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SEDE DI COMO



Facoltà di Scienze Matematiche, Fisiche e Naturali
Dipartimento di Scienze Chimiche e Ambientali

Dottorato in Scienze Chimiche XXIII Ciclo

**Synthesis of Fused-Ring Heterocycles from
Intramolecular Reactions on Alkene Derivatives**

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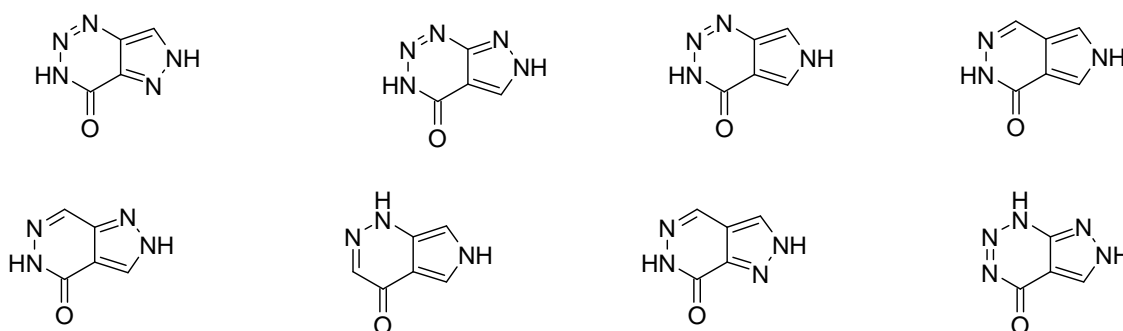
1. Introduction

Heterocyclic chemistry is an inexhaustible resource of novel compounds. Almost unlimited combinations of carbon, hydrogen, and heteroatoms can be designed, making available compounds with the most diverse physical, chemical, and biological properties. Heterocycles provide the main source of new aromatic compounds.

Heterocycles form by far the largest of the classical divisions of organic chemistry and are of immense importance biologically, industrially, and indeed to the functioning of any developed human society. The majority of pharmaceuticals and biologically active agrochemicals are heterocyclic, as are countless additives and modifiers used in industries as varied as cosmetics, reprography, information storage, and plastics.¹

Among approximately 20 million chemical compounds identified by the end of the second millennium, more than two-third are fully or partially aromatic, and approximately half are heteroaromatic. Moreover, despite these numbers, known or unknown heteropolycycle systems can reveal different kind of properties, justifying the interest of the synthetic chemistry for new or differently substituted structures. For example, the paper “Heteroaromatic Rings of the Future” published by some authors of the University of Cambridge on the Journal of Medicinal Chemistry in 2009,² constitutes a stimulus to creative organic chemists. In fact, in this contribution is highlighted a small set of apparently simple, but unconquered, ring systems arising from five- and six-membered rings with one or more heteroatoms, that are predicted to be suitable in the development of novel synthetic protein ligands (Figure 1).

Figure 1

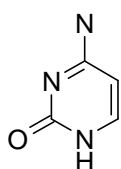


1.1. The importance of heterocyclic chemistry

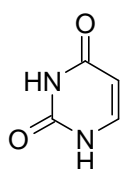
1.1.1. In biochemistry and life processes

Heterocycles play a major part in biochemical processes. DNA and RNA, the essential constituents of living cells, are based on pyrimidine [cytosine (1), uracil (2), and thymine (3)] and purine [adenine (4) and guanine (5)] bases (Figure 2), which are all aromatic heterocycles. Hydrolyses of DNA and RNA produce five nucleosides, 6-10, each being composed of an aromatic heterocyclic base, a phosphate, and a ribose moiety (Figure 3); the latter two form the backbones of the polymer, and in the DNA's double helix the C-G and A-T base pairs form the rungs of the ladder. The aromaticity, hydrogen-bonding properties, and catalytic activity of the pyrimidine and purine bases of RNA may explain why they were formed in prebiotic conditions and gave rise to the "RNA world", which evolved later into life on Earth.³

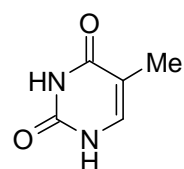
Figure 2



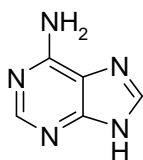
Cytosine 1



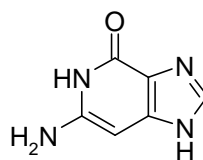
Uracil 2



Thymine 3

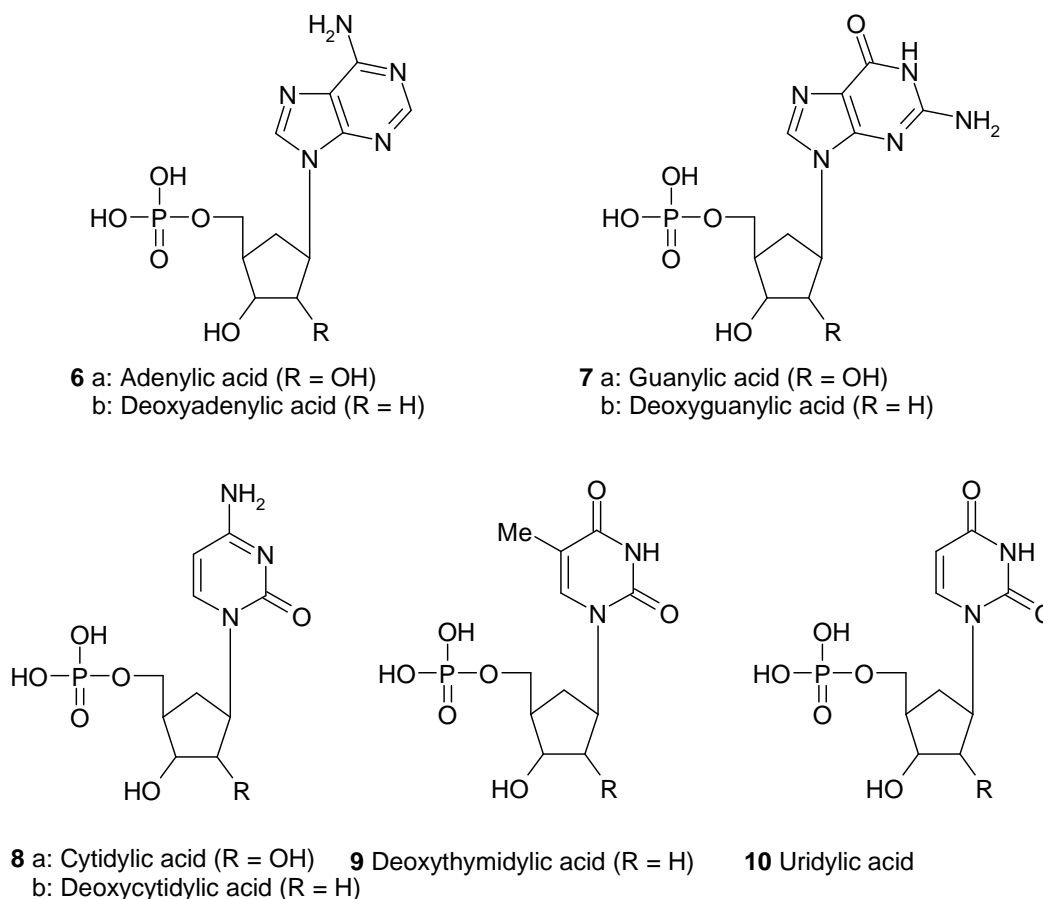


Adenine 4



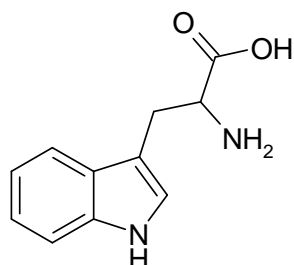
Guanine 5

Figure 3

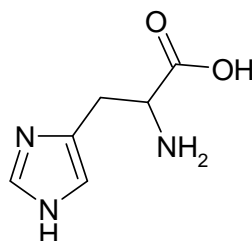


The essential amino acids tryptophan (**11**) and histidine (**12**) are aromatic heterocycles (Figure 4). They participate along with other amino acids in protein constitution through amide linkages. Histamine, formed by decarboxylation of histidine, is a powerful vasodilator, is released in allergic responses, and stimulates acid secretion in the stomach, causing heartburn. Histidine receptor antagonists are among the top pharmaceuticals. Serotonin, formed from tryptophan, is an important neurotransmitter. L-Tyrosine is oxidized biologically to L-dihydroxyphenylalanine (L-DOPA); this affords dopamine by decarboxylation, and its production may be involved in schizophrenia (dopamine excess) or Parkinson's disease (dopamine deficit, treatable by administering L-DOPA). A practically infinite number of proteins can be synthesized from the 20 naturally occurring amino acids with the aid of DNA via translation into RNA messenger and transcription according to the universal genetic code.

Figure 4



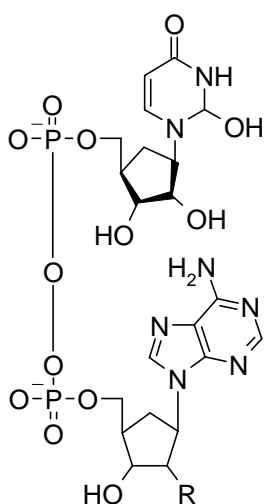
Tryptophan 11



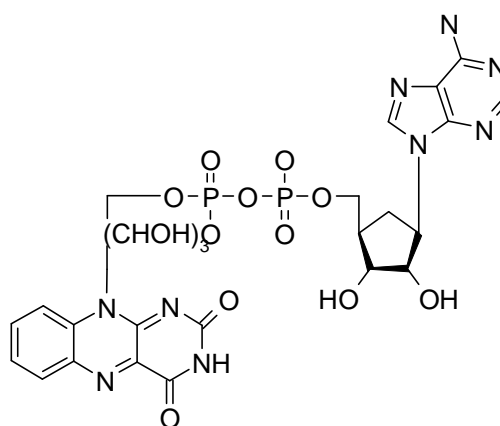
Histidine 12

Most coenzymes have aromatic heterocycles as major constituents. While enzymes possess purely protein structures, coenzymes incorporate non-amino acid moieties, most of them aromatic nitrogen heterocycles. Coenzymes are essential for the redox biochemical transformations, e.g., nicotinamide adenine dinucleotide (NAD, **13**) and flavin adenine dinucleotide (FAD, **14**) (Figure 5). Both are hydrogen transporters through their tautomeric forms that allow hydrogen uptake at the termini of the quinonoid chain.

Figure 5



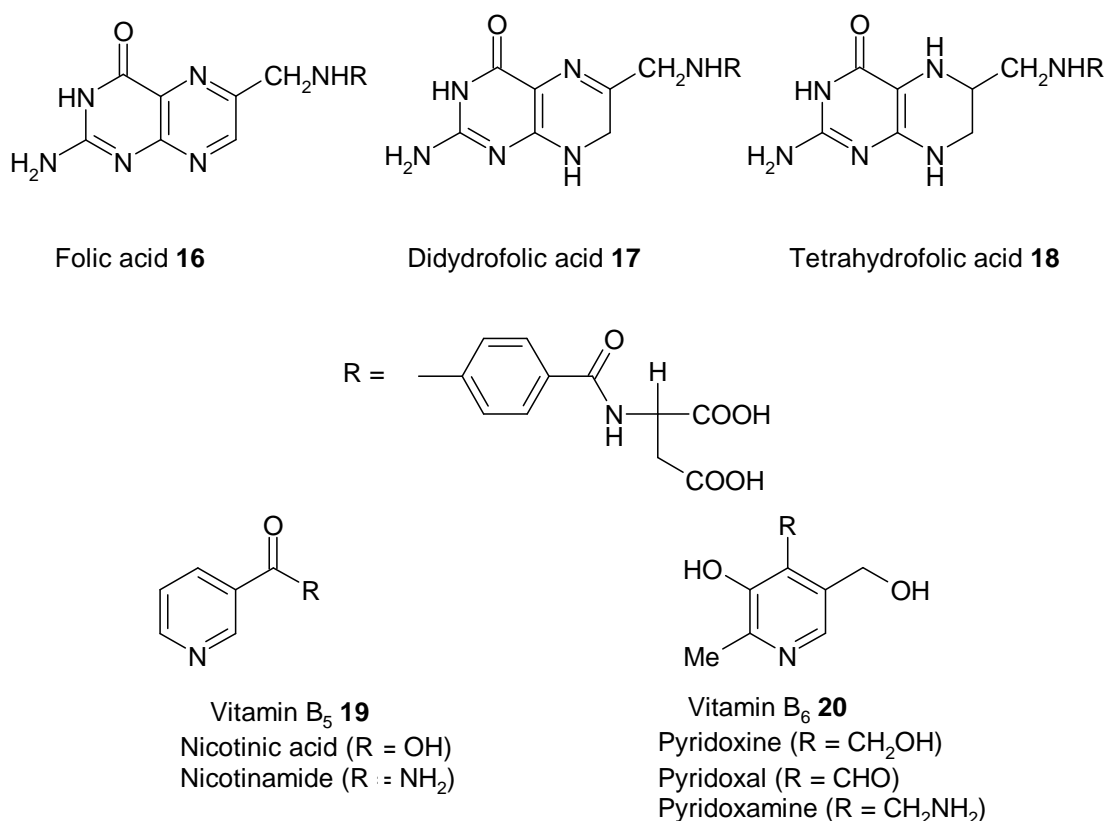
13 NAD (R = OH)
NADPH (R = OPO₃H₂)



14 Flavin adenine dinucleotide (FAD)

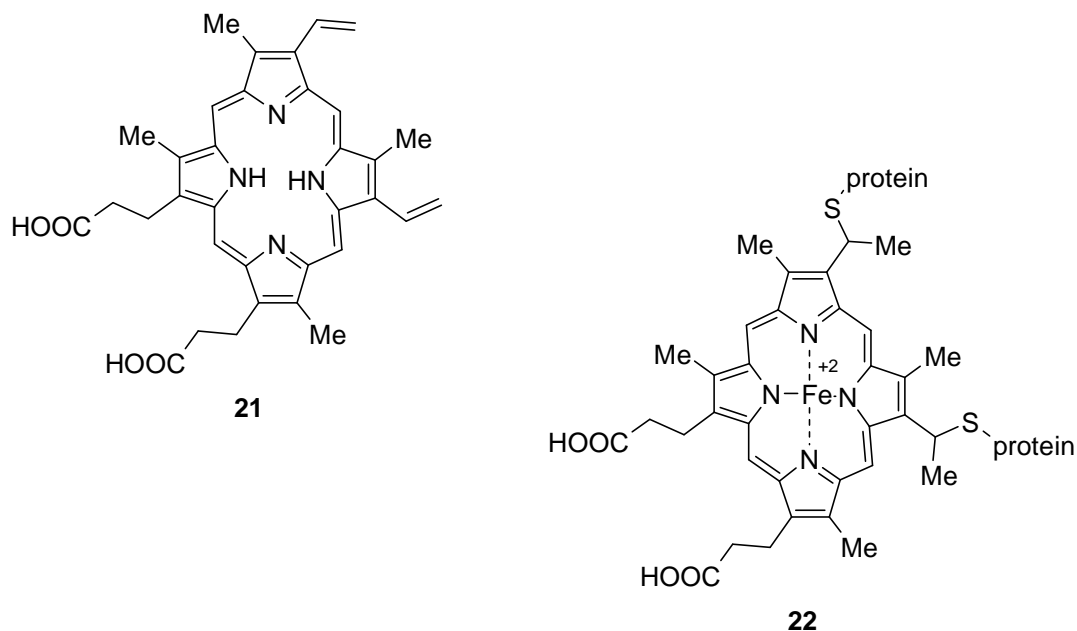
Some important vitamins, **16-20**, are constructed on an aromatic heterocyclic scaffold (Figure 6).

Figure 6



Porphyrins **21** are the backbone of major players in life cycles-cytochromes (Figure 7). There are three types of cytochromes, classified by their color, or more precisely by their long-wavelength absorption band, as *a* (600 nm), *b* (563 nm), and *c* (550 nm). They are protein conjugates of a porphyrin complex with iron(II), which is a coenzyme of protein hemoglobin called heme (**22**). Porphyrin derivatives are used in photodynamic therapy for dermatological diseases such as psoriasis, and for skin or subcutaneous cancer.³

Figure 7



Numerous plant and animal hormones have aromatic heterocycles as a major component.

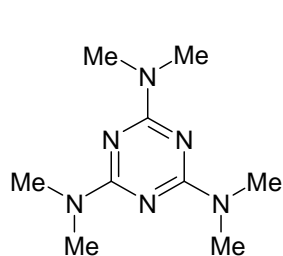
1.1.2. *In society*

Observations of life in nature by primitive communities led humans to the discovery of many healing materials. Many pharmaceutical products are mimics of natural products with biological activity, which include many heterocycles. In the fight against disease, some of the most significant advances have been and are being made by designing and testing new structures, many of which are heteroaromatic derivatives. The same is true for many pesticides. Antibiotics such as penicillins and cephalosporins, alkaloids such as vinblastine, ellipticine, morphine, and reserpine, and cardiac glycosides such as the class of digitalis are heterocyclic natural products of significance for human and animal health. Inspired by them, pharmaceutical researchers have constantly designed and produced better pharmaceuticals for a better living. In the same light, pesticides, insecticides, rodenticides, and weed killers followed natural models, and a significant part of such biologically active compounds are heterocycles.

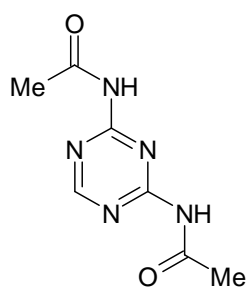
Modern life and civilization opened the way to other important practical applications of heterocycles, for example dyestuffs, copolymers, solvents,

photographic sensitizers and developers, and in the rubber industry antioxidants and vulcanization accelerators. Some of the sturdiest polymers, such as kevlar, have aromatic rings. Melamines (2,4,6-triamino-substituted triazines) are monomers with numerous applications as both homopolymers and copolymers. Figure 8 shows a few examples of compounds with various applications in our daily life, having in common the same building block, the aromatic triazine.

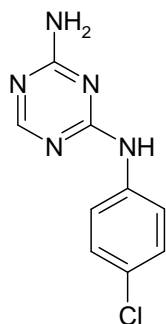
Figure 8



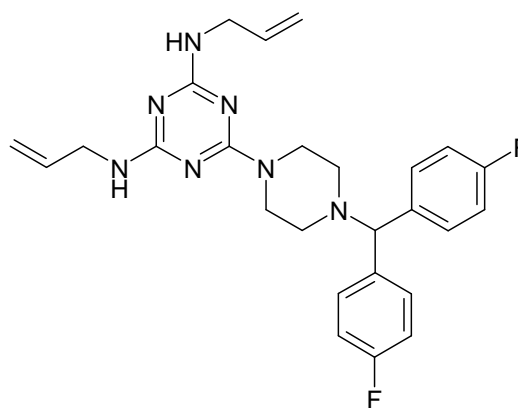
HMM (antitumor)



diacetylformoguanamine



Chlorazaniil (diuretic)



Altrimine (cancer therapy)

1.1.3. As a fundamental science

Apart from all the above reasons underlying the importance of heterocyclic chemistry as an applied science, it has much fascination as a subject for study in its own right.⁴

The work accomplished during my thesis deals with the synthesis of different fused polyheterocyclic compounds involving the combination of well-established methodologies of organic chemistry based on the functionalization of alkenes.

1.2. Aim of the thesis work

The work accomplished in this thesis concerns three different projects to achieve fused-ring heteropolycyclic systems having potential pharmacological properties. The synthetic procedures employed to reach this goal involve well known methodologies based on the functionalization of carbon-carbon double bonds.

Results will be presented in three different sections.

The first one deals with *diversity-oriented synthesis* to access complex structures containing a piperidine unit starting from enantiopure 2-allyl-piperidine.

The second section concerns the study of a synthetic protocol for a new class of enantiopure *tetracyclic 1,4-benzodiazepin-5-ones*, containing an imidazole and a pyrazole ring.⁵

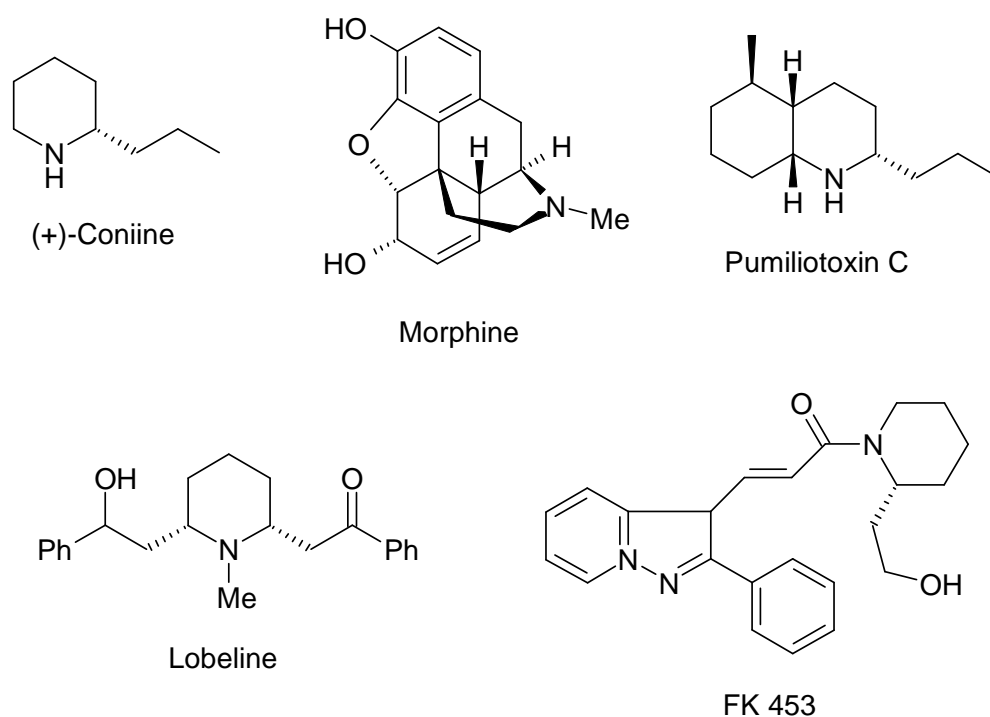
Finally, third part is related to the obtainment of *bicyclic oxazolidinone derivatives* by Pd(II)-CuCl₂ catalyzed intramolecular reactions on alkoxy-carbonyl-protected amino alkenes.

2. Results and discussion

2.1. Enantiopure 2-allyl-piperidine as building blocks in the “diversity-oriented synthesis” of piperidine derivatives

Piperidine is a heterocyclic ring widespread either in natural compounds or in biologically active molecules. The most of natural piperidinyl derivatives are mainly present in trees, but can be found also in insects and amphibians. In Figure 9 are collected only few examples which give idea of the widely different structures containing the piperidine unit. The highly structural diversity involves biological activities completely different.

Figure 9



Piperidine-containing compounds may be very simple, as in the case of (+)-coniine (an alkaloid found in poison hemlock and responsible of its neurotoxic effect), or more complex, as the morphine (one of the most known piperidinyl

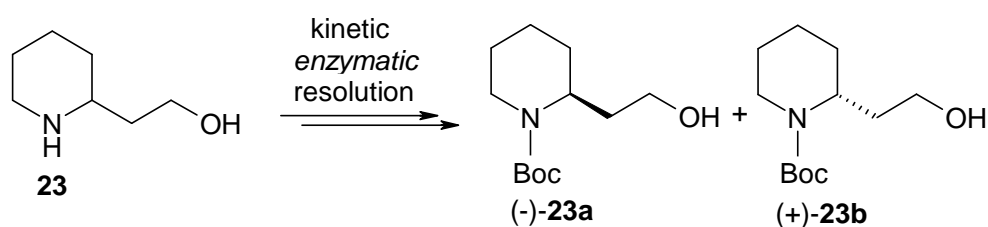
alkaloids and the most abundant of at least 50 alkaloids of several different types present in opium). Other example of piperidiny l alkaloids are Pumiliotoxin C, present in the poison of the *Dendrobates auratus* (a Central American species of frog), and Lobeline, extracted from *Lobelia inflata* and used as smoking cessation aid. Finally, piperidine nucleus can be found also in pharmacologically active man-made products such as FK453, an adenosine receptor antagonist with diuretic activity.

The wide presence of piperidine-containing structures among natural and biologically active compounds justifies new efforts toward the development of valuable synthetic approaches for complex and differently functionalized products.

Our contribution in this field was aimed to the achievement of new enantiopure heteropolycyclic piperidines having complex structures and/or particular functionalization groups by an approach of “diversity-oriented syntheses”, starting from a suitable building block. Diversity oriented synthesis (DOS) aims to synthesize a collection of compounds that differ substantially in their molecular structure.⁶ This has application in aspects of chemical genetics and drug discovery.

The planning of the work was inspired by an article published on Journal of Organic Chemistry 2003,⁷ that reported the obtainment of pure enantiomers of 2-(2-piperidinyl)ethanol (**23**) by kinetic enzymatic resolution of the racemic mixture (Scheme 1).⁸

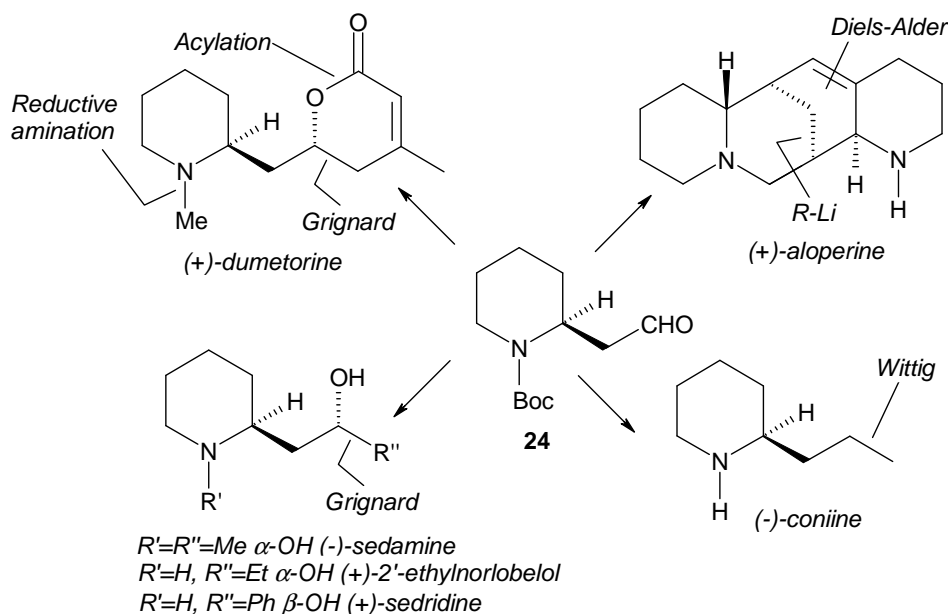
Scheme 1



The configurational stability of **23** and the wide spectrum of reactivity of the corresponding aldehyde **24** make possible to employ one of the enantiomers **23a** and **23b** as starting material for the enantioselective synthesis of a number of

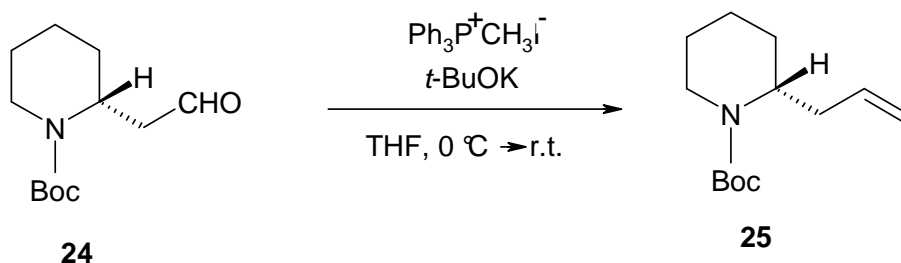
natural products. In Figure 10 are collected the results already obtained starting from **24**.^{9, 8}

Figure 10



In particular, we tried to widen this library exploiting the easy availability of enantiopure (*R*)- and (*S*)-2-allyl-piperidines **25**, obtained by Wittig reaction on the aldehyde derivative **24** (Scheme 2).^{8b}

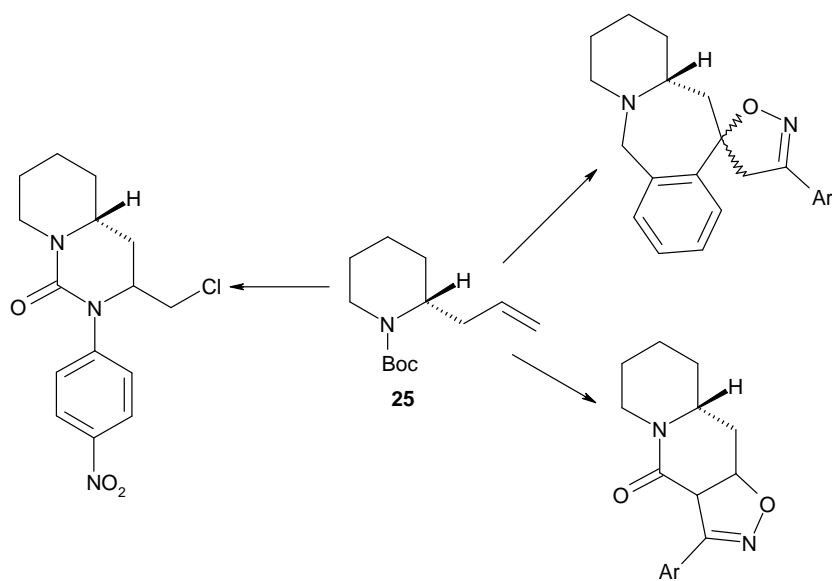
Scheme 2



This goal was achieved gaining the compounds depicted in Figure 11. In fact, we envisioned some suitable synthetic procedures based on intramolecular transition metal-catalyzed reactions involving the allylic carbon-carbon double bond and suitable tethers linked on the position 1 of the piperidine ring. The functionalization of the nitrogen atom gave access to six- or seven-membered

ring fused systems by Pd(0), Pd(II) and Ru catalyzed reactions. Moreover, the intrinsic value and the molecular complexity of the first-cyclization products containing a further carbon-carbon double bond was increased by following transformation into tri- or tetracyclic compounds by means of 1,3-dipolar cycloaddition reactions.

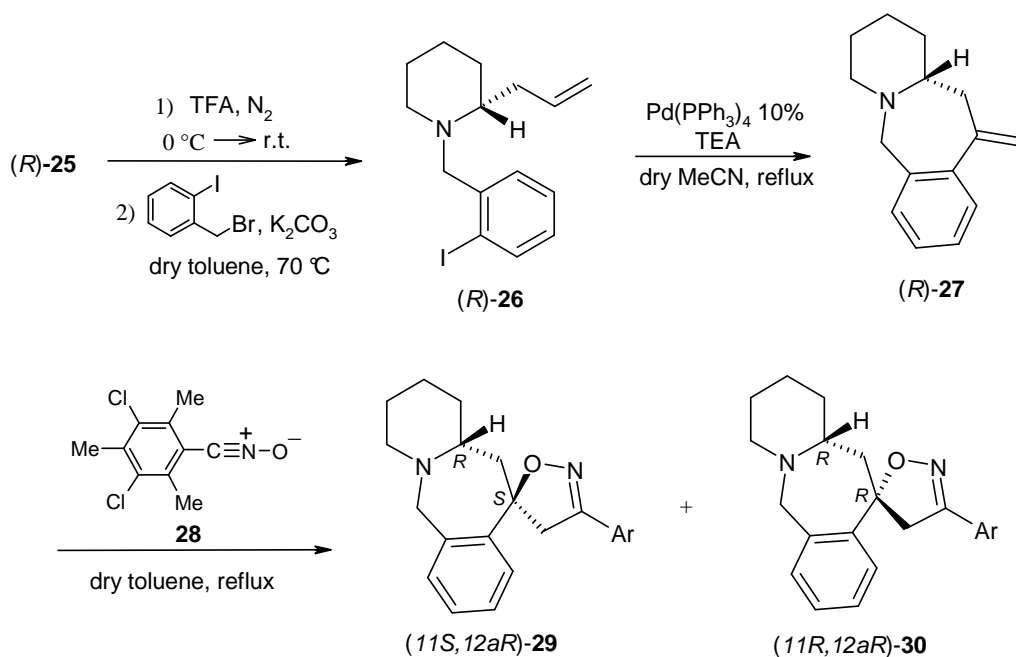
Figure 11



2.1.1. Synthetic sequence based on intramolecular Heck reaction

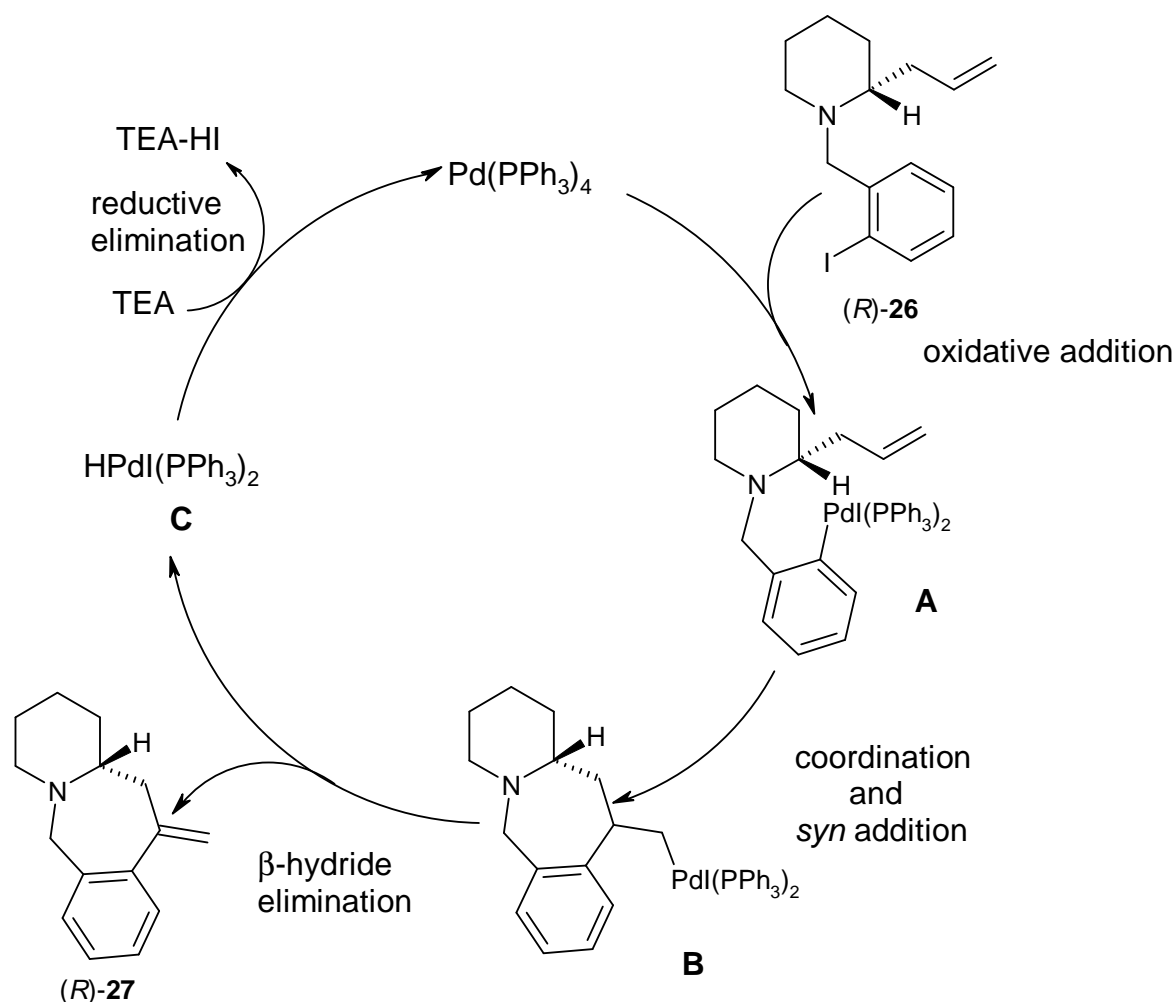
Firstly we took into account the compound (*R*)-**26**, suitable for an intramolecular Heck reaction. Removal of the tertbutoxycarbonyl group from (*R*)-**25** with TFA and following treatment of a toluene solution of the deprotected piperidine with the commercially available 2-iodo-benzyl bromide in the presence of K_2CO_3 gave the (*R*)-2-allyl-1-(2-iodobenzyl)-piperidine (**26**) (Scheme 3).

Scheme 3



The Heck reaction was performed either in the presence of $\text{Pd(PPh}_3)_4$ as catalyst and TEA as base in acetonitrile or in ligand-free conditions¹⁰ in the presence of Pd(OAc)_2 as catalyst, Na_2CO_3 and Bu_4NCl in DMF. Both the procedure were effective to promote the formation of the benzo[e]pyrido[1,2-a]azepine derivative (R) -27, even if the best result was obtained working with the former procedure (76% vs 38% yield). The related mechanism is depicted in Figure 12. The oxidative addition of the aryl iodide to the *in situ* generated $\text{Pd}(0)$ species generates the aryl- Pd(II) -complex **A**. Coordination of the alkene moiety and subsequent carbon-carbon bond formation by *syn* addition provide the σ -alkylpalladium(II) intermediate **B**, which readily undergoes β -hydride elimination to release the alkene Heck product (R) -27. The base is required for conversion of the hydridopalladium(II) complex **C** to the active $\text{Pd}(0)$ catalyst to complete the catalytic cycle.

Figure 12

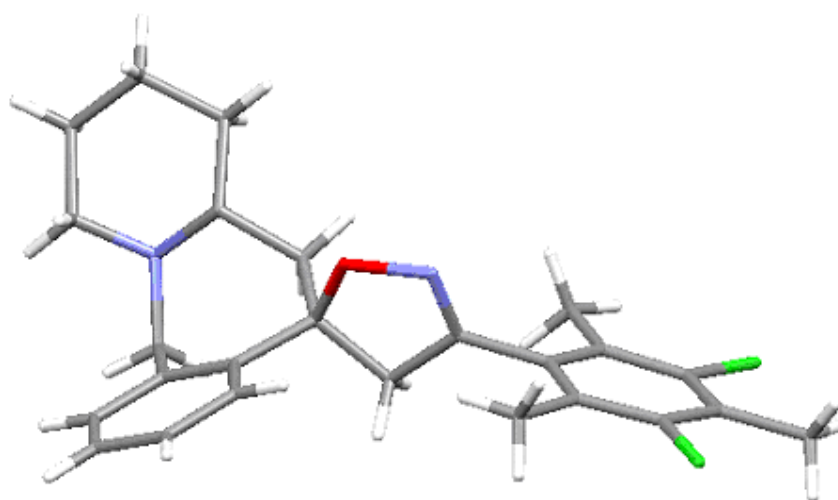


The presence of the exomethylene carbon-carbon double bond on the compound (R)-27, furnished the hint to reach more complex spiro-annulated structures by means of 1,3-dipolar cycloadditions. The dipolarophilic behaviour of the exocyclic carbon-carbon double bond was proven toward the 3,5-dichloro-2,4,6-trimethylbenzonitriloxide (28), chosen as 1,3-dipole due to its excellent stability.¹¹

The reaction between (R)-27 and 28 was performed in toluene at reflux by using equimolar amounts of the reactants. As foreseeable by literature data,¹² the cycloaddition took place with total regioselectivity giving, however, a mixture of

two diastereoisomeric products in approximately 3:1 ratio which were isolated by column chromatography in 68 and 19% yield, respectively. The 11-5' junction of the benzo[*e*]pyrido[1,2-*a*]azepine-isoxazole system was inferred by the ^1H and ^{13}C -NMR data, in particular by the geminal coupling constants greater than 17 Hz, which is compatible only with the methylenic group for a 4-position of the isoxazole ring.¹³ It should be pointed out that a total regioselectivity was observed, accordingly to the literature data dealing with nitrile oxide cycloadditions to 1,1-disubstituted ethylenes. The distinction between the diastereoisomeric spiro-compounds **29** and **30** was established by X-ray diffractometric analysis on **29** (Figure 13).

Figure 13

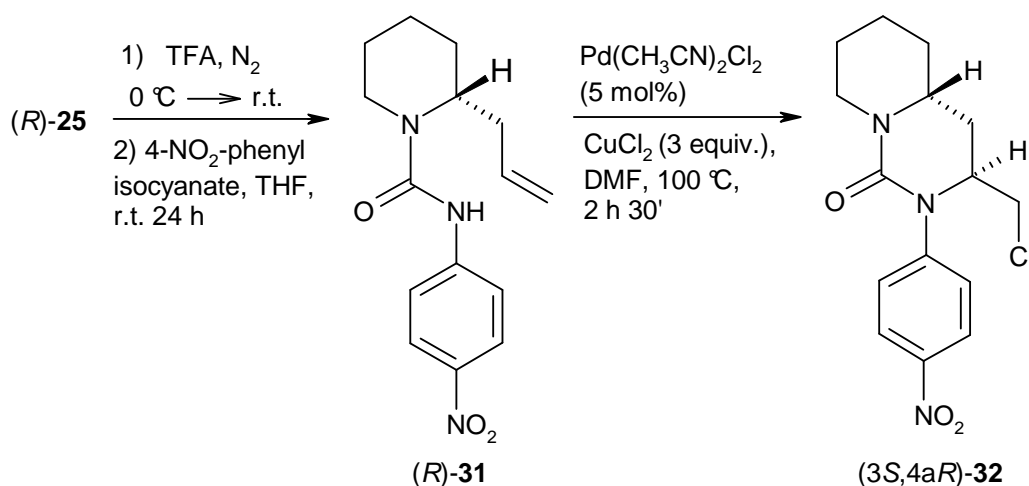


2.1.2. Synthetic sequence based on intramolecular Pd(II)-catalyzed chloroamination

The Pd(II)-catalyzed functionalization of unactivated C-H bonds is actually a challenging field in organic chemistry,¹⁴ where we recently put our interest.¹⁵ Recent literature seems particularly attracted by reactions achieving a double functionalization of double bonds, more specifically towards diamination or heteroamination processes.^{16, 14n} After an appropriate functionalization of the nitrogen atom, the ethylenic double bond present on compound (*R*)-**25** seemed therefore suitable to perform such a goal. After deprotection with TFA, reaction with 4-nitro-phenylisocyanate afforded compound (*R*)-**31**, which bears a

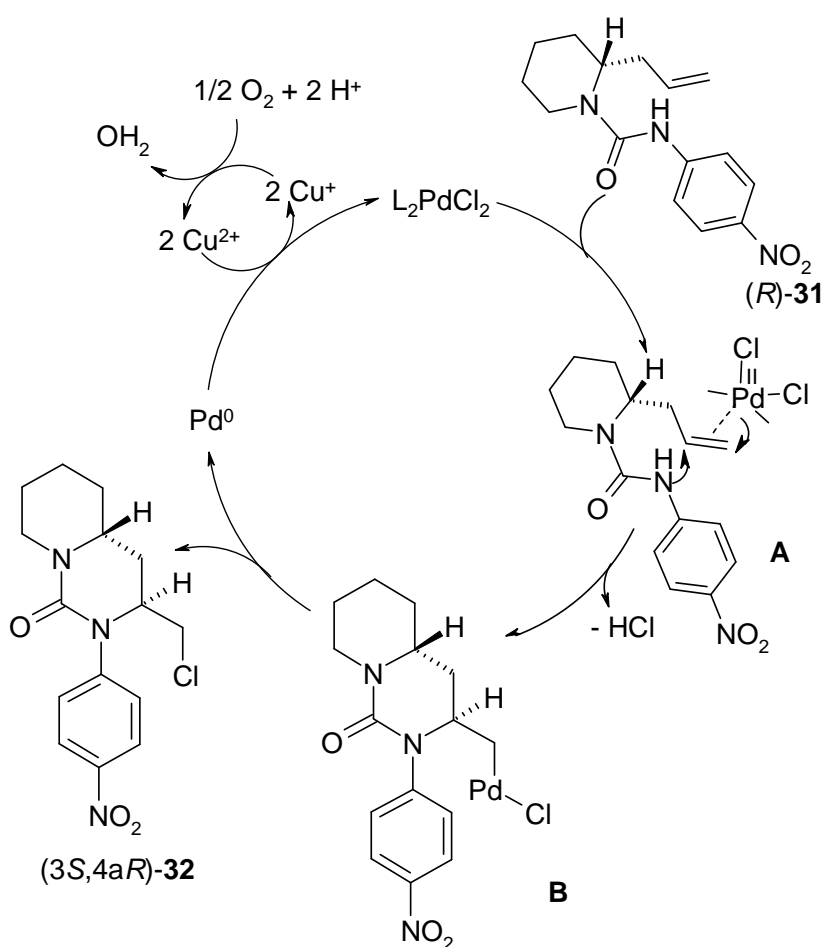
nucleophilic nitrogen atom (Scheme 4). This latter easily reacts with the carbon-carbon double bond using $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$ as catalyst and CuCl_2 as oxidant; the high amount of copper chloride warrants the massive presence of chloride anions in the reaction medium, thus letting them intercept the σ -alkyl-palladium intermediate before a competitive β -hydride elimination process could occur. Consequently, bicyclic pyrido[1,2-*c*]pyrimidinone (3*S*,4*aR*)-**32** is formed. This chlorinated product, whose stereochemistry has been undoubtedly assigned by a NOESY experiment, arises from a domino chloroamination process.

Scheme 4



Concerning the mechanism of the reaction, it is reasonable an initial coordination of palladium to the ethylenic double bond giving the π -olefin **A**, followed by nucleophilic attack of nitrogen atom on the internal carbon atom and formation of the σ -alkyl palladium complex **B**. The final step involves a reductive elimination of the metal giving the product **32**. In this case, the expected elimination of the hydrogen in β -position is inhibited probably due to the excess of chloride ions.¹⁷ Finally, palladium will be ejected in the oxidation state zero and will oxidize to Pd(II) by the copper chloride to restart a new catalytic cycle.

Figure 14

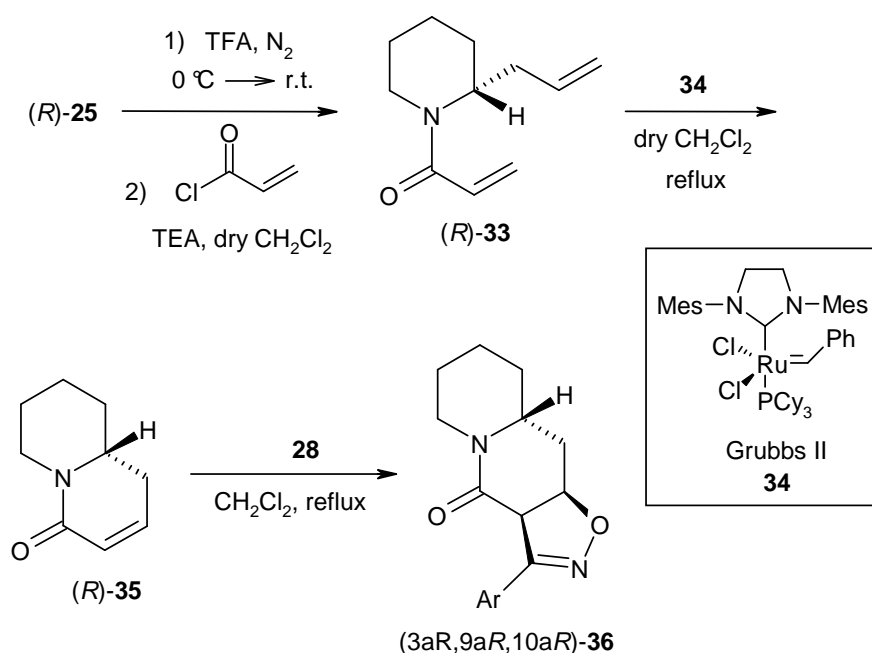


2.1.3. Synthetic sequence based on RCM reaction

Application of ring closing metathesis to build large- and medium-ring heterocycles has enormously increased in recent years, due to the high efficiency this process usually warrants.¹⁸ Reasoning once more on substrate **(R)-25**, we thought to build a six-membered fused-ring on the piperidine by a RCM process performed on a substrate obtained by functionalization of the nitrogen with an acryloyl group. Reaction of the deprotected allyl piperidine with

acryloyl chloride furnished the appropriate substrate containing two ethylenic double bonds, which lie juxtaposed for the construction of a six-membered fused ring. Moreover, the presence of an amide group instead an amine one should have warrant easier the following RCM. In fact, amide (*R*)-**33**, treated with a Grubbs catalyst of 2nd generation **34** in DCM at reflux, conveniently furnished quinolizinone (*R*)-**35** in quantitative yield (Scheme 5).

Scheme 5

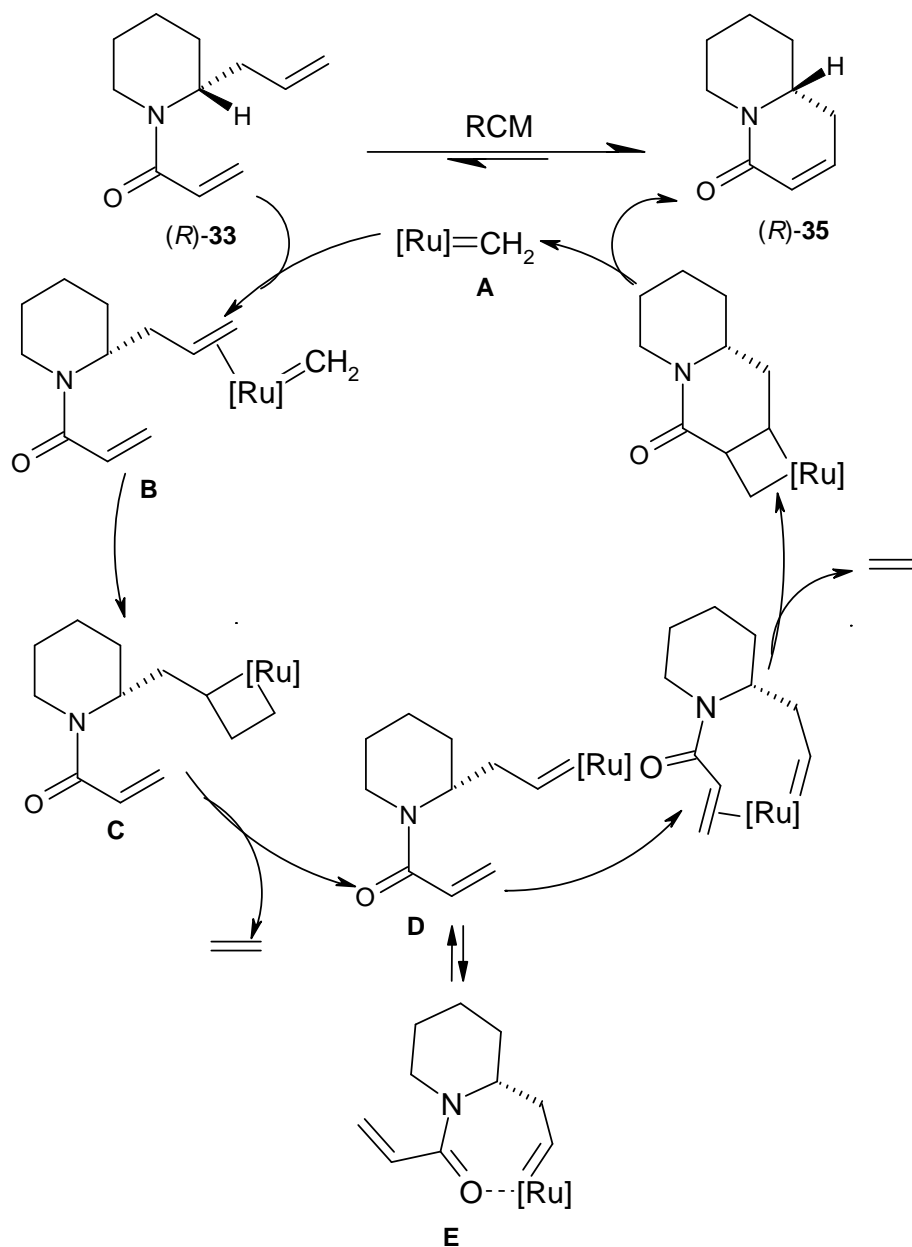


Generally, the mechanism of ring closing metathesis consists in an initial coordination of an olefin to the metal alkylidene species **A** giving **B**, formation of the metallacyclobutane complex **C** and subsequent release of a different olefin, results in the formation of a new metal alkylidene **D** (Figure 15). This species can then undergo the same sequence of transformations involving the ethylenic double bond of the acryloyl group to give the final product (*R*)-**35**.

As shown in Figure 15, reasonably first attack involves the allylic carbon-carbon double bond. In fact, olefin methatesis of electron-poor double bonds is less favoured compared to neutral olefins because the relative instability of electron-deficient metal carbene bonds.^{19,20,21} In the case of RCM between α,β -unsaturated carbonyl compounds and neutral terminal olefins it has been reported that the catalyst reacts preferentially with the neutral double bond,

before metathesizing the electron-poor olefin to form the cyclized product.^{20b} On the other hand, after metathesis of the unhindered olefin, the carbonyl function in the resulting carbene complex (**E**) can chelate to the metal center thereby lowering the rate catalyst.²²

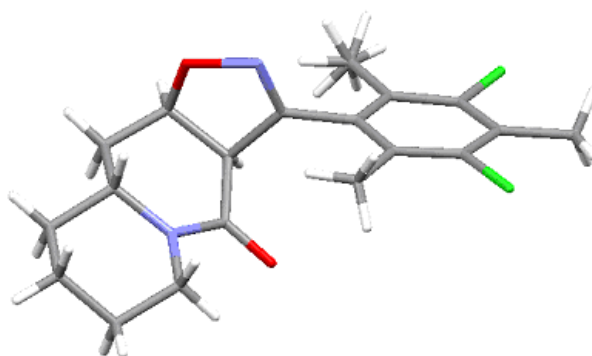
Figure 15



Then, we decided once more to increase the molecular complexity of our product envisaging to employ the endocyclic double bond as dipolarophile in a 1,3-dipolar cycloaddition with nitriloxide **28**. As in the case of the 1,1-disubstituted ethylenic compound (R)-**27**, the outcome of the cycloaddition on the 1,2-disubstituted ethylenic double bond was totally regioselective, allowing the

formation of a 4,5-dihydroisoxazole product in 72% yield. Spectroscopic data agree with the structure (*R*)-**36**, having the carbonyl group in 4-position of the new formed isoxazoline. From the stereochemical point of view, the cycloaddition process allowed exclusively a *cis*-disposition of the two new stereocentres, which relative configuration was proven to be *trans* with respect to the pre-existing one by X-ray diffractometric analysis (Figure 16).

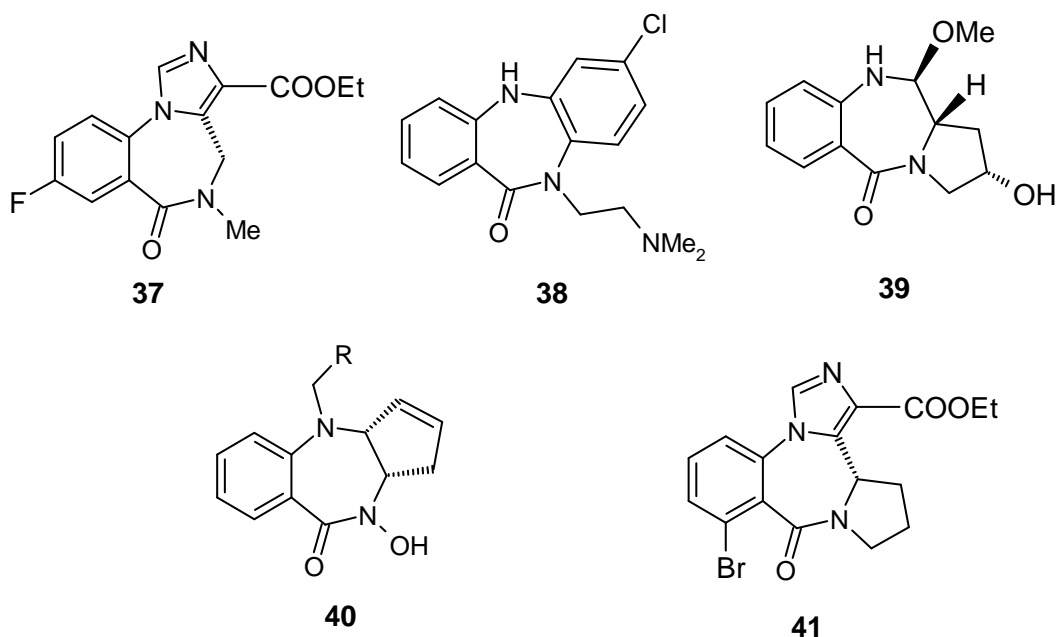
Figure 16



2.2. Synthesis of tetracyclic benzodiazepines

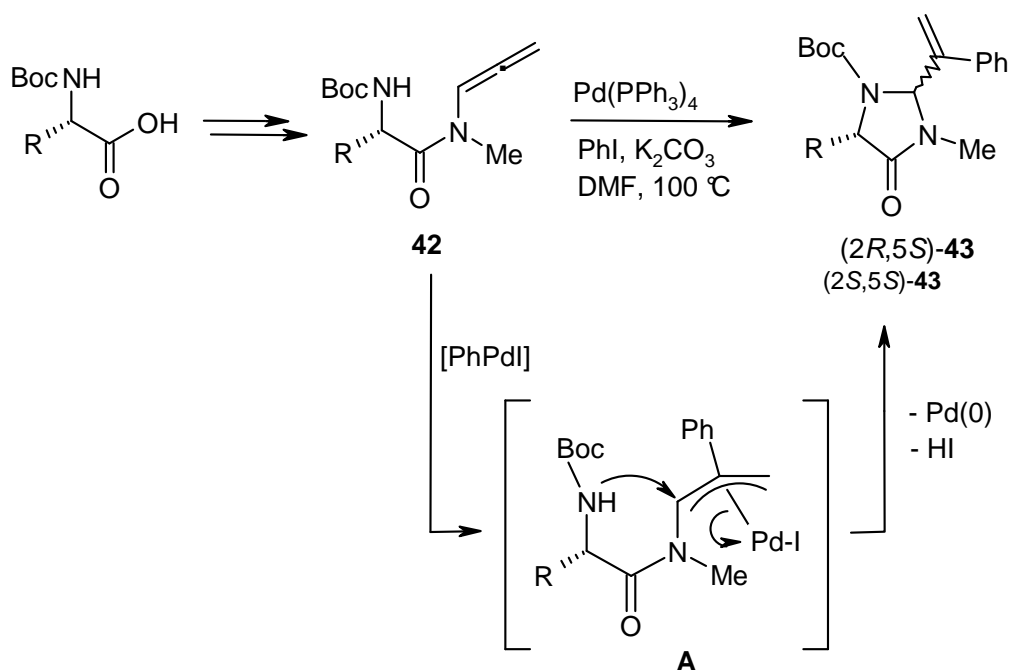
The second part of the thesis was inspired by the relevant role occupied in medicinal chemistry by 1,4-benzodiazepines.²³ Among them, one of the most privileged class of these structures is held by 1,4-benzodiazepin-5-ones, a subset recognized as endowed with the anxiolytic, anticonvulsant, antiepileptic, muscle relaxant, antidepressant, sedative and hypnotic activities related to the treatment of CNS disorders.²⁴ Moreover, this range of therapeutic activities has been strongly widened by annulations of the benzodiazepine skeleton to another carbo- or heterocyclic ring. Tricyclic 1,4-benzodiazepin-5-one systems, beyond solving anxiety and stress problems as in the case of flumazenil (**37**),²⁵ count antihistaminic compounds such as tarpane (**38**),²⁶ antibiotics like the pyrrolo-fused abbeymicin²⁷ (**39**) and antitumors having structure **40** (Figure 17).²⁸ More recently, inspired by the attention given to bretazenil (**41**) due to its potential application towards neurodegenerative diseases,²⁹ some tetracyclic 1,4-benzodiazepinones have appeared in the literature. These structures have the benzodiazepine nucleus fused to different hetero- and carbocycles such as pyrimidines, imidazoles, 1,2,4-triazoles, pyrazoles, benzopyrans or naphthalenes.³⁰

Figure 17



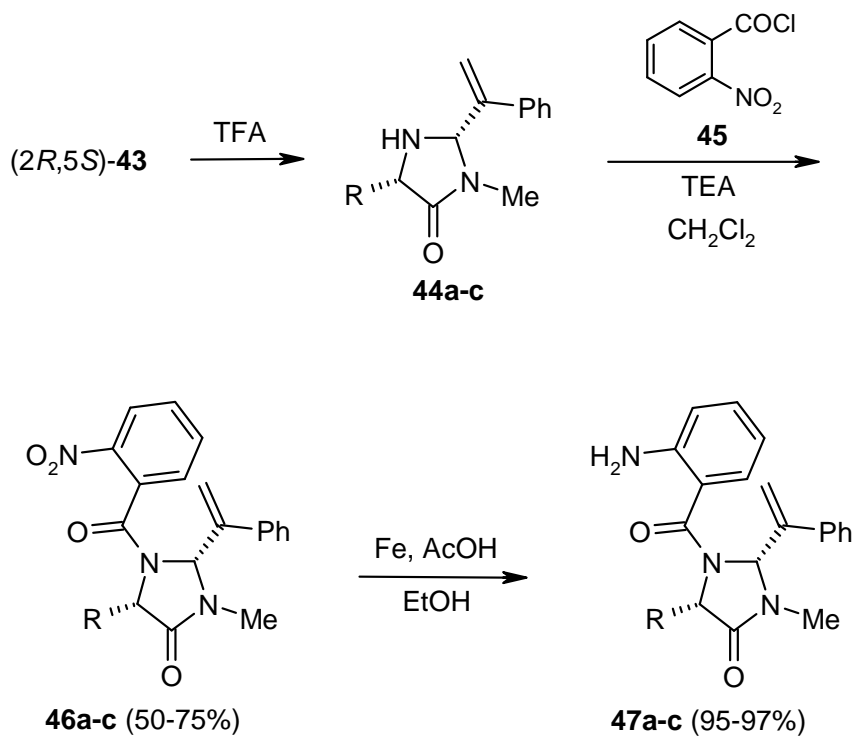
Now, this work concerns a synthetic protocol for a new class of tetracyclic 1,4-benzodiazepin-5-ones that we have been developed through our recent interest on allenylamides heterocyclization.³¹ The starting point for planning the new synthetic strategy is born from the recent achievement of the enantiopure 2-vinylimidazolidinones **43**, obtained by heteroannulation of the amino allenylamides **42** (Scheme 6).³¹ The reaction proceeds by a domino carbopalladation / 5-exo-allylic amination through the formation of the π -allyl-complex **A**. The imidazolidinones **43** have been advised as building blocks for the construction of the 1,3-dipolar substrates suitable to intramolecular cycloaddition due to the presence of the ethylenic C-C double bond as potential dipolarophile.

Scheme 6



First of all, having recognized the major diastereoisomer imidazolidinones (**(2R,5S)-43**) as the convenient starting materials, our approach required the synthesis of 2-aminobenzamides **47** as suitable compounds for accessing to the azide and nitrilimine 1,3-dipoles due to the presence of the aniline moiety. To this purpose, Boc-protection was removed by treatment with TFA to give imidazolidinones **44** (Scheme 7). These latter were functionalized by reaction with 2-nitrobenzoyl chloride (**45**) to give the 2-nitrobenzamides **46**, which in turn were reduced to the 2-aminobenzamides **47**.

Scheme 7

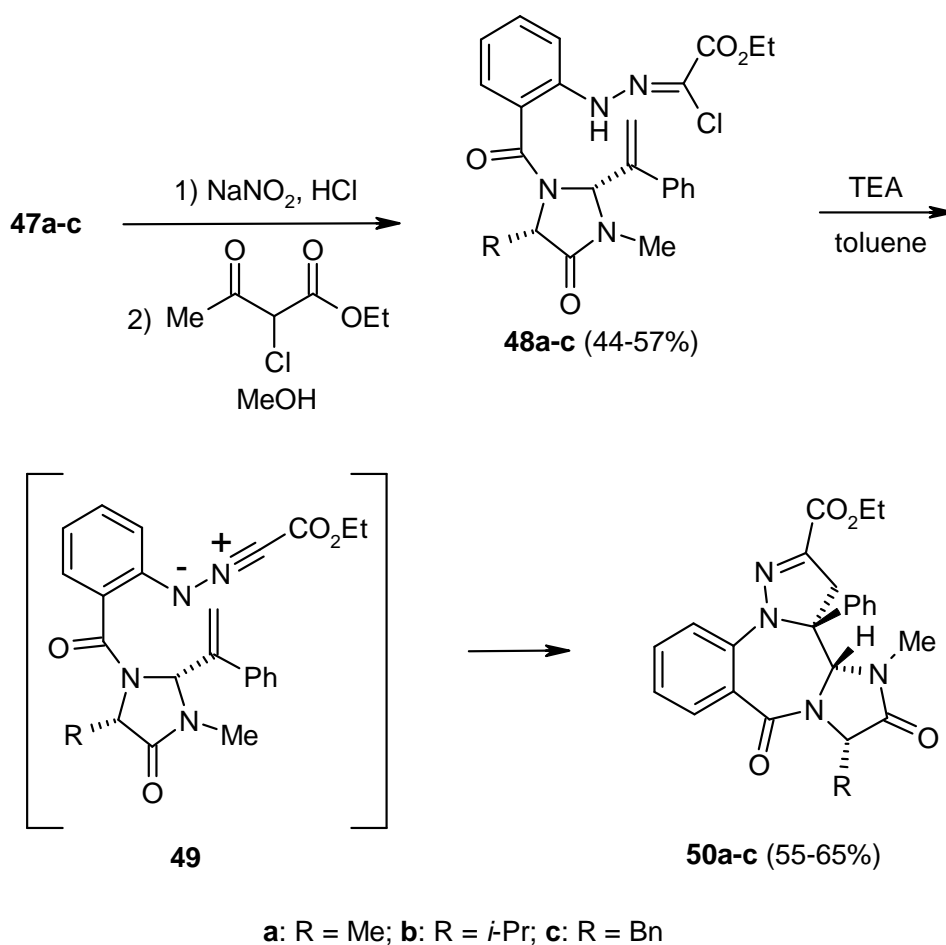


a: R = Me; b: R = *i*-Pr; c: R = Bn

The diazotization of the aniline unit permitted the access to the corresponding azido compounds, but their intramolecular 1,3-dipolar cycloadditions furnished unstable 4,5-dihydro-1,2,3-triazole products which evolved into complex mixtures without synthetic interest. Such a failure prompted us to turn our attention to the nitrilimine 1,3-dipole, being a well established functional group in the synthesis of variously substituted azoles.³² To this end, compounds **47** were submitted to diazotization and following coupling with ethyl 2-chloroacetate to furnish the hydrazonyl chlorides **48**, precursors of the transient nitrilimine species **49**. In fact, the treatment of **48** with triethylamine in boiling toluene gave directly the

tetracyclic imidazo[2,1-c]pyrazolo[1,5-a][1,4]benzodiazepin-5,8-dione systems **50** (Scheme 8).

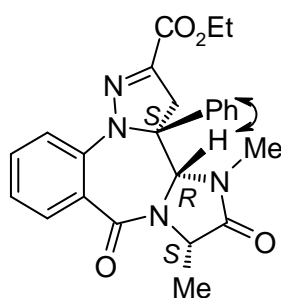
Scheme 8



Further to the total regiochemical outcome, that was expected as a consequence of the propargylic nature of the 1,3-dipole, the cycloaddition reaction was totally diastereoselective giving rise to only one diastereoisomer product. This feature, highly important from the synthetic point of view, probably arises from the bulky phenyl substituent and the rather rigid imidazolidinone moiety working against the intramolecular approach of the dipole to the *si* face of the dipolarophile, so dictating the exclusive formation of the *cis* diastereoisomer

50. The absolute configuration was assigned by $^1\text{H-NMR}$ NOESY experiments carried out on compound **50a**. As shown in Figure 18, further to obvious interactions between the hydrogens in 2- and 5-positions of the imidazole nucleus, the cross-peak between the hydrogen in position 2 of the imidazolidinone and those in *ortho* to the phenyl group resulted determinant to identify the *S*-configuration of the newly created stereocentre, determining the formation of the (3a*S*,3b*R*,6*S*)-diastereoisomer. The enantiomeric purity was proven to be better than 99.5% by HPLC analysis with AD chiral column of compound **50a**, performed in comparison to a sample of the corresponding racemic mixture synthesized starting from the (\pm)-alanine.

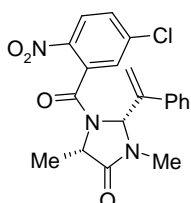
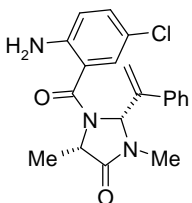
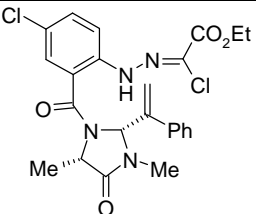
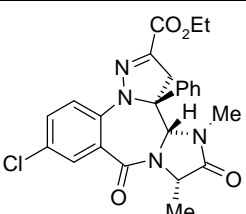
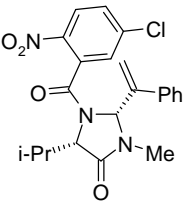
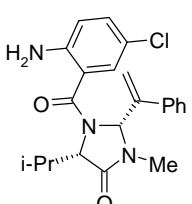
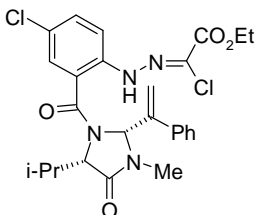
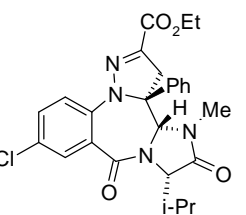
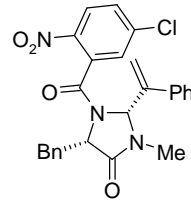
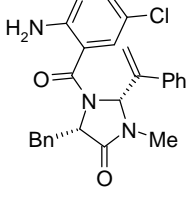
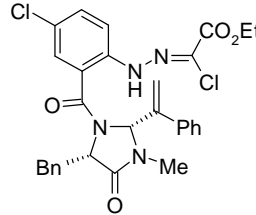
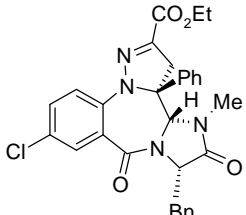
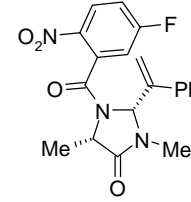
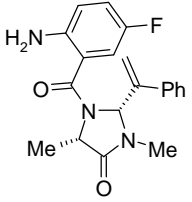
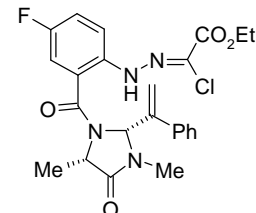
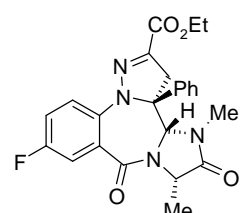
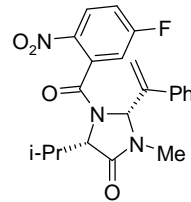
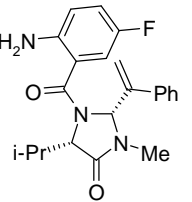
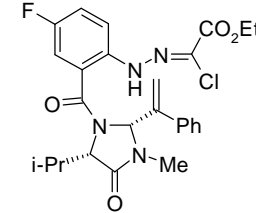
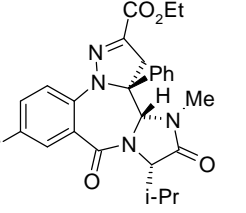
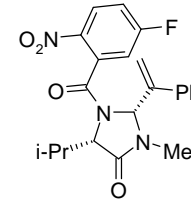
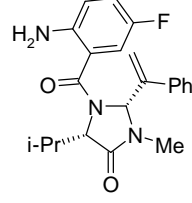
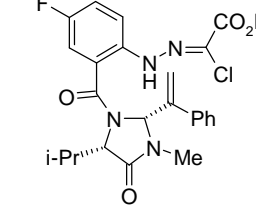
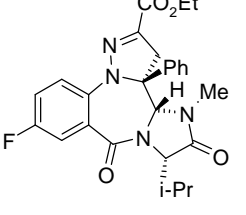
Figure 18



Selected NOESY correlations for compound **50a**.

We next examined the procedure by using imidazolidinones **43** and 5-chloro- and 5-fluoro-2-nitro-benzoyl chlorides in order to improve the scope of the reaction and the interest of the products from the biological point of view, having a halo-substituted 1,4-benzodiazepine nucleus. In Table 1 are collected the halide-containing 2-nitrobenzamides **46**, 2-aminobenzamides **47**, hydrazonyl chlorides **48**, and tetracyclic products **50**. The preparations of hydrazonyl chlorides as well as the nitrilimine cycloadditions occurred analogously to the ones described for the unsubstituted 2-nitrobenzoyl chloride.

Table 1

2-Nitrobenzamides (46)	2-Aminobenzamides (47)	Hydrazoneyl chlorides (48)	Benzodiazepinones (50)
 <p>46aa (55%)</p>	 <p>47aa (96%)</p>	 <p>48aa (62%)</p>	 <p>50aa (62%)</p>
 <p>46ba (34%)</p>	 <p>47ba (84%)</p>	 <p>48ba (82%)</p>	 <p>50ba (53%)</p>
 <p>46ca (62%)</p>	 <p>47ca (79%)</p>	 <p>48ca (43%)</p>	 <p>50ca (44%)</p>
 <p>46ab (60%)</p>	 <p>47ab (87%)</p>	 <p>48ab (49%)</p>	 <p>50ab (71%)</p>
 <p>46bb (49%)</p>	 <p>47bb</p>	 <p>48bb (57%)</p>	 <p>50bb (46%)</p>
 <p>46bb (49%)</p>	 <p>47bb</p>	 <p>48bb (57%)</p>	 <p>50bb (46%)</p>

2.3. Pd(II)/Cu(II) catalyzed intramolecular aminocarboxylation of aminoalkenes for the synthesis of bicyclic oxazolidinones

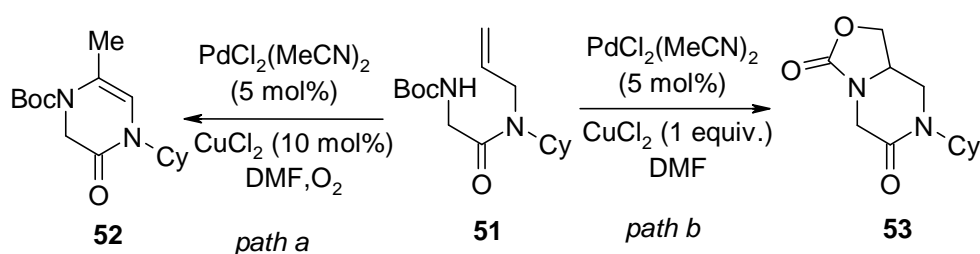
The third section of the thesis was focused on a divergent synthesis of piperazinones and bicyclic oxazolidinones starting from allyl amides of α -amino acids.

Piperazines and piperazinones have relevant biological and pharmacological interest, often present in the core-structures of compounds with antifungal,³³ antidepressant,³⁴ antimigraine,³⁵ antithrombotic,³⁶ antihistaminic,³⁷ and nootropic³⁸ activities. Moreover, bicyclic oxazolidinones constitute a fruitful source of hydroxylated nitrogen-containing ring systems.³⁹

The hint for these studies arose by our interest on the Pd(II)-catalyzed intramolecular reactions of nucleophiles, such as amides or electron-rich heteroaromatic compounds, onto multiple carbon-carbon bonds.^{15a-c} More specifically, during our investigations on amination reactions in oxidative conditions, we envisaged the cyclization of allyl amides of α -amino acids as route to access piperazinone derivatives.

Preliminary studies were performed on Boc-glycine-*N*-allyl-*N*-cyclohexyl amide **51** to examine the activity of different catalysts and oxidants, and revealed a remarkable role of CuCl₂. In fact, the divergent formation of cyclization products **52** and **53** was observed, depending solely on the amount of CuCl₂, either catalytic or stoichiometric (Scheme 9). In particular, compound **2** was obtained using PdCl₂(MeCN)₂ (5 mol%) and CuCl₂ (10 mol%)/O₂ as the oxidant system in DMF at 100 °C (Scheme 9, path a).

Scheme 9

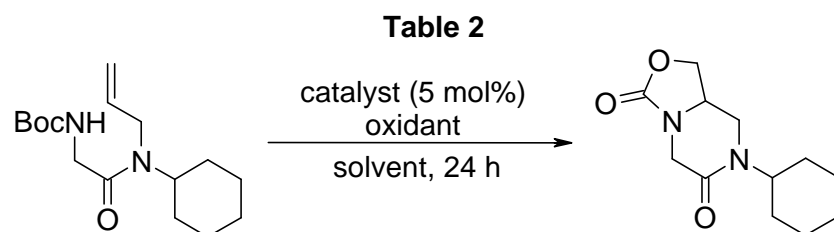


Albeit the amination reaction giving dihydropyridazinone **52** undoubtedly constitutes an unprecedented result in aza-Wacker type reactions, the alternative formation of the bicyclic oxazolidin-2-one **53** by exposure of **51** to a stoichiometric amount of CuCl_2 (Scheme 9, path b) represents a much more striking breakthrough. So, we devoted our efforts to improve the latter domino procedure, which would furnish hydroxymethyl-substituted piperazinone after oxazolidinone ring-opening. The interest for this result is increased because

- product **53** is generated by an unusual behavior of the carbamate oxygen which acts as a nucleophile in an oxidative Pd(II)-catalyzed reaction involving a domino aminocarboxylative process based on an initial carbon-nitrogen bond formation, followed by an intramolecular carboxylation reaction, involving the tert-butoxycarbonyl group.
- several procedures for the formation of oxazolidinones featuring a Pd-catalyzed cyclization of O-allyl carbamates have been reported, but these normally involve the C-N bond formation.⁴⁰ However, to the best of our knowledge, only a single example of carbamate cyclization via C-O bond formation has been described, which does not claim for a palladium intermediate.⁴¹

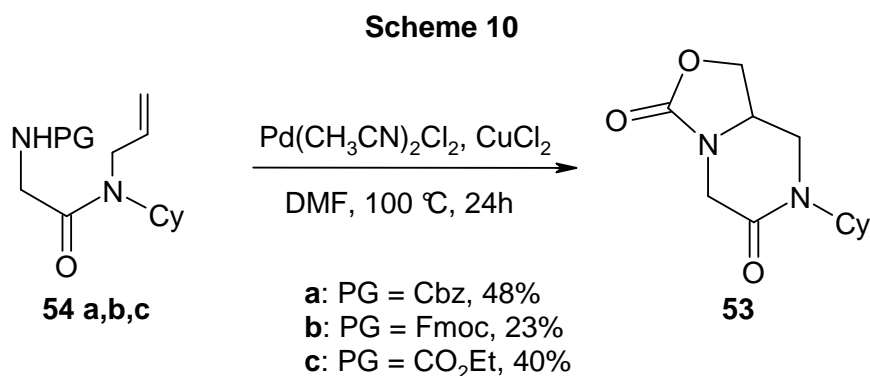
The reaction conditions were then investigated to optimize the formation of the synthetically valuable fused-oxazolidin-2-one bicyclic products **53**.⁴² An excess of CuCl_2 yielded **53** in higher amount (Table 1, entry 2 vs 1). Both palladium and cupric chloride were required, since the conversion of **51** was precluded by removal of $\text{PdCl}_2(\text{MeCN})_2$ as well as by the use of other oxidants such as $\text{Cu}(\text{OAc})_2$, 1,4-benzoquinone, or $\text{PhI}(\text{OAc})_2$ (entries 3-6).

Similar yields were obtained running the reaction in an open vessel or under nitrogen atmosphere. The reaction occurred also at room temperature, but the yield of **53** is noticeably lower (entry 7). Further screening of different solvents proved to be unfruitful to improve the yields or to gain milder conditions (entries 8-10). Changing the source of palladium, namely with $\text{Pd}(\text{OAc})_2$, no conversion took place (entries 11, 12). It is worth mentioning that the formation of the intramolecular amination product **52** was never observed using CuCl_2 in stoichiometric or excess amount.



Entry	Catalyst	Oxidant (eq.)	Solvent	T (°C)	Yield (%) ^a
1	PdCl ₂ (MeCN) ₂	CuCl ₂ (1)	DMF	100	69
2	PdCl ₂ (MeCN) ₂	CuCl ₂ (3)	DMF	100	81
3	-	CuCl ₂ (3)	DMF	100	n.r.
4	PdCl ₂ (MeCN) ₂	Cu(OAc) ₂ (3)	DMF	100	n.r.
5	PdCl ₂ (MeCN) ₂	1,4-BQ (2)	DMF	100	n.r.
6	PdCl ₂ (MeCN) ₂	PhI(OAc) ₂ (3)	DMF	100	Traces
7	PdCl ₂ (MeCN) ₂	CuCl ₂ (3)	DMF	r.t.	64
8	PdCl ₂ (MeCN) ₂	CuCl ₂ (3)	THF	Reflux	40
9	PdCl ₂ (MeCN) ₂	CuCl ₂ (3)	CH ₂ Cl ₂	Reflux	26
10	PdCl ₂ (MeCN) ₂	CuCl ₂ (3)	Toluene	80	n.r.
11	Pd(OAc) ₂	Cu(OAc) ₂ (3)	DMF	100	n.r.
12	Pd(OAc) ₂	1,4-BQ (2)	DMF	100	n.r.

The domino reaction is not dependent on the carbamate protecting-group (Scheme 10), as it operated also on Cbz-, Fmoc- and ethoxycarbonyl-glycine amides **54** providing the oxazolidin-2-one **53**, although in lower yields (48%, 23% and 40% respectively, vs 81% of the corresponding Boc-derivative)



The scope of this transformation was then explored, reacting the easily obtained allylamides **55a-h**, under the optimized conditions (Table 3).

Scheme 11

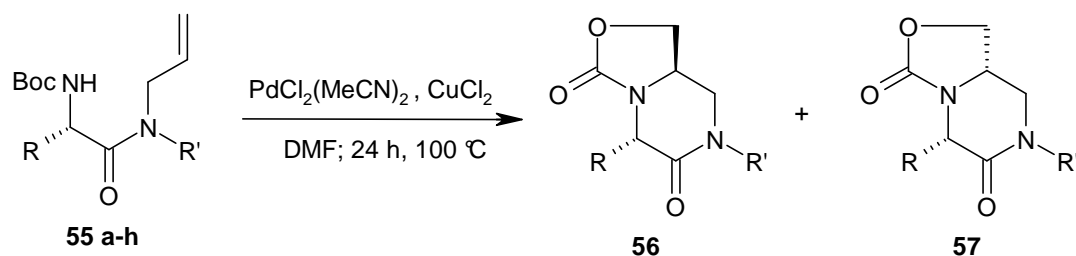
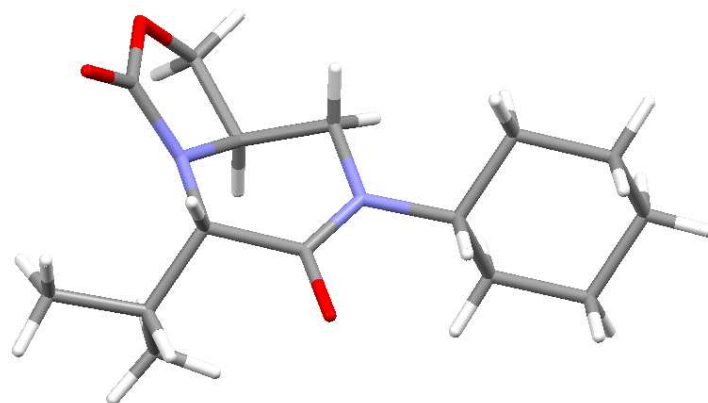


Table: 3

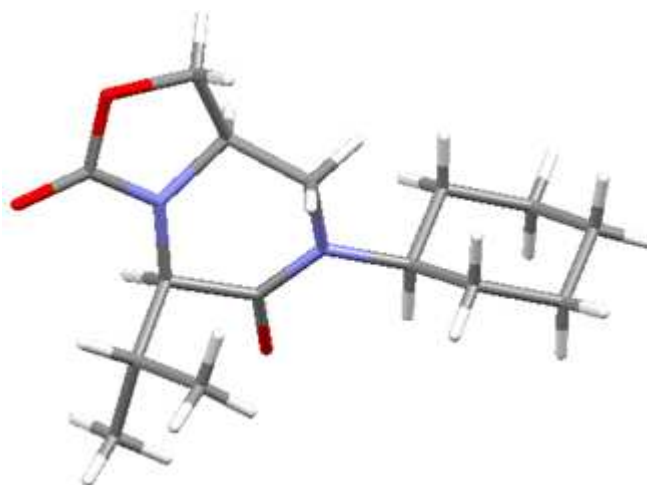
Entry	R	R'	Dr ratio	Isolated yields(%)
1	i-Pr	Cyclohexyl	70:30	56a (56%) 57a (23%)
2	i-Pr	Cyclopentyl	75:25	56b (48%) 57b (18%)
3	i-Bu	Cyclohexyl	80:20	56c (62%) 57c (15%)
4	i-Bu	Cyclopentyl	80:20	56d (62%) 57d (9%)
5	Bn	Cyclohexyl	75:25	56e (41%) 57e (13%)
6	Bn	Cyclopentyl	70:30	56f (57%) 57f (25%)
7	Me	Cyclohexyl	80:20	56g (55%)
8	Me	Cyclopentyl	80:20	56h (49%)

In all these cases, the reactions provided the desired oxazolo[3,4-a]pyrazine derivatives as a mixture of two diastereoisomers. The relative configurations of the major and minor products, namely trans and cis, were identified by single-crystal X-ray analysis, performed on isopropyl-substituted compounds **56b** and **57b** (Figure 19).

Figure 19

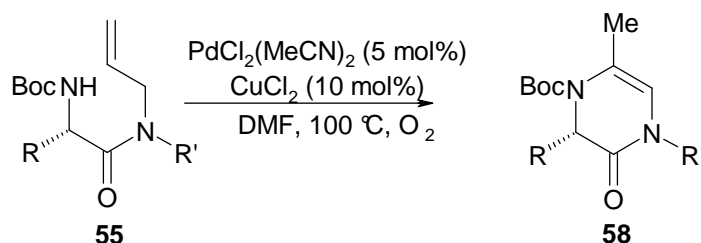


major Diastereoisomer



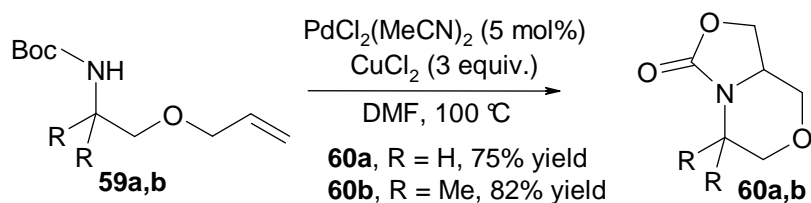
Minor Diastereoisomer

The amination products (Scheme 9, path a) were never isolated nor detected in the NMR spectra of the crude reaction mixtures. On the other hand, the dihydropyrazinone derivatives **58** resulted the sole products, when a number of allylamides were treated with CuCl_2 (10 mol%)/ O_2 as the oxidant system (Table 4)

Table 4

Entry	R	R'	Yield
1	<i>i</i> -Pr	Cy	58a (82%)
2	<i>i</i> -Pr	Me	58b (55%)
3	<i>i</i> -Bu	Cy	58c (82%)
4	<i>i</i> -Bu	Me	58d (72%)
5	Bn	Cy	58e (71%)
6	Bn	Me	58f (65%)
7	Me	Cy	58g (83%)
8	Me	Me	58h (70%)

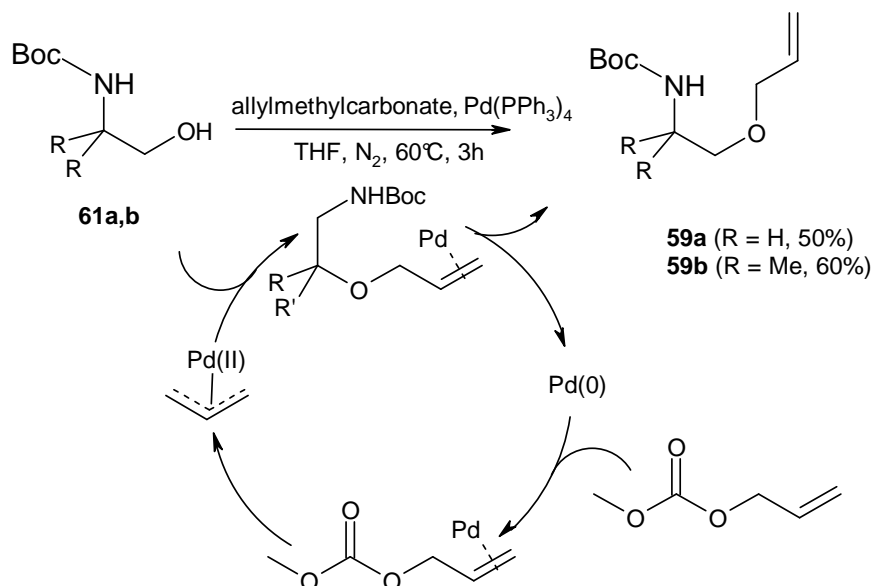
The domino process is not limited to the allylamides of α -amino acids, but can be extended to other carbamate-protected aminoalkenes having a more flexible tether. In fact, the Boc-amino allylethers **59a** and **59b**, synthesized gave the bicyclic morpholino derivatives **60a** and **60b** in good yields (Scheme 12).

Scheme 12

Boc-amino allylethers **59a** and **59b** were prepared from the corresponding 1,2-amino alcohol (Scheme 13). The introduction of allyl group on protected Boc-**61a,b**^{43,44} derivative was more laborious than expected. The allylation was done through palladium catalyst-allylation process using Pd(PPh₃)₄ (2 mol%) in THF

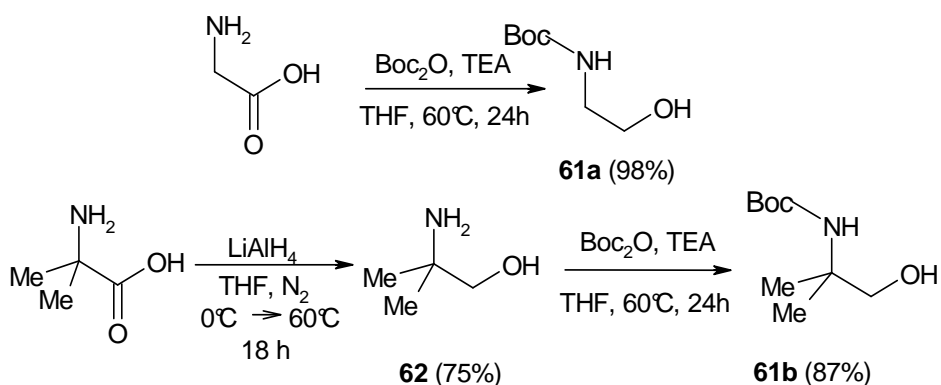
and allyl methyl carbonate.⁴⁵ In Scheme 13 is shown the mechanism of the outcome of the reaction. The species of Pd (0) coordinates to the double bond resulting in π -allyl complex, with removal of the carbonate group. Hydroxyl functionality at this point acts as a nucleophile, forming the allylether and expelling palladium which is again in the state of Pd (0).

Scheme 13



While glycinol is commercially available, its dimethyl-substituted analogue **62**⁴⁶ was prepared by reduction of the corresponding amino acid. The nitrogen protection of the 1,2-aminoalcohols afforded the two derivatives **61a,b** (Scheme 14).

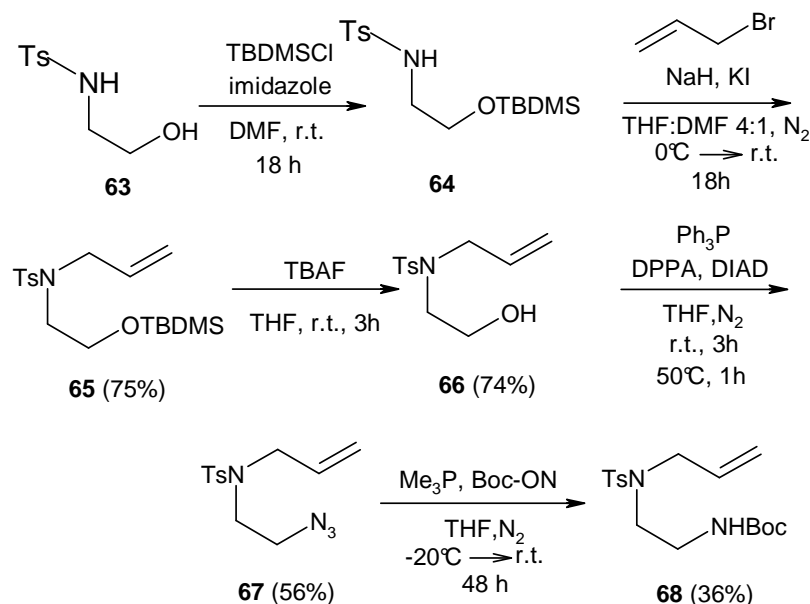
Scheme 14



Further, we investigated the feasibility of the reaction to N-allyl-N'-Boc ethylenediamine in order to access the oxazolidinones on fused piperazine ring. As the most suitable approach to access the desired compound **68** we envisaged the sequence depicted in Scheme 15. Firstly, the *N*-tosyl glycinol (**63**)⁴⁷ was

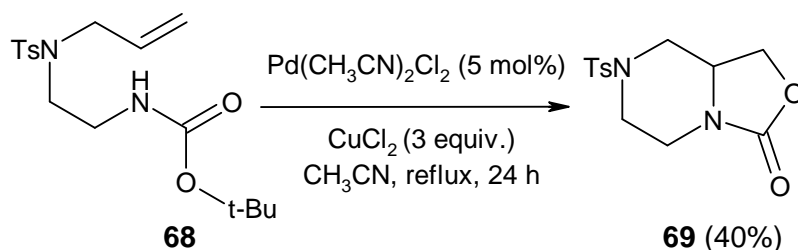
converted into the silyl derivative (**64**)⁴⁸ and subsequently treated with allyl bromide, sodium hydride as base, in a mixture of THF / DMF as solvent to give the product **65** in 75% yield. The protecting group was removed to form the alcohol **66**,⁴⁹ whose hydroxyl functionality was converted into an azide group via a Mitsunobu reaction yielding the derivative **67**. The formation of the Boc-protected amino group was achieved using Boc-ON, leading to the tosyl *N*-allyl-*N*-ethylenediamine **68**.

Scheme 15



The compound **68** was subjected to cyclization reaction under the aminocarboxylation conditions fruitfully used in case of derivatives **51**, **55** and **59**. The reaction led to the formation of a single product, which is a fused-bicycle ring structure that contains oxazolidinones and piperazine units. The product **69** was obtained in 40% yield (Scheme 16).

Scheme 16

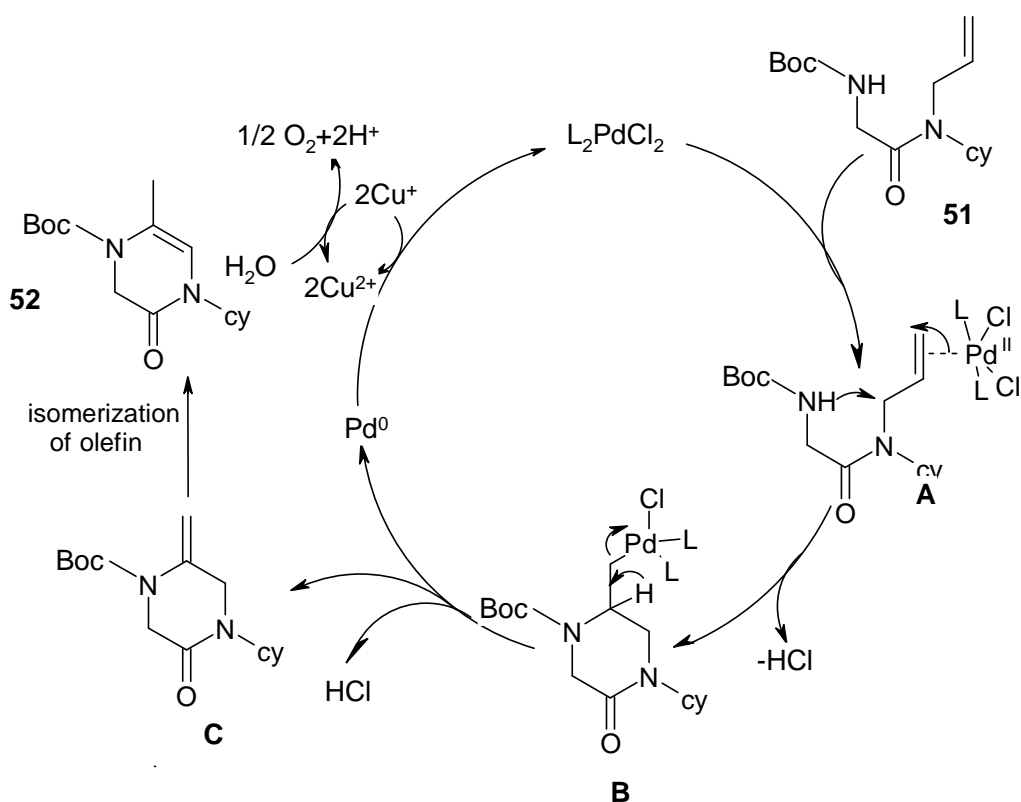


Although the mechanism leading to the dihydropyrazinone derivative **52** plausibly proceeds following a typical amination path, the aminocarboxylative

products arise from a more complex and unusual domino process, still unclear.

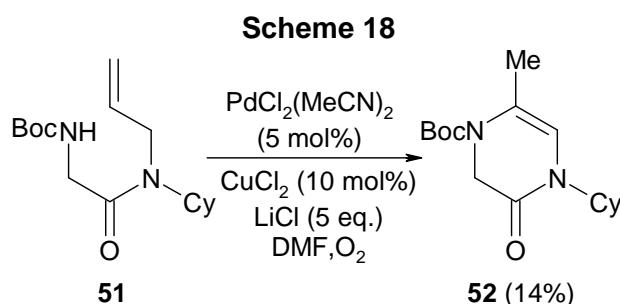
The amination process, shown in Scheme 17 for compound **51**, arose by initial coordination of the Pd(II) salt to the carbon-carbon double bond to give the π -olefin complex **A**, followed by the nucleophilic attack of the nitrogen atom with generation of the σ -alkyl-palladium complex **B**. Finally, β -hydride elimination produces the exo-methylene derivative **C**, neither isolated nor detected in the crude mixture, which underwent C-C double bond isomerization resulting in the dihydropyrazinone **52**.

Scheme 17

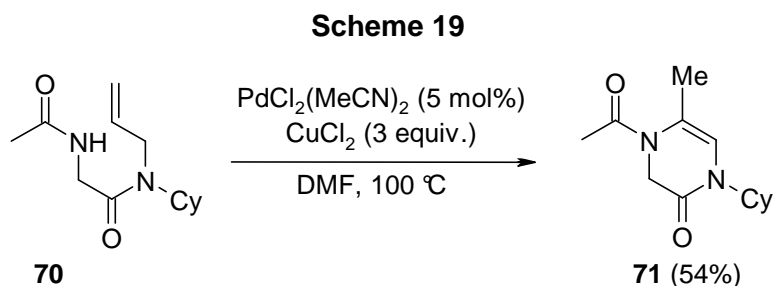


Product **53** is obtained via a domino aminocarboxylative process based on an initial carbon-nitrogen bond formation, followed by an intramolecular carboxylation reaction, involving the tertbutoxycarbonyl group. This is an unusual behavior of the carbamate oxygen which acts as a nucleophile in an oxidative Pd(II)-catalyzed reaction.

To have a better insight onto this domino aminocarboxylative process, two more reactions were studied. In a first instance, allylamide **51** was reacted using CuCl_2 (10 mol%)/ O_2 as oxidant in the presence of excess LiCl (5 equiv), leading only to **52** in low yield (14%) (Scheme 18).

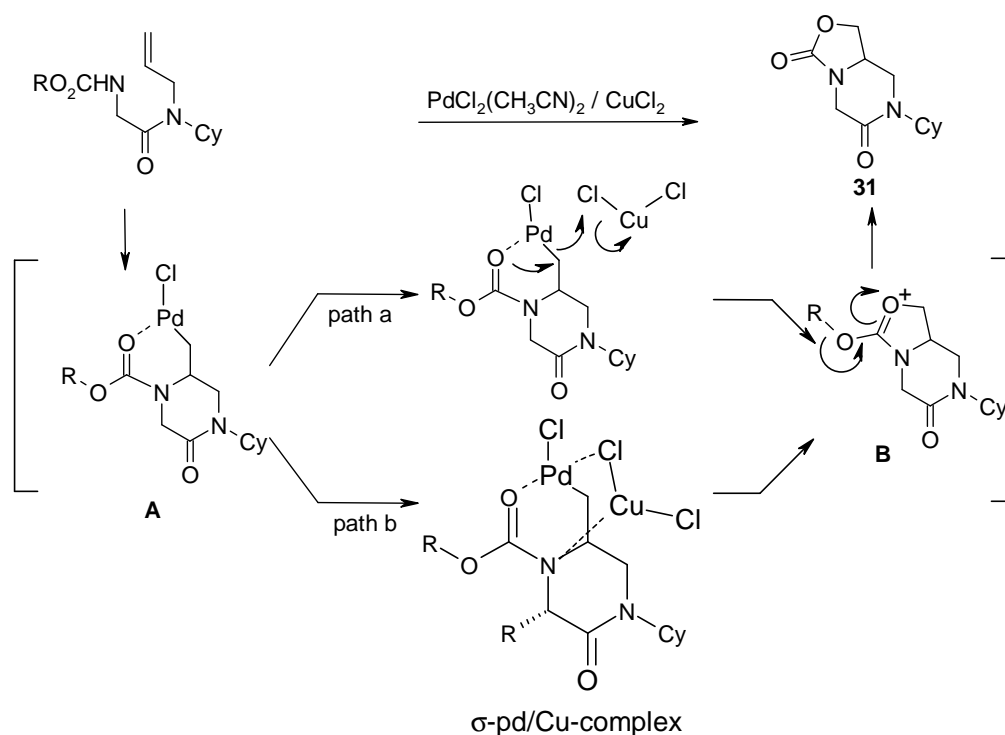


Subsequently, the cyclization of the acetyl glycine amide **70**, lacking the carbamate group, was investigated in the aminocarboxylative conditions. Also in this case, the reaction underwent only the β -hydride elimination process affording **71** (Scheme 19). In both reactions, a putatively stable chloro derivative, resulting from a nucleophilic substitution of the Pd(II) moiety by a chloride anion, was never detected.



A possible rationalization of the aminocarboxylative reaction consists in an oxidative CuCl_2 -assisted Pd-elimination from the σ -alkylpalladium complex **A**, arising from the initial aminopalladation (Scheme 20). In this case, the PdCl moiety behaves as a leaving group in the intramolecular nucleophilic attack of the carbamate oxygen, which generates the species **B**. CuCl_2 would inhibit the more straightforward palladium β -hydride elimination through a transient palladium oxidation (path a)⁵⁰ or by formation of a heterobimetallic σ -Pd/Cu complex (path b).⁵¹ Finally, **B** can evolve to the product **53** through the intervention of a nucleophile such as the chloride anion or water present in the reaction medium. However, further studies on mechanistic evaluations of this domino process are currently in progress.

Scheme 20



Conclusion

In summary, during the course of this Ph.D. thesis several goals concerning the access to fused-ring heterocycles were achieved. All the molecular targets were obtained in enantiopure form making use of reactions on ethylenic double bonds, very often in the presence of transition metal catalysts.

Firstly, the availability of the 2-allyl-piperidine synthon in enantiopure form allowed performing new synthetic methodologies which involve the olefin double bond in intramolecular reactions to increase the molecular complexity of piperidine-containing structures, suitable for further transformation. The different synthetic routes, in addition to the several ones already reported in the literature, make 2-allyl-piperidine as a valuable synthon for the Diversity Oriented Synthesis.

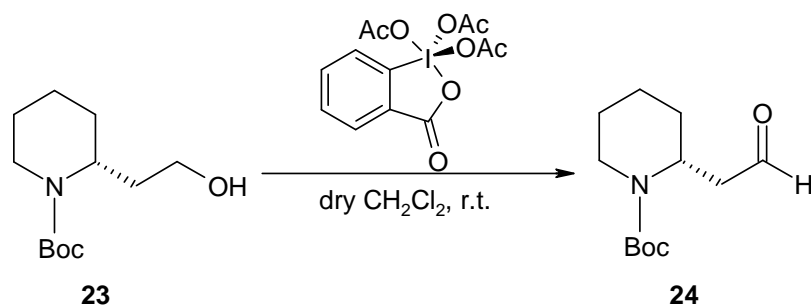
Secondly, we have reported the procedure for the synthesis of a new class of tetracyclic 1,4-benzodiazepin-5-ones, having an imidazo[2,1-c]pyrazolo[1,5-a][1,4]benzodiazepin-5,8-dione structure. The key steps upon which relies the synthetic protocol consist of *i*) a palladium-catalyzed heteroannulation of allenylamides, easily accessible from α -aminoacids, that gives rise to imidazole ring and *ii*) an intramolecular nitrilimine cycloaddition, providing the simultaneous formation of the 1,4-diazepine and pyrazole rings. Moreover, the novel scaffold of heteropolycyclic systems was accessible in enantiopure form, inferred by the starting α -aminoacids and well kept during the synthetic sequence.

Finally, we have discovered a divergent oxidative Pd(II)-catalyzed cyclization of carbamate protected aminoalkenes, strictly dependent on the amount of CuCl_2 (catalytic vs stoichiometric). The domino aminocarboxylative cyclization leads to bicyclic oxazolidinones via a C-O bond-forming reductive carboxylation triggered by stoichiometric CuCl_2 , after an initial aminopalladation step. This is, to the best of our knowledge, the first example of oxidative Pd(II)-catalyzed reactions involving the oxygen of a carbamate group as nucleophile.

3. Experimental section

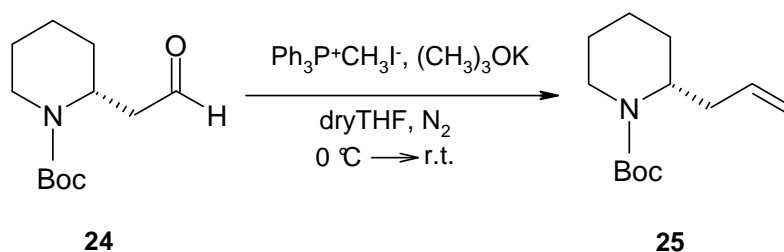
Melting points were determined by the capillary method with a Büchi B-540 apparatus. Optical rotations were measured with a Jasco P-1010 polarimeter at 25°C. ¹H NMR and ¹³C NMR spectra were recorded with an AVANCE 400 Bruker spectrometer. The chemical shifts are given in ppm and the coupling constant in Hz.

Synthesis of (*R*)-Tert-butyl 2-(2-oxoethyl)piperidine-1-carboxylate



To a solution of Dess Martin 97% (1.35 g, 3.10 mmol) in dry CH₂Cl₂ (23 mL) **23** (0.64 g, 2.82 mmol) was added. The reaction mixture was left at room temperature under agitation for 3 hours. Then Et₂O (29 mL) and NaOH 1 mol/L (29 mL) were added. The reaction mixture was left under agitation for other 10 minutes. The organic phase was washed by NaOH 1 mol/L (29 mL) and then by water (40 mL), the organic phase was dried with Na₂SO₄ and the solvent is evaporated at reduced pressure. We obtained colorless oil with 90 % yield.

Synthesis of (*R*)-Tert-butyl 2-allylpiperidine-1-carboxylate



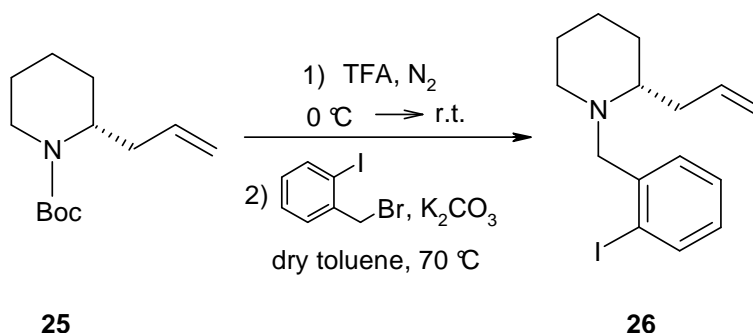
To a suspension of Ph₃P⁺CH₃I⁻ (2.06 g, 5.09 mmol) in dry THF (25 mL) under nitrogen atmosphere at 0 °C *t*-BuOK (0.57 g, 5.09 mmol) was added. The mixture was left at 0°C for 10 minutes. **24** (0.50 g, 2.21 mmol) dissolved in dry THF (8 mL) was added drop by drop, the reaction mixture was left under agitation at room temperature for 20 hours. THF was evaporated and water (15 mL) was added. Then it was extracted by AcOEt (30/25/20 mL) the organic phase was dried with Na₂SO₄ and then evaporated. The crude **25** was purified by column chromatography (hexane/AcOEt 24:1).

Yield = 72%

Colorless oil

[α]_D²⁵ = +49.5 (c = 0.910 g/L, CHCl₃)

Synthesis of compound (*R*)-2-Allyl-1-(2-iodo-benzyl)-piperidine



To compound **25** (0.355 g, 1.58 mmol) trifluoroacetic acid (1.8 mL, 23.65 mmol) was added drop by drop under nitrogen atmosphere at 0 °C. The reaction mixture was left under vigorous stirring for 3 h at room temperature. Trifluoroacetic acid was evaporated. The residue was dissolved in anhydrous toluene (4 mL) and was added drop by drop to a suspension of K₂CO₃ (6.45 g, 46.7 mmol) and 2-iodo-benzyl bromide (468 mg, 1.58 mmol) in anhydrous toluene (12 mL) at 40 °C. Then the reaction mixture was heated to 70 °C for one night. Ice-cold water (22 mL) was added to the reaction mixture and then was extracted by Et₂O (2 x 17 mL). The organic phase was dried over Na₂SO₄ filtered and concentrated under vacuum. The crude **26** was purified by silica gel column chromatography (EdP/AcOEt 98:2).

Yield: 94%

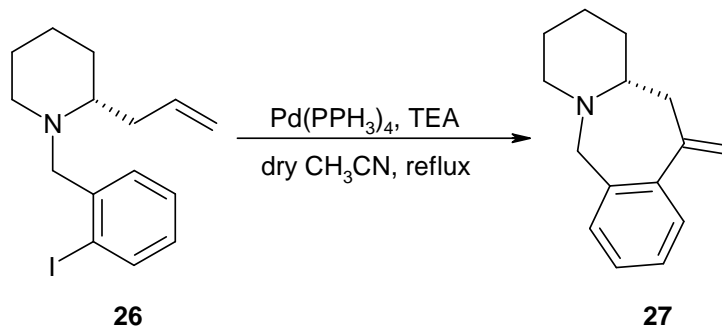
Yellow oil

$[\alpha]_{\text{D}}^{25} = +31.1$ (c = 1.093g/L, CHCl₃)

¹H-NMR (CDCl₃) δ 1.32-1.61 (4H, m), 1.63-1.78 (2H, m), 2.17-2.28 (1H, m), 2.30-2.45 (2H, m), 2.50-2.62 (1H, m), 2.68-2.76 (1H, m), 3.39, 3.91 (2H, AB system, *J* = 14.8 Hz), 5.03 (1H, d, *J* = 9.6 Hz), 5.05 (1H, d, *J* = 17.6 Hz), 5.84 (1H, ddt, *J* = 9.6, 17.6, 7.1 Hz), 6.94 (1H, dd, *J* = 7.3, 7.8 Hz), 7.33 (1H, dd, *J* = 7.3, 7.5 Hz), 7.54 (1H, d, *J* = 7.5 Hz), 7.81 (1H, d, *J* = 7.8 Hz)

¹³C-NMR (CDCl₃) δ 23.3 (t), 26.1 (t), 30.6 (t), 35.9 (t), 51.7 (t), 60.8 (d), 62.9 (t), 100.6 (s), 116.8 (t), 128.5 (d), 128.8 (d), 130.5 (d), 136.7(d), 139.6 (d), 142.6 (s)

**Synthesis of (*R*)-11-Methylene-1,2,3,4,6,11,12,12a-octahydro-
benzo[*e*]pyrido[1,2-*a*]azepine**



To a solution **26** (0.32 g, 0.931mmol) in anhydrous acetonitrile (10mL) Pd(PPh₃)₄ 99% (0.12 g, 0.0931 mmol) and triethylamine (389 mL, 2.79 mmol) were added. The reaction mixture was heated under reflux for 2 h, the solvent was evaporated under reduced pressure. Water (10 mL) was added to the residue and it was extracted by CH₂Cl₂ (2 x 16 mL). The organic phase was dried over Na₂SO₄ filtered and concentrated under vacuum. The crude **27** was purified by silica gel column chromatography (EdP/AcOEt 5:1).

Yield: 68%

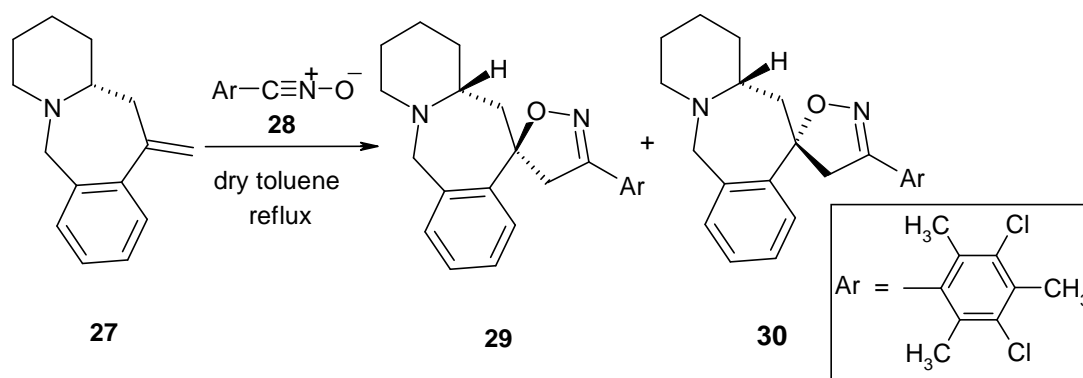
Dark yellow oil

$[\alpha]_D^{25} = -41.8$ (c = 0.250g/L, CHCl₃)

¹H-NMR (CDCl₃) δ 1.32-1.40 (1H, m), 1.54-1.77 (5H, m), 2.35-2.47 (2H, m), 2.48-2.62 (2H, m), 2.88-2.96 (1H, m), 3.74, 3.80 (2H, AB system, *J* = 14.9 Hz), 5.09 (1H, s), 5.25 (1H, s), 7.10 (1H, d, *J* = 8.4 Hz), 7.16-7.26 (2H, m), 7.34 (1H, d, *J* = 8.4 Hz)

¹³C-NMR (CDCl₃) δ 24.0 (t), 26.3 (t), 30.1 (t), 32.8 (t), 42.0 (t), 55.8 (t), 62.2 (t), 64.5 (d), 114.2 (t), 127.7 (d), 127.8 (d), 129.4 (d), 136.3 (s), 142.7 (s), 148.3 (s)

Cycloaddition reaction of 5 with 3,5-Dichloro-2,4,6-trimethylbenzonitriloxide (28).



To a solution **27** (61.0 mg, 0.286 mmol) in dry toluene (1.5 mL) **28** (65.8 mg, 0.286 mmol) was added. The reaction mixture was heated under reflux for 12 h; the solvent was evaporated under reduced pressure. The crude was purified by silica gel column chromatography (AcOEt/MeOH 98:2).

Major Diastereoisomero:

(11S,12aR)-3'-(3,5-Dichloro-2,4,6-trimethylphenyl)-spiro{benzo[e]pyrido[1,2-a]azepine-11,5'-isoxazole} (29).

Yield: 42%

White crystal

M.p. 185 - 186°C

$[\alpha]_D^{25} = +33.3$ (c = 0.271g/L, CHCl₃)

¹H-NMR (CDCl₃) δ 1.15-1.25 (2H, m), 1.38-1.52 (1H, m), 1.58-1.74 (3H, m), 2.13-2.35 (2H, m), 2.19 (3H, s), 2.24 (3H, s), 2.38-2.49 (2H, m), 2.53 (3H, s), 2.80-2.89 (1H, m), 3.29, 3.39 (2H, AB system, J = 17.5 Hz), 3.62, 4.29 (2H, AB system, J = 14.8 Hz), 7.14 (1H, d, J = 7.4 Hz), 7.25 -7.43 (2H, m), 7.63 (1H, d, J = 7.4 Hz).

¹³C-NMR (CDCl₃) δ 18.5 (q), 19.4 (q), 24.7 (t), 26.6 (t), 33.5 (t), 48.0 (t), 54.4 (t), 55.2 (t), 59.1 (d), 59.4 (t), 90.8 (s), 125.9

(d), 128.5 (d), 129.2 (s), 130.3 (s), 130.9 (d), 133.7 (s), 133.9 (s), 135.9 (s), 142.8 (s), 156.6 (s)

Minor Diastereoisomer

**(11R,12aR)-3'-(3,5-Dichloro-2,4,6-trimethylphenyl)-
spiro{benzo[e]pyrido[1,2-a]azepine-11,5'-isoxazole} (30).**

Yield: 29%

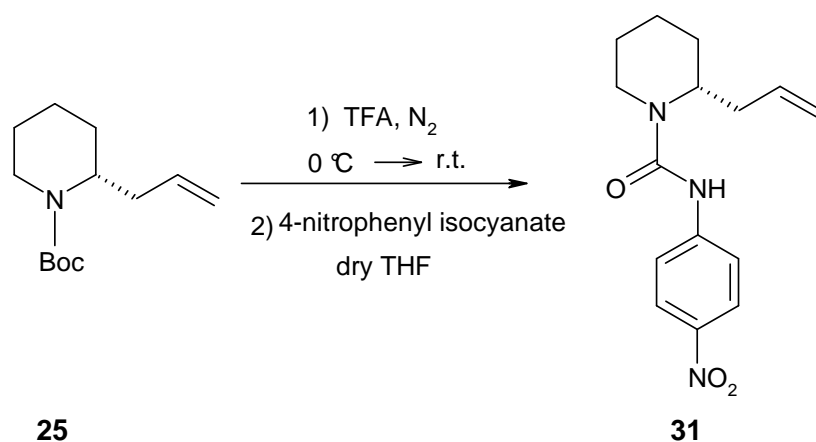
Brown oil

$[\alpha_d]_D^{25} = -37.7$ (C = 0.105g/L, CHCl₃)

¹H-NMR (CDCl₃) □□□ δ 1.23-1.72 (7H, m), 1.74-1.83 (1H, m), 2.02-2.09 (1H, m), 2.15 (6H, s), 2.42-2.51 (1H, m), 2.52 (3H, s), 2.78-2.87 (1H, m), 3.02, 3.61 (2H, AB system, *J* = 17.1 Hz), 3.63, 3.76 (2H, AB system, *J* = 14.5 Hz), 7.20 (1H, d, *J* = 7.7 Hz), 7.22-7.36 (2H, m), 7.73 (1H, d, *J* = 7.7 Hz)

¹³C-NMR (CDCl₃) δ 18.4 (q), 19.4 (q), 22.9 (t), 26.1 (t), 30.1 (t), 34.1 (t), 43.8 (t), 49.4 (t), 62.1 (d), 63.8 (t), 90.3 (s), 125.2 (d), 128.3 (d), 129.3 (s), 131.9 (d), 133.6 (s), 133.9 (s), 135.9 (s), 144.3 (s), 157.1 (s)

Synthesis of 2-Allyl-N-(4-nitrophenyl)piperidine-1-carboxamide



To compound **25** (0.355 g, 2.58 mmol) trifluoroacetic acid (1.8 mL, 23.65 mmol) was added drop by drop under nitrogen atmosphere at 0°C. The reaction mixture was left under vigorous stirring for 3 h at room temperature. Trifluoroacetic acid was evaporated. The residue was dissolved in anhydrous THF (4 mL) and 4-nitrophenyl isocyanate (423 mg, 2.58 mmol) was added. Then the reaction mixture was left under agitation at room temperature all night. The solvent was evaporated, brine (22 mL) was added to the residue and then the mixture was extracted by CH₂Cl₂ (2 x 17 mL). The organic phase was dried over Na₂SO₄ filtered and concentrated under vacuum. The crude **31** was purified by silica gel column chromatography (EdP/AcOEt 7:3)

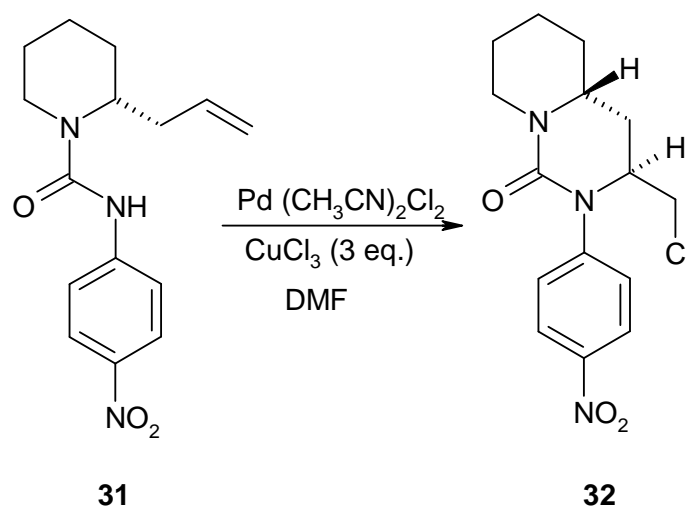
Yield: 72%

Yellow oil

¹H-NMR (CDCl₃) δ 1.62-1.69 (6H, m), 2.27-2.33 (1H, m), 2.49-2.55 (1H, m), 3.96 (1H, d, *J* = 16 Hz), 4.31 (1H, s, br), 5.10 (2H, dd, *J* = 18.8, 28 Hz), 5.77 (1H, q), 7.12 (1H, s, br), 7.51 (2H, d, *J* = 9.2 Hz), 8.11 (2H, d, *J* = 2.7 Hz)

¹³C-NMR (CDCl₃) δ 18.6 (t), 25.5 (t), 28.1 (t), 34.4 (t), 39.6 (t), 51.5 (d), 117.8 (t), 118.4 (d), 124.9 (d), 134.9 (d), 142.1 (s), 146.1 (s), 154.1 (s)

Synthesis of (3*S*, 4*R*)-3-(Chloromethyl)-2-(4-nitrophenyl)octahydro-1*H*-pyrido[1,2-*c*]pyrimidin-1-one



CuCl₂ 98 % (0.13 g, 1 mmol.) and Pd(CH₃CN)₂Cl₂ 99 % (0.01 g, 0.05 mmol.) were dissolved in dry DMF (10 mL). **31** (0.3 g, 1 mmol.) dissolved in dry DMF (10 mL) was added, the reaction mixture was left under agitation at 100°C for 2 h and 30 min. Brine was added to the reaction mixture and it was extracted 3 times with CH₂Cl₂. The organic phase was dried with Na₂SO₄ and the solvent is evaporated at reduced pressure. The obtained crude was purified by a column chromatography (EdP/AcOEt 1:1)

Yield: 32%

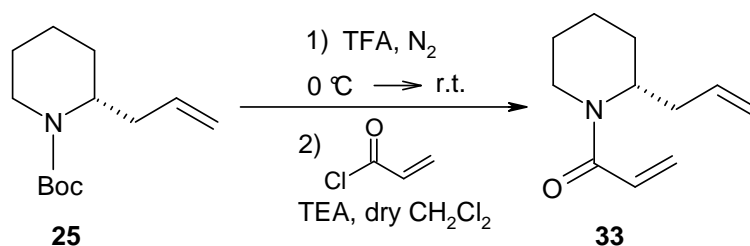
Red oil

[α_D]²⁵: -7.6 (c = 0.37 g/L, CHCl₃)

¹H-NMR (CDCl₃) δ 1.52-1.79 (7H, m), 2.53 (1H, m), 2.64 (1H, t), 3.44 (1H, m), 3.59 (1H, t), 3.7 (1H, dd, *J* = 4.2, 4.3 Hz), 4.09 (1H, m), 4.61 (1H, d, *J* = 14.6 Hz), 7.44 (2H, d, *J* = 15.2 Hz), 8.20 (2H, d, *J* = 15.2 Hz)

¹³C-NMR (CDCl₃) δ 23.7 (t), 25.1 (t), 31.1 (t), 33.6 (t), 42.6 (t), 43.7 (t), 50.8 (d), 57.3 (d), 124.4 (d), 125.4 (d), 144.4 (s), 148.7 (s), 152.8 (s)

Synthesis of (*R*)-1-(2-Allylpiperidin-1-yl) prop-2-en-1-one



To the compound **25** (0.31 g, 1.39 mmol) trifluoro acetic acid (1.6 mL, 20.83 mmol) was added at 0 °C under nitrogen. The reaction mixture was left at room temperature for 3 hours. The acid was evaporated. The amine was dissolved in dry CH₂Cl₂ (3 mL) and the triethylamine (581 μL, 4.17 mmol) and acryloyl chloride (0.15 g, 1.67 mmol) were added. The reaction mixture was left at room temperature for one night. Water (3 mL) was added. And the mixture was extracted by CH₂Cl₂ (5 mL). The organic phase was dried by Na₂SO₄ and evaporated to obtain yellow oil **33** that is purified by column chromatography. (EdP/AcOEt 4:1).

Yield: 70%

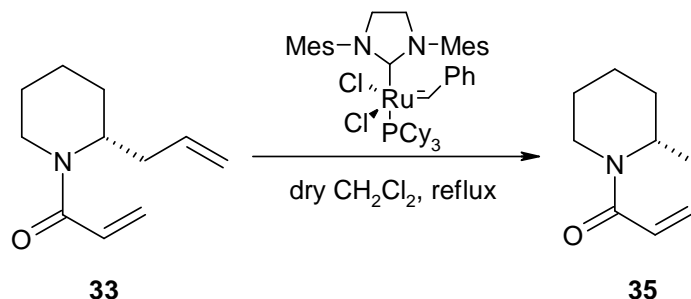
Colorless oil

$[\alpha_D]^{25} = +66.5$ (c = 0.632 g/L, CHCl₃)

¹H-NMR (CDCl₃, 50°C) δ 1.38-1.52 (1H, m), 1.60-1.74 (5H, m), 2.27-2.40 (1H, m), 2.44-2.53 (1H, m), 2.93 (1H, s br), 4.20 (1H, s br), 4.52 (1H, s br), 5.03-5.14 (2H, m), 5.61 (1H, d, *J* = 10.7 Hz), 5.69-5.80 (1H, m), 6.19 (1H, d, *J* = 16.9 Hz), 6.56 (1H, dd, *J* = 10.7, 16.9 Hz)

¹³C-NMR (CDCl₃, 50 °C) δ 19.3 (t), 26.0 (t), 29.9 (t), 35.0 (t), 39.6 (t), 50.8 (d), 117.5 (t), 126.7 (t), 129.2 (d), 135.0 (d), 166.4 (s)

Synthesis (*R*)-7,8,9,9a-Tetrahydro-1*H*-quinolizin-4(6*H*)-one



To a solution **33** (67.40 mg, 0.376 mmol) in dry CH₂Cl₂ (7 mL) Grubbs of second-generation (16.00 mg, 0.019 mmol) was added. The reaction mixture was heated under reflux for 2 hours, and then the solvent was evaporated. Brown oil was obtained and it was purified by column chromatography (EdP/AcOEt 3:1).

Yield: 98%

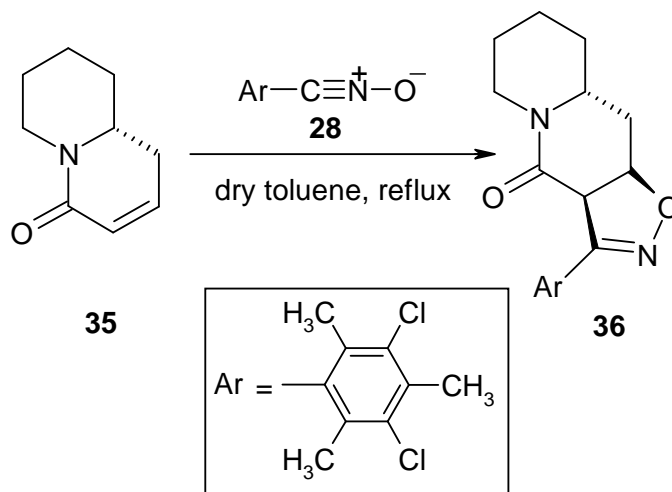
Yellow oil

$[\alpha]_{\text{D}}^{25} = -254.4$ (c = 0.533 g/L, CHCl₃)

¹H-NMR (CDCl₃) δ 1.37-1.49 (3H, m), 1.65-1.78 (2H, m), 1.80-1.86 (1H, m), 2.12-2.23 (1H, m), 2.44-2.55 (2H, m), 3.30-3.46 (1H, m), 4.48 (1H, d, *J* = 12 Hz), 5.85 (1H, d, *J* = 9.8 Hz), 6.41-6.48 (1H, m),

¹³C-NMR (CDCl₃) δ 24.3 (t), 25.2 (t), 31.4 (t), 33.7 (t), 43.3 (t), 55.1 (d), 124.9 (d), 138.5 (d), 165.8 (s)

(9a*R*)-3-(3,5-Dichloro-2,4,6-trimethylphenyl)-7,8,9,9a,10,10a-hexahydro-3a*H*-isoxazolo[5,4-*b*]quinolizin-4(6*H*)-one



To a solution **35** (56.8 mg, 0.376 mmol) in dry toluene (2.0 mL) **28** (86.5 mg, 0.376 mmol) was added. The reaction mixture was left under reflux for 18 hours, and then the solvent was evaporated. Brown oil was obtained and it was purified by column chromatography. (EdP/AcOEt 6:4)

Yield: 68%

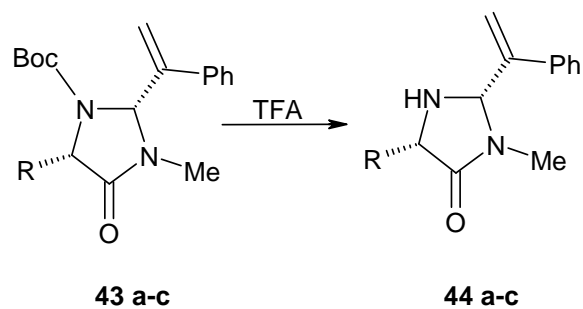
Beige oil.

$[\alpha_d]_D^{25} = -83.0$ (c = 0.912 g/L, CHCl_3)

$^1\text{H-NMR}$ (CDCl_3) δ 1.26-1.37 (1H, m), 1.41-1.50 (2H, m), 1.74-1.81 (1H, m), 1.83-2.00 (3H, m), 2.14 (3H, s), 2.33 (3H, s), 2.34-2.37 (1H, m), 2.38-2.42 (1H, m), 2.52 (3H, s), 3.60-3.68 (1H, m), 4.16 (1H, d, $J = 10.2$ Hz), 4.43-4.50 (1H, m), 5.06-5.13 (1H, m)

$^{13}\text{C-NMR}$ (CDCl_3) δ 18.9 (q), 19.4 (q), 23.3 (t), 25.0 (t), 33.2 (t), 33.3 (t), 42.8 (t), 50.5 (d), 57.6 (d), 77.4 (d), 128.4 (s), 133.1 (s), 134.4 (s), 136.1 (s), 157.4 (s), 163.1 (s)

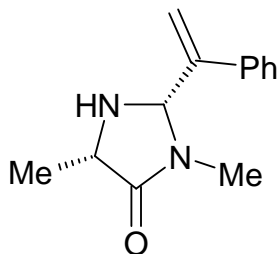
Synthesis of 44



a R = Me, **b** R = *i*-Pr, **c** R = Bn

A solution of (2*R*,5*S*)-**43**⁵² (2.55 mmol) in TFA (6 mL) was stirred at room temperature for 3 hours, then the solvent was evaporated under reduced pressure and the residue purified on column chromatography. (EdP/AcOEt 4:1).

(2S,5S)-2-(1-Phenylvinyl)-3,5-dimethyl-imidazolidin-4-one (44a)



Yield: 93%

Pale yellow oil

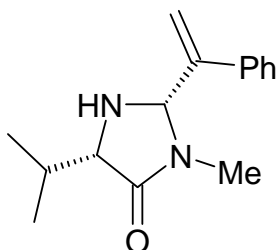
$[\alpha]_D^{25}$: +27.5 (c = 0.37 g/L, CHCl₃)

IR: 1670 cm⁻¹, 3430 cm⁻¹

¹H-NMR (CDCl₃) δ 1.38 (3H, d, *J* = 7.1 Hz), 3.04 (3H, s), 4.08 (1H, q, *J* = 7.1 Hz), 5.71 (1H, s), 5.72 (1H, s), 5.89 (1H, s), 6.57 (1H, br s), 7.28 - 7.30 (2H, m), 7.42 - 7.48 (3H, m)

¹³C-NMR (CDCl₃) δ 14.7 (q), 28.1(q), 54.1 (d), 74.2 (d), 122.9 (t), 126.9(d), 129.2 (d), 129.8 (d), 134.5 (s), 139.5 (s), 169.3 (s).

(2S,5S)-2-(1-Phenylvinyl)-5-isopropyl-3-methyl-imidazolidin-4-one (44b)



Yield: 95%

Cream crystals

M.p: 93°C

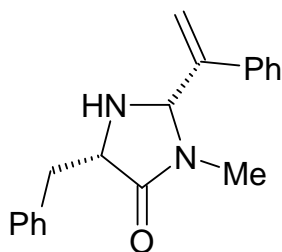
$[\alpha]_D^{25}$: +22.5 (c = 0.45 g/L, CHCl₃)

IR: 1664 cm⁻¹, 3428 cm⁻¹

¹H-NMR (CDCl₃) δ 0.87 (3H, d, *J* = 7.0 Hz), 1.00 (3H, d, *J* = 7.1 Hz),
2.39 (1H, dq, *J* = 3.9, 7.0, 7.1 Hz), 3.05 (3H, s),
4.19 (1H, d, *J* = 3.9 Hz), 5.74 (1H, s), 5.87 (1H, s),
5.98 (1H, s), 7.28 - 7.32 (2H, m), 7.41 - 7.50 (3H,
m), 11.07 (1H, br s)

¹³C-NMR (CDCl₃) δ 16.4 (q), 18.2 (q), 28.1 (d), 28.9 (q), 60.1 (d), 74.6
(d), 124.7 (t), 127.5 (d), 129.9 (d), 130.7 (d), 133.6
(s), 139.3 (s), 168.6 (s).

(2S,5S)-5-Benzyl-3-methyl-2-(1-phenylvinyl)imidazolidin-4-one (44c)



Yield: 93%

White crystal

M.p. 91 °C

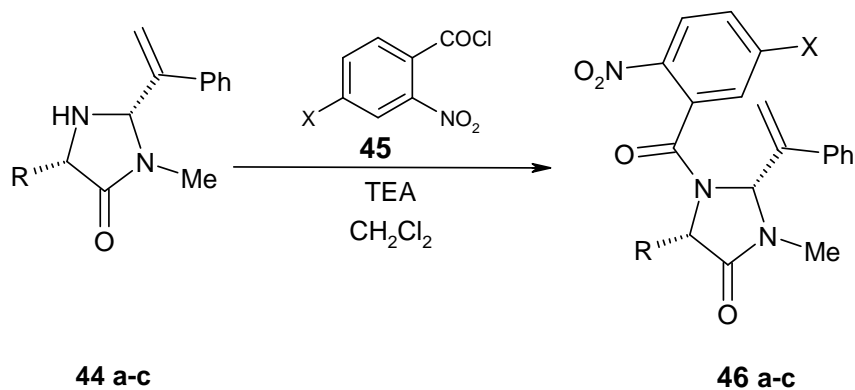
$[\alpha]_D^{25}$: -30.3 (c = 0.27 g/L, CHCl₃)

IR: 1682 cm⁻¹, 3444 cm⁻¹

¹H-NMR (CDCl₃) δ 2.86 (3H, s), 3.13 - 3.20 (2H, m), 4.14 - 4.18 (1H, m), 5.14 (1H, s), 5.38 (1H, s), 5.54 (1H, s), 5.75 (1H, br s), 7.08 - 7.36 (10H, m), 11.2 (1H, br s)

¹³C-NMR (CDCl₃) δ 28.8 (d), 34.3 (t), 59.3 (q), 74.9 (d), 124.1 (t), 127.3 (d), 129.2 (d), 129.8 (d), 129.9 (d), 130.2 (d), 130.4 (d), 132.1 (s), 134.0 (s), 139.6 (s), 168.4 (s).

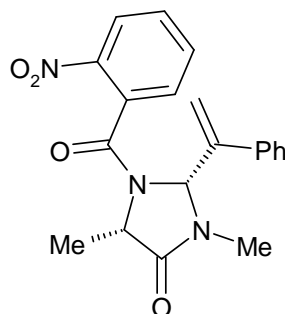
Synthesis of compound 46



a R = Me, **b** R = *i*-Pr, **c** R = Bn

To a solution of **44** (0.7 mmol) in dry CH_2Cl_2 (3 mL) TEA (0.51 mL, 3.64 mmol) was added. The mixture was cooled at 0 °C and a solution of **45** in dry CH_2Cl_2 (2 mL) was dropped under stirring. After 24 hours at room temperature the mixture was washed with 5% HCl (30 mL) and with aq. NaHCO_3 (30 mL) then the organic layer was dried over Na_2SO_4 . The solvent was evaporated and the crude mixture was purified on silica gel column chromatography (EdP/AcOEt 1:1) to give **46**.

(2*R*,5*S*)-2-(1-Phenylvinyl)-3,5-dimethyl-1-(2-nitrobenzoyl)-imidazolidin-4-one
(46a)



Yield: 51%

Pale yellow crystals

M.p: 160°C

$[\alpha]_D^{25}$: -10.20 (c = 0.10 g/L, CHCl₃)

IR: 1652 cm⁻¹, 1704 cm⁻¹.

(mixture of two conformers in ratio 2:1)

Major conformer

¹H-NMR (CDCl₃) δ 0.41 (3H, d, *J* = 6.9 Hz), 3.04 (3H, s), 3.78 (1H, q, *J* = 6.9 Hz), 5.56 (1H, s), 5.77 (1H, s), 6.06 (1H, s), 6.98 - 8.26 (9H, m)

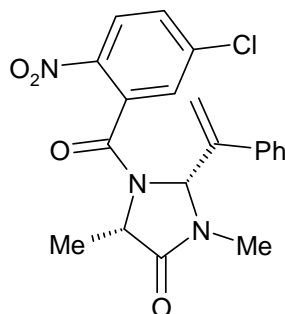
¹³C-NMR (CDCl₃) δ 18.2 (q), 27.5 (q), 55.6 (d), 79.2 (d), 122.3 (t), 124.9 (d), 128.0 (d), 128.8 (d), 129.0 (d), 129.4 (d), 131.0 (d), 132.0 (s), 134.8 (d), 138.1 (s), 144.4 (s), 144.8 (s), 167.5 (s), 170.2 (s).

Minor conformer

¹H-NMR (CDCl₃) δ 1.22 (3H, d, *J* = 6.9 Hz), 2.84 (3H, s), 4.65 (1H, q, *J* = 6.9 Hz), 4.69 (1H, s), 5.13 (1H, s), 5.31 (1H, s), 6.98 - 8.26 (9H, m)

¹³C-NMR (CDCl₃) δ 16.9 (q), 27.4 (q), 55.8 (d), 80.1 (d), 122.4 (t), 125.2 (d), 128.0 (d), 128.9 (d), 129.2 (d), 129.7 (d), 130.5 (d), 132.2 (s), 134.8 (d), 136.8 (s), 144.4 (s), 144.9 (s), 167.5 (s), 170.9 (s).

**(2*R*,5*S*)-2-(1-Phenylvinyl)-3,5-dimethyl-1-(5-chloro-2-nitrobenzoyl)-
imidazolidin-4-one (46 aa)**



Yield: 55%

Pale yellow crystals

M.p.: 62°C

$[\alpha]_D^{25}$: -13.50 (c = 26.7 g/L, CHCl₃)

IR: 1640 cm⁻¹, 1690 cm⁻¹

(mixture of two conformers in ratio 2:1)

Major conformer

¹H-NMR (CDCl₃) δ 0.40 (3H, d, *J* = 6.8 Hz), 2.97 (3H, s), 3.74 (1H, q, *J* = 6.8 Hz), 5.50 (1H, s), 5.70 (1H, s), 5.98 (1H, s), 6.97 - 8.12 (8H, m)

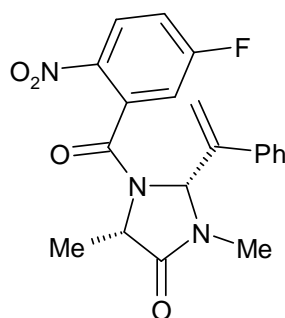
¹³C-NMR (CDCl₃) δ 17.8 (q), 27.1 (q), 55.0 (d), 78.6 (d), 121.8 (t), 126.0 (d), 126.4 (d), 127.3 (d), 128.4 (d), 128.7 (d), 130.6 (d), 133.0 (s), 137.5 (s), 141.1 (s), 142.8 (s), 143.8 (s), 165.3 (s), 169.4 (s).

Minor conformer

¹H-NMR (CDCl₃) δ 1.21 (3H, d, *J* = 6.5 Hz), 2.81 (3H, s), 4.57 (1H, q, *J* = 6.5 Hz), 4.75 (1H, s), 5.20 (1H, s), 5.32 (1H, s), 6.98 - 8.12 (8H, m)

¹³C-NMR (CDCl₃) δ 16.4 (q), 26.9 (q), 55.3 (d), 79.4 (d), 122.1 (t), 126.0 (d), 126.4 (d), 127.3 (d), 128.5 (d), 128.9 (d), 130.6 (d), 133.1 (s), 136.2 (s), 141.1 (s), 142.7 (s), 144.2 (s), 165.3 (s), 170.1 (s).

**(2*R*,5*S*)-2-(1-Phenylvinyl)-3,5-dimethyl-1-(5-fluoro-2-nitrobenzoyl)-
imidazolidin-4-one (46ab)**



Yield: 60%

Yellow oil

$[\alpha]_D^{25}$: -4.90 (c = 5.2 g/L, CHCl₃)

IR: 1638 cm⁻¹, 1702 cm⁻¹

(mixture of two conformers in ratio 2:1)

Major conformer

¹H-NMR (CDCl₃) δ 0.45 (3H, d, *J* = 6.9 Hz), 3.04 (3H, s), 3.77 (1H, q, *J* = 6.9 Hz), 5.57 (1H, s), 5.76 (1H, s), 6.03 (1H, s), 6.86 - 8.30 (8H, m)

¹³C-NMR (CDCl₃) δ 17.8 (q), 27.0 (q), 54.9 (d), 78.6 (d), 116.7 (dd, *J*_{C-F} = 23.2 Hz), 117.6 (dd, *J*_{C-F} = 23.0 Hz), 121.8 (t), 127.4 (d), 128.0 (dd, *J*_{C-F} = 9.9 Hz), 128.4 (d), 128.7 (d), 134.4 (d, *J*_{C-F} = 8.0 Hz), 137.5 (s), 140.7 (s), 143.8 (s), 165.2 (d, *J*_{C-F}¹ = 259.6 Hz), 169.4 (s), 170.1 (s).

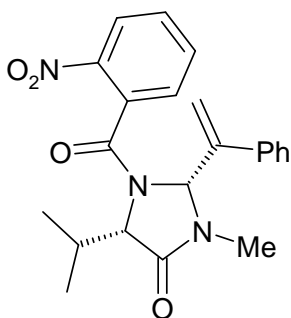
Minor conformer

¹H-NMR (CDCl₃) δ 1.27 (3H, d, *J* = 6.9 Hz), 2.86 (3H, s), 4.64 (1H, q, *J* = 6.9 Hz), 4.80 (1H, s), 5.25 (1H, s), 5.33 (1H, s), 6.86 - 8.30 (8H, m)

¹³C-NMR (CDCl₃) δ 16.4 (q), 26.9 (q), 55.3 (d), 79.2 (d), 115.9 (dd, *J*_{C-F} = 23.4 Hz), 117.5 (dd, *J*_{C-F} = 22.9 Hz), 122.0 (t), 127.3 (d), 127.7 (dd, *J*_{C-F} = 9.7 Hz), 128.4 (d), 128.8 (d), 134.5 (d, *J*_{C-F} = 8.0 Hz), 136.3 (s), 140.6

(s), 144.4 (s), 165.4 (d, $J_{C-F}^1 = 260.2$ Hz), 169.3 (s),
169.9 (s).

**(2*R*,5*S*)-2-(1-Phenylvinyl)-5-isopropyl-3-methyl-1-(2-nitrobenzoyl)-
imidazolidin-4-one (46b)**



Yield: 75%

Yellow oil

$[\alpha_D]^{25}$: -18.30 (c = 0.21 g/L, CHCl₃)

IR: 1665 cm⁻¹, 1688 cm⁻¹

MS: *m/z* 393 (M⁺).

(mixture of two conformers in ratio 3:1)

Major conformer

¹H-NMR (CDCl₃) δ 0.92 (3H, d, *J* = 5.9 Hz), 1.11 (3H, d, *J* = 6.6 Hz),
1.44 (1H, dq, *J* = 5.9, 6.6, 9.2 Hz), 2.84 (3H, s),
4.40 (1H, d, *J* = 9.2 Hz), 4.86 (1H, s), 5.34 (1H, s),
5.54 (1H, s), 6.92 - 6.94 (2H, m), 7.23 - 7.31 (3H,
m), 7.31 - 7.38 (2H, m), 7.54 - 7.63 (1H, m), 8.16 -
8.20 (1H, m)

Minor conformer

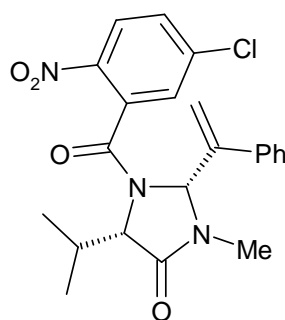
¹H-NMR (CDCl₃) δ 0.51 (3H, d, *J* = 5.9 Hz), 0.63 (3H, d, *J* = 6.3 Hz),
1.23 - 1.34 (1H, m), 2.94 (3H, s), 3.60 - 3.65 (1H,
m), 5.54 (1H, s), 5.67 (1H, s), 6.18 (1H, s), 6.91 -
8.24 (9H, m)

¹H-NMR (DMSO, T = 100°C) δ 0.83 (3H, d, *J* = 6.9 Hz), 0.89 (3H, d, *J* = 6.7
Hz), 1.55 (1H, dq, *J* = 6.7, 6.9, 7.3 Hz),
2.77 (3H, s), 4.06 (1H, d, *J* = 7.3 Hz), 5.15
(1H, s), 5.27 (1H, s), 5.71 (1H, s), 7.11 - 7.12

(2H, m), 7.13 - 7.31 (3H, m), 7.46 (1H, dd, $J = 1.3, 7.5$ Hz), 7.68 (1H, ddd, $J = 1.3, 7.7, 8.2$ Hz), 7.76 (1H, ddd, $J = 1.1, 7.5, 7.7$ Hz), 8.16 (1H, dd, $J = 1.1, 8.2$ Hz)

^{13}C -NMR (DMSO) δ 20.1 (q), 20.9 (q), 27.8 (d), 32.4 (q), 63.5 (d), 78.9 (d), 120.6 (s), 122.6 (t), 125.7 (d), 128.7 (d), 128.9 (d), 129.1 (d), 129.8 (d), 131.6 (d), 132.3 (s), 135.8 (d), 138.1 (s), 144.9 (s), 145.0 (s), 169.7 (s).

(2*R*,5*S*)-2-(1-Phenylvinyl)-5-isopropyl-3-methyl-1-(5-chloro-2-nitrobenzoyl)-imidazolidin-4-one (46ba)



Yield: 34%

White crystals

M.p. 145 °C

$[\alpha]_{\text{D}}^{25}$: +55.70 (c = 13.0g/l, CHCl_3)

IR: 1644 cm^{-1} , 1710 cm^{-1}

(mixture of two conformers in ratio 5:1)

Major conformer

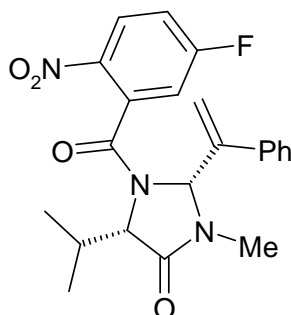
^1H -NMR (CDCl_3) δ 0.88 (3H, d, $J = 5.5$ Hz), 1.09 (3H, d, $J = 6.6$ Hz), 1.58 (1H, dq, $J = 5.5, 6.6, 8.9$ Hz), 2.85 (3H, s), 4.36 (1H, d, $J = 8.9$ Hz), 4.91 (1H, s), 5.26 (1H, s), 5.34 (1H, s), 6.95 - 8.07 (8H, m)

^{13}C -NMR (CDCl_3) δ 19.4 (q), 19.7 (q), 27.2 (d), 32.2 (q), 63.3 (d), 78.6 (d), 120.0 (s), 121.3 (t), 125.9 (d), 127.2 (d), 128.3 (d), 128.6 (d), 128.8 (d), 130.4 (d), 133.4 (s), 137.1 (s), 141.1 (s), 142.8 (s), 144.7 (s), 169.8 (s).

Minor conformer

$^1\text{H-NMR}$ (CDCl_3)	δ	0.55 (3H, d, $J = 5.6$ Hz), 0.67 (3H, d, $J = 5.9$ Hz), 1.20 - 1.26 (1H, m), 2.93 (3H, s), 3.57 - 3.63 (1H, m), 5.52 (1H, s), 5.62 (1H, s), 6.15 (1H, s), 6.95 - 8.07 (8H, m)
$^{13}\text{C-NMR}$ (CDCl_3)	δ	16.8 (q), 20.4 (q), 28.0 (d), 31.9 (q), 64.9 (d), 77.4 (d), 120.0 (s), 121.3 (t), 126.3 (d), 127.8 (d), 128.1 (d), 128.6 (d), 129.5 (d), 130.6 (d), 133.4 (s), 137.1 (s), 141.1 (s), 142.8 (s), 144.7 (s), 169.8 (s).

(2*R*,5*S*)-2-(1-Phenylvinyl)-5-isopropyl-3-methyl-1-(5-fluoro-2-nitrobenzoyl)-imidazolidin-4-one (46bb)



Yield: 49%

Yellow oil

$[\alpha]_{\text{D}}^{25}$: +0.24, (c = 28.7 g/L, CHCl_3)

IR: 1640 cm^{-1} , 1698 cm^{-1}

(mixture of two conformers in ratio 4:1)

Major conformers

$^1\text{H-NMR}$ (CDCl_3)	δ	0.88 (3H, d, $J = 5.9$ Hz), 1.07 (3H, d, $J = 6.6$ Hz), 1.55 (1H, dq, $J = 5.9, 6.6, 9.0$ Hz), 2.82 (3H, s), 4.33 (1H, d, $J = 9.0$ Hz), 4.94 (1H, s), 5.24 (1H, s), 5.35 (1H, s), 6.91 - 8.15 (8H, m)
$^{13}\text{C-NMR}$ (CDCl_3)	δ	19.3 (q), 19.8 (q), 27.2 (d), 32.2 (q), 63.4 (d), 78.4 (d), 116.6 (dd, $J_{\text{C-F}}^2 = 27.4$ Hz), 117.4 (dd, $J_{\text{C-F}}^2 = 23.1$ Hz), 120.9 (t), 127.2 (d), 127.6 (dd, $J_{\text{C-F}}^3 = 9.4$

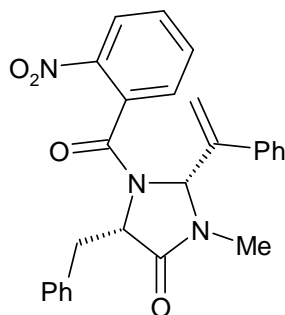
Hz), 128.3 (d), 128.6 (d), 134.4 (d, $J^3_{C-F} = 8.3$ Hz), 137.3 (s), 140.7 (s), 144.8 (s), 165.1 (d, $J^1_{C-F} = 259.7$ Hz), 166.4 (s), 169.8 (s).

Minor conformer

$^1\text{H-NMR}$ (CDCl_3) δ 0.49 (3H, d, $J = 6.2$ Hz), 0.64 (3H, d, $J = 6.6$ Hz), 1.32 - 1.42 (1H, m), 2.89 (3H, s), 3.54 - 3.61 (1H, m), 5.48 (1H, s), 5.60 (1H, s), 6.12 (1H, s), 6.70 - 8.29 (8H, m),

$^{13}\text{C-NMR}$ (CDCl_3) δ 16.6 (q), 20.4 (q), 28.0 (d), 31.8 (q), 64.8 (d), 77.3 (d), 116.4 (dd, $J^2_{C-F} = 27.2$ Hz), 117.6 (dd, $J^2_{C-F} = 23.5$ Hz), 120.0 (t), 127.2 (d), 127.8 (dd, $J^3_{C-F} = 9.0$ Hz), 128.0 (d), 128.6 (d), 134.2 (d, $J^3_{C-F} = 8.2$ Hz), 138.0 (s), 139.9 (s), 144.2 (s), 165.4 (d, $J^1_{C-F} = 259.4$ Hz), 166.8 (s), 170.1 (s).

(2*R*,5*S*)-5-Benzyl-2-(1-phenylvinyl)-3-methyl-1-(2-nitrobenzoyl)-imidazolidin-4-one (46c)



Yield: 50%

Yellow oil

$[\alpha_D]^{25}$: +4.27, ($c = 0.1$ g/L, CHCl_3)

IR: 1658 cm^{-1} , 1706 cm^{-1}

(mixture of two conformers in ratio 1:1)

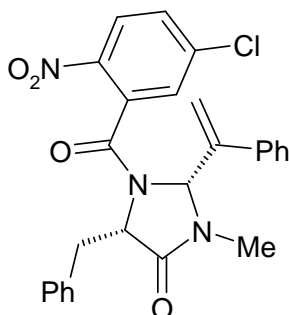
Major conformer

$^1\text{H-NMR}$ (CDCl_3) δ 2.46 - 2.52 (2H, m), 2.81 (3H, s), 3.10 (3H, s), 3.15 - 3.22 (2H, m), 3.93 - 4.12 (1H, m), 4.17 (1H, s),

4.85 - 4.88 (1H, m), 5.17 (1H, s), 5.43 (1H, s), 5.59 (1H, s), 5.71 (1H, s), 6.19 (1H, s), 6.48 - 7.92 (28H, m)

¹³C-NMR (CDCl₃) δ 26.9 (q), 27.6 (q), 36.8 (t), 39.0 (t), 60.5 (d), 61.4 (d), 76.7 (d), 78.7 (d), 121.4 (t), 121.8 (t), 125.1 (d), 125.7 (d), 126.2 (d), 127.0 (d), 127.5 (d), 128.0 (d), 128.2 (d), 128.3 (d), 128.4 (d), 128.5 (d, overlap), 128.6 (d), 129.3 (d), 129.4 (d), 129.8 (d), 130.0 (d), 130.3 (d), 130.4 (d), 130.8 (d), 132.4 (d), 133.0 (d), 136.1 (s), 136.9 (s), 137.2 (s), 137.4 (s), 141.1 (s), 141.4 (s), 142.5 (s), 142.7 (s), 143.9 (s), 144.0 (s), 168.6 (s), 168.8 (s), 169.2 (s), 169.6 (s).

(2R,5S)-5-Benzyl-2-(1-phenylvinyl)- 3-methyl-1-(5-chloro-2-nitrobenzoyl)-imidazolidin-4-one (46ca)



Yield: 62%

Pale yellow crystals

M.P. 75°C

[α_D]²⁵: +4.37, (c = 11.9 g/L, CHCl₃)

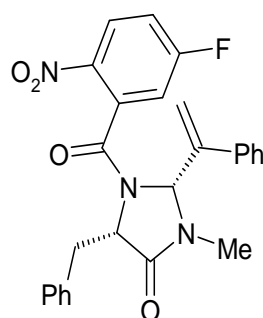
IR: 1636 cm⁻¹, 1688 cm⁻¹

(mixture of two conformers in ratio 1:1)

¹H-NMR (CDCl₃) δ 2.79 (3H, s), 2.84 - 2.95 (2H, m), 3.07 (3H,s), 3.12 - 3.20 (2H, m), 3.93 - 4.15 (1H, m), 4.21 (1H, s), 4.80 - 4.86 (1H, m), 5.16 (1H, s), 5.44 (1H, s), 5.57 (1H, s), 5.68 (1H, s), 6.18 (1H, s), 6.47 - 6.51 (2H, m), 6.75 - 7.48 (22H, m), 7.84 - 7.96 (2H, m),

$^{13}\text{C-NMR}$ (CDCl_3)	δ	26.9 (q), 27.6 (q), 36.8 (t), 39.0 (t), 60.5 (d), 61.4 (d), 76.9 (d), 78.6 (d), 121.5 (t), 121.7 (t), 125.7 (d), 126.1 (d), 126.3 (d), 126.9 (d), 127.2 (d), 128.2 (d), 128.3 (d), 128.4 (d), 128.5 (d), 128.6 (d, overlap), 128.7 (d), 129.4 (d), 129.7 (d), 129.8 (d), 130.0 (d), 130.3 (d), 130.4 (d), 132.4 (s), 133.0 (s), 136.1 (s), 136.9 (s), 137.2 (s), 137.7 (s), 141.0 (s), 141.2 (s), 142.4 (s), 142.5 (s), 144.0 (s), 168.6 (s), 168.7 (s), 169.1 (s), 169.4 (s).
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(2*R*,5*S*)-5-Benzyl-2-(1-phenylvinyl)- 3-methyl-1-(5-fluoro-2-nitrobenzoyl)-imidazolidin-4-one (46cb)



Yield: 65%

White crystals

M.p. 88°C

$[\alpha]_{\text{D}}^{25}$: -4.01, (c = 19.1 g/L, CHCl_3)

IR: 1660 cm^{-1} , 1700 cm^{-1}

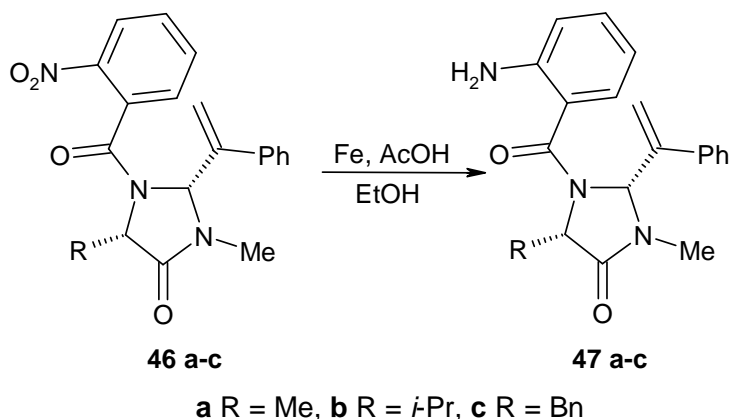
(mixture of two conformers in ratio 1:1)

$^1\text{H-NMR}$ (CDCl_3)	δ	2.48 - 2.56 (2H, m), 2.79 (3H, s), 3.08 (3H, s), 3.01 - 3.20 (2H, m), 3.92 - 4.13 (1H, m), 4.21 (1H, s), 4.82 - 4.89 (1H, m), 5.15 (1H, s), 5.44 (1H, s), 5.58 (1H, s), 5.69 (1H, s), 6.21 (1H, s), 6.25 - 6.42 (1H, m), 6.48 - 6.51 (2H, m), 6.75 - 7.08 (6H, m), 7.25 - 7.48 (10H, m), 7.98 - 8.05 (2H, m)
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$^{13}\text{C-NMR}$ (CDCl_3)	δ	26.9 (q), 27.6 (q), 36.8 (t), 39.1 (t), 60.6 (d), 61.5 (d), 76.7 (d), 78.6 (d), 116.0 (dd, $J_{\text{C-F}} = 21.8$ Hz), 116.2 (dd, $J_{\text{C-F}} = 22.0$ Hz), 117.1 (dd, $J_{\text{C-F}} = 21.6$
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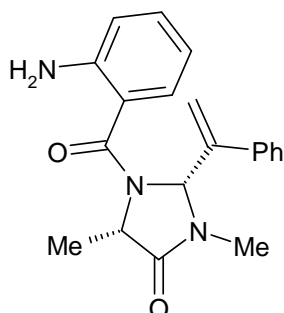
Hz), 117.4 (dd, $J_{C-F}^2 = 21.9$ Hz), 121.3 (t), 121.7 (t),
126.2 (d), 126.8 (dd, $J_{C-F}^3 = 11.6$ Hz), 127.4 (dd,
 $J_{C-F}^3 = 11.0$ Hz), 128.4 (d), 128.6 (d, overlap), 130.0
(d), 133.5 (d, $J_{C-F}^3 = 5.6$ Hz), 134.3 (d, $J_{C-F}^3 = 6.2$
Hz), 136.3 (s), 136.6 (s), 136.7 (s), 137.0 (s), 137.4
(s), 137.7 (s), 144.0 (s), 144.2 (s), 165.1 (d, $J_{C-F}^1 =$
231.6 Hz), 166.4 (s), 167.6 (d, $J_{C-F}^1 = 259.3$ Hz),
168.7 (s), 168.8 (s), 169.1 (s).

Synthesis of compound 46



A solution of **46** (1.04 mmol) in EtOH (10 mL) and 20% aq. AcOH (2.5 mL) was treated with Fe powder (0.464 g, 8.32 mmol), and refluxed for 5 hours under vigorous stirring. The mixture was diluted with AcOEt (50 mL) and filtered over a celite pad. The filtrate was washed with aq. NaHCO₃ (50 mL) and with water (2 × 25 mL), then the organic layer was dried over Na₂SO₄. The solvent was evaporated under reduced pressure and the products purified on column chromatography, (EdP/AcOEt 1:1).

(2*R*,5*S*)-1-(2-Aminobenzoyl)-2-(1-phenylvinyl)-3,5-dimethyl-imidazolidin-4-one (47a)



Yield: 96%

Yellow oil

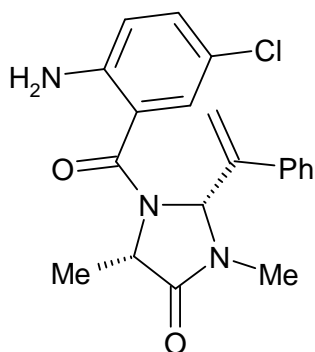
$[\alpha]_D^{25}$: +25.3 (c = 0.22 g/L, CHCl₃)

IR: 1648 cm⁻¹, 1698 cm⁻¹, 3488 cm⁻¹

¹H-NMR (CDCl₃) δ 0.66 (3H, d, *J* = 6.9 Hz), 2.96 (3H, s), 4.13 (2H, br s), 4.30 (1H, q, *J* = 6.9 Hz), 5.36 (2H, s), 5.87 (1H, s), 6.70 - 6.75 (2H, m), 7.00 - 7.35 (7H, m)

¹³C-NMR (CDCl₃) δ 17.3 (q), 27.5 (q), 55.9 (d), 79.5 (d), 117.1 (d), 118.2 (d), 119.2 (s), 121.3 (s), 121.8 (t), 127.2 (d), 127.6 (d), 128.8 (d), 128.9 (d), 131.4 (d), 137.8 (s), 144.7 (s), 144.9 (s), 171.1 (s).

(2*R*,5*S*)-1-(2-Amino-5-chlorobenzoyl)-2-(1-phenylvinyl)-3,5-dimethyl-imidazolidin-4-one (47aa)



Yield: 96%

Yellow crystal

m.p: 106°C

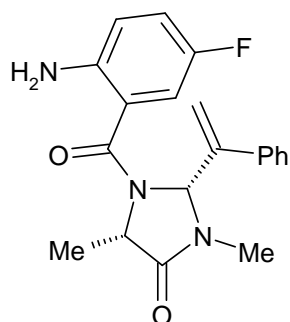
$[\alpha]_D^{25}$: +21.4 (c = 24.1 g/L, CHCl₃)

IR: 1636 cm⁻¹, 1694 cm⁻¹, 3448 cm⁻¹

¹H-NMR (CDCl₃) δ 0.55 (3H, d, *J* = 6.6 Hz), 2.80 (3H, s), 4.15 (1H, q, *J* = 6.6 Hz), 4.26 (2H, br s), 5.16 (1H, s), 5.20 (1H, s), 5.68 (1H, s), 6.51 - 6.54 (1H, m), 6.90 - 6.97 (4H, m), 7.13 - 7.21 (3H, m)

¹³C-NMR (CDCl₃) δ 16.6 (q), 26.9 (q), 55.2 (d), 79.0 (d), 117.4 (d), 121.4 (t), 121.5 (s), 121.6 (s), 126.5 (d), 128.0 (d), 128.3 (d), 128.4 (d), 130.6 (d), 137.1 (s), 143.1 (s), 144.2 (s), 170.0 (s), 170.3 (s).

(2*R*,5*S*)-1-(2-Amino-5-fluorobenzoyl)-2-(1-phenylvinyl)-3,5-dimethylimidazolidin-4-one (47ab)



Yield: 87%

Colorless oil

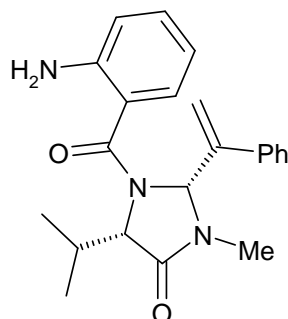
$[\alpha]_D^{25}$: +9.87 (c = 2.43 g/L, CHCl₃)

IR: 1654 cm⁻¹, 1702 cm⁻¹, 3450 cm⁻¹

¹H-NMR (CDCl₃) δ 0.67 (3H, d, *J* = 7.0 Hz), 2.96 (3H, s), 3.87 (2H, br s), 4.12 (1H, q, *J* = 7.0 Hz), 5.37 (2H, s), 5.82 (1H, s), 6.61 - 7.35 (8H, m)

¹³C-NMR (CDCl₃) δ 17.2 (q), 27.4 (q), 55.7 (d), 79.4 (d), 113.8 (dd, *J*_{C-F} = 23.7 Hz), 118.1 (dd, *J*_{C-F} = 22.1 Hz), 118.3 (dd, *J*_{C-F} = 7.2 Hz), 121.9 (t), 122.0 (d, *J*_{C-F} = 6.6 Hz), 128.6 (d), 128.8 (d), 129.0 (d), 137.5 (s), 140.7 (s), 144.8 (s), 155.5 (d, *J*_{C-F} = 238.3 Hz), 168.4 (s), 170.8 (s).

(2*R*,5*S*)-1-(2-Aminobenzoyl)-2-(1-phenylvinyl)-5-isopropyl-3-methyl-imidazolidin-4-one (47b)



Yield: 95%

Colorless oil

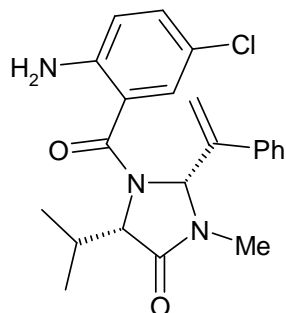
$[\alpha_D]^{25}$: +56.1 (c = 0.38 g/L in CHCl₃)

IR: 1640 cm⁻¹, 1690 cm⁻¹, 3492 cm⁻¹

¹H-NMR (CDCl₃) δ 0.75 (3H, d, *J* = 6.8 Hz), 0.97 (3H, d, *J* = 6.5 Hz),
1.26 - 1.29 (1H, qqd, *J* = 6.5, 6.8, 9.1 Hz), 2.81
(3H, s), 4.15 (2H, br s), 4.35 (1H, d, *J* = 9.1 Hz),
5.24 (1H, s), 5.36 (1H, s), 5.64 (1H, s), 6.70 - 6.75
(2H, m), 7.13 - 7.34 (7H, m)

¹³C-NMR (CDCl₃) δ 19.3 (q), 20.6 (q), 28.0 (d), 32.6 (q), 63.6 (d), 79.5
(d), 117.1 (d), 117.7 (d), 120.7 (s), 121.2 (t), 128.2
(d), 128.4 (d), 128.7 (d), 128.8 (d), 131.7 (d), 138.3
(s), 145.4 (s), 145.8 (s), 170.6 (s), 172.5 (s).

(2*R*,5*S*)-1-(2-Amino-5-chlorobenzoyl)-2-(1-phenylvinyl)-5-isopropyl-3-methyl-imidazolidin-4-one (47ba)



Yield: 84%

Colorless Oil

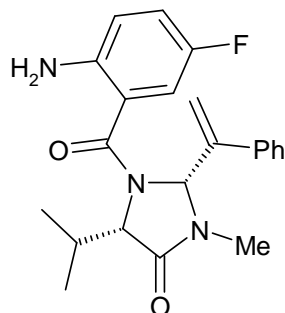
$[\alpha]_D^{25}$: +63.7 (c = 12.0 g/L in CHCl₃)

IR: 1654 cm⁻¹, 1706 cm⁻¹, 3466 cm⁻¹

¹H-NMR (CDCl₃) δ 0.67 (3H, d, *J* = 6.6 Hz), 0.96 (3H, d, *J* = 6.3 Hz),
1.23 - 1.25 (1H, m), 2.78 (3H, s), 4.30 (2H, br s),
4.32 - 4.36 (1H, m), 5.15 (1H, s), 5.36 (1H, s), 5.51
(1H, s), 6.63 - 6.65 (1H, m), 7.11 - 7.31 (7H,
m)

¹³C-NMR (CDCl₃) δ 19.0 (q), 20.0 (q), 27.5 (d), 32.1 (q), 62.9 (d), 79.5
(d), 117.8 (d), 120.9 (s), 121.5 (t), 121.9 (s), 127.9
(d), 128.0 (d), 128.4 (d), 128.5 (d), 131.0 (d), 137.4
(s), 143.7 (s), 145.0 (s), 170.0 (s), 171.0 (s).

(2*R*,5*S*)-1-(2-Aminobenzoyl)-2-(1-phenylvinyl)-5-isopropyl-3-methyl-imidazolidin-4-one (47bb)



Yield: 93%

White crystal

M.P.: 44°C

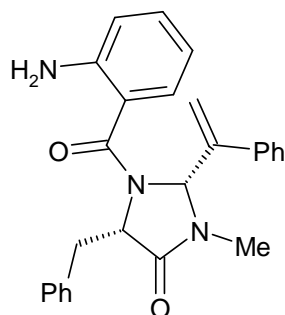
$[\alpha]_D^{25}$: +26.7 (c = 21.8 g/L, CHCl₃)

IR: 1640 cm⁻¹, 1696 cm⁻¹, 3438 cm⁻¹

¹H-NMR (CDCl₃) δ 0.73 (3H, d, *J* = 6.8 Hz), 0.97 (3H, d, *J* = 6.5 Hz),
1.32 (1H, qqd, *J* = 6.5, 6.8, 9.0 Hz), 2.83 (3H, s),
3.47 (2H, br s), 4.29 (1H, d, *J* = 9.0 Hz), 5.20 (1H,
s), 5.36 (1H, s), 5.60 (1H, s), 6.65 - 7.35 (8H, m)

¹³C-NMR (CDCl₃) δ 18.8 (q), 20.1 (q), 27.5 (d), 32.1 (q), 63.1 (d), 78.9
(d), 114.3 (dd, *J*_{C-F}² = 23.8 Hz), 117.7 (dd, *J*_{C-F}³ =
8.1 Hz), 117.8 (dd, *J*_{C-F}² = 20.2 Hz), 120.9 (t), 121.2
(d, *J*_{C-F}³ = 6.1 Hz), 127.9 (d), 128.3 (d), 128.4 (d),
137.6 (s), 140.8 (s), 145.2 (s), 154.8 (d, *J*_{C-F}¹ =
236.3 Hz), 169.9 (s), 170.6 (s).

(2*R*,5*S*)-1-(2-Aminobenzoyl)-5-benzyl-2-(1-phenylvinyl)-3-methylimidazolidin-4-one (47c)



Yield: 97%

Yellow crystals

M.p. 130 °C

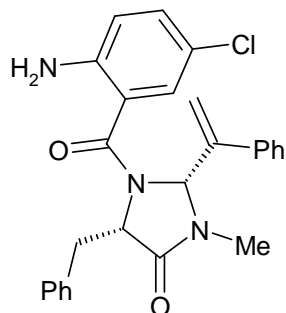
$[\alpha]_D^{25}$: +139 (c = 0.28 g/L, CHCl₃)

IR: 1642 cm⁻¹, 1696 cm⁻¹, 3472 cm⁻¹

¹H-NMR (CDCl₃) δ 1.87 - 1.94 (1H, m), 2.37 - 2.43 (1H, m), 2.93 (3H, s), 4.01 (2H, br s), 4.50 - 4.54 (1H, m), 5.19 (1H, s), 5.46 (1H, s), 5.80 (1H, s), 6.71 - 7.40 (14H, m)

¹³C-NMR (CDCl₃) δ 27.5 (q), 38.7 (t), 60.5 (d), 79.0 (d), 117.2 (d), 118.3 (d), 121.1 (s), 121.7 (t), 126.8 (d), 127.4 (d), 128.5 (d), 128.8 (d, overlap), 128.9 (d), 129.8 (d), 131.5 (d), 137.4 (s), 138.0 (s), 144.8 (s), 145.0 (s), 169.9 (s), 170.2 (s).

(2*R*,5*S*)-1-(2-Amino-5-chlorobenzoyl)-5-benzyl-2-(1-phenylvinyl)-3-methyl-imidazolidin-4-one (47ca)



Yield: 79%

Yellow oil

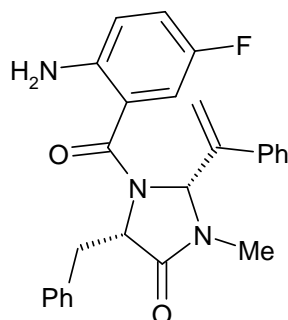
$[\alpha]_D^{25}$: +13.69 (c = 8.47 g/L in CHCl_3)

IR: 1650 cm^{-1} , 1696 cm^{-1} , 3480 cm^{-1}

$^1\text{H-NMR}$ (CDCl_3) δ 2.03 - 2.36 (2H, m), 2.93 (3H, s), 4.15 (2H, br s), 4.56 - 4.60 (1H, m), 5.12 (1H, s), 5.36 (1H, s), 5.70 (1H, s), 6.58 - 7.41 (13H, m)

$^{13}\text{C-NMR}$ (CDCl_3) δ 27.1 (q), 38.2 (t), 60.0 (d), 78.9 (d), 113.4 (d), 118.0 (d), 121.4 (s), 121.7 (t), 122.4 (s), 126.6 (d), 127.1 (d), 128.2 (d), 128.4 (d), 128.6 (d), 129.3 (d), 129.4 (d), 130.9 (d), 131.3 (d), 136.9 (s), 137.3 (s), 143.2 (s), 144.4 (s), 168.7 (s), 169.3 (s).

**(2*R*,5*S*)-1-(2-Aminobenzoyl)-5-benzyl-2-(1-phenylvinyl)-3-methyl-
imidazolidin-4-one (47cb)**



Yield: 60%

White crystal

M.p: 142°C

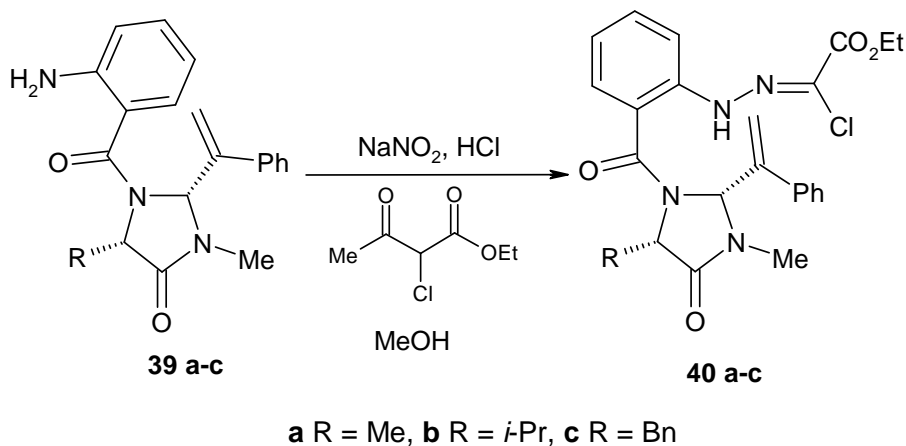
$[\alpha]_D^{25}$: +4.734 (c = 5.07 g/L, CHCl₃)

IR (nujol): 1662 cm⁻¹, 1708 cm⁻¹, 3490 cm⁻¹

¹H-NMR (CDCl₃) δ 2.03 - 2.36 (2H, m), 2.93 (3H, s), 4.15 (2H, br s),
4.56 - 4.60 (1H, m), 5.12 (1H, s), 5.36 (1H, s), 5.70
(1H, s), 6.58 - 7.41 (13H, m)

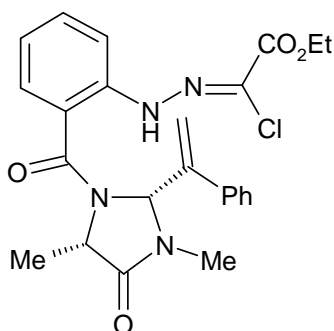
¹³C-NMR (CDCl₃) δ 27.1 (q), 38.2 (t), 60.0 (d), 78.6 (d), 113.7 (dd, J_{C-F}^2
= 23.7 Hz), 117.9 (dd, J_{C-F}^2 = 22.6 Hz), 118.1 (dd,
 J_{C-F}^3 = 7.4 Hz), 121.5 (t), 121.2 (d, J_{C-F}^3 = 6.1 Hz),
126.6 (d), 128.2 (d), 128.4 (d), 128.6 (d, overlap),
129.4 (d), 137.6 (s), 137.4 (s), 140.4 (s), 144.4 (s),
155.2 (d, J_{C-F}^1 = 236.8 Hz), 168.6 (s), 169.4 (s).

Synthesis of 48



To a solution of **47** (1.13 mmol) in MeOH (2 mL) and 6M HCl (0.65 mL) cooled at 0° C NaNO₂ (0.156 g, 2.26 mmol) was added portionwise. After 30 minutes AcONa was added until pH 5, then a solution of ethyl 2-chloroacetoacetate (1.13 mmol, 0.122 mL) in MeOH (1 mL) was dropped under vigorous stirring at room temperature for 24 hours. The solvent was evaporated under reduced pressure and the residue extracted with Et₂O (2 × 15 mL). The organic layer was washed with aq. NaHCO₃ (15 mL) and with water (30 mL), then dried over Na₂SO₄. The solvent was evaporated under reduced pressure and the products purified on silica gel column chromatography with light (EdP/AcOEt 1:1).

Ethyl (2*R*,5*S*)-2-chloro-2-{2-[2-(3,5-dimethyl-4-oxo-2-(1-phenylvinyl)imidazolidine-1-carbonyl)phenyl]hydrazono}acetate (48a)



Yield: 57%

Yellow crystal

M.p.: 65°C

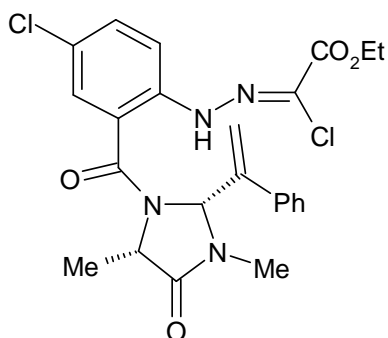
$[\alpha_D]^{25}$: +2.1 (c = 0.15 g/L, CHCl₃)

IR: 1650 cm⁻¹, 1703 cm⁻¹, 1716 cm⁻¹, 3338 cm⁻¹

¹H-NMR (CDCl₃) δ 0.62 (3H, d, *J* = 6.6 Hz), 1.42 (3H, t, *J* = 7.1 Hz),
2.98 (3H, s), 4.35 (1H, q, *J* = 6.6 Hz), 4.41 (2H, q, *J*
= 7.1 Hz), 5.38 (1H, s), 5.40 (1H, s), 5.91 (1H, s),
7.00 - 7.61 (9H, m), 9.40 (1H, s)

¹³C-NMR (CDCl₃) δ 14.6 (q), 17.1 (q), 27.5 (q), 56.2 (d), 63.3 (t), 79.9
(d), 116.7 (d), 118.5 (s), 121.0 (s), 122.1 (t), 122.4
(d), 127.3 (d), 128.8 (d), 128.9 (d), 132.1 (d), 132.2
(d), 137.4 (s), 140.3 (s), 144.7 (s), 159.2 (s), 168.5
(s), 170.7 (s).

Ethyl (2*R*,5*S*)-2-chloro-2-[2-[4-chloro-2-(3,5-dimethyl-4-oxo-2-(1-phenylvinyl)imidazolidine-1-carbonyl)phenyl]hydrazono}acetate (48aa)



Yield: 62%

Yellow solid

M.p.: 174°C

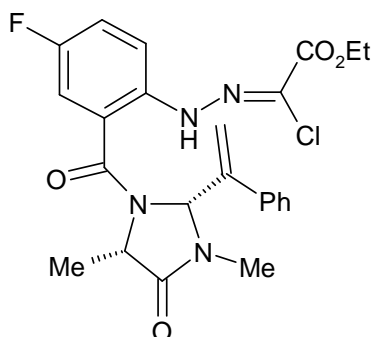
$[\alpha_D]^{25}$: +2.421 (c = 17.8 g/L, CHCl₃)

IR: 1646 cm⁻¹, 1694 cm⁻¹, 1728 cm⁻¹, 3392 cm⁻¹

¹H-NMR (CDCl₃) δ 0.66 (3H, d, *J* = 6.5 Hz), 1.37 (3H, t, *J* = 6.9 Hz),
2.94 (3H, s), 4.31 - 4.37 (3H, m), 5.37 (2H, s), 5.83
(1H, s), 7.04 - 7.47 (8H, m), 9.33 (1H, s)

¹³C-NMR (CDCl₃) δ 14.2 (q), 16.7 (q), 27.0 (q), 55.6 (d), 63.0 (t), 79.6
(d), 117.8 (d), 118.6 (s), 121.7 (s), 121.8 (s), 121.9
(t), 127.0 (d), 128.3 (d), 128.5 (d), 128.6 (d), 131.4
(d), 136.8 (s), 138.4 (s), 144.1 (s), 159.1 (s), 167.0
(s), 170.1 (s).

**Ethyl (2R,5S)-2-chloro-2-[2-[2-(3,5-dimethyl-4-oxo-2-(1phenylvinyl)imidazolidine-1-carbonyl)-4-fluorophenyl]hydrazono]acetate
(48ac)**



Yield: 49%

Yellow crystals

m.p.: 125°C

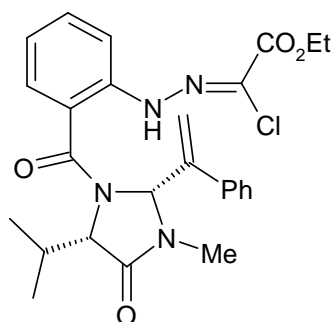
$[\alpha]_D^{25}$: -0.347 (c = 10.3 g/L, CHCl₃)

IR: 1642 cm⁻¹, 1708 cm⁻¹, 1732 cm⁻¹, 3412 cm⁻¹

¹H-NMR (CDCl₃) δ 0.64 (3H, d, *J* = 6.3 Hz), 1.39 (3H, t, *J* = 7.1 Hz),
2.96 (3H, s), 4.30 (1H, q, *J* = 6.3 Hz), 4.37 (2H, q, *J*
= 7.1 Hz), 5.38 (2H, s), 5.86 (1H, s), 6.95 - 7.51
(8H, m), 9.22 (1H, s)

¹³C-NMR (CDCl₃) δ 14.2 (q), 16.7 (q), 27.0 (q), 55.7 (d), 62.9 (t), 79.4
(d), 113.8 (dd, *J*_{C-F} = 24.3 Hz), 118.0 (s), 118.2
(dd, *J*_{C-F} = 7.5 Hz), 118.5 (dd, *J*_{C-F} = 22.4 Hz),
121.8 (t), 128.3 (d), 128.5 (d), 128.6 (d), 136.1 (s),
136.8 (s), 140.6 (s), 144.1 (s), 157.5 (d, *J*_{C-F}¹ =
242.8 Hz), 159.2 (s), 166.8 (s), 170.1 (s).

Ethyl (2R,5S)-2-chloro-2-[2-[2-(5-isopropyl-3-methyl-4-oxo-2-(1-phenylvinyl)imidazolidine-1-carbonyl)phenyl]hydrazono]acetate (48b)



Yield: 51%

Cream crystals

m.p.: 69°C

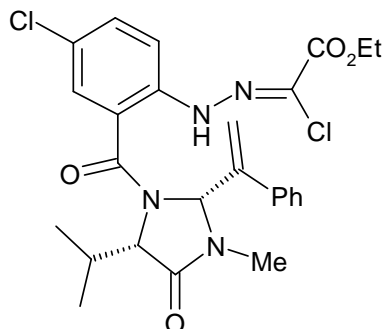
$[\alpha_D]_{25}^{25}$: +45.6 (c = 0.4 g/L, CHCl₃)

IR: 1656 cm⁻¹, 1688 cm⁻¹, 1724 cm⁻¹, 3436 cm⁻¹

¹H-NMR (CDCl₃) δ 0.72 (3H, d, *J* = 6.8 Hz), 0.98 (3H, d, *J* = 6.5 Hz),
1.17 - 1.21 (1H, m), 1.43 (3H, t, *J* = 7.1 Hz), 2.83
(3H, s), 4.39 – 4.45 (3H, m), 5.32 (1H, s), 5.42 (1H,
s), 5.68 (1H, s), 7.01 (1H, dd, *J* = 7.4, 7.5 Hz), 7.10
- 7.13 (2H, m), 7.27 - 7.36 (3H, m), 7.40 (1H, d, *J* =
7.5 Hz), 7.45 (1H, dd, *J* = 7.4, 8.2 Hz), 7.64 (1H, d,
J = 8.2 Hz), 9.51 (1H, br s)

¹³C-NMR (CDCl₃) δ 14.6 (q), 19.3 (q), 20.5 (q), 28.0 (d), 32.6 (q), 63.3
(t), 63.8 (d), 79.7 (d), 116.7 (d), 118.9 (s), 120.6 (s),
121.4 (t), 122.0 (d), 128.2 (d), 128.3 (d), 128.9 (d),
129.0 (d), 132.4 (d), 138.1 (s), 140.8 (s), 145.8 (s),
159.9 (s), 170.3 (s), 171.2 (s).

Ethyl (2*R*,5*S*)-2-chloro-2-{2-[4-chloro-2-(5-isopropyl-3-methyl-4-oxo-2-(1-phenylvinyl)imidazolidine-1-carbonyl)phenyl]hydrazono}acetate (48ba)



Yield: 82%

Pale yellow oil

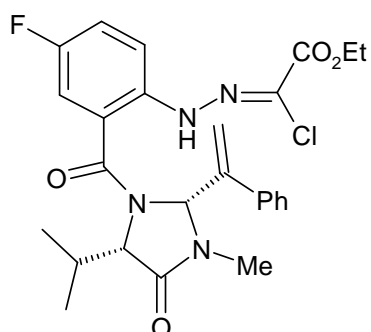
$[\alpha_D]^{25}$: -0.806 (c = 6.2 g/L, CHCl₃)

IR: 1634 cm⁻¹, 1686 cm⁻¹, 1716 cm⁻¹, 3424 cm⁻¹

¹H-NMR (CDCl₃) δ 0.62 (3H, d, *J* = 6.6 Hz), 0.91 (3H, d, *J* = 6.4 Hz), 1.00 - 1.09 (1H, m), 1.33 (3H, t, *J* = 7.1 Hz), 2.77 (3H, s), 4.27 - 4.35 (3H, m), 5.18 (1H, s), 5.36 (1H, s), 5.53 (1H, s), 7.05 - 7.48 (8H, m), 9.49 (1H, s)

¹³C-NMR (CDCl₃) δ 14.1 (q), 18.9 (q), 19.9 (q), 27.4 (d), 32.0 (q), 62.9 (t), 63.0 (d), 79.6 (d), 117.7 (d), 118.8 (s), 121.2 (s), 121.7 (t), 126.7 (s), 127.8 (d), 127.9 (d), 128.3 (d), 128.5 (d), 131.6 (d), 137.2 (s), 138.9 (s), 145.0 (s), 159.2 (s), 169.8 (s), 169.9 (s).

Ethyl (2*R*,5*S*)-2-chloro-2-{2-[4-fluoro-2-(5-isopropyl-3-methyl-4-oxo-2-(1-phenylvinyl)imidazolidine-1-carbonyl)phenyl]hydrazono}acetate (48bb)



Yield: 57%

Colorless oil

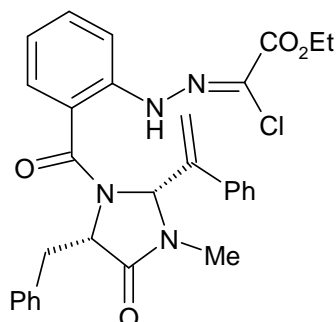
$[\alpha]_D^{25}$: +16.38 (c = 5.0 g/L, CHCl₃)

IR: 1638 cm⁻¹, 1710 cm⁻¹, 1722 cm⁻¹, 3384 cm⁻¹

¹H-NMR (CDCl₃) δ 0.70 (3H, d, *J* = 6.8 Hz), 0.97 (3H, d, *J* = 6.5 Hz),
1.18 - 1.23 (1H, m), 1.40 (3H, t, *J* = 7.1 Hz), 2.83
(3H, s), 4.33 - 4.41 (3H, m), 5.29 (1H, s), 5.42 (1H,
s), 5.64 (1H, s), 7.08 - 7.17 (4H, m), 7.27 - 7.33
(3H, m), 7.53 - 7.57 (1H, m), 9.30 (1H, br s)

¹³C-NMR (CDCl₃) δ 14.2 (q), 18.9 (q), 20.3 (q), 27.5 (d), 32.1 (q), 62.9
(t), 63.3 (d), 79.2 (d), 114.7 (dd, *J*_{C-F} = 24.4 Hz),
118.1 (dd, *J*_{C-F} = 7.4 Hz), 118.5 (s), 118.8 (dd, *J*_{C-F}
= 22.3 Hz), 121.3 (t), 127.8 (d), 128.6 (d), 128.9
(d), 136.6 (s), 137.3 (s), 140.0 (s), 145.2 (s), 157.2
(d, *J*_{C-F} = 242.7 Hz), 159.3 (s), 169.5 (s), 169.7 (s).

**Ethyl (2*R*,5*S*)-2-{2-[2-(5-benzyl-3-methyl-4-oxo-2-(1-phenylvinyl)imidazolidine-1-carbonyl)phenyl]hydrazono}-2-chloroacetate
(48c)**



Yield: 34%

Yellow oil

$[\alpha]_D^{25}$: -33.79 (c = 0.21 g/L, CHCl₃)

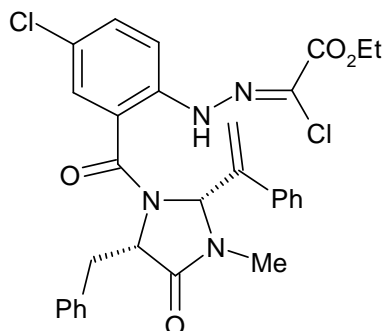
IR: 1646 cm⁻¹, 1692 cm⁻¹, 1720 cm⁻¹, 3404 cm⁻¹

MS: *m/z* 544 (M⁺).

¹H-NMR (CDCl₃) δ 1.42 (3H, t, *J* = 7.1 Hz), 2.01 - 2.05 (1H, m), 2.08 - 2.13 (1H, m), 2.98 (3H, s), 4.41 (2H, q, *J* = 7.1 Hz), 4.60 (1H, t, *J* = 4.7 Hz), 5.23 (1H, s), 5.37 (1H, s), 5.83 (1H, s), 6.75 - 7.56 (14H, m), 9.31 (1H, br s)

¹³C-NMR (CDCl₃) δ 14.6 (q), 27.5 (q), 38.7 (t), 60.9 (d), 63.3 (t), 79.4 (d), 116.8 (d), 118.5 (s), 120.9 (s), 122.0 (t), 122.4 (d), 126.5 (d), 126.9 (d), 127.5 (d), 128.6 (d), 128.8 (d), 129.3 (d), 129.7 (d), 132.1 (d), 136.8 (s), 137.8 (s), 140.3 (s), 144.8 (s), 159.8 (s), 168.9 (s), 169.6 (s).

Ethyl (2*R*,5*S*)-2-{2-[2-(5-benzyl-3-methyl-4-oxo-2-(1-phenylvinyl)imidazolidine-1-carbonyl)-4-chlorophenyl]hydrazono}-2-chloroacetate (48ca)



Yellow oil

Yield: 43%

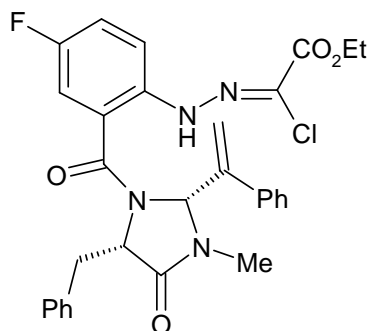
$[\alpha]_D^{25}$: +0.022 (c = 4.49 g/L, CHCl₃)

IR: 1650 cm⁻¹, 1702 cm⁻¹, 1726 cm⁻¹, 3456 cm⁻¹

¹H-NMR (CDCl₃) δ 1.41 (3H, t, *J* = 7.1 Hz), 2.22 - 2.26 (2H, m), 2.98 (3H, s), 4.40 (2H, q, *J* = 7.1 Hz), 4.65 (1H, t, *J* = 6.4 Hz), 5.19 (1H, s), 5.40 (1H, s), 5.79 (1H, s), 6.77 - 6.80 (2H, m), 7.10 - 7.43 (11H, m), 9.24 (1H, br s)

¹³C-NMR (CDCl₃) δ 14.2 (q), 27.1 (q), 38.3 (t), 60.3 (d), 63.0 (t), 79.3 (d), 117.8 (d), 118.7 (s), 121.3 (s), 122.0 (t), 126.6 (d), 127.0 (s), 127.1 (d), 128.3 (d), 128.7 (d), 128.8 (d, overlapped), 129.1 (d), 130.2 (d), 131.5 (d), 136.3 (s), 137.3 (s), 138.6 (s), 144.2 (s), 159.2 (s), 167.4 (s), 169.0 (s).

Ethyl (2*R*,5*S*)-2-{2-[2-(5-benzyl-3-methyl-4-oxo-2-(1-phenylvinyl)imidazolidine-1-carbonyl)-4-fluorophenyl]hydrazono}-2-chloroacetate (48cb)



Yield: 47%

Yellow solid

m.p.: 105°C

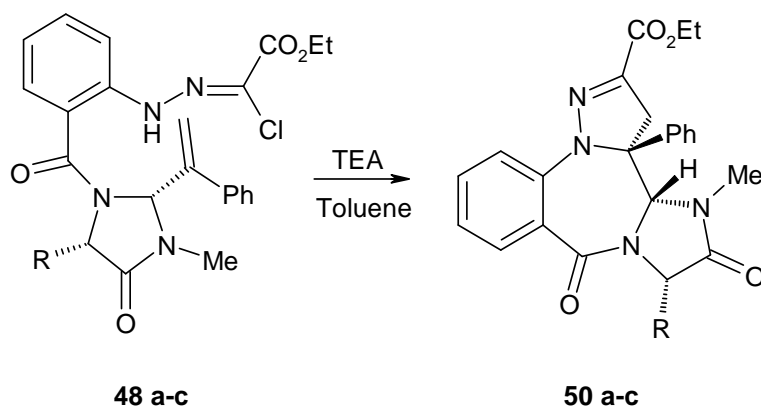
$[\alpha]_D^{25}$: -0.13 (c = 4.43 g/L, CHCl₃)

IR: 1647 cm⁻¹, 1704 cm⁻¹, 1728 cm⁻¹, 3462 cm⁻¹

¹H-NMR (CDCl₃) δ 1.40 (3H, t, *J* = 7.1 Hz), 2.17 - 2.25 (2H, m), 2.96 (3H, s), 4.39 (2H, q, *J* = 7.1 Hz), 4.60 (1H, t, *J* = 6.4 Hz), 5.17 (1H, s), 5.37 (1H, s), 5.83 (1H, s), 6.78 - 7.44 (13H, m), 9.12 (1H, br s)

³C-NMR (CDCl₃) δ 14.2 (q), 27.1 (q), 38.3 (t), 60.4 (d), 63.0 (t), 79.0 (d), 114.1 (dd, *J*_{C-F} = 24.3 Hz), 118.0 (s), 118.3 (dd, *J*_{C-F} = 7.5 Hz), 118.5 (dd, *J*_{C-F} = 22.4 Hz), 121.5 (s), 121.8 (t), 126.6 (d), 128.2 (d), 128.3 (d, overlapped), 128.6 (d), 129.2 (d), 136.1 (s), 136.3 (s), 137.3 (s), 144.2 (s), 157.4 (d, *J*_{C-F} = 243.0 Hz), 159.3 (s), 167.3 (s), 169.1 (s).

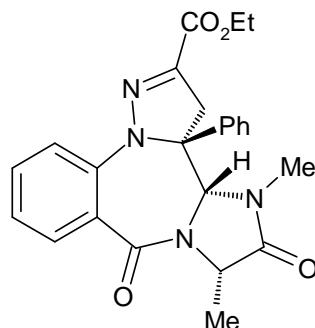
Synthesis of **41**



a R = Me, **b** R = *i*-Pr, **c** R = Bn

A solution of **41** (0.2 mmol) in toluene (9 mL) was treated with TEA (0.11 mL, 0.8 mmol) and refluxed for 24 hours. The organic layer was washed with aq. NaHCO₃ (10 mL) and with water (20 mL), then it was dried over Na₂SO₄. The solvent was evaporated under reduced pressure and the products purified on silica gel column chromatography (EdPr/AcOEt 1:1).

(3a*S*,3b*R*,6*S*)-ethyl 4,6-dimethyl-5,8-dioxo-3a-phenyl-3a,3b,4,5,6,8-hexahydro-3*H*-benzo[*e*]imidazo[1,2-*a*]pyrazolo[5,1-*c*][1,4]diazepine-2-carboxylate (50)



Yield: 55%

Yellow crystals

M.p.: 90°C

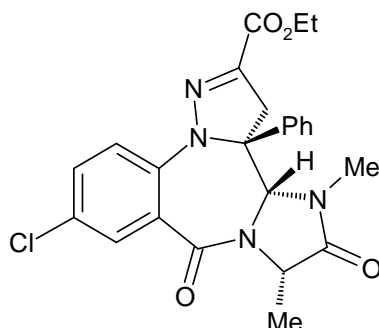
$[\alpha]_D^{25}$: +667 (c = 0.20 g/L, CHCl₃)

IR: 1652 cm⁻¹, 1705 cm⁻¹, 1716 cm⁻¹

¹H-NMR (CDCl₃) δ 0.32 (3H, d, *J* = 6.8 Hz), 1.37 (3H, t, *J* = 7.1 Hz), 3.25 (3H, s), 3.60 (1H, d, *J* = 16.1 Hz), 3.82 (1H, d, *J* = 16.1 Hz), 4.25 (1H, q, *J* = 6.8 Hz), 4.33 (2H, q, *J* = 7.1 Hz), 5.57 (1H, s), 7.13 (1H, dd, *J* = 7.4, 8.0 Hz), 7.18 - 7.21 (2H, m), 7.36 - 7.38 (3H, m), 7.52 (1H, ddd, *J* = 1.6, 7.4, 8.7 Hz), 7.84 (1H, d, *J* = 8.7 Hz), 8.11 (1H, dd, *J* = 1.6, 8.0 Hz)

¹³C-NMR (CDCl₃) δ 14.2 (q), 14.6 (q), 30.5 (q), 44.7 (t), 55.9 (d), 62.4 (t), 77.4 (d), 81.7 (s), 116.8 (s), 118.1 (d), 122.4 (d), 126.5 (d), 129.5 (d), 129.9 (d), 133.3 (d), 134.0 (d), 137.9 (s), 141.5 (s), 143.4 (s), 162.1 (s), 164.5 (s), 172.4 (s).

(3*aS*,3*bR*,6*S*)-ethyl 10-chloro-4,6-dimethyl-5,8-dioxo-3*a*-phenyl-3*a*,3*b*,4,5,6,8-hexahydro-3*H*-benzo[*e*]imidazo[1,2-*a*]pyrazolo[5,1-*c*][1,4]diazepine-2-carboxylate (50aa)



Yield: 62%

Yellow crystal

m.p.: 143°C

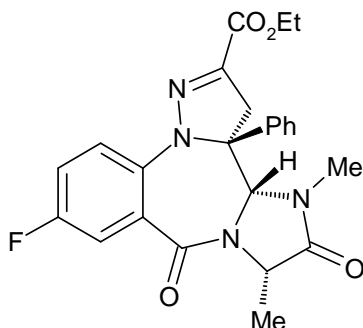
$[\alpha]_D^{25}$: +89.697 (c = 2.31 g/L, CHCl₃)

IR: 1647 cm⁻¹, 1704 cm⁻¹, 1728 cm⁻¹

¹H-NMR (CDCl₃) δ 0.32 (3H, d, *J* = 6.7 Hz), 1.33 (3H, t, *J* = 7.0 Hz),
3.21 (3H, s), 3.57 (1H, d, *J* = 16.1 Hz), 3.82 (1H, d,
J = 16.1 Hz), 4.17 (1H, q, *J* = 6.7 Hz), 4.28 (2H, q,
J = 7.0 Hz), 5.53 (1H, s), 7.11 - 7.40 (6H, m), 7.76 -
7.79 (1H, m), 8.04 (1H, s)

¹³C-NMR (CDCl₃) δ 13.7 (q), 14.2 (q), 30.1 (q), 44.4 (t), 55.5 (d), 62.1
(t), 76.7 (d), 81.1 (s), 117.2 (s), 119.3 (d), 126.6 (d),
127.2 (s), 129.1 (d), 129.6 (d), 132.1 (d), 133.4 (d),
137.2 (s), 139.7 (s), 143.5 (s), 161.4 (s), 162.7 (s),
171.8 (s).

(3*aS*,3*bR*,6*S*)-ethyl 10-fluoro-4,6-dimethyl-5,8-dioxo-3*a*-phenyl-3*a*,3*b*,4,5,6,8-hexahydro-3*H*-benzo[*e*]imidazo[1,2-*a*]pyrazolo[5,1-*c*][1,4]diazepine-2-carboxylate (50ab)



Yield: 71%

White crystal

m.p.: 145°C

Yield: 71%

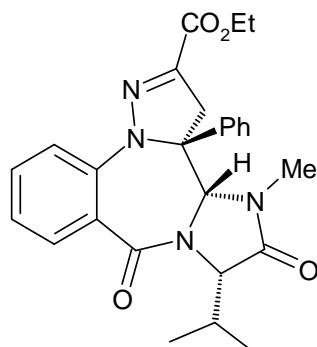
$[\alpha]_D^{25}$: +912.07 (c = 3.23 g/L, CHCl₃)

IR: 1655 cm⁻¹, 1690 cm⁻¹, 1724 cm⁻¹

¹H-NMR (CDCl₃) δ 0.29 (3H, d, *J* = 6.7 Hz), 1.35 (3H, t, *J* = 7.1 Hz),
3.24 (3H, s), 3.58 (1H, d, *J* = 16.1 Hz), 3.82 (1H, d,
J = 16.1 Hz), 4.21 (1H, q, *J* = 6.7 Hz), 4.31 (2H, q,
J = 7.1 Hz), 5.54 (1H, s), 7.15 - 7.40 (6H, m), 7.78 -
7.83 (2H, m).

¹³C-NMR (CDCl₃) δ 13.7 (q), 14.2 (q), 30.1 (q), 44.4 (t), 55.6 (d), 62.0
(t), 76.7 (d), 81.1 (s), 118.1 (s), 118.1 (d), 118.3
(dd, *J*_{C-F} = 24.6 Hz), 119.7 (dd, *J*_{C-F} = 6.7 Hz),
121.1 (dd, *J*_{C-F} = 22.7 Hz), 126.7 (d), 129.1 (d),
129.2 (d), 129.4 (d), 129.6 (d), 137.4 (s), 137.5 (s),
142.9 (s), 157.8 (d, *J*_{C-F} = 240.7 Hz), 161.5 (s),
162.8 (s), 171.8 (s).

(3a*S*,3b*R*,6*S*)-ethyl 6-isopropyl-4-methyl-5,8-dioxo-3a-phenyl-3a,3b,4,5,6,8-hexahydro-3*H*-benzo[*e*]imidazo[1,2-*a*]pyrazolo[5,1-*c*][1,4]diazepine-2-carboxylate (50b)



Yield: 62%

Yellow crystal

m.p.: 138°C

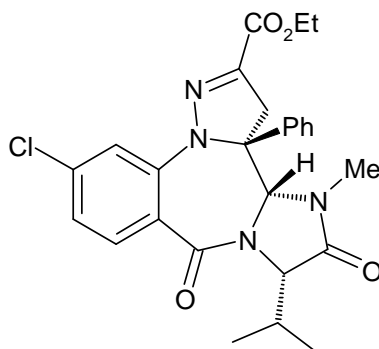
$[\alpha]_D^{25}$: +975 (c = 0.38 g/L, CHCl₃)

IR: 1644 cm⁻¹, 1702 cm⁻¹, 1720 cm⁻¹

¹H-NMR (CDCl₃) δ 0.16 (1H, qqd *J* = 6.6, 6.7, 9.8 Hz), 0.45 (3H, d, *J* = 6.7 Hz), 0.81 (3H, d, *J* = 6.6 Hz), 1.36 (3H, t, *J* = 7.1 Hz), 3.20 (3H, s), 3.55 (1H, d, *J* = 15.9 Hz), 3.76 (1H, d, *J* = 15.9 Hz), 4.04 (1H, d, *J* = 9.8 Hz), 4.32 (2H, q, *J* = 7.1 Hz), 5.42 (1H, s), 7.12 (1H, dd, *J* = 7.3, 8.1 Hz), 7.26 - 7.37 (5H, m), 7.50 (1H, ddd, *J* = 1.6, 7.3, 8.6 Hz), 7.80 (1H, d, *J* = 8.6 Hz), 8.19 (1H, dd, *J* = 1.6, 8.1 Hz)

¹³C-NMR (CDCl₃) δ 14.6 (q), 19.3 (q), 22.2 (q), 30.1 (d), 33.3 (q), 45.0 (t), 62.5 (t), 63.5 (d), 79.9 (d), 81.1 (s), 116.7 (s), 118.5 (d), 122.4 (d), 127.7 (d), 129.3 (d), 129.7 (d), 133.7 (d), 134.4 (d), 137.8 (s), 142.3 (s), 145.6 (s), 161.9 (s), 166.5 (s), 172.1 (s).

(3a*S*,3b*R*,6*S*)-ethyl 11-chloro-6-isopropyl-4-methyl-5,8-dioxo-3a-phenyl-3a,3b,4,5,6,8-hexahydro-3*H*-benzo[*e*]imidazo[1,2-*a*]pyrazolo[5,1-*c*][1,4]diazepine-2-carboxylate (50ba)



Yield: 53%

Yellow crystal

m.p.: 135°C

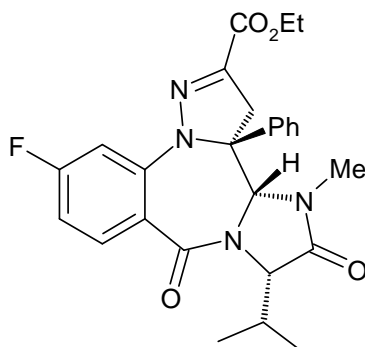
$[\alpha]_D^{25}$: +818 (c = 3.94 g/L, CHCl₃)

IR: 1652 cm⁻¹, 1688 cm⁻¹, 1716 cm⁻¹

¹H-NMR (CDCl₃) δ 0.18 (1H, qqd *J* = 6.6, 6.5, 9.7 Hz), 0.42 (3H, d, *J* = 6.7 Hz), 0.80 (3H, d, *J* = 6.5 Hz), 1.36 (3H, t, *J* = 7.2 Hz), 3.20 (3H, s), 3.56 (1H, d, *J* = 16.1 Hz), 3.76 (1H, d, *J* = 16.1 Hz), 4.03 (1H, d, *J* = 9.7 Hz), 4.32 (2H, q, *J* = 7.2 Hz), 5.42 (1H, s), 7.22 - 7.44 (6H, m), 7.79 (1H, d, *J* = 9.1 Hz), 8.18 (1H, s)

¹³C-NMR (CDCl₃) δ 14.2 (q), 18.9 (q), 21.7 (q), 29.8 (d), 32.9 (q), 44.7 (t), 62.2 (t), 63.2 (d), 76.5 (d), 80.6 (s), 117.1 (s), 119.7 (d), 127.1 (d), 127.4 (s), 129.0 (d), 129.4 (d), 132.6 (d), 133.8 (d), 137.1 (s), 140.4 (s), 145.3 (s), 161.4 (s), 164.8 (s), 171.5 (s).

(3*aS*,3*bR*,6*S*)-ethyl 11-fluoro-6-isopropyl-4-methyl-5,8-dioxo-3*a*-phenyl-3*a*,3*b*,4,5,6,8-hexahydro-3*H*-benzo[*e*]imidazo[1,2-*a*]pyrazolo[5,1-*c*][1,4]diazepine-2-carboxylate (50bb)



Yield: 46%

Yellow crystal

M.p: 144°C

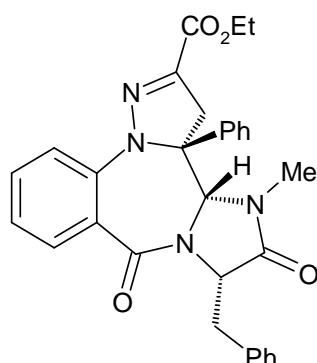
$[\alpha]_D^{25}$: +207.4 (c = 2.23 g/L, CHCl₃)

IR: 1644 cm⁻¹, 1701 cm⁻¹, 1733 cm⁻¹

¹H-NMR (CDCl₃) δ 0.07 (3H, d, *J* = 6.6 Hz), 0.45 (1H, qqd *J* = 6.6, 6.5, 9.1 Hz), 0.82 (3H, d, *J* = 6.5 Hz), 1.22 (3H, t, *J* = 7.2 Hz), 3.19 (3H, s), 3.53 (1H, d, *J* = 16.0 Hz), 3.75 (1H, d, *J* = 16.0 Hz), 4.02 (1H, d, *J* = 9.1 Hz), 4.31 (2H, q, *J* = 7.2 Hz), 5.32 (1H, s), 7.10 - 7.83 (8H, m)

¹³C-NMR (CDCl₃) δ 14.2 (q), 18.9 (q), 21.9 (q), 29.7 (d), 32.8 (q), 44.5 (t), 62.1 (t), 63.1 (d), 76.5 (d), 81.2 (s), 114.5 (d), 118.7 (d), 119.3 (dd, *J*_{C-F} = 23.7 Hz), 120.0 (dd, *J*_{C-F} = 7.5 Hz), 122.6 (d), 125.2 (dd, *J*_{C-F} = 22.4 Hz), 127.2 (d), 127.3 (d), 137.5 (s), 137.8 (s), 143.2 (s), 156.9 (d, *J*_{C-F} = 244.1 Hz), 160.8 (s), 163.0 (s), 170.6 (s).

(3*aS*,3*bR*,6*S*)-ethyl 6-benzyl-4-methyl-5,8-dioxo-3*a*-phenyl-3*a*,3*b*,4,5,6,8-hexahydro-3*H*-benzo[*e*]imidazo[1,2-*a*]pyrazolo[5,1-*c*][1,4]diazepine-2-carboxylate (50c)



Yield: 65%

Yellow oil

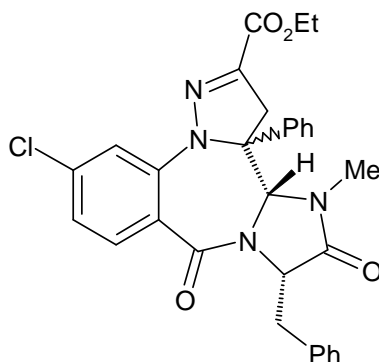
$[\alpha]_D^{25}$: +94.6 (c = 0.20 g/L, CHCl₃)

IR: 1643 cm⁻¹, 1691 cm⁻¹, 1735 cm⁻¹

¹H-NMR (CDCl₃) δ 0.82 - 0.91 (1H, m), 1.39 (3H, t, *J* = 7.1 Hz), 2.34 - 2.38 (1H, m), 3.24 (3H, s), 3.64 (1H, d, *J* = 16.1 Hz), 3.84 (1H, d, *J* = 16.1 Hz), 4.31 (2H, q, *J* = 7.1 Hz), 5.56 (1H, s), 7.15 - 8.16 (14H, m)

¹³C-NMR (CDCl₃) δ 14.6 (q), 28.7 (q), 35.0 (t), 44.7 (t), 60.6 (d), 60.8 (t), 76.8 (d), 81.7 (s), 116.8 (s), 118.2 (d), 122.5 (d), 126.8 (d), 127.5 (d), 128.5 (d), 129.6 (d), 129.8 (d), 130.2 (d), 133.3 (d), 134.1 (d), 137.9 (s), 138.3 (s), 141.6 (s), 143.7 (s), 162.0 (s), 164.5 (s), 171.2 (s).

(3*bR*,6*S*)-ethyl 6-benzyl-11-chloro-4-methyl-5,8-dioxo-3*a*-phenyl-3*a*,3*b*,4,5,6,8-hexahydro-3*H*-benzo[*e*]imidazo[1,2-*a*]pyrazolo[5,1-*c*][1,4]diazepine-2-carboxylate (50ca)



Yield: 44%

Yellow crystal

M.p: 141°C

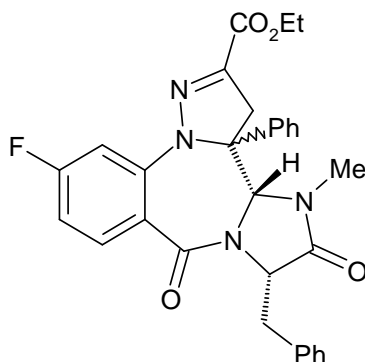
$[\alpha]_D$: +914 (c = 1.89 g/L in CHCl₃)

IR: 1641 cm⁻¹, 1708 cm⁻¹, 1722 cm⁻¹

¹H-NMR (CDCl₃) δ 0.86 - 0.92 (1H, m), 1.37 (3H, t, *J* = 7.2 Hz), 2.18 - 2.26 (1H, m), 3.23 (3H, s), 3.64 (1H, d, *J* = 16.1 Hz), 3.83 (1H, d, *J* = 16.1 Hz), 4.35 (2H, q, *J* = 7.2 Hz), 5.52 (1H, s), 7.13 - 8.13 (13H, m)

¹³C-NMR (CDCl₃) δ 14.2 (q), 30.3 (q), 34.6 (t), 44.5 (t), 60.3 (d), 62.2 (t), 76.3 (d), 81.1 (s), 117.2 (s), 119.4 (d), 126.5 (d), 126.9 (d), 127.7 (s), 128.2 (d), 129.2 (d), 129.3 (d), 129.9 (d), 132.2 (d), 133.6 (d), 137.2 (s), 137.8 (s), 139.7 (s), 143.6 (s), 161.4 (s), 162.7 (s), 170.7 (s).

(3*bR*,6*S*)-ethyl 6-benzyl-11-fluoro-4-methyl-5,8-dioxo-3*a*-phenyl-3*a*,3*b*,4,5,6,8-hexahydro-3*H*-benzo[*e*]imidazo[1,2-*a*]pyrazolo[5,1-*c*][1,4]diazepine-2-carboxylate (50*cb*)



Yield: 77%

Yellow solid

M.p: 146°C

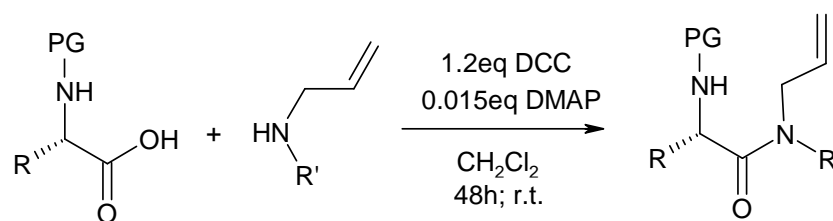
$[\alpha]_D^{25}$: +0.643 (c = 2.2 g/L, CHCl₃)

IR: 1646 cm⁻¹, 1692 cm⁻¹, 1734 cm⁻¹

¹H-NMR (CDCl₃) δ 0.82 - 0.88 (1H, m), 1.37 (3H, t, *J* = 7.1 Hz), 2.30 - 2.35 (1H, m), 3.23 (3H, s), 3.62 (1H, d, *J* = 16.0 Hz), 3.82 (1H, d, *J* = 16.0 Hz), 4.31 (2H, q, *J* = 7.1 Hz), 5.53 (1H, s), 7.13 - 7.79 (13H, m)

¹³C-NMR (CDCl₃) δ 14.2 (q), 29.9 (q), 34.6 (t), 44.2 (t), 60.3 (d), 62.0 (t), 76.4 (d), 81.2 (s), 114.0 (s), 119.7 (dd, *J*_{C-F} = 23.2 Hz), 120.2 (dd, *J*_{C-F} = 7.4 Hz), 125.6 (dd, *J*_{C-F} = 21.8 Hz), 126.4 (d), 127.1 (s), 128.1 (d), 129.2 (d), 129.4 (d), 129.8 (d), 130.2 (d), 130.3 (d), 135.4 (s), 137.6 (s), 137.9 (s), 142.1 (s), 157.8 (d, *J*_{C-F} = 245.6 Hz), 164.0 (s), 170.8 (s).

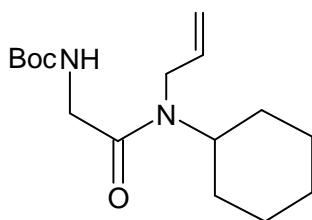
Synthesis of allyl –aminoamides



R = H, *i*Pr, *t*Bu, Bn, Me
R' = Cyclohexyl, Cyclopentyl, Me
PG = Boc, Cbz, Fmoc, CO_2Et

To a solution of *N*-protected amino acid (10 mmol) in CH_2Cl_2 (60 mL) cooled at 0°C were slowly added DCC (2.6 g, 10 mmol), the appropriate *N*-allylamine (8.3 mmol) and DMAP (0.015 g, 0.125 mmol). The resulting solution reacted at r.t. for 48 h, then was filtered on silica gel (EdP/ AcOEt 7:3) and the solvent was evaporated under reduced pressure. The crude residue was purified by silica gel column (EdP / AcOEt 7:3)

Tert-butyl 2-(allyl(cyclohexyl)amino)-2-oxoethylcarbamate (51)



Yield: 87 %

Yellow oil

IR: 1710, 1640 cm^{-1}

Rotamer ratio: 7/4

Major Rotamer

$^1\text{H-NMR}$ (CDCl_3) δ 1.16-1.85 (10H, m), 1.44 (9H, s), 3.11-3.13 (1H, m), 3.74-3.84 (2H, m), 4.41 (2H, m), 4.97-5.12 (2H, m), 5.22 (1H, d, $J = 7.7$ Hz), 5.68-5.76 (1H, m)

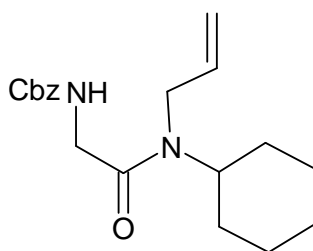
$^{13}\text{C-NMR}$ (CDCl_3) δ 25.2 (t), 25.7 (t), 26.2 (t), 28.3 (q), 30.5 (t), 31.8 (t), 45.0 (t), 45.8 (t), 54.3 (d), 84.6 (s), 116.7 (t), 134.6 (d), 155.8 (s), 172.8 (s).

Minor rotamer

$^1\text{H-NMR}$ (CDCl_3) δ 1.16-1.85 (10H, m), 1.44 (9H, s), 3.58-3.60 (1H, m), 3.74-3.84 (2H, m), 4.41 (2H, m), 4.97-5.12 (2H, m), 5.16 (1H, d, $J = 7.6$ Hz), 5.68-5.76 (1H, m)

$^{13}\text{C-NMR}$ (CDCl_3) δ 25.2 (t), 25.7 (t), 26.2 (t), 27.9 (q), 30.7 (t), 31.6 (t), 44.8 (t), 45.5 (t), 54.1 (d), 83.8 (s), 115.9 (t), 135.0 (d), 155.8 (s), 172.5 (s).

benzyl 2-(allyl(cyclohexyl)amino)-2-oxoethylcarbamate (54a)



Yield: 82 %

Yellow oil

Rotamer ratio: 5/4

Major Rotamer

¹H-NMR (CDCl₃) δ 1.24-1.81 (10H, m,), 3.93 (2H, d, *J* = 5.1 Hz), 3.99 (2H, d, *J* = 4.2 Hz), 4.37-4.39 (1H, m), 5.09-5.23 (4H, m), 5.73-5.83 (1H, m), 5.91 (1H, d), 7.27-7.38 (5H, m)

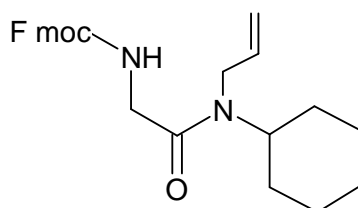
¹³C-NMR (CDCl₃) δ 25.5 (t), 25.7 (t), 26.1 (t), 30.5 (t), 31.7 (t), 43.1 (t), 44.8 (t), 56.3 (d), 66.8 (s), 116.2 (t), 127.0 (d), 127.6 (d), 128.1 (d), 128.5 (d), 128.8 (d), 134.3 (d), 136.5 (s), 156.2 (s), 168.2 (s).

Minor rotamer

¹H-NMR (CDCl₃) δ 1.24-1.81 (10H, m), 3.43-4.45 (1H, m), 3.82 (2H, d, *J* = 5.1 Hz), 4.08 (2H, d, *J* = 4.2 Hz), 5.09-5.23 (4H, m), 5.57 (1H, m), 5.73-5.83 (1H, m), 7.27-7.38 (5H, m)

¹³C-NMR (CDCl₃) δ 25.5 (t), 25.7 (t), 26.1 (t), 30.7 (t), 31.7 (t), 42.9 (t), 44.4 (t), 54.3 (d), 67.1 (t), 117.0 (t), 127.0 (d), 127.6 (d), 128.1 (d), 128.5 (d), 128.8 (d), 134.8 (d), 136.5 (s), 156.2 (s), 168.2 (s).

**9H-fluoren-9-yl)methyl 2-(allyl(cyclohexyl)amino)-2-oxoethylcarbamate
(54b)**



Yield: 75%.

Colorless oil

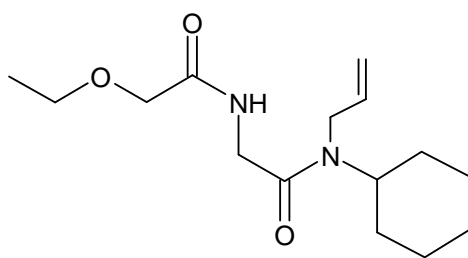
IR: 1712, 1640 cm^{-1} ;

Mixture of two rotamers with distinguishable peaks solely in the ^{13}C NMR spectrum;

^1H NMR (CDCl_3) δ 1.01 – 1.83 (10H, m), 3.72 – 3.76 (1H, m), 3.87 – 3.90 (1H, m), 3.96 – 3.99 (1H, m), 4.03 – 4.09 (2H, m), 4.16– 4.22 (1H, m), 4.30 – 4.35 (2H, m), 5.07 – 5.19 (2H, m), 5.60 – 5.86 (1H, m), 6.00 – 6.10 (1H, m), 7.26 (2H, dd, $J = 7.4, 7.3$ Hz), 7.34 (2H, dd, $J = 7.4, 7.3$ Hz), 7.59 (2H, d, $J = 7.3$ Hz), 7.70 (2H, d, $J = 7.4$ Hz)

^{13}C NMR (CDCl_3) δ 25.1 (t), 25.4 (t), 25.7 (t), 30.5 (t), 31.6 (t), 42.8 (t), 43.1 (t, rotamer peak), 44.4 (t), 44.9 (t, rotamer peak), 47.1 (d), 54.4 (d), 56.3 (d, rotamer peak), 67.1 (t), 116.2(t), 116.8 (t, rotamer peak), 119.9 (d), 125.2 (d), 127.0 (d), 127.6 (d), 134.4 (d), 134.9 (d, rotamer peak), 141.2 (s), 144.0 (s), 156.3 (s), 167.1 (s), 168.2 (s, rotamer peak).

Ethyl 2-(allyl(cyclohexyl)amino)-2-oxoethylcarbamate (54c)



Yield: 57%

Colorless oil

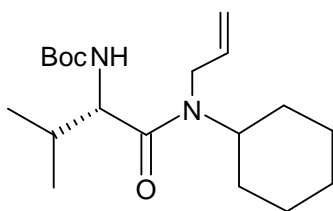
IR: 1708, 1642 cm^{-1}

Mixture of two rotamers with distinguishable peaks solely in the ^{13}C NMR spectrum

^1H NMR (CDCl_3) δ 0.75 – 1.98 (13H, m), 3.75 – 4.40 (7H, m), 4.98 – 5.19 (2H, m), 5.66 - 5.76 (2H, m)

^{13}C NMR(CDCl_3) δ 14.5 (q), 25.1 (t), 25.2 (t), 25.4 (t), 30.5 (t), 31.6 (t), 42.9 (t), 43.0 (t, rotamer peak), 44.3 (t), 44.9 (t, rotamer peak), 54.2 (d), 56.3 (d, rotamer peak), 60.9 (t), 116.1 (t), 116.8 (t, rotamer peak), 134.4 (d), 134.8 (d, rotamer peak), 156.5 (s), 167.3 (s), 168.4 (s, rotamer peak).

**(S)-Tert-butyl 1-(allyl(cyclohexyl)amino)-3-methyl-1-oxobutan-2-ylcarbamate
(55a)**



Yield: 72 %

Colourless oil

IR: 11635, 1709 cm^{-1}

$[\alpha_D]^{25}$: +74.9 (c=2.620 g/L, CHCl_3)

Rotamer ratio: 6:1

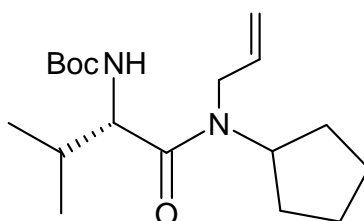
Major Rotamer

$^1\text{H-NMR}$ (CDCl_3)	δ	0.89-0.93 (6H, m), 1.08-1.96 (11H, m), 1.44 (9H, s), 3.75-4.16 (2H, m), 4.29-4.35 (1H, m), 4.50-4.51 (1H, m), 5.08-5.26 (2H, m), 5.29-5.31 (1H, m), 5.78-5.84 (1H, m)
$^{13}\text{C-NMR}$ (CDCl_3)	δ	17.3 (q), 20.0 (q), 25.7 (t), 26.0 (t), 26.2 (t), 28.5 (q), 30.5 (t), 31.9 (d), 32.1 (t), 44.4 (t), 54.3 (d), 57.4 (d), 79.2 (s), 115.9 (t), 135.7 (d), 156.0 (s), 171.6 (s).

Minor rotamer

$^1\text{H-NMR}$ (CDCl_3)	δ	0.98-1.00 (6H, m), 1.08-1.96 (11H, m), 1.44 (9H, s), 3.75-4.16 (2H, m), 4.29-4.35 (1H, m), 4.50-4.51 (1H, m), 5.08-5.26 (2H, m), 5.29-5.31 (1H, m), 5.78-5.84 (1H, m)
$^{13}\text{C-NMR}$ (CDCl_3)	δ	17.8 (q), 19.8 (q), 25.4 (t), 26.0 (t), 26.2 (t), 28.5 (q), 31.0 (t), 32.3 (t), 32.4 (d), 45.9 (t), 53.7 (d), 56.0 (d), 79.2 (s), 116.9 (t), 135.5 (d), 155.7 (s), 172.8 (s).

(S)-Tert-butyl 1-(allyl(cyclopentyl)amino)-3-methyl-1-oxobutan-2-ylcarbamate
(55b)



Yield: 70 %

White solid

$[\alpha_D]^{25}$: +2.4 (c=3.710 g/L in CHCl_3)

Rotamer ratio: 1:1

Major rotamer

$^1\text{H-NMR}$ (CDCl_3) δ 0.84-0.96 (6H, m), 1.53-1.95 (9H, m), 1.41 (9H, s),
3.67-4.03 (2H, m), 4.24-4.30 (2H, m), 5.06-5.11
(2H, m), 5.18-5.21 (1H, m), 5.78-5.85 (1H, m)

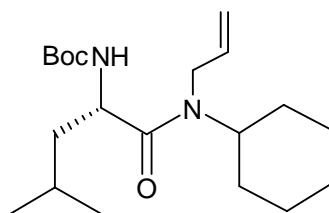
$^{13}\text{C-NMR}$ (CDCl_3) δ 17.1 (q), 19.6 (q), 23.9 (t), 25.7 (t), 28.3 (q), 29.3 (t),
29.8 (t), 32.0 (d), 44.2 (t), 55.1 (d), 58.6 (d), 78.2
(s), 115.5 (t), 134.8 (d), 155.5 (s), 172.5 (s).

Minor rotamer

$^1\text{H-NMR}$ (CDCl_3) δ 0.84-0.96 (6H, m), 1.53-1.95 (9H, m), 1.41 (9H, s),
3.67-4.03 (2H, m), 4.55 (1H, dd, $J = 5.7, 9.2$ Hz),
4.61-4.66 (1H, m), 5.06-5.11 (2H, m), 5.29-5.34
(1H, m), 5.78-5.85 (1H, m)

$^{13}\text{C-NMR}$ (CDCl_3) δ 17.5 (q), 19.8 (q), 23.9 (t), 25.7 (t), 28.3 (q), 29.3 (t),
30.2 (t), 32.2 (d), 46.4 (t), 55.9 (d), 56.3 (d), 78.2
(s), 116.7 (t), 134.9 (d), 155.5 (s), 172.5 (s).

(S)-Tert-butyl 1-(allyl(cyclohexyl)amino)-4-methyl-1-oxopentan-2-ylcarbamate (55c)



Yield: 87 %

Yellow oil

IR: 1639,1709 cm^{-1}

$[\alpha_D]^{25}$: -1.2 (c=1.940g/L, $CHCl_3$)

Rotamer ratio: 3:2

Major Rotamer

1H -NMR ($CDCl_3$) δ 0.78-0.92 (6H, m), 1.21-1.26 (3H, m), 1.30 (9H, s), 1.30-1.40 (3H, m), 1.54-1.66 (7H, m), 3.52-3.58 (1H, m), 3.68-4.02 (2H, m), 4.54-4.58 (1H, m), 4.92-5.12 (2H, m), 5.27-5.29 (1H, m), 5.63-5.78 (1H, m)

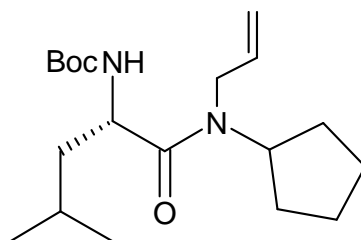
^{13}C -NMR ($CDCl_3$) δ 22.1 (q), 23.8 (q), 24.9 (d), 25.7 (t), 26.0 (t), 26.3 (t), 28.6 (q), 30.7 (t), 31.8 (t), 43.9 (t), 44.4 (t), 49.2 (d), 57.2 (d), 79.4 (s), 115.9 (t), 135.5 (d), 155.7 (s), 172.5 (s).

Minor rotamer

1H -NMR ($CDCl_3$) δ 0.78-0.92 (6H, m), 1.21-1.26 (3H, m), 1.30 (9H, s), 1.30-1.40 (3H, m), 1.54-1.66 (7H, m), 4.20-4.22 (1H, m), 3.68-4.02 (2H, m), 4.36-4.40 (1H, m), 4.92-5.12 (2H, m), 5.27-5.29 (1H, m), 5.63-5.78 (1H, m)

^{13}C -NMR ($CDCl_3$) δ 22.0 (q), 23.7 (q), 24.9 (d), 25.5 (t), 26.1 (t), 26.3 (t), 28.6 (q), 30.9 (t), 32.4 (t), 43.3 (t), 45.6 (t), 49.6 (d), 54.2 (d), 79.4 (s), 117.0 (t), 135.4 (d), 155.9 (s), 173.9 (s).

(S)-Tert-butyl 1-(allyl(cyclopentyl)amino)-4-methyl-1-oxopentan-2-ylcarbamate (55d)



Yield: 80 %

Yellow oil

$[\alpha_D]^{25}$: +19.1 (c=4.340g/L, CHCl₃)

Rotamer ratio 1:1

Major rotamer

¹H-NMR (CDCl₃) δ 0.85-0.99 (6H, m), 1.20-1.25 (3H, m), 1.43 (9H, s),
1.31-1.69 (8H, m), 3.67-3.82 (2H, m), 4.39-4.48
(2H, m), 5.07-5.18 (2H, m), 5.22-5.24 (1H, m),
5.83-5.87 (1H, m)

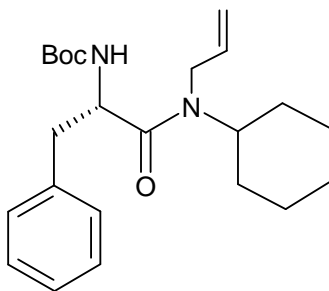
¹³C-NMR (CDCl₃) δ 21.8 (q), 23.7 (q), 24.6 (d), 25.5 (t), 26.0 (t), 28.3
(q), 29.2 (t), 30.2 (t), 31.5 (t), 43.7 (t), 51.7 (d), 58.3
(d), 80.2 (s), 115.4 (t), 134.8 (d), 153.5 (s), 172.2
(s).

Minor rotamer

¹H-NMR (CDCl₃) δ 0.85-0.99 (6H, m), 1.20-1.25 (3H, m), 1.43 (9H, s),
1.31-1.69 (8H, m), 3.67-3.82 (2H, m), 4.69-4.76
(2H, m), 5.07-5.18 (2H, m), 5.30-5.32 (1H, m),
5.83-5.87 (1H, m)

¹³C-NMR (CDCl₃) δ 21.8 (q), 23.7 (q), 24.7 (d), 25.3 (t), 25.9 (t), 28.3
(q), 29.1 (t), 29.7 (t), 31.7 (t), 44.2 (t), 50.0 (d), 56.0
(d), 80.2 (s), 116.6 (t), 134.7 (d), 153.5 (s), 173.6
(s).

N',N'-Allylmethylamide of N-Boc-phenylalanin (55e)



Yield: 61 %

Colorless oil

$[\alpha_D]^{25}$: +2.6 (c=1.229 g/L, CHCl₃)

Rotamer ratio: 5:4

Major rotamer

¹H-NMR (CDCl₃) δ 1.15-1.93 (10H, m), 1.36 (9H, s), 2,91-2,97 (2H, m),
3.33-3.38 (2H, m), 3.62-3.66 (1H, m), 4.60 (1H, dd,
J = 7.9, 15.0 Hz), 5.00-5.06 (2H, m), 5.33 (1H, d, *J*
= 8.2 Hz), 5.54-5.61 (1H, m), 7.18- 7.28 (5H, m)

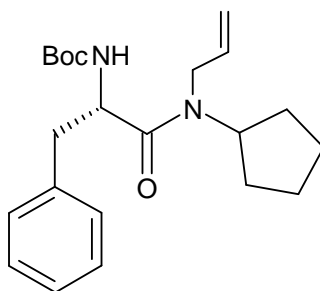
¹³C-NMR (CDCl₃) δ 25.6 (t), 25.8 (t), 26.2 (t), 28.7(q), 30,7 (t), 31.7 (t),
40.8 (t), 44.7 (t), 52.8 (d),54.3 (d), 79.7 (s), 116.7
(t), 127,1 (d) 127.7 (d), 128.8 (d), 129.0 (d), 130.0
(d), 135.4 (d), 137.2 (s), 155.2 (s), 171.5 (s)

Minor rotamer

¹H-NMR (CDCl₃) δ 1.15-1.93 (10H, m), 1.36 (9H, s), 2,91-2,97 (2H, m),
3.62-3.66 (1H, m), 3.90 (1H, dd, *J* = 5.4, 15.4 Hz),
4.27-4.32 (1H, m), 4.85 (1H, dd, *J* = 8.0, 14.7 Hz),
5.00-5.06 (2H, m), 5.46 (1H, d, *J* = 8.1 Hz), 5.65-
5.73 (1H, m), 7.18- 7.28 (5H, m),

¹³C-NMR (CDCl₃) δ 25.6 (t), 25.8 (t), 26.2 (t), 28.7(q), 30,7 (t), 32.4 (t),
40.8 (t), 45.3 (t), 51.8 (d),57.7 (d), 79.7 (s), 116.3
(t), 127,1 (d) 128.7 (d), 128.8 (d), 129.0 (d), 130.0
(d), 135.5 (d), 137.1 (s), 155.4 (s), 172.6 (s)

(S)-Tert-butyl 1-(allyl(cyclopentyl)amino)-1-oxo-3-phenylpropan-2-ylcarbamate (55f)



Yield: 90 %

Colorless oil

$[\alpha_D]^{25}$: +9.2 (c=3.760 g/L, CHCl₃)

Rotamer ratio: 5/4

Major rotamer

¹H-NMR (CDCl₃) δ 1.16-1.76 (8H, m), 1.40 (9H, s), 2.93-2.98 (2H, m), 3.31-3.36 (1H, m), 3.53-3.57 (1H, m), 4.01-4.04 (1H, m), 4.59-4.61 (1H, m), 5.00-5.12 (2H, m), 5.31 (1H, d, *J* = 8.5 Hz), 5.63-5.69 (1H, m), 7.17-7.33 (5H, m)

¹³C-NMR (CDCl₃) δ 23.4 (t), 23.8 (t), 28.3(q), 30.0 (t), 31.4 (t), 40.6 (t), 44.4 (t), 52.6 (d), 58.7 (d), 79.4 (s), 116.2 (t), 126.7 (d), 128.4 (d), 128.7 (d), 129.2 (d), 129.6 (d), 134.6 (d), 137.7 (s), 153.3 (s), 172.7 (s)

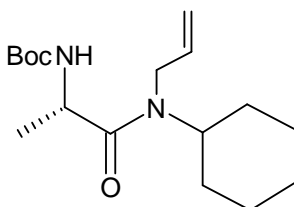
Minor rotamer

¹H-NMR (CDCl₃) δ 1.16-1.76 (8H, m), 1.40 (9H, s), 2.93-2.98 (2H, m), 3.65-3.70 (1H, m), 3.88-3.92 (1H, m), 4.71-4.74 (1H, m), 4.95-4.98 (1H, m), 5.00-5.12 (2H, m), 5.41 (1H, d, *J* = 8.6 Hz), 5.73-5.77 (1H, m), 7.17-7.33 (5H, m),

¹³C-NMR (CDCl₃) δ 23.4 (t), 23.9 (t), 28.2(q), 29.3 (t), 32.5 (t), 40.5 (t), 45.2 (t), 51.4 (d), 55.7 (d), 80.3 (s), 115.8 (t), 126.8 (d), 128.4 (d), 128.7 (d),

129.2 (d), 129.6 (d), 134.7 (d), 137.6 (s),
154.8 (s), 173.2 (s)

(S)-Tert-butyl 1-(allyl(cyclohexyl)amino)-1-oxopropan-2-ylcarbamate (55g)



Yield: 77 %

Yellow oil

$[\alpha_D]^{25}$: -0.9 (c=3.470 g/L, CHCl₃)

IR: 1641, 1709 cm⁻¹

Rotamer ratio: 4/3

Major Rotamer

¹H-NMR (CDCl₃) δ 1.25-1.29 (3H, m), 1.37-1.80 (10H, m), 1.45 (9H, s),
3.82-4.16 (2H, m), 4.35 (1H, s br), 4.65-4.67 (1H,
m), 5.08-5.15 (2H, m), 5.62-5.63 (1H, m), 5.77-5.86
(1H, m)

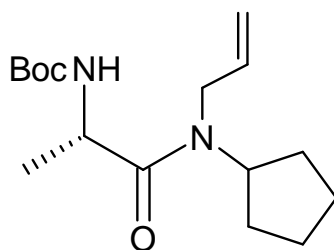
¹³C-NMR (CDCl₃) δ 19.6 (q), 25.3 (t), 25.5 (t), 25.9 (t), 28.3 (q), 30.6 (t),
31.9 (t), 45.4 (t), 46.5 (d), 54.0 (d), 78.9 (s), 116.3
(t), 135.7 (d), 155.0 (s), 171.8 (s).

Minor rotamer

¹H-NMR (CDCl₃) δ 1.32-1.35 (3H, m), 1.37-1.80 (10H, m), 1.45 (9H, s),
3.82-4.16 (2H, m), 4.35 (1H, s br), 4.48-4.52 (1H,
m), 5.20-5.24 (2H, m), 5.32-5.34 (1H, m), 5.77-5.86
(1H, m)

¹³C-NMR (CDCl₃) δ 19.3 (q), 25.3 (t), 25.5 (t), 25.9 (t), 28.3 (q), 30.4 (t),
32.1 (t), 44.2 (t), 46.7 (d), 56.8 (d), 78.9 (s), 115.5
(t), 135.3 (d), 155.0 (s), 173.4 (s).

(S)-Tert-butyl 1-(allyl(cyclopentyl)amino)-1-oxopropan-2-ylcarbamate (55h)



Yield: 70 %

Colorless oil

$[\alpha_D]^{25}$: -9.6 (c=3.210 g/L, CHCl₃)

Rotamer ratio: 6/4

Major rotamer

¹H-NMR (CDCl₃) δ 0.86-0.90 (3H, m), 1.07 (9H, s), 1.21-1.48 (8H, m),
3.46-3.50 (1H, m), 3.73-3.77 (1H, m), 3.90-3.95
(1H, m), 4.09-4.14 (1H, m), 4.71-4.86 (2H, m),
5.34-5.52 (2H, m)

¹³C-NMR (CDCl₃) δ 19.5 (q), 23.4 (t), 23.6 (t), 27.4 (q), 28.8 (t), 29.8 (t),
45.7 (t), 48.7 (d), 58.0 (d), 78.7 (s), 114.9 (t), 134.8
(d), 154.8 (s), 172.0 (s).

Minor rotamer

¹H-NMR (CDCl₃) δ 0.97-1.01 (3H, m), 1.07 (9H, s), 1.21-1.48 (8H, m),
3.57-3.61 (1H, m), 3.73-3.77 (1H, m), 4.31-4.38
(2H, m), 4.71-4.86 (2H, m), 5.34-5.52 (2H, m)

¹³C-NMR (CDCl₃) δ 19.1 (q), 23.4 (t), 23.5 (t), 27.4 (q), 28.6 (t), 29.4 (t),
45.8 (t), 49.8 (d), 55.9 (d), 78.7 (s), 115.9 (t), 134.5
(d), 154.8 (s), 173.5 (s).

Synthesis of hydroamination Product (53)

7-Cyclohexyldihydro-1*H*-oxazolo[3,4-*a*]pyrazine-3,6(5*H*,7*H*)-dione from glycine having different protecting functional group on nitrogen (54a-c)



The allylamide of a nitrogen protected glycine **54a-c** (1 mmol) was dissolved in 10 mL of DMF. CuCl₂ (3 mmol) and Pd(CH₃CN)₂Cl₂ (0.05 mmol) were added. The reaction mixture was left under agitation at 100°C for 24 hours. Brine was added to the reaction mixture and it was extracted with CH₂Cl₂ (3x 10 ml). The organic phase was dried with Na₂SO₄ and the solvent is evaporated at reduced pressure. The obtained crude was purified by a column chromatography (EdP / AcOEt 8:2)

Yield: 81 %

Yellow solid

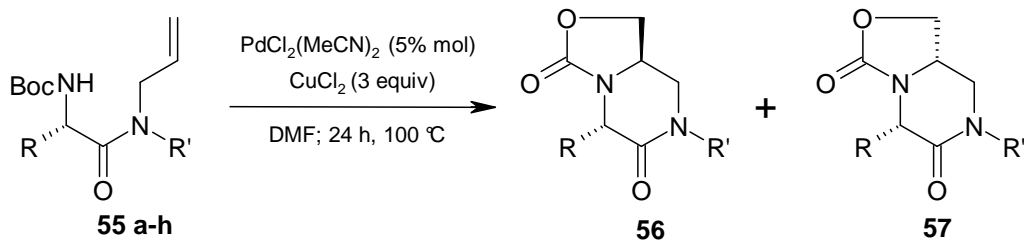
M.p.: 118-124 °C

IR: 1630, 1751 cm⁻¹

¹H-NMR (CDCl₃) δ 1.00-1.95 (10H, m), 3.26 (1H, dd, *J* = 12.1, 10.9 Hz), 3.39 (1H, dd, *J* = 12.1, 4.0 Hz), 3.89 (1H, A part of AB system, *J* = 14.0 Hz), 3.98-4.05 (1H, m), 4.11 (1H, dd, *J* = 3.48, 9.12 Hz), 4.36 (1H, B part of AB system, *J* = 14.0 Hz), 4.48-4.52 (2H, m)

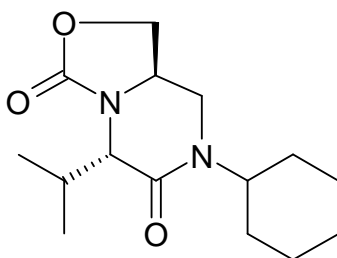
¹³C-NMR (CDCl₃) δ 25.3 (t), 25.4 (t), 25.5 (t), 29.3 (t), 29.7 (t), 44.2 (t), 45.0 (t), 50.6 (d), 52.6 (d), 65.2 (t), 156.4 (s), 163.4 (s).

Cyclisation of N',N'-Alkylallylamide



CuCl₂ 98 % (1 eq.) and Pd(CH₃CN)₂Cl₂ 99 % (0,05 eq.) were dissolved in dry DMF (10 mL). The allylaminoamide **55 a-h** (1 eq.) dissolved in dry DMF (10 mL) was added, the reaction mixture was left under agitation at 100 °C for 24 ore. Brine was added to the reaction mixture and it was extracted 3 times with CH₂Cl₂. The organic phase was dried with Na₂SO₄ and the solvent is evaporated at reduced pressure. The obtained crude was purified by a column chromatography (EdP/AcOEt 1:1)

(5*S*,8*aR*)-7-Cyclohexyl-5-isopropyl-dihydro-1*H*-oxazolo[3,4-*a*]pyrazine-3,6(5*H*,7*H*)-dione (56a)



Yield: 48 %

Red solid

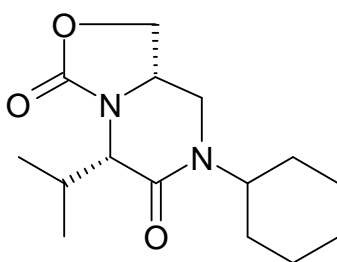
M.p.: 116-120 °C

$[\alpha_D]^{25} = +20.4$ (c=1.730g/L, CHCl₃)

¹H-NMR (CDCl₃) δ 0.84 (3H, d, *J* = 6.8 Hz), 0.99 (3H, dd, *J* = 6.8, 1.2 Hz), 1.15-1.80 (10H, m), 2.57-2.70 (1H, m), 3.19 (1H, dd, *J* = 11.9, 11.3 Hz), 3.30 (1H, dd, *J* = 11.9, 4.2 Hz), 3.97-4.06 (2H, m), 4.15 (1H, s br), 4.40-4.53 (2H, m)

¹³C-NMR (CDCl₃) δ 17.8 (q), 19.5 (q), 25.3 (t), 25.5 (t), 29.4 (t), 29.6 (t), 32.3 (d), 44.4 (t), 51.2 (d), 52.7 (d), 60.6 (d), 64.8 (d), 157.8 (s), 166.0 (s).

(5*S*,8*aS*)-7-Cyclohexyl-5-isopropyldihydro-1*H*-oxazolo[3,4-*a*]pyrazine-3,6(5*H*,7*H*)-dione (57a)



Yield: 18 %

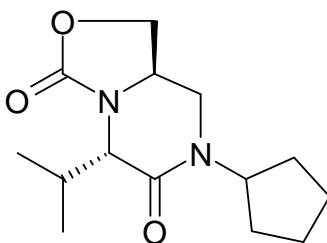
Red Solid

M.p.: 134-139 °C

$[\alpha_D^{25}]$: -57.8 (c=1.540g/L, CHCl₃)

¹ H-NMR (CDCl ₃)	δ	0.88 (3H, d, <i>J</i> = 7.4 Hz), 1.01-1.90 (10H, m), 1.17 (3H, d, <i>J</i> = 7.4 Hz), 2.86 (1H, dqq, <i>J</i> = 7.4, 7.4, 3.9 Hz), 3.20 (1H, dd, <i>J</i> = 12.0, 9.9 Hz), 3.45 (1H, dd, <i>J</i> = 12.0, 2.6 Hz), 3.88-3.98 (2H, m), 4.11 (1H, d, <i>J</i> = 2.6 Hz), 4.43-4.49 (2H, m)
¹³ C-NMR (CDCl ₃)	δ	16.1 (q), 19.8 (q), 25.2 (t), 25.4 (t), 25.6 (t), 29.1 (t), 29.5 (d), 30.3 (t), 43.6 (t), 53.0 (d), 53.2 (d), 62.2 (d), 65.4 (t), 155.7 (s), 165.3 (s).

(5*S*,8*aR*)-7-Cyclopentyl-5-isopropylidihydro-1*H*-oxazolo[3,4-*a*]pyrazine-3,6(5*H*,7*H*)-dione (56b)



Yield: 56 %

Red Solid

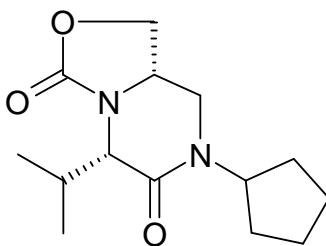
M.p.: 139-142 °C

$[\alpha]_D^{25}$: +66.9 (c=1.050g/L, CHCl₃)

¹H-NMR (CDCl₃) δ 0.89 (3H, d, *J* = 7.0 Hz), 1.04 (3H, d, *J* = 7.0 Hz),
1.30-1.88 (8H, m), 2.66 (1H, dqq, *J* = 7.0, 7.0, 3.2
Hz), 3.21-3.31(2H, m), 3.99-4.05 (1H, m), 4.08 (1H,
dd, *J* = 9.2, 1.6 Hz), 4.17 (1H, d, *J* = 3.2 Hz), 4.44-
4.49 (1H, m), 4.95-5.01 (1H, m)

¹³C-NMR (CDCl₃) δ 17.8 (q), 19.5 (q), 23.9 (t), 24.2 (t), 27.4 (t), 28.7 (t),
32.3 (d), 44.6 (t), 51.2 (d), 54.6 (d), 60.7 (d), 64.8
(t), 157.8 (s), 166.5 (s).

(5*S*,8*aS*)-7-cyclopentyl-5-isopropyl-dihydro-1*H*-oxazolo[3,4-*a*]pyrazine-3,6(5*H*,7*H*)-dione (57b)



Yield: 23 %

Yellow solid

M.p.: 117-120 °C

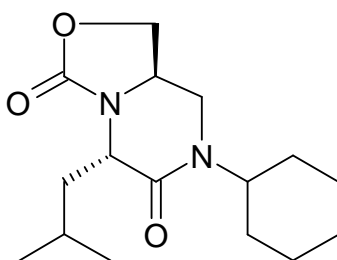
$[\alpha_D]^{25} = -13.8$

($c=1.420\text{g/L}$, CHCl_3)

$^1\text{H-NMR}$ (CDCl_3) δ 0.89 (3H, d, $J = 7.0$ Hz), 1.17 (3H, d, $J = 7.0$ Hz), 1.25-1.95 (8H, m), 2.85 (1H, ddq, $J = 7.0, 7.0, 3.0$ Hz), 3.27 (1H, dd, $J = 12.0, 10.0$ Hz), 3.36 (1H, dd, $J = 12.0, 2.6$ Hz), 3.95-3.98 (2H, m), 4.12 (1H, d, $J = 3.0$ Hz), 4.44-4.47 (1H, m), 4.90-4.99 (1H, m)

$^{13}\text{C-NMR}$ (CDCl_3) δ 16.1 (q), 19.8 (q), 24.0 (t), 24.1 (t), 28.2 (t), 28.3 (t), 29.3 (d), 43.8 (t), 53.1 (d), 54.6 (d), 62.4 (d), 64.7 (d), 155.6 (s), 165.8 (s).

(5*S*,8*aR*)-7-cyclohexyl-5-isobutyldihydro-1*H*-oxazolo[3,4-*a*]pyrazine-3,6(5*H*,7*H*)-dione (56c)



Yield: 62 %

Yellow Solid

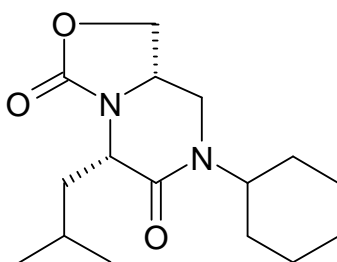
M.p.: 117-119 °C

$[\alpha_D^{25}]$: +18.8 (c=2.200g/L, CHCl₃)

¹H-NMR (CDCl₃) δ 0.91 (3H, d, *J* = 6.4 Hz), 0.99 (3H, d, *J* = 6.4 Hz),
1.25-1.85 (13H, m), 3.23 (1H, dd, *J* = 11.9, 10.9
Hz), 3.31 (1H, dd, *J* = 11.9, 4.5 Hz), 3.99-4.02 (1H,
m), 4.07 (1H, dd, *J* = 9.2, 6.0 Hz), 4.32 (1H, dd, *J* =
10.4, 3.6 Hz), 4.40-4.46 (2H, m)

¹³C-NMR (CDCl₃) δ 21.2 (q), 23.3 (q), 24.7 (d), 25.4 (t), 25.5 (t), 29.4
(t), 29.5 (t), 41.6 (t), 44.4 (t), 48.2 (d), 52.7 (d), 53.9
(d), 65.2 (t), 156.6 (s), 167.0 (s).

(5*S*,8*aS*)-7-Cyclohexyl-5-isobutyldihydro-1*H*-oxazolo[3,4-*a*]pyrazine-3,6(5*H*,7*H*)-dione (57c)



Yield: 9 %

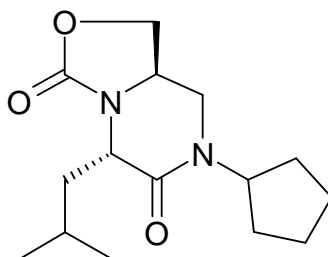
Orange solid

M.p.: 133-136 °C

$[\alpha_D^{25}]$: -36.5 (c=2.230 g/L, CHCl₃)

¹ H-NMR (CDCl ₃)	δ	0.80-1.02 (6H, m), 1.05-2.16 (13, m), 3.22 (1H, dd, <i>J</i> = 12.0, 10.0 Hz), 3.48 (1H, dd, <i>J</i> = 12.0, 2.3 Hz), 3.92-3.97 (2H, m), 4.17-4.21 (1H, m), 4.40-4.48 (2H, m)
¹³ C-NMR (CDCl ₃)	δ	22.2 (q), 23.7 (q), 24.5 (d), 25.3 (t), 25.4 (t), 25.5 (t), 29.2 (t), 29.7 (t), 39.3 (t), 43.8 (t), 53.0 (d), 53.1 (d), 56.3 (d), 65.4 (t), 155.6 (s), 167.3 (s).

(5*S*,8*aR*)-7-Cyclopentyl-5-isobutyldihydro-1*H*-oxazolo[3,4-*a*]pyrazine-3,6(5*H*,7*H*)-dione (56d)



Yellow solid

Yield: 62 %

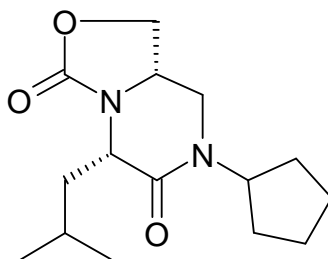
M.p.: 118-121 °C

$[\alpha_D]^{25}$: +29.3 (c=2.360 g/L, CHCl₃)

¹H-NMR (CDCl₃) δ 0.92 (3H, d, *J* = 6.5 Hz), 0.99 (3H, d, *J* = 6.5 Hz),
1.31-1.87 (11H, m). 3.22-3.32 (2H, m), 3.99-4.05
(1H, m), 4.09 (1H, dd, *J* = 9.2, 1.5 Hz), 4.31 (1H,
dd, *J* = 10.7, 3.0 Hz), 4.42 (1H, dd, *J* = 9.2, 8.2 Hz),
4.90-4.96 (1H, m)

¹³C-NMR (CDCl₃) δ 21.2 (q), 23.4 (q), 23.9 (t), 24.2 (t), 24.7 (d), 27.4
(t), 28.4 (t), 41.7 (t), 44.4 (t), 48.2 (d), 53.9 (d), 54.6
(d), 65.2 (t), 156.6 (s), 167.5 (s)

(5*S*,8*aS*)-7-Cyclopentyl-5-isobutyldihydro-1*H*-oxazolo[3,4-*a*]pyrazine-3,6(5*H*,7*H*)-dione (57d)



Yield: 15 %

Brown solid

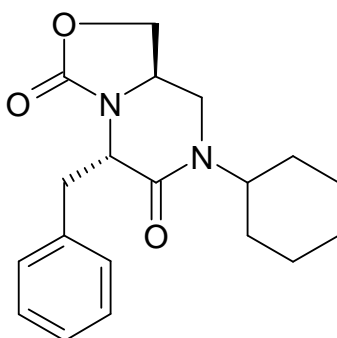
M.p.: 100-102 °C

$[\alpha]_D^{25}$: -8.3 (c=1.720 g/L, CHCl₃)

¹H-NMR (CDCl₃) δ 0.85-1.00 (6H, m), 1.20-2.17 (11H, m), 3.28 (1H, dd, *J* = 12.0, 9.4 Hz), 3.40 (1H, dd, *J* = 12.0, 1.2 Hz), 3.94-4.09 (2H, m), 4.20 (1H, dd, *J* = 7.1, 3.5 Hz), 4.48 (1H, s br), 4.91-4.99 (1H, m)

¹³C-NMR (CDCl₃) δ 22.0 (q), 23.7 (q), 24.0 (t), 24.2 (t), 24.4 (d), 27.8 (t), 28.3 (t), 39.3 (t), 44.0 (t), 53.0 (d), 54.7 (d), 56.4 (d), 65.4 (t), 155.5 (s), 167.8 (s).

(5*S*,8*aR*)-5-Benzyl-7-cyclohexyldihydro-1*H*-oxazolo[3,4-*a*]pyrazine-3,6(5*H*,7*H*)-dione (56e)



Yield: 57 %

Yellow solid

M.p.: 168-171 °C

$[\alpha]_D^{25}$: -6.6 (c=1.760 g/L, CHCl₃)

¹H-NMR (CDCl₃) δ 0.82-1.79 (10H, m), 2.75-2.83 (1H, m), 3.01-3.08 (3H, m), 3.57 (1H, dd, *J* = 13.4, 3.5 Hz), 3.85 (1H, dd, *J* = 8.9, 3.6 Hz), 4.17 (1H, dd, *J* = 8.9, 8.4 Hz), 4.47-4.58 (2H, m), 7.16-7.27 (5H, m)

¹³C-NMR (CDCl₃) δ 25.3 (t), 25.4 (t), 25.5 (t), 29.3 (t), 29.5 (t), 37.9 (t), 44.7 (t), 49.5 (d), 52.9 (d), 55.8 (d), 65.0 (t), 127.1 (d), 128.4 (d), 129.9 (d), 136.7 (s), 156.4 (s), 165.4 (s)

(5*S*,8*aS*)-5-Benzyl-7-cyclohexyldihydro-1*H*-oxazolo[3,4-*a*]pyrazine-3,6(5*H*,7*H*)-dione (57e)



Yellow solid

Yield: 25 %

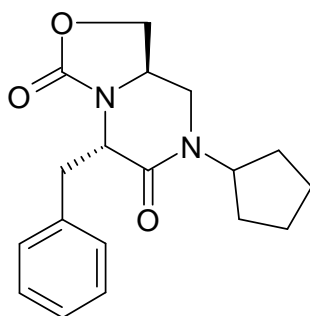
M.p.: 139-142 °C

$[\alpha_D]^{25}$: -88.3 (c=2.050 g/L, CHCl₃)

¹H-NMR (CDCl₃) δ 0.80-1.80 (11H, m), 2.95 (1H, dd, *J* = 8.5, 3.5 Hz),
3.24 (1H, dd, *J* = 13.6, 2.3 Hz), 3.64 (1H, dd, *J* =
10.5, 8.5 Hz), 3.80-3.90 (2H, m), 4.32-4.52 (3H, m),
7.16-7.27 (5H, m)

¹³C-NMR (CDCl₃) δ 25.2 (t), 25.3 (t), 25.5 (t), 29.3 (t), 29.4 (t), 35.2 (t),
42.4 (t), 52.1 (d), 52.8 (d), 57.5 (d), 65.5 (t), 127.2
(d), 128.2 (d), 130.4 (d), 135.8 (s), 155.6 (s), 166.2
(s).

(5*S*,8*aR*)-5-Benzyl-7-cyclopentyl-dihydro-1*H*-oxazolo[3,4-*a*]pyrazine-3,6(5*H*,7*H*)-dione (56f)



Yield: 41 %

Yellow solid

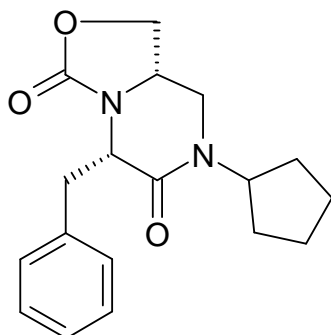
M.p.: 83-86 °C

$[\alpha_D]^{25}$: +10.1(c=2.220 g/L, CHCl₃)

¹H-NMR (CDCl₃) δ 1.07-1.90 (8H, m), 2.78-2.82 (1H, m), 2.92-3.14 (3H, m), 3.50 (1H, d, *J* = 13.1 Hz), 3.84 (1H, d, *J* = 6.4 Hz), 4.11-4.15 (1H, m), 4.51 (1H, s br), 4.93-4.99 (1H, m), 7.10-7.25 (5H, m)

¹³C-NMR (CDCl₃) δ 23.9 (t), 24.2 (t), 27.3 (t), 28.5 (t), 38.0 (t), 44.8 (t), 49.5 (d), 54.7 (d), 55.9 (d), 65.0 (t), 127.1 (d), 128.4 (d), 129.9 (d), 136.8 (s), 156.4 (s), 166.0 (s)

(5*S*,8*aS*)-5-Benzyl-7-cyclopentyl-dihydro-1*H*-oxazolo[3,4-*a*]pyrazine-3,6(5*H*,7*H*)-dione (57f)



Yield: 13 %

Orange solid

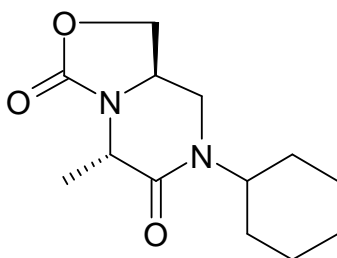
M.p.: 158-161 °C

$[\alpha]_D^{25}$: -8.9 (c=2.570 g/L, CHCl₃)

¹H-NMR (CDCl₃) δ 0.95-1.95 (9H, m), 2.83 (1H, dd, *J* = 12.0, 3.2 Hz),
3.22 (1H, dd, *J* = 9.6, 2.7 Hz), 3.64 (1H, dd, *J* =
10.6, 8.4 Hz), 3.82-3.88 (2H, m), 4.35 (1H, dd, *J* =
8.4, 7.8 Hz), 4.51 (1H, dd, *J* = 4.9, 2.7 Hz), 4.94-
4.99 (1H, m), 7.12-7.30 (5H, m)

¹³C-NMR (CDCl₃) δ 24.0 (t), 24.2 (t), 27.4 (t), 28.3 (t), 35.3 (t), 42.4 (t),
51.9 (d), 54.2 (d), 57.6 (d), 65.6 (t), 127.2 (d), 128.2
(d), 130.3 (d), 135.9 (s), 155.5 (s), 166.7 (s).

(5*S*,8*aR*)-7-Cyclohexyl-5-methyldihydro-1*H*-oxazolo[3,4-*a*]pyrazine-3,6(5*H*,7*H*)-dione (56g)



Yield: 49 %

Yellow solid

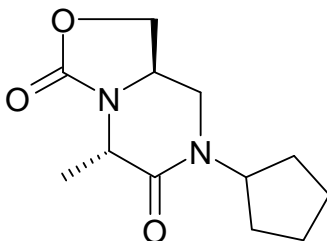
M.p.: 116-122 °C

$[\alpha_D]^{25}$: +27.2 (c=3.110 g/L, CHCl₃)

¹H-NMR (CDCl₃) δ 0.98-1.08 (1H, m), 1.20-1.45 (4H, m), 1.46 (3H, d, *J* = 7.1 Hz), 1.55-1.80 (5H, m), 3.22 (1H, dd, *J* = 11.9, 10.6 Hz), 3.36 (1H, dd, *J* = 11.9, 3.9 Hz), 3.99-4.08 (2H, m), 4.33 (1H, *J* = 7.1 Hz), 4.40-4.96 (2H, m)

¹³C-NMR (CDCl₃) δ 18.3 (q), 25.4 (t), 25.5 (t), 29.2 (t), 29.4 (t), 29.6 (t), 45.0 (t), 48.3 (t), 51.0 (d), 52.8 (d), 65.2 (t), 156.1 (s), 167.1 (s)

(5*S*,8*aR*)-7-Cyclopentyl-5-methyldihydro-1*H*-oxazolo[3,4-*a*]pyrazine-3,6(5*H*,7*H*)-dione (56h)



Yield: 55 %

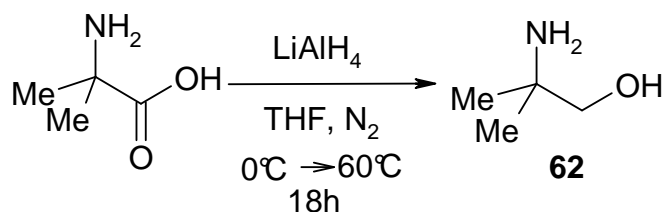
Red solid

M.p.: 134-138 °C

$[\alpha]_D^{25}$: +37.2 (c=1.640g/L, CHCl₃)

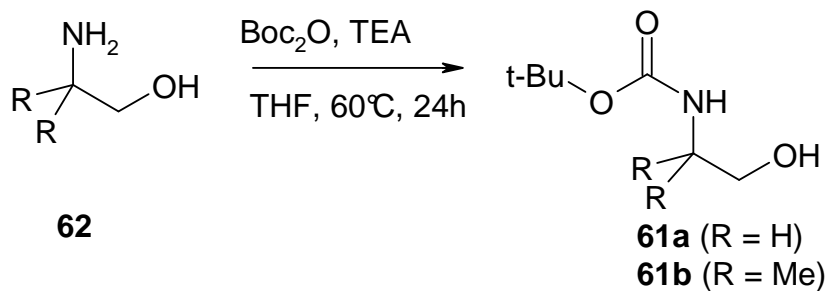
¹ H-NMR (CDCl ₃)	δ	1.30-1.87 (8H, m), 1.46 (3H, d, <i>J</i> = 7.1 Hz), 3.29 (2H, d, <i>J</i> = 7.0 Hz), 4.00-4.09 (2H, m), 4.35 (1H, q, <i>J</i> = 7.1 Hz), 4.43-4.48 (1H, dd, <i>J</i> = 8.6, 8.1 Hz), 4.90-4.99 (1H, m)
¹³ C-NMR (CDCl ₃)	δ	18.2 (q), 23.9 (t), 24.2 (t), 27.5 (t), 28.4 (t), 45.0 (t), 48.3 (d), 51.0 (d), 54.6 (d), 65.3 (t), 156.1 (s), 167.4 (s).

Reduction of 2-Aminoisobutirric acid (62)



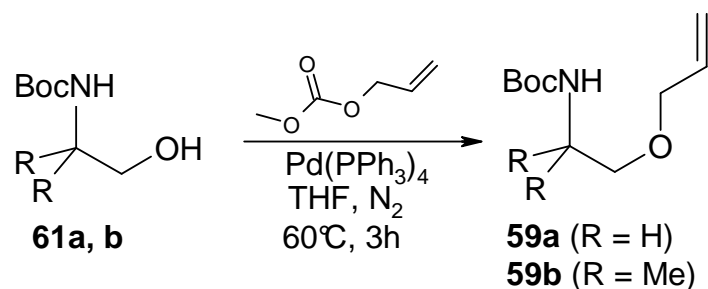
LiAlH₄ (2.4 g, 63 mmol) was dissolved in 60 mL of dry THF under nitrogen atmosphere, the mixture was cooled to 0°C and the amino acid (2.0 g, 19 mmol) was added drop wise. Then the reaction mixture was heated to a 60°C. The reaction was monitored by TLC (BuOH / MeOH/ H₂O/ AcOH 10:4.5:5:4). After 5 hours 2 mL of H₂O, 2 mL of NaOH at 15% were added and then other 6 mL of H₂O. The reaction mixture was left under agitation all night. Then Na₂SO₄ was added until the mixture became transparent and then it was filtered on celite.

Synthesis of *N*-Boc protected Aminoalchol (61a,b)



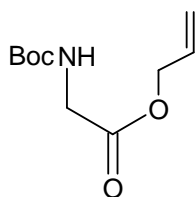
The aminoalcohol (50 mmol) was dissolved in dry THF (30-70 mL), TEA (2.95g, 50 mmol) and then Boc₂O (10.9 g, 50 mmol) were added. The reaction mixture was left under agitation at room temperature for 24 hours. The solvent was evaporated, 20 mL of H₂O was added then it was extracted by AcOEt (40 mL x 3). The organic phase was dried with Na₂SO₄ and the solvent is evaporated at reduced pressure

General procedure for the preparation of Allylethers (59a,b)



A solution of N-protected amino alcohol (1 mmol) in anhydrous THF (10 mL) was degassed (vacuum-N₂ flush) and treated with allyl methyl carbonate (0.16g, 1.4 mmol). A catalytic amount of tetrakis(triphenylphosphine)palladium (0.02 mol%) was added. The mixture was heated at 60° C for about 3 h. The THF was removed under reduced pressure. The residue was diluted with ethyl acetate and washed with aqueous saturated NaHCO₃ solution. The organic layer was dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography. (EdP/ AcOEt 95:5)

Tert-Butyl 2-(allyloxy)ethylcarbamate (59a)



Yield: 50%

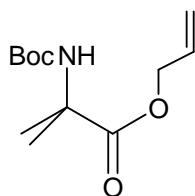
Colorless oil

IR: 1711 cm^{-1}

^1H NMR (CDCl_3) δ 1.43 (9H, s), 3.28 – 3.31 (2H, m), 3.47 – 3.50 (2H, m), 3.94 – 3.98 (2H, m), 4.96 (1H, br s), 5.16 (1H, dd, $J = 11.8, 1.2$ Hz), 5.25 (1H, dd, $J = 17.2, 1.2$ Hz), 5.83 – 5.92 (1H, m)

^{13}C -NMR (CDCl_3) δ 28.3 (q), 40.4 (t), 69.1 (t), 71.9 (t), 79.5 (s), 117.1 (t), 134.5 (d), 155.9 (s)

Tert-Butyl 1-(allyloxy)-2-methylpropan-2-ylcarbamate (59b)



Yield: 60%

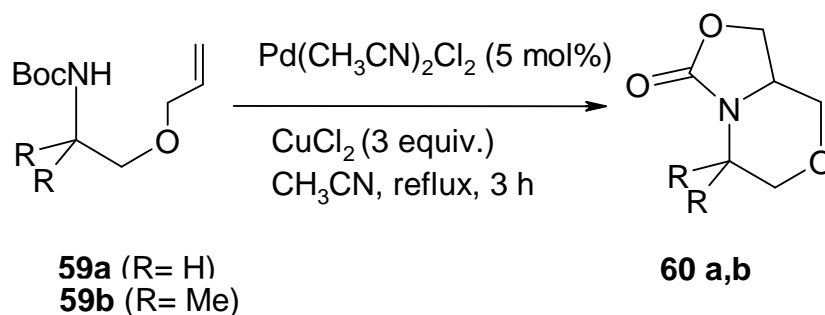
Colorless oil

IR: 1709 cm^{-1}

^1H NMR (CDCl_3) δ 1.27 (6H, s), 1.40 (9H, s), 3.34 (2H, br s), 3.95 – 3.99 (2H, m), 4.73 (1H, br s), 5.14 (1H, dd, $J = 10.4, 1.6$ Hz), 5.23 (1H, dd, $J = 17.2, 1.6$ Hz), 5.83 – 5.88 (1H, m)

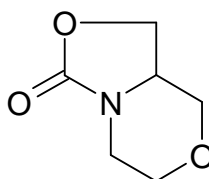
^{13}C NMR (CDCl_3) δ 24.2 (q), 28.4 (q), 52.6 (s), 72.2 (t), 76.4 (t), 79.8 (s), 116.8 (t), 134.7 (d), 154.8 (s).

**Cyclisation of Allylethers of *N*-Boc protected Aminoalcohols
(59a, 59b)**



The *N*-Boc protected allylether of the aminoalcohols **59a,b** (1 mmol) were dissolved in 10 mL of CH₃CN, CuCl₂ (0.39g, 3 mmol) and Pd(CH₃CN)₂Cl₂ (0.05 mmol) were added. The mixture was left under reflux for 24 hours. Brine was added to the reaction mixture and it was extracted with CH₂Cl₂ (3x 10 ml). The organic phase was dried with Na₂SO₄ and the solvent is evaporated at reduced pressure. The obtained crude was purified by a column chromatography (EdP/ AcOEt 7:3)

Tetrahydrooxazolo[4,3-c][1,4]oxazin-3(1H)-one (60a)



Yield: 75%

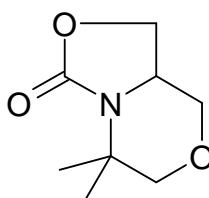
Colorless oil

IR: 1745 cm^{-1}

$^1\text{H-NMR}$ (CDCl_3) δ 3.17-3.33 (2H, m), 3.45 (1H, ddd, $J = 3.0$, $J = 11.8$, $J = 11.7$), 3.72 (1H, dd, $J = 3.0$, $J = 13.3$), 3.87-3.97 (4H, m), 4.40 (1H, dd, $J = 7.9$, $J = 8.0$)

$^{13}\text{C-NMR}$ (CDCl_3) δ 41.3 (t), 52.3 (d), 64.2 (t), 66.1 (t), 69.8 (t), 156.6 (s).

5,5-Dimethyltetrahydrooxazolo[4,3-c][1,4]oxazin-3(1H)-one (60b)



Yield: 82 %

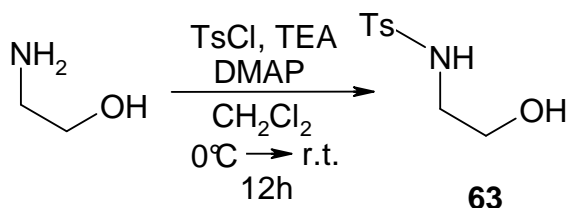
Colorless oil

IR: 1740 cm^{-1}

$^1\text{H-NMR}$ (CDCl_3) δ 1.32 (3H, s), 1.51 (3H, s), 3.16-3.26 (2H, m), 3.47 (1H, d, $J = 12.6$), 3.68-3.72 (1H, m), 3.92-4.00 (1H, m), 4.04 (1H, dd, $J = 3.6$, $J = 10.4$), 4.29 (1H, dd, $J = 7.7$, $J = 8.1$)

$^{13}\text{C-NMR}$ (CDCl_3) δ 20.5 (q), 22.5 (q), 50.8 (d), 53.1 (s), 63.9 (t), 70.1 (t), 76.5 (t), 155.9 (s).

Synthesis of *N*-Tosyl-glycinol (**63**)



To a solution of glycinol (3.0 g, 49 mmol), DMAP (598 mg, 4.9 mmol) and TEA (9.9 g, 98 mmol) in CH₂Cl₂ (100 mL) at 0°C, TsCl (9.8 g, 51.5 mmol) was added drop by drop in CH₂Cl₂ (100 mL). The reaction mixture was left under agitation at room temperature for one night. Then the mixture was washed by H₂O (50 mL x 3) and then by brine (50 mL x 1). The organic phase was dried with Na₂SO₄, filtered and evaporated.

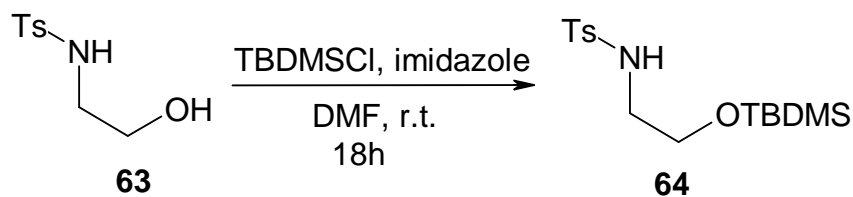
Yield: 97%

White solid

M.p. 53-55°C

Product is already reported.⁴⁸

Synthesis of *N*-Tosyl-*O*-*tert*-butyldimethylsilyl-glycinol (**64**)



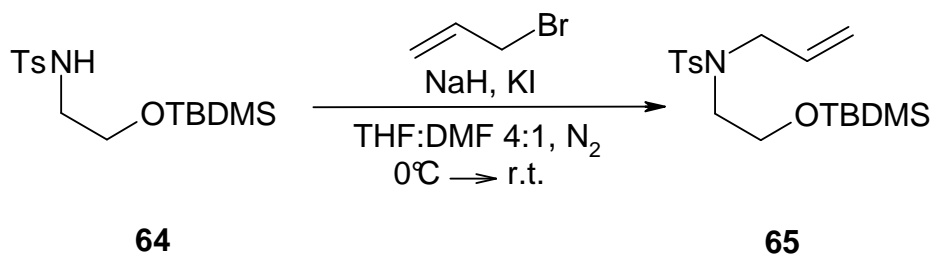
A mixture of *N*-tosyl-glycinol **63** (4.9 g, 23 mmol), TBDMSCl (6.9 g, 46 mmol) and imidazole (3.1 g, 46 mmol) in DMF (40 mL) were left under agitation at room temperature for one night. Brine (40 mL) was then added and extracted with Et₂O (40 mL x 3). The organic phase was dried with Na₂SO₄, filtered and evaporated. The crude was purified by column chromatography.

Colorless oil

Yield: 98%

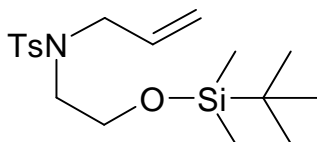
Product is already reported⁴⁹

**Synthesis of
N-allyl-*N*-Tosyl-*O*-*tert*-butyldimethylsilyl-glycinol (**65**)**



To a suspension of NaH (432 mg, 18 mmol) in THF/DMF 4:1 (20 mL) at 0°C and under nitrogen atmosphere KI (3.0 g, 18 mmol) was added and then a solution of *N*-tosyl-*O*-*tert*-butyldimethylsilyl-glycinol **64** (3.9 g, 12 mmol) in THF/DMF 4:1 (20 mL) was added drop by drop. The mixture was left under agitation at room temperature at 0°C for 30 minutes. A solution of allylbromide (2.2 g, 18 mmol) in THF/DMF 4:1 (20 mL) was added drop by drop at 0°C. The reaction mixture was then left at room temperature for one night. 1 mL of H₂O was added, the solvent was then evaporated. 30 mL of brine was added and extracted by Et₂O (20 mL x 3). The organic phase was dried with Na₂SO₄, filtered and evaporated. The crude was purified by column chromatography.

N-Allyl-*N*-tosyl-*O*-*tert*-butyldimethylsilyl-glycinol (**65**)



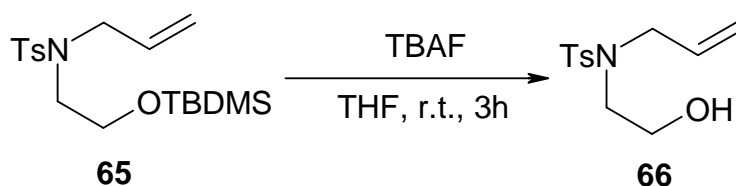
Yield: 75%

Colorless oil

$^1\text{H-NMR}$ (CDCl_3) δ 0.04 (6H, s), 0.87 (9H, s), 2.43 (3H, s), 3.22 (2H, t, $J = 6.4$), 3.73 (2H, t, $J = 6.4$), 3.88 (2H, d, $J = 6.4$), 5.14 (1H, dd, $J = 1.3$, $J = 10.1$), 5.17 (1H, dd, $J = 1.3$, $J = 17.1$), 5.61-5.72 (1H, m), 7.28 (2H, d, $J = 7.9$), 7.69 (2H, d, $J = 7.9$)

$^{13}\text{C-NMR}$ (CDCl_3) δ 5.4 (q), 18.2 (s), 21.5 (q), 25.9 (q), 48.9 (t), 52.0 (t), 62.3 (t), 118.8 (t), 127.2 (d), 129.6 (d), 133.3 (d), 137.3 (s), 143.1 (s).

Synthesis of *N*-allyl-*N*-tosyl-glycinol (**66**)



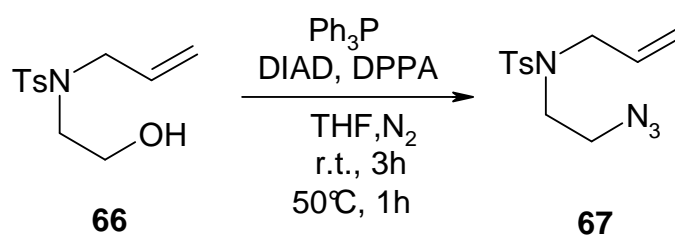
The mixture of *N*-allyl-*N*-tosyl-*O*-*tert*-butyldimethylsilyl-glycinol **65** (3.3 g, 9 mmol) and TBAF (2.8 g, 10.8 mmol) in THF were left under agitation at room temperature for 3 hours. The solvent was evaporated, H_2O (30 mL) was added and it was extracted by CH_2Cl_2 (30 mL x 3). The organic phase was dried with Na_2SO_4 , filtered and evaporated. The crude was purified by column chromatography.

Yield: 74%

Colorless oil

Product is already reported⁵⁰

Synthesis of *N*-allyl-*N*-tosyl-2-azido ethylamine (**67**)



The *N*-allyl-*N*-tosyl-glycinol **66** (1.3 g, 5 mmol) was dissolved in 60 mL of dry THF. Under nitrogen atmosphere Ph_3P (2.6 g, 10 mmol), DIAD (2.0 g, 10 mmol) and DPPA (2.8 g, 10 mmol) were added. The reaction mixture was left under agitation at room temperature for 3 hours. The reaction mixture then was heated to 50°C for one hour. The solvent was evaporated and the crude was purified by column chromatography. (EdP / AcOEt 85:15)

Yield: 56%

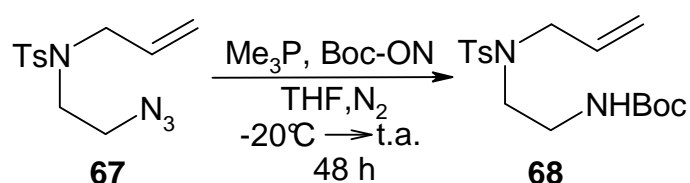
Colorless oil

IR: 2104 cm^{-1}

$^1\text{H-NMR}$ (CDCl_3) δ 2.44 (3H, s), 3.26 (2H, t, $J = 6.5$), 3.47 (2H, t, $J = 6.5$), 3.85 (2H, d, $J = 6.5$), 5.19 (1H, dd, $J = 1.3$, $J = 9.9$), 5.20 (1H, dd, $J = 1.3$, $J = 17.2$), 5.58-5.75 (1H, m), 7.33 (2H, d, $J = 8.2$), 7.72 (2H, d, $J = 8.2$)

$^{13}\text{C-NMR}$ (CDCl_3) δ 21.5 (q), 46.2 (t), 50.4 (t), 52.1 (t), 119.6 (t), 127.2 (d), 129.8 (d), 132.8 (d), 137.2 (s), 143.7 (s).

Synthesis of *N*-Allyl-*N*-tosyl-*N'*-*tert*-butoxycarbonyl ethylendiamine (**68**)



The *N*-allyl-*N*-tosyl-2-azido ethylamine **67** (392 mg, 1.4 mmol) was dissolved in 10 mL of dry THF and under nitrogen atmosphere at -20°C Me₃P (213 mg, 2.8 mmol) and Boc-ON (382 mg, 1.5 mmol) were added. The mixture was left at -20°C for 30 minutes and then at room temperature for 48 hours. 150 mL of CH₂Cl₂ were added and then it was washed by H₂O (50 mL x 4) and brine (50 mL x 1). The organic phase was dried with Na₂SO₄ filtered and evaporated. The crude was purified by column chromatography. (EdP / AcOEt 8:2)

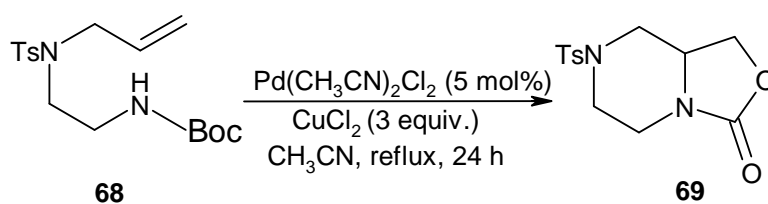
Yield: 36%

Colorless oil

¹H-NMR (CDCl₃) δ 1.45 (9H, s), 2.44 (3H, s), 3.20 (2H, t, *J* = 5.8), 3.29 (2H, t, *J* = 5.8), 3.81 (2H, d, *J* = 6.5), 5.95 (1H, br s), 5.17 (1H, dd, *J* = 1.3, *J* = 10.0), 5.19 (1H, dd, *J* = 1.3, *J* = 17.0), 5.51-5.68 (1H, m), 7.32 (2H, d, *J* = 8.1), 7.70 (2H, d, *J* = 8.1)

¹³C-NMR (CDCl₃) δ 21.9 (q), 28.4 (q), 46.9 (t), 51.7 (t), 65.9 (t), 79.5 (s), 119.5 (t), 127.2 (d), 129.8 (d), 132.7 (d), 136.3 (s), 143.5 (s), 155.0 (s).

Cyclisation of *N*-Allyl-*N*-tosyl-*N'*-*tert*-butoxycarbonyl ethelendiamine (**68**)



The *N*-allyl-*N*-tosyl-*N'*-*tert*-butoxycarbonyl ethelendiamine **68** (106 mg, 0.3 mmol) was dissolved in 10 mL of CH₃CN, CuCl₂ (121 mg, 0.9 mmol) and Pd(CH₃CN)₂Cl₂ (4 mg, 0.015 mmol) were added. The reaction mixture was left under reflux for 24 hours. 10 mL of brine were added and extracted by CH₂Cl₂ (20 mL x 3). The organic phase was dried by Na₂SO₄, filtered and evaporated. The crude was purified by column chromatography. (EdP / AcOEt 6:4)

7-p-Tosyltetrahydro-1H-oxazolo[3,4-a]pirazin-3(5H)-one (**69**)

Yield: 40%

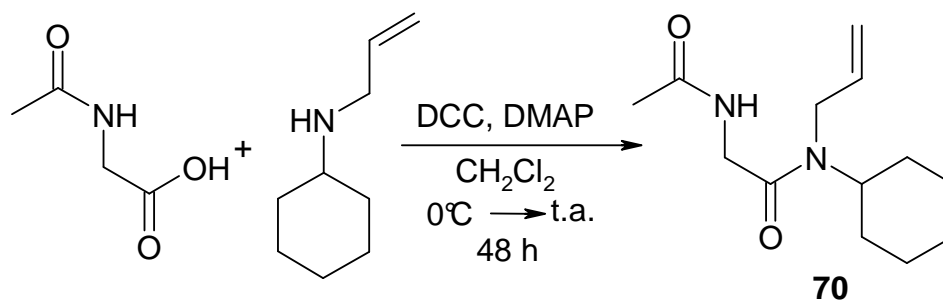
Colorless oil

IR: 1738 cm⁻¹

¹H-NMR (CDCl₃) δ 2.45 (3H, s), 3.16-3.25 (2H, m), 3.73 (1H, d, *J* = 3.7), 3.76 (1H, d, *J* = 3.7), 3.84 (1H, d, *J* = 3.7), 3.88 (1H, dd, *J* = 2.4, *J* = 3.7), 3.90-3.92 (1H, m), 3.94-4.02 (1H, m), 4.42 (1H, dd, *J* = 8.4, *J* = 8.5), 7.36 (2H, d, *J* = 8.2), 7.62 (2H, d, *J* = 8.2)

¹³C-NMR (CDCl₃) δ 21.5 (q), 40.5 (t), 45.1 (t), 49.2 (t), 52.7 (d), 64.9 (t), 127.6 (d), 130.3 (d), 132.3 (s), 144.5 (s), 156.4 (s).

Synthesis of 2-Acetamido-*N*-allyl-*N*-cyclohexylacetamide (70)



The *N*-acetyl glycine (140 mg, 1.2 mmol) was dissolved in 20 mL of dry CH₂Cl₂, the mixture was cooled at 0° C. DCC (10 mmol), the appropriate *N*-allylamine (8.3 mmol) and DMAP (0.125 mmol) were slowly added. The resulting solution reacted at r.t. for 48 h, then was filtered on silica gel (EdP / AcOEt 7:3) and the solvent was evaporated under reduced pressure. The crude residue was purified by silica gel column (EdP / AcOEt 7:3)

Yield : 82%

Yellow oil

IR: 1632,1740 cm⁻¹

Rotamer ratio 7/4

Major Rotamer

¹H-NMR (CDCl₃) δ 0.91-1.95 (10H, m), 2.18 (3H, s), 3.11-3.15 (1H, m),
3.74-3.81 (2H, m), 4.30-4.48 (2H, m), 4.97-5.10
(2H, m), 5.20 (1H, d, *J* = 7.5), 5.68-5.75 (1H, m)

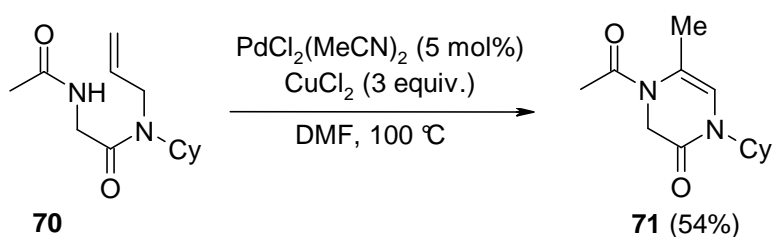
¹³C-NMR (CDCl₃) δ 25.2 (t), 25.7 (t), 26.2 (t), 30.3 (q), 30.5 (t), 31.8 (t),
45.0 (t), 45.8 (t), 54.2 (d), 116.7 (t), 134.6 (d), 155.8
(s), 172.8 (s).

Minor rotamer

¹H-NMR (CDCl₃) δ 0.91-1.95 (10H, m), 2.15 (3H, s), 3.58-3.60 (1H, m),
3.74-3.80 (2H, m), 4.31-4.50 (2H, m), 4.97-5.10
(2H, m), 5.11 (1H, d, *J* = 7.5), 5.69-5.76 (1H, m)

¹³C-NMR (CDCl₃) δ 25.2 (t), 25.6 (t), 26.1 (t), 30.7 (q), 30.9 (t), 32.6 (t),
44.8 (t), 45.5 (t), 54.1 (d), 115.9 (t), 135.0 (d), 153.8
(s), 172.5 (s)

**Synthesis of 4-Acetyl-1-cyclohexyl-5-methyl-3,4-dihydropyrazin-2(1H)-one
(71)**



The 2-Acetamido-*N*-allyl-*N*-cyclohexylacetamide **68** (106 mg, 0.3 mmol) was dissolved in 10 mL of DMF, CuCl₂ (121 mg, 0.9 mmol) e Pd(CH₃CN)₂Cl₂ (4 mg, 0.015 mmol) were added. The reaction mixture was left under reflux for 24 hours. 10 mL of brine were added and extracted by CH₂Cl₂ (20 mL x 3). The organic phase was dried by Na₂SO₄, filtered and evaporated. The crude was purified by column chromatography. (EdP / AcOEt 6:4)

Yield: 44%

Colorless oil

IR: 1684, 1707 cm⁻¹

¹H-NMR (CDCl₃) δ 0.70-1.80 (10H, m), 2.03 (3H, d, *J* = 1.2), 2.18 (3H, s), 4.08 (2H, s), 4.21-4.38 (1H, m), 5.56 (1H, d, *J* = 1.2)

¹³C-NMR (CDCl₃) δ 17.5 (q), 25.3 (t), 25.6 (t), 28.2 (q), 30.9 (t), 48.6 (t), 51.4 (d), 111.5 (d), 121.6 (s), 152.3 (s), 164.1 (s).

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