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NITROGEN HETEROCYCLES: SELECTIVE SYNTHETIC METHODS AND APPLICATIONS

Settore Scientifico Disciplinare CHIM/06

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Summary

General introduction

Many organic compounds contain cyclic systems.[1] A heterocycle is a cyclic compound made up of carbon atoms and at least one other element. The most common elements present in the heterocyclic systems along with carbon are nitrogen, oxygen and sulphur. Heterocycles are widely spread in nature and they are fundamental in living systems as key component for biological processes, as well as application in human life as pharmaceutical, agrochemical, veterinary products and new materials with increasing relevance in different domains.[2] In 1988 Evans introduced the term 'privileged structures' to define molecular frameworks 'capable of providing useful ligands for more than one receptor', that upon modifications 'could be a valuable alternative in the search for new receptor agonists and antagonists'.[3] Even if initially this expression was referred to benzodiazepine scaffolds, now it applies to many other compounds such as biphenyls, 1,4-dihydropyridines, pyridazines, benzopyrans, isoxazoles, monosaccharides.[4]

In biological systems, there are numerous examples of molecules made up of heterocycles. For example, carbohydrates are made up of monosaccharides in their cyclic form (namely cellulose and starch are important biopolymers of glucose). Moving to nitrogen heterocycles, chlorophyll and heme contain the porphyrin ring, while pyrimidine and purine ring systems are the constituent of nucleic acid bases, DNA and RNA, which contain genetic information of every

[1] T. L. Gilchrist, *Heterocyclic chemistry*, 3rd ed, Longman: Harlow, UK, 1997, ch. 1.
[2] (a) M. Obana, T. Fukino, T. Hikima, T. Aida, *J. Am. Chem. Soc.* **2016**, *138*, 9246-9250; (b) H. Yamagishi, H. Sato, A. Hori, Y. Sato, R. Matsuda, K. Kato, T. Aida, *Science* **2018**, *361*, 1242-1246.
[3] B. E. Evans, K. E. Rittle, M. G. Bock, R. M. DiPardo, R. M. Freidinger, W. L. Whitter, G. F. Lundell, D. F. Veber, P. S. Anderson, R. S. L. Chang, V. J. Lotti, D. J. Cerino, T. B. Chen, P. J. Kling, K. A. Kunkel, J. P. Springer, J. J. Hirshfield, *J. Med. Chem.* **1988**, *31*, 2235-2246.
[4] (a) D. A. Horton, G. T. Bourne, M. L. Smythe, *Chem. Rev.* **2003**, *103*, 893-930; (b) C. G. Wermuth, *Med. Chem. Commun.* **2011**, *2*, 935-941.

living individual. Vitamins such as thiamine, riboflavin, nicotinamide and ascorbic acid are very important diet ingredients for human wellness. Proline, one of the 20 amino acids involved in the synthesis of proteins in which the side group is a pyrrolidine ring, prevents an ordinated secondary structure making possible a polypeptide folding. Moreover, heterocycles are widely used as synthetic intermediates due to their easy manipulation to achieve many other functionalities. On this basis, it is not surprising that nowadays synthesis and properties of heterocyclic compounds are the object of countless research works.

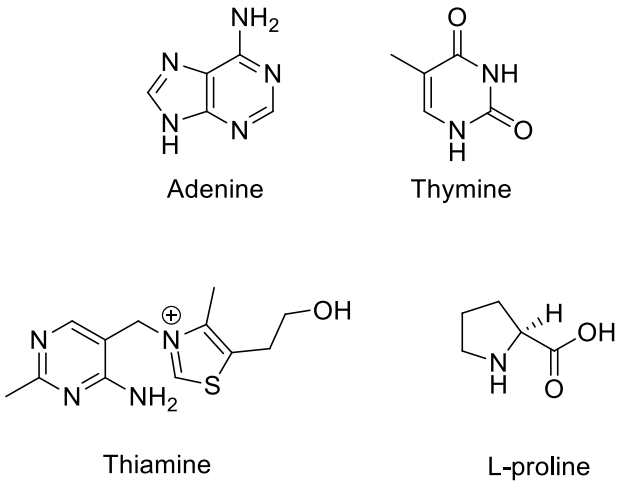


Figure I.1 - Examples of bioactive nitrogen heterocycles.

According to the enormous interest associated to heterocyclic systems, this thesis work was focused on azaheterocycles, and in particular on derivatives which reactivity is associated with the presence of a pyridine ring.

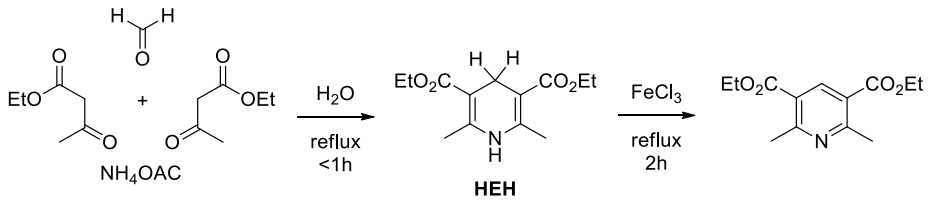
I.1 Pyridine and its derivatives

Pyridine is the simplest and best-known heterocyclic compound. The structure of pyridine is analogous to benzene's one with the replacement of a C-H group with a nitrogen atom. Even if it was prepared by early alchemists in impure form, the credit for its discovery is attributed to the Scottish scientist Thomas Anderson.[5] In 1849, Anderson heated animal bones at high temperature and he examined the content of the oil. He recovered, among other substances, a colourless liquid with unpleasant smell, from which he isolated pure pyridine two years later. He described this compound as highly soluble in water, readily soluble in concentrated acids and salts upon heating, and only slightly soluble in oils. The structural relationship between pyridine and benzene was determined many years after its discovery independently by Wilhelm Körner (1869)[6] and James Dewar (1871).[7] They suggested that, by analogy between quinoline and naphthalene, the structure of pyridine is derived from benzene by substituting one C-H unit with a nitrogen atom. The first synthesis of a heteroaromatic compound was performed in 1876 by William Ramsay, that combined acetylene and hydrogen cyanide into pyridine in a red-hot iron-tube furnace.[8]

In 1881, Arthur Rudolf Hantzsch described the first major synthesis of pyridine derivatives. His procedure typically uses a 2:1:1 mixture of a β-keto acid derivative (often ethyl acetoacetate), an aldehyde (often formaldehyde), and ammonia or its salt as the nitrogen donor and affords 1,4-dihydropyridines (Scheme I.1).[9] For instance, the so-called Hantzsch ester (HEH, diethyl 1,4-

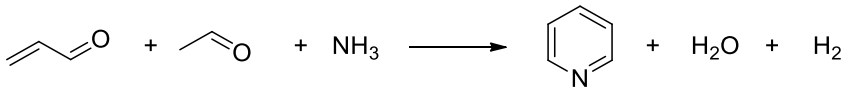
[5] T. Anderson, *Ann. Chem. Pharm.* **1846**, *16*, 123-136.
[6] W. Koerner, *Giornale di Scienze Naturali ed Economiche* **1869,** *5*, 111-114.
[7] (a) J. Dewar, *Chemical News* **1871**, *23*, 38–41; (b) A. J. Rocke, *Bulletin for the History of Chemistry* **1988**, *2*, 4.
[8] W. Ramsay, *Lond. Edinb. Dubl. Phil. Mag*. **1876**, *2*, 269-281.
[9] A. Hantzsch, *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 1437-1638.

dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate) is a commercial reagent nowadays widely applied in organocatalytic enantioselective reduction of imines as stoichiometric reducing agent.[10]



Scheme I.1 - Sythesis of Hantzsch ester and its oxidation to substituted pyridine.

In that period, pyridine was extracted from coal tar or obtained as a byproduct of coal gasification. The process was labour-consuming and inefficient: coal tar contains only about 0.1% of pyridine,[11] and therefore a multi-stage purification was required, which further reduces the yield. A breakthrough came in 1924 when the Russian chemist Aleksei Chichibabin invented a pyridine synthesis reaction (Scheme I.2) based on inexpensive reagents.[12] Nowadays, most pyridine is produced synthetically using various reactions, such as Chichibabin synthesis, dealkylation of alkylpyridines, Bönnemann cyclization and other methods.[13]

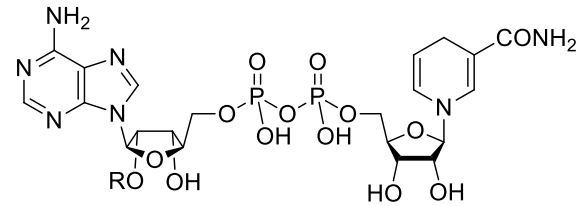


Scheme I.2 - Chichibabin pyridine synthesis.

[10] F. Foubelo, Y. Miguel, *Chemical record* **2015**, *15*, 5, 907-924.
[11] A. Täufel, W. Ternes, L. Tunger, M. Zobel, *Lebensmittel-Lexikon*, 4th ed., Behr: Hamburg, 2005, p. 226.
[12] A. E. Chichibabin, *J. Prakt. Chem.* **1924**, *107*, 122-128.
[13] S. Shimizu, N. Watanabe, T. Kataoka, T. Shoji, N. Abe, S. Morishita, H. Ichimura, *Ullmann's Encyclopedia of Industrial Chemistry*, Ed. B. Elvers, Wiley-VCH, 2000, Vol. 30, pp. 557-586.

The presence of the nitrogen atom introduces an element of asymmetry that allows the synthesis of three different monosubstituted pyridines. The nitrogen atom is assigned position-1, while the position in a monosubstituted pyridine can be designed either by the numeric system or by the Greek alphabet. The three methylpyridines, have both systematic and trivial names (picoline). The six dimethylpyridines are named luditines and an equal number of trimethyl substituted derivatives are known as collidines.[14]

The pyridine ring is highly common in nature being the core of many important alkaloids. Moreover, this system is present in biological environment because it is the fundamental constituent of main coenzymes such as nicotinamide adenine dinucleotide (NADH) and its phosphate (NADPH) (Figure I.2) involved in biological redox processes.



NADH: R = H
NADPH: R = PO_3^{2-}

Figure I.2 - Chemical structure of NADH/NADPH.

Experimental evidence that pyridine is an aromatic molecule, with a resonance energy quite similar with that of benzene, and with a bond angle of 117° instead of 120°. Its chemistry resembles that of benzene in some aspects, although there are many important differences due to the presence of the ring nitrogen atom.

[14] R. K. Bansal, *Heterocyclic Chemistry*, 3rd ed., New Age International (P) Ltd.: New Delhi, 1999, ch. 6.

For example, electrophilic substitutions on the ring are difficult in pyridine with respect to benzene, while nucleophilic additions/substitutions are easier.

Quinoline is a heterocyclic aromatic compound, which is a benzofused pyridine, named benzo[*b*]pyridine.[15] Quinoline can be derived from naphthalene by replacement of one α-CH group with respect to the junction with nitrogen. It is a colourless liquid with a strong smell, but old samples became yellow and then brown. Quinoline has many analogies with naphthalene and pyridine in molecular geometry and bond parameters. Quinoline itself has few applications, but its derivatives are very useful in many fields. Quinaldine and lepidine (i.e. 2- and 3-methylquinoline), 4-quinolone and the quinolinium ion are important derivatives of quinoline. Moreover, the quinoline structure is part of natural alkaloids such as quinine (Figure I.3), used in medical field to treat malaria.[16]

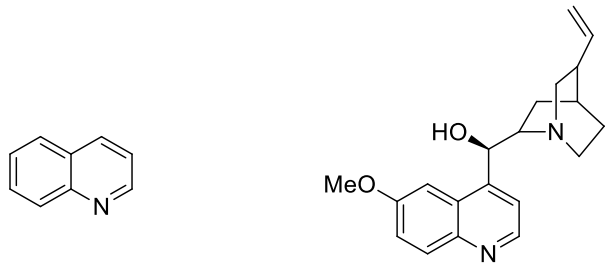


Figure I.3 - Quinoline and quinine.

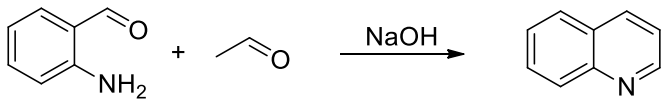
In 1834, the German chemist Fiedlieb Ferdinand Runge was the first scientist who isolated quinoline.[17] Quinoline was extracted from coal tar, and this

[15] T. Eicher, S. Hauptmann, A. Speicher *The Chemistry of Heterocycles: Structures, Reactions, Synthesis, and Applications*, 3rd ed., Wiley-VHC: Weinheim, 2003, ch. 5**.**

[16] J. W. W. Stephens, W. Yorke, B. Blacklock, J. W. S. Macfie, C. F. Cooper, *Ann. Trop. Med. Parasit.* **1917**, *11*, 113-125.

[17] (a) F. F. Runge, *Ann. Phys.* **1834**, *31*, 68; (b) C. Hung, *Encyclopaedia Britannica*, 11th ed., University Press: Cambrige 1911, Vol. 22, pp. 758-759.

method remains the principal source of commercial quinoline.[18] There are many syntheses, starting from substituted aniline to close the heterocyclic ring. For example, the Friedlaender synthesis is the reaction between 2-aminobenzaldehyde and acetaldehyde (Scheme I.3) to form quinoline.[19]



Scheme I.3 - Friedlaender synthesis of quinoline.

I.2 Isoxazole and its derivatives

Azoles are a class of aromatic five-membered heterocycles containing at least one nitrogen atom in the ring.[15] Compounds made up by one more heteroatom such as nitrogen, oxygen, or sulphur are called respectively, according to the atom that they contain, diazoles, oxazoles, and thiazole and they exist in two isomeric forms. Concerning diazoles, the trivial names pyrazole and imidazole are commonly applied for isomers with nitrogen atoms in 1,2- and 1,3-positions, respectively. Oxygen and sulphur derivatives are usually called isoxazole and isothiazole or oxazole and thiazole if the heteroatoms are respectively in 1,2- or 1,3-positions (Figure I.4).

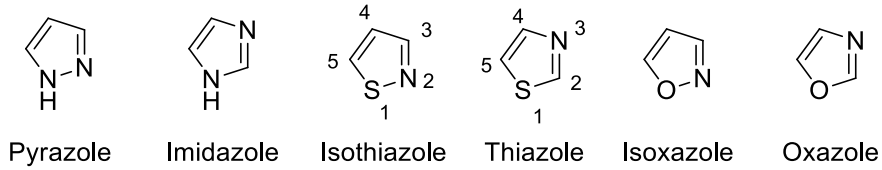


Figure I.4 - Azoles: structure and trivial names.

[18] G. Collin, H. Hoke*, Ullmann's Encyclopedia of Industrial Chemistry*, Ed. B. Elvers, Wiley-VCH, 2000, Vol. 31, pp. 1-6.
[19] P. Friedlaender, *Ber. Dtsch. Chem. Ges.* **1882**, *15*, 2572-2575.

The isoxazole system was discovered in 1888 by Claisen, who synthesized 3-methyl-5-phenylisoxazole.[20] In 1903, studying the reaction of propargylaldehyde and hydroxylamine, Claisen observed the formation of a cyclic compound, i.e. isoxazole, coming from cyclization of the oxime intermediate.[21]

Between 1929 and 1946 Quilico and Speroni gave an important push to the study of isoxazoles.[22] They discovered the high reactivity of nitrile oxides and fulminic acid with aliphatic alkynes and alkenes forming, respectively, isoxazole and isoxazoline derivatives. Since 1980s these compounds were studied extensively, due to their versatility in the synthesis of various compounds, and for their application in several fields, such as industry, medicine and agriculture.[23] Nowadays, the most common methods for the synthesis of isoxazoles are: 1,3-dipolar cycloadditions (1,3-DC) of nitrile oxides to alkynes/alkenes under thermal conditions, usually with low regioselectivity; formal Cu(I)-catalized 1,3-DC of nitrile oxides to terminal alkynes affording regioselectively 3,5-disubstituted isoxazoles (click reaction);[24] condensation of hydroxylamine with 1,3-dicarbonyl compounds or equivalent systems such as α,β-unsaturated carbonyl compounds; cycloisomerization, building an appropriate substrate and promoting the cyclization by a suitable catalyst;

[20] L. Claisen, O. Lowman, *Ber. Dtsch. Chem. Ges.* **1888**, *21*, 1149-1157.
[21] L. Claisen, *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 3664-3673.
[22] A. Quilico, G. Speroni, L. C. Behr, R. L. Mc Kee, *Chemistry of Heterocyclic Compounds*, Ed.: R. H. Wiley, John Wiley & Sons: New York – London, 1962, pp. 5-94.
[23] A. M. S. Silva, A. C. Tome and T. M. V. Pinho e Melo, J. Elguero, *Modern Heterocyclic Chemistry*, Eds.: J. Alvarez-Builla, J. J. Vaquero, J. Barluenga, Wiley-VCH, Weinheim, 2011, 727–808.
[24] (a) H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem., Int. Ed.* **2001**, *40*, 2004-2021; (b) F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless, V. V. Fokin, *J. Am. Chem. Soc.* **2005**, *127*, 210-216.

intramolecular nitro group addition to unsaturated C-C bonds, with a mechanism close to 1,3-DC.[25]

Isoxazole is a moiety rarely found in nature, but its derivatives show important biological applications. For example, muscimol (Figure I.5), isolated from *amanita muscaria*, is a potent CNS depressant and agonist of GABA. Several reports show that compounds containing isoxazole exhibit antioxidant, antibacterial, anti-aging, antiviral, analgesic, anti-inflammatory, antifungal, antitubercular and antitumoral activities.[26]

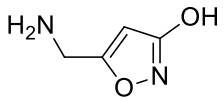


Figure I.5 - Muscimol.

* * *

On the basis of these considerations showing the multifacet reactivity of the azaheterocycles previously reported, this thesis work will be focused on the study of heterocyclic systems such as 1-(2-quinolyl)-2-propen-1-ol , phenyl(2-quinolyl)methanol, (2-quinolyl)(4-tolyl)methanol, and 3-methyl-4-nitro-5-(trichloromethyl)isoxazole (Figure I.6) in different domains, properly discussed in the following chapters.

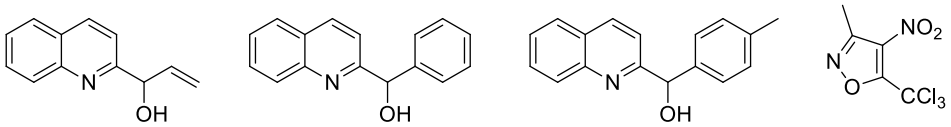


Figure I.6 - Pyridyl, quinolyl, and isoxazolyl derivatives.

[25] T. Morita, S. Yugandar, S. Fuse, H. Nakamura, *Tetrahedron Lett.* **2018**, *59*, 1159-1171.
[26] Y. Hassan, S. O. Ajibade, *Chemistry Research Journal* **2017**, *2*, 182-192.

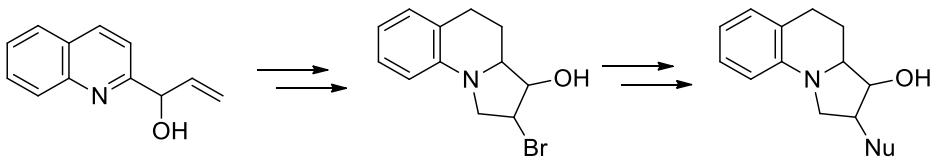
In particular, the three carbinols can be applied in different contexts which exploited the quinolyl system as well as the vinyl moiety present in quinolylpropenol.

The project involving 3-methyl-4-nitro-5-(trichloromethyl)isoxazole has been developed in the laboratory Prof. Mauro Adamo at University College of Dublin during a four months stage. This study concerns the conversion of 3-methyl-4-nitro-5-(trichloromethyl)isoxazole into other isoxazole derivatives through reaction with different nucleophiles.

Accordingly, the thesis work will be described through the following chapters:

1. **Synthesis of hydroxyindolizidine derivatives from 1-(2-quinolyl)-2-propen-1-ol**

Hydroxyindolizidines are a class of compounds that show significant biological/pharmacological activities. In order to develop more efficient and potent drugs, 1-(2-quinolyl)-2-propen-1-ol can be used to synthesize new benzofused hydroxyindolizidines applying a general method developed in our laboratory (Scheme I.4).[27]

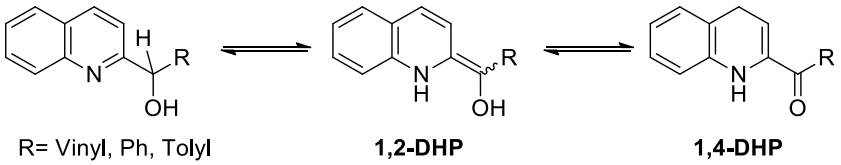


Scheme I.4 - General strategy to access hydroxyindolizines from quinolylpropenol.

[27] D. Giomi, R. Alfini, A. Micoli, E. Calamai, C. Faggi, A. Brandi, *J. Org. Chem.* **2011**, *76*, 9536-9541.

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

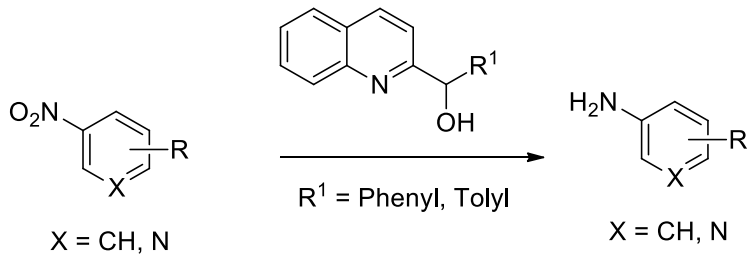
The shown carbinols, due to the weak acidity of the 'picoline type' hydrogen atom, can give rise to tautomeric equilibria able to afford 1,4-dihydropyridine structures (Scheme I.5).



Scheme I.5 - Tautomeric equilibria for quinolylcarbinols.

For quinolylpropenol this behaviour, which is attributed to the presence of the vinyl group, could be responsible for different reaction pathways leading to complex reaction mixtures. On the other hand, the tautomeric forms **1,2-DHP** and **1,4-DHP** can be responsible for phenylquinolylmethanols a reactivity as hydrogen donors, as observed for Hantzsch ester (HEH) (Scheme I.1), opening the way to their application in metal-free reduction of different functional groups. In particular they are able to selectively reduce nitro groups in aromatic and heteroaromatic nitro compounds as well as activated imines to the corresponding amines (Scheme I.6).[28,29]

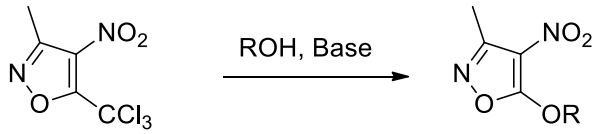
[28] D. Giomi, R. Alfini, A. Brandi, *Tetrahedron* **2011**, *67*, 167-172.
[29] D. Giomi, R. Alfini, J. Ceccarelli, A. Salvini, A. Brandi, *ChemistrySelect* **2016**, *1*, 5584-5589.



Scheme I.6 - Metal-free reductions using quinolyl carbinols.

3. Reactivity of 3-methyl-4-nitro-5-(trichloromethyl)isoxazole with nucleophiles

Nucleophilic addition of alcohols to 3-methyl-4-nitro-5-(trichloromethyl)isoxazole in an alkaline environment can be exploited to access 4-nitroisoxazoles variously substituted at position 5 (Scheme I.7).[30]



Scheme I.7 - Synthesis of new 4-nitroisoxazoles from 3-methyl-4-nitro-5-(trichloromethyl)isoxazole.

[30] Unpublished results.

Chapter 1 – Synthesis of hydroxy indolizidines

1.1 Introduction

1.1.1 Polyhydroxylated alkaloids as glycosidases inhibitors

Polyhydroxylated alkaloids containing a pyrrolidine, piperidine, pyrrolizidine and indolizidine ring system, are well known mimics of monosaccharides. These compounds, containing a nitrogen atom in the ring instead of the endocyclic oxygen, are among the most interesting discoveries in the field of natural products in recent years.[31] These azasugars, also named iminosugars, are classified in five classes on the basis of their heterocyclic skeleton: pyrrolidines, piperidines, pyrrolizidines, indolizidines, and nortropanes. These alkaloids are able to bind specifically to the active site of the glycosidase enzymes mimicking the corresponding natural substrate.

1.1.2 Glycosidases and glycoproteins

Glycosidases are enzymes that catalyze the hydrolysis of glycoside bonds in complex carbohydrates and glycoconjugates. These enzymes are essential for the surviving of every living organism because of the wide variety of processes they are involved. Digestive glycosidases, for example, break down complex sugars to release monosaccharides which can be easily adsorbed and used in metabolic processes, while lysosomal glycosidases catabolize glycoconjugate intracellularly.[32] A wide variety of glycosidases are involved in the biosynthesis of the oligosaccharide portions of glycoproteins and glycolipids located on the

[31] (a) B. La Ferla, F. Nicotra, *Iminosugars as Glycosidases Inhibitors: Nojirimicin and Beyond*, Ed.: A. E. Stulz, Wiley-VCH, Weinheim, 1999, 68-92; (b) N. Asano, R. J. Nash, R. J. Molyneux, G. W. J. Fleet, *Tetrahedron: Asymmetry* **2000**, *11*, 1645-1680.
[32] A. A. Watson, G. W. J. Fleet, N. Asano, R. J. Molyneux, R. J. Nash, *Phytochemistry* **2001**, *56*, 265-295.

cell surface. Glycoconjugates are responsible of the communications between cells and its environment. These systems can act as receptors to identify hormones, useful for the cell life, and other molecules in the environment. This peculiarity is important for the immune system, because cells can identify and destroy pathogenic invaders such as viruses and bacteria. Moreover polysaccharides are involved in the binding of proteins to proteins of adjacent cells, creating new connections (junctions) useful to communicate between cells.

Glycosidases are enzymes involved in a wide range of anabolic and catabolic processes, based on molecular recognition. For this reason, the interest in these glycosidases inhibitors as potential therapeutic agents and future drugs for the treatment of many kinds of diseases has grown up in the last years.[33]

Iminosugars have been shown to act as inhibitors of hydrolytic glycosidases enzymes, capable to break the glycosidic bond between polysaccharides units, and glycosyltransferases. Both these enzymes are involved in the fundamental intracellular process of glycoproteins and glycolipids synthesis.[34] Glycosidases catalyze with high selectivity the hydrolytic cleavage of glycoproteic chains in precursors of the final glycoproteins. Specific glycosyltransferases further elaborate the glycosidic portion that is recombined to produce the final glycoproteins. Iminosugars can strongly interfere in these processes.

The awareness of the fact that these iminosugars may have a huge therapeutic power for the treatment of diseases connected with these processes, or in cell protection mechanisms, because they modify glycoproteins glycosylation and (or) catabolism, or they block glycosidases in the recognition of specific sugars, stimulated the study of these compounds as potential anticancer, antiviral and

[33] F. Cardona, A. Goti, A. Brandi, *Eur. J. Org. Chem.* **2007**, 1551-1565.

[34] (a) S. A. W. Gruner, E. Locardi, E. Lohof, H. Kessler, *Chem. Rev.* **2002**, *102*, 491-514; (b) V. H. Lellelund, H. H. Jensen, X. Liang, M. Bols, *Chem. Rev.* **2002**, *102*, 515-553.

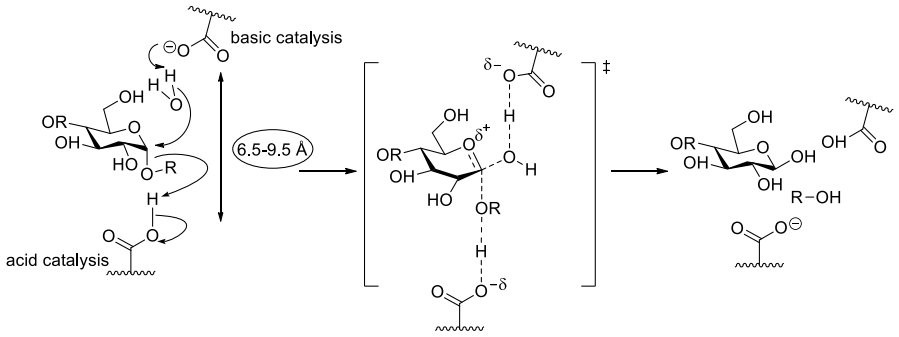
antidiabetics drugs.[35] In particular, the antiviral activity of the glycosidase inhibitors involves the glycosylation inhibition of a part of a glycoprotein (gp 160) in the endoplasmic reticulum, preventing the formation of infected viral particles,[36] or the inhibition of the fusion between the viral particle and the membrane of the host cell mediated by a surface glycoprotein.[37]

The hydrolisis of the glycoside bond occurs because of two residues present in the catalytic site of enzymes: an acidic residue (proton donor) and a basic residue (nucleophilic). According to the spatial position of the residues, the hydrolysis may occur through complete inversion (Scheme 1.1) o total retention of the anomeric carbon configuration (Scheme 1.2).

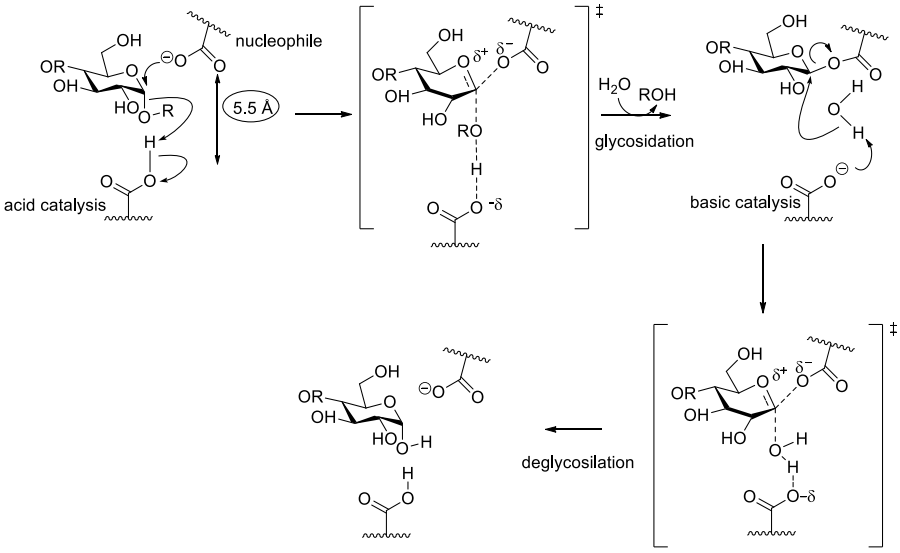
[35] (a) N. Ischida, K. Kumagai, T. Niida, T. Tsuroka, H. Yumoto, *J. Antibiot., Ser. A* **1967**, *20*, 66-71; (b) P. S. Sunkara; D. L. Taylor, M.S. Kang, T. L. Bowlin, P. S. Liu, A. S. Tyms, A. Sjoerdsma, *Lancet* **1989**, *333*, 1206; (c) G. W. J. Fleet, A. Karpas, R. A. Dwek, L. E. Fellows, A. S. Tyms, S. Petursson, S. K. Namgoong, N. G. Ramsden, P. W. Smith, J. C. Son, F. Wilson, D. R. Witty, G. S. Jacob, T. W. Rademacher, *FEBS Lett.* **1988**, *237*, 128-132; (d) D. B. Walker, M. Kowalski, W. C. Goh, K. Kozarski, M. Krieger, C. Rosen, L. Rohrschneider, A. W. Haseltine, J. Sodroski, *Proc. Natl. Acad. Sci. USA* **1987**, *84*, 8120; (e) J. W. Dennis, K. Koch, D. Beckner, *J. Nat. Cancer Inst.* **1989**, 81, 1028-1033; (f) S. A. Newton, S. L. White, M. J. Humphries, K. Olden, *J. Nat. Cancer Inst.* **1989**, *81*, 1024-1027; (g) G. K. Ostrander, N. K. Scribner, L. R. Rohrschnerider, *Cancer Res.* **1988**, *48*, 1091-1094; (h) W. Leonhardt, M. Hanefeld, S. Fischer, J. Schulze, *European J. Clin. Invest.* **1994**, *24*, 45-49; (i) A. J. J. Reuser, H. A. Wisselaar, *European J. Clin. Invest.* **1994**, *24*, 19-24; (j) H. Bischoff, *European J. Clin. Invest.* **1994**, *24*, 3-10.

[36] (a) P. Fischer, M. Collin, G. B. Karlsson, W. James, T. D. Butters, S. J. Davis, S. Gordon, R. A. Dwek, F. M. Platt, *J. Virol.* **1995**, *69*, 5791-5797; (b) P. Cos, L. Maes, D. Vanden Berghe, N. Hermans, L. Pieters, A. Vlietinck, *J. Nat. Prod.* **2004**, *67*, 284-293.

[37] M. J. Papandreou, R. Barbouche, R. Guieu, M. P. Kieny, E. Fenouillet, *Mol. Pharmacol.* **2002**, *61*, 186-193.



Scheme 1.1 - Hydrolysis with inversion of configuration.



Scheme 1.2 - Hydrolysis with retention of configuration.

On these bases, polyhydroxylated alkaloids appear to be extremely powerful and specific inhibitors of glycosidases, because they mimic the furanosyl or pyranosyl moiety of the natural substrate. It has been demonstrated that when an iminosugar binds an active site of a glycosidase, the protonation of the compound permits the formation of an ionic couple between the inhibitor and the carboxylate anion. The protonated inhibitor behaves as a transition state analog of the natural substrate. This is enough to justify the great affinity of the

enzyme for the molecule: the efficiency of the inhibition, depends on the pKa values of the inhibitor with respect to the optimal pH of the enzyme. Moreover, the number, position and configurations of the hydroxy groups of each alkaloid determine the kind of glycosidase enzyme they can inhibit. These features are very important, because they can influence the selectivity of a single enzyme, an aspect that is not yet generally solved or understood, and is of peculiar importance for the applications of these molecules as drugs.

In the last years selective syntheses of new iminosugars, both natural and non-natural, have been performed for the study of cellular biological processes in addition to their applications as potential drugs. Two iminosugars are already commercially available as drugs: Zavesca[37] and Celgosivir[38] (Figure 1.1).

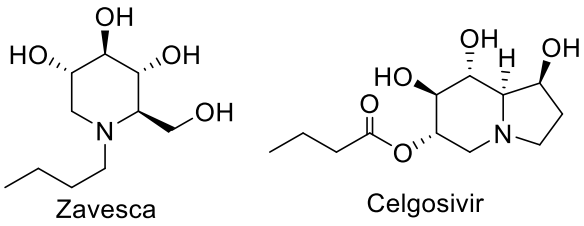


Figure 1.1 - Zavesca and Celgosivir.

Zavesca has been applied for the treatment of Gaucher's disease, a genetic disorder in which glucocerebroside (a sphingolipid, also known as glucosylceramide) accumulates in cells and certain organs.

Celgosivir has been developed for the treatment of hepatitis C virus (HCV) infection, and it acts as prodrug of the natural castanospermine that inhibits alpha-glucosidase I, an enzyme that plays a critical role in viral maturation. Celgosivir mechanism of action makes it work both *in vitro* and *in vivo* against other viruses such as HIV-1, herpes (HSV) or bovine viral diarrhea (BVB).

[38] T. Cox, R. Lachmann, C. Hollak, J. Aerts, S. van Weely, M. Hrebicek, F. Platt, T. Butters, R. Dwek, C. Moyses, I. Gow, D. Elstein, A. Zimran, *Lancet* **2000**, *355*, 1481-1485.

1.1.3 Natural polyhydroxylated alkaloids

In 1966 Inouye and co-workers discovered the first natural polyhydroxylated alkaloid, nojirimycin (nj): it was isolated in a filtrate of *Streptomyces*, and it showed a surprising activity as a powerful inhibitor of α- and β- glucosidases.[39] The first 1-deoxy derivative, 1-deoxynojirimicyn (DNJ), has been synthesized by the same authors by reduction of the anomeric carbon. Later, DNJ has been isolated from mulberry trees and *Streptomyces* cultures, and it showed to act as inhibitor of α-glucosidases as well as other glucosidases,[33] and was also found to be a powerful inhibitor for the viral replication of HIV.[32]

The first pyrrolizidine iminosugar isolated from natural sources has been alexina, obtained by the legume *Alexa leiopetala*. Casuarina, already used in Samoa for the treatment of breast cancer, has been identified in the cortex of *Casaurina equistetifoglia*. These compounds showed a strong inhibitory activity towards α- and β- glucosidases and β-galactosidases.

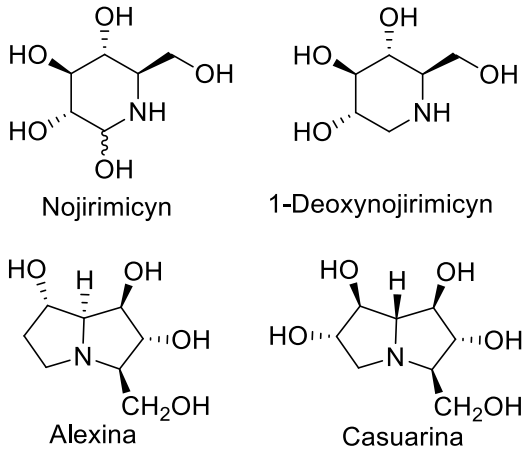


Figure 1.2 - Examples of natural polyhydroxylated alkaloids.

Moving to indolizidine alkaloids, the first compound identified has been swainsonine, isolated in 1979 from the leaves of *Swainsona canescens*[40] and

[39] S. Inouye, T. Tsuruoka, T. Ito, T. Niida, *Tetrahedron* **1968**, *24*, 2125-2144.
[40] S. M. Colegate, P. R. Dorling, C. R. Huxtable, *Austr. J. Chem.* **1979**, *32*, 2257-2264.

later from *Astragalus* together with swainsonine *N*-oxide. Swainsonine is a potent inhibitor of α-mannosidases.

Castanospermine has been isolated from the seeds of *Castanospermum australis*,[41] and it is a powerful inhibitor of α- and β- glucosidases.

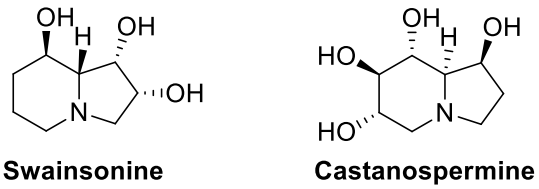


Figure 1.3 - Swainsonine and Castanospermine.

Lentiginosine was isolated in 1990 by Elbein et al. by extraction in methanol from the leaves of *Astragalus lentiginosus*, together with swainsonine and 2-*epi*-lentiginosine.[42]

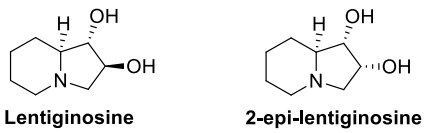


Figure 1.4 - Lentiginosine, 2-epi-*lentiginosine and* Astragalus lentiginosus.

Lentiginosine has been isolated because in the methanolic extracts of *Astragalus lentiginosus* an α-amyloglucosidases inhibitor, that is an enzyme able to hydrolyze 1,4- and 1,6-α-glucosidic bonds, has been observed. Once isolated and purified, lentiginosine resulted to be a good inhibitor of these enzymes, with

[41] L. D. Hohenschutz, E. A. Bell, P. J. Jewess, D. P. Leworthy, R. J. Pryce, E. Arnold, J. Clardy, *Phytochemistry* **1981**, *20*, 811-814.
[42] I. Pastuszak, R. J. Molineux, L. F. James, A. D. Elbein, *Biochemistry* **1990**, *29*, 1886-1891.

an IC_{50}= 5 μg/mL. Later on, a major inhibitory power has been observed for the synthetic compound in the inhibition of amyloglucosidases (from *Aspergillus niger*), probably because of impurities present in the alkaloid extracted from natural sources.[33] 2-*Epi*-lentiginosine is totally inactive: this is an evidence of how crucial is the relative configuration of the two hydroxy groups to determine the biological activity. The peculiarity of the lentiginosine is that it is the first inhibitor for glycosidases having only two hydroxy groups; violating the empiric rule according to which the substrate should have at least 3 OH groups in a β-position with respect to nitrogen to show any inhibitory properties. Moreover, it is one of the most selective derivatives, because it does not inhibit the other tested glycosidases.

Recent studies demonstrated other interesting biological properties for the natural (+)-lentiginosine, in addition to the inhibition of glycosidases. In particular, it was found to be a powerful inhibitor of Heat Shock Protein 90 (HSP90).[43]

1.1.4 Synthesis of 1,2-dihydroxyindolizidines from pyridine precursors

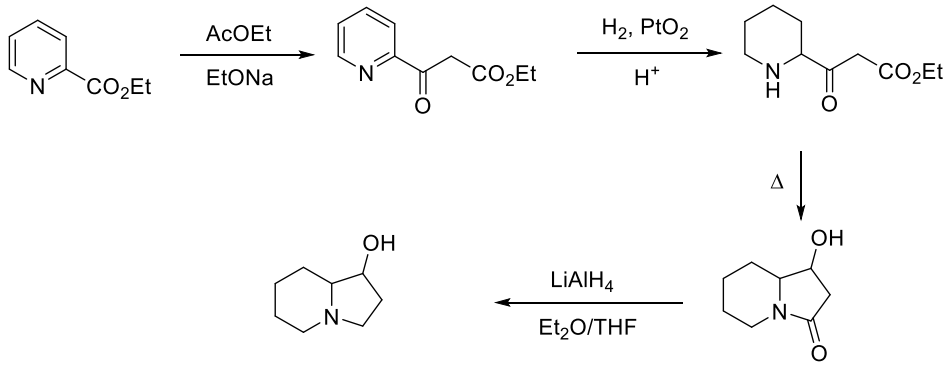
In the last few years, the research of easy and efficient methods for the synthesis of chiral compounds including pyridine nucleus has been significantly increased according to the wide field of application of these systems: supramolecular chemistry, asymmetrical catalysis, synthesis of natural compounds.[44] Consequently, many pyridine derivatives are now easily available and usable.

Regarding indolizidine alkaloids, the most part of the synthetic procedures described is focused on the construction of the pyrrole or piperidine unit, opportunely functionalized, with the aim to obtain the bicyclic skeleton by cyclization. Aromatic pyridine derivatives appears to be interesting building

[43] F. M. Cordero, D. Giomi, A. Brandi, *Curr. Med. Chem.* **2014**, *14*, 10.
[44] A. Landa, A. Minkkila, G. Blay, K. A. Jorgensen, *Chem. Eur. J.* **2006**, *12*, 3472-3483.

blocks for the synthesis of indolizidine systems. Despite these considerations, in the literature procedures for the synthesis of 1,2-dihydroxyindolizidines that exploit this approach are very limited.

A first example of the application of pyridine compounds appeared in 1961, and was related to the synthesis of 1-hydroxiindolizidine derivatives.[45] Ethyl picolinate has been converted into the appropriate precursor by Claisen condensation with ethyl acetate. Hydrogenation on PtO_2 and heating led to the bicyclic lactam, then reduced with $LiAlH_4$ (Scheme 1.3).

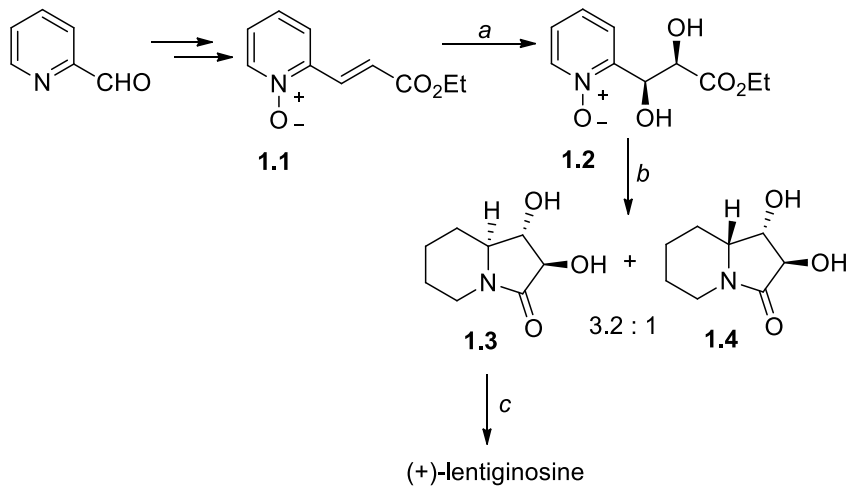


Scheme 1.3 - Synthesis of 1-hydroxyindolizidine starting from ethyl picolinate.

In 2003, Zhou et al. developed a new enantioselective total synthesis of (+)-lentiginosine, which is the shortest route using non-chiral starting materials.[46] In fact, (+)-lentiginosine has been obtained in 20% overall yield in only 3 steps, starting from ethyl 3-(2-pyridyl)acrylate *N*-oxide (**1.1**), through Sharpless asymmetric dihydroxylation (AD) and cyclization (Scheme 1.4). The starting material has been synthesized from picolinaldehyde by Wittig reaction followed by dihydroxylation. The asymmetric dihydroxylation (AD), was conducted with a higher excess of $(DHQ)_2PHAL$ and K_2CO_3 with respect to the normal reaction conditions, leads to the formation of the diol **1.2** in an enantiomeric excess >

[45] V. Carelli, F. Liberatore, F. Morlacchi, *Annali di Chimica* **1961**, *51*, 467-476.
[46] Z. Feng, A. Zhou, *Tetrahedron Lett.* **2003**, *44*, 497-498.

99%. By Pd-catalyzed hydrogenation they obtained a lactam mixture in 3.2:1 ratio. After the removal of **1.4** by crystallization from ethyl acetate, the reduction of compound **1.3** with $BH_3 \cdot SMe_2$ in THF provided (+)-lentiginosine.



(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/tBuOH (1:1), 24h, 62% with 20% starting material recovery; (b) 10% Pd/C, 10 atm H_2, MeOH, 24h, 43% of **1.3**; (c) $BH_3 \cdot SMe_2$, THF, from 0°C to 20°C, 10h, 75%.

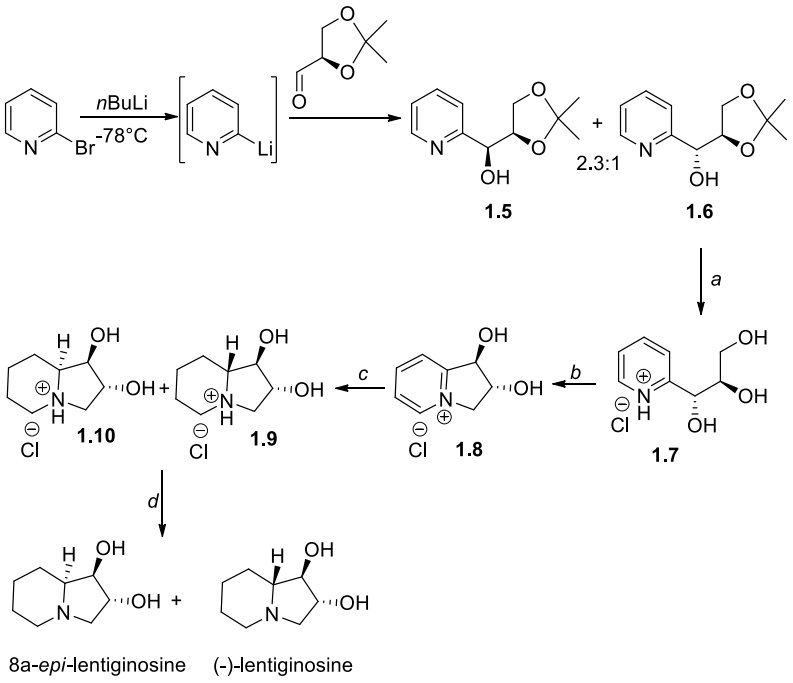
Scheme 1.4 - Zhou method for the enantioselective total synthesis of (+)-lentiginosine.

An analogous procedure has been applied to the synthesis of (–)-swainsonine and (–)-2,8a-di-*epi*-swainsonine.[47]

In 2008 a 5 steps synthesis of (–)-lentiginosine starting from 2-bromopyridine was published (Scheme 1.5). This synthetic strategy exploited the Mitsunobu reaction to create the dihydroxylated 5-member ring contained in the indolizidine skeleton. Treating 2-bromopyridine with *n*-BuLi (-78 °C), 2-litiumpyridine was generated that easily reacted with (*R*)-2,3-*O*-isopropylidenglyceraldehyde to give a mixture of diastereoisomers **1.5** and **1.6**,

[47] G. Heimgärtner, D. Raatz, O. Reiser, *Tetrahedron* **2005**, *61*, 643-655.

resolved by chromatography. Deprotection of acetonide **1.6** in weakly acidic environment yielded triol **1.7** which, through intramolecular cyclization in Mitsunobu conditions, evolves in the bicyclic pyridine salt **1.8**. The PtO_2-catalyzed hydrogenation of **1.8** generated a mixture of diastereoisomers **1.9** and **1.10** (0.8:1), that yielded the non-natural systems (–)-lentiginosine and 8a-*epi*-lentiginosine, in 28% and 31% yields, respectively, from 2-bromopyridine.[48]



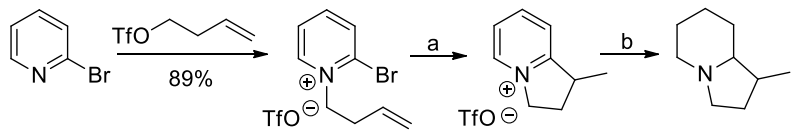
(*a*) HCl acq, 99%; (*b*) PPh_3, DIAD, acetonitrile, 2h, 98%; (*c*) H_2/PtO_2 H_2O, EtOH, 97%; (*d*) KOH, 96%.

Scheme 1.5 - Enantioselective total synthesis of (-)-lentiginosine starting from 2-bromopyridine.

***

[48] R. Azzuz, C. Fruit, L. Bischoff, F. Marsais, *J. Org. Chem.* **2008**, *73*, 1154-1157.

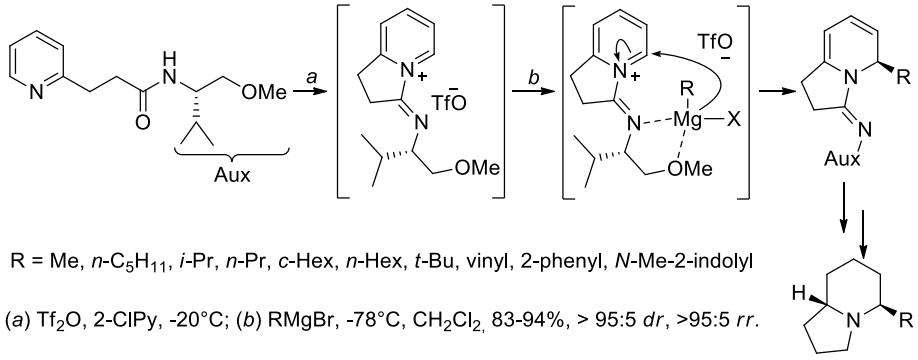
Earlier, 2-bromopyridine has been used in the synthesis of the indolizidine moiety *via* conversion into the corresponding *N*-alkenylpyridinium salts and subsequent radical cyclization in the presence of tributyltin hydride (Scheme 1.6).[49]



(a) Bu_3SnH, AIBN, toluene, reflux, 12h, 74%; (b) H_2, PtO_2, MeOH, 24h, 20 °C, 40 psi, 52%.

Scheme 1.6 - Indolizidine skeleton synthesis by radical cyclization.

Recently, 5-substituted indolizidines were obtained in high regio- and diastereoselectivity from pyridine precursors through the intramolecular activation of the pyridine ring and subsequent asymmetric dearomatization with a Grignard reagent (Scheme 1.7).[50]



R = Me, *n*-C_5H_{11}, *i*-Pr, *n*-Pr, *c*-Hex, *n*-Hex, *t*-Bu, vinyl, 2-phenyl, *N*-Me-2-indolyl

(*a*) Tf_2O, 2-ClPy, -20°C; (*b*) RMgBr, -78°C, CH_2Cl_2, 83-94%, > 95:5 *dr*, >95:5 *rr*.

Scheme 1.7 - Synthesis of 5-substituted indolizidines.

[49] A. P. Dobbs, K. Jones, K. T. Veal, *Tetrahedron Lett.* **1997**, *38*, 5383-5386.
[50] G. Barbe, G. Pelletier, A. B. Charette, *Org. Lett.* **2009**, *11*, 3398-3401.

Pyridine systems have also been applied as direct precursors of tetrahydropyridines,[51] dihydropyridines,[52] and aminocyclopentane ring systems,[53] which were eventually converted into indolizidines products.

1.1.5 Benzoindolizidine derivatives

With the goal of synthesizing new potent and selective iminosugars, the research was focused on the modification of the indolizidine skeleton through the conjugations with substructures, such as variously functionalized chains or aminoacidic structures. These functionalizations regarded mainly the 6-membered ring of the indolizidine skeleton. Benzocondensed indolizidine systems, as well as their oxidized or reduced forms, are widely represented in natural compounds and in pharmacologically active compounds. In 2000, Pearson and Fang reported the synthesis of benzofused azabicyclo[*m.n.*0]alkanes through Schmidt reaction and its application to the gephyrotoxin formal synthesis.[54]

Computational studies show significant effects associated to the presence of aromatic substituent: for example, for benzoderivatives of lentiginosine is foresighted a better interaction with the enzymatic active site.[55]

Natural polyhydroxylated aryl-substituted pyrrolizidines, such as conodopsine and radicamine (Fig. 1.5), also showed interesting biological activities.

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[51] Y. N. Bubnov, E. V. Klimkina, A. V. Ignatenko, *Russ. Chem. Bull.* **1998**, *47*, 941-949.
[52] D. L. Comins, A. B. Fulp, *Org. Lett.* **1999**, *1*, 1941-1943.
[53] Z. Zhao, L. Song, P. S. Mariano, *Tetrahedron* **2005**, *61*, 8888-8894.
[54] W. H. Pearson, W. Fang, *J. Org. Chem.* **2000**, *65*, 7158-7174.
[55] F. M. Cordero, B. B. Khairnar, P. Bonanno, A. Martinelli, A. Brandi, *Eur. J. Org. Chem.* **2013**, *22*, 4879-4886.

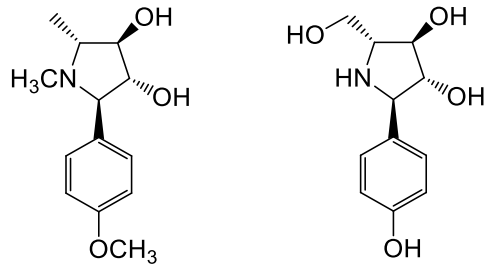


Figure 1.5 - Codonopsine and Radicamine.

Tylophorine, a phenantroindolizidine alkaloid, has been isolated from *Tylophora indica*, plant belonging to the family of *Asclepiadaceae*.[56] Leaves of this plant have been used, in India, for the treatment of asthma, bronchitis, rheumatism, and dysentery. Tylophorine and its derivatives possess anti-inflammatory and antitumoral properties, and they target many enzymes such as thymidylate synthase and dihydrofolate reductase.[57] A total synthesis of tylophorine has been reported by Comins and Morgan in 1991, starting from pyridine precursors via formation of N-acyldihydropyridons. These systems allowed to obtain a diaryl substituted indolizidine alkaloid, septicine, able to evolve in the final compound by oxidative coupling.[58] A general synthetic method for the synthesis of benzofused indolizidine alkaloids has been developed starting from similar precursors.[59]

[56] E. Gellert, *Alkaloids: Chemical and Biological Perspectives*, Pelletier SW. New York: Academic Press; 1987, 55-132.
[57] S. Saraswati, P. K. Kanaujia, S. Kumar, A. A, Alhaider, *Molecular Cancer* **2013**, *12*:82
[58] D. L. Comins, L. A. Morgan, *Tetrahedron Lett.* **1991**, *32*, 5919-5922.
[59] D. L. Comins, K. Higuchi, *Beilstein J. Org. Chem.* **2007**, *3*, No. 42.

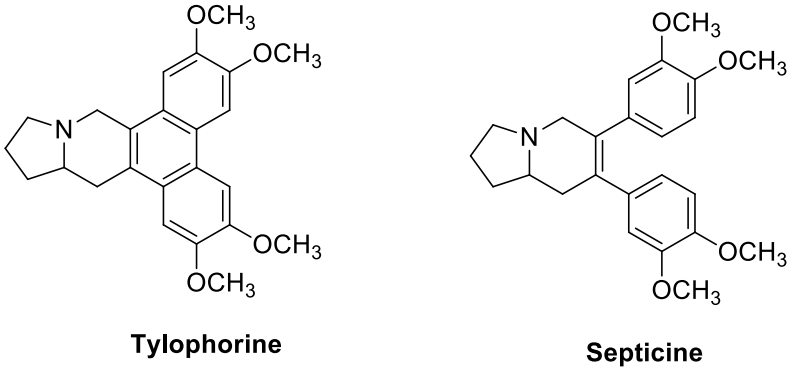


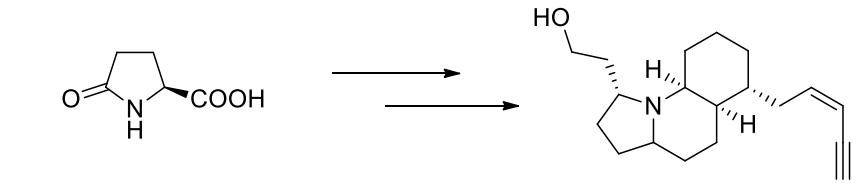
Figure 1.6 - Tylophorine and Septicine.

Gephyrotoxin is a natural alkaloid in which the indolizidine moiety is condensed with a cyclohexane ring instead of a benzene. This alkaloid is a naturally occurring product secreted by the Colombian tropical frog *Dendrobates histrionicus* (Figure 1.7).[60]

Figure 1.7 - Dendrobates histrionicus.

[60] M. Santarem, C. Vannucci-Bacqué, G. Lhommet, *J. Org. Chem.* **2008**, *73*, 6466-6469.

Gephyrotoxin is a member of the class of histrionicotoxins and has been isolated for the first time in 1977 by Daly and coworkers from the skin secretions of tropical frogs. This compound is a relatively non-toxic chemical. At first, it showed activity as slight muscarinic antagonist, but recent studies showed other interesting neurological activities. These new and interesting biological activities and the scarcity of both frogs and alkaloids in the frogs stimulated the search for new syntheses of such compounds. The first total synthesis of (+)-gephyrotoxin was reported by Kishi and coworkers in 1981. They prepared gephyrotoxin by L-pyroglutammic acid in 18 steps (Scheme 1.8).[61]



L-pyroglutamic Acid **(+)-Gephyrotoxin**

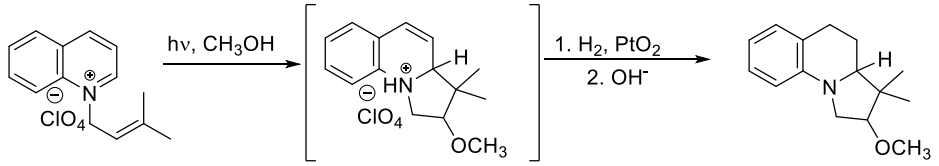
Scheme 1.8 - Total syntesis of (+)-gephyrotoxin by Kishi.

1.1.6 Synthesis of benzoindolidine derivatives

In 1983 Mariano and coauthors described the synthesis of a benzoindolizidine derivative by photochemical cyclization starting from *N*-prenylquinolinium perchlorate. Upon irradiation at λ > 310 nm of the methanolic solution of *N*-prenylquinolinium perchlorate, immediate hydrogenation on PtO_2 catalyst of the crude, neutralization, and chromatographic separation on silica gel, diastereomeric benzoindolizidines were obtained in 27% overall yield (Scheme 1.9). It is mandatory to execute the hydrogenation step before the neutralization of the crude photolysate to obtain observable quantities of

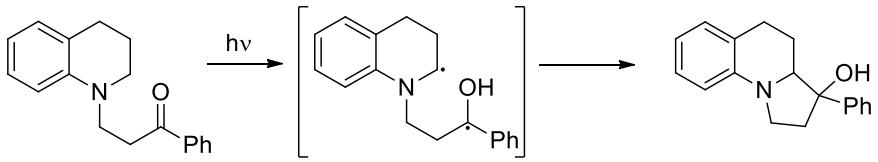
[61] R. Fujimoto, Y. Kishi, *Tetrahedron Lett. 1981*, *42*, 4197-4198.

benzoindolizidine compounds. This phenomenon probably resulted from the extreme lability of the 1,2-dihydroquinoline ring that would be produced after deprotonation. Another problem involves the formation of significant quantities of by-products, deriving from the cleavage of the C-N bond in the *N*-prenylquinolinium perchlorate.[62]



Scheme 1.9 - Photochemical synthesis of benzoindolizidines from N-prenylquinolinium perchlorate.

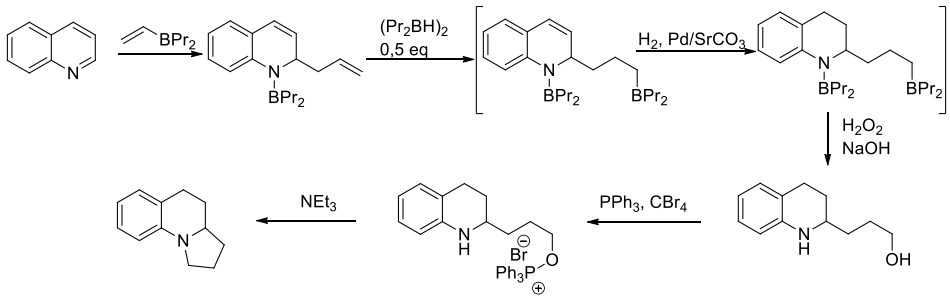
Hill and coworkers described the photochemical synthesis of 1-hydroxy-1-phenyl-benzo[*e*]indolizidine, starting from a suitable ketoamine (Scheme 1.10). The reaction involved a photochemical abstraction of hydrogen in α-position with respect to nitrogen, and the presence of a carbonyl group at opportune distance, allowoing the radical cyclization. The product was unfortunately unstable and difficult to purify.[63]



Scheme 1.10 - Photochemical formation of benzoindolizidines from ketoamines.

[62] U. C. Yoon, S. L. Quillen, P. S. Mariano, R. Swanson, J. L. Stavinoha, E. Bay, *J. Am. Chem. Soc.* **1983**, *105*, 1204-1218.
[63] S. A. Ashraf, J. Hill, F. Ikhlef, A. M'Hamedi, H. J. Zerizer, *Chem. Research (S)* **1993**, 266-267.

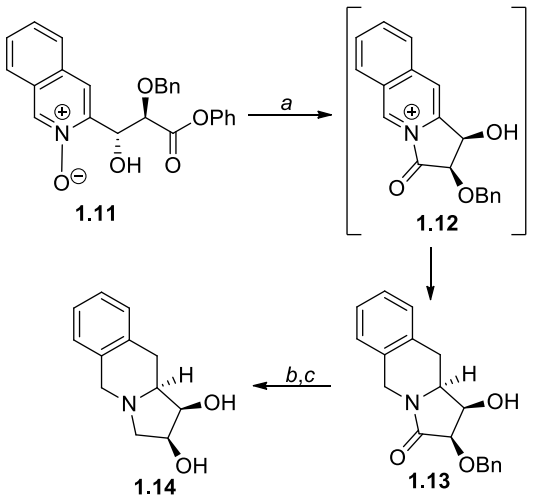
In 1996 Bubnov et al. reported the synthesis of a benzoindolizidine via reductive allylation of quinoline. The synthesis consisted in the addition of allyl-dipropylboron to positions 1 and 2 of the quinoline ring, followed by hydroboration with dipropylboron hydride. At this point the dihydroquinoline derivative was hydrogenated on $Pd/SrCO_3$ and then oxidized with hydrogen peroxide in NaOH, to yield an aminoalcohol. At the end, treatment with PPh_3 in CBr_4 and then with NEt_3, allowed to obtain benzoindolizidine in 55% yield (Scheme 1.11).[64]



Scheme 1.11 - Benzoindolizidine synthesis via reductive allylation of quinoline.

An analogous procedure to that applied by Zhou on pyridine derivatives[46] has been used by Jorgensen to synthesize the non-natural compound (1*R*,2*S*,10a*S*)-1,2-dihydroxy-1,2,3,5,10,10a-esahydrobenzo[*f*]indolizidine (**1.14**).[44] The synthesis consisted in the use of the optically active *N*-oxide **1.11**, obtained by Mukaiyama asymmetric aldol condensation of ketene silyl acetal with isoquinolinecarboxyaldehyde-*N*-oxide in the presence of chiral bisoxazoline Cu(II) complexes. The tricyclic system **1.13** obtained by *N*-oxide reduction, cyclization, and diastereoselective reduction of the intermediate pyridinium salt **1.12**, was converted into indolizidine derivative **1.14** (Scheme 1.12).

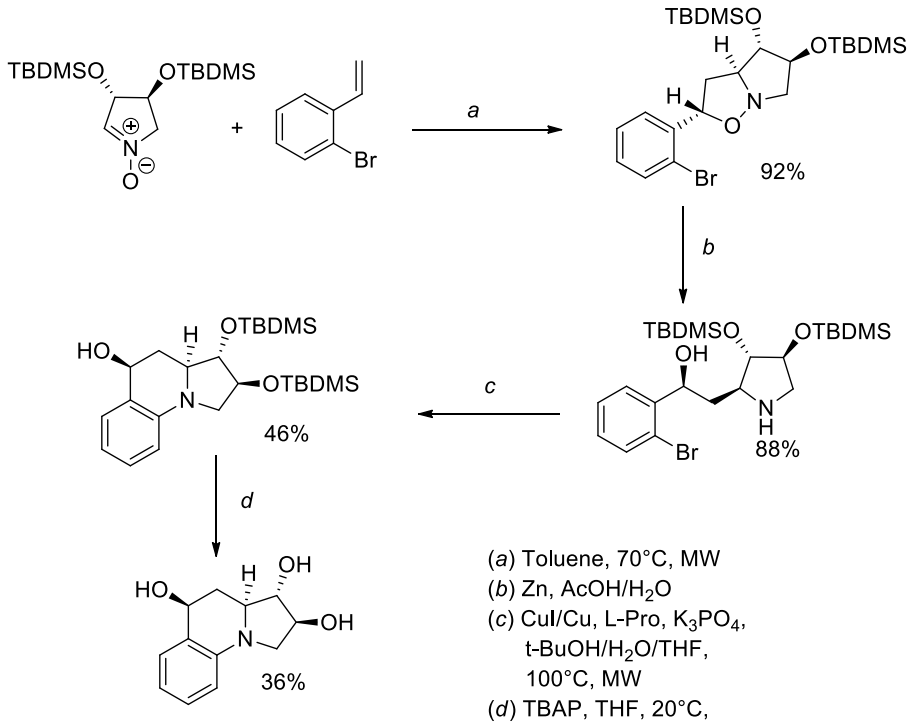
[64] Y. N. Bubnov, M. E. Gurskii, T. V. Potapova, *Russ. Chem. Bull.* **1996**, *45*, 2665-2667.



(*a*) 10% Pd/C, NH_4CO_2H (5 equiv); *i*PrOH, 20°C, 54%; (*b*) CF_3CO_2H (cat.), 10% Pd/C, MeOH, 20°C, 16h, 98%; (*c*) BH_3 SMe_2 (1.2 equiv), THF, 16h; then EtOH, 5h, 71%.

Scheme 1.12 - Jorgensen method for the synthesis of benzoindolizidine derivatives.

Recently, enantiopure 2,3,5-trihydroxybenzo[*e*]indolizidine was synthesized by 1,3-dipolar cycloaddition of a pyrroline *N*-oxide to 2-bromostyrene.[55] Reductive ring opening of the isoxazolidine intermediate and cyclization using Ullmann's conditions via copper-catalyzed aromatic amination of pyrroline derivatives led to the final product (Scheme 1.13).

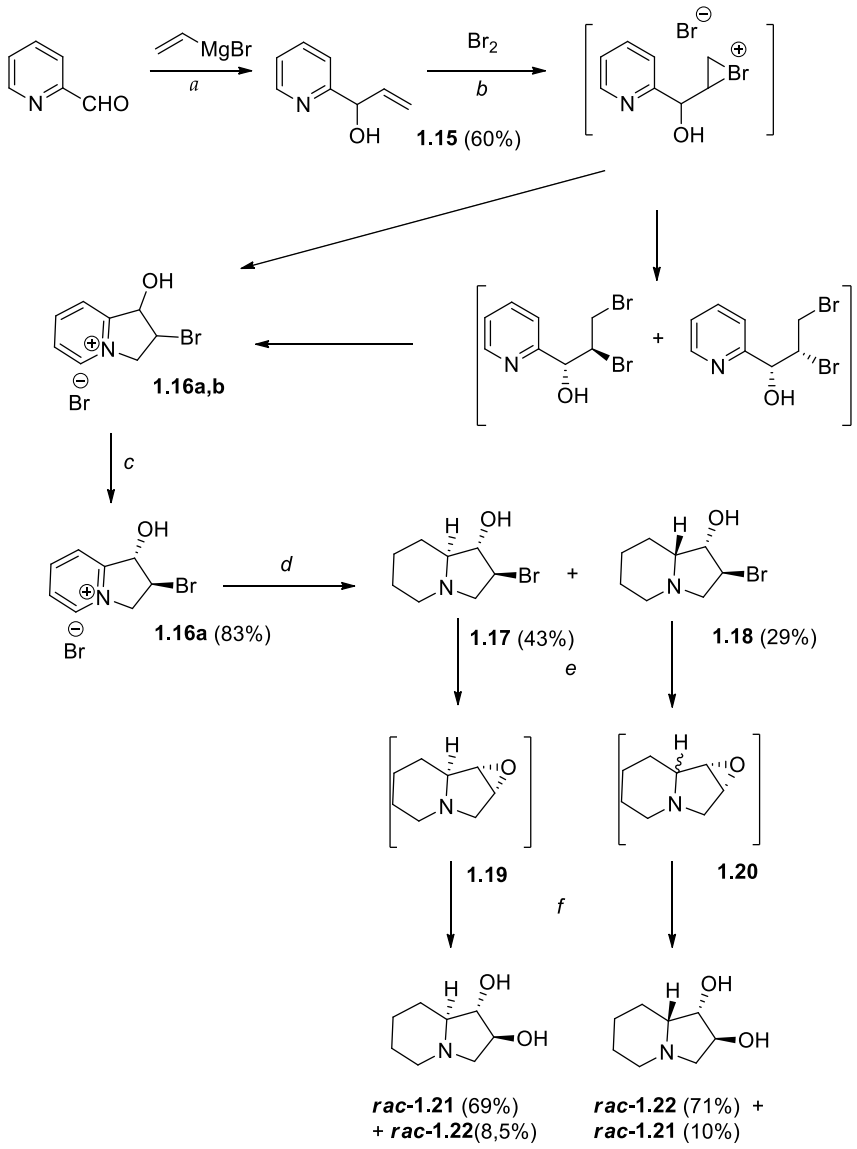


Scheme 1.13 - Synthesis of trihydroxybenzo[e]indolizidine.

***

Recently our laboratory developed a new synthesis of racemic lentiginosine starting from the commercially available pyridine-2-carboxaldehyde.[27] Treatment with vinyl-magnesium bromide afforded 1-(2-pyridil)-2-propen-1-ol (**1.15**), which reacted easily with Br_2 (or NBS) to give a couple of diastereomeric indolizinium salts (**1.16a,b**) via intramolecular nucleophilic substitution on the bromination intermediate. The *cis* diastereoisomer is less stable than the *trans* one (since it decomposes in reducing environment), but it isomerized quantitatively into the *trans* salt **1.16a** by heating at 80 °C in water for 5 days. The *trans* salt was fully reduced to give two diastereomeric bromohydrins (**1.17** and **1.18**, dr 1.5:1) resolved by chromatographic column. Bromohydrins was converted into the corresponding epoxides (**1.19** and **1.20**) by alkaline

treatment. A regio- and diastereoselective oxirane ring opening of these epoxides generated lentiginosine (**1.21**) and 8a-*epi*-lentiginosine (**1.22**) (Scheme 1.14).



(*a*) 1. Et_2O dry, 0°C, 1h, 2. H_2O; (*b*) CH_2Cl_2, 1h; (*c*) H_2O, 80°C, 5d; (*d*)H_2/PtO_2, EtOH, 6h; (*e*) KOH/H_2O, THF, 40 °C, 16h; (*f*) H_2SO_4 1M, 100°C, 7h.

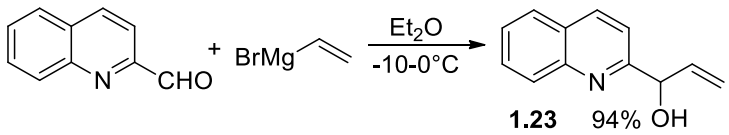
Scheme 1.14 -Synthesis of rac-lentiginosine from 1-(2-pyridyl)-2-propen-1-ol.

This synthesis was extremely attractive because *rac*-lentiginosine was obtained in 27% overall yield starting from alcohol **1.15** in only 4 steps (bromocyclization, reduction, nucleophilic substitution via elimination/addition). Moreover, the availability of opportunely functionalized pyridine precursors offers the possibility of a facile access to other variously functionalized dihydroxyindolizidine derivatives.

On the basis of these results and the literature data previously discussed, the present chapter will be oriented to the employment of useful derivatives of 2-pyridincarboxaldehyde to synthesize variously functionalized lentiginosines. In particular, according to the interest associated to the benzoindolizidine systems, it will be studied the use of benzofused aldehydes, such as 2-quinolincarboxaldehyde and 1-isoquinolinecarboxaldehyde.

1.2 Results

1.2.1 Synthesis of 1-(2-quinolyl)-2-propen-1-ol (**1.23**)



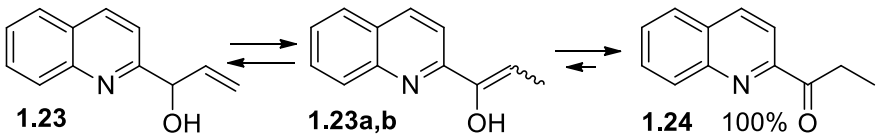
Scheme 1.15 – Synthesis of 1-(2-quinolyl)-2-propen-1-ol.

The planned synthetic strategy started with the addition of vinyl-magnesium bromide to the carbonyl group of 2-quinolinecarboxaldehyde (or 1-isoquinolinecarboxaldehyde, see later), to obtain the corresponding allyl alcohol, following Uenishi's procedure.[65]

To a solution of 2-quinolinecarboxaldehyde dissolved in dry diethyl ether, and cooled between 0 and -10 °C, a solution of vinyl-magnesium bromide (1.3 equiv) was added dropwise. After quenching and extraction, alcohol **1.23** was isolated in 94% yield.

However, ^{1}H NMR controls evidenced an easily isomerization of **1.23** into the enols **1.23a,b** that evolve quantitatively in the more stable compound, 1-(2-quinolyl)-1-propanone (**1.24**)[66] (Scheme 1.15). The isomerization is complete after 24h in $CDCl_3$ at room temperature, but it also works, even if with lower rate, at low temperature (at -40 °C the full conversion was observed after 7 days). For this reason, propenol **1.23** cannot be further purified and it has to be immediately used to avoid the transformation in the ketone **1.24**.

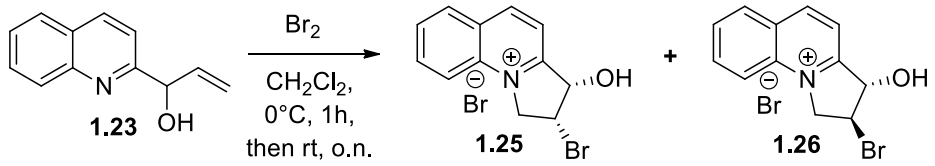
[65] J. Uenishi, T. Hiraoka, S. Hata, K. Nishiwaki, O. Yonemitsu, *J. Org. Chem.* **1998**, *63*, 2481-2487.
[66] Q. Tan, M. Hayashi, *Adv. Synth. Catal.* **2008**, *350*, 2639-2644.



Scheme 1.16 - Isomerization of 1-(2-quinolyl)-2-propen-1-ol.

This behavior was also previously observed for pyridylpropenol **1.15**, even if more slowly,[67] and can be associated to the weak acidity of the "picoline-type" hydrogen. Its mobility, also responsible for the formation of dihydroquinoline tautomers, appears now enhanced because of the lower aromaticity of quinoline with respect to pyridine.[29]

1.2.2 Bromination of 1-(2-quinolyl)-2-propen-1-ol (**1.23**)

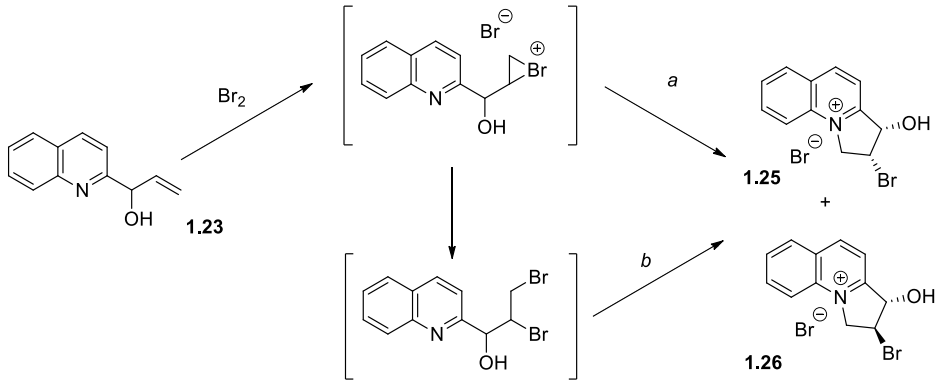


Scheme 1.17 - Bromination of 1-(2-quinolyl)-2-propen-1-ol.

The first step of the synthetic process was the study of the addition of bromine to the allylic double bond of **1.23**,[68] with the aim to obtain a bromocyclization to isolate tricyclic benzoindolizinium salts. The reaction was performed by dropwise addition of a solution of bromine (1 equiv) in CH_2Cl_2 in 1h to a solution of **1.23** in the same solvent, cooled at 0 °C. After the addition, the mixture was

[67] D. Giomi, M. Piacenti, R. Alfini, A. Brandi, *Tetrahedron* **2009**, *65*, 7048-7055.
[68] D. Giomi, J. Ceccarelli, A. Brandi, *ACS Omega* **2018**, *3*, 3183–3189.

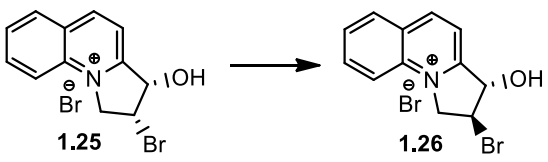
warmed to room temperature, and left overnight under stirring. Indolizinium salts **1.25** and **1.26** (1:2 – 1:3 ratio) were obtained filtrations in 97% overall yield. From a mechanistic point of view, the formation of benzo[*e*]indolizinium salts can be rationalized through an intramolecular nucleophilic attack of the quinoline nitrogen atom at the level of an intermediate bromonium ion (*route* **a**) or dibrominated derivatives (*route* **b**), as possible reaction intermediates (Scheme 1.17).



Scheme 1.18 - Bromination mechanism of 1-(2-quinolyl)-2-propen-1-ol.

Benzoindolizinium salts obtained in this way contained aromatic impurities that cannot be identified nor removed. It was not possible to perform chromatographic purification, and washing with solvent was not effective.

1.2.3 Isomerization of (1*SR*,2*RS*)-2-bromo-1-hydroxy-1*H*,2*H*,3*H*-benzo[*e*]indolizinium bromide



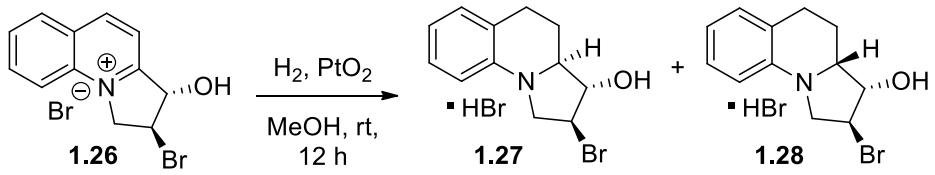
Scheme 1.19 - Isomerization of (1SR,2RS)-2-bromo-1-hydroxy-1H,2H,3H-benzo[e]indolizinium bromide.

^{1}H NMR analysis on the mixture of **1.25** and **1.26** in DMSO-d_6 at room temperature showed a total and immediate transformation of the *cis* salt into the corresponding *trans* diastereoisomer. This process is very easy, and the total isomerization could be performed by simple stirring in water at room temperature for 3 days.

From a mechanistic point of view, the *cis*/*trans* isomerization process can be rationalized through a S_N2 nucleophilic attack of the bromide ion on C-2 of the benzo[*e*]indolizinium salt **1.25**, with formation of the *trans* diastereoisomer, more stable than the *cis* diastereoisomer from a thermodynamic point of view. This process is easy in polar solvents, thanks to the dissociation of the ionic couple indolizinium/bromide, operated by the solvent.

The process is easily observed by ^{1}H NMR analysis because in the mixtures the signals of the diastereoisomeric salts in both aromatic and aliphatic zones are separated. After treatment with water, the signals related to the *cis* salt disappear, and it is possible to quantitatively recover only the *trans* diastereoisomer **1.26**.

1.2.4 Reduction of (1*SR*,2*SR*)-2-bromo-1-hydroxy-1*H*,2*H*,3*H* - benzo[*e*]indolizinium bromide (**1.26**)

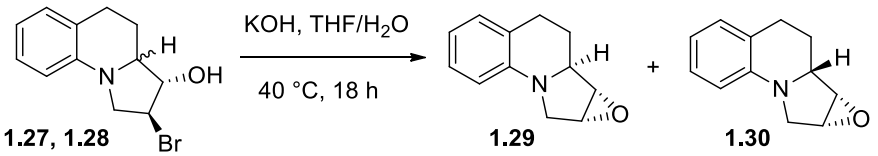


*Scheme 1.20 - Reduction of the benzo[e]indolizinium bromide **1.26**.*

With compound **1.26** in hand, its reactivity was explored in reduction processes to achieve benzo[*e*]indolizidine derivatives. Salt **1.26** was then subjected to reduction under different conditions. The use of $NaBH_4$ led to complex reaction

mixtures, whereas no reduction was observed for hydrogenation in the presence of Pd/C. Luckily, hydrogenation using monohydrate PtO_2 as the catalyst afforded the diastereomeric tetrahydroquinolines **1.27** and **1.28** as hydrobromides (Scheme 1.20). The salts **1.27** and **1.28** are completely stable but attempts to isolate the bromohydrins as free bases were unsuccessful.

1.2.5 Reaction of bromohydrins with KOH



Scheme 1.21 - Reaction of bromohydrions with KOH.

The mixture of **1.27** and **1.28** was then treated with aqueous KOH in tetrahydrofuran (THF) affording diastereomeric epoxides **1.29** and **1.30** (Scheme 1.21) isolated in 23 and 16% yield from **1.26** respectively. It is worthy to note that epoxides **1.29** and **1.30** were the first product purified after four steps, then involving an average of 80% yield for each step.

The *trans*-OH/Br relationship in **1.27** and **1.28** is certainly responsible for intramolecular S_N2 reactions leading to oxiranes **1.29** and **1.30**, respectively, via formal HBr elimination (Figure 1.8).

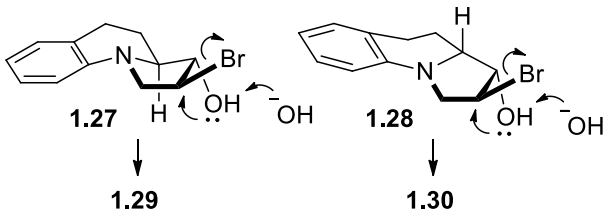
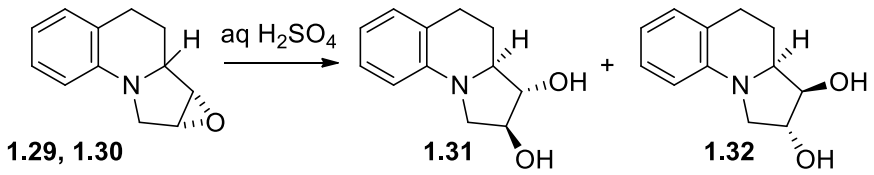


*Figure 1.8 - Intramolecular S_N2 reactions on bromohydrins **1.27** and **1.28**.*

With oxiranes **1.29** and **1.30** in hands, ring opening reactions with different nucleophiles were studied.

1.2.6 Nucleophilic attack of water on oxiranes **1.29** and **1.30**

*Table 1.1 - Nucleophilic attack of water on oxiranes **1.29** and **1.30**.*

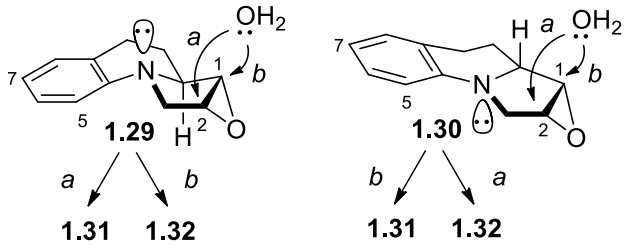


Entry	Oxirane	solvent	T (°C)	time	Conversion[a]	**1.31**:**1.32** ratio[b]
1	**1.29**	THF	100	24 h	100%	3:1
2	**1.29**	D_2O	60	15 d	100%	7:1
3	**1.29**	D_2O	80	72 h	100%	3.5:1
4	**1.29**	D_2O	100	24 h	100%	2.5:1
5	**1.30**	THF	100	24 h	100%	1:4
6	**1.30**	D_2O	40	24 h	100%	1:4
7	**1.30**	D_2O	60	24 h	100%	1:4
8	**1.30**	H_2O	40	60 h	100%	1:3.5

[a] Determined via ^1H NMR; [b] Isolated yields.

When oxirane **1.29** was treated with aqueous H_2SO_4 in THF at 100 °C in a screw-cap tube for 24 h, a 3:1 mixture of diols **1.31** and **1.32** was recovered in 35% yield (Table 1.1, entry 1). The formation of the reaction products can be

rationalized trough a totally *anti* diastereoselective and highly C-2 regioselective nucleophilic attack of water on epoxide **1.29** activated by protonation at oxygen and/or nitrogen (Scheme 1.22).



*Scheme 1.22 - Formation of diols **1.31** and **1.32** from oxiranes **1.29** and **1.30**.*

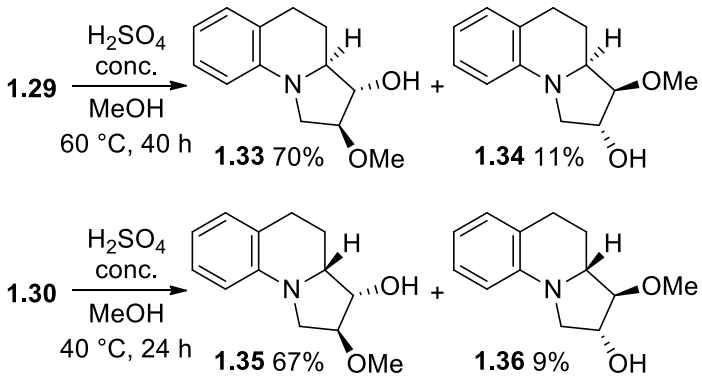
The separation of diols was unsuccessful. The same reaction was also performed in D_2O under different conditions to evaluate the selectivity of the process via ^1H NMR analyses. The formation of diol **1.31** indeed improved at 60 °C, but the reaction times were too long (Table 1.1, entry 2), whereas operating at 80 or 100 °C the transformation was faster, but the selectivity decreased (Table 1.1, entries 3 and 4).

An analogous study was performed on oxirane **1.30**. Operating in THF at 100 °C diols **1.31** and **1.32** were isolated in 64% yield as a 1:4 mixture (Table 1.1, entry 5). ^1H NMR analyses of reactions performed in D_2O showed a higher reactivity for **1.30**, compared to **1.29**, that underwent a total conversion even at 40 or 60 °C (Table 1.1, entries 6 and 7). Operating in water at 40 °C a 1:3.5 mixture of diols was recovered in 72% yield (Table 1.1, entry 8).

1.2.7 Nucleophilic attack of methanol on oxiranes **1.29** and **1.30**

Reactions of oxiranes **1.29** and **1.30** in dry MeOH, in the presence of H_2SO_4 conc., provided to recover the methoxy derivatives **1.33-1.36** in 70 and 11% yields and

67 and 9% yields, respectively (Scheme 1.23). In this case the selectivity was higher, and the major isomer derives again from a totally *anti* diastereoselective and highly C-2 regioselective nucleophilic attack of methanol on activated epoxides **1.29** and **1.30**. Small amounts of diols **1.31** and **1.32** were also recovered.



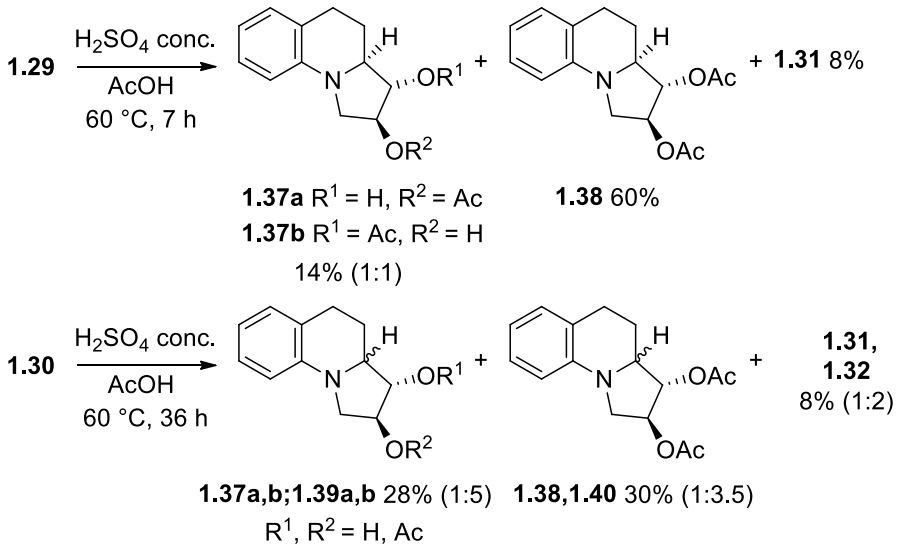
*Scheme 1.23 - Formation of methoxy derivatives **1.33-1.36** from oxiranes **1.29** and **1.30**.*

1.2.8 Nucleophilic attack of acetic acid on oxiranes **1.29** and **1.30**

Oxiranes ring opening was then studied in acetic acid as solvent. When heated at 60 °C for three days, compound **1.29** afforded only traces of monoacetates, while total decomposition of the starting material was observed for compound **1.29** after 48 and 24 hours at 80 and 100 °C, respectively, and even for epoxide **1.30** when heated at 60 °C for 4 days.

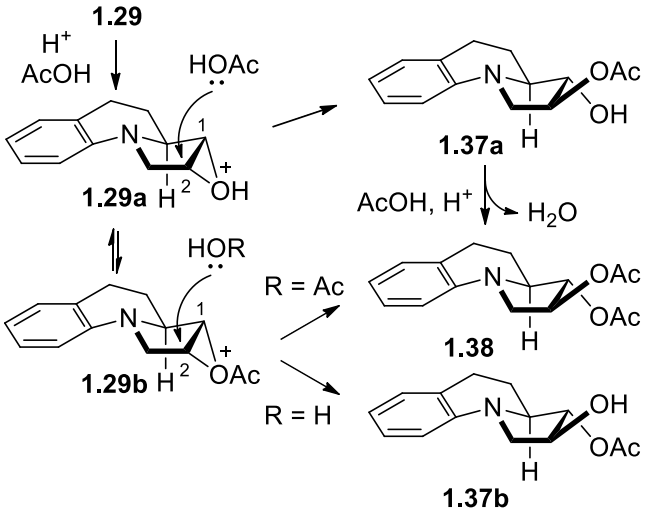
The results were different for the reaction in AcOH in the presence of concentrated H_2SO_4. Heating compound **1.29** for 7 hours in glacial AcOH at 60 °C allowed to isolate the diacetate **1.38** in 60% yield, along with minor amounts of regioisomeric monoacetates **1.37a,b** (1:1 ratio, 14%) and diol **1.31** (8%) (Scheme 1.25).

In contrast, epoxide **1.30**, under the same conditions for 36 hours, gave a complex reaction mixture of isomeric mono-, diacetates, and diols (^{1}H NMR). Careful chromatographic separation allowed to recover a 1:3.5 mixture of diacetates **1.38** and **1.40** in 30% yield, along with monoacetates **1.37a,b** and **1.39a,b** (1:5 ratio, 28%) and diols **1.31** and **1.32** (1:2 ratio, 8%) (Scheme 1.24).



*Scheme 1.24 - Ring opening of oxirane **1.29** and **1.30** with AcOH and H_2SO_4.*

It is worth to note that in the case of oxirane **1.29** all the reaction products show the same relative stereochemistry on the three stereogenic centres as the fruit of totally *anti* diastereoselective and totally C-2 regioselective nucleophilic attacks on the epoxide ring. This result can be rationalized considering different nucleophilic attacks on suitably activated intermediates (Scheme 1.25).

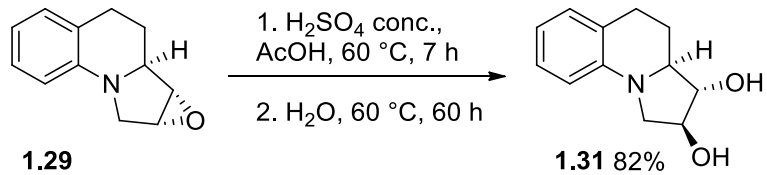


*Scheme 1.25 - Ring opening of oxirane **1.29** with AcOH: mechanistic rational.*

Anti diastereoselective attack of AcOH on C-2 carbon of protonated oxirane **1.29a** affords monoacetate **1.37a**, which was easily converted into the diacetate **1.38** by esterification. Compound **1.38** can also arise from acetylated epoxide **1.29b**, via nucleophilic attack of AcOH at position 2, while nucleophilic attack of H_2O can give the monoacetate **1.37b**. Hydrolysis of all the reaction products can produce diol **1.31**.

The same mechanism can rationalize the results observed for epoxide **1.30**, invoking totally *anti* diastereoselective attacks but, in this case, only preferential regioselective attacks at position 2.

On the basis of these results, by running for compound **1.29** a one-pot reaction including oxirane ring opening in $AcOH/H_2SO_4$, followed by hydrolysis in the same conditions, allowed to isolate *rac*-benzo[*e*]lentiginosine **8** as the sole reaction product in 82% yield (Scheme 1.26).



*Scheme 1.26 - One-pot formation of rac-benzo[e]lentiginosine **1.31** from oxirane **1.29**.*

Concerning diol **1.31**, the relative stereochemistry of the stereogenic centres was unambiguously confirmed by NOESY-1D experiments recorded in $CDCl_3$ evidencing dipolar couplings for proton H-10a at δ 3.32 with H-2 (pseudo quartet at 4.37 ppm) and H-3α (doublet of doublets at 3.68 ppm) (Figure 1.9).

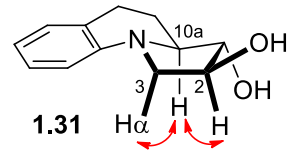


*Figure 1.9 - Dipolar couplings for compound **1.31** (from NOESY-1D experiments).*

As previously evidenced, oxiranes ring opening in acidic water or MeOH show a higher reactivity for **1.30** compared to **1.29,** probably due to a more difficult *anti* nucleophilic attack, in the latter, for the presence of the nitrogen lone pair (see Scheme 1.23 diols). On the other hand, compound **1.29** showed a higher reactivity (with total regioselectivity) in AcOH, after addition of H_2SO_4 (complete transformation at 60 °C in 7 hours for **1.29** and in 36 hours for **1.30**). This different behaviour could be rationalized in term of acid-base interactions between AcOH and the ring nitrogen. This coordination could favor the *anti* nucleophilic attack only in oxirane **1.29** because in compound **1.30** the nitrogen lone pair is on the same side with respect to the oxirane bridge (Figure 1.10). Likely for **1.29**, the same coordination is also able to direct the nucleophilic attack of AcOH exclusively at position 2.

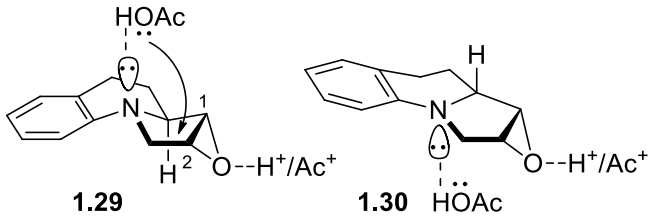
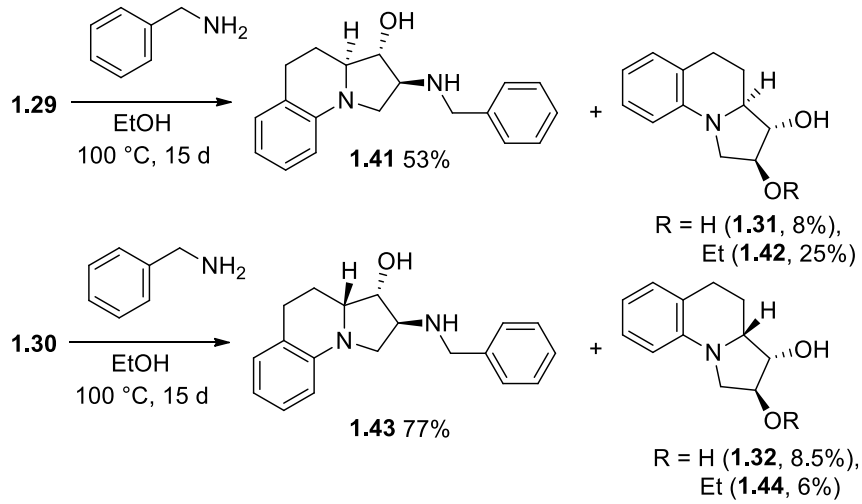


*Figure 1.10 - Ring openings of **1.29** and **1.30** in AcOH/H_2SO_4.*

1.2.9 Nucleophilic attack of benzylamine on oxiranes **1.29** and **1.30**



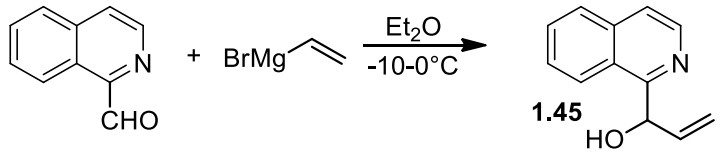
*Scheme 1.27 - Ring opening of oxirane **1.29** and **1.30** with benzylamine.*

A nitrogen nucleophile, such as benzylamine, was also tried to achieve the ring opening of epoxides **1.29** and **1.30** (Scheme 1.27). For both epoxides the major product resulted from nucleophilic attack of benzylamine on C-2 carbon, and compounds **1.41** and **1.43** were isolated in 53 and 77% yields, respectively. As by-products, the diols (**1.31** and **1.32** recovered in 8% and 8.5% yields, respectively) and the ethoxy derivatives (**1.42** in 25% and **1.44** in 6% yields) resulting from the attack on C-2 were isolated.

This result shows the possibility of extending the ring opening to different nucleophiles in order to access to variously functionalized benzo[*e*]indolizidines.

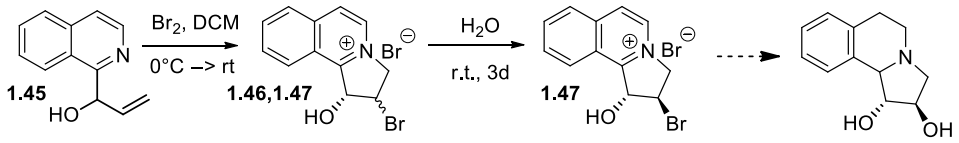
1.2.10 Synthesis of 1-(1-isoquinolyl)-2-propen-1-ol (**1.45**)

In order to extend this methodology, this synthetic pathway was applied to 1-methylisoquinoline, that was oxidized to the corresponding aldehyde[69] and treated with vinyl magnesium bromide to synthesize 1-(1-isoquinolyl)-2-propen-1-ol.[70] Alcohol **1.45** was isolated in 82% yield and used as starting material in the previously reported synthetic route (Scheme 1.28).



*Scheme 1.28 - Synthesis of 1-(1-isoquinolyl)-2-propen-1-ol (**1.45**).*

1.2.11 Synthesis of (1*RS*,2*RS*)-2-bromo-1-hydroxy-2,3-dihydro-benzo[*g*]indolizinium bromide (**1.47**)

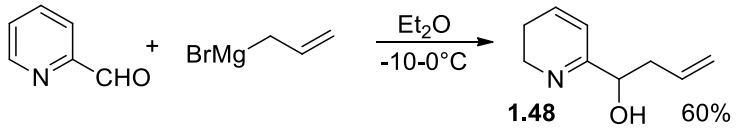


*Scheme 1.29 - Synthesis of the trans benzo[g]indolizinium bromide **1.47**.*

[69] M. Setoguchi, S. Iimura, Y. Sugimoto, Y. Yoneda, J. Chiba, T. Watanabe, F. Muro, Y. Iigo, G. Takayama, M. Yokoyama, T. Taira, M. Aonuma, T. Takashi, A. Nakayama, N. Machinaga, *Bioorg. Med. Chem.* **2012**, *20*, 1201-1212.
[70] R. Unno, H. Michishita, H. Inagaki, Y. Suzuki, Y. Baba, T. Jomori, M. Moku, T. Nishikawa, M. Isobe, *Bioorg. Med. Chem.* **1997**, *5*, 903-919.

Following the procedure previously described for alcohol **1.23**, involving bromination and isomerization, *trans* benzo[*g*]indolizinium bromide **1.47** was synthesized and isolated in 90% yield (Scheme 1.29). Also in this case it is impossible to purify the salt that will be submitted to the following reduction step. The study needs to be completed to verify the possibility to access variously functionalized benzo[*g*]indolizidines.

1.2.12 Synthesis of 1-(2-pyridyl)-3-buten-1-ol (**1.48**)



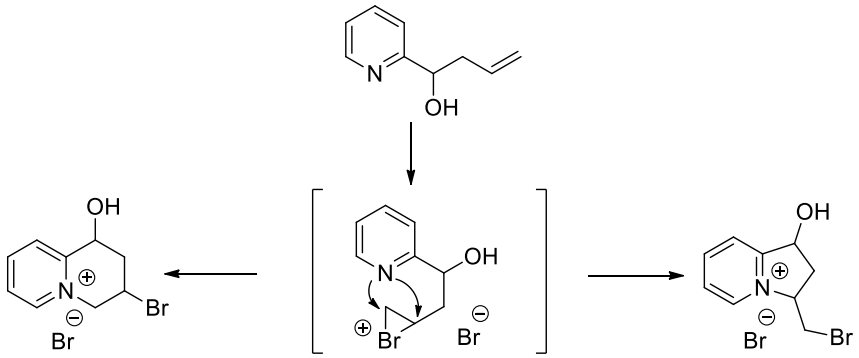
*Scheme 1.30 - Synthesis of 1-(2-pyridyl)-3-buten-1-ol (**1.48**).*

In order to further extend the methodology, it was explored the possibility to modify the olefin moiety, by reaction of 2-pyridincarboxaldehyde with allyl-magnesium bromide[71] in the same condition reported for **1.23**. After chromatographic resolution, pyridylbutenol **1.48** was isolated in 60% yield (Scheme 1.30).

1.2.13 Bromination of 1-(2-pyridyl)-3-buten-1-ol (**1.48**)

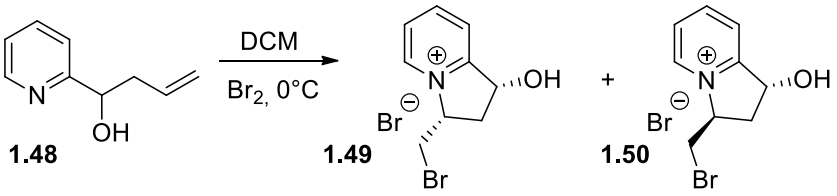
Performing the bromocyclization on **1.48**, in the same conditions reported for **1.23**, there was the possibility of two kinds of ring closing on the bromonium intermediate leading to 5-membered or 6-membered rings (Scheme 1.31).

[71] A.-T. Hou, Y.-J. Liu, X.-Q. Hao, J.-F. Gong, M.-P. Song, *J. Organomet. Chem.* **2011**, *696*, 2857-2862.



Scheme 1.31 - Possible bromocyclizations.

In this specific case, the reaction was totally chemoselective, and led selectively to the 5-membered ring closure, allowing to obtain a couple of diastereomeric indolizinium bromides **1.49** and **1.50**, that cannot be easily isomerized (Scheme 1.32). In this case the nucleophilic substitution of bromide ion (responsible for *cis*/*trans* isomerization) is difficult due to the absence in the five-membered ring of a good leaving group.

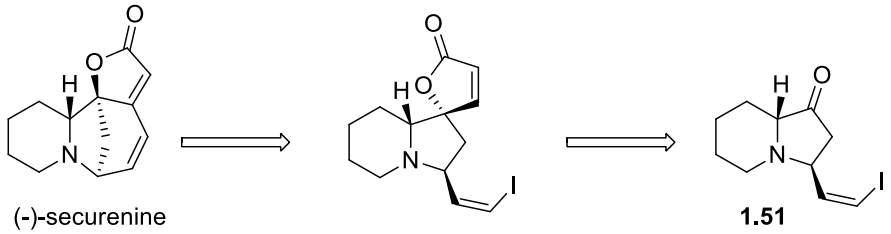


*Scheme 1.32 - Bromination of 1-(2-pyridyl)-3-buten-1-ol (**1.48**).*

This approach should be more deeply investigated to access differently substituted indolizidines. This study appears also promising for the synthesis of precursors of (–)-securenine, an alkaloid first isolated in 1956 by Russian scientists from the leaves of the *Securinega suffruticosa* plant.[72] (–)-Securenine exhibits a range of biological activities, and its actual clinical use, albeit limited,

[72] V. I. Murav'eva, I. Ban'kovskii, *Dokl. Akad. Novk. SSSR* **1956**, *110*, 998-1000.

concerns the treatment of serious diseases, such as amyotrophic lateral sclerosis (ALS) and poliomyelitis. A possible retrosynthetic analysis is shown in Scheme 1.33,[73] in which the precursor **1.51** may be obtained from **1.50** in few synthetic steps.



Scheme 1.33 - Retrosynthetic analysis for the access to (-)-securenine.

[73] B. Dhudshia, B. F. T. Cooper, C. L. B. Macdonald, A. N. Thadani, *Chem. Commun.* **2009**, 463-465.

1.3 Conclusions

In conclusion, these results clearly show the possibility of a general application of this new methodology exploiting pyridine-2-carboxaldehyde derivatives as commercially available starting materials for the synthesis of pyridyl-2-propen-1-ol systems converted into variously functionalized indolizidines through a four-step approach involving bromination/reduction/nucleophilic substitution via elimination/addition. In particular, the use of 2-quinolinecarboxaldehyde allowed the synthesis of polynuclear tetrahydroquinolines well recognized as privileged structures with many different applications. For instance, the tricyclic moiety of benzo[*e*]indolizidine is present in naturally occurring alkaloids, such as incargranine B isolated from *Incarvillea mairei* var. *grandiflora*, a member of the genus *Incarvillea* from which several derivatives with strong antinociceptive activity have been isolated (Figure 1.11).[74] Moreover, synthetic tetracyclic derivatives of type **1.52** showed good in vitro inhibiting activity towards human lung cancer cells, human hepatoma cells, acute myeloid leukemia cells (Figure 1.11).[75]

[74] (a) Y.-H. Shen, Y.-Q. Su, J.-M. Tian, S. Lin, H.-L. Li, J. Tang, W.-D. Zhang, *Helv. Chim. Acta* **2010**, *93*, 2393-2396; (b) L. Liu, C. Wang, Q. Liu, Y. Kong, W. Chang, J. Li, *Eur. J. Org. Chem.* **2016**, 3684-3690; (c) X.-L. Yu, L. Kuang, S. Chen, X.-L. Zhu, Z.-L. Li, B. Tan, X.-Y. Liu, *ACS Catal.* **2016**, *6*, 6182-6190.

[75] Wu, Y.; Hai, L.; Wu, J. B.; Pei, S. C.; Li, X. C. *cis*-Heterocycle fused 1,2,3,4-tetrahydroquinoline derivative and its application. Faming Zhuanli Shenqing CN 102887905, A, 2013.

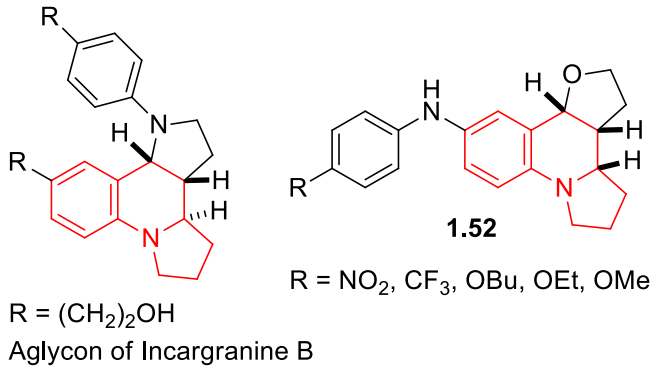


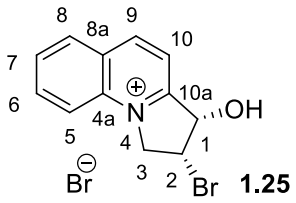
Figure 1.11 - Benzo[e]indolizidine derivatives.

1.4 Experimental section

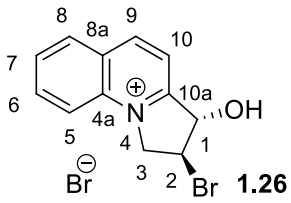
1.4.1 General

Melting points were taken on a Stuart Scientific SIMP3 apparatus and are uncorrected. Silica gel plates (Merck F_{254}) and silica gel 60 (Merck, 230-400 mesh) were used for TLC and flash chromatography (FC), respectively; petroleum ether (PE) employed for chromatography refers to the fraction of bp 40-70 °C. IR spectra were recorded with a Shimadzu FT-IR 84 00S spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded with Varian Mercuryplus 400 and Varian Inova instruments, 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.

1.4.2 (1*SR*,2*RS*)-2-Bromo-1-hydroxy-benzo[*e*]indolizinium bromide (**1.25**) and (1*SR*,2*SR*)-2-Bromo-1-hydroxy-benzo[*e*]indolizinium bromide (**1.26**)



1.25



1.26

In a typical procedure 2-quinolinecarboxaldehyde (1.000 g, 6.36 mmol) was dissolved in dry diethyl ether (80 mL) and 1.0 M solution of vinyl-magnesium bromide in THF (8.26 mmol, 8.26 mL) was added at 0 °C. After workup 1-(2-quinolyl)-2-propen-1-ol (**1.23**) (1.108 g, 5.98 mmol, 94% yield) was recovered as

an orange oil that was immediately dissolved in CH_2Cl_2 (24 mL) and a solution of bromine (0.956 g, 0.306 mL, 5.98 mmol) in the same solvent (12 mL) was added dropwise (ca. 1 hour), keeping the reaction vessel at 0°C under magnetic stirring. At the end of the addition, the reaction mixture was stirred for 30 minutes at 0°C and then left at room temperature overnight. An approximately 3:1 mixture (^{1}H NMR) of salts **1.25** and **1.26** (1.754 g, 85% with respect to **1**) as a dark green solid was recovered by filtration. ^{1}H NMR (CD_3OD): δ [9.27 (d, *J* = 8.8 Hz, 1H, H-9)], 9.18 (d, *J* = 8.7 Hz, 1H, H-9), 8.54 (d, *J* = 8.1 Hz, 1H, H-5), [8.46 (d, *J* = 7.9 Hz, 1H, H-8)], 8.40-8.35 (m, 1H, H-5 of **1.26** + 1H, H-8 of **1.25**), [8.31 (m, 1H, H-6)], 8.25-8.16 (m, 2H, H-6 and H-10 of **1.25** + 1H, H-10 of **1.26**), [8.08 (m, 1H, H-7)], 8.01 (m, 1H, H-7), 5.96 (d, *J* = 2.0 Hz, 1H, H-1), [5.87 (d, *J* = 6.8 Hz, 1H, H-1)], [5.80 (dd, *J* = 13.1 and 7.7 Hz, 1H, H-3)], [5.23 (dd, *J* = 13.0 and 7.8 Hz, 1H, H-3)], 4.96 (ddd, *J* = 10.2, 5.1 and 2.0 Hz, 1H, H-2), [4.81 (m, 1H, H-2)], 4.16-4.05 (m, 2H, 3-CH_2) ppm. ^{13}C NMR (CD_3OD): δ [162.1 (s, C-10a)], 162.0 (s, C-10a), [149.7 (d, C-9)], 148.7 (d, C-9), 138.95 (s, C-4a), [137.8 (s, C-4a)], [137.5 (d, C-6)], 136.6 (d, C-6), [131.6 (d, C-7 and C-8)], 131.45 (d, C-7), [131.0 (s, C-8a)], 130.6 (d, C-8), 129.95 (s, C-8a), 121.6 (d, C-5), 120.85 (d, C-10), [119.8 (d, C-5 and C-10)], [82.4 (d, C-1)], 70.5 (d, C-1), [61.5 (t, C-3)], 55.6 (d, C-2), [46.0 (d, C-2)], 32.5 (t, C-3) ppm.

Further filtrations allowed to recover a second crop of salts **1.25** and **1.26** (0.248 g, 12% with respect to **1.23**).

The spectra of diastereomeric mixture has been recorded in CD_3OD because in DMSO-d_6 the *cis* salt immediately isomerizes into the trans one.

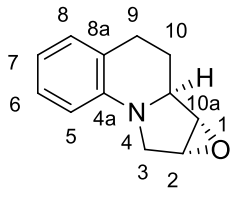
The data reported in square brackets refer to the *trans* indolizinium bromide **1.26**.

1.4.3 (1*SR*,2*SR*)-2-Bromo-1-hydroxy-benzo[*e*]indolizinium bromide (**1.26**)

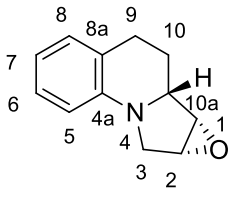
The mixture of salts **1.25** and **1.26** (0.690 g, 2.00 mmol) was dissolved in water (100 mL) and stirred at room temperature for 3 days, affording compound **1.26** as a black solid (0.690 g, 100%): mp > 370 °C. IR, ν_{max} (KBr) 3134, 3076, 2990, 2966, 1620, 1596, 1527, 1055, 847, 779 cm^{-1}. ^1H NMR (DMSO-d_6): δ 9.34 (d, J = 8.5 Hz, 1H, H-9), 8.52 (d, J = 7.4 Hz, 1H, H-8), 8.44 (d, J = 8.5 Hz, 1H, H-5), 8.30 (m, 1H, H-6), 8.22 (d, J = 8.6 Hz, 1H, H-10), 8.06 (pseudo t, J = 7.6 Hz, 1H, H-7), 5.82 (d, J = 7.4 Hz, 1H, H-1), 5.76 (dd, J = 12.9 and 7.8 Hz, 1H, H-3), 5.14 (dd, J = 12.7 and 8.4 Hz, 1H, H-3), 4.83 (pseudo q, J = 7.8 Hz, 1H, H-2) ppm. ^{13}C NMR (DMSO-d_6): δ 160.7 (s, C-10a), 147.9 (d, C-9), 135.7 (d, C-6), 135.6 (s, C-4a), 130.1 (d, C-8), 130.0 (d, C-7), 128.6 (s, C-8a), 118.9 (d, C-5), 118.6 (d, C-10), 80.0 (d, C-1), 59.45 (t, C-3), 45.6 (d, C-2) ppm.

Anal. Calcd for $C_{12}H_{11}Br_2NO$: C, 41.77; H, 3.21; N, 4.06. Found: C, 42.22; H, 2.95; N, 4.01.

1.4.4 (1*SR*,2*RS*,10a*SR*)-benzo[*e*]oxireno[*a*]indolizine (**1.29**) and (1*SR*,2*RS*,10a*RS*)-benzo[*e*]oxireno[*a*]indolizine (**1.30**)



1.29



1.30

Compound **1.26** (0.345 g, 1.0 mmol) was added to a suspension of $PtO_2 \cdot H_2O$ (0.023 g, 0.1 mmol) in MeOH (16 mL) and the mixture was stirred at room temperature under atmospheric pressure of hydrogen for 12 hours. The solution was filtered through a celite pad, washed with MeOH and CH_2Cl_2, and

evaporated to dryness affording a mixture of **1.27** and **1.28** as the major compounds that was dissolved in THF (12 mL) and water (4 mL), added with solid KOH (0.168 g, 3.0 mmol), and heated at 40°C for 24 hours. The reaction crude was extracted with ethyl acetate (4x10 mL) and the resulting organic phase was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. Chromatographic resolution with CH_2Cl_2 as eluent allowed to isolate compound **1.30** (R_f = 0.59, 0.030 g, 16%): mp 58-59 °C (ivory crystals from pentane/Et_2O). IR, ν_{max} (KBr) 3040, 2928, 2892, 2841, 1603, 1503, 1459 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.05 (t, *J* = 7.7 Hz, 1H, H-6), 6.97 (d, *J* = 7.4 Hz, 1H, H-8), 6.58 (td, *J* = 7.5, 1.0 Hz, 1H, H-7), 6.34 (d, *J* = 8.1 Hz, 1H, H-5), 3.74 (dd, *J* = 3.2, 1.3 Hz, 1H, H-2), 3.72 (ddd, *J* = 3.2, 1.2, 0.3 Hz, 1H, H-1), 3.66 (ddd, *J* = 11.3, 2.9, 1.2 Hz, 1H, H-10a), 3.63 (d, *J* = 11.5 Hz, 1H, H-3a), 3.34 (dd, *J* = 11.5, 1.2 Hz, 1H, H-3b), 2.94-2.78 (m, 2H, H-9), 2.10 (ddt, *J* = 12.5, 5.3, 2.7 Hz, 1H, H-10), 1.77 (m, 1H, H-10) ppm. ^{13}C NMR ($CDCl_3$): δ 144.3 (s, C-4a), 128.6 (d, C-8), 127.1 (d, C-6), 120.5 (s, C-8a), 115.6 (d, C-7), 110.0 (d, C-5), 58.5 (d, C-1), 57.2 (d, C-10a), 54.5 (d, C-2), 48.9 (t, C-3), 27.3 (t, C-9), 21.9 (t, C-10) ppm.

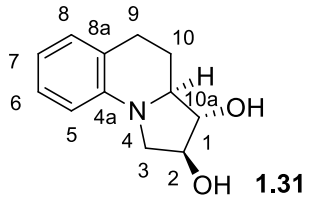
HRMS(ESI): m/z calcd for $C_{12}H_{14}NO$ $[MH]^+$ 188.1070, found 188.1074.

The slowest moving fraction afforded oxirane **1.29** (R_f = 0.27, 0.044 g, 23%) that was crystallized from pentane/Et_2O in ivory flakes: mp 63-64 °C. IR, ν_{max} (KBr) 3034, 2929, 2847, 1602, 1494, 1455 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.08 (t, *J* = 7.6 Hz, 1H, H-6), 7.00 (d, *J* = 7.4 Hz, 1H, H-8), 6.67 (td, *J* = 7.4, 0.8 Hz, 1H, H-7), 6.60 (d, *J* = 8.1 Hz, 1H, H-5), 3.96 (d, *J* = 11.4 Hz, 1H, H-3a), 3.85 (dd, *J* = 2.9, 2.0 Hz, 1H, H-2), 3.71 (d, *J* = 3.1 Hz, 1H, H-1), 3.67 (dd, *J* = 12.6, 2.4 Hz, 1H, H-10a), 3.26 (dd, *J* = 11.3, 1.8 Hz, 1H, H-3b), 2.93-2.78 (m, 2H, H-9), 1.97 (ddt, *J* = 12.2, 5.0, 2.5 Hz, 1H, H-10), 1.39 (qd, *J* = 12.4, 5.5 Hz, 1H, H-10) ppm. ^{13}C NMR ($CDCl_3$): δ 145.2 (s, C-4a), 129.1 (d, C-8), 127.0 (d, C-6), 122.2 (s, C-8a), 117.4 (d, C-7), 114.8 (d, C-5), 60.3 (d, C-1), 58.8 (d, C-10a), 56.7 (d, C-2), 52.1 (t, C-3), 27.9 (t, C-9), 21.9 (t, C-10) ppm. HRMS(ESI): m/z calcd for $C_{12}H_{14}NO$ $[MH]^+$ 188.1070, found 188.1069.

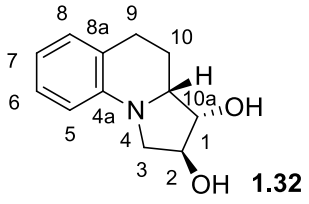
1.4.5 Ring openings of oxiranes **1.29** and **1.30** with oxygen nucleophiles. General procedure.

A solution of oxirane (0.094 g, 0.5 mmol) in the reported solvent (10 mL) was added with H_2SO_4 and heated at the reported temperature for the reported time in a screw-cap tube (Pyrex N. 22) under magnetic stirring. The resulting mixture was made basic by addition of NH_4OH 30% (ca. 0.5 mL), evaporated to dryness under reduced pressure and resolved by flash chromatography.

*1.4.5.1 (1SR,2SR,10aSR)-1,2-dihydroxy-benzo[e]indolizidine (**1.31**) and (1RS,2RS,10aSR)-1,2-dihydroxy-benzo[e]indolizidine (**1.32**)*



1.31



1.32

A) Oxirane **1.29** and aqueous H_2SO_4 (1M, 1.25 mL, 1.25 mmol) were heated in THF at 100 °C for 24 hours. Chromatographic resolution (toluene/MeOH/AcOH 7:2:0.15 v/v) allowed to isolate a 3:1 mixture of **1.31** and **1.32** (R_f = 0.42, 0.036 g, 35%).

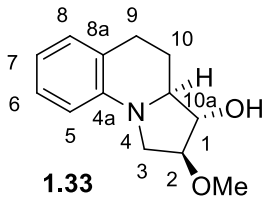
B) Operating as above with oxirane **1.30** a 1:4 mixture of **1.31** and **1.32** (R_f = 0.42, 0.066 g, 64%) was isolated.

C) Operating in water as solvent, a 1:3.5 mixture of **1.31** and **1.32** (R_f = 0.42, 0.074 g, 72%) was recovered by heating oxirane **1.30** at 40 °C for 60 hours. A small amount of pure diol **1.32** was isolated by flash chromatography as a sticky solid. IR, ν_{max} (KBr) 3386, 3043, 2931, 2849, 1604, 1505 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.07 (t, *J* = 7.4 Hz, 1H, H-6), 7.00 (d, *J* = 7.4 Hz, 1H, H-8), 6.60 (t, *J* = 7.4 Hz, 1H, H-7), 6.41 (d, *J* = 7.8 Hz, 1H, H-5), 4.33 (d, *J* = 4.8 Hz, 1H, H-2), 4.05 (d, *J* = 3.0 Hz,

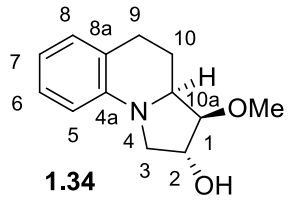
1H, H-1), 3.79 (dt, *J* = 11.8 and 3.3 Hz, 1H, H-10a), 3.65 (dd, *J* = 11.1 and 4.8 Hz, 1H, H-3α), 3.18 (d, *J* = 11.1 Hz, 1H, H-3β), 2.99-2.80 (m, 2H, H-9), 2.03-1.97 (m, 1H, H-10), 1.95-1.51 (vbr s, 2H, 2xOH), 1.79 (pseudo qd, *J*=12.3 and 4.8 Hz, 1H, H-10) ppm. ^{13}C NMR ($CDCl_3$): δ144.4 (s, C-4a), 128.5 (d, C-8), 127.3 (d, C-6), 121.3 (s, C-8a), 115.8 (d, C-7), 110.1 (d, C-5), 77.5 (d, C-1), 75.2 (d, C-2), 59.1 (d, C-10a), 53.5 (t, C-3), 27.5 (t, C-9), 20.3 (t, C-10) ppm.

HRMS(ESI): m/z calcd for $C_{12}H_{16}NO_2$ $[MH]^+$ 206.1176, found 206.1177.

*1.4.5.2 (1SR,2SR,10aSR)-1-hydroxy-2-methoxy-benzo[e]indolizidine (**1.33**) and (1RS,2RS,10aSR)-2-hydroxy-1-methoxy-benzo[e]lentiginosine (**1.34**)*



1.33



1.34

Concentrated H_2SO_4 (0.069 mL, 1.25 mmol) was added to a solution of **1.29** in dry MeOH (6 mL). After heating at 60 °C for 40 hours, the reaction mixture was subjected to chromatographic separation with CH_2Cl_2/EtOAc 5:1 v/v as eluent. The first moving band gave a 4:1 mixture (^{1}H NMR) of methoxy derivatives **1.33** and **1.34** (R_f = 0.39, 0.060 g, 55%). ^{1}H NMR ($CDCl_3$): δ7.12-7.02 (m, 2H, H-6), 7.01-6.96 (m, 2H, H-8), 6.62 (td, *J* = 7.4, 0.8 Hz, 1H, H-7), [6.57 (t, *J* = 7.3 Hz, 1H, H-7)], [6.38 (d, *J* = 7.9 Hz, 1H, H-5)], 6.37 (d, *J* = 8.0 Hz, 1H, H-5), [4.42 (d, *J* = 4.6 Hz, 1H, H-2)], 3.97 (pseudo q, *J* = 6.7 Hz, 1H, H-2), 3.86 (dd, *J* = 8.3, 7.0 Hz, 1H, H-1), [3.82 (dt, *J* = 11.7, 3.6 Hz, 1H, H-10a)], 3.68-3.61 (m, 2H, H-3α **1.33** and H-1 **1.34**), [3.54 (dd, *J* = 10.9, 4.6 Hz, 1H, H-3α)], 3.50 (s, 3H, OCH_3), [3.43 (s, 3H, OCH_3)], 3.30 (ddd, *J* = 11.4, 8.4, 3.1 Hz, 1H, H-10a), [3.22 (d, *J* = 10.9 Hz, 1H, H-3β)], 3.17 (dd, *J* = 9.6, 6.4 Hz, 1H, H-3β), 2.95-2.75 (m, 4H, H-9), 2.61 (brs, 2H, 2xOH), 2.33-2.23 (m, 1H, H-10), [1.99-1.90 (m, 1H, H-10)], [1.82 (pseudo qd, *J* = 12.6, 4.9 Hz, 1H,

H-10)], 1.58 (pseudo qd, *J* = 11.8, 6.0 Hz, 1H, H-10) ppm. ^{13}C NMR ($CDCl_3$): δ [144.5 (s, C-4a)], 143.9 (s, C-4a), 128.7 (d, C-8), [128.3 (d, C-8)], 127.2 (d, C-6), [127.1 (d, C-6)], [121.5 (s, C-8a)], 121.3 (s, C-8a), 116.2 (d, C-7), [115.3 (d, C-7)], [109.9 (d, C-5)], 109.7 (d, C-5), [86.3 (d, C-1)], 84.5 (d, C-2), 80.6 (d, C-1), [72.0 (d, C-2)], 61.0 (d, C-10a), [59.3 (d, C-10a)], 58.2 (q, OCH_3), [58.1 (q, OCH_3)], [54.0 (t, C-3)], 49.6 (t, C-3), [27.8 (t, C-9)], 27.2 (t, C-9), 25.3 (t, C-10), [20.3 (t, C-10)] ppm.

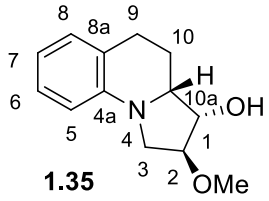
The data reported in square brackets refer to the compound **1.34**.

The following band afforded compound **1.33** (R_f = 0.29, 0.029 g, 26%) that was crystallized from Et_2O/pentane in pale yellow pearls: mp 109-110 °C. IR, ν_{max} (KBr) 3427, 3038, 2926, 2849, 1601, 1502 cm^{-1}^{1}H NMR ($CDCl_3$): δ 7.08 (t, *J* = 7.5 Hz, 1H, H-6), 6.99 (d, *J* = 7.3 Hz, 1H, H-8), 6.61 (td, *J* = 7.4, 1.0 Hz, 1H, H-7), 6.37 (d, *J* = 7.8 Hz, 1H, H-5), 3.97 (pseudo q, *J* = 7.0 Hz, 1H, H-2), 3.86 (t, *J* = 7.4 Hz, 1H, H-1), 3.65 (dd, *J* = 9.6, 7.7 Hz, 1H, H-3α), 3.50 (s, 3H, OCH_3), 3.30 (ddd, *J* = 11.3, 8.0, 3.1 Hz, 1H, H-10a), 3.17 (dd, *J* = 9.6, 6.4 Hz, 1H, H-3β), 2.90-2.76 (m, 2H, H-9), 2.33-2.25 (m, 1H, H-10), 1.64-1.52 (m, 2H, H-10 + OH) ppm. ^{13}C NMR ($CDCl_3$): δ 143.9 (s, C-4a), 128.7 (d, C-8), 127.2 (d, C-6), 121.3 (s, C-8a), 116.0 (d, C-7), 109.7 (d, C-5), 84.7 (d, C-2), 80.7 (d, C-1), 61.0 (d, C-10a), 58.1 (q, OCH_3), 49.6 (t, C-3), 27.2 (t, C-9), 25.3 (t, C-10) ppm.

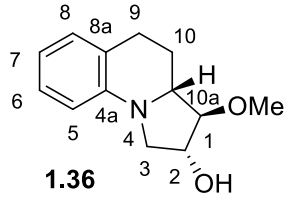
HRMS(ESI): m/z calcd for $C_{13}H_{18}NO_2$ $[MH]^+$ 220.1332, found 220.1334.

The slowest moving fraction gave diols **1.31** and **1.32** (R_f = 0.04, 0.013 g, 13%) in 1.5:1 ratio determined via ^{1}H NMR.

*1.4.5.3 (1SR,2SR,10aRS)-1-hydroxy-2-methoxy-benzo[e]indolizidine (**1.35**) and (1RS,2RS,10aRS)-2-hydroxy-1-methoxy-benzo[e]indolizidine (**1.36**)*



1.35



1.36

Operating as above on oxirane **1.30**, the reaction mixture was heated at 40 °C for 24 hours and then resolved by flash chromatography (CH_2Cl_2/EtOAc 7:1 v/v). The first band afforded compound **1.35** (R_f = 0.44, 0.054 g, 49%) as an orange sticky product. IR, ν_{max} (KBr) 3422, 3039, 2930, 2849, 1604, 1502 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.07 (t, *J* = 7.6 Hz, 1H, H-6), 6.99 (d, *J* = 7.4 Hz, 1H, H-8), 6.59 (td, *J* = 7.6, 1.0 Hz, 1H, H-7), 6.41 (d, *J* = 8.0 Hz, 1H, H-5), 4.15 (d, *J* = 3.0 Hz, 1H, H-1), 3.85 (d, *J* = 5.1 Hz, 1H, H-2), 3.65 (dt, *J* = 11.8, 3.2 Hz, 1H, H-10a), 3.58 (dd, *J* = 11.0, 5.2 Hz, 1H, H-3α), 3.42 (s, 3H, OCH_3), 3.21 (d, *J* = 11.0 Hz, 1H, H-3β), 2.99-2.79 (m, 2H, H-9), 2.03-1.96 (m, 1H, H-10), 1.81-1.68 (m, 2H, H-10 + OH) ppm. ^{13}C NMR ($CDCl_3$): δ 144.6 (s, C-4a), 128.4 (d, C-8), 127.2 (d, C-6), 121.3 (s, C-8a), 115.7 (d, C-7), 110.0 (d, C-5), 84.2 (d, C-2), 74.7 (d, C-1), 59.4 (d, C-10a), 57.0 (q, OCH_3), 50.5 (t, C-3), 27.4 (t, C-9), 20.5 (t, C-10) ppm.

HRMS(ESI): m/z calcd for $C_{13}H_{18}NO_2$ $[MH]^+$ 220.1332, found 220.1335.

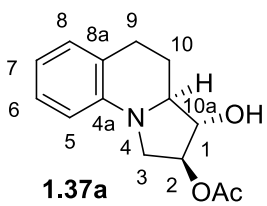
The following band gave a mixture of methoxy derivatives **1.35** and **1.36** (R_f = 0.34, 0.030 g, 27%) in about 2:1 ratio (^1H NMR). ^1H NMR ($CDCl_3$): δ 7.11-7.03 (m, 2H, H-6), 6.99 (d, *J* = 7.3 Hz, 2H, H-8), 6.65-6.56 (m, 2H, H-7), 6.42 (d, *J* = 8.0 Hz, 1H, H-5), [6.38 (d, *J* = 8.1 Hz, 1H, H-5)], [4.39 (dt, *J* = 7.4, 5.7 Hz, 1H, H-2)], 4.15 (d, *J* = 2.6 Hz, 1H, H-1), 3.86 (d, *J* = 5.2 Hz, 1H, H-2), 3.66 (dt, *J* = 11.8, 3.1 Hz, 1H, H-10a), 3.61-3.55 (m, 3H, H-3α **1.35** and H-1 and H-3α **1.36**), [3.58 (s, 3H, OCH_3)], 3.42 (s, 3H, OCH_3), [3.27 (ddd, *J* = 11.0, 7.6, 3.0 Hz, 1H, H-10a)], 3.22-3.17 (m, 2H, H-3β), 3.00-2.77 (m, 4H, H-9), [2.34-2.28 (m, 1H, H-10)], 2.04-1.95 (m, 1H, H-10),

1.84 (br s, 2H, OH), 1.82-1.61 (m, 2H, H-10 **1.35** and **1.36**). ^{13}C NMR ($CDCl_3$): δ 144.6 (s, C-4a), [144.1 (s, C-4a)], [128.7 (d, C-8)], 128.5 (d, C-8), 127.2 (d, C-6), [127.1 (d, C-6)], [121.4 (s, C-8a)], 121.3 (s, C-8a), [116.2 (d, C-7)], 115.7 (d, C-7), [110.2 (d, C-5)], 110.1 (d, C-5), [91.3 (d, C-1)], 84.2 (d, C-2),[75.0 (d, C-2)], 74.7 (d, C-1), [60.9 (d, C-10a)], 59.4 (d, C-10a), [58.8 (q, OCH_3)], 57.1 (q, OCH_3), [52.4 (t, C-3)], 50.5 (t, C-3), 27.4 (t, C-9), [27.3 (t, C-9)], [26.3 (t, C-10)], 20.6 (t, C-10).

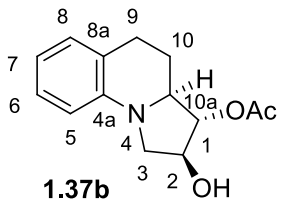
The data reported in square brackets refer to the compound **1.36**.

The slowest moving fractions afforded diols **1.29** and **1.30** (R_f = 0.04, 0.009 g, 9%) in 1:1.5 ratio (^{1}H NMR).

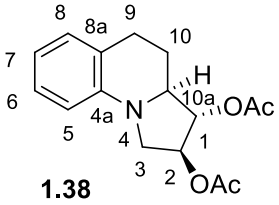
*1.4.5.4 (1SR,2SR,10aSR)-1-hydroxybenzo[e]indolizin-2-yl acetate (**1.37a**), (1SR,2SR,10aSR)-2-hydroxybenzo[e]inolizidin-1-yl acetate (**1.37b**), and (1SR,2SR,10aSR)-benzo[e]indolizidine-1,2-diyl diacetate (**1.38**)*



1.37a



1.37b



1.38

A solution of oxirane **1.29** and concentrated H_2SO_4 (0.138 mL, 2.5 mmol) in glacial AcOH was heated at 60 °C for 7 hours. Basic workup by addition of NH_4OH 30% (ca. 20 mL), extraction with EtOAc (4x10 mL) and evaporation to dryness of the organic phase dryed over anhydrous Na_2SO_4 led to a residue that was resolved by flash chromatography with PE/EtOAc 4:1 v/v as eluent. The first band gave compound **1.38** (R_f = 0.61, 0.087 g, 60%) that was cristallyzed from pentane/Et_2O in white needles: mp 71-72 °C. IR, ν_{max} (KBr) 3041, 2943, 2847, 1744, 1601, 1501, 1366, 1238 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.08 (t, *J* = 7.8 Hz, 1H, H-6), 7.00 (d, *J* = 7.4 Hz, 1H, H-8), 6.66 (td, *J* = 7.4, 1.0 Hz, 1H, H-7), 6.40 (d, *J* = 7.5 Hz, 1H, H-5), 5.31 (ddd, *J* = 7.3, 5.2, 4.2 Hz, 1H, H-2), 5.16 (dd, *J* = 7.3, 5.2 Hz, 1H,

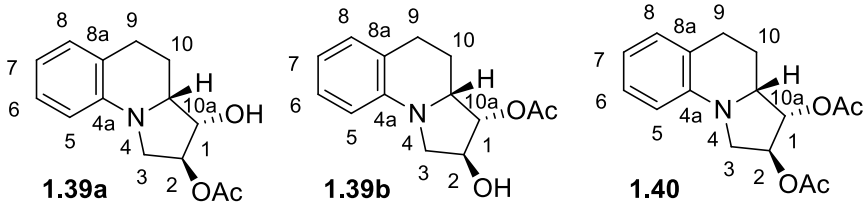
H-1), 3.71 (dd, *J* = 10.8, 7.3 Hz, 1H, H-3α), 3.37 (dd, *J* = 10.7, 4.2 Hz, 1H, H-3β), 3.35 (ddd, *J* = 11.3, 7.3, 2.9 Hz, 1H, H-10a), 2.92-2.70 (m, 2H, H-9), 2.27-2.19 (m, 1H, H-10), 2.13 (s, 3H, 1-OAc), 2.09 (s, 3H, 2-OAc), 1.82-1.70 (m, 1H, H-10) ppm. ^{13}C NMR ($CDCl_3$): δ 170,7 (s, 2-O*C*OCH_3), 170.3 (s, 1-O*C*OCH_3), 143.7 (s, C-4a), 128.9 (d, C-8), 127.1 (d, C-6), 121.5 (s, C-8a), 117.0 (d, C-7), 110.8 (d, C-5), 79.9 (d, C-1), 75.6 (d, C-2), 60.3 (d, C-10a), 51.0 (t, C-3), 26.7 (t, C-9), 25.3 (t, C-10), 20.95 (q, CH_3), 20.9 (q, CH_3) ppm.

Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.04; H, 6.89; N, 4.51.

The following band afforded an almost 1:1 mixture of monoacetates **1.37a,b** (R_f = 0.20, 0.017 g, 14%). ^{1}H NMR ($CDCl_3$): δ 7.11-7.06 (m, 2H, H-6), 7.03-6.97 (m, 2H, H-8), 6.67-6.61 (m, 2H, H-7), 6.44-6.36 (m, 2H, H-5), 5.05 (ddd, *J* = 8.2, 5.4, 4.8 Hz,, 1H, H-2 **1.37a**), 4.64 (dd, *J* = 8.2, 5.5 Hz, 1H, H-1 **1.37b**), 4.44-4.39 (m, 1H, H-2 **1.37b**), 3.90 (dd, *J* = 8.2, 5.6 Hz, 1H, H-1 **1.37a**), 3.66-3.59 (m, 2H, H-3a), 3.46-3.35 (m, 3H, H-10a and H-3 b of **1.37b** and H-3b of **1.37a**), 3.28 (ddd, *J* = 11.1, 8.2, 2.9 Hz, 1H, H-10a **1.37a**), 2.95-2.76 (m, 4H, H-9), 2.40-2.32 (m, 1H, H-10 **1.37a**), 2.27-2.21 (m, 1H, H-10 **1.37b**), 2.17 (s, 3H, CH_3 **1.37b**), 2.15 (s, 3H, CH_3 **1.37a**), 1.77-1.62 (m, 4H, 2xH-10 and 2xOH) ppm. ^{13}C NMR ($CDCl_3$): δ 173.0 (s, O*C*OCH_3 **1.37a**), 172.8 (s, O*C*OCH_3 **1.37b**), 143.9 (s, C-4a **1.37a**), 143.8 (s, C-4a **1.37b**), 128.8 (d, C-8 **1.37b**), 128.7 (d, C-8 **1.37a**), 127.2 (d, C-6 **1.37b**), 127.1 (d, C-6 **1.37a**), 121.8 (s, C-8a **1.37a**), 121.4 (s, C-8a **1.37b**), 116.9 (d, C-7 **1.37a**), 116.8 (d, C-7 **1.37b**), 110.6 (d, C-5 **1.37b**), 110.4 (d, C-5 **1.37a**), 86.2 (d, C-1 **1.37a**), 81.1 (d, C-1 **1.37b**), 80.8 (d, C-2 **1.37b**), 74.8 (d, C-1 **1.37a**), 61.7 (d, C-10a **1.37a**), 59.9 (d, C-10a **1.37b**), 52.7 (t, C-3 **1.37b**), 50.0 (t, C-3 **1.37a**), 27.0 (t, 2xC-9), 25.6 (t, C-10 **1.37a**), 25.5 (t, C-10 **1.37a**), 20.9 (q, 2xCH_3) ppm.

The slowest moving band led to diol **1.31** (R_f = 0.08, 0.008 g, 8%).

*1.4.5.5 Reaction of oxirane **1.30** with AcOH/H_2SO_4: synthesis of (1SR,2SR,10aSR)-benzo[e]indolizidine-2,3-diyl diacetate (**1.38**) and (1SR,2SR,10aRS)-benzo[e]indolizidine-2,3-diyl diacetate (**1.40**)*



Operating as above, chromatographic resolution (PE/EtOAc 4:1 v/v) of the reaction mixture obtained from oxirane **1.29** after heating for 36 hours led to a 1:3.5 mixture of diacetates **1.38** and **1.40** (R_f = 0.61, 0.043 g, 30%). ^{1}H NMR ($CDCl_3$): δ 7.13-7.05 (m, 2H, H-6), 7.01 (d, *J* = 7.3 Hz, 2H, H-8), [6.66 (td, *J* = 7.4, 1.0 Hz, 1H, H-7)], 6.61 (td, *J* = 7.4, 0.9 Hz, 1H, H-7), 6.42-6.36 (m, 2H, H-5), [5.34-5.28 (m, 1H, H-2)], 5.32 (d, *J* = 3.5 Hz, 1H, H-1), 5.24 (d, *J* = 5.1 Hz, 1H, H-2), [5.16 (dd, *J* = 7.3, 5.2 Hz, 1H, H-1)], 3.89 (dt, *J* = 11.6, 3.4 Hz, 1H, H-10a), [3.75-3.66 (m, 1H, H-3α)], 3.70 (dd, *J* = 11.5, 5.1 Hz, 1H, H-3α), [3.41-3.32 (m, 2H, H-3β and H-10a)], 3.32 (d, *J* = 11.5 Hz, 1H, H-3β), 2.97-2.76 (m, 4H, H-9), [2.26-2.18 (m, 1H, H-10)], [2.13 (s, 3H, 1-OAc)], 2.10 (s, 3H, OAc), [2.09 (s, 3H, 2-OAc)], 2.06 (s, 3H, OAc), 2.02-1.94 (m, 1H, H-10), [1.82-1.70 (m, 1H, H-10)], 1.65-1.53 (m, 1H, H-10) ppm. ^{13}C NMR ($CDCl_3$): δ [170.8 (s, 2-O*C*OCH$_3$)], [170.7 (s, 1-O*C*OCH$_3$)], 169.9 (s, 2xO*C*OCH$_3$), [143.7 (s, C-4a)], 143.6 (s, C-4a), [128.9 (d, C-8)], 128.5 (d, C-8), 127.4 (d, C-6), [127.1 (d, C-6)], [121.5 (s, C-8a)], 121.0 (s, C-8a), [117.0 (d, C-7)], 115.9 (d, C-7), [110.8 (d, C-5)], 109.9 (d, C-5), [79.8 (d, C-1)], 76.2 (d, C-2), [75.6 (d, C-2)], 74.8 (d, C-1), [60.3 (d, C-10a)], 59.0 (d, C-10a), 51.5 (t, C-3), [51.0 (t, C-3)], 27.3 (t, C-9), [27.0 (t, C-9)], [25.3 (t, C-10)], 21.0 (q, CH_3), [20.9 (q, 2xCH_3), 20.7 (q, CH_3), 20.6 (t, C-10) ppm.

The data reported in square braked refer to compound **1.38**.

The following band afforded an almost 1:5 mixture of the couples of monoacetates **1.37a,b** and **1.39a,b** (R_f = 0.20, 0.035 g, 28%).
The slowest moving band led to a 1:2 mixture of diols **1.31** and **1.32** (R_f = 0.08, 0.008 g, 8%).

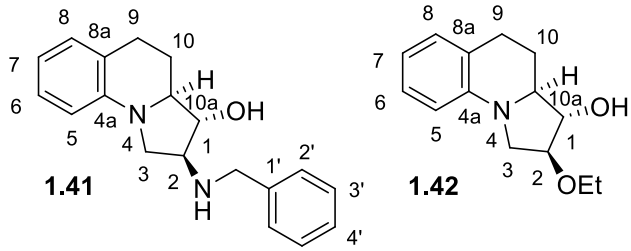
*1.4.5.6 (1SR,2SR,10aSR)-1,2-dihydroxy-benzo[e]indolizidine (**1.31**)*

A solution of oxirane **1.29** and concentrated H_2SO_4 (0.138 mL, 2.5 mmol) in glacial AcOH was heated at 60 °C for 7 hours. Then water (10 mL) was added and the resulting mixture was heated at the same temperature for 60 hours. Basic workup by addition of NH_4OH 30% (ca. 20 mL), extraction with EtOAc (4x10 mL) and evaporation to dryness of the dryed organic phase gave a residue that was subjected by flash chromatography with CH_2Cl_2/MeOH 9.5:0.5 v/v as eluent. Compound **1.31** (R_f = 0.37, 0.084 g, 82%) was recovered and crystallized from Et_2O in ivory crystals: mp 150-151 °C. IR, ν_{max} (KBr) 3360, 3304, 3212, 3074, 2957, 2916, 2839, 1602, 1505 cm^{-1}. ^1H NMR ($CDCl_3$): δ7.07 (t, *J* = 7.7 Hz, 1H, H-6), 6.99 (d, *J* = 7.4 Hz, 1H, H-8), 6.61 (td, *J* = 7.4, 1.0 Hz, 1H, H-7), 6.36 (d, *J* = 7.8 Hz, 1H, H-5), 4.37 (pseudoq, *J* = 7.3 Hz, 1H, H-2), 3.79 (dd, *J* = 8.1, 7.3 Hz, 1H, H-1), 3.68 (dd, *J* = 9.6, 7.9 Hz, 1H, H-3α), 3.32 (ddd, *J* = 11.4, 8.3, 3.2 Hz, 1H, H-10a), 3.14 (dd, *J* = 9.7, 7.0 Hz, 1H, H-3β), 2.89-2.74 (m, 2H, H-9), 2.49 (br s, 2H, 2xOH), 2.32-2.25 (m, 1H, H-10), 1.57 (pseudoqd, *J* = 11.4, 6.4 Hz, 1H, H-10) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ143.6 (s, C-4a), 128.7 (d, C-8), 127.3 (d, C-6), 121.3 (s, C-8a), 116.1 (d, C-5), 109.7 (d, C-7), 82.2 (d, C-1), 76.1 (d, C-2), 61.2 (d, C-10a), 51.4 (t, C-3), 27.2 (t, C-9), 25.2 (t, C-10) ppm.
Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 60.83; H, 7.73; N, 6.60.

1.4.6 Ring openings of oxiranes **1.29** and **1.30** with benzylamine. General procedure.

A solution of oxirane (0.094 g, 0.5 mmol) in the ethanol (6 mL) was added with $BzNH_2$ (1.2 equiv, 0.065 mL, 0.6 mmol) and heated at 100 °C for 15 days in a screw-cap tube (Pyrex N. 22) under magnetic stirring. The resulting mixture was evaporated to dryness under reduced pressure and resolved by flash chromatography.

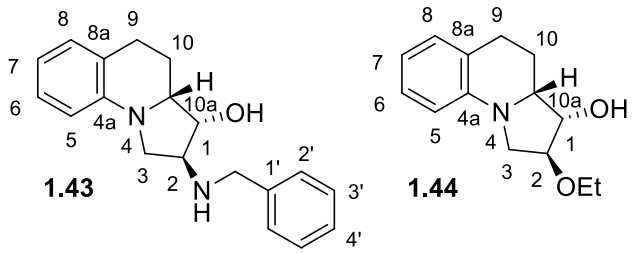
*1.4.6.1 (1SR,2SR,10aSR)-2-(N-benzyl)amino-1-hydroxy-benzo[e]indolizidine (**1.42**)*



Oxirane **1.29** was heated in the conditions described above. Flash chromatography with a gradient of eluent, EtOAc/PE 1:1 v/v as first and then EtOAc. First moving band was the diol **1.31** (R_f = 0.45, 0.008 g, 8%), second moving band was compound **1.42** (R_f = 0.37, 0.029 g, 25%). ^{1}H NMR ($CDCl_3$): δ 7.05 (t, *J* = 7.6 Hz, 1H, H-6), 6.98 (d, *J* = 7.3 Hz, 1H, H-8), 6.56 (td, *J* = 7.4, 1.0 Hz, 1H, H-7), 6.37 (d, *J* = 8.0 Hz, 1H, H-5), 4.38 (dd, *J* = 3.2, 1.5 Hz, 1H, H-1), 3.98-3.78 (m, 3H, H-2 + C*H*$_2$), 3.64 (m, 1H, H-3α), 3.21-3.14 (m, 2H, H-10a + H-3β), 3.01-2.76 (m, 2H, H-9), 2.01-1.91 (m, 3H, H-10 + C*H*$_3$), 1.83-1.68 (m, 1H, H-10) ppm. Changing eluent, using EtOAc, it was isolated compound **1.41** (R_f = 0.37, 0.078 g, 53%) as a sticky product. IR, ν_{max} (KBr) 3389, 3237, 3062, 2932, 2844, 1670, 1599, 1501, 1454 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.37-7.27 (m, 5H, Ph), 7.07 (t, *J* = 7.7 Hz, 1H,

H-6), 6.98 (d, *J* = 7.3 Hz, 1H, H-8), 6.59 (t, *J* = 7.1 Hz, 1H, H-7), 6.32 (d, *J* = 7.9 Hz, 1H, H-5), 3.87 (q, *J* = 12.9 Hz, 2H, C*H*$_2$), 3.68-3.55 (m, 2H, H-1 + H-3α), 3.37-3.24 (m, 2H, H-2 + H-10a), 2.98 (dd, *J* = 8.9, 8.2 Hz, 1H, H-3β), 2.87-2.73 (m, 2H, H-9), 2.55 (br s, 2H, OH + NH), 2.32-2.21 (m, 1H, H-10), 1.56-1.37 (m, 1H, H-10) ppm. ^{13}C NMR (100 MHz, $CDCl_3$), δ 143.8 (s, C-4a), 139.4 (s, C-1'), 128.6 (d, C-3') 128.3 (d, C-2'), 127.4 (d, C-6), 127.2 (d, C-4'), 121.2 (s, C-8a), 115.6 (d, C-7), 109.3 (d, C-5), 80.6 (d, C-1), 62.8 (d, C-2 ?), 61.6 (d, C-10a), 52.7 (t, *C*H_2NH), 50.9 (t, C-3), 27.3 (t, C-9), 25.3 (t, C-10) ppm.

*1.4.6.2 (1SR,2SR,10aRS)-2-(N-benzyl)amino-1-hydroxy-benzo[e]indolizidine (**1.43**)*



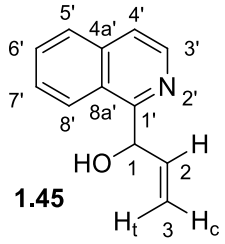
Oxirane **1.30** was heated in the conditions described above. Flash chromatography with EtOAc/PE 1:1 v/v as eluent. First moving band was compound **1.44** (R_f = 0.31, 0.007 g, 6%). ^{1}H NMR ($CDCl_3$): δ 7.05 (t, *J* = 7.3 Hz, 1H, H-6), 6.98 (d, *J* = 7.3 Hz, 1H, H-8), 6.58 (t, *J* = 6.9 Hz, 1H, H-7), 6.40 (d, *J* = 7.8 Hz, 1H, H-5), 4.14 (dd, *J* = 3.2, 1.5 Hz, 1H, H-1), 3.96 (d, *J* = 5.2 Hz, 1H, H-2), 3.70 (dt, *J* = 11.8, 3.1 Hz, 1H, H-10a), 3.64-3.56 (m, 3H, H-3α + C*H*$_2$), 3.20 (d, *J* = 10.9 Hz, 1H, H-3β), 3.01-2.76 (m, 2H, H-9), 2.04-1.93 (m, 1H, H-10), 1.86-1.68 (m, 1H, H-10), 1.21 (t, *J* = 7.0 Hz, 3H, C*H*$_3$) ppm.

Second band moving was the product **1.43** (R_f = 0.24, 0.113 g, 77%) as a sticky solid. IR, ν_{max} (KBr) 3368, 3062, 2932, 1670, 1604, 1503, 1462 cm^{-1}. ^{1}H NMR

($CDCl_3$): δ 7.38-7.27 (m, 5H, Ph), 7.01 (t, *J* = 7.7 Hz, 1H, H-6), 6.99 (d, *J* = 7.5 Hz, 1H, H-8), 6.59 (t, *J* = 7.4 Hz, 1H, H-7), 6.41 (d, *J* = 7.5 Hz, 1H, H-5), 4.08 (dd, *J* = 3.5, 1.3 Hz, 1H, H-1), 3.87 (d, *J* = 2.6 Hz, 2H, CH_2), 3.71 (dt, *J* = 11.7, 3.3 Hz, 1H, H-10a), 3.64 (dd, *J* = 10.2, 6.1 Hz, 1H, H-3α), 3.37-3.31 (m, 1H, H-2), 3.03 (dd, *J* = 10.2, 2.1 Hz, 1H, H-3β), 2.98-2.75 (m, 2H, H-9), 2.33 (br s, 2H, OH + NH), 1.97 (ddt, *J* = 12.5, 5.3, 2.7 Hz, 1H, H-10), 1.81-1.71 (m, 1H, H-10) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.8 (s, C-4a), 139.4 (s, C-1'), 128.6 (d, 2C, C-3'), 128.5 (d, C-8), 128.2 (d, 2C, C-2'), 127.3 (d, C-6), 127.1 (d, C-4'), 121.5 (s, C-8a), 115.8 (d, C-7), 109.3 (d, C-5), 76.2 (d, C-1), 63.2 (d, C-2), 59.7 (d, C-10a), 52.0 (t, *C*H_2NH), 51.8 (t, C-3), 27.7 (t, C-9), 20.8 (t, C-10) ppm.

The slowest band moving was the diol **1.30** (R_f = 0.14, 0.009 g, 8.5%).

1.4.7 Synthesis of 1-(1-isoquinolyl)-2-propen-1-ol (**1.45**)

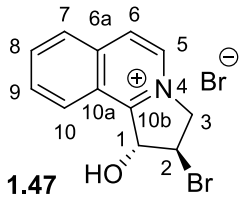


1.45

Following the procedure previously reported for the synthesis of **1.23**, 1-isoquinolincarboxaldehyde (1 mmol, 0.157 g) was dissolved in dry Et_2O, cooled between -10 and 0 °C, and added with a 1M solution of vinyl-magnesium bromide (1.3 equiv, 1.3 mL) for 1 hour. Finishing the addition, the mixture was warmed to room temperature under stirring and then quenched with water. After extraction with EtOAc, the solution was dried on Na_2SO_4 and purified by flash chromatography on silica gel, using EtOAc/EP 1:1 v/v as eluent. Alcohol **1.45** (R_f = 0.30, 0.152 g, 82%) was isolated as yellow oil. ^{1}H NMR ($CDCl_3$): δ 8.47 (d, *J* = 5.8 Hz, 1H, H-3'), 7.90 (d, *J* = 8.5 Hz, 1H, H-5'), 7.74 (t, *J* = 7.6 Hz, 1H, H-4'),

7.68-7.61 (m, 2H, H-6' and H-8'), 6.12-6.01 (m, 1H, H-2), 5.90 (d, *J* = 6.3 Hz, 1H, H-1), 5.56 (dt, *J* = 17.0, 1.2 Hz, 1H, H-3 *trans*), 5.26 (dd, *J* = 10.2, 1.1 Hz, 1H, H-3 *cis*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3 (s, C-1'), 139.6 (d, C-3'), 139.0 (d, C-2), 136.7 (s, C-4a'), 130.8 (d, C-4'), 127.7 (d, (C-8' or C-6'), 127.5 (d, C-7'), 125.0 (s, C-8a'), 124.6 (d, C-5'), 121.2 (d, C-6' or C-8'), 116.8 (t, C-3), 71.2 (d, C-1).

1.4.8 Bromination of 1-(1-isoquinolyl)-2-propen-1-ol (**1.45**)



1.47

Acting as described above for the bromination of **1.23**, alcohol **1.45** (1 mmol, 0.185 g) was dissolved in CH_2Cl_2 (4 mL), cooled to 0 °C, and dropwise added with a solution of Br_2 (1 equiv, 0.051 mL, 1 mmol) in the same solvent (2 mL) under magnetic stirring. At the end of addition, the reaction mixture was stirred for 30 mins at 0 °C and maintained at room temperature overnight. A mixture of salts **1.46** and **1.47** (0.310 g, 90%) was recovered in 1:4 ratio, and the salt **1.46** was completely isomerized into the *trans* benzo[*g*]indolizinium bromide **1.47** by dissolving in DMSO (immediate and complete isomerization) or by stirring in H_2O/MeOH (3:1 ratio) for 7 days.

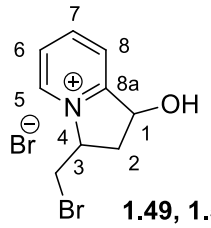
Mp > 370 °C. IR, ν_{max} (KBr) 3151, 3117, 2970, 1631, 1615, 1547, 1451, 1255, 1210, 1157, 830, 776, 685 cm^{-1}.^{1}H NMR (DMSO): δ 8.86-8.77 (m, 2H, H-5 and H-10), 8.64 (d, *J* = 6.7 Hz, 1H, H-6), 8.42 (d, *J* = 8.3 Hz, 1H, H-7), 8.28 (t, *J* = 7.7 Hz, 1H, H-8), 8.12 (t, *J* = 7.7 Hz, 1H, H-9), 6.28 (d, *J* = 4.4 Hz, 1H, H-1), 5.62 (dd, *J* = 14.2, 6.6 Hz, 1H, H-3), 5.16 (dd, *J* = 14.2, 5.1 Hz, 1H, H-3), 4.96 (dt, *J* = 6.5, 4.9 Hz, 1H, H-2) 4.99-4.93 (m, 1H, H-2) ppm. ^{13}C NMR (DMSO): δ 158.2 (s, C-10b), 138.3 (d,

C-10), 136.8 (d, C-8), 137.9 (s, C-10a), 131.5 (d, C-9), 128.3 (d, C-7), 127.8 (d, C-5), 126.6 (d, C-6), 124.2 (s, C-6a), 80.0 (d, C-1), 64.0 (t, C-3), 46.8 (d, C-2) ppm.

1.4.9 Synthesis of 1-(2-pyridyl)-3-buten-1-ol (**1.48**)

Following the procedure previously reported for the synthesis of **1.23**, 2-pyridincarboxaldehyde (4.66 mmol, 0.500 g, 444 mL) was dissolved in dry Et_2O, cooled between -10 and 0 °C, and added with a 1M solution of allyl-magnesium bromide (1.4 equiv, 6.5 mL, 6.5 mmol) for 1 hour. Finishing the addition, the mixture was warmed to room temperature under stirring and then quenched with water. After extraction with EtOAc, the solution was dried on Na_2SO_4 and purified by flash chromatography on silica gel, using EtOAc/EP 2:3 v/v as eluent. Alcohol **1.48** (R_f = 0.35, 0.417 g, 60%) was isolated as yellow oil.

1.4.10 Bromination of 1-(2-pyridyl)-3-buten-1-ol (**1.48**)



1.49, 1.50

Acting as described above for the bromination of **1.23**, alcohol **1.48** (1 mmol, 0.149 g) was dissolved in CH_2Cl_2 (4 mL), cooled to 0 °C, and dropwise added with a solution of Br_2 (1 equiv, 0.051 mL, 1 mmol) in the same solvent (2 mL) under magnetic stirring. At the end of addition, the reaction mixture was stirred for 30 mins at 0 °C and maintained at room temperature overnight. A mixture of salts **1.49** and **1.50** (0.247 g, 80%) was recovered in 1:2 ratio. ^{1}H NMR (DMSO): δ9.29-9.16 (m, 2H, H-5 **1.49** and **1.50**), 8.77-8.59 (m, 2H, H-7 **1.49** and **1.50**), 8.30-8.11

(m, 4H, H-6 and H-8 **1.49** and **1.50**), 6.74 (br s, 2H, OH **1.49** and **1.50**), [5.81-5.71 (m, 1H, H-3)], [5.67 (t, *J* = 7.4 Hz, 1H, H-1), 5.54 (t, *J* = 8.1 Hz, 1H, H-1), 5.41 (br s, 1H, H-3), 4.55 (dd, *J* = 11.9, 4.7 Hz, 1H, C*H*$_2$Br), 4.33-4.11 (m, 3H, 1H C*H*$_2$Br **1.49** and 2H C*H*$_2$Br **1.50**), 3.07-2.90 (m, 1H, H-2), [2.77-2.63 (m, 1H, H-2)], [2.57-2.40 (m, 1H, H-2)], 2.21-2.06 (m, 1H, H-2) ppm. ^{13}C NMR (DMSO): δ 160.0 (s, C-8a), [159.3 (s, C-8a)], [147.2 (d, C-7)], 146.7 (d, C-7), [140.6 (d, C-5)], 139.8 (d, C-5), [127.4 (d, C-6)], 127.0 (d, C-6), [124.7 (d, C-8)], 124.3 (d, C-8), [70.8 (d, C-1)], 70.3 (d, C-1), [68.6 (d, C-3)], 67.0 (d, C-3), [36.2 (t, C-2)], 35.9 (t, C-2), [35.5 (t, CBr)], 34.0 (t, CBr) ppm.

The data reported in square braked refer to compound **1.49**.

Chapter 2 - Phenyl(2-quinolyl)methanols as a new class of hydrogen donors in metal free reductions

2.1 Introduction

Amines are key functional groups in the synthesis of pharmaceuticals, agrochemicals, dyes, and pigments, and one of the most important ways to obtain them is the reduction of nitro compounds.[76] The basic aromatic amine, aniline, is nowadays industrially obtained in two steps. First, benzene is nitrated with a concentrated mixture of nitric acid and sulfuric acid, at 50-60 °C to give nitrobenzene, then hydrogenated (typically at 200-300 °C) in the presence of metal catalysts.[77] The reduction of nitrobenzene to aniline was firstly performed by Nickolay Zinin in 1842, using stoichiometric sodium sulfide as reducing system (Zinin reaction).[78] Some years later, Piria reduced nitrobenzene to aniline in a two-step procedure, via the aminosulfonic acid intermediate,[79] while Antoine Béchamp in 1854, exploiting iron in acidic media, developed a general method for the synthesis of primary anilines that has been for a long time the main industrial process (Béchamp reduction).[80]

For instance, the highly diffused analgesic and antipyretic paracetamol was synthesized by Morse in 1878 via reduction of *p*-nitrophenol with tin in glacial

[76] M. Orlandi, D. Brenna, R. Harms, S. Jost, M. Benaglia, *Org. Process Res. Dev.* **2018**, *22*, 430-445.

[77] Blaser, H.-U.; Steiner, H.; Studer, M. *Chem. Cat. Chem.* **2009**, *1*, 210-221, and references therein.

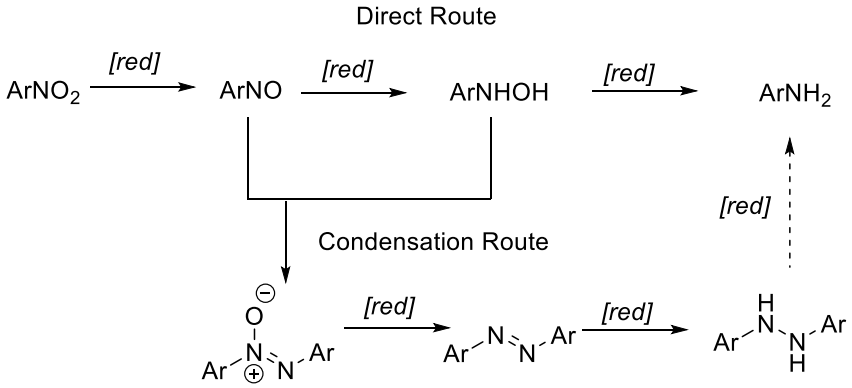
[78] N. Zinin, *J. Prakt. Chem*. **1842**, *27*, 140-153.

[79] R. Piria, R. *Liebigs Ann.* **1851**, *78*, 31–68.

[80] A. Bechamp, *J. Ann. Chim. Phys.* **1854**, *42*, 186-196.

acetic acid.[81] Its wide use in pharmacology started in the second half of XX century. Earlier, phenacetin and acetanilide, molecules in which paracetamol is the active metabolite, were used, but they showed higher toxicity for the patient. Nowadays, paracetamol on industrial scale is synthesized by reduction of *p*-nitrophenol with hydrogen on Raney-Ni catalyst followed by acetylation with acetic anhydride, evidencing the strength of the nitro reduction method to achieve amine synthesis.[82]

As shown by Haber in 1898 on the base of electrochemical experiments, the nitrobenzene reduction is a stepwise process.[83] A direct route involves the conversion of the nitro compound at first into a nitroso compound, then the formation of hydroxylamine which is eventually reduced to aniline. Alternatively a route involving a nitroso-hydroxylamine self- condensation can lead to azoxybenzene later converted into azo and hydrazo intermediates and finally into aniline (Scheme 2.1).[84]



Scheme 2.1 - Mechanism for the reduction of nitro compounds (red = reduction).

[81] H. N. Morse, *Ber. Dtsch. Chem. Ges.* **1878**, *11*, 232-233.
[82] E. Friedrichs, T. Christoph, H. Buschmann, Analgesic and Antipyretics, Ullmann's Encyclopedia of Industrial Chemistry, Wiley, 2007.
[83] F. Z. Haber, *Elektrochem* **1898**, *4*, 506-514.
[84] (a) D. Formenti, F. Ferretti, F. K. Scharnagl, M. Beller, **2019**, *119*, 2611-2680; (b) Y. Ma, Z. Lang, J. Du, L. Yan, Y. Wang, H. Tan, S. U. Khan, Y. Liu, Z. Kang, Y. Li, *J. Catal.* **2019**, *377*, 174-182.

Likely, if the reduction process is not sufficiently fast to go from nitro compound to aniline, azoxy, azo and hydrazo intermediates could be observed and isolated from the reaction mixture. However, the conversion of azoxy, azo and hydrazo derivatives into amines is not easily achieved and usually requires the presence of metal catalysts.[85]

2.1.1 Reduction of nitro compounds

As earlier stated, the reduction of nitro compounds is a facile and effective method to synthesize amines.

The common methods for the reduction of nitro compounds to the corresponding amines are mainly five:

-Metal Dissolving Reductions;

-Catalytic hydrogenations;

-Catalytic Transfer Hydrogenations;

-Hydride Transfer Reductions;

-Metal-Free Reductions.

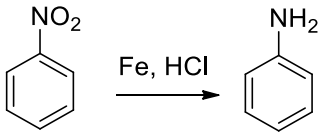
2.1.1.1 Metal Dissolving Reductions

Metal dissolving methods to effect the reductions of nitro compounds are well-known since the nineteenth century.[86] Typical metals used in these reactions are

[85] (a) F. Alonso, G. Radivoy, M. Yus, *Tetrahedron* **2000**, *56*, 8673-8678, and references cited therein; (b) P. Selvam, S. U. Sonavane, S. K. Mohapatra, R. V. Jayaram, *Tetrahedron Lett.* **2004**, *45*, 3071-3075. (c) A. Toti, P. Frediani, A. Salvini, L. Rosi, C. Giolli, *J. Organomet. Chem*. **2005**, *690*, 3641-3651. (d) F. Ren, Y. Zhang, L. Hu, M. Luo, *Arkivoc* **2013**, *iii*, 165-173, and references cited therein.

[86] (a) E. Kock, *Ber. Dtsch. Chem. Ges.* **1887**, *20*,1567; (b) S. E. Hazlet, C. A. Dornfeld, *J. Am. Chem. Soc.* **1944**, *66*, 1781.

Fe (Bechamp)[80,87], Zn,[88] Al,[89] In,[90] and Sm,[91] in combination with several proton sources, usually mineral acids as HCl, or, sometimes, water, AcOH, NH_4Cl, etc (Scheme 2.2).



Scheme 2.2 - Reduction of nitrobenzene to aniline with Fe/HCl

2.1.1.2 Catalytic hydrogenation

Molecular hydrogen is one of the most relevant reducing agents used in industrial transformations for the reduction of nitro compounds. The classic system, such has H_2 and Pd/C, shows low chemoselectivity in the presence of other functionalities susceptible of reduction in the molecule. Accordingly research has been focused on developing new catalysts for highly chemoselective nitro groups hydrogenations in the presence of heterogenous or homogeneous catalysts. Heterogeneous catalysts are mainly nanoparticles with different properties, such as shape, size, and the nature of the support (i.e. magnetic for an easier recovery).[92] Homogenous catalysts for the hydrogenation of nitro groups have been developed to work in aqueous biphasic systems. For

[87] S. Chandrappa, T. Vinaya, T. Ramakrishnappa, K. S. Rangappa, *Synlett* **2010**, 3019-3022.
[88] (a) V. S. Sadavarte, S. S. Swami, D.G. Desai, *Synth. Commun.* **1998**, *28*, 1139-1142; (b) D, G. Desai, S. S. Swami, S. B. Hapase, *Synth. Commun.* **1999**, *29*, 1033-1036.
[89] D. Nagaraja, M. A. Pasha, *Tetrahedron Lett.* **1999**, *40*, 7855-7856.
[90] Y. S. Cho, B. K. Jun, S. Kim, J. H. Cha, A. N. Pae, H. Y. Koh, M. H. Chang, S.-Y. Han, *Bull. Korean Chem. Soc.* **2003**, *24*, 653-654.
[91] C. Yu, B. Liu, L. Hu, *J. Org. Chem.* **2001**, *66*, 919-924.
[92] H. K. Kadam, S. G. Tilve, *RSC Adv.* **2015**, *5*, 83391-83407.

example, in 2004 Chaudhari and co-workers[93] reported a chemoselective catalytic hydrogenation of substituted nitroarenes using a water-soluble iron complex ($FeSO_4 \cdot 7H_2O$ + $EDTANa_2$), able to perform the reaction in biphasic conditions because the reagent, as well as the product, form a water immiscible organic phase.

2.1.1.3 Catalytic transfer hydrogenation

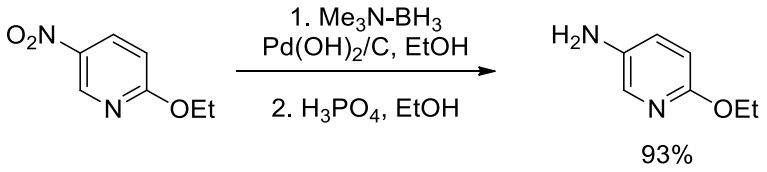
Transfer hydrogenation does not use H_2 gas as hydrogen source, but reagents such as HCOOH, $HCOONH_4$, *i*-PrOH, NH_2NH_2, with the advantage to avoid high-pressure reactors or other elaborate experimental conditions, commonly required for the traditional hydrogenation. Also in this case, a metal catalyst is needed. For example, Cao et al. reported in 2011[94] the reduction of nitroarenes with $HCOONH_4$ as hydrogen source catalyzed by TiO_2-supported gold nanoparticles. In a more recent work[95] the same authors described a very efficient reduction of aliphatic nitro groups using the same reducing system, but different reaction conditions.

2.1.1.4 Hydride transfer reductions

Hydride transfer is one of the classical ways to perform reduction. In this domain, one of the most common reagent is aluminum hydride, that is able to perform the reduction of nitro groups to aliphatic amines and aromatic azo compounds.[96] Other common and inexpensive reagents as borohydrides[92,97] and

[93] R. M. Deshpande, A. N. Mahajan, M. M. Diwakar, P. S. Ozarde, R. V. Chaudhari, *J. Org. Chem.* **2004**, *69*, 4835-4838.
[94] X. Lou, L. He, Y. Qian, Y. Liu, Y. Cao, K. Fan, *Adv. Synth. Catal.* **2011**, *353*, 281-286.
[95] L. Yu, Q. Zhang, S.-S Li, J. Huang, Y.-M. Liu, H.-Y. He, Y. Cao, Y. *ChemSusChem* **2015**, *8*, 3029-3035.
[96] R. F. Nystrom, W. G. Brown, *J. Am. Chem. Soc.* **1948**, *70*, 3738-3740.
[97] E. R. Burkhardt, K. Matos, *Chem. Rev.* **2006**, *106*, 2617-2650.

silanes[92,98] are not reactive towards nitro groups, and require the use of a catalyst (usually transition metal reagents) to promote the reduction. Thus Beaudin and co-workers, in order to synthesize a drug for Alzheimer's disease, used palladium catalyzed hydrogenation with trimethylamine borane (TMAB) to perform the reduction of an aromatic nitro group to aniline, and they were able to isolate the product as a crystalline solid in 93% yield (Scheme 2.3).[99]



Scheme 2.3 - Reduction of a heteroaromatic nitro compounds with borane Pd-catalyzed.

However, nitro compounds are not easily reduced by borohydrides. In 1956 Weill and coauthors[100] published a research in which they were able to achieve the reduction of nitrobenzene to azoxybenzene in presence of sodium borohydride, but they were not able to perform the reduction of 1-nitropropane under similar conditions. After few years, Shine and co-workers[101] exploited the reactivity of potassium borohydride with variously substituted aromatic nitro compounds and observed that the substituent influenced the nature of the products. Indeed, *meta*- and *para*-substituted nitrobenzenes carrying a substituent with a positive value of the Hammett sigma constant were reduced in good yield by potassium borohydride to the corresponding azoxy compounds while nitrobenzenes bearing substituents with negative sigma constants were

[98] S. Park, I. S. Lee and J. Park, *Org. Biomol. Chem.* **2013**, *11*, 395.
[99] J. Beaudin, D. E. Bourassa, P. Bowles, M. J. Castaldi, R. Clay, M. A. Couturier, G. Karrick, T. W. Makowski, R. E: McDermott, C. N. Meltz, M. Meltz, J. E. Phillips, J. A. Ragan, D. H. B. Ripin, R. A. Singer, J. L. Tucker, L. Wie, *Org. Process Res. Dev.* **2003**, *7*, 873-878.
[100] C. E. Weill, G. S. Panson, *J. Org. Chem.* **1956**, *21*, 803.
[101] H. J. Shine, H. E. Mallory, *J. Org. Chem.* **1962**, *27*, 2390-2391.

not reduced. In 1971 Hutchins and co-workers[102] confirmed these results using sodium borohydride as reducing agent. Working in DMSO or sulfolane, they were able to obtain mixtures of azo and azoxy derivatives, as well as aniline in some cases, and observed no reactivity in substrates with substituents having high negative Hammet sigma constant such as *p*-nitroaniline. Reductions of aromatic nitro compounds (and also nitriles and amides) with $NaBH_4$ in the presence of metal catalysts, such as $CoCl_2$ or $CuCl_2$, led to azoxy compounds and anilines, respectively, depending on the reaction conditions.[103] Since these pioneering works, several methods for the reduction of nitro compounds under metal catalysis have been developed.[104]

In 2006, Zeynizadeh and co-workers[105] developed a simple method able to reduce aromatic nitro compounds to anilines in good to excellent yields, using $NaBH_4$ in aqueous medium as reducing agent in the presence of charcoal at 60 °C. In 2016, Yang and coworkers even reported the application of nitrogen-doped graphene catalysts for nitroarenes reduction in water, in presence of $NaBH_4$. [106]

Aliphatic and aromatic nitro derivatives were reduced in transition metal-free conditions using trichlorosilane/NR_3[107] and triethylsilane/$B(C_6F_5)_3$[108].

[102] R. O. Hutchins, D. W. Lamson, L. Rua, C. Milewski, B. Maryanoff, *J. Org. Chem.* **1971**, *36*, 803-806.
[103] (a) T. Satoh, S. Suzuki, Y. Suzuki, Y. Miyaji, Z. Imai, *Tetrahedron Lett.* **1969**, *10*, 4555-4558. (b) B. Ganem, J. O. Osby, *Chem. Rev*. **1986**, *86*, 763-780.
[104] O. Mazaheri, R. J. Kalbasi, *RSC Adv.* **2015**, *5*, 34398-34414, and references therein.
[105] B. Zeynizadeh, D. Setamdideh, *Synth. Commun.* **2006**, *36*, 2699-2704.
[106] F. Yang, C. Chi, C. Wang, Y. Wang, Y. Li, *Green Chem.* **2016**, *18*, 4254-4262.
[107] M. Orlandi, F. Tosi, M. Bonsignore, M. Benaglia, *Org. Lett*. **2015**, *17*, 3941-3943.
[108] D. Porwal, M. Oestreich, *Eur. J. Org. Chem.* **2016**, 3307-3309.

2.1.1.5 Metal-free and transition metal-free reductions

In the last decades, the focus on green and sustainable methodologies, even associated to the progress of organocatalysis, stimulated the study of metal-free processes.

According with Dalko's definition,[109] the term "*organocatalysis*" describes the acceleration of chemical reactions through the addition of a substoichiometric quantity of an organic compound which does not contain a metal atom. Organocatalysis is related to the use of small molecules as organic catalysts (even called 'artificial enzymes'[110]) to activate substrates[111] for reactions, working in metal-free conditions, with a series of advantages with respect to the use of metals or organometallic compounds which presents some environmental issues because of their toxicity, generation of polluting metal waste, in addition to high costs and specific manipulations. Organocatalysis can be greener than traditional catalysis for many reasons. At first, the catalysis is a green principle because it permits the reduction of the activation energy of the reaction, and so it is possible to employ milder conditions, and consequently to save energy. Organocatalytic methods are generally less toxic and do not require anhydrous conditions. Organocatalysts are designed to be compatible with different functional groups then reducing reaction's steps, waste, and, overall, the cost of the process. Moreover, organocatalytic approaches allow to solve the problem of product contamination by traces of metals, essential feature in medicinal chemistry.[112]

In this context, even the reduction of nitro compounds has been performed in metal-free conditions. A great variety of non-metal and transition metal-free

[109] P. I. Dalko, L. Moisan, *Angew. Chem., Int. Ed.* **2004**, *43*, 5138-5175.
[110] (a) R. Breslow, *Science* **1982**, *218*, 532-537. (b) P. I. Dalko, L. Moisan, *Angew. Chem., Int. Ed.* **2001**, *40*, 3726-3748.
[111] D. W. C. MacMillan, *Nature* **2008**, *455*, 304-308.
[112] V. da Gama Oliveira, M. F. do Carmo Cardoso, L. da Silva Magalhaes Forezi, L. *Catalysts* **2018**, *8*, 605.

reagents were exploited for the reduction of nitro aromatics to anilines such as 9,10-dihydroanthracene,[113] 1,4-dihydropyridine systems,[114] elemental sulfur,[115] thiols,[116] Baker's Yeast in basic solution,[117] fullerene/H_2,[118] glucose,[119] vasicine,[120] diboron compounds,[121] viologen/$Na_2S_2O_4$,[122] *N*,*N*'-bis(trimethylsilyl)-4,4'-bipyridinylidene,[123] carbon-based catalysts in the presence of N_2H_4,[124] isopropanol,[125] or subcritical water[126] as hydrogen sources.

2.1.2 Reduction of imines

The reduction of imines to the corresponding amines is one of the most important reactions in organic synthesis.[127] It is most frequently performed by catalytic hydrogenation in the presence transition metals or transition metal

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[113] M. Coellen, C. Rüchardt, *Chem. Eur. J.* **1995**, *1*, 564-567.
[114] K. V. Maslov, A. G. Egorov, T. I. Akimova, V. A. Kaminski, *Chem. Heterocycl. Compd.* **2002**, *38*, 560-563.
[115] M. A. McLaughlin, D. M. Barnes, *Tetrahedron Lett.* **2006**, *47*, 9095-9097.
[116] Z. Duan, S. Ranjit, X. Liu, *Org. Lett.* **2010**, *12*, 2430-2433.
[117] W. Baik, J. L. Han, K. C. Lee, H. M. Lee, B. H. Kim, J. T. Hahn, *Tetrahedron Lett*. **1994**, *35*, 3965-3966.
[118] B. Li, Z. Xu, *J. Am. Chem. Soc*. **2009**, *131*, 16380-16382.
[119] M. Kumar, U. Sharma, S. Sharma, V. Kumar, B. Singh, N. Kumar, *RSC Adv*. **2013**, *3*, 4894-4898.
[120] S. Sharma, M. Kumar, V. Kumar, N. J: Kumar, *J. Org. Chem.* **2014**, *79*, 9433-9439.
[121] (a) K. Yang, F. Zhou, Z. Kuang, G. Gao, T. G. Driver, Q. Song, *Org. Lett*. **2016**, *18*, 4088-4091; (b) H. Lu, Z. Geng, J. Li, D. Zou, Y. Wu, Y. Wu, *Org. Lett*. **2016**, *18*, 2774-2776. (c) D. Chen, Y. Zhou, H. Zhou, S. Liu, Q. Liu, K. Zhang, Y. Uozumi, Y. *Synlett* **2018**, 29, 1765-1768.
[122] K. K. Park, C. H. Oh, W. K. Joung, *Tetrahedron Lett*. **1993**, *34*, 7445-7446.
[123] A. Bhattacharjee, H. Hosoya, H. Ikeda, K. Nishi, H. Tsurugi, K. Mashima, *Chem. Eur. J.* **2018**, *24*, 11278-11282.
[124] (a) C. Liao, B. Liu, Q. Chi, Z. Zhang, *ACS Appl. Mater. Interfaces* **2018**, *10*, 44421-44429; (b) F. Yang, Y. Cao, Z. Chen, X. He, L. Hou, Y. Li, *New J. Chem.* **2018**, *42*, 2718-2725.
[125] H. Yang, X. Cui, X. Dai, Y. Deng, F. Shi, *Nat. Commun.* 6:6478 doi: 10.1038/ncomms7478 (2015).
[126] S. Tadrent, D. Luart, O. Bals, A. Khelfa, R. Luque, C. Len, *J. Org. Chem.* **2018**, *83*, 7431-7437.
[127] (a) D. J. Ager, A. H. M. de Vries, J. G. de Vries, *Chem. Soc. Rev.* **2012**, *41*, 3340-3380; (b) H.-U Blaser, C. Malan, B. Pugin, F. Spinder, H. Steiner, M. Studer, *Adv. Synth. Cat.* **2003**, *345*, 103-151.

complexes (Ru, Ir, Rh, Pd, Fe, Zn, lanthanides or also bimetallic systems).[128] However, as earlier stated, metal catalysts are expensive and pollutant, justifying the search for other systems. As an alternative to transition metals, stoichiometric amounts of reducing agents such as borohydrides and organoboranes,[129] silanes,[130] and formic acid[131] have been employed. Even 1,4-dihydropyridine systems have been used, in combination with metal catalysts, as hydrogen donor for imine reduction.[132]

However, in the last years, the attention was focused on metal-free reductions, in particular to perform enantioselective processes. The enantioselective reduction of carbon-nitrogen double bonds attracts a great interest, especially in pharmacological field, but the synthesis of enantiopure amines is still hard. Metal catalyzed enantioselective hydrogenation cannot be used because of problems of poisoning of the catalyst due to nitrogen and/or sulphur present in the substrates, and moreover metallic residues can contaminate the final product. Nowadays, there are three organocatalytic methodologies for the metal-free and transition metal-free reduction of imines: a) reduction with 1,4-dihydropyridines as reducing agent, generally catalyzed by binaphthol derivatives of phosphoric acids; b) reduction mediated by trichlorosilane in the presence of Lewis bases as catalysts; c) metal-free hydrogenation via Frustrated Lewis Pairs (FLP)-methodology.[133]

Frustrated Lewis Pairs are Lewis acids (LA) and bases (LB) extremely hindered, which cannot form the classic adduct LA-LB.[134] These compounds are able to

[128] D. Wang, D. Astruc, *Chem. Rev.* **2015**, *115*, 6621-6686.
[129] A. F. Abel-Magid, S. J. Mehrman, *Org. Processes Res. Dev.* **2006**, *10*, 971.
[130] B. H. Lipshutz, H. Shimizu, *Angew. Chem., Int. Ed.* **2004**, *43*, 2228-2230.
[131] H. Xu, P. Yang, P. Chuanprasit, H. Hiro, J. Zhou, *Angew. Chem., Int. Ed.* **2015**, *54*, 5112-5116.
[132] (a) C. Zheng, S.-L. You, *Chem. Soc. Rev.* **2012**, *41*, 2498-2518; (b) J. G. de Vries, N. Mrsic, *Catal. Sci. Technol.* **2011**, *1*, 51-59.
[133] (a) S. Rossi, M. Benaglia, E. Massolo, L. Raimondi, *Catal. Sci. Technol.* **2014**, *4*, 2708-2723; (b) J. G. de Vries, N.Mrsic, *Catal. Sci. Technol.* **2011**, *1*, 727-735.
[134] D. W. Stephan, G. Erker, *Angew. Chem., Int. Ed.* **2015**, *54*, 6400-6441.

realize the heterolytic H-H bond cleavage, known to be promoted exclusively by transition metals.[135]

The reduction of C=N double bonds with trichlorosilane in presence of chiral Lewis bases, such as α-aminoacids like proline, valine, pipecolic acid, allowed to realize enantioselective processes. High yields and enantiomeric excesses were achieved using derivatives of 4-Cl- or 4-Br-picolinic acid as catalyst.[131a]

The metal-free reduction of imines is commonly performed using 1,4-dihydropyridines, and the first example of asymmetric metal-free reduction was reported in 1989 by Singh and Batra.[136] Prochiral imines were reduced using Hantzsch ester (HEH) in the presence of hydrochlorides of α-aminoacids, or enantiopure acids, to obtain amines with moderate enantioselectivity. Recently, Rueping et al. described the use of chiral phosphoric acids as efficient catalysts.[137] Binaphthol derivatives (BINOL) were widely used as chiral skeletons to build enantiopure phosphoric acids, successfully applied to the organocatalyzed imine reduction.

The methods described above were also applied to multicomponent reactions, as reductive amination, starting from amine and carbonyl compounds, one of the most powerful and used reactions in organic chemistry for the access to amino derivatives. Reductive amination of aldehydes and ketones has been performed with different kinds of reagents as formic acid, metal hydrides, hydrogen and catalysts.[138]

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[135] G. C. Welch, R. R. San Juan, J. D. Masuda, D. W. Stephan, *Science* **2006**, *314*, 1124-1126.

[136] S. Singh, U. K. Barta, *Indian J. Chem. Sect. B* **1989**, *28*, 1-2.

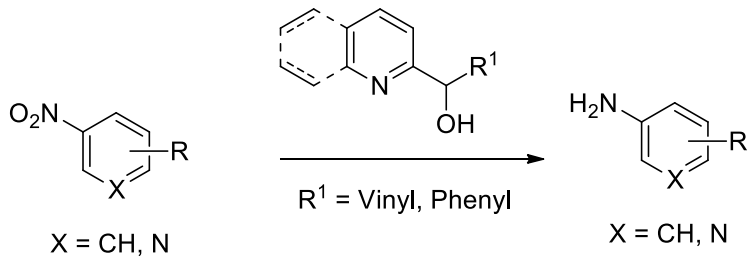
[137] M. Rueping, E. Sugiono, C. Azap, T. Theissmann, M. Bolte, *Org. Lett.* **2005**, *7*, 3781-3783.

[138] (a) S. Gomez, J. A. Peters, T. Maschmeyer, *Adv. Synth. Catal.* **2002**, *344*, 1037-1057; (b) T. Ohkuma, R. Noyori, In *Comprehensive Asymmetric Catalysis. Suppl. 1*; E. N. Jacobsen, A. Pfaltz, H. Yamamoto, *Eds.; Springer*, New York, **2004**; (c) V. I. Tararov, A. Borner, *Synlett* **2005**, 203-211.

However, in 2006 McMillan and co-workers reported the first example of organocatalyzed reductive amination of ketones in presence of HEH and chiral phosphoric acids.[139] On the basis of this result, other organic catalysts and hydrogen donors have been tested for reductive amination of aromatic and aliphatic carbonyl compounds.[140]

2.1.3 Use of Pyridylmethanols as Hydrogen Donors

Recent studies from our laboratory showed the possibility to use pyridylmethanols as hydrogen donors, mimetic of Hantzsch ester, for metal-free reductions of aromatic and heteroaromatic nitro compounds and imines to the corresponding amino derivatives under thermal conditions without catalysts (Scheme 2.4).[8,29,141]



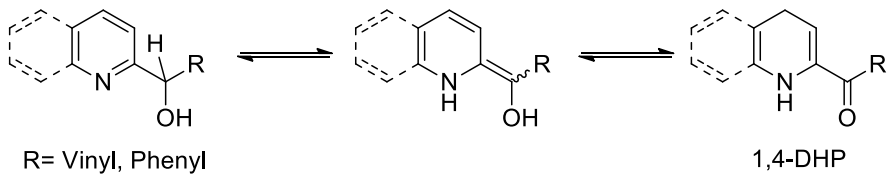
Scheme 2.4 - General scheme for the reduction of nitro compounds by pyridyl methanols.

From a stoichiometric point of view, 3 equiv of pyridylmethanol are required to reduce the nitro group to the amino group, because each molecule of alcohol can donate one molecule of H_2, and 3 molecules of hydrogen are required for the reduction of the nitro group to amine. This process produces 3 equiv of the corresponding pyridyl ketone that can be recovered and converted back to the

[139] R. I. Storer, D. E. Carrera, Y. Ni, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 84-86.
[140] A. M. Faisca Phillips, A. J. L. Bombeiro, *Org. Biomol. Chem.* **2017**, *15*, 2307-2340.
[141] D. Giomi, R. Alfini, A. Brandi, *Tetrahedron Lett*. **2008**, *49*, 6977-6979.

alcohol by reduction with $NaBH_4$[142] and recycled, making the methodology environmentally friendly.

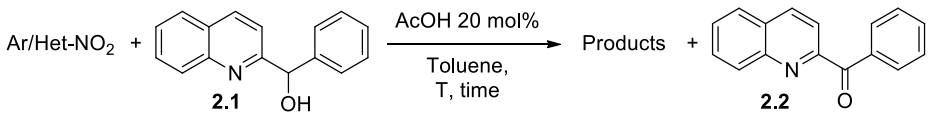
Moreover, quinolyl derivatives show a higher reactivity with respect to the corresponding pyridyl one, because of the lower aromaticity of quinoline with respect to pyridine that implies an easier access to the 1,4-dihydropyridine moiety (1,4-DHP), likely the reactive tautomer present at the equilibrium (Scheme 2.5).



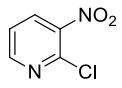
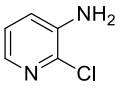
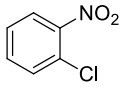
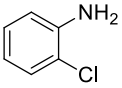
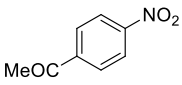
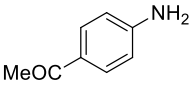
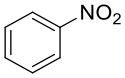
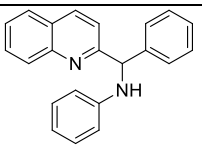
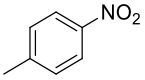
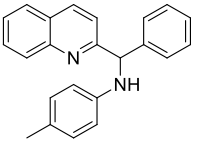
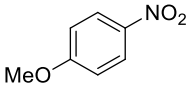
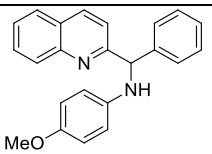
Scheme 2.5 - Tautomeric equilibria for quinolylmethanols.

In particular, phenyl(2-quinolyl)methanol (PQM) (**2.1**) was efficiently applied in quite mild reaction conditions to the selective reduction of variously functionalized nitroarenes, showing good tolerance towards many functionalities such as halogen, carbonyl, ester, ether, vinyl, alkyl groups.[29] The use of electron-poor nitroarenes afforded the corresponding anilines (Table, entries 1-3), employing 3 equiv of PQM, while electron-rich starting reagents allowed a multi-step process involving NO_2 reduction and reductive amination of phenyl (2-quinolyl) ketone (PQK) (**2.2**) (coming from oxidation of **2.1**) with the aniline derivative (Table, entries 4-6), by using one more equiv of PQM.

*Table - Reactions of PQM (**2.1**) with aromatic and heteroaromatic nitro compounds.*



[142] H. V. Kamath, K. S. Nargund, S. N. Kulkarni, *Indian J. Chem., Sect. B* **1978**, *16B*, 903–906.

Entry	Reagent	T (°C)	t (h)	**2.1** (equiv)	Product	Yield (%)[a]
1[b]		70 110	18 14	3.1		70 90
2		70 70	24 48[c]	3.1		56 87
3		70	72	3.1		70
4		70	144	4.1		45
5		110	48	4.1		76
6		100	72	4.1		82

[a] isolated yields; [b] reaction performed without AcOH; [c] 3.5 equiv.

On this ground, the thesis work has been focused on the application of quinolylmethanols **2.1** and **2.3** as hydrogen donors for the metal-free reductions of nitro aromatic/heteroaromatic compounds (Figure 2.1). In particular, on the basis of the easy conversion of ketones **2.2** and **2.4** into the corresponding alcohols, and with the aim of improving efficiency and sustainability of this method, the application of quinolylmethanols as organocatalysts (instead of stoichiometric reducing agents), regenerated in a parallel catalytic cycle, has been investigated. Moreover, preliminary studies have been addressed to the synthesis of solid-phase supported quinolylmethanols exploiting derivative **2.3**.

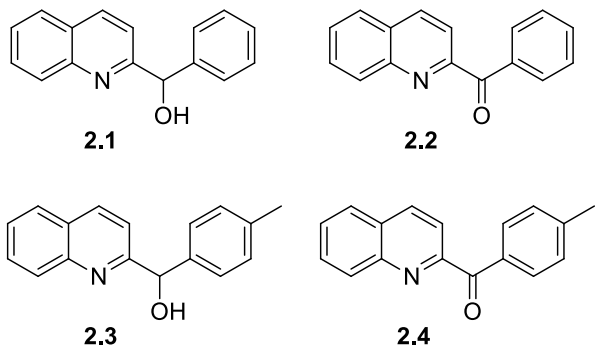


*Figure 2.1 - Quinolylmethanols (**2.1** and **2.3**) and their oxidized forms (**2.2** and **2.4**).*

***

With the aim to reach the above goals, two research lines have been developed:

1. *Use of phenyl(2-quinolyl)methanol (PQM) (**2.1**) as organocatalyst.*

   Operating with substoichiometric amounts of alcohol **2.1**, in the presence of an excess of a cheap and easy to use reducing agent, able to perform a catalytic cycle for the *in situ* regeneration of **2.1** from phenyl (2-quinolyl) ketone (PQK) **2.2**, it would be possible to decrease the amount of quinolylmethanol involved in the reaction, making even easier the products recovery.

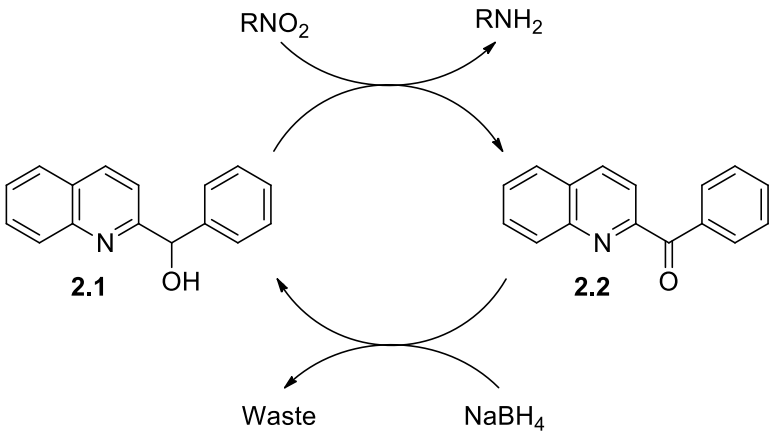
2. *Synthesis of a solid-phase supported quinolylmethanol.*

   This system could be synthesized starting from (2-quinolyl)(4-tolyl)methanol (QTM) (**2.3**) exploiting the methyl group as point of attack on the resin. This approach could allow an easy recovery of the reagent, as well as the reaction products (for instance by filtration).

2.2 Results

2.2.1 Use of phenyl(2-quinolyl)methanol (**2.1**) as organocatalyst

A catalytic cycle is a multistep reaction that involves a catalyst. Since catalysts are regenerated, catalytic cycles are usually described as a sequence of chemical reactions, in the form of a loop, in which the substrate reacts with the catalyst to give the reaction product through consumption of catalyst itself that can be constantly regenerated by a stochiometric, inexpensive and green reagent.
in this context, the reduction of aromatic and heteroaromatic nitro compounds has been studied using a catalytic amount of **2.1** and an excess of inexpensive reducing agent such as $NaBH_4$ (Scheme 2.6).



*Scheme 2.6 - Use of phenyl(2-quinolyl)methanol **(2.1)** as organocatalyst.*

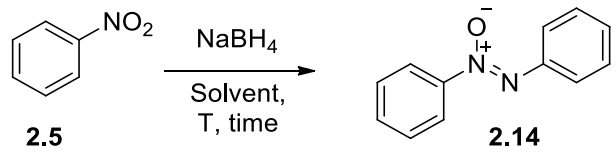
2.2.1.1 Reactions of aromatic nitro compounds with $NaBH_4$

To evaluate the possibility of a background reduction by $NaBH_4$, the nitro aromatics were treated with the above reagent, in absence of **2.1**, in different conditions. The reaction of nitrobenzene was initially studied. No reactivity was observed in toluene or EtOH as solvents, at 70 °C (Table 2.1, entries 1 and 2).

Using solvent mixtures as Toluene/EtOH 2:1 v/v or Toluene/THF 1:1 v/v at the same temperature, the starting material still remains the predominant species in the reaction crudes but minor amounts of the azoxy compound **2.6** were formed (Table 2.1, entries 3 and 6).

Operating at 110 °C, analogous results were obtained in Toluene/EtOH 2:1 v/v, for 24 or 96 hours (Table 2.1, entries 4 and 5) while in toluene/THF, after 96 hours, the azoxy derivative was the only reaction product, isolated in 92% yield (Table 2.1, entry 8).

Table 2.1 - Reactions between nitrobenzene and $NaBH_4$. [a]



2.5 **2.14**

Entry	Solvent	T (°C)	t (days)	**2.5**[b] (%)	**2.6**[b] (%)
1	Toluene	70	7	100	0
2	EtOH	70	7	100	0
3	Toluene/EtOH 2:1[c]	70	7	75	25
4	Toluene/EtOH 2:1[c]	110	1	75	25
5	Toluene/EtOH 2:1[c]	110	4	75	25
6	Toluene/THF 1:1	70	7	87	13
7	Toluene/THF 1:1	110	1	80	20
8	Toluene/THF 1:1	110	4	0	92[d]

[a] Reaction conditions: Pyrex screw cap tube N°13, nitrobenzene **2.5** (0.062 g, 0.5 mmol, 0.051 mL) and $NaBH_4$ (0.037 g, 1 mmol), in the solvent (1 mL); [b] molar ratio evaluated by ^1H NMR; [c] reaction performed with 1.5 ml of solvent; [d] isolated yield.

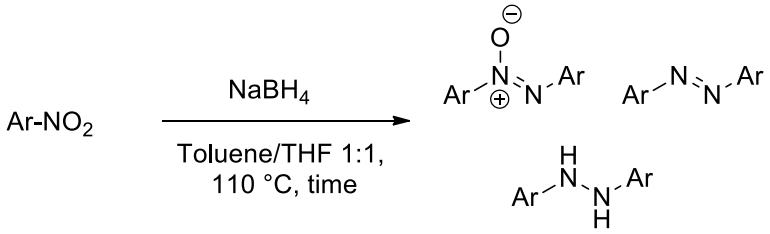
The data reported in Table 2.1 show the inability of $NaBH_4$ to reduce nitrobenzene to aniline, regardless the solvent used. However, concerning the solvent choice, the mixture toluene/THF 1:1 appears more promising (see later, Table 2.3), mainly, because in toluene/EtOH hydrogen gas evolution was observed, that could work as reducing agent in addition to PQM influencing the reaction pathway. Then, this solvent mixture was used to check the reactivity of other aromatic nitro compounds towards $NaBH_4$, as reported in Table 2.2.

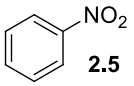
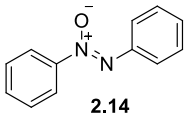
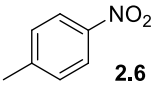
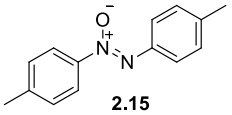
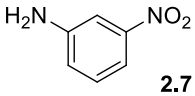
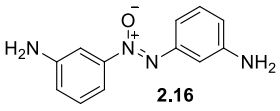
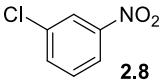
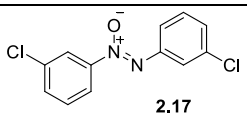
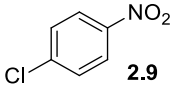
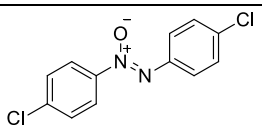
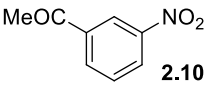
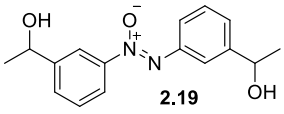
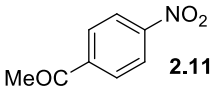
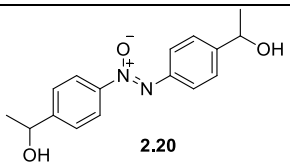
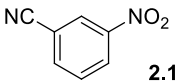
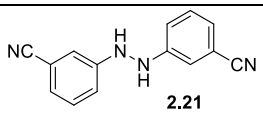
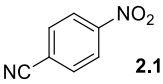
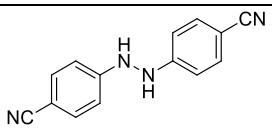
Nitro aromatics **2.7**-**2.11** showed a similar reactivity to that observed for nitrobenzene, leading to the corresponding azoxy or azo derivatives, depending both on the substrate and on reaction times.

With 3- and 4-nitroacetophenone **2.10** and **2.11**, the reduction of the carbonyl group was observed along with that of the nitro group, affording the azoxyphenylethanols **2.19** and **2.20** (Table 2.2, entries 6 and 7).

A different behavior was observed for 3- and 4-nitrobenzonitrile **2.12** and **2.13**: the CN group was inert towards $NaBH_4$ and, depending on the reaction time, the formation of the corresponding hydrazo derivatives **2.21** and **2.22** was observed in 24 hours (Table 2.2, entries 9 and 10).

Table 2.2 - Reactions of nitro aromatics and $NaBH_4$. [a]



Entry	Reagent	Product[b]	t (h)	Yield (%)[c]
1	 **2.5**	 **2.14**	96	92
2	 **2.6**	 **2.15**	96	94
3	 **2.7**	 **2.16**	96	95
4	 **2.8**	 **2.17**	24	97
5	 **2.9**	 **2.18**	24	96
6	 **2.10**	 **2.19**	24	96
7	 **2.11**	 **2.20**	18	96
9	 **2.12**	 **2.21**	24	93
10	 **2.13**	 **2.22**	24	93

[a] Reaction conditions: Pyrex screw cap tube N°13, nitroarene (0.5 mmol) and $NaBH_4$ (0.037 g, 1 mmol), in Toluene (0.5 mL) and THF (0.5 mL); [b] observed *via* ^1H NMR; [c] isolated yields.

Not any reactivity was observed subjecting nitro derivatives **2.23-2.31** (Figure 2.2) to the above reaction conditions for 24 hours.

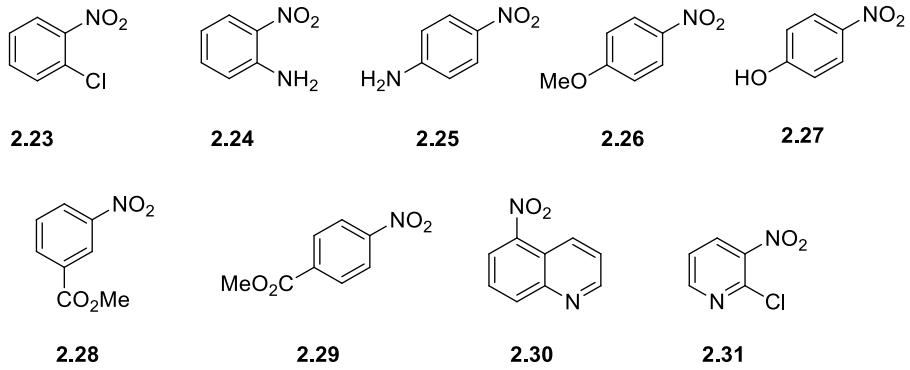
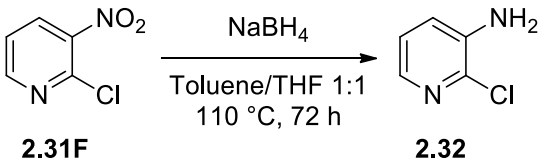


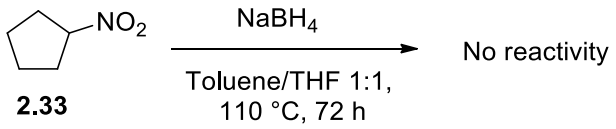
Figure 2.2 - Unreactive nitroarenes towards $NaBH_4$.

However, with 2-chloro-3-nitropyridine (**2.31**) contrasting results were observed in relation to the chemical manufacturer. Compound **2.31** from Sigma-Aldrich did not show any reactivity, while the same reagent from Fluka was completely consumed leading to 3-amino-2-chloropyridine (**2.32**), isolated in 38% yield (Scheme 2.7). This different behavior is probably due to an impurity that catalyse the reaction.



*Scheme 2.7 - Reduction of **2.31F** (from Fluka) to **2.32** with $NaBH_4$.*

An aliphatic nitro compound, such as nitrocyclopentane (**2.33**), was absolutely inert in the above conditions.



*Scheme 2.8 - Attempt to reduce nitrocyclopentane (**2.31**) with $NaBH_4$.*

As a whole, according with previous data (see Ref. 101 and 102), the ability of $NaBH_4$ to reduce nitro aromatics to azoxy/azo derivatives depends on the electronic effect of the substituents present on the ring. In 1962 Shine at *al.*, reducing nitroarenes with KBH_4 in ethanol or pyridine, observed that '*m*- and *p*-substituted nitrobenzenes carrying a substituent with a positive value of Hammett sigma constant are reduced in good yield to the azoxy compound, while nitrobenzenes with negative sigma constants are not reduced'.

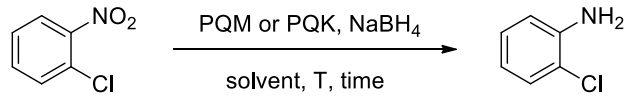
In particular, the above results show the absolute inertness of electron-rich and strongly electron-poor systems (see, Figure 2.2) that can be recovered unchanged from the reaction mixtures. On the other hand, weakly activated/deactivated nitroarenes can be reduced by $NaBH_4$ following the condensation pathway (see, Scheme 2.1). However, the differences in the behavior of 3- and 4-nitrobenzonitrile **2.12** and **2.13** in comparison with the corresponding esters **2.28** and **2.29**, as well as for 1-chloro-2-nitrobenzene **2.23** with respect to *meta*- and *para*-isomers **2.8** and **2.9** , are not easily rationalized considering mesomeric/inductive effects, then evidencing the influence of many different factors on the reactivity.

2.2.1.2 Organocatalytic reduction of nitroarenes to aniline derivatives with PQM and $NaBH_4$

On the basis of the above results and previous data concerning the use of PQM (**2.1**) as stoichiometric metal-free reducing agent in thermal conditions,[29] the application of **2.1** (or **2.2**) as organocatalyst, was studied in the presence of $NaBH_4$.

First, 1-chloro-2-nitrobenzene (**2.23**) was treated with 0.5-1.0 equiv of PQM (**2.1**) or PQK (**2.2**) and an excess of $NaBH_4$ and the resulting mixtures were heated in different conditions. Operating at 70 °C in toluene/EtOH 2:1 as solvent for 72 or 96 hours, the reaction mixture resulted quite complex and only traces of 2-chloroaniline (**2.34**) were observed (Table 2.3, entries 1 and 2). The reaction was significantly improved performing the above reaction in toluene/THF 1:1, affording 2-chloroaniline as the main reaction product (Table 2.3, entries 3 and 4). A sharp improvement was observed by heating at 110 °C: the conversion of **2.23** was complete after 6 hours (Table 2.3, entries 5 and 6) and 2-chloroaniline was isolated in 90% yield after column chromatography. No differences were observed using PQM (**2.1**) or PQK (**2.2**) as organocatalysts and the 0.5:1 molar ratio with respect to **2.23** is sufficient to perform the reduction process, while with a molar ratio 0.2:1 minor amounts of azoxy derivative were detected in the reaction mixture along with **2.34**. (Table 2.3, entry 7). Thus, these results confirm the possibility of decreasing the reducing agent from stoichiometric (3:1) to catalytic (0.5:1) amounts. Moreover, the excess of $NaBH_4$ allows to recover **2.1** directly from the reaction mixture, for further applications.

*Table 2. 3 - Organocatalytic reductions of 1-chloro-2-nitrobenzene (**2.23**) with PQM or PQK and $NaBH_4$.[a]*



2.23 **2.34**

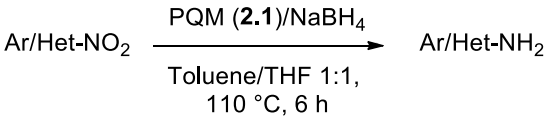
Entry	Solvent	T (°C)	t (hours)	PQM or PQK (equiv)	**2.34** (%)[b]
1	Toluene/EtOH 2:1[c]	70	72	PQK (1.0)	traces
2	Toluene/EtOH 2:1[c]	70	96	PQK (0.5)	traces
3	Toluene/THF 1:1	70	72	PQK (1.0)	80
4	Toluene/THF 1:1	70	72	PQK (0.5)	80
5	Toluene/THF 1:1	110	6	PQK (0.5)	> 90
6	Toluene/THF 1:1	110	6	PQM (0.5)	> 90
7	Toluene/THF 1:1	110	6	PQM (0.2)	> 80[d]

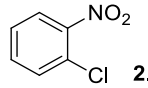
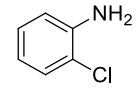
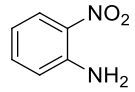
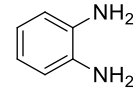
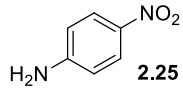
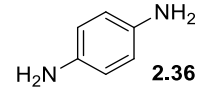
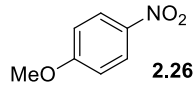
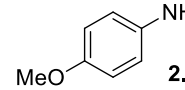
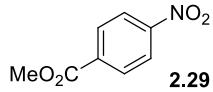
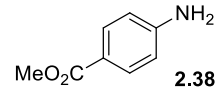
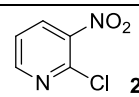
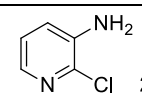
[a] Reaction conditions: Pyrex screw cap tube N°13, 1-cloro-2-nitrobenzene (**2.22**) (0.039 g, 0.25 mmol), PQM or PQK, $NaBH_4$ (0.019 g, 2 mmol), in the solvent (1 mL); [b] Analises GC-MS and ^1H NMR; [c] reaction performed with 1.5 ml of solvent; [d] azoxy derivative (ca. 20%) detected in the reaction mixture.

With these optimized conditions in hand, other nitroarenes were tested and the results are summarized in Table 2.4. Nitroanilines **2.24** and **2.25** showed an analogous behavior with respect to 1-chloro-2-nitrobenzene (**2.23**), leading to phenylendiamines **2.35** and **2.36** in 70 and 65% yields, respectively (Table 2.4, entries 2 and 3). The reaction of 4-nitroanisole (**2.26**) was performed with 1.1 equiv of PQM to favor the formation of *p*-anisidine (**2.37**), isolated in 65% yield along with the corresponding azo derivative (17%, Table 2.4, entry 4). By treatment of methyl 4-nitrobenzoate (**2.29**) in the above conditions, a partial reduction of the quinoline ring of **2.1** was observed, along with the formation of the corresponding aniline and hydrazo compound. Decreasing the temperature at 70 °C, reduction of PQM was avoided, but the ^1H NMR spectrum showed the presence of aniline (20% ca.) and condensation products. Luckily, performing the reaction at 70 °C, with 1 equiv of alcohol **2.1**, methyl 4-aminobenzoate (**2.38**) was recovered in 46% yield together with unchanged PQM (Table 2.4, entry 5).

A different behavior was observed for 2-chloro-3-nitropyridine (**2.31**): performing the reaction at 110 or 90 °C the total reduction of **2.31** to **2.32** in 6 hours was observed. Unfortunately, this process showed the formation of partially reduced alcohol **2.1** (^{1}H NMR) leading to 1,2,3,4-tetrahydroquinoline derivatives; decreasing the temperature at 70 °C, after 18 hours, the starting materials were recovered unchanged.

Table 2.4 - Reduction of nitroaromatics with PQM/$NaBH_4$: synthesis of aniline derivatives.[a]



Entry	Reagent	PQM (equiv)	Product	Yield (%)[b]
1	 **2.23**	0.5	 **2.34**	91
2	 **2.24**	0.5	 **2.35**	70
3	 **2.25**	0.5	 **2.36**	66
4	 **2.26**	1.0	 **2.37**	65[c]
5	 **2.29**	1.0[d]	 **2.38**	47
6	 **2.31**	0.5	 **2.32**	40 [e]

[a] Reaction conditions: Pyrex screw cap tube N°13, nitroarene (0.25 mmol), PQM (0.030 g, 0.13 mmol), $NaBH_4$ (0.037 g, 1 mmol), in Toluene (0.5 mL)/THF (0.5 mL); [b] isolated yields; [c] the corresponding azo derivative was also isolated in 13% yield; [d] reaction performed at 70 °C for 24 h; [e] alcohol **2.1** was almost totally reduced in these conditions.

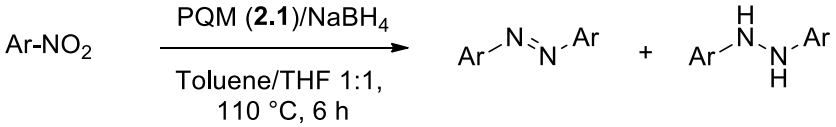
The above results show that nitroaromatics **2.23**-**2.26**, **2.29**, and **2.31**, inert towards $NaBH_4$ are easily reduced by PQM/$NaBH_4$ in the organocatalyzed process, with high chemoselectivity.

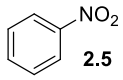
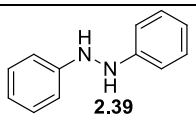
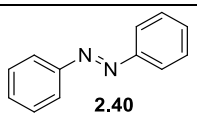
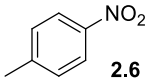
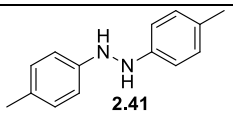
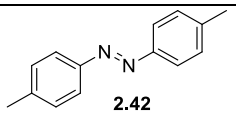
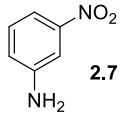
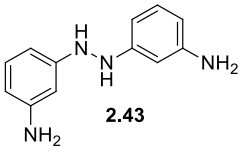
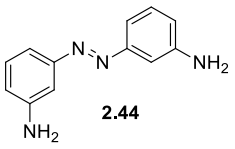
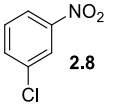
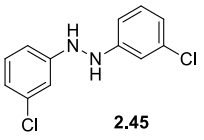
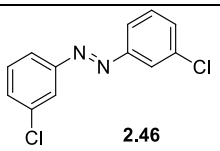
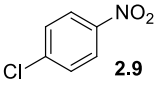
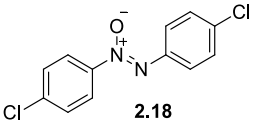
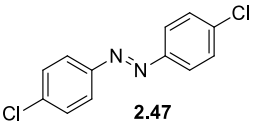
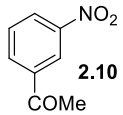
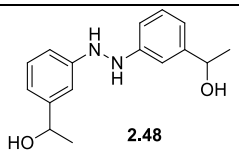
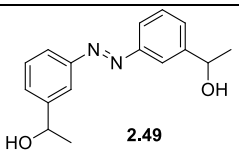
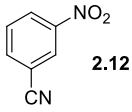
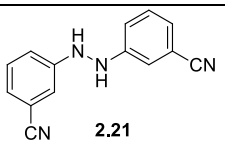
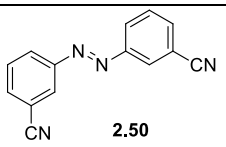
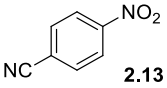
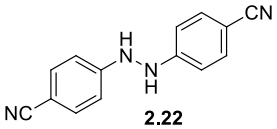
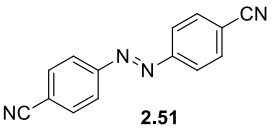
On the other hand, a different behavior was observed with nitro arenes **2.5**-**2.10**, **2.12** and **2.13** that react with PQM/$NaBH_4$ to give mixtures of azo and hydrazo derivatives (Table 2.5), never observed in the thermal processes. Even in these conditions, compound **2.10** underwent reduction of both COMe and NO_2 groups (Table 2.5, entry 6), while the nitro group of *p*-nitroacetophenone (**2.11**), methyl 3-nitrobenzoate (**2.28**), and 5-nitroquinoline (**2.30**) was almost totally inert, and only the reduction of the keto group in **2.11** was observed.

No reactivity was observed when nitrocyclopentane (**2.33**) was treated with alcohol **2.1** and $NaBH_4$ in the above conditions, even for longer times (72 hours).

These results clearly show that the addition of PQM is not able to change the reaction outcome for nitro compounds able to react with $NaBH_4$ through the condensation pathway (see, Scheme 2.1). The only effect of the addition of PQM is an increasing of the reaction rates for the formation of condensation products.

Table 2.5 - Reduction of nitroaromatics with PQM/$NaBH_4$: formation of condensation products.[a]



Entry	Reagent	Major product[b]	Minor product[b]
1	 **2.5**	 **2.39**	 **2.40**
2	 **2.6**	 **2.41**	 **2.42**
3	 **2.7**	 **2.43**	 **2.44**
4	 **2.8**	 **2.45**	 **2.46**
5	 **2.9**	 **2.18**	 **2.47**
6	 **2.10**	 **2.48**	 **2.49**
7	 **2.12**	 **2.21**	 **2.50**
8	 **2.13**	 **2.22**	 **2.51**

[a] Reaction conditions: Pyrex screw cap tube N°13, nitroarene (0.25 mmol), PQM (0.030 g, 0.13 mmol), $NaBH_4$ (0.037 g, 1 mmol), in Toluene (0.5 mL)/THF (0.5 mL); [b] observed *via* ^1H NMR analyses.

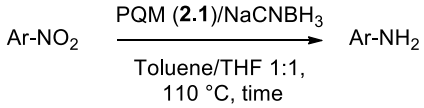
2.2.1.3 Organocatalytic reduction of nitroarenes to aniline derivatives with PQM and $NaCNBH_3$

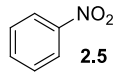
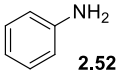
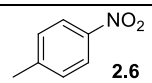
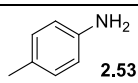
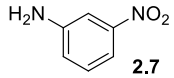
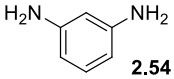
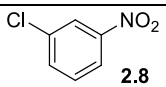
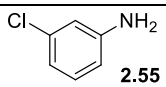
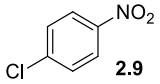
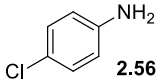
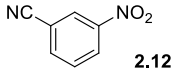
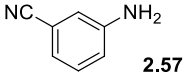
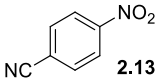
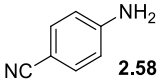
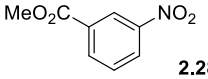
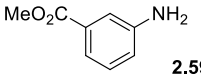
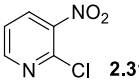
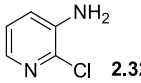
The main problem observed in the reduction with PQM and $NaBH_4$ was the competition between the reducing action of the organocatalyst and that of the stoichiometric reducing agent. Then, with the aim to gain better inside, the 'milder' $NaCNBH_3$ was tested in place of $NaBH_4$.

When nitroarenes were treated with $NaCNBH_3$ alone at 110 °C for 24 hours, no reduction of the nitro group was observed [only the carbonyl function was reduced in *p*-nitroacetophenone (**2.11**)]. However, the reduction of **2.2** to **2.1** promoted by $NaCNBH_3$ was slow (12 hours) at 110 °C and did not occur at 70 °C. On this basis, 1-chloro-2-nitrobenzene (**2.23**) was treated with PQM and $NaCNBH_3$ in toluene/THF 1:1 as solvent, but after 24 hours at 110 °C the conversion into aniline **2.34** was only partial, in contrast with our earlier observation with the PQM/$NaBH_4$ system. For this reason, the system PQM/$NaCNBH_3$ was not tested on nitroaromatics **2.24**-**2.26** and **2.29**. The system PQM/$NaCNBH_3$ has been applied on nitro derivatives **2.5**-**2.13** and **2.28**, mainly reduced to give the azo-compounds with PQM/$NaBH_4$. Unfortunately, even if depending on the nature of substrates to be reduced, the application of the system PQM/$NaCNBH_3$ for long reaction times can determine the partial reduction of the quinoline ring of **2.1** to the 1,2,3,4-tetrahydroquinoline derivative (^{1}H NMR), then with loss of the reducing agent.

Nitrobenzene (**2.5**), 4-nitrotoluene (**2.6**), and 1-chloro-4-nitrobenzene (**2.9**) were able to give the corresponding anilines in quite satisfactory yields (Table 2.6, entries 1, 2, and 4), while compounds **2.8**, **2.12**, **2.13** and **2.28** gave anilines **2.55** and **2.57**-**2.59** only in low yields (Table 2.6, entries 3, 5, and 6). Both 3- and 4-nitroacetophenone **2.10** and **2.11** led to complex reaction mixtures in these conditions.

*Table 2.6 - Reactivity of nitro compounds with **2.1** and $NaCNBH_3$.* [a]

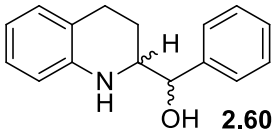


Entry	Reagent	t (hours)	Product	Yield[b] (%)
1	 **2.5**	45	 **2.52**	64[c]
2	 **2.6**	72	 **2.53**	60[d]
3	 **2.7**	42	 **2.54**	52[e]
4	 **2.8**	36	 **2.55**	56[f]
5	 **2.9**	24	 **2.56**	75[g]
6	 **2.12**	18	 **2.57**	17[h]
7	 **2.13**	24	 **2.58**	34[i]
8	 **2.28**	18	 **2.59**	40
9	 **2.31**	18	 **2.32**	53[j]

[a] Reaction conditions: Pyrex screw cap tube N. 13, nitroarene (0.25 mmol), **2.1** (0.030 g, 0.13 mmol), and $NaCNBH_3$ (0.024 g, 0.38 mmol), in Toluene (0.5 ml)/THF (0.5 ml), 110 °C; [b] isolated yields; [c] isolated also 13% of **2.40**; [d] isolated also 8% of **2.42**; [e] recovered 23% of **2.7**; [f] isolated also 16% of **2.45** and 20% of **2.46**; [g] isolated also 22% of **2.47**; [h] isolated also 10% of **2.50**; [i] isolated also 17% of **2.22** and 14% of **2.51**; [j] small amounts of **2.60** were recovered.

* * *

As a final test, attempts to reduce **2.6** and **2.12** with PQM **2.1** in the presence of BH_3/THF (1 M) (110 °C, 48 and 24 hours respectively) were unsuccessful, showing only the reduction of alcohol **2.1** to the corresponding tetrahydroquinoline derivatives **2.60** (Figure 2.3).



2.60

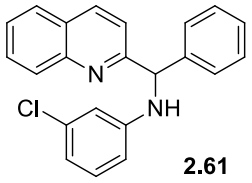
Figure 2.3 – Phenyl(1,2,3,4-tetrahydroquinolin-2-yl)methanol

2.2.1.4 Thermal reduction of nitroarenes PQM (**2.1**) as stoichiometric reducing agent

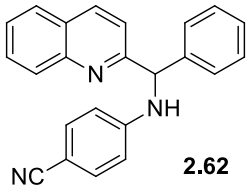
Because of the poor results obtained for nitro compounds **2.7**, **2.8**, **2.12**, **2.13**, **2.27**, **2.28** and **2.29** with the catalytic method, the metal-free reduction of these systems was studied under thermal conditions employing a stoichiometric amount of **2.1** (3.1 or 4.1 equiv).

As previously reported for other substrates,[29] electron-rich nitroarenes are able to give univocally the reductive amination product, instead of the free amine. In fact, by treatment of 3-nitroaniline (**2.7**) and 4-nitrophenol (**2.27**) with 4.1 equiv of PQM (**2.1**), both in presence and in absence of a catalytic amount of AcOH, compounds **2.63** and **2.64** were isolated in 31 and 82% (96% relative yield considering the recovery of 4-nitrophenol) yields, respectively (Table 2.7, entries 6 and 7). 3-Nitroaniline afforded a more complex reaction mixture leading to minor amount of reductive amination product.

Electron-poor nitroarenes **2.8**, **2.12**, **2.13**, **2.28**, and **2.29** gave rise to the corresponding anilines isolated in 44-85% yields. However, an unexpected behavior was observed for 1-chloro-3-nitrobenzene (**2.8**) and 4-nitrobenzonitrile (**2.13**). In fact, operating with or without a catalytic amount of AcOH, small amounts of the corresponding reductive amination compounds **2.61** and **2.62**, respectively, were isolated by chromatography (Table 2.7, entries 1 and 3). This trend was never observed earlier for other EWG substituted nitroarenes.



2.61



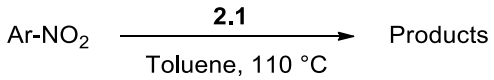
2.62

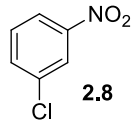
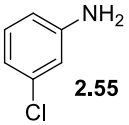
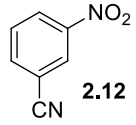
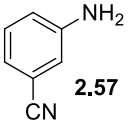
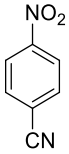
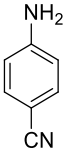
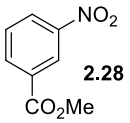
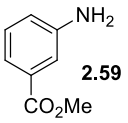
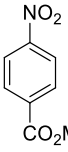
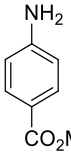
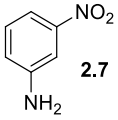
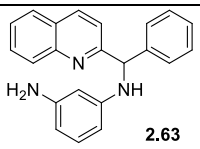
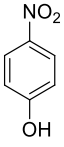
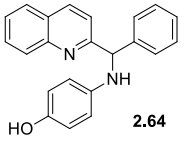
Figure 2.4 - Reductive amination products.

Moreover, the presence of AcOH in the thermal reaction of 4-nitrobenzonitrile (**2.13**) and methyl 4-nitrobenzoate (**2.29**) led to small amounts of condensation products (mainly hydrazo derivatives), while operating in the same conditions but in absence of AcOH condensation products were not observed in the reaction mixture.

No reactivity was observed for nitrocyclopentane (**2.33**) even in the thermal process, confirming the inability of PQM to reduce aliphatic nitro compounds.

*Table 2.7 - Thermal reduction of nitrocompounds with **2.1**.[a]*

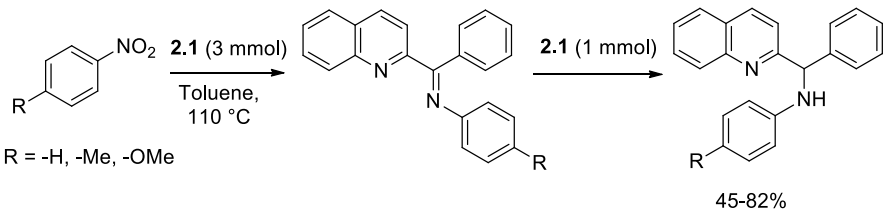


Entry	Reagent	t (hours)	PQM (equiv)	AcOH cat[b]	Product	Yield (%)[c]
1[d]	 **2.8**	18	3.1	Yes	 **2.55**	64
2	 **2.12**	18	3.1	No	 **2.57**	72
3[e]	 **2.13**	18	3.1	No	 **2.58**	78
4[f]	 **2.28**	24	3.1	Yes	 **2.59**	70
5	 **2.29**	18	3.1	No	 **2.38**	85
6	 **2.7**	72	4.1	Yes	 **2.63**	31
7	 **2.27**	90	4.1	No	 **2.64**	82[g]

[a] Reaction conditions: Pyrex screw cap tube N. 13, nitroarene (0.25 mmol), **2.1**, Toluene (0.5 mL); [b] AcOH 20 mol% in toluene; [c] isolated yields; [d] recovered also product **2.61** (17%); [e] recovered also product **2.62** (8%); [f] reaction performed at 70 °C; [g] recovered unreacted 4-nitrophenol **2.27** (14%).

* * *

The above results show a multifaceted picture of the reactivity of PQM as organocatalyst in conjunction with $NaBH_4$ or $NaCNBH_3$. The experimental data, and mainly the synthetic applications of both systems, strongly depend on the kind (and position) of the substituent present in the aromatic ring. Nitroarenes **2.23**-**2.26**, **2.29**, and **2.31** afforded the corresponding amines in 40-91% yields when treated with PQM/$NaBH_4$, while **2.5**-**2.9**, **2.12**, **2.13**, **2.28**, and **2.31** were reduced to amines, isolated in 17-75% yields, with PQM/$NaCNBH_3$. These results, however, are significant because the systems PQM/$NaBH_4$ and PQM/$NaCNBH_3$ can play a complementary role with respect to the thermal processes. In fact, previous studies concerning thermal reactions,[29] showed the formation of reductive amination products when electron-rich nitro compounds (**2.6** and **2.26**) and nitrobenzene (**2.5**) were reduced with PQM (see, Table, entries 4-6). The nucleophilic attack of the aniline system on the carbonyl moiety of PQK (**2.2**), coming from oxidation of **2.1**, gave rise to an imine then reduced with PQM (Scheme 2.9). On the contrary, in the organocatalytic process the amount of PQK is always low, thanks to the easy in situ reduction to PQM, making possible anilines recovery without consumption of the reducing agent.



*Scheme 2.9 - Reductive amination of nitroaromatics with PQM (**2.1**).*

2.2.2 Synthesis of a solid-phase supported quinolylmethanol

In order to obtain an easy recovery of the reducing agent, the possibility to synthesize a solid phase supported quinolylmethanol has been studied. For the design of this kind of reagent, two main possibilities can be planned involving quinoline or phenyl moieties (Figure 2.3).

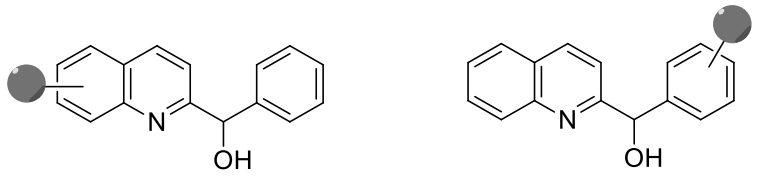
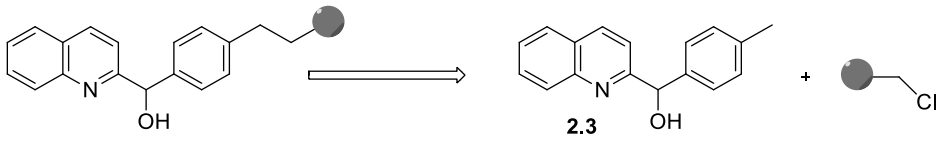


*Figure 2.5 - Possible ways to support **2.1** on a solid phase.*

In a first attempt, the linkage of the solid support *via* a C-C bond on the phenyl ring looked a promising option, likely implying a scarce impact on the reactivity of the supported reducing agent with respect to **2.1**.



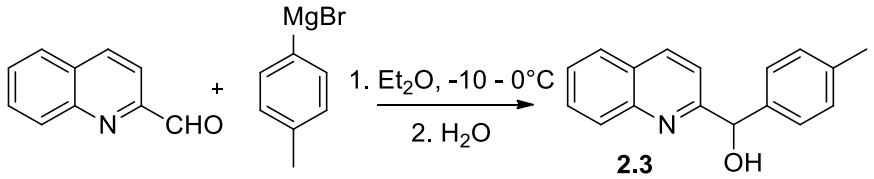
Scheme 2.10 - Retrosynthetic analysis.

From a retrosynthetic viewpoint (Scheme 2.10), a possible approach could involve the use of commercially available Merrifield resin and alcohol **2.3**, which differs from **2.1** just for the presence of a methyl group, able to allow more functionalizations. Merrifield resin is a cross-linked polystyrene resin that carries chlorobenzyl units. Developed by Robert Bruce Merrifield[143] (winner of the Nobel Prize in Chemistry in 1984), it is commonly used in solid-phase synthesis.

[143] A. R. Vaino, K. D. Janda, *J. Comb. Chem.* **2000**, *2*, 579-596.

The material is typically available as white beads, which must be swelled in suitable solvents (such as THF)[144] to permit the chlorine atoms substitutions.

The synthesis of alcohol **2.3**[145] was performed, analogously to the synthesis of **2.1**, following the Uenishi's procedure,[65] namely the reaction of 2-quinolylcarboxaldehyde with *p*-tolylmagnesium bromide (Scheme 2.11) and purification *via* column chromatography.



*Scheme 2.11 - Synthesis of (2-quinolyl)(4-tolyl)methanol (**2.3**).*

The presence of a methyl group in *para*-position, that acts as electron-donating group (EDG), could increase the electronic density of the molecule, then decreasing the acidity of the 'picoline-type' hydrogen atom. To evaluate this effect, the reactivity of **2.1** and **2.3** were compared before linking **2.3** to the solid support.

2.2.2.1 Reduction of nitroarenes with **2.3** as reducing agent

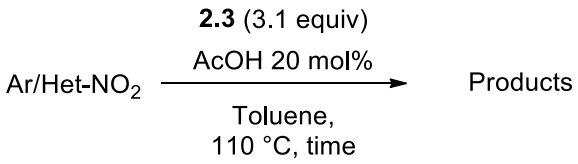
The reactivity of alcohol **2.3** as reducing agent was explored following the previously reported procedure.[29]

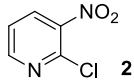
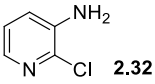
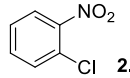
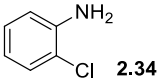
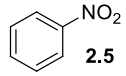
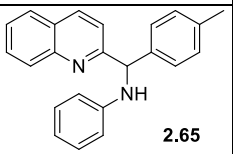
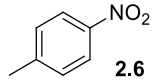
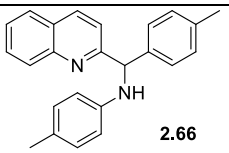
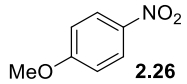
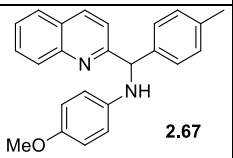
Satisfactory results were obtained increasing the reaction temperature at 110 °C for all the substrates. The same kind of reactivity with respect to **2.1** was observed (Table 2.8), allowing the isolation of the target anilines, as well as the

[144] R. Santini, M. C. Griffith, M. Qi, *Tetrahedron Lett.* **1998**, *39*, 8951-8954.
[145] B. Qiao, C. Li, X. Zhao, Y. Yin, Z. Jiang, *Chem. Commun.* **2019**, *55*, 7534-7537.

reductive amination products when more electron-rich nitro derivatives were employed, even if in somewhat lower yields.

*Table 2.8 - Reactivity of (2-quinolyl)(4-tolyl)methanol (**2.3**).with aromatic and heteroaromatic nitro compounds.*[a]



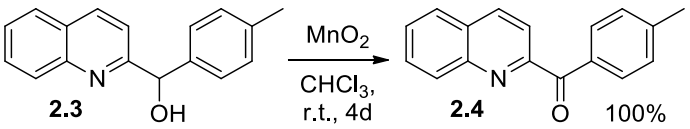
Entry	Reagent	t (hours)	**2.3** (equiv)	Product	Yield (%)[b]
1	 **2.31**	18	3.1	 **2.32**	78
2	 **2.23**	24	3.1	 **2.34**	75
3	 **2.5**	120	4.1	 **2.65**	31
4	 **2.6**	48	4.1	 **2.66**	74
5	 **2.26**	72	4.1	 **2.67**	66

[a] Reaction conditions: Pyrex screw cap tube N. 13, nitroarene (0.5 mmol), **2.3**, in Toluene (1 mL), AcOH 20 mol%; [b] isolated yields.

With these results in hand, the synthesis of the solid-phase supported quinolyltolylmethanol, following the previously envisaged retrosynthetic analysis, was investigated.

2.2.2.2 Synthesis of solid-phase supported **2.3**

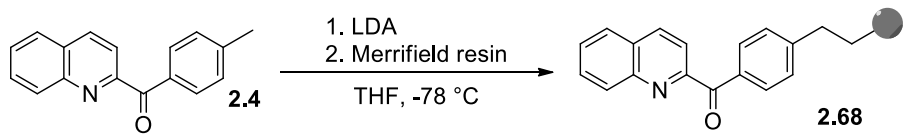
The strategy envisions the deprotonation of the methyl group of **2.3** using a strong non-nucleophilic base to substitute the benzyl chlorine atom of the Merrifield. Carrying out this reaction on the alcohol could lead to by-products because of the presence of a hydroxyl group as well as the 'picoline-type' hydrogen showing a week acidity. For this reason, the oxidation of alcohol **2.3** to ketone **2.4**,[146] using MnO_2 in chloroform[147] (Scheme 2.12), was the first synthetic step.



*Scheme 2.12 - Oxidation of **2.3** to **2.4**.*

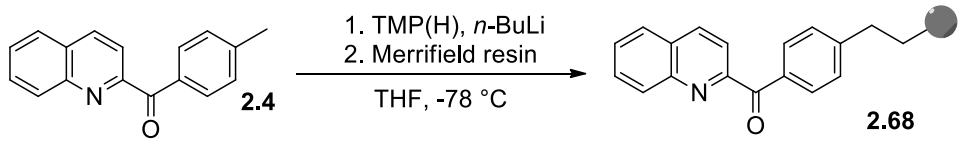
With ketone **2.4** in hands, the first attempt of deprotonation was performed by addition of ketone **2.4** to *in situ* generated LDA (Scheme 2.13) followed by addition of the resin. The loading of the resin, determined on the basis of elemental analysis was found poor (42%) and the unreacted ketone **2.4** was recovered as alcohol (likely, LDA can act as reducing system on the keto function). The synthesis of the solid-supported ketone **2.68** was also confirmed by FT-IR analysis, evidencing the presence of a strong band at 1656 cm^{-1} for the C=O stretching.

[146] Y. Siddaraju, M. Lamari, K. R. Prabhu, *J. Org. Chem.* **2014**, *79*, 3856-3865.
[147] (a) K. Kohata, Y. Kawamonzen, T. Odashina, H. Ishii, *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3398-3404; (b) F. Shisahara, R. Sugiura, E. Yamaguchi, A. Kitigawa, T. Murai, *J. Org. Chem.* **2009**, *74*, 3566-3568.



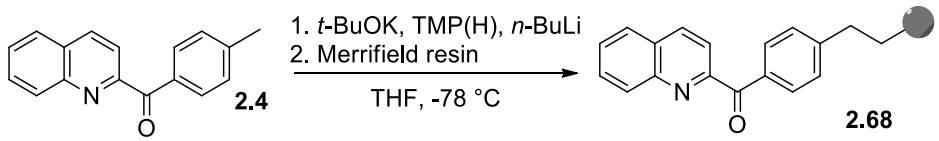
*Scheme 2.13 - Reaction between **2.4** and Merrifield resin in presence of LDA.*

To avoid the reduction of ketone **2.4**, 2,2,6,6-tetramethypiperidine, TMP(H), was used instead of diisopropylamine (DIPA), in the same reaction conditions (Scheme 2.14). In this case, unreacted ketone **2.4** was recovered, but the loading of the resin was even lower (23%).



*Scheme 2.14 - Reaction of **2.4** with Merrifield resin in presence of TMP(H)/BuLi.*

Since the result was still unsatisfactory, *t*-BuOK was added to the mixture (Scheme 2.15) to originate a lithium-potassium amide superbase,[148] but also in this case the resin loading was poor (28%). For this reason, the functionalization of the resin was repeated in the same conditions on the previously functionalized resin, allowing to obtain a resin with 31% loading.



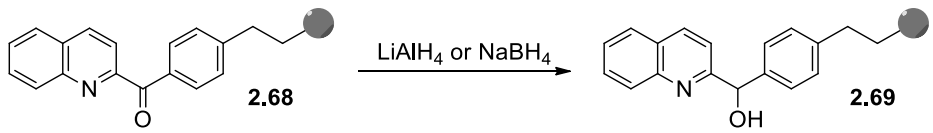
*Scheme 2.15 - Reaction of **2.4** with Merrifield resin in presence of TMP(H)/BuLi and t-BuOK.*

[148] A. Manvar, P. Fleming, D. F. O'Shea, *J. Org. Chem.* **2015**, *80*, 8727-8738.

Working without *t*-BuOK, but using a higher excess of base, it was possible to improve the loading until 35%, then evidencing some limits for this procedure.

The solid-supported ketone **2.68** was then reduced to the supported alcohol (Scheme 2.16). Two hydrides were tested for this reaction: $NaBH_4$ and $LiAlH_4$. Employing $NaBH_4$ the only reduction of the C=O group was achieved to reach the solid-supported alcohol **2.69-Cl**, as evidenced *via* FT-IR (the band at 1656 cm^{-1} disappared, while the O-H stretching band at 3390 cm^{-1} was observed). The more reactive $LiAlH_4$, in addition to C=O reduction, was also able to reduce C-Cl bonds ,[149] removing the unreacted chloromethyl functionalities leading to **2.69-H** (in the FT-IR spectrum it was not observed the strong band at 660-670 cm^{-1} for C-Cl stretching). Then, after the first complete reduction with $LiAlH_4$, the recovered oxidized resin **2.68-H**, could be recycled by milder reactions with $NaBH_4$ to give **2.69-H**.

Unfortunately, the reduction steps showed a weak decreasing in the resin loadings. Preliminary studies concerning the reduction of 2-chloro-3-nitropyridine **2.31**, in toluene and/or THF as solvent (to evaluate the swelling of the supported reagent) were not satisfactory, probably due to the low loading of the resin. A careful study of the conditions (solvent, as well temperature, time, etc.) for solid-phase supported reactions, will be fundamental to apply this methodology.



*Scheme 2.16 - Reduction of **2.58** to **2.59**.*

[149] (a) L. W. Trevay, W. G. Brown, *J. Am. Chem. Soc.* **1949**, *71*, 11675-1678; (b) W. E. Parham, C. D. Wright, *J. Org. Chem.* **1957**, *22*, 1473-1477; (c) A. Liguori, G. Sindona, N. Uccella, *Tetrahedron* **1983**, *39*, 683-687.

2.3 Conclusions

The reported results clearly confirm for phenyl(2-quinolyl)methanol (PQM, **2.1**), as well as (2-quinolyl)(4-tolyl)methanol (QTM, **2.3**), the reactivity as highly chemoselective metal-free reducing agents for nitro aromatic/heteroaromatic compounds and aromatic imines, in thermal conditions (70-110 °C). This reactivity is complementary to that of a well-known hydrogen-transfer reagent like Hantzsch ester, unable, however, to reduce the nitro functionality.[28]

Phenyl(2-quinolyl)methanol (PQM, **2.1**) has also been exploited as organocatalyst, in association with $NaBH_4$ or $NaCNBH_3$, to perform a catalytic cycle for nitroarenes reduction using substoichiometric amounts of PQM, that can be recovered at the end of the process.

The observed results strongly depend on the substituents present on the aromatic ring. In particular, 2- and 4-nitroaniline, 4-nitroanisole, 1-chloro-2-nitrobenzene, methyl 4-nitrobenzoate and 2-chloro-3-nitropyridine (see, Table 2.4), can be reduced with PQM/$NaBH_4$ to the corresponding anilines (40-91% yields), while nitrobenzene, 4-nitrotoluene, 3-nitroaniline, 1-chloro-3-nitro, 1-chloro-4-nitrobenzene, 3- and 4-nitrobenzonitrile, methyl 3-nitrobenzoate and 2-chloro-3-nitropyridine (see, Table 2.6) can be converted into anilines (17-75% yields) using PQM/$NaCNBH_3$ as reducing system.

From a mechanistic viewpoint, the reduction products, coming from the direct way in the thermal processes, in the organocatalyzed reactions can arise from both competitive pathways involving direct reduction or condensation (see, Scheme 2.1), as confirmed by the recovery of anilines and/or condensation products, depending on the substrates and reaction conditions. For this reason, the effects of substituents in the organocatalyzed processes are more difficult to rationalize.

Concerning the reactions of chloronitrobenzenes **2.8**, **2.9** and **2.23** with PQM/$NaBH_4$, a surprising reactivity was observed for 1-chloro-2-nitrobenzene

2.23, easily converted into 2-chloroaniline **2.34**, while the *metha* and *para* isomers **2.8** and **2.9** afforded condensation products. This different behaviour is not easily rationalized on the basis of –I and +M effects of chlorine atom, in fact only minor differences could be expected for *ortho* and *para* isomers (as observed for *ortho*- and *para*-nitroanilines). On this ground, a tentative rationalization could take into account an 'halogen bond' (XB) between chlorine atom and the oxygen of the NO_2 group at *ortho*-position: this 'noncovalent interaction between halogen atoms (Lewis acids) and neutral or anionic Lewis bases' could increase the electron density of the ring and then disfavour the condensation route, as observed for electron-rich nitroarenes.[150]

From a synthetic viewpoint, these processes show high chemoselectivity for the NO_2 group reduction with total tolerance of other functionalities such as Cl, OMe, NH_2, CN, CO_2Me (the only exception was the COMe group, reduced faster than the NO_2 one, but attempts to reduce nitroacetophenones to anilines were unsuccessful, giving rise to very complex reaction mixtures).

The use of PQM as organocatalyst allows more sustainable processes: reaction products are easily isolated thanks to the use of substoichiometric amounts of PQM, directly recovered at the end of the process and recycled. In this context, it is important to note that PQM, together with $NaBH_4$ or $NaCNBH_3$, can play a complementary role with respect to the thermal method avoiding reductive aminations processes involving PQK (see Scheme 2.9): indeed $ArNO_2$ (Ar = *p*-$MeOC_6H_4$, *p*-MeC_6H_4, *o*-$NH_2C_6H_4$, *m*-$NH_2C_6H_4$, *p*-$NH_2C_6H_4$, Ph) were converted into anilines.

On the other hand, the thermal methodology continues to be more efficient with strongly electron-poor derivatives (**2.12**, **2.13**, **2.28** and **2.29**):

[150] For an exhaustive discussion on 'halogen bond' see: (a) G. Cavallo, P. Metrangolo, R. Milani, T. Pilati, A. Priimagi, G. Resnati, G. Terraneo, *Chem. Rev.* **2016**, *116*, 2478-2601; (b) P. Metrangolo, H. Neukirch, T. Pilati, G. Resnati, *Acc. Chem. Res*. **2005**, *38*, 386-395.

aminobenzonitriles and methyl aminobenzoates (**2.57**-**2.59** and **2.38**) were isolated in 70-85% yields. As expected, 4-nitrophenol **2.27** gave the corresponding reductive amination compound **2.64** in 82% yield.
(2-Quinolyl)(4-tolyl)methanol **2.3** is also efficient as a reducing agent in metal-free thermal processes justifying its application in the synthesis of solid-phase supported systems. At this purposes, however preliminary results showed some problems probably related to the kind of resin and/or the applied procedure.
On this basis, other resins, as well as other approaches, are under investigation. For instance, a polymer-supported PQM could be synthesized through polymerization of suitable functionalized phenylquinolylmethanols, as reported in the literature for the synthesis of polymer-supported Hantzsch ester.[151]

Further studies to evaluate the synthetic potential of quinolylmethanols in the metal-free reduction of other functional groups as well as their applications to asymmetric reduction processes are underway in our laboratories.

[151] (a) R. He, P. H. Toy, Y. Lam, *Adv. Synth. Catal.* **2008**, *350*, 54-60; (b) J. Che, Y. Lam, *Adv. Synth. Catal.* **2010**, *352*, 1752-1758.

2.4 Experimental section

2.4.1 General

Melting points were taken on a Stuart Scientific SIMP3 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 chromatographic workup refers to the fraction of bp 40-70 °C. IR spectra were recorded with a Shimadzu FT-IR 84 00S spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded with Varian Mercuryplus 400 and Varian Inova instruments, 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.

2.4.2 General procedure for the reduction of nitroarenes with $NaBH_4$

In a screw cap Pyrex tube N°13, nitroarene (0.5 mmol) and $NaBH_4$ (0.037 g, 1 mmol) were dissolved a mixture of toluene (0.5 mL) and THF (0.5 mL) and heated at 110 °C for the allotted time. Excess of $NaBH_4$ was quenched by addition of water (0.5 mL). After extraction (EtOAc, 3x1 mL), the product was isolated.

*2.4.2.1 Synthesis of **2.14** from nitrobenzene (**2.5**)*

Starting from nitrobenzene (**2.5**) (0.062 g, 0.051 mL), after 96 hours azoxybenzene **2.14** was isolated (0.045 g, 92%) and its structure confirmed by ^{1}H NMR.

*2.4.2.2 Synthesis of **2.15** from 4-nitrotoluene (**2.6**)*

Starting from 4-nitrotoluene (**2.6**) (0.069 g), after 96 hours 1,2-di-*p*-tolyldiazene oxide **2.15** was isolated (0.053 g, 94%) and its structure confirmed by ^{1}H NMR.

*2.4.2.3 Synthesis of **2.16** from 3-nitroaniline (**2.7**)*

Starting from 3-nitroaniline (**2.7**) (0.069 g), after 96 hours 1,2-bis(3-aminophenyl)diazene oxide **2.16** was isolated (0.054 g, 95%) and its structure confirmed by ^{1}H NMR.

*2.4.2.4 Synthesis of **2.17** from 1-chloro-3-nitrobenzene (**2.8**)*

Starting from 1-chloro-3-nitrobenzene (**2.7**) (0.079 g), after 18 hours 1,2-bis(3-chlorophenyl)diazene oxide **2.17** was isolated (0.061 g, 97%) and its structure confirmed by ^{1}H NMR.

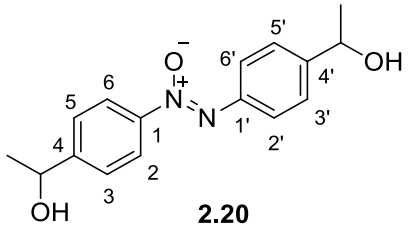
*2.4.2.5 Synthesis of **2.18** from 1-chloro-4-nitrobenzene (**2.9**)*

Starting from 1-chloro-4-nitrobenzene (**2.9**) (0.079 g), after 72 hours 1,2-bis(4-chlorophenyl)diazene oxide **2.18** was isolated (0.060 g, 96%) and its structure confirmed by ^{1}H NMR.

*2.4.2.6 Synthesis of **2.19** from 3-nitroacetophenone (**2.10**)*

Starting from 3-nitroacetophenone (**2.10**) (0.083 g), after 18 hours 1,2-bis(3-(1-hydroxyethyl)phenyl)diazene oxide **2.19** was isolated (0.069 g, 96%) and its structure confirmed by ^{1}H NMR.

*2.4.2.7 Synthesis of **2.20** from 4-nitroacetophenone (**2.11**)*



2.20

Starting from 4-nitroacetophenone (**2.11**) (0.083 g), after 18 hours 1,2-bis(4-(1-hydroxyethyl)phenyl)diazene oxide **2.20** was isolated (0.069 g, 96%). ^{1}H NMR ($CDCl_3$) δ: 8.27 (d, J = 8.7 Hz, 2H, H-2 and H-6), 8.17 (d, J = 8.5 Hz, 2H, H-2' and H-6'), 7.56-7.44 (m, 4H, H-3, H-5, H-3' and H-5'), 5.11-4.88 (m, 2H, C*H*OH and C*H*OH'), 2.01 (br s, 1H, O*H*), 1.96 (br s, 1H, O*H*), 1.53 (d, J = 6.5 Hz, 6H, CH_3 and CH_3') ppm. ^{1}H NMR ($CDCl_3$) δ: 149.6 (s, C-4), 147.4 (s, 2C, C-1 and C-4'), 143.2 (s, C-1'), 125.8 (d, 2C, C-2' and C-6'), 125.7 (d, 2C, C-3 and C-5 or C-3' and C-5'), 125.6 (d, 2C, C-3 and C-5 or C-3' and C-5'), 122.5 (d, 2C, C-2 and C-6), 70.1 (d, *C*HOH), 69.7 (d, *C*HOH), 25.4 (q, *C*H_3), 25.2 (q, *C*H_3) ppm.

*2.4.2.8 Synthesis of **2.21** from 3-nitrobenzonitrile (**2.12**)*

Starting from 3-nitrobenzonitrile (**2.12**) (0.074 g), after 18 hours 3,3'-(hydrazine-1,2-diyl)dibenzonitrile **2.21** was isolated (0.054 g, 93%) and its structure confirmed by ^{1}H NMR.

*2.4.2.9 Synthesis of **2.22** from 4-nitrobenzonitrile (**2.13**)*

Starting from 4-nitrobenzonitrile (**2.13**) (0.074 g), after 18 hours 4,4'-(hydrazine-1,2-diyl)dibenzonitrile **2.22** was isolated (0.054 g, 93%) and its structure confirmed by ^{1}H NMR.

*2.4.2.10 Synthesis of **2.32** from 2-chloro-3-nitropyridine (**2.31F**)*

Starting from 2-chloro-3-nitropyridine (**2.29F**) (0.079 g), after 72 hours 3-amino-2-chloropyridine (**2.30**) was isolated (0.024 g, 0.19 mmol, 38%) and its structure confirmed by ^{1}H NMR.

2.4.3 General procedure for the organocatalytic reduction of nitroarenes with $NaBH_4$ as stoichiometric reducing agent

In a screw cap Pyrex tube N°13, the nitro compound (0.25 mmol), alcohol **2.1** (0.030 g, 0.13 mmol) and $NaBH_4$ (0.019 g, 0.5 mmol) were suspended in a mixture of toluene (0.25 mL) and THF (0.25 mL) and heated at 110 °C for 6 hours. Excess of $NaBH_4$ was quenched by addition of water (0.5 mL). After extraction (EtOAc, 3x1 mL), the reaction products were recovered by flash chromatography on silica gel. The structure of anilines was confirmed by comparison with authentic samples and/or literature data.

*2.4.3.1 Reduction of 1-chloro-2-nitrobenzene (**2.23**)*

Starting from 1-chloro-2-nitrobenzene (**2.23**) (0.039 g), chromatographic resolution (eluent PE/CH_2Cl_2 1:1 v/v) allowed to recover 2-chloroaniline (**2.34**) (R_f = 0.52, 0.029 g, 91%) and alcohol **2.1** (R_f = 0.14, 0.029 g, 97%).

*2.4.3.2 Reduction of 2-nitroaniline (**2.24**)*

Starting from 2-nitroaniline (**2.24**) (0.035 g), chromatographic resolution (eluent PE/EtOAc 2:1 v/v) allowed to recover *o*-phenylendiamine (**2.35**) (R_f = 0.18, 0.019 g, 70%) as second band moving after alcohol **2.1** (R_f = 0.79, 0.030 g, 98%).

*2.4.3.3 Reduction of 4-nitroaniline (**2.25**)*

Starting from 4-nitroaniline (**2.25**) (0.039 g), chromatographic resolution (eluent PE/EtOAc 2:1 v/v) allowed to recover *p*-phenylendiamine (**2.36**) (R_f = 0.20, 0.018 g, 66%) as second band moving after alcohol **2.1** (R_f = 0.79, 0.030 g, 98%).

*2.4.3.4 Reduction of 4-nitroanisole (**2.26**)*

Starting from 4-nitroanisole (**2.26**) (0.038 g) and using a double amount of alcohol **2.1** (0.060 g, 0.25 mmol), chromatographic resolution (eluent PE/EtOAc 5:1 v/v) allowed to recover 1,2-bis(4-methoxyphenyl)diazene (R_f = 0,86, 0.004 g, 13%) as first moving band, alcohol **2.1** (R_f = 0.34, 0.057 g, 97%) as second moving band, and 4-aminoanisole (**2.37**) (R_f = 0.15, 0.020 g, 65%).

*2.4.3.5 Reduction of methyl 4-nitrobenzoate (**2.29**)*

Heating at 70 °C methyl 4-nitrobenzoate (**2.29**) (0.045 g) for 24 h and using a double amount of alcohol **2.1** (0.060 g, 0.25 mmol), chromatographic resolution (eluent PE/EtOAc 5:1 v/v) allowed to recover alcohol **2.1** (R_f = 0.34, 0.058 g, 99%) as first moving band and methyl 4-aminobenzoate (**2.38**) (R_f = 0.23, 0.018 g, 47%).

*2.4.3.6 Reduction of 2-chloro-3-nitropyridine (**2.31**)*

Starting from 2-chloro-3-nitropyridine (**2.31**) (0.039 g), chromatographic resolution (eluent PE/EtOAc 2:1 v/v) allowed to recover 3-amino-2-chloropyridine (**2.32**) (R_f = 0.15, 0.013 g, 40%) as second band moving after a mixture alcohol **2.1** and the diastereomeric mixture of phenyl(1,2,3,4tetrahydro-2-quinolyl)methanol (R_f = 0.76, ratio 1:8 ^{1}H NMR, 0.026 g).

2.4.4 General procedure for the organocatalytic reduction of nitroarenes with $NaCNBH_3$ as stoichiometric reducing agent

In a screw cap Pyrex tube N°13, the nitro compound (0.25 mmol), alcohol **2.1** (0.030 g, 0.13 mmol) and $NaCNBH_3$ (0.024 g, 0.38 mmol) were suspended in a mixture of dry toluene (0.25 mL) and dry THF (0.25 mL) and heated at 110 °C for the allotted time. Excess of $NaCNBH_3$ was quenched by addition of water (0.5 mL). After extraction (EtOAc, 3x1 mL), a flash chromatography on silica gel was performed. The structure of anilines was confirmed by comparison with authentic samples and/or literature data.

*2.4.4.1 Reduction of nitrobenzene (**2.5**)*

Starting from nitrobenzene (**2.5**) (0.031 g, 0.026 mL) the mixture was heated for 45 hours, and chromatographic resolution (eluent PE/EtOAc 6:1 v/v) allowed to recover azobenzene **2.40** (R_f = 0,83, 0.003 g, 13%), ketone **2.2** (R_f = 0.65, 0.015 g, 50%), aniline (**2.52**) (R_f = 0.35, 0.015 g, 64%), and finally alcohol **2.1** (R_f = 0.24, 0.006 g, 20%).

*2.4.4.2 Reduction of 4-nitrotoluene (**2.6**)*

Starting from 4-nitrotoluene (**2.6**) (0.034 g) the mixture was heated for 72 hours, and chromatographic resolution (eluent PE/CH_2Cl_2 1:5 v/v) allowed to recover 1,2-bis(4-methylphenyl)diazene **2.42** (R_f = 0,85, 0.002 g, 8%), *p*-toluidine (**2.53**) (R_f = 0.58, 0.016 g, 60%), ketone **2.2** (R_f = 0.42, 0.015 g, 50%), and alcohol **2.1** (R_f = 0.22, 0.006 g, 20%) as last moving band.

*2.4.4.3 Reduction of 3-nitroaniline (**2.7**)*

Starting from 3-nitroaniline (**2.7**) (0.035 g), the mixture was heated for 42 hours, and chromatographic resolution (eluent PE/EtOAc 4:1 v/v) allowed to recover ketone **2.2** (R_f = 0.75, 0.008 g, 26%), alcohol **2.1** (R_f = 0.43, 0.022 g, 72%),and unreacted 3-nitroaniline (**2.7**) (R_f = 0.31, 0.008 g, 23%). *m*-Phenylendiamine (**2.54**) (R_f = 0.20, 0.014 g, 52%) was isolated using PE/EtOAc 2:1 v/v as eluent.

*2.4.4.4 Reduction of 1-chloro-3-nitrobenzene (**2.8**)*

Starting from 1-chloro-3-nitrobenzene (**2.8**) (0.039 g), the mixture was heated for 36 hours, and chromatographic resolution (eluent PE/CH_2Cl_2 1:1 v/v) allowed to recover 1,2-bis(3-chlorophenyl)diazene **2.46** (R_f = 0.94, 0.006 g, 20%) 1,2-bis(3-chlorophenyl)hydrazine **2.45** (R_f = 0.57, 0.005 g, 16%), 3-chloroaniline (**2.55**) (R_f = 0.50, 0.018 g, 56%), ketone **2.2** (R_f = 0.29, 0.002 g, 7%) and alcohol **2.1** (R_f = 0.14, 0.028 g, 92%).

*2.4.4.5 Reduction of 1-chloro-4-nitrobenzene (**2.9**)*

Starting from 1-chloro-4-nitrobenzene (**2.9**) (0.039 g), the mixture was heated for 24 hours, chromatographic resolution (PE/CH_2Cl_2 1:1 v/v) allowed to recover 1,2-bis(4-chlorophenyl)diazene **2.47** (R_f = 0.94, 0.007 g, 22%, 4-chloroaniline (**2.56**) (R_f = 0.51, 0.024 g, 75%), and alcohol **2.1** (R_f = 0.14, 0.029 g, 95%).

*2.4.4.6 Reduction of 3-nitrobenzonitrile (**2.12**)*

Starting from 3-nitrobenzonitrile (**2.12**) (0.037 g) the reaction mixture was heated for 18 hours, and chromatographic resolution (eluent PE/EtOAc 4:1 v/v) afforded 3,3'-(diazene-1,2-diyl)dibenzonitrile **2.50** (R_f = 0,89, 0.003 g, 10%),

ketone **2.2** (R_f = 0.75, 0.008 g, 26%), alcohol **2.1** (R_f = 0.43, 0.013 g, 43%) and finally 3-aminobenzonitrile (**2.57**) (R_f = 0.22, 0.005 g, 17%).

*2.4.4.7 Reduction of 4-nitrobenzonitrile (**2.13**)*

Operating as above, chromatographic resolution (eluent PE/EtOAc 4:1 v/v) allowed recovery 4,4'-(diazene-1,2-diyl)dibenzonitrile **2.51** (R_f = 0,89, 0.004 g, 14%), ketone **2.2** (R_f = 0.75, 0.031 g, 99%), 4,4'-(hydrazine-1,2-diyl)dibenzonitrile **2.22** (R_f = 0.30, 0.005 g, 17%) and 4-aminobenzonitrile (**2.58**) (R_f = 0.20, 0.010 g, 34%).

*2.4.4.8 Reduction of methyl 3-nitrobenzoate (**2.28**)*

Starting from methyl 3-nitrobenzoate **2.28** (0.045 g) the reaction mixture was heated for 18 hours, and chromatographic resolution (eluent PE/EtOAc 4:1 v/v) allowed to recover ketone **2.2** (R_f = 0.75, 0.009 g, 30%), alcohol **2.1** (R_f = 0.43, 0.018 g, 60%) and to isolate methyl 3-aminobenzoate (**2.59**) (R_f = 0.19, 0.015 g, 40%).

*2.4.4.9 Reduction of 2-chloro-3-nitropyridine (**2.31**)*

Starting from 2-chloro-3-nitropyridine (**2.31**) (0.039 g), chromatographic resolution (eluent PE/EtOAc 2:1 v/v) allowed to recover ketone **2.2** (R_f = 0.91, 0.008 g, 26%), a mixture alcohol **2.1** and the diastereomeric mixture of phenyl(1,2,3,4tetrahydro-2-quinolyl)methanol (R_f = 0.76, 0.012, ratio 1:1) and 3-amino-2-chloropyridine (**2.32**) (R_f = 0.15, 0.017 g, 53%).

*2.4.4.10 Reduction of PQK (**2.2**)*

A) Phenyl (2-quinolyl) ketone (PQK, **2**) (0.058 g, 0.25 mmol) was added to $NaCNBH_3$ (0.031 g , 0.5 mmol) in dry toluene (0.25 mL) and dry THF (0.25 mL) and the resulting mixture was heated at 110 °C for 6 hours. After water addition (0.5 mL) and extraction with EtOAc (3x1 mL), evaporation to dryness of the organic extracts allowed to recover alcohol **2.1** (0.053 g, 90%).

B) When the reaction mixture was heated for 48 hours, operating as above the diastereomeric couple of phenyl(1,2,3,4-tetrahydro-2-quinolyl)methanol (**2.60a,b**) (0.048 g, 81%) was isolated; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46-7.31 (m, 5H), 7.03-6.93 (m, 2H), 6.65 (t, *J* = 6.8 Hz, 1H), [6.57 (d, *J* = 7.1 Hz, 1H, **2.60b**)], 6.46 (d, *J* = 8.5 Hz, 1H, **2.60a**), 4.65 (d, *J* = 6.2 Hz, 1H, **2.60a**), [4.54 (d, *J* = 7.4 Hz, 1H, **2.60b**)], 3.56-3.41 (m, 1H), 2.86-2.63 (m, 2H), 2.07-1.99 (m), 1.91-1.78 (m), 1.74-1.63 (m).

2.4.5 General procedure for the thermal reduction of nitroarenes

In a screw cap Pyrex tube N°13, the nitro compound (0.25 mmol) and alcohol **2.1** were degassed by several vacuum-nitrogen cycles to reduce the air oxidation of alcohol **2.1** to ketone **2.2**, dissolved in a toluene (0.5 mL) and heated at the reported temperature for the allotted time. A flash chromatography on silica gel was performed to isolate the products. The structure of anilines was confirmed by comparison with authentic samples and/or literature data.

*2.4.5.1 Reduction of 1-chloro-3-nitrobenzene (**2.8**)*

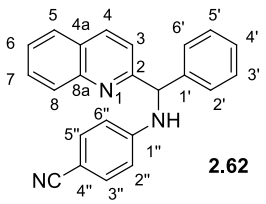
1-chloro-3-nitrobenzene (**2.8**) (0.039 g) and alcohol **2.1** (0.182 g, 0.78 mmol, 3.1 equiv) were added with a 20 mol% solution of AcOH in toluene (0.1 mL) and heated at 110 °C for 18 hours. Removal of the solvent in vacuo and purification

by FC (eluent PE/CH_2Cl_2 1:1 v/v) allowed to recover a 1 to 4 mixture (^{1}H NMR, R_f = 0.51) of **2.61** (ca. 17%) and 3-chloroaniline (**2.55**) (ca. 64%), and ketone **2.2** (R_f = 0.35, 0.171 g, 95%).

*2.4.5.2 Reduction of 3-nitrobenzonitrile (**2.12**)*

3-Nitrobenzonitrile (**2.12**) (0.37 g) and alcohol **2.1** (0.183 g, 0.78 mmol, 3.1 equiv) were added with a 20 mol% solution of AcOH in toluene (0.1 mL) and heated at 110 °C for 18 hours. Removal of the solvent in vacuo and purification by FC (eluent PE/EtOAc 4:1 v/v) allowed recovery ketone **2.2** (R_f = 0.75, 0.176 g, 97%) and to isolate 3-aminobenzonitrile (**2.57**) (R_f = 0.22, 0.027 g, 90%), which structure was confirmed by comparison by comparison with literature data.

*2.4.5.3 Reduction of 4-nitrobenzonitrile (**2.13**)*



2.62

4-Nitrobenzonitrile (**2.13**) (0.37 g) and alcohol **2.1** (0.183 g, 0.78 mmol, 3.1 equiv) were added with a 20 mol% solution of AcOH in toluene (0.1 mL) and heated at 110 °C for 18 hours. Removal of the solvent in vacuo and purification by FC (eluent PE/EtOAc 4:1 v/v) allowed after the recovery of ketone **2.2** (R_f = 0.75, 0.172 g, 97%), to isolate **2.62** (R_f = 0.36, 0.07 g, 8%) as a yellow pale solid; ^{1}H NMR (400 MHz, CD_3OD) δ: 8.32 (d, *J* = 8.6 Hz, 1H, H-4), 8.12 (d, *J* = 8.5 Hz, 1H, H-8), 7.92 (d, *J* = 7.7 Hz, 1H, H-5), 7.80 (t, *J* = 7.7 Hz, 1H, H-7), 7.61 (d, *J* = 8.1 Hz, 2H, H-3 and H-6), 7.49 (d, *J* = 8.5 Hz, 2H, H-2', H-6'), 7.41-7.31 (d, 4H, H-3' and H-5' and H-3'', H-5''), 7.28 (d, *J* = 7.4 Hz, 1H, H-4'), 6.77 (d, *J* = 8.8 Hz, 2H, H-2'', H-6''), 5.92 (s, 1H, C*H*N) ppm.

The third moving band afforded 3-aminobenzonitrile (**2.58**) (R_f = 0.20, 0.023 g, 78%).

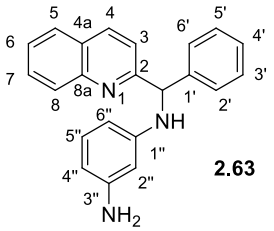
*2.4.5.4 Reduction of methyl 3-nitrobenzoate (**2.28**)*

Methyl 3-nitrobenzoate (**2.28**) (0.045 g) and alcohol **2.1** (0.183 g, 0.78 mmol, 3.1 equiv) were added with a 20 mol% solution of AcOH in toluene (0.1 mL) and heated at 70 °C for 25 hours. Removal of the solvent in vacuo and purification by FC (eluent PE/EtOAc 4:1 v/v) allowed recovery ketone **2.2** (R_f = 0.75, 0.176 g, 97%) and to isolate methyl 3-aminobenzoate (**2.59**) (R_f = 0.19, 0.026 g, 70%).

*2.4.5.5 Reduction of methyl 4-nitrobenzoate (**2.29**)*

Methyl 3-nitrobenzoate (**2.29**) (0.045 g) and alcohol **2.1** (0.183 g, 0.78 mmol, 3.1 equiv) were heated at 110 °C for 18 hours. Removal of the solvent in vacuo and purification by FC (eluent PE/EtOAc 4:1 v/v) allowed recovery ketone **2.2** (R_f = 0.75, 0.176 g, 97%) and to isolate methyl 4-aminobenzoate (**2.38**) (R_f = 0.19, 0.032 g, 85%).

*2.4.5.6 Reduction of 3-nitroaniline (**2.7**)*

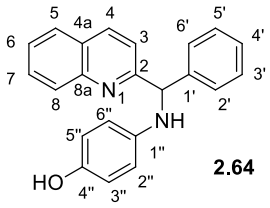


2.63

3-Nitroaniline (**2.7**) (0.035 g) and alcohol **2.1** (0.242 g, 1.03 mmol, 4.1 equiv) were added with a 20 mol% solution of AcOH in toluene (0.1 mL) and heated at 110 °C for 72 hours. Removal of the solvent in vacuo and purification by FC (eluent PE/EtOAc 4:1 v/v) allowed recovery ketone **2.2** (R_f = 0.91, 0.211 g, 95%)

and compound **2.63** (R_f = 0.21, 0.025 g, 31%) as sticky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.17 (d, *J* = 8.4 Hz, 1H), 8.05 (d, *J* = 8.6 Hz, 1H), 7.81-7.66 (m, 2H), 7.63-7.48 (m, 3H), 7.45 (d, *J* = 8.5 Hz, 1H), 7.36-7.27 (m, 2H), 7.25-7.20 (m, 1H), 6.92 (t, *J* = 7.7 Hz, 1H), 6.18 (d, *J* = 9.2 Hz, 1H), 6.10-5.99 (m, 2H), 5.71 (s, 1H) ppm.

*2.4.5.7 Reduction of 4-nitrophenol (**2.26**)*



2.64

4-Nitrophenol (**2.26**) (0.035 g) and alcohol **2.1** (0.242 g, 1.03 mmol, 4.1 equiv) were heated at 110 °C for 90 hours. Removal of the solvent in vacuo and purification by FC (eluent DCM/Et_2O 25:1 v/v) allowed recovery ketone **2.2** (R_f = 0.64, 0.183 g, 95%), to recover 4-nitrophenol (**2.26**) (R_f = 0.39, 0.005 g, 14%) and to isolate compound **2.64** (R_f = 0.15, 0.067 g, 82%), as a yellow pale solid. ^{1}H NMR (400 MHz, CD_3OD) δ: 8.11 (d, *J* = 8.6 Hz, 1H, H-4), 8.04 (d, *J* = 8.5 Hz, 1H, H-8), 7.75 (d, *J* = 7.0 Hz, 1H, H-5), 7.67 (ddd, *J* = 8.5, 5.2, 1.5 Hz, 1H, H-7), 7.59 (d, *J* = 8.6 Hz, 1H, H-3), 7.52-7.41 (m, 3H, H-6 and H-2', 6'), 7.27 (t, *J* = 4.3 Hz, 2H, H-3' and H-5'), 7.17 (t, *J* = 7.4 Hz, 1H, H-4'), 6.66-6.51 (m, 4H, H-2'', 6'', 3'' and 5''), 5.71 (s, 1H, C*H*N) ppm. ^{13}C NMR (100 MHz, CD_3OD) δ: 164.1 (s, C-2), 150.5 (s, C-4'') 148.3 (s, C-8a), 143.2 (s, C-1''), 141.7 (s, C-1'), 138.7 (d, C-4), 131.0 (d, C-7), 129.7 (d, 2C, C-3' and C-5'), 129.0 (d, C8), 129.9 (d, C-5), 128.8 (s, C-4a), 128.7 (d, 2C, C-2' and C-6'), 128.6 (d, C-4'), 127.6 (d, C-6),121.1 (d, C-3), 116.8 (d, 2C, C-2'' and C-6'' or C-3'' and C-5''), 116.7 (d, 2C, C-2'' and C-6'' or C-3'' and C-5''), 66.3 (d, *C*HNH) ppm.

2.4.6 Synthesis of (2-quinolyl)(4-tolyl)methanol (**2.3**)

A 1.0 M solution of 4-tolylmagnesium bromide in THF (33.1 mmol, 33.1 mL) was added dropwise to an ice-cooled solution of 2-quinolinecarbaldehyde (4 g, 25.45 mmol) in anhydrous diethyl ether (300 mL), at such a rate that the internal reaction temperature is maintained below 0 °C. At the end of the addition, the mixture was stirred for 2 hours, quenched with ice-water (10 mL), and extracted with EtOAc (3 x 80 mL). The collected organic phases were washed with water (2 x 50 mL), brine (2 x 50 mL), and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by FC (PE/EtOAc 4:1 v/v) affording compound **2.3** (R_f = 0.38, 5.64 g, 89%) as a white solid. Alcohol **2.3** was recrystallized by iPr2O/Et2O 1:1 v/v, as a white solid, with a melting point of 107-108 °C, and its identity was confirmed by comparation with literature data.

2.4.7 General procedure for the reduction of nitroarenes using alcohol **2.3**

Nitro compound (0.5 mmol) and alcohol **2.3** were mixed in toluene (1 mL), and added with a 20 mol% solution of AcOH in toluene (0.2 mL), degassed by several vacuum-nitrogen cycles to reduce the air oxidation of alcohol **2.3** to ketone **2.4**, and heated at 110 °C for the reported time. Removal of the solvent in vacuo and purification by FC allowed to isolate the reaction product and ketone **2.4**. The excess alcohol **2.3** was recovered and recycled.

*2.4.7.1 Reduction of 2-chloro-3-nitropyridine (**2.31**)*

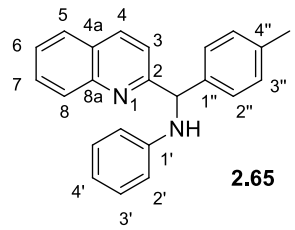
The reaction crude obtained by heating 2-chloro-3-nitropyridine (0.079 g) and alcohol **2.3** (0.386 g, 1.55 mmol) for 18 hours was resolved by FC (EP/EtOAc 5:1) leading to ketone **2.4** (R_f = 0.52, 0.370 g, 95%) and amine **2.32** (R_f = 0.11, 0.050

g, 78%). This compound is commercially available, and its identity was confirmed by comparison of the ^{1}H NMR spectrum with that of an authentic sample.

*2.4.7.2 Reduction of 1-chloro-2-nitrobenzene (**2.23**)*

FC (PE/CH_2Cl_2 1:1) resolution of the reaction crude obtained by heating 2-chloronitrobenzene (**2.23**) (0.079 g) and alcohol **2.3** (0.386 g, 1.55 mmol) for 24 hours allowed to isolate 2-chloroaniline (**2.34**) (R_f = 0.52, 0.048 g, 75%) and ketone **2.3** (R_f = 0.26, 0.371 g, 97%). Compound **2.34** is commercially available, and its identity was confirmed by comparison of the ^{1}H NMR spectrum with that of an authentic sample.

*2.4.7.3 Reduction of nitrobenzene (**2.5**)*



2.65

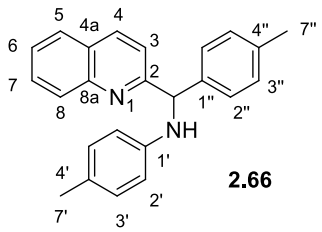
The reaction mixture obtained by heating alcohol **2.3** (0.510 g, 2.05 mmol) and nitrobenzene (**2.5**) (0.062 g, 0.052 mL) for 120 hours was subjected to FC with CH_2Cl_2/PE 3:2. The fastest moving band led to compound **2.65** (R_f = 0.47, 0.070 g, 45%) as white needles, mp: 57-58 °C (from PE/Et_2O 5:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.25 (d, *J* = 6.6 Hz, 1H, H-8), 8.09 (d, *J* = 8.6 Hz, 1H, H-4), 7.81-7.71 (m, 2H, H-5, H-7), 7.58-7.48 (m, 2H, H-3 and H-6), 7.45 (d, *J* = 8.0 Hz, 2H, H-3''),7.19-7.10 (m, 4H, 2 H-2'' and 2 H-3'), 6.73 (d, *J* = 8.4 Hz, 2H, H-2'), 6.68 (t, *J* = 7.3 Hz, 1H, H-4'), 5.78 (s, 1H, C*H*N), 2.30 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.8 (s, C-2), 146.9 (s, 2C C-8a and C-1'), 139.1 (s, C-1''), 137.4 (d, C-4), 131.6 (d, C-5), 129.6 (d, 2C, C-3'), 129.1 (d, 2C C-3''), 128.9 (d, C-8), 127.5 (d, 2C, C-2''), 127.3 (d, C-7), 126.6 (d, C-6), 126.3 (s, C-4''), 119.9 (d, C-

3), 117.4 (d, C-4'), 113.6 (d, 2C, C-2'), 63.0 (d, *C*HNH), 21.2 (q, *C*H_3) ppm. Elemental analysis:

Ketone **2.4** (R_f = 0.35, 0.472 g, 93%) was recovered from the slowest fractions.

*2.4.7.4 Reduction of 4-nitrotoluene (**2.6**)*



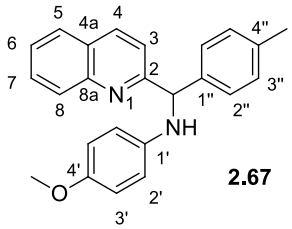
2.66

The reaction mixture obtained by heating alcohol **2.3** (0.510 g, 2.05 mmol) and 4-nitrotoluene **2.6** (0.068 g) 48 hours was resolved by FC (Toluene/CH_2Cl_2 1:3 v/v). The first moving band led to compound **2.66** (R_f = 0.58, 0.125 g, 74%) as a sticky solid.

^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.17 (d, *J* = 8.5 Hz, 1H, H-8), 8.05 (d, *J* = 8.5 Hz, 1H, H-4), 7.79-7.69 (m, 2H, H-5, H-7), 7.52 (t, *J* = 8.1 Hz, 1H, H-6), 7.46 (d, *J* = 8.5 Hz, 1H, H-3), 7.42 (d, *J* = 8.1 Hz, 2H, H-3'', H-5''), 7.13 (d, *J* = 8.1 Hz, 2H, H-2'', H-6''), 6.94 (d, *J* = 8.4 Hz, 2H, H-3', H-5'), 6.64 (d, *J* = 8.4 Hz, 2H, H-2', H-6'), 5.87 (vbr s, 1H, N*H*), 5.70 (s, 1H, C*H*N), 2.30 (s, 3H, H-7''), 2.21 (s, 3H, H-7') ppm. ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 161.0 (s, C-2), 147.1 (s, C-8a), 144.8 (s, C-1'), 139.5 (s, C-4''), 137.2 (d, C-4), 136.9 (s, C-1''), 129.8 (d, C-7), 129.6 (d, 2C, C-2''), 129.5 (d, 2C, C3'), 129.1 (d, C-8), 127.5 (d, 2C, C-3''), 127.2 (d, C-5), 126.3 (d, C-6), 123.5 (s, C-4'), 119.9 (d, C-6), 113.7 (d, 2C, C-2'), 63.4 (d, *C*HNH), 21.1 (q, C-7''), 20.4 (q, C-7') ppm.

The following moving bands led to ketone **2.4** (Rf = 0.35, 0.379 g, 99%) and unreacted alcohol **2.3** (Rf = 0.10, 0.010 g).

*2.4.7.5 Reduction of 4-nitroanisole (**2.26**)*



The reaction crude obtained by heating alcohol **2.3** (0.510 g, 2.05 mmol) and 4-nitroanisole **2.26** (0.080 g, 0.5 mmol) for 72 hours was subjected to FC (PE/EtOAc 10:1). Ketone **2.4** (R_f = 0.49, 0.370 g, 97%) was recovered from the first moving band while the second one led to compound **2.67** (Rf = 0.37, 0.117 g, 66%) as white needles, mp: 127-128 °C (from PE/Et_2O 5:1).

^{1}H NMR (400 MHz, CD_3OD) δ: 8.22 (d, *J* = 8.6 Hz, 1H, H-4), 8.06 (d, *J* = 8.5 Hz, 1H, H-8), 7.86 (d, *J* = 8.1 Hz, 1H, H-5), 7.75 (t, *J* = 7.7 Hz, 1H, H-7), 7.65 (d, *J* = 8.6 Hz, 1H, H-3), 7.55 (t, *J* = 7.5 Hz, 1H, H-6), 7.36 (d, *J* = 8.1 Hz, 2H, H-3''), 7.12 (d, *J* = 8.1 Hz, 2H, H-2''), 6.65 (s, 4H, 2 H-2' and 2 H-3'), 5.70 (s, 1H, C*H*N), 3.63 (s, 3H, OC*H*$_3$), 2.27 (s, 3H, C*H*$_3$) ppm. ^{13}C NMR (100 MHz, CD_3OD) δ: 164.5 (s, C-2), 153.7 (s, C-4'), 148.4 (s, C-8a), 142.9 (s, C-1'), 140.3 (s, C-4''), 138.7 (d, C-4), 138.4 (s, C-1'), 131.0 (d, C-5), 130.3 (d, 2C, C-2''), 129.0 (d, C-8), 128.9 (d, C-7), 128.7 (d, 2C, C-3''), 127.6 (d, C-6), 121.1 (d, C-3), 123.5 (s, C-4'), 116.4 (d, 2C, C-2' or C-3'), 115.6 (d, 2C, C-2' or C-3'), 66.0 (d, *C*HNH), 56.0 (q, O*C*H_3), 21.1 (q, *C*H_3) ppm.
Elementar analysis:
The slowest moving band afforded unreacted 1 (Rf = 0.17, 0.008 g).

2.4.8 Oxidation of alcohol **2.3** to ketone **2.4**

To a solution of alcohol **2.3** (1.05 g, 4.2 mmol) in $CHCl_3$ (20 mL) was added activated MnO_2 (1.5 g), and the mixture was stirred at room temperature for 4

days. Then it was performed a filtration on celite, and ketone **2.4** was recovered in quantitative yield and its identity was confirmed by comparation with literature data.

2.4.9 General procedure for the synthesis of the solid-supported reagent **2.68**

In a dried three-necked round-bottomed flask equipped with a refrigerant and two dropping funnels, isopropylamine or 2,2,6,6-tetramethylpiperidine was dissolved in dry THF (8 mL) and cooled at -78 °C. Then it was added dropwise a solution 1.6 M of *n*-BuLi in hexane and after 20 minutes, a solution of ketone **2.4** (0.494 g, 2 mmol) in THF (10 mL). The reaction mixture was kept at -78 °C under stirring and after 30 minutes solid Merrifield resin (0.465 g, 2 mmol) was added portionwise. After the end of the additions, the crude was stirred at -78 °C for 2 hours, then warmed to r.t. and kept under stirring overnight.

The reaction was quenched then with aq. NH_4Cl (10 mL) and filtered on Gouch funnel, washed with abundant water as first and Et_2O later. The solid product was dried and analyzed *via* FT-IR and elemental analysis. Evaporation of the organic phase gave ketone **2.4** (or alcohol **2.3**).

The elemental analysis for the commercial resin was: C, 77.46; H, 6.53. On the base of this data, the minimal formula was: $C_{14}H_{14}Cl$. IR, ν_{max} (KBr) 3019, 2921, 2855, 1604, 1509, 1490, 1446, 1419, 1258, 821, 748, 696, 661, 530 cm^{-1}.

On this ground, compound **2.68** should have the following minimal formula: $C_{31}H_{26}NO$, corresponding to a complete functionalization. Then the theoretical elemental analysis should be: C, 86.88; H, 6.17; N, 3.27.

The loading for the functionalized resin **2.68** was calculated by the ratio of the nitrogen percentage of the functionalized resin (**2.68**) and the theoretical nitrogen percentage.

2.4.9.1 Reaction with LDA

To a solution of isopropylamine (0.404 g, 0.560 mL, 4 mmol) were added *n*-BuLi 1.6 M (2.5 mL, 4 mmol), ketone **2.4** and the Merrifield resin. By evaporation of organic phase, alcohol **2.3** (0.328 g, 1.3 mmol, 65%) was recovered. By filtration, the solid-supported ketone **2.68** (0.539 g) was recovered.

IR, ν_{max} (KBr) 3030, 2921, 2850, 1656, 1601, 1511, 1446, 1413, 1261, 816, 759, 696, 685, 524 cm^{-1}. Anal. Found: C, 75.08; H, 6.11; N, 1.36.

2.4.9.2 Reaction with 2,2,6,6-tetramethylpiperidine and n-BuLi

(a) To a solution of 2,2,6,6-tetramethylpiperidine (0.318 g, 0.380 mL, 2.25 mmol) were added *n*-BuLi 1.6 M (1.4 mL, 2.25 mmol), ketone **2.4** and the Merrifield resin. By evaporation of organic phase, ketone **2.4** (0.417 g, 1.7 mmol) was recovered. By filtration, the solid-supported ketone **2.68** (0.390 g) was recovered.

(b) To a solution of 2,2,6,6-tetramethylpiperidine (565 g, 0.678 mL, 4 mmol) were added n-BuLi 1.6 M (2.5 mL, 4 mmol), ketone **2.4** and the Merrifield resin. By evaporation of organic phase, ketone **2.4** (0.440 g, 1.8 mmol) was recovered. By filtration, the solid-supported ketone **2.68** (0.436 g) was recovered. Anal. Found: C, 78.29; H, 6.45; N, 0.76.

2.4.9.3 Reaction with t-BuOK, 2,2,6,6-tetramethylpiperidine and n-BuLi

To a suspension of *t*-BuOK (0.269 g, 2.4 mmol) were added a solution of 2,2,6,6-tetramethylpiperidine (0.339 g, 0.405 mL, 2.40 mmol) in 2 mL of THF, n-BuLi 1.6 M (1.5 mL, 2.4 mmol), ketone **2.4** and the Merrifield resin. Ketone **2.4** (0.338 g, 1.4 mmol) and functionalized resin (0.384 g) were recycled for a second attempt of functionalization. By evaporation of organic phase, ketone **2.4** (0.355 g, 1.44

mmol) was recovered. By filtration, the solid-supported ketone **2.68** (0.396 mg) was recovered. Anal. Found: C, 76.06; H, 6.87; N, 1.00.

2.4.10 Reduction of the solid-supported ketone **2.68** with $NaBH_4$

In a two necked round-bottomed flask equipped with refrigerant, the functionalized resin **2.68** (200 mg) was suspended in THF (6 mL) and MeOH (3 mL) and cooled at 0 °C. Solid $NaBH_4$ (0.134 g, 3.5 mmol) was added in small portions in 10 minutes. After 20 minutes, the crude was warmed to rt, and left under stirring overnight. The reaction was quenched with H_2O (10 mL) and after filtration, **2.69-Cl** was recovered as white solid (0.126 g).
IR, ν_{max} (KBr) 3390, 3030, 2921, 2855, 1599, 1506, 1495, 1446, 1413, 1263, 1059, 819, 764, 745, 699, 666, 535 cm^{-1}. Anal. Found: C, 77.55; H, 6.30; N, 0.41.

2.4.11 Reduction of the solid-supported ketone **2.68** with $LiAlH_4$

To a solution of $LiAlH_4$ (0.087 g, 2.3 mmol) in dry THF (15 mL) cooled at 0 °C, resin **2.68** (0.270 g, 1.2 mmol) was added. At the end of the additions, the suspension was heated at reflux for 3 hours, and then quenched with ice in an ice bath, and added with a 15% v/v solution of HCl (5 mL). After multiple treatments with aq. $NaHCO_3$ (sat) and HCl (15% v/v) (3 times), the resin was washed with Et_2O and dried until constant weight (0.130 g) to obtain **2.69-H**.
IR, ν_{max} (KBr) 3390, 3019, 2915, 2855, 1599, 1511, 1492, 1452, 1111, 811, 754, 694, 530 cm^{-1}. Anal. Found: C, 78.96; H, 7.07; N, 0.27.

Chapter 3: Reactivity of 3-methyl-4-nitro-5-(trichloromethyl)isoxazole with oxygen nucleophiles

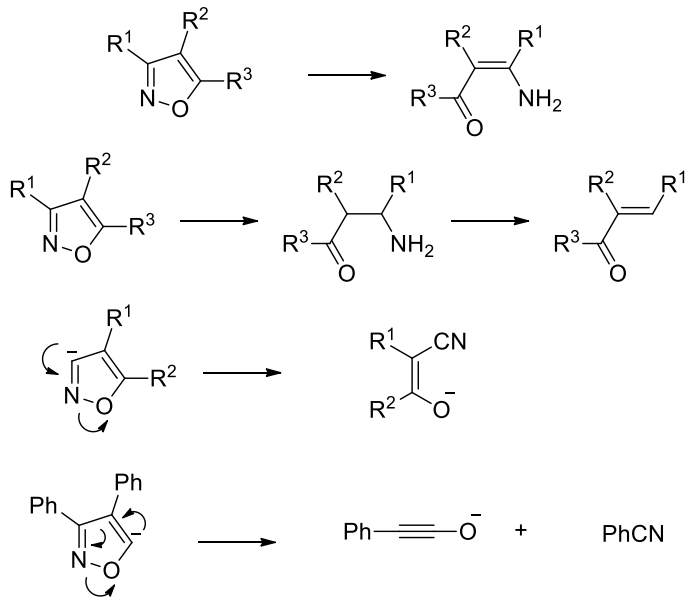
3.1 General introduction

Many heterocyclic systems may be applied as precursors of different categories of organic compounds and, in particular, isoxazole derivatives are excellent intermediates for the synthesis of important acyclic, alicyclic and heterocyclic compounds.[152]

This behavior is essentially associated with a facile ring opening due to the presence of a labile N-O bond. General methods of cleavage involve catalytic reduction, metal-ammonia reduction in alcoholic medium, as well as cleavage of 3-isoxazolide and 5-isoxazolide anions (for instance obtained from isoxazoles unsubstituted at position 3 or 5 under basic conditions), affording a wide variety of 'masked functionalities'. On this ground, isoxazoles can act as synthetic equivalents of enaminones, β-aminoketons, α,β-unsaturated ketones, 1,3-diketons, β-hydroxyketons, α-cyanoketones, etc… (Scheme 3.1).[153]

[152] (a) S. A. Lang, Y.-I. Lin, Isoxazoles and their benzoderivatives, in *Comprehensive Heterocyclic Chemistry*, Eds.: A. R. Katritzky, C. Rees, Pergamon: Oxford, 1984 Vol. 6, pp 1-130; (b) M. Sutharchanadevi, R. Murugan, Isoxazoles in *Comprehensive Heterocyclic Chemistry II*, Eds.: A. R. Katritzky, C. Rees, E. F. V. Scriven, Pergamon: Oxford, 1996; Vol. 3, pp 221-260; (c) D. Giomi, F. M. Cordero, F. Machetti, Isoxazoles in *Comprehensive Heterocyclic Chemistry III*, Eds.: A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven and R. J. K. Taylor, Elsevier: Oxford, 2008; Vol. 4, pp 365-486.

[153] T. L. Gilchrist, *Heterocyclic chemistry*, 3rd ed, Longman: Harlow, UK, 1997, p.328.



Scheme 3.1 – Isoxazole ring opening reactions.

3.1.1 Electrophilic substitution

The direct functionalization of preformed isoxazoles has been widely applied as useful method for the preparation of complex derivatives. The reactivity of isoxazole is typically that of an aromatic system. The calculated π-electron density is higher at the 4-position, followed by 5- and 3-positions, respectively (Figure 3.1). Calculation are coherent with the experimental observations that show the 4-position as the favoured site for electrophilic substitutions.[154]

[154] (a) R. E. Wasylishen, J. B. Rowbotham, T. Schaefer, *Can. J. Chem.* **1974**, *52*, 833-837; (b) G. Berthier, G. Del Re, *J. Chem. Soc.* **1965**, 3109-3117; (c) T.-K. Ha, *J. Mol. Struct.* **1979**. *51*, 87-98. (d) T. Eicher, S. Hauptmann, *The chemistry of heterocycles* Thieme: Stuttgart, D, 1995, p. 138.

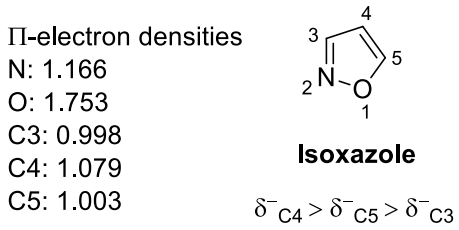
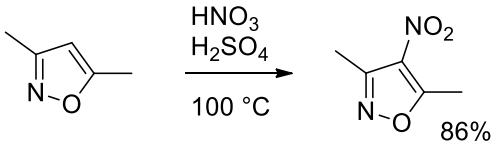


Figure 3.1 - Calculated π-electron density distribution on the isoxazole ring

The proneness of the isoxazole ring to electrophilic substitutions is according with the simultaneous presence in the system of a 'pyridine type' nitrogen atom, deactivating for electron withdrawing effect, and an oxygen atom, which activates the molecule for electron donation. The 4-position is generally the only active site for electrophilic attack. Isoxazoles can be easily nitrated and halogenated at the 4-position, while acylation and sulfonation need drastic conditions and afford the reaction products in low yields. The nitration of both substituted and unsubstituted isoxazoles can be achieved using various reagents, as solfonitric mixture, acetylnitrate and trifluoroacetylnitrate (Scheme 3.2).[155]



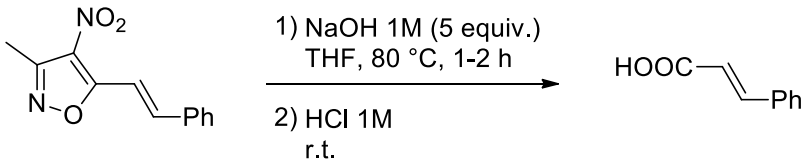
Scheme 3.2 - Nitration of 3,5-dimethyl isoxazole with sulfonitric mixture.

3.2 Reactivity of 4-nitroisoxazoles

The presence of the nitro group modify the electronic distribution of an isoxazole ring and thus, its reactivity.[152] For example, the 4-nitroisoxazole nucleus can be considered as a masked carboxylic acid or ester, as observed for

[155] P Grunanger, P. Vita-Finzi, J. E. Dowling, *Chemistry of Heterocyclic Compounds*, John Wiley & Sons, Inc., **2008**, pp. 1-416.

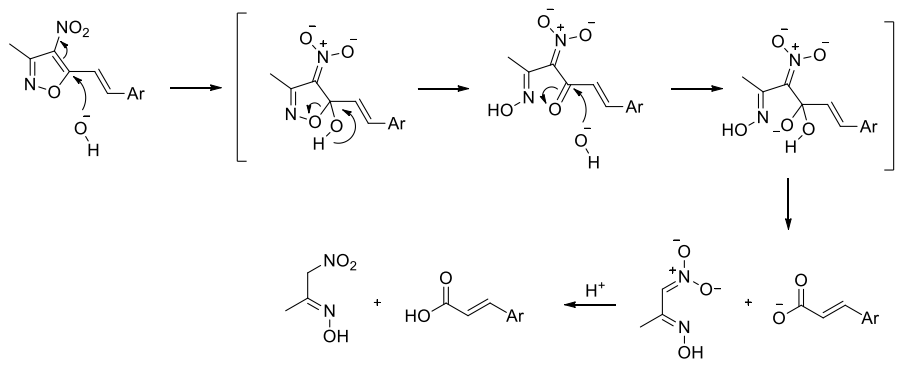
3 methyl-4-nitro-5-styrylisoxazole by treatment with NaOH, as reported in 1977 by Sarti-Fantoni (Scheme 3.3).[156]



Scheme 3.3 - Preparation of cinnamic acid via basic hydrolysis of 3-methyl-4-nitro-5-styrylisoxazole

Investigation on the mechanism of this reaction were published in 1980 by the same authors: using $Na^{18}OH$, carboxylic acids bearing two ^{18}O-labelled atoms in the carboxylic group were formed,[157] as the result of two consecutive attacks of hydroxide ions on C-5 carbon of the isoxazole ring. The first hydroxide ion leads to the breaking of the C-O bond, to generate a carbonyl group, that is attacked by the second hydroxide ion, leading to a ketal, which rearrangement leads to the breaking of the C4-C5 bond. Final acidification affords carboxylic acid and nitroacetonoxime (Scheme 3.4).

[156] D. Donati, M. Fiorenza, E. Moschi, P. Sarti-Fantoni, *J. Heterocycl. Chem.* **1977**, *14*, 951-952.
[157] P. Sarti-Fantoni, D. Donati, F. De Sio, G. Moneti, *J. Heterocycl. Chem.* **1980**, *17*, 1643-1644.



Scheme 3.4 - Proposed mechanism for the basic hydrolysis of 3-methyl-4-nitro-5-styrylisoxazole

3.2.1 3,5-dimethyl-4-nitroisoxazole

3,5-dimethyl-4-nitroisoxazole has emerged in the last decades as a powerful tool in synthetic chemistry.[158] Its reactivity is related to the presence of a nitro group at the 4-position, responsible for two primary characteristics of the system (Figure 3.2):

- The methyl group at 5-position is conjugated to the nitro group. This implies an increased acidity for the hydrogen atoms of methyl group in the 5-position that can be easily deprotonated by weak organic and inorganic bases. In this way, the deprotonated isoxazole may act as soft nucleophile in different types of reactions with electrophiles.
- The C-5 carbon is the most electrophilic in the 4-nitroisoxazole ring. For this reason, it becomes susceptible of attack by strong nucleophiles.

[158] F. Hu, M. Szostak, *Adv. Synth. Catal.* **2015**, *357*, 2583-2614.

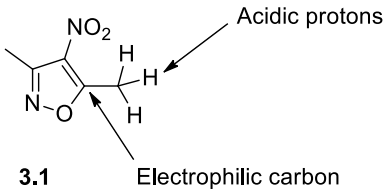
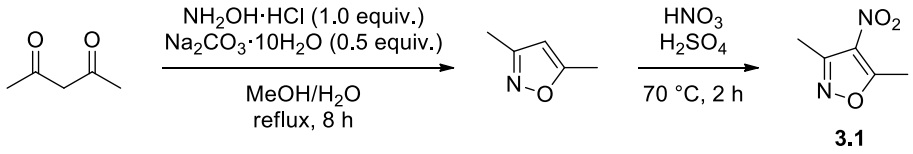


*Figure 3.2 - Properties of 3,5-dimethyl-4-nitroisoxazole (**3.1**).*

These peculiar features have been exploited in the preparation of valuable compounds.[159] The typical reaction sequence involves generally the functionalization of the methyl group at position 5 of **3.1** by reaction with the desired electrophile, bringing about the formation of stable substituted isoxazoles, which can be further elaborated, for instance to reveal the carboxylic acid functionality.

Nitroisoxazole **3.1** is commercially available, but it can also be easily synthesized in two steps and high overall yield from inexpensive materials. Acetylacetone is reacted with hydroxylamine hydrochloride in the presence of sodium carbonate to obtain 3,5-dimethylisoxazole, that is subjected to nitration with nitric and sulfuric acids to give **3.1** (Scheme 3.5).



*Scheme 3.5 - Preparation of 3,5-dimethyl-4-nitroisoxazole (**3.1**).*

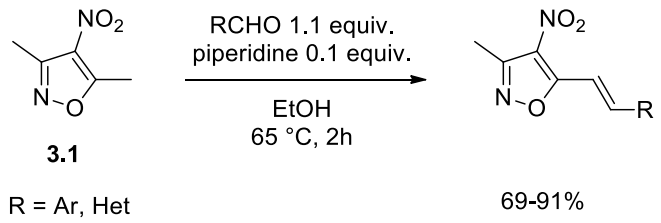
[159] (a) M. F. A. Adamo, V. R. Konda, D. Donati, P. Sarti-Fantoni, T. Torroba, *Tetrahedron* **2007**, *63*, 9741-9745; (b) M. F. A. Adamo, S. Suresh, *Tetrahedron* **2009**, *65*, 990-997; (c) R. Wells, M. Moccia, M. F. A. Adamo, *Tetrahedron Lett.* **2014**, *55*, 803-805.

3.2.2 Nucleophilic behavior of 3,5-dimethyl-4-nitroisoxazole (**3.1**)

3.1 has been shown to react under basic conditions as nucleophile in Knoevenagel-like reactions and 1,2-addition to carbonyl groups.

3.2.2.1 Knoevenagel reactions

Knoevenagel condensation of **3.1** were carried out with different aromatic and aliphatic aldehydes. The use of aromatic reagents allowed to synthesize the corresponding 'styryl' derivatives.[160] The reaction is usually performed in EtOH with a catalytic amount of piperidine as base, and affords 3-methyl-4-nitro-5-styrylisoxazoles as the only (*E*)-isomers (Scheme 3.6).[161]



*Scheme 3.6 - Preparation of 3-methyl-4-nitro-5-styrylisoxazoles from **3.1**.*

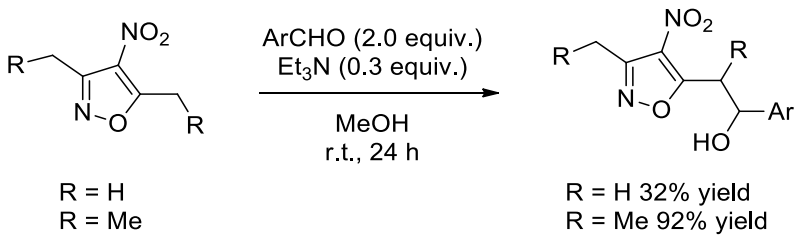
Even if this method is very good for the preparation of aromatic and heteroaromatic derivatives, it was not enough efficient in the reactions with aliphatic aldehydes, affording low yields of the desired products due to the formation of by-products. To overcome this limitation, Adamo and coworkers proposed a multistep sequence, involving the reaction between **3.1** and the aliphatic aldehyde under basic catalysis (NaOH), and the following dehydration

[160] A. Quilico, C. Musante, *Gazz. Chim. Ital*. **1942**, *72*, 399-411.
[161] M. F. A. Adamo, E. F. Duffy, V. R. Konda, F. Murphy, *Heterocycles* **2007**, *71*, 1173-1181.

by treatment with MsCl and NEt_3, to obtain the desired (*E*)-3-methyl-4-nitro-5-alkenylisoxazoles in high yields.[162]

3.2.2.2 Addition to carbonyl compounds

In 2009, Adamo et al. reported the vinylogous Henry (nitroaldol) reaction of **3.1** with aromatic aldehydes,[159b] but the corresponding benzyl alcohols were obtained in only modest yield. On the other hand, the reactions on 3,5-diethyl-4-nitroisoxazoles were more efficient and the corresponding products were isolated in higher yields (Scheme 3.7).

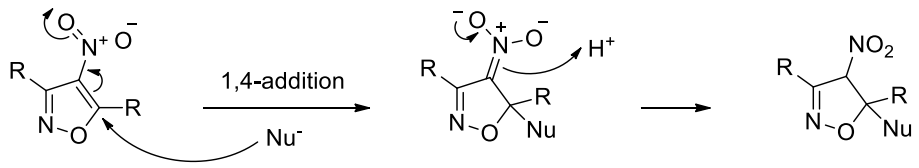


Scheme 3.7 - Vinylogous Henry reaction with aromatic aldehydes.

3.2.3 Electrophilic behavior of 3,5-dimethyl-4-nitroisoxazole (**3.1**)

As previously stated, in 4-nitroisoxazoles the C-5 carbon easily reacts with nucleophiles, thanks to the presence of the nitro group in the 4-position. Different kind of nucleophiles can react with 3,5-disubstituted-4-nitroisoxazoles, and the attack on C-5 breaks the aromaticity of the system, producing a nitronate intermediate, that after protonation on C-4 leads to the formation of 4,5-dihydroisoxazoles (Scheme 3.8).

[162] M. Moccia, M. Cortigiani, C. Monasterolo, F. Torri, C. Del Fiandra, G. Fuller, B. Kelly, M. F. A. Adamo, *Org. Proc. Res. Dev.* **2015**, *19*, 1274-1281.



Scheme 3.8 - 1,4-addition of nucleophiles on the 4-nitroisoxazole core.

In 1982 Tedeschi and *al.* showed that *n*-BuLi reacted with **3.1** at position 5, producing 3,5-dimethyl-5-butyl-4-nitro-4,5-dihydroisoxazole, in an attempt to perform a silylation on the side chain.[163]

In a similar way, Albertola and coworkers were able to perform the attack at C-5 of isoxazole **3.1** with different carbon nucleophiles, such as organolithium, Grignard and organoaluminium reagents, obtaining the corresponding 5-substituted isoxazolines.[164]

3.3 Electrophilic chlorination of ketones

α-Haloketones, first obtained and described as early as the end of the eighteenth century,[165] are interesting as building blocks for the preparation of many classes of compounds because of their high reactivity.[166] Monohalogenated derivatives, in particular, possess two electrophilic centers, carbonyl and α-carbon (bonded to the halogen atom), as well as a nucleophilic center that could be generated by deprotonation of the α-carbon.

There are a lot of methods for the synthesis of α-haloketones via electrophilic chlorination since a wide variety of chlorinating reagents have been

[163] R. Pepino, A. Ricci, M. Taddei, P. Tedeschi, *J. Organomet. Chem.* **1982**, *231*, 91-94.
[164] A. Albertola, L. F. Antolin, A. Gonzalez, M. A. Laguna, F. J. Pulido, *J. Chem. Soc., Perkin Trans. 1* **1988**, 791-794.
[165] E. Emmerling, A. Engler, *Ber.* **1871**, *4*, 148.
[166] A. W. Erian, S. M. Sherif, H. M. Gaber, *Molecules* **2003**, *8*, 793-865.

developed.[167] There is no general procedure: the choice of the chlorinating agent depends on the structure of the ketone and on the desired degree of chlorination. For example, the use of chlorine gas, depending on the reaction conditions, affords both mono- or poly-substituted products. In addition to Cl_2, one of the most employed chlorinating reagents is *N*-chlorosuccinimide (NCS). *N*-chlorosuccinimide, is widely used in radical halogenation of different substrates, but it is not selective in the chlorination of ketones, leading to mixtures of polychlorinated products.[168]

[167] (a) N. De Kimpe, R. Verhé, *α-Haloketones, α-Haloaldehydes and α-Haloimines*, Eds.:S. Patai, Z. Rappoport, John Wiley & Sons, Inc.: Chichester, 1988, pp. 1-119; (b) N. De Kimpe, R. Verhé, α-Haloketones, α-Haloaldehydes and α-Haloimines, Eds.:S. Patai, Z. Rappoport, John Wiley & Sons, Inc.: Chichester, 1988, pp. 369-449.

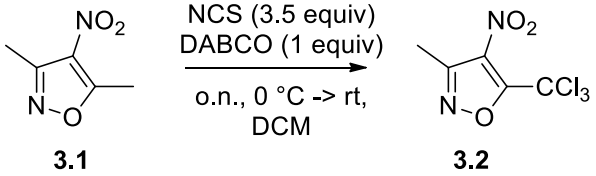
[168] J. Wang, H. Li, D. Zhang, P. Huang, Z. Wang, R. Zhang, Y. Liang, D. Dong, *Eur. J. Org. Chem.* **2013**, 5376-5380.

3.4 Results and discussion

With the aim to synthesize 5-functionalized isoxazoles, compound **3.1** was subjected to chlorination, to introduce a good leaving group in the molecule, and then performing nucleophilic substitutions with oxygen and carbon nucleophiles.

3.4.1 Synthesis of 3-methyl-4-nitro-5-trichlorometylisoxazole

Electrophilic chlorination of **3.1** was performed with NCS in presence of DABCO (1,4-diazabicyclo[2,2,2]octane). The reaction was totally selective affording the 5-trichloromethylisoxazole derivative: the first chlorination is the hardest, while the following ones are easier because the acidity of the protons increases with substitution. Using this strategy, compound **3.2** was isolated in almost quantitative yield.



3.1 **3.2**

*Scheme 3.9 - Chlorination of **3.1** with NCS.*

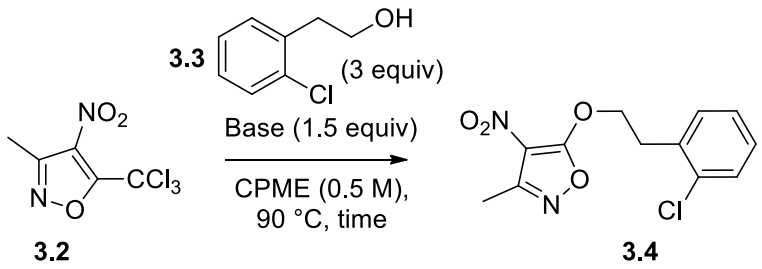
3.4.2 Nucleophilic substitutions on **3.2** with oxygen nucleophiles

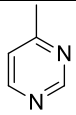
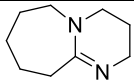
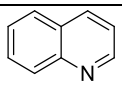
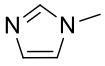
*3.4.2.1 Use of 2-(2-chlorophenyl)ethanol (**3.3**) as nucleophile*

The reaction between **3.2** and 2-(2-chlorophenyl)ethanol (**3.3**), in cyclopentylmethylether (CPME) was studied using different kinds of organic bases. The mandatory aspect in the choice of the base is the absence of

nucleophilic character to avoid competition with the alcohol in the nucleophilic substitution. The nature of the base affected the reaction time, as well as the conversion and the yield of the reaction, as reported in Table 3.1.

*Table 3.1 – Reaction of **3.2** with alcohol **3.3**: effect of the base.*[a]



Entry	Base	t (days)	Yield (%)[b]	Unreacted SM (%)[c]
1[d,e]		3	0	0
2[e]		1	0	0
3		4	15	50
4		2	1.5, 3[f]	-
5		6	-	70

[a] Reaction conditions: in a test tube to a solution of **3.2** (0.061 g, 0.25 mmol) in CPME was added alcohol **3.3** (0.099 mL, 0.75 mmol) and a base (0.38 mmol); [b] isolated yield; [c] determined by ^{1}H NMR; [d] 110 °C; [e] decomposition; [f] reaction performed with a double amount of starting material (SM).

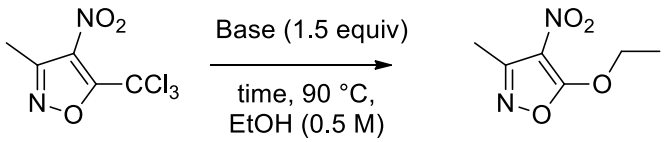
Analyzing the data reported in Table 3.1, quinoline results the best base tested, even if the conversion is low. Concerning the nucleophile, as well as the solvent, other conditions were studied.

3.4.2.2 Use of EtOH as nucleophile and solvent

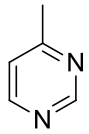
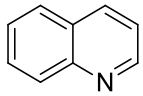
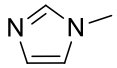
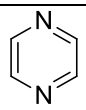
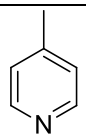
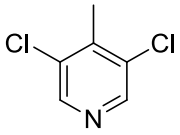
With the aim to explore different reaction conditions, EtOH was used as nucleophile as well as solvent.

Again, the first step of the setup of the reaction was a screening for the organic bases. Several heterocyclic bases were tested with different results, keeping constant the temperature and changing reaction times to optimize the reaction conditions for every single attempt. Results of this screening are reported in Table 3.2.

*Table 3.2 - Bases used in the reaction of **3.2** with EtOH.*[a]



3.2 **3.5**

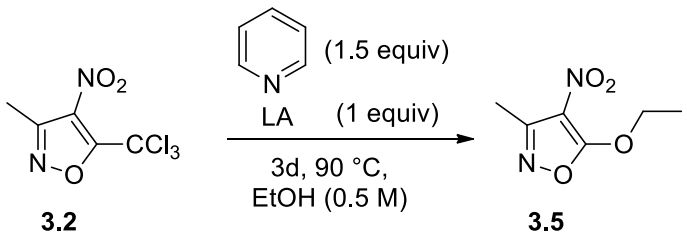
Entry	Base	t (days)	Yield (%)[b]	Conversion (%)[b]
1		4	18[c]	51
2		6	-	69
3		6	-	45
4		4	-[d]	-[d]
5		6	-	35
6		4	-	35
7		4	-	15

[a] Reaction conditions: in a test tube, to a solution of **3.2** (0.061 g, 0.25 mmol) in EtOH (0.5 mL), was added a base (0.38 mmol) and the resulting mixture was stirred at 90 °C for the allotted time; [b] determined by ^{1}H NMR; [c] isolated yield; [d] decomposition.

As shown in Table 3.2, ^{1}H NMR studies were performed on all the reaction crudes. On the basis of the spectral analyses, the use of pyridine as base gave the higher conversion but the reaction product was not recovered from the reaction mixture. These results were not satisfactory: the isolation of the

reaction product was low (Table 3.2, entry 1) because of the scarce conversion. With the aim to obtain better results, the addition of a Lewis Acid was studied to further activate the nitro group and then make easier the nucleophilic attack (Table 3.3).

*Table 3.3 - Use of different LA in the reaction of **3.2** with EtOH and pyridine.*[a]



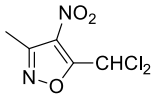
3.2 **3.5**

Entry	LA	Yield (%)	Conversion (%)[b]
1	$MgBr_2$	-	42
2	$Sc(OTf)_3$	-	13
3	$CeCl_3$	-	38
4	$InBr_3$	-	49
5	$SnCl_2$	-	59[c]
6	$ZnCl_2$	-	47
7	$MgCl_2$	43[d]	55

[a] Reaction conditions: in a test tube, to a solution of **3.2** (0.037 g, 0.15 mmol) in EtOH (0.3 mL) was added pyridine (0.018 mL, 0.23 mmol), a solid Lewis Acid (0.15 mmol or 0.045 mmol) and the resulting mixture was stirred at 90 °C for 3 days; [b] determined by ^{1}H NMR analysis; [c] formation of **3.6** in lieu of **3.5**; [d] reaction performed with 0.3 equiv of LA.

Among the tested Lewis Acids, $MgCl_2$, $InBr_3$ and $ZnCl_2$ gave rise to higher conversion and using $MgCl_2$ compound **3.5** was isolated in 43% yield.

A particular behavior was observed with $SnCl_2$, which was able to promote the replacement of a chlorine atom with a proton, leading to the dichlorinated product **3.6** with high conversion (^{1}H NMR).

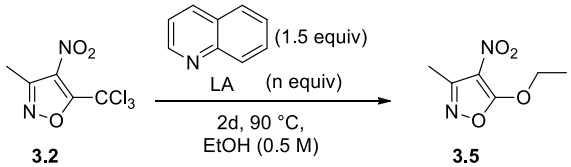


3.6

*Figure 3.3 - 5-dichloromethyl-3-methyl-4-nitroisoxazole **3.6**.*

Further attempts were achieved employing another good base, such as quinoline, in presence of Lewis Acids, to evaluate the reactivity with respect to pyridine. The best Lewis Acids used with pyridine as base, were tested in different amounts (0.3 and 1.0 equiv), and the results are resumed in Table 3.4.

*Table 3.4 - Use of different LA in the reaction of **3.2** with EtOH and quinoline.[a]*



3.2 **3.5**

Entry	LA	LA (equiv)	Yield (%)	Conversion (%)[b]
1	$MgBr_2$	0.3	-	33
2	$CeCl_3$	0.3	-	40
3	$InBr_3$[c]	1.0	-	46
4	$ZnCl_2$[c]	1.0	-	38
5	$MgCl_2$	0.3	-	31

[a] Reaction conditions: in a test tube, to a solution of **3.2** (0.037 mg, 0.15 mmol) in EtOH (0.3 mL) was added quinoline (0.027 mL, 0.23 mmol), a solid Lewis Acid (0.15 mmol or 0.045 mmol) and the resulting mixture was stirred at 90 °C for 2 days; [b] determined by ^{1}H NMR; [c] reaction performed for 4d.

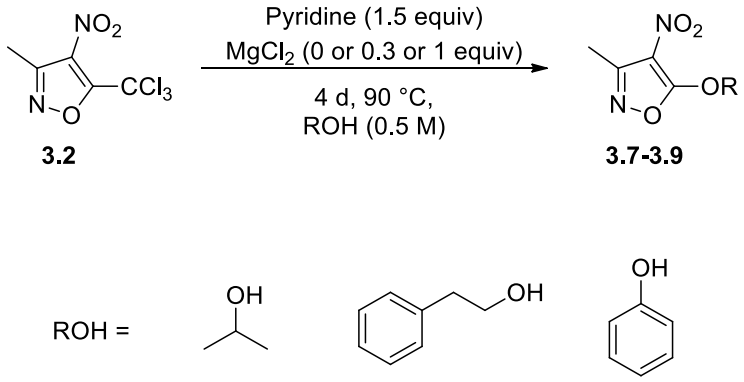
Unfortunately, the use of quinoline instead of pyridine did not enhanced the reactivity.

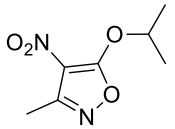
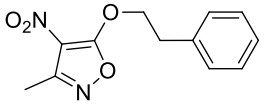
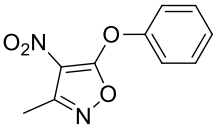
3.4.2.3 Use of other oxygen nucleophiles

Other oxygen nucleophiles, such as isopropanol, benzyl alcohol, 2-phenylethanol, and phenol were tested, applying the conditions reported in Table 3.3 (entry 7) for the synthesis of **3.5**.

The application of this strategy allowed the synthesis of compounds **3.7**-**3.9** in 19-53% yields, as reported in Table 3.5.

*Table 3.5 – Nucleophilic substitutions of **3.2** with oxygen nucleophile[].*

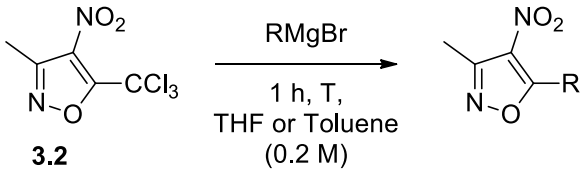


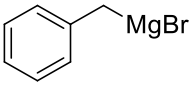
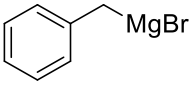
Entry	LA	LA (equiv)	Isolated yield (%)	Product
1	No	0.0	35	 **3.7**
3	$MgCl_2$	0.3	53	 **3.8**
4	$MgCl_2$	0.3	19	 **3.9**

3.4.3 Nucleophilic substitution on **3.2** with carbon nucleophiles

In order to apply the procedure to other nucleophiles, Grignard reagents were tested as carbon nucleophiles. As show before for **3.1**, Grignard reagents attack C-5 carbon, and the product is the corresponding 4,5-dihydroisoxazole. Performing the same reaction on **3.2** the aim is to obtain a substitution instead of the addition, thanks to the presence of a good leaving group. Three different RMgBr were tested in different conditions, and the results are shown in Table 3.6. Unfortunately, only compound **3.6** was obtained from the reaction with vinylmagnesium bromide (Table 3.6, entry 3).

*Table 3.6 - Reactions of Grignard reagents with **3.2**.[a]*



Entry	Reagent	equiv	T (°C)	Product[b]	Yield (%)[c]
1		3	0	-[d]	-
2		3	-80	-[d]	-
3		2	0	**3.6**	40
4		2	-80	**3.6**	-
5		2	0	-[d]	-
6		2	-80	-[d]	-

[a] Reaction conditions: a solution of **3.2** (0.049 g, 0.20 mmol) in dry THF (1 mL, 0.2 M) in a Schlenk, was cooled at the allotted temperature. Then a solution in THF of the Grignard reagent was added and the resulted mixture was stirred for 1 hour; [b] determined by ^{1}H NMR; [c] isolated yield; [d] complex reaction mixture.

3.5 Conclusions

In conclusion, an easy and efficient procedure for the selective electrophilic trichlorination of 3,5-dimethyl-4-nitro-isoxazole **3.1** has been developed. This approach involves the use of NCS as electrophilic chlorinating agent and DABCO as base and allows to isolate 3-methyl-4-nitro-5-trichloromethylisoxazole **3.2** in almost quantitative yield. The reactivity of **3.2** towards different *N*- *O*- *S*- and *C*-nucleophiles is under investigation for the development of a new methodology for the transition metal-free functionalization of 4-nitro-5-trichloromethylisoxazoles (as well as other heteroaromatic systems characterized by the presence of a methyl-NO_2 conjugated moiety), through a novel aromatic haloform-type reaction. In this context, preliminary data concerning the reactivity of **3.2** with various primary and secondary amines in the presence of K_2CO_3 in mild reaction conditions show an easy access to 3-methyl-4-nitro-5-aminoisoxazoles.

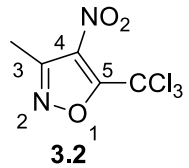
Unfortunately, on the basis of the above results, the use of O- and C-nucleophiles appears more difficult then requiring further studies related to the application of different reaction conditions (kind of bases, Lewis acids, type of nucleophiles, etc…) to access 5-functionalized derivatives.

3.6 Experimental section

3.6.1 General

Silica gel plates (Merck F_{254}) and silica gel 60 (Merck, 230-400 mesh) were used for TLC and flash chromatographies (FC), respectively. ^{1}H and ^{13}C NMR spectra were recorded with Varian VnmrS spectrometer, equipped with an auto-tunable broadband probe and an autosampler with 50 slots, operating at 400 and 100 MHz, respectively.

3.6.2 Synthesis of 3-methyl-4-nitro-5-trichloromethylisoxazole **3.2**

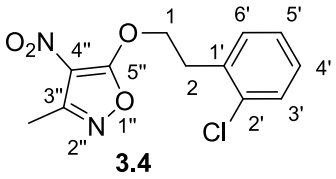


3.2

To a solution of **3.1** (1.0289 g, 7.24 mmol) in DCM (20 mL), was added DABCO (0.813 g, 7.24 mmol, 1 equiv). The solution was cooled to 0 °C with an ice bath (the solution dyed to yellow after the addition of DABCO) and NCS (3.40 g, 25.4 mmol, 3.5 equiv) was added in portions, warmed at r.t. and stirred overnight. After a TLC analysis, that confirmed the total disappearing of the reagent, was added Et_2O to precipitate succinimide and then was performed a celite filtration. The filtered solution was concentrated *in vacuo* and purified by FC (Pentane/EtOAc 99:1 v/v) obtaining **3.2** g (R_f = 0.56 in Pentane/EtOAc 7:3, 1.653 g, 93%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.60 (s, 3H, C*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1 (s, C-5), 158.1 (s, C-3), 128.1 (s, C-4), 83.8 (s, *C*Cl_3), 11.7 (q, *C*H_3) ppm.

HRMS found: $[M]^+$ 243.9216, $C_5H_3N_2O_3Cl_3$ requires 243.9209.

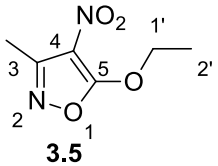
3.6.3 Synthesis of **3.4**



3.4

To a solution of **3.2** (0.061 g, 0.25 mmol) in CPME (cyclopentyl-methyl ether) in a test tube, was added alcohol **3.3** (0.099 mL, 0.75 mmol, 3 equiv) and a base (0.38 mmol, 1.5 equiv) and stirred at 90 °C for the time allotted. Completion the reaction was determined by TLC (Pentane/Et_2O 4:1, R_f = 0.71) and ^1H NMR spectrum of a crude sample dissolved in $CDCl_3$. The crude mixture was concentrated *in vacuo* and purified by silica gel chromatography (Pentane/Et_2O 100:3). ^1H NMR: δ 7.42-7.31 (m, 1H), 7.26-7.09 (m, 3H), 4.35 (t, *J* = 7.1 Hz, 1H, H-1), 3.12 (t, *J* = 7.1 Hz, 1H, H-2), 1.54 (s, 3H, C*H*$_3$) ppm. ^{13}C NMR: δ 154.9, 134.9, 134.2, 131.2, 129.6, 128.3, 126.9, 66.6 (t, C1), 32.9 (t, C2).

3.6.4 General procedure for the synthesis of **3.5**



3.5

To a solution of **3.2** (0.061 g, 0.25 mmol) in EtOH (0.5 mL) in a test tube, was added a base (0.38 mmol, 1.5 equiv) and stirred at 90 °C for the time allotted. Completion the reaction was determined by TLC (Pentane/Et_2O 4:1, R_f = 0.69) and ^1H NMR spectrum of a crude sample dissolved in $CDCl_3$.

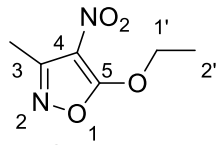
3.6.5 General procedure for the synthesis of **3.5** using pyridine as base and a Lewis Acid

To a solution of **3.2** (0.037 mg, 0.15 mmol) in EtOH (0.3 mL) in a test tube, was added pyridine (0.018 mL, 0.23 mmol, 1.5 equiv), a solid Lewis Acid (0.15 mmol, 1 equiv or 0.045 mmol, 0.3 equiv) and stirred at 90 °C for 3 days. Completion the reaction was determined by TLC (Pentane/Et_2O 4:1) and ^1H NMR spectrum of a crude sample dissolved in $CDCl_3$.

3.6.6 General procedure for the synthesis of **3.5** using quinoline as base and a Lewis Acid

To a solution of **3.2** (0.037 mg, 0.15 mmol) in EtOH (0.3 mL) in a test tube, was added quinoline (0.027 mL, 0.23 mmol, 1.5 equiv), a solid Lewis Acid (0.15 mmol, 1 equiv or 0.045 mmol, 0.3 equiv) and stirred at 90 °C for 2 days. Completion the reaction was determined by TLC (Pentane/Et_2O 4:1) and ^1H NMR spectrum of a crude sample dissolved in $CDCl_3$.

3.6.7 Synthesis of **3.5** with pyridine as base and $MgCl_2$ as Lewis Acid

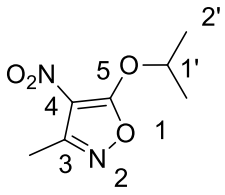


3.5

To a solution of **3.2** (0.037 g, 0.15 mmol) in EtOH (0.3 mL) in a test tube, was added pyridine (0.018 mL, 0.23 mmol, 1.5 equiv), solid $MgCl_2$ as Lewis Acid (0.004 g, 0.045 mmol, 0.3 equiv) and stirred at 90 °C for 4 days. Completion the reaction was determined by TLC (Pentane/Et_2O 4:1) and ^1H NMR spectrum of a crude sample dissolved in $CDCl_3$. The mixture was then resolved by chromatographic column (Pentane/Et_2O 100:1) and were recovered 3.2 (7.9 mg,

0.032 mmol, 21.5% yield) and 3.5 (11.1 mg, 0.065 mmol, 43% yield). ^{1}H NMR (400 MHz, CDCl3), δ: 4.52 (q, *J* = 7.1 Hz, 1H, H-1'), 2.58 (s, 3H, isox-C*H*$_3$), 1.43 (t, *J* = 7.1 Hz, 6H, H-2') ppm. ^{13}C NMR (100 MHz, CDCl3), δ: 157.8 (s, C-NO2), 155.5 (s, C-5), 155.0 (s, C-3), 64.1 (t, C-1'), 13.8 (q, C-2'), 10.8 (q, isox-*C*H$_3$) ppm.

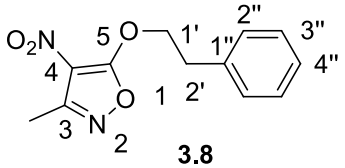
3.6.8 Synthesis of **3.7**



3.7

To a solution of **3.2** (0.037 g, 0.15 mmol) in *i*PrOH (0.3 mL) in a test tube, was added pyridine (0.018 mL, 0.23 mmol, 1.5 equiv), solid $MgCl_2$ as Lewis Acid (0.004 g, 0.045 mmol, 0.3 eq) and stirred at 90 °C for 4 days. Completion the reaction was determined by TLC (Pentane/Et_2O 4:1, R_f = 0.65) and ^{1}H NMR spectrum of a crude sample dissolved in $CDCl_3$. The mixture was then resolved by chromatographic column (Pentane/Et_2O 100:1) and was recovered **3.7** (0.011 g, 0.06 mmol, 39% yield). ^{1}H NMR (400 MHz, CDCl3), δ: 5.37 (hept, *J* = 6.3 Hz, 1H, H-1'), 2.57 (s, 3H, isox-C*H*$_3$), 1.42 (d, *J* = 6.3 Hz, 6H, H-2') ppm. ^{13}C NMR (100 MHz, CDCl3), δ: 158.3 (s, 1C, C-NO2), 155.4 (s, 1C, C-5), 154.7 (s, 1C, C-3), 77.9 (d, 1C, C-1'), 21.4 (q, 2C, C-2'), 10.8 (q, 1C, isox-*C*H$_3$) ppm.

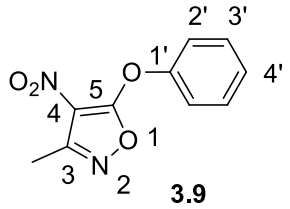
3.5.9 Synthesis of **3.8**



3.8

To a solution of **3.2** (0.037 mg, 0.15 mmol) in 2-phenyl-1-ethanol (0.3 mL) in a test tube, was added pyridine (0.018 mL, 0.23 mmol, 1.5 equiv), solid $MgCl_2$ as Lewis Acid (0.004 g, 0.045 mmol, 1 equiv) and stirred at 90 °C for 4 days. Completion the reaction was determined by TLC (Pentane/Et_2O 4:1, R_f = 0.67) and ^1H NMR spectrum of a crude sample dissolved in $CDCl_3$. The mixture was then resolved by chromatographic column (Pentane/Et_2O 100:1) and was recovered **3.8** (0.020 mg, 0.079 mmol, 53% yield). ^1H NMR (400 MHz, CDCl3), δ: 7.36-7.22 (m, 5H, Ph), 4.66 (t, *J* = 7.1 Hz, 2H, H-1'), 3.10 (t, *J* = 7.1 Hz, 2H, H-2'), 2.58 (s, 3H, C*H*$_3$) ppm. ^{13}C NMR (100 MHz, CDCl3), δ: 157.4 (s, 1C, C-NO2), 155.6 (s, 1C, C-5), 154.9 (s, 1C, C-3), 136.4 (s, 1C, C-1''), 128.9 (d, 2C, C-3''), 128.7 (d, 2C, C-2''), 127.0 (d, 1C, C-4''), 68.1 (t, 1C, C-1'), 34.6 (t, 1C, C-2'), 10.8 (q, 1C, *C*H_3) ppm.

3.6.10 Synthesis of **3.9**



3.9

To a solution of **3.2** (0.037 g, 0.15 mmol) in phenol (0.3 mL at 50 °C) in a test tube, was added pyridine (0.018 mL, 0.23 mmol, 1.5 eq.), solid $MgCl_2$ as Lewis Acid (0.004 g, 0.045 mmol, 1 equiv) and stirred at 90 °C for 4 days. Completion the reaction was determined by TLC (Pentane/Et_2O 4:1, R_f = 0.61) and ^1H NMR spectrum of a crude sample dissolved in $CDCl_3$. The mixture was then resolved by chromatographic column (Pentane/Et_2O 100:1) and was recovered **3.9** (0.006 mg, 0.028 mmol, 19% yield). 1H NMR δ: 7.23 (t, *J* = 8.0 Hz, 2H, H-3'), 6.91 (t, *J* = 7.5 Hz, 1H, H-4'), 6.86 (d, *J* = 7.7 Hz, 2H, H-2'), 2.59 (s, 3H, C*H*$_3$) ppm.

3.6.11 Attempts of nucleophilic substitution on **3.2** with carbon nucleophiles

3.6.11.1 Ethyl-magnesium bromide

A solution of **3.2** (0.049 g, 0.20 mmol) in dry THF (1 mL, 0.2 M) in a Schlenk, was cooled at the allotted temperature. Then was added a solution 2.9 M in THF of EtMgBr (0.170 mL, 0.5 mmol, 2.5 equiv) and stirred for 1 hour. The reaction was quenched by addition of a NH_4Cl sat., extracted by DCM and dried on Na_2SO_4. TLC and ^1H NMR spectrum show a very complex mixture, not resolved by column.

3.6.11.2 Vinyl-magnesium bromide at 0 °C

A solution of **3.2** (0.049 mg, 0.20 mmol) in dry THF (1 mL, 0.2 M) in a Schlenk, was cooled at 0 °C. Then was added a solution 1.7 M in THF of Vinyl-MgCl (0.235 mL, 0.4 mmol, 2 equiv) and stirred for 1 hour. The reaction was quenched by addition of a NH4Cl sat., extracted by DCM and dried on Na_2SO_4. After chromatographic resolution (Pentane/EtOAc 2:8)., was recovered **3.6** (Rf = 0.45 16 mg, 0.08 mmol, 40%) as a white solid. ^1H NMR (400 MHz, CDCl3) δ: 7.38 (s, 1H, C*H*Cl_2), 2.61 (s, 3H, C*H*$_3$).
^{13}C NMR (100 MHz, CDCl3) δ: 165.9 (s, C-5), 156.2 (s, C-3), 128.4 (s, C-4), 57.7 (d, C*H*Cl_2), 11.7 (q, *C*H_3) ppm. HRMS found: $[M]^+$ 209.9604, $C_5H_4Cl_2N_2O_3$ requires 209.9599.

3.6.12.3 Vinyl-magnesium bromide at -80 °C

A solution of **3.2** (0.049 mg, 0.20 mmol) in THF (1 mL, 0.2 M) in a dry Schlenk, was cooled at -80 °C. Then was added a solution 1.7 M in THF of Vinyl-MgCl

(0.235 mL, 0.4 mmol, 2 equiv) and stirred for 1 hour. The reaction was quenched by addition of a NH_4Cl sat., extracted by DCM and dried on Na_2SO_4. After TLC analysis, compound **3.6** was identified but no further manipulations have been done.

3.6.11.4 Benzyl-magnesium bromide

A solution of **3.2** (0.049 mg, 0.20 mmol) in dry THF (1 mL, 0.2 M) in a Schlenk, was cooled at the allotted temperature. Then was added a solution 1.4 M in THF of Benzyl-MgCl (0.285 mL, 0.4 mmol, 2 equiv) and stirred for 1 hour. The reaction was quenched by addition of a NH_4Cl sat., extracted by DCM and dried on Na_2SO_4. TLC and ^1H NMR analysis show a complex reaction mixture.