UNIVERSITÀ DEGLI STUDI DI MILANO

FACOLTÀ DI FARMACIA

DIPARTIMENTO DI SCIENZE MOLECOLARI APPLICATE AI BIOSISTEMI

SEZIONE DI CHIMICA ORGANICA "A. MARCHESINI"

DOTTORATO DI RICERCA IN CHIMICA DEL FARMACO CICLO XXIII

SYNTHESIS AND REACTIVITY OF *N*-CONTAINING HETEROCYCLES THROUGH CATALYTIC METHODS

Tesi di dottorato

Dott. Luca Basolo

Matricola N. R07652

Docente Guida: Chiar.ma Prof.ssa EGLE MARIA BECCALLI

Coordinatore: Chiar.mo Prof.CARLO DE MICHELI

ANNO ACCADEMICO 2009/2010

A Sara,

nella buona e nella cattiva sorte

INDICE

INTRODUCTION

What is expected from an experimental thesis it is a series of data justifying an idea, supporting a theory, leaving results that say: we think to do this, we perform several experiments and finally we have one or more solid answers. I do not have more answers than the first day of my PhD. I have more questions. So I can't say I am at the end of a journey, nor I believe to have better answer. I only hope to have better questions and in the future I wish to have the right ones…

Laboratory practice is quite simple. It needs care and some experience but everyone with a bit of intelligence and practical ability can perform good experiments.

When we make a reaction, we feel able to generate something new or to control physical and chemical phenomena… and it is simply astonishing! Let's think to crystallization, kinetic control of reactions, column chromatography and so on!

Although the enormous number of sometime incontrollable variables operating in our reactions, practical and theoretical aspects must be complementary to guide us in predicting the outcome of a reaction.

Our reality is made of atoms, electrons and their interactions. We can classify interatomic interactions, made of electron density, as bonded or non-bonded. We can further subdivide bonded interactions into ionic, metallic, covalent, coordinate covalent, and partial bonds (as at transition states), and we can subdivide non-bonded interactions into charge transfer interactions, hydrogen bonds, dipolar interactions, dispersion (London forces or VdW interaction), and so forth. Mixed cases are also possible, such as polar covalent (e.g., an HF bond is about 50% ionic and 50% covalent) or a much more complicated range of possibilities for non-bonded interactions. When we put reactants together, a lots (or sometimes all) of the interactions listed above act at the same time and the balance of the playing forces leads electrons to rearrange in a preferred way that we try to foresight! Everything can guide the forces toward a predictable result: interaction with solvent, relative disposition of the reactant, number of beats between molecules, partial charges and so on. To understand how our reactions go, today we have in hand some good models. From an historical point of view our theory has been generated in the early '900 with relativity theory. In particular the work of Erwin Schrödinger on eigenvalue[1] that contains the famous Schrödinger's equation able to describe every system from a particle to the universe in the most complete way. Such an equation is almost impossible to solve as is. This is simply understandable if we consider that for a single particle, only for position, there are 4 variables, 3 for space and 1 for time. Two particles lead to 8 variables and so on. Moreover in the calculation, at each time, we must

consider both the relative position and energy of every particle to each other, the kinetic energy etc. When we say "particle" we mean electron or nucleus, thus for h_2 molecule, in vacuum, Schrödinger's equation must account for 4 particles and 16 variables each one influencing the other only for their position! It was immediately clear that approximations are needed. In the subsequent years the extraordinary effort of an entire generation of physics and mathematics leads to the first utilizable approximation that finally lead in the'70, '80 and '90, when computer becomes fast enough, to great results, even in perfect accordance with experimental data. Theory, algorithms and computers are still evolving and today we can perform on our pc calculation able to reproduce experimental data!

Here are the questions: how are our theories reliable? How is our computer reliable? How are the approximations reliable?

So we must be really careful when we start a computational study, we have to be confident about our computer, we have to choose the theory that better reproduce the data we are looking for and also is not too engaging in term of computational time; but the critical point is the approximation we make. If we want to consider all the variables involved in a reaction the system surely becomes too large, we can't consider even a "molecule" of our system comprising all reactants, molecules of solvent, external energy, reaction intermediates without utilizing some further approximation (for example the solvent is normally approximated by a model). Today the only way to overcome this problem is still the experience of the chemist and his careful evaluation may lead to right approximation obviously within the human error.

In spite of all this variables in this work we reach some good results, so we finally can conclude that our theory and our practice, although not perfect, are good enough to be an invaluable instrument.

GENERAL PART

Our research is always oriented to synthesis and functionalization of different types of heterocycles with biological interest. In particular we focus our attention on N-containing heterocycles because they are the more represented in natural products and drugs. Synthesis and functionalization of this structure is nowadays an established reality with several limitations such as construction of high complexity policycles, green procedure, extend scope and reduce limitation of already known reactions.

Our research has been focused on various aspects of heterocycles synthesis and reactivity. For this purpose we usually use transition metals catalysis, among which Pd has a central role. In fact this catalytic method allows synthesis otherwise impossible. It is not a case that 2010 chemistry Nobel Prize winners are professors who work on palladium catalysis. In our experience, and always taking theory with us, Pd catalyst is a great force in our hand to guide reactions where we would like!

Palladium catalysis has achieved the status of an indispensable tool for the current organic synthesis and a wealth of reviews and books on organopalladium chemistry has been published.[2]

Palladium is a member of the Nickel triad in the Periodic Table. Palladium complexes exist in three oxidation states: Pd(0), Pd(II) and Pd(IV). The facile interconversion between these oxidation states is responsible for the broad utility of palladium in organic chemistry, since each oxidation state exhibits different chemistry.

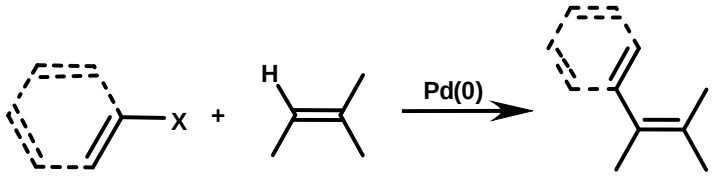
Pd(0)-catalyzed reactions

1. Heck type arylations on azines and diazines

Among basic types of palladium-catalyzed transformations, the Heck reaction and related chemistry occupies a special place. During the last thirty-five years this reaction has emerged as highly efficient and well documented mild procedure for carbon-carbon bonds formation.[3]

The success of the Heck reaction is subject to the identification of the class of Heck reaction in terms of both the type of alkene (whether electron rich or poor) and the electrophile (whether a halide or a trifluoromethanesulfonate is the leaving group). In order to maximize the conversion is then essential to select the appropriate conditions. The reaction consists on the coupling of an aryl or vinyl halide with an olefin, according to scheme 1.

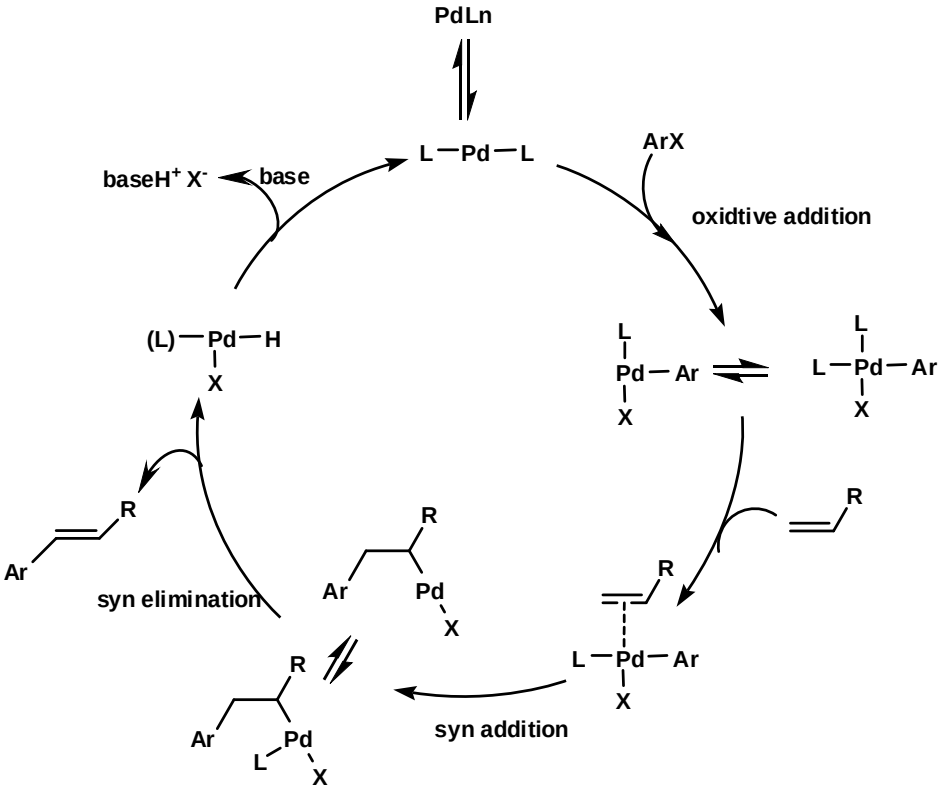
Scheme 1



The readily available starting materials make this strategy useful for construction and functionalization of carbocyclic and heterocyclic systems.[4]

The mechanism proposes that the active catalytic unit is the coordinately unsaturated 14 electron species PdL_2. This would seem reasonable since PdL_2 is electron rich and nucleophilic in character and has vacant sites so that the organic electrophile RX can undergo oxidative addition to give the known RPdX intermediate in which the R group (aryl or vinyl) is σ-bonded to the Pd(II). A vacant site must now be created to receives and activate the alkene, so that a neutral $RPdX(CH_2{=}CHR)$ species is formed. The coordinated alkene then undergoes *syn* addition to form an unstable σ-bonded complex, which will rotate around the carbon-carbon bond so that the palladium and ß-hydrogen are *syn* coplanar, and ß-hydride elimination takes place to generate the observed *trans* substituted alkene and the catalytically inactive HPdX as outlined in Figure 2. The base which must be present to enact a successful catalytic cycle, eliminates HX to regenerate Pd(0) and the whole cycle repeats.

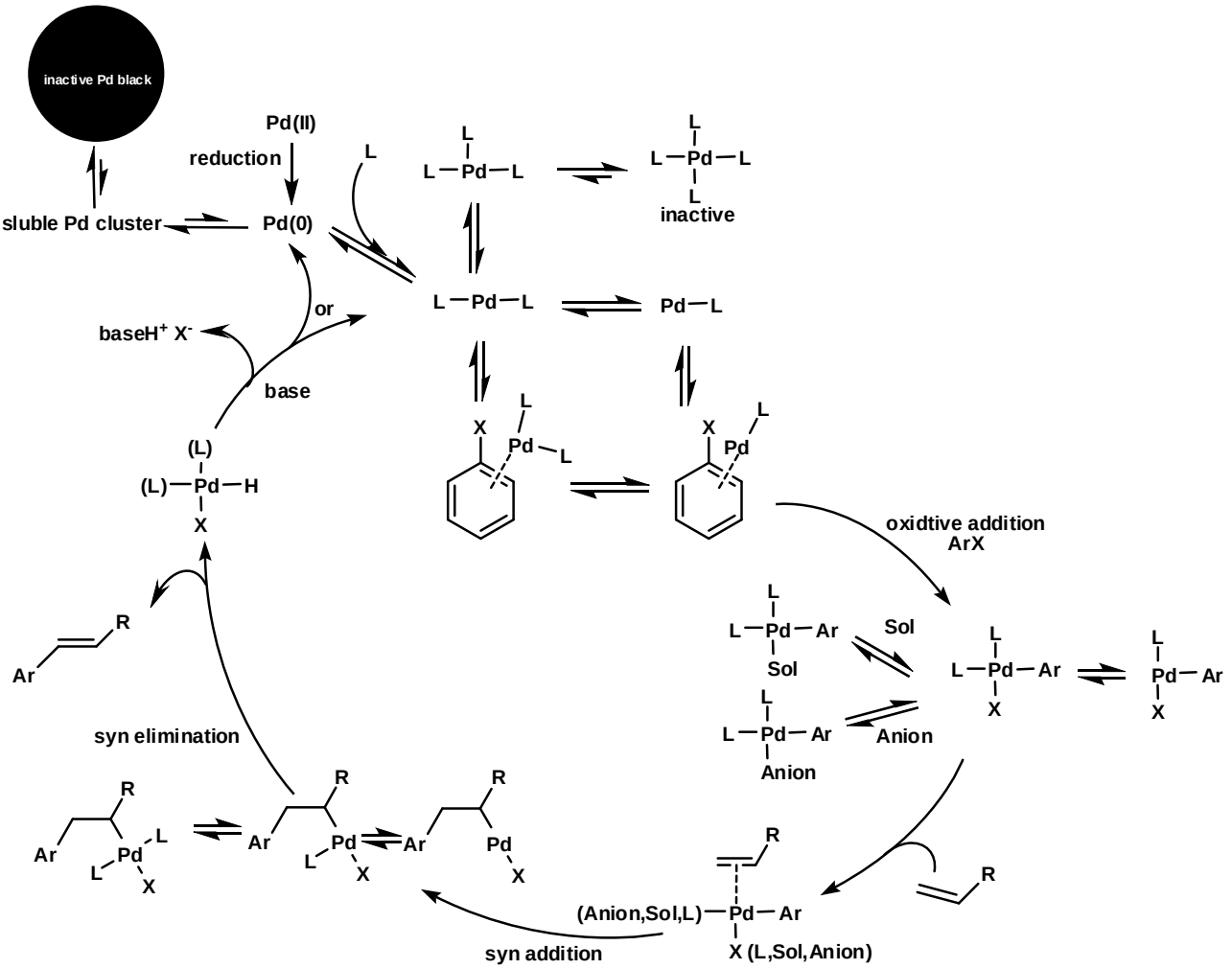
Scheme 2



A more detailed scheme of the whole catalytic cycle of Heck-type reaction can be obtained merging some recent excellent works on the subject[5] with the established knowledge superbly reported in Neghishi's book.[3b]

We can see in scheme 3 that PdL_2 is not the only species able to undergo oxidative addition but also mono-ligated Pd species was experimentally observed and may be responsible for the first step. It is also important to note that only soluble Pd cluster can lead to active palladium, so concentration plays a central role. Various molecules, for example the solvent, and ions may act as ligands for Pd and sometimes this kind of coordination makes reaction possible thanks to their electronic effects.

Scheme 3

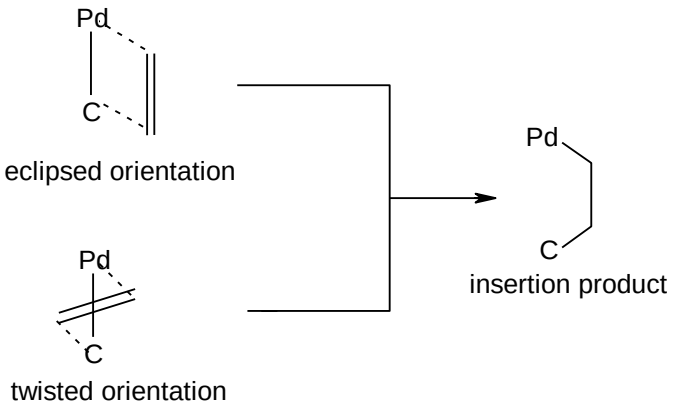


The general procedure involves up to 1 mol% of catalyst, 2 equiv of triarylphosphine (stabilizing the arylpalladated intermediates and catalytic Pd in solution). The rate-limiting step is the oxidative addition of ArX that depends on the nature of X (ArI > ArOTf > ArBr >> ArCl). The temperature range is 70-120 °C and the most common medium for the reaction is one of the aprotic polar solvents, such as DMF, DMA, DMSO and CH_3CN. The Heck reaction is also reported to be highly regioselective as shown in Scheme 1. Depending on which ligand is used, α-regioisomers or ß-regioisomers may be selectively formed.

For intramolecular Heck cyclization the reaction conditions appear to vary depending on whether a tertiary or quaternary centre is being formed, on the ring size and the stereochemistry of the alkene. Depending upon the geometry (enforced by the substrate structure), the alkene can approach the palladium-carbon σ-bond by two limiting orientations, the eclipsed orientation and the twisted orientation (scheme 4). Either insertion orientation can access to the cyclization product but eclipsed orientation is preferred: in this case the

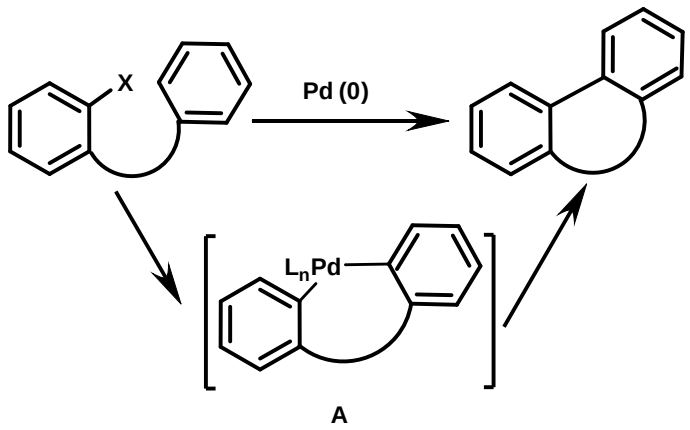
palladium-carbon σ-bond approaches the alkene in the plane of the alkene σ-bond en route to the insertion product.

Scheme 4



Arenes also participate in the intramolecular Heck reaction. Mechanistically, these reactions differ from alkene reactions and are thought to occur via reductive elimination of the intermediate **A**. Intermediate **A** could arise from an intramolecular electrophilic aromatic substitution or a Pd(IV) intermediate (scheme 5). The literature reports experimental supports for either reaction pathway. Afterwards we will discuss our hypothesis on this matter on the base of the results obtained.

Scheme 5

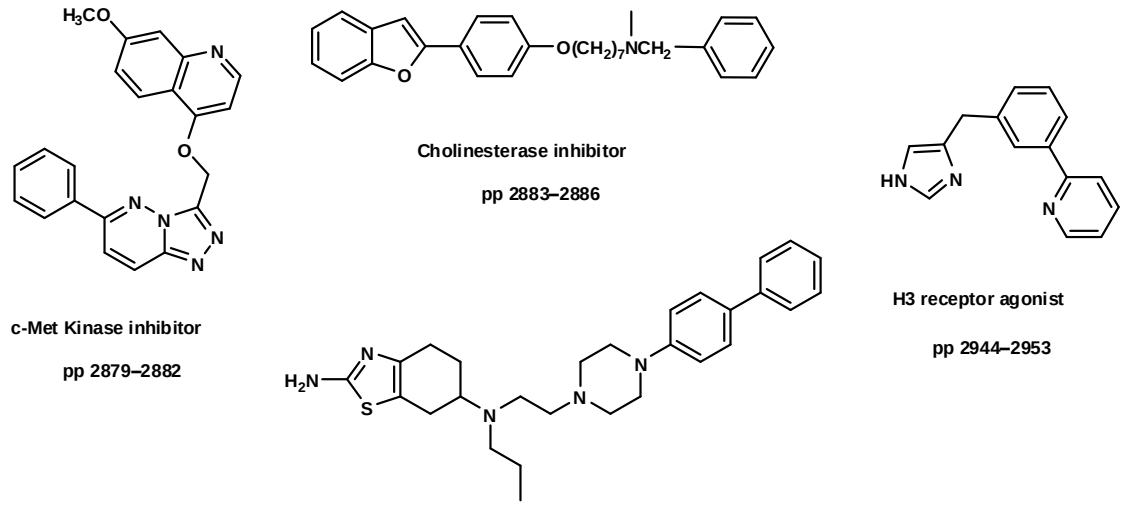


For the construction of aryl-aryl bonds the above mentioned Heck-type arylations are of particular interest.[6] Respect to the cross-coupling reactions, the advantages of these reactions consist in the opportunity to start from very simple and readily available reactants, through the substitution of one of the functionalized arenes, normally the organometallic coupling partner, with arenes, obtaining an economical and practical advantage. Besides this

methodology was pointed out as environmental benign strategy owed to low waste production and improvement in term of atom economy.

Moreover bi(hetero)aryl structural motif is a predominant feature in many pharmaceutically relevant and biologically active compounds[7] as shown in fig. 1 where we report for a single JMC issue the pages were we found these structures.

Figure 1



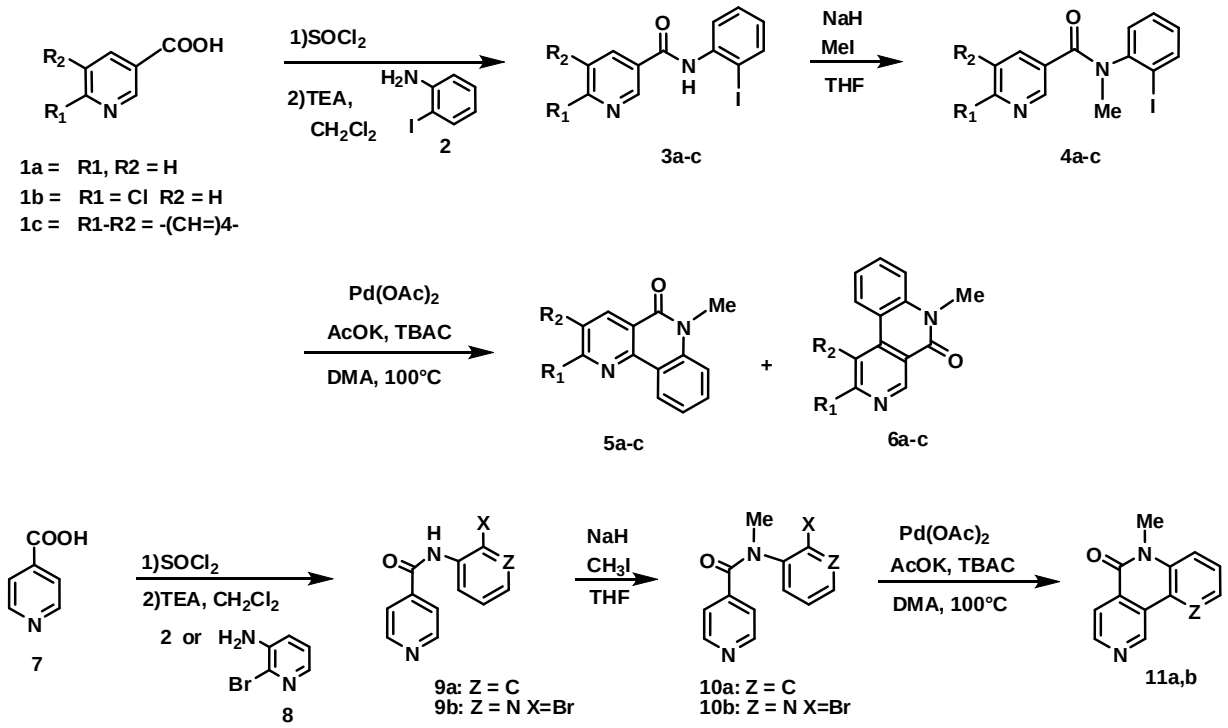
Our previous contribution in this area concerned the intramolecular direct arylations of electron-rich heterocycles bearing both electron-withdrawing and electron-donor substituents in the presence of Pd(0)-catalyst, under different conditions (ligand or ligand-free conditions).[8] This process allowed us a straighforward method to generate aza-substituted ring fused to (hetero)arenes.

In contrast to the numbers of papers reporting the utilization of electron-rich heterocycles in the direct arylation process[9] both as intra- and intermolecular reactions, the direct arylation of simple aromatic rings remains a significant challenge[10] and even more the use of electron-poor heterocycles, such as azines and diazines is rare. In these cases the few reported results gave five or six member rings formation, in very low yields and following harsh reaction conditions.[11] Recently Fagnou reported the intermolecular arylations of azines and diazines exploiting the trasformation of these substrates on the more electron-rich azine- and diazine N-oxides.[12] We report here our results on direct arylation on electron-poor arenes; the described results are much more noteworthy due to the literature data on the poor reactivity of these substrates.[13]

Starting from nicotinic acids **1a,b** and 3-quinolinecarboxylic acid **1c**, the reaction with the 2-iodoaniline **2** followed by methylation on the amides **3a-c**, gave the corresponding tertiary amides 4**a-c** suitable substrates for the direct arylation reaction (Scheme 1). The intramolecular process, obtained using $Pd(OAc)_2$ as catalyst, AcOK as base, TBAC as additive and DMA as solvent, afforded two regioisomers **5a-c** and **6a-c** arising from the cyclization on position 2 or 4 of the pyridyl ring, in 3:1 ratio in favour of the *para* position. Similarly the reaction of the isonicotinic acid **7** with 2-iodoaniline **2** or 2-bromo-3-aminopyridine **8** and subsequent methylation of **9a,b** afforded the amide **10a,b**, the cyclization of which gave the trycyclic systems **11a,b**. Although usually direct arylation for rings of low reactivity necessitated the use of electron-rich and sterically-hindered trialkylphosphines.[14]

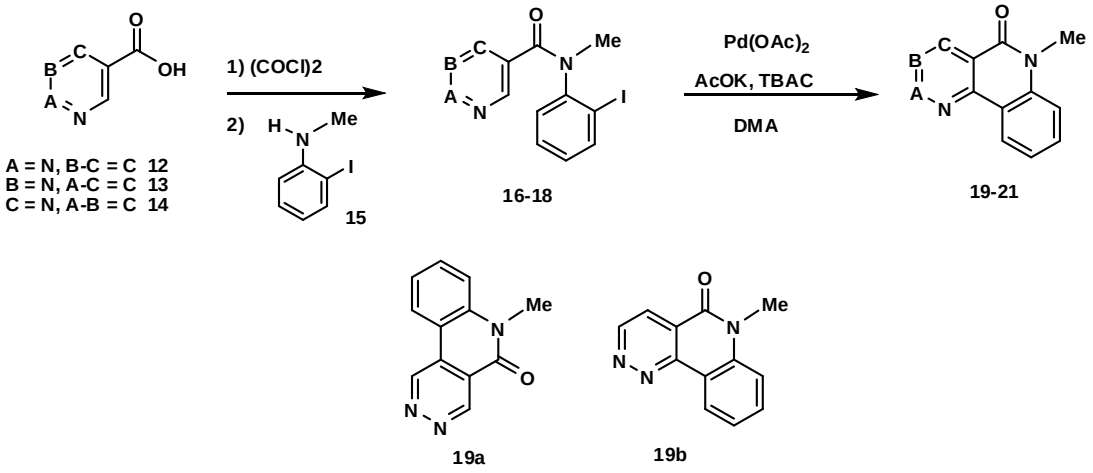
Compared to the procedure used previously, it should be noted that ligand-free conditions (Jeffery's conditions) have been successfully used. On the contrary, optimizing the reaction conditions, we discovered that the presence of the base and polar solvent are required to obtain the products. In fact the absence of AcOK or solvent different than DMA or DMF, resulted in unreacted substrate. The addition of TBAC improves the yields. If temperatures higher than 100 °C are used for similar reactions and in most cases heating for several hours to days is necessary, the reaction time (45 min) was considerably reduced when the use of microwaves was tested.

Scheme 6



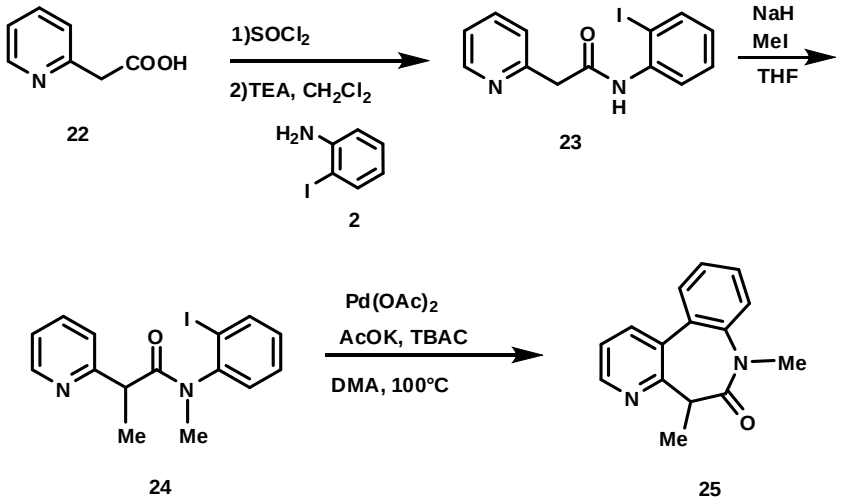
To probe the feasibility of the arylation reactions on electron-poor heterocycles, we considered other substrates as the amides arising from the 1,2-, 1,3- and 1,4-diazines carboxylic acids **12-14**. In these cases, the amides **16-18** were obtained by reaction with 2-iodo-*N*-methylaniline **15** on the unisolated acyl chloride. In fact the methylation step carried out on the secondary amide must be avoided giving methylation also on the heterocyclic nitrogen atom. The cyclized products **19-21** were formed in one step from the corresponding amides. In the case of amide **16**, the cyclization reaction gave two regioisomers **19a,b** in 1:1 ratio, corresponding to the cyclization product respectively on position 3 and 5 of the piridazyl ring, showing any selectivity in coupling reaction. (scheme 7).

Scheme 7



To consider the possible influence of the ring size on the cyclization process and with the aim to obtain more challenging seven-membered rings, we focused our attention on the homologous of pyridine carboxylic acid, the pyridin-2-yl acetic acid **22** from which the corresponding amide was prepared via unisolable acyl chloride in the presence of triethylamine. The methylation step necessary to avoid the nitrogen coordination to palladium, gave in this case double methylation, involving benzylic carbon. The obtained tertiary amide **24** was then treated following the reported conditions, to give in very good yield the cyclized product **25** as shown in Scheme 8.

Scheme 8



Several pathways have been proposed for the palladium-catalyzed arylation of aromatic compounds, the process depending on the (hetero) aromatic substrate, base, ligand and solvent used. The involvement of an electrophilic aromatic substitution (S_EAr) was commonly accepted for π-electron-rich substrates,[15] while other mechanisms such as Heck-type process,[16] or proton-abstraction could be envisaged for different substrates.

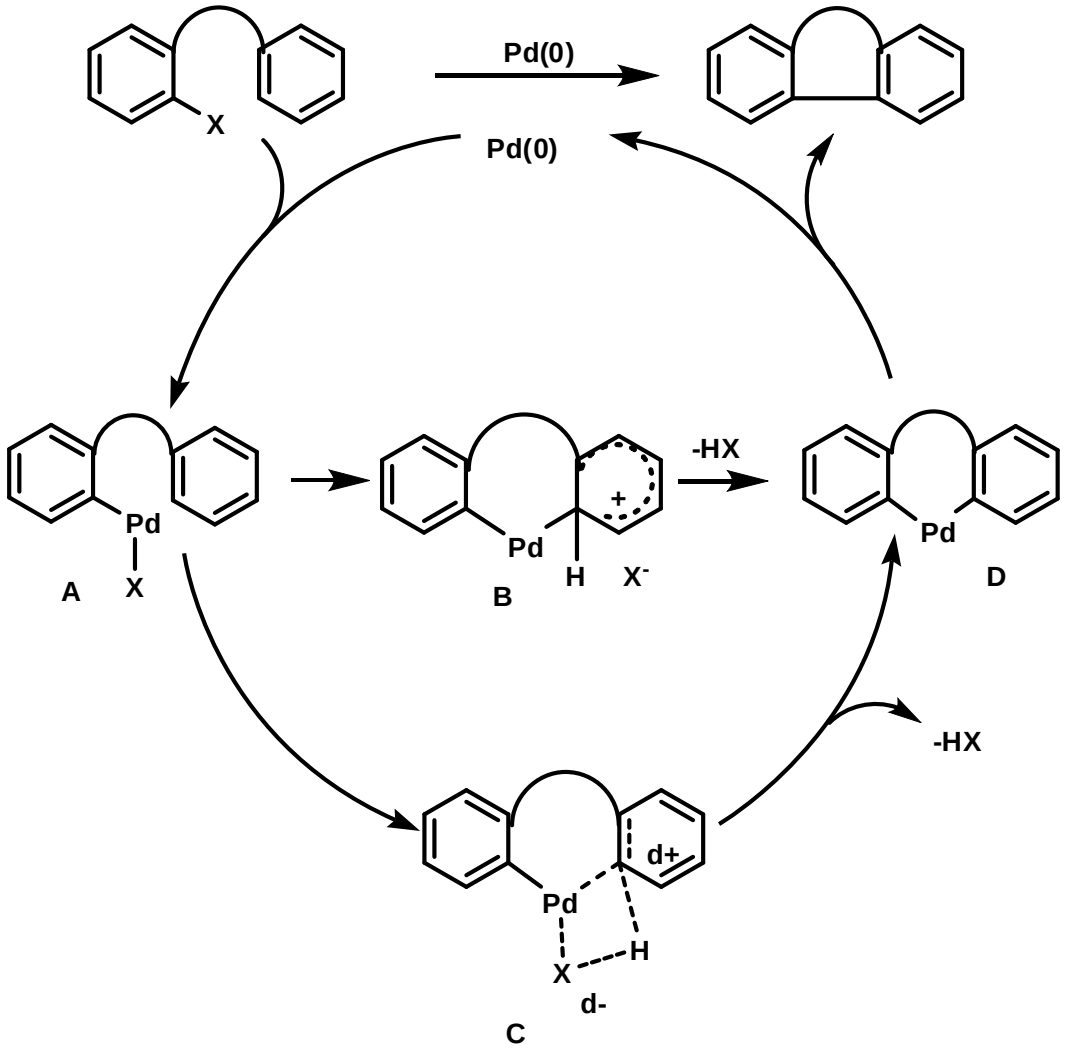
In all the proposed mechanisms, the first step generally occurs via oxidative addition of the aryl halide to the transition metal to give the intermediate **A**, followed by different possible carbon-carbon bond formation paths (scheme 9). The electrophilic aromatic substitution (S_EAr) suggested for electron-rich heterocyclic substrates, through the intermediate **B** gave the palladacycle structure **D,** which in turn gets the cyclized product *via* reductive elimination of Pd(0) with the contemporary catalyst regeneration. This hypothesis is not applicable in the case of electron-deficient heterocyclic nucleus.

Recent work indicated the Heck-type process rather unlikely,[17] and the literature data showed as a more probable mechanism the concerted proton abstraction path (by the halogen anion or by an external base) operating *via* a four-membered transition state as showed for the intermediate **C**.[18]

The truthfulness of the latter mechanism was proven through the comparison of two different arenes and the observation that the more electron-deficient one reacted preferentially.[19]

This outcome was inconsistent with a S_EAr mechanism.

Scheme 9



2. Functionalization of indolines through Pd(0)-catalyzed amination reactions

The amination reaction is nowadays one of the most powerful tools to obtain C-N bond formation.[20]

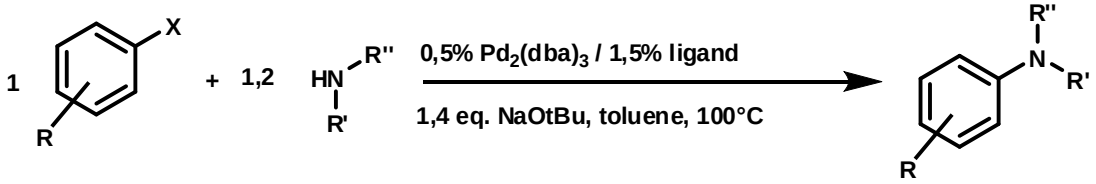
Palladium competes strongly with non-precious metals like copper, nickel, and, more recently, iron to this aim. Even though nickel, copper, and iron, are truly more cost-effective, palladium-catalyzed bond formation presents some advantages:

1. Palladium catalysts often possess a higher activity than their metal alternatives enabling the conversion of less reactive substrates
2. Pd works at relatively low temperatures
3. Pd posses higher catalyst turnover numbers (TONs) up to 10^6.

Considering this reaction typology, the use of weak base has been demonstrated very important to leave intact other functional groups. Moreover the use of different ligands and their optimization lead to the improvement of yields and applicability. Our work tried to further enlarge the scope and to use environmental friendly procedures and to develop economic and scalable synthesis to shift the use of this reaction from research to industry

A typical example of amination reaction between an aryl halides and an amine is reported below (scheme 10).[21]

Scheme 10



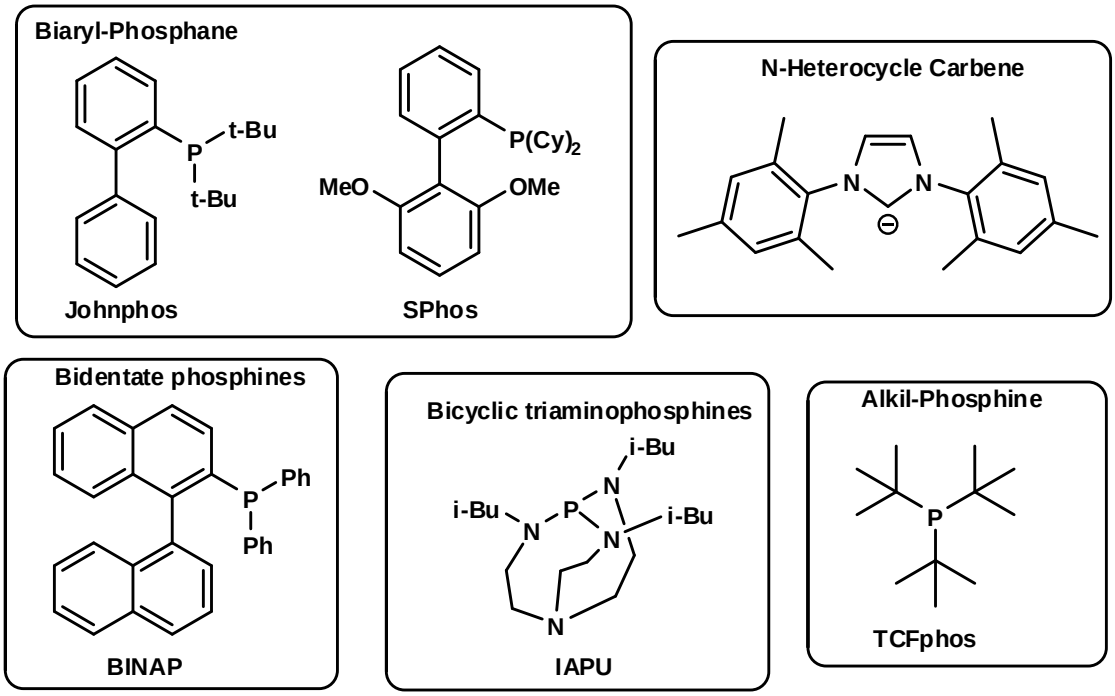
The spectrum of suitable amine is very large, in fact using right condition almost everyone can react; the only limitation is the presence of other reacting functional groups.

As aromatic partner iodides and bromides are the most suitable, but also chlorides and triflates may be successfully used. Pd catalyst employed are in general $Pd_2(dba)_3$ or $Pd(OAc)_2$. 10 to 10^{-6} %

Different phosphine and carbene ligands may be used selected on the basis of their steric and electronic properties. On the basis of the choice reaction may be successful or not; they play a central role in the oxidative addition (the rate limiting step), in Pd solubilization (preventing

precipitation as inactive palladium black) and in making Pd coordination site available for catalysis; some example are reported below in fig. 2:

Figure 2



The concentration of phosphine ligand is very important because in some cases an excess may results in a "phosphine poisoning" of the catalytic palladium.

For what concern bases, organic or inorganic bases can be used. Weak bases as K_2CO_3 or Cs_2CO_3 need larger excess than the standard 1.4/1 used for t-BuOK. Recent studies show that working in a large excess of K_2CO_3 up to 5/1 may give better results.

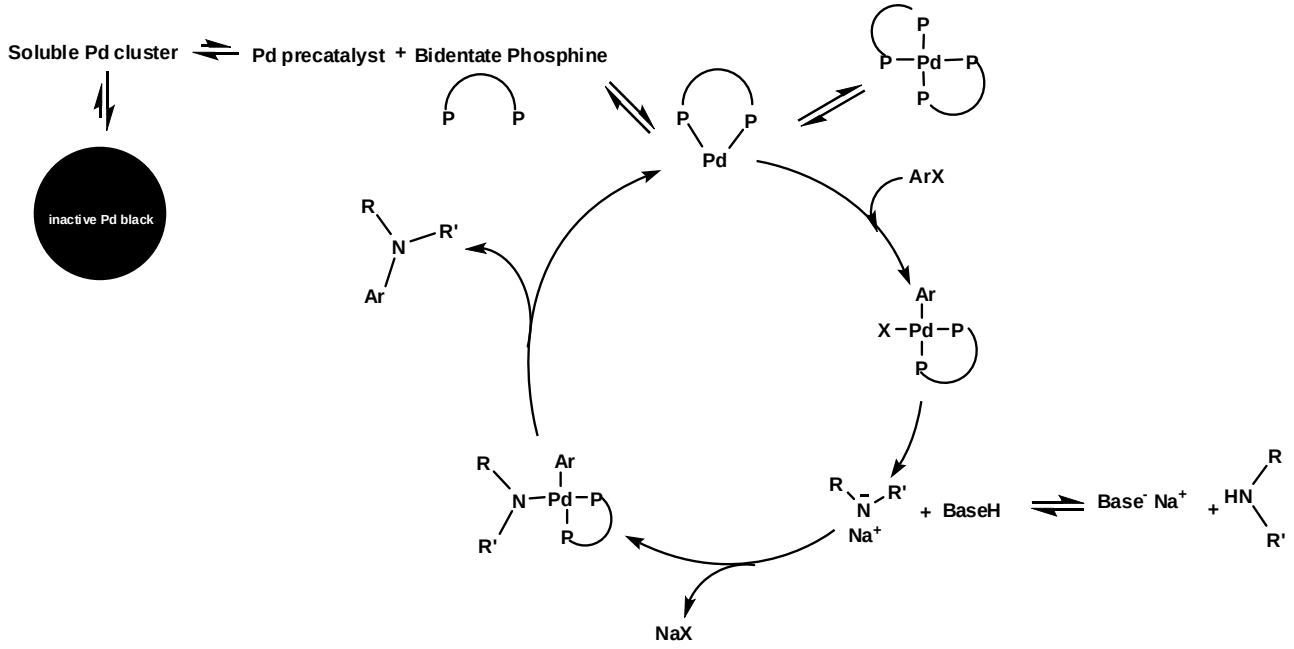
The role of the solvent is not well known; in general the better ones are toluene or THF but many other have been tested giving good results; sometimes ter-Butanol or water are used . Rare cases of solvent free are reported, for example alumina supported reaction.[22]

The mechanism of this reaction was deeply investigated by Buchwald and Hartwig.[23]

The accepted catalytic cycle, when bidentate phosphine are used is reported in scheme 11. At first, a Pd(0) complex is formed from Pd(0) precatalyst or after reduction of $Pd(OAc)_2$ and phosphine ligand. This step play a central role because it is possible the formation of an inactive tetracoordinate Pd (0) lying out of the catalytic cycle(phosphine poisoning). The di-coordinate Pd(0) complex undergoes oxidative addition of aryl halide and the resulting arylpalladium halide is converted to an arylpalladium amide in the presence amine and base. The arylpalladium amide can then undergo reductive elimination to form the desired

arylamine product and regenerate double coordinated Pd(0). This reaction results zero-order in amine, first-order in arylhalide, and inverse first-order in added ligand.

Scheme 11

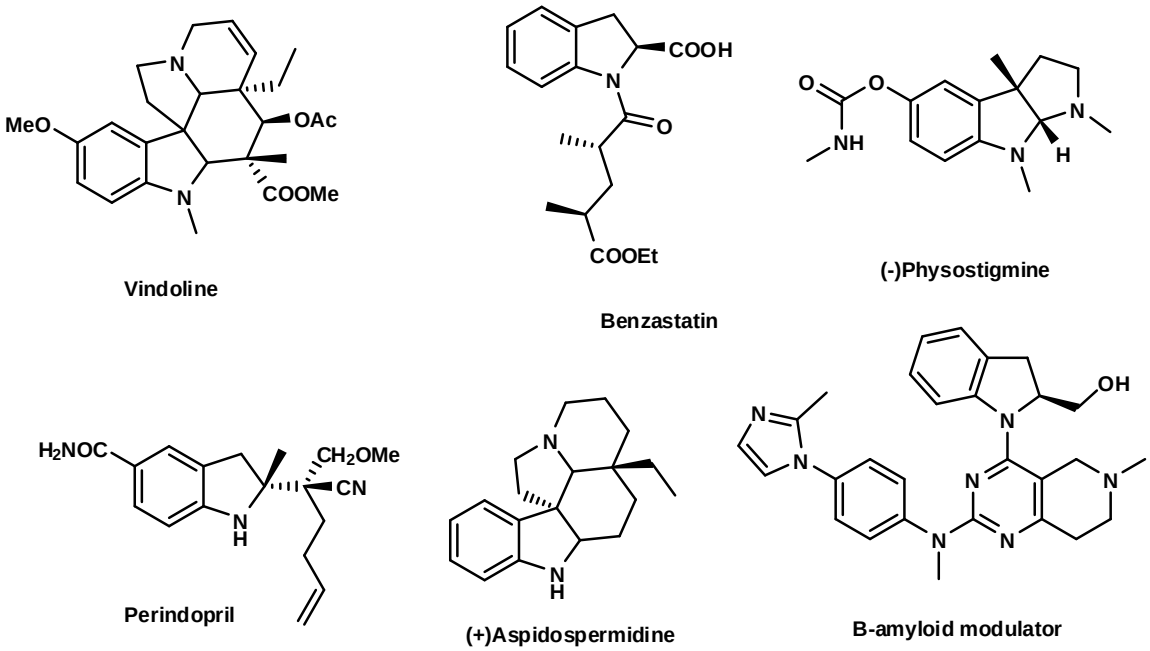


Regarding the synthesis of heterocyclic systems, Pd-catalyzed reactions have been extensively applied.[2h]

The amination reaction is a substantial part of our research and we apply this reaction expecially to indoles.[24] Nowadays indole chemistry is broadly known and studied, so we like to focus on a little different heterocycle: indoline.

In spite of indoline chemistry is very interesting, it's not so explored. The indoline skeleton is an ubiquitous scaffold found in a range of biologically active alkaloids and pharmaceutically active compounds[25] as shown in fig. 3.

Figure 3



Indolines have also been successfully employed as chiral auxiliaries in asymmetric synthesis.[26] and references cited therein. On the other hand indolines are also useful for various applications ranging from dyes, dye sensitized solar cell**,** to fuel cell (H_2 storage).[27]
The initial efforts to search for the best catalytic conditions were made on indoline and the good partner heteroarylhalide 2-bromopyridine (scheme 12 and table 1).

Scheme 12

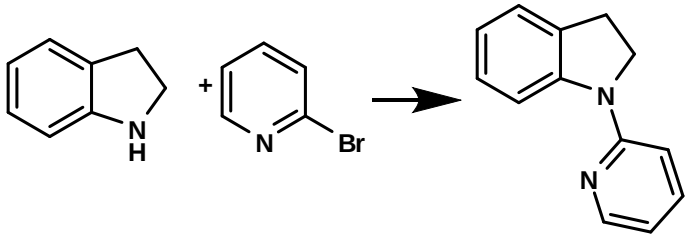


Table 1.					
Entry	**Catalyst[a]**	**Ligand[b]**	**Base**	**T °C/h**	**Yield (%)**
1	2% A	2% BINAP	5 Cs_2CO_3	120°C 24	10
2	2% A	2% 1,1′-Bis(diphenylphosphino)ferrocene	1,4 t-BuOK	120°C 24h	5
3	2% A	4% 2-Dicyclohexylphosphino-2′-(*N*,*N*- dimethylamino)biphenyl	1,4 t-BuOK	140°C 10 min	5
4	2% A	4% IAPU	5 Cs_2CO_3	120°C 24h	25
5	5% B	10% BINAP	1,4 t-BuOK	120°C 24h	60
6	1% B	2% BINAP	1,4 t-BuOK	120°C 24h	40
7	5% B	10% BINAP	2 Cs_2CO_3	100°C 24h	70
8	1% B	4% IAPU	1,4 t-BuOK	100°C 24h	80
9	1% B	4% IAPU	1,5 Cs_2CO_3	100°C 24h	55
10	1% B	4% IAPU	5 K_2CO_3	100°C 24h	75
11	0,5% B	2% IAPU	5 K_2CO_3	100°C 24h	75
[a] A=$Pd(OAc)_2$ B=$Pd_2(dba)_3$ [b] IAPU= (2,8,9-triisobutyl-2,5,8,9-tetraaza-1-phospha-bicyclo[3.3.3]undecane					

The two better conditions found (entries 7 and 8) are:

a) $Pd_2(dba)_3$, IAPU,[28] t-BuOK, toluene

b) $Pd_2(dba)_3$, BINAP, Cs_2CO_3, toluene

The first one gives better yield, the second uses a weaker basis. The use of a large excess of K_2CO_3 as in the entries 10 and 11 allow the use of IAPU even without strong bases and give us the impulse to develop our work toward a totally new approach.

Surprisingly a lot of these simple products have not yet been synthesized.

Nowadays the goal of an organic chemist is not only to obtain the product but also to make new kind of synthesis as sustainable as possible. Green chemistry and sustainability are becoming more and more important in everyday organic synthesis.[29]

Within this subject, the elimination of solvents is advantageous, since supply, purification, and disposal of these can be omitted. The accompanying reduction of solvent waste is the major motivation for the development of a broad variety of solvent-free synthetic reaction protocols.[30]

While reactions are often carried out in a solvent-free manner using classical laboratory equipment, the application of microwave heating represented an added value. From an economical point of view, according to the results reported by Gronnow *et al.*,[31] the use of microwave irradiation heating process was expected to significantly reduce (up to 85-fold) the amount of energy required to perform the reaction (by comparison with what would be necessary in a thermal conventional way). In these terms, this procedure can also be considered as a green process. Besides a lot of solvent-free procedures are carried out utilizing one of the reactants as solvent, substantially limiting the scope.

What is the meaning of sustainability? Two points are the key to apply it:

1. Use of reagents with the lowest environmental impact (that is: greener solvents or no solvents at all, no hazardous elements or a very low concentration of it, no waste products or few waste and above all the waste must be rather safe).
2. Lowering of operators, energy and reagents costs.

To develop a sustainable method we apply the aforesaid criteria: no solvent, no waste, lowest Pd load, use of microwaves to reduce time and energy consumption.

Starting from the observation that C-N bond formation is improved by excess base we test the reaction with the reacting mixture (indoline, bromopyridine, $Pd_2(dba)_3$, IAPU) and K_2CO_3 as "solvent". Because this "solvent" is not a liquid, we have first of all dissolved the mixture in DCM to obtain an homogeneous distribution of reactants, then we add a very large excess of K_2CO_3 and then we remove the DCM in vacuum to recover it for the next reaction. In this way (SOLVENT "QUASI" FREE reaction) the only solvent used is reusable many times!

Moreover microwave irradiation is an advantageous method to furnish energy to the mixture reagents; thermal heating do not allow reaction.

With a great pleasure we found that the above-mentioned conditions work well!

The use of K_2CO_3 deserves some comments, in particular three conditions to be satisfied:

1. It must be finely powdered; this is due to the total exposed area which grows a lot reducing particle size. When we try to do this reaction on granular K_2CO_3 the reaction yield drop dramatically to one third.
2. It must be adequately hydrated. If K_2CO_3 is absolutely dry reaction does not take place. But if K_2CO_3 is too hydrated reaction yield drop to one half.
3. It is necessary to well pack the powder after its introduction in the reactor.

The traditional and SOLVENT "QUASI" FREE reactions are comparable in term of yields (78 vs 75%) but SOLVENT "QUASI" FREE shows no presence of by-product (as oxidation product indole, dehalogenated aryl halide, Ullman type biaryl product) and also when the yields are scarce we recover only unreacted substrates. Table 2 shows the comparison yields between the traditional thermal heating and the microwaves irradiation SOLVENT "QUASI" FREE.

Considering the synthetic importance of chiral indolines, in particular as building blocks for drugs and as chiral auxiliaries in asymmetric synthesis, enantiopure 2-substituted indolines are obtained when the reaction is performed on chiral substrates (Table 2, entry 11). In fact despite the presence of a base the (*S)*-indoline-2-carboxylic acid give (*S)*-1-(4-nitrophenyl) indoline with enantiomeric purity better than 99.5% as confirmed by chiral HPLC analysis with an AD chiral column and in comparison with a sample of the corresponding racemic mixture synthesized starting from (±)-indoline-2-carboxylic acid. This result also represents a rare example in which a base-sensitive substrate has been employed for palladium-catalyzed amination reaction.[32]

Scheme 13

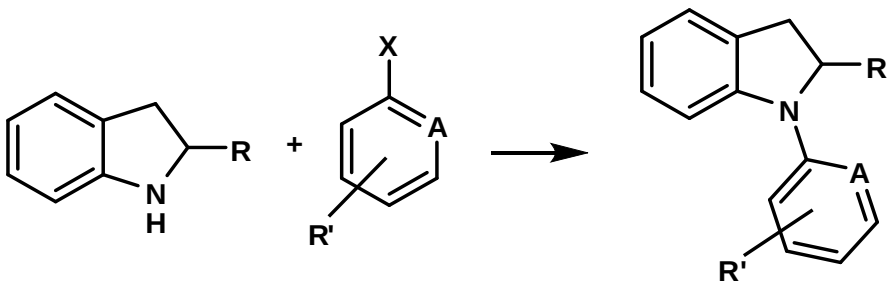
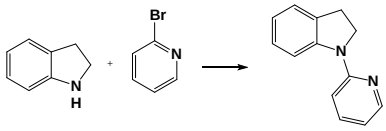
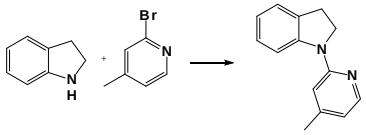
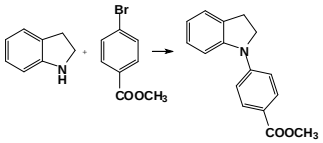
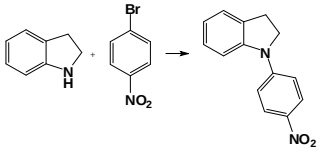
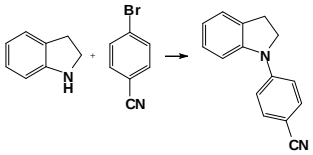
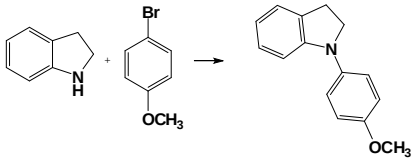
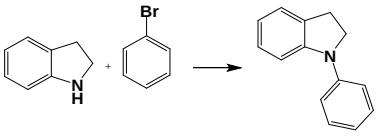
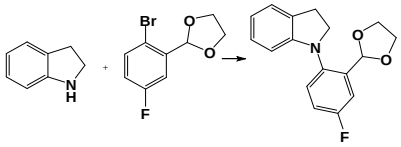
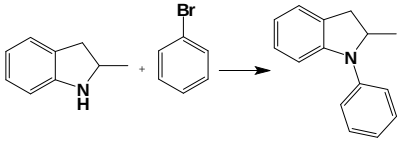


TABLE 2. *N*-ARYLATION OF INDOLINES WITH ARYL BROMIDES

ENTRY[a]	REACTION	PRODUCT	YIELD Δ	YIELD MW
1		**26**	78	76
2		**27**	0	24
3		**28**	30	62
4		**29**	5	75
5		**30**	57	71
6		**31**	68	77
7		**32**	52	59
8		**33**	70	45
9		**34**	68	68

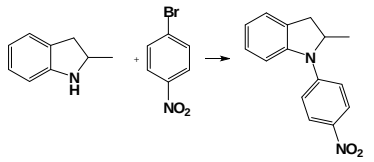
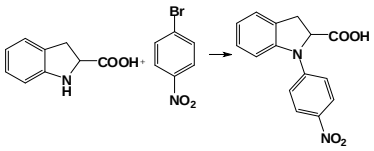
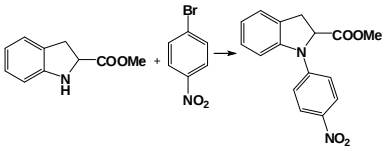
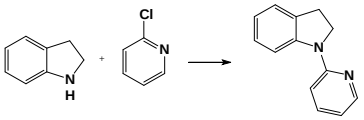
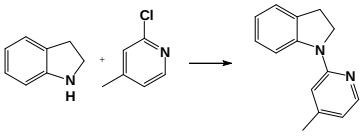
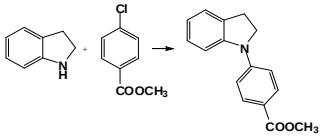
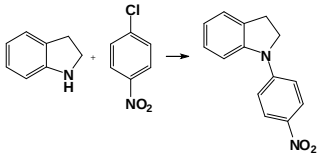
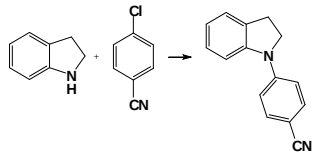
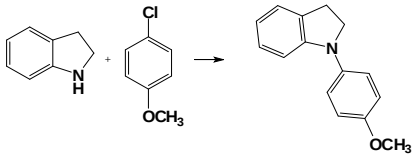
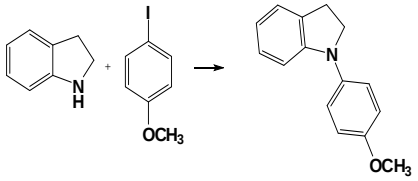
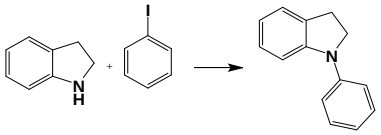
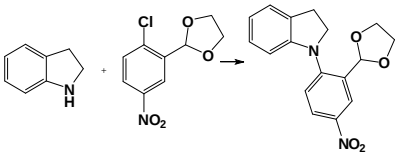
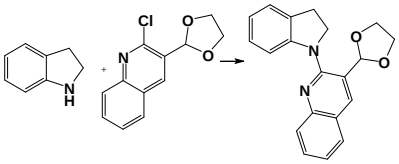
10		**35**	5	65
11		**36**	0	53
12		**37**	51	54

TABLE 3. *N*-ARYLATION OF INDOLINES WITH ARYL CHLORIDES AND IODIDES

ENTRY[a]	REACTION	PRODUCT	YIELD Δ	YIELD MW
1		**26**	46	66
2		**27**	70	80
3		**28**	37	50
4		**29**	59	67

5		**30**	40	60
6		**31**	72	66
7		**31**	88	84
8		**32**	68	71
9		**38**	75	48
10		**39**	73	50

The alternative catalytic system to obtain C-N bond formation in the presence of base sensitive groups and especially carboxylic acid is Cu(II) in polar solvent. We test this condition to synthesize N-substituted indoline-2-carboxylic acid and found a substantial inferior yield (30%).

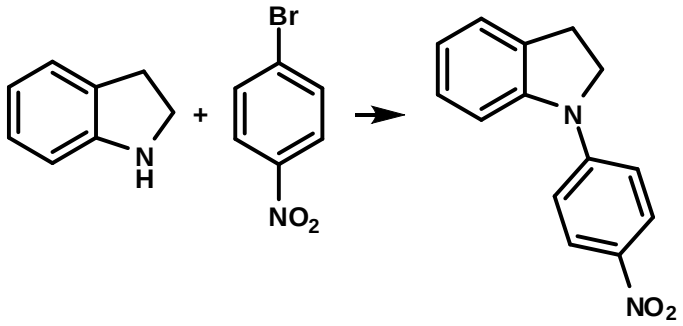
Reasoning about the Pd-catalyzed C-N bond formation, we wonder how much phosphines should be important once Pd is fixed on carbonate. The use of ligands in Pd-catalyzed amination reactions is something established; their use enable synthesis otherwise hard or impossible to achieve. The problem is that ligands are sometimes more expensive than precious metals and are not so safe as waste. We decide to try ligandless conditions. In the initial solubilisation step the role of phosphine may be crucial avoiding Pd black aggregation

and consequent catalyst inactivation. What we must avoid, in the absence of phosphines is Pd aggregation.

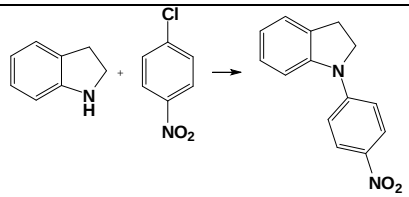
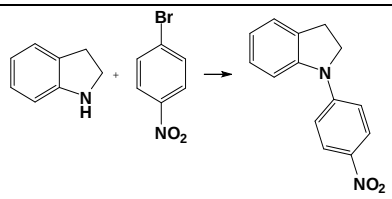
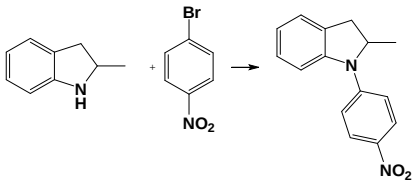
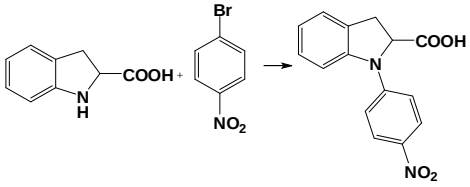
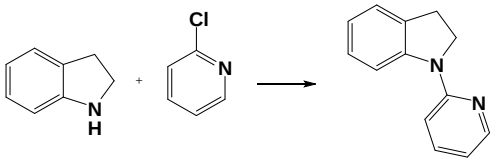
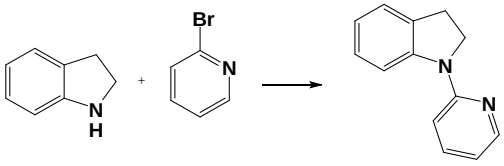
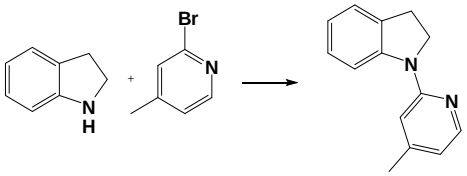
In order to avoid Pd particles aggregates as Pd black, removal of the solvent is the critical step.

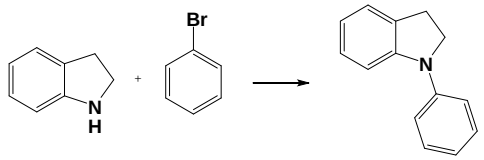
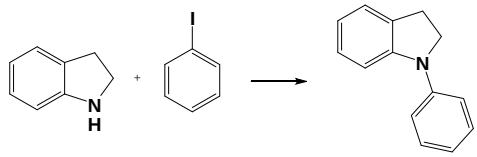
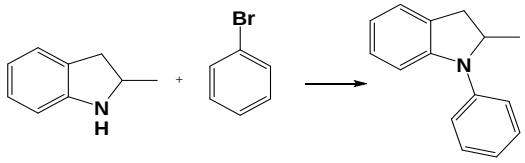
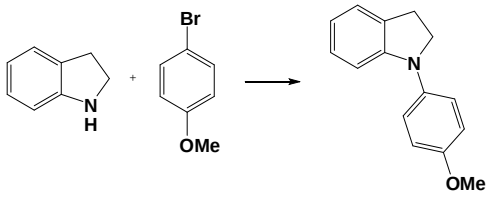
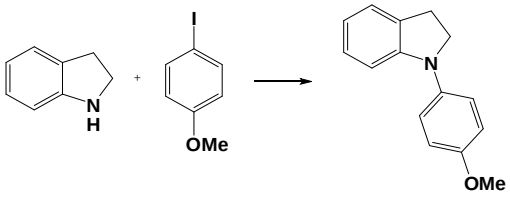
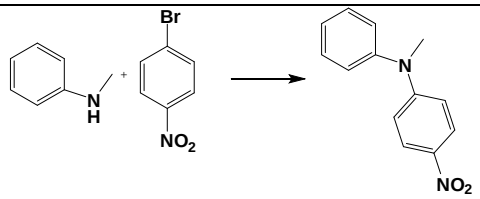
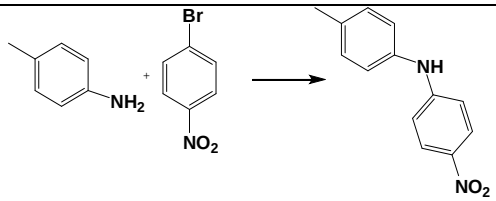
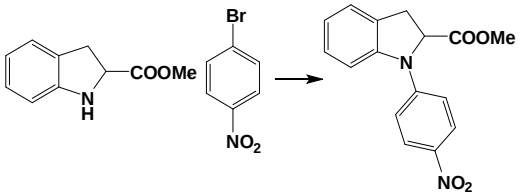
The reaction we choose as model is between indoline and 4-bromonitrobenzene (scheme 14) because it gives good yield in SOLVENT "QUASI" FREE protocol and is prone to all parasite reactions.

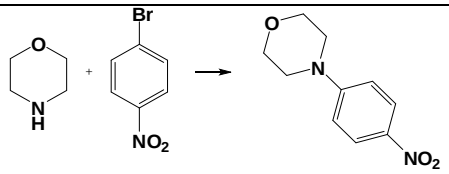
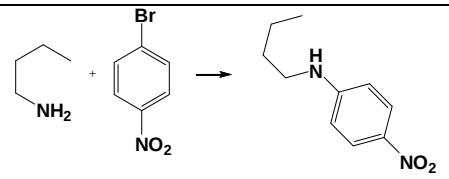
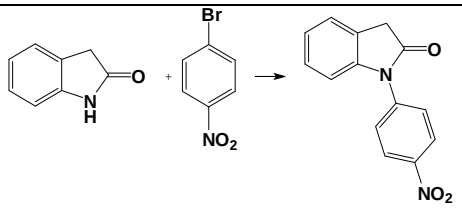
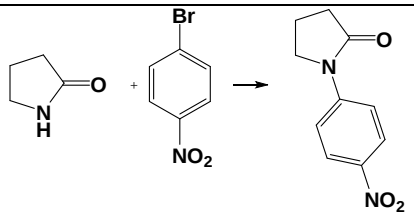
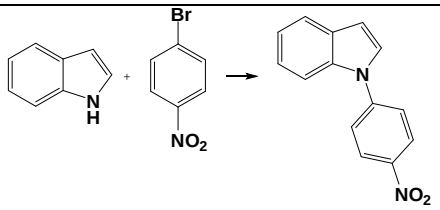
Scheme 14



First of all we try a low catalyst yield and condition similar to SOLVENT-"QUASI" FREE with 2 minutes of beats for compression. The aspect of the powder in the MW reactor after heating show a red coloration (our product is orange-red) near temperature probe where powder is more compressed, so we think that the low yield may be due to an insufficient compression. Following this idea we push powder with 4 minutes of beats and try to elevate the reaction temperature. Yield results tripled. To improve our results we double the Pd load. Yield results increased up to 34%. The subsequent trials lead us to optimize Pd loading to 1% leaving other parameters unchanged. In table 4 we report all the experiment we perform.

TABLE 4. *N*-ARYLATION OF INDOLINES SOLVENT&LIGAND FREE			
Entry	Reaction	Product	Yield
1		**29**	0%
2		**29**	60%
3		**35**	48%
4		**36**	40%
5		**26**	0%
6		**26**	60%
7		**27**	35%

8		**32**	40%
9		**33**	25%
10		**34**	35%
11		**31**	50%
12		**31**	38%
13		**40**	50%
14		**41**	25%
15		**37**	35%

16		**42**	0%
17		**43**	0%
18		**44**	0%
19		**45**	traces
20		**46**	15%

As we can note in table 4, some common feature are evident:

1. Aryl bromides and iodides react, chlorides are unsuitable for this method.
2. Aryl bromides are more efficient than iodides (maybe for Iodide poisoning of Pd)
3. Yields are moderate but we do not recover by-product, after reaction only product and reactant are recovered.
4. Solvent and ligand FREE condition work on aromatic amines, secondary one are preferred. Amides seem to be nonreactive.

This new procedure is the first example of solvent and ligand-free palladium-catalyzed amination reaction. Although not exceptional yield and limited scope reduce its applicability maybe this is a good starting point for future development. Conditions seems to be very mild for reactants, in fact reagents do not undergoes other parasite reactions, a typical problem of Buchwald-Hartwig reaction when condition are not optimized to obtain yields over 90%. When we try to prolong reaction time we can't observe any improvement and in some cases few by-products appears. The use of higher temperature is a suitable way to improve yield, but

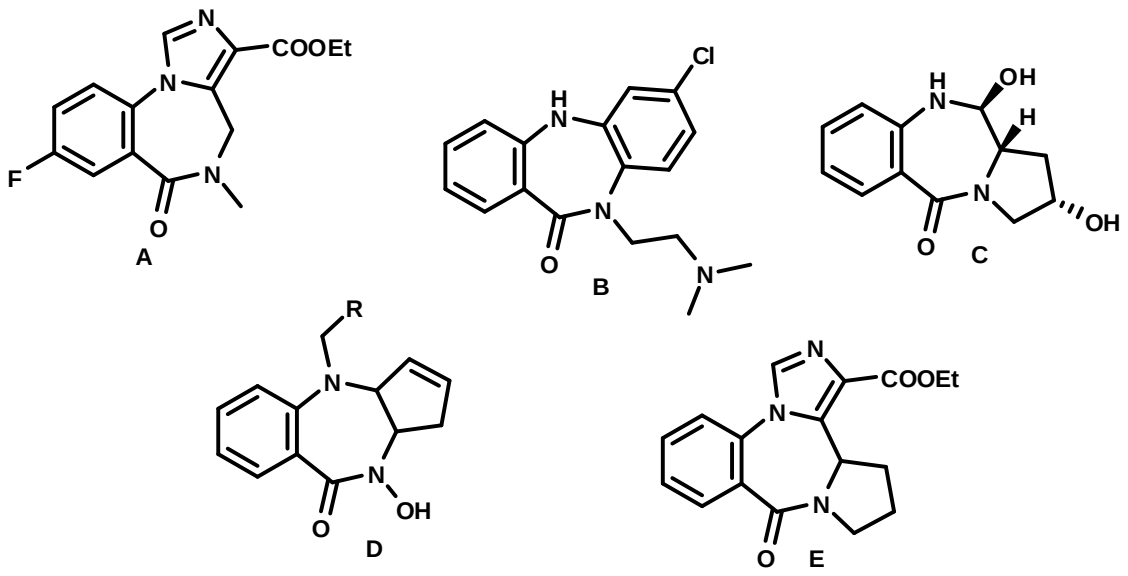
heating at 160°C is sometimes difficult due to the absence of solvent and the advantage is not so great, not above 10% yield increase.
There are some parameters to be careful about: procedure must be followed rigorously, different degree of particle size of K_2CO_3 influence a lot the outcome and the time spent in mortar and pestle use is critical; different Pd_2dba_3 may influence yield up to react or not; the initial microwave oven power must be very high to overcome the inertial barrier of the solid reacting mixture.

3. Benzodiazepines synthesis through π-allyl Pd-complex

1,4-Benzodiazepines play an important role in medicinal chemistry due to a wide range of pharmaceutical applications.[33]

1,4-Benzodiazepin-5-ones, one of the most significant classes of these molecules, are recognized as being endowed with anxiolytic, anticonvulsant, antiepileptic, muscle relaxant, antidepressant, sedative, and hypnotic activities related to the treatment of CNS disorders.[34] Moreover, this range of therapeutic activities has been significantly enhanced by annulation of the benzodiazepine skeleton to another carbo- or heterocyclic ring. Tricyclic 1,4-benzodiazepin-5-one systems, beyond solving benzodiazepine overdose problems, as in the case of flumazenil (fig. 4, compound **A**),[35] are also antihistaminic compounds,like tarpane (fig. 4, compound **B**),[36] antibiotics, like the pyrrolo-fused abbeymicin (fig. 4, compound **C**)[37] and antitumor agents, such as structures **D** (Fig. 4).[38] More recently, inspired by the attention given to bretazenil (fig. 4, compound **E**) due to its potential application in neurodegenerative diseases,[39] some tetracyclic 1,4-benzodiazepinones have appeared in the literature. These structures have the benzodiazepine nucleus fused to different hetero- and carbocycles such as pyrimidines, imidazoles, 1,2,4-triazoles, pyrazoles, benzopyrans, or naphthalenes.[40]

Figure 4



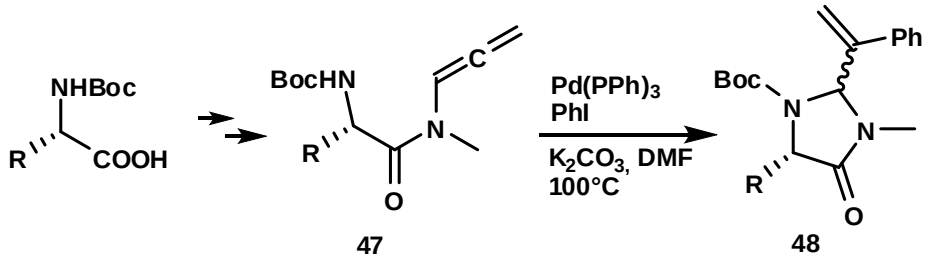
Among the several procedures reported in articles and patents to synthesize 1,4-benzodiazepin-5-ones, approaches involving the formation of the 1–2 nitrogen–carbon bond as the final step are commonly used. Intramolecular cyclization of amines with carbonyls[41] or acetals/thioacetals,[42] reductive cyclization of nitro derivatives with carbonyls,[43] intramolecular 1,3-dipolar cycloadditions of azides[44] and nitrilimines[45] to alkenes and/or alkynes, aza-Wittig

ringclosure of iminophosphoranyls with carbonyls,[46] intramolecular Michael addition of amines to enones,[47] intramolecular nucleophilic substitutions by aniline derivatives,[48] ring-opening reactions of amines on furan moieties,[49] intramolecular Pd-catalyzed cyclizations,[50] and the cyclization of amines with nitriles[51] on differently substituted benzamides have proven to be fruitful methodologies for promoting the formation of the nitrogen–carbon bond, eventually with the simultaneous construction of a new ring.

We have developed our synthesis of a new class of tetracyclic 1,4-benzodiazepin-5-ones through our recent interest in allenylamide heterocyclization[52] and long-time experience of 1,3-dipolar cycloaddition reactions.[53]

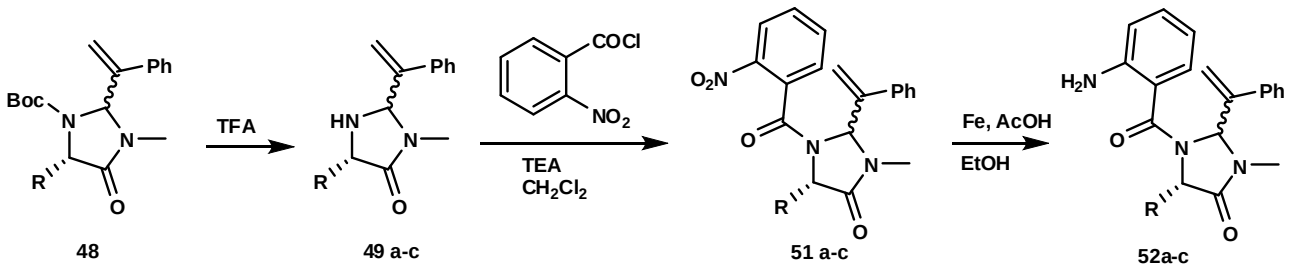
The starting point for planning the new synthetic strategy arose from the recent synthesis of the enantiopure 2-vinylimidazolidinones **48**, obtained by heteroannulation of the amino-allenylamides **47** (Scheme 15). The imidazolidinones **48** are ideal starting point for a final step involving a 1,3-dipolar cycloaddition bearing a double bond as dipolarophile.

Scheme 15



Our approach required the synthesis of 2-aminobenzamides **52** as suitable compounds for accessing the azide and nitrilimine 1,3-dipoles due to the presence of the aniline moiety. With this aim, the Boc-protecting group was removed by treatment with TFA to give imidazolidinones **49** (Scheme 16). These latter compounds were functionalized by reaction with 2-nitrobenzoyl chloride (**50**) to give the 2-nitrobenzamides **51**, which in turn were reduced to the 2- aminobenzamides **52**.

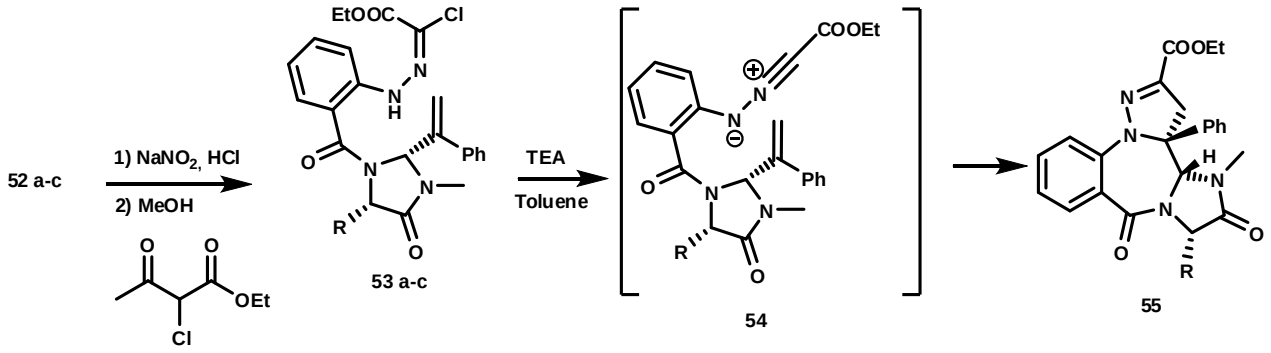
Scheme 16



The diazotization of the aniline moiety permitted access to the corresponding azido compounds, but their intramolecular 1,3-dipolar cycloaddition furnished unstable 4,5-dihydro-1,2,3-triazole products, which decomposed into complex mixtures with no synthetic interest. Such a failure prompted us to turn our attention to the nitrilimine 1,3-dipole, a well-established functional group in the synthesis of variously substituted azoles.[54]

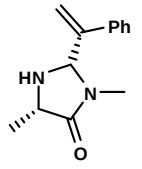
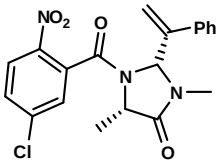
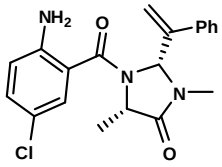
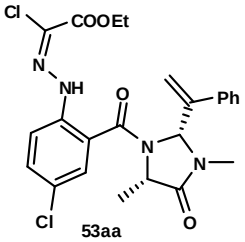
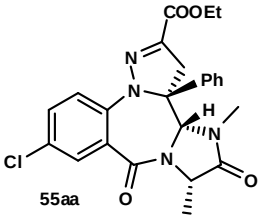
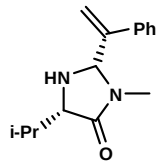
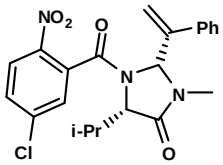
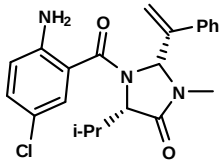
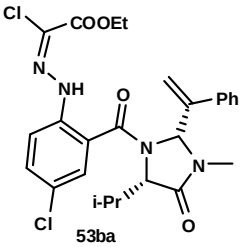
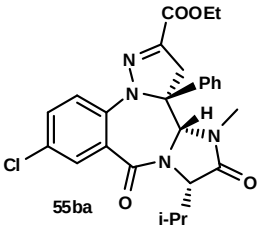
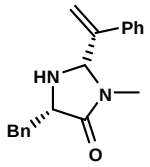
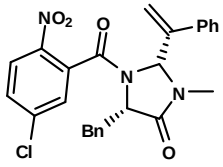
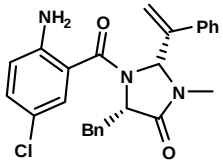
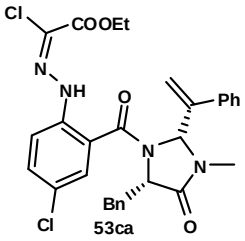
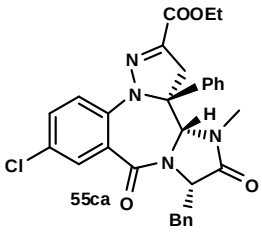
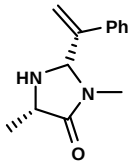
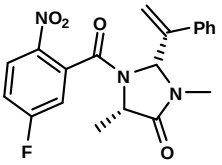
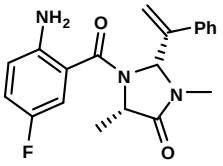
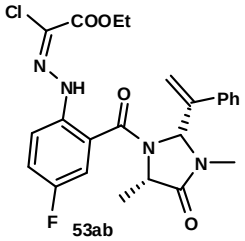
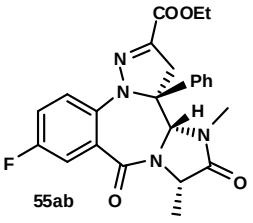
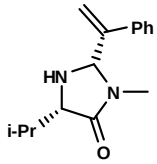
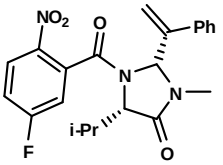
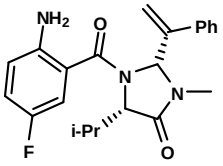
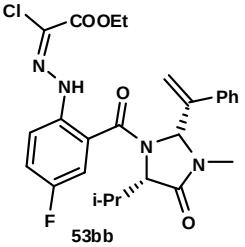
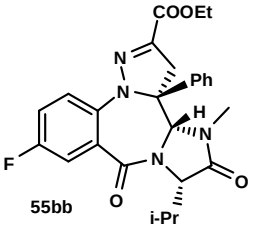
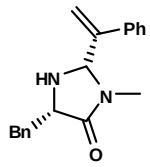
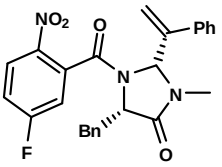
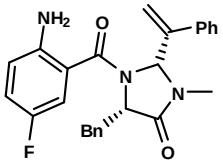
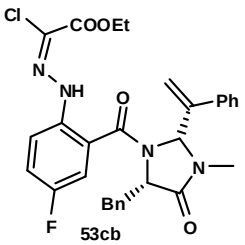
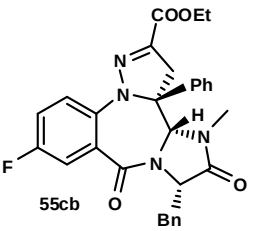
To this end, compounds **52** were submitted to diazotization and subsequent Japp–Klingemann reaction[55] that is, coupling with ethyl 2-chloroacetoacetate, furnished the hydrazonyl chlorides **53**, precursors of the transient nitrilimine species **54**. In fact treatment of **53** with triethylamine in boiling toluene gave directly the tetracyclic imidazo[2,1-c]pyrazolo[1,5-a][1,4]-benzodiazepine-5,8-dione systems **55** (scheme 17).

Scheme 17



We next examined the reactions of imidazolidinones **48** and 5-chloro- and 5-fluoro-2-nitrobenzoyl chlorides (**50a** and **50b**, respectively) to broaden the scope of the reaction and for the interest of the products from a biological point of view, having a halo-substituted 1,4-benzodiazepine nucleus. The halide-containing products, 2-nitrobenzamides **51**, 2-aminobenzamides **52**, hydrazonyl chlorides **53**, and tetracyclic products **55**, are presented in Table 1. The preparation of hydrazonyl chlorides as well as the nitrilimine cycloaddition reactions occurred analogously to those described for the unsubstituted 2-nitrobenzoyl chloride. All compounds synthesized are reported in table 5.

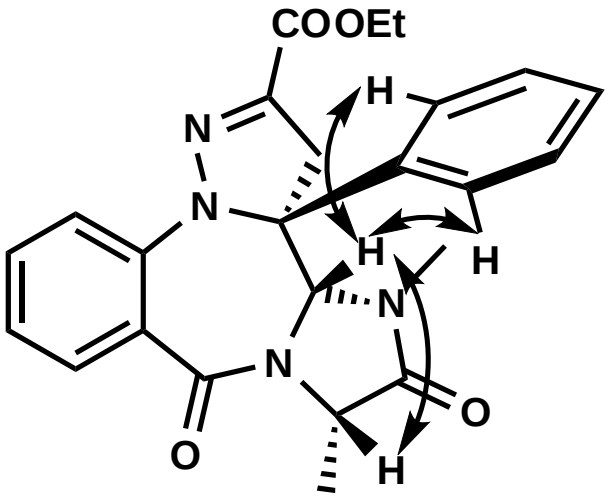
Table 5

Imidazolidinones	2-Nitrobenzamides	2-Aminobenzamides	Hydrazonyl chlorides	Benzodiazepinones
 49a	 51aa	 52aa	 53aa	 55aa
 49b	 51ba	 52ba	 53ba	 55ba
 49c	 51ca	 52ca	 53ca	 55ca
 49a	 51ab	 52ab	 53ab	 55ab
 49b	 51bb	 52bb	 53bb	 55bb
 49c	 51cb	 52cb	 53cb	 55cb

Further to the total regiochemical outcome that was expected as a consequence of the propargylic nature of the 1,3-dipole, the cycloaddition reaction was totally diastereoselective giving rise to only one diastereoisomeric product.

The absolute configuration of the simplest term was assigned on the basis of ^{1}H NMR NOESY experiments carried out on compound **55a**. As shown in Figure 2, further to obvious interactions between the hydrogen atoms at the 2- and 5-positions of the imidazole nucleus, the cross-peak between the hydrogen at the 2-position of the imidazolidinone and the ortho hydrogen atoms on the phenyl group resulted in the determination of the S configuration of the newly created stereocenter and thus the (3aS,3bR,6S) diastereoisomer. The enantiomeric purity was proven to be better than 99.5% by HPLC analysis of compound **55a** with an AD chiral column and in comparison with a sample of the corresponding racemic mixture synthesized starting from (±)-alanine.

Figure 5



To deeply investigate this non-common feature we start a theoretical study. To make a more eclectic work we decide to compare the old wave function method HF with DFT method in order to see if results are in agreement and which one is the best one to solve our problem. We have also take a look on computational calculation cost in order to give a better overall evaluation.

Further to broadly used DFT and WFT theory, today we have a new theory which could be seen as a complement to the classical quantum chemical tool and is able to interpreter the results obtained by wave function resolution in a very familiar way for a laboratory organic chemist. This theory is called AIM, acronym of Atoms In Molecules (also known as QTAIM where QT means Quantum Theory), and was developed between '70 and '80 by R. W. F. BADER. He summarized his findings in a book edited in 1990[56] where there is explained how

this theory is rigorously derived only by wave function applying mathematical and physical theorems without arbitrary assumptions.

AIM theory focus on interpretation of wave function results in terms of electron density. Applying the mathematical principles of topology it explain how we can assign to each atom in a molecule a defined region of space, not only in terms of electron density $\nabla\rho$, but also as its second derivative $\nabla^2\rho$, otherwise known as Laplacian, or even the kinetic energy density, the virial of the forces etc.

The strength of AIM theory is the ability to describe bond, not only covalent bond, but also the ones described (erroneously) as "interaction" or particular kind of bond like H-bonds, π-π bonds, ionic bonds, metallic bonds, coordination bonds, VdW bonds etc.

Such a powerful tool could lead us to interesting conclusions. When we observe how a reactant becomes a product, both weak and transient bond and interaction may play a very central role carrying to a specific kind of product (instead of the other).

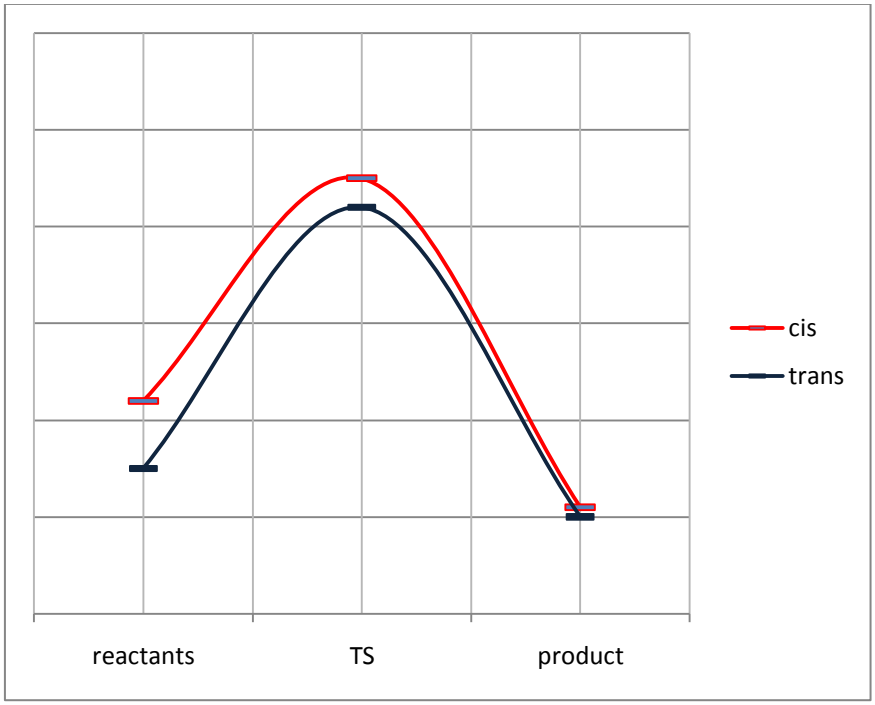
Unfortunately at the date of writing there are only few articles in which AIM theory is used to analyze reaction pathways;[57] in particular it's still not clear the fundamental role played by AIM theory in this area. Consequently this is our purpose and we like to explore this field.

We refer to the two possible products as reported below in fig. 6.

Simple calculation of the two product energies don't give results in agreement with experiment: HF/631Gd or HF/6311+Gdp provide Zero Point corrected Energy of about 1 Kcal/mole favorable to TRANS. B3LYP/631Gd and B3LYP/6311+Gdp give the same result with energy differences of about 2 Kcal/mole. Since the solvent used is always toluene, that doesn't influence a lot the outcome, as we expected, calculations with salvation model, give almost identical results.

To justify our results we decide to locate the two possible TS in order to trace the reaction energy profile. In our hypothesis the reaction energy profile must support experimental data giving rise to a typical graph like the one reported below (graph 1).

Graph 1

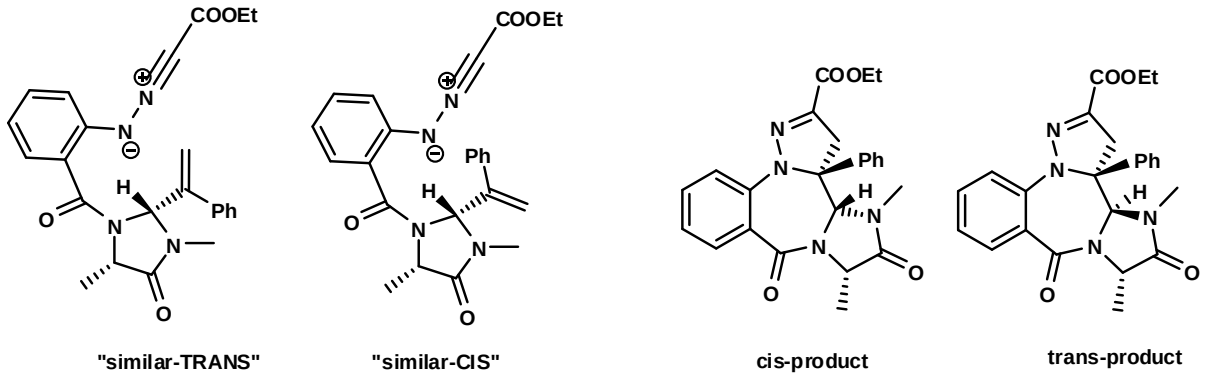


As showed we expect that while "similar-trans" starting products and TS, are more stable than the corresponding cis, the energy difference between trans and cis products, as we have already calculated, is only 1 or 2 Kcal/mol. But we also think to find an overall energetic gap very large in favor of cis.

This gap is the sum of the differences between starting substrates to TS and TS to products. The first difference must be low to make easier for the molecule reaching its TS. This profile is improved when TS and reactant are similar as implied in Hammond's postulate. The latter difference must be higher because a big energy jump can be the leading force for the formation of one product instead of the other.

The first step is an optimization, HF and DFT, of the four molecules involved in the reaction and reported in fig. 6. Products were already optimized in the early stage of our research as reported above.

Figure 6



The optimization of reactants is not so simple. For nitrilimine moiety, in term of geometry, we start from the good data find by Ponti et al.[58] But we have also to face with another important feature: the relative position of the nitrilimine moiety to the styrene-like one. To be sure avoiding errors we perform a potential energy surface scan. We place H and phenyl in "similar-cis" and "similar-trans" position and scan the rotation of the nitrilimine moiety around the amidic C-N bond indicated.

We found in fact an interesting feature: the two reactants assume a very different spatial disposition and "cis" reactant is less stable but with nitrilimine and double bond closer. See fig. 7 e fig. 8 to better understand.

Figure 7

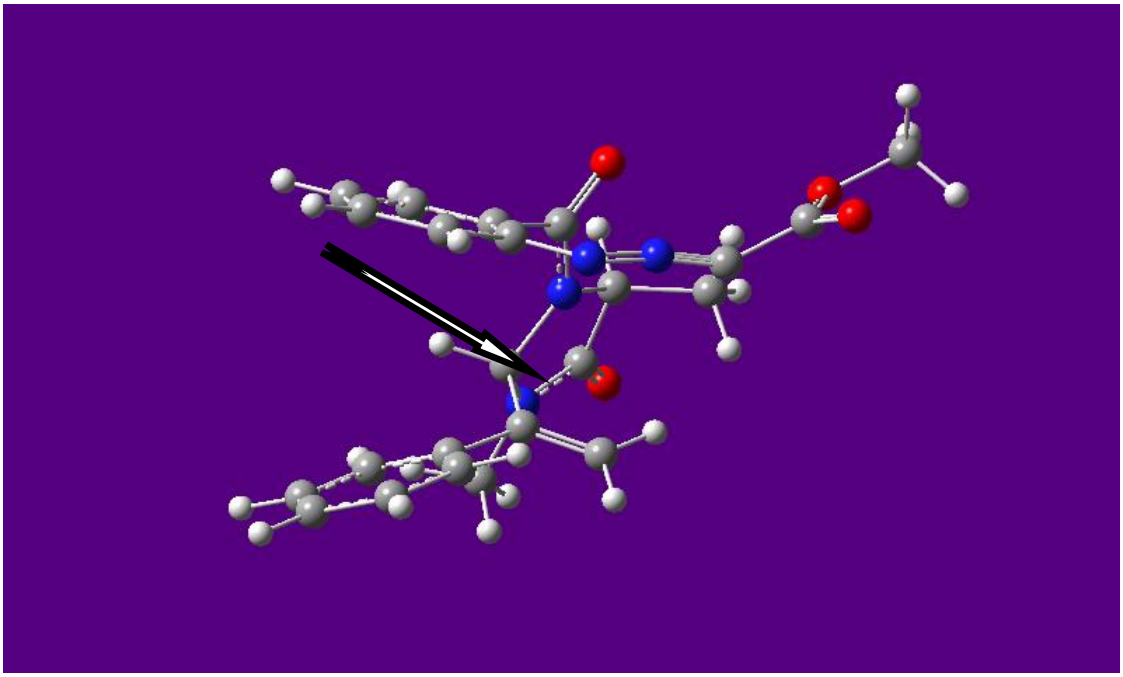
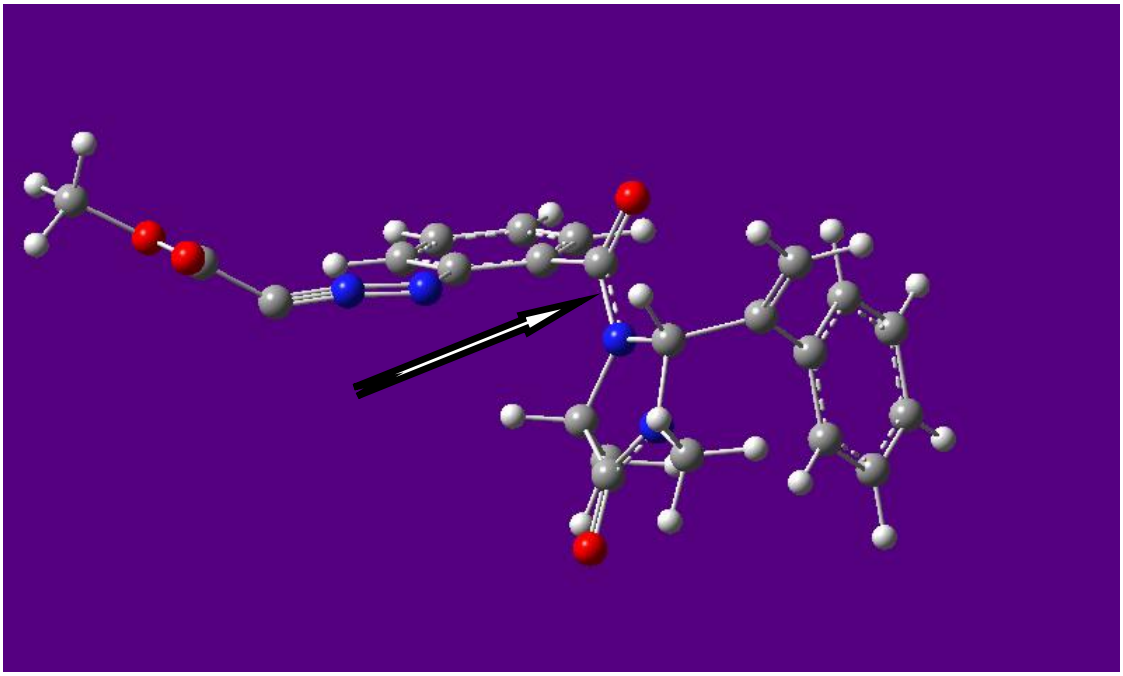


Figure 8

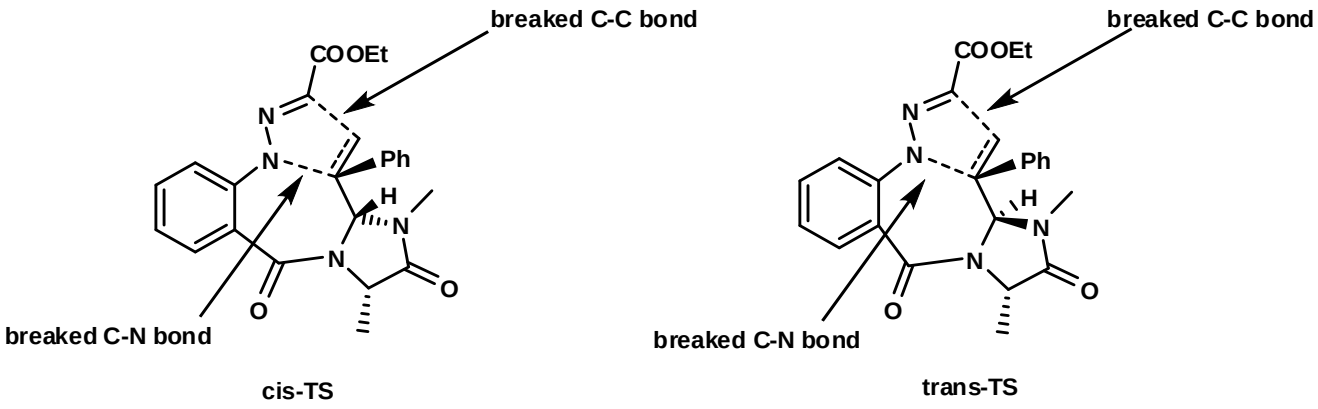


Bearing in mind Hammond's postulate we could see that the "cis" reactant is very similar in spatial disposition to the TS; that's make simpler its evolution to TS.

To locate the TS we use a strategy based on two different but, in the same time, synergic starting method:

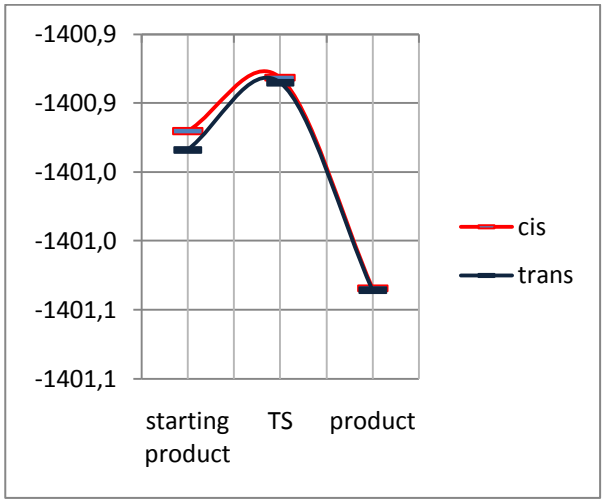
We start from optimized product, break the two bond formed in the reaction and, on the basis of literature data on 1,3-dipolar cycloaddiction,[59] we assign the distances between dipole and dipolariphile double bond. First we optimize these molecules fixing the length of the partially formed bond, and then we try to locate the TS (fig. 9).

Figure 9



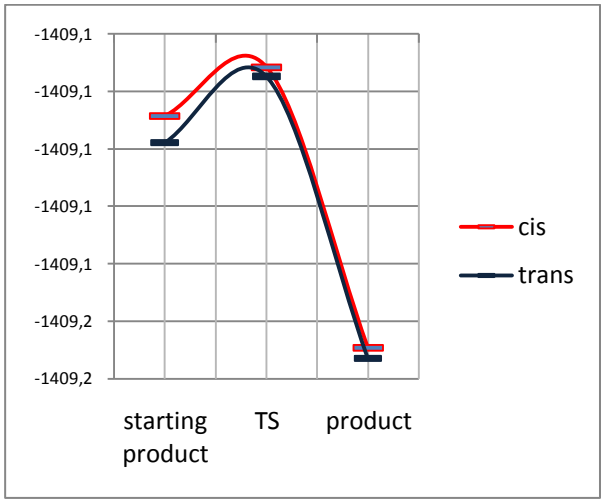
After calculation we find the reaction energy profile reported in the two graphs 2 and 3.

Graph 2



HF 631Gd

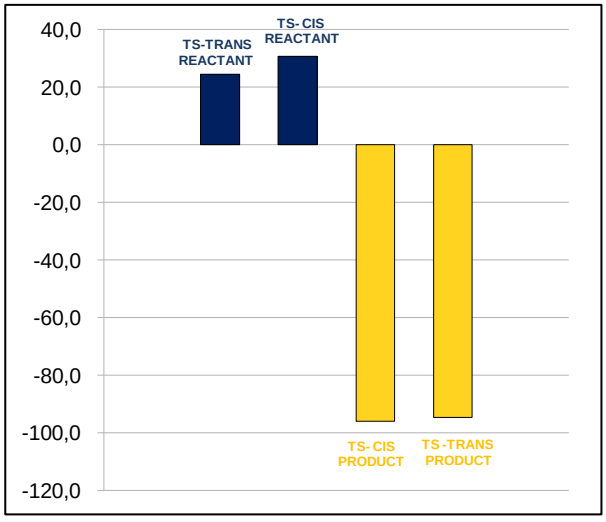
Graph 3



DFT B3LYP 631Gd

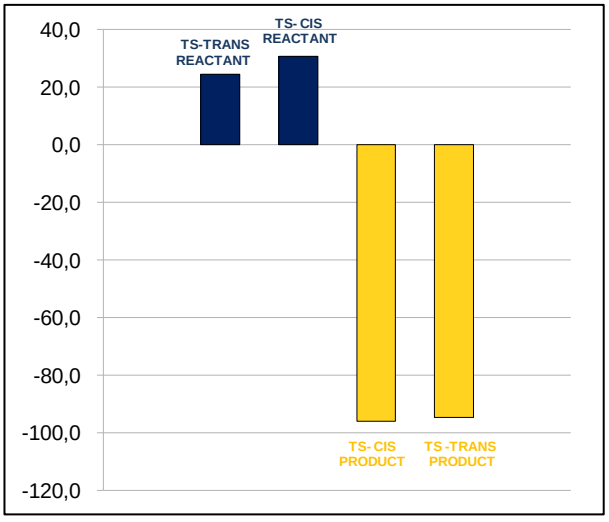
It's clear that results don't agree with experimental data: in fact in both cases TRANS product seems to be more stable and TRANS starting molecule is more stable too. However the energetic gap, as explained before, seems to be consistent with experimental data.
In graphs 4 and 5 we try to emphasize the energetic differences enabling cis product to form.

Graph 4



HF 631Gd

Graph 5



B3LYP 631Gd

In the graph 4 we report the differences, in Kcal/mol, between TS and reactant (blue), product and TS (yellow). Two things are clear: first of all for "similar-trans" reactant is more difficult to reach its TS; second, the energetic gain in the formation of product is slightly favorable to

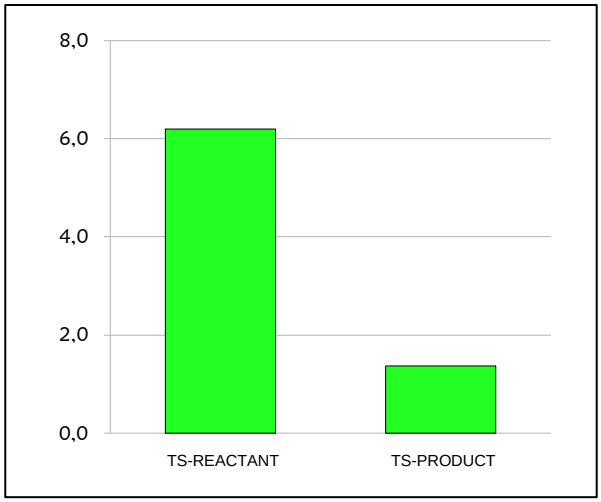
the cis transition from TS to product. To magnify this concept we can use a mathematical trick: plot in a graph the differences between the commutation energy:

1) [(TS-transRectant)-(TS-cisReactant)]

2) [(transProduct-TS)-(cisProduct-TS)]

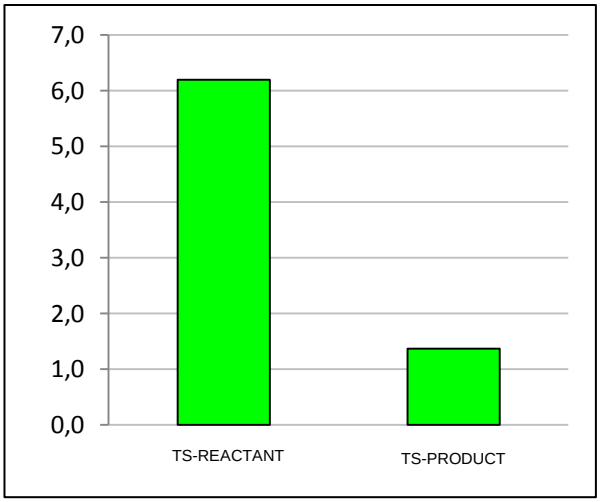
In this way the first formula gives the differences of the differences in energy needed for reactants to reach TS, this energy is lower if the transition is favored. The second formula gives the differences in ΔE between product and the originating TS; these ΔE are negative and greater when transformation is favored so that the difference we use must be above 0 if transformation is favorable to cis product formation.

Graph 6



HF 631Gd

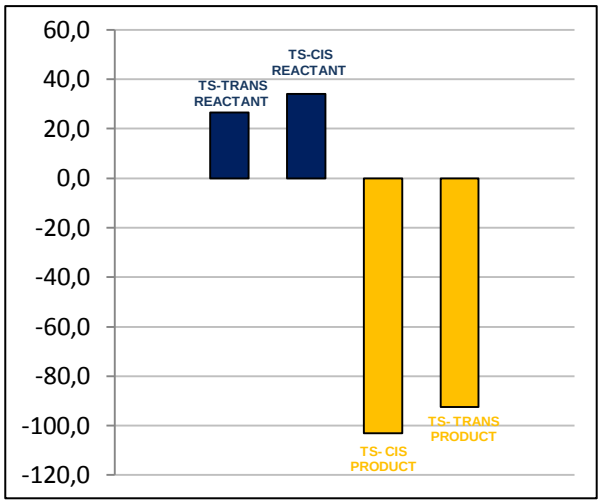
Graph 7



B3LYP 631Gd

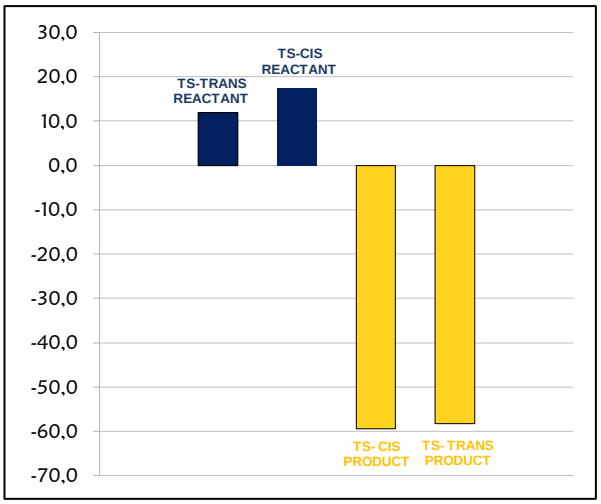
At this medium-low level of BS we already see that the energetic gap lead to CIS product, HF and DFT are in agreement. To convince ourselves of the truthfulness of our results we perform a systematic enlargement of BS up to 6-311G++2d3p and then we also make an extrapolation at infinite BS. In graphs 8 and 9 and in graphs 10 and 11 below we can see results at the higher BS used.

Graph 8



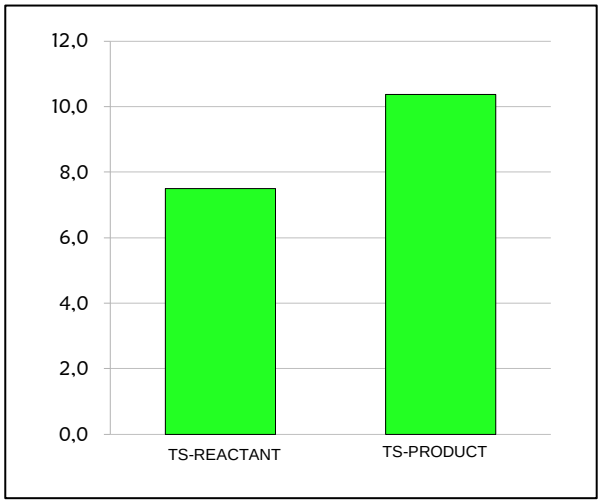
HF 6311++G2d3p

Graph 9



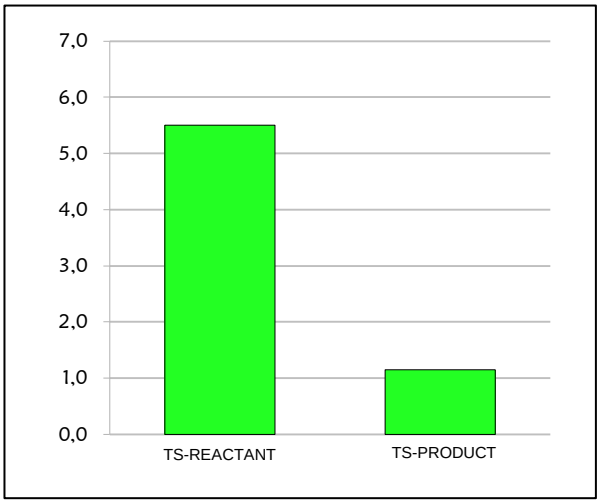
B3LYP 6311++G2d3p

Graph 10



HF 6311++G2d3p

Graph 11



B3LYP 6311++G2d3p

Utilizing triple split, enlarging the use of diffuse function and additional function on H and C gives good results for DFT and HF too, with computational time lower for DFT calculations. After all these calculations we can justify our experimental results considering that the overall gain in energy seems to push the reaction toward the CIS product. The difference between the two products is little, near or below the error, but decrease as basis set increase. Besides this fact at the higher basis set used, in the case of HF calculation we obtain a difference of about 8 Kcal/mole in favor of CIS product, and almost no differences (below 0,4 Kcal/mole) for DFT.

We must also note that the higher basis set used places more function on hydrogen (3p) than on heavy atom (2d). This not well balanced basis set, also thanks to heavy use of diffuse functions, seems to reach better results. This fact could be due to a fortuitous case or to the strong influence that VdW and dispersive interaction play in our specific case.

The question now is: how we can trust these theoretical results? If we don't really have in hand experimental results and we want to make previsions, do we foresee the right results?

From an organic chemist point of view, the study of a reaction based on energy and ΔG, ΔH, ΔS is not immediately clear; sometimes we find numbers hard to interpret, other time, with the current instruments and approximations, we can't find an unambiguous answer.

In our case it is possible that improving DFT functional, since B3LYP is somewhat dated, may lead to better results. On the other hand the use of a post-HF WFT method like MP2 could be better, but for a system of 53 atoms it becomes quite prohibitive in terms of computational cost.

As reported after we have a further instrument: AIM.

To apply AIM theory to our problem we try to investigate various aspects and features of electron density and his derived and subtended properties.

First of all we try to understand if there is a correlation between several properties at the bond critical point (BCP) and the overall reaction result. To account for the evolution from reactants to products we consider the three new critical points (CP) formed at the level of TS: the two BCP, C-C and C-N, and the RCP (Ring Critical Point) deriving from cycloaddiction.

We analyze the electron density, the laplacian of electron density, the kinetic energy density and the virial of the forces exerted at the critical points by the electron density.

Utilizing wave function deriving from HF calculation we state some common feature. In particular the laplacian of ρ is always negative and superior in the trans TS.

The electron density at the same CP for the two TS is higher for CIS both at the C-N and ring critical point, while it is lower for C-C BCP; we observe the same behavior for kinetic energy density and virial of the forces. We don't exactly know the real meaning of this; we can only formulate an interpretation: the first bond formed in cycloaddiction is the C-N bond which guides the generation of the RCP, and then C-C bond is formed.

This interpretation lack of the data deriving from $-\nabla^2\rho$ that is always favorable to TRANS even if with little value.

On the other hand DFT data are different because they show a laplacian favorable to CIS product, with electron density and virial almost equal for C-N and RCP, whilst $\nabla\rho$ and virial of BCP C-C favorable to TRANS.

It is interesting to note that the value of laplacian are similar at every level of BS used, so we can conclude that results do not suffer of strong base dependencies as already noted in several articles(ref.).

A deep investigation of these results and the use of higher level of theory could give better results. To put a critical interpretation on computational data, we try to find a simpler, more reliable and rapid way able to give realistic results, in accordance with experimental one.

This goal implies a deep understanding of the mechanism and the forces involved in the reaction pathways. What can guide the formation of one product instead of the other is weak and transient interaction, forces difficult to see and account for utilizing simply outcome of QM calculation. AIM theory, as said after, can account for the abovementioned "interaction" and characterize them.

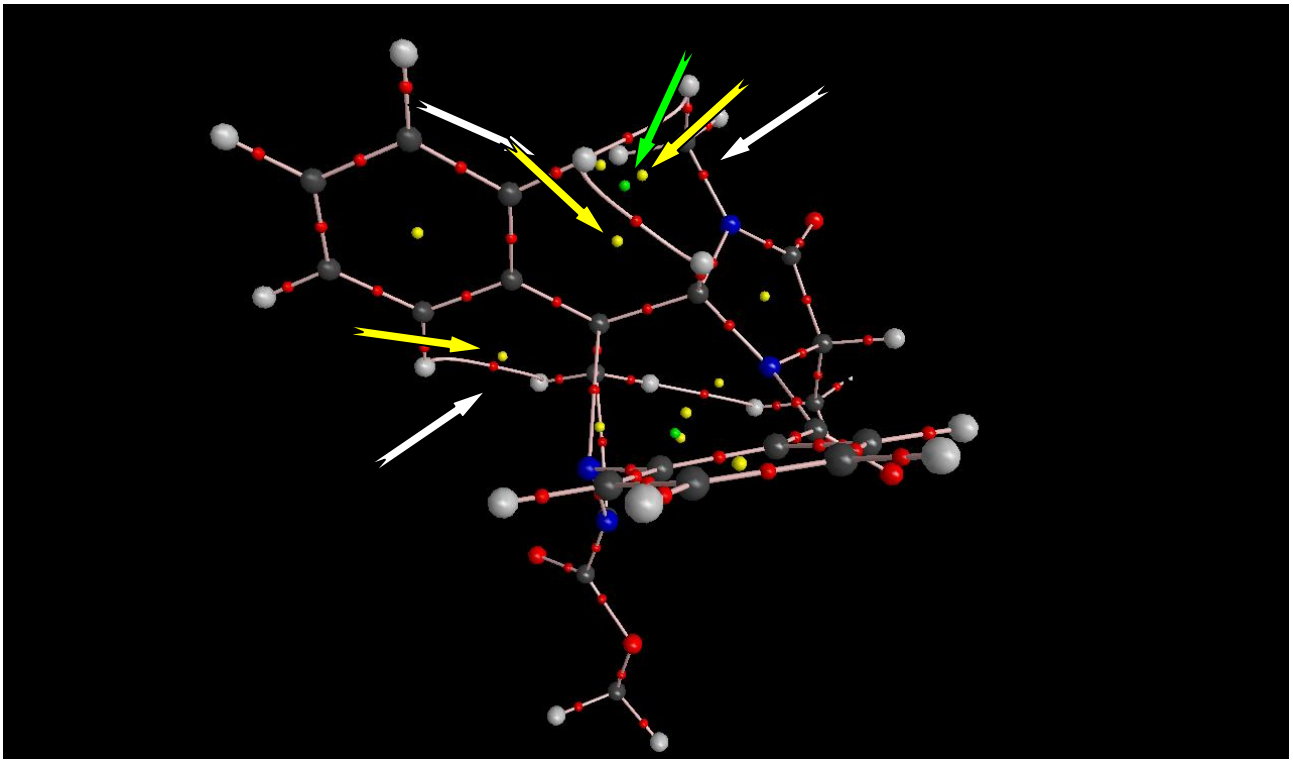
At this point we decide to look out for differences about the weakness of bond between the two TS and surprisingly we can see substantial differences that strongly justify experimental data. CIS TS bear three weak bond involving phenyl and H that are the two groups considered for the cis-trans isomerism. TRANS TS shows only one weak bond. See figure NN

This is not all. In fact the two more bonds in CIS TS lead to two additional critical points, one ring CP (fig. 10, yellow arrows) and above all a cage CP (fig. 10, green arrow). This feature strongly pushes the reaction toward CIS product because the forces involved in this interaction, although invisible from standard QM calculation outcome and not high enough to be reliably calculated, are visible with AIM analysis and in doubtful cases could lead to a good solution.

It is encouraging that this weak bond are present in AIM analysis based in every calculation, spanning from HF to DFT and from 6-31Gd to 6-311G++2d3p. These homogeneous results should arise from the basis of AIM theory: once we found equilibrium geometry, the forces are zero and we obtain the right distribution of the electron density. Although we can't trust the value obtained at low level of theory, we can see at a glance the interaction we couldn't see otherwise.

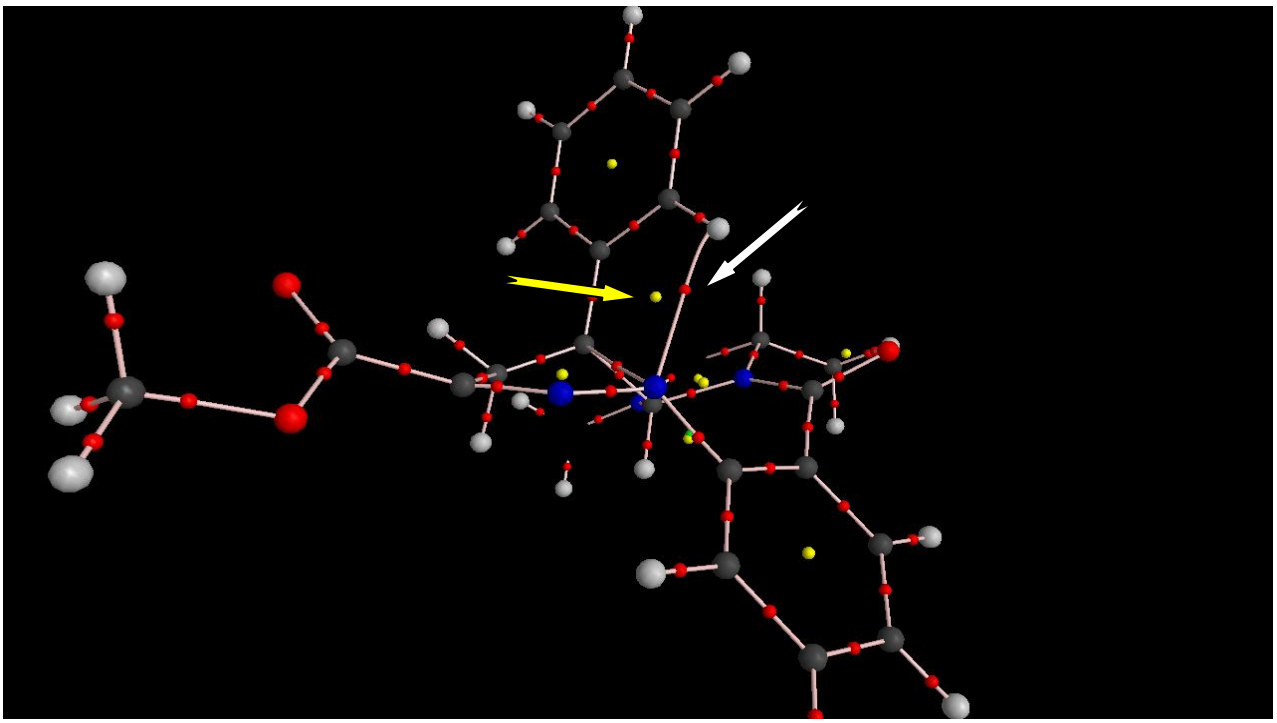
In our case we state the existence of weak interaction addressing the outcome of the reaction, we can then move in this way to address the problem, for example we can tell that large use of additional basis, especially on hydrogen, lead to a better result in term of energy and is not a casual issue. On the other hand we can try to use DFT functional which better account for weak interactions. In any case we observe interaction otherwise invisible only based on wave function. This interaction are evident thanks to the use of AIM theory which we can say in the future will became surely a breakthrough mean to interpret obscure data arising from wave function and better understand the various aspect of organic chemistry.

Figure 10



CIS TS, white arrow indicates BCP of weak interaction, yellow arrow indicates ring CP, green arrow indicates cage CP generating from weak interaction ring.

Fig ure 11



TRANS TS, white arrow indicates BCP of weak interaction, yellow arrow indicates ring CP.

Pd(II)-catalyzed reactions

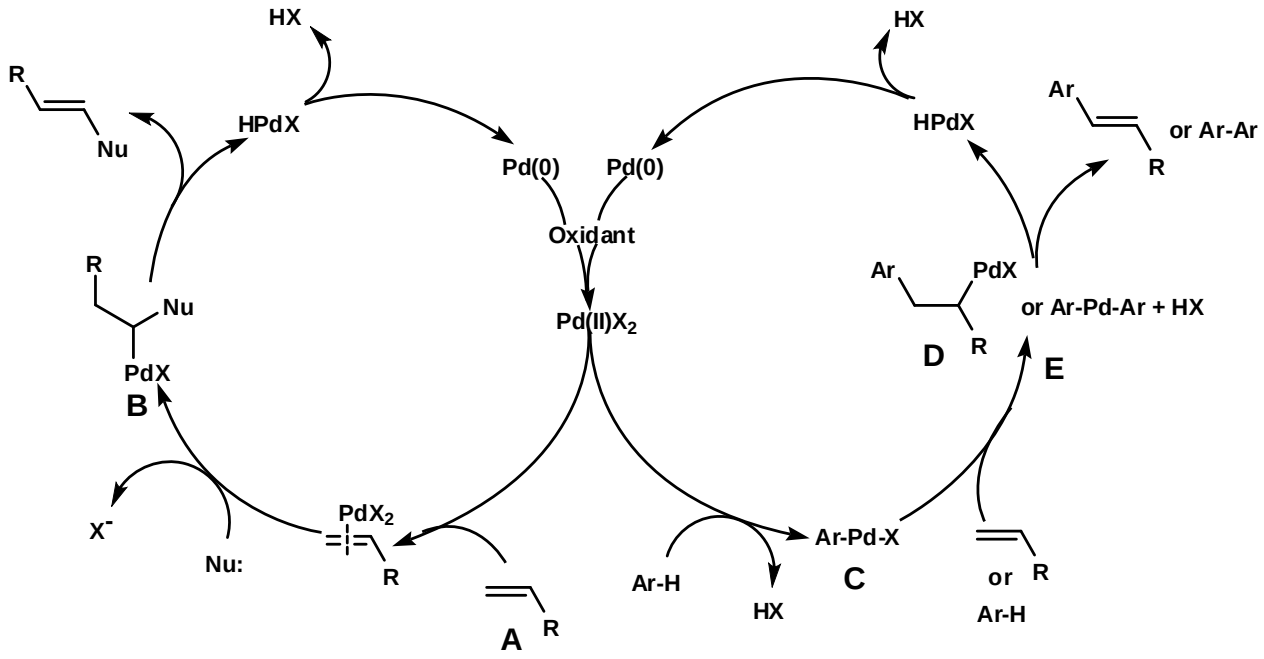
4. Alkenylation of isoxazol-5-ones through Pd(II)-catalyzed C-H activation

In the wide range of Pd-catalyzed reactions, oxidative coupling and amination reaction of alkenes and alkynes have been less employed despite the easy availability of the starting materials, compared to the halogenated substrates necessary for reactions like the Heck reaction and the Buchwald-Hartwig reaction.

The oxidative coupling is a catalytic process which allows the formation of carbon-carbon bond. The literature data report oxidative inter- or intra-molecular coupling like arylation of aromatic heterocycles and alkenylation of arenes with olefins through the cleavage of sp^2 C-H bond in the presence of palladium complexes. Most of the applications of palladium described in literature use a stoichiometric amount of palladium complexes. The synthetic advantage of this oxidative process consists on the use of catalytic amount of palladium.

Palladium(II) salts are electrophilic species and tend to react with electron-rich substrates such as olefins, alkynes and arenes. The mechanism of these processes has been extensively studied. The typical reaction with alkenes starts with the complexation of the olefin by Pd(II) salt, as reported in scheme 18 on the left side. The resulting π-olefin complex **A** can undergo an intermolecular or intra-molecular nucleophilic attack, usually at the less substituted vinylic carbon, to give a π-alkylpalladium(II)-complex **B**. The final product arises normally from β-hydride elimination of HPdX but also different processes may be observed.

Scheme 18



With aromatic substrates different mechanism has been proposed which involves the electrophilic substitution of an aryl hydrogen by palladium giving **C** and the formation of a π-bonded aryl-Pd(II)complex **D** (scheme 18, on the right side). This palladate intermediate can give rise to homocoupling reaction or, in the presence of alkenes, vinylic substitution reaction. Also in this case elimination of HPdX gives the final product.

In situ regeneration of Pd(II) from Pd(0) is the crucial step for catalytic cycle; for this purpose, several re-oxidation reagents have been already reported such as copper acetate, *tert*-butyl hydroperoxide, butyl perbenzoate, BQ and oxygen.

We try to apply this kind of reaction to isoxazol-5-ones which may act as heterocycles or nucleophiles.

Isoxazol-5-ones are particular heterocycles existing in three tautomeric forms. This characteristic is strongly influenced by solvent as we can note in the reported NMR: in $CDCl_3$ we observe the presence of CH_2 and CH_3 as singlet as it is possible for tautomer 1 and 3, but we also observe the C-H of tautomer 2 which shows the splitting of CH_2 signals and is about 50% of the other tautomer (based on relative value of integrals for CH_3).

Scheme 19

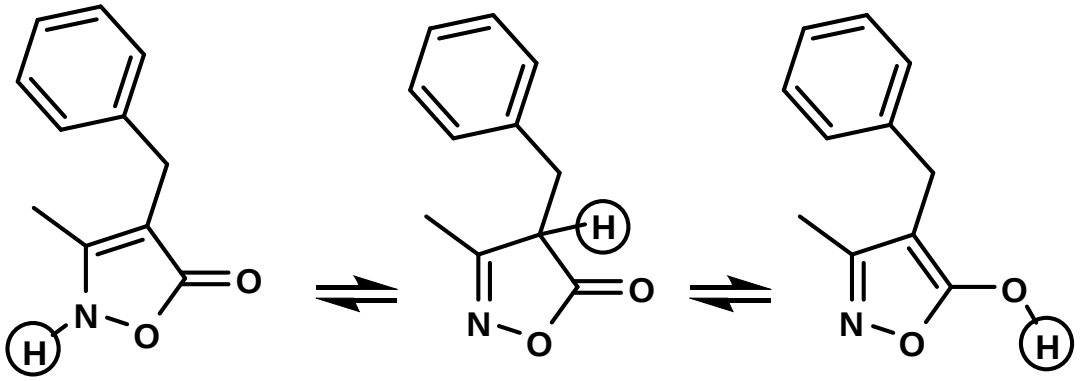
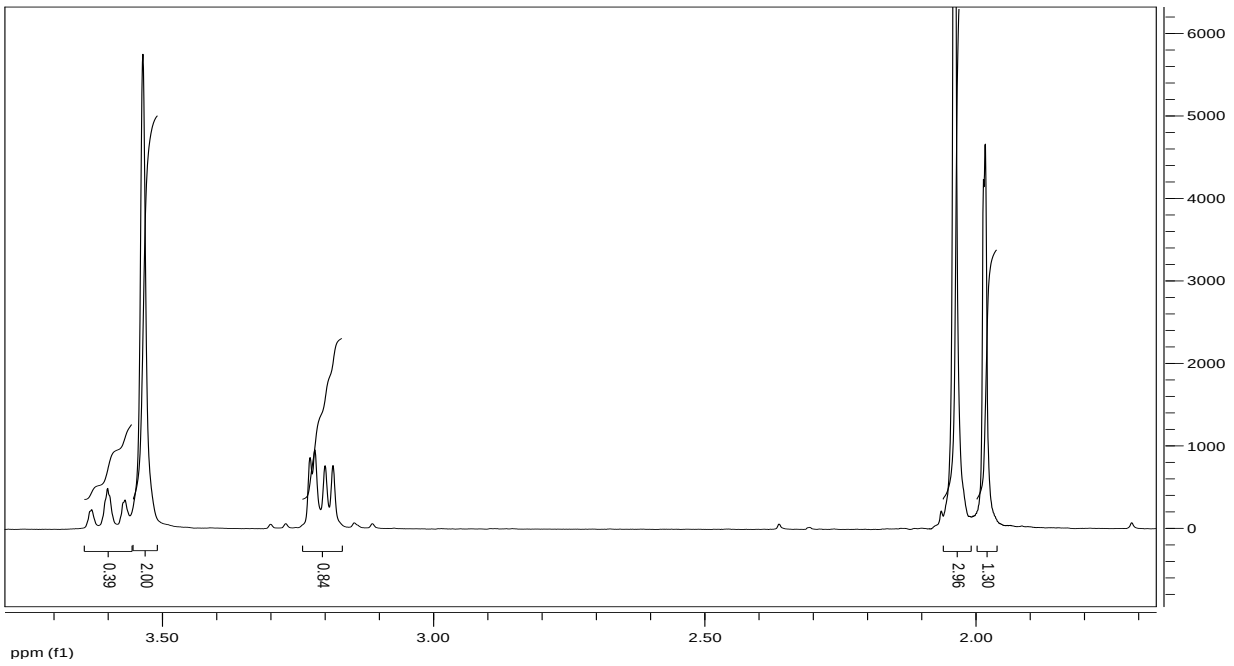
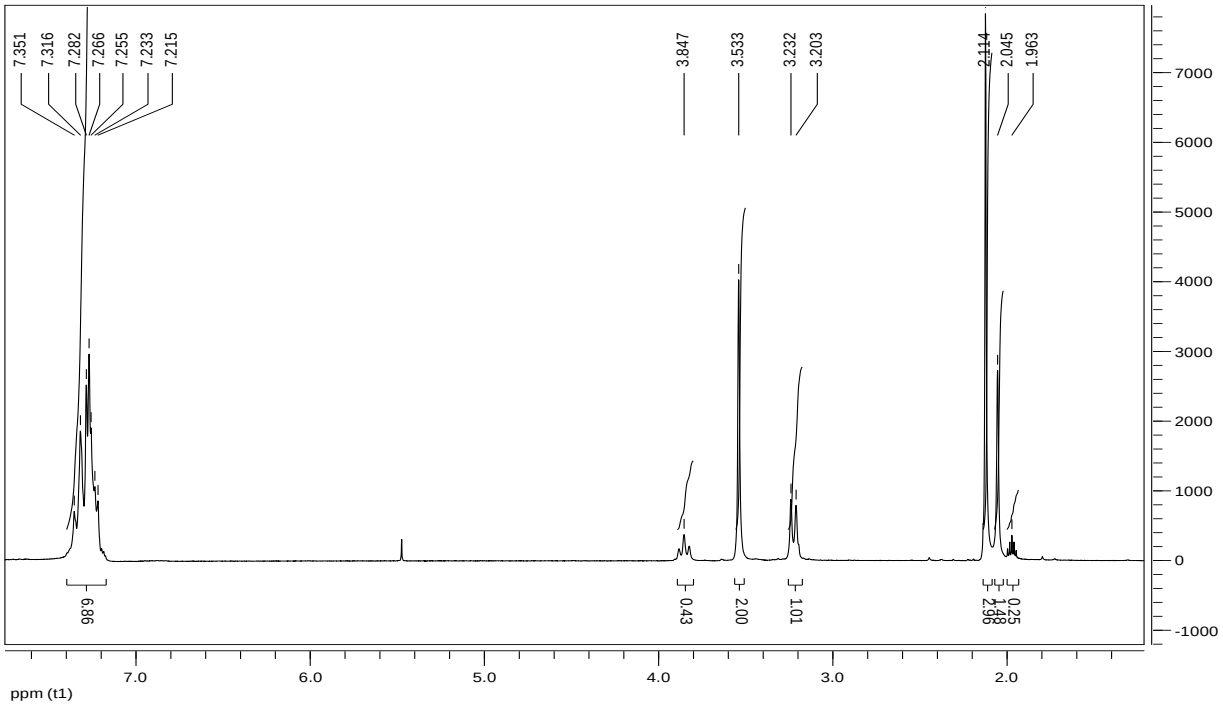


Figure 12 (CDCl3)



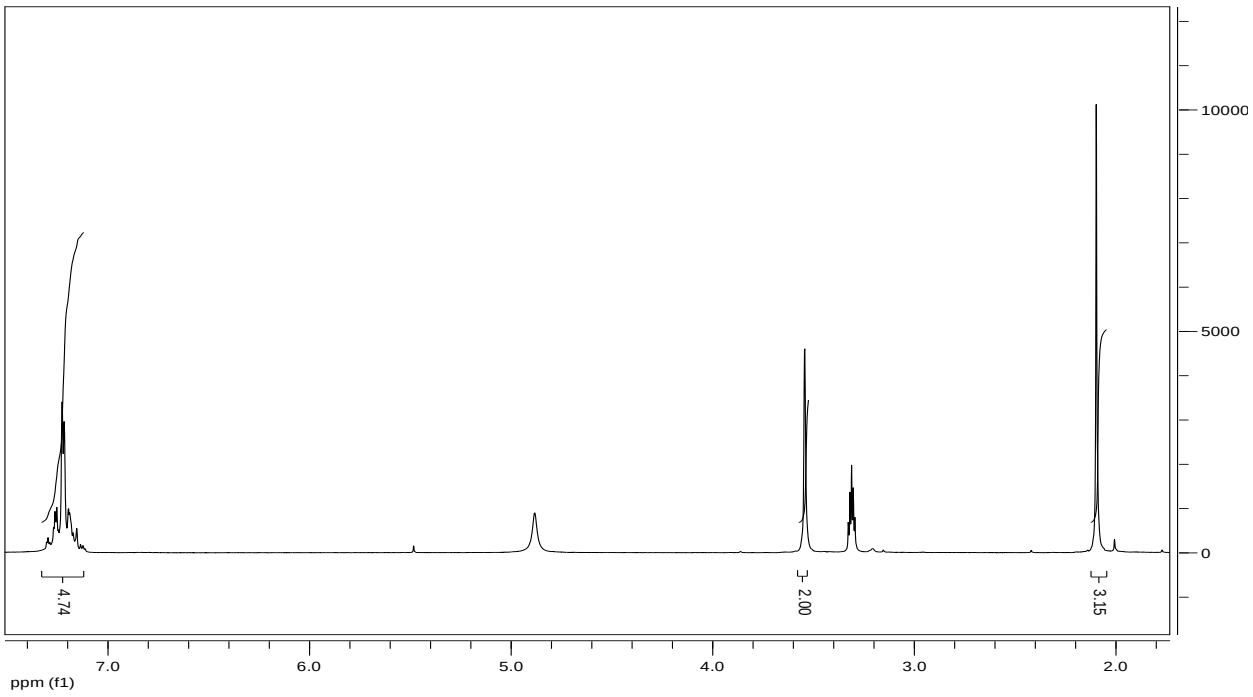
In acetonitrile we still observe the two tautomers and the relative ratio is the same 2/1 in favor of NH or OH form.

Figure 13 (CD3CN)



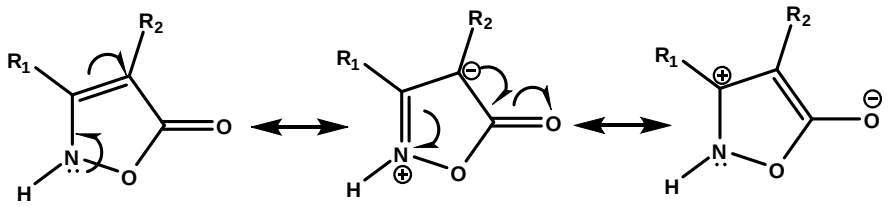
When we observe spectra acquired in protic solvent we note that only one form is present and C-H tautomer is unobserved.

Figure 14 (Methanol D4)



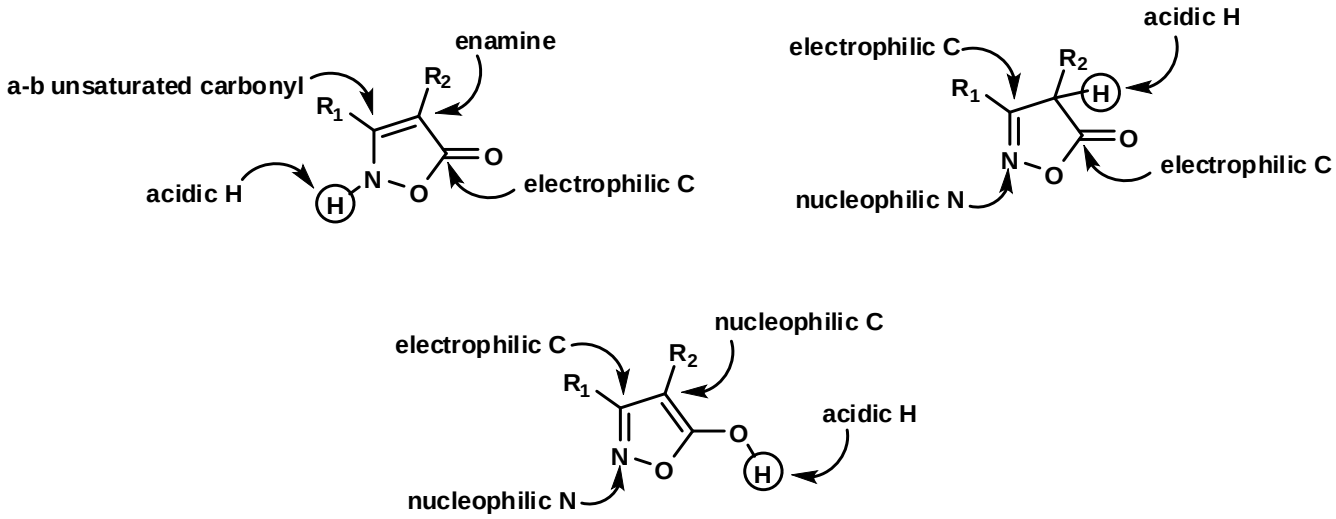
On the basis of charge separated limiting Lewis structure, we can note that there are a lot of possible reacting sites (scheme 20). This characteristic is a double-edged blade leading to a great number of synthetic possibilities but a very difficult regio- and chemo-selectivity control.

Scheme 20



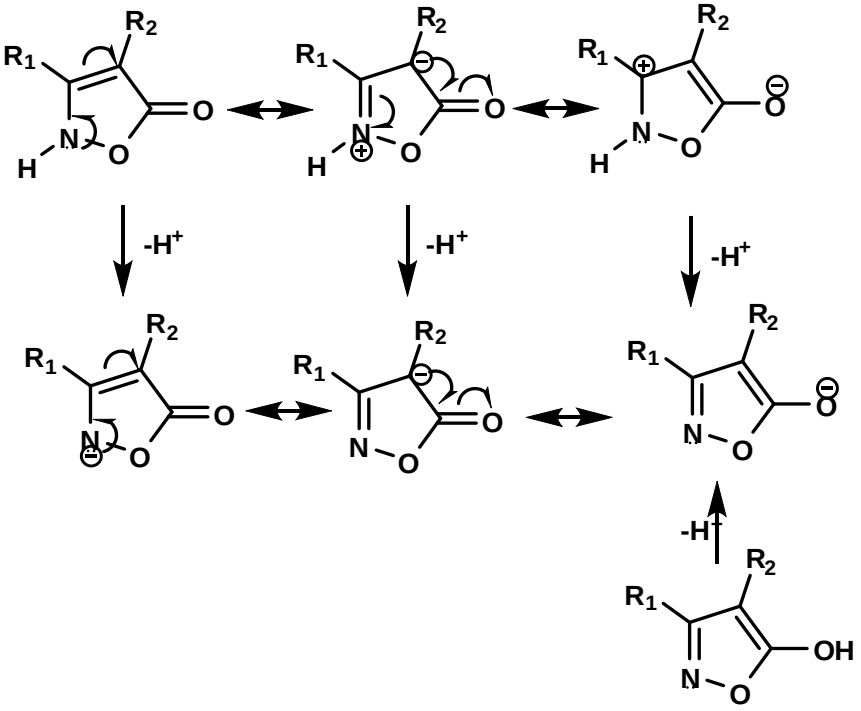
The three resonance forms are reported below associated to their possible reactivity (Figure 15):

Figure 15



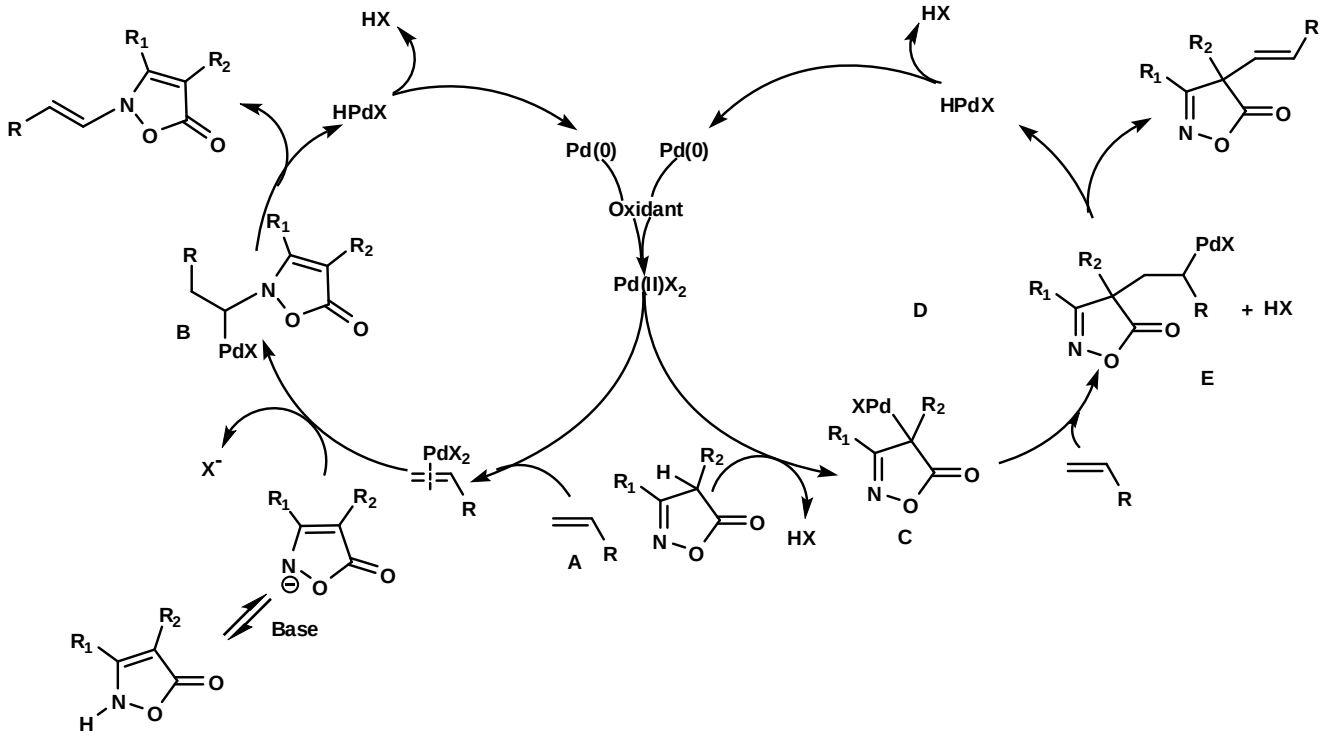
Another interesting but also problematic feature is the tautomerism of the anion, solvent and base dependent, easily generated even with weak bases (scheme 21).

Scheme 21



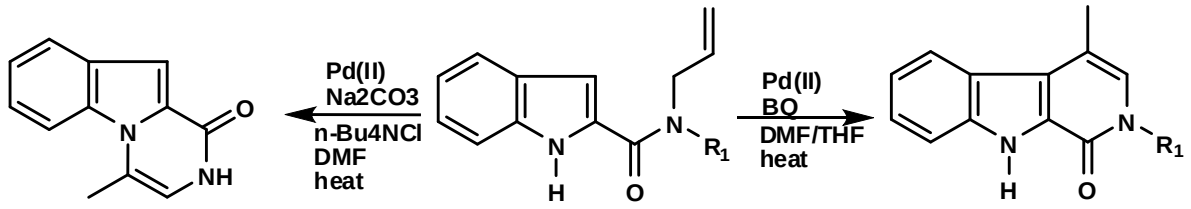
Isoxazol-5-ones could act as heterocycles or nucleophile in C-H activation reactions, especially in the presence of a base that generates the anions. If we look at the general catalytic cycle reported for oxidative coupling in our case we probably have something like scheme 22.

Scheme 22

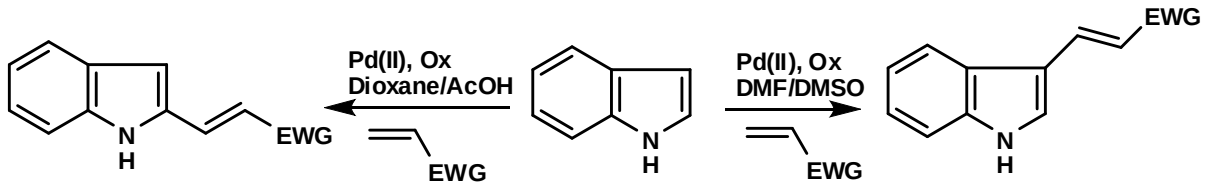


Previous works on Pd(II) catalyzed reactions report a solvent-based regioselectivity[60] (scheme 23 and 24). We find interesting to try the feasibility of such a kind of reaction on isoxazol-5-ones because of the possible influence of solvent and catalytic system on the outcome. In spite of the difficulty we wonder if it is possible the total control of regioselectivity and to lead reaction exactly in the desired direction playing on simple adjustable parameters.

Scheme 23



Scheme 24



The first problem to solve is the choice of the oxidant agent. It must be outline that with isoxazol-5-ones benzoquinone and MnO_2 gave in good yields C-C and C-N dimerization derivatives[61] (scheme 25).

The second problem is the formation of by-product where isoxazol-5-ones incorporate the oxidant as in the case of benzoquinone.

Table 6 shows all the trials done

Scheme 25

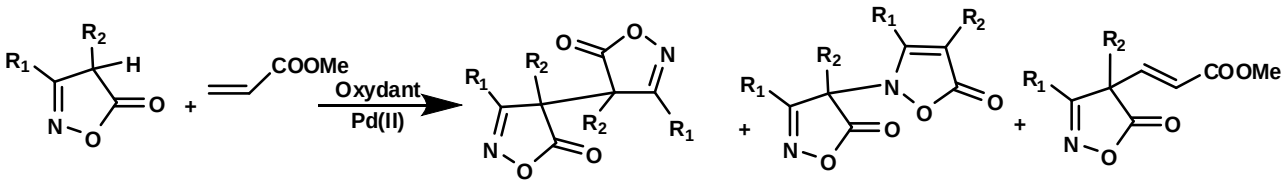


TABLE 6. OXIDANTS TESTED	
OXIDANT	PRODUCT
MnO_2	Dimer +product
$Cu(OAc)_2$	Dimer +product
I_2	Dimer
H_2O_2	Dimer/Hydroxylated
Benzoquinone	Adduct with BQ
IodoPhenyldiAcetate	Dimer + product
Oxone	Dimer

Surprisingly we have found the solution to our problem in the O_2. In spite of its di-radical structure, molecular oxygen is unable to dimerize isoxazol-5-ones, at least if it is used at 1 atm. At this point we try to obtain a certain regioselectivity playing with different solvents.

Scheme 26

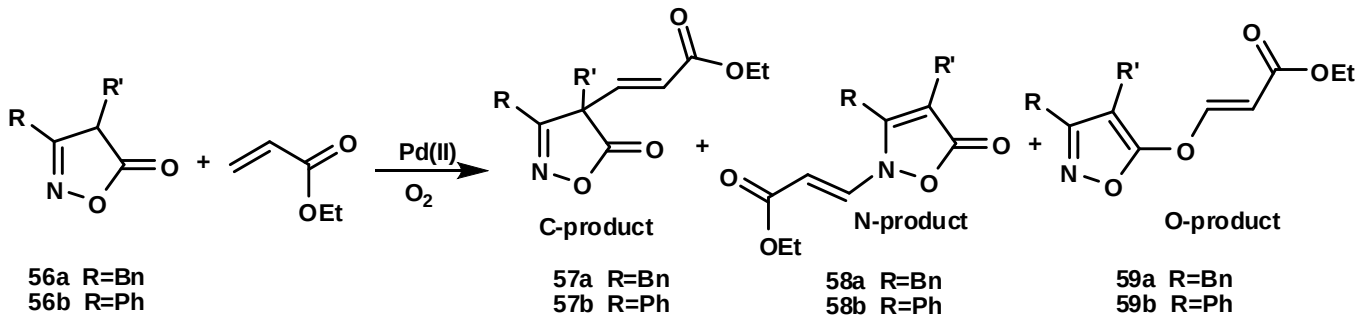


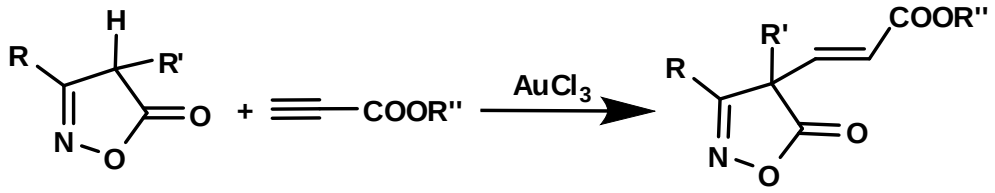
Table 7 reports our results.

TABLE 7				
Isoxazol-5-one (R,R')	Solvent	C-product **57 a** or **b**	N-product **58 a** or **b**	O-product **59 a** or **b**
Me-Bn **56a**	AcOH	2	1	0
Me-Bn **56a**	AcOH /CH_3CN 1/3	1	0	0
Me-Bn **56a**	AcOH /Dioxane 1/3	1	4	1
Me-Bn **56a**	THF/DMF 2/1	1	0	0
Me-Ph **56b**	AcOH	0	1	0
Me-Ph **56b**	AcOH /CH_3CN 1/3	0	0	1
Me-Ph **56b**	AcOH /Dioxane 1/3	1	2	1
Me-Ph **56b**	THF/DMF 2/1	0	0	1

The reported data show that it is possible to achieve solvent-based regioselectivity, even total. As already reported regioselectivity is also substrate-dependent: the differences in term of electronic environment and sterical hindrance seem to play a role in the reaction outcome. Unfortunately the great drawback of isoxazol-5-ones alkenylations is the low yield. We try to improve outcome in different way, but till now we can't obtain yield better than 25%. Maybe the bottleneck is the balance between the oxidative recycle of Pd(II) and the parasite reaction that oxidant do: if we improve oxidation, increasing Pd activity, we raise-up by-product, but on the other hand, weak oxidation is unable to efficiently recycle Pd(II).

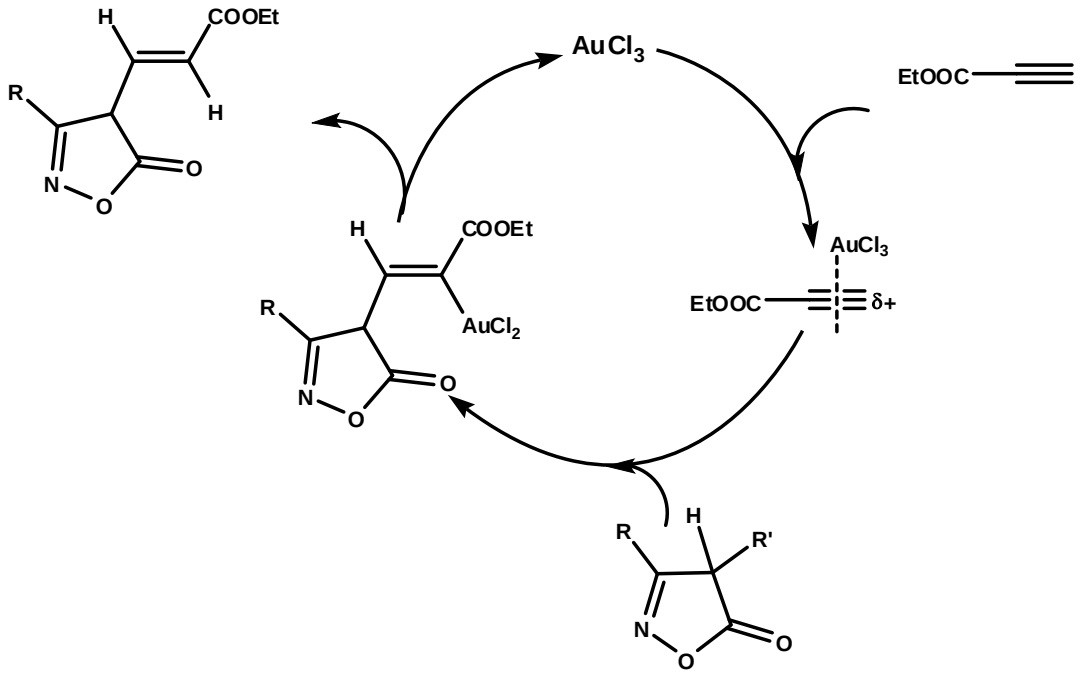
This problem lead us to try another catalyst, Au(III). Gold catalysis attract lots of attention in the past fifteen years due to its simply usage and broad scope.[62] Among the Au-catalyzed reactions we focus on triple bond activation which could act as C-H activation and give hydroalchenilation as reported in the scheme 27. The product is the same of a simple Michael addition, the added value that gold could gives is the regioselectivity.

Scheme 27



The simplified mechanism of this reaction (scheme 28) involves an initial coordination of the triple bond by gold(III) that enable the triple bonded C to react as electrophile; after the formation of C-C bond and production of HCl, the unstable Au-complex with the intervention of the HCl gives the desired product and regenerates catalytically active Au(III).

Scheme 28



As we have hoped, we are succeeded improving yield up to 40% and obtain a solvent-based dependent regioselectivity (table 8). In every case O-product is absent, while in general C product is the preferred one. Testing different triple bonds lead to the conclusion that an electron withdrawing group is necessary for this reaction. Maybe the presence of the electron withdrawing group improve the effect of gold(III) lowering the electron density on the terminal C atom.

TABLE 8. Product of Au-catalyzed reactions					
Isoxazol-5-one	alkine	Solvent	C-product **57 a** or **b**	N-product **58 a** or **b**	O-product **59 a** or **b**
Me-Bn **56a**	Ethyl propiolate	AcOH	1	1	0
Me-Bn **56a**	Ethyl propiolate	Dioxane	2.5	1	0
Me-Bn **56a**	Ethyl propiolate	CH_3CN	1	0	0
Me-Bn **56a**	Fenilacetilene	CH_3CN	0	0	0
Me-Bn **56a**	2-nitro-Fenilacetilene	CH_3CN	1	0	0

CONCLUSION

In this thesis we exploit a wide range of different synthetic strategy to obtain or functionalize N-containing heterocycles. Besides we also find conditions useful for a more sustainable chemistry. In this field the use of transition metal catalysis seems to be contradictory, but our effort in reducing all the other non-green aspects and the metal load is one good way toward this goal. We report several reactions useful for synthesis hard to perform till now. Moreover we demonstrate that Pd-catalyzed amination could be performed even without a ligand and we hope this finding will open new possibilities. Above all we always try to understand as deep as we can every aspects of our synthetic work. In fact thanks to our effort in understanding chemistry, we realize a study that justifies an uncommon reaction feature utilizing a new method and applying a recent and somewhat neglected theory.

We synthesize a number of new compounds never reported before. Among these there are a lot of potentially active compounds or molecules with special characteristics, useful in a wide range of possible applications.

Our research already gives its results, but it seems to be still plenty of possibility and always with immediate applicability. On the other hand the study of the mechanisms that rule the reactions surely lead to new interesting results.

EXPERIMENTAL PART

Melting points have been determined on a Büchi B-540 heating apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra have been obtained on a VARIAN 200. Chemical shifts are given in ppm downfield from $SiMe_4$. ^{13}C NMR spectra are ^{1}H-decoupled and the determination of the multiplicities has been achieved by the APT pulse sequence. IR spectra have been recorded on a Jasco FT/IR 5300 spectrophotometer.

CHAPTER 1

General procedure for the synthesis of the heteroaryl amides. 3a–c, 9a,b and 23

A mixture of acids **1a–c, 7** or **22** (10 mmol) and $SOCl_2$ (10 mL, 137 mmol) was stirred at 100°C for 2.5 h. After evaporation of the solvent, the residue was dissolved with CH_2Cl_2 (20 mL). A solution of **2** or **8** (15 mmol) and TEA (2.1 mL, 15 mmol) in CH_2Cl_2 (5 mL) was added dropwise at 0°C. After stirring for 5 h at room temperature, the solution was washed with 5% HCl (2x20 mL) and then with 5% aqueous NaOH (2x20 mL). The organic layer was dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was chromatographed on a silica gel column, using CH_2Cl_2 as eluent, to give compounds **3, 9** and **23**.

N-(2-Iodophenyl)-pyridine-3-carboxamide (3a)

White solid, mp 134–136°C; yield 67%. IR (Nujol): 3300, 1631 cm^{-1}. ^{1}H NMR: d 6.92 (1H, dd, J¼5.0, 7.5 Hz), 7.41 (1H, dd, J¼7.5, 7.8 Hz), 7.48 (1H, dd, J¼5.0, 7.5 Hz), 7.83 (1H, d, J¼7.8 Hz), 8.27–8.30 (1H, m), 8.32 (1H, br s, exch. D_2O), 8.33–8.39 (1H, m), 8.80 (1H, d, J¼5.0 Hz), 9.22 (1H, s). ^{13}C NMR: d 91.1 (s), 122.6 (d), 124.1 (d), 127.0 (d), 129.8 (d), 130.6 (s), 135.6 (d), 138.1 (s), 139.3 (d), 148.5 (d), 153.2 (d), 163.8 (s). Anal. Calcd for $C_{12}H_9IN_2O$ (324.12): C, 44.47; H, 2.80; N, 8.64. Found: C, 44.34; H, 2.79; N, 8.80.

N-(2-Iodophenyl)-6-chloro-pyridine-3-carboxamide (3b)

White solid, mp 142–144°C; yield 88%. IR (Nujol): 3280, 1638 cm^{-1}. ^{1}H NMR: d 6.88–6.96 (1H, m), 7.38–7.46 (1H, m), 7.49 (1H, dd, J¼0.6, 8.4 Hz), 7.82 (1H, dd, J¼1.3, 8.1 Hz), 8.20 (1H, br s, exch. D_2O), 8.22 (1H, dd, J¼2.6, 8.4 Hz), 8.34 (1H, dd, J¼1.3, 8.1 Hz), 8.98 (1H, dd, J¼0.6, 2.6 Hz). ^{13}C NMR: d 90.9 (s), 122.3 (d), 124.9 (d), 127.0 (d), 129.4 (s), 129.8 (d), 137.7 (s), 138.2 (d), 139.2 (d), 148.6 (d), 155.2 (s), 162.6 (s). Anal. Calcd for $C_{12}H_8ClIN_2O$ (358,56): C, 40.20; H, 2.25; N, 7.81. Found: C, 40.06; H, 2.36; N, 7.94.

N-(2-Iodophenyl)-quinoline-3-carboxamide (3c)

Light brown solid, mp 221–222°C dec; yield 76%. IR (Nujol): 3290, 1640 cm^{-1}. ^{1}H NMR: d 6.95–7.03 (1H, m), 7.39–7.47 (1H, m), 7.82–7.90 (2H, m), 8.00–8.09 (2H, m), 8.18 (1H, d, J¼8.4 Hz), 8.64 (1H, d, J¼8.4 Hz), 9.27–9.28 (1H, m), 9.71 (1H, br s), 10.05 (1H, s). ^{13}C NMR: d 91.5 (s), 123.0 (d), 127.1 (d), 127.3 (s), 127.5 (s), 128.5 (d), 128.6 (d), 129.3 (d), 129.7 (d), 132.7 (d), 137.9 (d), 138.1 (s), 139.2 (d), 147.5 (d), 148.1 (s), 163.3 (s). Anal. Calcd for $C_{16}H_{11}IN_2O$ (374.18): C, 51.36; H, 2.96; N, 7.49. Found: C, 51.30; H, 3.10; N, 7.56

N-(2-Iodophenyl)-pyridine-4-carboxamide16 (9a)

White solid, mp 122–124°C (lit. mp 122–123°C); yield 80%.

N-(2-Bromopyridin-3-yl)-pyridine-4-carboxamide (9b)

White solid, mp 139–141°C; yield 57%. IR (Nujol): 3298, 1623 cm^{-1}. ^{1}H NMR: d 7.35 (1H, dd, J¼4.5, 8.1 Hz), 7.82–7.71 (2H, overlapping), 8.17 (1H, dd, J¼1.5, 4.5 Hz), 8.54 (1H, br s, exch. D_2O), 8.81 (1H, dd, J¼1.5, 8.1 Hz), 8.80–8.94 (2H, overlapping). ^{13}C NMR: d 121.1 (d), 124.1 (d), 124.2 (d), 129.3 (d), 133.4 (s), 134.0 (s), 141.1 (s), 145.7 (d), 145.8 (d), 151.4 (d), 164.0 (s). Anal. Calcd for $C_{11}H_8BrN_3O$ (278.11): C, 47.51; H, 2.90; N, 15.11. Found: C, 47.63; H, 3.07; N, 15.22.

N-(2-Iodophenyl)-2-pyridin-2-yl-acetamide (23)

White solid, mp 110–112°C; yield 53%. IR (Nujol): 3258, 1632 cm^{-1}. ^{1}H NMR: d 3.96 (2H, s), 6.82 (1H, dd, J¼7.5, 7.6 Hz), 7.26–7.35 (3H, m) 7.73 (1H, dd, J¼7.8, 8.2 Hz), 7.78 (1H, d, J¼7.8Hz), 8.24 (1H, d, J¼8.2Hz), 8.70 (1H, d, J¼4.2 Hz), 9.88 (1H, s, exch. with D_2O). ^{13}C NMR: d 46.4 (t), 89.7 (s), 122.7 (d), 122.8 (d), 124.5 (d), 126.2 (d), 129.3 (d), 137.9 (d), 138.4 (s), 139.5 (d), 149.7 (d), 155.2 (s), 167.9 (s). Anal. Calcd for $C_{13}H_{11}IN_2O$ (338.15): C, 46.18; H, 3.28; N, 8.28. Found: C, 46.30; H, 3.31; N, 8.20.

General procedure for the synthesis of the N-methylheteroamides 4a–c, 10a,b and 24

To a stirred solution of **3, 9** or **23** (2 mmol) in dry THF (15 mL) cooled to 0°C, 60% NaH (0.2 g, 5 mmol) was added under nitrogen atmosphere. The resulting mixture was allowed to warm to rt; then a solution of MeI (0.37 mL, 6 mmol) in dry THF (5 mL) was added dropwise. After 4 h the solvent was evaporated and the residue diluted with 1 M HCl (20 mL) and extracted with Et_2O (2x20 mL). The organic layer was dried with Na_2SO_4 and solvent was evaporated under reduced pressure. The residue was chromatographed on a silica gel column, eluent CH_2Cl_2/AcOEt 3:1.

N-(2-Iodophenyl)-N-methyl-pyridine-3-carboxamide (4a)

White solid, mp 117–118°C; yield 58%. IR (Nujol): 1641 cm^{-1}. ^{1}H NMR: d 3.39 (3H, s), 6.92–6.96 (1H, m), 7.05–7.36 (3H, overlapping), 7.69–7.81 (2H, overlapping), 8.39–8.56 (2H, overlapping). ^{13}C NMR: d 37.4 (q), 99.9 (s), 123.2 (d), 129.5 (d), 129.9 (d), 130.2 (d), 130.4 (d), 140.8 (d), 141.7 (d), 143.4 (s), 145.9 (s), 148.7 (d), 165.3 (s). Anal. Calcd for $C_{13}H_{11}IN_2O$ (338.15): C, 46.18; H, 3.28; N, 8.28. Found: C, 46.30; H, 3.10; N, 8.31.

N-(2-Iodophenyl)-N-methyl-6-chloro-pyridine-3-carboxamide (4b)

White solid, mp 114–115°C; yield 95%. IR (Nujol): 1627 cm^{-1}. ^{1}H NMR: d 3.38 (3H, s), 6.94–7.02 (1H, m), 7.14–7.22 (2H, m), 7.27–7.36 (1H, m), 7.69 (1H, dd, J¼2.4, 8.2 Hz), 7.81 (1H, dd, J¼1.3, 8.0 Hz), 8.3 (1H, d, J¼2.4 Hz). ^{13}C NMR: d 37.8 (q), 99.3 (s), 123.7 (d), 130.0 (d), 130.1 (d), 130.2 (d), 130.7 (d), 139.0 (d), 140.8 (s), 146.1 (s), 149.6 (d), 152.6 (s), 167.3 (s). Anal. Calcd for $C_{13}H_{10}ClIN_2O$ (372.59): C, 41.91; H, 2.71; N, 7.52. Found: C, 42.06; H, 2.58; N, 7.61.

N-(2-Iodophenyl)-N-methyl-quinoline-3-carboxamide (4c)

Light orange solid, mp 163–161°C; yield 97%. IR (Nujol): 1632 cm^{-1}. ^{1}H NMR: d 3.39 (3H, s), 6.79–6.88 (1H, m), 7.19–7.21 (2H, m), 7.39–7.47 (1H, m), 7.59–7.72 (3H, m), 7.93 (1H, d, J¼8.6 Hz), 8.15 (1H, d, J¼1.4 Hz), 8.82 (1H, s). ^{13}C NMR: d 37.9 (q), 99.5 (s), 126.7 (s), 127.3 (d), 128.7 (d), 129.0 (s), 129.3 (d), 129.9 (d), 130.0 (d), 130.2 (d), 130.3 (d), 136.9 (d), 140.6 (d), 146.4 (s), 148.1 (s), 149.5 (d), 168.4 (s). Anal. Calcd for $C_{17}H_{13}IN_2O$ (388.20): C, 52.60; H, 3.38; N, 7.22. Found: C, 52.77; H, 3.29; N, 7.29.

N-(2-Iodophenyl)-N-methyl-pyridine-4-carboxamide (10a)

White solid, mp 80–82°C (diisopropyl ether); yield 63%. IR (Nujol): 1623 cm^{-1}. ^{1}H NMR: d 3.38 (3H, s), 6.94 (1H, ddd, J¼1.8, 7.6, 8.0 Hz), 7.12 (1H, dd, J¼1.4, 7.8 Hz), 7.20–7.29 (3H, m), 7.79 (1H, dd, J¼1.2, 8.0 Hz,), 8.39–8.46 (2H, m). ^{13}C NMR: d 37.4 (q), 99.1 (s), 122.2 (d), 129.8 (d), 129.9 (d), 130.1 (d), 130.2 (d), 140.5 (d), 140.7 (d), 143.4 (s), 145.9 (s), 149.7 (d), 168.4 (s). Anal. Calcd for C13H11IN2O (338.15): C, 46.18; H, 3.28; N, 8.28. Found: C, 46.34; H, 3.11; N, 8.21.

N-(2-Bromopyridin-3-yl)-N-methyl-pyridine-4-carboxamide (10b)

White solid, mp 119–121°C (diisopropyl ether); yield 47%. IR (Nujol): 1623 cm^{-1}. ^{1}H NMR: d 3.40 (3H, s), 7.18–7.35 (3H, m), 7.41 (1H, d, J¼7.2 Hz), 8.25 (1H, br s), 8.42–8.55 (2H, m). ^{13}C NMR: d 37.4 (q), 99.8 (s), 123.2 (d), 129.7 (d), 129.9 (d), 130.3 (d), 130.6 (d), 141.5 (d), 142.7 (d), 144.6 (s), 146.9 (s), 168.4 (s). Anal. Calcd for $C_{12}H_{10}BrN_3O$ (292.14): C, 49.34; H, 3.45; N, 14.38. Found: C, 49.49; H, 3.51; N, 14.22.

N-(2-Iodophenyl)-N-methyl-2-pyridin-2-ylpropionamide (24)

White solid, mp 82–84°C; yield 75%. IR (Nujol): 1622 cm^{-1}. ^{1}H NMR: d 1.50 (3H, d, J¼6.8 Hz), 3.21 (3H, s), 3.65 (1H, q, J¼6.8 Hz), 6.72 (1H, d, J¼7.7 Hz), 7.01 (1H, dd, J¼7.5, 7.7 Hz), 7.07–7.15 (3H, m), 7.56 (1H, dd, J¼7.6, 7.7 Hz), 7.93 (1H, d, J¼7.8 Hz), 8.41 (1H, br s). ^{13}C NMR: d 19.6 (q), 36.9 (d), 47.3 (q), 100.3 (s), 122.0 (d), 129.5 (d), 129.7 (d), 130.1 (d), 130.2 (d), 137.0 (d), 140.3 (d), 145.8 (s), 149.3 (d), 161.5 (s), 173.0 (s). Anal. Calcd for $C_{15}H_{15}IN_2O$ (366.20): C, 49.20; H, 4.13; N, 7.65. Found: C, 49.34; H, 4.31; N, 7.60.

General procedure for the synthesis of amides 16–18

The acid **12**, **13** or **14** (0.124 g, 1 mmol) was suspended in DME (dimethoxyethane) (8 mL), cooled at 0°C under nitrogen atmosphere. A solution of N-methyl-2-iodoaniline (**15**) (0.28 g, 1.2 mmol) in DME (4 mL) was dropped then a solution of DMC (2-chloro-1,3-dimethylimidazolium chloride) (0.169 g, 1 mmol) in CH_2Cl_2 (3 mL) and finally a solution of TEA (280 mL, 2 mmol) in CH_2Cl_2 (3 mL) was added. The reaction mixture was stirred for 1 h at 0°C then allowed to warm to rt and left to react overnight. The mixture was then diluted with 300 mL of AcOEt and washed with 30 mL of water, 30 mL of a saturated solution of $NaHCO_3$, 30mL of water and 30 mL of brine. The organic layer was dried with Na_2SO_4 and the solvent evaporated under reduced pressure. The residue was chromatographed on a silica gel, eluent AcOEt, to give compounds **16–18**.

N-(2-Iodophenyl)-N-methyl-pyridazine-4-carboxamide (16)

Light amber-coloured solid, mp 166–168°C; yield 70%. IR (Nujol): 1636 cm^{-1}. ^{1}H NMR: d 3.38 (3H, s), 6.96–7.04 (1H, m), 7.20–7.36 (3H, m), 7.75–7.79 (1H, m), 9.06 (1H, s), 9.05 (1H, s). ^{13}C NMR: d 37.6 (q), 99.2 (s), 124.7 (d), 130.0 (d), 130.3 (d), 130.7 (d), 133.9 (s), 140.8 (d), 145.0 (s), 149.5 (d), 151.1 (d), 165.8 (s). Anal. Calcd for $C_{12}H_{10}IN_3O$ (339.13): C, 42.50; H, 2.97; N, 12.39. Found: C, 42.36; H, 3.09; N, 12.22.

N-(2-Iodophenyl)-N-methyl-pyrimidine-5-carboxamide (17)

White solid, mp 97–98°C; yield 80%. IR (Nujol): 1630 cm^{-1}. ^{1}H NMR: d 3.36 (3H, s), 6.92–7.00 (1H, m), 7.21–7.36 (2H, m), 7.75–7.80 (1H, m), 8.64 (2H, s), 9.00 (1H, s). ^{13}C NMR: d 37.7 (q), 99.4 (s), 129.9 (s), 130.0 (d), 130.2 (d), 130.5 (d), 140.8 (d), 145.5 (s), 156.4 (2d), 159.1 (d), 165.7 (s). Anal. Calcd for $C_{12}H_{10}IN_3O$ (339.13): C, 42.50; H, 2.97; N, 12.39. Found: C, 42.39; H, 3.08; N, 12.27. L. Basolo et al. / Tetrahedron 65 (2009) 3486–3491 3489

N-(2-Iodophenyl)-N-methyl-pyrazine-2-carboxamide (18)

Pearl grey solid, mp 94–96°C; yield 55%. IR (Nujol): 1640 cm^{-1}. ^{1}H NMR: d 3.42 (3H, s), 6.90–7.01 (1H, m), 7.26–7.36 (2H, m), 7.74–7.80 (1H, m), 8.16–8.19 (1H, m), 8.40 (1H, d, J¼2.6 Hz), 8.97 (1H, s). ^{13}C NMR: d 37.6 (q), 99.3 (s), 129.4 (d), 129.6 (d), 130.2 (d), 139.9 (d), 142.5 (d), 145.1 (d), 145.5 (d), 146.1 (s), 149.3 (s), 166.3 (s). Anal. Calcd for $C_{12}H_{10}IN_3O$ (339.13): C, 42.50; H, 2.97; N, 12.39. Found: C, 42.37; H, 3.09; N, 12.28.

General procedure for the cyclization of amides 4, 10, 16–18 and 24

A solution of **4a–c** or **10a,b** or **16–18** or **24** (1 mmol), $Pd(OAc)_2$ (0.011 g, 0.05 mmol), AcOK (0.196 g, 2 mmol) and Bu_4NCl (0.278 g, 1 mmol) in DMA (8 mL) was stirred at 100°C for 24 h. For compounds **4a–c** and **16–18** the cyclization was performed by microwaves irradiation for 45 min at 120°C at 300W. After cooling to room temperature, the mixture was diluted with brine (15 mL) and extracted with Et_2O (3x30 mL). The organic layer was dried with Na_2SO_4 and solvent evaporated under reduced pressure. The residue was chromatographed on a silica gel column, eluent hexane/AcOEt 2:1, to give the cyclized product. In the case of amides **4a–c** the two regioisomers **5a–c** and **6a–c** were isolated, in ratio 1:3 nearly.

6-Methyl-benzo[h][1,6]naphthyridin-5-(6H)-one (5a)17

White solid, mp 169–171°C (lit. mp 173–175°C); yield 18%. IR (Nujol): 1630 cm^{-1}. ^{1}H NMR: d 3.82 (3H, s), 7.36–7.46 (2H, m), 7.51 (1H, dd, J¼4.6, 8.1 Hz), 7.60–7.69 (1H, m), 8.77 (1H, dd, J¼1.8, 8.1 Hz), 8.90 (1H, dd, J¼1.8, 7.9 Hz), 9.00 (1H, dd, J¼1.8, 4.6 Hz). ^{13}C NMR: d 30.1 (q), 114.8 (d), 120.9 (s), 123.1 (d), 123.2 (d), 125.5 (d), 129.2 (s), 131.6 (d), 137.0 (d), 139.4 (s), 150.5 (s), 153.9 (d), 161.9 (s). Anal. Calcd for $C_{13}H_{10}N_2O$ (210.23): C, 74.27; H, 4.79; N, 13.33. Found: C, 74.39; H, 4.86; N, 13.24.

6-Methyl-benzo[c][2,7]naphthyridin-5-(6H)-one (6a)17

White solid, mp 188–191°C (lit. mp 194–196°C); yield 62%. IR (Nujol) 1662 cm^{-1}. ^{1}H NMR: d 3.80 (3H, s), 7.25–7.46 (2H, m), 7.67 (1H, dd, J¼7.6, 7.8 Hz), 8.03 (1H, d, J¼5.6 Hz), 8.27 (1H, d, J¼7.6 Hz), 8.88 (1H, d, J¼5.6 Hz), 9.72 (1H, s). ^{13}C NMR: d 29.9 (q), 115.5 (d), 117.4 (s), 123.0 (d), 124.2 (d), 129.7 (d), 130.2 (s), 131.9 (d), 136.0 (d), 139.9 (s), 140.0 (s), 140.6 (d), 168.3 (s). Anal. Calcd for C13H10N2O (210.23): C, 74.27; H, 4.79; N, 13.32. Found: C, 74.43; H, 4.90; N, 13.22.

2-Chloro-6-methylbenzo[h][1,6]naphthyridin-5-(6H)-one (5b)

White solid, mp 170–172°C; yield 13%. IR (Nujol): 1625 cm^{-1}. ^{1}H NMR: d 3.80 (3H, s), 7.38–7.44 (2H, m), 7.48 (1H, d, J¼8.2 Hz), 7.62–7.77 (1H, m), 8.68 (1H, d, J¼8.2 Hz), 8.81 (1H, dd, J¼1.3, 7.9 Hz). ^{13}C NMR: d 30.0 (q), 114.8 (d), 115.7 (s), 119.9 (s), 123.3 (d), 124.0 (d), 125.9 (d), 132.3 (d), 139.9 (d), 151.1 (s), 153.0 (s), 155.9 (s), 161.1 (s). Anal. Calcd for $C_{13}H_9ClN_2O$ (244.68): C, 63.81; H, 3.71; N, 11.45. Found: C, 63.98; H, 3.89; N, 11.40.

2-Chloro-6-methylbenzo[c][2,7]naphthyridin-5-(6H)-one (6b)

White solid, mp 212–214°C; yield 48%. IR (Nujol): 1635 cm^{-1}. ^{1}H NMR: d 3.80 (3H, s), 7.34–7.47 (2H, m), 7.66–7.75 (1H, m), 8.07 (1H, s), 8.20 (1H, dd, J¼1.3, 8.1 Hz), 9.50 (1H, s). ^{13}C NMR: d 30.0 (q), 115.4 (d), 115.8 (d), 116.5 (s), 119.6 (s), 123.3 (d), 124.4 (d), 132.9 (d), 140.1 (s), 142.5 (s), 153.0 (d), 154.9 (s), 160.4 (s). Anal. Calcd for $C_{13}H_9ClN_2O$ (244.68): C, 63.81; H, 3.71; N, 11.45. Found: C, 63.92; H, 3.80; N, 11.38.

5-Methyl-dibenzo[b,h][1,6]naphthyridin-6-(5H)-one (5c)18

Light yellow solid, mp 214–216°C (lit. mp not reported); yield 16%. IR (Nujol): 1630 cm^{-1}. ^{1}H NMR: d 3.84 (3H, s), 7.39–7.47 (2H, m), 7.58–7.71 (2H, m), 7.84–7.93 (1H, m), 8.05–8.09 (1H, m), 8.25–8.29 (1H, m), 9.10–9.15 (1H, m), 9.35 (1H, s). ^{13}C NMR: d 30.1 (q), 114.9 (d), 119.8 (s), 121.3 (s), 123.2 (d), 126.1 (d), 126.9 (d), 127.5 (s), 129.4 (d), 129.6 (d), 131.8 (d), 132.3 (d), 139.0 (d), 139.9 (s), 149.5 (s), 150.5 (s), 162.2 (s). Anal. Calcd for $C_{17}H_{12}N_2O$ (260.29): C, 78.44; H, 4.65; N, 10.76. Found: C, 78.55; H, 4.64; N, 10.68.

5-Methyl-dibenzo[c,f][2,7]naphthyridin-6-(5H)-one (6c)19

Cream solid, mp 211–213°C (lit. mp 217–218°C); yield 45%. IR (Nujol): 1639 cm^{-1}. ^{1}H NMR: d 3.83 (3H, s), 7.36–7.45 (1H, m), 7.51–7.55 (1H, m), 7.66–7.75 (2H, m), 7.82–7.91 (1H, m), 8.26–8.31 (1H, m), 8.67 (1H, d, J¼8.6 Hz), 8.79 (1H, d, J¼8.6 Hz), 9.85 (1H, s). ^{13}C NMR: d 30.4 (q), 115.5 (d), 118.1 (s), 118.3 (s), 122.6 (s), 122.7 (d), 127.2 (d), 127.6 (d), 129.7 (d), 130.8 (d), 130.9 (d), 131.6 (d), 138.9 (s), 140.3 (s), 150.1 (s), 150.3 (d), 161.2 (s). Anal. Calcd for $C_{17}H_{12}N_2O$ (260.29): C, 78.44; H, 4.65; N, 10.76. Found: C, 78.29; H, 4.79; N, 10.92.

6-Methyl-6H-benzo[c][2,6]naphthyridin-5-one (11a)16

White solid, mp 192–194°C (lit. mp 197–199°C); yield 58%. IR (Nujol): 1659 cm^{-1}. ^{1}H NMR: d 3.74 (3H, s), 7.32 (1H, dd, J¼7.5, 7.8 Hz), 7.37 (1H, d, J¼7.8 Hz), 7.56 (1H, dd, J¼7.5, 8.0 Hz), 8.19 (1H, d, J¼5.1 Hz), 8.28 (1H, d, J¼8.0 Hz), 8.75 (1H, d, J¼5.1 Hz), 9.58 (1H, s). ^{13}C NMR: d 30.5 (q), 115.6 (d), 117.4 (s), 117.5 (s), 121.0 (d), 123.0 (d), 123.5 (d), 128.0 (s), 130.8 (d), 138.5

(s), 145.8 (d), 148.3 (d), 160.5 (s). Anal. Calcd for $C_{13}H_{10}N_2O$ (210.24): C, 74.27; H, 4.79; N, 13.32. Found: C, 74.39; H, 4.87; N, 13.43.

6-Methyl-6H-pyrido[2,3-f][2,6]naphthyridin-5-one (11b)

White solid, mp 215–218°C (diisopropyl ether); yield 69%. IR (Nujol): 1630 cm^{-1}. ^1H NMR: d 3.81 (3H, s), 7.54 (1H, dd, J¼4.4, 8.5 Hz), 7.74 (1H, d, J¼8.5 Hz), 8.26 (1H, d, J¼5.1 Hz), 8.66 (1H, d, J¼4.4 Hz), 8.93 (1H, d, J¼5.1 Hz), 10.18 (1H, s). ^{13}C NMR: d 30.1 (q), 120.5 (d), 122.4 (d), 124.8 (d), 128.7 (s), 132.3 (s), 134.8 (s), 136.4 (s), 144.8 (d), 148.2 (d), 150.1 (d), 160.3 (s). Anal. Calcd for $C_{12}H_9N_3O$ (211.22): C, 68.24; H, 4.29; N, 19.89. Found: C, 68.39; H, 4.11; N, 19.96.

6-Methyl-pyridazino[4,5-c]quinolin-5-(6H)-one (19a)

Cream solid, mp 250–252°C; yield 28%. IR (Nujol): 1626 cm^{-1}. ^1H NMR: d 3.85 (3H, s), 7.44–7.55 (2H, m), 7.74–7.83 (1H, m), 8.39–8.44 (1H, m), 10.01 (1H, d, J¼1.2 Hz), 10.10 (1H, d, J¼1.2 Hz). ^{13}C NMR: d 30.5 (q), 114.8 (s), 115.9 (d), 120.0 (s), 123.9 (d), 124.0 (d), 129.8 (s), 133.5 (d), 140.8 (s), 145.9 (d), 149.2 (d), 159.3 (s). Anal. Calcd for $C_{12}H_9N_3O$ (211.22): C, 68.24; H, 4.29; N, 19.89. Found: C, 68.37; H, 4.33; N, 19.75.

6-Methyl-pyridazino[4,3-c]quinolin-5-(6H)-one (19b)

Light yellow solid, mp 200–202°C; yield 24%. IR (Nujol): 1630 cm^{-1}. ^1H NMR: d 3.83 (3H, s), 7.45–7.53 (2H, m), 7.70–7.78 (1H, m), 8.39 (1H, d, J¼5.3 Hz), 9.20–9.25 (1H, m), 9.55 (1H, d, J¼5.3 Hz). ^{13}C NMR: d 30.4 (q), 115.1 (d), 118.3 (s), 121.5 (s), 124.0 (d), 124.2 (d), 125.5 (d), 132.8 (d), 139.4 (s), 150.6 (d), 151.0 (s), 160.6 (s). Anal. Calcd for $C_{12}H_9N_3O$ (211.22): C, 68.24; H, 4.29; N, 19.89. Found: C, 68.33; H, 4.36; N, 19.80.

6-Methyl-pyrimido[5,4-c]quinolin-5-(6H)-one (20)

White solid, mp 190–192°C; yield 79%. IR (Nujol): 1628 cm^{-1}. ^1H NMR: d 3.36 (3H, s), 6.92–7.00 (1H, m), 7.21–7.36 (2H, m), 7.75–7.80 (1H, m), 8.64 (1H, s), 9.00 (1H, s). ^{13}C NMR: d 29.9 (q), 115.0 (d), 117.9 (s), 118.8 (s), 123.4 (d), 125.9 (d), 133.9 (d), 141.1 (s), 155.9 (s), 159.4 (d), 160.4 (s), 160.9 (d). Anal. Calcd for $C_{12}H_9N_3O$ (211.22): C, 68.24; H, 4.29; N, 19.89. Found: C, 68.35; H, 4.35; N, 19.77. 3490 L. Basolo et al. / Tetrahedron 65 (2009) 3486–3491

4.12 6-Methyl-pyrazino[2,3-c]quinolin-5-(6H)-one (21)

Ivory-coloured solid, mp 195–197°C; yield 49%. IR (Nujol): 1633 cm^{-1}. ^1H NMR: d 3.88 (3H, s), 7.39–7.49 (2H, m), 7.67–7.75 (1H, m), 8.84 (1H, dd, J¼1.6, 7.9 Hz), 8.91–8.97 (2H, m,). ^{13}C NMR: d 30.7 (q), 115.0 (d), 119.3 (s), 119.6 (s), 123.5 (d), 125.8 (d), 132.6 (d), 136.8 (s), 139.3 (s),

145.5 (d), 148.3 (d), 160.7 (s). Anal. Calcd for $C_{12}H_9N_3O$ (211.22): C, 68.24; H, 4.29; N,19.89. Found: C, 68.40; H, 4.38; N, 19.83.

5,7-Dimethyl-5H,6H,7H-pyrido[2,3-d][1]benzazepin-6-one (25)

White solid, mp 162–164°C; yield 90%. IR (Nujol): 1632 cm^{-1}. ^1H NMR: d 1.70 (3H, d, J¼6.7 Hz), 3.37 (3H, s), 3.60 (1H, q, J¼6.7 Hz), 7.33–7.37 (2H, m), 7.41 (1H, d, J¼8.0 Hz), 7.49–7.56 (2H, m), 7.88 (1H, d, J¼7.6 Hz), 8.68 (1H, d, J¼4.7 Hz). ^{13}C NMR: d 11.7 (q), 36.7 (d), 43.2 (q), 122.6 (d), 123.0 (d), 125.7 (d), 129.6 (d), 130.1 (d), 132.0 (s), 132.1 (s),135.8 (d),142.0 (s),149.5 (d),156.1 (s),172.4 (s). Anal. Calcd for $C_{15}H_{14}N_2O$ (238.29): C, 75.61; H, 5.92; N, 11.76. Found: C, 75.54; H, 5.81; N, 11.60.

CHAPTER 2

General procedure for the synthesis of *N*-aryl indolines

Procedure 1 (solvent, thermal heating)

The base was suspended in toluene in an oven dried round bottom flask, the suspension was flushed with nitrogen for 10 minutes, then aryl chloride, palladium precatalyst, ligand and indoline were added in this exact order. A further 5 minutes nitrogen was flushed, then the reaction mixture was refluxed for 24 hours. After this time the suspension was cooled to room temperature, added of ethyl acetate and filtered over celite®. The resulting solution was washed three times with brine, dried with sodium sulphate and filtered; solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography using hexane/ethyl acetate (4/1) as eluent.

Procedure 2 (solvent-free, microwave heating)

A round bottom flask was charged with palladium precatalyst and the aryl halide. Then 3 grams of finely powdered K_2CO_3 was added. At this point the ligand was added on the resulting surface of K_2CO_3 and a solution of indoline in 10 ml CH_2Cl_2 was used to dissolve reactant and suspend K_2CO_3. The CH_2Cl_2 was then removed under reduced pressure and recovered for use in the following reaction. The residual powder was diluted with 1 gram of K_2CO_3 and grinded with mortar and pestle for 5 minutes. Microwave oven reactor was charged with reactant powder which was compacted as much as possible. After microwave heating to 140°C for 20 minutes at a medium of 350 W, a flash silica gel column was charged with the powder and eluted with hexane/ethyl acetate (4/1) to recover purified product.

Note: the only exception for procedure 2 was the case of indoline-2-carboxylic acid. It needs an elaboration before column chromatography and a special care for the column itself: in fact, after microwave heating, the powder was dissolved in water and extracted with Et_2O to remove non acidic compound (mainly unreacted aryl halide), then the basic water was

acidified to pH 3 and extracted three times with ethyl acetate. The combined organic layer was dried over sodium sulphate, filtered and solvent was removed under reduced pressure. The residue was purified by a short column chromatography flushed with nitrogen during the elution made by ethyl acetate/methanol (20/1).

Procedure C (solvent&ligand-free, microwave heating)

A round bottom flask was charged with indoline followed by 1 gram of finely grinded K_2CO_3, and then by the aryl halide. A finely grinded mix of 1 gram of K_2CO_3 with $Pd_2(dba)_3$ was prepared and suspended in 10 ml CH_2Cl_2. The suspension was added in the round bottom flask and the CH_2Cl_2 was immediately removed under reduced pressure and recovered for use in the following reaction. The residual powder was diluted with 1 gram of K_2CO_3 and grinded with mortar and pestle for 5 minutes. Microwave oven reactor was charged with reactant powder which was compacted as much as possible (4-5 minutes of beats over semirigid surface). After microwave heating to 140°C for 30 minutes at a medium of 400 W, a flash silica gel column was charged with the powder and eluted with hexane/ethyl acetate (4/1) to recover purified product.

Note: the only exception for procedure C was the case of indoline-2-carboxylic acid as for procedure B. See above.

1-(4'-nitrophenyl)indoline 29

^{1}H NMR (200 MHz, $CDCl_3$, 20°C, TMS): δ=8.18-8.26 (m, 2H), 7.15-7.36 (m, 5H), 6.83 (ddd, *J*=0.9, 7.3, 8.4 Hz, 1H), 4.07 (t, *J*=8.3 Hz, 2H), 3.21 (t, *J*=8.3 Hz, 2H). ^{13}C NMR (200 MHz, $CDCl_3$): δ=149.4 (s), 144.5 (s), 139.9 (s), 132.7 (s), 127.5 (d), 125.9 (d, 2C), 125.8 (d), 121.9 (d), 115.0 (d, 2C), 110.8 (d), 52.3 (t), 28.2 (t). IR (KBr): $\bar{\nu}$=1294 cm^{-1} (Aromatic C-N). MS (ESI) *m/z (%)*: 241.3 (100) [M$^+$H]. Elemental analysis: calcd (%) for $C_{14}H_{12}N_2O_2$ (240.3): C 69.99, H 5.03, N 11.66; found: C 69.89, H 5.09, N 11.62.

4-(indolin-1-yl)benzonitrile 30[63]

^{1}H NMR (200 MHz, $CDCl_3$, 20°C, TMS): δ=7.56-7.60 (m, 2H), 7.10-7.29 (m, 5H), 6.88 (ddd, *J*=1.1, 7.14, 8.2 Hz, 1H), 4.00 (t, *J*=8.3 Hz, 2H), 3.18 (t, *J*=8.3 Hz, 2H). ^{13}C NMR (200 MHz, $CDCl_3$, 20°C, TMS): δ=147.5 (s), 144.9 (s), 133.8 (d), 132.4 (s), 127.4 (d), 125.8 (d, 2C), 121.3 (d), 120.1 (d), 116.1 (d, 2C), 110.1 (d), 101.1 (s), 52.0 (t), 28.2 (t).

Methyl 4-(indolin-1-yl)benzoate 28

^{1}H NMR (200 MHz, $CDCl_3$, 20°C, TMS): δ= 7.98-8.05 (m, 2H), 7.10-7.31 (m, 5H), 6.85 (ddd, *J*=0.9, 7.5, 8.2 Hz, 1H), 4.00 (t, *J*=8.4 Hz, 2H), 3.91 (s, 3H), 3.15 (t, *J*=8.4 Hz, 2H). ^{13}C NMR (200 MHz, $CDCl_3$, 20°C, TMS): δ=167.1 (s), 148.1 (s), 145.6 (s), 132.1 (s), 131.3 (s), 127.4 (d), 125.5 (d, 2C), 121.4 (s), 120.6 (d), 115.6 (d, 2C), 109.9 (d), 52.0 (t), 51.9 (q), 28.3 (t). IR (KBr):

$\bar{\nu}$=1321 cm^{-1} (Aromatic C-N). MS (ESI) *m/z (%)*: 254.1 (100) $[M^+H]$. Elemental analysis: calcd (%) for $C_{16}H_{15}NO_2$ (253.1): C 75.87, H 5.97, N 5.53; found: C 75.61, H 6.10, N 5.50.

2-methyl-1-(4-nitrophenyl)indoline 35

^1H NMR (200 MHz, $CDCl_3$, 20°C, TMS): δ= 8.15-8.23 (m, 2H), 7.15-7.31 (m, 5H), 6.91-6.99 (m, 1H), 4.44-4.59 (m, 1H), 3.40-3.52 (dd, *J*=8.6, 15.6 Hz, 1H), 2.69 (dd, *J=2.*7, 15.6 Hz, 1H), 1.37-1.40 (d, *J*=6.2 Hz, 3H). ^{13}C NMR (200 MHz, $CDCl_3$, 20°C, TMS): δ=149.1 (s), 143.7 (s), 140.1 (s), 131.6 (s), 127.5 (d), 126.1 (d, 2C), 126.0 (d), 122.1 (d), 115.2 (d, 2C), 112.2 (d), 59.9 (d), 37.0 (t), 20.2(q). IR (KBr): $\bar{\nu}$=1294 cm^{-1} (Aromatic C-N). MS (ESI) *m/z (%)*: 255.2 (100) $[M^+H]$. Elemental analysis: calcd (%) for $C_{15}H_{14}N_2O_2$ (254.3): C 70.85, H 5.55, N 11.02; found: C 70.77, H 5.88, N 11.00.

1-(4-methylpyridin-2-yl)indoline 27[64]

^1H NMR (200 MHz, $CDCl_3$, 20°C, TMS): δ=8.12-8.22 (m, 2H), 7.14-7.21 (m, 2H), 6.85 (ddd, *J*=1.1, 7.3, 8.4 Hz, 1H), 6.60-6.63 (m, 2H br), 4.05 (t, *J*=8.6 Hz, 2H), 3.20 (t, *J*=8.6 Hz, 2H), 2.31 (s, 3H). ^{13}C NMR (200 MHz, $CDCl_3$, 20°C, TMS): δ=155.6 (s), 148.0 (s), 147.5 (s), 144.9 (s), 131.2 (s), 127.1 (d), 124.4 (d), 120.1 (d), 115.8 (d), 113.2 (d), 108.9 (d), 49.4 (t), 27.8 (t), 21.5 (q).

1-(pyridin-2-yl)indoline 26[65]

^1H NMR (200 MHz, $CDCl_3$, 20°C, TMS): δ=8.33 (m, 1H), 8.16-8.20 (m, 1H), 7.14-7.20 (m, 2H), 7.57 (m, 1H), 6.85 (ddd, *J*=1.0, 7.3, 7.6 Hz, 1H), 6.71-6.79 (m, 2H), 4.03 (t, *J*=8.6 Hz, 2H), 3.20 (t, *J*=8.6 Hz, 2H). ^{13}C NMR (200 MHz, $CDCl_3$, 20°C, TMS): δ=155.3 (s), 147.8 (s), 144.9 (s), 137.1 (d), 131.2 (s), 127.1 (d), 124.4 (d), 120.3 (d), 114.3 (d), 113.2 (d), 108.6 (d), 49.4 (t), 27.8 (t).

1-phenylindoline[66]

^1H NMR (200 MHz, $CDCl_3$, 20°C, TMS): δ=7.30-7.34 (m, 2H), 7.19-7.23 (m, 2H), 7.04-7.16 (m, 3H), 6.90-6.97 (m, 1H), 6.71-6.75 (m, 1H), 3.92 (t, *J*=8.4 Hz, 2H), 3.10 (t, *J*=8.4 Hz, 2H). ^{13}C NMR (200 MHz, $CDCl_3$, 20°C, TMS): δ=147.1 (s), 144.2 (s), 131.2 (s), 129.2 (d, 2C), 127.1 (d), 125.0 (d), 120.9 (d), 118.8 (d, 2C), 117.7 (d), 108.2 (d), 52.1 (t), 28.2 (t).

2-methyl-1-phenylindoline 34

^1H NMR (200 MHz, $CDCl_3$, 20°C, TMS): δ=7.58-7.63 (m, 2H), 7.24-7.49 (m, 4H), 6.99-7.12 (m, 2H), 6.69-6.80 (m, 1H), 4.30-4.47 (m, 1H), 3.33 (dd, *J*=8.8, 15.6 Hz, 1H), 2.76 (dd, *J=7.5*, 15.6 Hz, 1H), 1.33 (d, *J*=6.2 Hz, 3H). ^{13}C NMR (200 MHz, $CDCl_3$, 20°C, TMS): δ=148.9 (s), 141.5 (s), 129.7 (s), 129.4 (d, 2C), 128.9 (d), 125.0 (d), 123.1 (d), 122.0 (d, 2C), 118.9 (d), 108.6 (d), 60.2

(d), 37.4 (t), 20.2 (q). IR (KBr): $\bar{\nu}$=1311 cm^{-1} (Aromatic C-N). MS (ESI) *m/z (%)*: 210.2 (100) $[M^+H]$. Elemental analysis: calcd (%) for $C_{15}H_{15}N$ (209.3): C 86.08, H 7.22, N 6.69; found: C 86.23, H 7.58, N 6.50.

(S)-1-(4-nitrophenyl)indoline-2-carboxylic acid 36

^1H NMR (200 MHz, MeOD, 20°C, TMS): δ=8.20 (d, *J=8.9 Hz, 2H*), 7.19-7.41 (m, 5H), 6.97 (dd, *J=1.1, 7.3 Hz, 1H*), 4.85 (dd *J=2.9, 10.6 Hz, 1H*), 3.69 (dd *J=10.6, 16.1 Hz, 1H*), 3.31 (dd *J=2.9, 16.1 Hz, 1H*). ^{13}C NMR (200 MHz, $CDCl_3$, 20°C, TMS): δ=175.9 (s), 148.9 (s), 144.2 (s), 141.0 (s), 129.9 (s), 127.9 (d), 125.9 (2C, d), 125.6 (d), 122.5 (s), 115.7 (2C, d), 111.9 (d), 65.0 (d), 33.8 (t). IR (KBr): $\bar{\nu}$=1299 cm^{-1} (Aromatic C-N). MS (ESI-) *m/z (%)*: 283.1 (100) $[M^+-H]$. Elemental analysis: calcd (%) for $C_{15}H_{12}N_2O_4$ (284.3): C 63.38, H 4.25, N 9.85; found: C 63.45, H 4.58, N 9.79. $[\alpha]_D^{20}$=−40.4 (*c*=0.02 in $CHCl_3$).

1-(4-nitrophenyl)indoline-2-carboxylate 37

^1H NMR (200 MHz, $CDCl_3$, 20°C, TMS): δ= 8.17-8.22 (m, 2H), 7.18-7.37 (m, 5H), 6.92-6.99 (m, 1H), 4.85 (dd, J=*3.5, 10.4 Hz, 1H*), 3.76 (s, 3H), 3.64 (dd, *J=10.4, 16.1 Hz, 1H*), 3.26 (dd *J=3.5, 16.1 Hz, 1H*). ^{13}C NMR (200 MHz, $CDCl_3$, 20°C, TMS): δ=165.2 (s), 148.9 (s), 144.3 (s), 133.0 (s), 129.9 (s), 127.9 (d), 125.9 (2C, d), 125.6 (d), 122.4 (d), 115.7 (2C, d), 111.8 (d), 65.3 (d), 52.9 (q), 33.8 (t). IR (KBr): $\bar{\nu}$=1313 cm^{-1} (Aromatic C-N). MS (ESI-) *m/z (%)*: 297.1 (100) $[M^+-H]$. Elemental analysis: calcd (%) for $C_{16}H_{14}N_2O_4$ (284.3): C 64.42, H 4.73, N 9.39; found: C 64.54, H 4.84, N 9.12.

1-(4-methoxyphenyl)indoline 31

^1H NMR (200 MHz, $CDCl_3$, 20°C, TMS): δ= 7.10-7.24 (m, 3H), 7.03-7.07 (m, 1H), 6.91-6.98 (m, 3H), 6.69-6.77 (m, 1H), 3.89 (t, *J*=8.2 Hz, 2H), 3.83 (s, 3H), 3.13 (t, *J*=8.2 Hz, 2H). ^{13}C NMR (200 MHz, $CDCl_3$, 20°C, TMS): δ=155.2 (s), 148.9 (s), 138.3 (s), 130.9 (s), 127.3 (d), 125.1 (d), 121.1 (d, 2C), 118.4 (d), 114.9 (d, 2C), 107.7 (d), 55.8 (q), 53.4 (t), 28.6 (t). IR (KBr): $\bar{\nu}$=1248 cm^{-1} (Aromatic C-N). MS (ESI) *m/z (%)*: 226.2 (100) $[M^+H]$. Elemental analysis: calcd (%) for $C_{15}H_{15}NO$ (225.3): C 79.97, H 6.71, N 6.22; found: C 80.02, H 6.91, N 6.02.

1-(2-(1,3-dioxolan-2-yl)-4-nitrophenyl)indoline 38

^1H NMR (200 MHz, $CDCl_3$, 20°C, TMS): δ=8.59 (s, 1H), 8.19 (d, *J*=8.9 Hz, 1H), 7.47 (d, *J*=8.9, 1H), 7.23 (d, *J*=6.8 Hz, 1H), 7.04-7.11 (m, 1H), 6.81-6.88 (m, 1H), 6.67 (d, *J*=7.3 Hz, 1H), 3.93-4.24 (m, 6H), 6.06 (s, 1H), 3.18 (t, *J*=8.4 Hz, 2H). ^{13}C NMR (200 MHz, $CDCl_3$, 20°C, TMS): δ=151.1 (s), 148.7 (s), 144.4 (s), 134.4 (s), 131.6 (s), 127.5 (d), 125.8 (d), 125.4 (d), 124.8 (d), 123.0 (d), 120.8 (d), 110.5 (d), 99.3 (d), 65.8 (t, 2C), 56.6 (t), 29.3 (t). IR (KBr): $\bar{\nu}$=1337 cm^{-1}

(Aromatic C-N). MS (ESI) *m/z (%)*: 313.0 (100) [M^+H]. Elemental analysis: calcd (%) for $C_{17}H_{16}N_2O_4$ (312.3): C 65.38, H 5.16, N 8.97; found: C 65.47, H 5.22, N 8.86.

1-(2-(1,3-dioxolan-2-yl)-4-fluorophenyl)indoline 33

^1H NMR (200 MHz, $CDCl_3$, 20°C, TMS): δ=7.25-7.40 (m, 2H), 6.96-7.18 (m, 3H), 6.72 (ddd, *J*=0.9, 7.3, 8.2 Hz, 1H), 6.28 (1H, d, *J*=7.3 Hz, 1H), 6.08 (d, *J*=1.6 Hz, 1H), 3.64-4.20 (m br, 6H), 3.14 (t, *J*=8.2 Hz, 2H). ^{13}C NMR (200 MHz, $CDCl_3$, 20°C, TMS): δ=161.1 (d, J=246 Hz), 151.9 (s), 141.3 (d, *J*=3.0 Hz), 138.7 (d, *J*=8.0 Hz), 130.4 (s), 127.6 (d, *J=8.1 Hz*), 127.5 (d), 124.8 (d), 118.8 (d), 118.0 (d, *J*=23.8 Hz), 114.4 (d, *J*=23.8 Hz), 108.9 (d), 99.65 (d, *J*=1.3 Hz), 65.7 (t, 2C), 57.4 (t), 29.2 (t). IR (KBr): $\bar{\nu}$=1301 cm^{-1} (Aromatic C-N). MS (ESI) *m/z (%)*: 286.1 (100) [M^+H]. Elemental analysis: calcd (%) for $C_{17}H_{16}FNO_2$ (285.3): C 71.56, H 5.65, N 4.91; found: C 71.52, H 5.70, N 4.83.

3-(1,3-dioxolan-2-yl)-2-(indolin-1-yl)quinoline 39

^1H NMR (200 MHz, $CDCl_3$, 20°C, TMS): δ=8.46 (s, 1H), 7.79-7.91 (m, 2H), 7.60-7.69 (ddd, *J=1.3, 7.0,* 8.5 Hz, 1H), 7.39-7.47 (m, 1H), 7.21 (d, *J=7.3 Hz, 1H*), 7.02-7.10 (m, 1H), 6.78-6.94 (m, 2H), 6.11 (s, 1H), 3.98-4.25 (m, 6H), 3.13-3.22 (t, *J*=8.5 Hz, 2H), ^{13}C NMR (200 MHz, $CDCl_3$, 20°C, TMS): δ=154.7 (s), 148.8 (s), 148.2 (s), 137.8 (d), 131.7 (s), 130.5 (s), 128.2 (d), 128.1 (d), 127.1 (d), 127.0 (s), 126.4 (s), 125.5 (d), 125.1 (d), 120.6 (d), 110.8 (d), 100.2 (d), 65.7 (t, 2C), 53.6 (t), 29.1 (t). IR (KBr): $\bar{\nu}$=1262 cm^{-1} (Aromatic C-N). MS (ESI) *m/z (%)*: 319.2 (100) [M^+H]. Elemental analysis: calcd (%) for $C_{20}H_{18}N_2O_2$ (318.4): C 75.45, H 5.70, N 8.80; found: C 75.52, H 5.80, N 8.73.

N-methyl-4-nitro-N-phenylaniline 40 see Urgaonkar et al., *J. Org. Chem*. **2004**, *69*, 9135-9142

4-methyl-N-(4-nitrophenyl)aniline 41 see Buchwald et al. J. AM. CHEM. SOC**. 2009**, *131*, 17423–17429

1-(4-nitrophenyl)-1H-indole 46 see Mino et al. *SYNLETT* **2008**, 4, 614–620

CHAPTER 3

General Procedure for the Synthesis of Compounds 49

A solution of (2*R*,5*S*)-**48** (2.55 mmol) in TFA (6 mL) was stirred at room temperature for 3 h. The solvent was then evaporated under reduced pressure and the residue purified by column chromatography using light petroleum ether/AcOEt (4:1) as eluent.

(2*S*,5*S*)-3,5-Dimethyl-2-(1-phenylvinyl)imidazolidin-4-one (49a)

Yield 93%; pale-yellow oil. [*a*]D 25 = +27.5 (*c* = 0.37, $CHCl_3$). IR (Nujol): ν̃ = 1670, 3430 cm–1. ^1H NMR (400 MHz, $CDCl_3$): *δ* = 1.38 (d, *J* = 7.1 Hz, 3 H), 3.04 (s, 3 H), 4.08 (q, *J* = 7.1 Hz, 1 H), 5.71 (s, 1 H), 5.72 (s, 1 H), 5.89 (s, 1 H), 6.57 (br. s, 1 H), 7.28–7.30 (m, 2 H), 7.42–7.48 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): *δ* = 14.7 (q), 28.1 (q), 54.1 (d), 74.2 (d), 122.9 (t), 126.9 (d), 129.2 (d), 129.8 (d), 134.5 (s), 139.5 (s), 169.3 (s) ppm. MS: *m*/*z* = 216 $[M]^+$. $C_{13}H_{16}N_2O$ (216.28): calcd. C 72.19, H 7.46, N 12.95; found C 72.26, H 7.38, N 12.86.

(2*S*,5*S*)-5-Isopropyl-3-methyl-2-(1-phenylvinyl)imidazolidin-4-one (49b)

Yield 95 %; cream crystals; m.p. 93°C (*i*Pr2O). [*a*]D 25 = +22.5 (*c* = 0.45, CHCl3). IR (Nujol): ν̃ = 1664, 3428 cm–1. ^1H NMR (400 MHz, CDCl3, 25 °C): *δ* = 0.87 (d, *J* = 7.0 Hz, 3 H), 1.00 (d, *J* = 7.1 Hz, 3 H), 2.39 (dqq, *J* = 3.9, 7.0, 7.1 Hz, 1 H), 3.05 (s, 3 H), 4.19 (d, *J* = 3.9 Hz, 1 H), 5.74 (s, 1 H), 5.87 (s, 1 H), 5.98 (s, 1 H), 7.28–7.32 (m, 2 H), 7.41–7.50 (m, 3 H), 11.07 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, CDCl3, 25 °C): *δ* = 16.4 (q), 18.2 (q), 28.1 (d), 28.9 (q), 60.1 (d), 74.6 (d), 124.7 (t), 127.5 (d), 129.9 (d), 130.7 (d), 133.6 (s), 139.3 (s), 168.6 (s) ppm. MS: *m*/*z* = 244 $[M]^+$. C15H20N2O (244.33): calcd. C 73.74, H 8.25, N 11.47; found C 73.82, H 8.09, N 11.25.

(2*S*,5*S*)-5-Benzyl-3-methyl-2-(1-phenylvinyl)imidazolidin-4-one (49c)

Yield 93%; white crystals; m.p. 91°C (*i*Pr_2O). [*a*]D 25 = –30.3 (*c* = 0.27, $CHCl_3$). IR (Nujol): ν̃ = 1682, 3444 cm– 1. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): *δ* = 2.86 (s, 3 H), 3.13–3.20 (m, 2 H), 4.14–4.18 (m, 1 H), 5.14 (s, 1 H), 5.38 (s, 1 H), 5.54 (s, 1 H), 5.75 (br. s, 1 H), 7.08–7.36 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): *δ* = 28.8 (d), 34.3 (t), 59.3 (q), 74.9 (d), 124.1 (t), 127.3 (d), 129.2 (d), 129.8 (d), 129.9 (d), 130.2 (d), 130.4 (d), 132.1 (s), 134.0 (s), 139.6 (s), 168.4 (s) ppm. MS: *m*/*z* = 292 $[M]^+$. $C_{19}H_{20}N_2O$ (292.37): calcd. C 78.05, H 6.89, N 9.58; found C 77.93, H 7.02, N 9.74.

General Procedure for the Synthesis of Compounds 51

TEA (0.51 mL, 3.64 mmol) was added to a solution of **49** (0.7 mmol) in dry CH_2Cl_2 (3 mL). The mixture was cooled to 0 °C and a solution of **50** in dry CH_2Cl_2 (2 mL) was added dropwise whilst stirring. After 24 h at room temperature the mixture was washed with 5% HCl (30 mL) and with aq. $NaHCO_3$ (30 mL) and then the organic layer was dried with Na_2SO_4. The solvent was evaporated and the crude mixture was purified by silica gel column chromatography with light petroleum ether/AcOEt (1:1) as eluent to give **51**.

(2*R*,5*S*)-3,5-Dimethyl-1-(2-nitrobenzoyl)-2-(1-phenylvinyl)imidazolidin-4-one (51a)

Yield 51% (as a mixture of two conformers in a ratio of 2:1); pale-yellow crystals; m.p. 160°C (*i*Pr$_2$O). [*α*]D 25 = –10.2 (*c* = 0.10, $CHCl_3$). IR (Nujol): ν̃ = 1652, 1704 cm–1. Major conformer: ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): *δ* = 0.41 (d, *J* = 6.9 Hz, 3 H), 3.04 (s, 3 H), 3.78 (q, *J* = 6.9 Hz, 1 H), 5.56 (s, 1 H), 5.77 (s, 1 H), 6.06 (s, 1 H), 6.98–8.26 (m, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): *δ* = 18.2 (q), 27.5 (q), 55.6 (d), 79.2 (d), 122.3 (t), 124.9 (d), 128.0 (d), 128.8 (d), 129.0 (d), 129.4 (d), 131.0 (d), 132.0 (s), 134.8 (d), 138.1 (s), 144.4 (s), 144.8 (s), 167.5 (s), 170.2 (s) ppm. Minor conformer: ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): *δ* = 1.22 (d, *J* = 6.9 Hz, 3 H), 2.84 (s, 3 H), 4.65 (q, *J* = 6.9 Hz, 1 H), 4.69 (s, 1 H), 5.13 (s, 1 H), 5.31 (s, 1 H), 6.98–8.26 (m, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): *δ* = 16.9 (q), 27.4 (q), 55.8 (d), 80.1 (d), 122.4 (t), 125.2 (d), 128.0 (d), 128.9 (d), 129.2 (d), 129.7 (d), 130.5 (d), 132.2 (s), 134.8 (d), 136.8 (s), 144.4 (s), 144.9 (s), 167.5 (s), 170.9 (s) ppm. MS: *m*/*z* = 365 [M]$^+$. $C_{20}H_{19}N_3O_4$ (365.38): calcd. C 65.74, H 5.24, N 11.50; found C 65.98, H 5.09, N 11.44.

(2*R*,5*S*)-1-(5-Chloro-2-nitrobenzoyl)-3,5-dimethyl-2-(1-phenylvinyl)-imidazolidin-4-one (51aa)

Yield 55% (as a mixture of two conformers in a ratio of 1.25:1); pale-yellow crystals; m.p. 62°C (*i*Pr$_2$O). [*α*]D 25 = –13.5 (*c* = 26.7, $CHCl_3$). IR (Nujol): ν̃ = 1640, 1690 cm–1. Major conformer: ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): *δ* = 0.40 (d, *J* = 6.8 Hz, 3 H), 2.97 (s, 3 H), 3.74 (q, *J* = 6.8 Hz, 1 H), 5.50 (s, 1 H), 5.70 (s, 1 H), 5.98 (s, 1 H), 6.97–8.12 (m, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): *δ* = 17.8 (q), 27.1 (q), 55.0 (d), 78.6 (d), 121.8 (t), 126.0 (d), 126.4 (d), 127.3 (d), 128.4 (d), 128.7 (d), 130.6 (d), 133.0 (s), 137.5 (s), 141.1 (s), 142.8 (s), 143.8 (s), 165.3 (s), 169.4 (s) ppm. Minor conformer: ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): *δ* = 1.21 (d, *J* = 6.5 Hz, 3 H), 2.81 (s, 3 H), 4.57 (q, *J* = 6.5 Hz, 1 H), 4.75 (s, 1 H), 5.20 (s, 1 H), 5.32 (s, 1 H), 6.98–8.12 (m, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): *δ* = 16.4 (q), 26.9 (q), 55.3 (d), 79.4 (d), 122.1 (t), 126.0 (d), 126.4 (d), 127.3 (d), 128.5 (d), 128.9 (d), 130.6 (d), 133.1 (s), 136.2 (s), 141.1 (s), 142.7 (s), 144.2 (s), 165.3 (s), 170.1 (s) ppm. MS: *m*/*z* = 399 [M]$^+$. $C_{20}H_{18}ClN_3O_4$ (399.83): calcd. C 60.08, H 4.54, N 10.51; found C 60.20, H 4.31, N 10.73.

(2*R*,5*S*)-1-(5-Fluoro-2-nitrobenzoyl)-3,5-dimethyl-2-(1-phenylvinyl)-imidazolidin-4-one (51ab)

Yield 60% (as a mixture of two conformers, in a ratio of 2:1); yellow oil. [*α*]D 25 = –4.9 (*c* = 5.2, $CHCl_3$). IR (Nujol): ṽ = 1638, 1702 cm–1. Major conformer: ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): *δ* = 0.45 (d, *J* = 6.9 Hz, 3 H), 3.04 (s, 3 H), 3.77 (q, *J* = 6.9 Hz, 1 H), 5.57 (s, 1 H), 5.76 (s, 1 H), 6.03 (s, 1 H), 6.86–8.30 (m, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): *δ* = 17.8 (q), 27.0 (q), 54.9 (d), 78.6 (d), 116.7 (dd, *2J*C-F = 23.2 Hz), 117.6 (dd, 2*J*C-F = 23.0 Hz), 121.8 (t), 127.4 (d), 128.0 (dd, 3*J*C-F = 9.9 Hz), 128.4 (d), 128.7 (d), 134.4 (d, 3*J*C-F = 8.0 Hz), 137.5 (s), 140.7 (s), 143.8 (s), 165.2 (d, 1*J*C-F = 259.6 Hz), 169.4 (s), 170.1 (s) ppm. Minor conformer: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): *δ* = 1.27 (d, *J* = 6.9 Hz, 3 H), 2.86 (s, 3 H), 4.64 (q, *J* = 6.9 Hz, 1 H), 4.80 (s, 1 H), 5.25 (s, 1 H), 5.33 (s, 1 H), 6.86–8.30 (m, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): *δ* = 16.4 (q), 26.9 (q), 55.3 (d), 79.2 (d), 115.9 (dd, 2*J*C-F = 23.4 Hz), 117.5 (dd, 2*J*C-F = 22.9 Hz), 122.0 (t), 127.3 (d), 127.7 (dd, 3*J*C-F = 9.7 Hz), 128.4 (d), 128.8 (d), 134.5 (d, 3*J*C-F = 8.0 Hz), 136.3 (s), 140.6 (s), 144.4 (s), 165.4 (d, 1*J*C-F = 260.2 Hz), 169.3 (s), 169.9 (s) ppm. MS: *m*/*z* = 383 $[M]^+$. $C_{20}H_{18}FN_3O_4$ (383.37): calcd. C 62.66, H 4.73, N 10.96; found C 62.88, H 4.56, N 11.07.

(2*R*,5*S*)-5-Isopropyl-3-methyl-1-(2-nitrobenzoyl)-2-(1-phenylvinyl)-imidazolidin-4-one (51b)

Yield 75% (as a mixture of two conformers in, a ratio of 3:1); yellow oil. [*α*]D 25 = –18.3 (*c* = 0.21, $CHCl_3$). IR (Nujol): ṽ = 1665, 1688 cm–1. Major conformer: ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): *δ* = 0.92 (d, *J* = 5.9 Hz, 3 H), 1.11 (d, *J* = 6.6 Hz, 3 H), 1.44 (dqq, *J* = 5.9, 6.6, 9.2 Hz, 1 H), 2.84 (s, 3 H), 4.40 (d, *J* = 9.2 Hz, 1 H), 4.86 (s, 1 H), 5.34 (s, 1 H), 5.54 (s, 1 H), 6.92–6.94 (m, 2 H), 7.23–7.31 (m, 3 H), 7.31–7.38 (m, 2 H), 7.54–7.63 (m, 1 H), 8.16–8.20 (m, 1 H) ppm. Minor conformer: ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): *δ* = 0.51 (d, *J* = 5.9 Hz, 3 H), 0.63 (d, *J* = 6.3 Hz, 3 H), 1.23–1.34 (m, 1 H), 2.94 (s, 3 H), 3.60–3.65 (m, 1 H), 5.54 (s, 1 H), 5.67 (s, 1 H), 6.18 (s, 1 H), 6.91–8.24 (m, 9 H) ppm. ^{1}H NMR (400 MHz, $[D_6]$DMSO, 100°C): *δ* = 0.83 (d, *J* = 6.9 Hz, 3 H), 0.89 (d, *J* = 6.7 Hz, 3 H), 1.55 (dqq, *J* = 6.7, 6.9, 7.3 Hz, 1 H), 2.77 (s, 3 H), 4.06 (d, *J* = 7.3 Hz, 1 H), 5.15 (s, 1 H), 5.27 (s, 1 H), 5.71 (s, 1 H), 7.11–7.12 (m, 2 H), 7.13–7.31 (m, 3 H), 7.46 (dd, *J* = 1.3, 7.5 Hz, 1 H), 7.68 (ddd, *J* = 1.3, 7.7, 8.2 Hz, 1 H), 7.76 (ddd, *J* = 1.1, 7.5, 7.7 Hz, 1 H), 8.16 (dd, *J* = 1.1, 8.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $[D_6]$DMSO, 100°C): *δ* = 20.1 (q), 20.9 (q), 27.8 (d), 32.4 (q), 63.5 (d), 78.9 (d), 120.6 (s), 122.6 (t), 125.7 (d), 128.7 (d), 128.9 (d), 129.1 (d), 129.8 (d), 131.6 (d), 132.3 (s), 135.8 (d), 138.1 (s), 144.9 (s), 145.0 (s), 169.7 (s) ppm. MS: *m*/*z* = 393 $[M]^+$. $C_{22}H_{23}N_3O_4$ (393.44): calcd. C 67.16, H 5.89, N 10.68; found C 67.34, H 5.67, N 10.75.

(2*R*,5*S*)-1-(5-Chloro-2-nitrobenzoyl)-5-isopropyl-3-methyl-2-(1-phenylvinyl) imidazolidin-4-one (51ba)

Yield 34% (as a mixture of two conformers in a ratio of 5:1); white crystals; m.p. 145°C (*i*Pr$_2$O). [*α*]D 25 = +55.7 (*c* = 13.0, CHCl$_3$). IR (Nujol): ν̃ = 1644, 1710 cm–1. Major conformer: ^{1}H NMR (400 MHz, CDCl$_3$, 25°C): *δ* = 0.88 (d, *J* = 5.5 Hz, 3 H), 1.09 (d, *J* = 6.6 Hz, 3 H), 1.58 (dqq, *J* = 5.5, 6.6, 8.9 Hz, 1 H), 2.85 (s, 3 H), 4.36 (d, *J* = 8.9 Hz, 1 H), 4.91 (s, 1 H), 5.26 (s, 1 H), 5.34 (s, 1 H), 6.95–8.07 (m, 8 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$, 25°C): *δ* = 19.4 (q), 19.7 (q), 27.2 (d), 32.2 (q), 63.3 (d), 78.6 (d), 120.0 (s), 121.3 (t), 125.9 (d), 127.2 (d), 128.3 (d), 128.6 (d), 128.8 (d), 130.4 (d), 133.4 (s), 137.1 (s), 141.1 (s), 142.8 (s), 144.7 (s), 169.8 (s) ppm. Minor conformer: ^{1}H NMR (400 MHz, CDCl$_3$, 25°C): *δ* = 0.55 (d, *J* = 5.6 Hz, 3 H), 0.67 (d, *J* = 5.9 Hz, 3 H), 1.20–1.26 (m, 1 H), 2.93 (s, 3 H), 3.57–3.63 (m, 1 H), 5.52 (s, 1 H), 5.62 (s, 1 H), 6.15 (s, 1 H), 6.95–8.07 (m, 8 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$, 25°C): *δ* = 16.8 (q), 20.4 (q), 28.0 (d), 31.9 (q), 64.9 (d), 77.4 (d), 120.0 (s), 121.3 (t), 126.3 (d), 127.8 (d), 128.1 (d), 128.6 (d), 129.5 (d), 130.6 (d), 133.4 (s), 137.1 (s), 141.1 (s), 142.8 (s), 144.7 (s), 169.8 (s) ppm. MS: *m*/*z* = 427 [M]$^+$. $C_{22}H_{22}ClN_3O_4$ (427.88): calcd. C 61.75, H 5.18, N 9.82; found C 61.89, H 5.03, N 10.02.

(2*R*,5*S*)-1-(5-Fluoro-2-nitrobenzoyl)-5-isopropyl-3-methyl-2-(1-phenylvinyl) imidazolidin-4-one (51bb)

Yield 49% (as a mixture of two conformers, in a ratio of 4:1); yellow oil. [*α*]D 25 = +0.24 (*c* = 28.7, CHCl$_3$). IR (Nujol): ν̃ = 1640, 1698 cm–1. Major conformer: ^{1}H NMR (400 MHz, CDCl$_3$, 25°C): *δ* = 0.88 (d, *J* = 5.9 Hz, 3 H), 1.07 (d, *J* = 6.6 Hz, 3 H), 1.55 (dqq, *J* = 5.9, 6.6, 9.0 Hz, 1 H), 2.82 (s, 3 H), 4.33 (d, *J* = 9.0 Hz, 1 H), 4.94 (s, 1 H), 5.24 (s, 1 H), 5.35 (s, 1 H), 6.91–8.15 (m, 8 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$, 25°C): *δ* = 19.3 (q), 19.8 (q), 27.2 (d), 32.2 (q), 63.4 (d), 78.4 (d), 116.6 (dd, 2*J*C-F = 27.4 Hz), 117.4 (dd, 2*J*C-F = 23.1 Hz), 120.9 (t), 127.2 (d), 127.6 (dd, 3*J*C-F = 9.4 Hz), 128.3 (d), 128.6 (d), 134.4 (d, 3*J*C-F = 8.3 Hz), 137.3 (s), 140.7 (s), 144.8 (s), 165.1 (d, 1*J*C-F = 259.7 Hz), 166.4 (s), 169.8 (s) ppm. Minor conformer: ^{1}H NMR (400 MHz, CDCl$_3$, 25°C): *δ* = 0.49 (d, *J* = 6.2 Hz, 3 H), 0.64 (d, *J* = 6.6 Hz, 3 H), 1.32–1.42 (m, 1 H), 2.89 (s, 3 H), 3.54–3.61 (m, 1 H), 5.48 (s, 1 H), 5.60 (s, 1 H), 6.12 (s, 1 H), 6.70–8.29 (m, 8 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$, 25°C): *δ* = 16.6 (q), 20.4 (q), 28.0 (d), 31.8 (q), 64.8 (d), 77.3 (d), 116.4 (dd, 2*J*C-F = 27.2 Hz), 117.6 (dd, 2*J*C-F = 23.5 Hz), 120.0 (t), 127.2 (d), 127.8 (dd, 3*J*C-F = 9.0 Hz), 128.0 (d), 128.6 (d), 134.2 (d, 3*J*C-F = 8.2 Hz), 138.0 (s), 139.9 (s), 144.2 (s), 165.4 (d, 1*J*C-F = 259.4 Hz), 166.8 (s), 170.1 (s) ppm. MS: *m*/*z* = 411 [M]$^+$. $C_{22}H_{22}FN_3O_4$ (411.43): calcd. C 64.22, H 5.39, N 10.21; found C 64.44, H 5.12, N 10.32.

(2*R*,5*S*)-5-Benzyl-3-methyl-1-(2-nitrobenzoyl)-2-(1-phenylvinyl)imidazolidin-4-one (51c)

Yield 50% (as a mixture of two conformers, in a ratio of 1:1); yellow oil. [*α*]D 25 = +4.3 (*c* = 0.1, $CHCl_3$). IR (Nujol): ν̃ = 1658, 1706 cm–1. ^1H NMR (400 MHz, $CDCl_3$, 25°C): *δ* = 2.46–2.52 (m, 2 H), 2.81 (s, 3 H), 3.10 (s, 3 H), 3.15–3.22 (m, 2 H), 3.93–4.12 (m, 1 H), 4.17 (s, 1 H), 4.85–4.88 (m, 1 H), 5.17 (s, 1 H), 5.43 (s, 1 H), 5.59 (s, 1 H), 5.71 (s, 1 H), 6.19 (s, 1 H), 6.48–7.92 (m, 28 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): *δ* = 26.9 (q), 27.6 (q), 36.8 (t), 39.0 (t), 60.5 (d), 61.4 (d), 76.7 (d), 78.7 (d), 121.4 (t), 121.8 (t), 125.1 (d), 125.7 (d), 126.2 (d), 127.0 (d), 127.5 (d), 128.0 (d), 128.2 (d), 128.3 (d), 128.4 (d), 128.5 (d, overlapped), 128.6 (d), 129.3 (d), 129.4 (d), 129.8 (d), 130.0 (d), 130.3 (d), 130.4 (d), 130.8 (d), 132.4 (d), 133.0 (d), 136.1 (s), 136.9 (s), 137.2 (s), 137.4 (s), 141.1 (s), 141.4 (s), 142.5 (s), 142.7 (s), 143.9 (s), 144.0 (s), 168.6 (s), 168.8 (s), 169.2 (s), 169.6 (s) ppm. MS: *m*/*z* = 441 $[M]^+$. $C_{26}H_{23}N_3O_4$ (441.48): calcd. C 70.73, H 5.25, N 9.52; found C 70.50, H 5.51, N 9.43.

(2*R*,5*S*)-5-Benzyl-1-(5-chloro-2-nitrobenzoyl)-3-methyl-2-(1-phenylvinyl) imidazolidin-4-one (51ca)

Yield 62% (as a mixture of two conformers in a ratio of 1:1); pale-yellow crystals; m.p. 75°C (*i*Pr_2O). [*α*]D 25 = +4.4 (*c* = 11.9, $CHCl_3$). IR (Nujol): ν̃ = 1636, 1688 cm–1. ^1H NMR (400 MHz, $CDCl_3$, 25°C): *δ* = 2.79 (s, 3 H), 2.84–2.95 (m, 2 H), 3.07 (s, 3 H), 3.12–3.20 (m, 2 H), 3.93–4.15 (m, 1 H), 4.21 (s, 1 H), 4.80–4.86 (m, 1 H), 5.16 (s, 1 H), 5.44 (s, 1 H), 5.57 (s, 1 H), 5.68 (s, 1 H), 6.18 (s, 1 H), 6.47–6.51 (m, 2 H), 6.75–7.48 (m, 22 H), 7.84–7.96 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): *δ* = 26.9 (q), 27.6 (q), 36.8 (t), 39.0 (t), 60.5 (d), 61.4 (d), 76.9 (d), 78.6 (d), 121.5 (t), 121.7 (t), 125.7 (d), 126.1 (d), 126.3 (d), 126.9 (d), 127.2 (d), 128.2 (d), 128.3 (d), 128.4 (d), 128.5 (d), 128.6 (d, overlapped), 128.7 (d), 129.4 (d), 129.7 (d), 129.8 (d), 130.0 (d), 130.3 (d), 130.4 (d), 132.4 (s), 133.0 (s), 136.1 (s), 136.9 (s), 137.2 (s), 137.7 (s), 141.0 (s), 141.2 (s), 142.4 (s), 142.5 (s), 144.0 (s), 168.6 (s), 168.7 (s), 169.1 (s), 169.4 (s) ppm. MS: *m*/*z* = 475 $[M]^+$. $C_{26}H_{22}ClN_3O_4$ (475.92): calcd. C 65.62, H 4.66, N 8.83; found C 65.43, H 4.81, N 8.96.

(2*R*,5*S*)-5-Benzyl-1-(5-fluoro-2-nitrobenzoyl)-3-methyl-2-(1-phenylvinyl)-imidazolidin-4-one (51cb)

Yield 65% (as a mixture of two conformers in a ratio of 1:1); white crystals; m.p. 88°C (*i*Pr_2O). [*α*]D 25 = –4.0 (*c* = 19.1, $CHCl_3$). IR (Nujol): ν̃ = 1660, 1700 cm–1. ^1H NMR (400 MHz, $CDCl_3$, 25°C): *δ* = 2.48–2.56 (m, 2 H), 2.79 (s, 3 H), 3.08 (s, 3 H), 3.01–3.20 (m, 2 H), 3.92–4.13 (m, 1 H), 4.21 (s, 1 H), 4.82–4.89 (m, 1 H), 5.15 (s, 1 H), 5.44 (s, 1 H), 5.58 (s, 1 H), 5.69 (s, 1 H), 6.21 (s, 1 H), 6.25–6.42 (m, 1 H), 6.48–6.51 (m, 3 H), 6.75–7.08 (m, 7 H), 7.25–7.48 (m, 12 H), 7.98–8.05 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): *δ* = 26.9 (q), 27.6 (q), 36.8 (t), 39.1 (t),

60.6 (d), 61.5 (d), 76.7 (d), 78.6 (d), 116.0 (dd, 2*J*C-F = 21.8 Hz), 116.2 (dd, 2*J*C-F = 22.0 Hz), 117.1 (dd, 2*J*C-F = 21.6 Hz), 117.4 (dd, 2*J*C-F = 21.9 Hz), 121.3 (t), 121.7 (t), 126.2 (d), 126.8 (dd, 3*J*C-F = 11.6 Hz), 127.4 (dd, 3*J*C-F = 11.0 Hz), 128.4 (d), 128.6 (d, overlapped), 130.0 (d), 133.5 (d, 3*J*C-F = 5.6 Hz), 134.3 (d, 3*J*C-F = 6.2 Hz), 136.3 (s), 136.6 (s), 136.7 (s), 137.0 (s), 137.4 (s), 137.7 (s), 144.0 (s), 144.2 (s), 165.1 (d, 1*J*C-F = 231.6 Hz), 166.4 (s), 167.6 (d, 1*J*C-F = 259.3 Hz), 168.7 (s), 168.8 (s), 169.1 (s) ppm. MS: *m*/*z* = 459 $[M]^+$. $C_{26}H_{22}FN_3O_4$ (459.47): calcd. C 67.97, H 4.83, N 9.15; found C 67.84, H 4.99, N 9.26.

General Procedure for the Synthesis of Compounds 52

A solution of **51** (1.04 mmol) in EtOH (10 mL) and 20% aq. AcOH (2.5 mL) was treated with Fe powder (0.464 g, 8.32 mmol) and heated at reflux for 5 h under vigorous stirring. The mixture was diluted with AcOEt (50 mL) and filtered through a pad of Celite. The filtrate was washed with aq. $NaHCO_3$ (50 mL) and water (2x25 mL) and then the organic layer was dried with Na2SO4. The solvent was evaporated under reduced pressure and the products purified by column chromatography with light petroleum ether/AcOEt (1:1) as eluent.

(2*R*,5*S*)-1-(2-Aminobenzoyl)-3,5-dimethyl-2-(1-phenylvinyl)-imidazolidin-4-one (52a)

Yield 96%; yellow oil. [*a*]D 25 = +25.3 (*c* = 0.22, $CHCl_3$). IR (Nujol): ν˜ = 1648, 1698, 3488 cm–1. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): *δ* = 0.66 (d, *J* = 6.9 Hz, 3 H), 2.96 (s, 3 H), 4.13 (br. s, 2 H), 4.30 (q, *J* = 6.9 Hz, 1 H), 5.36 (s, 2 H), 5.87 (s, 1 H), 6.70–6.75 (m, 2 H), 7.00–7.35 (m, 7 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): *δ* = 17.3 (q), 27.5 (q), 55.9 (d), 79.5 (d), 117.1 (d), 118.2 (d), 119.2 (s), 121.3 (s), 121.8 (t), 127.2 (d), 127.6 (d), 128.8 (d), 128.9 (d), 131.4 (d), 137.8 (s), 144.7 (s), 144.9 (s), 171.1 (s) ppm. MS: *m*/*z* = 335 $[M]^+$. $C_{20}H_{21}N_3O_2$ (335.40): calcd. C 71.62, H 6.31, N 12.53; found C 71.45, H 6.52, N 12.33.

(2*R*,5*S*)-1-(2-Amino-5-chlorobenzoyl)-3,5-dimethyl-2-(1-phenylvinyl)-imidazolidin-4-one (52aa)

Yield 96%; yellow crystals; m.p. 106°C (*i*Pr2O). [*a*]D 25 = +21.4 (*c* = 24.1, $CHCl_3$). IR (Nujol): ν˜ = 1636, 1694, 3448 cm–1. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): *δ* = 0.55 (d, *J* = 6.6 Hz, 3 H), 2.80 (s, 3 H), 4.15 (q, *J* = 6.6 Hz, 1 H), 4.26 (br. s, 2 H), 5.16 (s, 1 H), 5.20 (s, 1 H), 5.68 (s, 1 H), 6.51–6.54 (m, 1 H), 6.90–6.97 (m, 4 H), 7.13–7.21 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): *δ* = 16.6 (q), 26.9 (q), 55.2 (d), 79.0 (d), 117.4 (d), 121.4 (t), 121.5 (s), 121.6 (s), 126.5 (d), 128.0 (d), 128.3 (d), 128.4 (d), 130.6 (d), 137.1 (s), 143.1 (s), 144.2 (s), 170.0 (s), 170.3 (s) ppm. MS: *m*/*z* = 369 $[M]^+$. $C_{20}H_{20}ClN_3O_2$ (369.84): calcd. C 64.95, H 5.45, N 11.36; found C 64.87, H

5.61, N 11.27. *Eur. J. Org. Chem.* 2010, 1694–1703 © 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim www.eurjoc.org 1699.

(2*R*,5*S*)-1-(2-Amino-5-fluorobenzoyl)-3,5-dimethyl-2-(1-phenylvinyl)-imidazolidin-4-one (52ab)

Yield 87%; colorless oil. [*a*]D 25 = +9.9 (*c* = 2.43, $CHCl_3$). IR (Nujol): ṽ = 1654, 1702, 3450 cm–1. ^1H NMR (400 MHz, $CDCl_3$, 25°C): *δ* = 0.67 (d, *J* = 7.0 Hz, 3 H), 2.96 (s, 3 H), 3.87 (br. s, 2 H), 4.12 (q, *J* = 7.0 Hz, 1 H), 5.37 (s, 2 H), 5.82 (s, 1 H), 6.61–7.35 (m, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): *δ* = 17.2 (q), 27.4 (q), 55.7 (d), 79.4 (d), 113.8 (dd, 2*J*C-F = 23.7 Hz), 118.1 (dd, 2*J*C-F = 22.1 Hz), 118.3 (dd, 3*J*C-F = 7.2 Hz), 121.9 (t), 122.0 (d, 3*J*C-F = 6.6 Hz), 128.6 (d), 128.8 (d), 129.0 (d), 137.5 (s), 140.7 (s), 144.8 (s), 155.5 (d, 1*J*C-F = 238.3 Hz), 168.4 (s), 170.8 (s) ppm. MS: *m*/*z* = 353 $[M]^+$. $C_{20}H_{20}FN_3O_2$ (353.39): calcd. C 67.97, H 5.70, N 11.89; found C 67.86, H 5.82, N 11.74.

(2*R*,5*S*)-1-(2-Aminobenzoyl)-5-isopropyl-3-methyl-2-(1-phenylvinyl)-imidazolidin-4-one (52b)

Yield 95%; colorless oil. [*a*]D 25 = +56.1 (*c* = 0.38, $CHCl_3$). IR (Nujol): ṽ = 1640, 1690, 3492 cm–1. ^1H NMR (400 MHz, $CDCl_3$, 25°C): *δ* = 0.75 (d, *J* = 6.8 Hz, 3 H), 0.97 (d, *J* = 6.5 Hz, 3 H), 1.26–1.29 (qqd, *J* = 6.5, 6.8, 9.1 Hz, 1 H), 2.81 (s, 3 H), 4.15 (br. s, 2 H), 4.35 (d, *J* = 9.1 Hz, 1 H), 5.24 (s, 1 H), 5.36 (s, 1 H), 5.64 (s, 1 H), 6.70–6.75 (m, 2 H), 7.13–7.34 (m, 7 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): *δ* = 19.3 (q), 20.6 (q), 28.0 (d), 32.6 (q), 63.6 (d), 79.5 (d), 117.1 (d), 117.7 (d), 120.7 (s), 121.2 (t), 128.2 (d), 128.4 (d), 128.7 (d), 128.8 (d), 131.7 (d), 138.3 (s), 145.4 (s), 145.8 (s), 170.6 (s), 172.5 (s) ppm. MS: *m*/*z* = 363 $[M]^+$. $C_{22}H_{25}N_3O_2$ (363.45): calcd. C 72.70, H 6.93, N 11.56; found C 72.58, H 7.02, N 11.78.

(2*R*,5*S*)-1-(2-Amino-5-chlorobenzoyl)-5-isopropyl-3-methyl-2-(1-phenylvinyl)-imidazolidin-4-one (52ba)

Yield 84%; colorless oil. [*a*]D 25 = +63.7 (*c* = 12.0, $CHCl_3$). IR (Nujol): ṽ = 1654, 1706, 3466 cm–1. ^1H NMR (400 MHz, $CDCl_3$, 25°C): *δ* = 0.67 (d, *J* = 6.6 Hz, 3 H), 0.96 (d, *J* = 6.3 Hz, 3 H), 1.23–1.25 (m, 1 H), 2.78 (s, 3 H), 4.30 (br. s, 2 H), 4.32–4.36 (m, 1 H), 5.15 (s, 1 H), 5.36 (s, 1 H), 5.51 (s, 1 H), 6.63–6.65 (m, 1 H), 7.11–7.31 (m, 7 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): *δ* = 19.0 (q), 20.0 (q), 27.5 (d), 32.1 (q), 62.9 (d), 79.5 (d), 117.8 (d), 120.9 (s), 121.5 (t), 121.9 (s), 127.9 (d), 128.0 (d), 128.4 (d), 128.5 (d), 131.0 (d), 137.4 (s), 143.7 (s), 145.0 (s), 170.0 (s), 171.0 (s) ppm. MS: *m*/*z* = 397 $[M]^+$. $C_{22}H_{24}ClN_3O_2$ (397.90): calcd. C 66.41, H 6.08, N 10.56; found C 66.53, H 6.01, N 10.44.

(2*R*,5*S*)-1-(2-Amino-5-fluorobenzoyl)-5-isopropyl-3-methyl-2-(1-phenylvinyl)-imidazolidin-4-one (52bb)

Yield 93%; white crystals; m.p. 44°C (*i*Pr$_2$O). [*a*]D 25 = +26.7 (*c* = 21.8, CHCl$_3$). IR (Nujol): ν̃ = 1640, 1696, 3438 cm–1. ^{1}H NMR (400 MHz, CDCl$_3$, 25°C): *δ* = 0.73 (d, *J* = 6.8 Hz, 3 H), 0.97 (d, *J* = 6.5 Hz, 3 H), 1.32 (qqd, *J* = 6.5, 6.8, 9.0 Hz, 1 H), 2.83 (s, 3 H), 3.47 (br. s, 2 H), 4.29 (d, *J* = 9.0 Hz, 1 H), 5.20 (s, 1 H), 5.36 (s, 1 H), 5.60 (s, 1 H), 6.65–7.35 (m, 8 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$, 25°C): *δ* = 18.8 (q), 20.1 (q), 27.5 (d), 32.1 (q), 63.1 (d), 78.9 (d), 114.3 (dd, 2*J*C-F = 23.8 Hz), 117.7 (dd, 3*J*C-F = 8.1 Hz), 117.8 (dd, 2*J*C-F = 20.2 Hz), 120.9 (t), 121.2 (d, 3*J*C-F = 6.1 Hz), 127.9 (d), 128.3 (d), 128.4 (d), 137.6 (s), 140.8 (s), 145.2 (s), 154.8 (d, 1*J*C-F = 236.3 Hz), 169.9 (s), 170.6 (s) ppm. MS: *m*/*z* = 381 [M]$^+$. $C_{22}H_{24}FN_3O_2$ (381.44): calcd. C 69.27, H 6.34, N 11.02; found C 69.41, H 6.12, N 11.29.

(2*R*,5*S*)-1-(2-Aminobenzoyl)-5-benzyl-3-methyl-2-(1-phenylvinyl)-imidazolidin-4-one (52c)

Yield 97%; yellow crystals; m.p. 130°C (*i*Pr$_2$O). [*a*]D 25 = +130.0 (*c* = 0.28, CHCl$_3$). IR (Nujol): ν̃ = 1642, 1696, 3472 cm–1. ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): *δ* = 1.87–1.94 (m, 1 H), 2.37–2.43 (m, 1 H), 2.93 (s, 3 H), 4.01 (br. s, 2 H), 4.50–4.54 (m, 1 H), 5.19 (s, 1 H), 5.46 (s, 1 H), 5.80 (s, 1 H), 6.71–7.40 (m, 14 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$, 25°C): *δ* = 27.5 (q), 38.7 (t), 60.5 (d), 79.0 (d), 117.2 (d), 118.3 (d), 121.1 (s), 121.7 (t), 126.8 (d), 127.4 (d), 128.5 (d), 128.8 (d, overlapped), 128.9 (d), 129.8 (d), 131.5 (d), 137.4 (s), 138.0 (s), 144.8 (s), 145.0 (s), 169.9 (s), 170.2 (s) ppm. MS: *m*/*z* = 411 [M]$^+$. $C_{26}H_{25}N_3O_2$ (411.50): calcd. C 75.89, H 6.12, N 10.21; found C 76.02, H 5.97, N 10.40.

(2*R*,5*S*)-1-(2-Amino-5-chlorobenzoyl)-5-benzyl-3-methyl-2-(1-phenylvinyl)-imidazolidin-4-one (52ca)

Yield 79%; yellow oil. [*a*]D 25 = +13.7 (*c* = 8.47, CHCl$_3$). IR (Nujol): ν̃ = 1650, 1696, 3480 cm–1. ^{1}H NMR (400 MHz, CDCl$_3$, 25°C): *δ* = 2.03–2.36 (m, 2 H), 2.93 (s, 3 H), 4.15 (br. s, 2 H), 4.56–4.60 (m, 1 H), 5.12 (s, 1 H), 5.36 (s, 1 H), 5.70 (s, 1 H), 6.58–7.41 (m, 13 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$, 25°C): *δ* = 27.1 (q), 38.2 (t), 60.0 (d), 78.9 (d), 113.4 (d), 118.0 (d), 121.4 (s), 121.7 (t), 122.4 (s), 126.6 (d), 127.1 (d), 128.2 (d), 128.4 (d), 128.6 (d), 129.3 (d), 129.4 (d), 130.9 (d), 131.3 (d), 136.9 (s), 137.3 (s), 143.2 (s), 144.4 (s), 168.7 (s), 169.3 (s) ppm. MS: *m*/*z* = 445 [M]$^+$. $C_{26}H_{24}ClN_3O_2$ (445.94): calcd. C 70.03, H 5.42, N 9.42; found C 70.18, H 5.31, N 9.38.

(2*R*,5*S*)-1-(2-Amino-5-fluorobenzoyl)-5-benzyl-3-methyl-2-(1-phenylvinyl)-imidazolidin-4-one (52cb)

Yield 60%; white crystals; m.p. 142°C (*i*Pr$_2$O). [*a*]D 25 = +4.7 (*c* = 5.07, CHCl$_3$). IR (Nujol): ν̃ = 1662, 1708, 3490 cm–1. ^{1}H NMR (400 MHz, CDCl$_3$, 25°C): *δ* = 2.03–2.36 (m, 2 H), 2.93 (s, 3 H), 4.15 (br. s, 2 H), 4.56–4.60 (m, 1 H), 5.12 (s, 1 H), 5.36 (s, 1 H), 5.70 (s, 1 H), 6.58–7.41 (m, 13 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$, 25°C): *δ* = 27.1 (q), 38.2 (t), 60.0 (d), 78.6 (d), 113.7 (dd, 2*J*C-F = 23.7 Hz), 117.9 (dd, 2*J*C-F = 22.6 Hz), 118.1 (dd, 3*J*C-F = 7.4 Hz), 121.5 (t), 121.2 (d, 3*J*C-F = 6.1 Hz), 126.6 (d), 128.2 (d), 128.4 (d), 128.6 (d, overlapped), 129.4 (d), 137.6 (s), 137.4 (s), 140.4 (s), 144.4 (s), 155.2 (d, 1*J*C-F = 236.8 Hz), 168.6 (s), 169.4 (s) ppm. MS: *m*/*z* = 429 [M]$^+$. $C_{26}H_{24}FN_3O_2$ (429.49): calcd. C 72.71, H 5.63, N 9.78; found C 72.60, H 5.81, N 9.61.

General Procedure for the Synthesis of Compounds 53

$NaNO_2$ (0.156 g, 2.26 mmol) was added portion wise to a solution of **52** (1.13 mmol) in MeOH (2 mL) and 6 N HCl (0.65 mL) cooled to 0°C. After 30 min AcONa was added until pH 5 and then a solution of ethyl 2-chloroacetoacetate (1.13 mmol, 0.122 mL) in MeOH (1 mL) was added dropwise under vigorous stirring at room temperature. After 24 h the solvent was evaporated under reduced pressure and the residue extracted with Et_2O (2x15 mL). The organic layer was washed with aq. $NaHCO_3$ (15 mL) and water (30 mL) and then dried with Na_2SO_4. The solvent was evaporated under reduced pressure and the products purified by silica gel column chromatography with light petroleum ether/AcOEt (1:1) as eluent.

Ethyl (2*R*,5*S*)-2-Chloro-2-(2-{2-[3,5-dimethyl-4-oxo-2-(1-phenylvinyl)-imidazolidin-1-ylcarbonyl]phenyl}hydrazono)acetate (53a)

Yield 57%; pale-yellow crystals; m.p. 65°C (*i*Pr$_2$O). [*a*]D 25 = +2.1 (*c* = 0.15, CHCl$_3$). IR (Nujol): ν̃ = 1650, 1703, 1716, 3338 cm–1. ^{1}H NMR (400 MHz, CDCl$_3$, 25°C): *δ* = 0.62 (d, *J* = 6.6 Hz, 3 H), 1.42 (t, *J* = 7.1 Hz, 3 H), 2.98 (s, 3 H), 4.35 (q, *J* = 6.6 Hz, 1 H), 4.41 (q, *J* = 7.1 Hz, 2 H), 5.38 (s, 1 H), 5.40 (s, 1 H), 5.91 (s, 1 H), 7.00–7.61 (m, 9 H), 9.40 (s, 1 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$, 25°C): *δ* = 14.6 (q), 17.1 (q), 27.5 (q), 56.2 (d), 63.3 (t), 79.9 (d), 116.7 (d), 118.5 (s), 121.0 (s), 122.1 (t), 122.4 (d), 127.3 (d), 128.8 (d), 128.9 (d), 132.1 (d), 132.2 (d), 137.4 (s), 140.3 (s), 144.7 (s), 159.2 (s), 168.5 (s), 170.7 (s) ppm. MS: *m*/*z* = 468 [M]$^+$. $C_{24}H_{25}ClN_4O_4$ (468.93): calcd. C 61.47, H 5.37, N 11.95; found C 61.34, H 5.48, N 11.77.

Ethyl (2*R*,5*S*)-2-Chloro-2-(2-{4-chloro-2-[3,5-dimethyl-4-oxo-2-(1-phenylvinyl)-imidazolidin-1-ylcarbonyl]phenyl}hydrazono)acetate (53aa)

Yield 62%; pale-yellow crystals; m.p. 174°C (*i*Pr$_2$O). [*a*]D 25 = +2.4 (*c* = 17.8, CHCl$_3$). IR (Nujol): ν̃ = 1646, 1694, 1728, 3392 cm–1. ^{1}H NMR (400 MHz, CDCl$_3$, 25°C): *δ* = 0.66 (d, *J* =

6.5 Hz, 3 H), 1.37 (t, *J* = 6.9 Hz, 3 H), 2.94 (s, 3 H), 4.31–4.37 (m, 3 H), 5.37 (s, 2 H), 5.83 (s, 1 H), 7.04–7.47 (m, 8 H), 9.33 (s, 1 1700 ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 14.2 (q), 16.7 (q), 27.0 (q), 55.6 (d), 63.0 (t), 79.6 (d), 117.8 (d), 118.6 (s), 121.7 (s), 121.8 (s), 121.9 (t), 127.0 (d), 128.3 (d), 128.5 (d), 128.6 (d), 131.4 (d), 136.8 (s), 138.4 (s), 144.1 (s), 159.1 (s), 167.0 (s), 170.1 (s) ppm. MS: *m*/*z* = 502 $[M]^+$. $C_{24}H_{24}Cl_2N_4O_4$ (503.38): calcd. C 57.26, H 4.81, N 11.13; found C 57.40, H 4.62, N 11.21.

Ethyl (2*R*,5*S*)-2-Chloro-2-(2-{2-[3,5-dimethyl-4-oxo-2-(1-phenylvinyl)-imidazolidin-1-ylcarbonyl]-4-fluorophenyl}hydrazono)acetate (53ab)

Yield 49%; yellow crystals; m.p. 125°C (*i*Pr_2O). [*a*]D 25 = –0.35 (*c* = 10.3, $CHCl_3$). IR (Nujol): ν̃ = 1642, 1708, 1732, 3412 cm–1. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 0.64 (d, *J* = 6.3 Hz, 3 H), 1.39 (t, *J* = 7.1 Hz, 3 H), 2.96 (s, 3 H), 4.30 (q, *J* = 6.3 Hz, 1 H), 4.37 (q, *J* = 7.1 Hz, 2 H), 5.38 (s, 2 H), 5.86 (s, 1 H), 6.95–7.51 (m, 8 H), 9.22 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 14.2 (q), 16.7 (q), 27.0 (q), 55.7 (d), 62.9 (t), 79.4 (d), 113.8 (dd, 2*J*C-F = 24.3 Hz), 118.0 (s), 118.2 (dd, 3*J*C-F = 7.5 Hz), 118.5 (dd, 2*J*C-F = 22.4 Hz), 121.8 (t), 128.3 (d), 128.5 (d), 128.6 (d), 136.1 (s), 136.8 (s), 140.6 (s), 144.1 (s), 157.5 (d, 1*J*C-F = 242.8 Hz), 159.2 (s), 166.8 (s), 170.1 (s) ppm. MS: *m*/*z* = 486 $[M]^+$. $C_{24}H_{24}ClFN_4O_4$ (486.92): calcd. C 59.20, H 4.97, N 11.51; found C 59.08, H 5.12, N 11.31.

Ethyl (2*R*,5*S*)-2-Chloro-2-(2-{2-[5-isopropyl-3-methyl-4-oxo-2-(1-phenylvinyl)-imidazolidin-1-ylcarbonyl]phenyl}hydrazono)acetate (53b)

Yield 51%; cream crystals; m.p.69°C (*i*Pr_2O). [*a*]D 25 = +45.6 (*c* = 0.4, $CHCl_3$). IR (Nujol): ν̃ = 1656, 1688, 1724, 3436 cm–1. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 0.72 (d, *J* = 6.8 Hz, 3 H), 0.98 (d, *J* = 6.5 Hz, 3 H), 1.17–1.21 (m, 1 H), 1.43 (t, *J* = 7.1 Hz, 3 H), 2.83 (s, 3 H), 4.39–4.45 (m, 3 H), 5.32 (s, 1 H), 5.42 (s, 1 H), 5.68 (s, 1 H), 7.01 (dd, *J* = 7.4, 7.5 Hz, 1 H), 7.10–7.13 (m, 2 H), 7.27–7.36 (m, 3 H), 7.40 (d, *J* = 7.5 Hz, 1 H), 7.45 (dd, *J* = 7.4, 8.2 Hz, 1 H), 7.64 (d, *J* = 8.2 Hz, 1 H), 9.51 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 14.6 (q), 19.3 (q), 20.5 (q), 28.0 (d), 32.6 (q), 63.3 (t), 63.8 (d), 79.7 (d), 116.7 (d), 118.9 (s), 120.6 (s), 121.4 (t), 122.0 (d), 128.2 (d), 128.3 (d), 128.9 (d), 129.0 (d), 132.4 (d), 138.1 (s), 140.8 (s), 145.8 (s), 159.9 (s), 170.3 (s), 171.2 (s) ppm. MS: *m*/*z* = 496 $[M]^+$. $C_{26}H_{29}ClN_4O_4$ (496.99): calcd. C 62.83, H 5.88, N 11.27; found C 62.71, H 5.96, N 11.10.

Ethyl (2*R*,5*S*)-2-Chloro-2-(2-{4-chloro-2-[5-isopropyl-3-methyl-4-oxo-2-(1-phenylvinyl)imidazolidin-1-ylcarbonyl]phenyl}hydrazono)-acetate (53ba)

Yield 82%; pale-yellow oil. [*a*]D 25 = –0.81 (*c* = 6.20, $CHCl_3$). IR (Nujol): ν̃ = 1634, 1686, 1716, 3424 cm–1. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 0.62 (d, *J* = 6.6 Hz, 3 H), 0.91 (d, *J* = 6.4 Hz,

3 H), 1.00–1.09 (m, 1 H), 1.33 (t, *J* = 7.1 Hz, 3 H), 2.77 (s, 3 H), 4.27–4.35 (m, 3 H), 5.18 (s, 1 H), 5.36 (s, 1 H), 5.53 (s, 1 H), 7.05–7.48 (m, 8 H), 9.49 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 14.1 (q), 18.9 (q), 19.9 (q), 27.4 (d), 32.0 (q), 62.9 (t), 63.0 (d), 79.6 (d), 117.7 (d), 118.8 (s), 121.2 (s), 121.7 (t), 126.7 (s), 127.8 (d), 127.9 (d), 128.3 (d), 128.5 (d), 131.6 (d), 137.2 (s), 138.9 (s), 145.0 (s), 159.2 (s), 169.8 (s), 169.9 (s) ppm. MS: *m*/*z* = 530 $[M]^+$. $C_{26}H_{28}Cl_2N_4O_4$ (531.43): calcd. C 58.76, H 5.31, N 10.54; found C 58.54, H 5.44, N 10.43.

Ethyl (2*R*,5*S*)-2-Chloro-2-(2-{4-fluoro-2-[5-isopropyl-3-methyl-4-oxo-2-(1-phenylvinyl)imidazolidin-1-ylcarbonyl]phenyl}hydrazono)-acetate (53bb)

Yield 57%; colorless oil. [*a*]D 25 = +16.4 (*c* = 5.00, $CHCl_3$). IR (Nujol): ν̃ = 1638, 1710, 1722, 3384 cm–1. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 0.70 (d, *J* = 6.8 Hz, 3 H), 0.97 (d, *J* = 6.5 Hz, 3 H), 1.18–1.23 (m, 1 H), 1.40 (t, *J* = 7.1 Hz, 3 H), 2.83 (s, 3 H), 4.33–4.41 (m, 3 H), 5.29 (s, 1 H), 5.42 (s, 1 H), 5.64 (s, 1 H), 7.08–7.17 (m, 4 H), 7.27–7.33 (m, 3 H), 7.53–7.57 (m, 1 H), 9.30 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 14.2 (q), 18.9 (q), 20.3 (q), 27.5 (d), 32.1 (q), 62.9 (t), 63.3 (d), 79.2 (d), 114.7 (dd, 2*J*C-F = 24.4 Hz), 118.1 (dd, 3*J*C-F = 7.4 Hz), 118.5 (s), 118.8 (dd, 2*J*C-F = 22.3 Hz), 121.3 (t), 127.8 (d), 128.6 (d), 128.9 (d), 136.6 (s), 137.3 (s), 140.0 (s), 145.2 (s), 157.2 (d, 1*J*C-F = 242.7 Hz), 159.3 (s), 169.5 (s), 169.7 (s) ppm. MS: *m*/*z* = 514 $[M]^+$. $C_{26}H_{28}ClFN_4O_4$ (514.98): calcd. C 60.64, H 5.48, N 10.88; found C 60.88, H 5.23, N 10.65.

Ethyl (2*R*,5*S*)-2-(2-{2-[5-Benzyl-3-methyl-4-oxo-2-(1-phenylvinyl)-imidazolidin-1-ylcarbonyl]phenyl}hydrazono)-2-chloroacetate (53c)

Yield 44%; yellow oil. [*a*]D 25 = –33.8 (*c* = 0.21, $CHCl_3$). IR (Nujol): ν̃ = 1646, 1692, 1720, 3404 cm–1. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 1.42 (t, *J* = 7.1 Hz, 3 H), 2.01–2.05 (m, 1 H), 2.08–2.13 (m, 1 H), 2.98 (s, 3 H), 4.41 (q, *J* = 7.1 Hz, 2 H), 4.60 (t, *J* = 4.7 Hz, 1 H), 5.23 (s, 1 H), 5.37 (s, 1 H), 5.83 (s, 1 H), 6.75–7.56 (m, 14 H), 9.31 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 14.6 (q), 27.5 (q), 38.7 (t), 60.9 (d), 63.3 (t), 79.4 (d), 116.8 (d), 118.5 (s), 120.9 (s), 122.0 (t), 122.4 (d), 126.5 (d), 126.9 (d), 127.5 (d), 128.6 (d), 128.8 (d), 129.3 (d), 129.7 (d), 132.1 (d), 136.8 (s), 137.8 (s), 140.3 (s), 144.8 (s), 159.8 (s), 168.9 (s), 169.6 (s) ppm. MS: *m*/*z* = 544 $[M]^+$. $C_{30}H_{29}ClN_4O_4$ (545.03): calcd. C 66.11, H 5.36, N 10.28; found C 65.98, H 5.54, N 10.12.

Ethyl (2*R*,5*S*)-2-(2-{2-[5-Benzyl-3-methyl-4-oxo-2-(1-phenylvinyl)-imidazolidin-1-ylcarbonyl]-4-chlorophenyl}hydrazono)-2-chloroacetate (53ca)

Yield 43%; yellow oil. [*a*]D 25 = +0.022 (*c* = 4.49, $CHCl_3$). IR (Nujol): ν̃ = 1650, 1702, 1726, 3456 cm–1. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 1.41 (t, *J* = 7.1 Hz, 3 H), 2.22–2.26 (m, 2 H), 2.98 (s, 3 H), 4.40 (q, *J* = 7.1 Hz, 2 H), 4.65 (t, *J* = 6.4 Hz, 1 H), 5.19 (s, 1 H), 5.40 (s, 1 H), 5.79 (s, 1 H), 6.77–6.80 (m, 2 H), 7.10–7.43 (m, 11 H), 9.24 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$,

25°C): δ = 14.2 (q), 27.1 (q), 38.3 (t), 60.3 (d), 63.0 (t), 79.3 (d), 117.8 (d), 118.7 (s), 121.3 (s), 122.0 (t), 126.6 (d), 127.0 (s), 127.1 (d), 128.3 (d), 128.7 (d), 128.8 (d, overlapped), 129.1 (d), 130.2 (d), 131.5 (d), 136.3 (s), 137.3 (s), 138.6 (s), 144.2 (s), 159.2 (s), 167.4 (s), 169.0 (s) ppm. MS: *m*/*z* = 578 $[M]^+$. $C_{30}H_{28}Cl_2N_4O_4$ (579.47): calcd. C 62.18, H 4.87, N 9.67; found C 61.95, H 5.04, N 9.87.

Ethyl (2*R*,5*S*)-2-(2-{2-[5-Benzyl-3-methyl-4-oxo-2-(1-phenylvinyl)-imidazolidin-1-ylcarbonyl]-4-fluorophenyl}hydrazono)-2-chloroacetate (53cb)

Yield 47%; yellow crystals; m.p. 105°C (*i*Pr_2O). [*a*]D 25 = –0.13 (*c* = 4.43, $CHCl_3$). IR (Nujol): ṽ = 1647, 1704, 1728, 3462 cm–1. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 1.40 (t, *J* = 7.1 Hz, 3 H), 2.17–2.25 (m, 2 H), 2.96 (s, 3 H), 4.39 (q, *J* = 7.1 Hz, 2 H), 4.60 (t, *J* = 6.4 Hz, 1 H), 5.17 (s, 1 H), 5.37 (s, 1 H), 5.83 (s, 1 H), 6.78–7.44 (m, 13 H), 9.12 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 14.2 (q), 27.1 (q), 38.3 (t), 60.4 (d), 63.0 (t), 79.0 (d), 114.1 (dd, 2*J*C-F = 24.3 Hz), 118.0 (s), 118.3 (dd, 3*J*C-F = 7.5 Hz), 118.5 (dd, 2*J*C-F = 22.4 Hz), 121.5 (s), 121.8 (t), 126.6 (d), 128.2 (d), 128.3 (d, overlapped), 128.6 (d), 129.2 (d), 136.1 (s), 136.3 (s), 137.3 (s), 144.2 (s), 157.4 (d, 1*J*C-F = 243.0 Hz), 159.3 (s), 167.3 (s), 169.1 (s) ppm. MS: *m*/*z* = 562 $[M]^+$. $C_{30}H_{28}ClFN_4O_4$ (563.02): calcd. C 64.00, H 5.01, N 9.95; found C 63.81, H 5.13, N 10.07.

General Procedure for the Synthesis of Compounds 55

A solution of **53** (0.2 mmol) in toluene (9 mL) was treated with TEA (0.11 mL, 0.8 mmol) and heated at reflux for 24 h. The organic layer was washed with aq. $NaHCO_3$ (10 mL) and water (20 mL) and then it was dried with Na_2SO_4. The solvent was evaporated under reduced pressure and the products purified by silica gel column chromatography with light petroleum ether/AcOEt (1:1) as eluent.

Ethyl (3a*S*,3b*R*,6*S*)-4,6-Dimethyl-5,8-dioxo-3a-phenyl-3,3a,3b,4,5,6-hexahydro-8*H*-benzo[*e*]imidazo[1,2-*a*]pyrazolo[5,1-*c*][1,4]diazepine-2-carboxylate (55a)

Yield 55%; yellow crystals; m.p. 90°C (*i*Pr_2O). [*a*]D 25 = +667.0 (*c* = 0.20, $CHCl_3$). IR (Nujol): ṽ = 1652, 1705, 1716 cm–1. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 0.32 (d, *J* = 6.8 Hz, 3 H), 1.37 (t, *J* = 7.1 Hz, 3 H), 3.25 (s, 3 H), 3.60 (d, *J* =16.1 Hz, 1 H), 3.82 (d, *J* = 16.1 Hz, 1 H), 4.25 (q, *J* = 6.8 Hz), 4.33 (q, *J* = 7.1 Hz, 2 H), 5.57 (s, 1 H), 7.13 (dd, *J* = 7.4, 8.0 Hz, 1 H), 7.18–7.21 (m, 2 H), 7.36–7.38 (m, 3 H), 7.52 (ddd, *J* = 1.6, 7.4, 8.7 Hz, 1 H), 7.84 (d, *J* = 8.7 Hz, 1 H), 8.11 (dd, *J* = 1.6, 8.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 14.2 (q), 14.6 (q), 30.5 (q), 44.7 (t), 55.9 (d), 62.4 (t), 77.4 (d), 81.7 (s), 116.8 (s), 118.1 (d), 122.4 (d), 126.5 (d), 129.5 (d), 129.9 (d), 133.3 (d), 134.0 (d), 137.9 (s), 141.5 (s), 143.4 (s), 162.1 (s), 164.5 (s), 172.4 (s) ppm. MS:

m/*z* = 432 [M]+. $C_{24}H_{24}N_4O_4$ (432.47): calcd. C 66.65, H 5.59, N 12.96; found C 66.41, H 5.70, N 12.82.

Ethyl (3a*S*,3b*R*,6*S*)-10-Chloro-4,6-dimethyl-5,8-dioxo-3a-phenyl-3,3a,3b,4,5,6-hexahydro-8*H*-benzo[*e*]imidazo[1,2-*a*]pyrazolo[5,1-*c*]-[1,4]diazepine-2-carboxylate (55aa)

Yield 62%; yellow crystals; m.p. 143°C (*i*Pr2O). [*a*]D 25 = +89.7 (*c* = 2.31, $CHCl_3$). IR (Nujol): ν˜ = 1647, 1704, 1728 cm–1. 1H NMR (400 MHz, $CDCl_3$, 25°C): *δ* = 0.32 (d, *J* = 6.7 Hz, 3 H), 1.33 (t, *J* = 7.0 Hz, 3 H), 3.21 (s, 3 H), 3.57 (d, *J* = 16.1 Hz, 1 H), 3.82 (d, *J* = 16.1 Hz, 1 H), 4.17 (q, *J* = 6.7 Hz, 1 H), 4.28 (q, *J* = 7.0 Hz, 2 H), 5.53 (s, 1 H), 7.11–7.40 (m, 6 H), 7.76–7.79 (m, 1 H), 8.04 (s, 1 H) ppm. 13C NMR (100 MHz, $CDCl_3$, 25°C): *δ* = 13.7 (q), 14.2 (q), 30.1 (q), 44.4 (t), 55.5 (d), 62.1 (t), 76.7 (d), 81.1 (s), 117.2 (s), 119.3 (d), 126.6 (d), 127.2 (s), 129.1 (d), 129.6 (d), 132.1 (d), 133.4 (d), 137.2 (s), 139.7 (s), 143.5 (s), 161.4 (s), 162.7 (s), 171.8 (s) ppm. MS: *m*/*z* = 466 [M]+. $C_{24}H_{23}ClN_4O_4$ (466.92): calcd. C 61.74, H 4.97, N 12.00; found C 61.48, H 5.23, N 12.27.

Ethyl (3a*S*,3b*R*,6*S*)-10-Fluoro-4,6-dimethyl-5,8-dioxo-3a-phenyl-3,3a,3b,4,5,6-hexahydro-8*H*-benzo[*e*]imidazo[1,2-*a*]pyrazolo[5,1-*c*]-[1,4]diazepine-2-carboxylate (55ab)

Yield 71%; white crystals; m.p. 145°C (*i*Pr2O). [*a*]D 25 = +912.1 (*c* = 3.23, $CHCl_3$). IR (Nujol): ν˜ = 1655, 1690, 1724 cm–1. 1H NMR (400 MHz, $CDCl_3$, 25°C): *δ* = 0.29 (d, *J* = 6.7 Hz, 3 H), 1.35 (t, *J* = 7.1 Hz, 3 H), 3.24 (s, 3 H), 3.58 (d, *J* = 16.1 Hz, 1 H), 3.82 (d, *J* = 16.1 Hz, 1 H), 4.21 (q, *J* = 6.7 Hz, 1 H), 4.31 (q, *J* = 7.1 Hz, 2 H), 5.54 (s, 1 H), 7.15–7.40 (m, 6 H), 7.78–7.83 (m, 2 H) ppm. 13C NMR (100 MHz, $CDCl_3$, 25°C): *δ* = 13.7 (q), 14.2 (q), 30.1 (q), 44.4 (t), 55.6 (d), 62.0 (t), 76.7 (d), 81.1 (s), 118.1 (s), 118.3 (dd, 2*J*C-F = 24.6 Hz), 119.7 (dd, 3*J*C-F = 6.7 Hz), 121.1 (dd, 2*J*C-F = 22.7 Hz), 126.7 (d), 129.2 (d), 129.6 (d), 137.4 (s), 137.5 (s), 142.9 (s), 157.8 (d, 1*J*C-F = 240.7 Hz), 161.5 (s), 162.8 (s), 171.8 (s) ppm. MS: *m*/ *z* = 450 [M]+. $C_{24}H_{23}FN_4O_4$ (450.46): calcd. C 63.99, H 5.15, N 12.44; found C 64.08, H 5.02, N 12.31.

Ethyl (3a*S*,3b*R*,6*S*)-6-Isopropyl-4-methyl-5,8-dioxo-3a-phenyl-3,3a,3b,4,5,6-hexahydro-8*H*-benzo[*e*]imidazo[1,2-*a*]pyrazolo[5,1-*c*]-[1,4]diazepine-2-carboxylate (55b)

Yield 62 %; yellow crystals; m.p. 138°C (*i*Pr2O). [*a*]D 25 = +975.0 (*c* = 0.38, $CHCl_3$). IR (Nujol): ν˜ = 1644, 1702, 1720 cm–1. 1H NMR (400 MHz, $CDCl_3$, 25°C): *δ* = 0.16 (qqd, *J* = 6.6, 6.7, 9.8 Hz, 1 H), 0.45 (d, *J* = 6.7 Hz, 3 H), 0.81 (d, *J* = 6.6 Hz, 3 H), 1.36 (t, *J* = 7.1 Hz, 3 H), 3.20 (s, 3 H), 3.55 (d, *J* = 15.9 Hz, 1 H), 3.76 (d, *J* = 15.9 Hz, 1 H), 4.04 (d, *J* = 9.8 Hz, 1 H), 4.32 (q, *J* =

7.1 Hz, 2 H), 5.42 (s, 1 H), 7.12 (dd, *J* = 7.3, 8.1 Hz, 1 H), 7.26–7.37 (m, 5 H), 7.50 (ddd, *J* = 1.6, 7.3, 8.6 Hz, 1 H), 7.80 (d, *J* = 8.6 Hz, 1 H), 8.19 (dd, *J* = 1.6, 8.1 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 14.6 (q), 19.3 (q), 22.2 (q), 30.1 (d), 33.3 (q), 45.0 (t), 62.5 (t), 63.5 (d), 79.9 (d), 81.1 (s), 116.7 (s), 118.5 (d), 122.4 (d), 127.7 (d), 129.3 (d), 129.7 (d), 133.7 (d), 134.4 (d), 137.8 (s), 142.3 (s), 145.6 (s), 161.9 (s), 166.5 (s), 172.1 (s) ppm. MS: *m*/*z* = 460 $[M]^+$. $C_{26}H_{28}N_4O_4$ (460.52): calcd. C 67.81, H 6.13, N 12.17; found C 67.54, H 6.24, N 12.02.

Ethyl (3a*S*,3b*R*,6*S*)-10-Chloro-6-isopropyl-4-methyl-5,8-dioxo-3aphenyl-3,3a,3b,4,5,6-hexahydro-8*H*-benzo[*e*]imidazo[1,2-*a*]pyrazolo-[5,1-*c*][1,4]diazepine-2-carboxylate (55ba)

Yield 53%; yellow crystals; m.p. 135°C (*i*Pr_2O). [*a*]D 25 = +818.0 (*c* = 3.94, $CHCl_3$). IR (Nujol): ν̃ = 1652, 1688, 1716 cm–1. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 0.18 (qqd, *J* = 6.6, 6.5, 9.7 Hz, 1 H), 0.42 (d, *J* = 6.6 Hz, 3 H), 0.80 (d, *J* = 6.5 Hz, 3 H), 1.36 (t, *J* = 7.2 Hz, 3 H), 3.20 (s, 3 H), 3.56 (d, *J* = 16.1 Hz, 1 H), 3.76 (d, *J* = 16.1 Hz, 1 H), 4.03 (d, *J* = 9.7 Hz, 1 H), 4.32 (q, *J* = 7.2 Hz, 2 H), 5.42 (s, 1 H), 7.22–7.44 (m, 6 H), 7.79 (d, *J* = 9.1 Hz, 1 H), 8.18 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 14.2 (q), 18.9 (q), 21.7 (q), 29.8 (d), 32.9 (q), 44.7 (t), 62.2 (t), 63.2 (d), 76.5 (d), 80.6 (s), 117.1 (s), 119.7 (d), 127.1 (d), 127.4 (s), 129.0 (d), 129.4 (d), 132.6 (d), 133.8 (d), 137.1 (s), 140.4 (s), 145.3 (s), 161.4 (s), 164.8 (s), 171.5 (s) ppm. MS: *m*/*z* = 494 $[M]^+$. $C_{26}H_{27}ClN_4O_4$ (494.97): calcd. C 63.09, H 5.50, N 11.32; found C 63.27, H 5.29, N 11.44.

Ethyl (3a*S*,3b*R*,6*S*)-10-Fluoro-6-isopropyl-4-methyl-5,8-dioxo-3aphenyl-3,3a,3b,4,5,6-hexahydro-8*H*-benzo[*e*]imidazo[1,2-*a*]pyrazolo-[5,1-*c*][1,4]diazepine-2-carboxylate (55bb)

Yield 46%; yellow crystals; m.p. 144°C (*i*Pr_2O). [*a*]D 25 = +207.4 (*c* = 2.23, CHCl3). IR (Nujol): ν̃ = 1644, 1701, 1733 cm–1. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 0.07 (d, *J* = 6.6 Hz, 3 H), 0.45 (qqd, *J* = 6.6, 6.5, 9.1 Hz, 1 H), 0.82 (d, *J* = 6.5 Hz, 3 H), 1.22 (t, *J* = 7.2 Hz, 3 H), 3.19 (s, 3 H), 3.53 (d, *J* = 16.0 Hz, 1 H), 3.75 (d, *J* = 16.0 Hz, 1 H), 4.02 (d, *J* = 9.1 Hz, 1 H), 4.31 (q, *J* = 7.2 Hz, 2 H), 5.32 (s, 1 H), 7.10–7.83 (m, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 14.2 (q), 18.9 (q), 21.9 (q), 29.7 (d), 32.8 (q), 44.5 (t), 62.1 (t), 63.1 (d), 76.5 (d), 81.2 (s), 114.5 (d), 118.7 (d), 119.3 (dd, 2*J*C-F = 23.7 Hz), 120.0 (dd, 3*J*C-F = 7.5 Hz), 125.2 (dd, 2*J*C-F = 22.4 Hz), 127.2 (d), 127.3 (d), 137.5 (s), 137.8 (s), 143.2 (s), 156.9 (d, 1*J*C-F = 244.1 Hz), 160.8 (s), 163.0 (s), 170.6 (s) ppm. MS: *m*/ *z* = 478 $[M]^+$. $C_{26}H_{27}FN_4O_4$ (478.52): calcd. C 65.26, H 5.69, N 11.71; found C 65.51, H 5.44, N 11.43.

Ethyl (3a*S*,3b*R*,6*S*)-6-Benzyl-4-methyl-5,8-dioxo-3a-phenyl-3,3a,3b,4,5,6-hexahydro-8*H*-benzo[*e*]imidazo[1,2-*a*]pyrazolo[5,1-*c*]-[1,4]diazepine-2-carboxylate (55c)

Yield 65%; yellow oil. [*a*]D 25 = +94.6 (*c* = 0.20, $CHCl_3$). IR (Nujol): ν̃ = 1643, 1691, 1735 cm–1. ^1H NMR (400 MHz, $CDCl_3$, 25°C): δ = 0.82–0.91 (m, 1 H), 1.39 (t, *J* = 7.1 Hz, 3 H), 2.34–2.38 (m, 1 H), 3.24 (s, 3 H), 3.64 (d, *J* = 16.1 Hz, 1 H), 3.84 (d, *J* = 16.1 Hz, 1 H), 4.29–4.38 (m, 3 H), 5.56 (s, 1 H), 7.15–8.16 (m, 14 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 14.6 (q), 28.7 (q), 35.0 (t), 44.7 (t), 60.6 (d), 60.8 (t), 76.8 (d), 81.7 (s), 116.8 (s), 118.2 (d), 122.5 (d), 126.8 (d), 127.5 (d), 128.5 (d), 129.6 (d), 129.8 (d), 130.2 (d), 133.3 (d), 134.1 (d), 137.9 (s), 138.3 (s), 141.6 (s), 143.7 (s), 162.0 (s), 164.5 (s), 171.2 (s) ppm. MS: *m*/*z* = 508 $[M]^+$. $C_{30}H_{28}N_4O_4$ (508.57): calcd. C 70.85, H 5.55, N 11.02; found C 70.69, H 5.67, N 11.13.

Ethyl (3a*S*,3b*R*,6*S*)-6-Benzyl-10-chloro-4-methyl-5,8-dioxo-3aphenyl-3,3a,3b,4,5,6-hexahydro-8*H*-benzo[*e*]imidazo[1,2-*a*]pyrazolo-[5,1-*c*][1,4]diazepine-2-carboxylate (55ca)

Yield 44%; yellow crystals; m.p. 141°C (*i*Pr_2O). [*a*]D 25 = +914.0 (*c* = 1.89, $CHCl_3$). IR (Nujol): ν̃ = 1641, 1708, 1722 cm–1. ^1H NMR (400 MHz, $CDCl_3$, 25°C): δ = 0.86–0.92 (m, 1 H), 1.37 (t, *J* = 7.2 Hz, 3 H), 2.18–2.26 (m, 1 H), 3.23 (s, 3 H), 3.64 (d, *J* = 16.1 Hz, 1 H), 3.83 (d, *J* = 16.1 Hz, 1 H), 4.33–4.41 (m, 3 H), 5.52 (s, 1 H), 7.13–8.13 (m, 13 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 14.2 (q), 30.3 (q), 34.6 (t), 44.5 (t), 60.3 (d), 62.2 (t), 76.3 (d), 81.1 (s), 117.2 (s), 119.4 (d), 126.5 (d), 126.9 (d), 127.7 (s), 128.2 (d), 129.2 (d), 129.3 (d), 129.9 (d), 132.2 (d), 133.6 (d), 137.2 (s), 137.8 (s), 139.7 (s), 143.6 (s), 161.4 (s), 162.7 (s), 170.7 (s) ppm. MS: *m*/*z* = 542 $[M]^+$. $C_{30}H_{27}ClN_4O_4$ (543.01): calcd. C 66.36, H 5.01, N 10.32; found C 66.12, H 5.14, N 10.55.

Ethyl (3a*S*,3b*R*,6*S*)-6-Benzyl-10-fluoro-4-methyl-5,8-dioxo-3aphenyl-3,3a,3b,4,5,6-hexahydro-8*H*-benzo[*e*]imidazo[1,2-*a*]pyrazolo-[5,1-*c*][1,4]diazepine-2-carboxylate (55cb)

Yield 77%; yellow crystals; m.p. 146°C (*i*Pr_2O). [*a*]D 25 = +0.64 (*c* = 2.2, $CHCl_3$). IR (Nujol): ν̃ = 1646, 1692, 1734 cm–1. ^1H NMR (400 MHz, $CDCl_3$, 25°C): δ = 0.82–0.88 (m, 1 H), 1.37 (t, *J* = 7.1 Hz, 3 H), 2.30–2.35 (m, 1 H), 3.23 (s, 3 H), 3.62 (d, *J* = 16.0 Hz, 1 H), 3.82 (d, *J* = 16.0 Hz, 1 H), 4.31–4.37 (m, 3 H), 5.53 (s, 1 H), 7.13–7.79 (m, 13H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.2 (q), 29.9(q), 34.6 (t), 44.2 (t), 60.3 (d), 62.0 (t), 76.4 (d), 81.2 (s), 114.0 (s), 119.7 (dd, 2*J*C-F = 23.2 Hz), 120.2 (dd, 3*J*C-F = 7.4 Hz), 125.6 (dd, 2*J*C-F = 21.8 Hz), 126.4 (d), 127.1 (s), 128.1 (d), 129.2 (d), 129.8 (d), 130.2 (d), 130.3 (d), 135.4 (s), 137.6 (s), 137.9 (s), 142.1 (s), 157.8 (d, 1*J*C-F = 245.6 Hz), 164.0 (s), 170.8 (s) ppm. MS: *m*/*z* = 526 $[M]^+$. $C_{30}H_{27}FN_4O_4$ (526.56): calcd. C 68.43, H 5.17, N 10.64; found C 68.20, H 5.34, N 10.88.

CHAPTER 4

General procedure for palladium catalyzed reactions: 1 mmole of isoxazol-5-one was dissolved in the solvent, 4 mmole of acrylate and 0.1 mmole of Palladium acetate was added. The solution was refluxed for 24 hours under 1 atm of oxygen. After cooling at RT, solvent was removed under reduced pressure. The residue was diluted with water, extracted 3 times with CH_2Cl_2 and the combined organic layer was washed with brine; then it was dried with Na_2SO_4. The solvent was evaporated under reduced pressure and the products purified by silica gel column chromatography with light petroleum ether/ CH_2Cl_2 (1:1) as eluent.

General procedure for gold catalyzed reactions: 1 mmole of isoxazol-5-one was dissolved in the solvent, 4 mmole of acrylate and 0.02 mmole of $AuCl_3$ was added. The solution was refluxed for 24 hours. After cooling at RT, solvent was removed under reduced pressure. The residue was diluted with water, extracted 3 times with CH_2Cl_2 and the combined organic layer was washed with brine; then it was dried with Na_2SO_4. The solvent was evaporated under reduced pressure and the products purified by silica gel column chromatography with light petroleum ether/ CH_2Cl_2 (1:1) as eluent.

For compound **56a** and **56b** see Marchesini et al. J.Het.Chem. **1980**, 763.

Ethyl 3-(4-benzyl-3-methyl-5-oxo-4,5-dihydroisoxazol-4-yl)acrylate 57a

Yield: with Pd catalysis DMF/THF 2/1 as solvent: 25%. With Au catalysis CH_3CN as solvent: 40%. ; yellow oil; ^{1}H NMR δ = 1.31 (t, J = 7.1 Hz, 3 H), 2.12 (s, 3 H), 3.08-3.38 (AB system, 2H, J = 13.6, 44.8 Hz), 4.24 (q, J = 7.1 Hz, 2H), 6.15 (d, J = 15.7 Hz, 1H), 6.84 (d, J = 15.7 Hz, 1H), 7.09-7.14 (m, 2H), 7.28-7.33 (m, 3H) ppm. ^{13}C NMR δ = 13.1 (q), 14.1 (q), 40.2 (t), 58.5 (s), 61.5 (t), 125.9 (d), 128.5 (d), 129.2 (d, 2C), 129.5 (d, 2C),132.7 (s), 138.7 (d), 165.1 (s), 166.1 (s), 177.0 (s) ppm. MS: m/z = 288,1 $[M+H]^+$.

Ethyl 3-(3-methyl-5-oxo-4-phenyl-4,5-dihydroisoxazol-4-yl)acrylate 57b

Unisolable traces; ^{1}H NMR after elaboration shows peak compatible with this product mixed with by-products. MS presents a peak m/z = 274.1 $[M+H]^+$ compatible with this product

Ethyl 3-(4-benzyl-3-methyl-5-oxoisoxazol-2(5H)-yl)acrylate 58a

Best yield (AcOH/Dioxane 3/1) 10%; yellow oil; ^{1}H NMR δ = 1.31 (t, J = 7.1 Hz, 3 H), 2.12 (s, 3 H), 3.70 (s, 2H), 4.24 (q, J = 7.1 Hz, 2H), 5.75 (d, J = 13.2 Hz, 1H), 7.08-7.16 (m, 2H), 7.27-7.37 (m, 3H), 7.53 (d, J = 13.2 Hz, 1H), ppm. ^{13}C NMR δ = 13.9 (q), 14.5 (q), 39.2 (t), 61.5 (t), 100.3 (s), 102.2 (d), 125.9 (d), 129.2 (d, 2C), 129.5 (d, 2C), 139.9 (s), 140.7 (d), 145.1 (s), 166.4 (s), 171.0 (s) ppm. MS: m/z = 288,1 $[M+H]^+$.

Ethyl 3-(3-methyl-5-oxo-4-phenylisoxazol-2(5H)-yl)acrylate 58b

Best yield (AcOH/Dioxane 3/1) 10%; yellow oil; ^{1}H NMR δ = 1.31 (t, J = 7.1 Hz, 3 H), 2.48 (s, 3 H), 4.24 (q, J = 7.1 Hz, 2H), 5.85 (d, J = 13.2 Hz, 1H), 7.35-7.46 (m, 5H),7.66 (d, J = 13.2 Hz, 1H), ppm. ^{13}C NMR δ = 14.0 (q), 14.3 (q), 61.3 (t), 99.3 (d), 105.2 (s), 126.8 (d), 128.2 (d, 2C), 128.3 (d, 2C), 133.9 (s), 140.5 (d), 143.1 (s), 165.2 (s), 165.4 (s) ppm. MS: m/z = 274,1 $[M+H]^+$.

Ethyl 3-(4-benzyl-3-methylisoxazol-5-yloxy)acrylate 59a

Best yield: unisolable traces; ^{1}H NMR after elaboration shows peak compatible with this product mixed with by-products. MS presents a peak m/z = 288.1 $[M+H]^+$ compatible with this product

Ethyl 3-(3-methyl-4-phenylisoxazol-5-yloxy)acrylate 59b

Best yield: unisolable traces; ^{1}H NMR after elaboration shows peak compatible with this product mixed with by-products. MS presents a peak m/z = 274.1 $[M+H]^+$ compatible with this product.

REFERENCES

1. Schrödinger, An undulatory theory of the mechanics of atoms and molecules, Physical Review 1928, 1049-1070

2. *(a) Phan, et al., Adv. Synth. Catal.* ***2006****, 348, 609. (b) Buchwald et al., Adv. Synth. Catal.* ***2006****, 348, 23. (c) Cacchi et al. Chem. Rev.* ***2005****, 105, 2873. (d) Larock et al. Chem. Rev.* ***2004****, 104, 2285. (e) Handbook of organopalladium chemistry for organic synthesis, Negishi, E., Ed.; Wiley and Sons: New York,* ***2002****. (f) Tsuji, J. Palladium Reagents and Catalysts: New Perspectives for the 21st Century; Wiley and Sons: New York,* ***2003****. (g) Heck, R. F. Palladium Reagents in Organic Synthesis; Academic Press: New York,* ***1985****. (h) Li, J. J.; Gribble, G.W. Palladium in Heterocyclic Chemistry, Pergamon: New York* ***2000****.*

3. (a)*Beletskaya et al., A. V. Chem. Rev.* ***2000****, 100, 3009. (b) Handbook of organopalladium chemistry for organic synthesis, Negishi, E., Ed.; Wiley and Sons: New York,* ***2002****. (c) Tsuji, J. Palladium Reagents and Catalysts: Innovations in Organic Synthesis; Wiley and Sons: New York,* ***1995****. (d) Tsuji, J. Palladium Reagents and Catalysts: New Perspectives for the 21st Century; Wiley and Sons: New York,* ***2003****. (e) Palladium in Organic Synthesis, Tsuji, J., Ed.; Springer: Berlin,* ***2005****. (f) Heck, R. F. Palladium Reagents in Organic Synthesis; Academic Press: New York,* ***1985****. (g) Li, J. J.; Gribble, G.W. Palladium in Heterocyclic Chemistry, Pergamon: New York* ***2000****.*

4. (a) *J.J. Li, G.W. Gribble Palladium in Heterocyclic Chemistry: A Guide for the Synthetic Chemist, Pergamon: New York, 2000. (b) J.T. Link, Org. React.* ***2002****, 60, 157. (c) Zhang et al., Tetrahedron Lett.* ***2002****, 43, 8235. (d) Hughes et al., Tetrahedron.* ***2004****, 60, 9675.*

5. De Vries, *Dalton Trans.*, 2006, 421–429, Norrby et al., *Organometallics* **2006,** *25,* 2066-2073.

6. (a)*Li et al., Synlett* ***2008****, 949–957. (b) Alberico et al., M. Chem. Rev.* ***2007****, 107, 174–238. (c) Seregin et al., V. Chem. Soc. Rev.* ***2007****, 36, 1173–1193. (d) Campeau et al., K. Chem. Commun.* ***2006****, 1253–1264.*

7. (a)*Albrecht et al., J. Med. Chem.* ***2008****, 51, 2879–2882. (b) Wijtmans et al., J. P. J. Med. Chem.* ***2008****, 51, 2944–2953.*

8. (a)*Beccalli et al., Synthesis* ***2008****, 136–140. (b) Beccalli et al., Synthesis* ***2006****, 2404–2412. (c) Abbiati et al., Synthesis* ***2005****, 2881–2886. (d) Beccalli et al., Eur. J. Org. Chem.* ***2005****, 2091–2096.*

9. (a)*Wang et al., Org. Lett.* ***2008****, 10, 2923–2926. (b) Majumdar et al., Tetrahedron Lett.* ***2008****, 49, 1609–1612. (c) Turner et al., Angew. Chem., Int. Ed.* ***2007****, 46, 7996–8000. (d) Bellina et al., J. Org. Chem.* ***2007****, 72, 8543–8546. (e) Lane et al., J. Am. Chem. Soc.* ***2005****, 127, 8050–8057. (f) Parisien et al., J. Org. Chem.* ***2005****, 70, 7578–7584. (g) Bellina et al., J. Org. Chem.*

***2005**, 70, 3997–4005. (h) Park et al., VOrg. Lett. **2004**, 6, 1159–1162. (k) Glover et al., Org. Lett. **2003**, 5, 301–304. (j) McClure et al., Org. Lett. **2001**, 3, 1677–1680. (i) Okazawa et al., J. Am. Chem. Soc. **2002**, 124, 5286–5287. (l) Zhang et al., Tetrahedron Lett. **2002**, 43, 8235–8239. (m) Lavenot et al. J. Organomet. Chem. **1998**, 567, 49–55.*

10. (a)*Caronet al., Org. Lett. **2008**, 10, 4533–4536. (b) Bernini et al., Synthesis **2008**, 729–738. (c) Campeau et al., J. Am. Chem. Soc. **2004**, 126, 9186–9187. (d) Huang et al., J. Am. Chem. Soc. **2004**, 126, 7460–7461. (e) Campo et al., J. Am. Chem. Soc. **2003**, 125, 11504–11506.*

11. (a)*Zhuet al., J. Bioorg. Med. Chem. **2006**, 14, 3131–3143. (b) Hostyn et al., Tetrahedron **2005**, 61, 1571–1577. (c) Jonckers et al., Synlett **2003**, 615–618.*

12. (a*) Leclerc et al., Angew. Chem., Int. Ed. **2006**, 45, 7781–7786. (b) Campeau et al., J. Am. Chem. Soc. **2005**, 127, 18020–18021.*

13. *Hennings et al., J. Org. Chem. **1997**, 62, 2–3.)*

14. (a) *Bonnaterre et al., J. Org. Chem. **2008**, 4, 1–6. (b) Campeau et al., J. Am. Chem. Soc. **2006**, 128, 581–590.*

15. (a) *Alberico et al., Chem. Rev. 2007, 107, 174–238. (b) Lane et al., J. Am. Chem. Soc. 2005, 127, 8050. Park et al., Org. Lett. 2004, 6, 1159–1162.*

16. *Glover et al., Org. Lett. 2003, 5, 301–304.*

17. *(a) Goerlitzer et al., J. Pharmazie **2007**, 62, 15–26. (b) Ferraris et al., J. Med. Chem. **2003**, 46, 3138–3151. (c) Suresh et al., Asian J. Chem. **2003**, 15, 855–8591.*

18. *(a) Lafrance et al., J. Am. Chem. Soc. **2006**, 128, 8754–8756. (b) Mota et al., J. Am. Chem. Soc. **2005**, 127, 7171–7182. (c) Davies et al., J. Am. Chem. Soc. **2005**, 127, 13754–13755.*

19. *(a) Gorelsky et al., J. Am. Chem. Soc. **2008**, 130, 10848–10849. (b) Garcia-Cadrado et al., J. Am. Chem. Soc. **2007**, 129, 6880–6886. (c) Garcia-Cuadrado et al., J. Am. Chem. Soc. **2006**, 128, 1066–1067. (d) Lafrance et al., J. Am. Chem. Soc. **2006**, 128, 16496–16497.*

20. *(a) Schlummer et al., Adv. Synth.Catal. **2004**, 346, 1599. (b) D. B. Damon, R. W. Dugger, R. W. Scott, Int. Patent WO 2002088085A2, **2001**. (c) D.B. Damon, R. W. Dugger, R. W. Scott, Int. Patent WO 2002088069A2, **2001**. (d) Damon et al., Org. Process Res. Dev. **2006**, 10, 472. (e) Nakamura et al., Y. Chem. Rev. **2004**, 104, 2127.*

21. *Buchwald et al., J. Am. Chem. Soc. **1998**,120, 9722.*

22. *Sarka et al., Synlett **2005**, No. 8, 1275–127817.05.205.*

23. *Buchwald, Hartwig, J. Am. Chem. Soc. **2006**, 128, 3584-3591.*

24. (a) Beccalli et al., Synlett **2006**. (b) Beccalli et al., Tet **2005**. (c) Beccalli et al., Org. Lett. **2009**)

25. *(a) Boger et al., J. A. Chem. Rev. **1997**, 97, 787. (b) Horton et al., Chem. Rev. **2003**, 103, 893. (c) Sunazuka et al., III J. Am. Chem. Soc. **2000**, 122, 2122. (d) Gan et al., Angew.*

Chem., Int. Ed. ***2005****, 44, 1366. (e) Dounay et al., J. Am. Chem. Soc.* ***2005****, 127, 10186. (f) Nicolaou et al., Angew. Chem., Int. Ed.* ***2003****, 42, 1753. (g) Gueritte, F.; Fahy, J. In Anticancer Agents from Natural Products. (h) Cragg, G. M., Kingston, D. G. I., Newman, D. J., Eds.CRC Press: Boca Raton,* ***2005****, pp 123– 135. (i) Dewick, P. M. Medicinal Natural Products. A Biosynthetic Approach, 2nd ed., John Wiley and Sons, Ltd: New York,* ***2002****. (l) Bromidge et al., J. Med. Chem.* ***1997****, 40, 3494. (m) Hobson et al., J. Org. Process Res. Dev.* ***2007****, 11, 985. (n) Somei et al., Nat. Prod. Rep.* ***2004****, 21, 278. (o) Xiang et al., Phytochemistry 66,* ***2005,*** *2595–2601.*

26. *(a) Mino et al., Tetrahedron: Asymmetry* ***2008****, 19, 2711. (b) Andersson et al., Tetrahedron: Asymmetry* ***2006****, 17, 1952* and references cited therein.

27. *(a)J. Am. Chem. Soc.* ***2008****, 130, 17195-17203. (b) An. Bioan. Chem.* ***2005****, 382, 259-268). (c) Angew. Chem. Int. Ed.* ***2008****, 47, 1923. (d) Solar Energy Materials & Solar Cells 93,* ***2009****, 1143–1148.*

28. Urgaonkar et al., *J. Org. Chem.* **2004**, *69*, 9135-9142.

29. *(a) Anastas et al., Green Chemistry: Theory and Practice, Oxford University Press, Oxford, UK,* ***1998****. (b) Winterton, Green Chem.,* ***2001****, 3, G73–G75. (c) Anastas et al., Environ. Sci.Technol.,* ***2003****, 37, 94A–101A. (d) Tang et al., Green Chem.,* ***2005****, 7, 761–762. (e) Tundo et al., Methods and Reagents For Green Chemistry, John Wiley & Sons, Oxford, UK,* ***2007****.*

30. *(a) Metzger, Angew. Chem., Int. Ed.,* ***1998****, 37, 2975 and Angew. Chem.,* ***1998****, 110, 3145–3148). (b) Varma, Green Chem.,* ***1999****, 1, 43. (c) Tanaka et al., Chem. Rev.,* ***2000****, 100, 1025. (d) Garay et al., Chem. Soc. Rev.,* ***2007****, 36, 846. (e) Rodr´ıguez et al., Adv. Synth. Catal.,* ***2007****, 349, 2213. (f) Tanaka et al., Solvent-Free Organic Synthesis, Wiley-VCH, Weinheim,* ***2009****. (g) Kaupp, CrystEngComm,* ***2009****,* ***11****, 388–403.*

31. Gronnow *et al., Org. Process Res. Dev.,* ***2005****, 9, 516.*

32. *(a) Lundgren et al., Eur. J. Org. Chem.* ***2010****, 16, 1963. (b) Buchwald et al., J. Am. Chem. Soc.* ***2003****, 66530.*

33. *(a) D. J. Greenblatt, R. I. Shader, in: Benzodiazepines in Clinical Practice, Raven Press, New York,* ***1974****. (b) Benzodiazepines divided: A Multidisciplinary Review (Ed.: M. Trimble), Wiley, New York,* ***1983****. (c) Evans et al., J. Med. Chem.* ***1988****, 31, 2235–2246. (d) Bock et al., J. Med. Chem.* ***1989****, 32, 13–16. (e) A. Walser, R. I. Fryer, in: Bicyclic Diazepines, Wiley, New York,* ***1991****, chapter VII. (f) Thurston et al., Chem. Rev.* ***1994****, 94, 433–465. (g) Patchett et al., Annu. Rep. Med. Chem.* ***2000****, 35, 289–298.*

34. *(a) A. A. Santilli, T. S. Osdene, U.S. Patent 3336330,* ***1967*** *[Chem. Abstr.* ***1967****, 68, 21972]. (b) A. A. Santilli, T. S. Osdene, U.S. Patent 3457258,* ***1969*** *[Chem. Abstr.* ***1969****, 71, 101898]. (c) Meguro et al., Tetrahedron Lett.* ***1970****, 11, 4039–4042. (d) Hester et al., J. Med. Chem.*

***1971**, 14, 1078–1081. (e) J. B. Hester, U.S. Patent 3896109, **1975** [Chem. Abstr. **1975**, 84, 17440]. (f) Kaneko et al., J. Med. Chem. **1985**, 28, 388– 392. (g) Mohiuddin et al., Heterocycles **1986**, 24, 3489–3530. (h) Keenan et al., J. Med. Chem. **1999**, 42, 545–559. (i) Osman et al., Ind. J. Chem. Sect. B **2002**, 41, 871–874.*

35. *(a) Frostl et al., Pharmacopsych. **1989**, 22, 54–101. (b) Broggini et al., Tetrahedron **1999**; 55, 14803–14806. (c) Broggini et al., Org. Prep. Proced. Int. **2003**, 35, 609–612.*

36. *(a) Hanze et al., J. Med. Chem **1963**, 6, 767–771 (b) Hunziker et al., Arzneim.Forsch. **1963**, 13, 324–328. (c) Waldvogel et al., Helv.Chim. Acta **1976**, 59, 866–877.*

37. *3 (a) Eguchi et al., J. Org. Chem. **1995**, 60, 4006–4012. (b) Molina et al., Tetrahedron **1995**, 51, 5617–5630. (c) Kamal et al., Tetrahedron **1997**, 53, 3223–3230. (d) Kraus et al., Tetrahedron **1998**, 54, 11749–11754. (e) Kamal et al., Bioorg. Med. Chem. Lett. **2000**, 10, 2311–2313. (f) Zhou et al., J. Am. Chem. Soc. **2001**, 123, 4865–4866. (i) O'Neil et al., Tetrahedron Lett. **2003**, 44, 7809–7812.*

38. *Tardibono et al., Org. Lett. **2009**, 11, 1575–1578.*

39. *Katsifis et al., Aust. J. Chem. **1999**, 52, 1061–1070.*

40. *(For examples concerning pyrimidine-fused benzodiazepines, see: Zheng et al., J. Comb. Chem. **2006**, 8, 381–387. For examples of azolic-fused benzodiazepines, see: Gerecke et al., Heterocycles **1994**, 39, 693– 721. For examples of carbocyclic-fused benzodiazepines, see: Tóth et al., Liebigs Ann. Chem. **1992**, 803–807).*

41. (*a) Tiberghien et al., Bioorg. Med. Chem. Lett. **2008**, 18, 2073–2077. (b) Kamal et al., Adv. Synth. Catal. **2006**, 348, 249–254. (c) Philipova et al., Helv. Chim. Acta **2005**, 88, 1711–1733. (d) Chen et al., Bioorg. Med. Chem. Lett. **2004**, 14, 1547–1549. (e) Masterson et al., Bioorg. Med. Chem. Lett. **2004**, 14, 901–904. (f) Kang et al., Chem. Commun. **2003**, 1688–1689.*

42. *(a) Kamal et al., Bioorg. Med. Chem. Lett. **2008**, 18, 3769–3773. (b) Kamal et al., Bioorg. Med. Chem. Lett. **2008**, 18, 2594–2598. (c) Lee et al., Chem. Commun. **2007**, 3714–3716.*

43. (*a) Hemming et al., Tetrahedron **2004**, 60, 3349–3357. (b) Kaneko et al., J. Med. Chem. **1985**, 28, 388–392. (c) Miyamoto et al., J. Antibiot.**1977**, 30, 340–343. (d) Weber et al., Arch. Pharm. **1969**, 302, 584–590.*

44. *(a) Broggini et al., Synthesis **1995**, 647–648. (b) Akritopoulou-Zanze et al., Tetrahedron Lett. **2004**, 45, 8439–8441. (c) Beccalli et al., Tetrahedron: Asymmetry **2004**, 15, 687–692.*

45. (*a) Molteni et al., Tetrahedron: Asymmetry **2002**, 13, 2491–2495. (b) Broggini et al., Tetrahedron: Asymmetry **1999**, 10, 2203–2212. (c) Broggini et al., Synthesis **2005**, 2246–2252*

46. *(a) Anwar et al., Tetrahedron Lett. **2000**, 41, 10107–10110. (b) Sugimori et al., Tetrahedron **1998**, 54, 7997–8008. (c) Eguchi et al., Synlett **1992**, 295–297.*

47. *White et al., Tetrahedron **1970**, 26, 233–242*

48. *(a) Banfi et al., J. Org. Chem. **2007**, 72, 2151–2160. (b) Kraus et al., Tetrahedron Lett. **1995**, 36, 7595–7598*

49. *Stroganova et al., Synlett **2007**, 7, 1106–1109*

50. *Beccalli et al., J. Org. Chem. **2004**, 69, 5627–5630. (c) Beccalli et al., Tetrahedron **2005**, 61, 61–68.*

51. *Julia et al., Chim. Therapeutica **1970**, 5, 343–346.*

52. (*a) Broggini et al., Tetrahedron Lett. **2009**, 50, 1447–1449. (b) Beccalli et al., Org. Lett. **2009**, 11, 1563–1566. (c) Manzo et al., Tetrahedron Lett. **2009**, 50, 4696–4699*

53. *(a) Broggini et al., Gazz. Chim. Ital. **1996**, 126, 479–488. (b) Broggini et al., Heterocycles **2003**, 59, 823–858. (c) Broggini et al., J. Org. Chem. **1994**, 59, 8271–8274. (d) Beccalli et al., J. Org. Chem. **2000**, 65, 8924–8932. (e) Beccalli et al., Org. Lett. **2006**, 8, 4521–4524. (f) Borsini et al., Eur. J. Org. Chem. **2008**, 2808–2816.*

54. *(a) Shawali, Chem. Rev. **1993**, 93, 2731–2777. (b) Broggini et al., Heterocycles **1998**, 47, 541–557. (c) Benelbaghdadi et al., Synth. Commun. **1998**, 28, 4221–4232. (d) Broggini et al., Tetrahedron: Asymmetry **1999**, 10, 4447–4454. (e) Aatif et al., Synth. Commun. **2000**, 30, 2647–2659. (f) Broggini et al., Tetrahedron: Asymmetry **1999**, 10, 487–492. (g) Broggini et al., Tetrahedron: Asymmetry **2000**, 11, 1975–1983. (h) Molteni et al., Heterocycles **2005**, 65, 2513–2537. (i) Shawali et al., ARKIVOC **2006**, 292–365.*

55. *Phillips, Org. React. **1959**, 10, 143–178.*

56. Bader, R. F. W. *Atoms in Molecules: A Quantum Theory*; Oxford University Press: New York, **1990**

57. *(a) Pakiari et al. Journal of Molecular Structure: THEOCHEM, **2006** 51–60. J. Chem. Theory Comput. **2006,** 2, 1220-1227 (b) Hall et al. **J**. AM. CHEM. SOC. **2007**, 129, 12068-12069 (c) Yu et al. Chem. Eur. J. **2008**, 14, 4361 – 4373.*

58. *Ponti et al., Chem. Commun., **2006**, 1030.*

59. *(a) J. Org. Chem., Vol. 66, No. 15, **2001**. (b) Tetrahedron: Asymmetry 19, **2008**, 1381–1384.*

60. (Beccalli et al. *J. Org. Chem.* **2003**, *68*, 7625-7628, Beccalli et al. *Chem. Rev.*, **2007**, *107* (11), 5318–5365).

61. Marchesini et al. J.Het.Chem. **1980**, 763.

62. *(a)Hashmi et al. Applied Catalysis A: General 291 (**2005**) 238–246 (b) Krause et al. Org.Biomol.Chem.,2005,**3**,387–391 (c) He et al., J. Organometallic Chem. 690 (**2005**) 5049–5054.*

63. Lipshutz, et al., *Org. Lett.*, **2008**, *10* (19), 4279–4282.

64. Murai et al., *J. Org. Chem.* **2002**, *67*, 7557-7560.

65. *Murai et al. J. Am. Chem. Soc., **2001**, 123 (44), 10935–10941.*

66. *Beller et al., Angew. Chem. Int. Ed. 1998, 37, 3389.*