Università degli Studi di Firenze

DOTTORATO DI RICERCA IN SCIENZE CHIMICHE

SETTORE DISCIPLINARE CHIMICA ORGANICA CHIM/06

XXIII CICLO

PYRIDYL CARBINOLS AS MULTIPURPOSE REAGENTS IN ORGANIC CHEMISTRY: FROM NEW CARBON NUCLEOPHILIC SUBSTITUTIONS TO INNOVATIVE BIOMIMETIC APPLICATIONS

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2008 - 2010

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Chapter I

GENERAL INTRODUCTION

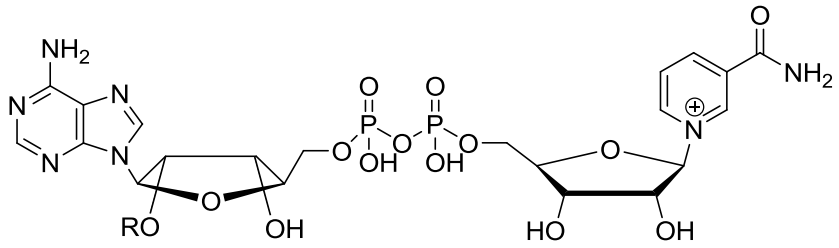
Many organic compounds contain ring systems.[1] If the ring is made up of atoms of carbon and at least one other element, the compound can be classed as heterocyclic. The elements that occur most commonly with carbon in ring systems are nitrogen, oxygen and sulphur. Heterocyclic compounds have a wide range of applications: they are predominant among the types of compounds used as pharmaceutical, agrochemical and as veterinary products. They are also widely distributed in nature. Many are of fundamental importance to living systems: in many cases an heterocyclic compound is the key component in a biological process. For example nucleic acid bases are derivatives of the pyrimidine and purine ring systems. Chlorophyll and heme contain the porphyrin ring. Essential diet ingredients such as vitamins (thiamin, riboflavin, pyridoxol, nicotinamide and ascorbic acid) are heterocycles. On this basis, it is not surprising that a great deal of current research work is concerned with the methods of synthesis and properties of heterocyclic compounds. One of the reasons for the widespread use of heterocycles as synthetic intermediates is their easy manipulation to achieve other functionalities.

[1] Gilchrist, T. L. *Heterocyclic chemistry*, 2nd ed, Longman: Harlow, UK, 1992, p.1, 122.

In the light of the enormous interest associated to heterocyclic systems, we decided to focus our attention on azaheterocycles and in particular on systems in which the reactivity is associated to the presence of a pyridine ring.

1.1. PYRIDINE AND ITS DERIVATIVES

Pyridine is a six-membered fully unsaturated heterocycle formally related to benzene where one of the carbon is replaced by a nitrogen atom, without altering the character of the π-orbitals. Like benzene, pyridine is planar. This compound and several methyl- and ethylpyridines are available on a large scale from the carbonization of coal. The three methylpyridines (formerly called picolines) are all obtained from coal tar and can be manufactured by ring synthesis. These pyridine derivatives show a peculiar reactivity. Moreover, pyridine ring is a component of the structure of important coenzymes, such as nicotinamide adenine dinucleotide (NAD^+) and its phosphate ($NADP^+$) (Figure 1.1), involved into biochemical redox process (see Chapter 3).



R = H (NADH)
R = **P**, (NADPH)

Figure 1.1. *Chemical structures of NADH/NADPH.*

Experimental data evidence that pyridine is an aromatic molecule, with a resonance energy comparable with that of benzene. Its chemistry resembles that of benzene in some respects, although there are many important differences which are due to the presence of the ring nitrogen atom. This observation is at the base of the discovery of new reactions of heterocyclic systems as 1-(2-pyridyl)-2-propen-1-ol (**1**), phenyl(2-

pyridyl)methanol (**2**) and phenyl(2-quinolyl)methanol (**3**), investigated during this thesis work and described in the following chapters (Figure1.2).

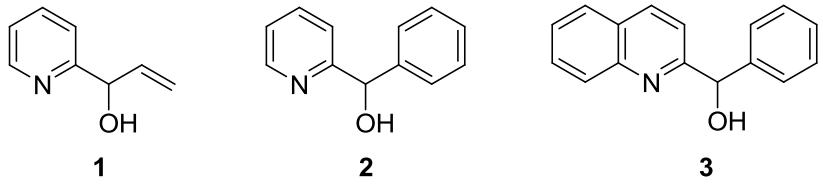
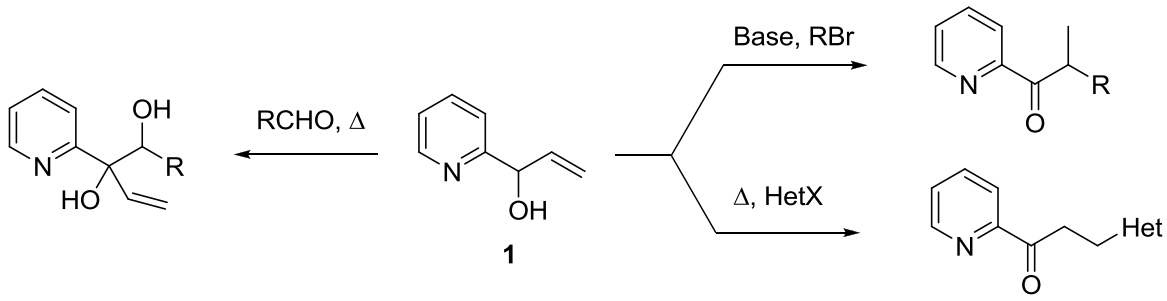


Figure 1.2. *Pyridyl carbinols **1**, **2** and **3**.*

The thesis develops along the three following main chapters:

1. New reactivity of hydroxyallylpyridyl derivatives as carbon nucleophiles.

Hydroxyallylpyridyl derivative **1**, likely due to the weak acidity of the 'picoline type' hydrogen atom, behaves regioselectively as C-1, C-2 and C-3 carbon nucleophile depending on the thermal or base promoted experimental conditions and on the kind of electrophile (Scheme 1.1).



Scheme 1.1. *Hydroxyallylpyridyl derivatives as carbon nucleophiles.*

2. (2-Pyridyl)phenyl methanols as a new class of hydrogen donors in metal free reductions.

Pyridyl carbinols **1**, **2** and **3** show an unprecedented and unexpected reactivity, similar to that of Hantzsch ester (HEH, Figure 1.3) as 1,4-dihydropyridine mimics for the metal free reduction of different functional groups.

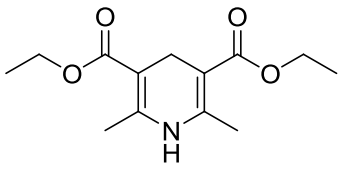
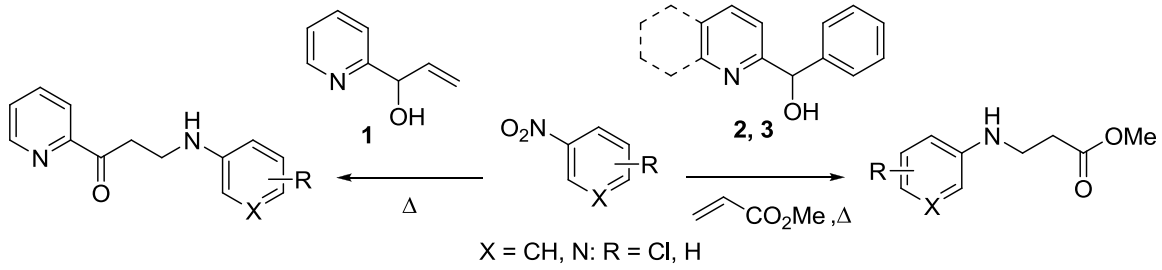


Figure 1.3. *Chemical structure of Hantzsch ester.*

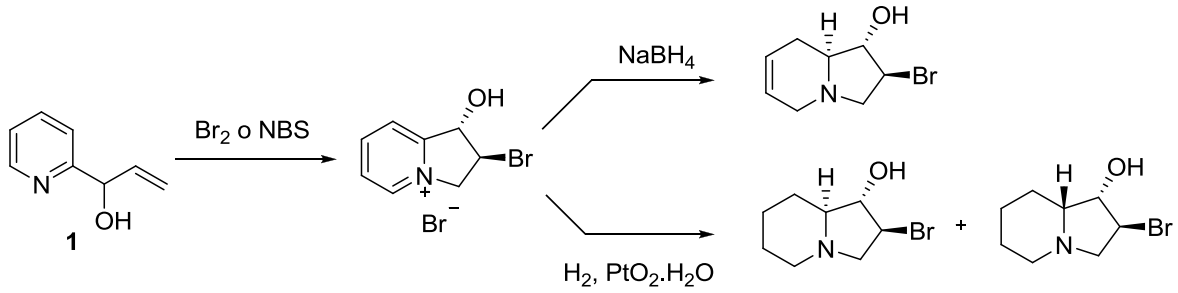
For example they are able to reduce the nitro group of aromatic and heteroaromatic nitro compounds to the corresponding amino function (Scheme 1.2).



Scheme 1.2. *Carbinols **1**, **2** and **3** as a new class of reducing agents.*

3. Synthesis of new indolizidine derivatives from 1-(2-pyridyl)-2-propen-1-ol (1).

In the last years, the enormous interest towards the treatment of many diseases as diabetes, viral infections, tumour metastasis and genetic disorders has determined an increasing interest and demand for naturally occurring polyhydroxylated indolizidines and their nonnatural analogues. Starting from 1-(2-pyridyl)-2-propen-1-ol (**1**), a new easy and general synthetic methodology for the synthesis of functionalized indolizidines has been developed (Scheme 1.3).



Scheme 1.3. *Synthesis of the indolizidine nucleus starting from carbinol **1**.*

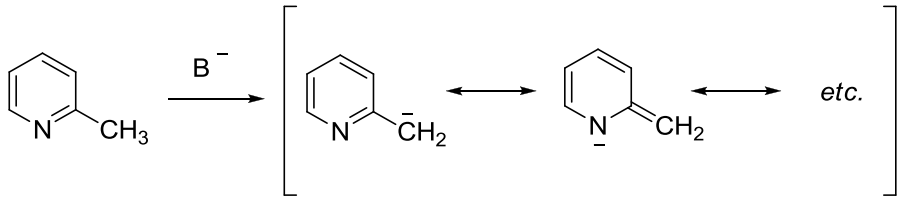
The highly diastereoselective electrophilic bromine addition on the double bond of the allyl moiety of **1** afforded almost quantitatively the bicyclic indolizinium salt. Its partial and total reductions allowed to isolate the corresponding bromohydroxyindolizidines derivatives. The presence of the bromo substituent, as well as the double bond, opens the way to the synthesis of polyfunctionalized indolizidines variously substituted in the five- and six-membered rings.

Chapter II

NEW REACTIVITY OF HYDROXYALLYLPYRIDYL DERIVATIVES AS CARBON NUCLEOPHILES

2.1. INTRODUCTION

Alkyl groups at α- and γ-positions of the pyridine ring are significantly more reactive than alkyl groups attached to a benzene ring, particularly in base-catalyzed processes involving deprotonation of the alkyl substituent. This is because the corresponding carbanion is stabilized by charge delocalization on the ring, and, in particular, on the electronegative nitrogen atom (Scheme 2.1).



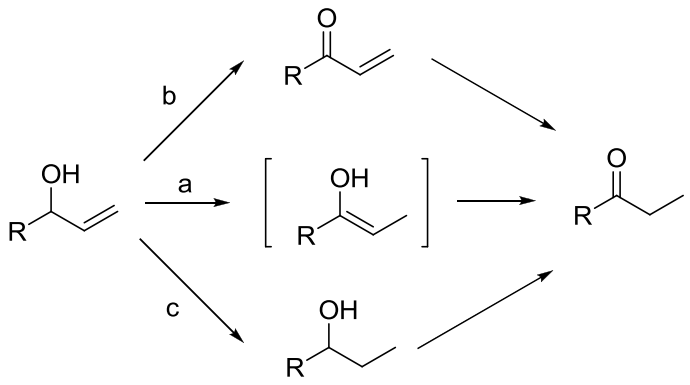
Scheme 2.1. *Negative charge delocalization in the picoline carbanion.*

As a consequence, treatment of α- and γ-alkylpyridines with strong bases, such as sodium amide in liquid ammonia or organolithiums, results in an essentially quantitative deprotonation affording stabilized carbanions, as a result of charge delocalization on the ring nitrogen. These intermediates are able to react with a wide range of electrophiles, such as alkyl halides and tosylates, acyl halides, carbon dioxide, aldehydes, ketones, etc., in a large array of different reactions.[2]

Moreover, the isomerization of allyl alcohols to the corresponding saturated carbonyl compounds is a very attractive synthetic approach. Adjustment of oxidation level by internal reorganization, represents a highly efficient synthetic protocol. Double-bond isomerization, a process promoted by many transition metals, constitutes the equivalent of internal reduction-oxidation. In those cases where such isomerizations concern olefins with hydroxyl groups, irreversible tautomerization to ketones can occur as a disproportion between an alcohol and an olefin (Scheme 2.2, *via* a). Rearranging the oxidation levels in such a manner represents a more atom economical approach to redox chemistry, with respect to processes which involve sequential oxidation and reduction (*via* b) or vice versa (*via* c).[3]

[2] (a) Uff, B. C. In *Comprehensive Heterocyclic Chemistry*; Boulton, A., McKillop, A., Eds.; Pergamon: Oxford, UK, 1984; Vol. 2, pp 329; (b) Dennis, N. In *Comprehensive Heterocyclic Chemistry II*; McKillop, A., Eds.; Pergamon: Oxford, UK, 1996; Vol. 5, pp 101.

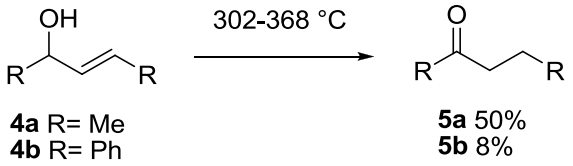
[3] (a) Trost, B. M.; Kulawiec, R. J. *J. Am. Chem.* Soc. **1993**, *115*, 2027; (b) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695.



Scheme 2.2. *Isomerization processes of allyl alcohols.*

The above rearrangement has been mainly and efficiently performed under catalysis of transition-metal complexes.[4] Both heterogeneous and homogeneous catalysts have been used, but the second ones generally offer a higher reaction rate and improved selectivities.

To our knowledge, only one example of thermal isomerization of allyl alcohols to saturated ketones has been reported in the literature.[5] The two systems chosen for the above study were *trans*-1,3-dimethyl- and *trans*-1,3-diphenylprop-2-en-1-ol (**4a**,**b**, Scheme 2.3).

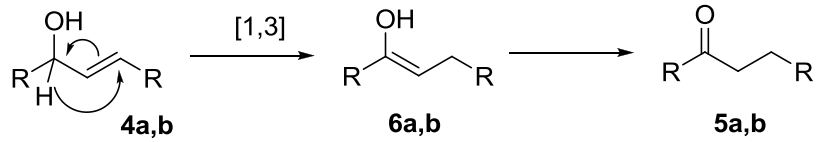


Scheme 2.3. *Thermal rearrangement of allyl alcohols*

The two alcohols, when heated in a sealed tube at 368 and 302 °C, gave the corresponding saturated ketones in 50 and 8% yields, respectively. The isomerization of allyl alcohols **4a,b** likely involves [1,3] hydrogen shift to enols **6a,b**, easly converted into the more stable ketone tautomers **5a,b** (Scheme 2.4).

[4] For reviews on metal catalysed isomerisation of allyl alcohols, see: (a) Van der Drift, R. C.; Bouwman, E.; Drent, E. *J. Organomet. Chem.* **2002**, *650*, 1; (b) Bellemin-Laponnaz, S.; Le Ny, J.-P. *C. R. Chimie* **2002**, *5*, 217; (c) Uma, R.; Crévisy, C.; Grée, R. *Chem. Rev.* **2003**, *103*, 27.

[5] Andrist, A.H.; Silvon, L. E.; Graas, J.E. *J. Org. Chem.*, **1978**, *43*, 634.



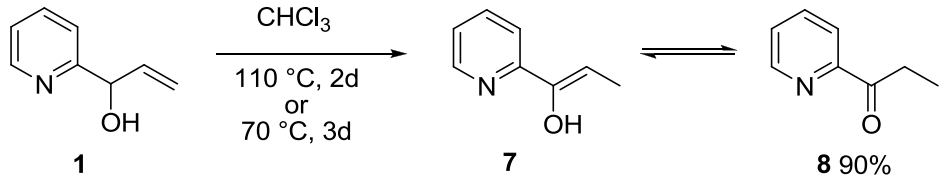
Scheme 2.4. *Proposed isomerization mechanism for allyl alcohols **4a,b**.*

On this ground and in the light of preliminary data,[6] we decided to gain better insight into the thermal insomerisation of 1-(2-pyridyl)-2-propen-1-ol (**1**),[7] as well as the *O*-protected derivatives **1a**,[8] **1b** and **1c**.[9]

2.2. THERMAL BEHAVIOUR OF ALLYL DERIVATIVES 1, 1a-c

2.2.1. RESULTS AND DISCUSSION

When a solution of **1** in chloroform was heated at 110 °C in a sealed tube for two days, complete disappearance of the starting material was observed, with the concurrent formation of 2-propionylpyridine (**8**)[10] in 90% yield. The same conversion was also evidenced by heating at 70 °C for three days (Scheme 2.5).

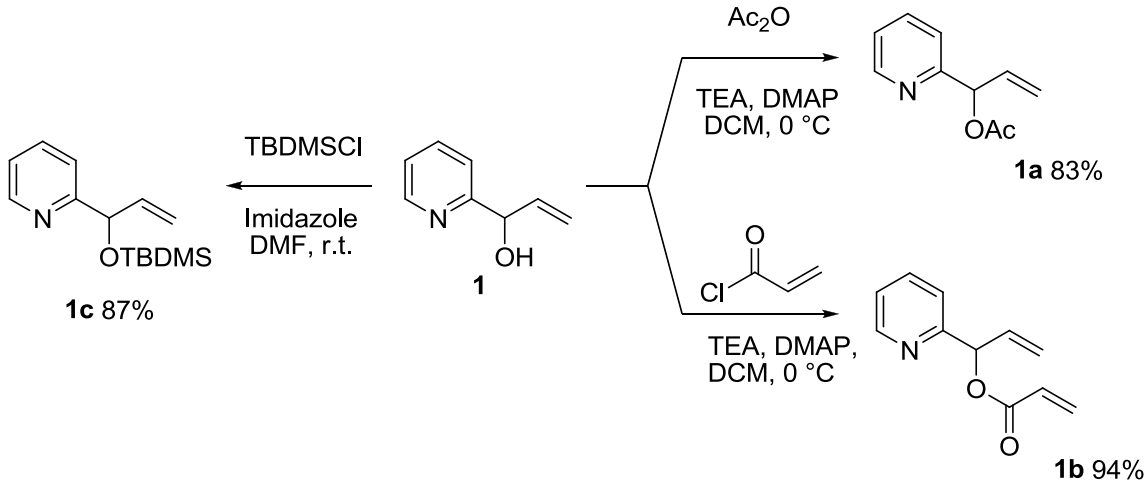


Scheme 2.5. *Thermal isomerization of alcohol **1**.*

In contrast, the acetyl derivative **1a**, the *tert*-butyldimethylsilyl ether **1c** and the new acryloyl derivative **1b** proved to be more stable. While **1c** was synthesized according to the Uenishi procedure,[9] **1a** and **1b** were prepared in 85% and 94% yields by treatment of the alcohol **1** with acetic anhydride and acryloyl chloride, respectively, in the

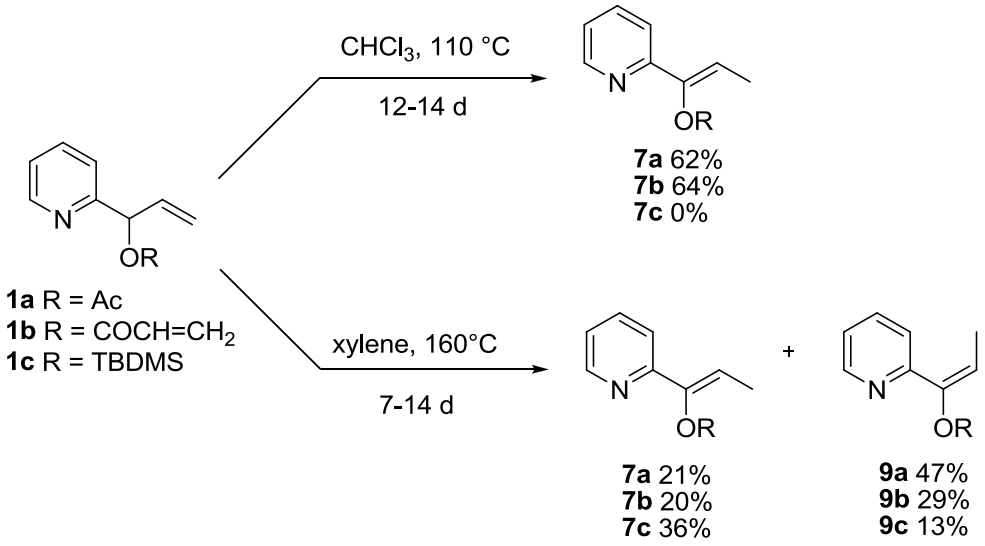
[6] Giomi, D.; Piacenti, M.; Brandi, A. *Tetrahedron Lett.* **2004**, *45*, 2113.
[7] Uenishi, J.; Hiraoka, T.; Hata, S.; Nishiwaki, K.; Yonemitsu, O. *J. Org. Chem.* **1998**, *63*, 2481.
[8] For enantiopure synthesis of **1a** in enantiopure form, see Ref. 7.
[9] Uenishi, J.; Hiraoka, T.; Yuyama, K.; Yonemitsu, O. *Heterocycles* **2000**, *52*, 719.
[10] Sato, N.; Marita, N. *Synthesis* **2001**, 1551.

presence of triethylamine and a catalytic amount of 4-dimethylaminopyridine at 0 °C (Scheme 2.6).



Scheme 2.6. *Synthesis of protected allyl alcohols **1a-c**.*

When **1a** was heated at 110 °C in a sealed tube for 12 days, the vinyl acetate **7a** was obtained in 62% yield. On the other hand, by heating **1a** in xylene at 160 °C for 14 days the diastereomeric vinyl acetates **7a** and **9a** were isolated in 21% and 47% yields, respectively (Scheme 2.7).



Scheme 2.7. *Thermal isomerization of compounds **1a-c**.*

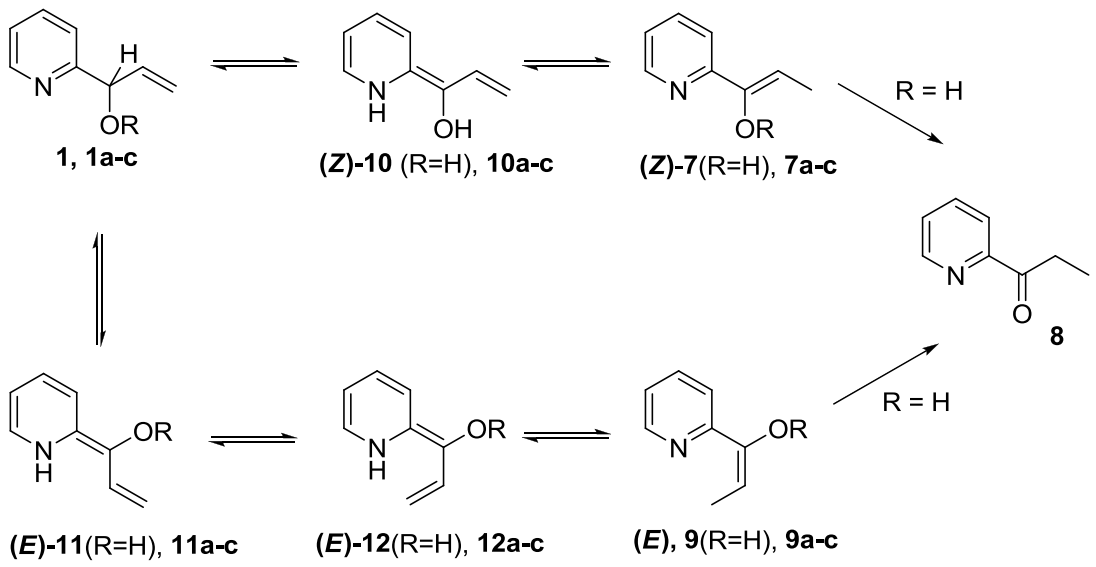
Compound **7a** was recovered completely unchanged after heating in xylene at 160 °C, ruling out the possibility of its thermal isomerization into **9a**. Therefore their formation derives directly from **1a** in the isomerization process. The *tert*-butyldimethylsilyl ether **1c** appeared perfectly stable in chloroform at 110 °C for weeks and only after 10 days at 160 °C in xylene it was partially converted (ca. 66%, ^{1}H-NMR) into **7c** and **9c**, isolated by flash column chromatography in 36% and 13% yields, respectively.[11] As observed for **1a**, when the acryloyl derivative **1b** was heated at 110 °C in chloroform in a sealed tube for 14 days only compound **7b** was recovered in 20% yield whereas, operating in xylene at 160 °C for 7 days, the two diastereomers **7b** and **9b** were isolated respectively in 20% and 29% yields. As compound **7a**, also the (*Z*)-isomers **7b,c** resulted completely stable in xylene at 160 °C.

The structures of (*Z*)- and (*E*)-diastereisomers were easily assigned on the basis of NOESY-1D experiments; moreover the quartet of the H-2 proton (J = 7.1 Hz and 7.4-7.5 Hz, respectively) appears at higher frequencies in diastereomers **7a-c** (δ 5.98-6.63) with respect to **9a-c** (δ 5.29-5.80), likely due to the anisotropy of the pyridine ring.

2.2.2. MECHANISTIC HYPOTESIS

A mechanistic rationale of the above results could be proposed taking into account the weak acidity of the 'picoline-type' hydrogen atom on the C-1 carbon of the allyl residue of compounds **1** and **1a-c**. A 1,3-hydrogen shift can give rise to the fully conjugate diastereomeric enamines (*Z*)-**10** and (*E*)-**11**. While **10** could evolve into the (*Z*)-enol derivatives **7** and ketone **8** (coming from the corresponding enol form) by simple intermolecular proton transfer, **11** could give rise to the (*E*)-isomers **9**, as well as compound **8**, through a [1,5] sigmatropic hydrogen shift involving the higher energy *s-cis* conformers (*E*)-**12** (Scheme 2.8).

[11] The reported yields were determined on the basis of the recovered starting material.



Scheme 2.8. *Proposed mechanism for thermal isomerization of **1** and **1a-c**.*

The mechanistic assumption allowed to explain the experimental results. While the enol forms coming from the free alcohol **1**, immediately evolve into pyridyl ketone **8**, the protected alcohols **1a-c** afford different enol derivatives **7a-c** and **9a-c**, depending on the reaction conditions and, consequently, on the inter- or intramolecular operating mechanism. In particular, as the intramolecular sigmatropic hydrogen shift leading to the diastereoisomers **9a-c** requires a higher temperature, the exclusive formation of **7a** and **7b** at lower temperature is fully justified. The higher reactivity of **1** with respect to **1a-c** could be likely ascribed to the contribution of an intramolecular hydrogen bond between the OH and the ring nitrogen, which could favor the initial proton abstraction by stabilization of the tautomers of type **10** (Figure 2.1).

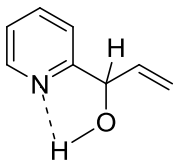


Figure 2.1. *Intramolecular hydrogen bond in alcohol **1**.*

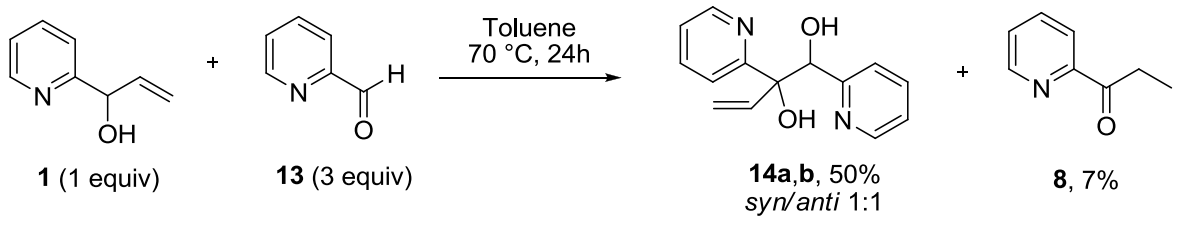
Moreover, the poor reactivity of **1c** with respect to **1a** and **1b** could be justified by the presence of the strongly electron donating silyl ether group, which should reduce the acidity of the methane proton being unable to stabilize a vicinal negative charge.
On the basis of this new reactivity of **1** and **1a-c**, and their behavior as enamines or, even vinilogous enamines, as evidenced in the tautomers of type **10**, we decided to investigate their reactions towards different electrophiles.[12]

2.3. REACTIVITY OF 1-(2-PYRIDYL)-2-PROPEN-1-OL (1) TOWARDS DIFFERENT NUCLEOPHILES

The studies were focused on alcohol **1** because, under neutral thermal conditions, the less reactive oxygen-protected derivatives **1a-1c** required long reaction times and drastic conditions leading to complex reaction mixtures.

2.3.1. REACTIVITY AS C-1 CARBON NUCLEOPHILE

Alcohol **1** reacted in a sealed tube with an excess (3 equiv) of 2-pyridinecarboxaldehyde (**13**) in dry toluene at 110 °C for 24 h, giving an almost 1:1 mixture of the diastereomeric diols **14a**,**b**, isolated in 50% yield, along with a minor amount of pyridyl ketone **8** (Scheme 2.9).[13]



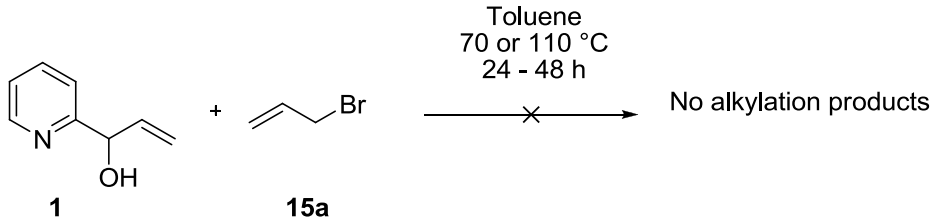
Scheme 2.9. *Reaction of **1** with 2-pyridinecarboxaldehyde (**13**).*

[12] Giomi, D.; Piacenti, M.; Alfini, R.; Brandi, A. *Tetrahedron* **2009**, *65*, 7048.
[13] Ketone **8** (a volatile liquid, 50 °C/4 Torr, see Ref. 10), was sometimes lost upon evaporation to dryness under reduced pressure.

The vicinal diols **14a**,**b** are the products of an aldol reaction occurring through nucleophilic attack of the C-1 carbon atom of the allyl residue of **1** (via enamine tautomers **10** and **11** shown in Scheme 2.8) on the carbonyl group of **13**. The stability of the diols, not undergoing H_2O elimination, could be likely due to intramolecular hydrogen bonds between the OH groups and the pyridine rings nitrogen atoms. Anyway the enamine reactivity in aldol type reaction seems to be limited to activated aromatic aldehydes. In fact, alcohol **1** was totally inert towards benzaldehyde and furaldehyde at 110 °C in toluene or chloroform as solvents.

2.3.2. REACTIVITY AS C-2 CARBON NUCLEOPHILE

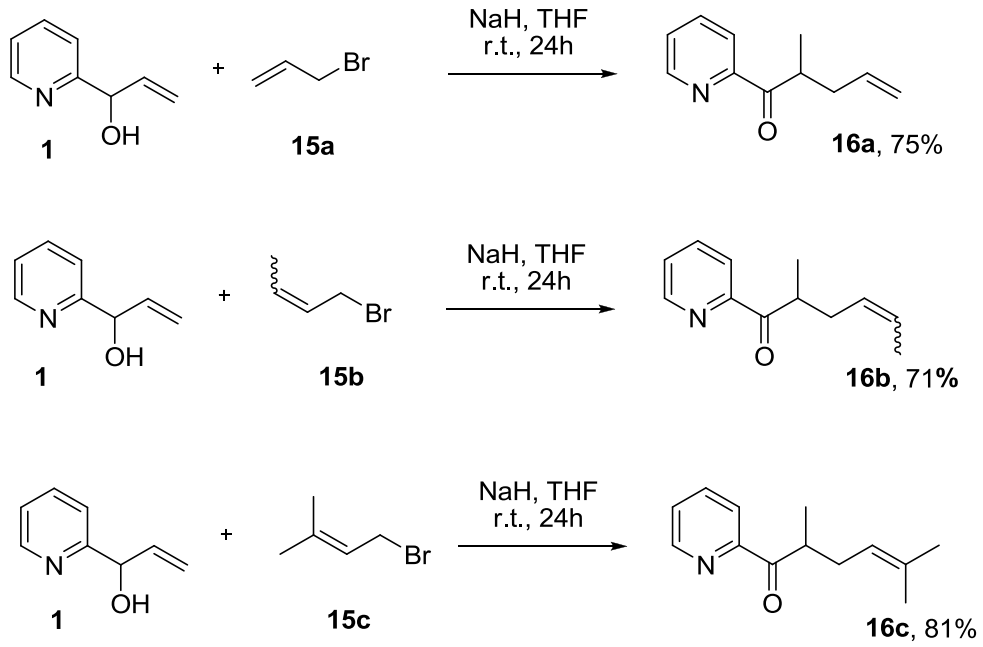
Switching to study the alkylation with halides, the thermal reaction of **1** with an excess of allyl bromide **15a** in dry toluene at 70 °C or 110 °C for 24-48 h led to the exclusive formation of ketone **8** (Scheme 2.10).



Scheme 2.10. *Thermal reaction of compound **1** with allyl bromide **15a**.*

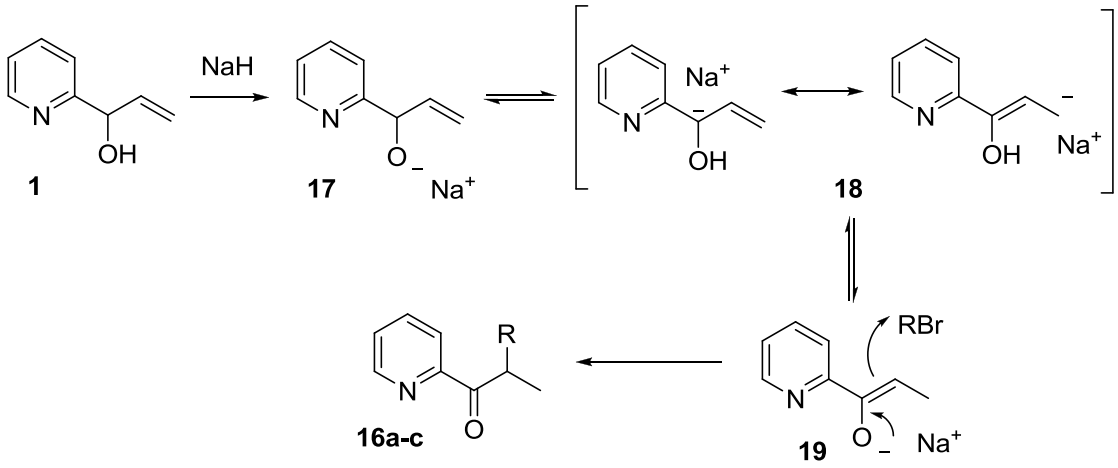
Nevertheless, operating in the presence of bases, alkylation products were obtained. By treatment with an equivalent amount of sodium hydride at room temperature in THF, **1** reacted with allyl bromide **15a-c** in 24 h to give compounds **16a-c**[14] in 75%,[15] 71% and 81% yields, respectively. These products resulted from the nucleophilic attack of the C-2 carbon of the allyl moiety of **1** on the bromide (Scheme 2.11).

[14] Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 17180.
[15] The reported yield was determined on the basis of the recovered starting material.



Scheme 2.11. *Reactions of **1** with allyl bromides.*

In such reaction conditions, operating at room temperature, the formation of ketone **8** was almost completely avoided allowing the isolation of the substitution products in satisfactory yields. A reasonable mechanistic hypothesis could involve the formation of the enolate **19** as reactive species from the deprotonated alcohol **17**, via the mesomeric allyl anions **18** (Scheme 2.12).



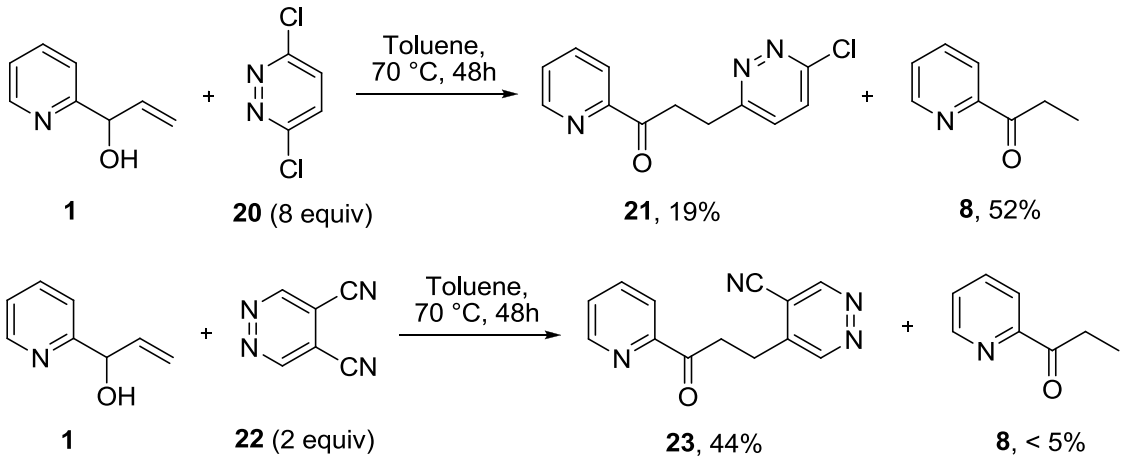
Scheme 2.12. *Proposed mechanism accounting for the formation of **16a-c**.*

Considering the easy isomerization of allyl alcohols into the corresponding ketones by treatment with bases,[16] the above alkylation derivatives might derive also from ketone **8**, as the first reaction product, via enolate formation and nucleophilic substitution. In fact, in the same reaction conditions, compound **8** gave similar results under deprotonation with NaH. However, the recovery of unreacted alcohol **1** in the reaction with allyl bromide (**15a**, Scheme 2.11) after 24 h (see the Experimental Section 2.5) seems to rule out the conversion of alcohol **1** into ketone **8** before nucleophilic substitution.

2.3.3. REACTIVITY AS C-3 CARBON NUCLEOPHILE

As previously observed with aldehydes, the non catalysed thermal reactions of allyl pyridine **1** as carbon nucleophile seem to require highly activated electrophiles. For this reason reactions toward activated heterocyclic electrophiles were investigated.
When **1** was allowed to react in a sealed tube with an excess (8 equiv) of 3,6-dichloropyridazine (**20**) in anhydrous toluene at 70 °C for 48 h, the substitution product **21** was isolated by flash column chromatography in 19% yield, along with a significant amount (ca. 52%) of the volatile pyridyl ketone **8**. Analogously, treatment of **1** with 2 equivalents of 4,5-dicyanopyridazine (**22**, DCP)[17] gave, together with a minor amount of ketone **8** (< 5%, ^{1}H-NMR), compound **23**, deriving from nucleophilic attack on DCP and HCN elimination, in 44% yield (Scheme 2.13).

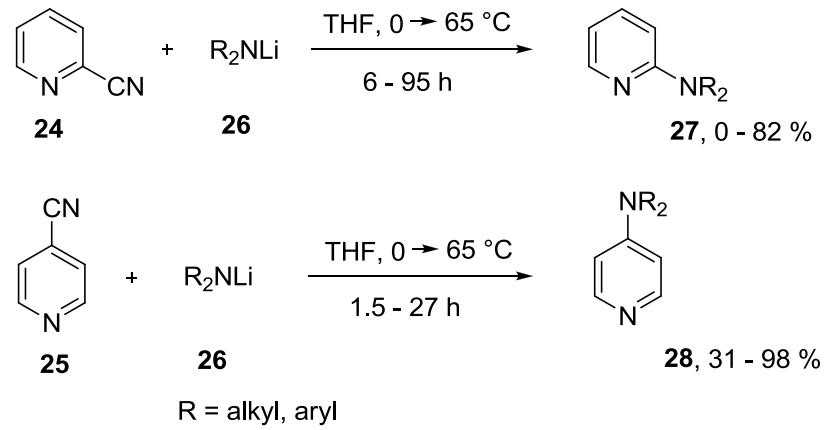
[16] (a) Yanovskaya, L., A.; Shakhidaystov, Kh. *Russ. Chem. Rev.* **1970**, *39*, 859; (b) Dimmel, D. R.; Fu, W. Y.; Gharpure, S. B. *J. Org. Chem* **1976**, *41*, 3096.
[17] Di Stefano L.; Castle, R. N. *J. Heterocycl. Chem.* **1968**, *5*, 53; For the electrophilic behavior of **22**, see: (a) Cecchi, M.; Micoli, A.; Giomi, D. *Tetrahedron* **2006**, *62*, 12281; (b) Alfini, R.; Cecchi, M.; Giomi, D. *Molecules* **2010**, *15*, 1722.



Scheme 2.13. *Reactions of **1** with heterocyclic electrophiles **20** and **22**.*

Attempts to improve the formation of compounds **21** and **23** by varying the experimental conditions (amounts of electrophile, solvent, reaction temperature) were unsuccessful likely due to the competitive isomerization affording compound **8**. The sizeable enhancement of reactivity observed for 4,5-dicyanopyridazine (**22**) could be tentatively associated to the presence of the leaving group (the CN group) in γ-position with respect to the nitrogen atom, rather than in α-position as in compound **20**. Likely, as reported for nucleophilic attack on ribopyranoside derivatives,[18] a repulsive dipolar interaction due to the proximity of the lone pair of an heteroatom could hamper the approach of the incoming nucleophile. An analogous repulsive effect involving the nitrogen lone pair could be invoked to explain the lower reactivity of 2-cyanopyridine (**24**) with respect to the 4-cyano derivative **25** in nucleophilic aromatic substitutions with lithium amides **26** to give the amination products **27** and **28**, (Scheme 2.14),[19] as well as the weaker acidity determined in THF of 2-picoline compared with the 4-isomer.[20]

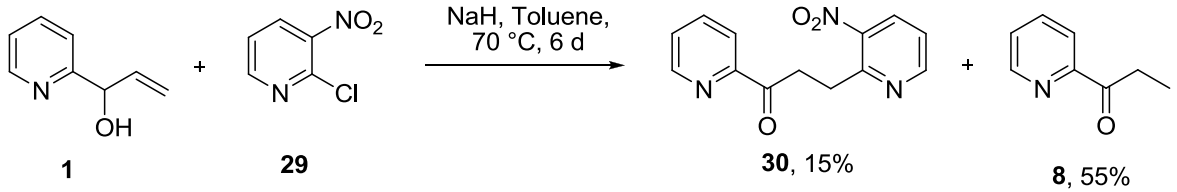
[18] Vasudeva, P. K.; Nagarajan, M *Tetrahedron* **1996**, *52*, 5607.
[19] Penney, J. M. *Tetrahedron Lett.* **2004**, *45*, 2667.
[20] Fraser, R. R.; Mansour, T. S.; Savard, S. *J. Org. Chem.* **1985**, *50*, 3232.



Scheme 2.14. *Direct amination of 2- and 4-cianopyridines (**24**) and (**25**) with lithium amides.*

Several electrophiles were allowed to react with alcohol **1** in the above reaction conditions (mono- and bis-halosubstituted pyridazines, pyrimidines, and pyridines), even rising the reaction temperature to 110 °C. In all the cases, the formation of ketone **8** was largely favoured and substitution products were never observed. These results clearly show that only very reactive electron-poor heterocyclic electrophiles can participate in the reaction.

On the other hand, a peculiar behaviour was observed with 2-chloro-3-nitropyridine (**29**). Nucleophilic substitution product **30** was isolated in poor 15% yield, together with ketone **8** as the major product (55% yield), only after long reaction times (6 days) and addition of 1.3 equiv of NaH (Scheme 2.15).



Scheme 2.15. *Reaction of **1** with **29** in the presence of sodium hydride.*

Using different types of organic bases (pyridine or DABCO) complex reaction mixture were obtained. Working under thermal conditions only, at 70 °C or at higher temperature (110 °C), the main reaction product was a new amino pyridyl ketone (**54**, Scheme 3.9). This anomalous behaviour of 2-chloro-3-nitropyridine (**29**) in the reaction

with **1** under thermal conditions, allowed the discovery of another unprecedented reaction path for 1-(2-pyridyl)-2-propen-1-ol (**1**) as a reducing agent (see Chapter 3).
Finally, the use of catalytic or stoichiometric quantities of KOH or *tert*-butilate led to reaction crudes where ketone **8** and the amino derivative **54** were the major products while compound **30** formed in small amounts (TLC and ^{1}H-NMR).
The products **21**, **23** and **30** are the result of a 'vinylogous picolination' that is unprecedented, to our knowledge, in the literature. In fact, they come from nucleophilic attack of the C-3 carbon atom of the allyl residue of alcohol **1** on the electrophilic C-3, C-4, and C-2 carbons, respectively, of **20**, **22** and **29** followed by leaving group displacement.

2.4. CONCLUSIONS

The reported results clearly show a peculiar thermal behaviour of hydroxyallylpyridyl derivatives likely associated to the weak acidity of the 'picoline-type' hydrogen atom and responsible for the formation of allyl inversion products. In fact, the alcohol **1** and its oxygen-protected derivatives **1a-c** can be easily isomerised to ketone **8** and vinyl derivatives **7a-c** and **9a-c**, respectively, under thermal neutral conditions. From a synthetic viewpoint, even if the competitive thermal isomerisation to ketone **8** is almost always present as side reaction, the allyl alcohol **1** can behave regioselectively as C-1, C-2 or C-3 carbon nucleophile depending on the experimental conditions and the electrophilic counterparts. In particular, reactivity as C-1 carbon nucleophile was observed in the thermal aldol reaction with pyridinecarboxaldehyde (**13**), while allyl bromides, in the presence of NaH at room temperature, afforded the corresponding propionylpyridines allyl substituted at position 2 of the lateral chain through reaction of the C-2 carbon atom in good yields. On the other hand, treatment of **1** with activated heterocyclic electrophiles (as well as nitroalkenes, see Scheme 3.14, Chapter 3) allowed a 'vinylogous picolination', via nucleophilic attack of the C-3 carbon of the allyl moiety of **1**, leading to new polyfunctionalized nitrogen heterocycles.

2.5. EXPERIMENTAL SECTION

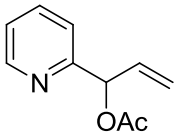
2.5.1. PREPARATION OF ALCOHOL 1.[7]

To an ethereal solution (250mL) of 2-pyridinecarboxaldehyde (**13**), (2 g, 28 mmol) was added vinylmagnesium bromide in THF (36.4 mL, 36.4mmol) at 0 °C. The mixture was stirred for 1 h, quenched with ice water (7.5 mL), and extracted with EtOAc (2 x 150 mL). The extract was washed with water and brine and dried over Na_2SO_4. The solvent was removed, and the residue was purified by column chromatography on silica gel eluted with PE/EtOAc 2:3 (R_f= 0.27). The product **1** was obtained as a yellow oil (2.8 g, 75%).

2.5.2. PREPARATION OF DERIVATIVES 1a AND 1b. GENERAL PROCEDURE.

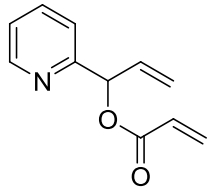
Acetic anhydride (0.613 g, 0.566 mL, 6.0 mmol) or acryloyl chloride (0.543 g, 0.487 mL, 6.0 mmol), triethylamine (0.911 g, 1.25 mL, 9.0 mmol) and DMAP (0.073 g, 0.6 mmol) were added at 0 °C to a solution of alcohol **1** (0.405 g, 3 mmol) in dry dichloromethane (17 mL). After 5 hours at room temperature, the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (17 mL) and extracted with dichloromethane (3x30 mL). The extract was washed with water (30 mL) and brine (30 mL), dried over Na_2SO_4 and evaporated to dryness under reduced pressure giving a reaction crude which was resolved by FC.

*2.5.2.1. (2-Pyridyl)-2-propenyl acetate (**1a**).[7]*



Colourless oil (0.505 g, 83%); [R_f (PE/EtOAc 3:1) 0.33].

*2.5.2.2. (2-Pyridyl)-2-propenyl acrylate (**1b**).*



Colourless oil (0.539 g, 94%); [Found: C, 69.91; H, 5.83; N, 7.34. $C_{11}H_{11}NO_2$ requires C, 69.83; H, 5.86; N, 7.40%]; [R_f (PE/EtOAc 7:1) 0.39].

MW: 189.21.

IR, ν_{max}: (film) 3087, 3014, 2990, 1728, 1590, 1405, 1186 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$) δ: 5.32 (br d, J = 10.3 Hz, 1H, CHCH=CH_2), 5.41 (br d, J = 17.2 Hz, 1H, CHCH=CH_2), 5.89 (dd, J = 10.3 and 1.5 Hz, 1H, COCH=CH_2), 6.06-6.31 (m, 2H, 2xCH=CH_2), 6.38 (d, J = 6.2 Hz, 1H, CHCH=CH_2), 6.50 (dd, J = 17.4 and 1.6 Hz, 1H, COCH=CH_2), 7.22 (dd, J = 7.0 and 5.5 Hz, 1H, 5-H), 7.38 (d, J = 7.7 Hz, 1H, 3-H), 7.70 (ddd, J = 7.7, 7.7 and 1.8 Hz, 1H, 4-H), 8.61 (d, J = 4.4 Hz, 1H, 6-H).

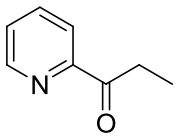
^{13}C-NMR (50 MHz, $CDCl_3$) δ: 76.9 (d), 117.7 (t), 121.0 (d), 122.7 (d), 128.0 (d), 131.3 (t), 134.8 (d), 136.7 (d), 149.3 (d), 157.9 (s), 164.8 (s);

MS *m/z* (EI) 189 (4, M^+), 118 (100%).

2.5.3. THERMAL ISOMERIZATIONS OF COMPOUNDS 1 AND 1a-c. GENERAL PROCEDURE.

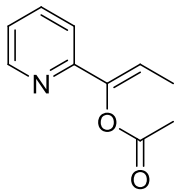
A solution of the allyl pyridyl derivative (**1** or **1a-c**), (1.0 mmol) in chloroform or xylene (2 mL) was heated in a sealed tube at 110 °C or 160 °C, respectively, for the reported time. After evaporation to dryness, the reaction crude was subjected to FC.

*2.5.3.1. 2-Propionylpyridine (**8**).*[10]



Chromatographic resolution (PE/EtOAc 6:1) of the reaction crude obtained by heating **1** at 110 °C for 2 days gave compound **8** (R_f = 0.51, 0.122 g, 90%).

*2.5.3.2. (1Z)-1-(2-Pyridyl)-1-propenyl acetate (**7a**).*



Purification by FC (PE/EtOAc 6:1) of the residue coming from heating **1a** at 110 °C for 12 days led to compound **7a** (0.110 g, 62%) as a colourless oil; [Found: C, 68.02; H, 6.13; N, 8.09. $C_{10}H_{11}NO_2$ requires C, 67.78; H, 6.26; N, 7.90%]; R_f (PE/EtOAc 6:1) 0.33.

MW= 177.20

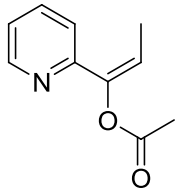
IR, ν_{max} (film): 3055, 3008, 2919, 1759, 1585, 1470, 1432, 1370, 1205 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.76 (d, J = 7.2 Hz, 3H, CH_3), 2.34 (s, 3H, $OCOCH_3$), 6.56 (q, J = 7.1 Hz, 1H, =C*H*CH_3), 7.17 (dd, J = 7.5 and 4.9 Hz, 1H, 5-H), 7.30 (d, J = 8.0 Hz, 1H, 3-H), 7.66 (ddd, J = 7.8, 7.8, and 1.5 Hz, 1H, 4-H), 8.54 (d, J = 4.9 Hz, 1H, 6-H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ: 11.5 (q), 20.5 (q), 117.1 (d), 118.5 (d), 122.6 (d), 137.1 (d), 145.7 (s), 148.7 (d), 151.7 (s), 168.7 (s).

MS *m/z* (EI) 177 (3, M^+), 135 (82), 106 (29), 79 (100%).

*2.5.3.3. (1E)-1-(2-Pyridyl)-1-propenyl acetate (**9a**).*



Operating as above, chromatographic resolution of the reaction crude obtained by heating **1b** at 160 °C for 14 days allowed the isolation of, along with compound **7a** (R_f = 0.33, 0.038 g, 21%), the diastereomer **9a** (0.084 g, 47%) as colourless oil; [Found: C, 68.15; H, 6.01; N, 8.22. $C_{10}H_{11}NO_2$ requires C, 67.78; H, 6.26; N, 7.90%]; R_f (PE/EtOAc 6:1) 0.24.

MW= 177.20.

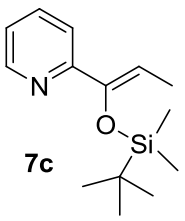
IR, ν_{max} (film): 3048, 3012, 2911, 1741, 1580, 1451, 1210 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 2.00 (d, J = 7.6 Hz, 3H, CH_3), 2.21 (s, 3H, $OCOCH_3$), 5.75 (q, J = 7.5 Hz, 1H, =C*H*CH_3), 7.18 (ddd, J = 7.6, 4.8, and 1.0 Hz, 1H, 5-H), 7.37 (ddd, J = 8.0, 1.0, and 1.0 Hz, 1H, 3-H), 7.69 (ddd, J = 7.8, 7.8, and 1.9 Hz, 1H, 4-H), 8.63 (ddd, J = 4.9, 1.8, and 1.0 Hz, 1H, 6-H).

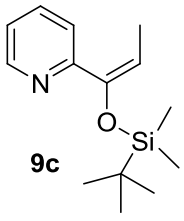
^{13}C-NMR (100MHz, $CDCl_3$) δ: 12.7 (q), 20.8 (q), 118.2 (d), 122.5 (d), 122.7 (d), 136.1 (d), 145.4 (s), 149.2 (d), 152.8 (s), 169.9 (s).

MS *m/z* (EI) 177 (4, M^+), 135 (78), 106 (31), 79 (100%).

*2.5.3.4. Tert-butyl(dimethyl)silyl (1Z)-1-(2-pyridyl)-1-propenyl ether (**7c**) and tert-butyl(dimethyl)silyl (1E)-1-(2-pyridyl)-1-propenyl ether (**9c**).*



7c



9c

The reaction crude coming from heating **1c** at 160 °C for 10 days was resolved by FC (PE/EtOAc 50:1). The first band gave compound **9c** (0.023 g, 13%) as colourless oil; [Found: C, 67.04; H, 8.90; N, 5.98. $C_{14}H_{23}NSiO$ requires C, 67.42; H, 9.29; N, 5.62%]; R_f (PE/EtOAc 50:1) 0.22.

MW: 249.42

IR, ν_{max} (film): 3043, 2966, 2941, 2864, 1647, 1581, 1331 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.08 [s, 6H, $Si(CH_3)_2$], 0.94 [s, 9H, $C(CH_3)_3$], 1.93 (d, *J* = 7.3 Hz, 3H, CH_3), 5.29 (q, *J* = 7.4 Hz, 1H, =C*H*CH_3), 7.15 (dd, *J* = 7.6 and 5.1 Hz, 1H, 5-H), 7.49 (d, *J* = 8.0 Hz, 1H, 3-H), 7.68 (ddd, *J* = 7.8, 7.8, and 1.8 Hz, 1H, 4-H), 8.59 (d, *J* = 5.0 Hz, 1H, 6-H).

^{13}C-NMR (50 MHz, CDCl3) δ: 4.6 (q), 12.7 (q), 18.1 (s), 25.8 (q), 109.0 (d), 121.9 (d), 122.5 (d), 135.9 (d), 147.9 (s), 148.2 (d), 156.7 (s).

The second band afforded derivative **7c** (0.064 g, 36%) as colourless oil; [Found: C, 67.02; H, 9.61; N, 6.00. $C_{14}H_{23}NSiO$ requires C, 67.42; H, 9.29; N, 5.62%]; R_f (PE/EtOAc 50:1) 0.18.

MW: 249.42

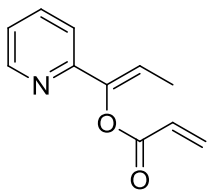
IR, ν_{max} (film): 3054, 2956, 2929, 2858, 1653, 1584, 1472, 1326 cm^{-1}.

^{1}H-NMR (200MHz, $CDCl_3$) δ: 0.04 [s, 6H, $Si(CH_3)_2$], 1.02 [s, 9H, $C(CH_3)_3$], 1.79 (d, *J* = 7.3 Hz, 3H, CH_3), 5.98 (q, *J* = 7.1 Hz, 1H, =C*H*CH_3), 7.12 (dd, *J* = 7.6 and 5.0 Hz, 1H, 5-H), 7.45 (d, *J* = 8.0 Hz, 1H, 3-H), 7.63 (ddd, *J* = 7.8, 7.8, and 1.7 Hz, 1H, 4-H), 8.50 (d, *J* = 4.9 Hz, 1H, 6-H).

^{13}C-NMR (50MHz, $CDCl_3$) δ: 3.9 (q), 11.8 (q), 18.35 (s), 25.9 (q), 108.8 (d), 119.4 (d), 121.9 (d), 136.1 (d), 148.7 (d), 148.75 (s), 156.2 (s).

The slowest moving band gave unreacted **1c** (R_f = 0.13, 0.072 g, 29%).

*2.5.3.5. (1Z)-1-(2-Pyridyl)-1-propenyl acrylate (**7b**).*



Chromatographic resolution (PE/EtOAc 8:1) of the reaction crude obtained by heating **1b** at 110 °C for 14 days led to compound **7b** (0.128 g, 64%) as a colourless oil; [Found: C, 69.46; H, 5.70; N, 7.37. $C_{11}H_{11}NO_2$ requires C, 69.83; H, 5.86; N, 7.40%]; R_f (PE/EtOAc 8:1) 0.29.

MW: 189.21

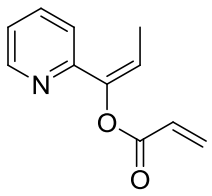
IR, ν_{max} (film): 3055, 3008, 2983, 2918, 1741, 1584, 1470, 1404, 1238, 1160 cm^{-1}.

^{1}H-NMR (200MHz, $CDCl_3$) δ: 1.78 (d, J = 7.0 Hz, 3H, CH_3), 6.04 (dd, J = 10.3 and 1.4 Hz, 1H, COCH=CH_2), 6.38 (dd, J = 17.2 and 10.2 Hz, 1H, COCH=CH_2), 6.63 (q, J = 7.1 Hz, 1H, =C$H$$CH_3$), 6.65 (dd, J = 17.3 and 1.2 Hz, 1H, COCH=CH_2), 7.16 (dd, J = 7.5 and 4.8 Hz, 1H, 5-H), 7.27 (d, J = 7.7 Hz, 1H, 3-H), 7.64 (ddd, J = 7.7, 7.7, and 1.5 Hz, 1H, 4-H), 8.55 (d, J = 4.6 Hz, 1H, 6-H).

^{13}C-NMR (50MHz, $CDCl_3$) δ: 11.4 (q), 116.6 (d), 118.2 (d), 122.4 (d), 127.3 (d), 132.7 (t), 136.7 (d), 145.8 (s), 149.1 (d), 151.8 (s), 163.7 (s).

MS *m/z* (CI) 190 (48, MH^+), 189 (2, M^+), 136 (100%).

*2.5.3.6. (1E)-1-(2-Pyridyl)-1-propenyl acrylate (**9b**).*



Operating as above, chromatographic resolution of the reaction crude obtained by heating **1b** at 160 °C for 7 days allowed the isolation of, along with compound **7b** (R_f = 0.29, 0.038 g, 20%), the diastereomer **9b** (0.055 g, 29%) as colourless oil; [Found: C, 69.57; H, 5.58; N, 7.19. $C_{11}H_{11}NO_2$ requires C, 69.83; H, 5.86; N, 7.40%]; R_f (PE/EtOAc 8:1) 0.23.

MW: 189.21

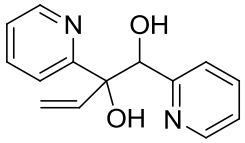
IR, ν_{max} (film): 3048, 3011, 2976, 1735, 1578, 1468, 1411, 1231, 1172 cm^{-1}.

^{1}H-NMR (200MHz, $CDCl_3$) δ: 2.04 (d, J = 7.3 Hz, 3H, CH_3), 5.80 (q, J = 7.4 Hz, 1H, =C*H*CH_3), 5.94 (dd, J = 10.3 and 1.2 Hz, 1H, COCH=CH_2), 6.27 (dd, J = 17.2 and 10.3 Hz, 1H, COC*H*=CH_2), 6.54 (dd, J = 17.2 and 1.3 Hz, 1H, COCH=CH_2), 7.19 (dd, J = 7.6 and 4.7 Hz, 1H, 5-H), 7.38 (d, J = 8.0 Hz, 1H, 3-H), 7.70 (ddd, J = 7.8, 7,8, and 1.5 Hz, 1H, 4-H), 8.63 (d, J = 4.5 Hz, 1H, 6-H).

^{13}C-NMR (50MHz, $CDCl_3$) δ: 12.7 (q), 118.4 (d), 122.5 (d), 122.6 (d), 127.8 (d), 132.2 (t), 136.1 (d), 145.0 (s), 149.1 (d), 152.7 (s), 164.9 (s).

MS *m/z* (CI) 190 (39, MH^+), 189 (3, M^+), 136 (100%).

2.5.4. SYNTHESIS OF 1,2-DI(2-PYRIDYL)-3-BUTEN-1,2-DIOLS (14a,b).



A mixture of alcohol **1** (0.068 g, 0.5 mmol) and 2-pyridinecarboxaldehyde (**13**) (0.161 g, 0.14 mL, 1.5 mmol) in anhydrous toluene (1 mL) was heated at 70 °C for 24 hours. Chromatographic resolution (PE/EtOAc 6:1) of the residue left by evaporation to dryness gave a 1:1 mixture of compounds **14a,b** (0.061 g, 50%) as pale yellow solid; [Found: C, 69.27; H, 6.08; N, 11.51. $C_{14}H_{14}N_2O_2$ requires C, 69.41; H, 5.82; N, 11.56%]; R_f (PE/EtOAc 6:1) 0.14.

MW: 242.27

IR, ν_{max} (KBr): 3158, 2890, 1597, 1571, 1468, 1061 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 4.98 (s, 1H, 1-H), 5.00 (dd, J = 10.7 and 1.8 Hz, 1H, 4-H), 5.10 (s, 1H, 1-H), 5.21 (dd, J = 10.6 and 1.7 Hz, 1H, 4-H), 5.26 (dd, J = 17.2 and 1.8 Hz, 1H, 4-H), 5.36 (vbr s, 2H, 2xOH), 5.41 (dd, J = 17.2 and 1.6 Hz, 1H, 4-H), 5.80 (vbr s, 2H, 2xOH), 6.32(dd, J = 17.1 and 10.6 Hz, 1H, 3-H), 6.55 (dd, J = 17.1 and 10.6 Hz, 1H, 3-H), 7.04-7.09 (m, 2H, Ar-2H), 7.18-7.23 (m, 2H, Ar-2H), 7.57-7.64 (m, 4H, Ar-4H), 7.62-7.76 (m, 4H, Ar-4H), 8.30-8.32 (m, 2H, Ar-2H), 8.45-8.49 (m, 2H, Ar-2H).

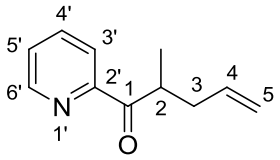
^{13}C-NMR (100MHz, $CDCl_3$) δ: 76.4 (d), 78.0 (d), 78.1 (s), 78.5 (s), 114.65 (t), 114.75 (t), 121.3 (d), 121.4 (d), 122.0 (d), 122.15 (d), 122.2 (d), 122.25 (d), 122.3 (d), 122.4 (d), 136.8

(d), 136.95 (d), 137.1 (d), 137.5 (d), 139.2 (d), 141.2 (d), 146.7 (d), 146.8 (d), 146.9 (d), 146.95 (d), 160.3 (s), 161.4 (s), 163.3 (s), 164.0 (s).

2.5.5. REACTIONS OF 1 WITH ALLYL BROMIDES 15a-c. GENERAL PROCEDURE.

A solution of alcohol **1** (0.068 g, 0.5 mmol) in anhydrous THF (1 mL) was added dropwise, under nitrogen, at room temperature to a solution of NaH (0.012 g, 0.5 mmol) in the same solvent (0.25 mL). The reaction mixture was stirred at room temperature for 2 hours and then the suitable allyl bromide (1 mmol,) was added. The resulting mixture (which turned red during the addition) was stirred at room temperature overnight and then decomposed with aqueous hydrochloride (10%, 0.5 mL) and water (1 mL). Extraction with diethyl ether (3 × 3 mL), evaporation to dryness, and prolonged evacuation gave pure alkylation products.

*2.5.5.1. 2-Methyl-1-(2-pyridyl)-4-penten-1-one (**16a**).*[14]



Compound **16a** (0.050 g, 75%) was obtained as a pale yellow oil; [Found: C, 75.08; H, 7.74; N, 7.68. $C_{11}H_{13}NO$ requires C, 75.40; H, 7.48; N, 7.99%].

MW: 175.23

IR, ν_{max} (film): 3076, 3055, 2975, 2932, 1699, 1641, 1583 cm^{-1}.

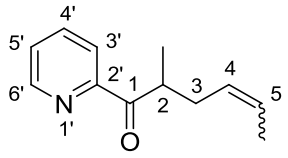
^{1}H-NMR (200MHz, $CDCl_3$) *δ*: 1.20 (d, *J* = 7.0 Hz, 3H, C*H*$_3$), 2.40 (m, 2H, H-3), 4.18 (sextet, *J* = 7.0 Hz, 1H, H-2), 5.00 (m, 2H, H-5), 5.80 (m, 1H, H-4), 7.47 (m, 1H, H-5'), 7.85 (ddd, *J* = 7.7, 7.7, and 1.5 Hz, 1H, H-4'), 8.05 (d, *J* = 7.9 Hz, 1H, H-3'), 8.70 (d, *J* = 4.4 Hz, 1H, H-6').

^{13}C-NMR (50MHz, $CDCl_3$) *δ*: (50 MHz) 16.3 (q), 37.1 (t), 38.8 (d), 116.4 (t), 122.3 (d), 126.9 (d), 136.0 (d), 136.8 (d), 148.8 (d), 152.9 (s), 204.7 (s).

MS *m/z* (EI) 175 (2, M^+), 160 (16), 147 (17), 106 (19), 79 (100%).

Neutralization of the aqueous phase with a saturated solution of $NaHCO_3$, and extraction with diethyl ether (3 × 3 mL) allowed the recovery of unreacted **1** (0.016 g, 24%).

*2.5.5.2. Methyl-1-(2-pyridyl)-4-hexen-1-one (**16b**).*



Compound **16b** was obtained (0.067 g, 71%) as pale orange oil; [Found: C, 75.81; H, 8.25; N, 7.15. $C_{12}H_{15}NO$ requires C, 76.16; H, 7.99; N, 7.40%].

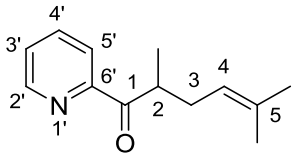
MW: 189.25

IR, ν_{max} (film): 3054, 3018, 2969, 2934, 1697, 1583, 1456 cm^{-1}.

^{1}H-NMR (200MHz, $CDCl_3$) δ: 1.17 (d, J = 7.0 Hz, 3H, CH_3-2), 1.59 (m, 3H, CH_3-5), 2.09-2.53 (m, 2H, H-3), 4.11 (sextet, J = 6.9 Hz, 1H, H-2), 5.42 (m, 2H, H-4 and H-5), 7.46 (m, 1H, H-5′), 7.84 (ddd, J = 7.8, 7.8, and 1.4 Hz, 1H, H-4′), 8.04 (d, J = 8.0 Hz, 1H, H-3′), 8.69 (d, J = 4.0 Hz, 1H, H-6′).

^{13}C-NMR (50MHz, $CDCl_3$) δ: (the values in square brackets refer to some resonances of the minor diastereomer) [12.9 (q)], 16.3 (q), 17.9 (q), [30.4 (t)], 36.1 (t), 39.4 (d), 122.2 (d), [125.5 (d)], 126.6 (d), 126.8 (d), [127.4 (d)], 128.2 (d), 136.6 (d), 148.6 (d), 152.8 (s), 204.7 (s); **MS** *m/z* (EI) 189 (5, M^+), 161 (18), 146 (14), 106 (30), 91 (80), 79 (100%).

*2.5.5.3. 2,5-Dimethyl-1-(2-pyridyl)-4-hexen-1-one (**16c**).*



Compound **16c** was obtained (0.082 g, 81%) as pale orange oil; [Found: C, 76.49; H, 8.64; N, 6.54. $C_{13}H_{17}NO$ requires C, 76.81; H, 8.43; N, 6.89%].

MW: 203.28

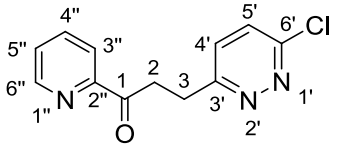
IR, ν_{max} (film): 3054, 2970, 2930, 1697, 1583, 1456 cm^{-1}.

^{1}H-NMR (200MHz, $CDCl_3$) δ: (200 MHz) 1.18 (d, *J* = 7.0 Hz, 3H, CHCH_3), 1.58 (s, 3H, CH_3), 1.64 (s, 3H, CH_3), 2.30 (m, 2H, 3-CH_2), 4.09 (sextet, *J* = 6.9 Hz, 1H, 2-H), 5.12 (t, *J* = 7.1 Hz, 1H, 4-H), 7.46 (m, 1H, 5'-H), 7.85 (ddd, *J* = 7.8, 7.8, and 1.5 Hz, 1H, 4'-H), 8.04 (d, *J* = 8.0 Hz, 1H, 3'-H), 8.69 (d, *J* = 4.8 Hz, 1H, 6'-H).

^{13}C-NMR (50MHz, $CDCl_3$) δ: 16.1 (q), 17.7 (q), 25.7 (q), 31.6 (t), 39.8 (d), 121.7 (d), 122.3 (d), 126.8 (d), 133.2 (s), 136.8 (d), 148.8 (d), 153.1 (s), 205.3 (s).

MS *m/z* (EI) 203 (1, M^+), 188 (2), 175 (11), 160 (9), 106 (11), 79 (100%).

2.5.6. SYNTHESIS OF 3-(6-CHLOROPYRIDAZIN-3-YL)-1-(2-PYRIDYL)-1-PROPANONE (21).



The reaction mixture obtained by heating 3,6-dichloropyridazine (**20**) (1.192 g, 8 mmol) and alcohol **1** (0.135 g, 1 mmol) in anhydrous toluene (2 mL) at 70 °C for 48 h was resolved by FC (PE/EtOAc 1:1) to afford, after the isolation of ketone **8** (R_f = 0.82, 0.070 g, 52%), compound **21** (0.048 g, 19%) as a white solid, mp 92-93 °C (from pentane); [Found: C, 57.81; H, 3.98; N, 16.71. $C_{12}H_{10}ClN_3O$ requires C, 58.19; H, 4.07; N, 16.97%]; R_f (PE/EtOAc 1:1) 0.28.

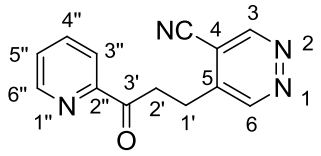
MW: 247.68

IR, ν_{max} (KBr): 3087, 3049, 2921, 1701, 1676, 1581, 1437 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 3.74 (t, *J* = 7.2 Hz, 2H, 2-CH_2), 4.56 (t, *J* = 7.2 Hz, 2H, 3-CH_2), 6.90 (d, *J* = 9.7 Hz, 1H, 4'-H), 7.15 (d, *J* = 9.7 Hz, 1H, 5'-H), 7.45 (ddd, *J* = 7.6, 4.8, and 1.3 Hz, 1H, 5''-H), 7.85 (ddd, *J* = 7.7, 7.7, and 1.6 Hz, 1H, 4''-H), 8.04 (dd, *J* = 7.8 and 1.2 Hz, 1H, 3''-H), 8.65 (ddd, *J* = 4.8, 1.5, and 0.9 Hz, 1H, 6''-H).

^{13}C-NMR (100MHz, $CDCl_3$) δ: 36.2 (t, C-2), 47.65 (t, C-3), 121.8 (d, C-3''), 127.35 (d, C-5''), 131.8 (d, C-4'), 133.5 (d, C-5'), 137.0 (d, C-4''), 137.3 (s, C-6'), 149.0 (d, C-6''), 152.9 (s, C-2''), 158.9 (s, C-3'), 199.0 (s, CO).

2.5.7. SYNTHESIS OF 5-[3-OXO-3-(2-PYRIDYL)PROPYL]-4-PYRIDAZINECARBONITRILE (23).



4,5-dicyanopyridazine (**22)** (0.130 g, 1 mmol) was added to a solution of alcohol **1** (0.068 g, 0.5 mmol) in anhydrous toluene (1 mL) and. the resulting mixture was heated at 70 °C for 48 h. The crude product left by evaporation to dryness was subject to FC (PE/EtOAc 1:1) to afford compound **23** (0.053 g, 44%) as a pale orange solid, mp 89-90 °C (from diethyl ether/dichloromethane); [Found: C, 65.44; H, 4.22; N, 23.21. $C_{13}H_{10}N_4O$ requires C, 65.54; H, 4.23; N, 23.52%]; R_f (PE/EtOAc 1:1) 0.28.

MW: 238.24

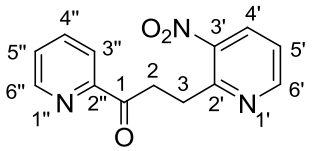
IR, ν_{max} (KBr): 3071, 3051, 2930, 2236, 1698, 1583, 1567, 1362 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 3.31 (t, J = 7.1 Hz, 2H, 1'-CH_2), 3.76 (t, J = 7.1 Hz, 2H, 2'-CH_2), 7.50 (ddd, J = 7.6, 4.8, and 1.3 Hz, 1H, 5''-H), 7.85 (ddd, J = 7.7, 7.7, and 1.7 Hz, 1H, 4''-H), 8.02 (dd, J = 7.8 and 1.2 Hz, 1H, 3''-H), 8.65 (ddd, J = 4.8, 1.6, and 0.9 Hz, 1H, 6''-H), 9.23 (d, J = 1.0 Hz, 1H, 3-H), 9.42 (d, J = 1.0 Hz, 1H, 6-H).

^{13}C-NMR (100MHz, $CDCl_3$) δ: 25.8 (t C-1'), 36.8 (t, C-2'), 113.35 (s, C-4), 113.6 (s, CN), 121.9 (d, C-3''), 127.7 (d, C-5''), 137.1 (d, C-4''), 143.5 (s, C-5), 149.1 (d, C-6''), 150.2 (d, C-3), 152.3 (s, C-2''), 152.65 (d, C-6), 198.5 (s, CO).

ESI *m/z* (EI) 238 (11, M^+), 222 (5), 210 (13), 209 (26), 132 (31), 106 (24), 79 (100), 78 (92), 51 (95%).

2.5.8. SYNTHESIS OF 3-(3-NITRO-2-PYRIDYL)-1-(2-PYRIDYL)-1-PROPANONE (30).



2-Chloro-3-nitropyridine (**29)** (0.396 g, 2.5 mmol) was added to a solution of alcohol **1** (0.068 g, 0.5 mmol) and NaH (0.016 g, 0.67 mmol) in anhydrous toluene (1 mL), previously stirred at room temperature for three hours. The reaction mixture was then heated at 70 °C for six days. The resulting crude was treated with aqueous hydrochloride (10%, 0.5 mL) and water (1 mL) and extracted with dichloromethane (3 x 5 mL). The crude product left by evaporation to dryness was subjected to FC with PE/EtOAc 2:1 as eluent leading to ketone **8** (R_f = 0.45, 0.027 g, 40%) and with PE/EtOAc 1:2 to isolate the nitro derivative **30** (0.020 g, 15%) as a pale orange solid, mp 144-145 °C (from ethyl acetate); [Found: C, 60.37; H, 4.24; N, 16.10. $C_{13}H_{11}N_3O_3$ requires C, 60.70; H, 4.31; N, 16.33%]; R_f (PE/EtOAc 1:2) 0.24.

MW: 257.24

IR, ν_{max} (KBr) 3120, 3052, 2923, 1694, 1679, 1598, 1523, 1355 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 3.86 (t, J = 6.0 Hz, 2H, 2-CH_2), 4.49 (t, J = 6.0 Hz, 2H, 3-CH_2), 6.28 (dd, J = 7.7 and 6.6 Hz, 1H, 5'-H), 7.48 (ddd, J = 7.7, 4.7, and 1.4 Hz, 1H, 5''-H), 7.83 (ddd, J = 7.7, 7.7, and 1.6 Hz, 1H, 4''-H), 7.98 (ddd, J = 7.7, 1.1, and 1.1 Hz, 1H, 3''-H), 8.07 (dd, J = 6.6 and 2.1 Hz, 1H, 6'-H), 8.30 (dd, J = 7.7 and 2.0 Hz, 1H, 4'-H), 8.65 (ddd, J = 4.7, 1.6, and 1.0 Hz, 1H, 6''-H).

^{13}C-NMR (100MHz, $CDCl_3$) δ: 36.35 (t, C-2), 47.0 (t, C-3), 102.9 (d, C-5'), 121.6 (d, C-3''), 127.7 (d, C-5''), 136.9 (d, C-4''), 138.6 (s, C-3'), 138.8 (d, C-4'), 146.1 (d, C-6'), 149.2 (d, C-6''), 152.4 (s, C-2''), 154.4 (s, C-2'), 199.6 (s, CO).

MS *m/z* (EI) 257 (1, M^+), 212 (13), 133 (62), 132 (42), 105 (88), 80 (49), 78 (100%).

Chapter III

(2-PYRIDYL)PHENYL METHANOLS AS A NEW CLASS OF HYDROGEN DONORS IN METAL FREE REDUCTIONS

3.1. INTRODUCTION

In the chemical domain, the most common broad-spectrum reducing agents are certainly metal hydrides and hydrogen in conjuction with metal catalysts. On the other hand, biochemical processes rely on organic cofactors such as nicotinamide adenine

dinucleotide (NADH) in combination with metalloenzymes.[21] Dehydrogenases add two hydrogen atoms to the substrate, using a suitable coenzymes donor.[22] The reduced forms NADH and NADPH are conveniently regarded as hydride-donating reducing agents. During the reduction sequence, there is a stereospecific transfer of hydride from a prochiral centre on the dihydropyridine ring, and the hydride is also delivered to the hydrogen acceptor (e.g. the carbonyl group) in a stereospecific manner (Figure 3.1).

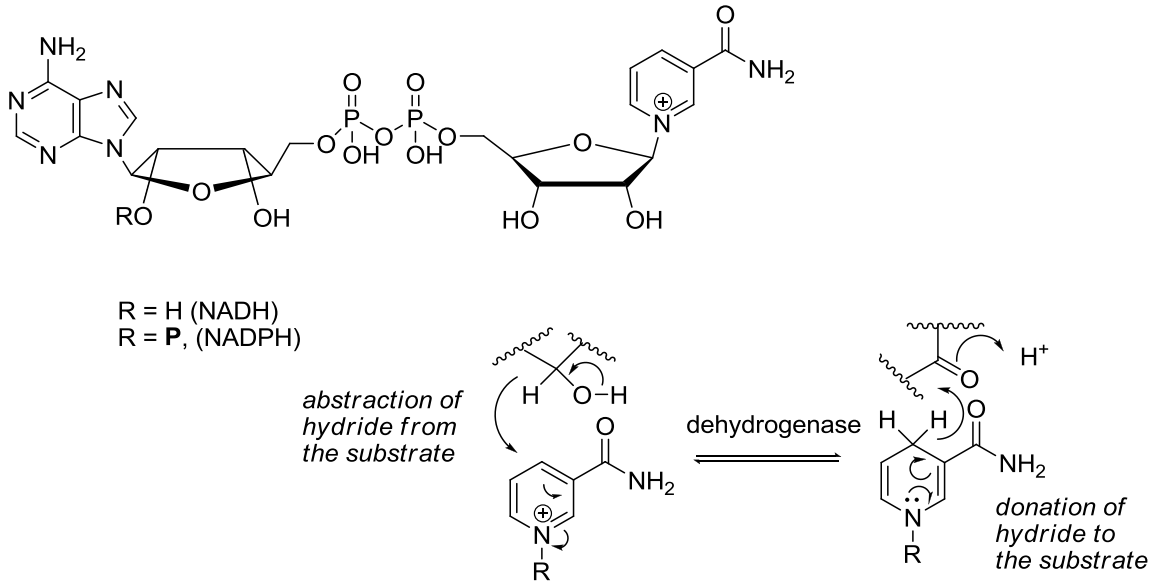


Figure 3.1. *Biological mechanism of oxidation-reduction operating by NAD(P)⁺/NAD(P)H*

The reduction may be compared with the chemical reduction process involving complex metal hydrides namely nucleophilic addition of hydride and subsequent protonation. As shown in Figure 3.1, the nicotinamide nucleus (Figure 3.2) plays a vital role in oxidation–reduction reactions. This pyridine unit has its origins in nicotinic acid (vitamin B3; Figure 3.2), the vitamin sometimes called niacin. This vitamine is the most important electron carrier in the primary metabolism.

[21] Dickinson, F.; Dalziel, K. *Nature* **1967**, *214*, 31.
[22] Dewick, M. P. *Medicinal Natural Products*, 3rd ed, Wiley: Chichester, UK, 2009, p. 24.

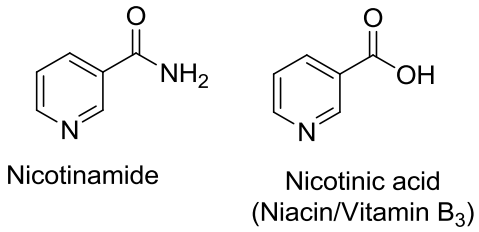


Figure 3.2. *Chemical structures of nicotinamide and nicotinic acid.*

In order to understand the mechanism of the hydride transfer, many 1,4-dihydropyridine derivatives have been extensively investigated as NADH models for the reduction of unsaturated organic compounds[23] in the absence of metal ions. In particular, after the pioneering works of Braude and Dittmer,[24] noteworthy results in the last fifty years demonstrated that Hantzsch ester (HEH, Figure 1.3) and other 1,4-dihydropyridine systems work as efficient and versatile reducing agents, mimicking the NADH/NADPH systems.[25] Moreover, even if the most common methods applied for the reduction of organic compounds exploit metal catalysts in conjuction with an hydrogen sources, in the last decade great attention has been devoted to the development of environmentally friendly organocatalysis,[26] namely the acceleration of chemical reactions through the addition of a substoichiometric amount of an organic compound which does not contain a metal atom. This combines significant preparative advantages (reactions performed under aerobic conditions, in wet solvents, with inexpensive catalysts, etc…) and in many cases extremely high enantioselectivities.[27] Therefore, new biomimetic organocatalytic strategies have been performed replacing enzymes and cofactors with small molecule as organocatalysts and Hantzsch ester

[23] (a) Eisner, U.; Kuthan, G. *Chem. Rev.* **1972**, *72*, 1. (b) Stout, D. M. *Chem. Rev.* **1982**, *82*, 223. (c) Murakami, Y.; Kikuchi, J.; Hisaeda, Y.; Hayashida, O. *Chem. Rev.* **1996**, *96*, 721. (d) Lavilla, R. *J. Chem. Soc., Perkin Trans. I* **2002**, 1141.

[24] Braude, E. A.; Hannah, J.; Linstead, R. *J. Chem. Soc.* **1960**, 3257. (b) Dittmer, D. C.; Kolyer, J. M. *J. Org. Chem.* **1962**, *27*, 56 and reference therein.

[25] Huang, Y. *Synlett* **2007**, 2304 and reference therein.

[26] For recent general reviews on organocatalysis, see: (a) MacMillan, D. W. C. *Nature* **2008**, *455*, 304. (b) Dondoni, A.; Massi, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 4638. (c) Palomo, C.; Oiarbide, M.; Lopez, R. *Chem. Soc. Rev.* **2009**, *38*, 632. (d) Zhang, Z.; Schreiner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187. (e) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178.

[27] (a) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2001**, *40*, 3726. (b) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138-5175.

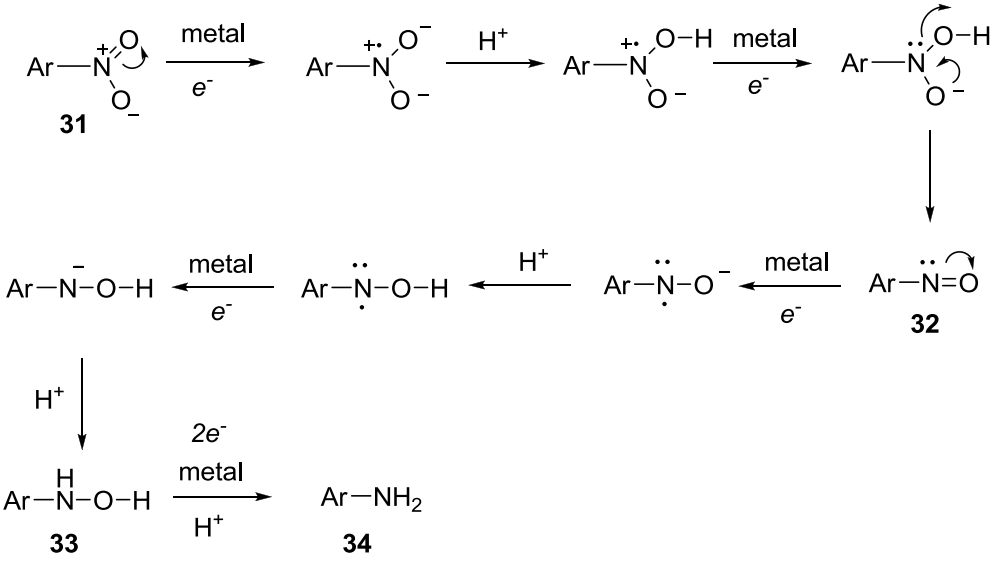
dihydropyridine (HEH) as hydrogen donor. These methodologies were successfully exploited in enantioselective transfer hydrogenation of unsatured carbonyl compounds, imines, heteroaromatic compounds, reductive amination,[28] as well as in the biomimetic reduction of conjugated nitroalkenes.[29] On this basis, new metal-free organocatalytic strategies based on the use of small molecules as organocatalysts and 1,4-dihydropyridine systems (*e.g.*, HEH) as hydrogen donors have been found applications in several examples.[30] In the last fifty years, the above methodology has been successfully applied to different substrates and recent results concern HEH metal-free reduction of activated olefins,[31] exocyclic double bonds,[32] tertiary amides,[33] as well as new applications involving polymer-supported HEH.[34]

3.1.1. REDUCTION OF NITRO COMPOUNDS

Concerning nitro compounds, their synthetic applications and, hence, their reduction processes have been extensively reviewed.[35] Many reducing agents have been used to reduce both aliphatic and aromatic nitro compounds, though the reaction has been applied much more often to aromatic nitro compounds, owing to their greater availability and interest.[36] The reduction of aromatic nitro derivatives to amines has been mainly performed with metals and acid, by catalytic hydrogenation, or with hydrides and various catalysts. The mechanism of these reductions has not much studied, though it is usually presumed that, at least with some reducing agents, nitroso

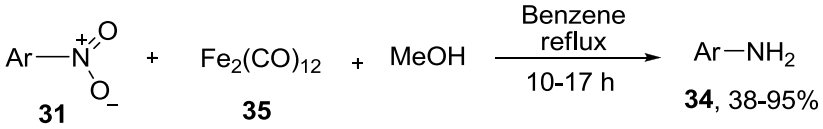
[28] (a) Ouellet, S. G.; Waljl, A. M.; MacMillan, D. W. C. *Acc. Chem. Res.* **2007**, *40*, 1327 and refereces therein. (b) Zhou, Y.-G. *Acc. Chem. Res.* **2007**, *40*, 1357 and refereces therein.
[29] Zhang, Z.; Shreiner, P. R. *Synthesis* **2007**, 2559.
[30] (a) Ref. 28. (b) Connon, S. *J. Org. Biomol. Chem.* **2007**, *5* 3407. (c) You, S.-L. *Chem. Asian J.* **2007**, *2*, 820. (d) Rueping, M.; Tato, F.; Schoepke, F. R. *Chem. Eur. J.* **2010**, *16*, 2688.
[31] (a) Ref. 25. (b) Zhu, X.-Q.; Wang, H.-Y.; Wang, J.-S.; Liu, Y.-C. *J. Org. Chem.* **2001**, *66*, 344.
[32] (a) Garden, S. J.; Guimarães, C. R. W.; Corréa, M. B.; Fernandes de Oliveira, C. A.; Pinto, A. C.; Bicca de Alencastro, R. *J. Org. Chem.* **2003**, *68*, 8815. (b) Liu, Z.; Han, B.; Liu, Q.; Zhang, W.; Yang, L. Liu, Z.-L.; Yu, W. *Synlett* **2005**, 1579.
[33] Barbe, G.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 18.
[34] He, R.; Toy, P. H.; Lam, Y. *Adv. Synth. Catal.* **2008**, 350, 54.
[35] (a) Adams, J. P.; Box, D. S. *Contemp. Org. Synth.* **1997**, 4, 415-434. (b) Adams, J. P.; Box, D. S. *J. Chem. Soc., Perkin Trans.1* **1999**, 749-764. (c) Adams, J. P.; Paterson, J. R. *J. Chem. Soc., Perkin Trans.1* **2000**, 3695-3705. (d) Adams, J. P. *J. Chem. Soc., Perkin Trans.1* **2002**, 2586-2597.
[36] Smith, B. M.; March, J. *Advanced Organic Chemistry*, 5th ed, Wiley: New York, 2001, p.1552.

compounds **32** and hydroxylamines **33** are reaction intermediates. With metals and acids the reduction path of aromatic nitro derivatives **31** into the corresponding amines **34** is suggested in Scheme 3.1.



Scheme 3.1. *Reduction path of the aromatic nitro derivative **31** operating with metal and acid.*

With some reducing agents, the reduction can be stopped at an intermediate stage and hydroxylamines, hydrazobenzenes, azobenzenes and azoxybenzenes can be obtained. Methanolic solutions of dodecacarbonyltriiron [$Fe_2(CO)_{12}$] (**35**) specifically reduce the nitro group of nitroaryls to a primary amine (**34**) in the presence of other functional groups (*e.g.*, C=C, C=O, CO_2R, NHAc) in high yields (Scheme 3.2).[37]

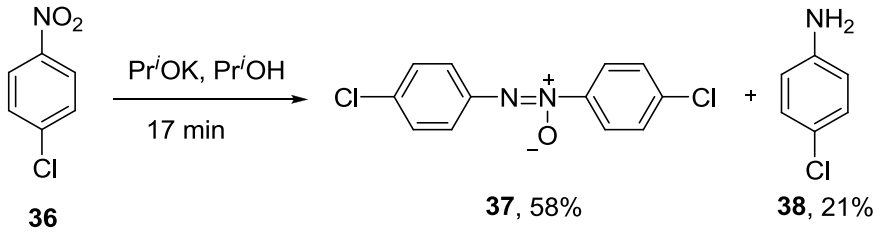


Scheme 3.2. *Reduction of nitro aromatic derivatives with [$Fe_2(CO)_{12}$] in alcoholic solution.*

While reduction of nitroaromatic compounds to the corresponding anilines in acidic media is a well established synthetic procedure, reduction under basic conditions has

[37] Landesberg, J. M.; Katz, L.; Olsen, C. *J. Org. Chem.* **1972**, *37*, 930.

received far less attention.[38] Treatment of 1-chloro-4-nitrobenzene (**36**) with potassium isopropoxide in propan-2-ol under deoxygenated atmosphere, reduced **36** into the 4,4'-dichloroazozybenzene (**37**), coming from the condensation among reduction intermediates. The 4-chloroaniline (**38**), coming from hydrolysis of an imino intermediate, was not obtained by the direct reduction of the starting nitro derivative.[39]

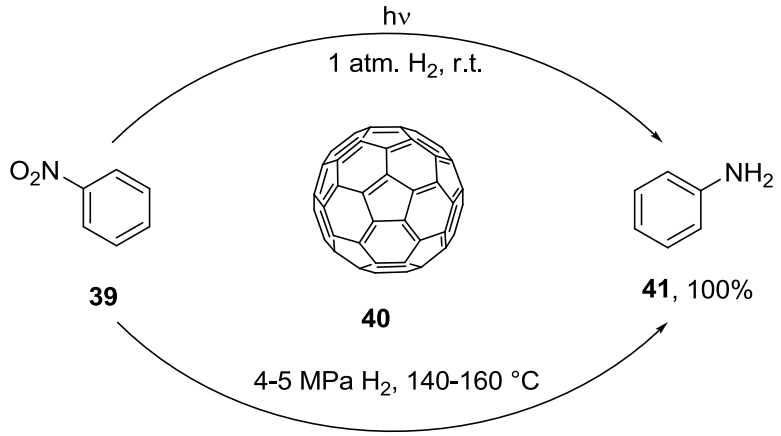


Scheme 3.3. *Reduction in basic media of chloronitrobenzene* ***36****.*

3.1.2. METAL-FREE REDUCTION OF NITRO COMPOUNDS

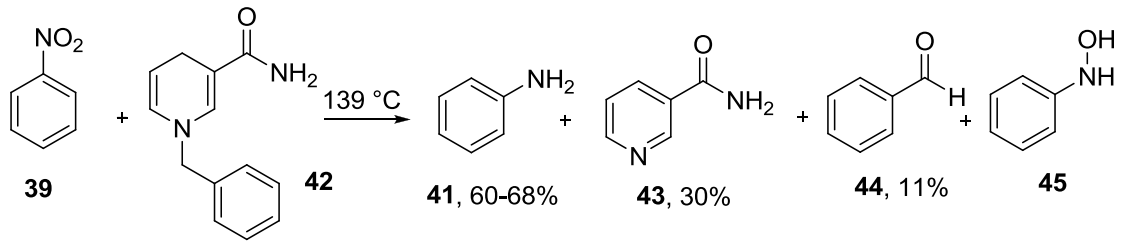
Recently, hydrogenation of nitrobenzene (**39**) to aniline (**41**) has been performed in the presence of fullerene (**40**). Fullerene can activate molecular hydrogen and it is a novel nonmetal hydrogenation catalyst. The hydrogenation of aromatic nitro compounds to amino aromatics was achieved on fullerene (the catalyst) in high yield and selectivity under atmospheric pressure of H_2 and light irradiation at room temperature. The reaction runs well without UV irradiation, but required higher temperature and pressure (Scheme 3.4).[40]

[38] (a) Richardson, D. H.; Smith, F. W. *J. Chem. Soc.* **1932**, 2955. (b) Dains, F. B.; Kenyon, W. O. *J. Am. Chem. Soc.* **1931**, *53*, 2357.
[39] Prato, M.; Quintily, U.; Scorrano, G. *J. Chem. Soc., Perkin Trans.1* **1986**, 1419.
[40] Li, B.; Xu, Z. *J. Am. Chem. Soc.* **2009**, *131*, 16380.



Scheme 3.4. *Reduction of nitrobenzene (**39**) in the presence of fullerene (**40**) under H_2 pressure.*

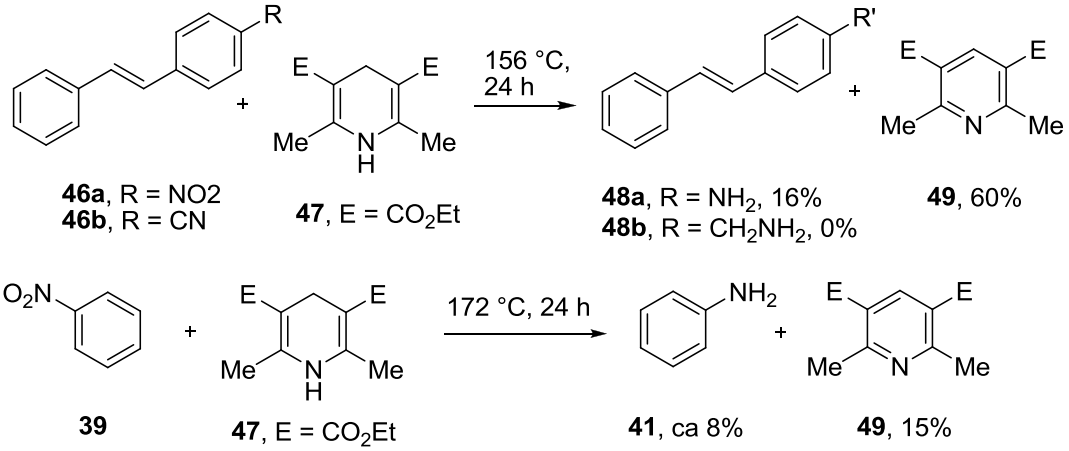
In the literature, only few examples of purely thermal metal-free reductions of aromatic nitro compounds were reported. Heating at 139 °C nitrobenzene (**39**) and 1-benzyl-1,4-dihydronicotinamide (**42**) under nitrogen, Dittmer and Kolyer found aniline (**41**) as the major product of the reduction reaction, while nicotinamide (**43**), benzaldehyde (**44**), phenylhydroxylamine (**45**) were identified after an acqueous acid treatment of the reaction mixture along with other condensation by-products. Aniline (**41**) was shown to be present in the reaction mixture before the hydrolysis (Scheme 3.5).[24b] Other substituted nitrobenzenes were tested, while aliphatic nitro compounds were not reduced.



Scheme 3.5. *Reduction of nitrobenzene (**39**) using the 1,4-dihydropyridine **42**.*

Diethyl 1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (Hantzsch ester, HEH, **47**) has been found to reduce a variety of hydrogen acceptors, such as suitably activated ethylenes, azomethines and azo- and nitro-compounds. In particular, while nitrobenzene (**39**) reacted poorly and only at high temperature, 4-nitrostilbene (**46a**)

was much more readly reduced to 4-aminostilbene (**48a**). 4-Cyanostilbene (**46b**) and benzonitrile were absolutely inert under similar conditions (Scheme 3.6).



Scheme 3.6. *Thermal reductions of nitro derivatives **46a,b** and **39** using HEH (**47**).*

Moreover, it was found that 1,2-dihydroquinoline (Figure 3.3) gave the same type of reduction faster than the dihydropyridine donors. In this case the substrate was successfully tested on chloranil, maleic anhydride, azobenzene and benzylideneaniline.[24a]

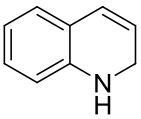
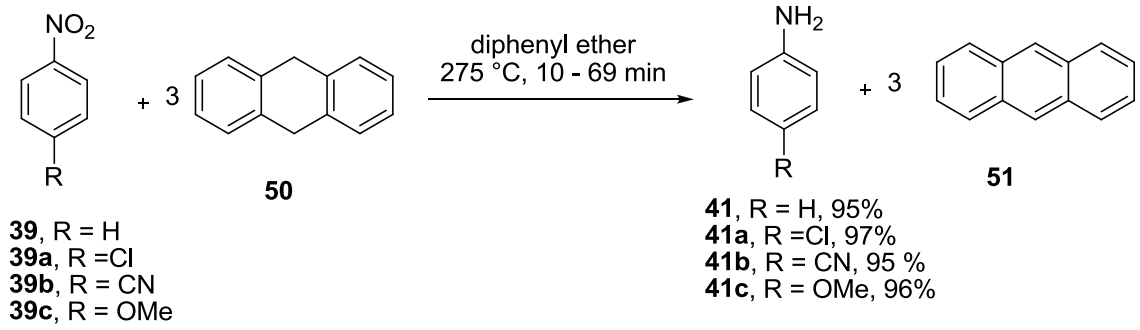


Figure 3.3. *Chemical structure of 1,2-dihydroquinoline.*

Nitrobenzenes **39** and **39a-c** were reduced almost quantitatively to the corresponding aniline derivatives **41** and **41a-c**, when heated to 230-300 °C with an excess of 9,10-dihydroanthracene (DHA, **50**) (Scheme 3.7).[41] The reduction followed an homolytic retrodisproportion path.

[41] Coellen, M.; Rüchardt, C. *Chem. Eur. J.* **1995**, *1*, 564.



Scheme 3.7. *Reduction of nitrobenzenes **39** and **39a-c** performed by DHA (**50**).*

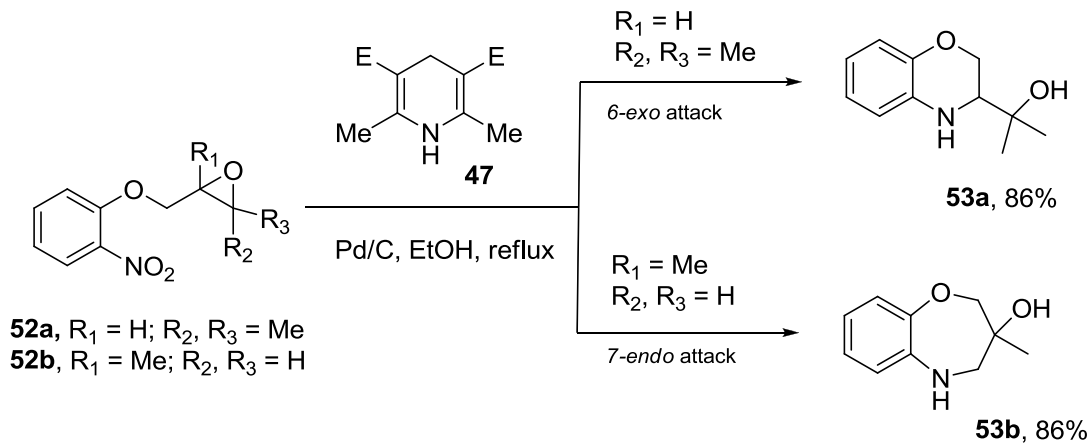
Intramolecular condensation of alicyclic 1,5-diketone with 2- and 4-nitroanilines and 2,4-dinitroaniline, generated 1,4-dihydropyridine intermediates through reduction of the nitro groups.[42]

Compared with the reaction described in Scheme 3.6, the reducing potential of HEH (**47**) was dramatically enhanced in the presence of Pd/C. Using the hydrogen donor **47** in the presence of Pd/C, a domino reaction led to benzoxazine derivatives **53a,** from 2-epoxy-3-(2-nitroaryloxy)propane **52a**. Selective reduction of the nitro group was observed, followed by a *6-exo* attack on the epoxide ring. The *7-endo* mode of attack was obtained from **52b**, affording the benzoxazepine derivative **53b** (Scheme 3.8).

The reaction was performed using substrates variously substituted in the aromatic ring to give the corresponding domino reaction products in high yields.[43]

[42] Maslov, K. V.; Egorov, A. G.; Akimova, T. I.; Kaminski, V. A. *Chem. Heterocycl. Compd.* **2002**, *38*, 560.

[43] For a dramatic enhancement of the reduction ability of HEH in the presence of Pd/C, see: Meng, Q.-y.; Liu, Q.; Li, J.; Xing, R.-G.; Shen, X.-X.; Zhou, B. *Synlett* **2009**, 3283 and references therein.

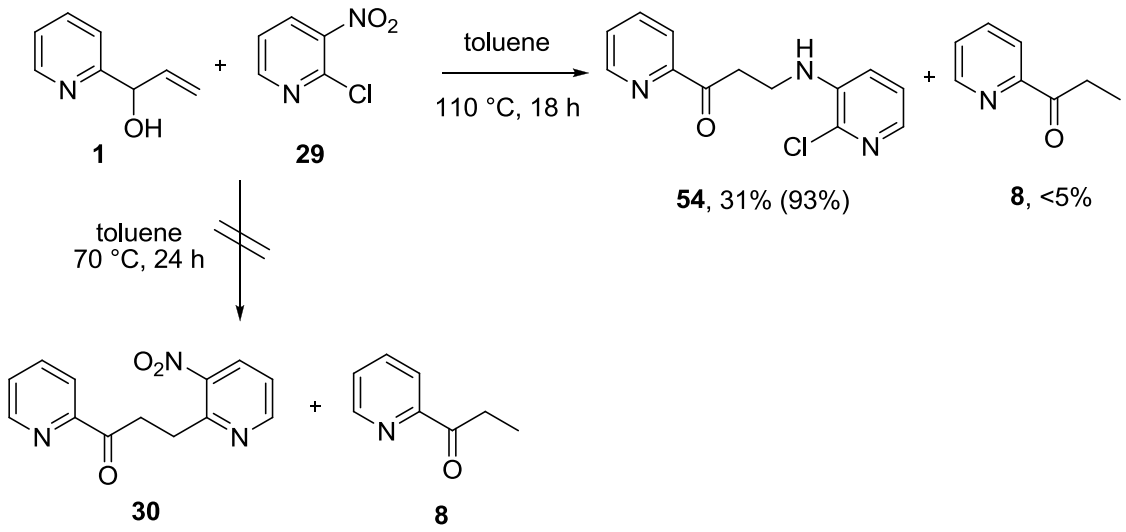


Scheme 3.8. *Reactions of epoxy(nitroaryloxy)propanes* ***52a*** *and* ***52b*** *with HEH and Pd/C.*

3.2. NEW REACTIVITY OF 1-(2-PYRIDYL)-2-PROPEN-1-OL (1) WITH NITRO DERIVATIVES.

3.2.1. FIRST RESULTS AND MECHANISTIC HYPOTESIS.

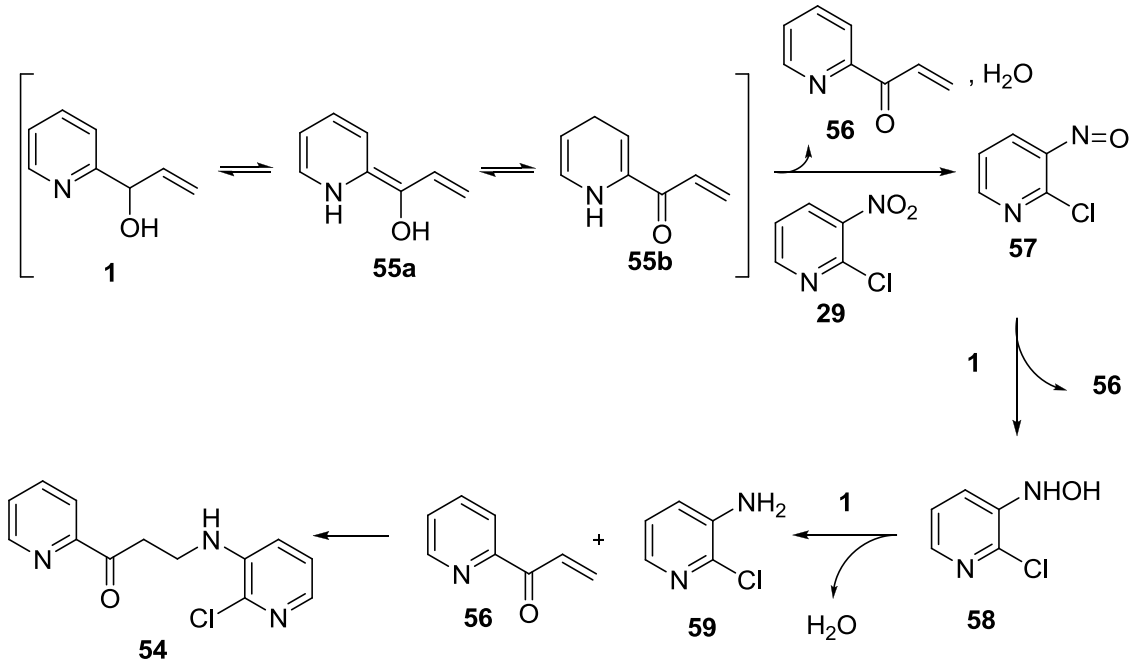
In Chapter 2 we described a new reactivity of 1-(2-pyridyl)-2-propen-1-ol (**1**) as 'vinilogous picoline' C-3 carbon nucleophile towards strongly activated heterocyclic electrophiles. This reaction were ascribed to the weak acidity of the 'picoline type' hydrogen atom on C-1 carbon of the allyl group. For the sake of a generalization of the 'vinilogous picoline' reactivity of **1** with 2-chloro-3-nitropyridine (**29**), the expected compound **30** was never observed working under purely thermal conditions (Scheme 3.9), whereas a new product **54** formed besides ethyl ketone **8**, the common side product derived from thermal isomerization (Chapter II, Scheme 2.5).



Scheme 3.9. *Thermal reaction of **1** with cloronitropyridine **29**.*

In fact, when alcohol **1** was heated with 5 equiv. of **29** in toluene at 110 °C for 18 h, compound **54** was isolated by flash chromatography in 31% yield (referred to the moles of alcohol **1**) that corresponds to 93% yield on the basis of the proposed reaction mechanism (Scheme 3.10). The presence of the amino functionality in compound **54** suggested a novel behavior of **1** as a reducing agent.[44] The reactivity of **1** is likely justified by its isomerization to the 1,4-dihydropyridine form **55b**, promoted by the weak acidity of the C(1)-H hydrogen of the allyl moiety (Scheme 3.10).

[44] (a) see Ref. 12. (b) Giomi, D.; Alfini, R.; Brandi, A. *Tetrahedron Lett*. **2008**, *49*, 6977.



Scheme 3.10. *Proposed mechanism for the reduction of* ***29*** *operated by alcohol* ***1****.*

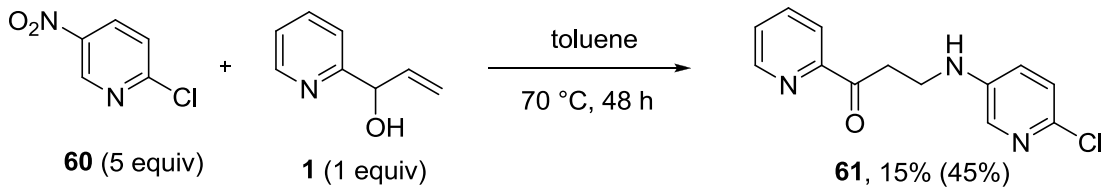
This equilibration allowed **1** to react as an HEH mimic which was able to reduce the heteroaromatic nitro group and to convert **1** into the oxidation product **56**. Then, a novel domino process occurred involving a cascade reduction of the nitro group of **29** into the corresponding amino derivative **59**. In the proposed mechanism, the reaction stoichiometry alcohol/nitro compound (*e.g.*, reducing agent/oxidizing agent), was 3:1, because the reduction cascade passed through the formation of two reactive intermediates as the nitroso and hydroxylamino derivatives **57** and **58**. An aza-Michael addition of the amine **59** to the pyridylvinyl ketone **56**, concluded the one-pot synthesis of the β-aminoester **54**. Likely, the vinyl ketone **56** being an optimal acceptor, the free amine **59** was never observed in the reaction mixture. The unreacted **56** was never isolated from the reaction mixture, likely due to concomitant decomposition/ polymerization processes. The excess of the reagent **29** (recovered by chromatography) was necessary to reduce the formation of **8**. Operating under the same reaction conditions but with an excess of alcohol **1** (ratio **1**/**29** ca 4:1), ethyl ketone **8** became the predominant product (ratio **8**/**54** ca 2:1, ^{1}H-NMR). Working at 70 °C, the reduction process took place, but alcohol **1** disappeared only after 72 h, while in the presence of a

base as NaH, the nucleophilic substitution was the favorite path leading to product **30** (Chapter 2, Scheme 2.15).

To test the synthetic potential of this new reactivity of **1**, the study was extended to other nitro derivatives.

3.2.2. REACTIONS WITH OTHER NITRO DERIVATIVES.

Similar results, albeit lower yields, were obtained when compound **1** was allowed to react with 5 equiv. of 2-chloro-5-nitropyridine (**60**). In this case a better result was obtained operating at lower temperature (70 °C rather than 110 °C) for a longer time (48 h); however, compound **61** was isolated in only 15% (45%) yield (Scheme 3.11).



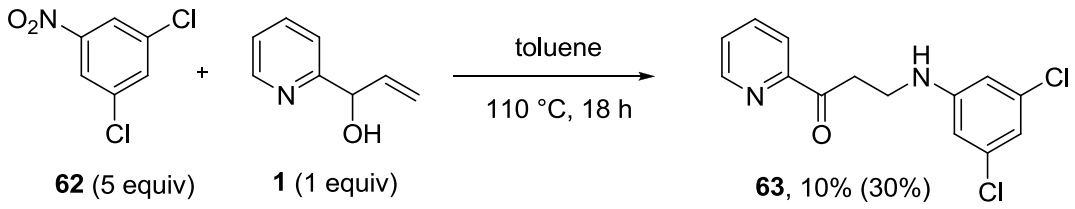
60 (5 equiv) **1** (1 equiv) **61**, 15% (45%)

Scheme 3.11. *Thermal reaction of **1** with chloronitropyridine **60**.*

Ethyl ketone **8** was always the only side product formed in variable yields depending on the reaction conditions. The amount of **8** was estimated via ^{1}H-NMR analyses of the reaction crude. In fact, due to its volatility (see Ref. 13), the amounts of **8** recovered after column chromatography and evaporation of the solvent at reduced pressure are significantly lower than in the original reaction mixture. Compared to compound **29**, reaction of **60** was faster, likely due to the reduced steric hindrance of the 2,5-disubstituted substrate.

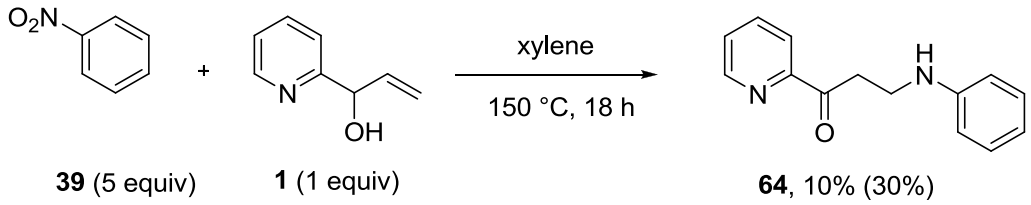
Less electron poor nitrobenzenes also participated in the reaction process, although at higher temperatures. The reaction of 1 with 5 equiv. of 3,5-dichloro-1-nitrobenzene (**62**) in toluene at 110 °C for 18 h led to aminoketone **63** in 10% (30%)[45] yield (Scheme 3.12).

[45] Yields in brackets refer to a reaction stoichiometry alcohol **1**/nitro derivative 3:1, according to the proposed mechanism.



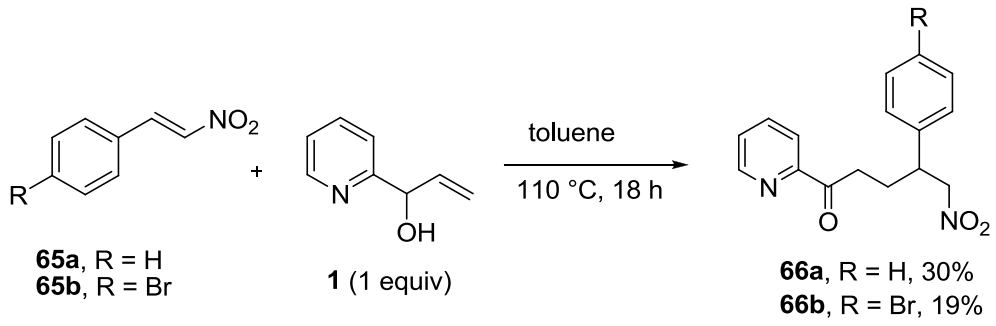
Scheme 3.12. *Thermal reaction of **1** with dichloronitrobenzene **62**.*

Nitrobenzene (**39**) resulted even less reactive at 110 °C, but rising the temperature at 150 °C in xylene led to the formation of compound **64**[46] in 11% (33%) yield (Scheme 3.13).



Scheme 3.13. *Thermal reaction of **1** with nitrobenzene (**39**).*

A different behaviour was observed with α,β-usaturated nitro compounds. In fact, when alcohol **1** was reacted with *trans*-β-nitrostyrene (**65a**) in toluene at 110 °C for 18 hours, the reduction process did not occur either for the NO_2 group or for the C=C double bond, and only the conjugate addition product **66a** was isolated in 30% yield, along with ketone **8**.



Scheme 3.14. *Reactions of **1** with nitroalkenes.*

[46] Kano, S.; Ebata, T.; Shibuya, S. *Chem. Pharm. Bull.* **1979**, *27*, 2450.

p-Bromonitrostirene (**65b**)[47] gave similar results leading to **66b** in 19% yield. Again, the formation of **66a,b** could be ascribed to the reactivity of **1** as vinylogous picoline C-3 carbon nucleophile (see Chapter II), now able to give conjugate addition to the electrophilic nitro alkenes **65a,b** (Scheme 3.14.).

The crucial role of the pyridine ring in the reduction processes was well evidenced by studying the reactivity of (2-pyridyl)phenyl methanol (**2**).[48] To avoid the low chemical efficiency of the reduction with propenol **1**, due to its competitive thermal isomerisation into the corresponding ethyl ketone **8**, we decided to test carbinol **2** as hydrogen donor.

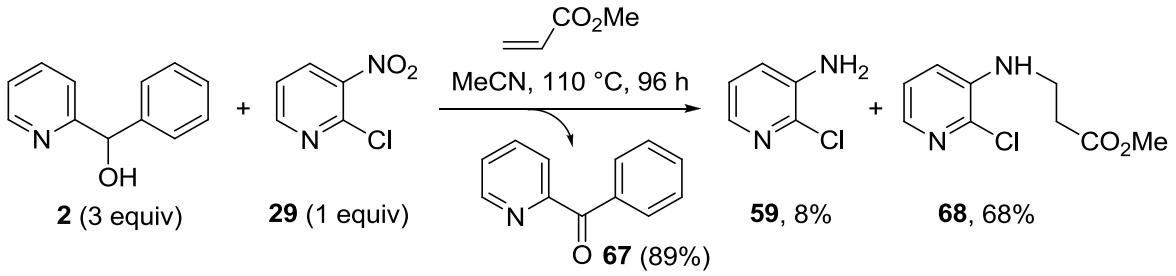
3.3. (2-PYRIDYL)PHENYL METHANOL: A NEW REAGENT FOR METAL-FREE REDUCTION OF NITRO AROMATIC COMPOUNDS[49]

3.3.1. FIRST RESULTS AND MECHANISTIC HYPOTESIS.

When alcohol **2** (3 equiv) was allowed to react with chloronitropyridine **29** (1 equiv) in toluene at 110 °C for 96 h, ketone **67**[48a,48d,50] was evidenced as the predominant product in the reaction mixture (^{1}H-NMR), while the formation of 3-amino-2-chloropyridine (**59**), originating from the reduction of **29**, was only observed via GC/MS analysis. In fact, aromatic amines are often quite unstable compounds for which direct trapping during their synthesis is strongly preferred to avoid different competitive reaction pathways. Among them, however concerning **59**, the condensation with ketone **67** should be ruled out as the corresponding product was never observed in the reaction

[47] Dominguez, X. A.; Slim, J.; Elizondo, A. *J. Am. Chem. Soc.* **1953**, *75*, 4581.
[48] (a) Tilford, C. H.; Shelton, R. S.; Van Campen, M. G. *J. Am. Chem. Soc.* **1948**, *70*, 4001. (b) Hemmerich, P.; Fallab, S. *Helv. Chim. Acta* **1958**, *41*, 498. (c) Bolm, C.; Muñiz, K. *Chem. Commun.* **1999**, 1295. (d) Trécourt, F.; Breton, G.; Bonnet, V.; Mongin, F.; Marsais, F.; Quéguiner, G. *Tetrahedron* **2000**, *56*, 1349. (e) Leprêtre, A.; Turck, A.; Plé, N.; Quéguiner, G. *Tetrahedron* **2000**, *56*, 3709. (f) Sugimoto, O.; Yamada, S.; Tanji, K. *J. Org. Chem.* **2003**, *68*, 2054. (g) Doudouh, A.; Woltermann, C.; Gros, P. C. *J. Org. Chem.* **2007**, *72*, 4978.
[49] Giomi, D.; Alfini, R.; Brandi, A. *Tetrahedron* **2011**, *67*, 167.
[50] Couve-Bonnaire, S.; Carpentier, J.-F.; Mortreux, A.; Castanet, Y. *Tetrahedron* **2003**, *59*, 2793.

crude. The above reaction was then repeated in acetonitrile in the presence of methyl acrylate (4 equiv) as an aza-Michael acceptor, added with the aim to trap the reduction product and to confirm the reactivity of **2** as a reducing agent (Scheme 3.15).

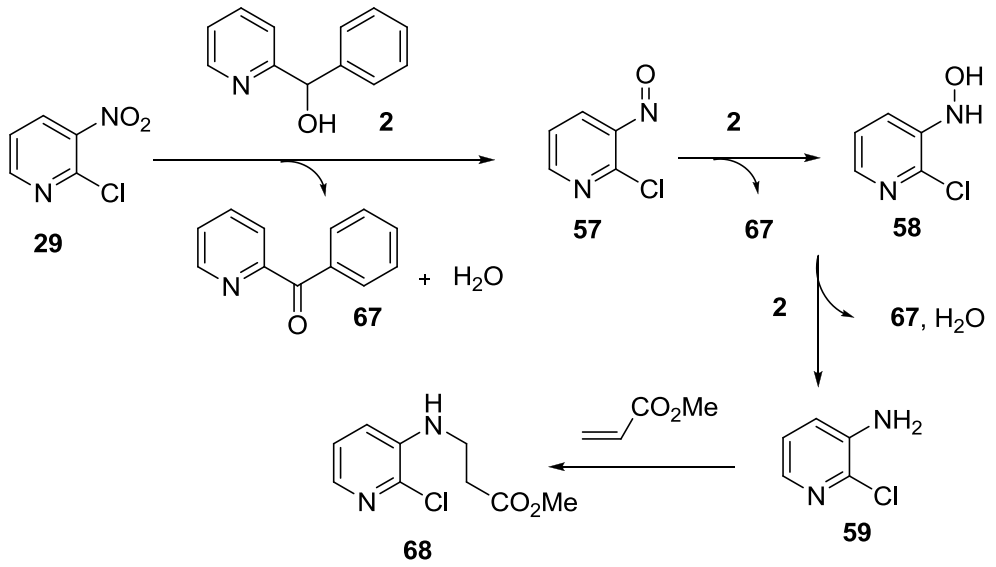


Scheme 3.15. *Reaction of alcohol* ***2*** *with 2-chloro-3-nitropyridine (****29****).*

The conjugate addition product **68** was isolated in 68% yield by flash chromatography along with ketone **67** recovered in 89% yield, referred to the full amount of alcohol **2** used. An excess of the nitro compound it was not necessary because for the carbinol **2**, with respect to the pyridylpropenol **1**, any thermal isomerisation is forbidden. By-the-way, the use of a "correct" stoichiometric ratio (3:1) between the reducing compound (carbinol **2**) and the oxidizing nitro derivative **29**, is a further confirmation of the proposed domino process involving this new class of HEH biomimetic reducing agents (Scheme 3.10). Moreover, the method provided an excellent access to □-amino esters in a domino multicomponent reaction. β-Amino acids and their derivatives are valuable synthetic intermediates.[51] Attempts to complete the conversion of **29** into **68** by operating with a larger excess of acrylate or by addition of a catalytic amount of acetic acid were unsuccessful.

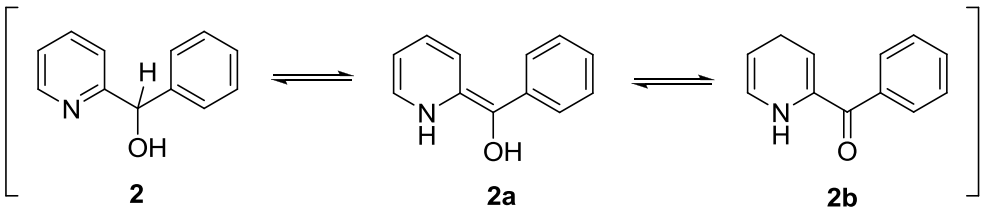
From a mechanistic viewpoint, the reaction stoichiometry (alcohol/nitro derivative ratio at least 3:1), associated with the recovery of ketone **67**, confirms the proposed reduction mechanism. Alcohol **2** acts as a reducing agent able to transform 2-chloro-3-nitropyridine (**29**), via the nitroso and hydroxylamino intermediates **57** and **58**, into the amino derivative **59**, converted into the final product **68** through aza-Michael addition to methyl acrylate (Scheme 3.16).

[51] Amore, K. M.; Leadbeater, N. E.; Miller, T. A.; Schmink; J. R. *Tetrahedron Lett.* **2006**, *47*, 8583.



Scheme 3.16. *Mechanistic rationale accounting for the formation of compound* ***68****.*

As previously supposed for pyridylpropenol **1**, such a reactivity of alcohol **2** could be ascribed to its behaviour as HEH mimic through the involvement of a 1,4-dihydropyridine tautomer **2b** generated as a consequence of the mobility of the hydrogen atom of the methanol residue (Scheme 3.17).

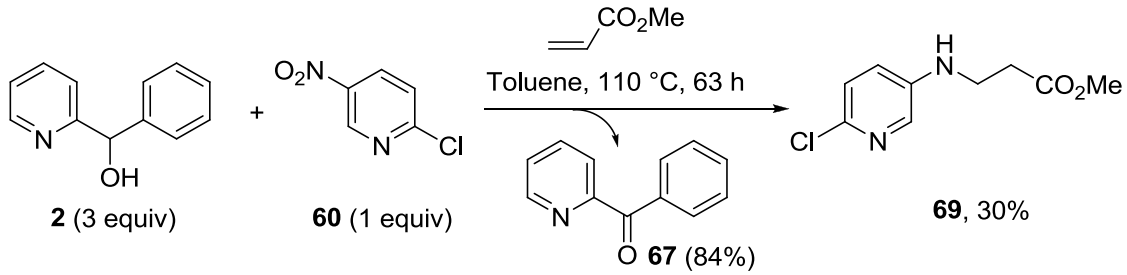


Scheme 3.17. *Tautomeric equilibration of alcohol* **2***.*

Reaction of other nitro heterocycles with alcohol **2** were studied to demonstrate the general application of the process.

3.3.2. REACTIVITY TOWARDS OTHER NITRO DERIVATIVES.

Operating under the same reaction conditions, a complex reaction mixture was obtained from the isomeric 2-chloro-5-nitropyridine (**60**): the amino ester **69** was isolated in only 30% yield, while ketone **67** was recovered in 84% yield (Scheme 3.18). The switch to acetonitrile as solvent did not change the poor result, probably due to side reactions of the intermediate 5-amino-2-chloropyridine. Operating without methyl acrylate, only traces of the free amine were detected in the reaction mixture (GC-MS analysis).

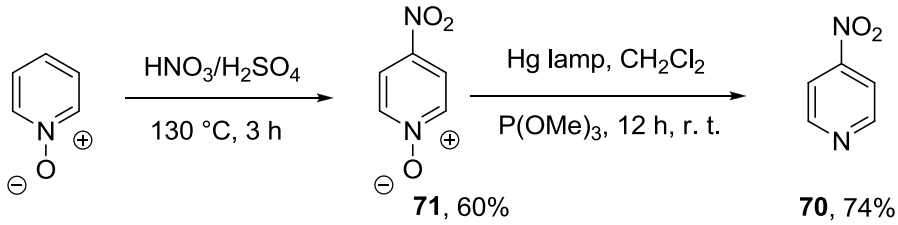


Scheme 3.18. *Thermal reaction of* ***2*** *with nitro derivative* ***60*** *in the presence of methyl acrylate.*

On the basis of the interest in 4-aminopyridine in the pharmacological domain,[52] and with the aim to test monofunctional nitropyridines to limit competitive pathways likely due to the presence of the chlorine atom on the pyridine ring, 4-nitropyridine (**70**) was allowed to react with **2**.

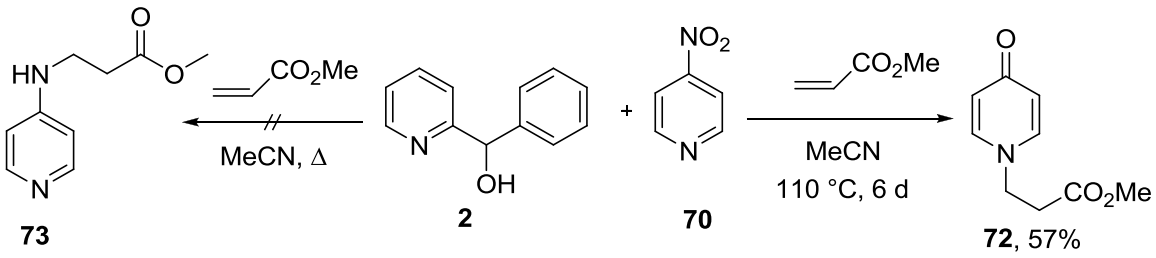
For the synthesis of compound **70**, a well known procedure was followed.[53] After the nitration of the pyridine-*N*-oxide, deoxygenation of the intermediate 4-nitropyridine-*N*-oxide (**71**) was realized operating in the presence of trimethylphosphite under UV radiation (Scheme 3.19).

[52] Mullin, R. *Chem. Eng. News* **2010**, *88* (*11*), 21.
[53] (a) Ochiai, E. *J. Org. Chem.* **1953**, *18*, 534. (b) Kaneko, C.; Yamamoto, A.; Gomi, M. *Heterocycles* **1979**, *12*, 227.



Scheme 3.19. *Synthesis of 4-nitropyridine (**70**).*

However, under thermal conditions a completely different behaviour of nitropyridine **70** with respect to the chloronitro derivatives **29** and **60** was observed. Operating in acetonitrile at 110 °C, the formation of the corresponding β-amino ester **73** was not observed, while the pyridone derivative **72** was isolated in 57% yield (Scheme 3.20).[54]

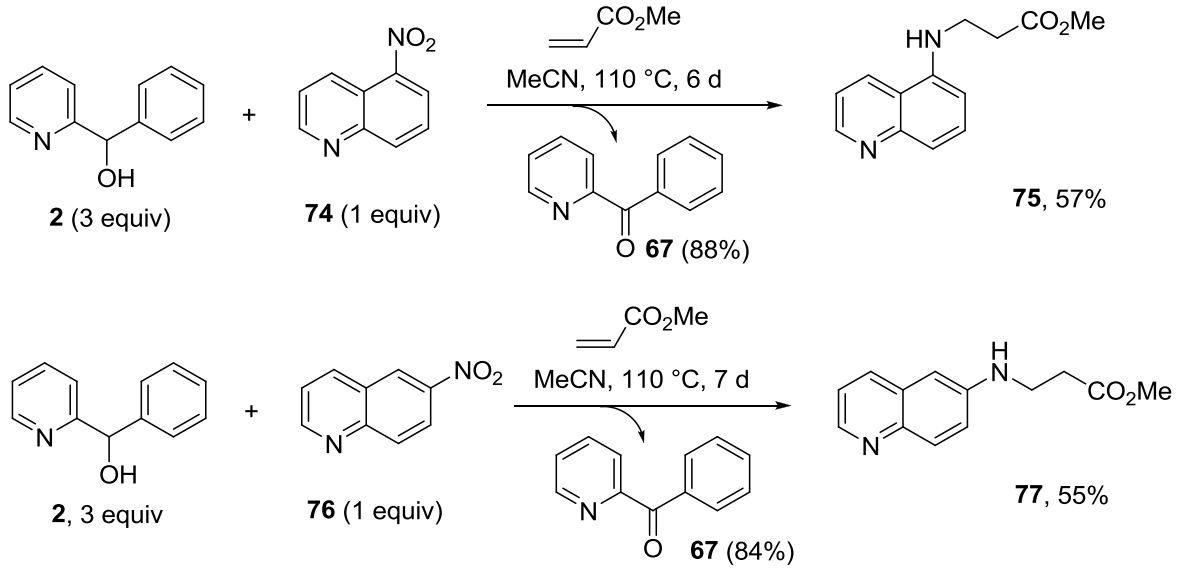


Scheme 3.20. *Thermal behaviour of 4-nitropyridine (**70**).*

Control experiments showed that compound **72** formed also in the absence of **2**, likely due to the hydrolysis of 4-nitropyridine to 4-pyridone[55,56] followed by an aza-Michael addition on methyl acrylate. However, 4-nitropyridine (**70**) was recovered unchanged after heating at 110 °C in dry toluene in the presence of alcohol **2** and molecular sieves. Likely, traces of water were able to promote the hydrolysis of 4-nitropyridine (**70**) to 4-pyridone.

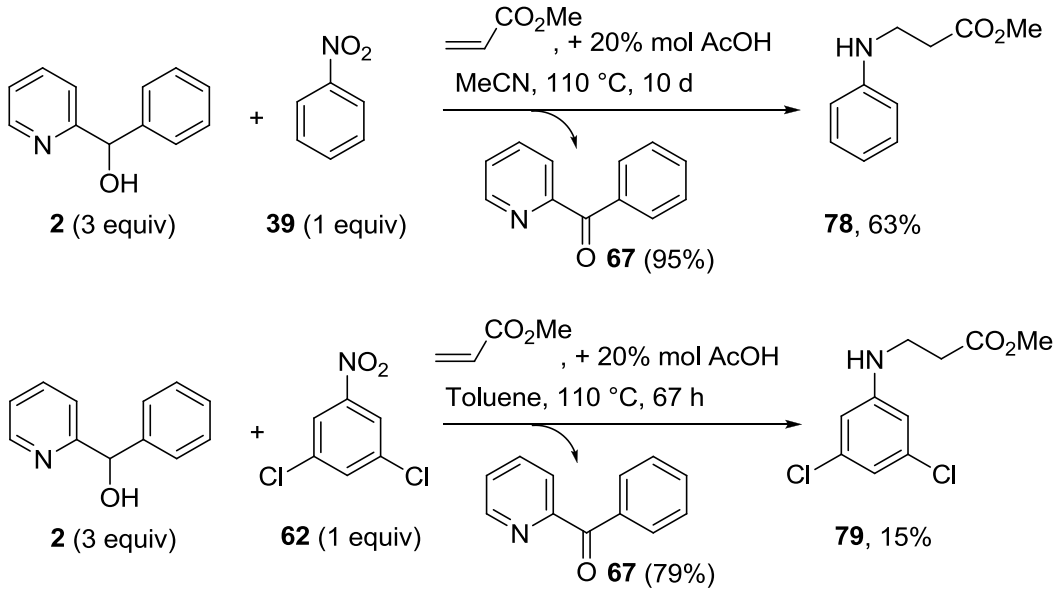
[54] The same behavior was observed in toluene, but with higher thermal conversion of alcohol **2** into ketone **67** (^{1}H-NMR).
[55] Den Hertog, H. J.; Broekman, F. W.; Combé, W. P. *Recl. Trav. Chim. Pays-Bas* **1951**, *70*, 105.
[56] Operating at 110 °C in non anhydrous conditions, and without methyl acrylate, 4-nitropyridine was converted to *N*-(4'-pyridyl)-4-pyridone, according with Ref. 55.

Better results were obtained with monofunctionalyzed nitro heterocycles such as 5-nitroquinoline (**74**) and 6-nitroquinoline (**76**) which gave, in acetonitrile as solvent, the valuable β-amino esters **75** and **77** in 57 and 55% yields, respectively (Scheme 3.21).



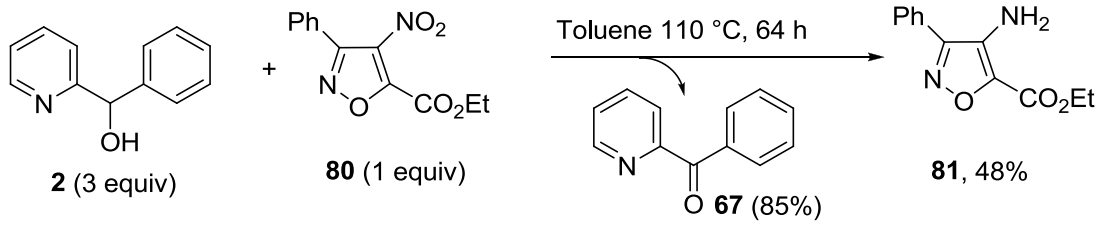
Scheme 3.21. *Reactions of carbinol* **2** *with nitroquinolines* **74** *and* **76**.

Nitrobenzene derivatives could be also reduced by alcohol **2**. The reactions were performed in the presence of 20 mol% of AcOH to favor the aza-Michael addition. Nitrobenzene (**39**) gave the β-anilino ester **78** in 63% yield by prolonged heating in MeCN, whereas the more activated dichloro derivative **62** was more quickly converted in toluene into the amino ester **79**, however isolated in only 15% yield (Scheme 3.22).



Scheme 3.22. *Reactions of carbinol* ***2*** *with nitrobenzenes* ***39*** *and* ***62****.*

The reactivity of **2** was also tested towards different heterocycles like nitroisoxazoles. A chemoselective reduction of the NO_2 group of the nitro ester **80**[57] leading to the corresponding amino isoxazole **81** in 48% yield was achieved (Scheme 3.23).

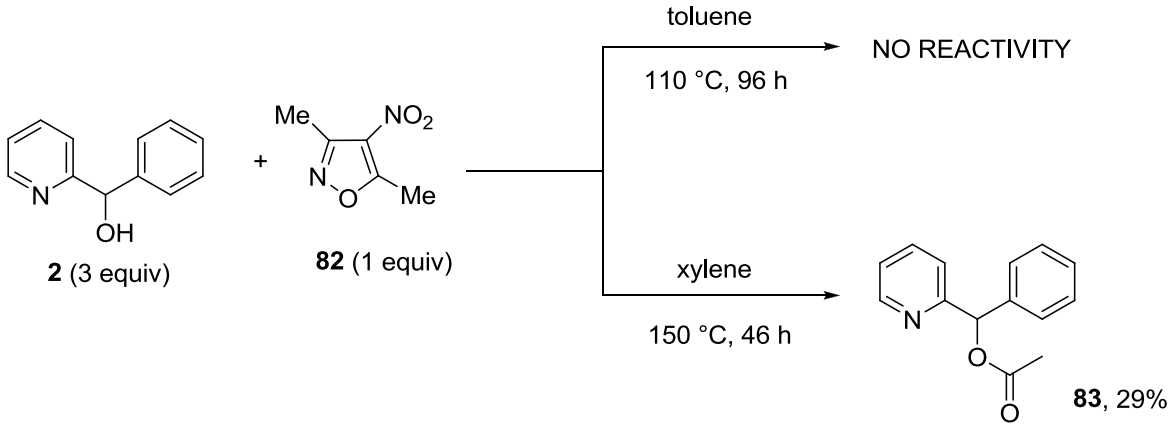


Scheme 3.23. *Reaction of carbinol* ***2*** *with nitroisoxazole* ***80****.*

Attempts to convert **81** into the corresponding β–amino ester operating in the presence of methyl acrylate were unsuccessful, likely due to the less nucleophilic character of the amino function.

3,5-Dimethyl-4-nitroisoxazole (**82**), however was recovered unchanged after heating with an excess of **2** in toluene at 110 °C for 96 hours, while when operating in xylene at 150 °C only the acetate derivative **83** was isolated in 29% yield (Scheme 3.24).

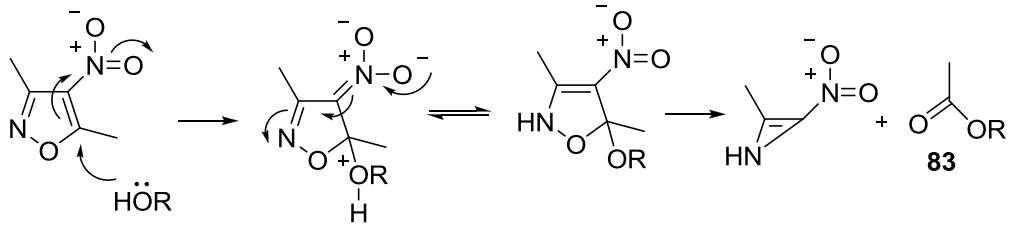
[57] Nesi, R.; Chimichi, S.; Sarti-Fantoni, P.; Buzzi, A.; Giomi, D. *Heterocycles* **1985**, *23*, 1465.



Scheme 3.24. *Reactions of carbinol* **2** *with nitroisoxazole* **82**.

The previous reaction is a further demonstration that an electron-poor nitro derivative is necessary to realize the reductive process.

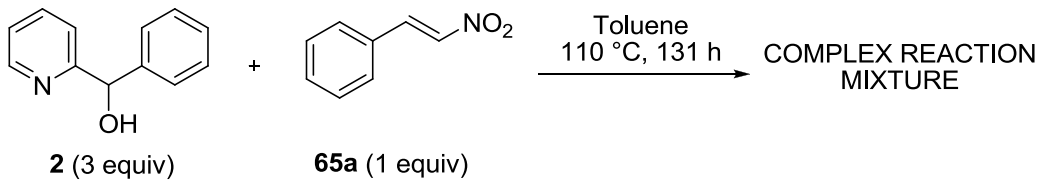
Concerning the formation of acetate **83**, it is likely that thermal decomposition of the isoxazole **82** prevails in these condition, showing its reactivity as a masked acetate (Scheme 3.25).[58] Nucleophilic attack of alcohol **2** on the C-5 carbon atom of the isoxazole ring with subsequent ring opening gave derivative **83**.



Scheme 3.25. *Mechanistic rationale for the formation of compound* **83**.

With an α,β-unsaturated system as *trans*-β-nitrostyrene (**65a**), working in toluene at 110 °C, the starting nitro derivative disappeared after 131 h, but it was not possible to resolve the resulting complex reaction mixture. No traces of reduction products were detected, while a conversion of 50% of the alcohol **2** into ketone **67** was estimated by ^{1}H-NMR and GC-MS analyses (Scheme 3.26).

[58] Adamo, M. F. A.; Duffy, E. F. *Org. Lett.* **2006**, *8*, 5157.

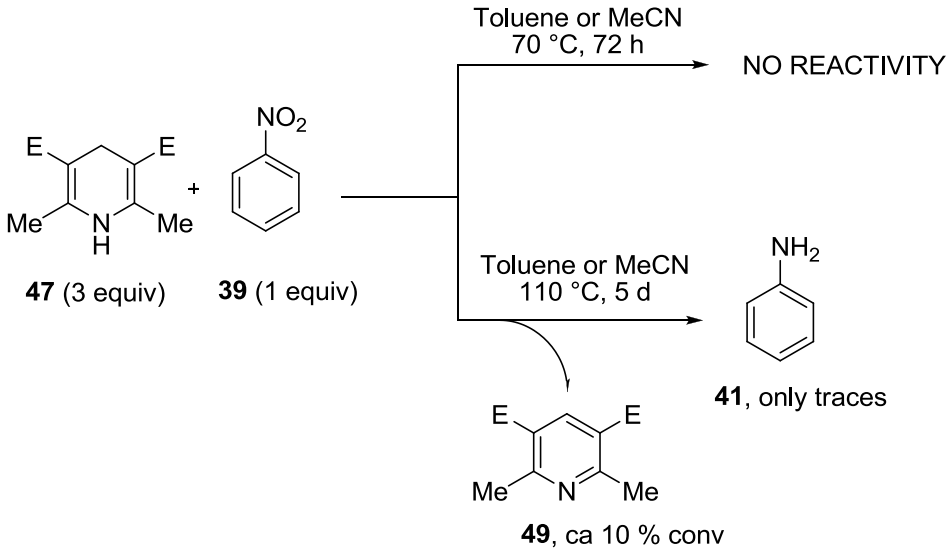


Scheme 3.26. *Reaction of carbinol* **2** *with nitrostyrene* ***65a****.*

3.3.3. REACTIVITY OF HEH TOWARDS NITRO DERIVATIVES.

To evaluate the potential of (2-pyridyl)phenyl methanol (**2**) in the reduction of nitro aromatics and heteroaromatics, its reactivity towards the poorly activated nitrobenzene (**39**) was compared with that of Hantzsch ester **47** in the same reaction conditions.

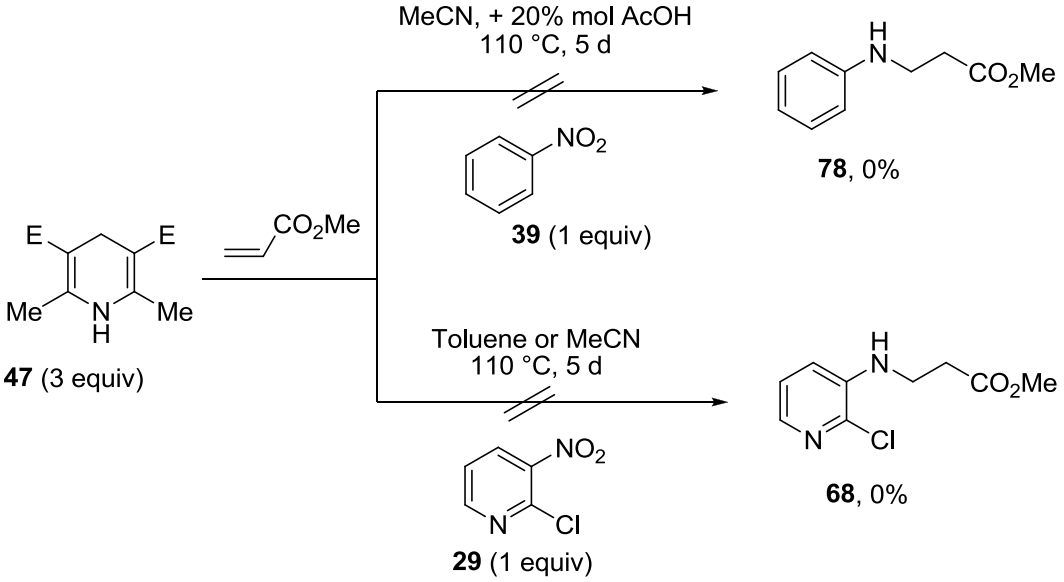
When nitrobenzene (**39**) was heated in a screw-cap tube with an excess of **47** (3 equiv) in toluene or MeCN, after 72 h at 70 °C the reaction mixture appeared unchanged. Raising the temperature to 110 °C for 5 days, the conversion of **47** into the corresponding pyridine derivative **49** was the only significant process, and only trace amounts of aniline (**41**) were observed (GC-MS) along with unreacted **39** (Scheme 3.27). These results well agree with the literature data[59] about the uncatalyzed aerial oxidation of Hantzsch ester **47** in different organic solvents.



Scheme 3.27. *Thermal reaction of HEH (****47****) with nitrobenzene (****39****).*

[59] Xu, X.; Xu, H. *Asian J. Chem.* **2009**, *21*, 4599.

Operating under the same conditions described for alcohol **2** (MeCN, in the presence of methyl acrylate and AcOH as catalyst), after 5 days at 110 °C, **78** was completely absent in the reaction mixture that contained only pyridine **49** and nitrobenzene (**39**)(Scheme 3.28). The same result was also observed when the more activated 2-chloro-3-nitropyridine (**29**) was heated with ester **47** and methyl acrylate at 110 °C in MeCN for 4 days: only unreacted **29** and the aromatic derivative **49** were detected in the reaction mixture (Scheme 3.28).



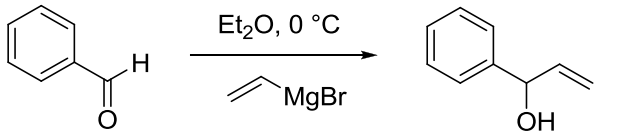
Scheme 3.28. *Reaction of **47** with nitro derivatives **39** and **29** in the presence of methyl acrylate.*

As previously reported, these data, confirmed further the poor reducing power of the 1,4-dihydropyridine Hantzsch ester (**47**) towards nitro aromatic and heteroaromatic compounds.[24a] The lack of reactivity of HEH (**47**) is remarkable, as this popular reagent has been employed in a vast array of hydrogen transfer reductions,[25,28,30] and provides even more interest in (2-pyridyl)phenyl methanol (**2**) as a new reducing agent. An explanation of the different reactivity is rather premature, although a brief structural comparison of the two compounds shows the presence of sterically bulky substituents in the dihydropyridine ring of Hantzsch ester that might slow down its reactivity compared to **2**.

3.4. MECHANISTIC CONFIRMATIONS.

To confirm the proposed mechanistic hypothesis (Schemes 3.10 and 3.16), the behaviors of phenylpropenol **84** and (4-nitrophenyl)phenyl methanol **86** towards nitro pyridine **29** were investigated.

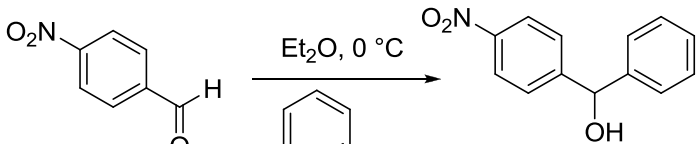
According with the synthesis of alcohol **1**, carbinol **84** was obtained by addition of vinylmagnesium bromide to benzaldehyde (**44**) (Scheme 3.29).[60]



44 **84**, 47%

Scheme 3.29. *Synthesis of phenylpropenol 84.*

Carbinol **86** was similarly obtained by reaction between p-nitrobenzaldehyde (**85**) and phenylmagnesium bromide (Scheme 3.30).[61]

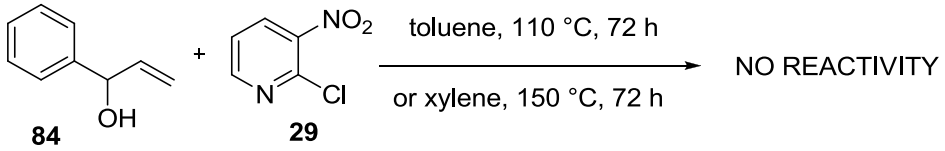


85 **86**, 44%

Scheme 3.30. *Synthesis of carbinol 86.*

Operating in toluene at 110 °C for 72 h, alcohol **84** appeared totally inert toward compound **29**. After heating in xylene at 150 °C for 72 h, only traces of the corresponding ethyl ketone (deriving from the themal isomerisation of **84**) were observed (^{1}H-NMR) along with unchanged starting material (Scheme 3.31).

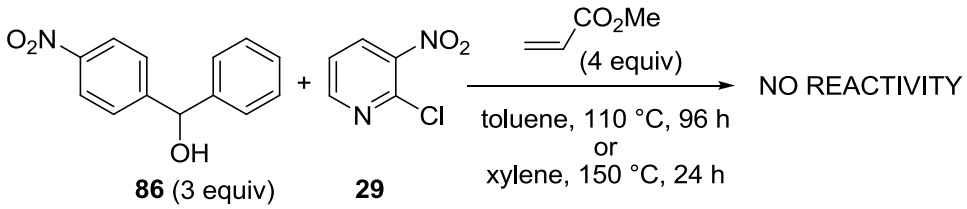
[60] Lehmann, J.; Lloyd-Jones, G. C. *Tetrahedron* **1995**, *51*, 8863.
[61] (a) Wang, J.-T.; Fan, X.; Feng, X.; Qian, Y.-M. *Synthesis* **1989**, 291. (b) Lerebours, R.; Wolf, C. *J. Am. Chem. Soc.* **2006**, *128*, 13052.



Scheme 3.31. *Reaction of phenyl carbinol **84** with nitro compound **29**.*

These results are an important evidence of the role played by the pyridyl ring of **1** and by the dihydropyridyl intermediates **55a**,**b** (Scheme 3.10) in order to rationalize the reactivity of pyridylpropenol **1** as reducing agent towards nitro aromatic and heteroaromatic systems.

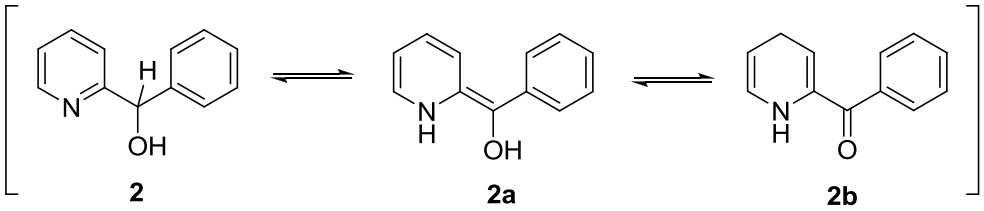
Nitrophenyl derivative **86**, apparently analogous to alcohol **2**, with a 4-nitrophenyl group in place of the pyridyl ring, was only poorly converted to 4-nitrobenzophenone when heated in toluene at 110 °C or in xylene at 150 °C in the presence of **29** and methyl acrylate,[62] and reduction products were absent from the reaction mixture mainly containing the starting reagents (Scheme 3.32).



Scheme 3.32. *Reactions of carbinol **86** with 2-chloro-3-nitropyridine (**29**).*

These results clearly evidenced the key role of the pyridine ring in promoting the reactivity of **2** as a reducing agent. These data underlined that such a reactivity of alcohol **2** could be ascribed to its behaviour as HEH mimic, through the involvement of 1,4-dihydropyridine tautomers, generated as a consequence of the mobility of the hydrogen atom of the methanol residue (Scheme 3.33).

[62] (a) For a facile oxidation of secondary benzyl alcohols to ketones, see: Sano, Y.; Tanaka, T.; Hayashi, M. *Chem. Lett.* **2007**, *36*, 1414. (b) An experiment control showed that alcohol **86** was converted to some extent (ca. 25 %) into the corresponding ketone by heating in toluene at 110 °C for 4 days.

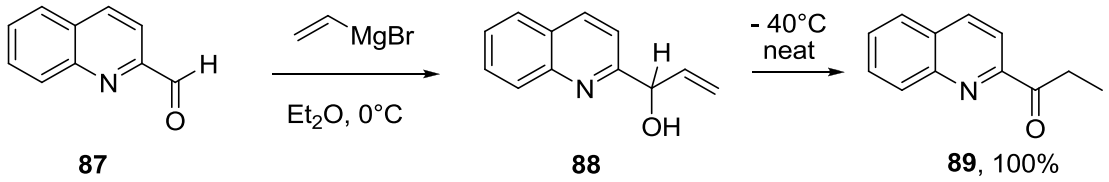


Scheme 3.33. *Tautomeric forms of alcohol* **2**.

3.5. (2-QUINOLYL)PHENYL METHANOL: A NEW VERY PROMISING REAGENT FOR THERMAL AND METAL-FREE REDUCTION

3.5.1. INTRODUCTION

With the aim to use quinolylpropenol **88** as starting material for the syntheses of new benzoindolizidines (see Chapter 4), its thermal behaviour was studied. Surprisingly, alcohol **88** isomerized into the corresponding ethyl ketone **89**,[63] although the crude reaction mixture coming from the treatment of quinolinecarboxaldehyde (**87**) with vinylmagnesium bromide was kept at – 40°C (Scheme 3.34).



Scheme 3.34. *Isomerization of alcohol 88 into ethyl ketone 89.*

As for the corresponding pyridyl derivative **1** (see Chapter 2, Scheme 2.5 and 2.8), a mechanistic rationale of the above result could be proposed taking into account the weak acidity of the 'picoline-type' hydrogen atom on the C-1 carbon of the allyl residue of compound **88**. At the same time the stability of allyl alcohol **1** at low temperature

[63] Tan, Q.; Hayashi, M. *Adv. Synt. Catal.* **2008**, *350*, 2639.

(pyridylpropenol **1** was converted into the corresponding ethyl ketone after heating for 48h at 110 °C, see Chapter 2, Scheme 2.5) suggested the greater acidity of the 'picoline type' hydrogen in **88** with respect to **1**. A less aromatic character of the quinoline ring of **88** with respect to the pyridyl one can be invoked to explain the major mobility of the proton at C-1.

In fact, although the criterion of the aromatic character provided by the Huckel rule[64] strictly applies only to monocyclic compounds, it has been long recognized, however, that compounds with structures in which a benzene ring is fused to another aromatic ring system (*e.g.*, pyridine) retain their aromatic properties, albeit in modified form. Some criteria are used to evaluate the aromaticity: bond lengths, the presence of a ring current showed in NMR spectra and physical probes of electronic structure (ultraviolet absorption spectra, photoelectron or electron trasmission spectroscopy). The *empirical resonace energy*, the *delocalization energy* and the calculated *resonance energies* are other estimates of aromaticity and they are particularly useful to make a comparison of the aromaticities of different heterocycles. Two types of the thermochemical determination have commonly been used to estimate the stabilization of aromatic compounds: measurement of the standard enthalpy of combustion and the standard enthalpy of hydrogenation. The heat of formation can be calculated by adding together individual bond energy values, as the molecule appears a 'localized bonds' system. The difference between experimental and calculated values is a measure of the stabilization of the delocalized system and it is the *empirical resonance energy*.

The energy of the π molecular orbitals can be expressed in terms of two constants. The first, the *Coulomb integral*, denoted by the symbol α, is the energy of an electron in an isolated π-orbital before overlap. The second term, the *resonance integral* (β), is a measure of the stabilization gained by interaction of adjacent π-orbitals. The measure of aromatic stabilization could be based on a comparison between the aromatic species and a simple unconjugated π-electron acyclic system as model. The energy difference is the *delocalization energy*.

[64] The *Huckel rule*, which is based on simply molecular orbital calculations, states that planar molecules with a complete and uninterrupted cycle of π-orbitals are stabilized, with respect to acyclic counterparts, when they contain $(4n+2)$ π-electrons, n being zero or an integer. Benzene, as pyridine, obey the Huckel rule for $n = 1$.

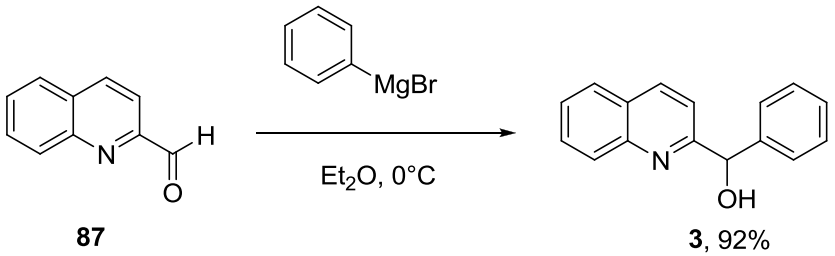
In seeking a better measure of aromatic character the reference system becomes a 'cyclic nonaromatic' model rather than a 'nonconjugated' one. Cyclic systems that show additional π binding energy compared with the calculated reference value are termed 'aromatic'. The additional energy is called *resonance energy*. And it can be calculated by simple Huckel MO method. In order to make a comparison of the aromaticities of different heterocycles, it is useful to calculate the resonance energy per π-electron (REPE), by dividing the resonance energy by the number of π-electrons in the molecule (Table 3.1).

	Empirical resonance energy	**REPE (β)**
	Kcal mol^{-1}	
Benzene	35.9	0.065
Pyridine	27.9	0.058
Quinoline	48.4	0.052

Table 3.1. *Empirical resonance energy and REPE for aromatic compounds.*

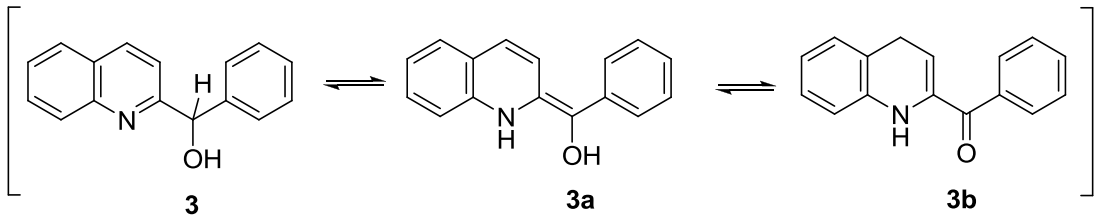
For known systems (*e.g.*, benzene, pyridine and quinoline) the values correlate well with other criteria of aromaticity. The method can be used to predict the degree of aromaticity of heterocycles. A benzofused heterocycle, as quinoline, has got a lower stabilization than pyridine. Following these observations, the quinolylphenyl carbinol **3**[65] was considered a good candidate for the hydrogen transfer processes. Compound **3** was isolated by chromatographic purification of the crude reaction mixture resulting from the reaction of quinolylcarboxaldehyde **87** and phenylmagnesium bromide (Scheme 3.35).[66]

[65] (a) Gros, P.; Fort, Y.; Caubère, P. *J. Chem. Soc. Perkin Trans. 1* **1997**, 3597. (b) Dumouchel, S.; Mongin, F.; Trécourt, F.; Quéguiner, G. *Tetrahedron* **2003**, *59*, 8629.
[66] De Diesbach, H.; Pugin, A.; Morard, F.; Nowaczinski, W.; Dessibourg, J. *Helv. Chim. Acta* **1952**, *35*, 2322.



Scheme 3.35. *Synthesis of carbinol* ***3****.*

Thermal isomerization of derivative **3** is forbidden thanks to the replacement of the vinyl group of compound **88** with a phenyl ring. Moreover, the minor aromatic character of quinoline with respect to pyridine leads to an improved C(1)-H proton mobility, promoting the equilibration towards the 'dihydropyridine' tautomers (Scheme 3.36). Therefore, the formation of the 1,4-dihydropyridine form **3b** from carbinol **3** will be easier than the formation of dihydropyridine tautomer **2b** from the pyridine system **2** (Scheme 3.17).



Scheme 3.36. *Tautomeric forms of alcohol* ***3****.*

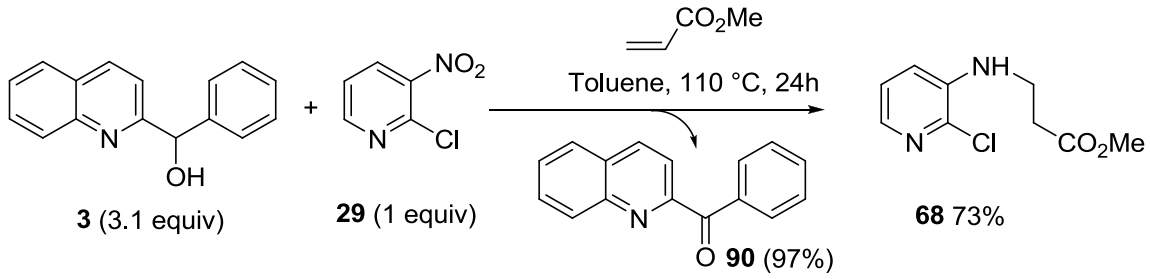
In the light of these considerations, the new carbinol system **3** was tested as HEH mimic towards hetero- and aromatic nitro compounds. In fact, as demonstrated in the previous sections, the dihydropyridine forms of type **2b** and **3b** play a key role in the reducing metal free processes.

3.5.2. SYNTHESES OF β-AMINO ESTERS

Following the same procedure used for alcohol **2**, carbinol **3** was tested as reducing agent in the thermal one-pot syntheses of β-amino esters from nitro derivatives and

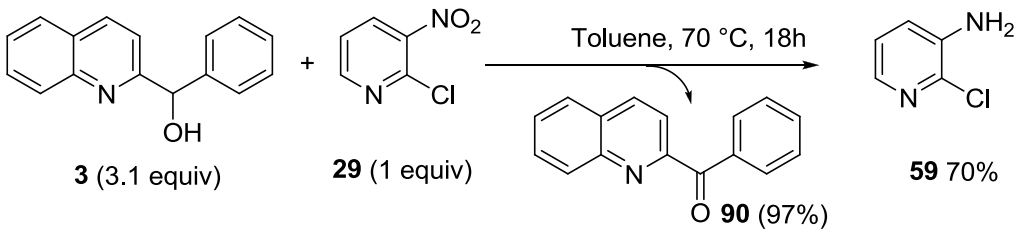
methyl acrylate, used as Michael acceptor. All the reactions showed improvements with respect to the use of pyridylphenyl methanol **2**.

First the activated 2-chloro-3-nitropyridine (**29**) was tested. Performing the reaction for 24 h at 110 °C in toluene, the quinolyl(phenyl) ketone **90**[67] was isolated by chromatographic resolution as the major reaction product deriving from the oxidation of the starting carbinol **3**, while the β-amino ester **68** was obtained in 73% yield (Scheme 3.37).



Scheme 3.37. *Reaction of carbinol **3** with nitro derivative **29** in the presence of methyl acrylate.*

Longer reaction times (96h) were necessary to perform the same reaction using carbinol **2**, even affording compound **68** in a lower yield (68%, Scheme 3.15). The reaction mechanism is that depicted in Scheme 3.16. The reduction of the nitro group of **29** was also observed working at lower temperature (70 °C) for 18 h (Scheme 3.38).

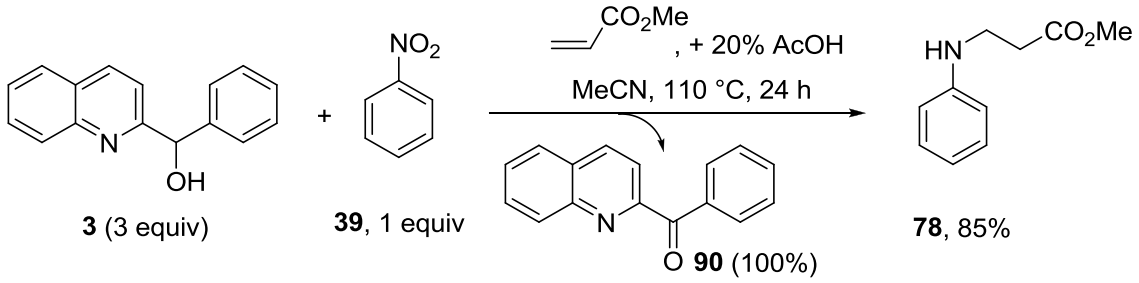


Scheme 3.38. *Reaction of carbinol **3** with nitro derivative **29** in the absence of methyl acrylate.*

[67] Gomez, I.; Alonso, E.; Ramon, D. J.; Yus, M. *Tetrahedron* **2000**, *56*, 4043.

Working with the pyridyl system **2** at 110 °C for longer reaction times, in the absence of methyl acrylate, the formation of 3-amino-2-chloropyridine (**59**) was only observed via GC/MS analysis: in these more drastic conditions the instability of amine **59** led to a complex reaction mixture. Anyway, working in the presence of methyl acrylate, higher temperatures were necessary to perform the aza-Michael addition of the aminochloropyridine **59** to the methyl acrylate. Moreover, the use of carbinol **3** as reducing agent allowed to improve the reactions with less activated nitro systems, as nitrobenzene (**39**). In fact, as evidenced in the Schemes 3.16 and 3.22, compound **39** reacted with pyridylpropenol **1** by heating at 150 °C for 18 h and with pyridyl carbinol **2** at 110° for 10 days.

The reaction of **3** with nitrobenzene (**39**) was performed in only 24 h at 110 °C, and chromatographic resolution of the crude reaction mixture afforded ketone **90** in quantitative yield and β-amino ester **78**, deriving from Michael addition of aniline to methyl acrylate in 85% yield (Scheme 3.39).



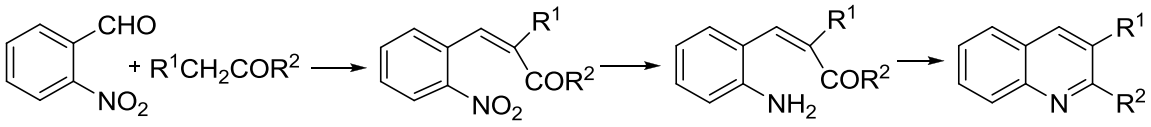
Scheme 3.39. *Synthesis of compound **78** using carbinol **3**.*

3.5.3. SYNTHESIS OF QUINOLINE

An interesting synthetic application of the quinolyl carbinol **3** was the synthesis of quinoline (**92**), starting from *trans-ortho*-nitrocinnamaldehyde (**91**). In fact an *ortho*-disubstituted benzene was the basis for the access to the quinoline ring (Friedländer synthesis).[68] In this type of reaction an *o*-aminobenzaldehyde or an *o*-aminoketone is cyclized by reaction with an α-methylene ketone in the presence of a base. Its synthetic

[68] Gilchrist, T. L. *Heterocyclic chemistry*, 2nd ed, Longman: Harlow, UK, 1992, p. 155.

use is limited by the difficulty in preparing *o*-aminoaryl carbonyl compounds. A useful modification is the reaction of an *o*-nitroaryl carbonyl compound with the activated methylene derivative allowed by the *in situ* reduction of the nitro group to the corresponding amino functionality (Scheme 3.40).

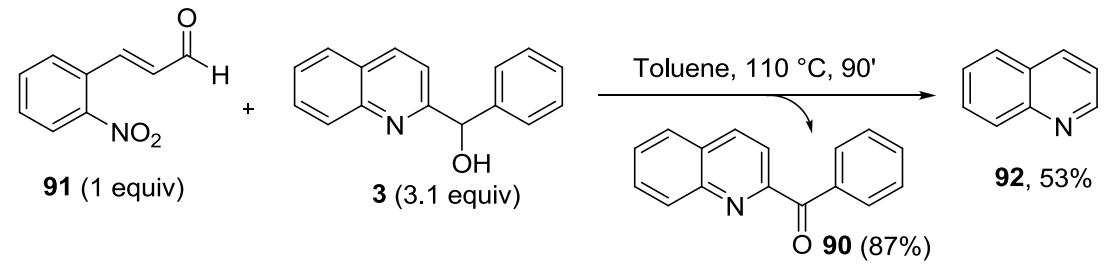


Scheme 3.40. *Modification of the quinoline Friedländer synthesis.*

Different methodologies have been exploited to perform the reduction process. Nitro group is reduced by ferrous sulphate heptahydrate and hydrochloric acid leading to **92** in 82% yield.[69] While the use of $[PdCl_2(PPh_3)_2]$–$SnCl_2$ in CO atmosphere in sealed reactor gave quinoline (**92**) in low yield,[70] indium/ammonium chloride in acqueus ethanol was found to be a very effective reagent in the reductive cyclization.[71] H_2 in the presence of Pd/C was also used to perform the reduction.[72] An interesting metal-free reductive cyclization of variously functionalized *o*-nitrocinnamaldehydes made use of bakers' yeast in NaOH media. Quinoline (**92**) was obtained in 88% yield.[73]

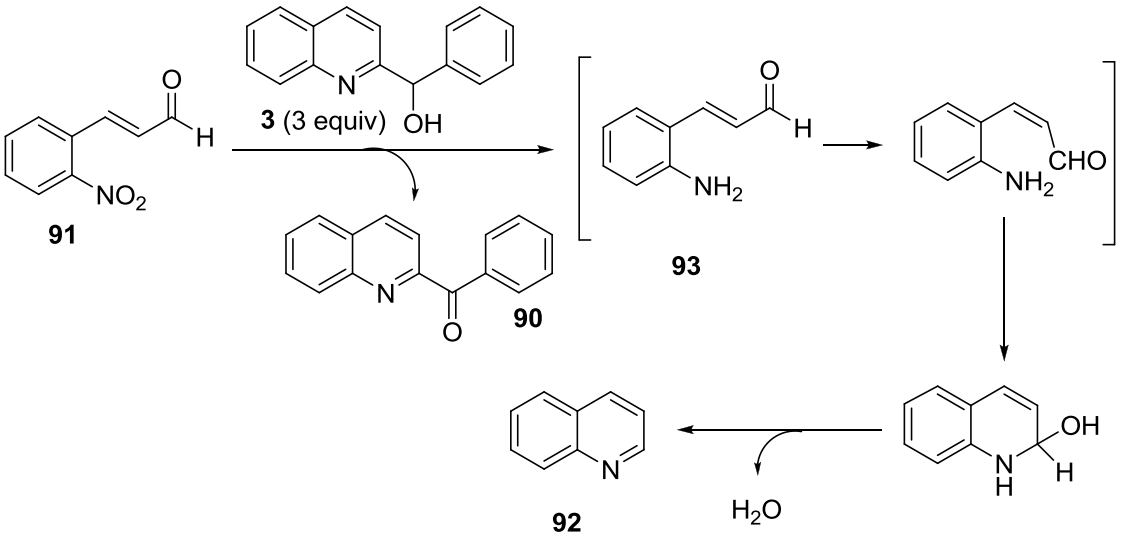
When alcohol **3** was allowed to react with nitrocinnamaldehyde **91** in toluene at 110 °C, for 1h and half, quinoline (**92**) was isolated in 53% yield, along with ketone **90**, recovered in 87% yield (Scheme 3.41).

[69] Davey, W.; Gwilt, J. R. *J. Chem. Soc.* **1955**, 1384.
[70] Akazome, M.; Kondo, T.; Watanabe, Y. *J. Org. Chem.* **1994**, *59*, 3375.
[71] Banik, B. K.; Banik, I.; Samajdar, S.; Wilson, M. *Heterocycles* **2004**, *63*, 283.
[72] Some, S.; Ray, J. K.; Banwell, M. G.; Jones, M. T. *Tetrahedron Lett.* **2007**, *48*, 3609.
[73] Baik, W.; Kim, D. I.; Lee H. J.; Chung W.-J.; Kim, B. H.; Lee S. W. *Tetrahedron Lett.* **1997**, *38*, 4579.



Scheme 3.41. *Metal-free synthesis of the quinoline* ***92****.*

Hydrogen transfer, likely involving the dihydropyridine form **3b**, allowed to convert **91** into aminocinnamaldehyde **93**; then, isomerization of the *trans* double bond into the *cis* one led to a correct geometry for a 6-*exo*-trig cyclization involving the intramolecular nucleophilic attack of the amino group to the aldehyde. Water elimination gave quinoline (**92**) (Scheme 3.42).

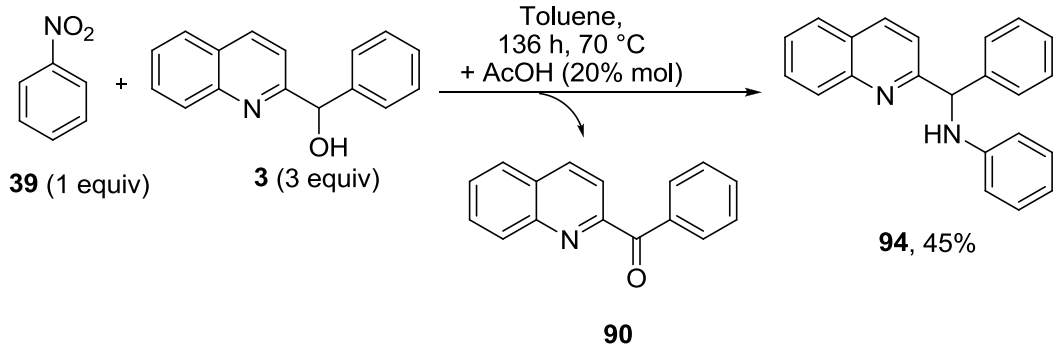


Scheme 3.42. *Mechanistic rationale for the metal free synthesis of quinoline (****92****).*

By running the reaction overnight at 50 or 70 °C, the starting material disappeared, but in the crude reaction mixture only trace amounts of the amino derivative **93** were detected via GC/MS analyses, suggesting the thermal instability of the reduced product **93**. It was, then, synthetically more useful to work at higher temperatures to favor the cyclization process, which involves the *trans*/*cis* isomerization of the C=C double bond.

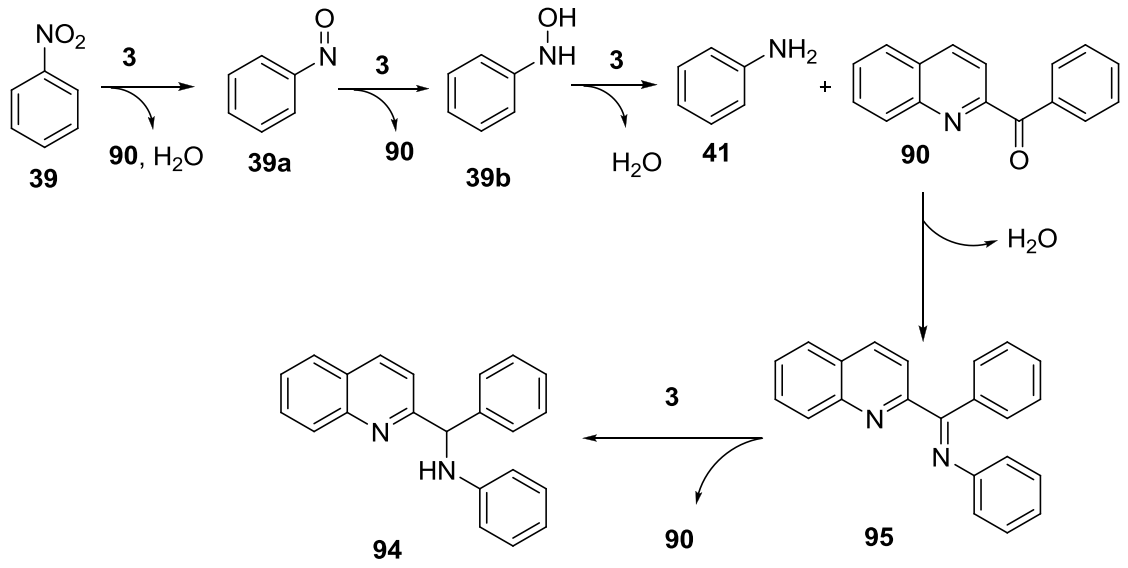
3.5.4. REDUCTIVE AMINATION

By reacting nitrobenzene (**39**) and quinolyl carbinol **3** (4 equiv) in the absence of methyl acrylate, a new *N*-phenylmethylamine **94** was isolated in 45% yield after 136h at 70 °C along with ketone **90** (Scheme 3.43).



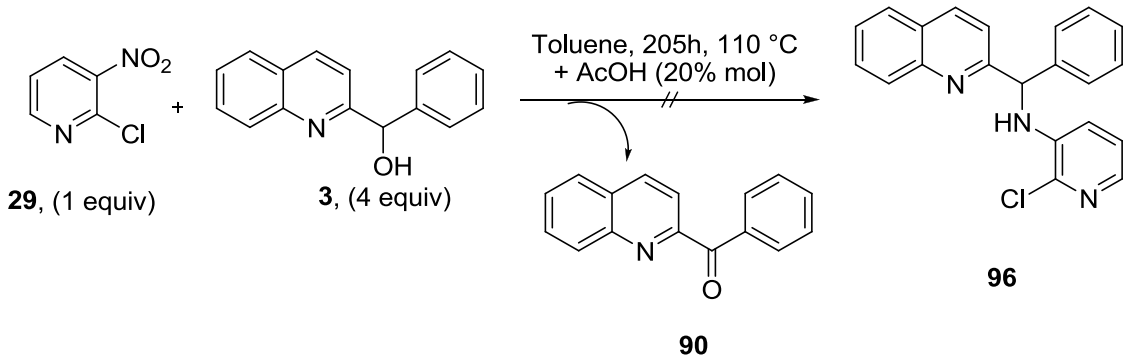
Scheme 3.43. *Reaction of the carbinol **3** with nitrobenzene (**39**).*

As in the previous reactions with methyl acrylate, the new product is the result of a multi-component process: a cascade reduction, exploiting 3 equivalents of the reducing agent **3**, leads to aniline (**41**) involved in a reductive amination of ketone **90**, made possible by excess of **3** (Scheme 3.44).



Scheme 3.44. *Mechanistic rationale accounting for the formation of compound **94**.*

Attempts to perform a similar reaction starting from the more activated 2-chloro-3-nitropyridine (**29**) led to a complex crude reaction mixture. In fact, operating for longer reaction times (205 h) at higher temperature (110 °C), the alcohol **3** was completely oxidized to the corresponding ketone **90**, but the expected product **96** didn't form and only traces of amine **59** were detected via GC/MS analyses (Scheme 3.45).



Scheme 3.45. *Reaction of the chloronitropyridine* ***29*** *with carbinol* ***3****.*

Apparently, the chlorine atom prevents the attack of the amine functionality of **59** on ketone **90**, hampering the formation of the corresponding imine.

In organic synthesis, a useful method to prepare amines is the reduction of imines (or iminium salts). The overall process, from carbonyl compound to amine, is called reductive amination. It can be performed in two steps, isolating the intermediate imines, but, due to their instability, the most convenient way is to form and reduce imines in one-pot reactions. The selective reduction of iminium ions can be realized by sodium cyanoborohydride. When $NaCNBH_3$ is added in a typical imine-formation reaction, it reacts with the product, but not with the starting carbonyl compound.[74] An alternative method for reductive amination uses molecular hydrogen and a metal catalyst (*e.g.*, Ni) to reduce the imine in the presence of the starting carbonyl compound.[74] Other reducing agents can be used: among them zinc and HCl, sodium triacetoxyborohydride, sodium borohydride, iron pentacarbonyl and alcoholic KOH,

[74] Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. *Organic Chemistry*, Oxford University Press: New York, USA, 2001, p. 354.

BH_3-pyridine, and formic acid.[75] The reactions, of course, produce racemic amines but the methodology allows a general access to stereogenic C-N bonds, a fundamental structural element found in natural products and medicinal agents. In contrast, Nature exploits reductive amination as a powerful in vivo chemical tool for the enantioselective syntheses of amino acids via selective reduction of hydrogen-bond activated pyruvate-derived ketimines.

In organic synthesis, while a variety of protocols have been described for the asymmetric reduction of ketimines (a strategy that requires access to preformed bench stable imines),[76] it is surprising that few laboratory methods are known for enantioselective reductive amination.[77] All these procedures are based on the use of metal catalysts. Recently, the first metal free organocatalytic reductive amination, a biomimetic reaction that allows the asymmetric coupling of complex fragments using chiral hydrogen-bonding catalysts and Hantzsch ester (**47**), was reported.[76,78]

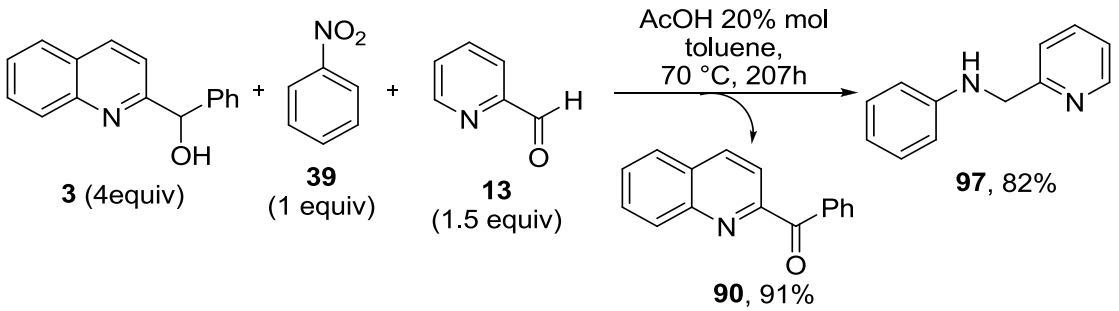
* * *

In the light of these considerations and on the basis of the first promising result (Scheme 3.43), some preliminary reactions to test the synthetic potential of alcohol **3** in reductive aminations were performed following simple multicomponent procedures with the aim to realize organocatalytic processes.

Nitrobenzene (**39**) was allowed to react with 4 equiv of quinolyl carbinol **3** in the presence of 2-picolinealdehyde (**13**). After heating the reaction mixture in toluene for

[75] Smith, B. M.; March, J. *Advanced Organic Chemistry,* 5th ed, Wiley, New York, 2001, p.1188.
[76] Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84 and references therein.
[77] (a) Blaser, H-U; Buser, H. -P.; Pugin, B.; Spindler, F. *Synlett* **1999**, 867. (b) Kadyrov, R.; Riermeier, T. H. *Angew. Chem. Int. Ed.* **2003**, *42*, 5472. (c) Kadyrov, R.; Riermeier, T. H.; Dingerdissen, U.; Tararov, V.; Börner, A. *J. Org. Chem.* **2003**, *68*, 4067. (d) Chi, Y. X.; Zhou, Y. G.; Zhang, X. M. *J. Org. Chem.* **2003**, *68*, 4120.
[78] Hoffmann, S.; Nicoletti, M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13074. (c) For the first asymmetric organocatalytic HEH reduction of imines, see Singh, S.; Batra, U.K. *Indian J. Chem.,Sect. B* **1989**, *28*, 1. Improvements in this type of ketimines reductions were reported in: (d) Rueping, M.; Sugiono, E.; Azap, C.; Theissmann, T.; Bolte, M. *Org. Lett.* **2005**, *7*, 378. (e) Hoffmann, S.; Seayad, A. M.; List, B. *Angew. Chem. Int. Ed.* **2005**, *44*, 7424.

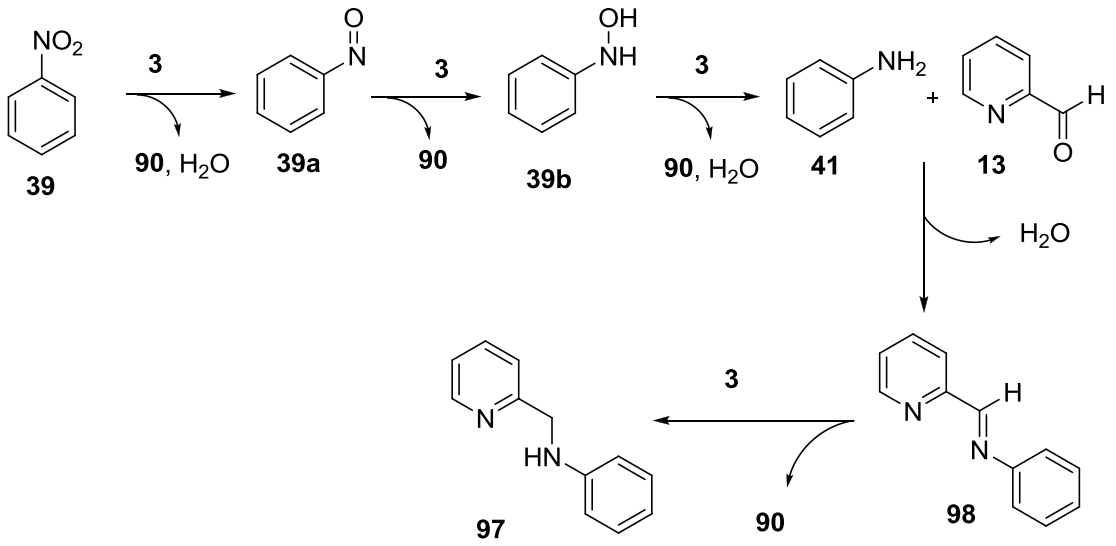
207 h at 70 °C, *N*-phenyl-*N*-(2-pyridylmethyl)amine **97**[79] was isolated in 82% yield by chromatographic separation, along with ketone **90** obtained in 91% yield (Scheme 3.46).



Scheme 3.46. *Reduction of nitrobenzene (**39**) in the presence of activated aldehyde **13**.*

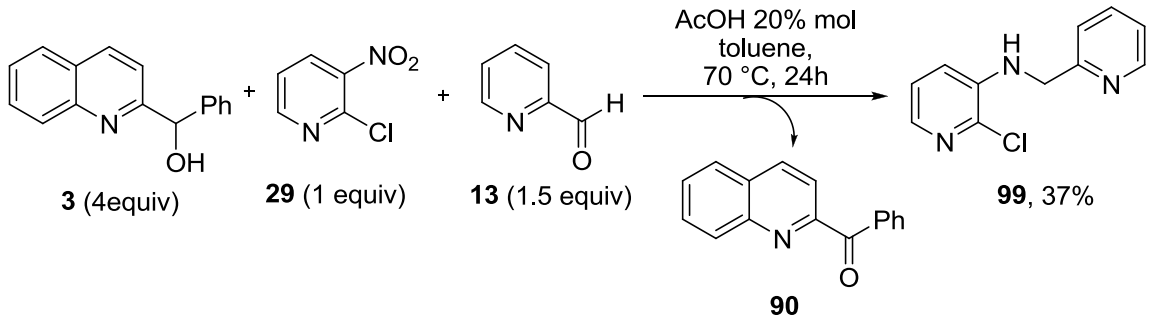
A mechanistic rationale for the formation of the product **97** follows the pathway described in Scheme 3.44: three equivalents of alcohol **3** were used to reduce nitrobenzene (**39**) to aniline (**41**); then, the reaction of **41** with carbonyl compound **13** gave imine **98**, reduced to the product **97** by the remaining carbinol **3** (Scheme 3.47). Although ketone **90**, deriving from the oxidation of **3** was in excess with respect to aldehyde **13** in the reaction environment, product **94** didn't formed. Likely, the carbonyl group of **13** resulted not only more activated than that in **90**, but also less hindered, favoring the formation of imine **98** with respect to imine **95**.

[79] Cho, B. T.; Kang, S. K. *Tetrahedron* **2005**, *61*, 5725.



Scheme 3.47. *Mechanistic rationale accounting for the formation of compound* ***97.***

Working with a more activated nitro derivative as 2-chloro-3-nitropyridine (**29**), in analogous reaction conditions the reductive amination process was observed after a shorter reaction time (24 h), but product **99** was isolated in only 37% yield (Scheme 3.48).



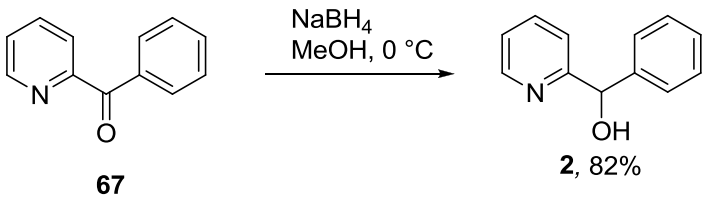
Scheme 3.48. *Reduction of nitro compound* ***29*** *in the presence of activated aldehyde* ***13****.*

In this case, the reductive amination product **99** was isolated from a complex crude reaction mixture: likely the presence of a chlorine atom in the starting reagent and in the corresponding reduction intermediates can give rise to the formation of different byproducts through competitive processes.

3.6. CONCLUSIONS

In conclusion, the results reported in this Chapter show an unprecedented and unexpected reactivity of pyridylallyl alcohol **1**, related to the weak acidity of the 'picoline type' hydrogen atom. This compound, in fact, not only is able to react as a carbon nucleophile towards activated counterparts (see Chapter II) but also, in the presence of electron-poor aromatic and heteroaromatic nitro derivatives, it behaves as 1,4-dihydropyridine HEH mimic for the metal free reduction of the nitro group to the corresponding amino function. Moreover, the redox mechanism becomes part of a domino process involving a direct trapping of the amino intermediates, leading to the one-pot formation of new functionalized aminoacylpyridines. The facile thermal methodology appears clearly limited to activated aromatic and heteroaromatic nitro compounds (as both nitro and alkene functions of nitro olefins seem unaffected by the redox ability of **1**) and suffers of the large excess of recoverable nitro reagent necessary to overcome the spontaneous thermal isomerization of pyridylallyl alcohol **1** to pyridyl ethyl ketone **8**. To avoid this problem, the observed reducing reactivity of alcohol **1** was extended to phenylpyridyl methanol **2**. This carbinol proves to be a superior reagent for this chemistry, as the replacement of the vinyl group with the phenyl ring prevents competitive reactions observed for pyridylpropenol 1, such as thermal isomerisation or nucleophilic substitutions/additions, allowing the use of almost stoichiometric amounts of the reducing agent. Alcohol **2**, moreover, is a very simple available reagent, because not only it is obtained through crystallization from diisopropylether of the reaction mixture deriving from phenylmagnesium bromide and 2-picolinaldehyde (**13**), but it can be recovered and recycled through reduction of the ketone **67** with $NaBH_4$ (Scheme 3.49).[80]

[80] Sudbrake, C; Vahrenkamp, H. *Inorg. Chim. Acta* **2001**, *318*, 23.



Scheme 3.49. *Reduction of ketone* **67** *with* $NaBH_4$.

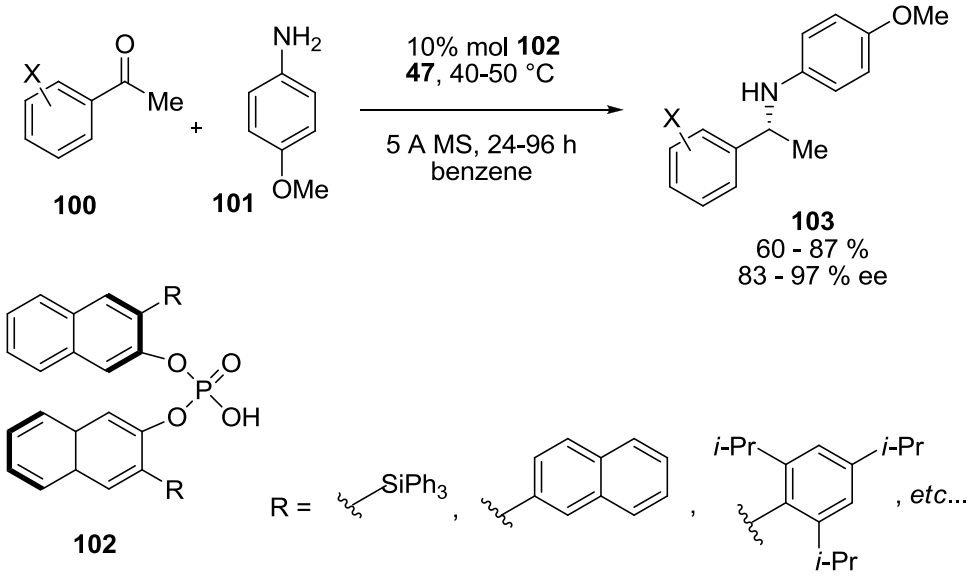
Despite the isolation of the free amines being impractical, operating in the presence of methyl acrylate as aza-Michael acceptor, a domino process involving reduction and conjugate addition allows the one pot formation of several β-amino esters as the products of multicomponent reactions (3-MCR)[81] involving alcohol **2**, the nitro compound and methyl acrylate. Comparing the reactivity of carbinols **2** and **86** as well as carbinol **1** with phenylpropenol **84**, the crucial role of the pyridine nucleus to make this purely thermal reactivity of **1** and **2** possible is well evidenced. In fact, only in the cases of alcohol **1** and **2** a dihydropyridine tautomer can be generated by the mobility of the C(1)-H hydrogen atom. Moreover, the reducing ability of **2** is even more striking if compared with the inertness of Hantzsch ester **47** in reducing 2-chloro-3-nitropyridine (**29**) and nitrobenzene (**39**) in purely thermal conditions. The β-amino esters syntheses, passing through the reduction cascade process and aza-Michael addition to methyl acrylate, need long reaction times, high temperatures and the reaction products yields are not often satisfactory. The method finds a marked improvement with the quinolyl methanol **3**, that reacts in shorter reaction times leading to higher products yields. The 1,4-dihydropyridine form is now more favoured due to the less aromatic character of the quinoline ring with respect to the pyridine one, allowing an improvement of the C(1)-H hydrogen mobility. Similarly to the pyridyl derivative **2**, alcohol **3** can be recovered and recycled by reduction of ketone **90** with $NaBH_4$.[82]

By substituting methyl acrylate with an activated aldehyde as 2-picolinaldehyde (**13**), working with 4 equivalents of **3**, it is possible to realize a reductive amination process of the carbonyl acceptor and the amines obtained by reduction of the nitro derivatives.

[81] For an accurate definition of multicomponent reactions, see: Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123.
[82] Kamath, Mrs. H. V.; Nargund, K. S.; Kulkarni, S. N. *Indian J. Chem, Sect B* **1978**, *16B(10)*, 903.

The preliminary results obtained in this promising synthetic field, open the way to the applications of quinolyl system **3** (or others pyridyl carbinols) in asymmetric organocatalytic reductive aminations as well as other organocatalytic processes.

For example, the reductive potential of **3** in organocatalysis could be evaluated with variously substituted acetophenones of type **100** and *p*-anisidine **101**. In the literature[83], the reductive amination makes use of HEH **47** as hydrogen source in the presence of hydrogen-bonding catalyst, as one of the Terada and Akiyama enantiopure binol phosphoric acids of type **102**.[84] The corresponding amines **103** are obtained in high yields and with good enantiomeric excess (Scheme 3.50).



Scheme 3.50. *Organocatalytic reductive amination in the presence of HEH **47** and catalyst **102**.*

Some preliminary results demonstrated that attempts to perform the reductive amination process showed in Scheme 3.50, under thermal conditions (50 °C or higher temperatures) for long times and in the absence of any hydrogen bonding catalysts were unsuccessfull, using carbinol **3** as well as HEH **47**. Then, further studies involving the use of different catalysts are underway in our laboratory.

[83] Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84.

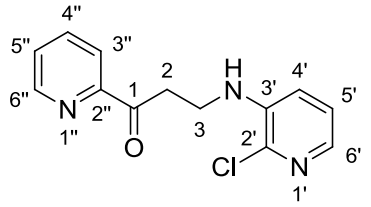
[84] (a) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth, Catal.* **2006**, *348*, 999. (b) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566. (c) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804. (d) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356.

3.7. EXPERIMENTAL SECTION

3.7.1. REACTION OF 1 WITH NITRO DERIVATIVES 29, 60, 62, 39 AND 65a,b. GENERAL PROCEDURE.

Alcohol **1** (0.068 g, 0.5 mmol) was heated at 70 or 110 °C in toluene or xylene (1 mL) with the suitable nitro compound until its complete disappearance. Removal of the solvent in vacuo and purification by FC allowed, after the recovery of unreacted nitro compound, to isolate the reaction products along with different amounts of ketone **8**.

*3.7.1.1. 3-[(2-Chloro-3-pyridyl)amino]-1-(2-pyridyl)-1-propanone (**54**).*



The mixture of alcohol **1** and 2-chloro-3-nitropyridine (**29**) (0.396 g, 2.5 mmol) in toluene (1 mL) was stirred at 110 °C in a sealed tube (Pyrex N. 13) for 18 h. Removal of the solvent in vacuo and purification by column chromatography (petroleum ether 40-70 °C/ethyl acetate 3:1) gave unreacted **8** (R_f = 0.41, 0.337 g, <5%) and product **54** [0.041 g, 31% (93%)] as a yellow thick oil, R_f (PE/EtOAc 3:1) 0.20.

MW: 261.71

IR, ν_{MAX} (liquid film): 3394, 3059, 2916, 1694, 1584, 1494 cm^{-1}.

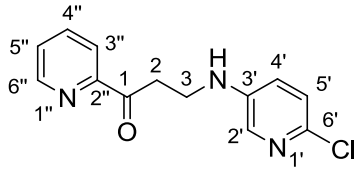
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.70 (ddd, J = 4.8, 1.6, and 1.0 Hz, 1H, H-6"), 8.07 (ddd, J = 7.8, 1.1 and 1.1 Hz, appears as dt, 1H, H-3"), 7.86 (ddd, J = 7.7, 7.7 and 1.7 Hz, appears as td, 1H, H-4"), 7.69 (dd, J = 4.5 and 1.6 Hz, 1H, H-6'), 7.50 (ddd, J =7.6, 4.7 and 1.1 Hz, 1H, H-5"), 7.09 (dd, J = 8.1 and 4.6 Hz, 1H, H-5'), 6.98 (dd, J = 8.1 and 1.5 Hz, 1H, H-4'), 4.96 (br s, 1H, NH), 3.62 (m, 2H, $3CH_2$), 3.55 (m, 2H, $2CH_2$).

^{13}C-NMR (100MHz, $CDCl_3$) δ: 200.3 (s, CO), 152.9 (s, C-2″), 149.1 (d, C-6″), 140.6 (s, C-3′), 137.2 (s, C-2′), 137.1 (d, C-4″), 136.3 (d, C-6′), 127.5 (d, C-5″), 123.4 (d, C-5′), 121.9 (d, C-3″), 117.3 (d, C-4′), 38.7 (t, C-3), 36.9 (t, C-2).

MS (EI) *m/z* (%) 263 (4) [M+2]+, 261 (13) [M]+, 226 (2), 208 (13), 157 (9), 155 (24), 134 (27), 79 (100).

HRMS(ESI): $[M+H]^+$, found: 262.0742, $C_{13}H_{12}ClN_3O$; calcd: 262.0742.

*3.7.1.2. [(6-Chloro-3-pyridyl)amino]-1-(2-pyridyl)-1-propanone (**61**).*



The reaction mixture obtained by heating **1** and **60** (0.396 g, 2.5 mmol) in toluene at 70 °C for 48 hours was resolved with PE/EtOAc 2:1, leading to ketone **8** (R_f = 0.45, 0.013 g, 19 %) and compound **61** (0.020 g, 15%) as ivory coloured needles, m.p. 112-113 °C (from *n*-hexane/acetone); [Found: C, 59.53; H, 4.53; N, 15.77. $C_{13}H_{12}ClN_3O$ requires C, 59.66; H, 4.62; N, 16.06%]; R_f (PE/EtOAc 2:1) 0.14.

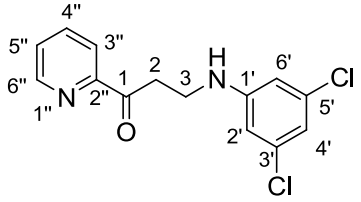
MW: 261.71

IR, ν_{max} (KBr) 3395, 3055, 2858, 1690, 1585, 1459, 1326 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.54 (m, 2H, 2-CH_2), 3.58 (m, 2H, 3-CH_2), 4.25 (br s, 1H, NH), 6.93 (dd, *J* = 8.6 and 3.1 Hz, 1H, 4′-H), 7.08 (d, *J* = 8.6 Hz, 1H, 5′-H), 7.50 (m, 1H, 5′′-H), 7.80 (d, *J* = 2.9 Hz, 1H, 2′-H), 7.86 (ddd, *J* = 7.7, 7.7, and 1.7 Hz, 1H, 4′′-H), 8.05 (d, *J* = 7.8 Hz, 1H, 3′′-H), 8.68 (d, *J* = 4.3 Hz, 1H, 6′′-H).

^{13}C-NMR (100MHz, $CDCl_3$) δ: 37.2 (t,C-2), 39.4 (t, C-3), 122.2 (d, C-3″), 122.7 (d, C-4′), 124.4 (d, C-5′), 127.9 (d, C-5″), 135.0 (d, C-2′), 137.4 (d, C-4″), 139.3 (s, C-6′), 143.3 (s, C-3′), 149.4 (d, C-6″), 153.2 (s, C-2″), 200.9 (s, CO).

*3.7.1.3. 3-(3,5-Dichloroanilino)-1-(2-pyridyl)-1-propanone (**63**)*



Chromatographic resolution (PE/EtOAc 4:1) of the crude obtained by heating **1** and **62** (0.48 g, 2.5 mmol) in toluene at 110 °C for 18 hours afforded ketone **8** (R_f = 0.49, 0.009 g, 13%) and compound **63** (0.015 g, 10%) as pale yellow oil; R_f (PE/EtOAc 4:1) 0.21.

MW: 295.16

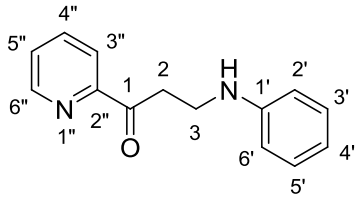
IR, ν_{max} (film): 3395, 3057, 2916, 1694, 1590, 1569 cm^{-1}.

^{1}H-NMR (400Mz, $CDCl_3$) δ: 3.49 (m, 2H, 2-CH_2), 3.55 (m, 2H, 3-CH_2), 4.41 (br s, 1H, NH), 6.49 (d, *J* = 1.6 Hz, 2H, 2′-H and 6′-H), 6.63 (t, *J* = 1.7 Hz, 1H, 4′-H), 7.49 (ddd, *J* = 7.7, 4.7, and 1.2 Hz, 1H, 5′′-H), 7.84 (ddd, *J* = 7.8, 7.8, and 1.6 Hz, 1H, 4′′-H), 8.04 (dd, *J* = 7.8 and 1.0 Hz, 1H, 3′′-H), 8.69 (ddd, *J* = 4.8, 1.8. and 1.0 Hz, 1H, 6′′-H).

^{13}C-NMR (100MHz, $CDCl_3$) δ: 37.0 (t, C-2), 38.8 (t, C-3), 111.0 (d, C-2′ and 6′), 117.0 (d, C-4′), 121.9 (d, C-3″), 127.5 (d, C-5″), 135.5 (s, C-3′ and 5′), 137.1 (d, C-4″), 149.0 (d, C-6″), 149.5 (s, C-1′), 152.9 (s, C-2″), 200.6 (s, CO).

HRMS (**ESI**): MNa^+, found 317.0222, $C_{14}H_{12}Cl_2N_2NaO$; requires: 317.0219.

*3.7.1.4. 3-Anilino-1-(2-pyridyl)-1-propanone (**64**)*[46]



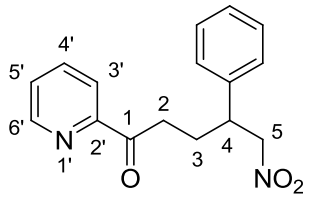
Chromatographic resolution (PE/EtOAc 3:1) of the crude obtained by heating **1** and **39** (0.554 g, 0.46 mL, 4.5 mmol) in xylene at 150 °C for 4 hours afforded ketone **8** (R_f = 0.51, 0.010 g, 15%) and amino ketone **64** (0.013 g, 11%) as a pale solid, m.p. 78-79 °C (from methanol-ether); R_f (PE/EtOAc 3:1) 0.28.

MW: 226.27

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.62 (m, 4H, 2-CH_2 and 3-CH_2), 5.45 (br s, 1H, NH), 6.81-6.85 (m, 3H, Ar-3H), 7.19-7.23 (m, 2H, Ar-2H), 7.47 (ddd, *J* = 7.6, 4.9, and 1.2 Hz, 1H, 5'-H), 7.83 (ddd, *J* = 7.7, 7.7, and 1.8 Hz, 1H, 4'-H), 8.03 (dd, *J* = 7.8 and 1.2 Hz, 1H, 3'-H), 8.65 (ddd, *J* = 4.8, 2.0. and 0.8 Hz, 1H, 6'-H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ:36.8 (t, C-2), 40.7 (t, C-3), 114.8 (d, C-2' and 6'), 119.5 (d, C-4'), 121.8 (d, C-3''), 127.4 (d, C-5''), 129.4 (d, C-3' and 5'), 136.95 (d, C-4''), 149.0 (d, C-6''), 149.05 (s, C-1'), 152.95 (s, C-2''), 200.6 (s, CO).

3.7.1.5. 5-*Nitro-4-phenyl-1-(2-pyridyl)-1-pentanone (**66a**).*



The reaction mixture obtained by heating **1** and **65a** (0.373 g, 2.5 mmol) in toluene at 110 °C for 18 hours was resolved with PE/EtOAc 4:1, leading to ketone **8** (R_f = 0.38, 0.021 g, 30%) and compound **66a** (0.043 g, 30%) as a pale oil; R_f (PE/EtOAc 4:1) 0.16.

MW: 284.31

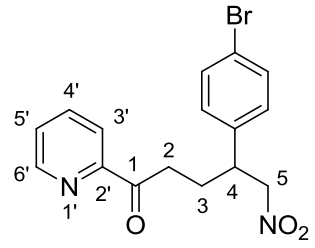
IR, ν_{max} (film): 3053, 2922, 1695, 1541, 1379 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.16 (m, 2H, 3-CH_2), 3.14 (m, 2H, 2-CH_2), 3.60 (m, 1H, 4-H), 4.63 (AB part of an ABX system, *J* = 12.2 and 7.7 Hz, 2H, 5-CH_2), 7,22-7.36 (m, 5H, Ph), 7.43 (ddd, *J* = 7.6, 4.8, and 1.0 Hz, 1H, 5'-H), 7.80 (ddd, *J* = 7.7, 7.7, and 1.7 Hz, 1H, 4'-H), 7.98 (ddd, *J* = 7.8, 1.2 and 1.2 Hz, 1H, 3'-H), 8.60 (ddd, *J* = 4.6, 1.7. and 0.9 Hz, 1H, 6'-H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ: 27.1 (t, C-3), 35.0 (t, C-2), 43.75 (d, C-4), 80.8 (t, C-5), 121.7 (d, C-3'), 127.2 (d, C-5'), 127.6 (d, Ph), 127.8 (d, Ph), 128.9 (s, Ph), 129.0 (d, Ph), 136.9 (d, C-4'), 148.9 (d, C-6'), 153.0 (s, C-2'), 200.7 (s, CO).

HRMS (ESI): MH^+, found 285.1237, $C_{16}H_{17}N_2O_3$; requires 285.1234.

*3.7.1.6. 5-Nitro-4-(4-bromophenyl-1-(2-pyridyl)-1-pentanone (**66b**).*



Operating as above with **65b** (0.570 g, 2.5 mmol), chromatographic resolution (PE/EtOAc 3:1) gave ketone **8** (R_f = 0.52, 0.012 g, 18 %) and compound **66b** (0.035 g, 19%) as a pale yellow oil; R_f (PE/EtOAc 3:1) 0.21.

MW: 363.21

IR, ν_{max} (film): 3051, 2926, 1690, 1546, 1383 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.12 (m, 2H, 3-CH_2), 3.12 (m, 2H, 2-CH_2), 3.58 (m, 1H, 4-H), 4.61 (AB part of an ABX system, J = 12.5 and 7.6 Hz, 2H, 5-CH_2), 7.11 (m, 2H, Ar-2H), 7.43-7,46 (m, 3H, 5'-H and Ar-2H), 7.81 (ddd, J = 7.7, 7.7, and 1.8 Hz, 1H, 4'-H), 7.98 (ddd, J = 7.8, 1.0 and 1.0 Hz, 1H, 3'-H), 8.60 (ddd, J = 4.7, 1.7. and 0.9 Hz, 1H, 6'-H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ: 27.1 (t, C-3), 34.8 (t, C-2), 43.2 (d, C-4), 80.5 (t, C-5), 121.7 (d, C-3'), 127.3 (d, C-5'), 129.1 (s, Ph), 129.4 (d, Ph), 132.0 (s, Ph), 132.2 (d, Ph), 136.9 (d, C-4'), 148.9 (d, C-6'), 152.9 (s, C-2'), 200.5 (s, CO).

HRMS (ESI): MH^+, found 363.0342, $C_{16}H_{16}BrN_2O_3$; requires: 363.0339.

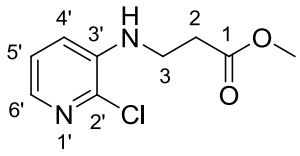
3.7.2. REACTIONS OF 2 WITH NITRO DERIVATIVES 29, 60, 71, 74, 76, 39, 62, 82 AND 80. GENERAL PROCEDURE.

Nitro compound (0.5 mmol), alcohol **2** (0.324 g, 1.75 mmol), and methyl acrylate (0.180 mL, 2 mmol) were mixed in toluene or acetonitrile (1 mL) degassed by several vacuum-nitrogen cycles to reduce the air oxidation of alcohol **2** to ketone **67**. The resulting mixture was heated at 110 °C in a screw-cap tube (Pyrex N. 15) until the disappearance of the starting nitro compound. Removal of the solvent in vacuo and purification by FC gave the β-amino ester and ketone **67**. The excess alcohol **2** was recovered and recycled.

*3.7.2.1. 3-Amino-2-chloropyridine (**59**)*

In the reaction crude obtained by heating 2-chloro-3-nitropyridine (**29**) (0.079 g, 0.5 mmol) and alcohol **1** (0.324 g, 1.75 mmol) in toluene (1 mL) at 110 °C for 96 h, without methyl acrylate, ketone **67** was the predominant product (ca. 90%, ^{1}H-NMR spectroscopy) while only trace amounts of amine **59** (ca. 5%, ^{1}H-NMR spectroscopy) were detected.

*3.7.2.2. Methyl 3-[(2-chloro-3-pyridyl)amino]propanoate (**68**)*



The reaction mixture obtained by heating 2-chloro-3-nitropyridine (**29**) (0.079 g, 0.5 mmol), alcohol **2** (0.324 g, 1.75 mmol), and methyl acrylate (0.180 mL, 2 mmol) in acetonitrile (1 mL) at 110 °C for 96 h, was resolved by FC (DCM/EtOAc 100:3), leading to ketone **67** (R_f = 0.43, 0.244 g, 89% referred to reacted **2**), 3-amino-2-chloropyridine (**59**) (R_f = 0.20, 0.005 g, 8%) and compound **68** (R_f = 0.18, 0.073 g, 68%) as a dark yellow oil.

MW: 214.65

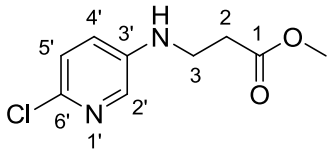
IR, ν_{MAX} (film): 3402, 3059, 2954, 2918, 1734, 1586, 1495, 1176 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 2.66 (t, J = 6.4 Hz, 2H, 2-CH_2), 3.50 (t, J = 6.4 Hz, 2H, 3-CH_2), 3.71 (s, 3H, OCH_3), 4.90 (br s, 1H, NH), 6.95 (dd, J = 8.0 and 1.5 Hz, 1H, 4'-H), 7.12 (dd, J = 8.0 and 4.7 Hz, 1H, 5'-H), 7.73 (dd, J = 4.7 and 1.4 Hz, 1H, 6'-H).

^{13}C-NMR (100MHz, $CDCl_3$) δ: 33.4 (t, C-2), 38.7 (t, C-3), 52.0 (q, CH_3), 117.7 (d, C-4'), 123.5 (d, C-5'), 136.2 (d, C-6), 136.9 (s, C-2'), 140.4 (s, C-3'), 172.1 (s, CO).

HRMS (ESI): MH^+, found 215.0582, $C_9H_{12}{}^{35}ClN_2O_2$; requires: 215.0586.

*3.7.2.3. Methyl 3-[(6-chloro-3-pyridyl)amino]propanoate (**69**)*



The crude obtained by heating alcohol **2** (0.324 g, 1.75 mmol), compound **60** (0.079 g, 0.5 mmol) and methyl acrylate (0.180 mL, 2 mmol) in toluene (1 mL) for 63 h was subjected to FC with DCM/EtOAc 20:1 as eluent leading to ketone **67** (R_f = 0.47, 0.229 g, 84% referred to reacted **2**) and with DCM/EtOAc 6:1 to isolate compound **69** (R_f = 0.23, 0.032 g, 30%) as ivory needles, mp 86-87 °C (from PE/Et_2O 4:1); [Found: C, 50.08; H, 4.96; N, 12.97. $C_9H_{11}ClN_2O_2$ requires: C, 50.36; H, 5.17; N, 13.05%].

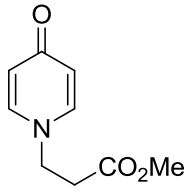
MW: 214.65

IR, ν_{MAX} (KBr): 3397, 3051, 2947, 2890, 2853, 1723, 1594, 1461, 1441, 1209 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 2.62 (t, J = 6.1 Hz, 2H, 2-CH_2), 3.43 (q, J = 6.2 Hz, 2H, 3-CH_2), 3.71 (s, 3H, OCH_3), 4.16 (br s, 1H, NH), 6.88 (dd, J = 8.4 and 3.3 Hz, 1H, 4'-H), 7.09 (d, J = 8.3 Hz, 1H, 5'-H), 7.77 (d, J = 3.4 Hz, 1H, 2'-H).

^{13}C-NMR (100MHz, $CDCl_3$) δ: 33.3 (t, C-2), 39.2 (t, C-3), 51.9 (q, CH_3), 122.4 (d, C-4'), 124.1 (d, C-5'), 134.7 (d, C-2'), 139.4 (s, C-6'), 142.7 (s, C-3'), 172.4 (s, CO).

*3.7.2.4. Methyl 3-[4-oxo-1-(4H)-pyridyl]propanoate (**72**)*[85]



4-Nitropyridine (**71**) (0.062 g, 0.5 mmol), alcohol **2** (0.324 g, 1.75 mmol), and methyl acrylate (0.180 mL, 2 mmol) were heated in MeCN (1 mL) at 110 °C for 43 h. Chromatographic resolution (EtOAc/MeOH/NEt_3 7:2:2) gave alcohol **2** and ketone **67**

[85] Somekawa, K.; Miyazato, M.; Masumori, R.; Kumamoto, S. *Nippon Kagaku Kaishi*, **1978**, 1276.

as a 3:1 mixture (^{1}H-NMR spectroscopy) (R_f = 0.86, 0.310 g) and compound **72** (R_f = 0.33, 0.052 g, 57%) as a pale yellow oil.

MW: 181.19

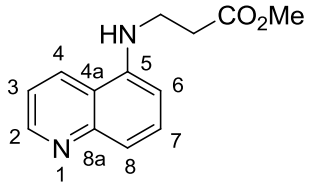
IR, ν_{MAX} (film): 3004, 2956, 1737, 1641, 1578, 1190 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 2.78 (t, J = 6.3 Hz, 2H, CH_2CO$_2$Me), 3.69 (s, 3H, OCH$_3$), 4.09 (t, J = 6.3 Hz, 2H, CH_2NH), 6.35 (d, J = 7.8 Hz, 2H, 3-H and 5-H), 7.35 (d, J = 7.8 Hz, 2H, 2-H and 6-H).

^{13}C-NMR (400MHz, $CDCl_3$) δ: 35.0 (t), 51.9 (t), 52.3 (q), 118.8 (d), 139.9 (d), 170.5 (s), 178.7 (s).

HRMS (ESI): MH$^+$, found 182.0814, $C_9H_{12}NO_3$; requires: 182.0817.

*3.7.2.5. Methyl 3-(5-quinolylamino)propanoate (**75**)*



The residue coming from heating alcohol **2** (0.324 g, 1.75 mmol), 5-nitroquinoline (**74**) (0.087 g, 0.5 mmol) and methyl acrylate (0.180 mL, 2 mmol) at 110°C in MeCN (1 mL) for 6 days, was resolved by FC with PE/EtOAc 3:1 as eluent leading to ketone **67** (R_f = 0.43, 0.242 g, 88% referred to reacted **2**) and with PE/EtOAc 1:1 to isolate compound **75** (R_f = 0.18, 0.065 g, 57%) as yellow needles, mp 79–80 °C (from PE/Et$_2$O 3:1); [Found: C, 67.72; H, 6.41; N, 12.29. $C_{13}H_{14}N_2O_2$ requires: C, 67.81; H, 6.13; N, 12.17%].

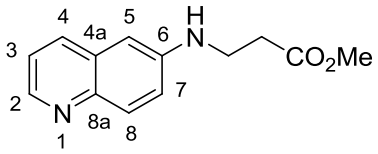
MW: 230.26

IR, ν_{MAX} (KBr): 3269, 3085, 2946, 1729, 1583, 1204, 1119 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 2.75 (t, J = 6.4 Hz, 2H, CH_2CO$_2$Me), 3.59 (m, 2H, CH_2NH), 3.71 (s, 3H, OCH$_3$), 4.97 (br s, 1H, NH), 6.63 (d, J = 7.6 Hz, 1H, 6-H), 7.30 (dd, J = 8.4and 4.3 Hz, 1H, 3-H), 7.48-7.57 (m, 2H, 7-H and 8-H), 8.16 (d, J = 8.3 Hz, 1H, 4-H), 8.85 (dd, J = 4.3 and 1.4 Hz, 1H, 2-H).

^{13}C-NMR (400MHz, $CDCl_3$) δ: 33.1 (t, CH_2CO), 39.5 (t, CH_2N), 51.8 (q, CH_3), 104.7 (d, C-6), 118.7 (s, C-4a), 118.8 (d, C-C8), 119.4 (d, C-3), 128.8 (d, C-4), 130.2 (d, C-7), 143.1 (s, C-5), 149.2 (s, C-8a), 150.0 (d, C-2), 172.9 (s, CO).

*3.7.2.6. Methyl 3-(6-quinolylamino)propanoate (***77***)*



Operating as above with compound **76** (0.087 g, 0.5 mmol) for 7 days, chromatographic resolution with DCM/EtOAc 4:1 as eluent gave ketone **67** (R_f = 0.61, 0.230 g, 84% referred to reacted **2**) while the use of EtOAc/DCM 3:1 gave derivative **77** (R_f = 0.20, 0.063 g, 55%) as a pale yellow oil; [Found: C, 67.47; H, 6.35; N, 11.83. $C_{13}H_{14}N_2O_2$ requires: C, 67.81; H, 6.13; N, 12.17%].

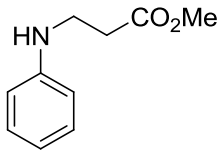
MW: 230.26

IR, ν_{MAX} (film): 3393, 3266, 3024, 2950, 1734, 1624, 1174 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 2.70 (t, J = 6.3 Hz, 2H, CH_2CO_2Me), 3.57 (q, J = 6.1 Hz, 2H, CH_2NH), 3.72 (s, 3H, OCH_3), 4.37 (br s, 1H, NH), 6.72 (d, J = 2.7 Hz, 1H, 5-H), 7.09 (dd, J = 9.2 and 2.5 Hz, 1H, 7-H), 7.26 (dd, J = 8.4 and 4.1 Hz, 1H, 3-H), 7.87 (d, J = 9.3 Hz, 1H, 8-H), 7.10 (dd, J = 8.4 and 1.3 Hz, 1H, 4-H), 8.62 (dd, J = 4.1 and 1.5 Hz, 1H, 2-H).

^{13}C-NMR (100MHz, $CDCl_3$) δ: 33.3 (t, CH_2CO), 39.3 (t, CH_2N), 51.8 (q, CH_3), 103.1 (d, C-5), 121.3 (d, C-3), 121.4 (d, C-7), 130.0 (s, C-4a), 130.3 (d, C-8), 133.7 (d, C-4), 143.3 (s, C-8a), 145.5 (s, C-6), 146.3 (d, C-2), 172.6 (s, CO).

*3.7.2.7. Methyl 3-anilinopropanoate (**78**)*[86]

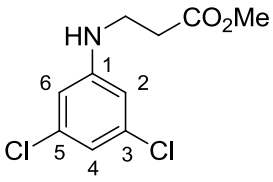


The reaction mixture obtained by heating alcohol **2** (0.324 g, 1.75 mmol), nitrobenzene (**39**) (0.062 g, 0.052 mL, 0.5 mmol), methyl acrylate (0.180 mL, 2 mmol), and glacial acetic acid (0.006 g, 0.006 mL, 0.1 mmol) in acetonitrile (1 mL) at 110°C for 10 days was resolved with DCM/EtOAc 100:1 as eluent to give compound **78** (R_f = 0.19, 0.056 g, 63%) as a yellow sticky solid (lit. mp 37-38 °C).

^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.64 (t, J = 6.4 Hz, 2H, CH_2CO$_2$Me), 3.47 (t, J = 6.5 Hz, 2H, CH_2NH), 3.70 (s, 3H, OCH_3), 4.01 (br s, 1H, NH), 6.64 (d, J = 7.6 Hz, 2H, 2-H and 6-H), 6.73 (t, J = 7.4 Hz, 1H, 4-H), 7.19 (t, J = 7.5 Hz, 2H, 3-H and 5-H).

The slowest moving fractions gave ketone **67** (R_f = 0.10, 0.260 g, 95% referred to reacted **2**).

*3.7.2.8. Methyl 3-(3,5-dichloroanilino)propanoate (**79**)*[87]



Chromatographic resolution (DCM/PE 1.5:1) of the material obtained by heating nitro derivative **62** (0.096 g, 0.5 mmol), alcohol **2** (0.324 g, 1.75 mmol), methyl acrylate (0.180 mL, 2 mmol), and glacial acetic acid (0.006 g, 0.006 mL, 0.1 mmol) in toluene (1 mL) at 110°C for 67 h afforded compound **79** (R_f = 0.32, 0.019 g, 15%) as a pale yellow oil; [Found: C, 48.79; H, 4.83; N, 5.75. $C_{10}H_{11}Cl_2NO_2$ requires: C, 48.41; H, 4.47; N, 5.65%].

[86] Chen, X.; She, J.; Shang, Z.; Wu, J.; Zhang, P. *Synthesis* **2008**, 3931.
[87] Nasu, R.; Yoshizawa, H.; Okamoto, S. From *Jpn. Kokai Tokkyo Koho* (1993), JP 05155856 A 19930622.

MW: 248.11

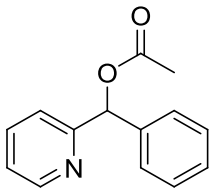
IR, ν_{MAX} (film): 3394, 3102, 2951, 1731, 1594, 1572 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.61 (t, *J* = 6.2 Hz, 2H, CH_2CO_2Me), 3.41 (t, *J* = 6.2 Hz, 2H, CH_2NH), 3.71 (s, 3H, OCH_3), 4.23 (br s, 1H, NH), 6.46 (d, *J* = 1.8 Hz, 2H, 2-H and 6-H); 6.67 (t, *J* = 1.8 Hz, 1H, 4-H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ: 33.3 (t, CH_2CO), 39.0 (t, CH_2N), 51.9 (q, OCH_3), 111.0 (d, C-2 and 6), 117.3 (d, C-4), 135.5 (s, C-3 and 5), 149.2 (s, C-1), 172.4 (s, CO).

Ketone **67** was recovered with DCM/EtOAc 3:1 as eluent (R_f = 0.74, 0.216 g, 79% referred to reacted **2**).

*3.7.2.9. Phenyl-2-pyridylmethyl acetate (**83**)*[88]



Operating as above, but without methyl acrylate, chromatographic resolution (PE/EtOAc 3:1) of the material obtained by heating carbinol **2** (0.324 g, 1.75 mmol) and compound **82** (0.072 g, 0.5 mmol) in xylene (1 mL) at 150°C for 46 h allowed the isolation of, along with ketone **67** (R_f = 0.40, 0.163 g, 51% referred to **2**) coming from oxidation of alcohol **2**, derivative **83** (R_f = 0.14, 0.031 g, 29%) as a pale yellow oil.

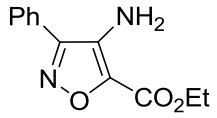
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.18 (s, 3H, CH_3), 6.86 (s, 1H, $CHOCOCH_3$), 7.17 (ddd, *J* = 7.6, 4.9, and 1.0 Hz, 1H, 5-H), 7.25-7.34 (m, 3H, Ar-3H), 7.39-7.42 (m, 3H, Ar-2H and 3-H), 7.67 (ddd, *J* = 7.6, 7.6, and 1.8 Hz, 1H, 4-H), 8.56 (br d, *J* = 4.8 Hz, 1H, 6-H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ: 21.2 (q), 77.8 (d), 121.0 (d), 122.7 (d), 127.3 (d), 128.2 (d), 128.55 (d), 136.9 (d), 138.9 (s), 149.3 (d), 159.1 (s), 169.9 (s).

The slowest moving bands led to unreacted **2** (R_f = 0.07, 0.099 g).

[88] Traynelis, V. J.; Pacini, P. L. *J. Am. Chem. Soc.* **1964**, *86*, 4917.

*3.7.2.10. Ethyl 4-amino-3-phenylisoxazole-5-carboxylate (**81**)*[89]



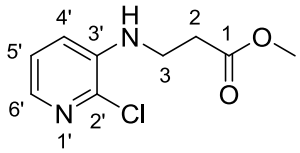
The reaction mixture obtained by heating compound **80** (0.132 g, 0.5 mmol) and alcohol **2** (0.324 g, 1.75 mmol) in toluene (1 mL) at 110°C for 64 h, without methyl acrylate, was resolved by FC (DCM/EtOAc 120:1) to give amino ester **81** (R_f = 0.44, 0.056 g, 48%) as pale yellow needles, mp 62-63 °C (from *n*-hexane) (lit.[89] 61-62 °C).

^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.42 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 4.45 (q, J = 7.0 Hz, 2H, OCH_2CH_3), 4.68 (br s, 2H, NH_2), 7.48-7.61 (m, 3H, Ar-3H), 7.68-7.83 (m, 2H, Ar-2H).

The slowest moving bands gave ketone **67** (R_f = 0.20, 0.230 g, 85% referred to reacted **2**).

3.7.3. REACTIONS OF 3 WITH NITRO DERIVATIVES 29 AND 39. SYNTHESIS OF β-AMINO ESTERS 68, 78 AND AMINO DERIVATIVE 59.

*3.7.3.1. Methyl 3-[(2-chloro-3-pyridyl)amino]propanoate (**68**)*

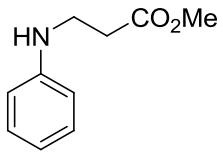


Nitro compound **29** (0.079 g, 0.5 mmol), alcohol **3** (0.364 g, 1.55 mmol), and methyl acrylate (0.180 mL, 2 mmol) were mixed in toluene (1 mL) and degassed by several vacuum-nitrogen cycles to reduce the air oxidation of alcohol **3** to ketone **90**. The resulting mixture was heated at 110 °C in a screw-cap tube (Pyrex N. 15) for 24 h until the disappearance of the starting nitro compound. After removal of the solvent in vacuo, the reaction crude was purified by FC with PE/EtOAc 5:1 to isolate ketone **90**

[89] Nesi, R.; Giomi, D.; Quartara, L.; Papaleo, S.; Tedeschi, P. *Heterocycles* **1987**, *26*, 2419.

(R_f = 0.47, 0.34 g, 97%) and the β-amino ester **68** (R_f = 0.17, 0.078 g, 73%) . The excess alcohol **3** was recovered and recycled.

*3.7.3.2. Methyl 3-anilinopropanoate (**78**)*[86]



Nitrobenzene (**39**) (0.031 g, 0.026 mL, 0.25 mmol), alcohol **3** (0.182 g, 0.78 mmol), glacial acetic acid (0.003 g, 0.003 mL, 0.05 mmol) and methyl acrylate (0.090 mL, 1 mmol) were mixed in CH_3CN (0.5 mL) and degassed by several vacuum-nitrogen cycles. The resulting mixture was heated at 110 °C in a screw-cap tube (Pyrex N. 15) for 24 h until the disappearance of the starting nitro compound. After removal of the solvent in vacuo, the reaction crude was purified by FC with PE/EtOAc 8:1 to isolate ketone **90** (R_f = 0.47, 0.188g, 100%) and β-amino ester **78** (R_f = 0.33, 0.038g, 85%). The excess alcohol **3** was recovered and recycled.

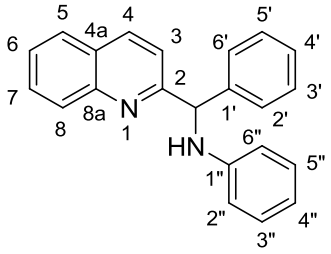
*3.7.3.3. 3-Amino-2-chloropyridine (**59**)*

A mixture containing nitro derivative **39** (0.079 g, 0.5 mmol) and quinolyl carbinol **3** (0.364 g, 1.55 mmol), after several vacuum-nitrogen cycles to reduce the air oxidation of the alcohol, was heated at 70 °C for 18 h in a screw-cap tube (Pyrex N. 15). The resulting crude, after removal of the solvent, was resolved by flash chromatography with EtOAc/PE 1:2 to give ketone **90** (R_f = 0.40, 0.325 g, 92%) and compound **59** (R_f = 0.15, 0.045 g, 70%).

3.7.4. SYNTHESES OF AMINO DERIVATIVES 94, 97 AND 99. GENERAL PROCEDURE.

Nitro compound, alcohol **3**, glacial acetic acid and picolinaldehyde (**13**) were mixed in toluene (1 mL) and degassed by several vacuum-nitrogen cycles to reduce the air oxidation of alcohol **3** to ketone **90**. The resulting mixture was heated at 70 °C in a screw-cap tube (Pyrex N. 13) until the disappearance of the starting nitro compound. Removal of the solvent in vacuo and purification by FC gave the amination reductive product and ketone **90**. The excess alcohol **3** was recovered and recycled.

*3.7.4.1. N-[Phenyl(2-quinolyl)methyl]aniline (**94**)*



The reaction mixture obtained by mixing alcohol **3** (0.482 g, 2.05 mmol) and nitrobenzene (**39**), (0.062 g, 0.052 mL, 0.5 mmol) in the presence of glacial acetic acid (0.006 g, 0.006 mL, 0.1 mmol) was heated for 136 h at 70 °C. After solvent removal, the crude was resolved by FC with DCM/PE 5:1, leading to compound **94** (R_f = 0.43, 0.070 g, 45%), as white needles (from PE/Et_2O 5:1, mp = 132.6 – 133.3 °C); [Found: C, 85.12; H, 5.77; N, 9.02 $C_{22}H_{18}N_2$; Requires: C, 85.15; H, 5.85; N, 9.03].

MW = 310.39

IR, ν_{max} (KBr): 3368; 3052; 1599; 1507; 1424; 1314 cm^{-1}.

MS *m/z (%)*: 310 (63); 233 (15); 218 (65); 182 (100).

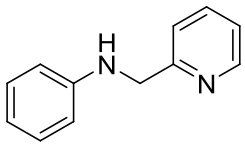
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 5.73 (s, 1H, CHN); 6.15 (br s, 1H, NH); 6.67 (td, *J* = 7.3 and 1 Hz, 1H, H-4″); 6.72 (dd, *J* = 8.6 and 1 Hz, 2H, H-2″, H-6″); 7.14 (td, *J* = 7.5 and 1 Hz, 2H, H-3″, H-5″); 7.24 (d, *J* = 7.5, 1H, H-4′); 7.32 (dd, *J* = 2 and 1 Hz, 2H, H-3′, H-5′); 7.42 (d, *J* = 8.5 Hz, 1H, H-3); 7.51 (dd, *J* = 8.0 and 1 Hz, 1H, H-6); 7.55 (d, *J* = 7.3 Hz, 2H,

H-2', H.6'); 7.72 (dd, *J* = 8.5 and 1.2 Hz, 1H, H-7); 7.80 (d, *J* = 8.7 Hz, 1H, H-5); 8.04 (d, *J* = 8.3 Hz, 1H, H-4); 8.18 (d, *J* = 7.8 Hz, 1H, H-8).

^{13}C-NMR (100 MHz, $CDCl_3$) δ: 63.4 (d, CHN); 113.6 (d, C-2", C-6"); 117.3 (d, C-4"); 120.1 (d, C-3); 126.4 (d, C-6); 127.3 (s, C-4a); 127.5 (d, C-5); 127.5 (d, C-2', C-6'); 127.5 (d, C-4'); 128.8 (d, C-3', C-5'); 129.1 (d, C-3", C-5"); 129.2 (d, C-8); 129.6 (d, C-7); 136.8 (d, C-4); 142.5 (s, C-1'); 147.0 (s, C-1"); 147.2 (s, C-8a); 160.4 (s, C-2).

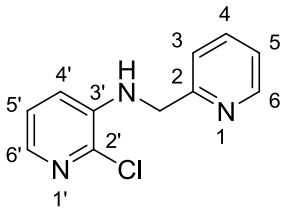
Ketone **90** (R_f = 0.27, 0.330 g) was recovered from the slowest fractions.

*3.7.4.2. N-Phenyl-N-(2-pyridinemethyl)amine (**97**)*[79]



Chromatographic resolution (PE/EtOAc 7:1) of the material obtained by heating nitrobenzene (**39**) (0.031 g, 0.026 mL, 0.25 mmol), glacial acetic acid (0.003 g, 0.003 mL, 0.05 mmol), alcohol **3** (0.232 g, 1.03 mmol) and 2-picolinaldehyde (**13**), (0.030 g, 0.026 mL, 0.275 mmol) at 70 °C for 207 h afforded ketone **90** (R_f = 0.60; 0.214 g, 91%). Compound **97** (R_f = 0.23, 0.038 g, 82%) was obtained using PE/EtOAc (3:1) as eluent.

*3.7.4.3. N-(2-chloro-3-pyridyl)-N-(2-pyridylmethyl)amine (**99**)*



The reaction mixture obtained by stirring compound **39** (0.040 g, 0.25 mmol), alcohol **3** (0.232 g, 1.03 mmol), glacial acetic acid (0.003 g, 0.003 mL, 0.05 mmol) and 2-picolinaldehyde (**13**), (0.030 g, 0.026 mL, 0.275 mmol) at 70 °C for 24 h, was resolved by

FC (PE/EtOAc 9:1) to give ketone **90** (R_f = 0.57, 0.233 g, 100%). The reductive amination product **99** (R_f = 0.30, 0.041 g, 37%) was recovered by elution with PE/EtOAc 1:1 as a pale yellow oil.

MW: 219.67

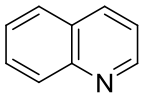
IR, ν_{max} (film): 3371; 3061; 2924; 1690; 1585; 1490; 1435; 1391 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 4.53 (s, 2H, CH_2); 5.52 (br s, 1H, NH); 6.85 (dd, *J* = 7.9 and 1.6 Hz, 1H, H-4'); 7.04 (dd, *J* = 8.1 and 4.7 Hz, 1H, H-5'); 7.24 (dd, *J* = 7.0 and 5.1 Hz, 1H, H-5); 7.33 (d, *J* = 7.8, 1H, H-3); 7.70 (ddd, *J* = 8.0, 8.0 and 1.6 Hz, 1H, H-4); 7.72 (dd, *J* = 4.7 and 1.6 Hz, 1H, H-6'); 8.61 (m, 1H, H-6).

^{13}C-NMR (100MHz, $CDCl_3$) δ: 48.2 (t, CH_2); 117.8 (d, C-4'); 121.5 (d, C-3); 122.6 (d, C-5); 123.3 (d, C-5'); 136.7 (d, C-6'); 137.2 (d, C-4); 137.4 (s, C-2'); 137.7 (s, C-3'); 149.0 (d, C-6); 156.8 (s, C-2).

HRMS (ESI): MH^+, found 220.06359, $C_{11}H_{11}N_3Cl$; requires: 220.0563.

3.7.5. SYNTHESIS OF QUINOLINE 92.



Nitro compound **91** (0.045 g, 0.25 mmol) and alcohol **3** (0.182 g, 0.775 mmol) were mixed in toluene (1 mL) and degassed by several vacuum-nitrogen cycles to reduce the air oxidation of alcohol **3** to ketone **90**. The resulting mixture was heated at 110 °C in a screw-cap tube (Pyrex N. 13) for 1 h and half, until the disappearance of the starting nitro compound. After the removal of the solvent in vacuo, the reaction crude was purified by FC with Toluene/EtOAc 10:1 to isolate ketone **90** (R_f = 0.63, 0.153 g, 87%). Quinoline (**92**), (R_f = 0.23; 0.018 g, 53%) was obtained by elution with Toluene/EtOAc 5:1. The excess alcohol **3** was recovered and recycled [R_f (Toluene/EtOAc 7:1) = 0.34].

Chapter IV

NEW SYNTHESIS OF HYDROXYINDOLIZIDINES FROM 1-(2-PYRIDYL)-2-PROPEN-1-OL

4.1. INTRODUCTION

4.1.1. GLYCOSIDASES AND GLYCOPROTEINS

Glycosidases are enzymes that catalyse the hydrolysis of the glycosidic bonds in complex carbohydrates and glycoconjugates. The wide variety of anabolic and catabolic processes based on molecular recognition (such as intestinal digestion, post-traslational processing of glycoproteins and the lysosomal catabolism of glycoconjugates) in which glycosidases are involved, makes them essential for the survival and existence of all living organisms. So, digestive glycosidases break down

large sugar to release monosaccharides which can be more easily taken up and used metabolically by the organism; lysosomal glycosidases catabolise glycoconjugates intracellularly; and a wide range of glycosidases are involved in the biosynthesis of the oligosaccharide portions of glicoproteins and glycolipids which play vital roles in mammalian cellular structure and function (Figure 4.1). In particular, cell surface glycoconjugates (*e.g.*, glycolipids and glycoproteins) are responsible for a host of functions involving interaction and communication between the cell and its environment. These functions are essential for the workings of cells, which therefore heavily rely on the biosynthesis and maintenance of these glycoconjugates.

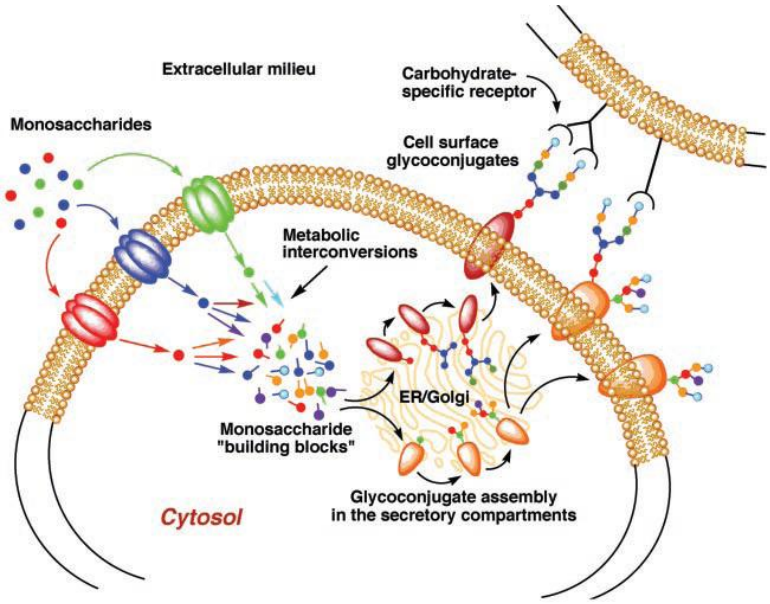


Figure 4.1. *Intracellular glycoconjugates synthesis.*

Thus, membrane glycoproteins include receptors for biologically important molecules such as hormones, low-density lipoprotein or acetylcholine while others are involved in cell-cell adhesions (Figure 4.2).

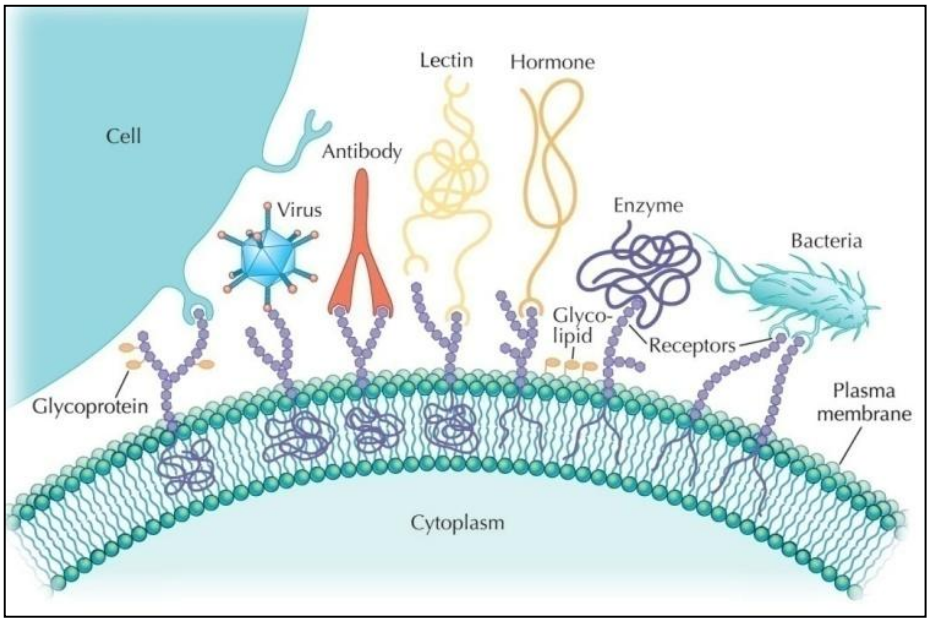


Figure 4.2. *Some biological functions of membrane glicoproteins.*

The oligosaccharide chains play an important role in the correct functioning of these proteins by stabilizing them and ensuring that they have the correct conformation and they may also be involved in the targeting mechanism of certain proteins. Not surprisingly, defects in their biosynthesis and function is implicated in the pathology of a host of diseases. In fact, aberrant glycosilation of glycoproteins and glycolipids, in which glycosidases are involved, was reported to be one o the molecular changes that accompany malignant transformation and growth of tumor cells.[90]

Since the mode of action of glycosidases involves the cleavage of glycosidic bonds between sugar molecules, individual glycosidases show specificity for certain sugar molecules and for a specific anomeric configuration of that sugar.

The hydrolysis of glycosides, operated by specific glycosidases, *e.g.* β-glucosidase for β-glucosides and β-galactosidase for β-galactosides is readily achieved by acid-catalysed processes and may invert (Figure 4.3) or retain (Figure 4.4) the configuration at the anomeric. The process involves two functional groups of the active site: an acid system and a basic or nucleophilic centre.[91]

[90] Macchi, B.; Minutolo, A.; Grelli, S.; Cardona, F.; Cordero, F. M.; Mastino, A.; Brandi, A. *Glycobiology* **2010**, *20*, 500.
[91] Dewick, P. M. *Medicinal Natural Products*, 3rd ed, Wiley: Chichester, UK, 2009, p. 30.

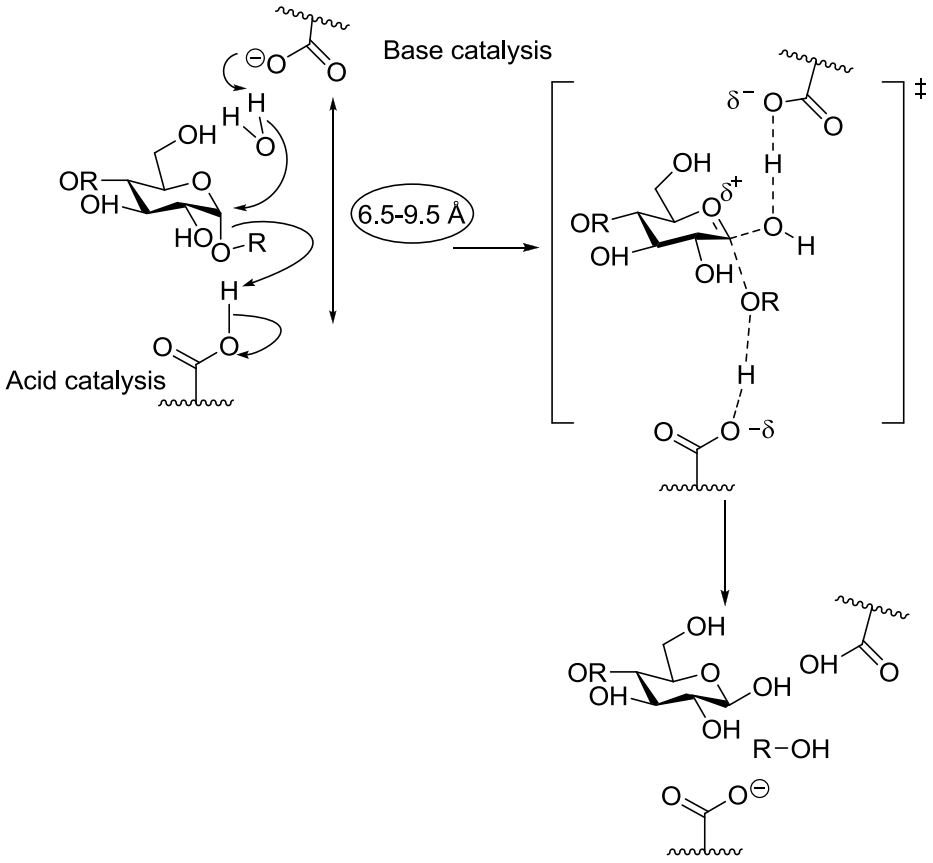


Figure 4.3. *Glycoside hydrolysis with inversion of configuration at the anomeric carbon.*

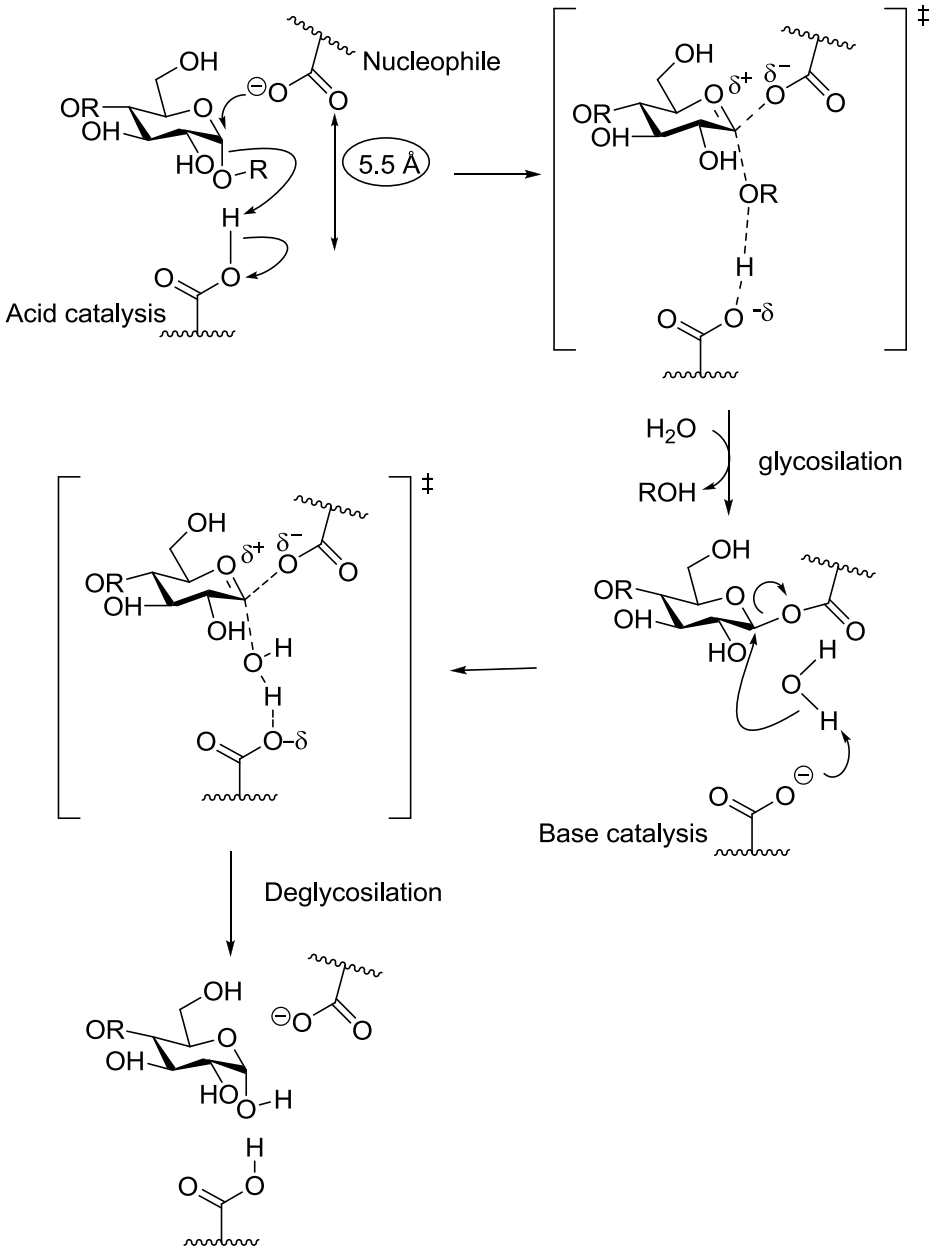


Figure 4.4. *Glycoside hydrolysis with retention of configuration at the anomeric carbon.*

4.1.2. GLYCOSIDASES INHIBITION

As underlined in the previous section, the collective names of the enzymes, which are responsible for the biosynthesis and maintenance of the glycolipid and glycoprotein units, are glycosyltransferases and glycosidases. Their inhibition can significantly

modulate the function or response of the cell, and therefore they make excellent targets for medicinal intervention. This approach has been particularly important in the treatment of diabetes mellitus, cancer, viral and bacterial infections and neurological diseases resulting from the mishandling of sphingolipid storage in the body.

Polyhydroxylated alkaloids can be extremely potent and specific inhibitors of glycosidases by mimicking the pyranosyl or furanosyl moiety of their natural substrates. Therefore, the number, position and configuration of the hydroxyl groups of each alkaloid dictate the type of glicosidases which are inhibited. For example, the configuration of the hydroxyl substituents of the glucosidase inhibitor Nojirimycin, discovered 40 years ago from cultured broth of the *Streptomyces* species, corresponds to that of glucose in the pyranose configuration.[92] It was shown that Nojirimycin inhibits α- and β- glucosidases. (Figure 4.5).

Figure 4.5. *Chemical structure of glucose and its corresponding imino sugar Nojirimycin.*

These alkaloids, that are sugar mimics with a nitrogen in the ring, are classified into five structural classes: polyhydroxylated piperidines, pyrrolidines, indolizidines, pyrrolizidines and nortropanes. Although the spatial arrangement of the hydroxyl groups of polyhydroxylated alkaloids serves as a means of recognition by specific glycosidases, it is the influence of the endocyclic nitrogen atom on the conformation and electrostatic properties of the molecule that is important for inhibition of enzyme activity. It has been suggested that when a polyhydroxylated alkaloid binds to the active site of a glycosidase, protonation of the compound leads to the formation of an ion pair between the inhibitor and a carboxylate anion in the active site of the enzyme. The protonated inhibitor closely resembles the transition state of the natural substrate

[92] Inouye, S.; Tsuruoka, T.; Niida, T. *J. Antibiot.* **1966**, *19*, 288.

and hence the enzyme has an high affinity for the molecules. However the strength of the binding and hence the effectiveness of the inhibition depends on the p*Ka* of the inhibitor and the pH optimum for the enzyme.[93] After the discovery of nojirimycin (Figure 4.5), over 100 glycosidase inhibitors have been isolated from plants and microorganisms. Modifying or blocking biological processes by specific sugar mimics has revealed the vital functions of glycosidases in living systems. Thus, because enzyme-catalyzed carbohydrate hydrolysis is a biologically widespread process, glycosidases inhibitors have many potential applications as agrochemicals and therapeutic agents. The inhibition process can have profound effects on quality control, maturation, transport and secretion of glycoproteins and can alter cell-cell or cell-virus recognition processes. This principle is the basis for the potential use of glycosidase inhibitors in viral infections, cancer, diabetes and genetic disorders.[94] There is now a vast amount of literature on the inhibition of glycosidases by particular natural polyhydroxylated alkaloids and an overview of this area is given by some reviews.[95] Also great synthetic effort has been carried out to afford several of these natural products and their non-natural analogues.[96] The development of efficient and general synthetic methods for these compounds is a challenging task due to their complex chemical structures. At the same time, it is a valuable objective in consideration of the poor yield that is usually obtained from natural sources. In addition, the synthesis of non-natural analogues opens the way to structure-activity-relation studies (SAR).

After the discovery of the first natural polyhydroxylated alkaloid Nojirimycin in 1966, Inouye and coworkers synthesized the first 1-deoxy derivative, 1-Deoxynojirimycin through reduction of the anomeric carbon. Only later, Deoxynojirimycin was isolated

[93] Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry* **2001**, *56*, 265.

[94] Asano, N. *Glycobiology* **2003**, *13*, 93R.

[95] (a) Asano, N.; Kizu, H.; Oseki, K.; Tomioka, E.; Matsui, K.; Okamoto, M.; Baba, M. *J. Med. Chem* **1995**, *38*, 2349. (b) Legler, G. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 319. (c) Winchester, B.; Fleet, G.W.J. *Glycobiology.* **1992**, *2*, 199. (d) Asano, N.; Nash, R.J.; Molyneux, R.J.; Fleet, G.W.J. *Tetrahedron Asimmetry* **2000**, *11*, 1645. (e) Ref. 2.

[96] (a) Afarinkia, K.; Bahar, A. *Tetrahedron Asimmetry* **2005**, *16*, 1239. (b) Pearson, M.S.M.; Mathè-Allainmat, M.; Fargeas, V.; Lebreton, J. *Eur. J. Org. Chem* **2005**, 2159.

from mulberry trees and streptomyces cultures and found to be a potent inhibitor of α-glucosidases and other glycosydases (Figure 4.6).[97]

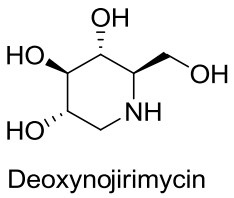


Figure 4.6. *Chemical structure of Deoxynojirimycin.*

4.1.3. INDOLIZIDINE INHIBITORS

Indolizidine alkaloids[98] are characterized by fused six- and five-membered rings, with a nitrogen atom at the ring fusion. For indolizidine alkaloid biosynthesis,[99] starting from L-lysine aminoacid, pipecolic acid forms with retention of the α-amino group nitrogen.

This can then act as starter for malonate chain extension, incorporating an extra C2 unit. The 1-indolizidinone may then be produced by simple reactions, though no details are known (Figure 4.7).

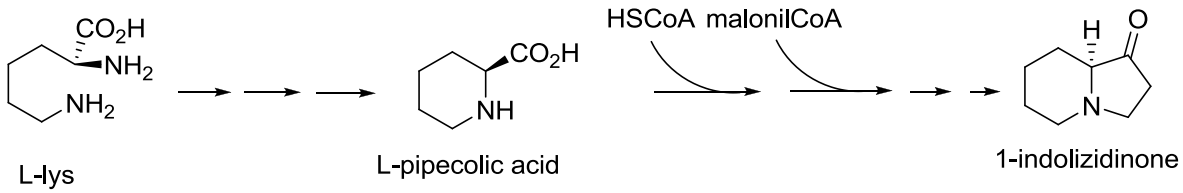


Figure 4.7. *Biosynthesis of 1-indolizidinone.*

[97] Inouye, S.; Tsuruoka, T.; Ito, T.; Niida, T. *Thetrahedron* **1968**, *24*, 2125.
[98] For recent reviews on indolizidine alkaloids, see: (a) Michael, J. P. *Nat. Prod. Rep.* **2001**, *18*, 520. (b) *ibid* **2002**, *19*, 719. (c) *ibid* **2003**, *20*, 458. (d) *ibid* **2004**, *21*, 625. (e) *ibid* **2005**, *22*, 603. (f) *ibid* **2007**, *24*, 191. (g) *ibid* **2008**, *25*, 139.
[99] (a) Ref. 90. (b) Cardona, F.; Goti, A.; Brandi, A. *Eur. J. Org. Chem.* **2007**, 1551.

This compound leads to castanospermine by a sequence of hydroxylations, but it is also a branch-point compound to alkaloids such as swainsonine which has the opposite configuration at the ring fusion (Figure 4.8).

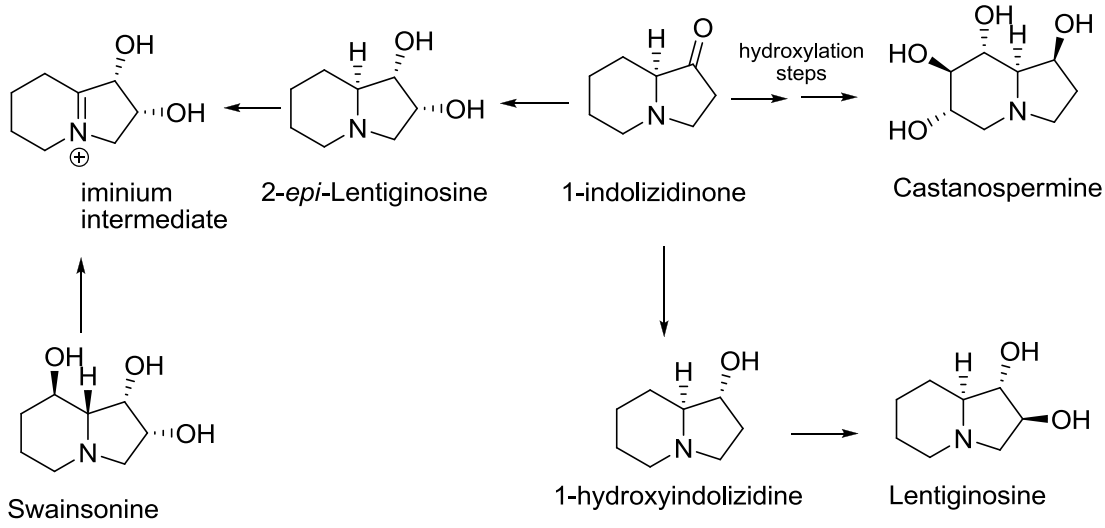
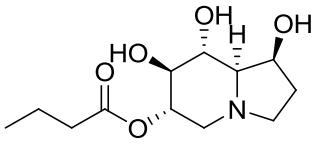


Figure 4.8. *Biosynthesis of some polyhydroxylated indolizidines.*

Swainsonine,[100] isolated from the leaves of *Swainsona canescens* (Leguminosae) and *Astragalus* spp. (Leguminosae), is a potent inhibitor of Golgi α-mannosidase II.[101] Castanospermine, a bicyclic analogue of Deoxynojirimycin, was isolated from the seeds of *Castanospermum australe*. It is a potent inhibitor of α-glucosidases (including human glucosidases I and II) and β-glucosidases.[102]

Polyhydroxyindolizidines such as swainsonine and castanospermine displayed activity against the AIDS virus HIV, by their ability to inhibit glycosidase enzymes involved in glycoprotein biosynthesis. The glycoprotein coating is essential for the proliferation of AIDS and some other viruses. This has stimulated considerable researches on related structures and their mode of action. The ester 6-*O*-butanoyl-castanospermine (celgosivir; Figure 4.9) was unsuccessful in clinical trials as an anti-AIDS agent, but it is still evaluated against hepatitis C.[91]

[100] Colegate, S.M.; Dorling, P.M.; Huxtable, C.R. *Aust. J. Chem*. **1979**, *32*, 2257.
[101] Molyneux, R.J.; James, L.F. *Science* **1982**, *216*, 190.
[102] (a) Saul, R.; Chambers, J.P.; Molyneux, R.J.; Elbein, A.D. *Arch. Biochem. Biophys.* **1983**, *221*, 593. (b) Saul, R.; Ghidoni, J.J.; Molyneux, R. J.; Elbein, A. D. *Proc. Natl. Acad. Sci. USA* **1985**, *82*, 93.



Celgosivir

Figure 4.9. *Chemical structure of Celgosivir.*

4.1.3.1. Lentiginosine

In 1990[103] Elbein and coworkers, on fractionating the hot methanol extracts from the leaves of *Astragalus Lentiginosus*, isolated Lentiginosine together with the major alkaloid Swainsonine and with a second dihydroxyindolizidine, the 2-epimer of Lentiginosine. Lentiginosine is thought to form by a similar biosynthetic pathway of swainsonine, that involves hydroxylation at C-2 *trans* to the existing OH group of a 1-hydroxyindolizidine, which is derived by diastereoselective reduction of 1-indolizidinone (Figure 4.7). Among imino sugars, Lentiginosine appears to be the least hydroxylated inhibitor of all the amyloglucosidases,[104] which are enzymes that hydrolyse 1,4- and 1,6-α-glucosidic linkages. Nonetheless, it proved to be a very active and selective compound. It was the first compound that violate the empirical rule stating that at least 3-hydroxy functionalities (β to the nitrogen atom) should be needed for the imino sugars to posses inhibitory properties toward glycosidases.[105]

4.1.3.2. Optical rotation of natural Lentiginosine.

Some confusion around the absolute configuration of natural Lentiginosine arose from the reported value of the optical rotation for the isolated material. On the basis of biological activity data of both (+) and (–)-Lentiginosine, it was discovered[104] that the natural product is dextrorotatory ($[a]_D$ = +3.3) and the negative rotation initially

[103] (a) Pastuszak, I.; Molyneux, R. J.; James, L. F., Elbein, A. D. *Biochemistry* **1990**, *29*, 1886. (b) Ref 95b.
[104] Brandi, A.; Cicchi, S.; Cordero, F. M.; Frignoli, R.; Goti, A.; Picasso, R.; Vogel, P. *J. Org. Chem* **1995**, *60*, 6806.
[105] (a) Elbein, A. D.; Molyneux, R. J. *Alkaloids: Chemical and Biological Perspectives* , Ed.: S. W. Pelletier, Wiley-Interscience, New York, **1987**, vol. 5, ch. 1. (b) Ref. 99b.

reported was due to impurities present in the natural product and also visible in the published ^{1}H-NMR spectrum.[103a] Most of the troubles experienced with Lentiginosine and its assignement of absolute configuration and sign of optical rotation were due to its low value of $[a]_D$ which then requires accurate measurements carried out on very pure samples.

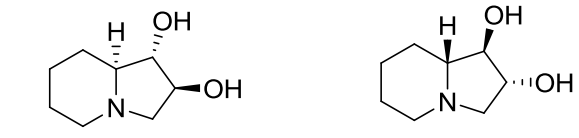
4.1.3.3. Biological activity.

Synthetic pure natural L-(+)-Lentiginosine, is twice as potent as castanospermine in its inhibition of amyloglucosidase, (IC50 = 0.43 mg/L versus IC50 = 0.82 mg/L towards amyloglucosidase from *Aspergillus niger*), which makes the alkaloid the most potent imino sugar type inhibitor towards the enzyme. 2-*Epi*-Lentiginosine was completely inactive when tested, so, evidencing that the relative configuration of the two hydroxyl groups was crucial for the activity. (+)-Lentiginosine behaved as a competitive inhibitor of amyloglucosidase and displayed high specificity even at high concentrations (100 mg/mL).

The peculiarity of Lentiginosine rests in the fact that it is the first potent glycosidase inhibitor bearing only two hydroxyl groups. Moreover, it is one of the most selective inhibitor.

The natural swainsonine has shown the ability to inhibit tumor cell growth and metastasis and it was assayed also in phase I clinical trials.[90] Castanospermine, its ester (Celgosivir) and salt derivatives have also shown to exhibit inhibition of tumor growth and of tumore metastasis.[90]

A test of natural (+)-Letiginosine and nonnatural (–)-Lentiginosine (Figure 4.10) on human mixed lymphocytes was recently carried out.



L(+)-Lentiginosine D(-)-Lentiginosine

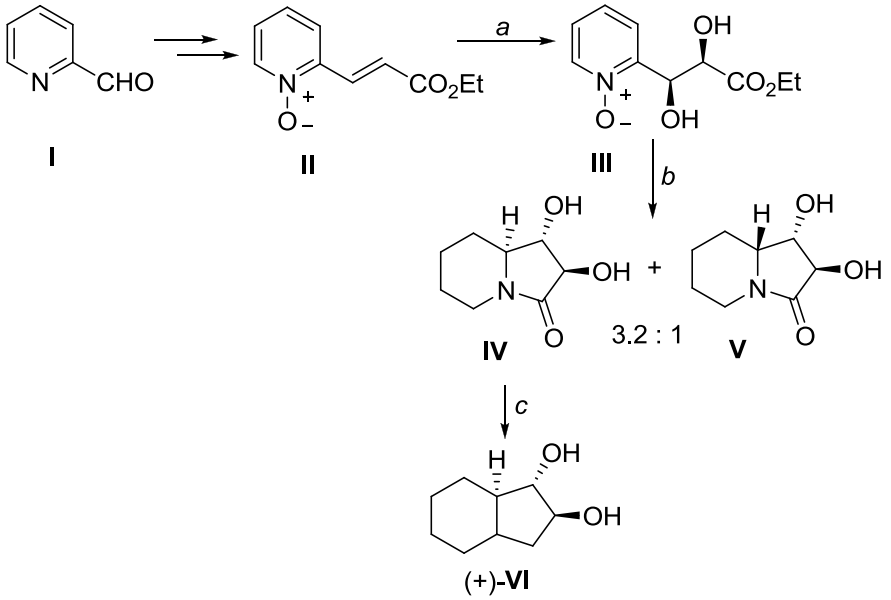
Figure 4.10. *Chemical structures of natural Lentiginosine and its nonnatural enantiomer.*

Both enantiomers slightly increased cell proliferation at low concentration (5 μM), but at higher concentration (0.5-1 mM), the effect of the two enantiomers was remarkably different. Both enantiomers inhibithed cell proliferation, but the effect was much more potent for (–)-Lentiginosine. Moreover, while the effect of (+)-Lentiginosine was simply to slow down cell proliferation, (–)-Lentiginosine seemed to act as a cytotoxic agent. A preliminary study showed clearly that the behavior of the two enantiomers was different. Apoptosis, the first described form of programmed cell death, proceeds via a highly regulated, energy conserved mechanism. Apoptosis plays a pivotal role in the healthy state in controlling cell growth. Moreover, apoptosis biology and disruption underlie both the development of malignant diseases and potential anticancer therapeutic applications. In order to investigate more deeply their biological activity, a series of experiments on the effects of both enantiomers of Lentiginosine on cell death in a panel of tumor cell lines of different origin was performed.[90] Further investigation is necessary to exactly clarify the relationship between apoptotic, toxic effects of (–)-Lentiginosine and related events. In order to an application as cytotoxic proapoptotic drug, it is conceivable to hypothesize that further modifications of this molecule could lead to an improvement of its biologic, potentially antitumor activity in vitro.

4.1.4. SYNTHESIS OF HYDROXILATED INDOLIZIDINE FROM PYRIDINE SYSTEMS.

Since 1990 until today, numerous syntheses of polyhydroxylated indolizidines and structural analogues have been published, evidencing that the interest of the scientific community in this topic remains undiminished. In this field, because its relevant biological activity and its relatively simple structure, Lentiginosine has insipired a lot of synthetic work, mostly based on chiral pool starting materials, and only occasionally relying on enantioselective synthesis.[98,99b] Some of them are especially valuable because they are very concise and afford good yields of the chiral products with high enantiomeric excess. Nevertheless, some processes exploiting suitably functionalized non chiral aromatic pyridines as precursors have been recently reported. For example, the most part of the synthetic procedures described in the literature, is based on the

construction of the functionalized pyrrolidine or piperidine unit, followed by a cyclization leading to the bicyclic skeleton. For this reason, aromatic pyridyl derivatives, easily convertible into the corresponding saturated systems, are interesting starting materials. Indeed, after the first approach of Shibasaki and co-workers starting from a dihydropyridone derivative,[106] Zhou and coworkers realized in 2003 a very concise enantioselective total synthesis of (+)-Lentiginosine, starting from based on 3-(pyridin-2-yl)acrylate *N*-oxide (**II**), derived from picolinaldehyde **I**, trough an improved Sharpless asymmetric dihydroxylation as the key step. Asymmetric dihydroxylation, performed with a higher excess of $(DHQ)_2PHAL$ and K_2CO_3 compared to the usual AD system, gave diol **III** with >99.9% *ee*. Hydrogenation under 10 atm H_2 over 10% Pd-C in MeOH afforded a 3.2:1 mixture of lactams **IV** and **V**. After removal of the minor isomer by recrystallization from ethyl acetate, reduction of **IV** with $BH_3{\cdot}SMe_2$ in THF furnished (+)-Lentiginosine (**VI**), in 20% overall yield from **II** (Scheme 4.1).[107]

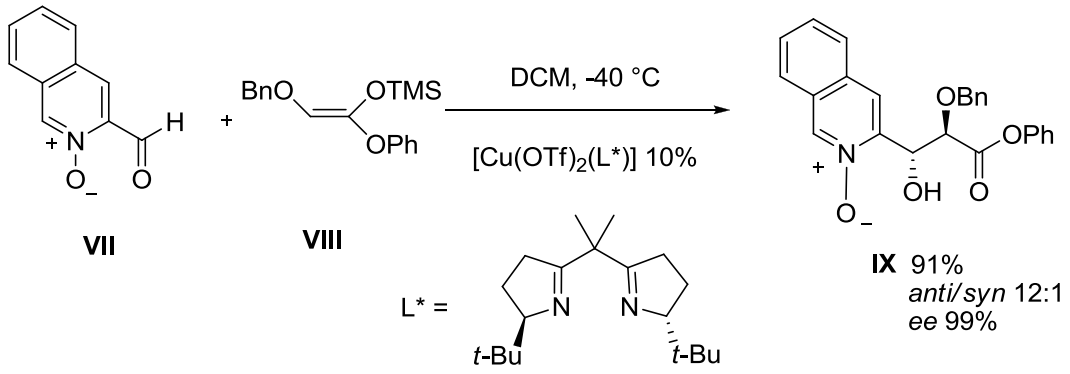


(*a*) 0.4 mol% $K_2[OsO_2(OH)_4]$, 3 mol% $(DHQ)_2PHAL$, $K_3[Fe(CN)_6]$ (3 equiv), K_2CO_3 (5 equiv), $MeSO_2NH_2$ (1 equiv), H_2O/*t*BuOH (1:1), 24 h, 62% with 20% recovery of the starting material; (*b*) 10% Pd/C, 10 atm H_2, MeOH, 24 h, 43% of **XIV**; (*c*) $BH_3{\cdot}SMe_2$, THF, 0°C - rt, 10 h, 75%.

Scheme 4.1. *Enantioselective synthesis of the (+)-Lentiginosine (**VI**) starting from pyridyl acrylate **II**.*

[106] Nukui, S.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 398.
[107] Feng, Z.-X.; Zhou, W.-S. *Tetrahedron Lett.* **2003**, *44*, 497.

Jørgensen and coworkers[108] found that 1-oxypyridine-2-carboxaldehydes were perfect substrates to be used as a prochiral starting material for synthesizing optically active pyridine units. A catalytic and asymmetric Mukaiyama aldol reaction between ketene silyl acetals **VIII** and 1-oxypyridine-2-carboxaldehyde **VII** catalyzed by a chiral copper (II)-bis(oxazoline) complex, gave the optically active 2-(hydroxyalkyl)pyridine derivative **IX** in good yields and diastereoselectivity, and in excellent enantioselectivity excess (Scheme 4.2.).

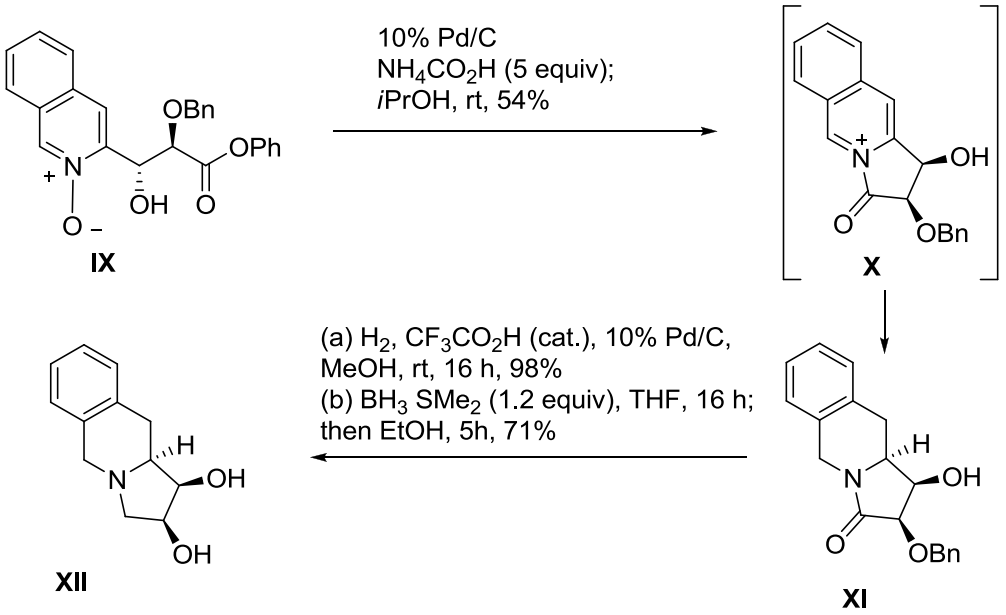


Scheme 4.2. *Catalytic enantioselective Mukaiyama aldol reaction: synthesis of derivative **IX**.*

Using a stepwise transformation, the synthesis of the nonnatural, but biologically interesting and optically active, (1*R*,2*S*,10*aS*)-1,2-dihydroxy-1,2,3,5,10,10a-hexahydrobenzo[*f*]indolizidine (**XII**) was performed in a stereocontrolled manner.

A reduction of the *N*-oxide **IX** and subsequent intramolecular cyclization afforded a rigid chiral pyridinium ring intermediate **X**, which was activated toward hydrogenation by ammonium formate from the less hindered side of the molecule. Then the *O*-debenzylation of **XI** with H_2 with Pd/C carried out in MeOH and CF_3COOH (cat.) and a reduction with $BH_3{\cdot}Me_2S$ in THF furnished **XII** in 70% yield from **XI** (Scheme 4.3).

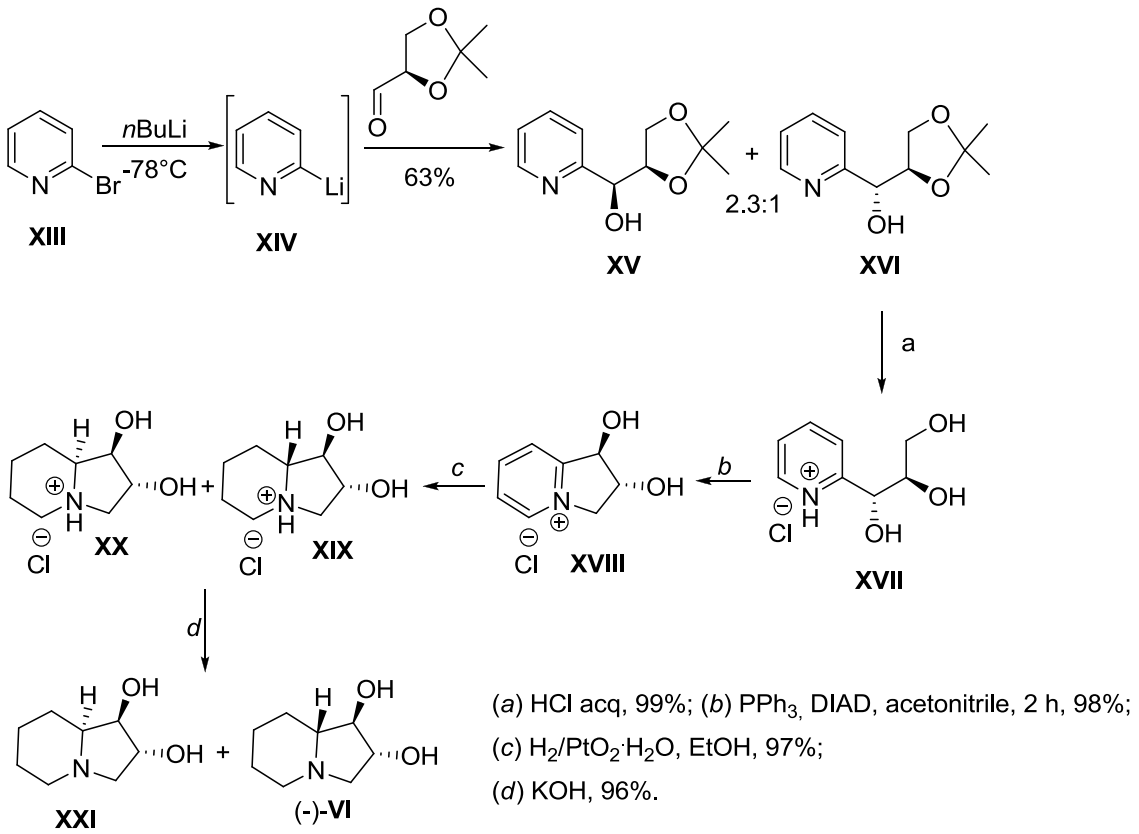
[108] Landa, A.; Minkkilä, A.; Blay, G.; Jørgensen, K. A. *Chem. Eur. J.* **2006**, *12*, 3472.



Scheme 4.3. *Synthesis of benzolentiginosine **XII**.*

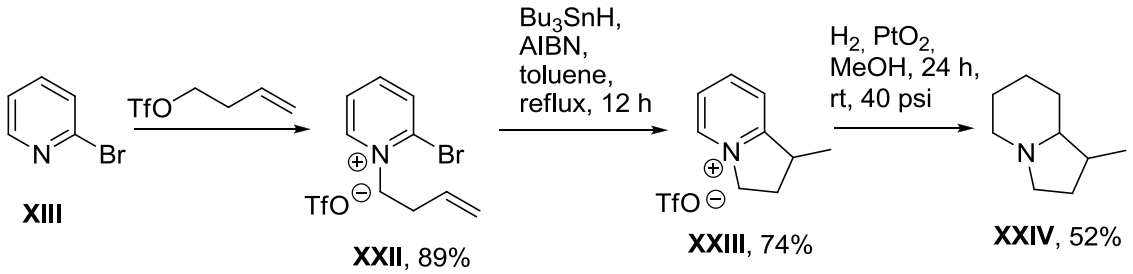
Fruit and Bischoff[109] described in 2007 a four steps synthesis of (–)-Lentiginosine and its 8a-epimer starting from 2-bromopyridine (**XIII**). In this methodology the key step consisted of a quaternarization of a fully unprotected pyridinium-polyol **XVII** using Mitsunobu methodology. The pyridinium salt was obtained by the treatment with HCl aq. of compound **XVI**, deriving from the reaction of 2-lithiopyridine (**XIV**) and (*R*)-2,3-*O*-isopropylidene glyceraldheyde, prepared from D-mannitol. PtO_2-Catalyzed diastereoselective hydrogenation of the pyridinium ring of **XVIII**, followed by basic treatment, led to the expected dihydroxyindolizidines, (–)-Lentiginosine and its 8a-epimer **XXI,** in excellent yields (Scheme 4.4).

[109] Azzouz, R.; Fruit, C.; Bischoff, L.; Marsais, F. *J. Org. Chem.* **2008**, *73*, 1154.



Scheme 4.4. *Synthesis of (–)-Lentiginosine (**VI**) and its 8a-epimer **XXI**.*

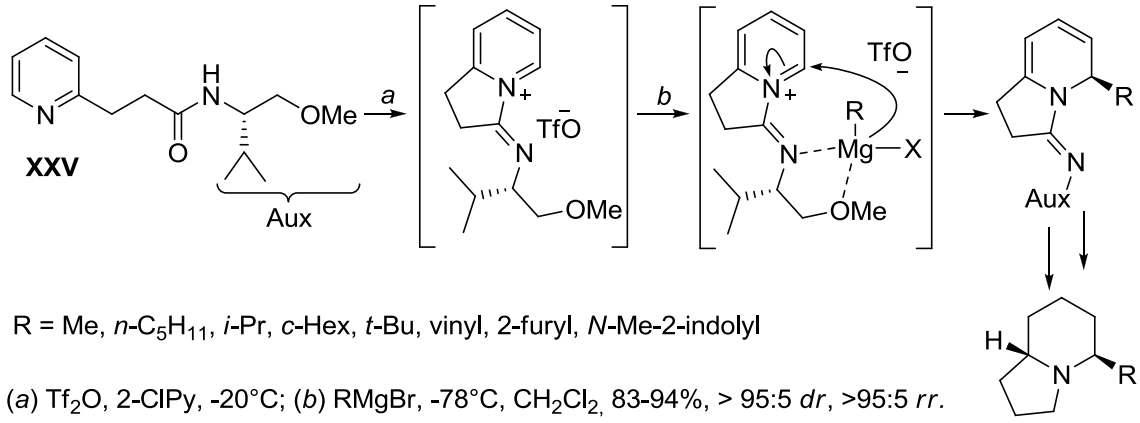
Previously,[110] 2-bromopyridine (**XIII**) has been used to build the indolizidine system, through *N*-alkylation with a suitable alkyl chain bearing a radical receptor to form *N*-alkenylpyridinium salt **XXII**, which was cyclised under normal tin hydride conditions, using Bu_3SnH in the presence of AIBN. Then, the indolizidine nucleus **XXIV** was obtained by reduction of the bicyclic salt **XXIII** (Scheme 4.5).



[110] Dobbs, A. P.; Jones, K.; Veal, K. T. *Tetrahedron Lett.* **1997**, *38*, 5383.

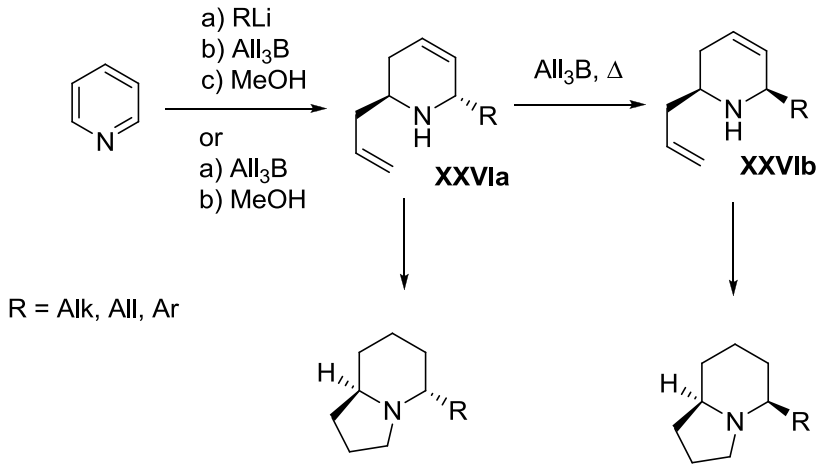
Scheme 4.5. *Construction of the indolizidine nucleus starting from bromopyridine* ***XIII****.*

Recently,[111] starting from pyridine derivative **XXV,** an unprecedented intramolecular pyridine activation-asymmetric dearomatization allowed a highly region- and diastereostereoselective synthesis of 5-substituted indolizidines in excellent yields (Scheme 4.6).



Scheme 4.6. *Synthesis of 5-substituted indolizidines.*

Moreover a general method for the synthesis of 5-substituted indolizidines based on cyclization of 6-substituted *trans*- and *cis*-2-allyl-1,2,3,6-tetrahydropyridines **XXVIa**,**b** obtained from pyridine and triallylborane, has been reported (Scheme 4.7).[112]



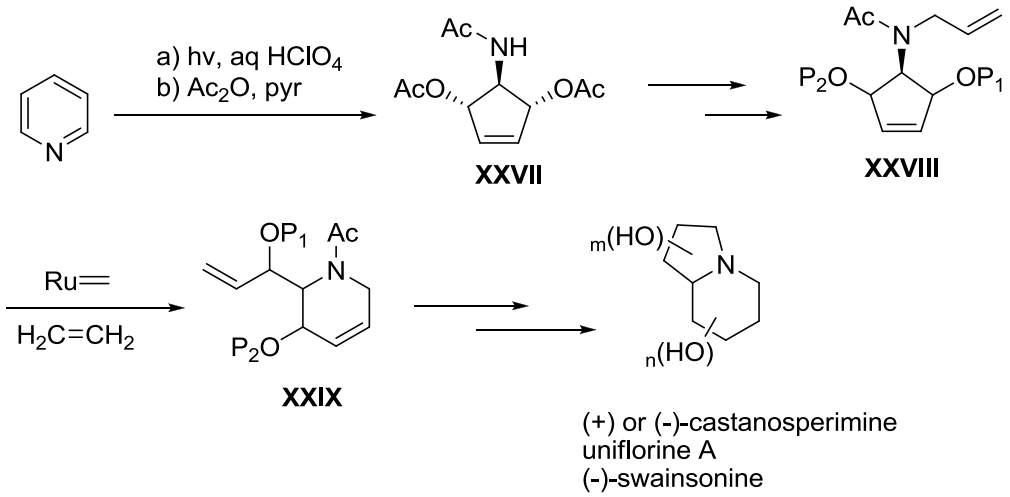
[111] Barbe, G.; Pelletier, G.; Charette, A. B. *Org. Lett.* **2009**, *11*, 3398.
[112] Bubnov, Yu. N.; Klimkina, E. V.; Ignatenko, A. V. *Russ. Chem. Bull.* **1998**, *47*, 941.

Scheme 4.7. *Synthesis of 5-substituted indolizidines from pyridine.*

In conclusion, most of the synthetic routes to Lentiginosine rely on the construction of the pyrrolidine or piperidine unit, in numerous steps, featuring the appropriate functionalities able to secure the generation of the bicyclic skeleton.

Moreover, in the literature, synthesis of a hydroxylated indolizidine framework from pyridine is sparse. In 2005, the strategy of Zhou and Feng[107] for the synthesis of (+)-Lentiginosine was taken up to synthesize (–)-Swainsonine and (–)-2,8a-di-*epi*-Swainsonine starting from readily available 2-pyridinecarbaldehyde and 3-hydroxypyridine.[113]

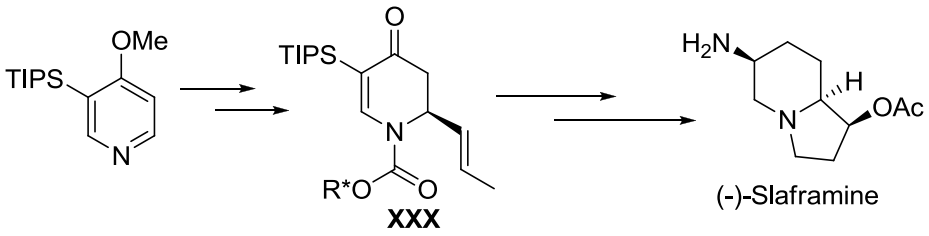
Passing through a photocyclization of pyridinium perchlorate and a subsequent transformation of the 4-amino-3,5-cyclopentendiol derivative **XXVII** into *N*-acetamido-*N*-allylcyclopentenes **XXVIII**, Mariano and coworkers[114] realized a ruthenium alkylidene catalyzed ring rearrangement metathesis (RRM) reaction to generate the corresponding 6-allyltetrahydropyridines **XXIX**, easily transformed to the indolizidine targets (Scheme 4.8).



Scheme 4.8. *Synthesis hydroxylated indolizidines starting from pyridine.*

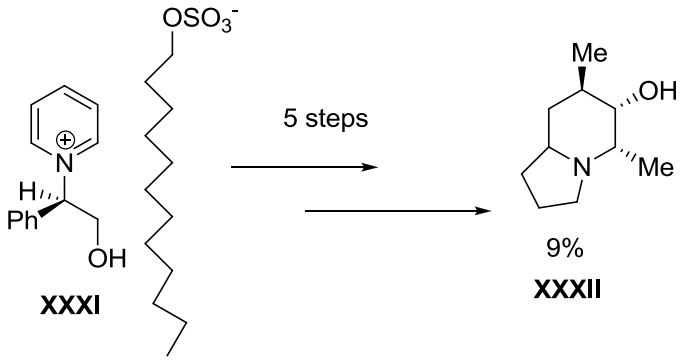
[113] Heimgärtner, G.; Raatz, D.; Reiser, O. *Tetrahedron* **2005**, *61*, 643.
[114] Zhao, Z.; Song, L.; Mariano, P. S. *Tetrahedron* **2005**, *61*, 8888.

An asymmetric synthesis of (–)-slaframine and *N*-acetylslaframine has been accomplished starting from an enantiopure dihydropyridone building block **XXX** (Scheme 4.9).[115]



Scheme 4.9. *Synthesis of Slaframine starting from pyridine ring.*

Enantioselective synthesis of hydroxyindolizidine **XXXII** was realized through a stereocontrolled alkylation of a chiral pyridinium salt **XXXI** with a Grignard reagent (Scheme 4.10).[116]



Scheme 4.10. *Synthesis hydoxyindolizidine **XXXII** from pyridinium salt **XXXI**.*

Others synthesis concerning indolizidine and indolizine derivatives from pyridine systems have been reported.[117]

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[115] Comins, D. L.; Fulp, A. B. *Org. Lett*. **1999**, *1*, 1941.

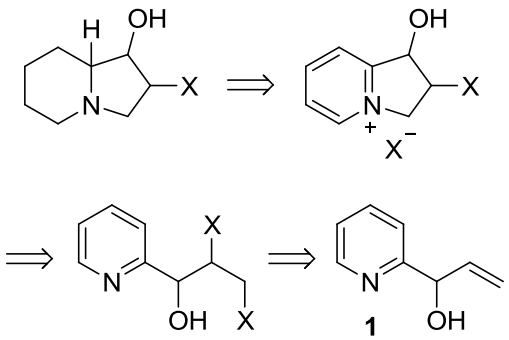
[116] Guilloteau-Bertin, B.; Compère, D.; Gil, L.; Marazano, C.; Das, B. C. *Eur. J. Org. Chem.* **2000**, 1391.

[117] (a) Heimann, J.; Schäfer, H. J.; Fröhlich, R.; Wibbeling, B. *Eur. J. Org. Chem.* **2003**, 2919. (b) Chai, W.; Kwok, A.; Wong, V.; Carruthers, N. I.; Wu, J. *Synlett* **2003**, 2086. (c) Comins, D. L.; Higuchi, K. *Beilstein Journal of Organic Chemistry* **2007**, *3*, No. 42, doi: 10.1186/1860-5397-3-42. (d) Smith, C. R.; Bunnelle, E. M.; Rhodes, A. J.; Sarpong, R. *Org. Lett.* **2007**, *9*, 1169. (e) Sun, Z.; Yu, S.; Ding, Z.; Ma, D. *J. Am. Chem. Soc.* **2007**, *129*, 9300. (f) Kim, I.; Kim, K. *Org. Lett.* **2010**, *12*, 2500.

4.2 – SYNTHESIS OF NEW HYDROXYINDOLIZIDINES FROM 1-(2-PYRIDYL)-1-PROPEN-1-OL

4.2.1. RETROSYNTHETIC APPROACH

In the light of the showed approaches (Section 4.1.4) to the synthesis of the indolizidine nucleus starting from pyridyl derivatives, we decided to test the potential of 1-(2-pyridyl)-2-propen-1-ol (**1**) as precursor of the indolizidine system. The presence at position 2 of the pyridine ring of a three-carbon atom chain containing a hydroxyl function could make alcohol **1** a good candidate to access hydroxyindolizidines. The suitably activated double bond appears in fact promising for electrophilic additions. Then, as depicted in Scheme 4.11, a retrosynthetic approach to 1-hydroxyindolizidine derivatives, substituted at position 2, could involve halogenation of **1**, intramolecular cyclization, and reduction of the pyridinium ring. Further synthetic elaborations could allow the synthesis of Lentiginosine and its analogues in few steps and with high atom economy.

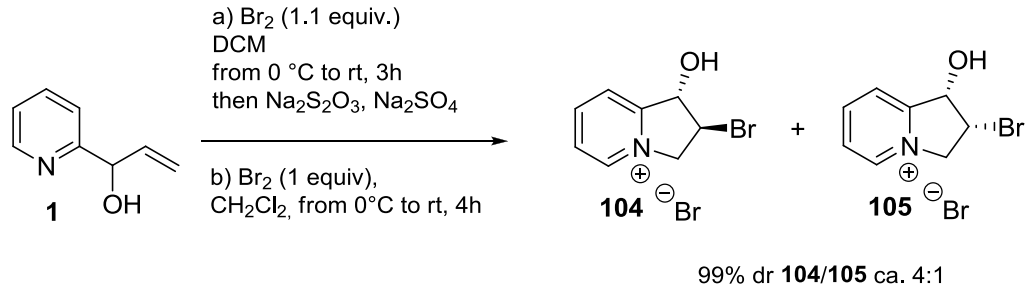


Scheme 4.11. *Retrosynthetic approach to 1-hydroxyindolizidines from alcohol **1**.*

4.2.2. BROMINATION OF ALCOHOL 1

4.2.2.1. *Bromine addition – method A*

With this hypothesis in mind, bromination of alcohol **1** was studied first. Following a typical synthetic addition strategy on alkene double bond, a bromine solution (1.1 equiv) in dichlorometane was added dropwise at 0 °C to a solution of alcohol **1** in the same solvent, then the mixture was stirred for 3 h at room temperature. A white precipitate formed. An oversaturated solution of $Na_2S_2O_3$ was added to destroy the excess of the reactant, and the solvent was filtered. After evaporation of the dichloromethane, the *trans* indolizinium salt **104** was recovered in 59% yield as a pearl grey solid. By extraction from the residue with acetone, a mixture of salt **104** and its corresponding *cis* derivative **105** was otained (ratio **104**/**105** ca 1:1, ^{1}H-NMR) (Scheme 4.12, path *a*, see method A in the experimental section 4.6).



Scheme 4.12. *Bromination of 1-(2-pyridyl)-2-propen-1-ol (**1**) with Br_2*

The applied methodology leads to the quantitative formation of the bicyclic salts **104** and **105** through a diastereoselective pathway in favor of the *trans* derivative (dr ca. 4:1). The salts show a quite good solubility in high polar solvents as MeOH, H_2O, DMF, DMSO (see Section 4.2.2.5), but they couldn't be purified by crystallization due to their insolubility in the most of other organic solvents. In the light of the following synthetic steps, the use of an excess of bromine has to be avoided because the treatment with $Na_2S_2O_3$, necessary to destroy unreacted Br_2 (path b, Scheme 4.12), prevents the following reduction step (H_2, $PtO_2{\cdot}H_2O$), likely due to the poisoning of the catalyst (see Section 4.2.3.2).

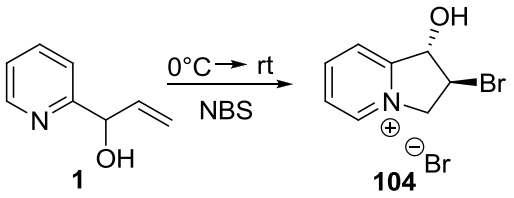
4.2.2.2. *Bromine addition – method B*

A stoichiometric amount of bromine was used to avoid the treatment with $Na_2S_2O_3$. Working in dichloromethane the indolizinium salts **104** and **105** were isolated by filtration as inseparable mixture (ratio ca. 1:1, ^{1}H-NMR) in 51% yield, while evaporation of the solvent allowed to recover the *trans* diastereomer **104** in 48% yield as a pearl grey solid (Scheme 4.12, path *b*, see method B in the experimental section).

4.2.2.3. *Use of NBS - Method C*

The tricky bromine addition could be avoided using NBS, a milder bromination agent. In non-polar solvent, NBS generates radical species used for allylic bromination, while in polar solvent as water, electrophilic bromine is generated in low concentrations. In this condition other nucleophilic agent, as water, could open the bromonium intermediate, and bromohydroxy species were obtained.[118]
The reaction was performed in a mixture of THF and water (Table 4.1).

[118] Krow, G. R.; Grandla, D.; Guo, W.; Centafont, R. A.; Lin, G.; Debrosse, C.; Sonnet, P. E.; Ross III, C. W.; Ramjit, M. G.; Carroll, P. J.; Cannon, K. C. *J. Org. Chem.* **2008**, *73*, 2114.



	NBS (equiv)	Solvent	Time (days)	**104** yield (%)
A	1	THF/H_2O (2:1)	1	Complex reaction crude
B	1	THF	1	Complex reaction crude
C	2.5	THF/10% H_2O	3	53
D	4	THF/10% H_2O	3	35
E	1.3	THF/H_2O (3:10)	3	Complex reaction crude

Table 4.1. *Reaction conditions for the bromination of **1** using NBS.*

Analytical and spectroscopic evidences showed that only *trans* derivative **104** formed, while the expected dihydroxy substituted indolizinium salt was not present in the reaction mixture. This methodology was totally diastereselective, but suffered of a lower yield. In fact, working with 2.5 equiv. of NBS in THF with 10% of water (Table 4.1, entry C), by filtration only (1*SR*,2*SR*)-2-bromo-1-idrossi-1*H*,2*H*,3*H*-indolizinium bromide (**104**) was obtained in 53% yield. Attempts to improve yields varying the amount of water or NBS, were unsuccessful (Table 4.1, entries A, B, D, E). Spectroscopic analysis on the mother liquor, showed the presence of different soluble pyridinium salts likely coming from the anionic exchange of the bromide ion. Even the addition of LiBr (2.5 equiv.) to favor the precipitation of indolizidinium **104**, was unsuccessful.

In conclusion this methodology (see Method C in the Experimental section 4.6) appeared as a totally diastereoselective path to obtain *trans* bicyclic salt **104**, while direct bromine addition gave rise to mixtures of *cis* and *trans* diastereoisomers isolated by filtration along with pure *trans* salt **104**. In the synthetic procedures B and C the salts

were isolated in pure form and used directly for the following synthetic steps. The chemical structure and the relative configurations at C-1 and C-2 carbon atoms of indolizinium bromide **104** were confirmed by powder diffraction X-ray analysis (Figure 4.11).

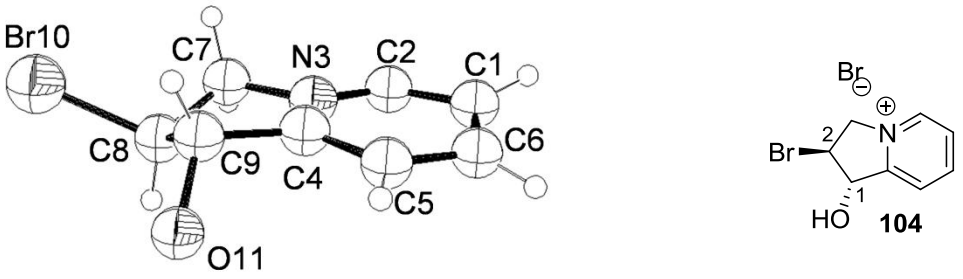
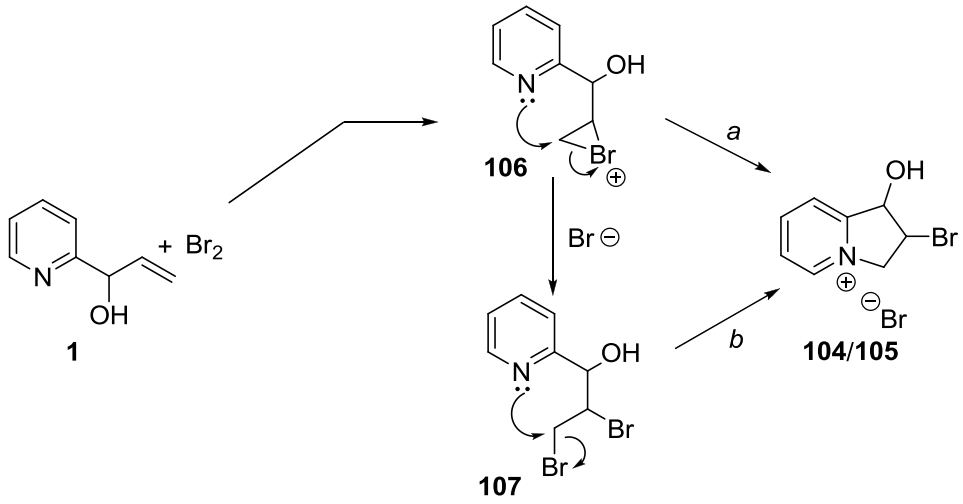


Figure 4.11. *ORTEP drawing of salt **104**.*

4.2.2.4. *Mechanistic hypothesis*

An NMR mechanistic study was performed to follow the pathway of the bromine addition reaction on the double bond of alcohol **1**. The diastereoselective formation of indolizinium salts **104** and **105** (*dr* ca. 4:1, in favor of the *trans* diastereoisomer), could be rationalized through a domino process involving an electrophilic addition of bromine on the alkene moiety of **1** and intramolecular cyclization of the bromonium ion **106** (pat *a*) or the dibromo intermediate **107** (pat *b*, Scheme 4.13).

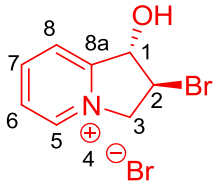


Scheme 4.13. *Reaction pathways leading to indolizinium salts **104** and **105**.*

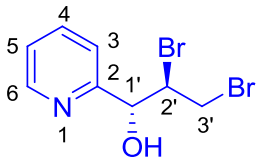
Performing the above reaction in $CDCl_3$ as solvent, after the disappearance of **1**, a small amount of the solution was taken and studied through NMR analysis (^{1}H- and ^{13}C-NMR, g-HSQC and g-HMBC). The experiments clearly evidenced a transient open-chain dibromo derivative along with the predominant *trans* indolizinium salt **104** (ratio ca. 2:1). The observed intermediate, that disappeared after 3 - 4 hours, was likely the *anti* diastereomer **107a** (Figure 4.12), being quickly converted into salt **105** that separated from the solution together with some amounts of **104**.[119]

In particular, the presence in the ^{1}H-NMR spectrum of a quartet (J = 5.8 Hz) at δ 4.44 ppm for the CHBr resonance well supported the open-chain structure of type **107**, free from conformation constrains with respect to the bromonium system **106** (Scheme 4.13). As evidenced in figure 4.12, the doublet at δ 5.06 ppm (J=5.8 Hz) belongs to H-1′, while the multiplet at δ 3.90 ppm, belonging to the CH_2Br (H-3′) moiety of the open chain structure **107**, corresponds to the XY part of a AMXY system, partially overlapped to the ^{1}H-NMR signal of H-3 of **104** at δ 3.85 ppm. The only heteronuclear correlation evidenced in the g-HMBC spectrum between C-1′ (δ=73.8 ppm) and H-3 (δ=7.44 ppm), is a further confirmation of the presence of a labile monosubstituted pyridine intermediate. Finally, concerning the pyridine moiety of **107**, only the H-3 proton showed a well-separated doublet at 7.44 ppm (J= 7.8 Hz), while the other signal were overlapped to ones of the main product **104**.

[119] The insoluble precipitate was recovered, dissolved in DMSO-d_6 and analysed via ^{1}H-NMR, showing the presence of a mixture of **104** and **105** in ca. 2:1 ratio.



104



107a, *anti*

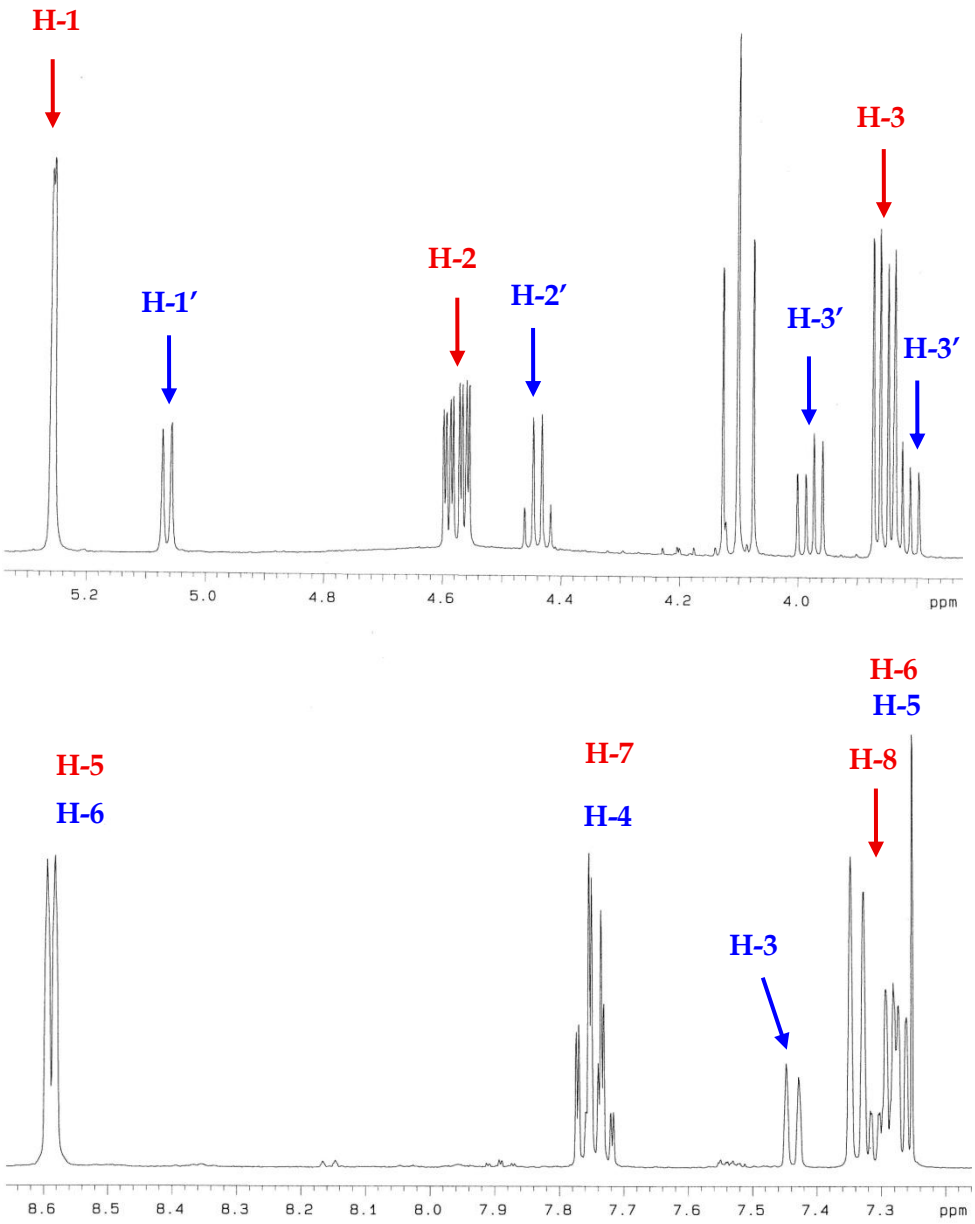
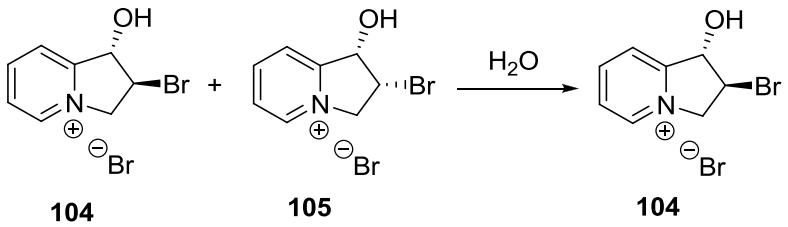


Figure 4.12. *Chemical structure of the anti dibromo intermediate* ***107a*** *and* ^{1}*H-NMR spectrum in* $CDCl_3$ *of the bromination reaction.*

4.2.2.5. *Thermal isomerization*

When the mixture of diastereomers **104** and **105** (ca. 1:1) was dissolved in polar solvents as DMSO or DMF and stirred for some days (4-11 days) at room temperature, a quantitatively conversion of **105** into **104** was observed. However, the recovery of a clean indolizinium salt **104** from these high boiling solvents was quite difficult. Moreover operating in methanol, in the presence of small amounts of a polar solvents, as DMSO or CH_3CN, the thermal conversion was unsuccessful.

Better results were obtained switching on water. Attempts to find the best conversion conditions (*e.g.*, temperature, concentration, reaction time) were performed in D_2O (table 4.2).



104 **105** **104**

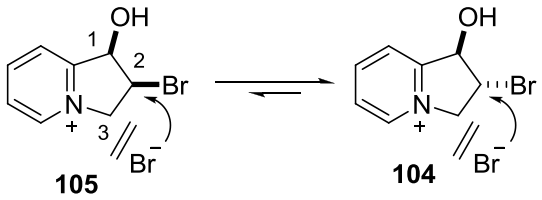
	T (°C)	Conc. (M)	time (days)	conversion (%)	**104** yield (%)
A	rt	0.16	3	0	---
B	70	0.16	9	100	85
C	60	0.12	11	100	88
D	80	0.02	5	100	84

Table 4.2. *Thermal conversions of **105** into **104** in water.*

The isomerization process in water at room temperature resulted very low (table 4.2, entry A). At higher temperature (70 °C), the *cis* diastereoisomer **105** signals disappeared after 9 days and the *trans* diastereoisomer **104** was recovered in 85% yield.

With the aim to reduce the thermal decomposition, different conditions (changes of salt concentration and temperature) were tested. Working at 60 °C with a 0.12 M solution concentration, the reaction time resulted too long (11 days for a total *cis*/*trans* conversion, table 4.2, entry C); then, the better compromise between reasonable reaction time and good product yield was obtained operating at 80 °C for 5 days with a 0.02M solution concentration. The *trans* diastereoisomer was recovered in 84% yield (table 4.2, entry D).

Likely, in polar solvents, the solvent-separated ion pairs in **104** and **105** were able to evolve via S_N2 nucleophilic attack of the bromine ion on the C-2 carbon atom. Isomerization of **105** into the more stable *trans* isomer **104** was then observed (Scheme 4.14).



Scheme 4.14. *Conversion of indolizinium salt **105** into **104**.*

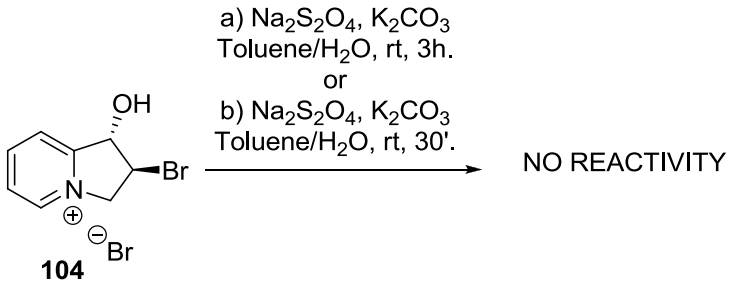
In conclusion the thermal isomerization in water of the *cis* salt **105** into the *trans* one **104** allowed to obtain only one isomer starting from a mixture of inseparable diastereoisomers. Then, the bromination and the following isomerization led to the formation of the *trans* salt **104**, obtained in a pure form starting from pyridylpropenol **1** in 83% yield over two synthetic steps.

4.2.3. REDUCTION OF THE INDOLIZINIUM SALT 104.

The next step was the reduction of salt **104**. The reaction allows the direct formation of the indolizidine systems.

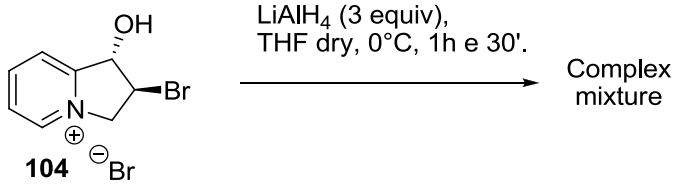
4.2.3.1. *Partial reduction.*

First mild reducing agents were considered. With the aim to obtain 1,4-dihydropyridine systems, sodium dithionite was tested in a two-phase solution (toluene/water).[120] Unfortunately **104** didn't react in this reaction conditions, as well as at higher temperature (Scheme 4.15).



Scheme 4.15. *Reaction of salt **104** with sodium dithionite.*

Pyridinium systems are easily reduced by metal hydrides, affording partial reduction products.[121] $LiAlH_4$ reacted quickly with (1*SR*,2*SR*)-2-bromo-1-hydroxy-1*H*,2*H*,3*H*-indolizinium (**104**), leading to a complex reaction mixture (^{1}H-NMR, TLC) (Scheme 4.16).



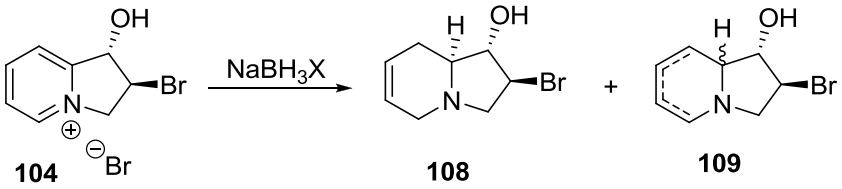
Scheme 4.16. *Reaction of salt **104** with $LiAlH_4$*

Better results were obtained with sodium borohydride ($NaBH_4$) and sodium cyano borohydride ($NaBH_3CN$). The reaction is essentially a nucleophilic addition of hydride to the pyridinium nucleus. In particular operating for 2 h with 2 equiv of $NaBH_4$ in

[120] Wong, Y-S; Marazano, C.; Gnecco, D.; Das, B. C. *Tetrahedron Lett.* **1994**, *35*, 707.
[121] (a) Pottd, K. T.; Liljegren, D.R. *J. Org. Chem.* **1963**, *28*, 3066; (b) Elderfield, R. C.; Fisher, B.; Lagowski, J. M. *J. Org. Chem.* **1957**, *22*, 1376.

THF/EtOH the tetrahydro derivative **108** was isolated in 30% yield from a complex reaction crude containing several regio- and diastereoisomers (table 4.3, entry D). Attempts to improve the yield of the process using different reaction conditions (solvent, reaction times, type and amount of reducing agent) were unsuccessful (Table 4.3, entries A,C,D,E).

Considering the other regio- and diasteoreoisomers of type **109**, the reducing process was performed in 56% overall yield.



104 **108** **109**

	X	$NaBH_3X$ (equiv.)	solvent	T	Time	**108** yield (%)
A	H	2	EtOH	rt	5h	16%
B	H	2	THF/EtOH[a] (2:1)	0°C-rt	1-2h	32%
C	H	2	THF/EtOH (4:1)	0°C-rt	1h	21%
D	H	3	THF/EtOH (9:1)	rt	3 giorni	30%
E	CN	2	THF/EtOH (2:1)	0°C-rt	1 giorno	18%

Table 4.3. *Reduction of **104** with sodium borohydrides.*

The structure of **108**, as well as the relative stereochemistry on C-1. C-2 and C-8a carbon atoms, was unambiguously established by single-crystal X-ray diffraction analysis (Figure 4.13).

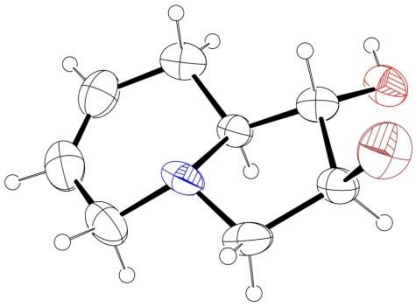
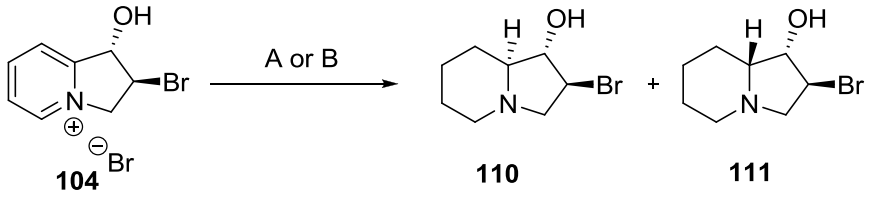


Figure 4.13. *ORTEP drawing of compound* ***108.***

4.2.3.2. *Total reduction*

When a mixture of salts **104** and **105** (obtained from alcohol **1** by treatment with 1.1 equiv of bromine followed by addition of $Na_2S_2O_3$ to destroy the excess of reagent – Method A, see the Experimental section) was subjected to hydrogenation with molecular H_2 in the presence of Pd/C or $PtO_2{\cdot}H_2O$ as catalysts, the reductive process was absolutely inhibited either operating at atmospheric or higher pressure.[122] The same result was observed with ammonium formate as hydrogen source in the presence of Pd/C.[123] The reduction was performed with H_2 in the presence of $PtO_2{\cdot}H_2O$ by using salts coming from synthetic procedure B or C (see the Experimental section), that employ respectively stoichiometric amounts of Br_2 or NBS, excluding the treatment with $Na_2S_2O_3$. While the use of Pd/C afforded a complex mixture crude, working with *trans* salt **104** in EtOH for 6h at room temperature allowed to isolate the diastereoisomeric *trans* bromohydroxyindolizidines **110** and **111** in 43 and 29% yields, respectively (table 4.4, entry B). Longer reaction times led to worst yields (Table 4.4, entry A). Clearly, sulphur salts are likely responsible for the poisoning of the metal catalyst with a consequent hamper of the reduction.

[122] In this case the hydrogenation was performer in autoclave.
[123] Zacharie, B.; Moreau, N.; Dockendorff, C. *J. Org. Chem.* **2001**, *66*, 5264.



	Cat.	P (H_2) (atm)	solvent	T	Time	110 yield %	111 yield %
A	$PtO_2 \cdot H_2O$ (10%mol)	1	EtOH	rt	16h	33%	20%
B	$PtO_2 \cdot H_2O$ (10%mol)	1	EtOH	rt	6h	43%	29%

Table 4.4. *Hydrogenation of salt **104** with H_2 in the presence of $PtO_2 \cdot H_2O$ as catalyst.*

It's important to underline that the main product of the reaction (diastereoisomer **110**) has got the same relative configuration at C-1, C-2 and C-8a of the natural Lentiginosine.

* * *

Then these results appear useful to assure a facile access to new polyfunctionalyzed indolizidine systems, starting from pyridyl propenol **1** through only three synthetic steps.

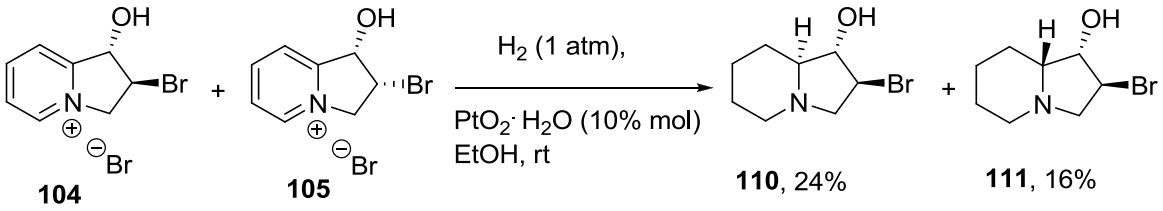
1) Electrophilic bromine addition to the double bond, with following one-pot 5-*exo*-*tet* intramolecular cyclization of the reaction intermediate affording the bicyclic indolizinium salts **104** and **105**;

2) Isomerization of the *cis* diastereisomer **105** into the *trans* one **104** in polar solvent;

3) Catalytic hydrogenation in the presence of $PtO_2 \cdot H_2O$.

Finally, the behavior of the *cis* diastereoisomer **105** in the hydrogenation process was studied.

Performing the hydrogenation on the inseparable mixture of the two diastereoisomers obtained by the Method B, four diastereoisomeric bromo hydroxylindolizidines were expected. Surprisingly, chromatographic resolution afforded products only deriving from reduction of the *trans* indolizinium salt: compounds **110** and **111** were in fact isolated in 24% and 16% yields, respectively. Once again, these results stressed the different reactivity and stability of the two diastereoisomers (Scheme 4.17).



Scheme 4.17. *Hydrogenation of the cis/trans indolizinium salts mixture.*

The structures of **110** and **111**, that differ just for the configuration at position 8a, were confirmed by single-crystal X-ray diffraction analyses (Figures 4.14. and 4.15).

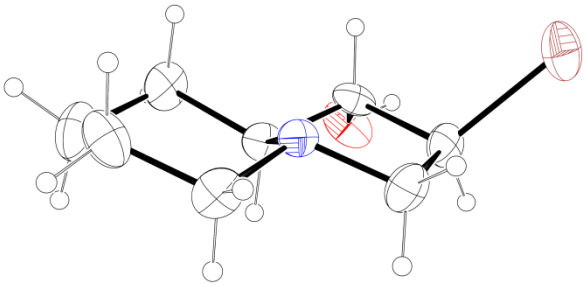


Figure 4.14. *ORTEP drawing of compound **110**.*

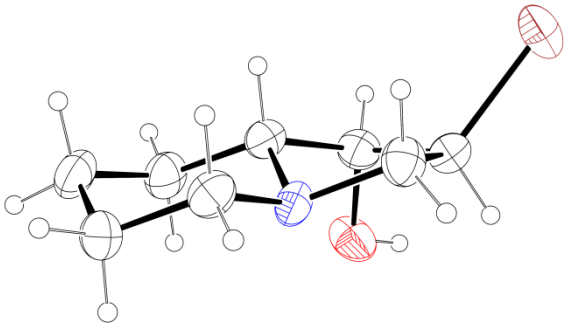
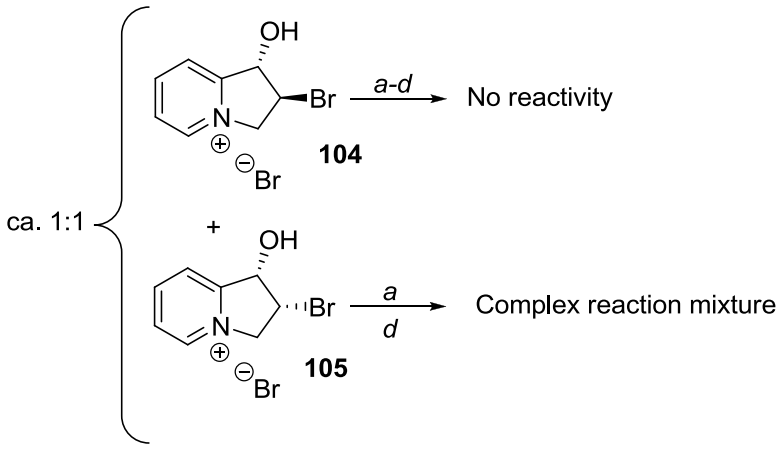


Figure 4.15. *ORTEP drawing of compound **111**.*

4.2.4. NUCLEOPHILIC SUBSTITUTION REACTIONS

4.2.4.1 *Nucleophilic substitutions on indolizinium salts.*

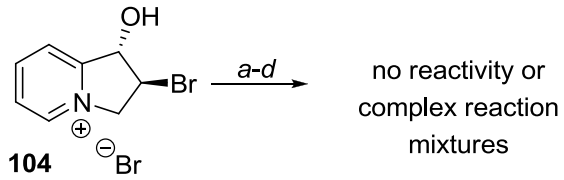
The presence of a good leaving group, as a bromine atom on the indolizidine skeleton, suggested to test the new substrates towards nucleophilic substitution reactions.
Working with the mixture of the indolizinium salts **104** and **105**, the nucleophilic substitution products were never observed. In particular, with a nitrogen nucleophile as benzylamine, the *cis* diastereoisomer disappeared at room temperature, while *trans* pyridinium salt **104**, stable at 70 °C in DMSO, decomposed at 110 °C (Scheme 4.18). Similar results were obtained with cesium floride in methanol (Scheme 4.18).



(*a*) NH_2CH_2Ph, DMSO, rt; (*b*) idem, 50°C; (*c*) idem, 70°C; (*d*) CsF, CD_3OD, rt.

Scheme 4.18. *Nucleophilic substitutions on salts **104** and **105**.*

Even attempts to perform nucleophilic substitutions with *O*-nucleophiles (NaOAc, NaOBn and NaOH) failed (Scheme 4.19).



(*a*) NaOAc, EtOAc/EtOH, rt; (*b*) NaOAc, MeCN, rt; (*c*) NaOH, THF, rt; (*d*) NaOBn, BnOH, rt

Scheme 4.19. *Nucleophilic substitutions on salt* ***104***

4.2.4.2. *Nucleophilic substitution on bromohydroxyindolizidines 110 and 111*

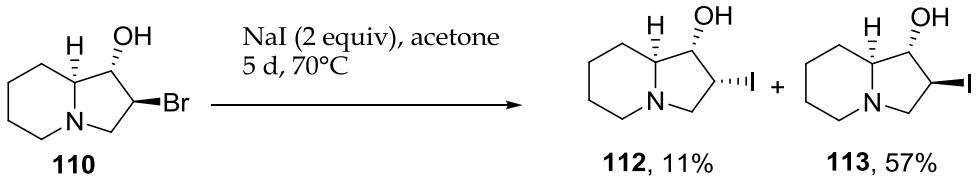
A-Use of benzylamine

First, the reactivity of 2-bromo-1-hydroxyindolizidine **110** towards benzylamine was studied. Working in polar solvents as mixture of acetonitrile and dichloromethane or chloroform or methanol at room temperature or at 70 °C, no reactivity was observed, while working with an excess of nucleophile (2 equiv.) and rising up the temperature (until 110 °C) for long reaction times (1 or 5 days) the reactive species evolved towards complex crude reaction mixtures or decomposition. Some improvement was observed operating in the presence of a Lewis acid (*e.g.*, $MgBr_2$).
Bromohydroxy indolizidine **111** reacted with 1.1 equiv. of *N*-benzylamine in methanol at 70 °C, but led to a complex reaction crude.

B- Use of sodium iodide

These first attempts clearly showed the difficulty to remove the bromine atom bonded to C-2 carbon in the indolizidine systems. So with the aim to study the mobility of the leaving group, the reactions of indolizidines **110** and **111** towards NaI were studied. It is important to underline that a process of double S_N2 on **110** and **111** could be able to introduce another OH functionality on C-2, with retention of configuration, leading to Lentiginosine and 8a-*epi*-Lentiginosine in racemic form.
A mixture of indolizidine **110** and 2 equiv. of NaI was stirred at 70 °C in acetone. After 5 day the starting material disappeared and a white precipitate (NaBr) formed. By

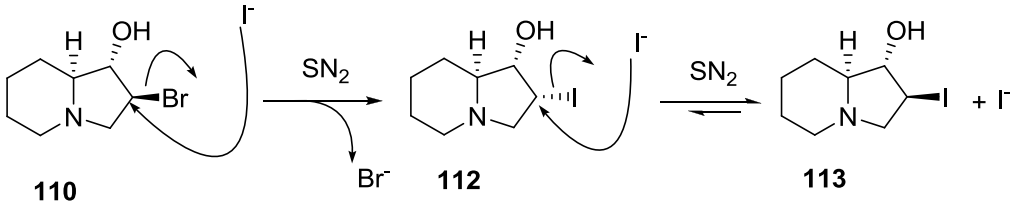
chromatographic resolution (1*SR*,2*SR*,8a*SR*)-1-hydroxy-2-iodoindolizidine (**113**) was isolated along with a mixture of (1*SR*,2*RS*,8a*SR*)-1-hydroxy-2-iodoindolizidine (**112**) and **113** in ratio ca 1.6: 1 (^{1}H-NMR, see the Experimental section). The total yield of *trans* diastereoisomer **113** was 57% while the (H, OH, I) *all-cis* isomer **112** was obtained in a not pure form with 11% yield (^{1}H-NMR, Scheme 4.20).



110 **112**, 11% **113**, 57%

Scheme 4.20. *Reaction of compound **110** with NaI in acetone*

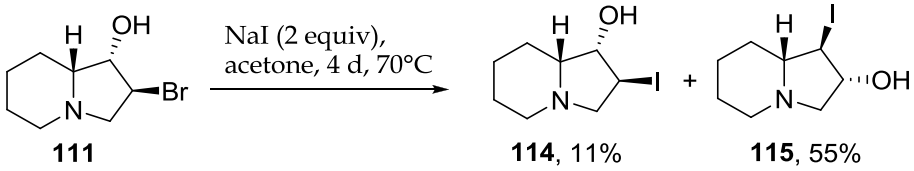
The formation of both diastereoisomers could be rationalized on the basis of an S_N1 mechanism, involving a preferential attack of I^- on the less hindered face of the carbocation intermediate leading to trans iodoindolizidine **113** as the predominant product. However, the supposed carbocation (even if secondary) does not present significant stabilization via charge delocalization (being cyclic carbocation stabilization via hiperconjugation quite difficult to realize) and an S_N2 mechanisms could be also considered. A direct bimolecular nucleophilic substitution on **110** could be rise to **112**, through inversion of the configuration on C-2 carbon. However, being I^- a better leaving group than Br^-, a second sterically favored S_N2 attack of I^- on **112** could be easier than the corresponding attack on **110** leading to the major product **113**. Moreover, the higher stability of the *trans* isomer **113** with respect to the *cis* one **112**, for steric and electronic effects, can justify its preferential formation. Then, the retention of configuration at C-2 in **113**, would be the consequence of the double inversion (Scheme 4.21).



110 **112** **113**

Scheme 4.21. *Mechanist rationale for the formation of compound **112** and **113**.*

On this basis the reaction of mono-bromohydroxyindolizidine **111** with NaI was also studied. After heating for four days at 70 °C and chromatographic separation (1*RS*,2*RS*,8a*RS*)-1-iodo-2-hydroxyindolizidine (**115**) was isolated in 55% yield along with a mixture of a minor quantity (ca 11% yield, ^{1}H-NMR) of (1*SR*,2*SR*,8a*RS*)-1-hydroxy-2-iodoindolizidine (**114**) and derivative **115** (**114**/**115** ratio 1:1.6, ^{1}H-NMR). A careful spectroscopic analysis evidenced the *trans* stereochemistry and the different regiochemistry of the two products (Scheme 4.22).

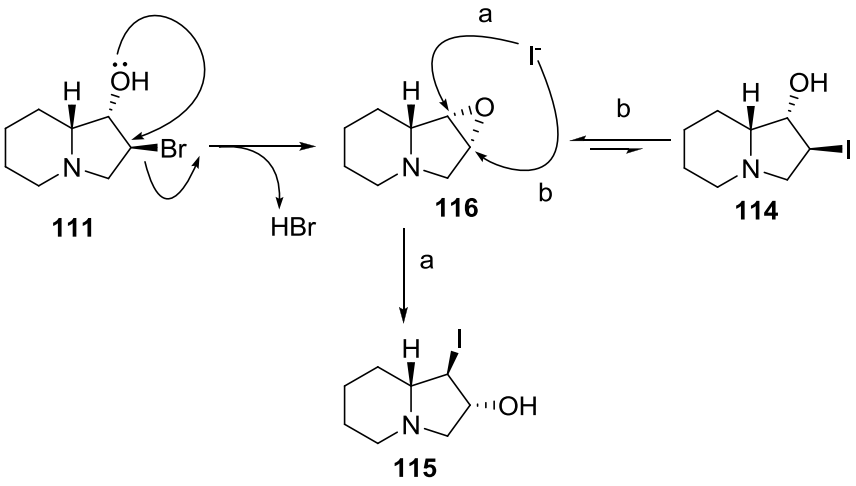


111 **114**, 11% **115**, 55%

Scheme 4.22. *Reaction of indolizidine **111** with NaI.*

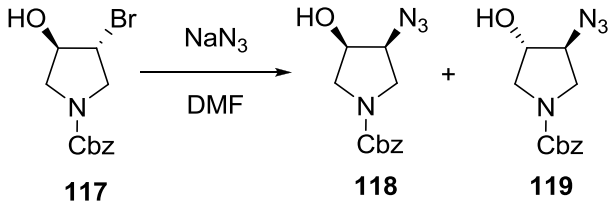
With the aim to rationalize the products formation, the reaction was repeated in a screw cap NMR tube in hexadeuteroacetone and followed with ^{1}H-NMR. The formation of the two iodo derivatives didn't occur at the same time. The peculiar ^{1}H-NMR signals of the main reaction product **115** appeared after the ones of **114** and were associated to a decrease of the NMR signals of **114**. After the desappearence of the starting bromoindolizidine **111**, heating the mixture for long time led to a little decrease of the intensity of the signals of **114** with respect to those of **115**.

The behavior of **111** toward NaI was completely different with respect to **110**. In this case the formation of the two *trans* regioisomers **114** and **115** likely involved the reactive epoxide intermediate **116**. The I- attack, according with an S_N2 mechanism, could occurr on C-1 or C-2 carbons, leading to the two *trans* 1,2-disubstituted regioisomers. As a consequence of the *trans* stereochemistry of the two functional groups in compound **111**, the vicinal OH could participate to an intramolecular S_N2 process as the result of a symphoric effect leading to peculiar stereochemical outputs (Scheme 4.23).



Scheme 4.23. *Mechanistic rationale of the reaction of **111** with NaI.*

An analogous inter- and intramolecular S_N2 sequence was supposed in nucleophilic substitution reactions on *trans* 3-bromo-4-hydroxypyrrolidines (**117**).[124] By treatment with sodium NaN_3, the two diastereoisomeric azides **118** and **119** were isolated. While the *cis* compound **118** is the result of a S_N2 process, the *trans* diastereoisomer **119** formed through the ring-opening of an epoxide intermediate operated by the nucleophile (Scheme 4.24).



Scheme 4.24. *Reaction of compound **117** with sodium azide*

An analogous mechanism could occurr in the reaction of the bromohydroxyindolizine **110** with NaI, due to the *trans* relationship between Br and OH functionalities. In this hypothesis, the main reaction product **113**, could derive from a nucleophilic attack of I^- on the epoxide intermediate analogous of **116**. However the absence of other

[124] Kamal, A.; Shaik, A. A.; Sandbhor, M.; Malik, S. M.; Azeeza, S. *Tetrahedron: Asymmetry* **2006**, *17*, 2876.

regioisomers and the isolation of the *cis* derivative **112** could be considered a good evidence of a direct S_N2 mechanism, that could work on **110** or **112**.

Although the different hypotheses need other close examination, the different stereochemistry of the hydrogen at C-8a of compounds **110** and **111** seems to play an important role influencing the geometry of the compound. In fact, theoretical studies evidenced a different dihedral C1-OH and C2-Br angles for the two diastereoisomeric bromohydroxyindolizidines (157° for indolizidine **111** and 93° for **110**, Figure 4.16).[125]

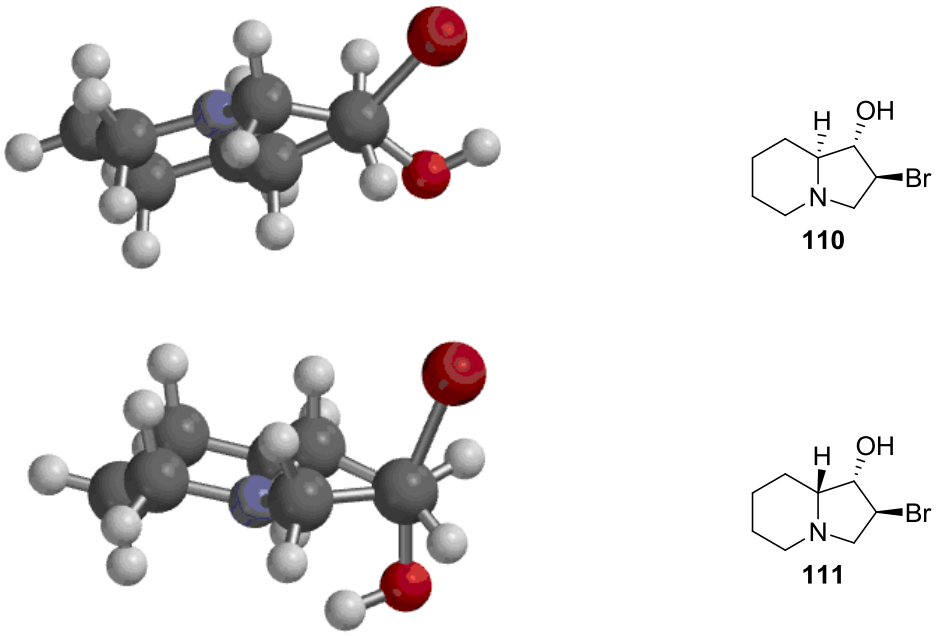


Figure 4.16. *Calculated dihedral angles C1-OH, C2-Br for indolizidines **110** and **111**.*

These data were in quite good agreement with those obtained by single-crystal X-ray diffraction analyses. A dihedral angle of about 99° between the OH and Br groups was measured in indolizidine **110**, while the corresponding angle was 133° in **111**. The first value, characteristic for an almost orthogonal arrangement between OH and Br, well agree with the proposed intermolecular substitution process. On the other hand the larger value observed for **111**, could likely make possible on intramolecular mechanism involving the formation of an epoxide intermediate as a consequence of an

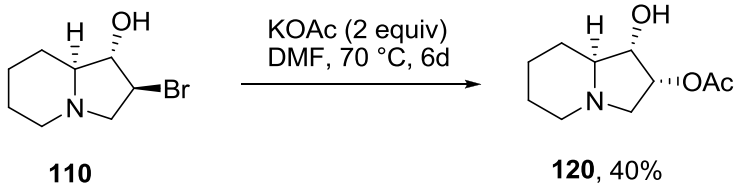
[125] Dihedral angles determined at the HF 3.21G* level of the theory using PC Spartan 0.8 program, Wavefunction, Inc.

"anticlinal/antiperiplanar" arrangement of substituents at C-1 and C-2 carbons (Figures 4.14 and 4.15).

C- Use of potassium acetate

In the light of the previous results, other nucleophiles were tested. In particular, the use of the acetate could be able to obtain the introduction of another protected OH functionality, opening the way to the syntheses of 1,2-dihydroxy substituted indolizidines.

The bromohydroxyindolizidine **110** was heated at 70° in DMF with KOAc (2 equiv) for 6 days. Acetate **120** (ca. 40% yield, ^{1}H-NMR, Scheme 4.25) was isolated by chromatographic resolution along with another isomer whose structure was difficult to resolve due to the overlap of some diagnostic signals with those of the major product.



110 **120**, 40%

Scheme 4.25. *Reaction of indolizidine **110** with KOAc.*

The structure and the *cis* geometry of the two functional groups was determined by spectral analyses and, although further studies are necessary, the formation of **120** could be rationalized through a nucleophilic S_N2 attack of the acetate on the C-2 carbon.

4.2.4.3. *Spectroscopic considerations*

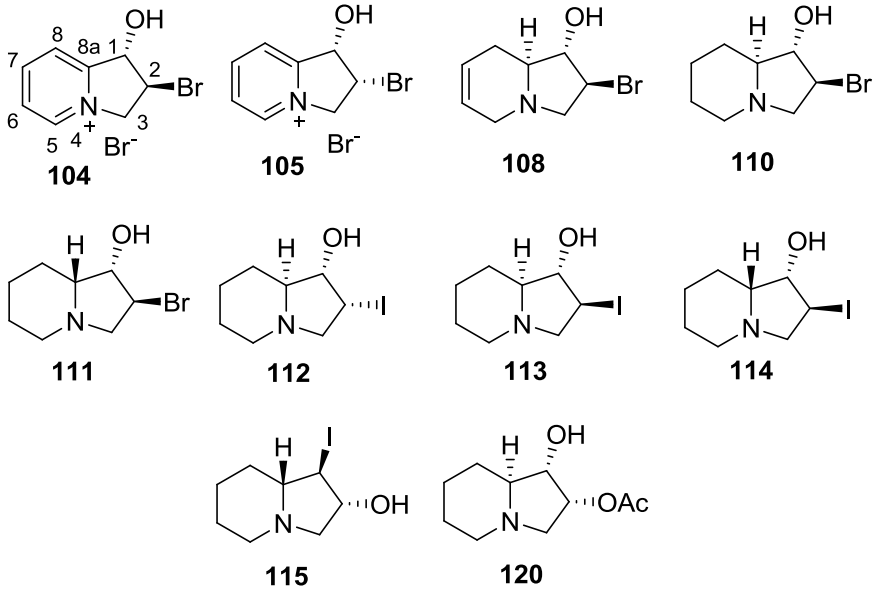


Figure 4.17. *Hydoxyindolizidines obtained by the synthetic strategy described in Chapter IV.*

The structures of the new bicylic derivatives **104**, **105**, **108, 110**, **111**, **112**, **113**, **114**, **115** and **120** were determined by spectral analyses. In particular the relative configuration of the substituents at C-1, C-2 and C-8a carbon atoms in the salt **104** and bromohydroxy derivatives **108**, **110** and **111** was confirmed by X-ray diffraction analyses (Figures 4.13, 4.14 and 4.15).

In particular, heteronuclear correlation experiments performed on **104** allowed to establish the bicyclic structure. In fact the bidimensional g-HMBC spectrum shows correlation peaks between C-3 at δ 62.7 and the H-5 doublet at δ 9.12, and between C-5 at δ 141.8 and the two doublets of doublets of the H-3α and H-3β protons (δ 5.04 and 5.43) due to a $^{3}J_{C,H}$ coupling. It's important to underline that the $^{3}J_{1,2}$ value of the diastereoisomeric compounds **104** and **105** (J = 6.0 and 4.7 Hz, respectively) doesn't allow to determine the relative stereochemistry of the two substituents. The problem was resolved by comparison of the coupling constants of compounds **108, 110** and **111** (coming from partial or total reduction of **104**) with the corresponding experimental data of natural and nonnatural hydroxyindolizidines reported in the literature and with theoretical studies about coupling constants $^{3}J_{H,H}$ of *cis* or *trans* cyclopentane

derivatives.[126] In fact, the H-1 and H-2 signals at δ 4.17 and 4.02 of **110** show a $^3J_{1,2}$ = 4.2 Hz in accordance with a *trans* geometry of the two functional groups, because the $^3J_{H,H}$ *cis* are higher (ca 7-8 Hz).[126] Moreover, Lentiginosine shows a similar $^3J_{1,2}$ value (4.0 Hz).[127] In the diastereoisomeric derivative **111**, epimer of **110** at C-8a, $^3J_{1,2}$ is minor of 1 Hz as a consequence of the different stereochemistry at C-8a. This result well agrees with the spectral data of 8a-*epi*-Lentiginosine.[127]

Similar considerations allowed to determine the stereochemistry of the hydrogen at position 8a. $^3J_{1,8a}$ of indolizidine **110** is 8.1 Hz (obtained from the H-1 doublet of doublets), near to the corresponding value of **108** ($^3J_{1,8a}$ = 7.2 Hz). On the other hand, **111** shows a *cis* type geometry characterized by a $^3J_{1,8a}$ = 3.5 Hz, according with the literature data of analogous derivatives.[127]

The structures and the stereochemistry of compounds **112-115** were also assigned by spectroscopic NMR analyses. The *trans* geometry of H-1 and H-8a in compounds **112** and **113** is confirmed by the $^3J_{1,8a}$ coupling constants of ca 7.4[128] and 8.0 Hz, respectively. The signals of H-1 and H-2 show different shapes and chemical shifts as a consequence of a different stereochemistry. The analogies between compounds **113** and **110** are confirmed by the presence of a doublet of doublets ($^3J_{1,8\alpha}$ = 8.0 Hz and $^3J_{1,2}$ = 5.3 Hz) at δ 4.27 (vs. 4.17 for **110**) and a doublet of doublets of doublets ($^3J_{2,3\alpha}$ = 8.6 Hz, $^3J_{1,2}$ = 5.1 Hz and $^3J_{2,3\beta}$ = 2.7 Hz) at δ 3.98 (vs. 4.02 of **110**), assigned to H-1 and H-2 protons, respectively.

As a consequence of a *cis* stereochemistry of OH and I groups in **112**, H-1 is shielded (*pseudo* triplet at δ 3.30 with *J* = ca 7.4 Hz[128]) and H-2 is deshielded (*pseudo* quartet at δ 4.55, J = 7.6 Hz) with respect to the corresponding signals of **113**. The different signal shape for H-2 of **112** agrees with a *cis* H-1/H-2 stereochemistry ($^3J_{1,2}$ = 8.2 Hz) as observed for 2-*epi*-Lentiginosine ($^3J_{1,2}$ = 7.0 Hz).[129]

The different regiochemistry of the iodohydroxyindolizidines **114** and **115** (obtained from reaction of **111** with NaI) is well evidenced by analyses of the bidimensional g-

[126] Wu, A.; Cremer, D.; Auer, A. A.; Gauss, J. *J. Phys. Chem. A* **2002**, *106*, 657-667.
[127] El-Mazhawy, A. O. H.; El-Diwani, H. I.; Schimdt, R. R. *Eur. J. Org. Chem.* **2002**, 4137.
[128] An overlap of the signal of H-1 of **112** with H-3β of **113** does not allow to get an accurate value.
[129] W. Pastuszak, I.; Molyneux, R. J.; James, L. F.; Elbein, A. D. *Biochemistry* **1990**, *29*, 1886.

COSY, g-HSQC and g-HMBC spectra. In g-HSQC spectrum, the major product **115** shows a correlation between C-1 at δ 34.7 and the doublet of doublets at δ 3.57 (J = 9.7 and 3.7 Hz) and a correlation between C-2 at δ 80.1 and the doublet of doublets of doublets at δ 4.44 (J = 6.4, 3.9 and 1.0 Hz), allowing to assign the corresponding protons in the ^{1}H-NMR spectrum. The g-COSY spectrum allows to assign undoubtedly the 1-iodo-2-hydroxyindolizidine structure (compound **115**, Figure 4.18): in particular, couplings between C*H*OH and the 3-CH_2 protons and between CHI and H-8a are diagnostic for the unexpected regiochemistry of the product. A further confirmation has been obtained from g-HMBC spectrum. A $^3J_{C,H}$ correlation between C-8 at δ 28.4 and the doublet of doublets at δ 3.57 of the CHI proton agrees with a 1-iodoindolizidine structure.

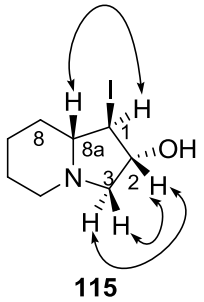


Figure 4.18. *Diagnostic g-COSY couplings for the structure **115**.*

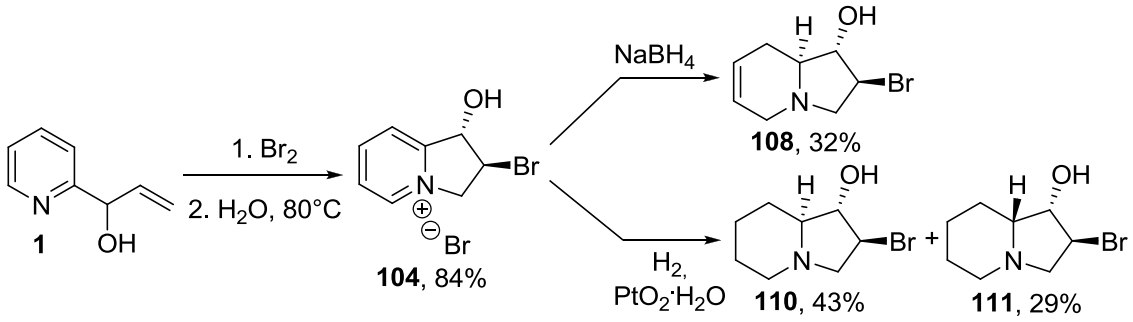
The *trans* stereochemistry H-1/H-2 and H-1/H-8a is confirmed by the ^3J coupling constants (3.6 and 9.7 Hz, respectively). Finally, the ^{1}H-NMR spectrum of the minor reaction product **114** is very similar to that of **111**.

The structure of the acetate derivative **120** is confirmed by comparison of the 1H-NMR spectrum with that of compound **112**. The *cis* H-1/H-2 stereochemistry is confirmed by the presence of a ddd at δ 4.99 ($^3J_{1,2}$ = $^3J_{2,3\beta}$ = 7.2 Hz and $^3J_{2,3\alpha}$ = 5.2 Hz) for H-2, while the doublet of doublets at δ 3.75 ($^3J_{1,8a}$ = 8.2 Hz and $^3J_{1,2}$ = 7.4 Hz) assigned to H-1 is a confirmation of a *trans* H-1/H-8a stereochemistry.

4.3. CONCLUSIONS

The discussed synthetic processes show clearly a new feature of the reactivity of the 1-(2-pyridyl)-2-propen-1-ol (**1**). The allyl alcohol **1** in fact reacted not only as a carbon nucleophile towards activated electrophilic counterparts (see Chapter 2) or as a reducing agent for thermal metal-free reduction of hetero- and aromatic nitro compounds (see Chapter 3, Section 3.2), but it resulted even a good promising reagent for indolizidine systems construction. As a first step, a new easy and general methodology was studied to access several variously functionalized indolizidines. In fact, bromine addition on the double bond of the allyl moiety of **1** allowed direct access to bicyclic indolizinium salts **104** and **105**, through a highly diastereoselective 5-*exo*-tet cyclization of the brominated intermediate in favor of the *trans* bromohydroxy substituted salt **104**. A simple isomerization of the *cis* salt **105** into **104** was performed by heating in polar solvents to convert the mixture of inseparable salts into the *trans* diastereoisomer. Then, the sequence bromination/isomerization allowed the sole transformation of alcohol **1** into the *trans* indolizinium salt **104** in high yield. The isomerization process resulted even more significant in the light of the instability of the *cis* salt **105** in different reaction conditions.

Partial reduction of the pyridinium ring using $NaBH_4$ led to (1*SR*, 2*SR*, 8a*SR*)-1-hydroxy-2-bromo-1,2,3,5,8,8a-hexahydroindolizine (**108**), while PtO_2-catalyzed hydrogenation gave (1*SR*, 2*SR*, 8a*SR*)- and (1*SR*, 2*SR*, 8a*RS*)-1-hydroxy-2-bromoindolidizines (**110**) and (**111**). The indolizidine skeleton was built up in only three synthetic steps starting from pyridylpropenol **1**, (Scheme 4.26).



Scheme 4.26. *Synthetic pathway for the indolizidines synthesis starting from alcohol **1**.*

While attempts of a direct nucleophilic substitutitions on the indolizinium salts failed, the displacements of bromine atom in the indolizidines **110** and **111** was investigated. Treatment with NaI and KOAc allowed the syntheses of new hydroxyindolizidines, functionalized at positions 1 and 2 (Figure 4.19).

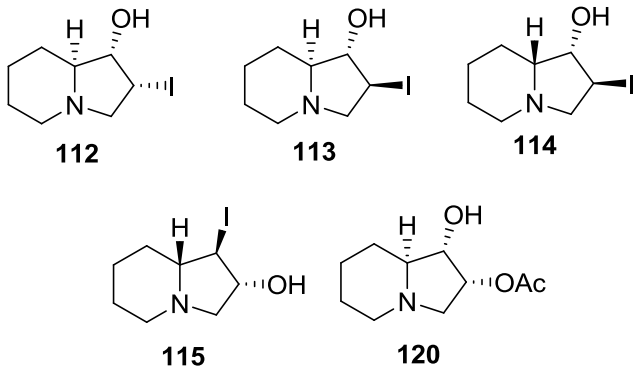


Figure 4.19. *Indolizidines obtained by nucleophilic substitution reactions on **110** and **111**.*

In particular the formation of the four iodoindolizidines involved different reaction pathways as a consequence of a different stereochemistry at C-8a of the two starting bromohydroxy derivatives **110** and **111**.

* * *

On this basis future studies will be directed to the treatment of **110** and **111** with *O*- or *N*- nucleophiles, to introduce new functionalities in the pyrrolidine ring.

Similar treatments could be operated on dehydroindolizidine **108**. Moreover, the presence of a C(5)-C(7) double bond opens the way to the functionalization of the piperidine ring for the synthesis polyhydroxyindolizidines.

The overall synthetic pathway makes it possible to access variously functionalized indolizidines starting from substituted pyridinecarbaldehydes, as well as quinolyl- or isoquinolylcarbaldehydes.

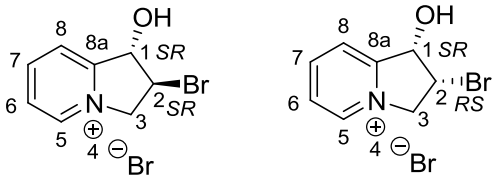
With the aim to obtain enantiopure products for biological screening, the described synthetic procedure could be applied to enantiopure pyrididylpropenol **1** as well as to asymmetric enantioselective reactions. On this basis an asymmetric vinylation of the starting reactant (*e.g.*, 2-pyridinecarbaldehyde) in the presence of enantiopure catalysts could be considered for the enantioselective synthesis **1** in addition to the enzymatic racemic resolution reported in the literature.[130]

[130] Uenishi, J.; Hiraoda, T.; Hata, S.; Nishiwaki, K.; Yonemitsu, O. *J. Org. Chem.* **1998**, *63*, 2481.

4.4. EXPERIMENTAL SECTION

4.4.1. REACTION OF THE 1-(2-PYRIDYL)2-PROPEN-1-OL WITH BROMINE: (1*SR*,2*SR*)-2-BROMO-1-HYDROXY-1*H*,2*H*,3*H*-INDOLIZINIUM BROMIDE (104) AND (1*SR*,2*RS*)-2-BROMO-1-HYDROXY-1*H*,2*H*,3*H*-INDOLIZINIUM BROMIDE (105).

4.4.1.1. Method A (section 4.2.2.1).



A bromine solution (0.176 g, 56 mL, 1.1 mmol) in CH_2Cl_2 (1.5 mL) was added dropwise at 0 °C to a solution of alcohol **1** (0.135 g, 1 mmol) in the same solvent (2mL) and a white precipitate formed. The reaction mixture was stirred at room temperature for 10 minutes. After the addition of a oversaturated solution of $Na_2S_2O_3$, to destroy the excess of Br_2, the reaction mixture was dried over Na_2SO_4. The solution was filtered and concentrated in vacuo to obtain **104** as a pearl grey solid (0.174 g, 59%).

MW = 294.97

IR, ν_{max} (KBr): 3122 (O-H), 3050, 2980, 1628 (C=N, C=C), 1499, 1121 (C-O) cm^{-1}.

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 9.12 (d, ^3J = 6.1 Hz, 1H, H-5), 8.70 (td, ^3J = 7.9 Hz, ^4J = 0.7 Hz, 1H, H-7), 8.25 (br d, ^3J = 8.0 Hz, 1H, H-8), 8.18 (ddd, ^3J = 7.8, 6.1 Hz, ^4J = 1.2 Hz, 1H, H-6), 7.29 (br s, 1H, OH), 5.63 (d, ^3J = 6.0 Hz, 1H, H-1), 5.43 (dd, ^2J = 13.6 Hz, ^3J = 6.9 Hz, 1H, H-3), 5.04 (dd, ^2J = 13.7 Hz, ^3J = 6.8 Hz, 1H, H-3), 4.77 (ddd, ^3J = 6.9, 6.8, 6.0 Hz, 1H, H-2).

^{13}C-NMR (100 MHz, DMSO-d_6) δ: 156.6 (s, C-8a), 147.0 (d, C-7), 141.8 (d, C-5), 127.6 (d, C-6), 124.5 (d, C-8), 78.95 (d, C-1), 62.7 (t, C-3), 46.8 (d, C-2).

Extraction with acetone from the reaction residue gave, after evaporation to dryness under reduced pressure, a mixture of **104** and **105** (diasteromeric ratio: 1:1, 0.144 g, 49%).

MW = 294.97

^{1}H-NMR (400 MHz, DMSO-d_6)[131] δ: 9.14 [(d, ^3J = 5.5 Hz, 1H, H-5)], 9.11 (d, ^3J = 6.1 Hz, 1H, H-5), 8.66 (t, ^3J = 7.8 Hz, 2H, H-7), 8.21 (d, ^3J = 7.8 Hz, 1H, H-8), 8.16-8.11 (m, 3H, H-6 e H-8 di **3**), 5.69 [(d, ^3J = 4.7 Hz, 1H, H-1)], 5.59 (d, ^3J = 6.1 Hz, 1H, H-1), 5.40 (dd, ^2J = 13.6 Hz, ^3J = 6.9 Hz, 1H, H-3), 5.35-5.31 [(m, 2H, H-3, H-2)], 5.19 [(dd, ^2J = 16.0 Hz, ^3J = 1.8 Hz, 1H, H-3)], 5.0 (dd, ^2J = 13.6 Hz , ^3J = 6.8, 1H, H-3), 4.74 (ddd, ^3J = 6.8, 6.8 e 6.0 Hz, 1H, H-2).

^{13}C-NMR (100 MHz, DMSO-d_6) δ: 157.1 [(s, C-8a)], 156.7 (s, C-8a), 147.0 (d, C-7), 146.8 [(d, C-7)], 142.2 [(d, C-5)], 141.8 (d, C-5), 127.6 (d, C-6), 127.2 [(d, C-6)][a], 124.5 (d, C-8), 124.4 [(d, C-8)], 78.9 (d, C-1), 73.4 [(d, C-1)], 64.2 [(t, C-3)], 62.7 (t, C-3), 55.1 [(d, C-2)], 46.8 (d, C-2).

4.4.1.2. Method B (section 4.2.2.2).

A bromine solution (0.320 g, 102.5 mL, 2 mmol) in CH_2Cl_2 (6 mL) was added dropwise at 0 °C to a solution of pyridylpropenol **1** (0.270 g, 2 mmol) in CH_2Cl_2 (8 mL) and kept at 0 °C for 20 minutes. Then the reaction mixture was stirred at room temperature for 5 h. After filtration, the precipitate was washed with CH_2Cl_2 and the organic layer was collected. By concentration of the solution, salt **104** (0.148 g, 25 %) was obtained as pearl grey solid, while the white precipitate contained a mixture of salt **104** and **105** in a diastereomeric ratio of 2.5:1 in favor of salt **104** (0.435 g, 74%)[Found: C, 32.25; H, 2.91; N, 4.53. $C_8H_9Br_2NO$ requires C, 32.57; H, 3.08; N, 4.75%];.

MW = 294.97

[131] The data reported in square brackets referred to the *cis* salt **105**.

4.4.1.3. Method C (section 4.2.2.3).

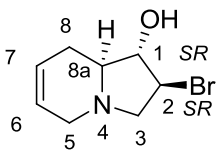
To a solution of alcohol **1** (0.135 g, 1 mmol) in THF + 5% H_2O (7 mL + 350 μl), NBS (0.215 g, 1.2 mmol) was added in small portions in 40 minutes at 0 °C. The resulting mixture was stirred for 24 h at rt and a precipitate formed. A first filtration gave salt **104** (0.058 g, 20%). After a second addition of NBS (0.178 g, 1 mmol) and H_2O (350 μL) to the solution, the resulting mixture was stirred at rt for 24 h. A second filtration of the precipitate afforded other salt **104** (0.066 g, 23%). A further addition of NBS (0.089 g, 0.5 mmol) to the solution led, after 24 h, to a third precipitate containing again salt **104** (0.030 g, 10%). The total yield of the *trans* indolizinium salt **104** was 53 %. [Found: C, 31.96; H, 3.09; N, 4.44. $C_8H_9Br_2NO$ requires C, 32.57; H, 3.08; N, 4.75%].
MW = 294.97

4.4.2. ISOMERIZATION OF INDOLIZINIUM SALT 105 INTO 104.

A mixture of the diastereomeric salts **104** and **105** (**104**/**105** ca 1:1, 0.136 g, 0.46 mmol) was stirred in H_2O (23 mL) at 80 °C in a screw-cap tube (Pyrex N.25) for 5 days. After the filtration of an insoluble black residue, evaporation to dryness of the solution afforded salt **104** as a black powder (0.114 g, 84%).
MW = 294.97
ESI-MS *m/z(%)*:= 216 (8.3), 188 (1.0), 134 (22.5), 118 (7.6), 106 (100.0), 92 (0.7), 78 (0.5).

4.4.3. REDUCTION OF THE PYRIDINIUM RING

*4.4.3.1. Use of $NaBH_4$: synthesis of (1SR,2SR,8aSR)-2-bromo-1,2,3,5,8,8a-hexahydro-1-indolizinol (**108**).*



To a solution of (1*SR*,2*SR*)-2-bromo-1-hydroxy-1*H*,2*H*,3*H*-indolizinium bromide (**104**), (0.285 g, 1 mmol) in dry THF (15 mL), $NaBH_4$ (0.076 g, 2 mmol) was added in 1 h in small portions, keeping the mixture at 0 °C. Then, the mixture was stirred for 1 h and 30′ at rt. The excess of hydride was destroyed adding an oversaturated solution of Na_2SO_4. Then, the dried mixture was filtered through Celite pad and washed with THF. Chromatographic resolution (EtOAc/PE 3:2) gave product **108** ((R_f = 0.48, 0.070 g, 32%). The product crystallized from PE/Et_2O in white needles. [Found: C, 43.99; H, 5.56; N, 6.42 $C_8H_{12}BrNO$ requires C, 44.06; H, 5.55; N, 6.42].

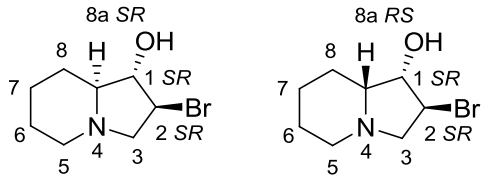
MW= 218.09

IR, ν_{MAX} (KBr): 3121 (O-H), 2970, 2808, 1462, 1339, 1209, 1105 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 5.81-5.76 (m, 1H, H-7), 5.72-5.66 (m, 1H, H-6), 4.27 (dd, ^3J = 7.2, 4.1 Hz, 1H, H-1), 4.12 (ddd, ^3J = 7.8, 4.1, 2.6 Hz, 1H, H-2), 3.48-3.41 (m, 1H, H-5), 3.44 (dd, ^2J = 11.5 Hz, ^3J = 2.6 Hz, 1H, H-3β), 3.05 (dd, ^2J = 11.5 Hz, ^3J = 7.8 Hz, 1H, H-3α), 2.88 (m, 1H, H-5), 2.44-2.37 (m, 1H, H-8), 2.32-2.27 (m, 1H, H-8a), 2.25-2.16 (m, 1H, H-8), 2.06 (vbr s, 1H, OH).

^{13}C-NMR (100 MHz, $CDCl_3$) δ: 124.6 (d, C-6), 124.4 (d, C-7), 86.5 (d, C-1), 65.1 (d, C-8a), 62.4 (t, C-3), 51.9 (t, C-5), 50.8 (d, C-2), 29.5 (t, C-8).

*4.4.3.2. Use of PtO_2: synthesis of (1SR,2SR,8aSR)-2-bromooctahydro-1-indolizinol (**110**) and (1SR,2SR,8aRS)-2-bromooctahydro-1-indolizinol (**111**)*



Pyridinium salt **104** (0.0147 g, 0.5 mmol) was added to a pre-activated suspension of catalyst $PtO_2{\cdot}H_2O$ (0.011 g, 0.048 mmol) in EtOH (8 mL), and the mixture was stirred at rt under atmospheric pressure of hydrogen for 6 h. The solution was filtered over Celite, washed with EtOH and MeOH, and evaporated to dryness. A quick chromatographic purification with EtOAc/MeOH 10:1 as eluent, allowed to remove completely the inorganic materials. Then, purification of the crude by flash

chromatography using as eluent EA as eluent, gave **110** (R_f = 0.37, 0.045 g, 43%) as white needles (mp = 128 – 129°C, from PE/Et_2O); [found: C, 43.64; H, 6.38; N, 6.04 $C_8H_{14}BrNO$; requires: C, 43.65; H, 6.41; N, 6.36].

PM = 220.11

IR, ν_{max} (KBr): 3118 (O-H), 2931, 2804, 1325, 1133, 1052 cm^{-1}.

MS *m/z(%)*: 219 (0.9) e 221 (0.9) [M^+], 140 (76), 84 (100).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.17 (dd, ^3J = 8.1, 4.3 Hz, 1H, H-1), 4.02 (ddd, ^3J = 8.0, 4.2, 2.1 Hz, 1H, H-2), 3.28 (dd, ^2J = 11.5 Hz, ^3J = 2.0 Hz, 1H, H-3β), 2.99 (dt, ^2J = 10.7 Hz, ^3J = 3.0 Hz, 1H, H-5β), 2.93 (dd, ^2J = 11.3 Hz, ^3J = 8.0 Hz, 1H, H-3α), 2.19 (1H, OH), 1.94-2.04 (m, 2H, H-5α, H-8), 1.80-1.85 (m, 2H, H-7, H-8a), 1.60 (m, 2H, 6-CH_2), 1.28-1,38 (m, 1H, H-8), 1.15-1.27 (m, 1H, H-7).

^{13}C-NMR (100 MHz, $CDCl_3$) δ: 86.0 (d, C-1), 69.8 (d, C-8a), 62.8 (t, C-3), 52.8 (t, C-5), 51.4 (d, C-2), 28.4 (t, C-8), 24.6 (t, C-6), 23.7 (t, C-7).

The slowest moving band afforded indolizidine **111** (R_f = 0.14, 0.031 g, 29%) as white needles (mp = 122-123 °C, from PE/Et_2O 3:1) [found: C, 43.91; H, 6.38; N, 6.21 $C_8H_{14}BrNO$; requires: C, 43.65; H, 6.41; N, 6.36].

MW = 220.11

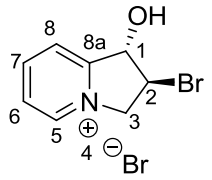
IR, ν_{max} (KBr): 3127 (O-H), 2942, 2827, 2788, 1138, 1097 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.15 (br d, ^3J = 3.6 Hz, 1H, H-1), 4.04 (ddd, ^3J = 7.3, 6.2, 1.0 Hz, 1H, H-2), 3.72 (dd, ^2J = 10.7 Hz, ^3J = 7.5 Hz, 1H, H-3α), 3.08 (br d, ^2J = 11.1 Hz, 1H, H-5β), 2.53 (dd, ^2J = 10.7 Hz, ^3J = 6.1 Hz, 1H, H-3β), 2.42 (vbr s, 1H, OH), 2.30 (dt, ^3J = 11.2 e 3.4 Hz, 1H, H-8a), 2.08 (ddd, ^2J = 11.3 Hz, ^3J = 11.3 e 3.0 Hz, 1H, H-5α), 1.89-1.84 (m, 1H, H-7), 1.77-1.71 (m, 1H, H-8), 1.67-1.61 (m, 1H, H-6), 1.55-1.43 (m, 2H, H-6, H-8), 1.35-1.19 (m, 1H, H-7).

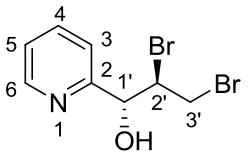
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 81.3 (d, C-1), 65.1 (d, C-8a), 63.3 (t, C-3), 52.8 (t, C-5), 49.4 (d, C-2), 25.1 (t, C-6), 24.6 (t, C-8), 23.6 (t, C-7).

4.4.4. SPECTRAL ANALYSES ANALYSIS OF THE BROMINATION INTERMEDIATE

A solution of Br_2 (0.056 g, 17.8 μL, 0.35 mmol) in $CDCl_3$ (2 mL) was added dropwise under stirring at 0 °C to a solution of pyridylpropenol **1** (0.040 g, 0.29 mmol) in $CDCl_3$ (1 mL) during 20 minutes. A white precipitate formed. After the complet disappearance of **1** (TLC), a portion of solution was taken and studied through NMR experiments (^{1}H-NMR, ^{13}C-NMR, g-HMBC, g-HSQC).



104



107a, *anti*

^{1}H-NMR (400 MHz, $CDCl_3$)[132] *δ*: 8.59 (m, 2H, H-5 of **104** + H-6 of **107a**), 7.76 (m, 2H, H-7 of **104** + H-4 of **107a**), [7.44 (d, *J* = 7.8 Hz, 1H-H-3)], 7.36-7.27 (m, 3H, H-8 of **104**, H-6 of **104** and H-5 of **107a**), 5.26 (d, *J* = 1.6 Hz, 1H, H-1), [5.06 (d, *J* = 5.8 Hz 1H, H-1')], 4.58 (ddd, *J* = 10.7, 4.7 e 1.8 Hz, 1H, H-2), [4.44 (q, *J* = 5.8 Hz, 1H, H-2')], 4.20 (vbrs, 2H, 2 X OH) 4.11 (dd, *J* = 10.5, 10.1, 1H, H-3), [3.90 (XY part of an AMXY system, 2H, 3'-CH_2)], 3.86 (dd, *J* = 9.9 e 4.5 Hz, 1H, H-3).

^{13}C-NMR (100 MHz, $CDCl_3$)[132] *δ*: 158.2 (s, C-8a), [153.65 (s, C-2], [148.6 (d, C-6)], 148.1 (d, C-5), 137.1 (d, C-7), [137.1 (d, C-7), [136.7 (d, C-4)], [123.6 (d, C-5)], 123.6 (d, C-5)], 123.05 (d, C-6), [122.7 (d, C-3)], 120.1 (d, C-8), [73.8 (d, C-1')], 70.2 (d, C-1), 57.9 (d, C-2), [56.8 (d, C-2')], [34.0 (t, C-3')] 32.5 (t,C-3).

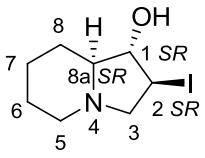
4.4.5. REACTIONS WITH NaI.

*4.4.5.1. Syntheses of (1SR,2RS,8aSR)-2-iodooctahydro-1-indolizinol (**112**) and (1SR,2SR,8aSR)-2-iodooctahydro-1-indolizinol (**113**).*

A solution of indolizidine **110** (0.030 g, 0.14 mmol) and NaI (0.041 g, 0.28 mmol) in acetone (0.5 mL) was stirred at 70 °C in a sealed tube (Pirex N. 13) for 5 days. After filtration of the precipitate (NaBr), the solvent was removed and the reaction crude was

[132] The data in square brackets refer to the resonances of compound **107a**.

purified by flash chromatography (EtOAc/PE 20:1) over silica gel. Compound **113** (EtOAc/PE 20:1) (R_f = 0.50, 0.018 g, 50%) was obtained as a white solid.



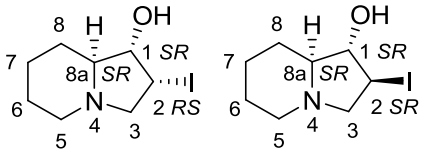
MW = 267.11

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.27 (dd, $J_{1,8a}$ = 8.0 Hz e $J_{1,2}$ = 5.3 Hz, 1H, H-1) 3.98 (ddd, J = 8.6, 5.1 e 2.7 Hz, 1H, H-2), 3.34 (dd, J =11.4 e 2.6 Hz, 1H, H-3β), 3.00-2.93 (m, 2H, H-5β e H-3α), 2.60 (vbrs, 1H, OH), 2.07-1.93 (m, 2H, H-5α e H-8), 1.83-1.77 (m, 2H, H-7 e H-8a), 1.62-1.55 (m, 2H, 6-CH_2), 1.36-1.19 (m, 2H, H-8a e H-7).

^{13}C-NMR (100 MHz, $CDCl_3$) δ: 87.5 (d, C-1), 69.55 (d, C-8a), 64.2 (t, C-3), 52.7 (t, C-5), 28.3 (t, C-8), 25.2 (d, C-2), 24.6 (t, C-6), 23.8 (t, C-7).

ESI *m/z(%)*: 268 (92.7), [M^++1], 141 (48.8), 124 (49.6), 84 (100).

The following band (Rf = 0.20, 0.007 g, 18%) gave a mixture of **112** and **113** (ratio **113**/**112** 1:1.6, ^{1}H-NMR, 7% for **113** and 11% for **112**).



^{1}H-NMR (400 MHz, $CDCl_3$)[133] δ: 4.55 (pseudo q, J = 7.6 Hz, 1H, H-2), [4.25 (dd, J = 8.2 e 5.1 Hz, 1H, H-1)], [3.98 (ddd, J = 8.6, 5.1 e 2.7 Hz, 1H, H-2)], 3.67 (dd, $J_{3\alpha,\,3\beta}$ = 10.1 e $J_{2,\,3\beta}$ = 7.4 Hz, 1H, H-3β), [3.33 (dd, J = 11.3 e 2.6 Hz, 1H, H-3β)], 3.30 (pseudo t, J = 7.4 Hz, 1H, H-1), 3.00-2.91 (m, 4H, H-5β e H-3α of **112** and **113**), 2.40 (vbrs, 1H, OH), 2.10-1.77

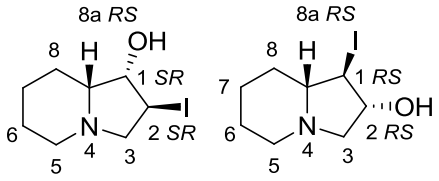
[133] The data in square brackets refer to the resonances of compound **112**.

(m, 8H, H-8, H-8a, H-5α, e H-7 of **112** and **113**), 1.64-1.44 (m, 4H, 6-CH_2 of **113** and **114**), 1.35-1.20 (m, 4H, H-8 e H-7 of **112** and **113**).

^{13}C-NMR (100 MHz, $CDCl_3$)[133] *δ*: [87.6 (d, C-1)], 73.9 (d, C-1),], [69.5 (d, C-8a)], 68.8 (d, C-8a), 64.35 (t, C-3), [64.2 (t, C-3)], 52.6 (t, C-5), 32.3 (d, C-2), 28.45 (t C-8), [28.4 (t, C-8)], [25.1 (d, C-2)], 25.05 (t, C-6), [24.65 (t, C-6)], 23.9 (t, C-7), [23.8 (t, C-7)].

*4.4.5.2. Synthesis of (1SR,2SR,8aRS)-2-iodooctahydro-1-indolizinol (**114**) and (1RS,2RS,8aRS)-1-iodoctahydro-2-indolizinol (**115**).*

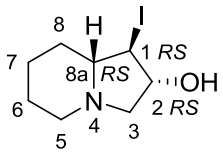
A solution of indolizidine **111** (0.032 g, 0.14 mmol) and NaI (0.045 g, 0.30 mmol) in acetone (0.9 mL) was stirred at 70 °C in a sealed tube (Pirex N. 13) for 5 days. After filtration of the precipitate (NaBr), the solvent was removed and the reaction crude was purified by flash chromatography over silica gel (DCM/MeOH/NH_3 50:1:1). Compound **114** was isolated along with indolizidine **115** [R_f = 0.35, 0.011 g, ratio 1:1.6 ^{1}H-NMR, 11% **114** and 16% **115**].



^{1}H-NMR (400 MHz, $CDCl_3$)[134] *δ*: [4.44 (ddd, *J* = 6.3, 4.0 e 1.0 Hz, 1H, H-2)], 4.30 (brd, *J* = 3.1 Hz, 1H, H-1), 4.02 (pseudo t, *J* = 7.5 Hz, 1H, H-2), 3.82 (dd, *J* = 10.5 e 7.7 Hz, H-3), [3.59 (dd, *J* = 9.7 e 3.8, 1H, H-1)], 3.17 (m, 1H, H-5), [3.08 (m, 1-5, H-5)], [2.97 (d, *J* = 10.3, 1H, H-3α)], 2.90 (vbrs, 2H, OH X 2), 2.76 (dd, *J* = 10.5 e 7.0, 1H, H-3), [2.56 (dd, *J* = 10.4 e 6.4 Hz, 1H, H-3β], 2.41 (m, 1H, H-8a,), [2.18 (m, 1H, H-8a,)], 2.14 (m, 1H, H-5), [2.04-1.94 (m, 2H, H-5 e H-8)], 1.89-1.74 (m, 3H, H-7 of **115** and H-7 and H-8 of **114**), 1.68-1.52 (m, 4H, 6-CH_2 of **115** and 6-CH_2 of **114**), 1.38-1.14 (m, 4H, H-7 and H-8 of **114** and **115**).

[134] The data in square brackets are relative to the resonances of only compound **115**.

^{13}C-NMR (100 MHz, $CDCl_3$)[134] δ: 82.8 (d, C-1), [80.1 (d, C-2)], [73.6 (d, C-8a)], 65.75 (d, C-8a), 64.7 (t, C-3), [62.1 (t, C-3)], 52.65 (t, C-5), [52.6 (t, C-5)], [34.3 (d, C-1)], [28.3 (t, C-8)], [25.0 (t, C-6)], 24.7 (t,), 24.4 (t), [23.8 (t,C-7)], 23.4 (t).



The following band gave indolizidine **115** as a white solid (R_f = 0.21, 0.015 g, 39%).

MW = 267.11

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.44 (ddd, *J* = 6.4, 3.9 e 1.0 Hz, 1H, H-2), 3.57 (dd, *J* = 9.7 e 3.7 Hz, 1H, H-1), 3.21, (vbrs, 1H, OH), 3.05 (dt, *J* = 10.6 e 2.6 Hz, 1H, H-5β) 2.94 (d, *J* = 10.1 Hz, 1H, H-3α), 2.53 (dd, *J* = 10.3 e 6.4 Hz, H-3β), 2.15 (td, *J* = 9.9 e 2.5 Hz, 1H, H-8a), 2.01-1.94 (m, 2H, H-5α e H-8), 1.87-1.82 (m, 1H, H-7), 1.62-1.50 (m, 2H, 6CH_2), 1.29-1.11 (m, 2H, H-7 e H-8).

^{13}C-NMR (100 MHz, $CDCl_3$) δ: 80.1 (d, C-2), 73.5 (d, C-8a), 62.2 (t, C-3), 52.7 (t, C-5), 34.7 (d, C-1), 28.4 (t, C-8), 25.1 (t, C-6), 23.9 (t, C-7).

APPENDIX

General experimental details

Melting points were taken on a Büchi 510 apparatus and are uncorrected. Silica gel plates (Merck F_{254}) and silica gel 60 (Merck, 230-400 mesh) were used for TLC and flash chromatographies (FC), respectively; petroleum ether (PE) employed for crystallizations and chromatographic workup refers to the fractions of bp 30-50 and 40-70 °C, respectively. IR spectra were recorded with a Perkin-Elmer Spectrum BX FT-IR System spectrophotometer. ^{1}H and ^{13}C-NMR spectra were recorded in $CDCl_3$ solutions with a Varian Mercuryplus 400 instrument, operating at 400 and 100 MHz, respectively. Elemental analyses were performed with a Perkin-Elmer 2400 analyzer. Accurate mass spectra were recorded on a LTQ-Orbitrap high-resolution mass spectrometer (Thermo, San Jose, CA, USA), equipped with a conventional ESI source.

RINGRAZIAMENTI E…

Desidero ringraziare, insieme alla Prof. ssa Donatella Giomi,

il Professor Alberto Brandi, sulla cui disponibilità e competenza scientifica

è sempre stato possibile fare affidamento per lo svolgimento delle ricerche

presentate in questa tesi.

…SALUTI

Un saluto a tutti i professori, ricercatori e al personale tecnico-amministrativo

del dipartimento di Chimica "Ugo Shiff" del Polo Scientifico di Sesto Fiorentino,

presso cui si è svolto il dottorato di ricerca.

Un abbraccio speciale a tutti gli amici e compagni conosciuti

durante il percorso di studi universitari.

R. A.

28-12-2010

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