difference between the two bases. Furthermore, we decided to avoid the use of bases during the quench, due to the lability of the stereogenic center of the product, and we stopped the reaction by adding methanol (see experimental section for details).

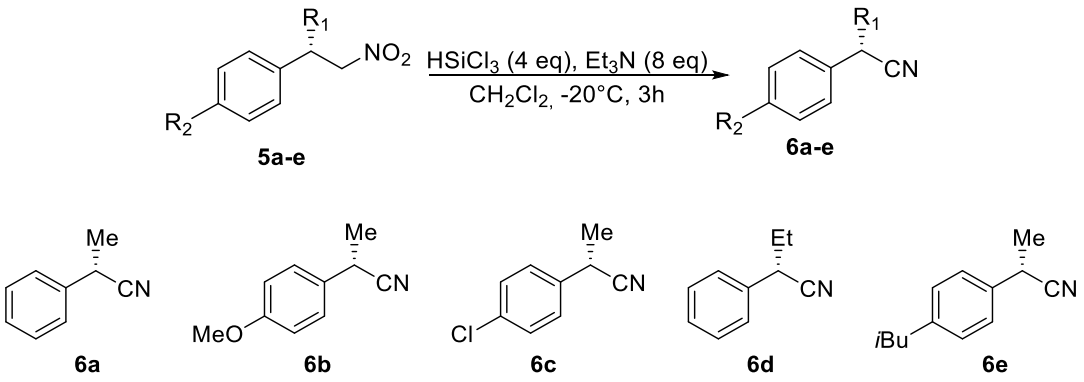
The deoxygenation protocol was first tested on optically active β-alkyl nitroalkanes. This first class of compounds was prepared by the stereoselective reduction of nitroalkenes, mediated by Hantzsch ester in the presence of a chiral organocatalyst, based on a thiourea scaffold.[75] Nitroalkanes themselves came from the nitration, performed by $AgNO_2$/TEMPO,[76] of differently substituted styrenes, obtained by Wittig reaction starting from aryl ketones. All the starting materials were prepared also in the racemic form, obtained via non-stereoselective reduction of nitroalkenes performed by sodium borohydride (Scheme 34). [77]



Scheme 34

The thus obtained β-alkyl nitroalkanes were reacted with 4 eq of trichlorosilane, in the presence of 8 eq. of triethyliamine in dichlorometane, at -20 °C, for 3 hours and afforded the nitriles in modest to good yields (Scheme 35). Preparative useful yields were obtained when R1 is an alkyl group, while a minimum loss of

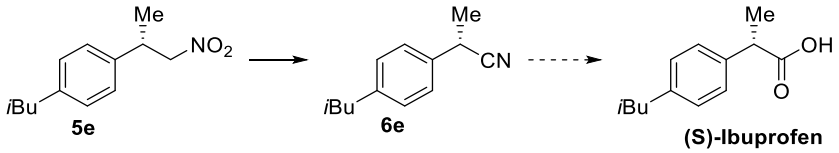
optical activity was observed (Table 5). In all cases, no unreacted starting material was recovered; traces of the corresponding oxime were in some cases present in the NMR crude but were not isolated. A direct precursor of Ibuprofen (compound **6e**, Scheme 36) was successfully synthetized in 57% yield and without any loss in enantiomeric excess.



Scheme 35

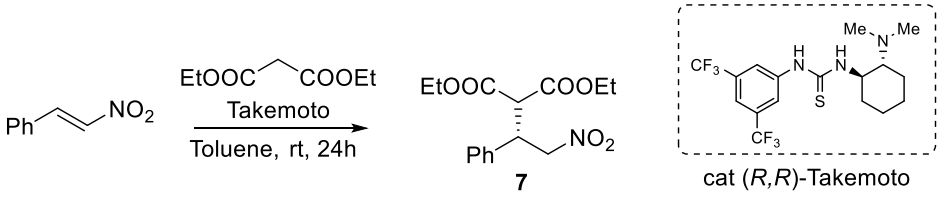
Table 5

Entry	Compound	R_1	R_2	y (%)	*ee* SM (%)	*ee* prod. (%)	Δ *ee* (%)
1	**5a**	Me	H	38	87	87	0
2	**5b**	Me	OMe	54	87	84	3
3	**5c**	Me	Cl	42	82	75	7
4	**5d**	Et	H	52	85	80	5
5	**5e**	Me	*i*Bu	57	85	85	0



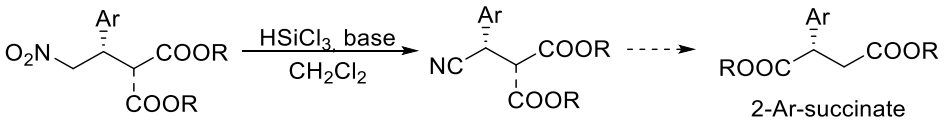
Scheme 36

An even more challenging class of substrates derived from the stereoselective addition of diethylmalonate to nitrostyrene was then synthetized, using the well-known Takemoto catalyst (Scheme 37).[78]



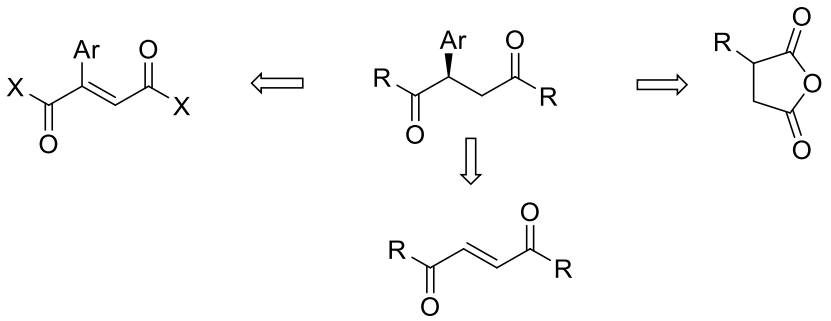
Scheme 37

The corresponding nitrile product, obtained by the application of our deoxygenation protocol, would be a direct precursor of a very synthetically useful class of substrates, enantioenriched 2-aryl succinate derivatives (Scheme 37).



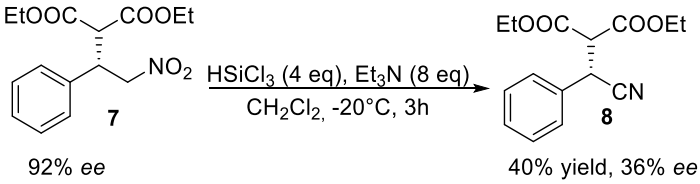
Scheme 38

These are versatile building blocks for the preparation of biologically active compounds. Their synthesis is challenging, since they are usually prepared by organocatalyitic or transition metal-catalyzed stereoselective hydrogenation of prochiral aryl-substituted fumaric *(E)* and maleic *(Z)* acid derivatives or enantioselective β-protonation of β,β-disubstituted enals, 1,4-additions of arylboronic acids to fumarate derivatives and kinetic resolution of monosubstituted succinic anhydrides (Scheme 39).[79][80][81]



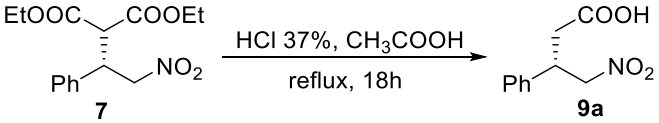
Scheme 39

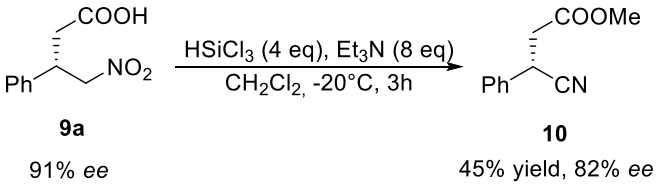
To demonstrate the synthetic utility of our methodology, we subjected compound **7** to our reaction conditions. Unfortunately, a loss in the enantiomeric excess was observed, and the corresponding nitrile **8** was isolated in 40% yield and only 36% *ee* (Scheme 40).



Scheme 40

To overcome this issue, the starting material was derivatized by decarboxylation to the corresponding 4-nitro-3-phenyl butanoic acid **9a**, and subjected to our reaction conditions. That allowed us to decrease the loss in enantiomeric excess, obtaining the corresponding nitrile **10** in 45% yield and 82% *ee*. The product was isolated as methylester, since esterification happened during the quenching of the reaction, performed with methanol (Scheme 41).





9a

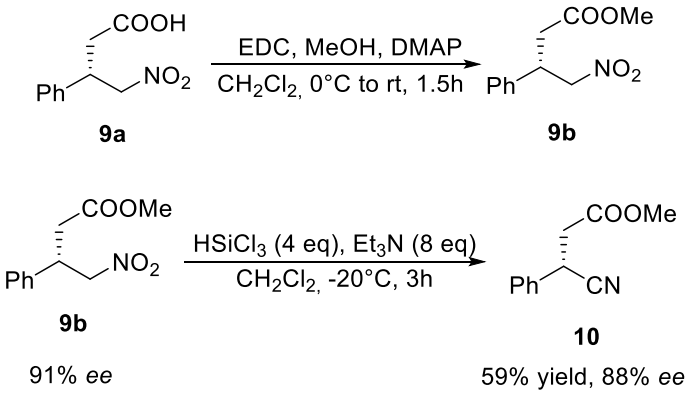
91% *ee*

10

45% yield, 82% *ee*

Scheme 41

To further increase the yield, we decided to run the transesterification before the deoxygenation. The corresponding methyl 3-cyano-3-phenyl ethanoate **10** was obtained this time in 59% yield and 88% *ee.* Not only, in this case, the yield was higher, but also almost no racemization was observed (Scheme 42).



9a

9b

9b

91% *ee*

10

59% yield, 88% *ee*

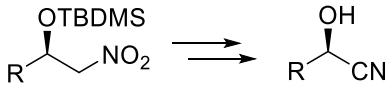
Scheme 42

The results for this class of compounds are summarized in Table 6, showing the improvements achieved both in the yield and enantiomeric excess of the products, by derivatizing the starting material before the deoxygenation reaction.

Table 6

Entry	Compound	R_1	y (%)	*ee* SM (%)	*ee* prod. (%)	Δ *ee* (%)
1	**7**	$CH_2(COOEt)_2$	40	92	36	56
2	**9a**	CH_2COOH	45	91	82	9
3	**9b**	CH_2COOMe	59	91	88	3

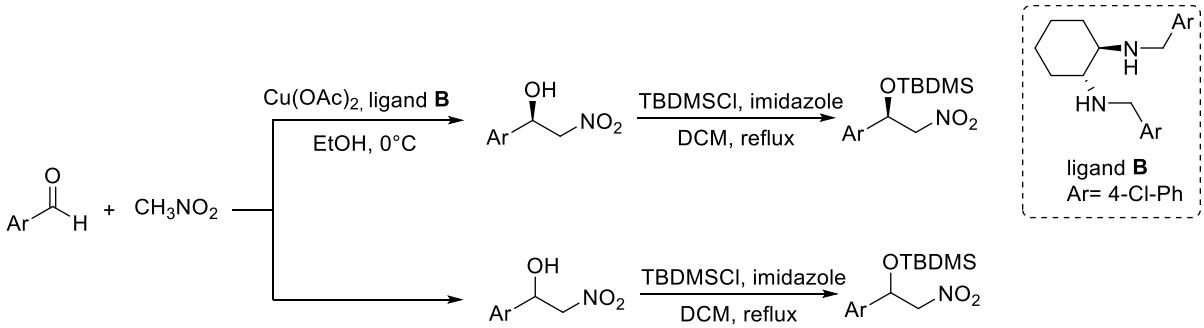
Another class of optically active substrates tested for the deoxygenation were β-hydroxy nitroalkanes, protected as silylethers. (Scheme 43) This are precursors of chiral cyanohydrines, important subunits frequently found in biologically active compounds and versatile building blocks for further transformations.[82][83][84]



Scheme 43

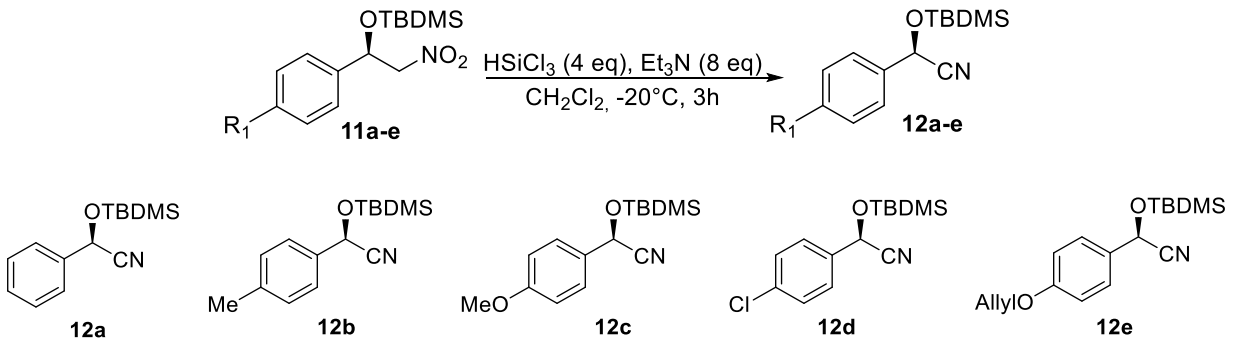
Cyanohydrins contain two functional groups: a nitrile and an alcohol, which may be prepared in protected form. These two functional groups can be readily manipulated to produce a diverse range of 1,2-difunctional compounds, including many which are often found as components of pharmaceuticals. Methodology has been developed to allow these transformations to be achieved whilst preserving the stereochemistry associated with the cyanohydrin and, where new stereocenters are created, to allow the configuration of these to be controlled.

For the stereoselective synthesis of nitroalcohols, we performed a stereoselective Henry reaction mediated by a copper (II) species in the presence chiral ligand **B**, that is derived from (*S,S*)-diaminocyclohexane.[85] The hydroxy moiety was subsequently protected as the silylether, by reaction with tertbutyl-dimethylsilyl-chloride (Scheme 44). The protection was successfully accomplished without any loss in the enantiomeric excess of the starting material.[85] The protection was proved to be necessary, since reaction on the unprotected hydroxy moiety did not led to the isolation of the desired product, because the OH group can interact with trichlorosilane and interfere with the reaction outcome.



Scheme 44

When this class of compounds was tested, all the corresponding nitriles were obtained in good yields, and no erosion of the enantiomeric excess was never observed. (Scheme 45, Table 7).



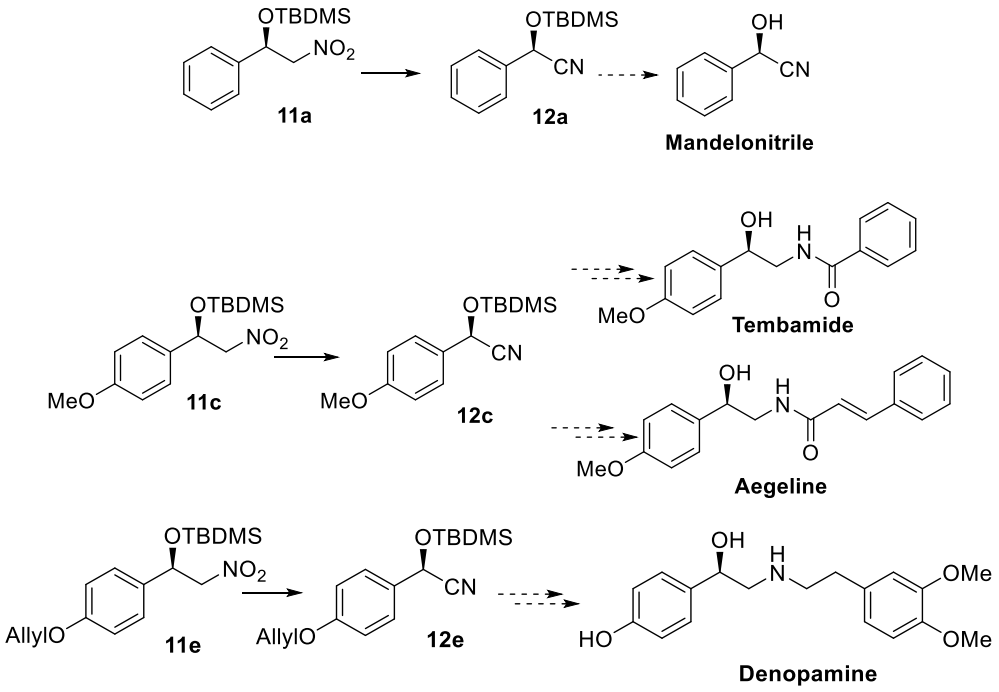
Scheme 45

Table 7

Entry	Compound	R_1	12 (y%)	*ee* (%)
1	**11a**	H	79	91
2	**11b**	Me	79	89
3	**11c**	OMe	70	87
4	**11d**	Cl	62	86
5	**11e**	OAllyl	54	75

Compound **12b**, bearing a methyl group in 4-position, was successfully obtained in 79% yield, comparable to the product bearing an unsubstituted phenyl group, **12a**. Two different products, bearing an ether in 4-position, were also obtained: compound **12c** and **12e**. Also a halogen substituent was demonstrated to be compatible to our reaction conditions, as in compound **12d.**

Different interesting products were successfully prepared: protected mandelonitrile and two different advanced precursors of Denopamine, Tembamide and Aegeline (Scheme 46).[86][87]

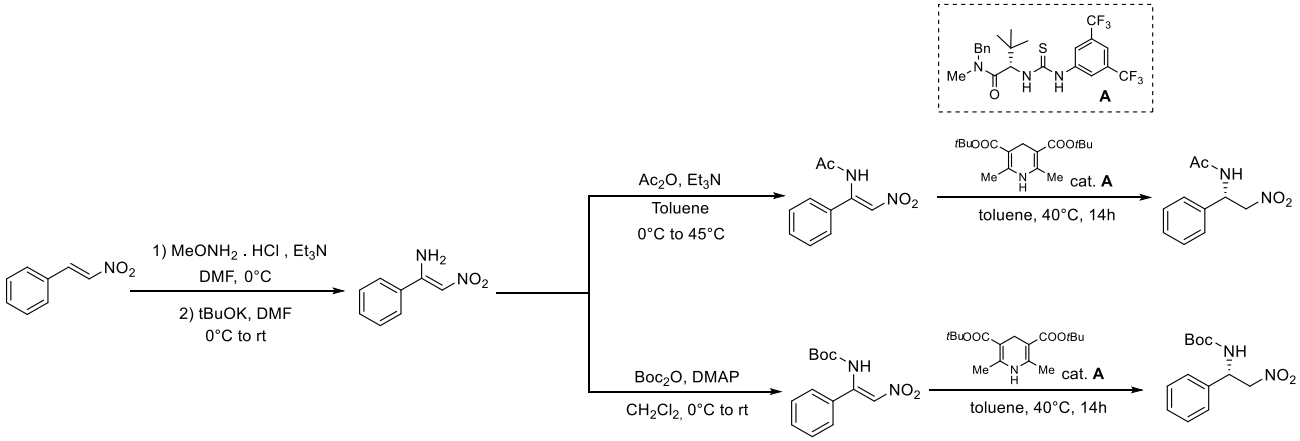


Scheme 46

We then decided to test the influence of a different heteroatom in β-position, and we switched to *N*-substituted nitroalkanes: this kind of substrate should yield optically active α-aminonitriles as product of deoxygenation. This class of compounds play a significant role in organic chemistry, being precursors of chiral α-aminoacids. Moreover, after deprotonation α-amino nitriles also act as valuable and versatile equivalents of acyl anions, and when they lose a cyanide anion under certain conditions, they act as iminium ion equivalents, which play

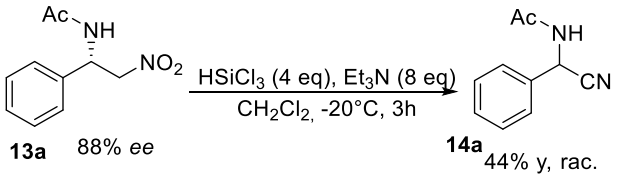
important roles in the synthesis of natural products, heterocycles, and others. Usually, they are synthetized via stereoselective Strecker reaction.[88][43]

Substrates bearing a different protecting group over the amino moiety were tested. They were synthetized starting from β-nitrostyrene, through amination with methoxylamine. The obtained product was protected using acetic anhydride or di-tertbutyl dicarbonate, and subsequently stereoselectively reduced by Hantzsch ester in the presence of the same catalyst used for β-alkyl nitroalkenes (Scheme 47).[75]



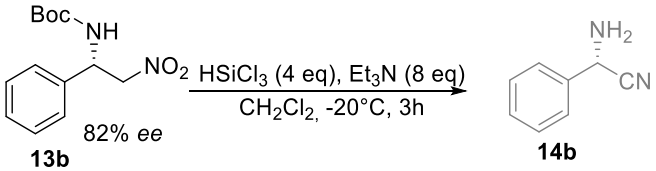
Scheme 47

We started by testing the *N*-acetyl protected substrate **13a**: this would have led to an interesting and versatile class of protected α-aminonitriles. Unfortunately, when it was subjected to our reaction conditions, the desired product was **14a** obtained in 44% yield, while complete racemization occurred (Scheme 48).



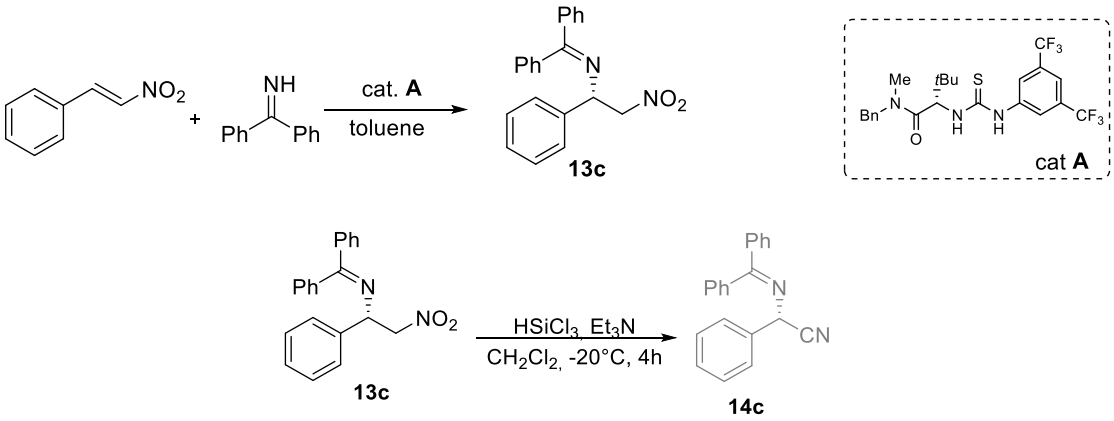
Scheme 48

On the other hand, we knew that the Boc-protecting group of compound **13b** would have not resisted the acidic reaction condition of our synthetic method, and we hoped to be able to recover the deprotected amine. Unfortunately, a very dirty crude was obtained, and it was not possible to identify any product (Scheme 49).



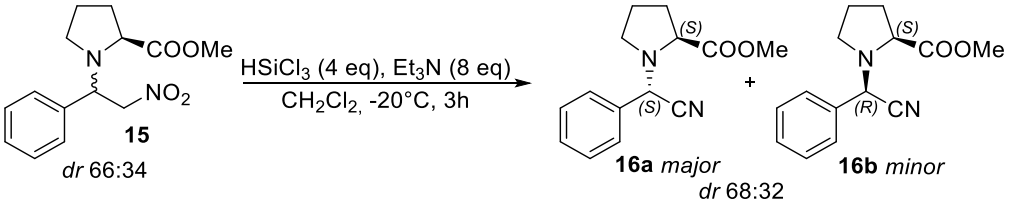
Scheme 49

Subsequently, we tested also compound **13c**, derived from the stereoselective addition of benzophenone imine to nitrostyrene, hoping that it would have been more resistant to acid. However, this was not true, and we recovered only benzophenone at the end of reaction (Scheme 50).



Scheme 50

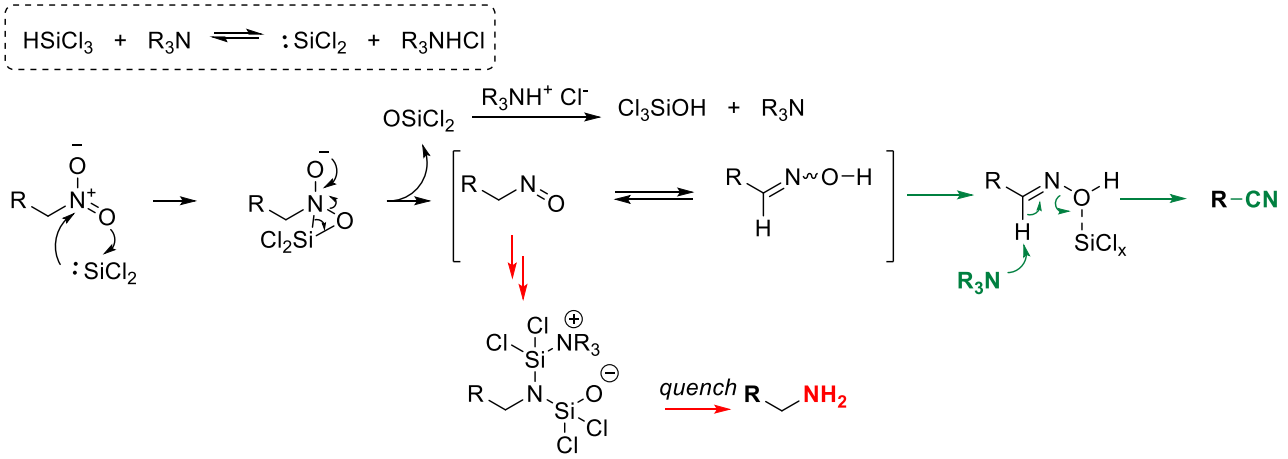
To avoid racemization, we decided to switch to compound **15**, derived from the addition of proline-methylester to nitrostyrene, obtained in a 66:34 diastereomeric ratio: when this substrate was subjected to our procedure, the two diastereomer where isolated separately in 48% yield, with the same diastereomeric ratio of the starting material (Scheme 51).[88] Even if this α-aminonitrile belongs to a less general class of compounds, since the amino moiety is not bearing a cleavable protecting group, it's still an important proof of concept, opening the road to further studies to broaden the versatility of this procedure.



Scheme 51

Preliminary mechanistic hypothesis

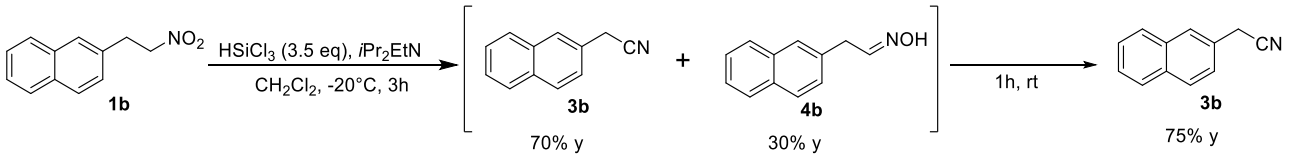
Based on the formation of the oxime, observed in many of the cases presented before, we tried to rationalize a mechanism. In our first hypothesis, the oxime could be an intermediate of the transformation: in fact, the oxime is in tautomeric equilibrium with the nitroso derivative, known to be the product of the first reduction step of the nitro group. From here, two more reduction steps, to afford the corresponding amine, are possible.[89] Alternatively, a different reaction pathway leading to the nitrile, depending on reaction conditions, could be envisaged. Indeed, this proposed pathway, could explain the crucial role of the base in the outcome of the reaction: if the base is involved not only in the formation of the reducing species, as already demonstrated in the mechanistic analysis of the reduction of nitrobenzene reported in 2016,[89] but also in a base promoted dehydration of the oxime, we could account for the importance not only of the number of equivalents, but also of the steric hindrance. This hypothesis was supported also by the fact that the oxime is a known reaction intermediate in many of the methodologies reported in the literature for the transformation from nitro to nitrile.



Scheme 52

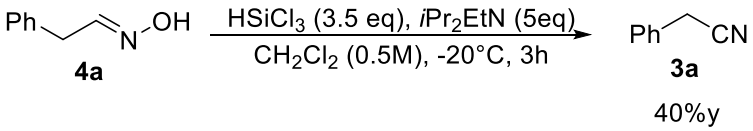
To evaluate the reliability of the proposed reaction mechanism, preliminary experiments were set up.

Since our hypothesis considered the oxime as a reaction intermediate, we tried to push the reaction by increasing the temperature, after the starting material was completely consumed, using naphtylnitroethane **1b** as model substrate, since this nitroalkane gave us the highest yield in the formation of the oxime (30%). Indeed, lower yields were observed for the oxime, detected only in traces, but no significant increment for the formation of the nitrile were achieved (Scheme).



Scheme 53

Subsequently, we synthetized oxime **4a** derived from phenylacetaldehyde and hydroxylamine, and subjected it to our reaction conditions. Only 40% of the corresponding nitrile **3a** was isolated, while the rest was unreacted starting material.

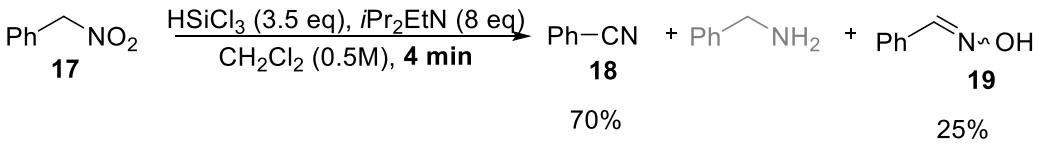


Scheme 54

This result was not conclusive: the yield is quite low, and this can be explained by the fact that the oxime generated in situ during the reaction could be silylated, and thus not present as a free oxime, meaning that reaction conditions are not completely reproduced when starting from the isolated compound.

To further understand our new synthetic methodology, we decided to test a starting material featuring peculiar characteristics, phenylnitromethane **5**. Indeed, the acidity of the protons in α-position is higher, and if a deprotonation of the latter plays a significant role, we could expect to envisage a great difference in the reaction

outcome. We performed a fast screening of reaction conditions, obtaining indeed different results from the previous case.



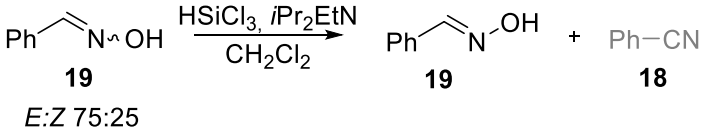
Scheme 55

No trace of amine was found, but 25% of aldoxime was formed. Some issues were encountered also for this substrate in the optimization of the work-up procedure, due to the lability of the oxime to aqueous bases, and the volatility of benzonitrile **18.** It is important to point out that the reaction was complete during the addition of trichlorosilane, meaning that it proceeded much faster than in the case of phenylnitroethane **1**.

We tried once again to promote the dehydration of the oxime in our reaction conditions: adding the base first, followed by trichlorosilane, gave complete recover of the starting oxime, while switching the order ($HSiCl_3$ first, then the base) gave benzonitrile only in traces.

For this particular substrate, only the *E*-oxime was found in the reaction crude, while in all other cases, mixtures of the *E* and *Z* products in various ratios were observed. Since it is reported that the *Z*-oxime is more prone to dehydration and also more kinetically favored,[90] we supposed that the incomplete conversion to benzonitrile was due to isomerization.

Hence, we synthetized a mixture of *E*/*Z* 75/25, and submitted that to dehydration with trichlorosilane, but only complete isomerization to the *E* isomer was observed.



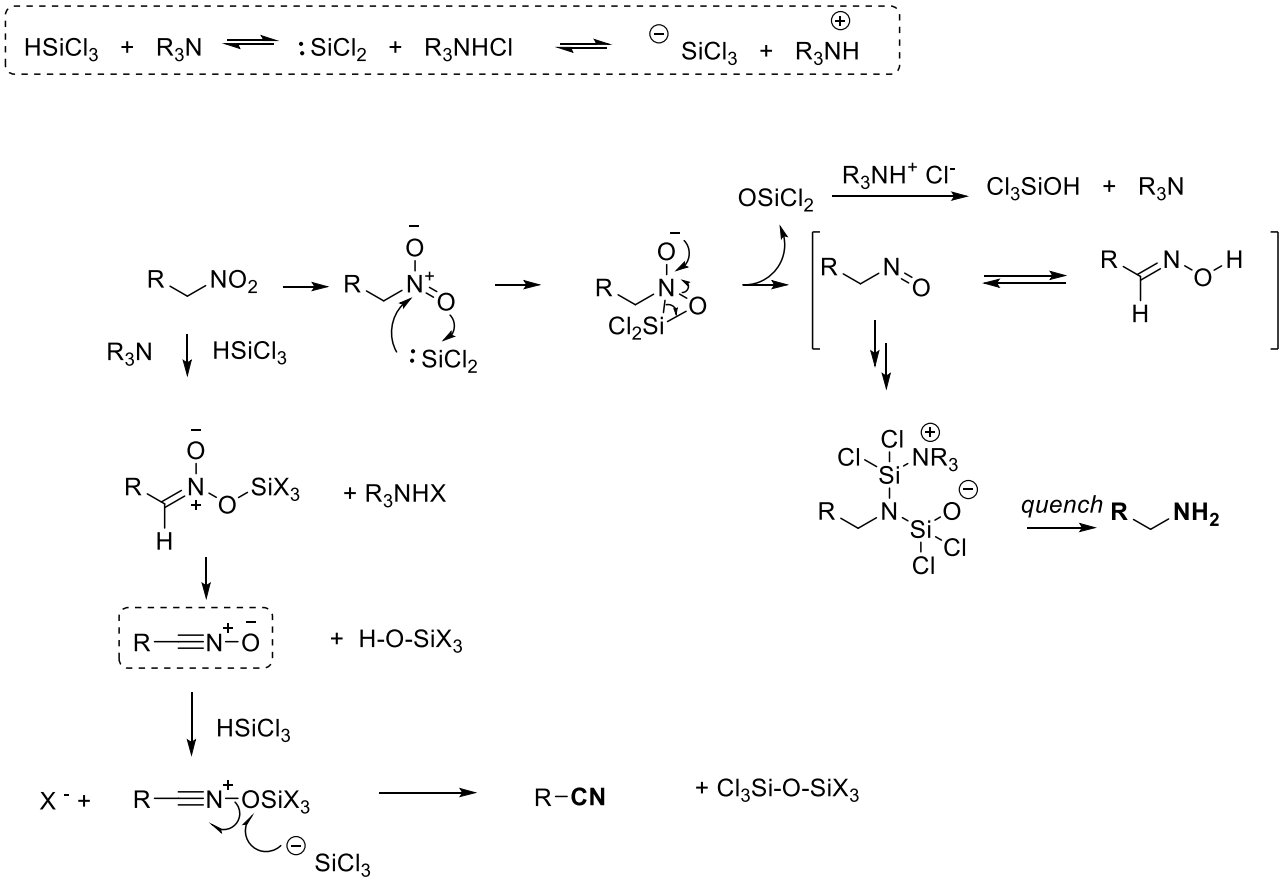
Scheme 56

We decided to abandon this substrate, since it is clear that the different structure plays a crucial role in our reaction conditions, and it is possible that this influences also the mechanism of our reaction.

Since our mechanistic hypothesis was not demonstrated in a conclusive way, we have also considered alternative pathways. For example, the deprotonation of the silylated nitro alkane could lead to the formation of nitrileoxide; the synthesis of nitrile oxides from nitro alkanes in the presence of dehydrating agents has been described.[91,92] Therefore, under the present conditions, with an excess of a tertiary amine and trichlorosilyl derivative, the formation *in situ* of a nitriloxide cannot be excluded. Then, the reaction of such intermediate with a Si (II) species could account for the reductive step that generates the nitrile with the formation of a silyl-oxi species and reoxidation of the Si(II) atom to Si(IV) (Scheme 57).

However, the formation of a nitrileoxide intermediate is only a preliminary hypothesis that must be further investigated, for example by running some control experiments aimed to trap the nitrileoxide through a 1,3-dipolar cycloaddition.[93] In this alternative mechanism, the oxime would not be an intermediate for the formation

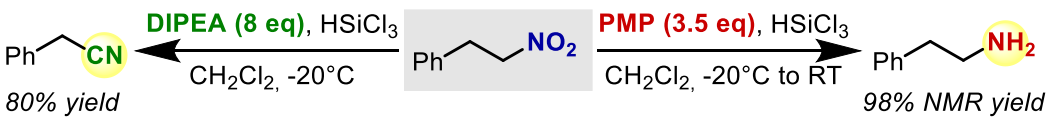
of the nitrile, and this could explain why its dehydration in our reaction conditions proceeds poorly. Finally, the possibility that the reaction occurs via both the proposed mechanisms cannot be ruled out.



Scheme 57

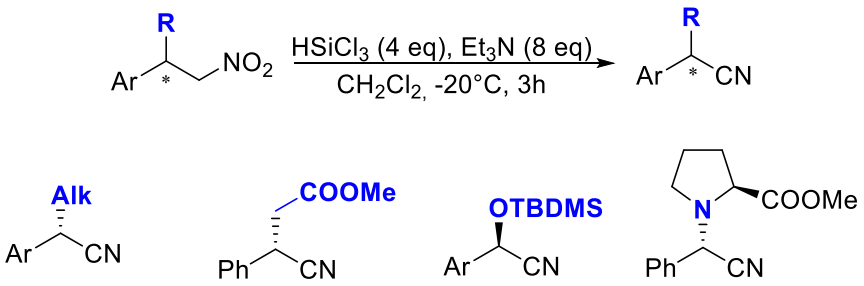
Conclusions

In summary, a new chemoselective divergent methodology for the reduction of aliphatic nitro compounds into nitriles and amines has been developed. Best reaction conditions for the selective formation of the amine or the nitrile were established; for the deoxygenation of nitroalkanes to give the corresponding nitrile, 8 equivalents of diisopropylethylamine are needed, in combination with 3.5 equivalents of trichlorosilane, while for the reduction into amine, a more hindered base, like PMP, in stoichiometric amount is needed (3.5 equivalents) in the presence of the same amount of trichlorosilane (Scheme 58). Also, the work-up of the reaction for the isolation of phenylethylamine was optimized, and a Boc-protection was found as best option.



Scheme 58

The protocol proved to be convenient for the synthesis of optically active nitriles starting from chiral nitroalkanes. The ability to access a range of optically active nitriles through a sequence that involves catalytic enantioselective reduction of nitroalkanes, or stereoselective Michael addition, followed by conversion into nitrile as described above, considerably expands the scope of such approaches to the synthesis of functionalized chiral molecules. The protocol provides access to a class of compounds that are otherwise not easily accessed by known methods in catalytic stereoselective synthesis (Scheme 59). Salient features of the method include the use of inexpensive bulk chemicals and avoidance of heavy metals, meaning the exlusion of potential contamination by metal impurities in the final product.



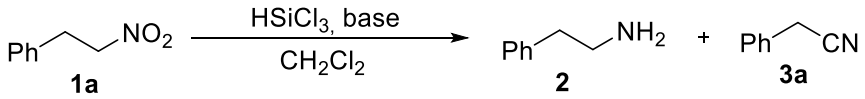
Scheme 59

Experimental section

Materials and methods

Reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F_{254} pre-coated glass plates (0.25 mm thickness) and visualized using UV light. Flash chromatography was carried out on silica gel (230-400 mesh). Proton NMR spectra were recorded on spectrometers operating at 300 MHz (Bruker Avance 300); proton chemical shifts are reported in ppm (δ) relative to tetramethylsilane (TMS, $CDCl_3$: δ=7.26 ppm). ^{13}C-NMR spectra were recorded on 300 MHz spectrometers (Bruker Avance 300) operating at 75 MHz, with complete proton decoupling; carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, : δ = 77.0 ppm). ^{19}F-NMR spectra were recorded on 300 MHz spectrometers (Bruker Avance 300) operating at 282.1 MHz; fluorine chemical shifts are reported in ppm (δ) relative to $CFCl_3$ with the respective solvent resonance as the internal standard ($CFCl_3$: δ = 77.0 ppm). Mass spectra and accurate mass analysis were carried out on a VG AUTOSPEC- M246 spectrometer (double-focusing magnetic sector instrument with EBE geometry) equipped with EI source or with LCQ Fleet ion trap mass spectrometer, ESI source, with acquisition in positive ionization mode in the mass range of 50-2000 m/z. Optical rotations were obtained on a Perkin-Elmer 241 polarimeter at 589 nm using a cell with a length of 1 dm. For HPLC analyses on chiral stationary phase, to determine enantiomeric excesses, it was used an Agilent Instrument Series 1100. The specific operative conditions for each product are reported from time to time. Commercially available $HSiCl_3$ was freshly distilled before use.

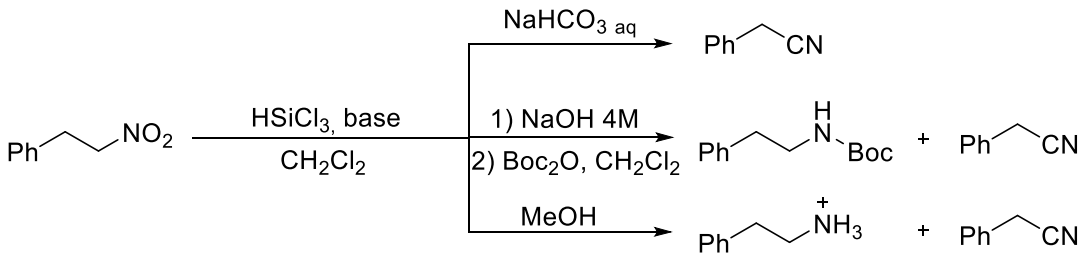
Reaction conditions optimization



For the optimization of reaction conditions, an internal standard was used, and the yields were calculated via GC injection (biphenyl used as internal standard) or via ^{1}H-NMR of the crude (1,3,5-trimethoxybenzene used as internal standard). We encountered several problems in the detection and isolation of the amine, after an aqueous basic workup, probably due to the difficult cleavage of the N-Si bond present at the end of reaction and to the hydrophilicity of phenylethylamine. We verified the mass balance of the reaction using an internal standard and performing ^{1}H-NMR of the reaction mixture in deuterated dichloromethane. Since no other by-products were formed, and the mass balance between unreacted starting material, nitrile and amine was 100%, for all the subsequent tests the yield for the amine was calculated via GC injection as:

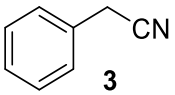
$$\text{yield NH}_2 = \frac{[\text{mmol } SM - (mmol\ CN + mmol\ unSM)]}{\text{mmol SM}} * 100\%$$

were SM is starting material, CN is the nitrile, unSM is unreacted starting material.



Experimental procedure: in a round bottomed flask phenyl nitroethane (1 eq.), the proper internal standard (0.3 eq.) and the desired base in the proper amount (see Table 1-3), were dissolved into a portion of dry dichloromethane (2/3, final concentration 0.2-0.25 M) under magnetic stirring and nitrogen atmosphere. The reaction mixture was cooled to the desired temperature and a solution of $HSiCl_3$ in the remaining solvent was added dropwise over 2 minutes. The addition is exothermic and, independently from final reaction temperature, was always performed at -20°C. After stirring for the desired time, the reaction was quenched. Three different quenching were used:

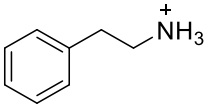
- To isolate the nitrile, a saturated aqueous solution of $NaHCO_3$ was slowly added, until basic pH was reached. The organic phase was directly injected into GC after dilution with dichloromethane. In some cases, the aqueous phase was extracted with CH_2Cl_2, the combined organic phases dried over Na_2SO_4, filtered and then evaporated under reduced pressure. Phenylacetonitrile was isolated by column chromatography to confirm the GC yield.
- To isolate the amine, a 4M solution of NaOH was slowly added, until basic pH was reached. Then, a solution of *ditert*-butyl dicarbonate (1 eq.) in dichloromethane (0.1 M) was added dropwise and the reaction mixture was stirred at room temperature for 24 hours. The organic phase was separated, and the aqueous layer was extracted 3 times with dichloromethane. The combined organic layers were washed with brine, dried over Na_2SO_4, and the solvent evaporated *in vacuo*. *N*-Boc-phenyltethylamine was isolated by column chromatography.
- to confirm the yield of the amine at the end of reaction time, MeOH was slowly added, followed by removal of the volatiles under reduced pressure. ^{1}H-NMR of the crude allowed to calculate the yield of each product, thanks to the internal standard.



3

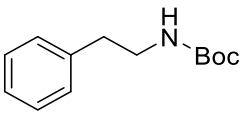
The best results were achieved using 8 eq. of *i*Pr_2EtN, at -20°C for 3 h. The product was purified by column chromatography (95:5 hexane/ ethyl acetate). All analytical data are in agreement with literature. [94] GC yield = 80%; isolated yield = 80%.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.38 (m, 5H), 3.70 (s, 2H).



The best results were achieved using 3.5 eq. of pentamethyl piperidine, at room temperature for 3 h. After quenching with MeOH, the product was not isolated, and the yield calculated via NMR of the crude performed in deuterated methanol, with 1,3,5-trimethoxybenzene. All analytical data are in agreement with literature.[95] NMR yield= 98%.

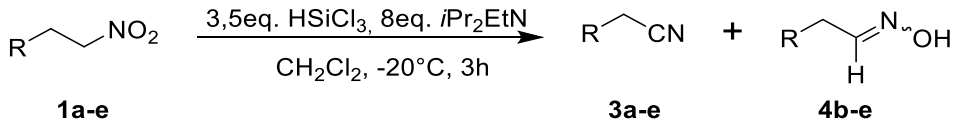
^{1}H NMR (300 MHz, CD_3OD) δ: 7.24-7.06 (m, 5H), 3.05-2.96 (m, 2H), 2.94-2.87 (m, 2H).



The compound was obtained after column chromatography (95:5 hexane: ethyl acetate) as a white solid. All analytical data are in agreement with literature.[96] Isolated yield= 50% (over 2 steps).

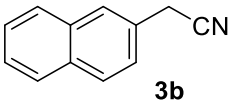
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.26 (t, 2H), 7.19-7.14 (m, 3H), 4.72 (brs, 1H), 3.38 (t, 2H), 2.81 (t, 2H), 1.46 (s, 9H).

General procedure for synthesis of nitriles starting from achiral compounds



1a-e **3a-e** **4b-e**

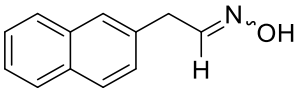
In a round bottomed flask the appropriate nitro-compound (1 eq.) and *N,N*-diisopropylethylamine were dissolved into a portion of the dry dichloromethane (2/3, final concentration 0.25 M) under magnetic stirring and nitrogen atmosphere. The reaction mixture was cooled to -20°C and a solution of $HSiCl_3$ in the remaining solvent was added dropwise over 2 minutes. After stirring for 3h, the reaction mixture was quenched with a saturated solution of $NaHCO_3$, slowly added. The aqueous phase was separated and extracted 3 times with dichloromethane. The combined organic phases were dried over Na_2SO_4, filtered and then evaporated under reduced pressure. The resulting mixture was purified by column chromatography.



3b

The product was purified by column chromatography (9:1 hexane/ ethyl acetate) and obtained as a yellow solid in 70% yield. All analytical data are in agreement with literature.[97]

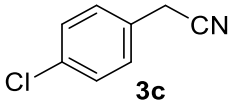
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.89-7.84 (m, 4H), 7.56-7.53 (m, 2H), 7,42 (dd, 1H), 3.92 (s, 2H).



4b

The product was purified by column chromatography (9:1 hexane/ ethyl acetate) and obtained as a yellow solid in 30% yield. All analytical data are in agreement with literature.

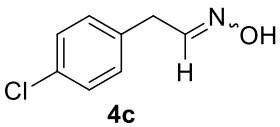
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.89-7.84 (m, 4H), 7.56-7.53 (m, 3H), 7.28 (dd, 1H), 3.95 (brs, 1H), 3.74 (d, 2H).



3c

The product was purified by column chromatography (9:1 hexane/ ethyl acetate) and obtained as yellowish oil in 51% yield. All analytical data are in agreement with literature.[98]

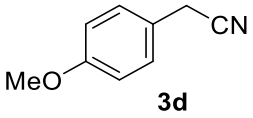
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39 (d, J = 9 Hz, 2H), 7.29 (d, J = 9 Hz, 2H), 3.72 (s, 2H).



4c

The product was purified by column chromatography (9:1 hexane/ ethyl acetate) and obtained as a yellowish oil in 22% yield. All analytical data are in agreement with literature.[99]

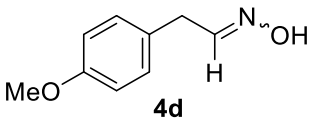
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.53 (t, 1H), 7.39-7.29 (m, 4H), 6.94 (brs, 1H), 3.76 (dd, J = 6 Hz, 2H).



3d

The product was purified by column chromatography (8:2 hexane/ ethyl acetate) and obtained as a white solid in 66% yield. All analytical data are in agreement with literature.[100]

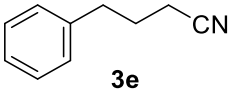
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.26 (d, J = 6Hz, 2H), 6.93 (d, J = 9 Hz, 2H), 3.82 (s, 3H), 3.70 (s, 2H).



4d

The product was purified by column chromatography (8:2 hexane/ ethyl acetate) and obtained in 11% yield. All analytical data are in agreement with literature.[101]

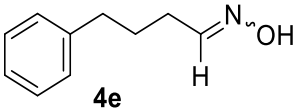
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.55 (t, 1H), 7.18 (m, 2H), 6.90-6.86 (m, 2H), 3.82 (s, 3H), 3.72 (d, 1H), 3.50 (d, 1H).



3e

Synthetized using Et_3N as base. The product was purified by column chromatography (9:1 hexane/ ethyl acetate) and obtained as a colourless oil in 66% yield. All analytical data are in agreement with literature.[102]

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39-7.23 (m, 5H), 2.81 (t, J = 7.4 Hz, 2H), 2.33 (t, J = 7.4 Hz, 2H), 2,01 (qui, 2H).

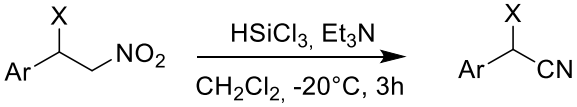


4e

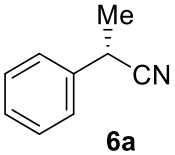
Synthetized using Et_3N as base. The product was purified by column chromatography (9:1 hexane/ ethyl acetate) and obtained in 16% yield. All analytical data are in agreement with literature.[103]

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.49 (t, J = 6 Hz, 1H); 7.33-7.19 (m, 4H); 6.79 (brs, 1H); 2.71 (m, 2H); 2.44 (q, J = 2.3, 1H); 2.30 (q, J = 7.08, 1H); 1.91 (m, 2H).

<u>General procedure for the synthesis of enantioenriched nitriles</u>



In a round bottom flask the appropriate nitro-compound (1 eq.) and triethylamine (8 eq) were dissolved into a portion of the dry dichloromethane (2/3, final concentration 0.25 M) under magnetic stirring and nitrogen atmosphere. The reaction mixture was cooled to -20°C and a solution of $HSiCl_3$ in the remaining solvent was added dropwise over 2 minutes. After stirring for 3h, the reaction mixture was quenched, unless otherwise stated, with a saturated solution of $NaHCO_3$ which was slowly added. The crude mixture was extracted with CH_2Cl_2, dried over Na_2SO_4, filtered and the solvent removed under reduced pressure.



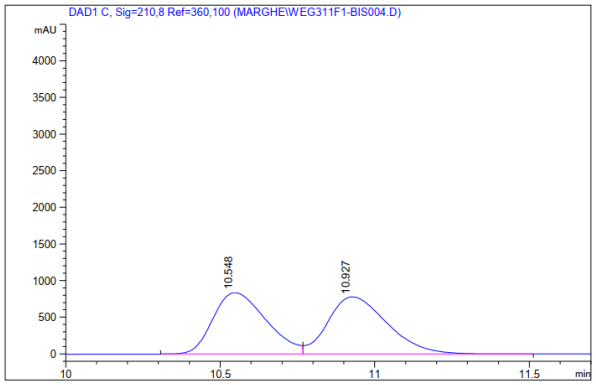
6a

The product was purified by column chromatography (95:5 hexane/ ethyl acetate) and obtained as a colourless oil in 38% yield and 90% *ee.* All analytical data are in agreement with literature.[104]

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.41-7.34 (m, 5H), 3.91 (q, 1H), 1.68 (d, 3H).

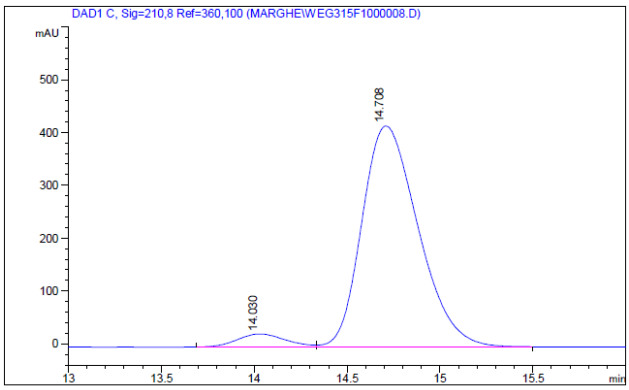
$[\alpha]_D^{26}$= -31.1° (c=5.6 mg/ml, λ=589 nm, $CHCl_3$, *ee*=90%).

The enantiomeric excess was determined by HPLC on chiral stationary phase with LUX CELLULOSE-3 3µ column: eluent Hexane/*i*PrOH = 99/1, flow rate 1 mL/min, λ=210 nm, τ_{minor} = 14 min, τ_{major} = 15 min.



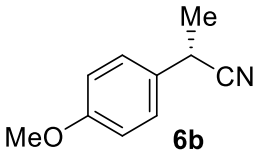
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	10.548	BV	0.187	9987.122	48.908	
2	10.927	VB	0.206	10433.260	51.092	



Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	14.030	BV	0.278	445.857	4.818	
2	14.708	VB	0.326	8808.974	95.182	



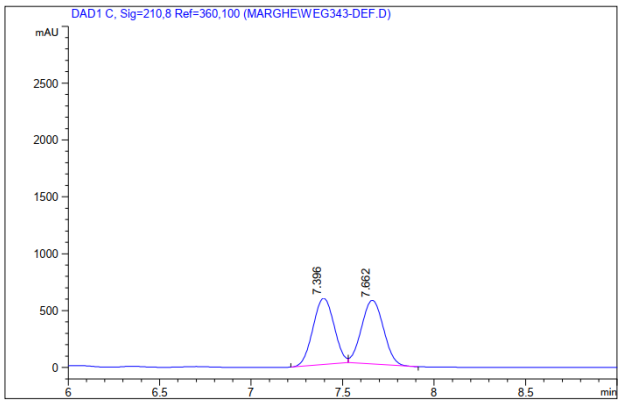
6b

The product was purified by column chromatography (98:2 hexane/ ethyl acetate) and obtained as a yellow oil in 54% yield and 84% *ee.* All analytical data are in agreement with literature.[105]

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.26 (d, 2H), 6.90 (d, 2H), 3.85 (q, 1H), 3.81 (s, 3H), 1.62 (d, 3H).

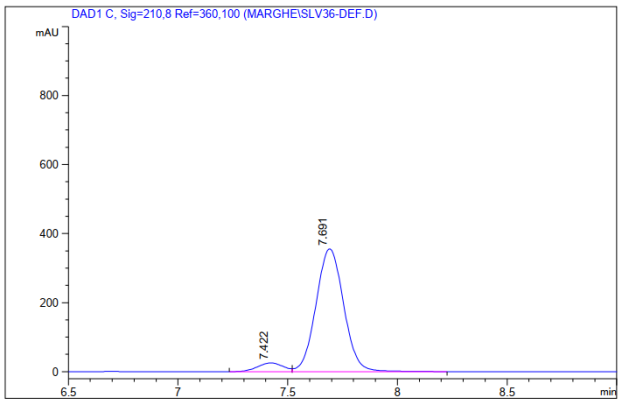
$[\alpha]_D^{26}$= +17.6° (c=3.48, λ=589 nm, $CHCl_3$, *ee*=84%).

The enantiomeric excess was determined by HPLC on chiral stationary phase with LUX CELLULOSE-1 3µ column: eluent Hexane/*i*PrOH = 95/5, flow rate 0.8 mL/min, λ=210 nm, τ_{minor} = 7 min, τ_{major} = 8 min.



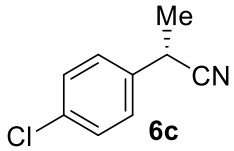
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	7.396	MM	0.133	4659.292	50.183	
2	7.662	MM	0.138	4625.362	49.817	



Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	7.422	BV	0.130	208.778	6.238	
2	7.691	VB	0.139	3137.839	93.762	



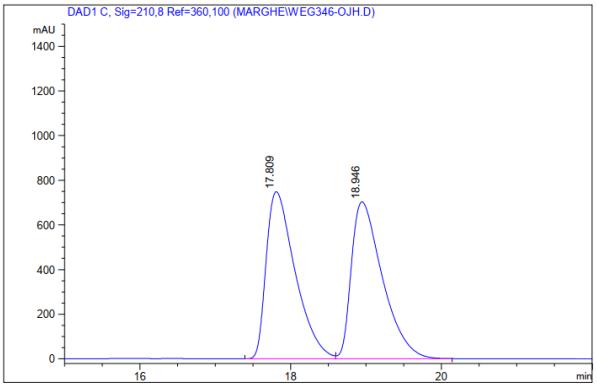
6c

The product was purified by column chromatography (98:2 hexane/ ethyl acetate) and obtained as a colourless oil in 42% yield and 75% *ee.* All analytical data are in agreement with literature.[106]

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39 (d, 2H), 7.31 (d, 2H), 3.90 (q, 1H), 1.65 (d, 3H).

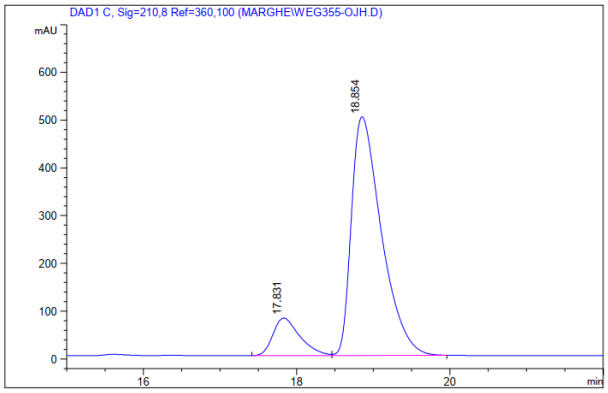
$[\alpha]_D^{26}$= -12.4 (c=0.61, λ=589 nm, $CHCl_3$, *ee*=75%).

The enantiomeric excess was determined by HPLC on chiral stationary phase with chiralpack OJ-H column: eluent Hexane/*i*PrOH = 9/1, flow rate 0.8 mL/min, λ=210 nm, τ_{minor} = 18 min, τ_{major} = 19 min.



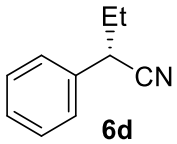
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	17.809	BV	0.404	20014.742	49.831	
2	18.946	VB	0.437	20150.488	50.169	



Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	17.831	BV	0.368	1920.572	12.377	
2	18.854	VB	0.411	13596.683	87.623	



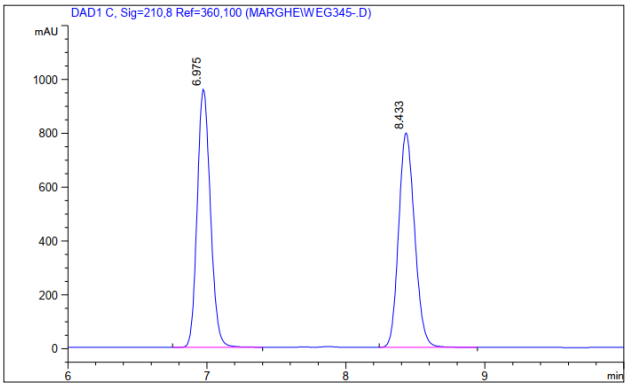
6d

The product was purified by column chromatography (98:2 hexane/ ethyl acetate) and obtained as a colourless oil in 52% yield and 80% *ee.* All analytical data are in agreement with literature.[105]

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40-7.32 (m, 5H), 3.74 (t, 1H), 1.95 (dt, 2H), 1.08 (t, 3H).

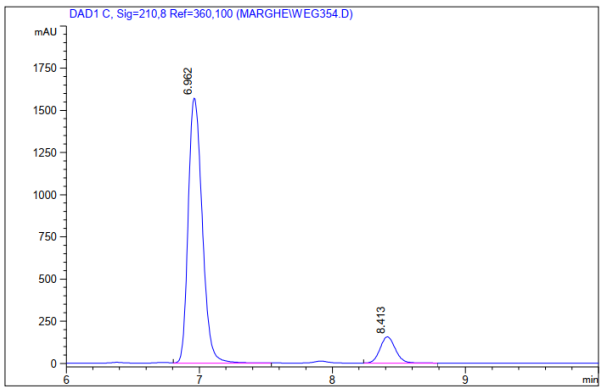
$[\alpha]_D^{26}$= -49.5° (c=14 mg/ml, λ=589 nm, $CHCl_3$, *ee*=80%).

The enantiomeric excess was determined by HPLC on chiral stationary phase with chiralpack AS-3 column: eluent Hexane/*i*PrOH = 9/1, flow rate 1 mL/min, λ=210 nm, τ_{minor} = 8 min, τ_{major} = 7 min.



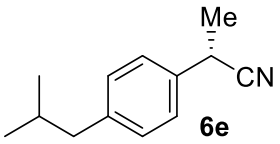
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	6.975	VB	0.103	6332.027	49.860	
2	8.433	BB	0.123	6367.540	50.140	



Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	6.962	VB	0.115	11471.564	90.212	
2	8.413	BB	0.123	1244.654	9.788	



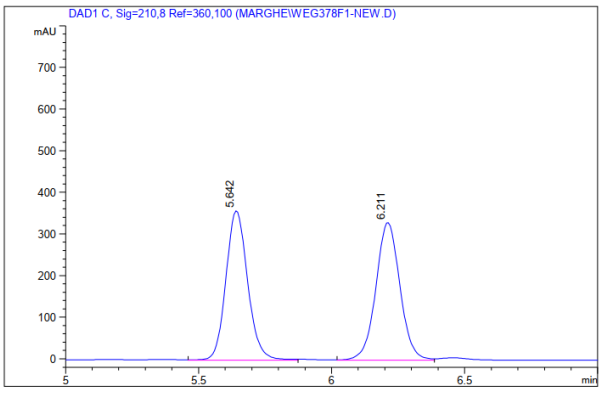
6e

The product was purified by column chromatography (99:1 hexane/ ethyl acetate) and obtained as a light yellow oil in 57% yield and 85% *ee.* All analytical data are in agreement with literature.[105]

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.30-7.20 (d, 2H), 7.16 (d, 2H), 3.87 (q, 1H), 2.47 (d, 2H), 1.91-1.79 (m, 1H), 1.63 (d, 3H), 0.90 (d, 6H).

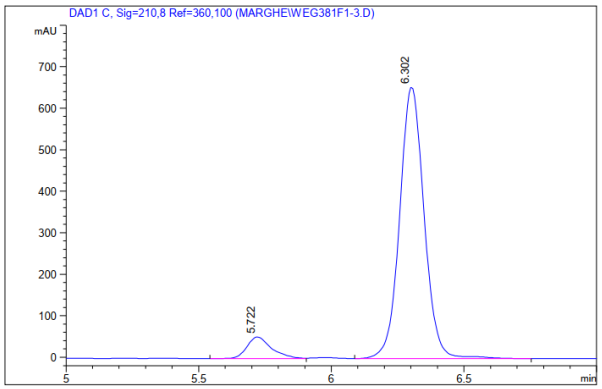
$[\alpha]_D^{26}$= -22.0° (c=2.7, λ=589 nm, $CHCl_3$, *ee*=85%).

The enantiomeric excess was determined by HPLC on chiral stationary phase with chiralpack AS-3 column: eluent Hexane/*i*PrOH = 95/5, flow rate 1 mL/min, λ=210 nm, τ_{minor} = 5 min, τ_{major} = 6 min.



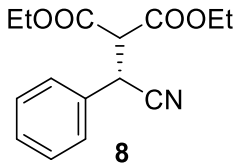
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	5.642	VB	0.088	2040.756	49.511	
2	6.211	BV	0.097	2081.026	50.489	



Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	5.722	VV	0.098	338.564	7.456	
2	6.302	VB	0.099	4202.132	92.544	

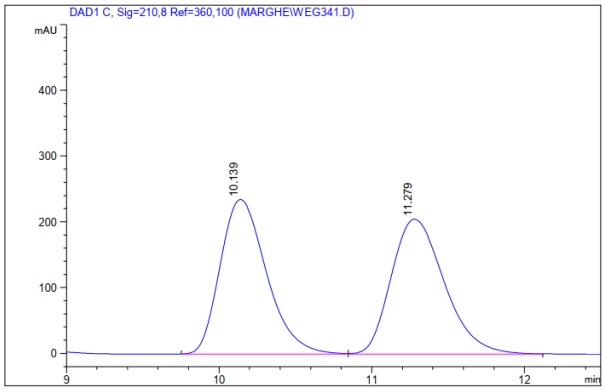


8

The quenching was performed with slow addition of methanol, followed by removal of all volatiles. The crude was triturated in ethyl acetate, the insoluble triethylamine hydrochloric salt removed by filtration, and the solvent removed under reduced pressure. The product was purified by column chromatography (98:2 hexane/ ethyl acetate) and obtained as white solid. All analytical data are in agreement with literature.[107]

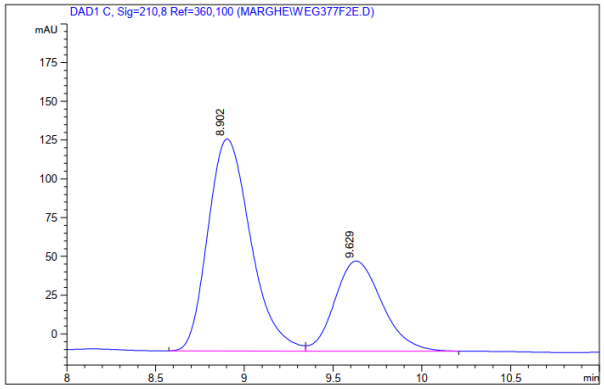
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.36 (br s, 5H), 4.52 (d, 1H), 4.27 (q, 2H), 4.03 (q, 2H), 3.87 (d, 1H), 1.28 (t, 3H), 1.07 (t, 1H).

The enantiomeric excess was determined by HPLC on chiral stationary phase with chiralcel OD-H column: eluent Hexane/*i*PrOH = 9/1, flow rate 0.8 mL/min, λ=210 nm, τ_{minor} = 10 min, τ_{major} = 9 min.



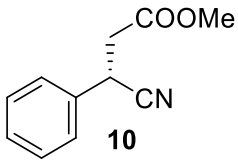
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	10.139	BV	0.328	4963.921	50.052	
2	11.279	VB	0.380	4953.597	49.948	



Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	8.902	BV	0.263	2289.607	68.037	
2	9.629	VB	0.290	1075.650	31.963	



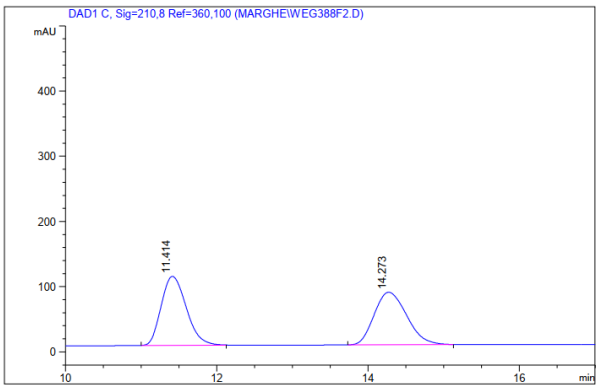
10

Synthetized starting from 4-nitro-3-phenyl butanoic acid, or methyl 4-nitro-3-phenyl butanoate. In both cases the quenching was performed with slow addition of methanol, followed by removal of all volatiles. The crude was triturated in ethyl acetate, the insoluble triethylamine hydrochloric salt removed by filtration, and the solvent removed under reduced pressure. The product was purified by column chromatography (95:5 hexane/ ethyl acetate) and obtained as white solid. All analytical data are in agreement with literature.[108]

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.30-7.20 (d, 2H), 7.16 (d, 2H), 3.87 (q, 1H), 2.47 (d, 2H), 1.91-1.79 (m, 1H), 1.63 (d, 3H), 0.90 (d, 6H).

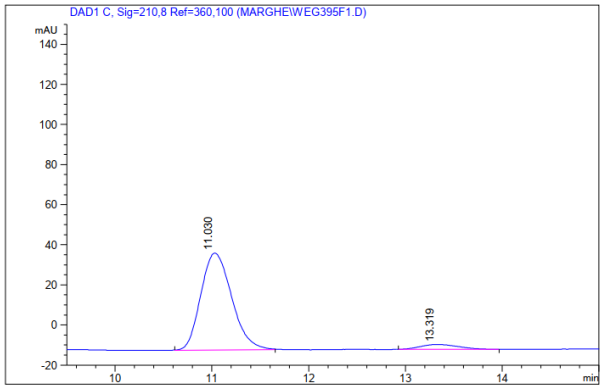
$[\alpha]_D^{26}$= +6.7° (c=2.1, λ=589 nm, $CHCl_3$, *ee*=81.5%).

The enantiomeric excess was determined by HPLC on chiral stationary phase with chiralcel OD-H column: eluent Hexane/*i*PrOH = 9/1, flow rate 1 mL/min, λ=210 nm, τ_{minor} = 13 min, τ_{major} = 11 min.



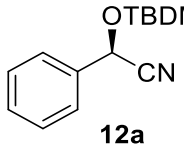
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	11.414	BB	0.364	2432.561	50.272	
2	14.273	BB	0.476	2406.230	49.728	



Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	11.030	BB	0.351	1070.716	94.059	
2	13.319	BB	0.337	67.632	5.941	



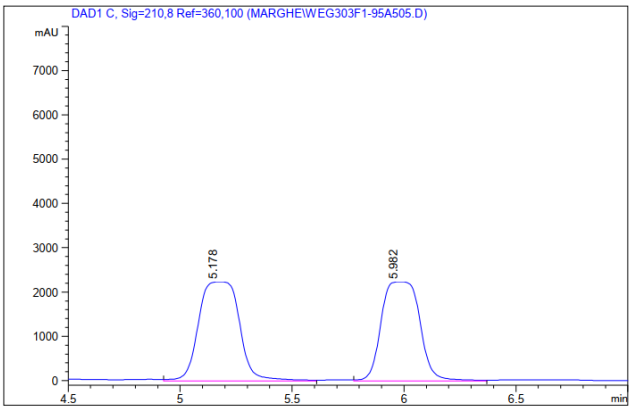
12a

The product was purified by column chromatography (9:1 hexane/ ethyl acetate) and obtained as a colourless oil in 79% yield and 87% *ee*. All analytical data are in agreement with literature.[109]

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.49-7.42 (m, 5H), 5.55 (s, 1H), 0.97 (s, 9H), 0.26 (s, 3H), 0.18 (s, 3H).

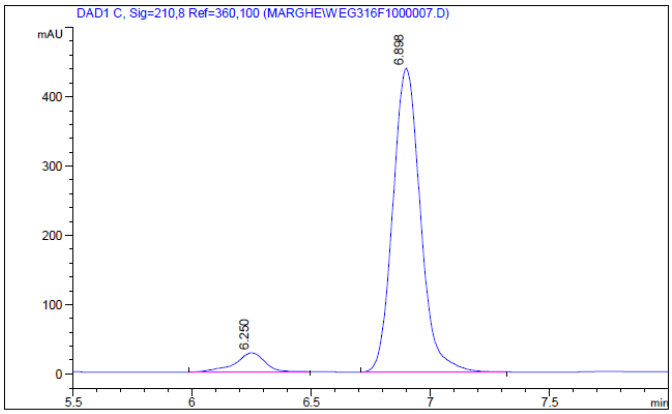
$[\alpha]_D^{26}$= +11.8° (c=2.5, λ=589 nm, $CHCl_3$, *ee*=87%).

The enantiomeric excess was determined by HPLC on chiral stationary phase with LUX CELLULOSE-3 3μ column: eluent Hexane/*i*PrOH = 95/5, flow rate 0.8 mL/min, λ=210 nm, τ_{minor} = 6 min, τ_{major} = 7 min.



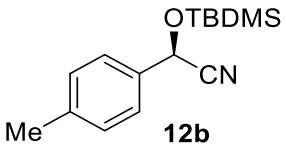
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	5.178	VV	0.203	28123.168	51.495	
2	5.982	VV	0.190	26490.068	48.505	



Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	6.250	BB	0.130	248.529	6.596	
2	6.898	BB	0.126	3519.536	93.404	



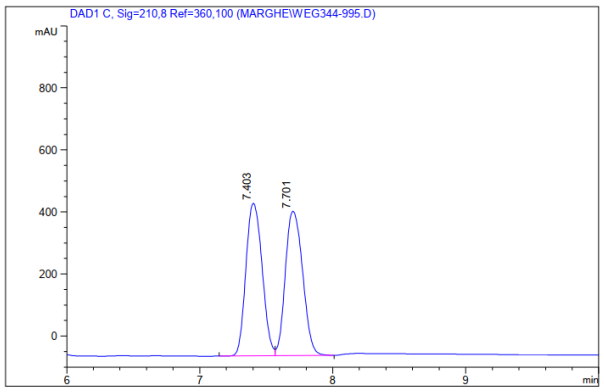
12b

The product was purified by column chromatography (98:2 hexane/ ethyl acetate) and obtained as a white solid in 79% yield and 89% *ee*. All analytical data are in agreement with literature.[109]

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37 (d, 2H), 7.24 (d, 2H), 5.50 (s, 1H), 2.39 (s, 3H), 0.97 (s, 9H), 0.23 (s, 3H), 0.16 (s, 3H).

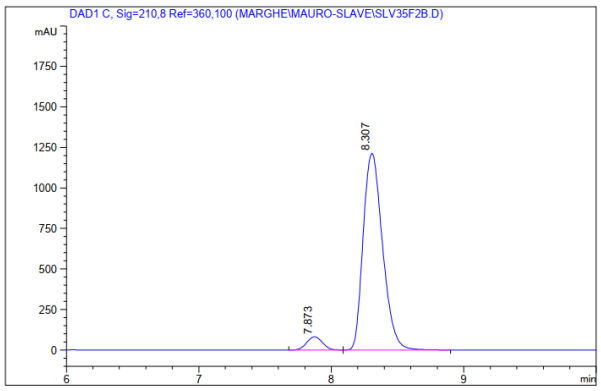
$[\alpha]_D^{26}$= +16.2° (c=0.5, λ=589 nm, $CHCl_3$, *ee*=89%).

The enantiomeric excess was determined by HPLC on chiral stationary phase with LUX CELLULOSE-1 3µ column: eluent Hexane/*i*PrOH = 99.5/0.5, flow rate 0.8 mL/min, λ=210 nm, τ_{minor} = 7 min, τ_{major} = 8 min.



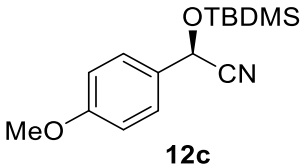
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	7.403	BV	0.137	4185.775	49.842	
2	7.701	VV	0.146	4212.333	50.158	



Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	7.873	BV	0.132	686.697	5.261	
2	8.307	VB	0.159	12366.974	94.739	



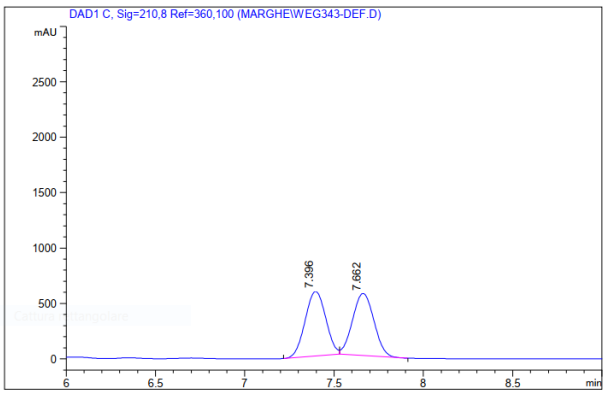
12c

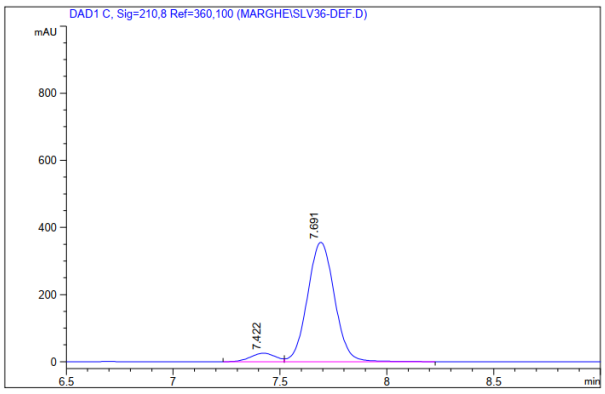
The product was purified by column chromatography (98:2 hexane/ ethyl acetate) and obtained as a colourless oil in 70% yield and 87% *ee*. All analytical data are in agreement with literature.[109]

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40 (d, 2H), 6.95 (d, 2H), 5.48 (s, 1H), 3.85 (s, 3H), 0.95 (s, 9H), 0.23 (s, 3H), 0.15 (s, 3H).

$[\alpha]_D^{26}$= +11.4° (c=2.6, λ=589 nm, $CHCl_3$, *ee*=87%).

The enantiomeric excess was determined by HPLC on chiral stationary phase with LUX CELLULOSE-1 3µ column: eluent Hexane/*i*PrOH = 95/5, flow rate 0.8 mL/min, λ=210 nm, τ_{minor} = 7 min, τ_{major} = 8 min.



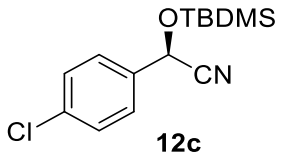


Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	7.396	MM	0.133	4659.292	50.183	
2	7.662	MM	0.138	4625.362	49.817	

Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	7.422	BV	0.130	208.778	6.238	
2	7.691	VB	0.139	3137.839	93.762	



12c

The product was purified by column chromatography (98:2 hexane/ ethyl acetate) and obtained as a colourless oil in 62% yield and 85% *ee*. The product was completely characterized.

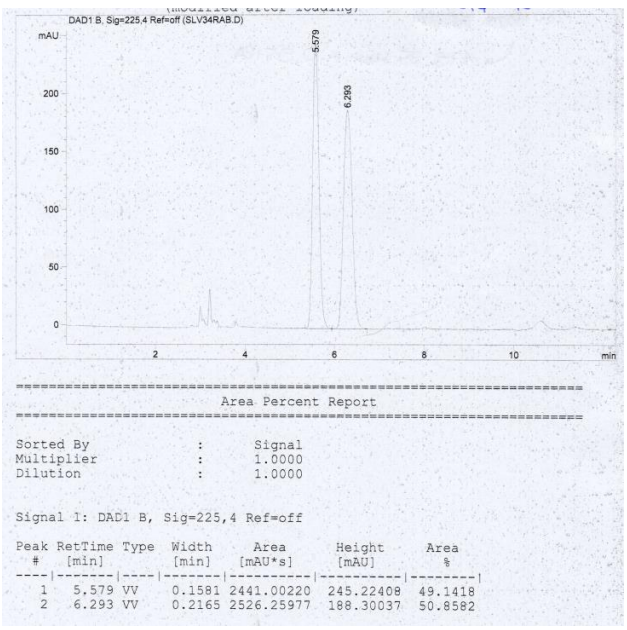
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.42 (brs, 5H), 5.51 (s, 1H), 0.96 (s, 9H), 0.25 (s, 3H), 0.18 (s, 3H).

^{13}C NMR (90 MHz, $CDCl_3$) δ: 135.27, 135.07, 129.18, 127.48, 118.89, 63.39, 25.52, 18.17, -5.06, -5.19.

HRMS (ESI) m/z calculated for $C_{14}H_{19}NOClSi$ $[M-H]^-$: 280.0924, found: 280.0925.

$[\alpha]_D^{26}$= +5.28° (c=1.7, λ=589 nm, $CHCl_3$, *ee*=85%).

The enantiomeric excess was determined by HPLC on chiral stationary phase with LUX CELLULOSE-2 3µ column: eluent Hexane/*i*PrOH = 99.4/0.6, flow rate 1 mL/min, λ=225 nm, t_{minor} = 7 min, t_{major} = 6 min.

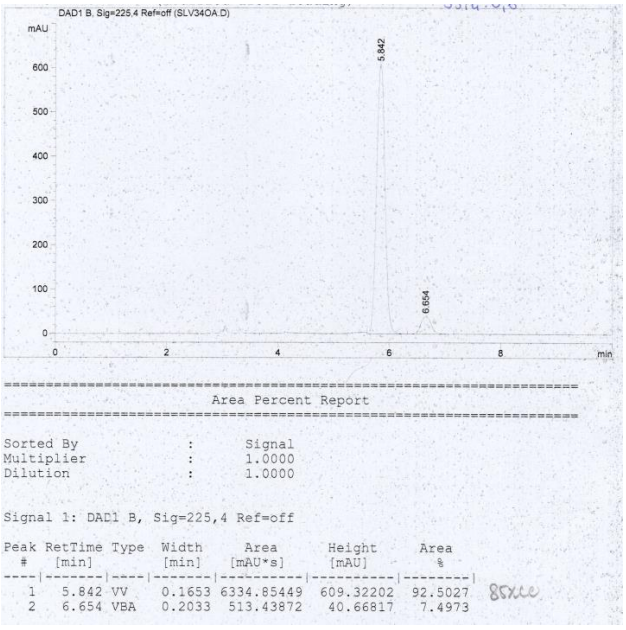


Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: DAD1 B, Sig=225,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.579	VV	0.1581	2441.00220	245.22408	49.1418
2	6.293	VV	0.2165	2526.25977	188.30037	50.8582

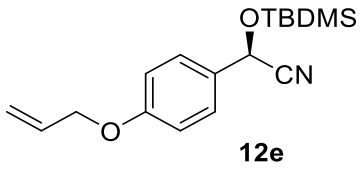


Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: DAD1 B, Sig=225,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.842	VV	0.1653	6334.85449	609.32202	92.5027
2	6.654	VBA	0.2033	513.43872	40.66817	7.4973



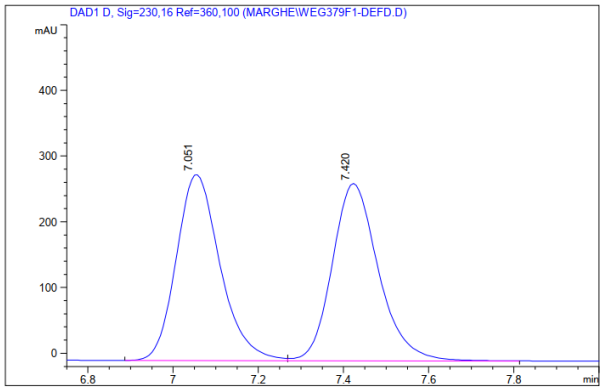
12e

The product was purified by column chromatography (98:2 hexane/ ethyl acetate) and obtained as a colourless oil in 54% yield and 75% *ee*. All analytical data are in agreement with literature.[86]

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.38 (d, 2H), 6.95 (d, 2H), 5.47-5.31 (m, 1 H), 5.47 (s, 1H), 5.41-5.31 (m, 1H), 5.57 (d, 2H), 0.95 (s, 9H), 0.23 (s, 3H), 0.15 (s, 3H).

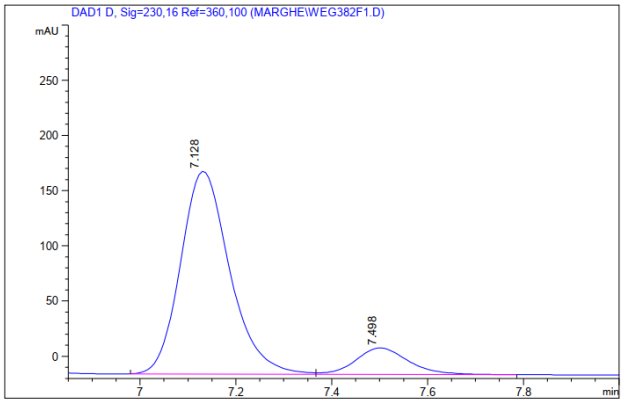
$[\alpha]_D^{26}$= +3.1° (c=2.8, λ=589 nm, $CHCl_3$, *ee*=75%).

The enantiomeric excess was determined by HPLC on chiral stationary phase with LUX CELLULOSE-5 3μ column: eluent Hexane/*i*PrOH = 95/5, flow rate 0.8 mL/min, λ=230 nm, τ_{minor} = 7.5 min, τ_{major} = 7 min.



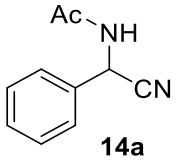
Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	7.051	BV	0.109	2020.668	49.833	
2	7.420	VB	0.114	2034.194	50.167	



Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	7.128	BV	0.109	1312.132	87.655	
2	7.498	VB	0.118	184.788	12.345	

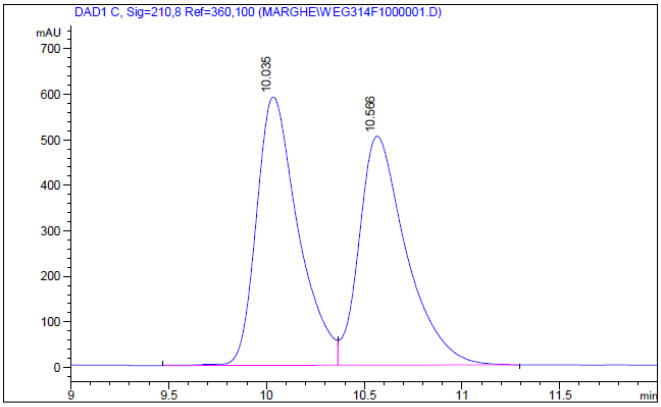


14a

Quenching was performed with slow addition of methanol (trying to avoid racemization), followed by removal of all volatiles. The crude was triturated in ethyl acetate, the insoluble triethylamine hydrochloric salt removed by filtration, and the solvent removed under reduced pressure. The product was purified by column chromatography (9:1 hexane/ ethyl acetate) and obtained as a white solid in 44% yield. All analytical data are in agreement with literature.[110]

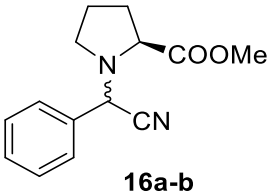
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.47-7.44 (m, 5H), 6.39 (brs, 1H), 6.12 (d, J= 9 Hz, 1H), 2.07 (s, 3H).

The enantiomeric excess was determined by HPLC on chiral stationary phase with chiralcel OJ-H column: eluent Hexane/*i*PrOH = 8/2, flow rate 0.8 mL/min, λ=210 nm, τ = 10 min, τ = 10.6 min.



Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	10.035	BV	0.221	8730.294	50.898	
2	10.566	VB	0.249	8422.103	49.102	



16a-b

The product was purified by column chromatography (9:1 hexane/ ethyl acetate) and obtained in 48% yield in 68:32 *dr*. The diastereoisomers were separated and obtained both as colourless oils. All analytical data are in agreement with literature.[88]

^{1}H NMR (300 MHz, $CDCl_3$) δ: *major (S,R):* 7.51-7.49 (m, 2H), 7.40-7.36 (m, 3H), 5.17 (s, 1H), 3.51-3.46 (dd, 1H), 3.40-3.33 (m, 1H), 3.32 (s, 3H), 2.96 (dt, 1H), 2.20-1.70(m, 4H); *minor (S,S):* 7.60 (m, 2H), 7.43-7.31 (m, 3H), 5.40 (s, 1H), 3.81 (s, 3H), 3.63 (dd, 1H), 2.76 (ddd, 1H), 2.60 (dt, 1H), 2.38-2.23 (m, 1H), 2.20-2.06 (m, 1H), 1.90-1.81 (m, 2H).

^{13}C NMR (90 MHz, $CDCl_3$) δ: *major (S,R):* 174.00, 132.94, 129.10, 128.64 (2C), 128.35 (2C), 116.62, 61.03, 58.66, 53.06, 51.54, 30.42, 23.86; *minor (S,S):* 173.20, 133.73, 128.87 (2C), 128.78 (2C), 127.67, 116.01, 63.07, 58.12, 52.16, 48.23, 28.84, 22.81.

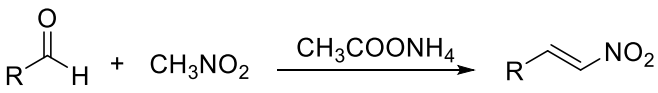
HRMS (EI) m/z calculated for $C_{14}H_{16}N_2O_2$ [M]: 244.121178, found: 244.121800.

$[\alpha]_D^{26}$= -26.9° (c=4.4, λ=589 nm, $CHCl_3$, *ee*=100%).

$[\alpha]_D^{26}$= -74.93° (c=2, λ=589 nm, $CHCl_3$, *ee*=100%).

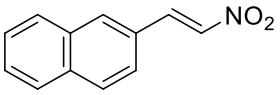
Synthesis of substrates

Synthesis of nitroalkenes



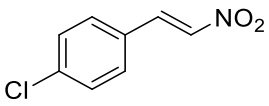
General procedure A:[111] a round bottom flask was charged with the proper substituted benzaldehyde (1 eq.), ammonium acetate (20 mol%), and nitromethane (27eq.). The mixture was refluxed overnight, and the bulk of the nitromethane was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 and washed with brine and water. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude that was purified to give the desired nitro alkene.

General procedure B:[112] aryl aldehyde (1 eq.), ammonium acetate (0.20 eq.) and nitromethane (12 eq.) were introduced in a microwave vial. The stirring mixture was subjected to 200 W microwave irradiation and heated to 95°C, until complete conversion of the starting material, checked by TLC (60-90 minutes). Constant microwave irradiation as well as simultaneous air-cooling were used during the entire reaction time. After cooling to room temperature, the reaction mixture was evaporated under reduced pressure to give a brown oil and purified by recrystallisation or by column chromatography on silica gel.



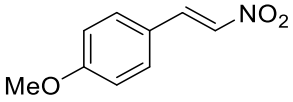
Synthetized according to general procedure **A**. The product was purified by recrystallization (1:3 CH_2Cl_2/hexane) and obtained as a yellow solid, all analytical data are in agreement with literature.[76] Yield = 79%.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.22 (d, J = 15 Hz, 1H), 8.05 (s, 1H), 7.93-7.90 (3H), 7.75 (d, J = 15 Hz, 1H), 7.70-7.62 (3H).



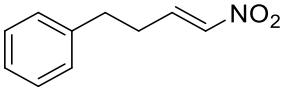
Synthetized according to general procedure **B**. The product was purified by column chromatography (9:1 hexane/ethyl acetate), all analytical data are in agreement with literature.[111] Yield = 39%.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.01 (d, J = 15 Hz, 1H); 7.60-7.43 (5H).



Synthetized according to general procedure **B**. The product was purified by column chromatography (9:1 hexane/ethyl acetate), all analytical data are in agreement with literature.[111] Yield = 56%.

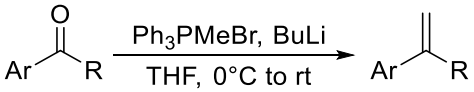
^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.02 (d, J = 12Hz, 1H); 7.56-7.51 (3H); 6.99-6.96 (2H); 3.89 (s, 3H).



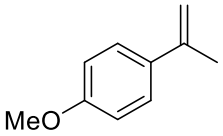
Synthetized according to general procedure **A**. The product was purified by column chromatography (99:1 hexane/ethyl acetate), all analytical data are in agreement with literature.[76] Yield = 56%.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.25-7.20 (m, 2H), 7.20-7.13 (m, 2H), 7.13-7.08 (m, 2H), 6.96-6.79 (dt, J = 13.4, 1.6 Hz, 1H), 2.78-2.70 (t, J=7.5, 2H), 2.55-2.45 (qd, 2H).

Synthesis of styrenes[113]

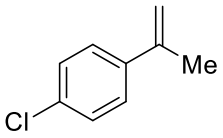


In a two-necked round-bottomed flask under nitrogen atmosphere, a solution of Ph_3PMeBr (1.2 eq.) in THF (0.25 M) was prepared and cooled to 0°C. A 2.5M solution in hexane of *n*-BuLi (1.2 eq.) was slowly added. After stirring the reaction mixture for 1 h at the same temperature, the desired ketone (1 eq.) was added (if solid, in a concentrated THF solution). The reaction mixture was stirred at room temperature overnight, then an aqueous saturated solution of NH_4Cl was added to quench the reaction. The aqueous phases were extracted 3 times with petroleum ether, the combined organic phases were dried over sodium sulphate, concentrated *in vacuo* and the crude material was purified by flash chromatography with only hexane as eluent, to afford the pure alkene.



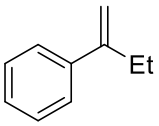
Obtained as a colorless oil after purification. All analytical data are in agreement with literature.[113] Yield = 76%.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.46 (d, 2H), 6.91 (d, 2H), 5.34 (s, 1H), 5.04 (s, 1H), 3.84 (s, 3H), 2.18 (s, 1H).



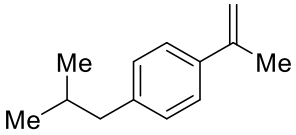
Obtained as a colorless liquid after purification. All analytical data are in agreement with literature.[113] Yield = 99%.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.41 (d, 2H), 7.31 (d, 2H), 5.38 (s, 1H), 5.12 (s, 1H), 2.15 (s, 1H).



Obtained as a colorless liquid after purification, All analytical data are in agreement with literature.[113] Yield = 55%.

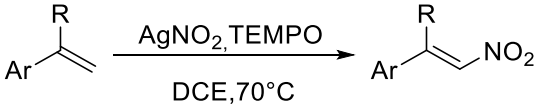
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39-7.33 (m, 2H), 7.27 (t, 2H), 7.23-7.18 (m, 1H), 5.22 (s, 1H), 5.01 (s, 1H), 2.46 (q, 2H), 1.05 (t, 3H).



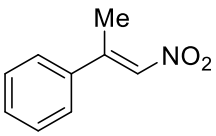
Obtained as a colorless liquid after purification. All analytical data are in agreement with literature.[114] Yield = 30%.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.41 (d, 2H), 7.13 (d, 2H), 5.38 (s, 1H), 5.06 (s, 1H), 2.49 (d, 2H), 2.16 (s, 3H), 1.89 (m, 1H), 0.94 (d, 6H).

Nitration of styrenes[76]

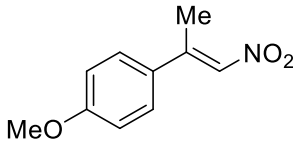


To an oven-dried screw cap test tube charged with a magnetic stir-bar was added $AgNO_2$ (3 eq.), TEMPO (0,4 eq.), the desired olefin, oven-dried molecular sieves (1,2 g) and solvent (DCE, 34 mL, 0,25M). The tube was placed in a preheated oil bath at 70°C and stirred vigorously for 12h. Then it was cooled to room temperature, filtered through a pad of celite and washed with ethyl acetate. The crude was purified by column chromatography.



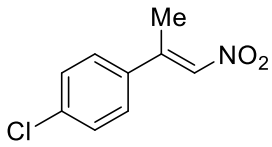
Obtained as a yellow oil after purification, performed using 95:5 hexane/ethyl acetate as eluent. All analytical data are in agreement with literature.[76] Yield = 95%.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.49-7.46 (5H); 7.33 (d, J=15 Hz, 1H); 2.67 (s, 3H).



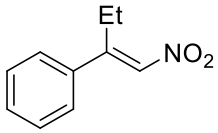
Obtained as a yellow solid after purification, performed using 95:5 hexane/ethyl acetate as eluent. All analytical data are in agreement with literature.[115] Yield = 95%.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.45-7.42 (m, 2H), 7.34 (q, 1H), 6.97-6.93 (m, 2H), 3.86 (s, 3H), 2.64 (d, J=1.3 Hz, 3H).



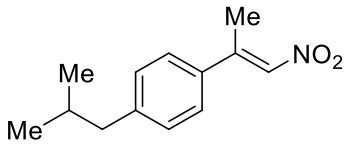
Obtained as a yellow solid after purification, performed using 95:5 hexane/ethyl acetate as eluent. All analytical data are in agreement with literature.[116] Yield = 37%.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.45-7.32 (m, 4H), 7.28 (q, 1H), 2.62 (d, J=1.4 Hz, 3H).



Obtained as a yellow oil after purification, performed using 95:5 hexane/ethyl acetate as eluent. All analytical data are in agreement with literature.[116] Yield = 88%.

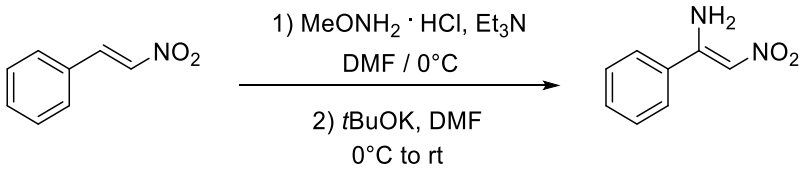
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.46-7.41 (5H), 7.19 (s, 1H), 3.08 (q, 2H), 1.15 (t, 3H).



Obtained as a yellow oil after purification, performed using 95:5 hexane/ethyl acetate as eluent. All analytical data are in agreement with literature.[115] Yield = 65%.

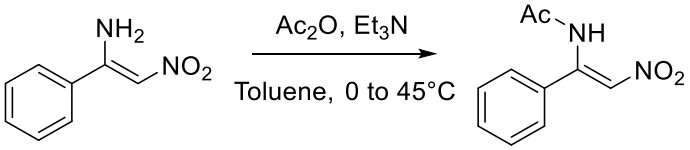
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.44-7.32 (m, 3H), 7.24-7.21 (d, 2H), 2.66 (d, J=1.4 Hz, 3H), 2.53 (d, 2H), 1.90 (m, 1H), 0.94 (d, 6H).

Synthesis of (Z)-2-nitro-1-phenylethenamine[117]



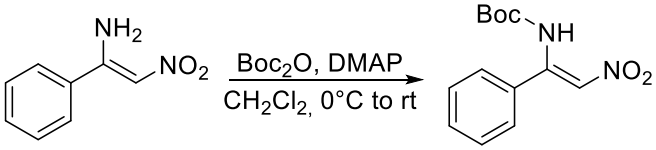
Triethylamine (1 eq.) was added to a solution of methoxylamine hydrochloride (1 eq.) in dimethylformamide (0.62 M) at 0°C. β-nitrostyrene (1 eq.) was then added and the resulting suspension was stirred at 0°C for 15 min and at room temperature for 5 min. The precipitate was removed by filtration and washed with small amounts of DMF. The combined filtrate was transferred into an addition funnel and was added dropwise to a *t*BuOK (2 eq.) solution in DMF (0.83 M) at 0°C. The cooling bath was then removed, and the reaction mixture was stirred at room temperature for 30 minutes. The reaction was quenched with saturated aq. NH_4Cl. The solvents were distilled under reduced pressure and the residue dissolved in CH_2Cl_2. The obtained organic phase was washed with water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* and the crude was purified by column chromatography (CH_2Cl_2: ethyl acetate 6/1) to afford the desired product in 42% yield. All analytical data are in agreement with literature.[118]

^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.24 (brs, 1H), 7.62 – 7.48 (m, 5H), 6.86 (s, 1H), 5.88 (brs, 1H).



A stirred solution of the β-amino nitro olefin (1 eq.) in toluene (0.3 M) under N_2 was cooled to 0°C and triethylamine (4 eq.) followed by acetic anhydride (3 eq.) were added. The cooling bath was then removed, and the solution was stirred at 45°C overnight. The mixture was then concentrated *in vacuo* and purified by column chromatography (CH_2Cl_2: ethyl acetate 1/1) to afford the desired product in 76% yield as a pale-yellow solid. All analytical data are in agreement with literature.[117]

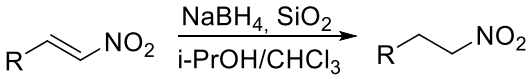
^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.82 (brs, 1H), 7.55 – 7.36 (m, 5H), 6.72 (s, 1H), 2.27 (s, 3H).



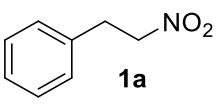
A stirred solution of β-amino nitroolefin in CH_2Cl_2 (0.6 M) was cooled at 0 °C and di-*t*-butyl-dicarbonate (1.2 eq.) followed by 4-dimethylamino pyridine (DMAP, 0.05 eq.) were added. The cooling bath was then removed, and the solution was stirred at rt for 1 hour. The reaction was then quenched with water and extracted with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, filtered, concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (CH_2Cl_2/petroleum ether 3:1) to afford the desired β-*t*-butyloxycarbonylamino nitroolefin as a pale yellow solid in 60% yield. The obtained spectroscopic data were in accord with those previously published.[117]

^{1}H-NMR (300 MHz, $CDCl_3$): δ 10.31 (s, 1H), 7.54-7.44 (m, 5H), 6.66 (s, 1H), 1.41 (s, 9H).

Synthesis of achiral nitroalkanes[77]



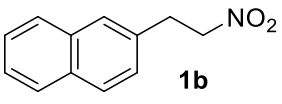
In a round bottomed flask, differently substituted β-nitrostyrene (1 eq.) and SiO_2 (18 eq.) were added to a mixture of *i*-PrOH/$CHCl_3$ (1:5,4). $NaBH_4$ (3 eq.) was added in four portions, within 45 min. The reaction mixture was stirred at room temperature for 15 minutes after the last addition. The reaction was quenched with HCl 1M, filtered over a celite pad and washed with CH_2Cl_2. The residue was extracted with CH_2Cl_2, washed with water, dried over Na_2SO_4 and the solvent removed under reduced pressure.



1a

The product was purified by column chromatography (95:5 hexane/ethyl acetate) and obtained as a yellow oil. All analytical data are in agreement with literature.[119] Yield = 79%.

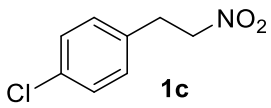
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.30 (m, 5H), 4.64 (t, J = 6 Hz, 2H), 3.34 (t, J=6 Hz, 2H).



1b

The product was purified by column chromatography (95:5 hexane/ethyl acetate) and obtained as a white solid. All analytical data are in agreement with literature.[120] Yield = 74%.

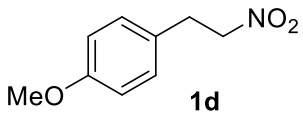
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.83-7.80 (m, 3H), 7.67 (s, 1H), 7.52-7.47 (m, 2H), 7.33-7.31 (m, 1H), 4.70 (t, 2H), 3.49 (t, 2H).



1c

The product was purified by column chromatography (95:5 hexane/ethyl acetate) and obtained as a yellow oil. All analytical data are in agreement with literature.[121] Yield = 45%.

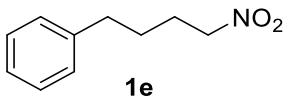
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.31 (d, J = 6 Hz, 2H), 7.15 (d, J = 9 Hz, 2H), 4.61 (t, J = 6 Hz, 2H) 3.31 (t, J = 6 Hz, 2H).



1d

The product was purified by column chromatography (95:5 hexane/ethyl acetate) and obtained as an orange oil. All analytical data are in agreement with literature.[120] Yield = 69%.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.13 (d, J = 9 Hz, 2H), 6.86 (d, J = 9 Hz, 2H), 4.59 (t, J = 6 Hz, 2H), 3.81 (s, 3H); 3.28 (t, J = 6 Hz, 2H).



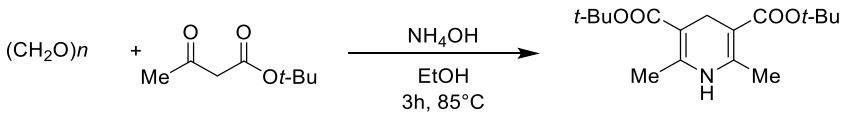
1e

The product was purified by column chromatography (7:3 hexane/ CH_2Cl_2) and obtained as a colourless oil. All analytical data are in agreement with literature.[122] Yield = 91%.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.33-7.14 (m, 5H), 4.40 (t, 2H), 2.70 (t, 2H), 2.06 (qui, 2H), 1.76 (qui, 2H).

Stereoselective synthesis of nitroalkanes

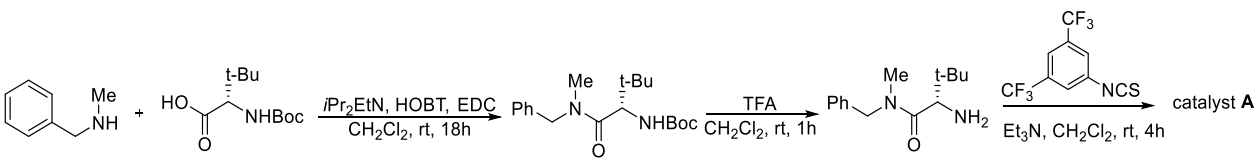
Synthesis of Hantzsch ester[123]



A solution of paraformaldehyde (1 eq.), *tert*-butyl acetoacetate (2 eq.) and aqueous NH_4OH (5 M, 3 eq.) in ethanol (1.25 M) was heated at reflux for 3h. The mixture was then cooled to rt, poured into ice-water and extracted with Et_2O. The ether phase was washed with 10% aqueous solution of NaOH, water, 5% aqueous solution of HCl and water. The ether solution was dried over $NaSO_4$ and filtered. The solvent was removed *in vacuo* to afford a yellow solid. The residue was purified by crystallization with dry MeOH under inert atmosphere. Yield = 34%.

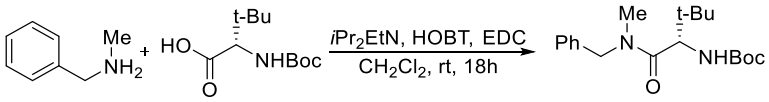
^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.01 (s, 1H); 3.15 (s, 2H); 2.13 (s, 6H); 1.46 (s, 18H).

*Synthesis of chiral catalyst **A**[124]*



N-Boc-L-tert-leucine I II

*Compound **I***

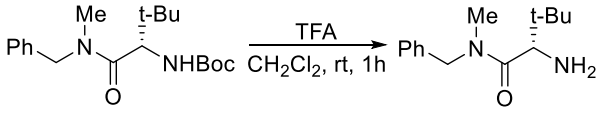


I

A round bottomed flask was charged with *N*-Boc-*tert*-leucine (1 eq.), HOBT (1 eq.), and anhydrous chloroform (0,12 M) under nitrogen atmosphere. After 5 min of stirring, EDC (3 eq.) and *N*-methylbenzylamine were added, and the reaction mixture was stirred at rt for 18h. Next 1M HCl was added, the aqueous layer extracted with CH_2Cl_2, and the organic phases were washed with saturated aqueous $NaHCO_3$, water and dried over Na_2SO_4. Solvent removal *in vacuo* afforded analytically pure amide (4.19 mmol, 97% yield) as a thick oil that was used without further purification.

^{1}H-NMR (300 MHz, $CDCl_3$; compound exists as a 4:1 mixture of rotamers, only the major is indicated): δ 7.33-7.26 (m, 5H); 5.40 (br d, 1H); 4.70 (d, 1H, *J* = 3.3 Hz); 4.55 (d, 1H, *J* = 3.3 Hz); 3.08 (s, 3H); 1.45 (s, 9H); 1.01 (s, 9H) ppm.

*Compound **II***

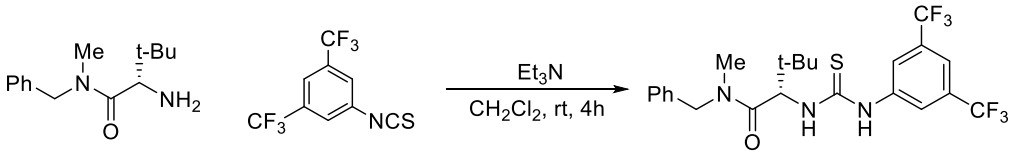


I **II**

To a solution of **I** (1 eq.) in CH_2Cl_2 (0,21 M) was added TFA (10 eq.). The mixture was stirred for 1h at room temperature, then quenched with saturated Na_2CO_3 solution and extracted with CH_2Cl_2. The organic layers were dried over sodium sulphate, filtered and concentrated *in vacuo*, to afford **II** as a white solid, used in the next step without further purification.

^{1}H-NMR (300 MHz, $CDCl_3$; compound exists as a 5:1 mixture of rotamers, only the major is indicated): δ 7.33-7.26 (m, 5H); 5.40 (brs d, 1H); 4.70 (d, 1H, *J* = 3.3 Hz); 4.55 (d, 1H, J = 3.3 Hz); 3.08 (s, 3H); 1.01 (s, 9H) ppm.

*Catalyst **A***

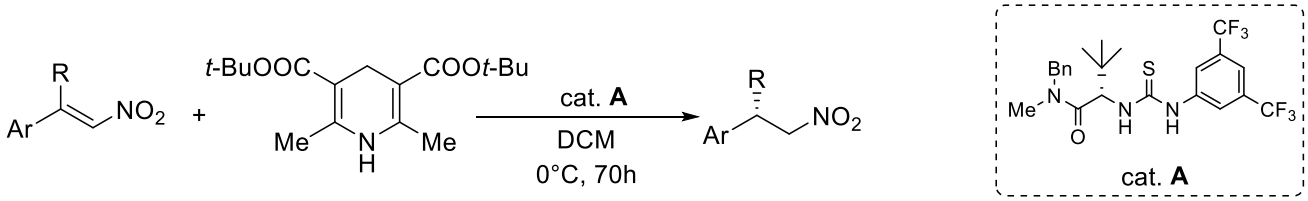


II catalyst **A**

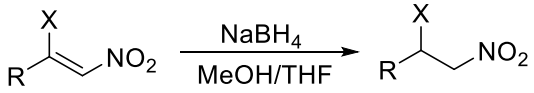
To a solution of **II** (1 eq.) in CH_2Cl_2 (0,08 M) under inert atmosphere was added TEA (3,3 eq.), followed by 3,5-bis-(trifluoromethyl)phenyl-isothiocyanate (1,1 eq.). The reaction was stirred overnight at room temperature and then concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate 7:3) to give catalyst **A** (66% yield over three steps) as a white solid.

^{1}H-NMR (300 MHz, $CDCl_3$; compound exists as a 4:1 mixture of rotamers, only the major is indicated): δ 9.8 (brd s, 1H); 8.12 (s, 3H); 7.58 (s, 1H); 7.24-7.14 (m, 5H); 5.55 (d, 1H, *J* = 3.3 Hz); 4.78 (d, 1H, *J* = 14.4 Hz); 4.44 (d, 1H, *J* = 14.4 Hz); 3.31 (s, 3H); 1.14 (s, 9H) ppm.

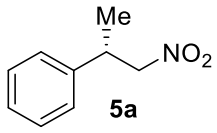
<u>Synthesis of alkylsubstituted nitroalkanes</u>



General procedure for the stereoselective synthesis:[75] in a round bottom flask under nitrogen atmosphere, catalyst **A** (0.1 eq.) and Hantzsch ester (1.5 eq.) were sequentially added at 0°C to a solution of the proper nitroalkene (1 eq.) in dichloromethane (0.5 M). The reaction mixture was stirred for 70 h at 0°C, then subjected directly to column chromatography (8:2 hexane/ethyl acetate).



General procedure for the synthesis of racemic compounds:[117] in a round bottomed flask, the substituted nitrostyrene (1 eq.) was added to a mixture of MeOH/THF (1:10, 0.15 M). $NaBH_4$ (1,5 eq.) was added in four portions, within an hour. The reaction mixture was stirred at room temperature for 15 minutes after the last addition, then quenched with HCl 1M, filtered over a celite pad and washed with CH_2Cl_2. The residue was extracted with CH_2Cl_2, washed with water, dried over Na_2SO_4 and the solvent removed under reduced pressure.

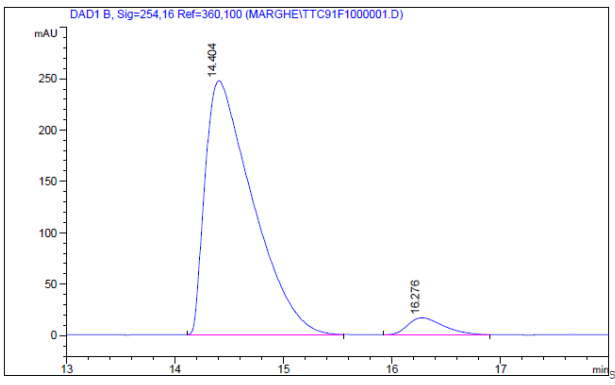


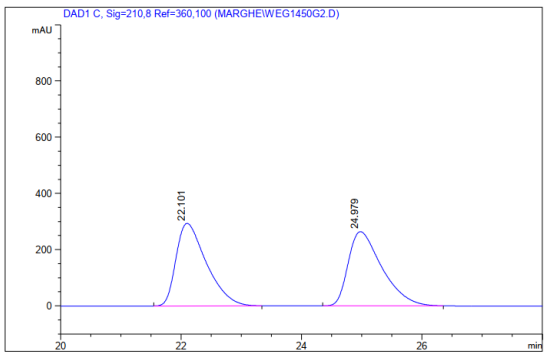
5a

The product was obtained pure as an oil in 74% yield and 90% *ee*. All analytical data are in agreement with literature.[75]

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37-7.24 (5H), 4.54 (dd, 2H), 3.67 (ddq, 1H), 1.41 (d, J = 3 Hz, 3H).

The enantiomeric excess was determined by HPLC on chiral stationary phase with Chiralcel OJ-H column: eluent Hexane/ *i*PrOH = 9/1, flow rate 0.75 mL/min, λ=254 nm τ_{major} = 14.4 min, τ_{minor} = 16.3 min.



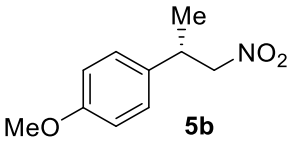


Signal 1: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	14.404	BB	0.456	7534.770	95.204	
2	16.276	BB	0.349	379.577	4.796	

Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	4.020	BB	0.149	55.800	0.270	
2	4.517	BB	0.257	20.766	0.100	
3	22.101	BB	0.528	10306.938	49.840	
4	24.979	BB	0.587	10296.706	49.790	

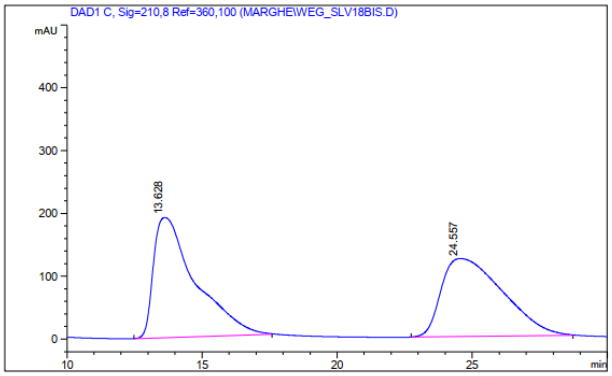


5b

The product was obtained pure as an oil in 37% yield and 87% *ee*. All analytical data are in agreement with literature.[115]

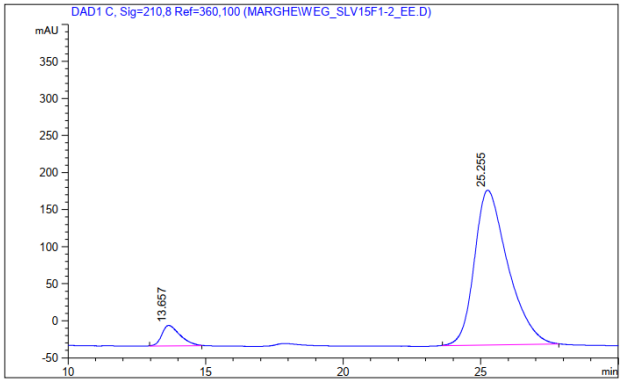
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.16 (d, 2H), 6.90 (d, 2H), 4.50 (dd, 2H), 3.81 (s, 3H), 3.61 (tq, 1H), 1.37 (d, 3H).

The enantiomeric excess was determined by HPLC on chiral stationary phase with Chiralcel OD column: eluent Hexane/ *i*PrOH = 98/2, flow rate 1 mL/min, λ=210 nm τ_{major} = 25 min, τ_{minor} = 13 min.



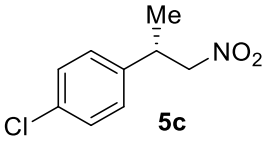
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	13.628	BB	1.537	20548.139	51.242	
2	24.557	BB	2.124	19551.752	48.758	



Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	13.657	BB	0.659	1257.293	6.607	
2	25.255	BB	1.224	17771.074	93.393	

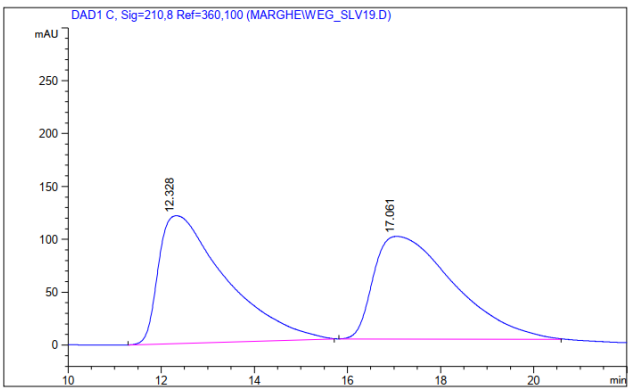


5c

The product was obtained pure as an oil in 46% yield and 82% *ee*. All analytical data are in agreement with literature.[114]

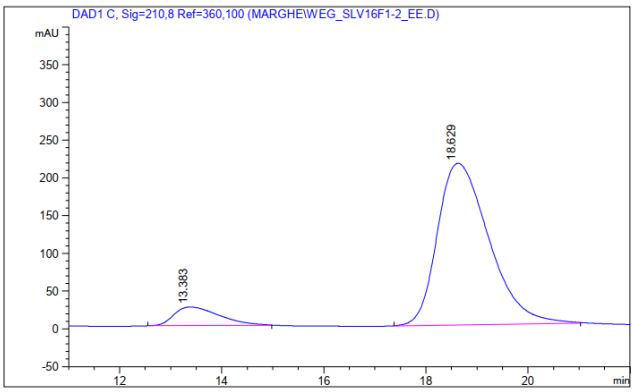
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.34 (d, 2H), 7.18 (d, 2H), 4.51 (dd, 2H), 3.64 (tq, 1H), 1.39 (d, 3H).

The enantiomeric excess was determined by HPLC on chiral stationary phase with Chiralcel OD column: eluent Hexane/ *i*PrOH = 98/2, flow rate 1 mL/min, λ=210 nm τ_{major} = 18 min, τ_{minor} = 13 min.



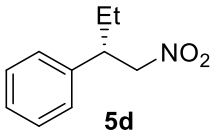
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	12.328	BB	1.413	12103.490	50.965	
2	17.061	BB	1.576	11644.965	49.035	



Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	13.383	BB	0.858	1532.378	9.243	
2	18.629	BB	1.076	15046.244	90.757	

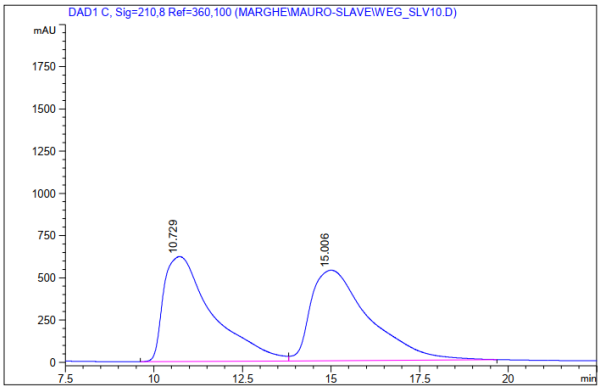


5d

The product was obtained pure as an oil in 65% yield and 85% *ee*. All analytical data are in agreement with literature.[114]

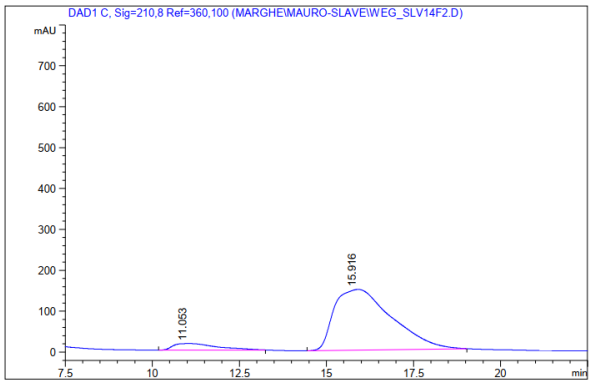
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.38-7.29 (m, 3H), 7.29-7.19 (m, 2H), 4.58 (dd, 2H), 3.38 (ddt, 1H), 1.77 (dq, 2H), 0.87 (t, 3H).

The enantiomeric excess was determined by HPLC on chiral stationary phase with Chiralcel OD column: eluent Hexane/ *i*PrOH = 98/2, flow rate 1 mL/min, λ=210 nm τ_{major} = 16 min, τ_{minor} = 11 min.



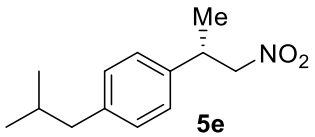
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	10.729	BB	1.399	59719.414	49.394	
2	15.006	BB	1.696	61185.723	50.606	



Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	11.053	BB	1.060	1429.346	7.703	
2	15.916	BB	1.551	17125.855	92.297	

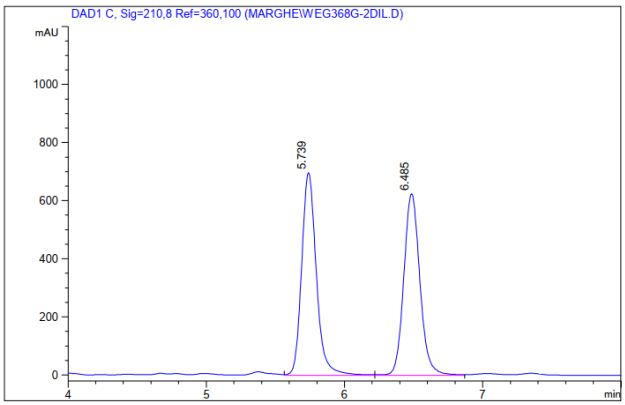


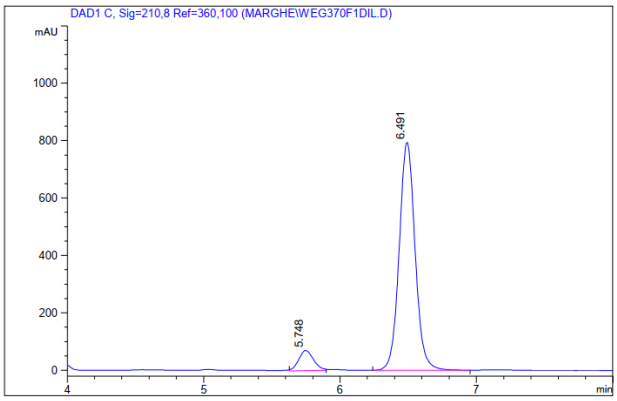
5e

The product was obtained pure as an oil in 93% yield and 85% *ee*. All analytical data are in agreement with literature.[115]

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.14 (brs, 4H), 4.52 (dd, 2H), 3.63 (ddq, 1H), 2.47 (d, 2H), 1.86 (dept, 1H), 1.39 (d, 3H), 0.91 (d, 6H).

The enantiomeric excess was determined by HPLC on chiral stationary phase with LUX CELLULOSE-1 3μ column: eluent Hexane/ *i*PrOH = 9/1, flow rate 1 mL/min, λ=210 nm τ_{major} = 7 min, τ_{minor} = 6 min.



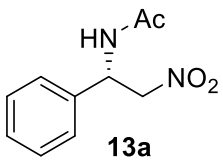


Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	5.739	VV	0.112	5147.247	50.393	
2	6.485	VV	0.125	5066.875	49.607	

Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	5.748	MM	0.125	522.249	7.491	
2	6.491	BB	0.125	6449.664	92.509	

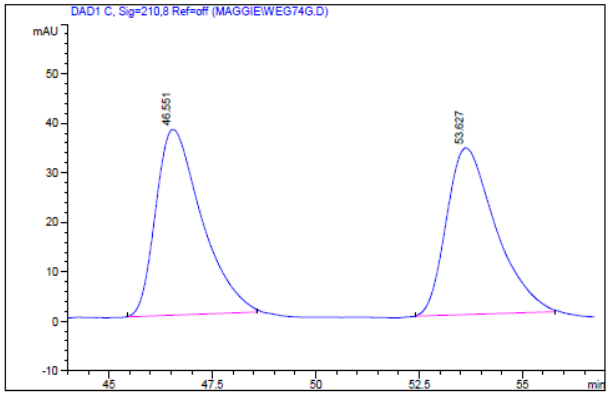


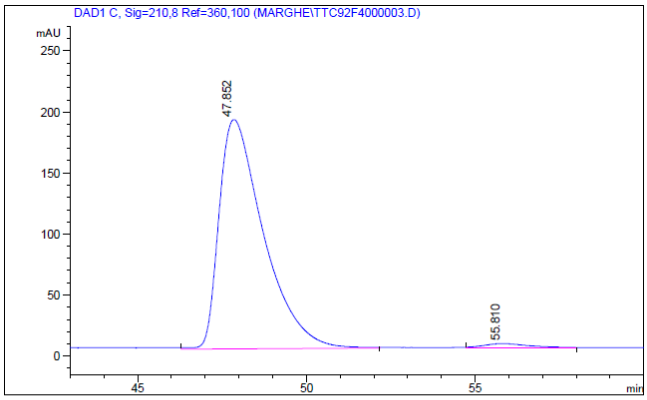
13a

Synthesized using the same procedure, conducted in toluene at 40°C for 14 h. The product purified by recrystallization from ether and obtained as a white solid in 90% yield and 95% *ee*. All analytical data are in agreement with literature.[117]

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.38-7.28 (m, 5H), 6.35 (s, 1H), 5.73 (q, J = 6 Hz, 1H), 4.97-4.90 (dd, J = 6, 13 Hz, 1H), 4.78-4.72 (dd, 1H), 2.07 (s, 3H).

The enantiomeric excess was determined by HPLC on chiral stationary phase with Chiralcel OJ-H column: eluent Hexane/ *i*PrOH = 9/1, flow rate 1 mL/min, λ=210 nm τ_{major} = 48 min, τ_{minor} = 56 min.





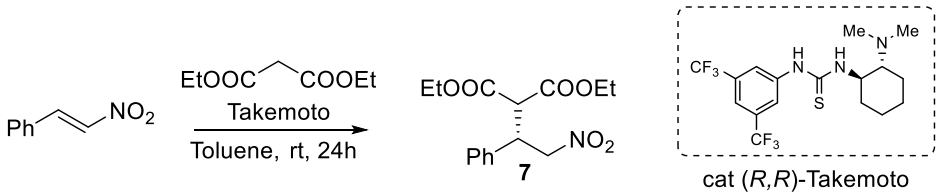
Signal 1: DAD1 C, Sig=210,8 Ref=off

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	46.551	BB	1.086	2888.841	50.829	
2	53.627	BB	1.150	2794.655	49.171	

Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	47.852	MM	1.530	17248.461	97.737	
2	55.810	MM	1.733	399.447	2.263	

<u>Stereoselective addition of diethylmalonate to nitrostyrene</u>[78]

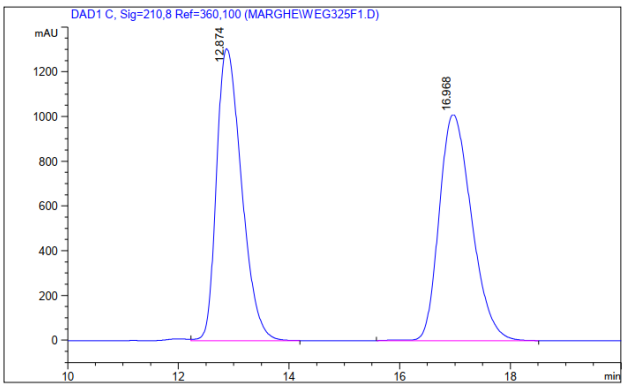


To a stirred solution of diethylmalonate (2 eq.) and (*R,R*)-Takemoto catalyst (0.1 eq.) in dry toluene (0.5 M), was added *trans*-β-nitrostyrene at room temperature. After 24 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/acetate 9/1 as eluent) to afford the desired product as a white solid in 96% yield and 91% *ee*. All analytical data are in agreement with literature.

The racemic compound was synthetized according to literature procedure,[125] using NaH (2 eq.) as base, in dry THF (0.1 M), at room temperature for 18h.

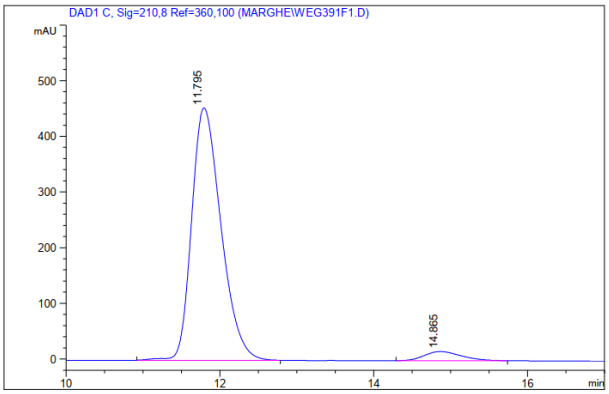
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.42-7.10 (m, 5H),4.93 (dd, 1H), 4.86 (dd, 1H), 4.33-4.15 (m, 3H), 4.00 (q, 2H), 3.82 (d, 1H), 1.25 (t, 3H), 1.03 (t, 3H).

The enantiomeric excess was determined by HPLC on chiral stationary phase with chiralpack AD column: eluent Hexane/ EtOH = 9/1, flow rate 1 mL/min, λ=210 nm τ_{major} = 13 min, τ_{minor} = 17 min.



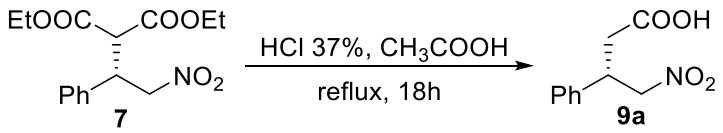
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	12.874	VB	0.491	41006.102	49.858	
2	16.968	BB	0.636	41239.707	50.142	



Signal 1: DAD1 C, Sig=210,8 Ref=360,100

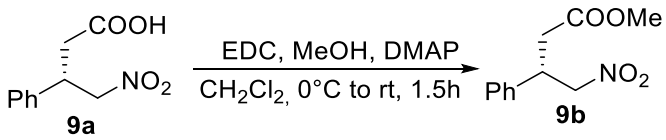
Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	11.795	BB	0.412	12050.991	95.622	
2	14.865	BB	0.510	551.809	4.378	



Following literature procedure,[126] the starting material was subjected to reflux, at 95°C, in a mixture of acetic acid and HCl 37% (3/1), with a total concentration of 0.2M. After 18h, the reaction mixture was cooled to room temperature, water was added, and the product was extracted three times with ethyl acetate. The combined organic phases were dried over sodium sulphate, filtered and the solvent removed under reduced pressure. The crude was purified by column chromatography (7:3 hexane/ethyl acetate) to yield the desired product as

a colourless oil in 70% yield. The *ee* was not evaluated on the free acid, but after derivatization as methyl ester almost no erosion was observed. All analytical data are in agreement with literature.[127]

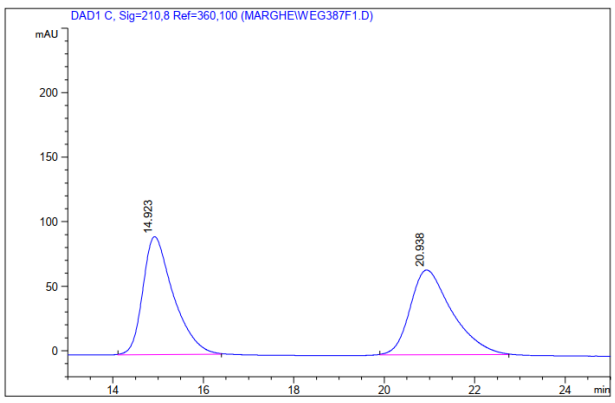
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.43-7.12 (m, 5H), 4.67 (dd, 2H), 3.97 (m, 1H), 2.83 (d, 2H).



Following a literature procedure,[128] the starting material was dissolved in dichloromethane (0.1 M). Methanol (2.5 M to the starting material) was added, and the mixture was cooled to 0°C. EDC (1.1 eq.) and DMAP (0.1 eq.), were added, and the mixture was allowed to reach room temperature, and stirred for another 1.5h. After that time, a saturated solution of NH_2Cl was added, the phases were separated, and the aqueous layer extracted 3 times with diethyl ether. The combined organic phases were dried over sodium sulphate, filtered and the solvent removed under reduced pressure. The crude was purified by column chromatography (eluent 8:2 hexane/ethyl acetate), and the product obtained as a pale yellow solid in 67% yield, with the same *ee* of the starting adduct. All analytical data are in agreement with literature.[127]

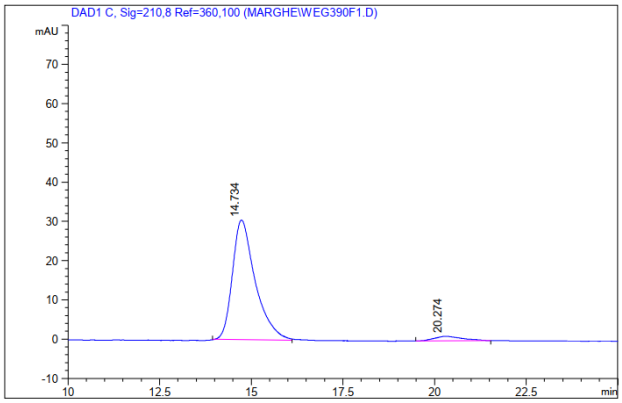
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.38-7.23 (m, 5H), 4.74 (dd, 2H), 3.99 (tdd, 1H), 3.63 (s, 3H), 2.85 (d, 2H).

The enantiomeric excess was determined by HPLC on chiral stationary phase with chiralcel OD column: eluent Hexane/ *i*PrOH = 9/1, flow rate 1 mL/min, λ=210 nm τ_{major} = 15 min, τ_{minor} = 20 min.



Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	14.923	BB	0.689	4284.591	50.262	
2	20.938	BB	0.926	4239.938	49.738	

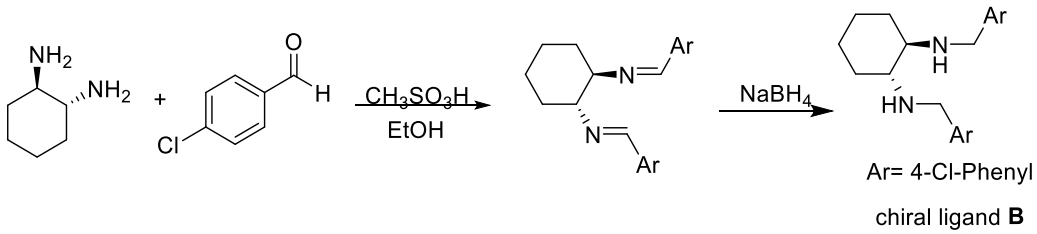


Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	14.734	MM	0.723	1322.647	95.670	
2	20.274	MM	0.874	59.863	4.330	

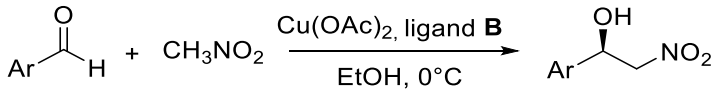
Stereoselective synthesis of nitroalcohols[85]

Synthesis of chiral ligand **B**[129]

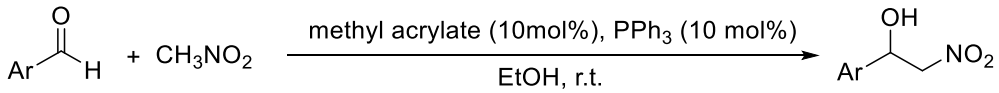


In a round bottom flask, 4-chlorobenzaldehyde (2 eq.) was dissolved in ethanol (0.05 M) and (1*S*,2*S*)-(+)-1,2-diaminocyclohexane (1 eq.) was added at 0°C. The reaction mixture was then stirred at this temperature for 1 h, and then refluxed overnight. After completion of the reaction (checked by TLC), the mixture was cooled to 0°C, and sodium borohydride (4 eq.) was added in small portions within an hour. The resulting solution thus obtained was refluxed overnight. The reaction was quenched with water, the residue extracted with CH_2Cl_2, dried over Na_2SO_4 and the solvent removed under reduced pressure. The product was purified by column chromatography (96:4 CH_2Cl_2/methanol) and obtained as a yellow/orange oil in 73% yield. All analytical data are in agreement with literature.[130]

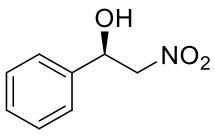
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.24-7.22 (m, 5H), 3.89 (dd, J = 15 Hz, 2H), 3.64 (dd, 2H), 2.20 (m, 2H), 2.14 (m, 2H), 1.91 (brs, 2H), 1.72 (brs, 2H), 1.20 (t, 2H), 1.03 (br, 2H).



The chiral ligand **B** (0.12 eq.) and Cu $(OAc)_2{\cdot}H_2O$ (0.1 eq.) were added to a round bottom flask and dissolved in anhydrous EtOH (0.05 M) under inert atmosphere. A green solution was formed under stirring, which was continued for 1h at room temperature, and then a solution of the aldehyde (1 eq.) in ethanol (1 M) was added. The reaction mixture was cooled to 0°C and stirred for 15 min, followed by addition of nitromethane (10 eq.). Stirring was continued at the same temperature for 48 h, after which the crude mixture was directly poured over a pad of silica gel and washed with a mixture of hexane and ethyl acetate (6:1). The combined solvents were dried under reduced pressure and the crude purified by column chromatography, to give the desired enantioenriched nitroalcohol.



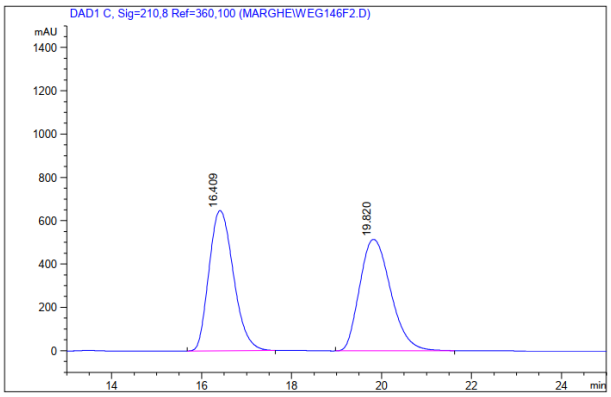
The racemic nitroalcohols were prepared following literature procedure:[131] a mixture of substituted benzaldehyde (1 eq.), nitromethane (2 eq.), triphenylphosphine (0.1 eq.), and methyl acrylate (0.1 eq.) in ethanol (0.1 M) was stirred in a vial at room temperature overnight. The resulting mixture was concentrated and purified by column chromatography.

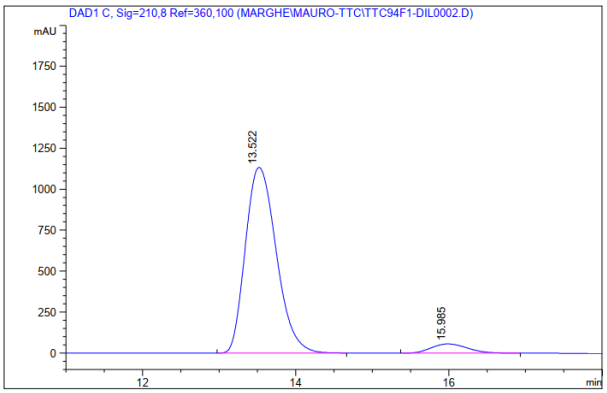


The product was obtained pure as an oil (eluent for the column hexane: ethyl acetate 6:1) in 85% yield and 89% *ee*. All analytical data are in agreement with literature.[129]

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.44-2.42 (m, 5H), 5.51-5.48 (dd, 1H), 4.63-4.55 (dd, 2H), 2.86 (brs, 1H).

The enantiomeric excess was determined by HPLC on chiral stationary phase with chiralcel OD-H column: eluent Hexane/ *i*PrOH = 9/1, flow rate 0.8 mL/min, λ=250 nm τ_{major} = 13 min, τ_{minor} = 16 min.



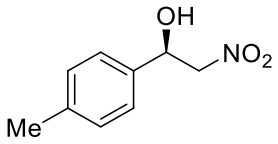


Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	16.409	BB	0.595	24478.914	49.797	
2	19.820	BB	0.749	24678.027	50.203	

Signal 1: DAD1 C, Sig=210,8 Ref=360,100

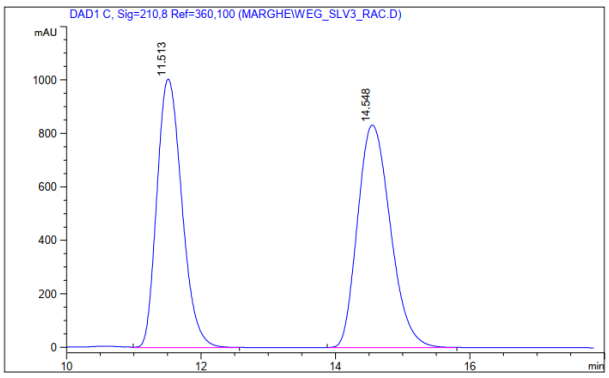
Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	13.522	BB	0.443	31801.225	94.459	
2	15.985	BB	0.527	1865.598	5.541	

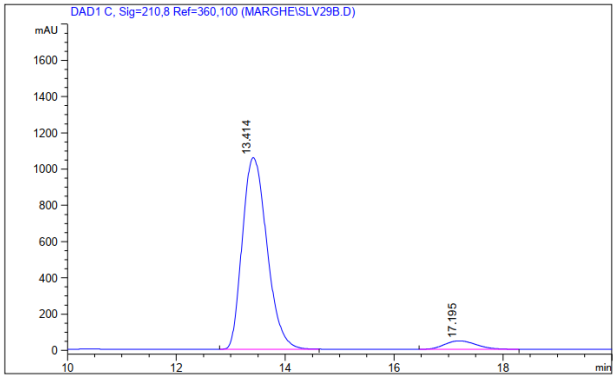


The product was obtained as an oil in 99% yield and 89% *ee* and used without further purification. All analytical data are in agreement with literature.[132]

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.30 (d, 2H), 7.22 (d, 2H), 5.43 (dd, 1H), 4.65-4.47 (m, 2H), 2.38 (s, 3H).

The enantiomeric excess was determined by HPLC on chiral stationary phase with chiralcel OD-H column: eluent Hexane/ *i*PrOH = 9/1, flow rate 1 mL/min, λ=250 nm τ_{major} = 13 min, τ_{minor} = 17 min.



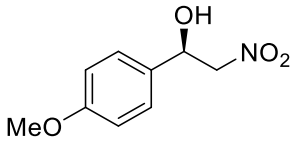


Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	11.513	VB	0.405	25896.828	47.842	
2	14.548	BB	0.534	28233.230	52.158	

Signal 1: DAD1 C, Sig=210,8 Ref=360,100

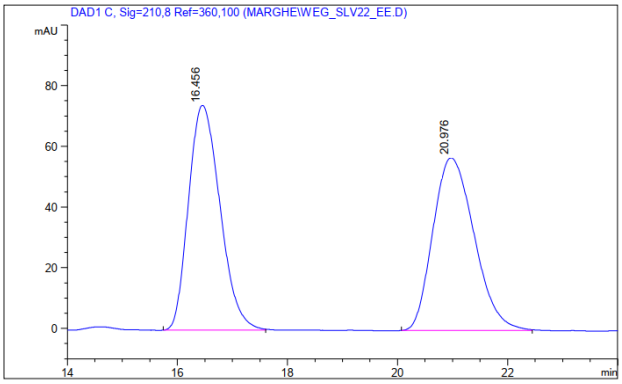
Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	13.414	BB	0.496	33307.832	94.643	
2	17.195	BB	0.634	1885.346	5.357	

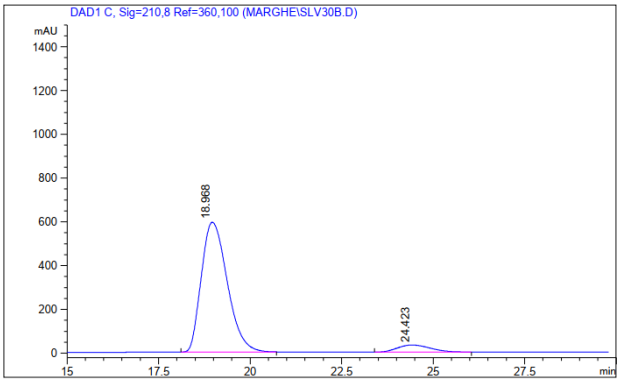


The product was obtained pure as an oil (eluent for the column hexane: ethyl acetate 9:1) in 40% yield and 87% *ee*. All analytical data are in agreement with literature.[129]

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.35 (d, 2H), 6.95 (d, 2H), 5.46-5.41 (dd, 1H), 4.66-4.47 (dd, 2H), 3.84 (s, 3H).

The enantiomeric excess was determined by HPLC on chiral stationary phase with chiralcel OD-H column: eluent Hexane/ *i*PrOH = 9/1, flow rate 0.8 mL/min, λ=250 nm τ_{major} = 19 min, τ_{minor} = 24 min.



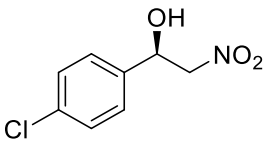


Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	16.456	BB	0.637	2950.655	49.883	
2	20.976	BB	0.828	2964.492	50.117	

Signal 1: DAD1 C, Sig=210,8 Ref=360,100

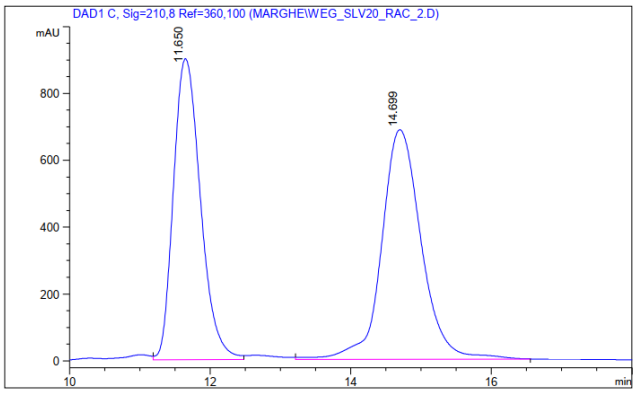
Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	18.968	BB	0.776	29273.240	93.479	
2	24.423	BB	0.965	2042.015	6.521	

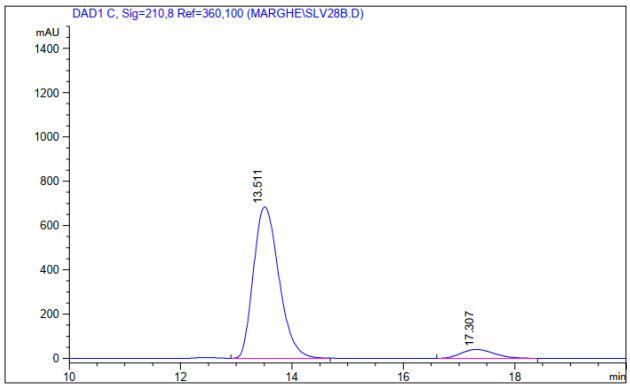


The product was obtained as an oil in 85% yield and 86% *ee*, and used directly without further purification. All analytical data are in agreement with literature.[129]

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.42-2.35 (m, 4H), 5.49-5.45 (dd, 1H), 4.64-4.48 (dd, 2H), 2.88 (brs, 1H).

The enantiomeric excess was determined by HPLC on chiral stationary phase with chiralcel OD-H column: eluent Hexane/ *i*PrOH = 9/1, flow rate 0.8 mL/min, λ=250 nm τ_{major} = 13 min, τ_{minor} = 17 min.



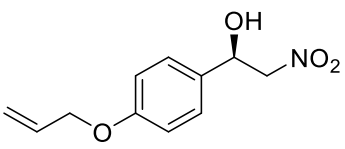


Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	11.650	VV	0.418	24076.375	47.224	
2	14.699	VB	0.597	26906.504	52.776	

Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	13.511	VB	0.497	21733.131	92.926	
2	17.307	BB	0.646	1654.412	7.074	



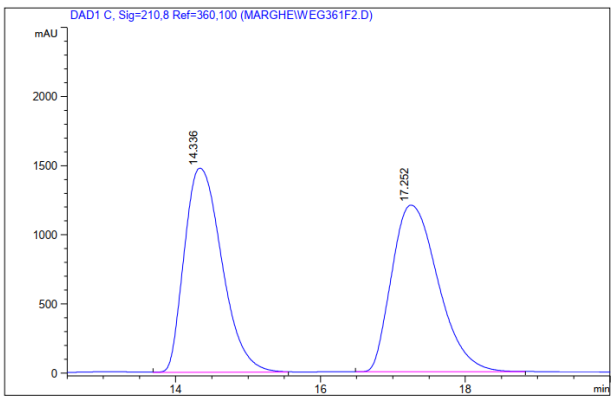
The product was obtained pure as an oil (eluent for the column hexane: ethyl acetate 8:2) in 45% yield and 76% *ee*. The product was completely characterized.

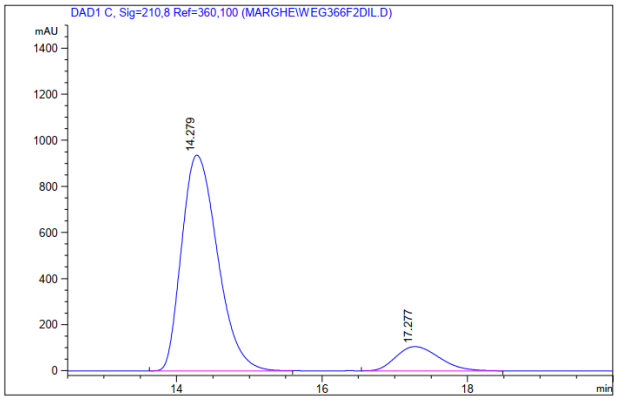
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.36 (d, 2H), 6.95 (d, 2H), 6.10-6.01 (m, 1H), 5.46-5.30 (m, 3H), 4.66-4.47 (m, 4H).

^{13}C NMR (90 MHz, $CDCl_3$) δ: 159.08, 132.94, 130.35 (2C), 127.27, 117.90, 115.23 (2C), 81.25, 70.67, 68.88.

HRMS (EI) m/z calculated for $C_{11}H_{13}N_1O_4$ [M]: 223.072490, found: 223.084458.

The enantiomeric excess was determined by HPLC on chiral stationary phase with chiralcel OD-H column: eluent Hexane/ *i*PrOH = 9/1, flow rate 0.8 mL/min, λ=250 nm τ_{major} = 14 min, τ_{minor} = 17 min.





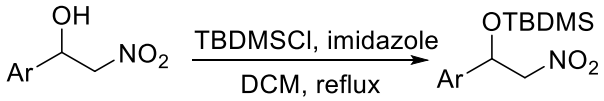
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	14.336	MM	0.603	53498.336	49.901	
2	17.252	BB	0.698	53710.566	50.099	

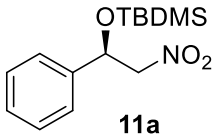
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	14.279	BB	0.542	32075.307	88.049	
2	17.277	BB	0.661	4353.602	11.951	

Protection as *tert*-butyl dimethylsilane[133]



To a solution of the nitro alcohol (1 eq.) in dichloromethane (0,16 M) *tert*-butyldimethylsilylchloride (1.5 eq.) and imidazole (2 eq.) were added. The resulting mixture was heated to reflux for 16 h and after being cooled to room temperature, the medium was hydrolysed with water. The organic phase was separated, and the aqueous phase was extracted three times with dichloromethane. The combined organic phases were dried with Na_2SO_4, filtered and concentrated.

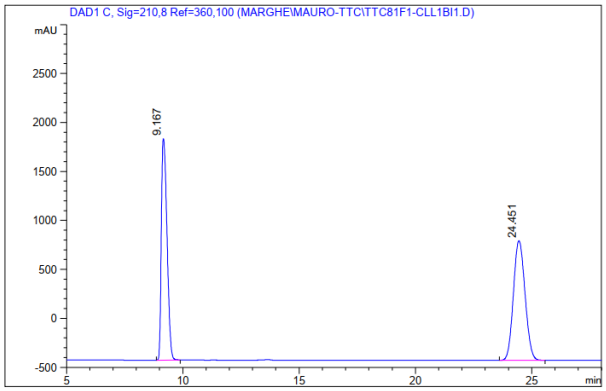


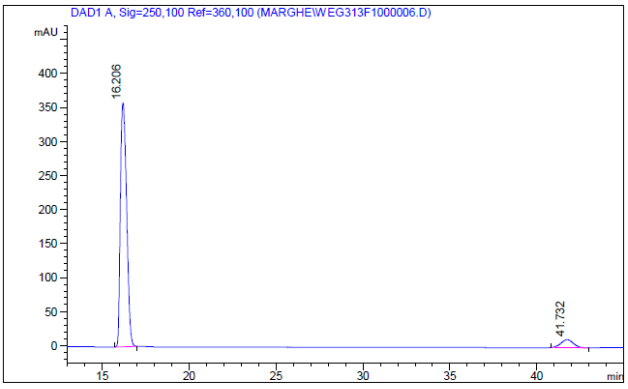
11a

The product was purified by silica gel column chromatography with 97:3 hexane/ethyl acetate as eluent and obtained as a colourless oil in 90% yield and 87% *ee.* All analytical data are in agreement with literature.[134]

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.41-7.36 (m, 5H), 5.46-5.42 (dd, 1H), 4.56-4.37 (dd, 2H), 0.86 (s, 9H), -0.47 (s, 3H), -0.13 (s, 3H).

The enantiomeric excess was determined by HPLC on chiral stationary phase with LUX CELLULOSE-1 3μ column: eluent Hexane/ *i*PrOH = 99/1, flow rate 1.2 mL/min, λ=250 nm τ_{major} = 16 min, τ_{minor} = 42 min.



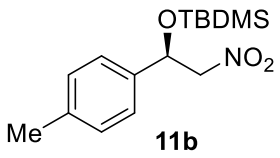


Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	9.167	BB	0.272	38331.594	47.434	
2	24.451	BB	0.543	42478.699	52.566	

Signal 1: DAD1 A, Sig=250,100 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	16.206	BB	0.411	8936.171	93.938	
2	41.732	BB	0.730	576.702	6.062	



11b

The product was purified by silica gel column chromatography with 98:2 hexane/ethyl acetate as eluent and obtained as a colourless oil in 61% yield and 89% *ee*. The product was completely characterized.

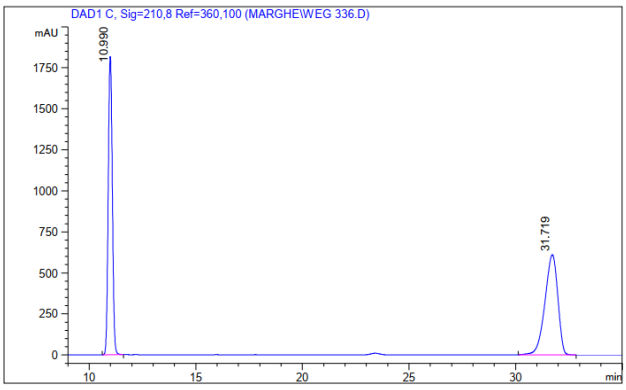
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.27 (d, 2H), 7.19 (d, 2H), 5.40 (dd, 1H), 4.58-4.34 (dd, 2H), 2.37 (s, 3H), 0.86 (s, 9H), 0.04 (s, 3H), -0.13 (s, 3H).

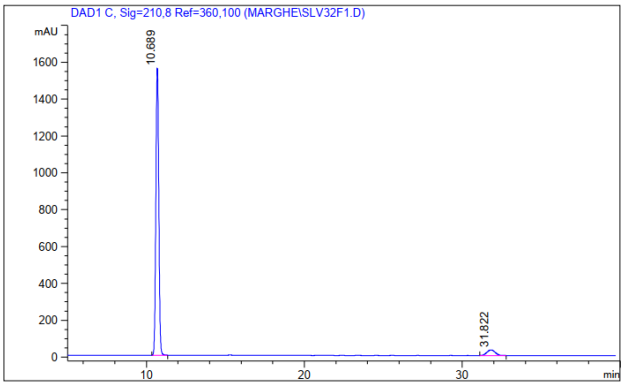
^{13}C NMR (90 MHz, $CDCl_3$) δ: 138.48, 136.32, 129.44 (2C), 126.06 (2C), 82.90, 72.59, 25.56 (3C), 21.18, 18.05, -4.79, -5.57.

HRMS (EI) m/z calculated for $C_{11}H_{16}NO_3Si$ [M-*t*Bu]: 238.090, found: 238.0760.

$[\alpha]_D^{26}$= -62.7° (c=1.9, λ=589 nm, $CHCl_3$, *ee*=89%).

The enantiomeric excess was determined by HPLC on chiral stationary phase with LUX CELLULOSE-1 3μ column: eluent Hexane/ *i*PrOH = 95/5, flow rate 0.8 mL/min, λ=210 nm τ_{major} = 11 min, τ_{minor} = 32 min.



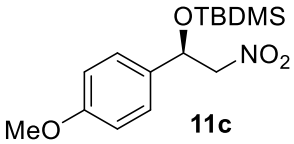


Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	10.990	VB	0.213	24453.541	48.894	
2	31.719	BB	0.649	25560.135	51.106	

Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	10.689	BB	0.202	20012.457	94.667	
2	31.822	BB	0.565	1127.390	5.333	



11c

The product was purified by silica gel column chromatography with 97:3 hexane/ethyl acetate as eluent and obtained as a colourless oil in 90% yield and 87% *ee.* The product was completely characterized.

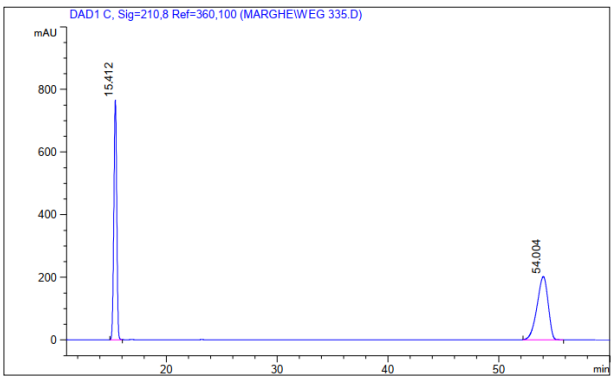
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.30 (d, 2H), 6.91 (d, 2H), 5.38 (dd, 1H), 4.58-4.33 (dd, 2H), 3.83 (s, 3H), 0.85 (s, 9H), 0.04 (s, 3H), -0.13 (s, 3H).

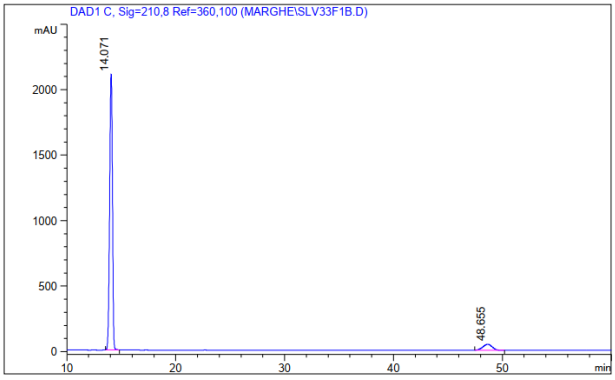
^{13}C NMR (90 MHz, $CDCl_3$) δ: 159.81, 131.34, 127.39 (2C), 114.14 (2C), 82.87, 72.32, 55.28, 25.56 (3C), 18.04, -4.80, -5.57.

HRMS (EI) m/z calculated for $C_{11}H_{16}NO_4Si$ [M-*t*Bu]: 254.085, found: 254.0846.

$[\alpha]_D^{26}$= -54.8° (c=1.8, λ=589 nm, $CHCl_3$, *ee*=87%).

The enantiomeric excess was determined by HPLC on chiral stationary phase with LUX CELLULOSE-1 3μ column: eluent Hexane/ *i*PrOH = 95/5, flow rate 0.8 mL/min, λ=210 nm τ_{major} = 15 min, τ_{minor} = 54 min.



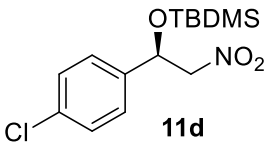


Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	15.412	BB	0.285	13859.444	49.809	
2	54.004	BB	1.068	13965.767	50.191	

Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	14.071	BB	0.285	37727.727	93.319	
2	48.655	BB	0.919	2701.145	6.681	



11d

The product was purified by silica gel column chromatography with 97:3 hexane/ethyl acetate as eluent and obtained as a colourless oil in 90% yield and 86% *ee.* The product was completely characterized.

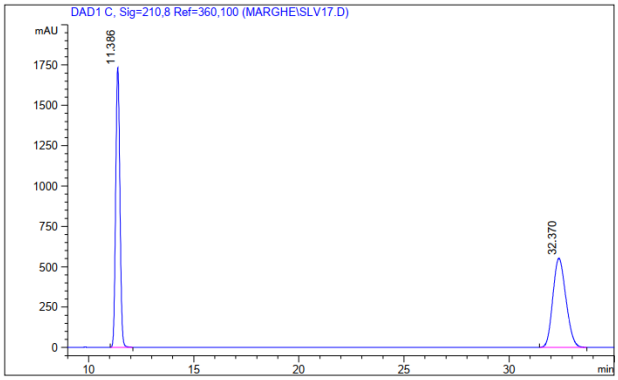
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39-7.33 (m, 4H), 5.41 (dd, 1H), 4.56-4.34 (dd, 2H), 0.86 (s, 9H), 0.05 (s, 3H), -0.12 (s, 3H).

^{13}C NMR (90 MHz, $CDCl_3$) δ: 138.85, 134.53, 129.06 (2C), 127.46 (2C), 82.54, 72.03, 25.50(3C), 17.99, -4.84, -5.59.

HRMS (EI) m/z calculated for $C_{10}H_{12}NO_3Si$ [M-*t*Bu]: 258.035, found: 258.

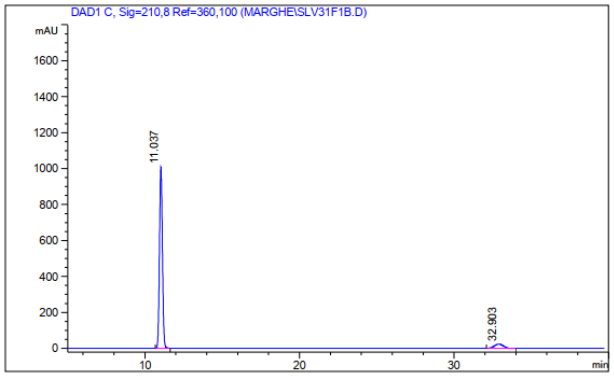
$[\alpha]_D^{26}$= -53.0° (c=3.0, λ=589 nm, $CHCl_3$, *ee*=86%).

The enantiomeric excess was determined by HPLC on chiral stationary phase with LUX CELLULOSE-1 3μ column: eluent Hexane/ *i*PrOH = 95/5, flow rate 0.8 mL/min, λ=210 nm τ_{major} = 11 min, τ_{minor} = 32 min.



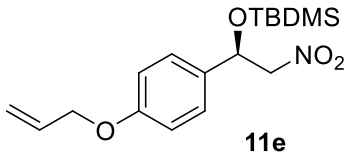
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	11.386	BB	0.218	24091.469	50.224	
2	32.370	BB	0.677	23876.582	49.776	



Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	11.037	BB	0.206	13298.867	92.932	
2	32.903	BB	0.640	1011.443	7.068	



11e

The product was purified by silica gel column chromatography with 97:3 hexane/ethyl acetate as eluent and obtained as a colourless oil in 90% yield and 74% *ee.* The product was completely characterized.

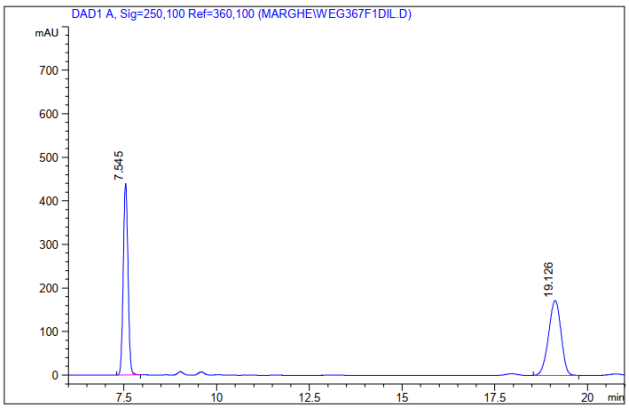
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.30 (d, 2H), 6.93 (d, 2H), 6.14-6.01 (m, 1H), 5.47-5.30 (m, 2H), 4.59-4.55 (m, 3H), 4.36 (dd, 1H), 0.86 (s, 9H), 0.04 (s, 3H), -0.13 (s, 3H).

^{13}C NMR (90 MHz, $CDCl_3$) δ: 158.83, 133.05, 131.50, 127.39 (2C), 117.83, 114.93 (2C), 82.86, 72.31, 68.85, 25.56 (3C), 18.04, -4.79, -5.56.

HRMS (EI) m/z calculated for $C_{13}H_{18}NO_4Si$ [M-*t*Bu]: 280.100512, found: 280.099900.

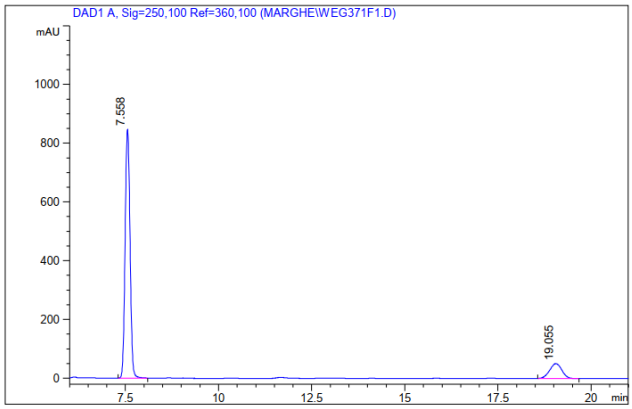
$[\alpha]_D^{26}$= -42.6° (c=2.3, λ=589 nm, $CHCl_3$, *ee*=74%).

The enantiomeric excess was determined by HPLC on chiral stationary phase with LUX CELLULOSE-1 3μ column: eluent Hexane/ *i*PrOH = 9/1, flow rate 0.8 mL/min, λ=210 nm τ_{major} = 7 min, τ_{minor} = 19 min.



Signal 1: DAD1 A, Sig=250,100 Ref=360,100

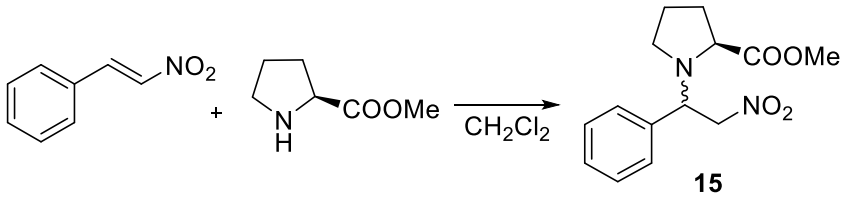
Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	7.545	BB	0.142	3911.511	49.342	
2	19.126	BB	0.368	4015.883	50.658	



Signal 1: DAD1 A, Sig=250,100 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	7.558	BB	0.145	7775.608	87.070	
2	19.055	BB	0.358	1154.694	12.930	

Synthesis of proline methylester/β-nitrostyrene adduct

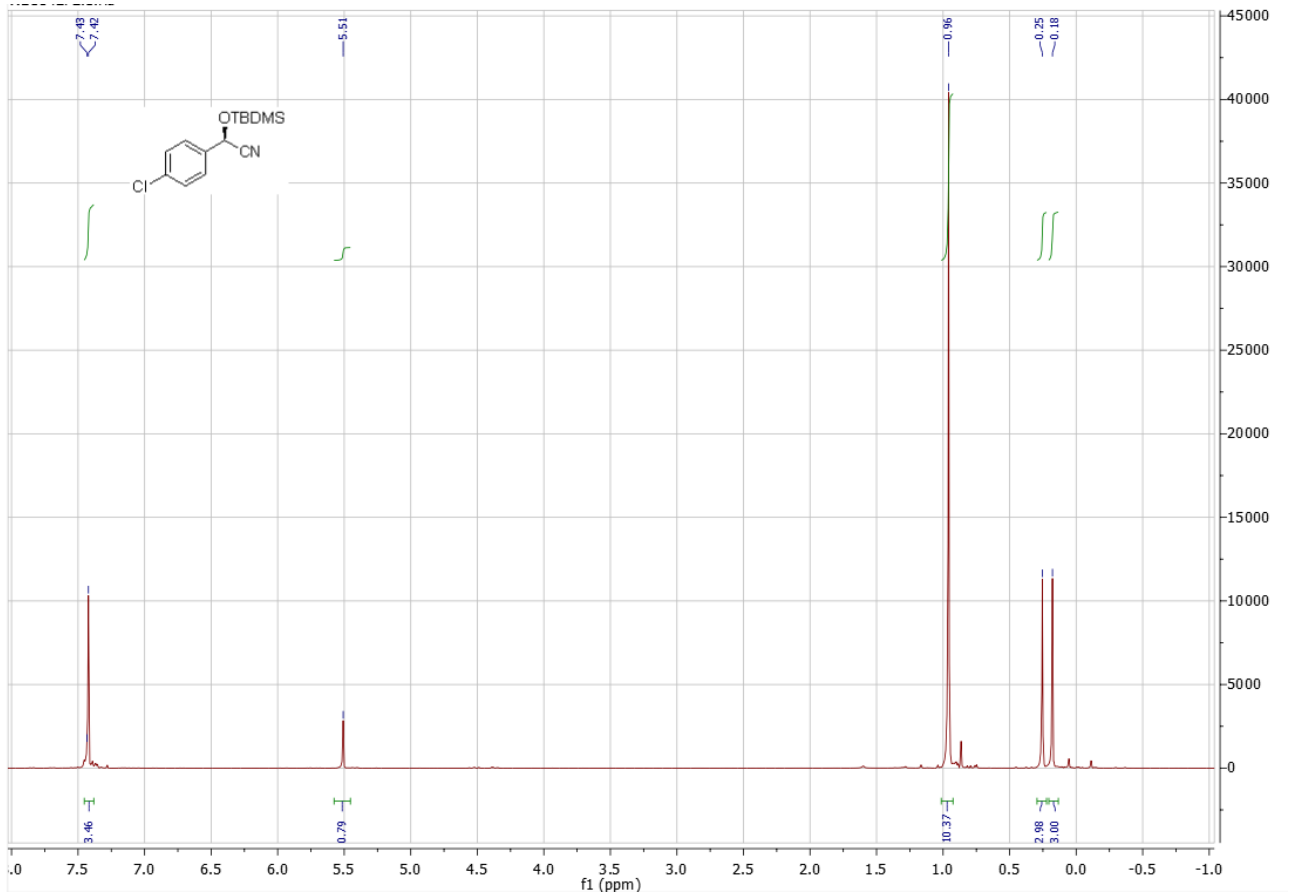


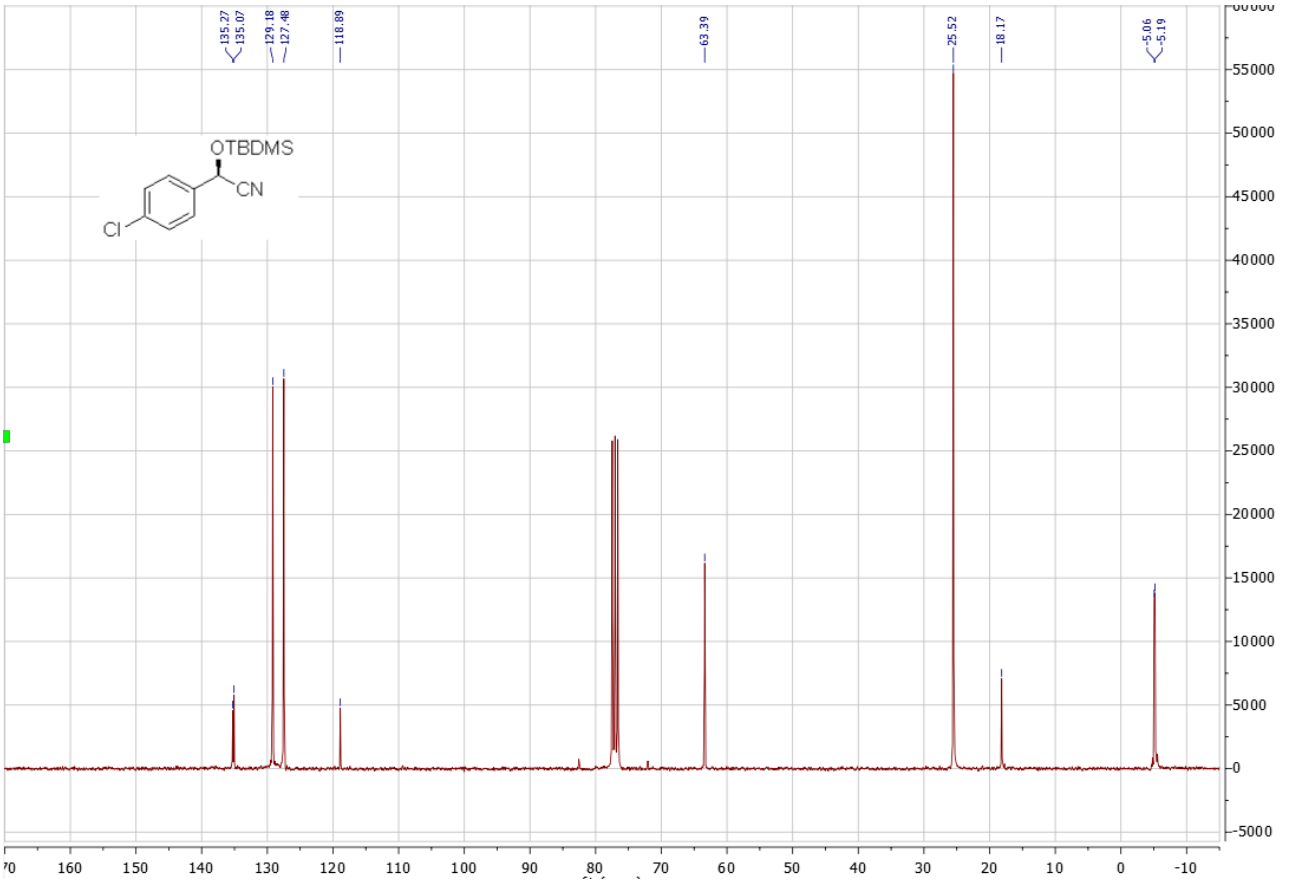
15

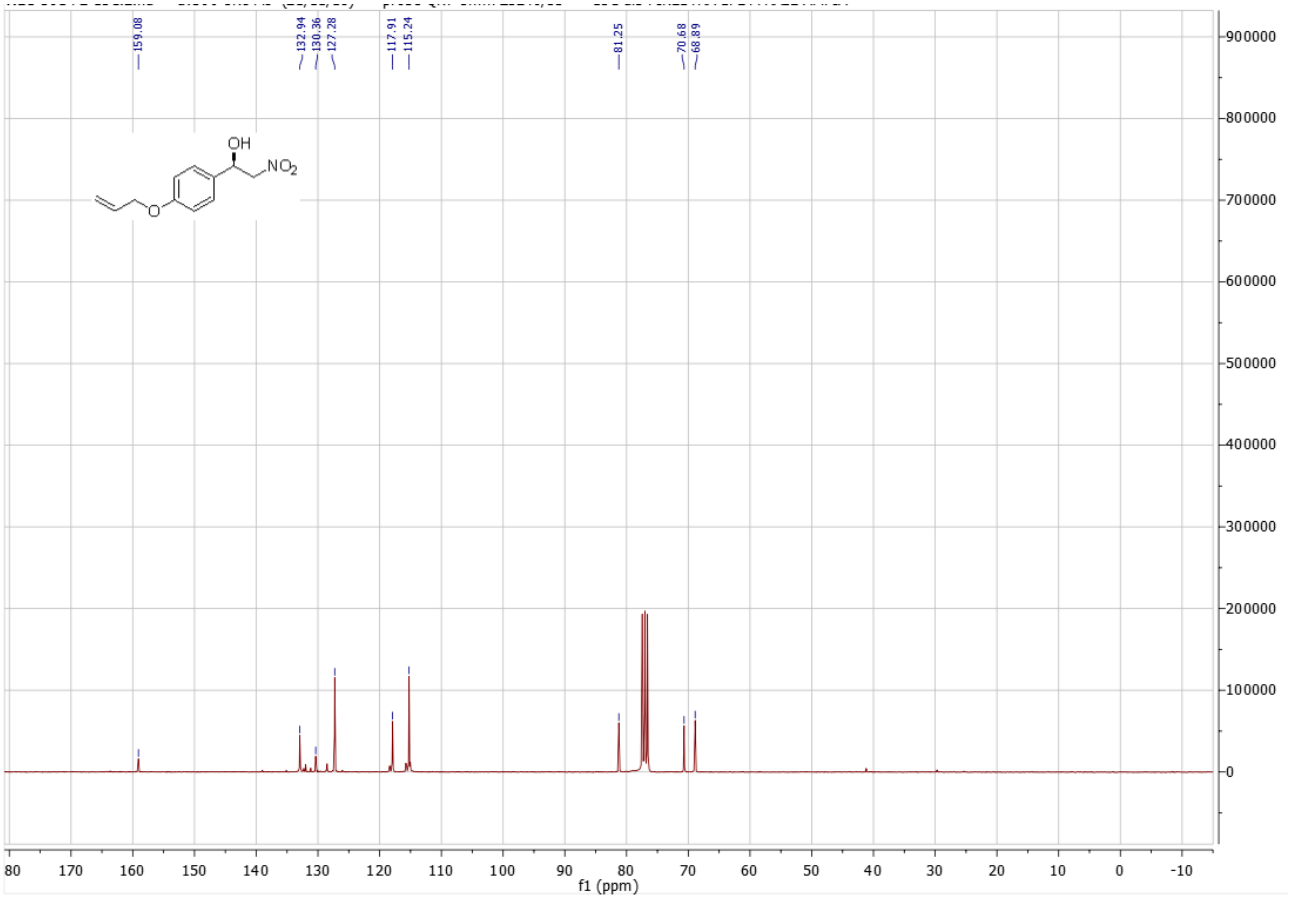
Proline methylester and β-nitrostyrene were mixed in a 1:1 mixture in dichloromethane (0.2M) for 4 h. The solvent was removed under reduced pressure, and the crude subjected to ^{1}H NMR to evaluate the *dr* to 65:35. The product is unstable, so that complete characterization or purification were not possible, and it was directly used in our reaction.

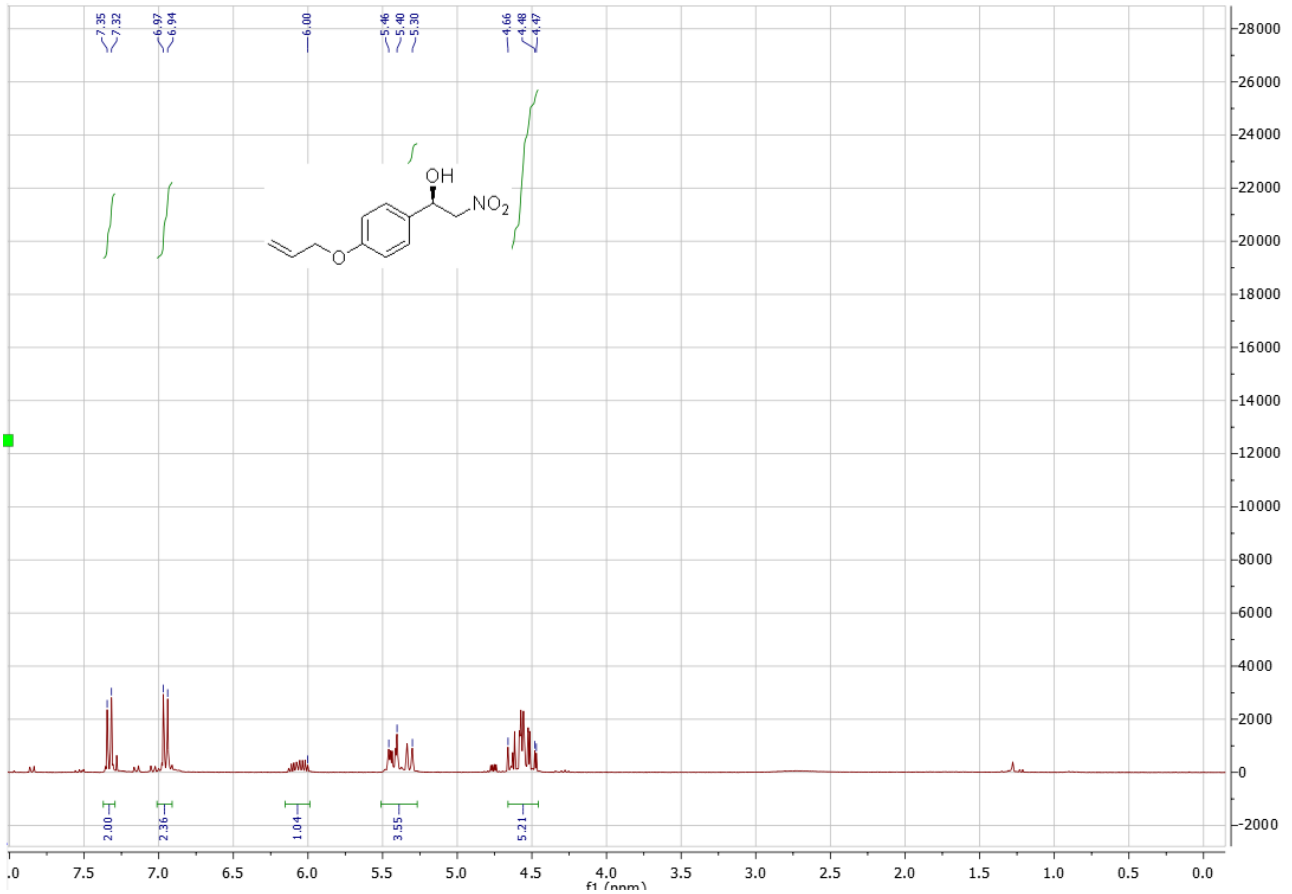
^{1}H NMR (300 MHz, $CDCl_3$) δ: *major (S,R):* 77.39-7.24 (m, 5H), 5.02-4.93 (dd, 1H), 4.76-4.55 (m, 2H), 3.71 (s, 3H), 3.41-3.37 (m, 1H), 3.07-3.02 (m, 1H), 2.63-2.59 (m, 1H), 2.0-1.78 (m, 4H); *minor (S,S):* 77.39-7.24 (m, 5H), 5.02-4.93 (dd, 1H), 4.76-4.55 (m, 2H), 3.56 (s, 3H), 2.50-3.46 (m, 1H), 3.16-3.10 (m, 1H), 1.78-2.70 (m, 1H), 1.86-1.68 (m, 4H).

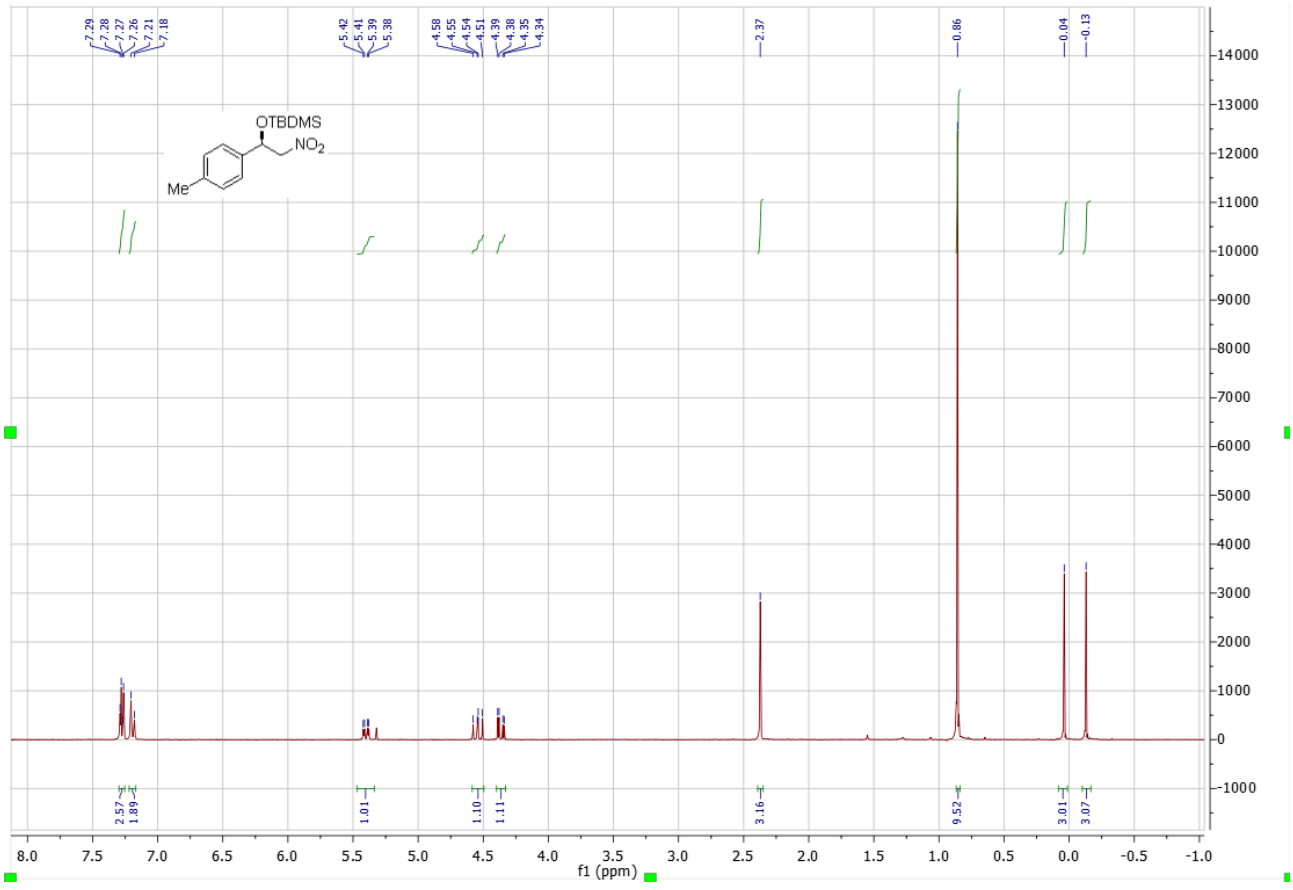
Selected NMR spectra

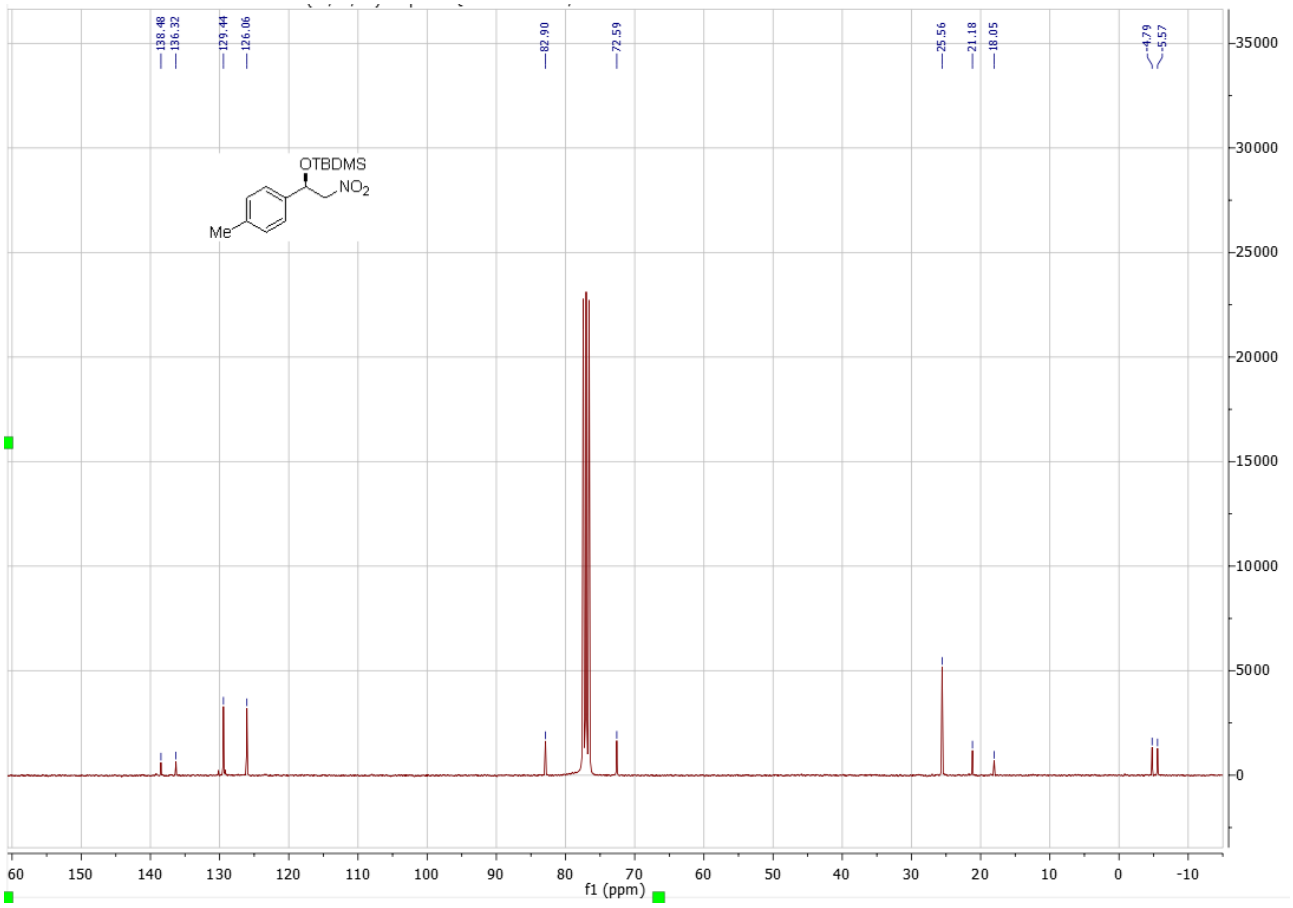


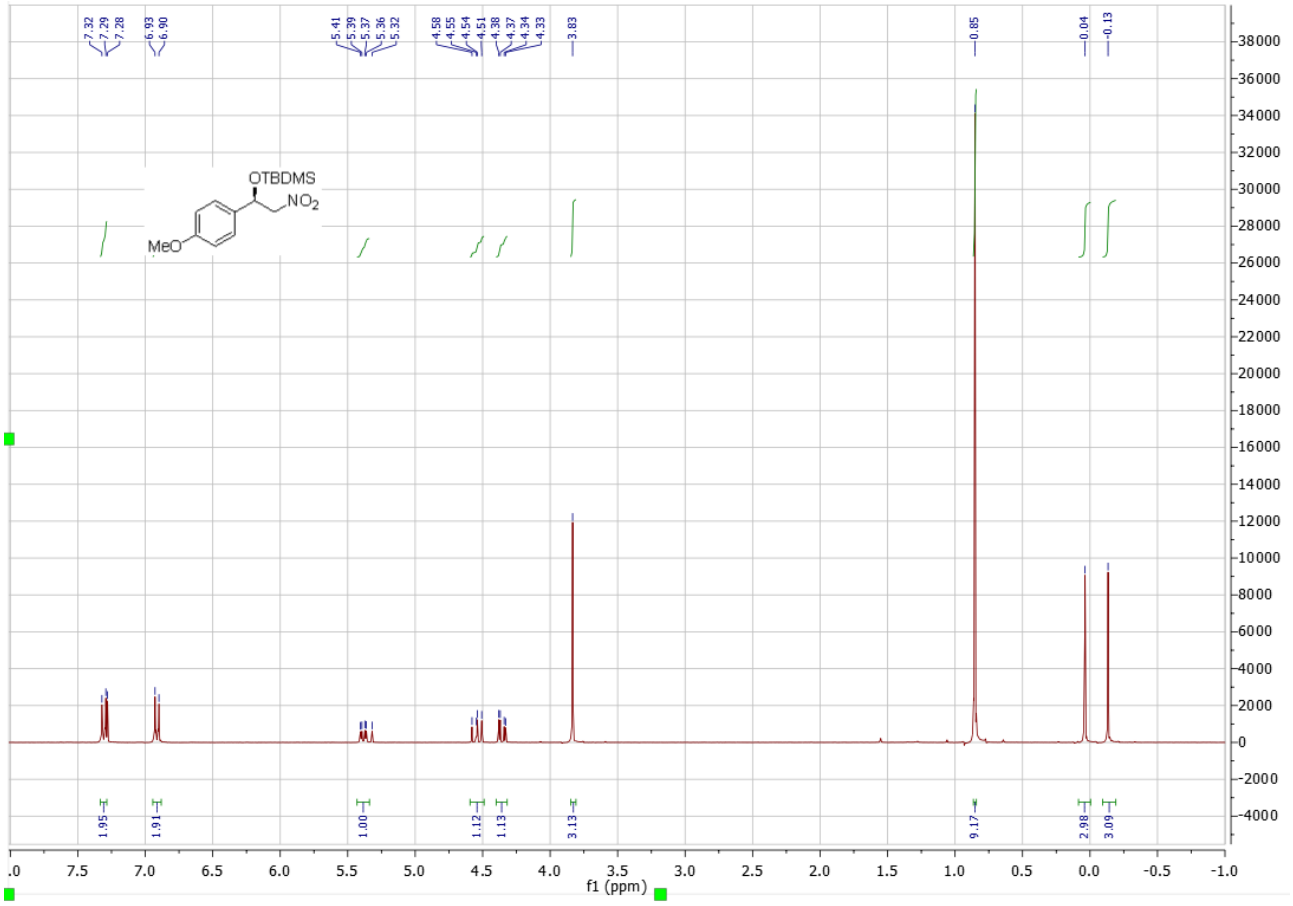


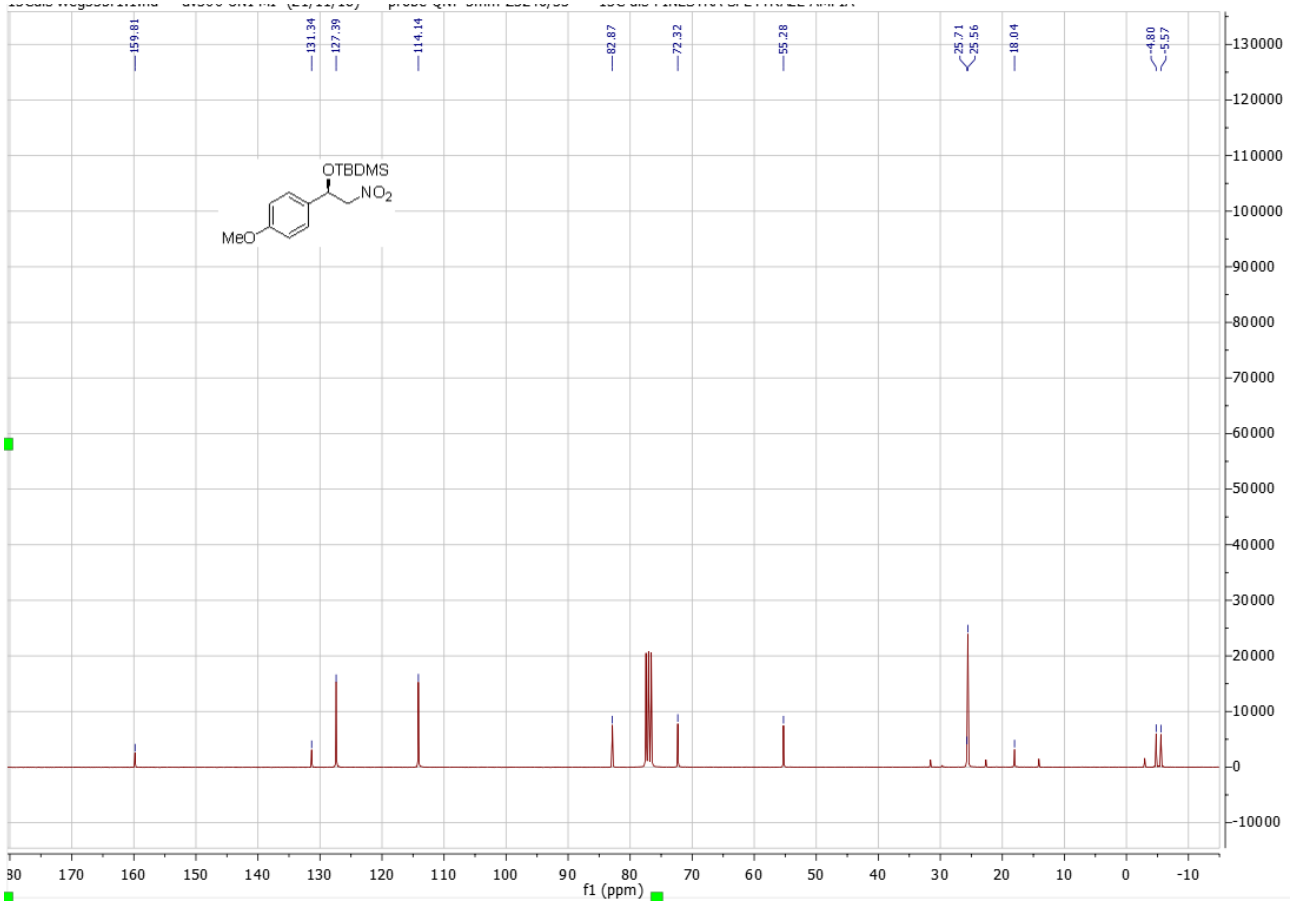

159.08
132.94
130.36
127.28
117.91
115.24
81.25
70.68
68.89
OH
NO2
O
f1 (ppm)


7.35
7.32
6.97
6.94
6.00
5.46
5.40
5.30
4.66
4.48
4.47
OH
NO2
O
2.00
2.36
1.04
3.55
5.21
f1 (ppm)


7.29
7.28
7.27
7.26
7.21
7.18
5.42
5.41
5.39
5.38
4.58
4.55
4.54
4.51
4.39
4.38
4.35
4.34
2.37
0.86
0.04
-0.13
OTBDMS
NO2
Me
2.57
1.89
1.01
1.10
1.11
3.16
9.52
3.01
3.07
f1 (ppm)


138.48
136.32
129.44
126.06
82.90
72.59
25.56
21.18
18.05
-4.79
-5.57
OTBDMS
NO2
Me
f1 (ppm)


7.32
7.29
7.28
6.93
6.90
5.41
5.39
5.37
5.36
5.32
4.58
4.55
4.54
4.51
4.38
4.37
4.34
4.33
3.83
0.85
0.04
-0.13
OTBDMS
NO2
MeO
1.95
1.91
1.00
1.12
1.13
3.13
9.17
2.98
3.09
f1 (ppm)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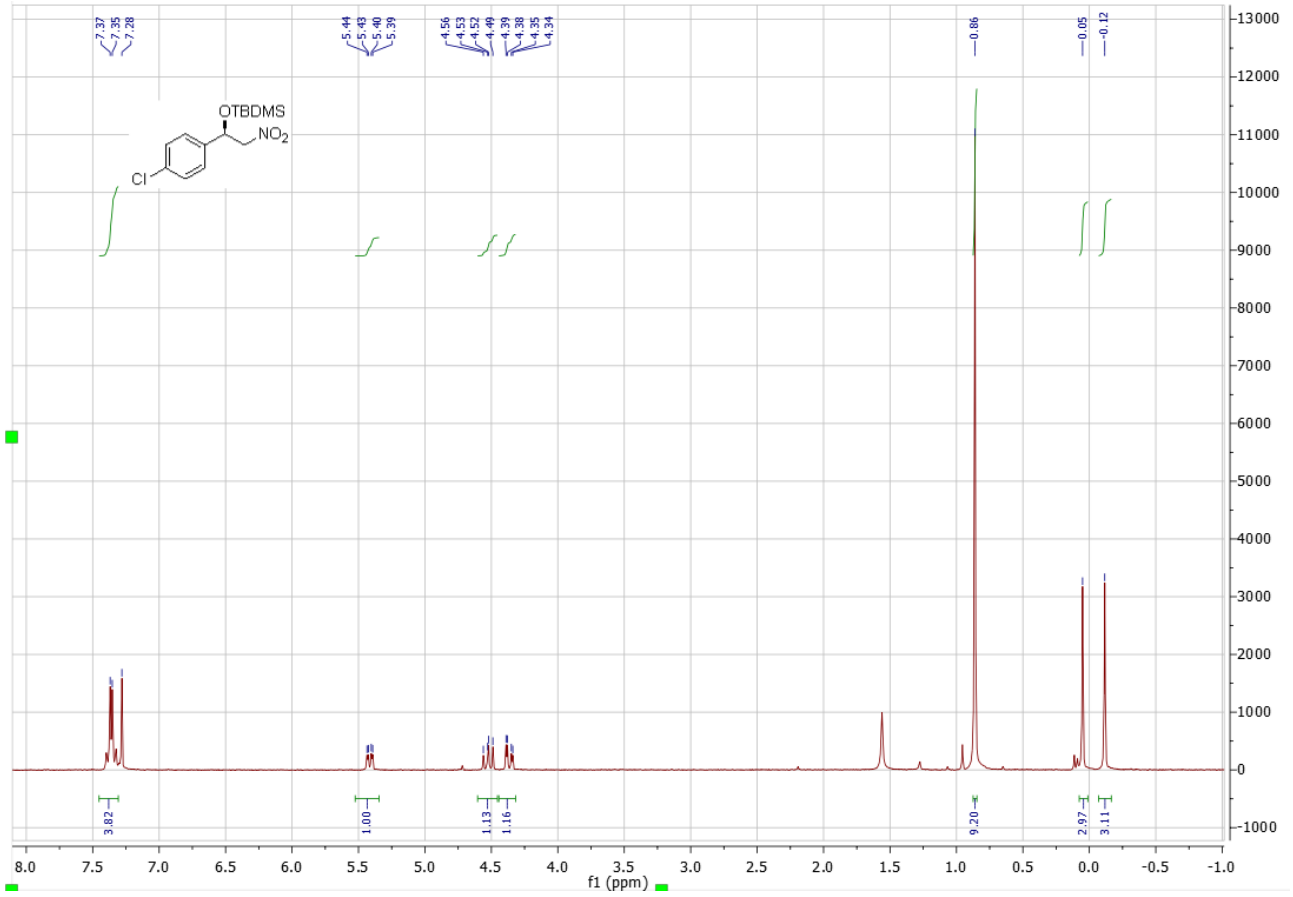
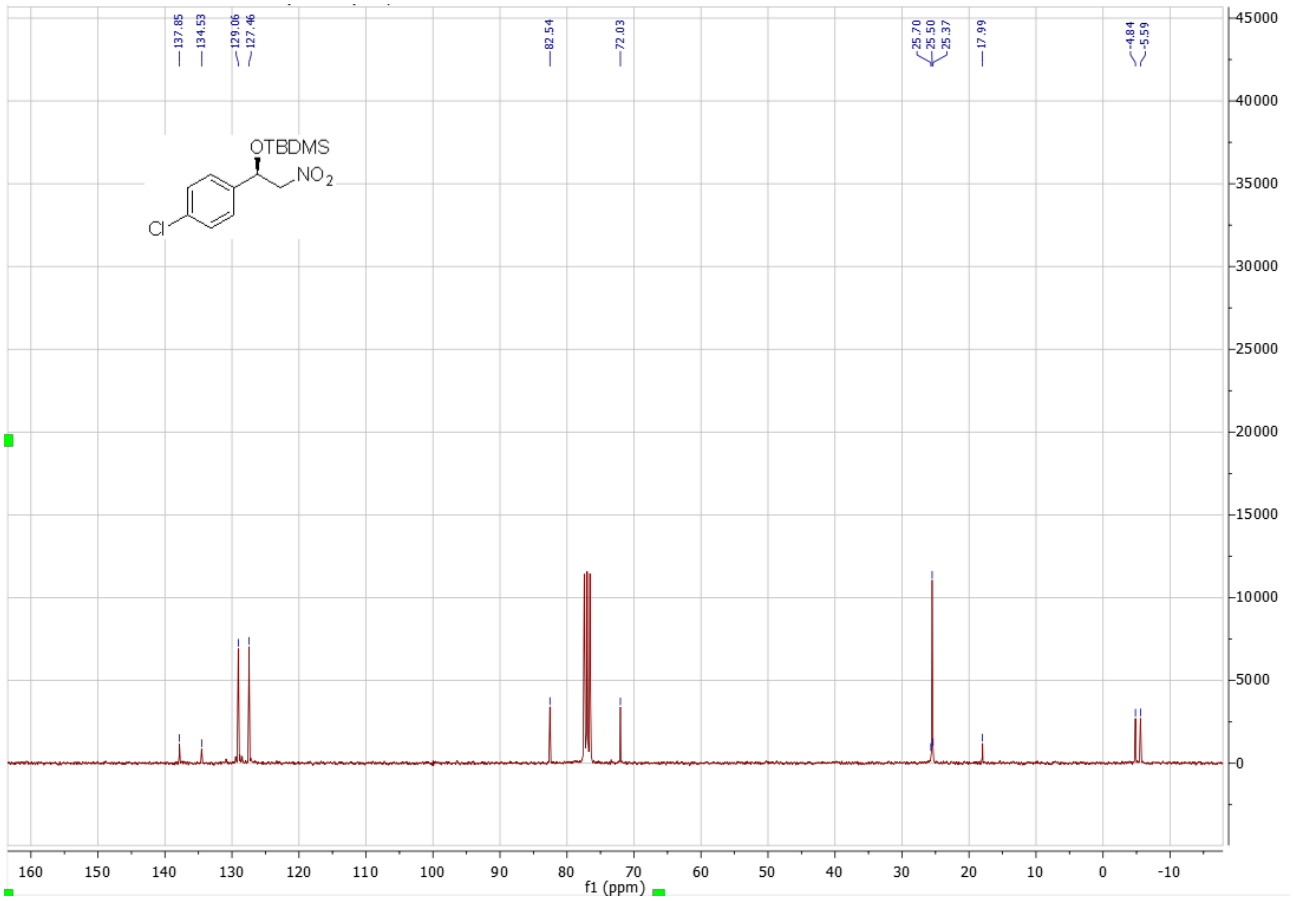
131.34
127.39
114.14
82.87
72.32
55.28
25.71
25.56
18.04
-4.80
-5.57
OTBDMS
NO2
MeO
f1 (ppm)


7.37
7.35
7.28
5.44
5.43
5.40
5.39
4.56
4.53
4.52
4.49
4.39
4.38
4.35
4.34
0.86
0.05
-0.12
OTBDMS
NO2
Cl
3.82
1.00
1.13
1.16
9.20
2.97
3.11
f1 (ppm)


137.85
134.53
129.06
127.46
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72.03
25.70
25.50
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17.99
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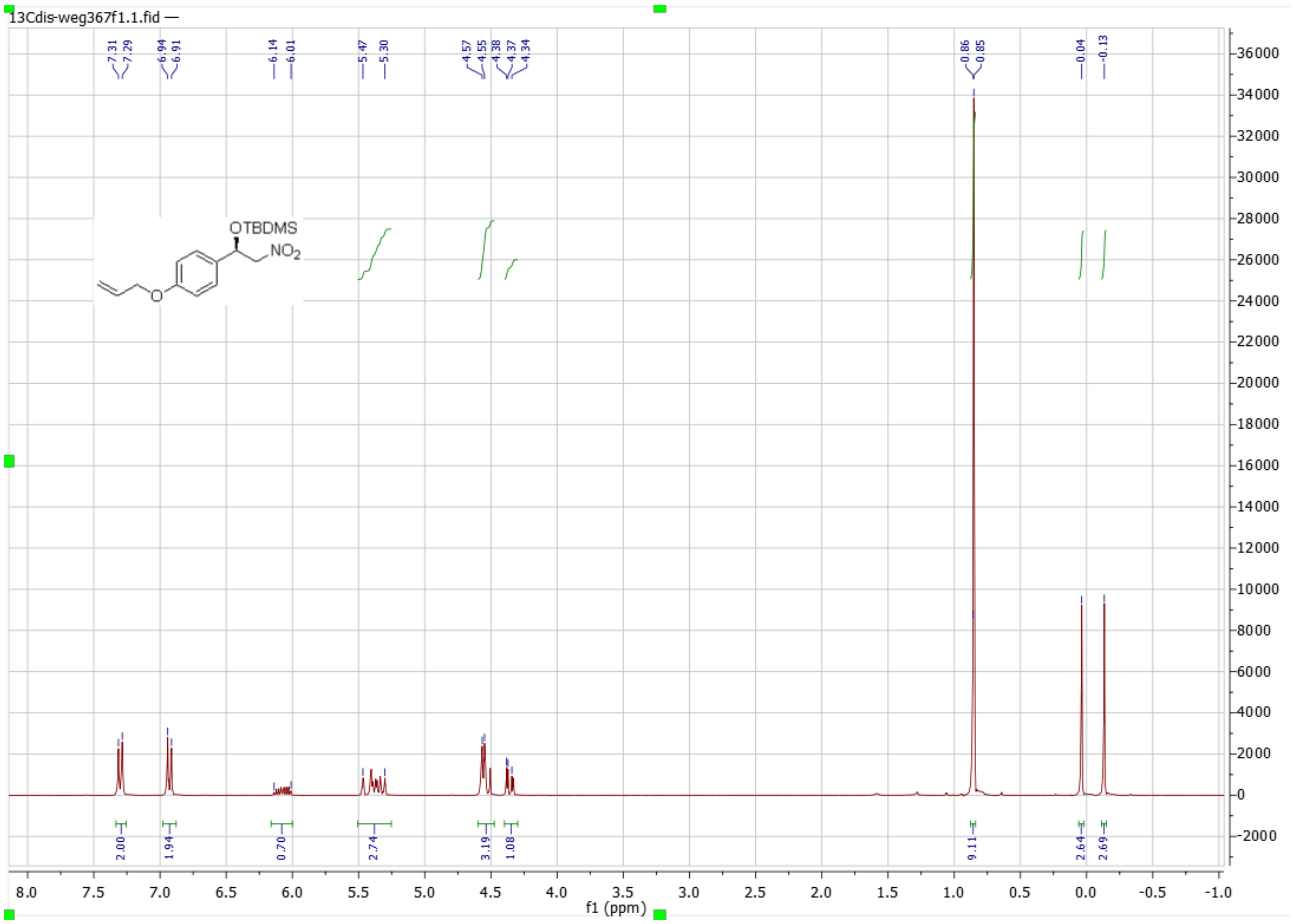
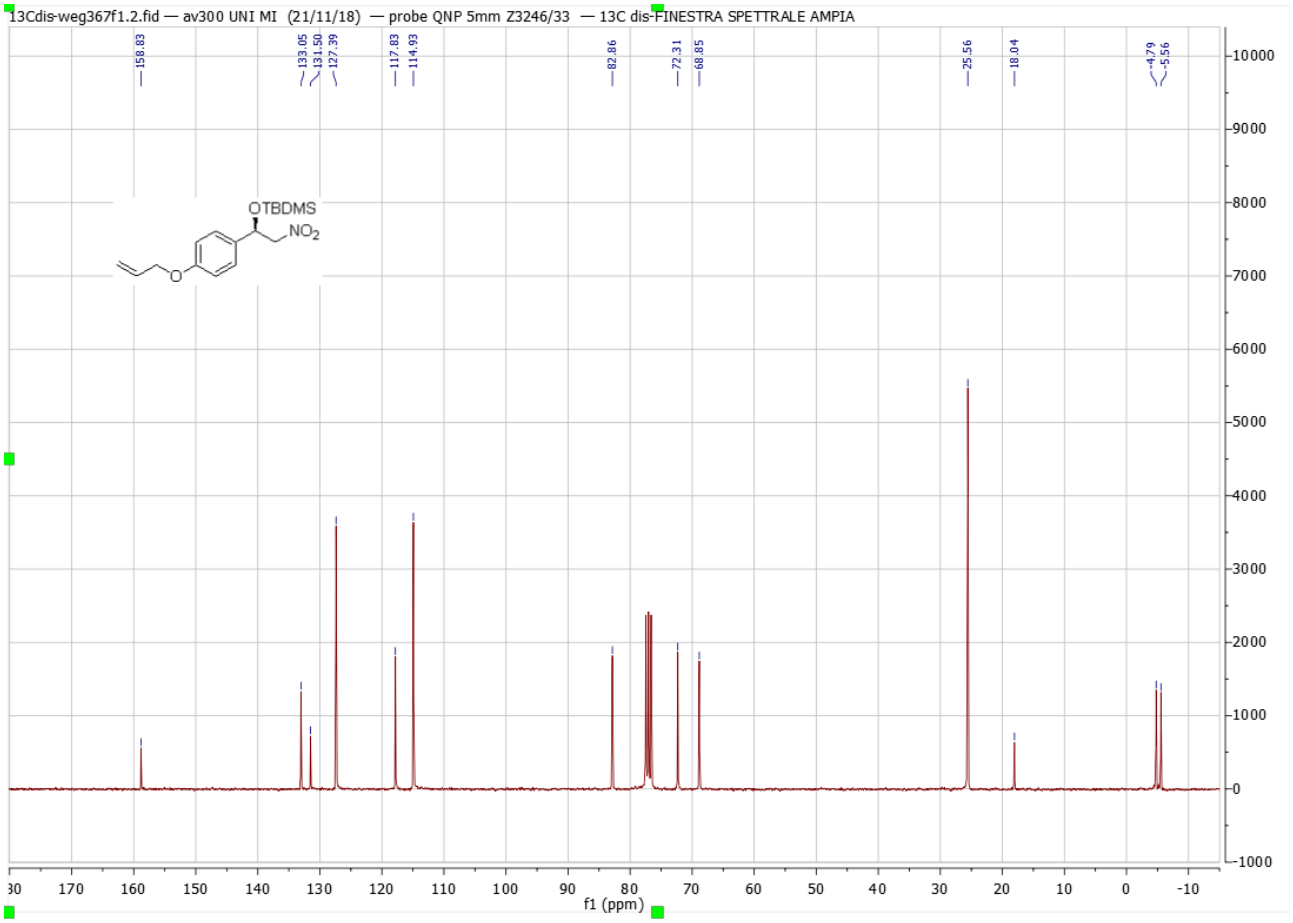
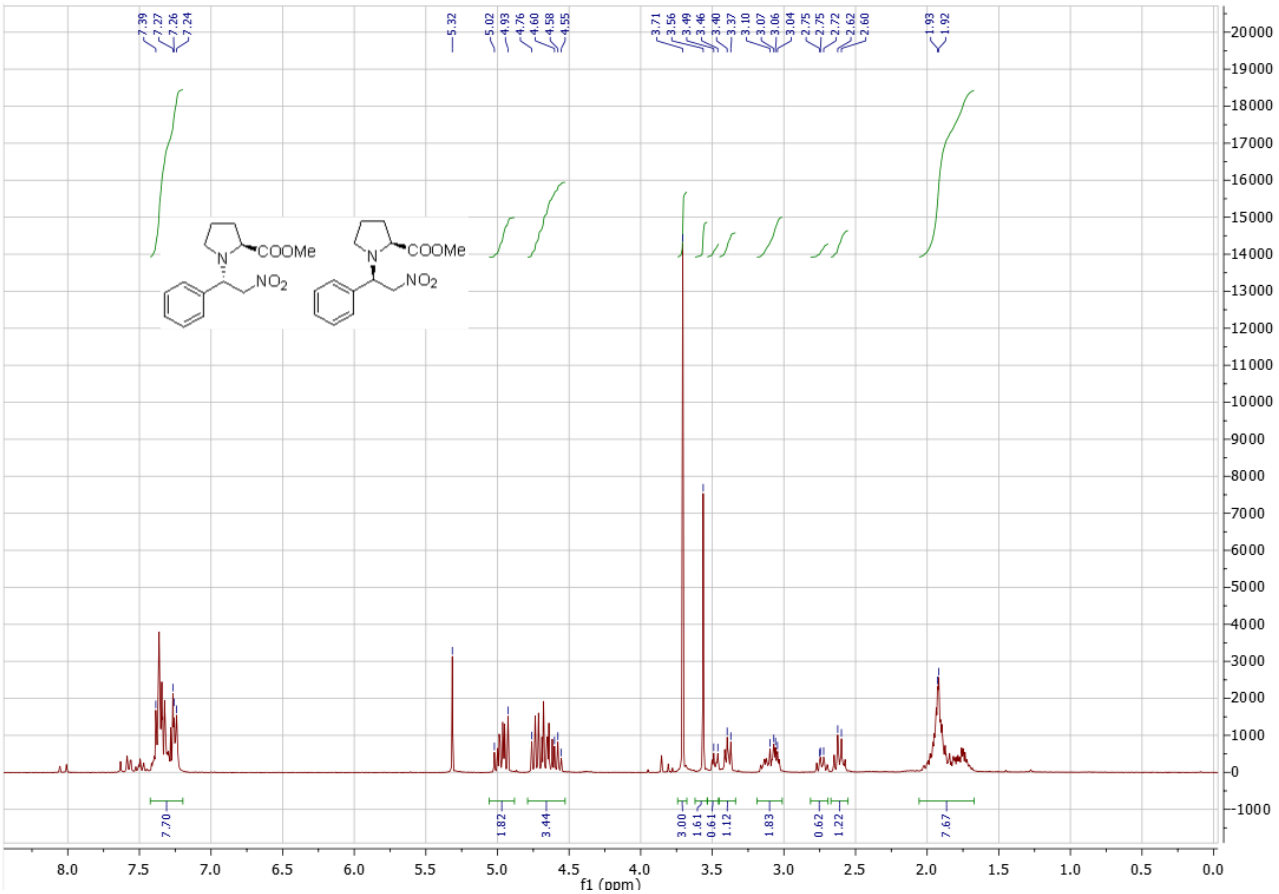
OTBDMS
NO2
Cl
f1 (ppm)


13Cdis-weg367f1.1.fid —
7.31
7.29
6.94
6.91
6.14
6.01
5.47
5.30
4.57
4.55
4.38
4.37
4.34
0.86
0.85
0.04
-0.13
OTBDMS
NO2
O
2.00
1.94
0.70
2.74
3.19
1.08
9.11
2.64
2.69
f1 (ppm)


13Cdis-weg367f1.2.fid — av300 UNI MI (21/11/18) — probe QNP 5mm Z3246/33 — 13C dis-FINESTRA SPETTRALE AMPIA
158.83
133.05
131.50
127.39
117.83
114.93
82.86
72.31
68.85
25.56
18.04
-4.79
-5.56
OTBDMS
NO2
O
f1 (ppm)


7.39
7.27
7.26
7.24
5.32
5.02
4.93
4.76
4.60
4.58
4.55
3.71
3.56
3.49
3.46
3.40
3.37
3.10
3.07
3.06
3.04
2.75
2.75
2.72
2.62
2.60
1.93
1.92
COOMe
NO2
COOMe
NO2
7.70
1.82
3.44
3.00
1.61
0.61
1.12
1.83
0.62
1.22
7.67
f1 (ppm)

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Chapter 2: introduction to flow chemistry

Traditionally, organic synthesis has always relied on batch reactions. Substrates, solvents and catalysts are added into a flask and then stirred at a given temperature for a precise reaction time after which the crude mixture is analyzed, and the product is isolated. The production of fine chemicals (*i.e.* drugs, food additives, agrochemicals or flavors) has always been based on sequential batch processes constituted by multiple unit operations.

A conceptually different approach to chemical synthesis is represented by flow processes (Figure 1) where the reagents are continuously pumped into a reactor which can be heated, cooled or irradiated (with microwaves or light) and can contain immobilized reagents, catalysts or scavengers in order to eliminate side-products or trace metals.

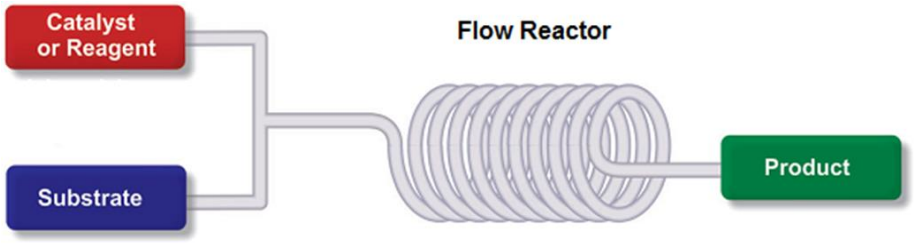


Figure 1

Continuous flow reactors are generally constituted by coiled tubing or chip-based devices having high surface area/volume ratio. This results in several advantages over classical batch reactors, in particular an improved heat and mass transfer. All reaction parameters can be precisely monitored thus making the process reliable and reproducible. In this way, in some cases reaction time can be reduced, increasing the efficiency of a synthesis. A better control of reaction temperature in a small media like a coiled tube, disfavors also the presence of hot-spots, often related to the formation of undesired side-products.[1]

The closed environment where a continuous flow reaction takes place ensures other benefits, mainly concerning safety issues: hazardous and highly toxic chemicals or reaction intermediates can be generated *in-situ* and converted into more elaborated molecules by combining different reagent streams. This minimizes risks for the operator because no handling or accumulation of dangerous species is required.

Flow processes are suitable for automation and offer the opportunity to run multistep reactions without isolation of intermediates: reactions that involves the formation of instable or dangerous species become in that way more feasible. Furthermore, real time analysis for optimal reaction conditions and minimization of waste is made easier.[2]

The choice of the specific reactor is fundamental, and it is determined by the characteristics of the synthetic process being performed. Principal aspects are the physical state of the reagents employed (liquids, solids, gases), the reaction thermodynamic (exo- or endo-thermic), reaction kinetics, mixing, heat and mass transfer and residence time. A lot of commercially available systems to perform continuous flow reactions are available on the market, offering solutions to different problems. Tube based laboratory reactors are typically coiled and they are usually made of stainless steel Hastelloy, copper, polyether ether ketone (PEEK) or perfluorinated polymers. The choice of the material depends on the reaction conditions and on the stability toward the chemicals employed. The volumes range from 1 µL to liters with channel diameters spanning from 100 µm to

16 mm, depending on the specific requirements of the system. It's important to distinguish between micro-sized reactors (10 - 500 µm channel width) and meso-sized reactors (500 µm – some mm channel width): the combination of internal diameter of the tube and flow-rate is a key parameter for the properties of the system.[1,3]

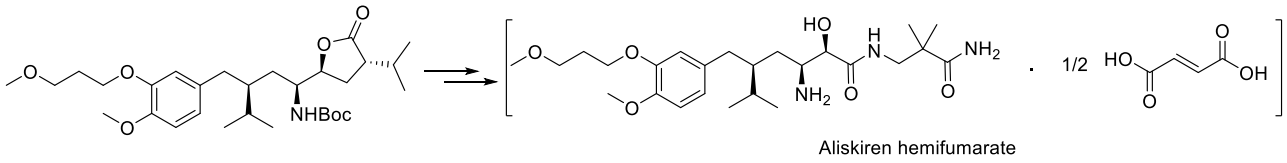
Even though flow reactors offer some benefits over batch procedures, also limitations still need to be overcome. The main issue is related to the precipitation of solid species which can cause the clogging of the reactor. The precipitation of inorganic salts or insoluble materials during a reaction is a very common situation in synthetic chemistry. It is easy to understand that this represents a big problem in the case a flow system. Recently new technologies for the handling of solids in flow have been developed, however technical advances are still required to avoid undesirable situations.

When operating with multiphase systems an extremely accurate control of reaction parameters is required, since otherwise non efficient mixing into the reactor may occur. Recently some technologies to overcome this issue have been developed (*e.g.* tube-in-tube reactor for gas-liquid biphasic systems)[4] but some improvement for large scale application is still required.

In the academia, a huge interest has recently emerged towards the preparation of APIs using continuous flow techniques;[5,6] despite this boost, in the fine chemical industry and in particular in the pharmaceutical one the switch towards the flow chemistry is still ongoing. The U.S. Food and Drug Administration has recognized continuous manufacturing as an economically and environmentally impactful resource, allowing a more reliable scale-up, a greater flexibility both in size and location, as well as enhanced safety, greenness and control of operations.[7]

The implementation of continuous flow processes in pharmaceutical and fine chemical industries is still relatively limited. Until recently, a continuous manufacturing approach was a prerogative of petrochemical and bulk chemical companies where large volumes of relatively simple compounds were produced. The challenge for the application of continuous manufacturing in the fine chemical sector has always been the complexity and diversity of the products, and the associated complex process conditions. Usually, molecules produced by pharma and agrochemical companies require 6 to 10 synthetic steps (convergent or sequential) and might involve chemo- regio- and stereo-selective transformations which necessitate quenching, work-up, separation and purification operations. These products are generally produced in relatively small volumes and they possess a short lifetime. For these reasons, batch procedures involving the use of multipurpose plants still dominate the production of fine chemicals: a small number of temperature- and pressure-controlled vessels can be used for virtually all the reactions, separations and purification steps associated to a long and complex synthetic route. However thanks to the recent development of commercially available modular devices to perform continuous flow synthesis and to the growing interest of the scientific community (at the academic and industrial level) toward flow chemistry, the continuous manufacturing of pharmaceutical is rapidly expanding becoming an enabling tool for process and medicinal chemists.

Several examples of continuous manufacturing of APIs are reported in the literature. The first one is the Aliskiren hemifumarate[6,8] continuous production, carried out by MIT and Novartis group (Scheme 1).



Scheme 1

Here, the flow technology is not only related to the synthetic aspect, but all the operations (quench, phase separation, crystallizations, drying, and formulation) involved in the production of the final drug were carried out under continuous flow mode in a complete automated process. The productivity of the apparatus is impressive: with a reactor volume of 0.7 Liter, 100 g/hour API could be prepared, on two different synthetic steps (Figure 2).

Figure 2

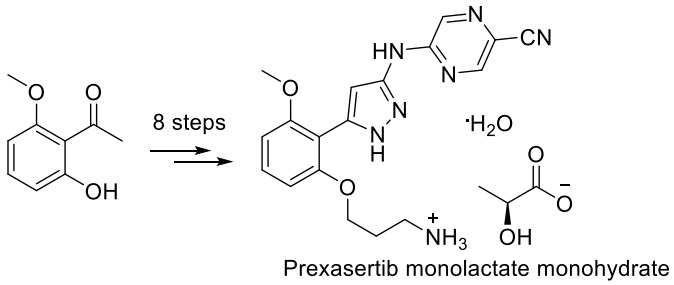
The second example was reported by Adamo et al[9] in 2016: working at MIT, they developed a continuous flow manufacturing platform that can produce thousands of formulated, ready-to-use, liquid drug doses per day.[9] This work represent a tremendous advancement in the continuous flow synthesis of pharmaceuticals and addresses challenges in reconfiguration for multiple synthesis of diverse compounds, being able not only to perform the synthesis but also all the purification steps required (e.g. crystallizations) and the liquid formulate preparation.

The machine has little dimensions, comparable to a commonly used refrigerator, (*h*: 1.8 m, *l*: 0.7 m, *w*: 1.0 m; 100 kg) and is capable of complex multistep synthesis, multiple in line purifications, reaction workup, semi-batch crystallization, real-time process analysis and formulation of high purity drug products. The synthesis of four active pharmaceutical ingredients (diphenhydramine hydrochloride, lidocaine hydrochloride, diazepam and fluoxetine) in compliance to CGMP (current good manufacturing practice) standards has been demonstrated. As illustrated in Figure 3 **,** the system is composed by two main units: the upstream unit contains reaction-based equipment for the manufacture of APIs (feeds, pumps, flow reactors, separators, back-pressure regulators, in-line analytical instruments); the downstream unit is dedicated to the purification and formulation of the final drug product. Despite having many complex operations, the entire platform can be managed easily by a single operator.

Figure 3

This reconfigurable platform enables the on-demand synthesis and formulation of many drug products. The reproduction of this platform would be simpler, cheaper and faster to operate than a full batch plant. The possibility to produce drugs on-site could be particularly advantageous for products with a short shelf-life.

In 2017 a group of researchers at Eli Lilly reported the synthesis of Prexasertib monolactate monohydrate in kilogram-scale under continuous-flow CGMP conditions (Scheme 2).[10] Eight continuous unit operations were conducted, using small continuous reactors, extractors, evaporators, crystallizers and filters in laboratory fume hoods.



Scheme 2

The continuous process afforded improved performance and safety relative to batch processes: the possibility to work at higher temperatures than the boiling point of solvent, by safely working under pressure improved the performance, while avoidance of exposure of plant personnel to the high potent drug as well as hazardous reagents (like hydrazine in the first reaction step), attention to equipment cleaning to avoid cross contaminations, contributed to the safety of the process. Online process analytical technology and process automation were on the other hand responsible of an increased quality assurance and process understanding.

One of the most recent examples was reported this year by Gilead's scientists, related to the development of a large-scale cyanation step in the synthesis of Remdesivir,[11] one of the drug candidates for the treatment of COVID-19, the infection related to the spreading of the novel coronavirus, SARS-CoV-2. The previously reported six-step synthesis of Remdesivir included a stereoselective cyanation, that was performed under

cryogenic conditions and had the potential to liberate hydrogen cyanide. In sight of a multikilogram synthesis of the target, this step was developed under continuous flow conditions, to address selectivity and safety issues. Smaller quantities of the hazardous reaction mixture were handled at the same time and were rapidly quenched in small volumes once the reaction stream exited the flow reactor (Figure 4). Also, a better control of reaction parameter resulted in increased selectivity, since temperature rises provided by exothermic reactions were easily controlled by bath cooling of the stainless-steel reactor.

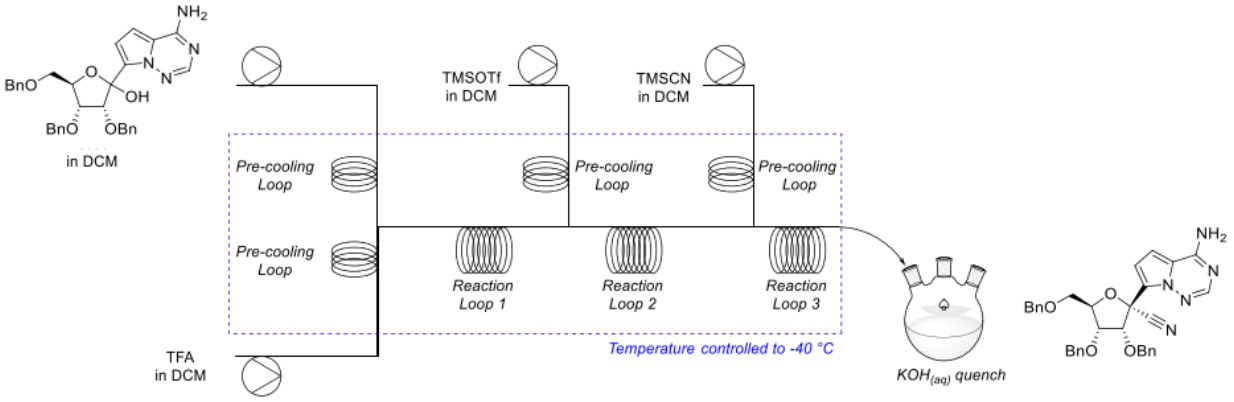


Figure 4

Another aspect to take into consideration regarding flow chemistry is that it can be easily combined to many enabling technologies in order to increase process efficiency.[9] Representative enabling technologies combined to continuous processes are supported reagents or catalysts, microreactor technology, 3D printing, photochemistry, microwave irradiation, inductive heating, electrochemistry or new solvent systems (Figure 5). This combination allows the development of fully automated process with an increased throughput.

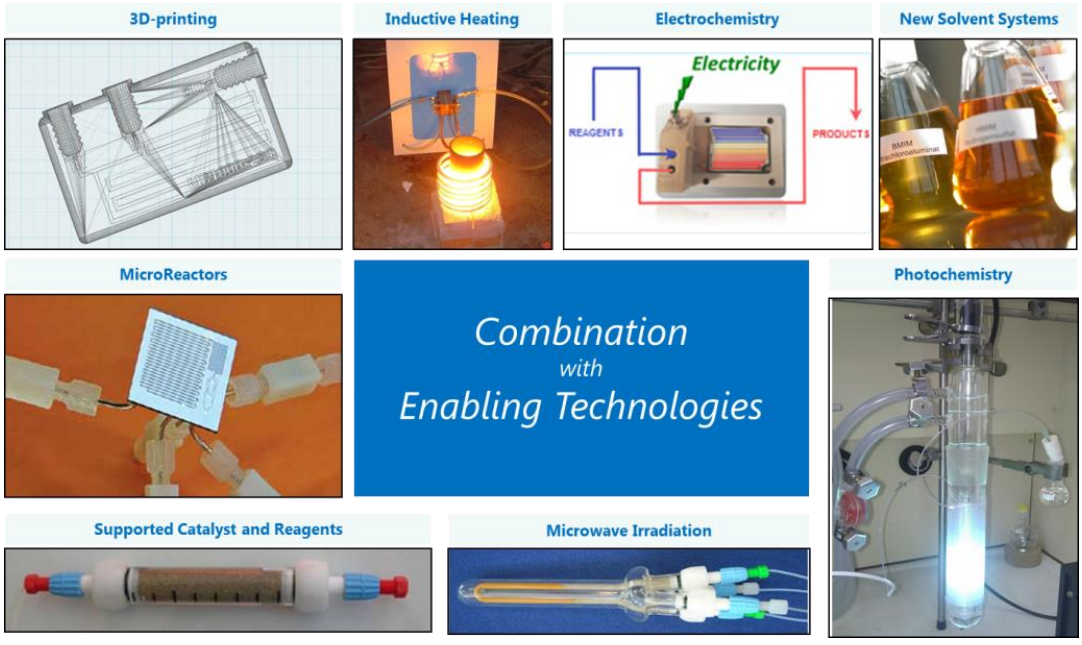


Figure 5

In the present chapter, we will discuss two examples of application of continuous flow technology to stereoselective organocatalytic synthesis. In both cases, our focus will be on the possibility to take advantage of this technology to develop telescopic multistep processes avoiding isolation and manipulation of intermediates. In particular, in **Chapter 2.1** we will present the synthesis of a specific target, a fluorinated analogue of an API, while in **Chapter 2.2** a more general synthetic strategy affording optically active 1,2-diamines starting from nitroenamines will be shown.

Chapter 2.1: **Batch and flow stereoselective organocatalytic synthesis of a fluorinated analogue of retro-thiorphan: a comparative study**

Introduction

The field of application of organofluorine compounds is really wide in scope, ranging from pharmaceutical, agrochemical and veterinary areas to material science.[12–14] The role of fluorinated molecules in drug discovery has become of fundamental importance; in fact, fluorine has been found in around 15–20% of all the new chemical entities (NCIs) licensed each year for the clinical market and 30% of the leading pharmaceutical blockbusters contain fluorine.[15] This is due to the ability of fluorine to modify the physico-chemical, biological and metabolic properties through concomitant alteration of steric, electronic and lipophilic characteristics of a molecule, conferring new and unprecedented therapeutic profiles. In particular, it affects pKa values, binding affinity, pharmacokinetics and bioavailability.[16]

In this context, enantiopure trifluoromethylated molecules are at the forefront of innovation in modern organofluorine chemistry because of the increasing occurrence of this motif in a wide range of biologically active compounds, but also in optically active reagents and in materials designed for optoelectronic devices.[16,17]. In particular, researchers are looking for efficient methods to control the configuration at carbon centers endowed with a fluorinated motif.[18] At present, two complementary strategies could be applied: (i) the direct introduction of a single fluorine atom or of a fluorinated moiety through nucleophilic, electrophilic, or radical reactants; (ii) the exploitation of fluorinated substrates as building blocks.[19,20]

Among the incredibly high number of fluorinated molecules of interest, chiral amines play a fundamental role in medicinal chemistry. A few selected examples of chiral amines carrying a trifluoromethyl group on a stereogenic carbon are reported in Figure 6; many of them are well recognizable as important drugs, while others are fluorinated analogues, which activity has been tested, since the trifluoromethyl group typically guarantees improved lipophilicity and metabolic stability over the corresponding non-fluorinated compounds.

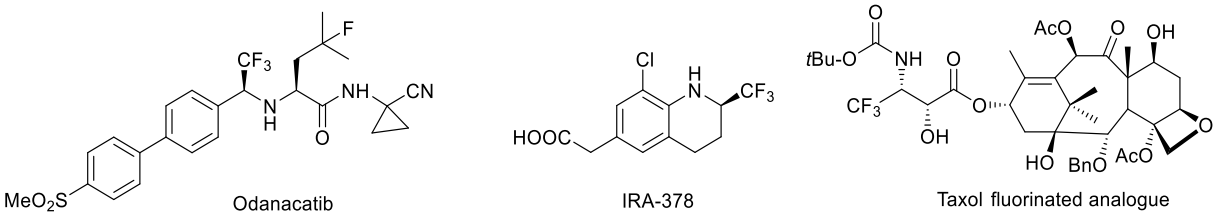
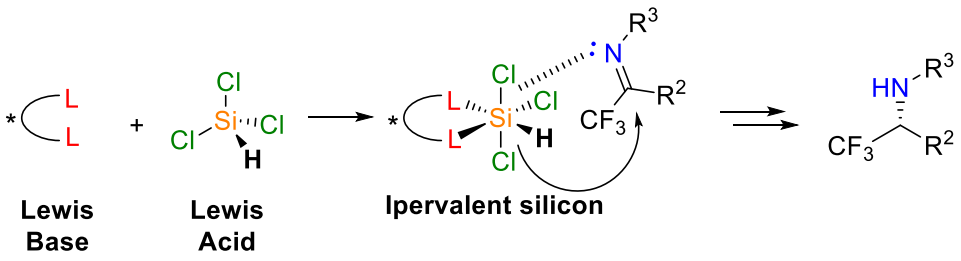


Figure 6

Considering that trifluoromethyl ketones are readily accessible, and many of them are even commercially available, the catalytic enantioselective reduction of the corresponding ketimine derivatives offers a viable approach to the synthesis of enantiomerically pure α-trifluoromethyl amines. Indeed, few examples of enantioselective hydrogenations have been reported in the literature for this class of substrates, either involving metal-catalyzed hydrogenations, in the presence of a chiral catalyst,[21,22] or H_2-free reductions and isomerizations.[23,24]

Considering metal-free options, the use of chiral Lewis bases in combination with trichlorosilane to access α-trifluoromethyl chiral amines via stereoselective reduction of the corresponding imines was also reported (Scheme 3).[25,26] (For the stereoselective reduction of imines mediated by trichlorosilane, see Introduction).



Scheme 3

Chiral picolinamides derived from ephedrine (catalyst **A,** Figure 7),[27] binaphthyl diamine (catalyst **C**),[28] and from prolinol (catalyst **B**)[29], as well as other Lewis bases like (*S*)-prolinol-derived phosphinic amide (catalyst **D**)[30], chiral bis-phosphine oxides (catalyst **E**)[31] and *O*-benzyl-substituted imidazolidinone (catalyst **F**)[32] have been employed to promote the enantioselective reduction of ketoimines derived from trifluoromethyl phenyl ketone in up to 91% *ee* and >90% yield (Scheme 4). [20]

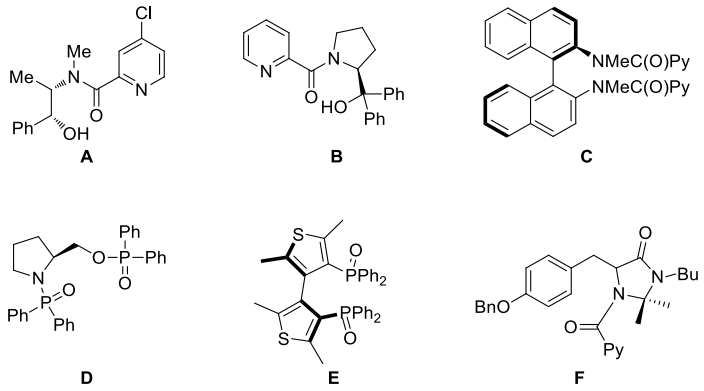
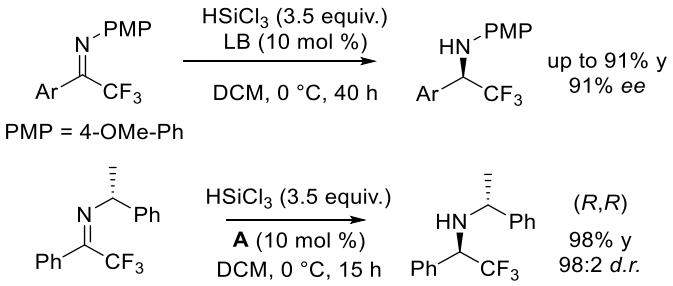


Figure 7



Scheme 4

As previously stated, the incorporation of a trifluoromethyl group has found application also in peptides and proteins, in the attempt to improve their biological activity and modify their metabolic properties.[33] Of particular interest is the replacement of a peptide or amide bond [CONH] with trifluoroethylamine units, to provide the so called ψ [CH(CF_3)NH] isosteres.[34] In this context, Zanda and co-workers, provided a synthesis of a mimic of retro-thiorphan **B** (Figure 8), which is a potent and selective inhibitor of the metalloproteinase NEP (neutral endopeptidase) sparing another zinc proteinase ACE (angiotensin converting enzyme), which has a key role in the control of blood pressure. The trifluoromethyl analogue **A** was as well tested as inhibitor of metalloproteinase NEP.[35]

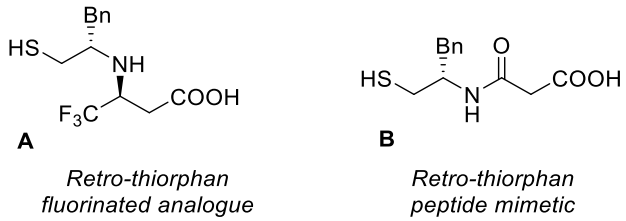
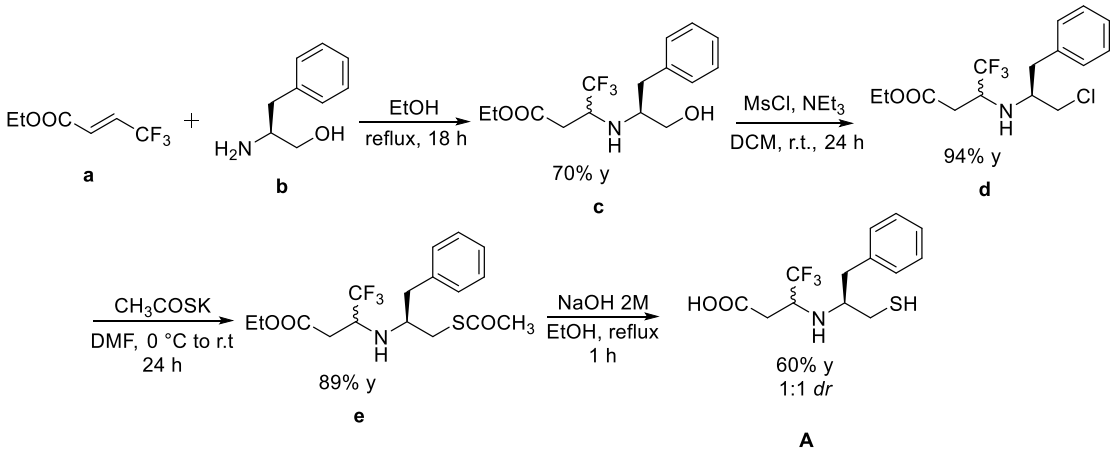


Figure 8

Previous reported synthesis

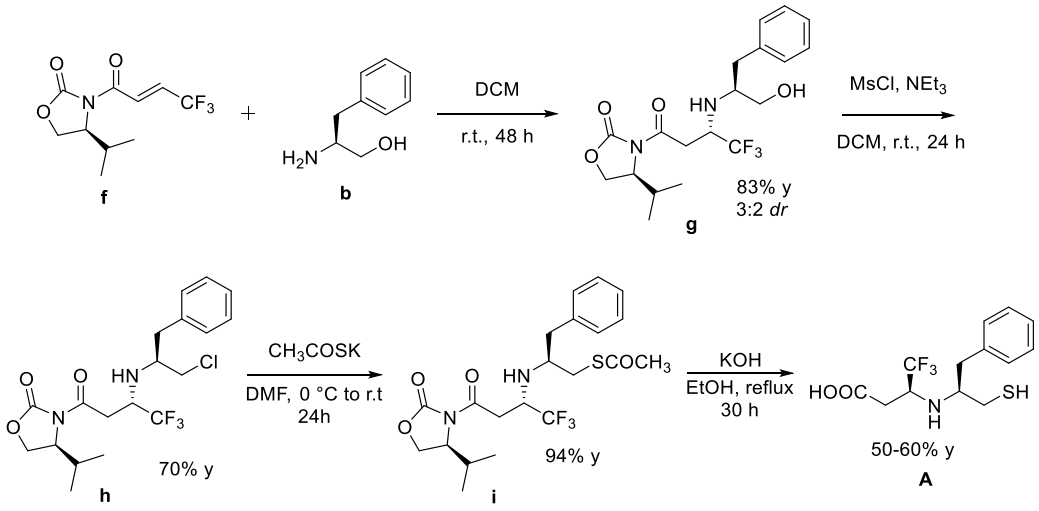
Indeed, only few synthetic strategies have been reported to prepare these molecules.[35] The first reported synthesis, involves commercially available ethyl trifluorocrotonate as Michael acceptor (Scheme 5).



Scheme 5

Addition of phenylalaninol **b** to ethyl trifluorocrotonate **a** took place in good yield but with no stereocontrol. Product **c** was indeed obtained as an equimolar mixture of epimers that were treated with MsCl to afford **d** and subsequently with AcSK to access **e**. The final cleavage of both terminal ester and thioester functionalities was achieved by basic hydrolysis, which provided retro-thiorphan **A** as a 1:1 diastereomeric mixture.

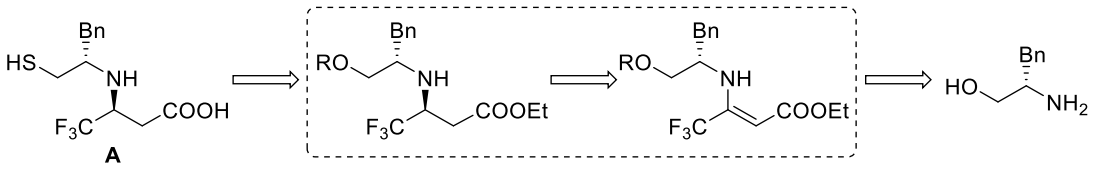
An alternative stereoselective synthesis, involved a diastereoselective aza-Michael addition of phenylalaninol **b** to the fluorinated acceptor **f,** bearing a chiral auxiliary, Evan's oxazolidinone. A chromatographic purification was required in order to separate the two diastereoisomers and obtain pure **g** (Scheme 6). The following addition of MsCl and trimethylamine afforded the chlorinated derivative **h** in 70% yield. Treatment of **h** with AcSK produced thioacetate **i** in good yield, which upon double cleavage under basic hydrolysis provided diastereomerically pure retrothiorphan **A** in moderate yields. In this case, the reaction conditions were found to be hardly reproducible, since the reaction outcome was apparently strongly dependent on purity degree of solvents and reagents. Furthermore, since the diastereomeric ratio was low, only 3:2 *dr,* and the undesired diasteroisomer was discharged, improvement also in the efficiency of the synthesis were required.



Scheme 6

None of the two reported procedures for the synthesis of this fluorinated compound was completely satisfactory: the first strategy although being solid and reproducible, did not lead to the isolation of a single diastereoisomer, while the second synthetic approach, gives a diastereomerically pure compound, but the procedure proved to be not completely reliable.

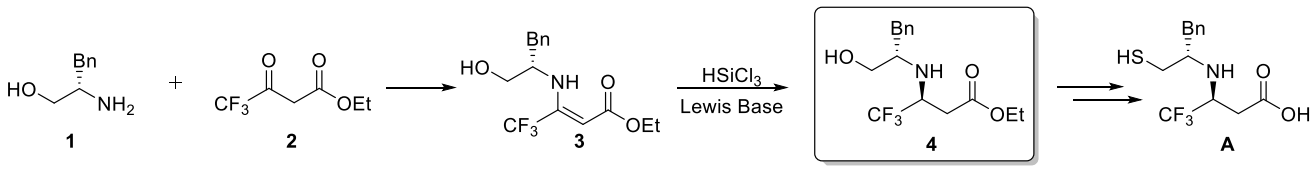
Thus, a new, more practical strategy is needed to realize a truly efficient diastereoselective synthesis of this target compound. The key step of our approach towards the synthesis of the fluorinated analogue of Retrothiorphan would be a diastereoselective reduction with a proper $HSiCl_3$/Lewis base combination (Scheme 7).



Scheme 7

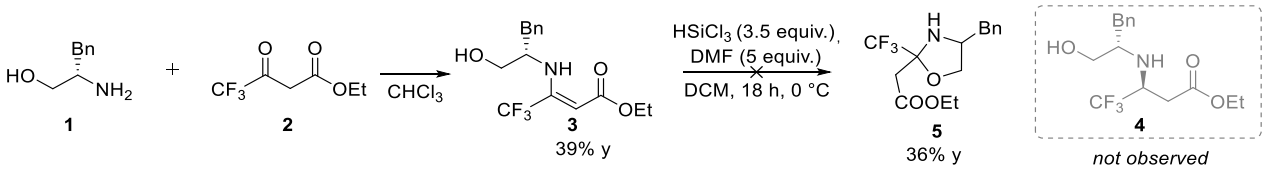
Results and discussion

At first, we wanted to prepare of enamine **3** starting from (*S*)-phenylalaninol **1** and α-trifluoromethyl-β-ketoester **2**, followed by reduction of C-N double bond with trichlorosilane (Scheme 8).



Scheme 8

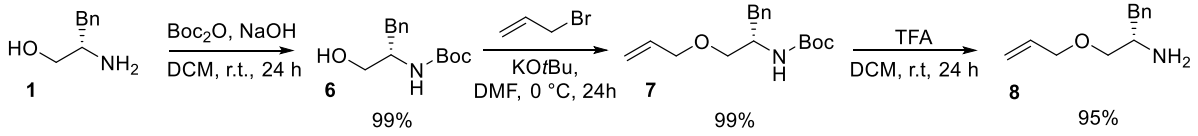
Condensation of ethyl 4,4,4-trifluoro-3-oxobutanoate **2** and (*S*)-2-amino-3-phenylpropan-1-ol **1** in chloroform gave the desired product in 39% yield. Then, enamine **3** was reduced with trichlorosilane in the presence of DMF, as achiral Lewis Base (Scheme 9). In this case the formation of amine **4** was not observed, due to the formation of byproduct **5**, derived from intramolecular cyclization.



Scheme 9

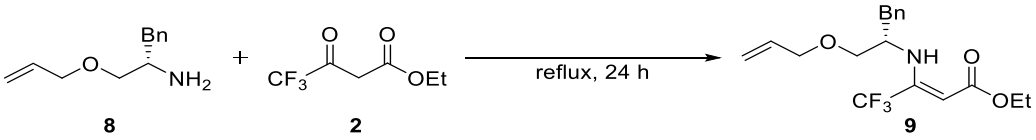
The undesired byproduct **5** was also obtained when **3** was submitted to reduction with $NaBH_4$. Hence, we decided to protect the hydroxyl group in order to prevent such side reaction.

So, the *N*-Boc-protected amino alcohol **6** was synthetized, and subsequently reacted with allylbromide and KO*t*Bu in DMF, to give the corresponding allylated compound **7** in 99% yield. Then, the Boc-protection was cleaved with trifluoroacetic acid (TFA) in dichloromethane. After a basic cleavage of the ammonium salt, product **8** was obtained in 95% yield (Scheme 10).[36]



Scheme 10

Different attempts for enamine formation were performed on ethyl 4,4,4-trifluoroacetate, to form **9**. Obtained results proved that a catalytic amount of acid and dry ethanol as solvent under inert atmosphere are the best conditions for this condensation (Scheme 11, Table 1). It is important to underline that unreacted functionalized amine **8** can be recovered by column chromatography, and recycled in order to minimize the loss, even if the yield is not very high. Only one of the two possible isomer of the enamine was formed, as evaluated by ^{1}H and ^{19}F NMR of the crude – before purification by column chromatography; the product was identified as the *Z*-isomer, in analogy to previously reported compounds with a similar structure.[37]



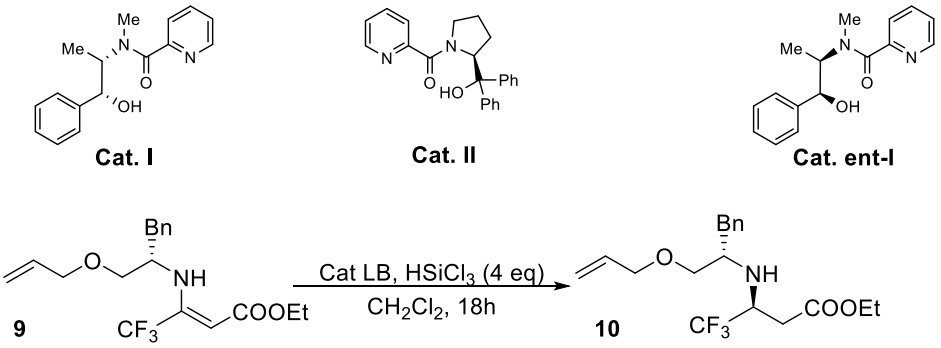
Scheme 11

Table 1

Entry	Solvent	T (°C)	Catalytic acid	Drying agents	Yield (%)
1	$CHCl_3$	60	-	MS* and $MgSO_4$	23
2	Toluene	110	-	MS* and $MgSO_4$	22
3	EtOH	80	10% *p*-TsOH	-	56

*Molecular sieves

Compound **9** was found to be unstable even when stored at low temperatures and needed to be directly used in the subsequent step. With fluorinated enamine **9** in our hands we investigated its catalytic reduction with trichlorosilane in the presence of a Lewis base (Scheme 12).



Scheme 12

Table 2

Entry	Lewis Base	Cat. eq	T (°C)	*d.r.*[1]	Yield (%)[2]
1[3]	DMF	5	0	67:34	22
2	Cat. **I**	0.2	0 to rt	34:66	40
3	Cat. **II**	0.2	0 to rt	81:19	38
4	Cat. ent-**I**	0.2	0 to rt	83:17	70
5	Cat. ent-**I**	0.2	-10	95:5	60
6	Cat. ent-**I**	0.1	-10	95:5	53
7	Cat. ent-**I**	0.1	-20	96:4	37

[1] Calculated by ^{19}F NMR. [2] Isolated yield. [3] Reaction time 48 h.

First, the addition of *N,N*-dimethylformamide (DMF) as achiral Lewis Base was performed, to evaluate the simple diastereoselectivity exerted by the stereocenter of the phenylalaninol residue. The reaction afforded product **10** in 22% yield and 67:34 diastereomeric ratio (Scheme 12 and Table 2, entry 1).

Then catalyst **I**, derived from the chiral scaffold of (−)-(1*R*,2*S*)-ephedrine,[38] was tested; the reduction yield was improved, but the other diastereoisomer was preferentially obtained, thus proving to be a mismatch couple with the chiral substrate (entry 2). Therefore, we decided to test catalyst **II**, known to lead to the formation of the opposite enantiomer of catalyst **I**, when used in the presence of fluorinated substrates. Catalyst **II** showed to be indeed a matching combination with enamine **9** and gave slightly better results than DMF, improving both yield and diastereomeric ratio (entry 3). However, since the yield was still not satisfactory, we decided to synthetize the opposite enantiomer of catalyst **I**, starting from (+)-(1*S*,2*R*)-ephedrine, that proved to be a very active catalyst; at lower temperature, the diastereomeric ratio was improved up to 95:5 (entry 6). It is important to point out that when low yields were observed, it was not possible to recover the unreacted starting material **9** due to hydrolysis of the enamine moiety during the aqueous work-up.

In order to confirm the hypothesized absolute configuration of the key intermediate **10**, the chiral amine was treated with an equimolar amount of HCl in diethl ether, to afford the corresponding hydrochloride salt **10**/HCl. Slow crystallization from a Et_2O/Hexane mixture afforded light yellow crystals; X-ray analysis allowed to unambiguously determine the absolute configuration of the product to be (*S,S*), as reported in Figure 9 .

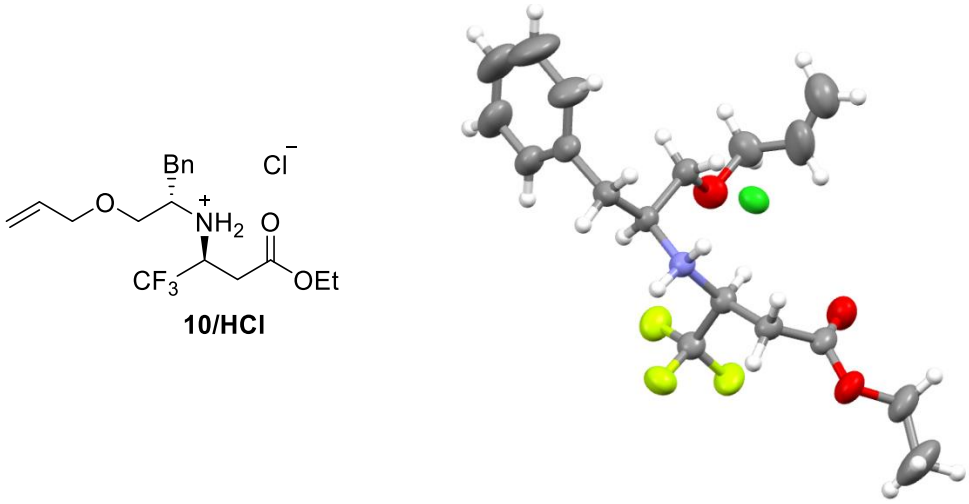
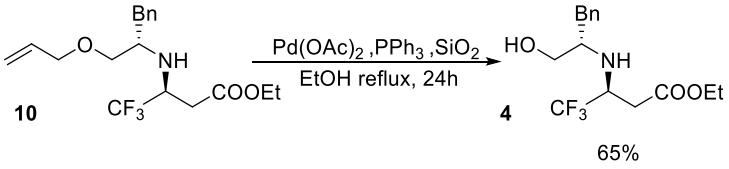


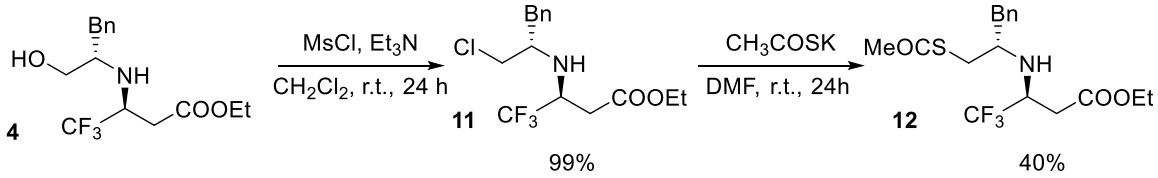
Figure 9

After the reduction, product **10** was deprotected with $Pd(OAc)_2$ and PPh_3 in EtOH to give the amino-alcohol **4** in 65% yield (Scheme 13). Compound **4** is a known precoursor of our target molecule, the florinated analogue of retrothiorphan, and a formal synthesis was completed.



Scheme 13

Compound **4** was reacted with methanesulphonylchloride to give the corresponding chloride **11** in 99% yield, which was used as crude and reacted with potassium thioacetate, to afford in 40% yield product **12**, direct precursor of the final analogue, following already reported literature procedures (Scheme 14).[35]



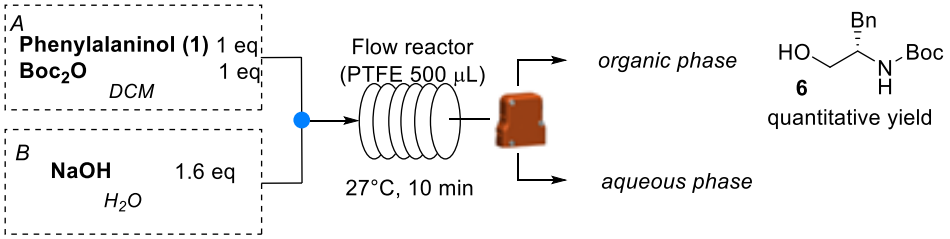
Scheme 14

Continuous Flow strategy

Considering the raising interest for the in-flow preparation of API's,[5,6,39] based on these results and with the aim to further accelerate the reaction, we explored the possibility of developing a continuous flow method for the preparation of the target compound. Even a simple reaction, like a Boc-protection, can hide safety issues:

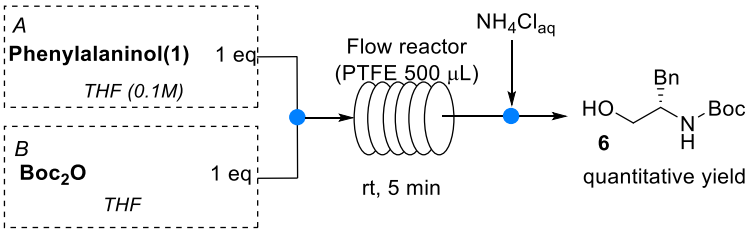
Boc_2O is highly toxic by inhalation, with a lethal concentration comparable with the one of phosgene,[40] so the possibility of a confined handling is much desirable. Furthermore, a byproduct of the reaction is CO_2, and scale-up of gas producing reactions implies great concerns; under continuous flow conditions, small volumes of gas are produced over time, and a better control of the internal pressure is ensured in the system.

Boc-protection of phenylalaninol was performed under the same conditions as in batch (Scheme 10), with a continuous phase separator at the end of the coil reactor. All continuous flow reactions were performed in a PTFE coil reactor (1.58 mm OD, 0.58 mm ID, different lengths depending on the desired reactor volume, as indicated in pictures). We were able to obtain the desired product with complete conversion, just by solvent evaporation (Scheme 15).



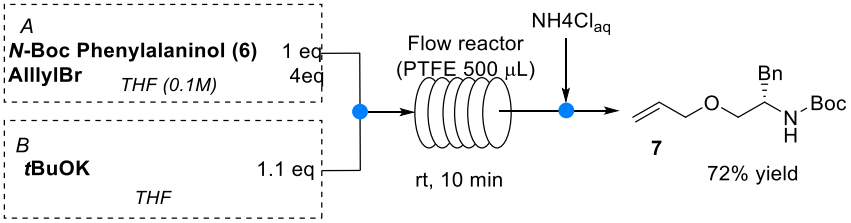
Scheme 15

With the aim of developing a multistep continuous synthesis, without isolation of intermediates, we decided to switch to THF as solvent for the first step, since dichloromethane is not compatible with the use of potassium *tert*-butoxide (fast clogging of the tubing was observed). Using a different solvent, THF, experimental evidences showed that an external base was not needed, and the desired Boc-protected aminoalcohol could be obtained in just 5 minutes of residence time at room temperature (Scheme 16).



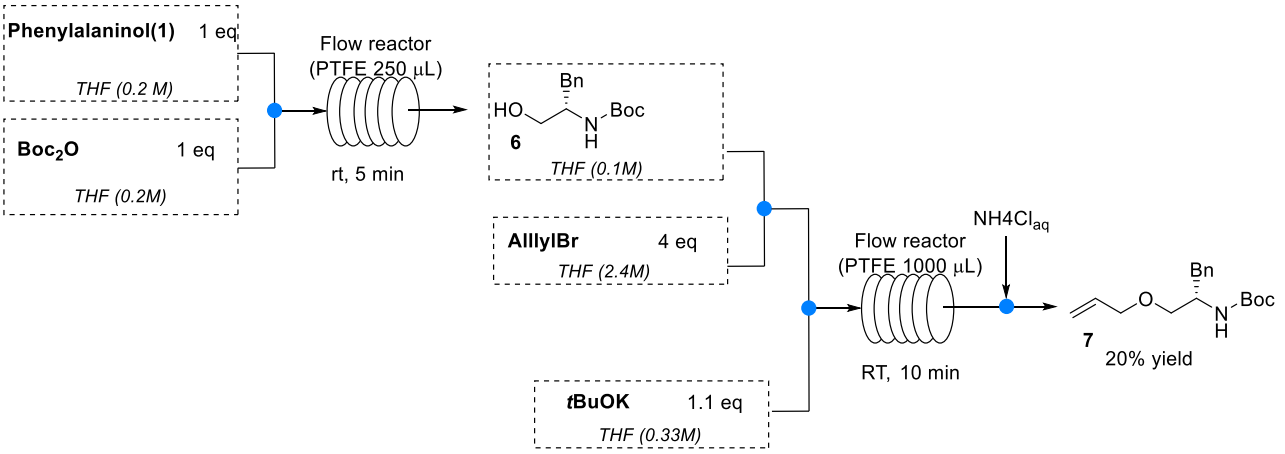
Scheme 16

Then we tested the second step under continuous flow, and we were pleased to see that in only 10 minutes of residence time, the desired product **7** was obtained in 72% yield (Scheme 17). We could not further optimize this reaction, due to solubility problems giving clogging of the system.



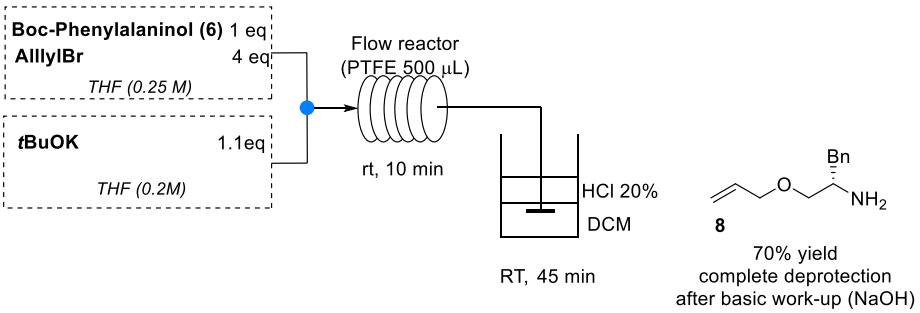
Scheme 17

Unfortunately, when the two steps were combined in a single continuous flow system (Scheme 18), low yields were observed for the second reaction, probably due to the influence of byproducts formed in the first transformation. In particular, gaseous CO_2, formed during the Boc-protection, could be partially dissolved in the solvent (no bubbles could be observed in the flow reactor), and quenching part of the base of the second step can occur. *Tert*-butanol could also be influencing negatively the second step. This kind of issues can be in principle overcome by modifications of the system, like adding a de-gassing step or using open systems that favor the removal of gas.



Scheme 18

Therefore, we decided to start from commercially available Boc-protected phenylalaninol **6** and synthesize the O-allyl protected phenyl alaninol ether; after the in-flow allylation, the reaction outcome was poured directly into a biphasic mixture of dichloromethane and aqueous HCl (20%), where it was stirred for 45 minutes (Scheme 19). After an aqueous basic work-up, the desired product **8** was obtained with the same yield as before, but completely de-protected.

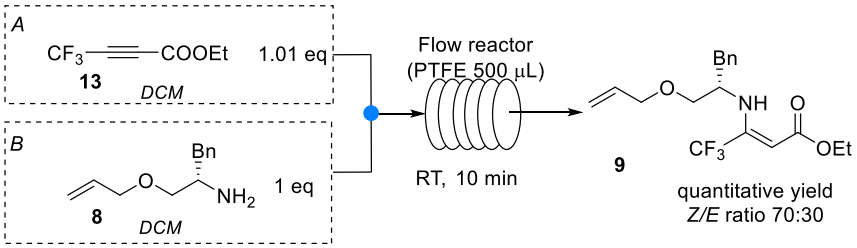


Scheme 19

In order to develop a continuous flow strategy for the synthesis of enamine **9**, we decided to change the coupling partner of our amine, choosing commercially available fluorinated alkyne **13.**[37] Our main concerns were related to the solvent used in batch for the synthesis of **9** (ethanol) that was not compatible with the subsequent reduction step, performed by trichlorosilane. Furthermore, usually reactions that benefits from a continuous-flow approach are fast reactions, and the condensation of amine **8** to the fluorinated β-ketoester **2** required a long reaction time and high temperatures. Our new synthetic pathway, the addition of amine **8** to the properly substituted alkyne **13**, would introduce concern from a safety point of view. Compounds like **13**, containing instable functional group, (e.g. the triple bond), especially together with low molecular weight, as in

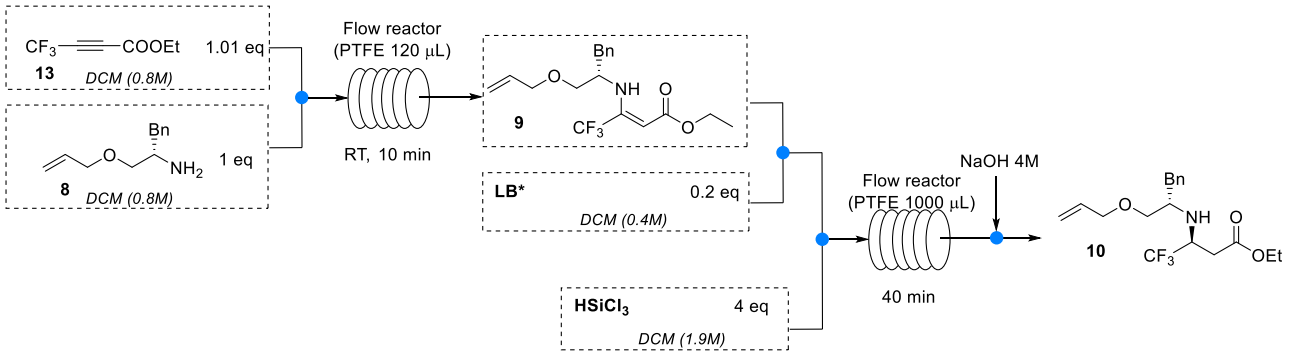
the present molecule, are very likely to possess high decomposition energy. Performing this new synthesis, would definitely benefit from a continuous manufacturing approach: avoiding the accumulation of such compounds in a reaction vessel it's highly desirable. Moreover, removing isolation and manipulation of compound **9** could help overcome instability issues.

The reaction occurred with complete conversion in just 10 minutes of residence time, in dichloromethane, the same solvent of the subsequent diastereoselective reduction. The enamine was obtained in a *Z/E* ratio of 70:30. The *E*-isomer was never observed in the synthesis performed by condensation of the amine and the fluorinated β-ketoester and it was found to be prone to isomerization, since after purification by column chromatography, the product was isolated all as the *Z*-isomer (Scheme 20). Then we looked at the catalytic enamine reduction mediated by trichlorosilane.



Scheme 20

Our group already demonstrated that $HSiCl_3$-mediated diastereoselective imine reduction could be efficiently performed in (micro)-mesoreactors under continuous flow condition.[41] The reaction, performed in coil reactor (PTFE, 1.58 mm OD, 0.58 mm ID, tubes connected using standard HPLC connectors) afforded the expected product, although the reduction step required long residence times (Scheme 21). To increase the yield, we heated up the reactor to 35°C, obtaining up to 37% yield, but with lower *dr*, while cooling to room temperature, the yield was below 20%, with 95:5 diastereomeric ratio. The presence of the *E*-isomer of the enamine could be influencing the reduction step, most likely in the diastereomeric ratio, as previously observed for this kind of transformations.[41] Since the *E*-isomer is actually prone to isomerization into the more stable *Z*-isomer, as experienced in the synthesis at high temperature under batch conditions, as well as during purification by column chromatography of the mixture, future development to improve reaction outcome could come from the addition of an "isomerization step", to increase the yield and the diastereomeric ratio.



Scheme 21

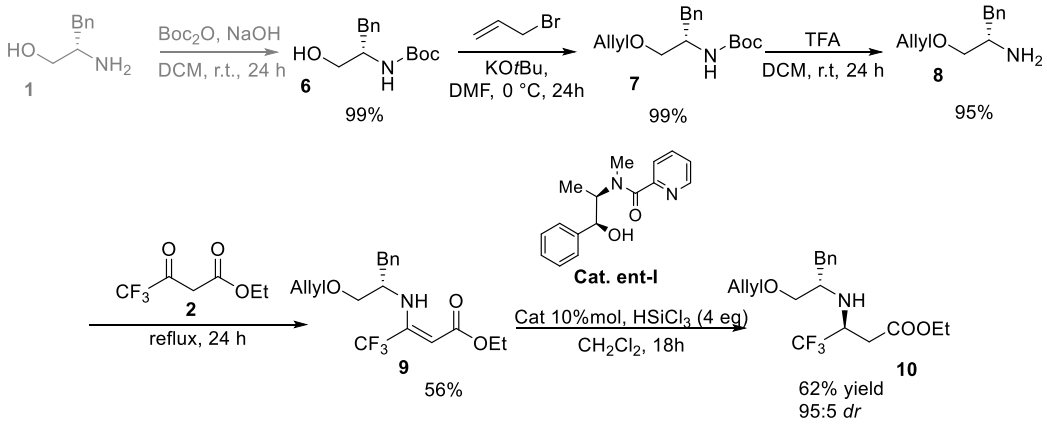
Table 3

Entry	T (°C) 2nd step	Yield (%)	*d.r.*[1]
1	rt	<20	>95:5
2	35	37	83:17

[1]Evaluated by ^{19}F NMR

Conclusions

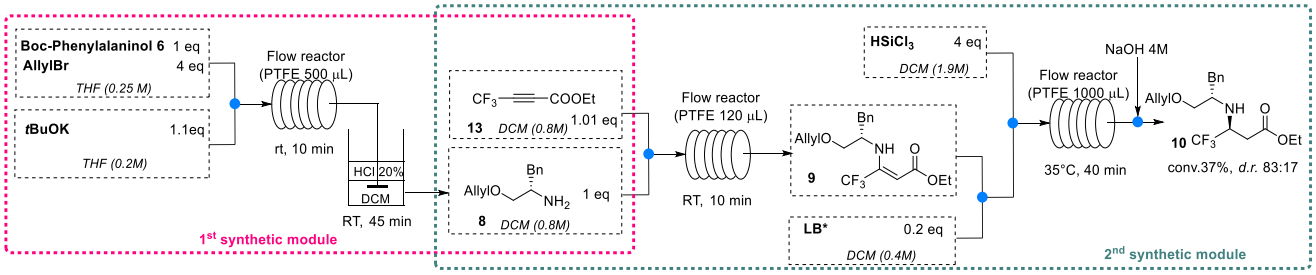
In the present study, a highly stereoselective, metal-free strategy for the synthesis of fluorinated chiral amine **10**, direct precursor of retro-thiorphan fluorinated analogue, was developed. Under batch conditions, the desired intermediate was synthetized in 5 steps, starting from commercially available phenylalaninol, with an overall yield of 32% and in 95:5 diastereomeric ratio (Scheme 22). The whole synthetic sequence requires almost five days of reaction times, without considering work-up and isolation of intermediates.



Scheme 22

The synthesis under batch conditions was also continued for three more steps, to obtain **12** (Scheme 14) a direct precursor of the fluorinated analogue of retrothiorphan.

After setting up reaction conditions in batch, the synthesis was efficiently performed also under continuous flow conditions. In particular, two synthetic modules were set up, avoiding isolation and purification of intermediates, starting from commercially available Boc-phenylalaninol. In our set-up, only two solvents were used in 4 reaction steps, thanks to the optimization of our reaction conditions. The desired product **10**, was obtained in 26% overall yield and 83:17 *dr*, performing the last reaction step at 35°C, while in 14% overall yield and >95:5 *dr* performing the last step at room temperature. The overall reaction time was found to be 1h and 45 minutes, without considering work-up and isolation of the only intermediate of this set-up, intermediate **9** (Scheme 23).



Scheme 23

Future improvements will regard the implementation of the Boc-protection step in our first synthetic module, by adding an in-line work up to get rid of by-products (like CO_2 or *tert*-butanol), as well as improving the yield of the last reduction step, by increasing reaction time. The present work represents a further step towards the development of a multistep continuous flow process for the synthesis of enantiomerically pure fluorinated pharmaceutically relevant products.

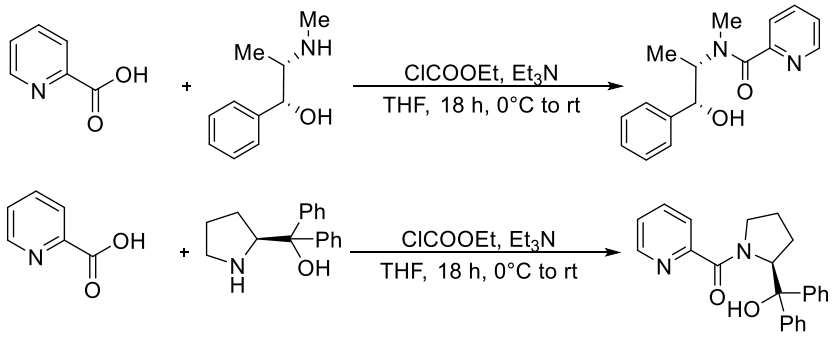
Experimental section

Materials and Methods

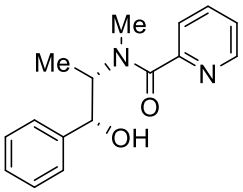
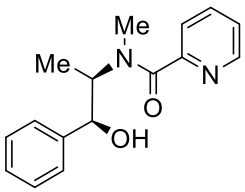
Reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F_{254} pre-coated glass plates (0.25 mm thickness) and visualized using UV light. Flash chromatography was carried out on silica gel (230-400 mesh). Proton NMR spectra were recorded on spectrometers operating at 300 MHz (Bruker Avance 300); proton chemical shifts are reported in ppm (δ) relative to tetramethylsilane (TMS, $CDCl_3$: δ=7.26 ppm). ^{13}C-NMR spectra were recorded on 300 MHz spectrometers (Bruker Avance 300) operating at 75 MHz, with complete proton decoupling; carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, : δ = 77.0 ppm). ^{19}F-NMR spectra were recorded on 300 MHz spectrometers (Bruker Avance 300) operating at 282.1 MHz; fluorine chemical shifts are reported in ppm (δ) relative to $CFCl_3$ with the respective solvent resonance as the internal standard ($CFCl_3$: δ = 77.0 ppm). Mass spectra and accurate mass analysis were carried out on a VG AUTOSPEC- M246 spectrometer (double-focusing magnetic sector instrument with EBE geometry) equipped with EI source or with LCQ Fleet ion trap mass spectrometer, ESI source, with acquisition in positive ionization mode in the mass range of 50-2000 m/z. Optical rotations were obtained on a Perkin-Elmer 241 polarimeter at 589 nm using a cell with a length of 1 dm. For HPLC analyses on chiral stationary phase, to determine enantiomeric excesses, it was used an Agilent Instrument Series 1100. The specific operative conditions for each product are reported from time to time. Commercially available $HSiCl_3$ was freshly distilled before use.

The fluidic device was realized by assembling coil-reactors, connected, by T-junctions using standard HPLC connectors. Coil-reactors consisted in PTFE tubing (internal diameter: 0,58 mm) coiled in a bundle. Syringe pump: Chemix Fusion 100, equipped with two Hamilton gastight syringes, of different volumes.

Synthesis of catalysts I, II and ent-I[29]

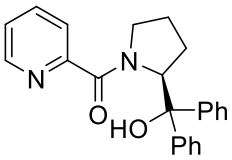


A solution of ethyl chloroformate (1 mmol, 1 eq.) in dry THF (2 mL) was dropped in a solution of 2-picolinic acid (1 mmol, 1 eq.) and Et_3N (1 mmol, 1 eq.) in dry THF (25 mL) at 0 °C within 15 min. The resulting mixture was stirred for 1 h before 1 mmol (1 eq.) of the proper amino alcohol in dry THF (10 mL) was added dropwise. The mixture was stirred at 0°C for 1 h and then at room temperature overnight. The mixture was quenched with water. The aqueous layer was extracted with ethyl acetate (3 × 15 mL) and the combined organic layers were dried over $MgSO_4$ for 2 h, filtered and concentrated under reduced pressure.

Purified by flash column chromatography, obtained as a white solid. Yield 73%.

^{1}H NMR (300 MHz, $CDCl_3$) δ: *rotamer 1:* 7.40–7.10 (m, 10H), 6.98 (s, 1H), 4.81 (s, 1H), 4.50 (br s, 1H), 2.60 (s, 3H), 1.33 (d, 3H); *rotamer 2:* 7.40–7.10 (m, 10H), 6.90 (s, 1H), 4.50 (s, 1H), 4.30 (br s, 1H), 2.90 (s, 3H),1.40 (d, 3H).

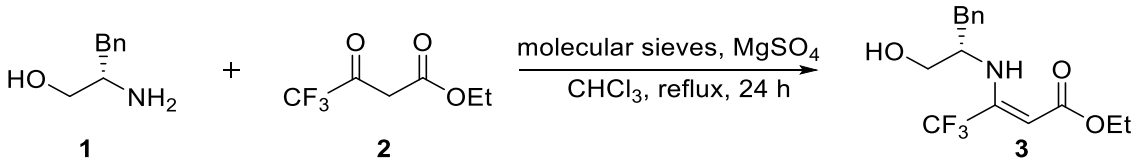


Purified by flash column chromatography. White solid, yield 43%.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.56 and 8.26 (2×br s, 1H), 7.71-7.77 (m, 1H), 7.15-7.52 (m, 12H), 6.69 (s, 1H), 5.42-5.50 (m, 1H), 3.19-3.97 (m, 2H), 2.03-2.14 (m, 2H), 1.50-1.82 (m, 1H), 0.75-1.25 (m, 1H).

<u>In batch synthesis of the target molecule</u>

Synthesis of enamine **3**



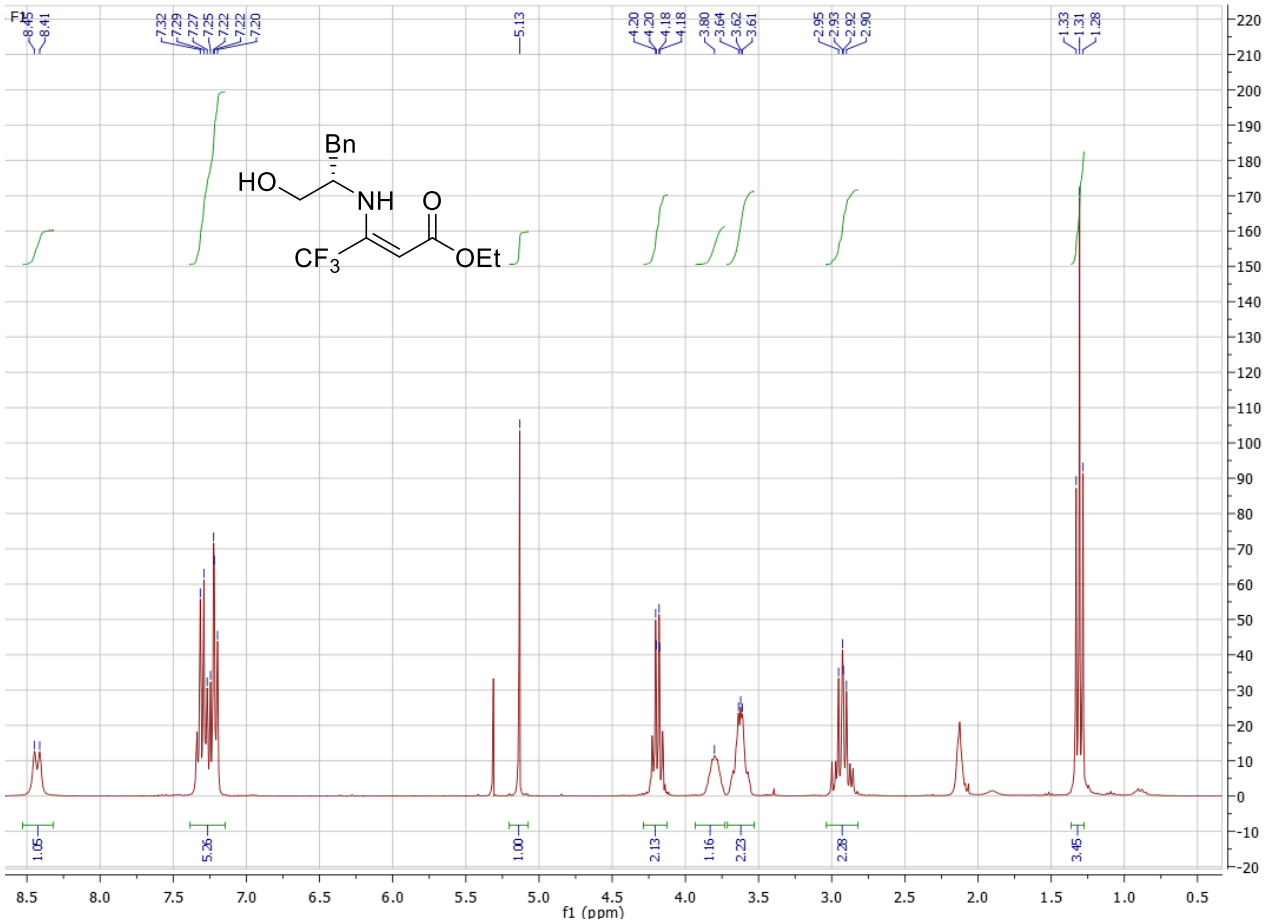
A solution of amino alcohol **1** (3.31 mmol, 1 eq.) in dry $CHCl_3$ was added ethyl 4,4,4-trifluoro-3-oxobutanoate **2** (3.31 mmol, 1 eq.) with 4 Å molecular sieves and $MgSO_4$ under nitrogen atmosphere. After 24 h, the reaction mixture was diluted with CH_2Cl_2 and filtrated over celite. After solvent removal, the crude was purified by column chromatography (silica gel, hexane/AcOEt = 9:1) to afford **3** as a yellow oil.

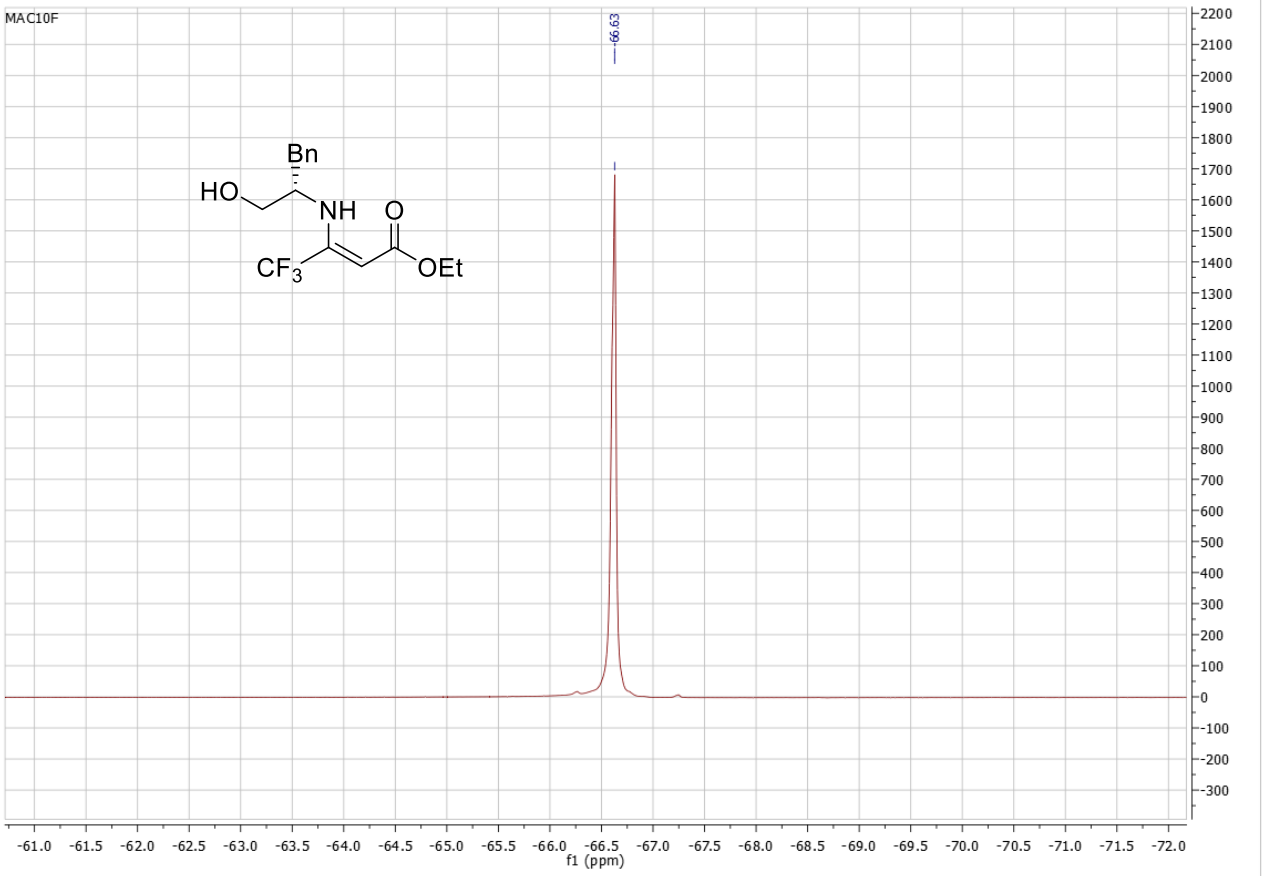
Yield = 39%

Rf = 0.23 in hexane/AcOEt 8:2

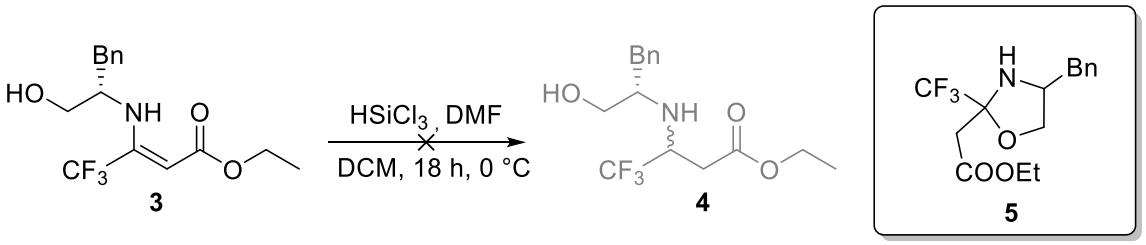
^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.43 (d, *J* = 10.5 Hz, 1H), 7.42 – 7.13 (m, 5H), 5.13 (s, 1H), 4.32 – 4.09 (m, 2H), 3.83 (dd, *J* = 24.5, 20.3 Hz, 1H), 3.72 – 3.50 (m, 2H), 3.04 – 2.80 (m, 2H), 1.31 (t, *J* = 7.1 Hz, 3H).

^{19}F NMR (300 MHz, $CDCl_3$) δ: -66.63 (s)


Bn
HO
NH
O
CF3
OEt
f1 (ppm)


MAC10F
Bn
HO
NH
O
CF3
OEt
f1 (ppm)

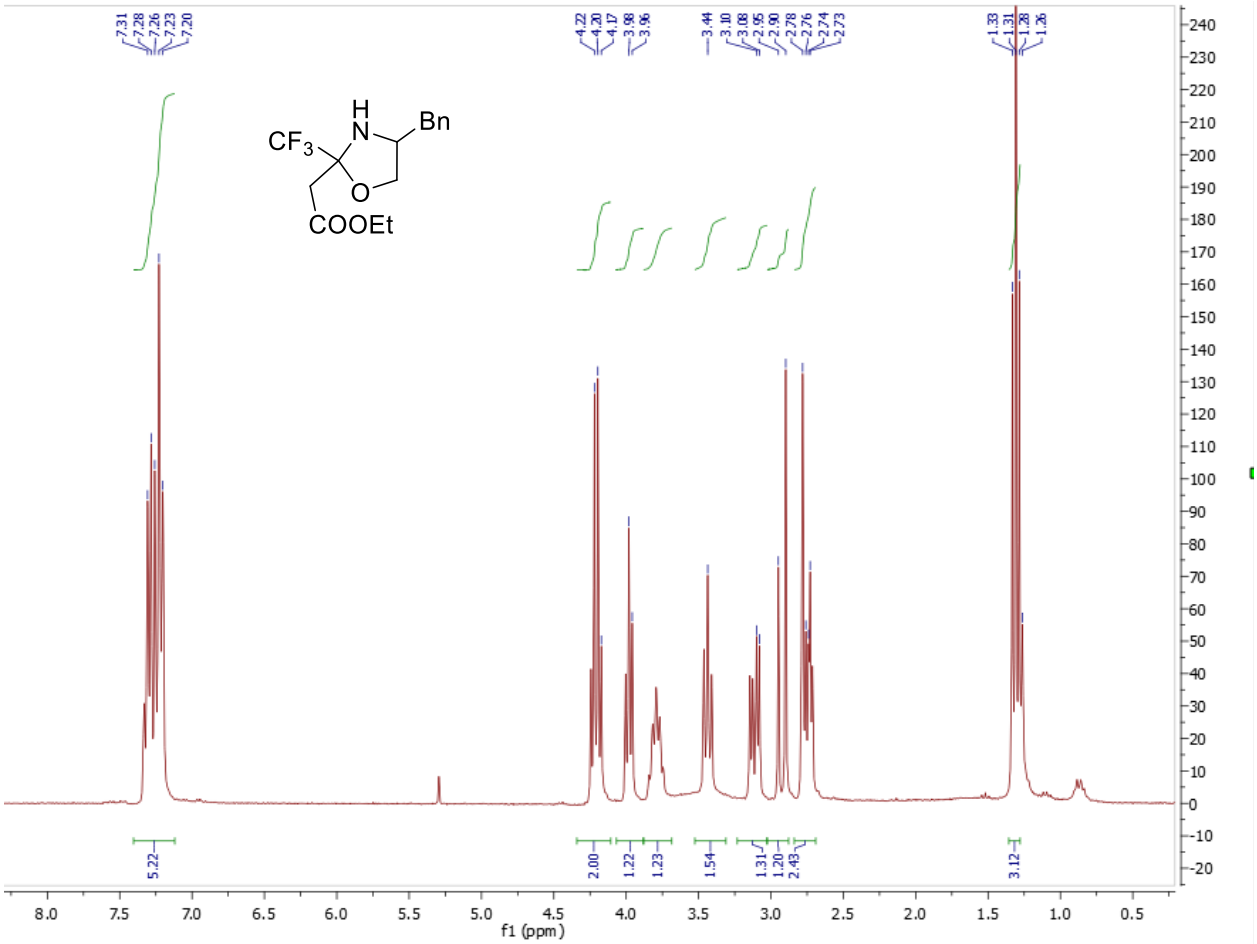
Reduction of enamine **3**

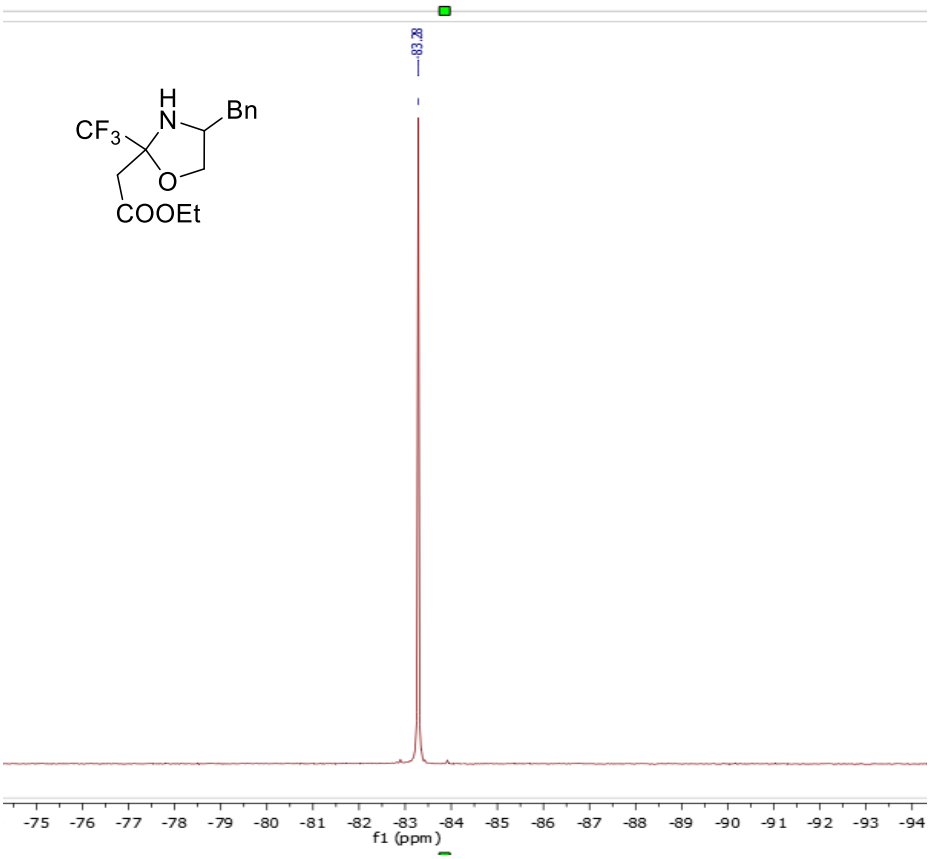


Dry DMF (0.75 mmol, 5 equiv.) and a 0.1 M solution of the imine **3** in dry CH_2Cl_2 were introduced in a round bottomed flask under nitrogen atmosphere. The mixture was cooled to 0 °C. $HSiCl_3$ (0.53 mmol, 3.5 equiv.) was added to the reaction mixture. After the desired time, the reaction was quenched with a 1 M solution of NaOH until basic pH was reached. The resulting slurry was washed with CH_2Cl_2 and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/AcOEt = 8:2) to afford a yellow oil. In this case the formation of **4** was not observed, obtaining instead **5** (yield 36%), deriving from intramolecular cyclization.

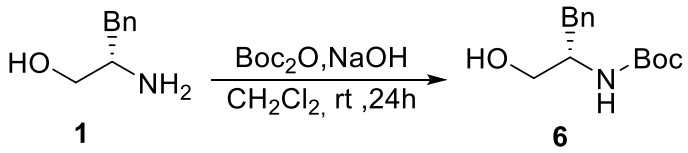
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.33 – 7.05 (m, 5H), 4.27 – 4.03 (m, 2H), 3.90 (d, J = 6.9 Hz, 1H), 3.81 – 3.61 (m, 1H), 3.36 (s, 1H), 3.02 (d, J = 5.8 Hz, 1H), 2.85 (d, J = 15.3 Hz, 1H), 2.68 (dd, J = 10.6, 4.9 Hz, 2H), 1.23 (t, J = 7.1 Hz, 3H).

^{19}F NMR (300 MHz, $CDCl_3$) δ: -83.28 (s).


7.31
7.28
7.26
7.23
7.20
4.22
4.20
4.17
3.98
3.96
3.44
3.10
3.08
2.95
2.90
2.78
2.76
2.74
2.73
1.33
1.31
1.28
1.26
H
N
Bn
CF3
O
COOEt
5.22
2.00
1.22
1.23
1.54
1.31
1.20
2.43
3.12
f1 (ppm)


-83.28
H
N
Bn
CF3
O
COOEt
f1 (ppm)

Synthesis of **2**[36]



1 **6**

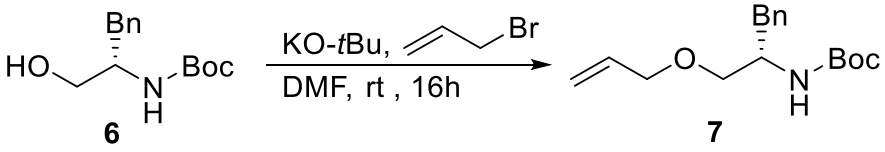
A solution of tert-butyl dicarbonate (1eq, 6.7mmol) in CH_2Cl_2 (14 mL) was added dropwise to a solution of *(S)-2-amino-3-phenylpropan-1-ol* (**1**) (1eq, 6.7mmol) in a mixture of CH_2Cl_2 (14 mL) and 1N NaOH (11 mL). The reaction mixture was then stirred at room temperature for 24 h, and the organic phase was separated. The aqueous layer was extracted with CH_2Cl_2 (10 mL x 2). The combined organic layers were washed with water (10 mL x 1) and dried over Na_2SO_4. The solvent was evaporated in vacuo, to afford **6** as a white solid; the crude has been used without further purification in the following synthetic cascade. All analytical data are in agreement with literature.

Yield = 99%

Rf = 0.1 in hexane/AcOEt 7:3

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.32 – 7.21 (m, 5H); 4.72 (br d, 1H); 3.89 (m, 1H); 3.67 - 3.55 (m, 2H); 2.86 (d, 2H); 1.43 (s; 9H).

Synthesis of **3**[36]



6 **7**

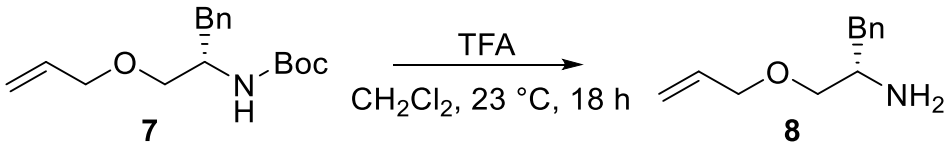
A solution of **6** (1 eq, 6.7 mmol), 4eq. of allylbromide and DMF (0.1 M) was prepared in a flask and stirred under ice bath for 15 min. 1.1eq of KO-*t*Bu were added to the solution portion-wise. The thus obtained mixture was stirred for 4h at 0°C and for 12h at rt. The mixture was diluted with AcOEt and treated with HCl 10%, then the organic phase was treated with $NaHCO_3$ (ss), and finally washed with brine. The organic phases were reunited, dried over Na_2SO_4, filtered, and then concentrated under vacuum at high temperature to give a crude colourless oil which was used without further purification in the following synthetic step. All analytical data are in agreement with literature.

Yield = 99%

Rf = 0.55 in hexane/AcOEt 7:3

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.32 – 7.22 (m, 5H), 5.98 – 5.87 (m, 1H), 5.30 - 5.19 (m, 2H), 4.86 -4.74 (br, 1H), 3.98 – 3.88 (m, 3H), 3.36 (m, 2H), 2.80 (dd, 2H), 1.44 (s, 9H).

Synthesis of **8**[36]

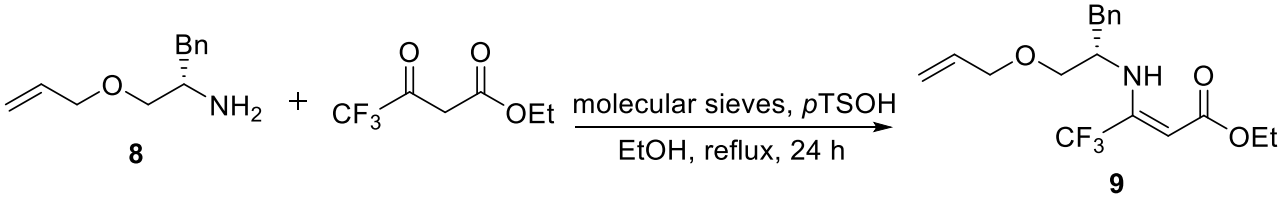


To the *O*-allyl amine **7** (0.39 mmol, 1 eq.) in 10 mL of dry CH_2Cl_2, TFA (3.94 mmol, 10 eq.) was added at 0 °C. Then the solution was stirred at r.t. for 18 h. After completion of the reaction, the excess of TFA was evaporated in vacuo. 10 mL of Na_2CO_3 (10 % aqueous solution) were added cautiously and the mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to give a yellow oil. The crude product has been used in the next step without further purification. All analytical data are in agreement with literature.

Yield = 99%

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.31 – 7.06 (m, 5H), 5.98 – 5.72 (m, 1H), 5.31 – 5.04 (m, 2H), 3.92 (d, J = 5.6 Hz, 2H), 3.44 – 3.29 (m, 1H), 3.28 – 3.09 (m, 2H), 2.72 (dd, J = 13.3, 4.9 Hz, 1H), 2.56 – 2.41 (m, 1H).

Synthesis of **9**



O-allyl amine **8** (0.39 mmol,1 eq.) and ethyl 4,4,4-trifluoro-3-oxobutanoate (0.39 mmol, 1 eq.) were charged in a round bottomed flask under nitrogen atmosphere and 4 Å molecular sieves and 10 mol% of p-toluensulfonic acid were added. Then dry EtOH (3.9 mL) was added, and the reaction was heated to reflux and stirred for 24 h. The mixture was diluted with CH_2Cl_2 and filtrated over celite. After solvent removal, the crude was purified by column chromatography (silica gel, hexane/AcOEt = 8:2) to afford **9** as a colorless oil. Only the *Z*-isomer was obtained, in analogy with similar literature compounds.[37]

Yield = 56%

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.46 (d, *J* = 10.5 Hz, 1H), 7.32-7.12 (m, 5H), 6.01-5.72 (m, 1H), 5.34-5.12 (dd, 2H), 5.08 (s, 1H), 4.19 (q, 2H), 4.02 (m, 2H), 3.82 (brs, 1H), 3.41-3.36 (m, 2H), 2.85-3.03 (m, 2H), 1.30 (t, 3H).

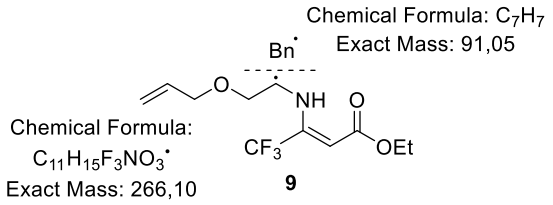
^{19}F NMR (282 MHz, $CDCl_3$) δ: -66.12 (s).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.6 (s), 147.5 (q), 137.6 (s), 129.4 (s), 128.4 (s), 126.6 (s), 122.2 (q), 117.0 (s), 85.1 (q), 72.2 (s), 70.4 (s), 59.6 (s), 56.0 (s), 39.4 (s), 14.3 (s).

MS mass (ESI): 357.78 (M+)

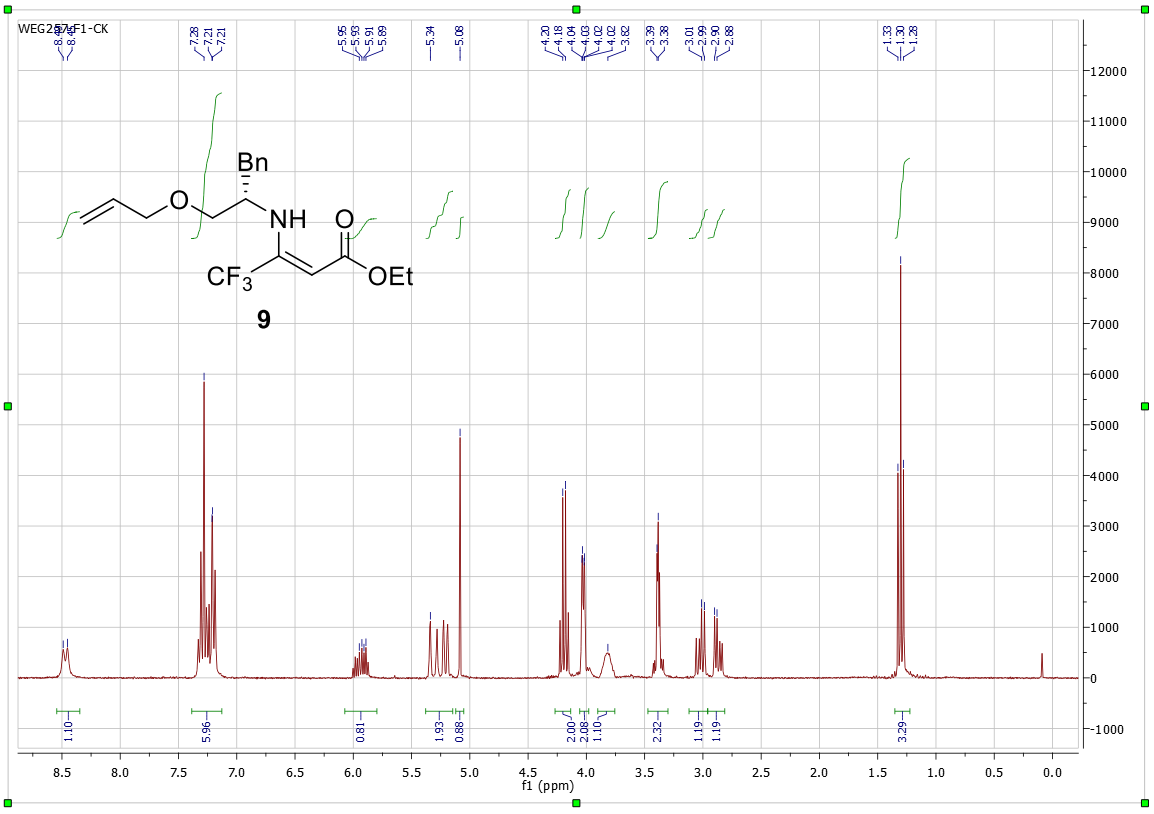
During high resolution EI mass analysis the benzyl portion is lost:

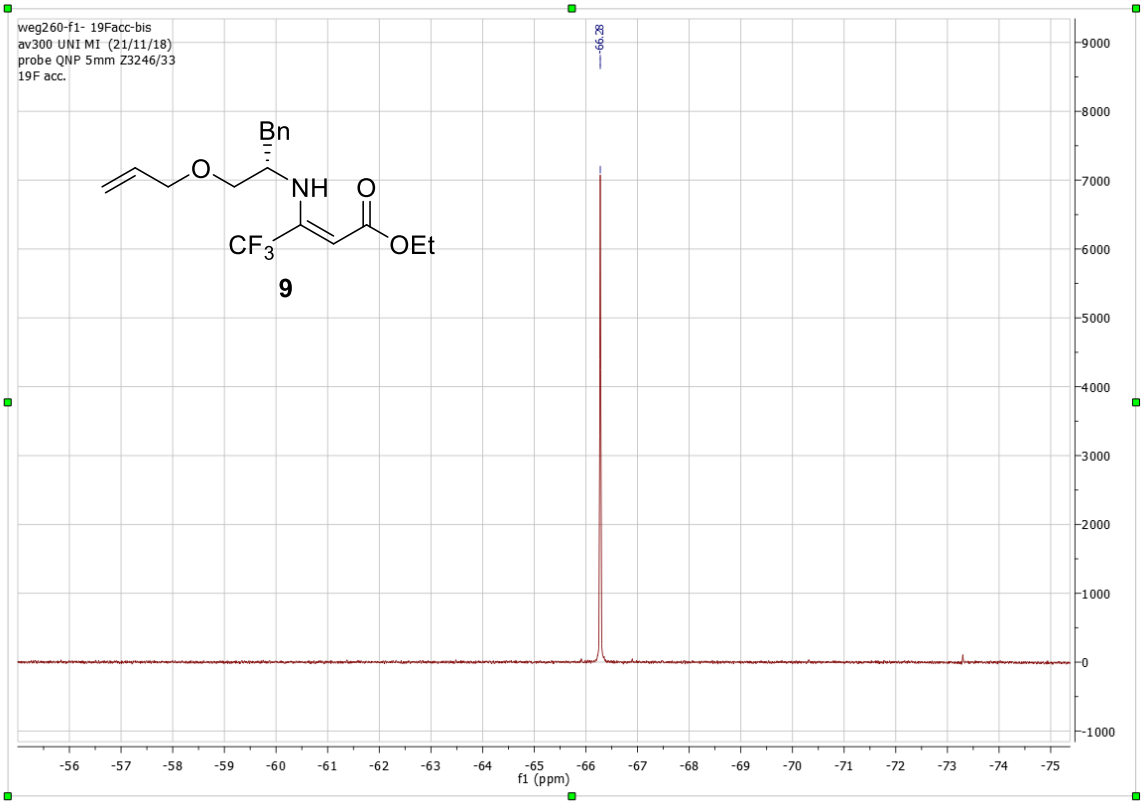
HRMS (EI): calcd for C11H15F3O3N1: 266.100403, found: 266.100100

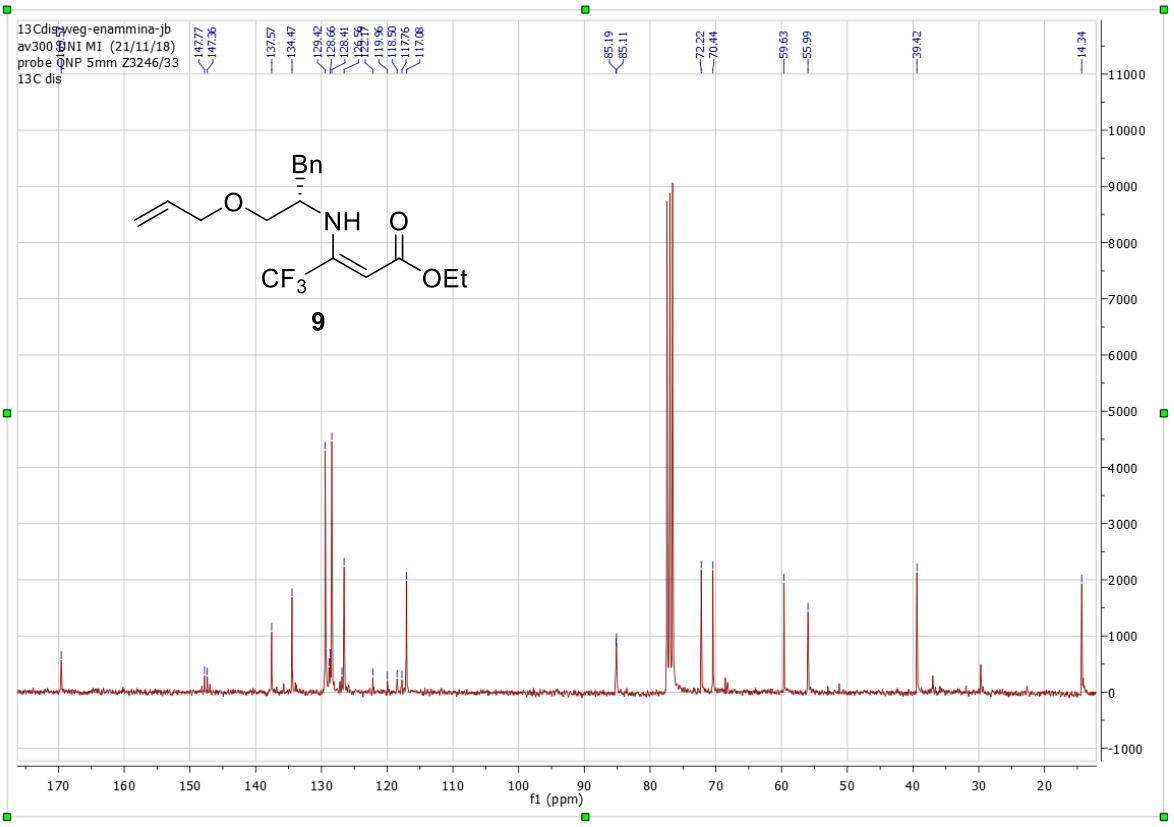


9

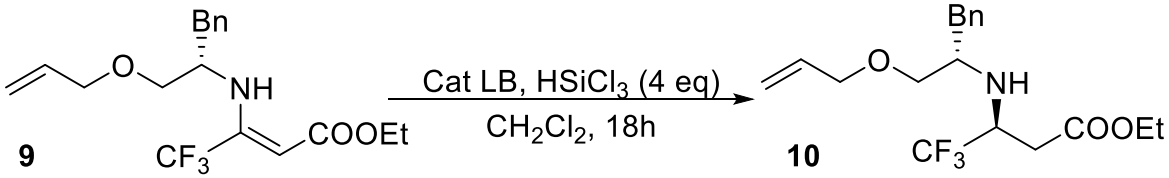
$[\alpha]^{20}_{D}$= -207.81 (c=1.14, λ=546 nm, $CHCl_3$).


WEG257-F1-CK
Bn
O
NH
O
CF3
OEt
9
f1 (ppm)


weg260-f1- 19Facc-bis
av300 UNI MI (21/11/18)
probe QNP 5mm Z3246/33
19F acc.
-66.28
Bn
O
NH
O
CF3
OEt
9
f1 (ppm)



Synthesis of **10**



Dry DMF or the appropriate catalytic chiral Lewis Base in the reported amount (see Table 2 in the main paragraph), and a 0.1 M solution of enamine **9** (1 eq.) in dry CH_2Cl_2 were introduced in a round bottomed flask under nitrogen atmosphere. The mixture was cooled down to the indicated temperature and $HSiCl_3$ (3.5 eq.) was added to the reaction mixture. After the desired time, the reaction was quenched with a 4 M solution of NaOH until basic pH was reached. The resulting mixture was extracted with CH_2Cl_2, and the organic phase dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/AcOEt = 98:2) to afford **10** as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.31-7.10 (m, 5H), 5.98-5.84 (m, 1H), 5.29-5.16 (m, 2H), 4.18 (q, 2H), 3.95 (d, *J* = 7.1 Hz, 2H), 3.80 (br s, 1H), 3.34-3.20 (m, 3H), 2.78-2.74 (m, 2H), 2.68 (dd, 1H), 2.45 (dd, 1H), 1.29 (t, 3H).

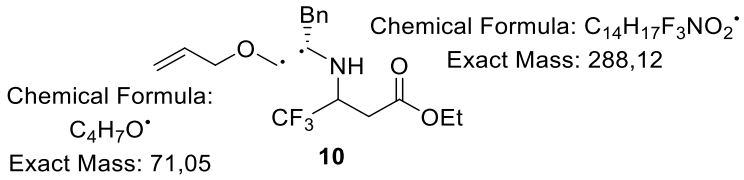
^{19}F NMR (282 MHz, $CDCl_3$) δ: -75.32 (d) *minor diast.;* -75.90 (d) *major diast*.

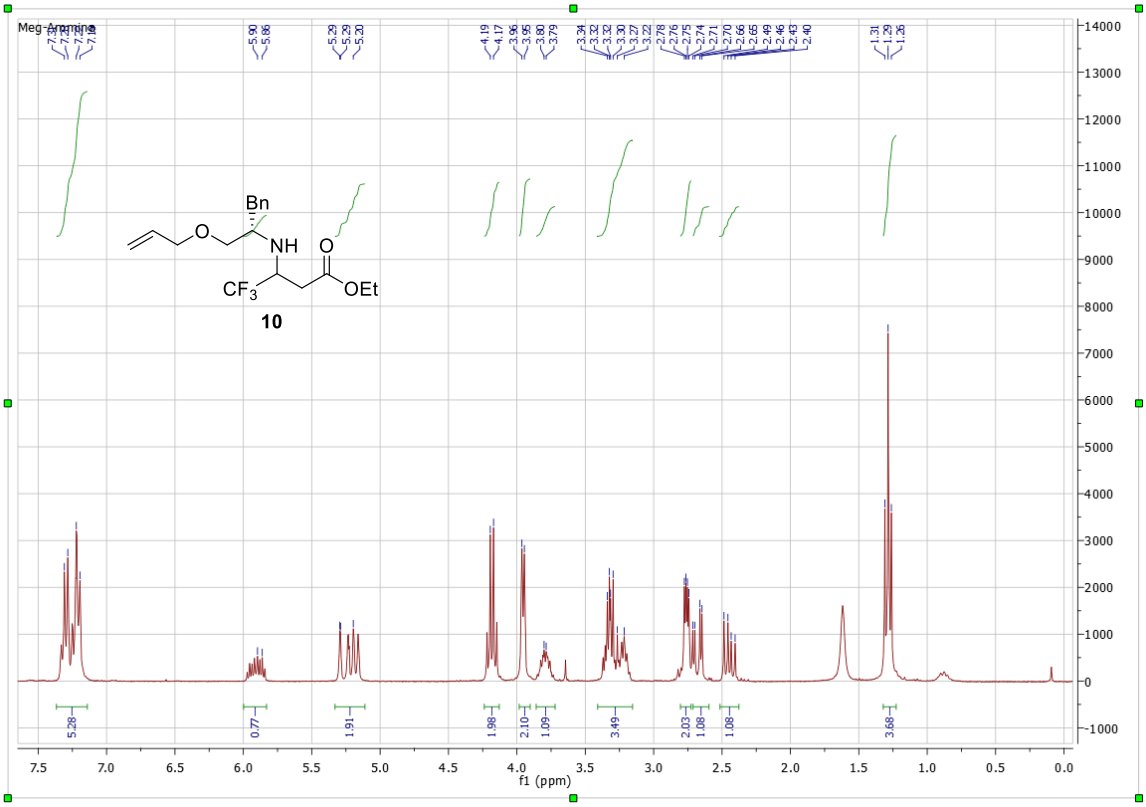
^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.0 (s), 138.3 (s), 134.7 (s), 129.3 (s), 128.5 (q), 128.4 (s), 126.3 (s), 116.7 (s), 72.0 (s), 61.0 (s), 57.2 (s), 54.8 (q), 39.0 (s), 35.47 (s), 14.1 (s).

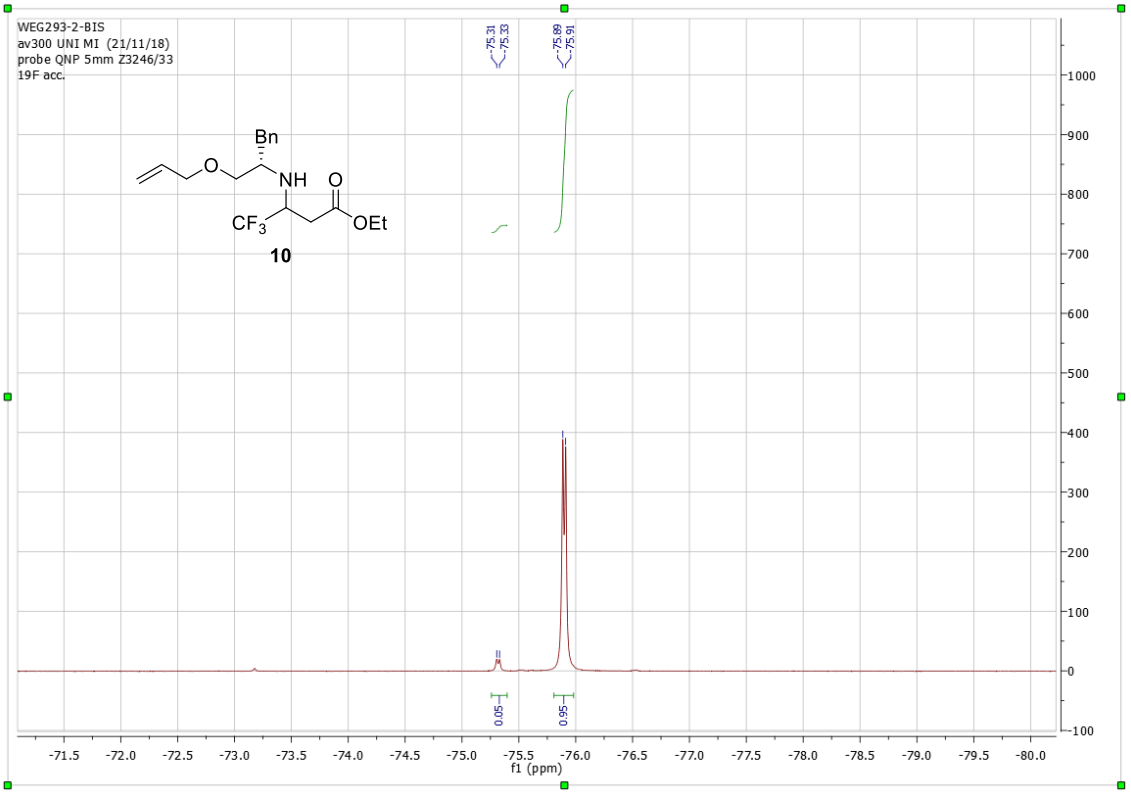
MS mass (ESI): 382.12 (M + 23).

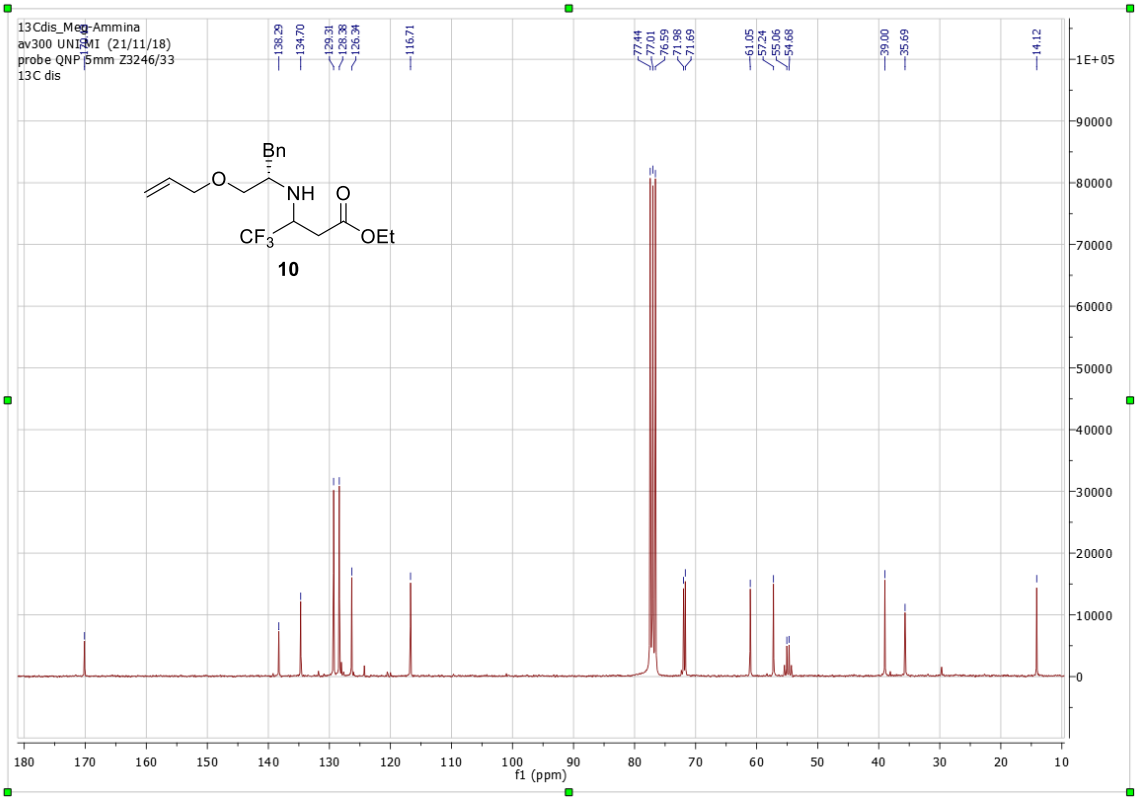
During high resolution EI mass analysis the allylic portion is lost:

HRMS (EI): calcd for C14H17F3O2N1: 288.121139, found: 288.121790

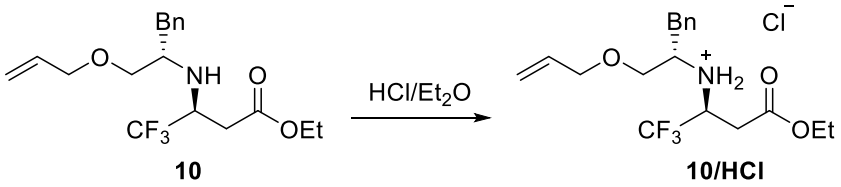




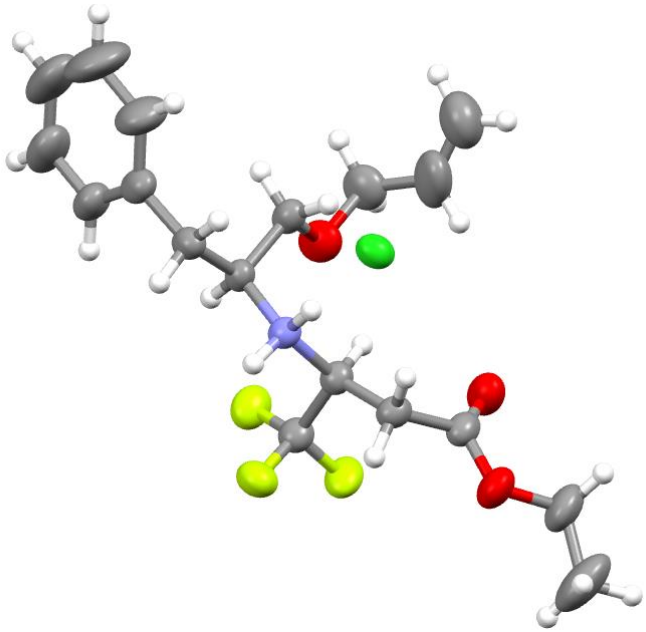

WEG293-2-BIS
av300 UNI MI (21/11/18)
probe QNP 5mm Z3246/33
19F acc.
Bn
O
NH
O
CF3
OEt
10
-75.31
-75.33
-75.89
-75.91
0.05
0.95
f1 (ppm)


13Cdis_Meg-Ammina
av300 UNI MI (21/11/18)
probe QNP 5mm Z3246/33
13C dis
Bn
O
NH
O
CF3
OEt
10
138.29
134.70
129.31
128.38
126.34
116.71
77.44
77.01
76.59
71.98
71.69
61.05
57.24
55.06
54.68
39.00
35.69
14.12
f1 (ppm)

In order to perform X-ray analysis, a sample of compound **6** was treated with an equimolar amount of HCl in Et_2O. The product was slowly crystallized from a mixture of Et_2O/hexane to afford light-yellow crystals of **10**/HCl. Absolute configuration was determined to be (*S*,*S*).



10 **10/HCl**



A summary of the experimental details concerning the single-crystal X-ray diffraction study of **10/HCl** is reported in Table S1. X-ray data were collected on a Bruker Smart Apex CCD area detector equipped with fine-focus sealed tube operating at 50 kV and 30 mA, using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). Data reduction was made using SAINT programs;[a] absorption corrections based on multiscan were obtained by SADABS.[a] The structures were solved by SHELXS-97[b] and refined on F2 by full-matrix least-squares using SHELXL-14.[c] The program ORTEP-III[d] was used for molecular graphics.

[a] Bruker, SMART, SAINT and SADABS; Bruker AXS Inc.: Madison, Wisconsin, USA, 1997.
[b] Sheldrick, G.M. A short history of SHELX. Acta Cryst. 2008, A64, 112–122.
[c] Sheldrick, G.M. Crystal structure refinement with SHELXL. Acta Cryst. 2015, C71, 3–8.
[d] M. N. Burnett, C. K. Johnson, ORTEP-III: Oak Ridge Thermal Ellipsoid Plot Program for Crystal Structure Illustrations, Oak Ridge National Laboratory Report ORNL-6895, 1996.

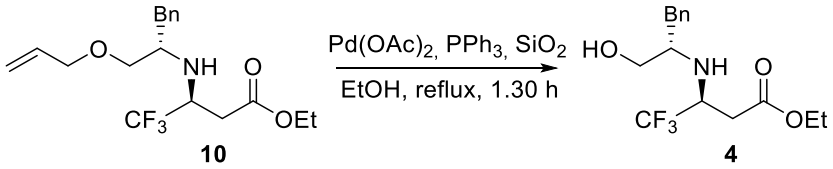
Table S1. Crystallographic data, data collection details and results of refinement for 10/HCl

formula, M_r	$(C_{18}H_{25}F_3NO_3)Cl$, 395.84
crystal system	Monoclinic
space group, Z	$P2_1$, 2
D_{calc}, g cm^{-3}	1.300
a, Å	12.6047(15)
b, Å	6.5793(8)
c, Å	12.8724(15)
β, °	108.694(2)
V, Å^3	1011.2(2)
crystal size, mm	0.52×0.05×0.03
color, habit	colorless, needle
μ, mm^{-1}	0.232
radiation	MoK$_\alpha$
T, K	180(2)
$2\theta_{max}$, °	52.77
h, k, l ranges	-15→15; -8→8; -16→16
intensity decay, %	0.00
adsorption correction	multi-scan
T_{min}, T_{max}	0.691, 0.745
measured reflections	15272
R_{int}	0.0535
independent reflections	4126
reflections with $I>2\sigma(I)$	3015
no. of parameters	236

R, *wR* [$F^2>2\sigma(F^2)$]	0.0481, 0.0995
Flack parameter	-0.02(4)
goodness of fit	0.991
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (eÅ^{-3})	0.356, -0.165

Tables of atomic coordinates, anisotropic thermal parameters, bond lengths and angles of $C_{18}H_{24}F_3NO_3$ may be obtained free of charge from The Director CCDC, 12 Union Road, Cambridge CB2 1 EZ, UK, on quoting the deposition numbers CCDC 1914889 the names of the authors and the journal citation (fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk; web site: http://www.ccdc.cam.ac.uk).

Synthesis of **4**



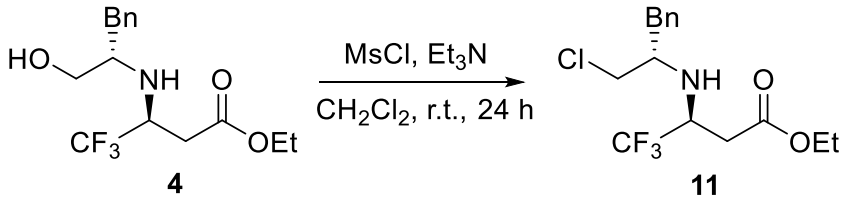
Compound **10** (0.13 mmol, 1 eq.) in EtOH (1.5 mL) was introduced in a two necks round-bottomed flask equipped with a condenser under nitrogen atmosphere. $Pd(OAc)_2$ (0.03 mmol, 0.2 eq.) and PPh_3 (0.11 mmol, 0.88 eq.) in EtOH (1.5 mL) were added to the solution, followed by 300 mg of SiO_2. The reaction mixture was stirred at reflux for 20 h. After completion of reaction, the mixture was diluted with CH_2Cl_2 and filtered over celite. After solvent removal, the crude was purified by column chromatography (silica gel, hexane/AcOEt = 9:1) to afford **4** as a yellow oil. All analytical data are in agreement with literature.[36]

Yield = 65%

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.33 – 7.20 (m, 5H), 4.25 (q, 2H), 3.75 (d, 2H), 3.37 (m, 1H), 3.23 (m, 1H), 3.20 (br s, H), 2.76 – 2.71 (m, 3H), 2.44 (m, 1H), 1.22 (t, 3H).

^{19}F NMR (300 MHz, $CDCl_3$) δ: -75.12 (d), -75.99 (d).

Synthesis of **11**[36]

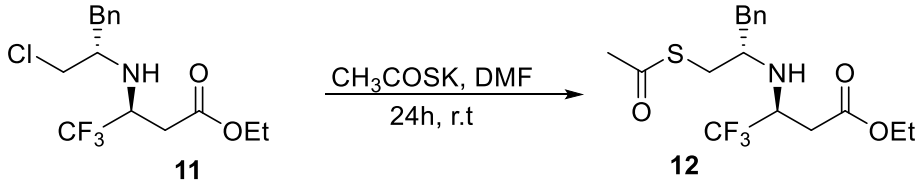


Dry Et_3N (0.31 mmol, 3 eq) and MsCl (0.31 mmol, 3 eq.) were consecutevely added to a solution of **4** (0.10 mmol, 1 eq) in dry CH_2Cl_2 (0.1 M solution) at room temperature under nitrogen. After 24 h the mixture was diluted with water and extracted with CH_2Cl_2. The collected organic layers were dried (Na_2SO_4), filtered, concentrated under reduced pressure, to afford **11** as a yellow oil. The product was used without further purification, all analytical data are in agreement with literature.

Yield = 99%

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.45-6.97 (m, 5H), 4.11 (d, 2H), 3.60 (s, 1H), 3.40 (m, 2H), 3.19 (d,1H), 2.88 – 2.46 (m, 3H), 2.35 (dd, 1H), 1.20 (t,3H).

Synthesis of **12**[36]



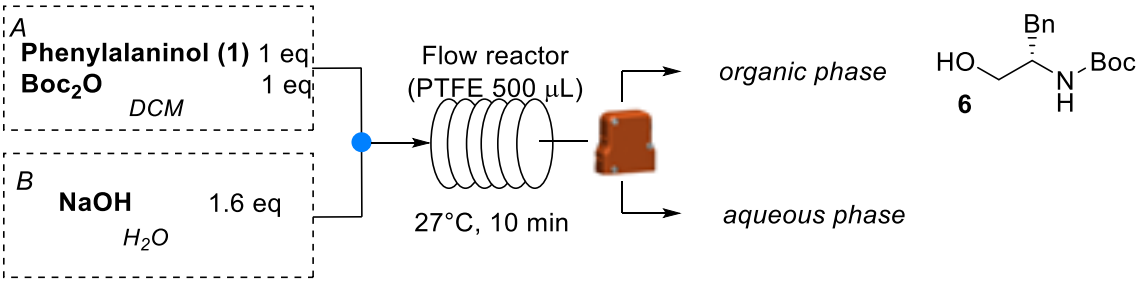
A solution of dry DMF (0.5 mL) and crude **8** (0.22 mmol, 1eq) were subsequently added to a solution of CH_3COSK (0.22 mmol, 1 eq) in dry DMF (0.5 mL) at 0°C under nitrogen. After 24h at room temperature, the mixture was diluted with water and extracted with AcOEt. The collected organic layers were dried (Na_2SO_4), filtered, concentrated under reduced pressure, the crude was purified by column chromatography (silica gel, n-hexane/AcOEt from 9:1 to 7:3) to afford **9** as a brown-yellow oil. All analytical data are in agreement with literature.

Yield = 40%

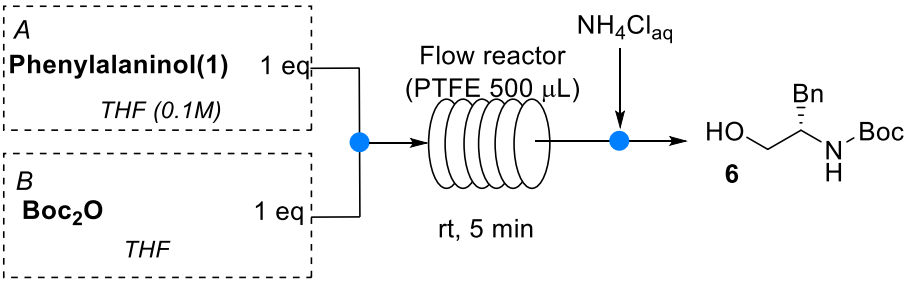
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.34-7.18 (m, 5H), 4.25-4.16 (m, 2H), 3.60 (s, 1H), 3.28-3.17 (m, 2H), 2.87-2.81 (m, 2H), 2.68-2.59 (m, 2H), 2.38 (s, 3H), 1.55-1.32 (m, 1H), 1.32-1.28 (t, 3H).

In flow synthesis of the target molecule

In flow synthesis of **6**



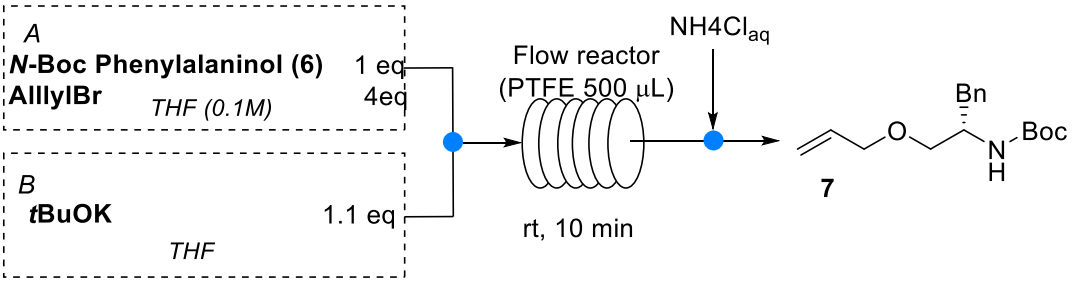
Two 2.5 mL Hamilton gastight syringes, containing *A* compound **1** (1 eq.) and Boc_2O (1 eq.) in 2 mL of CH_2Cl_2 (0.25 M), and *B* aqueous NaOH (2 mL of a 1N solution in water) were connected by a PEEK tee junction to a 500 µL PTFE coil reactor. Both syringes fed the solutions ad 25 µL/min, giving a residence time of 10 minutes. The outcome of the reactor was connected to a *Zaiput liquid liquid phase separator*, to separate the organic phase from the aqueous phase. The organic phase was dried over Na_2SO_4 and evaporated under vacuo, to give pure product **6**, as evaluated by ^1H NMR, in quantitative yield.



Two 2.5 mL Hamilton gastight syringes, containing *A* compound **1** (1 eq.) in 2 mL of THF (0.2 M), and *B* Boc_2O (1 eq.) in 2 mL of THF were connected by a PEEK tee junction to a 500 µL PTFE coil reactor. Both syringes fed the solutions ad 50 µL/min, giving a residence time of 5 minutes. The outcome of the reactor was collected into a vial containing saturated NH_4Cl. The organic phase was separated, dried over Na_2SO_4 and evaporated under vacuo, to give pure product **6**, as evaluated by ^1H NMR, in quantitative yield.

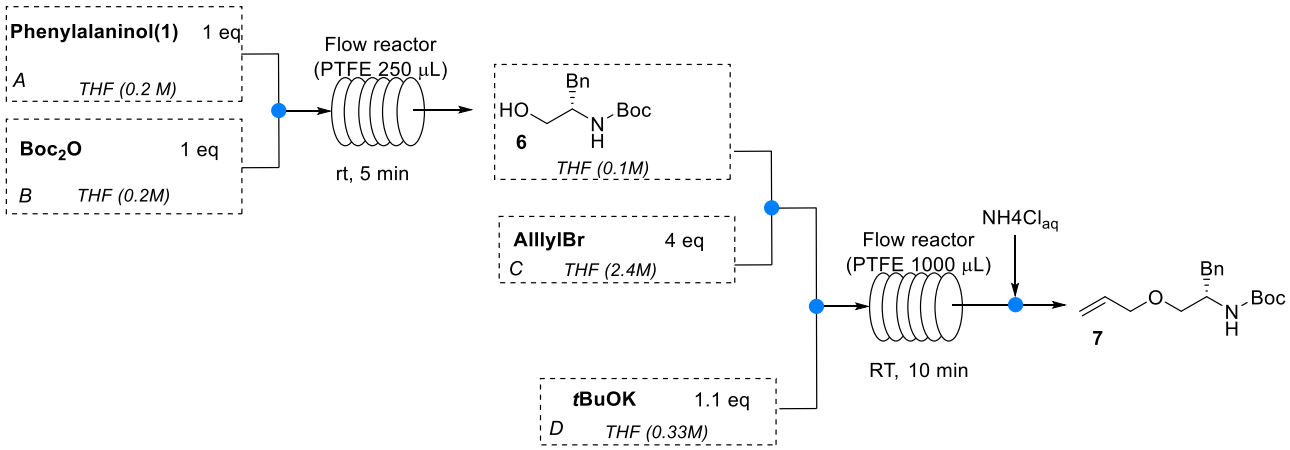
Analytical data are in agreement with product obtained using batch procedure.

In flow synthesis of **7**



Two 2.5 mL Hamilton gastight syringes, containing *A* compound **6** (1 eq.) in 2 mL of THF (0.1 M), and 4 eq. of allylbromide, and *B* *t*BuOK (1.1 eq.) in 2 mL of THF were connected by a PEEK tee junction to a 500 µL PTFE coil reactor. Both syringes fed the solutions ad 25 µL/min, giving a residence time of 10 minutes. The outcome of the reactor was collected into a vial containing saturated NH_4Cl. The organic phase was separated, dried over Na_2SO_4 and evaporated under vacuo, to give product **7** with a 75% yield, evaluated by ^1H NMR, and confirmed as isolated yield.

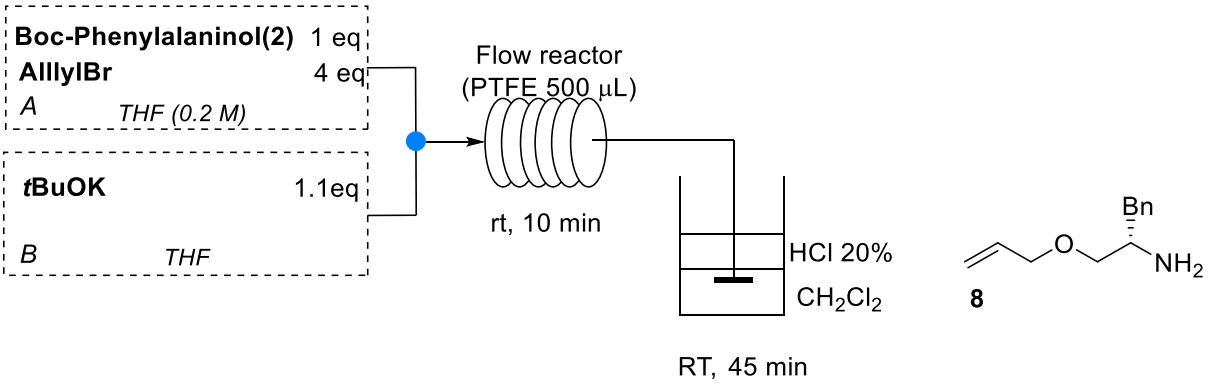
Analytical data are in agreement with product obtained in batch procedure.



Two 2.5 mL Hamilton gastight syringes, containing *A* compound **1** (1 eq.) in 2 mL of THF (0.2 M), and *B* Boc_2O (1 eq.) in 2 mL of THF were connected by a PEEK tee junction to a 250 µL PTFE coil reactor. Both syringes fed the solutions ad 25 µL/min, giving a residence time of 5 minutes. The outcome of the reactor was connected to another tee junction, fed by a 1 mL Hamilton gastight syringe *C*, containing allylbromide (0.8 mL of 2.4 M solution in THF, 4 equivalents) feeding at 10 µL/min. The outcome of this second tee was connected to another tee junction, fed by a 5 mL Hamilton gastight syringe, *D*, containing *t*BuOK (1.6 mL of a 0.33 M solution in THF, 1.1 equivalents) with a flow rate of 20 µL/min. The outcome of this third tee was connected to a 1000 µL PTFE coil reactor, with a total flow rate of 80 µL/min, and a subsequent residence time of 12.5 minutes. The outcome of the reactor was collected into a vial containing saturated NH_4Cl. The organic phase was separated, dried over Na_2SO_4 and evaporated under vacuo, to give product **7** with a 20% conversion, evaluated by ^1H NMR, and confirmed as isolated yield.

Analytical data are in agreement with product obtained in batch procedure.

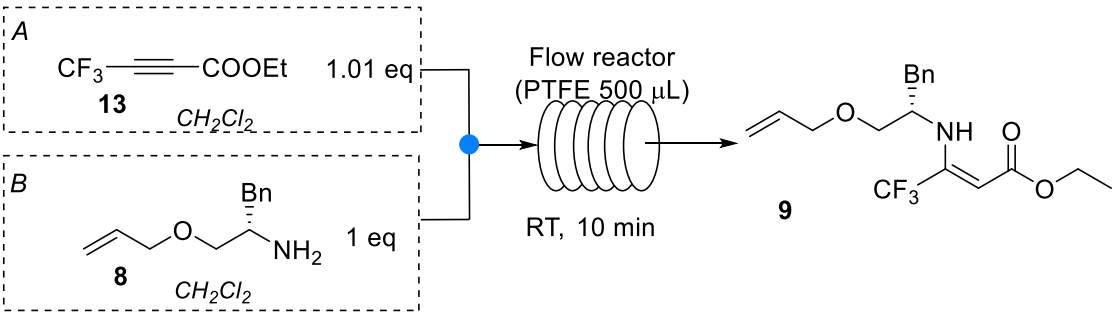
In flow synthesis of **8**



Two 2.5 mL Hamilton gastight syringes, containing *A* compound **2** (1 eq.) in 2 mL of THF (0.1 M), and 4 eq. of allylbromide, and *B* *t*BuOK (1.1 eq.) in 2 mL of THF were connected by a PEEK tee junction to a 500 µL PTFE coil reactor. Both syringes fed the solutions ad 25 µL/min, giving a residence time of 10 minutes. The outcome of the reactor was collected into a vial containing 10% HCl, were it was stirred for further 40 min. Then 1N NaOH was added until basic pH was reached, the organic phase was separated, dried over Na_2SO_4 and evaporated under vacuo, to give product **9** with a 75% conversion, evaluated by ^1H NMR, and confirmed as isolated yield.

Analytical data are in agreement with product obtained in batch procedure.

In flow synthesis of **9**



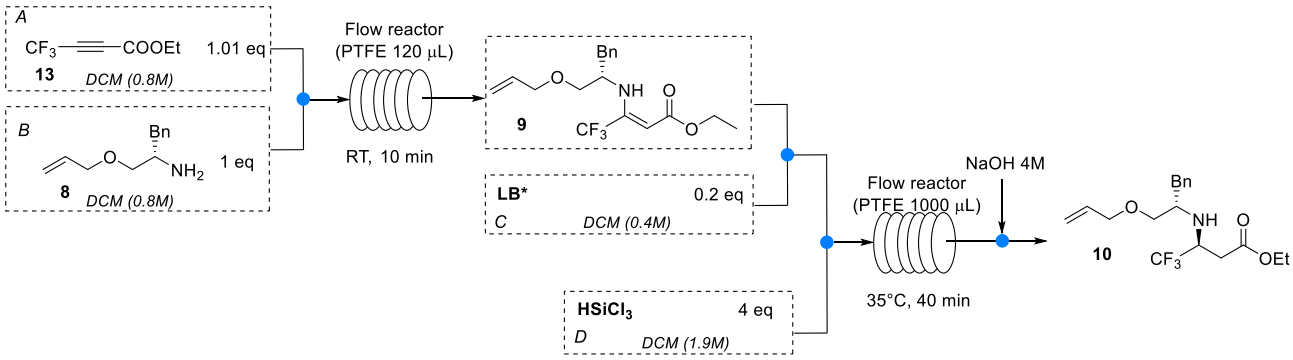
Two 2.5 mL Hamilton gastight syringes, containing *A* compound **13** (2 mL of a 0.8 M solution in CH_2Cl_2, 1.03 equivalents) and *B* compound **8** (2 mL of a 0.8 M solution in CH_2Cl_2, 1 equivalent) were connected by a PEEK tee junction to a 500 µL PTFE coil reactor. Both syringes fed the solutions ad 25 µL/min, giving a residence time of 10 minutes. The outcome of the reactor was collected in a vial cooled to -78°C, diluted with $CDCl_3$ (without removing CH_2Cl_2 to avoid the proceeding of the reaction during evaporation) and subjected to ^{19}F NMR, to evaluate the conversion of the starting material to the product. The desired enamine was formed with

a Z/E ratio of 7:3, evaluated by ^{19}F NMR. After purification, performed by column chromatography to confirm the isolated yield, the E isomer converted into the Z isomer.

^{1}H NMR (300 MHz, $CDCl_3$) δ: Z isomer: 8.46 (d, *J* = 10.5 Hz, 1H), 7.32-7.12 (m, 5H), 6.01-5.72 (m, 1H), 5.34-5.12 (dd, 2H), 5.08 (s, 1H), 4.19 (q, 2H), 4.02 (m, 2H), 3.82 (brs, 1H), 3.41-3.36 (m, 2H), 2.85-3.03 (m, 2H), 1.30 (t, 3H).

^{19}F NMR (282 MHz, $CDCl_3$) δ: -66.12 (s) (Z isomer); -65.23 (s) (E isomer).

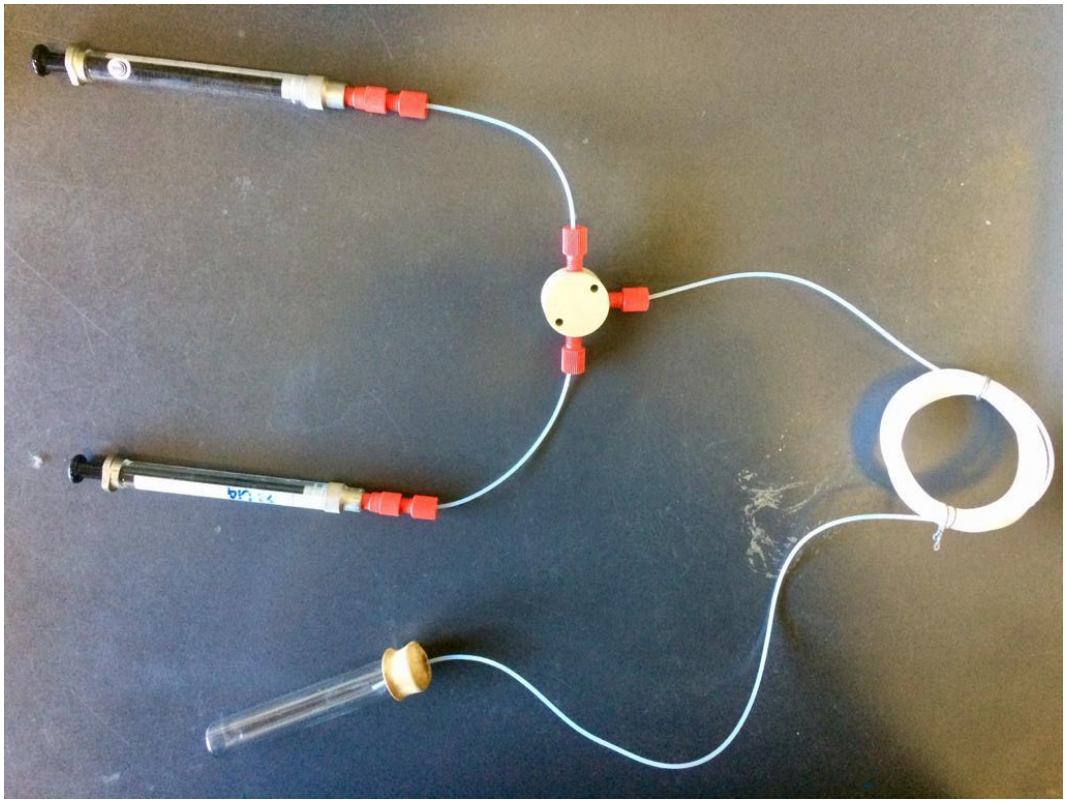
In flow synthesis of **10**

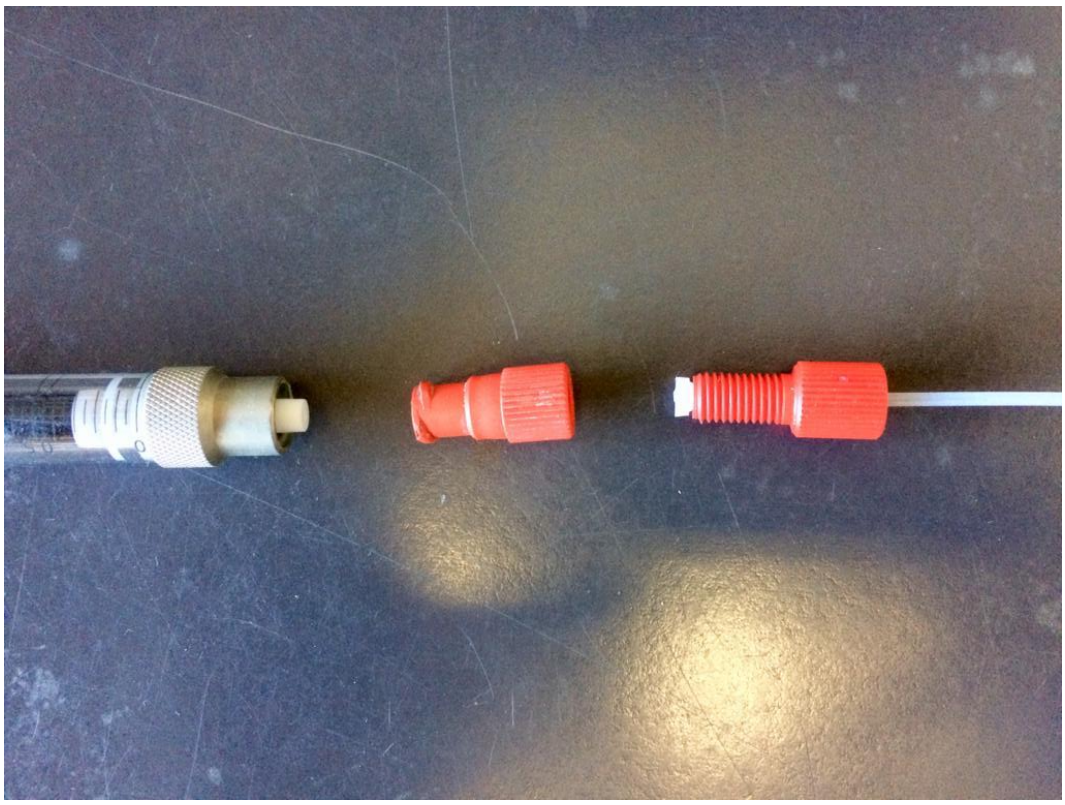


Two 2.5 mL Hamilton gastight syringes, containing *A* compound **13** (2 mL of a 0.8 M solution in CH_2Cl_2, 1.03 equivalents) and *B* compound **8** (2 mL of a 0.8 M solution in CH_2Cl_2, 1 equivalent) were connected by a PEEK tee junction to a 120 µL PTFE coil reactor. Both syringes fed the solutions ad 6 µL/min, giving a residence time of 10 minutes. The outcome of the reactor was connected to another tee junction, fed by a 1 mL Hamilton gastight syringe, *C*, containing **cat. ent-II** (0.8 mL of 0.4 M solution in CH_2Cl_2, 0.2 equivalents) feeding at 2.5 µL/min. The outcome of this second tee was connected to another tee junction, fed by a 5 mL Hamilton gastight syringe, *D*, containing $HSiCl_3$ (3.3 mL of a 1.9 M solution in CH_2Cl_2, 4 equivalents) with a flow rate of 10 µL/min. The outcome of this third tee was connected to a 1000 µL PTFE coil reactor, heated at 35°C, with a total flow rate of 24.5 µL/min, and a subsequent residence time of 40 minutes. The outcome of the reactor was collected into a NaOH 4 M solution at 0°C. After the first 2 volumes were discharged, steady state conditions were reached. The conversion of **10,** evaluated by ^{1}H NMR, was reported as an average of three reactors volume, separately collected. Reactors volumes were reunited and purified by column chromatography to confirm the conversion as isolated yield.

Analytical data are in agreement with product obtained in batch procedure.

Pictures of Flow reactors set up





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Chapter 2.2: A continuous-flow, two-step, metal-free process for the synthesis of differently substituted chiral 1,2-diamino derivatives

Introduction

Enantiopure 1,2-diamines are common structural motifs in numerous natural compounds, as well as in pharmaceuticals. Furthermore, they are excellent Lewis Bases, able to chelate other compounds and act as chiral ligands for stereoselective reactions mediated by both organocatalysts and transition-metal catalysts.[1] They represent valuable starting materials for further synthetic manipulations aimed to the synthesis of complex molecules. It is thus not surprising that the development of efficient routes to the synthesis of enantiopure 1,2-diamines has received considerable attention from the synthetic chemists' community.

Synthetic strategies for the preparation of this class of compounds include addition of amines to aziridines, nucleophilic addition to α-aminoamines, Mannich and nitro-Mannich reactions, and alkene diamination. Also, few examples of stereoselective hydroamination are present in the literature (Figure 1), either of an allylic amine or a proper enamine. Of course, in this case, the regioselectivity must be strictly controlled, as well as the enantioselectivity.[2–5]

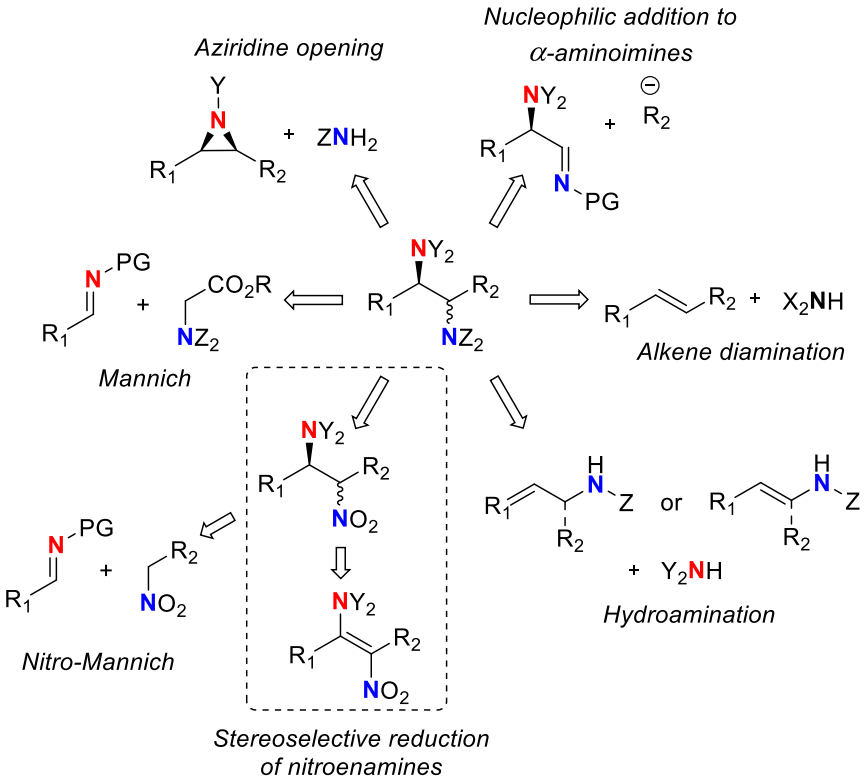
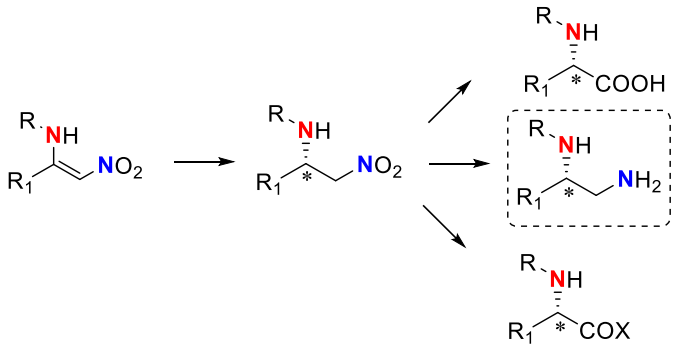


Figure 1

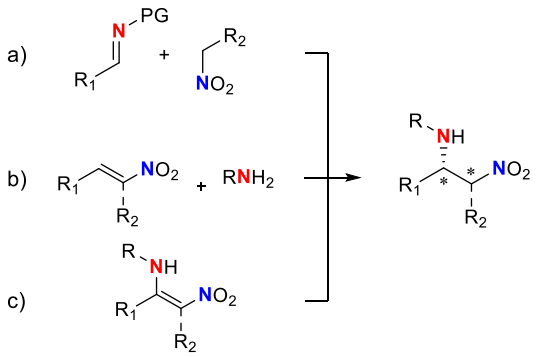
In particular, attention has been drawn to methodologies that included the possibility to modify the two amino groups of a chiral scaffold in different moments of the synthetic sequence; in this regard, the catalytic stereoselective reduction of nitroenamines is an efficient approach, that leads to the formation of enantiomerically pure 2-nitro amines, easily converted to the corresponding diamine derivatives by reduction of the nitro group (Scheme 1).

Enantiomerically pure β-amino nitroalkanes can be easily converted not only into 1,2-diamines, as previously stated, but are also precursors of α-amino acids, monoamines or α-amino carbonyls.



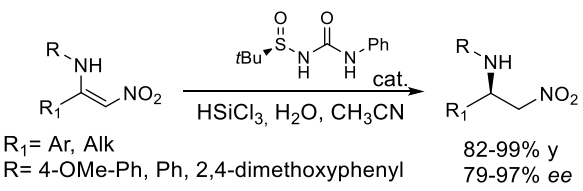
Scheme 1

Traditionally this class of compounds derives from aza-Henry (nitro-Mannich) reactions, in which a metal complex or an organocatalyst is used to afford a stereoselectivity (Scheme 2, eq. a).[6] Another approach involves the asymmetric aza-Michael addition of amines to nitroalkenes, proceeding via enamine catalysis (Scheme 2, eq. b).[7,8] The stereoselective reduction of β-amino nitroolefins, on the other hand, constitutes a straightforward pathway to form β-amino nitroalkanes, due to the availability of the starting materials (Scheme 2, eq. c). This transformation has been achieved using different approaches, both involving metal-catalysis or with metal-free approach.



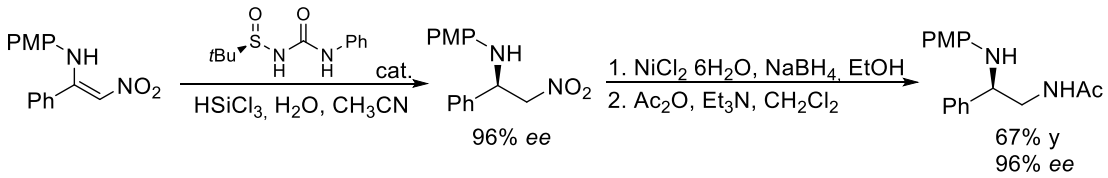
Scheme 2

One of the first examples goes back to 2012, when the Sun group reported the stereoselective reduction of β-amino nitroolefines, bearing an aromatic ring on the nitrogen atom of the enamine moiety, mediated by trichlorosilane in the presence of a *N*-sulfinyl urea as bifunctional catalyst (Scheme 3).[9] The transformation was successfully achieved also on gram scale, and a range of differently substituted β-nitroamines were synthetized in high yields and enantioselectivities.



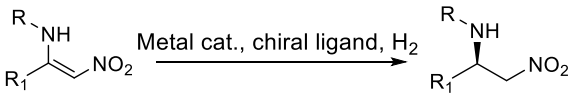
Scheme 3

The authors also demonstrated the possibility to further derivatize the obtained product, by reduction of the nitro moiety or by cleavage of the protecting group of the amino moiety, without affecting the stereochemical integrity of the compound (Scheme 4).

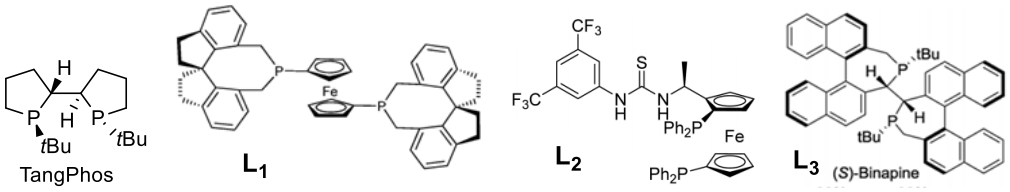


Scheme 4

Subsequently, three metal-catalyzed direct hydrogenations were reported: in 2013 Wang e Zhang developed a Rh-Tangphos complex, that proved to be efficient only for the preparation of β-aryl-β-amino nitroalkanes.[10] Hou reported the same transformation for β-acylamino nitroolefins the next year, by using an Ir-spiroPhos complex in the presence of 20 atm of H_2,[11] while Hu Dong and Zhang reported a rhodium/bifunctional biphosphine thiourea ligand complex (**L_2**), able to perform the stereoselective reduction in the presence of 50 atm of H_2.[12] The most recent direct hydrogenation of nitroenamines goes back to 2017, relying for the first time on the use of a cheap transition metal catalyst, Nickel, in the presence of a high molecular weight diphosphine chiral ligand **L_3**, (*S*)-Binapine (Scheme 5).[13]

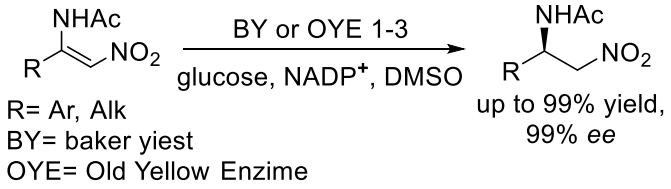


Conditions: [Rh(COD)TangPhos]BF_4 (1mol%), H_2(5 atm), TFE, rt
$Rh(NBD)_2BF_4/L_1$, H_2 (50 atm), CH_2Cl_2, rt
$[Ir(COD)Cl]_2/L_2$ (0.5mol%), H_2 (20 atm), CH_2Cl_2, 80°C
$Ni(OAc)_2$ (5mol%), L_3 (5.6mol%), H_2 (5-10 atm), TFE, rt



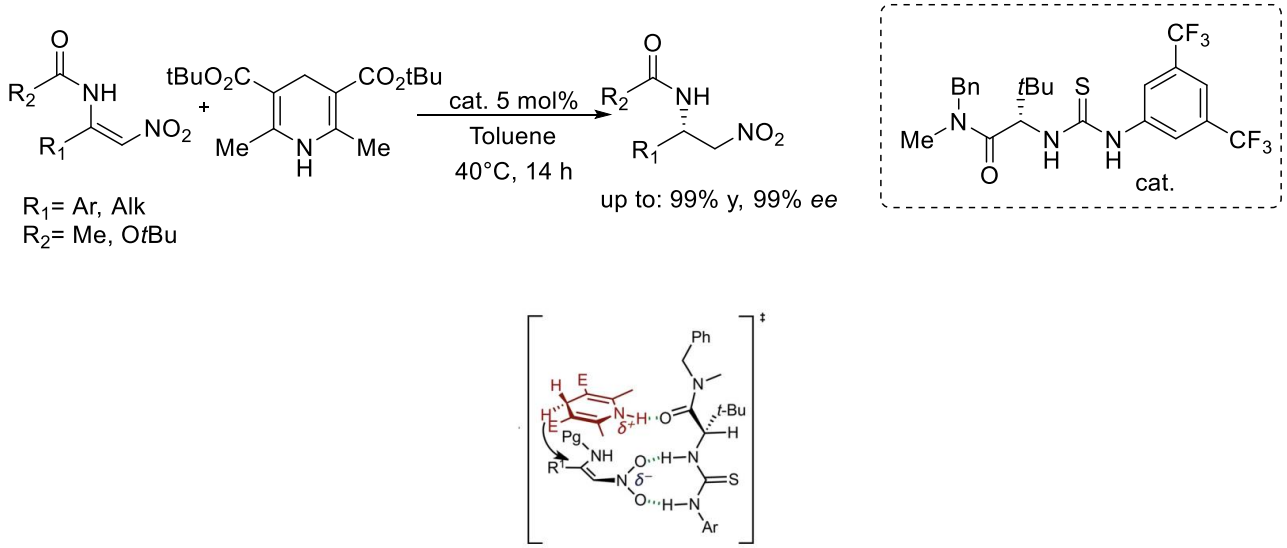
Scheme 5

In the same year, a different metal-free approach was reported, based on the bio-catalytic stereoselective reduction of *N*-acetyl-nitroenamines, performed by an ene-reductase.[14] The methodology resulted feasible for both aryl and alkyl substituted substrates, and the screening was performed using isolated Old Yellow enzymes as well as baker yeast (Scheme 6). Interestingly, to further demonstrate the synthetic utility of their new transformation, the authors were able to further reduce the nitro group, without isolation of the intermediate, and synthetize a chiral 1,2-diamine.



Scheme 6

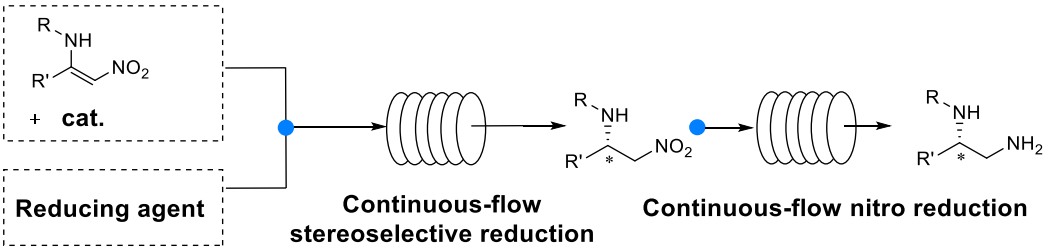
Our interest has always been related to the development of metal-free synthetic methodologies; therefore, we turned our attention to the enantioselective transfer hydrogenation developed by Bernardi and Fochi,[15] that relies on the use of a bifunctional thiourea-based organocatalyst. Tert-butyl Hantzsch ester was used as hydrogen source, and the methodology was successfully applied on β-amino nitroalkanes bearing an acyl moiety at the amine but also the corresponding compounds with a Boc-protecting group, synthetically more versatile (Scheme 7).



Scheme 7

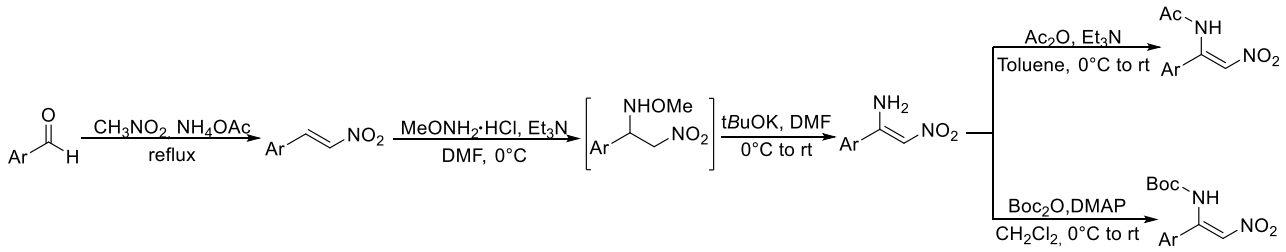
Results and discussion

Our idea was to assess the possibility to perform the nitroenamine reduction under continuous flow conditions trying to take advantage of the possible improvements associate with this kind of technology, as discussed in the introduction of **Chapter 2**, meaning for example a reduction of reaction time due to improved heat and mass transfer. Furthermore, we wanted to perform a telescopic synthesis, avoiding isolation and manipulation of the intermediate β-nitroamine, by reducing the nitro moiety and obtain access, through a one-pot-two-step synthesis, to chiral enantioenriched 1,2-diamines (Scheme 8).



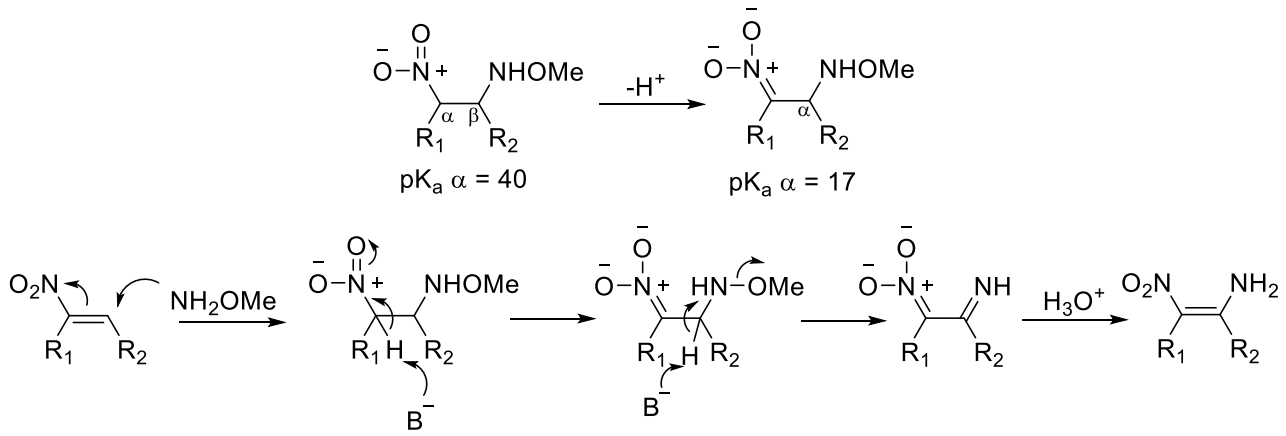
Scheme 8

Preliminary work involved the preparation of the chiral catalyst, *tert*-butyl Hantzsch ester, and the starting material, both in the *N*-acylated and *N*-Boc-protected form (Scheme 9).



Scheme 9

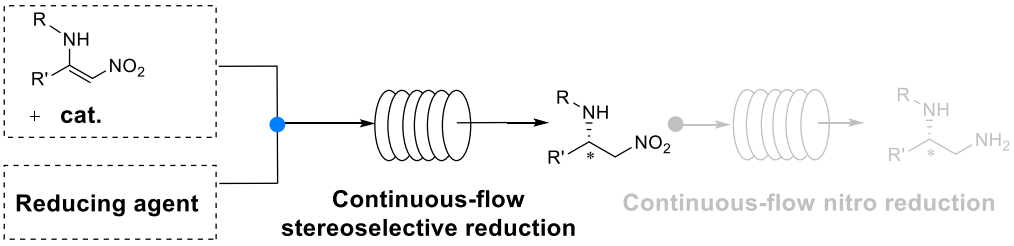
The amination of nitroolefins with methoxyamine in the presence of a base is known to give unprotected β-nitroenamines in good yields, in a direct synthesis by nucleophilic substitution of the vinylic hydrogen.[16] No leaving group at the β-position is required, since the authors claimed that computational analysis predicts that the pk_a value of the α-position (referring to the nitro moiety) is considerably lowered after the deprotonation of the β-position. The proposed mechanism suggests that in the presence of two equivalent of base, the reaction proceeds via two subsequent deprotonations, as depicted in Scheme 10. [16]



Scheme 10

Stereoselective reduction of nitroenamines under continuous flow

With all the starting materials in our hands, we began to work on the first reaction step, meaning the stereoselective reduction of beta-nitroenamines by Hantzsch ester in the presence of a chiral thiourea based organocatalyst (Scheme 11).

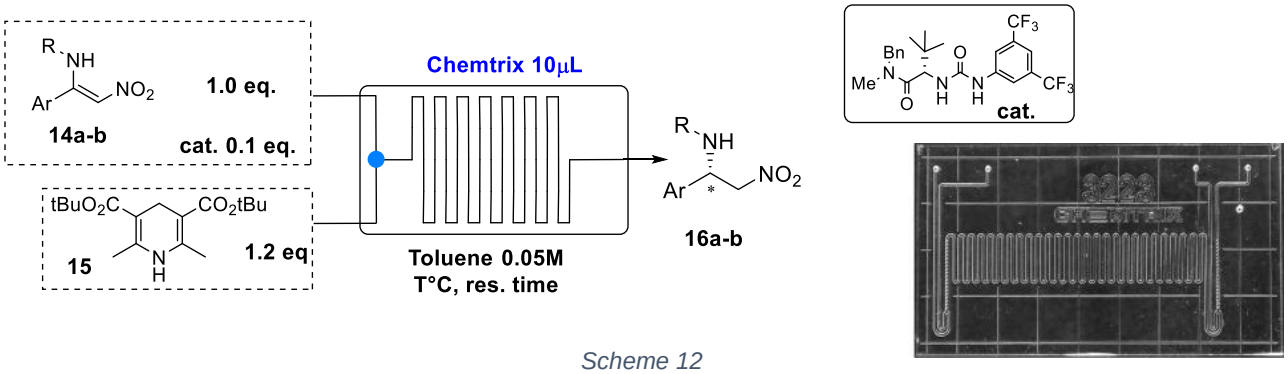


Scheme 11

We focused on reproducing the reaction in the same conditions reported in the paper by Bernardi et al.[15] We immediately noticed that under batch conditions, the reaction is an heterogeneous one, since the reaction mixture presents undissolved materials through all reaction time, when run in toluene at the reported concentration. We tested the solubility of the single components and of different mixtures with defined ratios, in toluene, and we evaluated that the least soluble compounds are the Hantzsch ester and the product. This, even if does not undermine the good results in terms of yield and enantiomeric excess, is definitely an issue in the extent of performing the reaction under continuous flow. Solubility issues were addressed by diluting the reaction mixture, using the same solvent of the reported reaction (toluene). More precisely, we worked at 0.05M concentration, compared to the 0.3M concentration of the batch literature procedure. We preliminarily studied the feasibility of the method, by screening some experimental conditions in a commercially available Chemtrix Labtrix® Start Standard platform (Figure 2**Errore. L'origine riferimento non è stata trovata.**), using

Figure 2

a 10µl reactor (reported in Scheme 12). This kind of equipment is particularly useful to screen different conditions in a short time and without consuming large quantities of starting materials (especially when they are not commercially available, as in our case).



Scheme 12

The results reported in Table 1 highlights a screening of reaction conditions under continuous flow in the microreactor (Scheme 12). The reaction was stopped by crash cooling the outcome of the reactor in a cool bath at -10°C, followed by removal of the solvent in high vacuum at low temperature.

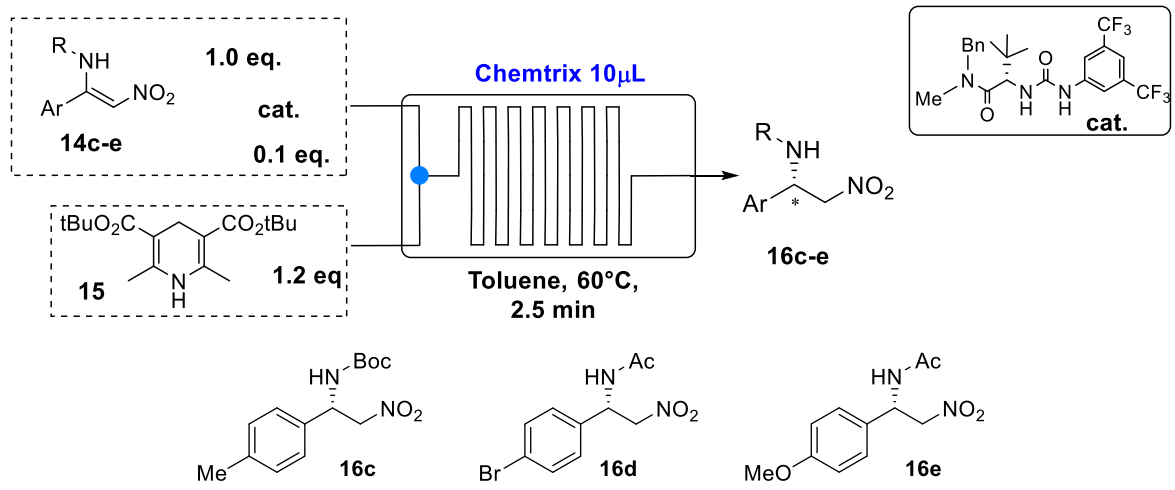
Reaction temperature is a key parameter but going to temperatures higher than 60°C does not improve the conversion. At 60°C, with a residence time of only 2.5 min., the nitro amine **16a** was continuously produced in 70% yield and 97% *ee* (entry 3, Table 1). Similarly, the in-flow reaction of *N*-acetyl protected nitroenamine **14b** with Hantzsch ester 1**5** afforded the corresponding amine **16b** in 70% yield and 93% of enantioselectivity (entry 5). We were pleased to see that the reduction of protected nitroenamines **14a-b** can be efficiently performed in continuo, with short residence times, good yields and remarkably high enantioselectivities.

Table 1

Entry	R, Ar	Imine	Flow (µL/min)	Res.Time (min)	T (°C)	y (%)[1]	*ee* (%)
1	Boc, Ph	**14a**	2	5	40	50	>99
2	Boc, Ph	**14a**	2	5	60	70	97
3	Boc, Ph	**14a**	4	2.5	60	70	97
4	Boc, Ph	**14a**	4	2.5	80	70	96
5	Ac, Ph	**14b**	4	2.5	60	70	93

[1]Evaluated as molar ratio between the product and the SM, since no other substantial by-product was ever observed.

After finding optimized reaction conditions (4 µL/min flow rate in a 10 µL microreactor heated up to 60°C) the reaction was successfully extended to other 1-aryl substituted nitroenamines, **14c-e**; the reductions led to the corresponding nitroamines **16ce** in similar yields and with enantioselectivities constantly higher than 90% (Table 2 and Scheme 13).



Scheme 13

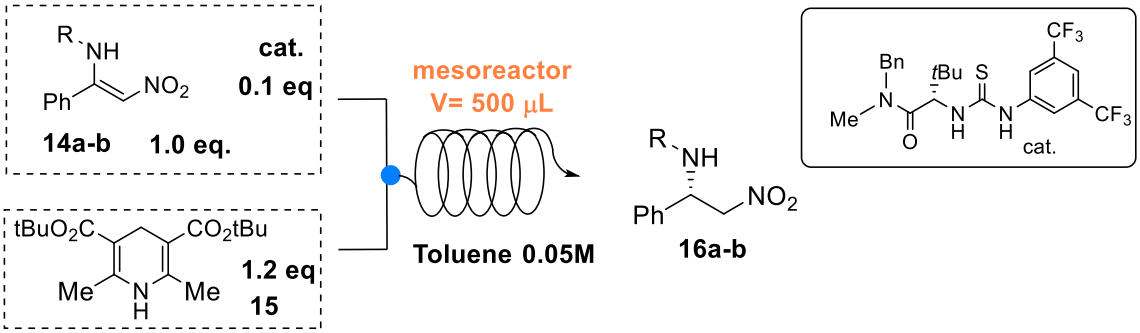
Table 2

Entry	R, Ar	Product	T (°C)	y (%) [1]	*ee* (%)
1	Ac, 4-OMePh	**16c**	60	40	92
2	Ac, 4-BrPh	**16d**	60	80	91
3	Boc, 4-MePh	**16e**	60	70	98

[1]Evaluated as molar ratio between the product and the SM, since no other substantial by-product was ever observed.

Since our goal was to perform a telescopic synthesis, meaning reducing the nitro group without isolating the intermediate, we needed to switch to a different set up. The reason is that we had in mind to perform the nitro reduction mediated by trichlorosilane in the presence of a tertiary amine, and this method is not compatible with the use of Chemtrix Labtrix. The small dimensions of the reactor channels (elliptic section, 0.3*0.12 mm major axis *minor axis) would lead to clogging of the system due to the tendency of trichlorosilane to form insoluble siloxanes in the presence of moisture. Furthermore, our Chemtrix system is built with PEEK connections, that are not compatible with the presence of trichlorosilane (probably due to hydrogen chloride released in the presence of moisture).

Hence we decided to perform a little scale-up, employing a meso-reactor, realized by using PTFE tubing (0.58 mm inner diameter, 1.89 m length, 500 µL effective volume) coiled in a bundle and immersed in an oil bath heated to the desired temperature (Scheme 14). We knew that switching to higher diameters, without the help of a static mixer, could have led to a worse mixing, and so lower yields for the same residence time.[17]



Scheme 14

Table 3

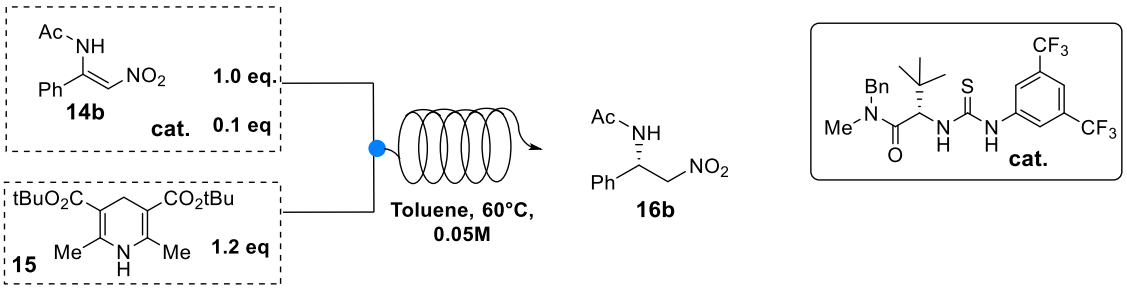
Entry	R, Ar	Imine	Flow (μL/min)	Res. Time (min)	T (°C)	y (%) [1]	*ee* (%)
1	Boc, Ph	**14a**	50	10	40	31	96
2	Boc, Ph	**14a**	25	20	40	45	96
3	Boc, Ph	**14a**	100	5	60	35	96
4	Boc, Ph	**14a**	50	10	60	43	96
5	Boc, Ph	**14a**	25	20	60	55	97
6	Ac, Ph	**14b**	50	10	60	57	93
7	Ac, Ph	**14b**	25	20	60	65	91

[1]Evaluated as molar ratio between the product and the SM, since no other substantial by-product was ever observed

At 40 °C, with a 10 minutes residence time, the reduction of **14a** afforded the product **16a** in 31% yield and 96% *ee* (entry 1, Table 3); doubling the residence time, improved the conversion up to 45%. In the attempt to further improve the productivity, the reaction temperature increased up to 60°C (entry 3-5), with residence times ranging from 5 to 20 minutes. The desired product was isolated in up 55% yield and 97% *ee*. The *N*-acylated enamine was also tested in the optimized condition (60°C, 10-20 minutes of residence time, entry 6-7), and the corresponding reduced product was obtained in up to 65% yield and 91% *ee.*

It is interesting to attempt a comparison of the results obtained by running the reaction in a micro- or meso-reactor. As previously stated, we expected lower yields for the meso-reactor compared to the previous results obtained in the micro-reactor, due to mixing differences. This can be seen by confronting entry 3 of Table 1 to entry 2 of Table 3: performing the reaction at 60°C, with 5 minutes of residence time, allowed us to obtain 70% yields using the micro-reactor, while 35% yield using the meso-reactor, with similar *ee* (96 vs 97%).

This is clearly shown also by preliminary kinetic studies. For sake of comparison, we performed the reaction in the same optimized conditions (60°C, 0.05 M in toluene, 10 mol% of catalyst loading) also in batch, and we confronted the kinetic profile of the reaction in the three different systems (micro-, meso-reactor and batch). For reaction times shorter than 20 minutes, the yields of the batch process are clearly lower, compared to those observed by performing the reaction in the meso-reactor, where a 65% yield was observed after 20 minutes, (Scheme 15) while in batch 18% yield was determined. In micro-reactors, the reduction worked even better, affording the product in 70% yield after only 2.5 minutes of reaction (Figure 3), always maintaining a very high level of enantioselectivity, constantly higher than 91%.



Scheme 15

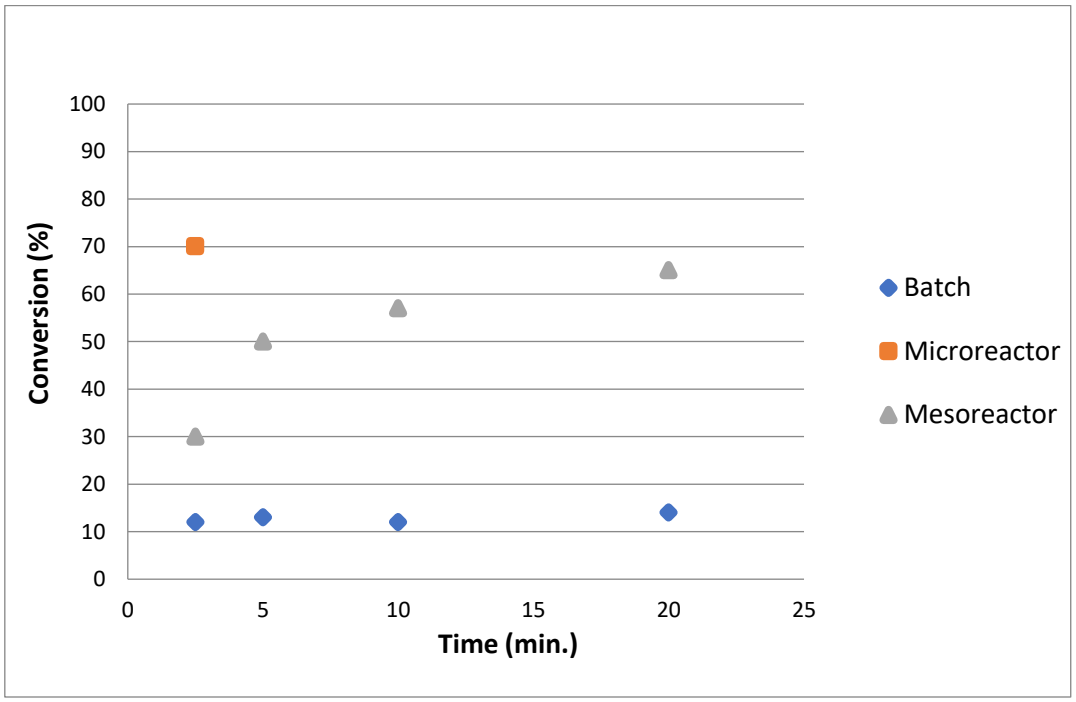


Figure 3

It is important to point out that in this case, the batch reaction was not in its optimized conditions, because of increased dilution, that surely affected both the kinetic profile and the yield: our aim was to confront the systems in exactly the same conditions, to study the effect of an improved mixing. To really compare the efficiency of the different systems, it is worth to confront different process in the optimized conditions of each technology.

In order to have an idea of the productivity of these systems ,we decided to compare the process by using space-time yield,[18] calculated as mmol of product per volume of the reactor per reaction time (mmol/ml^{-1}h^{-1}). For this parameter, the yield, the concentration, and the reaction time are taken into consideration: if the batch reaction has the advantage to be conducted in more concentrated conditions, our developed continuous synthesis are giving high yields in very short residence time, and for this reason, they show better results in terms of space-time yield.

Using a 25 µL/min flow rate in a 500 µL mesoreactor, the product **16a** was continuously synthesized with a space-time yield of 82 mmol/ml^{-1}h^{-1} (entry 2 in Table 4). With microreactors, space time yields were even higher, up to 840 mmol/ml^{-1}h^{-1} (entries 1, Table 4), compared to a 19.3 mmol/ml^{-1}h^{-1} for the batch reaction. It is important to point out also that the batch reaction is run with 5 mol% of catalyst (compared to the 10 mol%

of the continuous flow synthesis), an aspect that is not taken into account for this parameter, but has for sure an important role.

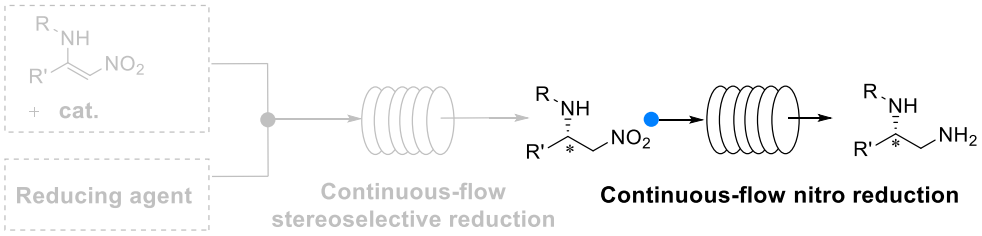
Table 4

Entry	Reactor	Imine	Conc. [M]	Res. Time (min)	T (°C)	y (%)[a]	*ee* (%)	Space-time yield [b]
1	microreactor	**14a**	0.05	2.5	60	70	97	840.0
2	mesoreactor	**14a**	0.05	20	40	55	97	82.0
3[c]	Batch	**14a**	0.3	840	60	90	99	19.3

[a] Evaluated as molar ratio between the product and the SM, since no other substantial by-product was ever observed; [b] Calculated as mmol product / reactor volume x reaction time x 1000 (mmol/ml^{-1}h^{-1}); [c] reaction condition: 5 mol% of catalyst, 0.3M, 14h of reaction time.

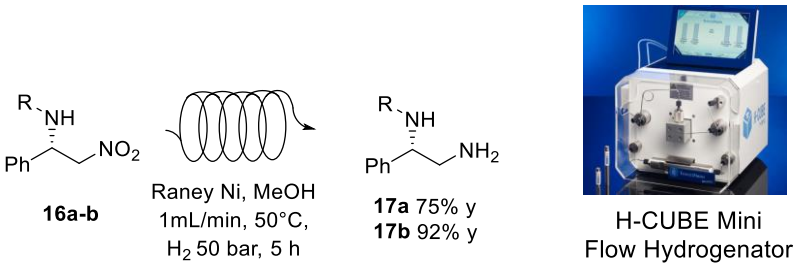
Reduction of the nitro group

The subsequent step involved the reduction of the nitro group, performed under continuous flow conditions (Scheme 16).



Scheme 16

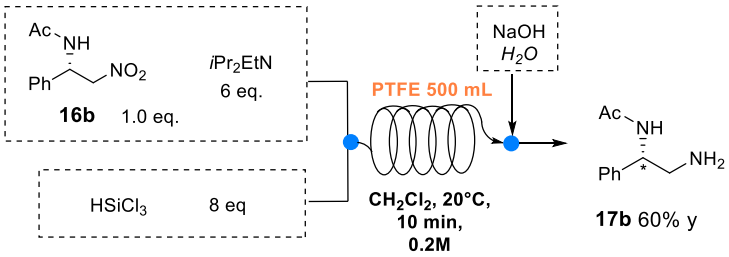
The reaction was run in a ThalesNano H-Cube Mini™, equipped with a 10% Raney Ni cartridge (Scheme 17).[19] After preliminary studies on chiral amine **4a**, it was found that the continuous-flow hydrogenation[20] could be efficiently performed operating at 50°C and 50 bar, leading to the isolation of the diamine derivative **6a** in 75% yield after 5 hours. Analogously, the reduction of *N*-acetyl derivative **4b** afforded the product **6b** in 92% yield, without any loss of stereochemical integrity, as confirmed by HPLC on chiral stationary phase.



Scheme 17

In the attempt to develop a completely metal-free two-step, continuous-flow process for the stereoselective, catalytic synthesis of 1,2-diamines, the reduction of the nitro group was also performed by employing

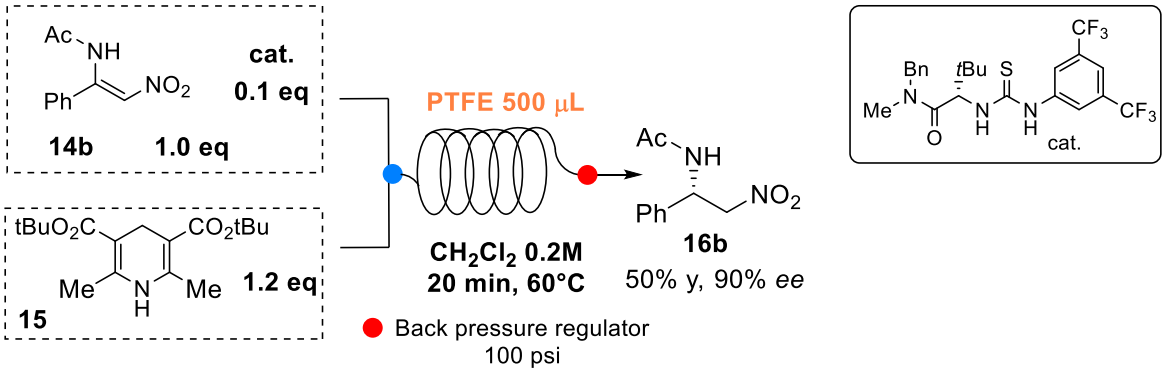
trichlorosilane in the presence of a tertiary amine (Scheme 18).[21] Unfortunately, the Boc-protecting group is not compatible with the acidic conditions of the trichlorosilane mediated reduction of the nitro group, and it was not possible to isolate the completely deprotected diamine. On the other hand, it was observed that the continuous-flow reduction of *N*-acetyl amino nitroderivative **16b** could be realized in a PTFE meso-reactor, in dichloromethane as reaction solvent; the expected *N*-acetyl monoprotected 1,2-diamine **17b** was produced in 60% yield and with the same optical purity of the starting material.



Scheme 18

Continous flow two-step process

In order to couple the two reaction steps (the stereoselective reduction of nitroenamine, and the reduction of the nitro group) in a telescopic synthesis, further experiments were run to possibly match the solvents used. Since toluene is not compatible with the reduction of the nitro group performed by trichlorosilane, as already known in the literature,[22] we switched to dichloromethane for the first step, the stereoselective reduction. The reaction could be performed with 50% yield in dichloromethane, with a decrease also in the enantioselectivity (90% *ee* vs 97% in toluene, Scheme 19, Table 5). In this case, the concentration was increased up to 0.2 M, due to the better solubility, of both the reagents and the product in this solvent. A back-pressure regulator was also used in order to heat up the reaction to temperatures higher than the boiling point of dichloromethane, thus highlighting the possibility to safely work with pressurized systems in continuous flow synthesis.



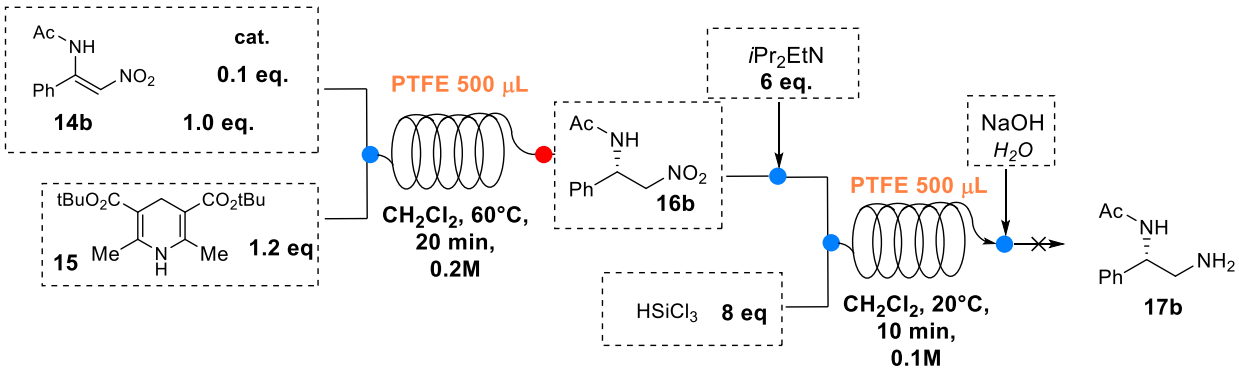
Scheme 19

Table 5

Entry	Flow (µL/min)	Res. Time (min)	y (%) [a]	*ee* (%)
1	50	10	35	91
2	25	20	50	90

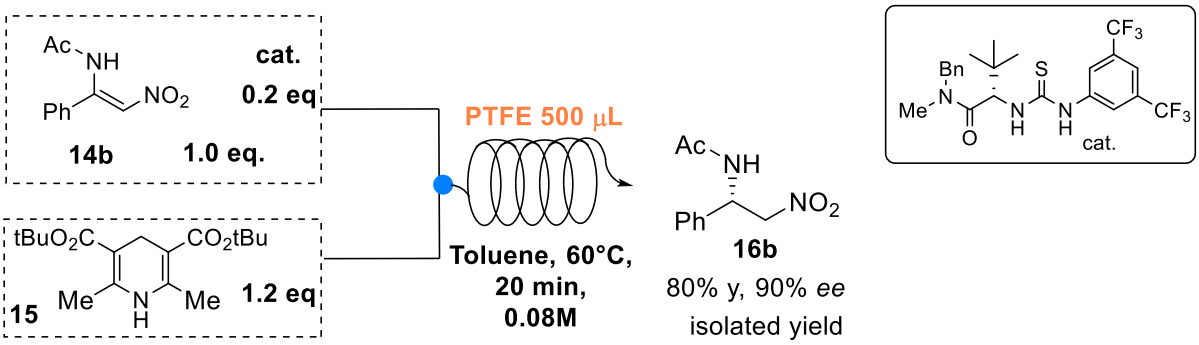
[a] Evaluated as molar ratio between the product and the SM, since no other substantial by-product was ever observed;

A multistep, in-continuo synthesis of chiral mono *N*-acetyl protected diamine **17b** was subsequently studied. After the first enantioselective, organocatalytic step in dichloromethane, the organic solution was directly introduced in a second reactor for the nitro group reduction. Diisopropylethylamine and trichlorosilane were subsequently added using T-junctions, and the reactor outcome connected to a second coiled PTFE 500 µl reactor. The mixture was quenched by pouring it into an aqueous basic solution at low temperature (Scheme 20). However, the presence of considerable amounts of unreacted nitroenamine, since the conversion of the first step in this conditions is known to be 50%, as well as unreacted Hantzsch ester and the formed pyridine by-product, led to a complex reaction mixture, difficult to purify, and only traces of the final product were detected.



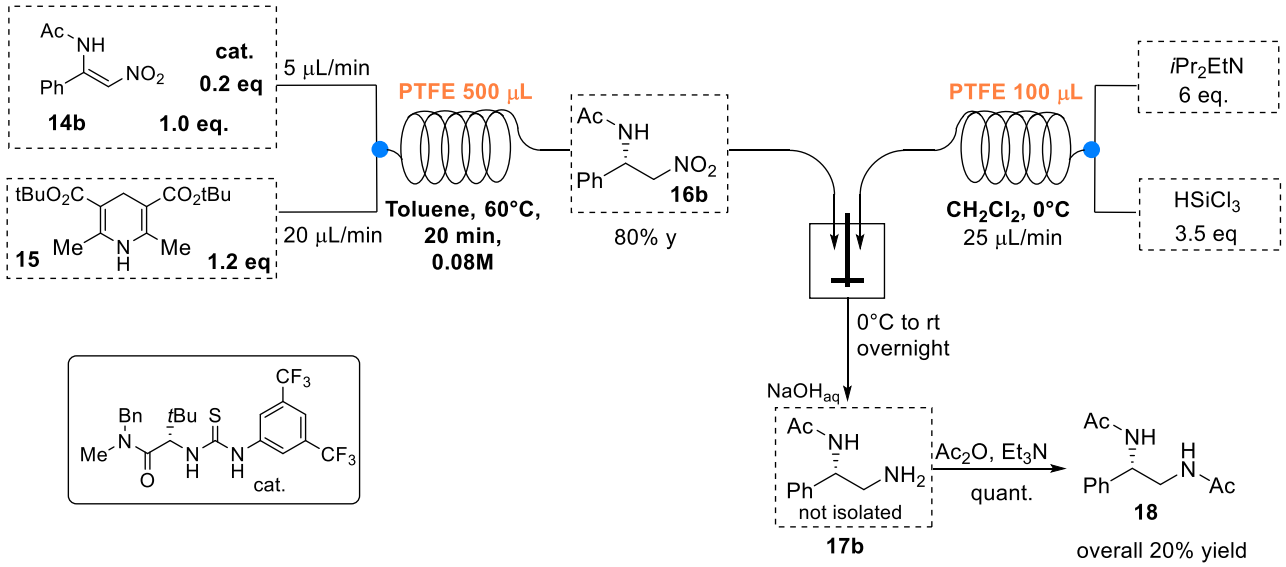
Scheme 20

Therefore, we decided to study a different procedure; since it seemed clear that a good conversion of the first reaction step is crucial for the success of the nitro reduction step, we focused on maximizing the yield of **16b**. This could be done by increasing the equivalent of the catalyst to 20 mol%, and increasing the concentration, up to 0.08M in toluene. Even if the system is more prone to clogging, and there is risk of clogging, we were able to achieve 80% conversion, with 90% *ee* (Scheme 21).



Scheme 21

The final set up for the continuous-flow, two-step, metal-free process for the synthesis **16b** is described in Scheme 22. After performing the catalytic enantioselective reduction under our improved conditions in toluene, in a PTFE meso-reactor, the product **16b** was further reacted in a flask, where the nitro reduction was accomplished by adding the reducing reagents combination ($HSiCl_3$ / iPr_2EtN) generated in situ in a second PTFE meso-reactor. The mono *N*-acetyl protected diamine **17b** was detected (30% yield) and converted to the bis acetyl product **18**, that was purified and completely characterized.



Scheme 22

Conclusions

In conclusion, the enantioselective, metal-free catalytic reduction of nitro enamines was accomplished for the first time under continuous-flow conditions. Micro-reactors were used in a preliminary screening that allowed to establish the best performing conditions, that were then successfully replicated in a meso-reactor, obtaining remarkably high yields in short residence times, and enantioselectivities constantly higher than 90%. The nitro group reduction was also successfully realized, either by continuous-flow Nickel-catalyzed hydrogenation and by trichlorosilane-mediated reduction. The present work is a further demonstration that the development of a multistep continuous flow process for the synthesis of enantiomerically pure products is today feasible and will bring to further applications in the near future.

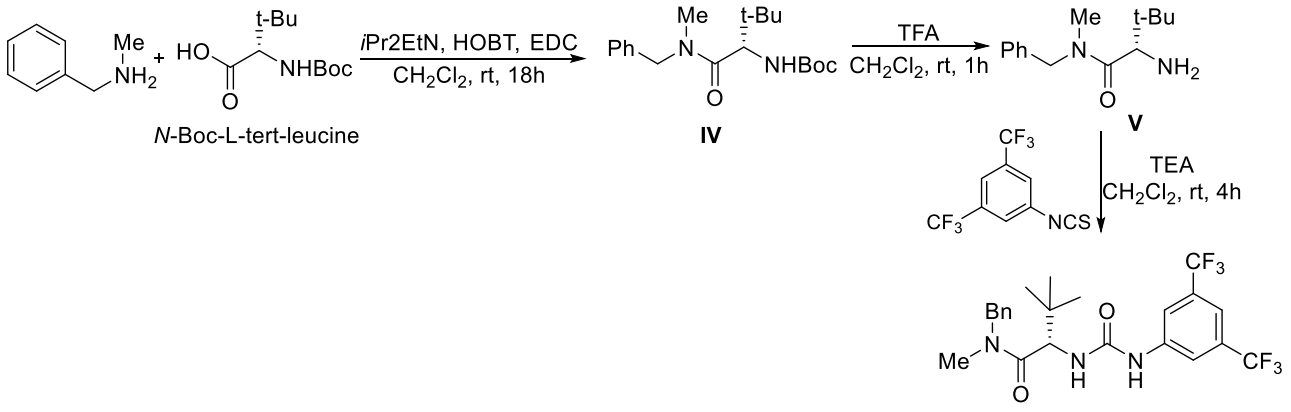
Experimental section

Materials and Methods

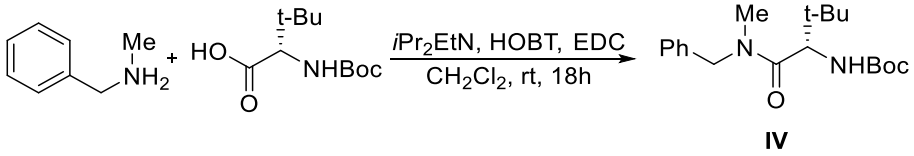
Reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F_{254} pre-coated glass plates (0.25 mm thickness) and visualized using UV light. Flash chromatography was carried out on silica gel (230-400 mesh). Proton NMR spectra were recorded on spectrometers operating at 300 MHz (Bruker Avance 300); proton chemical shifts are reported in ppm (δ) relative to tetramethylsilane (TMS, $CDCl_3$: δ=7.26 ppm). ^{13}C-NMR spectra were recorded on 300 MHz spectrometers (Bruker Avance 300) operating at 75 MHz, with complete proton decoupling; carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, : δ = 77.0 ppm). ^{19}F-NMR spectra were recorded on 300 MHz spectrometers (Bruker Avance 300) operating at 282.1 MHz; fluorine chemical shifts are reported in ppm (δ) relative to $CFCl_3$ with the respective solvent resonance as the internal standard ($CFCl_3$: δ = 77.0 ppm). Mass spectra and accurate mass analysis were carried out on a VG AUTOSPEC- M246 spectrometer (double-focusing magnetic sector instrument with EBE geometry) equipped with EI source or with LCQ Fleet ion trap mass spectrometer, ESI source, with acquisition in positive ionization mode in the mass range of 50-2000 m/z. Optical rotations were obtained on a Perkin-Elmer 241 polarimeter at 589 nm using a cell with a length of 1 dm. For HPLC analyses on chiral stationary phase, to determine enantiomeric excesses, it was used an Agilent Instrument Series 1100. The specific operative conditions for each product are reported from time to time. Commercially available $HSiCl_3$ was freshly distilled before use.

The fluidic device was realized by assembling coil-reactors, connected, by T-junctions using standard HPLC connectors. Coil-reactors consisted in PTFE tubing (internal diameter: 0,58 mm) coiled in a bundle. Syringe pump: Chemix Fusion 100, equipped with two Hamilton gastight syringes, of different volumes. Chemtrix Labtrix® Start Standard platform was equipped with a 10 µL chip (nr 3223, 0.3x0.12 mm oval channel), connected with the desired syringes.

Catalyst synthesis[23]



Compound **IV**

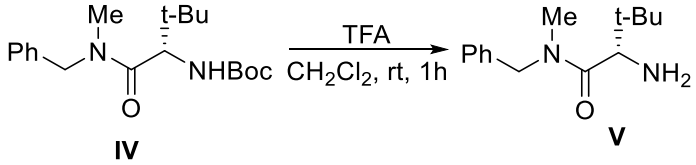


IV

A round bottomed flask was charged with *N*-Boc-t-leucine (1g, 4.32 mmol), HOBT (1.5g, 4.32 mmol), and 35 ml of anhydrous chloroform under nitrogen atmosphere. After 5 min of stirring, EDC (2.49g, 12.97 mmol) and *N*-methylbenzylamine were added, and the reaction mixture was stirred at room temperature for 18h. Next, 1M HCl was added and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with saturated aqueous $NaHCO_3$, water, and then dried over Na_2SO_4. Solvent removal *in vacuo* afforded analytically pure amide (4.19 mmol, 97% yield) as a thick oil that was used without further purification.

^{1}H-NMR (300 MHz, $CDCl_3$; compound exists as a 4:1 mixture of rotamers, only the major is indicated): δ 7.33-7.26 (m, 5H); 5.40 (br d, 1H); 4.70 (d, 1H, *J* = 3.3 Hz); 4.55 (d, 1H, *J* = 3.3 Hz); 3.08 (s, 3H); 1.45 (s, 9H); 1.01 (s, 9H) ppm.

Compound **V**

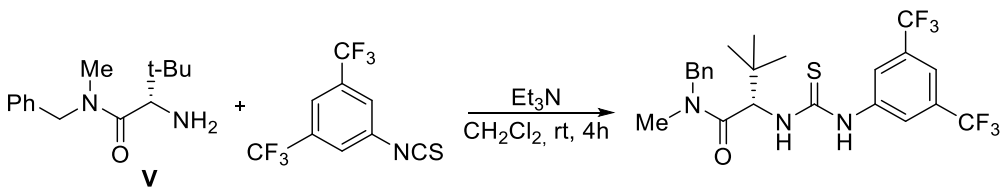


IV **V**

To a solution of **IV** (1.4g, 4.2 mmol) in CH_2Cl_2 (20 ml) was added TFA (42 mmol, 3.2 ml). The mixture was stirred for 1h at room temperature, then quenched with saturated Na_2CO_3 solution and extracted with CH_2Cl_2. The organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*, to afford **V** as a white solid, used in the next step without further purification.

^{1}H-NMR (300 MHz, $CDCl_3$; compound exists as a 5:1 mixture of rotamers, only the major is indicated): δ 7.33-7.26 (m, 5H); 5.40 (br d, 1H); 4.70 (d, 1H, *J* = 3.3 Hz); 4.55 (d, 1H, *J* = 3.3 Hz); 3.08 (s, 3H); 1.01 (s, 9H) ppm.

Catalyst



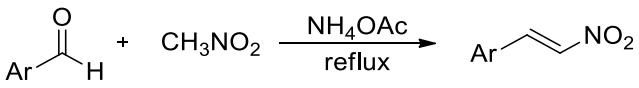
V

To a solution of **V** (0.2 g, 0.65 mmol) in CH_2Cl_2 (8.5 ml) under nitrogen atmosphere was added TEA (0.3 ml, 2.13 mmol), followed by 3,5-bis-(trifluoromethyl)phenyl-isothiocyanate (0.13 ml, 0.71 mmol). The reaction was stirred overnight at room temperature and then concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (ETP/AcOEt 7:3) to give catalyst B (0.25 g, 66% yield) as a white solid.

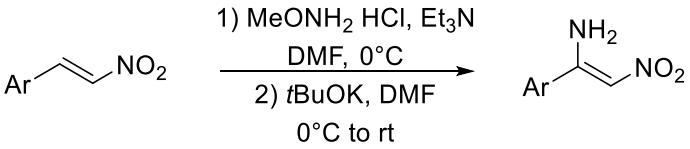
^{1}H-NMR (300 MHz, $CDCl_3$; compound exists as a 4:1 mixture of rotamers, only the major is indicated): δ 9.8 (br s, 1H); 8.12 (s, 3H); 7.58 (s, 1H); 7.24-7.14 (m, 5H); 5.55 (d, 1H, *J* = 3.3 Hz); 4.78 (d, 1H, *J* = 14.4 Hz); 4.44 (d, 1H, *J* = 14.4 Hz); 3.31 (s, 3H); 1.14 (s, 9H) ppm.

General procedure for the synthesis of β-amino nitroolefins **14a-e**

β-Aryl substituted nitroolefins were prepared according to literature procedure.[24]

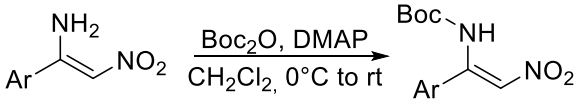


A stirred solution of the proper aldehyde (8 mmol) and ammonium acetate (2 mmol, 150 mg) in nitromethane (40 mL) was heated at reflux overnight. The obtained solution was poured into water and extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, evaporated under reduced pressure. The residue was purified by recrystallization from ethanol. The obtained spectroscopic data were in agreement with those previously published.

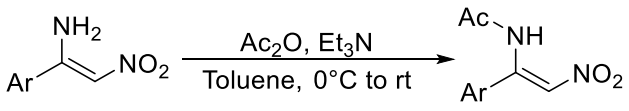


Triethylamine (0.7 mL, 5.0 mmol) was added to a solution of methoxyamine-HCl (0.42 g, 5.0 mmol) in dimethylformamide (DMF, 8 mL) at 0 °C. The proper substituted *β*-nitrostyrene (5.0 mmol) was then added and the resulting suspension was stirred at 0°C for 15 min and at room temperature for 5 min. The 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 room temperature. The reaction was quenched with saturated aq. NH_4Cl (30 mL). The volatiles were removed *in vacuo* and the residue was dissolved in CH_2Cl_2. The obtained organic phase was washed with water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was used without further purification in the next step.

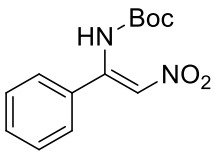
The obtained spectroscopic data were in accordance with those previously published.[16]



General procedure **A:** a stirred solution of *β*-amino nitroolefin in CH_2Cl_2 (0.6 M) was cooled at 0 °C and di-*tert*-butyl-dicarbonate (1.2 equiv) followed by 4-dimethylamino pyridine (DMAP, 0.05 equiv) were added. The cooling bath was then removed, and the solution was stirred at room temperature for 1 hour. The reaction was then quenched with water and extracted with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, filtered, concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (CH_2Cl_2/petroleum ether 3:1) to afford the desired *β-tert*-butyloxycarbonylamino nitroolefin. The obtained spectroscopic data were in accord with those previously published.[15]

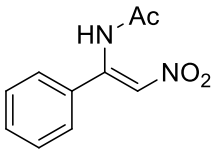


General procedure **B:** a stirred 0.3M solution of *β*-amino nitrolefin in toluene was cooled to 0 °C and triethylamine (4.0 equiv) followed by Ac_2O (3.0 equiv) were added. The cooling bath was then removed, and the solution was stirred at 45°C overnight. The mixture was then concentrated under vacuum and the residue was purified by flash column chromatography on silica gel (CH_2Cl_2/ethyl acetate 9:1) to afford the desired *β*-acylamino nitroolefin. The obtained spectroscopic data were in accord with those previously published.[11]



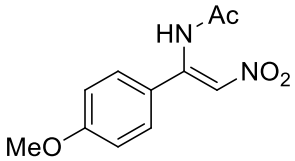
14a: prepared according to general procedure **A**. Yield over two steps: 60%; pale yellow solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H 10.31 (s, 1H), 7.54-7.44 (m, 5H), 6.66 (s, 1H), 1.41 (s, 9H).



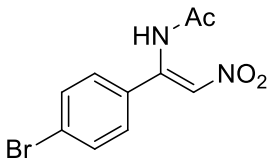
14b: prepared according to general procedure **B**. Yield over two steps: 50%; pale yellow solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H 10.82 (s, 1H), 7.54-7.38 (m, 5H), 6.72 (s, 1H), 2.27 (s, 3H).



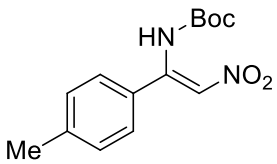
14c*:* prepared according to general procedure **B**. Yield over two steps: 35%; white solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H 10.80 (s, 1H), 7.38-7.36 (m, 2H), 6.96-6.93 (m, 2H), 6.74 (s, 1H), 3.86 (s, 3H), 2.24 (s, 3H).



14d: prepared according to general procedure **B**. Yield over two steps: 30%; pale brown solid.

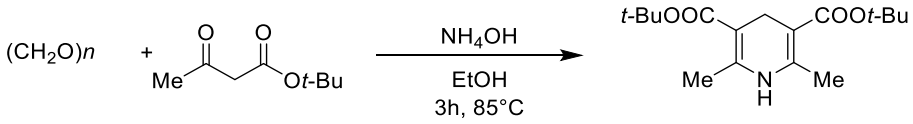
^{1}H-NMR (300 MHz, $CDCl_3$): δ_H 10.81 (s, 1H), 7.60-7.57 (m, 2H), 7.28-7.26 (m, 2H), 6.68 (s, 1H), 2.28 (s, 3H).



14e: prepared according to general procedure **B**. Yield over two steps: 50%; pale yellow solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H 10.30 (s, 1H), 7.33-7.31 (m, 2H), 7.28-7.24 (m, 2H), 6.66 (s, 1H), 2.43 (s, 3H), 1.43 (s, 9H).

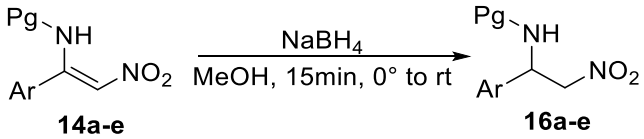
Synthesis of Hantzsch ester **15**



A solution of paraformaldehyde (0.75 g), *tert*-butyl acetoacetate (8.25 ml), aqueous NH_4OH (15 ml, 5M) in EtOH was heated at 85°C for 4h. The mixture was then cooled to room temperature, poured into ice-water, and extracted with Et_2O. The organic phase was washed with 10% aqueous solution of NaOH, water, 5% HCl aqueous solution and water, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude yellow solid was crystallized with dry methanol under nitrogen atmosphere. The title compound was obtained as a yellow solid in 80% yield as a mixture of 95:5 of dihydropyridine and the corresponding pyridine derivative, due to oxidation. The obtained spectroscopic data were in accord with those previously published.[25]

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H 5.16 (br s, 1H), 3.19 (s, 2H), 2.16 (s, 6H), 1.48 (s, 18H).

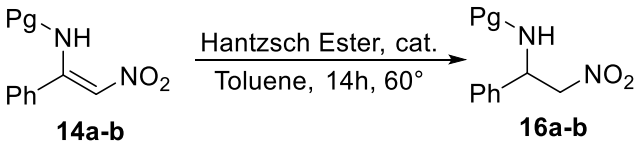
General procedure for the synthesis of racemic β-amino nitroalkanes



Prepared following literature procedure.[15]

A stirred solution of the proper β-nitroenamine (0.5 mmol) in MeOH (2.5 mL) was cooled to 0°C, and $NaBH_4$ (1 mmol, 40 mg) was added in one portion. The reaction was allowed to reach room temperature and stirred for 15 minutes. Then it was quenched with saturated NH_4Cl, and extracted with CH_2Cl_2, dried over Na_2SO_4 and concentrated under vacuum. The desired products were obtained pure without further purification.

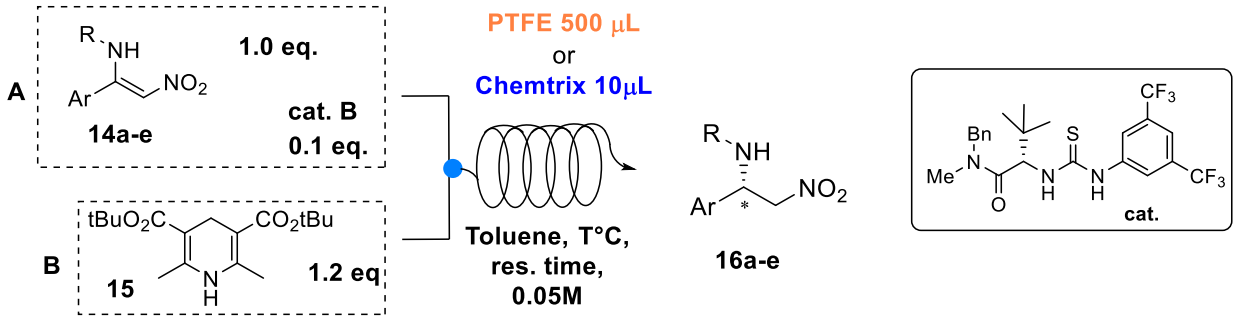
General procedure for the β-nitroenamines reduction with Hantzsch ester in batch



In a screw cap vial, the nitroenamine (0.15 mmol) was dissolved in toluene (0.3 M or 0.05M). The catalyst (5 or 10 mmol%) and Hantzsch Ester (1.2 equivalents) were added, the vial was saturated with nitrogen atmosphere, heated to 60°C and stirred for the desired time.

The crude mixture was then concentrated in vacuum, and the conversion of the starting material was evaluated by ^{1}H-NMR or by isolation via column chromatography.

General procedure for the β-nitroenamines reduction with Hantzsch ester under *continuous flow*



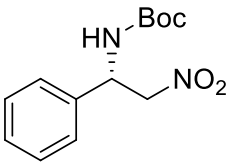
The reactor (500 µL coil-reactor or 10 µL microreactor) heated at the desired temperature was fed with two 2.5 ml Hamilton gastight syringes, at the selected flow rate.

In the case of reactions run in dichloromethane, the coil reactor was equipped with a back-pressure regulator (100 psi) in order to be able to heat at 60°:

Syringe A was filled with a 0.1 M solution of β-nitroenamine (0.25 mmol, 1 mol eq.) and catalyst (0.025 mmol, 0.1 mol eq.) in dry toluene (2.5 ml).

Syringe B was filled with a solution of Hantzsch ester (0.3 mmol, 1.2 mol eq.) dissolved in dry toluene. The reaction mixture was collected into vials cooled to -10°C. The solvent was then removed in high vacuum at low temperature, and the crude mixture subjected to ^{1}H NMR.

After the first two volumes were discharged, the steady-state conditions were reached; the reported yield values are given as average of five different samples collected at different times.

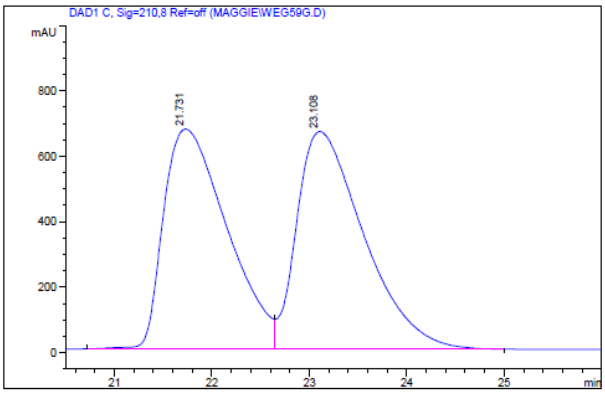


16a: Prepared according to the general procedure. The crude mixture was purified by column chromatography on silica gel eluting with CH_2Cl_2/hexane 6:1 to afford the title product as a white solid. All analytical data are in agreement with literature. [15]

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H 7.39-7.32 (m, 5H), 5.40 (m, 2H), 4.84 (m, 1H), 4.71 (dd, 1H), 1.47 (s, 9H) ppm.

The enantiomeric excess was determined by HPLC on chiral stationary phase with Daicel Chiralcel OJ-H column: eluent Hexane/*i*PrOH = 9/1, flow rate 0.75 mL/min, λ=210 nm, τ_{minor} = 21 min, τ_{major} = 23 min.

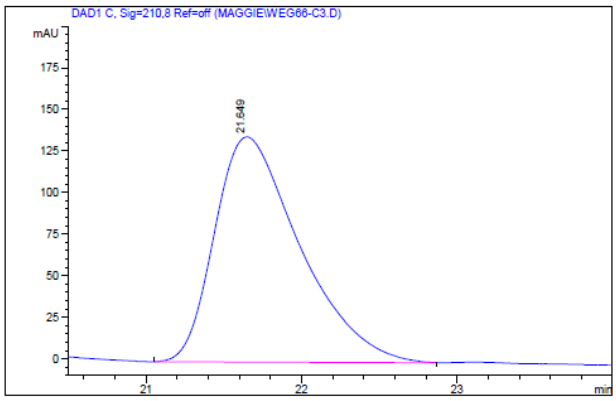
CHIRALPAK OJ-H Hex/IPrOH 9/1 0.75 mL/min 31 Bar



Signal 1: DAD1 C, Sig=210,8 Ref=off

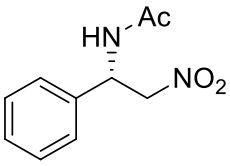
Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	21.731	BV	0.705	30526.586	48.903	
2	23.108	VB	0.727	31896.217	51.097	

OJ-H Hex/iPrOH 9/1 0.75 mL/min 30 Bar



Signal 1: DAD1 C, Sig=210,8 Ref=off

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	21.649	BB	0.576	5152.747	100.000	

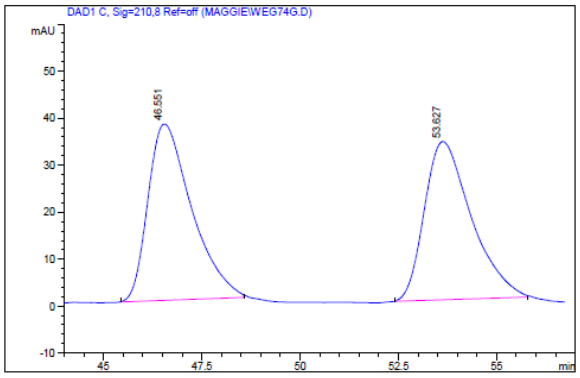


16b: prepared according to the general procedure. The crude mixture was purified by column chromatography on silica gel eluting with hexane/ethyl acetate 1:4 afford the title product as a white solid. All analytical data are in agreement with literature. [15]

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H 7.42-7.32 (m, 5H), 6.25 (br s, 1H), 5.70 (q, 1H), 4.95 (dd, 1H), 4.77 (dd, 1H), 2.09 (s, 1H) ppm.

The enantiomeric excess was determined by HPLC on chiral stationary phase with Daicel Chiralcel OJ-H column: eluent Hexane/*i*PrOH = 9/1, flow rate 0.75 mL/min, λ=210 nm, τ_{minor} = 52.8 min, τ_{major} = 45.7 min.

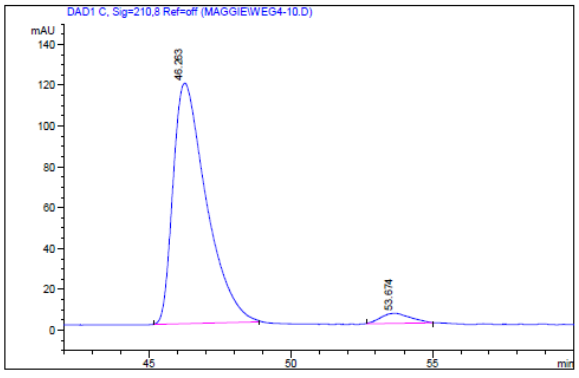
OJ-H Hex/iPrOH 9:1 0.75 ml/min, 31 bar



Signal 1: DAD1 C, Sig=210,8 Ref=off

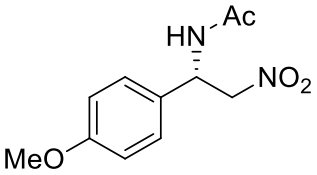
Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	46.551	BB	1.086	2888.841	50.829	
2	53.627	BB	1.150	2794.655	49.171	

OJ-H Hex/iPrOH 9:1 0.75 ml/min, 30 bar



Signal 1: DAD1 C, Sig=210,8 Ref=off

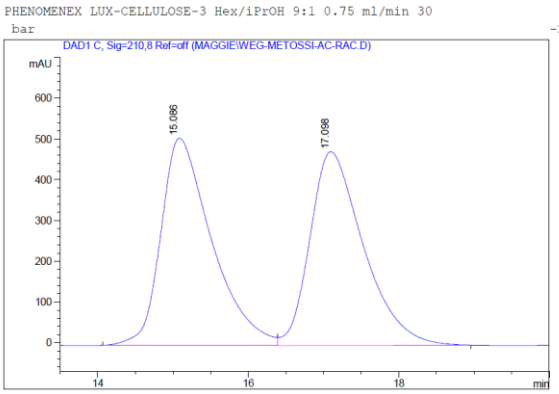
Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	46.263	BB	1.198	9595.075	96.340	
2	53.674	BB	0.872	364.501	3.660	



16c: Prepared according to the general procedure. The crude mixture was purified by column chromatography on silica gel eluting with hexane/ethyl acetate 1:4 to afford the title product as a white solid. All analytical data are in agreement with literature. [15]

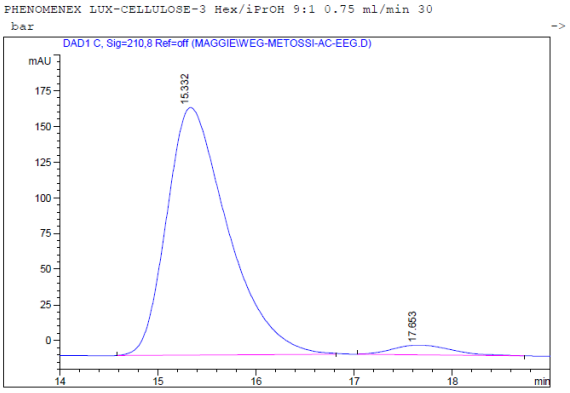
^{1}H-NMR (300 MHz, $CDCl_3$) δ_H 7.25 (d, 2H), 6.93 (d, 2H), 6.12 (d, 1H), 5.62 (m, 1H), 4.93 (dd, 1H), 4.72 (dd, 1H), 3.82 (s, 3H), 2.07 (s, 3H) ppm.

The enantiomeric excess was determined by HPLC on chiral stationary phase with Phenomenex Lux-Cellulose-3 column: eluent Hexane/*i*PrOH = 9/1, flow rate 0.75 mL/min, λ=210 nm, τ_{minor} = 18 min, τ_{major} = 15 min.



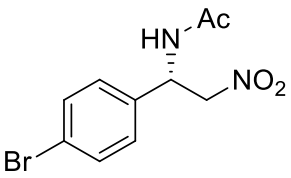
Signal 1: DAD1 C, Sig=210,8 Ref=off

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	15.086	BV	0.693	23918.957	50.472	
2	17.098	VB	0.740	23472.037	49.528	



Signal 1: DAD1 C, Sig=210,8 Ref=off

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	15.332	BB	0.647	7503.368	96.339	
2	17.653	BB	0.583	285.160	3.661	

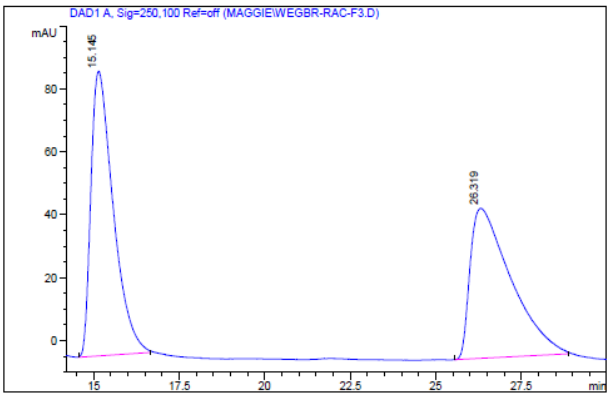


16d: prepared according to the general procedure. The crude mixture was purified by column chromatography on silica gel eluting with hexane/ethyl acetate 1:4 to afford the title product as a white solid. All analytical data are in agreement with literature.[11]

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H 7.52-7.51 (d, 2H), 7.22-7.19 (d, 2H), 6.63 (d, 1H), 5.65 (m, 1H), 4.89 (dd, 1H), 4.72 (dd, 1H), 2.06 (s, 3H) ppm.

The enantiomeric excess was determined by HPLC on chiral stationary phase with Daicel Chiralcel AD column: eluent Hexane/*i*PrOH = 9/1, flow rate 1 mL/min, λ=250 nm, τ_{minor} = 26 min, τ_{major} = 15 min.

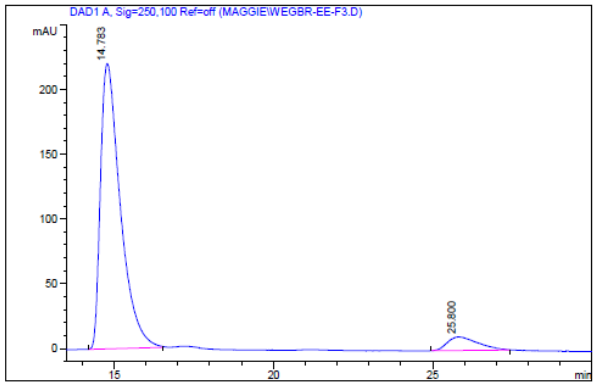
AD Hex/iPrOH 9:1 1.0 ml/min 22 bar



Signal 1: DAD1 A, Sig=250,100 Ref=off

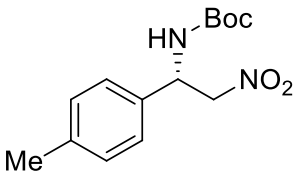
Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	15.145	BB	0.656	4105.392	50.891	
2	26.319	BB	1.082	3961.689	49.109	

AD Hex/iPrOH 9:1 1.0 ml/min 22 bar



Signal 1: DAD1 A, Sig=250,100 Ref=off

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	14.783	BB	0.628	9490.753	93.065	
2	25.800	BB	0.798	707.260	6.935	

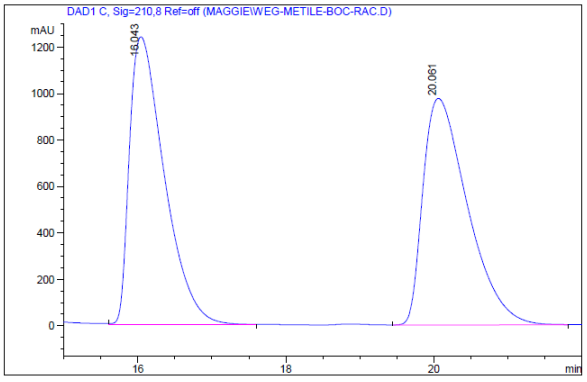


16e: prepared according to the general procedure. The crude mixture was purified by column chromatography on silica gel eluting with CH_2Cl_2/hexane 6:1 to afford the title product as a white solid. All analytical data are in agreement with literature.[15]

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H 7.20 (m, 4H), 5.32 (m, 1H), 5.21 (br s, 1H), 4.84 (m, 1H), 4.69 (dd, 1H), 2.36 (s, 3H), 1.45 (s, 9H) ppm.

The enantiomeric excess was determined by HPLC on chiral stationary phase with Daicel Chiralcel OJ-H column: eluent Hexane/*i*PrOH = 9/1, flow rate 0.75 mL/min, λ=210 nm, τ_{minor} = 20 min, τ_{major} = 15 min.

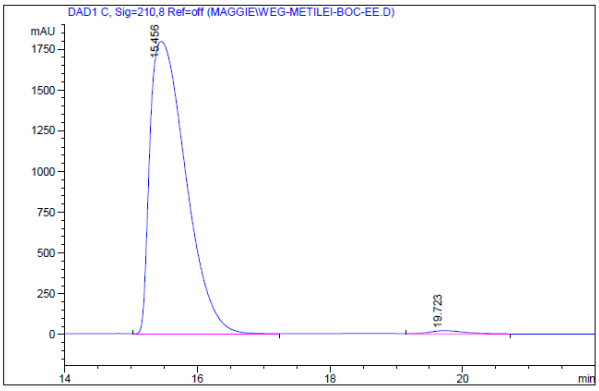
OJ-H Hex/iPrOH 9:1 0.75 ml/min 30 bar



Signal 1: DAD1 C, Sig=210,8 Ref=off

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	16.043	VB	0.502	40526.090	49.851	
2	20.061	VB	0.646	40768.234	50.149	

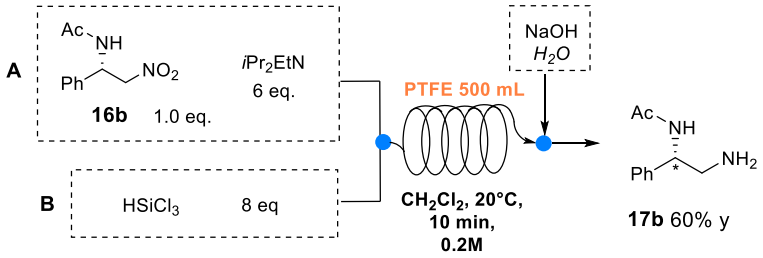
OJ-H Hex/iPrOH 9:1 0.75 ml/min 30 bar



Signal 1: DAD1 C, Sig=210,8 Ref=off

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	15.456	VB	0.593	67276.258	98.904	
2	19.723	BB	0.587	745.670	1.096	

General procedure for trichlorosilane-mediated nitro reduction



Syringe A was loaded with a solution of nitro compound **16b** (0.6 mmol) and diisopropilethylamine (3.6 mmol) in dry CH_2Cl_2 (2.5 mL).

Syringe B was filled with a solution of $HSiCl_3$ (2.4 mmol) in dry CH_2Cl_2 (2.5 mL).

Syringes A and B were connected to a syringe pump and the reagents were pumped into the mesoreactor at 0.05 mL/min at 20°C. The outcome of the reactor was collected into vials containing 4M NaOH solution at 0°C. Five reactor volumes were collected, dried with Na_2SO_4 and concentrated *in vacuo*. The product was obtained pure as a yellow solid and characterized without further purification.

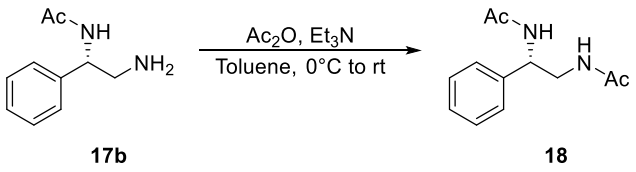
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.52-7.29 (m, 5H), 6.44 (br s, 1H), 5.04 (q, 1H), 3.10 (ddd, 2H), 2.07 (s, 3H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 169.2, 143.1, 128.7 (2C), 127.5, 126.5 (2C), 54.6, 46.6, 126.3, 29.6 ppm.

$[\alpha]_D^{25}$ +24 (c 0.006, $CHCl_3$)

HRMS (ESI) m/z calculated for $C_{10}H_{15}O_1N_2$ (+1): 179.1179; found 179.1179.

Synthesis of **18**



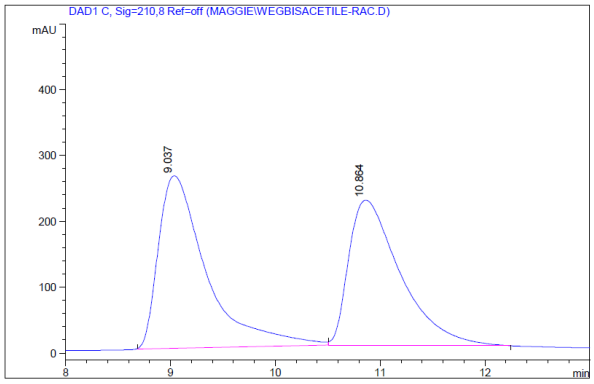
In order to evaluate the enantiomeric excess of the final product, it was necessary to derivatize it into the bis-acetyl derivative.

A stirred 0.3M solution of **17b** in toluene was cooled to 0 °C; subsequently triethylamine (4.0 equiv) followed by Ac_2O (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 flash column chromatography on silica gel (CH_2Cl_2/MeOH 9:1) to afford the desired product in 75% yield as a yellow solid. All analytical data are in agreement with literature.[26]

^{1}H-NMR (300 MHz, MeOD) δ_H 7.36-7.20 (m, 5H), 5.07 (m, 1H), 3.49 (m, 2H), 2.00 (s, 3H), 1.92 (s, 3H) ppm.

The enantiomeric excess was determined by HPLC on chiral stationary phase with Daicel Chiralcel OJ-H column: eluent Hexane/*i*PrOH = 9/1, flow rate 0.8 mL/min, λ=210 nm, τ_{minor} = 9 min, τ_{major} = 10.4 min. In all the cases the enantiomeric excess was maintained during the reduction of the nitro group.

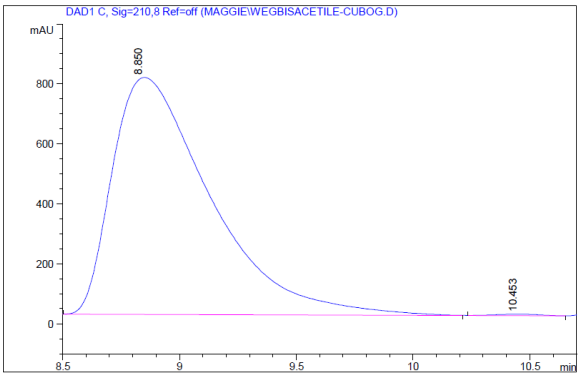
OJ-H Hex/iPrOH 9:1 0.8 ml/min 20bar



Signal 1: DAD1 C, Sig=210,8 Ref=off

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	9.037	MM	0.533	8386.409	52.746	
2	10.864	MM	0.568	7513.169	47.254	

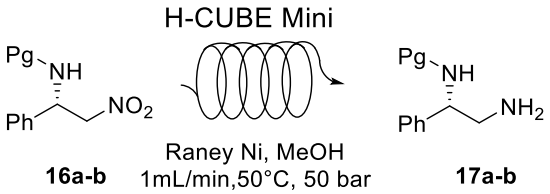
OJ-H Hex/iPrOH 9:1 0.8 ml/min 20bar



Signal 1: DAD1 C, Sig=210,8 Ref=off

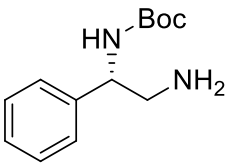
Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	8.850	MM	0.487	23095.398	99.723	
2	10.453	MM	0.215	64.096	0.277	

<u>General procedure for metal catalysed nitro-reduction</u>



16a-b **17a-b**

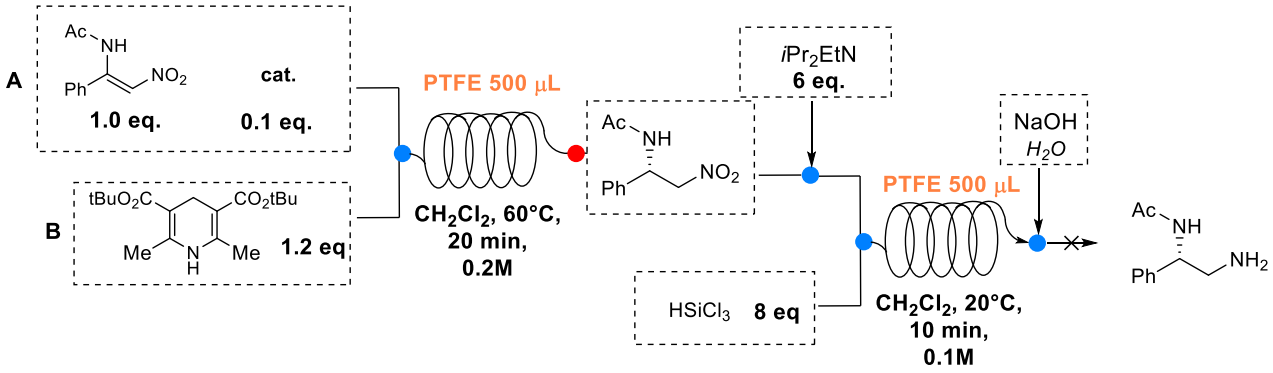
A 0.02M solution of the nitro compound **16a-b** (0.4 mmol) dissolved in methanol (18 mL) was charged into a vial connected with the pump of the H-CUBE Mini, equipped with a 30 mm cartridge of Raney Nichel. The instrument was previously stabilized at 50°C and 50 bar and at 1 mL/min as flow rate. The reaction was run in a close loop for 5 hours. After that time, the solvent was removed *in vacuo*, and the crude mixture dissolved in AcOEt and washed with 5% NaOH.



6a: yellowish liquid, 75% yield. The product was purified by column chromatography (eluent: ethyl acetate/hexane 8:2 +1% Et_3N). All analytical data are in agreement with literature.[27]

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H 7.36-7.24 (m, 5H), 5.43 (br s, 1H), 4.66 (br s, 1H), 3.00 (d, 2H), 1.42 (s, 9H) ppm.

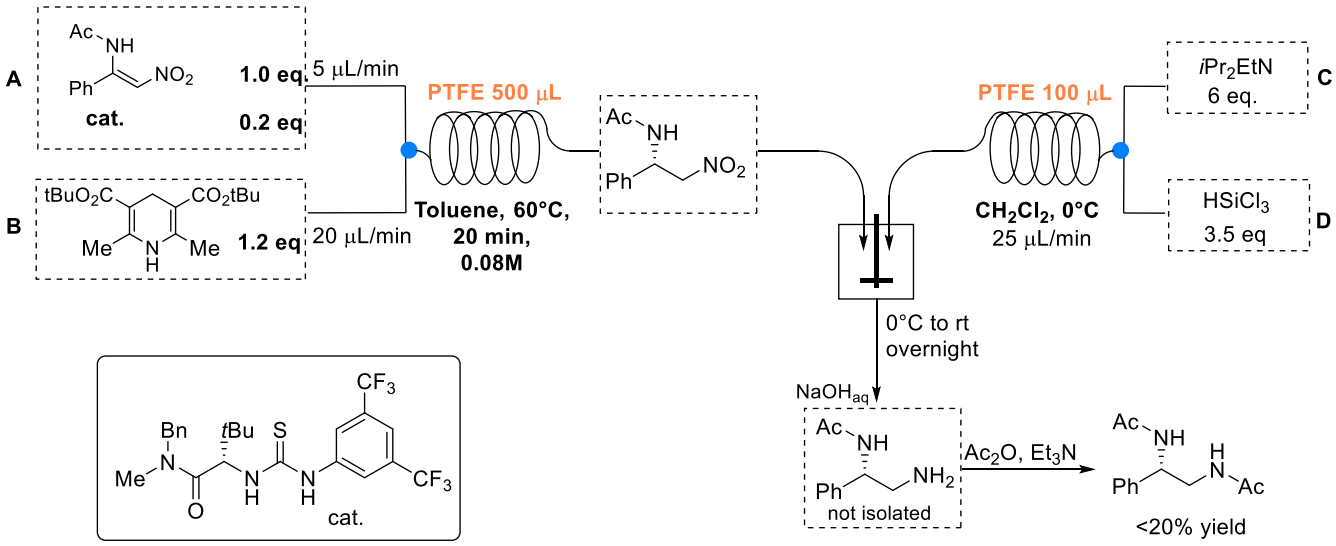
Preliminary studies: two-steps all in flow continuous synthesis of chiral 1,2-diamines



The first reactor (500 µL PTFE coil-reactor) at 60°C was fed with two 2.5 ml Hamilton gastight syringes, at 0.0125 mL/min. Syringe **A** was filled with a 0.4 M solution of nitroenamine (1 mmol) and the catalyst (0.1 mmol) in dry CH_2Cl_2. Syringe **B** was filled with a solution of Hantzsch ester (1.2 mmol) in dry CH_2Cl_2. The reactor was equipped with a backpressure regulator (100 psi). The outcome of the reactor was directly connected with a T-junction, cooled to 0°C, where it was mixed with diisopropylethylamine (6 mmol) at 0.005 mL/min as flow rate. The outcome was directly mixed with a solution of $HSiCl_3$ (8 mmol) in dry CH_2Cl_2 (2M solution) in a T-junction connected to the second reactor (500 µL PTFE coil-reactor), maintained at 20°C.

The reaction mixture was collected into vial cooled to 0°C, containing 4M NaOH aqueous solution. Five reactor volumes were collected, dried with Na_2SO_4 and concentrated *in vacuo*.

Two-steps synthesis of chiral 1,2-diamines



Syringe **A** was filled with 1 mL of a 0.33M solution of the nitroenamine and the catalyst (0.2 equivalents); syringe **B** was filled with 4 mL of a 0.1M solution of Hantzsch ester; syringe **C** was filled with 2.5 mL of a solution of 6 equivalents of diisopropylethylamine base in dichloromethane; syringe **D** was filled with 2.5 mL of a solution of 3.5 equivalents of trichlorosilane in dichloromethane. Syringe **A** and **B** pumped in a 500 µL mesoreactor heated to 60°C, at two different flow rates, in order to have a residence time of 20 minutes (overall rate: 25 µL/min, 5µL/min for syringe **A**, 20µL/min for syringe **B**), and a concentration of 0.08M of the

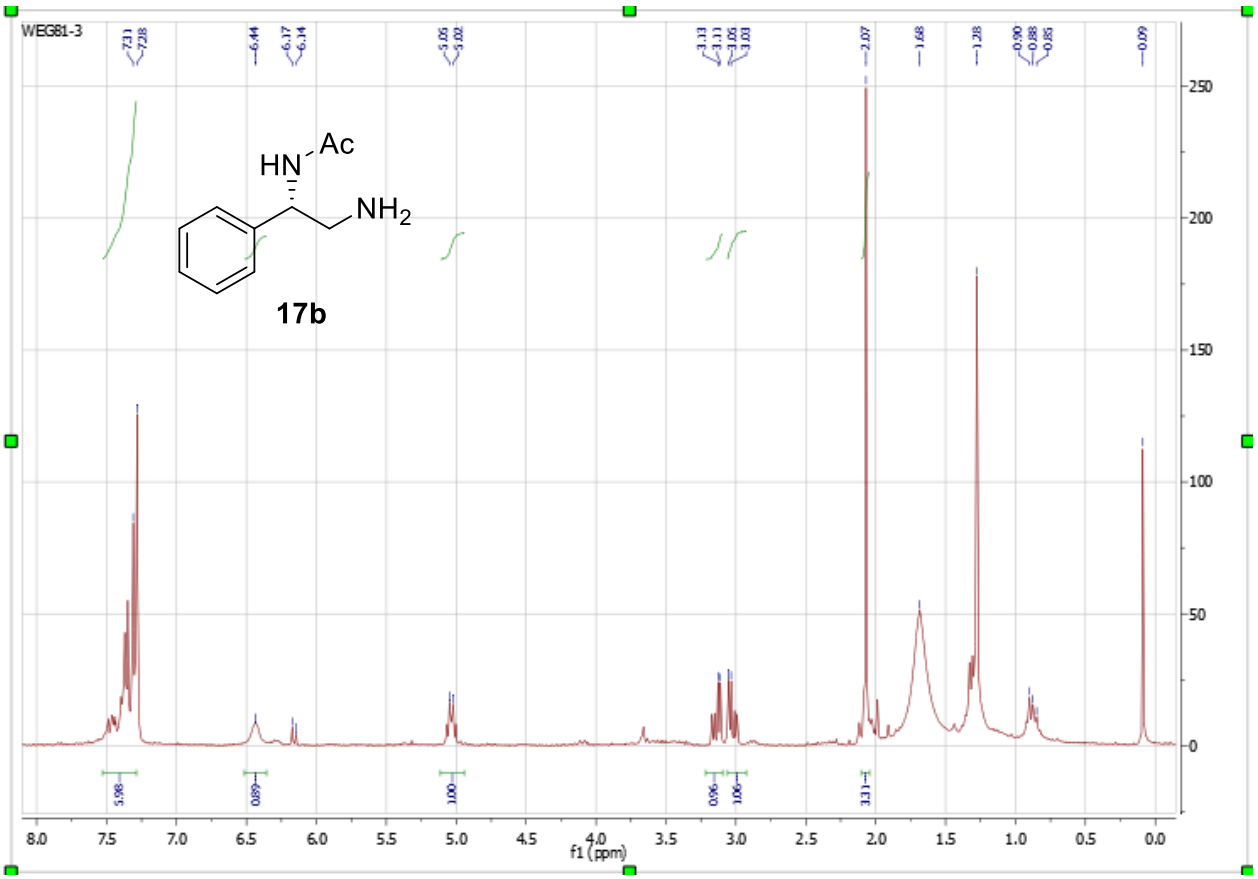
nitroenamine in the reactor. Syringe **C** and **D** pumped at the same flow rate in a 100 µL mesoreactor cooled to 0°C, in order to premix the reducing agent and the Lewis Base.

The outcome of the reactors was collected in the same round bottomed flask under nitrogen atmosphere cooled to 0°C, where the nitro reduction took place, after the first two volumes were discharged. After stirring at room temperature overnight, the reaction was quenched with stoichiometric NaOH 4M solution, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude was directly subjected to derivatization.

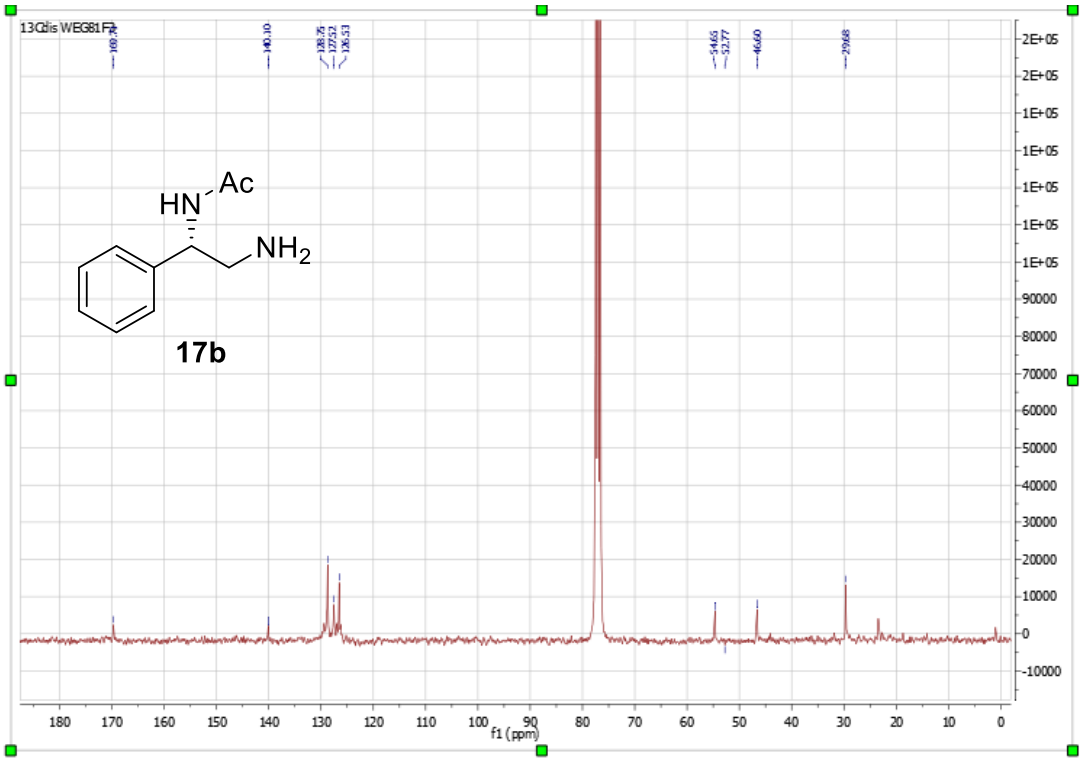
A stirred solution of the crude in 4 mL toluene was cooled to 0 °C, subsequently triethylamine (4.0 equiv) followed by Ac_2O (3.0 equiv) were added. The cooling bath was then removed, and the solution was stirred at 45°C overnight. The mixture was then concentrated under vacuum and the residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH 9:1) to afford the desired product in 20% yield.

Selected NMR Spectra

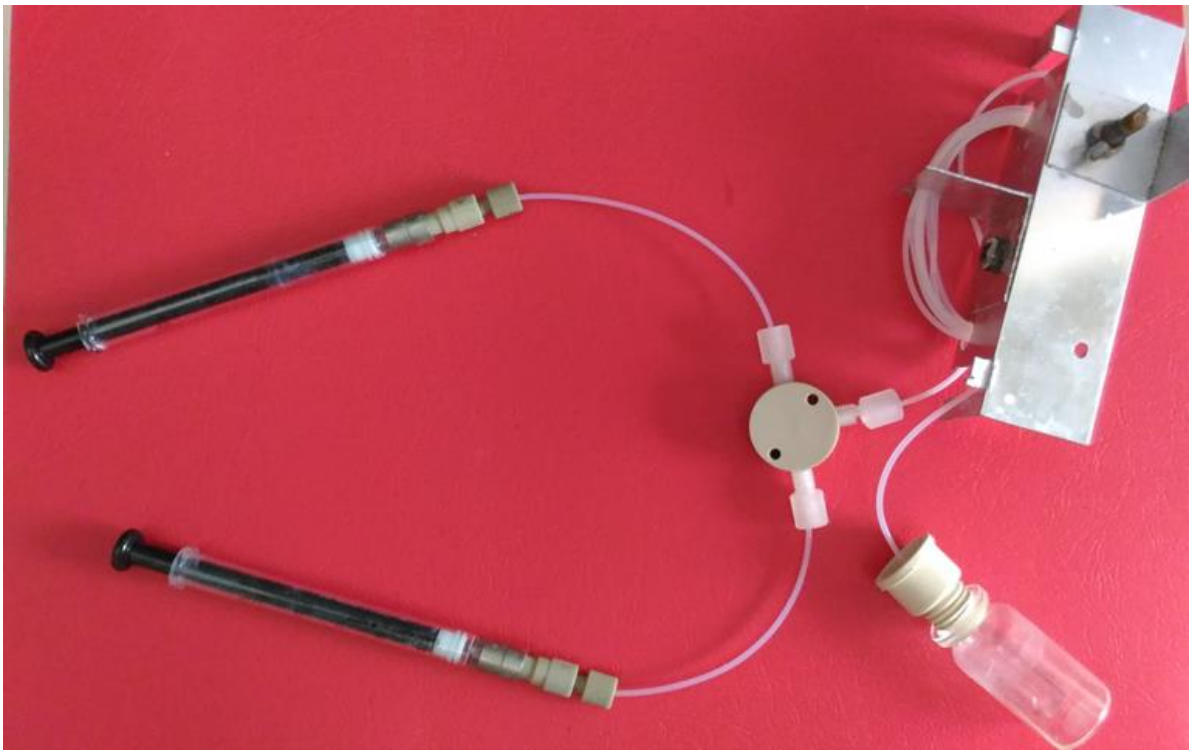
^{1}H-NMR

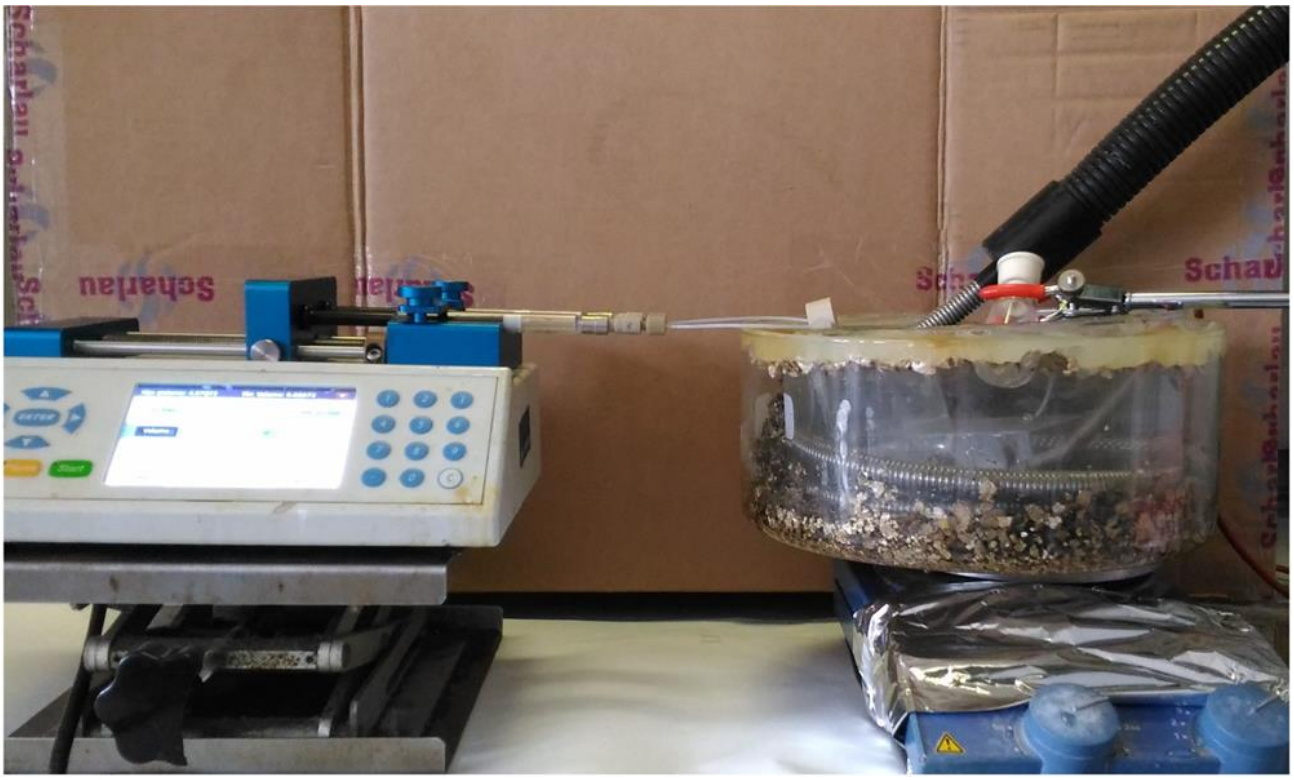


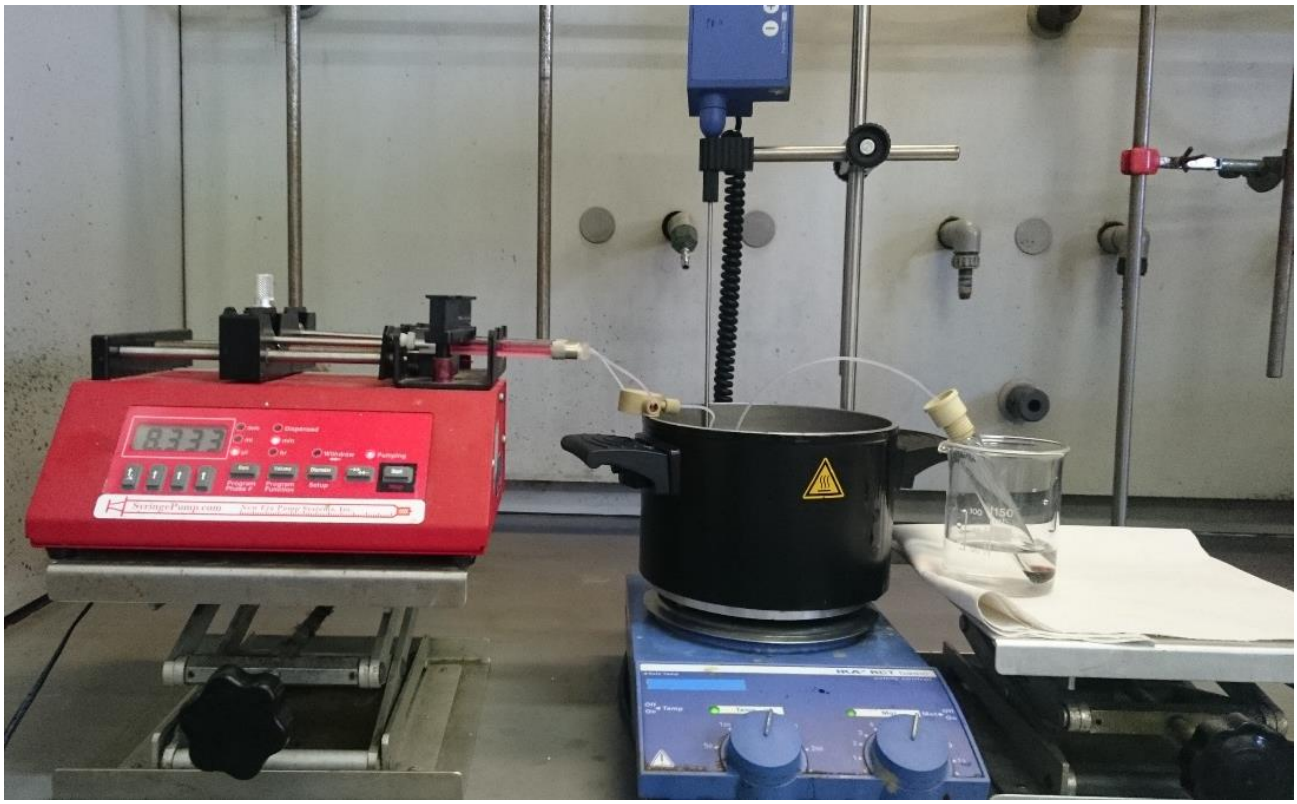
^{13}C-NMR



Pictures of the Continuous flow set-up







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Appendix: the pharmaceutical industry

Companies that are producing APIs for the market, can be mainly divided in different categories:

The innovative pharmaceutical companies: they are the first to develop a new drug, to afford the huge cost linked to trials and approval process, to face the high rate of failures (less than 10% of the drugs reach the market). In this companies, the IP department has a great importance, they could build or use specific facilities/technologies for a targeted product. These companies have the resources and the time to perform complete toxicological screen on the impurity profile of the final product.

The generics drug producers: these companies start to commercialize the finished pharmaceutical product when the patent has expired, hence their main target is to produce a competitive product in terms of price. The target quality of the compound is referenced to the drug already on the market, however since usually these companies have no time and resources for the complete toxicologic screen of the impurity profile on the final drug, they aim to produce a purer product compare to the generator. Typically, they have highly versatile factories since the market for the generic drug is very dynamic.

The generic APIs producers: these companies prepare and commercialize APIs when the intellectual property has expired. They sell the active ingredient on the market to other companies that prepare the formulation and sell the final generic drug.

The customer synthesis provider: these companies are devoted to custom synthesis and to the preparation of key intermediate. The production of intermediates requires complete flexibility on the production in terms of machinery and multi-purpose equipment: speed is the key for these companies.

All these companies have different goals and objective. However, each one must follow the rules and the guidelines of the regulatory agencies in order to obtain the approval for their API (or advanced intermediates) into the market.

The definition of an API according to the World Health Organization is: "Any substance or combination of substances used in a finished pharmaceutical product, intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting, or modifying physiological functions in human beings."[1]

In order to be commercialized the API must be **effective** against the targeted disease and clearly **safe** for the patient. Two actors play a crucial role in the APIs commercialization and registration: the *pharma companies*, and the *regulatory agencies*. There are different regulatory agencies (FDA, AIFA, EMEA, FMDA, swiss medic); in particular, the agencies responsible for the registration of an API are two, the one from the country of production and the one for the country of destination.

In sight of a global compatibility, a harmonized guideline was developed; in order to obtain the registration of pharmaceutical compounds for human use (ICH guidelines - https://www.ich.org/page/ich-guidelines) in the mayor world market (USA, Europe and Japan).

Four main areas are covered by the ICH Guidelines:

Quality: *stability studies*, defining relevant thresholds for *impurities testing* and a more flexible approach to pharmaceutical quality based on *Good Manufacturing Practice (GMP)*.

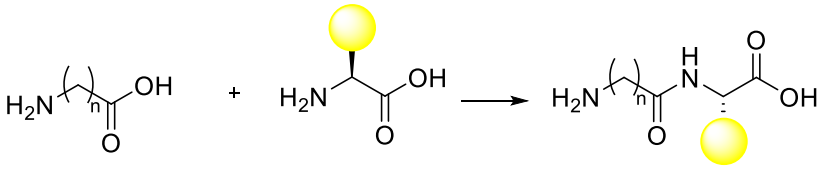
Efficacy: heading is concerned with the *design, conduct, safety and reporting of clinical trials.*

Safety: comprehensive set of *safety Guidelines* to uncover potential risks like *carcinogenicity, genotoxicity and reprotoxicity.*

Multidisciplinary: cross-cutting topics which do not fit uniquely into one of the Quality, Safety, and Efficacy categories.

During my PhD I decided to spend a two months traineeship in a pharmaceutical company, Flamma Innovation, based in Chignolo (BG). Flamma is a generic API producer and a custom synthesis provider. I was included in the generic team of the R&D department, where I worked on the early stages of a project aimed to the scouting of new possible synthetic routes for an already manufactured generic API. The final goal was to obtain a safer and more robust process, along with a reduction of costs. It is important to point out that changing an existent process in not an easy task in an industry, because of regulatory aspects: the whole process development, especially if you change the synthetic route, must be performed once again from the beginning (impurity testing, intermediate stability and so on) and a small difference in the costs is usually not enough to trigger a change.

The final target of the project was a dipeptide, formed by the simple condensation of two readily available aminoacids, one bearing one stereogenic center (Scheme 1).

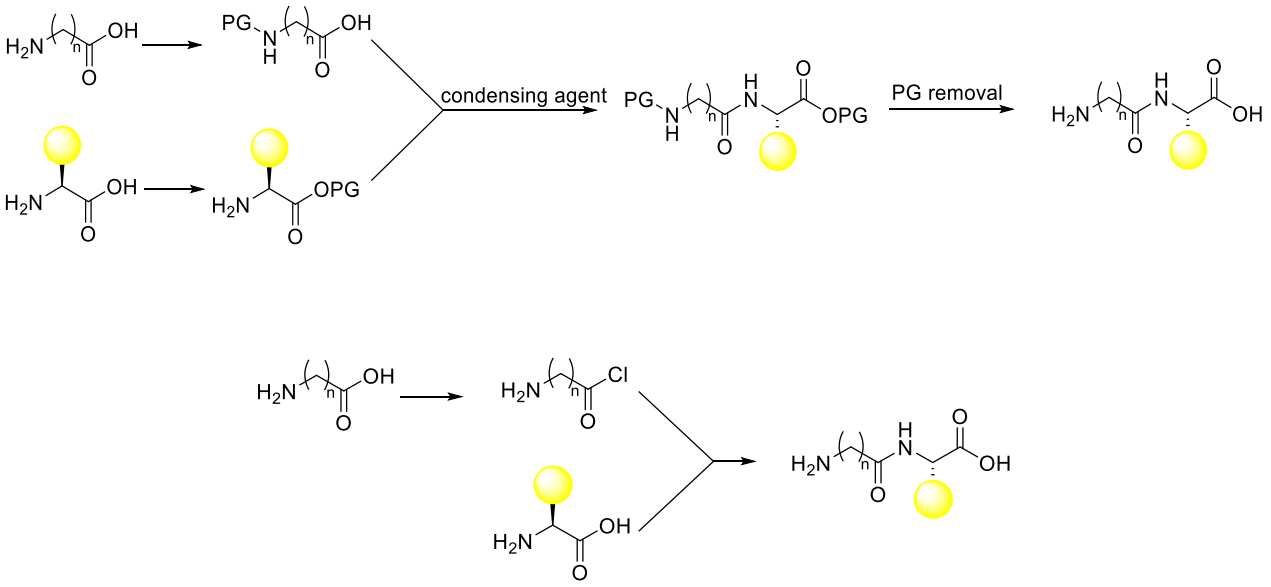


Scheme 1

Due to non-disclosure agreements, I will not be able to enter into experimental details. However, I will be focusing on the general approach either than on the single reactions. The target molecule is indeed quite simple, and in the literature hundreds of different possibilities are reported to achieve this kind of dipeptide, but not all of them are appliable on large scale or fulfill the requirements of industrial scale up.

The amide function is unarguably of primary importance in organic synthesis and is achieved by different synthetic routes. Among them, we can find direct thermal amidation: in principle it is the ideal method, having water as the only byproduct, but being energetically challenging, can happen only under forcing conditions, and that makes it incompatible with complex structure.[2] For this reason, a wide *plethora* of methods has been devised, relying on mediators used either in catalytic or stoichiometric amount.[3][4] The ideal condensing reagent is inexpensive, widely available, nontoxic, safe, simple to handle, easy to purge from reaction mixtures, and contributes only minimally to waste streams; the most used for large scale applications are carbodiimides, acid chloride prepared with thionyl chloride and oxalyl chloride, and CDI, as well as by preparation of mixed anhydrides,[5] and all of them were considered in the early stages of our project at Flamma. The ideal strategy does not exist, the choice of the successful approach being strongly depending on the substrates. Several

issues need to be considered in the evaluation and selection of the methodology: possible racemization when using chiral, not racemic, starting materials, and chemoselectivity for the amidation in the presence of unprotected functional groups, as in our case, still represent a challenge. To avoid undesired side-reactions, in particular self-condensation or the formation of trimers, the use of protecting group is a straightforward approach. It goes without saying that the introduction and subsequent removal of a protecting group adds at least two synthetic steps: ideally, only skeleton-constructing reactions should constitute a synthesis,[6] but reality is that an equilibrium between many factors have to be found (Scheme 2). Increasing the number of steps by introducing protecting groups could not be per se a negative thing, if that leads to higher yields and/or a purer product.



Scheme 2

In pharmaceutical products, impurities are defined as substances that provide no therapeutic benefit but do have the potential to cause adverse effects. Therefore, the impurity profile of a product is a key issue in developing a process: for example, the time required to develop a synthetic process can be significantly increased when it is necessary to carry out multiple attempts to characterize and remove impurities to acceptable levels.

The impurity profile is highly dependent on the route and reaction conditions of the synthesis and several other factors such as the purity of the starting material, method of isolation, purification, conditions of storage etc.

According to ICH guidelines, impurities related to drug substances can be classified into three main categories: organic impurities, inorganic (elemental) impurities, and residual solvents.

Organic impurities may arise from starting materials, byproducts, synthetic intermediates and degradation products. Inorganic impurities may be derived from the manufacturing process and are normally known and identified as reagents, ligands, inorganic salts, heavy metals, catalysts, filter aids and charcoal etc. Residual solvents are the impurities introduced with solvents. Within these categories, genotoxic impurities form a

special case that poses a significant safety risk, even at low concentrations, because they may be mutagenic and are therefore potentially damaging to DNA. As a result, they can lead to mutations or cause cancer.[7]

Due to the short period of time, only preliminary results were achieved on the project for the scouting of a synthetic route toward the desired dipeptide, and no conclusive considerations on the specific synthesis can be drawn. However, from the point of view of someone coming from academia, the most difficult goal to achieve, was for sure related to costs. Reducing the cost of a synthetic process, is no easy task, especially when dealing with small molecules, prepared from functionalized starting materials in few synthetic steps. Dealing with costs means analyzing the whole process, taking in account also experimental factors, solvents, reaction temperature, work up and isolation procedures, all affecting the cost of the final production. Furthermore, as mentioned above, the extent of the costing reduction must be adequate to outweigh the effort required by performing a process development from the beginning.

In conclusion, during the traineeship in Flamma, I was able to start to become aware of the great differences in approach between academia and industry: working in the early stages of the scouting of a new synthetic route for a seemingly straightforward transformation, even if for a short amount of time, made me realize how many different aspects must be taken into account, and how complex a simple condensation can become.

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