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Organic and Medicinal Chemistry Group

**ASYMMETRIC EPOXIDATION OF
ELECTRON-DEFICIENT OLEFINS
AND SYNTHETIC APPLICATIONS**

PhD Thesis
Andreu Vidal Albalat
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Els directors Dr. Florenci V. González Adelantado i Dr. Santiago Rodríguez Pastor, professors titulars del Departament de Química Inorgànica i Orgànica de la Universitat Jaume I de Castelló,

CERTIFIQUEN: Que la tesi doctoral “*Asymmetric epoxidation of electron-deficient olefins and synthetic applications*” ha estat desenvolupada per Andreu Vidal Albalat, sota la seua direcció, en l’Àrea de Química Orgànica del Departament de Química Inorgànica i Orgànica de la Universitat Jaume I de Castelló.

I per a què així conste, en compliment de la legislació vigent, signen aquesta certificació a Castelló 12 de juliol de 2016:

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Santiago Rodríguez Pastor

Aquesta Tesi Doctoral s'ha realitzat amb una beca predoctoral concedida per la Generalitat Valenciana, dins del programa VALi+D del 2013 per a la formació de personal investigador (FPI). El període de gaudi de la beca ha estat comprés entre l'1 de juny de 2013 al 31 de maig del 2016.

La Tesi Doctoral s'ha complementat amb una estada d'investigació a la Università degli Studi di Salerno (Itàlia), sota la supervisió de la professora Alessandra Lattanzi, en un període comprés entre l'1 de setembre de 2014 i el 31 de desembre de 2014. Aquesta estada ha estat finançada per les ajudes VALi+D 2014 a la mobilitat de l'estudiantat de doctorat.

Aquesta tesi s'ha realitzat i serà defesa seguint els requeriments exigits per l'obtenció del títol de Doctorat Internacional.

Prèviament a la defensa d'aquesta Tesi Doctoral, el treball ha estat avaluat per dos experts internacionals independents, relacionats directament amb l'àrea d'investigació i de reconegut prestigi internacional: Prof. Dr. Karl A. Jørgensen del departament de química de la Aarhus University (Aarhus, Dinamarca) i el Dr. Jean-Luc Decout del departament de Química Molecular i Farmacoquímica de la University Joseph Fourier (Grenoble, França).

Agraïments

A pesar de què el gruix de la tesi està escrit en anglès, aquestes paraules apareixeran escrites en la meua llengua, perquè en estes pàgines es parlarà d'afecte, i és una cosa que no es pot expressar plenament en una llengua que no siga la pròpia.

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*“Somewhere, something incredible
is waiting to be known”*

Carl Sagan

*“La llengua és l’expressió
del que un és”*

Raimon

“Where words fail, music speaks”

Hans Christian Andersen

Abbreviations

2-HEAF = 2-Hydroxyethyl ammonium formate

AcOH = Acetic acid

AIBN = Azobisisobutyronitrile

AKR = Asymmetric kinetic resolution

Boc = *tert*-Butoxycarbonyl

ca. = *circa* (approximately)

Cp = Cyclopentadienide

CPCM = Conductor-like polarizable continuum model

DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene

DCC = *N,N'*-Dicyclohexylcarbodiimide

DCE = 1,2-Dichloroethane

DCM = Dichloromethane

DFT = Density functional theory

DMSO = Dimethyl sulphoxide

DYKAT = Dynamic kinetic asymmetric transformation

EI = Electronic impact

ESI = Electrospray ionization

et al. = *et alii* (and others)

EtOAc = Ethyl acetate

EtOH = Ethanol

GC/MS = Gas chromatography/ Mass spectra

HFIP = 1,1,1,3,3,3-Hexafluoroisopropanol

HIV = Human immunodeficiency virus

HPLC = High performance liquid chromatography

IR = Infrared

LC = Liquid chromatography

MeOH = Methanol

MsCl = Methanesulfonyl chloride

MW = Microwave

NBS = *N*-Bromosuccinimide

NMR = Nuclear magnetic resonance

NOE = Nuclear Overhauser effect

PC = Product complex
PES = Potential energy surface
PTC = Phase transfer catalysis
QTOF = Quadrupol – Time of flight
r.t. = room temperature
RC = Reactant complex
TBHP = *tert*-Butyl hydroperoxide
TBS = *tert*-Butyldimethylsilyl
TFA = Trifluoroacetic acid
THF = Tetrahydrofuran
TLC = Thin layer chromatography
TMS = Trimethylsilyl
TS = Transition state
TsCl = *para*-Toluenesulfonyl chloride
UV = Ultraviolet

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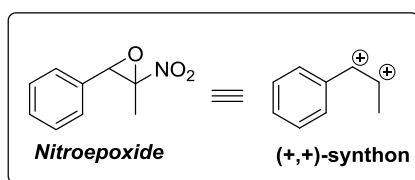
Chapter 1

General Introduction

1. Nitroepoxides

One of the milestones for a synthetic organic chemist is the achievement of complex molecules from simple and available molecules. Moreover, the ideal synthesis of those complex molecules must be economic, non-toxic and environmentally friendly. For that purpose, exists a family of molecules called *building blocks*, since their reactivity allow the formation of new bonds with easyness in mild conditions, such as jigsaws in a puzzle.

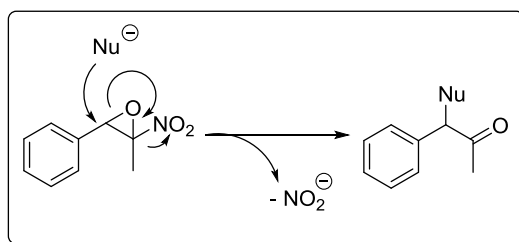
Nitroepoxides are the main family of compounds studied in this research work. Nitroepoxides are strained systems which display two highly oxidized vicinal positions by nature of their chemical connectivity and hence are potentially exploitable as synthons with vicinal electrophilic centers (Scheme 1). Nitroepoxides were firstly described by Newman and Angier in 1969.¹ Since then, many synthetic applications were reported but the interest in this class of compounds decreased through the years. However, in the last decade the interest for the nitroepoxides as building blocks has raised, and we think this tendency will increase partly due to an enantioselective epoxidation of nitroalkenes to obtain optically active nitroepoxides with high chemical yields and enantioselectivity, as reported on this Thesis. This introductory chapter will provide a brief background on the use of nitroepoxides in organic synthesis, focusing on the most recent examples.



Scheme 1. Nitroepoxides as 1,2-electrophilic synthons.

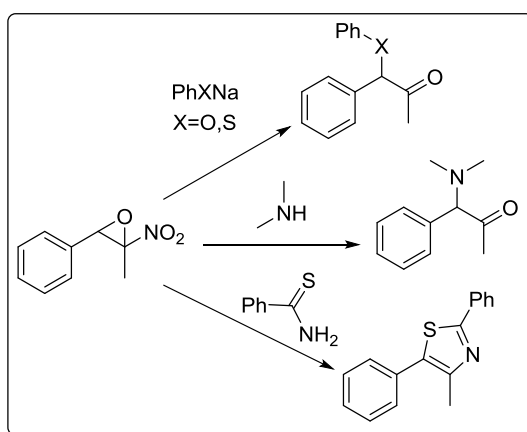
¹ Newman, H.; Angier, R. B. *J. Chem. Soc. D Chem. Commun.* **1969**, 186, 369.

In their research, Newman and Angier synthesized the corresponding epoxide from *trans*- β -methyl- β -nitrostyrene, and tested different conditions in order to study its reactivity.² As expected, the behaviour of the nitroepoxide towards a series of representative nucleophiles was rationalized as an S_N2 , in which the nucleophiles attack the beta position to the nitro group affording the corresponding ketone upon nitrous acid extrusion (Scheme 2). This reactivity makes nitroepoxides an interesting alternative to haloketones.



Scheme 2. Reactivity of nitroepoxides generates a carbonylic compound.

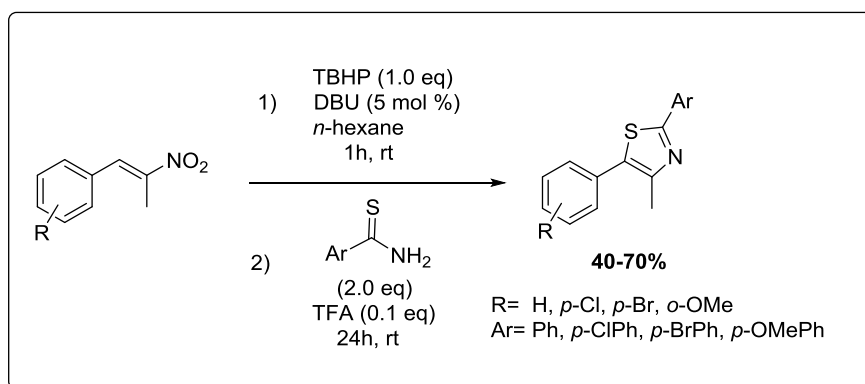
The tested nucleophiles were sodium phenoxide, sodium thiophenolate, dimethylamine and thiobenzamide (Scheme 3). The nitroepoxide also showed reactivity under acidic conditions. In diluted sulfuric acid, the α -hydroxyketone and the oxidation product diketone were isolated. When treated with Lewis acid $BF_3 \cdot Et_2O$, the reaction gave a complex mixture of compounds.²



Scheme 3. Examples of ring-opening reactions

² Newman, H.; Angier, R. B. *Tetrahedron* **1970**, 26, 826.

More recent works have explored further the reactivity of nitroepoxides. Tsogoeva's group³ found interest in the formation of thiazoles from nitroepoxides using thiobenzamides, briefly reported before by Newman and Angier.² Her group focused attention on the development of one-pot processes for the syntheses of 1,3-thiazoles *via* organocatalyzed epoxidation of nitroalkenes. First, they optimized the conditions for the organocatalytic epoxidation of *trans*- β -methyl- β -nitrostyrene using TBHP-DBU system as previously reported for the epoxidation of α,β -unsaturated- δ -lactones.⁴ The best conditions for the epoxidation resulted to be the use of 2 equivalents of TBHP, 5 mol% of DBU in *n*-hexane as a solvent, at room temperature. Next, the ring opening step with one equivalent of thiobenzamide was carried out by using the same conditions *i.e.*, *n*-hexane as a solvent at room temperature. However, the 1,3-thiazole was isolated only in 34% yield. When using MeOH as a solvent, the chemical yield raised up to 62% and when two equivalents of the thiobenzamide were used instead, the yield raised up to 66% in *n*-hexane and up to 80% in MeOH. Then, MeOH was used as an additive in the second step of the reaction in the one-pot sequence. Other additives were tested and finally, TFA gave the best results (Scheme 4).

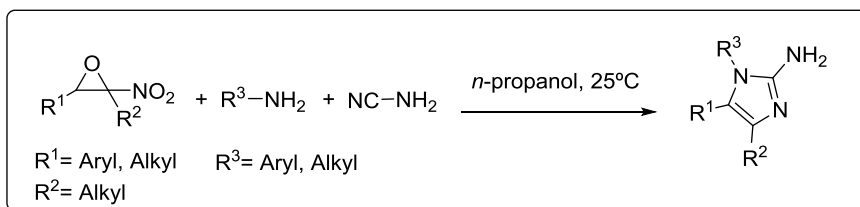


Scheme 4. One-pot synthesis of 1,3-thiazoles from nitroepoxides.

³ Weiss, K. M.; Wei, S.; Tsogoeva, S. B. *Org. Biomol. Chem.* **2011**, 9 (9), 3457.

⁴ Yadava, V. K.; Kapoor, K. K. *Tetrahedron* **1995**, 51 (31), 8573.

X. Guo *et al.* published a synthetic methodology to obtain functionalized 2-aminoimidazoles from α -nitroepoxides.⁵ The 2-aminoimidazole scaffold is present in a great variety of biologically relevant molecules, such as β -secretase inhibitors⁶ and compounds with anticancer activity.⁷ The privileged structure of nitroepoxides with two vicinal electrophilic centers allowed the one-pot synthesis of 2-aminoimidazole using an amine (generally *p*-substituted anilines) and cyanamide (Scheme 5). The first conditions involved the use of a base, but the reaction gave higher yields in the absence of base. Also, many solvents were screened to conclude *n*-propanol to be the best solvent. The scope of the reaction was examined by coupling nitroepoxides with cyanamide and amines. Anilines bearing an electron-donating group (methyl or methoxy) afforded the desired 2-aminoimidazoles in a higher yield than those with electron-withdrawing group (-F, -Cl or -Br). However, no reaction was observed with *p*-nitroaniline.



Scheme 5. One-pot synthesis of 2-aminoimidazoles from nitroepoxides.

X. Guo *et al.* also reported a different approach to obtain imidazoles from nitroepoxides.⁸ In this case, amidines were used instead of cyanamide and an amine. This approach was useful to achieve the

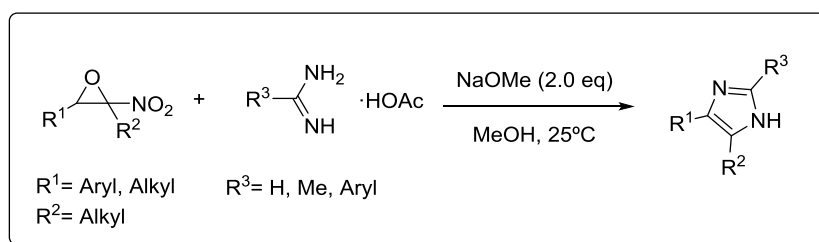
⁵ Guo, X.; Chen, W.; Chen, B.; Huang, W.; Qi, W.; Zhang, G.; Yu, Y. *Org. Lett.* **2015**, *17* (5), 1157.

⁶ Malamas, M. S.; Erdei, J.; Gunawan, I.; Barnes, K.; Johnson, M.; Yu, H.; Turner, J.; Yun, H.; Wagner, E.; Fan, K.; Olland, A.; Bard, J.; Robichaud, A. J. *J. Med. Chem.* **2009**, *52* (20), 6314.

⁷ Li, W.-T.; Hwang, D.-R.; Song, J.-S.; Chen, C.-P.; Chuu, J.-J.; Hu, C.-B.; Lin, H.-L.; Huang, C.-L.; Huang, C.-Y.; Tseng, H.-Y.; Lin, C.-C.; Chen, T.-W.; Lin, C.-H.; Wang, H.-S.; Shen, C.-C.; Chang, C.-M.; Chao, Y.-S.; Chen, C.-T. *J. Med. Chem.* **2010**, *53* (6), 2409.

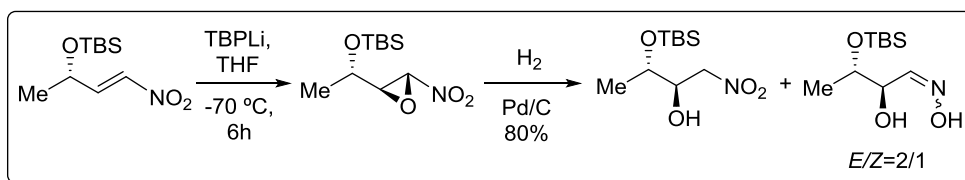
⁸ Guo, X.; Shao, J.; Liu, H.; Chen, B.; Chen, W.; Yu, Y. *RSC Adv.* **2015**, *5* (64), 51559.

formation of the imidazole scaffold with other substituents different to amino groups, *i.e.* -H, alkyl or aryl (Scheme 6). In this work, the use of a base was found to be necessary: two equivalents of NaOMe in MeOH at room temperature afforded the imidazole in the highest yield of the selected example (91%). Again, the chemical yields were higher when electron-donor substituents were present in the amidine. The reaction of nitroepoxide with 2-aminopyridine using the same conditions afforded the imidazo-[1,2-a]-pyridine scaffold.



Scheme 6. Synthesis of imidazoles from nitroepoxides.

Our research group has showed interest in nitroepoxides as well.^{9,10} 3-Hydroxy-1-nitroalkenes were prepared from optically pure O-protected (S)-lactaldehyde or (S)-mandelaldehyde *via* nitroaldol reaction followed by elimination. The epoxidation of the obtained nitroolefins with lithium (or potassium) *tert*-butylperoxide gave the corresponding nitroepoxide with high stereoselectivity (up to 19/1). The palladium catalyzed hydrogenation of the resulting nitroepoxides afforded the corresponding *anti*-nitroaldols as main product and oximes as a secondary product (Scheme 7).

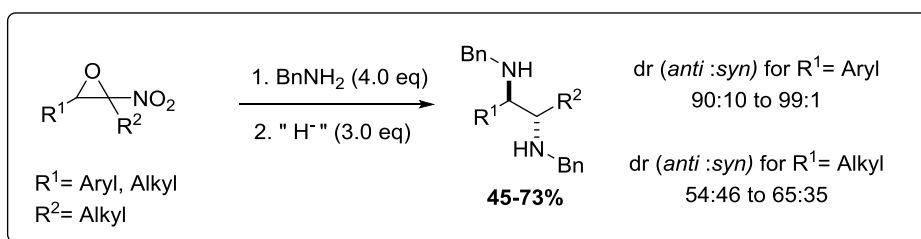


Scheme 7. Stereoselective synthesis of nitroaldols.

⁹ Jain, A.; Rodríguez, S.; López, I.; González, F. V. *Tetrahedron* **2009**, *65* (40), 8362.

¹⁰ Agut, J.; Vidal, A.; Rodríguez, S.; González, F. V. *J. Org. Chem.* **2013**, *78* (11), 5717.

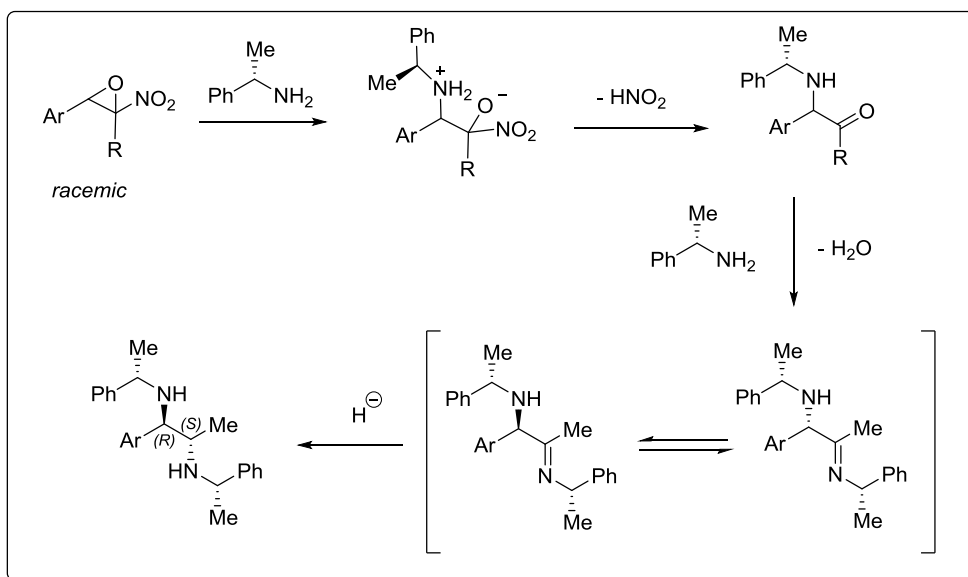
Our most interesting contribution to the chemistry of the α -nitroepoxides was the synthesis of 1,2-diamines starting from nitroepoxides.¹⁰ We began our studies of the preparation of vicinal diamines by combining the α -methyl- β -phenyl-nitroepoxide with 2 equivalents of benzylamine in dichloromethane for 2h and then, 2 equivalents of sodium borohydride for 12h. The corresponding diamine was obtained as a 9:1 mixture of stereoisomers, with the *anti*- isomer as the major one (Scheme 8). The chemical yield and the stereoselectivity were improved when some changes were introduced: the use of 1,2-dichloroethane as a solvent, sodium triacetoxyborohydride as a reducing agent and the first step was carried out for longer. To study the scope of the reaction some nitroepoxides displaying different substituents on the structure were subjected to optimal reaction conditions. The nitroepoxides having an aryl group at the β -position and an alkyl group at the α -position gave good yields and high stereoselectivity, while compounds with alkyl groups at both positions gave poor selectivities.



Scheme 8. Synthesis of vicinal diamines from nitroepoxides.

Under the same reaction conditions as mentioned above but, when chiral L- α -methyl benzylamine was used, we observed something interesting. Chiral diamines were prepared with 55-70% yield and one of the possible four isomers (*1R*, *2S*) was formed with high stereoselectivity (>88% d.e.). Our understanding of this interesting process is as follows. In the case of using a chiral amine, the process constitutes a DYKAT. The reaction between aminoketone and a second equivalent of the amine would yield an isomeric mixture of α -aminoimines (Scheme 9). These intermediates would go into a

DYKAT: isomeric α -aminoimines can interconvert to furnish the *R* isomer as the main product, which upon reduction would furnish the final diamine. With this methodology, chiral vicinal diamines, which are important building blocks found in many chiral catalysts and intermediates in the synthesis of biologically active small molecules,¹¹ can be obtained in high stereoselectivity.



Scheme 9. DYKAT occurs when optically active amine is used.

2. Heterocyclic Compounds

2.1. Quinoxalines

Quinoxaline derivatives are an important class of heterocyclic compounds in which N replaces the positions 1 and 4 of the naphthalene ring. Quinoxaline structure serves as a precursor to assembly a large number of new compounds for diverse applications in

¹¹ (a) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chemie - Int. Ed.* **1998**, 37 (19), 2580. (b) Kim, H. J.; Kim, W.; Lough, A. J.; Kim, B. M.; Chin, J. *J. Am. Chem. Soc.* **2005**, 127 (48), 16776. (c) Marqués-López, E.; Merino, P.; Tejero, T.; Herrera, R. *European J. Org. Chem.* **2009**, 15, 2401.

electrochemical materials and in pharmacological industry.¹² Examples of natural products with the quinoxaline moiety exhibiting biological activities are scarce, *e.g.* echinomycin and triostin A (Figure 1), but there is also a vast scope of synthetic quinoxaline derivatives which exhibited antibacterial,¹³ antiviral¹⁴ and/or anticancer¹⁵ activities. Thus, the development of new facile methodology to construct these heterocyclic compounds, results interesting since the actual synthetic routes have several limitations.

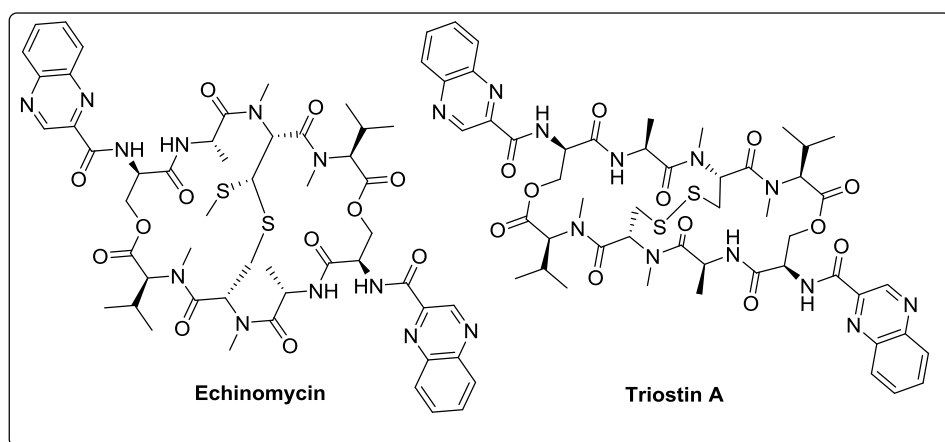


Figure 1. Natural bioactive compounds that exhibit quinoxaline moiety.

A common method for the preparation of the quinoxaline ring is the condensation of 1,2-dicarbonyl compounds with 1,2-diamines.¹⁶ However, synthetic approaches to differently substituted 1,2-dicarbonyl compounds are usually step intensive and typically involve redox approaches. Other synthetic approaches have been reported to circumvent this limitation; for example, Antoniotti *et al.* reported the

¹² Pereira, J.; Pessoa, A. M.; Cordeiro, M. N. D. S.; Fernandes, R.; Prudêncio, C.; Noronha, J. P.; Vieira, M. *Eur. J. Med. Chem.* **2015**, *97*, 664.

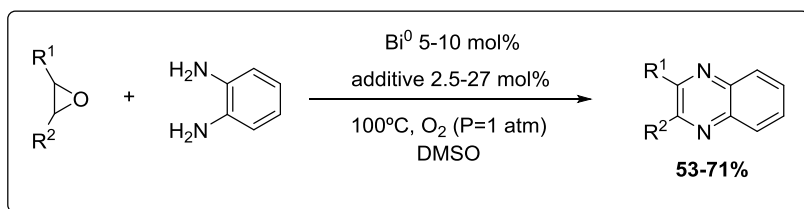
¹³ Vieira, M.; Pinheiro, C.; Fernandes, R.; Noronha, J. P.; Prudêncio, C. *Microbiol. Res.* **2014**, *169* (4), 287.

¹⁴ You, L.; Cho, E. J.; Leavitt, J.; Ma, L.-C.; Montelione, G. T.; Anslyn, E. V.; Krug, R. M.; Ellington, A.; Robertus, J. D. *Bioorg. Med. Chem. Lett.* **2011**, *21* (10), 3007.

¹⁵ Zarranz, B.; Jaso, A.; Aldana, I.; Monge, A. *Bioorg. Med. Chem.* **2004**, *12* (13), 3711.

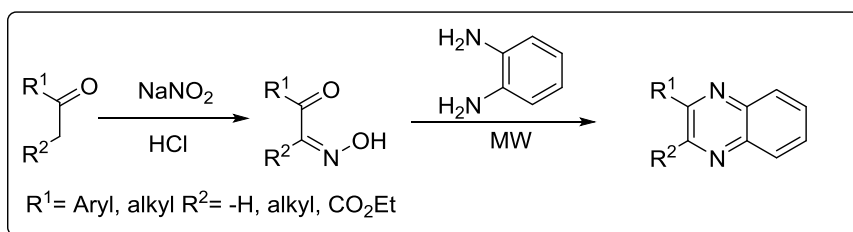
¹⁶ Bandyopadhyay, D.; Mukherjee, S.; Rodriguez, R. R.; Banik, B. K. *Molecules* **2010**, *15* (6), 4207.

synthesis of quinoxalines from simple epoxides via oxidative coupling with 1,2-diamino aryl compounds catalyzed by bismuth powder in the presence of an additive (copper (II) triflate or triflic acid) (Scheme 10).¹⁷ However, under these conditions polymerization of some epoxides was observed and in consequence lower yields were obtained. This approach also needs high temperatures and DMSO as a solvent, which completely removal is usually laborious.



Scheme 10. Synthesis of quinoxalines from epoxides

An interesting and fast two-step sequential synthesis of quinoxalines starting from simple ketones via their α -hydroxyimino ketone derivatives, and condensation of the latter with 1,2-diaminobenzene under microwave irradiation, was described by Padmavathy *et al.*¹⁸ In a first step, simple ketone was converted into α -hydroxylamine ketone intermediate using concentrated HCl – sodium nitrite combination. Then, the oxime intermediate was mixed with 1,2-diaminobenzene and the mixture was subjected to MW irradiation during 9 min. With this fast methodology (overall process <2h), quinoxalines were prepared in high chemical yields (Scheme 11).



Scheme 11

¹⁷ Antoniotti, S.; Duñach, E. *Tetrahedron Lett.* **2002**, 43 (22), 3971.

¹⁸ Padmavathy, K.; Nagendrappa, G.; Geetha, K. V. *Tetrahedron Lett.* **2011**, 52 (4), 544.

There are many reports that describe one-pot procedures to obtain quinoxalines from different starting materials, such as 1,2-diols,¹⁹ alkynes²⁰ or arylallenes.²¹ However, all these procedures are suspect to involve the *in situ* formation of diketone followed by condensation with *o*-phenylenediamine, since all of them need oxidative conditions and the use of organometallic catalysts, such as ruthenium or gold.

Tsogoeva's group proposed a one-pot organocatalytic synthesis to afford quinoxalines from nitroepoxides.²² In that study, *trans*- β -methyl- β -nitrostyrene was epoxidized to the corresponding nitroepoxide by using TBHP as an oxidant, hexane as a solvent and DBU as a catalyst. Then, *o*-phenylenediamine was added to the obtained nitroepoxide and the reaction mixture was stirred to afford the quinoxaline compound. However, these conditions afforded quinoxalines in low yield (30%), then yields were increased (67%) by addition of hexafluoroisopropanol (HFIP) within the *o*-phenylenediamine. The differences between her reaction and ours will be explained in the corresponding chapter of this Thesis.

2.2. 1,2,3,4 – Tetrahydroquinoxalines

1,2,3,4 – Tetrahydroquinoxaline is a class of heterocyclic compounds which consists of a benzene ring fused with a piperazine ring or in other words, it is a reduced form of quinoxaline. Compounds that possess a tetrahydroquinoxaline system have been studied as potent cholesteryl ester transfer protein inhibitors,²³ anticonvulsants,²⁴ and

¹⁹ Cho, C. S.; Oh, S. G. *Tetrahedron Lett.* **2006**, *47*, 5633.

²⁰ Chen, C.-Y.; Hu, W.-P.; Liu, M.-C.; Yan, P.-C.; Wang, J.-J.; Chung, M.-I. *Tetrahedron* **2013**, *69* (46), 9735.

²¹ Cui, D.-M. M.; Zhuang, D.-W. W.; Chen, Y.; Zhang, C. *Beilstein J. Org. Chem.* **2011**, *7* (I), 860.

²² Ibrahim, M. M.; Grau, D.; Hampel, F.; Tsogoeva, S. B. *European J. Org. Chem.* **2014**, *2014* (7), 1401.

²³ Eary, C. T.; Jones, Z. S.; Groneberg, R. D.; Burgess, L. E.; Mareska, D. a.; Drew, M. D.; Blake, J. F.; Laird, E. R.; Balachari, D.; O'Sullivan, M.; Allen, A.; Marsh, V. *Bioorganic Med. Chem. Lett.* **2007**, *17* (9), 2608.

anti- HIV agents.²⁵ Besides medicinal chemistry, tetrahydroquinoxaline derivatives have been studied as dyes with useful photophysical properties.²⁶

Methods for the preparation of tetrahydroquinoxalines suffer from the same drawbacks as quinoxalines, since they are usually prepared from reduction of quinoxalines.²⁷ Nevertheless, useful asymmetric reductions of quinoxalines have been developed *i.e.*, hydrogenation of quinoxalines catalyzed by iridium-diphosphine complexes.²⁸ Despite the variety of examples of different iridium catalysts employed for this reaction, the scope seems to be limited to quinoxalines with only one substitution in the heterocyclic ring. To surpass this limitation, Jie Qin and coworkers have developed cationic ruthenium complexes of chiral monotosylated diamines to afford 2- (aryl or alkyl) and 2,3- (alkyl, alkyl) tetrahydroquinoxalines.²⁹ However, no details were reported for the hydrogenation of 2,3- aryl, alkyl or 2,3- aryl, aryl quinoxalines. Another disadvantage of both iridium and ruthenium catalyzed hydrogenations; is that high H₂ pressures are required.

Other methodologies are reported in the literature. One of them involves the formation of the tetrahydroquinoxaline core from appropriate 2-nitrosoaniline and an unsaturated electrophile via Michael addition followed by aza-aldol reaction, completed by reduction of the hydroxylamine formed (Scheme 12).³⁰ Although only catalytic amount of base was necessary to perform the first step of the reaction from a

²⁴ Pouw, B.; Nour, M.; Matsumoto, R. R. *Eur. J. Pharmacol.* **1999**, *386*, 181.

²⁵ Patel, M.; McHugh, R. J.; Cordova, B. C.; Klabe, R. M.; Bachelier, L. T.; Erickson-Viitanen, S.; Rodgers, J. D. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1943.

²⁶ Chandrasekaran, Y.; Dutta, G. K.; Kanth, R. B.; Patil, S. *Dye. Pigment.* **2009**, *83* (2), 162.

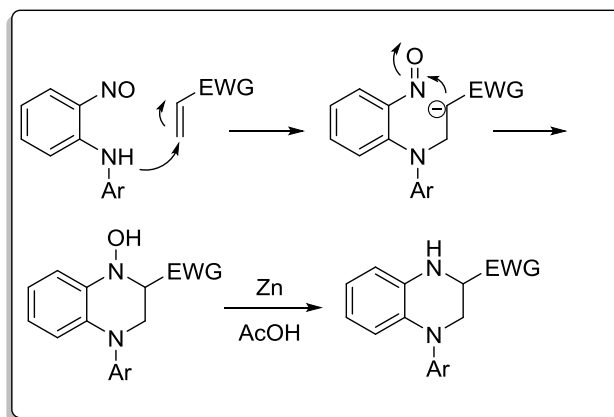
²⁷ Figueras, J. *J. Org. Chem.* **1966**, *31* (March), 803.

²⁸ Cartigny, D.; Nagano, T.; Ayad, T.; Genêt, J.-P.; Ohshima, T.; Mashima, K.; Ratovelomanana-Vidal, V. *Adv. Synth. Catal.* **2010**, *352* (11-12), 1886.

²⁹ Qin, J.; Chen, F.; Ding, Z.; He, Y.-M.; Xu, L.; Fan, Q.-H. *Org. Lett.* **2011**, *13* (4), 6568.

³⁰ Królikiewicz, M.; Błaziak, K.; Danikiewicz, W.; Wróbel, Z. *Synlett* **2013**, *24* (15), 1945.

mechanistic point of view, an excess of base was used to accelerate the reaction because of the instability of intermediate. When catalytic amount of base was used, product was formed so slowly that the rate of its decomposition competed with that of its formation. Due to intermediate instability, the reduction step using Zn and acetic acid was performed without purification. A similar, but microwave-assisted procedure described by Merisor *et al.* starts from *N*-prenyl-2-nitroanilines instead of 2-nitrosoanilines, and triethyl phosphite as a reducing agent.³¹ The proposed mechanism begins with the reduction of nitro group into nitroso group, which undergoes an intramolecular ene reaction with the 2-methylpropenyl group of the molecule, resulting in the formation of a cyclic hydroxyl amine that is finally reduced by the phosphite to yield the cyclic amine. However, the formation of byproducts consisting on the N-ethylation of one or both nitrogen atoms could not be suppressed by using microwaves.



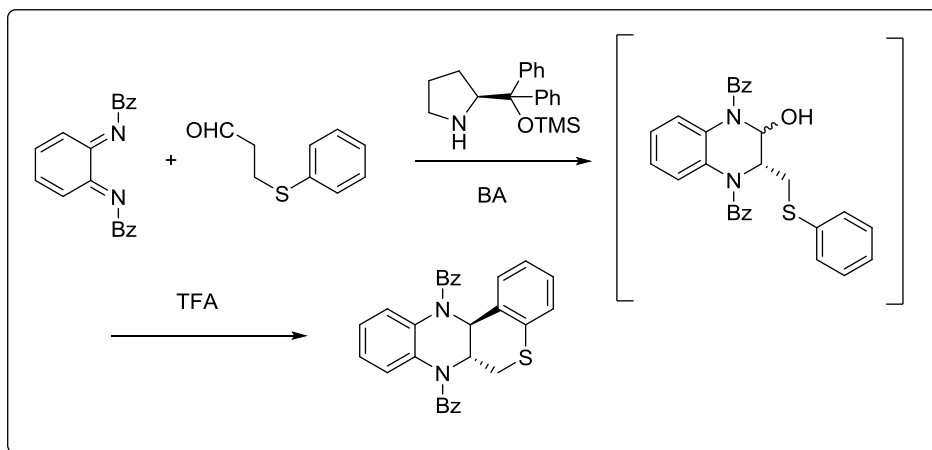
Scheme 12. Synthesis of tetrahydroquinoxalines from 2-nitrosoanilines.

An interesting method for the preparation of tetrahydroquinoxaline core and further conversion into more complex fused rings was described by Si-Li Zhou and coworkers.³² The reaction consists on an asymmetric hetero-Diels-Alder reaction to form the tetrahydroquinoxaline moiety, followed by Friedel-Crafts to construct the fused ring (Scheme 13). 1,2-

³¹ Merisor, E.; Conrad, J.; Mika, S.; Beifuss, U. *Synlett* **2007**, 2007 (13), 2033.

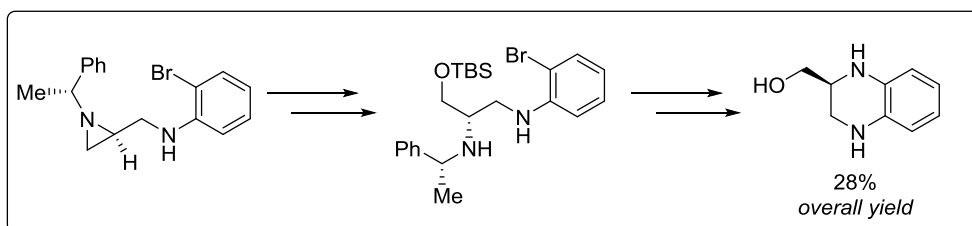
³² Zhou, S.-L.; Li, J.-L.; Dong, L.; Chen, Y.-C. *Org. Lett.* **2011**, 13 (21), 5874.

Diimide (diene) and an aldehyde (which enol form constitutes the dienophile) were reacted in the presence of *O*-TMS-diphenylprolinol and benzoic acid (BA) to form the corresponding tetrahydroquinoxaline and then, TFA was added to obtain the final product with 66% yield and 94% ee.



Scheme 13. Synthesis of tetrahydroquinoxalines by hetero-Diels-Alder.

Another asymmetric methodology for the synthesis of substituted heterocycles *via* aziridine, afforded the synthesis of (1,2,3,4-tetrahydroquinoxalin-2-yl)methanols from the corresponding 2-bromoanilines, which were converted into 2-aminomethyl substituted aziridines which were used as chiral scaffolds for the following synthesis.³³ After many protection/deprotection steps, aziridines were sequentially transformed into the final tetrahydroquinoxaline compounds (Scheme 14).



Scheme 14. Synthesis of tetrahydroquinoxalines from aziridines.

³³ Chan Kim, J.; Choi, H. G.; Kim, M. S.; Ha, H.-J.; Lee, W. K. *Tetrahedron* **2010**, *66* (40), 8108.

2.3. Piperazines

The piperazine moiety has been classified as a “privileged scaffold” in medicinal chemistry³⁴ and is frequently found in many natural products as well as being a large class of biologically active compounds (Figure 2). Aqueous soluble piperazine derivatives are also relevant in environmental chemistry, since piperazine can react with atmospheric carbon dioxide forming stable carbamates and consequently enhance its solubility in water.³⁵ Although the condensation of α -amino acids to obtain diketopiperazines is quite common in the literature,³⁶ procedures to obtain substituted piperazines are scarce and will be summarized below.

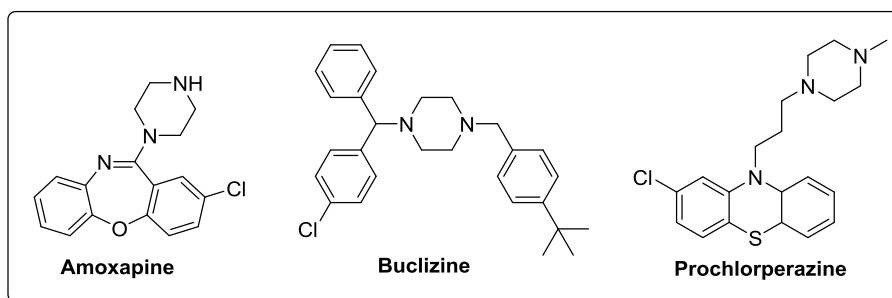


Figure 2. Bioactive compounds that exhibit piperazine moiety.

One of the first described methods consists on the condensation of 1,2-diketones with ethylenediamine followed by reduction.³⁷ This method has the same disadvantages than those to prepare tetrahydroquinoxalines: the accesibility of diketones and the proper reducing agent to generate stereoselectivity. A similar approach that solve these issues and could be used to synthetize optically pure chiral

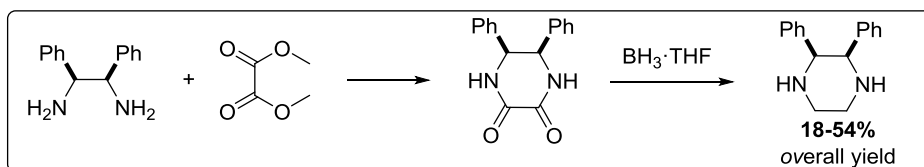
³⁴ Horton, D.; Bourne, G. T.; Smythe, M. L. *Cancer Res.* **2003**, *103* (3), 893.

³⁵ Ramazani, R.; Mazinani, S.; Jahanmiri, A.; Van der Bruggen, B. *Int. J. Greenh. Gas Control* **2016**, *45*, 27.

³⁶ Bull, S. D.; Davies, S. G.; Garner, C.; Parkes, A. L.; Roberts, P. M.; Sellers, T. G. R.; Smith, A. D.; Tamayo, J.; Thomson, J. E.; Vickers, R. J. *New J. Chem.* **2007**, *31* (4), 486.

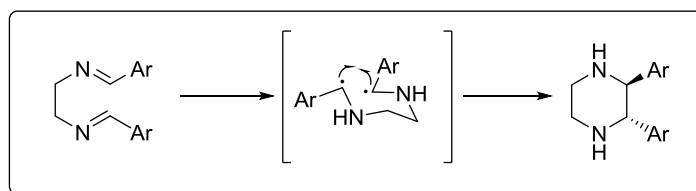
³⁷ Giardinà, D.; Gulini, U.; Massi, M.; Piloni, M. G.; Pompei, P.; Rifaiani, G.; Melchiorre, C. *J. Med. Chem.* **1993**, *36* (6), 690.

piperazines was reported by Gust *et al.*³⁸ They used 1,2-diaryl ethylenediamine instead of ethylenediamine, and dimethyl oxalate (Scheme 15). The reaction affords the 2,3-diarylpiperazine-5,6-dione as an intermediate, which already has the substitution in C_{sp3}, and thus the ketone can be reduced to methylene with borane without creating new stereogenic centers. However, authors didn't exploit this feature because the final obtained piperazines were symmetric.



Scheme 15. Synthesis of piperazines from 1,2-diesters.

Diastereoselective synthesis of 2,3-diarylpiperazines *via* intramolecular reductive coupling of bisimines using a Brønsted acid and Manganese (0).³⁹ The process presumably involves activation of the imine by the Brønsted acid followed by reduction of the iminium on the manganese surface to form a carbon-centered radical. They proposed a six-membered transition state model for diradical termination which is consistent with the observed diastereocontrol (Scheme 16). In this model, the imine substituents are oriented *trans*- to each other in equatorial sites.



Scheme 16. Proposed transition state which explains diastereocontrol.

Madsen and coworkers have presented an atom-economical procedure for the synthesis of piperazines from amines and 1,2-diols in which

³⁸ Gust, R.; Keilitz, R.; Schmidt, K. *J. Med. Chem.* **2002**, *45* (11), 2325.

³⁹ Mercer, G. J.; Sigman, M. S. *Org. Lett.* **2003**, *5* (9), 1591.

water is produced as the only byproduct.⁴⁰ The reaction is catalyzed by $[\text{Cp}^*\text{IrCl}_2]_2$ and can be achieved in toluene as well as in aqueous solution. 1,2-Diamines condense with 1,2-diols to afford a variety of piperazines with different substitution patterns in a proposed mechanism in which the key step is an isomerization of the initially formed hydroxy imine to the corresponding amino aldehyde/ketone, followed by imination and finally a reductive elimination of the catalyst. When benzylamine is used instead of 1,2-diamines, piperazines are equally formed but two equivalents of ethyleneglycol are required. This methodology resulted to be quite substrate-dependent since the yields were excellent for the reaction between ethylenediamine and mono- or di-substituted ethyleneglycols (70 to 100 %), but lower when unsubstituted ethylene diamine or *o*-phenylenediamine was condensed with unsubstituted ethyleneglycol (35 to 69%).

2.4. Pyrazines

Compounds containing the pyrazine heterocycle find numerous applications in materials science,⁴¹ medicinal chemistry,⁴² compounds that are responsible for the flavor and aroma of several foodstuffs and wines,⁴³ and compounds with herbicidal activity.⁴⁴ Recently, tetrasubstituted pyrazines have been discovered as semio-chemicals in orchids.⁴⁵

Main synthetic procedures for the synthesis of substituted pyrazines can be divided in two groups: self-condensation of α -amino aldehydes⁴⁶

⁴⁰ Lorentz-Petersen, L. L. R.; Nordstrøm, L. U.; Madsen, R. *European J. Org. Chem.* **2012**, 2012 (34), 6752.

⁴¹ Mondal, R.; Ko, S.; Bao, Z. *J. Mater. Chem.* **2010**, 20 (47), 10568.

⁴² Seitz, L. E.; Suling, W. J.; Reynolds, R. C. *J. Med. Chem.* **2002**, 45, 5604.

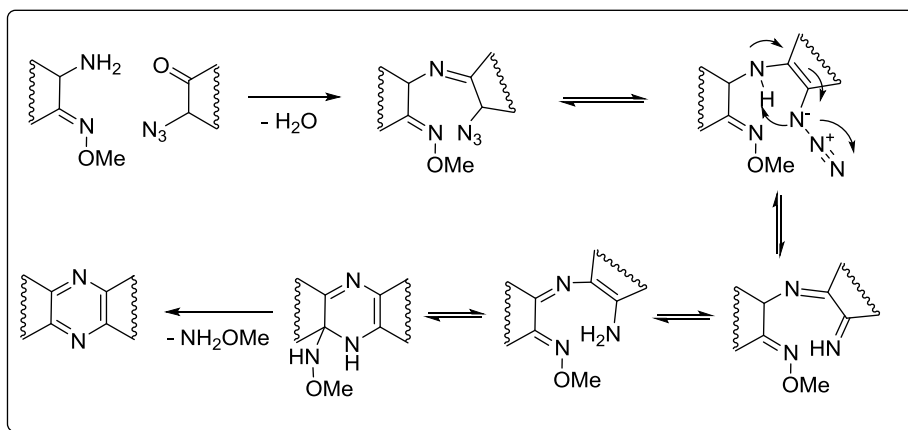
⁴³ Adams, A.; Kimpe, N. D. *Food Chem.* **2009**, 115 (4), 1417.

⁴⁴ Doležal, M.; Krá, K. **2011**. *Synthesis and Evaluation of Pyrazine Derivatives with Herbicidal Activity, Herbicides, Theory and Applications*, Prof. Marcelo Larramendy (Ed.), ISBN: 978-953-307-975-2, InTech

⁴⁵ Bohman, B.; Jeffares, L.; Flematti, G.; Byrne, L. T.; Skelton, B. W.; Phillips, R. D.; Dixon, K. W.; Peakall, R.; Barrow, R. a. *J. Nat. Prod.* **2012**, 75 (9), 1589.

⁴⁶ Badrinarayanan, S.; Sperry, J. *Org. Biomol. Chem.* **2012**, 10 (10), 2126.

and condensation of 1,2-diketones with primary 1,2-diamines.²⁰ The first one is limited to symmetrically substituted pyrazines and sometimes instability of α -amino aldehydes intermediates to certain conditions limits the scope of the reaction. The latter shares the same main limitation as quinoxaline-synthesis procedures, *i.e.* the access to 1,2-diketones. However, there are a few methods that describe the synthesis of unsymmetrical pyrazines avoiding the use of 1,2-diketones, *e.g.* the work presented by Guo and coworkers.⁴⁷ In this work the total synthesis of cephalostatin 1 was described. Cephalostatin 1 is a member of a family of thirty trisdecacyclic pyrazines isolated from the marine tube worm *Cephalodiscus gilchristi*, which inhibits cell growth and induces apoptosis.⁴⁸ In this approach, a coupling between an α -amino methoxime and an α -azido ketone was performed. A mechanistic pathway was also proposed (Scheme 17) in which, assuming initial formation of intermediate imine, prototropic equilibration would provide enamine which is exquisitely suited for fragmentation to bis-imine. The experimental details that evoked the elucidation of the proposed mechanism were the formation of N_2 gas and that the medium became basic through the production of methoxyamine.

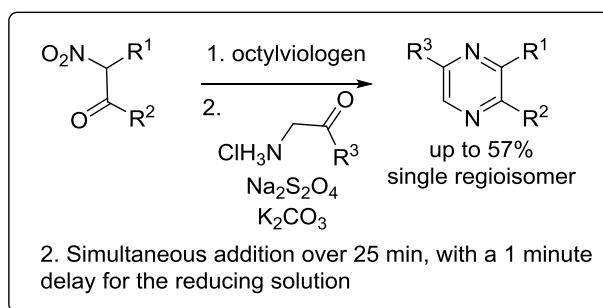


Scheme 17. Synthesis of pyrazines described by Guo *et al.*

⁴⁷ Guo, C.; Bhandaru, S.; Fuchs, P. L. *J. Am. Chem. Soc.* **1996**, *118* (43), 10672.

⁴⁸ Pettit, G. R.; Inoue, M.; Kamano, Y.; Herald, D. L.; Arm, C.; Dufresne, C.; Christie, N. D.; Schmidt, J. M.; Doubek, D. L.; Krupa, T. S. *J. Am. Chem. Soc.* **1988**, *110* (6), 2006.

Another reported synthetic strategy to obtain substituted pyrazines with regiocontrol is based on reacting α -nitro ketone with α -amino ketone protected as the hydrochloride salt under reducing conditions, where octylviologen is used as the reducing agent.⁴⁹ The use of classic reducing agents to reduce the nitro group of the nitro ketone such as zinc, tin, or iron in the presence of an acid gave a mixture of regioisomers, and in some cases, the reaction stopped at an intermediate stage, yielding hydrazines. Reaction conditions were optimized in order to afford the regiomerically pure pyrazines and avoid undesired regioisomers. Addition of the α -amino ketone along with a hydrogen sulfite solution to the α -nitro ketone and octylviologen solution using a syringe pump ensures that only one regioisomer is formed. Simultaneous addition over 25 min afforded a much cleaner product. However, it was also revealed that addition of the amino ketone must begin and end 1 min before the hydrogen sulfite/potassium carbonate mixture in order to obtain a pure product. Delaying addition of the amino ketone by 1 min ensures that the amino ketone is always in excess, thus preventing reduction and self-condensation of the nitroketone, which would result in a mixture of alkylpyrazines. The use of the syringe pump, which allows for the simultaneous addition of precise quantities of both the α -amino ketone and the hydrogen sulfite solutions over precisely controlled times, was found to be crucial to this method (Scheme 18).



Scheme 18. Synthesis of pyrazines from 1,2-nitroketones

⁴⁹ Elmaaty, T. A.; Castle, L. W. *Org. Lett.* **2005**, 7 (24), 5529.

3. Asymmetric Epoxidation of Electron-Deficient Olefins

Epoxides are extremely versatile synthetic compounds⁵⁰ and are also present in a large array of natural products and biologically active molecules (Figure 3).⁵¹ Epoxidation of olefins constitutes one of the most convenient systems to synthesize the oxirane ring; hence the asymmetric epoxidation represents an important tool for the synthetic chemist to afford those chiral epoxides. The development by Sharpless in the early 1980s of a system which can efficiently and predictably produce either enantiomer of an epoxide from an allylic alcohol using substoichiometric quantities of titanium and tartrate became a reference for today's catalytic asymmetric synthesis. There are many reviews that illustrate the wide variety of epoxidation methodologies of olefins.⁵² According to the purpose of this PhD Thesis, representative and relevant examples for the organocatalytic asymmetric epoxidation of electron-deficient olefins will be presented.

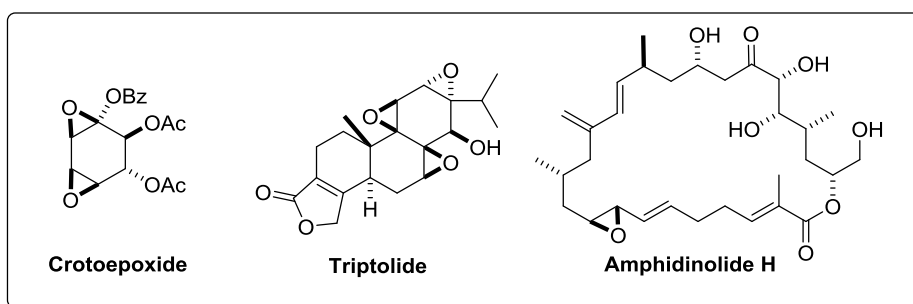


Figure 3. Epoxide moiety in natural bioactive compounds.

3.1. Peptide Catalysis

In recent decades, peptides have become attractive catalysts for asymmetric transformations. In early 80s, Julià and coworkers (and

⁵⁰ a) Schneider, C. *Synthesis* **2006**, 3919

⁵¹ Miyashita, K.; Imanishi, T. *Chem. Rev.* **2005**, *105* (12), 4515.

⁵² (a) Porter, M. J.; Skidmore, J. *Chem. Commun.* **2000**, 1215. (b) Davis, R. L.; Stiller, J.; Naicker, T.; Jiang, H.; Jørgensen, K. A. *Angew. Chemie Int. Ed.* **2014**, *53* (29), 7406. (c) Zhu, Y.; Wang, Q.; Cornwall, R. G.; Shi, Y. *Chem. Rev.* **2014**, *114*, 8199.

later in collaboration with Colonna) reported a polypeptide-catalyzed asymmetric epoxidation of (*E*)-chalcone with H₂O₂ – NaOH in toluene – water.⁵³ The reaction system was triphasic due to the insolubility of the polypeptide catalyst in toluene and water. Chalcone epoxide was obtained in 85% yield and 93% ee with poly-L-alanine at room temperature for 24 h. In their collaborative research, Julià and Colonna concluded that an increase of the poly-L-alanine chain from *n* = 5 to 30 resulted in an increase of enantioselectivity from 11% to 96%, respectively. Effect of solvent, polypeptide nature, and scope of the substrate were also studied. Attempts to achieve the corresponding epoxide from trans- β -methyl- β -nitrostyrene using this methodology failed since the desired compound was obtained with only 50% yield and 7% ee.

3.2. Bifunctional Base-Catalyzed Epoxidation

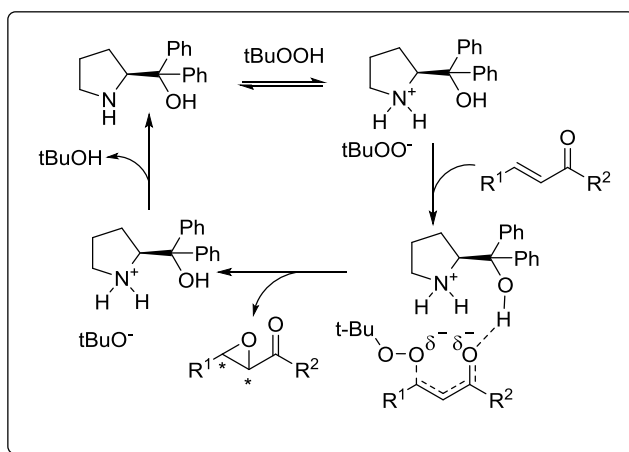
Many chiral bifunctional bases have been developed for the asymmetric epoxidation of electron-deficient olefins. The general behavior of that class of catalyst includes in the same entity a basic amine to deprotonate the corresponding hydroperoxide and a moiety that binds non-covalently the substrate. A common example of those catalysts is the chiral β -amino alcohols.⁵⁴ In 2005, Lattanzi reported that readily available α,α -diphenyl-L-prolinol could act as the catalyst for epoxidation of enones with TBHP, giving up to 80% ee for chalcones.⁵⁵ In this reaction, TBHP was deprotonated by the amine of the catalyst to form a tight ion pair. The hydroxyl group of the catalyst was thought to coordinate with the enone via hydrogen bonding to activate the double bond and direct addition of the peroxide anion stereoselectively (Scheme 19). Many other amino alcohols different from

⁵³ Julià, S.; Guixer, J.; Masana, J.; Rocas, J.; Colonna, S.; Annuziata, R.; Molinari, H. *J. Chem. Soc. Perkin Trans. I* **1982**, 1317.

⁵⁴ Meninno, S.; Lattanzi, A. *Chem. Commun.* **2013**, 49 (37), 3821.

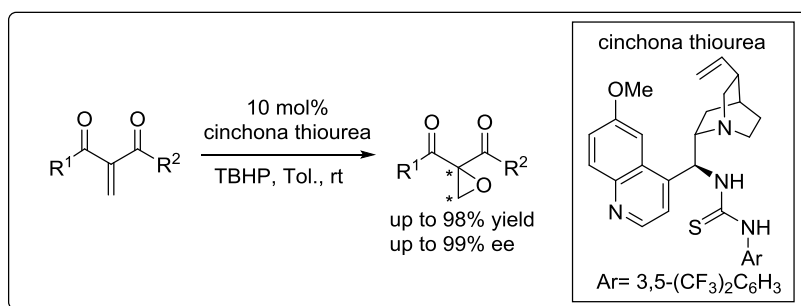
⁵⁵ Lattanzi, A. *Org. Lett.* **2005**, 7 (13), 2579.

diphenylprolinol were tested for the epoxidation of various electron-deficient olefins aside from chalcones.^{56,57}



Scheme 19. Catalytic asymmetric epoxidation of enones with diphenyl prolinol.

Cinchona alkaloids and their derivatives have also been investigated for asymmetric epoxidation. Lattanzi and co-workers also reported that 1,1-dicarbonyl terminal olefins were enantioselectively epoxidized with cinchona thiourea catalyst and TBHP to give terminal epoxides with ee up to 99% (Scheme 20).⁵⁸ Analogously to the aforementioned amino alcohols, the amino group from the quinuclidine moiety deprotonates TBHP and the thiourea activates the enone via H-bonding.



Scheme 20. Asymmetric epoxidation of terminal olefins with cinchona-derived thiourea catalyst.

⁵⁶ Zheng, C. W.; Li, Y. W.; Yang, Y. Q.; Wang, H. F.; Cui, H. F.; Zhang, J. K.; Zhao, G. *Adv. Synth. Catal.* **2009**, *351* (10), 1685.

⁵⁷ Russo, A.; Lattanzi, A. *Org. Biomol. Chem.* **2010**, *8* (11), 2633.

⁵⁸ Russo, A.; Galdi, G.; Croce, G.; Lattanzi, A. *Chem. - A Eur. J.* **2012**, *18* (20), 6152.

3.3. Pyrrolidine-Based Catalysis

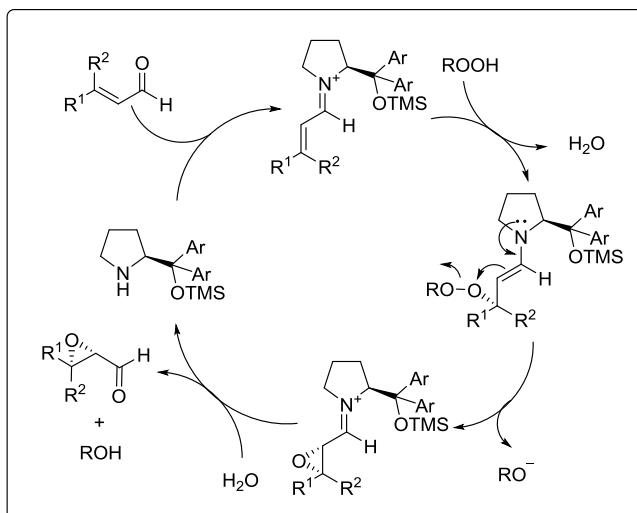
One of the most versatile families of catalysts for the enantioselective epoxidation of olefins, as well in other reactions like Michael addition, is the diaryl prolinol derivatives family. These catalysts were developed independently in 2005 by Hayashi's⁵⁹ and Jørgensen's⁶⁰ groups. Concerning the application for the asymmetric synthesis of epoxides, α,β -unsaturated aldehydes were epoxidized in high chemical yields, high dr values ($\geq 90:10$) and high ee's (up to 98%) using benign conditions such as EtOH:H₂O (3:1) solvent mixture and H₂O₂ as an oxidant.⁶¹ The proposed mechanism firstly involves a reaction between the chiral amine catalyst and the α,β -unsaturated aldehyde to generate an iminium salt intermediate to which H₂O₂ nucleophilically adds at the β -carbon to form an enamine intermediate. Upon ring closure and subsequent hydrolysis of the epoxy iminium ion, the chiral epoxide is formed with regeneration of the amine catalyst (Scheme 21). In a subsequent computational study,⁶² Santos and co-workers indicated that besides being an oxidant, H₂O₂ could act also as a cocatalyst to promote initial formation of the iminium ion intermediate, and a hydroxyl ion was likely involved in the epoxidation.

⁵⁹ Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chemie - Int. Ed.* **2005**, *44* (27), 4212.

⁶⁰ Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chemie - Int. Ed.* **2005**, *44* (5), 794.

⁶¹ Zhuang, W.; Marigo, M.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 3883.

⁶² Duarte, F. J. S.; Santos, A. G. *Org. Biomol. Chem.* **2013**, *11* (41), 7179.



Scheme 21. Enamine catalytic asymmetric epoxidation of enals.

Chiral pyrrolidine derivatives have also been developed for enantioselective epoxidation of olefins. For example, a series of β -fluorinated pyrrolidines was investigated for epoxidation of enals by Gilmour and co-workers. Among them, (*S*)-2-(fluorodiphenylmethyl)-pyrrolidine (Figure 4) was found to be a highly effective catalyst, giving epoxides with up to 98% ee.⁶³ The higher ee obtained using the aforesaid catalyst, as compared to non-fluorinated version of the catalyst (Figure 4), could be attributed to the fluorine–iminium ion gauche effect, which allowed the iminium ion to adopt a conformation more favorable for asymmetric induction.

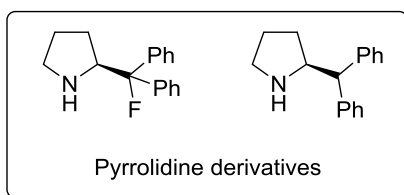


Figure 4. Pyrrolidine derivatives.

Asymmetric epoxidation of enals with diarylprolinol silyl ether catalysts has been applied to the synthesis of a number of building

⁶³ Sparr, C.; Schweizer, W. B.; Senn, H. M.; Gilmour, R. *Angew. Chemie - Int. Ed.* **2009**, *48* (17), 3065.

blocks, natural products, and bioactive molecules. For example, hirsutellone B, (–)-aspinolide A and jaspines A and B were synthesized using chiral epoxide intermediates obtained via enamine/iminium catalysis.⁶⁴

3.4. Chiral Amine Salt Catalysis

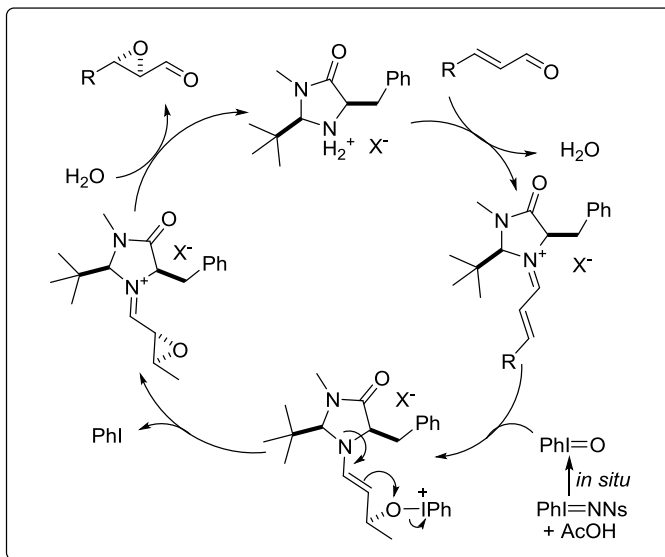
Various chiral amine salt catalysts were investigated for epoxidation of α,β -unsaturated aldehydes and ketones. In 2006, MacMillan and co-workers reported that a variety of enals were effectively epoxidized with a chiral imidazolidinone salt catalyst in the presence of iminoiodinane $\text{PhI}=\text{NNs}$ and AcOH , giving the corresponding epoxides in 72–95% yield and 85–97% ee.⁶⁵ The epoxidation was proposed to proceed via an iminium/enamine pathway such as proline/pyrrolidine derived catalysts. Studies showed that $\text{PhI}=\text{O}$ was slowly released *in situ* from $\text{PhI}=\text{NNs}$ under mild acidic conditions and acted as the real oxidant.⁶⁵ In that case, the enantioselectivity was controlled by the ammonium chiral structure, but other authors have reported catalysts being a chiral counteranion the responsible for the enantiocontrol⁶⁶ or a catalyst with both chiral structures ammonium and counteranion increasing the ee (Scheme 22).⁶⁷

⁶⁴ (a) Nicolaou, K. C.; Sarlah, D.; Robert Wu, T.; Zhan, W. *Angew. Chemie - Int. Ed.* **2009**, *48* (37), 6870. (b) Shelke, A. M.; Rawat, V.; Suryavanshi, G.; Sudalai, A. *Tetrahedron Asymmetry* **2012**, *23* (22-23), 1534. (c) Urano, H.; Enomoto, M.; Kuwahara, S. *Biosci. Biotechnol. Biochem.* **2010**, *74* (1), 152.

⁶⁵ Lee, S.; MacMillan, D. W. C. *Tetrahedron* **2006**, *62* (49), 11413.

⁶⁶ Wang, X.; List, B. *Angew. Chemie - Int. Ed.* **2008**, *47* (6), 1119.

⁶⁷ Lifchits, O.; Reisinger, C. M.; List, B. *J. Am. Chem. Soc.* **2010**, *132* (30), 10227.

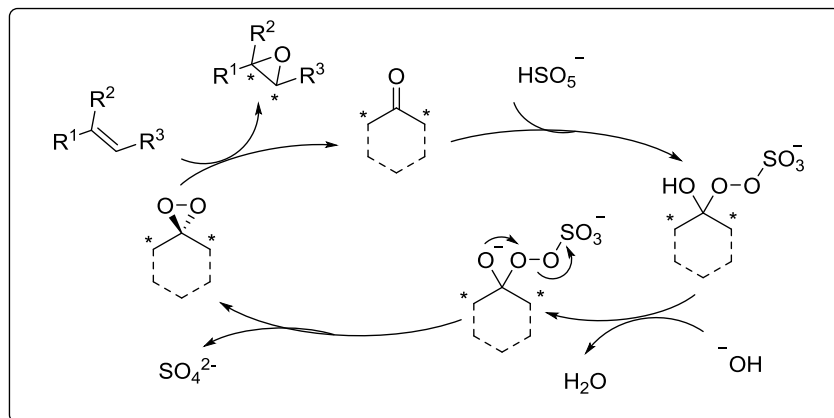


Scheme 22. Imidazolinone salt catalysis.

3.5. Chiral Ketone-Catalyzed Epoxidation

Dioxiranes are highly effective species for epoxidation of olefins. A chiral dioxirane can be generated *in situ* from a chiral ketone and an oxidant such as oxone ($2\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$) or H_2O_2 and resulting dioxirane is converted back to the ketone upon epoxidation of an olefin to complete a catalytic cycle (Scheme 23). Significant progress has been made for the ketone-catalyzed asymmetric epoxidation. A variety of structurally diverse ketone catalysts have been investigated and reported by a number of laboratories. A wide range of olefins, particularly unfunctionalized *trans*-olefins and trisubstituted olefins, have been effectively epoxidized with high enantioselectivity.⁶⁸

⁶⁸ (a) Adam, W.; Saha-Möller, C. R.; Ganeshpure, P. A. *Chem. Rev.* **2001**, *101* (11), 3499. (b) Wong, O. A.; Shi, Y. *Chem. Rev.* **2008**, *108* (9), 3958.



Scheme 23. Asymmetric epoxidation promoted by optically active dioxiranes.

Among all methodologies involving the *in situ* formation of a chiral dioxirane catalyst, Shi's epoxidation is probably the most known.⁶⁹ His group reported the discovery of fructose-derived ketone, which displayed good reactivity and high selectivity to a wide range of olefins, including aromatic and aliphatic *trans*-olefins and trisubstituted olefins,⁷⁰ silyl enol ethers and enol esters,⁷¹ and many others.

3.6. Phase Transfer Catalysis

In 1971, Starks introduced the term “phase-transfer catalysis” to explain the critical role of tetraalkylammonium or phosphonium salts in the reactions between two substances located in different immiscible phases.⁷² For example, the displacement reaction of 1-chlorooctane with aqueous sodium cyanide is accelerated many thousandfold by the addition of hexadecyltributylphosphonium bromide as a phase-transfer catalyst. Key to this tremendous enhancement in reactivity is the generation of quaternary phosphonium cyanide, which makes the cyanide anion soluble in organic solvents and sufficiently nucleophilic (Scheme 24). The high rate of displacement is mainly due to two of the

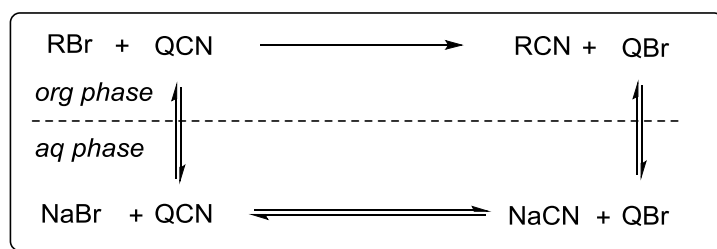
⁶⁹ Tu, Y.; Wang, Z.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118* (40), 9806.

⁷⁰ Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119* (46), 11224.

⁷¹ Adam, W.; Fell, R. T.; Saha-möller, C. R.; Zhao, C. *Tetrahedron: Asymmetry* **1998**, *9*, 397.

⁷² Starks, C. M. *J. Am. Chem. Soc.* **1971**, *93* (1), 195.

three characteristic features of the pairing cation (Q^+): high lipophilicity and the large ionic radius.



Scheme 24. General scheme for phase transfer catalysis

The use of PTC in asymmetric synthesis has been reported in wide variety of organic reactions, such as alkylations, fluorinations, Darzens, reduction and epoxidation, among others.⁷³ Representative examples of chiral epoxidation of electron-deficient olefins (mostly enones), with catalysts such as quaternary ammonium salts and crown ethers in the presence of oxidants, will be next presented in this Thesis introduction.

3.6.1. Cinchona Alkaloid-Derived Quaternary Ammonium Salts

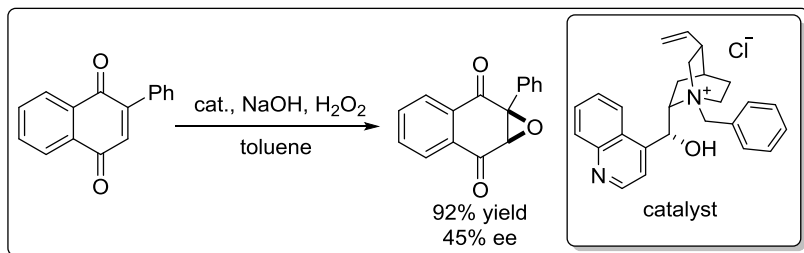
One of the first asymmetric epoxidation attempts was reported in 1976 by Wynberg and co-workers⁷⁴ utilizing *N*-benzyl quininium chloride salt to catalyze the epoxidation of α,β -unsaturated ketones with up to 45% ee (Scheme 25). *N*-benzylated salts from cinchona tree alkaloids (cinchonine, cinchonidine, quinine and quinidine) have been prepared and widely reported as catalysts for the synthesis of epoxide-containing natural products such as (+)-manumycin A⁷⁵ or palmarumycin C₂.⁷⁶

⁷³ For leading reviews, see: (a) Ooi, T.; Maruoka, K. *Angew. Chemie - Int. Ed.* **2007**, *46* (23), 4222. (b) Dalko, P. I.; Moisan, L. *Angew. Chemie - Int. Ed.* **2001**, *40*, 3726.

⁷⁴ Helder, R.; Hummelen, J. C.; Wiering, J. S.; Wynberg, H. *Tetrahedron Lett.* **1976**, *17* (21), 1831.

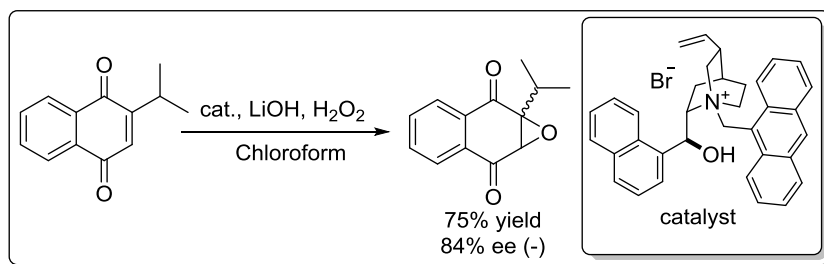
⁷⁵ Alcaraz, L.; Macdonald, G.; Ragot, J. P.; Lewis, N.; Taylor, R. J. K. *J. Org. Chem.* **1998**, *63* (11), 3526.

⁷⁶ Barrett, A. G. M.; Blaney, F.; Campbell, A. D.; Hamprecht, D.; Meyer, T.; White, A. J. P.; Witty, D.; Williams, D. J. *J. Org. Chem.* **2002**, *67* (9), 2735.



Scheme 25. Asymmetric epoxidation of 2-phenyl-naphthoquinone using a cinchonidinium salt.

The catalytic effect of various nitrogen substituents on cinchona alkaloids has been investigated by many research groups. In 1998, Arai and co-workers reported that the substituents on the phenyl ring of the *N*-benzyl unit in the cinchona alkaloid-derived catalysts played an important role in the asymmetric induction. Up to 92% ee was obtained for epoxidation of chalcones using catalyst *N*-*p*-iodobenzyl cinchoninium bromide.⁷⁷ However, only 2% ee was obtained when the secondary alcohol of the catalyst was protected as allyl ether. In 2002, Dehmlow and co-workers reported their studies on analogues of cinchona alkaloids without the quinoline nitrogen atom as phase-transfer catalysts. Up to 84% ee was obtained for epoxidation of 2-isopropyl-1,4-naphthoquinone with the modified *epi*-cinchonidine catalyst (Scheme 26).⁷⁸



Scheme 26. Asymmetric epoxidation catalyzed by a cinchonidinium analogue.

In 1999, Corey and co-workers demonstrated remarkably high enantioselectivity (91–98.5% ee) for epoxidation of enones with

⁷⁷ Arai, S.; Tsuge, H.; Shioiri, T.; City, N. *Tetrahedron Lett.* **1998**, *39*, 7563.

⁷⁸ Dehmlow, E. V.; Düttmann, S.; Neumann, B.; Stammeler, H.-G. *European J. Org. Chem.* **2002**, *83*, 2087.

catalyst *O*-benzyl-*N*-anthracenyl dihydrocinchonidinium bromide using KOCl as an oxidant.⁷⁹ He proposed that the epoxidation proceeds via three-component transition state (Figure 5) with 4'-fluoro chalcone as substrate example. In this transition state, bromide ion is displaced by hypochlorite anion, which forms an ion pair with the cinchonidinium cation. The α,β -enone in the complex is situated so that the 4-fluorophenyl group is wedged between the ethyl and quinoline substituents on the quinuclidine ring and simultaneously the carbonyl oxygen is placed as close to N^+ as permitted by Van der Waals forces. In this arrangement the nucleophilic oxygen of hypochlorite is proximate to the β -carbon of the α,β -enone, *i.e.*, correctly positioned for nucleophilic epoxidation by conjugate addition. In fact, as the nucleophilic attack occurs, the negative charge which is developed at the carbonyl oxygen in the transition state is electrostatically stabilized by the proximate N^+ of the catalyst. Another feature of this geometry is that it allows a smooth transition of the resulting conjugate adduct to the α,β -epoxy ketone and chloride with the latter contact ion paired to cation. Other authors have reported that a π - π -stacking between the aryl group of the quaternary nitrogen substituent and an aryl group of the substrate could be involved during the molecular approach in the transition state.⁸⁰

⁷⁹ Corey, E. J.; Zhang, F. Y. *Org. Lett.* **1999**, *1* (8), 1287.

⁸⁰ Wu, S.; Pan, D.; Cao, C.; Wang, Q.; Chen, F. X. *Adv. Synth. Catal.* **2013**, *355* (10), 1917.

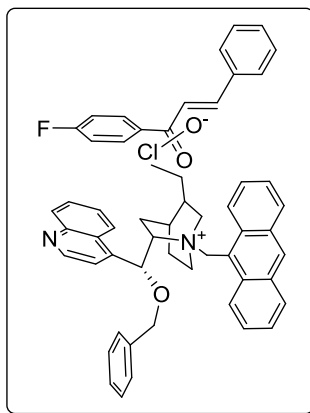


Figure 5. Proposed transition state by E. J. Corey.

3.6.2. Other Quaternary Ammonium Salts

Other quaternary ammonium salt catalysts have been investigated for asymmetric epoxidation of olefins (Figure 6). In 2004, Maruoka and co-workers showed that binaphthyl-based spiro quaternary ammonium salts, containing two diaryl methanol groups, were highly effective catalysts for epoxidation of enones.⁸¹ A variety of α,β -epoxy ketones were obtained in 80–99% yield and 89–99% ee using such catalysts with NaOCl as oxidant. The hydroxyl groups of the catalyst appeared to be important for the reactivity and enantioselectivity of the epoxidation. In 1994, Masaki and co-workers reported their studies on the epoxidation of (E)-chalcones with pyrrolidinium salts as catalysts.⁸² However, enantioselectivity was low for all the tested substrates (up to 6.7% ee).

⁸¹ Ooi, T.; Ohara, D.; Tamura, M.; Maruoka, K. *J. Am. Chem. Soc.* **2004**, *126* (22), 6844.

⁸² Shi, M.; Kazuta, K.; Satoh, Y.; Masaki, Y. *Chem. Pharm. Bull.* **1994**, *42* (12), 2625.

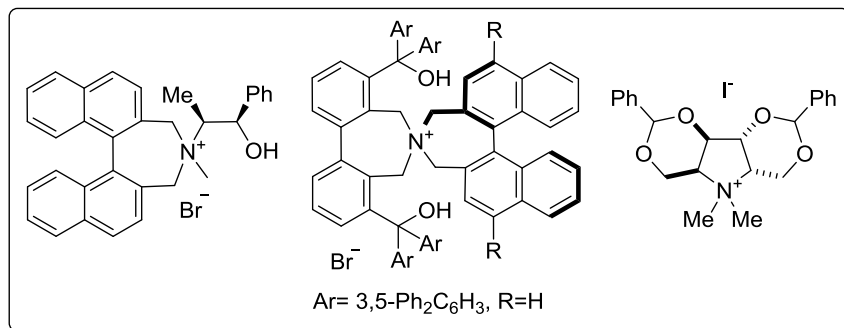


Figure 6. Ammonium phase transfer catalysts non-based on cinchona derivatives.

3.6.3. Crown Ether-Type Catalysts.

Crown ether-type phase-transfer catalysts with attached chiral moieties have also been examined for olefin epoxidation. Bakó and co-workers reported monosaccharide-based crown ether-type catalysts (Figure 7) for the epoxidation of chalcones, affording up to >99% ee with TBHP as oxidant.⁸³ The obtained results suggested that the nature of the monosaccharide unit of the catalyst is decisive with respect to the configuration of the epoxyketone. Thus, glucose-based catalyst promoted mostly the formation of the enantiomer with the negative specific rotation, while the mannose-based gave mostly the positive enantiomer.

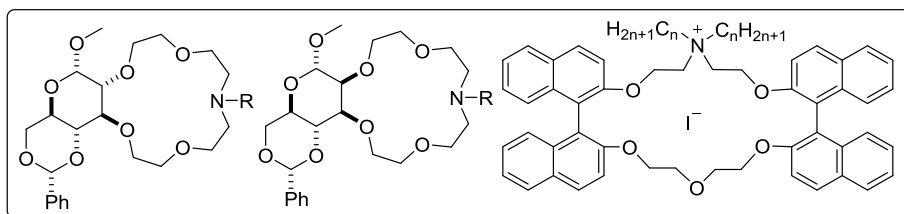


Figure 7. Crown ether-type catalysts

⁸³ Makó, A.; Rapi, Z.; Keglevich, G.; Szöllösy, Á.; Drahos, L.; Hegeds, L.; Bakó, P. *Tetrahedron Asymmetry* **2010**, *21* (8), 919.

Chapter 2

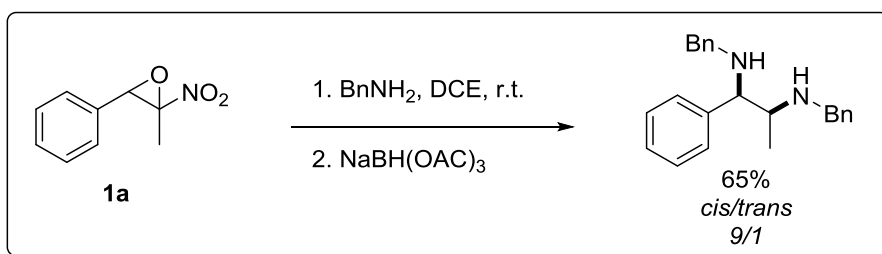
Nitroepoxides as Precursors of 1,4-Diaminoheterocycles

1. Objectives

- Exploit the 1,2-electrophilic reactivity of the nitroepoxides as building blocks for organic chemistry
- Development of a new general synthetic methodology for the synthesis of different 1,4-heterocyclic diamino compounds, improving those previously reported in the literature.

2. Results and Discussion

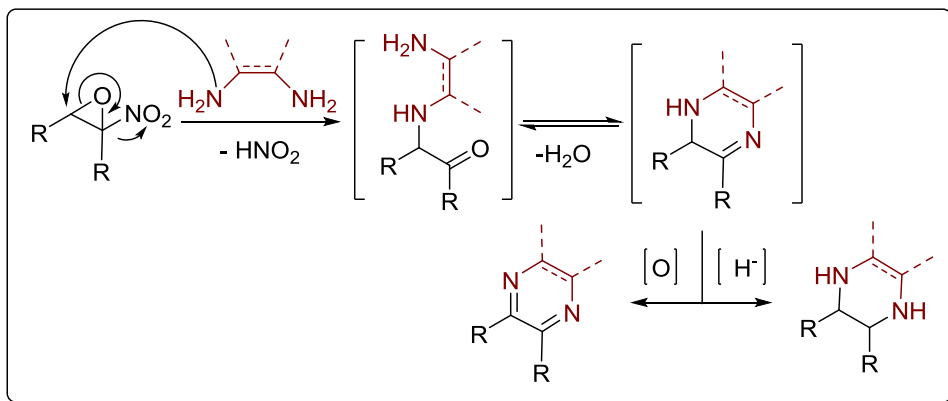
Previously to this Thesis research, our group reported the conversion of nitroepoxides into 1,2-diamines in a two-step sequence procedure involving nucleophilic attack followed by reductive amination.⁸⁴ The model reaction consisted in the reaction between the nitroepoxide **1a** and a stoichiometric excess of benzylamine in 1,2-dichloroethane (DCE), followed by the addition of sodium triacetoxyborohydride as a reductive agent in one-pot process to achieve the corresponding 1,2-diamine in excellent diastereomeric ratio (Scheme 27).



Scheme 27. Synthesis of 1,2-diamines from nitroepoxides.

The reaction described above proceeds via an amino-ketone intermediate, followed by a second step with an extra equivalent of benzylamine to form the corresponding amino-imine before reduction. Following this mechanistic hypothesis, we envisioned the ring-opening of the nitroepoxide using diamines in order to synthesize heterocyclic amino-imine intermediates, which using proper conditions, can be either oxidized or reduced to obtain unsaturated or saturated compounds, respectively (Scheme 28).

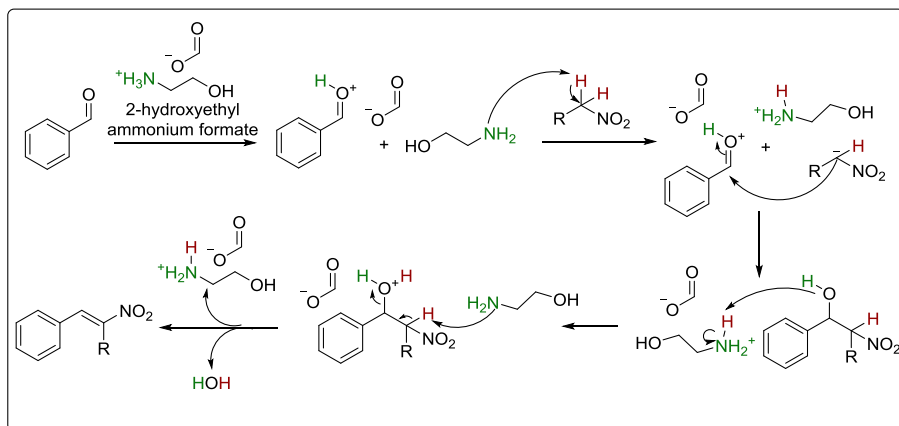
⁸⁴ Agut, J.; Vidal, A.; Rodríguez, S.; González, F. V. *J. Org. Chem.* **2013**, 78 (11), 5717.



Scheme 28. Pathway to the synthesis of 1,4-diamino heterocycles from nitroepoxides.

The idea was to prepare 1,4-diamino heterocycles by using a variety of 1,2-diamines and starting from nitroepoxides displaying a range of substituents. Nitroepoxides would be prepared by epoxidation of the corresponding nitroalkenes. Nitroalkenes that were not commercially available would be synthesized from the corresponding aldehyde and nitroalkane according to two different methodologies. One of them involved a classical basic catalyzed Henry reaction, followed by dehydration of the obtained nitroaldol by mesylation of the hydroxyl group. Other method and most preferred one due to its operation easiness, was the reaction between the aldehyde and the nitroalkane in 2-hydroxyethyl ammonium formate (2-HEAF).⁸⁵ This ionic liquid can perform both acid and basic catalysis for the addition and elimination steps (Scheme 29).

⁸⁵ Alizadeh, A.; Khodaei, M. M.; Eshghi, A. *J. Org. Chem.* **2010**, 75 (23), 8295.



Scheme 29. Mechanistic pathway for the synthesis of nitroalkenes using ionic liquid 2-HEAF.

Nitroepoxides were prepared from the corresponding nitroalkenes with hydrogen peroxide and NaOH in high chemical yield. Fully detailed experimental procedures are available in the experimental section of this chapter.

2.1. Quinoxalines

We began our studies of the preparation of quinoxalines by combining nitroepoxide **1a** with 1,2-diaminobenzene (1.5 equivalents) in 1,2-dichloroethane at room temperature (ca. 25°C) under nitrogen atmosphere. The excess of diamine was used to quench the nitrous acid since it can potentially react with amines to afford *N*-nitrosamines.⁸⁶ The initial goal was to isolate the amino-imine intermediate to process it separately in oxidant and reductive media. However, the ¹H NMR spectrum of the crude mixture of the reaction showed mainly the oxidized compound quinoxaline **2a**. Starting material **1a** and another compound, which seemed to be the aminoketone intermediate, were also observed (Figure 8).

⁸⁶ Ellison, G.; Williams, D. L. H. *J. Chem. Soc. Perkins Transactions 2* **1981**, No. 4, 699.

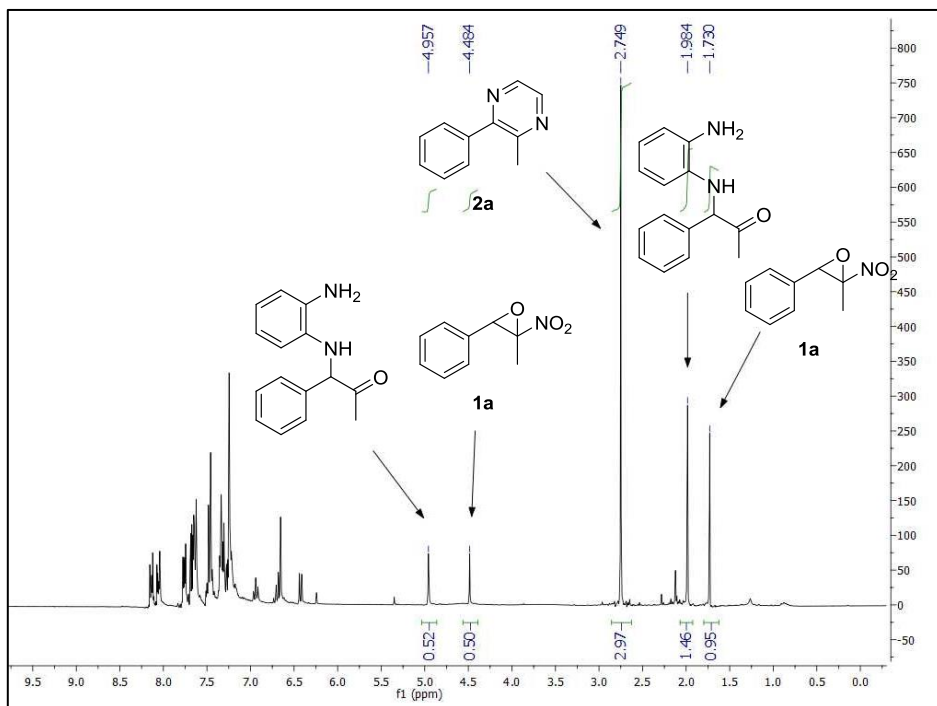
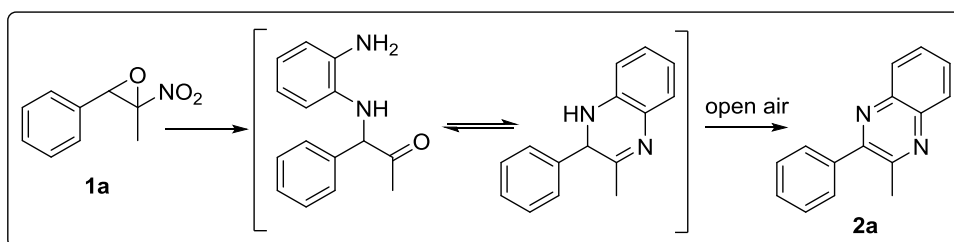


Figure 8. ¹H NMR spectrum of the crude mixture for the synthesis of quinoxaline **2a**.

The crude mixture was purified through silica gel liquid chromatography in order to isolate quinoxaline **2a** and the observed intermediate. For our surprise, the intermediate could not be isolated and the isolated amount of quinoxaline (72% yield) was greater than expected. This fact was rationalized as follows: the amino-ketone cyclizes into amino-imine which is easily oxidized by atmospheric oxygen into quinoxaline **2a** during the work-up of the reaction (Scheme 30).

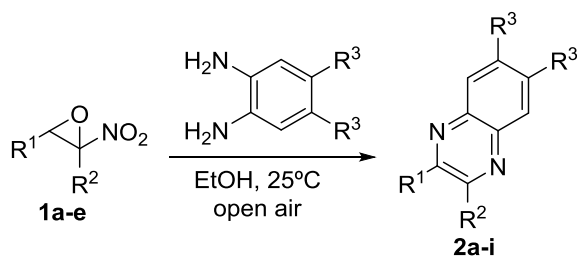


Scheme 30. Synthesis of quinoxaline **2a** through oxidation of amino-imine intermediate.

Few optimization experiments to achieve excellent yields were required. The change of solvent from DCE to ethanol increased the yield (86%, isolated yield) and also the rate of the reaction presumably, due to the solubility enhancement of *o*-phenylenediamine. The reaction was also performed in an open flask to favor the oxidative process. The mixture turned into an intense dark red when the quinoxaline was formed, which was used as an indicator of reaction completion. Finally, the purification step consisted on a filtration through a short pad of silica gel by using a mixture of hexanes/EtOAc (8:2) as eluent. With the optimal conditions in our hands, the scope of the reaction was studied using different epoxide substrates and phenylenediamines (Table 1).

As it can be observed, chemical yields were good in all cases and slightly higher for those compounds without substitution in the quinoxaline ring. For alkyl-alkyl disubstituted quinoxalines **2h** and **2i** yields were notably lower.

Table 1. Synthesis of Quinoxalines.^a

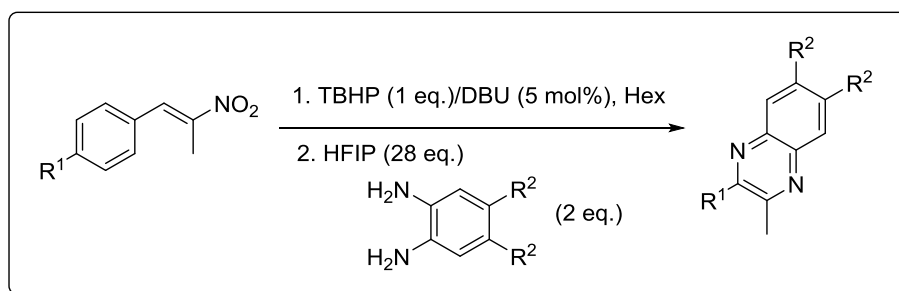


Entry	R ¹ , R ²	Epoxide	R ³	Quinoxaline	Yield (%) ^b
1 ^c	Ph, Me	1a	H	2a	72
2	Ph, Me	1a	H	2a	86
3	Ph, Me	1a	Cl	2b	82
4	<i>p</i> -F-Ph, Me	1b	H	2c	80
5	<i>p</i> -F-Ph, Me	1b	Cl	2d	75
6	<i>p</i> -Me-Ph, Me	1c	H	2e	78

7	<i>p</i> -Me-Ph, Me	1c	Cl	2f	70
8	<i>p</i> -F-Ph, Et	1d	H	2g	80
9	<i>n</i> -Pr, Me	1e	H	2h	63
10	<i>n</i> -Pr, Me	1e	Cl	2i	48

^aReactions were carried out using nitroepoxide (1.0 equiv) and 1,2- benzenediamine (1.5 equiv) at room temperature for 16 h. ^bYield of isolated product. ^cReaction was performed using 1,2-dichloroethane as a solvent.

Simultaneously to our work, Tsogoeva's research group had published a one-pot procedure to afford quinoxalines from nitroalkenes.⁸⁷ Their approach comprises the organocatalytic generation of α -nitroepoxides with the 1,8-diazabicycloundec-7-ene (DBU)/TBHP system and their subsequent treatment with 1,2-phenylenediamines (Scheme 31). The main disadvantage of their methodology is the use of hexane as a solvent for the epoxidation step, since *o*-phenylenediamine is quite insoluble in non-polar solvents; hence they are obliged to use polar "additives" for the second step of the reaction. Methanol resulted to be no good option since it is not miscible in hexane, so they end up using HFIP (28 equivalents), which is very expensive in comparison with our chosen solvent ethanol. Moreover, except for one case yielding 82%, yields were quite moderate (36-67%).

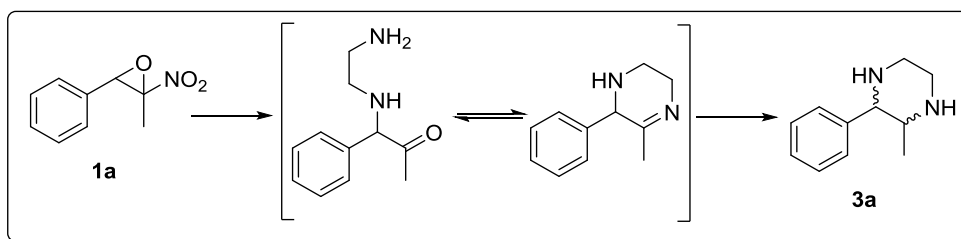


Scheme 31. Tsogoeva's approach for the synthesis of quinoxalines.

⁸⁷ Ibrahim, M. M.; Grau, D.; Hampel, F.; Tsogoeva, S. B. *European J. Org. Chem.* **2014**, 2014 (7), 1401.

2.2. Piperazines

Motivated by the results of quinoxalines, we decided to move forward to the synthesis of piperazines. Since aromatization of intermediate was not expected by simply atmospheric oxygen (two oxidative steps are required in this case compared to quinoxalines) the chosen strategy consisted in a one-pot ring-opening of the nitroepoxide with ethylenediamine, followed by reduction (Scheme 32). Initial conditions were identical to our previous work for the synthesis of 1,2-diamines from nitroepoxides: nitroepoxide was mixed with a stoichiometric excess of 1,2-ethylenediamine in DCE and stirred until the formation of the intermediate (*ca.* 6h), then $\text{NaBH}(\text{OAc})_3$ was added and the mixture stirred overnight. After non-extractive work-up, the crude piperazine **3a** was obtained. However, in this case the reaction did not proceed as smoothly as for the quinoxalines or the vicinal diamines, the NMR spectra of the crude mixture also showed many unidentified byproducts. In addition, the desired product could not be isolated by liquid chromatography purification in a first attempt.

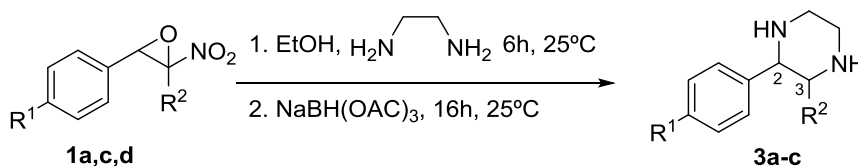


Scheme 32. Synthesis of piperazines through reduction of the amino-imine intermediate.

We guessed that the formation of byproducts might be a matter of concentration of the reaction media. So, the reaction was repeated at lower concentration and the NMR spectra showed in this case a much cleaner product. However, after liquid chromatography, piperazine **3a** was obtained in very low yield and some byproducts were isolated instead.

Chemical yield could be increased by using ethanol as a solvent of the reaction, and by adding triethylamine to the eluent mixture in the purification step. Piperazine **3a** was obtained in 44% yield as a mixture of *cis/trans* isomers and the scope of the reaction was analyzed (Table 2). In some cases, separation by LC was not good enough to separate piperazine from remaining ethylenediamine, but the purification could be accomplished by performing liquid-liquid extraction under aqueous phase pH control. Acidity was regulated by addition of 2M aqueous NaOH until a pH of 10. At this pH the piperazine was extracted with dichloromethane and the ethylenediamine remained in the aqueous phase.

Table 2. Synthesis of Piperazines.^a



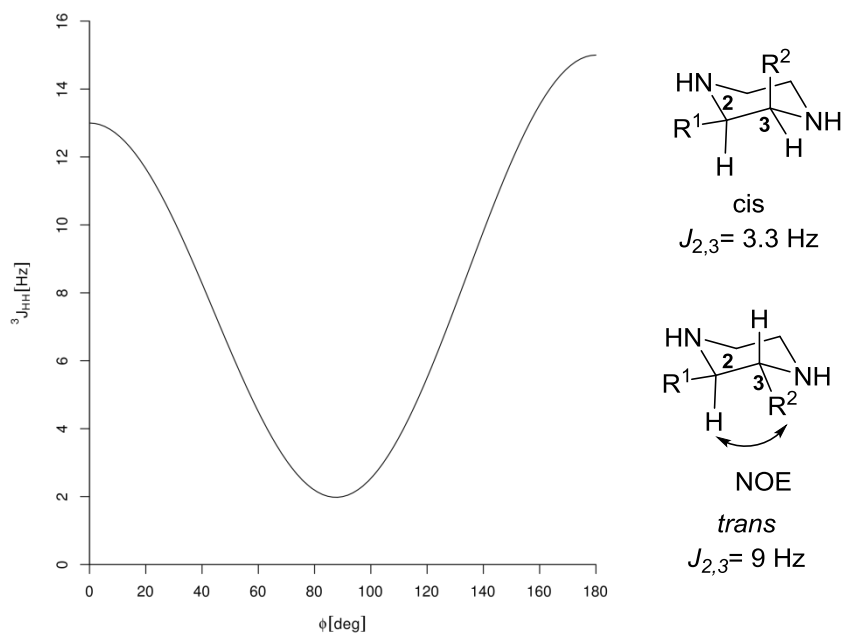
Entry	R ¹ ,R ²	Epoxide	Piperazine	Yield (%) ^b	d.r. (<i>cis/trans</i>)
1	H, Me	1a	3a	44%	2:1
2	Me, Me	1c	3b	64%	4:1
3	F, Et	1d	3c	58%	2.2:1

^aReactions were carried out using nitroepoxide (1.0 equiv) and 1,2-ethylenediamine (1.5 equiv) at room temperature for 6 h. Then, NaBH(OAc)₃ (3.0 equiv) was added and the mixture was stirred for 16 h. ^bYield of isolated product.

The stereochemistry of the piperazines **3a–c** was assigned by NMR coupling constants ($J_{2,3}$ for *trans* higher than for *cis*) and by NOE experiments. According to Karplus equation,⁸⁸ hydrogen atoms that form a dihedral angle close to 0° or 180° have a higher J -coupling

⁸⁸ a) Karplus, M. *J. Chem. Phys.* **1959**, *30* (1), 11. b) Gutowsky, H. S.; Karplus, M.; Grant, D. M. *J. Chem. Phys.* **1959**, *31* (5), 1278. c) Minch, M. J. *Concepts Magn. Reson.* **1994**, *6*, 41.

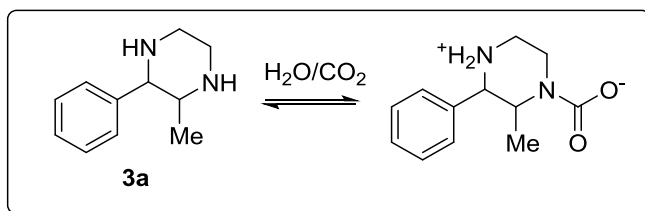
constant than those which are close to 90° angles (Scheme 33). In our case, supposing a chair conformation for the piperazine ring, *trans* conformation implies the hydrogen atoms on positions 2,3 are both in axial, forming a dihedral angle near to 180° and consequently, J value should be high ($J > 5$ Hz). For the *cis* conformation, one hydrogen atom is in axial position while the other is equatorial, which means their dihedral angle is near 90° ($J = 2-3$ Hz). Piperazine **3a** showed for the major isomer a coupling constant of 3.3 Hz and for the minor isomer a constant of 9 Hz, so *cis* conformation was assigned for the major isomer and *trans* for the minor. NOE experiment results were consistent with our analysis (Scheme 33). Piperazines **3b** and **3c** showed the same tendency and then stereochemistry was assigned by analogy.



Scheme 33. General Karplus equation for ethane conformers (left). Assignment of stereochemistry for piperazines (right).

An interesting observation was made when the piperazine compound was kept on the bench: the oily product turned into a solid which was not soluble in organic solvents but it was in water. Amazed by this fact, we reached for literature in order to look for a reasonable explanation,

and we found that aqueous piperazine can be employed in chemical engineering as a post-combustion CO₂ removal technology.⁸⁹ The rationalization is as follows: piperazine **3a** is a highly hygroscopic compound which reacts with atmospheric CO₂ to give the carbamate salt, in acid-basic equilibrium (Scheme 34). This is consistent with the fact that the aqueous solution of the salt gives slightly acidic pH and the oily piperazine **3a** can be recovered by liquid-liquid extraction with dichloromethane from basified aqueous media. This reactivity results interesting and further experiments are considered in order to exploit its ability as potential carbon dioxide captor.



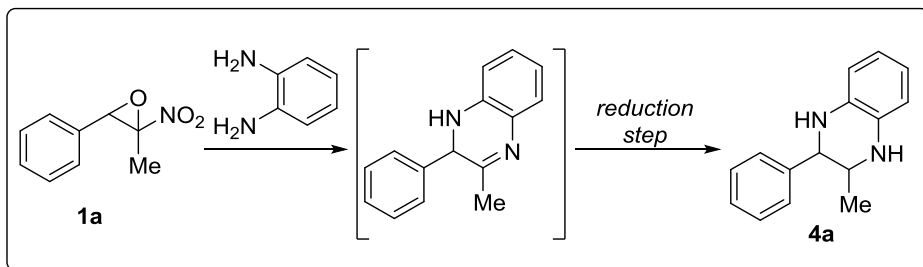
Scheme 34. Piperazine **3a** as carbon dioxide trap.

2.3. 1,2,3,4-Tetrahydroquinoxalines

As it has been pointed out in the introduction section, many compounds that possess the tetrahydroquinoxaline moiety have been studied in the medicinal chemistry field, but methods for the preparation of tetrahydroquinoxalines suffer from the same drawbacks as quinoxalines, since they are usually prepared through reduction of quinoxalines.⁹⁰ A one-pot synthesis of 1,2,3,4-tetrahydroquinoxaline **4a** starting from nitroepoxide **1a** was envisioned (Scheme 35).

⁸⁹ Rochelle, G.; Chen, E.; Freeman, S.; Van Wagener, D.; Xu, Q.; Voice, A. *Chem. Eng. J.* **2011**, *171* (3), 725.

⁹⁰ Figueras, J. *J. Org. Chem.* **1966**, *31*, 803.

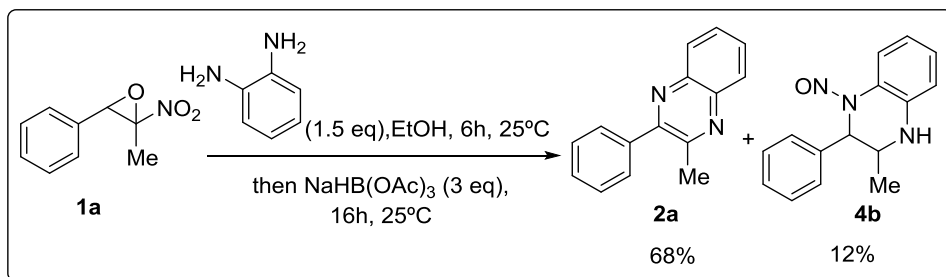


Scheme 35. Scheme for the synthesis of tetrahydroquinoxaline **4a**.

Since the amino-imine intermediate from the reaction between nitroepoxide **1a** and *o*-phenylenediamine aromatizes easily in the presence of atmospheric oxygen, we imagined that controlling this step would be the key to success in the synthesis of the saturated heterocycle **4a**, so the experiment was designed in order to keep inert atmosphere in every step. Firstly, a previously purged diamine solution in ethanol was added. After the consumption of nitroepoxide (ca. 3 hours), $\text{NaBH}(\text{OAc})_3$ was added through an addition funnel under N_2 atmosphere and stirred overnight. However, NMR spectra of the crude mixture showed mainly quinoxaline **2a**, which was obtained in a 68% yield after chromatography. Moreover, a new compound which seemed the desired compound **4a** was isolated in 15% of total weight, but MS analysis did not show the expected molecular peak. The NMR and MS spectra were examined intensively, and we supposed that the unidentified product could be the *N*-nitroso tetrahydroquinoxaline **4b** (Scheme 36). It had been described in the literature that similar compounds such as dihydroquinoxalinones⁹¹ can react with nitrite under acidic conditions to form the *N*-nitroso derivatives. When performing ESI-MS, the peak corresponding to the compound **4b** plus Na cation ($m/z = 276.2$) was also detected. IR spectra showed an intense sharp peak at 1433 cm^{-1} that match with the

⁹¹ MEDIVATION TECHNOLOGIES, INC.; Chakravarty, S.; Hart, B. P.; Jain, R. P. **Patent:** WO2011/103460 A1, 2011.

signal for N-NO bond.⁹² The reaction was repeated using the same conditions and being especially careful with keeping it away from atmospheric oxygen, but the results were not significantly different. The proposed structure for compound **4b** is tentative and more experiments are needed to properly elucidate the chemical structure.

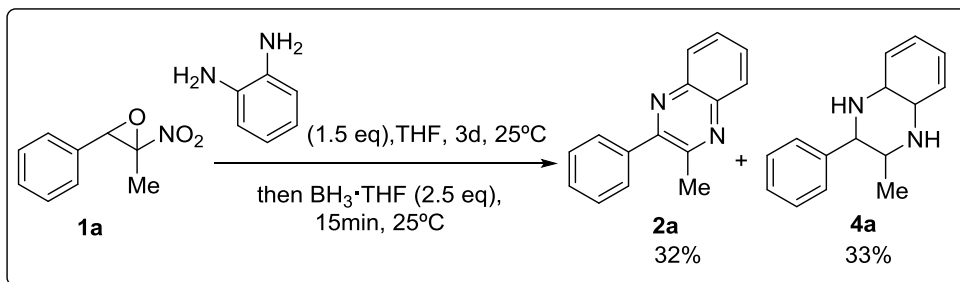


Scheme 36. First attempt for the synthesis of tetrahydroquinoxaline **4a** resulted into **2a** and **4b**.

At that point, the strategy for the reduction of the intermediate was changed. According to the work by Savrides *et al.*,⁹³ quinoxalines can be reduced to tetrahydroquinoxalines with borane-tetrahydrofuran complex solution, so we used this reductive agent so as to perform the reduction of the amino-imine intermediate. The reaction was performed as mentioned above but using tetrahydrofuran as solvent reaction instead of ethanol due to incompatibility with borane. Unfortunately and unexpectedly, the rate step of the ring-opening reaction decreased significantly and consequently, the consumption of the nitroepoxide took three days to be almost complete. Long reaction time allowed the formation of new byproducts as spotted by TLC. In spite of that, borane in THF solution was added and performed as described in the literature.⁹³ After purification by silica gel LC, tetrahydroquinoxaline **4a** was isolated in 33% yield (Scheme 37), along with quinoxaline **2a** (yield 32%) and other unidentified compounds.

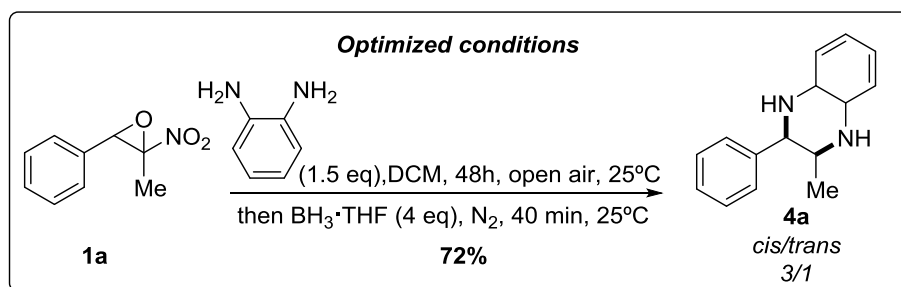
⁹² Pretsch, E.; Clerc, T.; Seibl, J.; Simon, W. *Tablas para la determinación estructural por métodos espectroscópicos*, 3rd ed.; Springer Verlag: Berlin, 1990 (Spanish edition)

⁹³ McKinney, A. M.; Jackson, K. R.; Salvatore, R. N.; Savrides, E.; Edattel, M. J.; Gavin, T. J. *Het. Chem* **2005**, *42*, 1031.



Scheme 37. One-pot process for the synthesis of **4a** in THF.

Finally, nitroepoxide **1a** was transformed into tetrahydroquinoxaline **4a** in higher yield by treatment with 1,2-benzenediamine in dichloromethane as a solvent for 48 h in the open air to allow the formation of the quinoxaline moiety and then, addition of borane–tetrahydrofuran complex (4 equivalents) (Scheme 38). Hence, tetrahydroquinoxaline **4a** was obtained from **1a** in 72% yield in one-pot process as a diastereomeric mixture (*cis/trans* 3:1). The stereochemistry of tetrahydroquinoxaline **4a** was assigned by NMR as mentioned above for piperazines **3a–c**.



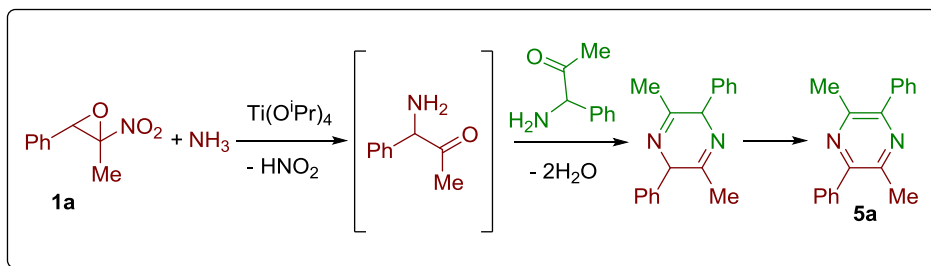
Scheme 38. Optimized conditions of the one-pot process for the synthesis of **4a**.

2.4. Piperazines

During our early work about reactions between nitroepoxides and amines,⁸⁴ we used ammonia to open the oxirane ring in mild conditions. Since reductive amination of ketones is described using titanium (IV) isopropoxide,⁹⁴ we treated nitroepoxide **1a** with a commercially available methanolic ammonia solution (7M in methanol) and $\text{Ti}(\text{iPrO})_4$,

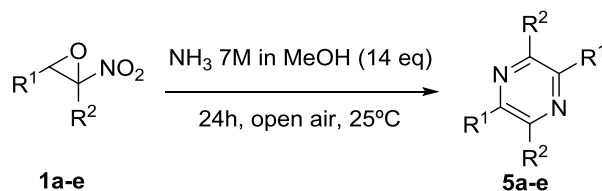
⁹⁴ Muñoz, L.; Rodríguez, A. M.; Rosell, G.; Bosch, M. P.; Guerrero, A. *Org. Biomol. Chem.* **2011**, *9* (23), 8171.

followed by a reductive agent and a non-extractive work-up. However, only the dimer product pyrazine **5a** was observed. Presumably the primary amine intermediate is more reactive than ammonia, and then it will react over another equivalent of aminoketone faster than ammonia, giving rise to a diimine intermediate which upon will furnish pyrazine (Scheme 39).



Scheme 39. Pathway of the reaction between epoxide **1a** and ammonia.

To optimize conditions for the synthesis of pyrazines, reaction was repeated without $\text{Ti}(\text{O}^i\text{Pr})_4$ and the result was similar when using Lewis acid. Purification step was also optimized. ^1H NMR spectrum of the crude mixture showed quite clean product but when purified by silica gel LC, yield decreased and some decomposition byproducts were also isolated. By simply changing a non-extractive work-up for a liquid-liquid extraction with diethyl ether and water, pyrazine **5a** was purely obtained as yellow needle-like crystals in 93% yield and no further purification was needed. The scope of the reaction was studied for diverse compounds (Table 3).

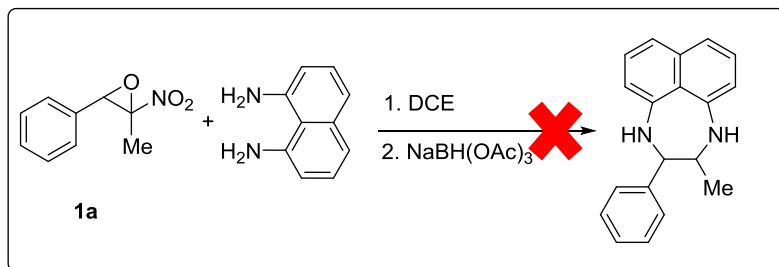
Table 3. Synthesis of Pyrazines.^a

Entry	R ¹ , R ²	Epoxide	Pyrazine	Yield (%) ^b
1	Ph, Me	1a	5a	93
2	<i>p</i> -F-Ph, Me	1b	5b	92
3	<i>p</i> -Me-Ph, Me	1c	5c	90
4	<i>p</i> -F-Ph, Et	1d	5d	96
5	<i>n</i> -Pr, Me	1e	5e	89

^aReactions were carried out using nitroepoxide (1.0 equiv) and a 7M methanolic ammonia solution (14 equiv) at room temperature for 24 h.

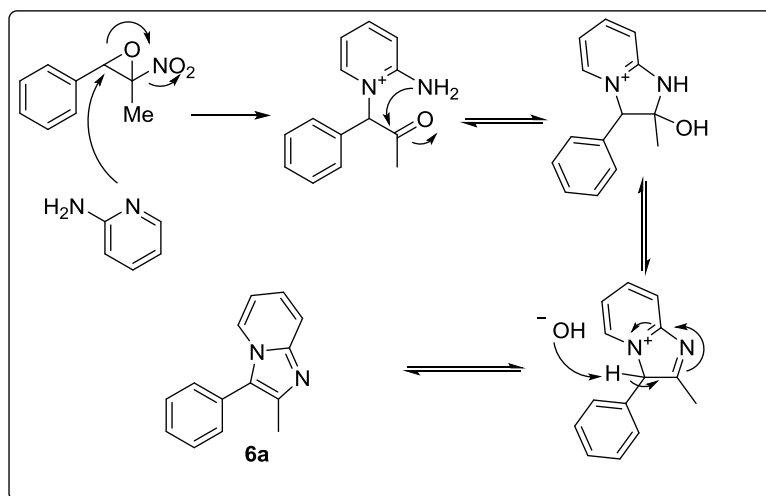
2.5. Imidazopyridines

For this study, other diamines were also considered for the ring-opening of nitroepoxides. Firstly we tried 1,8-diaminonaphthalene through a two-step sequence involving ring-opening and reduction as usual (Scheme 40). TLC analysis and NMR spectra of the crude mixture revealed the formation of many products, but all of them turned to be unstable, and no other compound besides starting material **1a** and 1,8-diaminonaphthalene could be isolated. The research on this reaction was abandoned due to lack of interesting results.



Scheme 40. Ring-opening attempt with 1,8-diaminonaphthalene.

More promising results were observed when nitroepoxide **1a** was reacted with 2-aminopyridine in 1,2-DCE without reducing agent. The aim of this reaction was, analogously for the quinoxalines, the synthesis of amino-iminium intermediate which might undergo to aromatization to afford more stable compound imidazo[1,2-a]pyridine **6a** (Scheme 41). The first results showed full conversion of **1a** after 40h, but at least four products were formed according to ¹H NMR spectrum since four singlet signals corresponding to methyl were observed. Compounds from the mixture were separated by silica gel liquid chromatography, but the fraction containing the expected compound resulted to be impure and not enough amount for identification.



Scheme 41. Mechanistic pathway for the synthesis of imidazo[1,2-a]pyridine **6a**.

Reaction was repeated under reflux instead of room temperature in order to favor the formation of the aromatic compounds. In this

occasion, NMR spectra of the crude mixture showed a different ratio of compounds since one of the methyl peaks was higher than the rest. The imidazo[1,2-a]pyridine compound **6a** was isolated with a 21% chemical yield and NMR spectra matched for the regioisomer resulting from the nucleophilic attack by the nitrogen in the pyridine ring to the epoxide ring according to literature.⁹⁵ However, since the opposite regioisomer **6b** was not purely isolated, NMR experiments were performed in order to confirm the correct structure.

Signals on ¹H NMR were assigned according to computational prediction. The triplet at 6.7 ppm was assigned to the H on the β-C in the pyridine ring (Figure 9, signal B). One-dimensional NOE irradiation over that signal showed coupling with a doublet at 8.1 ppm, assigned to the H on the α-C in the pyridine ring (Figure 9, signal A), and with a triplet at 7.1 ppm (Figure 9, signal C). Then, NOE irradiation of methyl signal showed coupling with the proton on phenyl group at 7.4 ppm (Figure 10). Once main signals were assigned, NOESY experiment was performed and the interaction between proton from pyridine ring at 8.1 ppm and proton from phenyl at 7.4 ppm confirmed the proposed structure.

⁹⁵ Cao, H.; Zhan, H.; Lin, Y.; Lin, X.; Du, Z.; Jiang, H. *Org. Lett.* **2012**, *14* (7), 1688.

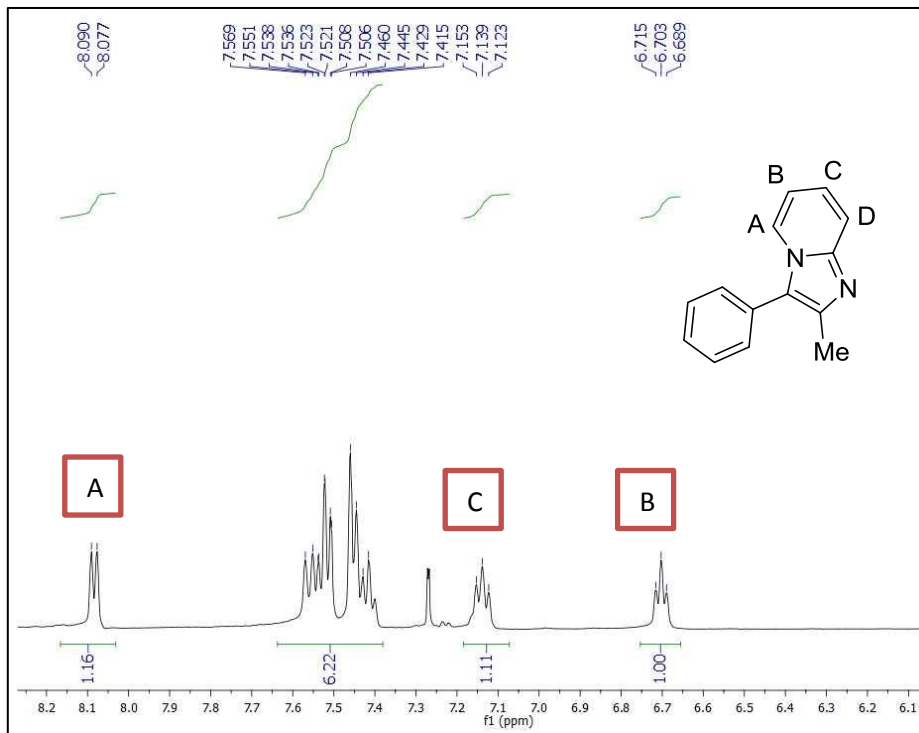


Figure 9. Signal assignment for the identification of the regioisomer.

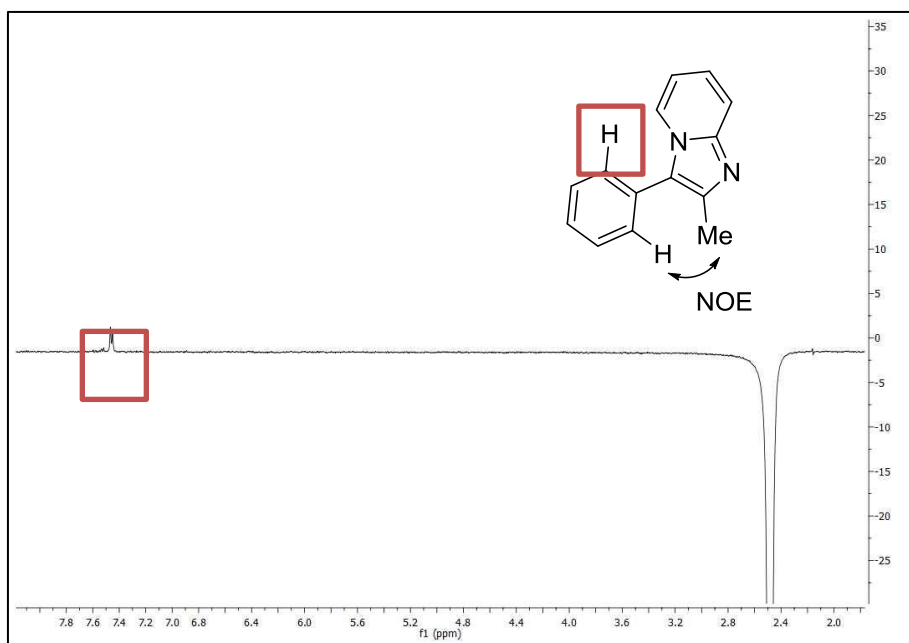
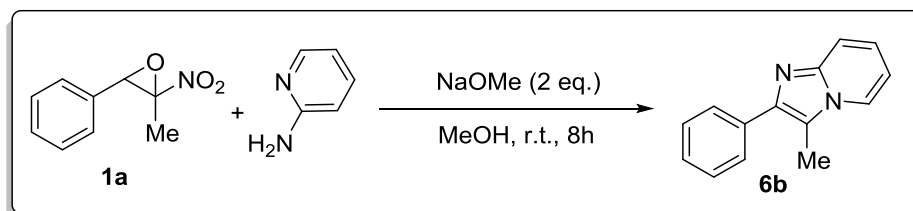


Figure 10. Identification of regioisomer by one-dimensional NOE experiment.

Several experiments were performed in order to increase the chemical yield, however no significant increase of the yield was observed by modification of the solvent, addition of Lewis acid catalysts (*e.g.* $\text{Ti}(\text{O}^i\text{Pr})_4$) or variations on the substrate. Temperature had an effect on the conversion rate, but not in the yield or regioselectivity. At lower temperatures than 0°C , the reaction barely proceeded. These results were not included in our publication but interestingly, X. Guo *et al.*⁹⁶ reported recently the synthesis of the opposite regioisomer **6b** from nitroepoxide **1a** by using two equivalents of sodium methoxide in MeOH in a 43% yield (Scheme 42).



Scheme 42. Guo's synthesis of the opposite regioisomer of **6b**.

⁹⁶ Guo, X.; Shao, J.; Liu, H.; Chen, B.; Chen, W.; Yu, Y. *RSC Adv.* **2015**, 5 (64), 51559.

3. Conclusions

- In summary, we reported that aromatic heterocycles such as quinoxalines and pyrazines can be easily prepared by treating nitroepoxides with 1,2-benzenediamines and ammonia, respectively. These reactions give very high yields using environmentally friendly ethanol as a solvent.⁹⁷
- Piperazines can also be prepared in a one-pot procedure when nitroepoxides are treated with 1,2-ethylenediamine and then sodium triacetoxyborohydride as a reductive agent in ethanol.
- In addition, tetrahydroquinoxalines can be easily obtained by using 1,2-benzenediamine in dichloromethane and then borane–tetrahydrofuran complex as a reductive agent.

⁹⁷ Vidal-Albalat, A.; Rodríguez, S.; González, F. V. *Org. Lett.* **2014**, *16* (6), 1752.

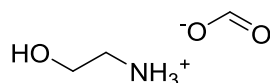
4. Experimental Section

General Information

Unless otherwise specified, all reactions were carried out under nitrogen atmosphere with magnetic stirring. All solvents and reagents were obtained from commercial sources and were purified according to standard procedures before use. ^1H NMR spectra and ^{13}C NMR spectra were measured in CDCl_3 (^1H , 7.27 ppm; ^{13}C 77.0 ppm) solution at 30 °C on a 300 MHz or a 500 MHz NMR spectrometer. Mass spectra were measured in a QTOF I (quadrupole-hexapole-TOF) mass spectrometer with an orthogonal Z-spray-electrospray interface. EM Science Silica Gel 60 was used for column chromatography while TLC was performed with precoated plates (Kieselgel 60, F₂₅₄, 0.25 mm).

Experimental Procedures

Experimental Procedure for the Preparation of 2-Hydroxyethyl Ammonium Formate (2-HEAF):⁹⁸

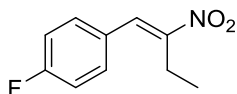


2-Amino ethanol (20.2 g, 331 mmol) was placed in a two-necked flask equipped with a reflux condenser and a dropping funnel. The flask was mounted in an ice bath. Under vigorous stirring with a magnetic stirring bar, formic acid (12.8 mL, 331 mmol) was added dropwise to the flask in about 45 min. The stirring was continued for 24 h at room temperature, to obtain a slightly orange viscous liquid. No further purification was performed. ^1H NMR (300 MHz, DMSO-d_6) δ 8.40 (s, 1H), 7.30 (bs, 4H), 3.55 (t, $J = 5.1$ Hz, 2H), 2.80 (t, $J = 5.4$ Hz, 2H).

⁹⁸ Bicak, N. *J. Mol. Liq.* **2005**, *116* (1), 15.

General Experimental Procedure for the Preparation of Nitroalkenes:⁸⁵

A mixture of the aldehyde (7 mmol, 1 eq), the nitroalkane (7 mmol, 1eq), and 2-HEAF (7 mL) was vigorously stirred for 24h at room temperature. An insoluble solid was observed in the mixture. Then, addition of water (7 mL) to the flask led to the immediate formation of a solid which was filtered and washed with water to afford yellow crystals. The 2-HEAF was rinsed with EtOAc (2x10 mL), the water from the aqueous phase removed under vacuum, and the ionic liquid used again. The purification of the crude solid was performed only when indicated.

**(E)-1-Fluoro-4-(2-nitrobut-1-en-1-yl)benzene.**

Yellow crystals, mp 63–70 °C (yield 1.09 g, 80%): ¹H NMR (300 MHz, CDCl₃) δ 7.93 (s, 1H), 7.45–7.35 (m, 2H), 7.11 (t, J = 8.6 Hz, 2H), 2.81 (q, J = 7.4 Hz, 2H), 1.23 (t, J = 7.4 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 163.4 (d, J = 250.5 Hz), 153.1, 131.9, 131.7 (d, J = 9 Hz), 128.5, 116.2 (d, J = 21.8 Hz), 20.6, 12.3 ppm; HRMS (EI) calcd for C₁₀H₁₀FNO₂ (M) 195.0696, found 195.0697; IR (KBr) δ 3052, 2976, 1520, 1328, 1232, 1159, 836 cm⁻¹.

Experimental Procedure for the Preparation of (E)-2-nitro-2-hexene:⁹⁹

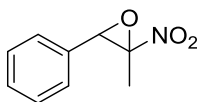
To a stirred solution of butyraldehyde (2.7 mL, 30 mmol) in nitroethane (11 mL, 150 mmol) at room temperature was added dropwise triethylamine (420 μL, 3 mmol). The resulting mixture was stirred under N₂ for 16h. The excess solvent was evaporated in vacuo and the crude nitroaldol was dissolved in CH₂Cl₂ (12 mL), cooled with an ice-bath and then methanesulfonylchloride (2.9 mL, 36 mmol) and ethyldiisopropylamine (11.1 mL, 63 mmol) were added. The solution

⁹⁹ Anderson, J. C.; Blake, A. J.; Mills, M.; Ratcliffe, P. D. *Org. Lett.* **2008**, *10* (18), 4141.

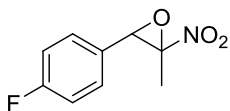
was allowed to warm up to room temperature and stirred until TLC analysis indicated consumption of nitroaldol (19 h). Water and CH_2Cl_2 (10 mL each) were added, and the organic phase was separated, washed with 2M HCl (10 mL), brine, dried (MgSO_4) and concentrated to yield an orange oil, which was purified by silica-gel chromatography (9:1 to 7:3, hexane/ethyl acetate) to give the pure product as an orange oil. 2.65g, (yield 68%). ^1H NMR (300 MHz, CDCl_3) δ 7.02 (t, $J = 7.9$ Hz, 1H), 2.14 (q, $J = 7.4$ Hz, 2H), 2.07 (s, 3H), 1.64–1.25 (m, 2H), 0.88 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 147.6, 136.0, 30.0, 21.5, 13.5, 12.2 ppm; HRMS (EI) calcd for $\text{C}_6\text{H}_{11}\text{NO}_2$ (M) 129.0790, found 129.0791; IR (KBr) δ 3056, 2961, 1671, 1512, 1389, 1330 cm^{-1} .

General Experimental Procedure for the Preparation of Nitroepoxides 1a-e:

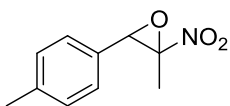
To a stirred ice-bath suspension of the corresponding nitroalkene (12.1 mmol) in methanol (37.6 mL) containing hydrogen peroxide 50% aqueous solution (2400 μL , 42.8 mmol) was added aqueous NaOH 2M (3900 μL , 6.1 mmol) and stirred at 0°C for 10 minutes. Then, ice water was added (30 mg), extracted with diethyl ether (3x50 mL), the combined organic phases washed with brine (45 mL), dried with Na_2SO_4 and concentrated under vacuum to afford a yellowish oil. When needed, crude oil was purified by silica gel liquid chromatography (hexane/ethyl acetate, 9:1).



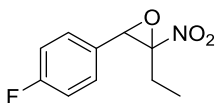
2-methyl-2-nitro-3-phenyloxirane 1a, pale yellow oil, 1.8g (yield 84%): ^1H NMR (500 MHz, CDCl_3) δ 7.41 (m, 3H), 7.30 (m, 2H), 4.56 (s, 1H), 1.78 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 131.0, 129.3, 128.7, 126.3, 88.8, 62.6, 12.2 ppm; HRMS (EI) calcd for $\text{C}_9\text{H}_9\text{NO}_3$ (M^+) 179.0582, found 179.0587; IR (KBr) δ 3062, 3028, 2948, 1555, 1495, 1448, 1354, 1158, 1105, 982, 899 cm^{-1}



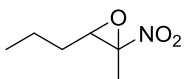
3-(4-fluorophenyl)-2-methyl-2-nitrooxirane 1b, colorless oil, 1.9 g (yield 79%): ^1H NMR (300 MHz, CDCl_3) δ 7.33–7.26 (m, 2H), 7.13–7.05 (m, 2H), 4.51 (s, 1H), 1.76 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 163.2 (d, $J = 247.8$ Hz), 128.3 (d, $J = 8.4$ Hz), 126.8 (d, $J = 4.0$ Hz), 115.8 (d, $J = 22.0$ Hz), 88.8, 62.1, 12.1 ppm; HRMS (EI) calcd for $\text{C}_9\text{H}_8\text{NFO}_3$ (M^+) 197.0488, found 197.0492 IR (KBr) δ 3059, 3024, 2944, 1546, 1490, 1452, 1205, 896, 830 cm^{-1} .



2-methyl-2-nitro-3-(p-tolyl)oxirane 1c, yellow oil, 1.7 g (yield 75%): ^1H NMR (500 MHz, CDCl_3) δ 7.26–7.17 (m, 4H), 4.50 (s, 1H), 2.38 (s, 3H), 1.80 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 139.6, 129.5, 128.0, 126.4, 89.1, 62.8, 21.1, 12.4 ppm; HRMS (EI) calcd for $\text{C}_{10}\text{H}_{11}\text{NO}_3$ (M^+) 193.0739, found 193.0745; IR (KBr) δ 3062, 3025, 2948, 1552, 1449, 1346, 1158, 899, 768 cm^{-1} .



2-Ethyl-3-(4-fluorophenyl)-2-nitrooxirane 1d, yellow oil, 2.2 g (yield 88%): ^1H NMR (300 MHz, CDCl_3) δ 7.37–7.19 (m, 2H), 7.10 (t, $J = 8.6$ Hz, 2H), 4.49 (s, 1H), 2.45 (dq, $J = 15.1, 7.4$ Hz, 1H), 1.67 (dq, $J = 14.8, 7.3$ Hz, 1H), 1.05 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 163.2 (d, $J = 247.5$ Hz), 128.2 (d, $J = 8.3$ Hz), 127.0 (d, $J = 2.3$ Hz), 115.9 (d, $J = 21.8$ Hz), 92.37, 62.62, 19.44, 7.53 ppm; HRMS (EI) calcd for $\text{C}_{10}\text{H}_{10}\text{FNO}_3$ (M^+) 211.0645, found 211.0651; IR (KBr) δ 3052, 2979, 1710, 1606, 1552, 1510, 1347, 1227, 1156 cm^{-1} .

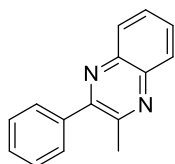


2-methyl-2-nitro-3-propyloxirane 1e, yellow oil 1.2 g (yield 68%): ^1H NMR (300 MHz, CDCl_3) δ 3.39 (t, $J = 5.7$ Hz, 1H), 1.89 (s, 3H), 1.66–1.43 (m, 4H), 0.96 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75

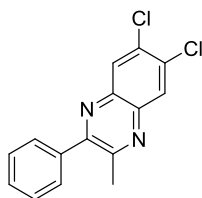
MHz, CDCl₃) δ 87.9, 62.9, 29.7, 19.1, 13.6 ppm; HRMS (EI) calcd for C₆H₁₁NO₃ (M⁺) 145.0739, found 145.0741; IR (KBr) δ 3028, 1555, 1029 cm⁻¹

General Experimental Procedure for the Synthesis of Quinoxalines 2a-2i:

To a solution of the corresponding nitroepoxide (0.558 mmol) in ethanol (3.1 mL), 1,2-benzenediamine (0.837 mmol) was added in one-portion and the mixture was stirred in the open air for 20 h. Intense red color was an indicator of reaction completion. Then anhydrous MgSO₄ (50mg) was added and stirred for 15 minutes. Then the mixture was filtered washing with EtOAc, and concentrated under vacuum. A red viscous oil was obtained which was further purified through a silica-gel chromatography (hexane/ethyl acetate, 8:2).



2-Methyl-3-phenylquinoxaline 2a, red solid, 106 mg (yield 86%), mp 50-55°C (lit.¹⁰⁰ 54-56°C): ¹H NMR (300 MHz, CDCl₃) δ 8.04 (ddt, *J* = 10.1, 4.9, 2.1 Hz, 2H), 7.71 – 7.56 (m, 4H), 7.53 – 7.39 (m, 3H), 2.73 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 154.7, 152.3, 141.1, 140.9, 138.9, 129.5, 129.1, 129.0, 128.8, 128.4, 128.2, 24.2.; HRMS (ESI) calcd for C₁₅H₁₃N₂ (M+H⁺) 221.1079, found 221.1076. IR (KBr) δ 3051, 2983, 1641, 1413, 1369, 1266, 902 cm⁻¹.

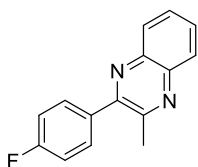


6,7-Dichloro-2-methyl-3-phenylquinoxaline 2b, red crystal, 132 mg (82% yield) mp 148-152 °C (lit.¹⁰¹ 152-154 °C): ¹H

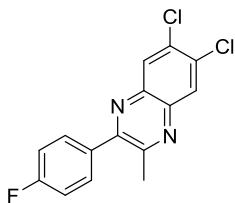
¹⁰⁰ Padmavathy, K.; Nagendrappa, G.; Geetha, K. V. *Tetrahedron Lett.* **2011**, 52 (4), 544.

¹⁰¹ Chen, Y.; Li, K.; Zhao, M.; Li, Y.; Chen, B. *Tetrahedron Lett.* **2013**, 54 (13), 1627.

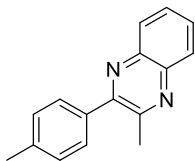
NMR (300 MHz, CDCl₃) δ 8.17 (s, 1H), 8.11 (s, 1H), 7.67 – 7.59 (m, 2H), 7.56 – 7.46 (m, 3H), 2.74 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 155.8, 153.9, 139.9, 139.7, 138.3, 134.0, 133.6, 129.8, 129.4, 129.1, 128.9, 128.6, 24.5.; HRMS (ESI) calcd for C₁₅H₁₁Cl₂N₂ (M+H⁺) 289.0299, found 289.0295; IR (KBr) δ 3059.1, 2982, 1444, 1366, 1258, 891, 747 cm⁻¹.



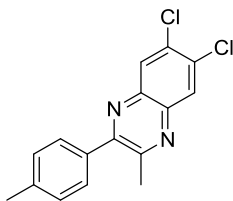
2-(4-Fluorophenyl)-3-methylquinoxaline 2c, pale orange solid, 106 mg (yield 80%), mp 76-79 °C (lit.¹⁰⁰ 78 °C): ¹H NMR (300 MHz, CDCl₃) δ 8.04 (dd, *J* = 11.0, 9.4 Hz, 2H), 7.72 – 7.58 (m, 4H), 7.18 (t, *J* = 8.5 Hz, 2H), 2.74 (s, *J* = 1.3 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 163.2 (d, *J* = 249.0 Hz), 153.7, 152.2, 141.2, 140.9, 135.1 (d, *J* = 3.4 Hz), 130.9 (d, *J* = 8.4 Hz), 129.8, 129.3, 129.1, 128.3, 115.6 (d, *J* = 21.7 Hz), 24.3. HRMS (ESI) calcd for C₁₅H₁₂FN₂ (M+H⁺) 239.0985, found 239.0979; IR (KBr) δ 3022, 2983, 1643, 1351, 1281, 846 cm⁻¹.



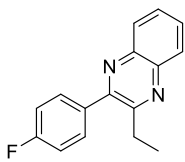
6,7-Dichloro-2-(4-fluorophenyl)-3-methylquinoxaline 2d, pale orange crystal, 128 mg (75% yield), mp 167-169 °C: ¹H NMR (300 MHz, CDCl₃) δ 8.18 (s, 1H), 8.15 (s, 1H), 7.65 (dd, *J* = 8.9, 5.3 Hz, 2H), 7.22 (t, *J* = 8.8 Hz, 2H), 2.75 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 163.5 (d, *J* = 249.9 Hz), 154.8, 153.7, 140.0, 139.8, 134.4, 133.9, 131.0 (d, *J* = 8.4 Hz), 129.8, 129.1, 115.8 (d, *J* = 21.8 Hz), 24.5. HRMS (ESI) calcd for C₁₅H₁₀Cl₂FN₂ (M+H⁺) 307.0205, found 307.0203; IR (KBr) δ 3035, 2953, 1677, 1452, 1332, 1265, 999, 761 cm⁻¹.



2-Methyl-3-(*p*-tolyl)quinoxaline 2e, yellow-brown solid, 101 mg, (yield 78%), mp 59-62 °C, (lit.¹⁰² 60-61 °C): ¹H NMR (300 MHz, CDCl₃) δ 8.08 (d, *J* = 10.6 Hz, 1H), 8.03 (d, *J* = 9.2 Hz, 1H), 7.71 – 7.66 (m, 2H), 7.54 (d, *J* = 6.8 Hz, 2H), 7.31 (d, *J* = 7.6 Hz, 2H), 2.77 (s, 3H), 2.43 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 154.9, 152.6, 141.1, 141.1, 139.0, 136.2, 129.5, 129.2, 129.1, 129.0, 128.9, 128.3, 24.4, 21.3. HRMS (ESI) calcd for C₁₆H₁₅N₂ (M+H⁺) 235.1235, found 235.1235; IR (KBr) δ 3042, 2963, 2917, 1644, 1345, 1264, 1001, 838 cm⁻¹.



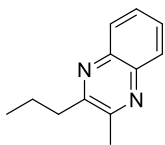
6,7-Dichloro-2-methyl-3-(*p*-tolyl)quinoxaline 2f, brown solid, 118 mg (70% yield), mp 126-128 °C: ¹H NMR (500 MHz, CDCl₃) δ 8.19 (s, *J* = 7.6 Hz, 1H), 8.14 (s, 1H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 2.76 (s, 3H), 2.44 (s, *J* = 27.5 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 156.0, 154.0, 140.0, 139.8, 139.6, 135.5, 134.0, 133.6, 129.8, 129.3, 129.1, 128.9, 24.6, 21.4; HRMS (ESI) calcd for C₁₆H₁₃Cl₂N₂ (M+H⁺) 303.0456, found 303.0454; IR (KBr) δ 3055, 2988, 1439, 1320, 1267, 1003, 761 cm⁻¹



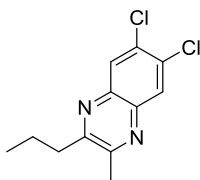
2-Ethyl-3-(4-fluorophenyl)quinoxaline 2g, orange solid, 112 mg (yield 80%), mp 73-76 °C: ¹H NMR (300 MHz, CDCl₃) δ 8.08 (d, *J* = 8.6 Hz, 2H), 7.79 – 7.66 (m, 2H), 7.59 (dd, *J* = 7.0, 5.3 Hz, 2H), 7.20 (t, *J* = 8.7 Hz, 2H), 3.04 (q, *J* = 7.5 Hz, 2H), 1.29 (t, *J* = 7.5 Hz,

¹⁰² Schwaiger, W.; Ward, J. P. *Recl. des Trav. Chim. des Pays-Bas* **1972**, *91* (10), 1175.

3H). ^{13}C NMR (75 MHz, CDCl_3) δ 163.2 (d, $J = 248.9$ Hz), 156.9, 153.8, 141.4, 140.7, 135.1 (d, $J = 3.6$ Hz), 130.8 (d, $J = 8.4$ Hz), 129.8, 129.3, 129.1, 128.5, 115.6 (d, $J = 21.7$ Hz), 29.3, 13.0. HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{14}\text{FN}_2$ ($\text{M}+\text{H}^+$) 253.1141, found 253.1145; IR (KBr) δ 3024, 2982, 2932, 1648, 1345, 1268, 857 cm^{-1}



2-Methyl-3-propylquinoxaline 2h, brown solid, 65 mg (yield 63%), mp 58-63 °C (lit.¹⁰³ 60-61.5 °C): ^1H NMR (300 MHz, CDCl_3) δ 7.98 – 7.85 (m, 2H), 7.58 (dd, $J = 6.4, 3.4$ Hz, 2H), 2.90 (dd, $J = 8.6, 6.9$ Hz, 2H), 2.68 (s, $J = 3.9$ Hz, 3H), 1.93 – 1.72 (m, 2H), 1.02 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 156.6, 153.0, 141.1, 140.8, 128.6, 128.6, 128.5, 128.2, 37.7, 22.7, 21.3, 14.1. HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{15}\text{N}_2$ ($\text{M}+\text{H}^+$) 187.1235, found 187.1236; IR (KBr) δ 3046, 3056, 2965, 2939, 1269, 759 cm^{-1}



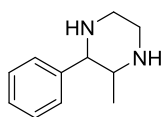
6,7-Dichloro-2-methyl-3-propylquinoxaline 2i, brown solid, 68 mg (48% yield) mp 92-95 °C, (lit.¹⁰⁴ 90-91 °C): ^1H NMR (500 MHz, CDCl_3) δ 8.05 (s, 1H), 8.01 (s, 1H), 2.91 (dd, $J = 8.3, 7.1$ Hz, 2H), 2.69 (s, 3H), 1.91 – 1.78 (m, 2H), 1.04 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 158.0, 154.6, 139.9, 139.6, 133.0, 132.9, 129.3, 129.3, 129.1, 129.0, 37.7, 22.8, 21.0, 14.1; HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{13}\text{Cl}_2\text{N}_2$ ($\text{M}+\text{H}^+$) 255.0456, found 255.0454; IR (KBr) δ 3047, 2973, 2918, 1450, 1329, 1268, 751 cm^{-1}

¹⁰³ Kaiser, E. M.; Petty, J. D. *J. Organomet. Chem.* **1976**, 108 (2), 139

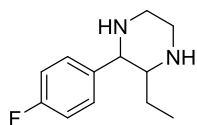
¹⁰⁴ Shaabani, A.; Maleki, A. *Chem. Pharm. Bull. (Tokyo)*. **2008**, 56 (1), 79

General Experimental Procedure for the Synthesis of Piperazines 3a-c.

To a solution of the corresponding nitroepoxide (0.837 mmol) in ethanol (4.6 mL), 1,2-ethylenediamine (90 μ L, 1.225 mmol) was added dropwise. The resulting mixture was stirred for 6 hours at room temperature under N_2 atmosphere. Then $NaBH(OAc)_3$ (549 mg, 2.511 mmol) was added and the resulting mixture was stirred for additional 16 hours. Then a solution of aqueous NaOH 50% (200 μ L, 5 mmol) was added and the mixture was stirred for 2 h. Then magnesium sulfate (84 mg, 0.7 mmol) was added and the mixture was stirred for additional 1.5 hours. Then the mixture was filtered and concentrated to yield a yellow crude oil, which was purified through silica gel chromatography ($CH_2Cl_2/MeOH/Et_3N$, 95:4:1). If the resulting compound was contaminated by 1,2-ethylenediamine, the product was solved in the minimum amount of water, then treated with 5 % aqueous NaOH solution (until pH=10) and extracted with dichloromethane (3 x 10 mL) to afford a yellowish oil after evaporation.

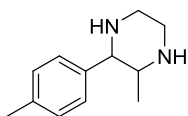


2-Methyl-3-phenylpiperazine 3a, yellowish oil, 65 mg (44% yield): 1H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.28 (m, 5H), 4.16 (d, $J = 3.4$ Hz, 1H), 3.34 (dt, $J = 10.3, 6.8$ Hz, 2H), 3.23 – 3.13 (m, 1H), 3.11 – 3.03 (m, 1H), 2.55-2.25 (bs, 2H), 2.90 – 2.80 (m, 1H), 1.03 (d, $J = 6.8$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.6, 128.2, 128.0, 126.8, 64.0, 53.1, 47.8, 40.2, 12.8; HRMS (ESI) calcd for $C_{11}H_{17}N_2$ ($M+H^+$) 177.1392, found 177.1393; IR (KBr) δ 3342, 3056, 2965, 2939, 1269, 759 cm^{-1}



2-Ethyl-3-(4-fluorophenyl)piperazine 3b, pale yellow oil, 101 mg (64% yield): 1H NMR (500 MHz, $CDCl_3$) δ 7.37 (dd, $J = 8.5, 5.4$ Hz, 2H), 7.00 (t, $J = 8.6$ Hz, 2H), 5.00-4.57 (bs, 2H), 4.38 (d, J

= 3.2 Hz, 1H), 3.32 – 2.98 (m, 5H), 1.86 – 1.71 (m, 1H), 1.40 – 1.26 (m, 1H), 0.75 (t, $J = 7.5$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 162.2 (d, $J = 246.3$ Hz), 135.6 (d, $J = 3.1$ Hz), 128.8 (d, $J = 8.0$ Hz), 115.3 (d, $J = 21.3$ Hz), 60.7, 59.4, 44.6, 39.5, 17.7, 11.0. HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{16}\text{FN}_2$ ($\text{M}+\text{H}^+$) 209.1454, found 209.1451; IR (KBr) δ 3358, 3026, 2977, 2966, 1414, 1255, 898 cm^{-1}

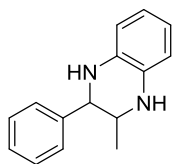


2-Methyl-3-(*p*-tolyl)piperazine 3c, pale yellow oil 92 mg (58% yield): ^1H NMR (300 MHz, CDCl_3) δ 7.20 (d, $J = 8.1$ Hz, 2H), 7.10 (d, $J = 8.1$ Hz, 2H), 3.99 (d, $J = 3.3$ Hz, 1H), 2.30 (s, 3H), 1.74 (br s, 2H), 2.69-3.19 (m, 5H), 0.94 (d, $J = 8.1$ Hz, 3H) (majoritary), 0.77 (d, $J = 7.8$ Hz, 3H) (minoritary). ^{13}C NMR (75 MHz, CDCl_3) δ 139.7, 136.3, 128.9, 126.7, 63.8, 53.2, 47.8, 40.3, 21.0, 12.9. HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{19}\text{N}_2$ ($\text{M}+\text{H}^+$) 191.1548, found 191.1542; IR (KBr) δ 3338, 3054, 2982, 1427, 1268, 889 cm^{-1}

Experimental Procedure for the Synthesis of Tetrahydroquinoxaline 4a.

To a solution of nitroepoxide **1a** (50 mg, 0.279 mmol) in dichloromethane (1.6 mL), 1,2-benzenediamine (46mg, 0.418 mmol) was added in one-portion and the mixture was stirred in the open air for 48h. After the formation of quinoxaline (TLC, reaction mixture turned red), dichloromethane (1 mL) was added in order to compensate the solvent lost by evaporation. Then the atmosphere was purged with N_2 and the reaction mixture was cooled down with an ice-bath. Then 1M borane-tetrahydrofuran complex in THF solution (1.1 mL, 1.116 mmol) was added dropwise, and the resulting reaction mixture was stirred at room temperature for 40 minutes. Then methanol (4 mL) was added, then concentrated under vacuum, methanol (4 mL) added again and concentrated under vacuum. The resulting residue was dissolved in dichloromethane (10 mL), treated with an aqueous 5% NaOH solution (10 mL) and extracted with dichloromethane (4 x 5 mL). The combined

organic layers were dried (MgSO_4), filtered and concentrated under vacuum. The crude was purified through silica gel chromatography (hexanes/ethyl acetate, 8:2) to afford an orange-brown oil. (When pure compound **4** was stored under non-inert conditions it was gradually converted into the corresponding quinoxaline **2a**).



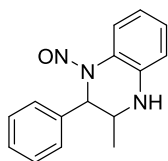
***cis*-2-Methyl-3-phenyl-1,2,3,4-tetrahydroquinoxaline**

4a, orange-brown oil 45 mg (yield 72%) ^1H NMR (300 MHz, CDCl_3) δ 7.38 – 7.26 (m, 5H), 6.79 – 6.60 (m, 3H), 6.58 (d, $J = 7.3$ Hz, 1H), 4.56 (d, $J = 3.1$ Hz, 1H), 3.75 (qd, $J = 6.5, 3.3$ Hz, 1H), 0.98 (d, $J = 6.5$ Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 141.7, 133.4, 128.6, 128.3, 127.6, 127.4, 119.6, 118.4, 115.2, 114.1, 58.5, 49.6, 17.4; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{17}\text{N}_2$ ($\text{M}+\text{H}^+$) 225.1392, found 225.1396; IR (KBr) δ 3400, 3042, 2979, 1604, 1500, 1440, 1014 cm^{-1}

General Experimental Procedure for the Synthesis of *N*-Nitroso-Tetrahydroquinoxaline **4b.**

For this reaction, all solvents and reagents were manipulated under inert conditions. A solution of nitroepoxide **1a** (150 mg, 0.837 mmol) in dry ethanol (4.6 mL) was added under N_2 atmosphere into a two-necked round bottom flask equipped with a magnetic stirrer and an addition funnel. Then, a previously purged solution of 1,2-diaminobenzene (139 mg, 1.225 mmol) in dry ethanol (2 mL), was added and the reaction mixture was stirred for 5 hours. Then, powdered $\text{NaBH}(\text{OAc})_3$ was added through the addition funnel under N_2 atmosphere, and the reaction mixture was stirred overnight. A non-extractive work-up was performed by adding 200 μl of 25 M aqueous NaOH and the mixture was stirred for 2 hours. Then, MgSO_4 (ca. 84 mg) was added and the mixture stirred for additional 1.5 h. Finally, the reaction mixture was filtered under vacuum, dried with MgSO_4 and filtered again and the solvent was removed under vacuum to afford a

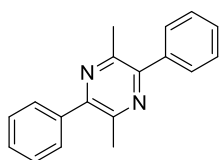
yellowish oil which was purified by silica gel liquid chromatography (hexanes/ethyl acetate 8:2).



3-methyl-1-nitroso-2-phenyl-1,2,3,4-tetrahydroquinoxaline 4b, orange-brown oil, 25 mg (12% yield). ^1H NMR (300 MHz, CDCl_3) δ 8.03 (d, $J = 8.2$ Hz, 1H), 7.61 – 7.32 (m, 5H), 7.25 – 7.08 (m, 1H), 7.00 – 6.78 (m, 2H), 5.33 (qd, $J = 6.5, 3.3$ Hz, 1H), 4.45 (d, $J = 3.3$ Hz, 1H), 4.18 (bs, 1H), 0.86 (d, $J = 6.6$ Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 137.9, 134.3, 128.9, 128.3, 127.0, 119.7, 116.8, 116.1, 57.1, 48.0, 10.0. MS (ESI) calcd for $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}$ ($\text{M}+\text{Na}$) $^+$ 276.1, found 276.2; IR (KBr) δ 3362, 2918, 1488, 1433, 1271, 1146, 752 cm^{-1}

General Experimental Procedure for the Synthesis of Pyrazines 6a-e.

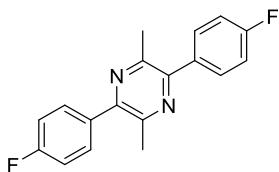
The corresponding nitroepoxide (0.558 mmol) was solved into a commercially available 7 N solution of ammonia in MeOH (1.1 mL). The mixture was stirred for 24 hours at room temperature. Then the mixture was concentrated under vacuum, water (5 mL) and ethyl ether (5 mL) were added and the resulting mixture was extracted with ethyl ether (3 x 5 mL), the combined organic phases were washed with brine (15 mL), dried (MgSO_4) and concentrated. The resulting yellow solid resulted to be highly pure compound.



2,5-Dimethyl-3,6-diphenylpyrazine 5a, pale yellow solid, 67 mg (93% yield), mp 120-125 $^\circ\text{C}$ (lit.¹⁰⁵ 125-126 $^\circ\text{C}$): ^1H NMR (300 MHz, CDCl_3) δ 7.63 (d, $J = 6.6$ Hz, 4H), 7.54 – 7.41 (m, 6H), 2.64 (s, 6H). ^{13}C NMR (75 MHz, CDCl_3) δ 151.1, 147.8, 138.8, 129.1,

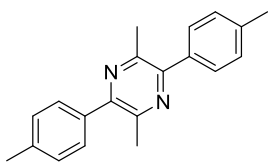
¹⁰⁵ Schmitt, V.; Moschel, S.; Detert, H. *European J. Org. Chem.* **2013**, 25, 5655

128.6, 128.5, 22.7; HRMS (ESI) calcd for $C_{18}H_{17}N_2$ ($M+H^+$) 261.1392, found 261.1391 IR (KBr) δ 3057, 2987, 1682, 1424, 1391, 904 cm^{-1}



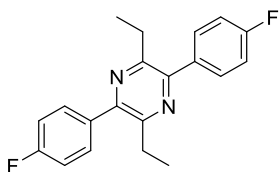
2,5-Bis(4-fluorophenyl)-3,6-dimethylpyrazine

5b, pale yellow crystals, 76 mg (92% yield), mp 179-181 °C: 1H NMR (300 MHz, $CDCl_3$) δ 7.62 (dd, $J = 7.7, 5.4$ Hz, 4H), 7.17 (t, $J = 8.6$ Hz, 4H), 2.62 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.0 (d, $J = 248.5$ Hz), 150.1, 147.7, 134.7 (d, $J = 3.3$ Hz), 131.0 (d, $J = 8.3$ Hz), 115.5 (d, $J = 21.7$ Hz), 22.7; HRMS (ESI) calcd for $C_{18}H_{15}F_2N_2$ ($M+H^+$) 297.1203, found 297.1204; IR (KBr) δ 3036, 2968, 1610, 1504, 1412, 1220, 850 cm^{-1}



2,5-Dimethyl-3,6-di-*p*-tolylpyrazine **5c**,

pale yellow solid, 72 mg (90% yield), mp 162-166 °C (lit.¹⁰⁶ 168 °C): 1H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, $J = 8.0$ Hz, 4H), 7.29 (d, $J = 7.7$ Hz, 4H), 2.64 (s, 6H), 2.42 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.8, 147.6, 138.4, 136.0, 129.1, 129.0, 22.7, 21.3; HRMS (ESI) calcd for $C_{20}H_{21}N_2$ ($M+H^+$) 289.1705, found 289.1707; IR (KBr) δ 3062, 2984, 1692, 833 cm^{-1}

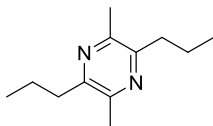


2,5-Diethyl-3,6-(4-fluorophenyl)pyrazine **5d**,

pale yellow crystals, 87 mg (96% yield), mp 115-116 °C: 1H NMR (500 MHz, $CDCl_3$) δ 7.61 (dd, $J = 8.5, 5.4$ Hz, 2H), 7.17 (t, $J = 8.6$ Hz, 2H), 2.91 (q, $J = 7.5$ Hz, 2H), 1.27 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (126 MHz,

¹⁰⁶ Tiffeneau; Levy; Ditz, *Bull. Soc. Chim. Fr.* **1935**, 5, 1855.

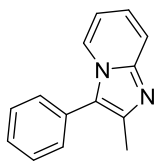
CDCl_3) δ 163.0 (d, $J = 248.2$ Hz), 152.1, 150.0, 135.0 (d, $J = 3.3$ Hz), 130.9 (d, $J = 8.3$ Hz), 115.4 (d, $J = 21.6$ Hz), 27.8, 13.5; HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{19}\text{F}_2\text{N}_2$ ($\text{M}+\text{H}^+$) 325.1516, found 325.1514; IR (KBr) δ 3044, 2979, 2936, 1608, 1509, 1409, 1229, 855 cm^{-1}



2,5-Dimethyl-3,6-dipropylpyrazine 5e, orange oil 48 mg (89% yield): ^1H NMR (300 MHz, CDCl_3) δ 2.73 – 2.61 (m, 1H), 2.45 (s, 1H), 1.66 (dq, $J = 14.9, 7.4$ Hz, 1H), 0.95 (t, $J = 7.4$ Hz, 2H). ^{13}C NMR (75 MHz, CDCl_3) δ 151.7, 147.8, 36.6, 22.1, 21.0, 14.1; HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{21}\text{N}_2$ ($\text{M}+\text{H}^+$) 193.1705, found 193.1703; IR (KBr) δ 3053, 2983, 2963, 1673, 1424, 1260, 900 cm^{-1}

Experimental Procedure for the Synthesis of Imidazopyridine 6.

To a solution of nitroepoxide **1a** (120 mg, 0.670 mmol) in ethanol (3.7 mL), 2-aminopyridine (96 mg, 1.004 mmol) was added in one-portion and the mixture was stirred for 20 h. Then anhydrous MgSO_4 (50mg) was added and stirred for 15 minutes. Then the mixture was filtered washing with EtOAc, and concentrated under vacuum. An orange/yellow oil was obtained which was further purified through a silica-gel chromatography (hexane/ethyl acetate, 8:2 to 6:4). Spectra of the pure compound matched with those reported in the literature.⁹⁵



2-methyl-3-phenylimidazo[1,2-a]pyridine 6, yellow oil, 29 mg (21% yield): ^1H NMR (500 MHz, CDCl_3) δ 8.08 (d, $J = 6.9$ Hz, 1H), 7.53 (m, 3H), 7.44 (m, 3H), 7.14 (t, $J = 7.5$ Hz, 1H), 6.70 (t, $J = 6.5$ Hz, 1H), 2.47 (s, 3H).

Chapter 3

Asymmetric Epoxidation of Dicyanoalkylidenes

1. Objectives

The work present in this chapter was performed during a four-month stay at Università degli Studi di Salerno (Italy) under the supervision of Professor Alessandra Lattanzi and in collaboration with Dr. Sara Meninno.

The main purpose of the work in this chapter is the asymmetric epoxidation of dicyanoalkylidenes, which is organized as follows:

The synthesis of dicyanoalkylidene **7** as study for the optimization study of the asymmetric epoxidation conditions.

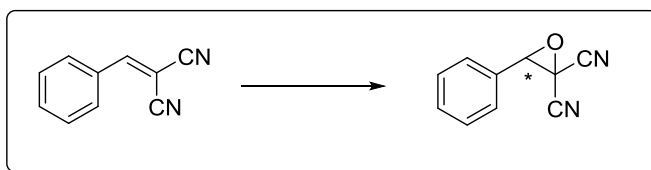
The synthesis of the racemic epoxide **8** from the corresponding dicyanoalkylidene **7** and the separation of the enantiomers by HPLC for identification.

The rational design and synthesis of various bifunctional catalysts to achieve the asymmetric epoxidation of dicyanoalkylidenes.

The screening of the conditions for the optimization of the enantioselective epoxidation of dicyanoalkylidene **7**.

2. Introduction

As it is extensively reported in the general introduction of the present Thesis dissertation, plenty of organocatalytic methodologies have been described for the synthesis of chiral epoxides from electron-deficient alkenes with high chemical yields and enantioselectivity. Despite the success, there is room to expand the substrate scope of electron-deficient alkenes, whose enantioenriched epoxides would be potentially highly attractive for further elaborations such as readily available alkylidenemalononitriles (Scheme 43).



Scheme 43. Epoxidation of 2-benzylidenemalononitrile generates a tertiary stereocenter.

These alkenes are challenging Michael acceptors as demonstrated by the few methodologies reported on asymmetric carbon–carbon bond formation,¹⁰⁷ likely ascribed to their significant reactive nature¹⁰⁸ and weak H-bonding acceptor ability of the cyano group.¹⁰⁹ The only example by Sekiya and co-workers on an asymmetric epoxidation of alkylidenemalononitriles using alkyl hydroperoxides or molecular oxygen and stoichiometric amounts of chiral bases afforded nearly racemic epoxides in low chemical yield (Scheme 44).¹¹⁰

¹⁰⁷ a) Yue, L.; Du, W.; Liu, Y. K.; Chen, Y. C. *Tetrahedron Lett.* **2008**, 49 (24), 3881.

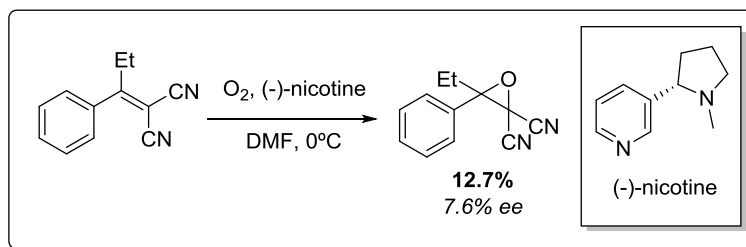
b) Xiao, H.; Chai, Z.; Zheng, C. W.; Yang, Y. Q.; Liu, W.; Zhang, J. K.; Zhao, G.

Angew. Chem. Int. Ed. **2010**, 49 (26), 4467. c) Ding, D.; Zhao, C. G. *Tetrahedron Lett.* **2010**, 51 (9), 1322.

¹⁰⁸ Lemek, T.; Mayr, H. *J. Org. Chem.* **2003**, 68 (18), 6880.

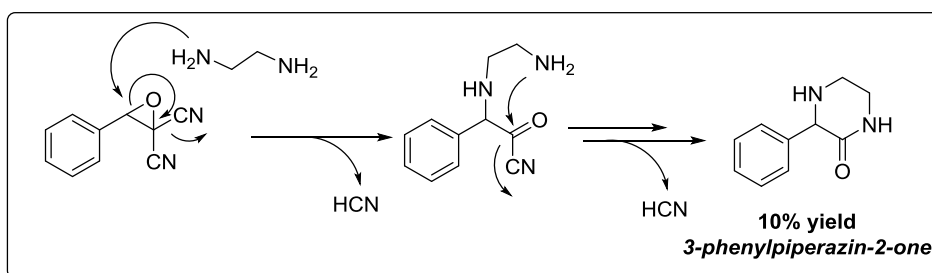
¹⁰⁹ Sagawa, N.; Shikata, T. *J. Phys. Chem. B* **2014**, 16, 13262.

¹¹⁰ Nanjo, K.; Suzuki, K.; Sekiya, M. *Chem. Pharm. Bull.* **1981**, 29, 336.



Scheme 44. Epoxidation of alkyldenemalononitriles using molecular oxygen.

It has been demonstrated by a few reports that racemic gem-dicyanoepoxides behave like the synthetic equivalent of dication ketenes. For example, Baudy-Floc'h *et al.* isolated a 3-aryl piperazin-2-one in 10% yield working under mild conditions.¹¹¹ The reaction proceeded at room temperature via regioselective ring-opening of the corresponding gem-dicyanoepoxide by ethylenediamine as a binucleophile (Scheme 45).



Scheme 45. Pathway for the synthesis of 2-piperazinones from α,α -dicyanoepoxides.

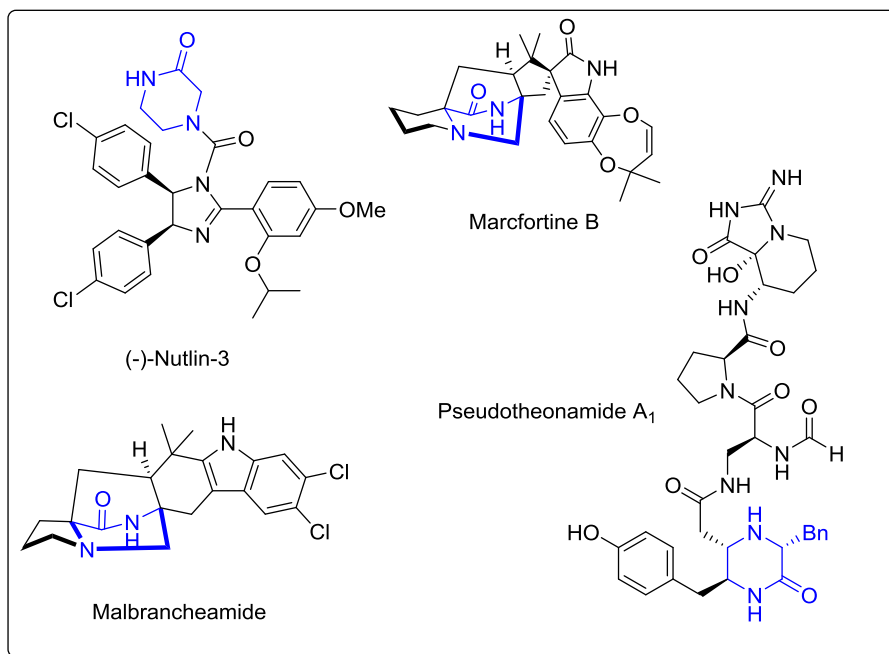
Chiral substituted piperazin-2-ones have shown interest in medicinal chemistry since the synthesis of various bioactive compounds with this chemical moiety have been reported.¹¹² For example, piperazin-2-one moiety can be found on the p53/MDM2 inhibitor (-)-nutlin-3¹¹³ and in several naturally occurring bioactive compounds including the

¹¹¹ Hurtaud, D.; Baudy-Floc'h, M.; Robert, A.; Le Grel, P. *J. Org. Chem.* **1994**, *59* (16), 4701

¹¹² a) Kakarla, R.; Liu, J.; Naduthambi, D.; Chang, W.; Mosley, R. T.; Bao, D.; Steuer, H. M. M.; Keilman, M.; Bansal, S.; Lam, A. M.; Seibel, W.; Neilson, S.; Furman, P. A.; Sofia, M. J. *J. Med. Chem.* **2014**, *57*, 2136. b) Yamashita, T.; Hatamoto, E.; Takenaka, H.; Kojima, Y.; Inoue, Y., Gemba, M.; Yasuda, M. *Chem. Pharm. Bull. (Tokyo)* **1996**, *44* (4), 856.

¹¹³ Korch, K. M.; Eidamshaus, C.; Behenna, D. C.; Nam, S.; Horne, D.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2015**, *54* (1), 179

marcfortines,¹¹⁴ pseudotheonamides,¹¹⁵ and malbrancheamides¹¹⁶ (Scheme 46).



Scheme 46. Bioactive compounds containing the piperazin-2-one moiety.

¹¹⁴ Prangé, T.; Billion, M. A.; Vuilhorgne, M.; Pascard, C.; Polonsky, J. *Tetrahedron Lett.* **1981**, 22 (21), 1977

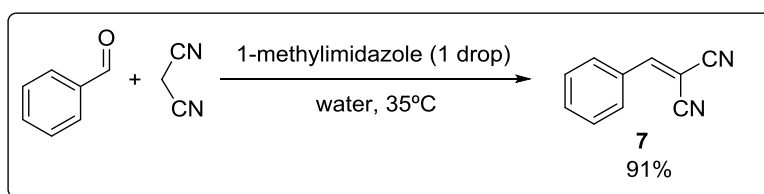
¹¹⁵ Nakao, Y.; Masuda, A.; Matsunaga, S.; Fusetani, N. *J. Am. Chem. Soc.* **1999**, 121 (11), 2425.

¹¹⁶ Martínez-Luis, S.; Rodríguez, R.; Acevedo, L.; González, M. C.; Lira-Rocha, A.; Mata, R. *Tetrahedron* **2006**, 62 (8), 1817.

3. Results and Discussion

3.1. Synthesis of Precursor 7

2-Benzylidenemalononitrile **7** was selected as the compound for the optimization study. It was easily prepared according to literature¹¹⁷ from benzaldehyde and malononitrile via Knoevenagel condensation reaction catalyzed by 1-methylimidazole in water (Scheme 47). The reaction underwent cleanly and fast, affording the pure alkene **7** as white solid which was isolated from the reaction mixture by simply filtration when the reaction was complete (ca. 1 hour).



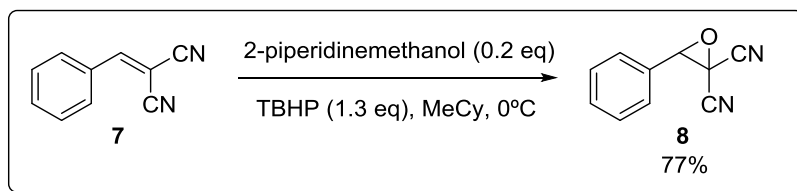
Scheme 47. Synthesis of 2-benzylidenemalononitrile **7**.

3.2. Synthesis of Racemic 8

First of all, before starting with the optimization for the asymmetric epoxidation, compound **7** was epoxidized under racemic conditions to identify compound **8** by NMR and to split the enantiomeric peaks by HPLC. A general methodology, which consisted in a nucleophilic epoxidation with TBHP (1.3 eq) as oxidizing agent and 2-piperidinemethanol (0.2 eq) as catalyst, afforded epoxide **8** from alkene **7** within 2 hours. The same methodology was further applied to all reported racemic epoxides (Scheme 48).¹¹⁸

¹¹⁷ Pande, A.; Ganesan, K.; Jain, A. K.; Gupta, P. K.; Malhotra, R. C. *Org. Proc. Res. Dev.* **2005**, *9* (2), 133.

¹¹⁸ Meninno, S.; Vidal-Albalat, A.; Lattanzi, A. *Org. Lett.* **2015**, *17* (17), 4348.

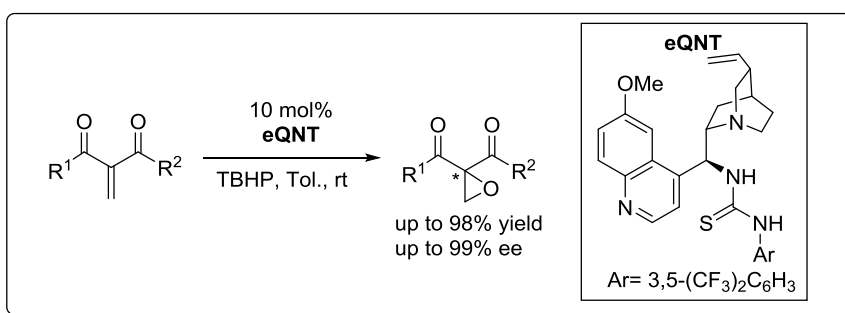


Scheme 48. Synthesis of 3-phenyloxirane-2,2-dicarbonitrile **8**.

The racemic epoxide **8** was purified by flash chromatography, and the corresponding enantiomers were successfully separated by HPLC with Chiralcel OD-H column, 90:10 *n*-hexane:2-propanol, 1 mL/min, 254 nm; resulting in retention times of 9.8 min and 10.9 min. There is more detailed information in the experimental section of this chapter.

3.3. Synthesis of the Catalysts 10 and 12a-e

For the present work, it was envisioned that bifunctional catalysts bearing double H-bonding donors would have been effective in engaging an H-bonding network with alkylidenemalononitrile. This idea was supported by recent published research performed by Lattanzi's group, which disclosed the ability of cinchona derived thioureas, namely *epi*-quinine thiourea (**eQNT**) to catalyze the enantioselective nucleophilic epoxidation of electron-poor 1,1-disubstituted terminal alkenes with TBHP (Scheme 49).¹¹⁹



Scheme 49. Asymmetric epoxidation of terminal alkenes.

Many cinchona derived ureas, thioureas and squaramides have been described as bifunctional organocatalysts for several reactions such as

¹¹⁹ Russo, A.; Galdi, G.; Croce, G.; Lattanzi, A. *Chem. Eur. J.* **2012**, *18* (20), 6152.

Michael, aldol and Strecker-type reactions.¹²⁰ Inspired by the plenitude of examples in the literature, catalysts **10** and **12a-e** (Figure 11) were designed in order to test them as organocatalysts for the asymmetric epoxidation of **7** and furtherly, to elucidate how changes in the stereochemistry and the structure affect the conversion and the enantiomeric ratio.

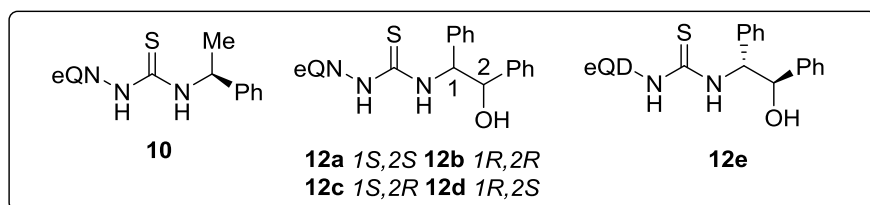


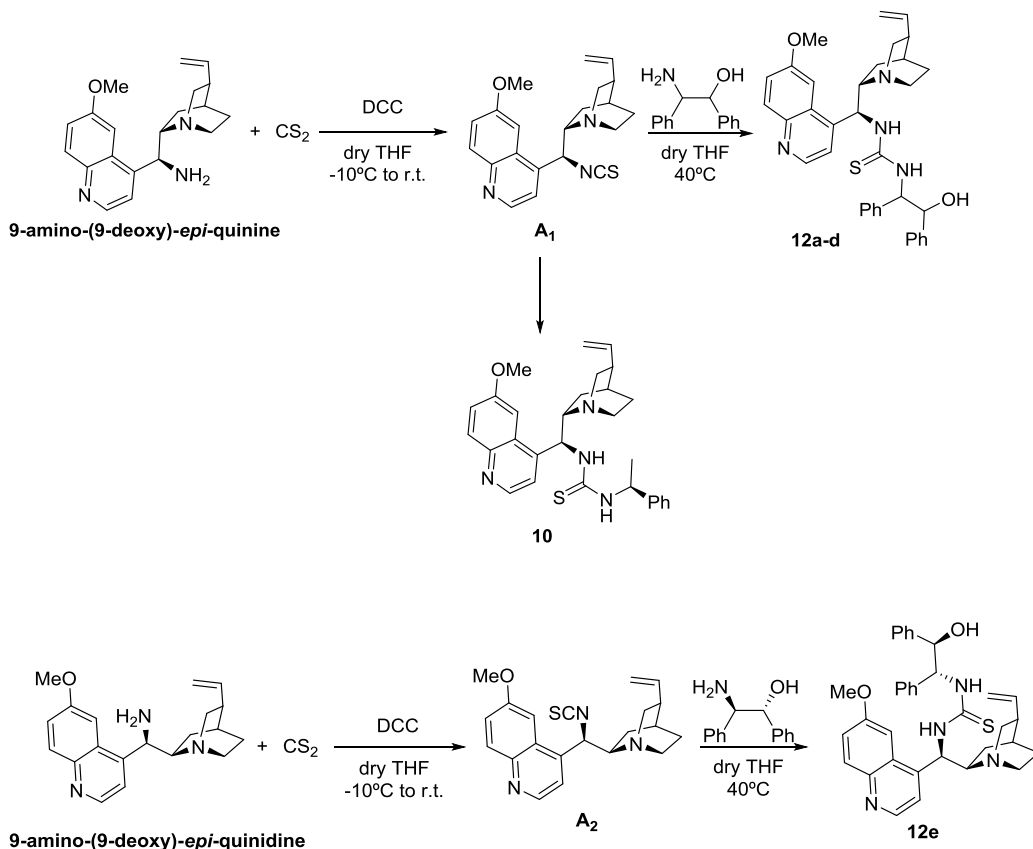
Figure 11. Catalysts **10** and **12a-e**.

Catalyst **12c** is a known compound described by Ma *et al.*¹²¹ and the rest of the aforementioned compounds were prepared in a similar procedure. Starting from quinine and quinidine, a Mitsunobu reaction was performed to obtain the 9-amino-(9-deoxy)-*epi*-quinine and 9-amino-(9-deoxy)-*epi*-quinidine.¹²² Then, both were activated with DCC and treated with carbon disulfide to obtain the isothiocyanate intermediates **A₁** and **A₂**, which were finally converted into catalysts **12a-e** when the appropriate chiral 2-amino-1,2-diphenylethanol was used, or α -(*S*)-methylbenzylamine in the case of catalyst **10** (Scheme 50). Full description of the synthesis is available on the experimental section of the current chapter.

¹²⁰ a) For a mini-review on cinchona derived ureas and thioureas: Connon, S. J. *Chem. Commun.* **2008**, (22) 2499. b) Li, N.; Liu, Z.; Huang, X.; Zhang, J.; Chen, X.; Wang, Y.; Wang, X. *RSC Adv.* **2013**, *3*, 9154. c) Bassas, O.; Huuskonen, J.; Rissanen, K.; Koskinen, A. M. P. *Eur. J. Org. Chem.* **2009**, 1340.

¹²¹ Ma, H.; Matsuzaki, K.; Yang, Y.-D.; Tokunaga, E.; Nakane, D.; Ozawa, T.; Masuda, H.; Shibata, N. *Chem. Commun.* **2013**, 49 (95), 11206

¹²² Cassani, C.; Martín-Rapún, R.; Arceo, E.; Bravo, F.; Melchiorre, P. *Nat. Protoc.* **2013**, *8* (2), 325.

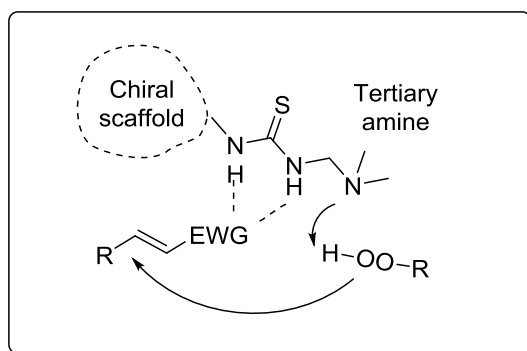


Scheme 50. Synthetic route to catalysts **10** and **12a-e** from quinine and quinidine amino-derivatives.

3.4. Screening of the Catalysts

As previously intensely described in the general introduction chapter of this PhD Thesis, bifunctional organocatalysis follows this general mechanism: a basic moiety in the organocatalyst structure (usually a tertiary amine) deprotonates the pronucleophile while a non-covalent H-bonding interaction activates the electrophile, forming a transition state which controls the enantioselectivity by the chiral scaffold of the catalyst (Scheme 51). According to that, initial experiments were performed with phenylidenemalononitrile **7** and TBHP in toluene at room temperature screening different organocatalysts at a 10 mol % loading (Table 4). We were pleased to observe that *epi*-quinine thiourea

eQNT satisfactorily catalyzed the reaction affording the epoxide with a 67.5:32.5 er value (entry 1). The corresponding urea **eQNU** and squaramide **eQNS** proved to be slightly less efficient (entries 2 and 3, respectively). One possible explanation can be found in the literature, since some studies have recently examined the structure-activity-stereoselectivity regarding the acidity of (thio)urea moiety in the catalyst for the Michael reaction.¹²³ In general, it was found that the more acid the thiourea is, the more catalytic effect is observed, both in terms of conversion and enantioselectivity.¹²³ However, that shouldn't be taken as the only factor in consideration, since pKa of **eQNT** is 12.4¹²³, higher than the pKa of **eQNS** which is 10.5¹²³. The observed results for the tested catalysts cannot be explained only by invoking acidity and strongness of H-bonds. Other structural modifications of the catalyst can have a great impact on activity and enantioselectivity.



Scheme 50. Common transition state rationalization

At that point, considering that the thiourea based catalyst gave better results than urea and squaramide, other thiourea amine catalysts were prepared. First, other easily available thiourea catalysts derived from different cinchona alkaloids, *i.e.*, cinchonidine, hydroquinine and quinidine were tested. The epoxidation reactions performed with *epi*-cinchonidine thiourea **eCDT** and *epi*-hydroquinine thiourea **eHQNT**

¹²³ a) Li, X.; Deng, H.; Zhang, B.; Li, J.; Zhang, L.; Luo, S.; Cheng, J. P. *Chem. Eur. J.* **2010**, *16* (2), 450. b) Jakab, G.; Tancon, C.; Zhang, Z.; Lippert, K. M.; Schreiner, P. R. *Org. Lett.* **2012**, *14* (7), 1724 c) Ni, X.; Li, X.; Wang, Z.; Cheng, J. P. *Org. Lett.* **2014**, *16* (6), 1786

were less effective (entries 4 and 5), whereas the pseudoenantiomeric *epi*-quinidine thiourea **eQDT** afforded the opposite enantiomer of the epoxide in high yield but with lower enantioselectivity (entry 6).

Catalyst **9**, where the thiourea moiety is positioned in the quinoline ring, was tested in order to check the effect of spatial distribution of functional groups over the quinine's core in terms of reactivity and enantioselectivity. Unfortunately, it proved to be the worst in the series, indicating that the quinuclidine nitrogen and hydrogen bonding donating groups are catalytically more effective when located in proximity (entry 7).

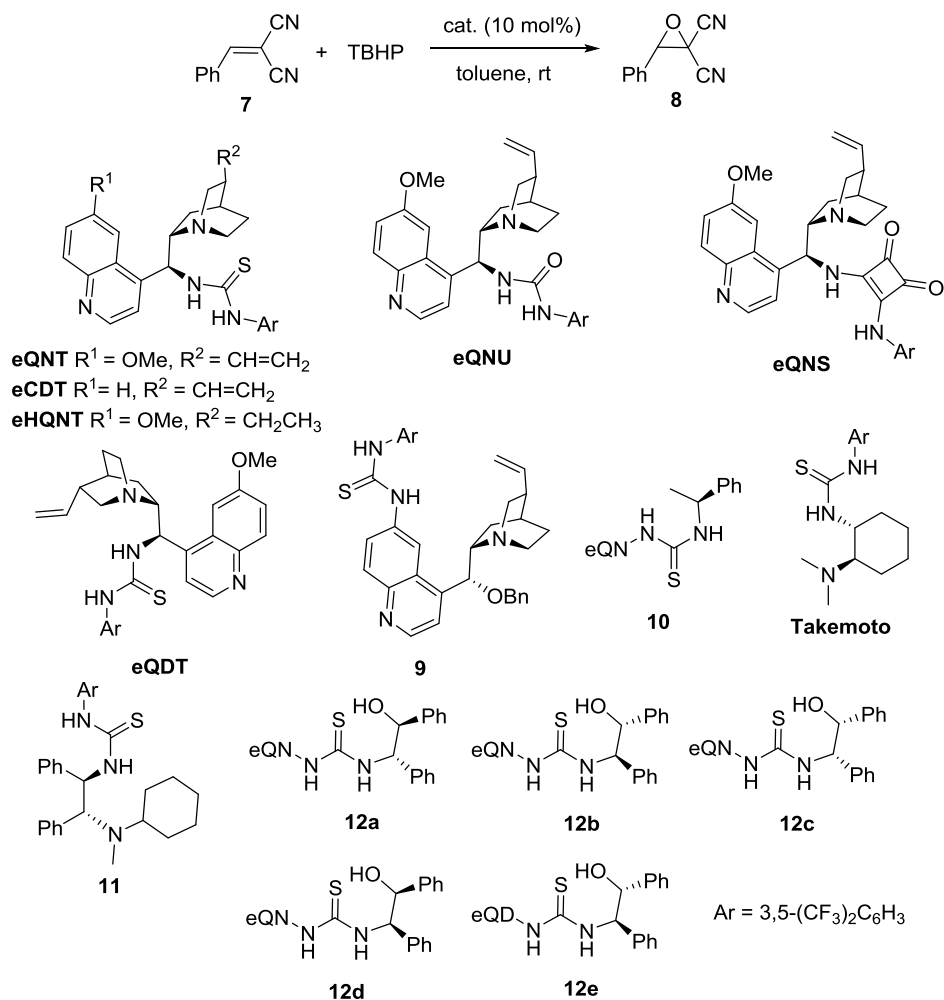
Previously described catalysts have in common the achiral 3,5-bis(trifluoromethyl)-phenyl group attached to thiourea moiety. Derived *epi*-quinine catalyst **10** was designed to test its activity when the aromatic ring is replaced with a chiral fragment. The conversion was good (72%) in a relatively short period of time. However, the presence of a chiral amine moiety was detrimental for the enantioselectivity (entry 8). These results clearly suggested the involvement of mismatching effects on affecting the catalytic activity. Structurally different thiourea amines such as Takemoto's bifunctional catalyst and **11** (entries 9 and 10) did not improve the result obtained with **eQNT** (entry 1).

Given the reactive nature of alkylidene malononitrile, we thought improvements might be achieved using amine thioureas bearing multiple hydrogen-bonding donors incorporating chiral aminoalcohol moieties.¹²⁴ The catalytic activity of *epi*-quinine derived thioureas **12a–e** was then investigated under the standard conditions (entries 11 – 15). Pleasingly for us, promoter **12a** (entry 11) proved to be more active and enantioselective than **eQNT** (entry 1), with the best matching effect displayed by the (*S,S*)-amino alcohol portion, giving epoxide **8** in 90% yield and 77.2:22.8 er. The absolute configuration of

¹²⁴ For a recent review: Fang, X.; Wang, C.-J. *Chem. Commun.* **2015**, 51 (7), 1185

the amino alcohol played an important role as the opposite enantiomer of **8** was obtained when passing from catalyst **12a** to **12b**, containing the enantiomeric amino alcohol moiety (entries 11 and 12), which was translated in a great loss of enantioselectivity. The corresponding amino alcohol diastereomers **12c** and **12d** showed also diverse results (entries 13 and 14). Curiously **12c**, having the opposite absolute configuration of the carbinol than **12a**, gave a similar result in yield and er (entry 13). On the other hand, catalyst **12d**, bearing the same enantiomeric amino alcohol portion than that used for **12c**, afforded almost a racemic product (entry 14). The pseudoenantiomeric catalyst **12e** (with respect to **12a**) nicely afforded the opposite enantiomer of product **7** with the same level of enantioselectivity (entry 15).

Table 4. Screening of Catalysts in the Asymmetric Epoxidation of Alkene 7^a



Entry	Catalyst	Time (h)	Yield (%) ^b	er (%) ^c
1	eQNT	15	58	67.5:32.5
2	eQNU	16	48	65.4:34.6
3 ^d	eQNS	40	70	62.2:37.8
4	eCDT	21	57	59.5:40.5

5	eHQNT	24	63	56.2:43.8
6^e	eQDT	21	84	44.9:55.1
7	9	29	43	54.2:45.8
8	10	15	72	52.4:47.6
9^e	Takemoto	24	55	44.3:55.7
10^e	11	24	34	31.3:68.7
11	12a	22	90	77.2:22.8
12^e	12b	21	80	42.8:57.2
13	12c	18	75	71:29
14^e	12d	17	74	49.8:50.2
15^e	12e	16	87	23:77

^aReactions were carried out at 0.1 mmol scale of **7** (C 0.2 M) using TBHP (1.2 equiv).

^bDetermined by ¹H NMR analysis with 1,3,5-(MeO)₃C₆H₃ as an internal standard.

^cDetermined by chiral HPLC analysis. ^dReaction carried out with 5 mol % of **eQNS** in CHCl₃. ^eThe opposite enantiomer was preferentially obtained.

On the basis of experimental data, a plausible transition state model for the oxa-Michael step of the nucleophilic epoxidation is proposed (Figure 12). The alkylidenemalononitrile is activated and oriented by a H-bonding network of the thiourea NH and the OH bonds. A possible transition state where each cyano group is H-bonded by a single NH of the thiourea moiety was not considered, since Qi *et al.* recently reported a DFT study that showed the latter interaction to be less plausible.¹²⁵

¹²⁵ Qi, Z.-H.; Zhang, Y.; Ruan, G.-Y.; Zhang, Y.; Wang, Y.; Wang, X.-W. *RSC Adv.* **2015**, *5* (43), 34314.

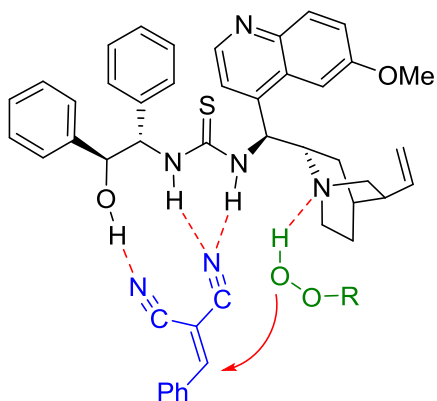


Figure 12. Proposed transition state for the enantioselective epoxidation.

Compound **12a** was chosen as the best performing catalyst and an extensive screening of the reaction conditions such as solvent, oxidant and temperature, was designed to further optimize the process. The screening of conditions won't be reported in this Thesis since it was performed by Dr. Sara Meninno and the results are fully available on the Supporting Information of the published article.¹¹⁸

4. Conclusions

- Extensive screening of catalysts for the asymmetric epoxidation of 2-benzylidenemalononitrile **7** was performed.
- Asymmetric epoxidation of **7** was successfully achieved in great yield and er with catalyst **12a** in mild conditions, which opens the door to further optimization of the reaction parameters.
- A transition state was proposed to explain activity and enantioselectivity according to the obtained experimental data.

5. Experimental Section

General Methods

All reactions requiring dry or inert conditions were conducted in flame-dried glassware under a positive pressure of nitrogen. THF and DCM were freshly distilled prior to use respectively over metallic Na and calcium hydride and stored under nitrogen, all other solvents were dried over molecular sieves. Molecular sieves (Aldrich Molecular Sieves, 3 Å, 1.6 mm pellets) were activated under vacuum at 200 °C overnight. Reactions were monitored by thin layer chromatography (TLC) on Macherey-Nagel pre-coated silica gel plates (0.25 mm) and visualized by UV light and, when necessary, by phosphomolybdic acid, ninhydrin, KMnO_4 staining solutions or I_2 vapor. Flash chromatography was performed on Merck silica gel (60, particle size: 0.040–0.063 mm). ^1H NMR and ^{13}C NMR spectra were recorded on Bruker Avance-400 spectrometer, Bruker Avance-300 or Bruker Avance-250 spectrometer in CDCl_3 or methanol- d_4 as solvent at room temperature. Chemical shifts for protons are reported using residual solvent protons (^1H NMR: $\delta = 7.26$ ppm for CDCl_3 , $\delta = 3.33$ ppm for methanol- d_4) as internal standard. Carbon spectra were referenced to the shift of the ^{13}C signal of CDCl_3 ($\delta = 77.0$ ppm), CD_3OD ($\delta = 49.0$ ppm).

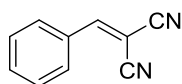
The following abbreviations are used to indicate the multiplicity in NMR spectra: (s) singlet; (d) doublet; (t) triplet; (q) quartet; (dd) double doublet; (ddd) doublet of doublet of doublet; (dt) doublet of triplets; (td) triplet of doublets; (m) multiplet; (bs) broad signal. FTIR spectra were recorded as thin films on KBr plates using Bruker Tensor 27 spectrometer and absorption maxima are reported in wavenumber (cm^{-1}). ESI-MS was performed using a Bio-Q triple quadrupole mass spectrometer (Micromass, Manchester, UK) equipped with an electrospray ion source. Elemental analyses were carried out by using Flash EA 1112 (Thermo Electron Corporation) analyzer. Melting points

were measured with a Stuart Model SMP 30 melting point apparatus and are uncorrected.

Experimental Procedures

General experimental procedure for the synthesis of 2-benzylidenemalononitrile 7.

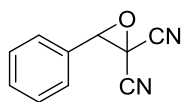
To a mixture of malononitrile (1.00 g, 0.015 mol) and 1-methylimidazole (0.01 g, 1 mol %) in water (8.2 mL) at 35 °C, benzaldehyde (0.015 mol) was added with constant stirring. A crystalline white solid was obtained, separated by filtration and dried under vacuum at room temperature. The product was used without further purification.



2-Benzylidenemalononitrile (7). White solid, 2.08 g, 90% yield. **mp** 83°C [lit. 82-84°C].¹²⁶ NMR spectra matched with that reported in the literature.¹¹⁷

General Experimental Procedure for the Synthesis of Racemic epoxide 8.

2-Benzylidenemalononitrile **7** (1 mmol) in anhydrous toluene (10 mL), 2-piperidinemethanol (23 mg, 0.2 mmol) followed by TBHP (~5.5 M in decane, 240 μ L, 1.3 mmol) were added. The reaction was stirred at 0 °C for 1.5 hours. Product **8** was isolated by flash chromatography (eluting from PE/ ethyl acetate 100/1 to 90/10).



3-phenyloxirane-2,2-dicarbonitrile. White solid, 146 mg, 86% yield. **mp** 50-52 °C. **FTIR** ν (KBr)/ cm^{-1} 3069, 3039, 2257, 1498, 1457, 1399, 1382, 1318, 1298, 1268, 1192, 893, 875, 762, 697, 637, 620. **¹H NMR** (CDCl_3 , 400 MHz): δ 7.56-7.40 (m, 5H), 4.71 (s, 1H). **¹³C NMR** (CDCl_3 , 100 MHz): δ 131.4, 129.1, 127.5, 126.8, 111.6,

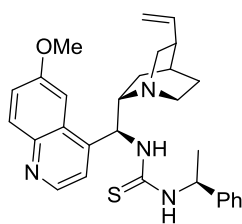
¹²⁶ Gupta, P.; Kour, M.; Paul, S.; Clark, J. H. *RSC Adv.* **2014**, *4*, 7461.

110.2, 65.8, 41.7. Elemental analysis calcd (%) for $C_{10}H_6N_2O$: C, 70.58; H, 3.55; N, 16.46; found C, 70.84; H, 3.64; N, 16.30. HPLC analysis with Chiralcel OD-H column, 90:10 *n*-hexane:2-propanol, 1 mL/min, 254 nm; $t_{R1} = 9.8$ min, $t_{R2} = 10.9$ min.

General Experimental Procedure for the Synthesis of Catalysts 10, 12a-e

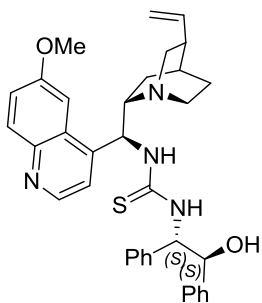
Precursors A_1^{120} and A_2^{120} are known compounds and were prepared according to the literature.

To a stirred solution of A_1 or A_2 (401 mg, 1.1 mmol) under nitrogen atmosphere in dry THF (2 mL) a solution of appropriate chiral 2-amino-1,2-diphenylethanol or methylbenzylamine (1mmol) in dry THF (2 mL) was added *via* syringe. The mixture was stirred at 40 °C for 24-72 h, monitored by TLC (eluent diethyl ether/MeOH 8/2). The products **12a-e** were isolated by flash chromatography (eluent: diethyl ether to diethyl ether /MeOH 90/10). Catalyst **12c** is a known compound and spectral data were consistent with those in the literature.

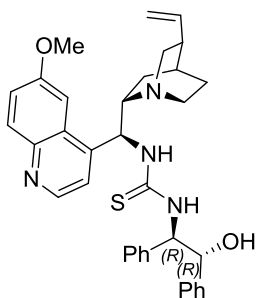


Thiourea derived from quinine and *S*-(-)- α -methylbenzylamine. **1-((S)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)-3-((S)-1-phenylethyl)thiourea (10)**. Pale yellow solid, 62.0 mg, 79% yield (the reaction was carried out at 0.16 mmol scale of A_1). **mp** 86.7-90.0 °C. $[\alpha]_D^{26} = -120.9$ (*c* 0.55, $CHCl_3$). **FTIR** ν_{max} (KBr)/ cm^{-1} 2927, 1622, 1534, 1508, 1474, 1453, 1432, 1347, 1262, 1242, 1228, 1083, 1030, 918, 853, 759, 700. **1H NMR** ($CDCl_3$, 400 MHz): δ 8.74 (d, 1H, $J = 4.5$ Hz), 8.03 (d, 1H, $J = 9.2$ Hz), 7.58 (s, 1H), 7.41-7.22 (m, 7H), 6.76 (bs, 1H), 5.66-5.55 (m, 1H), 5.29 (bs, 1H), 4.98-4.87 (m, 3H), 3.94 (s, 3H), 3.04- 2.62 (m, 3H), 2.57-2.42 (m, 1H), 2.25-2.12 (m, 1H), 1.64-1.57 (m, 1H), 1.55-1.45 (m,

2H), 1.39 (d, 3H, $J = 6.4$ Hz), 1.34-1.21 (m, 2H), 0.95-0.90 (m, 1H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 181.9, 157.8, 147.7, 144.8, 142.5, 140.7, 131.9, 128.9, 128.5, 127.7, 126.8, 126.0, 125.7, 121.7, 114.8, 101.9, 55.7, 55.1, 54.4, 51.3, 40.2, 39.2, 30.3, 29.7, 27.5, 27.2, 25.7, 25.5. MS (ESI m/z) 487.5 [$\text{M}+\text{H}^+$, 100%].

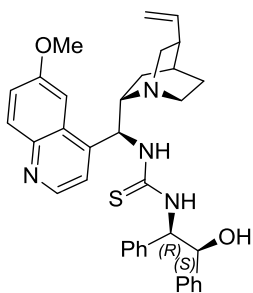


Thiourea derived from quinine and (1*S*,2*S*)-2-amino-1,2-diphenylethanol. **1-((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)-3-((*S*)-(6-methoxyquino-lin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)thiourea (12a)**. White solid, 463 mg, 80% yield (the reaction was carried out at 1.1 mmol scale of **A**₁). mp 156.5-158.2 °C. $[\alpha]_{\text{D}}^{27} = -117.0$ (c 0.56, CHCl_3). FTIR ν_{max} (KBr)/ cm^{-1} 3456, 2948, 2866, 1623, 1510, 1474, 1454, 1263, 1242, 1228, 1029, 775, 701. ^1H NMR (CDCl_3 , 400 MHz): δ 8.54 (bs, 1H), 7.96 (d, 1H, $J = 9.4$ Hz), 7.69 (s, 1H), 7.36 (d, 1H, $J = 8.8$ Hz), 7.32-6.77 (partially overlapped by CDCl_3 , m, 12H), 5.64-5.53 (m, 1H) partially overlapped with 5.70 (br, 1H) and 5.39 (br, 1H), 4.94-4.84 (m, 3H), 3.94 (s, 3H), 3.18 (br, 1H), 2.91 (br, 1H), 2.58-2.36 (m, 2H), 2.26-2.13 (m, 1H), 1.87 (br, 1H), 1.64-1.46 (m, 3H), 1.32-1.20 (m, 2H), 0.90-0.77 (m, 1H). ^{13}C NMR (CD_3OD , 100 MHz): δ 184.2, 159.6, 148.1, 145.0, 143.2, 142.1, 131.0, 130.1, 129.0, 128.6, 128.2, 127.5, 123.9, 120.8, 115.2, 104.3, 77.4, 65.0, 61.2, 56.6, 56.4, 42.8, 40.4, 28.7, 28.1, 26.8. MS (ESI m/z) 579.8 [$\text{M}+\text{H}^+$, 100%].



Thiourea derived from quinine and (1*R*,2*R*)-2-amino-1,2-diphenylethanol.

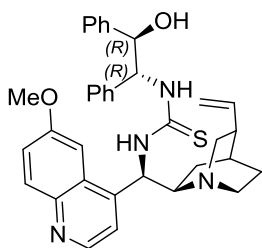
1-((1*R*,2*R*)-2-hydroxy-1,2-diphenylethyl)-3-((*S*)-(6-methoxyquino-*lin*-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)thiourea (12b). Yellow solid, 54.1 mg, 68% yield (the reaction was carried out at 0.137 mmol scale of **A**₁). **mp** 119.3 - 122.6 °C. $[\alpha]_{\text{D}}^{27} = -62.8$ (*c* 0.51, CHCl₃). **FTIR** ν_{max} (KBr)/cm⁻¹ 3445, 2931, 2864, 1624, 1541, 1508, 1474, 1454, 1262, 1242, 1229, 1029, 757, 700. **¹H NMR** (CDCl₃, 400 MHz): δ 8.70 (d, 1H, *J* = 4.4 Hz), 8.01 (d, 1H, *J* = 9.1 Hz), 7.61 (s, 1H), 7.52 (br, 1H), 7.38 (dd, 1H, *J* = 9.3, 2.0 Hz), 7.30 - 7.27 (m, 1H), 7.25-7.15 (m, 7H), 7.13-7.02 (m, 4H), 5.67-5.55 (m, 1H) partially overlapped with 5.38 (bs, 2H), 4.99-4.88 (m, 2H), 4.81 (d, 1H, *J* = 5.8 Hz), 3.90 (s, 3H), 3.33-2.88 (m, 3H), 2.67-2.51 (m, 1H), 2.28-2.16 (m, 1H), 1.87 (br, 1H), 1.68-1.47 (m, 3H), 1.36-1.17 (m, 2H), 0.94-0.76 (m, 1H). **¹³C NMR** (CD₃OD, 100 MHz): δ 184.0, 159.5, 148.1, 145.0, 142.9, 142.3, 141.3, 131.1, 130.0, 129.0, 128.9, 128.7, 128.4, 128.1, 128.0, 123.7, 121.2, 115.1, 104.1, 78.1, 65.7, 61.7, 56.6, 56.5, 42.7, 40.6, 28.7, 28.3, 26.9. **MS** (ESI *m/z*) 579.7 [M+H⁺, 21%].



Thiourea derived from quinine and (1*R*,2*S*)-2-Amino-1,2-diphenylethanol.

1-((1*R*,2*S*)-2-hydroxy-1,2-diphenylethyl)-3-((*S*)-(6-methoxyquino-*lin*-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-

vinylquinuclidin-2-yl)methyl)thiourea (12d). White solid, 80.8 mg, 85% yield (the reaction was carried out at 0.164 mmol scale of **A**₁). **mp** 130.9-132.6 °C. $[\alpha]_{\text{D}}^{27} = -63.6$ (*c* 0.57, CHCl₃). **FTIR** ν_{max} (KBr)/cm⁻¹ 3443, 2944, 2865, 1623, 1538, 1511, 1475, 1453, 1262, 1242, 1229, 1029, 755, 705. **¹H NMR** (CDCl₃, 400 MHz): δ 8.76 (d, 1H, *J* = 4.5 Hz), 8.05 (d, 1H, *J* = 9.2 Hz), 7.61 (bs, 1H), 7.58-7.38 (m, 3H), 7.23-7.11 (m, 5H), 7.06 (s, 2H), 6.94-6.87 (m, 2H), 6.87-6.80 (m, 2H), 5.61 (ddd, 1H, *J* = 17.2, 10.0, 7.4 Hz), 5.30 (bs, 2H), 5.06 (bs, 1H), 4.96-4.89 (m, 2H), 3.94 (s, 3H), 3.01 (br, 1H), 2.81 (br, 1H), 2.67-2.49 (m, 1H), 2.26-2.14 (m, 1H), 1.79-1.58 (m, 5H), 1.58-1.46 (m, 1H), 1.39-1.28 (m, 1H), 0.97-0.88 (m, 1H). **¹³C NMR** (CD₃OD, 100 MHz): δ 183.3, 159.6, 148.2, 145.1, 142.5, 142.4, 138.9, 131.0, 130.1, 129.6, 129.1, 129.0, 128.7, 128.5, 128.1, 127.5, 123.8, 121.0, 115.1, 104.2, 79.5, 76.2, 65.0, 61.8, 56.8, 56.6, 42.9, 40.6, 28.8, 28.4, 27.0. **MS** (ESI *m/z*) 579.8 [M+H⁺, 100%].



Thiourea derived from quinidine and (1*R*,2*R*)-2-Amino-1,2-diphenylethanol. **1-((1*R*,2*R*)-2-hydroxy-1,2-diphenylethyl)-3-((*R*)-(6-methoxyquino-lin-4-yl)((1*S*,2*R*,4*S*,5*R*)-5-**

vinylquinuclidin-2-yl)methyl)thiourea (12e). White solid, 53.5 mg, 67% yield (the reaction was carried out at 0.137 mmol scale of **A**₂). **mp** 135.6-139.3 °C. $[\alpha]_{\text{D}}^{27} = +184.6$ (*c* 0.55, CHCl₃). **FTIR** ν_{max} (KBr)/cm⁻¹ 3449, 2940, 2872, 1623, 1534, 1509, 1474, 1455, 1433, 1242, 1227, 1029, 754, 701. **¹H NMR** (CDCl₃, 300 MHz): δ 8.56 (bs, 1H), 7.96 (d, 1H, *J* = 9.2 Hz), 7.61 (bs, 1H), 7.45-7.00 (partially overlapped by CDCl₃, m, 11H), 6.79 (br, 2H), 5.84 (ddd, 1H, *J* = 17.3, 10.4, 6.0 Hz), 5.42 (br, 2H) partially overlapped with 5.19-5.09 (m, 2H), 4.81 (d, 1H, *J* = 5.9 Hz), 3.96 (s, 3H), 3.26-2.67 (m, 4H), 2.35-2.17 (m, 1H), 1.73-1.38 (m, 4H), 1.31-1.16 (m, 2H), 1.01-0.77 (m, 1H). **¹³C NMR**

(CD₃OD, 75 MHz): δ 189.1, 159.6, 148.1, 145.0, 143.8, 143.2, 141.2, 131.0, 130.1, 129.0, 128.7, 128.2, 127.5, 124.1, 120.0, 115.5, 104.1, 77.4, 65.2, 65.0, 61.4, 56.6, 40.9, 39.8, 28.6, 26.8, 26.3. **MS** (ESI m/z) 579.6 [M+H⁺, 100%].

Chapter 4

Asymmetric Epoxidation of Nitroalkenes

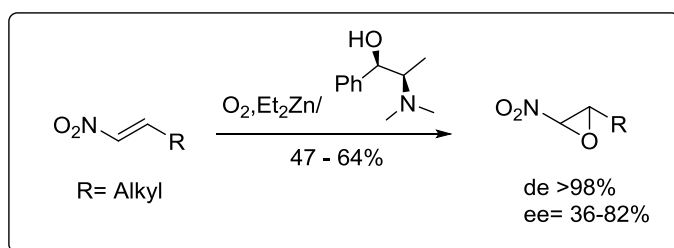
1. Objectives

The main goal of this work is the organocatalytic asymmetric epoxidation of nitroalkenes, which can be summarized as follows:

- The study of diverse organocatalytic epoxidation systems and selection of the most suitable in terms of chemical yield, ee, and operability.
- The study and screening of solvents and conditions such as temperature, concentration, etc., to achieve the optimum media for asymmetric epoxidation.
- The rational design and synthesis of diverse catalysts to achieve the asymmetric epoxidation of nitroalkenes.
- The proof-based elucidation of a transition state which explains catalytic activity and enantioselectivity.

2. Results and Discussion

Since some time ago, our group has shown interest in nitroepoxides as useful synthons for organic synthesis.¹²⁷ Few examples of diastereoselective epoxidation of nitroalkenes have been reported¹²⁸ and as far as we know only one methodology, described by Enders' group, is reported in the literature for the enantioselective epoxidation of nitroalkenes in moderate chemical yields and moderate to good ee.¹²⁹ Still, in the aforementioned example, the scope of the reaction is limited to the synthesis of 3-alkyl-2-nitrooxiranes and with high variations on ee depending on the substrate (Scheme 51). There's another example reported by Julià and Colonna, using a chiral polypeptide as a catalyst, but the reported enantioselectivity barely reached a 7% ee for the corresponding nitroepoxides.¹³⁰



Scheme 51. Enders' asymmetric epoxidation of nitroalkenes.

More recently, S. Mennino *et al.* have reported the synthesis of enantioenriched nitroepoxides via catalytic enantioselective aminolytic kinetic resolution (AKR).¹³¹ In their approach, ring-opening reaction of racemic α -nitroepoxides with aniline in the presence of a bifunctional thiourea catalyst affords unreacted epoxides in up to 95% ee (Scheme

¹²⁷ Agut, J.; Vidal, A.; Rodríguez, S.; González, F. V. *J. Org. Chem.* **2013**, 78 (11), 5717.

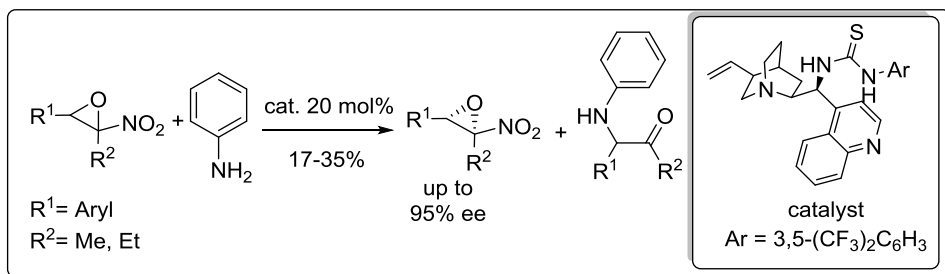
¹²⁸ a) Jain, A.; Rodríguez, S.; López, I.; González, F. V. *Tetrahedron* **2009**, 65 (40), 8362. b) Jackson, R. F. W.; Palmer, N. J.; Wythes, M. J.; Clegg, S. W. *J. Org. Chem.* **1995**, 60 (5), 6431.

¹²⁹ Enders, D.; Kramps, L.; Zhu, J. *Tetrahedron: Asymmetry* **1998**, 9 (22), 3959.

¹³⁰ Julià, S.; Guixer, J.; Masana, J.; Rocas, J.; Colonna, S.; Annuziata, R.; Molinari, H. *J. Chem. Soc. Perkin Trans. I* **1982**, 1317.

¹³¹ Mennino, S.; Napolitano, L.; Lattanzi, A. *Catal. Sci. Technol.* **2015**, 5 (1), 124.

52). Although it is an interesting approach to obtain enantioenriched nitroepoxides, the main inconvenience of this methodology resides in the kinetic resolution itself since it limits the yield to a maximum of 50%. An asymmetric epoxidation with high chemical and enantioselective yields would be more desirable.



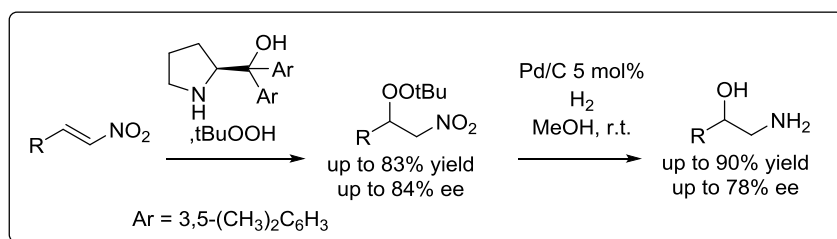
Scheme 52. Asymmetric kinetic resolution of nitroepoxides.

2.1. Early Stage Experiments

As described in Chapter 1, many methodologies have been reported for the synthesis of epoxides from electron-deficient olefins. When facing the nitroalkenes, we envisioned their organocatalytic epoxidation by oxa-Michael addition of peroxides to nitroalkenes followed by ring-closure, catalyzed by diarylprolinol derivatives since they were previously reported as effective catalysts for epoxidation of enones.¹³² However, Russo and Lattanzi already tested that catalytic system for the epoxidation of nitroalkenes and they found that the system was ineffective for the epoxidation. Instead, they found that the reaction stopped at oxa-Michael addition step, affording asymmetric peroxides which could be further transformed into 1,2-aminoalcohols (Scheme 53). Developing that catalytic methodology for the enantioselective β -addition of peroxides to nitroalkenes, they afforded the corresponding peroxides in high yields (up to 83%) and ee (up to 84%), and the

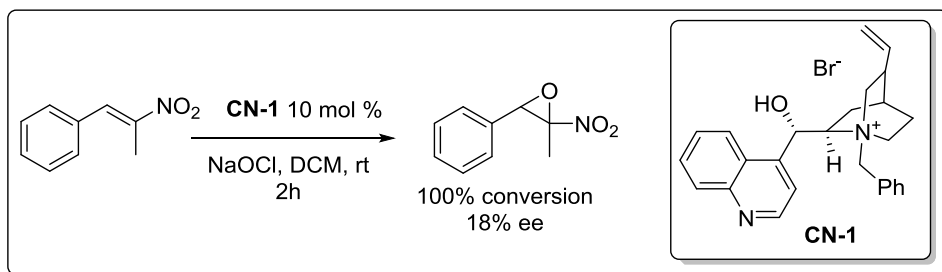
¹³² a) Lattanzi, A. *Org. Lett.* **2005**, 7 (13), 2579. b) Lattanzi, A. *Adv. Synth. Catal.* **2006**, 348 (3), 339.

corresponding 1,2-aminoalcohols also in high chemical yields but with a bit loss of enantioselectivity (Scheme 53).¹³³



Scheme 53. Epoxidation attempts with diphenyl prolinol and *ter*-butyl peroxide.

Due to the present limitations for the epoxidation of nitroalkenes by non-covalent bifunctional catalysts, we decided to change strategy into phase transfer catalysis. Initial tests involved the epoxidation of *trans*- β -methyl- β -nitrostyrene using *N*-benzyl cinchoninium bromide (**CN-1**) as a catalyst (10 mol % load) and an oxidant (sodium hypochlorite, hydrogen peroxide and TBHP) in DCM (Scheme 54). Gratifyingly, reaction with sodium hypochlorite afforded nitroepoxide in full conversion within two hours, and an ee of 18%. This result encouraged us to optimize conditions in order to develop a phase transfer catalytic system able to epoxidize a variety of nitroalkenes in high chemical yields and ee.



Scheme 54. Phase transfer catalyzed epoxidation of *trans*- β -methyl- β -nitrostyrene.

2.2. Optimization Reactions

An optimization study of the reaction was carried out by modifying the following parameters: amount of oxidant, reaction solvent,

¹³³ Russo, A.; Lattanzi, A. *Adv. Synth. Catal.* **2008**, 350 (13), 1991.

organic/aqueous phase ratio, concentration, catalyst load, catalyst structure and temperature. Influence of number of equivalents of NaOCl over conversion and enantioselectivity was studied first. For that purpose, the volume ratio between organic and aqueous phases was kept constant 1:1, *ergo* the volume of the aqueous phase was adjusted with distilled water when the number of equivalents of oxidant was decreased. The reactions were carried out at a scale of 20 mg of *trans*- β -methyl- β -nitrostyrene, 10 mol % catalyst **CN-1** load, 0.15M concentration of the alkene in DCM (Table 5).

Table 5. Influence of Number of Equivalents of NaOCl over Conversion and Enantioselectivity.^a

Entry	Eq. of NaOCl	Conversion (%) ^b	e.r. ^c
1	14	100	58:42
2	12	95	56.5:43.5
3	10	97	56:44
4	7	96	56:44
5	5	95	56:44
6	1.5	84	55:45

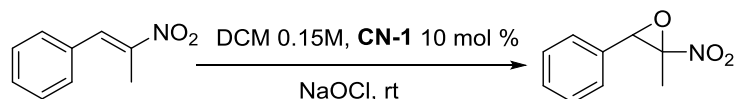
^aReactions were carried out at room temperature for 2 hours with vigorous stirring, with 1:1 ratio of organic and aqueous phase. ^bBased on ¹H NMR. ^cMeasured on HPLC chiralpak-IA with *n*-hexane/*i*-propanol.

Results revealed no significant differences in terms of conversion when the number of equivalents of oxidants were reduced (Table 5, entries 1-5), except for the last one (entry 6) in which a small excess of oxidant leads to a decrease of conversion. Comparing the obtained data, we observed a small decrease of enantioselectivity with the reduction of NaOCl equivalents (entries 1-3), which was more evident for the

reaction with less excess of oxidant (entry 6). However, results did not expose a clear correlation between oxidant equivalents and enantioselectivity.

We thought that variations of conversion and enantioselectivity shown in Table 5 might be caused by a dilution effect of the aqueous phase rather than by the amount of oxidant. To check that hypothesis, a battery of reactions was performed with decreasing amounts of the commercial NaOCl solution but without any volume compensation (Table 6).

Table 6. Effect of the Amount of Oxidant at a Constant Concentration^a



Entry	Eq. of NaOCl	Org:Aq ratio ^b	Time (h)	Conversion (%) ^c	e.r. ^d
1	14	1:1	2	100	58:42
2	13	8:7	2.5	100	57:43
3	9	8:5	18	100	57:43
4	5	8:3	20	97	57:43
5	3	16:3	20	95	57:43
6	1.1	40:3	28	31	56.5:44.5

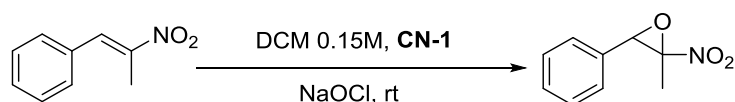
^aThe reactions were carried out at scale of 20 mg of *trans*- β -methyl- β -nitrostyrene, 10 mol % catalyst load, 0.15 M concentration of the alkene in DCM and a commercially available solution of NaOCl (14.5% in active chlorine), for the specified time. ^bRatio in volume of each phase. ^cMeasured on ¹H NMR. ^dMeasured on HPLC chiralpak-IA with *n*-hexane/*i*-propanol.

After comparing the data of Table 5 and 6, the drawn conclusions were that the amount of oxidant did have no effect on enantioselectivity but it had effect on reaction time, which was severely prolonged when almost stoichiometric amount of NaOCl was used (Table 6, entry 6).

The solvents volume had no significant effect on the enantioselectivity or the conversion. From that moment, the commercially available concentrated solution of NaOCl was used since it seemed to work better in terms of reaction rate or enantioselectivity.

The properties that an ideal asymmetric organocatalytic system must have include fast and full conversion of the substrate, absolute control of enantioselectivity and/or diastereoselectivity, reusability of the catalyst and low load of the catalyst. The efficiency of our system in front of catalyst load was examined (Table 7). Initial conditions reproduced previous results when a 10 mol% load of **CN-1** was used in DCM at room temperature (entry 2). Unfortunately, enantioselectivity and conversion rate decreased along with the lowering of catalyst load (entries 3 and 4). Furthermore, increasing the catalyst load to 20 mol% did not improve enantioselectivity enough to justify double catalyst loading (entry 1). 10 mol% was established as the optimum load of catalyst for further optimization studies.

Table 7. Effect of Catalyst Load on Conversion and Enantioselectivity^a



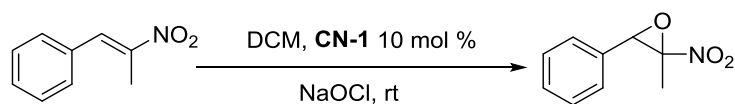
Entry	Catalyst load	Time (h)	Conversion (%) ^b	e.r. ^c
1	20 mol%	2	100	59:41
2	10 mol%	2	100	58:42
3	5 mol%	2	76	54:46
4	1 mol%	4	20	50.5:49.5

^aThe reactions were carried out at scale of 20 mg of *trans*- β -methyl- β -nitrostyrene, in DCM with 1:1 org:aq phase ratio of a commercially available solution of NaOCl (14.5% in active chlorine), for the specified time. ^bMeasured on ¹H NMR. ^cMeasured on HPLC chiralpak-IA with *n*-hexane/*i*-propanol.

As reported by Lygo *et al.*¹³⁴, concentration of the substrate in the organic phase was found to be an important parameter to be optimized. In their case, the asymmetric epoxidation of chalcones with a cinchona salt derivative as PTC and NaOCl as oxidant, by varying the concentration of substrate it was possible to obtain 100% conversion of the chalcone within 24 h at 25°C with catalyst loading down to 0.5 mol%. They also found that the more concentrated was the organic phase, the less catalyst load was needed to achieve the same conversion and enantioselectivity. However, they observed that for a 0.5 mol% catalyst load (or lower) the reaction led to a significant reduction in enantioselectivity, even for highly concentrated solutions. For example, excellent e.e. were obtained when using 1-10 mol% load of the catalyst and an initial chalcone concentration of 0.09 M-0.34 M in toluene (86% ee), but the enantioselectivity dropped considerably when an initial chalcone concentration of 3.4 M and 0.1 mol% of PTC were used (60% ee).

We tested how concentration would affect to our catalytic system, and for that we designed a series of reactions varying the organic phase concentration, but keeping a constant catalyst load and oxidant amount and therefore, the volume of the aqueous phase (Table 8).

Table 8. Variation of Yield and e.r. Depending on Organic Phase Concentration^a



Entry	Conc. (M)	Org:Aq ratio ^b	Time (h)	Conversion (%) ^c	e.r. ^d
1	0.6	1:1	2.5	100	54:46
2	0.3	2:1	3	100	59:41
3	0.15	4:1	5	100	57:43

¹³⁴ Lygo, B.; To, D. C. M. *Chem. Commun.* **2002**, 20, 2360

4	0.07	7.5:1	6	96	55:45
5	0.024	25:1	20	90	53:47

^aThe reactions were carried out at a scale of 20 mg of *trans*- β -methyl- β -nitrostyrene, 10 mol % load of catalyst **CN-1**, in DCM and a commercially available solution of NaOCl (14.5% in active chlorine), for the specified time. ^bRatio in volume of each phase. ^cMeasured on ¹H NMR. ^dMeasured on HPLC chiralpak-IA with *n*-hexane/*i*-propanol.

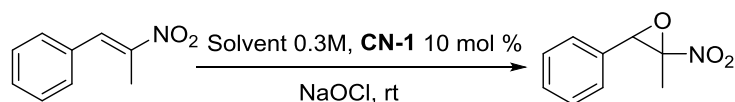
Obtained data suggested that enantioselectivity is strongly dependent of the organic phase concentration. The measured enantiomeric ratio diminished along with the concentration (entries 2-5). However, for higher concentrations (entry 1), enantioselectivity was also negatively affected. As suggested by Lygo¹³⁴, higher concentrations lead to a lower solubility of catalyst **CN-1** (during the reaction, a considerable amount of PTC remained visibly as a solid suspension) which resulted in a loss of catalytic efficiency. Higher concentration might also imply a change in the reaction media, concerning the polarity and intermolecular interactions. Since a concentration of 0.3 M and an organic: aqueous phase ratio of 2:1 showed the best results in terms of conversion and enantioselectivity, those conditions were used for further optimization experiments.

Another parameter expected to be relevant for the catalytic activity was the solvent. Many authors have reported excellent results when non-polar solvents were used for epoxidation in phase-transfer catalytic systems, which were significantly reduced when polar solvents were used instead.¹³⁵ We performed the solvent screening to elucidate the mechanism of the reaction and how the phase transfer catalyst activity was affected by the media. The optimization of the solvent was carried out at a scale of 20 mg of *trans*- β -methyl- β -nitrostyrene, 10 mol % load of catalyst **CN-1**, 0.3 M concentration of the nitroalkene in the

¹³⁵ a) Macdonald, G.; Alcaraz, L.; Lewis, N. J.; Talyor, R. J. K. *Tetrahedron Lett.* **1998**, *39*, 5433. b) Arai, S.; Tsuge, H.; Oku, M.; Miura, M.; Shioiri, T. *Tetrahedron* **2002**, *58* (8), 1623. c) Arai, S.; Tsuge, H.; Shioiri, T. *Tetrahedron Lett.* **1998**, *39*, 7563. d) Lygo, B.; Wainwright, P. G. *Tetrahedron* **1999**, *55*, 6289.

specified solvent (Table 9) and a commercially available aqueous solution of NaOCl (14.5% in chlorine) in 2:1 organic phase:aqueous phase ratio.

Table 9. Screening of the Solvent and its Effect on Enantioselectivity and Conversion Rates.^a



Entry	Solvent	Time (h)	Conversion (%) ^b	e.r. ^c
1	DCM	2	100	59:41
2	EtOAc	6	48	50:50
3	Toluene	24	20	n.d. ^d
4	Hexane	24	<5	n.d.
5	Methanol	24	No reaction	n.d.
6	THF	6	45	50:50
7	Et ₂ O	24	No reaction	n.d.
8	1,2-DCE	2	75	55:45
9	Chloroform	1.5	70	74:26

^aReactions were carried out at room temperature with vigorous stirring, with 2:1 ratio of organic and aqueous phase. ^bMeasured on ¹H NMR. ^cMeasured on HPLC chiralpak-IA with *n*-hexane/*i*-propanol. ^dNot determined.

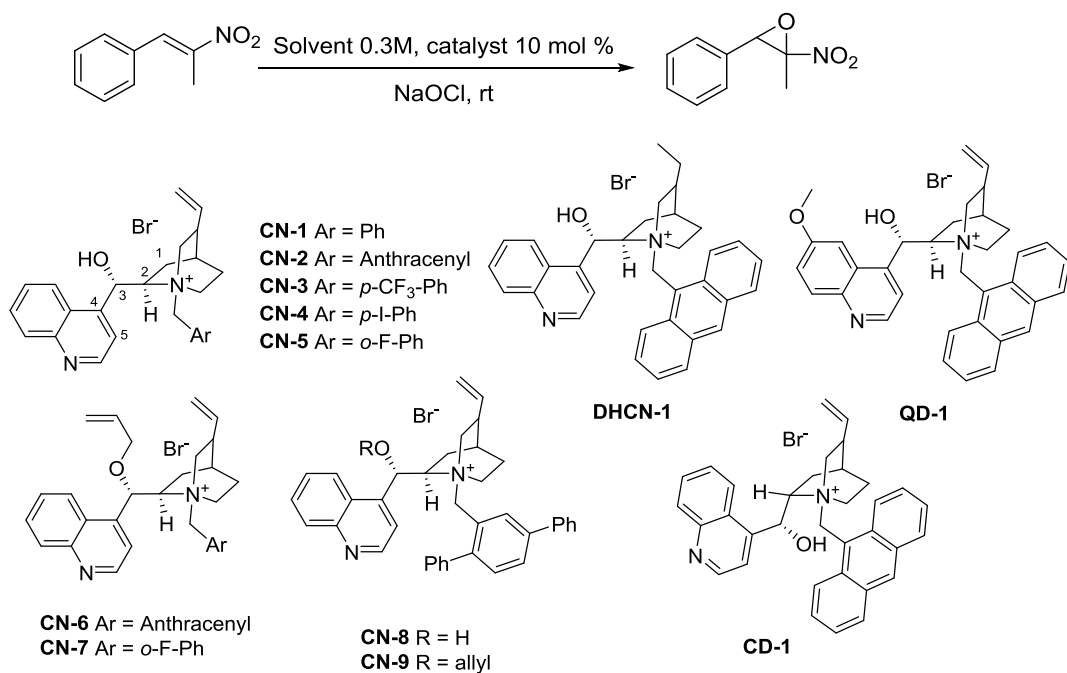
Solvent, indeed, resulted to be a very important parameter to take in consideration. Dichloromethane was used as a control (entry 1) giving full conversion with short times and 18% ee. Ethyl acetate was able to solubilize both the substrate and the catalyst **CN-1** and the reaction underwent smoothly with a 48% conversion in 6 hours, although the enantioselectivity was null (entry 2). Non-polar solvents such as hexane and diethyl ether (entries 4 and 7) barely showed conversion, probably due to the lack of solubility of **CN-1** in those solvents. For our concern,

one of the most employed solvents in phase transfer catalysis, toluene (entry 3), afforded the conversion of nitroalkene into nitroepoxide only with 20% yield. In that case, **CN-1** seemed to be more soluble than in hexane or diethyl ether, but still not completely soluble. When methanol was used (entry 5), no reaction occurred since its miscibility with aqueous media caused homogenization of the system. However, despite being an aqueous miscible solvent, tetrahydrofuran (entry 6) allowed a biphasic system while stirring, which afforded nitroepoxide in 45% yield but with no enantioselectivity. Halogenated non-polar solvents such as 1,2-dichloroethane (entry 8) and chloroform (entry 9) were good in terms of catalyst solubility and showed fast conversion in short times. While enantioselectivity for 1,2-dichloroethane was poor compared to dichloromethane, chloroform afforded satisfactory results both in terms of reactivity, 70% conversion in only one and a half hours, and enantioselectivity, 48% ee. Carbon tetrachloride was expected to be even greater solvent because it is less polar than chloroform, but due to environmental and economic restrictions, it was not tested at that moment.

Having optimized the conditions for the enantioselective epoxidation of nitroalkenes, we proceeded to the screening of the catalyst (Table 10). Following bibliographic work, first modification on the catalyst involved the insertion of methylantracene group in the N atom of the quinuclidine ring from the cinchonine to form the corresponding ammonium salt (**CN-2**).¹³⁶ For our content, **CN-2** exhibited good results in CHCl_3 at 10 mol% load in terms of conversion and enantioselectivity (entry 2). As it is described in literature, electronic interactions and major steric hindrance of the anthracenyl group compared to benzyl might be responsible of the increment on the selectivity.¹³⁷

¹³⁶ Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, 38 (49), 8595.

¹³⁷ Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, 119 (50), 12414.

Table 10. Screening of the Catalyst^a

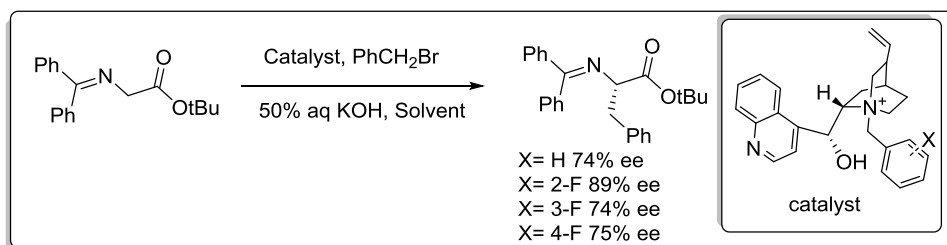
Entry	Solvent	Catalyst	Time (h)	Conversion (%) ^b	e.r. ^c
1	CHCl ₃	CN-1	5	100	74:26
2	CHCl ₃	CN-2	3	100	84:16
3	CHCl ₃	CN-3	5	100	81:19
4	CHCl ₃	CN-4	3	100	81:19
5	CHCl ₃	CN-5	5	100	53:47
6	CHCl ₃	DHCN-1	2	100	81:19
7	CCl ₄	CN-2	2	100	89:11
8	Toluene	CN-2	24	100	87:13
9	Toluene	CN-4	16	60	84:16
10	CHCl ₃	QD-1	4	100	62:38

11	Toluene	QD-1	4	98	75:25
12	CHCl ₃	CN-6	5	80	45:55
13	Toluene	CN-6	5	100	33.5:66.5
14	CHCl ₃	CN-7	4	38	50:50
15	Toluene	CN-7	4	98	39.5:60.5
16	Toluene	CN-8	4.5	100	41:59
17	Toluene	CN-9	5	100	25:75
18^d	Toluene	CN-2	16	92 ^e	96.5:3.5
19^d	Toluene	CD-1	16	86 ^e	18:82

^aThe reactions were carried out at a scale of 20 mg of *trans*- β -methyl- β -nitrostyrene, 10 mol % load of catalyst, with 0.3M concentration of substrate and a commercially available solution of NaOCl (14.5% in active chlorine) in a 2:1 organic:aqueous phase ratio, at room temperature. ^bMeasured on ¹H NMR. ^cMeasured on HPLC chiralpak-IA with *n*-hexane/*i*-propanol. ^dReaction was carried out at -20°C. ^eIsolated yield.

Arai and coworkers reported that substitutions on the benzyl ring of **CN-1** had a tremendous impact on enantioselectivity for the asymmetric epoxidation of diverse enones.^{135b,c} For example, electron-withdrawing groups such as I- at position 4 increased enantioselectivity, while electron-donor groups had the opposite effect. Moreover, the position of the substituent was found to be also crucial, since the efficacy of catalyst diminished when iodine atom was placed in positions 2 or 3. Thus, catalyst with trifluoromethyl group in *para* position **CN-3** (entry 3) and catalyst with iodide group in *para* position **CN-4** (entry 4) were tested for the enantioselective epoxidation of nitroalkenes. Both catalysts showed better efficiency than the unsubstituted catalyst **CN-1** (entry 1), but the obtained results also indicated that both **CN-3** and **CN-4** were slightly worse than the cinchoninium salt with the anthracenyl group **CN-2** (entry 2). Despite the aforementioned, it has been reported that unusual aromatic-F electronic effect enhanced the enantioselectivity of PTC mediated

alkylation of a glycine anion equivalent when the corresponding cinchonidinium catalyst possessed a fluoride in *ortho*- position at benzylic ring (Scheme 55).¹³⁸ We tested the cinchoninium analogue **CN-5** (entry 5) for the epoxidation reaction in chloroform, but we did not obtain the expected result. In fact, the enantioselectivity dropped to a 6% ee, quite much lower than the previous entries.



Scheme 55. F-effect on enantioselectivity in a phase transfer alkylation.

In one of the many studies published by Lygo and Wainwright, they reported an increase of the enantioselectivity when a hydrogenated analogue of cinchonine or chinconidine was used as phase transfer catalyst.¹³⁶ According to that, we prepared *N*-anthracenylmethyl dihydrocinchoninium bromide **DHCN-1** and tested it for the epoxidation of *trans*- β -methyl- β -nitrostyrene (entry 6). A slight increment on the rate of the reaction was observed, but the enantioselectivity was identical to that obtained with the unsaturated analogue **CN-2** (entry 2). We decided to continue the experiments with **CN-2** because its synthesis requires one step less than for **DHCN-1** and the catalytic activity has been exposed to be practically the same.

With the present results, we decided to test more apolar solvent than chloroform, namely carbon tetrachloride with catalyst **CN-2** (entry 7). Enantioselectivity rose from 68% ee (entry 2) to 78% ee. However, we were still intrigued by the fact that most published research on anthracenylmethyl cinchona derived salts describes toluene-water as the optimal solvent system. So, we performed the reaction with **CN-2**

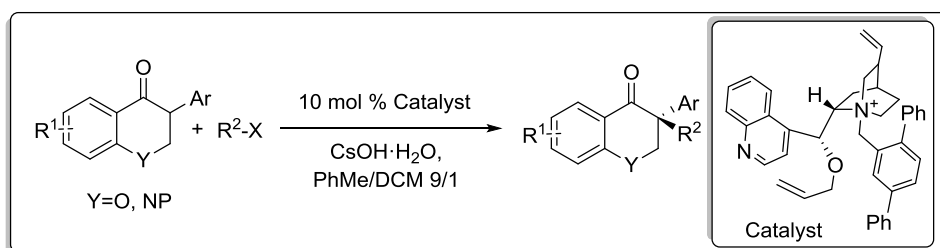
¹³⁸ Jew, S. S.; Yoo, M. S.; Jeong, B. S.; Park, I. Y.; Park, H. G. *Org. Lett.* **2002**, *4* (24), 4245.

in toluene (entry 8) and we found that the reaction became slower, but it was compensated with a 74% ee, which was better than with chloroform. We tested toluene also for catalyst **CN-4** (entry 9) in order to find how enantioselectivity was affected, by comparing the results with those for the reaction in chloroform (entry 4). Interestingly, the same results for enantioselectivity were observed but worse conversion was obtained. Affinity between solvent and catalyst seemed to be a decisive factor regarding efficiency of the enantioselective epoxidation. Since toluene is more environmentally acceptable solvent than carbon tetrachloride, further optimization was performed with toluene.

Quinidine is a cinchona alkaloid that displays the same stereochemistry than cinchonine. We guessed that a methoxy group in the quinoline ring might modify the activity of the catalyst. In order to study that hypothesis, we synthesized *N*-anthracenylmethyl quinidinium bromide and assayed it for the epoxidation reaction in chloroform (entry 10) and toluene (entry 11). In both experiments, it resulted that quinidine salt is less effective than its cinchonine analogue. Another common structural modification is the alkylation of the hydroxyl group in position 9. For example, E. J. Corey reported excellent results for the enantioselective epoxidation of chalcones using *O*-allyl-*N*-anthracenylmethyl cinchonidinium bromide as a catalyst and KOCl as an oxidant.¹³⁹ Catalysts **CN-6** (entries 12 and 13) and **CN-7** (entries 14 and 15) were prepared and tested for our epoxidation system and surprisingly, the opposite nitroepoxide enantiomer was obtained in moderate enantioselectivity (< -33% ee). In the light of the obtained results, we hypothesized that the hydroxyl group must be somehow, via polar interaction or via H-bond, partially responsible of the interaction between catalyst and substrate determining the conformation of the transition state.

¹³⁹ Corey, E. J.; Zhang, F. Y. *Org. Lett.* **1999**, *1* (8), 1287.

Having suggested that *N*-anthracenylmethyl catalyst **CN-2** worked better for its steric hindrance compared to benzyl group in **CN-1**, we looked for a more voluminous group. We found that K. A. Scheidt and coworkers designed a cinchonidinium salt catalyst with a 2,5-diphenyl benzyl group in the quinuclidine nitrogen efficiently used for the asymmetric alkylation of isoflavanones (Scheme 56).¹⁴⁰ We synthesized the cinchoninium analogues **CN-8** and **CN-9** and tested for the epoxidation of nitroalkenes (entries 16 and 17, respectively). Unexpectedly, catalyst **CN-8** (entry 16) showed an inversion on enantioselectivity, affording nitroepoxide in -8% ee. To explain that experimental observation, we reasoned that the 2,5-diphenyl group might be too voluminous for the nitroalkene to adopt the proper transition state geometry since the present phenyl substituents can afford non-planar conformation in comparison with anthracenyl group which is completely planar. The *O*-allylated compound **CN-9** (entry 17) afforded the epoxide with bigger enantioselectivity (-50% ee) than the analogue **CN-8**, also with opposite enantioselectivity.



Scheme 56. Asymmetric alkylation of disubstituted isoflavanones.

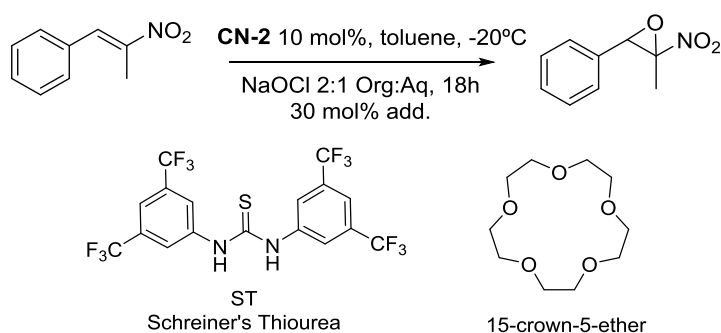
Being catalyst **CN-2** in toluene the best results in our hands (entry 8) we proceeded to the temperature optimization. We set up the reaction at -20°C with a cryogenic bath and the enantioselectivity was greatly increased up to 93% ee (entry 18). At lower temperatures, aqueous phase freezes and the reaction did not advance. With the optimized conditions, we also performed the reaction with the pseudoenantiomeric catalyst *N*-anthracenylmethyl cinchonidinium

¹⁴⁰ Nibbs, A. E.; Baize, A. L.; Herter, R. M.; Scheidt, K. A. *Org. Lett.* **2009**, *11* (17), 4010.

bromide **CD-1** (entry 19). Then, the opposite enantiomer was obtained with a -64% ee.

The effect of diverse additives was also studied. It has been reported for many kinds of organic reactions that the presence of some additives in catalytic amounts can increase the yields and enantioselectivities.¹⁴¹ We tested commonly employed additives such as Lewis acid metal salts and organocatalysts (Table 11).

Table 11. Effect of Additives on Conversion and Enantioselectivity^a



Entry	Additive	Conversion (%) ^b	e.r. (%) ^c
1	-	100	96.6:3.4
2	LiCl	95	94:6
3	ST	No reaction	n.d.
4	CuCl	70	86:14
5	AlCl ₃	Decomposition	n.d.
6	CsF	94	90.5:9.5
7	15-crown-5	90	90:10

^aThe reactions were carried out at a scale of 20 mg of *trans*- β -methyl- β -nitrostyrene, 10 mol % load of catalyst, 30 mol% load of additive, with 0.3M concentration of

¹⁴¹ a) For a general review: Vogl, E. M.; Gröger, H.; Shibasaki, M. *Angew. Chemie - Int. Ed.* **1999**, *38* (11), 1570. b) Lee, J. M.; Na, Y.; Han, H.; Chang, S. *Chem. Soc. Rev.* **2004**, *33* (5), 302. c) Roy, D.; Patel, C.; Sunoj, R. B. *J. Org. Chem.* **2009**, *74* (18), 6936.

substrate and a commercially available solution of NaOCl (14.5% in active chlorine) in a 2:1 organic:aqueous phase ratio, at -20°C. ^bMeasured on ¹H NMR. ^cMeasured on HPLC chiralpak-IA with *n*-hexane/*i*-propanol.

When LiCl was used as an additive (entry 2), a bit loss of conversion rate and enantioselectivity was observed, although it was not significant. However, when a thiourea was used (entry 3), no reaction occurred and only starting material was recovered. A feasible explanation might be that thiourea moiety interacts with the nitro group via H-bond avoiding nitroalkene to interact with **CN-2** impeding the reaction to occur. In the case of Cu (I) salt (entry 4), conversion was severely affected and a loss of enantioselectivity could also be observed. The use of a stronger Lewis acid such as AlCl₃ (entry 5) resulted in the decomposition of the starting material. CsF (entry 6) also had a minor negative effect on conversion and enantioselectivity. Crown ethers function as an ion trap enhancing the activity of the counterion. However, 15-crown-5-ether (entry 7) did not favor the epoxidation reaction. We thought that 15-crown-5-ether might be able to trap sodium cation liberating the hypochlorite as a consequence, but that had no positive impact on enantioselectivity. In view of the results, we decided not to further investigate the use of additives to improve the enantioselectivity.

With the best results in our hands (Table 10, entry 18), reaction was scaled up to 200 mg of the substrate and the same results were obtained. During the process, several problems occurred, mainly involving the stirring. A proper interphase is necessary for the reaction to happen, since the catalyst must carry counterions from aqueous phase to organic phase and vice versa. So, homogeneous and vigorous stirring is needed to achieve maximum yield and enantioselectivity (ca. 1000 rpm). Another significant problem we found was the degradation of commercial hypochlorite solution; that is, lower concentration of oxidant in the aqueous phase, which was translated into higher freezing point. That problem affected reproducibility of the reaction at -20°C but it was easily solved by purchasing a new aqueous solution of NaOCl.

Work-up was simplified by pouring hexane to the reaction mixture, which caused precipitation of the catalyst, and filtering the mixture through an anhydrous magnesium sulfate pad to afford the pure nitroepoxide without further purification. Since **CN-2** seemed not completely soluble in the final conditions, we thought we could reduce the catalyst load without affecting the yield or the enantioselectivity. In fact, we were able to reduce the catalyst load to 8 mol% without affecting conversion and enantioselectivity.

Absolute configurations of enantiopure nitroepoxides **13a** and **13g** were assigned by X-ray crystallography (Figure 14) and **13a** was also confirmed by optical rotation in comparison with the enantiomeric nitroepoxide reported by Lattanzi *et al.*¹³¹

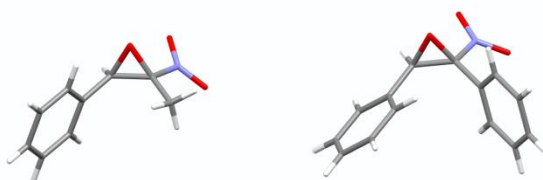
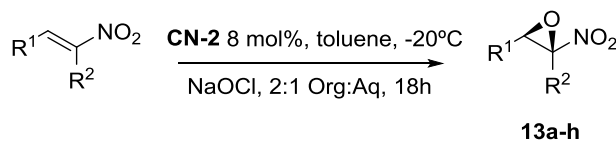


Figure 14. X-ray crystal structure for compounds **13a** (left) and **13g** (right).

2.3. Scope of the Reaction

With the optimized conditions, the scope of the epoxidation reaction was explored (Table 12). The reactions were carried out at a scale of 50 mg of the corresponding nitroalkene at 0.3M concentration in toluene, with 8 mol% load of **CN-2**, at -20°C.

Table 12. Scope of the Reaction for the (+)-Nitroepoxide.

Entry	R ¹ , R ²	Epoxide	Yield (%) ^b	e.r. (%) ^c
1	Ph, Me	13a	92	96.6:3.4
2	<i>p</i> -F-Ph, Me	13b	96	96.1:3.9
3	<i>p</i> -Cl-Ph, Me	13c	92	94.2:5.8
4	<i>m</i> -Cl-Ph, Me	13d	87	91.5:8.5
5	<i>p</i> -F-Ph, Et	13e	91	95.1:4.9
6	<i>p</i> -Me-Ph, Me	13f	92	91.3:8.7
7	Ph, Ph	13g	90	91.5:8.5
8	<i>i</i> -Bu, Me	13h	63	56.5:43.5

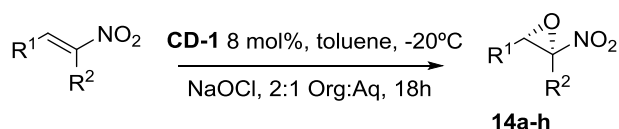
^aThe reactions were carried out at a scale of 50 mg of the corresponding nitroalkene, 8 mol % load of **CN-2**, with 0.3M concentration of substrate and a commercially available solution of NaOCl (14.5% in active chlorine) in a 2:1 organic:aqueous phase ratio, at -20°C. ^bIsolated yield. ^cMeasured on HPLC chiralpak-IA with *n*-hexane/*i*-propanol.

Diverse nitroalkenes were epoxidized under the optimized conditions. Being R¹ an aryl group and R² an alkyl group (entries 1-6), results were excellent both in terms of yield and enantioselectivity. When olefin substituents were both phenyl groups, good results were also obtained (entry 7). However, when both substituents were alkyl group, the yield and the enantioselectivity were considerably lower (entry 8). The volatility of both the starting material and the nitroepoxide **13h** might explain the decrease in the yield. The loss of enantioselectivity suggested that nitroalkene's aryl group might have stabilizing interactions with the anthracenyl group, *e.g.* π - π interactions, which

directs the position of the nitroalkene in the transition state affording preferably one enantiomer over the other.

We also explored the epoxidation of the aforementioned nitroalkenes with the pseudoenantiomeric catalyst **CD-1** (Table 13).

Table 13. Scope of the Reaction for the (-)-Nitroepoxide.



Entry	R ¹ , R ²	Epoxide	Yield (%) ^b	e.r. (%) ^c
1	Ph, Me	14a	86%	18:82
2	<i>p</i> -F-Ph, Me	14b	85%	16:84
3	<i>p</i> -Cl-Ph, Me	14c	92%	13:87
4	<i>m</i> -Cl-Ph, Me	14d	92%	27.5:72.5
5	<i>p</i> -F-Ph, Et	14e	87%	22:78
6	<i>p</i> -Me-Ph, Me	14f	90%	15.5:84.5
7	Ph, Ph	14g	88%	25:75
8	<i>i</i> -Bu, Me	14h	63%	26:74

^aThe reactions were carried out at a scale of 50 mg of the corresponding nitroalkene, 8 mol % load of **CD-1**, with 0.3M concentration of substrate and a commercially available solution of NaOCl (14.5% in active chlorine) in a 2:1 organic:aqueous phase ratio, at -20°C. ^bIsolated yield. ^cMeasured on HPLC chiralpak-IA with *n*-hexane/*i*-propanol.

As expected, the epoxidation of nitroalkenes with **CD-1** as a catalyst afforded the opposite nitroepoxides **14a-h** with similar yields and a loss of enantioselectivity compared with the synthesis of **13a-h** with **CN-2** (Table 12). However, for the alkyl-alkyl disubstituted nitroepoxide **14h** (Table 13, entry 8) an increase of the enantioselectivity was observed compared with **13h**.

2.4. Computational Studies

In order to explain the experimental data, computational studies were performed by Dr. Katarzyna Świderek and Prof. Vicent Moliner from Computational Biochemistry group at Universitat Jaume I. Quantum molecular simulations have been employed to study the observed catalytic enantioselective epoxidation of *trans*- β -methyl- β -nitrostyrene by catalyst **CN-2**. All calculations have been carried out in toluene solution with the conductor-like polarizable continuum model (CPCM),¹⁴² as implemented in Gaussian 09 package.¹⁴³ The calculations have been performed at density functional theory (DFT) level with the B97d hybrid functional,¹⁴⁴ which has been proved to provide exceptionally good performance for non-covalently bound systems¹⁴⁴ involving large polynuclear aromatic molecules.¹⁴⁵ The selected reaction was the one corresponding to the entry 18 in Table 10. The first step of the study was exploring the possible conformers adopted by the catalyst **CN-2** in toluene. In this regard, a Potential Energy Surface (PES) has been generated as a function of the dihedral angles describing the relative orientation of the quinoline moiety (Figure 15), similarly to previous conformational analysis of different cinchona alkaloid scaffolds.¹⁴⁶

¹⁴² a) Barone, V.; Cossi, M. *J. Phys. Chem. A* **1998**, *102* (11), 1995. b) Cossi, M.; Rega, N.; Scalmani, G.; Barone, V. *J. Comput. Chem.* **2003**, *24* (6), 669.

¹⁴³ M. J. Frisch, et al Gaussian 09, revision D.01; Gaussian, Inc., Wallingford CT, **2009**

¹⁴⁴ Grimme, S. *J. Comput. Chem.* **2006**, *27* (15), 1787.

¹⁴⁵ Peverati, R.; Baldrige, K.K. *J. Chem. Theory Comput.* **2008**, *4*, 2030.

¹⁴⁶ a) Prakash, G.K.S.; Wang, F.; Ni, C.; Shen, J.; Haiges, R.; Yudin, A. K.; Mathew, T.; Olah, G. O. *J. Am. Chem. Soc.* **2011**, *133*, 9992. b) Prakash, G.K.S.; Wang, F.; Rahm, M.; Zhang, Z.; Ni, C.; Shen, J.; Olah, G. A. *J. Am. Chem. Soc.* **2014**, *136*, 10418.

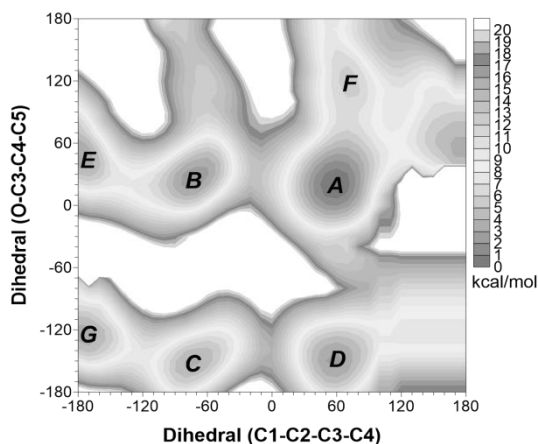


Figure 15. Gas phase PES computed at B97d/6-31+G(d,p) level as a function of the dihedral angles describing the relative orientation of the quinoline moiety and -OH group of **CN-2** catalyst. See Table 10 for numbering of the atoms.

All possible conformations of **CN-2** catalyst were explored. From the two lowest energy **CN-2** conformers A and B (Figure 15), the study of the binding of the ClO^- and the nitroalkene substrate provides different reactant complex, RC, conformations. Interestingly, while the conformation of **CN-2** is comparable to the one observed for other cinchona-based catalysts,¹⁴⁷ this is not the case when comparing the RCs. Indeed our most stable RCs for the epoxidation reaction show π - π stacking interactions between the catalyst and the substrate (Figure 16), which is not detected in the indanone-catalyst complexes previously reported for the cinchoninium ion asymmetric phase transfer catalyzed alkylation reaction.¹⁴⁷ Moreover, the ClO^- moiety interacts by a hydrogen bond with the hydroxyl group of the catalyst in both RCs dictating the orientation and interaction between the nitroalkene and the catalyst. The difference between both RCs structures depends on the π - π stacking interaction that is established between the nitroalkene and the aryl substituent of the catalyst; while RC in A.II.1 interacts through the anthracenyl moiety of the catalyst, RC in A.II.2 interacts through the quinoline moiety. Interestingly, there is no significant difference in

¹⁴⁷ Martins, E. F.; Pliego, J. R. *ACS Catal.* **2013**, *3*, 613.

energy between both conformations. Nevertheless, this is not the case when comparing the transition states, TSs, and product complexes, PCs, that connect with the RCs. Thus, the reaction from RC A.II.1 shows lower energy barrier than the reaction from RC A.II.2 (8.4 vs. 12.5 kcal·mol⁻¹), and more stable PCs (-44.2 and -41.4 kcal·mol⁻¹, respectively). Importantly, the nitroepoxides that are obtained in both reactions are different enantiomers: (2S,3R)-nitroepoxide **13a** in reaction from A.II.1 and (2R,3S)-nitroepoxide **14a** in reaction from A.II.2. According to the relative energies of their corresponding TSs and PCs, (2S,3R)-nitroepoxide would be the most favorable enantiomer when employing catalysts **CN-2** from the thermodynamic and kinetic point of view. This computational result is in very good agreement with the experimental data reported in Table 10 entry 18, where 2S,3R enantiomer is obtained in a 96.5/3.5 ratio.

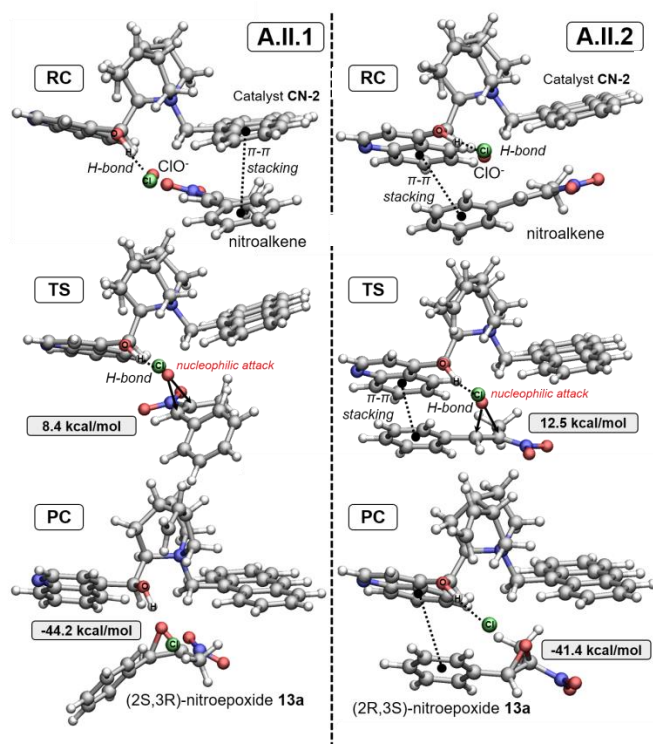


Figure 16. Optimized structures and relative energies of RC, TS and PC of the epoxidation of *trans*- β -methyl- β -nitrostyrene catalyzed by **CN-2** starting from the most stable conformations of the nitroalkene–ClO–**CN-2** reactant complexes.

A deep analysis of the RCs, TSs and PCs structures reveals that the π - π stacking interaction between the aromatic rings of the catalysts and the substrate are important to stabilize and to orient the two moieties in RCs. This explains the synthesis of nitroepoxide **13h**, having no aromatic substituent, not to be enantioselective. Nevertheless, the presence of hydrogen bond interactions and the most favourable conformation of the catalyst appear to be the factor determining the relative energies of TSs and PCs that, in turn, determines the ratio of obtained enantiomers.

It is important to point out that the epoxidation of *trans*- β -methyl- β -nitrostyrene catalyzed with **CD-1** has been also studied from different RC conformers. Any alternative reaction path has been revealed as not only thermodynamically but kinetically less favourable than the reaction from A.II.1 displayed in Figure 15.

2.5. Synthetic Derivations of Nitroepoxides

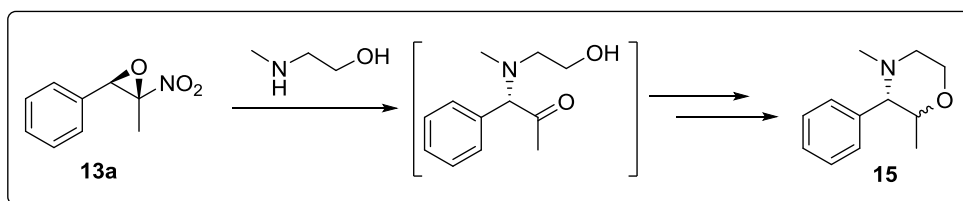
In order to increase the interest of the enantioselective epoxidation of nitroalkenes, we envisioned many synthetic applications of asymmetric nitroepoxides. Lattanzi¹³¹ already reported the one-pot synthesis of highly valuable 1,2-aminoalcohol¹⁴⁸ from nitroepoxides in great diastereoselective and enantioselective fashion.

From our experience with nitroepoxides and their conversion into heterocycles (Chapter 2 of the present PhD Thesis), we envisioned the synthesis of morpholine **15** from nitroepoxide **13a** using 1,2-aminoalcohols (Scheme 57). Morpholines are considered to be privileged scaffolds in medicinal chemistry.¹⁴⁹ Some commercial drugs display morpholine moiety (Figure 17). For example, phenmetrazine is

¹⁴⁸ For a review on enantioenriched 1,2-aminoalcohols: Klingler, F. D. *Acc. Chem. Res.* **2007**, *40* (12), 1367.

¹⁴⁹ a) Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. *J. Med. Chem.* **2014**, *57*, 5845.
b) Wijtmans, R.; Vink, M. K. S.; Schoemaker, H. E.; van Delft, F. L.; Blaauw, R. H.; Rutjes, F. P. J. T. *Synthesis* **2004**, 641.

a potent releaser of norepinephrine and dopamine.¹⁵⁰ Phendimetrazine (Bontril) is an anorexigenic drug,¹⁵¹ and aprepitant (Emend) is a potent and orally active NK1 receptor antagonist for chemotherapy-induced emesis, depression and other potential indications¹⁵² (Figure 17). Although some works have been reported for the preparation of morpholines,¹⁵³ their use is currently limited by the scarcity of methods for their preparation, particularly for 2,3-disubstituted morpholines.



Scheme 57. Synthetic approach to morpholines from nitroepoxides

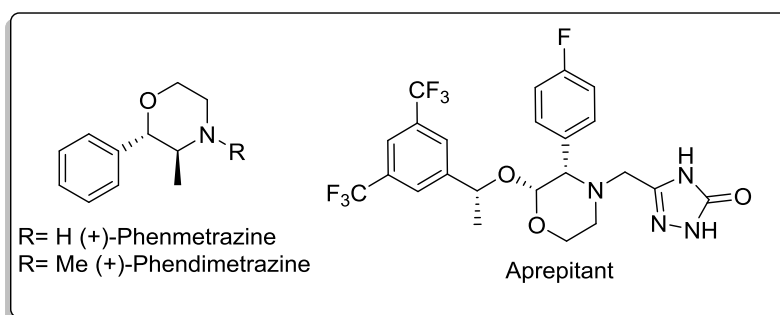


Figure 17. Commercial drugs with morpholine moiety

Racemic nitroepoxide **1a** was submitted to reaction with 2-(methylamino)ethanol to afford morpholinol **16** with high chemical

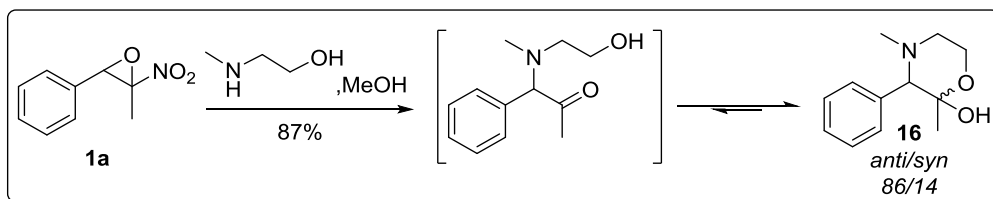
¹⁵⁰ Rothman, R. B.; Katsnelson, M.; Vu, N.; Partilla, J. S.; Dersch, C. M.; Blough, B. E.; Baumann, M. H. *Eur. J. Pharmacol.* **2002**, *447* (1), 51.

¹⁵¹ Rogovik, A. L.; Chanoine, J.-P.; Goldman, R. D. *Drugs* **2010**, *70* (3), 335.

¹⁵² Brands, K. M. J.; Payack, J. F.; Rosen, J. D.; Nelson, T. D.; Candelario, A.; Huffman, M. A.; Zhao, M. M.; Li, J.; Craig, B.; Song, Z. J.; Tschaen, D. M.; Hansen, K.; Devine, P. N.; Pye, P. J.; Rossen, K.; Dormer, P. G.; Reamer, R. A.; Welch, C. J.; Mathre, D. J.; Tsou, N. N.; McNamara, J. M.; Reider, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 2129

¹⁵³ a) Lai, J.-Y.; Shi, X.-X.; Gong, Y.-S.; Dai, L.-X. *J. Org. Chem.* **1993**, *58* (18), 4775. b) Ritzen, B.; Hoekman, S.; Verdasco, E. D.; Van Delft, F. L.; Rutjes, F. P. J. T. *J. Org. Chem.* **2010**, *75* (10), 3461. c) Uozumi, Y.; Tanahashi, A.; Hayashi, T. *J. Org. Chem.* **1993**, *58* (24), 6826. d) Zhou, L.; Tan, C. K.; Zhou, J.; Yeung, Y. Y. *J. Am. Chem. Soc.* **2010**, *132* (30), 10245.

yield and a diastereomeric mixture of 86/14 (Scheme 58). The hydroxy ketone resulting from the attack of the secondary amine to the nitroepoxide, cyclized into hemiacetalic form (Scheme 58).



Scheme 58. Synthesis of morpholinol **16**.

Although their presence in literature is not so relevant compared to morpholines, morpholinols are still an interesting scaffold in medicinal chemistry.¹⁵⁴ Stereochemistry of **16** was determined by NMR measurements (Figure 18). As it can be observed in the monodimensional NOE experiment, irradiation of the methyl group on the major diastereomer (1.10 ppm) gave NOE effect with the benzylic proton (3.06 ppm), whilst irradiation of methyl on the minor diastereomer (1.25 ppm) did not show correlation with the benzylic proton, or at least it was not so evident.

¹⁵⁴ Rekka, E.; Kourounakis, P. *Eur. J. Med. Chem.* **1989**, 24 (2), 179.

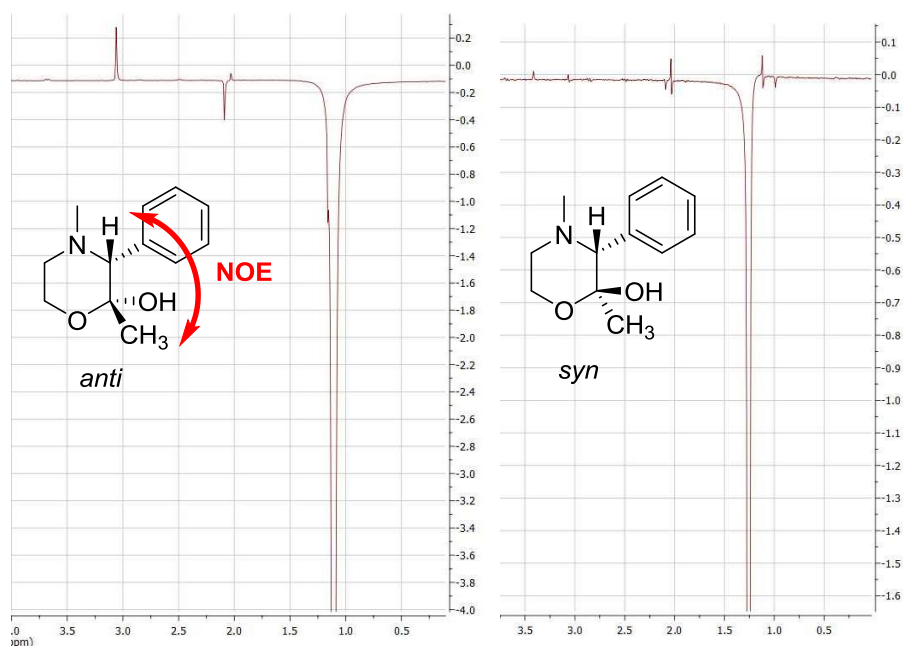
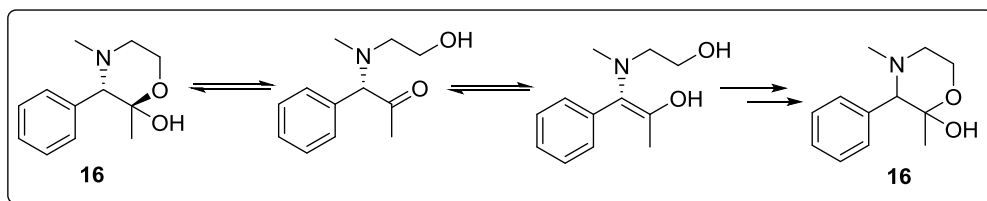


Figure 18. 1D NOE experiment.

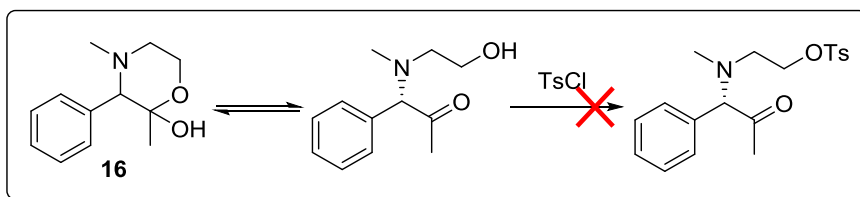
We performed the same reaction with optically active nitroepoxide **13a**. For our surprise, despite the racemic **16** was a solid, the obtained compound was a yellow oil. After HPLC analysis, we observed a great loss of enantioselectivity, from 96.6:3.4 e.r. of **13a** to 65:35 e.r. of morpholinol. After two weeks, HPLC was repeated and the mixture became almost racemic and the oil became solid. Aminoketone form derived from morpholinol **16** is supposed to racemize resulting in racemization of morpholinol **16** (Scheme 59).



Scheme 59. Racemization of enantiomerically pure morpholinol.

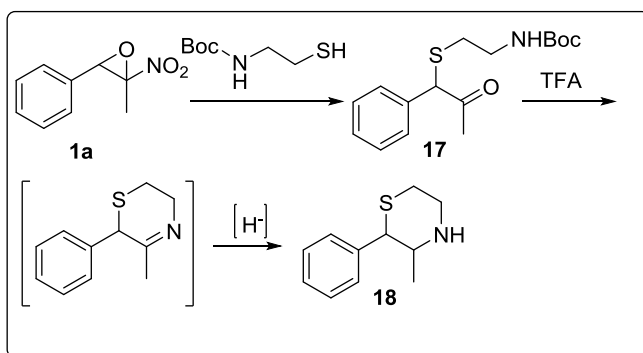
Another strategy that we designed was the tosylation of the hydroxy group to favor the equilibrium into the open conformation (Scheme 60). Morpholinol **16** was then subjected to reaction with tosyl chloride in

the presence of a base. Despite the efforts, only starting material was recovered. We thought that, at least in solution, morpholinol was the more stable isomer and the equilibrium is entirely displaced to its side.



Scheme 60. Tosylation attempt of the open form.

Since we did not succeed in transforming optically pure nitroepoxides into optically active chiral morpholines or morpholinols, we envisioned an approach to obtain thiomorpholines by the use of 2-aminoethanethiol (Scheme 61). Thiomorpholine is a bioisostere of morpholine, an analogue in which oxygen atom is replaced by a sulfur atom, which might behave in similar way in biological systems.¹⁵⁵ Our approach consisted in a ring-opening of the nitroepoxide with *N*-Boc-aminoethanethiol, followed by deprotection and finally reductive amination (Scheme 61).

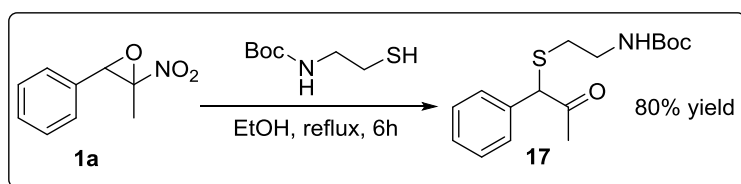


Scheme 61. Synthetic approach to thiomorpholine 18.

The best conditions for the first step were found to be reflux of the nitroepoxide and *N*-Boc-aminoethanethiol in ethanol, affording 1,2-thioether intermediate 17 in 80% yield (Scheme 62). However, we

¹⁵⁵ a) Brown, N. In *Bioisosteres in Medicinal Chemistry*; 2012; pp 1–14. b) Barillari, C.; Brown, N. In *Bioisosteres in Medicinal Chemistry*; 2012; pp 15–29.

found several problems during deprotection step. We started with standard conditions for Boc deprotection which consisted in the use of a TFA/DCM 1/1 solution. Those conditions seemed too harsh for the compound since the mass of the crude was reduced considerably and lots of products were observed on ^1H NMR spectrum. Different deprotection conditions were tested, but all of them failed. Then, we tested one-pot sequential deprotection/reductive amination with different deprotecting acid and reductive agent combination. Finally, with a stoichiometric excess of H_3PO_4 in DCE^{156} and $\text{NaBH}(\text{OAc})_3$ as a reducing agent, we were able to obtain a cleaner reaction crude which was purified by LC. However, the isolated compound was not the expected thiomorpholine **18**.



Scheme 62. Ring-opening with N-protected ethanethiolamine.

The isolated product was analyzed by ^1H and ^{13}C NMR spectroscopy and interesting peaks were observed (Figure 19). In the ^1H NMR spectrum, three different C backbones were observed, namely an ethyl group, a three sp^3 carbon and a phenyl group (Figure 19). ^{13}C NMR showed coherent signals because five sp^3 carbon signals were observed and also four sp^2 carbon signals on the aromatic region. No ketone peaks were observed. The more reasonable structure seemed to be a derived product from thiomorpholine **18** in which the C-S bond has been cleaved. However, when mass spectrometry was performed, the product seemed to decompose and no peaks could be identified. More

¹⁵⁶ Li, B.; Berliner, M.; Buzon, R.; Chiu, C. K. F.; Colgan, S. T.; Kaneko, T.; Keene, N.; Kissel, W.; Le, T.; Leeman, K. R.; Marquez, B.; Morris, R.; Newell, L.; Wunderwald, S.; Witt, M.; Weaver, J.; Zhang, Z.; Zhang, Z. *J. Org. Chem.* **2006**, *71* (24), 9045.

experiments are undergoing to confirm the structure and elucidate the reaction mechanism.

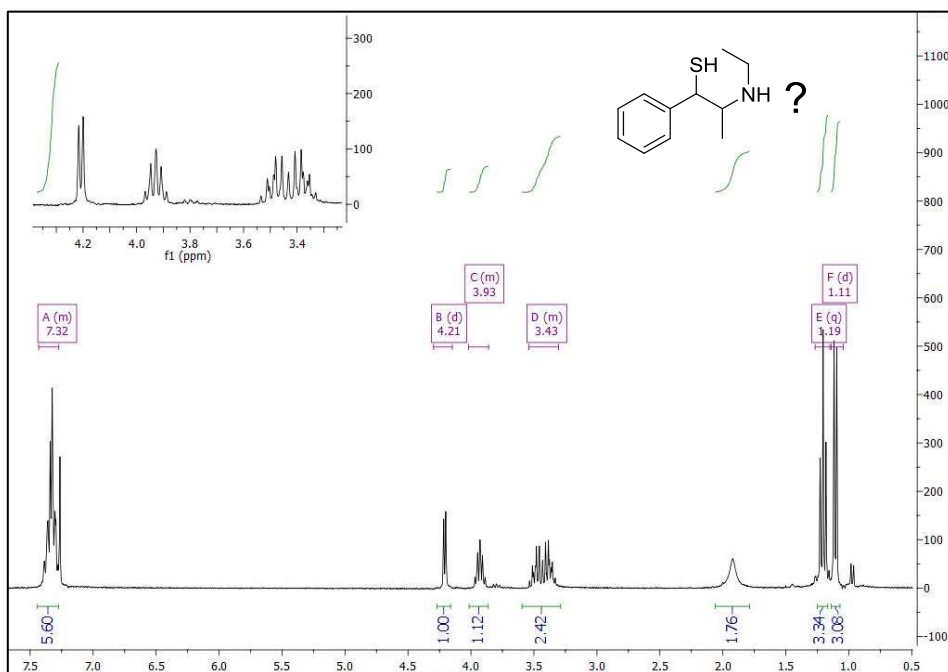
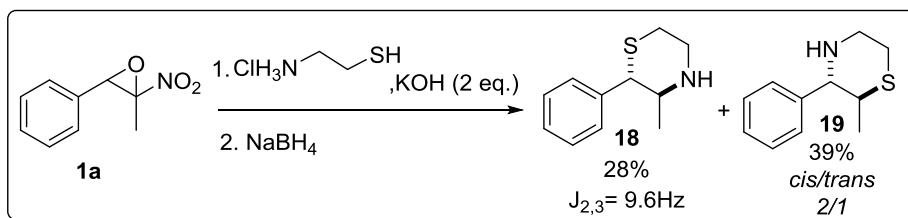


Figure 19. Unidentified isolated compound

A different strategy for the synthesis of thiomorpholine **18** from nitroepoxide **1a** was used. Considering that nitroepoxides can be described as synthetic equivalents of α -haloketones, we used a reported experimental procedure for the synthesis of thiomorpholines from α -bromoketones.¹⁵⁷ We started from the commercially available cysteamine hydrochloride salt, which was solved in ethanol under inert conditions and two equivalents of KOH were precisely measured and added to the solution (Scheme 63). Then, one equivalent of nitroepoxide was added and stirred until consumption to finally add NaBH₄ as reducing agent. The crude showed three similar compounds identified as the two regiomer thiomorpholines **18** and **19** as a diastereomeric mixture (Scheme 63).

¹⁵⁷ Ziakas, G. N.; Reka, E. A.; Gavalas, A. M.; Eleftheriou, P. T.; Kourounakis, P. N. *Bioorganic Med. Chem.* **2006**, *14* (16), 5616.



Scheme 63. Synthesis of thiomorpholines **18** and **19**

In order to differentiate the two regioisomers, we isolated the compounds by LC and compared the signals on ¹H NMR (Figure 20). As reported in the literature for similar compounds,^{157,158} when the ring-opening is performed by the sulfur atom the benzylic proton chemical (3.6 ppm in CDCl₃) shift is lower than the equivalent signal when the ring opening is performed by the nitrogen atom (4.0 ppm). The observed diastereomer was assigned to the regioisomer **19** due to its benzylic proton chemical shift (4.2 ppm).

¹⁵⁸ García Ruano, J. L.; Martínez, M. C.; Rodríguez, J. H.; Olefirowicz, E. M.; Eliel, E. L. *J. Org. Chem.* **1992**, 57 (15), 4215.

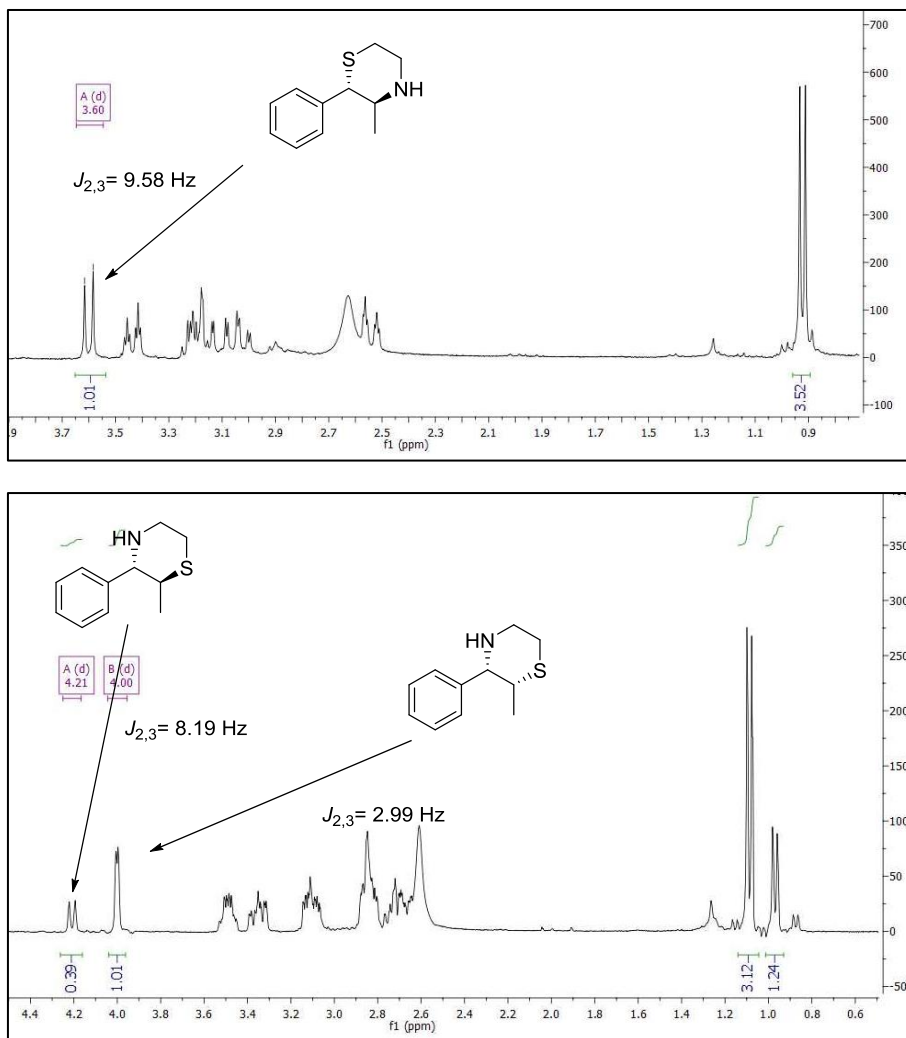


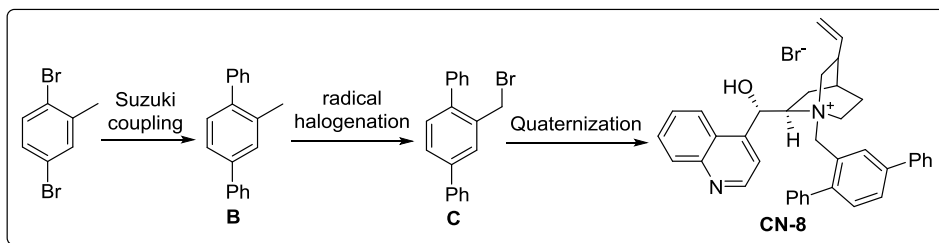
Figure 20. ¹H NMR spectra and signals assignment for thiomorpholines **18** (up) and **19** (down).

The stereochemistry of the corresponding isomers was elucidated by analogy with the piperazines on Chapter 2. For thiomorpholine **19**, the main diastereomer had a coupling constant between the benzylic and the homobenzylic proton of 2.99 Hz (*cis*- isomer) whilst the minor diastereomer had a coupling constant of 8.19 Hz (*trans*- isomer). Thiomorpholine **18** was isolated as single diastereomer, with a coupling constant of 9.58 Hz so *trans*- isomer was assigned by analogy.

The reaction was then performed with the optically pure epoxide **13a**. Unfortunately, both thiomorpholines **18** and **19** were obtained as a racemic mixture. We supposed that the ketone intermediate was very sensitive to epimerization by enolization in the basic media. Despite we could not afford enantiomerically pure compounds, we succeeded in the transformation of nitroepoxides into interesting heterocycles. An extensive research study for the synthesis of thiomorpholines, morpholinols and further morpholines and benzoxazines was performed in collaboration with MSc, student Estefania Capel and it has been already accepted for publication.¹⁵⁹ Asymmetric applications of enantioenriched nitroepoxides are currently being investigated.

3. Synthesis of Precursors

The synthesis of precursors did not present a big challenge since most of them are well known compounds (see experimental section for detail and bibliographic references). Synthesis of nitroalkenes and racemic nitroepoxides has already been described on Chapter 2. PTCs **CN-1** to **CN-5**, **CN-8**, **DHCN-1**, **QD-1** and **CD-1** were prepared by refluxing the corresponding cinchona alkaloid with the corresponding bromides. Those bromides were commercially available or easily synthesizable by bromination with PBr_3 . It might be worthy to describe the preparation of catalysts **CN-8** and **CN-9** (Scheme 64).



Scheme 64. Synthetic route to the synthesis of catalyst **CN-8**

Starting with 2,5-dibromotoluene, a double Suzuki coupling was performed to obtain the intermediate 2,5-diphenyl toluene **B**, which

¹⁵⁹ Capel, E.; Vidal-Albalat, A.; Rodríguez, S.; González, F. V. *Synthesis* **2016**, *48*, A-1

was isolated by silica flash liquid chromatography. Then, radical bromination with *N*-bromo succinimide and AIBN was performed to obtain the disubstituted benzyl bromide **C**, which was used without further purification for the synthesis of **CN-8**.

Catalysts **CN-6**, **CN-7** and **CN-9** were synthesized from the corresponding PTCs by alkylation with allyl bromide.

4. Conclusions

- Different organocatalytic systems were tested, but phase transfer catalysis was chosen among them due to operability, availability of reagents and the promising results that first trials offered.
- Solvent, substrate concentration, catalyst and many other parameters were wisely optimized to achieve great results in terms of yield and enantioselectivity.
- The scope of the reaction was demonstrated to be suitable for nitroalkenes with aryl and alkyl substitution, and also good results were obtained for aryl and aryl substitution. However, the methodology was not suitable for alkyl and alkyl substrates.
- Experimental evidences suggested that aromatic group in the nitroalkene interacts non-covalently with the aromatic moiety in the N-substitution of the cinchoninium catalyst, probably π - π stacking interactions. Having a hydroxyl group on position 9 of the catalyst was crucial for enantioselectivity, since alkylation with allyl bromide resulted in inversion of enantioselectivity. Those hypotheses were consistent with the computational calculations.
- Preparation of interesting heterocyclic compounds such as morpholinols, thiomorpholines, morpholines and benzoxazines from nitroepoxides was done, even though optical activity is lost when starting from optically pure nitroepoxides.

5. Experimental Section

General Information

Unless otherwise specified, all reactions were carried out under nitrogen atmosphere with magnetic stirring. All solvents and reagents were obtained from commercial sources and were purified according to standard procedures before use. ^1H NMR spectra and ^{13}C NMR spectra were measured in CDCl_3 (^1H , 7.27 ppm; ^{13}C 77.0 ppm) solution at 30 °C on a 300 MHz or a 500 MHz NMR spectrometer. Mass spectra were measured in a QTOF I (quadrupole-hexapole-TOF) mass spectrometer with an orthogonal Z-spray-electrospray interface. EM Science Silica Gel 60 was used for column chromatography while TLC was performed with precoated plates (Kieselgel 60, F₂₅₄, 0.25 mm).

Catalyst **CD-1** was synthesized from cinchonidine following a procedure described by Corey,¹³⁹ catalysts **CN-1**, **CN-2** and **CN-3** from cinchonine as described by Q. Meng,¹⁶⁰ catalyst **CN-4** as described by Arai,^{135b} catalyst **CN-6** as described by O'Donnell.¹⁶¹

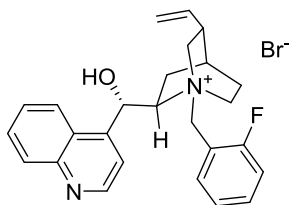
Experimental Procedures

General Experimental Procedure for the Synthesis of Ammonium Salts Catalysts **CN-5** and **CN-8**:

Following a modified experimental procedure: To a suspension of cinchonine (0.71 mmol, 1 eq) in THF (7.1 mL) was added the corresponding bromide (0.78 mmol, 1.1 eq), and the mixture was stirred at reflux for 18h. The mixture was cooled to 23 °C and then, diethyl ether was added. The solid was filtered, washed with cold diethyl ether and the resulting slightly-colored solid was finally collected and dried under vacuum.

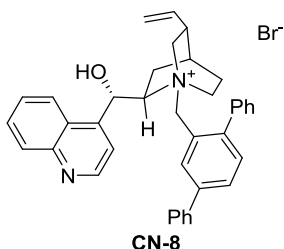
¹⁶⁰ Lian, M.; Li, Z.; Du, J.; Meng, Q.; Gao, Z.; *Eur. J. Org. Chem.* **2010**, 6525-6530.

¹⁶¹ O'Donnell, M.J.; Delgado, F.; Pottorf, R.S.; *Tetrahedron* **1999**, 55, 6347



CN-5 *N*-(2-fluorobenzil)cinchoninium bromide **CN-5**

5: White solid (mp 225 - 228 °C) (yield 554 mg, 92%). ^1H NMR (500 MHz, DMSO- d_6) δ 9.00 (d, $J = 4.4$ Hz, 1H), 8.38 (d, $J = 8.2$ Hz, 1H), 8.12 (d, $J = 8.4$ Hz, 1H), 7.85 (dd, $J = 14.5, 5.9$ Hz, 2H), 7.76 (t, $J = 7.6$ Hz, 1H), 7.68 (dd, $J = 13.7, 5.8$ Hz, 1H), 7.53 - 7.39 (m, 2H), 6.87 (d, $J = 3.3$ Hz, 1H), 6.54 (s, 1H), 6.02 (ddd, $J = 17.4, 10.5, 7.1$ Hz, 1H), 5.28 - 5.18 (m, 1H), 5.08 (s, 1H), 4.28 - 4.18 (m, 1H), 3.99 (dd, $J = 19.8, 9.4$ Hz, 2H), 3.37 (t, $J = 11.1$ Hz, 1H), 3.18 - 3.05 (m, 1H), 2.68 (dd, $J = 17.2, 8.1$ Hz, 1H), 2.36 - 2.24 (m, 1H), 1.93 - 1.71 (m, 3H), 1.05 (ddd, $J = 13.7, 9.1, 4.9$ Hz, 1H) ppm. ^{13}C NMR (126 MHz, DMSO- d_6) δ 162.2 (d, $J = 249.3$ Hz), 150.6 (d, $J = 29.2$ Hz), 148.1, 145.4, 137.6, 137.4, 136.3 (d, $J = 21.8$ Hz), 130.3, 127.8, 127.5, 125.8, 125.5, 124.9, 124.2, 120.6, 120.5, 117.5, 116.6, 115.8, 115.7, 67.5 (d, $J = 22.7$ Hz), 65.4 (d, $J = 21.8$ Hz), 56.4, 37.3, 37.1, 26.5, 23.5, 21.1 ppm. HRMS (ESI) $[\text{M}^+]$ calcd for $\text{C}_{26}\text{H}_{28}\text{FN}_2\text{O}^+$ 403.2186, found 403.2184; IR (KBr) δ 3607, 3037, 2966, 1655, 1418, 1312, 1028, 909, 770 cm^{-1}



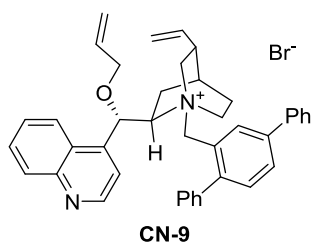
CN-8 *N*-(2,5-diphenylbenzil)cinchoninium bromide **CN-8**

8: Orange solid (mp 180 °C) (yield 156 mg, 92%). ^1H NMR (500 MHz, CDCl_3) δ 8.67 (s, 1H), 8.62 (s, 1H), 8.39 (m, 1H), 7.72 - 7.17 (m, 13H), 6.61 (s, 1H), 6.40 (m, 1H), 6.00 (m, 1H), 5.77 (br s, 1H), 5.53 (m, 1H), 5.01 (d, $J = 10.5$ Hz, 1H), 4.76 (d, $J = 17.2$ Hz, 1H), 3.00 (m, 1H),

3.48 (m, 1H), 2.94 (s, 1H), 2.68 (m, 1H), 2.12 (s, 1H), 1.80 (m, 1H), 1.59 – 1.44 (m, 2H), 0.49 (m, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ 149.7, 147.2, 145.2, 143.7, 140.4, 139.7, 138.6, 135.4, 134.4, 131.9, 129.8, 129.2, 128.9, 128.5, 127.8, 127.0, 126.8, 125.4, 124.0, 123.0, 119.8, 117.6, 65.2, 55.9, 54.0, 45.8, 37.7, 29.6, 26.8, 23.9, 21.5, 8.5 ppm; HRMS (ESI) $[\text{M}^+]$ calcd for $\text{C}_{39}\text{H}_{37}\text{N}_2\text{O}$ 537.2906, found 537.2906. IR (KBr) δ 3339, 3057, 3029, 2948, 1715, 1555, 1495, 1468, 1354, 1007, 922, 839, 761, 730 cm^{-1} .

General Experimental Procedure for O-alkylation of Phase Transfer Catalysts for the Preparation of Catalysts, CN-6, CN-7 and CN-9:

To a suspension of the corresponding phase transfer catalyst (0.11 mmol, 1 eq) in 450 μL of DCM was added allyl bromide (0.33 mmol, 3 eq) and 30 μL of 50% aqueous KOH (0.55 mmol). The resulting mixture was stirred vigorously at 23 $^\circ\text{C}$ for 4 h, during which time all of the solids dissolved. The mixture was diluted with 2 mL of water and was extracted with DCM (3 x 5 mL). The combined organic extracts were dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Recrystallization of the residue from methanol-diethyl ether (diethyl ether was added dropwise until a solution of the product in methanol turned cloudy at 23 $^\circ\text{C}$) at -20 $^\circ\text{C}$ to afford the pure compound.

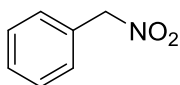


O-allyl-N-(2,5-diphenylbenzyl)cinchoninium

bromide CN-9: Orange-brown solid (mp 229 $^\circ\text{C}$); ^1H NMR (300 MHz, CDCl_3) δ 9.14 (s, 1H), 8.89 (d, $J = 4.4$ Hz, 3H), 8.11 (d, $J = 8.2$ Hz, 2H), 7.92 (d, $J = 7.2$ Hz, 4H), 7.87 – 7.75 (m, 4H), 7.59 – 7.33 (m, 19H), 6.51 (d, $J = 11.7$ Hz, 2H), 6.10 (s, 2H), 5.81 – 5.45 (m, 4H), 5.30

– 5.12 (m, 4H), 5.06 (d, $J = 11.7$ Hz, 4H), 4.92 (d, $J = 17.0$ Hz, 2H), 4.61 (s, 2H), 3.78 (qd, $J = 11.4, 4.9$ Hz, 4H), 3.36 (dd, $J = 16.0, 6.1$ Hz, 2H), 3.28 – 3.05 (m, 2H), 2.99 – 2.81 (m, 2H), 2.36 (dd, $J = 15.7, 7.8$ Hz, 2H), 2.29 – 2.09 (m, 2H), 1.96 – 1.79 (m, 3H), 1.16 – 0.97 (m, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 149.7, 147.3, 145.2, 143.8, 140.5, 139.8, 138.6, 135.4, 134.4, 131.9, 129.8, 129.3, 128.9, 128.6, 127.8, 127.0, 126.8, 125.5, 124.1, 123.1, 119.9, 117.6, 77.20, 65.2, 56.0, 54.1, 45.8, 37.7, 29.7, 26.8, 23.9, 21.5. HRMS (ESI) $[\text{M}^+]$ calcd for $\text{C}_{41}\text{H}_{41}\text{N}_2\text{O}^+$ 577.3219, found 577.3211. IR (KBr) δ 3051, 2980, 2949, 1585, 1419, 1259, 1049, 983, 893, 701, 698 cm^{-1}

Experimental Procedure for the Preparation of Phenylnitromethane:¹⁶²



To a solution of the benzyl alcohol (5 mL, 47.3 mmol) in DCM (130 mL) was added NaNO_2 (11.7 g, 167.8 mmol). To this mixture was added acetic acid (7 mL) at room temperature and after 5 minutes, conc. HCl (2.4 mL) was added to this mixture and it was left at r.t. without stirring for 6 hours. The reaction mixture was diluted with DCM (150 mL) and the precipitated NaOAc was filtered off. The organic phase was evaporated in vacuo and the residue was dissolved in hexane (100 mL) and washed with cold water (5x200 mL) to remove the acid. The organic phase was dried over anhydrous sodium sulfate, filtered and finally concentrated in vacuo. The crude oil was purified by silica gel LC (hexanes-ethyl acetate, 9:1) to afford a yellow oil (3.4 g, 52% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.49-7.42 (m, 5H), 5.45 (s, 2H).

¹⁶² Baruha, A.; Kalita, B.; Barua, N.C.; *Synlett* **2000**, 7, 1064.

General Experimental Procedure for the Preparation of Nitroalkenes:^{163,164}

As described in Chapter 2 and the indicated bibliographic references.

General Experimental Procedure for the Preparation of Racemic Nitroepoxides:

Racemic epoxides were prepared as reported in Chapter 2.¹⁶⁵

General Experimental Procedure for the Optimization of the Epoxidation Reaction:

20 mg of *trans*- β -methyl- β -nitrostyrene were placed in a small vial with a proper magnetic stirrer and solved with the indicated solvent. Then, the corresponding catalyst was added and the mixture stirred to homogenization. Finally, NaOCl solution was added and the mixture was constantly and vigorously stirred until consumption of nitroalkene. The reaction was stopped by addition of water, the crude extracted with DCM or EtOAc and concentrated under vacuum. The conversion was measured on ¹H NMR and the enantioselectivity on chiral HPLC using ChiralPak IA column (Hexane/*i*-PrOH 99/1, 1 mL/min, 254 nm), Rt₁ (minor) = 8.5 min, Rt₂ (major) = 9.7 min; er = 96.1:3.9

General Experimental Procedure for the Assymmetric Synthesis of Nitroepoxides:¹⁶⁶

To a cold solution (-20°C) of the corresponding nitroalkene (0.253 mmol, 1 eq) and the phase transfer catalyst **CN-2** (0.020 mmol, 8 mol%) in toluene (840 μ l, 0.3M), NaOCl aqueous solution (10-15% in Cl, 420 μ l) was added dropwise and the mixture was vigorously stirred at -20°C for 18 hours. Then, hexanes (3 mL) was added and the mixture

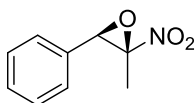
¹⁶³ Alizadeh, A.; Khodaei, M.M.; Eshghi, A. *J. Org. Chem.* **2010**, *75*, 8295.

¹⁶⁴ Anderson, J. C.; Blake, A. J.; Mills, M.; Ratcliffe, P. D.; *Org. Lett.* **2008**, *10*, 141.

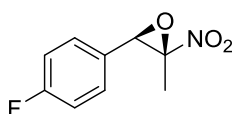
¹⁶⁵ Vankar, Y. D.; Shah, K.; Bawa, A.; Singh, S. P.; *Tetrahedron* **1991**, *47*, 8883.

¹⁶⁶ Lygo, B.; Crosby, J.; Lowdon, T. R.; Peterson, J. A.; Wainwright, P. G. *Tetrahedron* **2001**, *57*, 2403.

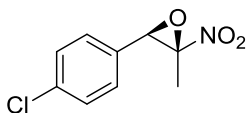
was filtered through an anhydrous MgSO_4 pad, washed with an extra amount of hexane, and the filtered solution was concentrated under vacuum to afford the pure nitroepoxide, which was stored at -20°C to solidification.



(2S,3R)-2-Methyl-2-nitro-3-phenyloxirane 13a. The product obtained was a pale yellow oil which crystallized when stored at -20°C as a white solid (mp = $82 - 85^\circ\text{C}$) (yield 42 mg, 92%). $[\alpha]_{\text{D}}^{23} + 72.0$ (c = 1.2, CHCl_3). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.41 (m, 3H), 7.30 (m, 2H), 4.56 (s, 1H), 1.78 (s, 3H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 131.0, 129.3, 128.7, 126.3, 88.8, 62.6, 12.2 ppm; HRMS (EI) calcd for $\text{C}_9\text{H}_9\text{NO}_3$ (M) 179.0582, found 179.0587; IR (KBr) δ 3062, 3028, 2948, 1555, 1495, 1448, 1354, 1158, 1105, 982, 899 cm^{-1} . Enantiomers were separated by GC/MS Cyclosil-B chiral capillar column (He carrier gas, 1 mL/min), Rt_1 (minor) = 11.2 min, Rt_2 (major) = 11.7 min; er = 96.6:3.4.

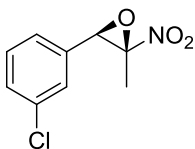


3-(4-Fluorophenyl)-2-methyl-2-nitrooxirane 13b. The product obtained was a colorless oil which crystallized when stored at -20°C as a white solid (mp = $60-63^\circ\text{C}$) (yield 48 mg, 96%). $[\alpha]_{\text{D}}^{23} + 68.0$ (c = 1.2, CHCl_3). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.33–7.26 (m, 2H), 7.13–7.05 (m, 2H), 4.51 (s, 1H), 1.76 (s, 3H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 163.2 (d, $J = 247.8$ Hz), 128.3 (d, $J = 8.4$ Hz), 126.8 (d, $J = 4.0$ Hz), 115.8 (d, $J = 22.0$ Hz), 88.8, 62.1, 12.1 ppm; HRMS (EI) calcd for $\text{C}_9\text{H}_8\text{NFO}_3$ (M) 197.0488, found 197.0492. IR (KBr) δ 3059, 3024, 2944, 1546, 1490, 1452, 1205, 896, 830 cm^{-1} . HPLC: ChiralPak IA (Hexane/*i*-PrOH 500/1, 1 mL/min, 254 nm), Rt_1 (minor) = 14.5 min, Rt_2 (major) = 17.5 min; er = 96.1:3.9.



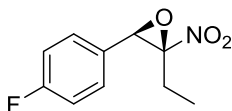
3-(4-Chlorophenyl)-2-methyl-2-nitrooxirane 13c.

The product obtained was an orange solid (mp = 50-56 °C) (yield 50 mg, 92%). $[\alpha]_D^{23} + 71.0$ (c= 2.0, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ 7.39 (d, *J* = 8.5 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 4.51 (s, 2H), 1.77 (s, 3H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ 135.47, 129.47, 129.02, 127.74, 88.60, 61.95, 12.30 ppm; IR (KBr) δ 3052, 2984, 1560, 1420, 1259, 894, 697 cm⁻¹. LRMS (EI): Mass calcd for C₉H₈ClO [M-NO₂]⁺ : 167.0; found 167.1, Mass calcd for C₆H₄Cl [M-C₃H₄NO₃]⁺ : 111.0; found 111.0. HPLC: ChiralPak IA (Hexanes/*i*-PrOH 500/1, 1 mL/min, 254 nm), Rt₁ (minor) = 15.4 min, Rt₂ (major) = 19.2 min; er = 97:3.



3-(3-Chlorophenyl)-2-methyl-2-nitrooxirane 13d.

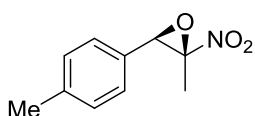
The product obtained was a yellow oil which crystallized when stored at -20 °C as a yellow solid (mp = 38-42 °C) (yield 47 mg, 87%). $[\alpha]_D^{23} + 80.0$ (c= 1.0, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ 7.42 – 7.34 (m, 1H), 7.31 (s, 1H), 7.22 (d, *J* = 6.9 Hz, 1H), 4.53 (s, 1H), 1.80 (s, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 134.97, 133.03, 130.12, 129.66, 126.46, 124.59, 88.54, 61.72, 12.40; IR (KBr) δ 3052, 2982, 1559, 1419, 1259, 893, 700, 698 cm⁻¹. LRMS (EI): Mass calcd for C₉H₈ClO [M-NO₂]⁺ : 167.0; found 167.0, mass calcd for C₆H₄Cl [M-C₃H₄NO₃]⁺ : 111.0; found 111.0 ; HPLC: ChiralPak IA (Hexane/*i*-PrOH 99/1, 1 mL/min, 254 nm), Rt₁ (minor) = 9.0 min, Rt₂ (major) = 13.0 min; er = 91.5:8.5.



2-Ethyl-3-(4-fluorophenyl)-2-nitrooxirane 13e.

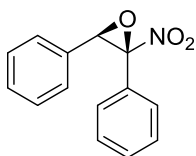
The product obtained was a pale yellow oil which crystallized when stored at -20°C as a pale yellow solid (mp = 30-37 °C) (yield 49 mg, 91%). $[\alpha]_D^{23} + 32.3$ (c= 1.3, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ

7.37–7.19 (m, 2H), 7.10 (t, $J = 8.6$ Hz, 2H), 4.49 (s, 1H), 2.45 (dq, $J = 15.1, 7.4$ Hz, 1H), 1.67 (dq, $J = 14.8, 7.3$ Hz, 1H), 1.05 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 163.2 (d, $J = 247.5$ Hz), 128.2 (d, $J = 8.3$ Hz), 127.0 (d, $J = 2.3$ Hz), 115.9 (d, $J = 21.8$ Hz), 92.37, 62.62, 19.44, 7.53 ppm; HRMS (EI) calcd for $\text{C}_{10}\text{H}_{10}\text{FNO}_3$ (M) 211.0645, found 211.0651; IR (KBr) δ 3052, 2979, 1710, 1606, 1552, 1510, 1347, 1227, 1156 cm^{-1} . HPLC: ChiralPak IA (Hexane/*i*-PrOH 500/1, 1 mL/min, 254 nm), Rt_1 (minor) = 11.9 min, Rt_2 (major) = 12.8 min; er = 95.1:4.9.



2-Methyl-2-nitro-3-(*p*-tolyl)oxirane 13f. The

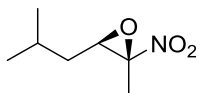
product obtained was a yellow oil which crystallized when stored at -20°C as a white solid (mp = $65\text{--}67^\circ\text{C}$) (yield 45 mg, 92%). $[\alpha]_{\text{D}}^{22} +82.5$ ($c = 0.8$, CHCl_3). ^1H NMR (500 MHz, CDCl_3) δ 7.26–7.17 (m, 4H), 4.50 (s, 1H), 2.38 (s, 3H), 1.80 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 139.6, 129.5, 128.0, 126.4, 89.1, 62.8, 21.1, 12.4 ppm; HRMS (EI) calcd for $\text{C}_{10}\text{H}_{11}\text{NO}_3$ (M) 193.0739, found 193.0745; IR (KBr) δ 3062, 3025, 2948, 1552, 1449, 1346, 1158, 899, 768 cm^{-1} . HPLC: ChiralPak IA (Hexane/*i*-PrOH 99/1, 1 mL/min, 254 nm), Rt_1 (major) = 7.1 min, Rt_2 (minor) = 8.0 min; er = 91.3:8.7.



2-Nitro-2,3-diphenyloxirane 13g. The product

obtained was a pale yellow solid (mp = $65\text{--}70^\circ\text{C}$) (yield 55 mg, 90%); $[\alpha]_{\text{D}}^{22} -64.0$ ($c = 0.8$, CHCl_3). ^1H NMR (500 MHz, CDCl_3) δ 7.54 – 7.31 (m, 5H), 7.29 – 7.16 (m, 3H), 7.05 (d, $J = 7.8$ Hz, 2H), 4.78 (s, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ 134.72, 131.06, 130.61, 130.54, 130.37, 129.40, 129.34, 128.67, 128.36, 128.27, 126.90, 126.36, 91.68, 63.79. IR (KBr) δ 3051, 2983, 2300, 1642, 1419, 1258, 893, 789, 697 cm^{-1} . LRMS (EI): $\text{C}_{14}\text{H}_{11}\text{NO}_2$ $[\text{M}-\text{O}]^+$: 225.1; found 225.1, Mass calcd

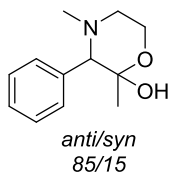
for $C_{14}H_{11}O$ $[M-NO_2]^+$: 195.1; found 195.0, Mass calcd for C_6H_5 $[M-C_8H_6NO_3]^+$: 77.0; found 77.1. Absolute configuration was assigned by X-Ray crystall resolution. HPLC: ChiralPak IA (Hexane/*i*-PrOH 99/1, 1 mL/min, 254 nm), R_{t1} (major) = 8.7 min, R_{t2} (minor) = 9.9 min; er = 91.5:8.5.



3-Isobutyl-2-methyl-2-nitrooxirane 13h. Yellowish oil (yield 25 mg, 63%). 1H NMR (300 MHz, $CDCl_3$) δ 3.33 (dd, J = 6.8, 5.3 Hz, 1H), 1.80 (s, 3H), 1.72–1.85 (m, 1H), 1.52–1.31 (m, 2H), 0.90 (d, J = 6.7 Hz, 3H), 0.89 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 87.6, 62.0, 36.1, 26.0, 22.3, 22.2, 13.4 ppm; HRMS (EI) calcd for $C_7H_{13}NO_3$ (M) 159.0895, found 159.0901; IR (KBr) δ 2940, 1561, 1167 cm^{-1} . HPLC: ChiralPak IA (Hexane/*i*-PrOH 99/1, 1 mL/min, 254 nm), R_{t1} (minor) = 5.6 min, R_{t2} (major) = 6.6 min; er = 56.5:43.5.

Experimental Procedure for the Preparation of Morpholinol 16:

To an ice-bath cold solution of the corresponding nitroepoxide (0.56 mmol) in MeOH (1 mL), *N*-methyl 2-ethanolamine (90 μ L; 1.12 mmol) was added. The resulting mixture was stirred for 3.5 hours at room temperature, then H_2O (5 mL) was added, extracted with EtOAc (3 x 20 mL), washed with brine (20 mL), dried with Na_2SO_4 and concentrated under vacuum. The resulting crude oil was purified through silica flash liquid chromatography with hexanes/EtOAc (1:1), EtOAc and EtOAc/MeOH (9:1) to afford desired product.

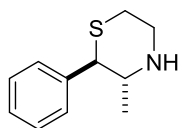


2,4-dimethyl-3-phenylmorpholin-2-ol, 16. white solid, 101 mg (yield 87 %) mp 64–66 °C: 1H NMR (300 MHz, $CDCl_3$) δ 7.49 – 7.27 (m, 5H), 5.29 (s, 1H), 4.23 (ddd, J = 15.4, 8.8, 2.6 Hz, 1H), 3.68

(ddd, $J = 12.0, 4.0, 1.1$ Hz, 1H), 3.07 (s, 1H), 2.87 (ddd, $J = 11.6, 2.9, 1.0$ Hz, 1H), 2.50 (ddd, $J = 12.5, 11.7, 4.0$ Hz, 1H), 2.04 (s, 3H), 1.10 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 137.53, 128.04, 127.85, 95.69, 77.24, 59.44, 56.15, 44.15, 25.03. HRMS (ESI) calcd. for $\text{C}_{12}\text{H}_{18}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 208.1338, found $[\text{M}+\text{H}]^+$ 208.1335; IR (KBr) δ 3500, 3049, 2985, 1601 cm^{-1} ;

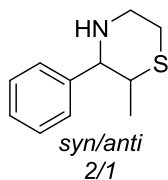
Experimental Procedure for the Preparation of Thiomorpholines **18** and **19**.

2-Amino-ethanethiol hydrochloride (55 mg, 0.47 mmol) was solved with a solution of KOH (53 mg, 0.95 mmol) in EtOH (1.2 mL) at 0°C and under inert conditions. To this mixture, a previously purged solution of nitroepoxide **1a** (85 mg, 0.47 mmol) in dry EtOH (0.4 mL) was added and the mixture was stirred below 5°C until consumption of nitroepoxide (ca. 3 h). Then, solid NaBH_4 (37 mg, 0.95 mmol) was added to the cold mixture and kept stirring for 1.5 h. Then, the reaction mixture was quenched with 5% aqueous solution of NH_4Cl (5 mL) and extracted with dichloromethane (3x10 mL), the combined organic phases washed with brine, dried over MgSO_4 , filtered and finally concentrated under vacuum to afford a yellow oil. The crude was purified by silica flash LC eluting sequentially with EtOAc/MeOH 9:1 to 7:3 to afford 3-methyl-2-phenylthiomorpholine, **18** as a pale yellow solid, 26 mg (28% yield):



***trans*-3-methyl-2-phenylthiomorpholine 18.** ^1H NMR (300 MHz, CDCl_3) δ 7.42 – 7.27 (m, 5H), 3.60 (d, $J = 9.6$ Hz, 1H), 3.44 (dt, $J = 12.0, 2.7$ Hz, 1H), 3.25 – 3.12 (m, 2H), 3.10 – 2.98 (m, 1H), 2.63 (bs, 1H), 2.59 – 2.50 (m, 1H), 0.91 (t, $J = 6.8$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 139.7, 128.6, 128.2, 127.6, 58.1, 52.0, 48.0, 30.1, 20.5 ppm. MS (EI) calcd. for $\text{C}_{11}\text{H}_{15}\text{NS}^+$ $[\text{M}]^+$ 193.1, found 193.1 IR (KBr) 3360, 3032, 2940, 1574, 1404, 1268, 1070, 707 cm^{-1} ;

and then, compound **19** as a yellow oil:



2-methyl-3-phenylthiomorpholine 19 ^1H NMR (400 MHz, CDCl_3) δ 7.40 – 7.14 (m, 10H), 4.16 (dd, $J = 8.3, 1.7$ Hz, 1H) (minor), 4.06 (d, $J = 3.2$ Hz, 1H) (major), 3.49 (qd, $J = 6.6, 3.3$ Hz, 1H) (major), 3.32 – 3.24 (m, 1H), 3.14 – 3.05 (m, 1H), 2.90 (m, 3H), 2.84 – 2.68 (m, 4H), 1.07 (d, $J = 6.7$ Hz, 1H) (major), 0.91 (d, $J = 6.4$ Hz, 1H) (minor). ^{13}C NMR (75 MHz, CDCl_3) δ 141.9, 128.3, 127.8, 127.2, 127.0, 77.7, 77.2, 60.1, 54.3, 48.2, 45.2, 42.5, 39.1, 27.2, 16.6, 15.4 ppm; MS (EI) calcd. for $\text{C}_{11}\text{H}_{15}\text{NS}^+$ $[\text{M}]^+$ 193.1, found 193.1 IR (KBr) 3307, 3022, 2918, 1595, 1448, 1268, 1024, 707 cm^{-1}

General Conclusions and Future Work

General Conclusions and Future Work

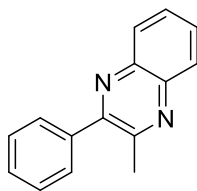
The general conclusions that can be obtained from the work of the present PhD Thesis are detailed as follow:

- The singular reactivity of nitroepoxides has been studied.
- An easily accessible methodology for the synthesis of 1,4-diazaheterocyclic compounds, including quinoxalines, pyrazines tetrahydroquinoxalines and piperazines, from nitroepoxides has been developed.
- Advances in the enantioselective epoxidation of dicyanoalkylidenes *via* bifunctional organocatalysts were made during a 4-month stay at Università degli Studi di Salerno (Italy).
- The enantioselective synthesis of nitroepoxides, mediated by phase transfer catalysis, has been achieved with high yields and enantioselectivities (e.r. > 90:10) for the substrates with aryl-alkyl substitution. Currently, the work is under review in a scientific journal.
- Nitroepoxides have been transformed into morpholinols and thiomorpholines. However, optical activity of the nitroepoxide was lost after the transformation.

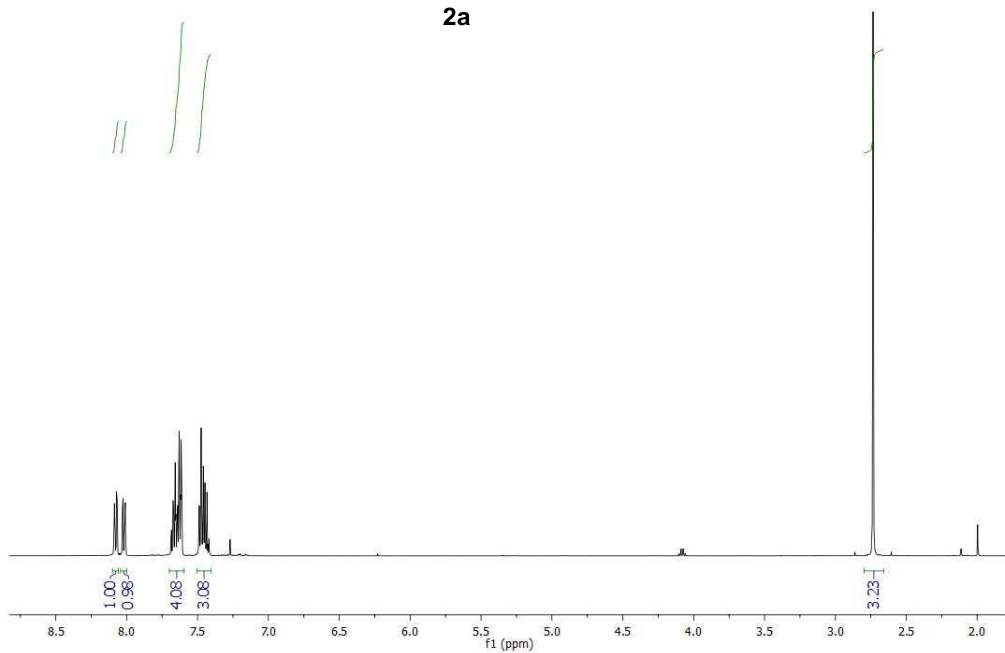
We think there is still place to study further the reactivity of nitroepoxides and develop new applications. A brief summary of the ongoing work:

- Develop new synthetical applications of nitroepoxides without loss of optical activity.
- Exploit the chemical features of nitroepoxides for the synthesis of new heterocycles in a simple and accessible methodology.
- Study the behaviour of the reaction between nitroepoxides and amines for the synthesis of 1,2-diamines, starting from optically pure nitroepoxides.

Selected Spectra

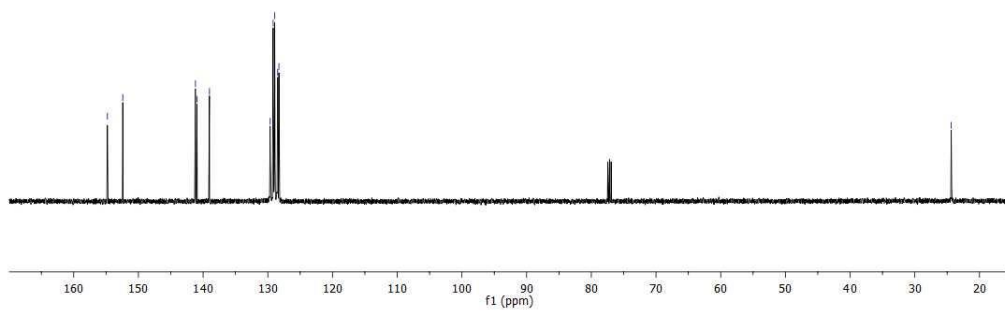


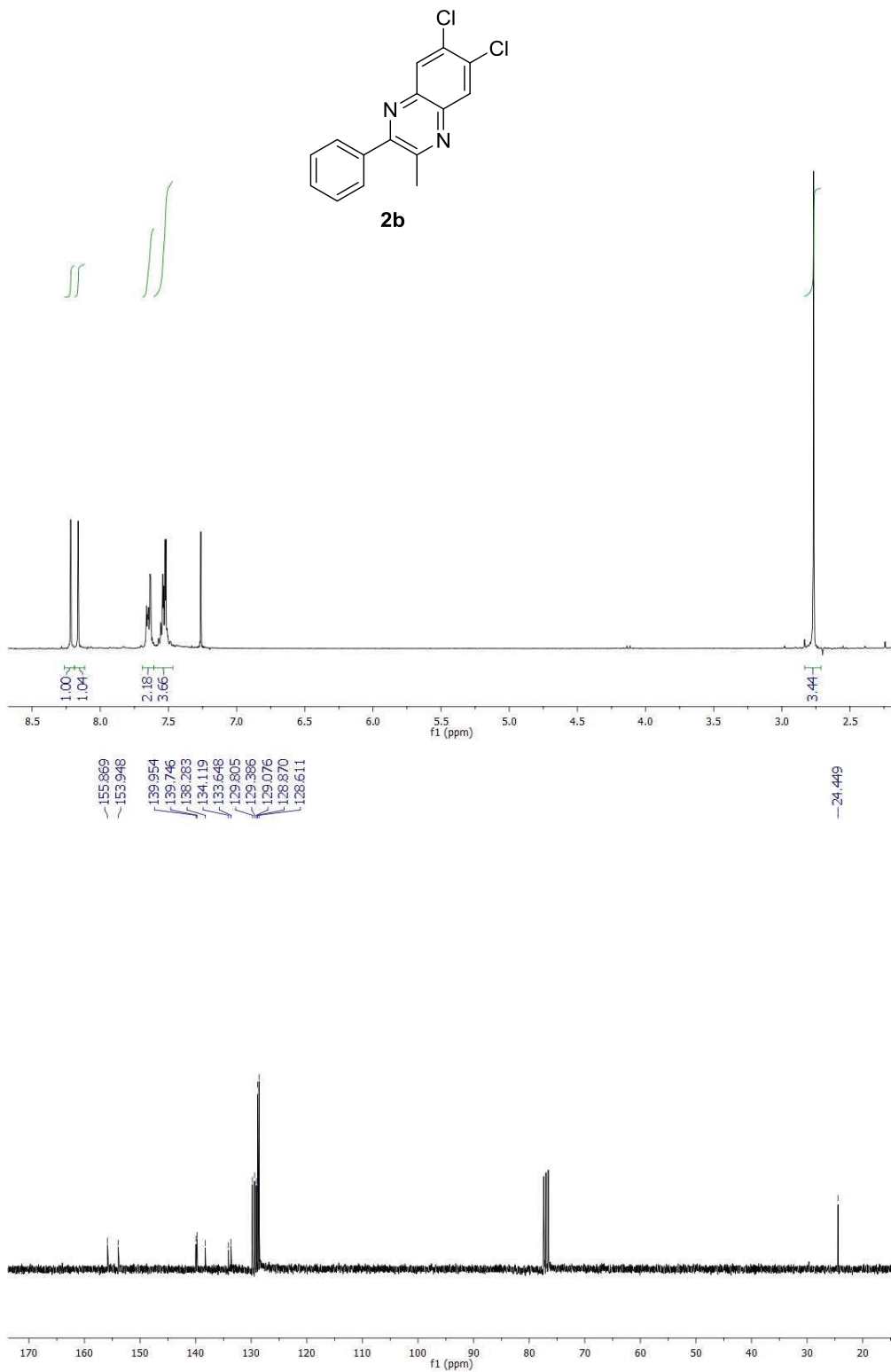
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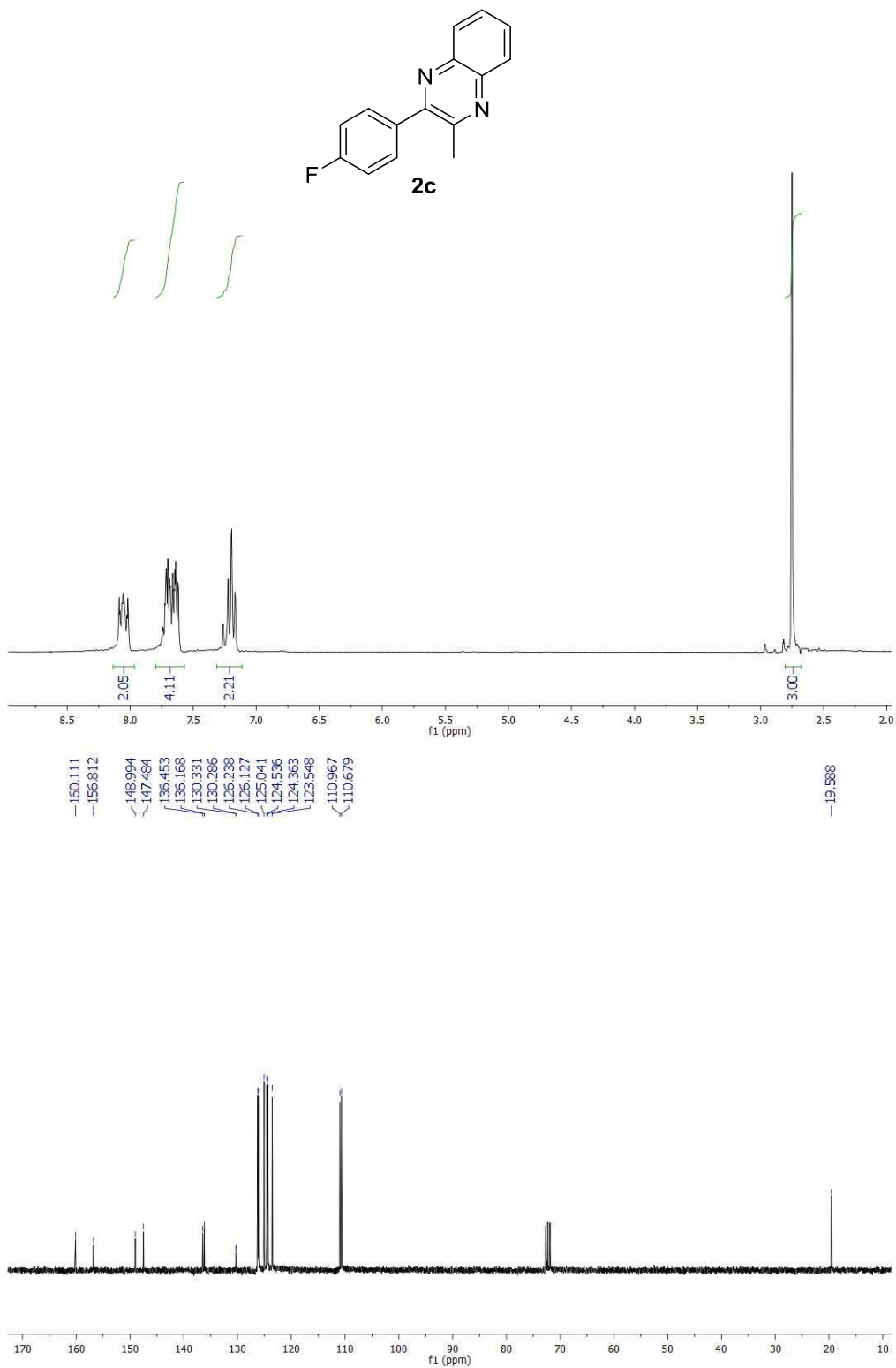


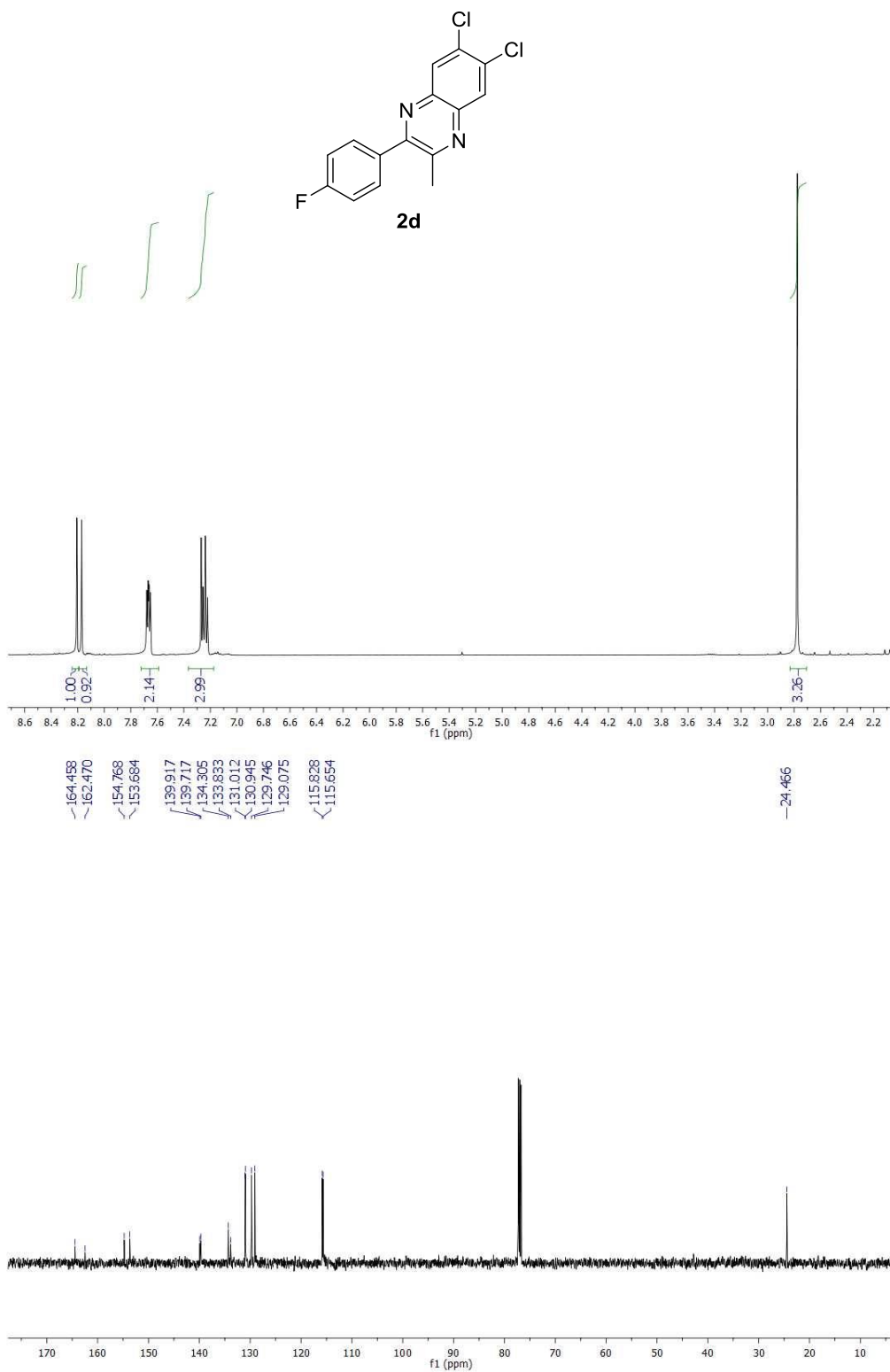
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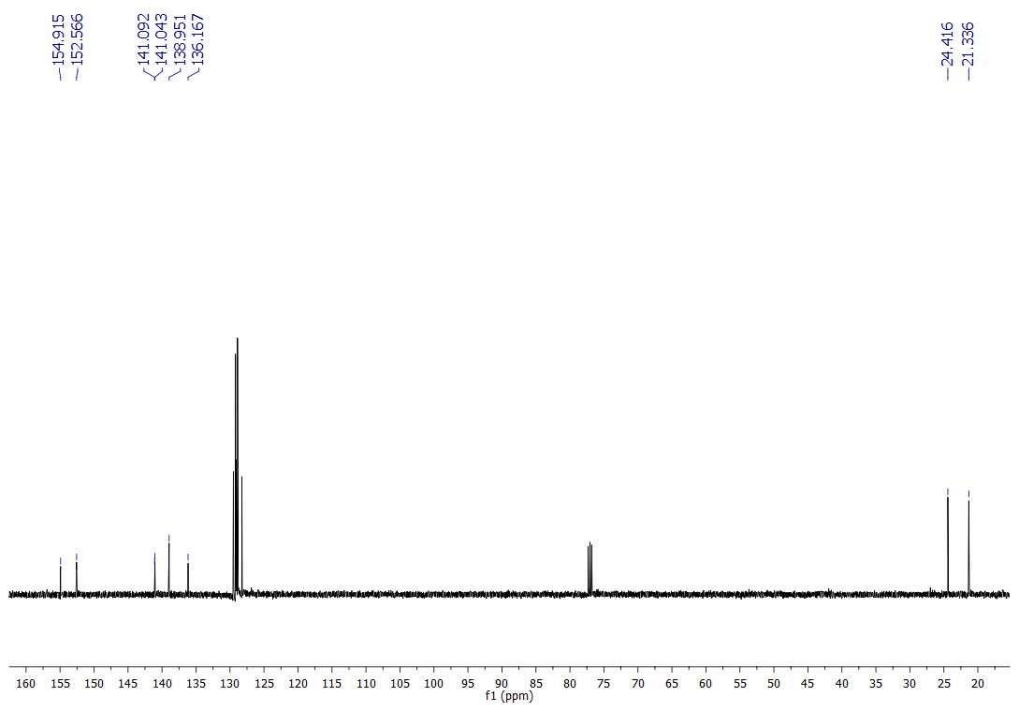
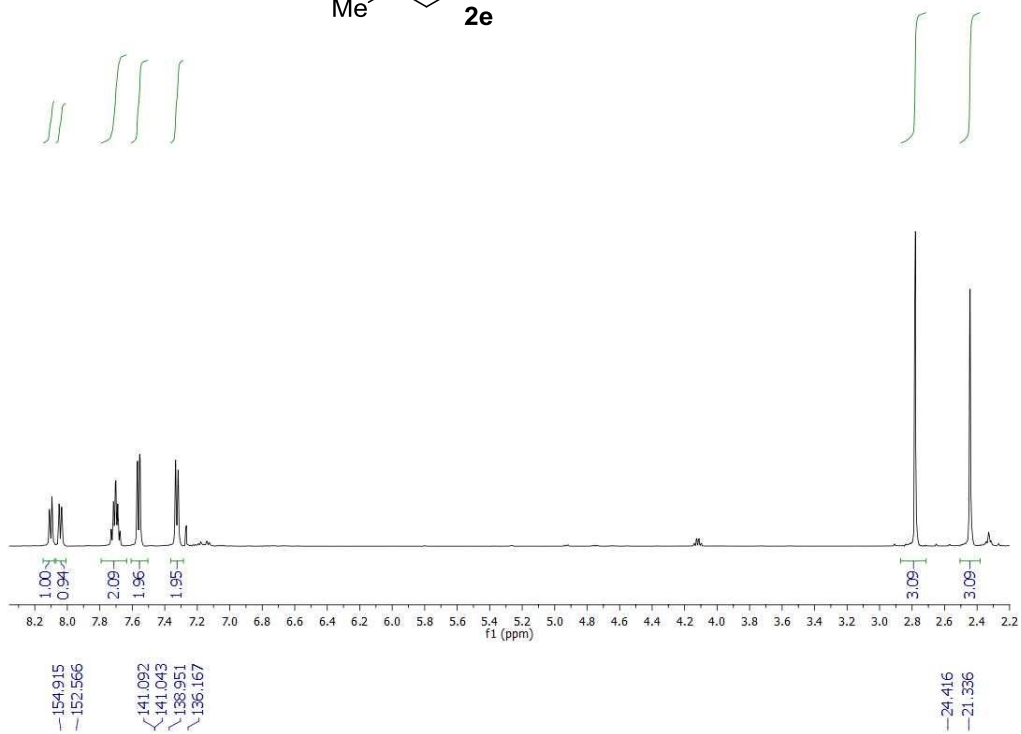
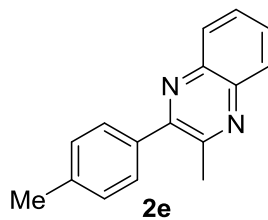
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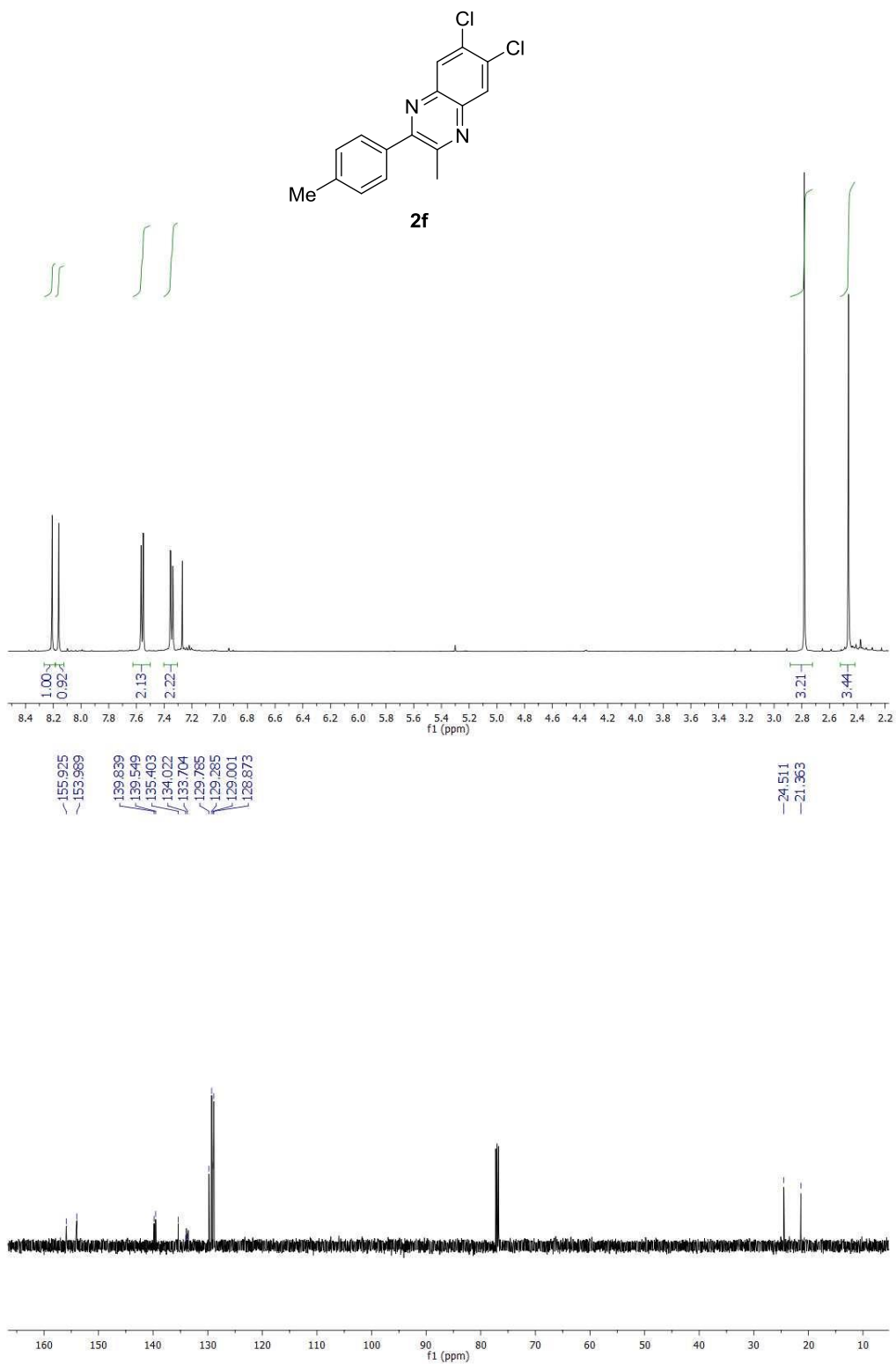


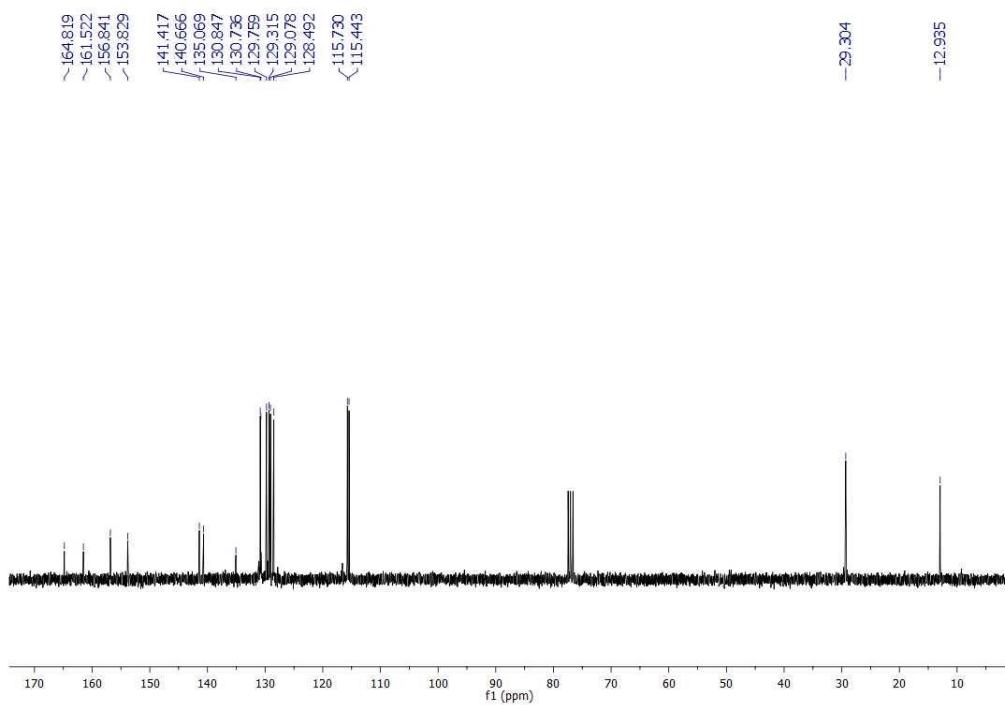
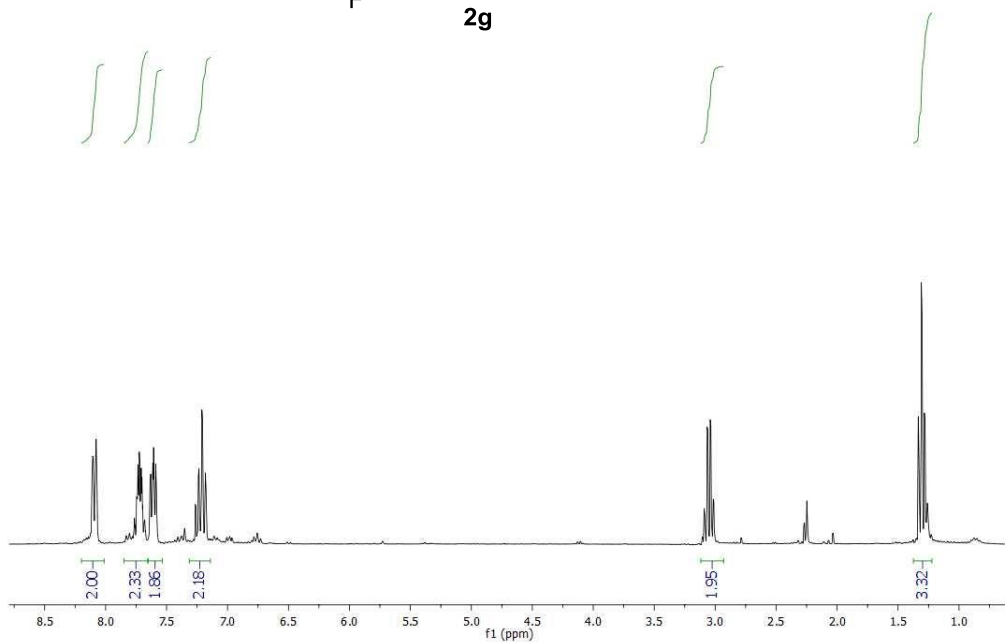
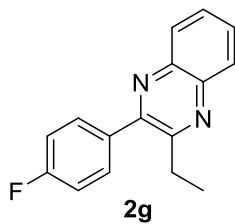


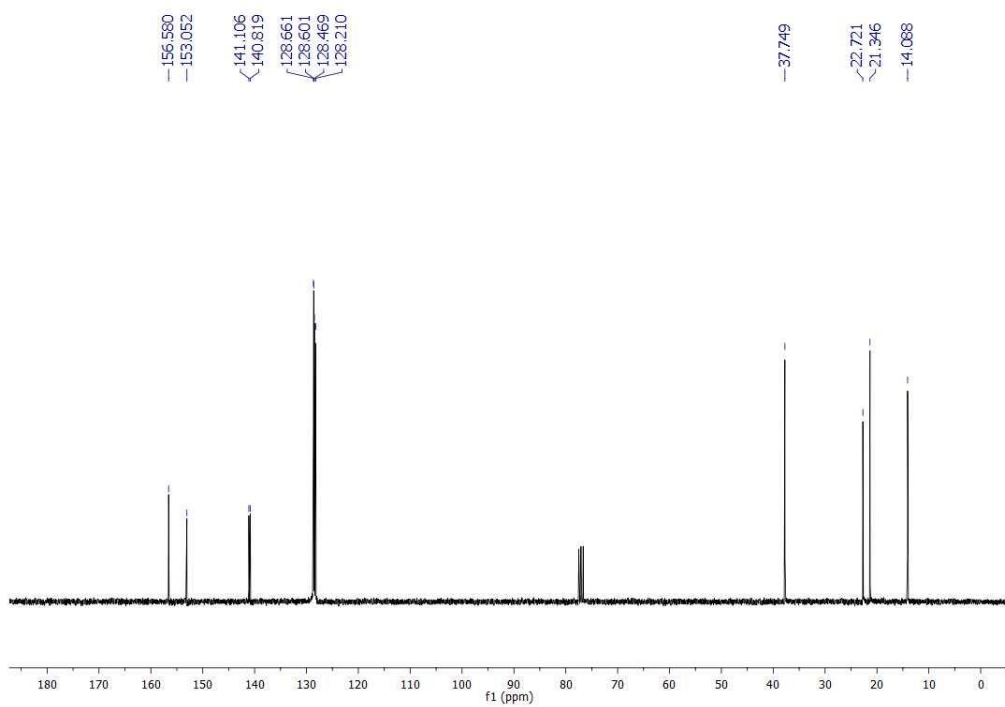
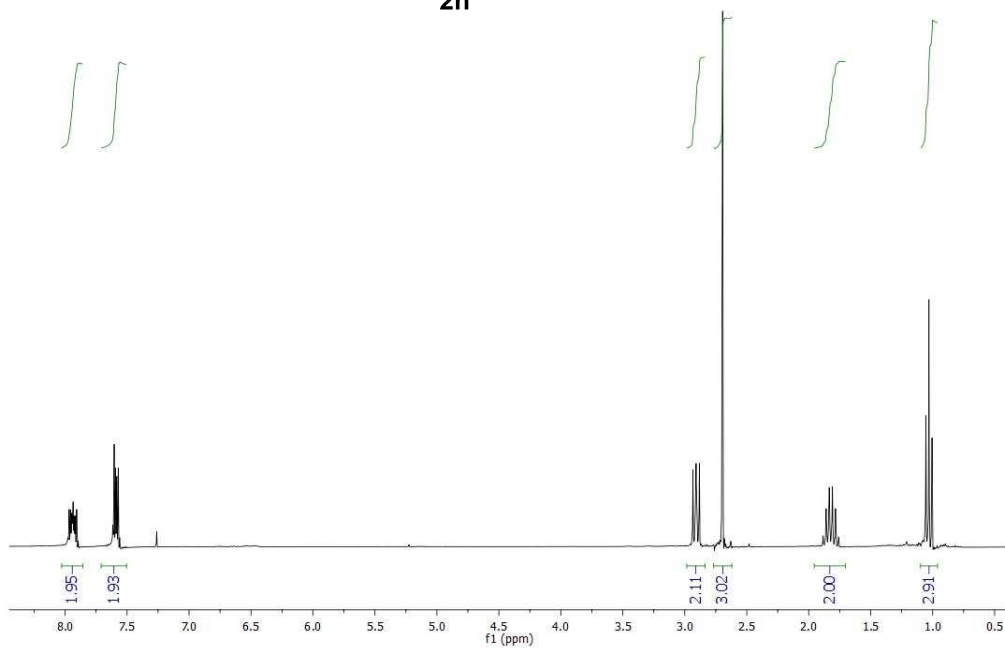
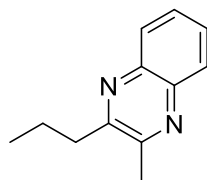


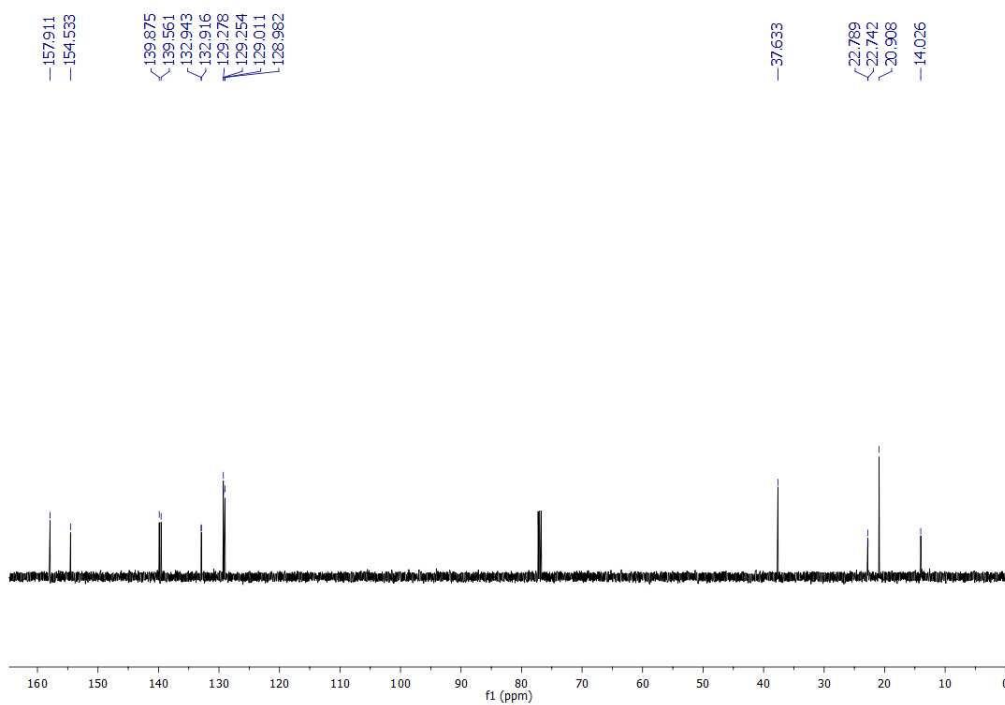
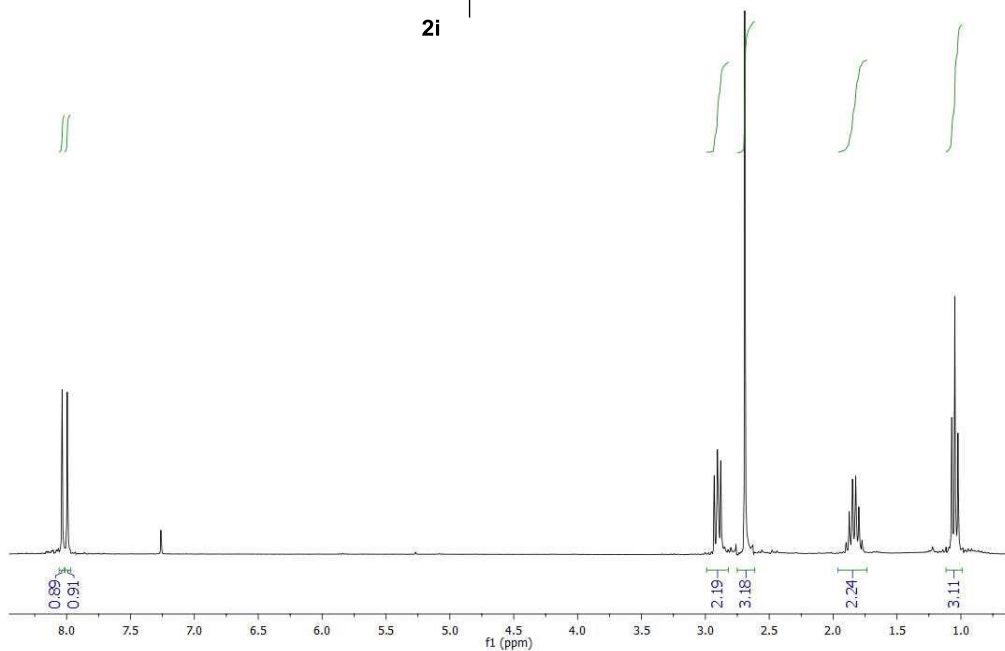
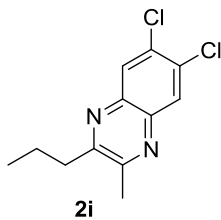


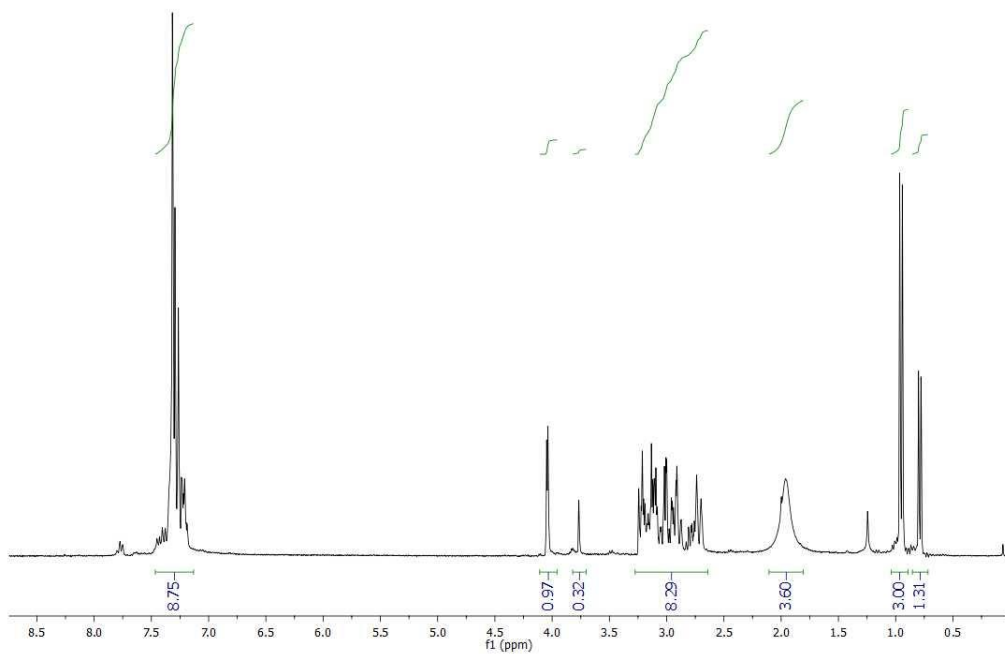
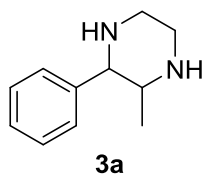








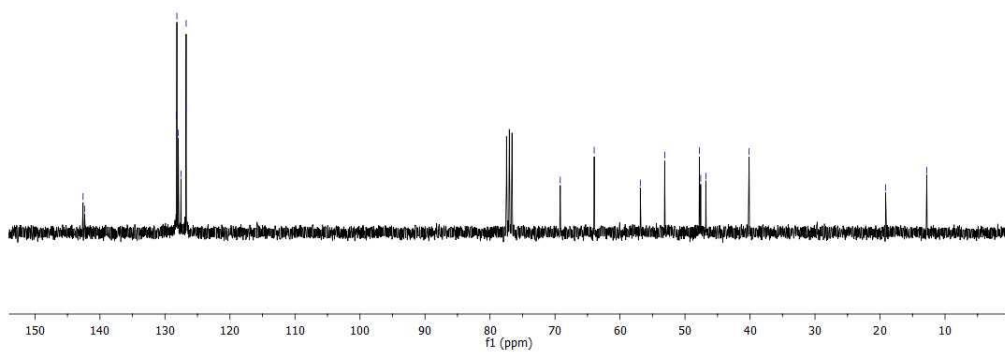


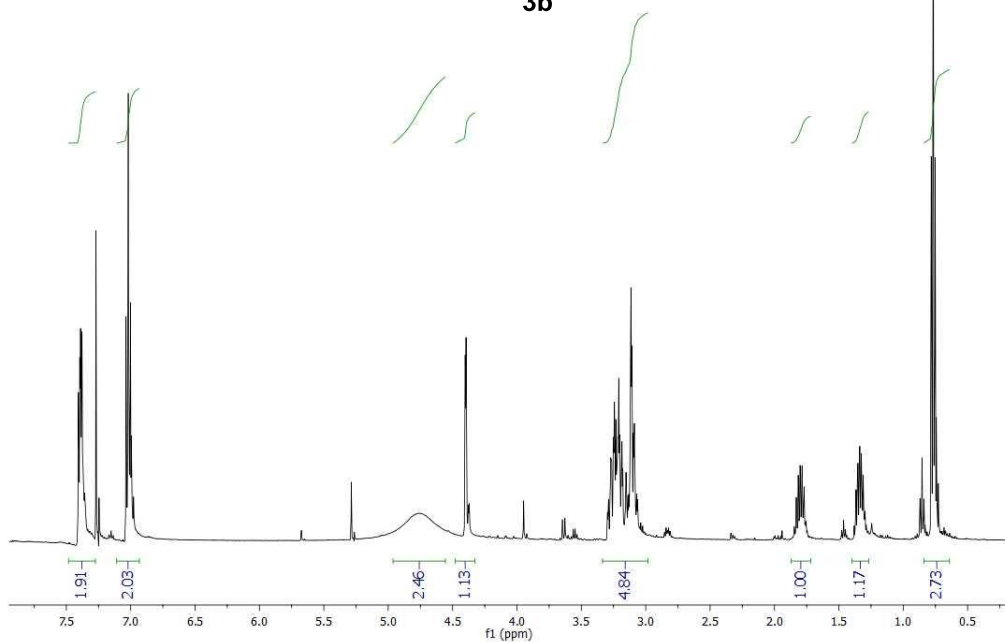
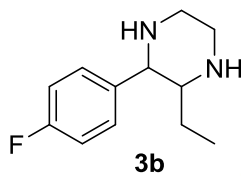


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142.343
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128.168
127.956
127.521
126.776
126.742

-69.187
-63.970
-56.878
-55.121
-47.781
-47.584
-46.802
-40.140

-19.141
-12.804





163.826
160.559

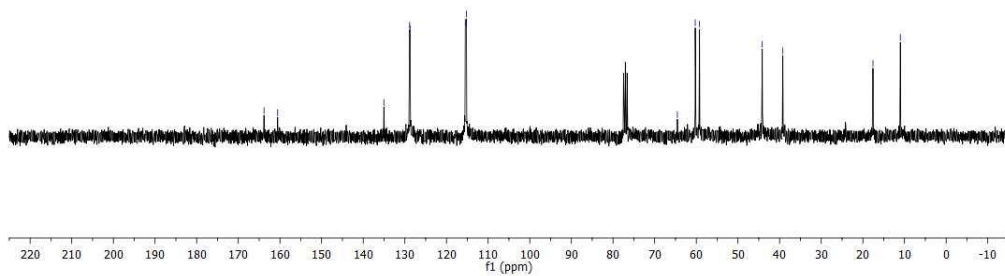
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128.853
128.750

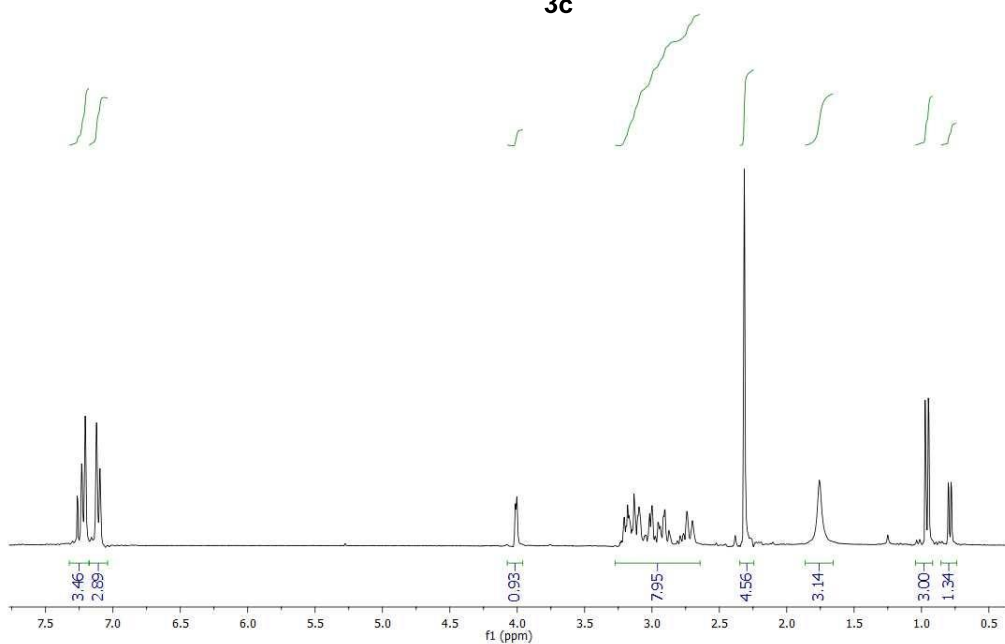
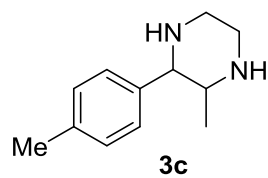
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115.208

64.551
60.256
59.238

44.159
39.221

17.579
10.997

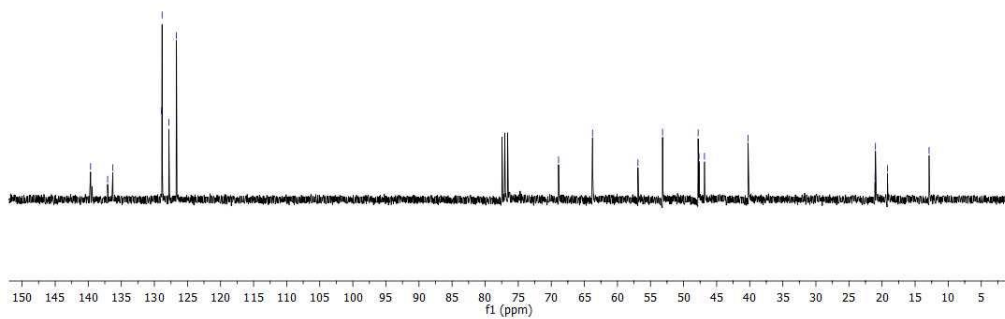


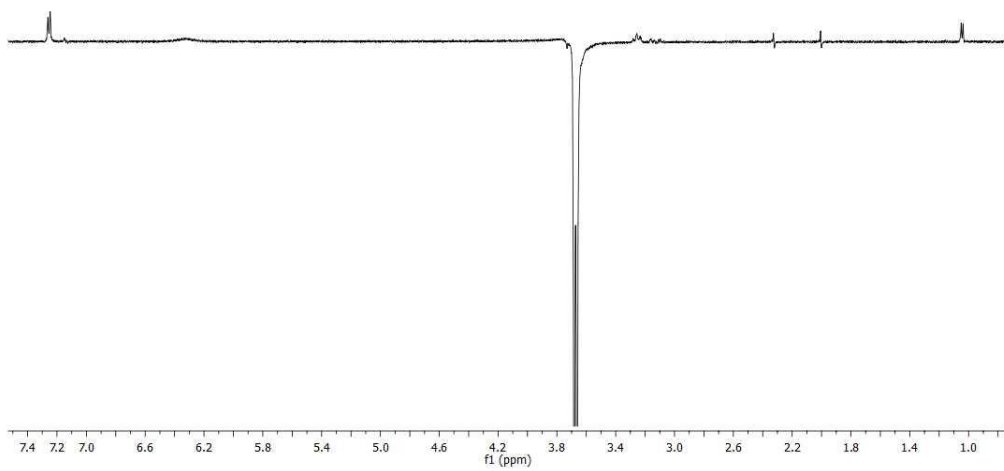
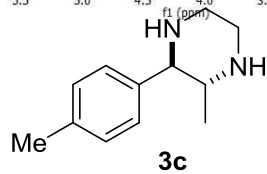
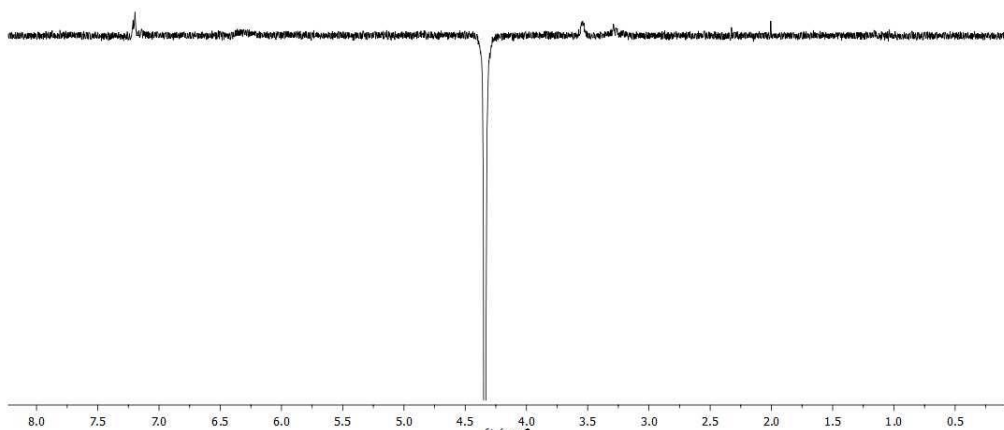
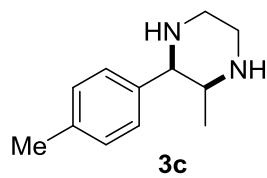


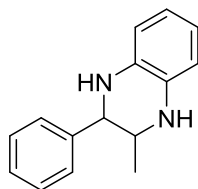
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136.280
128.930
128.834
127.815
126.667

-68.901
-63.767
-56.900
-53.179
-47.800
-47.671
-46.890
-40.251

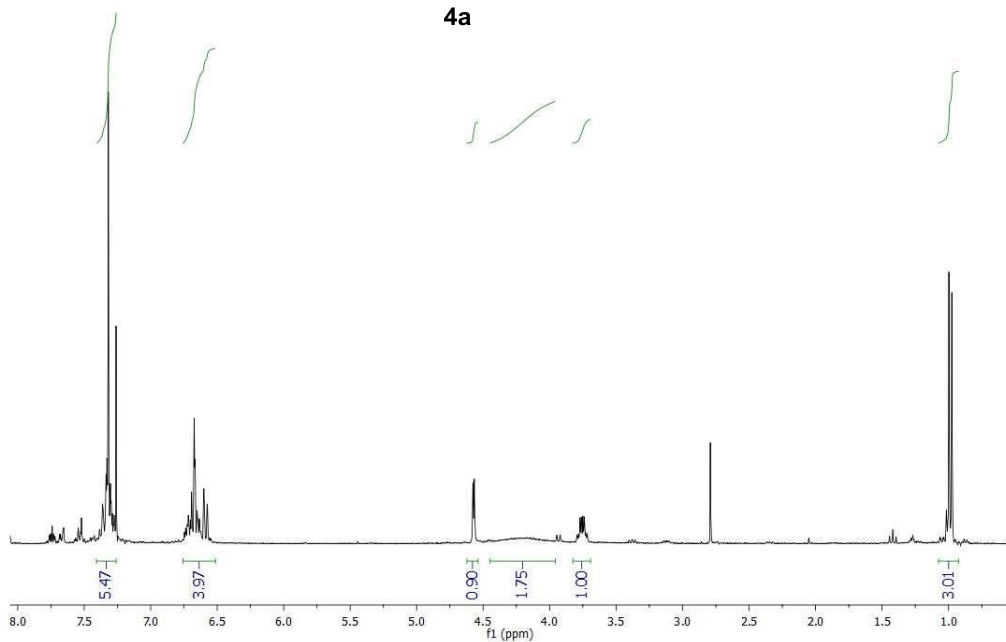
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-20.994
-19.189
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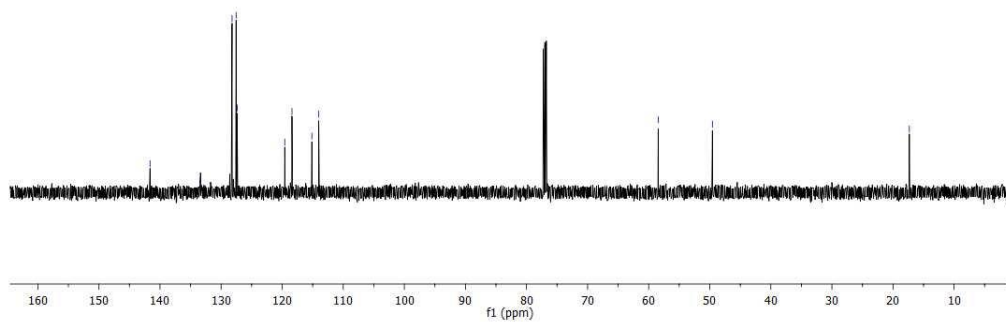
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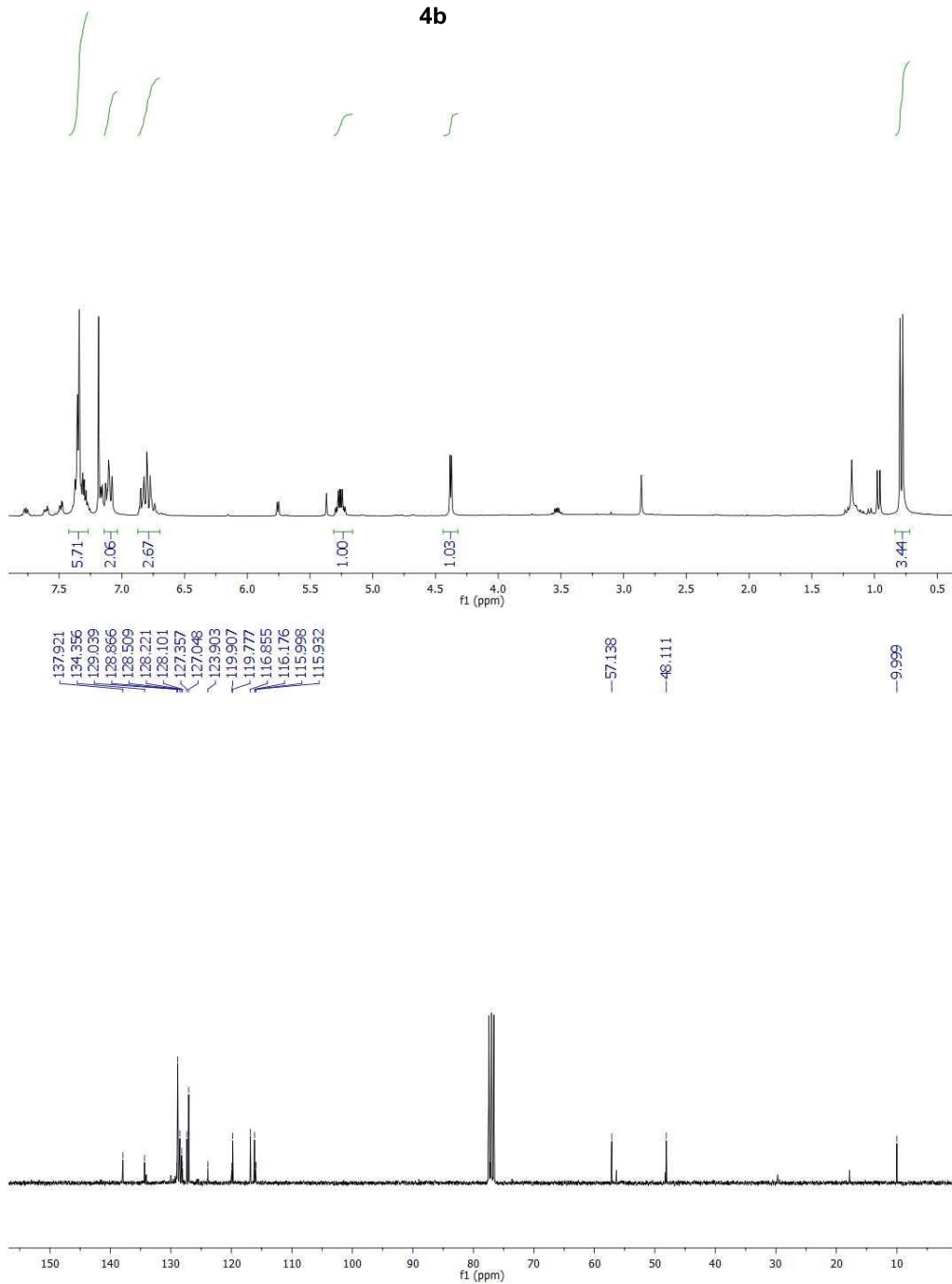
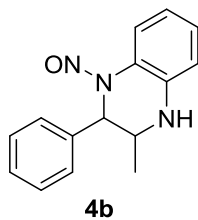


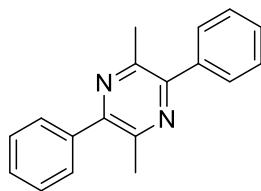
—141.632
/133.465
/128.204
/127.546
/127.368
/119.578
/118.395
/115.145
/114.011

—58.448
—49.568

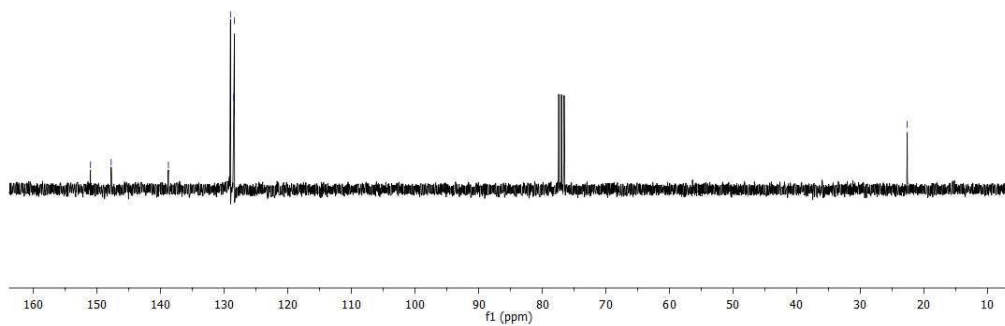
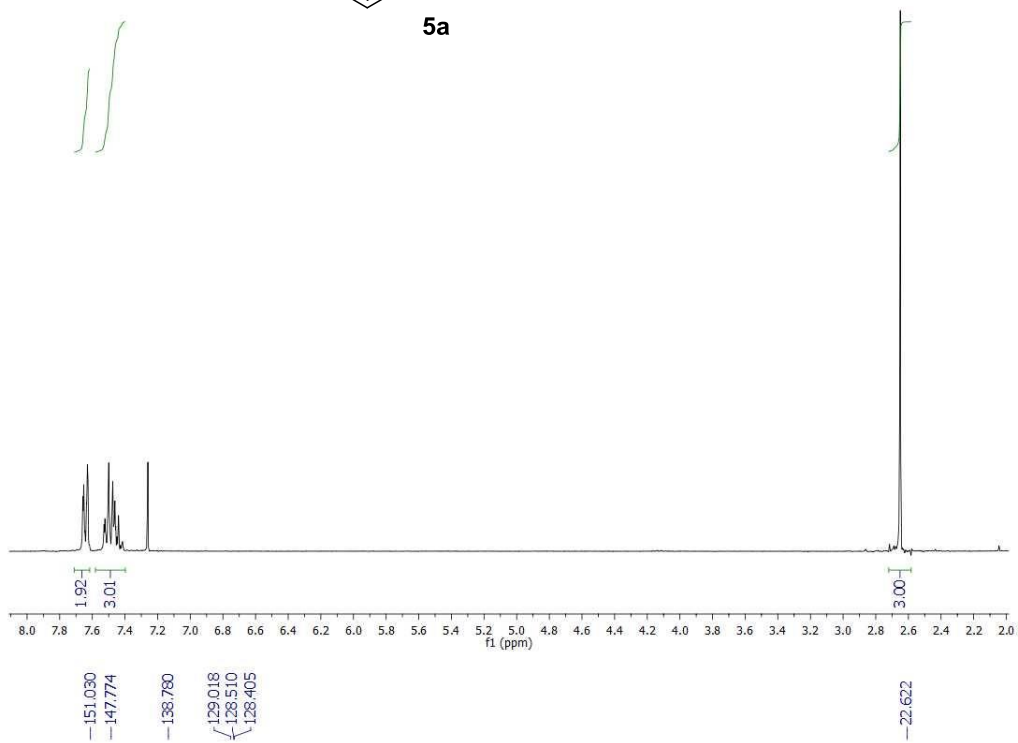
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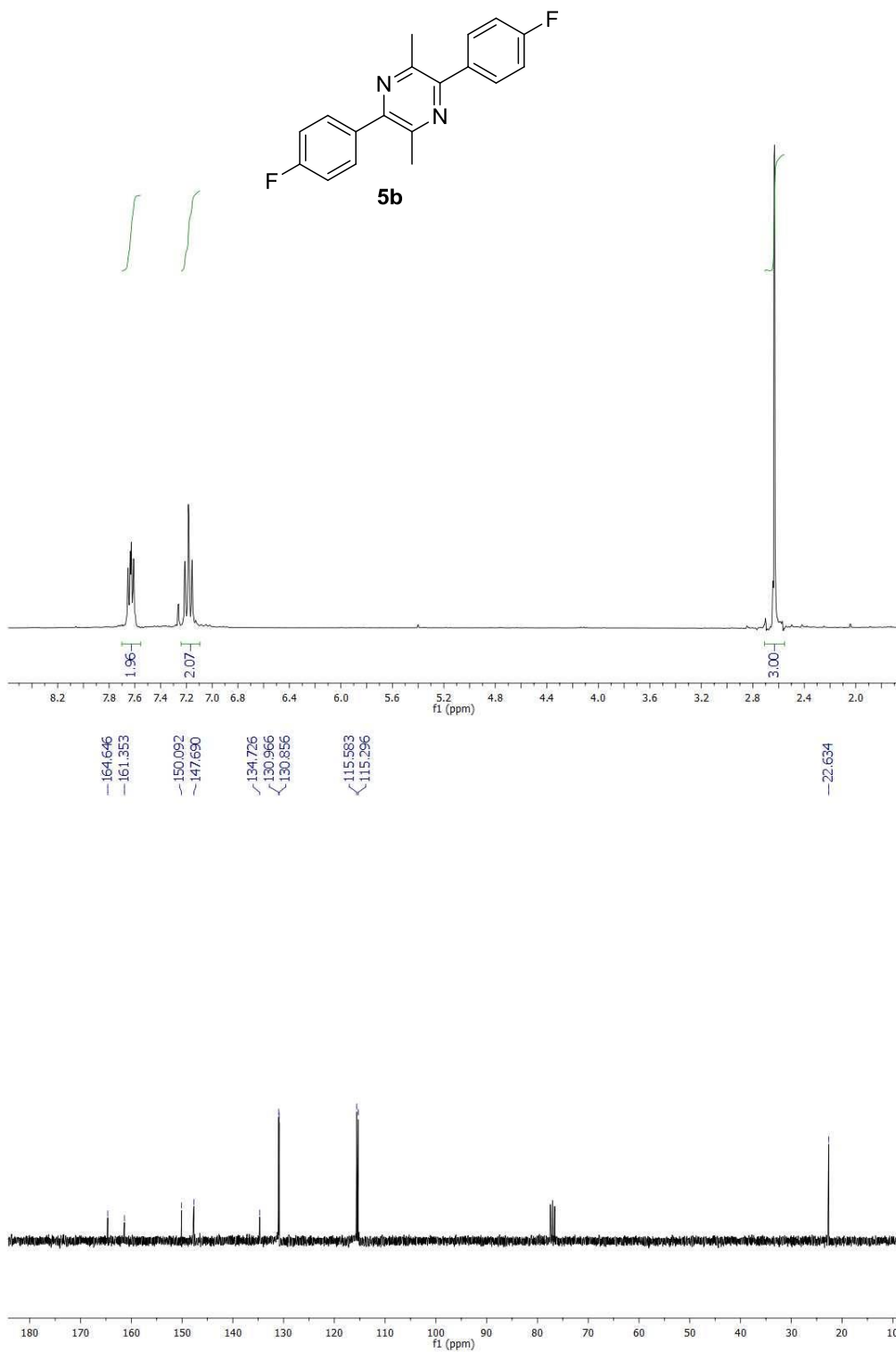


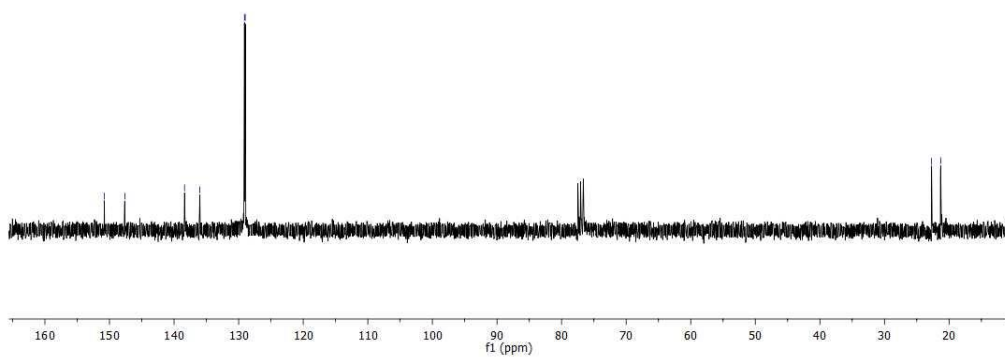
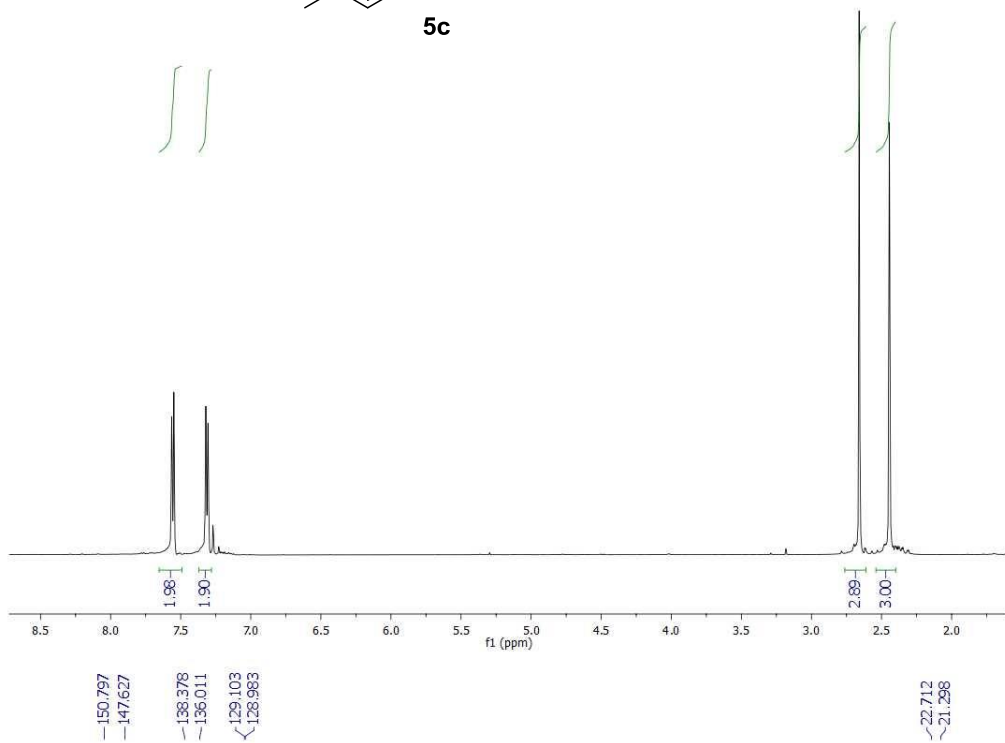
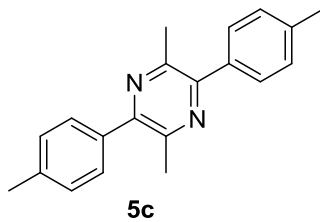


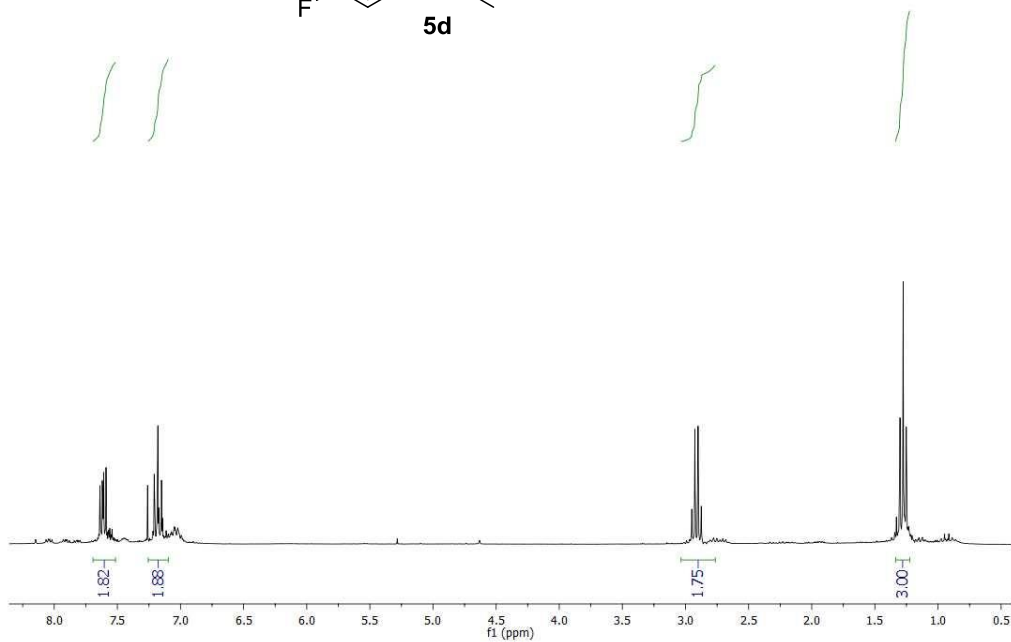
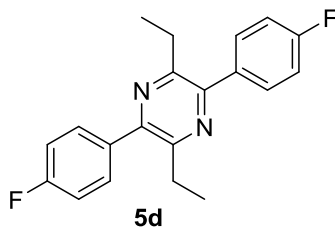


5a







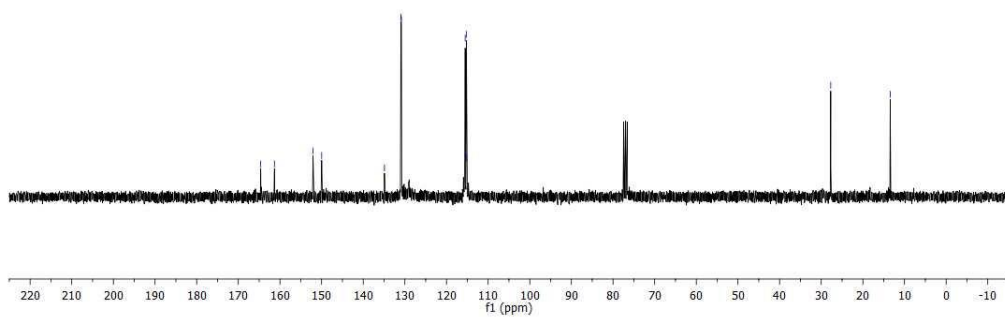


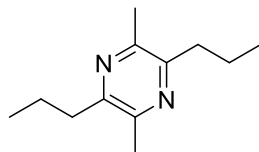
~164.616
~161.327
~152.053
~149.973

~134.896
~130.938
~130.828
~115.515
~115.443
~115.229
~115.157

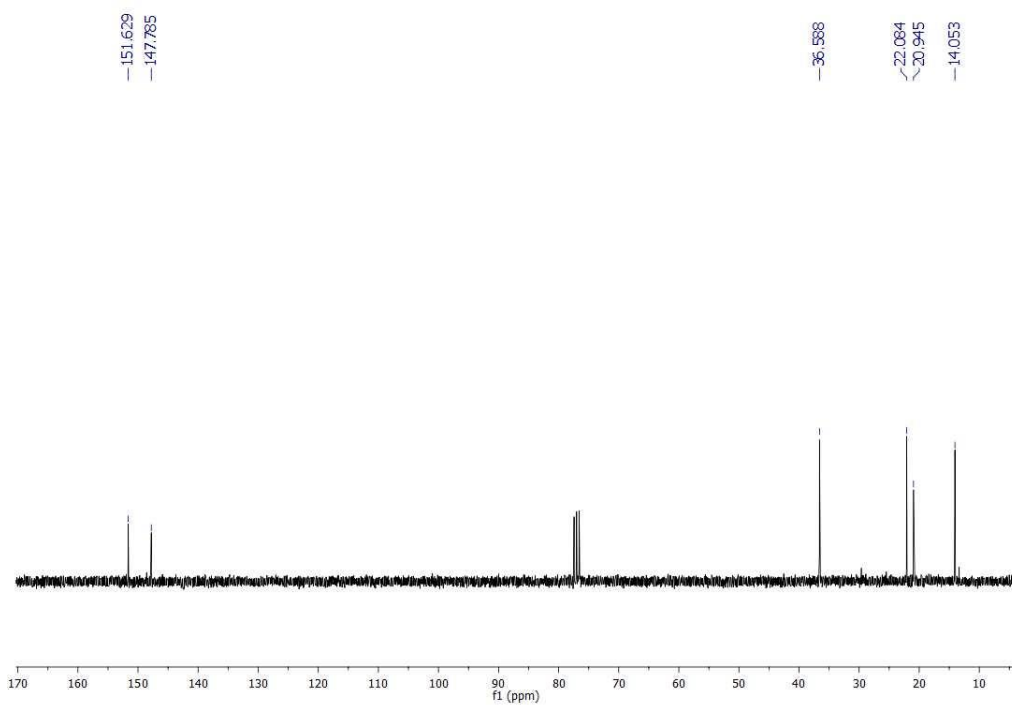
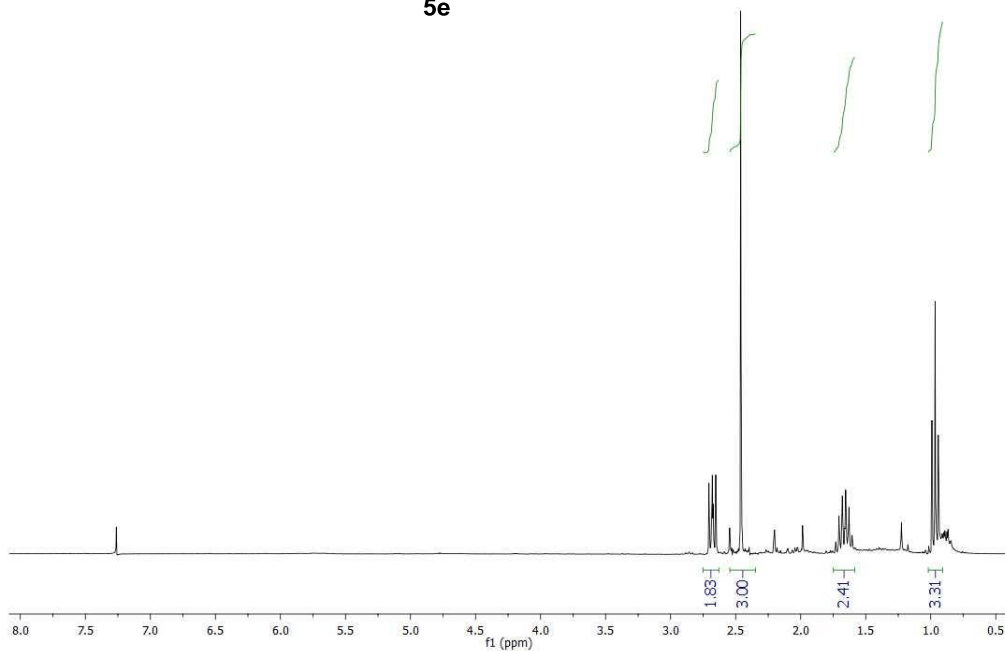
~27.720

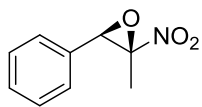
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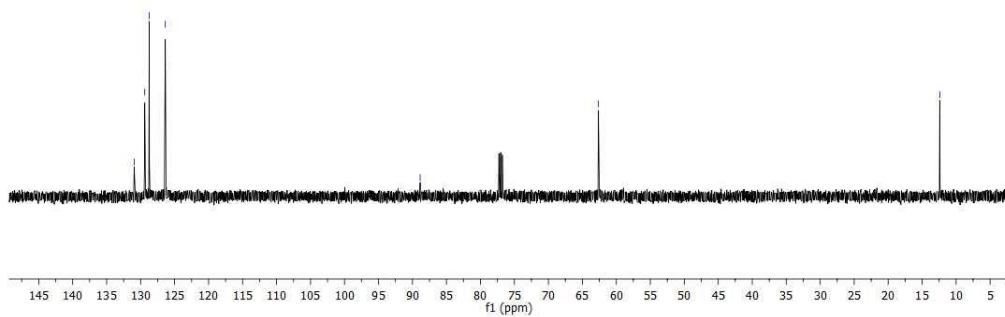
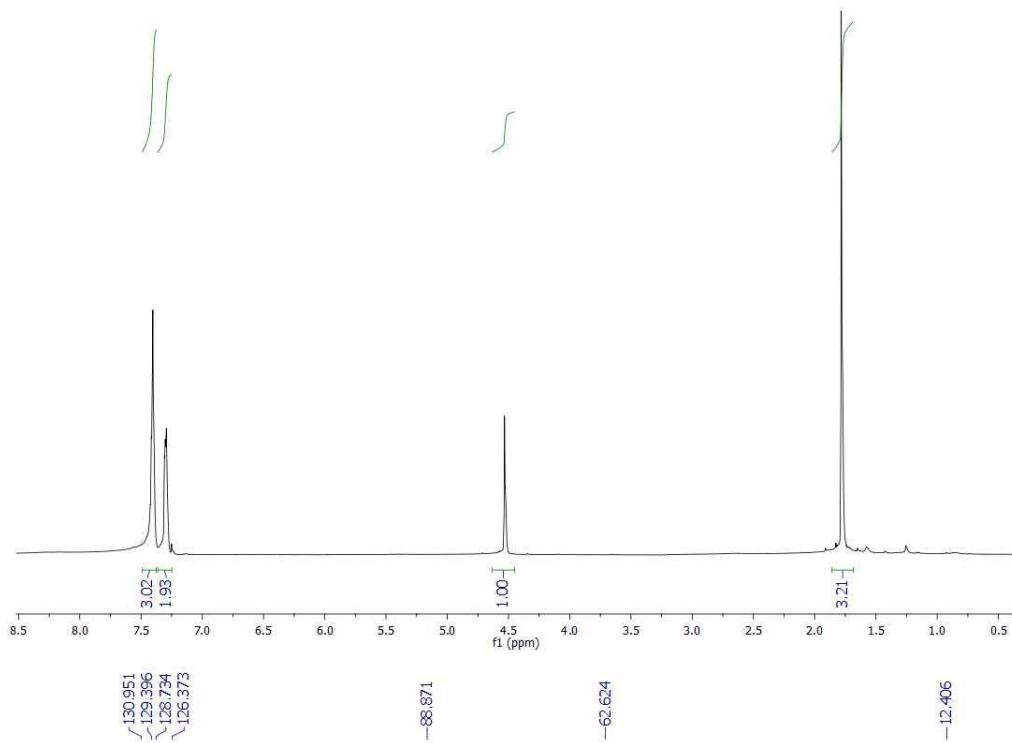


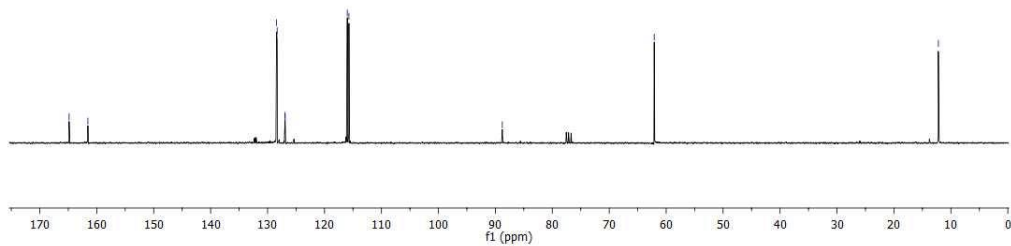
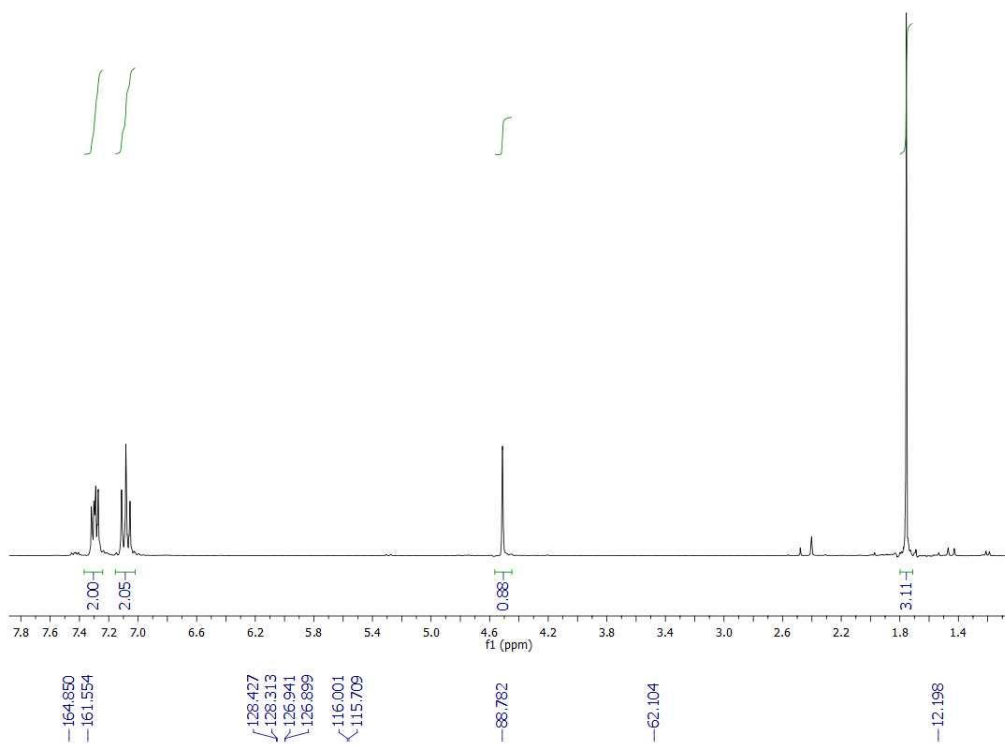
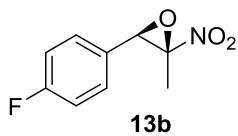
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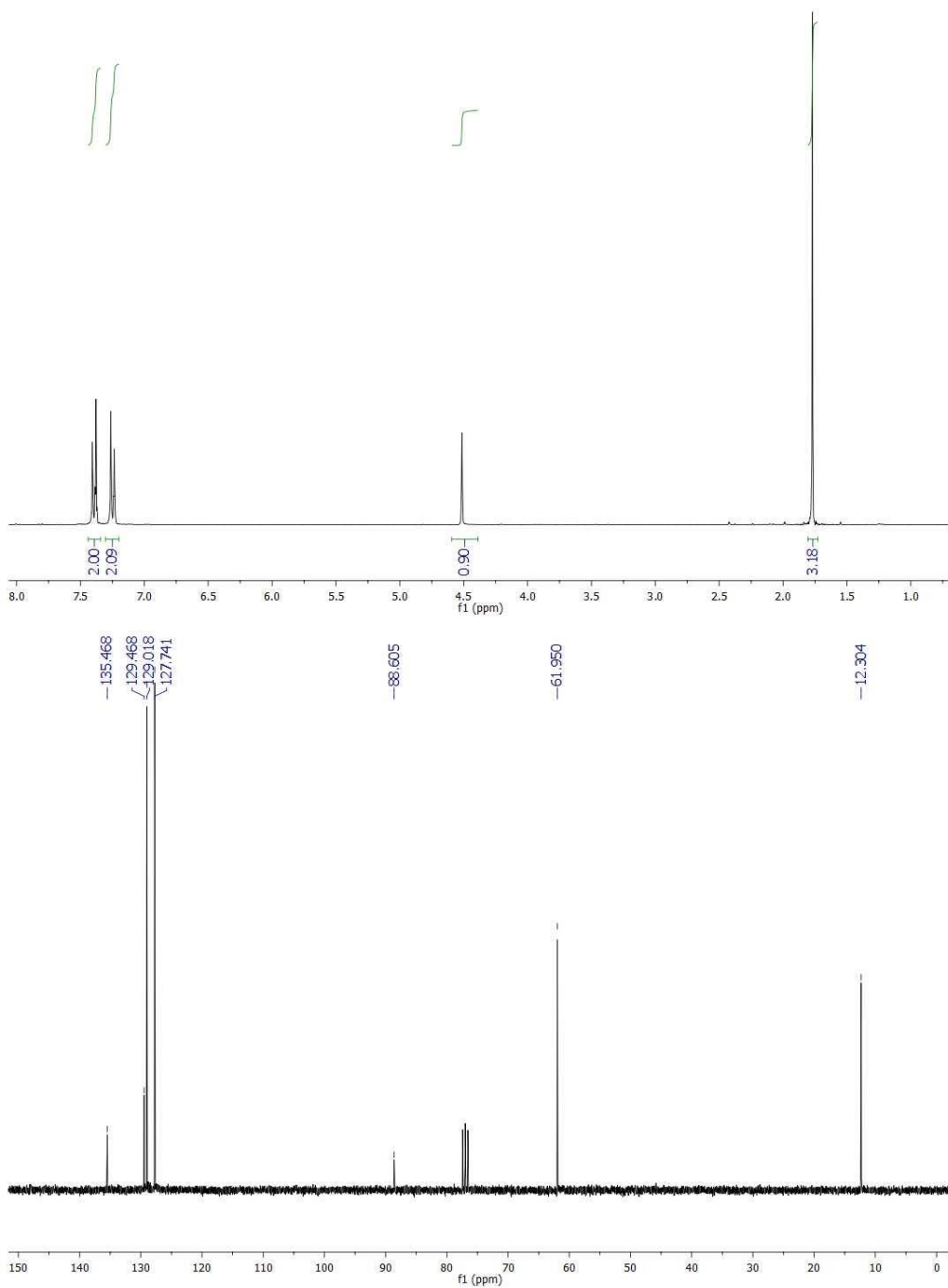
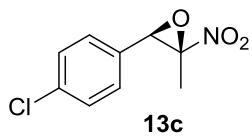


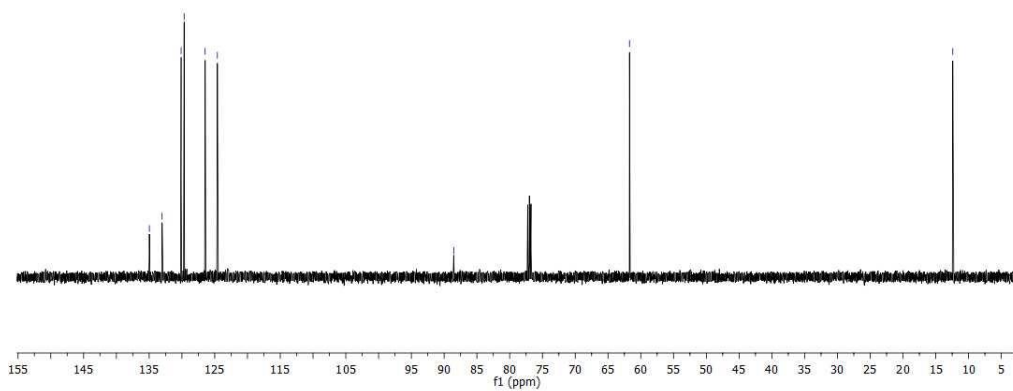
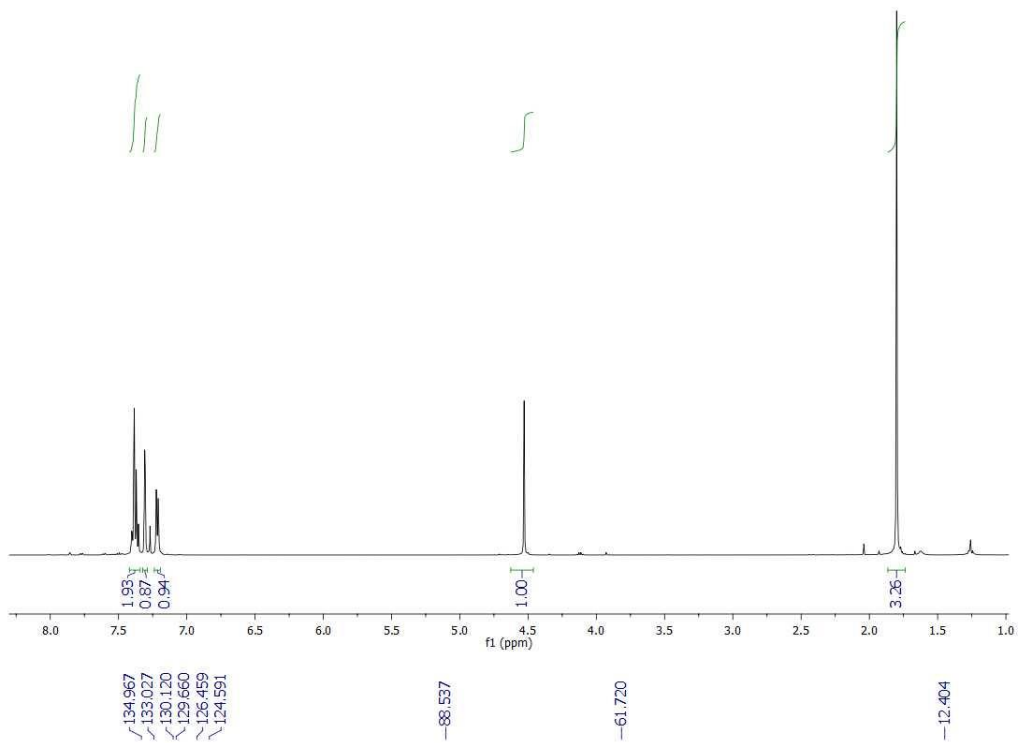
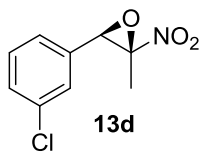


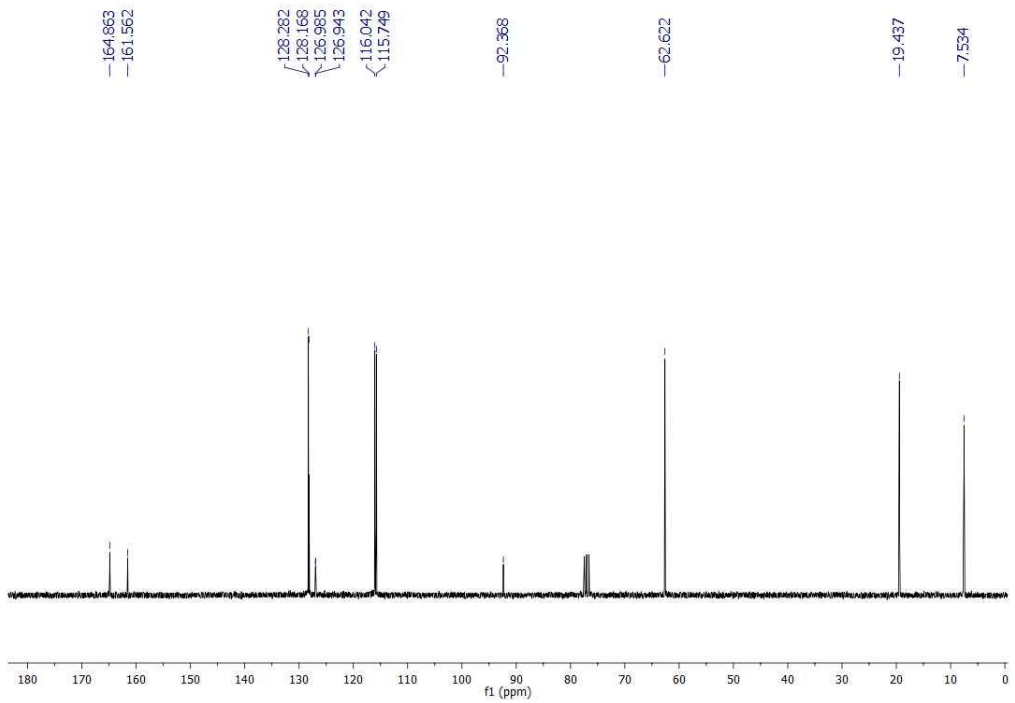
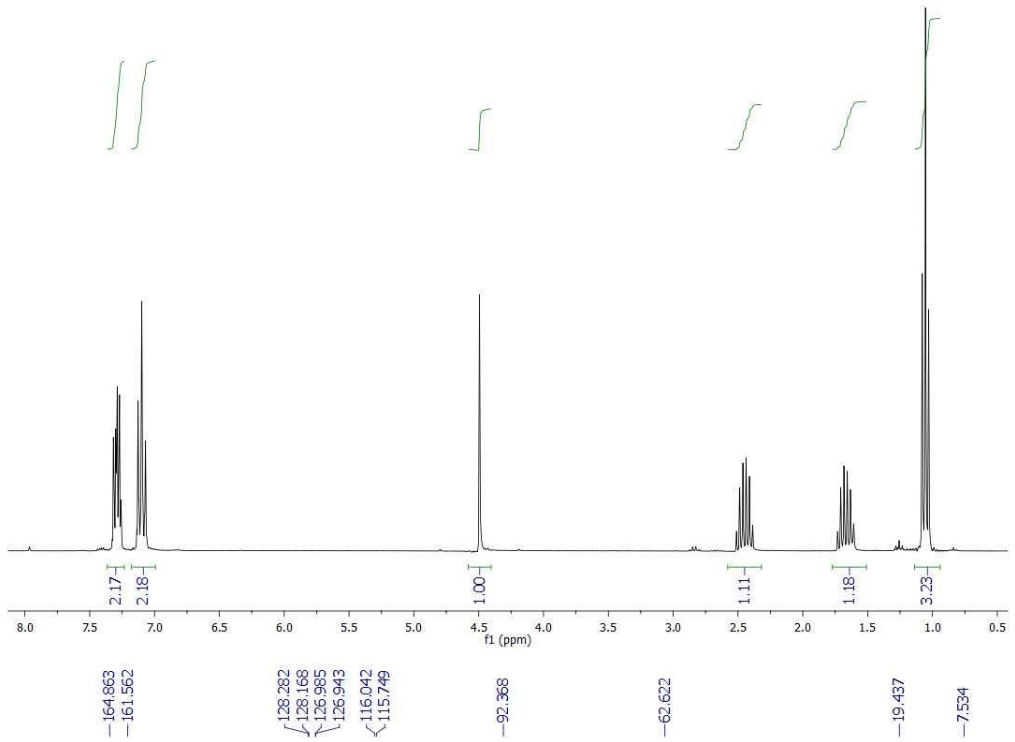
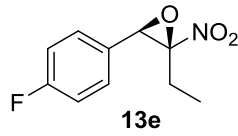
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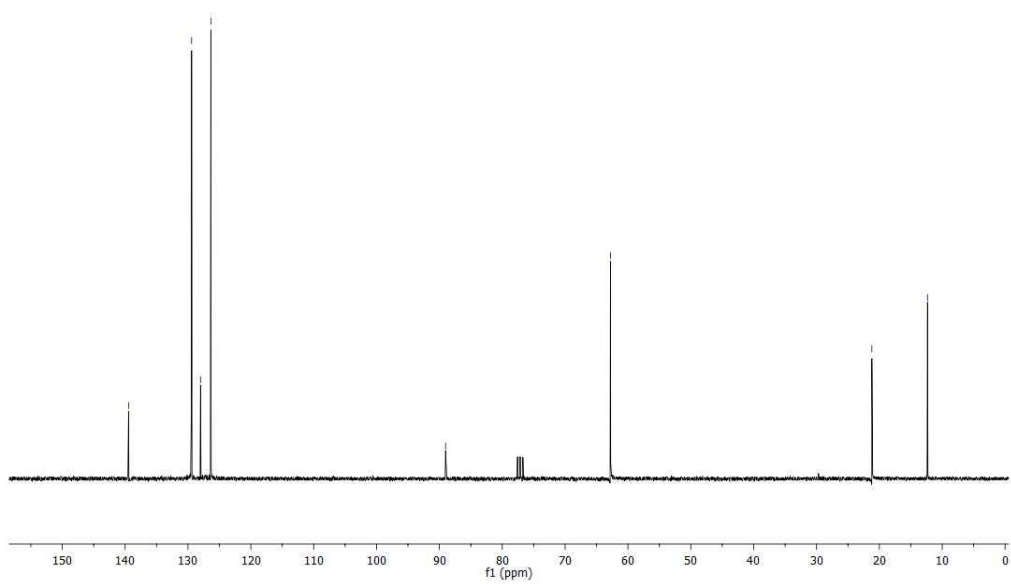
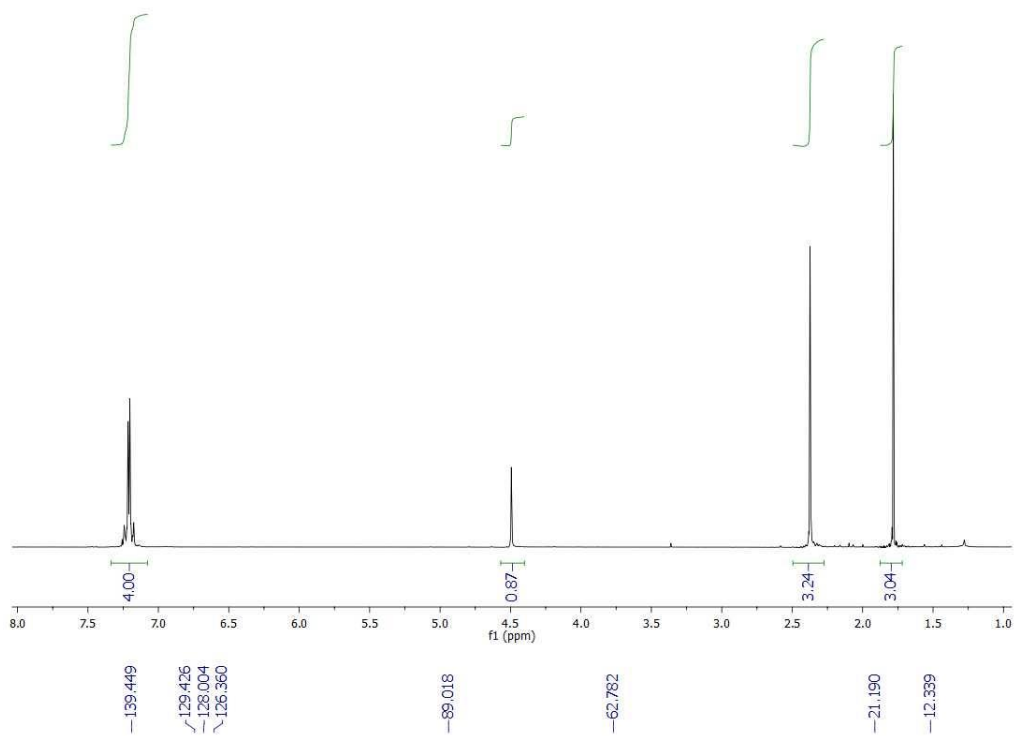
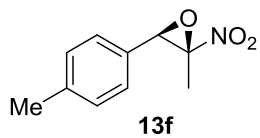


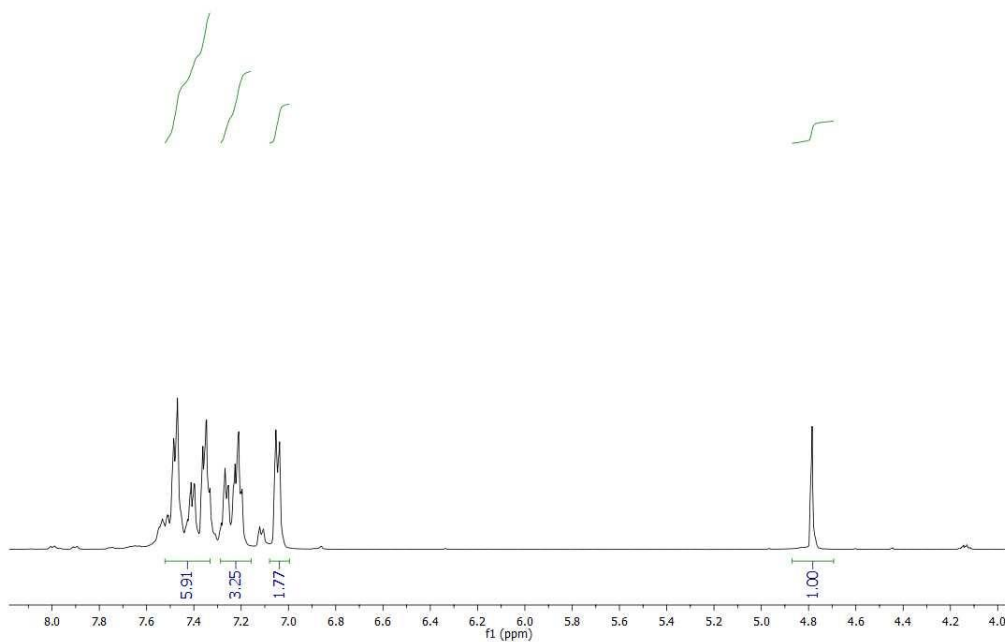
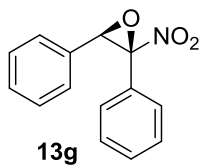








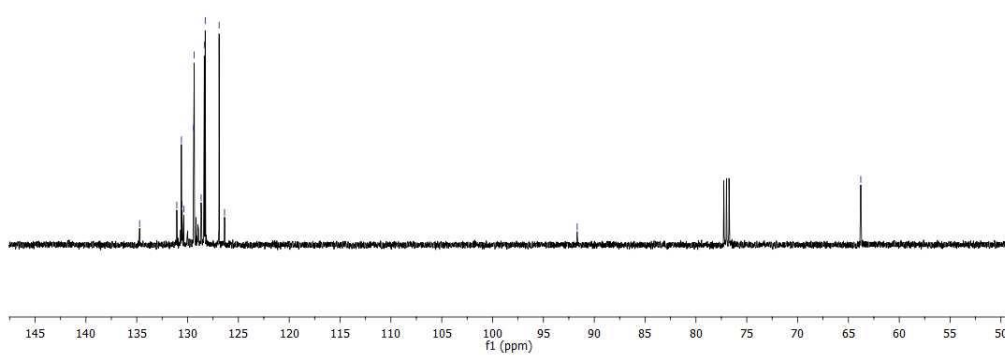


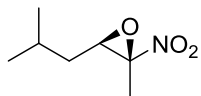


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131.062
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130.537
130.374
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128.667
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126.364

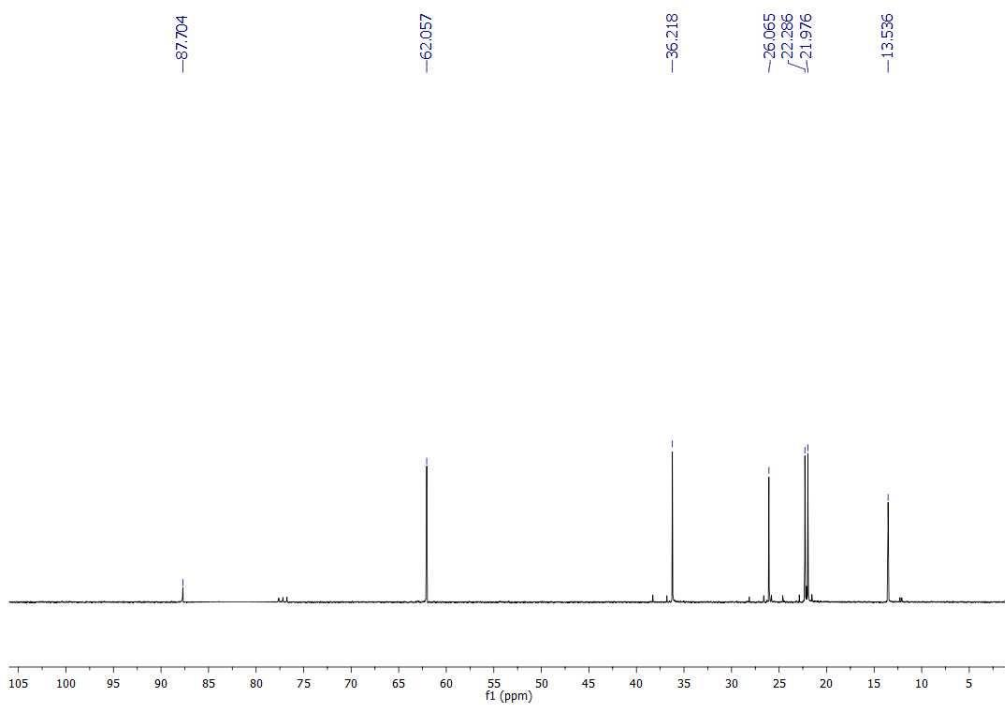
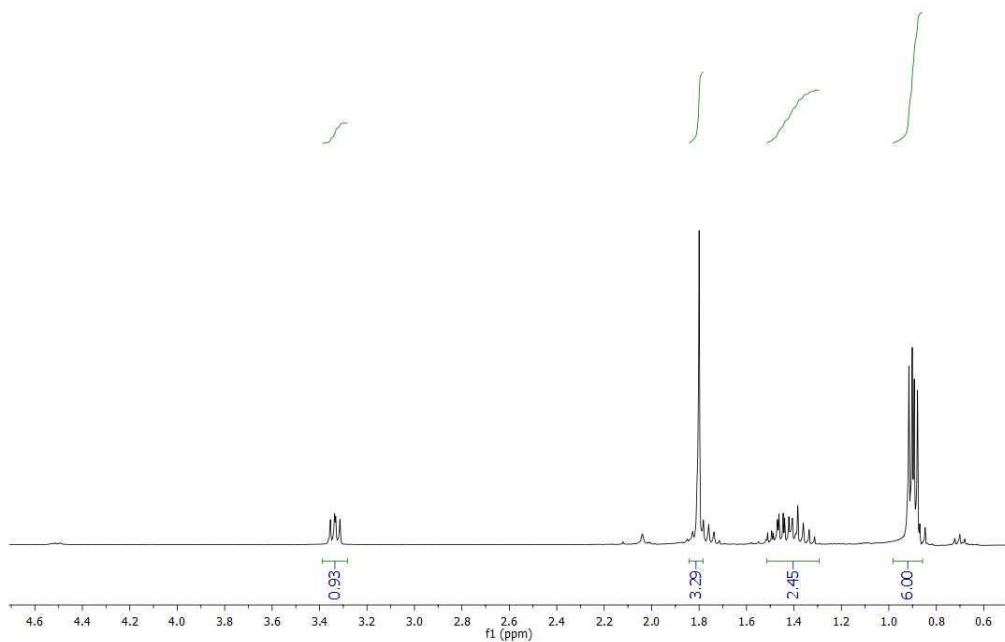
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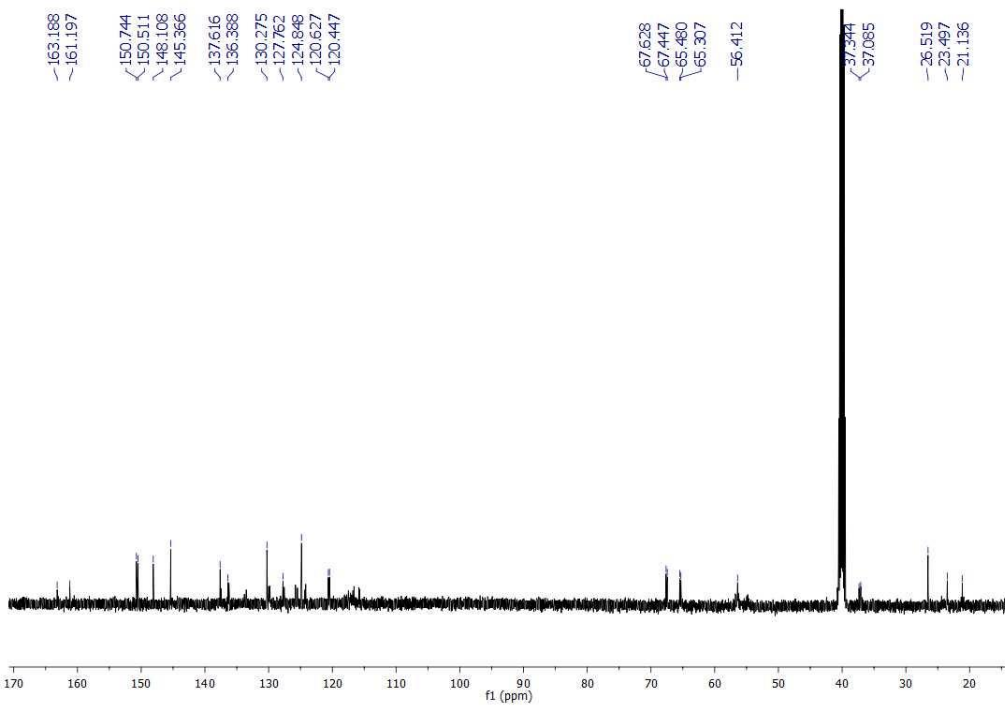
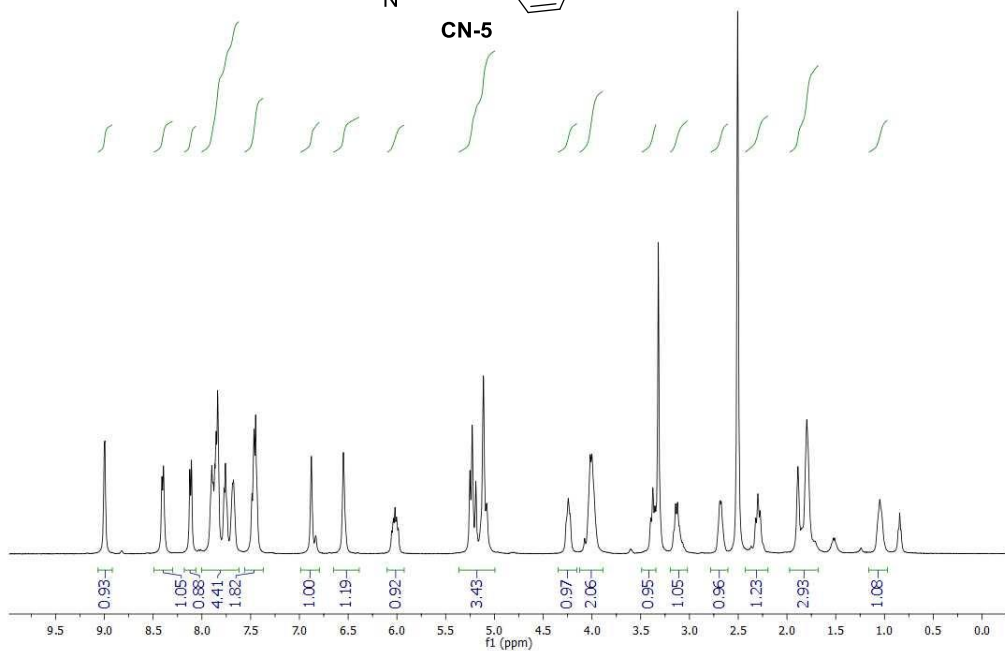
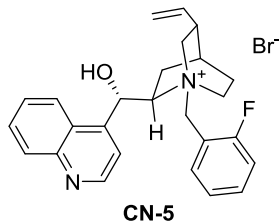
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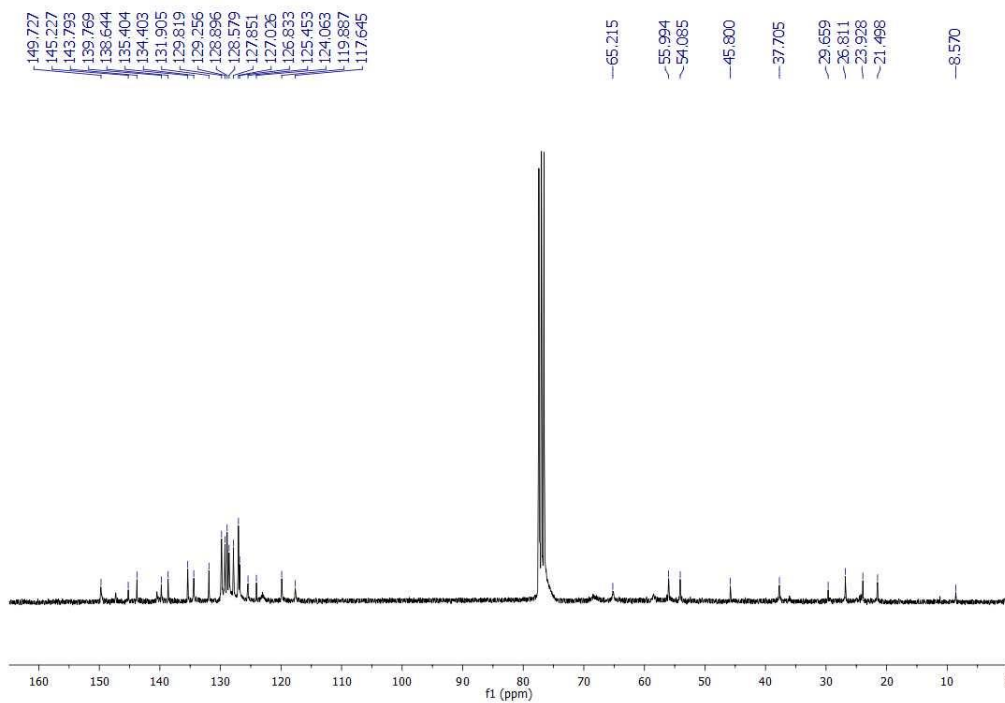
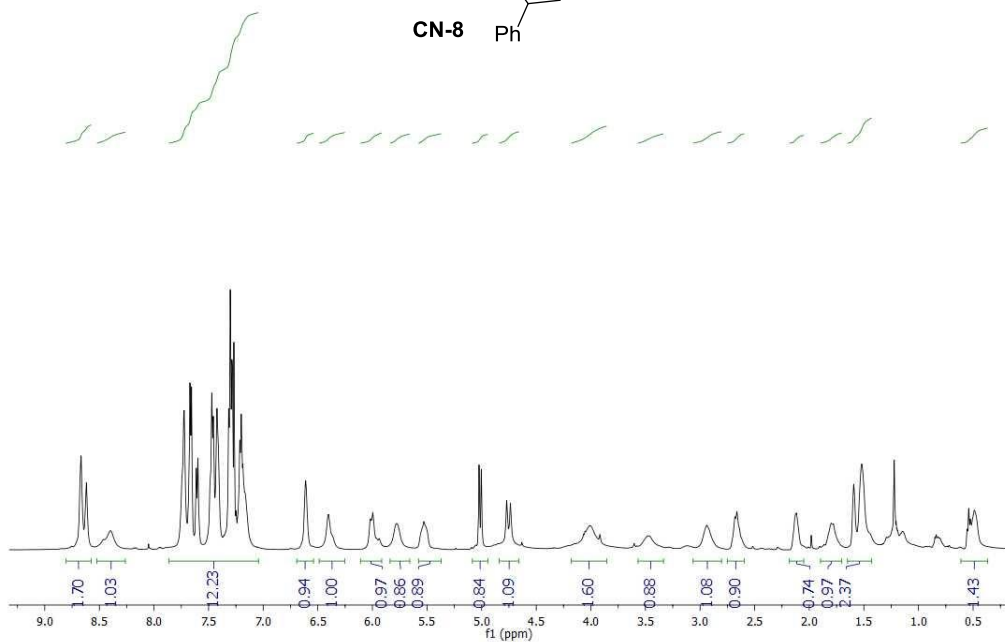
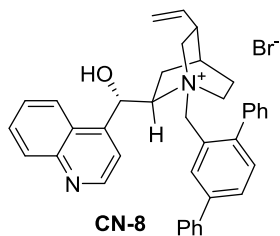


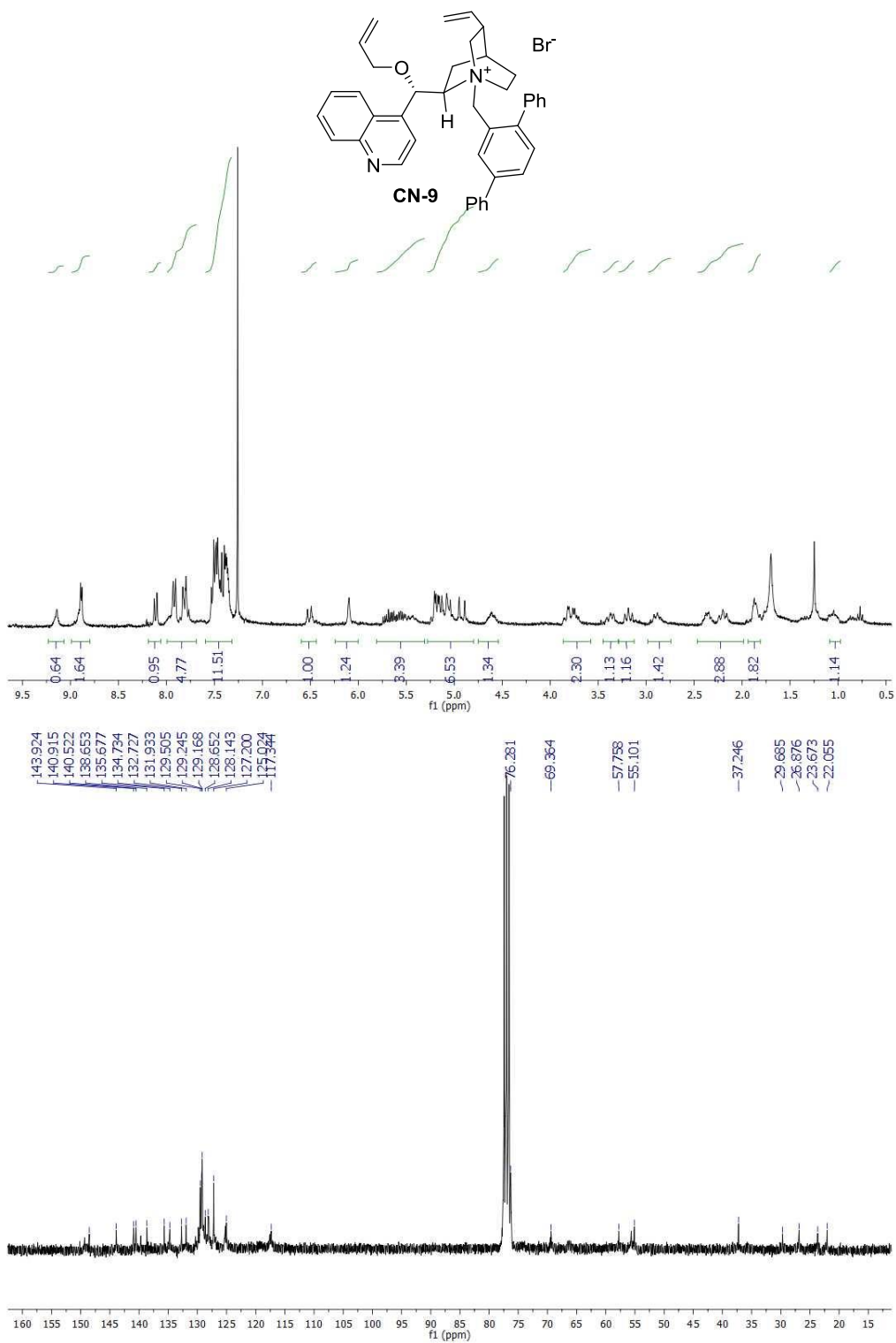


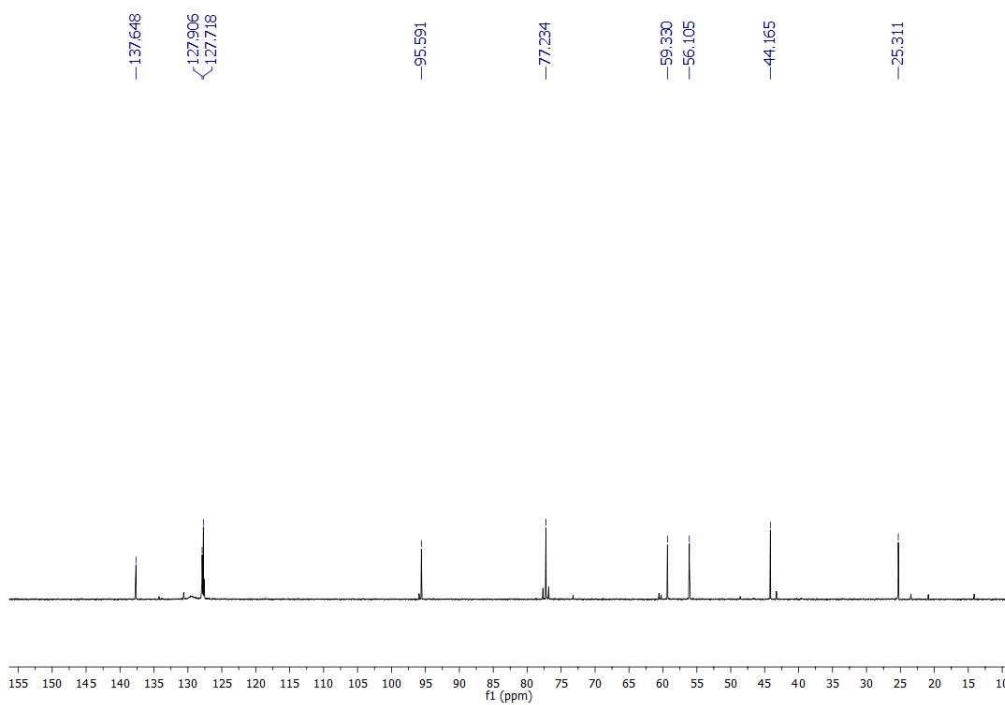
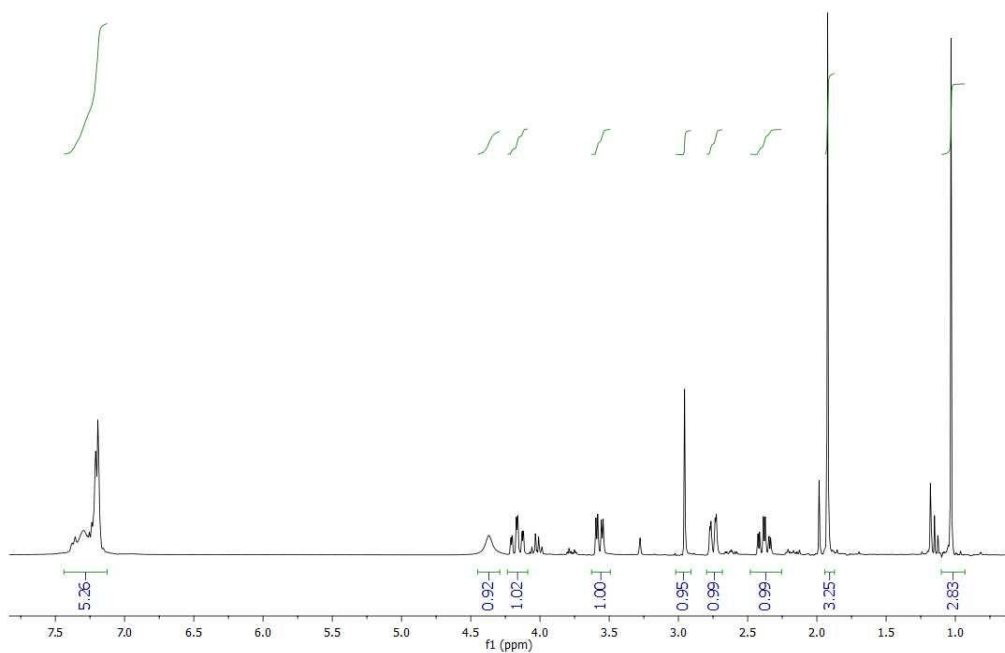
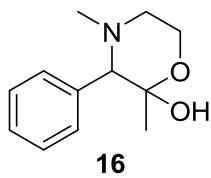
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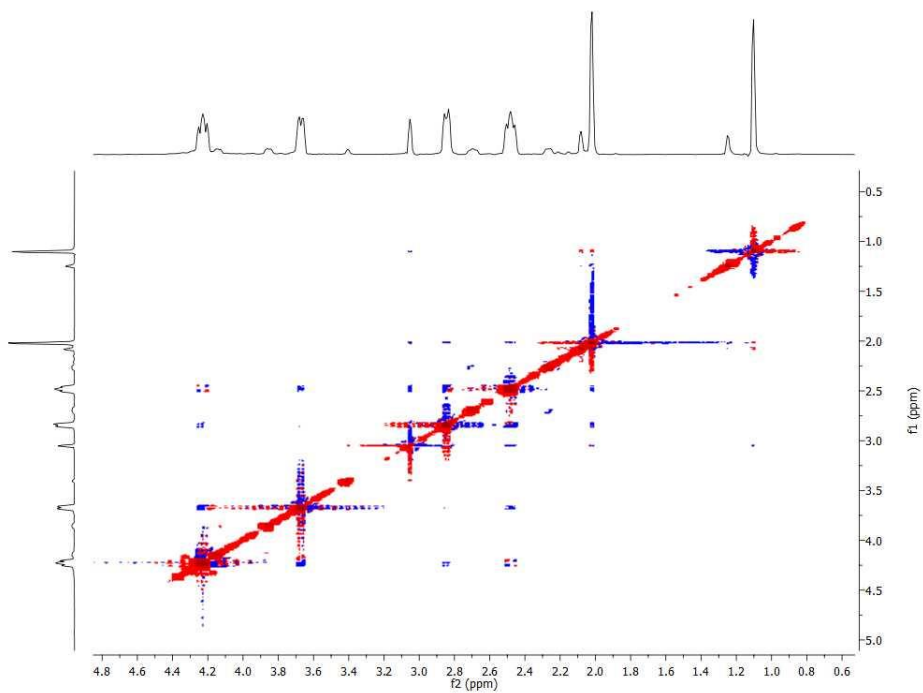
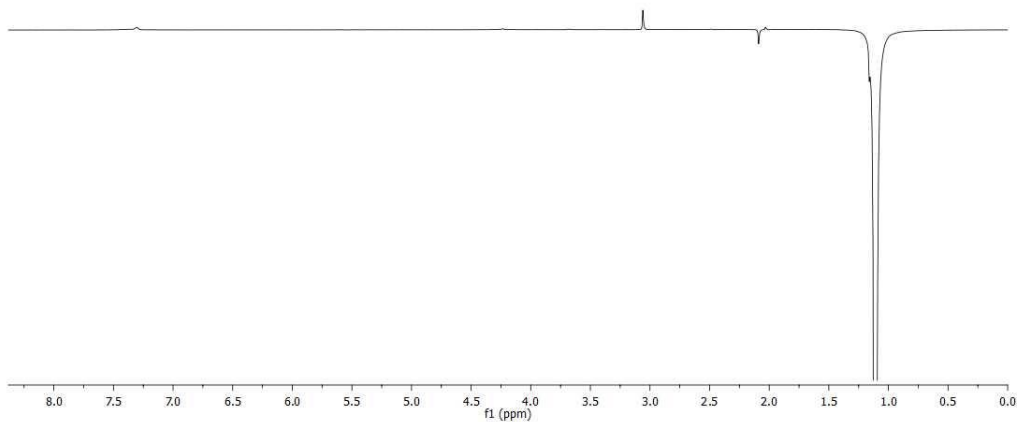


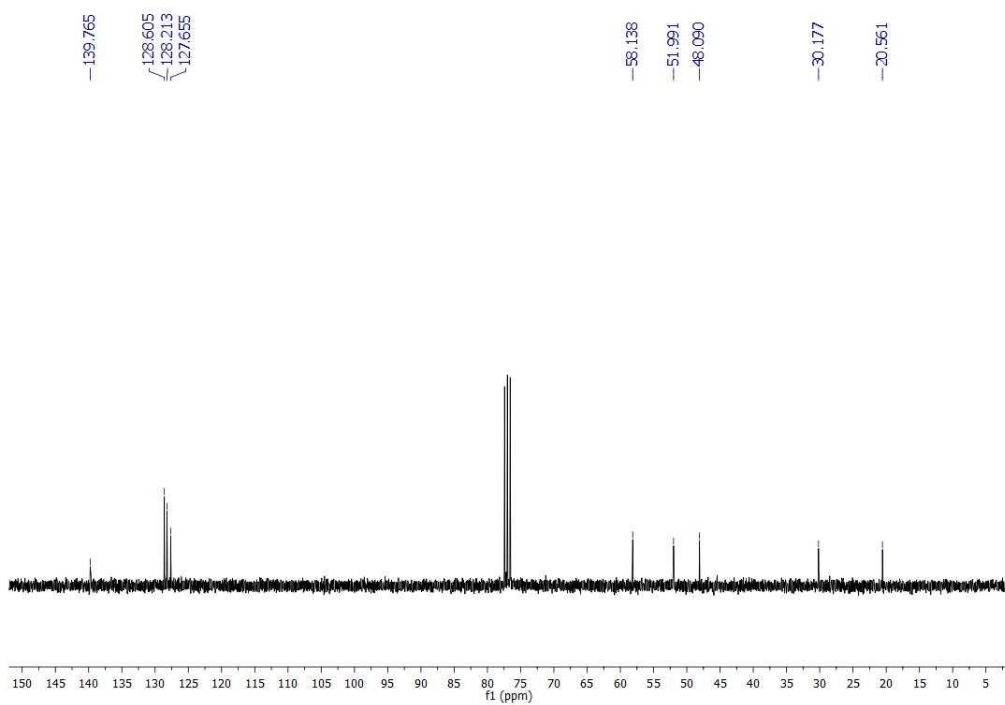
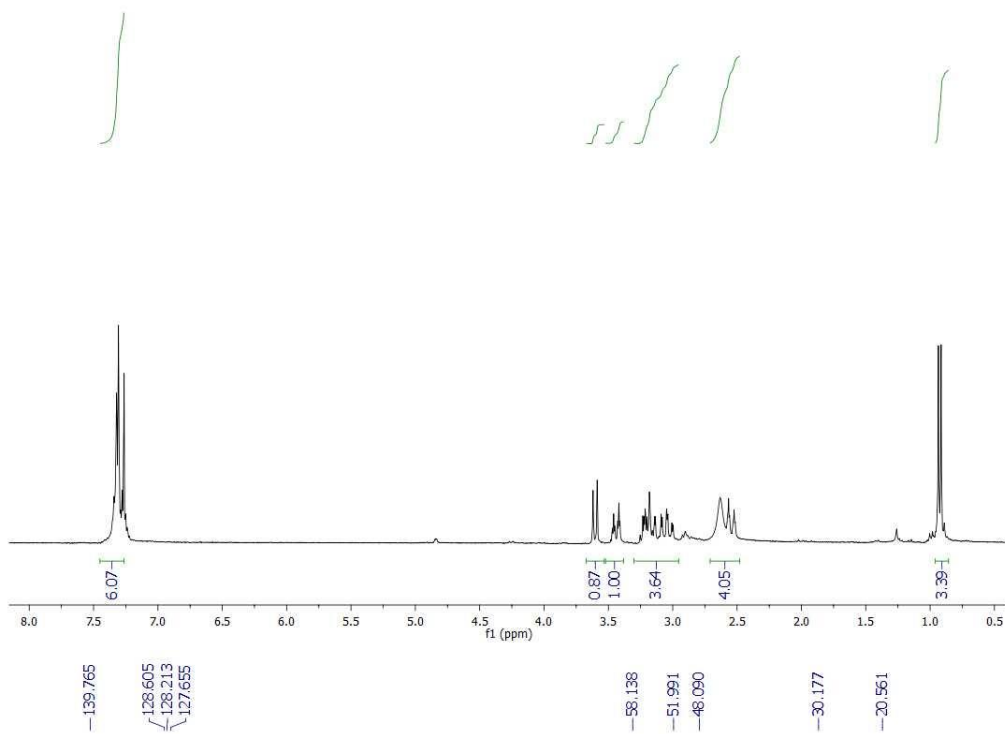
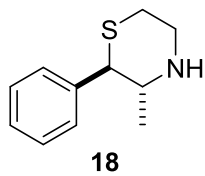


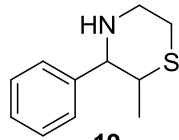
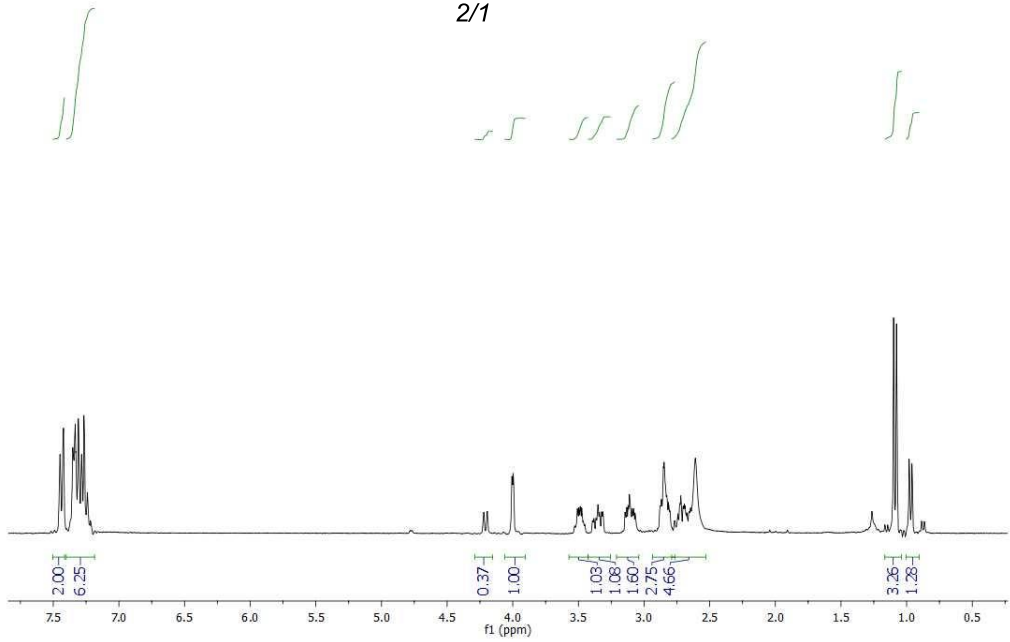




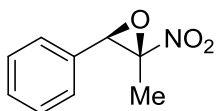






**19***syn/anti*
2/1

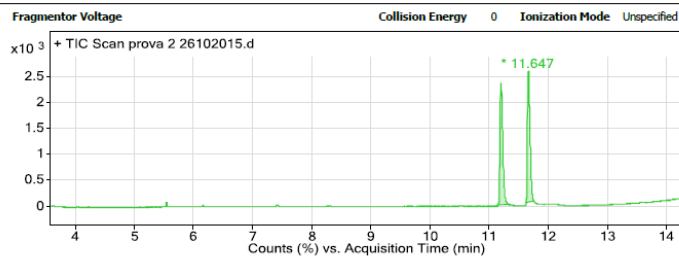
HPLC and GC Chromatograms



2a

Racemic compound

User Chromatograms

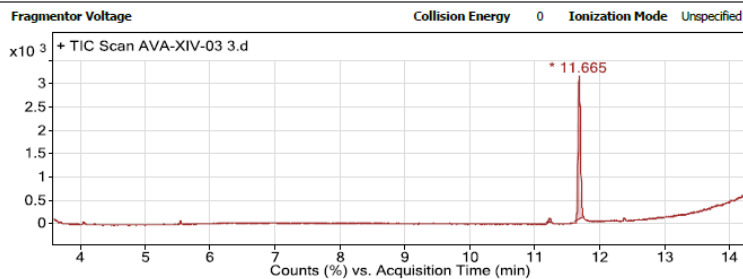


Integration Peak List

Peak	Start	RT	End	Height	Area	Area %
1	11.12	11.183	11.365	2515523.24	7882617.43	100
2	11.607	11.647	11.745	2706469.15	7871661.24	99.86

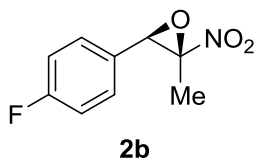
Enantioenriched compound

User Chromatograms

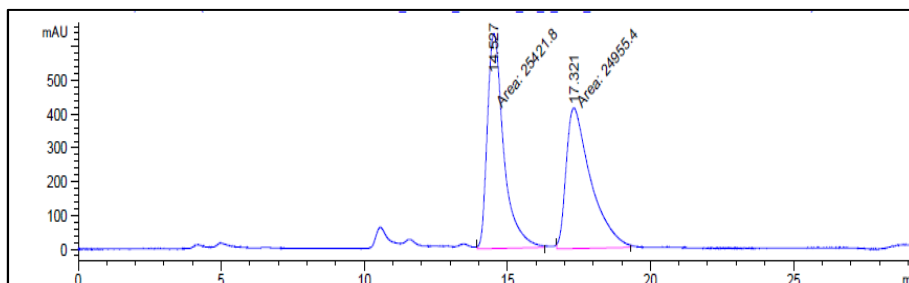


Integration Peak List

Peak	Start	RT	End	Height	Area	Area %
1	11.173	11.216	11.254	18189.91	45982.84	3.48
2	11.615	11.665	11.736	532984.35	1322667	100

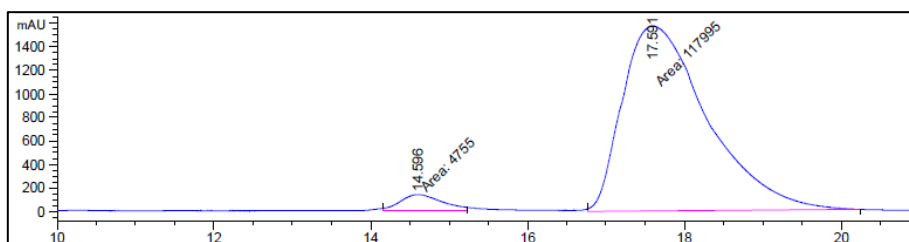


Racemic compound

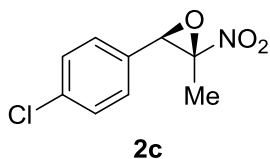


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.527	MM T	0.6650	2.54218e4	637.14856	50.4630
2	17.321	MM T	0.9982	2.49554e4	416.68872	49.5370

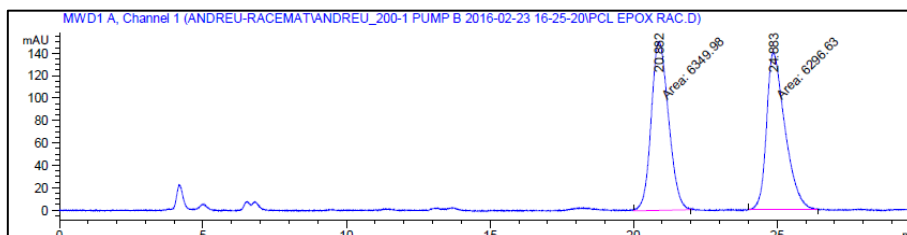
Enantioenriched compound



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.596	MM T	0.6021	4755.00391	131.63168	3.8737
2	17.591	MM T	1.2516	1.17995e5	1571.29956	96.1263



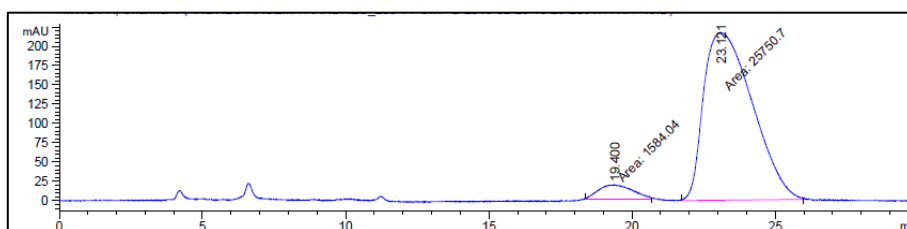
Racemic compound



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.882	MM	0.7005	6349.97705	151.07651	50.2109
2	24.883	MM	0.7480	6296.62988	140.29599	49.7891

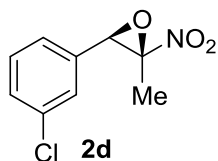
Totals : 1.26466e4 291.37250

Enantioenriched compound

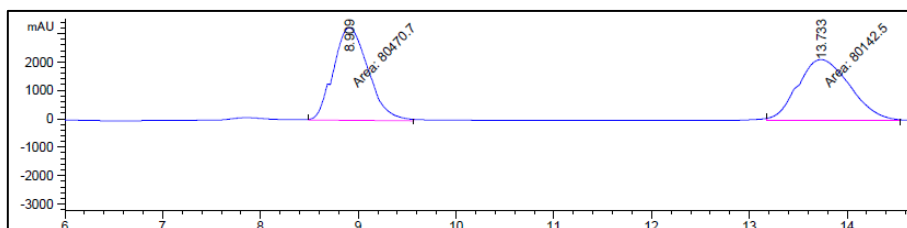


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.400	MM	1.4059	1584.03833	18.77824	5.7950
2	23.121	MM	1.9731	2.57507e4	217.51802	94.2050

Totals : 2.73347e4 236.29626

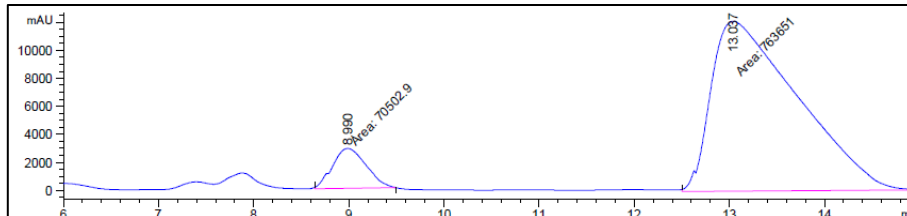


Racemic compound

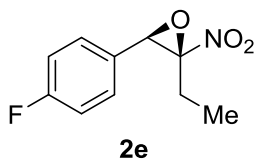


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.909	MM	0.4119	8.04707e4	3255.96362	50.1022
2	13.733	MM	0.6215	8.01425e4	2149.02832	49.8978

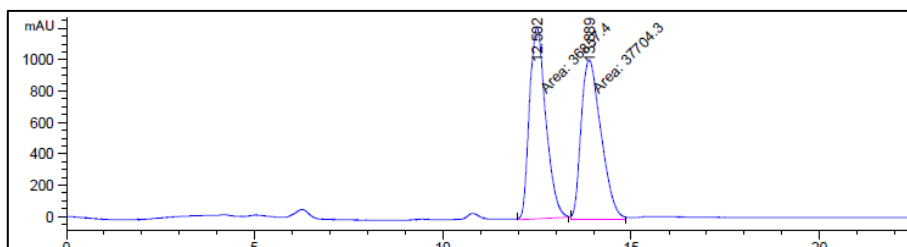
Enantioenriched compound



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.990	MM T	0.4120	7.05029e4	2851.80151	8.4520
2	13.037	MM T	1.0497	7.63651e5	1.21246e4	91.5480

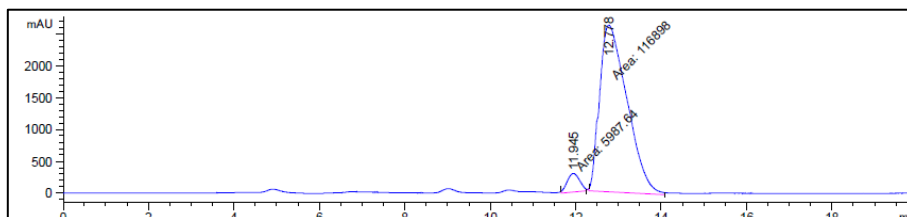


Racemic compound

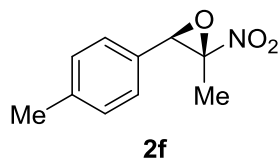


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.502	MM T	0.5025	3.68574e4	1222.45691	49.4321
2	13.889	MM T	0.6156	3.77043e4	1020.87122	50.5679

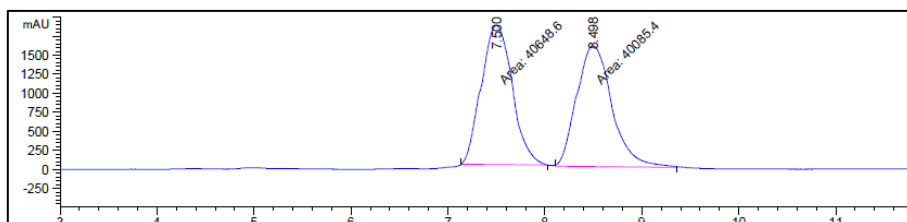
Enantioenriched compound



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.945	MM T	0.3396	5987.64063	293.85883	4.8725
2	12.778	MM T	0.7431	1.16898e5	2621.72461	95.1275

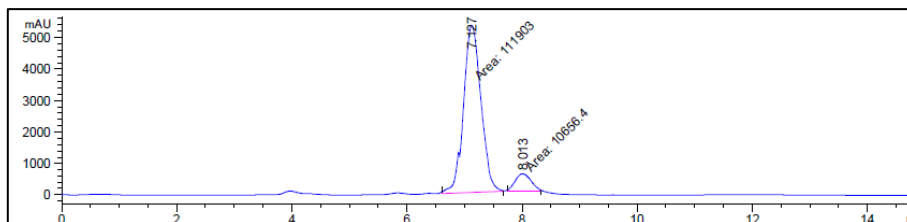


Racemic compound

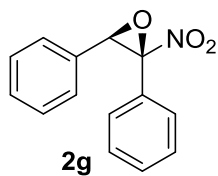


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.500	MM T	0.3704	4.06486e4	1829.03882	50.3488
2	8.498	MM T	0.4206	4.00854e4	1588.58411	49.6512

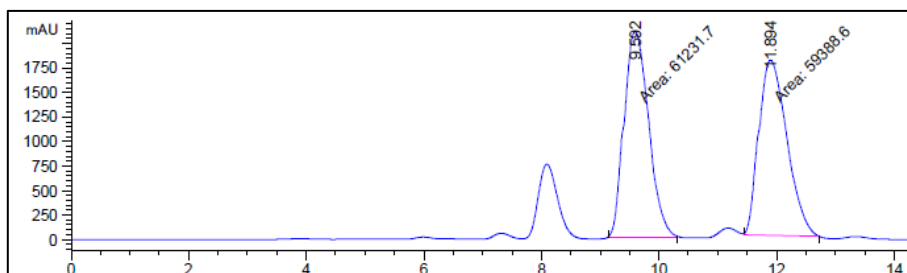
Enantioenriched compound



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.127	MM T	0.3510	1.11903e5	5313.81494	91.3051
2	8.013	MM T	0.3218	1.06564e4	551.91034	8.6949

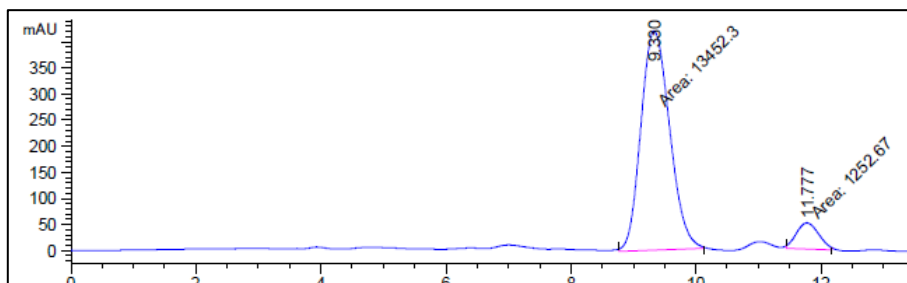


Racemic compound



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.592	MM	0.4846	6.12317e4	2106.07007	50.7640
2	11.894	MM	0.5546	5.93886e4	1784.80640	49.2360

Enantioenriched compound



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.330	MM	0.5329	1.34523e4	420.72076	91.4813
2	11.777	MM	0.4155	1252.66675	50.25192	8.5187

Annex

List of Publications:

Related to this PhD Thesis:

- **“Dynamic Kinetic Asymmetric Ring-Opening/ Reductive Amination Sequence of Racemic Nitroepoxides with Chiral Amines: Enantioselective Synthesis of Chiral Vicinal Diamines”**
Agut, J.; Vidal, A.; Rodríguez, S.; González, F. V. *J. Org. Chem.* **2013**, *78* (11), 5717.
- **“Nitroepoxides as Versatile Precursors to 1,4-Diaminoheterocycles”**
Vidal-Albalat, A.; Rodríguez, S.; González, F. V. *Org. Lett.* **2014**, *16* (6), 1752.
- **“Asymmetric Epoxidation of Alkylidenemalononitriles: Key Step for One-Pot Approach to Enantioenriched 3-Substituted Piperazin-2-ones”**
Meninno, S.; Vidal-Albalat, A.; Lattanzi, A. *Org. Lett.* **2015**, *17* (17), 4348.
- **“Preparation of Morpholines and Benzoxazines Starting from Nitroepoxides”**
Capel, E.; Vidal-Albalat, A.; Rodríguez, S.; González, F. V. *Synthesis* **2016**, *48*, A-1
- **“Catalytic Enantioselective Epoxidation of Nitroalkenes”**
Vidal-Albalat, A.; Świderek, K.; Izquierdo, J.; Rodríguez, S.; Moliner, V.; González, F.V. *Chem. Commun.*, under review

Collaborations and other publications:

- **“Development and Validation of a Liquid Chromatography Isotope Dilution Mass Spectrometry Method for the Reliable Quantification of Alkylphenols in Environmental Water Samples by Isotope Pattern Deconvolution”**
Fabregat-Cabello, N.; Sancho, J. V.; Vidal, A.; González, F. V.; Roig-Navarro, A. F. *J. Chromatogr. A* **2014**, *1328*, 43
- Book Chapter: **“Natural Products as Cathepsin Inhibitors”**
Vidal-Albalat, A.; González, F. V. *Studies in Natural Products Chemistry*, Accepted

Resum en Català

1. Objectius generals

Els objectius generals d'aquesta tesi doctoral queden englobats en els següents punts:

- Estudi de la reactivitat característica que converteix els nitroepòxids en “peces de construcció” interessants per la seua aplicació en la síntesi química de molècules més complexes.
- Derivació dels nitroepòxids en heterocicles nitrogenats com per exemple quinoxalines, pirazines, piperazines i tetrahydroquinoxalines, que són entitats moleculars que tenen un interès especial en la química mèdica.
- Estudi d'epoxidació asimètrica organocatalítica de dicianoalquilidens per la seua aplicació sintètica.
- Disseny racional i síntesi de catalitzadors de transferència de fase i la seua aplicació per l'epoxidació enantioselectiva de nitroalquens.

2. Introducció

Una de les fites més importants per un químic orgànic sintètic és aconseguir la síntesi d'una molècula específica amb un alt rendiment i puresa, però emprant mitjans econòmics, de baix impacte per la salut i l'ambient, i que les operacions realitzades per aquesta finalitat siguin pràctiques, simples i de temps optimitzat. Els darrers anys, els químics orgànics han batejat les molècules que ajuden a aconseguir aquest objectiu com a *building blocks* (peces de construcció en anglès), ja que es poden comparar amb peces de trencaclosques que permeten múltiples enllaços i combinacions amb diferents grups funcionals per tal de sintetitzar entitats més complexes que tinguen una aplicació en altres branques de la química com puga ser la mèdica o de materials.

El grup d'investigació de la Universitat Jaume I dirigit pel professor Florenci V. González ha enfocat la seua recerca en una determinada família de compostos que compleixen les característiques dels anteriorment mencionats *building blocks*. Aquests compostos són els nitroepòxids (Figura 1). Els nitroepòxids van ser descrits per primera vegada el 1969 per Newman i Angier i es caracteritzen per posseir un grup nitro en la posició α a l'epòxid, retirant densitat electrònica convertint-lo així en un grup més electrofílic.¹ En altres paraules, els nitroepòxids es podrien considerar sintons amb dues posicions electrofíliques contigües (Figura 1), tret que els converteix en bons *building blocks*.

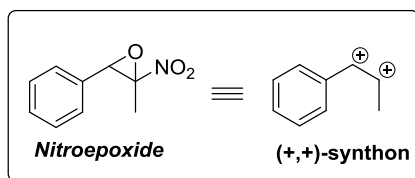
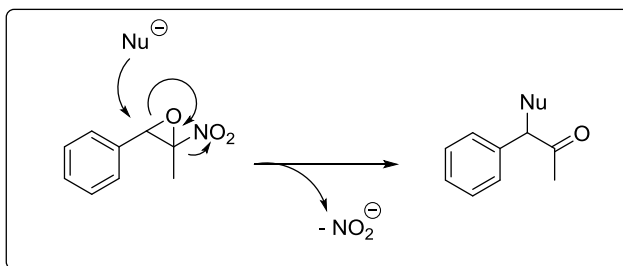


Figura 1. Nitroepòxids com sintons 1,2-electrofílics.

En el seu treball, Newman i Angier descriuen la síntesi de l'epòxid provinent del *trans*- β -metil- β -nitroestirè i la posterior apertura dels epòxids utilitzant diversos nucleòfils.¹ La reactivitat particular dels

¹ a) Newman, H.; Angier, R. B. *J. Chem. Soc. D Chem. Commun.* **1969**, 186, 369. b) Newman, H.; Angier, R. B. *Tetrahedron* **1970**, 26, 826.

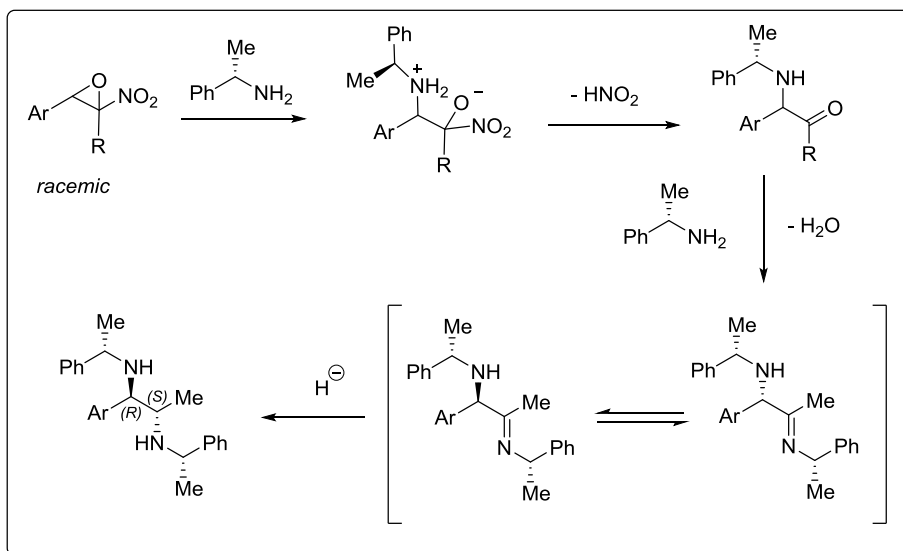
nitroepòxids fa que el nucleòfil ataque primer a la posició β respecte al grup nitro, ja que aquesta és la menys impedida, provocant l'apertura de l'epòxid i seguidament, degut a que el nitro és molt bon grup eixent, és produeix l'expulsió del grup nitro donant lloc a la cetona com a producte de la reacció (Esquema 1).



Esquema 1. Reactivitat del nitroepòxid enfront un nucleòfil.

Els precedents estudiats en el nostre grup es basen en l'apertura de nitroepòxids emprant amines com a nucleòfils i en un segon pas, utilitzant un altre equivalent de la mateixa amina seguit d'un agent reductor per dur a terme una aminació reductiva i obtenir 1,2-diamines.² Un fet interessant que vam observar, és que el procés global era diastereoselectiu (depenent dels substrats, la diastereoselectivitat variava de 90:10 a 99:1). A més, si s'emprava una amina amb un centre quiral de la reacció s'obtenia la diamina amb un 55-70% de rendiment i un dels quatre possibles diastereoisòmers amb elevada selectivitat (e.d. > 88%). Donat que una resolució no donaria un rendiment superior al 50%, aquest fet va ser interpretat com una transformació asimètrica dinàmico-cinètica, o DYKAT en les seues segles en anglés (Esquema 2).

² Agut, J.; Vidal, A.; Rodríguez, S.; González, F. V. *J. Org. Chem.* **2013**, 78 (11), 5717.



Esquema 2. Transformació asimètrica dinàmico-cinètica o DYKAT.

Donada la reactivitat dels nitroepòxids enfront de les amines per obtenir 1,2-diamines, una de les possibles aplicacions pensades per la realització d'aquesta tesi doctoral és la conversió dels nitroepòxids en 1,4-diazaheterocicles, com per exemple quinoxalines, pirazines, tetrahydroquinoxalines i piperazines. Aquests compostos tenen una certa rellevància en la química mèdica ja que són comuns en molts fàrmacs antibacterians³, antivirals⁴ i anticancerígens⁵ (Figura 2). A banda, les quinoxalines i les pirazines tenen una certa presència en la química dels materials, com per exemple tints orgànics per a cèl·lules fotovoltaiques, degut a les seues propietats fotoquímiques⁶.

³ Vieira, M.; Pinheiro, C.; Fernandes, R.; Noronha, J. P.; Prudêncio, C. *Microbiol. Res.* **2014**, *169* (4), 287.

⁴ a) You, L.; Cho, E. J.; Leavitt, J.; Ma, L.-C.; Montelione, G. T.; Anslyn, E. V.; Krug, R. M.; Ellington, A.; Robertus, J. D. *Bioorg. Med. Chem. Lett.* **2011**, *21* (10), 3007. b) Patel, M.; McHugh, R. J.; Cordova, B. C.; Klabe, R. M.; Bacheler, L. T.; Erickson-Viitanen, S.; Rodgers, J. D. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1943.

⁵ a) Zarranz, B.; Jaso, A.; Aldana, I.; Monge, A. *Bioorg. Med. Chem.* **2004**, *12* (13), 3711. b) Horton, D.; Bourne, G. T.; Smythe, M. L. *Cancer Res.* **2003**, *103* (3), 893.

⁶ a) Chandrasekaran, Y.; Dutta, G. K.; Kanth, R. B.; Patil, S. *Dye. Pigment.* **2009**, *83* (2), 162. b) Mondal, R.; Ko, S.; Bao, Z. *J. Mater. Chem.* **2010**, *20* (47), 10568.

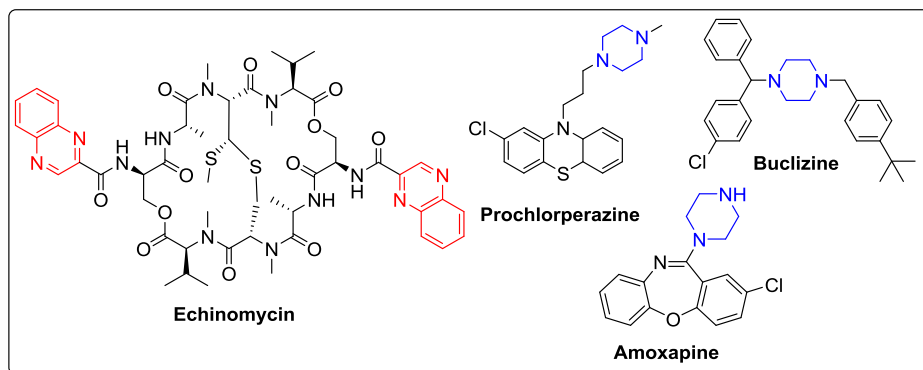


Figura 2. Exemples de fàrmacs i productes naturals bioactius que contenen 1,4-diazaheterocicles en la seua estructura.

La síntesi d'aquests heterocicles està comunament lligada a precursors de difícil accés com per exemple 1,2-dicetones, la qual cosa fa que la seua obtenció siga limitada. És per això que, donat el caràcter 1,2-electrofílic dels nitroepòxids és semblant al de les 1,2-dicetones però la seua síntesi molt més assequible, per la realització d'aquesta tesi s'ha pensat amb els nitroepòxids com a precursors sintètics d'aquests compostos.

Donada la versatilitat sintètica dels epòxids, i concretament en aquest cas dels nitroepòxids, la seua versió asimètrica proporcionaria una ferramenta valuosa per la síntesi de compostos òpticament actius. Els nitroepòxids es preparen mitjançant l'epoxidació del nitroalquè corresponent. No obstant, a data d'avui no s'ha documentat cap mètode d'epoxidació enantioselectiva de nitroalquens, excepte un treball d'Enders el qual té les seues limitacions per ser molt substrat-dependent⁷. L'únic mètode d'obtenció de nitroepòxids enantioenriquits que apareix en la literatura es tracta d'una resolució d'una mescla racèmica de nitroepòxids mitjançant anilina i un organocatalitzador quiral⁸. Tanmateix, aquesta metodologia presenta limitacions considerables, tenint en compte que amb la resolució quiral d'una mescla racèmica no es pot obtenir més del 50% del producte desitjat. És per això, que l'epoxidació enantioselectiva de nitroalquens suposaria un avenç destacable per la síntesi asimètrica.

⁷ Enders, D.; Kramps, L.; Zhu, J. *Tetrahedron: Asymmetry* **1998**, 9 (22), 3959.

⁸ Meninno, S.; Napolitano, L.; Lattanzi, A. *Catal. Sci. Technol.* **2015**, 5 (1), 124.

A pesar de què no hi ha cap mètode disponible per l'epoxidació asimètrica de nitroalquens, en la bibliografia es poden trobar diversos mètodes per l'epoxidació alquens; des de l'epoxidació enantioselectiva de Sharpless amb un catalitzador quirals de titani, fins l'epoxidació d'alquens electró-deficients com les xalcones mitjançant diversos organocatalitzadors i agents oxidants⁹.

Entre els mètodes organocatalítics per l'epoxidació asimètrica d'alquens electró-deficients es podrien destacar els treballs de Julià-Colonna amb polipèptids com a catalitzadors¹⁰, l'epoxidació a través d'enamina catalitzada amb el derivat de prolinol de Jørgensen-Hayashi (Esquema 3)¹¹, les sals d'imidazolidinona de MacMillan¹² o l'epoxidació mitjançant dioxirans desenvolupada per Shi¹³. No obstant, aquesta tesi s'ha centrat en l'epoxidació per catalitzadors bifuncionals i per catalitzadors de transferència de fase.

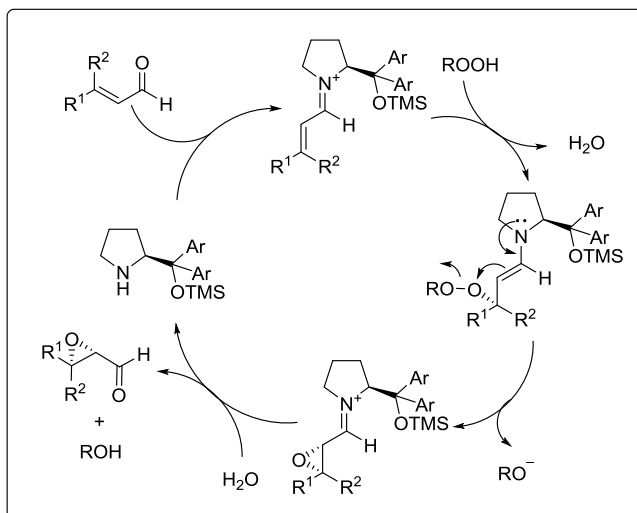
⁹ Per una revisió general: Zhu, Y.; Wang, Q.; Cornwall, R. G.; Shi, Y. *Chem. Rev.* **2014**, *114*, 8199.

¹⁰ Julià, S.; Guixer, J.; Masana, J.; Rocas, J.; Colonna, S.; Annuziata, R.; Molinari, H. *J. Chem. Soc. Perkin Trans. I* **1982**, 1317.

¹¹ a) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chemie - Int. Ed.* **2005**, *44* (27), 4212. b) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chemie - Int. Ed.* **2005**, *44* (5), 794. c) Zhuang, W.; Marigo, M.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 3883.

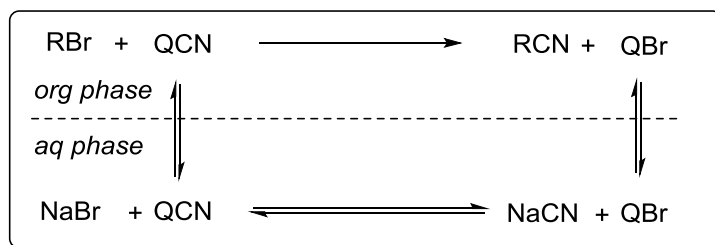
¹² Lee, S.; MacMillan, D. W. C. *Tetrahedron* **2006**, *62* (49), 11413.

¹³ Tu, Y.; Wang, Z.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118* (40), 9806.



Esquema 3. Procés catalític d'epoxidació enantioselectiva mitjançant un catalitzador de diarilprolinol.

Generalment, s'anomena catalitzador bifuncional a aquell que posseeixi en la seua estructura molecular un grup funcional que actuï com àcid de Lewis i un altre com a base de Lewis. Probablement el més conegut siga el catalitzador de Takemoto¹⁴, que està compost per una tiourea i una amina terciària. D'altra banda, la catàlisi per transferència de fase, emprada en sistemes bifàsics (dissolucions en fase aquosa i orgànica, per exemple) amb catalitzadors que són capaços de transportar ions d'una fase a l'altra gràcies a la seua solubilitat en ambdues fases (Esquema 4). Els catalitzadors d'aquest tipus més comunament emprats són sals d'amoni quaternàries derivades d'alcaloides de cincona, en combinació amb solucions aquoses de peròxid o d'hipoclorit sòdic.



Esquema 4. Representació general d'una reacció de transferència de fase on Q representa el catalitzador.

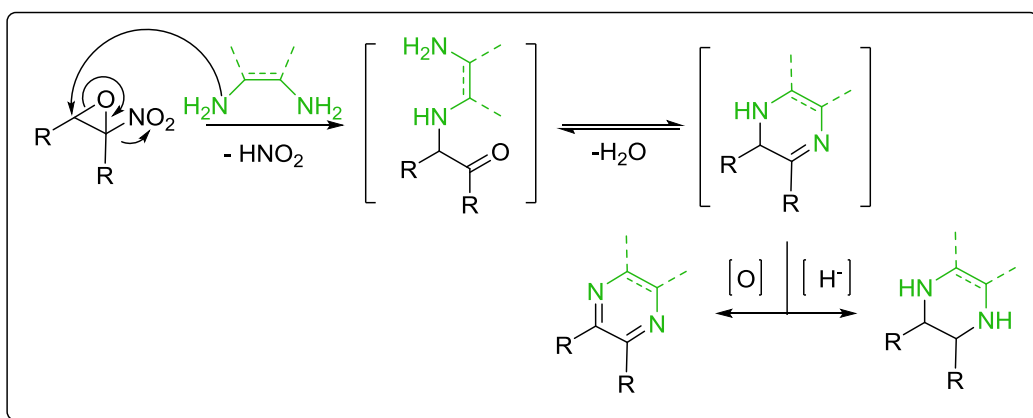
¹⁴ Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125* (42), 12672.

En l'apartat de resultats i discussió s'oferiran els detalls experimentals sobre els objectius especificats i la seua relació amb el que s'ha explicat en aquest apartat d'introducció.

3. Resultats i discussió

3.1. Heterocicles

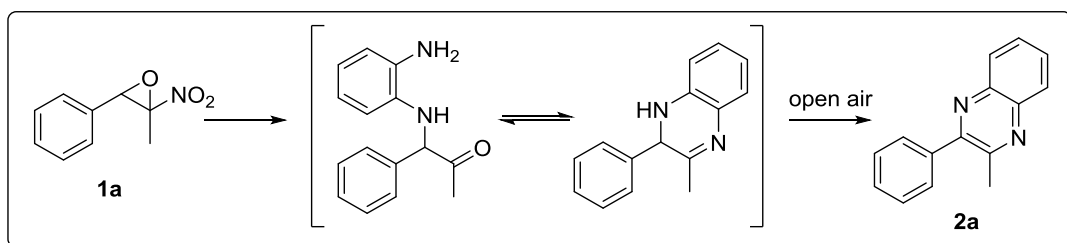
Tenint en compte la reactivitat dels nitroepòxids amb les amines per obtenir 1,2-diamines², es va dissenyar l'apertura de l'anell epoxídic amb compostos que ja contingueren l'estructura 1,2-diamina per tal de formar heterocicles de nitrogen. A més, donat que l'intermedi de reacció vindria a ser una amino-imina, s'obtidria una situació ideal per tal de de sintetitzar un heterocicle aromàtic o saturat treballant en condicions oxidants o reductores, respectivament (Esquema 5).



Esquema 5. Transformació de nitroepòxids en heterocicles de nitrogen insaturats i saturats.

La primera prova d'apertura de l'epòxid del *trans*- β -metil- β -nitroestirè (**1a**) es va dur a terme emprant 1,2-diaminobenzè com a nucleòfil i 1,2-dicloroetà (DCE) com a dissolvent a temperatura ambient durant 24 hores. Per la nostra sorpresa, una anàlisi per RMN d'una alíquota de reacció va mostrar la formació de l'heterocicle oxidat, la quinoxalina **2a**, a banda de la formació de la cetona, sense l'addició de cap agent oxidant. La nostra interpretació dels resultats consistia en què una vegada es tanca el cicle, l'oxigen atmosfèric és capaç d'oxidar l'intermedi amino-imina el qual guanya aromaticitat i és converteix en un compost més estable (Esquema 6). Aquesta hipòtesi es va veure reforçada quan, després d'haver parat la reacció en condicions ambient,

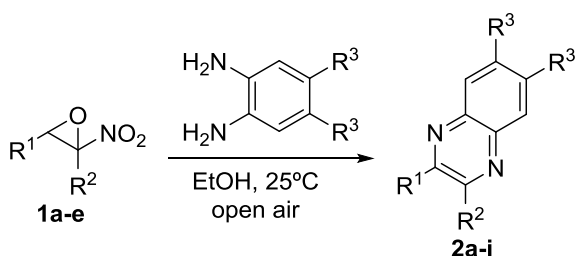
al RMN únicament es veia el producte aromàtic **2a** sense restes dels possibles intermedis.



Esquema 6. Formació de l'intermedi amino-imina i aromatització amb oxigen atmosfèric per obtindre **2a**.

El procés d'optimització de la reacció va ser senzill: canviar de dissolvent a etanol va augmentar la solubilitat dels reactius afavorint així el rendiment i acurtant el temps de reacció. Fer la reacció amb el matràs obert a l'atmosfera també va augmentar la velocitat de reacció. Es va establir com a criteri general un canvi de color en la dissolució, de groc clar a roig intens, com a indicador de formació de la quinoxalina. Diversos substrats es van testar en les mateixes condicions, obtenint diverses quinoxalines amb bons rendiments (70-83%), excepte en el cas de què els substituents del nitroepòxid fossin ambdós grups alquil (Taula 1).

Taula 1. Síntesi de quinoxalines.^a



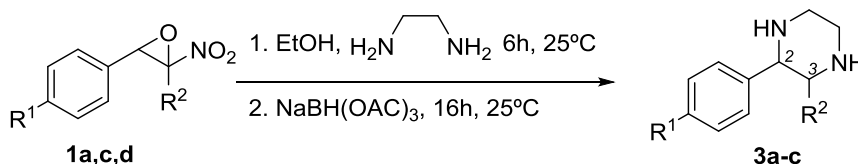
Entrada	R ¹ , R ²	Epòxid	R ³	Quinoxalina	Rendiment (%) ^b
1	Ph, Me	1a	H	2a	86
2	Ph, Me	1a	Cl	2b	82
3	<i>p</i> -F-Ph, Me	1b	H	2c	80
4	<i>p</i> -F-Ph, Me	1b	Cl	2d	75
5	<i>p</i> -Me-Ph,	1c	H	2e	78

	Me				
6	<i>p</i> -Me-Ph, Me	1c	Cl	2f	70
7	<i>p</i> -F-Ph, Et	1d	H	2g	80
8	<i>n</i> -Pr, Me	1e	H	2h	63
9	<i>n</i> -Pr, Me	1e	Cl	2i	48

^aLes reaccions es van dur a terme emprant nitroepòxid (1.0 equiv) i 1,2-diaminobenzè (1.5 equiv) a temperatura ambient per 16 h. ^bRendiment sobre el producte aïllat.

Motivats pels resultats de les quinoxalines, vam decidir sintetitzar piperazines, emprant 1,2-etilendiamina i NaBH(OAc)₃ com agent reductor, en DCE a temperatura ambient. En aquest cas, els resultats no van ser tan bons com en el cas de les quinoxalines, però després d'un treball d'optimització i purificació, es van obtenir piperazines amb rendiments moderats i una lleugera diastereoselectivitat (Taula 2).

Taula 2. Síntesi de piperazines.^a

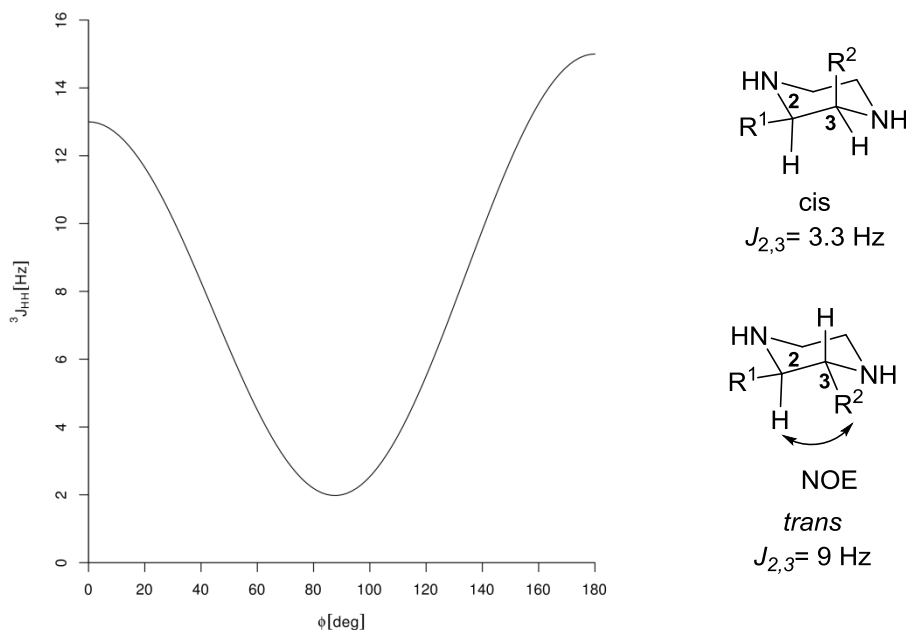


Entrada	R ¹ ,R ²	Epòxid	Piperazina	Rendiment (%) ^b	d.r. (<i>cis/trans</i>)
1	H, Me	1a	3a	44%	2:1
2	Me, Me	1c	3b	64%	4:1
3	F, Et	1d	3c	58%	2.2:1

^aLes reaccions es van dur a terme emprant nitroepòxid (1.0 equiv) i 1,2-etilendiamina (1.5 equiv) a temperatura ambient durant 6 h. Després, es va afegir NaBH(OAc)₃ (3.0 equiv) i la mescla es va seguir agitant per 16 h. ^bRendiment sobre el producte aïllat.

L'estereoquímica dels diastereoisòmers es va assignar per les constants d'acoblament en l'espectre de ¹H RMN (la constant *J*_{2,3} és major per l'isòmer *trans* que per al *cis*) i per experiments de NOE. La piperazina **3a** va mostrar una constant d'acoblament de 3.3 Hz per l'isòmer majoritari, mentre que el minoritari va mostrar una constant de 9 Hz.

Tenint en compte la relació descrita per Karplus¹⁵ entre constant d'acoblament i angle dièdric, a l'isòmer majoritari se li va assignar la conformació *cis* i al minoritari *trans* (Esquema 7). A més, els experiments de NOE van confirmar acoblament en l'isòmer *trans* (Esquema 7).



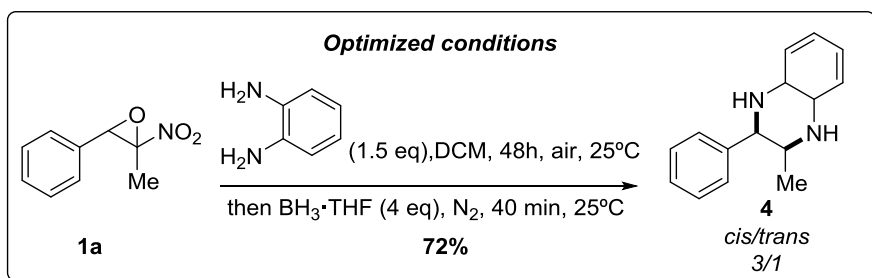
Esquema 7. Equació general de Karplus per els confòrmers d'età (esquerra).

Assignació de l'estereoquímica de les piperazines (dreta).

El següent pas va consistir en l'obtenció del cicle de tetrahydroquinoxalina **4** per la reducció *in situ* de l'intermedi amino-imina, provinent de l'epòxid **1a**, amb NaBH(OAc)₃. No obstant, amb aquesta metodologia, la quinoxalina **2a** seguia sent el compost majoritari. Després de diversos intents d'optimitzar les condicions, es va decidir canviar d'estratègia, i afegir el reductor, en aquest cas BH₃·THF, una volta s'hagués format el compost **2a**. D'aquesta manera, la tetrahydroquinoxalina **4** es va obtenir en un procés *one-pot* amb un 72% de rendiment, sobre el producte aïllat, i una mescla de diastereoisòmers (*cis/trans* 3:1) (Esquema 8). La configuració dels

¹⁵ a) Karplus, M. *J. Chem. Phys.* **1959**, *30* (1), 11. b) Gutowsky, H. S.; Karplus, M.; Grant, D. M. *J. Chem. Phys.* **1959**, *31* (5), 1278. c) Minch, M. J. *Concepts Magn. Reson.* **1994**, *6*, 41.

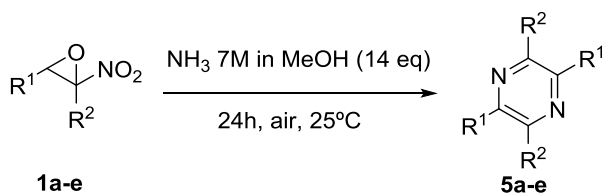
diastereoisòmers es va assignar de la mateixa manera que per les piperazines **3a-c**.



Esquema 8. Condicions optimitzades per la síntesi *one-pot* de **4**.

Finalment, es van sintetitzar una sèrie de pirazines a partir de diferents nitroepòxids (Taula 3). Per aconseguir-ho, es van fer reaccionar els nitroepòxids amb una dissolució metanòlica d'amoníac. En un primer pas, l'amoníac reacciona amb l'epòxid per formar l'intermedi amino-cetona, què immediatament condensa amb una altra amino-cetona per formar un dímer. Aquest, en presència d'oxigen, aromatitza per tal de formar la pirazina. La reacció va resultar ser ràpida i neta, obtenint-se les pirazines amb rendiments elevats i sense més necessitat de purificació que una extracció amb èter etílic del medi de reacció.

Taula 3. Síntesi de pirazines.^a



Entada	R ¹ ,R ²	Epòxid	Pirazina	Rendiment (%) ^b
1	Ph, Me	1a	5a	93
2	<i>p</i> -F-Ph, Me	1b	5b	92
3	<i>p</i> -Me-Ph, Me	1c	5c	90
4	<i>p</i> -F-Ph, Et	1d	5d	96
5	<i>n</i> -Pr, Me	1e	5e	89

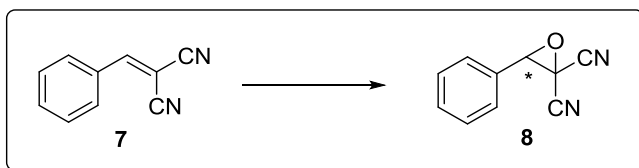
^aLes reaccions es van dur a terme emprant nitroepòxid (1.0 equiv) i una dissolució 7M d'amoníac en metanol (14 equiv) a temperatura ambient durant 24 h. ^bRendiment sobre el producte aïllat.

La síntesi de diversos heterocicles, aromàtics i no aromàtics, a partir de nitroepòxids i diamines (o amoníac en el cas de les pirazines) ha quedat constatada en aquest resum, i el treball s'ha publicat en una revista d'alt índex d'impacte en l'àmbit de la química orgànica.¹⁶

¹⁶ Vidal-Albalat, A.; Rodríguez, S.; González, F. V. *Org. Lett.* **2014**, *16* (6), 1752.

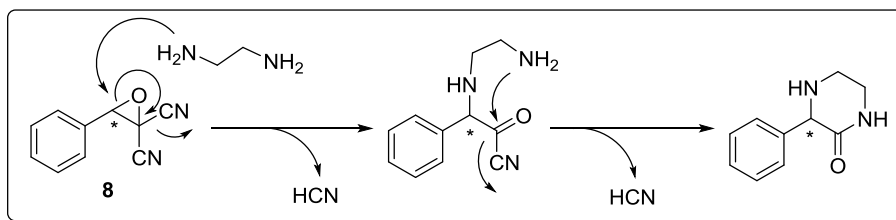
3.2. Epoxidació enantioselectiva de dicianoalquilidens

El treball descrit en aquest apartat es va realitzar durant una estada de 4 mesos a la Universitat degli Studi di Salerno (Itàlia), sota la supervisió de la professora Alessandra Lattanzi. Aquest estudi es va centrar en l'epoxidació organocatalítica enantioselectiva del dicianoalquilidè **7** per obtenir l'epòxid **8** (Esquema 9). A l'igual que passa amb el grup nitro, els grups ciano són electró-atraents, per la qual cosa l'epòxid **8** es converteix en un *building block* electròfil.



Esquema 9. Esquema general per la conversió de **7** en **8**.

Les aplicacions d'un sintètiques de l'epòxid **8** serien molt interessants, ja que per exemple, si es fa reaccionar el dicianoepòxid amb 1,2-etilendiamina, al tindre dos grups ixents, es formaria una piperazin-2-ona quiral (Esquema 10). Aquest tipus d'estructura és comuna en alguns productes d'origen natural que podrien presentar activitat biològica interessant des d'un punt de vista farmacològic¹⁷.



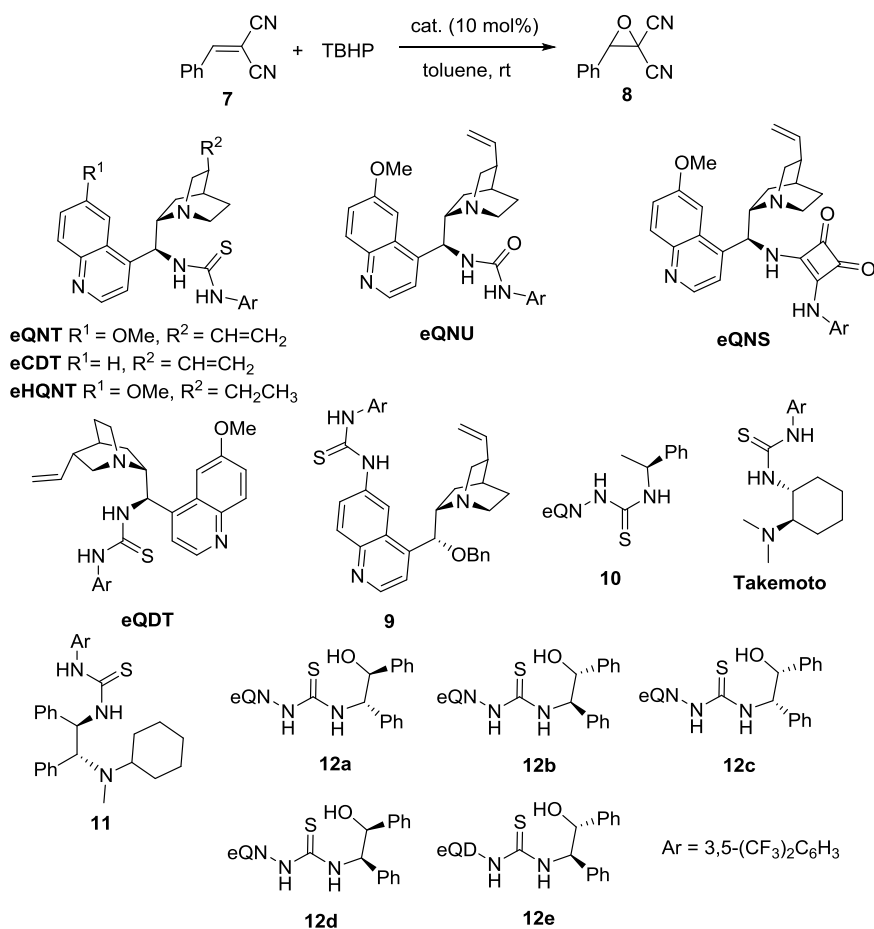
Esquema 10. Ruta mecanística per la síntesi de piperazin-2-ones a partir de dicianoepòxids

Per tal d'aconseguir l'epoxidació asimètrica dels dicianoalquilidens, es va optar per l'epoxidació amb hidroperòxids catalitzada per tiourees

¹⁷ a) Korch, K. M.; Eidamshaus, C.; Behenna, D. C.; Nam, S.; Horne, D.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2015**, *54* (1), 179. b) Prangé, T.; Billion, M. A.; Vuilhorgne, M.; Pascard, C.; Polonsky, J. *Tetrahedron Lett.* **1981**, *22* (21), 1977. c) Nakao, Y.; Masuda, A.; Matsunaga, S.; Fusetani, N. *J. Am. Chem. Soc.* **1999**, *121* (11), 2425. d) Martínez-Luis, S.; Rodríguez, R.; Acevedo, L.; González, M. C.; Lira-Rocha, A.; Mata, R. *Tetrahedron* **2006**, *62* (8), 1817.

bifuncionals, ja que treballs anteriors de la professora Lattanzi havien donat bons resultats quan s'havia optat per aquest sistema¹⁸. El mecanisme general que descriu el paper d'un organocatalitzador bifuncional en una reacció d'epoxidació, es podria resumir d'aquesta manera: una funció bàsica de la molècula (generalment, una amina terciària) desprotona l'hidroperòxid mentre un altre grup funcional del catalitzador activa l'electròfil (a través de ponts d'H, per exemple) per fer-lo més reactiu. Si a més, el catalitzador és òpticament actiu, pot orientar els substrats per tal d'afavorir la formació d'un enantiòmer respecte el seu oposat. Diversos catalitzadors s'han sintetitzat i testat per l'epoxidació de **7** en les mateixes condicions (Taula 4).

Taula 4. Proves de catalitzadors per l'epoxidació asimètrica de **7.**^a



¹⁸ Russo, A.; Galdi, G.; Croce, G.; Lattanzi, A. *Chem. Eur. J.* **2012**, *18* (20), 6152.

Entrada	Catalitzador	Temps (h)	Rendiment (%) ^b	e.r. (%) ^c
1	eQNT	15	58	67.5:32.5
2	eQNU	16	48	65.4:34.6
3 ^d	eQNS	40	70	62.2:37.8
4	eCDT	21	57	59.5:40.5
5	eHQNT	24	63	56.2:43.8
6 ^e	eQDT	21	84	44.9:55.1
7	9	29	43	54.2:45.8
8	10	15	72	52.4:47.6
9 ^e	Takemoto	24	55	44.3:55.7
10 ^e	11	24	34	31.3:68.7
11	12a	22	90	77.2:22.8
12 ^e	12b	21	80	42.8:57.2
13	12c	18	75	71:29
14 ^e	12d	17	74	49.8:50.2
15 ^e	12e	16	87	23:77

^aLes reaccions es van dur a terme a una escala de 0.1 mmol per a **7** (C = 0.2 M) emprant TBHP (1.2 equiv). ^bDeterminat per anàlisi ¹H RMN amb 1,3,5-(MeO)₃C₆H₃ com a patró intern. ^cDeterminat per anàlisi quiral d'HPLC. ^dLa reacció es va fer a escala 5 mol % de eQNS en CHCl₃. ^eEs va obtenir preferentment l'enantiòmer oposat.

Una sèrie de catalitzadors es van preparar utilitzant l'estructura de derivats de cincona (quinina, per exemple) als quals se'ls va afegir un grup funcional amb l'habilitat d'afavorir ponts d'hidrogen (tiourea, urea i esquaramida). Comparant els resultats del catalitzador de tiourea, urea i esquaramida derivats de l'*epi*-quinina (entrades 1 – 3, respectivament) que en termes de conversió i enantioselectivitat, el catalitzador de tiourea eQNT era més eficient per al sistema estudiat. Arran dels resultats obtinguts, es va decidir seguir amb el grup tiourea, però modificant els esquelets de cincona (entrades 4 – 6). Canviar la quinina (entrada 1) per cinconidina (entrada 4) va resultar en un detriment de l'enantioselectivitat i la velocitat de reacció, mentre que per al pseudoenantiòmer de quinidina (entrada 6) la conversió va ser bona, però l'enantioselectivitat, a banda de canviar de signe com s'esperava, també es va veure reduïda. Canviar la posició de la tiourea en l'estructura de quinina o el seu substituent (entrades 7 – 8) tampoc van afavorir l'enantioselectivitat. El catalitzador de Takemoto (entrada 9) tampoc va donar bons resultats però en canvi, utilitzar el catalitzador 11 (entrada 10) va millorar l'enantioselectivitat, tot i què per l'enantiòmer oposat i amb la pitjor conversió de la taula.

Arribats a aquest punt, i donada la naturalesa dels dicianoalquilidens, vam pensar que afegir més grups donadors de hidrogen per enllaços no covalents podria resultar en una millora de l'efectivitat del catalitzador. Una sèrie de catalitzadors amb la funcionalitat de 1,2-aminoalcohol (entrades 11 – 15) es va dissenyar i testar per la reacció d'epoxidació. Afortunadament, el catalitzador **12a** (entrada 11) va donar millors resultats tant en termes de conversió com d'enantioselectivitat. El catalitzador **12e** (entrada 15) es va preparar amb quinidina, l'estructura de cincona pseudoenantiomèrica respecte a **12a**, i els resultats entre ambdós en termes d'enantioselectivitat van ser quasi idèntics, però de signe contrari. Altres variables van ser testades per la doctora Sara Meninno per tal de millorar els resultats amb **12a** com a millor catalitzador i estendre les condicions a altres substrats, aconseguint millorar els excessos enantiomèrics¹⁹.

A la vista dels resultats, i d'acord amb les observacions experimentals, es va proposar un estat de transició per tal d'explicar l'enantioselectivitat (Figura 3). Un dels grups ciano estaria activat per l'hidroxil del catalitzador, mentre que l'altre estaria activat pels NH de la funció tiourea. Aquesta hipòtesi es va fer en base a un estudi computacional que afirmava que era més plausible una doble activació del grup ciano per ambdós NH que solament amb un²⁰.

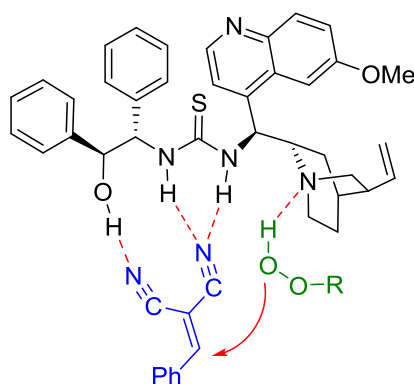


Figura 3. Estat de transició proposat per l'epoxidació enantioselectiva de dicianoalquilidens.

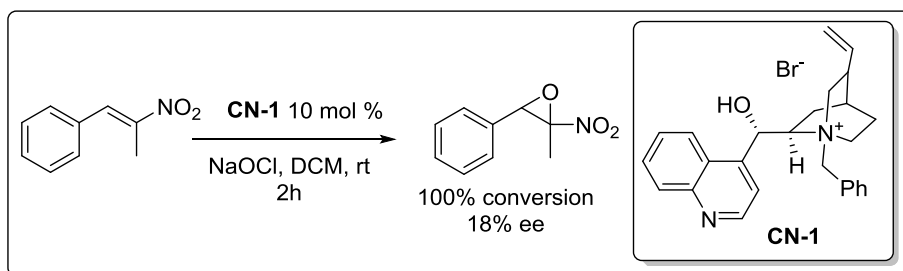
¹⁹ Meninno, S.; Vidal-Albalat, A.; Lattanzi, A. *Org. Lett.* **2015**, *17* (17), 4348.

²⁰ Qi, Z.-H.; Zhang, Y.; Ruan, G.-Y.; Zhang, Y.; Wang, Y.; Wang, X.-W. *RSC Adv.* **2015**, *5* (43), 34314.

3.3. Epoxidació asimètrica de nitroalquens

Donat l'interès que presenten els nitroepòxids per l'aplicació en química sintètica com a *building blocks*, ser capaços d'obtindre'ls de forma asimètrica proporcionaria una ferramenta molt valuosa de cara a la síntesi orgànica. Tal com s'ha mencionat abans, a dia d'avui no hi ha un mètode efectiu i general per l'epoxidació asimètrica de nitroalquens.

Russo i Lattanzi van intentar epoxidar els nitroalquens emprant catalitzadors bifuncionals del tipus tiourea sense gaire èxit, obtenint principalment el peròxid com a producte d'addició oxa-Michael²¹. Així que, nosaltres vam decidir canviar d'estratègia i provar l'epoxidació mitjançant catàlisi de transferència de fase (PTC en anglès). Les primeres proves van donar resultats esperançadors ja que la conversió de la reacció era completa a les dues hores, a pesar de què l'excés enantiomèric fóra només del 18%. Per aquesta reacció, vam emprar el bromur de N-benzil cinconini com a catalitzador, en diclorometà, i una dissolució concentrada de hipoclorit sòdic com a catalitzador (Esquema 11).



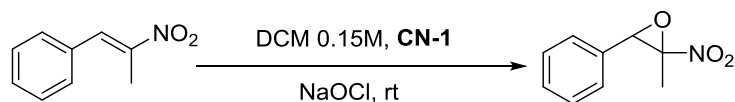
Esquema 11. Prova d'epoxidació asimètrica mitjançant PTC.

Al ser un sistema bifàsic, el nombre de variables per estudiar i optimitzar era considerable. En primer lloc, es van estudiar la quantitat d'oxidant i la seua concentració en la fase aquosa. Es va observar que en ambdós casos, quan es reduïa el nombre d'equivalents d'oxidant o la seua concentració en la fase aquosa, la velocitat de reacció disminuïa, però l'enantioselectivitat no es va veure afectada de forma significativa. En canvi, la càrrega de catalitzador sí que va tindre un impacte en l'enantioselectivitat (Taula 5). A mesura que disminuïa la càrrega de

²¹ Russo, A.; Lattanzi, A. *Adv. Synth. Catal.* **2008**, 350 (13), 1991.

catalitzador, també ho feia l'enantioselectivitat. Malauradament, augmentar la càrrega més del 10% mol, no suposava un augment significatiu de l'enantioselectivitat (entrada 1). Sobre aquest fet, hem proposat la hipòtesi de què la concentració de catalitzador arriba al seu punt de saturació i llavors la porció de catalitzador que queda en suspensió no participa de forma significativa en la catàlisi.

Taula 5. Efecte de la càrrega de catalitzador sobre la conversió i l'enantioselectivitat.^a

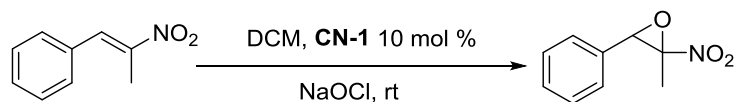


Entrada	Càrrega cat.	Temps (h)	Conversió (%) ^b	e.r. ^c
1	20 mol%	2	100	59:41
2	10 mol%	2	100	58:42
3	5 mol%	2	76	54:46
4	1 mol%	4	20	50.5:49.5

^aLes reaccions es van dur a terme a escala de 20mg del trans- β -metil- β -nitrostirè, en DCM amb una proporció 1:1 org/aq i durant el temps indicat. ^bMesurat sobre ¹H NMR. ^cMesurat en HPLC.

Lygo ja havia postulat que la concentració de catalitzador en la fase orgànica era un tret important²². Una sèrie d'experiments es van realitzar a diferents concentracions de la fase orgànica respecte al nitroalquè (Taula 6). Tal com es pot observar en la taula, el millor resultat va ser a una concentració de 0.3M (entrada 2).

Taula 6. Variació de conversió i e.r. en funció de la concentració.^a



Entry	Conc. (M)	Org/Aq ^b	Temps (h)	Conversion (%) ^c	e.r. ^d
1	0.6	1:1	2.5	100	54:46
2	0.3	2:1	3	100	59:41
3	0.15	4:1	5	100	57:43
4	0.07	7.5:1	6	96	55:45

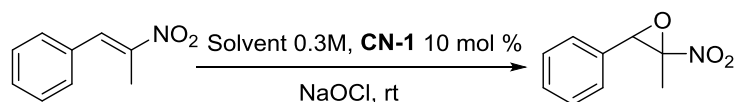
²² Lygo, B.; To, D. C. M. *Chem. Commun.* **2002**, 20, 2360.

5	0.024	25:1	20	90	53:47
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^aLes reaccions es van dur a terme a escala de 20mg del *trans*- β -metil- β -nitrostirè, en DCM amb una quantitat constant d'oxidant i durant el temps indicat. ^bProporció de volum. ^cMesurat sobre ¹H NMR. ^dMesurat en HPLC.

Un altra variable que segons la literatura sembla ser primordial, és el dissolvent emprat (Taula 7). En aquells sistemes on el catalitzador no era soluble, o hi havia miscibilitat entre la fase aquosa i l'orgànica, no hi va haver reacció (entrades 5 i 7), o en el cas d'haver-la (entrada 6), no hi va haver enantioselectivitat. La reacció va resultar ser més efectiva en els dissolvents apolars, especialment en el cas del cloroform (entrada 9). Curiosament, en el cas del toluè (entrada 3), a pesar de ser un dissolvent bastant comú en aquest tipus de sistemes, la conversió va ser molt baixa i l'enantioselectivitat no es va mesurar.

Taula 7. Estudi de l'efecte del dissolvent en la conversió i l'enantioselectivitat.^a



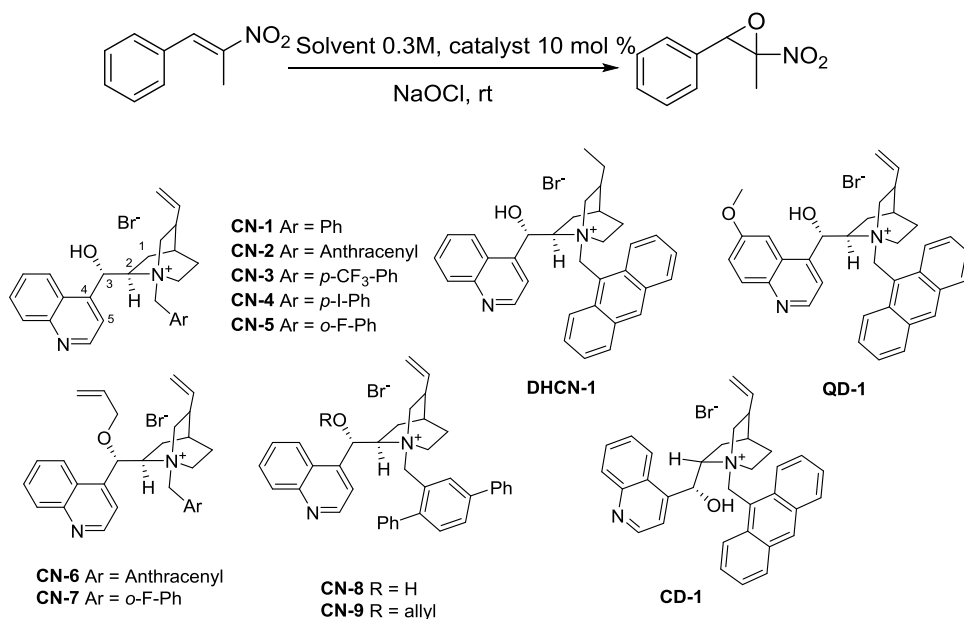
Entry	Solvent	Time (h)	Conversion (%) ^b	e.r. ^c
1	DCM	2	100	59:41
2	EtOAc	6	48	50:50
3	Toluene	24	20	n.d. ^d
4	Hexane	24	<5	n.d.
5	Methanol	24	No reaction	n.d.
6	THF	6	45	50:50
7	Et ₂ O	24	No reaction	n.d.
8	1,2-DCE	2	75	55:45
9	Chloroform	1.5	70	74:26

^aLes reaccions es van dur a terme a escala de 20mg del *trans*- β -metil- β -nitrostirè, a una concentració de 0.3M amb una proporció de fase 1:1 org/aq i durant el temps indicat. ^bMesurat sobre ¹H NMR. ^cMesurat en HPLC. ^dSense dades.

Amb les principals condicions estudiades, sols quedava estudiar l'efecte de l'estructura del catalitzador sobre la reacció (Taula 8). Diversos catalitzadors es van dissenyar i estudiar a mesura que nous dubtes i observacions experimentals anaven sorgint. Utilitzant l'estructura de la cinconina, diversos compostos es van emprar per

quaternitzar el nitrogen de l'anell de quinuclidina (entrades 1 – 5), amb el millor resultat per al catalitzador **CN-2** amb el grup metilantracè com a substituent (entrada 2).

Taula 8. Estudi sobre els efectes del catalitzador.^a



Entrada	Solvent	Catalitzador	Temps (h)	Conversió (%) ^b	e.r. ^c
1	CHCl ₃	CN-1	5	100	74:26
2	CHCl ₃	CN-2	3	100	84:16
3	CHCl ₃	CN-3	5	100	81:19
4	CHCl ₃	CN-4	3	100	81:19
5	CHCl ₃	CN-5	5	100	53:47
6	CHCl ₃	DHCN-1	2	100	81:19
7	CCl ₄	CN-2	2	100	89:11
8	Toluene	CN-2	24	100	87:13
9	Toluene	CN-4	16	60	84:16
10	CHCl ₃	QD-1	4	100	62:38
11	Toluene	QD-1	4	98	75:25
12	CHCl ₃	CN-6	5	80	45:55
13	Toluene	CN-6	5	100	33.5:66.5
14	CHCl ₃	CN-7	4	38	50:50
15	Toluene	CN-7	4	98	39.5:60.5
16	Toluene	CN-8	4.5	100	41:59
17	Toluene	CN-9	5	100	25:75

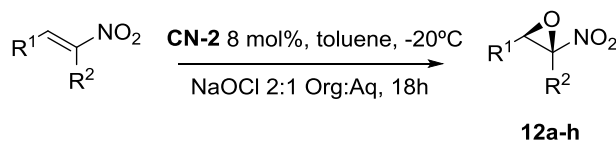
18^d	Toluene	CN-2	16	92 ^e	96.5:3.5
19^d	Toluene	CD-1	16	86 ^e	18:82

^aLes reaccions es van dur a terme a escala de 20mg del trans- β -metil- β -nitrostrirè, a una concentració de 0.3M amb una proporció de fase 2:1 org/aq a temperatura ambient i durant el temps indicat. ^bMesurat sobre ¹H NMR. ^cMesurat en HPLC. ^dTemperatura de la reacció -20°C. ^eRendiment aïllat.

L'efectivitat de **CN-2** es va mesurar també en CCl₄ i en toluè (entrades 7 i 8, respectivament) obtenint millors resultats que amb cloroform (entrada 2). Es va seguir amb el toluè per ser un dissolvent més benigne tan des d'un punt de vista ambiental com toxicològic. Diverses modificacions en l'estructura del catalitzador es van testar (entrades 10 – 17). Curiosament, per aquells catalitzadors en els quals s'havia alquilat l'hidroxil, l'enantioselectivitat no solament es va veure reduïda, sinó que va canviar de signe (12 – 15). Aquest fet sembla indicar que l'hidroxil podria dirigir la reacció i controlar l'enantioselectivitat. També es va veure un canvi de signe quan un grup més voluminós es va introduir (entrades 16 – 17). Com a conclusió, es va argumentar que el grup antracènil podria afavorir interaccions del tipus π - π *stacking* entre el catalitzador i el substrat.

L'efecte d'additius, generalment àcids de Lewis, també es va estudiar, però cap d'ells va donar un resultat favorable. Així, amb les condicions ja optimitzades per al compost d'estudi, es va estudiar la naturalesa del substrat en l'efectivitat de la reacció (Taula 9).

Taula 9. Abast de la reacció^a



Entrada	R ¹ ,R ²	Epòxid	Rendiment (%) ^b	e.r. (%) ^c
1	Ph, Me	12a	92	96.6:3.4
2	<i>p</i> -F-Ph, Me	12b	96	96.1:3.9
3	<i>p</i> -Cl-Ph, Me	12c	92	94.2:5.8
4	<i>m</i> -Cl-Ph, Me	12d	87	91.5:8.5
5	<i>p</i> -F-Ph, Et	12e	91	95.1:4.9
6	<i>p</i> -Me-Ph, Me	12f	92	91.3:8.7
7	Ph, Ph	12g	90	91.5:8.5

8	iPr, Me	12h	63	56.5:43.5
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^aLes reaccions es van dur a terme a escala de 50mg del nitroalquè, a una concentració de 0.3M amb una proporció de fase 2:1 org/aq a - 20°C i durant el temps indicat.

^bRendiment aïllat. ^cMesurat en HPLC.

Com es pot observar, per als compostos on el substituent R¹ és un grup aril (entrades 1 – 6) els rendiments són alts, així com l'enantioselectivitat; mentre que en el cas de ser ambdós substituents grups alquílics (entrada 8), l'enantioselectivitat es veu afectada dràsticament. Açò esta en concordança amb la hipòtesis de les interaccions π - π *stacking* entre el substrat i el catalitzador. Càlculs computacionals també s'han realitzat per tal d'elucidar la relació estructura/activitat del catalitzador, i vénen a confirmar que l'hidroxil i les interaccions π - π *stacking* tenen un pes considerable en la conformació de l'estat de transició.

Els mateixos substrats s'han epoxidat amb el catalitzador pseudoenantiomèric **CD-1** obtenint bons resultats en termes de rendiment, i una inversió en la quiralitat de l'epòxid obtingut. No obstant, l'enantioselectivitat no ha estat tan elevada com en els compostos de la taula 9.

Finalment, s'han intentat diverses transformacions sintètiques sobre el nitroepòxid òpticament pur, però malauradament no s'han trobat les condicions adequades per conservar la puresa òptica. Tot i així, els resultats obtinguts han sigut mereixedors d'una publicació, ja que s'ha desenvolupat un mètode senzill i efectiu per l'obtenció d'heterocicles a partir de nitroepòxids, tal com morfolinols, morfelines, tiomorfolines i benzoxazines²³.

²³ Capel, E.; Vidal-Albalat, A.; Rodríguez, S.; González, F. V. *Synthesis* **2016**, 48, A-1

5. Conclusions generals

Del treball realitzat per aquesta tesi, es poden traure aquestes conclusions generals:

- S'ha estudiat la reactivitat característica dels nitroepòxids i la seua aplicació a la química sintètica.
- S'ha desenvolupat una metodologia senzilla que permet accedir a compostos heterocíclics nitrogenats tals com quinoxalines, piperazines, tetrahydroquinoxalines i pirazines, a partir de nitroepòxids.
- Durant l'estada d'investigació a la Università degli Studi di Salerno (Itàlia), s'ha avançat en l'epoxidació enantioselectiva de dicianoalquilidens mitjançant organocatalitzadors quirals. Posteriorment, el treball s'ha millorat obtenint bons resultats.
- S'ha reportat la síntesi enantioselectiva de nitroepòxids a partir de nitroalquens mitjançant catalitzadors de transferència de fase, amb rendiments elevats i e.r. > 90:10 en els casos on els substituents eren aril-alquil. El treball es troba actualment sota revisió en la revista *Chemical Communications*.
- S'han convertit els nitroepòxids en morfelines i tiomorfelines, a pesar de què no s'ha conservat la puresa òptica.

D'aquest treball han sorgit noves idees, i d'altres n'han quedat pendents de ser explotades o s'han obtingut resultats que encara necessiten ser millorats; com per exemple:

- Derivar els nitroepòxids òpticament purs en compostos d'interès sintètic o farmacològic sense perdre la seua puresa òptica.
- Explotar els nitroepòxids per la síntesi de nous heterocicles amb una metodologia senzilla i pràctica.
- Estudiar el comportament de la síntesi de 1,2-diamines a partir dels nitroepòxids òpticament purs.