UNIVERSITAT DE BARCELONA

Palladium Catalyzed C–H activation of arylethyl amines and their derivatives: application to the construction of heterocyclic compounds

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Tesis Doctoral

PALLADIUM CATALYZED C–H ACTIVATION OF ARYLETHYL AMINES AND THEIR DERIVATIVES: APPLICATION TO THE CONSTRUCTION OF HETEROCYCLIC COMPOUNDS

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1. INTRODUCTION AND OBJECTIVES

1.1. Transition metal-catalyzed C–H functionalization

Traditional synthetic organic chemistry deals with the formation of carbon-carbon bonds by the reaction between a nucleophile and an electrophile or with the interconversion of functional groups linked to or contained into a scaffold of carbon atoms.

In many cases, these processes involve the cleavage of C–H bonds: acidic protons are often removed to generate the nucleophile in the nucleophilic substitutions, while electrophilic aromatic substitutions place functional groups or create a C–C bond at the position of a C–H bond. The difficulty of generating a C–C bond arises when the C–H bond that should be cleaved has limited acidity or reactivity. In this case a system reactive enough to break an un-activated C–H bond would interact fast with other (more active) functionalities that are contained in the molecules.

Some transition metals, such as palladium, rhodium, ruthenium or iridium, present greater reactivity for the cleavage of inert C–H bonds in certain conditions than for the insertion into a O–H or N–H or weak C–H bonds. In this way, for instance, inert sp^2 C–H bonds of arenes are easily substituted by more reactive carbon-metal bond, in a process known as metal catalyzed sp^2 C–H functionalization.

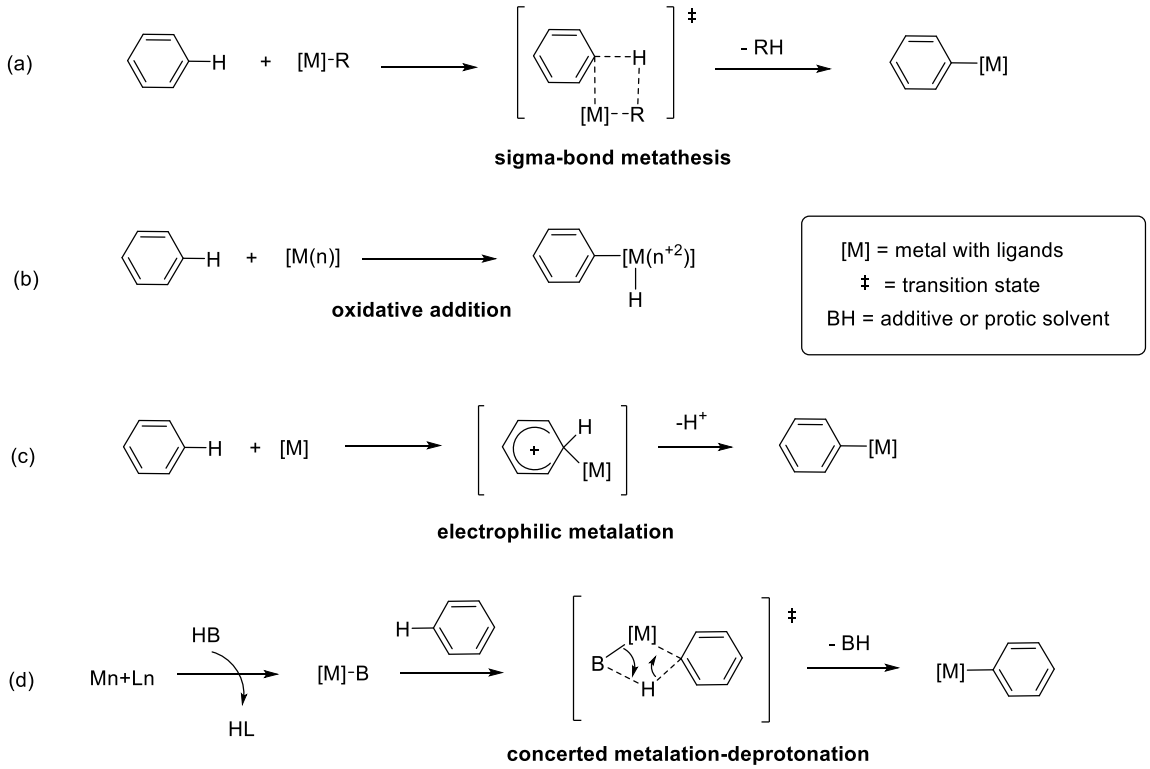
Four general mechanistic pathways have been suggested to explain the metalation of aromatic C–H bonds.

The first possibility is the σ-bond metathesis that is a concerted exchange between an alkyl complex R-M and an aryl complex Ar-H to generate the new complex Ar-M (Scheme 1, process *a*). However, this process is observed only for metals with one stable oxidation state (e.g. the metals of the group 3, scandium, lanthanides, and actinides) that cannot undergo oxidative additions or reductive eliminations.

Electron-rich, low valent complex of the metals placed on the right side of the periodic table (Re, Fe, Ru, Os, Rh, Ir, Pt) can undergo an oxidative addition into the C–H bond (Scheme 1, process *b*). This is the path followed by pioneering works about the C–H activation chemistry,[1] but the reactive metallic species employed in these cases are coordinatively unsaturated and hence unstable (they are almost always generated *in situ* by thermal or photochemical decomposition of suitable stable precursors).[2]

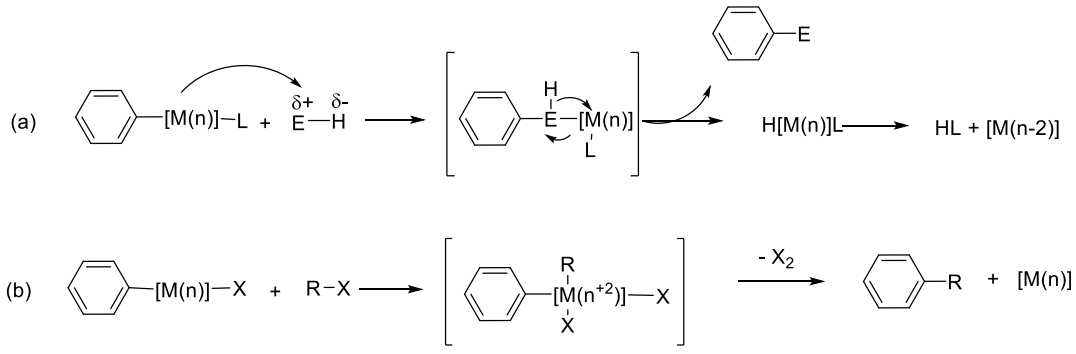
However, the most common processes employ more stable catalyst with higher oxidation state. In these conditions, the electrophilic substitution of an aromatic proton by the metals is observed. Mechanistic studies demonstrated that almost always the metalation does not follow the classic path of the aromatic electrophilic substitution generating a Wheland intermediate (Scheme 1, process *c*), but it involves a concerted metalation-deprotonation mechanism where the removal of the proton is assisted by one of the ligands of the metal that acts as an intramolecular base (this is called agostic interaction).[3] The most common ligands that promote this activation are carboxylates, carbonates, triflates or *p*-toluenesulfonates, but in some cases other species have been

used. It is possible to directly employ catalysts containing the appropriate ligand or to introduce them by ligand exchange with the solvent (for example acetic acid) or with additives (acid or salts) (Scheme 1, process *d*).



Scheme 1.

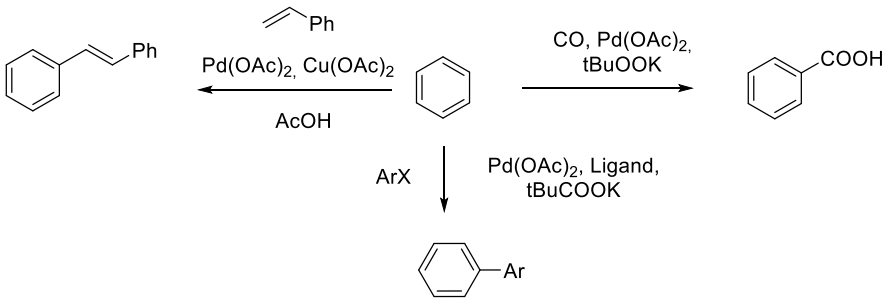
The new C–M bond can easily react with electrophiles (e.g. alkenes or carbonyl compounds, (Scheme 2a) or with electron-poor species (e.g. haloarenes via an oxidative addition-reductive elimination path, Scheme 2b) leading to a new carbon-carbon or carbon-heteroatom bond.



Scheme 2.

Thanks to this strategy, chemical transformations that were unimaginable until that moment could be performed. Thus, in 1969 Fujiwara and co-workers reported the palladium-catalyzed coupling between benzene and styrene.[4] Some years later, the same group achieved the carboxylation of unactivated arenes,[5] while the arylation of

unactivated aromatic compounds leading to biaryl products was finally accomplished by various groups[6,7] (Scheme 3).



Scheme 3.

More recently, the metal catalyzed C–H functionalization has become a real important topic for the scientists that have studied an incredible amount of different functionalization processes with several applications. The possibility to introduce directly substituents in several organic compounds without the necessity of preparing activated intermediates is a real practical advantage in terms of step-economy and especially in terms of time-saving. For example, the ability of placing various functional groups in an aromatic unactivated compound in just one step, is really helpfully in the cases in which one needs to prepare quickly several similar molecules to study the effect of the functionalization over the physical or biological properties.

Furthermore, these metodologies often employed in the total synthesis of drugs or natural products. For example, Yu's group described an alternative synthesis of the (+)-Lithospermic acid (a natural anti-oxidative agent) by connecting two fragments of the molecule via a palladium-catalyzed arene-alkene coupling reaction,[8] while Bringmann and co-workers reported the synthesis of Dioncophylline C (a strong antimalarial and anti-HIV alkaloid) linking the arene to the isoquinoline skeleton by an arene-haloarene palladium-catalyzed coupling reaction (Figure 1).[9]

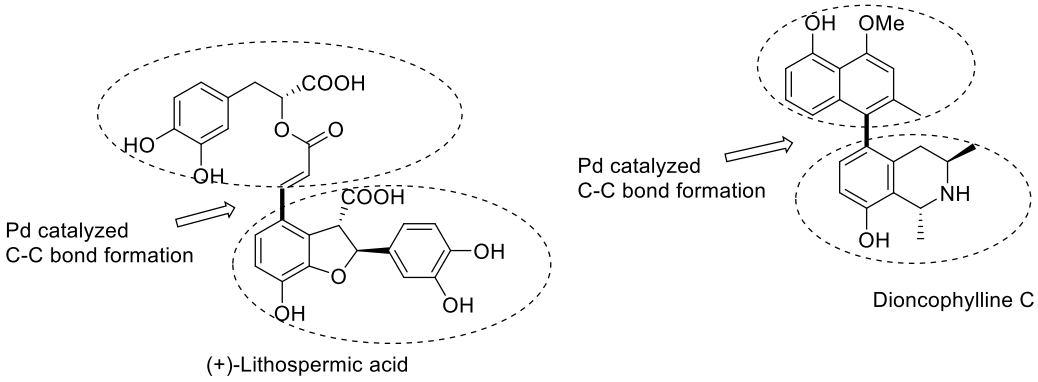


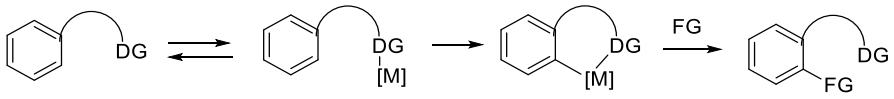
Figure 1.

1.1.1. The selectivity issue

The mayor challenge that scientists had to face in the development of metal-catalyzed C–H bond functionalization methodologies is to get selective processes: in a typical reaction mixture, there are several C–H bonds with identical or similar properties and reactivity, from which arises the risk of functionalizing different molecules in different sites or of inserting more substituents in the same molecule, leading to a mixture of products.

In the last years, some research lines focused on the use of the intrinsic properties of the protons that have to be removed in order to obtain selective metal catalyzed C–H functionalization.[10] However, functional group assisted C–H bond cleavage is the strategy that gave better results in terms of novel transformations for the last two decades.

The strategy consists in the introduction of a chelating group (directing group) in the structure of the aromatic compound that must be functionalized, in order to coordinate the catalyst in a specific position. A rearrangement of the initial intermediate allows the C–H activation in the desired site. Then the new C–M bond can react with different funtionalities (Scheme 4).



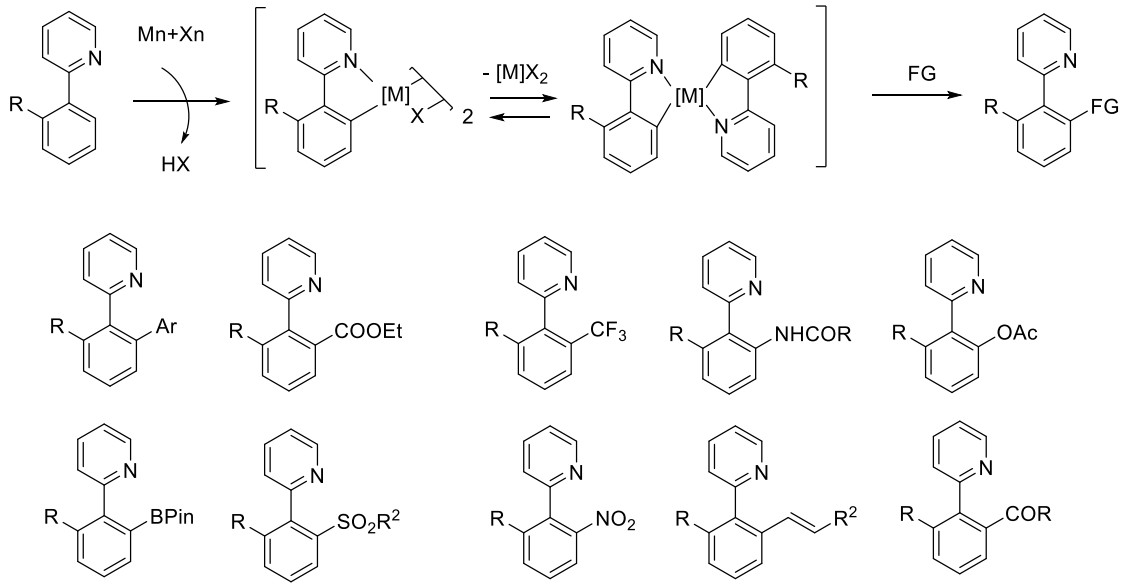
Scheme 4.

Many groups have used different directing moieties, such as carboxylic or sulfonic acids,[11] ketones,[12] esters,[13] phenols or alcohols,[14] ethers or thioethers,[15] sulfoxides,[16] phosphonates,[17] silanes[18], and so on, for a variety of functionalizations catalyzed by different transition metals. However most of the works that have been reported took advantage of nitrogen-based directing moieties.

1.1.2. Nitrogen-based directing groups

Many functional groups containing a chelating N atom have been used for transition metal-catalyzed C–H activation, due to the capacity of the N atom to complex the metals with its lone pair.

Among them, pyridine and amides derivatives are the two classes of compounds that have been more successfully employed and that have shown to be more versatile for different transformations. In particular, 2-phenylpyridine is probably the most used moiety in the studies about the C–H activation.



Scheme 5.

Arylation is a mayor issue in this field. Thus bi-aryl compounds have been prepared by selective arylation with aryl halides,[19] carboxylation with azo dicarboxylates,[20] alkylation with CF_3^+,[21] amidation,[22] oxidation to acetate,[23] borylation,[24] sulfonylation,[25] nitration with sodium nitrate,[26] olefination[27] or acylation[28] on the *ortho* position with total selectivity and good yields (Scheme 5). For this purpose 2-arylpyridines have been used as substrates in the presency of different transition metals as catalysts (e.g. palladium, ruthenium and rhodium).

Other pyridines derivatives, as the ones showed in Figure 2, were successfully used as substrates for the metal-catalyzed C–H activation.[29] In some cases the pyridine moiety was introduced in the structure of simpler compounds as temporary directing groups for their functionalization (Figure 2b).[30]

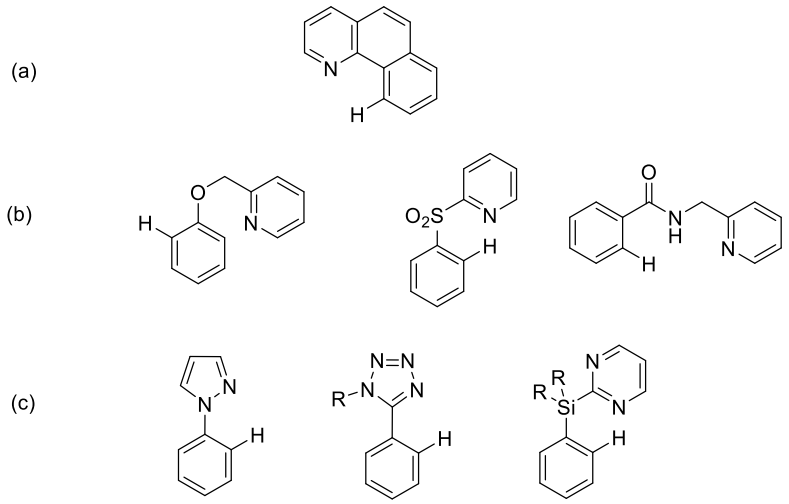
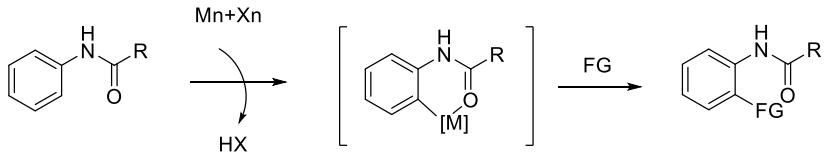


Figure 2.

Other nitrogenated heterocycles as pyrazoles,[31] tetrazoles[32] and pyrimidine[33] were employed as common directing groups but not in a such exhaustive way as pyridine (Figure 2c).

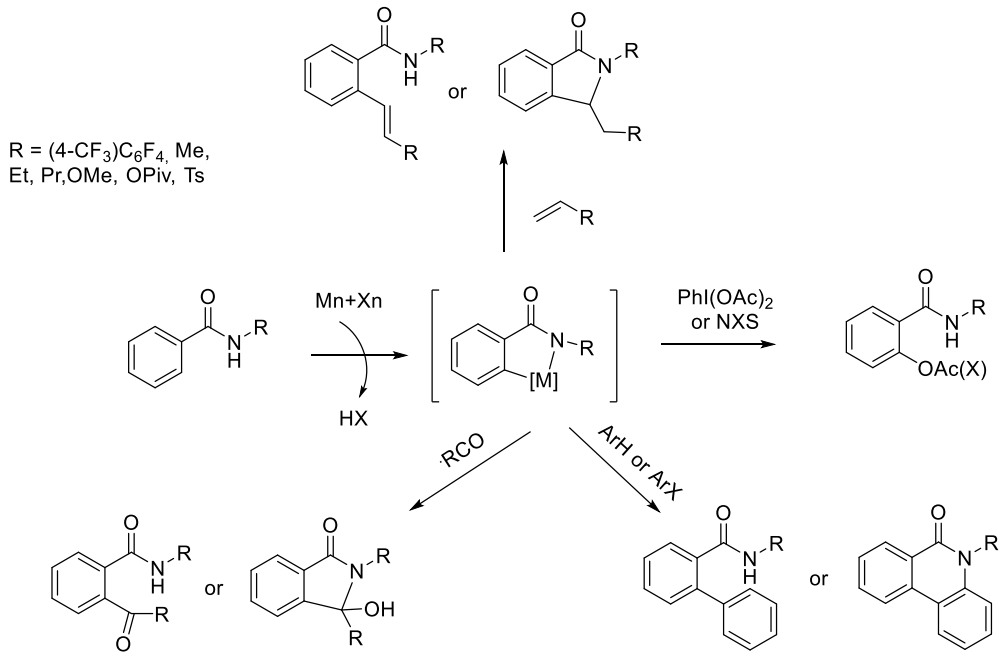
Amides and their derivatives are also relevant functionalities as chelating groups for assisted C–H activation.

Thus, almost every possible functionalization (e.g. olefination, arylation, carboxylation, acylation, oxidation, etc.) on the *ortho* aromatic C–H bond of acylanilines has been reported.[34] It should be pointed out that the coordinating atom is the oxygen and not the nitrogen in such processes (Scheme 6).



Scheme 6.

Benzamides have been reported to be good substrates for several metal catalyzed transformations. Secondary or *N*-substituted amides have been employed in many processes, while only the palladium-catalyzed arylation was reported for primary benzamides. [35] *N*-Aryl amides have been arylated, aminated, and borylated by palladium catalysis,[36] while *N*-alkyl benzamides have been used in ruthenium or rhodium catalys to perform the arylation, olefination and acylation of the *ortho* position of the aromatic ring (Scheme 7).[37]



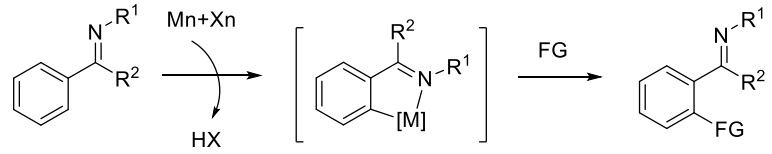
Scheme 7.

N-Alkoxybenzamides are good substrate for the palladium-catalyzed olefination and acylation of the aromatic ring as well as the ruthenium catalyzed olefination. Rhodium catalysis was also successfully used on these compounds.[38]

Sulfonamides constitute as well a class of compounds that have been used as directing group in palladium-catalyzed reactions such as the olefination or oxidation of the *ortho* position of the aromatic ring.[40] Even tosyl-protected benzamides have been described as directing groups for the selective palladium-catalyzed olefination-annulation and oxidation of the C–H bond.[39]

Imines and oximes represent other nitrogen-based functional groups that have been employed extensively in C–H activation processes. The majority of these reactions were rhodium catalyzed olefination with alkenes or alkynes. *N*-Benzyl,[41] *N*-tosyl,[42] *N*-alkyl[43] or free imines[44] have been also used.

N-Aryl imines and *O*-methyloximes are the most used imine derivatives for this processes (Scheme 8) in which different transition metals have been used. For example, the ruthenium or palladium-catalyzed arylation[45] and the ruthenium-catalyzed olefination[46] of *N*-aryl imines have been described as well as the palladium-catalyzed arylation[47] and acylation[48] or the ruthenium-catalyzed olefination[49] of *O*-methyloximes.



R1 = Ar, OMe

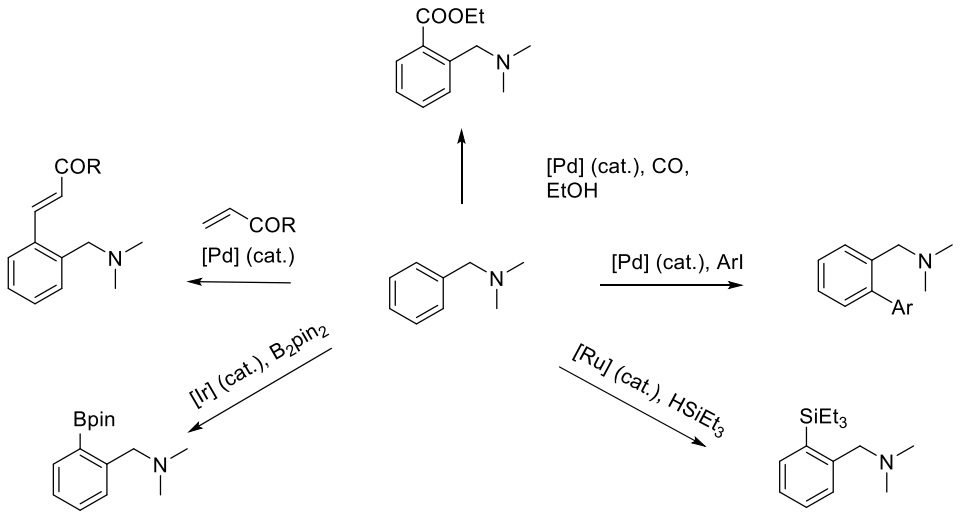
Scheme 8.

Other nitrogen-based directing groups that can be found in less extent in the literature are ureas and guanidines, [34i,50] diazenes,[51] triazenes[52] or pyridine *N*-oxide derivatives.[53]

1.1.3. Amines as nitrogen-based directing groups

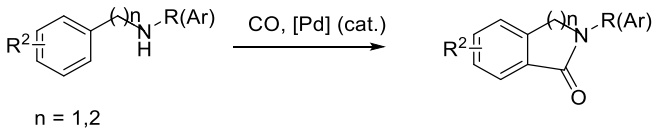
Amines have been scarcely studied as directing groups in C–H activation processes, despite their importance as functional group in organic synthesis and their presence in many natural products and drugs. Likely, this is because their strong Bronsted base behavior: the unprotected nitrogen can coordinate too strongly the transition metal inhibiting the reactions. Particularly, the use of primary amines as directing groups has been reported in only few examples for the last 10 years. The NH_2 group, in addition to the thight coordination to transition metal centers, is too reactive towards different organic functions generating the possibility of secondary reactions.

Regarding tertiary amines, the palladium-catalyzed *ortho*-olefination[54], *ortho*-carbonylation[55] and *ortho*-arylation[56] of *N*-*N*-dimethylbenzylamine have been achieved and described, as well as the iridium-catalyzed borylation[57] and the ruthenium-catalyzed silylation[58] (Scheme 9).



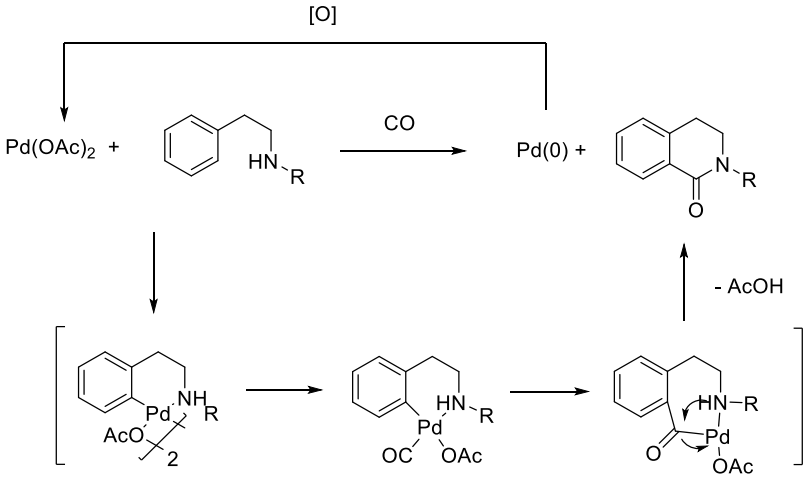
Scheme 9.

Only the palladium-catalyzed carbonylation process leading to five or six membered benzolactams has been described using secondary amines as directing groups[59] (alkyl benzylamines and alkyl or aryl phenylehtylamines, Scheme 10).



Scheme 10.

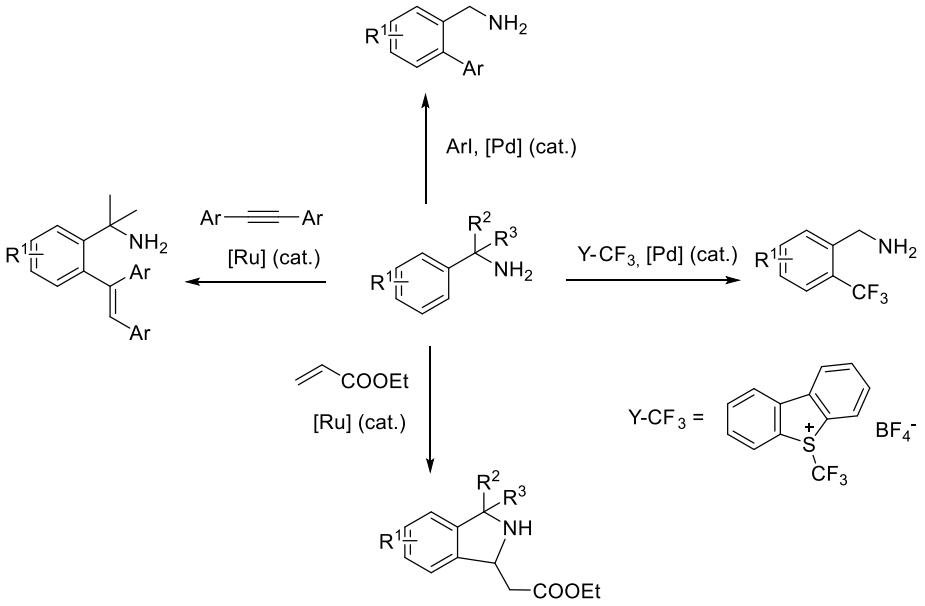
Remarkably, in this transformation the amine as directing functionality promotes the metalation in the first part of the reaction and later it behaves as nucleophile in the second part of the process, when the nitrogen is added to the CO and allows the intramolecular cyclization (Scheme 11).



Scheme 11.

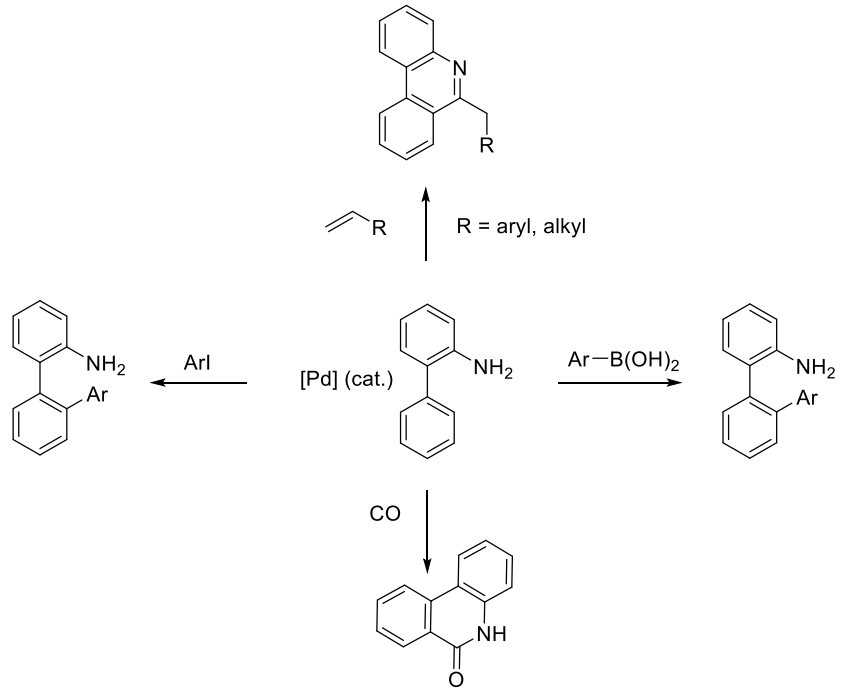
Regarding primary amines, some results have been reported in the literature involving the use of benzylamines or anilines.

The palladium-catalyzed arylation[60] and recently the trifluoromethylation[61] (using an electrophilic CF_3 reagent) have been performed starting from primary benzylamines, as well as the ruthenium-catalyzed olefination-annulation[62] or alkenylation with alkynes[63] (Scheme 12).



Scheme 12.

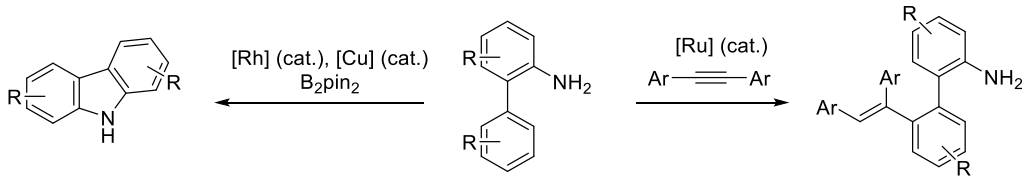
At the same time free anilines have been often employed as directing groups for the construction of functionalized biaryl-2-amines.



Scheme 13.

The palladium-catalyzed arylation[64] and the alkenylation[65] (followed by a cycloamination to afford phenanthridines) of 2-arylaniline were described by Zhang and co-workers that also developed a Suzuki-Miyaura-type coupling reaction of these substrates with aryl boronic acids[66]. The palladium-catalyzed aminocarbonylation of free aniline derivatives with CO for the synthesis of (NH)-phenanthridinones has been also recently described[67] (Scheme 13).

Finally, rhodium catalysis has been reported to allow the intramolecular amination of 2-arylaniline for the formation of carbazoles[68], via borylation and subsequent copper catalyzed ring closure, while ruthenium has been employed for the regioselective alkenylation of aniline derivatives[63] (Scheme 14).



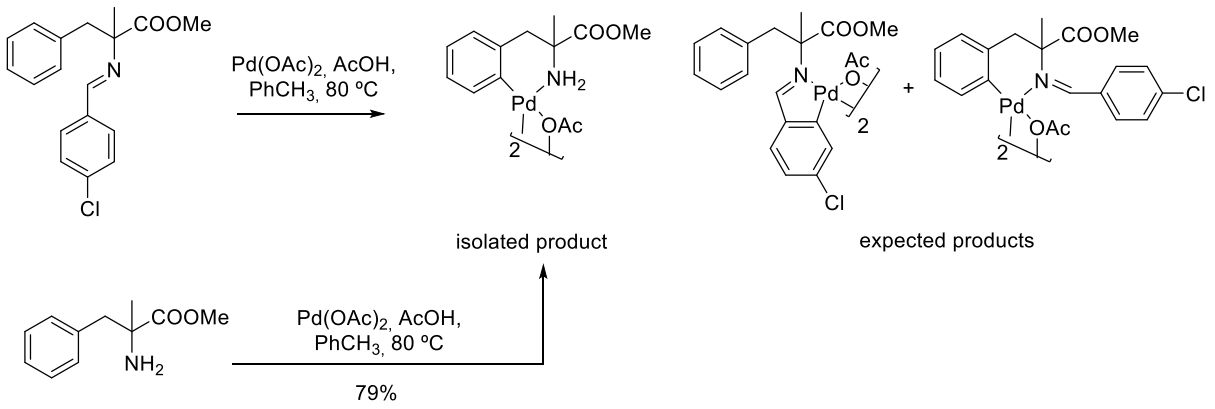
Scheme 14.

Despite the interest and the synthetic utility of these works, the amount of articles describing the C–H activation of amines is really small when it is compared to the huge amount of works devoted to the use of their derivatives (such as amides or imines) or others nitrogen-based directing groups for metal-catalyzed functionalization, as illustrated in the previous section.

1.1.4. Previous results of our research group

In the last decade, the SM Biocom research group started a collaboration with Professors Jaume Granell and Joan Albert from the Section of Inorganic Chemistry of the University of Barcelona.

Their group was interested on the metalation of imines derived from amino esters with palladium acetate.[69] As result of the collaboration, it was found that, in some cases, these substrates did not lead to the expected complexes. Surprisingly, a complex deriving from the metalation of the free amino ester was isolated. Direct palladation of the unprotected amine afforded the same complex in good yield (Scheme 15). Thus, partial hydrolysis of the imine to amine and its subsequent metalation was occurring. After this discovery, various palladacycles derived from amino esters could be prepared, isolated and characterized.[70,71]

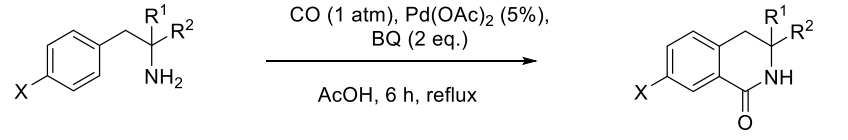


Scheme 15.

These results were in sharp contrast with those previously observed for different derivatives of aminoacids suggesting that the metalation of primary amines is usually a challenging task requiring peculiar conditions.[72]

The reactivity of the new isolated complexes was further studied and it was found that these palladacycles could be easily carbonylated to obtain benzolactams, using 1 atmosphere of CO.

The results prompted us to develop a new catalytic process for the carbonylation of primary amines affording benzolactams. In fact, some examples about the carbonylation of secondary phenethylamines had been previously reported,[59] but the authors stated in their same work that the palladium-catalyzed CO addition to primary amines only led to the formation of ureas. However, the catalytic carbonylation could be performed and optimized and several benzolactams could be synthetized starting from primary phenethylamines and using benzoquinone (BQ) as oxidant (Scheme 16).



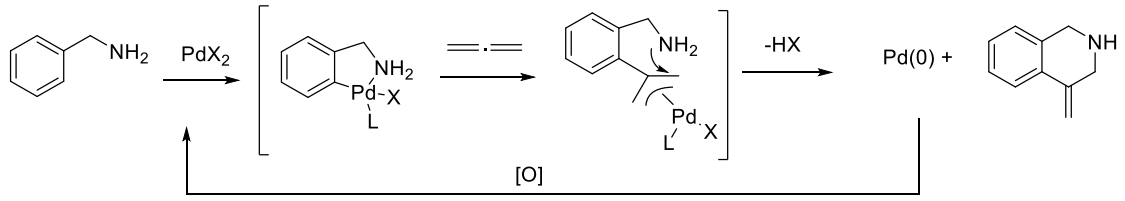
R^1 = COOMe, Me;
R^2 = Me, Pr, iPr, Bn;
X = NO_2, OMe, CN, OH, OPr;

15 examples, up to 98% yield

Scheme 16.

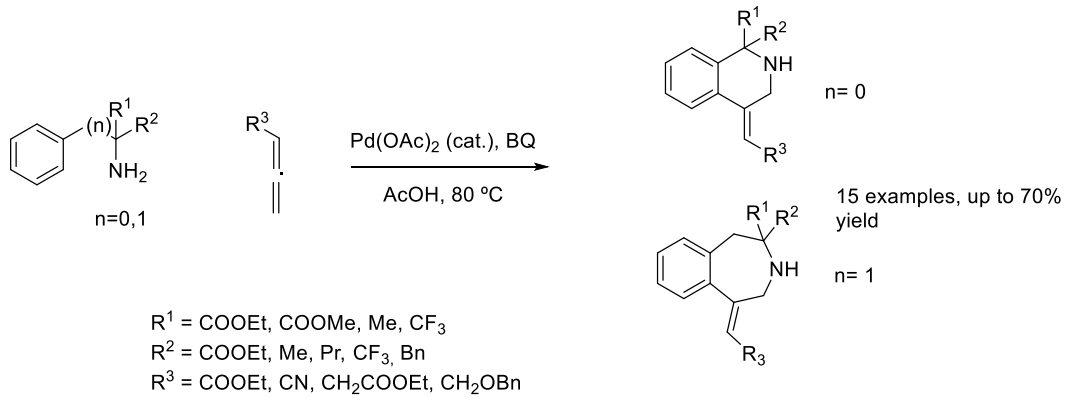
The acquired experience on the stoichiometric and catalytic metalation of primary phenylethyl amines was used some years later to perform the annulation of such amines (and benzylamines) with allenes.[73]

This is another case in which the NH_2 group plays two roles: i) as directing group for the formation of the reactive metallacycle; ii) and afterwards as nucleophile, performing in this case a Tsuji-Trost reaction on the π-allyl complex resulting from the insertion of the allene (Scheme 17).



Scheme 17.

In this way, functionalized tetrahydroisoquinolines (THIQ) were synthesized from α-quaternary benzylamines while tetrahydro-3-benzazepines were obtained from α-functionalized phenethylamines by addition of functionalized allenes. The products were obtained from good to excellent yield when the amines were substituted in α with electron-withdrawing groups and an excellent regio-selectivity was observed when conjugated allenes with electron withdrawing groups were employed (Scheme 18).



Scheme 18.

1.2. Objectives

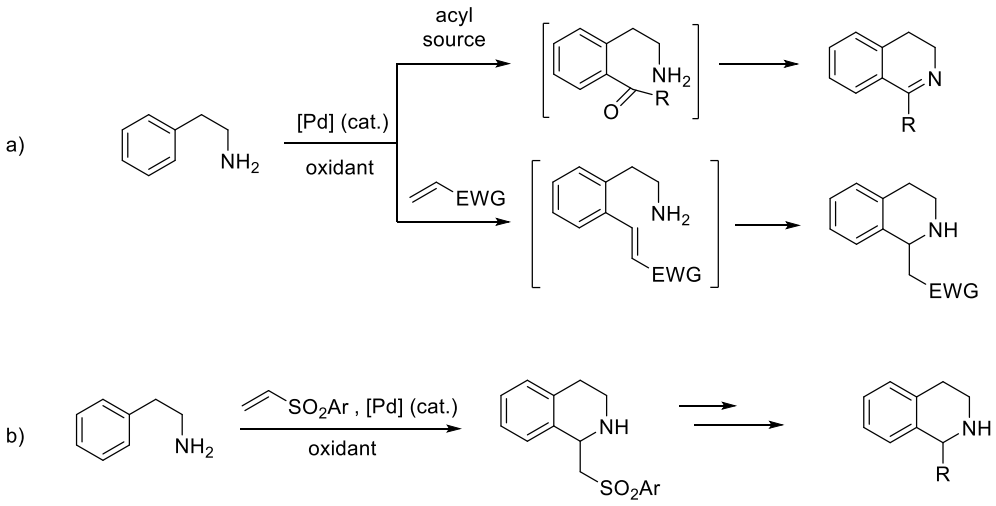
1.2.1. C–H activation of primary amines and application to the synthesis of heterocyclic compounds

According to the research line of the group, devoted to the discovery of new reactions of aromatic primary amines (or analogues) promoted by transition metals (actually palladium), the objective of this thesis is the development of processes in which the directing group could be used as directing group as well as reacting moiety, leading to the formation of heterocyclic compounds. For this reason, the introduction of electrophilic groups, (able to react again with an NH_2 group), on the aryl ring of aromatic amines was attempted (Scheme 19).

1) In the first part of this thesis some experiments aimed to the introduction of a carbonyl group or an acyl group in the *ortho* position of the aromatic ring will be presented. These intermediates should have promoted an intramolecular condensation leading to functionalized isoquinolines or lactames.

2) The completion of an ongoing project involving the alkylation of the phenyl ring of arylethyl amines with Michael acceptors, in order to synthesize isoquinoline skeletons, was next addressed.

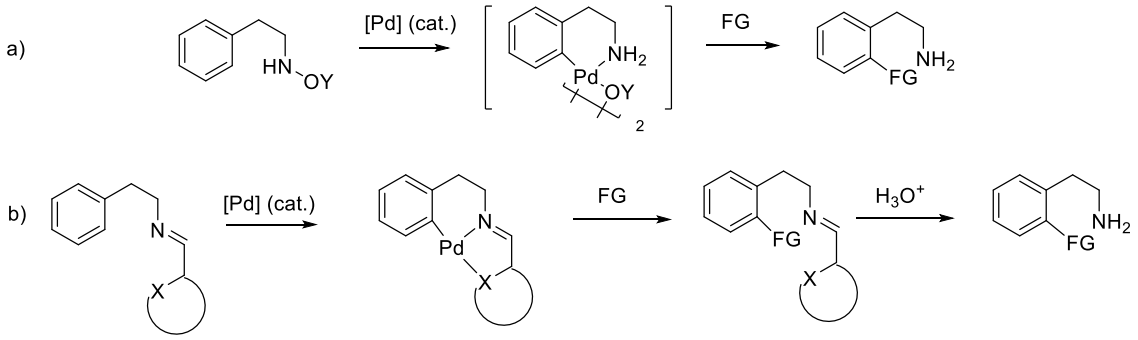
3) Finally, the palladium-catalyzed preparation of heterocyclic compounds containing a sulfone moiety and the studies about their reactivity aimed at the synthesis of more functionalized *N*-heterocyclic molecules will be commented (Scheme 19b).



Scheme 19.

1.2.2. C–H activation of some synthetic analogs of the amines and application to the synthesis of heterocyclic compounds

The second aim of this experimental thesis was the study of some derivatives of the amines as new directing groups in order to improve the efficiency of some known processes and to develop new palladium-catalyzed reaction for the synthesis of heterocyclic compounds.



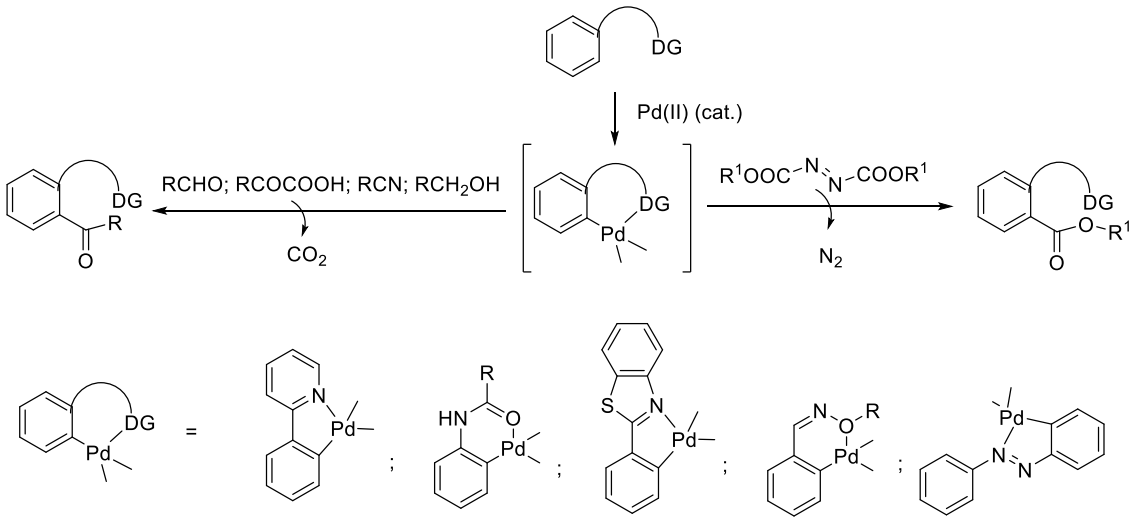
Scheme 20.

The preparation and evaluation of hydroxylamines and *O*-acylhydroxylamines as oxidizing directing groups in free-oxidant palladium-catalyzed processes will be reported (Scheme 20a) as well as the use of imines as easily removable directing groups (Scheme 20b).

2. PALLADIUM-CATALYZED ACYLATION AND CARBOXYLATION OF PRIMARY AMINES

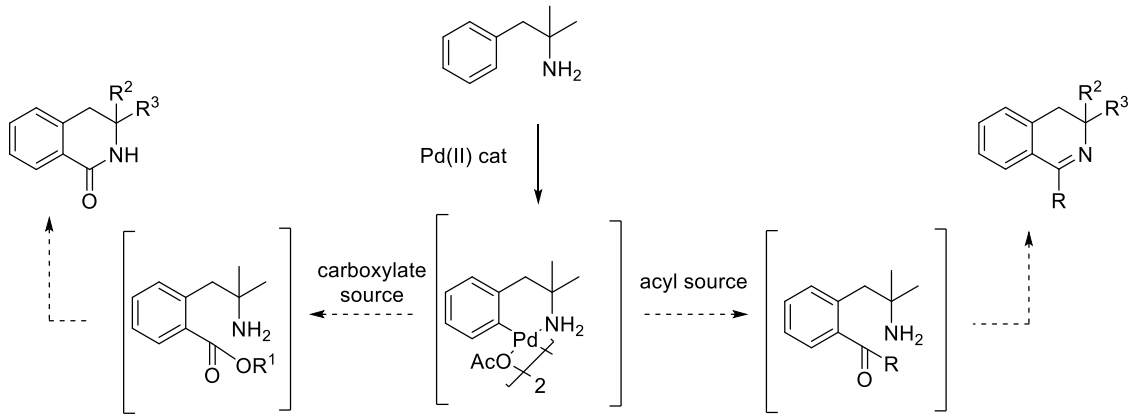
2.1. Palladium-catalyzed acylation of arenes with aroyl surrogates

Selective acylation or alkoxycarbonylation of arenes or heteroarenes through transition metals catalyzed C–H activation has been abundantly described in the literature.



Scheme 21.

There are several works reporting the palladium-catalyzed acylation of aromatic compounds with different acyl sources (e.g. aldehydes, β-carbonyl carboxylic acids, nitriles or benzyl alcohols) and promoted by several directing groups as pyridines[20,28,76], amides[77], triflamides[78], benzothiazoles[79], o-methyloximes[48], phenyl diazenes[14,51] (Scheme 21). However, a primary aromatic amine has never been employed as chelating moiety for this transformation. In the same way, the selective carboxylation of aromatic compound using azodicarboxylates has been reported using various directing functionalities,[20,77b,80] but not with primary amines.



Scheme 22.

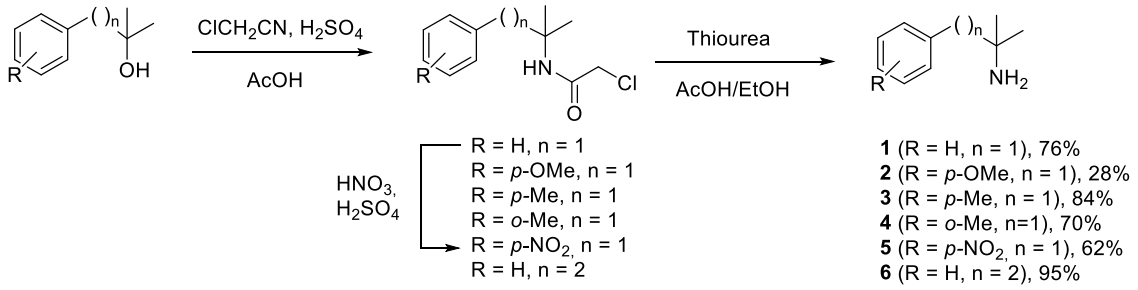
Thus, we envisaged a new palladium-catalyzed process for the selective aromatic acylation or carboxylation of primary phenylethylamines, considering the good performance that the palladium complexes derived from primary amines (that had been previously studied by our research group)[71] showed towards electrophiles (see the planned processes in Scheme 22).

The interest on the proposed process was enhanced by the assumption that the products expected from the C–H functionalization should have easily undergone a further intramolecular condensation or nucleophilic acyl substitution affording heterocyclic compounds (substituted dihydroisoquinolines or benzolactames, as shown in Scheme 22).

2.1.1. Preparation of 2-phenylethyl amines and derivatives

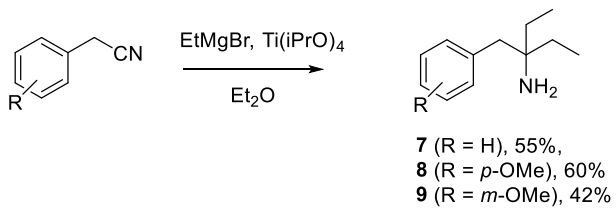
Amines and their derivatives were used as starting material in the development of the project, hence several models were prepared. The strategies for the preparation of some of the starting amines are reported in this section.

Phenylethylamines **1-4** and amine **6** were obtained in good yields from the correspondent tertiary alcohols by a Ritter reaction followed by a known hydrolysis of the 2-chloroacetamide intermediate (Scheme 23).[74a] Tertiary alcohols that were not commercially available were prepared by alkylation of the corresponding ketone or ethyl ester with methyl magnesium bromide (as reported in the experimental section).



Scheme 23.

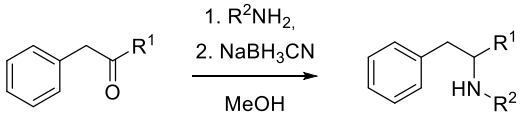
Only the amine **2** was obtained in low yield because of the partial demethylation of the methoxyphenyl group in the first step of the reaction, due to the acidic conditions. Amine **5** was obtained in good yield by nitration of the unsubstituted amide intermediate followed by the deacetylation with thiourea.



Scheme 24.

1,1-Diethylphenylethyl amines **7-9** were directly prepared from commercially available 2-phenylacetonitriles by direct addition of ethyl magnesium bromide (Scheme 24).[74b]

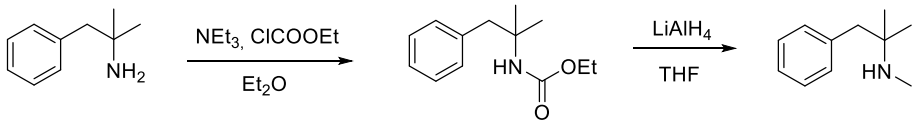
N-Methylphenethyl amines **10-11** were obtained by reductive amination of the corresponding commercially available ketones or aldehydes (Scheme 25) as well as 1-phenylpropan-2-amine **12** (ammonium acetate was used as source of ammonia in this case).



10 (R^1 = H, R^2 = Me), 57%
11 (R^1 = Me, R^2 = Me), 80%
12 (R^1 = Me, R^2 = H), 46%

Scheme 25.

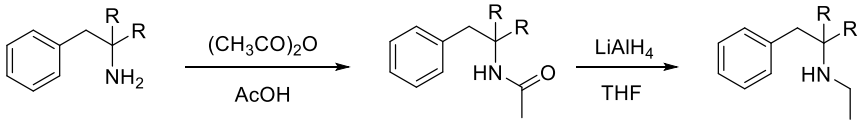
N-Methylamine **13** was prepared by the conversion of primary amine **1** in carbamate followed by reduction with $LiAlH_4$ (Scheme 26).



1 **13** 30%

Scheme 26.

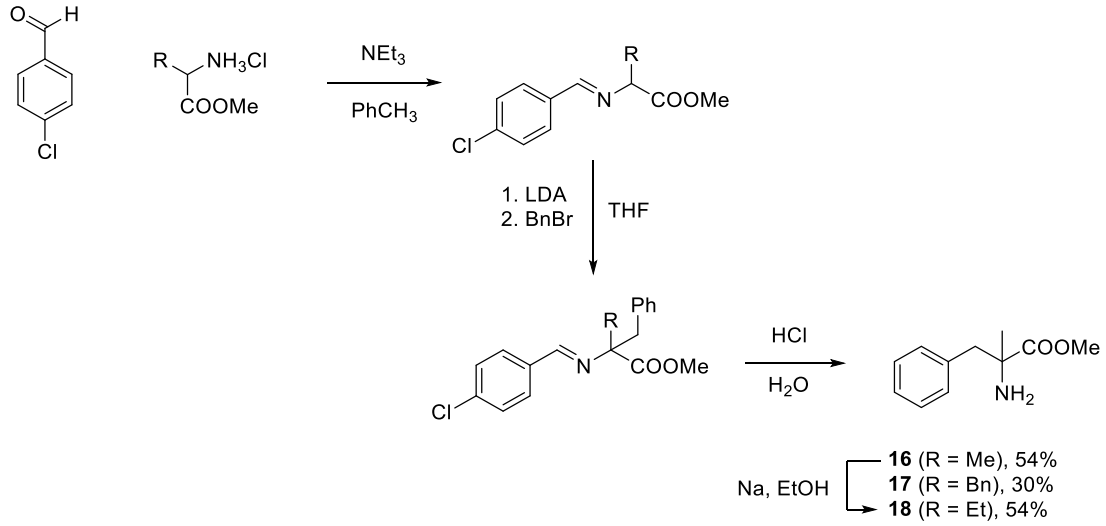
N-Ethylamines **14-15** were prepared respectively by acetylation of phenethylamine and amine **1** and subsequent reduction with $LiAlH_4$ in THF (Scheme 27).



14 (R = H), 95%
15 (R = Me), 82%

Scheme 27.

Racemic amino esters **16-17** were obtained from the commercially available hydrochloric salts of methyl alaninate and methyl phenylalaninate.

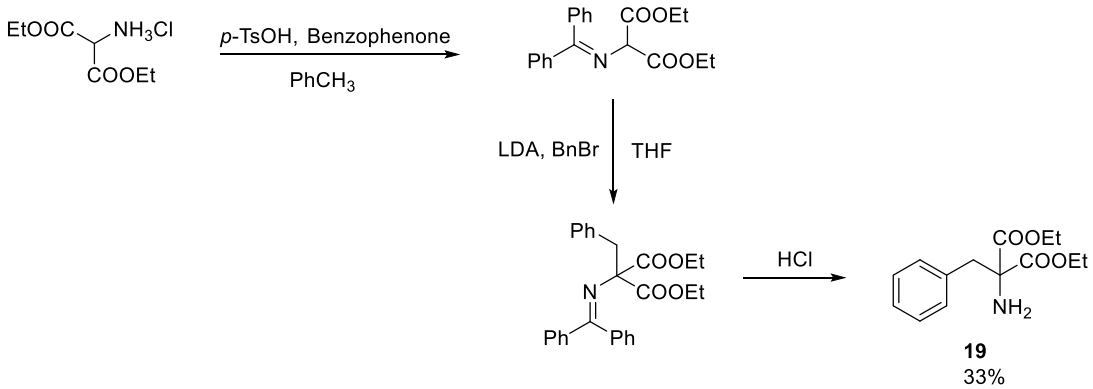


Scheme 28.

Conversion into imines followed by alkylation with benzyl bromide and hydrolysis in acidic conditions afforded the α-benzylated amino acids **16-17** (Scheme 28).[71]

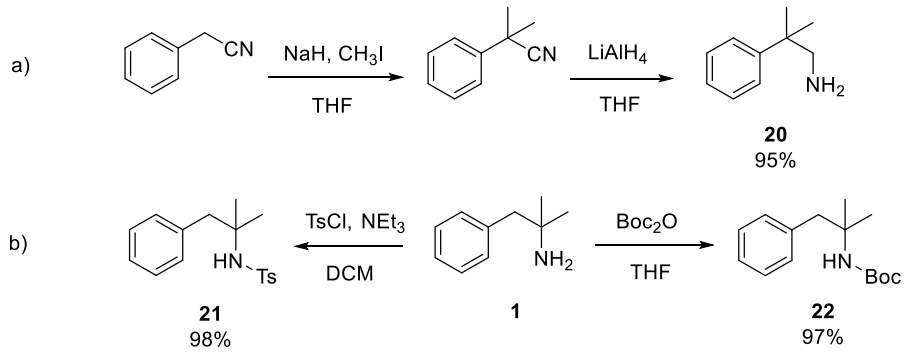
The ethyl amino ester **18** was prepared in quantitative yield from the methyl ester **16** by transesterification with ethanol and sodium ethoxide (Scheme 28).

The amino diester **19** was obtained from the commercially available hydrochloric salt of diethyl α-aminomalonate by a similar procedure involving the initial formation of a ketimine rather than an aldimine (Scheme 29).[75]



Scheme 29.

The primary amine **20** was obtained from 2-phenylacetonitrile, (details are given in the experimental section), while protected amines **21** and **22** were obtained from amine **1** by reaction with toluenesulfonyl chloride (TsCl) and di-*tert*-butyl dicarbonate (Boc_2O) respectively (Scheme 30).

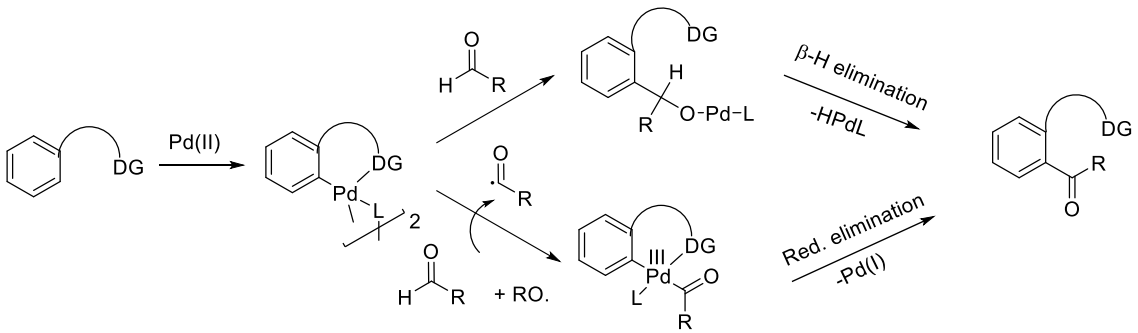


Scheme 30.

2.1.2.Attempts of acylation with aldehydes or benzyl alcohols

Aldehydes are the most described acyl sources for the selective palladium-catalyzed C–H acylation of arenes.[28,48,51,76a,77c,79]

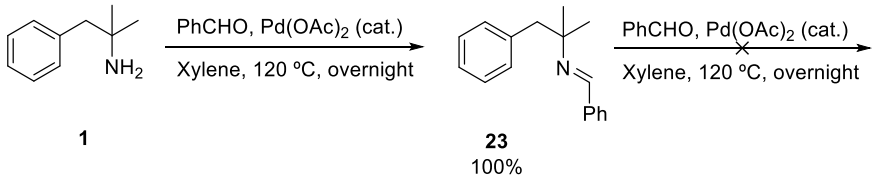
In general, two kinds of palladium-catalyzed reactions have been proposed[81] (Scheme 31). In the first one the palladacycle undergoes an insertion of C=O followed by a β-hydride elimination. Alternatively, a radical addition occurs when peroxides, or other radical-generating species, are added to the reaction mixture, leading to high valent palladium intermediates (Pd(III) or Pd(IV) complexes). These oxidized palladacycles allow the formation of the same product by the reductive elimination of Pd(II).



Scheme 31.

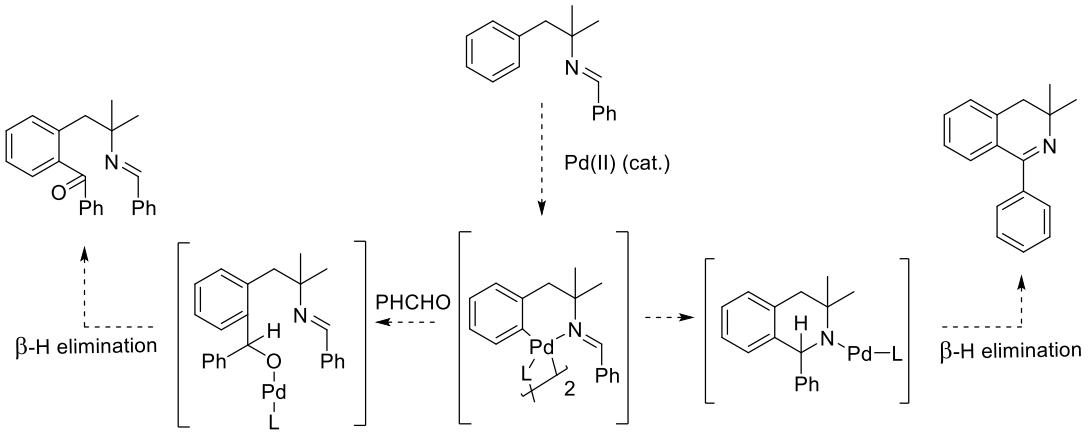
In the first case simply air is needed to re-oxidize Pd(0) to Pd(II), enabling the catalytic cycles, while TBHP is necessary in the second process to enable the formation of the radical species and the resulting high-valent complex. In the presence of that peroxide the acylation of various substrates with alkyl and aromatic aldehydes has been described, while only aromatic aldehydes have been successfully employed as aroyl surrogates using air as oxidant.

At the beginning we tried to assay the *ortho* acylation of the simple amine **1** with benzaldehyde using air as oxidant, but only a quantitative condensation between the reagents was observed leading to the formation of imine **23** (Scheme 32).



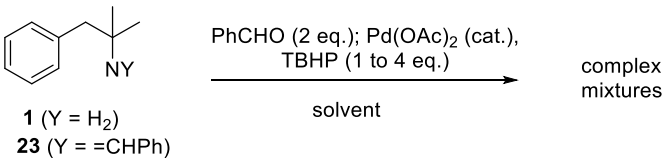
Scheme 32.

The condensation was, obviously, expected. However, our prediction was that the resulting imine would have complexed the palladium again, giving a palladacycle that could have experienced an intramolecular insertion of C=N or an intermolecular insertion of C=O (reacting, in this case, with an additional molecule of aldehyde). Both the intramolecular and intermolecular path would have leaded to interesting products (Scheme 33), but unfortunately we observed that the imine didn't undergo any transformation in these conditions. The reaction was also repeated starting from the isolated imine **23**, but only unreacted starting material was recovered (Scheme 32).



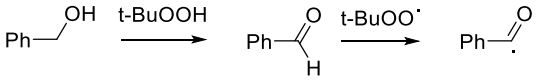
Scheme 33.

Therefore, we tried to perform the acylation in the presence of TBHP triyng to pursue the route of the radical process. Unfortunately, only complex mixtures were obtained operating at the new conditions: the rapid formation and disappearance of the imine **23** was observed by TLC, but neither more product nor intermediate was isolated from the reaction mixture operating with different solvents (p-xylene, chlorobenzene, toluene or acetic acid) and stoichiometric quantities of TBHP. Starting from the imine **23** the same results were obtained (Scheme 34).



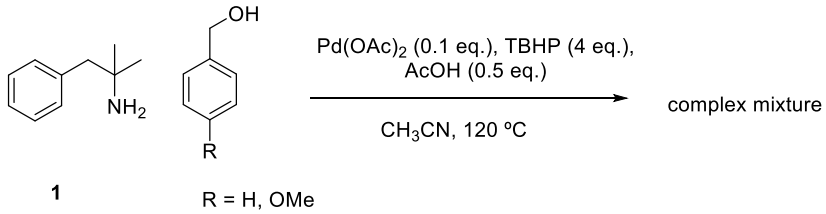
Scheme 34.

Benzyl alcohols have been also described as source of acyl radicals (in the presence of TBHP, Scheme 35) for the palladium-catalyzed acylation of anilides or benzyl triflamides.[78b,82]



Scheme 35.

We tried to adapt to amine **1** the conditions described by Kim *et al.* for the acylation of aromatic triflamides (Scheme 36), but we only obtained complex mixtures.



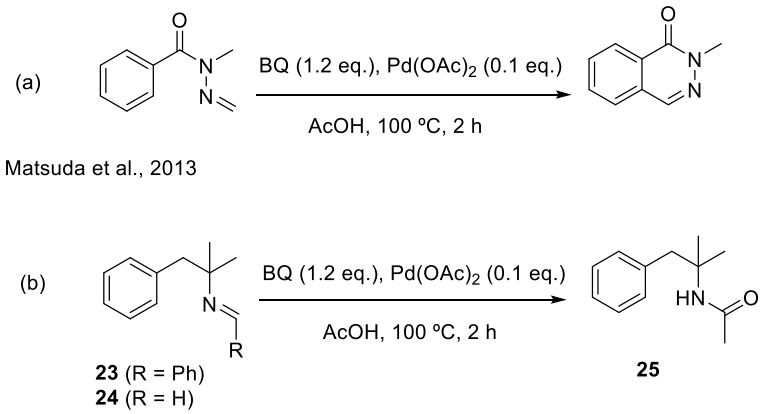
Scheme 36.

These results suggested that the radical path promoted by TBHP was not compatible with our substrate or with the palladacycle intermediates. We then turned our attention to other kinds of process, involving the insertion of the acyl sources without the necessity of employing peroxides and radicals.

On the other hand, we have previously reported that the employ of acetic acid as solvent and benzoquinone as oxidant (only air is not enough) are the best conditions for the palladium-catalyzed C–H functionalization of primary amines.[69,70]. Unfortunately this oxidant is not compatible with aldehydes since they are oxidized to carboxylic acids, as it can be said for other classic oxidizing agents, such as silver or copper salts.

Thus, to allow the use of oxidants, we attempted the intramolecular palladium-catalyzed cyclization of imines **23** and **24.** A similar transformation has been reported by Matsuda *et al.* starting from methylene benzohydrazides[83] using benzoquinone as oxidant in acetic acid (Scheme 37a). Unfortunately, independently of the kind of imine, we only observed the partial transformation of the substrates in the acetamide **25**, probably due to the hydrolysis of the imines and the subsequent reaction with the solvent (Scheme 37 b).

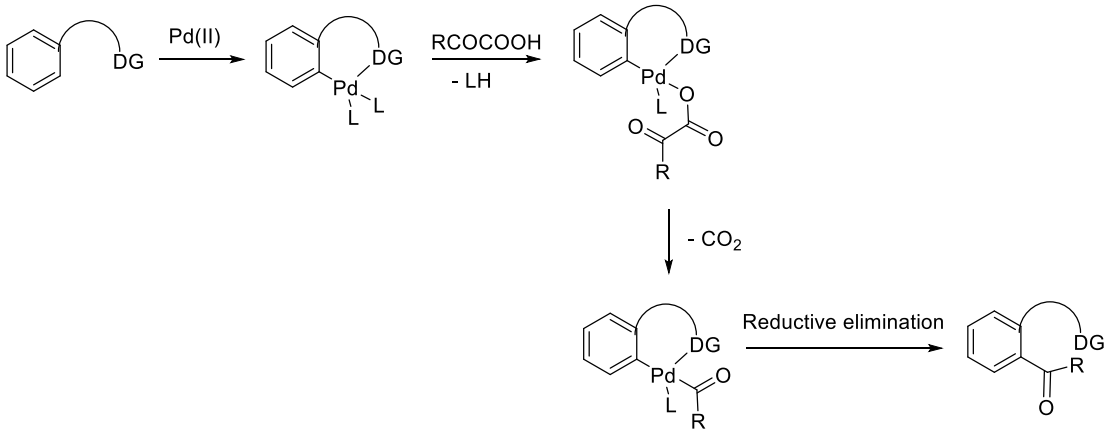
Due to the poor results obtained and to the incompatibility showed by aldehydes with several reactions conditions, we continued our investigation with other acyl sources.



Scheme 37.

2.1.3. Attempt of acylation with α-carbonyl carboxylic acids

As anticipated in the introduction of this chapter, α-carbonyl carboxylic acids may be good reagents for the palladium-catalyzed acylation of arenes. Many examples of acylation of 2-phenylpyridines[76b], anilides[84], aromatic o-methoximes[85], phenyl carbamates[86], aromatic amides[87], etc. performed in a variety of reaction media and experimental conditions have been described using this acyl source.



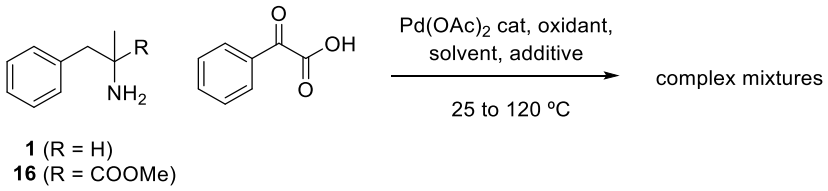
Scheme 38.

According to the literature, this process proceeds through an addition-decarboxylation mechanism that does not involve the formation of radical species[84] (Scheme 38) and allows the utilization of alternative oxidants to air and of various reaction media. Hence, we thought we had more chances with this acyl source, allowing us to operate at different conditions.

To this aim, we reproduced several conditions that are reported in the literature. Despite various solvents (diglyme, dichloroethane, dioxane, acetonitrile, toluene, acetic acid) were combined with several oxidants (ammonium and potassium persulfate, silver carbonate, copper (II) acetate and chloride, air) in presence or absence of additives (like triflic acid, acetic acid or DMSO), only complex mixtures were obtained after the

disappearance of the starting amines at room temperature, 70, 100 or 120 ºC (Scheme 39).

In any case traces of the expected product were not detected by ^{1}H NMR or TLC and any compound was not isolated and characterized from the reaction crudes.



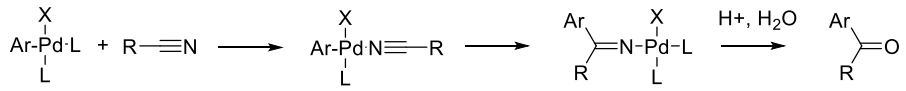
1 (R = H)
16 (R = COOMe)

Scheme 39.

The amino ester **16** was also used as substrate in some attempts, since the previous results in our group indicated that an electron-withdrawing functionality close to the nitrogen could have changed the efficiency of the palladium-catalyzed process, but appreciable changes in the results were not observed.

2.1.4. Attempts of acylation with nitriles

There are several examples in which aromatic carbon-palladium bonds undergo the insertions of nitriles, leading to the construction of aromatic ketimines that can be easily transformed into aryl ketones[88] (Scheme 40).

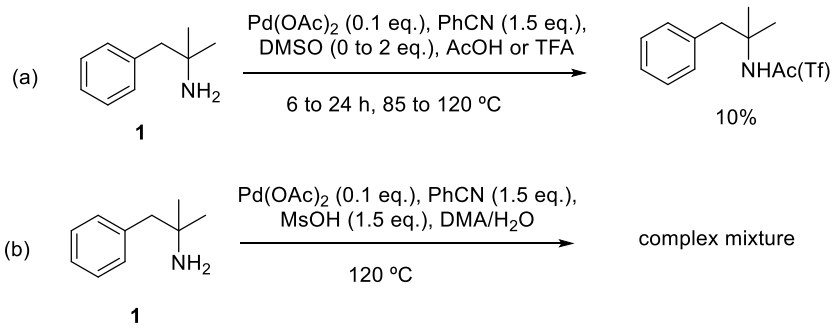


Scheme 40.

So, we tried to adapt some described procedures to primary amines. We were hopeful since the reported conditions for the acylation of arene complexes using nitriles seemed to be useful for primary amines.[71,73]

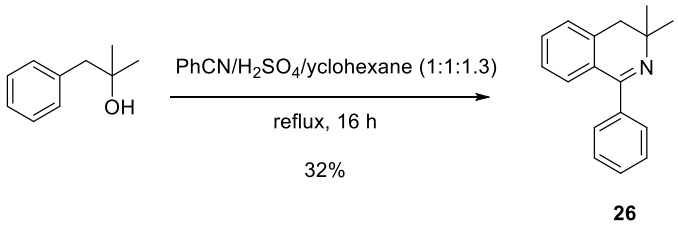
Despite the good expectations, the assumed products arising from amine **1** were not obtained and starting material was always recovered in different conditions. The only transformation observed was the partial conversion of the substrate into amides when acidic solvents were used (Scheme 41a). The use of no-acidic solvents led to complex mixtures (Scheme 41b).

Similar results were observed for the amino ester **16**: starting material was recovered operating in acidic mediums, while the hydrolysis of the ester group and other degradations were observed at different conditions.



Scheme 41.

In view of the negative results, we verified the stability of the expected products at the conditions in which we were operating. Thus we prepared the dihydroisoquinoline **26** by a described Bischler-Napieralsky reaction[89] (Scheme 42) and we tested its stability.



Scheme 42.

Compound **26** showed perfect resistance to silica and acid water (2 N aqueous solution of HCl).

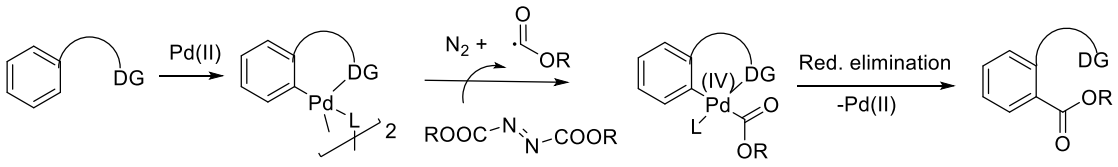
Finally, it was heated to reflux overnight in acetic acid in the presence of a 10% molar amount of palladium and almost the totality of the compound was recovered at the end of the reaction without having undergone any transformation.

Hence, we confirmed that the problems we were facing were not due to the degradation of the desired products, but probably to the inability of the palladacycles derived from primary phenylethyl amines to undergo the insertion of acyl sources.

2.2. Carboxylation with azodicarboxylates

Azodicarboxylates thermally decompose generating molecular nitrogen and acyloxy radicals. The decomposition may also occur at room temperature at the presence of radical-generator species.

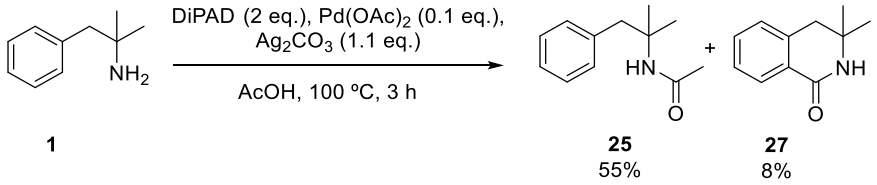
Several reports describe the reaction of acyloxy radicals with palladium-activated aromatic C–H bonds (Scheme 43). Thus, arylpyridines[20], aromatic *O*-methyl oximes[20], 2-arylpyrimidines[80] and anilides[77b] have been selectively *ortho*-acylated.



Scheme 43.

We tried to apply a similar protocol to our phenylethylamine in order to obtain intermediates leading to benzolactames (as explained in the introduction of this chapter).

We were pleased to observe that a small amount of the desired product **27** was obtained using amine **1** as substrate and diisopropyl azodicarboxylate (DiPAD) as radical source, in acetic acid with silver carbonate as oxidant. However, a large amount of the acetamide **25** was also isolated (Scheme 44).



Scheme 44.

Thus, we started the optimization of the process by screening several possible oxidants (Table 1).

Table 1.

Entry[a]	**Oxidant**	**Ratio 1 : 25 : 27 (crude ^{1}H NMR)**	**27 (Yield, %)**[b]
1	Ag_2CO_3	14 : 72 : **14**	8
2	$(NH_4)_2S_2O_8$	59 : 12 : **26**	< 5
3	$K_2S_2O_8$	25 : 0 : **75**	10
4	BQ	0: 75 : **25**	n.d.[c]
5	$Cu(OAc)_2{\cdot}H_2O$	0: 71 : **29**	20
6	TBHP	0 : 100 : **0**	0
7	Oxone	58 : 16 : **26**	12
8	$CuCl_2$	0: 100 : **0**	0

*a) Reaction conditions: amine **1** (0.5 mmol), DiPAD (1 mmol), oxidant (0.6 mmol), acetic acid (2.5 mL), 100 ºC, 3 h; b) isolated yields; c)the mixture was not purified.*

Remarkably, the formation of acetamide was not observed using potassium persulfate (entry 3), but the reaction mixture was complex even before the total consumption of the starting material and the product was isolated in low yield. With ammonium persulfate (entry 2), a large quantity of amine **1** was observed in the reaction mixture and just a few milligrams of lactame **27** were isolated from the crude. In this case the formation of the undesired product **25** was detected again.

Oxone promoted the formation of **27** as the mayor product (entry 7), but a lot of unreacted starting material was recovered and the yield was only a 10%.

TBHP and $CuCl_2$ just enabled the formation of byproduct **25** (entries 6 and 8).

The best yield (20%) was achieved using $Cu(OAc)_2 \cdot H_2O$ (entry 5). However, the relative quantity of the cyclized product was poor compared to the acetamide. This copper salt was also the oxidant which enabled the best conversion of the starting material into the two amides.

At the sight of these results a further optimization of the reaction was tried employing $Cu(OAc)_2 \cdot H_2O$ as oxidant and trying to avoid or limit the utilization of the acetic acid in order to minimize the formation of amide **25** (Table 2).

Table 2.

Entry[a]	Solvent	Ratio 1 : 25 : 27 (crude ^{1}H NMR)	27 (Yield, %)[g]
1[b]	Toluene	100 : 0 : **0**	0
2[b,c]	Toluene	Complex mixture	0
3	AcOH/Toluene1/9	0 : 80 : **20**	n.d.[h]
4	AcOH/Toluene1/4	0 : 70 : **30**	20%
5	AcOH/DCE 1/4	0 : 80 : **20**	n.d[h]
6	AcOH/DMF 1/4	0 : 91 : **9**	n.d.[h]
7[b,f]	None	0 : 100 : **0**	0
8[b]	DCE	100 : 0 : **0**	0
9[b,d,e]	DCE	Complex mixture	0

*a) Reaction conditions: amine **1** (0.5 mmol), DiPAD (1 mmol), $Cu(OAc)_2.H_2O$ (0.6 mmol), solvent (2.5 mL), 100 ºC, 3 h; b) MsOH (0.5 mmol) as additive, c) the reaction was stirred overnight at 100 ºC; d) T = 25 ºC; e) PBA(0.1 eq) as radical generator; f) 6 eq of DiPAD, 50 ºC; g) isolated yields; h) the mixture was not purified.*

Unfortunately, the importance of the acetic acid for the formation of the desired product appeared clear: the relative quantity of byproduct **25** raises when the quantity of acetic acid decreases as observed when entries 3 and 4 were compared. The lactame **27** was not obtained in any experiment in absence of this solvent. Toluene resulted to be the best co-solvent between the tested ones but, in any case, we could reach the formation of **27** using it as the only reaction medium, in presence or absence of additives. The most surprising result was that the complete conversion of the amine **1** into **25** was obtained in the solvent free reaction (entry 7): that means that the acetates contained in the oxidant are enough to convert the amine **1** into **25**. However, the switch to copper chloride was ineffective, as observed in the entry 8 of Table 1.

Another interesting consideration can be made looking at the differences between the entries 8 and 9: the presence of a radical generator led to a complex mixture even if the reaction was performed at room temperature while in the same conditions no reaction was observed at 100 °C in absence of PBA (perbenzoic acid). This seemed to confirm

that the primary amines are not compatible with most radical species in presence of palladium acetate.

The use of oxone as oxidant did not improve the yield (Table 3). Although 24% of the starting material was recovered after 24 hours, a 50% of the substrate was converted into a complex mixture in 3 hours (entries 1 and 3).

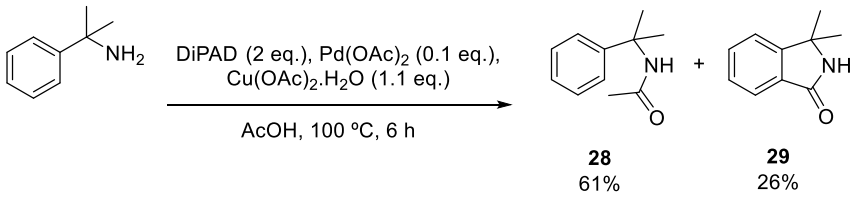
Table 3.

Entry[a]	Conditions	Ratio 1 : 25 : 27 (crude ^{1}H NMR)	27 (Yield, %)[b]
1	3 h, 100 ºC	59 : 15 : **26**	13
2	6 h, 100 ºC	50 : 19 : **31**	n.d.[c]
3	24 h, 100 ºC	46 : 16 : **38**	20

*a) Reaction conditions: amine **1** (0.5 mmol), DiPAD (1mmol), oxone (0.6 mmol), Toluene/AcOH 4/1 (2.5 mL);b) isolated yields; c) the mixture was not purified.*

The change of the alkoxy radical source was also attempted: DEAD (diethyl azodicarboxylate) was employed instead of DiPAD (diisopropyl azodicarboxylate) but worst results were achieved. Only traces of the product **27** were obtained using oxone as oxidant in the best conditions, while a 10% yield was reached with $Cu(OAc)_2$.

Our last attempt was the achievement of a five-membered aromatic lactame starting from commercially available cumyl amine. The expected compound **29** was obtained in low yield besides a large quantity of byproduct **28** (Scheme 45) in the best tested conditions.



Scheme 45.

2.3. Summary and conclusions

In this chapter a quite exhaustive exploration on the interaction between palladium activated aromatic primary amines and several acyl or carboxyl sources have been reported. Relevant results have not been reached in this field.

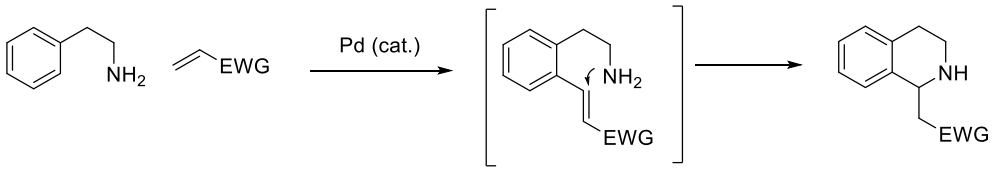
In absence of radical species, we have performed some attempts of acylation applying conditions similar to those successfully used in our group in the carbonylation or annulations of phenylethylamines. In these cases, we often recovered the starting material. This suggested that the aromatic C–H bond is not active enough to undergo the insertion of C=O or C=N.

On the other hand, a selective reaction for the activation of the *ortho*-position of phenethylamines in the presence of radical species seemed to be impossible. In almost all the reactions in which radical species were generated an extense or partial conversion of the starting material in complex mixtures was observed. In the reactions performed with azodicarboxylates a significant part of the reaction crude always consisted in a mixture of unidentified compounds when the decomposition of the radical source (DiPAD or DEAD) and the consequent formation of radicals occurred.

3. PALLADIUM-CATALYZED TANDEM OLEFINATION-ANNULATION OF PHENYLETHYL AMINES WITH ELECTRON-DEFICIENT ALKENES

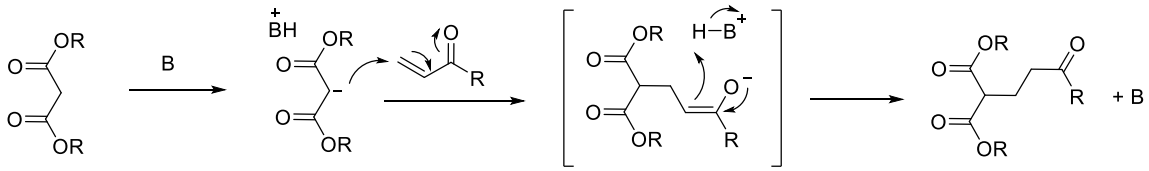
3.1. Electron deficient alkenes: Michael acceptors

In this chapter of the thesis we studied the palladium-catalyzed insertion of electron deficient alkenes into the sp^2 carbon-hydrogen bond of arylethyl amines. We expected a subsequent intramolecular conjugated addition to afford heterocyclic compounds in this process (Scheme 46).



Scheme 46.

Electron deficient alkenes are popular reagents in organic chemistry thanks to their property as "soft" electrophiles. The most common are α-β-unsaturated carbonyl, carboxyl, or nitryl compounds. They are also called Michael acceptors because they can actuate as electrophile in the Michael reaction (Scheme 47).

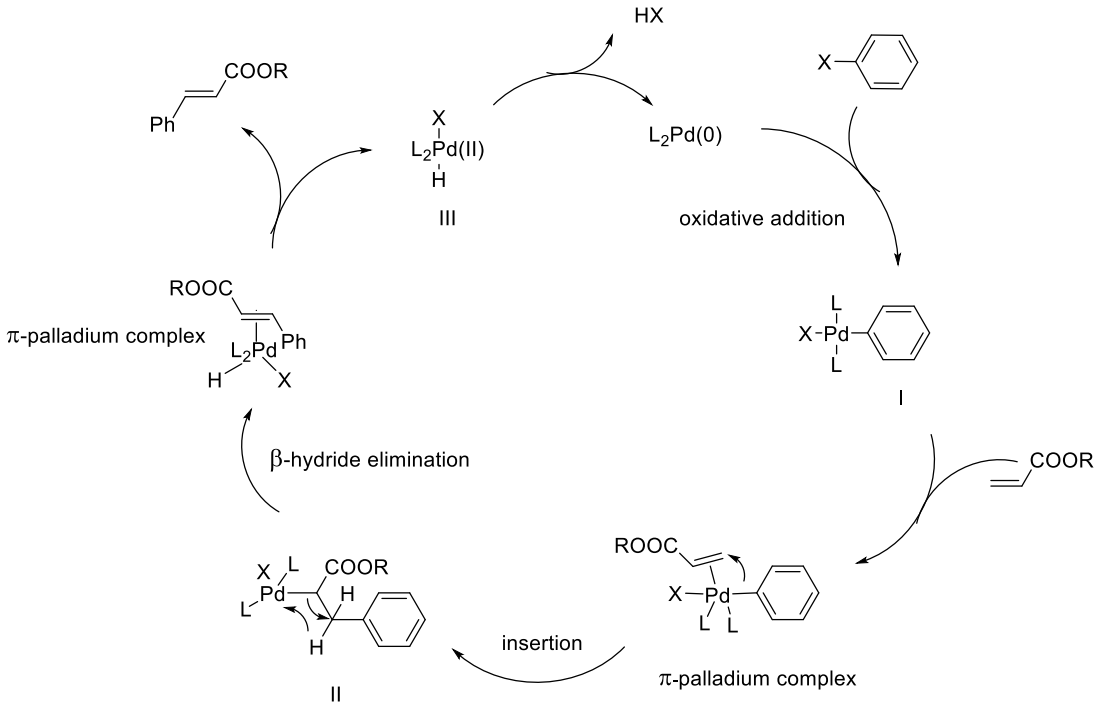


Scheme 47.

In addition to the use in conjugate addictions, their most important application is certainly the industrial polymerization for the production of polyacrylates that are commonly used as cosmetics and adhesives.

Excluding these classical utilizations, Michael acceptors represent one of the most employed alkylating agents in metal-catalyzed reactions aimed to create C–C bonds. In this sense the most famous reaction that involves the use of activated alkenes is the Mizoroki-Heck reaction[90], a process developed in 1974 that allow the coupling between aryl (or vinyl) halides and olefins (Scheme 48).

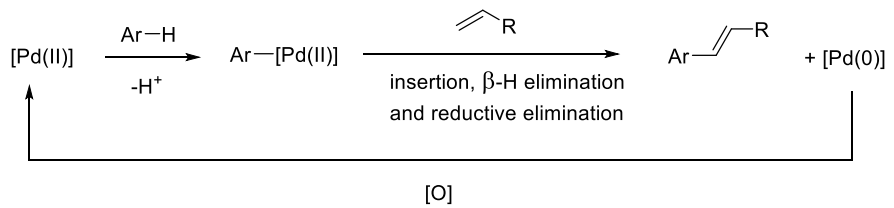
In this process, Pd(0) (that is normally generated *in situ*) inserts into the aryl-halogen bond via an oxidative addition. Then, the coordination of the alkene generates a π-palladium complex. At that point the alkene inserts into the activated C–Pd bond generating the intermediate **II** that undergoes a β-hydride elimination. A new π-palladium complex is formed from which the olefinated arene and the Pd(II) intermediate **III** are generated. The palladium intermediate **III** finally undergoes a reductive elimination restoring the Pd(0) catalyst.



Scheme 48.

The scope of this outstanding methodology is limited to activated arenes (to allow the oxidative addition of the transition metal) that restricts the application of the process to the unique utilization of pre-halogenated substrates.

A similar transformation called Fujiwara-Moritani reaction allows the coupling between alkenes and unactivated arenes, as shown in the introduction of this thesis. In this case the inert arene is activated by a Pd(II) catalyst (via a concerted metalation-deprotonation path) generating an Ar-Pd complex that undergoes the same coordination and insertion of the alkene, followed by the β-hydride elimination occurring in the Heck reaction. The Pd(0) generated at the end of the process has to be re-oxidized to Pd(II) by an oxidizing agent to be able to interact with a new molecule of arene (Scheme 49).[4,91]

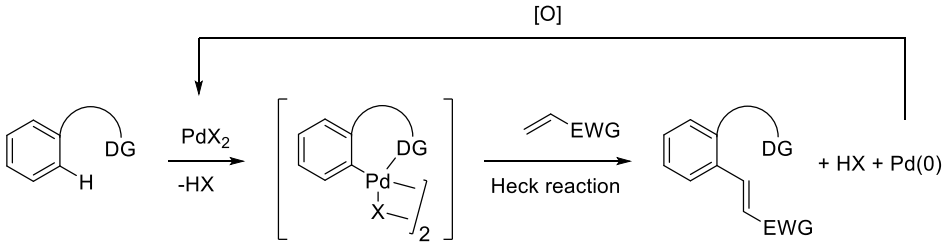


Scheme 49.

Actually, this reaction is in fact an extension to unactivated arenes of the well known Heck reaction. However, it appears the problem of the regioselectivity because of the equivalence between the various C–H bonds in the aromatic compounds that did not allow regioselectivity for the metalation and the subsequent alkylation.[92]

Thus, several methods have been developed adapting these reactions to the olefination of aromatic compounds containing directing groups for the metalation. These strategies

involve the chelation-assisted aryl C–H bond activation that ensures the selectivity of the process, followed by the Heck reaction that generates the product (Scheme 50).



Scheme 50.

Many directing groups have been used for the palladium-catalyzed *ortho* olefination of aromatic compounds such as ureas[93] or guanidines,[50] pyridines, [30a,30b,50,94] perfluoroanilines,[40c] carboxylic acids, [95] esters,[96] alcohols,[14e] silanols,[18a,97] ethers[15a] or thioethers,[15b] leading to different alkenylated aromatic compounds as shown in Figure 3.

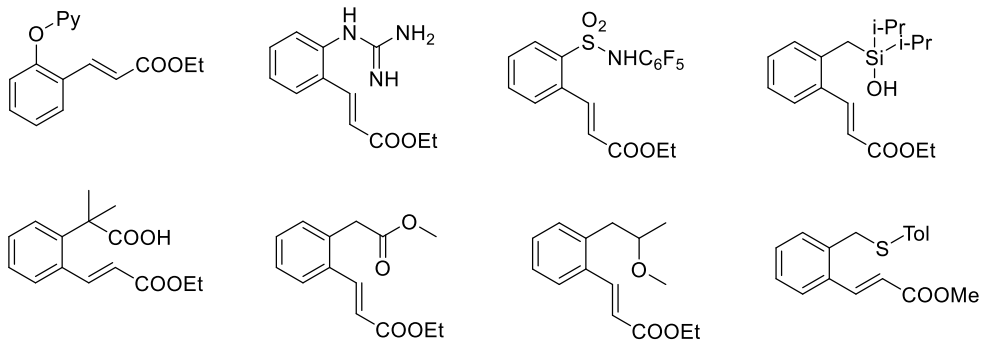
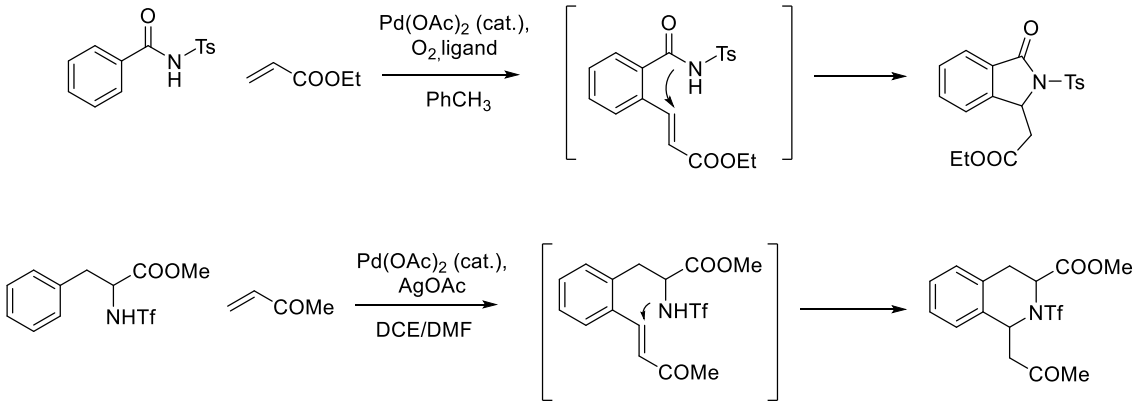


Figure 3.

As indicated in the introduction of this thesis, there is only a previous work, dating back to 2007, that describes the palladium-catalyzed functionalization of aromatic amines with Michael acceptors.[54]

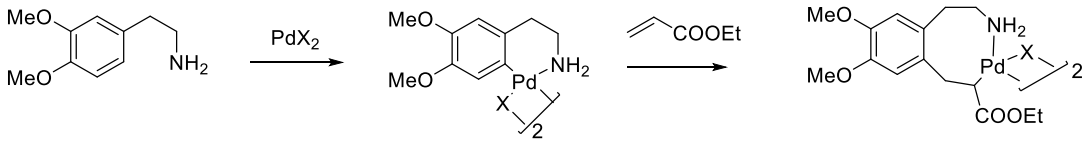
On the other hand, interesting results have been described using amides or their derivatives as directing group, since, in some cases, the products arising from the olefination are able to undergo an intramolecular conjugate addiction to lead to heterocyclic compounds. In 2011 Zhu *et al.* described the *N*-tosylamide directed olefination-annulation reaction to give isoindolines[39a], while some years earlier Yu's group reported the tandem C–H alkenylation and aza-Michael addition process to obtain tetrahydroisoquinolines (THIQ) from arylethyl triflamides (Scheme 51). The intramolecular cyclization only works employing α,β-unsaturated ketones as electrophiles: when other electrophiles, such as acrylates, are employed the non-cyclized olefin is obtained.[40a]



Scheme 51.

3.2. Addition of Michael acceptors to phenylethyl amines

Previous results in our research group showed a high reactivity of the 6-membered palladacycles, generated from the metallation of α-functionalized phenethylamines and phenethylamino esters, with electrophiles.[70,71,73] In this connexion, Vicente *et al.* demonstrated in 2012 that six-membered palladacycles generated from the metalation of primary phenylethylamine undergo the insertion of acrylates into the C–Pd bond leading to eight membered palladacycles (Scheme 52).[98]



Scheme 52.

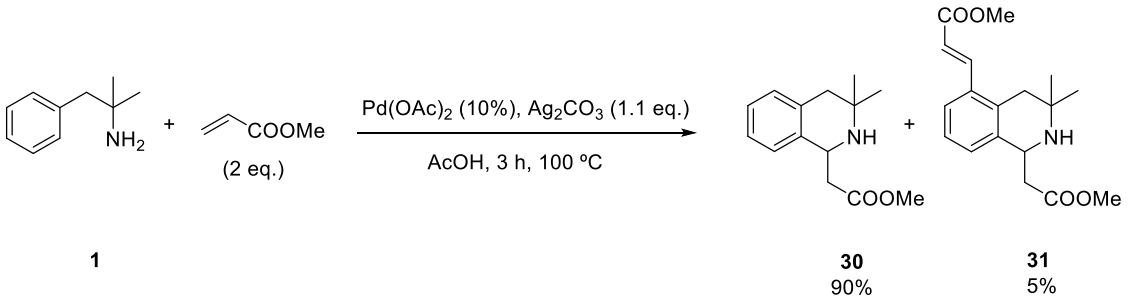
3.2.1. Initial results

Taking into account these evidences, in 2012 students H. Etxabe and C. Alamillo started the study of the addition of phenethylamines to electron deficient-alkenes during their experimental Master at the University of Barcelona. The aim of the project was the development of a tandem process, similar to that described by Yu (Scheme 51), for the olefination and subsequent cyclization via an intramolecular aza-Micheal reaction of primary amines.

The preliminary catalytic studies were focused on the reaction of the primary amine **1** with methyl acrylate using commercially available palladium acetate as catalyst and benzoquinone as the oxidant, in acetic acid at 100 ºC. These conditions had shown to be the best for the carbonylation of primary amines catalyzed by palladium[70], and in that case, the choice of benzoquinone as the oxidant was a key factor for the success of the catalytic process.

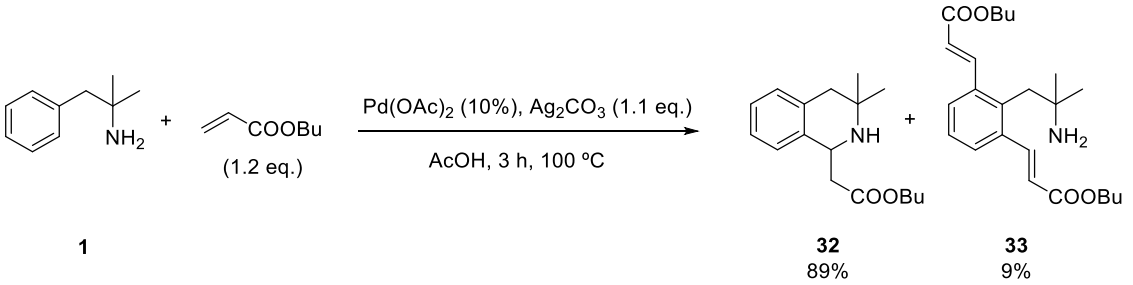
Some experiments were performed modifying the stoichiometric amount of oxidant and acrylate with respect to the amine and the reaction time. To our satisfaction, the desired

product **30** was obtained, but in low to moderate yield (29-54%), depending on the conditions. The by-product **31** coming from the activation of both the *ortho* positions of the aromatic ring was always observed although in low yield (3-8%). Once again, the decisive change during the optimization of the process was the choice of the oxidant: silver salts were used as alternative oxidants.[40a] In this way the almost quantitative conversion of the starting material into the desired products was obtained using Ag_2CO_3 and two equivalents of acrylate (Scheme 53).



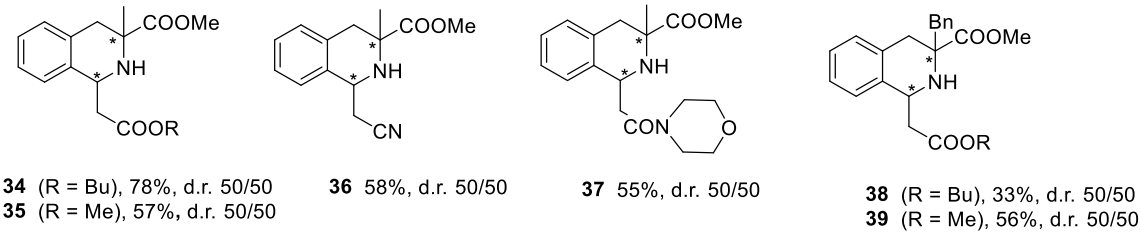
Scheme 53.

Later, C. Alamillo optimized the addition of the amine **1** to butyl acrylate using 1.2 equivalents of olefin and the mono and di-alkylated products **32** and **33** were obtained in quantitative yield (Scheme 54).



Scheme 54.

Applying the same conditions, some tetrahydroisoquinolines (THIQs) were prepared in good yields combining different phenethylamines and Michael acceptors (Figure 4).



34 (R = Bu), 78%, d.r. 50/50
35 (R = Me), 57%, d.r. 50/50

36 58%, d.r. 50/50

37 55%, d.r. 50/50

38 (R = Bu), 33%, d.r. 50/50
39 (R = Me), 56%, d.r. 50/50

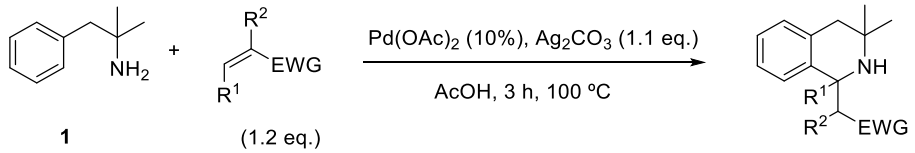
Figure 4.

3.2.2. Reactivity of Michael acceptors

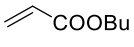
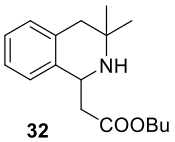
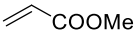
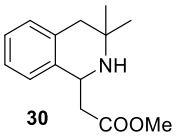
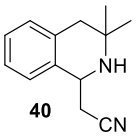
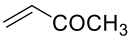
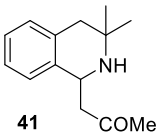
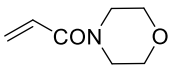
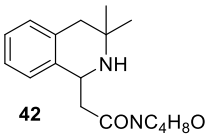
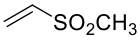
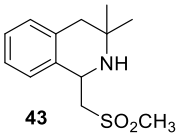
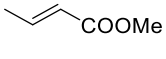
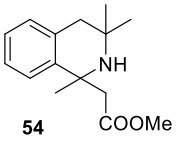
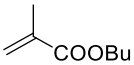
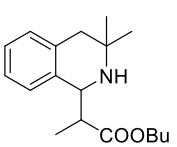
The pioneer work of Carla and Haizea was continued in this thesis. A more extensive study of the scope of the reaction and of the structural limitations of this process was performed and a wide range of different THIQs was synthesized.

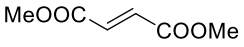
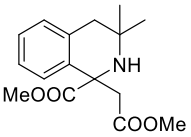
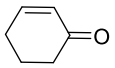
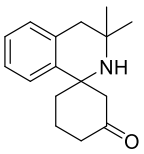
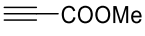
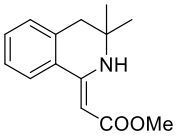
Initially, the reactivity of several electrophiles with the amine **1** was explored (Table 4).

Table 4.



1 (1.2 eq.)

Entry[a]	Unsaturated compound	Product	Yield (%)[b]
1		 **32**	90
2		 **30**	60[c]
3		 **40**	42
4		 **41**	51
5		 **42**	42
6		 **43**	55
7		 **54**	28
8			0

9			0
10			0
11			0

*a) Reaction conditions: 0.5 mmol of amine **1**, 0.6 mmol of alkene, 0.05 mmol of catalyst, 0.55 mmol of oxidant, 3 mL of AcOH in a sealed vial; b) isolated yields; c) yield = 90% using 2.0 equiv. of acrylate.*

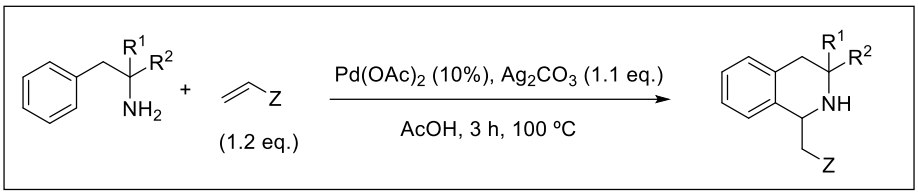
As shown, excellent yields can be obtained with acrylates. Butyl acrylate led to the products in better yields, in comparison with the correspondent methyl ester, operating at the same conditions (entries 1, 2). Acrylonitrile, vinyl ketones, acrylamides and vinylsulfones showed to be fairly good electrophiles for this transformation, leading to the construction of the desired products in moderate yields (entries 3 to 6). The possibility of introducing the sulfone functionality in the structure of the tetrahydroisoquinolines was an interesting result as it will be explained in the last chapter of this memory.

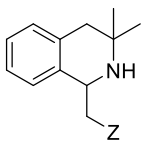
The attempt of alkylation with methacrylate only afforded a complex mixture, while the formation of the desired product was observed in low yield using a crotonate as electrophile (entries 7, 8). Conversely, only starting material was observed in the reaction mixture when the reaction is performed with the correspondent fumarate, (entry 9).

Despite the positive result obtained with but-3-en-2-one as electrophile (entry 4) the use of a similar cyclic ketone afforded the formation of complex mixtures (entry 10).

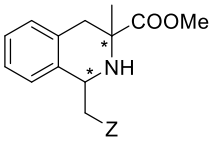
Finally, the alkylation of amine **1** with alkynes was tested in order to obtain unsaturated THIQs, but no reaction was observed in this case.

After this exploration, we applied the optimized process to the synthesis of some new tetrahydroisoquinolines combining different amines with different electron-deficicient alkenes that had shown to be useful for this transformation, in order to complete the table of compounds shown in Scheme 55.

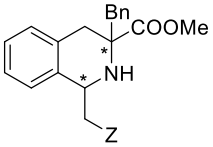




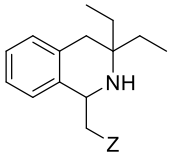
30 (Z = COOMe), 60%*
32 (Z = COOBu), 90%
40 (Z = CN), 42%
41 (Z = $COCH_3$), 51%
42 (Z = $CONC_4H_8O$), 42%
43 (Z = SO_2CH_3), 55%



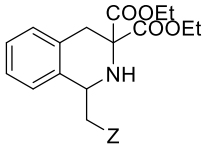
34 (Z = COOBu), 78%, d.r. 50/50
35 (Z = COOMe), 57%, d.r. 50/50
36 (Z = CN), 58%, d.r. 50/50
37 (Z = $CONC_4H_8O$), 55%, d.r 50/50



38 (Z = COOBu), 33%, d.r. 50/50
39 (Z = COOMe), 56%, d.r. 50/50



44 (Z = COOBu), 62%
45 (Z = COOMe), 57%*
46 (Z = CN), 42%



47 (Z = COOBu), 73%
48 (Z = CN), 80%

* **30** and **45** were obtained in 90% and 80% yield respectively by using 2 eq. of methyl acrylate

Scheme 55.

To explain the yields showed in Scehme 52 two issues regarding the substitution on the C bearing the NH_2 group seem important: the effect of the steric hindrance and the electronic one.

In agreement with previous works in our group it was observed that the presence of electron-withdrawing groups that are vicinal to the nitrogen had a positive effect on the efficiency of insertion of CO or allenes into the activated amines (in the case of the annulation with allenes the yields of the process dramatically changed).[73] In this reaction, the electronic effect seems to be significant for the reactions performed with the less reactive Michael acceptors, while it does not seem to be decisive with good electrophiles. In this last case the steric hindrance seems to play the key role.

It is possible to observe increasing yields in the formation of compounds **40**, **36** and **48**. A similar trend is observed for **42** and **37**: acrylonitrile and 1-morpholinoprop-2-en-1-one showed to be poorly efficient as alkylating agents (compared to acrylates) and the introduction of electron withdrawing groups in the α-position of the starting amine increases significantly the efficiency of their insertion, despite the increasing of the steric hindrance on the nitrogen. Conversely comparison of the yields of formation of compounds **32**, **34** and **47** (obtained by the addition to the best working electrophile) showed that the steric hindrance plays the key role: the trend of the efficiency of the

process is opposed to the presence of electron withdrawing groups in α to the nitrogen and the yields decrease with the increasing of the presence of groups around the nitrogen. The difference between the yields of compounds **32** and **44** seems to confirm this theory.

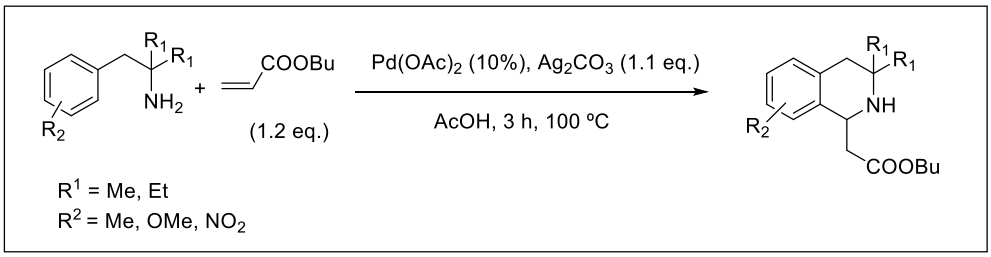
A further evidence of the existence of a steric effect is the fact that the smaller electrophiles are not affected by the increasing of the dimensions of the substituents in α to the nitrogen: compounds **40** and **46** were isolated in the same yield.

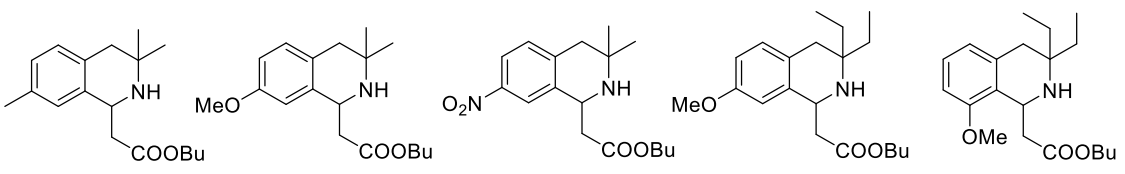
All the reactions performed with methyl acrylate furnished more or less the same yield. We considered that the difference between methyl and butyl acrylate should be due to the volatility of the smaller Michael acceptor. This speculation is confirmed by the evidence that increasing the quantity of electrophile, the efficiency of the reaction improves, a consequence that was not observed for other alkenes.

A final consideration should be pointed out: when the reaction was performed starting from racemic amino esters **16** and **17**, a 1 to 1 mixture of diastereoisomers was always obtained. Thus, no stereoselectivity was detected.

3.2.3. Reactivity of the aromatic ring

The effect of the substitution of the aromatic ring was also studied. A set of substituted amines were alkylated as shown in Scheme 56. We could observe that the substituted amines also led to isoquinolines **49-53** independently of the introduction of electron-withdrawing or electron-donor groups in *para*. The yields decreased with respect to the unsubstituted compound when a nitro group or a methoxide were introduced, while the tetrahydroisoquinoline **49** was obtained almost in the same yield than the analogous compound **32**.





49 85% **50** 70% **51** 66% **52** 54% **53** 52%

Scheme 56.

The *meta*-substituted THIQ **53** was prepared in almost identical yield to the corresponding *para*-substituted compound **52**.

3.2.4. Structural requeriments of the starting amines

Early, in the pioneering experiments performed by Haizea Etxabe, the necessity of the presence in the substrates of a quaternary center in α to the nitrogen resulted as the most important structural limitation for the insertion of Michael acceptors into phenethylamines. Without this condition, only complex mixtures were obtained from commercially available substrates like phenylethylamine and methyl phenylalaninate (Table 5, entries 1, 2).

Different models of phenylethylamines, with different functionalization in the α-position and on the nitrogen atom, were prepared as described in the second chapter of this report and they were employed as substrate in order to acquire a larger view about the scope and the limitations of the reaction for the synthesis of tetrahydroisoquinolines (Table 5).

First of all, we explored the consequences of the introduction of some substituents on the nitrogen of α-quaternary amines. For this purpose, we prepared the secondary amines **15** and afterwards **13** introducing respectively an ethyl and a methyl group on the nitrogen: this kind of substrates resulted totally unreactive in this process. The equivalent sulfonamide **21,** carbamate **22**, and acetamide **25** were also unreactive.

Subsequently the effect of the introduction of a quaternary center in the benzylic position of phenethylamine (keeping the α-position free, entry 8) was tested, but the substrate **20** showed the same behavior of the unsubstituted phenylethylamine and only a complex mixture was obtained.

Some better results were observed from unsubstituted secondary phenylethylamines **14** and **10** (entries 9, 10): in this case the formation of the desired products **55** and **56** was observed in low yield. We could not completely isolate and characterize these compounds due to the complexity of the reaction mixtures, but the information showed by the NMR (compared to similar products we obtained in other reactions or we found in the literature)[99] and the mass spectroscopy seemed to confirm the formation of the desired isoquinolines. The yield was slightly higher for the THIQ **55**.

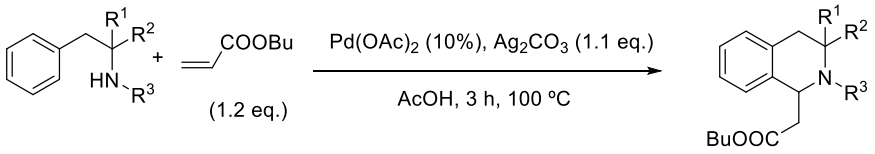
Finally, we examined the reactivity of the α-monosubstituted analogue of the amine **10** (entry 11, compound **11**) and the desired product **57** was obtained in 20% yield. This was the better observed conversion from the reacted amine into the desired product (40%), but the yield remained low and the crude showed a complex composition (it was impossible to completely isolate the product).

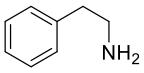
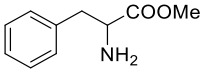
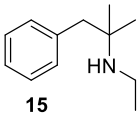
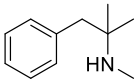
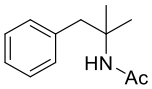
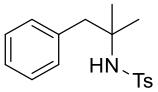
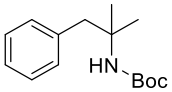
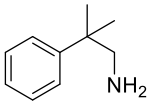
A screening of conditions was made for the amines **11** and **14** in order to obtain **55** and **57** in better yield. The alkylation was also performed in trifluoroethanol and toluene as solvents, and *para*-toluenesulfonic acid and/or acetyl glycine were tested as additives, but yields were lower than 30% at different temperature and reaction times. In all the

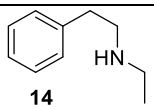
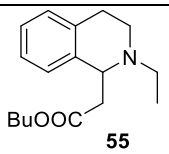
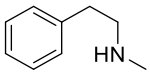
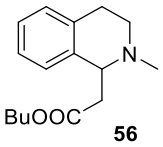
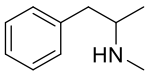
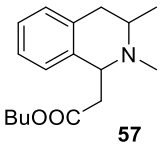
reactions, messy mixtures were obtained and the products were never completely isolated from the impurities. In the reactions performed with the amine **11**, the starting material was never consumed completely.

From this analysis, we could conclude that a steric hindrance near the nitrogen is a necessary condition to limit the reactivity of the substrates in the reaction conditions and to obtain the desired products, but at the same time when the nitrogen atom is too much hindered no reaction is observed (Scheme 57). Without the quaternary center in α only secondary amines lead to the desired products in low yields, in the other cases the substrates were too much reactive and the formation of complex mixtures was observed.

Table 5.

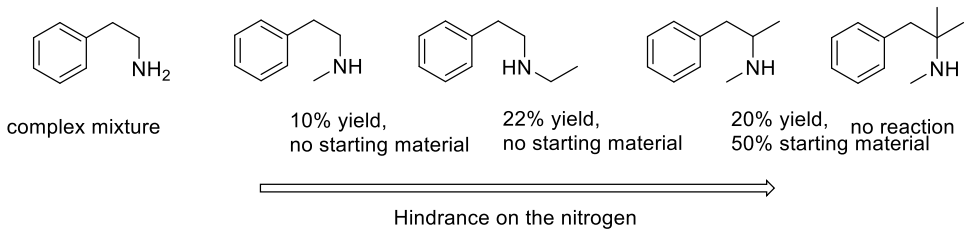


Entry[a]	Substrate	Product	Yield (%)	Starting material (recovered, %)
1		--	0[b]	0
2		--	0[b]	0
3	 **15**	--	0	100
4	 **13**	--	0	100
5	 **25**	--	0	100
6	 **21**	--	0	100
7	 **22**	--	0	100
8	 **20**	--	0[b]	0

9	 **14**	 **55**	22[c]	0
10	 **10**	 **56**	< 10[c]	0
11	 **11**	 **57**	20[c]	50

a) Reaction conditions: 0.5 mmol of amine, 0.6 mmol of butyl acrylate, 0.05 mmol of $Pd(OAc)_2$, 0.55 mmol of Ag_2CO_3, 3 mL of AcOH in a sealed vial; b) complex mixtures; c) the yield was estimated by analysis of NMR spectra of the crude mixture.

Finally, it should be remarked that α-quaternary sulfonamides are not reactive in our conditions, though it is known from the literature[40a] that α-monosubstituted phenyl ethyl sulfonamides can be olefinated with activated alkenes.



Scheme 57.

3.3. Summary and conclusions

In this chapter of the thesis a new and efficient method which allows the easy access to tetrahydroisoquinoline skeletons from phenethylamines has been presented. An extensive study about the kind of amines and electron-poor alkenes that allow this transformation has been performed and several examples of functionalized isoquinolines have been synthesized in moderate to excellent yields.

Acrylates showed to be the best electrophiles for this reaction. An electronic and a steric effect depending on the functionalization vicinal to the nitrogen of the starting amine have been observed but the importance of both these influences changes in relation to the electrophile that is employed in the reaction.

Finally, the need to have a quaternary center in α to the nitrogen has been demonstrated: without this condition, only complex mixtures were obtained from primary amines. During these experiments, it was possible to obtain the annulation of the secondary phenylethylamines **10**, **11** and **14** but the yields and the selectivity were really low and,

in our hands, it was not possible to improve the results. Anyhow, the olefination-annulation of secondary phenethylamines has never been described in the literature.

4. OXIDIZED ANALOGUES OF AMINES: OXIDANT FREE PALLADIUM-CATALYZED OLEFINATION OF *O*-ACYLATED *N*-PHENYLETHYL HYDROXYLAMINES

4.1. C–H functionalization under oxidant-free conditions

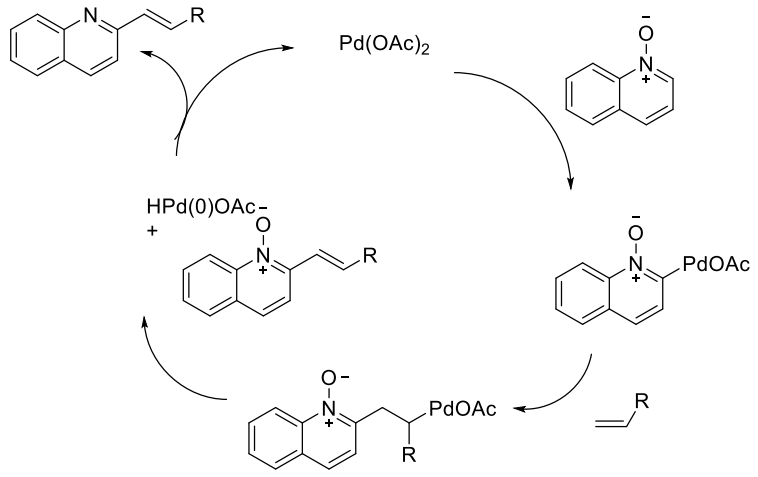
Most of the metal catalyzed C–H activation processes involve the reductive elimination of the transition metal at the end of the catalytic cycle that results in the necessity of stoichiometric quantities of oxidants (such as Cu(II) or Ag(I) salts, benzoquinone or persulfates) in the reaction mixture to re-oxidize the metal and complete the process. The resulting production of stoichiometric amounts of reduced oxidants as waste decreases the atom economy of the process. This is in sharp contrast with the principles of the metal catalyzed C–H activation chemistry since it should aim to find the conditions for easier and greener processes.

Furthermore, the choice of the right oxidant in a catalytic process could be often a challenging task since it can seriously change the result of the reactions, in term of products and yields.

In the last ten years, the use of internal oxidants as directing moieties has been investigated by some research groups: the strategy involves the use of entities that can act as directing groups and oxidants at the same time.[100] The proposed internal oxidant usually involves a covalent X–Y bond within the directing group that can oxidize the metal catalyst. Their initial design employed nitrogen-oxygen bonds (e.g. N-oxide[101], N-pivaloyloxy[102] or N-methoxy[103]), but nitrogen-nitrogen[104], nitrogen-sulfur[105], sulfur chlorine[106] bonds and others were found to be useful in some cases as well.

The oxidized directing groups can work in two ways. In the first case the cleavage of the X–Y bond occurs at the end of each catalytic cycle re-oxidizing the metal after the β-hydride elimination.

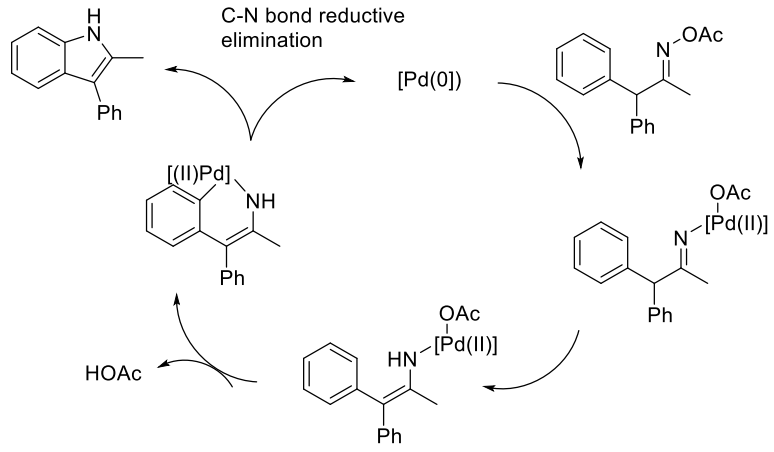
In 2009 Wu *et al.* reported the palladium-catalyzed olefination of the *ortho*-C–H bond of pyridine N-oxides (Scheme 58).[100a]



Scheme 58.

In this case the deprotection of the nitrogen at the end of the process re-oxidizes the palladium (after the β-hydride elimination of the metal) making the use of an external oxidant not necessary as well as an appropriate reaction for the cleavage of the *N*-oxide.

A second way was proposed by Hartwig *et al.* in the preparation of indoles using an oxime ester as directing group and internal oxidant at the same time. In this case a palladium(0) catalyst was employed and the metal underwent an oxidative insertion into the N-O bond at the beginning of the process, leading to a palladium(II) intermediate that was able to rearrange, performing the selective metalation of the aromatic ring and starting again the catalytic cycle (Scheme 59).[100b]



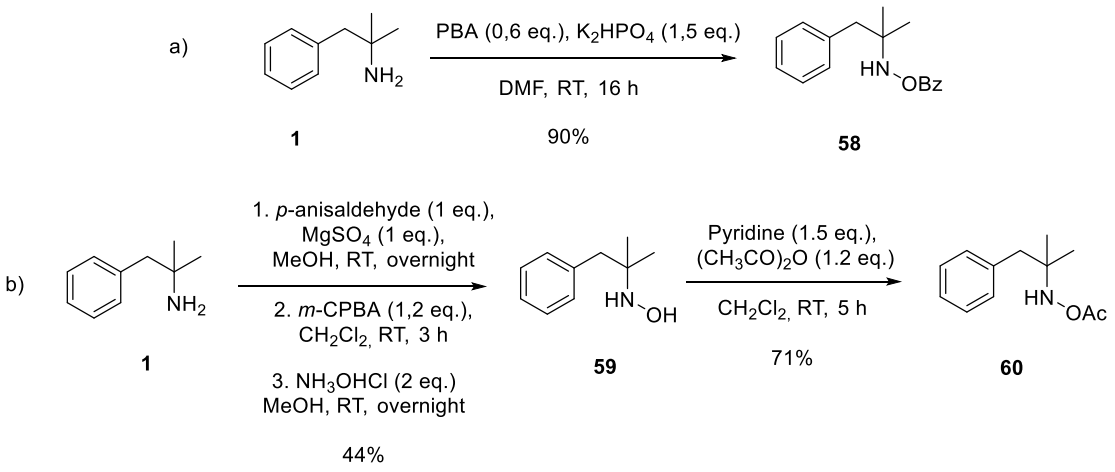
Scheme 59.

4.1.1. Oxidized analogs of phenylethyl amines

Despite the interest and the potential importance of the published papers, the use of oxidized directing groups for the metal catalyzed C–H activation of aromatic compounds is a field that has not been fully explored. Therefore, we embarked on a study aimed at examining the behavior of oxidized analogues of the amines in the catalytic C–H activation processes, in order to perform external-oxidant-free catalytic cycles for the construction of heterocyclic compounds.

We also thought that the use of different directing groups could have furnished a different coordination of the transition metal, leading to new palladium complexes that could have shown different stability and reactivity compared to the ones that had been studied before. In this way, the study of the oxidized directing groups was also an opportunity to try to overcome the structural limitations we observed in our processes.

First of all, we prepared three different models: the hydroxylamine **59**, and *O*-acylhydroxylamines **58** and **60**. The *O*-benzoyl hydroxylamine **58** was prepared by direct oxidation of the amine **1** with benzoyl peroxide (Scheme 60a), whereas the hydroxylamine **59** required a longer process reported in the literature[107] involving the formation of an imine, followed by its oxidation to oxaziridine with *meta*-chloroperbenzoic acid and by the subsequent cleavage of the C–N bond. The acylation of the hydroxylamine leaded to the third model **60** (Scheme 60b).

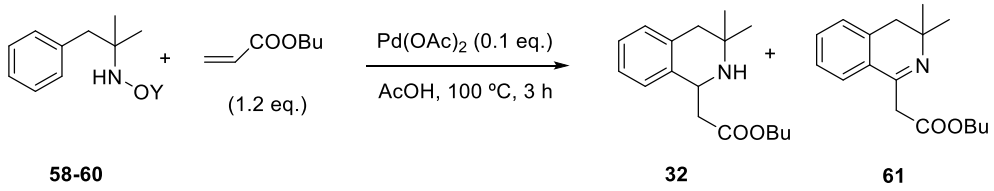


Scheme 60.

The models **58-60** were tested as substrates for the palladium-catalyzed addition to Michael acceptors, using the optimized conditions described in the precedent chapter for this reaction, except for the absence of external oxidants.

We were pleased to obtain the expected THIQ **32** in good yields just adding in the reaction flask the *O*-acylhydroxylamines **58** or **60**, the acrylate, the catalyst and the solvent, without the need of any further oxidizing agent. A completely different result was observed for the free hydroxylamine **59**.

Table 6.



Entry	Y	Starting material	32 (Yield, %)[a]	61 (Yield, %)[a]
1	H	**59**	0	10
2	Ac	**60**	56	0
3	Bz	**58**	60	0

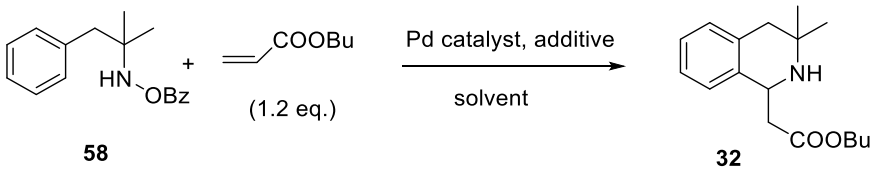
a) Isolated yields.

In this last case, the dihydroisoquinoline **61** was obtained instead of the desired tetrahydroisoquinoline **32** and the yield of the process matched with the load of catalyst. This outcome suggested that the rupture of the N–OH bond by oxidative addition to Pd(0) is slower than in N–OBz/N–OAc case, and H_20 elimination pathway is favoured. Thus, Pd(0) is not reoxidized and the catalytic cycle is interrupted. On the contrary almost the similar efficiency was showed by the *O*-acylated compounds **58** and **60**, independently of the aromatic or aliphatic nature of the substituent (Table 6, entries 2 and 3).

4.1.2. Optimized conditions for Pd-catalyzed olefination of *O*-acylated *N*-phenyltehyl hydroxylamines

Several solvents, reaction conditions, catalysts and additives were changed in order to optimize the process (Table 7).

Table 7.



58 **32**

Entry[a]	Catalyst (%)	Solvent	Additive (eq.)	Conditions	Yield (%)[b]
1	$Pd(OAc)_2$ (10)	AcOH		3 h, 100 ºC	60
2	$Pd(OAc)_2$ (10)	AcOH		1,5 h, 100 ºC	38
3	$Pd(OAc)_2$ (10)	AcOH		3 h, 50 ºC	19[c]
4	$Pd(PPh)_3$ (10)	AcOH		3 h, 100 ºC	50
5	$Pd_2(dba)_3$ (5)	AcOH		3 h, 100 ºC	65
6	$Pd_2(dba)_3$ (5)	AcOH		3 h, 100 ºC	62[e]
7	$Pd_2(dba)_3$ (5)	AcOH		16 h, RT	0[c]
8	$Pd_2(dba)_3$ (5)	AcOH		1,5 h, 100 ºC	50
9	$Pd_2(dba)_3$ (5)	AcOH		3 h, 50 ºC	29[c]
10	$Pd_2(dba)_3$ (5)	Toluene		3 h, 100 ºC	0[d]
11	$Pd_2(dba)_3$ (5)	2:1 Toluene/AcOH		3 h, 100 ºC	68
12	$Pd_2(dba)_3$ (5)	Toluene	TsOH (1)	3 h, 100 ºC	56
13	$Pd_2(dba)_3$ (5)	Toluene	AcOH (1)	3 h, 100 ºC	48
14	$Pd_2(dba)_3$ (5)	Toluene	TFA (1)	3 h, 100 ºC	32
15	$Pd_2(dba)_3$ (5)	TFA		3 h, 100 ºC	0[d]
16	$Pd_2(dba)_3$ (5)	DMF		3 h, 100 ºC	0[d]
17	$Pd_2(dba)_3$ (5)	DMF	TsOH (1)	3 h, 100 ºC	35
18	$Pd_2(dba)_3$ (5)	AcOEt		3 h, 100 ºC	0[d]
18	$Pd_2(dba)_3$ (5)	1:1 THF/$H_2$0		3 h, 100 ºC	0[d]

*a) Reaction conditions: 0.5 mmol of **58**, 0.6 mmol of acrylate, 0.05 mmol of Pd, 3 mL of solvent in a sealed vial; b) isolated yields; c) starting material was recovered; d) a complex mixture was obtained, e) 1 mmol of butyl acrylate was used.*

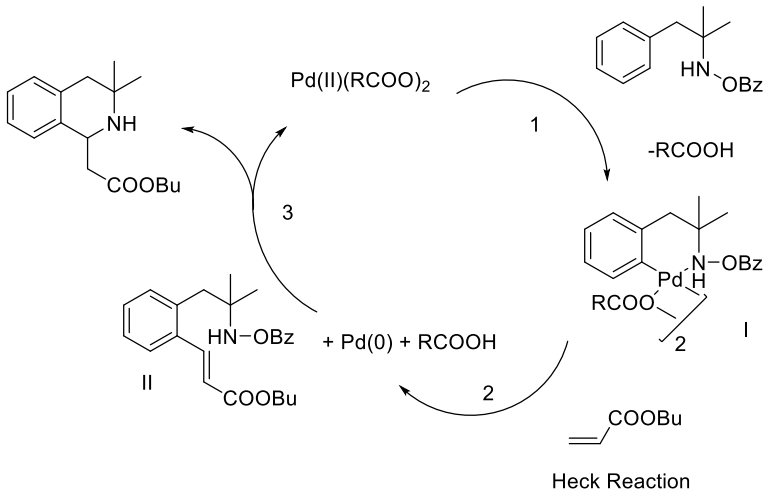
As expected, the necessity of an acidic reaction medium was observed. The process only works well in acetic acid or in a limited number of solvents in the presence of acid additives as methyl sulfonic acid, acetic acid or TFA. The effect of the acid additive does not depend on its pK_a (entries 12, 13, 14: the pK_a scale is not reflected in the yields of the reaction). Furthermore, it was observed that the TFA can actuate as acid additive, but not as reaction medium: a complex mixture was obtained performing the reaction in

this solvent. We could conclude that acetic acid is the better reaction medium since it can act as acidic medium and ligand at the same time.

Although the presence of starting material was negligible after three hours at 100 ºC, lower yields were observed decreasing the reaction time or temperature (entries 2, 3, 7, 8, 9).

One of the most important results was the possibility of running the process using both palladium(II) or palladium(0) catalysts. Since the reaction could follow two different pathways depending on the conditions.

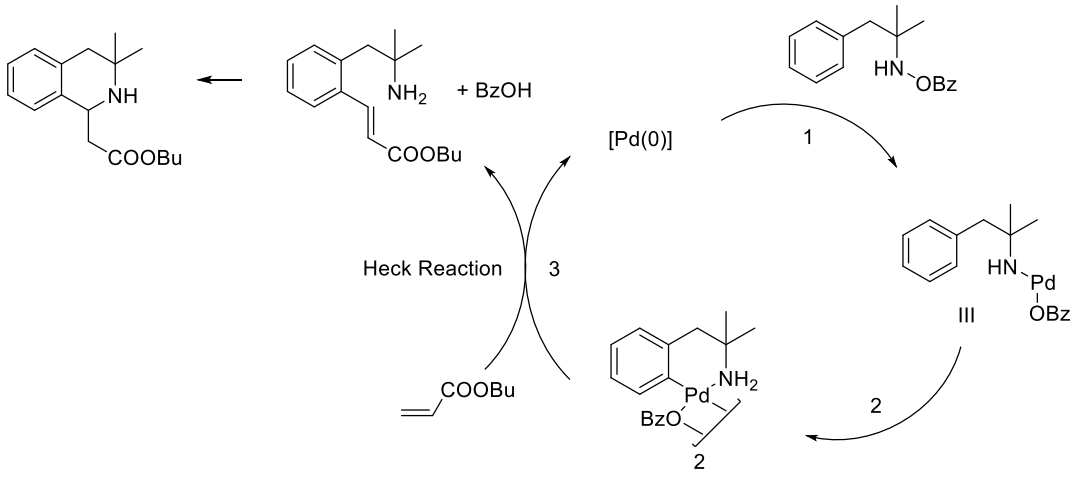
We speculated about two different mechanisms. Using Pd(II) the reaction should follow the same pathway we hypothesized with the external oxidant, but after the Heck reaction and the consequent reductive elimination, the metal is re-oxidized by the resulting functionalized *O*-acyl-hydroxylamine intermediate **II**, giving the desired unprotected THIQ and restoring the catalyst (Scheme 61).



Scheme 61.

When palladium(0) is employed the metal undergoes an oxidative insertion into the N–O bond and the resulting intermediate **III** rearranges performing the metalation of the aromatic ring. The palladium(0) that is generated after the "Heck reaction" can insert again into the N-O bond of a new molecule of substrate to start a new catalytic cycle (Scheme 62).

Discovering that better results came from the use of a palladium(0) catalyst (entries 5 and 10 of Table 7) was encouraging. The different initial coordination of the metal and the different mechanism could turn the process exploitable to substrates that were not working in the classic conditions. Thus, we started the study of the scope of this reaction using $Pd_2(dba)_3$ as a catalyst.



Scheme 62.

4.1.3. Scope of the reaction

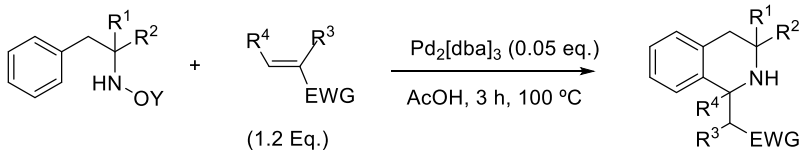
Initially, we compared the results previously observed for amines with the external oxidant and the new information acquired performing the reaction with the correspondent oxidized substrates (Table 8).

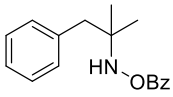
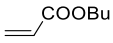
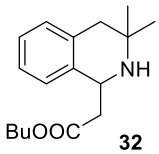
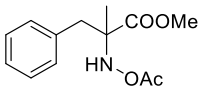
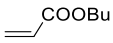
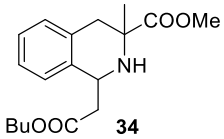
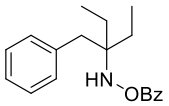
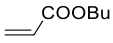
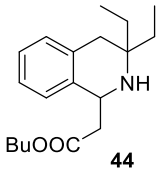
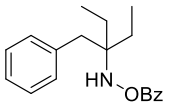
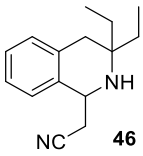
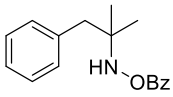
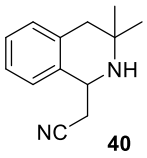
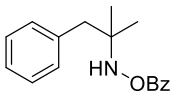
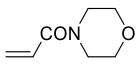
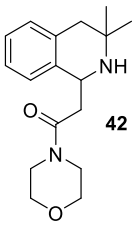
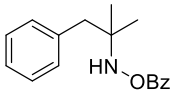
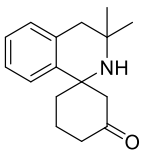
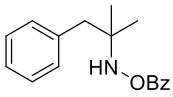
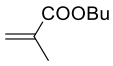
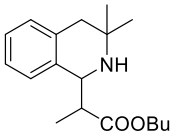
We could not synthesize the *O*-benzoyl analogue of the amino ester **16**, because, as it is known[107], amines containing electron-withdrawing groups in α lead to benzamides rather than to *O*-benzoylhydroxylamines when they are directly oxidized with benzoyl peroxide. However, we managed to synthesize the correspondent hydroxylamine and convert it into compound **62** by its acylation with acetic anhydride (as shown in Scheme 60b for compound **60**): *O*-acetyl and *O*-benzoyl hydroxylamines are supposed to show similar properties in accordance to what was observed and reported in Table 6.

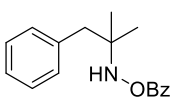
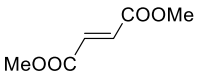
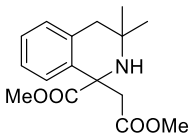
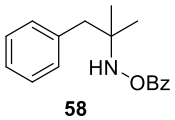
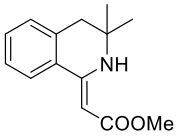
Starting from the hydroxylamine derivate **58** conflicting results were observed: the butyl acrylate, that showed excellent efficiency alkylating the free amines **1**, presented lower reactivity when it was inserted into the oxidized substrate **58** (entry 1). However, acrylonitrile and the acrylamide (entry 5, 6) that we considered fairly good electrophiles for the functionalization of free amines showed to be significantly more effective reacting with the *O*-acylhydroxylamine (the yield in the case of the THIQ **42** increase drammatically). Nonetheless, the types of electrophiles that did not react with the amine **1**, such as methacrylates, fumarates, alkynes or cyclic ketones, neither did it with the oxidized analogue **58** (entries 7 to 10).

The worst result was obtained starting from the *O*-acylhydroxylamino ester **62** since the yield of the desired product **34** decreased dramatically (entry 2). On the other hand, the sterically hindered oxidized substrate **63** showed a notable better efficiency compared to the correspondent free amine **7** and it afforded compound **44** in high yield (entry 3).

Table 8.



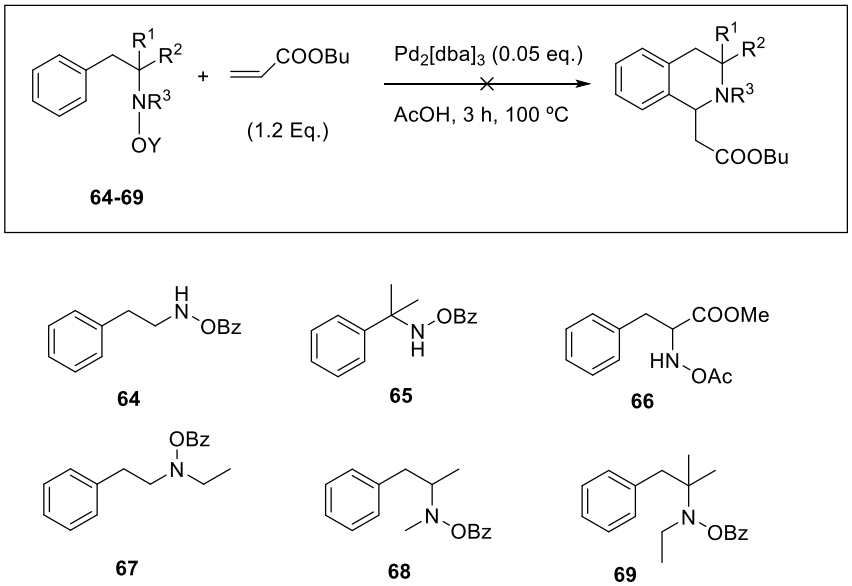
Entry[a]	Substrate	Electrophile	Product	Yield[b] (%)	Yield from amine (%)
1	 **58**		 **32**	65	90
2	 **62**		 **34**	34	78
3	 **63**		 **44**	86	62
4	 **63**		 **46**	65	43
5	 **58**		 **40**	55	42
6	 **58**		 **42**	80	42
7	 **58**			0[c]	0[c]
8	 **58**			0[c]	0[c]

9	 **58**			0	0
10	 **58**			0	0

a) reaction conditions: 0.5 mmol of O-acylhydroxylamine, 0.6 mmol of acrylate, 0.05 mmol of Pd, 3 mL of solvent in a sealed vial; b) isolated yields c) complex mixture;.

Meanwhile, these interesting data seemed to suggest a reversal of the reactivity of both substrates and electrophiles when *O*-acyl-hydroxylamines are used instead of free amines. In the previous chapter we described that the electron-withdrawing effect of the substituent seemed to improve the yield of the reactions, while the steric hindrance seemed to be a limitation in some cases: when hydroxylamines are used for the same transformation the better results were obtained from the substrate **63** that presented the most electron-donating and hindering groups in α to the nitrogen, while the worst yield was obtained starting with the oxidized amino ester **62**. Furthermore, better yields were obtained employing the electrophiles that showed worst efficiency in the original process.

At the sight of these differences we decided to prepare a series of oxidized amines derived of substrates that had previously resulted to be not useful in our process for the synthesis of isoquinolines (Scheme 63).



Scheme 63.

Oxidized derivatives of primary amines (**64-66**) and of secondary amines (**67-69**) were prepared and used as substrate in order to study the effect of modifying the center in α

to the nitrogen and the substitution of the N atom. Unfortunately, only complex mixtures were obtained starting from *O*-acyl-hydroxylamines **64-68**, while starting material was recovered running the reaction with compound **69** (as observed for the correspondent unprotected amine **15**).

Again, the presence of a quaternary center in α to the nitrogen and the un-functionalization of the N atom (the larger structural limitations observed in the reactions with the external oxidant) continue to be necessary conditions for the efficiency of the process, also with the oxidized directing group.

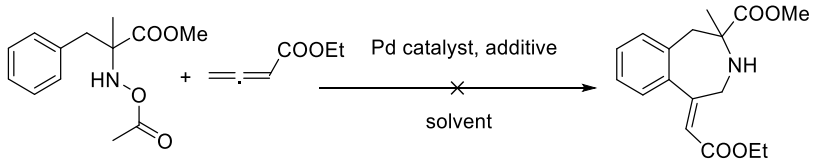
The impossibility to obtain indolines by olefination-annulation of benzylamines in our conditions was also confirmed despite the use of the *O*-acylhydroxylamine **65**.

4.1.4. Application to other processes

Finally, the application of the *O*-acylhydroxylamines to other some processes previously explored for amines in our research group was studied.

The addition of phenylethylamines to allenes for the synthesis of benzo[*d*]azepine[73] was successfully developed in the last years (see the introduction of this memory), but the reaction presented more or less the same structural limitations that we observed in the case of the alkenes.

Table 9.



62

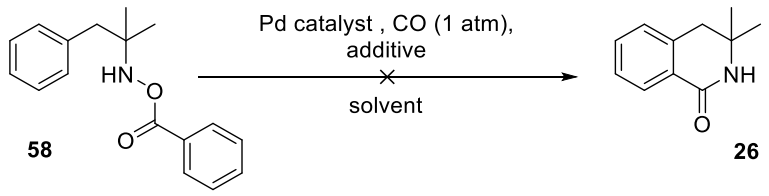
Entry[a]	Catalyst (%)	Solvent	Additive (eq.)	Conditions	Result
1	$Pd(OAc)_2$ (10)	AcOH		1 h, 80 ºC	complex mixture
2	$Pd(OAc)_2$ (10)	Toluene	TsOH (1)	1 h, 80 ºC	complex mixture
3	$Pd_2(dba)_3$ (5)	AcOH		1 h, 50 ºC	starting material
4	$Pd_2(dba)_3$ (5)	Toluene	TsOH (1)	1 h, 50 ºC	starting material
5	$Pd_2(dba)_3$ (5)	AcOH		1 h, 80 ºC	complex mixture
6	$Pd_2(dba)_3$ (5)	Toluene	TsOH (1)	1 h, 80 ºC	complex mixture

*a) Reaction conditions: 0.5 mmol of **62**, 0.6 mmol of acrylate, 3 mL of solvent in a sealed vial.*

Unfortunately, when the reaction was performed starting from compound **62** only complex mixtures or the recovery of the starting material were observed (depending on the conditions) despite the use of Pd(0) or Pd(II) catalysts (Table 9). In previous experiments the desired benzo[*d*]azepine was obtained in 50% yield from the free amine **16** using benzoquinone as oxidant.

Also the utilization of oxidized amines for the construction of functionalized benzamides by addition to CO was tested.

Table 10.



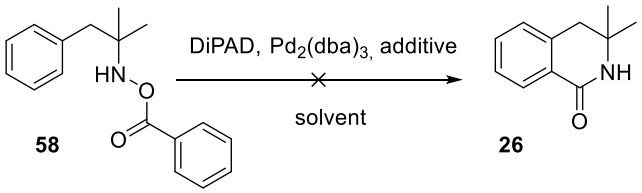
Entry[a]	Catalyst (%)	Solvent	Additive (eq.)	Conditions	Result
1	$Pd(OAc)_2$(10)	AcOH		5 h, 100 ºC	starting material
2	$Pd(OAc)_2$ (10)	AcOH		24 h, 100 ºC	complex mixture
3	$Pd_2(dba)_3$ (5)	Toluene	TsOH (1)	24 h, 25 ºC	starting material
4	$Pd_2(dba)_3$ (5)	Toluene	TsOH (1)	24 h, 80 ºC	starting material
5	$Pd_2(dba)_3$ (5)	Toluene	TsOH (1)	24 h, 100 ºC	starting material

*a) Reaction conditions: 0.5 mmol of **58**, 1 atm CO, 3 mL of solvent in a sealed vial.*

In general, no reaction was observed (Table 10). Starting material was usually recovered, except when the reaction was performed overnight in acetic acid at high temperature (entry 2): in this case the decomposition of the substrate leading to a complex mixture was observed.

Finally, *O*-acylhydroxylamine **58** was tested in the process for the carbonylation of amines with azodicarboxylates. It should be pointed out the relevance of the oxidant for the success of that process (see chapter 1 of this report). Only complex mixtures were observed in the best conditions we described in chapter 1, while starting material was recovered in milder conditions (Table 11).

Table 11.



Entry[a]	Catalyst (%)	Solvent	Additive (eq.)	Conditions	Result
1	$Pd_2(dba)_3$ (5)	AcOH		3 h, 100 ºC	complex mixture
2	$Pd_2(dba)_3$ (5)	Toluene	TsOH (1)	3 h, 100 ºC	complex mixture
3	$Pd_2(dba)_3$ (5)	neat[b]	TsOH (1)	6 h, 50 ºC	starting material

*a) Reaction conditions: 0.5 mmol of **58**, 1.0 mmol of DiPAD, 0.05 mmol of Pd, 3 mL of solvent in a sealed vial; b) 3 mmol of DiPAD were used.*

4.2. Summary and conclusions

In conclusion, a new reaction for the external-oxidant-free addition of *O*-acylhydroxylamines to Michael acceptors has been developed and optimized, using an inedited directing group. This process has shown in some cases a good efficiency. On the other hand, we have demonstrated that both palladium(II) or palladium(0) catalysts can be used. The results suggest that the reaction could proceed through two different catalytic pathways.

We tried to isolate some palladacycles generated from these substrates in collaboration with the Section of Inorganic Chemistry of the University of Barcelona: with stoichiometric quantities of palladium the only result we could observe was the de-protection of the amine. This last data seems to confirm the possibility of the insertion of the metal into the N–O bond.

On the other hand, the same reaction performed with an external oxidant showed in general better efficiency in terms of yield (with some exceptions) and scope (oxidized amino esters seemed to be poor substrates for our transformation), starting from more available substrates. Furthermore, despite the probable discovering of a new catalytic path, the structural limitations for the substrates found in the original process (with the external oxidant) were not overcome. In conclusion, the oxidized substrates do not seem to be easily useable in different reactions like the carbonylation or carboxylation of amines.

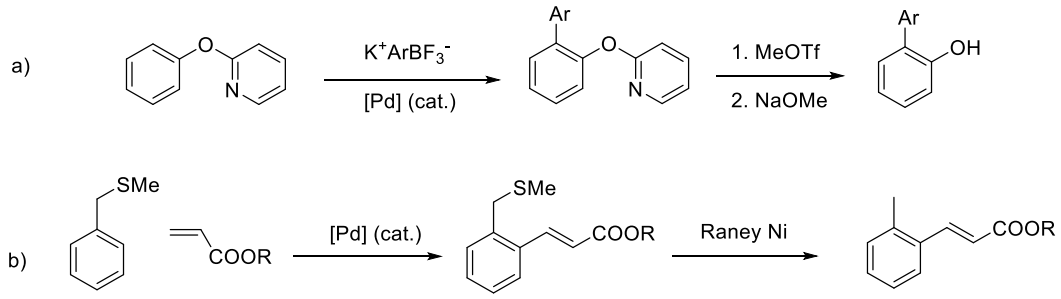
For these reasons the applicability of the notions adquired in this chapter of the thesis to the synthesis of heterocyclic compounds is limited.

5. IMINES AS ANALOGS OF AMINES: DEVELOPMENT OF A NEW PALLADIUM(II)-PALLADIUM(IV) CATALYTIC CYCLE

5.1. Removable directing groups in metal-catalyzed C–H activation

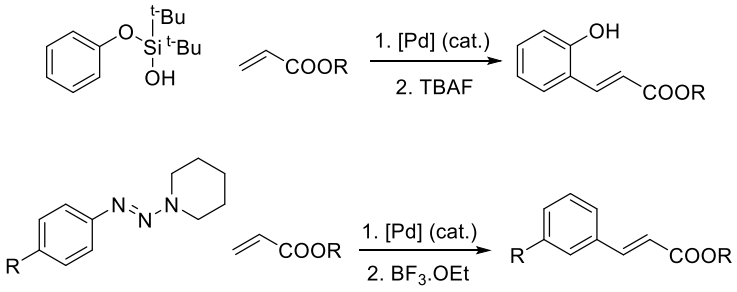
The use of directing groups in C–H activation processes is a strategy that provides precise site selectivity, but at the same time it involves the introduction of functional entities in the structure of substrates that remains in the skeleton of the products. Two different ways can be used to face this potential limitation: the introduction of directing groups capable to undergo intramolecular reactions with the newly installed functionalities (e.g. the olefination-annulation reported in the second and third chapters of this memory) or the use of easily removable directing moieties.

In the last years, many efforts have been devoted to the use of removal directing groups for C–H activation. For example, 2-phenoxypyridines can undergo the palladium-catalyzed *ortho*-arylation and then be converted into phenols by treating with MeOTf and NaOMe under reflux (Scheme 64a).[108] Thioethers have been described to be good directing groups for the olefination of arenes. At the same time, they can be converted into a methyl group at the end of the process by using Raney Nickel that selectively eliminates the sulfur without reducing the double bond (Scheme 64b).[15b]



Scheme 64.

More recently, some milder conditions to remove the directing groups have been developed: for instance, silanols[18a,97] and triazenes[52] are two classes of excellent directing groups for the oxidative Heck coupling reaction and they can be easily cleaved at room temperature by fluorine (Scheme 65). Silicon based groups and triazenes can also be converted to or replaced by other groups by simple reactions.[18a,109]



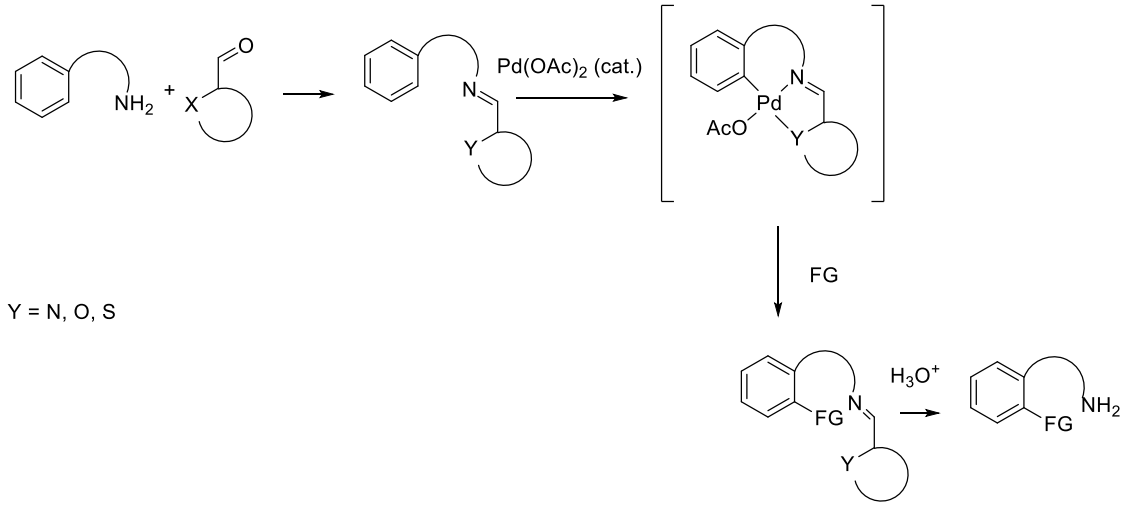
Scheme 65.

5.2. Imines as analogs of amines

In the following section of this work the utilization of imines as synthetic analogue of the amines in C–H activation processes is described.

The aim of this chapter of the thesis was the introduction of functional groups in the structure of aromatic amines that could be able to complex the palladium generating triple-coordinated palladium complexes. This class of metallacycles was expected to show better stability and consequently different reactivity in comparison to the amine-derivated complexes that have been discussed in the previous parts of the present report.

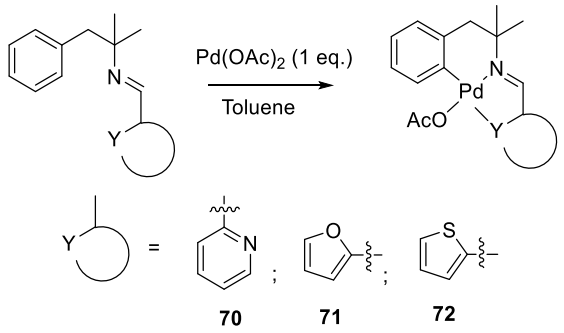
The reason for introducing complexing groups through the construction of imines is due to the possibility of an easy hydrolysis of the eventual products after the C–H activation, restoring in this way the amine (Scheme 66).



Scheme 66.

5.3. Palladacycles of imines

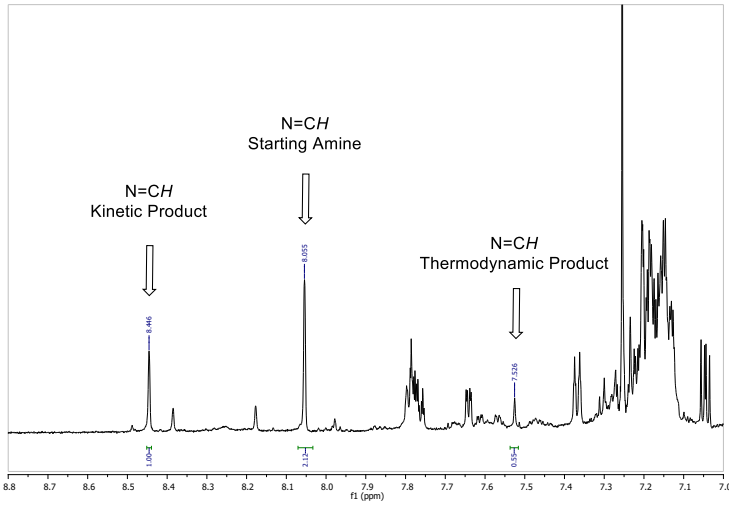
Three different models of imines containing various hetero-arenes in the structure were easily prepared by the condensation of the amine **1** with the corresponding aldehydes. With the imines in hand, preliminary reactions with stoichiometric quantities of catalyst were performed (in collaboration with the Inorganic Chemistry Section of the University of Barcelona), with the aim of isolating some triple coordinated palladacycles (Scheme 67). Although the isolation of the complexes derived from each model was not possible, we could get some interesting information from this part of the work.



Scheme 67.

Model **71** just furnished complex mixtures in the preliminary tests, while in the case of imine **72** the equilibrium between a thermodynamic product and a kinetic one was observed in the crude ^{1}H NMR spectrum. The products were detected in different proportion depending on the reaction conditions (Table 12).

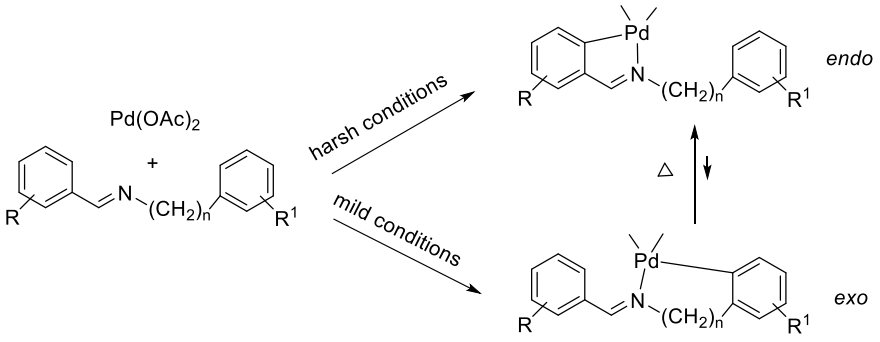
Table 12.



Entry[a]	Conditions	Ratio[b] Starting Material : Kinetic Product : Thermodynamic Product
1	02 h, 60º C	100 : **0** : 0
2	24 h, 60º C	12 : **8** : 80
3	24 h, 40º C	56 : **28** : 14
4	96 h, 40º C	6 : **0 :** 94
5	24 h, 25º C	56 : **44** : 0
6	96 h, 25º C	17 : **83** : 0

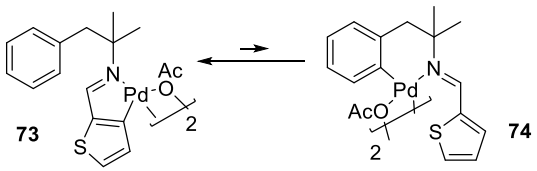
a) Reaction conditions: 0.5 mmol of imine, 0.5 mmol of $Pd(OAc)_2$, toluene (30 mL); b) determined by ^{1}H NMR of the crude.

Previous works of Prof. Jaume Granell and Joan Albert, from the Section of Inorganic Chemistry of our Department described the formation of two kinds of products through the interaction of aromatic imines with palladium acetate.[110]



Scheme 68.

In harsh conditions, only the formation of the *endo*-type complexes (in which the C=N bond is part of the palladacycle) is allowed while in milder conditions it is possible to isolate *exo*-type metallacycles (in which the C=N bond is not included in the cycle). They also demonstrated that *exo*-cycles are transformed into *endo*-complexes at high temperatures (Scheme 68).[110b] In our case, the *endo* and the *exo* metallacycles could be represented by structures **73** and **74** (Scheme 69), the thermodynamic product and the kinetic one, respectively.



Scheme 69.

We were not able to isolate pure complex **73**, but the ^{1}H NMR spectra of the reaction mixtures gave us some information that confirmed our theory: the methine proton appears right shifted compared to the starting free imine (typical of endo complexes)[110a] and a doublet with the coupling constant of the thiophene double bond (J = 5 Hz) appears significantly low shifted, consistent with a close interaction with a carbon-palladium bond (Figure 5).

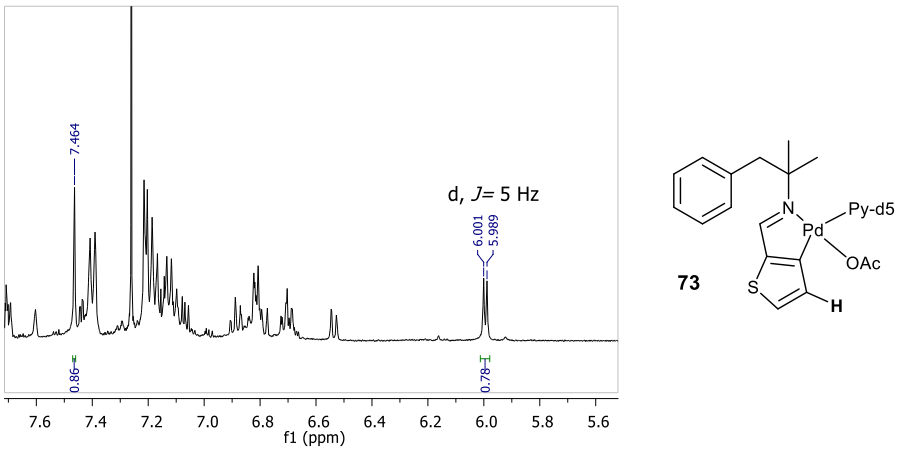


Figure 5.

Furthermore, we achieved the isolation of the kinetic complex **74** by precipitation from a crude mixture (experiment 6 of Table 12). The compound was not pure enough to perform a full characterization, but some conclusions could be drawn from the ^{1}H NMR analysis.

We could appreciate that the structure of the kinetic complex kept the three C–H bonds of the thiophene, while one aromatic C–H of the starting imine disappeared. Furthermore, the signals corresponding to the protons of the phenyl appeared low-shifted with respect to the starting material (suggesting the H atoms next to a carbon palladium bond) and the methinic proton is shifted downfield compared to the starting imine (as it is described for *exo* complexes)[110a]. Moreover, the hydrogen atoms in the benzylic position became diastereotopics as if they were embedded in an asymmetric ring (Figure 6).

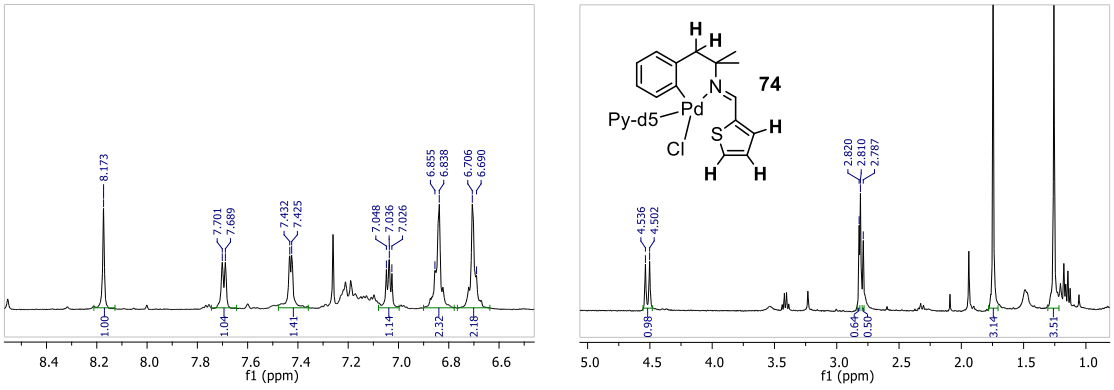
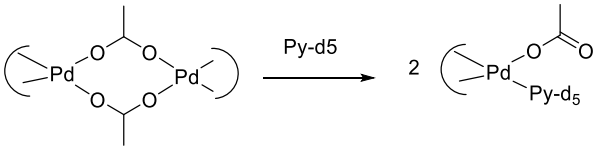


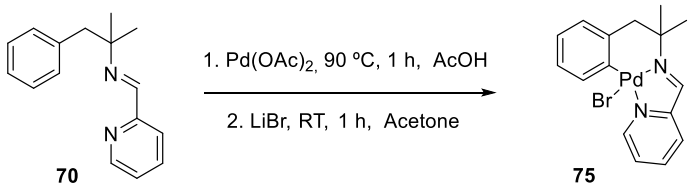
Figure 6.

Although we could not complete the characterization of complexes **73** and **74** it seemed clear from their ^{1}H NMR spectra that a triple coordinated complex was not obtained. The equilibrium between the two species demonstrates that in those complexes the *S* atom did not stabilize the *exo* specie, as we expected, by coordination of the metal. Furthermore, the addiction of deuterated pyridine clarified NMR spectra and it is a further evidence that we were facing some dimeric compounds. The pyridine coordinates the palladium atom breaking the acetate bridges of bidentate complexes (Scheme 70).



Scheme 70.

Conversely, it was possible to isolate and characterize the expected three-coordinated complex derived from the imine **70** (Scheme 71). The metallated imine **75** showed also good stability as it was obtained as unique product in the reaction conditions and it could be isolated almost without purifications.

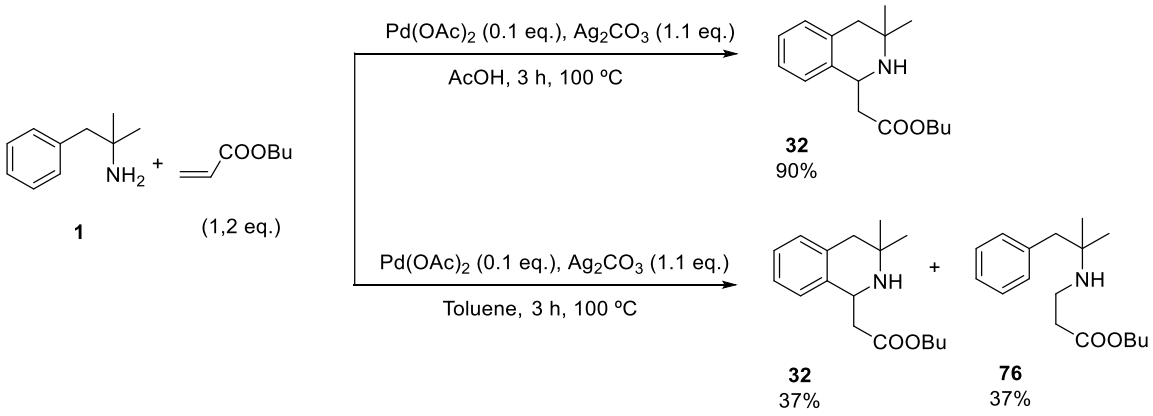


Scheme 71.

These preliminary results were really interesting, even though we were not able to characterize all the species observed in the first experiments. Thus, we assumed that oxygen and sulfur do no have the necessary coordinating power to enable the formation of three coordinated complexes with palladium. Conversely the nitrogen of the pyridine can stabilize the *exo* product, preventing the formation of the endo metallacycle or other species. This hypothesis was confirmed by the application of models **70**-**72** in different palladium-catalyzed reactions, as it will be reported in the next sections of this chapter.

5.4. Alkenylation of imines

The palladium-catalyzed olefination of models **70**-**72** was tested in parallel to the stoichiometric reactions for the isolation of palladacycles.



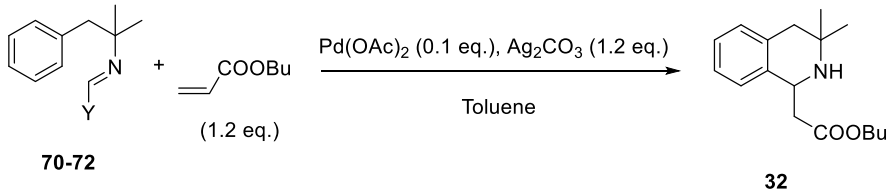
Scheme 72.

We reported above that amine **1** can be easily added to electron-deficient alkenes in acetic acid leading to heterocyclic compounds in good yields. The solvent was critical for the efficiency of the process since lower yield and formation of byproducts were observed in other reaction media. When the reaction is performed in toluene the desired product is obtained in moderate yield accompanied by the compound **76**, derived from the intermolecular conjugated addition of the amine to the acrylate, in a roughly 1:1 ratio (Scheme 72).

We studied the addition of imines **70**-**72** to Michael acceptors in toluene to assess whether the better stability of the derived complexes could allow us the use of diverse solvents and to prevent the partial hydrolysis of the imine that could arise from an acidic medium. After a rapid screening (Table 13) we could appreciate several differences between the reactivity of amine **1** and imines **70**-**72** in our reaction conditions.

The pyridine-derivative model **70** did not show any reactivity in this process: the totality of the unreacted starting material was recovered at the end of the reaction. The total conversion of the thiophene derived imine **72** into the desired product **32** was observed in low yield (entry 2). The furan-derived **71** furnished the desired product in higher yields but, in any conditions, the total consumption of the starting imine was observed. The formation of the un-cycled product **76** was never detected independently of the substrate and the reaction conditions.

Table 13.



70-72 **32**

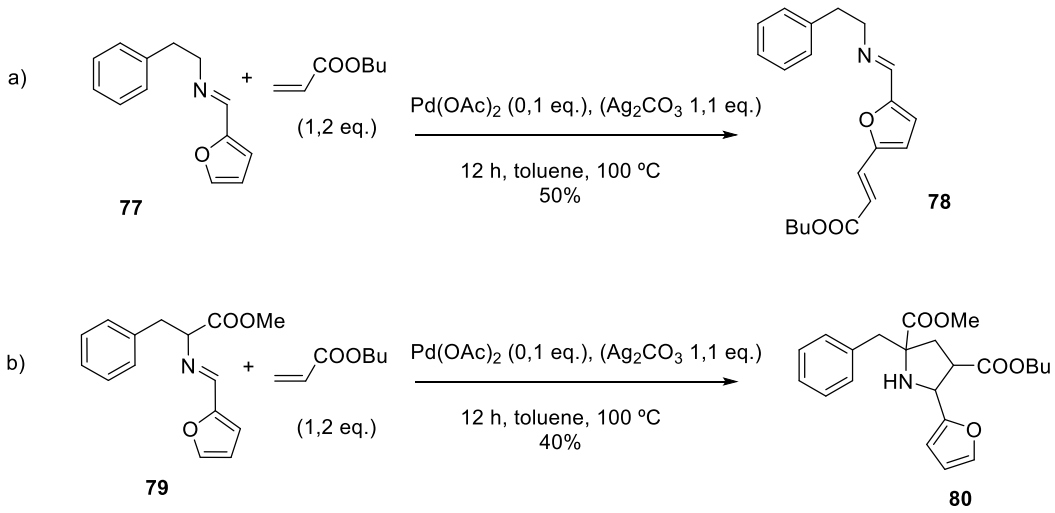
Entry[a]	Imine	Yield (%)[d]	Recovered starting imine (%)
1	**70**	0	100
2	**72**	22	78
3	**71**	50	17
4[b]	**71**	27	41
5[c]	**71**	35	17

a) Reaction conditions: 0.5 mmol of imine, 3 mL of Toluene, 100 ºC, 16 h in a sealed vial; b) 100 º C, 3 h; c) 100 ºC, 72 h; d) isolated yields.

We could conclude that imines showed lower reactivity compared to the corresponding amine in this catalytic reaction. Thus, we prepared some new imines as models starting from amines that led to complex mixtures when applied in this process.

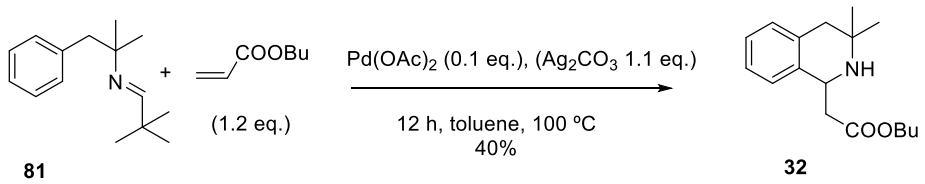
In particular, we had concluded that amines without a quaternary center in α to the nitrogen only afford to complex mixtures in this process since their nitrogens are too reactive. Our expectation was the possibility of obtaining different results transforming this kind of amine into imine.

Unfortunately, the attempts were unsuccessful: the only products we could isolate derived from side reactions. When the imine was not α-substituted (e.g. imine **77**), the alkylation of the heterocycle was observed (Scheme 73a). The imine **79**, containing an acidic proton in the vicinal position to the nitrogen, affords a new product due to the cycloaddition of the imine to the acrylate (Scheme 73b).



Scheme 73.

At the sight of these results we were interested in verifying whether the different behavior observed for the imines **71-72** (compared to the free amine **1**) was due to the formation of different palladacycles intermediates or simply to the lower reactivity of the protected nitrogen. Thus, imine **81** was prepared by condensation of the amine **1** with pivalaldehyde with the aim of introducing a group that cannot coordinate the palladium in the structure of the substrate.



Scheme 74.

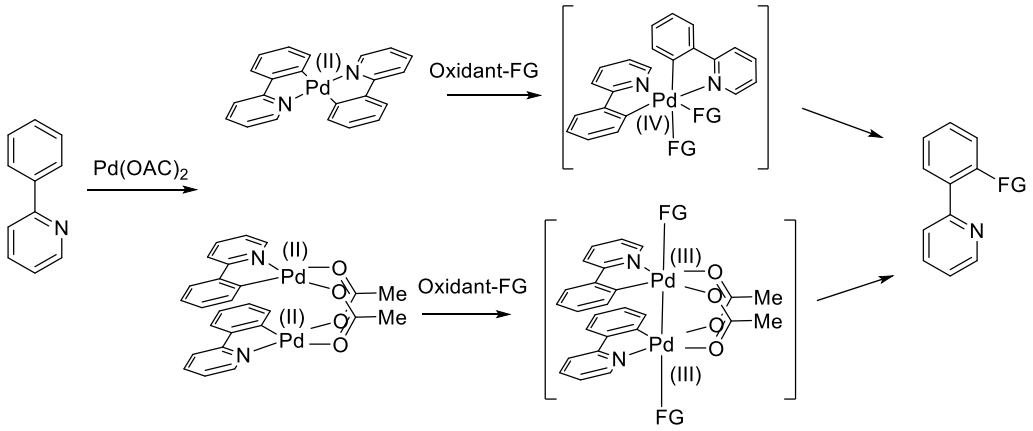
The formation of byproducts was not detected neither performing the catalytic alkylation starting from this last substrate: we could only observe the presence of the desired product in moderate yields in the reaction mixture (Scheme 74). In this case the starting material was not recovered due to the unstability of the aliphatic imine.

Thus, the evidences provided by both stoichiometric and catalytic experiments showed that stable palladacycles, involving the participation of the heteroatom, are not produced by the interaction of models **71-72** with the transition metal. Thus, the introduction of a furan or thiophene group in the structure of aromatic primary amines did not afford the desired reaction with olefins, or alternatively the development of new reactions. Furthermore, in addition to the lack of advantages, this kind of functionalization opens the way to secondary reactions over the C=N bond and the heterocyclic rings.

In sharp contrast, compound **70** appeared totally unreactive in the reaction conditions we utilized, confirming its attitude to form a more stable palladacycle. Hence, we focused on the application of this substrate to palladium-catalyzed processes where strongly coordinated complexes are required, as it will be reported in the next sections.

5.5. High-valent palladium-catalyzed processes

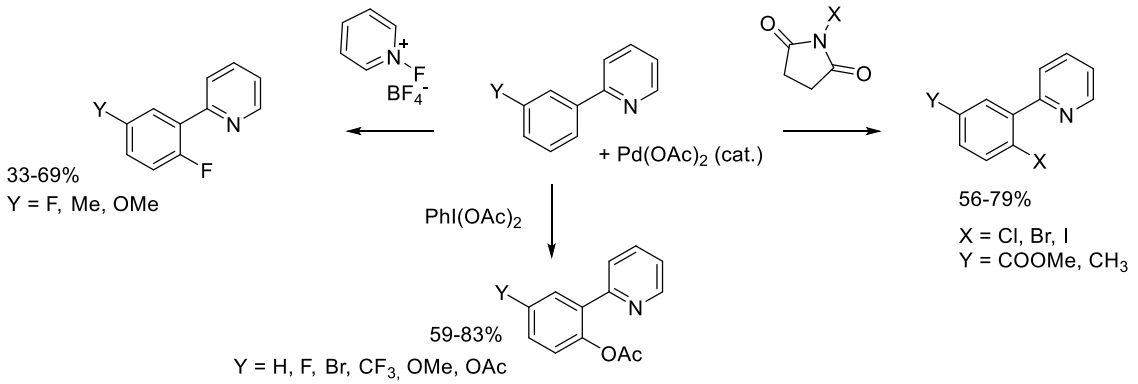
Pd(II) complexes with high stability can react with strong oxidants to lead to octahedral high-valent intermediates. In particular, pyridine derivatives have been abundantly studied and described in this kind of processes[111].



Scheme 75.

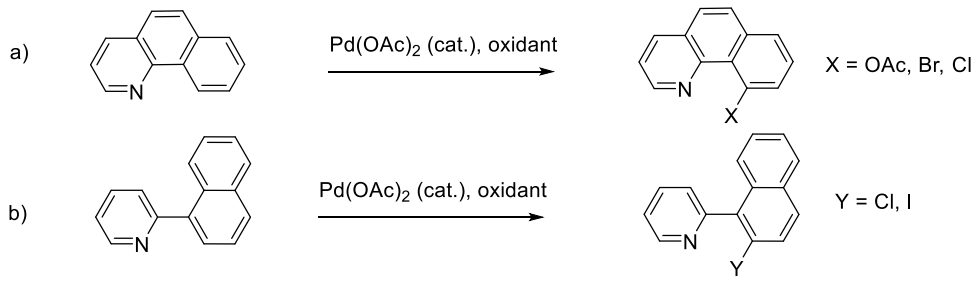
For example, 2-phenylpyridine derivatives coordinate palladium acetate giving monometallic or bimetallic complexes which can be respectively oxidized to trivalent or tetravalent palladium intermediates. This species both lead to reductive elimination of Palladium (II) and consequent functionalization of the aromatic C–H bond (Scheme 75).[112]

Different authors took advantage of these properties to get selectively oxidation in the *ortho* position of various 2-phenylpyridine derivatives.



Scheme 76.

In this way, selective acetoxylation using diacetoxy iodobenzene[23,111a], carbon-halogen bond formation performed with *N*-halosuccinimides[113,114], and fluorination with *N*-fluoropyridinium tetrafluoroborate[115] have been reported in different works (Scheme 76). Other pyridine derivatives have been also used in similar reactions[111a,113] (Scheme 77).



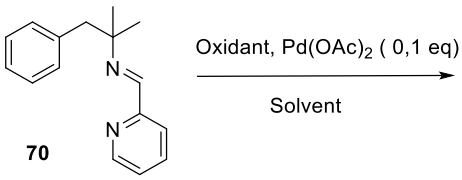
Scheme 77.

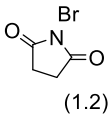
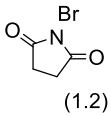
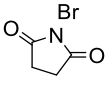
Based on these precedents, we though that our imine **70** could be a suitable substrate for this kind of reactions. We undertook some preliminary experiments with different oxidants in similar conditions to those described in the literature for the use of pyridine as directing group (Table 14). [114,116-118]

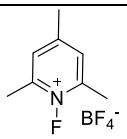
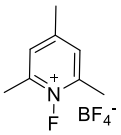
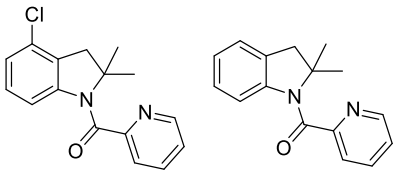
In the case of NBS[114,116] and trimethylfluoropyridinium tetrafluoroborate[117] only complex mixtures were obtained following the described methodologies, while products **82** and **83** were isolated in low yield instead of the expected acetoxylated product using $PhI(OAc)_2$ as unique oxidant.

Characterization of compounds **82** and **83** was not trivial, since the aromatic proton in *ortho* to the amide appears in the ^1H NMR spectra as a low-shifted wide peak. Furthermore, cross-peak signals are not visible in two-dimensional magnetic resonance experiments (COSY, HSQC) for this proton.

Table 14.



Entry	Oxidant (Equivalents)	Products (Yields, %)
1[a]	 (1.2)	Complex mixture
2[b]	 (1.2)	Complex mixture
3[c]	 + $PhI(OAc)_2$ (2) (1.5)	Complex mixture

4[d]	 (2)	Complex mixture
5[e]	 (2)	Complex mixture
6[f]	$PhI(OAc)_2$ (1.2)	 **82** 9% **83** 26%

*Reaction conditions: a) 0.5 mmol of **70**, CH_3CN, 100 ºC, 12 h; b) CH_3CN, 100 ºC, 3 h; c) DCE, 60 ºC, 3 h; d) 1.25 eq. of DMF, DCE 120 ºC, 24 h; e) 1.25 eq. DMF, DCE 120 ºC, 2 h; f) DCE, 90º C, 12 h.*

So, to confirm the structure of our new products, an X-ray crystallographic analysis was performed in collaboration with Dr. L. Barrios of the Section of Inorganic Chemistry of our Department. Unfortunately, we only could obtain amorphous solids from products **82** and **83**, but we could achieve an X-ray spectrum from crystals made from few milligrams of compound **84**, a byproduct we isolated in traces from the reaction mixture (Figure 7).

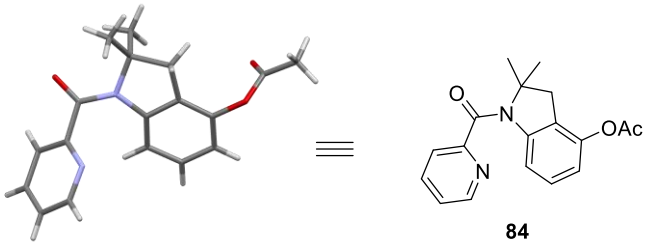
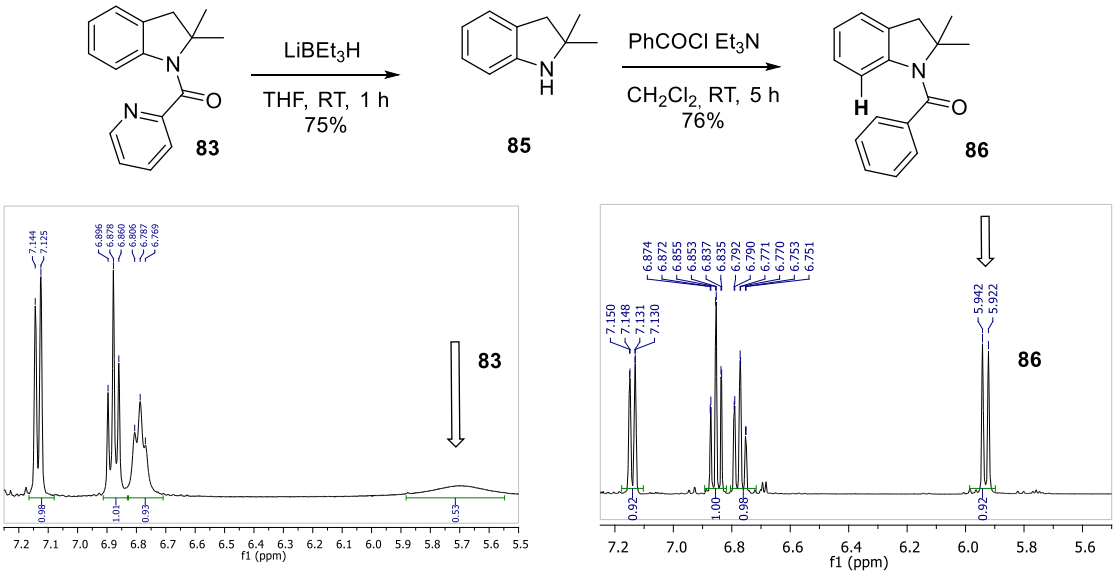


Figure 7.

We also prepared a derivative of compound **83**, substituting the pyridine ring with benzene, in order to assign all the NMR peaks. The signal of the aromatic proton in *ortho* to the nitrogen in the derivate **86** remaines low-shifted, but his multiplicity is well defined. This demonstrates that the low shift of the signal was just due to the anisotropic effect of the aromatic ring of the pyridine, but the low definition was a specific consequence to the electronic effect of the lone pair of the nitrogen on the region of the *ortho* position of the phenyl ring (Scheme 78).

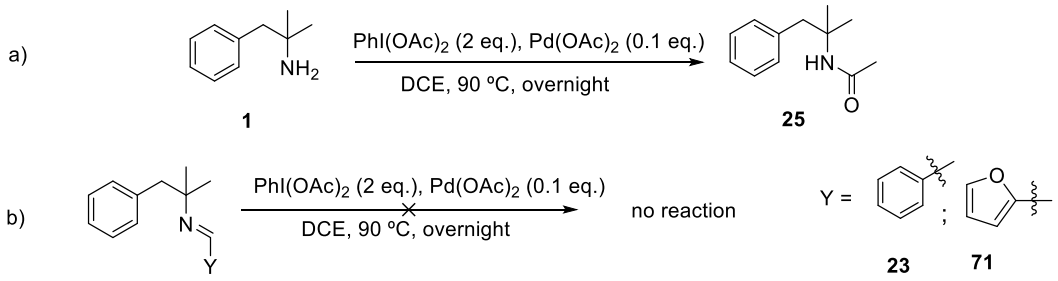


Scheme 78.

5.5.1. Study of a new C–H activation process

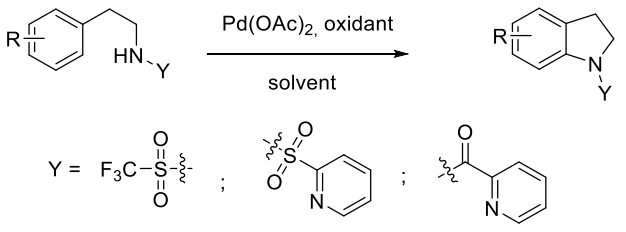
Once we determined the structure of the products, we investigated their formation.

Initially, we verified that the same compounds could not be obtained in the same way from amine or other types of aromatic imines. As we expected, different substrates showed different behavior in the same reaction conditions. Only the corresponding acetamide **25** was observed starting from amine **1**, while no reaction was detected starting from aromatic imines **23** and **71** (Scheme 79).



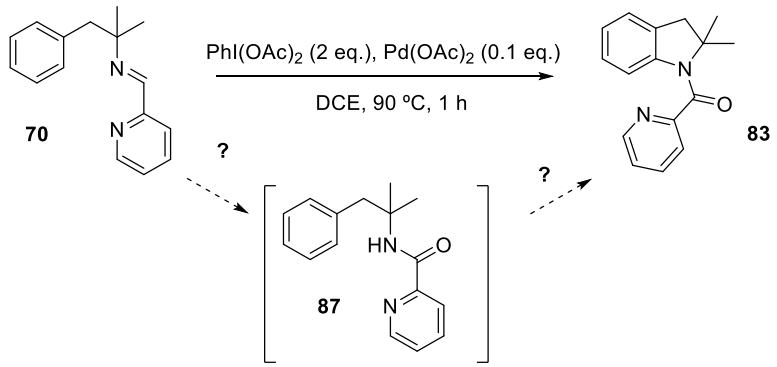
Scheme 79.

The palladium-catalyzed intramolecular amination of aromatic compounds is a topic that has been taking the attention of the researchers for the last five years. The application of this methodology leading to precursors of indolines (like compounds **82** and **83**) has been described in several works, but almost all of them employed amides as substrate (Scheme 80). Thus in 2009 Yu described the direct synthesis of indoline derivatives from triflamide-protected phenylethylamines[117]. Later the same group used the preparation of sulfonamides to introduce a pyridine as removal directing group to perform the same kind of cyclization[119], while in 2012 Nadres and co-workers described the use of picolinamides to perform the intramolecular amidation[120].



Scheme 80.

Similar works reported the introduction of different removable coordinating groups, but always by the formation of an amidic bond, while there are not relating works describing the palladium-catalyzed intramolecular amination starting from imines. For this reason, it was important for us to discover whether it was just the oxidation of the imine to the correspondent picolinamide followed by the transformation described by Nadres group (Scheme 81), or we were facing a new kind of process. Hence, the reaction was studied in order to try to understand the mechanism followed by the process and also to justify the formation of compound **82**.



Scheme 81.

First of all, the process was optimized and the effects of several different conditions were studied (Table 15). Initially, we noticed that two equivalents of oxidant were necessary to complete the process. Starting material was recovered after 24 hours at 90 ºC adding one equivalent of oxidant, while it disappeared after 30 minutes using two equivalents of $PhI(OAc)_2$ (entries 2, 9).

In absence of palladium or oxidant we did not observe any reaction and the starting material was recovered (entry 7 and 8). Furthermore, the process resulted significantly slower when a 5% molar of catalyst was employed instead of 10% (entry 6).

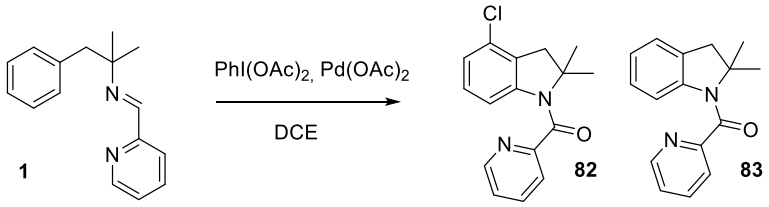
The best global yield (77%, entry 4) was accomplished at 90 ºC for 1 h. The process was significantly slower when the temperature was reduced to 60 ºC (almost half of the starting material was detected after one hour, entry 10) while the products started to decompose after one hour at 90 ºC and the reaction mixture became more complex (entry 3).

We could even observe that the starting material has been entirely consumed after 30 minutes of reaction at 90 ºC, but the products were not completely formed yet (entry 9).

This means that some intermediates were formed, but we were not able to isolate them. We did not have any evidence that amide **87** was an intermediate in the reaction, since we never isolated it from our reaction mixtures and we never observed it in crude NMR spectra.

Afterwards we studied the effect of different solvents trying to further optimize the process and to demonstrate the origin of the chlorine atom of the product **82** from dichloroethane, the only sensible source of chlorine in the reaction (Table 16).

Table 15.

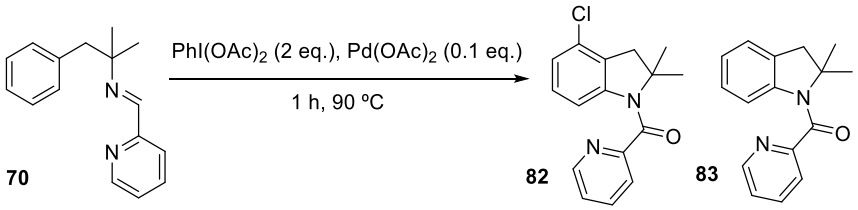


Entry[a]	Temperature (º C)	Time (h)	82 (Yield, %)[g]	83 (Yield, %)[g]	Recovered starting material (%)
1	25	24	0	0	100
2[b]	90	24	9	26	15
3	90	3	7	37	0
4	90	1	16	61	0
5[c]	90	1	8	66	0
6[d]	90	1	12	40	21
7[e]	90	1	0	0	100
8[f]	90	1	0	0	100
9	90	0,5	10	40	0
10	60	1	Traces	27	40
11	60	24	8	60	0

*a) Reaction conditions: 0.5 mmol of **70**; 0.05 mmol of $Pd(OAc)_2$; 1 mmol of $PhI(OAc)_2$; b) 0.5 mmol of $PhI(OAc)_2$; c) 1.5 mmol of $PhI(OAc)_2$; d) 0,025 mmol of $Pd(OAc)_2$; e) absence of $PhI(OAc)_2$; f) absence of $Pd(OAc)_2$; g)isolated yields.*

As expected, the formation of the chlorinated compound **82** only was observed in dichloroethane. We could even appreciate that this solvent was the best for our porpouse, since other suitable ones (for reactions at 90 ºC) gave lower yields.

Table 16.



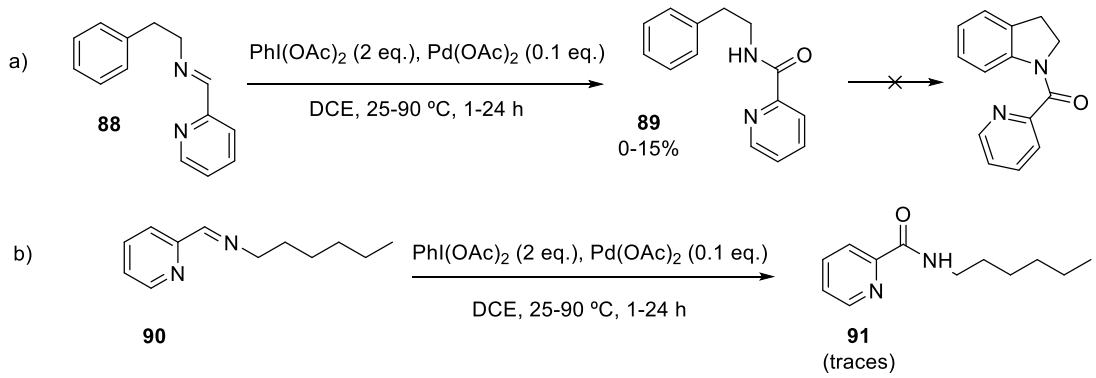
Entry	Solvent	82 (Yield, %)[a]	83 (Yield, %)[a]
1	AcOH	0	20
2	CH_3CN	0	40
3	Toluene	0	50
4	$ClCH_2CH_2Cl$	16	61

a) Isolated yield.

In order to definitively demonstrate that our process did not proceed from the oxidation of the imine **70** to amide **87** and its consequent cyclization, we prepared the models **88** and **90** (Scheme 82).

Compound **88** is the imine corresponding to the amide described by Nadres *et al.* (Scheme 80). If we were performing the same process, we would have obtained the same product in our reaction conditions. However, we only obtained complex mixtures from this substrate at 90 ºC, while starting material with small quantities of un-cyclized amide **89** was observed operating at milder conditions (Scheme 82a).

Imine **90** cannot cyclize and therefore the corresponding amide **91** would be possible to isolate if it was an intermediate. In this way, we could find out whether the observed oxidation was, in fact, a general oxidation of an imine to an amide performed by a strong oxidant in presence of a Lewis acid (palladium, in our case) or something more complicated that involves the formation of a specific metallated intermediate. As expected, the compound **91** only was observed in traces and almost the totality of the reaction crude was composed by a complex mixture, in our reaction conditions (Scheme 82b). We have reported before that neither aromatic imines **23** and **71** led to amides (Scheme 79b) operating in the same way.



Scheme 82.

We would have liked to know whether the oxidation of the imine is a necessary condition for the intramolecular amination or it simply is a side reaction. Unfortunately, we could not synthesize imine **92** because of the high steric hindrance of both the precursors. It would have been a good model because it is the secondary ketimine corresponding to our substrate **70** and it cannot be oxidized. We managed to make and test compound **93**. It only furnished complex mixtures in the oxidation process, but it was not an interesting information because of the difference in the α-position between this structure and model **70** (Figure 8).

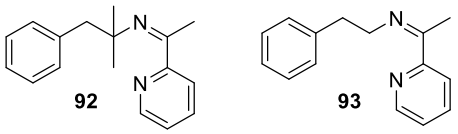
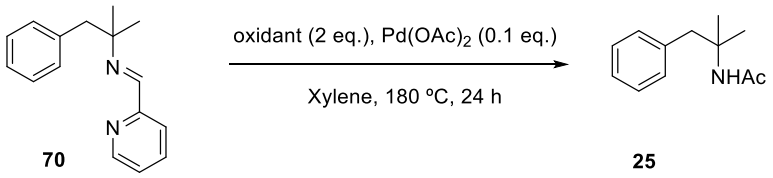


Figure 8.

Finally, to demonstrate that our cyclization involves a high valent palladium process, we tried to perform the reaction using metallic oxidants that cannot oxidize palladium (II) to palladium (IV). In that case, only the decomposition of the imine and the consequently oxidation of the resulting amine to acetamide **25** was observed at high temperature (Table 17).

Table 17.



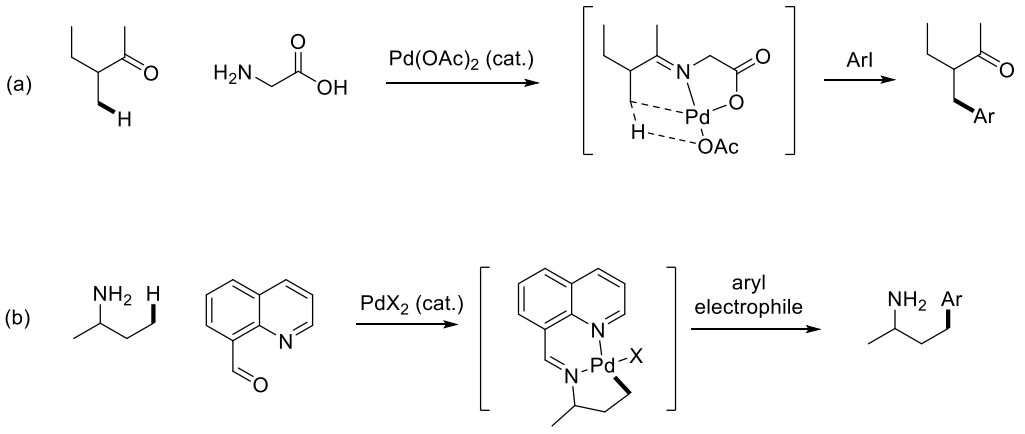
Entry	Oxidant	Yield (%)
1	$Cu(OAc)_2.H_2O$	100
2[a]	$Cu(OAc)_2.H_2O$	100
3[b]	AgOAc	33

a) No $Pd(OAc)_2$ added; b) 67% of starting material was recovered.

Oxone was also tested as oxidant, but it only furnished complex mixtures and the expected product **83** was never observed in any case.

5.5.2. Synthesis of *N*-acylated indolines by C–H activation of free amines

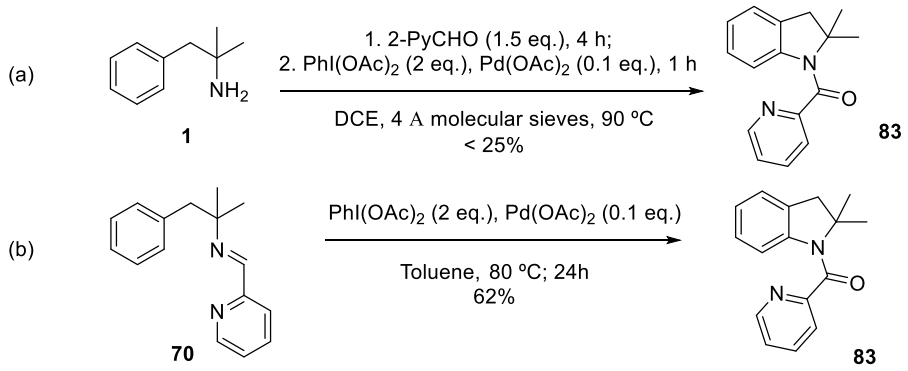
We had just developed the intramolecular palladium-catalyzed amination for the construction of an indoline precursor starting by an imine that was not described before, and demonstrated the novelty of the process. At that point we set out to optimize the synthesis of indolines precursors starting from primary amines, via the preparation *in situ* of imines.



Scheme 83.

The *in situ* formation of imines to promote the metal catalyzed C–H activation is a "hot topic" since important papers have come out very recently about this issue: the sp^3 C–H bond functionalization of aldehyde and ketones via the provisional introduction of a glycine as directing group has been reported by Yu's group (Scheme 83a),[121] while Dong and co-workers described the palladium-catalyzed sp^3 arylation of primary amines via *in situ* formation of imines (Scheme 83b).[122]

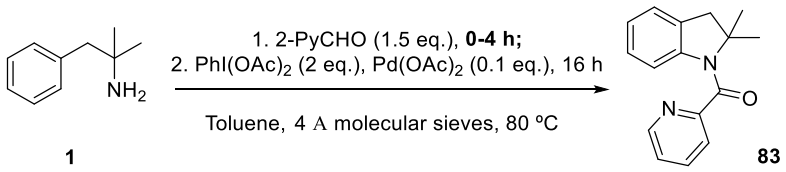
Our first attempt, under the best condition found for the pre-formed imine **70**, was not successful (only 25% yield, Scheme 84a). However, we could appreciate that the direct transformation of amines in the cyclized products was possible. Since we recovered a significant quantity of unreacted 2-pyridine carboxaldehyde (2-PyCHO), we considered that we should change the solvent, since dichloroethane is not a very useful medium for the formation of imines. So, we decided to optimize our methodology in toluene which is usually a good solvent for condensations.



Scheme 84.

We performed the cyclization in toluene starting from imine **70** in the best conditions described by Nadres *et al.* for picolinamides[120], and we achieved the same yield we had obtained in DCE at 90 ºC (Scheme 84b). Hence, we launched an optimization process from these parameters.

Table 18.



Entry	Condensation time (hours)	Yield (%)
1	0	35
2	1	40
3	4	54
4[a]	4	30
5[b]	1	55
6[b,c]	1	51

a) Anhydrous $CuSO_4$ was used instead of molecular sieves; b) $Pd(OAc)_2$ was added in step 1; c) 1 eq. of 2-PyCHO.

In the best conditions (Table 18, entries 3 or 5) we managed to obtain the indoline ring directly starting from amine **1** in 55% yield, not much lower than the yield achieved starting from the pre-formed imine **70**.

It became clear that the reaction cannot be performed by adding all the reagents at the same time: in the case of the entries 1 and 2 lower yields were observed and more aldehyde than the molar excess we added was recovered, which means that the imine had not completed its formation. In the case of the entries 5 and 6, it is interesting to indicate that the palladium catalyzed the formation of the imine at the beginning of the reaction, and later the oxidative cyclization.

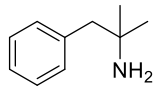
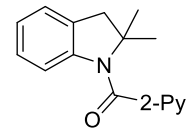
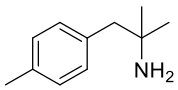
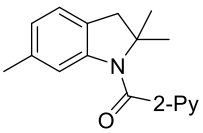
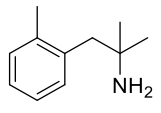
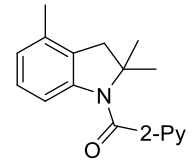
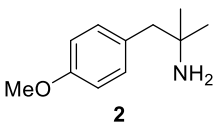
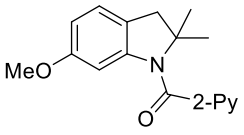
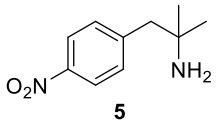
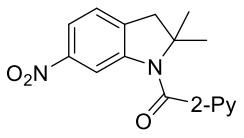
We tried to add anhydrous copper sulfate (entry 4) instead of 4 Å molecular sieves, since it should have trapped the water and catalyzed the formation of the imine at the same time, but the yield was significantly lower in this case.

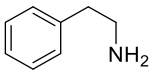
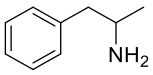
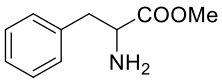
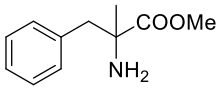
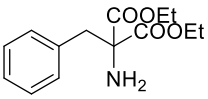
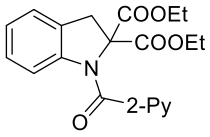
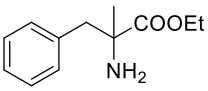
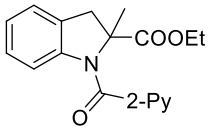
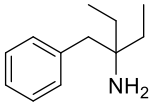
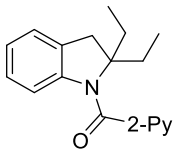
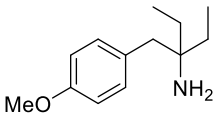
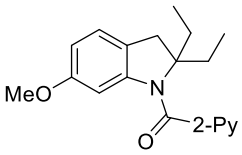
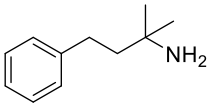
With the optimized process, we tried to synthesize various indoline precursors starting from different amines.

From the results reported in the Table 19 we knew that a quaternary center in α to the nitrogen is again a necessary condition for the formation of products: in the case of entries 6, 7, 8 only complex mixtures were obtained.

The comparison between entries 1 or 4 and the entries 12 or 13 shows that the steric hindrance nearby the nitrogen decreases the efficiency of the process. In contrast the presence of electron-withdrawing groups in α to the amine improves the yield of the reaction, despite the increase of the steric hindrance around the nitrogen (entries 10, 11). At the beginning the amino ester **16** was tested as substrate, but a complex mixture was obtained (entry 9). Thus, the methyl ester was changed to the more stable ethyl ester **19** and the compatibility of the process with this kind of molecules was demonstrated.

Table 19.

Entry[a]	Amine	Product	Yield (%)[b]
1	 **1**	 **83**	54
2	 **3**	 **94**	49
3	 **4**	 **95**	64
4	 **2**	 **96**	52
5	 **5**	 **97**	30

6		None	0
7		None	0
8		None	0
9	 **16**	None	0
10	 **18**	 **98**	57
11	 **19**	 **99**	59
12	 **7**	 **100**	27
13	 **8**	 **101**	27
14	 **6**	None	0

a) Reaction conditions: 1) 0.5 mmol of amine, 0.75 mmol of 2-PyCHO, 4 Å molecular sieves, toluene (3 mL), 80 ºC, 4 h; 2) 0.05 mmol of $Pd(OAc)_2$, 1 mmol of $PhI(OAc)_2$, 80 ºC, 12 h; b) isolated yields.

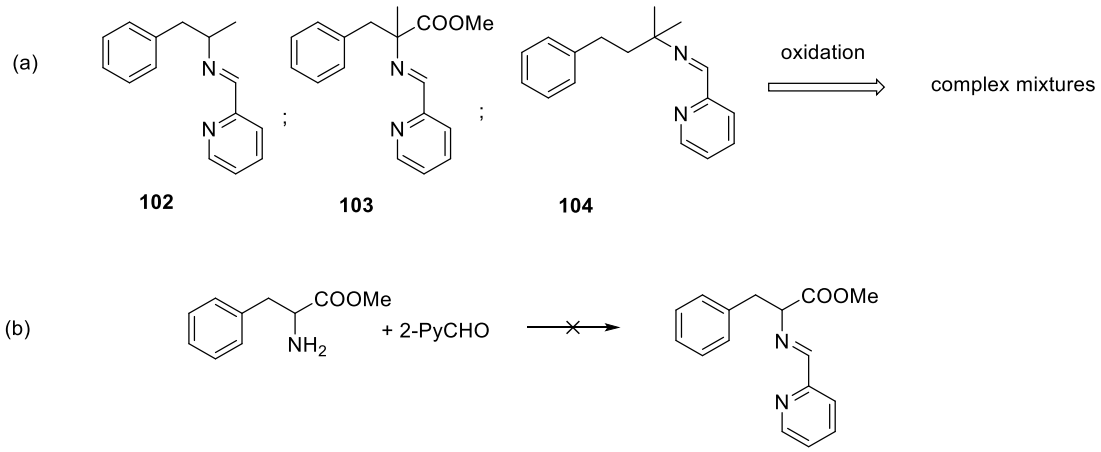
About the effect of the substitution of the arene, it was possible to observe that the introduction of a nitro group in the *para* position of the aromatic ring dramatically decrease the efficacy of the reaction (entry 5): in the case of the amine **5** a considerable amount of an unknown by-product appeared in the ^{1}H NMR of the crude, but we were

not able to isolate and to characterize it: chromatographic purification methods seems to be not applicable to this product probably because it is not stable.

Inductive electron-donors in the *para* position slightly decrease the yield of formation of the desired product (entry 2), while the presence of a methoxide did not affect the efficiency of the reaction (entry 4, 13).

Amine **4** gave the better yield (entry 3). This was predictable since in this structure one of the *ortho* positions of the aromatic ring is blocked and this prevents the formation of various possible byproducts such as the acetoxylated indoline **84** or the bis-acetoxylated opened compound.

Finally, we could not construct an isoquinoline-type structure with this methodology starting from amine **6** as it only afforded complex mixtures (entry 14).



Scheme 85.

Imines **102-104**, corresponding to amines **7, 9** and **13** were synthesized in order to repeat the catalyzed oxidation starting from already formed imines (Scheme 85a). Better results were not observed operating in this way, so we demonstrated that we were facing some structural limitations of the methodology and not problems due to the *in situ* formation of imines. On the contrary, we could not easily prepare the imine derived from the methyl phenylalaninate, probably because of the presence of an acidic proton in the structure of the amino ester that complicates the reaction leading to various products (Scheme 85b).

5.6. Summary and conclusions

In this part of the work we developed and optimized an innovative one-pot process to access to various indoline precursors directly starting from primary imines, via a new high-valent palladium-catalyzed cycle that had never been described before.

Unluckily the yields of the reactions are only moderate and the scope of the process is restricted by various structural limitations. Nevertheless, the whole process is

interesting from a mechanistic point of view. We must also conclude that the oxidation of the imines to amides observed in this new process contradicts our original aim of introducing easily removable directing groups since the conditions for the hydrolysis of amides are significantly hasher compared to imines.

However, interesting results have been achieved from the structural and mechanistic point of view. The collaboration with the Section of Inorganic Chemistry of the University of Barcelona is still ongoing for kinetic studies on the isolated three-coordinated complex **75**. Reactivity tests on this complex will be performed to explore the application in other processes. Furthermore, biological experiments will be performed to evaluate whether it presents anticarcinogenic properties as other palladium or platinum complexes sometimes do.

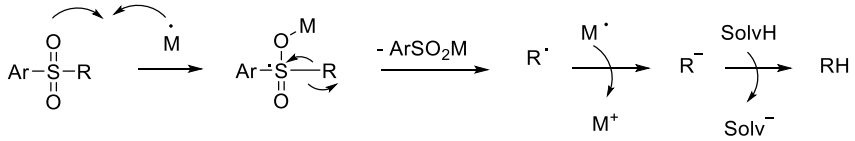
6. FUNCTIONALIZATION OF 1-SULFONYLMETHYL TETRAHYDROISOQUINOLINES

6.1. Sulfones and desulfonylation reactions

The sulfonyl functional group is an interesting electron-withdrawing group in organic synthesis that can be removed by reducing agents.[123] Thanks to its electron-withdrawing ability, it can be deprotonated and the correspondent carbanions are good nucleophiles that can be alkylated or functionalized. Thus, these compounds can be used for the generation of carbon-carbon bonds and then removed.

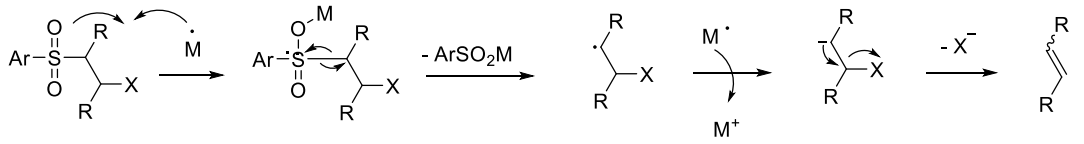
The removal of the sulfonyl group is normally a radical process and it generally involves the employment of active metals or salts, such as sodium amalgam or samarium(II) iodide. The most common processes are the reductive desulfonylation and the reductive elimination.

In the first case the metal transfers an electron to the sulfone generating a radical species that undergoes a fragmentation to a sulfinate anion and the more stable organic radical. The radical is immediately reduced by the metal and protonated by the solvent leading to the sulfur-free product R-H. Generally aryl sulfones are used in this process: aryl radicals are unstable so the cleavage of the R-S bond is favoured on the rupture of the Ar-S bond (that would generate the Ar radical) (Scheme 86).



Scheme 86.

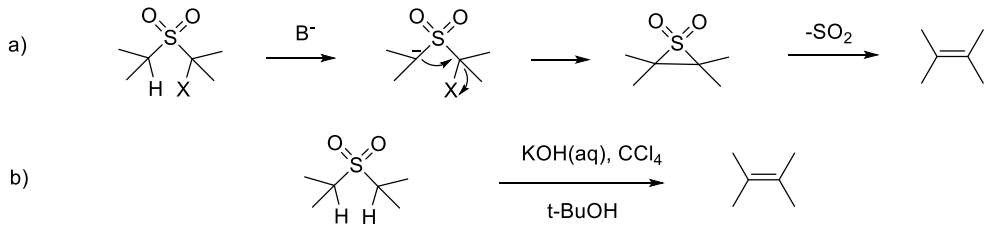
A reductive elimination happens when the sulfone presents a good leaving group in the β-position. A similar mechanism to the above cited cleavage is involved, but in this case the reduced carbanion undergoes the elimination of the leaving group generating an alkene (Scheme 87). Even though the carbanion is not configurationally or conformationally stable it prefers an arrangement with the R groups away that leads to the formation of the *E*-alkene.



Scheme 87.

Another interesting desulfunylation process is the Ramberg-Bäcklund reaction.[124] α-Halosulfones are suitable reactants for this transformation. In this case the elimination of the sulfone (leading to an alkene) is promoted by a base instead than a reducing agent: the deprotonation in α to the sulfone causes an intramolecular substitution and the subsequent formation of a thiirane dioxide (or episulfone) intermediate.[125] This instable intermediate readily eliminates SO_2 leading to an olefin (Scheme 88a). Although

various hypotheses have been proposed (a radical process or a chelotropic extrusion are the most reasonable), the mechanism for the elimination of the sulfur is still not clear.[126]

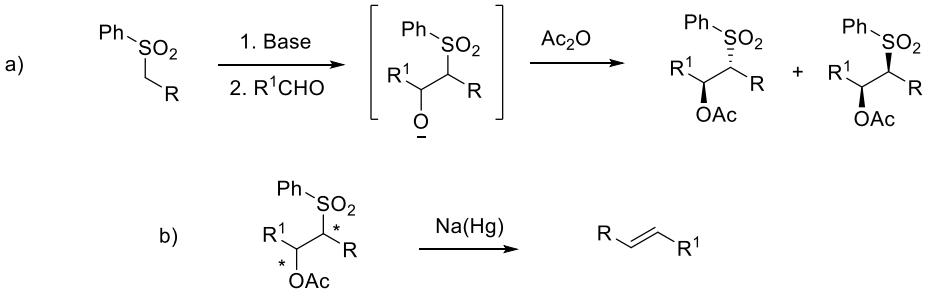


Scheme 88.

The E/Z selectivity of this reaction can be tuned by modifying some conditions as the strength of the base or the substituents. Furthermore an important variant of this process, known as Meyers' modification, which involves an *in situ* halogenation-Ramberg-Bäcklund reaction sequence and enables sulfones with protons in both α-positions to be converted directly into alkenes (scheme 88b).[127]

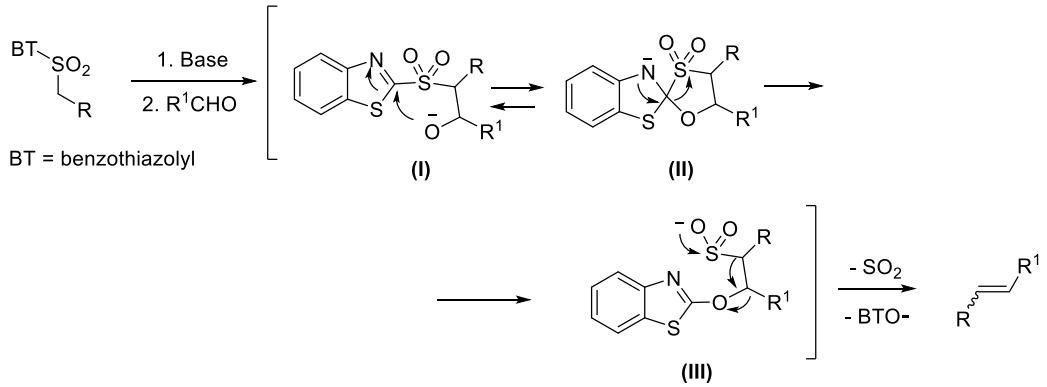
6.2. The Julia olefination and its modifications

Transformation of sulfones into alkenes is also possible by the process known as Julia olefination. The reaction consists in the deprotonation of the starting material followed by the nucleophilic attack of the resulting α-sulfonyl carbanion to an aldehyde and the *in situ* esterification of the generated alcoxide intermediate (Scheme 89a). The resultant mixture of diastereomers can undergo a reductive elimination of the sulfone (thanks to the presence of the acetate as leaving group in the β-position) affording to alkenes (scheme 89b). The reductive reaction presents good to excellent *E*-selectivity, as explained in the previous section.



Scheme 89.

The more important limitation of the Julia olefination is the low tolerance to reducible functionalities due to the necessity of using strong reducing agents to eliminate the sulfonyl group. For this reason modifications to the general procedure have been developed, in order to allow the nucleophilic attack and the elimination of the sulfone in a single step without the necessity of reducing agents. The one-step process has been made possible by replacing the phenyl sulfones with heteroaryl sulfones. The first example of modified Julia olefination was achieveded with benzothiazolyl sulfones.



Scheme 90.

When these sulfones are employed in the presence of a base, the alkoxide intermediate **I**, resulting from the nucleophilic attack of the carbanion to the aldehyde, reacts with the thiazole, undergoing a Smile rearrangement that leads to a sulfinate salt **III**. The subsequent spontaneous elimination of sulfur dioxide and benzothiazolone affords the final olefin (Scheme 90).

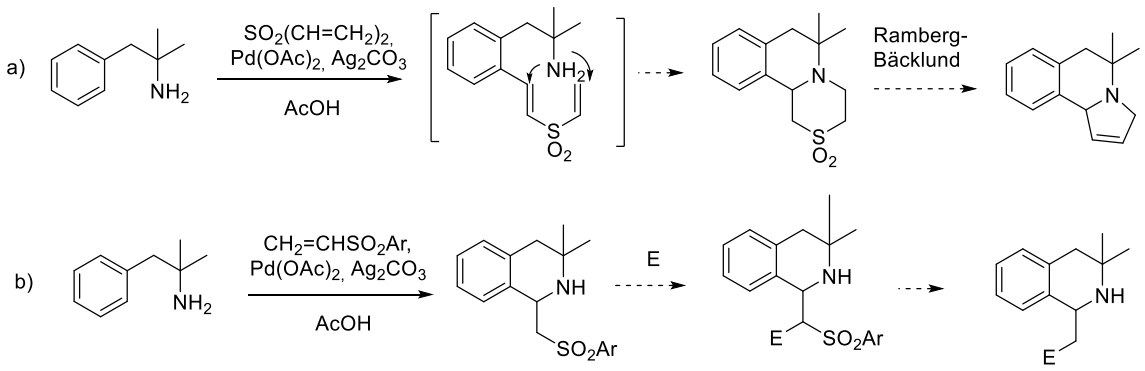
Different heteroaryl sulfones have been used for this process depending on the desired product: pyridinyl sulfones for example give high *Z*-selectivity, while 1-phenyl-1*H*-tetrazol-5-yl sulfones (PT-SO_2R) show better *E*-selectivity when compared to benzothiazolyl sulfones.

6.3. Application of vinyl sulfones to the synthesis of heterocyclic compounds

In the third chapter of this memory we reported the possibility of synthetizing THIQs skeletons containing a sulfone group (as compound **43**), thanks to the palladium catalyzed olefination-annulation reaction there reported. In the following part of this report we describe our results on the preparation of heterocyclic compounds containing a sulfone moiety and their following functionalization.

Initially, the use of divinyl sulfone as Michael acceptor for the palladium catalyzed olefination-annulation of primary arylethylamines was envisaged. We expected to get a double aza-Michael intramolecular addition after the catalytic olefination of the amine and the consequent formation of a tricyclic structure. The resulting cyclic sulfone would be a suitable substrate for the Meyers' modification of the Ramberg-Bäcklund reaction affording sulfur-free tricyclic products (Scheme 91a).

A second objective in this part of the work was the preparation of phenyl sulfones (as the model showed in Scheme 91b) to be used for the functionalization of their α-positions and subsequent elimination of sulfur leading to different 1-substituted THIQs

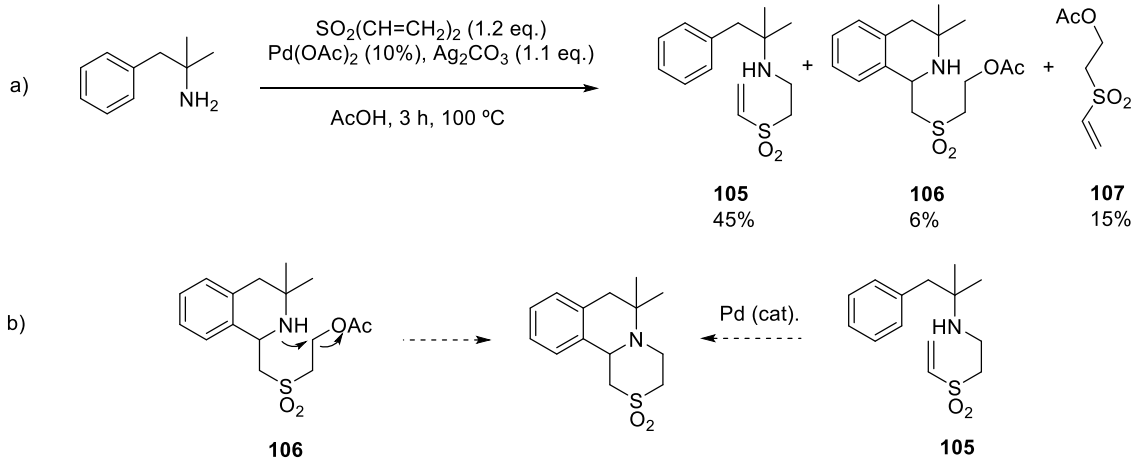


Scheme 91.

6.3.1. Reactions with divinyl sulfone

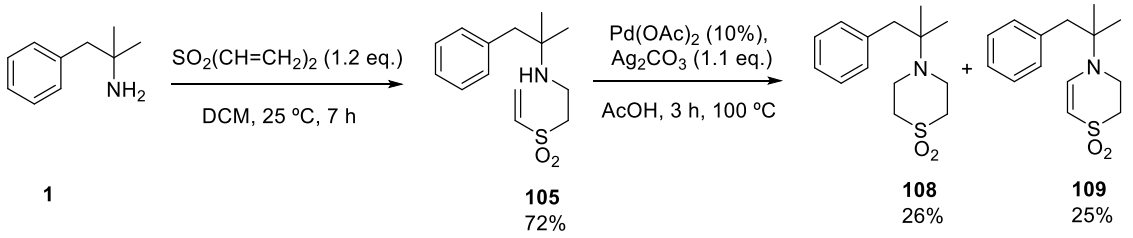
The reaction of amine **1** and divinyl sulfone afforded unexpected results, under the same conditions applied for the synthesis of compound **43** (see Chapter 2, Table 4). We observed a considerable amount of compound **105** deriving from the intermolecular Michael addiction of the amine to the vinyl sulfone. The desired tricyclic product was not detected in the reaction mixture. However, we could obtain the bicyclic product **106** in low yield: this compound derives from the insertion into the amine of the mono-acetoxylated alkene **107** (that was also isolated in low yield from the reaction mixture), formed by the reaction of the olefin with the solvent, (Scheme 92a). The 50% of the reaction crude was composed by a complex mixture of compounds we could not separate.

Both sulfones **105** and **106** could be potentially transformed into the expected tricyclic product under the same reaction conditions (Scheme 92b). Thus, we tried to increase the reaction time to six hours. Unfortunately, as we feared, the only result was the ulterior complication of the reaction mixtures and the consequent decrease of the global yields.



Scheme 92.

As conclusion after these preliminary experiments, divinyl sulfone is too reactive, it interacts strongly with palladium, and generates secondary reactions. As alternative, the next step was the synthesis and isolation of sulfone **105** in normal conditions and its use as substrate with the aim of achieving the desired product by an intramolecular Heck reaction. Unluckily, just a 1:1 mixture of compounds **108** and **109** was obtained in 50% yield and any product derived from the activation of the aromatic C–H bond was not detected (Scheme 93).

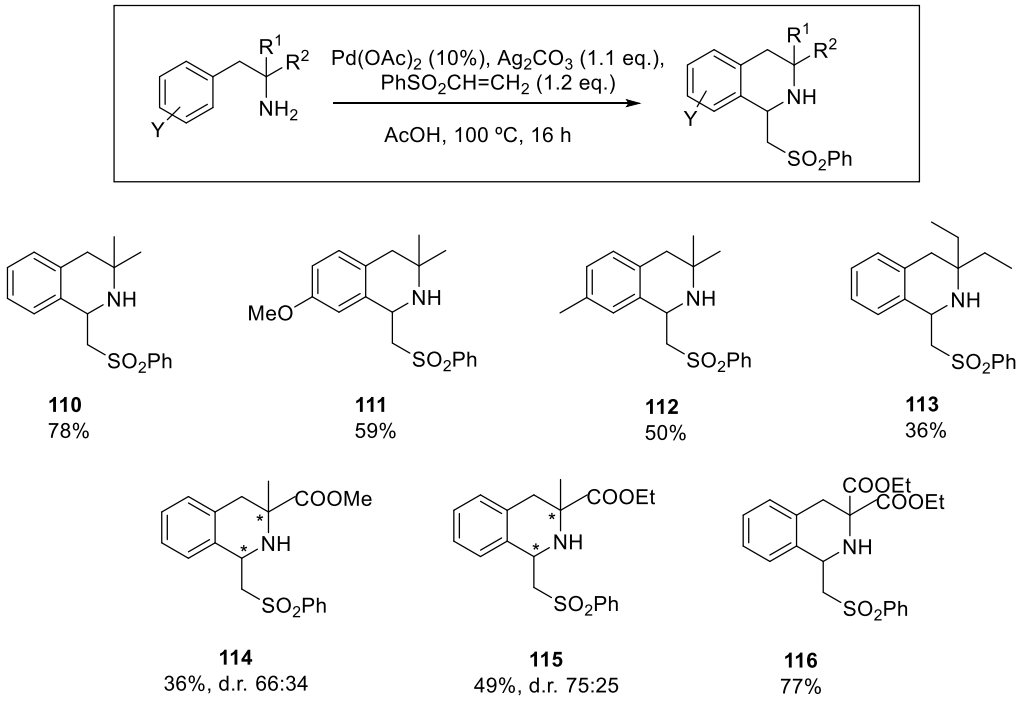


Scheme 93.

Due to the complex mixtures obtained in the reaction crudes and to the apparent impossibility of constructing the desired tricyclic compound this part of the project was abandoned.

6.3.2. Synthesis of phenyl sulfones

Conversely to what it was described in the previous section, the Heck reaction between arylethyl amines and phenyl vinyl sulfone gave good results in most of the cases (Scheme 94). In this way, some heterocycles were prepared in moderate to good yields.



Scheme 94.

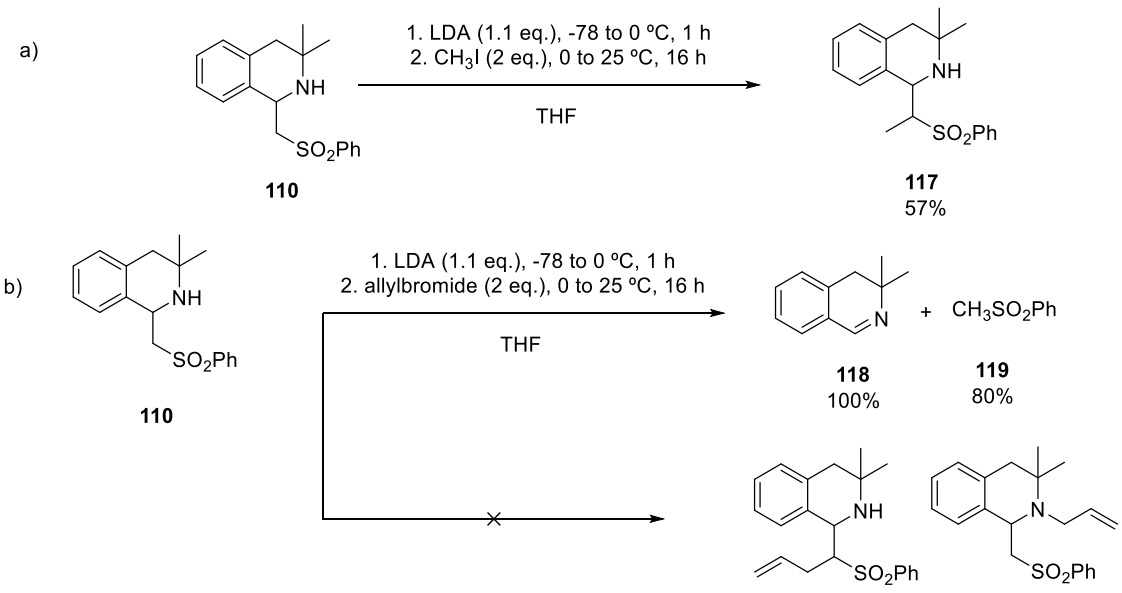
The difference between the yields of aminoester **115** and amino diester **116** can be explained on the basis of the same argument about the contraposition between the steric and the electronic efects, generated from the substitution in α to the starting amine. In fact, the steric hindered model **113** was also obtained in low yield. The ethyl ester **19** resulted to be a better substrate for this reaction with respect to the methyl homologous **16** probably because of a better stability.

The sulfone **116**, which could be decarboxylated or undergo other functionalizations in the α-position to the nitrogen, and the model **111**, which could undergo a reduction of the aromatic ring, represent two potential building block for the synthesis of heterocyclic compounds.

6.3.3. Alkylation of phenyl sulfone 110

Before the experiments aimed to the functionalization of the α-position of sulfone model **110**, we attempted the protection of the nitrogen to simplify the model. Conversely to what was expected this apparently easy task could not be performed: the nitrogen resulted unreactive to all the classical protecting reactants such as Boc_2O, ethyl chloroformiate and benzyl chloroformiate. In all the attempts the totality of the unreacted starting material was recovered. Also the alkylation of the nitrogen with an excellent electrophile as allyl bromide resulted impossible in absence of a strong base.

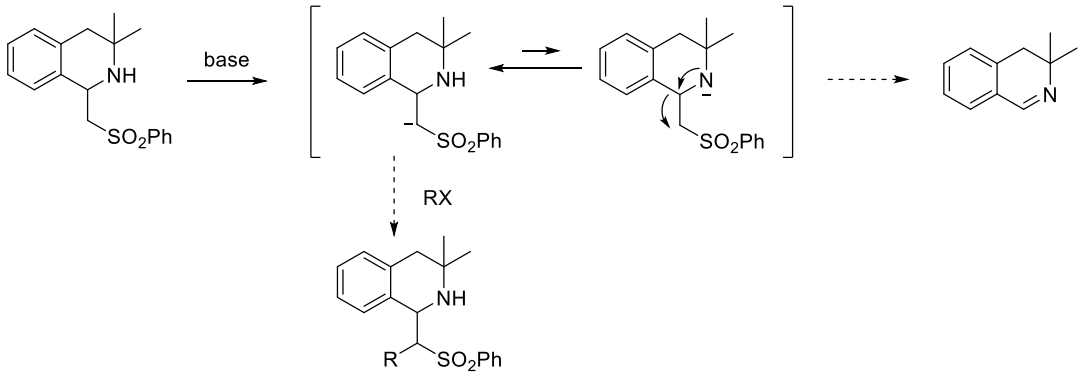
Bearing in the mind the difficulty of alkylating the amine group, we started using LDA as base and iodomethane as electrophile. Under the conditions showed in Scheme 95a the desired product **117** was isolated in 57% yield. Starting material or other products were not observed in the crude by ^1H NMR. The loss of mass was, however, unexpected.



Scheme 95.

The outcome of the following experiment was surprising: changing the electrophile to allyl bromide neither of the two expected products was obtained in the same conditions. However, the dihydroisoquinoline (DHIQ) **118** was isolated in quantitative yield (Scheme 95b), besides sulfone **119**.

A reasonable explanation to what observed appears in scheme 96. We can assume an equilibrium between the two possible anionic intermediates. If the electrophile reacts really fast with the carbanion the alkylation in α to the sulfone is observed (as in the case of the iodomethane). Otherwise the amide anion eliminates intramolecularly the sulfone (that is a good leaving group, thanks to the delocalization of the negative charge). This irreversible process shifts the equilibrium towards the formation of the amide, leading to the production of the imine in almost quantitative yields.



Scheme 96.

As confirmation of our conjectures, the treatment of the starting material in the same conditions, but in the absence of electrophiles, afforded the quantitative elimination of the sulfone leading to imine **118** and methyl phenyl sulfone **119**.

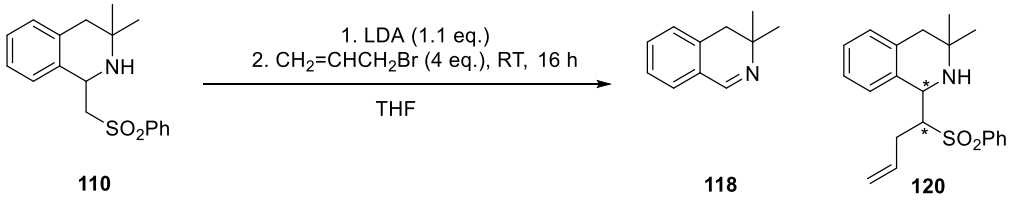
Thus, a screening of different conditions was performed, in order to favor the functionalization of the carbanion over the elimination (Table 20). The increase of the amount of the alkylating agent up to 4 equivalents did not allow the formation of the desired product. When the reaction mixture was allowed to reach 0 ºC during the deprotonation with LDA, only the imine was obtained, independently of the reaction time and on the excess of base (entries 1, 2, 3). Since allyl bromide cannot eliminate bromide under basic conditions, we tried to add LDA to a mixture of **110** and electrophile in THF (Barbier-type conditions): with this protocol, the isolation of the desired product **120** was possible in 43% yield, but almost the half of unreacted starting material was observed in the reaction mixture (entry 5).

When a weaker base is used (potassium tert-butoxyde, entry 4) any reaction was observed and the totality of the unreacted sulfone was recovered.

Finally we tried to perform the deprotonation with LDA at lower temperature. When the proton was extracted at -78º C more than the half of starting material resulted unreacted and the desired diastereomeric mixture **120** was obtained in only 20% yield. Finally,

when the deprotonation was run at -40 ºC for one hour, only the desired product was obtained as a mixture of diastereomers (dr 50:50) in 77% global yield.

Table 20.



110 118 120

Entry[a]	Deprotonation Time (h)	Deprotonation Temperature (ºC)	118 (Yield, %)[e]	120 (Yield, %)[e]	110 (Recovered, %)
1	1	-78 to 0	95	0	0
2[b]	1	-78 to 0	90	0	0
3	0.5	-78 to 0	96	0	0
4[c]	1	0	0	0	100
5[d]	0	-78 to 25	7	43	43
6	1	-78	traces	20	58
7	1	-40	traces	77	0

a) Standard conditions: the base (0.36 mmol) is added to a sulfone solution (0.33 mmol in 5 mL THF). The electrophile is added via a syringe after the required time; b) a sulfone solution (0.33 mmol in 3 mL THF) is added to a solution of LDA in THF (0.36 mmol in 2 mL THF); c) potassium tert-butoxyde was used as base; d) Barbier-type conditions; e) isolated yields.

Once the best conditions had been found for allyl bromide, we turned our attention to other electrophiles (Table 21).

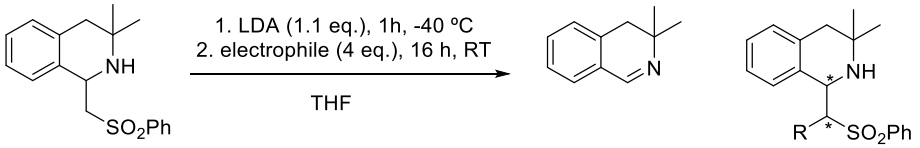
First of all, the first step of the Julia reaction employing hexanal as aldehyde was tested, but a mixture of starting material and DHIQ **118** was obtained.

Then we attempted the alkylation with different haloalkanes. Most of the experiments were not successful, independently on the alkane type and on the leaving anion (table 21, entries 2 to 5). The only exceptions were methyl iodide and benzyl bromide that afforded the desired products **117** and **121** (entries 6 and 7 respectively). It was clear that only very reactive electrophiles as iodomethane and benzyl or allyl halides can compete with the elimination process even in the optimal conditions.

Thus, satisfactory yield was obtained with benzyl bromide. As far as iodomethane is concerned, it can be assumed that iodomethane is the only electrophile that is able to interact also with the imide anion, thanks to his small size. When it was used as electrophile the product of the elimination was never detected in the reaction mixture, while a 16% of a compound that could correspond to the double methylated product (on the α-position to the sulfone and on the nitrogen) was observed, although we could not completely separate it from the major product **117** and characterize it. A considerable loss of mass was also observed in this reaction, as reported above in which the same nucleophile had been used. Thus, a possible explanation of the low yields is the

formation of an ammonium salt deriving from the double alkylation of the nitrogen. This organic salt would remain in water after the quench of the reaction.

Table 21.



110 **118** **117** R = Me **121** R = Bn

Entry[a]	Electrophile	Alkylated compound	Yield (%)[c]	d.r	118 (Yield, %)[c]	110 (Recovered, %)
1	Hexanal	--	0	--	47	34
2	2-iodopropane	--	0	--	98	0
3	Bromobutane	--	0	--	97	0
4	Iodoethane	--	0	--	60	30
5[b]	Iodoethane	--	0	--	60	39
6	Iodomethane	**117**	39	100:0	0	0
7	Benzyl bromide	**121**	81	50:50	traces	0

a) Standard conditions: the base is added to a sulfone solution (0.33 mmol in 5 mL THF) at -40 ºC. The electrophile is added via a syringe after 1 hour; b) the deprotonation was performed at -78º C; c) isolated yields.

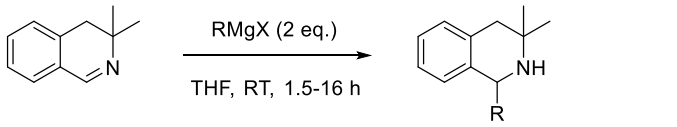
6.3.4. Alkylation of dihydroisoquinoline 118

Although in the last section we reported the limited applicability of our model to the functionalization of the α-position of the sulfone, the achieved results were certainly stimulating. Actually, we had just discovered an easy way for the quantitative cleavage of the sulfone, without the need of reducing agents, generating an electrophilic intermediate which can be functionalized by reaction with nucleophiles.

Thus, we focused our efforts in the functionalization of the intermediate **118**. Initially Grignard reactants were used as nucleophiles.

The scope of this process was quite limited (Table 22). The allyl and benzyl organomagnesium reagents allowed the formation of the desired products **122** (entry 3) and **123** (entry 4) in excellent yields while the alkyl magnesium halides resulted totally unreactive towards the imine **118**.

Table 22.



118

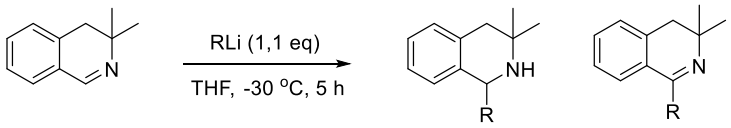
122 R = $CH_2CH=CH_2$
123 R = Bn

Entry	Grignard Reagent	Product	Yield (%)[a]
1	Methyl magnesium bromide	--	0
2	Ethyl magnesium bromide	--	0
3	Allyl magnesium bromide	**122**	100
4	Benzyl magnesium chloride	**123**	97

a) Isolated yieds.

At the sight of this results organolithium reagents were used as alkylating agents. In this case the functionalization of the imine with alkyl groups was possible in good yields as well as the introduction of a phenyl group (Table 23). However, the alkylation with an alkynyl lithium compound (generated *in situ*) was not possible since starting material was recovered.

Table 23.



118

124 R = Me
125 R = Bu
126 R = Ph

26

Entry	RLi	Product (Yield, %) [a]
1	Methyllithium	**124** (68)
2	Butyllithium	**125** (83)
3	Phenyllithium	**126** (66) + **26** (33)
4	hex-1-yn-1-yllithium	--

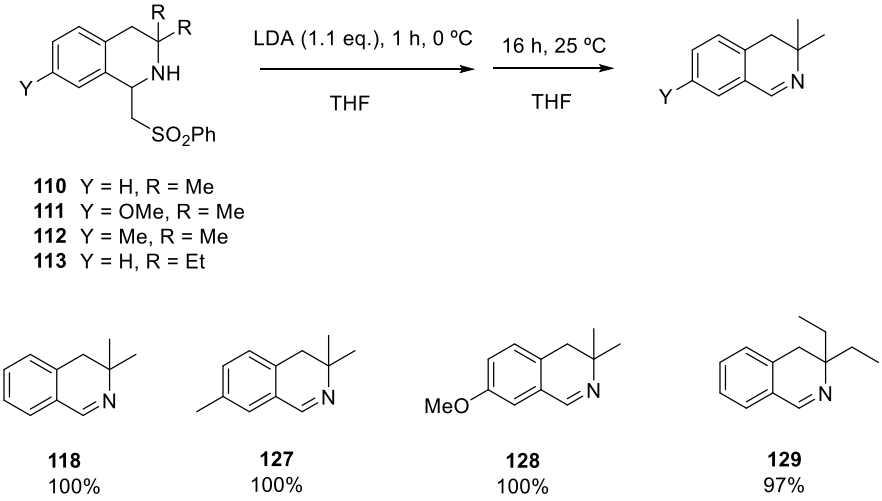
a) Isolated yieds.

Only in the case of phenyllithium a 33% of the correspondent DHIQ **26** was observed (entry 3).

6.3.5. Elimination of (methylsulfonyl)benzene

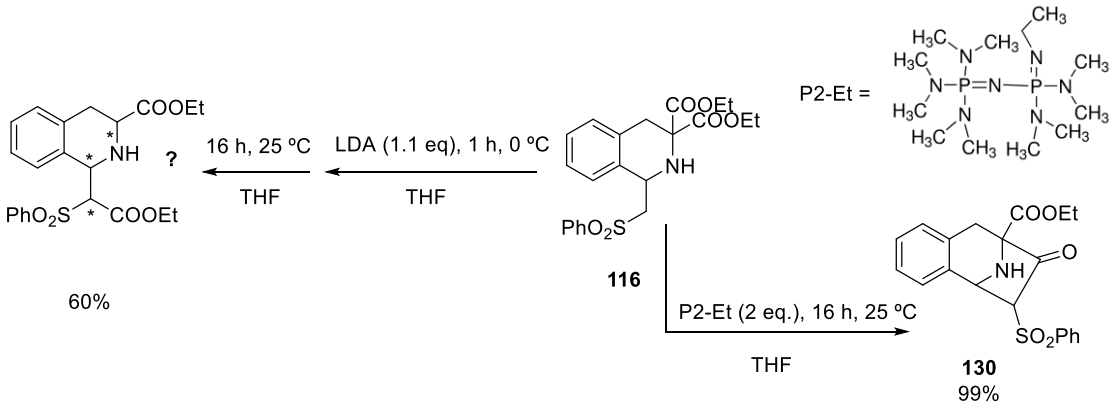
The conditions for the elimination of the methylphenyl sulfone, leading to dihydroisoquinoline **118**, were also applied to compounds **111-113** and **115-116** in order to verify the applicability of the process to different structures. As expected DHIQs **127-129** could be prepared in quantitative yield (Scheme 97), while different

considerations have to be done for the two compounds that contain an ester moiety in α to the nitrogen.



Scheme 97.

A mixture of products was obtained starting from the compound **116** that could not be properly separated. The evidences, coming by the analysis of the mass and the NMR spectra, suggested the migration of an ester group from the vicinal position to the nitrogen to the vicinal position to the sulfone with the consequent formation of a mixture of four diastereomers, but the impossibility of obtaining any pure product did not allow us to demonstrate this assumption.

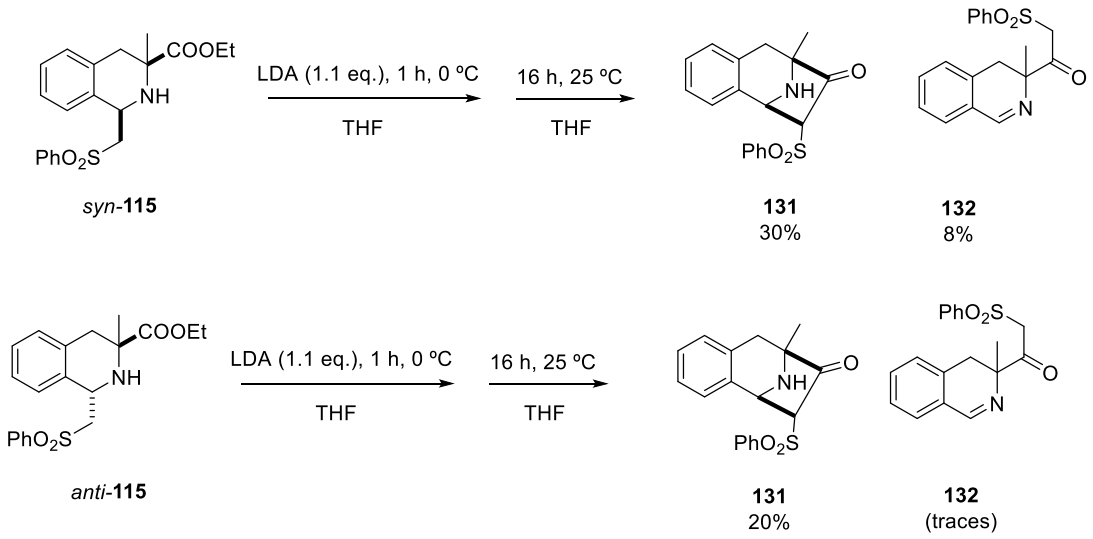


Scheme 98.

Changing LDA for the phosphazene base P2-Et, only the product **130** was obtained in almost quantitative yield from model **116**: it was produced by the attack of the α-sulfonyl carbanion to one of the esters with the consequent elimination of ethanol and formation of a tricyclic compound (Scheme 98).

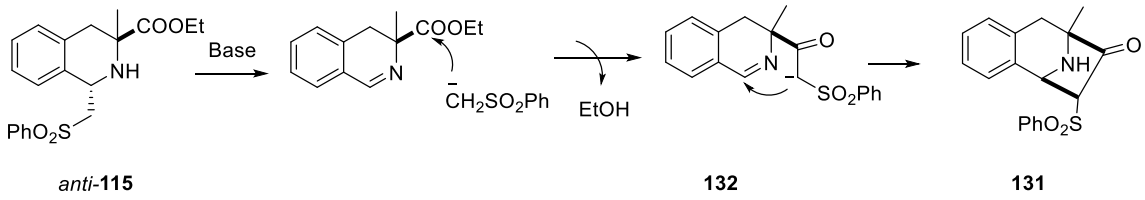
The situation appeared more complicated for the sulfone model **115**, since the two diastereomers showed different behaviors. No reaction was observed when *anti*-**115** was treated with base in the standard reaction conditions, while the *syn* isomer led to the

formation of the tricyclic compound **131** and his derivative DHIQ **132** as the only products, even if in low yield. Unexpectely, similar results in lower yield were noted from the *anti*-diastereomer, increasing the quantity of base to 2.5 equivalents (Scheme 99).



Scheme 99.

Obviously, the direct formation of compound **131** from *anti*-**115** is not possible because it would implicate a non-plausible epimerization of the substrate. A logical explanation could be the elimination of the sulfone, followed by its attack to the ester and the consequent acyl nucleophilic substitution leading to compound **132**. The excess of base allows the deprotonation of the α-position of the sulfone generating a carbanion that performs an intramolecular reaction leading to the tricyclic product **131** (scheme 100).



Scheme 100.

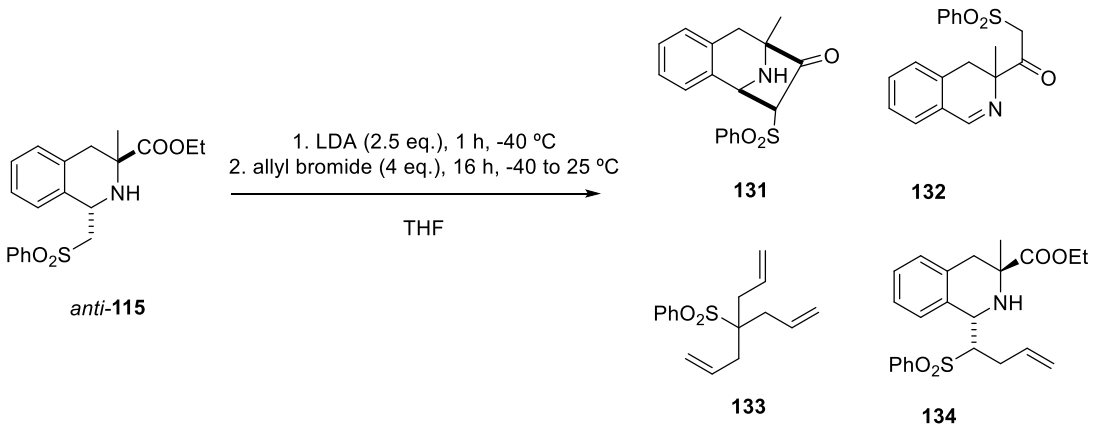
This assumption was confirmed by an easy experiment: stirring a mixture of compounds **131-132** in THF in the presence of LDA the ratio between the products changes during the time in favor of the tricyclic compound **131**.

6.3.6. Alkylation of *anti*-115

These last results suggested a lower reactivity of the amide anion generate from substrates **115** and **116** than that deriving from substrates **110-113**. This observation could be related with the stabilizing effect that the esters exert on the nitrogen. Hence, we thought that the α-carbanions generated from these sulfone models could be more

prone to be alkylated than compound **110**. Thus, alkylation of *anti*-**115** was attempted taking in mind that this substrate cannot undergo the migration of the ester group (as observed for **116**), neither the direct cyclization leading to product **131**, so it should have been the easier model to functionalize without side-reactions.

Table 24.



Entry	Deprotonation T (ºC)	Equivalents of Base	131 (Yield, %)[b]	132 (Yield, %)[b]	133 (Yield, %)[b]	134 (Yield, %)[b]
1[a]	0	1	traces	Traces	0	0
2	0	2.5	traces	7	36	36
3	-40	2.5	30	6	24	40

a) Almost all the starting material was recovered; b) isolated yields.

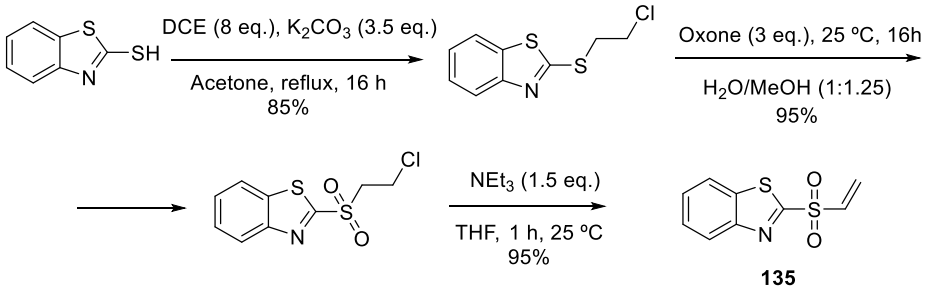
However, when the attempt of alkylation with allyl bromide was performed with one equivalent of LDA almost the totality of the starting material and only traces of compounds **131** or **132** were observed in the crude.

Changing to 2.5 equivalents of base the formation of the alkylated product **134** was observed in 36% yield, accompanied by a small quantity of compound **131** (entry 2). An interesting result concerns the formation of a respectable amount of the product **133.** This result seems to indicate the elimination of the sulfone, but the resulting dihydroisoquinoline was not isolated nor observed in the reaction mixture. Performing the deprotonation with 2.5 equivalents of base at lower temperature a cleaner mixture was obtained and also a good amount of the tricyclic product **131** was isolated (entry 3). Not even in this case the imine derived from the elimination of the sulfone was detected in spite of the presence of compound **133** in 24% yield. All the evidences observed in these experiments suggests that the DHIQ derived from compound **115** must undergo some degradation or transformations in the reaction conditions.

6.3.7. Modified Julia reaction

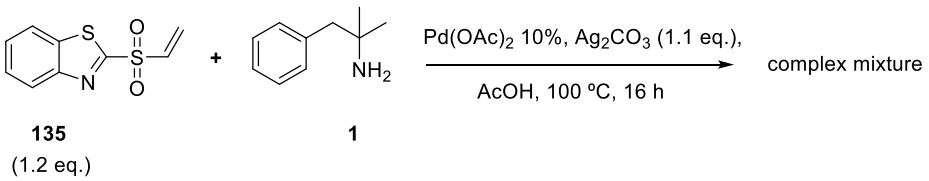
In parallel to what it is described above, an olefination process via a modified Julia reaction was considered. This approach would also have allowed the preparation of unsaturated structures, difficult to obtain through other strategies.

One first goal was the preparation of a vinyl benzothiazolyl sulfone. We envisaged its preparation from commercially available benzo[d]thiazole-2-thiol by slightly modifying a described procedure which involves the alkylation of the thiol with dichloroethane followed by its oxidation to sulfone.[128] Finally, the terminal alkene would be obtained via the elimination of a chloride (Scheme 101). In practice, the electron-deficient olefin **135** was easily prepared in 76% global yield.



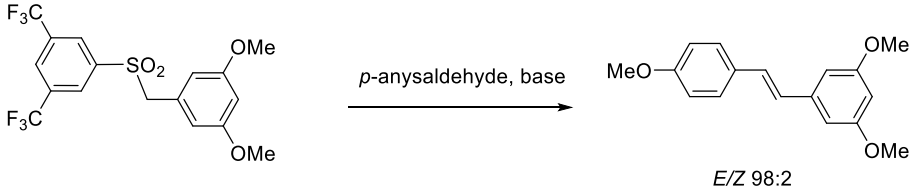
Scheme 101.

Unfortunately, the addition of the amine **1** to the freshly prepared vinyl sulfone **135** was not achieved: a complex mixture was obtained from the palladium catalyzed reaction under our optimized conditions (Scheme 102).



Scheme 102.

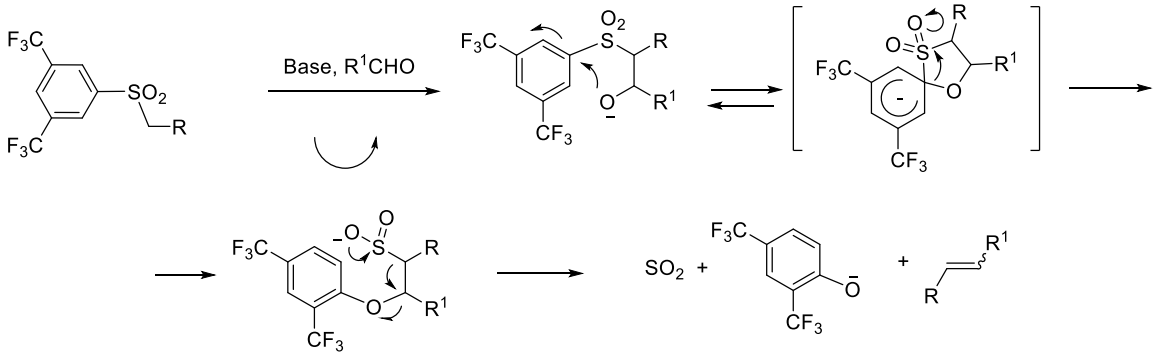
The reason of the failure might be the presence of heteroatoms in the structure of the sulfone that can interact with the catalyst, interfering with the reported catalytic cycle. This was really a problem, since almost all the heteroarenes that are used in modified Julia reactions contain atoms such us nitrogen or oxygen that are capable to coordinate the palladium (see the introduction of this chapter).



Scheme 103.

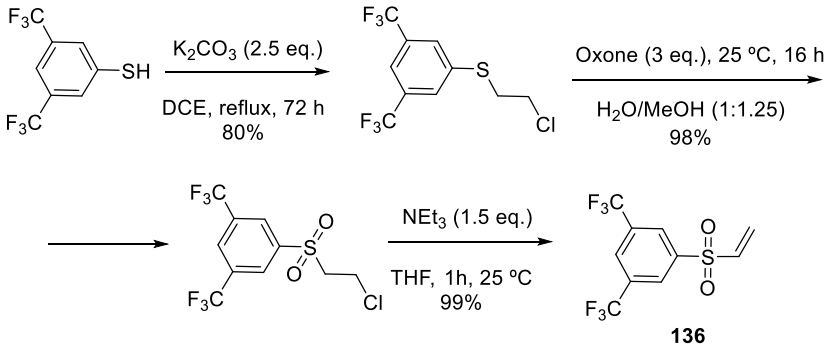
However, in 2004 Nájera and co-workers reported the synthesis of resveratrol via a modified Julia reaction involving the utilization of 3,5-bis(trifluoromethyl)phenyl

sulfones (Scheme 103).[129] This kind of sulfones allows the Smile rearrangement of the alkoxide generated from the addition of the sulfonyl carbanion to the aldehyde, thanks to the electron withdrawing groups on the aromatic ring. The resulting intermediate spontaneously eliminate 3,5-bis(trifluoromethyl)phenolate and sulfur dioxide affording the final olefin (Scheme 104).



Scheme 104.

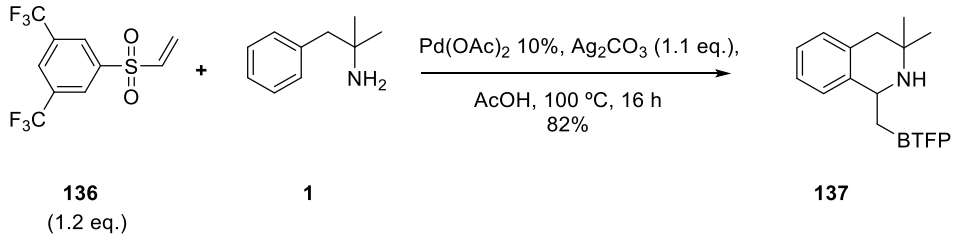
Thus, we engaged in the preparation of 3,5-bis(trifluoromethyl)phenyl (BTFP) vinyl sulfone **136** in order to use it as a suitable electrophile for the olefination-annulation of phenethylamines.



Scheme 105.

We managed to obtain the desired product in excellent global yield from the commercially available 3,5-bis(trifluoromethyl)benzene thiol (Scheme 105) by modifying another described method (similar to the one applied for the preparation of **135**) that also involves the alkylation with dichloroethane, oxidation to sulfone, and elimination of chloride.[130]

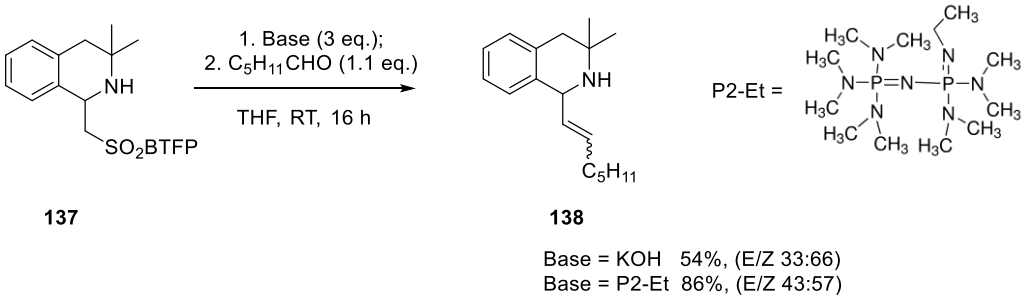
In this case the olefin could be used for the palladium catalyzed annulation of phenethylamines and the model **137** was prepared in excellent yield (Scheme 106).



Scheme 106.

With sulfone **137** in hand, we started the study of the olefination of the new model in the best conditions described by Nájera's group. They reported that the most useful bases for this modified Julia reaction resulted to be potassium hydroxide or the phophazene bases P2-Et or P4-*t*-Bu. Thus, we made two preliminary attempts to olefinate the sulfone **137** with hexanal in the presence of KOH and P2-Et (the most easily commercially available among the two proposed phosphazene bases).

The reaction with potassium hydroxide allowed the formation of a *E/Z* mixture of the desired alkenes. However, almost the half of unreacted sulfone was recovered. On the contrary, the totally consumption of the starting material and the formation of the mixture of alkenes **138** in 86% yield (43:57 *E/Z*) was achieved by switching to the phosphazene base (Scheme 107).

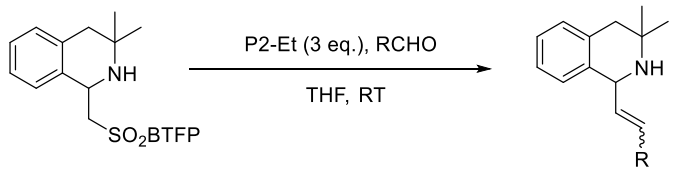


Scheme 107.

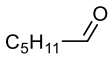
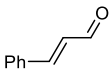
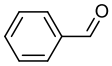
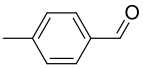
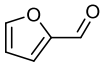
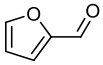
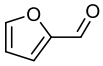
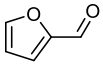
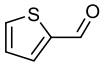
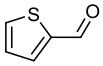
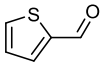
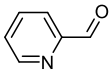
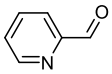
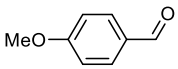
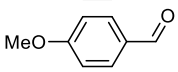
After these preliminary experiments, several aldehydes were employed for this modified Julia reaction with really interesting results (table 25). Aliphatic aldehydes furnished good yields in this transformation with the exception of pivalaldehyde, the most hindered one (entry 3), althoug a low *E/Z* selectivity was observed. Paraformaldehyde, as well as conjugated aldehydes (entries 4 to 6), resulted not suitable for this process since they only furnished complex mixtures (this incompatibility was also described by Nàajera's group).

Anyhow the most outstanding results became from aromatic aldehydes since they only led to the less stable *Z*-olefin with total selectivity. In the case of the benzaldehyde the formation of the *cis*-product **141** was quantitative, while in the case of the 4-methylbenzaldehyde the product **142** was selectively obtained in 80% yield (entries 7 and 8).

Table 25.



137 **138-145**

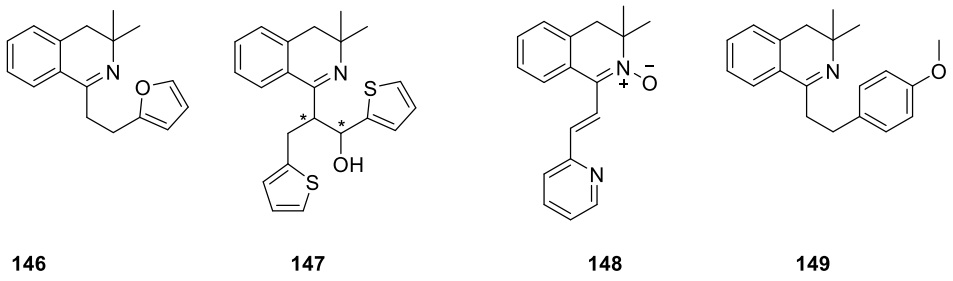
Entry[a]	RCHO	Reaction time (h)	Product	Yield (%)[e]	*E/Z* Ratio
1		16	**138**	86	43:57
2		16	**139**	81	75:25
3		16	**140**	42	62:38
4[b]		16	--	0	--
5[b]		16	--	0	--
6[b]		16	--	0	--
7		16	**141**	100	0:100
8		16	**142**	79	0:100
9		16	**143**	49	0:100
10		4	**143**	51	0:100
11[c]		4	**143**	54	0:100
12		7	**143**	65	0:100
13		16	**144**	69	0:100
14[d]		16	**144**	39	0:100
15		7	**144**	79	0:100
16		16	--	0	--
17		7	--	0	--
18		16	**145**	47	0:100
19		7	**145**	22	0:100

a) Reaction conditions: a suspension of 0.1 mmol of sulfone and 0.3 mmol of base was stirred 30 minutes at RT, then 0.11 mmol of aldehyde were added; b) complex mixture; c) 3 eq. of aldehyde; d) 2 eq. of aldehyde; e) isolated yields.

An optimization of the conditions was necessary for heteroaromatic aldehydes. Thus, the reaction performed with furfural or 2-thiophene carboxaldehyde initially gave lower yields (entries 9, 13) than that performed with benzaldehyde due to the formation of isomerization products such as **146** and **147** (Figure 9). In the case of the thiophene, the isomer can add another molecule of aldehyde in α to the imine in basic conditions leading to the di-alkylated product **147**: this is reflected in a dramatically decrease of the yield when more equivalents of aldehyde are used (entry 14). Once the problem had been analyzed it was possible to obtain the desired olefins **143** and **144** in good yields from these aldehydes tuning the reaction time (entries 10-12 and 15). Despite the presence of various isomerization products in the different conditions, the presence of *trans*-alkenes never was detected in these entries.

A completely different case was that of the aldehyde derived from the pyridine: it was not possible to obtain the desired product from this compound (entries 16 and 17): only the di-oxidized *trans*-olefin **148** was obtained from this aldehyde in 21% to 41% yield, depending on the conditions. The low yield could be explained by the tendency of the *N*-oxide to keep in the aqueous layer during the work-up.

Finally, the reaction with *p*-anisaldehyde gave the *cis*-olefin **145** in moderate yields. The presence of a 20% of the isomer **149** was observed in the reaction mixture when the reaction was performed in the standard conditions, but this time the decrease of the reaction time did not improve the yield (entries 18 and 19).



146 **147** **148** **149**

Figure 9.

6.4. Summary and conclusions

The possibility of constructing several dihydroisoquinolines and tetrahydroisoquinoline skeletons by functionalization of sulfones that can be obtained by our palladium-catalyzed olefination-annulation reaction has been demonstrated in this chapter of the thesis.

In particular, an unusual method for the cleavage of the sulfone has been discovered, leading to DHIQs that can be easily functionalized with common electrophiles. This strategy resulted incompatible with α-amino esters, however this kind of substrates showed to be useful for the construction of tricyclic skeletons.

A modified Julia reaction was also applied to an aryl sulfone model built with our olefination reaction and interesting results were obtained.

Most of the strategies that have been studied in this last chapter of the thesis could be potentially useful for the construction of several heterocyclic compounds.

7. EXPERIMENTAL PART

7.1. GENERAL PROCEDURES AND TECHNIQUES

Solvents were distilled and dried before use.[131] ^{1}H (400 MHz) and ^{13}C (101 MHz) nuclear magnetic resonance (NMR) spectra were registered in a Mercury 400 apparatus. $CDCl_3$ (99.9%) was used as solvent while $SiMe_4$ (TMS) was used as reference. The coupling constants (*J*) are expressed in Hz and the chemical shifts in part per million (ppm). The signals multiplicities are reported with the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). More complicated signals are described as combination of the indicated abbreviations: e.g dd (double doublet), dt (double triplet), etc. Bi-dimensional experiments (NOESY, HSQC) were realized in some cases to confirm the signal assignments. High resolution mass spectra (HRMS) were obtained in a Agilent LC/MSD-TOF by CCiTUB at University of Barcelona.

The thin layer chromatography (TLC) was performed by using 0.20 nm silica gel sheets (F_{254} Merk). Acidic solution of *p*-anhysaldehyde and potassium permanganate as well as UV light (259 nm) have been used as detectors. The column chromatography was performed with the middle pressure technique (flash) using 0.040 0.063 nm silica gel particles. The suitable eluents are reported for each case.

7.2. PREPARATION OF STARTING AMINES

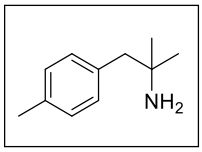
7.2.1. General procedure for the preparation of α,α-dimethyl phenylethylamines 1-4 and 6

Ethyl 2-(*p*-tolyl)acetate (1 mL, 5.61 mmol) was dissolved in dry THF (30 mL), then the mixture was cooled to 0 ºC and a 3 M solution of methylmagnesium bromide in THF was added via a syringe (6.5 mL, 20 mmol). The reaction mixture was allowed to room temperature and stirred for 1.5 h then a saturated aqueous solution of ammonium chloride was added.
Ethyl acetate was added, the phases were separated and the aqueous phase was extracted three times with ethyl acetate. The collected organic phases were washed twice with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated at reduced pressure to give the alcohol as a colorless oil that was used for the next step without further purifications (920 mg, 100%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14-7.08 (m, 4H, Ar*H*), 2.73 (s, 2H, ArC*H*$_2$), 2.33 (s, 3H, ArC*H*$_3$), 1.22 (s, 6H, 2 C*H*$_3$).).

The intermediate (920 mg, 5.61 mmol) was dissolved in 2-chloroacetonitrile (2 mL, 33.6 mmol) and acetic acid (2.7 mL). The solution was cooled to 0 ºC and sulfuric acid (2.7 mL, 50.4 mmol) was added dropwise. After the addition, the mixture was stirred for 5 hours at room temperature then ice was added carefully.
The mixture was extracted three times with diethyl ether and the collected organic phases were washed with a saturated solution of Na_2CO_3 (twice) and brine. Finally, the organic phase was dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The excess of 2-chloroacetonitrile was removed at vacuum to obtain 2-chloro-*N*-(2-methyl-1-(p-tolyl)propan-2-yl)acetamide as a white solid, which was directly used for the next steps without further purifications: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11 (d, *J* = 8.1 Hz, 2H, Ar*H*), 7.03 (d, *J* = 8.1 Hz, 2H, Ar*H*), 3.94 (s, 2H, C*H*$_2$Cl), 2.98 (s, 2H, ArC*H*$_2$), 2.33 (s, 3H, ArC*H*$_3$), 1.37 (s, 6H, 2 C*H*$_3$).

Thiourea (0.510 g, 6.72 mmol) was added to a solution of the crude chloroamide (5.61 mmol) in a 1:5 mixture of acetic acid and ethanol (60 mL). The reaction was heated to reflux overnight, then it was cooled and the ethanol was evaporated at reduced pressure. A 2 N aqueous solution of HCl was added and the resulting aqueous suspension was washed twice with dichloromethane. Then solid Na_2CO_3 was added until reaching pH 10-11 to the aqueous solution which was subsequently extracted three times with dichloromethane. The collected basic organic phases were dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure to afford the pure 2-methyl-1-(*p*-tolyl)propan-2-amine as a yellow oil (766 mg, overall yields of the three steps: 84%).

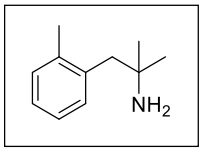
2-Methyl-1-(p-tolyl)propan-2-amine (3)



Colorless oil, 84% from ethyl-2-(*p*-tolyl)acetate. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.11 (d, *J* = 8.1 Hz, 2H, Ar*H*), 7.07 (d, *J* = 8.1 Hz, 2H, Ar*H*), 2.62 (s, 2H, ArC*H*$_2$), 2.33 (s, 3H, ArC*H*$_3$), 1.11 (s, 6H, 2 C*H*$_3$).

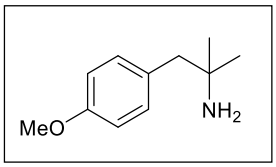
^{13}C NMR (101 MHz, $CDCl_3$): δ 135.7, 135.3, 130.3, 128.6, 50.7, 49.9, 30.3, 21.0. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{11}H_{18}N)$: 164.1434, found: 164.1428.

2-Methyl-1-(*o*-tolyl)propan-2-amine (4)



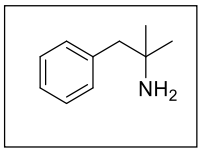
Colorless oil, 70% from ethyl 2-(o-tolyl)acetate (0.920 g). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.18-7.12 (m, 4H, Ar*H*), 2.73 (s, 2H, ArCH_2), 2.36 (s, 3H, ArCH_3), 1.15 (s, 6H, 2 CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 137.1, 136.9, 131.4, 130.6, 126.3, 125.4, 51.3, 46.7, 30.71 20.5. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{11}H_{18}N)$: 164.1434, found: 164.1428

1-(4-Methoxyphenyl)-2-methylpropan-2-amine (2)



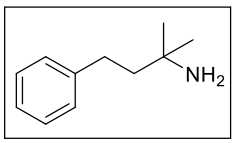
Colorless oil, 28% from 1-(4-methoxyphenyl)propan-2-one (0.611 g). The chloramide intermediate had to be purified by flash coloumn silica gel chromatography (hexane/ethyl acetate) due to the partial hydrolysis of the metoxide in the acidic conditions. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.10 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.84 (d, *J* = 8.6 Hz, 2H, Ar*H*), 3.80 (s, 3H, OCH_3), 2.60 (s, 2H, ArCH_2), 1.10 (s, 6H, 2 C*H3*). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 158.1, 131.3, 130.5, 113.4, 55.2, 55.2, 50.1 30.2. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{11}H_{18}NO)$: 180.1383, found: 180.1384.

2-Methyl-1-phenylpropan-2-amine (1)



Colorless oil, 76% from commercially available 2-methyl-1-phenyl-2-propanol (0.750 g, only the second and the third part of the general procedure were followed). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.32-7.18 (m, 5H, Ar*H*), 2.67 (s, 2H, ArCH_2), 1.22 (br s, 2H, NH_2), 1.12 (s, 6H, 2 CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 136.4, 130.4, 127.9, 126.2, 51.1, 44.5, 30.3. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{10}H_{16}N)$: 150.1277, found: 150.1280

2-Methyl-4-phenylbutan-2-amine (6)



Colorless oil, 95% from commercially available 2-methyl-4-phenylbutan-2-ol (1.30 g, only the second and the third part of the general procedure were followed). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.30-7.26 (m, 2H, Ar*H*), 7.23-7.15 (m, 3H, Ar*H*) 2.66 (m, 2H, ArCH_2CH$_2$), 1.68 (m, 2H, ArCH$_2$CH_2) 1.33 (br s, 2H, NH_2), 1.18 (s, 6H, 2 CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 142.8, 128.4, 128.3, 125.6, 49.5, 47.1, 31.1, 30.4. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{11}H_{18}N)$: 164.1434, found: 164.1439

7.2.2. Preparation of 2-Methyl-1-(4-nitrophenyl)propan-2-amine 5

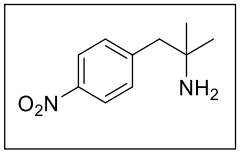
Compound **5** was prepared from the commercially available alcohol 2-methyl-1-phenyl-2-propanol following the general procedure with some modifications: 2-methyl-1-

phenyl-2-propanol (0.5 mL, 3.24 mmol) was dissolved in 2-chloroacetonitrile (1.25 mL, 19.45 mmol) and acetic acid (1.55 mL). The solution was cooled to 0 ºC and sulfuric acid (1.55 mL, 29.16 mmol) was added dropwise. After the addition, the mixture was stirred for 5 hours at room temperature then ice was added carefully.
The mixture was extracted three times with diethyl ether and the collected organic phases were washed with a saturated solution of Na_2CO_3 (twice) and brine. Finally, the organic phase was dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The excess of 2-chloroacetonitrile was removed at vacuum to obtain 2-chloro-*N*-(2-methyl-1-phenylpropan-2-yl)acetamide as a white solid, which was directly used for the next steps without further purifications.

An acidic mixture of H_2SO_4 (5.3 mL 97.2 mmol) and concentrated HNO_3 (6.8 mL, 162 mmol) was added to the crude chloroamide (3.24 mmol) at 0 ºC. After the addition, the mixture was stirred for 30 minuts at room temperature. The solution was diluted with water and extracted three times with dichloromethane. The collected organic phases were washed with a saturated aqueous solution of Na_2CO_3 and brine. Finally, the organic phase was dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure. The crude mixture was purified by flash column chromatography on silica gel (hexane/ethyl acetate) to afford the pure ortho nitrated compound as an orange solid (638 mg, overall yield of the two steps: 73%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17-8.14 (d, *J* = 8.7 Hz, 2H, Ar*H*), 7.31-7.29 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.16 (br s, 1H, N*H*), 3.97 (s, 2H, CH_2Cl), 3.23 (s, 2H, ArCH_2), 1.39 (s, 6H, 2 CH_3)).

Thiourea (213 mg, 2.80 mmol) was added to a solution of the nitrated compound (635 mg, 2.34 mmol) in a 1:5 mixture of acetic acid and ethanol (10 mL). The reaction was heated to reflux overnight, then it was cooled and the ethanol was evaporated at reduced pressure. A 2 N aqueous solution of HCl was added and the resulting aqueous mixture was washed three times with dichloromethane. Then solid sodium carbonate was added until reaching pH 10 and the aqueous solution was extracted three times with dichloromethane. The organic phase was dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure to afford pure 2-methyl-1-(4-nitrophenyl)propan-2-amine as an orange oil (389 mg, 85%).

2-Methyl-1-(4-nitrophenyl)propan-2-amine (5)

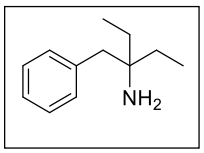


Orange oil, 62% from 2-methyl-1-phenyl-2-propanol. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.17 (d, *J* = 8.6 Hz, 2H, ArH), 7.37 (d, *J* = 8.6 Hz, 2H, ArH), 2.77 (s, 2H, ArCH_2), 1.25 (br s, 2H, NH_2), 1.14 (s, 6H, 2 CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 146.3, 131.1, 124.6, 122.6, 49.7, 49.5, 28.2. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$($C_{10}H_{14}N_2O_2$): 195.1128, found: 195.1125.

7.2.3. General procedure for the preparation of α,α-diethyl phenylethylamines 7-9

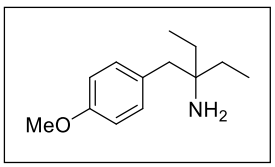
A 3M solution of ethyl magnesium bromide in diethyl ether (14 mL, 41 mmol) was added dropwise to a suspension of 2-phenylacetonitrile (1.2 mL, 10.24 mmol) and titanium (IV) isopropoxide (3.4 mL, 11.26 mmol) in diethyl ether (20 mL) at 0 ºC. The reaction was allowed to room temperature and stirred for 1 h, then it was cooled to 0 ºC and a 10% aqueous solution of NaOH (10 mL) was added. The heterogeneous solution was stirred at room temperature for 30 minutes then filtered through a pad of celite.
The biphasic mixture was extracted twice with diethyl ether then the collected organic phases were extracted several times with an aqueous 2 N solution of HCl. After that the aqueous layer was basified to pH 10-12 with sodium carbonate and extracted several times with dichloromethane. The organic solution was finally dried over anhydrous Na_2SO_4, filtered and the solvent eliminated at reduced pressure to afford pure 3-benzylpentan-3-amine as a colorless oil (1.00 g, 55%).

3-Benzylpentan-3-amine (7)



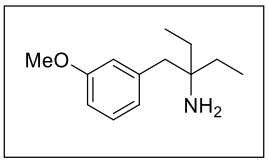
Colorless oil, 55% from 2-phenylacetonitrile (1.20 mL). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.31-7.18 (m, 5H, Ar*H*), 2.63 (s, 2H, ArCH_2), 1.36 (m, 4H, 2 CH_2CH$_3$), 0.91 (t, *J* = 7.5 Hz, 6H, 2 CH$_2$CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 138.2, 130.6, 127.9, 126.1, 54.1, 45.8, 31.3, 8.1. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$($C_{12}H_{20}N$): 178.1590, found: 178.1594

3-(4-Methoxybenzyl)-pentan-3-amine (8)



Colorless oil, 60% from 2-(4-methoxyphenyl)acetonitrile (0.082 g). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.11 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.83 (d, *J* = 8.7 Hz, 2H, Ar*H*), 3.79 (s, 3H, OCH_3), 2.58 (s, 2H, ArCH_2), 1.43-1.26 (m, 4H, 2 CH_2CH$_3$), 0.90 (t, *J* = 7.5 Hz, 6H, 2 CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 156.1, 131.4, 130.0, 113.4, 55.2, 54.1, 44.7, 31.1, 8.0. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$($C_{13}H_{22}NO$): 208.1696, found: 208.1695

3-(3-Methoxybenzyl)-pentan-3-amine (9)



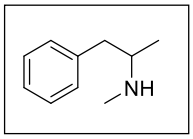
Colorless oil, 42% from 2-(3-methoxyphenyl)acetonitrile (0.082 g). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.23-7.17 (m, 1H, Ar*H*), 6.80-6.73 (m, 3H, Ar*H*), 3.80 (s, 3H, OCH_3), 2.61 (s, 2H, ArCH_2), 1.46-1.30 (m, 4H, 2 CH_2CH$_3$), 0.91 (t, *J* = 7.5 Hz, 6H, 2 CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 159.3, 128.9, 123.1, 116.5, 111.3, 55.1, 45.6, 31.1, 8.04. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$($C_{13}H_{22}NO$): 208.1696, found: 208.1695

7.2.4. General procedure for the preparation of *N*-methylamines 10-11

Titanium(IV) isopropoxide (5 mL, 19.5 mmol) was added to a commercially available solution of methylamine in ethanol (6 mL, 45 mmol) followed by the addiction of phenyl acetone (2 mL, 15 mmol). The solution was stirred at room temperature for 5

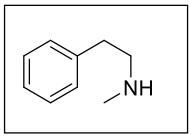
hours then sodium borohydride (570 mg, 15 mmol) and methanol (6 mL) were added and the resulting mixture was stirred for 2 additional hours. The reaction was quenched with water, the precipitate was eliminated by filtration and washed with diethyl ether. The filtrate was added to a separatory funnel, the organic layer was separated and the aqueous phase was extracted several times with diethyl ether.
The collected organic phases were extracted three times with a 2 M aqueous solution of hydrochloric acid then the combined acidic aqueous fractions were basified until pH 10 by slow addiction of a 10% w/v aqueous solution of NaOH and extracted three times with ether. The collected organic extracts were dried over anhydrous Na_2SO_4 and concentrated to give the pure amine as a colorless oil (1.79 g, 80%).

***N*-Methyl-1-phenylpropan-2-amine (11)**



Colorless oil, 80% from phenyl acetone (2.00 mL). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.30-7.25 (m, 2H, Ar*H*), 7.23-7.15 (m, 3H, Ar*H*), 2.85-2.75 (m, 1H, $ArCH_2CH$), 2.71 (dd, *J* = 13.2, 7.0 Hz, 1H, ArCH*H*), 2.61 (dd, *J* = 13.2, 6.2 Hz, 1H, ArCH*H*), 2.39 (s, 3H, NCH_3), 1.05 (d, *J* = 6.1 Hz, 3H, $NCHCH_3$). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 139.5, 129.3, 128.4, 126.2, 56.4, 43.4, 34.0, 19.7. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{10}H_{16}N$): 150.1277, found: 150.1275.

***N*-Methyl-2-phenylethan-1-amine (10)**

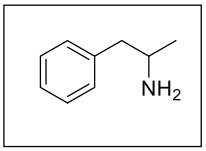


Colorless oil, 57% from phenyl acetaldehyde (0.980 mL). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.31-7.20 (m, 5H, Ar*H*), 2.85-2.76 (m, 4H, $ArCH_2CH_2N$), 2.43 (s, 3H, NCH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 140.1, 128.7, 128.4, 161.1, 53.3, 36.4, 36.3. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$($C_9H_{14}N$): 136.1121, found: 136.1129.

7.2.5. Preparation of 1-phenylpropan-2-amine (12)

Phenylacetone (0.50 mL, 3.75 mmol) was dissolved in methanol (10 mL) then ammonium acetate (2.89 g, 37.5 mmol) and sodium cyanoborohydride (236 mg, 3.75 mmol) were added. The mixture was stirred overnight at room temperature, then a 2 N aqueous solution of HCl was added carefully and the heterogeneous solution was stirred for 1 hour. After that the methanol was evaporated at reduced pressure and the resultant aqueous solution was washed twice with CH_2Cl_2, basified to pH 10-11 with Na_2CO_3 and extracted several times with CH_2Cl_2. The collected basic organic phases were dried over anhydrous $MgSO_4$, filtrated and the solvent was evaporated to afford the pure amphetamine (230 mg, 46%).

1-Phenylpropan-2-amine (12)



Colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.36-7.15 (m, 5H, Ar*H*), 3.21-3.14 (m 1H, $ArCH_2CH$) 2.72 (dd, *J*= 13.3, 5.4 Hz, 1H, ArC*H*H), 2.53 (dd, *J*= 13.3, 8.0 Hz, 1H, ArC*H*H),1.13 (d, *J*= 6.3 Hz, 3H, CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 135.8, 129.3, 128.9, 127.3, 49.8,

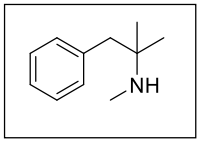
41.1, 18.1. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_9H_{14}N)$: 136.1121, found: 136.1119.

7.2.6. Preparation of *N*,2-dimethyl-1-phenylpropan-2-amine (13)

A solution of amine **1** (300 mg, 2 mmol) in dry ethyl ether (5 mL) was cooled to 0 ºC and treated with triethylamine (0.285 mL, 2.04 mmol). Ethyl chloroformate was added dropwise and the mixture was stirred at room temperature for 3.5 hours under nitrogen. Water was added and the product was extracted three times with diethyl ether. The collected organic extracts were dried over $MgSO_4$ and concentrated to give the crude carbamate that was purified by flash silica gel chromatography (hexane/ethyl acetate) to give the pure compound (274 mg, 62%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.05 (m, 5H, Ar*H*), 4.04 (q, *J* = 7.1 Hz, O*CH*$_2$CH$_3$), 2.69 (s, 2H, ArC*H*$_2$), 1.21 (s, 6H, 2 C*H*$_3$), 1.18 (t, *J* = 7.1 Hz, 3H, OCH$_2$*CH*$_3$)).

A solution of carbamate (274 mg, 1.24 mmol) in dry THF (5 mL) was treated carefully with a solution of $LiAlH_4$ (114 mg, 3 mmol) in dry THF (3 mL) and the mixture was heated to reflux 4 hours under nitrogen. Water was added carefully, the precipitate was filtered off and the solution was made acidic to pH 2 with conc. hydrochloric acid. The solvent was removed at reduced pressure and the residue was dissolved in water and washed with diethyl ether. The aqueous phase was basified to pH 10 with Na_2CO_3 and extracted three times with diethyl ether. The collected basic organic extracts were dried over Na_2SO_4 and the solvent was eliminated to give the pure amine **13** (100 mg, 50%).

***N*-2-Dimethyl-1-phenylpropan-2-amine (13)**



Colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.30-7.10 (m, 5H, Ar*H*), 2.69 (s, 2H, ArC*H*$_2$), 2.40 (s, 3H, NCH$_3$), 1.05 (s, 6H, 2 C*H*$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 138.4, 130.4, 128.0, 126.1, 53.1, 46.4, 28.8, 26.0. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{11}H_{18}N)$: 164.1434, found: 164.1429

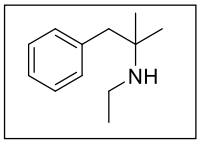
7.2.7. General procedure for the synthesis of *N*-ethyl amines 14-15

Amine **1** (300 mg, 2 mmol) was dissolved in AcOH (3 mL) and acetic anhydride was added. The mixture was stirred at room temperature for 3 hours and heated to reflux for an additional hour. The acetic acid was evaporated to give the crude amide that was directly used for the next step without further purifications.

The residue (2 mmol) was dissolved in dry THF (5 mL) and added via canula to a suspension of $LiAlH_4$ (228 mg, 6 mmol) in dry THF (5 mL). The resulting suspension was heated to reflux for 8 hours under nitrogen and cooled to room temperature. Ice was added carefully and the mixture was extracted three times with ethyl acetate. The combined extracts were washed with a 1 M aqueous solution of NaOH and H_2O. The solvent was evaporated then the residue was dissolved in CH_2Cl_2 and extracted three

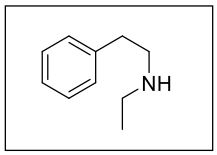
times with a 2 N aqueous solution of HCl. The combined acidic aqueous layers were basified to pH 10 with Na_2CO_3 and extracted with CH_2Cl_2. The collected basic organic phases were dried over anhydrous Na_2SO_4 and the solvent was removedto give the pure amine **14** (290 mg, 82%).

***N*-Ethyl-2-methyl-1-phenylpropan-2-amine (14)**



Colorless oil, 80% from amine **1.** **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.30-7.10 (m, 5H, Ar*H*), 2.72 (s, 2H, ArC*H*$_2$), 2.70 (q, *J* = 7.0 Hz, 2H, NC*H*$_2$CH$_3$), 1.11 (t, *J* = 7.0 Hz, 3H, NCH$_2$C*H*$_3$), 1.07 (s, 6H, 2 C*H*$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 136.3, 130.5, 128.0, 125.9, 50.8, 44.0, 39.3, 29.6, 16.8. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$($C_{12}H_{20}N$): 178.1590, found: 178.1591.

***N*-Ethyl-2-phenylethan-1-amine (15)**



Colorless oil, 95% from phenethylamine (0.245 g). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.33-7.17 (m, 5H, Ar*H*), 2.91-2.87 (m, 2H, ArCH$_2$C*HH*), 2.88-2.80 (m, 2H, ArC*HH*), 2.67 (q, *J* = 7.2 Hz, 2H, NC*H*$_2$CH$_3$), 1.09 (t, *J* = 7.2 Hz, 3H, NCH$_2$C*H*$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 140.0, 128.7, 128.4, 126.1, 51.0, 43.9, 36.3, 15.1. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$($C_{10}H_{16}N$): 150.1277, found: 150.1281.

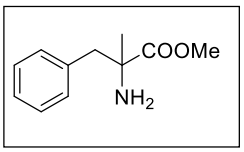
7.2.8. General procedure for the preparation of racemic amino esters 16-17

A suspension formed by alanine methyl ester hydrochloride (4.01 g, 28.12 mmol), 4-chlorobenzaldehyde, and triethylamine in toluene was heated to reflux for 3 hours with a Dean Stark montage. The resulting solution was washed with H_2O, a saturated solution of $NaHCO_3$ and brine. The organic phase was dried over Na_2SO_4 and the solvent was evaporated to obtain the imine as a yellow oil (5.21 g, 88%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (s, 1H, N=C*H*), 7.72 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.39 (d, *J* = 8.5 Hz, 2H, Ar*H*), 4.16 (q, *J* = 6.8 Hz, 1H, C*H*), 3.75 (s, 3H, OC*H*$_3$), 1.53 (d, *J* = 6.8 Hz, 3H, C*H*$_3$)).

A 2.5 M solution of *n*-BuLi in THF (15 mL, 37.53 mmol) was added to a solution of diisopropylamine (5.25 mL, 37.53 mmol) in dry THF (100 mL) at -78 ºC. The mixture was warmed to -40 ºC then the imine (5.20 g, 25.02 mmol) was added dropwise. The solution was stirred for one hour at -40º C then BnBr (5.92 mL, 50.04 mmol) was added dropwise and the mixture was allowed to room temperature and stirred for one hour. After that time the reaction was quenched with a saturated aqueous solution of NH_4Cl and the product was extracted several times with ethyl acetate. The collected organic phases were dried over anhydrous $MgSO_4$ and the solvent was evaporated. The resulting oil was directly used in the next step without purifications.

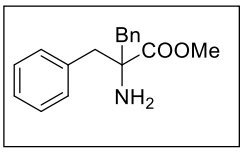
The crude imine (25 mmol) and a 1M aqueous solution of HCl (150 mL) were stirred at room temperature for one hour then diethyl ether was added. The phases were separated and the aqueous layer was washed twice with diethyl ether. Then the aqueous phase was basified to pH 10-11with Na_2CO_3 and extracted three times with diethyl ether. The ethereal phase was washed with water and brine, dried over anhydrous $MgSO_4$ and the solvent was evaporated at reduced pressure to give the pure amine (3.5 g, 62%).

Methyl 2-amino-2-methyl-3-phenylpropanoate (16)



Yellow oil, 54% from alanine methyl ester hydrochloride. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.31-7.13 (m, 5H, Ar*H*), 3.71 (s, 3H, OC*H*$_3$), 3.13 (d, *J* = 13.2 Hz, 1H, ArCH*H*), 2.81 (d, *J* = 13.2 Hz, 1H, ArC*H*H), 1.64 (br s, 2H, N*H*$_2$), 1.40 (s, 3H, C*H*$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 177.4, 136.5, 129.9, 128.3, 126.9, 58.8, 52.0, 46.9, 26.6. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{11}H_{16}NO_2)$: 194.1176, found: 194.1178.

Methyl 2-amino-2-benzyl-3-phenylpropanoate (17)

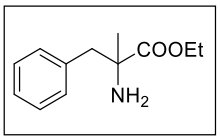


Yellow oil, 30% from phenylalanine methyl ester hydrochloride (4.02 g). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.30-7.16 (m, 10H, Ar*H*), 3.66 (s, 3H, OC*H*$_3$), 3.66 (d, *J* = 13.1 Hz, 2H, 2ArCH*H*), 2.86 (d, *J* = 13.1 Hz, 2H, 2ArC*H*H), 1.57 (br s, 2H, N*H*$_2$). **^{13}C NMR** (101 MHz, $CDCl_3$): δ176.3, 136.2, 129.9, 128.5, 127.1, 63.3, 51.8, 46.4. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{11}H_{16}NO_2)$: 270.1489, found: 270.1486.

7.2.9. Preparation of ethyl 2-amino-2-methyl-3-phenylpropanoate (18)

A suspension of sodium (56 mg, 2.43 mmol) in ethanol (10 mL), was stirred until all the metal was consumed, then a solution of amino ester **16** (134 mg, 0.69 mmol) in ethanol (5 mL) was added and the resulting mixture was stirred overnight at room temperature. The solvent was evaporated then ethyl acetate and water were added. The phases were separated and the aqueous layer was extracted two additional times with ethyl acetate. The collected organic phases were washed with brine, dried over Na_2SO_4, filtered, and the solvent was removed to afford the pure amino ester (140 mg, 98%)

Ethyl 2-amino-2-methyl-3-phenylpropanoate (18)



Brown oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.30-7.23 (m, 3H, Ar*H*), 7.18-7.14 (m, 2H, Ar*H*), 4.19-4.11 (m, 2H, OC*H*$_2$CH$_3$), 3.13 (d, *J* = 13.2 Hz, 1H, ArCH*H*), 2.80 (d, *J* = 13.2 Hz, 1H, ArC*H*H), 1.39 (s, 3H, C*H*$_3$), 1.26 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 177.0, 136.6, 130.0, 128.2, 126.8, 61.0, 58.6, 46.8, 26.7, 14.2. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{12}H_{18}NO_2)$: 208.1332, found: 208.1335.

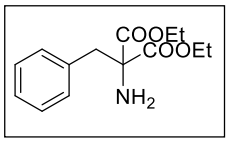
7.2.10. Preparation of diethyl 2-amino-2-benzylmalonate 19

A mixture of the hydrochloric salt of diethyl α-aminomalonate (1.05 g, 5 mmol), benzophenone (910 mg, 5 mmol), *p*-TSA (95 mg, 0,5 mmol) and toluene (50 mL) was heated to reflux overnight using a Dean-Stark montage. Then the solvent was removed under vacuum and the residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate) to give the pure imine intermediate (900 mg, 53%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69-7.18 (m, 10H, Ar*H*), 4.85 (s, 1H, C*H*$(COOEt)_2$), 4.30-4.20 (m, 4H, 2 OC*H*$_2$$CH_3$), 1.28 (t, *J* = 7.2 Hz, 6H, 2 OCH_2C*H*$_3$)).

A 2M solution of LDA in THF (1.6 mL, 3.2 mmol) was diluted with dry THF (50 mL) and cooled to -40º C. Then a solution of imine (1 g, 2.95 mmol) in THF (20 mL) was added dropwise and after the addiction the mixture was stirred for 1 hour at -40º C.
Then benzyl bromide was added at -40º C then the solution was allowed to room temperature and stirred overnight. The solvent was evaporated at reduced pressure and the resulting oil was directly purified by flash column chromatography on silica gel (hexane/ethyl acetate) to give the pure alkylated intermediate (1,14 g, 90%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61-7.58 (m, 2H, Ar*H*), 7.40-7.20 (m, 11H, Ar*H*), 7.15-7.12 (m, 2H, Ar*H*), 3.94-3.75 (m, 4H, 2 OC*H*$_2$$CH_3$), 3.49 (s, 2H, ArC*H*$_2$), 1.11 (t, *J* = 7.1 Hz, 6H, 2 OCH_2C*H*$_3$)).

The intermediate (1,14 g, 2.70 mmol) was added to a mixture of a 2 N aqueous solution of HCl (10 mL) and diethyl ether (50 mL) and the suspension was stirred overnight at room temperature. After that time the phases were separated and the organic layer was extracted twice with a 2 N aqueous solution of HCl. The collected aqueous phases were basified to pH 10-11 with Na_2CO_3 and extracted several time with dichloromethane. The collected basic organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated to give the pure amine (510 mg, 70%).

Diethyl 2-amino-2-benzylmalonate (19)



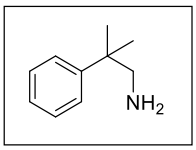
Colorless oil, 33% from diethyl α-aminomalonate hydrochloride. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.31-7.24 (m, 3H, Ar*H*), 7.20-7.16 (m, 2H, Ar*H*), 4.24 (q, *J* = 7.1 Hz, 4 H, 2 OC*H*$_2$$CH_3$), 3.32 (s, 2H, ArC*H*$_2$), 1.84 (br s, 2H, N*H*$_2$), 1.28 (t, *J* = 7.1 Hz, 6H, 2 OCH_2C*H*$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 171.1, 135.1, 130.2, 128.6, 127.4, 66.4, 62.1, 41.8, 14.2. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$($C_{14}H_{20}NO_4$): 266.1387, found: 266.1393.

7.2.11. Preparation of 2-methyl-2-phenylpropan-1-amine (20)

A suspension of NaH (206 mg of a 60% dispersion in mineral oil, 5.16 mmol) in dry THF (10 mL) was cooled to 0º C then 2-phenylacetonitrile (0.200 mL, 1.72 mmol) was added via a syringe and the mixture was stirred at 0º C for 30 minutes. Methyl iodide (0.320 mL, 5.16 mmol) was added and the suspension was stirred 30 minutes at 0º C, allowed to room temperature and stirred for a further 16 hours. Water was added and the

mixture was extracted 3 times with diethyl ether. The collected organic phases were washed with brine, dried over $MgSO_4$, filtered and the solvent was evaporated to give the pure intermediate that was employed directly in the second part of the reaction without further purifications.
A solution of the alkylated nitrile (1.72 mmol) in dry THF (5 mL) was cannulated on a suspension of lithium aluminium hydride (200 mg, 5.16 mmol) and the mixture was stirred for 4 hours at room temperature. Ice was added carefully and once it melted the reaction mixture was filtered through a celite pad. The biphasic solution was acidified until pH 1 with a 36% ww solution of HCl and washed 2 times with diethyl ether. The aqueous phase was then basified to pH 10 with Na_2CO_3 and extracted 2 times with dichloromethane. The collected basic organic phases were dried over Na_2SO_4, filtered and the solvent was removed to obtain the pure amine (243 mg, 95%)

2-Methyl-2-phenylpropan-1-amine (20)

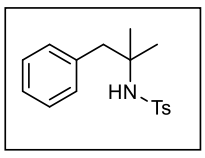


Colorless oil. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.36-7.32 (m, 4H, Ar*H*), 7.22-7.18 (m, 1H, Ar*H*), 2.80 (s, 2H, CH_2NH$_2$), 1.31 (s, 6H, 2 ArCCH_3). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 144.1, 128.9, 127.1, 125.9, 51.1, 37.3, 26.3. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$($C_{10}H_{16}N$): 150.1277, found: 150.1273.

7.2.12 Preparation of 4-methyl-*N*-(2-methyl-1-phenylpropan-2-yl) benzenesulfonamide (21)

Amine **1** (300mg, 2 mmol) and triethylamine (0.310 mL, 2.2 mmol) were dissolved in anhydrous dichloromethane (5 mL) and the solution was cooled to 0º C. A solution of *p*-toluenesulfonyl chloride (419 mg, 2.2 mmol) in dry dichloromethane (3 mL) was added via a canula and the mixture was stirred at the same temperature for 2 hours, allowed to room temperature and stirred for 1 further hour. Then a saturated aqueous solution of $NaHCO_3$ was added and the heterogeneous solution was stirred overnight at room temperature. After that the phases were separated and the aqueous layer was extracted two additional times with dichloromethane. The collected organic phases were washed with water and brine, dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated to afford the pure product (600 mg, 98%)

4-Methyl-*N*-(2-methyl-1-phenylpropan-2-yl) benzenesulfonamide (21)

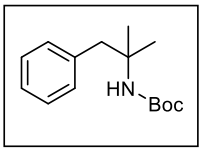


Yellow oil. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.4 Hz, 2H, Ar*H*) 7.34-7.22 (m, 7H, Ar*H*), 4.35 (br s, 1H, N*H*), 2.84 (s, 2H, ArCH_2), 2.41 (s, 3H, ArCH_3), 1.17 (s, 6H, 2 CH_3). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 142.8, 140.6, 136.6, 130.8, 129.4, 128.2, 126.9, 126.7, 56.9, 49.0, 27.3, 21.5. **HRMS (ESI) (m/z)** calcdfor$[M+H]^+$($C_{17}H_{22}NO_2S$): 304.1366, found: 304.1671

7.2.13. Preparation of *tert*-butyl (2-methyl-1-phenylpropan-2-yl)carbamate (22)

Amine **1** (300mg, 2 mmol) was dissolved in anhydrous THF (5 mL) then a solution of di-*tert*-butyl dicarbonate (523 mg, 2.4 mmol) in dry THF (5 mL) was added via a canula and the mixture was stirred at room temperature for 4 hours.
Water was added and the mixture was extracted three times with ethyl acetate. The collected organic extracts were washed with water and brine, dried over Na_2SO_4, filtered and the solvent was evaporated to give the crude carbamate that was purified by flash silica gel chromatography (hexane/ethyl acetate) to remove the excess of Boc (483 mg, 97%).

***Tert*-butyl (2-methyl-1-phenylpropan-2-yl)carbamate (22)**



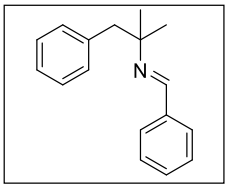
Colorless oil. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.29-7.14 (m, 5H, Ar*H*), 4.26 (br s, 1H, N*H*), 2.98 (s, 2H, ArCH_2), 1.47 (s, 9H, 3 OCCH_3), 1.27 (s, 6H, 2 CH_3). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ154.7, 138.4, 130.4, 127.6, 126.0, 85.5, 52.7, 44.9, 28.8, 27.1. **HRMS (ESI) (m/z)** calcdfor$[M+H]^+$($C_{15}H_{24}NO_2$): 250.1802, found: 250.1803.

7.3. CHAPTER 2: EXPERIMENTAL PART

7.3.1. General procedure for the preparation of imines 23-24

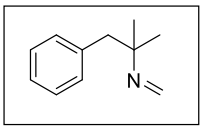
Benzaldehyde (636 mg, 6 mmol) was added to a solution of amine **1** (900 mg, 6 mmol) in toluene (60 mL). The solution was heated to reflux overnight with a Dean-Stark montage then it was cooled to room temperature and dried with $MgSO_4$. The crude mixture was filtered and the solvent was eliminated at reduced pressure to afford the pure product as a yellow oil (1.42 g, 100%).

***N*-(2-Methyl-1-phenylpropan-2-yl)-1-phenylmethanimine (23)**



Yellow oil, 100%. **^{1}H NMR** (400 MHz, $CDCl_3$): 7.99 (s, 1H, N=C*H*), 7.75-7.70 (m, 2H, Ar*H*), 7.42-7.38 (m, 3H, Ar*H*) 7.23-7.13 (m, 5H, Ar*H*), 2.91 (s, 2H, ArCH_2), 1.26 (s, 6H, 2 CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ157.1, 138.1, 136.4, 131.1, 129.8, 128.9, 128.5, 127.1, 125.0, 60.9, 49.6, 26.8. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{17}H_{20}N)$: 238.1590, found: 238.1590.

***N*-(2-Methyl-1-phenylpropan-2-yl)methanimine (24)**



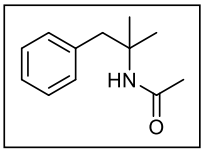
Colorless oil from amine **1** and paraformaldehyde, 100%. **^{1}H NMR** (400 MHz, $CDCl_3$): 7.30-7.10 (m, 7H, 5 Ar*H* + 2 N=C*H*H), 2.81 (s, 2H, ArCH_2), 1.15 (s, 6H, 2 CH_3). **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{11}H_{16}N)$: 162.1277, found: 162.1282.

7.3.2. General procedure for the reaction of amines with azodicarboxylates

Diisopropylazodicarboxylate (200 mg, 1 mmol) was added to a suspension of amine **1** (75 mg, 0.5 mmol), $Cu(OAc)_2{\cdot}H_2O$ (120 mg, 0.6 mmol) and $Pd(OAc)_2$ (11 mg, 0.05 mmol) in acetic acid (3 mL) and the mixture was stirred at 100º C for 6 hours in a sealed vial. After that time the crude was cooled to room temperature and filtered through a pad of celite. The solvent was removed at reduced pressure; the resulting oil was dissolved in dichloromethane and washed with a saturate aqueous solution of Na_2CO_3.

The organic layer was extracted twice with dichloromethane then the collected organic phases were dried with Mg_2SO_4 and filtered. The solvent was evaporated to give a brown oil which was purified by flash silica gel chromatography (hexane/ethyl acetate).

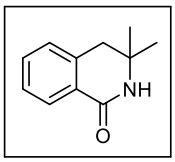
***N*-(2-Methyl-1-phenylpropan-2-yl)acetamide (25)**



Yellow oil, 47% from amine **1**. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.32-7.18 (m, 5H, Ar*H*), 5.05 (br s., 1H N*H*), 3.04 (s, 2H, ArCH_2), 1.90 (s, 3H, COCH_3), 1.32 (s, 6H, 2 CH_3).

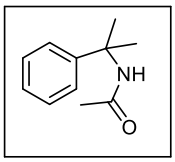
^{13}C-NMR (100 MHz, $CDCl_3$): δ 169.8, 138.1, 130.5, 127.9, 126.3, 54.0, 44.5, 27.4, 24.5. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{12}H_{18}NO)$: 192,1383, found: 192,1386.

3,3-Dimethyl-3,4-dihydroisoquinolin-1(2H)-one (27)



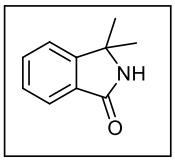
Yellow oil, 20% from amine **1**. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 8.06 (d, J = 7.6 Hz, 1H), 7.45 (dt, J = 1.5, 7.5 Hz, 1H, Ar*H*), 7.35 (m, 1H, Ar*H*), 7.19 (m, 1H, Ar*H*), 5.92 (br s, 1H, N*H*), 2.93 (s, 2H, ArCH_2), 1.32 (s, 6H, 2C H_3). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 165.5, 137.5, 132.3, 127.9, 127.8, 127.8, 127.0, 52.1, 41.6, 28.9. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{11}H_{14}NO)$:176.1070, found: 176.1069.

***N*-(2-Phenylpropan-2-yl)acetamide (28)**



Yellow oil, 61% from commercially available cumylamine (0.068 g).**^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.40-7.20 (m, 5H, Ar*H*), 5.76 (br s, 1H, NH), 1.98 (s, 3H, COCH_3), 1.70 (s, 6H, 2bvCH_3). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 170.6, 147.0, 128.2, 126.3, 124.7, 55.7, 29.2, 23.5. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{11}H_{16}NO)$: 178.1226, found: 178.1234.

3,3-Dimethylisoindolin-1-one (29)



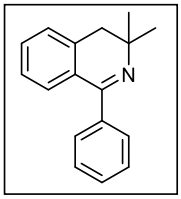
Yellow oil, 26% from commercially available cumylamine (0.068 g).**^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 7.5 Hz, 1H, Ar*H*), 7.56 (dt, *J* = 1.1, 7.5 Hz, 1H, Ar*H*), 7.45 (m, 1H, Ar*H*), 7.20 (m, 1H, Ar*H*), 5.89 (br s, 1H, N*H*), 1.54 (s, 6H, 2 CH_3). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 170.0, 153.1, 130.6, 130.0, 128.0, 123.7, 120.8, 59.1, 27.7. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{10}H_{12}NO)$: 162.0913, found: 162.0916.

7.3.3. Preparation of 3,3-Dimethyl-1-phenyl-3,4-dihydroisoquinoline 26

A 2:1 mixture of benzonitrile and cyclohexane (12 mL) was added dropwise to cooled (0ºC) concentrate sulfuric acid (8 mL). Then 2-methyl-1-phenylpropan-2-ol (500 mg, 3.33 mmol) in cyclohexane (8 mL) was added to the solution.

The mixture was allowed to room temperature and subsequently heated to reflux for 8 hours then it was cooled to room temperature and poured onto ice. After that the solution was neutralized with an aqueous solution (30%) of ammonia and extracted with dichloromethane. The organic layer was washed with brine, dried over sodium sulfate and filtered. The solvent was removed to afford the crude compound which was purified by flash column chromatography on silica gel (hexane/ethtyl acetate) to obtain the pure compound (250 mg, 32%).

3,3-Dimethyl-1-phenyl-3,4-dihydroisoquinoline (26)



White solid (m.p. 118-119 °C) **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.57-7.19 (m, 9H, Ar*H*), 2.81 (s, 2H, ArCH_2), 1.28 (s, 6H, 2 CH_3). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 164.5, 139.3, 137.5, 130.6, 128.9, 128.8, 128.2, 128.1, 128.0, 127.9, 126.4, 54.5, 38.8, 27.6. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{17}H_{18}N)$: 286.1434, found: 286.1433.

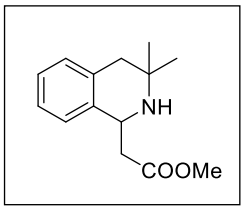
7.4. CHAPTER 3: EXPERIMENTAL PART

7.4.1. General method for the reaction of amines with Michael acceptors

The Michael acceptor (0.65 mmol) was added to a suspension of amine (0.54 mmol), $Pd(OAc)_2$ (12 mg, 0.054 mmol), and Ag_2CO_3 (164 mg, 0.6 mmol) in acetic acid (3 mL). The mixture was stirred at 100 ºC for 3 h in a sealed vial. Toluene was added and the solution was filtered through a pad of celite. The solvents were removed under vacuum. The crude mixture was dissolved in CH_2Cl_2 and a saturated aqueous solution of Na_2CO_3 was added. The aqueous phase was extracted three times with CH_2Cl_2, the collected organic phases were dried over $MgSO_4$, filtered, and the solvent was removed under vacuum. The crude yellow oil was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH or Hexane/AcOEt) to give the corresponding tetrahydroisoquinoline.

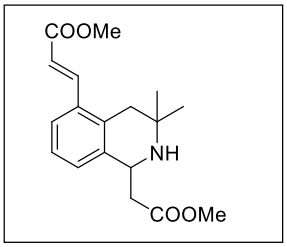
7.4.2. Characterization data for THIQ 30-57

Methyl 2-(3,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (30)



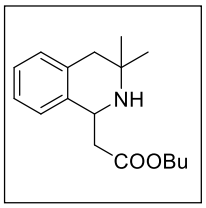
Yellow oil, 60% from amine **1** (0.074 g) and methyl acrylate. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.17-7.03 (m, 4H, Ar*H*), 4.46 (dd, *J* = 8.9, 3.2 Hz, 1H, ArC*H*NH), 3.67 (s, 3H, OCH_3) 3.02 (dd, *J* = 16.4, 8.9 Hz, 1H, ArCHC*H*H), 2.78 (d, *J* = 16.0 Hz, 1H, ArCH*H*), 2.71 (dd, *J* = 16.4, 3.2 Hz, 1H, ArCHC*H*H), 2.51 (d, *J* = 16.0 Hz, 1H, ArCH*H*), 1,24 (s, 3H, CH_3), 1.08 (s, 3H, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 172.9, 135.9, 135.1, 129.6, 126.4, 125.9, 124.8, 51,6, 49.7, 49.1, 42.3, 41.1, 31.5, 24.4. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$($C_{14}H_{19}NO_2$): 234.1489, found: 234.1483.

Methyl (*E*)-3-(1-(2-methoxy-2-oxoethyl)-3,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl)acrylate (31)



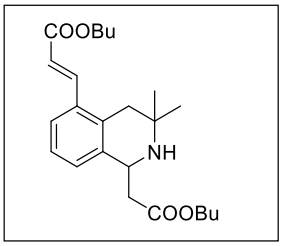
Yellow oil, 5% from amine **1** (0.074 g) and methyl acrylate. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.93 (d, *J* = 15.9 Hz, 1H, C*H*=CH), 7.43 (dd, *J* = 6.7, 2.1 Hz, 1H, Ar*H*), 7.17–7.03 (m, 2H, Ar*H*), 6.32 (d, *J* = 15.9 Hz, 1H, C*H*=CH), 4.48 (dd, *J* = 8.8, 3.3 Hz, 1H, ArC*H*NH), 3.79 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 2.97 (dd, *J* = 16.4, 3.3 Hz, 1H, ArCHC*H*H), 2.78 (d, *J* = 15.9 Hz, 1H, ArCH*H*), 2.66 (dd, *J* = 16.4, 8.8 Hz, 1H, ArCHC*H*H), 2.51 (d, *J* = 16.0 Hz, 1H, ArCH*H*), 1.29 (s, 3H, CH_3), 1.09 (s, 3H, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 172.7, 167.4, 142.2, 137.0, 134.7, 133.9, 129.6, 126.4, 124.8, 119.6, 51.6, 49.7, 48.8, 41.9, 39.3, 31.8, 24.5. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$($C_{18}H_{24}NO_4$): 402.2604, found: 402.2600.

Butyl 2-(3,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (32)



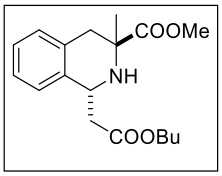
Yellow oil, 90% from amine **1** (0.074 g) and butyl acrylate. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.15-6.98 (m, 4H, Ar*H*), 4.41 (dd, *J* = 8.8, 3.2 Hz, 1H, ArC*H*NH), 4.04 (m, 2H, OCH_2), 2.97 (dd, *J* = 16.2, 3.3 Hz, 1H, ArCHC*H*H), 2.71 (d, *J* = 15.8 Hz, 1H, ArCH*H*), 2.65 (dd, *J* = 16.2, 8.8 Hz, 1H, ArCHC*H*H), 2.48 (d, *J* = 15.8 Hz, 1H, ArCH*H*), 1.89 (br s, 1H, N*H*), 1.56-1.48 (m, 2H, CH_2), 1.34-1.25 (m, 2H, CH_2), 1.20 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 0.87 (t, *J* = 7.3 Hz, 3H, CH_2CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 172.6, 136.3, 135.5, 129.6, 126.3, 125.8, 124.8, 64.4, 49.8, 48.9, 42.4, 41.5, 31.7, 30.6, 24.5, 19.1, 13.7. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{17}H_{25}NO_2)$: 276.1958, found: 276.1954.

Butyl (*E*)-3-(1-(2-butoxy-2-oxoethyl)-3,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl)acrylate (33)



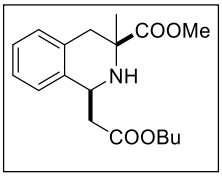
Yellow oil, 10% from amine **1** (0.074 g) and butyl acrylate. Significant **^{1}H NMR** peaks (400 MHz, $CDCl_3$): δ 7.89 (d, *J* = 15.8 Hz, 1H, C*H*=CH), 6.29 (d, *J* = 15.8 Hz, 1H, C*H*=CH). **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{24}H_{36}NO_4)$: 402.2604, found: 402.2600.

***anti*-Methyl 1-(2-butoxy-2-oxoethyl)-3-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (34a)**



Yellow oil, 39% from amine **16** (0.097 g) and butyl acrylate.**^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.15-7.04 (m, 4H, Ar*H*), 4.59 **(**dd, *J* = 9.8, 3.0 Hz, 1H, ArC*H*NH), 4.14 (m, 2H, OCH_2), 3.59 (s, 3H, OCH_3), 3.23 (d, *J* = 15.5 Hz, 1H, ArCH*H*), 2.96 (dd, *J* = 16.4, 3.0 Hz, 1H, ArCHCH*H*), 2.81 (d, *J* = 15.6 Hz, 1H, ArC*H*H), 2.60 (dd, *J* = 16.4, 9.8 Hz, 1H, ArCHC*H*H), 1.66-1.59 (m, 2H, CH_2), 1.44 (s, 3H, CH_3), 1.42-1.36 (m, 2H, CH_2), 0.94 (t, *J* = 7.4 Hz, 3H, CH_2CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 176.3, 172.4, 135.6, 133.9, 128.9, 126.4, 126.2, 125.4, 64.5, 58.4, 52.0, 50.6, 43.1, 38.6, 30.6, 27.7, 19.1, 13.7. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{18}H_{25}NO_4)$: 320.1856, found: 320.1858

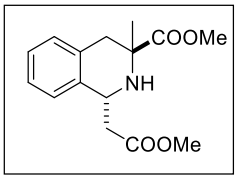
***syn*-Methyl 1-(2-butoxy-2-oxoethyl)-3-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (34b)**



Yellow oil, 39% from amine **16** (0.097 g) and butyl acrylate. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.18-7.09 (m, 4H, Ar*H*), 4.51 **(**dd, *J* = 9.3, 3.3 Hz, 1H, ArC*H*NH), 4.12 (m, 2H, OCH_2), 3.74 (s, 3H, OCH_3), 3.20 (d, *J* = 15.8 Hz, 1H, ArCH*H*), 2.99 (dd, *J* = 16.5, 3.4 Hz, 1H, ArCHCH*H*), 2.80 (d, *J* = 15.6 Hz, 1H, ArC*H*H), 2.70 (dd, *J* = 16.5, 9.2 Hz, 1H, ArCHC*H*H), 2.03 (s, 3H, CH_3), 1.63-1.54 (m, 2H, CH_2), 1.42-1.36 (m, 2H, CH_2), 0.94 (t, *J* = 7.4 Hz, 3H, CH_2CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 176.2, 172.3, 135.8, 133.4, 129.6, 126.6, 126.3, 124.9, 64.5, 57.0, 52.3, 49.4, 41.3, 37.8, 30.6,

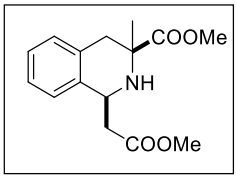
22.5, 19.1, 13.7. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{18}H_{25}NO_4)$: 320.1856, found: 320.1858.

***anti*-Methyl 1-(2-methoxy-2-oxoethyl)-3-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (35a)**



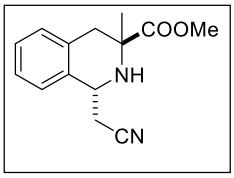
Yellow oil, 29% from amine **16** (0.097 g) and methyl acrylate. **^{1}H NMR (**400 MHz, $CDCl_3$): δ 7.16-7.03 (m, 4H, Ar*H*), 4.62 **(**dd, *J* = 9.9, 3.0 Hz, 1H, ArC*H*NH), 3.73 (s, 3H, OCH_3), 3.59 (s, 3H, OCH_3), 3.23 (d, *J* = 15.5 Hz, 1H, ArCH*H*), 2.97 (dd, *J* = 16.6, 3.0 Hz, 1H, ArCHCH*H*), 2.82 (d, *J* = 15.6 Hz, 1H, ArC*H*H), 2.60 (dd, *J* = 16.6, 9.9 Hz, 1H, ArCHC*H*H), 1.37 (s, 3H, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 176.4, 172.8, 135.6, 133.9, 128.9, 126.4, 126.2, 125.4, 58.4, 52.0, 51.7, 50.6, 43.1, 38.6, 27.7. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{15}H_{19}NO_4)$: 278.1387, found: 278.1397

***syn*-Methyl 1-(2-methoxy-2-oxoethyl)-3-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (35b)**



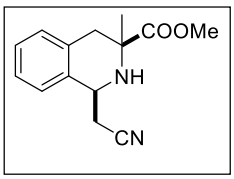
Yellow oil, 29% from amine **16** (0.097 g) and methyl acrylate. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.20-7.10 (m, 4H, Ar*H*), 4.54 (dd, *J* = 9.3, 3.4 Hz, 1H, ArC*H*NH), 3.75 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.21 (d, *J* = 15.8 Hz, 1H, ArCH*H*), 3.00 (dd, *J* = 16.6, 3.4 Hz, 1H, ArCHCH*H*), 2.81 (d, *J* = 15.8 Hz, 1H, ArC*H*H), 2.71 (dd, *J* = 16.6, 9.3 Hz, 1H, ArCHC*H*H), 1.44 (s, 3H, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 176.2, 172.7, 135.8, 133.4, 129.7, 126.7, 126.3, 124.9, 56.9, 52.3, 51.7, 49.4, 41.2, 37.8, 22.7. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{15}H_{19}NO_4)$: 278.1387, found: 278.1397.

***anti*-Methyl 1-(cyanomethyl)-3-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (36a)**



Yellow oil, 29% from amine **16** (0.097 g) and acrylonitrile. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.20-7.04 (m, 4H, Ar*H*), 4.62 (dd, *J* = 7.0, 4.0 Hz, 1H, ArC*H*NH), 3.55 (s, 3H, OCH_3), 3.22 (d, *J* = 15.5 Hz, 1H, ArCH*H*), 2.89 (d, *J* = 15.5 Hz, 1H, ArCH*H*), 2.80 (dd, *J* = 16.4, 4.0 Hz, 1H, ArCHCH*H*), 2.65 (dd, *J* = 16.4, 7.0 Hz, 1H, ArCHCH*H*), 1.46 (s, 3H, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 176.4, 133.9, 133.6, 129.0, 127.2, 126.7, 125.7, 118.1, 58.7, 52.2, 51.0, 38.5, 28.4, 27.5. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{14}H_{16}N_2O_2)$: 245.1285, found: 245.1283

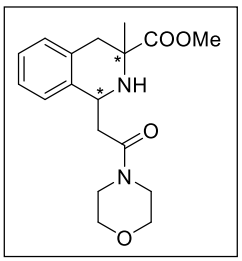
***syn*-Methyl 1-(cyanomethyl)-3-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (36b)**



Yellow oil, 29% from amine **16** (0.097 g) and acrylonitrile. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.25-7.13 (m, 4H, Ar*H*), 4.48 (dd, *J* = 7.6, 4.3 Hz, 1H, ArC*H*NH), 3.79 (s, 3H, OCH_3), 3.25 (d, *J* = 15.8 Hz, 1H, ArCH*H*), 2.90 (dd, *J* = 16.6, 4.4 Hz, 1H, ArCHCH*H*) 2.84 (d, *J* = 15.8 Hz, 1H, ArCH*H*), 2.76 (dd, *J* = 16.6, 7.5 Hz, 1H, ArCHCH*H*), 1.36 (s, 3H, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 175.8, 133.8, 133.4,

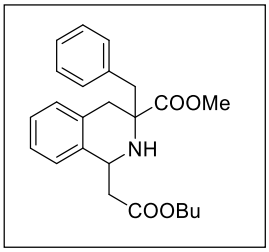
129.9, 127.6, 126.7, 125.0, 117.9, 57.0, 52.5, 49.9, 37.6, 26.4, 23.0. **HRMS (ESI) (m/z)**calcd for $[M+H]^+(C_{14}H_{16}N_2O_2)$: 245.1285, found: 245.1283

Methyl 3-methyl-1-(2-morpholino-2-oxoethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (37)



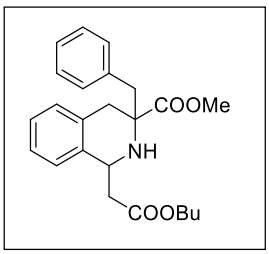
Yellow oil, 55% from amine **16** (0.097 g) and 1-morpholinoprop-2-en-1-one. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.19-7.05 (m, 8H, Ar*H*), 4.68 (m, 2H, ArC*H*NH), 3.75 (s, 3H, OCH_3), 3.67-3.58 (m, 12H, CH_2-morpholine), 3.60 (s, 3H, OCH_3), 3.47-3.35 (m, 4H, CH_2-morpholine), 3.23 (m, 2H, 2 ArC*H*H), 2.91 (m, 2H, 2 ArC*H*H), 2.79 (m, 2H, 2 ArCHC*H*H), 2.69 (dd, *J* = 9.6, 16.1 Hz, 1H, ArCHC*H*H), 2.60 (dd, *J* = 10.1, 16.2 Hz, 1H, ArCHC*H*H), 1.40 (s, 3H, CH_3), 1.34 (s, 3H, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 176.3, 176.2, 170.1, 169.9, 136.0, 134.2, 133.5, 129.9, 129.0, 126.5, 126.3, 126.1, 126.0, 125.5, 125.0, 66.9, 66.8, 66.5, 66.4, 58.2, 56.8, 52.3, 52.0, 50.8, 49.4, 45.7, 42.5, 41.8, 40.9, 38.8, 37.9, 27.7, 22.4. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{18}H_{24}N_2O_4)$: 333.1809, found: 333.1810.

Methyl 3-benzyl-1-(2-butoxy-2-oxoethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (38a)



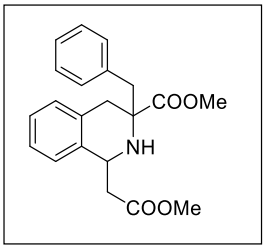
Yellow oil, 17% from amine **17** (0.100 g) and butyl acrylate. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.30-7.10 (m, 9H, Ar*H*), 4.57 **(**dd, *J* = 9.8, 3.7 Hz, 1H, ArC*H*NH), 4.12 (m, 2H, OCH_2), 3.47 (s, 3H, OCH_3), 3.20 (d, *J* = 15.4 Hz, 1H, ArCH*H*), 3.10 (d, *J* = 13.1 Hz, 1H, ArCH*H*), 2.97 (d, *J* = 13.1 Hz, 1H, ArCH*H*), 2.91 (d, *J* = 15.4 Hz, 1H, ArCH*H*), 2.91 (dd, *J* = 15.9, 3.7 Hz, 1H, ArCHCH*H*), 2.58 (dd, *J* = 15.6, 9.8 Hz, 1H, ArC*H*H), 1.61-1.55 (m, 2H, CH_2), 1.39-1.33 (m, 2H, CH_2), 0.93 (t, *J* = 7.4 Hz, 3H, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 175.1, 172.2, 136.1, 135.5, 133.4, 129.9, 128.9, 128.2, 127.1, 126.3, 126.2, 125.5, 64.4, 62.8, 51.6, 50.7, 47.4, 43.9, 37.6, 30.6, 19.1, 13.7. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{24}H_{29}NO_4)$: 396.2169, found: 396.2158.

Methyl 3-benzyl-1-(2-butoxy-2-oxoethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (38b)



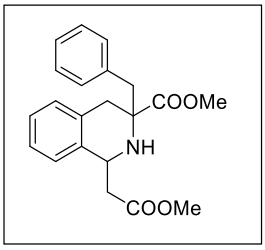
Yellow oil, 17% from amine **17** (0.100 g) and butyl acrylate. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.29-7.08 (m, 9H, Ar*H*), 4.71 (d, *J* = 9.8, 3.2 Hz, 1H, ArC*H*NH), 4.13 (m, 2H, OCH_2), 3.60 (s, 3H, OCH_3), 3.21 (d, *J* = 15.7 Hz, 1H, ArC*H*H), 2.98 (m, 4H, 3 ArCH*H* + ArCHC*H*H), 2.68 (dd, *J* = 16.4, 9.7 Hz, 1H, ArCHC*H*H), 1.63-1.56 (m, 2H, CH_2CH$_2$), 1.40-1.34 (m, 2H, CH$_2$CH_2), 0.93 (t, *J* = 7.4 Hz, 3H, CH$_2$CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 174.6, 172.2, 136.5, 136.2, 133.3, 129.9, 129.7, 129.4, 128.2, 128.2, 126.8, 128.7, 126.4, 125.0, 64.6, 61.9, 51.9, 49.5, 42.3, 41.9, 36.7, 30.6, 19.1, 13.7. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{24}H_{29}NO_4)$: 396.2169, found: 396.2158.

Methyl 3-benzyl-1-(2-methoxy-2-oxoethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (39a)



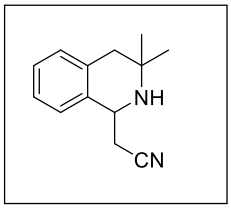
Yellow oil, 28% from amine **17** (0.100 g) and butyl acrylate. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.32-7.01 (m, 9H, Ar*H*), 4.58 (m, 1H, ArC*H*NH), 3.71 (s, 3H, OCH_3), 3.47 (s, 3H, OCH_3), 3.20 (d, *J* = 15.4 Hz, 1H, ArC*H*H), 3.10 (d, *J* = 13.0 Hz, 1H, ArCH*H*), 2.97 (d, *J* = 13.0, 1H, ArC*H*H), 2.91 (d, *J* = 15.3 1H, ArC*H*H), 2.91 (dd, *J* = 16.0, 3.4 Hz, 1H, ArCH_2), 2.58 (dd, *J* = 16.0, 9.8 Hz, 1H, ArCHCH*H*). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 175.1, 172.6, 136.0, 135.5, 133.4, 129.9, 128.9, 128.2, 127.1, 126.4, 126.3, 125.5, 62.8, 51.7, 51.6, 50.7, 47.3, 43.7, 37.6. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{21}H_{24}NO_4)$: 354.1700, found: 354.1690.

Methyl 3-benzyl-1-(2-methoxy-2-oxoethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (39b)



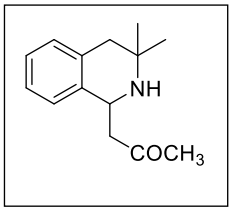
Yellow oil, 28% from amine **17** (0.100 g) and butyl acrylate. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.30-7.19 (m, 9H, Ar*H*), 4.71 (dd, *J* = 9.8, 3.4 Hz, 1H, ArC*H*NH), 3.73 (s, 3H, OCH_3), 3.40 (s, 3H, OCH_3), 3.37 (d, *J* = 13.1 Hz, 1H, ArC*H*H), 3.21 (d, *J* = 15.8 Hz, 1H, ArC*H*H), 3.03 (dd, *J* = 16.4, 3.4 Hz, 1H, ArCHCH*H*), 2.97 (d, *J* = 15.7 Hz, 1H, ArC*H*H), 2.85 (d, *J* = 13.1 Hz, 1H, ArC*H*H), 2.69 (dd, *J* = 16.4, 9.8 Hz, 1H, ArC*H*H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 175.3, 172.8, 135.8, 135.5, 133.2, 130.0, 128.9, 128.2, 127.1, 126.4, 126.3, 125.2, 62.8, 51.7, 51.6, 50.7, 47.3, 43.3, 37.1. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{21}H_{24}NO_4)$: 354.1700, found: 354.1690.

2-(3,3-Dimethyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetonitrile (40)



Yellow oil, 42% from amine **1** (0.149 mg) and acrylonitrile. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.23-7.05 (m, 4H, Ar*H*), 4.40 (dd, *J* = 7.5, 3.8 Hz, 1H, ArC*H*NH), 2.92 (dd, *J* = 16.5, 3.8 Hz, 1H, ArCHC*H*H), 2.82 (d, *J* = 15.7 Hz, 1H, ArCH*H*), 2.72 (dd, *J* = 16.5, 7.5 Hz, 1H, ArCHC*H*H) 2.53 (d, *J* = 15.8 Hz, 1H, ArCH*H*), 1.53 (br s, 1H, N*H*), 1,28 (s, 3H, CH_3), 1.08 (s, 3H, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 135.3, 134.2, 129.9, 127.2, 126.2, 124.8, 118.2, 49.9, 49.4, 42.2, 31.4, 26.5, 24.8. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{13}H_{16}N_2)$: 201.1386, found: 201.1387.

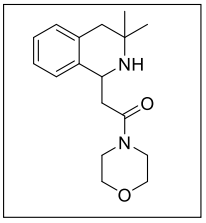
1-(3,3-Dimethyl-1,2,3,4-tetrahydroisoquinolin-1-yl)propan-2-one (41)



Yellow oil, 51% from amine **1** (0.075 mg) and pent-4-ene-2,3-dione. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.17-7.04 (m, 4H, Ar*H*), 4.52 (dd, *J* = 9.0, 3.1 Hz, 1H, ArC*H*NH), 3.12 (dd, *J* = 17.7, 3.1 Hz, 1H, ArCHC*H*H), 2.88 (dd, *J* = 17.6, 9.0 Hz, 1H, ArCHCH*H*), 2.80 (d, *J* = 15.8 Hz, 1H, ArC*H*H), 2.51 (d, *J* = 15.8 Hz, 1H, ArCH*H*), 2.19 (s, 3H, COCH_3), 2.00 (br s, 1H, N*H*), 1.24 (s, 3H, CH_3), 1.11 (s, 3H, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 208.6, 136.3, 135.1, 129.7, 126.3, 125.8, 124.6, 50.7, 49.0, 48.9, 42.3,

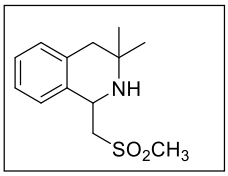
31.4, 40.7, 24.3. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{14}H_{19}NO)$: 218.1539, found: 218.1533.

2-(3,3-Dimethyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-morpholinoethan-1-one (42)



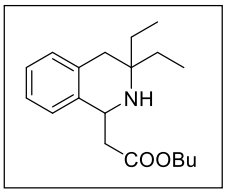
Yellow oil, 42% from amine **1** (0.075 mg) and 1-morpholinoprop-2-en-1-one. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.14-7.02 (m, 4H, Ar*H*), 4.56 (dd, *J* = 9.2, 2.7 Hz, 1H, ArC*H*NH), 3.68-3.39 (m, 8H, 4 CH_2 morpholine), 2.93 (dd, *J* = 16.3, 2.7 Hz, 1H, ArCHCH*H*), 2.82 (d, *J* = 15.8 Hz, 1H, ArCH*H*), 2.67 (dd, *J* = 16.2, 9.2 Hz, 1H, ArCHCH*H*), 2.47 (d, *J* = 15.7 Hz, 1H, ArCH*H*), 1.23 (s, 3H, CH_3), 1.08 (s, 3H, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 170.2, 136.3, 135.2, 129.7, 126.2, 125.7, 124.8, 66.8, 66.4, 49.6, 49.0, 45.7, 42.5, 41.8, 40.5, 31.5, 24.2. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{17}H_{24}N_2O_2)$: 289.1911, found: 289.1915.

3,3-Dimethyl-1-((methylsulfonyl)methyl)-1,2,3,4-tetrahydroisoquinoline (43)



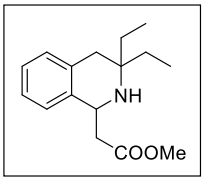
Yellow oil, 55% from amine **1** (0.75 mg) and methylvinyl sulfone. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.23-7.07 (m, 4H, Ar*H*), 4.74 (dd, *J* = 9.3, 1.7 Hz, 1H, ArC*H*NH), 3.60 (dd, *J* = 14.4, 1.7 Hz, 1H, ArCHCH*H*), 3.37 (dd, *J* = 14.4, 9.3 Hz, 1H, ArCHCH*H*), 3.06 (s, 3H, SO_2CH_3), 2.80 (d, *J* = 15.8 Hz, 1H, ArCH*H*), 2.53 (d, *J* = 15.8 Hz, 1H, ArCH*H*), 1.25 (s, 3H, CH_3), 1.10 (s, 3H, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 135.5, 134.3, 130.0, 127.0, 126.3, 125.2, 62.5, 49.1, 49.1, 43.1, 42.2, 31.0, 25.5. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ $(C_{13}H_{20}NO_2S)$: 254.1209, found: 254.1208.

Butyl 2-(3,3-diethyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (44)



Yellow oil, 62% from amine **7** (0.088 g) and butyl acrylate. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.15-7.06 (m, 4H, Ar*H*), 4.35 (dd, *J* = 9.5, 3.1 Hz, 1H, ArC*H*NH), 4.12 (q, *J* = 7.5 Hz, 2H, OCH_2) 3.05 (dd, *J* = 16.2, 3.1 Hz, 1H, ArCHC*H*H), 2.74 (d, *J* = 15.8 Hz, 1H, ArCH*H*), 2.65 (dd, *J* = 16.2, 9.5 Hz, 1H, ArCHC*H*H) 2.54 (d, *J* = 15.8 Hz, 1H, ArCH*H*), 1.64-1.27 (m, 8H, 2 CCH_2CH_3 + CH_2CH_2CH3), 0.93 (t, *J* = 7.4 Hz, 3H, CH_3), 0.92 (t, *J* = 7.5 Hz, 3H, CH_3), 0.85 (t, *J* = 7.5 Hz, 3H, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 172.7, 136.9, 135.1, 129.8, 126.2, 125.6, 124.6, 64.4, 53.3, 48.8, 41.6, 39.2, 32.0, 30.6, 24.5, 19.1, 13.7, 7.5, 7.3. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{19}H_{29}NO_2)$: 304.2271, found: 304.2272.

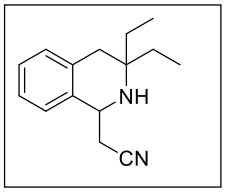
Methyl 2-(3,3-diethyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (45)



Yellow oil, 57% from amine **7** (0.089 g) and methyl acrylate. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.15-7.07 (m, 4H, Ar*H*), 4.37 (dd, *J* = 9.5, 3.1 Hz, 1H, ArC*H*NH), 3.71 (s, 3H, OCH_3), 3.06 (dd, *J* = 16.4, 3.1 Hz, 1H, ArCHC*H*H), 2.74 (d, *J* = 15.9 Hz, 1H, ArCH*H*), 2.65 (dd, *J* = 16.4, 9.5 Hz, 1H, ArCHC*H*H), 2.53 (d, *J* = 15.9 Hz, 1H, ArCH*H*), 2.21 (br s, 1H, N*H*), 1.54-1.30 (m, 4H, 2 CH_2CH_3), 0.91 (t, *J* = 7.6 Hz, 3H, CH_2CH_3), 0.84 (t, *J* = 7.5 Hz, 3H, CH_2CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 173.1, 136.8, 135.1,

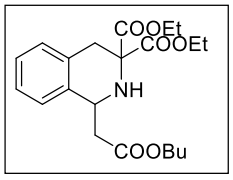
129.8, 126.3, 125.7, 124.6, 53.4, 51.6, 48.8, 41.3, 39.2, 31.9, 24.5, 7.6, 7.3. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{16}H_{23}NO_2)$: 262.1801, found: 262.1802.

2-(3,3-Diethyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetonitrile (46)



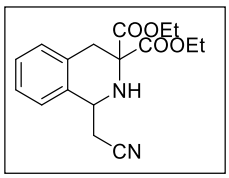
Yellow oil, 42% from amine **7** (0.150 g) and acrylonitrile. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.21-7.09 (m, 4H, Ar*H*), 4.32 (dd, *J* = 7.5, 3.9 Hz, 1H, ArC*H*NH), 2.92 (dd, *J* = 16.5, 3.9 Hz, 1H, ArCHC*H*H), 2.79 (d, *J* = 15.8 Hz, 1H, ArCH*H*), 2.70 (dd, *J* = 16.5, 7.7 Hz, 1H, ArCHC*H*H) 2.55 (d, *J* = 15.8 Hz, 1H, ArCH*H*), 1.66 (br s, 1H, N*H*), 1.57-1.44 (m, 2H, CH_2CH$_3$), 1.44-1.30 (m, 2H, CH_2CH$_3$), 0.95 (t, *J* = 7.5 Hz, 3H, CH_3), 0.82 (t, *J* = 7.5 Hz, 3H, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 135.2, 134.8, 130.0, 127.1, 126.0, 124.7, 118.3, 53.8, 49.3, 38.8, 31.8, 26.6, 25.1, 7.49, 7.48. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{15}H_{20}N_2)$: 229.1697, found: 229.1699

Diethyl 1-(2-butoxy-2-oxoethyl)-1,4-dihydroisoquinoline-3,3(2H)-dicarboxylate (47)



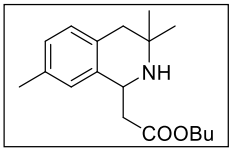
Yellow oil, 73% from amine **19** (0.095 g) and butyl acrylate. **^{1}H NMR** (400 MHz, $CDCl_3$): δ7.20-7.05 (m, 4H, Ar*H*), 4.62 (dd, *J* = 9.6, 3,1 Hz, 1H, ArC*H*NH), 4.30-4.10 (m, 4H, 2 OCH_2), 3.42 (d, *J* = 15.7 Hz, 1H, ArCH*H*), 3.22 (d, *J* = 15.7 Hz, 1H, ArCH*H*), 2.94 (dd, *J* = 16.5, 3.2 Hz, 1H, ArCHCH*H*), 2.66 (dd, *J* = 16.5, 9.6 Hz, 1H, ArCHCH*H*), 1.68-1.58 (m, 2H, CH_2), 1.44-1.34 (m, 2H, CH_2), 1.28 (t, *J* = 7.1 Hz, 3H, CH_3), 1.13 (t, *J* = 7.1 Hz, 3H, CH_3), 0.94 (t, *J* = 7.4 Hz, 3H, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 172.0, 170.3, 169.7, 135.8, 132.4, 128.9, 126.6, 126.5, 125.1, 65.9, 64.5, 62.0, 61.6, 50.5, 42.7, 34.2, 30.6, 19.1, 14.0, 13.7. **HRMS (ESI) (m/z)**calcd for $[M+H]^+(C_{21}H_{30}NO_6)$: 392.2068, found: 392.2073

Diethyl 1-(cyanomethyl)-1,4-dihydroisoquinoline-3,3(2H)-dicarboxylate (48)



Yellow oil, 80% from amine **19** (0.167 g) and acrylonitrile. **^{1}H NMR** (400 MHz, $CDCl_3$): δ7.26-7.08 (m, 4H, Ar*H*), 4.69 (m, 1H, ArC*H*NH), 4.30-4.23 (m, 2H, OCH_2), 4.06 (q, *J* = 7.1 Hz, 2H, OCH_2), 3.43 (d, *J* = 15.7 Hz, 1H, ArCH*H*), 3.31 (d, *J* = 15.7 Hz, 1H, ArCH*H*), 2.79 (dd, *J* = 16.5 4.6 Hz, 1H, ArCHCH*H*), 2.69 (dd, *J* = 16.5, 6.8 Hz, 1H, ArCHCH*H*), 1.30 (t, *J* = 7.1 Hz, 3H, CH_3), 1.07 (t, *J* = 7.1 Hz, 3H, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 170.4, 169.0, 134.0, 132.3, 129.2, 127.5, 127.1. 125.6, 117.8, 66.1, 62.3, 62.0, 51.2, 34.2, 28.1, 14.0, 13.9. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{17}H_{21}N_2O_4)$: 317.1496, found: 317.1491.

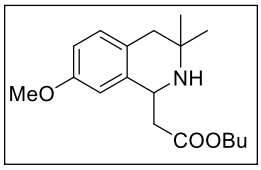
Butyl 2-(3,3,7-trimethyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (49)



Yellow oil, 85% from amine **3** (0.082 g) and butyl acrylate. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.95-6.90 (m, *3*H, Ar*H*), 4.41 (dd, *J* = 8.9, 3.2 Hz, 1H, ArC*H*NH), 4.11-4.06 (m, 2H, OCH_2), 2.99 (dd, *J* = 16.2, 3.2 Hz, 1H, ArCHC*H*H), 2.73 (d, *J* = 15.7 Hz, 1H, ArCH*H*), 2.70 (dd, *J* = 16.2, 8.9 Hz, 1H, ArCHCH*H*), 2.48 (d, *J* = 15.7 Hz, 1H, ArC*H*H), 2.30 (s,

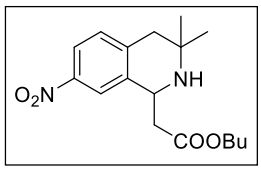
3H, ArC*H*$_3$), 1.63-1.54 (m, 2H, C*H*$_2$CH$_2$), 1.40-1.30 (m, 2H, CH$_2$C*H*$_2$), 1.24 (s, 3H, C*H*3), 1.08 (s, 3H, C*H*3), 0.91 (t, *J* = 7.4 Hz, 3H,CH$_2$C*H*$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 172.6, 135.9, 135.2, 132.2, 129.5, 127.2, 125.4, 64.3, 49.7, 48.9, 42.0, 41.5, 31.6, 30.6, 24.4, 21.2, 19.1, 13.7. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{18}H_{28}NO_2)$: 290.2115, found: 290.2118.

Butyl 2-(7-methoxy-3,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (50)



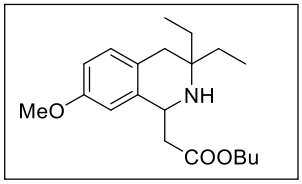
Yellow oil, 70% from amine **2** (0.090 g) and butyl acrylate. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.97 (d, *J* = 8.3 Hz, 1H, Ar*H*), 6.73 (d, *J* = 8.3 Hz, 1H, Ar*H*), 6.67 (s, 1H, Ar*H*), 4.41 (dd, *J* = 8.8, 3.3 Hz, 1H, ArC*H*NH), 4.10-4.07 (m, 2H, OC*H*2), 3.77 (s, 3H, OC*H*$_3$) 2.99 (dd, *J* = 16.2, 3.3 Hz, 1H, ArCHC*H*H), 2.73 (dd, *J* = 16.2, 8.8 Hz, 1H, ArCHCH*H*), 2.67 (d, *J* = 15.5 Hz, 1H, ArCH*H*), 2.47 (d, *J* = 15.5 Hz, 1H, ArC*H*H), 1.61-1.53 (m, 2H, C*H*$_2$CH$_2$), 1.37-1.30 (m, 2H, CH$_2$C*H*$_2$), 1.25 (s, 3H, C*H*3), 1.08 (s, 3H, C*H*3), 0.91 (t, *J* = 7.4 Hz, 3H, CH$_2$C*H*$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 172.5, 157.7, 137.2, 130.4, 127.4, 112.1, 110.3, 64.4, 55.2, 49.0, 49.0, 41.6, 41.4, 31.6, 30.6, 24.3, 19.1, 13.6. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{18}H_{28}NO_3)$: 306.2064, found: 306.2068.

Butyl 2-(3,3-dimethyl-7-nitro-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (51)



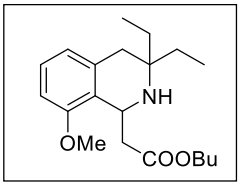
Yellow oil, 70% from amine **5** (0.110 g) and butyl acrylate. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.06 (s, 1H, Ar*H*), 8.01 (d, *J* = 8.3 Hz, 1H, Ar*H*), 7.22 (d, *J* =8.3 Hz, 1H,Ar*H*), 4.49 (dd, *J* = 8.4, 3.3 Hz, 1H, ArC*H*NH), 4.11-4.08 (m, 2H, OC*H*$_2$), 3.06 (dd, *J* = 16.3, 3.3 Hz, 1H, ArCHC*H*H), 2.84 (d, *J* = 16.6 Hz, 1H, ArCH*H*), 2.80 (dd, *J* = 16.3, 8.4 Hz,1H,ArCHCH*H*), 2.65 (d, *J* =16.6 Hz, 1H, ArC*H*H), 1.60-1.56 (m, 2H, C*H*$_2$CH$_2$), 1.37-1.32 (m, 2H, CH$_2$C*H*$_2$), 1.28 (s, 3H, C*H*$_3$), 1.09 (s, 3H, C*H*$_3$), 0.91 (t, *J* = 7.4 Hz, 3H,CH$_2$C*H*$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 171.7, 143.5, 138.0, 137.5, 130.6, 121.4, 120.2, 64.7, 49.7, 48.9, 42.6, 40.9, 31.4, 30.6, 24.4, 19.1, 13.6. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{17}H_{25}N_2O_4)$: 321.1809, found: 321.1820.

Butyl 2-(3,3-diethyl-7-methoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (52)



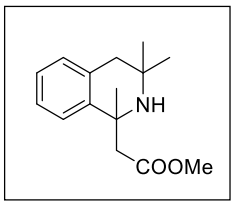
Yellow oil, 54% from amine **8** (0.104 g) and butyl acrylate. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.97 (d, *J* = 8.3 Hz, 1H, Ar*H*), 6.71 (d, *J* = 8.3 Hz, 1H, Ar*H*), 6.63 (s, 1H, Ar*H*), 4.29 (dd, *J* = 9.4, 3.1 Hz, 1H, ArC*H*NH), 4.12-4.08 (m, 2H, OC*H*$_2$), 3.76 (s, 3H, OC*H*$_3$) 3.00 (dd, *J* = 16.2, 3.1 Hz, 1H, ArCHC*H*H), 2.73 (dd, *J* = 16.2, 9.4 Hz, 1H, ArCHCH*H*), 2.73 (d, *J* = 15.5 Hz, 1H, ArCH*H*), 2.46 (d, *J* = 15.5 Hz, 1H, ArC*H*H), 1.64-1.23 (m, 8H, C*H*$_2$C*H*$_2$CH$_3$ + 2 C*H*$_2$CH$_3$), 0.91 (t, *J* = 7.5 Hz, 3H, CH$_2$C*H*$_3$), 0.89 (t, *J* = 7.5 Hz, 3H, CH$_2$CH$_2$C*H*$_3$), 0.82 (t, *J* = 7.5 Hz, 3H, CH$_2$C*H*$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 172.6, 157.6, 137.9, 130.6, 127.2, 112.1, 110.2, 64.4, 55.2, 53.4, 49.0, 41.5, 38.4, 31.9, 30.6, 24.3, 19.1, 13.7, 7.5, 7.3. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{20}H_{32}NO_3)$: 334.2377, found: 334.2383.

Butyl 2-(3,3-diethyl-8-methoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (53)



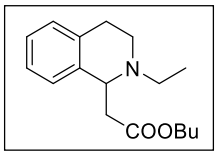
Yellow oil, 52% from amine **9** (0.207 g) and butyl acrylate. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.01 (d, *J* = 8.5 Hz, 1H, Ar*H*), 6.70 (dd, *J* = 8.5, 2.7 Hz, 1H, Ar*H*), 6.60 (d, *J* = 2.7 Hz, 1H, Ar*H*), 4.29 (dd, *J* = 9.4, 3.1 Hz, 1H, ArC*H*NH), 4.12-4.08 (m, 2H, OCH_2), 3.76 (s, 3H, OCH_3) 3.00 (dd, *J* =16.2, 3.1 Hz, 1H, ArCHC*H*H), 2.70 (d, *J* =15.8 Hz, 1H, ArCH*H*), 2.60 (dd, *J*= 16.2, 9.4 Hz, 1H, ArCHCH*H*), 2.49 (d, *J* = 15.8 Hz, 1H, ArC*H*H), 1.64-1.25 (m, 8H, CH_2CH_2CH_3 + 2 CCH_2CH_3), 0.92 (t, *J* = 7.5 Hz, 3H, CH_2CH_3), 0.80 (t, *J* = 7.5 Hz, 3H, CH_2CH_2CH_3), 0.83 (t, *J* = 7.5 Hz, 3H, CH_2CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 172.7, 157.9, 136.5, 129.0, 125.7, 114.3, 111.8, 64.4, 55.1, 53.3, 48.3, 41.6, 39.6, 31.9, 30.6, 24.4, 19.1, 13.6, 7.5, 7.3. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$($C_{20}H_{32}NO_3$): 334.2377, found: 334.2371.

Methyl 2-(1,3,3-trimethyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (54)



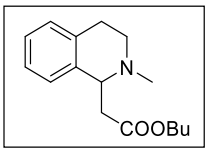
Yellow oil, 27% from amine **1** (0.075 g) and methyl crotonate. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.20-7.10 (m, 3H, Ar*H*), 7.03 (d, *J* = 7.7 Hz, 1H, Ar*H*), 3.54 (s, 3H, OCH_3), 2.75 (s, 2H, ArCCH_2), 2.69 (d, *J* = 15.3 Hz, 1H, ArCH*H*), 2.61 (d, *J* = 15.3 Hz, 1H, ArCH*H*), 1,58 (s, 3H, CCH_3), 1,23 (s, 3H, CH_3), 1.13 (s, 3H, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ170.1, 140.3, 134.7, 129.4, 126.3, 126.2, 125.6, 55.0, 51.3, 49.1, 49.0, 43.3, 32.3, 30.9, 29.2. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$($C_{14}H_{19}NO_2$): 234.1449, found: 234.1483.

Butyl 2-(2-ethyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (55)



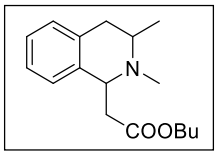
Brown oil, 22% from amine **14** (0.075 g) and butyl acrylate. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.20-7.05 (m, 4H, Ar*H*), 4.30 (dd, *J* = 8.3, 5.7 Hz, 1H, ArC*H*N), 4.11 (m, 2H, OCH_2), 3.17-3.11 (m, 1H, CH*H*), 2.98-2.86 (m, 2H, CH*H*), 2.80 (dd, *J* = 14.8, 8.3 Hz, 1H, ArCHC*H*H), 2.66-2.54 (m, 3H, CH*H* + NCH_2), 2.57 (dd, *J* = 14.8, 5.7 Hz, 1H, ArCHCH*H*), 1.65-1.57 (m, 2H, CH_2), 1.43-1.33 (m, 2H, CH_2), 1.11 (t, *J* = 7.1 Hz, 3H, NCH_2CH_3), 0.93 (t, *J* = 7.4 Hz, 3H, CH_3). **HRMS (ESI) (m/z)** calcd for $[M+H]^+$($C_{17}H_{25}NO_2$): 276.1958, found: 276.1954.

Butyl 2-(2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (56)



Brown oil, 10% from amine **10** (0.068 g) and butyl acrylate. Significant **^{1}H NMR** peaks (400 MHz, $CDCl_3$): δ 4.15 (dd, *J* = 7.1, 5.4 Hz, 1H, ArC*H*N), 4.10-4-06 (m, 2H, OCH_2), 2.60 (dd, *J* = 15.3, 5.4 Hz, 1H, ArCHCH*H*), 2.35 (s, 3H, NCH_3), 1.64-1.56 (m, 2H, CH_2), 1.42-1.30 (m, 2H, CH_2), 0.92 (t, *J* = 7.4 Hz, 3H, CH_3). **HRMS (ESI) (m/z)** calcd for $[M+H]^+$($C_{16}H_{24}NO_2$): 262.1802, found: 262.1805.

Butyl 2-(2,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (57)



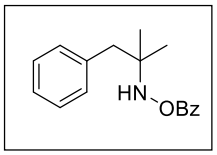
Brown oil, 20% from amine **11** (0.075 g) and butyl acrylate. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.20-7.04 (m, 4H, Ar*H*), 4.23 (dd, *J* = 8.7, 5.6 Hz, 1H, ArC*H*N), 4.12 (m, 2H, OCH_2), 3.25 (ddd, *J* = 10.2, 6.6, 5.2 Hz, 1H, $ArCH_2CH$), 2.85 (m, 1H, ArC*H*H), 2.80 (dd, *J* = 14.9, 8.7 Hz, 1H, ArCHC*H*H), 2.61 (dd, *J* = 18.0, 10.2Hz, 1H, ArCH*H*), 2.60 (dd, *J* = 14.9, 5.6 Hz, 1H, ArCHCH*H*), 2.30 (s, 3H, NCH_3), 1.65-1.55 (m, 2H, CH_2), 1.43-1.33 (m, 2H, CH_2), 1.17 (d, *J* = 6.6 Hz, 3H, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 172.2, 129.2, 128.9, 128.2, 127.4, 126.3, 125.9, 64.22, 61.40, 49.0, 47.0, 41.5, 35.6, 31.0, 19.1, 19.0, 13.7. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$($C_{17}H_{25}NO_2$): 276.1958, found: 276.1962.

7.5. CHAPTER 4: EXPERIMENTAL PART

7.5.1. General procedure for the synthesis of *O*-benzoyl-hydroxylamines 58, 63-65 and 67-69

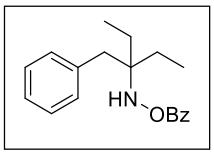
A solution of amine **1** (2.91 g, 19.4 mmol) in DMF (15 mL) was added to a suspension of benzoyl peroxide (3.68 g of a 75% solution in water, 11.4 mmol of oxidant) and K_2HPO_4 (2.98 g, 17.1 mmol) in DMF (60 mL) and the mixture was stirred overnight at room temperature. Water was added and the contents were stirred for several minutes until all solids dissolved. The mixture was extracted with EtOAc and the combined organic phase was washed twice with a saturated aqueous solution of $NaHCO_3$. The combined aqueous fractions were extracted three times with EtOAc then all the organic phases were collected and washed with brine. The organic solution was dried over Na_2SO_4, filtered and the solvent was evaporated to give the crude hydroxylamine that was purified by flash silica gel chromatography (hexane/ethyl acetate) to obtain the desired product as a colorless oil (2.79 g, 90%).

_O_-Benzoyl-_N_-(2-methyl-1-phenylpropan-2-yl)hydroxylamine (58)



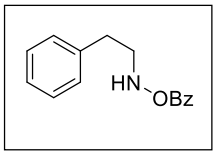
Colorless oil, 90% from amine **1**. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.04 (d, *J* = 7.7 Hz, 2H, Ar*H*), 7.60 (t, *J* = 7.4 Hz, 1H, Ar*H*), 7.48 (t, *J* = 7.7 Hz, 2H, Ar*H*), 7.35-7.20 (m, 5H, Ar*H*), 2.88 (s, 2H, ArCH_2), 1.99 (s, 6H, 2 CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 166.1, 137.5, 133.36, 130.6, 129.5, 128.6, 128.3, 126.7, 58.7, 45.3, 24.6. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{17}H_{20}NO_2$): 270.1489, found: 270.1493.

_O_-Benzoyl-_N_-(3-benzylpentan-3-yl)hydroxylamine (63)



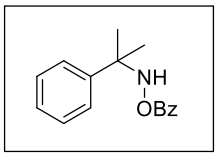
Colorless oil, 76% from amine **7** (1.62 g). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.00 (d, *J* = 7.7 Hz, 2H, Ar*H*), 7.59 (t, *J* = 7.4 Hz, 1H, Ar*H*), 7.50-7.44 (m, 2H, Ar*H*), 7.31-7.21 (m, 5H, Ar*H*), 2.87 (s, 2H, ArCH_2), 1.60-1.40 (m, 4H, 2 CH_2CH$_3$), 0.98 (t, *J* = 7.5, 6H, 2 CH$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$): δ165.8, 136.9, 133.1, 130.5, 129.2, 128.5, 128.2, 126.5, 63.1, 40.3, 25.6, 7.6. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$($C_{19}H_{24}NO_2$): 298.1802, found 298.1806.

O-Benzoyl-_N_-phenethylhydroxylamine (64)



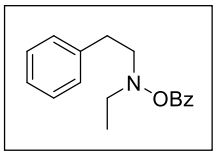
Yellow oil, 60% from commercially available phenethylamine (2.00 mL)**. ^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.00 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.61-7.56 (m,1H, Ar*H*), 7.46 (t, *J* = 7.8 Hz, 2H, Ar*H*), 7.34-7.30 (m, 2H, Ar*H*), 7.26-7.21 (m, 3H, Ar*H*), 3.45 (td, *J* = 7.2, 2.4 Hz, 2H, ArCH$_2$C*HH*), 2.98 (td, *J* = 7.2, 2.1 Hz, 2H, ArCH$_2$C*HH*). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 164.1, 140.4, 133.2, 129.9, 129.2, 128.8 128.5, 128.0, 126.3, 51.3, 33.8. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$($C_{15}H_{16}NO_2$): 242.1176, found 242.1181.

_O_-Benzoyl-_N_-(2-phenylpropan-2-yl)hydroxylamine (65)



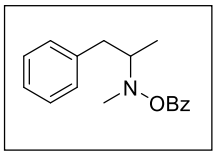
Colorless oil, 100% from commercially available cumyl amine (1 mL)**. ^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.94-7.88 (m, 2H, Ar*H*), 7.57-7.52 (m, 3H, Ar*H*), 7.42-7.34 (m, 4H, Ar*H*), 7.28-7.24 (m, 1H, Ar*H*), 1.60 (s, 6H, 2 CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 166.5, 144.6, 133.2, 129.8, 129.2, 128.4, 128.3, 127.1, 125.7, 60.7, 26.6. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$($C_{16}H_{18}NO_2$): 256.1332, found 256.1327.

_O_-Benzoyl-_N_-ethyl-N-phenethylhydroxylamine (67)



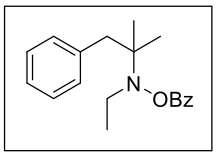
Colorless oil, 92% from amine **14** (0.180 g). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.03 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.60-7.56 (m, 1H, Ar*H*), 7.45 (t, *J* = 7.8 Hz, 2H, Ar*H*), 7.28-7.15 (m, 5H, Ar*H*), 3.26-3.20 (m, 2H, 2 ArCH_2C*H*), 3.10 (q, *J* = 7.1 Hz, 2H, N$CH_2$$CH_3$) 2.96-2.92 (m, 2H, 2 ArC*H*), 1.20 (t, *J* = 7.1 Hz, 3H, NCH_2CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 164.1, 140.0, 133.3, 129.9, 129.4, 128.9 128.4, 128.3, 126.3, 56.0, 49.0, 36.5, 14.1. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$($C_{17}H_{20}NO_2$): 270.1489, found 270.1496

_O_-Benzoyl-_N_-methyl-N-(1-phenylpropan-2-yl)hydroxylamine (68)



Colorless oil, 100% from amine **11** (0.390 g). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.03 (d, *J* = 7.6 Hz, 2H, Ar*H*), 7.60-7.56 (m, 1H, Ar*H*), 7.45 (t, *J* = 7.6 Hz, 2H, Ar*H*), 7.30-7.25 (m, 2H, Ar*H*), 7.21-7.17 (m, 3H, Ar*H*), 3.35-3.27 (m, 1H, ArCH_2C*H*), 3.22 (dd, *J* = 13.2, 3.9 Hz, 1H, ArC*H*), 2.94 (s, 3H, NCH_3), 2.58 (dd, *J* = 13.2, 9.6 Hz, 1H, ArC*H*), 1.20 (d, *J* = 6.4 Hz, 3H, NCHCH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 166.3, 139.6, 133.5, 129.4, 129.15, 128.8, 128.6, 128.2, 126.1, 60.5, 48.1, 34.6, 21.1. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$($C_{17}H_{20}NO_2$): 270.1489, found 270.1488

_O_-Benzoyl-_N_-ethyl-N-(2-methyl-1-phenylpropan-2-yl)hydroxylamine (69)



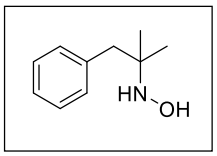
Colorless oil, 100% from amine **15** (0.180 g). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.98 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.53-7.49 (m, 1H, Ar*H*), 7.39 (t, *J* = 7.9 Hz, 2H, Ar*H*), 7.22-7.12 (m, 5H, Ar*H*), 3.08 (q, *J* = 7.0 Hz, 2H, N$CH_2$$CH_3$), 2.84 (s, 2H, Ar$CH_2$), 1.11 (t, *J* = 7.0 Hz, 3H, NCH_2CH_3), 1.05 (s, 6H, 2 CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 165.6, 136.9, 133.4, 130.5, 129.8, 129.4, 128.8, 128.3, 126.5, 58.7, 50.8, 45.3, 24.6, 13.4. **HRMS (ESI) (m/z)**calcd for $[M+H]^+$($C_{19}H_{24}NO_2$): 298.1802, found 298.1796.

7.5.2. General procedure for the synthesis of hydroxylamines

$MgSO_4$ (2.3 g, 19.1 mmol) and *p*-anysaldehyde (0.900 mL, 6.91 mmol) were added to a solution of 2-methyl-1-phenylpropan-2-amine (1.03 g, 6.91mmol) in methanol (25 mL). The solution was stirred overnight, filtered through a celite pad and the solvent evaporated at vacuum. The residue was dissolved in anhydrous CH_2Cl_2 (10 mL), cooled to 0 ºC and a solution of m-CPBA (2.26 g, 70%, 8.3 mmol) in CH_2Cl_2 (30 mL) was added dropwise. The reaction was stirred for one hour at 0 ºC, then allowed to room

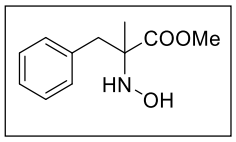
temperature and stirred for a further 3 hours. The resultant suspension was filtered and the solution was washed with saturated aqueous $NaHCO_3$and brine. The organic layer was dried over $MgSO_4$ and the solvent evaporated to yield the oxaziridine intermediate that was directly dissolved in anhydrous MeOH (20 mL), without further purifications. Hydroxylamine hydrochloride (0.960 g, 13.82 mmol) was added and the resultant solution was stirred overnight at room temperature. $CHCl_3$ was added, the suspension was filtered and the solvent evaporated.
Water and diethyl ether were added and the acidic aqueous solution was washed three times with diethyl ether, then saturated with $NaHCO_3$and extracted three times with diethyl ether. The combined basic organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated at reduced pressure to give the crude hydroxylamine that was triturated in hexane to afford the pure compound (0.500 g, 44%).

6.5.3. *N*-(2-Methyl-1-phenylpropan-2-yl)hydroxylamine (59)



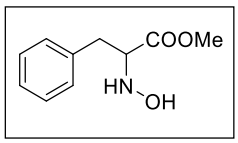
White solid, 44% from amine **1**. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.32-7.21 (m, 5H, Ar*H*), 2.77 (s, 2H, ArCH_2), 1.06 (s, 6H, 2 CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 137.7, 130.5, 128.2, 126.3, 57.5, 43.7, 24.0. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{10}H_{16}NO)$: 166.1226, found 166.1226.

Methyl 2-(hydroxyamino)-2-methyl-3-phenylpropanoate (62a)



White solid, 15% from amine **16** (1.10 g), was purified by recrystallization (Hexane/$CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.32-7.24 (m, 3H, Ar*H*), 7.16-7.13 (m, 2H, Ar*H*), 3.70 (s, 3H, OCH_3), 3.01 (d, *J* = 13.4 Hz, 1H, ArCH*H*), 2.93 (d, *J* = 13.4 Hz, 1H, ArCH*H*), 1.35 (s, 3H, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 174.9, 135.3, 130.1, 128.3, 127.0, 66.9, 52.1, 41.6, 19.8. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{11}H_{16}NO_3)$: 210.1125, found 210.1126

Methylhydroxyphenylalaninate (66a)



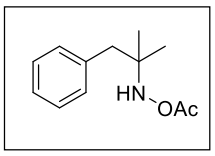
White solid, 39% from commercially available methyl phenylalaninate (2.15 g). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.35-7.15 (m, 5H, Ar*H*), 3.89 (dd, *J* = 8.6, 5.6 Hz, 1H, $ArCH_2CH$), 3.74 (s, 3H, OCH_3), 3.02 (dd, *J* = 13.9, 5.6 Hz, 1H, ArCH*H*), 2.90 (dd, *J* = 13.9, 8.6 Hz, 1H, ArCH*H*). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 177.0, 134.8, 130.4, 128.6, 126.7, 55.5, 51.7, 40.3. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{10}H_{14}NO_3)$: 196.0968, found 196.0963.

7.5.3. General procedure for the acylation of hydroxylamines

N-(2-methyl-1-phenylpropan-2-yl)hydroxylamine (155 mg, 1 mmol) was dissolved in dry CH_2Cl_2, then pyridine (0.120 mL, 1.5 mmol) and acetic anhydride (0.110 mL, 1.2 mmol) were added and the mixture was stirred at room temperature for 5 hours.

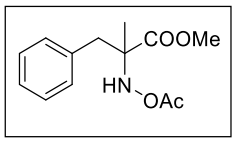
The reaction was quenched with a saturated aqueous solution of NH_4Cl, the organic layer was separated and the aqueous phase was extracted other twice with CH_2Cl_2. The collected organic fractions were dried with Na_2SO_4, filtered and the solvent was removed at vacuum to yield to the crude product that was purified by flash silica gel chromatography (hexane/acetate) to afford the pure acetyl hydroxylamine (140 mg, 71%).

_O_-Acetyl-_N_-(2-methyl-1-phenylpropan-2-yl)hydroxylamine (60)



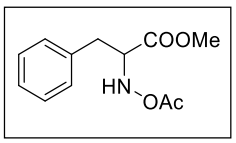
Colorless oil, 71% from **59**. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.30-7.13 (m, 5H, Ar*H*), 2.77 (s, 2H, ArC*H*$_2$), 2.14 (s, 3H, OCOC*H*$_3$) 1.10 (s, 6H, 2 C*H*$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 170.6, 137.0, 130.4, 128.1, 126.5, 58.2, 44.9, 24.4, 19.2. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{18}H_{18}NO_2)$: 208.1332, found 208.1337

Methyl 2-(acetoxyamino)-2-methyl-3-phenylpropanoate (62)



Yellow oil, 94% from **62a** (0.126 g). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.32-7.25 (m, 3H, Ar*H*), 7.16-7.12 (m, 2H, Ar*H*), 3.67 (s, 3H, OC*H*$_3$), 3.01 (m, 2H, ArC*HH*), 2.07 (s, 3H, OCO*CH*$_3$) 1.37 (s, 3H, C*H*$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 174.9, 168.2, 135.6, 129.9, 128.67, 126.7, 67.0, 52.3, 40.9, 19.5, 19.4. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{13}H_{18}NO_4)$: 252.1230, found 252.1228.

Methylacetoxyphenylalaninate (66)



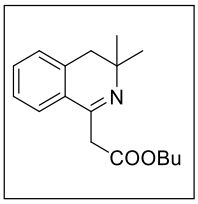
Yellow oil, 90% from **66a** (0.900 g). **^{1}H NMR**(400 MHz, $CDCl_3$): δ 7.30-7.19 (m, 5H, Ar*H*), 4.03 (dd, *J* = 6.5, 5.6 Hz, 1H, ArCH$_2$C*H*), 3.69 (s, 3H, OC*H*$_3$), 3.05 (dd, *J* = 13.0, 5.6 Hz, 1H, ArCH*H*), 3.00 (dd, *J* = 13.0, 6.5 Hz, 1H, ArCH*H*), 2.03 (s, 3H, NHOCOC*H*$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 175.9, 168.4, 136.1, 129.1, 128.2, 126.6, 55.8, 52.1, 41.5, 19.3. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{12}H_{16}NO_4)$: 238.1074, found 238.1081.

7.5.4. General procedure for the reaction of *O*-acylhydroxylamines and hydroxylamines with Michael acceptors

Butyl acrylate (93 µL, 0.65 mmol) was added to a suspension of the *O*-acylhydroxylamine (0.54 mmol) and $Pd_2(dba)_3$ (28 mg, 0.027 mmol) in acetic acid (3 mL). The mixture was stirred at 100 ºC for 3h then toluene was added and the solution was filtered through a pad of celite. The solvents were removed under vacuum then the crude mixture was dissolved in CH_2Cl_2 and a saturated aqueous solution of Na_2CO_3 was added. The phases were separated and the aqueous layer was extracted two additional times with CH_2Cl_2. The collected organic phases were dried over anhydrous Mg_2SO_4, filtered, and the solvent was removed under vacuum.

The crude yellow oil was purified by flash column chromatography on silica gel (hexane/ethyl acetate or dichloromethane/methanol) to give the desired THIQ.

Butyl 2-(3,3-dimethyl-3,4-dihydroisoquinolin-1-yl)acetate (61)



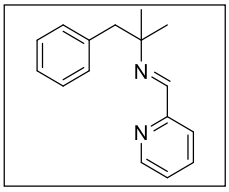
Yellow oil, 10% from hydroxylamine **59** (0.089 g)**.** **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.30-7.15 (m, 4H, Ar*H*), 4.09 (m, 2H, OCH_2), 3.88 (s, 2H, ArCHCH_2), 3.04 (s, 2H, ArCH_2), 1.60-1.50 (m, 2H, CH_2), 1.40 (s, 6H, 2 CH_3), 1.32-1.22 (m, 2H, CH_2), 0.85 (t, *J* = 7.4 Hz, 3H, CH_3). **HRMS (ESI) (m/z)** calcd for $[M+H]^+$($C_{17}H_{23}NO_2$): 274.1802, found: 274.1803.

7.6. CHAPTER 5: EXPERIMENTAL PART

7.6.1 General procedure for the preparation of imines

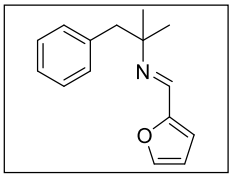
2-Pyridinecarboxaldehyde (570 µl, 6 mmol) was added to a solution of amine **1** (900 mg, 6 mmol) in toluene (60 mL). The solution was heated to reflux overnight with a Dean-Stark montage then it was cooled to room temperature and dried with $MgSO_4$. The crude mixture was filtered and the solvent was eliminated at reduced pressure to afford the pure product as a brown oil (1.43 g, 100%).

_N_-(2-Methyl-1-phenylpropan-2-yl)-1-(pyridin-2-yl)methanimine (70)



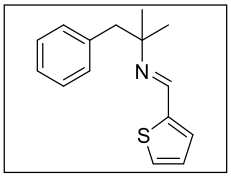
Brown oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8,63-8.61 (m, 1H, Ar*H*), 8.13 (s, 1H, N=C*H*), 8.09-8.06 (m, 1H, Ar*H*), 7.78-7.73 (m, 1H, Ar*H*), 7..32-7.28 (m, 1H, Ar*H*) 7.23-7.13 (m, 5H, Ar*H*), 2.92 (s, 2H, ArCH_2), 1.28 (s, 6H, 2 CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 157.0, 155.4 149.2, 138.3, 136.5, 130.7, 127.6, 126.1, 124.4, 120.8, 60.9, 49.6, 26.8. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$($C_{16}H_{19}N_2$): 239.1543, found: 239.1542

1-(Furan-2-yl)-_N_-(2-methyl-1-phenylpropan-2-yl)methanimine (71)



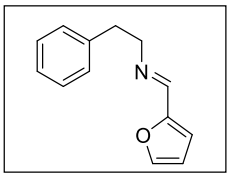
Brown oil, 100% from amine **1** (0.900 g) and furfural. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.77 (s, 1H, N=C*H*), 7.53 (d, *J* = 1.8 Hz, 1H, CH=C*H*O), 7.22-7.10 (m, 5H, Ar*H*), 6.66 (d, *J* = 3.4 Hz, 1H, OC=C*H*), 6.47 (dd, *J* = 3.4, 1.8 Hz, 1H, *CH*=CHO), 2.91 (s, 2H, ArCH_2), 1.24 (s, 6H, 2 CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 152.2, 145.2, 144.4, 138.2, 130.8, 127.6, 126.0, 113.7, 111.4, 60.7, 49.3, 26.8. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$($C_{15}H_{18}NO$): 228.1383, found: 228.1383

_N_-(2-Methyl-1-phenylpropan-2-yl)-1-(thiophen-2-yl)methanimine (72)



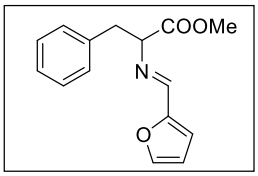
Orange oil, 100% from amine **1** (0.900 g) and 2-thiophenecarboxaldehyde. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.05 (s, 1H, N=C*H*), 7.37 (d, *J* = 5.0 Hz, 1H, CH=C*H*S), 7.22-7.12 (m, 6H, Ar*H* + SC=C*H*), 7.05 (dd, *J* = 5.0, 3.6 Hz, 1H, C*H*=CHS), 2.88 (s, 2H, ArCH_2), 1.24 (s, 6H, 2 CH_3). **HRMS (ESI) (m/z)** calcd for $[M+H]^+$($C_{15}H_{18}NS$): 244.1154, found: 244.1160

1-(Furan-2-yl)-_N_-phenethylmethanimine (77)



Brown oil, 100% from phenethylamine (0.500 mL) and furfural. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.97 (s, 1H, N=C*H*), 7.51 (d, *J* = 1.6 Hz, 1H, CH=C*H*O), 7.32-7.17 (m, 5H, Ar*H*), 6.70 (d, *J* = 3.4 Hz, 1H, OC=C*H*), 6.46 (dd, *J* = 3.4, 1.8 Hz, 1H, *CH*=CHO), 3.83 (m, 2H, ArCH_2), 3.03 (t, *J* = 7.6 Hz, 2H, $ArCH_2CH_2$). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 151.5, 150.0, 144.7, 139.7, 128.9, 128.3, 126.1, 113.9, 111.4, 63.3, 37.4. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$($C_{13}H_{14}NO$): 200.1070, found: 200.1069

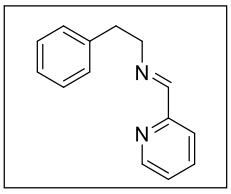
Methyl-2-((furan-2-ylmethylene)amino)-3-phenylpropanoate (79)



Brown oil, 100% from phenylalanine methylester (0.716 g) and furfural.

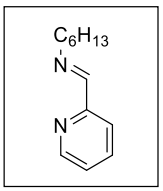
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (s, 1H, N=C*H*), 7.52 (d, *J* = 1.6 Hz, 1H, CH=C*H*O), 7.27-7.16 (m, 5H, Ar*H*), 6.72 (d, *J* = 3.7 Hz, 1H, OC=C*H*), 6.46 (dd, *J* = 3.4, 1.8 Hz, 1H, *CH*=CHO), 4.12 (dd, *J* =8.8, 5.2 Hz, 1H, $ArCH_2CH$), 3.74 (s, 3H, OCH_3) 3.38 (dd, *J* = 13.6, 5.2 Hz, 1H, ArCH*H*), 3.14 (dd, *J* = 13.6, 8.8 Hz, 1H, ArCH*H*). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 171.8, 151.9, 150.9, 145.3, 137.3, 129.7, 128.4, 126.6, 115.4, 111.7, 75.0, 52.3, 39.7. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{15}H_{16}NO_3)$: 258.1125, found: 258.1123

***N*-Phenethyl-1-(pyridin-2-yl)methanimine (88)**



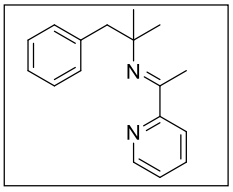
Brown oil, 100% from phenethylamine (1.00 mL) and 2-pyridine carboxaldehyde. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8,64-8.62 (m, 1H, Ar*H*), 8.30 (s, 1H, N=C*H*), 7.97-7.99 (m, 1H, Ar*H*), 7.72-7.77 (m, 1H, Ar*H*), 7.33-7.31 (m, 1H, Ar*H*), 7.29-7.19 (m, 5H, Ar*H*), 3.93 (t, *J* = 7.5 Hz, 2H, $ArCH_2$), 3.04 (t, *J* = 7.5 Hz, 2H, $ArCH_2CH_2$). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 162.3, 154.5, 149.4, 139.7, 136.5, 128.9, 128.4, 126.2, 124.7, 121.2, 62.9, 37.3. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{14}H_{15}N_2)$: 211.1230, found: 211.1226

***N*-Hexyl-1-(pyridin-2-yl)methanimine (90)**



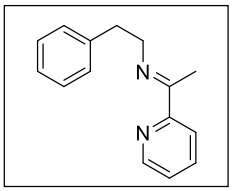
Yellow oil, 100% from hexylamine (0.695 mL) and 2-pyridinecarboxaldehyde (dry toluene at presence of 4 Å molecular sieves was used). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8,65-8.64 (m, 1H, Ar*H*), 8.37 (s, 1H, N=C*H*), 7.99-7.97 (m, 1H, Ar*H*), 7.76-7.71 (m, 1H, Ar*H*), 7.32-7.25 (m, 1H, Ar*H*), 3.67 (q, *J* = 7.0 Hz, 2H, NCH_2), 1.75-1.62 (m, 2H, NCH_2CH_2), 1,39-1.28 (m, 6H, $(CH_2)_3$), 0.39 (t, *J* = 7.0 Hz, 3H, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 161.6, 154.6, 149.3, 136.5, 124.5, 121.1, 61.6, 31.6, 30.6, 27.0, 22.6, 14.0. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{12}H_{19}N_2)$: 191.1543, found: 191.1539

***N*-(2-Methyl-1-phenylpropan-2-yl)-1-(pyridin-2-yl)ethan-1-imine (92)**



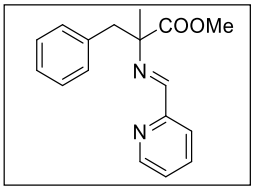
Brown oil, 25% from amine **1** (0.670 g) and 2-acetylpyridine (the product could not be separated from starting materials). Significant **^{1}H NMR** peaks (400 MHz, $CDCl_3$): δ 8.56-8.54 (m, 1H, Ar*H*), 8.10-8.08 (m, 1H, Ar*H*), 7.71-7.67 (m, 1H, Ar*H*), 3.00 (s, 2H, $ArCH_2$), 2.45 (s, 3H, $N=CCH_3$), 3.00 (s, 2H, $ArCH_2$), 1.37 (s, 6H, 2 CH_3).

***N*-Phenethyl-1-(pyridin-2-yl)ethan-1-imine (93)**



Brown oil, 100% from phenethylamine (0.225 mL) and 2-acetylpyridine. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.60-8.57 (m, 1H, Ar*H*), 8.10-8.04 (m, 1H, Ar*H*), 7.74-7.68 (m, 1H, Ar*H*), 7.34-7.18 (m, 6H, Ar*H*), 3.79 (t, *J* = 7.5 Hz, 2H, ArCH_2), 3.09 (t, *J* = 7.5 Hz, 2H, ArCH_2CH_2), 2.28 (s, 3H, N=CCH_3). **HRMS (ESI) (m/z)** calcd for $[M+H]^+$($C_{15}H_{17}N_2$): 225.1386, found: 225.1385

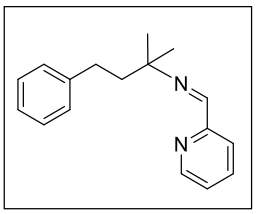
Methyl-2-methyl-3-phenyl-2-((pyridin-2-ylmethylene)amino)propanoate (103)



Brown oil, 100% from amine **16** (0.200 g) and 2-pyridinecarboxaldehyde.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8,65-8.62 (m, 1H, Ar*H*), 8.20 (s, 1H, N=C*H*), 8.10-8.08 (m, 1H, Ar*H*), 7.79-7.74 (m, 1H, Ar*H*), 7.34-7.31 (m, 1H, Ar*H*) 7.28-7.13 (m, 5H, Ar*H*), 3.74 (s, 3H, OCH_3) 3.29 (s, 2H, ArCH_2), 1.47 (s, 3H, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 173.9, 160.6, 154.6, 149.3, 136.7, 136.6, 130.8, 127.8, 126.7, 124.9, 121.3, 69.6, 52.3, 45.5, 22.0. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$($C_{17}H_{19}N_2O_2$): 283.1441, found: 283.1438

***N*-(2-Methyl-4-phenylbutan-2-yl)-1-(pyridin-2-yl)methanimine (104)**



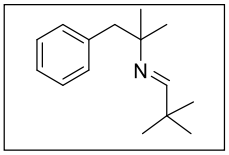
Brown oil, 100% from amine **6** (0.500 g) and 2-pyridinecarboxaldehyde.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8,65-8.62 (m, 1H, Ar*H*), 8.39 (s, 1H, N=C*H*), 8.08-8.05 (m, 1H, Ar*H*), 7.76-7.71 (m, 1H, Ar*H*), 7.31-7.27 (m, 1H, Ar*H*), 7.26-7.13 (m, 5H, Ar*H*), 2.65-2.57 (m, 2H, ArCH_2), 1.97-1.90 (m, 2H, ArCH_2CH_2), 1.35 (s, 6H, 2 CH_3) . **^{13}C NMR** (101 MHz, $CDCl_3$): δ 157.1, 155.5, 149.2, 142.9, 136.5, 128.3, 128.3, 125.6, 124.5, 120.9, 60.0, 45.5, 30.8, 27.1. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$($C_{17}H_{21}N_2$): 253.1699, found: 253.1702

7.6.2 Preparation of 2,2-dimethyl-*N*-(2-methyl-1-phenylpropan-2-yl)propan-1-imine (81)

Pivalaldehyde (750 µl, 6.81mmol) was added to a solution of amine **1** (677 mg, 4.54 mmol) in toluene (60 mL). The solution was heated to reflux overnight with a Dean-Stark montage then it was cooled to room temperature and dried with $MgSO_4$. The crude mixture was filtered and the solvent was eliminated at reduced pressure to afford the crude product, which was purified by flash silica gel chromatography (hexane/ethyl acetate) to afford imine **81** (85 mg, 8%).

2,2-Dimethyl-*N*-(2-methyl-1-phenylpropan-2-yl)propan-1-imine (81)



Yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$): 7.22-7.15 (m, 3H, Ar*H*), δ7.13 (s, 1H, N=C*H*), 7.10-7.07 (m, 2H, Ar*H*) 2.78 (s, 2H, ArCH_2), 1.11 (s, 6H, CH_3), 1.01 (s, 9H, C(CH_3)$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 175.0, 138.1, 128.5, 127.1, 125.0, 60.6, 49.4, 32.9, 27.2,

26.6. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{15}H_{24}N)$: 218.1903, found: 218.1900.

7.6.3. Isolation of complex 74

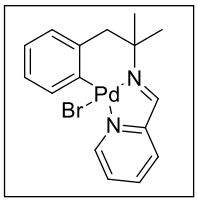
A suspension of imine **72** (144 mg, 0.59 mmol) and $Pd(OAc)_2$ (133 mg, 0.59 mmol) in dry toluene (50 mL) was stirred at room temperature during 96 hours. Then the solution was filtered to eliminate palladium residues and the solvent was eliminated at reduced pressure. The resultant oil was dissolved with acetone, LiCl (100 mg, 2.36 mmol) was added and the suspension was stirred for 2 hours at room temperature. After that time the solution was filtered and the acetone was evaporated to give a dark oil which was purified by flash silica gel chromatography (dichloromethane/methanol). The resultant amorphous solid was triturated in diethyl ether to give complex **74** as a dark solid.

Complex 74
Dark solid. **^{1}H NMR** (400 MHz, $CDCl_3$, Py-d_5): δ 8.17 (s, 1H, N=C*H*), 7.69 (d, *J* =4.9 Hz, 1H, NCHC=C*H*), 7.43 (d, *J* =3.6 Hz, 1H, CH=C*H*S), 7.04 (dd, *J*= 4.9, 3.8 Hz, 1H, C*H*=CHS), 6.89-6.80 (m, 2H, Ar*H*), 6.72-6.65 (m, 2H, Ar*H*), 4.52 (d, 1H, *J* =13.5 Hz ArC*H*H), 2.80 (d, 1H, *J* =13.5 Hz ArCH*H*), 1.74 (s, 3H, CH_3), 1.26 (s, 3H, CH_3).

7.6.4. Isolation of complex 75

Imine **70** (110 mg, 0.46 mmol) and $Pd(OAc)_2$ (103 mg, 0.46 mmol) were dissolved in glacial acetic acid (20 mL) and stirred for 1 hour at 90 ºC. The resulting mixture was filtered and the solution was concentrated under vacuum until obtain a brown solid (107 mg, 60%). The residue (107 mg, 0.27 mmol) was dissolved in acetone and LiBr (92 mg, 1.06 mmol) was added. The suspension was stirred one hour at room temperature then filtered under vacuum. The mother liquor was concentrated until obtain an ochre solid (134 mg, 70%).

Complex 75



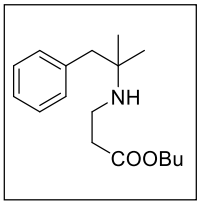
Ochre solid, 42% from imine **70**. **^{1}H NMR** (600 MHz, $CDCl_3$, -40 ºC): δ 9.47 (d, *J* = 5.2 Hz, Ar*H*) 8.60 (s, 1H, N=C*H*), 8.12-8.04 (m, 2H, Ar*H*), 7.86 (d, *J* = 7.7 Hz, 1H, Ar*H*), 7.71 (d, *J* = 6.6 Hz, 1H, Ar*H*), 7.04 (t, *J* = 7.2 Hz, 1H, Ar*H*), 6.94 (t, *J* = 7.9 Hz, 2H Ar*H*), 3.44 (d, *J* = 14.1 Hz, 1H, ArCH*H*), 2.76 (d, *J* = 14.1 Hz, 1H, ArC*H*H), 1.77 (s, 3H, CH_3), 0.94 (s, 3H, CH_3). **MS (ESI) (m/z)** calcd for $[M+Br]^+$ ($C_{16}H_{17}N_2Pd$): 343.0, found: 343.0. **Anal. Calcd** for $C_{16}H_{17}N_2PdBr$: C 45.4%, H 4.0%, N 6.6%. Found C 45.4%, H 4.0%, N 6.4%. **IR** (v, cm^{-1}) 1588.71 (CH=N), 1453.21, 1299.37, 1229.31, 1020.47, 763.69.

7.6.5 General procedure for the reaction of imines with with Michael acceptors

The imine (0.5 mmol) was dissolved in toluene (3 mL), then $Pd(OAc)_2$ (11 mg, 0.05 mmol), Ag_2CO_3 (130 mg, 0.55 mmol) and butyl acrylate (86 µl, 0.6 mmol) were added.

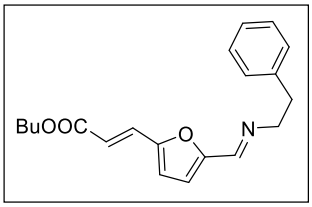
The reaction mixture was stirred at 100º C in a sealed vial then it was filtered through a pad of celite. The solvent was evaporated to give the crude product, which was purified by flash silica gel chromatography (hexane/ethyl acetate).

Butyl 3-[(2-methyl-1-phenylpropan-2-yl)amino]propanoate (76)



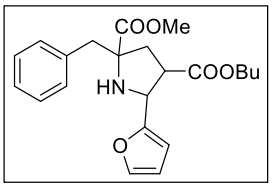
Yellow oil, 35% from amine **1** (0.075 g) and butyl acrylate in $PhCH_3$. Significant **^{1}H NMR** peaks (400 MHz, $CDCl_3$): δ 2.91 (t, *J* = 6.8 Hz, 2H, NHC*H*$_2$), 2.69 (s, 2H, ArC*H*$_2$), 2.49 (t, *J* = 6.8 Hz, 2H, C*H*$_2$COO), 1.05 (s, 6H, 2 C*H*$_3$), 0.93 (t, *J* = 7.3 Hz, 3H, CH_2C*H*$_3$). **HRMS (ESI) (m/z)** calcd for $[M+H]^+$($C_{17}H_{28}NO_2$): 278.2115, found: 278.2115.

Butyl-3-[5-[-(phenethylimino)methyl]furan-2-yl]acrylate (78)



Yellow oil, 50% from imine **77** (0.150 g) and butyl acrylate. **^{1}H NMR**(400 MHz, $CDCl_3$): δ 7.96 (s, 1H, N=C*H*), 7.42 (d, *J* = 15.8 Hz, 1H, CH=C*H*COO), 7.32-7.17 (m, 5H, Ar*H*), 6.78 (d, *J* = 3.6 Hz, 1H, OC=C*H*), 6.66 (d, *J* = 3.6, 1H, OC=C*H*), 6.51 (d, *J* = 15.8 Hz, 1H, C*H*=CHCOO) 4.19 (t, *J* = 6.7 Hz, 2H, ArC*H*$_2$), 4.12 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$) 3.83 (t, *J* = 6.7 Hz 2H, $ArCH_2$C*H*$_2$), 1.70-1.62 (m, 2H, C*H*$_2$$CH_2CH_3$), 1.46-1.36 (m, 2H, C*H*$_2$$CH_3$), 0.96 (t, *J* = 7.4 Hz, 3H, C*H*$_3$). **HRMS (ESI) (m/z)** calcd for $[M+H]^+$($C_{20}H_{24}NO_3$): 326.1751, found: 326.1758.

4-Butyl 2-methyl 2-benzyl-5-(furan-2-yl)pyrrolidine-2,4-dicarboxylate (80)

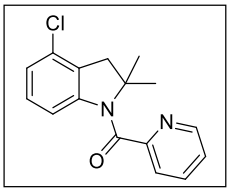


Brown oil, 40% from imine **79** (0.240 g) and butyl acrylate. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.32-7.17 (m, 6H, Ar*H* + OC*H*=CH), 6.23 (dd, *J* = 3.2, 1.8 Hz, 1H, OCH=C*H*), 6.13 (d, *J* = 3.3 Hz, 1H, OC=C*H*), 4.51 (d, *J* = 7.3, Hz, 1H, NHC*H*), 3.88-3.79 (m, 2H, OC*H*$_2$), 3.67 (s, 3H, OC*H*$_3$) 3.09 (dd, *J* = 7.7, 7.3 Hz, 1H, NHCH*CH*), 3.03 (d, *J* = 13,0 Hz, 1H, ArCH*H*), 2.88 (d, *J*= 13,0 Hz, 1H, ArC*H*H), 2.81 (dd, *J* = 13.7, 7.7 Hz, 1H, CCH*H*COOBu), 2.17 (dd, *J* = 13.7, 7.7 Hz, 1H, CC*H*HCOOBu), 1.42-1.34 (m, 2H, C*H*$_2$$CH_2CH_3$), 1.26-1.16 (m, 2H, C*H*$_2$$CH_3$), 0.84 (t, *J* = 7.3 Hz, 3H, C*H*$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 175.9, 172.0, 153.8, 141.6, 136.8, 130.2, 128.0, 126.7, 110.1, 106.6, 69.6, 64.5, 58.7, 52.2, 48.3, 46.8, 36.9, 30.4, 19.0, 13.6. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$($C_{22}H_{28}NO_5$): 386.1962, found: 386.1959

7.6.6. General procedure for the oxidation of imines

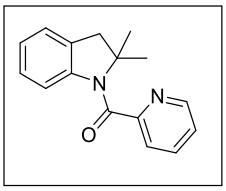
The imine (0.5 mmol) was dissolved in the suitable solvent (3 mL), then $Pd(OAc)_2$ (11 mg, 0.05 mmol) and $PhI(OAc)_2$ (322 mg, 1 mmol) were added. The reaction mixture was stirred at 90º C in a sealed vial then it was filtered through a pad of celite. The solvent was evaporated to give a crude mixture of products, which were purified by flash silica gel chromatography (hexane/ethyl acetate).

(4-Chloro-2,2-dimethylindolin-1-yl)(pyridin-2-yl)methanone (82)



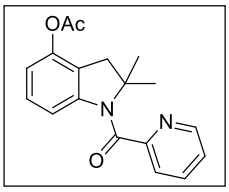
Pale oil**,** 16% from imine **70** (0.120 g) in DCE. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.58 (d, *J* = 4.8 Hz, 1H, Ar*H*), 7.88-7.83 (m, 1H, Ar*H*), 7.69-7.66 (m, 1H, Ar*H*), 7.43-7.40 (m, 1H, Ar*H*) 6.88 (d, *J* = 7.9 Hz, 1H, Ar*H*) 6.77-6.63 (m, 1H, Ar*H*), 5.64 (br s, 1H, Ar*H*), 3.08 (s, 2H, ArCH_2), 1.71 (s, 6H, 2 CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 167.3, 154.4, 149.1, 143.4, 137.3, 131.0, 129.0, 127.8, 125.5, 123.5, 122.9, 114.0, 67.6, 44.5, 26.0. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{16}H_{16}ClN_2O)$: 287.0951, found: 287.0950

(2,2-Dimethylindolin-1-yl)(pyridin-2-yl)methanone (83)



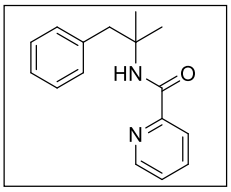
Pale oil**,** 61% from imine **70** (0.120 g). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.60 (d, *J* = 4.5 Hz, 1H, Ar*H*), 7.86-7.81 (m, 1H, Ar*H*), 7.66 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.42-7.38 (m, 1H, Ar*H*) 7.13 (d, *J* = 7.7 Hz, 1H, Ar*H*) 6.90-6.77 (m, 2H, Ar*H*), 5.71 (br m, 1H, Ar*H*), 3.05 (s, 2H, ArCH_2), 1.70 (s, 6H, 2 CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 167.2, 155.0, 149.2, 142.1, 137.2, 130.5, 126.4, 125.3, 125.2, 123.4, 123.1, 115.7, 67.5, 45.5, 25.9. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{16}H_{17}N_2O)$: 253.1335, found: 253.1339.

2,2-Dimethyl-1-picolinoylindolin-4-yl acetate (84)



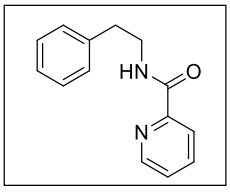
White solid**,** traces from imine **70** (0.120 g). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.62-8.60 (m, 1H, Ar*H*), 7.86-7.82 (m, 1H, Ar*H*), 7.65 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.43-7.40 (m, 1H, Ar*H*) 6.81-6.69 (m, 1H, Ar*H*), 6.64 (d, *J* = 8.1 Hz, 1H, Ar*H*), 5.62 (br m, 1H, Ar*H*), 2.91 (s, 2H, ArCH_2), 2.29 (s, 3H, COCH_3) 1.69 (s, 6H, 2 CH_3). **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{18}H_{19}N_2O_3)$: 311.1351, found: 311.1395.

***N*-(2-Methyl-1-phenylpropan-2-yl)picolinamide (87)**



White solid (m.p. 78-76 ºC), traces from imine **70** (0.120 g). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8,48-8.46 (m, 1H, Ar*H*), 8.22 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.92 (br s, 1H, N*H*), 7.84 (td, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.40-7.36 (m, 1H, Ar*H*), 7.26-7.14 (m, 5H, Ar*H*), 3.19 (s, 2H, ArCH_2), 1.47 (s, 6H, 2 CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 163.6, 150.6, 147.8, 137.9, 137.3, 130.6, 127.9, 126.2, 125.9, 121.7, 53.9, 45.3, 27.0. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{16}H_{19}N_2O)$: 255.1492, found: 255.1488.

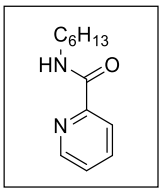
***N*-Phenethylpicolinamide (89)**



White solid (m.p. 138-135 ºC), 15% from imine **88** (0.105 g). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8,50-8.45 (m, 1H, Ar*H*), 8.20-8.18 (m, 1H, Ar*H*), 8.16 (br s, 1H, N*H*), 7.80-7.76 (m, 1H, Ar*H*), 7.37-7.34 (m, 1H, Ar*H*), 7.32-7.19 (m, 5H, Ar*H*), 3.75-3.70 (m, 2H, ArCH_2), 2.93 (t, *J* = 7.3 Hz, 2H, ArCH$_2$CH_2). **^{13}C NMR** (101 MHz, $CDCl_3$):

δ 164.4, 150.0, 148.1, 139.0, 137.4, 128.9, 128.7, 126.6, 126.2, 122.3, 40.9, 36.0. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{14}H_{15}N_2O)$: 227.1779, found: 227.1778.

***N*-Hexylpicolinamide (91)**

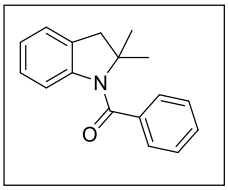


Colorless oil, traces from imine **90** (0.095 g). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8,53-8.51 (m, 1H, Ar*H*), 8.19-8.16 (m, 1H, Ar*H*), 8.04 (br s, 1H, N*H*), 7.84-7.78 (m, 1H, Ar*H*), 7.41-7.37 (m, 1H, Ar*H*), 3.44 (m, 2H, NCH_2), 1.65-1.58 (m, 2H, NCH$_2$CH_2), 1,40-1.26 (m, 6H, (CH_2)$_3$), 0.87 (t, *J* = 7.1 Hz, 3H, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 164.4, 150.0, 147.9, 137.2, 125.9, 122.1, 39.4, 31.5, 29.6, 26.6, 22.5, 14.0. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{12}H_{19}N_2O)$: 207.1492, found: 207.1487.

7.6.7. Preparation of (2,2-dimethylindolin-1-yl)(phenyl)methanone (86)

The amide **83** (120 mg, 0.5 mmol) was dissolved in dry THF (5 mL) and the mixture was cooled to 0 ºC in an ice bath. Then a 1.0 M solution de Super-Hydride in THF (lithium triethylborohydride, 2 mL, 2 mmol) was added dropwise. The solution was allowed to room temperature and stirred for an hour, then THF was evaporated and the crude reaction mixture was purified by flash silica gel chromatography (hexane) to afford pure 2,2-dimethylindoline **85** (55 mg, 75%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06 (d, *J* = 7.2 Hz, 1H, Ar*H*), 7.03-6.98 (m, 1H, Ar*H*), 6.71-6.66 (m, 1H, Ar*H*), 6.57 (d, *J* = 7.7 Hz, 1H, Ar*H*), 2.85 (s, 2H, ArCH_2), 1.33 (s, 6H, CH_3)).
The indoline (44 mg, 0.3 mmol) was dissolved in dry CH_2Cl_2 (2 mL), then trimethylamine (85 µl, 0.6 mmol) and benzoyl chloride (70 µl, 0.6 mmol) were added. The solution was stirred for 5 hours at room temperature then the reaction was quenched with a 1 M solution of NaOH (3 mL). The biphasic mixture was put in a separation funnel, the phases were separated and the aqueous layer was extracted 2 further times with CH_2Cl_2. The collected organic phases were dried with Na_2SO_4 and the solvent was removed. Purification by flash silica gel chromatography (hexane/dichloromethane) led to the pure benzamide (57 mg, 76%)

(2,2-Dimethylindolin-1-yl)(phenyl)methanone (86)



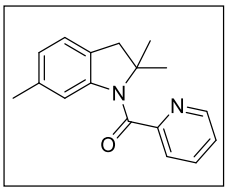
White solid (m.p. 85-83 ºC). **^{1}H NMR** (400 MHz, $CDCl_3$): δ7.57,-7.48 (m, 2H, Ar*H*), 7.47-7.46 (m, 1H, Ar*H*), 7.41-7.37 (m, 2H, Ar*H*), 7.14 (d, *J* = 7.4 Hz, 1H, Ar*H*), 6.87-6.75 (m, 2H, Ar*H*), 7.14 (d, *J* = 8.1 Hz, 1H, Ar*H*), 3.02 (s, 2H, ArCH_2), 1.69 (s, 6H, 2 CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 169.1, 142.8, 137.3, 130.9, 130.3, 128.6, 128.2, 126.4, 125.2, 122.6, 115.9, 67.5, 45.4, 25.7. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ $(C_{17}H_{18}NO)$: 252.1383, found: 252.1383.

7.6.8 General procedure for the direct cyclization of amines

2-pyridine carboxaldehyde (70 µL, 0.75 mmol) was added to a solution of amine **1** (0.075 g, 0.5 mmol) in dry toluene (3 mL) in presence of 4 Å molecular sieves. The

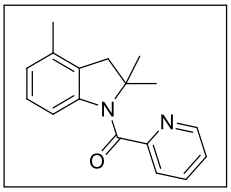
solution was stirred for 4 hours at 80 ºC in a sealed vial, then $Pd(OAc)_2$ (11 mg, 0.05 mmol) and $PhI(OAc)_2$ (322 mg, 1 mmol) were added.
The suspension was stirred overnight at 80 ºC in the sealed vial, then it was filtered through a pad of celite and the solvent was eliminated at reduced pressure.
The crude mixture was purified by flash silica gel chromatography (hexane/ethyl acetate) to afford (2,2-dimethylindolin-1-yl)(pyridin-2-yl)methanone **83** (68 mg, 54%).

Pyridin-2-yl(2,2,6-trimethylindolin-1-yl)methanone (94)



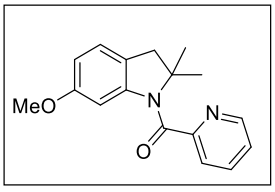
Pale oil, 49% from amine **3** (81.0 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.62-8.60 (m, 1H, Ar*H*), 7.86-7.82 (m, 1H, Ar*H*), 7.64 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.43-7.39 (m, 1H, Ar*H*), 7.01 (d, *J* = 7.5 Hz, 1H, Ar*H*), 6.71 (d, *J* = 7.5 Hz, 2H, Ar*H*), 5.51 (br s, 1H, Ar*H*), 3.00 (s, 2H, ArCH_2), 2.00 (s, 3H, ArCH_3) 1.68 (s, 6H, 2 CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 167.1, 155.1, 149.1, 142.2, 137.2, 136.1, 127.5, 125.0, 124.8, 123.9, 123.4, 116.7, 67.3, 45.2, 25.9, 21.6. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{17}H_{19}N_2O)$: 267.1492, found: 267.1491.

Pyridin-2-yl(2,2,4-trimethylindolin-1-yl)methanone (95)



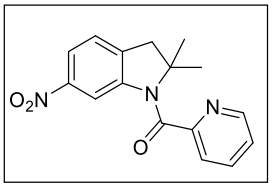
Pale oil, 64% from amine **4** (81 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.58 (d, 1H, *J* = 4.6 Hz, Ar*H*), 7.82-7.81 (m, 1H, Ar*H*), 7.64 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.40-7.38 (m, 1H, Ar*H*) 6.73-6.68 (m, 2H, Ar*H*), 5.51 (br m, 1H, Ar*H*), 2.97 (s, 2H, ArCH_2), 2.20 (s, 3H, ArCH_3) 1.72 (s, 6H, 2 CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 167.2, 155.0, 149.1, 141.7, 137.2, 134.6, 129.2, 126.5, 125.2, 124.1, 123.4, 113.2, 67.1, 44.3, 26.1, 15.6. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{17}H_{19}N_2O)$: 267.1492, found: 267.1494

(6-Methoxy-2,2-dimethylindolin-1-yl)(pyridin-2-yl)methanone (96)



Pale oil, 52% from amine **2** (90 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.65 (d, 1H, *J* = 4.8 Hz, Ar*H*), 7.86-7.82 (m, 1H, Ar*H*), 7.61 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.42-7.38 (m, 1H, Ar*H*), 7.01 (d, *J* = 8.2 Hz, 1H, Ar*H*) 6.44 (dd, *J* = 8.2, 2.2 Hz, 1 H, Ar*H*), 5.30 (br s, 1H, Ar*H*), 3.43 (s, 3H, OCH_3), 2.98 (s, 2H, ArCH_2), 1.69 (s, 6H, 2 CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 167.0, 158.5, 155.0, 149.2, 143.1, 137.3, 125.4, 125.2, 123.4, 122.6, 108.9, 101.6, 68.4, 55.1, 44.8, 25.9. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{17}H_{19}N_2O_2)$: 283.1441, found: 283.1442.

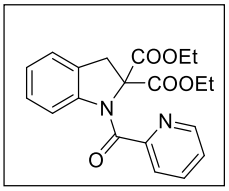
(2,2-Dimethyl-6-nitroindolin-1-yl)(pyridin-2-yl)methanone (97)



Pale oil, 30% from amine **5** (75 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.60-8.56 (m, 1H, Ar*H*), 7.98-7.94 (m, 1H, Ar*H*), 7.80-7.77 (m, 2H, Ar*H*), 7.52-7.49 (m, 1H, Ar*H*), 7.27 (d, *J* = 7.7 Hz, 1H, Ar*H*), 6.58 (br s, 1H, Ar*H*), 3.13 (s, 2H, ArCH_2), 1.72 (s,6H, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 167.4, 153.5,

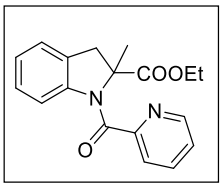
149.1, 147.2, 143.3, 137.9, 126.2, 125.2, 124.0, 123.9, 118.4, 110.7, 68.8, 45.1, 25.8. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{16}H_{16}N_3O_3)$: 298.1186, found: 298.1189.

Diethyl 1-picolinoylindoline-2,2-dicarboxylate (98)



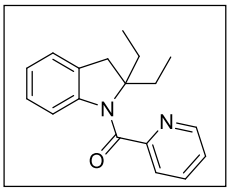
Pale oil, 57% from amine **18** (50 mg). **^{1}H NMR** (400 MHz, $CDCl_3$, 50 ºC): δ 8.49 (br m, 1H, Ar*H*), 8.05 (br m, 1H, Ar*H*), 7.87-7.82 (m, 1H, Ar*H*), 7.40-7.35 (m, 1H, Ar*H*) 7.15 (d, *J* = 7.7 Hz, 1H, Ar*H*), 7.05 (br m, 1H, Ar*H*) 7.04-6.98 (m, 1H, Ar*H*), 4.22-4.08 (br m, 4H, 2 OCH_2), 3.74 (s, 2H, ArCH_2), 1.34-1.02 (br m, 6H, 2 CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$, 45 ºC): δ 206.6, 168.1, 165.5, 152.9, 147.2, 137.2, 127.8, 127.3, 125.4, 124.2, 124.1, 116.9, 75.2, 62.0, 40.9, 13.8. Due to the electronic effect of the pyridine ^{1}H and ^{13}C magnetic nuclear experiments have been carried at 50 and 45 ºC respectively, since a lot of signals were not visible at room temperature. Nonetheless, a quaternary carbon of the phenyl is not visible in the ^{13}C-NMR spectrum as well as the proton in ortho to the amide is not detectable in the ^{1}H-NMR spectrum. All the C-H couplings of not quaternary carbons have been confirmed by an HSQC experiment at 45º C. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{20}H_{21}N_2O_5)$: 369.1445, found: 369.1450.

Ethyl 2-methyl-1-picolinoylindoline-2-carboxylate (99)



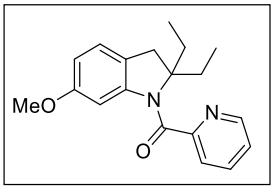
Pale oil, 59% from amine **19** (103 mg). **^{1}H NMR** (400 MHz, $CDCl_3$,): δ 8.62 (br m, 1H, Ar*H*), 7.83 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 7.63 (br m, 1H, Ar*H*), 7.42 (dd, *J* = 7.2, 5.3 Hz, 1H, Ar*H*), 7.14 (d, *J* = 7.7 Hz, 1H, Ar*H*), 6.95-6.75 (m, 2H, Ar*H*), 5.63 (br m, 1H, Ar*H*), 4.19 (br m, 2H, OCH_2), 3.53 (d, *J* = 15.7 Hz, 1H, ArC*H*H), 3.02 (d, *J* = 15.7 Hz, 1H, ArC*H*H), 1.79 (s, 3H, CCH_3), 1.21 (br s, 3H, CH_2CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 172.5, 166.0, 153.7, 149.5, 137.3, 129.4, 127.1, 125.4, 125.2, 123.8, 123.2, 114.7, 69.7, 61.5, 41.7, 21.6, 14.1. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{18}H_{19}N_2O_3)$: 311.1390, found: 311.1385.

(2,2-Diethylindolin-1-yl)(pyridin-2-yl)methanone (100)



Pale oil, 27% from amine **7** (88 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.62 (d, 1H, *J* = 4.6 Hz, Ar*H*), 7.85-7.80 (m, 1H, Ar*H*), 7.61 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.41-7.38 (m, 1H, Ar*H*), 7.12 (d, *J* = 7.3 Hz, 1H, Ar*H*) 6.87-6.71 (m, 2H, Ar*H*), 5.54 (br m, 1H, Ar*H*), 3.10 (s, 2H, ArCH_2), 2.54-2.40 (m, 2H, CH_2CH$_3$), 1.88-1.78 (m, 2H, CH_2CH$_3$), 0.93 (t, *J* = 7.4 Hz, 6H, 2 CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 167.1, 155.0, 149.4, 143.4, 137.2, 131.0, 126.4, 125.0, 124.9, 123.1, 122.9, 114.9, 73.6, 37.9, 30.4, 8.0. **HRMS (ESI) (m/z)** calcd for $[M+H]^+(C_{18}H_{21}N_2O)$: 281.1648, found: 281.1649.

(2,2-Diethyl-6-methoxyindolin-1-yl)(pyridin-2-yl)methanone (101)



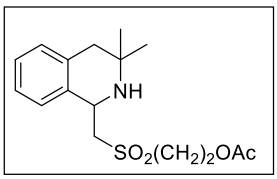
Pale oil, 27% from amine **8** (104 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.65 (d, 1H, *J* = 4.7 Hz, Ar*H*), 7.86,-7.82 (m, 1H, Ar*H*), 7.61 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.42-7.38 (m, 1H, Ar*H*), 6.99 (d, *J* = 8.2 Hz, 1H, Ar*H*) 6.42 (d, *J* = 8.2 Hz, 1H, Ar*H*), 5.12 (br s, 1H, Ar*H*), 3.39 (s, 3H, OCH_3), 3.02 (s, 2H, ArCH_2), 2.55-2.38 (m, 2H, CH_2CH$_3$), 1.86-1.77 (m, 2H, CH_2CH$_3$) 0.94 (t, *J* = 7.4 Hz, 6H, 2 CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 167.0, 158.4, 155.1, 149.4, 144.3, 137.2, 125.0, 125.0, 123.1, 123.1, 108.9, 101.6, 74.5, 55.0, 37.2, 30.5, 8.3. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$($C_{19}H_{23}N_2O_2$): 311.1754, found: 311.1755.

7.7. CHAPTER 6: EXPERIMENTAL PART

7.7.1. General procedure for the reaction of amine 1 with divinyl sulfone

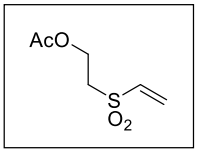
Divinyl sulfone (0,120 mL, 1.2 mmol) was added to a suspension of amine **1** (0.150 g, 1 mmol), $Pd(OAc)_2$ (22 mg, 0.1 mmol), and Ag_2CO_3 (0.303 g, 1.1 mmol) in acetic acid (5 mL). The mixture was stirred at 100 ºC in a sealed vial then toluene was added and the solution was filtered through a pad of celite. The solvents were removed under vacuum then the crude mixture was dissolved in CH_2Cl_2 and a saturated aqueous solution of Na_2CO_3 was added. The aqueous phase was extracted three times with CH_2Cl_2, the collected organic phases were dried over anhydrous Mg_2SO_4, filtered, and the solvent was removed under vacuum. The crude yellow oil was purified by flash column chromatography on silica gel.

2-[[(3,3-Dimethyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl]sulfonyl]ethyl acetate (106)



Yellow oil, 6%. **^{1}H RMN** (400 MHz, $CDCl_3$): δ 7.20-7.07 (m, 4H, Ar*H*), 4.76 (d, *J* = 9.6 Hz, 1H, ArC*H*NH), 4.60-4.50 (m, 2H, C*H*$_2$OAc), 3.65-3.57 (m, 2H, SO_2CH_2), 3.49-3.36 (m, 2H, 2 ArCHCH*H*), 2.79 (d, *J* = 15.8 Hz, 1H, ArCH*H*), 2.52 (d, *J* = 15.8 Hz, 1H, ArCH*H*), 2.07 (s, 3H, C*H*$_3$CO), 1.24 (s, 3H, C*H*$_3$), 1.09 (s, 3H, C*H*$_3$). **^{13}C RMN** (101 MHz, $CDCl_3$): δ 135.4, 134.1, 130.0, 127.1, 126.3, 125.1, 61.9, 57.7, 53.9, 48.8, 42.1, 30.9, 29.7, 25.2, 20.8. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{16}H_{24}NO_4S$): 326.1241, found: 326.1249.

2-(Vinylsulfonyl)ethyl acetate (107)

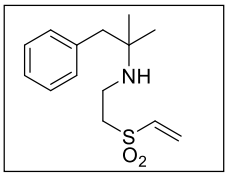


Yellow oil. **^{1}H RMN** (400 MHz, $CDCl_3$): δ 6.67 (dd, *J* = 16.6, 9.8 Hz, 1H, C*H*=CHH), 6.46 (d, *J* = 16.6, 1H, CH=C*H*H), 6.18 (d, *J* = 9.8 Hz, 1H, CH=CH*H*), 4.45 (t, J = 6.1 Hz, 2H, C*H*$_2$OAc), 3.32 (t, J = 6.1 Hz, 2H, SO_2CH_2), 2.06 (s, 3H, C*H*$_3$CO). **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_6H_{11}O_4S$): 179.0373, found: 179.0378.

7.7.2. Preparation of 2-methyl-1-phenyl-*N*-(2-(vinylsulfonyl)ethyl)propan-2-amine (105)

Amine **1** (0.250 g, 1.67 mmol) was dissolved in dry dichloromethane. Divinyl sulfone (0.170 mL, 1.67 mmol) was added by a syringe and the solution was stirred at room temperature for 7 hours. The solvent was evaporated and the crude mixture was purified by flash column chromatography on silica gel (hexane/ethyl acetate) to give the pure alkene (0.323g, 72%).

2-Methyl-1-phenyl-N-(2-(vinylsulfonyl)ethyl)propan-2-amine (105)

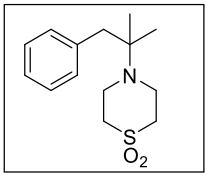


Yellow oil. **^{1}H RMN** (400 MHz, $CDCl_3$): δ 7.33-7.12 (m, 5H, Ar*H*), 6.71 (dd, *J* = 16.6, 9.9 Hz, 1H, C*H*=CHH), 6.40 (d, *J* = 16.6, 1H, CH=C*H*H), 6.09 (d, *J* = 9.9 Hz, 1H, CH=CH*H*), 3.18-3.08 (m, 4H, CH_2CH_2), 2.69 (s, 2H, ArCH_2) 1.08 (s, 6H, 2 CH_3). **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{14}H_{22}NO_2S$): 268.1366, found: 268.1372.

7.7.3. Intramolecular cyclization of 2-methyl-1-phenyl-N-(2-(vinylsulfonyl)ethyl) propan-2-amine

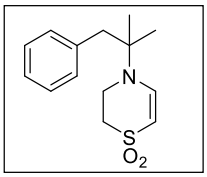
A suspension of compound **105** (0.150 g, 0.56 mmol), $Pd(OAc)_2$ (13 mg, 0.06 mmol), and Ag_2CO_3 (0.170 g, 0.62 mmol) in acetic acid (3 mL) was stirred at 100 ºC in a sealed vial. Toluene was added and the solution was filtered through a celite pad. The solvents were removed under vacuum then the crude mixture was dissolved in CH_2Cl_2 and a saturated aqueous solution of Na_2CO_3 was added. The aqueous phase was extracted three times with CH_2Cl_2, the collected organic phases were dried over anhydrous Mg_2SO_4, filtered, and the solvent was removed under vacuum. The crude yellow oil was purified by flash column chromatography on silica gel.

(2-Methyl-1-phenylpropan-2-yl)thiomorpholine 1,1-dioxide (108)



Colorless oil, 26%. **^{1}H RMN** (400 MHz, $CDCl_3$): δ 7.30-7.10 (m, 5H, Ar*H*), 3.19-3.10 (m, 4H, 2 SO_2CH_2) 3.04-2.97 (m, 4H, 2 NCH_2), 2.72 (s, 2H, ArCH_2) 1.08 (s, 6H, 2 CH_3). **^{13}C RMN** (101 MHz, CDCl3): δ 138.2, 130.4, 127.9, 126.2, 58.1, 52.8, 44.6, 44.5, 24.8. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{14}H_{22}NO_2S$): 268.1366, found: 268.1369.

4-(2-Methyl-1-phenylpropan-2-yl)-3,4-dihydro-2H-1,4-thiazine 1,1-dioxide (109)



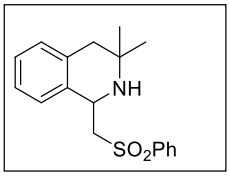
Colorless oil, 25%. **^{1}H RMN** (400 MHz, $CDCl_3$): δ 7.32-7.22 (m, 3H, Ar*H*), 7.10-7.05 (m, 2H, Ar*H*), 6.61 (d, *J* = 9.0 Hz, 1H, SO_2C*H*=CH), 4.99 (d, *J* = 9.0 Hz, 1H, SO_2CH=C*H*), 3.83-3.78 (m, 2H, SO_2CH_2) 3.05-2.99 (m, 2H, NCH_2), 2.79 (s, 2H, ArCH_2) 1.33 (s, 6H, 2 CH_3). **^{13}C RMN** (101 MHz, CDCl3): δ 139.7, 136.1, 130.2, 128.4, 127.1, 93.5, 60.8, 47.6, 46.6, 41.8, 27.1. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{14}H_{20}NO_2S$): 266.1209, found: 266.1216.

7.7.4. General procedure for the synthesis of phenyl sulfones

The phenyl vinyl sulfone (1.6 g, 9.6 mmol) was added to a suspension of amine **1** (1.2 g, 8.0 mmol), $Pd(OAc)_2$ (179 mg, 0.80 mmol), and Ag_2CO_3 (2.4 g, 0.8 mmol) in acetic acid (20 mL). The mixture was stirred at 100 ºC for 16 hours in a sealed vial then toluene was added and the solution was filtered through a pad of celite. The solvents were removed under vacuum then the crude mixture was dissolved in CH_2Cl_2 and a

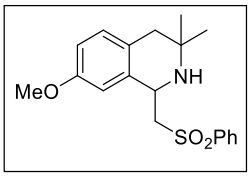
saturated aqueous solution of Na_2CO_3 was added. The aqueous phase was extracted three times with CH_2Cl_2, the collected organic phases were dried over anhydrous Mg_2SO_4, filtered, and the solvent was removed under vacuum.
The crude yellow oil was purified by flash column chromatography on silica gel (hexane/ethyl acetate/triethylamine) to give the desired THIQ **110** (1.96 g, 78%).

3,3-Dimethyl-1-[(phenylsulfonyl)methyl]-1,2,3,4-tetrahydroisoquinoline (110)



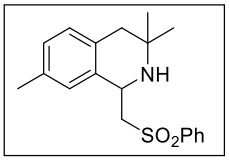
Yellow oil, 78%. **^{1}H RMN** (400 MHz, $CDCl_3$): δ 8.00 (d, *J* = 7.3 Hz, 2H, Ar*H*), 7.66 (t, *J* = 7.4 Hz, 1H, Ar*H*), 7.60 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.15-6.95 (m, 4H, Ar*H*), 4.69 (dd, *J* = 9.3, 1.7 Hz, 1H, ArC*H*NH), 3.72 (dd, *J* = 14.3, 1.7 Hz, 1H, ArCHCH*H*), 3.49 (dd, *J* = 14.3, 9.3 Hz, 1H, ArCHCH*H*), 2.81 (d, *J* = 15.8 Hz, 1H, ArCH*H*), 2.48 (d, *J* = 15.8 Hz, 1H, ArCH*H*), 1.24 (s, 3H, C*H*$_3$), 1.06 (s, 3H, C*H*$_3$). **^{13}C RMN** (101 MHz, $CDCl_3$): δ 139.8, 135.5, 134.0, 133.8, 129.9, 129.3, 128.0, 126.8, 126.0, 125.1, 63.9, 48.9, 48.7, 42.1, 31.2, 24.7. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{18}H_{22}NO_2S$): 316.1366, found: 316.1371.

7-Methoxy-3,3-dimethyl-1-[(phenylsulfonyl)methyl]-1,2,3,4-tetrahydroisoquinoline (111)



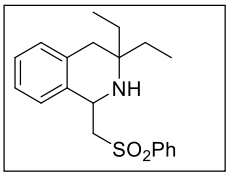
Yellow oil, 58% from amine **2** (0.140 g). **^{1}H RMN** (400 MHz, $CDCl_3$): δ 7.96 (d, *J* = 7.4 Hz, 2H, Ar*H*), 7.65 (t, *J* = 7.4 Hz, 1H, Ar*H*), 7.56 (t, *J* = 7.6 Hz, 2H, Ar*H*), 6.95 (d, *J* = 8.4 Hz, 1H, Ar*H*), 6.69 (d, *J* = 8.4 Hz, 1H, Ar*H*), 6.46 (s, 1H, Ar*H*), 4.63 (dd, *J* = 8.9, 1.6 Hz, 1H, ArC*H*NH), 3.72 (s, 3H, OC*H*$_3$), 3.73 (dd, *J* = 14.3, 1.6 Hz, 1H, ArCHCH*H*), 3.49 (dd, *J* = 14.3, 9.0 Hz, 1H, ArCHCH*H*), 2.71 (d, *J* = 15.4 Hz, 1H, ArCH*H*), 2.41 (d, *J* = 15.4 Hz, 1H, ArCH*H*), 1.21 (s, 3H, C*H*$_3$), 1.03 (s, 3H, C*H*$_3$). **^{13}C RMN** (101 MHz, $CDCl_3$): δ 157.0, 139.8, 135.0, 133.8, 130.7, 129.3, 128.0, 127.6, 112.5, 110.7, 63.9, 55.2, 49.0, 48.9, 41.3, 31.1, 24.6. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{19}H_{24}NO_3S$): 346.1471, found: 346.1468.

3,3,7-Trimethyl-1-[(phenylsulfonyl)methyl]-1,2,3,4-tetrahydroisoquinoline (112)



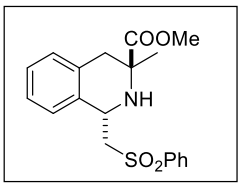
Yellow oil, 50% from amine **3** (0.244 g). **^{1}H RMN** (400 MHz, $CDCl_3$): δ 7.98 (d, *J* = 7.4 Hz, 2H, Ar*H*), 7.65 (t, *J* = 7.4 Hz, 1H, Ar*H*), 7.57 (t, *J* = 7.6 Hz, 2H, Ar*H*), 6.93 (m, *2*H, Ar*H*), 6.73 (s, 1H, Ar*H*), 4.65 (dd, *J* = 9.2, 1.9 Hz, 1H, ArC*H*NH), 3.72 (dd, *J* = 14.3, 1.9 Hz, 1H, ArCHCH*H*), 3.48 (dd, *J* = 14.3, 9.2 Hz, 1H, ArCHCH*H*), 2.75 (d, *J* = 15.6 Hz, 1H, ArCH*H*), 2.43 (d, *J* = 15.6 Hz, 1H, ArCH*H*), 2.23 (s, 3H, ArC*H*$_3$), 1.22 (s, 3H, C*H*$_3$), 1.04 (s, 3H, C*H*$_3$). **^{13}C RMN** (101 MHz, $CDCl_3$): δ 139.9, 135.4, 133.8, 133.7, 132.5, 129.7, 129.2, 128.0, 127.7, 125.6, 64.0, 48.9, 48.7, 41.8, 31.2, 24.6, 21.1. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{19}H_{24}NO2S$): 330.1522, found: 330.1520.

3,3-Diethyl-1-[(phenylsulfonyl)methyl]-1,2,3,4-tetrahydroisoquinoline (113)



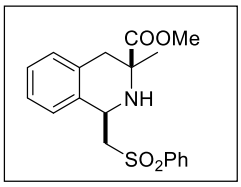
Yellow oil, 36% from amine **7** (0.265 g). **^{1}H RMN** (400 MHz, $CDCl_3$): δ 8.02-7.98 (m, 2H, Ar*H*), 7.70-7.55 (m, 3H, Ar*H*), 7.15-7.02 (m, 3H, Ar*H*), 6.92 (d, *J* = 8.4 Hz, 1H, Ar*H*), 4.55 (dd, *J* = 9.4, 1.8 Hz, 1H, ArC*H*NH), 3.75 (dd, *J* = 14.3, 1.8 Hz, 1H, ArCHCH*H*), 3.47 (dd, *J* = 14.3, 9.4 Hz, 1H, ArCHCH*H*), 2.74 (d, *J* = 15.8 Hz, 1H, ArCH*H*), 2.48 (d, *J* = 15.8 Hz, 1H, ArCH*H*), 1.50-1.30 (m, 4H, 2 C*H*$_2$CH$_3$), 0.89 (t, *J* = 7.5 Hz, 3H, C*H*$_3$), 0.82 (t, *J* = 7.5 Hz, 3H, C*H*$_3$). **^{13}C RMN** (101 MHz, $CDCl_3$): δ 139.8, 135.4, 134.7, 133.8, 130.1, 129.3, 127.9, 126.7, 125.8, 124.8, 64.1, 53.4, 47.9, 39.0, 31.6, 24.3, 7.5, 7.4. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{20}H_{26}NO_2S$): 344.1679, found: 344.1682.

***anti*-Methyl 3-methyl-1-[(phenylsulfonyl)methyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (114a)**



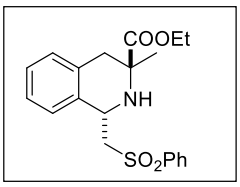
Yellow oil, 24% from amine **16** (0.193 g). **^{1}H RMN** (400 MHz, $CDCl_3$) δ 8.06-8.02 (m, 2H, Ar*H*), 7.70-7.66 (m, 1H, Ar*H*), 7.64-7.58 (m, 2H, Ar*H*), 7.12-7.03 (m, 3H, Ar*H*), 6.81-6.84 (m, 1H, Ar*H*), 4.70 (dd, *J* = 9.6, 1.6 Hz, 1H, ArC*H*NH), 3.65 (dd, *J* = 14.3, 1.6 Hz, 1H, ArCHCH*H*), 3.58 (s, 3H, OC*H*$_3$), 3.47 (dd, *J* = 14.4, 9.7 Hz, 1H, ArCHCH*H*), 3.20 (d, *J* = 15.6 Hz, 1H, ArCH*H*), 2.80 (d, *J* = 15,6 Hz, 1H, ArCH*H*), 1.43 (s, 3H, C*H*$_3$). **^{13}C RMN** (101 MHz, $CDCl_3$): δ 176.0, 139.4, 134.2, 133.9, 133.5, 129.3, 129.2, 128.1, 126.9, 126.4, 125.0, 64.9, 58.2, 52.1, 49.6, 38.4, 27.5. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{19}H_{22}NO_4S$): 360.1264, found: 360.1271.

***syn*-Methyl 3-methyl-1-[(phenylsulfonyl)methyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (114b)**



Yellow oil, 12% from amine **16** (0.193 g). **^{1}H RMN** (400 MHz, $CDCl_3$) δ 8.06-8.00 (m, 2H, Ar*H*), 7.70-7.63 (m, 1H, Ar*H*), 7.63-7.55 (m, 2H, Ar*H*), 7.18-7.05 (m, 3H, Ar*H*), 7.00-6.95 (m, 1H, Ar*H*), 4.78 (dd, *J* = 8.8, 2.3 Hz, 1H, ArC*H*NH), 3.75 (s, 3H, OC*H*$_3$), 3.66 (dd, *J* = 14.3, 2.3 Hz, 1H, ArCHCH*H*), 3.57 (dd, *J* = 14.3, 8.9 Hz, 1H, ArCHCH*H*), 3.22 (d, *J* = 15.8 Hz, 1H, ArCH*H*), 2.79 (d, *J* = 15,8 Hz, 1H, ArCH*H*), 1.33 (s, 3H, C*H*$_3$). **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{19}H_{22}NO_4S$): 360.1264, found: 360.1271.

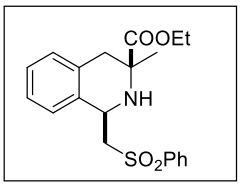
***anti*-Ethyl 3-methyl-1-[(phenylsulfonyl)methyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (115a)**



White foam, 37% from amine **18** (0.217 g). **^{1}H RMN** (400 MHz, $CDCl_3$) δ 8.06-8.02 (m, 2H, Ar*H*), 7.70-7.66 (m, 1H, Ar*H*), 7.63-7.58 (m, 2H, Ar*H*), 7.12-7.04 (m, 3H, Ar*H*), 6.84-6.81 (m, 1H, Ar*H*), 4.76 (dd, *J* = 9.6, 1.6 Hz, 1H, ArC*H*NH), 4.02 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$), 3.63 (dd, *J* = 14.3, 1.6 Hz, 1H, ArCHCH*H*), 3.47 (dd, *J* = 14.3, 9.6 Hz, 1H, ArCHCH*H*), 3.19 (m, *2*H, ArCH*H* + N*H*), 2.79 (d, *J* = 15.5 Hz, 1H, ArCH*H*), 1.41 (s, 3H, C*H*$_3$), 1.10 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$). **^{13}C RMN** (101

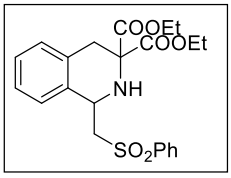
MHz, $CDCl_3$): δ 175.5, 139.6, 134.4, 133.8, 133.7, 129.4, 129.2, 128.1, 126.8, 126.4, 125.4, 65.2, 60.8, 58.1, 49.7, 38.5, 27.3, 14.1. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{20}H_{24}NO_4S$): 374.1421, found: 374.1430.

***syn*-Ethyl 3-methyl-1-[(phenylsulfonyl)methyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (115b)**



White foam, 12% from amine **18** (0.217 g). **^{1}H RMN** (400 MHz, $CDCl_3$) δ 8.05-8.00 (m, 2H, Ar*H*), 7.70-7.65 (m, 1H, Ar*H*), 7.63-7.58 (m, 2H, Ar*H*), 7.17-7.07 (m, 3H, Ar*H*), 7.00-6.94 (m, 1H, Ar*H*), 4.76 (dd, *J* = 9.0, 2.3 Hz, 1H, ArC*H*NH), 4.25-4.16 (m, 2H, OCH_2), 3.66 (dd, *J* = 14.3, 2.3 Hz, 1H, ArCHCH*H*), 3.59 (dd, *J* = 14.3, 9.0 Hz, 1H, ArCHCH*H*), 3.21 (d, *J* = 15.9 Hz, 1H, ArCH*H*), 2.78 (d, *J* = 15.9 Hz, 1H, ArCH*H*), 1.33 (s, 3H, CH_3), 1.30 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3). **^{13}C RMN** (101 MHz, $CDCl_3$): δ 175.4, 139.7, 133.9, 133.8, 133.8, 129.9, 129.4, 128.0, 127.1, 126.4, 125.2, 63.6, 61.2, 56.6, 48.4, 37.6, 23.0, 14.1.

Diethyl 1-[(phenylsulfonyl)methyl]-1,4-dihydroisoquinoline-3,3(2H)-dicarboxylate (116)

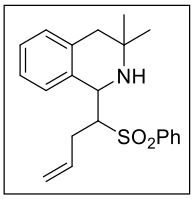


White foam, 77% from amine **19** (0.415 g). **^{1}H RMN** (400 MHz, $CDCl_3$): δ 8.03 (d, *J* = 7.3 Hz, 2H, Ar*H*), 7.68 (t, *J* = 7.4 Hz, 1H, Ar*H*), 7.60 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.20-7.10 (m, 3H, Ar*H*), 6.93 (m, 1H, Ar*H*), 4.84 (m, 1H, ArC*H*NH), 4.30-4.21 (m, 2H, OCH_2), 4,10 (q, *J* = 7.1 Hz, 2H, OCH_2), 3,75 (br s, 1H, N*H*), 3.62 (dd, *J* = 14.3, 2.0 Hz, 1H, ArCHCH*H*), 3.53 (dd, *J* = 14.3, 9.3 Hz, 1H, ArCHCH*H*), 3.39 (d, *J* = 15.8 Hz, 1H, ArCH*H*), 3.21 (d, *J* = 15,8 Hz, 1H, ArCH*H*), 1.30 (t, *J* = 7.1 Hz, 3H, CH_3), 1.14 (t, *J* = 7.1 Hz, 3H, CH_3). **^{13}C RMN** (101 MHz, $CDCl_3$): δ 170.0, 169.0, 139.6 133.8, 133.8, 132.5, 129.4, 129.2, 128.1, 127.2, 126.8, 125.3, 65.8, 64.6, 62.2, 61.8, 49.6, 34.1, 14.0. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{22}H_{26}NO_6S$): 432.1475, found: 432.1482.

7.7.5. General procedure for the alkylation of the sulfones

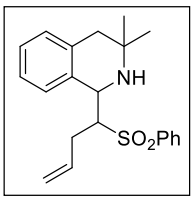
LDA (0.125 mL of a 2 M solution in THF, 0.275 mmol) was added to a solution of 3,3-dimethyl-1-((phenylsulfonyl)methyl)-1,2,3,4-tetrahydroisoquinoline **110** (79 mg, 0.25 mmol) in dry THF (5 mL) at -40 ºC under N_2 atmosphere. The mixture was stirred for 1 hour at the same temperature then allyl bromide (0.085 mL, 1 mmol) was added and the solution was allowed to room temperature and stirred for additional 16 hours. The reaction was quenched with a saturated aqueous solution of NH_4Cl then ethyl acetate was added, the phases were separated and the aqueous layer was extracted three times with ethyl acetate. The combined organic extracts were washed with brine, dried over Na_2SO_4 and the solvent was evaporated. The residue was purified by flash silica gel chromatography (hexane/ethyl acetate/triethylamine) to afford the pure diastereomers **120a** and **120b** (68 mg, 77% overall yield).

3,3-Dimethyl-1-[1-(phenylsulfonyl)but-3-en-1-yl]-1,2,3,4-tetrahydroisoquinoline (120a)



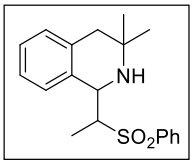
Yellow oil, 38% from sulfone **110** (91 mg) and allyl bromide. **^{1}H RMN** (400 MHz, $CDCl_3$): δ 7.61 (d, *J* = 7.3 Hz, 2H, Ar*H*), 7.43 (t, *J* = 7.5 Hz, 1H, Ar*H*), 7.29 (t, *J* = 7.8 Hz, 2H, Ar*H*) 7.00-6.85 (m, 4H, Ar*H*), 5.82-5.72 (m, 1H, C*H*=CH_2) 5.17-5.07 (m, 2H, CH=CH_2), 4.56 (m, 1H, ArC*H*NH), 3.77 (ddd, 1H, *J* = 9.8, 4.6, 2.5 C*H*SO_2), 2.95-2.80 (m, 2H, CH_2CH=CH_2), 2.63 (d, *J* = 15.7 Hz, 1H, ArCH*H*), 2.41 (d, *J* = 15.7 Hz, 1H, ArCH*H*), 1.25 (s, 3H, CH_3), 0.89 (s, 3H, CH_3). **^{13}C RMN** (101 MHz, $CDCl_3$): δ 140.0, 135.7, 134.0, 133.8, 133.0, 129.5, 128.5, 128.4, 126.2, 125.7, 125.1, 118.8, 68.5, 68.0, 52.3, 49.3, 42.2, 31.7, 30.1, 25.6, 23.6. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{21}H_{26}NO_2S$): 356.1679, found: 356.1683.

3,3-Dimethyl-1-[1-(phenylsulfonyl)but-3-en-1-yl]-1,2,3,4-tetrahydroisoquinoline (120b)



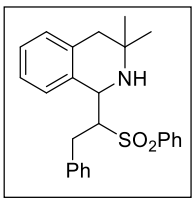
Yellow oil, 38% from sulfone **110** (91 mg) and allyl bromide. **^{1}H RMN** (400 MHz, $CDCl_3$): δ 7.99 (d, *J* = 7.3 Hz, 2H, Ar*H*), 7.66 (t, *J* = 7.5 Hz, 1H, Ar*H*), 7.58 (t, *J* = 7.3 Hz, 2H, Ar*H*) 7.15-6.90 (m, 4H, Ar*H*), 5.25-5.10 (m, 1H, C*H*=CH_2) 4.85 (m, 1H, ArC*H*NH), 4.66-4.53 (m, 2H, CH=CH_2), 3.63 (td, *J* = 6.1, 1.3 Hz, 1H, C*H*SO_2), 2.78 (d, *J* = 15.5 Hz, 1H, ArCH*H*), 2.70-2.50 (m, 2H, CH_2CH=CH_2), 2.41 (d, *J* = 15.5 Hz, 1H, ArCH*H*), 1.26 (s, 3H, CH_3), 1.00 (s, 3H, CH_3). **^{13}C RMN** (101 MHz, $CDCl_3$): δ 138.7, 136.4, 135.2, 133.9, 133.8, 129.8, 129.3, 128.7, 126.5, 125.7, 125.0, 116.1, 70.7, 63.7, 51.3, 48.5, 42.5, 31.7, 31.68, 28.2, 24.5.

3,3-Dimethyl-1-[1-(phenylsulfonyl)ethyl]-1,2,3,4-tetrahydroisoquinoline (117)



Colorless oil, 39% from sulfone **110** (70 mg) and methyl iodide. **^{1}H RMN** (400 MHz, $CDCl_3$): δ 7.99 (d, *J* = 7.1 Hz, 2H, Ar*H*), 7.67 (t, *J* = 6.9 Hz, 1H, Ar*H*), 7.56 (t, *J* = 7.3 Hz, 2H, Ar*H*), 7.13-6.94 (m, 4H, Ar*H*), 4.88 (d, *J* = 1.3 Hz, 1H, ArC*H*NH), 3.60 (dq, *J* = 6.9, 1.3 Hz, 1H, C*H*SO_2), 2.77 (d, *J* = 15.2 Hz, 1H, ArCH*H*), 2.41 (d, *J* = 15.2 Hz, 1H, ArCH*H*), 1.26 (s, 3H, CH_3), 1.12 (d, *J* = 6.9 Hz, 3H, CHCH_3), 1.06 (s, 3H, CH_3). **^{13}C RMN** (101 MHz, $CDCl_3$): δ 138.4, 136.7, 134.0, 133.7, 129.8, 129.2, 128.7, 126.5, 125.9, 124.6, 65.8, 51.2, 48.4, 42.5, 31.7, 24.5, 7.8. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{19}H_{24}NO_2S$): 330.1522, found: 330.1519.

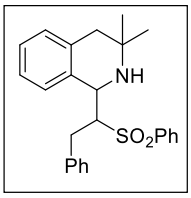
3,3-Dimethyl-1-[2-phenyl-1-(phenylsulfonyl)ethyl]-1,2,3,4-tetrahydroisoquinoline (121a)



Yellow oil, 41% from sulfone **110** (65 mg) and benzyl bromide. **^{1}H RMN** (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 7.6 Hz, 2H, Ar*H*), 7.58 (t, *J* = 7.6 Hz, 1H, Ar*H*), 7.47 (t, *J* = 7.6 Hz, 2H, Ar*H*), 7.06-6.84 (m, 7H, Ar*H*), 6.57-6.53 (m, 2H, Ar*H*), 4.97 (m, 1H, ArC*H*NH), 3.92 (m, 1H, C*H*SO_2), 3.16-3.12 (m 2H, CH_2Ph) 2.81 (d, *J* = 15.3 Hz, 1H, ArCH*H*), 2.40 (d, *J* = 15.3 Hz, 1H, ArCH*H*), 1.26 (s, 3H, CH_3), 1.02 (s, 3H, CH_3). **^{13}C**

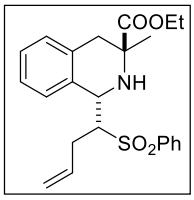
RMN (101 MHz, $CDCl_3$): δ 138.8, 138.8, 136.5, 135.5, 129.8, 129.1, 128.6, 128.5, 127.7, 126.5, 125.7, 125.6, 125.3, 72.5, 51.8, 48.5, 42.5, 31.7, 29.6, 24.7. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{25}H_{28}NO_2S$): 406.1835, found: 406.1843.

3,3-Dimethyl-1-[2-phenyl-1-(phenylsulfonyl)ethyl]-1,2,3,4-tetrahydroisoquinoline (121b)



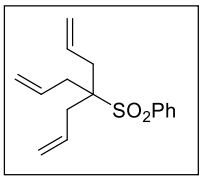
Yellow oil, 41% from sulfone **110** (65 mg) and benzyl bromide. **^{1}H RMN** (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.2 Hz, 2H, Ar*H*), 7.43 (t, *J* = 8.0 Hz, 1H, Ar*H*), 7.35-7.15 (m, 7H, Ar*H*), 6.97-6.79 (m, 4H, Ar*H*), 4.35 (m, 1H, ArC*H*NH), 3.97 (ddd, *J* = 11.0, 3.9, 2.4 Hz, 1H, C*H*SO_2Ph), 3.49 (dd, *J* = 13.6, 3.9 Hz, 1H, CH*H*Ph), 3.39 (dd, *J* = 13.6, 11.1 Hz, 1H, CH*H*Ph), 2.49 (d, *J* = 15.3 Hz, 1H, ArCH*H*), 2.38 (d, *J* = 15.3 Hz, 1H, ArCH*H*), 1.23 (s, 3H, CH_3), 0.82 (s, 3H, CH_3). **^{13}C RMN** (101 MHz, $CDCl_3$): δ 140.0, 137.4, 135.8, 133.7, 133.1, 130.0, 129.3, 128.5, 128.6, 128.3, 126.9, 126.1, 125.7, 125.1, 70.3, 51.5, 49.2, 42.2, 31.8, 31.0, 23.4.

Ethyl 3-methyl-1-[1-(phenylsulfonyl)but-3-en-1-yl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (134)



Yellow oil, 40% from *anti*-**115** (0.100 g) and allyl bromide. **^{1}H RMN** (400 MHz, $CDCl_3$): δ 8.07-8.03 (m, 2H, Ar*H*), 7.70-7.59 (m, 3H, Ar*H*), 7.12-6.95 (m, 3H, Ar*H*), 6.75 (d, *J* = 7.2 Hz, 1H, Ar*H*), 5.27-5.17 (m, 1H, C*H*=CH_2), 4.92 (m, 1H, ArC*H*NH), 4.73-4.68 (m, 1H, CH=CH*H*), 4.63-4.57 (m, 1H, CH=CH*H*), 3.97 (m, 2H, OCH_2), 3.51 (td, 1H, *J* = 6.1, 1.1 Hz, C*H*SO_2Ph), 3.15 (d, *J* = 15.3 Hz, 1H, ArCH*H*), 2.88 (br s, 1H, N*H*), 2.75 (d, *J* = 15.3 Hz, 1H, ArC*H*H), 2.73-2.60 (m, 2H, CH_2CH=CH_2), 1.44 (s, 3H, CH_3). 1.04 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3). **^{13}C RMN** (101 MHz, $CDCl_3$): δ 175.8, 138.4, 135.2, 135.1, 133.8, 133.5, 129.3, 129.1, 128.8, 126.6, 126.2, 125.5, 116.1, 71.4, 60.6, 57.9, 52.4, 38.9, 27.6, 27.4, 14.1. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{23}H_{28}NO_4S$): 414.1734, found: 414.1741

[(4-Allylhepta-1,6-dien-4-yl)sulfonyl]benzene (133)



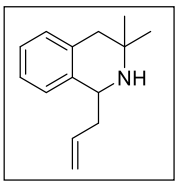
Colorless oil, 30% from *anti*-**115** (0.100 g) and allyl bromide. **^{1}H RMN** (400 MHz, $CDCl_3$): δ 7.85-7.80 (m, 2H, Ar*H*), 7.62-7.57 (m, 1H, Ar*H*), 7.53-6.46 (m, 2H, Ar*H*), 5.94-5.83 (m, 3H, 3 C*H*=CH_2), 5.10-5.00 (m, 6H, 3 CH=CH_2), 2.42 (d, *J* = 7.1 Hz, 6H, 3 CCH_2). **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{16}H_{21}O_2S$): 277.1257, found: 277.1259

7.7.6. General procedure for the alkylation of the imine 118 with Grignard reagents

3,3-dimethyl-3,4-dihydroisoquinoline **118** (52 mg, 0.33 mmol) was dissolved in dry THF and the solution was cooled to 0 ºC. Allyl magnesium bromide (0.50 mL of a 1M

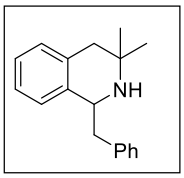
solution in diethyl ether, 0.5 mmol) was added and the mixture was allowed to room temperature and followed by TLC. Afterwards the reaction was quenched with a saturated aqueous solution of NH_4Cl then ethyl acetate was added, the phases were separated and the aqueous layer was extracted two further times with ethyl acetate. The combined organic extracts were washed with brine, dried over Na_2SO_4 and the solvent was evaporated. The residue was purified by flash silica gel chromatography (dichloromethane/methanol/triethylamine) to afford the pure tetrahidroisoquinoline **122** (66 mg, 100%).

1-Allyl-3,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (122)



Colorless oil, 100%. **^{1}H RMN** (400 MHz, $CDCl_3$): δ 7.26-7.02 (m, 4H, Ar*H*), 5.75-5.63 (m, 1H, C*H*=CH_2) 5.23-5.10 (m, 2H, CH=C*H*$_2$), 4.12 (dd, *J* = 7.2, 4.0 Hz, 1H, ArC*H*NH), 2.75-2.60 (m, 2H, C*H*$_2$CH=CH_2), 2.69 (d, *J* = 15.8 Hz, 1H, ArCH*H*), 2.54 (d, *J* = 15.8 Hz, 1H, ArCH*H*), 1.25 (s, 3H, C*H*$_3$), 1.06 (s, 3H, C*H*$_3$). **^{13}C RMN** (101 MHz, $CDCl_3$): δ 137.1, 135.3, 134.8, 129.5, 126.0, 125.9, 125.1, 118.3, 51.6, 48.9, 42.7, 40.4, 31.6, 24.3. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{14}H_{20}N$): 202.1590, found: 202.1598.

1-Benzyl-3,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (123)

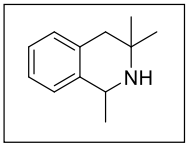


Colorless oil, 97% from imine **118** (55 mg) and benzyl magnesium chloride. **^{1}H RMN** (400 MHz, $CDCl_3$): δ 7.35-7.15 (m, 8H, Ar*H*), 7.5 (d, *J* = 7.4 Hz, 1H, Ar*H*), 4.37 (dd, *J* = 8.4, 3.9 Hz, 1H, ArC*H*NH), 3.40 (dd, *J* = 13.6, 3.9 Hz, *2*H, ArCHCH*H*), 2.94 (dd, *J* = 13.6, 8.4 Hz, *2*H, ArCHCH*H*), 2.67 (d, *J* = 15.7 Hz, 1H, ArCH*H*), 2.49 (d, *J* = 15.7 Hz, 1H, ArCH*H*), 1.16 (s, 3H, C*H*$_3$), 1.01 (s, 3H, C*H*$_3$). **^{13}C RMN** (101 MHz, $CDCl_3$): δ 138.8, 137.3, 135.3, 129.5, 129.4, 128.4, 126.4, 126.1, 125.7, 125.3, 53.5, 48.9, 42.8, 42.7, 31.6, 24.5. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{18}H_{22}N$): 252.1747, found: 252.1747.

7.7.7. General procedure for the alkylation of the imine 118 with organolithiums

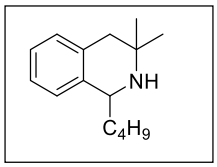
Imine **118** (42 mg, 0.26 mmol) was dissolved in dry THF and the solution was cooled to -30 ºC. Methyllithium (0.180 mL of a 1.6 M solution in Et_2O, 0.29 mmol) was added dropwise and the solution was stirred for 5 hours at the same temperature. Afterwards the reaction was quenched with a saturated aqueous solution of NH_4Cl then ethyl acetate was added, the phases were separated and the aqueous layer was extracted two further times with ethyl acetate. The combined organic extracts were washed with brine, dried over Na_2SO_4 and the solvent was evaporated. The residue was purified by flash silica gel chromatography (dichloromethane/methanol/triethylamine) to afford the pure isoquinoline **124** (35 mg, 68%).

1,3,3-Trimethyl-1,2,3,4-tetrahydroisoquinoline (124)



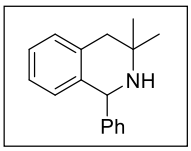
Colorless oil. **^{1}H RMN** (400 MHz, $CDCl_3$): δ 7.20-7.15 (m, 3H, Ar*H*), 7.06 (d, J = 7.0 Hz, 1H, Ar*H*), 4.27 (q, *J* = 6.5 Hz, 1H, ArC*H*NH), 2.96 (d, *J* = 16.2 Hz, 1H, ArCH*H*), 2.60 (d, *J* = 16.2 Hz, 1H, ArCH*H*), 1.62 (d, *J* = 6.5 Hz, 3H, CH_3), 1.26 (s, 3H, C*H*$_3$), 1.06 (s, 3H, C*H*$_3$). **^{13}C RMN** (101 MHz, $CDCl_3$): δ 129.5, 127.4, 126.9, 125.3, 49.0, 40.2, 28.4, 22.5, 20.1. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{12}H_{18}N$): 176.1434, found: 176.1431.

1-Butyl-3,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (125)



Colorless oil, 83% from imine **118** (53 mg) and butyllithium. **^{1}H RMN** (400 MHz, $CDCl_3$): δ 7.20-7.10 (m, 3H, Ar*H*), 7.06 (d, *J* = 7.3 Hz, 1H, Ar*H*), 4.05 (dd, *J* = 8.0, 2.6 Hz, 1H, ArC*H*NH), 2.72 (d, *J* = 15.7 Hz, 1H, ArCH*H*), 2.54 (d, *J* = 15.7 Hz, 1H, ArCH*H*), 2.04-1.94 (m, 1 H, ArCHCH*H*), 1.76-1.66 (m, 1 H, ArCHCH*H*), 1.40-1.30 (m, 4H, C*H*$_2$C*H*$_2$CH$_3$) 1.26 (s, 3H, C*H*$_3$), 1.06 (s, 3H, C*H*$_3$), 0.9 (m, 3H, CH$_2$C*H*$_3$). **^{13}C RMN** (101 MHz, $CDCl_3$): δ 138.3, 135.1, 129.4, 125.8, 125.7, 125.2, 52.5, 49.0, 42.8, 36.4, 31.8, 27.6, 24.4, 23.0, 14.1. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{15}H_{24}N$): 218.1903, found: 218.1904.

3,3-Dimethyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (126)



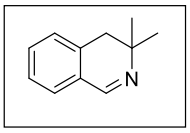
Colorless oil, 66% from imine **118** (44 mg) and phenyllithium. **^{1}H RMN** (400 MHz, $CDCl_3$): δ 7.40-7.00 (m, 8H, Ar*H*), 6.74 (d, *J* = 7.7 Hz, 1H, Ar*H*), 5.12 (s, 1H, ArC*H*NH), 2.92 (d, *J* = 15.8 Hz, 1H, ArCH*H*), 2.65 (d, *J* = 15.8 Hz, 1H, ArCH*H*), 1.29 (s, 3H, C*H*$_3$), 1.22 (s, 3H, C*H*$_3$). **^{13}C RMN** (101 MHz, $CDCl_3$): δ 129.2, 129.1, 128.5, 127.6, 127.4, 126.2, 125.6, 59.1, 49.8, 42.5, 31.8, 24.4. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{17}H_{20}N$): 238.1590, found: 238.1579.

7.7.8. General procedure for the elimination of (methylsulfonyl)benzene

LDA (0.79 mL of a 2 M solution in THF, 1.57 mmol) was added to a solution of 3,3-dimethyl-1-((phenylsulfonyl)methyl)-1,2,3,4-tetrahydroisoquinoline (450 mg, 1.43 mmol) in dry THF (30 mL) at -78 ºC under N_2 atmosphere.

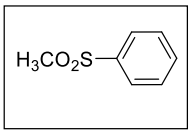
The mixture was warmed to 0 ºC and stirred for 1 hour then allowed to room temperature and stirred for additional 12 hours. The reaction was quenched with a saturated aqueous solution of NH_4Cl then ethyl acetate was added, the phases were separated and the aqueous layer was extracted three times with ethyl acetate. The combined organic extracts were washed with brine, dried over Na_2SO_4 and the solvent was evaporated to afford a pure 1/1 mixture of dihidroisoquinoline **118** and sulfone **119** that were separated by flash silica gel chromatography (dichloromethane/ methanol/triethylamine) to obtain the pure imine **118** (227 mg, 100%).

3,3-Dimethyl-3,4-dihydroisoquinoline (118)



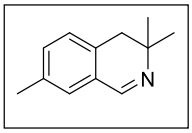
Brown oil. **^{1}H RMN** (400 MHz, $CDCl_3$): δ 8.16 (s, 1H, C*H*=N), 7.30-7.26 (m, 1H, Ar*H*), 7.22-7.20 (m, 2H, Ar*H*), 7.06 (dd, *J* = 7.3, 0.7 Hz, 1H, Ar*H*), 2.66 (s, 2H, ArCH_2), 1.17 (s, 6H, 2 CH_3). **^{13}C RMN** (101 MHz, $CDCl_3$): δ 157.5, 135.6, 131.1, 128.1, 127.4, 127.1, 127.0 54.8, 38.0, 28.0. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{11}H_{14}N$): 160.1121, found: 160.1111.

(Methylsulfonyl)benzene (119)



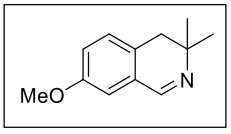
Colorless liquid, 89%. **^{1}H RMN** (400 MHz, $CDCl_3$): δ 7.97-7.94 (m, 2H, Ar*H*), 7.69-7.65 (m, 1H, Ar*H*), 7.61-7.53 (m, 2H, Ar*H*), 3.06 (s, 3H, SO_2CH_3). **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_7H_9O_2S$): 157.0318, found: 157.0321.

3,3,7-Trimethyl-3,4-dihydroisoquinoline (127)



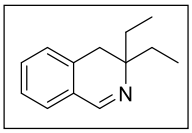
Brown oil, 100% from sulfone **112** (115 mg). **^{1}H RMN** (400 MHz, $CDCl_3$): δ 8.18 (s, 1H, C*H*=N), 7.16 (d, *J* = 7.6 Hz, 1H, Ar*H*), 7.08 (s, 1H, Ar*H*), 7.01 (d, *J* = 7.6 Hz, 1H, Ar*H*), 2.68 (s, 2H, ArCH_2), 2.35 (s, 3H, ArCH_3), 1.22 (s, 6H, 2 CH_3). **^{13}C RMN** (101 MHz, $CDCl_3$): δ 157.6, 136.5, 132.5, 131.7, 127.9, 127.8, 127.4, 54.9, 37.6, 28.1, 21.0. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{12}H_{16}N$): 174.1277, found: 174.1281.

7-**Methoxy-3,3-dimethyl-3,4-dihydroisoquinoline (128)**



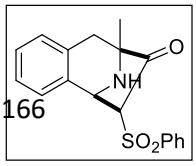
Brown oil, 100% from sulfone **111** (90 mg). **^{1}H RMN** (400 MHz, $CDCl_3$): δ 8.18 (s, 1H, C*H*=N), 7.03 (d, *J* = 8.2 Hz, 1H, Ar*H*), 6.89 (dd, *J* = 8.2, 2.6 Hz, 1H, Ar*H*), 6.82 (d, *J* = 2.6 Hz, 1H, Ar*H*), 3.81 (s, 3H, OCH_3), 2.65 (s, 2H, ArCH_2), 1.22 (s, 6H, 2 CH_3). **^{13}C RMN** (101 MHz, $CDCl_3$): δ 158.6, 157.4, 128.9, 128.1, 127.5, 116.7, 112.3, 55.4, 55.2, 37.1, 28.0. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{12}H_{16}NO$): 190.1226, found: 190.1234.

3,3-Diethyl-3,4-dihydroisoquinoline (129)



Brown oil, 97% from sulfone **113** (182 mg). **^{1}H RMN** (400 MHz, $CDCl_3$): δ 8.29 (s, 1H, C*H*=N), 7.35-7.29 (m, 1H, Ar*H*), 7.27-7.23 (m, 2H, Ar*H*), 7.10 (dd, *J* = 7.3, 0.8 Hz, 1H, Ar*H*), 2.69 (s, 2H, ArCH_2), 1.63-1.47 (m, 4H, 2 CH_2CH$_3$), 0.87 (t, *J* = 7.5 Hz, 6H, 2 CH_3). **^{13}C RMN** (101 MHz, $CDCl_3$): δ 157.7, 135.6, 131.0, 128.0, 128.0, 127.0, 126.8, 59.9, 32.6, 30.6, 8.4. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{13}H_{18}N$): 188.1434, found: 188.1428.

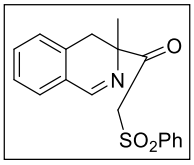
8-Methyl-6-(phenylsulfonyl)-5,6,8,9-tetrahydro-7H-5,8-epiminobenzo[7]annulen-7-one (131)



Colorless oil, 30% from sulfone *syn*-**115** (100 mg). **^{1}H RMN** (400 MHz, $CDCl_3$): δ 7.88-7.84 (m, 2H, Ar*H*), 7.73-7.65 (m, 1H, Ar*H*),

7.62-7.56 (m, 2H, Ar*H*), 7.20-7.09 (m, 2H, Ar*H*), 7.07-6.98 (m, 2H, Ar*H*), 5.20 (s, 1H, ArC*H*NH), 3.73 (s, 1H, C*H*SO_2Ph), 2.98 (d, *J* = 16.9 Hz, 1H, ArCH*H*), 2.79 (d, *J* = 16.9 Hz, 1H, ArCH*H*), 1.43 (s, 3H, CH_3). **^{13}C RMN** (101 MHz, $CDCl_3$): δ 209.8, 137.6, 137.0, 134.5, 132.7, 129.3, 129.1, 128.9, 128.3, 126.8, 125.4, 76.2, 65.0, 58.0, 40.2, 20.7. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{18}H_{18}NO_3S$): 328.1002, found: 328.0999.

1-(3-Methyl-3,4-dihydroisoquinolin-3-yl)-2-(phenylsulfonyl)ethan-1-one (132)

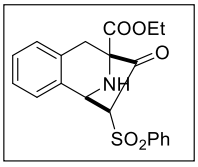


Colorless oil, 8% sulfone *syn*-**115** (100 mg). Significant **^{1}H RMN** (400 MHz, $CDCl_3$) peaks: δ 8.21 (s, 1H, ArC*H*=N), 4.77 (s, 2H, C$H_2$$SO_2$Ph), 3.05 (d, *J* = 16.5 Hz, 1H, ArCH*H*), 2.78 (d, *J* = 16.5 Hz, 1H, ArCH*H*), 1.17 (s, 3H, CH_3). **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{18}H_{18}NO_3S$): 328.1002, found: 328.1000.

7.7.9. Preparation of ethyl 7-oxo-6-(phenylsulfonyl)-5,6,7,9-tetrahydro-8H-5,8-epiminobenzo[7]annulene-8-carboxylate (130)

Sulfone **116** (65 mg, 0.15 mmol) was dissolved in dry THF then P2-Et was added dropwise under N_2 athmosphere and the solution was stirred overnight at room temperature. Afterwards the reaction was quenched with a saturated aqueous solution of NH_4Cl then ethyl acetate was added, the phases were separated and the aqueous layer was extracted three times with ethyl acetate. The combined organic extracts were washed with brine, dried over Na_2SO_4 and the solvent was evaporated to yield the crude olefin that was purified by flash silica gel chromatography (hexane/ethyl acetate/triethylamine) to afford pure **130** (57 mg, 99%)

Ethyl 7-oxo-6-(phenylsulfonyl)-5,6,7,9-tetrahydro-8H-5,8-epiminobenzo[7] annulene -8-carboxylate (130)



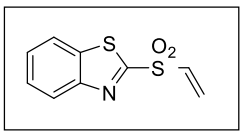
Colorless oil. **^{1}H RMN** (400 MHz, $CDCl_3$): δ 7.87-7.83 (m, 2H, Ar*H*), 7.73-7.69 (m, 1H, Ar*H*), 7.62-7.56 (m, 2H, Ar*H*), 7.24-7.13 (m, 2H, Ar*H*), 7.10-7.05 (m, 2H, Ar*H*), 5.30 (s, 1H, ArC*H*NH), 4.42-4.30 (m, 2H, OCH_2) 3.77 (s, 1H, C*H*SO_2Ph), 3.33 (d, *J* = 17.1 Hz, 1H, ArCH*H*), 3.19 (d, *J* = 17.1 Hz, 1H, ArCH*H*), 1.37 (t, *J* = 7.1 Hz, 3H, CH_3). **^{13}C RMN** (101 MHz, $CDCl_3$): δ 203.5, 166.7, 137.1, 136.5, 134.6, 131.5, 129.4, 129.3, 128.9, 128.6, 127.2, 125.3, 75.9, 71.3, 62.5, 58.2, 35.6, 14.1. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{20}H_{20}NO_5S$): 386.1057, found: 386.1058.

7.7.10. Preparation of 2-(vinylsulfonyl)benzo[*d*]thiazole (135)

benzo[*d*]thiazole-2-thiol (2g, 12 mmol) was dissolved in acetone (100 mL) then potassium carbonate (5.53 g, 40 mmol) and 1,2-dichloroethane (7.60 mL, 96 mmol) were added. The mixture was heated to reflux overnight then the acetone was removed at vacuum and the residue was dissolved in water and ethyl acetate. The phases were separated and the aqueous layer was extracted two additional times with ethyl acetate. The collected organic layers were dried over $MgSO_4$ and the solvent was removed to

afford the crude product that was purified by flash silica gel chromatography (hexane/acetate, 2.34 g, 85%, ^{1}H RMN (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8.2 Hz, 1H, Ar*H*), 7.76 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.45-7.40 (m, 1H, Ar*H*), 7.43-7.29 (m, 1H, Ar*H*), 3.92 (t, *J* = 7.4 Hz, 2H, CH_2CH_2Cl), 3.70 (t, *J* = 7.4 Hz, 2H, CH_2CH_2Cl)).
The thioether (2.34 g, 10.2 mmol) was dissolved in a 1.5/1 mixture of water and methanol (150 mL) then oxone (19 mg, 30.6 mmol) was added and the mixture was stirred overnight at room temperature. The methanol was evaporated, dichloromethane and water were added to the residue and the phases were separated. The aqueous layer was extracted two further times with dichloromethane and the collected organic fractions were washed with brine, dried over Na_2SO_4 and filtered.
The solvent was evaporated and the residue was dissolved in dry THF (15 mL). NEt_3 (2 mL, 15.3 mmol) was added and the mixture was stirred for 1.5 hours at room temperature. The resulting suspension was filtered through a celite pad to eliminate the ammonium salt then the THF was evaporated to afford the pure alkene (2.1 g, 92%).

2-(Vinylsulfonyl)benzo[*d*]thiazole (135)

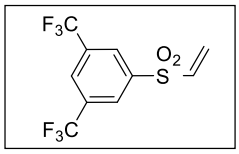


Orange foam, 78% from benzo[*d*]thiazole-2-thiol. **^{1}H RMN** (400 MHz, $CDCl_3$): δ 8.22 (d, *J* = 7.4, 1H Hz, Ar*H*), 8.01 (d, *J* = 7.2 Hz, 1H, Ar*H*), 7.66-7.57 (m, 2H, Ar*H*), 6.99 (dd, *J* = 16.6, 9.8 Hz, 1H, SO_2CH=CH_2), 6.74 (d, *J* = 16.6 Hz, 1H, SO_2CH=CH*H*), 6.34 (d, *J* = 9.8 Hz, 1H, SO_2CH=C*H*H). **^{13}C RMN** (101 MHz, $CDCl_3$): δ 166.0, 152.8, 136.9, 135.9, 132.3, 128.1, 127.7, 125.5, 122.3.

7.7.11. Preparation of 1,3-bis(trifluoromethyl)-5-(vinylsulfonyl)benzene (136)

3,5-bis(trifluoromethyl)benzenethiol (0.200 mL, 1.19 mmol) was added to a suspension of K_2CO_3 (415 mg, 3 mmol) in DCE (15 mL) and the mixture was heated to reflux for 72 hours. Water was added and the organic layer was extracted three times with dichloromethane. The combined organic extracts were washed with water and brine, dried over $MgSO_4$ and the solvent was eliminated to afford the thioether intermediate that was used for the next step without further purifications (307 mg, 84%, ^{1}H RMN (400 MHz, $CDCl_3$): δ 7.75 (s, 2H, Ar*H*), 7.71 (s, 1H, Ar*H*), 3.67 (dd, *J* = 8.2, 7.0 Hz, 2H, C*HH*Cl), 3.35 (dd, *J* = 8.2, 7.0 Hz, 2H, SC*HH*)).
The thioether (307 mg, 1 mmol) was dissolved in 1.5/1 mixture of water and methanol (15 mL) then oxone (1.84 mg, 3 mmol) was added and the mixture was stirred overnight at room temperature. The methanol was evaporated, dichloromethane and water were added to the residue and the phases were separated. The aqueous layer was extracted with dichloromethane two more times and the collected organic fractions were washed with brine, dried over Na_2SO_4 and filtered.
The solvent was evaporated and the residue was dissolved in dry THF (15 mL). NEt_3 (0.230 mL, 1.5 mmol) was added and the mixture was stirred for 1.5 hours at room temperature. The resulting suspension was filtered through a celite pad to eliminate the ammonium salt then the THF was evaporated to afford the pure alkene (292 mg, 96%).

1,3-Bis(trifluoromethyl)-5-(vinylsulfonyl)benzene (136)

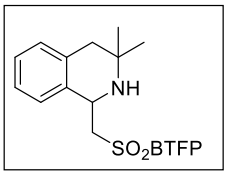


Yellow solid, 80% from 3,5-bis(trifluoromethyl)benzenethiol. **^{1}H RMN** (400 MHz, $CDCl_3$): δ 8.28 (s, 2H, Ar*H*), 8.07 (s, 1H, Ar*H*), 6.70 (dd, *J* = 16.5, 8.4 Hz, 1H, SO_2CH=CH_2), 6.64 (dd, *J* = 16.5, 0.5 Hz, 1H, SO_2CH=C*H*H), 6.25 (dd, *J* = 8.4, 0.5 Hz, 1H, SO_2CH=C*H*H). **^{13}C RMN** (101 MHz, $CDCl_3$): δ 142.6, 137.0, 133.3 (q, J_{C-F} = 34.7 Hz), 130.9, 128.27 (m), 127.3 (m), 122.3 (q, J_{C-F} = 273.5 Hz).
HRMS (ESI) (m/z) calcd for $[M+H]^+$ ($C_{10}H_7F_6O_2S$): 305.0065, found: 305.0057.

7.7.12. Preparation of 1-[[[(3,5-bis(trifluoromethyl)phenyl]sulfonyl]methyl]-3,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (137)

Compound **136** (0.173 g, 0.57 mmol) was added to a suspension of amine **1** (0.071 g, 0.47 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), and Ag_2CO_3 (0.140 g, 0.52 mmol) in acetic acid (3 mL). The mixture was stirred at 100 ºC for 3h in a sealed vial then toluene was added and the solution was filtered through a pad of celite. The solvents were removed under vacuum then the crude mixture was dissolved in CH_2Cl_2 and a saturated aqueous solution of Na_2CO_3 was added. The aqueous phase was extracted three times with CH_2Cl_2, the collected organic phases were dried over anhydrous Mg_2SO_4, filtered, and the solvent was removed under vacuum.
The crude yellow oil was purified by flash column chromatography on silica gel (dichloromethane/triethylamine) to give the desired isoquinoline (0.176 g, 82%).

1-[[[3,5-bis(Trifluoromethyl)phenyl]sulfonyl]methyl]-3,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (137)



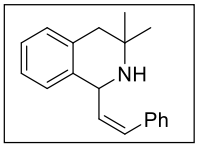
White foam. **^{1}H RMN** (400 MHz, $CDCl_3$): δ 8.41 (s, 2H, Ar*H*), 8.11 (s, 1H, Ar*H*) 7.15-7.08 (m, 2H, Ar*H*), 7.03 (d, *J* = 7.6 Hz, 1H, Ar*H*) 6.98 (d, *J* = 7.3 Hz, 1H, Ar*H*) 4.70 (dd, *J* = 9.2, 2.5 Hz, 1H, ArC*H*NH), 3.82 (dd, *J* = 14.5, 2.5 Hz, 1H, ArCHCH*H*), 3.61 (dd, *J* = 14.5, 9.2 Hz, 1H, ArCHCH*H*), 2.70 (d, *J* = 15.8 Hz, 1H, ArCH*H*), 2.49 (d, *J* = 15.8 Hz, 1H, ArCH*H*), 1.15 (s, 3H, C*H*$_3$), 1.01 (s, 3H, C*H*$_3$). **^{13}C RMN** (101 MHz, $CDCl_3$): δ 143.1, 135.5, 133.2, 133.1, 132.7, 130.1, 128.9 (m), 127.2 (m), 126.2, 124.9, 63.6, 49.2, 49.1, 42.0, 30.8, 24.8. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{20}H_{20}F_6NO_2S$): 452.1113, found: 452.1108.

7.7.13. General procedure for the modified Julia reaction

P2-Et (0.100 mL, 0.33 mmol) was added to a solution of **137** (50 mg, 0.11 mmol) in dry THF (3 mL) and the reaction was stirred for 30 minutes at room temperature. Fresh distilled benzaldehyde (0.013 mL, 0.12 mmol) was added and the solution was stirred overnight at room temperature under N_2 atmosphere.
Afterwards the reaction was quenched with a saturated aqueous solution of NH_4Cl then ethyl acetate was added, the phases were separated and the aqueous layer was extracted three times with ethyl acetate. The combined organic extracts were washed with brine,

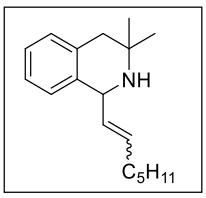
dried over Na_2SO_4 and the solvent was evaporated to yield the crude olefin that was purified by flash silica gel chromatography (hexane/ethyl acetate/triethylamine) to afford the pure THIQ (30 mg, 100%).

***(Z)*-3,3-Dimethyl-1-styryl-1,2,3,4-tetrahydroisoquinoline (141)**



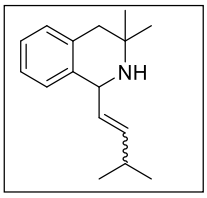
Yellow oil, 100% from sulfone **137** and benzaldehyde. **^{1}H RMN** (400 MHz, $CDCl_3$): δ 7.45-7.40 (m, 2H, Ar*H*), 7.37-7.32 (m, 2H, Ar*H*), 7.30-7.25 (m, 1H, Ar*H*), 7.20-7.14 (m, 3H, Ar*H*), 7.10-7.07 (m, 1H, Ar*H*), 6.77 (d, *J* = 11.4 Hz, 1H, CH=C*H*Ph), 5.72 (dd, *J* = 11.4, 9.7 Hz, 1H, C*H*=CHPh), 5.15 (d, *J* = 9.6 Hz, 1H, ArC*H*NH), 3.60 (br s, 1H N*H*), 2.85 (d, *J* = 16.2 Hz, 1H, ArCH*H*), 2.61 (d, *J* = 16.2 Hz, 1H, ArCH*H*), 1.30 (s, 3H, CH_3), 1.15 (s, 3H, CH_3). **^{13}C RMN** (101 MHz, $CDCl_3$): δ 136.5, 135.8, 134.2, 132.9, 132.2, 129.5, 128.4, 128.4, 127.4, 126.7, 126.6, 126.0, 50.7, 49.6, 41.8, 31.4, 24.9. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{19}H_{22}N$): 264.1747, found: 264.1745.

***(E/Z)*-1-(Hept-1-en-1-yl)-3,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (138)**



Yellow oil, 86% from sulfone **137** (66 mg) and hexaldehyde. **^{1}H RMN** (400 MHz, $CDCl_3$): δ 7.15-7.00 (m, 8H, Ar*H*), 5.79 (dt, *J* = 15.1, 6.7 Hz, 1H, NHCHCH=C*H*), 5.67 (dt, *J* = 10.8, 7.4 Hz, 1H, NHCHCH=C*H*), 5.49-5.39 (m, 2H, 2 NHCHC*H*), 4.89 (d, *J* = 9.0 Hz, 1H, NHC*H*CH), 4.47 (d, *J* = 8.5 Hz, 1H, NHC*H*CH), 2.79 (d, *J* = 16.0 Hz, 1H, ArCH*H*), 2.78 (d, *J* = 15.8 Hz, 1H, ArCH*H*), 2.57 (d, *J* = 16.0 Hz, 1H, ArCH*H*), 2.55 (d, *J* = 15.8 Hz, 1H, ArCH*H*), 2.30-2.20 (m, 2H, CH=CHC*HH*), 2.12-2.05 (m, 2H, CH=CHC*HH*), 1.50-1.25 (m, 12H, 2 *CH$_2$CH$_2$CH$_2$*CH$_3$), 1.27 (s, 6H, 2 CH_3), 1.17 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 0.95-0.85 (m, 6H, 2 CH$_2$*CH$_3$*). **^{13}C RMN** (101 MHz, $CDCl_3$): δ 136.7, 136.5, 134.5, 134.4, 134.2, 132.6, 132.1, 131.7, 129.3, 129.3, 126.8, 126.5, 126.2, 125.7, 125.6, 56.7, 50.2, 49.1, 42.1, 42.0, 32.2, 31.7, 31.7, 31.6, 31.5, 29.5, 29.0, 27.5, 24.9, 24.6, 22.5, 14.0. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{20}H_{24}N$): 278.1903, found: 278.1901.

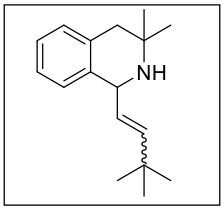
(*E/Z*)-3,3-Dimethyl-1-(3-methylbut-1-en-1-yl)-1,2,3,4-tetrahydroisoquinoline (139)



Rose oil, 81% from sulfone **137** (67 mg) and isobutyraldehyde. **^{1}H RMN** (400 MHz, $CDCl_3$): δ 7.17-7.04 (m, 8H, Ar*H*), 5.80 (dd, *J* = 15.3, 6.5 Hz, 1H, NHCHCH=C*H*), 5.52 (m, 1H, NHCHCH=C*H*), 5.42 (dd, *J* = 15.3, 8.6 Hz, 1H, NHCHC*H*), 5.31 (m, 1H, NHCH*CH*), 4.94 (d, *J* = 9.2 Hz, 1H, NHC*H*CH), 4.49 (d, *J* = 8.6 Hz, 1H, NHC*H*CH), 2.90 (br s, 2H, 2 N*H*), 2.86-2.76 (m, 3H, 2 ArCH*H*+ CH=CHC*H*CH$_3$), 2.60 (d, *J* = 16.1 Hz, 1H, ArCH*H*), 2.58 (d, *J* = 16.1 Hz, 1H, ArCH*H*), 2.34 (m, 1H, CH=CHC*H*CH$_3$), 1.31 (s, 3H, CC*H$_3$*), 1.21 (s, 3H, CC*H$_3$*), 1.16 (s, 3H, CC*H$_3$*), 1.13 (s, 3H, CC*H$_3$*), 1.10 (d, *J* = 6.6 Hz, 3H, CHC*H$_3$*), 1.03 (d, *J* = 6.8 Hz, 3H, CHC*H$_3$*), 1.00 (d, *J* = 6.8 Hz, 3H, CHC*H$_3$*), 0.95 (d, *J* = 6.6 Hz, 3H, CHC*H$_3$*). **^{13}C RMN** (101 MHz, $CDCl_3$): δ 141.6, 140.2, 136.3, 134.2, 130.5, 129.3, 129.2, 128.9, 128.0, 126.8, 126.5, 126.4, 126.4, 126.3, 125.8, 125.7, 56.6, 50.5, 49.2, 44.5, 42.1, 41.9, 31.5, 30.8, 26.8,

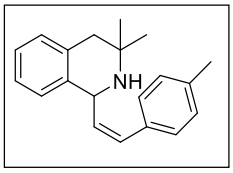
24.8, 24.5, 23.6, 23.5, 22.4, 22.3, 22.2. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{16}H_{24}N$): 230.1903, found: 230.1911.

***(E/Z)*-1-(3,3-Dimethylbut-1-en-1-yl)-3,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (140)**



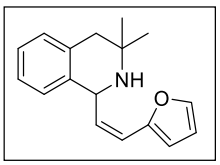
Rose oil, 42% from sulfone **137** (88 mg) and pivalaldehyde. **^{1}H RMN** (400 MHz, $CDCl_3$): δ 7.18-7.04 (m, 8H, Ar*H*), 5.83 (d, *J* = 15.4 Hz, 1H, NHCHCH=C*H*), 5.66 (d, *J* = 11.6 Hz, 1H, NHCHCH=C*H*), 5.38 (dd, *J* = 15.4, 8.6 Hz, 1H, NHCHC*H*), 5.25 (dd, *J* = 11.6, 10.1 Hz, 1H, NHCHC*H*), 5.15 (d, *J* = 10.1 Hz, 1H, NHC*H*CH), 4.47 (d, *J* = 8.6 Hz, 1H, NHC*H*CH), 2.95 (br s, 2H 2 N*H*), 2.84 (d, *J* = 16.1 Hz, 1H, ArCH*H*), 2.83 (d, *J* = 16.1 Hz, 1H, ArCH*H*), 2.58 (d, *J* = 16.1 Hz, 2H, 2 ArCH*H*), 1.30 (s, 3H, CCH_3), 1.29 (s, 3H, CCH_3), 1.24 (s, 9H, C(CH_3)$_3$), 1.20 (s, 3H, CCH_3), 1.16 (s, 3H, CCH_3), 1.05 (s, 9H, C(CH_3)$_3$). **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{17}H_{26}N$): 244.2060, found: 244.2057.

***(Z)*-3,3-Dimethyl-1-(4-methylstyryl)-1,2,3,4-tetrahydroisoquinoline (142)**



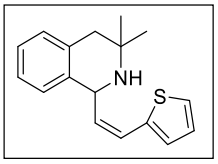
Yellow oil, 79% from sulfone **137** (62 mg) and 4-methylbenzaldehyde. **^{1}H RMN** (400 MHz, $CDCl_3$): δ 7.37 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.20-7.14 (m, 5H, Ar*H*), 7.10-7.05 (m, 1H, Ar*H*), 6.72 (d, *J* = 11.4 Hz, 1H, CH=C*H*Ar), 5.68 (dd, *J* = 11.4, 9.5 Hz, 1H, C*H*=CHAr), 5.13 (d, *J* = 9.5 Hz, 1H, ArC*H*NH), 2.82 (d, *J* = 16.1 Hz, 1H, ArCH*H*), 2.60 (d, *J* = 16.1 Hz, 1H, ArCH*H*), 2.36 (s, 3H, PhCH_3), 1.90 (br s, 1H N*H*), 1.29 (s, 3H, CH_3), 1.15 (s, 3H, CH_3). **^{13}C RMN** (101 MHz, $CDCl_3$): δ 137.0, 136.6, 134.5, 133.8, 133.0, 131.6, 129.4, 129.0, 128.5, 126.6, 126.4, 125.8, 50.7, 49.3, 42.0, 31.7, 25.0, 21.2. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{20}H_{24}N$): 278.1903, found: 278.1904.

***(Z)*-1-(2-(Furan-2-yl)vinyl)-3,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (143)**



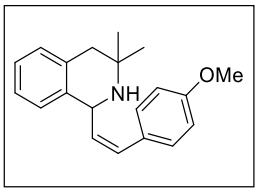
Brown oil, 65% from sulfone **137** (45 mg) and furfural. **^{1}H RMN** (400 MHz, $CDCl_3$): δ 7.40 (m, 1H, OC*H*=CH), 7.17-7.12 (m, 3H, Ar*H*), 7.09-7.06 (m, 1H, Ar*H*), 6.44-6.40 (m, 3H, OCH=C*H*, OC=C*H*, CH=C*H*Ar), 5.61 (dd, *J* = 11.5, 9.3 Hz, 1H, NHCHC*H*), 5.50 (d, *J* = 9.3 Hz, 1H, NHC*H*CH), 2.84 (d, *J* = 16.0 Hz, 1H, ArCH*H*), 2.61 (d, *J* = 16.0 Hz, 1H, ArCH*H*), 1.29 (s, 3H, CH_3), 1.23 (s, 3H, CH_3). **^{13}C RMN** (101 MHz, $CDCl_3$): δ 152.4, 142.1, 136.3, 134.5, 132.1, 129.4, 126.6, 126.3, 125.7, 119.0, 111.2, 110.2, 51.6, 49.2, 42.1, 31.7, 25.0. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{17}H_{20}NO$): 254.1539, found: 254.1531.

***(Z)*-3,3-Dimethyl-1-(2-(thiophen-2-yl)vinyl)-1,2,3,4-tetrahydroisoquinoline (144)**



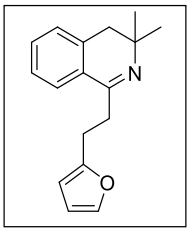
Yellow oil, 79% from sulfone **137** (68 mg) and thiophene-2-carbaldehyde. **^{1}H RMN** (400 MHz, $CDCl_3$): δ 7.27-7.25 (d, *J* = 5.1 Hz, 1H, SC*H*=CH), 7.19-7.13 (m, 3H, Ar*H* + SC=*CH*), 7.11-7.07 (m, 1H, Ar*H*), 7.03 (dd, *J* = 5.1, 3.6 Hz, 1H, SCH=C*H*), 6.79 (d, *J* = 11.3 Hz, 1H, CH=C*H*Ar), 5.65 (dd, *J* = 11.3, 9.5 Hz, 1H, NHCHC*H*), 5.44 (d, *J* = 9.5 Hz, 1H, NHC*H*CH), 2.85 (d, *J* = 16.0 Hz, 1H, ArCH*H*), 2.61 (d, *J* = 16.0 Hz, 1H, ArCH*H*), 1.29 (s, 3H, CH_3), 1.25 (s, 3H, CH_3). **^{13}C RMN** (101 MHz, $CDCl_3$): δ 139.3, 135.8, 134.6, 132.2, 129.5, 128.5, 127.0, 126.7, 125.8, 125.7, 124.0, 51.5, 49.2, 42.0, 31.7, 24.8. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{17}H_{20}NS$): 270.1311, found: 270.1306.

***(Z)*-1-(4-Methoxystyryl)-3,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (145)**



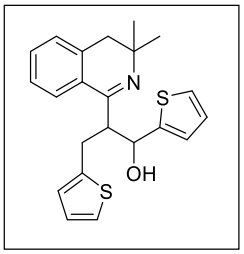
Brown oil, 47% from sulfone **137** (57 mg) and 4-methoxybenzaldehyde. **^{1}H RMN** (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 8.7 Hz, 2H, Ar*H*), 7.22-7.16 (m, 3H, Ar*H*), 7.12-7.07 (m, 1H, Ar*H*), 6.88 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.71 (d, *J* = 11.4 Hz, 1H, CH=C*H*Ar), 5.63 (dd, *J* = 11.3, 9.6 Hz, 1H, C*H*=CHAr), 5.18 (d, *J* = 9.6 Hz, 1H, ArC*H*NH), 3.95 (br s, 1H N*H*), 3.81 (s, 3H, OCH_3), 2.86 (d, *J* = 16.2 Hz, 1H, ArCH*H*), 2.64 (d, *J* = 16.2 Hz, 1H, ArCH*H*), 1.32 (s, 3H, CH_3), 1.18 (s, 3H, CH_3). **^{13}C RMN** (101 MHz, $CDCl_3$): δ 158.9, 135.9, 134.1, 131.8, 131.3, 129.7, 129.5, 129.0, 126.8, 126.6, 126.0, 113.8, 55.2, 50.7, 49.7, 41.8, 31.4, 24.8. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{20}H_{24}NO$): 294.1852, found: 294.1852.

(1)-(2-(Furan-2-yl)ethyl)-3,3-dimethyl-3,4-dihydroisoquinoline (146)



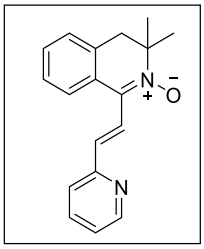
Brown oil from sulfone **137** (45 mg) and furfural. **^{1}H RMN** (400 MHz, $CDCl_3$): δ 7.48 (d, *J* = 7.5 Hz, 1H, Ar*H*), 7.35-7.31 (m, 1H, Ar*H*), 7.30 (d, *J* = 1.9 Hz, 1H, OC*H*=CH), 7.29-7.24 (m, 1H, Ar*H*), 7.14 (d, *J* = 7.3 Hz, 1H, Ar*H*), 6.26 (dd, *J* = 3.1, 1.9 Hz, 1H, OCH=C*H*), 6.00 (d, *J* = 3.1 Hz, 1H, C*H*=CO), 3.06-2.95 (m, 4H, CH_2CH_2), 2.65 (s, 2H, ArCH_2), 1.18 (s, 6H, 2 CH_3). **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{17}H_{20}NO$): 254.1539, found: 254.1534.

(2)-(3,3-Dimethyl-3,4-dihydroisoquinolin-1-yl)-1,3-di(thiophen-2-yl)propan-1-ol (147)



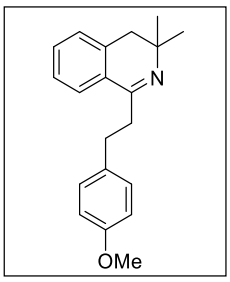
Brown oil from sulfone **137** (68 mg) and thiophene-2-carbaldehyde. **^{1}H RMN** (400 MHz, $CDCl_3$): δ 7.44 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.40-7.36 (m, 2H, Ar*H*), 7.29-7.27 (m, 1H, Ar*H*), 7.19 (d, *J* = 5.1 Hz, 1H, SC*H*=CH), 7.15 (d, *J* = 5.1 Hz, 1H, SC*H*=CH), 6.94 (dd, *J* = 5.1, 3.5 Hz, 1H, SCH=C*H*), 6.89 (dd, *J* = 5.1, 3.5 Hz, 1H, SCH=C*H*), 6.82 (d, *J* = 3.5 Hz, 1H, C*H*=CS), 6.68 (d, *J* = 3.5 Hz, 1H, C*H*=CS), 5.35 (d, *J* = 3.2 Hz, 1H, C*H*OH), 4.07 (m, 1H, *CH*CHOH), 3.27 (dd, *J* = 16.7, 4.6 Hz, 1H, CH*H*Ar), 3.2 (dd, *J* = 16.7, 9.0 Hz, 1H, C*H*HAr), 2.70 (s, 2H, ArCH_2), 1.27 (s, 3H, CH_3) 1.25 (s, 3H, CH_3). **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{22}H_{24}NOS_2$): 382.1294, found: 382.1289.

***(E)*-3,3-Dimethyl-1-(2-(pyridin-2-yl)vinyl)-3,4-dihydroisoquinoline 2-oxide (148)**



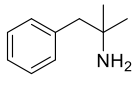
Yellow oil from sulfone **137** (68 mg) and 2-pyrydinecarboxaldheyde. **^{1}H RMN** (400 MHz, $CDCl_3$): δ 8.62 (d, *J* = 3.9 Hz, 1H, Ar*H*), 7.73 (d, *J* = 15.8 Hz, 1H, PyC*H*=CH), 7.70-65 (m, 2H, Ar*H*), 7.46-7.43 (m, 1H, Ar*H*), 7.42 (d, *J* = 15.8 Hz, 1H, PyCH=C*H*), 7.39-7.35 (m, 1H, Ar*H*), 7.33-7.27 (m, 1H, Ar*H*), 7.21-7.17 (m, 2H, Ar*H*), 2.73 (s, 2H, ArCH_2), 1.25 (s, 6H, 2 CH_3). **^{13}C RMN** (101 MHz, $CDCl_3$): δ 154.9, 149.7, 136.9, 136.5, 135.4, 130.7, 129.6, 128.3, 128.1, 126.8, 125.9, 123.0, 122.8, 54.3, 38.9, 27.7. **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{18}H19N_2O$): 279.1492, found: 279.1480.

1-(4-Methoxyphenethyl)-3,3-dimethyl-3,4-dihydroisoquinoline (149)



Brown oil, from sulfone **137** (57 mg) and 4-methoxybenzaldehyde **^{1}H RMN** (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 7.0 Hz, 1H, Ar*H*), 7.43-7.38 (m, 1H, Ar*H*), 7.35-7.30 (m, 1H, Ar*H*), 7.19 (d, *J* = 7.3 Hz, 1H, Ar*H*), 7.02 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.78 (d, *J* = 8.6 Hz, 2H, Ar*H*), 3.77 (s, 3H, OCH_3), 3.00 (dd, *J* = 10.1, 5.8 Hz, 2H, ArCH_2CH_2), 2.86 (dd, *J* = 10.1, 5.8 Hz, 2H, ArCH_2CH_2), 2.69 (s, 2H, ArCH_2), 1.21 (s, 6H, 2 CH_3). **HRMS (ESI) (m/z)** calcd for $[M+H]^+$ ($C_{20}H_{24}NO$): 294.1852, found: 294.1852.

INDEX OF COMPOUNDS



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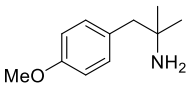

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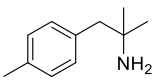

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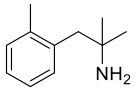

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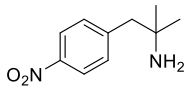

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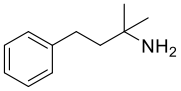

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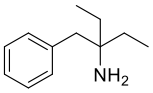

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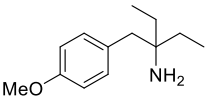

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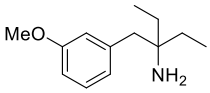

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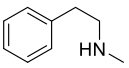

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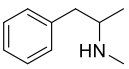

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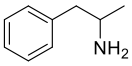

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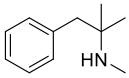

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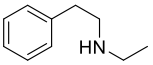

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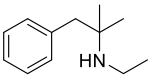

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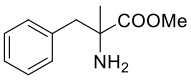

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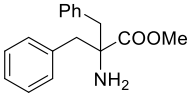

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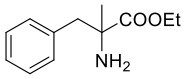

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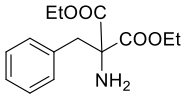

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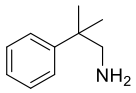

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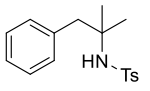

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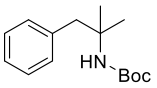

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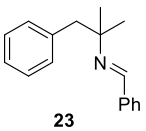

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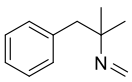

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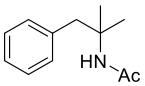

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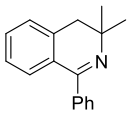

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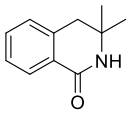

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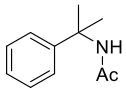

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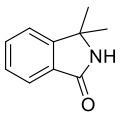

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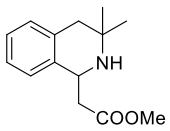

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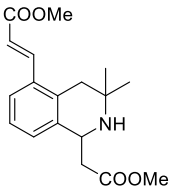

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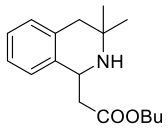

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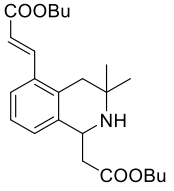

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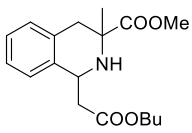

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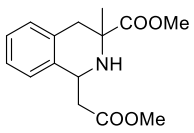

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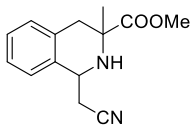

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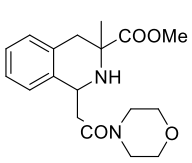

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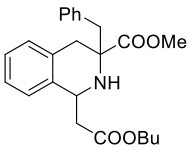

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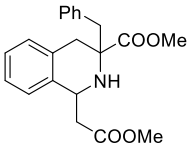

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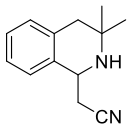

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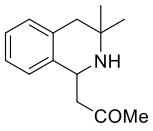

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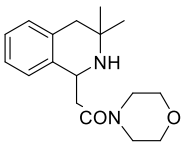

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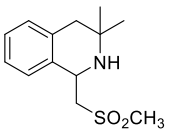

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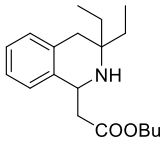

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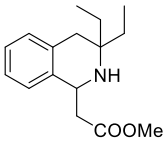

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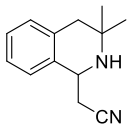

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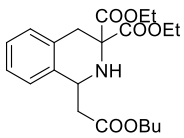

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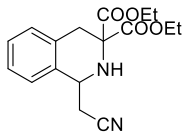

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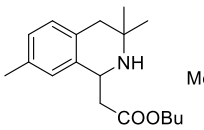

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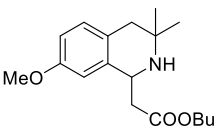

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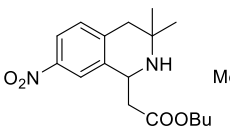

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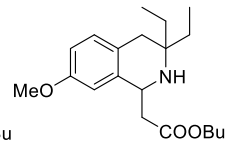

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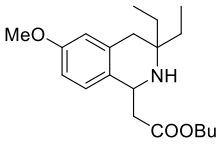

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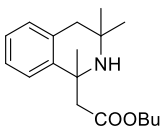

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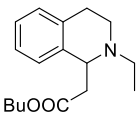

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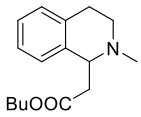

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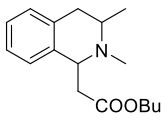

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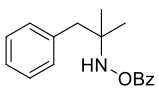

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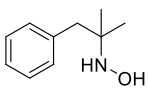

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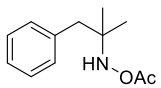

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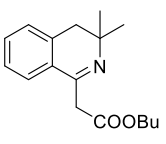

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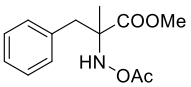

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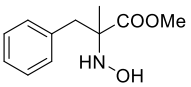

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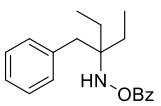

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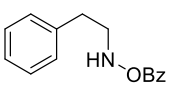

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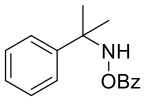

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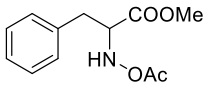

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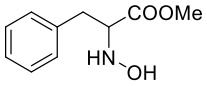

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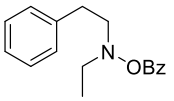

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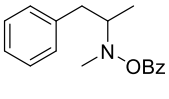

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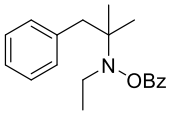

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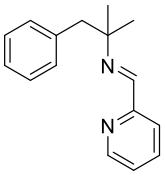

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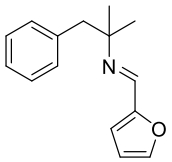

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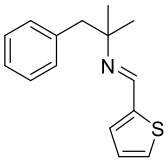

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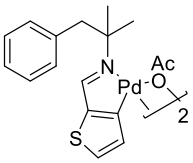

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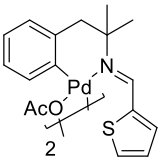

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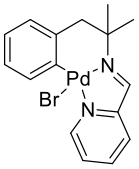

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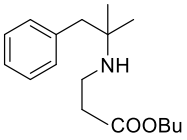

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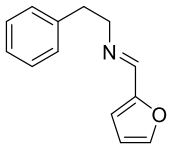

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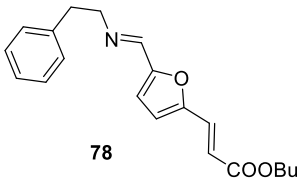

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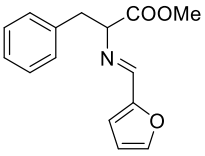

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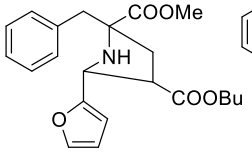

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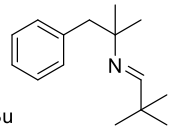

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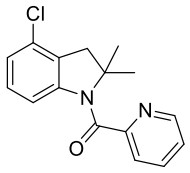

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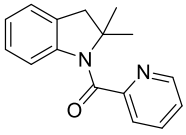

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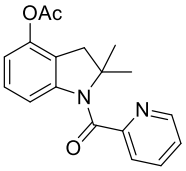

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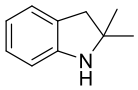

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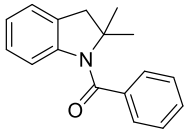

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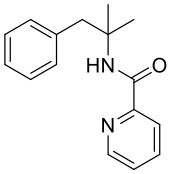

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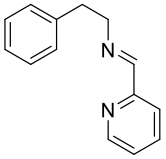

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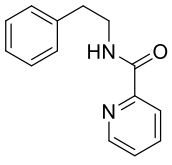

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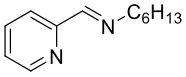

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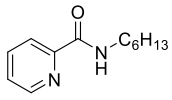

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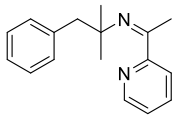

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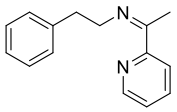

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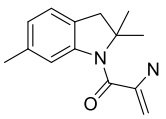

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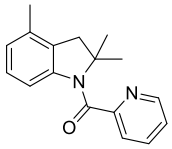

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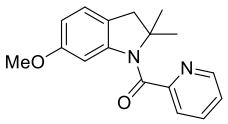

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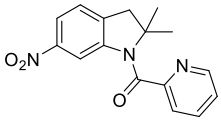

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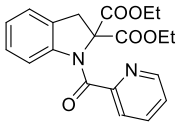

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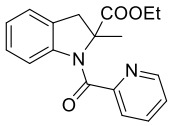

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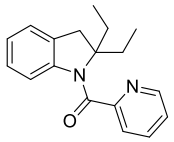

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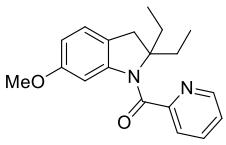

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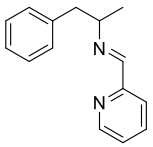

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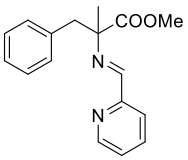

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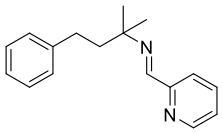

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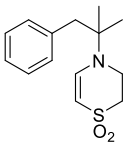

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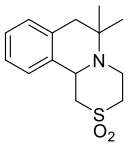

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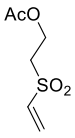

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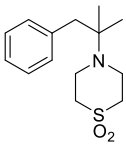

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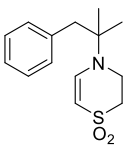

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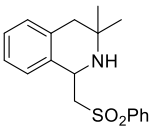

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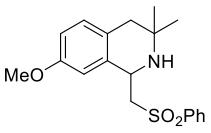

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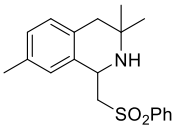

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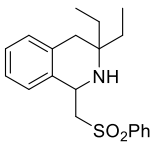

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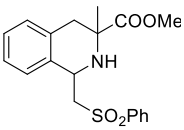

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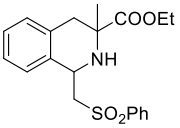

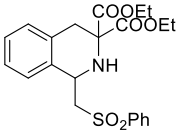

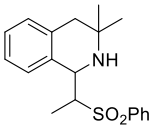

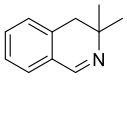

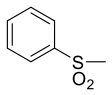

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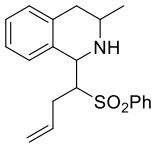

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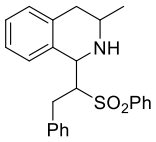

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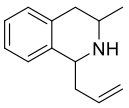

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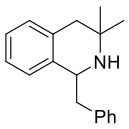

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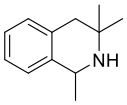

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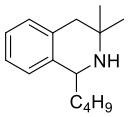

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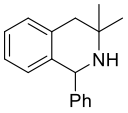

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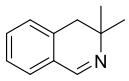

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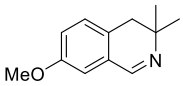

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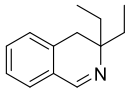

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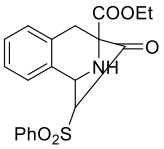

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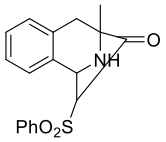

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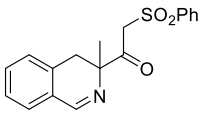

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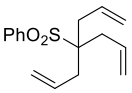

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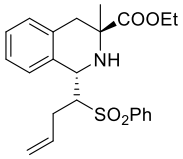

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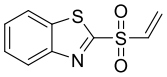

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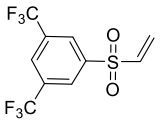

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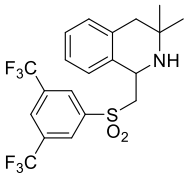

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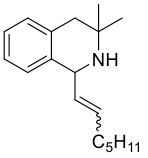

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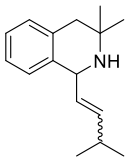

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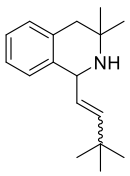

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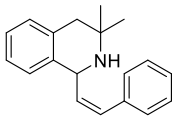

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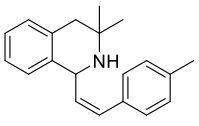

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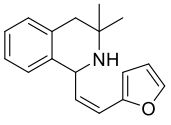

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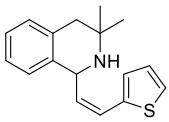

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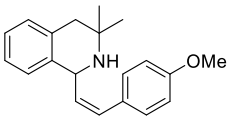

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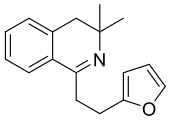

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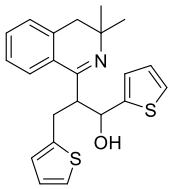

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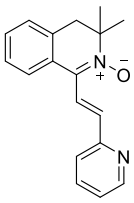

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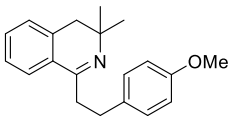

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ABBREVIATIONS AND ACRONYMS

Ac: acetyl
Ar: aryl
B: base
Bn: benzyl
BQ: 1,4-benzoquinone
BT: benzo[*d*]thiazolyl
BTFP: 3,5-bis(trifluomethyl)phenyl
Bz: benzoyl
DCE: dichloroethane
DCM: dichloromethane
DEAD: diethyl azodicarboxylate
DG: directing group
DHIQ: dihydroisoquinoline
DiPAD: diisopropyl azodicarboxylate
DMA: dimethylacetamide
DMF: dimethylformamide
DMSO: dimethyl sulfoxide
E: electrophile
ESI: electrospray
EWG: electron-withdrawing
FG: functional group
i-Pr: isopropyl
LDA: lithium diisopropylamide
M: metal
m-CPBA: meta-chloroperbenzoic acid
Ms: methanesulfonyl
NMR: nuclear magnetic resonance
NXS: *N*-halosuccinimide
P2-Et: 1-Ethyl-2,2,4,4,4-pentakis(dimethylamino)-2λ^5,4λ^5-catenadi(phosphazene), Tetramethyl(tris(dimethylamino)phosphoranylidene)phosphori ctriamid-Et-imin
P4-t-Bu: 1-*tert*-Butyl-4,4,4-tris(dimethylamino)-2,2-bis[tris(dimethylamino)-phosphoranylidenamino]-2λ^5,4λ^5-catenadi(phosphazene)
PBA: perbenzoic acid
Ph: phenyl
pin: pinacolate
Piv: pivaloyl
PT: 1-phenyl-1*H*-tetrazol-5-yl
Py: pyridinyl
Solv: solvent
TBHP: *tert*-butyl hydroperoxide
Tf: trifluoromethanesulfonyl

TFA: trifluoroacetic acid
THF: tetrahydrofurane
THIQ: tetrahydroisoquinoline
Ts: 4-toluene sulfonyl

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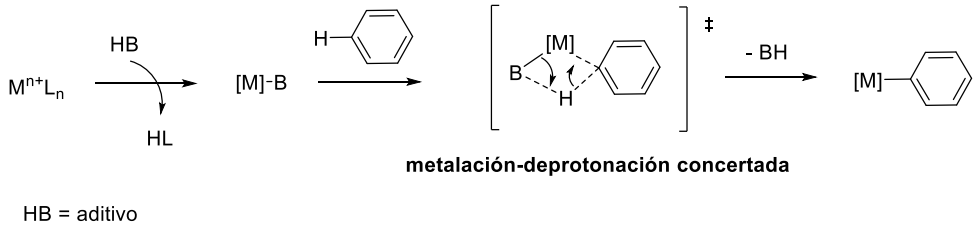
ACTIVACIÓN C-H CATALIZADA POR PALADIO DE ARILETIL AMINAS Y SUS DERIVADOS: APLICACIÓN A LA CONSTRUCCIÓN DE COMPUESTOS HETEROCÍCLICOS

(RESUMEN)

Introducción y objetivos

En la química orgánica tradicional la formación de enlaces carbono-carbono suele realizarse mediante procesos muy variados en los que intervienen nucleófilos y electrófilos, se modifican grupos funcionales, aparecen procesos radicalarios, etc. En la mayoría de estos procesos se ha requerido la ruptura homolítica o heterolítica de un enlace carbono-hidrogeno en un momento u otro. Un ejemplo importante es la sustitución electrófíla aromática en la que se reemplaza un enlace C-H, que se rompe al final, por un enlace C-C o C-heteroátomo. En muchos casos, la fácil abstracción de un protón relativamente ácido genera un nucleófilo que puede utilizarse luego en reacciones de sustitución. El problema en la formación de nuevos enlaces C-C surge cuando el hidrogeno que se tiene que eliminar no es especialmente ácido ni presenta reactividad peculiar alguna. En estos casos, si se utiliza un sistema tan reactivo como para reaccionar con enlaces C-H no "activados", los procesos de substitución no resultarían selectivos, dando lugar a mezclas de productos.

En este sentido, algunos metales de transición, como paladio, rodio, rutenio, o iridio presentan una considerable utilidad para la inserción en enlaces C-H inertes. Los metales de este tipo pueden romper fácilmente los enlaces C-H sp^2 de compuestos aromáticos estén o no no substituido. Este tipo de activación aparece en la mayoría de los casos de sustitución electrófila concertada en los que el metal actúa como electrófilo y se une al carbono, mientras uno de sus ligandos interacciona con el protón a substituir facilitando su eliminación (Esquema 1).[1] De esta manera se genera un enlace C-M, mucho más reactivo, en lugar de un enlace C-H aromático, prácticamente inerte. El nuevo enlace puede reaccionar con electrófilos o con otros tipos de moléculas deficientes de electrones permitiendo al final la substitución del átomo de hidrogeno original un nuevo grupo.



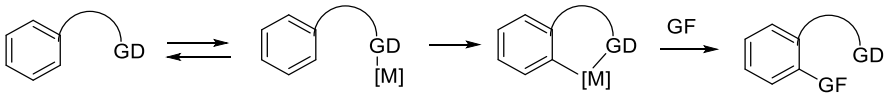
Esquema 1.

Gracias a propiedades de metales de transición, en los años 70 se empezaron a realizar transformaciones que hasta ese momento solo se habían podido imaginar, como la olefinación del benceno o la carboxilación de compuestos aromáticos no activados.[2,3]

Con el tiempo la activación de enlaces C-H inertes catalizada por metales se ha convertido en un campo de trabajo muy activo. La posibilidad de introducir directamente un sustituyente en una estructura o de juntar dos fragmentos de una molécula sin tener que pasar por la preparación de intermedios activados es muy

atractiva en el ámbito de la química sintética ya que ahorra recursos y sobre todo de tiempo.

El principal problema que se ha tenido que solucionar en relación a la funcionalización de enlaces C-H catalizada por metales de transición, es el tema de la selectividad. Las estructuras químicas presentan muchos enlaces C-H con propiedades y reactividad idénticas o muy parecidas. Por esta razón es necesario encontrar estrategias para que durante una reacción no se verifique la funcionalización de posiciones distintas de moléculas diferentes o de más sitios a la vez en la misma molécula. La forma más utilizada para superar esta dificultad ha sido el uso de grupos directores (GD): esta estrategia prevé la introducción en la estructura de la molécula que se quiere activar de funcionalidades que contengan un heteroátomo o un grupo de átomos capaces de coordinar el metal. La coordinación inicial del metal permite una activación selectiva del enlace C-H, frecuentemente en la posición vecina al grupo director (Esquema 2).



Esquema 2.

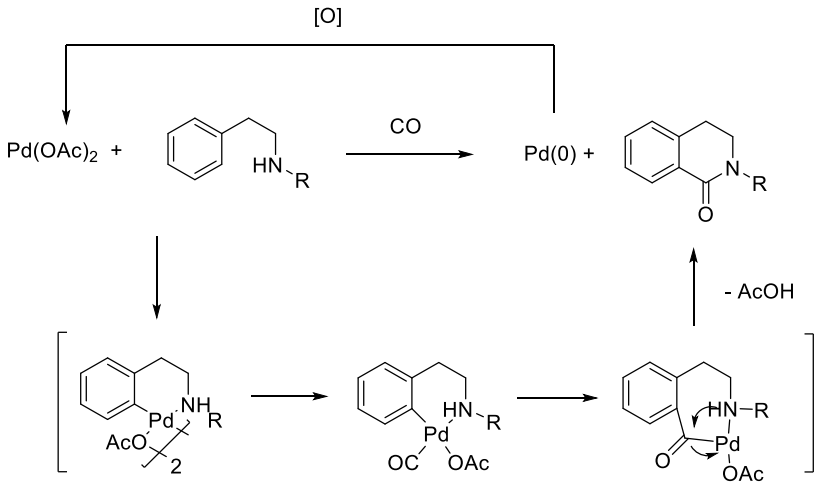
Los grupos directores suelen contener uno o más átomos de oxigeno o nitrógeno como átomos coordinantes y los más comunes son ácidos carboxílicos o sulfónicos,[4] cetonas[5] o alcoholes[6], amidas o sulfamidas[7-16], piridinas[17-26] o iminas y sus derivados. Gracias a esta estrategia en las últimas décadas se han descrito un gran número de procesos de funcionalización selectiva de compuestos aromáticos que contienen estos grupos funcionales. Las reacciones más comunes catalizadas por metales de transición que se han realizado sobre arenos han sido las olefinaciones, las arilaciones, las carbonilaciones o las acilaciones selectivas de la posición orto del anillo bencénico además de procesos oxidativos como halogenaciones o acetoxilaciones del enlace C-H.

Contrariamente a otros grupos funcionales nitrogenados, las aminas no juegan un papel destacado como grupos directores en la química de activación C-H, a pesar de su importancia en la síntesis orgánica y su presencia en muchos fármacos y productos naturales. La razón principal es su propiedad de base de Brönsted que le lleva a coordinar fuertemente los metales, impidiendo a menudo la correcta evolución del proceso catalítico. Además las aminas son muy reactivas frente a diferentes grupos funcionales y generan en muchos casos reacciones secundarias. La mayoría de los trabajos reportados en la literatura se refieren, en todo caso, a la activación C-H de aminas terciarias o 2-arilanilinas.[27-41] Así pues, sobre activación C-H dirigida por aminas primarias pueden encontrarse pocos artículos publicados y se limitan a ejemplos en la activación C-H de bencilaminas.

Sobre este tema, el grupo de investigación de los Drs. Ariza y García en el que se ha desarrollado este trabajo de tesis inició hace unos años una colaboración con los Drs. Albert y Granell del Departamento de Química Inorgánica de la Universitat de Barcelona. Al principio de la cooperación se logró el aislamiento de algunos complejos

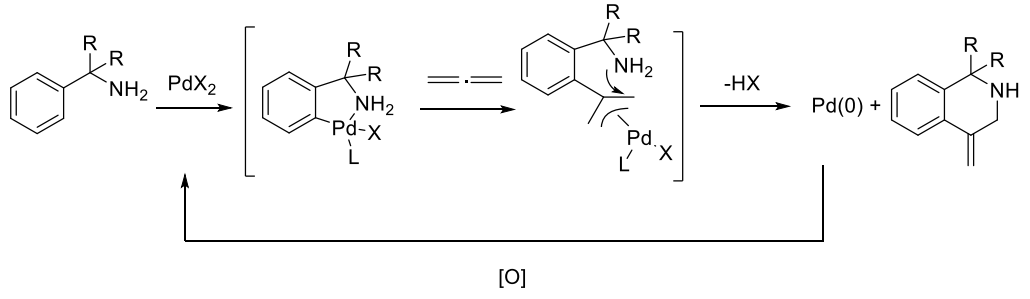
de paladio derivados de la metalación de ariletil aminoesters. Estos complejos presentaban alta reactividad hacia el monóxido de carbono, propiedad gracias a la cual se pudo conseguir por primera vez la puesta a punto de una reacción de carbonilación de aminas primarias catalizada por paladio para la obtención de benzolactamas.[42-43]

La carbonilación de ariletilaminas mostró ser un tema interesante debido a la doble función que ejerce el grupo director: en la primera parte del ciclo catalítico coordina el metal dirigiendo la metalación del anillo aromático a la posición *orto* deseada, para actuar luego como nucleófilo atacando el C=O activado por el Pd y promoviendo una ciclación con formación de la lactama (Esquema 3).



Esquema 3.

Otro logro de esta línea de investigación se consiguió algunos años después al poder realizar un proceso de inserción de alenos en la estructura de ciertas bencil- o feniletilaminas. También en este caso el nitrógeno promueve inicialmente la activación del enlace C-H generando un paladaciclo que se inserta en el carbono central del aleno. El complejo π-allil paladio resultante experimenta luego un ataque del NH_2 en uno de los extremos del sistema alílico generando el heterociclo final (Esquema 4).[44]



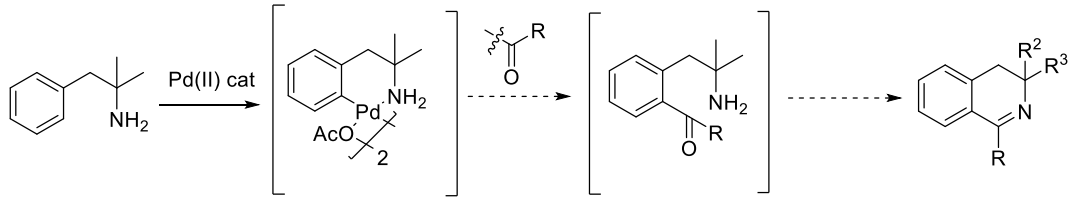
Esquema 4.

El principal objetivo de este proyecto de Tesis ha sido la búsqueda y desarrollo de nuevas reacciones catalizadas por paladio dirigidas a la funcionalización del enlace C-H de ariletilaminas en las que el grupo amina actuara como grupo director y nucleófilo al mismo tiempo. Se continuaba con ello una línea de trabajos precedentes del grupo de

investigación buscando la obtención de sistemas heterocíclicos nitrogenados de interés. Otro objetivo ha sido el estudio de algunos análogos de las aminas como nuevos grupos directores para reacciones de activación C-H.

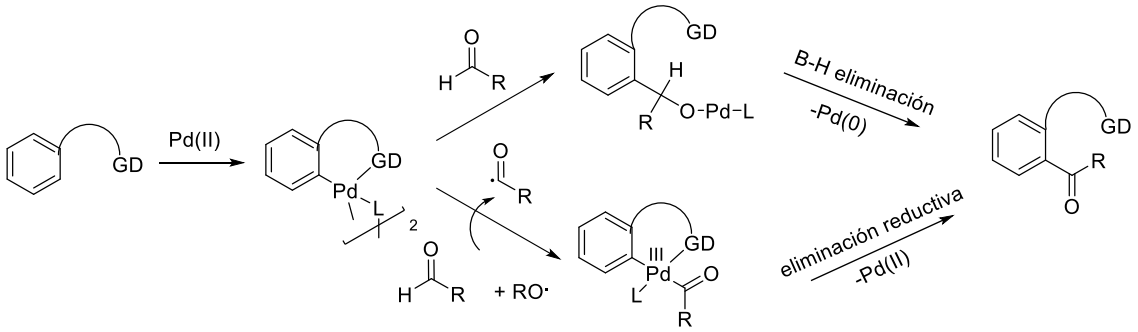
Capítulo 1

En el primer capítulo de esta Memoria se han descrito algunos intentos de acilación de la posición orto del anillo aromático de feniletilaminas. Este tipo de reacción tiene abundantes precedentes en la literatura donde se introduce el grupo arilcarbonilo (o distintos equivalentes sintéticos) gracias a procesos de activación C-H. Así, encontramos descritos ejemplos con aldehídos, alcohol bencílico, nitrilos y ácidos α-oxo carboxílicos).[26,45-47] En estas reacciones se han empleado distintos grupos directores nitrogenados que están presentes en el sistema aromático (piridinas, oximas, azo derivados, amidas....) pero no el grupo amina. Si tuviera lugar la acilación de ariletilaminas primarias sería probable una condensación posterior entre la amina y el nuevo grupo introducido, generando isoquinolinas funcionalizadas (Esquema 5).



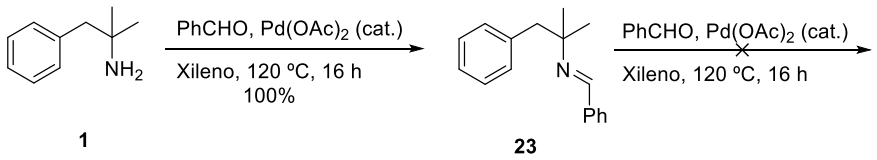
Esquema 5.

Este tipo de procesos puede transcurrir por dos mecanismos distintos, dependiendo del tipo de análogo de grupo aril carbonilo y de oxidante empleado para regenerar el Pd(II).[48] En la mayoría de los casos el electrófilo se inserta en el enlace C-Pd del areno activado y la posterior β-eliminación de un hidruro de Pd lleva a la formación del producto y a la reducción del catalizador. En cambio, en presencia de radicales la reacción evoluciona a través de la adición de un radical al complejo metal-areno que genera un complejo de paladio hipervalente. La eliminación reductiva del metal de transición proporciona el producto y vuelve a generar el catalizador (Esquema 6).



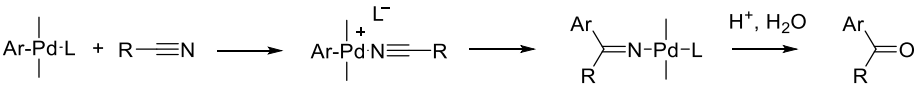
Esquema 6.

En los intentos de acilación de nuestro modelo de feniletilamina con el NH_2 sobre carbono cuaternario (compuesto **1**) con aldehídos se pudo observar la formación de la imina **23** que no evolucionaba hacia ningún otro producto en ausencia de especies radicalarias (Esquema 7). En cambio, en presencia de peróxidos siempre se obtenían mezclas complejas a partir tanto de la amina **1** como de la imina **23**, tanto si se utilizaban aldehídos como alcoholes bencílicos para generar los radicales.



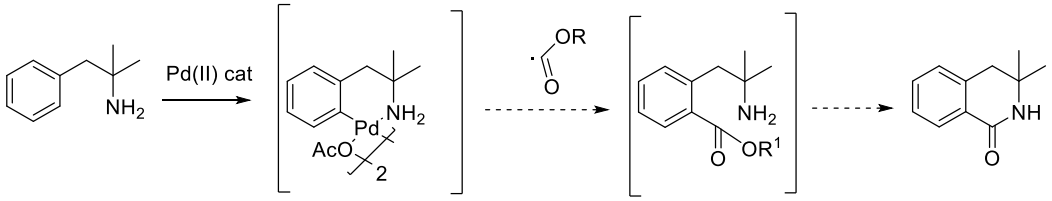
Esquema 7.

Las pruebas de acilación con ácidos α-oxo carboxílicos (buscando la generación del acilo por decarboxilación del ácido) sólo proporcionaron mezclas complejas usando distintas condiciones descritas en la literatura para este tipo de procesos con otros activadores. Finalmente se probó el uso de nitrilos para la obtención de cetiminas fácilmente transformables en cetonas, de acuerdo con algunos precedentes bibliográficos (el proceso esperado se muestra en el Esquema 8), pero en este caso no se observó reactividad alguna operando en medios ácidos, mientras que en otras condiciones se obtenían mezclas complejas.



Esquema 8.

Como parte del trabajo experimental correspondiente a este capítulo se probó también la carboxilación de nuestra amina **1** en presencia de Pd(II) con radicales alcoxicarbonilo generados espontáneamente por descomposición térmica de azodicarboxilatos.[49] En este caso la introducción de un grupo ester en el anillo aromático haría posible la amidación intramolecular para la formación de lactamas como se muestra en el Esquema 9.



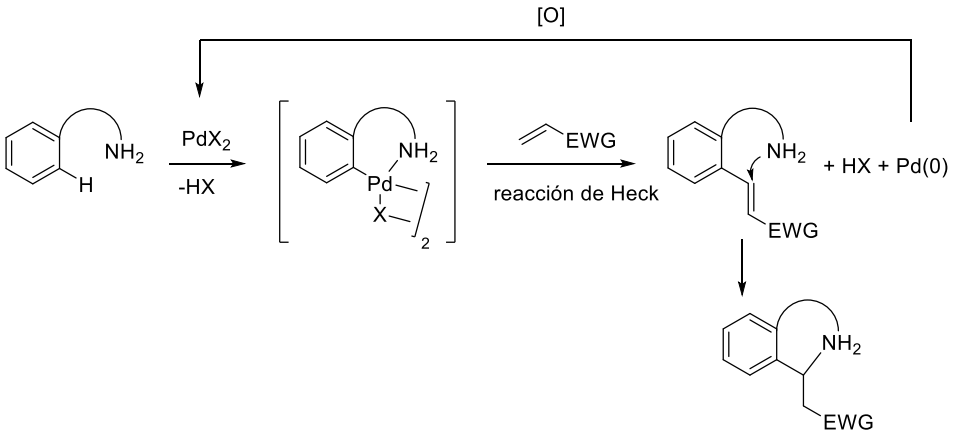
Esquema 9.

Efectivamente, el producto deseado se pudo obtener y aislar de los crudos de reacción, aunque con rendimientos que no superaban el 20% a pesar de los numerosos intentos de optimización que se efectuaron. El mayor problema de esta reacción era la formación, incluso en las mejores condiciones para la obtención de la lactama, de cantidades importantes de la correspondiente acetamida. El escaso éxito de los resultados obtenidos

con azodicarboxilatos nos movió a descartar más esfuerzos en la reacción entre feniletil aminas y radicales acilo promovidas por paladio.

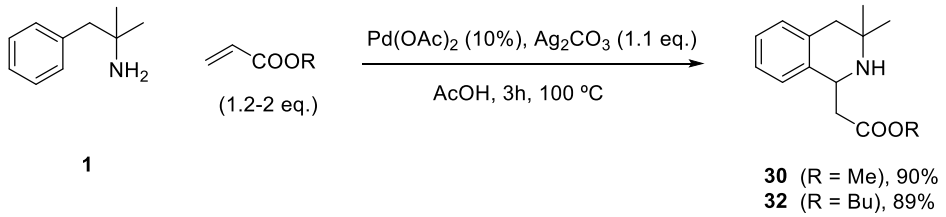
Capítulo 2

El capítulo más extenso de la presente Memoria de Tesis Doctoral corresponde al desarrollo y culminación de una reacción en la que dos miembros del grupo (C. Alamillo y H. Etxabe) habían trabajado en sus respectivos Máster Experimental en la Universidad de Barcelona. Se trataba de la inserción de alquenos deficientes de electrones en la estructura de feniletil aminas primarias. La reacción planeada se basaba en una reacción de Heck entre la amina y la olefina seguida de una adicción tipo Michael intramolecular del nitrógeno sobre el doble enlace (Esquema 10).



Esquema 10.

C. Alamillo y H. Etxabe estudiaron la adición de acrilatos de metilo y butilo a la amina **1** (Esquema 11) y obtuvieron también algunas isoquinolinas derivadas de amino esteres.



Esquema 11.

En este trabajo de tesis se ha estudiado la aplicabilidad y generalidad de este proceso sobre diferentes alquenos y aminas. En la Figura 1 aparecen los resultados más relevantes en forma de tabla de compuestos accesibles con este método. Como conclusión, respecto a los electrófilos se constató que mientras que los acrilatos de metilo y butilo proporcionaban los mejores rendimientos, otras olefinas conjugadas como acrilonitrilo, cetonas conjugadas, acrilamidas y vinil sulfonas, resultaban también adecuadas para la obtención de las isoquinolinas, ofreciendo rendimientos entre buenos y moderados. En cambio, olefinas cíclicas (como ciclohexanona) o más substituidas (como metacrilatos o fumaratos) no resultaron suficientemente reactivas. Una excepción

fue el crotonato de metilo con que se obtuvo el producto ciclado esperado, aunque en bajo rendimiento. En cuanto a las aminas, los datos parecen evidenciar un cierto balance entre el efecto estérico y el efecto electrónico que ejerce la presencia de un grupo atractor de electrones en C vecino al nitrógeno. Así, en la olefinación con buenos electrófilos el efecto negativo del impedimento estérico se hace patente (comparar, por ejemplo, compuestos **32** y **44**), mientras al utilizar olefinas menos activas, como acrilonitrilo o acrilamides, la presencia del grupo atractor de electrones mejora considerablemente la eficiencia del proceso, independientemente del tamaño del electrófilo (compuestos **36**, **37** y **48**).

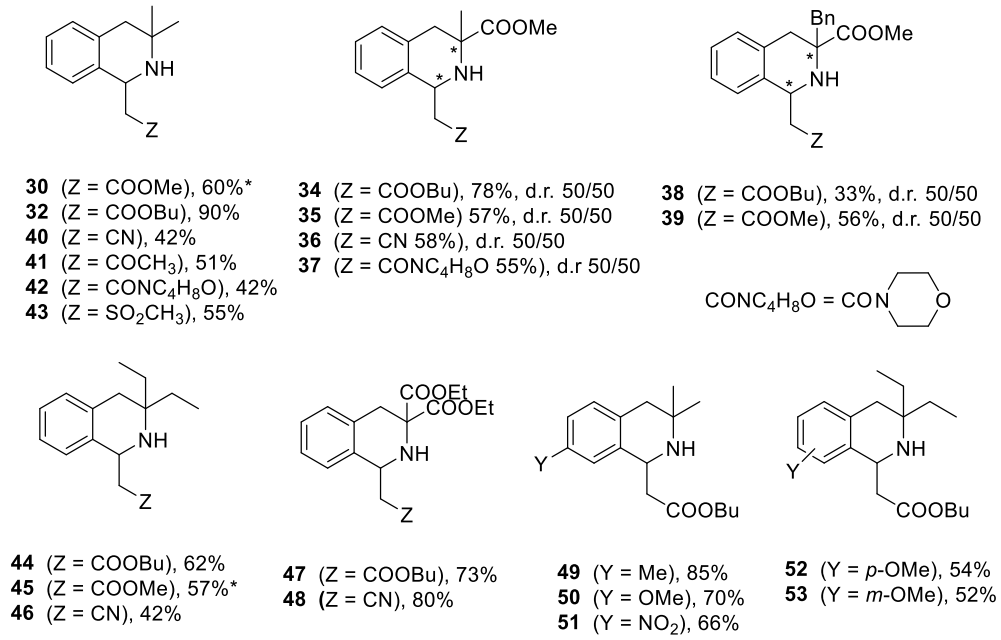
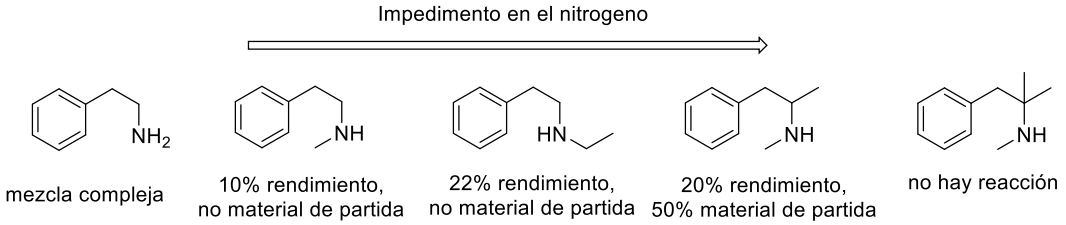


Figura 1.

Se ha demostrado también la posibilidad de acceder a otras tetrahidroisoquinolinas substituidas en el anillo aromático, aunque la introducción de grupos nitro o metóxido conducía rendimientos más bajos (compuestos **50-53**) respecto a los que se habían observado para los substratos no substituidos. Sin embargo, la introducción de un grupo metilo casi no afecta la extensión de la reacción (**49**).

Finalmente se buscaron las limitaciones estructurales del sustrato en este proceso. Para ello se prepararon varias aminas primarias, secundarias, o protegidas con distintos sustituyentes en la posición α respecto al nitrógeno para ensayar su efectividad en la condensación con olefinas. Como resultado se pudo constatar una dependencia de la reactividad de las aminas respecto al impedimento estérico alrededor del átomo de nitrógeno. La *N*-metilamina unida a un centro cuaternario ensayada, así como las aminas protegidas, no exhibían ninguna reactividad frente a aceptores de Michael. Por otra parte, las aminas primarias no substituidas o con un único sustituyente en la posición α proporcionaban mezclas complejas presentando una reactividad competitiva sobre el N en las condiciones de reacción. Las aminas secundarias sin o con un solo sustituyente en la posición α fueron los únicos modelos que llevaron a la formación de

los productos deseados, aunque con rendimiento muy bajo al tiempo que aparecían diferentes subproductos no identificados (Esquema 12).



Esquema 12.

Capítulo 3

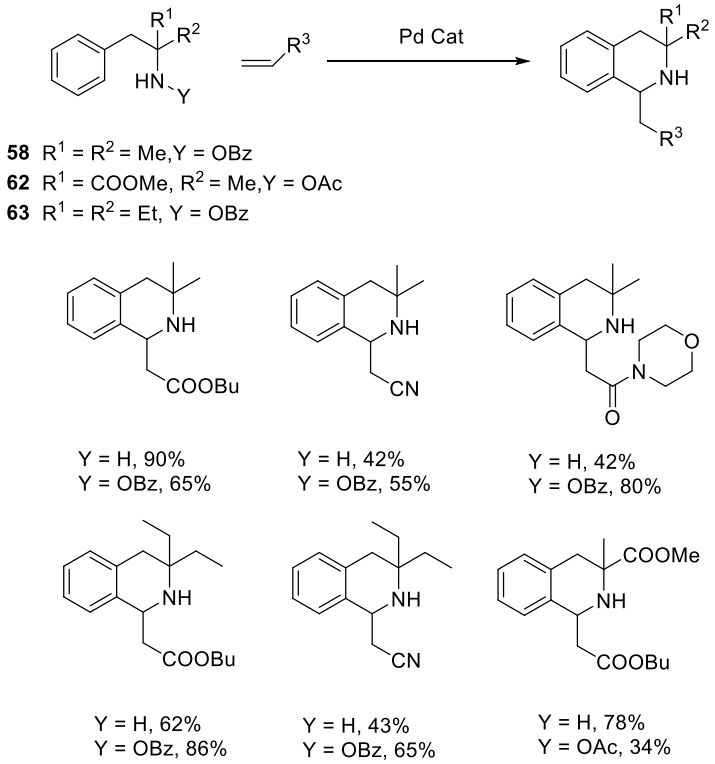
En el tercer capítulo de esta memoria se estudió el efecto de la substitución del grupo amino por algunos análogos oxidados como grupos directores en las reacciones.

La mayoría de los procesos de activación C-H catalizados por metales de transición (incluso los que se han descrito hasta ahora en los párrafos anteriores de este resumen) prevén la eliminación reductiva del catalizador al final de cada ciclo del proceso catalítico. Esto implica la necesidad de utilizar agentes que re-oxiden el metal de transición para que este pueda ser utilizado en cantidad catalítica, generando necesariamente cantidades estequiométricas de los agentes oxidantes, ahora en forma reducida, como desecho. Esto va en contra de los principios de "atom economy" de los que hacen bandera la química de activación C-H. Además, la elección del oxidante adecuado, que permita la re-oxidación del metal sin interactuar en otras maneras en los procesos, es una tarea que puede resultar difícil.

Por estas razones en los últimos diez años algunos grupos de investigación se han centrado en la utilización de grupos directores que sean quelantes y oxidantes al mismo tiempo.[50] En general estas funcionalidades contienen un enlace covalente X-Y capaz de oxidar el metal (por ejemplo, enlaces de tipo N-oxido o S-halógeno). Los grupos directores oxidados pueden operar potencialmente de dos maneras distintas. En un caso al final del ciclo catalítico ocurre la ruptura del enlace X-Y que permite la re-oxidación del catalizador. La otra posibilidad prevé la oxidación del metal al principio del ciclo catalítico, a través de la inserción oxidativa del mismo entre el enlace X-Y.

Los trabajos que describen la utilización de oxidantes internos a la estructura del substrato son escasos, por lo tanto se pensó en ensayar la reactividad de análogos oxidados de las aminas en procesos de activación C-H. El objetivo era el desarrollo de nuevos procesos más limpios y al mismo tempo el estudio del efecto que la protección de las aminas con grupo oxidantes presentaba en la coordinación del metal y en la estabilidad y reactividad de los metalaciclos resultantes, con la esperanza de poder ampliar el campo de las transformaciones posibles en comparación con las aminas libres.

Ya en las primeras pruebas exploratorias de esta posibilidad se observó que las *O*-acilhidroxilaminas permitían la inserción de aceptores de Michael catalizada por paladio sin la necesidad de oxidantes adicionales, mientras que las hidroxilaminas libres no eran aplicables al proceso. No obstante, en los numerosos intentos de optimización no fue posible obtener un rendimiento superior al 65% para la olefinación de la *O*-benzoilhidroxilamina **58** (Esquema 13). Por otra parte, durante esta fase se descubrió que el proceso se podía desarrollar tanto mediante el uso de catalizadores de Pd(0) como gracias a catalizadores de Pd(II). Esto parecía sugerir que la reacción podía pasar por dos mecanismos distintos correspondientes a las dos posibilidades que se han explicado en los párrafos anteriores.



Esquema 13.

Se prepararon entonces un conjunto de nuevas aminas "oxidadas" pensando que quizás podríamos obtener más información del mecanismo por el comportamiento y la reactividad de los diferentes sustratos y sus diferencias respecto a las aminas libres (Esquema 13). En primer lugar se observó que los aceptores de Michael que peor comportamiento presentaban en su condensación con aminas libres (como el acrilonitrilo o la acrilamida derivada de la morfolina) proporcionaban, en cambio, mayores rendimientos en su reacción con las *O*-acilhidroxilaminas. Por desgracia no se obtuvieron buenos resultados con las olefinas que se habían revelado inertes para la inserción dirigida por NH_2 (cetonas cíclicas o acrilatos substituidos). También fue remarcable que la hidroxilamina **63**, correspondiente a la amina estéricamente impedida, era la que proporcionaba mejores rendimientos en las reacciones con distintos alquenos, lo que contrastaba con lo que se había observado en la parte precedente de la tesis. Sin embargo, el modelo oxidado **62**, derivado del amino ester, daba un

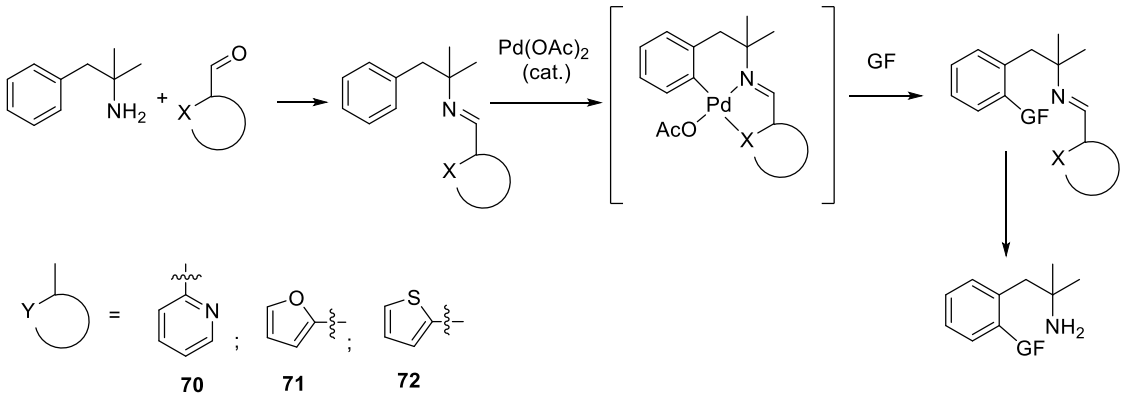
rendimiento bajo en esta reacción, a diferencia de lo que se había observado para la amina libre. Estos cambios de reactividad se justifican sin duda por el cambio en el mecanismo que opera, aun conduciendo a los mismos productos, en las aminas libre y las aminas "oxidadas".

Lamentablemente este cambio en la reactividad no permitió superar las limitaciones estructurales de los substratos que se habían observado por las aminas: los análogos oxidados de las aminas que no eran aptas por esta transformación se revelaron igualmente inutilizables.

Finalmente se intentó sin éxito la aplicación de las *O*-acilhidroxilaminas a otros procesos de activación C-H (carbonilación, reacción con radicales, etc…).

Capítulo 4

En el cuarto capítulo de esta memoria se describen algunas pruebas en la utilización de iminas como precursores de aminas que puedan funcionar como grupos directores "provisionales". Como ya se ha explicado antes, la utilización de grupos directores es la estrategia más utilizada para lograr regioselectividad en la química de activación C-H. Al utilizar esta opción suele aceptarse que los grupos quelantes permanecen en la estructura del substrato al final del proceso de funcionalización. Otra opción, no obstante, es el empleo de grupos directores que se puedan eliminar fácilmente. En este sentido, se ha descrito recientemente que los triazenos constituyen un buen grupo director nitrogenado fácil de eliminar en condiciones suaves.[51,52] El uso de iminas como grupos directores en activación C-H no es ninguna novedad pero en esta parte del trabajo se ha estudiado la activación con iminas que lleven incorporado un grupo quelante adicional en su estructura con el intento de obtener paladociclos con tres centros de coordinación, más estables de los conocidos por el grupo de investigación, a utilizar en nuevos procesos catalíticos (Esquema 14). Es obvio que la utilización de iminas como equivalentes a aminas primarias posibilita su hidrólisis posterior durante o al final del proceso estudiado recuperando así la amina inicial.

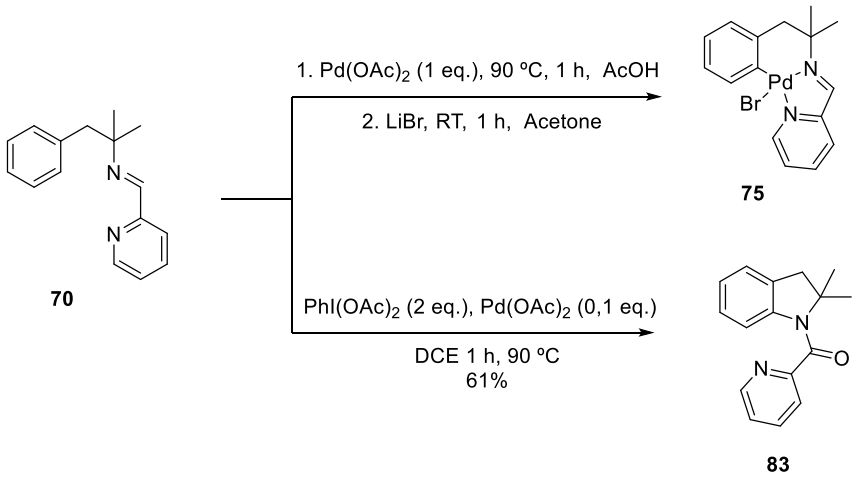


Esquema 14.

Se sintetizaron los compuestos modelo **70**-**72** provistos respectivamente de un anillo de piridina, de tiofeno y de furano como funcionalidades quelantes y con ellos se hicieron

al mismo tiempo dos tipos de pruebas: su metalación estequiometrica (con la finalidad de aislar los complejos metálicos) y también reacciones de olefinación con aceptores de Michael catalizadas por paladio.

Los substratos **71** y **72** parecieron actuar en todos los casos como simples aminas protegidas en las reacciones de olefinación y no se detectó la formación de complejos con tres centros de coordinación en los experimentos de metalación. En cambio, el modelo **70**, que poseía el anillo de piridina, resultó totalmente inerte en las reacciones de olefinación con aceptores de Michael y por otra parte se pudo aislar el complejo de paladio tri-coordinado **75** al tratar **70** con cantidades estequiométricas de Pd(II) (Esquema 15).

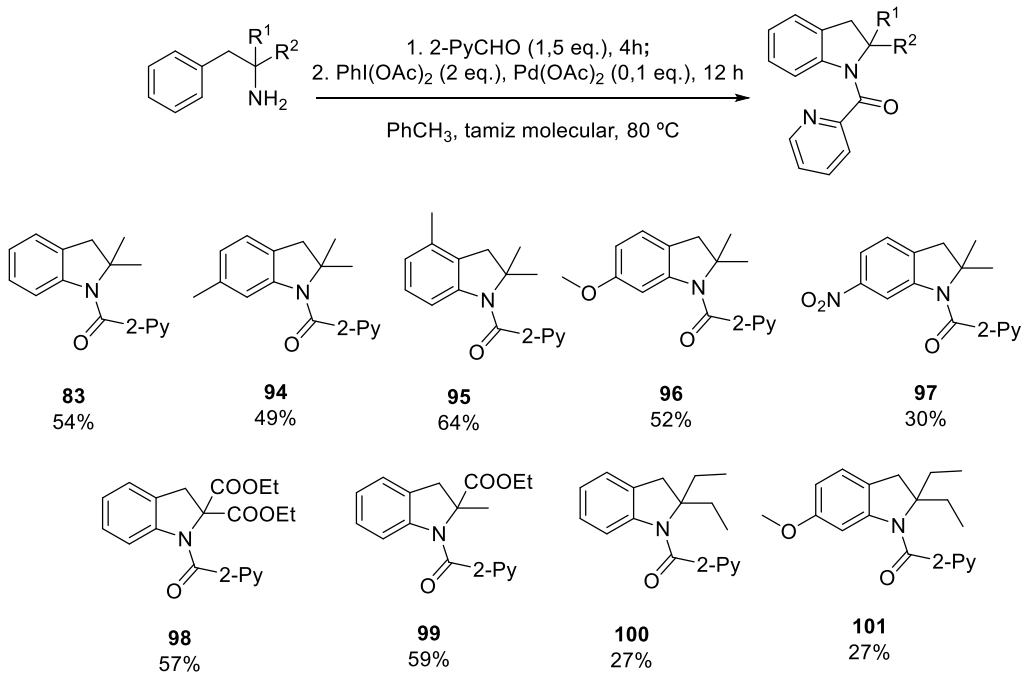


Esquema 15.

A la vista de estos resultados se planteó la posibilidad de usar este substrato en reacciones de tipo oxidativo que implican la formación de especies de paladio (III) o (IV) y que no son aplicables a las aminas. Después de ensayar distintos oxidantes capaces de generar complejos de metales hipervalentes (como *N*-halosuccinimidas, diacetoxiiodobenceno o sales de *N*-fluoropiridinio) se pudo descubrir y optimizar un proceso concertado que comportaba al mismo tiempo la oxidación de la imina **70** a amida y la amidación intramolecular del anillo aromático para la obtención de la indolina protegida **83** (Esquema 15). Este tipo de amidación intramolecular se ha descrito en la literatura a partir de varios tipos de amidas[53,54] pero nunca se ha realizado a partir de aminas o iminas.

El siguiente paso fue la búsqueda de unas condiciones de reacción adecuadas para la formación directa de precursores de indolinas a partir de aminas primarias, a través de la formación *in situ* de iminas. Este objetivo se pudo conseguir cambiando las condiciones de reacción de forma que se favorecía la condensación inicial. En seguida se aplicó el método a distintas aminas primarias para estudiar el campo de aplicabilidad de la reacción (Esquema 16). Se pudo constatar, una vez más, que la presencia de un centro cuaternario en α al nitrógeno era una condición necesaria a la obtención de los productos. Otras limitaciones estructurales que hacían bajar considerablemente el

rendimiento eran el impedimento estérico al alrededor del nitrógeno, así como la presencia de un grupo fuertemente atractor de electrones en el anillo aromático (Esquema 16).

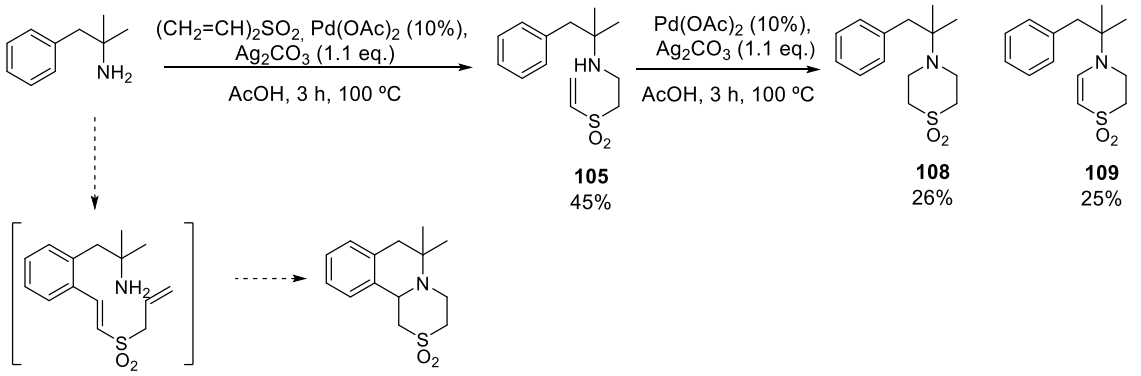


Esquema 16.

Capítulo 5

En el último capítulo del trabajo de tesis se estudió la inserción de vinilsulfonas en las ariletilaminas y su posterior funcionalización para la obtención de nuevos tipos de tetrahidroisoquinolinas funcionalizadas.

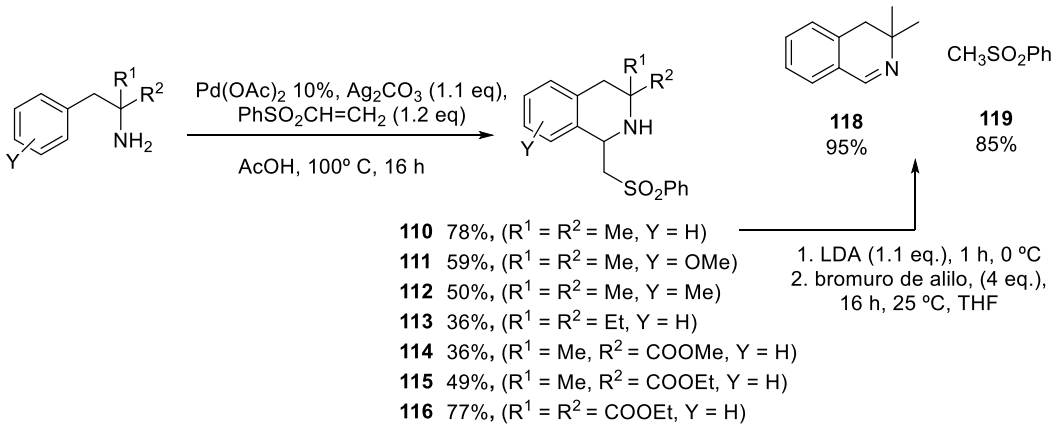
Las sulfonas son sin duda una funcionalidad interesante y versatil en la química sintética y se ha utilizado ampliamente en la formación de enlaces carbono-carbono: los α-sulfonil carbaniones, que son buenos nucleófilos, se pueden fácilmente funcionalizar y por otra parte el grupo sulfonilo se puede eliminar gracias a la estabilidad del grupo RSO_2^- o del dióxido de azufre como buenos grupos de salida.[55] De esta manera la alquilación seguida por una desulfurilación reductiva (que se obtiene gracias a metales activos) permite la formación de alcanos. De igual modo, otras reacciones, como la alquilación seguida por eliminación reductiva, la reacción de Ramberg-Bäcklund y la reacción de Julia, llevan a la formación de alquenos.



Esquema 17.

Nuestro primer objetivo fue el estudio de la olefinación de la amina **1** con divinil sulfona catalizada por paladio. Se esperaba que el aducto resultante de una inicial reacción de Heck pudiera experimentar luego una doble adición de Michael del NH_2 sobre las olefinas remanentes permitiendo la formación de un producto tricíclico. Tales compuestos serían muy interesantes ya que se habría podido eliminar la sulfona gracias a una reacción de Ramberg-Bäcklund modificada. Lamentablemente, operando en las mismas condiciones que se utilizaban para la adición de ariletilaminas a los aceptores de Michael, sólo se obtuvo una mezcla de compuestos en la que el mayoritario era el producto **105** resultante de la adición intermolecular de la amina sobre la divinil sulfona. Sobre el papel este subproducto podía transformarse en el compuesto deseado mediante una reacción de Heck intramolecular, pero a pesar de los esfuerzos realizados fue imposible llevar a cabo este proceso (Esquema 17).

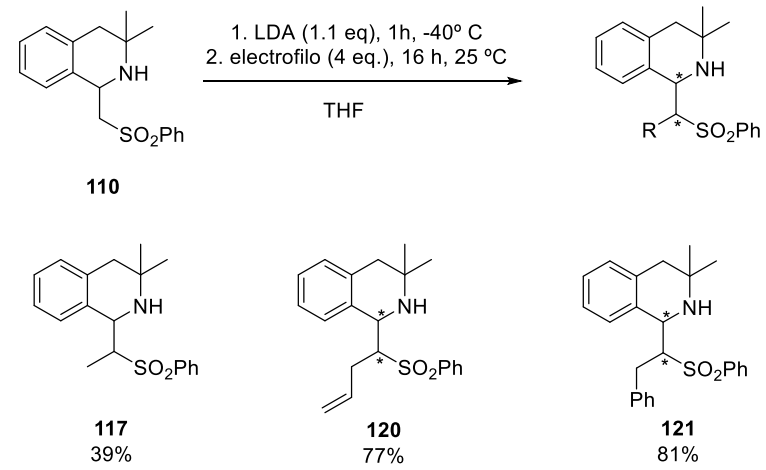
El siguiente paso fue la preparación de los modelos de sulfonas aromáticas **110-116** y se intentó la alquilación del modelo más sencillo, compuesto **110**. Sorprendentemente se descubrió que la alquilación buscada resultava desfavorecida predominando en cambio una inesperada eliminación de fenil metil sulfona con la formación de un heterociclo con estructura de dihidroisoquinolina (Esquema 18).



Esquema 18.

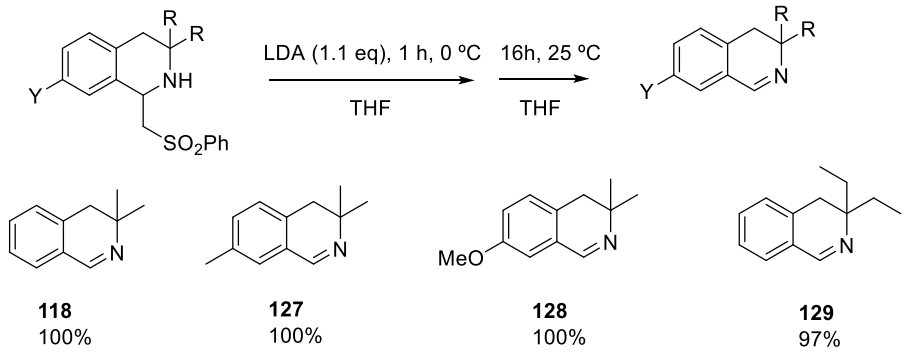
Ulteriores pruebas, realizadas en condiciones distintas, demostraron que la alquilación de la posición α de este tipo de sulfonas se podía conseguir modificando las condiciones

de reacción y sólo empleando electrófilos muy buenos, como iodometano o bromuros de alilo y de bencilo (Esquema 19).



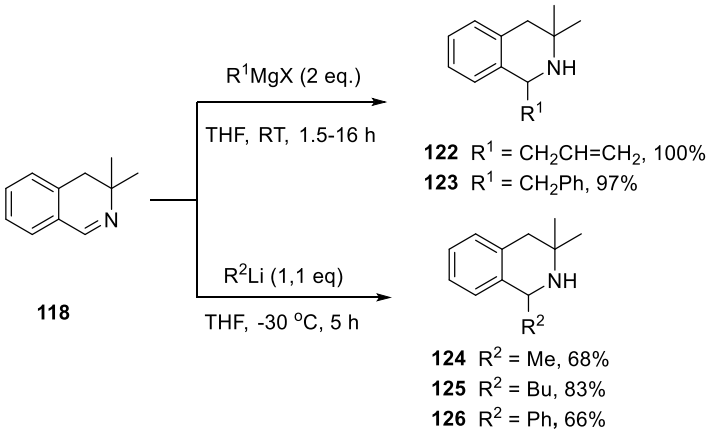
Esquema 19.

En cambio, la eliminación de la sulfona se pudo obtener en manera sencilla y cuantitativa a partir de todos los modelos (Esquema 20), a excepción de los amino esteres para los que se observaban reacciones secundarias por intervención del grupo éster.



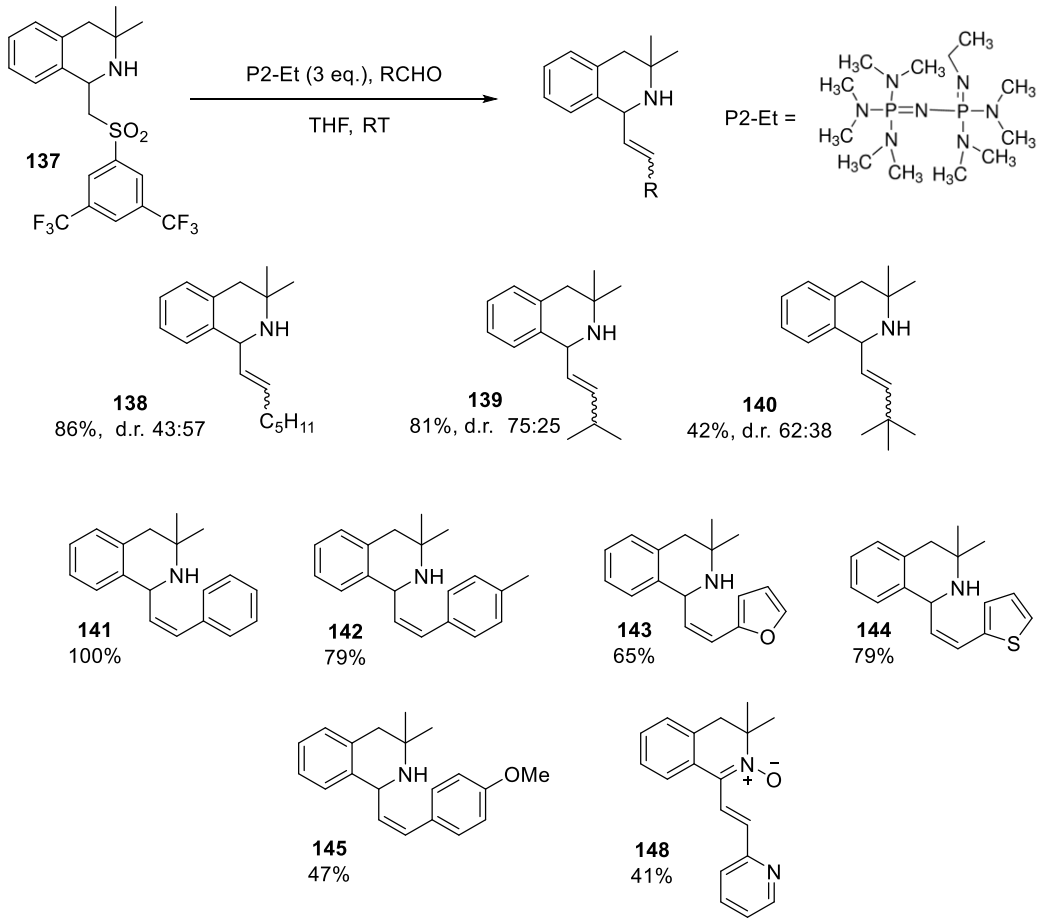
Esquema 20.

A la vista de estos resultados se planteó la posibilidad de adicionar un grupo alquilo a las dihidroisoquinolinas que se obtenían con esta novedosa eliminación. Operando con magnesianos se logró introducir los grupos alilo o bencilo con rendimiento cuantitativo en la estructura de la imina **118**, mientras el utilizo de órganolíticos permitió la funcionalización con alquilos o con fenilo (Esquema 21).



Esquema 21.

La última parte del trabajo consistió en la construcción de un modelo capaz de experimentar una reacción de Julia modificada para la obtención de tetrahidroisoquinolinas insaturadas funcionalizadas. Para ello se preparó la aril sulfona **137** y se buscaron condiciones adecuadas para su condensación con aldehídos.[56]



Esquema 22.

Se consiguieron excelentes resultados tanto en la adición de aldehídos alifáticos como aromáticos (Esquema 22). El resultado más interesante fue que todos los aldehídos

aromáticos llevaban a la formación del alqueno Z con selectividad total (a excepción del 2-piridincarboxaldehido a partir del cual se observa la formación del producto E oxidado **148**). Los aldehídos alifáticos en cambio conducían a la olefina en buenos rendimientos (en la mayoría de los casos) pero con escasa selectividad E/Z. Formaldehido y aldehídos conjugados revelaron ser poco adecuados para este proceso.

Resumen y conclusiones

En la Memoria de Tesis se recoje un amplio estudio de diferentes procesos basados en la activación C-H de ariletil aminas y sus derivados.

En la primera parte del trabajo se ensayó la reactividad de aminas primarias activadas por paladio con distintos equivalentes sintéticos de grupos carbonilos o con especies radicalarias. Resultó que los substratos utilizados no eran reactivos en ausencia de radicales, mientras que experimentaban muchas reacciones colaterales en su presencia. En ningún caso se pudo obtener una funcionalización mayoritaria de forma satisfactoria.

En la segunda parte de la tesis se trabajó en el desarrollo de una reacción catalizada por paladio para la obtención de tetrahidroisoquinolinas a partir de aminas primarias, basándonos en una potencial reacción de olefinación-ciclación catalizada por paladio. Desarrollamos una vasta exploración de las aminas y de las olefinas utilizables en el proceso y se logró la síntesis de muchas tetrahidroisoquinolinas funcionalizadas gracias a la combinación de diferentes ariletil aminas α-cuaternarias con varias olefinas.

Seguidamente se ensayó la reactividad en procesos de activación C-H de análogos oxidados de feniletil aminas con la finalidad de desarrollar procesos catalíticos en ausencia de oxidantes externos. Las *O*-acilhidroxilaminas permitieron realizar el proceso de olefinación-addición de Michael para la obtención de tetrahidroisoquinolinas (descrita en la precedente parte del trabajo) en ausencia de oxidante, llevando en algunos casos a la síntesis de los productos deseados en mayor rendimiento. Lamentablemente los substratos oxidados no se revelaron adecuados para superar las limitaciones estructurales que se habían observado por esta reacción ni para su utilizo en otros procesos de activación C-H.

En la cuarta parte del trabajo se ensayó el uso de iminas, como grupo director equivalente al grupo amino de las ariletil aminas pero que podía ser eliminado posteriormente por hidrólisis. Este estudio llevó al aislamiento de un nuevo complejo de paladio con tres centros de coordinación y al desarrollo de una reacción catalizada por paladio para la construcción de precursores de indolinas a partir de aminas primarias, nunca descrito anteriormente. Desafortunadamente los rendimientos y el campo de aplicabilidad del proceso fueron sólo moderados. Además, la oxidación de las iminas a amidas, que ocurría en el proceso de ciclación, no estaba de acuerdo con la idea inicial de introducir grupos quelantes fáciles de eliminar.

Finalmente se estudió la reactividad de modelos de sulfonas aromaticas construidas gracias a la reacción de olefinación-ciclación descrita en el segundo capítulo de la

memoria. Fruto de este trabajo se descubrió una reacción inusual de eliminación de la sulfona y la posterior formación de dihidroisoquinolinas. La funcionalización de estos productos y la búsqueda de condiciones adecuadas para una reacción de Julia modificada a partir de bis(trifluorometil)fenil sulfonas permitió la síntesis de varios tipos de tetrahidoisoquinolinas funcionalizadas o insaturadas, difíciles de obtener por otras metodologías.

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