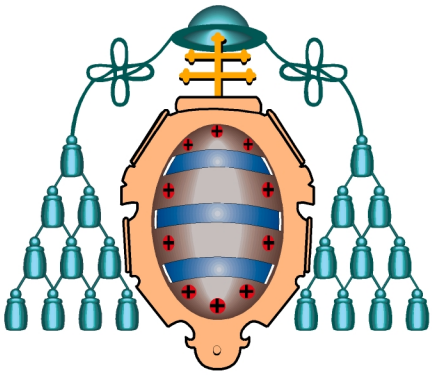

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Programa de Doctorado:

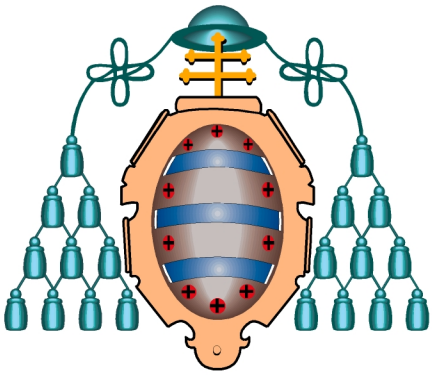
"Síntesis y Reactividad Química"

One-Pot Catalysis and Multicomponent Cascade Reactions for the Stereoselective Synthesis of Pyrrolidine and Indole Derivatives

Alicia Galván Álvarez

Tesis Doctoral

2015



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Memoria para optar al grado de Doctor en Química
con Mención de Doctor Internacional

Dissertation for the Degree of Doctor of Philosophy
in Chemistry with International Doctor Mention

RESUMEN DEL CONTENIDO DE TESIS DOCTORAL

1.- Título de la Tesis	
Español/Otro Idioma: Catalisis One-Pot y Reacciones Multicomponente en Cascada para la Síntesis Estereoselectiva de Derivados de Pirrolidina y de Indol	Inglés: One-Pot Catalysis and Multicomponent Cascade Reactions for the Stereoselective Synthesis of Pyrrolidine and Indole Derivatives

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RESUMEN (en español)

En esta memoria se encuentran recogidos los resultados referidos al estudio de nuevos procesos multicatalíticos en cascada “one-pot “ y procesos multicomponente para la síntesis de compuestos heterocíclicos. Esta memoria se ha dividido en dos capítulos.

En el Capítulo 1, se describen nuevas síntesis de derivados de pirrolidina a través de procesos “one-pot” en cascada promovidos por un sistema catalítico binario que consiste en un catalizador de platino y un ácido de Brønsted. Este capítulo se ha dividido en dos partes. En la Parte A, se muestra el desarrollo de nuevas reacciones en cascada de *N*-Boc alquinaminas con alquenos y alquinos que permite sintetizar derivados de pirrolooxazinona. Una extensión de estos procesos se describe en la Parte B. De este modo se muestra una nueva reacción en cascada que implica una doble cicloisomerización de *N*-Boc alquinaminas y alquinoles dando lugar a dos alquenos electrónicamente ricos, seguida de una heterodimerización formal de los dos alquenos generados *in situ*.

En el Capítulo 2, se muestran nuevas reacciones multicomponentes “one-pot” de indolcarbaldehídos, anilinas y alquenos electrónicamente ricos catalizadas por ácidos de Brønsted. En este caso el capítulo se ha dividido en tres partes. En la Parte A, se describe una vía de reacción alternativa a la conocida reacción de Povarov. En particular, se ha desarrolado una nueva carbociclación formal [3+2] de iminas derivadas de indol-2-carbaldehído y alquenos electrónicamente ricos para dar lugar a cyclopenta[*b*]indoles. En la Parte B se muestra una heterociclación formal [3+2] enantioselectiva de iminas derivadas del indol-2-carbaldehído sin sustituyentes en el átomo de nitrógeno y enol éteres promovida por una disulfonimida quiral que permite sintetizar pirrolo[1,2-*a*]indoles. Finalmente, en la Parte C se muestra el desarrollo de una heterociclación formal [4+2] sin precedentes entre iminas derivadas del indol-7-carbaldehído y alquenos electrónicamente ricos para dar lugar a pirrolo[3,2,1-*ij*]quinolinas a través de un proceso multicomponente.

RESUMEN (en Inglés)

The investigation developed and summarised in this dissertation was focused on the development of new one-pot multicatalytic cascade reactions and multicomponent processes towards the synthesis of interesting heterocyclic compounds. This dissertation has been organised in two chapters.

In Chapter 1, new syntheses of pyrrolidine derivatives through novel one-pot orthogonal-relay cascade processes promoted by a binary catalytic system consisting in a platinum-based metallic complex and a Brønsted acid are described. This chapter is also divided in two parts. In Part A, the development of new cascade reactions of *N*-Boc protected alkynamine derivatives with alkenes and alkynes for the synthesis of pyrrolooxazinone derivatives is described. An extention of the previous reactions is described in Part B. Thus, the development of a new cascade reaction involving a double cycloisomerisation reaction of *N*-Boc alkynamine and alkynol derivatives followed by a formal heterodimerisation of the two *in situ* generated electron-rich alkenes is shown.

In Chapter 2, novel one-pot Brønsted acid catalysed multicomponent reactions of indolecarbaldehydes, anilines and electron-rich alkenes are described. In this case, the chapter has been divided into three parts. In Part A, an alternative reaction pathway to the well-known Povarov reaction is described. Particularly, a new formal [3+2]-carbocyclisation reaction of the *in situ* formed indole-2-carbaldehyde imine derivatives and the electron-rich alkenes to give interesting cyclopenta[*b*]indoles has been developed. In Part B, an enantioselective formal [3+2]-heterocyclisation reaction of *N*-unsubstituted indole-2-carbaldehyde imines and enol ethers promoted by a chiral disulfonimide to give pyrrolo[1,2-*a*]indole derivatives is shown. Finally, the synthesis of pyrrolo[3,2,1-*ij*]quinoline derivatives through a multicomponent coupling reaction of indole-7-carbaldehydes, anilines and electron-rich alkenes is described in Part C. The new process supposes an unprecedented formal [4+2]-heterocyclisation of *in situ* formed indole-7-carbaldehyde imines and electron-rich alkenes.

SR. DIRECTOR DE DEPARTAMENTO DE QUÍMICA ORGÁNICA E INORGÁNICA
SR. PRESIDENTE DE LA COMISIÓN ACADÉMICA DEL PROGRAMA DE DOCTORADO EN SÍNTESIS Y REACTIVIDAD QUÍMICA

"Complex synthesis remains a challenging occupation requiring an exceptional level of experimental skill, extensive knowledge of both mechanistic and molecular reactivity, and a bold, inventive, and creative spirit. It is the combination of these qualities that transforms the synthesis process from one of simple logistics to an art form."

Steven V. Ley

Abbreviations and Acronyms

A

Å	ångström
Ac	acetyl
app	apparent
Aq.	aqueous
Ar	aryl group
atm	atmospheres

B

BINAM	2,2'-bis(diphenylphosphinoamino)-1,1'-binaphthyl
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br	broad
Bz	benzoyl
Bu	butyl
n-Bu	1-butyl
t-Bu	*tert*-butyl

C

^{o}C	degree Celsius
cat	catalyst
Cbz	benzyloxycarbonyl
COD	1,5-cyclooactadiene
COSY	Correlation Spectroscopy
Cp	cyclopentadiene
CSA	camphorsulfonic acid
Cy	cyclohexyl
Cyclopent	cyclopentyl

D

1,2-DCE	1,2-dichloroethane
d.r.	diastereomeric ratio

dba	dibenzylideneacetone
DCD	Dewar-Chatt-Duncanson
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DET	diethyl tartatre
DFT	density functional theory
DHF	2,3-dihydrofuran
diast	diastereoisomer
dig	*di*gonal
DiPAMP	ethane-1,2-diylbis[(2-methoxyphenyl)phenylphosphane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DNBSA	2,4-dinitrobenzenesulfonic acid
DOS	Diversity Oriented Synthesis
DPP	diphenylphosphate
dppf	1,1'-Bis(diphenylphosphino)ferrocene
DPPM	1,1'-Bis(diphenylphosphino)methane

E

E	electrophile
e.r.	enantiomeric ratio
EDG	electro-donating group
Ent	enantiomer
equiv	equivalents
Et	ethyl
EWG	electron-withdrawing group

G

g	grams

H

h	hours
HB	Brønsted acid
HMBC	Heteronuclear Multiple-Bond Correlation Spectroscopy
HMPA	Hexamethylphosphoramide
HOMO	Highest Occupied Molecular Orbital

HPLC	High-Performance Liquid Chromatography
HRMS	High-Resolution Mass Spectrometry
HSQC	Heteronuclear Single-Quantum Correlation Spectroscopy
Hz	hertz

I

IRC	Interest Rates Curves

J

JohnPhos	2-(Di-*tert*-butylphosphino)biphenyl

K

K	degrees Kelvin

L

L-DOPA	(*S*)-2-amino-3-(3,4-dihydroxyphenyl)propanoic acid
L	litre
LA	Lewis acid
LUMO	Lowest Unoccupied Molecular Orbital

M

M	metal
mp	melting point
MCRs	Multicomponent reactions
Me	methyl
mg	milligram
min	minute
mL	millilitre
mmol	millimole
mol	mole
MS	molecular sieves

N

NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser effect spectroscopy
Nu	nucleophile

O

ORTEP	Oak Ridge Thermal Ellipsoid Plot

P

Ph	phenyl
ppm	parts per million
Pr	propyl
*i*Pr	*iso*-propyl
PTSA	*para*-toluenesulfonic acid

R

RCM	Ring Closing Metathesis
R_f	retention factor
rota	rotamer
rt	room temperature

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Experimental Part

General Introduction

I.1 What is Catalysis and Why is it Important?

Catalysis (from the Greek "κατάλυσις", "dissolution") can be defined as the increase in the rate of a chemical reaction due to the participation of an additional substance, called catalyst, without modifying the overall standard Gibbs energy change of the process.[1] The catalyst is not consumed in the process; therefore, each catalyst molecule can participate in many consecutive cycles. This means that only a small amount of catalyst relative to substrate is required. Its relation (substrate/catalyst ratio) indicates the efficiency of the catalyst, measured as turnover number (TON) or turnover frequency (TOF).[2]

One of the most important features of catalytic processes is the waste minimisation. Thus, the necessity to live in a sustainable society (one that "meets the needs of the current generation without sacrificing the ability to meet the needs of future generations") makes catalysis an important tool. In fact, as far as chemistry is concerned, catalysis is the key to sustainability.[3] Hence, we can say that the main advantages of catalysis are that desired products are obtained faster, using fewer resources and generating less waste. Additionally, the use of a catalyst gives the chemist a good opportunity to develop selective routes to the desired compounds. In this sense, high chemo-, regio-, diastereo- and enantioselectivities are usually achieved by the use of appropriate catalysts.

I.2 Different Types of Catalysis

There are many different types of catalysts and catalysis, ranging from the proton, through Lewis acids, organometallic complexes, simple organic molecules, organic and inorganic polymers, all the way to enzymes. Catalysis is usually divided into three categories: homogeneous catalysis, heterogeneous catalysis and biocatalysis.

- ***Homogeneous catalysis:*** The reactants, products and catalyst are in the same phase. This could be either solid, liquid or gas phase, but most commonly, the homogeneous catalyst is codisolved in a solvent with the reactants.
- ***Heterogeneous catalysis:*** The catalyst and the substrates are in different phases. However, chemists usually refer to a system where the catalyst is a solid and the reactants are more often gases or liquids. Heterogeneous catalysts are typically supported over solids with high surface area. In this case

[1] K. J. Laidler, *Pure Appl. Chem*., **1996**, *68*, 149.

[2] G. Rothenberg, *Catalysis: Concepts and Green Applications*, Wiley-VCH, **2008**, Chapter 1.

[3] R. A. Sheldon, *Pure Appl. Chem.*, **2000**, *72*, 1233.

the catalyst is dispersed on a second material that enhances the effectiveness or minimises the cost.

- ***Biocatalysis:*** This is a special case, somewhere between homogeneous and heterogeneous catalysis, but it is often seen as a separate group. Usually the biocatalyst is an enzyme, which is a complex protein that catalyses the process in living cells.

I.3 A Brief History of Catalysis

"Wer die Vergangenheit nicht kennt, versteht auch nicht die Gegenwart."
(Who does not know the past, cannot understand the present.)
J. W. von Goethe

Catalysis origins date back to the dawn of civilisation at a date lost in time when mankind started to produce alcohol by fermentation.[4] Historical studies about catalysis are usually divided into periods marked by specific achievements of intellectual progress. Therefore, for a better understanding of the history of catalysis this subject has been divided into six distinct stages.[5]

I.3.1 First Period (Ø-1836)

This initial period consisted mainly on isolated observations that were sporadically documented without any effort to explain those phenomena. The first known reference to the use of an inorganic catalyst is from 1552, when Valerius Cordus, a German physician and botanist, used sulphuric acid to catalyse the conversion of ethanol to diethyl ether; which he called "sweet oil of vitriol".[6] In 1597, Andreas Libavius wrote "Alchemia", known as the first textbook of chemistry containing the first historical reference to catalysis as a chemical phenomenon. Some other scientists that also deserve to be mentioned from this period are Fulhame, Kirchhoff, Sir Humphry Davy, Erman, Thenard, Turner, Faraday and Mitscherlich.

This first stage of catalysis clearly ended, and a new period started, when the Swedish chemist Jöns Jacob Berzelius wrote a report, submitted in the year 1835 and published in 1836, where he introduced the concept of catalysis. His conclusions were based upon experimental work and discussions with contemporary scientists in Europe. Thus, he wrote:

[4] R. van Santen, *Catalysis: From Principles to Applications*, First Edition (Ed.: M. Beller, A. Renken and R. van Santen), Wiley-VCH, **2012**, Chapter 1.

[5] B. Lindström, L. J. Petterson, *Cattech,* **2003**, *7*, 130.

[6] B. I. Popov, N. G. Skomorokhova, *Reaction Kinetics and Catalysis Letters*, **1981**, *18*, 107.

"It is, then, proved that several simple or compound bodies, soluble and insoluble, have the property of exercising on other bodies an action very different from chemical affinity. By means of this action they produce, in these bodies, decompositions of their elements and different recombinations of these same elements to which they remain indifferent."[7]

Berzelius proposed then the existence of a new force, which he called the "catalytic force", and he called "catalysis" the decomposition of bodies by this force. It is assumed that this is probably the first recognition of catalysis as a wide-ranging natural phenomenon.

I.3.2 Second Period (1836-1888)

The second period was characterised by the systematic research and the discovery of new catalytic processes. Some of them were introduced in industry, and therefore significant financial gains were achieved. Important conceptual contributions also appeared during this second stage. In 1850, Wilhelmy proved that the rates of chemical reactions were dependent on the concentration of the reactants, which led to the recognition of reversibility of chemical reactions.[8] Le Chatelier originally presented the dependency of a chemical reaction on the temperature and pressure in 1884. In 1877, Lemoine showed that by applying a catalyst to a chemical reaction the rate at which equilibrium was reached could be increased.[9] Moreover, Wilhelm Ostwald claimed that a catalyst cannot initiate a chemical change, it can only accelerate or retard the process. He was the main responsible of the new perception of catalysis during this period as he wrote once that "there is probably no chemical reaction which can not be influenced catalytically".[10]

I.3.3 Third Period (1888-1918)

This third stage began during the end of the nineteenth century and it was characterised by the growth of academic knowledge translated into industrial applications. Thus, hundreds of catalytic processes were developed by that time, and the economic potential of some of them was highly recognised.

Moreover, as there was a growth in the demand for bulk chemicals, the minimisation of by-products by catalysis had several economic advantages. The

[7] J. J. Berzelius, *Annls. Chim. Phys.*, **1836**, *61*, 146.

[8] L. F. Wilhelmy, *Pogg. Ann.*, **1850**, *81*, 413.

[9] G. Lemoine, *Ann. Chim. Phys.*, **1877**, *12*, 145.

[10] G. M. Schwab, *Catalysis Science and Technology* (Ed: J. R. Anderson, M. Boudart), Springer, New York, **1981**, *Vol. 2*.

industrial production based on catalytic chemical reactions was especially high during World War I.

The development of an industrial procedure to synthesise ammonia at large scale was without any doubt the most significant achievement of this period and it is also usually described as "the most important technological invention of the 20th Century". Thus, it was in the year 1909 when Frizt Haber found a way of synthesising ammonia for fertiliser from nitrogen and hydrogen. Then, working with Carl Bosch, an engineer from the chemical company BASF, the Haber-Bosch process was developed. In this way, it was possible the production of huge amounts of fertiliser that increased crop yields banishing the fear of famine in large parts of the world.

Although the progress of catalysis during the war was slow some developments worth their mention. For example, the theories presented in 1915 by Irving Langmuir (Nobel Prize in Chemistry 1932) on the adsorption isotherm based upon early work done by Haber.[11]

Unfortunately, the third period of catalysis ended in a shame, as most of the catalytic developments were for the production of weapons of destruction.

I.3.4 Fourth Period (1918-1945)

The fourth period started with the decrease in the demand of explosives at the end of World War I. The most important catalytic developments during this period were developed in the context of the petroleum industry. In 1927, the knowledge of catalysis took a huge step when Hinshelwood presented his kinetic theory based on Langmuir earlier findings. These principles are still being applied nowadays in catalytic models.

In 1936, Eugène Houdry developed the catalytic cracking of petroleum. This is actually one of the most important chemical processes ever developed. Interestingly, subsequent improvements to this initial discovery enabled the Allied forces to provide fuel to its fighters during Wold War II.

I.3.5 Fifth Period (1945-1970)

This stage of catalysis can be characterised by the petrochemical industry and the development of catalytic processes for the manufacturing of synthetic polymers. At the beginning of this period, the world moved away from an economy based on the war. In Europe, there was an explosion in the automobile market and therefore, it caused an increase in the demand for petroleum.

[11] I. Langmuir, *J. Am. Chem. Soc.*, **1915**, *37*, 1139.

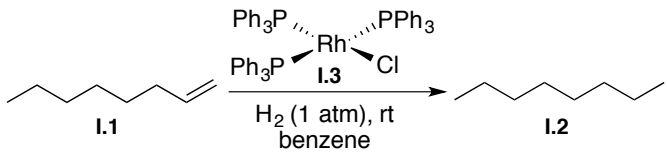
In the year 1949, the first scientific meeting in the field of catalysis took place at the University of Pennsylvania and one year later, in 1950 the Faraday Society organised the first conference on heterogeneous catalysis.

Another important year in the context of catalysis was 1962 as this year saw the birth of the *Journal of Catalysis*, the first journal devoted only to catalysis.

A particularly important reaction developed during this period that deserves a special mention is the catalytic hydrogenation of alkenes.

I.3.5.1 Catalytic Hydrogenation

Until this moment the hydrogenation process was clearly based on the use of heterogeneous catalysts. It was in 1966 when Geoffrey Wilkinson developed a homogeneous catalyst for the hydrogenation of alkenes.[12] Thus, it can be said that this achievement marked the beginning of a new field in the context of catalysis: homogeneous catalysis. The catalyst used in that initial reaction (known as Wilkinson´s catalyst), $RhCl(PPh_3)_3$ **I.3**, consisted on a single metallic centre stabilised by triarylphosphines. It was the first homogenous catalyst with the ability to selectively hydrogenate unhindered terminal alkenes (e.g. **I.1**) to alkanes (e.g. **I.2**) at a rate similar to that of heterogeneous catalysts, without having to resort to high pressures or temperatures in the process (**Scheme I.1**). This discovery gave Wilkinson the Nobel Prize in Chemistry in 1973.



Scheme I.1 Hydrogenation of olefins with Wilkinson's catalyst.

I.3.6 Sixth Period (1970-20??)

The sixth and current period of catalysis began when the world started to be aware of the impacts that industry had on the environment. This gave birth to the discipline of environmental catalysis, which was the first step towards the modern chemical industry. This period is characterised by the continuous invention of new catalytic processes and has not yet clearly passed into a seventh stage. Nowadays, catalysis is applied to almost every process, including the production of fine chemicals for pharmacy and the production of bulky chemicals and exhaust gas.

[12] a) J. A. Osborn, F. H. Jardine, J. F. Young, G. Wilkinson, *J. Chem. Soc. A*, **1966**, 1711. b) S. Montelatici, A. van der Ent, J. A. Osborn, G.Wilkinson, *J. Chem. Soc. A*, **1968**, 1054. c) G. Wilkinson, *Platinum Metals Rev.*, **1968**, *12*, 50.

This stage of catalysis has been mostly dominated by the use of transition metal complexes in organic transformations.[13] However, in the last decades, the use of small organic molecules as catalysts in a metal-free environment (organocatalysis) has also experienced an impressive growth (see **Section 1.4.2**).

As an illustration of the importance of transition metal-based homogeneous catalysis, it should be mentioned that in the last fifteen years, three Nobel Prizes in Chemistry (2001, 2005 and 2010) have been awarded in this area. These three outstanding achievements are briefly commented in the next sections.

I.3.6.1 Asymmetric Catalysis

In 2001, the Nobel Prize in Chemistry concerned the development of chiral transition metal catalysts for stereoselective hydrogenations and oxidations, two important classes of synthetic reactions. In this way, three chemists, William S. Knowles, Ryoji Noyori and K. Barry Sharpless shared the concession.

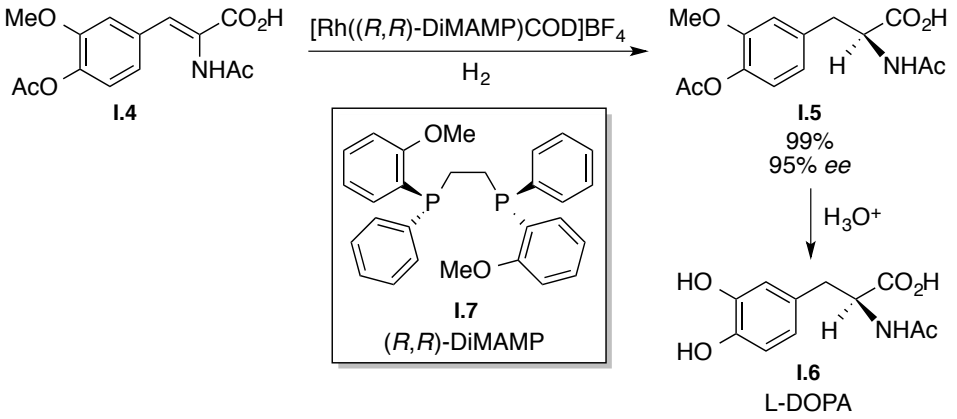
Finding new methods for asymmetric synthesis has become a key activity for organic chemists and thus, numerous catalytic asymmetric syntheses that convert prochiral substrates into chiral products with high enantioselectivity have appeared in the last years. These developments have had an enormous impact on academic and industrial organic syntheses, as one single chiral catalyst molecule can direct the stereoselection of millions of chiral product molecules. Hence, these reactions are highly productive and economical, and at this point, they make the waste resulting from racemate resolution and chiral-auxiliary based methods obsolete.

At the beginning of the sixties, the feasibility of the catalytic asymmetric hydrogenation process was unknown. In 1968, Knowles at Monsanto Company, St. Louis (Missouri USA), published this process using a chiral transition metal based catalyst, in particular a rhodium catalyst.[14] Knowles´approach was basically to replace triphenylphosphine in Wilkinson´s catalyst (**Scheme I.1**) with a chiral phosphine and hydrogenate a prochiral olefin. For example, enamide **I.4** was asymmetrically hydrogenated using a cationic rhodium complex containing (*R,R*)-DiPAMP **I.7**, a chelating diphosphine with two chiral phosphorus atoms. This protocol was applied to the synthesis of the rare amino acid L-DOPA **I.6**, used in the treatment of Parkinson´s disease (**Scheme I.2**). The Monsanto Process was the first commercialised catalytic asymmetric synthesis with a chiral transition metal

[13] J. Tsuji, *Transition Metal Reagents and Catalysts: Innovations in Organic Synthesis*, John Wiley & Sons, Chichester, **2000**.

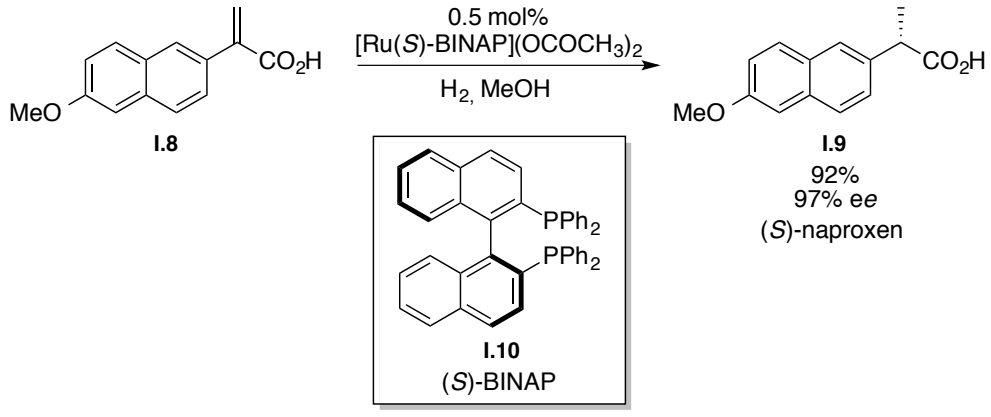
[14] W. S. Knowles, M. J. Sabacky, *Chem. Commun.* , **1968**, 1445.

complex and it has been in operation since 1974.[15]



Scheme I.2 The Monsanto synthesis of L-DOPA **I.6** using Knowles' asymmetric hydrogenation.

In 1980, Noyori along with Takaya, discovered an atropisomeric chiral diphosphine, BINAP **I.10**. Rhodium(I) complexes containing this chiral diphosphine ligand have been extremely effective in different asymmetric processes.[16] Additionally, Noyori´s discovery of the BINAP-Ru(II) complex catalysts was a huge advance in enantioselective organic synthesis as the range of application of these catalyst is very extent.[17] For instance, they have been used this complex in the synthesis of the anti-inflamatory agent (*S*)-naproxen **I.9** with high yield and enantiomeric excess (**Scheme I.3**) and in the industrial synthesis of the antibacterial levofloxacin.



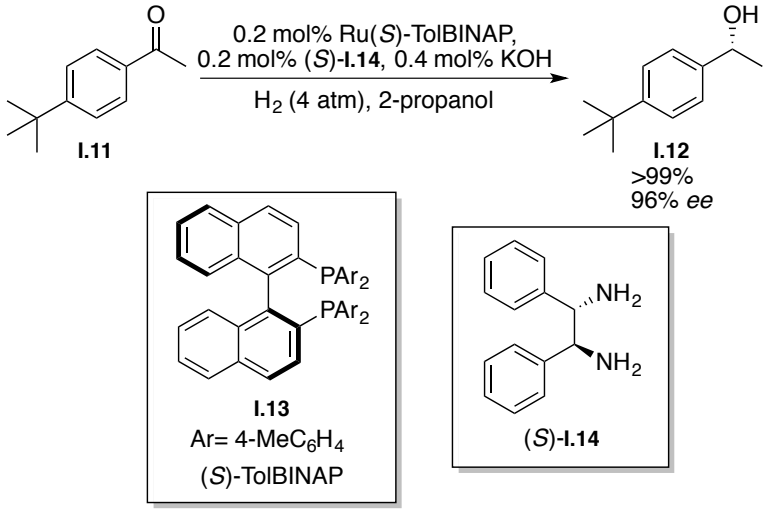
Scheme I.3 Synthesis of (*S*)-Naproxen **I.9** using Noyori's catalyst.

[15] W.S. Knowles, *Acc. Chem. Res.*, **1983**, *16*, 106.

[16] A. Miyashita, A. Yasuda, H. Takaya, K. Toriumi, T. Ito, T. Souchi, R. Noyori, *J. Am. Chem. Soc.*, **1980**, *102*, 7932.

[17] T. Ohta, H. Takaya, R. Noyori, *Inorg. Chem.*, **1988**, *27*, 566.

Another remarkable contribution was the enhancement in the reactivity of the Ru(II) catalyst by the addition of ethylene diamine and KOH in 2-propanol to achieve a chemoselective hydrogenation of a carbonyl moiety in a substrate containing carbon-carbon multiple bonds. The new ruthenium-based catalytic system was also expanded to its asymmetric version by the use of a chiral diamine (*S*)-**I.14** as ligand (**Scheme I.4**).[18]



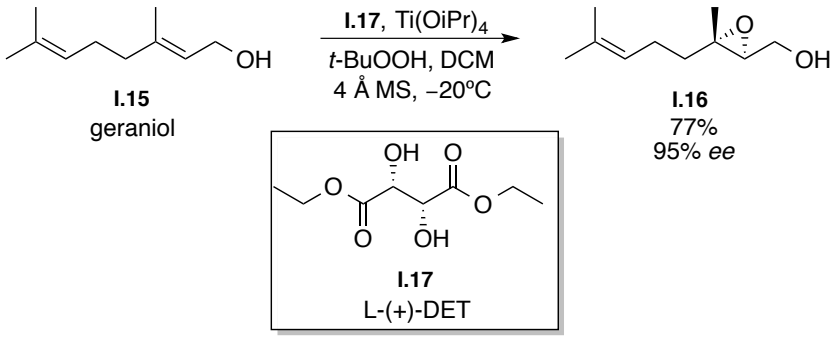
Scheme I.4 Enantioselective reduction of carbonyls developed by Noyori and co-workers.

In parallel, K. Barry Sharpless developed chiral catalytic processes for very important oxidation reactions. One of the most typical examples is the epoxidation reaction discovered in 1980 along with T. Katsuki. The use of titanium(IV) tetraisopropoxide, *tert*-butyl hydroperoxide and an enantiomerically pure dialkyl tartrate **I.17** affords the epoxidation of the allylic alcohol **I.15** with excellent stereoselectivity (**Scheme I.5**). Moreover the stereoselectivity can easily be predicted depending on the tartrate derivative used as ligand. This was undoubted the first practical method for asymmetric epoxydation.[19] On the other hand, he also reported the first non-enzymatic catalytic asymmetric dihydroxylation of alkenes.[20]

[18] T. Ohkuma, H. Ooka, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.*, **1995**, *117*, 2675.

[19] T. Katsuki, K.B. Sharpless, *J. Am. Chem. Soc.*, **1980**, *102*, 5974.

[20] E. N. Jacobsen, I. Marko, W.S. Mungall, G. Schröder, K.B. Sharpless, *J. Am. Chem. Soc.*, **1988**, *110*, 1968.



Scheme I.5 Enantio- and regioselective Sharpless epoxidation.

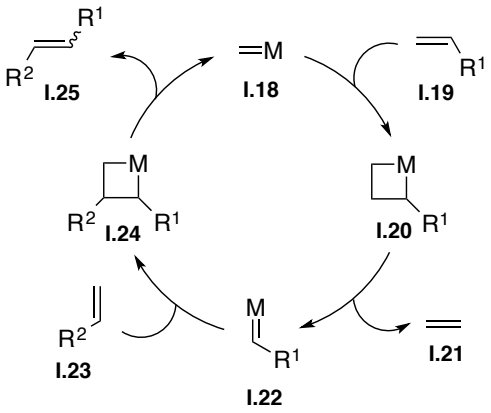
I.3.6.2 Metathesis

The Nobel Prize in Chemistry in 2005 was shared by three scientists: Frenchman Yves Chauvin and Americans Robert H. Grubbs and Richard R. Schrock as they have made metathesis one of the most important reactions in organic chemistry.

The etymology of the word metathesis comes from the Greek and means transposition, basically fragments changing place. This name was given for the first time to a chemical reaction developed by Calderon in 1967.[21] Although the first catalytic metathesis reaction was found in the 1950´s, at the end of the 1960´s it was still very mysterious. Some mechanistic ideas had appeared, but they did not match the experimental results properly. It was in 1971 when Yves Chauvin proposed the metathesis mechanism that is now widely accepted (**Scheme I.6**). This mechanism involves a [2+2]-cycloaddition of an alkene **I.19** to a transition metal-alkylidene **I.18** to form a metalacyclobutane intermediate **I.20**. This intermediate can now cyclorevert to give either the original alkene **1.19** or a new alkene **I.21** and metal-alkylidene **I.22**. After the formation of a new metalacyclobutane **I.24**, this species is broken giving the metathesis product **I.25** and the reformation of the metal-alkylidene **I.18** that can undergo another catalytic cycle.[22] The relevance of this mechanistic proposal was not only important for metathesis, as Chauvin introduced several new ideas essential for overall organometallic catalysis.

[21] N. Calderon, H.-Y. Chen, K. W. Scott, *Tetrahedron Lett.*, **1967**, *34*, 3327.

[22] Y. Chauvin, J.-L. Hérisson, *Makromol. Chem.*, **1971**, *141*, 161.



Scheme I.6 Metathesis mechanism proposed by Chauvin.

In 1974, Richard R. Schrock isolated the first metal-alkylidene complex $[Ta(CH_2CCH_3)_3(=CHCCH_3)]$.[23] Schrock was a PhD student of John Osborn, who himself had been a PhD student of Geoffrey Wilkinson. All chemists know how influential scientific filiations are for the determination of one's scientific area and ideas. Indeed, the influence of Wilkinson on his scientific grandson Schrock turned out to be noteworthy. Schrock brought to the chemical community the first stable metal-methylene, -alkylidene and -alkylidyne complexes, then the undoubted evidence of the validity of the Chauvin´s mechanism, and finally the first entire family of unimolecular very efficient catalysts for alkene and alkyne metathesis. Schrock alkylidenes for olefin metathesis of the type **I.26** (**Figure I.1**) started to be commercially available in 1990. He also developed the first examples of enantioselective metathesis catalysis.

Robert H. Grubbs had been interested for a long time in the metathesis reaction as well. In 1992, he reported the first molecularly well-defined air stable ruthenium-carbene complex $[RuCl_2(PR_3)(=CH–CH=CPh_2)]$ being R= Ph or Cy.[24] This initial ruthenium catalyst was followed in 1995 by what is nowadays known as the first generation Grubbs' catalyst **I.27** (**Figure I.1**). Shortly before the discovery of the second generation Grubbs' catalyst **I.28**, a very similar catalyst based on an unsaturated *N*-heterocyclic carbene (1,3-bis(2,4,6-trimethylphenyl)imidazole) was reported independently by Nolan[25] and Grubbs[26] in March 1999, and by Fürstner[27] in June of the same year. Thereafter, in August 1999, Grubbs reported the

[23] R. R. Schrock, *J. Am. Chem. Soc.*, **1974**, *96*, 6796.

[24] S. T. Nguyen, L. K. Johson, R. H. Grubbs, *J. Am. Chem. Soc.*, **1992**, *114*, 3974.

[25] J. Huang, E. D. Stevens, S. P. Nolan, J. L. Petersen, *J. Am. Chem. Soc.*, **1999**, *121*, 2674.

[26] M. Scholl, T. M. Trnka, J. P. Morgan, R. H. Grubbs, *Tetrahedron Lett.*, **1999**, *40*, 2247.

[27] L. Ackermann, A. Fürstner, T. Weskamp, F. J. Kohl, W. A. Herrmann, *Tetrahedron Lett.*, **1999**, *40*, 4787.

previously mentioned second generation catalyst **I.28**, based on a saturated *N*-heterocyclic carbene (1,3-bis(2,4,6-trimethylphenyl)dihydroimidazole). This new generation showed higher activity in addition to being stable toward moisture and air.

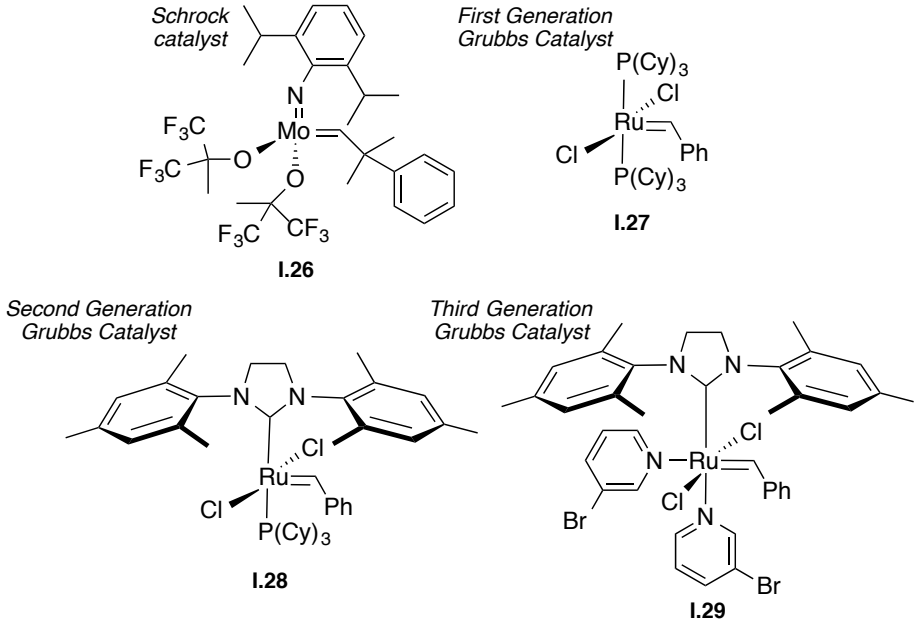


Figure I.1 Selected examples of Schrock and Grubbs catalysts.

Considerable benefits resulted from the discovery of Schrock and Grubbs' unimolecular catalysts such as tolerance of functional groups for organic synthesis, freedom from side reactions, stereoselectivity, control of polymer molecular weight and rationalisation for synthetic strategies.[28] Moreover, since the turn of the century, the use of metathesis has become pervasive and each of its basic modes of application has been cleverly exploited in the natural product area. For instance, the total synthesis of ciguatoxin CTX3C **I.30**, a natural product with marine origin, features the multiple use of Ring Closing Metathesis (RCM) and serves as an instructive example to illustrate the fact that even the highly unfavourable medium ring sizes are well within the reach of this transformation (**Figure I.2**).[29]

[28] D. Astruc, *New J. Chem.*, **2005**, *29*, 42.

[29] a) M. Inoue, K. Miyazaki, H. Uehara, M. Maruyama, M. Hirama, *Proc. Natl. Acad. Sci.*, **2004**, *101*, 12013. b) A. Fürstner, *Chem. Commun.*, **2011**, *47*, 6505.

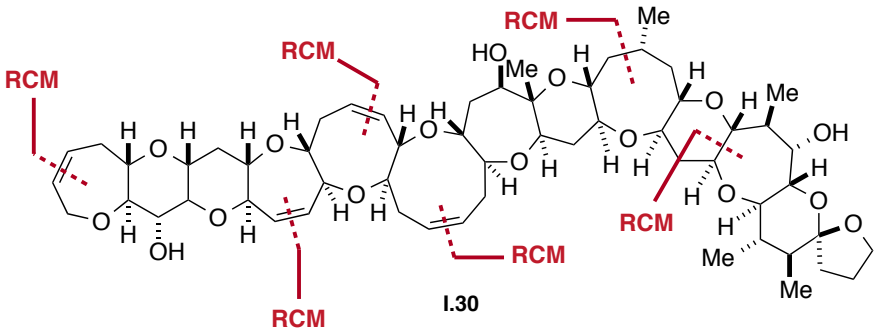


Figure I.2 Ciguatoxin CTX3C natural product: ring closing metathesis disconnections.

I.3.6.3 Cross-Coupling Reactions

The Nobel Prize in Chemistry in 2010 was awarded jointly to Richard F. Heck, Ei-ichi Negishi and Akira Suzuki for their work on palladium-catalysed cross-coupling reactions in organic synthesis. Of the three Nobel Prizes in transition metal-based homogeneous catalysis, perhaps the higher impact in practical terms has been made by these cross-coupling reactions.

The 1970s were full of innovation in the field of transition-metal catalysis with important contributions as well from Beletskaya, Corriu, Kumada, Kochi, Murahashi, Sonogashira, Stille, Trost, Tsuji, and Akio Yamamoto. These contributions along with the defining work by Heck, Negishi, and Suzuki, demonstrated that carbon atoms in all hybridisation states (dominated by sp^2 carbon) undergo carbon-carbon bond forming reactions under palladium catalysis (**Figure I.3**).[30]

[30] C. C. C. J. Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, *Angew. Chem. Int. Ed.*, **2012**, *51*, 5062.

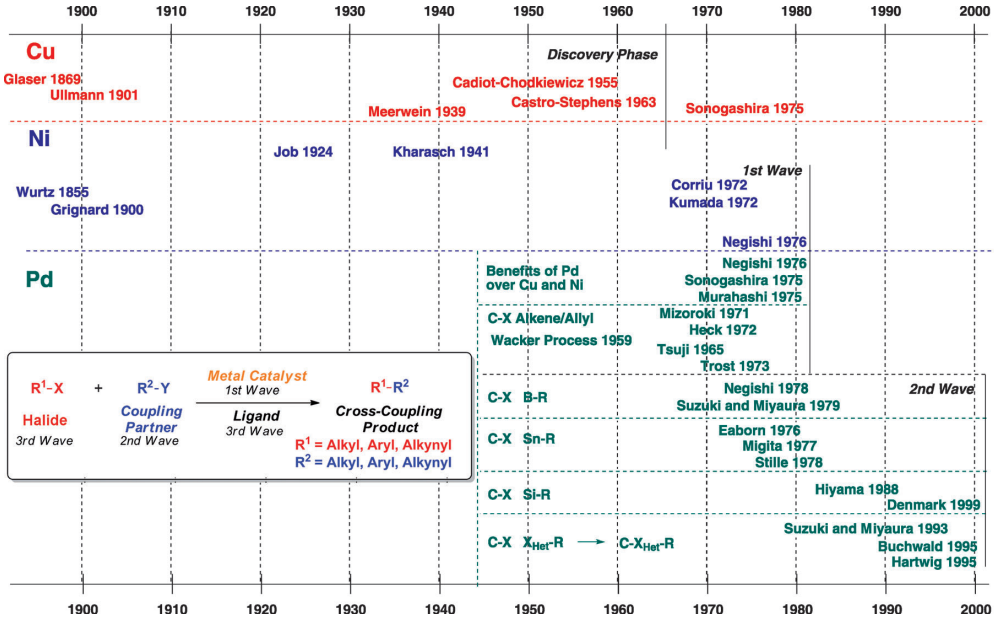


Figure I.3 Timeline of the discovery and development of metal-catalysed cross-coupling reactions.

Although this area began in the early 1970s, there were a very limited number of publications and patents in this field before the 1990s. However, this area has grown rapidly from 1990 onwards, specially since 2000 with the Suzuki cross-coupling proving by far the most popular, followed by the Heck and the Sonogashira coupling reactions (**Figure I.4**).

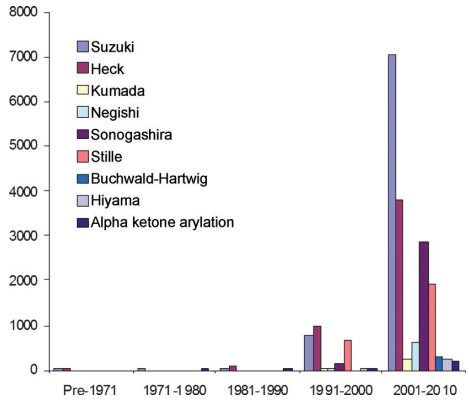
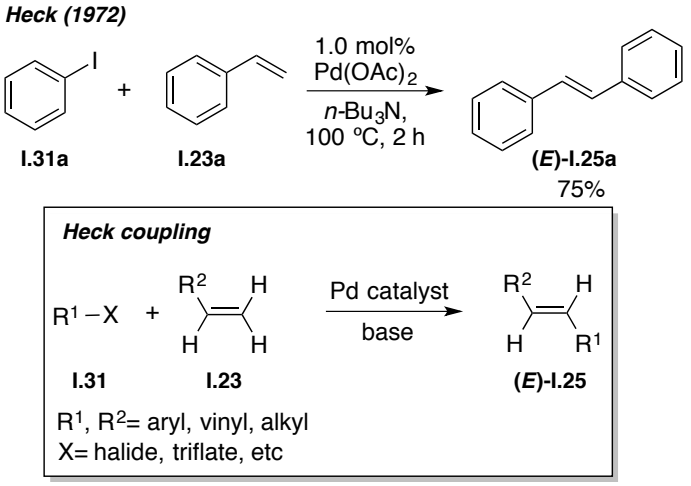


Figure I.4 Growth in the number of publications and patents on named metal-catalysed cross-coupling reactions.

- **Heck coupling**

Between 1968 and 1972, Mizoroki and co-workers[31] and Heck and co-workers[32] independently discovered the use of Pd(II) catalysts for the coupling of aryl, benzyl and styryl halides with olefinic compounds. Nowadays, this process is known as the Heck coupling reaction, as Heck was the first to elucidate the mechanism (**Scheme I.7**). Heck coupling has a broader range of uses if compared to the other coupling reactions as it can afford products of different regio- (linear and branched) and stereoisomerism (*cis* and *trans*). The selectivity of the process is influenced by the electron-withdrawing or electron-donating groups in the olefin **I.23**, the nature of ligands, halides, additives and solvents and also by the nature of the palladium source.

The applications are varied and include the synthesis of hydrocarbons, conducting polymers, light-emitting electrodes, active pharmaceutical ingredients and dyes. Moreover, it can also be used for the synthesis of natural products.



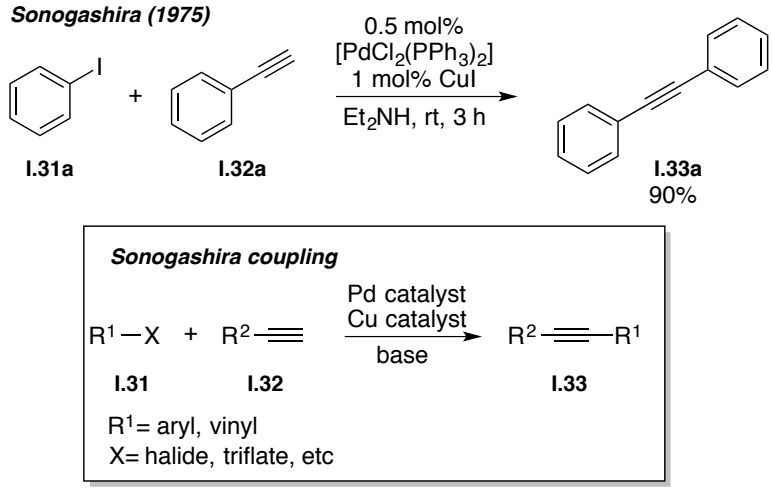
Scheme I.7 Heck coupling.

[31] a) T. Mizoroki, K. Moria, A. Ozaki, *Bull. Chem. Soc. Jpn*., **1971**, *44*, 581. b) K. Mori, T. Mizoroki, A. Ozaki, *Bull. Chem. Soc. Jpn*., **1973**, *46*, 1505.

[32] a) R. F. Heck, *J. Am. Chem. Soc*., **1968**, *90*, 5518. b) R. F. Heck, J. P. Nolley, *J. Org. Chem*., **1972**, *37*, 2320. c) H. A. Dieck, R. F. Heck, *J. Am. Chem. Soc*., **1974**, *96*, 1133.

- **Sonogashira coupling**

Until the middle of 1970s, the field of acetylene coupling was governed by the use of copper salts as catalysts (**Figure I.1**). It was in 1975 when three independent groups, Sonogashira,[33] Cassar[34] and Heck,[35] developed the palladium-catalysed coupling of acetylenes with aryl or vinyl halides concurrently. However, the results reported by Sonogashira employing copper as a co-catalyst made the reaction conditions extremely mild if compared to those developed by Cassar and Heck. Therefore, combined to the high funtional group tolerance of the method have placed the Sonogashira reaction in a premium position as it is widely used not only in the production of simple but very useful compounds but also in the last stages of the synthesis of complex molecules (**Scheme I.8**).[36]



Scheme I.8 Sonogashira coupling.

- **Negishi coupling**

During 1976 and 1977, Negishi[37] on the one hand and Fauvarque and Jutand[38] on the other, published the use of zinc reagents in cross-coupling reactions (**Scheme I.9**).

[33] K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.*, **1975**, *16*, 4467.

[34] L. Cassar, *J. Organomet. Chem.*, **1975**, *93*, 253.

[35] H. A. Dieck, F. R. Heck, *J. Organomet. Chem.*, **1975**, *93*, 259.

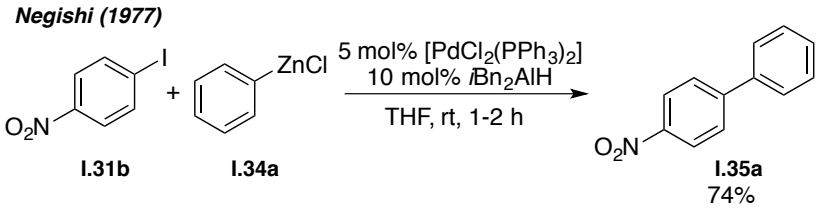
[36] I. Paterson, R. D. M. Davies, R. Marquez, *Angew. Chem. Int. Ed.*, **2001**, *40*, 603.

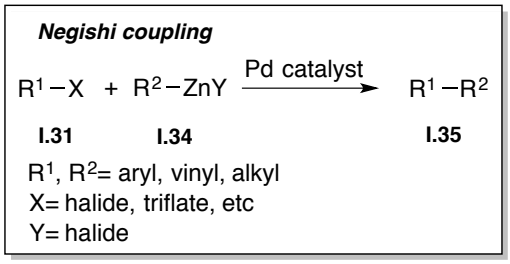
[37] a) E. Negishi, S. Baba, *J. Chem. Soc., Chem. Commun.*, **1976**, 596b. b) E. Negishi, A. O. King, N. Okukado, *J. Org. Chem.*, **1977**, *42*, 1821. c) A. O. King, N. Okukado, E. Negishi, *J. Chem. Soc., Chem. Commun.*, **1977**, 683.

[38] J. F. Fauvarque, A. Jutand, *J. Organomet. Chem.*, **1977**, *132*, C17.

In parallel, Kumada[39] and Corriu[40] independently reported that nickel–phosphine complexes were able to catalyse the coupling of aryl and alkenyl halides with Grignard reagents. In 1979, Kumada also reported the use of $PdCl_2$(dppf) as an effective catalyst for the cross-coupling of secondary alkyl Grignard reagents with organic halides. However, one common limitation to both Ni- and Pd-catalysed Kumada coupling reactions was that coupling partners, containing base sensitive functionalities were not tolerated due to the nature of the organomagnesium reagents.

The discovery that zinc reagents served as coupling partners showed that magnesium and lithium could be replaced with other metals in the transmetallation step. Therefore, Negishi carried out a metal screening in order to identify other possible organometallic reagents as coupling partners, observing that the use of zinc, boron and tin derivatives also provided the desired products. The use of organozinc reagents for palladium-catalysed cross-coupling processes to form a carbon–carbon single bond is nowadays known as the Negishi reaction.[41] Its applications include the synthesis of fine chemicals and additionally it has been used as a crucial step in natural products synthesis.[42]





Scheme I.9 Negishi coupling.

[39] a) K. Tamao, K. Sumitani, Y. Kiso, M. Zembayashi, A. Fujioka, S. Kodama, I. Nakajima, A. Minato, M. Kumada, *Bull. Chem. Soc. Jpn*., **1976**, *49*, 1958. b) K. Tamao, Y. Kiso, K. Sumitani, M. Kumada, *J. Am. Chem. Soc*., **1972**, *94*, 9268. c) K. Tamao, K. Sumitani, M. Kumada, *J. Am. Chem. Soc*., **1972**, 94, 4374.

[40] R. J. P. Corriu, J. P. Masse, *J. Chem. Soc., Chem. Commun*., **1972**, 144a.

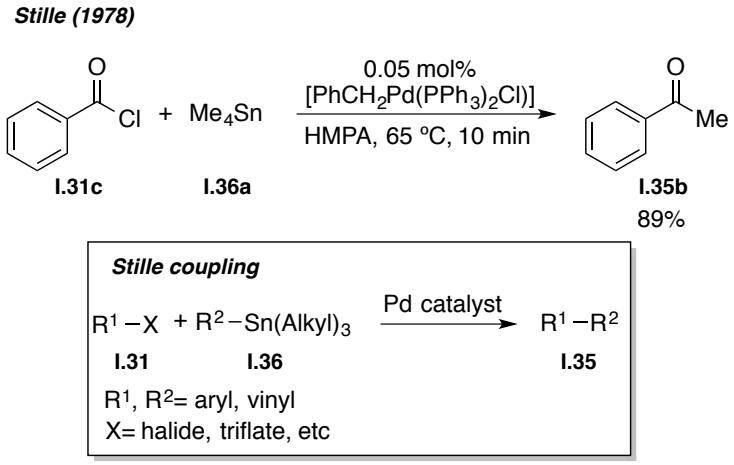
[41] For a review, see: E. Negishi, *Acc. Chem. Res*., **1982**, *15*, 340.

[42] a) S. Hirashima, S. Aoyagi, C. Kibayashi, *J. Am. Chem. Soc*., **1999**, *121*, 9873. b) P. Wipf, S. Lim, *J. Am. Chem. Soc*., **1995**, *117*, 558. c) B. A. Anderson, L. M. Becke, R. N. Booher, M. E. Flaugh, N. K. Harn, T. J. Kress, D. L. Varie, J. P. Wepsiec, *J. Org. Chem*., **1997**, *62*, 8634.

- **Stille Coupling**

Atwell and Bokermen proved in 1973 that the reaction of allyl halides with a disilane under palladium catalysis conditions gave the corresponding organosilane compound. [43] Matsumoto obtained same results with aryl bromides. [44] Nevertheless, these organosilanes did not undergo further coupling reactions, so the next step came with the use of organotin reagents.

After previous reports from Eaborn [45] and Migita [46] in 1976 and 1977 respectively, Stille developed in 1978 the synthesis of ketones by the coupling of aroyl chlorides **I.31** with organostannanes **1.36** under milder conditions (**Scheme I.10**). [47] Later on, he improved the reaction developing a high versatile methodology with broad functional group compatibility and very useful in total synthesis. Even though this methodology has the disadvantage of the toxicity of the organostannanes, it occupies the fourth place in terms of publications and patents in the last decade in the field of named metal-cataysed cross-coupling reactions (see **Figure I.4**).



Scheme I.10 Stille coupling.

[43] W. H. Atwell, G. N. Bokerman, U.S. Patent, 3772347, **1973**; W. H. Atwell, G. N. Bokerman, U.S. Patent, 3746732, **1973**; W. H. Atwell, G. N. Bokerman, U.S. Patent, 7966585, **1973**.

[44] H. Matsumoto, S. Nagashima, K. Yoshihiro, Y. Nagai, *J. Organomet. Chem.*, **1975**, *85*, C1.

[45] D. Azarian, S. S. Dua, C. Eaborn, D. R. M. Walton, *J. Organomet. Chem.*, **1976**, *117*, C55.

[46] For acyl halides, see; a) M. Kosugi, K. Sasazawa, Y. Shimizu, T. Migita, *Chem. Lett.*, **1977**, 301; b) M. Kosugi, Y. Shimizu, T. Migita, *J. Organomet. Chem.*, **1977**, *129*, C36. For aryl halides, see; c) M. Kosugi, Y. Shimizu, T. Migita, *Chem. Lett.,* **1977**, 1423.

[47] D. Milstein, J. K. Stille, *J. Am. Chem. Soc.*, **1978**, *100*, 3636.

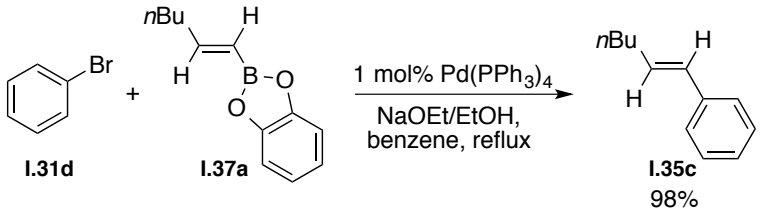
- **Suzuki-Miyaura coupling**

In 1979, a year after the seminal report on the Stille coupling,[47] Suzuki and Miyaura found out boron as the last remaining element out of the three (zinc, boron and tin) identified by Negishi as suitable countercations in cross-coupling reactions, and therefore the palladium-catalysed coupling between 1-alkenylboranes **1.37a** and aryl halides **1.31d** that is now known as the Suzuki coupling was published (**Scheme I.11**).[48]

It should be noted that Heck had already demonstrated in 1975 the transmetallation of a vinyl boronic acid reagent.[49] But perhaps, the greatest achievement of Suzuki was that he identified $PdCl_2(PPh_3)_2$ as an efficient cross-coupling catalyst, thereby proving the relatively easy reduction of Pd(II) to Pd(0) during catalysis.

The Suzuki-Miyaura coupling reaction is widely used in the synthesis of pharmaceutical ingredients such as losartan. Its applications have been extended to the coupling with alkyl groups and aryl chlorides through the work of other groups including Fu.[50] Following work from Buchwald, Hartwig, Nolan, Beller and others has expanded the scope of this reaction.

Suzuki and Miyaura (1979)



Suzuki-Miyaura coupling

$$R^1{-}X \;+\; R^2{-}BZ_2 \xrightarrow[\text{base}]{\text{Pd catalyst}} R^1{-}R^2$$

I.31 **I.37** **I.35**

R^1, R^2= aryl, vinyl, alkyl
X= halide, triflate, etc
Z= OH, OR, etc

Scheme I.11 Suzuki-Miyaura coupling.

[48] N. Miyaura, A. Suzuki, *J. Chem. Soc., Chem. Commun.*, **1979**, 866.

[49] H. A. Dieck, F. R. Heck, *J. Org. Chem.*, **1975**, *40*, 1083.

[50] A. F. Littke, G. C. Fu, *Angew. Chem. Int. Ed.*, **1998**, *37*, 3387.

I.4 Current Hot Topics in Catalysis

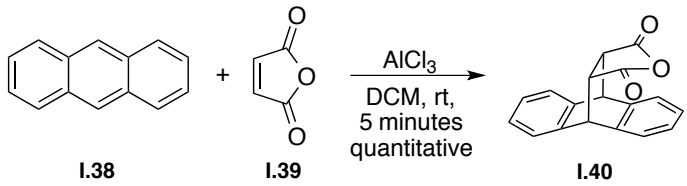
I.4.1 From σ- to π-Electrophilic Lewis Acids: Gold and Platinum-Based π-Acid Catalysis

I.4.1.1 Classic Lewis Acids

The power of organometallic compounds in the context of homogeneous catalysis has been clearly demonstrated with the examples shown in the previous sections that deserved a Nobel Prize in chemistry. However, the range of transformations able to be promoted by transition metal-based complexes is huge.

For example, a field where organometallic reagents have found wide application is Lewis-acid catalysis.[51] In this type of reactions the coordinating metallic atom forms an adduct with lone-pair bearing electronegative atom of the substrate, such as oxygen (both sp^2 or sp^3), nitrogen, sulfur, and halogens. This complexation has partial charge-transfer character and makes the lone-pair donor substrate effectively more electronegative, being therefore activated toward nucleophilic attack, heterolytic bond cleavage, or cycloaddition reactions.[52]

The first major achievement in this area was in 1960, when Yates and Eaton reported the significant acceleration of the Diels-Alder reaction between antracene **1.38** and maleic anhydride by the addition of $AlCl_3$ (**Scheme I.12**).[53]



I.38 **I.39** **I.40**

Scheme I.12 Accelerarion of Diels-Alder reaction by $AlCl_3$.

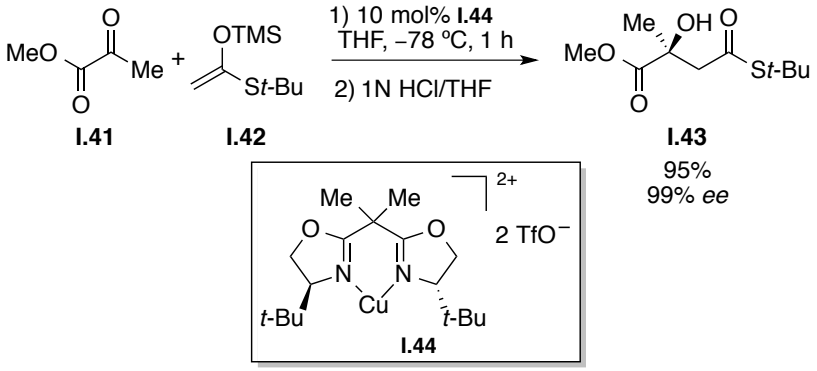
Just as an illustration of the prominence of organometallic reagents as Lewis acids, a highly efficient asymmetric aldol-type reaction is shown in **Scheme I.13**. This reaction reported by Evans and co-workers in 1997 involves the addition of a

[51] For the IUPAC definition of Lewis acid, see: a) H. Yamamoto, *Lewis Acid Reagents: a Practical Approach*, Oxford University Press, New York, **1999**. b) A. D. McNaught, A. Wilkinson, *IUPAC, Compendium of Chemical Terminology*, 2nd ed. (the "Gold Book"), Blackwell Scientific Publications, Oxford, **1997**.

[52] For theories related to Lewis acids, see: a) G. N. Lewis, *Valence and the Structure of Atoms and Molecules,* **1923**. b) R. H. Petrucci, W. S. Harwood, F. G. Herring, *General Chemistry*, Prentice-Hall, **2002**. c) G. L. Miessler, D. A. Tarr, *Inorganic Chemistry*, Prentice-Hall, **1998**.

[53] P. Yates, P. Eaton, *J. Am. Chem. Soc.*, **1960**, *82*, 4436.

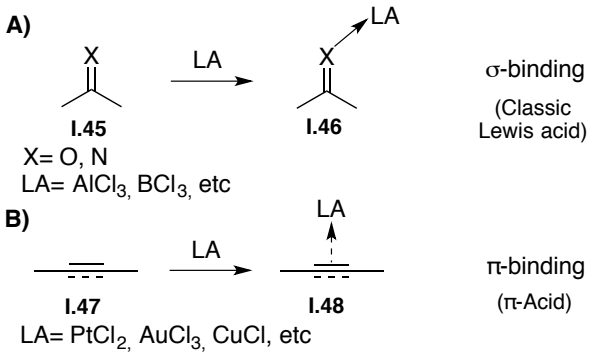
silyl enol ether **1.41** to a pyruvate esters **1.42** using the C_2-symmetric copper(II) complex **1.44** as chiral Lewis acid.[54]



Scheme I.13 Enantioselective aldol-type reaction catalysed by a bisoxazoline-derived copper (II) catalyst.

I.4.1.2 σ-Binding *vs.* π-Binding

As briefly commented in the last section, it is well known that classic Lewis acids, such as BCl_3, $AlCl_3$, etc., form adducts by coordination with electronegative atoms. For example, these compounds make strong σ-complexes **I.46** with carbonyl and imine groups (**Scheme I.14**, **eq. A**). In a similar way, it is also known that some salts of transition metals and transition metal complexes can coordinate carbon-carbon multiple bonds via π-binding (**I.48**, **Scheme I.14**, **eq. B**). Thus, metallic species with the ability to perform this type of coordination are known in the literature as π-acids.[55]



Scheme I.14 Relative ability of Lewis acids for making σ- and π-complexes.

[54] D. A. Evans, M. C. Kozlowski, C. S. Burgey, D. W. C. MacMillan, *J. Am. Chem. Soc.*, **1997**, *119*, 7893.

[55] For an illustrative account on σ- and π-electrophilic Lewis acids, see: Y. Yamamoto, *J. Org. Chem.*, **2007**, *72*, 7817.

This new bonding situation in transition metal complexes with carbon-carbon multiple bonds as π-ligands is usually discussed within the framework of the Dewar-Chatt-Duncanson (DCD) model, which considers the bond as a donor-acceptor interaction between two closed-shell fragments. This model was accepted by the scientific community when it was introduced in the early 1950s[56] and considers that a σ-bond is formed by overlap of the ligand's π-system with an empty metal orbital of appropriate symmetry and then, a π-interaction is generated through back-donation of electron density from a filled metal d orbital into an antibonding π* orbital of the π-system.

I.4.1.3 Activation of π-Systems towards Nucleophiles

In the same sense than a typical Lewis acid activates a carbonylic compound by σ-coordination, π-acids are able to activate carbon-carbon multiple bonds favouring a nucleophilic attack over one of the carbons of the unsaturation.

In principle, π-acids can activate all carbon-carbon π-systems (alkenes, dienes, alkynes, allenes, arenes), but nucleophilic addition to a metal-activated alkyne offers the most diverse range of reactions.

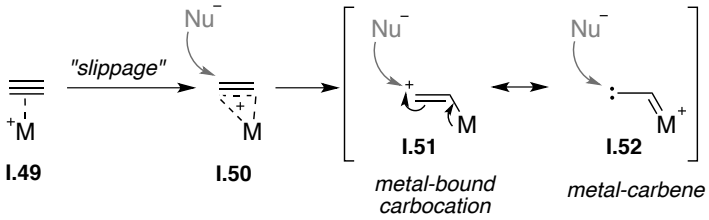
The electrophilic activation of an alkyne towards a nucleophile introduces a new level of complexity. Specifically, the slippage of the metal along the carbon-carbon triple bond axis polarises the substrate in the direction of a vinylic cation, with the regiochemistry of the addition being determined by the substituents (**Scheme I.15**).[57] The electrophility is enhanced upon $\eta^2 \rightarrow \eta^1$ deformation, as the relaxation of the symmetry allows the mixing of orthogonal orbitals and then facilitates charge transfer from the nucleophile to the π-ligand.[58] This intermediate **I.50** can be formulated as a "carbenoid" in its mesomeric forms, as a result of the potential of gold and platinum for instance to back-donate electron density. The bonding mode of these structures has been always ambiguous in the literature, as they can be formulated as metal-bound carbocations **I.51** or metal carbenes **I.52**. Nevertheless, it is unhelpful to make a strong distinction between both forms. As reported by Fürstner and Davies in 2007,[59] they are best viewed as "the two sides

[56] a) M. J. S. Dewar, *Bull. Soc. Chim. Fr.*, **1951**, *18*, C71-C79. b) J. Chatt, L. A. Duncanson, *J. Chem. Soc.*, **1953**, 2939.

[57] a) O. Eisenstein, R. Hoffmann, *J. Am. Chem. Soc.,* **1981**, *103*, 4308. b) The role of slippage has been reconfirmed by Car–Parinello molecular dynamics calculations, see: H. M. Senn, P. E. Blöchl, A. Togni, *J. Am. Chem. Soc.*, **2000**, *122*, 4098.

[58] a) A. D. Cameron, V. H. Smith, Jr., M. C. Baird, *J. Chem. Soc. Dalton Trans.,* **1988**, 1037. b) H. Fujimoto, T. Yamasaki, *J. Am. Chem. Soc.,* **1986**, *108*, 578. c)S.Sakaki,K.Maruta,K. Ohkubo, *Inorg. Chem.,* **1987**, *26*, 2499. d) J.-E. Bäckvall, E. E. Björkman, L. Pettersson, P. Siegbahn, *J. Am. Chem. Soc.*, **1984**, *106*, 4369. d) For pertinent experimental data, see: F. P. Fanizzi, F. P. Intini, L. Maresca, G. Natile, *J. Chem. Soc. Dalton Trans.*, **1992**, 309, and references therein.

of the same coin" for the purposes of interpreting reactivity data and predicting possible product structures.



Scheme I.15 Redistribution of electrons upon nucleophilic attack: mesomerics forms.

I.4.1.4 Platinum, Gold, and other π-Acids

The carbophilic activation of carbon-carbon multiple bonds via π-binding entered a new field of exponential growth shortly before the beginning of this century when it was discovered that some noble metals were more active and selective catalysts than what their "noble character" might suggest. In this context, platinum took the lead in the field, closely followed by gold, which soon became particularly popular.[59]

These π-acid-catalysed reactions have many advantageous qualities, as they are operationally safe, simple, practical to perform, and also do not generally require rigorously inert reaction conditions. From a chemical perspective, simple starting materials can be converted through an array of transformations into products of significantly increased complexity. Moreover, they are atom-economical and present excellent chemoselectivity towards carbon-carbon π-systems, thus leaving a diverse range of other functional groups untouched. Although platinum and gold are considered expensive, they are in fact comparable in cost to the palladium, rhodium, and iridium complexes that are commonly used for standard manipulations, including large-scale industrial applications. All these beneficial properties have made this area one of the most rapidly growing sub-disciplines of contemporary catalysis.

I.4.1.5 Cyclisation Reactions Promoted by π-Acids

One of the most important features of the carbophilic activation of carbon-carbon multiple bonds towards nucleophiles is its efficiency in the building of cyclic compounds. Thus, when the nucleophile is placed in the same molecule than the alkyne, after the intramolecular nucleophilic addition to the carbon-carbon triple bond, a cyclic compound is afforded. The nucleophilic component in this kind of processes is varied, ranging from heteroatom nucleophiles, such as alcohols,

[59] For a review, see: Alois Fürstner, P. W. Davies, *Angew. Chem. Int. Ed.*, **2007**, *46*, 3410.

amines, esters, amides, sulfoxides, imines, azides, etc., to carbonated ones such as arenes or activated olefins.[60]

In the next sections, a brief summary of the most interesting cyclisation reactions promoted by π-acid catalysts will be shown. The examples have been divided according to the nucleophilic counterpart of the reaction.

I.4.1.5.1 Heteroatomic Nucleophiles

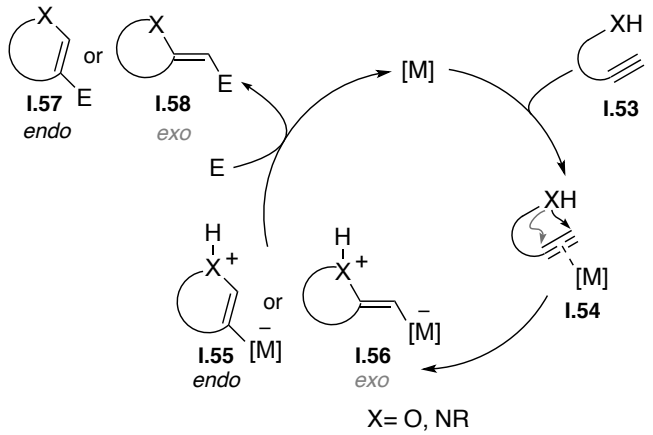
The intramolecular nucleophilic addition of a heteroatom to an activated alkyne easily affords a heterocycle. This synthetic tool has emerged within the last decade as a powerful strategy to access complex heterocyclic molecules.

For a better understanding of the results included in Chapter 1, the intramolecular nucleophilic addition of heteroatoms (basically alcohols and amines) to carbon-carbon triple bonds will be further explained.

In the following **Scheme I.16** the catalytic cycle widely accepted for these processes is shown. This mechanism begins with the coordination of the metallic species to the carbon-carbon triple bond of **I.53**, affording the activated intermediate **I.54**. The intramolecular addition of the nucleophilic counterpart to the activated alkyne generates the *endo* **I.55** or the *exo* **I.56** intermediate depending whether the bond broken during the ring closure is inside (*endo*) or outside (*exo*) the ring that is being formed. These intermediates react with an electrophile present in the reaction media (E), releasing the catalytic metallic species and affording the cyclic products **I.57** or **I.58**. Usually, the electrophile that closes the catalytic cycle is the proton initially attached to the heteroatom (-OH or –NHR). In these cases, the overall process supposes an intramolecular hydroalkoxylation or hydroamination of the alkyne.[61]

[60] For some reviews, see: a) S. F. Kirsch, *Synthesis,* **2008**, 3183. b) A. S. K. Hashmi, G. J. Hutchings, *Angew. Chem. Int. Ed.,* **2006**, *45*, 7896. c) G. Zeni, R. Larock, *Chem. Rev.,* **2004**, *104*, 2285. d) M. Álvarez-Corral, M. Muñoz-Dorado, I. Rodríguez-García, *Chem. Rev.,* **2008**, *108*, 3174. e) J.-M. Weibel, A. Blanc, P. Pale, *Chem. Rev.,* **2008**, *108*, 3149.

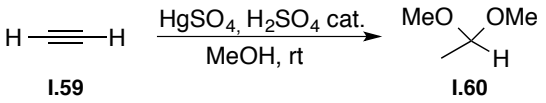
[61] The regiochemistry of these cyclisations follows the Baldwin's rules, see: J. E. Baldwin, *Chem. Comm.*, **1976**, 734.



Scheme I.16 Cycloisomerisation processes of alkynol and alkynamine derivatives: catalytic cycle and regiochemistry observed.

- **Oxygenated Nucleophiles**

At the beginning of the last century, Prof. Nieuwland developed the nucleophilic addition reaction of alcohols to alkynes catalysed by mercury(II) salts, which are π-acids (**Scheme I.17**).[62] This work can be considered as the starting point of the catalytic addition of alcohols to carbon-carbon triple bonds, which has led to the progress and development of the intramolecular hydroalkoxylation reactions.[63]



Scheme I.17 Catalytic synthesis of acetals through alcohol addition to alkynes.

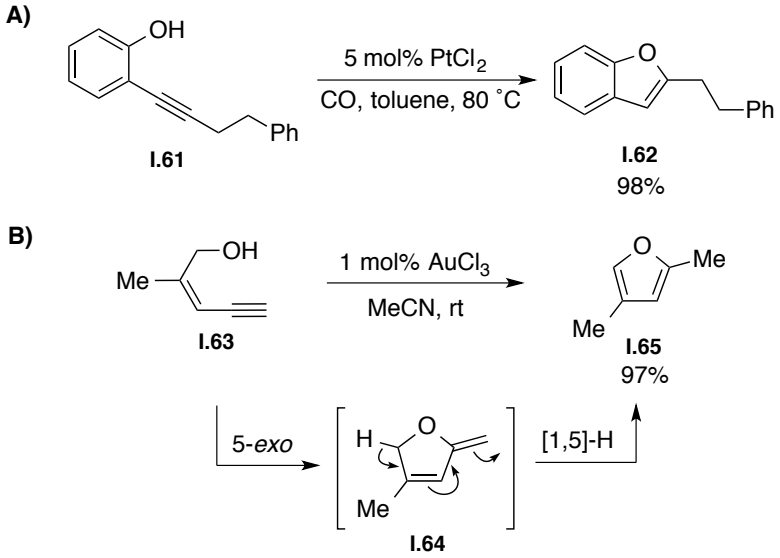
Some examples of the synthesis of oxygenated heterocycles using this methodology are shown in **Scheme I.18**. For instance, **eq. A** shows the synthesis of the functionalised benzo[*b*]furan derivative **I.62** through a platinum(II)-catalysed 5-*endo* hydroalkoxylation developed by Fürstner and co-workers.[64] This reaction proceeds at room temperature, although it is significantly faster when performed at 80 °C. Moreover, in **eq. B**, the functionalised furan **I.65** is obtained through a gold(III) catalysed process involving a 5-*exo* hydroalkoxylation reaction. *Exo*-cyclic enol ethers are unstable molecules and usually, they evolve in the presence of protic catalysts, Lewis acids or transition metal complexes affording their *endo*-

[62] J. S. Reichert, J. H. Bayley, J. A. Nieuwland, *J. Am. Chem. Soc.*, **1923**, *45*, 1552.

[63] The hydroalkoxylation process is indeed based on the hydration of alkynes. a) For the first example of the hydration of alkynes, see: M. Kucherov, *Chem. Ber.*, **1881**, *14*, 1540. b) For a revision on the hydration of alkynes, see: L. Hintermann, A. Labonne, *Synthesis* **2007**, 1121.

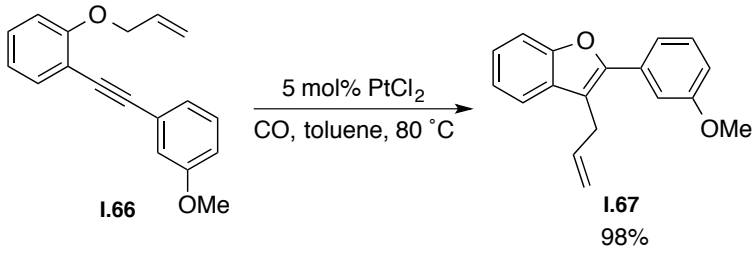
[64] A. Fürstner, P. W. Davies, *J. Am. Chem. Soc.*, **2005**, *127*, 15024.

isomers, which are more stable. Thus, in this example reported by Hashmi in 2000, the *exo*-cyclic enol ether **I.64** undergoes a [1,5]-H shift, giving rise to the functionalised furan **I.65**.[65,66]



Scheme I.18 Synthesis of benzo[*b*]furans (*endo*-cycloisomerisation, **eq. A**) and furans (*exo*-cycloisomerisation and [1,5]-H shift, **eq. B**).

As an example of a reaction with an oxygenated nucleophile without a proton directly attached, a process developed by Fürstner and co-workers for the synthesis of the 2,3-disubstituted benzofuran **I.67** is shown in **Scheme I.19**.

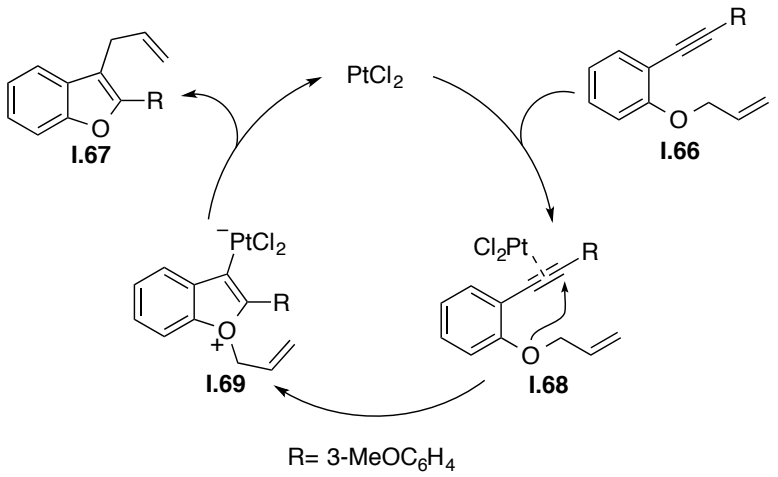


Scheme I.19 $PtCl_2$-catalysed benzofuran synthesis by intramolecular carboalkoxylation.

[65] a) A. S. K. Hashmi, L. Schwarz, J.-H Choi, T. M. Frost, *Angew. Chem. Int. Ed.*, **2000**, *39*, 2285.

[66] For some other examples of 5-*exo*-hydroalkoxylation processes catalysed by different metal complexes, see: a) B. Gabriele, G. Salerno, M. Costa, *Synlett,* **2004**, 2468. b) V. Cadierno, J. Díez, J. García-Álvarez, J. Gimeno, N. Nebra, J. Rubio-García, *Dalton Trans.,* **2006**, 5593. c) P. Pale, J. Chuche, *Eur. J. Org. Chem.,* **2000**, 1019. d) S. Elgafi, L. D. Field, B. A. Messerle, *J. Organomet. Chem.,* **2000**, 97. e) A. E. Díaz- Álvarez, P. Crochet, M. Zablocka, C. Duhayon, V. Cadierno, J. Gimeno, J.-P. Majoral, *Adv. Synth. Catal.,* **2006**, *348*, 1671. f) B. Çetinkaya, I. Özdemir, C. Bruneau, P. H. Dixneuf, *Eur. J. Inorg. Chem.,* **2000**, 29. g) J. Albers, V. Cadierno, P. Crochet, S. E. García-Garrido, J. Gimeno, *J. Organomet. Chem.,* **2007**, *692*, 5234.

The proposed mechanism for this reaction is shown in **Scheme I.20**. Thus, the activation of the alkyne of **I.66** by the electrophilic metallic species $PtCl_2$ enables the nucleophilic attack by the heteroatom, resulting in a trans-alkoxyplatination process. This formally generates an allyl cation fragment **I.69** that evolves by shift of the allyl group to the most nucleophilic position on the ring to give the product **I.67** regenerating the catalyst. Not only the allyl group but other entities able to stabilise positive charges might transfer in a similar fashion.[67]



Scheme I.20 Proposed mechanism for the intramolecular carboalkoxylation.

- **Nitrogenated Nucleophiles**

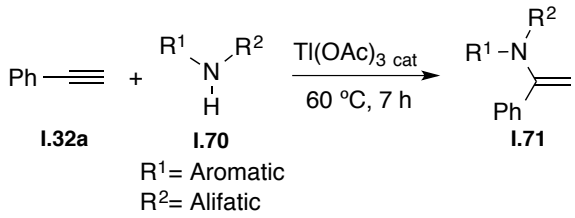
Nitrogen-containing complex molecules are privileged structures in Nature. Thus, many natural products as well as synthetic molecules with biological activity incorporate this heteroatom.[68] The formation of new carbon-nitrogen bonds for the construction of target molecules and nitrogen containing heterocycles in general is not trivial at all.[69] Therefore, the development of new methodologies based on the intramolecular hydroamination of alkynes catalysed by transition metal complexes has become a powerful tool for the synthesis of nitrogen-containing heterocycles.

[67] For other carboalkoxylations catalysed by $PtCl_2$, see: I. Nakamura, G. B. Bajracharya, H. Wu, K. Oishi, Y. Mizushima, I. D. Gridnev, Y. Yamamoto, *J. Am. Chem. Soc.*, **2004**, *126*, 15423 and references cited therein.

[68] a) J. A. Joule, K. Mills, *Heterocyclic Chemistry*, Blackwell, Oxford, **2000**, *589*. b) R. J. Sundberg, *Indoles*, Academic Press, San Diego, **1996**, 175. c) G. R. Humphrey, J. T. Kuethe, *Chem. Rev.*, **2006**, *106*, 2875. d) S. Cacchi, G. Fabrizi, *Chem. Rev.*, **2005**, *105*, 2873. e) T. Kawasaki, K. Higuchi, *Nat. Prod. Rep.*, **2005**, *22*, 761. f) M. Somei, F. Yamada, *Nat. Prod. Rep.*, **2005**, *22*, 73. g) M. Somei, F. Yamada, *Nat. Prod. Rep.*, **2004**, *21*, 278.

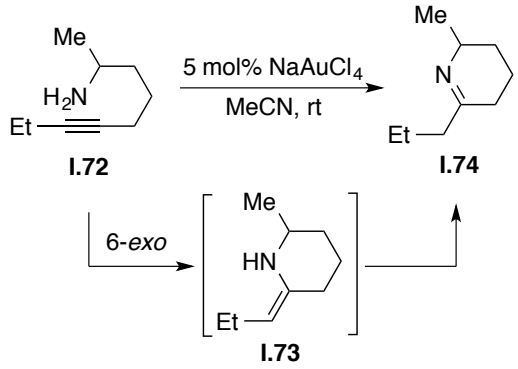
[69] O. Mitsonobu, *Comprehensive Organic Synthesis*, Pergamon Press, **1992**, vol. 6, 65.

The first reaction reported in the literature involving a catalytic addition of amines to alkynes is the one shown in **Scheme I.21**. This process, developed by J. Barluenga and F. Aznar in 1977, affords enamines under the catalytic presence of a thallium(III) salt.[70]



Scheme I.21 Catalytic addition of amines to alkynes reported by Barluenga and co-workers.

In the following years, similar processes were described using other transition metal complexes, and the intramolecular version was also studied.[71] For instance, the first example reported in the literature of intramolecular hydroamination of alkynes using a gold catalyst was reported in 1987 by Utimoto and co-workers (**Scheme I.22**). Thus, acyclic compound **I.72** undergoes a 6-*exo*-cyclisation reaction catalysed by $NaAuCl_4$, at room temperature, affording the *exo*-cyclic enamine **I.73**. This intermediate evolves to its imine tautomer **I.74** which is isolated as the product of the reaction.



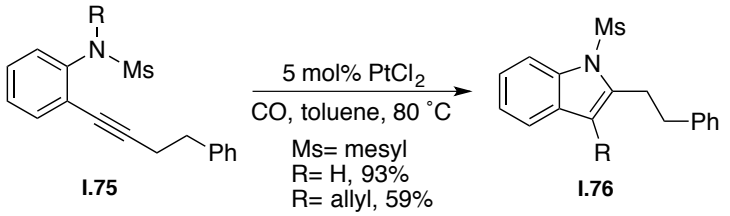
Scheme I.22 Intramolecular hydroamination process catalysed by Au(III).

[70] J. Barluenga, F. Aznar, *Synthesis*, **1977**, 195.

[71] For some revisions, see: a) B. Godoi, R. F. Schumacher, G. Zeni, *Chem. Rev.*, **2011**, *111*, 2937. b) T. E. Muller, K. C. Hultzsch, M. Yus, F. Foubelo, M. Tada, *Chem. Rev.*, **2008**, *108*, 3795. c) R. A. Widenhoefer, X. Han, *Eur. J. Org. Chem.*, **2006**, 2006, 4555.

In recent years, the number of publications involving this transformation has growth exponentially. Therefore, several transition metal complexes such as Au(III), [72] Pd(II), [73] Cu(I), [74] Rh(I), [75] and Ir(I) [76] derivatives can promote this intramolecular hydroamination process.

Thus, this reaction is nowadays widely used for the synthesis of relevant heterocycles. For example, indole derivatives **I.76** are easily synthesised from ortho-alkynilanilines **I.75** in the presence of $PtCl_2$ as catalyst (**Scheme I.23**).[64,77] Interestingly, when an *N*-allyl-substituted aniline derivative is used as starting material, an indole substituted with an allyl group at C3-position is obtained. This formal carboamination of the carbon-carbon triple bond proceeds through a mechanism analogous to the one shown in **Scheme I.20**.



Scheme I.23 Synthesis of indoles through intramolecular hydroamination and carboamination.

I.4.1.5.2 Carbonated Nucleophiles

In view of the previous discussion for heteroatom nucleophiles, it may not come as a surprise that alkynes activated by π-acids could react with carbon nucleophiles, such as aromatic rings, specially if they are electron rich, activated olefins or methylene compounds.

[72] a) Y. Fukuda, K. Utimoto, H. Nozaki, *Heterocycles*, **1987**, *25*, 297. b) Y. Fukuda, K. Utimoto, *Synthesis*, **1991**, *975*.

[73] a) R. Q. Su, T. E. Müller, *Tetrahedron*, **2001**, *57*, 6027. b) T. E. Müller, M. Grosche, E. Herdtweck, A.-K. Pleier, E. Walter, Y.-K. Yan, *Organometallics*, **1999**, *19*, 170. c) L. M. Lutete, I. Kadota, Y. Yamamoto, *J. Am. Chem. Soc.*, **2004**, *126*, 1622.

[74] J. Penzien, C. Haeßner, A. Jentys, K. Köhler, T. E. Müller, J. A. Lercher, *J. Catal.*, **2004**, *221*, 302.

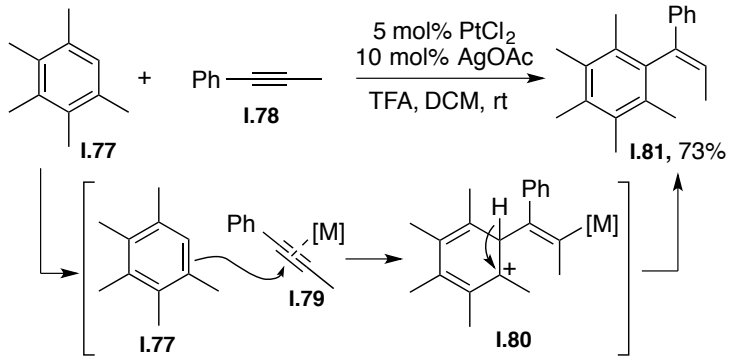
[75] S. Burling, L. D. Field, B. A. Messerle, P. Turner, *Organometallics*, **2004**, *23*, 1714.

[76] L. D. Field, B. A. Messerle, K. Q. Vuong, P. Turner, T. Failes, *Organometallics*, **2007**, *26*, 2058.

[77] For other synthesis of functionalised indoles via hydroamination processes catalysed by Au(III), Ir(I), Pd(II), Cu(I), Rh(I) and In(III), see: a) M. Alfonsi, A. Arcadi, M. Aschi, G. Bianchi, F. Marinelli, *J. Org. Chem.*, **2005**, *70*, 2265. b) S. Cacchi, G. Fabrizi, *Chem. Rev.*, **2005**, *105*, 2873. c) G. Battistuzzi, S. Cacchi, G. Fabrizi, *Eur. J. Org. Chem.*, **2002**, 2002, 2671. d) B. Z. Lu, W. Zhao, H.-X. Wei, M. Dufour, V.Farina, C. H. Senanayake, *Org. Lett.*, **2006**, *8*, 3271. e) H. Ohno, Y. Ohta, S. Oishi, N. Fujii, *Angew. Chem. Int. Ed.*, **2007**, *46*, 2295. f) B. M. Trost, A. McClory, *Angew. Chem. Int. Ed.*, **2007**, *46*, 2074. g) N. Sakai, K. Annaka, T. Konakahara, *Org. Lett.*, **2004**, *6*, 1527.

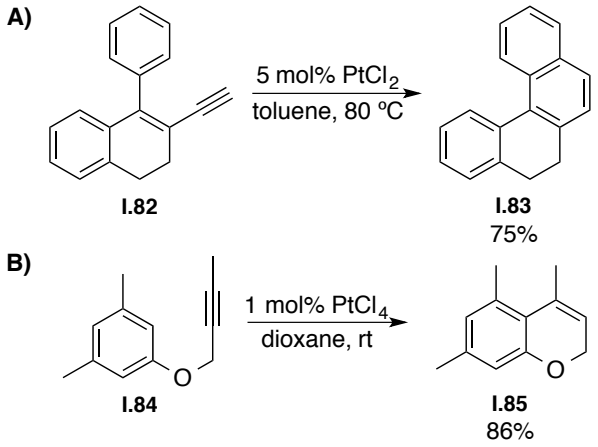
- **Arenes as Nucleophiles**

Fujiwara and co-workers published in 2000 an intermolecular catalytic hydroarylation of alkynes **I.78** by *in situ* generated Pd(II) or Pt(II) cationic species using a mixture of trifluoroacetic acid (TFA) and dichloromethane as solvent (**Scheme I.24**).[78] This reaction proceeds through the activation of the alkyne **I.78** by the π-acid affording **I.79** and the subsequent nucleophilic attack of the arene, affording intermediate **I.80** which undergoes a re-aromatisation step giving the final compound **I.81**.



Scheme I.24 Platinum-catalysed hydroarylarion of alkynes.

The intramolecular version has also been studied and interesting polycyclic aromatic and heteroaromatic systems (such as **I.83**, **eq. A** and **I.85**, **eq. B** in **Scheme I.25**) have been constructed applying this strategy.[79]



Scheme I.25 Platinum(II)- and (IV)-catalysed intramolecular hydroarylation of alkynes.

[78] a) C. Jia, D. Piao, J. Oyamada, W. Lu, T. Kitamura, Y. Fujiwara, *Science*, **2000**, *287*, 1992. b) C. Jia, W. Lu, J. Oyamada, T. Kitamura, K. Matsuda, M. Irie, Y. Fujiwara, *J. Am. Chem. Soc.*, **2000**, *122*, 7252.

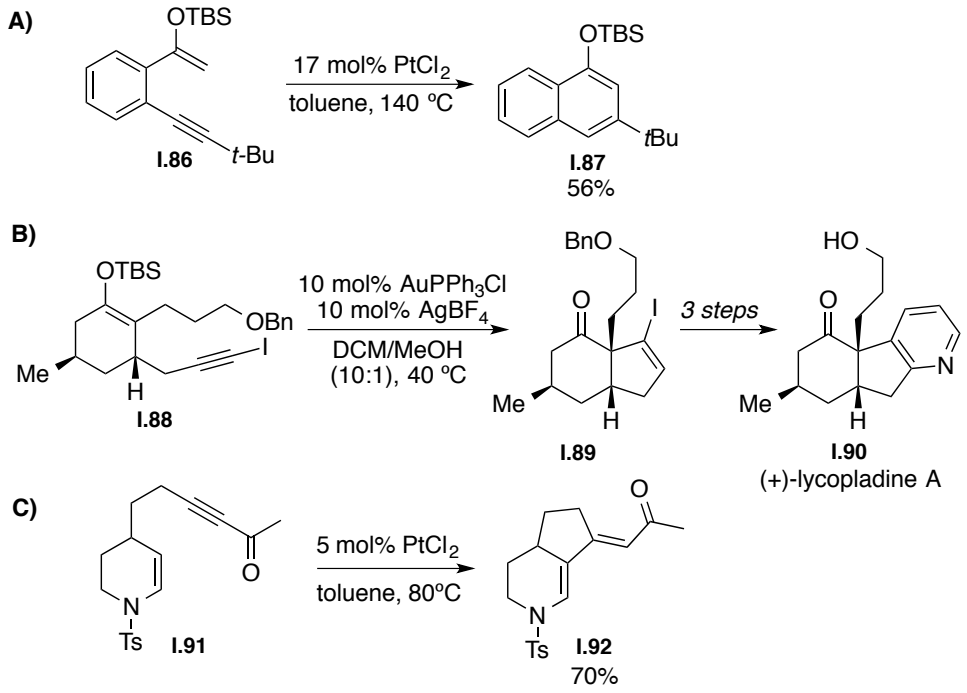
[79] a) A. Fürstner, V. Mamane, *J. Org. Chem.*, **2002**, *67*, 6264. b) S. J. Pastine, S. W. Youn, D. Sames, *Org. Lett.*, *5*, **2003**, 1055.

- **Activated Olefins as Nucleophiles**

The reactions of electron-rich olefins with metal-activated alkynes have also gained the attention of the scientific community during the last years.

Thus, the use of alkyl and silyl enol ethers resulted in the formation of the corresponding dienes, such as the substituted naphthalene derivative **I.87** (**Scheme I.26**, **eq. A**) or their hydrolysed enone forms **I.89** (**Scheme I.26**, **eq. B**) that have been used in the synthesis of natural products, such as (+)-lycopladine A **I.90**.[80]

Additionally, nitrogen-containing heterocyclic compounds like **I.92** can be similarly synthesised by the use of enamines (**I.91**, **Scheme I.26**, **eq. C**).[81]



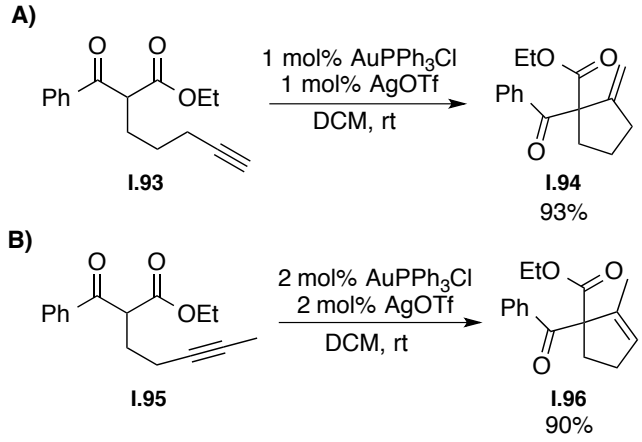
Scheme I.26 A) Platinum(II)-catalysed reaction of silyl enol ethers with alkynes. B) Application to the synthesis of (+)-Lycopladine A. C) Platinum(II)-catalysed reaction of enamines with alkynes.

[80] a) J. W. Dankwardt, *Tetrahedron Lett.*, **2001**, *42*, 5809. b) C. Nevado, D. J. Cárdenas, A. M. Echavarren, *Chem. Eur. J.*, **2003**, *9*, 2627. b) A. M. Echavarren, M. Méndez, M. P. Muñoz, C. Nevado, B. Martín-Matute, C. Nieto-Oberhuber, D. J. Cárdenas, *Pure Appl. Chem.*, **2004**, *76*, 453. c) For an application in total synthesis, see: S. T. Staben, J. J. Kennedy-Smith, D. Huang, B. K. Corkey, R. L. LaLonde, F. D. Toste, *Angew. Chem. Int. Ed.*, **2006**, *45*, 5991.

[81] a) T. J. Harrison, G. R. Dake, *Org. Lett.*, **2004**, *6*, 5023. b) T. J. Harrison, J. A. Kozak, M. Corbella-Pané, G. R. Dake, *J. Org. Chem.*, **2006**, *71*, 4525. c) P. Belmont, T. Belhadj, *Org. Lett.*, **2005**, *7*, 1793.

- **Activated Methylene Compounds as Nucleophiles**

In a related way, activated methylene compounds, such as malonates or β-keto-esters, can perform the nucleophilic addition towards gold-activated alkynes in a Conia-ene process through both *exo*- (**Scheme I.27**, **eq. A**) and *endo*-carbocyclisations (**Scheme I.27**, **eq. B**).[82]



Scheme I.27 Addition of activated methylene units to alkynes

I.4.1.6 Reactions of Enynes Promoted by π-Acids

Enynes chemistry probably represents the most widely studied field in the context of π-acid-promoted cycloisomerisation processes and this area deserves a separated section.[83] Due to the high number of different structurally interesting products obtained, an explanantion based on the reactivity of "nonclassical" carbocations was set up (**Scheme I.28**).

As previously mentioned, alkynes coordinated to metal complexes had been shown to have carbocationic character. In the case of enynes, it was concluded that simultaneous coordination of the alkene and the alkyne to the metal complex is not necessary,[84] and thus, only the alkyne is coordinated at the beginning of the process.[85] Theoretical studies also showed that they might exhibit considerable

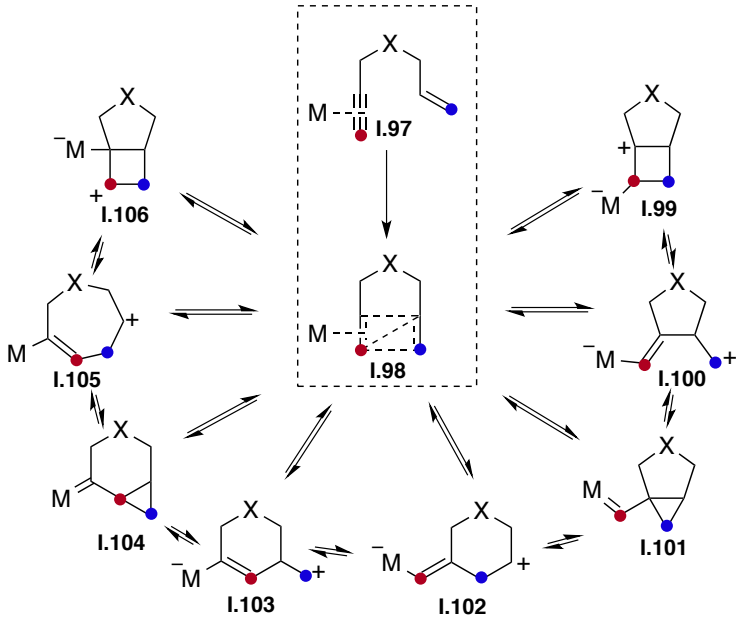
[82] J. J. Kennedy-Smith, S. T. Staben, F. D. Toste, *J. Am. Chem. Soc.*, **2004**, *126*, 4526. ; b) S. T. Staben, J. J. Kennedy-Smith, F. D. Toste, *Angew. Chem. Int. Ed.* **2004**, *43*, 5350.

[83] a) M. Méndez, V. Mamane, A. Fürstner, *Chemtracts*, **2003**, *16*, 397. b) G. C. Lloyd-Jones, *Org. Biomol. Chem.*, **2003**, *1*, 215. c) C. Aubert, O. Buisine, M. Malacria, *Chem. Rev.*, **2002**, *102*, 813. d) S. T. Diver, A. J. Giessert, *Chem. Rev.*, **2004**, *104*, 1317. e) B. M. Trost, M. J. Krische, *Synlett*, **1998**, 1. b) B. M. Trost, *Acc. Chem. Res.*, **2002**, *35*, 695.

[84] This may not even be possible if one considers the isolobal relationship between LAu^+ and H^+.

[85] This does not mean that the olefin does not coordinate to the metal, and may in fact preferentially do so. However, coordination of the alkyne appears to open up the most productive pathways for the substrate to react in this way.

cationic character. For the practical point of view only the potential resonance structures need to be considered to predict the outcome of these reactions.[86]



Scheme I.28 Interpretation of metal-activated enynes in the context of "nonclassical" carbocations.

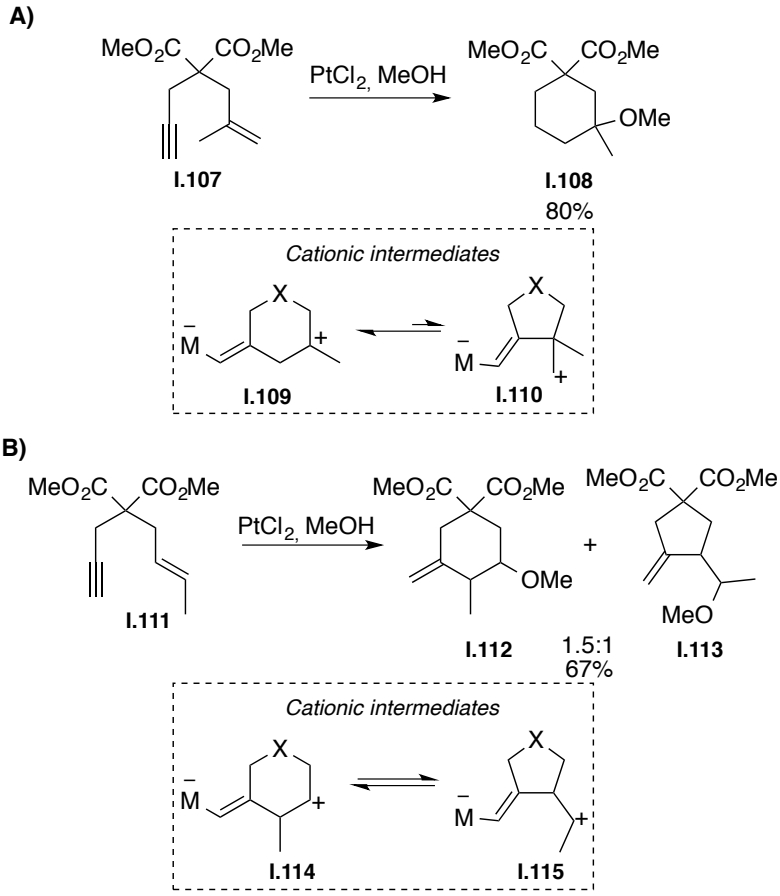
The scope of this area is immense; hence, only some examples showing different reaction pathways of enynes will be described.

A good example to explain the regioselectivity of these reactions is the Pt(II)-catalysed alkoxycyclisation of enynes shown in **Scheme I.29**. Thus, after the alkyne activation and subsequent cyclisation cationic intermediates are trapped with methanol. Formation of those cationic intermediates is determined by the stabilisation of the positive charge. In **eq. A**, only one alkoxylated product **I.108** is obtained as the most stable carbocation is the most substituted one (tertiary, **I.109**).

However, in **eq. B**, two different products are obtained, **I.112** and **I.113**, as in this case both tautomeric forms, **I.114** and **I.115**, are secondary carbocations.[87]

[86] For a review on the exact pathways and structures of the putative intermediates, see: C. Nieto-Oberhuber, S. López, E. Jiménez-Núñez, A. M. Echavarren, *Chem. Eur. J.*, **2006**, *12*, 5916.

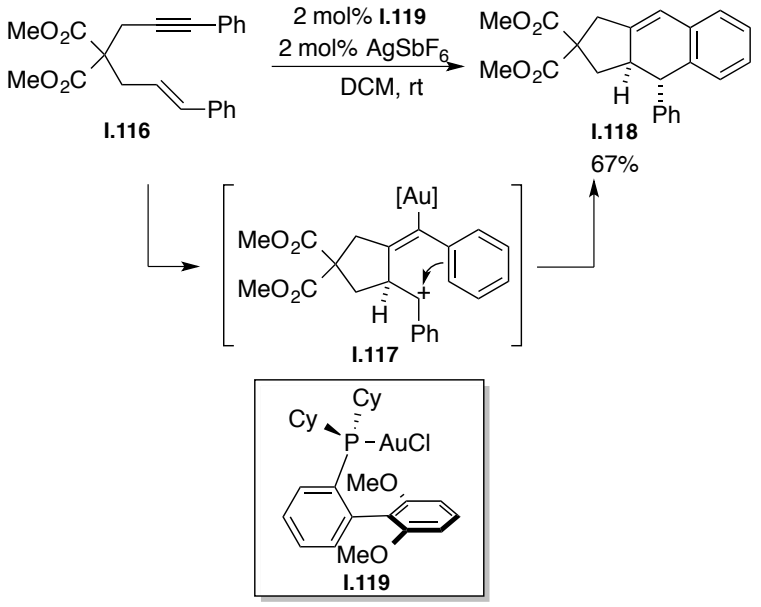
[87] M. Méndez, M. P. Muñoz, C. Nevado, D. J. Cárdenas, A. M. Echavarren, *J. Am. Chem. Soc.*, **2001**, *123*, 10511.



Scheme I.29 Alkoxycyclisation of enynes: regioselectivity.

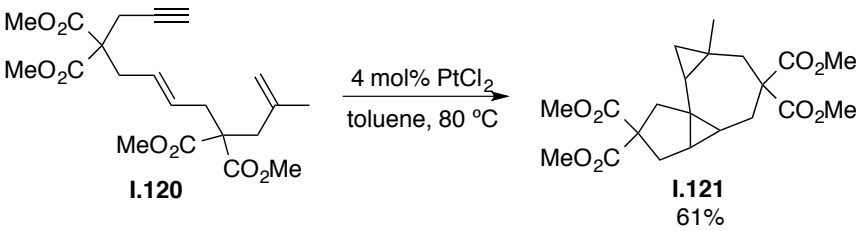
A different reaction pathway is observed when arylated enynes are the selected substrates. In this case the outcome of the reaction could also be predicted by considering the possible mesomeric forms of the nonclassical carbocations and studying the effect of the aromatic substituent. A gold-catalysed example is shown in **Scheme I.30**. In this process, developed by Echavarren and co-workers, a second aromatic ring reacts with the positive charge of **I.117** affording interesting tricyclic compound **I.118**.[88]

[88] C. Nieto-Oberhuber, S. López, A. M. Echavarren, *J. Am. Chem. Soc.*, **2005**, *127*, 6178.



Scheme I.30 Gold-catalysed cycloisomerisation of arylated enynes.

While the previous examples showed the cationic rendition of the key reactive intermediates in enyne cycloisomerisations, their carbenoid nature is especially evident in some polycyclisations. In the following example, a platinum(II) catalysed process involves two intramolecular cyclopropanations of **I.120**.[89] Other catalysts such as gold species have shown to be effective,[90] and intermolecular versions have also been reported.[91]



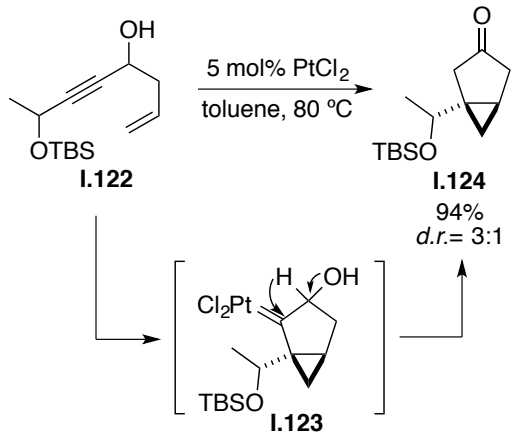
Scheme I.31 Cyclopropanations illustrating the "carbenoid" nature of alkynes activated by Pt(II).

[89] N. Chatani, K. Kataoka, S. Murai, N. Furukawa, Y. Seki, *J. Am. Chem. Soc.*, **1998**, *120*, 9104.

[90] C. Nieto-Oberhuber, S. López, M. Paz Muñoz, E. Jiménez- Núñez, E. Buñuel, D. J. Cárdenas, A. M. Echavarren, *Chem. Eur. J.*, **2006**, *12*, 1694.

[91] S. López, E. Herrero-Gómez, P. Pérez-Galán, C. Nieto- Oberhuber, A. M. Echavarren, *Angew. Chem. Int. Ed.,* **2006**, *45*, 6029.

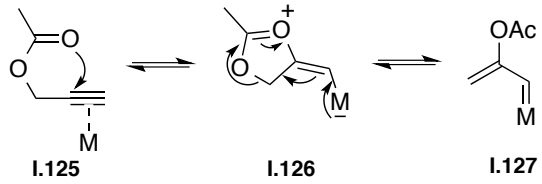
Reaction of 1,5- and 1,6-enynes bearing heteroatoms at the propargylic position such as **I.122** presents further support for the consideration of metal-activated alkynes as "1,2-biscarbene synthons". Thus, heteroatom assisted 1,2-hydrogen shift of **I.123** and metal elimination, very characteristic of the metal-carbene chemistry, terminates the reaction affording **I.124** (**Scheme I.32**).[92]



Scheme I.32 Cycloisomerisation of 1,5-enynes bearing heteroatoms at the progargylic position involving a 1,2-hydride shift.

I.4.1.7 Reactions of Propargylic Carboxylates Promoted by π-Acids

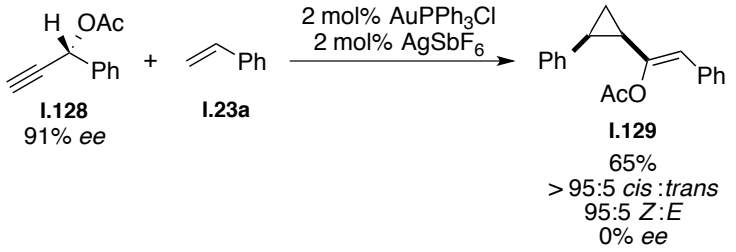
The use of propargylic carboxylates in catalytic processes is nowadays a growing area. In this particular case, the carbonyl unit acts as a nucleophile onto the metal-activated alkyne **I.125**. Then, its leaving group ability at the incipient allylic position in **I.126** is enhanced as it is readily ejected on back-donation from the metal to the ligand. The overall process results in the formation of a metal "carbenoid" **I.127** in which both the ester and the π-system have migrated, so the carboxylate group serves to achieve a metal-alkylidene species at the distal position of the alkyne (**Scheme I.33**).



Scheme I.33 Metal induced activation of propargyl acetate.

[92] V. Mamane, T. Gress, H. Krause, A. Fürstner, *J. Am. Chem. Soc.*, **2004**, *126*, 8654.

Propargylic carboxylates have been successfully used in intermolecular reactions by trapping external alkenes, such as the example shown in **Scheme I.34**.[93] It should be noted that the use of the enantiomerically enriched propargylic carboxylate **I.128** affords racemic products **I.129** which supports the presence of a planar alkylidene **I.127** (see, **Scheme I.33**) as an intermediate of the process. Replacing the olefin with a furan or thiophene ring affords the formation of conjugated trieneones after a heteroatom-driven opening of the heterocyclic system.[94]



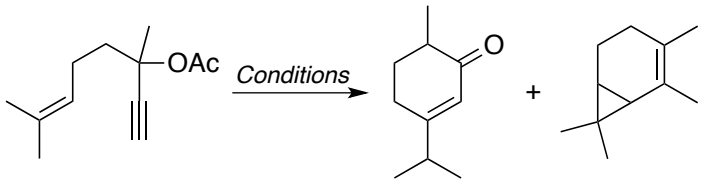
I.128
91% *ee*

I.23a

I.129
65%
> 95:5 *cis* : *trans*
95:5 *Z* : *E*
0% *ee*

Scheme I.34 Gold catalysed intermolecular cyclopropanations by the rearrangement of a propargylic carboxylate.

In the intramolecular reaction of propargylic carboxylates with alkenes a higher level of complexity is established as the presence of a second nucleophile give rise to questions such as which is the exact order of the individual steps. When enyne **I.130** was treated with a stoichiometric quantity of $ZnCl_2$ in benzene at 80 °C, only small amounts of **I.132** (Ohloff rearrangement) were obtained and the major product was the carvenone **I.131**. However, the use of 5 mol% of $AuCl_3$ at room temperature affords **I.132** almost quantitatively, illustrating the effectiveness of noble metal salts as π-acidic catalysts.[95]



I.130 **I.131** **I.132**

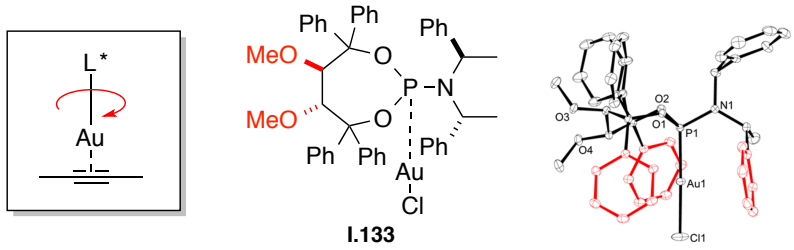
Conditions		
$ZnCl_2$, benzene, 80 °C	70%	5%
5 mol% $AuCl_3$, 1,2-DCE, rt		98%

Scheme I.35 Comparison of the efficacies of a gold and a zinc catalyst.

[93] M. J. Johansson, D. J. Gorin, S. T. Staben, F.D.Toste, *J. Am. Chem. Soc.*, **2005**, *127*, 18002.
[94] K. Miki, M. Fujita, S. Uemura, K. Ohe, *Org. Lett.*, **2006**, *8*, 1741.
[95] A. Fürstner, P. Hannen, *Chem. Eur. J.*, **2006**, *12*, 3006.

I.4.1.8 Asymmetric π-Acid Catalysis for Target Oriented Synthesis

As occurred with classic Lewis acids, the use of chiral ligands in π-acid catalysis has led to the development of asymmetric processes. However, particularly in the case of gold, it is inherently difficult to impose an enantioselective course upon an outer-sphere process triggered by the linear dicoordinate cation Au(I). This particular bonding situation means that the metal can accommodate only a non-chelating one-point-binding ligand held at maximum distance from the substrate. However, several creative solutions for this challenging problem have been proposed in the literature.[96] For instance, Fürstner reported in 2010 the design of a new type of phosphoramidite ligands comprising TADDOL-related diols with an acyclic dimethyl ether backbone (**Figure I.5**).[97]



I.133

Figure I.5 Asymmetric gold catalysis: Structure of a prototype gold-phosphoramidite complex developed by Fürstner.

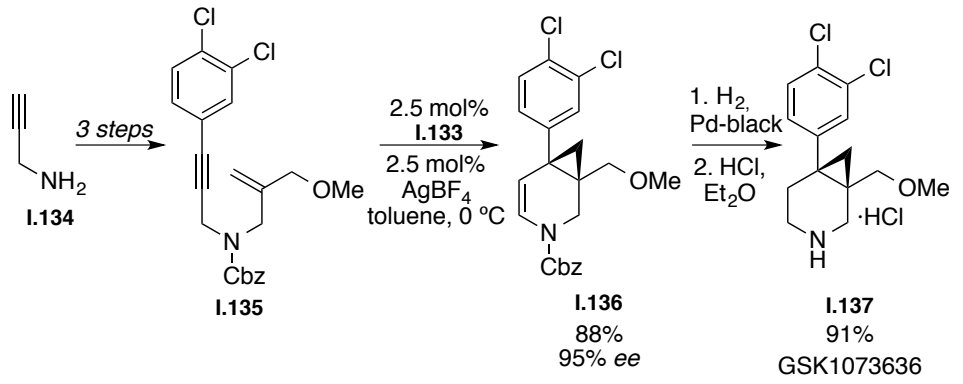
Crystallographic data show that they are able to craft an effective C3-symmetric chiral pocket about the metal that is largely invariant to rotation. These ligands allow remarkable levels of asymmetric induction to be achieved in a variety of gold-catalysed transformations.

An interesting example of its application in target-oriented synthesis is shown in **Scheme I.36**. Hence, the antidepressive drug candidate GSK1073636 **I.137** was synthesised in optically pure form in 2011 by Fürstner and co-workers.[98]

[96] For some recent developments in asymmetric catalysis in the presence of chiral gold complexes, see: A. Pradal, P. Y. Toullec, V. Michelet, *Synthesis*, **2011**, 1501.

[97] a) H. Teller, S. Flügge, R. Goddard, A. Fürstner, *Angew. Chem., Int. Ed.*, **2010**, *49*, 1949. b) H. Teller, M. Corbet, L. Mantilli, G. Gopakumar, R. Goddard, W. Thiel, A. Füstner, *J. Am. Chem. Soc.*, **2012**, *134*, 15331.

[98] H. Teller, A. Fürstner, *Chem. Eur. J.*, **2011**, *17*, 7764.



Scheme I.36 Enantioselective synthesis of an antidepressive drug candidate developed by Fürstner.

Therefore, enyne **I.135** was treated with the chiral gold(I) complex **I.133** affording the cyclopropane derivative **I.136** via cycloisomerisation, which occurred with excellent induction (95% *ee*). Subsequent saturation of the double bond over palladium black with concomitant hydrogenolysis of the *N*-Cbz group completed the synthesis of the drug candidate, which was isolated in the form of the crystalline hydrochloride salt **I.137** in no more than five steps, starting from propargylamine **I.134**, with an overall yield of 69%.

Interestingly, the gold-catalysed key step described in this synthesis constitutes the asymmetric version of the racemic platinum-catalysed cycloisomerisation chemistry previously developed by the same authors.[99] Thus, it shows that platinum and gold (and other carbophilic π-acids) may differ in their efficiency but qualitatively often exhibit similar outcome.

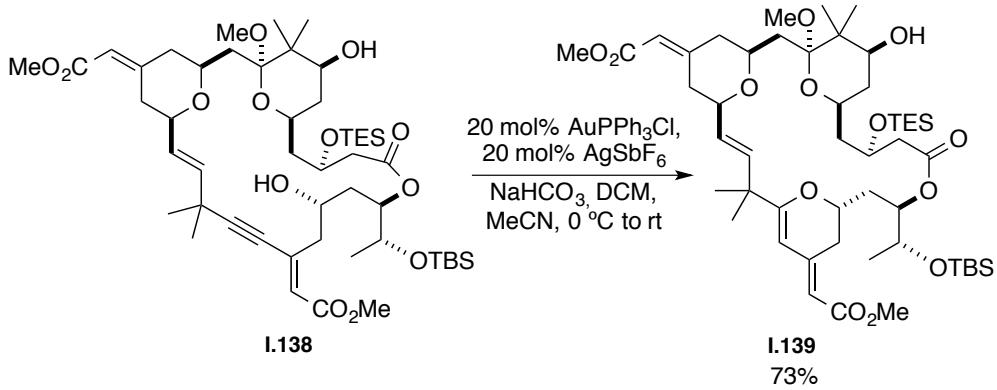
I.4.1.9 π-Acid Catalysis in Natural Product Total Synthesis

Of the concepts used to improve the efficiency of organic synthesis, two have been especially effective: atom economy and chemoselectivity. Total synthesis of complex natural products is the most demanding field in which to explore such principles, and π-acid catalysis has also been able to cope with molecular complexity and exhibit its efficiency in this area.

One particular example that illustrates these achievements is the total synthesis of briostatin 16 published by Trost and co-workers in *Nature* in 2008.[100] Briostatins, which were originally isolated from the marine bryozoan *Bugula neritina*, are a class of structurally complex macrolactone natural products that

[99] A. Fürstner, F. Stelzer, H. Szillat, *J. Am. Chem. Soc.*, **2001**, *123*, 11863.
[100] B. M. Trost , G. Dong, *Nature*, **2008**, *456*, 485.

exhibit exceptional biological activity, being the most notable their anticancer activity *in vivo*.[101] In this publication, the authors reported as one of the key steps of the synthesis a gold catalysed 6-*endo*-dig cyclisation of **I.138** enabling the formation of the dihydropirane ring in **I.139** (**Scheme I.37**). It should be noted that in this step the degree of chemoselectivity achieved is impressive, as even though this intermediate **I.138** presents four sites or unsaturation, the metallic complex exclusively activates the alkyne moiety.



I.138 **I.139**
73%

Scheme I.37 Gold- catalysed 6-*endo*-dig cyclisation as a key step in total synthesis.

[101] K. J. Hale, M. G. Hummersone, S. Manaviazar, M. Frigerio, *Nat. Prod. Rep.*, **2002**, *19*, 413.

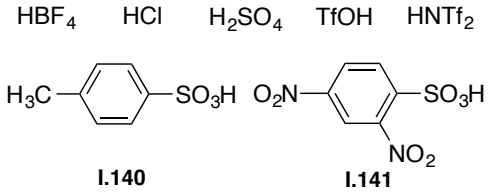
I.4.2 Metal-Free Catalysis

The power of organometallic reagents in the context of catalysis has been shown in the previous sections. However, on the other side of the homogeneous catalysis' spectrum are situated those processes promoted by non-metallic reagents.

During the last decades, the growth of this field has increased dramatically due to the advantages that it presents if compared to typical metal catalysis. The catalysts employed in this area are usually robust, as they can be stored for long periods of time, inexpensive and readily available and, what is more important, non-toxic, as they are considered environmentally friendly. Because of the absence of transition metals, these methods seem to be especially attractive for the preparation of compounds that do not tolerate metal contamination, such as pharmaceutical products. Moreover, due to their inertness toward moisture and oxygen, reaction conditions and special requirements are often simplified.[102]

I.4.2.1 Simple Brønsted Acids

The proton, H^+, can be considered as the smallest element of the Lewis acids. Although Lewis acid catalysts have been widely employed for carbon-carbon bond-forming reactions, Brønsted acids have been mainly used during the years for processes such as hydrolysis and/or formation of esters, acetals, etc. Thus, the synthetic utility of Brønsted acids as catalysts for carbon-carbon bond-forming reactions has been quite limited until recently. However, some important reactions promoted by simple Brønsted acids, such as those ones shown in **Figure I.6**, have appeared in the literature in the last decade.



I.140 **I.141**

Figure I.6 Examples of achiral Brønsted acids.

For instance, in 2006 B. List and co-workers reported that 2,4-dinitrobenzenesulfonic acid **I.141** (DNBSA) catalysed the Hosomi-Sakurai reaction of allylsilane with acetals (**Scheme I.38**, **eq. A**).[103] It should be noted that even

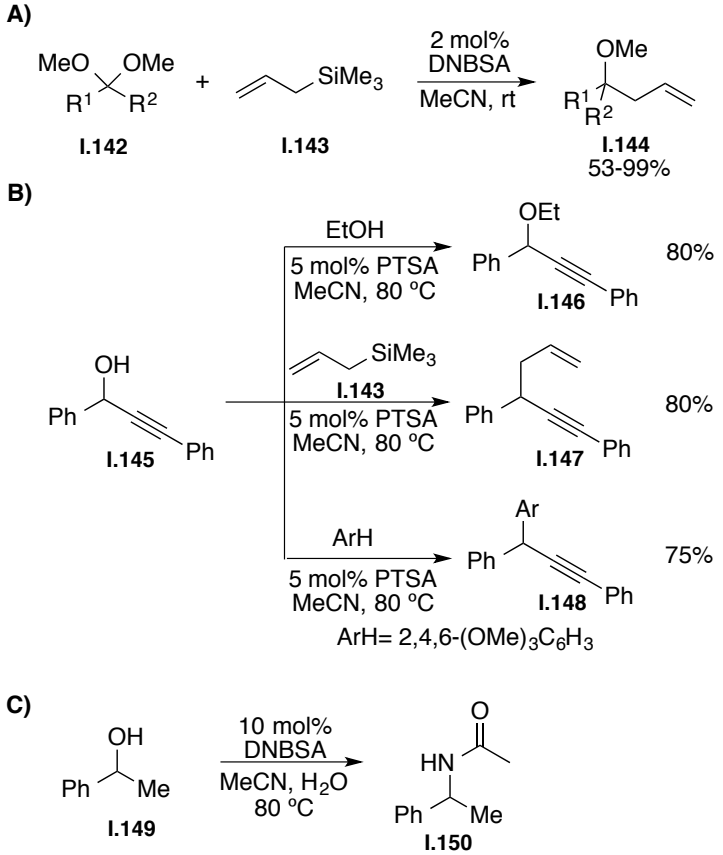
[102] G. Rothenberg, *Catalysis: Concepts and Green Applications*, Wiley-VCH, **2008**, Chapter 3.

[103] D. Kampen, B. List, *Synlett*, **2006**, 2589.

though the small catalyst loading, the corresponding homoallylic ethers **I.144** could be obtained in moderate to high yields.

In the same year, R. Sanz, F. Rodríguez and co-workers found that simple organic acids such as *p*-toluensulfonic acid monohydrate **I.140** (PTSA) were efficient in the direct propargylic substitution of hydroxyl groups by a range of heteroatom-and carbon-nucleophiles (**Scheme I.38**, **eq. B**).[104] Thus, this reaction performed in a metal-free environment gives water as the only byproduct.

One year later, in 2007, the same authors developed a Ritter reaction for the amidation of alcohols **I.149** under truly catalytic Brønsted acid conditions (**Scheme I.38**).[105] This methodology offered a good alternative to the well-established use of metallic catalysts or stoichiometric amounts of strong Brønsted acids and corrosive compounds such as sulphuric acid or triflic anhydride.



Scheme I.38 Simple Brønsted acid-catalysed reactions.

[104] R. Sanz, A. Martinez, J. M. Alvarez-Gutierrez, F. Rodriquez, *Eur. J. Org. Chem.*, **2006**, 1383.

[105] R. Sanz, A. Martínez, V. Guilarte, J. M. Álvarez-Gutiérrez, F. Rodríguez, *Eur. J. Org. Chem.*, **2007**, 4642.

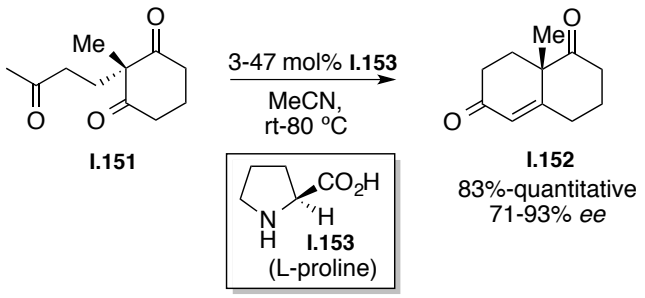
Other protic acid-catalysed processes, including three-component Mannich-type reactions, aza Diels-Alder, Friedel-Crafts, Mukaiyama aldol, aza Darzens, hydroxylation and hydroamination of alkenes, carbocyclisations, etc., have also been described in recent years.[106]

I.4.2.2 Asymmetric Organocatalysis

The use of small chiral organic molecules as catalysts in a metal-free environment has experienced an impressive growth in the last years. Therefore, asymmetric organocatalysis is nowadays considered the "third pillar" of enantioselective catalysis, together with biocatalysis and metal catalysis. Organocatalysts are purely organic molecules, mainly composed of carbon, hydrogen, nitrogen, sulphur and phosphorus.

The first example of an asymmetric organocatalytic reaction was reported by Bredig and Fiske in 1912, who found that cinchona alkaloids significantly accelerated the addition of HCN to benzaldehyde.[107] Unfortunately, the enantiomeric excess in most of the early examples were in the range ≤ 10%, so they were not efficient for preparative purposes.

Further improvements in enantioselectivity were achieved in the 1970s and 1980s. For instance, a pioneering proline-catalysed process developed in the 1971 was the Hajos-Parrish-Eder-Sauer-Wiechert reaction (**Scheme I.39**) affording ketone **I.152**, which is an important intermediate in steroid synthesis, in very good yield and from good to very good enantiomeric excess.[108]



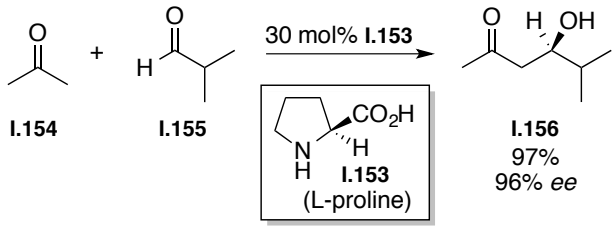
Scheme I.39 The Hajos-Parrish-Eder-Sauer-Wiechert reaction.

[106] For more examples of achiral Brønsted acids catalysed reactions, see: T. Akiyama, *Chem. Rev.*, **2007**, *107*, 5744.

[107] G. Bredig, W. S. Fiske, *Biochem Z.*, **1912**, *7*.

[108] a) U. Eder, G. Sauer, R. Wiechert, *Angew. Chem. Int. Ed*., **1971**, *10*, 496. b) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.*, **1974**, *39*, 1615.

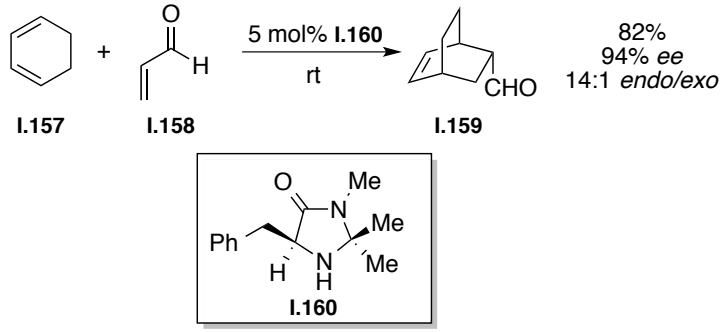
However, the catalytic potential of proline in asymmetric aldol reactions was not explored until the beginning of this century. List and co-workers reported pioneering studies in 2000 on intermolecular aldol reactions.[109] An example of the addition of acetone **I.154** to isobutyl aldehyde **I.155** is shown in **Scheme I.40**. Thus, the corresponding aldol **I.156** is obtained in excellent yields and enantiomeric purity.



Scheme I.40 L-proline-catalysed intermolecular aldol reaction reported by List.

This chemo- and enantioselectivity observed by List and co-workers triggered further research activity in proline-catalysed aldol, Mannich, Michael and related reactions.

In 2000 as well, MacMillan and co-workers developed a Diels-Alder reaction of α,β-unsaturated aldehydes in a process catalysed by the phenylalanine-derived secondary amine **I.160**.[110] This initial report was followed by numerous further applications of the catalyst **I.160** and related secondary amines.



Scheme I.41 Secondary amine-catalysed Diels-Alder reaction reported by MacMillan.

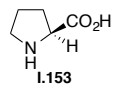
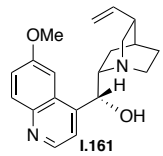
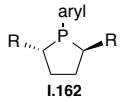
[109] a) B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.*, **2000**, 122, 2395. b) B. List, *Tetrahedron*, **2002**, *58*, 5573.

[110] K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.*, **2000**, *122*, 4243.

Therefore, first publications from the groups of MacMillan, List, Denmark, and Jacobsen paved the way.[111] These reports introduced highly enantioselective transformations that rivalled the metal-catalysed reactions in both yields and selectivities. Once this foundation was laid, interest in organocatalysis was reflected in a rapid increase in publications on this topic from a growing number of research groups. Thus, iminium and enamine-based organocatalysis (dienamine, trienamine…) now enables cycloadditions, Michael additions, aldol reactions, nucleophilic substitution and many other transformations with excellent enantioselectivity; new generations of phase transfer catalysis give almost perfect enantiomeric excess at low catalyst loading; chiral ureas and tioureas are extremely efficient in the enantioselective addition of nucleophiles to aldehydes and imines, etc.[112]

Organocatalysis stands out for the variety of its modes of activation, so the description of all of them would go out of the point of this section. Considering this fact and just to give an overall view of the domain of asymmetric organocatalysis, different type of organocatalysts with some typical examples, together with their reaction scope are listed in the following **Table I.1**.[112]

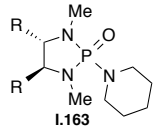
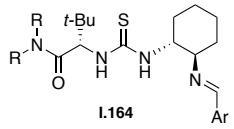
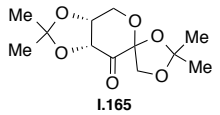
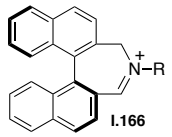
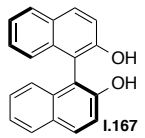
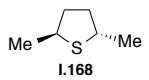
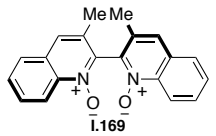
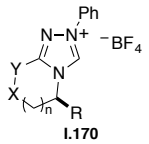
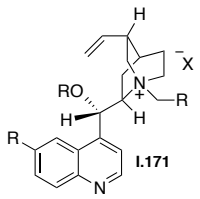
Table I.1 Different types of organocatalysts: seleccion of some examples.

	Structure	***Typical Reaction Scope***
Primary and Secondary Amine Catalysts	 **I.153**	*- Intermolecular Michael addition* *- Mannich reaction* *- Inter/Intramolecular aldol reaction* *- Aldol-related reactions* *- [3+2] and [4+2] cycloadditions*
Tertiary Amine and Piridine	 **I.161**	*- α-Halogenation of carbonyl compounds* *- Inter/Intramolecular Mannich addition* *- β-Lactam and β-Lactone synthesis* *- Morita-Baylis-Hillman reaction* *- Diels-Alder reaction* *- Desymmetrisations*
Phosphanes	 **I.162**	*- Kinetic resolution of racemic alcohols by acylation* *-Desymmetrisation of meso-diols* *(Continued)*

[111] For some revisions, see: a) B. List, *Chem. Rev.*, **2007**, *107*, 5413. b) P. I. Dalko, L. Moisan *Angew. Chem. Int. Ed.*, **2004**, *43*, 5138. c) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem. Int. Ed.*, **2007**, *46*, 1570. D) H. Pellissier, *Domino Reactions: Concepts for Efficient Organic Synthesis*, [Ed. L. F. Tietze] Wiley-VCH, Weinheim, **2014**, Chapter 10.

[112] a) A. Berkessel, H. Gröger, *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*, First edition, Wiley-VCH, Weinheim, **2005**. b) P. I. Dalko, Enantioselective Organocatalysis: Reactions and Experimental Procedures, First edition, Wiley-VCH, Weinheim, **2007**.

Table I.1 (Continued)

	Structure	***Typical Reaction Scope***
Phosphoramidites, Phosphoramides and Formamides	 **I.163**	*-Intermolecular aldol reaction* *- Allylation of aldehydes*
Ureas, Thioureas, Guanidines, Amidines	 **I.164**	*- Hydrocyanation of imines* *- Mannich reaction* *- Hydrophosphonylation of imines* *- [4+2] Cycloaddition* *- Diels-Alder reaction*
Ketones	 **I.165**	*- Epoxidation of olefins* *- Kinetic resolution of alcohols by oxidation*
Imines, Iminium Cations and Oxazolines	 **I.166**	*- Epoxidation of olefins*
Diols	 **I.167**	*- Hydrocyanation os aldehydes* *- Morita-Baylis.Hillman reaction* *- Reduction of carbonyl compounds*
Sulfides	 **I.168**	*- Aziridination of imines* *- Epoxidation of aldehydes*
N-Oxides and Nitroxyl Radicals	 **I.169**	*- Hydrocianation of imines* *- Allylation of aldehydes*
Heterocyclic Carbenes	 **I.170**	*- Benzoin condensation* *- Stetter-reaction*
Phase Transfer Catalysts	 **I.171**	*- Alkylations with formation of C-C bonds* *- Halogenations* *- Intermolecular Michael addition* *- Inter/Intramolecular aldol reaction* *- Alkylation of C=O double bonds* *- Darzens reactions* *- Reduction of carbonyl compounds* *- Horner-Wadsworth-Emmons reaction*

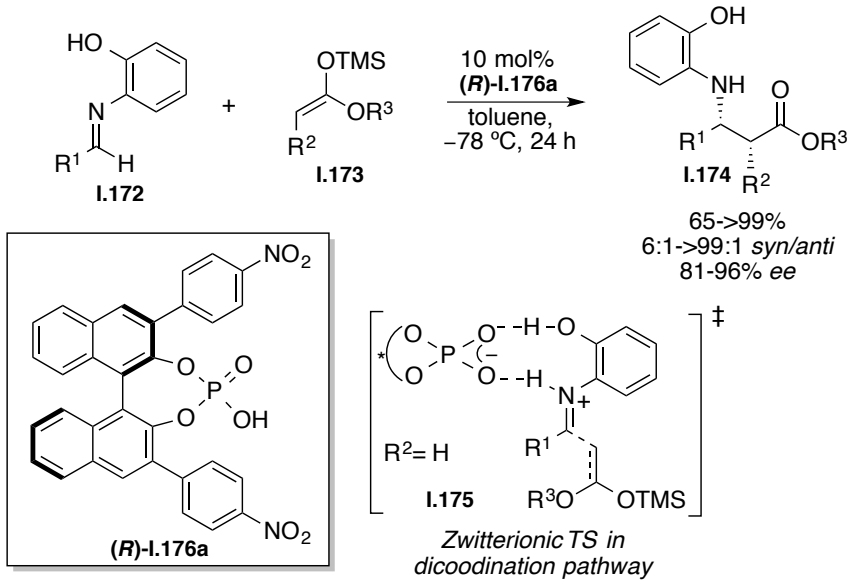
I.4.2.3 Chiral Brønsted Acids for Asymmetric Organocatalysis

Apart from those organocatalysts shown in the previous **Table I.1**, recent years have witnessed an impressive growth in the number of new chiral Brønsted acid-catalysed reactions.

Since some results included in this thesis are framed within this field, a deeper explanation on the use of chiral Brønsted acids in asymmetric reactions will be presented in the next sections.

- **Chiral Phosphoric Acids**

In 2004, Akiyama and Terada independently introduced a novel chiral motif for asymmetric catalysis: chiral-BINOL derived phosphoric acids **I.176**.[113] In both cases, the selected process for the application of the new organocatalyst was a Mannich reaction. The enantioselective Mannich reaction reported by Ayikama is shown in **Scheme I.42**.



Scheme I.42 Enantioselective Mannich reaction of silyl ketene acetals reported by Akiyama

Detailed mechanistic investigations based on DFT computational studies were disclosed by Akiyama, Yamanaka and co-workers in 2007.[114] Thus, theoretical studies elucidated that the two-point hydrogen bonding interaction makes the dicoordination pathway favoured over the monocoordination one in this Mannich-

[113] a) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem. Int. Ed.*, **2004**, *43*, 1566. b) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.*, **2004**, *126*, 5356.

[114] M. Yamanaka, J. Itoh, K. Fuchibe, T. Akiyama, *J. Am. Chem. Soc.*, **2007**, *129*, 6756.

type reaction. They found that the reaction proceeded through the protonation of the imine **I.172** followed by the nucleophilic attack of **I.173** via zwitterionic and nine-membered cyclic TS **I.175**.

This axially chiral phosphoric acid **(*R*)-I.176** presented some unique characteristics (**Figure I.7**):[115]

1. The phosphorous atom and its optically active ligand form a seven-membered ring, which prevents free rotation around the P-O bond fixing the conformation of the acid. Similar carboxylic or sulfonic acids do no present this structural feature.
2. Phosphoric acids with the appropriate acidity should potentially activate substrates via protonation, increasing its electrophilicity. Subsequent attack of a nucleophile to this activated intermediate will result in the formation of enantioenriched products by stereochemical communication between the cationic protonated substrate and the chiral phosphate anion.
3. As the phosphoryl oxygen atom provides an additional Lewis basic site, this new catalyst might act as a bifunctional catalyst (Brønsted acid/Lewis base).
4. Substituents "R" can be introduced on the ring system at the 3,3'-positions to provide a chiral environment for enantioselective transformations.

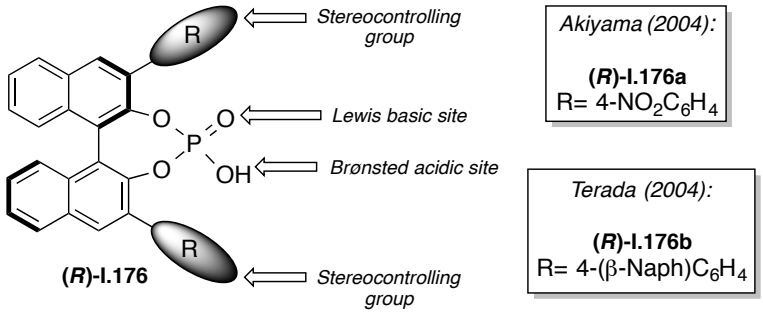


Figure I.7 Chiral (*R*)-BINOL-derived phosphoric acid.

These catalysts **I.176** can be easily synthesised in a few steps starting from commercially available (*R*)- or (*S*)-BINOL. The key step for the introduction of R groups usually includes a palladium-catalysed cross-coupling of boronic acids and aryl halides.

Once it was proved that BINOL-derived phosphoric acids **I.176** served as organocatalysts for asymmetric Mannich reactions, Akiyama and Terada proposed that this concept of electrophilic activation of imines might be applicable to

[115] D. Kampen, C. M. Reisinger, B. List, *Topics in Current Chemistry*, Springer-Verlag Berlin Heidelberg, **2009**, 395.

further asymmetric transformations. Other groups used the potential of these organocatalysts as well, showing that various nucleophiles can be also efficient. These catalysts have mediated the formation of C-C, C-H, C-O, C-N and C-P bonds in the last years and a variety of 1,2-additions and cycloaddition to imines have been reported. Moreover, it was found that they could activate not only imines, but also other substrates.[116]

The increase and development of new asymmetric reactions demanded the synthesis of other chiral Brønsted acids with different electronic and steric properties. Therefore, phosphorics acids such as H_8-BINOL-derived analogs prepared by slightly modified procedures, others derived from TADDOL **(*R*,*R*)-I.177**, VAPOL **(*R*)-I.178**, BINAM **(*R*,*R*)-I.180** or a bis-BINOL as a biphosphoric acid **(*R*,*R*)-I.181**, have been described in the literature (**Figure I.8**).

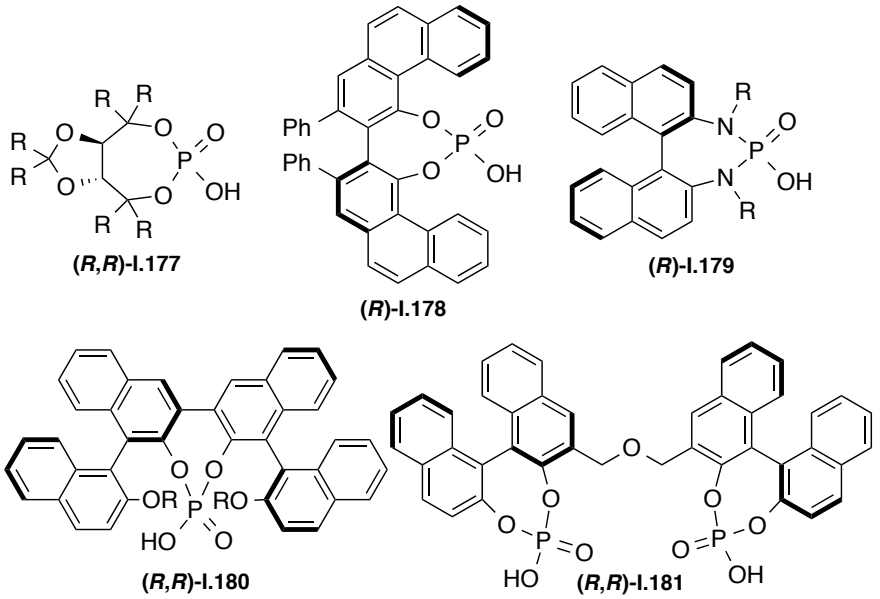
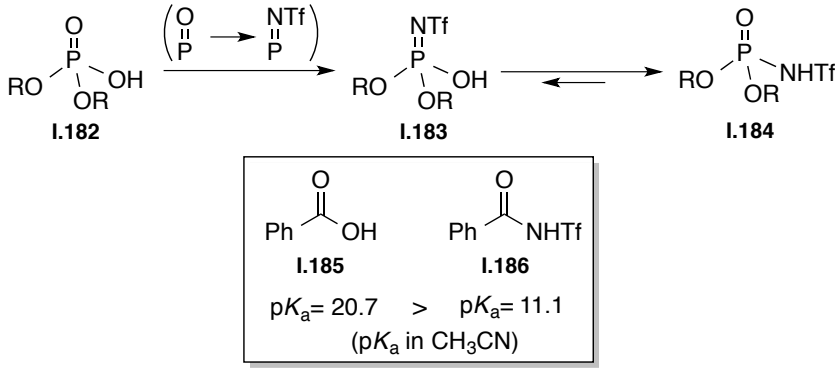


Figure I.8 Other chiral phosphoric acids.

[116] For some reviews of phosphorics acids catalysis, see: a) T. Akiyama, J Itoh, K. Fuchibe, *Adv. Synth. Catal*., **2006**, *348*, 999. b) A. G. Doyle, E. N. Jacobsen. *Chem. Rev*., **2007**, *107*, 5713. c) M. Terada, *Chem. Commun*., **2008**, 4097. d) A. Adair, S. Mukherjee, B. List, *Aldrichimica Acta*., **2008**, *41*, 31. e) H. Yamamoto, N. Payette, In "*Hydrogen Bonding in Organic Synthesis*" ed. by P. M. Pihko, Wiley–VCH, Weinheim, **2009**, 73. f) M. Terada, *Bull. Chem. Soc. Jpn*. **2010**, *83*, 101. g) M. Terada, *Synthesis,* **2010**, 1929. h) M. Terada, M. *Curr. Org. Chem*., **2011**, *15*, 2227. i) T. Akiyama, *J. Synth. Org. Chem*., *Jpn*. **2011**, *69*, 913. j) C. H. Cheon, H. Yamamoto, *Chem. Commun*., **2011**, *47*, 3043. k) M. Terada, *J. Synth. Org. Chem*., *Jpn*., **2013**, *71*, 480; and references 106 and 115.

- **Chiral *N*-Triflyl Phosphoramides**

Despite all the success achieved with the use of chiral phosphoric acids, until 2006, the acidity of BINOL-derived ones showed to be appropriate to activate mostly imine compounds, as mentioned before. At that point, the activation of simple carbonyl compounds by means of Brønsted acid catalysis was still a challenge. These compounds, and other less reactive substrates, required a stronger Brønsted acid catalyst. The acidity of the Brønsted acids could be increased by replacement of the oxygen moiety attached to the phosphorous for a strong electron-withdrawing group, such as *N*-trifluoromethanesulfonyl (*N*-tryfly, *N*Tf), which can stabilise the conjugate base (**Scheme I.43**).[117]



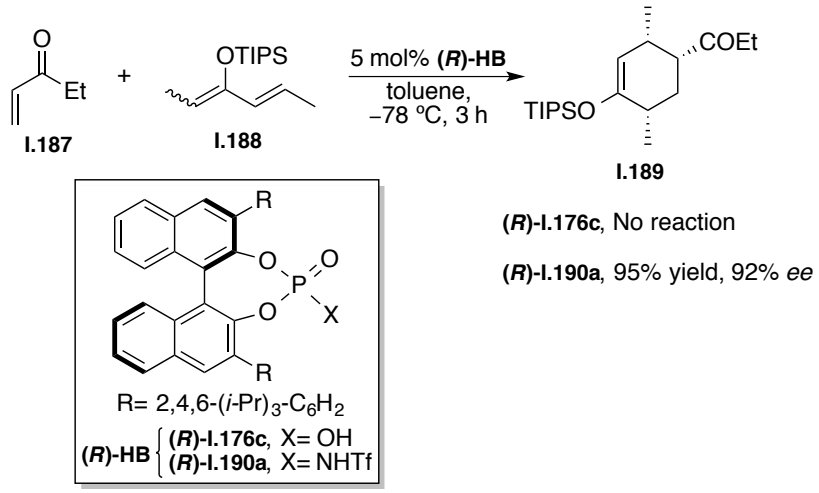
Scheme I.43 Enhancement of the acidity of a Brønsted acid by a strong electron-acceptor.

Therefore, in 2006, Yamamoto and Nakashima designed a chiral *N*-triflyl phosphoramide **(*R*)-I.190a** as a stronger Brønsted acid catalyst than the phosphoric acid, based on this concept.[118] X-ray crystallography analysis revealed that this Brønsted acid has P=O bond, a P-N single bond and that the proton is located on the N atom rather than on the O atom.[119] In their seminal report, whereas the previously described BINOL-derived phosphoric acids showed no catalytic activity, *N*-triflyl phosphoramides proved to be highly effective catalysts for a Diels-Alder reaction of the ethyl vinyl ketone **I.187** and silyloxydienes **I.188** (**Scheme I.44**). Moreover, it represented the first example of activation of carbonyl functionality in phosphoric acid-based catalysis. They also reported the preparation of this new catalysts, which are usually synthesised from the corresponding optically active 3,3'-substituted BINOL derivatives through a phosphorylation/amidation route.

[117] S. I. Hirashima, H. Yamamoto, *J. Synth. Org. Chem., Jpn.,* **2013**, *71*, 1116.

[118] D. Nakashima, H. Yamamoto. *J. Am. Chem. Soc*., **2006**, *128*, 9626.

[119] P. Jiao, D. Nakashima, H. Yamamoto, *Angew. Chem. Int. Ed*., **2008**, *47*, 2411.



Scheme I.44 Reactivity comparison of asymmetric Diels-Alder reaction described by Yamamoto.

Asymmetric formation of C-C, C-H, C-O and C-N bonds has been described with the use of chiral *N*-triflyl phosphoramides **I.90**. α,β-Unsaturated carbonyl compounds undergo 1,4-additions or cycloadditions in the presence of these catalysts as well.[120]

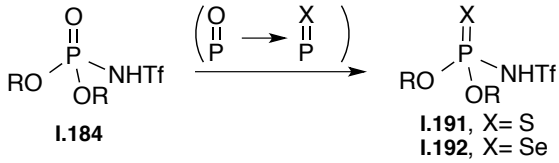
- **Chiral *N*-Triflyl Thio- and Seleno-Phosphoramides**

As previously described, the development of new asymmetric reactions after the seminal work of Yamamoto on more acidic Brønsted acids increased, and other groups reported several asymmetric transformations using chiral *N*-triflyl phosphoramides. However, it was not satisfactory for some functional groups activation. Therefore, continuing with their effort of making these catalysts more general for their use in organic synthesis they decided to design a new chiral Brønsted acid with higher acidity.

Generally, acidity increases going down a column in the periodic table due to the better stabilisation of the conjugate base in a more polarisable atom. Thus, they expected that by simple substitution of the oxygen in P=O bond in a *N*-triflyl

[120] a) M. Rueping, W. Ieawsuwan, A. P. Antonchick, B. J. Nachtsheim, *Angew. Chem. Int. Ed*., **2007**, *46*, 2097. b) M. Rueping, B. J. Nachtsheim, S. A. Moreth, M. Bolte, *Angew. Chem. Int. Ed*., **2008**, *47*, 593. c) M. Zeng, Q. Kang, Q.-L. He, S.-L You, *Adv. Synth. Catal*., **2008**, *350*, 2169. d) D. Enders, A. A. Narine, F. Toulgoat, T. Bisschops, *Angew. Chem. Int. Ed*., **2008**, *47*, 5661. e) M. Rueping, W. Ieawsuwan, *Adv. Synth. Catal*., **2009**, *351*, 78. f) M. Rueping, T. Theissmann, A. Kuenkel, R. M. Koenigs, *Angew. Chem. Int. Ed*., **2008**, *47*, 6798. g) S. Lee, S. Kim, *Tetrahedron Lett*., **2009**, *50*, 3345. h) M. Rueping, B. J. Nachtsheim, *Synlett,* **2010**, 119. i) D. Enders, M. Seppelt, T. Beck, *Adv. Synth. Catal*., **2010**, *352*, 1413.

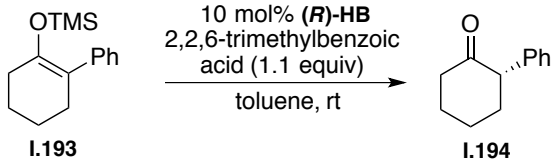
oxo-phosphoramide **I.184** with sulphur or selenium the acidity of the new Brønsted acid **I.191** or **I.192** will increase (**Scheme I.45**).[121]

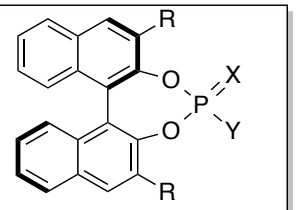


PhOH PhSH PhSeH
pK_a= 18.0 > pK_a= 10.3 > pK_a= 7.1
(pK_a in DMSO)

Scheme I.45 Enhancement of acidity by introduction of a more polarisable atom.

According to their expectations, Yamamoto and co-workers reported that these chiral acids **I.196** and **I.197** were highly effective for an enantioselective protonation reaction of silyl enol ethers **I.130**.[122] To compare the catalytic reactivity of these chiral Brønsted acids with the ones previously reported, they studied their efficiency in this reaction (**Scheme I.46**).





R= 2,4,6-(*i*-Pr)$_3$-C$_6$H$_2$

(*R*)-HB:

(*R*)-I.176c, X= O, Y= OH
(*R*)-I.195a, X= S, Y= OH
(*R*)-I.190a, X= O, Y= NHTf
(*R*)-I.196a, X= S, Y= NHTf
(*R*)-I.197a, X= Se, Y= NHTf

(*R*)-I.176c, No reaction

(*R*)-I.195a, traces

(*R*)-I.190a, >99% yield, 54% *ee*

(*R*)-I.196a, >99% yield, 78% *ee*

(*R*)-I.197a, >99% yield, 72% ee

Scheme I.46 Reactivity comparison of Brønsted acids in enantioselective protonation reaction.

[121] Similar acidity enhancement of Brønsted acid by introduction of a more polarisable atom was also reported, see: a) M. T. Robak, M. Trincado, J. A. Ellman, *J. Am. Chem. Soc*., **2007**, *129*, 15110. b) G. Pousse, A. Devineau, V. Dalla, L. Humphreys, M.-C. Lasne, J. Rouden, J. Blanchet, *Tetrahedron,* **2009**, *65*, 10617.

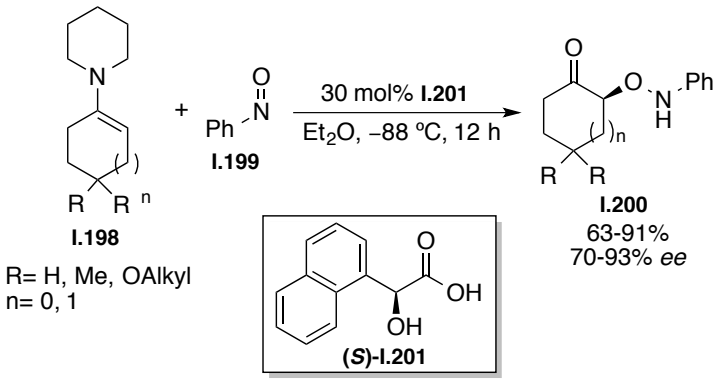
[122] C. H. Cheon, H. Yamamoto, *J. Am. Chem. Soc.*, **2008**, *130*, 9246.

It should be noted that almost no reaction was observed when chiral phosphoric acid **(*R*)-I.176c** and thio-phosphoric **(*R*)-I.195a** acid where used. Nevertheless, the catalytic activity was enhanced when *N*-triflyl oxo-phosphoramide **(*R*)-I.190a** was chosen. Interestingly, they found that the substitution of the oxygen with a sulphur or selenium in this last catalyst (**(*R*)-I.196a** and **(*R*)-I.197a**) improved enantioselectivity as well as reactivity (see **Scheme I.46**).

- **Chiral Carboxilic and Sulfonic Acids**

When developing Brønsted acid catalysis, the key feature sometimes is the choice of the proper acidity of the catalyst depending on the substrate properties. As mentioned before, less reactive substrates require stronger Brønsted acids, but sometimes acid-sensitive substrates tend to decompose under strongly acidic conditions. This makes the use of weaker chiral Brønsted acids also important.

Yamamoto and Momiyama described in 2005 the use of chiral carboxylic acids in asymmetric nitroso aldol reactions of achiral enamines **I.132** (**Scheme I.47**).[123] In this case, the conformational rigidity of the catalyst **(*S*)-I.201** might be due to the presence of an internal hydrogen bond between the carboxylic acid moiety and the oxygen lone pair of the hydroxyl group, allowing good selectivity.



Scheme I.47 Asymmetric reaction using chiral carboxylic acids.

Other chiral carboxylic acids introduced by Maruoka in 2007, and consisting on two carboxylic acid functionalities and an axially chiral binaphthyl moiety **(*R*)-I.202**, also gave positive results in this field (**Figure I.9**). They applied this new class of chiral Brønsted acid catalyst to the asymmetric alkylation of diazo compounds with *N*-Boc imines.[124]

[123] N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.,* **2005**, *127*, 1080.

[124] T. Hashimoto, N. Uchiyama, K. Maruoka, *J. Am. Chem. Soc.*, **2007**, *130*, 14380.

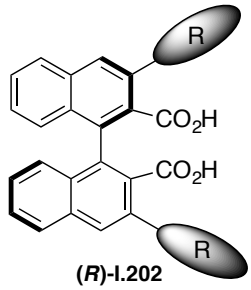
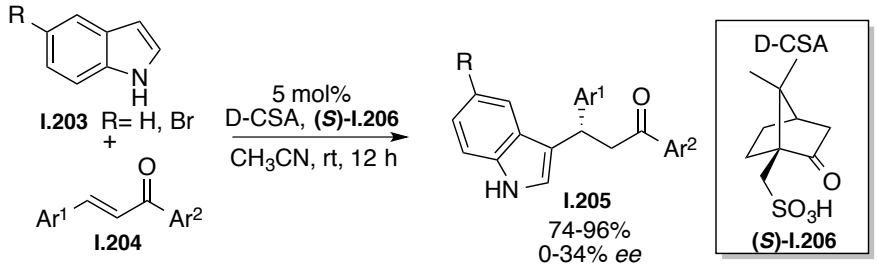


Figure I.9 Chiral binaphthyl-derived carboxylic acid.

In 2006, Xu and Xia and co-workers described an enantioselective Michael-type Friedel-Crafts addition of indoles **I.203** to chalcones **I.204** with moderate enantiomeric excess in a process catalysed by the commercially available D-camphorsulfonic acid (D-CSA) **(*S*)-I.206** (**Scheme I.48**). [125] Despite de low enantioselectivity achieved, this example represents the first report of the stereoselectivity of D-CSA **(*S*)-I.206** mediated transformations.



Scheme I.48 First stereoselective D-CSA-mediated transformation.

- **Chiral Disulfonimides**

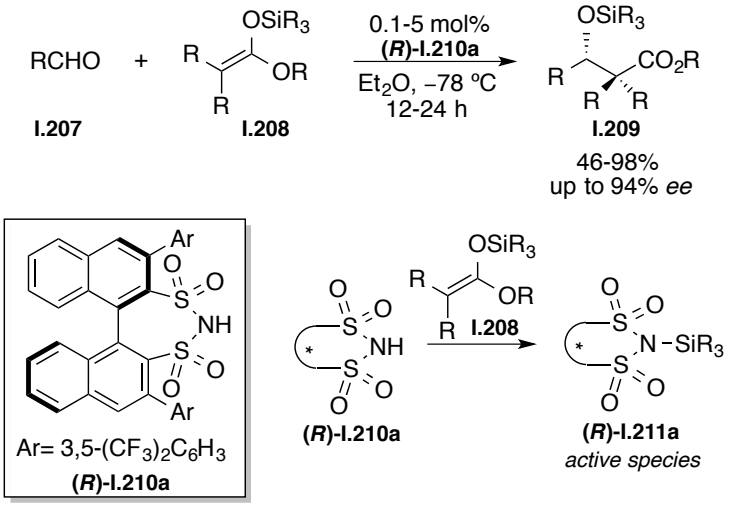
Asymmetric Mukaiyama aldol reactions, catalysed by Lewis acids and Lewis bases have been widely described in the literature. [126] However, only a few examples of chiral Brønsted acids catalysing this process have been reported. [127] In this context, List and co-workers developed in 2009 a chiral disulfonimide **(*R*)-I.210a** as a new strong Brønsted acid, proving that it successfully catalysed asymmetric Mukaiyama aldol reactions of unfunctionalised aldehydes **I.207** with

[125] W. Zhou, L.-W. Xu, L. Li, L. Yang, C.-G. Xia, *Eur. J. Org. Chem.*, **2006**, 5225.

[126] a) For a review of the Lewis acid catalysed Mukaiyama aldol reaction, see; E. Carreira, L. Kvaerno, *Classics in Stereoselective Synthesis*, Wiley–VCH, Weinheim Germany, **2009**. For a review of the Lewis base catalysed Mukaiyama aldol reaction, see; S. E. Denmark, S. Fujimori, S. in "*Modern Aldol Reactions*" ed. by Mahrwald, R. Wiley–VCH, Weinheim, Germany, **2004**, *2*, 229.

[127] a) W. Zhuang, T. B. Poulsen, K. A. Jørgensen, *Org. Biomol. Chem*., **2005**, *3*, 3284. b) J. D. McGilvra, A. K. Unni; K. Modi, V. H. Rawal, *Angew. Chem. Int. Ed*., **2006**, *45*, 6130. c) V. H. Gondi, K. Hagihara, V. H. Rawal, *Angew. Chem. Int. Ed*., **2009**, *48*, 776.

silyl acetals **I.208** as nucleophiles (**Scheme I.49**).[128] However, they reported that the active species in the process was the *N*-silyl imide **(*R*)-I.211a** acting then as a Lewis acid rather than a Brønsted acid itself.



Scheme I.49 Mukaiyama Aldol reaction reported by List using a chiral disulfonimide.

They also enhanced its topology, being different to the one of the phosphoric acids described before (**Figure I.10**). Thus, the C_2-symmetric binaphthyl disulfonimide in **(*R*)-I.210b** differs significantly to the corresponding pseudo-C_2-symmetric phosphoric acids such as **(*R*)-I.176d**. Analysis of the atom connectivity and three-dimensional structures of models as well revealed that the proton-carrying functional group is buried deeper in the chiral pocket of the disulfonimide **(*R*)-I.210b** if compared to the corresponding phosphate **(*R*)-I.176d**. This situation might lead to an increase on the stereochemical communication between catalyst and substrate in the reaction media.

Since their discovery, these chiral disulfonimides have recently been developed as powerful (pre)catalysts for a variety of reactions, especially in their application as precatalysts for reactions involving silicon-containing nucleophiles.[129]

[128] P. García–García, F. Lay, F.; P. García–García, C. Rabalakos, B. List, *Angew. Chem. Int. Ed*., **2009**, *48*, 4363.

[129] For a review of asymmetric catalysis using chiral, enantiopure disulfonimides, see: M. van Gemmeren, F. Lay, B. List, *Aldrichimica Acta*, **2014**, *47*, 3.

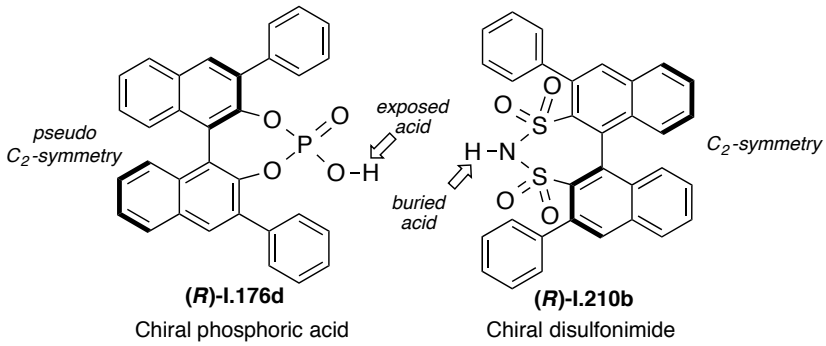
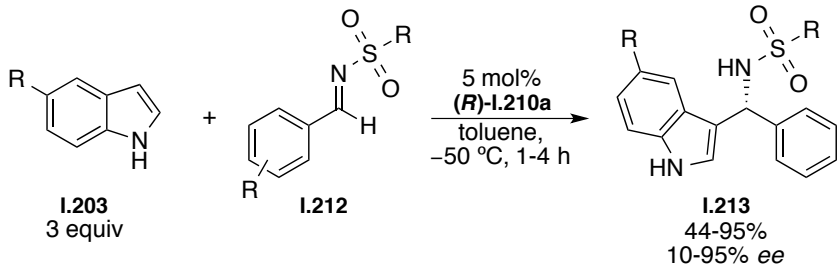


Figure I.10 Analysis of the structural topology differences of the phosphoric acid and disulfonimide motifs.

However, in the domain of Brønsted acid catalysis itself, chiral sulfonimides are still in their infancy. In 2011, Lee and co-workers reported the first use of these catalysts as Brønsted acids (**Scheme I.50**). Thus, an asymmetric Friedel-Crafts alkylation of indole derivatives **I.203** with imines **I.212** was described obtaining the products **I.213** in excellent yield and enantiomeric excess.[130]



Scheme I.50 Use of chiral disulfonimides as Brønsted acids reported by Lee.

In 2010, Berkessel and co-workers published the synthesis of a series of BINOL-derived catalysts containing a disulfurylimide moiety **I.147**.[131] These catalysts could be prepared from the corresponding BINOL derivatives in one step, giving the potential catalysts **I.147** in medium-to-good yields. Dughera, Ghigo, and co-workers have reported the five-step synthesis of **I.148**.[132] Although representing intriguing variants of the BINOL- derived disulfonimide motif, compounds **I.147** and **I.148** have not yet found application in highly stereoselective catalysis.

[130] L.-Y. Chen, H. He, W.-H. Chan, A. W. M. Lee, *J. Org. Chem.,* **2011,** *76*, 7141.

[131] A. Berkessel, P. Christ, N. Leconte, J.-M. Neudörfl, M. Schäfer, *Eur. J. Org. Chem.,* **2010**, 5165.

[132] a) M. Barbero, S. Bazzi, S. Cadamuro, L. Di Bari, S. Dughera, G. Ghigo, D. Padula, S. Tabasso, *Tetrahedron,* **2011,** *67*, 5789. b) M. Barbero, S. Cadamuro, S. Dughera, G. Ghigo, *Org. Biomol. Chem.,* **2012,** *10*, 4058.

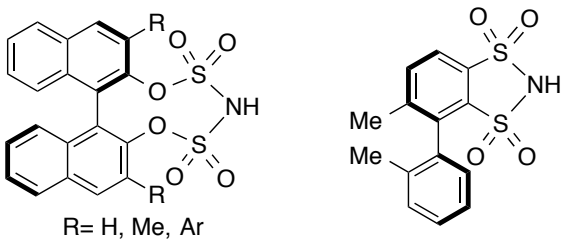


Figure I.11 Related potential catalysts.

- **Acidity Comparison of Chiral Brønstd Acids**

Computational studies on the acidic constants of chiral Brønsted acids in dimethyl sulfoxide where developed by Cheng and Li in 2014 showing the comparison of all the previously described catalysts altogether.[133,134] Then, this study should be helpful for enriching the catalyst library, developing new catalytic asymmetric reactions, and understanding mechanisms of the corresponding Brønsted acids catalysed processes. Some examples are shown in **Figure I.12**.

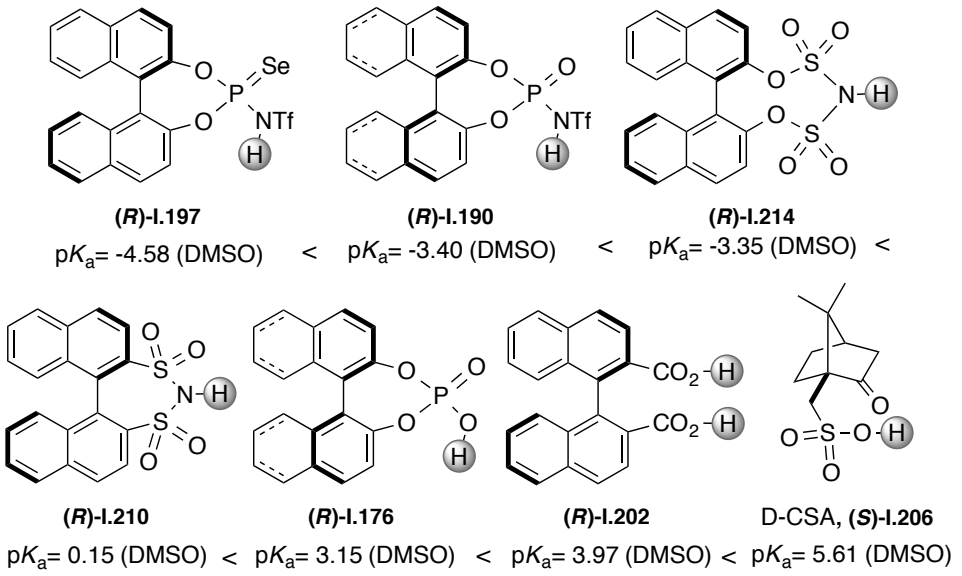


Figure I.12 Computational study on the acidic constants of chiral Brønsted acids in DMSO.

[133] C. Yang, X.-S. Xue, X. Li, J.-P. Cheng, *J. Org. Chem.*, **2014**, *79*, 4340.

[134] Other pK_a values of chiral Brønsted acids have also been previously reported in the literature, see: P. Chirst, A. G. Linsay, S. S. Vormittag, J.-M. Neudörfl, A. Berkessel, A C. O'Donoghue, *Chem. Eur. J.*, **2011**, *17*, 8524.

I.4.3 One-Pot Catalysis

One-pot catalysis allows many reactions to occur in a single flask, presenting a number of opportunities for synthetic organic chemist to improve chemical transformations. Thus, multiple catalysts operating concomitantly or sequentially, together with single catalysts performing multiple processes avoid often time, labour and yield losses associated with the isolation and purification of intermediates in multistep synthesis.

I.4.3.1 Classification

Some authors have done different classifications of one-pot catalysis in the last years. Hence, based upon the classification reported in 2012 by N. T. Patil and co-workers,[135] the different types of one-pot catalysis will be briefly described in the next sections (**Figure I.13**). These cascade processes can be promoted by a single catalyst (self-relay one-pot catalysis) or by a combination of different catalysts (cooperative, orthogonal-relay and sequential one-pot catalysis).

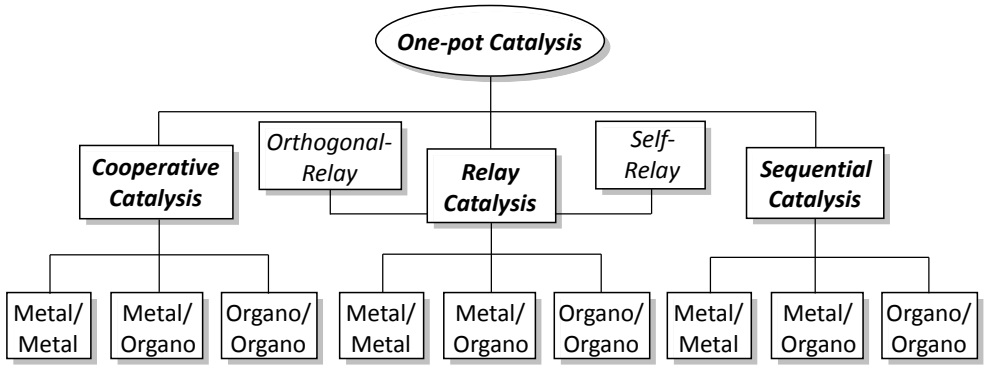


Figure I.13 One-pot catalysis classification.

- **Cooperative Catalysis**

In cooperative or synergistic catalysis two or more catalysts present at the onset of a reaction simultaneously and selectively activate and couple two substrates. The use of a single catalyst alone does not give the desired compound. While a catalyst works to lower the energy of reaction overall, a reaction using cooperative catalysts work together to increase the energy level of HOMO of one of the molecules and lower the LUMO of the other one (**Figure I.14**, **eq A**).[136]

[135] N. T. Patil, V. S. Shinde, B. Gajula, *Org. Biomol. Chem.*, **2012**, *10*, 211.

[136] A. E. Allen, D. W. C. MacMillan, *Chem. Sci.,* **2012***, 3,* 633.

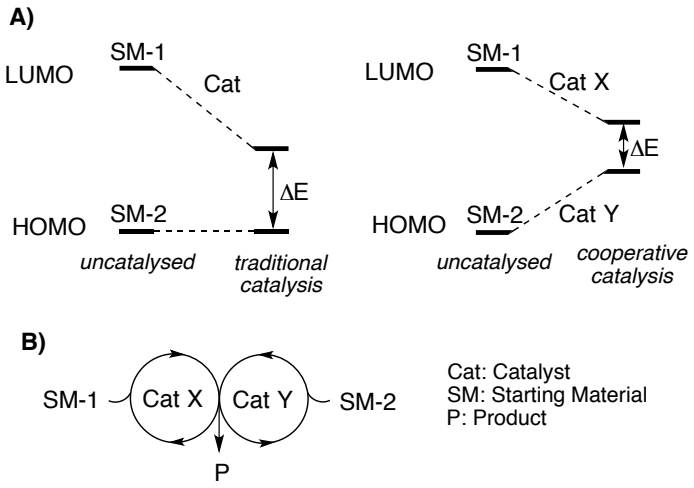
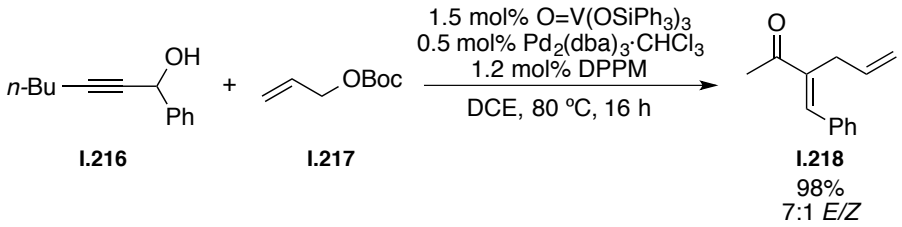


Figure I.14 Cooperative catalysis.

Thus, **Cat X** will activate one of the starting materials, **SM-1**, lowering the energy level of the LUMO for instance, and **Cat Y** will activate the other starting material, **SM-2**, increasing the energy level of the HOMO. If they are appropriately selected, these activated species can rapidly couple (**P**), enabling in many cases chemical reactions that are impossible or inefficient using traditional mono-catalytic methods (**Figure I.14**, **eq B**).

For instance, as a particular example of cooperative metal/metal catalysis, in 2011 B. M. Trost and co-workers established a novel cooperative catalytic system that combined a vanadium-catalysed 1,3-transposition of propargylic alcohols **I.216** (Meyer-Shuster rearrangement) and a palladium-catalysed alkylation of allylic carbonates **I.217** (**Scheme I.51**) in a process that selectively couples two highly reactive catalytic intermediates.[137] It generates a variety of α-allylated α,β-unsaturated ketones, which were not readily accessible by other methodologies. Notably, this cooperative catalysis (also known as dual catalysis) was achieved using low catalyst loadings (1.0 mol % [Pd], 1.5 mol % [V]) and giving good to excellent yields (up to 98%) of the desired products.

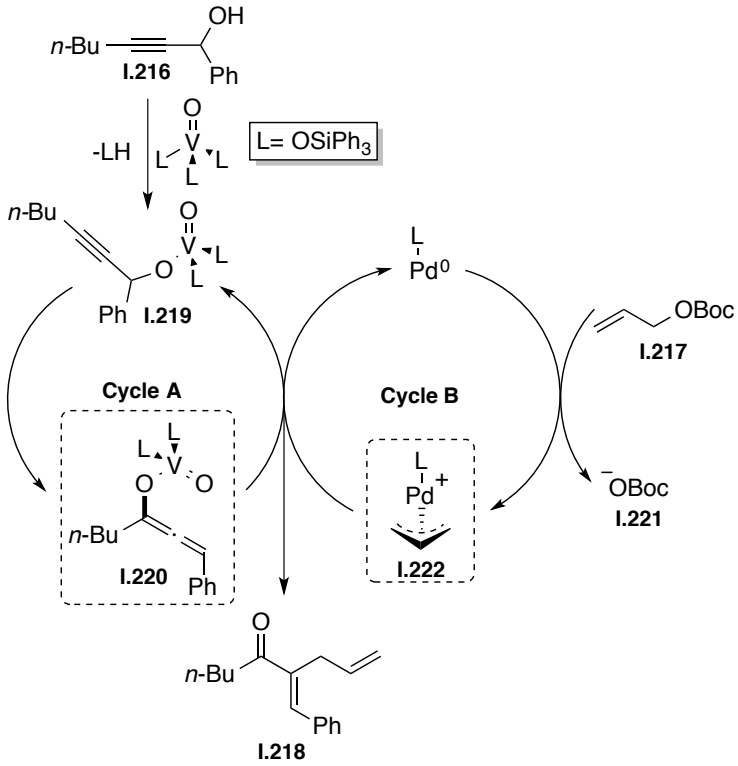


I.216 **I.217** **I.218**
98%
7:1 *E/Z*

Scheme I.51 Cooperative catalysis developed by B. M. Trost.

[137] B. M. Trost, X. Luan, *J. Am. Chem. Soc.*, **2011**, *133*, 1706.

The proposed mechanism it outlined in **Scheme I.52**. Thus, to enter the catalytic cycle A, the vanadium catalyst undergoes transesterification with the propargylic alcohol **I.216** to generate vanadium ester **I.219**. The ester **I.219** affords the vanadium-allenoate **I.220** via 1,3-transposition. Subsequently, in a cooperative catalysis manifold, the reactive allenoate intermediate **I.220** can be intercepted by the π-allyl-palladium intermediate **I.222** that is generated in the parallel catalytic cycle B to give the desired product **I.218**.



Scheme I.52 Proposed catalytic cycle: cooperative catalysis.

- **Relay Catalysis**

In relay catalysis one or more catalysts present at the onset of the reaction do not share the catalytic cycle. Thus, a set of reactions is catalysed independently by one single or two different catalysts in a consecutive manner. As shown in **Figure I.15**, the starting materials, **SM-1** and **SM-2**, first react by the presence of **Cat X** to form an intermediate **IM** in the first catalytic cycle. Subsequently, this intermediate **IM** is converted in the final product **P** by another independent catalytic cycle promoted by **Cat Y**. This type of catalysis is also subdivided in two different categories:

- ***Self-Relay Catalysis*:** One single catalyst, either metal or organocatalyst catalyses both processes in a consecutive manner.
- ***Orthogonal-Relay Catalysis*:** Different catalysts are employed and therefore each one will catalysed one of the catalytic cycles independently but in a consecutive manner. They must be present from the onset of the reaction, which makes the difference between this type of catalysis and sequential catalysis.

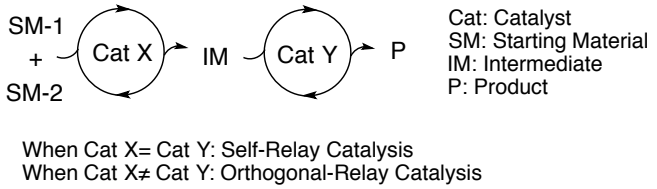
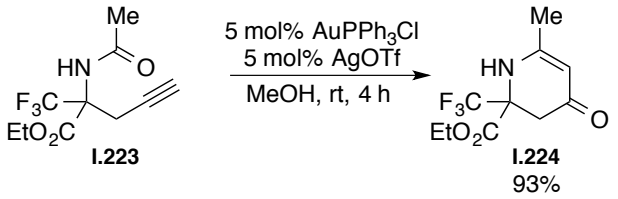


Figure I.15 Relay catalysis.

An example of a self-relay catalytic process due to S. Fustero and C. del Pozo is shown in **Scheme I.53**. Interestingly, this process that takes advantage of and unifies the σ- and π-Lewis acid properties of gold salts allows the synthesis of dihydropyridones **I.224**. The process is believed to proceed through a carbonyl addition/nucleophilic addition/Petasis–Ferrier rearrangement cascade reaction catalysed by the *in situ* genetated $AuPPh_3OTf$.[138]

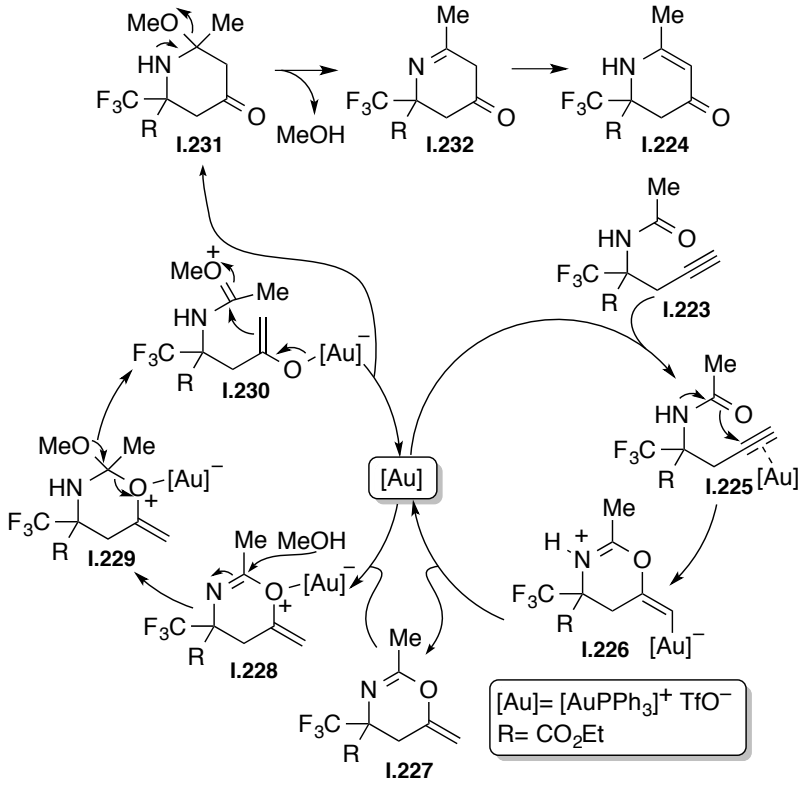


Scheme I.53 Example of self-relay catalysis reported by Fustero and del Pozo.

A plausible mechanism is depicted in **Scheme I.54**. Initially, the carbon-carbon triple bond of amide **I.223** is coordinated to the gold(I) species favouring the addition of the carbonyl group and affording intermediate **I.226**. Proto-deauration process renders oxazine **I.227**. The next step is the coordination of the gold(I) salt with the oxygen atom of the imidate functionality affording **I.228**, which activates it to the addition of an external nucleophile. When the nucleophile is methanol, the mixed acetal **I.229** formed undergoes a gold-catalysed Petasis-Ferrier rearrangement. Thus, the acetal moiety generates the oxonium ion **I.230** via ring-opening, which cyclises again into pyridine **I.231** regenerating the catalytic

[138] S. Fustero, J. Miró, María Sánchez-Roselló, C. del Pozo, *Chem. Eur. J.*, **2014**, *20*, 14126.

species. Methanol elimination and further isomerisation of the double bond of **I.232** gives rise to dihydropyridone **I.224**. [139]



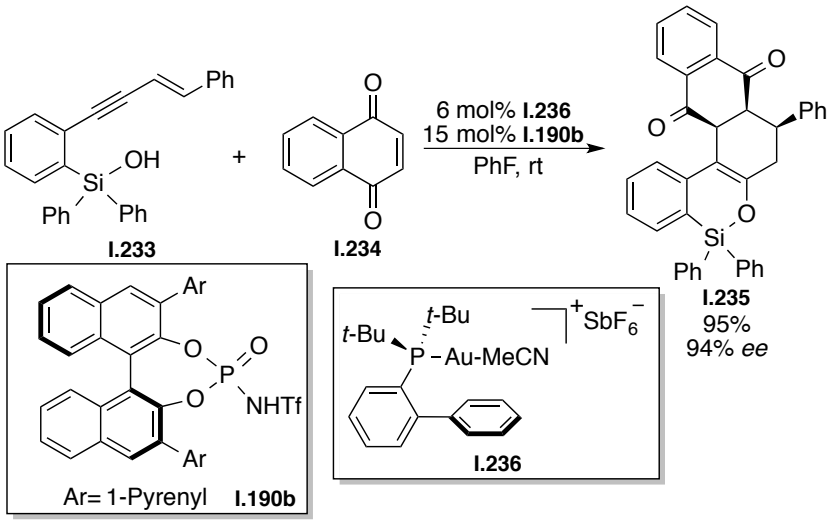
Scheme I.54 Proposed catalytic cycle: self-relay catalysis.

On the other side, a clear example of an orthogonal-relay catalytic process is the one reported by Gong and co-workers in 2012 involving an intramolecular hydrosiloxylation/Diels-Alder reaction of enynyl silanols **I.233** with quinones **I.234** to provide highly enantioenriched polycyclic compounds **I.235** (**Scheme I.55**).[140] This reaction is promoted by a metal/organo multicatalytic system that consists on a Au(I) catalytic species **I.236** on the one hand and a chiral Brønsted acid **(*R*)-I.190b** on the other one. The combination of catalysts from different disciplines, was first introduced by Krische and co-workers in 2003.[141] Since then, it has attracted increasing attention of the synthetic community in the last decade allowing unprecedented transformations not possible by the use of any catalyst alone. Therefore, synthetic methods are much more economical and practical.

[139] For more examples of self-relay catalysis, see: N. Shindoh, Y. Takemoto, K. Takasu, *Chem. Eur. J.*, **2009**, *15*, 12168.

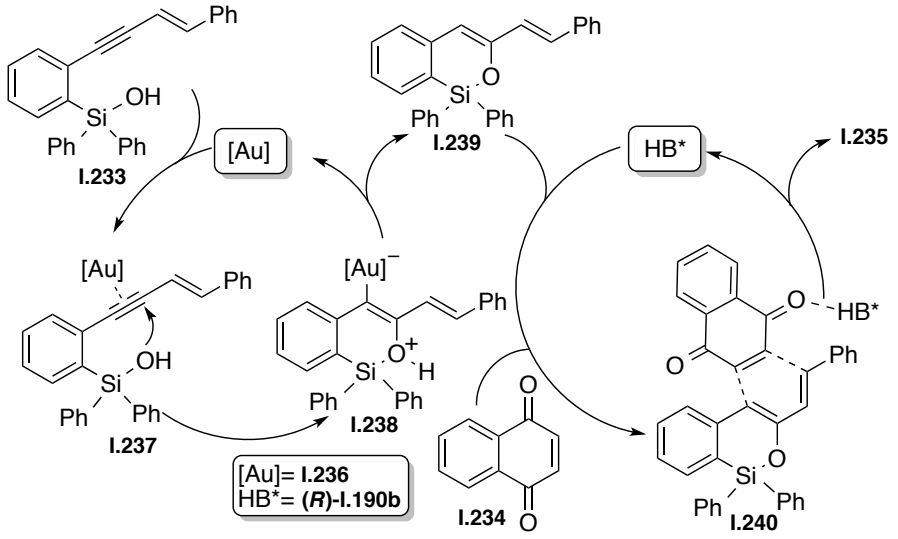
[140] Z.-Y. Han, D.-F. Chen, Y.-Y. Wang, R. Guo, P.-S. Wang, C. Wang, L.-Z. Gong, *J. Am. Chem. Soc.*, **2012**, *134*, 6532.

[141] B. G. Jellerichs, J.-R. Kong, M. J. Krische, *J. Am. Chem. Soc.*, **2003**, *125*, 7758.



Scheme I.55 Example of orthogonal-relay catalysis reported by Gong.

The proposed mechanism in this case is outlined in **Scheme I.56**. Thus, the enynyl silanol **I.223** is first coordinated to the gold(I) species via carbophilic π-activation. An intramolecular hydroalkoxylation process affords the diene intermediate **I.239** regenerating the metallic catalytic species. This intermediate **I.239** subsequently enters the second catalytic cycle where an asymmetric Diels-Alder reaction takes place, releasing the desired polycyclic compound **I.235** and regenerating the Brønsted acid catalyst **(*R*)-I.190b**.



Scheme I.56 Proposed catalytic cycle: orthogonal-relay catalysis.

- **Sequential Catalysis**

Finally, in sequential catalysis different catalysts catalyse a set of reactions in a stepwise manner in one-pot. As previously mentioned, its main difference with orthogonal-relay catalysis is that in this case the addition of the second catalyst (**Cat Y**) during the course of the reaction is necessary to avoid compatibility issues (**Figure I.16**). Thus, in the first catalytic cycle, promoted by **Cat X**, both starting materials **SM-1** and **SM-2** are activated to generate an intermediate **IM**. After completion of this first catalytic cycle, the second catalyst **Cat Y** is added, promoting the second process and affording the product of the reaction **P**.

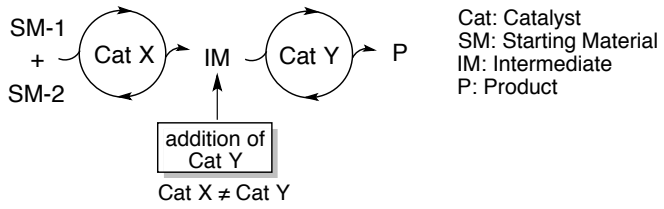
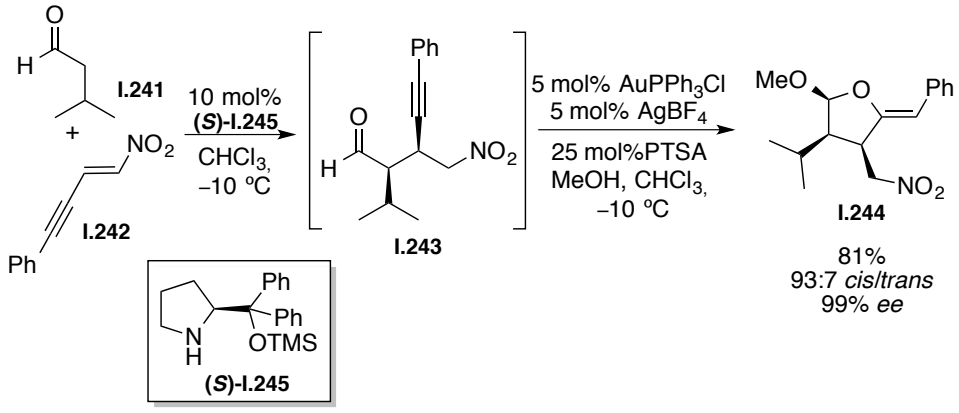


Figure I.16 Sequential catalysis.

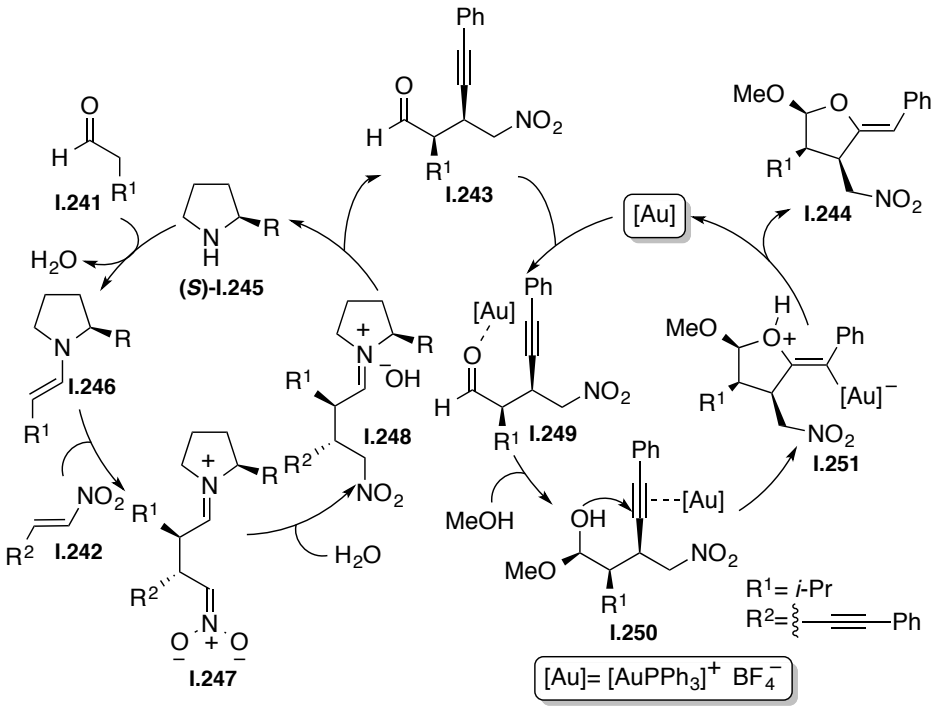
In 2009, Alexakis and co-workers reported a one-pot process consisting on an enantioselective organocatalytic Michael addition to nitroenynes **I.242** and a subsequent gold-catalysed acetalisation/cyclisation of the intermediate **I.243** *in situ* genetated (**Scheme I.57**). [142] Therefore, this sequence leads to the formation of nitro-substituted tetrahydrofuranyl ethers **I.244** with high diastereo- and enantioselectivities, enabling isolation of the products in higher yields relative to those for the step-wise process.



Scheme I.57 Sequential catalysis reported by A. Alexakis.

[142] S. Belot, K. A. Vogt, C. Besnard, N. Krause, A. Alexakis, *Angew. Chem. Int. Ed.*, **2009**, *48*, 8923.

In this particular example, the proposed mechanism (**Scheme I.58**) consists on the formation of an enamine **I.246** by condensation of the chiral amine **(*S*)-I.245** and the aldehyde **I.241**. The enamine **I.246** adds to the nitro alkene **I.242** to form the zwitterionic intermediate **I.247**. Protonation of the nitronate C-atom is followed by hydrolysis of the iminium ion **I.248** to yield the Michael product **I.243** with regeneration of the chiral amine **(*S*)-I.245**. Then, after the addition of the rest of the reactants, it is assumed that the second reaction is initiated by the formation of the cationic gold catalyst, $[AuPPh_3]BF_4$, which acts as an oxophilic Lewis acid to catalyse the acetalisation reaction of the aldehyde **I.241** thorugh the activated intermediate **I.249**. This step enables the generation of the corresponding hemiacetal **I.250**. Subsequently, this example shows again the efficiency of gold catalysts to activate alkynes by forming π-complexes, and the triple bond of **I.250** is activated towards the attack by the oxygen atom, leading to the tetrahydrofuran **I.251** which then undergoes protodemetalation, because to afford the corresponding tetrahydrofuranyl ether **I.244**.[143]



Scheme I.58 Proposed catalytic cycle: sequential catalysis.

[143] For more examples of the different types of catalysis, see: H. Pellisier, *Tetrahedron*, **2013**, *69*, 7171.

I.4.3.2 Multicomponent Reactions in One-pot Catalysis

In the previous sections it has been shown how one-pot catalysis presents new opportunities for synthetic organic chemist to improve chemical transformations avoiding time, labour and yield losses associated with the isolation and purification of intermediates in multistep synthesis.

Nowadays, a big challenge in the context of catalysis is to achieve the selective coupling of several reagents (multicomponent reactions, MCRs) by the action of one or more catalysts performing several reactions (one-pot catalysis).

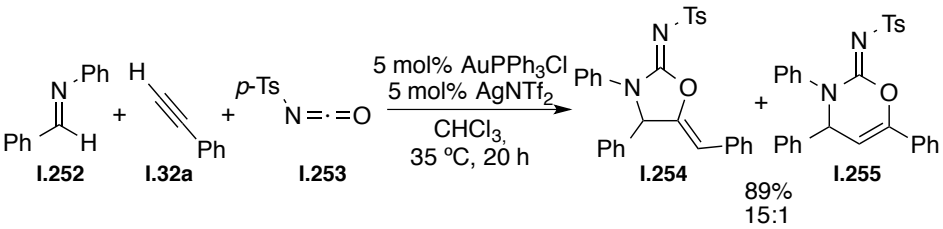
A multicomponent reaction can be defined as a process in which three or more different starting materials react together to yield ideally a major product that retains the majority of the atoms of the starting materials. These processes inherently lead to an increase in molecular diversity, offering significant advantages over uni- and bimolecular reactions.[144]

In addition to a purist point of view where all the reactants have to be present from the very beginning of the process, nowadays some variations are widely accepted, which are called one-pot multicomponent reactions. Thus, they can also be sequential one-pot multicomponent reactions, involving the sequential addition of reagents in a well-defined order without changing the reaction conditions; and consecutive one-pot multicomponent reactions, where those chemicals are added but conditions are changed stepwise in a single vessel.

An interesting example of a one-pot catalytic multicomponent reaction reported by F. D. Toste in 2011 is shown in **Scheme I.59**. This three-component reaction was used to prepare cyclic carbamimidates **I.254** from imines **I.252**, terminal alkynes **I.32a**, and *p*-toluensulfonylisocyanates **I.253** (multicomponent reaction). The process is catalysed by a Au(I) complex and interestingly, this catalyst promotes two different processes (self-relay one-pot catalysis).[145,]

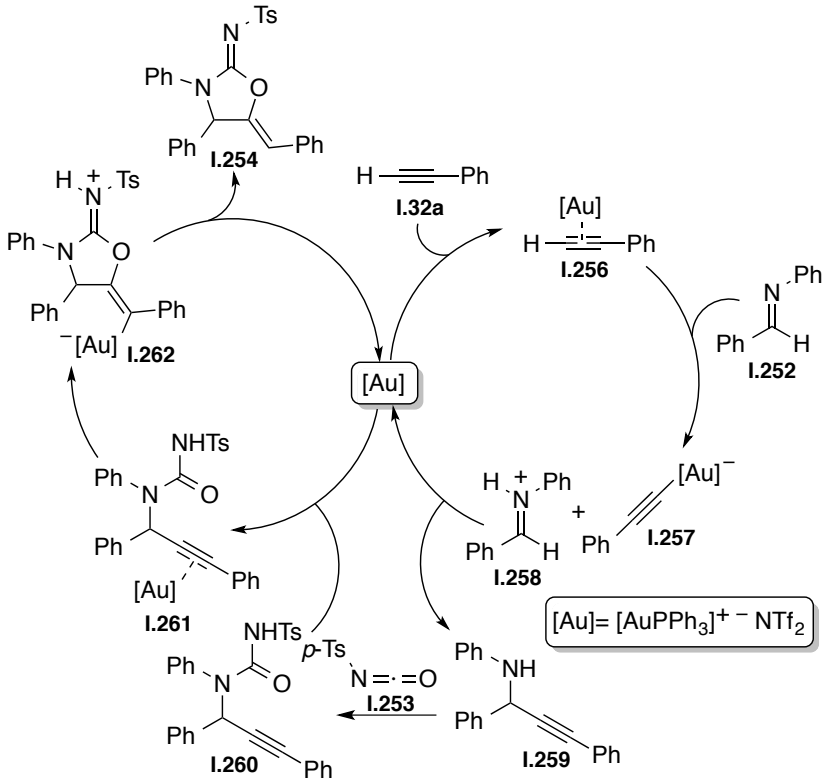
[144] a) J. Zhu, H. Bienayme, *Multicomponent Reactions*; Wiley-VCH: Weinheim, **2005**. b) H. Eckert From multicomponent-reactions (MCRs) towards multi-function-component-reactions, (MFCRs). *Heterocycles,* **2007**, *73*, 149.

[145] M. J. Campbell, F. D. Toste , *Chem. Sci.*, **2011**, *2*, 1369.



Scheme I.59 Self-relay catalysis developed by F. D. Toste.

In the proposed mechanism (**Scheme I.60**), initial coordination of alkyne **I.32a** to cationic gold species produces the alkyne π-complex **I.256** with acidification of the acetylenic hydrogen atom. Then, deprotonation by imine **I.252** affords the electrophilic iminium **I.258** with concurrent production of the Au(I)-acetylide **I.257**. An addition reaction produces propargylamine **I.259** regenerating the gold cationic species. Amine **I.259** is trapped with isocyanate **I.253** to generate the acyclic urea **I.260**. The alkyne motif of **I.260** coordinates to the metallic species to form the second alkyne π-complex **I.261**. 5-*Exo*-dig cyclisation by nucleophilic attack of the urea oxygen forms the vinyl gold carbamimidinium ion **I.262**, which undergoes proton transfer to release the product **I.254** and regenerate the Au(I) catalyst.



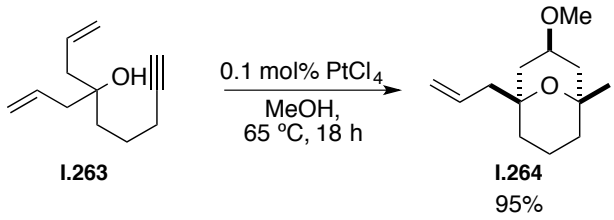
Scheme I.60 Multicomponent reaction developed by Toste.

I.4.3.3 Recent Contributions from our Group

Our research group has been working in recent years in the production of architecturally complex molecules from simple starting materials. In this sense, as previously described, cascade and multicomponent reactions in which multiple processes are combined into one synthetic operation offer a wide range of possibilities. Additionally, the development of these processes with a high degree of regio- and stereoselectivity has been one of our major challenges. Next, some relevant examples of relay catalysis and multicomponent reactions recently developed in our group will be highlighted.[146]

- **Self-Relay Catalysis in our Group**

In 2006 our research group described a cycloisomerisation/Prins-type cascade reaction catalysed by $PtCl_4$ (**Scheme I.61**).[147] In this process, functionalised bicyclic ethers **I.264** were easily obtained from simple allyl-substituted 5-hexyn-1-ol derivatives **I.263** in a process were the solvent serves as an external nucleophile trapping one of the cationic species formed as intermediate of the reaction.



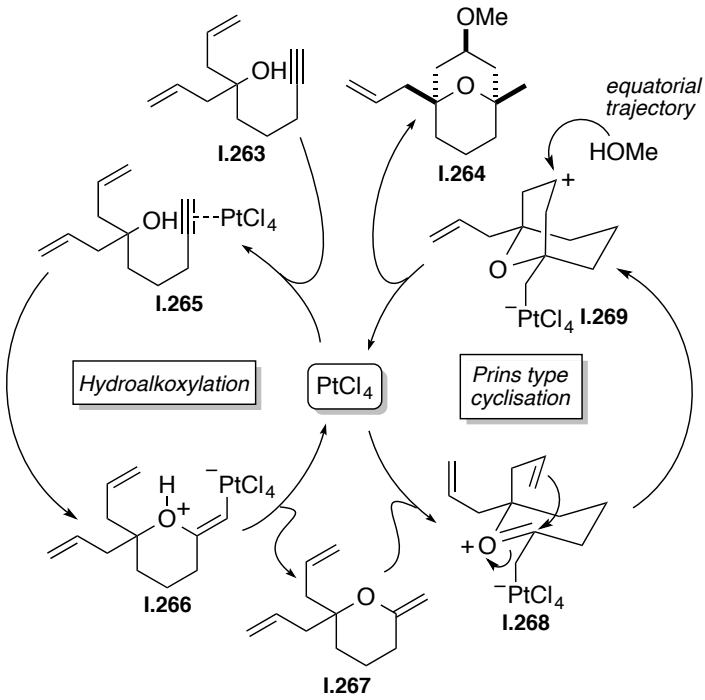
Scheme I.61 Platinum-catalysed cascade process (hydroalkoxylation/Prins-type cyclisation) of alkynol derivatives.

This reaction proceeds through a self-relay catalytic mechanism where the platinum salt promotes both reactions (cycloisomerisation/Prins-type cyclisation) (**Scheme I.62**). Thus, the reaction is initiated by the coordination of the platinum complex to the alkynol moiety of **I.263** to form the activated intermediate **I.265**. Subsequent intramolecular addition of the hydroxy group to the internal carbon atom of the triple bond generates **I.266**, which after a protodemetallation process affords the *exo*-cyclic enol ether **I.267** and regenerates the catalytic species. At this point, the second part of the self-relay mechanism, the Prins-type cyclisation, is initiated. Thus, after an initial coordination of the catalyst to the double bond of the enol ether, the oxonium intermediate **I.268** is formed. The following cyclisation step is believed to proceed through a chair-like transition state in which the axial

[146] For a review, see: F. Rodríguez, F. J. Fañanás, *Synlett,* **2013**, *24*, 1757.

[147] J. Barluenga, A. Diéguez, A. Fernández, F. Rodríguez, F. J. Fañanás, *Angew. Chem. Int. Ed.* **2006**, *45*, 2091.

allyl moiety reacts to form the oxocarbenium ion **I.269**. Further nucleophilic trapping from an equatorial trajectory by a molecule of methanol accounts for the formation of **I.264** and the regeneration of the platinum complex after a final proto-demetallation step.



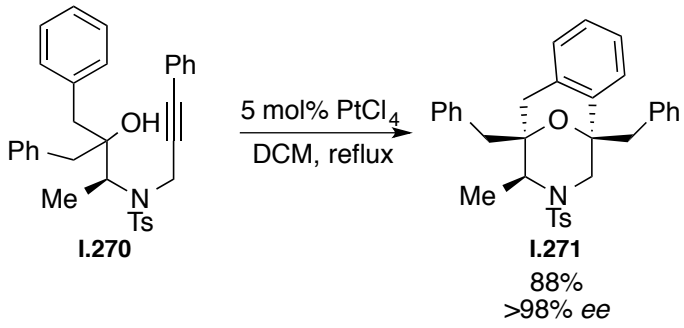
Scheme I.62 Mechanistic proposal: self-relay catalysis.

Moreover, our group has developed other self-relay cascade reactions incorporating different external nucleophiles in this type of processes where just one catalyst is required to promote both catalytic cycles. Apart from alcohols, carboxylic acids were also used as external nucleophiles. Nitrogen-containing heterocycles were also successfully obtained when acetonitrile was the selected solvent and a chlorine atom was incorporated when the reaction was performed in dichloromethane. Regarding the metallic species, these processes are promoted by gold(I), gold(III), platinum(II), or platinum(IV) catalysts.[148]

A logical extension of this process was to replace the alkene moiety of the starting materials by an aryl group. This aryl group reacted efficiently with the initially formed *exo*-cyclic enol ether to give benzo-fused cyclic ethers through a hydroalkoxylation/hydroarylation cascade reaction (**Scheme I.63**).

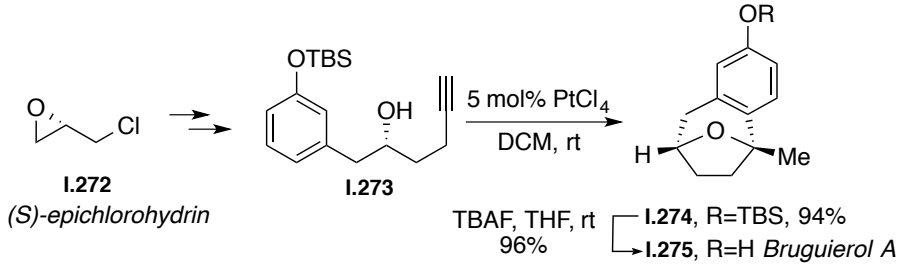
[148] J. Barluenga, A. Fernández, A. Diéguez, F. Rodríguez, F. J. Fañanás, *Chem. Eur. J.*, **2009**, *15*, 11660.

Therefore, following this strategy a series of benzo-fused cyclic ethers were easily synthesised in high yield from alkynol derivatives in our group. These processes were completely diastereoselective, allowing the synthesis of enantiopure products when starting from enantiopure alkynol derivatives. A selected example is shown in **Scheme I.63**, where the synthesis of enantionerically pure bicycle[3.3.1]nonanes **I.271** is achieved with a high degree of diversity in a platinum-catalysed cascade process.[149]



Scheme I.63 Platinum-catalysed cascade process (hydroalkoxylation/hydroarylation) of alkynol derivatives.

A related platinum-catalysed hydroalkoxylation/hydroarylation reaction was applied in the key step of a new synthesis of bruguierol A (**Scheme I.64**).[150]



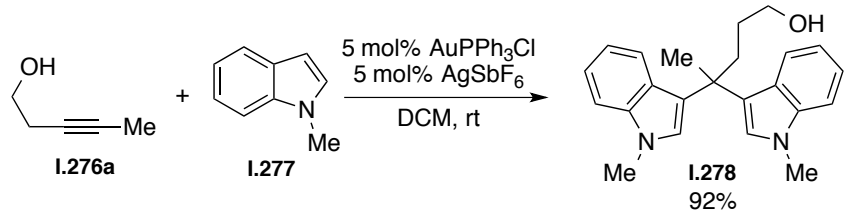
Scheme I.64 Total synthesis of Bruguierol A.

The totally intramolecular hydroalkoxylation/hydroarylation process above commented was further extended to an intermolecular version by treating a simple alkynol derivative with an aromatic compound in the presence of an appropriate catalyst. Thus, when the alkynol derivative **I.276a** was treated with 1-methyl-1-*H*-indol **I.277** in the presence of 5 mol% of $AuPPh_3Cl$ and 5 mol% of

[149] J. Barluenga, A. Fernández, A. Satrústegui, A. Diéguez, F. Rodríguez, F. J. Fañanás, *Chem. Eur. J.,* **2008**, *14*, 4153.

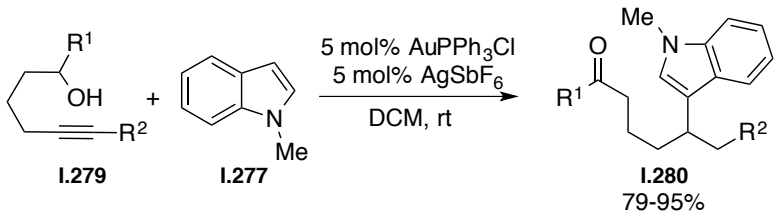
[150] F. J. Fañanás, A. Fernández, D. Çevik, F. Rodríguez, *J. Org. Chem.,* **2009**, *74*, 932.

$AgSbF_6$, the corresponding bis(indolyl)alkane derivative **I.278** was observed in high yield (**Scheme I.65**). [151]



Scheme I.65 Intermolecular hydroalkoxylation/hydroarylation: synthesis of bis(indolyl)alkane derivatives.

Particularly interesting results were observed when this reaction was performed using secondary hex-5-ynol derivatives **I.279**. In these case, the formation of products **I.280** instead of the expected bis(indolyl)alkane derivatives analogous to **I.278** was observed (**Scheme I.66**).[152]

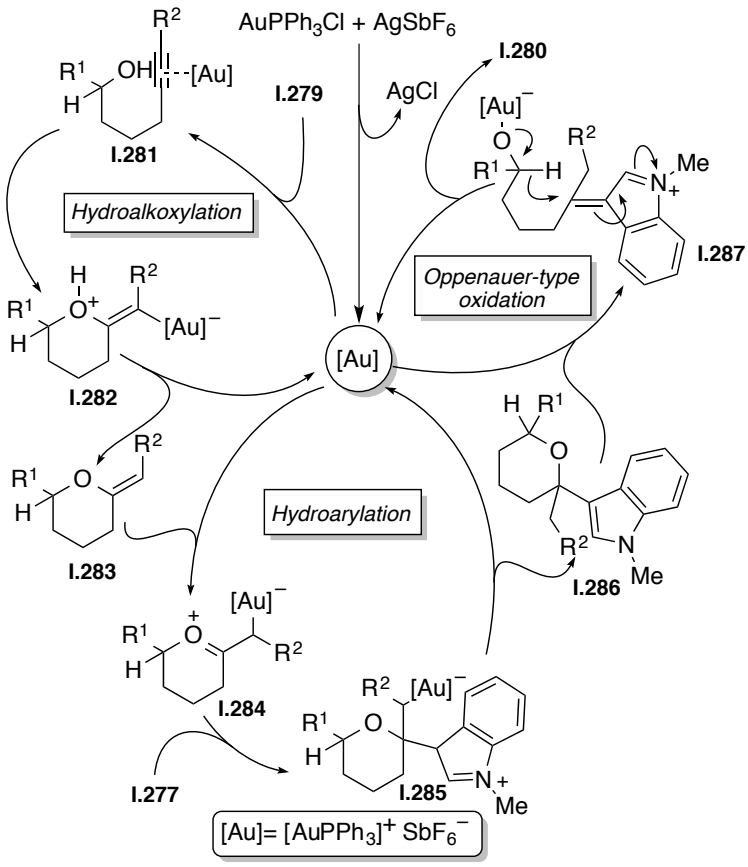


Scheme I.66 Synthesis of indole derivatives via hydroalkoxylation/hydroarylation/Oppenahuer-type oxidation cascade process.

The proposed mechanism was a self-relay process in which the gold(I) cationic complex promotes three different reactions: the hydroalkoxylation of alkynol derivatives **I.279** to give *exo*-cyclic enol ethers **I.283**, the hydroarylation of the carbon-carbon double bond of these intermediates to give new species **I.286**, and finally, an unusual intramolecular Oppenauer-type oxidation reaction to afford the final products **I.280** (**Scheme I.67**).

[151] a) J. Barluenga, A. Fernández, F. Rodríguez, F. J. Fañanás, *J. Organomet. Chem.* **2009**, *694*, 546. b) For related work, see: 1) C. Ferrer, C. H. M. Amijs, A. Echavarren, *Chem. Eur. J.,* **2007**, *13*, 1358. 2) S. Bhuvaneswari, M. Jeganmohan, C.-H. Cheng, *Chem. Eur. J.,* **2007**, *13*, 8285.

[152] J. Barluenga, A. Fernández, F. Rodríguez, F. J. Fañanás, *Chem. Eur. J.,* **2009**, *15*, 8121.



Scheme I.67 Mechanistic proposal: self-relay catalysis.

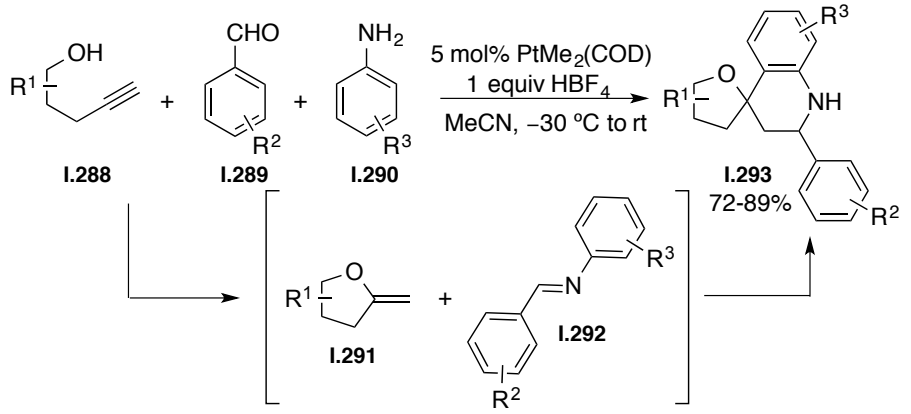
- **Orthogonal-Relay Catalysis in our Group**

Our group has also developed multicomponent cascade reactions in the context of orthogonal-relay catalysis, combining transition-metal catalysed processes with Brønsted acid catalysis in one-pot.

In 2008, the synthesis of interesting spiro[furan-2,4'-quinoline] derivatives **I.293** was efficiently achieved through a multicomponent and multicatalytic process promoted by a binary system consisting in a platinum(II)complex and a Brønsted acid (**Scheme I.68**).[153]

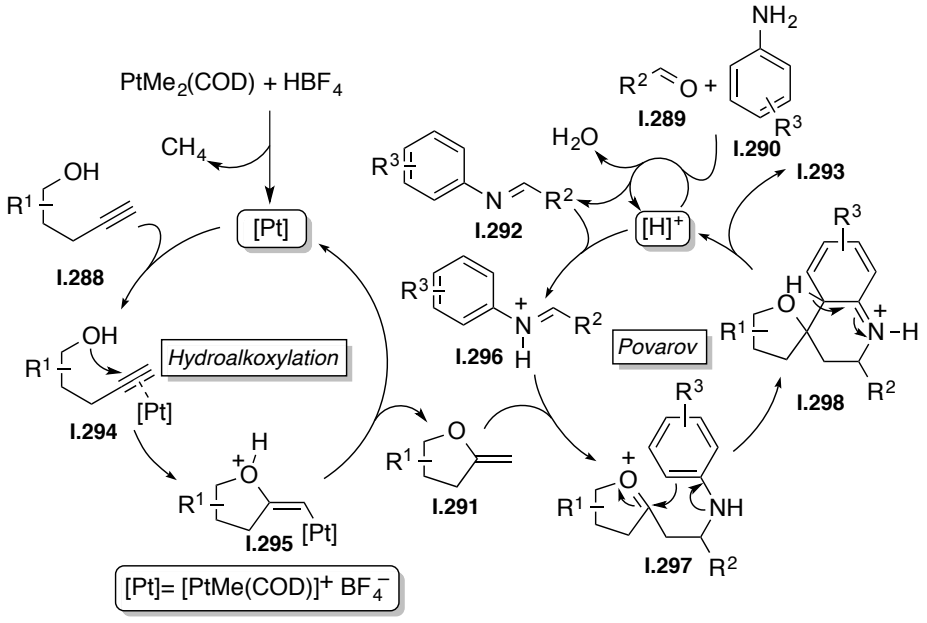
Interestingly, in this process, on the one hand, the *N*-aryl-imine **I.292** was *in situ* generated in the presence of the Brønsted acid via condensation of **I.289** and **I.290** and on the other hand, the *exo*-cyclic enol ether was also *in situ* generated via hydroalkoxylation reaction of pent-4-ynol derivatives **I.288**.

[153] J. Barluenga, A. Mendoza, F. Rodríguez, F. J. Fañanás, *Angew. Chem. Int. Ed.,* **2008**, *47*, 7044.



Scheme I.68 Multicomponent synthesis of spiro[furan-2,4'-quinoline] derivatives.

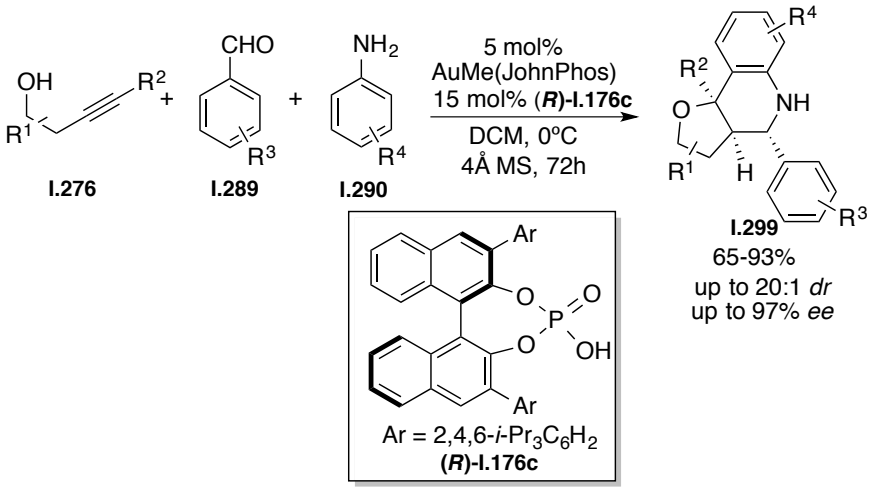
In this reaction, the Brønsted acid used, HBF_4, has a multiple role. First of all as previously mentioned, it promotes the condensation of the aldehyde **I.289** and the aniline **I.290** to give the *N*-aryl-imine **I.292**; then, the Povarov reaction between the exocyclic enol ether **I.291** and the *N*-arylimine **I.292** to give the final spiro[furan-2,4'-quinoline] derivative **I.293**. However, there is another very important role: the transformation of the precatalyst $PtMe_2(COD)$ into an active cationic platinum(II) complex by protonolysis. The orthogonal tandem catalytic mechanism is shown in **Scheme I.69**.



Scheme I.69 Mechanistic proposal: orthogonal-relay catalysis.

Thus, the reaction is initiated by coordination of the metal complex to the triple bond of the starting alkynol **I.288** to form intermediate **I.294**. Subsequent intramolecular addition of the hydroxyl group to the internal carbon atom of the triple bond generates **I.295**. Protodemetalation of **I.295** affords the *exo*-cyclic enol ether **I.291** and releases the catalytic species. Afterwards, this *exo*-cyclic enol ether **I.291** enters the second catalytic cycle where the protic acid is supposed to be the real catalytic species. Once the imine **I.292** if formed, further reaction with a proton renders the iminium salt **I.296**, which reacts with the preformed enol ether **I.291** to give the oxonium intermediate **I.297** through a Mannich-type process. Intramolecular nucleophilic addition of the electron-rich aromatic ring affording **I.298** followed by a rearomatisation step leads to the final products **I.293** and closes the second catalytic cycle as a proton is delivered in the rearomatisation reaction.

This methodology was also expanded to the use of butynol derivatives **I.276** in order to obtain furo[3,2-*c*]quinolines and, interestingly, an enantioselective version using a chiral catalyst was also achieved.[154] By the use of a multicatalytic system combining a metallic complex, AuMe(JohnPhos), to promote the cycloisomerisation of the butynol derivative **I.276** and a chiral phosphoric acid, (*R*)-**I.176c**, to promote the condensation of the aniline **I.290** with the aldehyde **I.289** and also the asymmetric Povarov reaction, the desired products **I.299** were obtained generally in high yield and with high enantioselectivity (**Scheme I.70**).



Scheme I.70 Enantioselective multicomponent synthesis of furo[3,2-*c*]quinoline derivatives.

[154] J. Calleja, A. B. González-Pérez, A. R. de Lera, R. Álvarez, F. J. Fañanás, F. Rodríguez, *Chem. Sci.,* **2014**, *5*, 996.

With this section concludes the General Introduction devoted to the field of catalysis in the context of organic synthesis.

In this context, the investigation developed and summarised in this dissertation was focused on the development of new multicatalytic cascade reactions and multicomponent processes towards the synthesis of interesting heterocyclic compounds.

This dissertation has been organised in two chapters:

In Chapter 1, new syntheses of pyrrolidine derivatives through novel one-pot orthogonal-relay cascade processes promoted by a binary catalytic system consisting in a platinum-based metallic complex and a Brønsted acid are described. This Chapter is also divided in two parts:

In Part A, the development of new cascade reactions of *N*-Boc protected alkynamine derivatives with alkenes and alkynes for the synthesis of pyrrolo[1,2-*c*][1,3]oxazin-1-one derivatives is described.

An extention of the previous reactions is described in Part B. Thus, the development of a new cascade reaction involving a double cycloisomerisation reaction of *N*-Boc alkynamine and alkynol derivatives followed by a formal heterodimerisation of the two *in situ* generated electron-rich alkenes is shown.

In Chapter 2, one-pot Brønsted acid catalysed multicomponent reactions of indolecarbaldehydes, anilines and electron-rich alkenes are described. In this case, the chapter has been divided into three parts:

In Part A, an alternative reaction pathway to the well-known Povarov reaction is described. Particularly, a new formal [3+2]-carbocyclisation reaction of the *in situ* formed indole-2-carbaldehyde imine derivatives and the electron-rich alkenes to give interesting cyclopenta[*b*]indoles has been developed.

In Part B, an enantioselective formal [3+2]-heterocyclisation reaction of *N*-unsubstituted indole-2-carbaldehyde imines and enol ethers promoted by a chiral disulfonimide to give pyrrolo[1,2-*a*]indole derivatives is shown.

Finally, the synthesis of pyrrolo[3,2,1-*ij*]quinoline derivatives through a multicomponent coupling reaction of indole-7-carbaldehydes, anilines and electron-rich alkenes is described in Part C. The new process supposes an unprecedented formal [4+2]-heterocyclisation of *in situ* formed indole-7-carbaldehyde imines and electron-rich alkenes.

Chapter 1

Synthesis of Pyrrolidine Derivatives by Platinum/Brønsted Acid Orthogonal Relay Catalytic Cascade Reactions

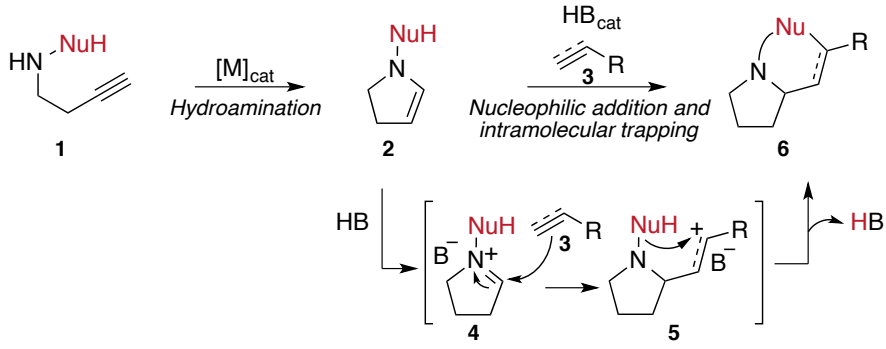
Part A

Cascade Reactions of N-Boc Protected Alkynamine Derivatives with Alkenes or Alkynes. Synthesis of Pyrrolo[1,2-c][1,3]oxazin-1-one Derivatives

1.A.1 Introduction and Objectives

As shown in the General Introduction of this thesis, our group has been working in recent years in the synthesis of architecturally complex molecules from simple starting materials through the development of new cascade processes involving an initial intramolecular hydroalkoxylation reaction of an alkyne (see Section I.4.3.3, General Introduction). In an attempt to go further in this field, it was decided to investigate on the development of new cascade reactions initiated by a metal-catalysed hydroamination reaction.

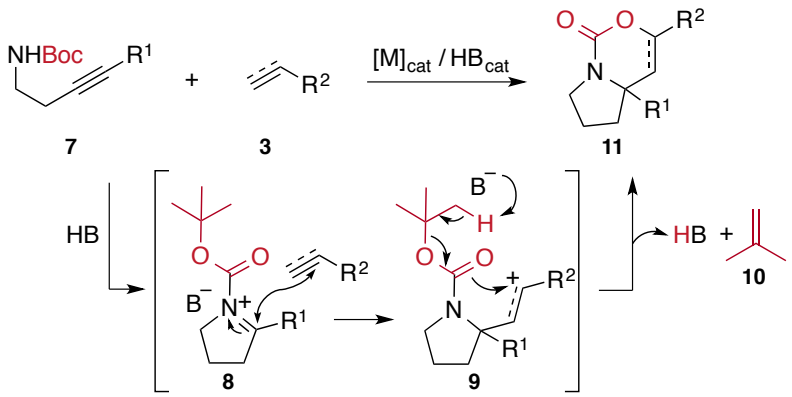
Particularly, it was thought that in the presence of a Brønsted acid (HB) the *in situ* generated cyclic enamine derivative **2** would form the electrophilic iminium species **4**, which could react with simple alkenes or alkynes to afford the cationic intermediate **5**. Afterwards, this cationic species **5** could be trapped by a nucleophile (NuH) appropriately installed on the nitrogen atom of the alkynamine derivative **1**. This final step would deliver interesting bicyclic compounds **6** and additionally it would release a molecule of the Brønsted acid rendering the global process catalytic not only with respect to the metallic species ([M]) but also to the protic acid (HB) (**Scheme 1.A.1**).



Scheme 1.A.1 Objective.

At this point, it was considered that the *tert*-butyloxycarbonyl (Boc) group could be an ideal nucleophilic counterpart (NuH) in our designed reaction because it is known that this group is able to trap cationic species through a process in which a molecule of isobutylene and a proton are released (**Scheme 1.A.2**).[155]

[155] C. Agami, F. Couty, *Tetrahedron*, **2002**, *58*, 2701.



Scheme 1.A.2 Boc as nucleophilic trapping group.

This reaction would led to the formation of interesting pyrrolidine derivatives (pyrrolo[1,2-*c*][1,3]oxazin-1-ones) **11** through a new cascade reaction catalysed by a metal/Brønsted acid binary system. In this context, it is important to remark that the pyrrolidine moiety is a privileged heterocyclic structural motif and it constitutes an essential nucleus of many biologically active natural products and pharmaceuticals.[156] Moreover, it exhibits an important role in the context of catalysis as many organocatalysts and ligands contain this structure.[157] Thus, the designed reaction could be a new easy way to afford these interesting molecules.

[156] a) J. Buckingham, K. H. Baggaley, A. D. Roberts, L. F. Szabó, in *Dictionary of Alkaloids*, 2nd ed., CRC press, Boca Raton, FL, **2009**. For some research on pharmaceutical uses of pyrrolidine derivatives, see: b) L. Anselm, D. W. Banner, J. Benz, K. G. Zbinden, J. Himber, H. Hilpert, W. Huber, B. Kuhn, J.-L. Mary, M. B. Otteneder, N. Panday, F. Ricklin, M. Stahl, S. Thomi, W. Haap, *Bioorg. Med. Chem. Lett.,* **2010**, *20*, 5313. b) P. Jablonski, K. Kawasaki, H. Knust, A. Limberg, M. Nettekoven, H. Ratni, C. Riemer, X. Wu (PCT Int. Appl.), WO 2009019163, **2009**; [*Chem. Abstr.* **2007**, *147*, 118261]. c) B. J. Backes, K. Longenecker, G. L. Hamilton, K. Stewart, C. Lai, H. Kopecka, T. W. von Geldern, D. J. Madar, Z. Pei, T. H. Lubben, B. A. Zinker, Z. Tian, S. J. Ballaron, M. A. Stashko, A. K. Mika, D. W. A. Beno, A. J. Kempf-Grote, C. Black-Schaefer, H. L. Sham, J. M. Trevillyan, *Bioorg. Med. Chem. Lett.,* **2007**, *17*, 2005.

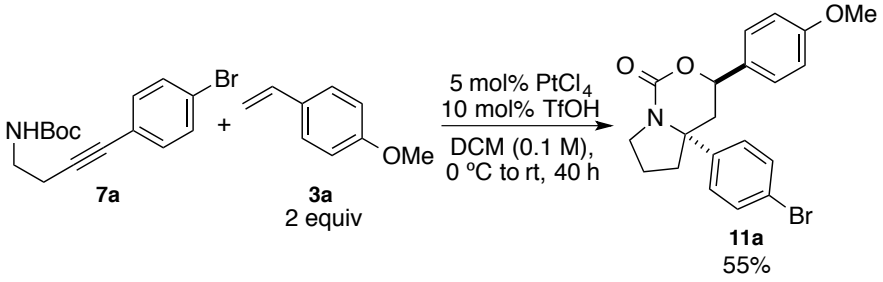
[157] *Privileged Chiral Ligands and Catalysts* (Ed: Q.-L. Zhou), WILEY-VCH, Weinheim, **2011**.

1.A.2 Results and Discussion

1.A.2.1 Reaction of *N*-Boc-Protected Alkynamine Derivatives with Simple Alkenes

1.A.2.1.1 Preliminary Studies

The proposed reaction was initially studied with alkynamine derivatives **7** and simple alkenes. Particularly, it was thought that relatively electron-rich styrene derivatives could be appropriate alkene counterparts. Moreover, regarding to the catalytic system, platinum(II) or platinum(IV)-derived metallic catalyst were selected because it is well known that they are highly efficient in hydroamination processes (see **Scheme I.23**, General Introduction). As the protic acid catalyst, triflic acid (TfOH) seemed appropriate to promote the formation of the desired electrophilic iminium intermediate **8**. Therefore, in an initial experiment *tert*-butyl [4-(4-bromophenyl)but-3-yn-1-yl]carbamate **7a** was reacted with 2 equivalents of 1-methoxy-4-vinylbenzene **3a** in the presence of 5 mol% of $PtCl_4$, 10 mol% of TfOH, in dichloromethane (0.1M) as solvent, from 0 °C to room temperature for 40 hours. Delightfully, under these reaction conditions the desired bicyclic product **11a** could be isolated in 55% yield and as single diastereoisomer (**Scheme 1.A.3**). It should be remarked that the hexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one derivative **11a** is generated through a cascade process where three new bonds and two stereogenic centres, being one of them quaternary, are stereoselectively formed.

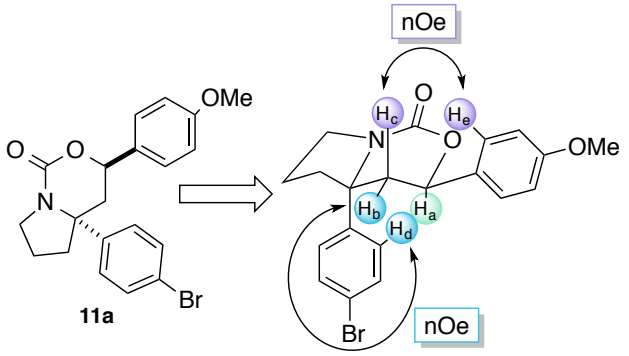


Scheme 1.A.3 Proof of concept.

1.A.2.1.2 Determination of Relative Configuration

The structure and relative configuration of the stereogenic centres of (3*R**,4a*R**)-4a-(4-bromophenyl)-3-(4-methoxyphenyl)hexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one **11a** were determined by one-dimensional and two-dimensional NMR experiments (**Figure 1.A.1**). The double doublet centred at 4.76 ppm (dd, *J*= 12.0 and 2.3 Hz) was assigned to $\mathbf{H_a}$. The double doublets centred at

2.59 (dd, *J*= 13.6 and 2.3 Hz) and 2.11 ppm (dd, *J*= 13.6 and 12.0 Hz) were assigned to $\mathbf{H_b}$ and $\mathbf{H_c}$, respectively. The value of the coupling constant between $\mathbf{H_a}$ and $\mathbf{H_b}$ (*J*= 2.3 Hz) on the one hand, and $\mathbf{H_a}$ and $\mathbf{H_c}$ (*J*= 13.6 Hz) on the other hand, enabled the assignment of a relative gauche disposition between $\mathbf{H_a}$ and $\mathbf{H_b}$ and an *anti* relationship between $\mathbf{H_a}$ and $\mathbf{H_c}$. All this indicates that the 4-methoxyphenyl substituent is placed in an equatorial position. Moreover, the cross-peak signals arising from protons close in space observed in the NOESY two-dimensional NMR experiment ($\mathbf{H_b}$ and $\mathbf{H_d}$ in blue, and $\mathbf{H_c}$ and $\mathbf{H_e}$ in purple, **Figure 1.A.1**) showed that the 4-methoxyphenyl substituent is placed in a *trans* disposition related to the 4-bromophenyl group.[158]



H_a, δ= 4.76 ppm (dd, *J*= 12.0 and 2.3 Hz)
H_b, δ= 2.59 ppm (dd, *J*= 13.6 and 2.3 Hz)
H_c, δ= 2.11 ppm (dd, *J*= 13.6 and 12.0 Hz)
H_d, δ= 7.22 ppm (d, *J*= 9.5 Hz)
H_e, δ= 7.18 ppm (d, *J*= 8.7 Hz)

$J_{a,b}$= 2.3 Hz
$J_{a,c}$= 13.6 Hz

Figure 1.A.1 Determination of the relative configuration of **11a** through ^{1}H–NMR and NOESY experiments.

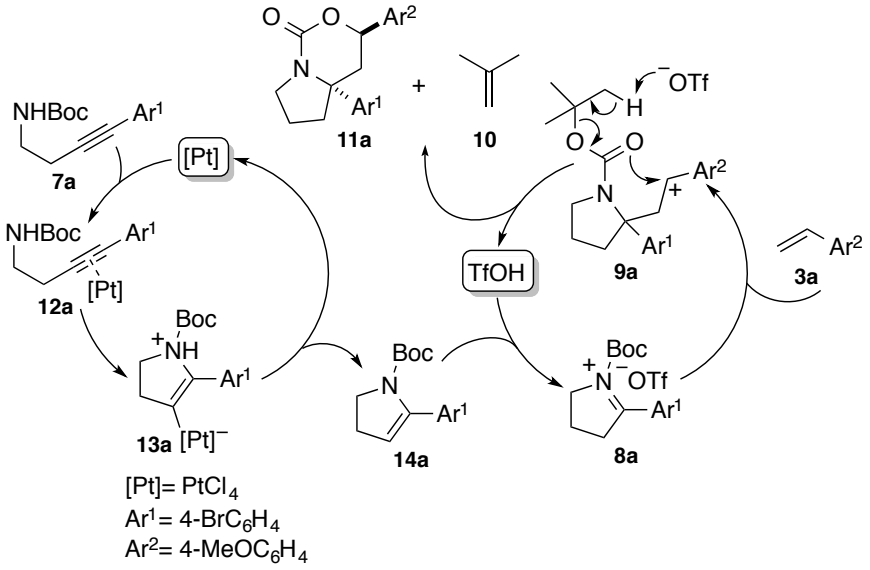
1.A.2.1.3 Mechanistic Proposal

As previously suggested, formation of the product **11a** could be easily explained by a platinum(IV)/triflic acid orthogonal-relay catalytic process (**Scheme 1.A.4**). In this context, it is supposed an initial cycloisomerisation of the *N*-Boc alkynamine derivative **7a** to give the *N*-Boc enamine **14a**. Thus, the coordination of the platinum catalyst to the carbon-carbon triple bond of **7a** leads to the formation of the alkyne-activated intermediate **12a**. Subsequently, intramolecular nucleophilic addition of the amino group to the distal carbon atom of the triple bond generates **13a**. Finally, a protodemetallation process affords the cyclic *N*-Boc enamine derivative **14a** regenerating the platinum(IV) catalyst.

Next, the *N*-Boc enamine derivative **14a** enters the second catalytic cycle. In this case, the Brønsted acid (TfOH) promotes the formation of the iminium species **8a**, which will react with the styrene derivative **3a** to give the cationic intermediate **9a**. The final cyclisation reaction to give the product **11a** implies the nucleophilic

[158] See the NMR Spectra Appendix.

attack of the oxygen of the carbonyl group to the cationic carbon with concomitant loss of a molecule of isobutylene **10** and regeneration of the triflic acid. As shown, both catalysts, $PtCl_4$ and TfOH, promote two different processes, being the global reaction a typical case of orthogonal-relay catalysis.



Scheme 1.A.4 Mechanistic proposal: orthogonal-relay catalytic cycle.

The observed stereochemical outcome of the reaction to give hexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one derivative **11a** as single diastereoisomers is consistent with the model shown in **Figure 1.A.2** in which the final cyclisation reaction in intermediate **9a** (see **Scheme 1.A.4**) would occur through the chair-like transition state **12a** where the aromatic group Ar^2 is placed in a pseudo-equatorial position.

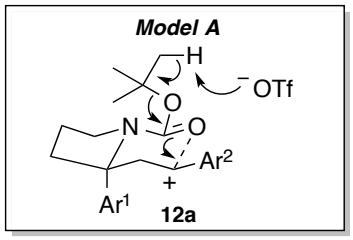


Figure 1.A.2 Proposed model to explain the diastereoselectivity of the process with alkene **3a**.

1.A.2.1.4 Scope of the Reaction: Synthesis of Hexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one Derivatives

Despite the deep investigation performed with our model reaction shown in **Scheme 1.A.3**, the isolated yield of **11a** could not be improved. This study included changes in the dilution, ratio of starting materials **7a** and **3a** and reaction times. It is important to remark that the use of other π-acid catalysts such as gold(I), gold(III) or platinum(II)-derived complexes gave similar results to those achieved with $PtCl_4$. Moreover, the use of weaker Brønsted acids with higher pK_a values than the triflic acid (pK_a= –11.4 in DCE),[159] such as diphenylphosphate or *p*-toluenesulfonic acid, did not afford the desired compound **11a**, and we could only observe the formation of the corresponding ketone derived from the hydration of **7a** at the distal carbon of the triple bond. Therefore, the conditions shown in **Scheme 1.A.3** were considered as optimal and they were used to investigate the scope of the reaction.

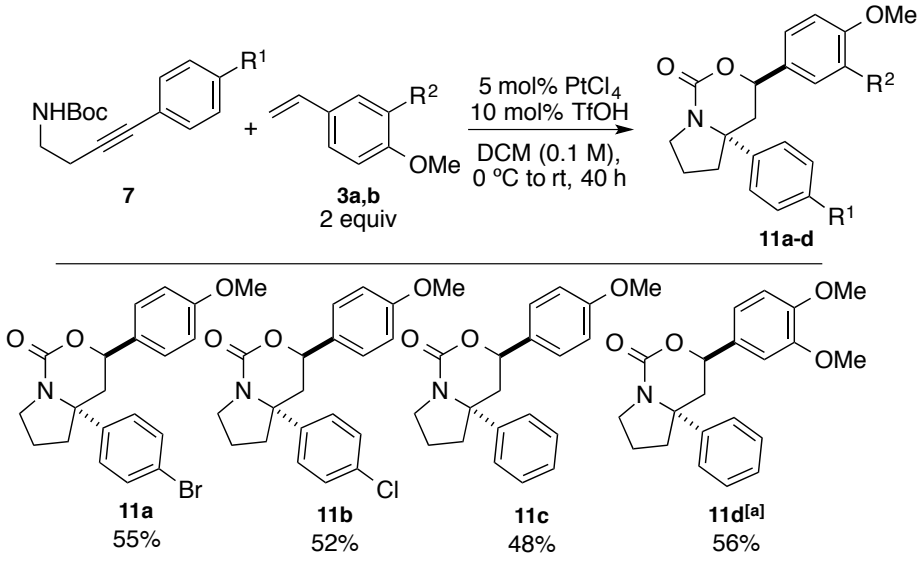
Unfortunately, the reaction resulted quite limited in terms of both reagents, the *N*-Boc alkynamine derivative **7** and the olefin **3**. Thus, moderate yields of the desired products **11a-c** were obtained with simple *N*-Boc alkynamines **7** and relatively electron-rich styrene derivative **3a** (48-55%, **Scheme 1.A.5**). When the reaction was performed with *N*-Boc alkynamine derivatives **7** substituted at the alkyl chain joining the protected amine group and the alkyne formation of the desired compounds **11** was not observed. Neither *N*-Boc alkynamines **7** possessing a terminal alkyne or substituted with an aliphatic group instead of an aromatic ring were appropriate substrates.

The influence of the substitution on the aromatic ring of the styrene derivative **3** was also studied. When the 1,2-dimethoxy-4-vinylbenzene **3b** was used as the alkene counterpart the product **11d** was also obtained in moderate yield (56%, **Scheme 1.A.5**).[160] However, when the corresponding alkene counterpart **3** was substituted with a simple phenyl or naphtyl group, the formation of the expected bicyclic compounds was not observed. Additionally, when a styrene derivative **3** containing a methoxy group in ortho or meta positions of the aromatic ring was used, the reaction did not give any positive result. Neither

[159] E. Raamata, K. Kaupmeesa, G. Ovsjannikova, A. Trummalb, A. Kütta, J. Saamea, I. Koppela, I. Kaljuranda, L. Lippinga, T. Rodimaa, V. Pihla, I. A. Koppela, I. Leito, *J. Phys. Org. Chem.*, **2013**, *26*, 162.

[160] Compound **11d** was isolated together with traces of the dipyrrolo[1,3]oxazin-5-one derivatives **24e**, as by-product of the process, coming from the reaction of two molecules of the corresponding *N*-Boc alkynamine derivative **7b**. Formation of dipyrrolo[1,3]oxazin-5-one derivatives **24** will be further described in Chapter 1, Part B (see **Scheme 1.B.12)**.

alkenes **3** monosubstituted with alkyl groups (instead of styrenes) were appropriate substrates.



[a] Compound **11d** was isolated with traces of a bis[pyrrolidine] derivative **24e**.

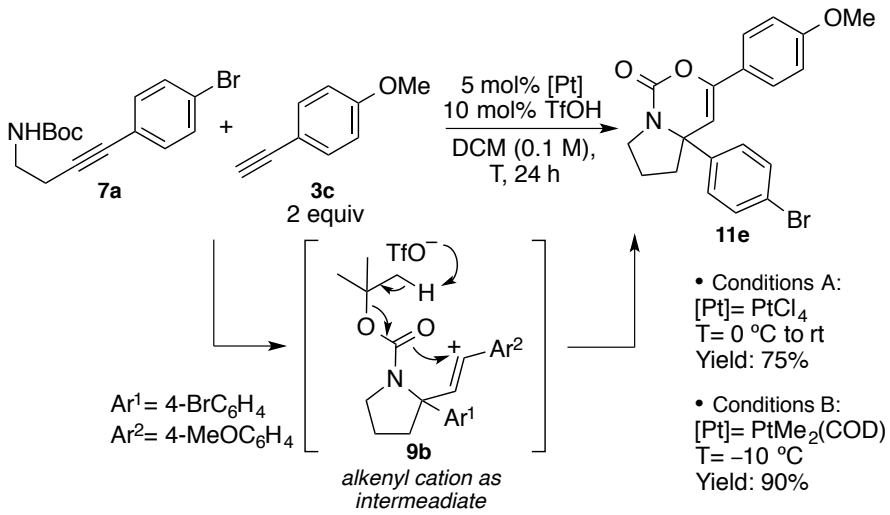
Scheme 1.A.5 Synthesis of hexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one derivatives **11a-d**.

1.A.2.2 Reaction of *N*-Boc-Protected Alkynamine Derivatives with Simple Alkynes

In order to further extend the scope of this new process, the study was moved to the use of alkynes **3** as carbon nucleophilic counterparts of the cascade reaction.

1.A.2.2.1 Preliminary Studies

In an initial experiment, *N*-Boc alkynamine **7a** and 1-ethylnyl-4-methoxybenzene **3c** were reacted under the same optimised conditions found before for alkenes (**Scheme 1.A.6**, Conditions A). Gratifyingly, we observed that the expected compound 4a-(4-bromophenyl)-3-(4-methoxyphenyl)-4a,5,6,7-tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one **11e** could be isolated in 75% yield. Moreover, after a brief optimisation study, we could further improve the isolated yield to 90% by using the precatalyst [$PtMe_2$(COD)] and lowering the temperature to –10 °C (**Scheme 1.A.6**, Conditions B).



Scheme 1.A.6 Alkynes as nucleophilic counterpart.

The mechanism of formation of **11e** is believed to be analogous to that previously described in **Scheme 1.A.4** for alkenes with the only difference that in the present reaction an alkenyl cation **9b** is formed (see **Scheme 1.A.6**) instead of the intermediate **9a** shown in **Scheme 1.A.4**.

1.A.2.2.2 Scope of the Reaction: Synthesis of Tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one Derivatives

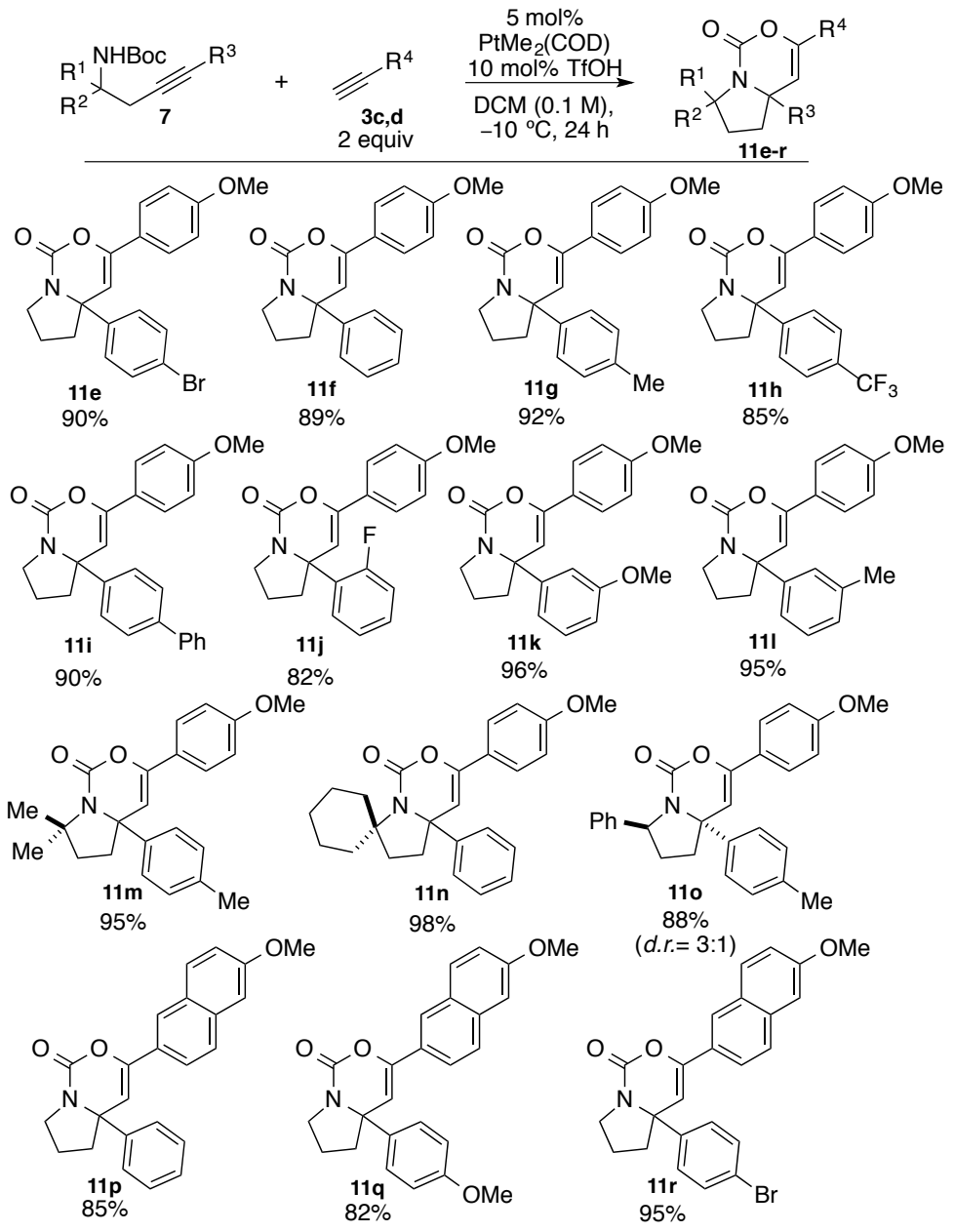
With optimised conditions in hand, we studied the scope of the reaction (**Scheme 1.A.7**). First of all, the behaviour of a set of different *N*-Boc alkynamine derivatives **7** was tested in reactions with the same alkyne **3c**. To our delight, this new process showed to be highly efficient when aromatic substituents with different electronic properties were placed in the triple bond of the *N*-Boc alkynamine **7** (82-96%, products **11e-l**).

N-Boc alkynamine derivatives substituted at the aliphatic chain were also appropriate substrates. Thus, bicyclic tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one derivative **11m**, bearing two methyl groups in the carbon attached to the nitrogen, was isolated in 95% yield, and an interesting spirocyclic compound **11n** was obtained almost quantitatively. Particularly interesting was the result observed when a chiral (racemic) alkynamine derivative **7** (R^1= Ph, R^2=H) was used. In this case, the final compound **11o** was isolated in high yield and as a mixture of two diastereoisomers (*d.r.*= 3:1) indicating that the chiral centre of the *N*-Boc

alkynamine exhibits a moderate influence in the formation of the new stereocenter in **11o**.[161]

Next, a study of the scope of the reaction regarding the alkyne **3** counterpart was developed. Pleasingly, compounds **11p-r** were easily prepared when 2-ethynyl-6-methoxynaphthalen **3d** was tested under the previously optimised reaction conditions (82-95%, **Scheme 1.A.7**). Other aromatic alkynes **3** such as simple ethynylbenzene, 1-ethynyl-3-methoxybenzene, 1-ethynyl-4-methylbenzene and 3-ethynyl-thiophene did not give the expected compounds **11**. In these cases, the main product observed was the ketone derived from the hydration of the starting *N*-Boc alkynamine **7** at the distal carbon of the triple bond. Particularly interesting resulted the experiment with 5-ethynyl-1-methyl-1*H*-imidazole, as in this example the *N*-Boc alkynamine starting material *7* was recovered unreacted. This observation suggests that the presence of the imidazole inhibits the catalytic activity of the platinum due to formation of an inactive complex by coordination of this heterocycle to the metal. Finally, neither simple ethoxyacetylene nor other aliphatic alkynes lead to the formation of the expected products.

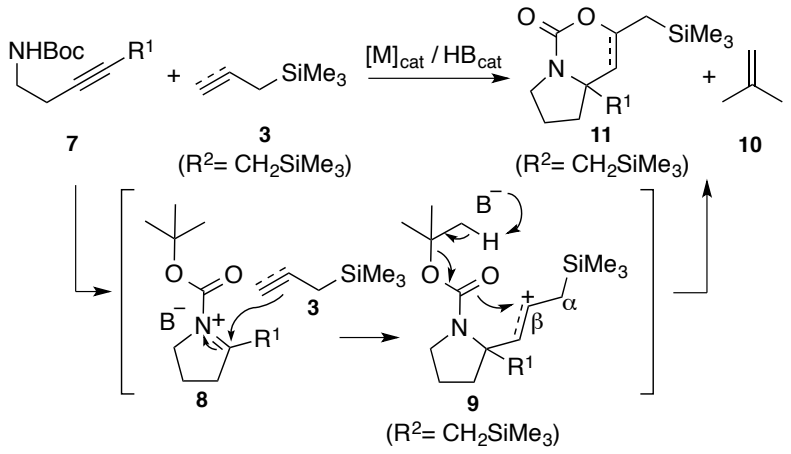
[161] The relative configuration of the derivative **11o** could not be determined. The representation shown was arbitrarily chosen.



Scheme 1.A.7 Scope of the reaction. Synthesis of tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one derivatives **11e-r**.

1.A.2.3 Reaction of *N*-Boc-Protected Alkynamine Derivatives with β-Silyl Alkenes and Alkynes

As previously mentioned, a key intermediate of the above described processes seems to be the carbocationic species **9** generated after the nucleophilic attack of the corresponding alkene or alkyne counterparts **3** to the iminium species **8** (**Scheme 1.A.2**). In this context, it was considered that allylsilanes **3d** and propargylsilanes **3e**, particular cases of alkyl-substituted alkenes and alkynes, could be appropriate partners for our desired process (**Scheme 1.A.8**).[162]



Scheme 1.A.8 Allylsilanes and propargylsilanes as nucleophiles.

It should be noted that after the addition of these reagents **3** (R^2= CH_2SiMe_3) to intermediates **8**, the formed cationic species **9** (R^2= CH_2SiMe_3) could be stabilised by the presence of a silicon atom in β-position with respect to the cation.[163] The β-silicon effect, also called silicon hyperconjugation in organosilicon chemistry, is a special type of hyperconjugation that describes the stabilising effect of a silicon atom placed in a β-position from a carbocation (**Figure 1.A.3**). This effect has been attributed to the overlap between the vacant *p* orbital of the β carbon atom and the σ orbital of the α-carbon-silicon bond. Maximum stabilisation only occurs if the vacant *p* orbital and the carbon-silicon bond are in

[162] For reactions of allylsilane derivatives in the context of gold and platinum catalysis, see: a) C. Fernández-Rivas, M. Méndez, C. Nieto-Ober- huber, A. M. Echavarren, *J. Org. Chem.*, **2002**, *67*, 5197. b) C.-C. Lin, T.-M. Teng, C.-C. Tsai, H.-Y. Liao, R.-S. Liu, *J. Am. Chem. Soc.,* **2008**, *130*, 16417. c)Y. Sawama, Y. Sawama, N. Krause, *Org. Lett.*, **2009**, 11, 5034. d) T.-M. Teng, M.-S. Lin, D. Vasu, S. Bhunia, T.-A. Liu, R.-S. Liu, *Chem. Eur. J.*, **2010**, *16*, 4744.

[163] Similar intramolecular trapping of a β-silyl carbocation by an *N*-Boc group had been reported. For some examples, see: a) S. Brocherieux-Lanoy, H. Dhimane, J.-C. Poupon, C. Vanucci, G. Lhommet, *J. Chem. Soc., Perkin Trans.*, **1997**, *1*, 2163. b) B. H. Shupe, E. E. Allen, J. P. MacDonald, S. O. Wilson, A. K. Franz, *Org. Lett.*, **2013**, *15*, 3218.

the same plane. Moreover, the increased stability of a carbocation in β-position with respect to silicon determines the regioselectivity of the reactions between electrophiles and these silicon-containing nucleophiles.[164]

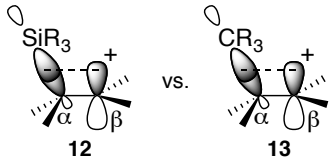


Figure 1.A.3 Stabilisation of β-carbocations by a silicon group.

Remarkably, in the designed reaction with allyl and propargylsilanes **3d,e** as starting materials, interesting silicon-containing bicyclic compounds **11** could be synthesised. Moreover, the presence of this atom could allow further derivatisation reactions.

1.A.2.3.1 Reaction of *N*-Boc-Protected Alkynamine Derivatives with Allyltrimethylsilane

1.A.2.3.1.1 Preliminary Studies and Optimisation of the Reaction Conditions

In order to establish the viability of the process, the *N*-Boc alkynamine derivative **7b** and allyltrimethylsilane **3d** were chosen as starting materials. Selected experiments of the optimisation study are shown in **Table 1.A.1**.[165]

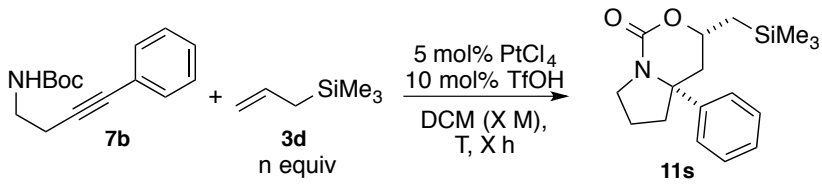
Therefore, *N*-Boc alkynamine **7b** and allyltrimethylsilane **3d** (2 equiv) were reacted in dichloromethane as solvent at room temperature in the presence of a catalytic system formed by the combination of $PtCl_4$ (5 mol%) and TfOH (10 mol%). Under these conditions, the only product observed was 5-phenyl-3,4-dihydro-2H-pyrrole (**Table 1.A.1**, **Entry 1)**. This product is formed by a simple *N*-Boc deprotection of the cyclic intermediate **8** (see **Scheme 1.A.8**) under acidic conditions. In order to avoid this undesired reaction, the next experiment was performed at a lower temperature (–10 °C) and thus, it was possible to isolate the desired silicon-containing 4a-phenyl-3-((trimethylsilyl)methyl)hexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one **11s** but in low yield (20%) and as a mixture of

[164] a) S. E. Thomas, *Organic Synthesis: The Roles of Boron and Silicon*, Oxford University Press Inc., New York, **1991**. b) S. G. Wierschke, J. Chandrasekhar, W. L. Jorgensen, *J. Am. Chem. Soc.,* **1985**, *107*, 1496.

[165] For some preliminary studies, see: Jonás Calleja Priede, *Tesis Doctoral*, Universidad de Oviedo, **2012**.

diastereoisomers (*d.r.*= 4.5:1) (**Table 1.A.1**, **Entry 2**).[166] However, by increasing the equivalents of allylsilane **3d** and performing the reaction at a higher dilution (0.02 M), the desired compound **11s** could be isolated in 46% yield after 24 hours of reaction (**Table 1.A.1**, **Entry 3**). Finally, the isolated yield of compound **11s** could be improved (88%) just by stirring the reaction mixture for longer reaction times (72 h) (**Table 1.A.1**, **Entry 4**). In order to improve the diastereomeric ratio of the reaction, some experiments were performed at lower temperatures than –10 °C (e.g. –30 °C), but at those temperatures the reaction became too slow (**Table 1.A.1**, **Entry 5**).

Table 1.A.1 Optimisation study of the reaction of *N*-Boc alkynamine derivative **7b** and allyltrimethylsilane **3d**.



Entry	n equiv.	Dilution (M)	T (°C)	t (h)	Yield [%][a]	*d.r.*[e]
1	2	0.1	rt	24	–[b]	–
2	2	0.1	–10	24	20[c]	4.5:1
3	10	0.02	–10	24	55	4.5:1
4	10	0.02	–10	72	88	4.5:1
5	10	0.02	–30	72	traces[d]	–

[a] Yield of isolated product (**11s** and **diast-11s**) based on starting material **7b**. [b] The corresponding 5-phenyl-3,4-dihydro-2*H*-pyrrole derived from the *N*-Boc deprotection under acidic conditions was the main product observed. [c] The corresponding homodimeric derivative **23e** was observed. [d] The corresponding ketone derived from the hydration of **7b** at the distal carbon was observed. [e] Determined by ^{1}H-NMR analysis of the crude of the reaction.

1.A.2.3.1.2 Determination of Relative Configuration

The structure and relative configuration of the stereogenic centers of **11s** was determined by one-dimensional and two-dimensional NMR experiments (**Figure 1.A.4**). The triple triplet centred at 4.47 ppm (tt, *J*= 7.9 and 5.2 Hz) was assigned to $\mathbf{H_a}$. The double doublets centred at 0.74 (dd, *J*= 14.6 and 7.9 Hz) and

[166] Moreover, under these reaction conditions the major product of the reaction was the dipyrrolo[1,3]oxazin-5-one derivatives **24e** (see **Scheme 1.B.12**, Chapter 1, Part B).

0.44 ppm (dd, *J*= 14.6 and 7.9 Hz) were assigned to $\mathbf{H_e}$ and $\mathbf{H_f}$. Thus, in this case, $\mathbf{H_a}$ should be placed in a pseudo-equatorial position as the coupling constants with the adjacent protons $\mathbf{H_b}$ and $\mathbf{H_c}$ (*J*= 5.2 Hz) exhibit a different coupling pattern if compared to the one of the compound **11a**. Therefore the proton $\mathbf{H_a}$ and the substituent CH_2SiMe_3 are both placed in pseudo-equatorial positions. Additionally, the cross-peak signals arising from protons close in space observed in the NOESY two-dimensional NMR experiment $\mathbf{H_d}$ and $\mathbf{H_e}$ on the one hand, and $\mathbf{H_d}$ and $\mathbf{H_f}$ on the other one (both in blue, **Figure 1.A.4**) showed that the $-CH_2SiMe_3$ group and the phenyl substituent are placed in a *cis* disposition.[167]

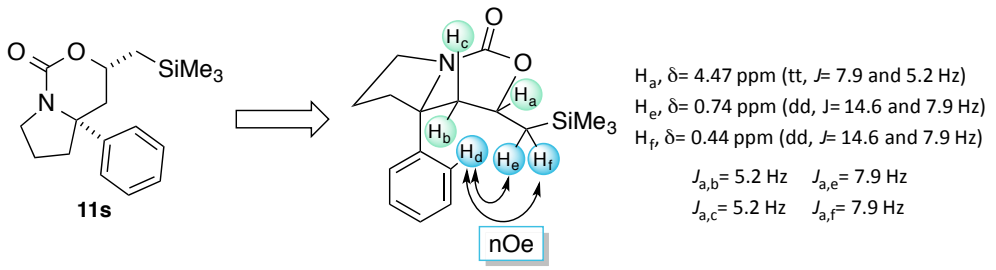


Figure 1.A.4 Determination of the relative configuration of **11s** through ^{1}H–NMR and NOESY experiments.

Again, the proposed mechanism for the formation of this new derivative **11s** involves an orthogonal-relay catalytic process similar to that outlined in **Scheme 1.A.4**.

It should be noted that, surprisingly, in this case the relative configuration of the stereocenters in the major diastereoisomer **11s** is opposite to that observed in **11a** (see **Figure 1.A.1**). Thus, the formation of this major diastereoisomer of **11s** could be explained by model B where the CH_2SiMe_3 group is placed in a pseudo-axial position. Moreover, a model similar to model A (just with CH_2SiMe_3 instead of Ar^2) could explain the formation of the minor diastereoisomer ***diast*-11s**.

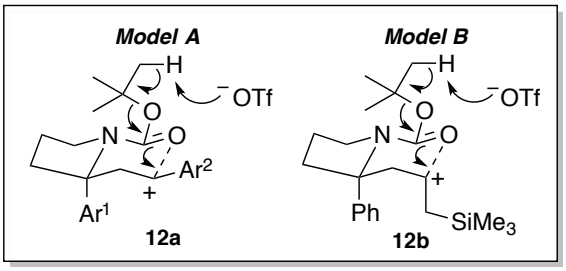
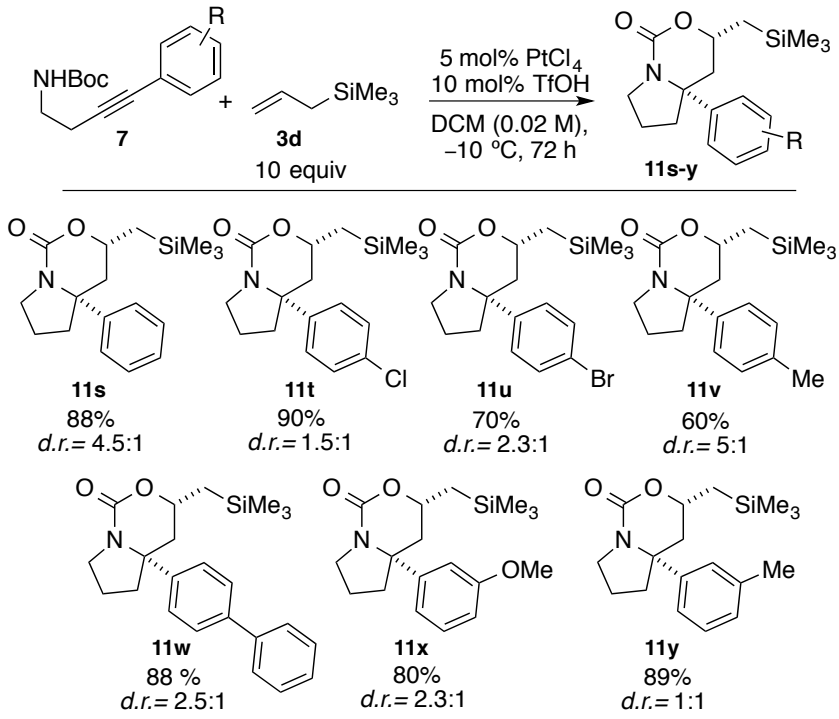


Figure 1.A.5 Proposed model to explain the diastereoselectivity of the process with allyltrimethylsilane **3d**.

[167] See Appendix NMR Spectra.

1.A.2.3.1.3 Scope of the Reaction: Synthesis of Silicon-Containing Hexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one Derivatives

Once the reaction was optimised, the scope of the new process was studied. On the one hand, a set of aromatic substituted *N*-Boc alkynamine derivatives **7** was tested. Thus, a series of silicon containing hexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one derivatives **11s-y** bearing electron-donating (products **11v, 11x** and **11y**) and electron-poor substituents (products **11t** and **11u**) at meta- and para- positions of the aromatic ring was easily prepared from moderate to excellent yields (60-90%, **Scheme 1.A.9**).



Scheme 1.A.9 Synthesis of hexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one derivatives **11s-y**.

However, although this process was more efficient in terms of chemical yield than the reaction with simple alkenes (see **Scheme 1.A.5**), compounds **11s-y** were always obtained as mixtures of diastereoisomers, ranging the ratios from 1:1 to 5:1. Unfortunately, when the reaction was performed with *N*-Boc alkynamine derivatives **7** substituted at the alkyl chain, formation of the desired compounds was not observed and neither when *N*-Boc alkynamines **7** possessing a terminal alkyne or substituted with an aliphatic group instead of an aromatic ring were

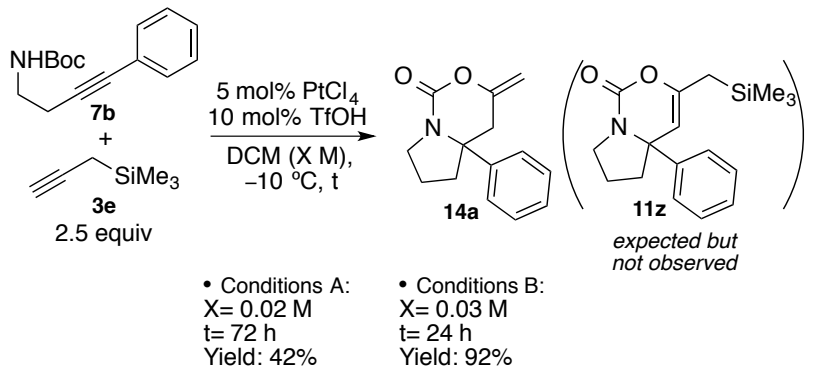
appropriate substrates. Regarding the allylsilane counterpart, unfortunately, formation of the desired compound **11** was not observed when other allylsilanes different from allyltrimethylsilane **3d** were tested.

1.A.2.3.2 Reaction of *N*-Boc-Protected Alkynamine Derivatives with Trimethylpropargylsilane

After the study of the process with allyltrimethylsilane **3d** as the nucleophilic counterpart, attention was moved to the use of trimethylpropargylsilane **3e**. Thus, as shown in **Scheme 1.A.8**, after the nucleophilic attack of the propargylsilane derivative **3e** and the subsequent intramolecular trapping of the cationic intermediate by the Boc group, the corresponding tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one derivatives **9** containing a silicon group would be the expected product.

1.A.2.3.2.1 Preliminary Studies

Investigations began with the reaction of alkynamine **7b** and 2.5 equivalents of trimethylpropargylsilane **3e** under the optimal conditions found before for allyltrimethylsilane **3d** (**Scheme 1.A.10**, Conditions A). Surprisingly, although in moderate yield (42%), the only isolated product was 3-methylene-4a-phenylhexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one **14a** containing an exocyclic carbon-carbon double bond and lacking the trimethylsilyl group. However, the expected compound **11z** could not be isolated or even identified in the crude of the reaction mixture. The isolation of this new product **14a** was considered an interesting result, and thus, attempts to improve the yield were done. Delightfully, when the reaction was performed under more concentrated conditions, compound **14a** could be obtained in very high yield (92%) after just 24 hours (**Scheme 1.A.10**, Conditions B).[165]



Scheme 1.A.10 Reaction of *N*-Boc alkynamine **7b** and trimethylpropargylsilane **3e**: initial experiments.

1.A.2.3.2.2 Mechanistic Studies

Formation of compound **14a** instead of the expected **11z** was an interesting result not only from the synthetic point of view but also because the mechanism for its formation was an intriguing issue. Considering that **14a** should be formed from **11z**, it was initially thought that the loss of the silicon group could have happened at different stages of the experiment. On the one hand, it could be lost as a consequence of the own reaction, and on the other hand this loss could have taken place during the work-up of the reaction.

In order to gain some insight, it was decided to follow the reaction by ^{1}H–NMR performing the same experiment described in **Scheme 1.A.10** (conditions B) in CD_2Cl_2 and taking an aliquot after 24 hours. The recorded ^{1}H–NMR spectrum is shown in **Figure 1.A.6**.

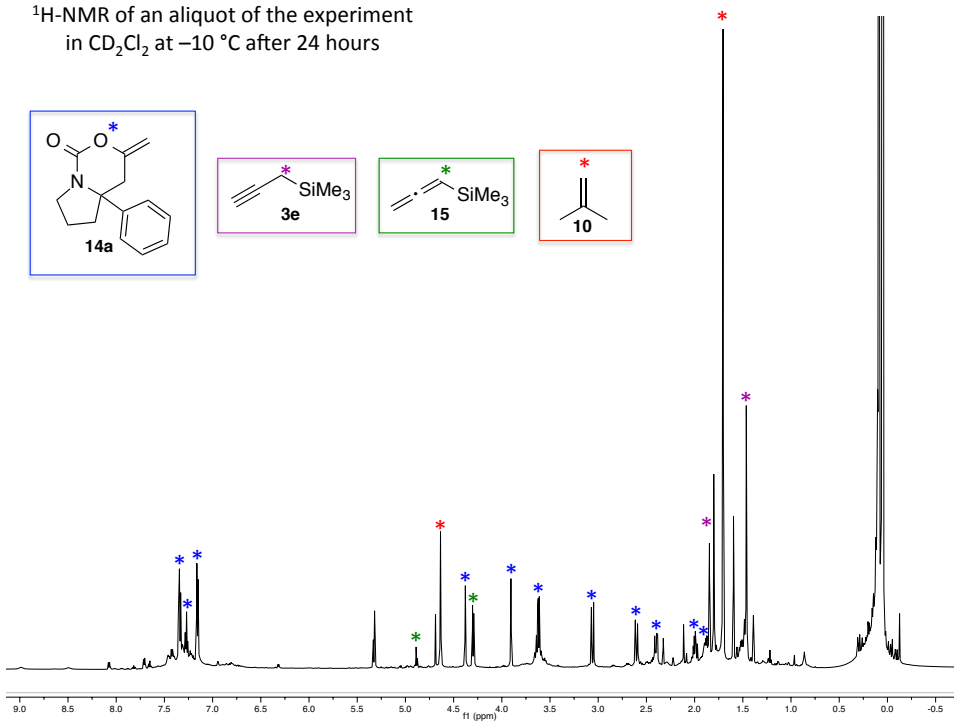
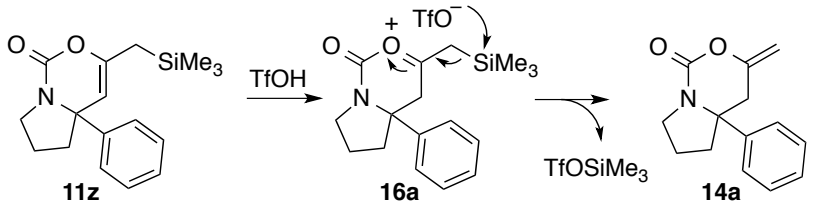


Figure 1.A.6 ^{1}H–NMR of an aliquot of the reaction.

As it is shown, the major compound in the reaction media was the previously isolated compound **14a** but the presence of the silicon-containing product **11z** was not observed. Other signals that were easily identified were those corresponding to the starting trimethylpropargylsilane **3e** and those of trimethylallenylsilane **15** (contained as by-product in the commercially available trimethylpropargylsilane **3e**) (**Figure 1.A.6**). Moreover, it was noticed the presence

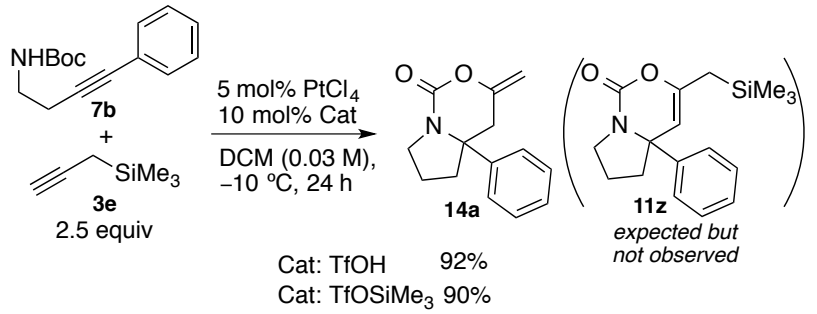
of isobutylene **10** (**Figure 1.A.6**). This compound comes from the decomposition of the Boc group after the intramolecular trapping (see **Scheme 1.A.8**). Thus, the presence of the product **14a** lacking the trimethylsilyl group suggested that the loss of the silicon group took place in the reaction media but not during the work-up. Other ^{1}H–NMR experiments performed at shorter reaction times did not show the presence of the intermediate **11z**.

A plausible explanation for the observed *in situ* loss of the trimethylsilyl group is outlined in **Scheme 1.A.11**. Once the compound **11z** bearing the silicon group is formed, a molecule of the Brønsted acid (TfOH) could be able to promote the formation of the oxonium intermediate **16a** and finally the silicon group could be lost assisted by the conjugated base (TfO^-) (**Scheme 1.A.11**). However, it has to be considered that this transformation consumes the triflic acid generating $TfOSiMe_3$ and taking into consideration that only 10 mol% of triflic acid was used in our reaction the yield of compound **14a** could not be higher than 10 mol%.



Scheme 1.A.11 Plausible explanation of the formation of **14a**.

In this context, the only rational explanation for the excellent yield observed in in our model reaction (92% yield, see **Scheme 1.A.10**) had to be that triflic acid was regenerated from $TfOSiMe_3$ under the reaction conditions. In order to probe if this assumption was right, we performed a comparative experiment by using $TfOSiMe_3$ as catalyst instead of triflic acid. As shown in **Scheme 1.A.12**, a similar result to that observed with triflic acid was obtained. So, it could be concluded that triflic acid was generated from $TfOSiMe_3$ under the reaction conditions by the action of an external reagent.



Scheme 1.A.12 Comparison of the reaction using TfOH and $TfOSiMe_3$ as catalysts.

Further support to our proposal was found when the recorded ^{1}H–NMR experiment was analysed looking for the presence of $TfOSiMe_3$. As it is shown in **Figure 1.A.7**, $TfOSiMe_3$ (**NMR A**, **Figure 1.A.7**) is not present in the reaction media (**NMR B**, **Figure 1.A.7**). Again, this indicates that $TfOSiMe_3$ is consumed under our reaction conditions presumably regenerating the triflic acid.

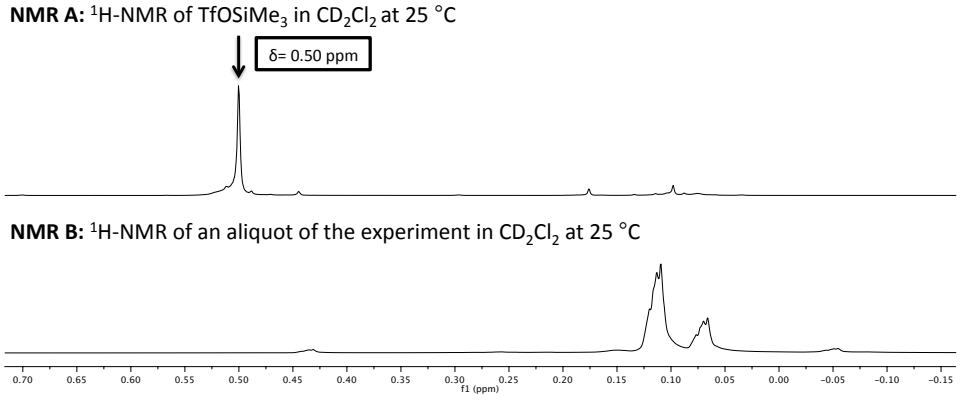


Figure 1.A.7 ^{1}H–NMR of an aliquot of the reaction and its comparison with a ^{1}H–NMR of $TfOSiMe_3$.

At this point we suspected that the presence of adventitious water in our reaction media could be the responsible for the regeneration of triflic acid from $TfOSiMe_3$. Thus, it was supposed that the reaction of $TfOSiMe_3$ (2 equiv) with H_2O (1 equiv) would deliver a molecule of hexamethyldisiloxane ($Me_3SiOSiMe_3$) and two molecules of triflic acid (**Scheme 1.A.13**).

$$2\ TfOSiMe_3 + H_2O \longrightarrow Me_3SiOSiMe_3 + 2\ TfOH$$

Scheme 1.A.13 Plausible regeneration of TfOH from $TfOSiMe_3$.

It should be noted that considering this proposed equation the presence of just 0.5 equivalents of water in the reaction media of our experiment should be enough to achieve a complete conversion of the starting materials into product **14a**.

Further ^{1}H–NMR experiments were performed to identify the presence of $Me_3SiOSiMe_3$ in the reaction media. The results are shown in **Figure 1.A.8**. **NMR C** shows the signals observed in a ^{1}H–NMR of an aliquot of the reaction performed in CD_2Cl_2 at 25 °C. One of the signals (δ= 0.11 ppm) corresponded to the remaining starting propargyltrimethylsilane **3e** (identified by comparison to **NMR B, Figure 1.A.8**). Nevertheless, a new signal appeared (δ= 0.06 ppm), corresponding to $Me_3SiOSiMe_3$ (assigned by comparison with the spectrum of an NMR experiment where $SiClMe_3$ was treated with H_2O to observe the *in situ* formation of

$Me_3SiOSiMe_3$, **NMR A, Figure 1.A.8**). Thus, this result confirmed our proposed mechanism for the regeneration of the triflic acid from $TfOSiMe_3$ due to the presence of adventitious water probably coming from the solvent of the reaction (**Scheme 1.A.13**).

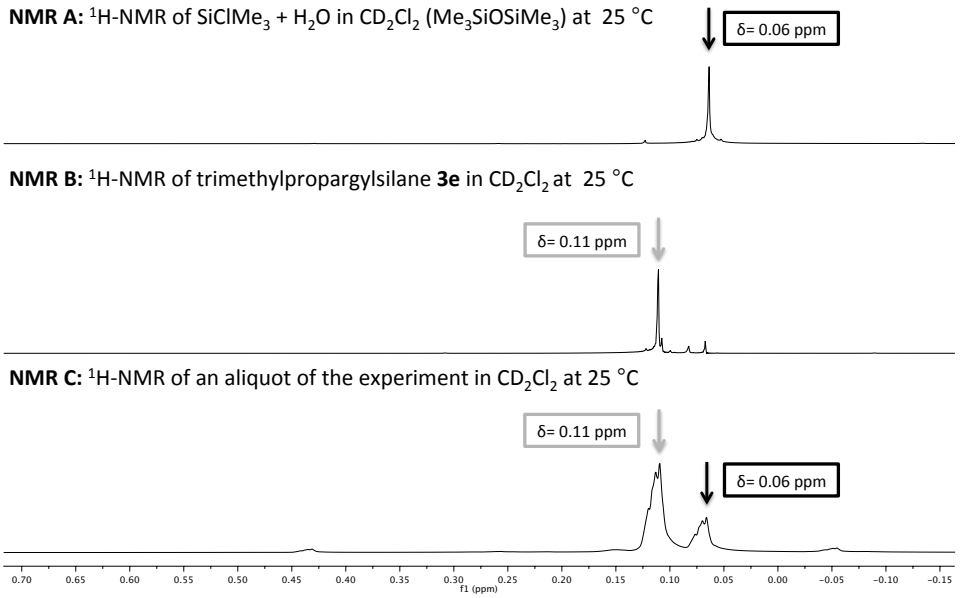
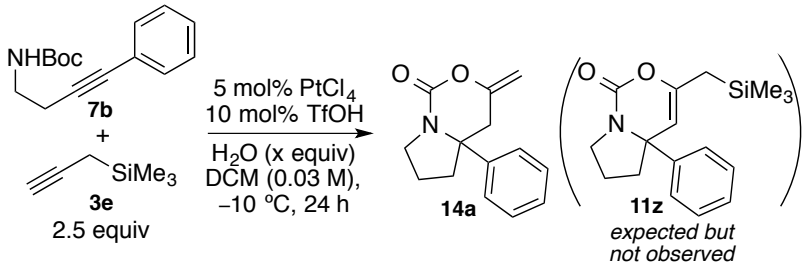


Figure 1.A.8 ^{1}H–NMR of an aliquot of the reaction and its comparison with a ^{1}H–NMR of trimethylpropargylsilane **3e** and a ^{1}H–NMR of $Me_3SiOSiMe_3$.

1.A.2.3.2.3 Study of Controlled Addition of Water to Freshly Dried Solvent

After completion of this study it was obvious to perform some experiments adding controlled amounts of water to freshly and carefully dried dichloromethane. The most relevant experiments are shown in **Table 1.A.2**. As expected, when the reaction was performed with freshly dried solvent without the addition of any amount of H_2O (**Table 1.A.2**, **Entry 1**), the product **14a** was isolated in less than 10% yield. On the contrary, when one equivalent of H_2O was added to the dried solvent, the main reaction was the undesired hydration of the carbon-carbon triple bond of the corresponding *N*-Boc alkynamine derivative **7b** at the distal carbon of the alkyne to give the corresponding ketone (**Table 1.A.2**, **Entry 2**). To our delight, we could isolate in very high yield (96%) the desired compound **14a** when just 0.5 equivalents of H_2O were added to the freshly dried dichloromethane (**Table 1.A.2**, **Entry 3**). This experiment confirmed our hypothesis regarding the necessity of just 0.5 equivalents of water for the complete regeneration of TfOH from the continuously formed $TfOSiMe_3$.

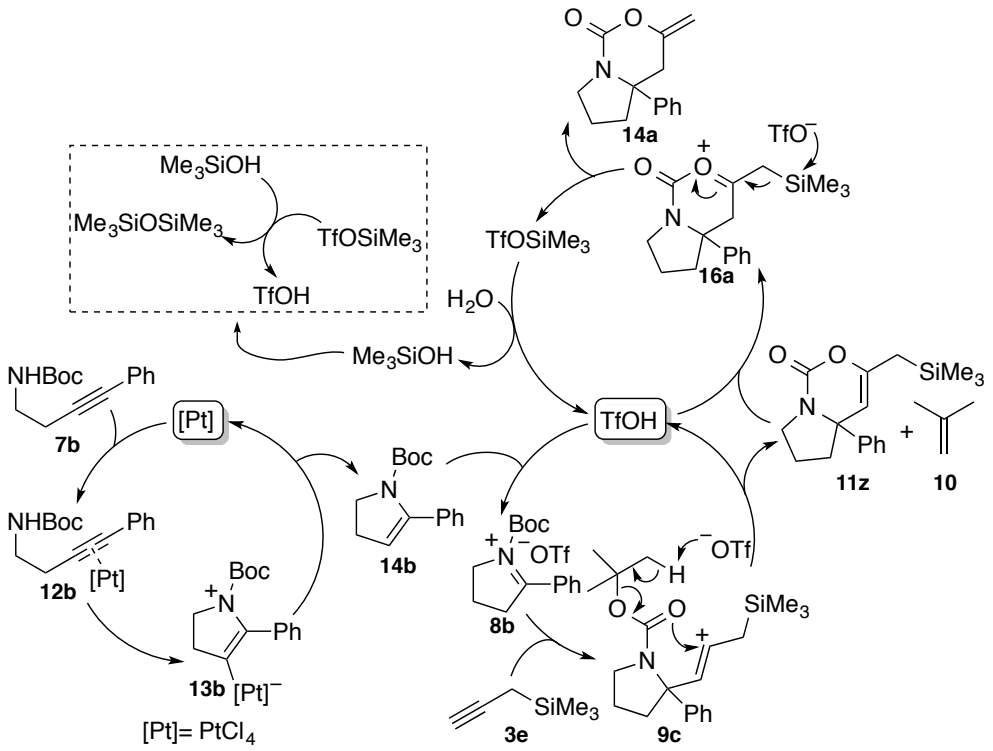
Table 1.A.2 Study of the addition of controlled amounts of H_2O.



Entry	Equivalents of H_2O (x)	Yield [%][a]
1	-	<10
2	1	Traces[b]
3	0.5	96

[a] Yield of isolated product based on starting material **7b**. [b] The corresponding ketone derived from the hydration of **7b** at the distal carbon was observed.

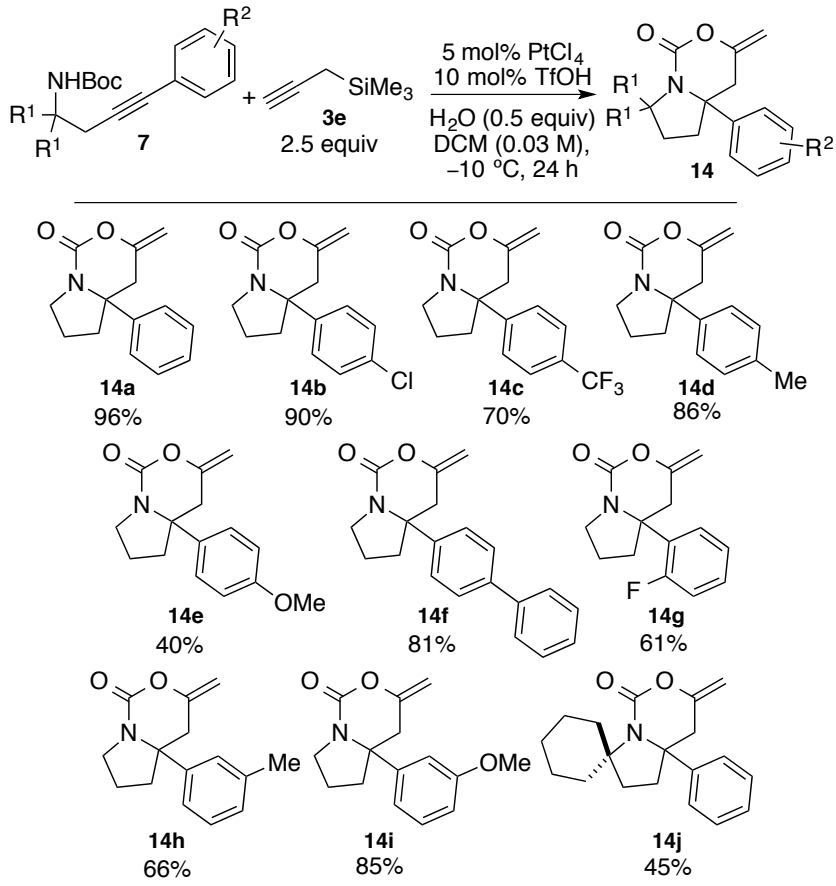
Finally, a complete mechanistic proposal for the formation of **14a** is outlined in **Scheme 1.A.14**. It should be noted that the silicon containing intermediate **11z** might be generated following an orthogonal-relay catalytic cycle analogous to that previously described (see **Scheme 1.A.4**). Once this intermediate **11z** is formed it would react in the presence of a molecule of TfOH to give intermediate **16a**, and finally after the loss of the silicon group assisted by the conjugate base, the final product **14a** will be afforded. Regeneration of the catalyst is supposed to occur by reaction of $TfOSiMe_3$ with H_2O. Apart from TfOH, a molecule of Me_3SiOH is formed in this reaction. This compound evolves to give $Me_3SiOSiMe_3$ and TfOH in the presence of another molecule of $TfOSiMe_3$. As previously mentioned, only 0.5 equivalents of H_2O are required for the transformation of **11z** into **14a**.



Scheme 1.A.14 Mechanistic proposal for the formation of compound **14a**.

1.A.2.3.2.4 Scope of the Reaction: Synthesis of 3-Methylene-hexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one Derivatives

Finally, with these optimised reaction conditions, the scope of the new reaction was studied. Thus, when a variety of *N*-Boc alkynamine derivatives **7** were reacted with 2.5 equivalents of trimethylpropargylsilane **3e** in the presence of 0.5 equivalents of H_2O, 5 mol% of $PtCl_4$ and 10 mol% of TfOH in freshly dried dichloromethane (0.03 M) at –10 °C, the corresponding 3-methylene-hexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one derivatives **14** were isolated in high yield in most of the cases (**Scheme 1.A.15**). Therefore, aromatic substituted compounds **14** bearing electron-donating and electron-poor substituents in para, meta and ortho-positions could be easily synthesised. Moreover, although in moderate yield, the corresponding spirocyclic derivative **14j** containing a cyclohexyl ring was isolated when a *N*-Boc alkynamine derivative **7** substituted at the aliphatic chain (R^1= -$(CH_2)_5$-) was used. It should be noted that the expected products analogous to **11z** could not be detected in any of our experiments.



Scheme 1.A.15 Synthesis of 3-methylene-hexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one derivatives **14**.

1.A.3 Summary

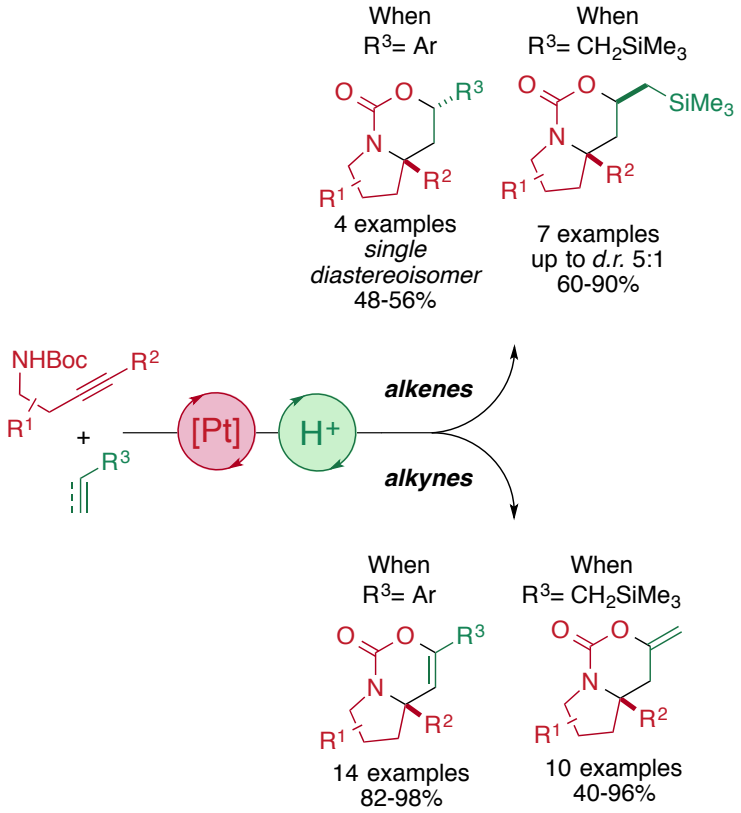
In summary, in Chapter 1, Part A it has been shown that *N*-Boc protected alkynamine derivatives are highly valuable precursors for the synthesis of interesting bicyclic pyrrolidine-containing compounds when they react with alkenes or alkynes in the presence of a platinum/triflic acid catalytic binary system (**Scheme 1.A.16**).

Therefore, these reactions proceed through a cascade process that implies the initial platinum-catalysed cycloisomerisation reaction of the alkynamine derivative followed by a triflic acid-promoted nucleophilic addition of the alkene or the alkyne moiety. Finally, the intramolecular trapping of the cationic species by the Boc group affords the final compounds, a molecule of isobutylene and a proton, rendering the process catalytic.

Additionally, these new processes further demonstrate the potential of orthogonal-relay one-pot catalytic cascade reactions for the synthesis of complex molecules from simple starting materials.

Particularly interesting resulted the reaction of alkynamine derivatives with allyltrimethylsilane, as bicyclic products containing a trimethylsilyl group are synthesised.

Finally, an unexpected result was found when trimethylpropargylsilane was used as the alkyne counterpart and thus, interesting bicyclic derivatives containing an exocyclic double bond are obtained in a process that curiously requires the addition of water to make the process catalytic with respect to the Brønsted acid.



Scheme 1.A.16 Summary.

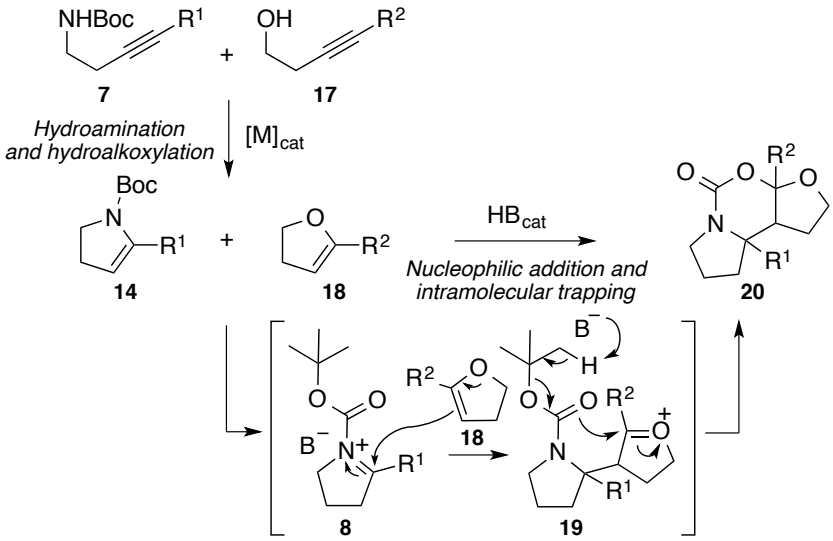
Part B

Cascade Reactions of N-Boc Protected Alkynamine and Alkynol Derivatives. Synthesis of 5H-furo[3,2-e]pyrrolo[1,2-c][1,3]oxazin-5-one Derivatives

1.B.1 Introduction and Objectives

It has been shown in the previous section that *N*-Boc enamine derivatives **14** *in situ* generated through a hydroamination reaction of *N*-Boc alkynamine derivatives **7** react with alkenes or alkynes **3** in a cascade process catalysed by a platinum/triflic acid binary system (see **Scheme 1.A.16**, Chapter 1, Part A).

In this context, it was thought that an interesting extension of this methodology would be the reaction of the *in situ* generated *N*-boc enamine derivatives **14** with enol ethers **18** (a particular type of alkenes) through the iminium intermediate **19** (**Scheme 1.B.1**). Moreover, considering that enol ethers are also easily available through a hydroalkoxylation reaction of alkynol derivatives **17**, the final objective would be the development of a double cycloisomerisation (hydroamination and hydroalkoxylation), nucleophilic addition and intramolecular trapping sequence. This reaction would led to the formation of interesting tricyclic furopyrroloxazinone derivatives (5*H*-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin-5-one) **20** through a new cascade reaction, catalysed by a metal/Brønsted acid binary system.



Scheme 1.B.1 Objective.

It should be remarked that this new cascade process could also be considered as a heterocoupling reaction of two different electron-rich alkenes (an enamine and an enol ether). This particular type of coupling reactions involving two electron-rich alkenes is an underdeveloped process probably due to the weaknesses and drawbacks that this heterocoupling reaction possesses. For instance, both substrates (enol ether and enamine) may react wit the protic acid

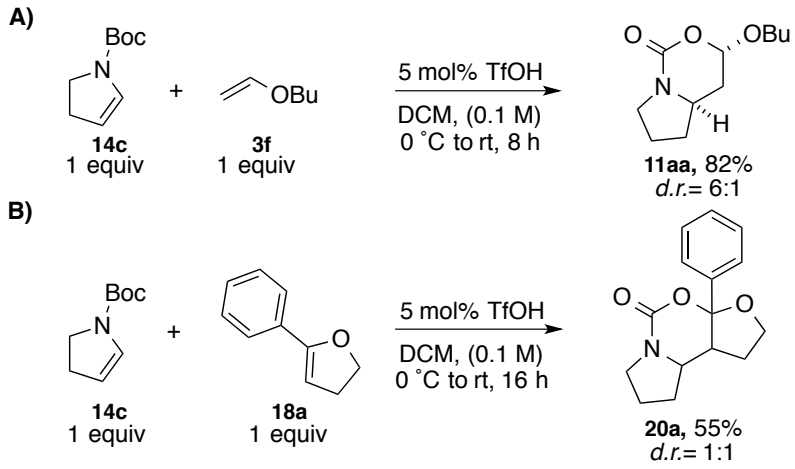
to afford the corresponding cationic intermediates (iminium or oxonium) and, as both substrates (enamine or enol ether) are nucleophiles they can react with both of these cationic intermediates through several equilibrium processes. This could result in the formation of different heterocoupling products and also in undesired homocoupling processes.[168] However, in our case, it was thought that these problems could be solved because the presence of the Boc group on the nitrogen atom of **7** could trap the oxonium intermediate **19** through an irreversible process.

1.B.2 Results and Discussion

1.B.2.1 Preliminary Studies

Investigations began with the study of the second part of the cascade reaction, particularly the acid-catalysed coupling of two commercially available starting materials (*tert*-butyl 2,3-dihydro-1*H*-pyrrole-1-carboxylate **14c** and butyl vinyl ether **3f**) (**Scheme 1.B.2**). Delightfully, when the *N*-Boc enamine derivative **14c** (1 equiv) and enol ether **3f** (1 equiv) were reacted in dichloromethane as solvent in the presence of 5 mol% of triflic acid, after 8 hours the formation of the desired bicyclic product 3-butoxyhexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one **11aa** was observed in 82% yield and as a mixture of diastereoisomers (*d.r.*= 6:1) (**Scheme 1.B.2**, **eq. A**, major diastereoisomer is shown). The study was next moved to the use of cyclic enol ethers derivatives such as 5-phenyl-2,3-dihydrofuran **18a**. In this case, when the reaction of the *N*-boc enamine derivative **14c** and enol ether **18a** was performed under the same reaction conditions, the expected tricyclic compound 3a-phenyloctahydro-5*H*-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin-5-one **20a** was isolated in moderate yield and as a mixture of diastereoisomers (*d.r.*= 1:1) (**Scheme 1.B.2**, **eq. B**). Although the yield was not very high, it was a promising result for the final goal of performing this reaction as part of a cascade process involving the initial cycloisomerisation of *N*-Boc alkynamine and alkynol derivatives **7** and **17**.

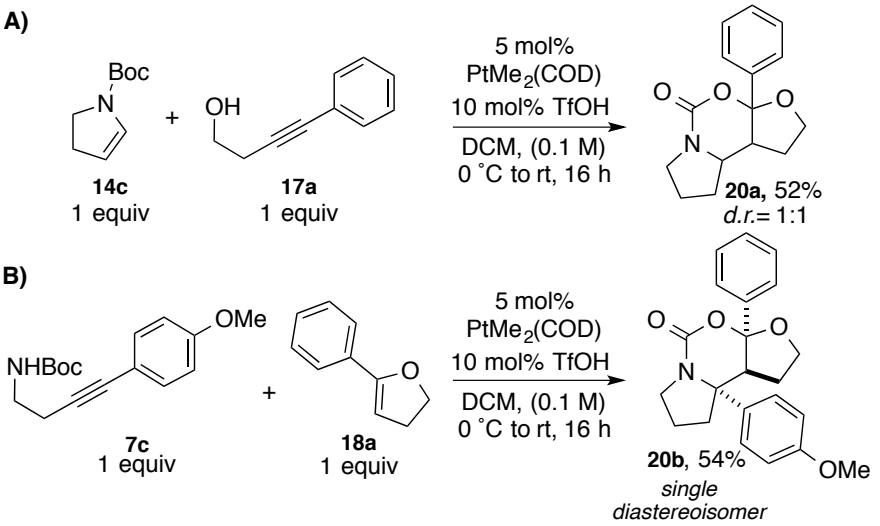
[168] a) For some examples of heterodimerisation of unbiased alkenes, see: P. W. Jolly, G. Wilke in *Applied Homogeneous Catalysis with Organometallic Compounds*, 2nd ed. (Eds.: B. Cornils, W. A. Herrmann), Wiley-VCH, Weinheim, **2002**, *Vol. 3*, pp. 1164. b) For some examples of the heterodimerisation of an unbiased alkene with an electron-poor alkene, see: Y. Ura, H. Tsujita, K. Wada, T. Kondo, T. Mitsudo, *J. Org. Chem.*, **2005**, *70*, 6623. c) For examples of the heterodimerisation of an unbiased alkene with an electron-rich alkene, see: H. Tsujita, Y. Ura, S. Matsuki, K. Wada, T. Mitsudo, T. Kondo, *Angew. Chem. Int. Ed.*, **2007**, *46*, 5160. d) For examples of the heterodimerisation of an unbiased alkene with an electron-rich alkene developed in our group, see: 1) J. Barluenga, L. Álvarez-Rodrigo, F. Rodríguez, F. J. Fañanás, *Angew. Chem. Int. Ed.*, **2004**, *43*, 3932. 2) J. Barluenga, L. Álvarez-Rodrigo, F. Rodríguez, F. J. Fañanás, *Angew. Chem. Int. Ed.*, **2006**, 45, 6362. 3) J. Barluenga, L. Álvarez-Rodrigo, F. Rodríguez, F. J. Fañanás, T. L. Sordo, P. Campomanes, *Angew. Chem. Int. Ed.*, **2007**, *46*, 2607.



Scheme 1.B.2 Initial experiments.

1.B.2.2 Studies Involving Independent Hydroamination or Hydroalkoxylation Reactions

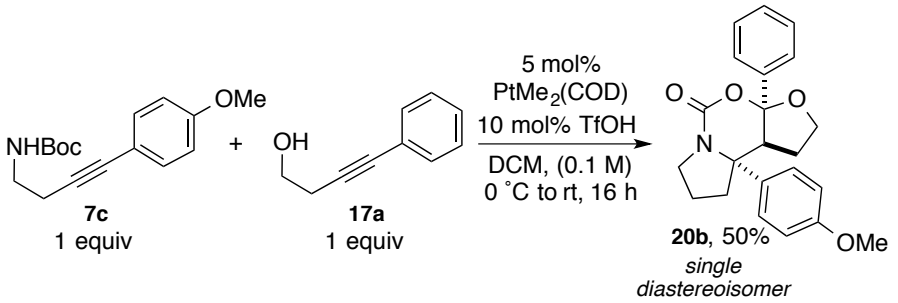
To study the feasibility of the proposed cascade process, the hydroalkoxylation of alkynols **17** and *N*-Boc alkynamines **7** was initially evaluated in independent experiments. In the first one, the reaction of the cyclic *N*-Boc enamine **14c** and 4-phenylbut-3-yn-1-ol **17a** was tested. In this case, the combination of 5 mol% of $PtMe_2(COD)$ and 10 mol% of triflic acid (TfOH) was chosen as catalytic binary system. When the reaction was performed in dichloromethane as solvent from 0 °C to room temperature for 16 hours, the compound **20a** was isolated in a yield similar to that obtained in the former experiment with the cyclic enol ether **18a** and again as a mixture of diastereoisomers (*d.r.*= 1:1) (**Scheme 1.B.3**, **eq. A**). In a second experiment, the feasibility of the hydroamination reaction of **7c** and the subsequent coupling with an enol ether (**18a** in this case) was evaluated. When the reaction was performed under the same reaction conditions tested before, the desired tricyclic compound (3a*S**,9a*R**,9b*S**)-9a-(4-methoxyphenyl)-3a-phenyloctahydro-5*H*-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin-5-one **20b** was isolated in moderate yield (54%) but interestingly as a single diastereoisomer (**Scheme 1.B.3**, **eq. B**).



Scheme 1.B.3 Studies involving a hydroamination or hydroalkoxylation reaction.

1.B.2.3 Double Cycloisomerisation/Heterocyclisation Cascade Process

Finally, the challenging double cycloisomerisation/heterocyclisation cascade process was studied. Thus, when one equivalent of the *N*-Boc alkynamine derivative **7c** was reacted with one equivalent of the alkynol derivative **17a** in the presence of 5 mol% of $PtMe_2(COD)$ and 10 mol% of TfOH in dichloromethane as solvent from 0 °C to room temperature for 16 hours, the desired tricyclic 5*H*-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin-5-one derivative **20b** was obtained in 50% yield and as single diastereoisomer (**Scheme 1.B.4**). It should be remarked that in this new transformation, in a single step and starting from two very simple acyclic compounds **7c** and **17a**, a tricyclic product **20b** is obtained in a process where four new bonds and three stereogenic centres (being two of them quaternary) are selectively formed.



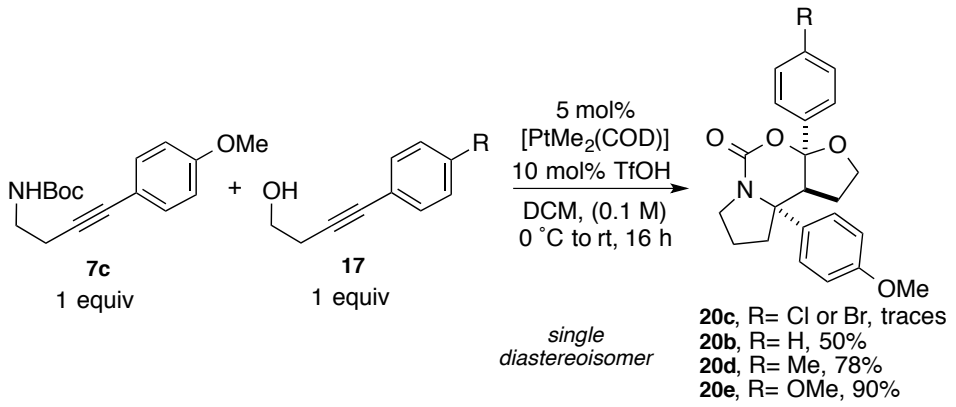
Scheme 1.B.4 Double cycloisomerisation/heterocyclisation cascade process.

1.B.2.4 Optimisation Studies

Once the viability of the proposed cascade reaction was demonstrated, investigations were centred on the optimisation of the reaction conditions. Several combinations of platinum-, gold-, and palladium-based metallic complexes ($PtMe_2(COD)$, $PtCl_4$, $PtCl_2$, AuCl, $AuCl_3$, $AuMePPh_3$, $[Pd(MeCN)_4](BF_4)_2$), Brønsted acids (TfOH, Tf_2NH, HBF_4) and solvents (DCM, THF, toluene, Et_2O, MeCN, DMF, MeOH, $CHCl_3$, fluorobenzene) were tested in the model reaction with the starting materials **7c** and **17a** from 0 °C to room temperature (see **Scheme 1.B.4**). Unfortunately, these attempts did not lead to significant improvements in the efficiency of the process and then, the conditions shown in **Scheme 1.B.4** were considered as the optimal (5 mol% $PtMe_2(COD)$ and 10 mol% TfOH).

As shown in **Scheme 1.B.1**, our proposal includes a step where the enol ether **18** reacts with the iminium species **8** through a nucleophilic attack. In this context, it was supposed that the nature of the R^2-group (**Scheme 1.B.1**) should exert an influence on the outcome of the reaction. Particularly, it was thought that an electron-donating R^2-group should improve the nucleophilic capacity of the formed enol ether **18** and the attack to **8** should be favoured.

In order to probe if this assumption was correct a set of experiments was performed with *N*-Boc alkynamine **7c** and different alkynol derivatives **17** containing in their structure an aromatic ring substituted with electron-donating, neutral and electron-withdrawing groups (**Scheme 1.B.5**, note that enol ethers **18** with different electronic properties would be generated). Thus, when the phenyl group was substituted by a 4-methylphenyl group, the isolated yield was improved to 78% and delightfully an electron-richer 4-methoxyphenyl substituent at the carbon-carbon triple bond of the alkynol **17** gave the desired compound **20e** in 90% isolated yield and as single diastereoisomer (**Scheme 1.B.5**). Notably, this efficient process was performed with equimolar amounts of the reactants (*N*-Boc alkynamine **7** and alkynol **17**) and the use of an excess of some of them is not required. Nevertheless, when alkynols **17** decorated with 4-chlorophenyl or 4-bromophenyl aromatic rings were tested, the corresponding products were observed as traces in the crude of the reaction mixtures. In these particular cases, formation of the corresponding ketones derived from the hydration of the triple bond of **7** and **17** at the distal carbon was the main reaction observed.



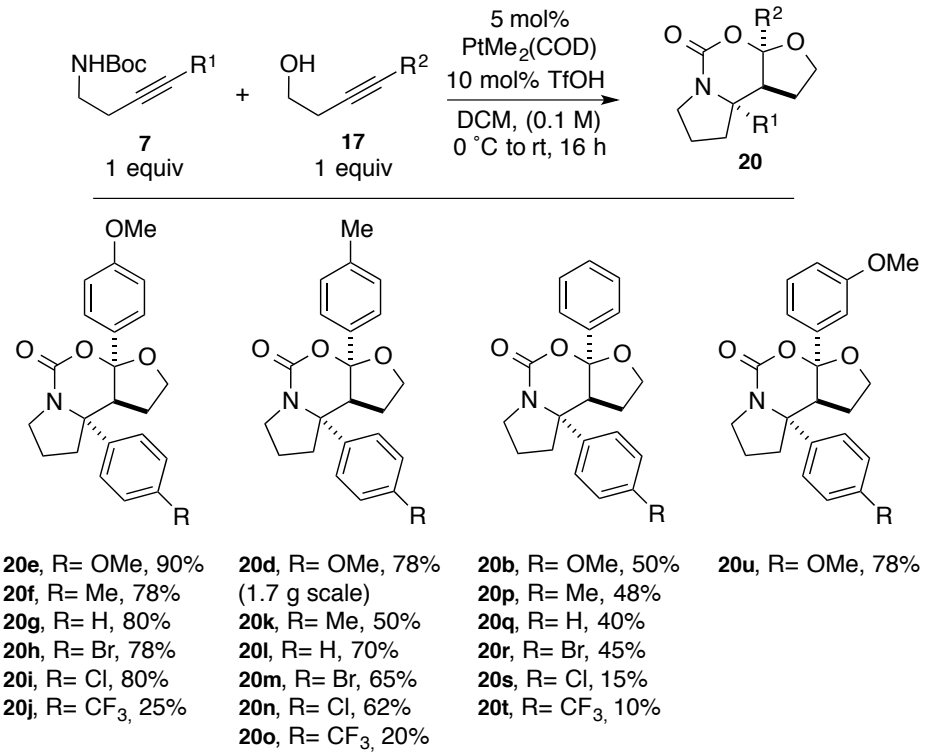
Scheme 1.B.5 Influence of the electronic properties of the aromatic rings in the alkynol counterpart **17**.

1.B.2.5 Scope of the reaction: Synthesis of 5*H*-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin-5-one Derivatives

The scope of this new cascade reaction was surveyed by probing changes to the *N*-Boc alkynamine and the alkynol derivatives (**7** and **17**). Firstly, a series of heterodimeric 5*H*-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin-5-one derivatives **20** were synthesised using unsubstituted starting materials at the aliphatic chain joining the corresponding *N*-Boc amine group or hydroxyl group and bearing in both cases aromatic groups at the carbon-carbon triple bond.

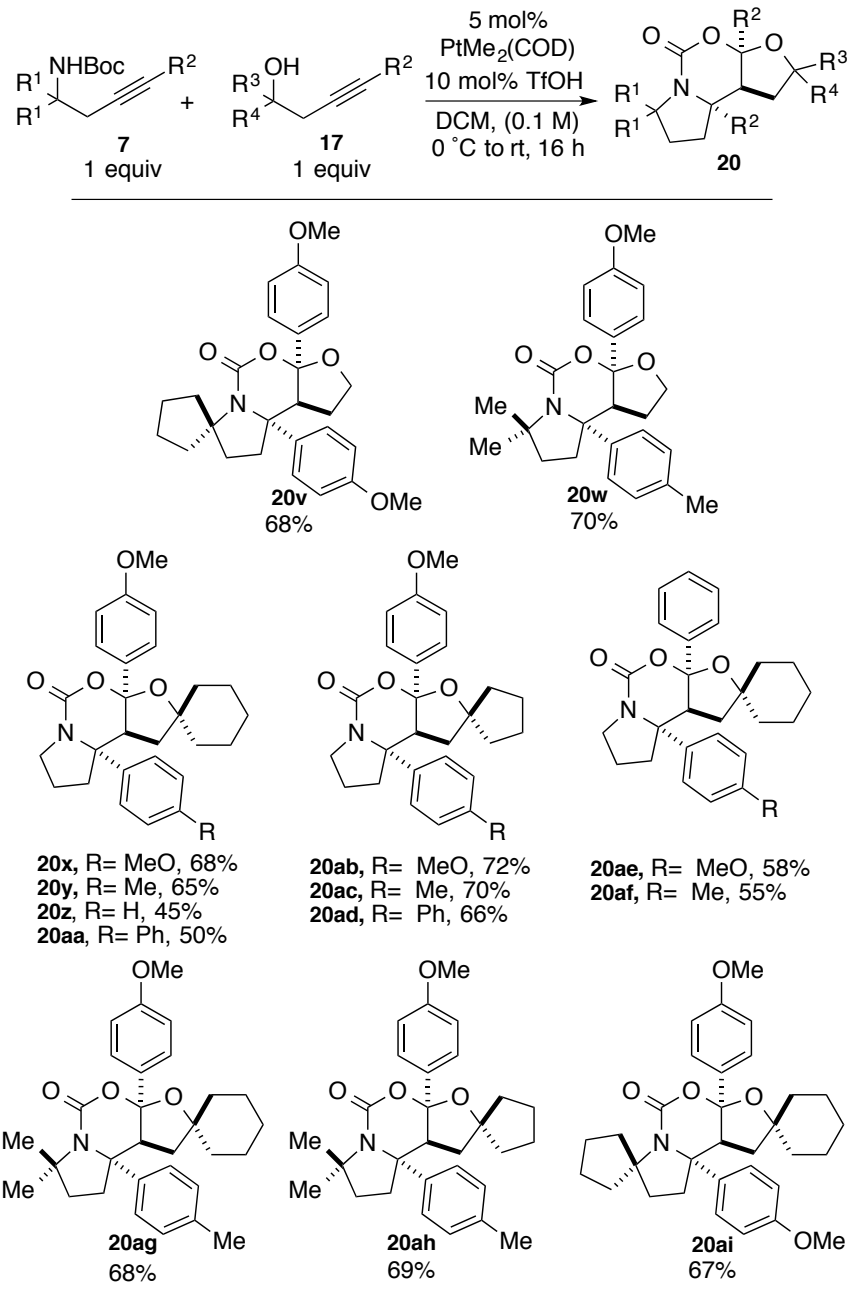
As it is shown in **Scheme 1.B.6**, the best results were obtained when 4-methoxyphenyl was placed at the triple bond of the alkynol counterpart **17** obtaining the desired compounds **20e-i** from very good to excellent yields when 4-methoxyphenyl, 4-methylphenyl, phenyl, 4-bromophenyl and 4-chlorophenyl were the substituents at the carbon-carbon triple bond of the alkynamine derivative **7** (78-90%). However, when the alkynamine **7** containing the electron-poorer 4-trifluoromethylphenyl group was used, the corresponding compound **20j** was isolated in only 25% yield. The use of the alkynol derivative **17** containing a 4-methylphenyl group as substituent gave slightly lower yields (**20d** and **20k-o**, 20–78%), and they were even lower when the alkynol counterpart **17** was substituted with a simple phenyl group (**20b** and **20p-t**, 10–60%). Moreover, alkynol derivatives **17** containing meta-substituted aromatic rings were also appropriate substrates giving the desired product **20u** in good yield (78%). It should be noted that in all the cases the desired products **20b-u** were isolated as single diastereoisomers. Furthermore, it was verified that the reaction could be perfomed on a gram scale, and thus, 1.7 grams of **20d** were easily prepared in one

batch without any negative influence in the yield or the stereoselectivity of the process.



Scheme 1.B.6 Scope of the reaction with *N*-Boc alkynamine and alkynol derivatives **7** and **17** unsubstituted on the aliphatic chain.

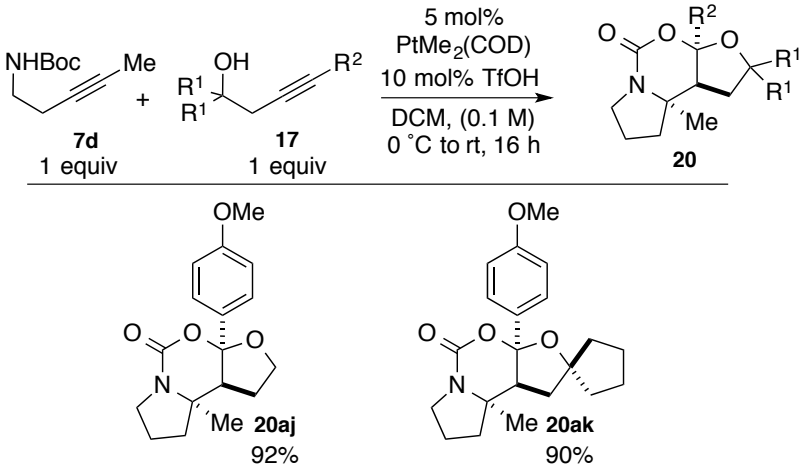
In the following step, the scope of the process was evaluated by the use of different alkynamines **7** and alkynol derivatives **17** substituted at the aliphatic chain. Therefore, a set of interesting polycyclic 5*H*-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin-5-one heterocoupling products **20** derived from the substitution of the alkynamine aliphatic chain (**20v** and **20w**), the alkynol aliphatic chain (**20x-20af**) and both of them (**20ag-20ai**) were easily synthesised in moderate to good yields (45–72%) and as single diastereoisomers (**Scheme 1.B.7**)



Scheme 1.B.7 Scope of the reaction with *N*-Boc alkynamine and alkynol derivatives **7** and **17** substituted on the aliphatic chain.

Moreover, regarding to the alkyne moiety substitution, *N*-Boc alkynamine derivatives **7** containing an aliphatic group at the carbon-carbon triple bond (i.e. **7d**) were also appropriate candidates for the cascade reaction, affording the methyl-substituted products **20aj** and 2**0ak** in excellent yields (92 and 90%) (**Scheme 1.B.8**). However, when the alkyne moiety of the alkynol derivative **17** was

alkyl-substituted it was not possible to observe the formation of the desired compound and neither when *N*-Boc alkynamine **7** and/or alkynol derivative **17** bearing a terminal alkyne were tested.



Scheme 1.B.8 Use of alkynamine derivative alkyl-substituted at the triple bond.

The structure and relative configuration of the stereogenic centres of the heterocoupling derivatives **20** was determined by single cristal X-ray diffraction analysis techniques performed on (3a*S**,9a*R**,9b*S**)-9a-(4-bromophenyl)-3a-(4-methoxyphenyl)octahydro-5*H*-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin-5-one **20h** (**Figure 1.B.1**).

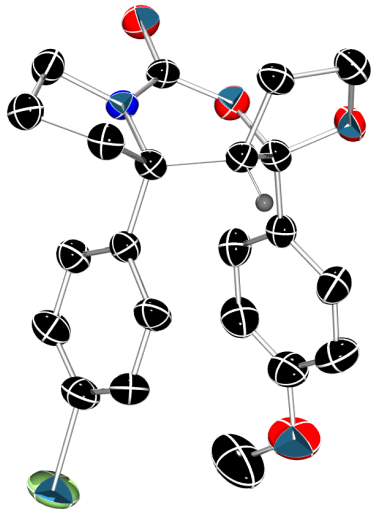
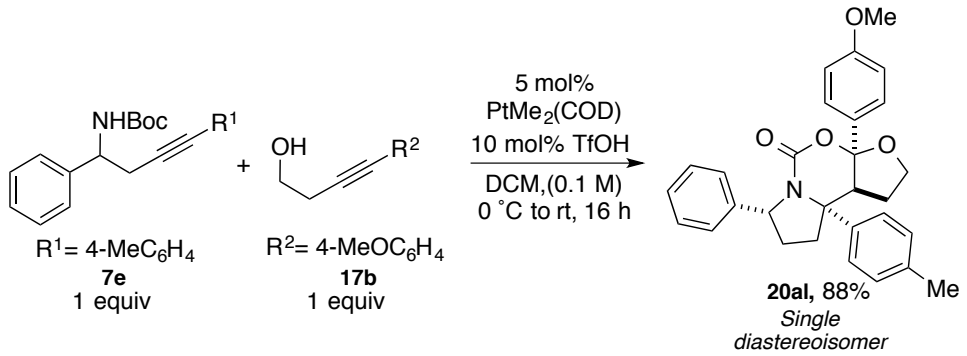


Figure 1.B.1 ORTEP representation of the structure of the heterocoupling derivative **20h** determined by single crystal X-ray diffraction techniques.

Therefore, as it is shown in the ORTEP representation, considering the furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin-5-one core, both aromatic rings are placed in *cis*-disposition in the molecule.

1.B.2.6 Use of Chiral (Racemic) Alkynamine Derivatives

A particularly interesting result was obtained when the chiral (racemic) *N*-Boc alkynamine derivative **7e** was used as starting material (**Scheme 1.B.9**). In this example, the expected product **20al** was isolated in very high yield and as a single diastereoisomer. Thus, a product with four stereogenic centres was selectively formed from a starting material with just one stereocenter, indicating that the chiral centre of the *N*-Boc alkynamine derivative **7e** influences efficiently the formation of the three new stereocenters in **20al**. This result is significant, because it indicates that it is possible to synthesise enantiomerically pure products **20** through a substrate-controlled process starting from chiral (non-racemic) *N*-Boc alkynamine derivatives **7**.



Scheme 1.B.9 Cascade reaction using the chiral (racemic) *N*-Boc alkynamine derivative **7e**.

The structure and relative configuration of the stereogenic centres of **20al** were determined by the two-dimensional NMR experiment NOESY (**Figure 1.B.2**). The double doublet centred at 7.42 ppm (dd, *J*= 7.2, 1.3 Hz) was assigned to $\mathbf{H_a}$ The doublets centred at 6.91 (d, *J*= 7.9 Hz) and 6.90 ppm (d, *J*= 8.9 Hz) and were assigned to $\mathbf{H_b}$ and $\mathbf{H_c}$, respectively. Finally, the double doublet centred at 3.37 ppm (dd, *J*= 10.9 and 8.7 Hz) was assigned to $\mathbf{H_d}$.

The cross-peak signals arising from protons close in space observed in the NOESY two-dimensional NMR experiment ($\mathbf{H_b}$ and $\mathbf{H_d}$, and $\mathbf{H_c}$ and $\mathbf{H_d}$ in blue, **Figure 1.B.2**) showed that the considering the furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin-5-one core, the 4-methoxyphenyl substituent is placed in a *cis* disposition related to the 4-methylphenyl group and both groups are in *cis* disposition with $\mathbf{H_d}$.[169] Thus, it

[169] See NMR Spectra Appendix.

could be concluded that the diastereoisomer obtained in this case is the same one previously assigned with the single crystal X-ray diffraction techniques analysis (see **Figure 1.B.1**). Moreover, the cross-peak signals between $\mathbf{H_c}$ and $\mathbf{H_b}$ (in purple, **Figure 1.B.2**) showed that the 4-methylphenyl group and the phenyl group are on the same face of the molecule.

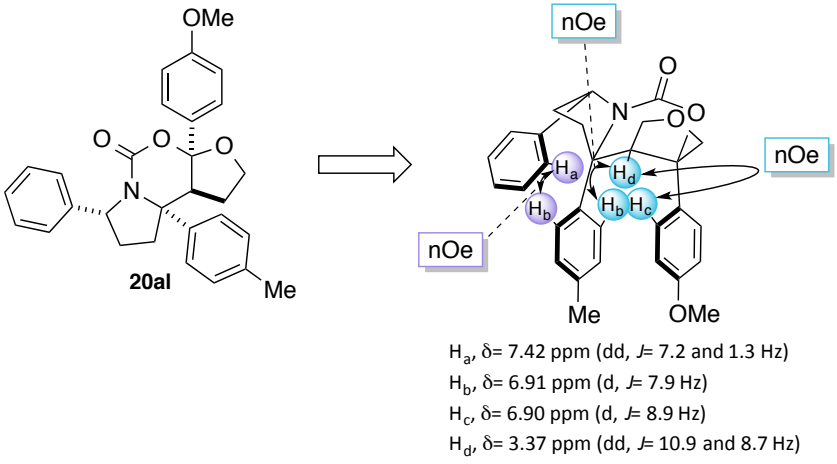
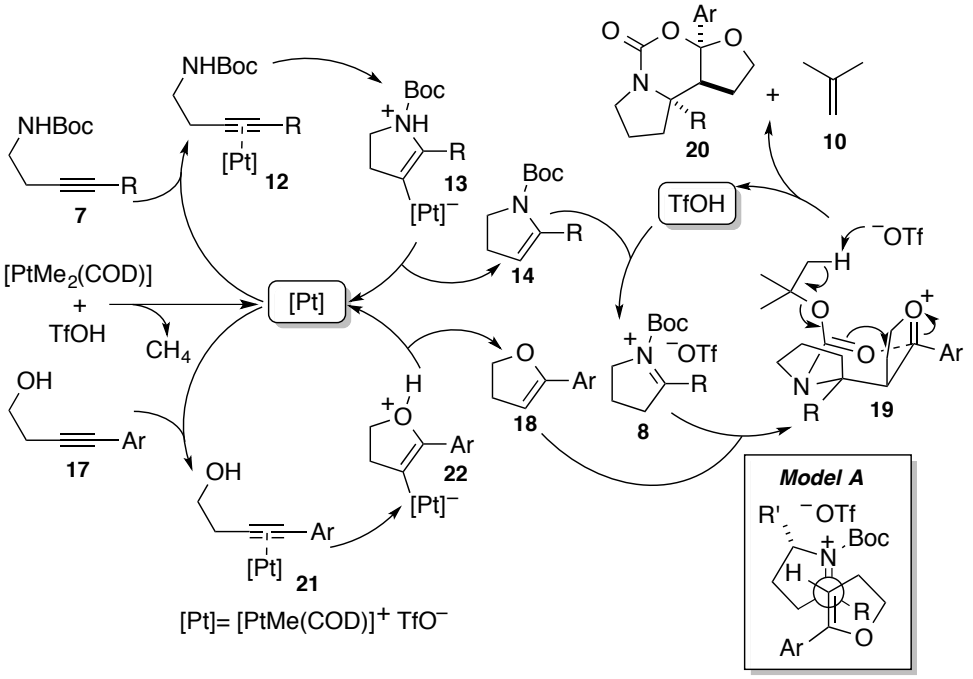


Figure 1.B.2 Determination of the relative configuration of **20al** through NOESY experiment.

1.B.2.7 Mechanistic Proposal

A plausible mechanism for the formation of the products **20** from alkynol **17** and *N*-Boc alkynamine derivatives **7** through a platinum(II)/triflic acid orthogonal-relay catalytic process is illustrated in **Scheme 1.B.10**. First of all, formation of a reactive cationic platinum complex $[PtMe(COD)]^{+}TfO^{-}$ from $PtMe_2(COD)$ by reaction with TfOH in a process in which a molecule of methane is released is supposed. This cationic platinum complex promotes the cycloisomerisation of both the *N*-Boc alkynamine derivative **7 and** the alkynol **17** in two independent catalytic cycles. Thus, coordination of the metallic complex to the triple bond of **7** and **17** affords intermediates **12** and **21**, respectively. Intramolecular addition of the amino group of **12** and the hydroxyl group of **21** to the distal carbon atom of the triple bond generates **13** and **22**. Further protodemetalation processes afford the *N*-boc enamine derivatives **14** and the enol ether **18**, correspondingly, after the release of the catalytic metallic species. At this point, the *N*-boc enamine **14** and the enol ether **18** enter the third catalytic cycle. Triflic acid promotes the formation of the iminium specie **8**, which reacts with the preformed enol ether **18** via nucleophilic attack to give the oxonium intermediate **19**. The observed stereochemical outcome of the reaction is consistent with model A (**Scheme 1.B.10**) in which the steric interactions are minimised. This model also justifies the

substrate-directed formation of a single diastereoisomer, when a chiral (racemic) starting alkynamine derivative **7e** is used as starting material (product **20al**). In model A, the enol ether **18** approaches the corresponding iminium species **8** from the opposite face from where the R' substituent is placed. The observed stereochemical outcome of the reaction is also consistent with a final cyclisation step through a chair-like transition state **19**. In this model, the R and Ar groups are placed in a pseudo-equatorial position. The situation of the oxygen atom of the oxonium ion in a pseudo-axial position may also be favoured by an anomeric effect. This final cyclisation would deliver the final products **20**, a molecule of isobutylene **10** and a molecule of triflic acid, which initiates a new catalytic cycle.

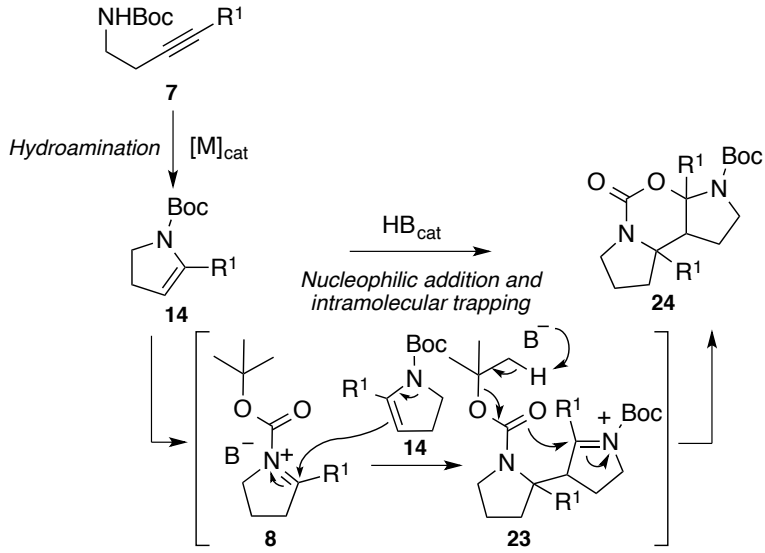


Scheme 1.B.10 Mechanistic proposal: orthogonal-relay catalytic cycle.

It should be remarked that, interestingly, in this orthogonal-relay catalytic cascade process a platinum cationic complex efficiently promotes two cycloisomerisation reactions (hydroamination and hydroalkoxylation) to afford the corresponding intermediates **14** and **18** in two independent catalytic cycles. Moreover, the Brønsted acid promotes, in a third catalytic cycle, the formation of the activated iminium species **8** from the *N*-Boc enamine derivative **14** favouring the nucleophilic attack of the enol ether counterpart **18**. This example further demonstrates the utility of multicatalytic reactions for the transformation of simple starting materials into complex molecules in a simple way.

1.B.2.8 Chemoselectivity of the Process

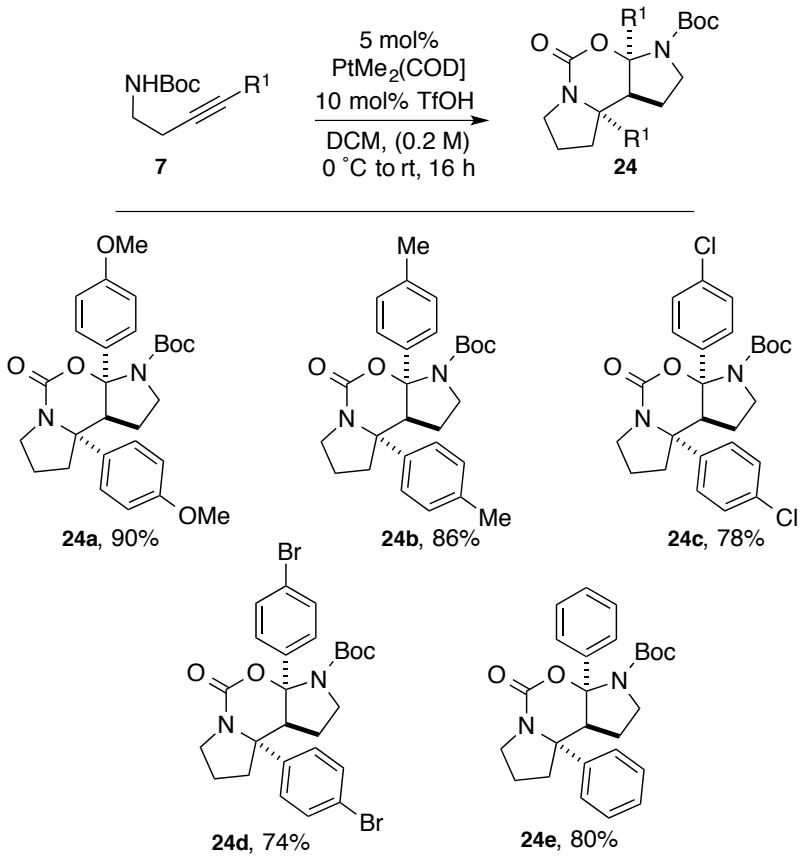
As shown in the mechanism of this reaction, once the iminium species **8** is formed, the nucleophilic attack of the preformed enol ether derivative **18** seems to be the preferred reaction (see **Scheme 1.B.10**). However, an alternative process could be that in which the nucleophilic attack of the *N*-boc enamine derivative **14** to the iminium species **8** would generate the cationic species 23 that would be trapped by the Boc group present in the molecule delivering the homodimer dipyrrolo[1,3]oxazin-5-one derivative **24** (**Scheme 1.B.11**). This alternative reaction was not observed in any of our experiments performed with alkynol derivatives **17**.[170]



Scheme 1.B.11 Formation of homocoupling product **24**.

However, it was thought that formation of the homodimers dipyrrolo[1,3]oxazin-5-one derivatives **24** could be possible by performing the reaction in the absence of the alkynol derivative **17**. In fact, when *N*-Boc alkynamines **7** were reacted in the presence of 5 mol% of $PtMe_2$(COD) and 10 mol% of TfOH, dipyrrolo[1,3]oxazin-5-one derivatives **24**, resulting from the reaction of two molecules of the corresponding *N*-Boc alkynamine derivative **7**, were formed and isolated in high yield and as single diastereoisomers (**Scheme 1.B.12**).

[170] Formation of dipyrrolo[1,3]oxazin-5-one derivative **24** was observed in Chapter 1, Part A as by-product in some experiments.



Scheme 1.B.12 Synthesis of homocoupling products from alkynamines **24**.

At this point, the high chemoselectivity (heterodimerisation vs. homodimerisation) of the reaction of *N*-Boc alkynamines **7** and alkynols **17** should be remarked, as when the cascade reactions are performed with just one equivalent of the alkynol **17** and one equivalent of the *N*-Boc alkynamine counterpart **7**, formation of heterodimers **20** was exclusive.

Again, the structure and relative configuration of the stereogenic centres of the dipyrrolo[1,3]oxazin-5-one derivatives **24** was determined by single crystal X-ray diffraction analysis techniques performed on *tert*-butyl (3a*S**,9a*R**,9b*S**)-5-oxo-3a,9a-di-*p*-tolyloctahydro-3*H*,5*H*-dipyrrolo[1,2-*c*:3',2'-*e*][1,3]oxazine-3-carboxylate **24b** (**Figure 1.B.3**). Therefore, as it is shown in the ORTEP representation, considering the dipyrrolo[1,3]oxazin-5-one core both aromatic rings are placed in *cis*-disposition in the molecule.

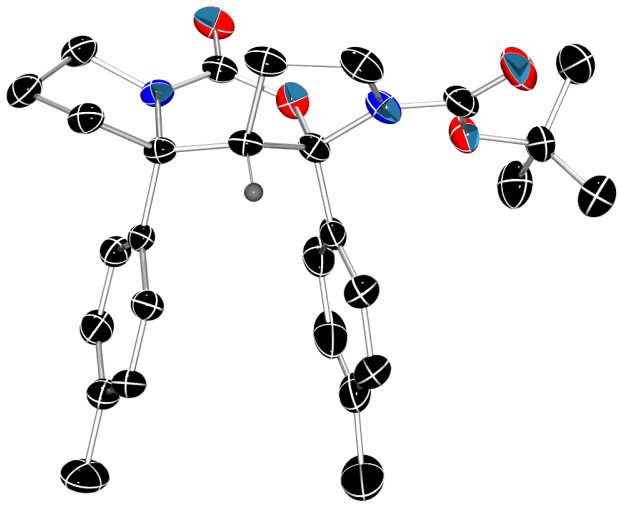


Figure 1.B.3 ORTEP representation of the structure of the homocoupling dipyrrolo[1,3]oxazin-5-one derivatives **24b** determined by single crystal X-ray diffraction techniques.

The exclusive formation of the 5*H*-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin-5-one heterocoupling derivatives **20** when the reaction is performed with equimolecular amounts of *N*-Boc alkynamines **7** and alkynols **17** could be tentatively explained by the nucleophilicity of the *N*-Boc enamine intermediate **14** and the enol ether **18**, and also considering that when these two intermediates react in the presence of a Brønsted acid, several equilibrium reactions might be involved.

Although the nucleophilicity of **14** and **18** should not be so different,[171] the enol ether **18** is considered a better nucleophile. This is in agreement with the observed chemical shift of C2 in ^{13}C–NMR of the corresponding derivatives **14** (~100 ppm) and **18** (~90 ppm) (**Figure 1.B.4**). This indicates that C2 of the enol ether counterpart **18** has a higher electronic density than the one of **14**, and so, it should be a better nucleophile.

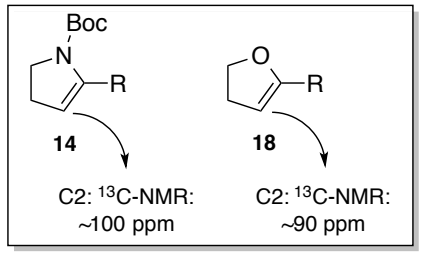
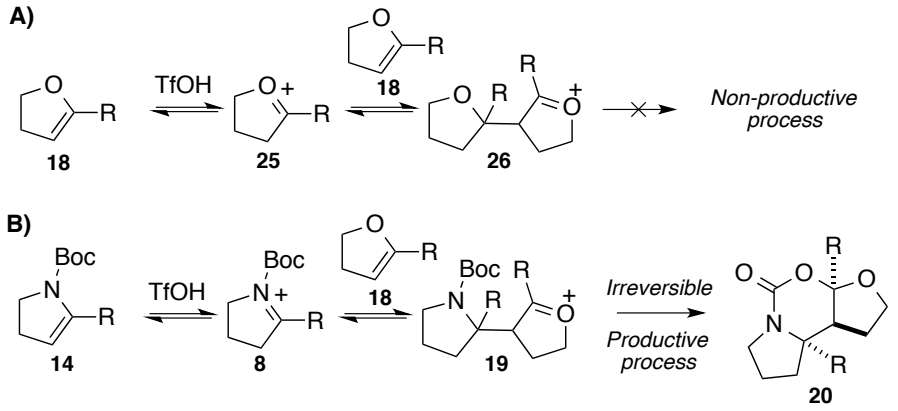


Figure 1.B.4 Chemical shift of C2 in ^{13}C–NMR of the corresponding derivatives **14** and **18**.

[171] B. Maji, S. Lakhdar, H. Mayr, *Chem. Eur. J.*, **2012**, *18*, 5732.

With all this in mind, it is supposed that in the presence of the Brønsted acid, the best nucleophile (enol ether **18**) should react with the acid at a higher extension than the enamine derivative **14**. Thus, equilibrium between **18** and the oxonium species **25** should be established. Intermediate **25**, in the presence of another molecule of the best nucleophile in the reaction media (enol ether **18**) should be in equilibrium with dimer **26**. It was thought that in this case, the absence of any terminating group able to trap the oxonium species **19** avoids further evolution of this species **26**. Thus, these equilibrium reactions are a non-productive process (**Scheme 1.B.13**, **eq. A**).

Although probably less favourable, an alternative pathway implies the protonation of the *N*-Boc enamine derivative **14** to give the iminium species **8** in small equilibrium concentrations. At this point, after the nucleophilic attack of the enol ether **18** to this activated species **8**, the presence of the Boc group seems to be crucial, because it serves as a terminating group, trapping the oxonium intermediate **19** through an irreversible process, and thus, making the global reaction a productive process affording compounds **20** (**Scheme 1.B.13**, **eq. B**).



Scheme 1.B.13 Plausible explanation of the chemoselectivity of the heterocoupling process.

This hypothesis would explain the absence of homodimerisation processes when the reactions were performed in the presence of the alkynol moiety **17**.

1.B.3 Summary

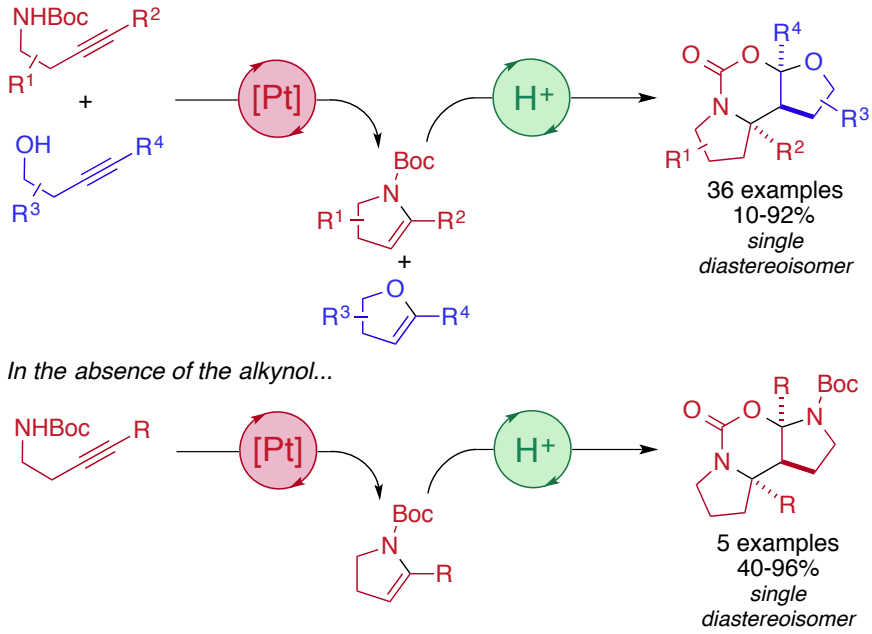
In summary, a new catalytic cascade reaction for the synthesis of complex heterocyclic products from simple *N*-Boc alkynamine and alkynol derivatives ihas been described (**Scheme 1.B.14**).

Moreover, this new double cycloisomerisation/heterodimerisation cascade reaction represents an unprecedented *in situ* generation and heterocoupling reaction of two different electron-rich alkenes.

The global transformation includes the formation of a tricyclic product from two simple acyclic starting materials in a process in which four new bonds and three stereogenic centers (two of them quaternary) are created in a stereocontrolled fashion.

This reaction proceeds through an orthogonal-relay one-pot catalytic cascade process that implies the initial platinum-catalysed cycloisomerisation reaction of the *N*-Boc alkynamine and alkynol derivative followed by a trilic acid-promoted nucleophilic addition of the *in situ* generated enol ether to the iminium species. The presence of the Boc group is crucial, making the process irreversible.

Finally, the high chemoselectivity of the process to get heterocoupling products should be remarked, as in the absence of the alkynol derivatives homodimers are obtained.



Scheme 1.B.14 Summary.

Chapter 2

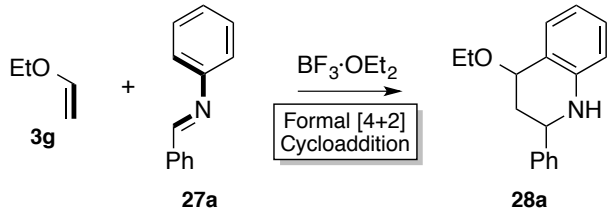
Brønsted Acid Catalysed Multicomponent Coupling Reactions of Indolecarbaldehyde Derivatives, Anilines and Electron-Rich Alkenes. Beyond the Povarov Reaction

2.1 Introduction

As outlined in the General Introduction of this thesis, our group has developed several new multicomponent cascade reactions promoted by the combination of a transition-metal catalyst and a Brønsted acid (see **Section I.4.3.3**, General Introduction). In this context, those multicomponent coupling reactions of aldehydes, anilines and alkynol derivatives are very attractive because they allow the assembly of interesting tetrahydroquinoline derivatives in a very straightforward way (**Schemes I.68** and **I.70**, General Introduction).[153, 154] These processes can be considered as formal [4+2]-cycloaddition reactions between *N*-arylimines and enol ethers in a process where these two reagents are formed *in situ*. It should be noted that these particular formal [4+2]-cycloaddition reactions are known as Povarov reactions. Because the results contained in this chapter are closely related to this reaction, a brief introduction about this process is presented in the next section.

2.1.1 Bibliographic Background: The Povarov Reaction

At the beginning of the 1960s, during their investigations on the application of enol ethers in the synthesis of heterocycles, L. S. Povarov and co-workers described the reaction between enol ethers and *N*-arylimines such as **3g** and **27a** catalysed by $BF_3{\cdot}Et_2O$ for the synthesis tetrahydroquinoline derivatives **28** (**Scheme 2.1**).[172]



Scheme 2.1 First Povarov reaction reported.

This process was classified as a formal [4+2]-cycloaddition reaction where the *N*-arylimine **27** represented an electron-poor diene and the enol ether **3** an electron-rich dienophile. Thus, this reaction was considered a hetero-Diels-Alder reaction with inverse electron demand. In recognition to this contribution, [4+2]-

[172] a) L. S. Povarov, B. M. Mikhailov, *Izv. Akad. Nauk SSR, Ser. Khim.*, **1963**, 953. b) L. S. Povarov, B. M. Mikhailov, *Seriya Khimicheskaya,* **1964**, 2221. c) L. S. Povarov, B. M. Mikhailov, *Seriya Khimicheskaya,* **1964**, 1910. d) L. S. Povarov, V. I. Grigos, B. M. Mikhailov, *Seriya Khimicheskaya*, **1965**, 2163. e) L. S. Povarov, B. M. Mikhailov, *Russ. Chem. Rev.,* **1967**, 656.

cycloaddition reactions between *N*-arylimines and electron-rich olefins are referred in the literature as Povarov reactions.

As previously pointed out, this process offers an easy access to tetrahydroquinoline derivatives, a key structural motif in many biologically active products, either natural or synthetic (**Figure 2.1**).[173] As a consequence, great effort has been made in the context of the Povarov reaction and significant advances have been reported in the last decade.[174]

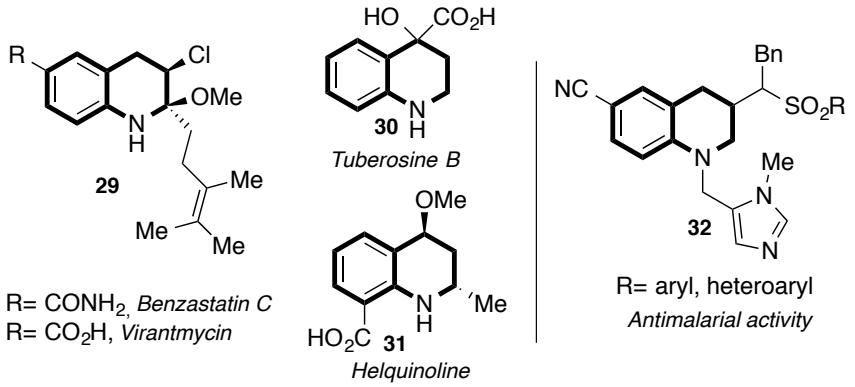


Figure 2.1 Tetrahydroquinoline-containing natural products and other biologically active molecules.

It should be noted that the Povarov reaction requires an acid to promote the cycloaddition process. First reactions reported in the literature involved the presence of stoichiometric amounts of Lewis acids. However, during the years several methodologies based on the use of catalytic acid species have appeared, including Lewis and Brønsted acids along with various metal salts and heterogeneous catalysts.

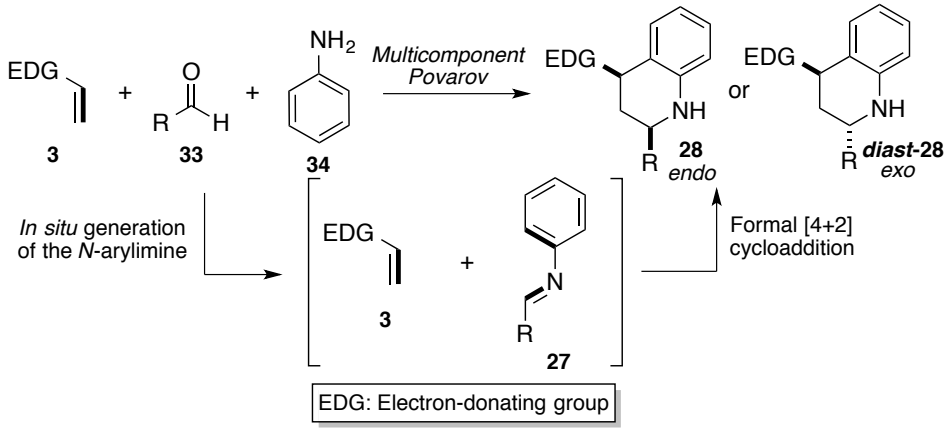
Most of the studies about the scope of the reaction have been made in the context of the olefin partner and thus, a large variety of electron-rich alkenes, ranging from vinyl (thio)ethers to cyclopentadiene, enamine/enamides and styrenes, have demonstrated their effectiveness. In this context, as previously described, our research group has been a pioneer in developing synthetic strategies that include the *in situ* generation of the electron-rich alkene through a

[173] Comprehensive reviews on the synthesis of tetrahydroquinolines and their biological significance: a) A. R. Katritzky, S. Rachwal, B. Rachwal, *Tetrahedron,* **1996**, *52*, 15031. b) V. Sridharan, P. A. Suryavanshi, J. C. Menéndez, *Chem. Rev.*, **2011**, *111*, 7157.

[174] For some revisions, see: a) V. A. Glushkov, A. G. Tolstikov, *Russ. Chem. Rev.*, **2008**, *77*, 137. b) V. V. Kouznetsov, *Tetrahedron* **2009**, *65*, 2721. c) V. Sridharan, P. A. Suryavanshi, J. C. Menendez, *Chem. Rev.*, **2011**, *111*, 7157. d) G. Masson, C. Lalli, M. Benohoud, G. Dagousset, *Chem. Soc. Rev.*, **2013**, *42*, 902. e) X. X. Jiang, R. Wang, *Chem. Rev.*, **2013**, *113*, 5515. f) M. Fochi, L. Caruana, L. Bernardi, *Synthesis,* **2014**, *46*, 135.

cycloisomerisation reaction (see **Schemes I.68** and **I.70**, General Introduction).

Regarding to the diene counterpart (the imine), it is particularly interesting the *in situ* generation of the *N*-arylimine **27** via condensation of the corresponding aldehyde **33** and the aromatic amine derivatives **34** (**Scheme 2.2**). This strategy allows the synthesis of tetrahydroquinoline derivatives **28** though a three-component coupling process.[175] The use of aromatic aldehydes gives very good results. Thus, a wide range of Povarov processes have been developed using aromatic and heteroaromatic aldehydes derivatives with different electronic properties (electron-poor, neutral or electron-rich). However, the scope of the Povarov reaction is very narrow when aliphatic aldehydes are used and the processes reported with this kind of substrates are not very efficient. Instead, the generality of the reaction with regard to the amine counterpart is diverse, and several aromatic and heteroaromatic primary amines have been used in this process.



Scheme 2.2 Multicomponent Povarov reaction.

As far as the stereochemistry of the reaction is concerned, most Povarov processes afford, with variable selectivity, 2,4-*cis*-tetrahydroquinoline derivatives **28** coming from a formal *endo* approximation between the diene and the dienophile. However, some exceptions to this 2,4-*cis* selectivity and some

[175] The three-component ABC combination is the most popular version of the multicomponent Povarov reaction. However, it is also amenable to other combination patterns, such as ABB' (the imine is formed by aniline addition to the alkene under acidic catalysis) or AA'BB' (the reaction occurs between an enamine and an imine, both derived from the same aldehyde and aniline species). For more information see ref. 174f.

examples of a formal *exo* approximation can be found in the literature, especially with some particular 1,2-disubstituted dienophiles (**Scheme 2.2**).[176,154]

The usefulness of the Povarov reaction is evidenced by its numerous applications in the synthesis of natural products and other biologically active molecules. Just as an example concerning natural products, alkaloids martinelline and martinellic acid **35** (**Figure 2.2**.) have been synthesised through this strategy.[177] Regarding the preparation of biologically active agents, the selective antagonist of the G protein coupled receptor GPR30 **36**, has been also synthesised by the multicomponent Povarov reaction between 2-bromopiperonal, aniline and cyclopentadiene (**Figure 2.2**).[178]

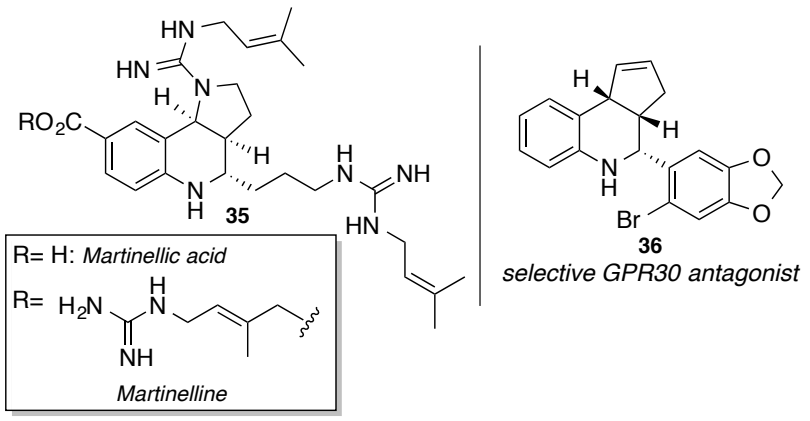


Figure 2.2 A natural product and a biologically active molecule prepared by Povarov cycloaddition reaction.

Asymmetric variants of the reaction have also been successfully achieved and enantiomerically pure tetrahydroquinolines have been synthesised in the presence of chiral catalysts. Although the first example was reported by Ishitani and Kobayashi in 1996,[179] studies on the enantioselective version of this reaction did not catch the attention of chemists in subsequent years. However, this has changed dramatically very recently due to the exponential growth of efficient Brønsted acid-based catalysts for imine activation.[174c,180] As previously described in

[176] See, for example: a) B. A. Batey, D. A. Powell, *Chem. Commun.*, **2001**, 2362. b) E. Vicente-García, F. Catti, R. Ramón, R. Lavilla, *Org. Lett.*, **2010**, *12*, 860. c) S. Maiti, J. C. Menéndez, *Synlett*, **2009**, 2249.

[177] D. A. Powell, R. A. Batey, *Org. Lett.*, **2002**, *4*, 2913.

[178] M. K. Dennis, R. Burai, C. Ramesh, W. Petrie, S. N. Alcon, T. Nayak, C. G. Bologa, A. Leitao, E. Brailoiu, E. Deliu, N. J. Dun, L. A. Sklar, H. J. Hathaway, J. B. Arterburn, T. I. Oprea, E. R. Prossnitz, *Nat. Chem. Biol.*, **2009**, *5*, 421.

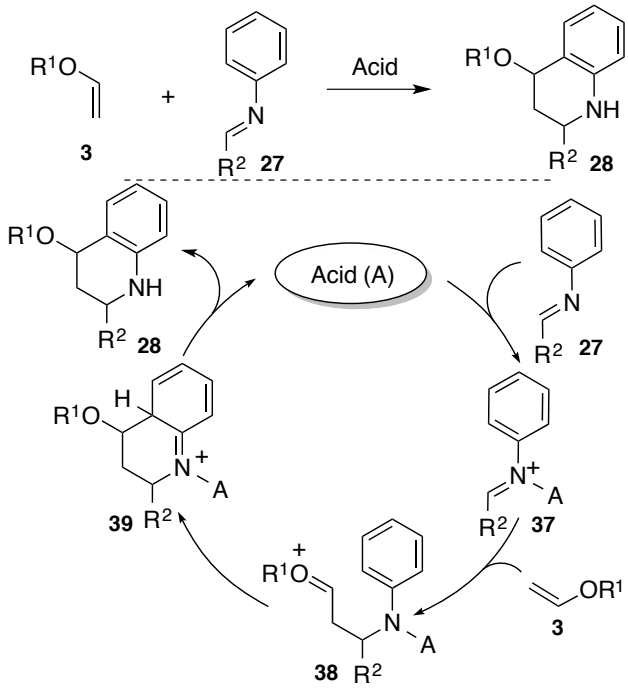
[179] Ishitani, H.; Kobayashi, S. *Tetrahedron Lett.*, **1996**, *37*, 7357.

[180] For some reviews on: 1) asymmetric Povarov reactions see: a) X. Jiang, R. Wang, *Chem. Rev.*, **2013**, *113*, 5515. 2) Brønsted-acid based catalysis: see **Section 1.4.2.3**, General Introduction.

the General Introduction, our research group has also contributed to this field by the development of a multicatalytic a multicomponent enantioselective Povarov reaction by the combination of a metallic complex and a chiral phosphoric acid.[154]

2.1.2 The Povarov Reaction: Mechanism

Although the Povarov reaction is defined as an inverse electron-demand aza-Diels-Alder process, it can be seen as well as a stepwise Mannich/Friedel-Crafts reaction (**Scheme 2.3**). Thus, a mechanistic proposal consisting on a stepwise process would start with the coordination of the catalytic acid species **A** to the imine **27** to form the activated species **37**. Subsequently, an oxonium ion intermediate **38** would be formed via the nuclephilic attack of the enol ether **3** to the activated imine **37**. This intermediate **38** would be trapped by the intramolecular nucleophilic addition of the electron-rich aromatic ring present in the molecule generating intermediate **39**. Finally, an aromatisation process would afford the final product **28**, closing the catalytic cycle and releasing the catalytic species **A**.



Scheme 2.3 Povarov reaction: stepwise mechanism.

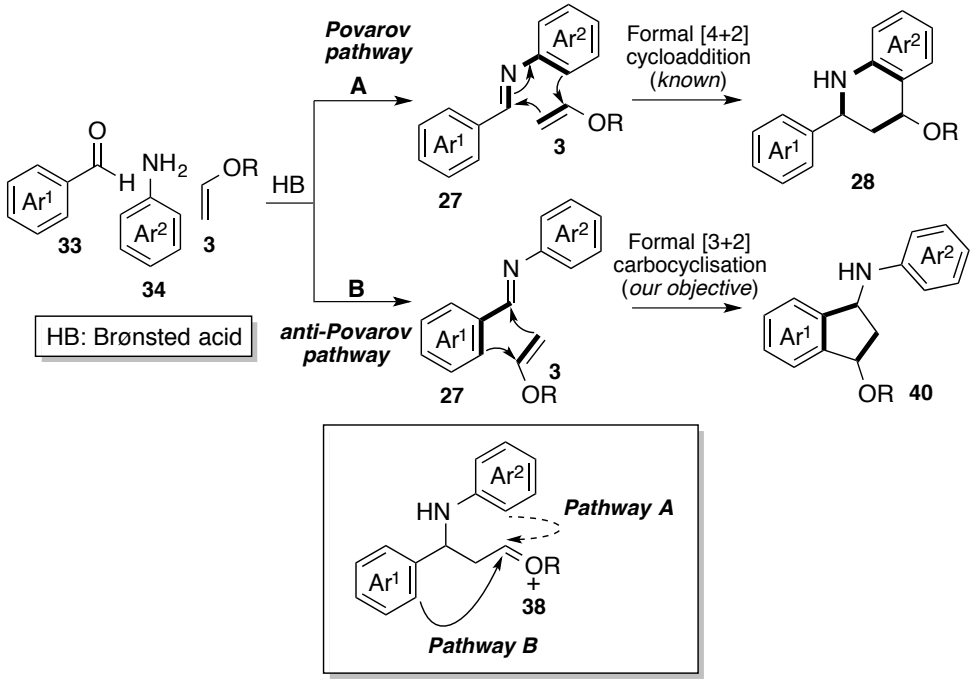
Part A

Stereoselective [3+2]-Carbocyclisation of 1-Substituted-1H-indol-2-carbaldehyde Imines and Electron-Rich Alkenes. A Divergent Synthesis of Cyclopenta[b]indole or Tetrahydroquinoline Derivatives

2.2.A Results and Discussion. Part A

2.2.A.1 Objective

The power of the formal [4+2]-cycloaddition Povarov reaction to synthesise tetrahydroquinoline derivatives **28** has been clearly shown in the previous section. Moreover, it has been described how this reaction can be understood as a process initiated by the formation of the cationic intermediate **38** (see **Scheme 2.4**, and see also mechanism in **Scheme 2.3**). The usual evolution of this intermediate is through the nucleophilic attack of the aromatic ring Ar^2 to the oxonium moiety to generate a tetrahydroquinoline derivative **28** (Povarov reaction; Pathway A, **Scheme 2.4**).



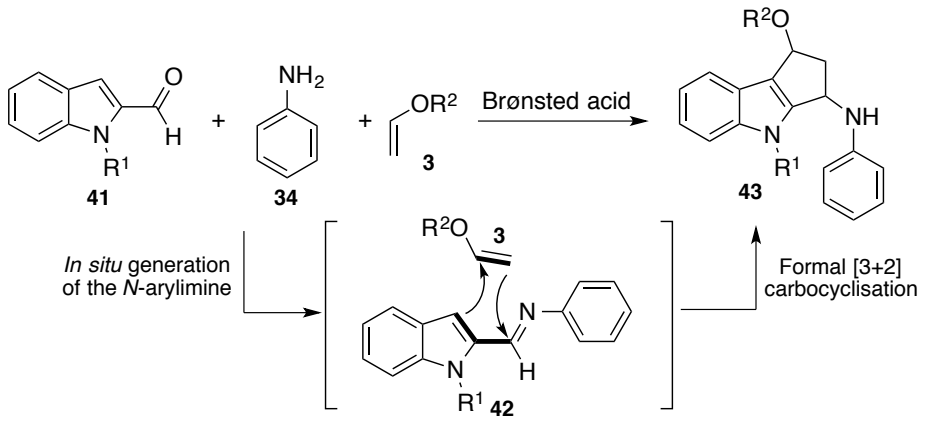
Scheme 2.4 Objective: new multicomponent formal [3+2]-carbocyclisation process.

However, it should be noted that in theory, once the oxonium intermediate **38** is formed, an alternative pathway implying the addition of the aromatic ring coming from the aldehyde counterpart **33** (Ar^1) to the oxonium in **38** is conceivable (Pathway B, **Scheme 2.4**). This process would afford interesting heterocyclic compounds **40** via a formal [3+2]-carbocyclisation reaction. Colloquially, we refer to this alternative pathway as an "anti-Povarov reaction". The development of this alternative pathway is a challenging goal because it should be remarked that despite the extensive studies on the Povarov reaction and related processes during the years, the proposed anti-Povarov [3+2]-carbocyclisation pathway has never

been described. Even in those cases where the reaction is performed with aldehydes containing electron-donating groups and then the attack of Ar^1 in intermediate **38** should be favoured, this alternative [3+2]-carbocyclisation reaction was not observed.

Despite all these negative forewarnings, it was decided to investigate this unknown Brønsted acid catalysed multicomponent [3+2]-carbocyclisation process between *in situ* generated *N*-arylimines **27** and enol ethers **3**. At this point, it was considered that the use of an indole as the Ar^1 aromatic ring would be an appropriate selection because the C3-position of this heteroaromatic ring is highly nucleophilic and therefore it might compete in the final step of the process with the electron-rich aromatic ring Ar^2.

With all this in mind, our final objective was the development of a Brønsted acid-catalysed multicomponent coupling reaction of indole-2-carbaldehydes **41**, anilines **34** and enol ethers **3** to afford cyclopenta[*b*]indole derivatives **43** through a new formal [3+2]-carbocyclisation reaction (**Scheme 2.5**).



Scheme 2.5 Objective: new multicomponent formal [3+2]-carbocyclisation process of *in situ* generated indole-2-carbaldehyde imines **42** and enol ethers **3**.

It should be remarked that indole is a privileged heterocyclic scaffold widely distributed in Nature. This bicyclic nitrogen-containing aromatic moiety is present in several natural and synthetic compounds that exhibit important biological activities and have found applications as pharmaceuticals and also as agrochemicals.

Thus, the preparation of new indole-containing complex molecules with unusual scaffolds represents an interesting field of research for organic chemists.[181, 182]

In this context, the cyclopenta[*b*]indole skeleton, present in the final derivatives **43** of our proposed strategy (see **Scheme 2.5**), is a privileged heterocyclic core for drug design and it can be found in pharmaceuticals such as laropiprant **48** and other drugs. This tricyclic moiety also forms part of natural products such as bruceollines **44**, (–)-paspaline **45**, yuehchukene **46** and ficherindoles **47** (**Figure 2.3**).[183]

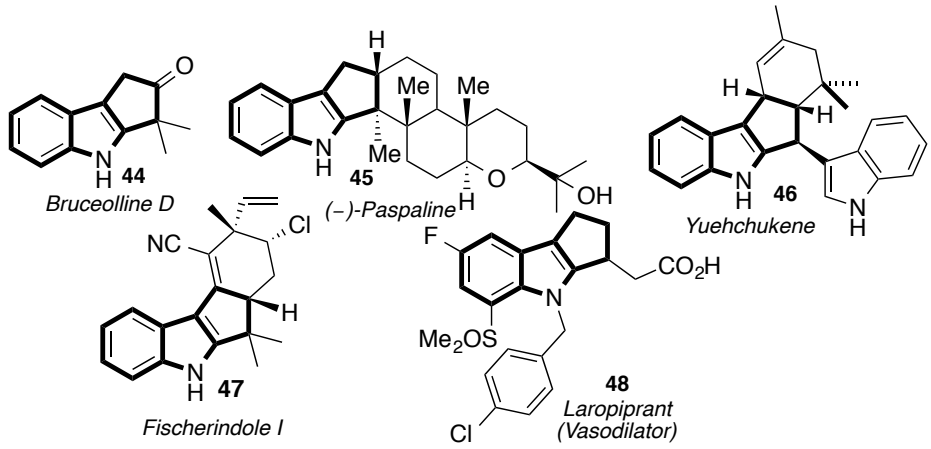


Figure 2.3 Natural products and pharmaceuticals containing a cyclopenta[*b*]indole core.

[181] a) R. J. Sundberg, *The Chemistry of Indoles*, Academic Press, New York, **1970**. b) R. J. Sundberg, in *Comprehensive Heterocyclic Chemistry* (Eds. A. R. Katritzky, C. W. Rees), Pergamon Press, Oxford, *Vol. 4,* **1984**. c) J. A. Joule, in *Science of Synthesis, Houben–Weyl Methods of Molecular Transformations* (Ed.: E. J. Thomas), George Thieme Verlag: Stuttgart, *Vol. 10*, **2000**, Chapter 10.13. d) G. W. Gribble, in *Comprehensive Heterocyclic Chemistry II* (Eds.: A. R. Katritzky, C. W. Ress, E. F. V. Scriven, C. W. Bird) Pergamon Press, Oxford, *Vol. 2*, **1996**, p 207. e) R. J. Sundberg, *Indoles*, Academic Press, London, **1996**. f) G. W. Gribble, in *Top. Heterocycl. Chem.*, *"Heterocyclic Scaffolds II: Reactions and Applications of Indoles"*, Springer-Verlag, Berlin, Heidelberg, *Vol. 26,* **2010**.

[182] For a review of indoles in multicomponent processes, see: S. Morteza, *Chem. Rev.*, **2012**, *112*, 3508.

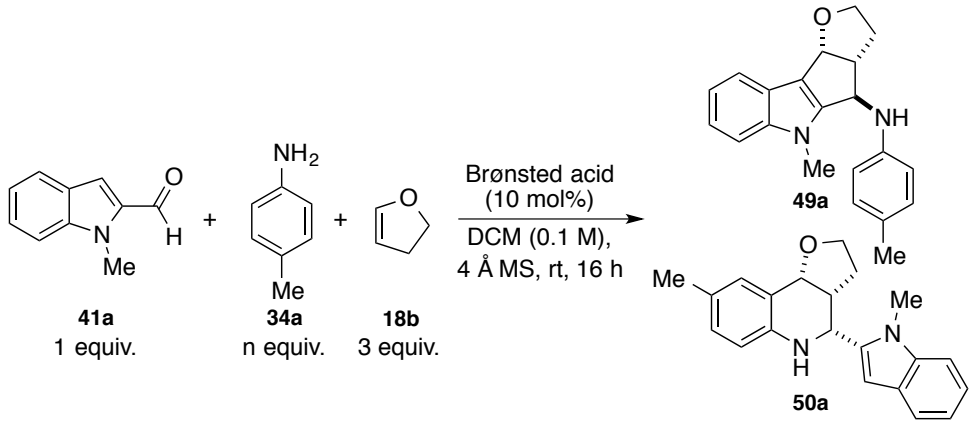
[183] a) Y. Ouyang, K. Koike, T. Ohmoto, *Phytochemistry,* **1994**, *37*, 575. b) J. P. Springer, J. Clardy, *Tetrahedron Lett.*, **1980**, *21*, 231. c) Y.-C. Kong, K.-F. Cheng, R. C. Cambie, P. G. Waterman, *J. Chem. Soc., Chem. Commun.*, **1985**, 47. d) A. Park, R. E. Moore, G. M. L. Patterson, *Tetrahedron Lett.*, **1992**, *33*, 3257. e) K. Stratmann, R. E. Moore, R. Bonjouklian, J. B. Deeter, G. M. L. Patterson, S. Shaffer, C. D. Smith, T. A. Smitka, *J. Am. Chem. Soc.*, **1994**, *116*, 9935. f) E. Lai, I. De Lepeleire, T. M. Crumley, F. Liu, L. A. Wenning, N. Michiels, E. Vets, G. O'Neill, J. A. Wagner, K. Gottesdiener, *Clin. Pharmacol. Ther.*, **2007**, *81*, 849. g) C. F. Sturino, G. O'Neill, N. Lachance, M. Boyd, C. Berthelette, M. Labelle, L. Li, B. Roy, J. Scheigetz, N. Tsou, Y. Aubin, K. P. Bateman, N. Chauret, S. H. Day, J.-F. Lévesque, C. Seto, J. H. Silva, L. A. Trimble, M.-C. Carriere, D. Denis, G. Greig, S. Kargman, S. Lamontagne, M.-C. Mathieu, N. Sawyer, D. Slipetz, W. M. Abraham, T. Jones, M. McAuliffe, H. Piechuta, D. A. Nicoll-Griffith, Z. Wang, R. Zamboni, R. N. Young, K. M. Metters, *J. Med. Chem.*, **2007**, *50*, 794.

2.2.A.2 Preliminary Studies and Optimisation of the Reaction Conditions

The proposed reaction was initially studied with 1-methyl-1*H*-indole-2-carbaldehyde **41a**, 4-methylaniline **34a** and 2,3-dihydrofuran **18b** as model reagents, and the behaviour of different Brønsted acid catalysts was evaluated. Thus, the corresponding acid was added to a dichloromethane solution of **41a** and **34a** (0.1 M) in the presence of 4 Å MS at 0 °C to form the desired imine. After 30 minutes at room temperature, the enol ether counterpart **18b** was added. Selected results are shown in **Table 2.1**. When TfOH was the selected Brønsted acid, formation of (3a*R**,4*R**,9b*R**)-8-methyl-4-(1-methyl-1*H*-indol-2-yl)-2,3,3a,4,5,9b-hexahydrofuro[3,2-*c*]quinoline **50a** coming from the known Povarov pathway (see **Scheme 2.4**, pathway A) was observed. However, the conversion was low (<10%) and the unreacted preformed imine was the major compound observed in the crude of the reaction mixture (**Table 2.1**, **Entry 1**). Unfortunately, the presence of the desired hexahydrocyclopenta[1,2-*b*]indole derivative **49a** could not be identified at any extent. Other relatively strong Brønsted acids such as triflimide ($NHTf_2$) or tetrafluoroboric acid (HBF_4) improved the conversion of the process, but disappointingly, formation of the hexahydrofuro[3,2-*c*]quinoline derivative **50a** as a single diastereoisomer was the only reaction observed (**Table 2.1**, **Entries 2 and 3**). The use of 2,4-dinitrobenzenesulfonic acid (DNBSA) as catalyst of the process did not give any positive result and again, the unreacted preformed imine was the main product observed in the crude of the reaction mixture (**Table 2.1**, **Entry 4**). However, a promising result was obtained when *p*-toluenesulfonic acid (PTSA) was used as the Brønsted acid. In this case, the formation of a 2:1 mixture of compounds **49a** and **50a** was observed (**Table 2.1**, **Entry 5**). Although the conversion (62%) and the selectivity of the process (**49a** vs. **50a**) were low, this result demonstrated the feasibility of the proposed formal [3+2]-carbocyclisation anti-Povarov reaction. Similar results were observed by using diphenylphosphate (DPP) or chlorosulfonic acid as catalysts (**Table 2.1**, **Entries 6 and 7**). At this point, a more detailed optimisation of the reaction conditions was performed with DPP as catalyst. The use of other solvents and temperatures did not improve the conversion nor the ratio **49a**:**50a**. However, it was observed that the use of a slight excess of the aniline counterpart **34a** (1.5 equiv) avoided the formation of the undesired hexahydrofuro[3,2-*c*]quinoline derivative **50a** being (3a*R**,4*R**,9c*R**)-5-methyl-*N*-(*p*-tolyl)-2,3,3a,4,5,9c-hexahydrofuro[2',3':3,4]cyclopenta[1,2-*b*]indol-4-amine **49a** the only product in the crude of the reaction mixture (**Table 2.1**, **Entry 8**). Moreover, the efficiency of the process could be further improved (>95% of conversion) by the slow addition

(5 hours) of the 2,3-dihydrofuran **18b** to the preformed imine in dichloromethane at room temperature. Under these reaction conditions, the hexahydrofurocyclopenta[1,2-*b*]indole derivative **49a** could be isolated in very good yield (82%) and as a single diastereoisomer (**Table 2.1**, **Entry 9**).

Table 2.1 Catalyst screening and optimisation of the reaction conditions.



Entry	Brønsted acid	Equiv. of 34a (n)	Products (ratio)[a]	Conversion [%][b] (yield)[c]
1	TfOH	1	**50a**	<10
2	$NHTf_2$	1	**50a**	75
3	HBF_4	1	**50a**	88
4	DNBSA	1	–	–[d]
5	PTSA	1	**49a**:**50a** (2:1)	62
6	DPP	1	**49a**:**50a** (2:1)	70
7	$ClSO_3H$	1	**49a**:**50a** (2:1)	68
8	DPP	1.5	**49a**	72
9[d]	DPP	1.5	**49a**	>95 (82)

[a] Ratio determined by ^{1}H–NMR analysis of the crude reaction mixture. [b] Conversion determined by ^{1}H–NMR analysis of the crude reaction mixture.[c] Isolated yield after chromatography.[c] Unreacted preformed imine was mainly observed in the crude reaction mixture. [d] The enol ether **18b** was slowly added (5 h) to the reaction mixture at room temperature.

It should be noted that the hexahydrofurocyclopenta[1,2-*b*]indole derivative **49a** is generated through a new multicomponent formal [3+2]-carbocyclisation reaction where three new bonds and three stereogenic centres are selectively

formed. Remarkably, formation of the undesired hexahydrofuro[3,2-*c*]quinoline **50a** coming from the known Povarov pathway could be completely avoided.

The structure and relative configuration of the stereogenic centres of (3a*R**,4*R**,9c*R**)-5-methyl-*N*-(*p*-tolyl)-2,3,3a,4,5,9c-hexahydrofuro[2',3':3,4]cyclopenta[1,2-*b*]indol-4-amine **49a** was determined by single crystal X-ray diffraction analysis techniques (**Figure 2.4**). As shown in the ORTEP representation, considering the cyclopenta[*b*]indole core, the arylamino group and the tetrahydrofuran ring are placed in *trans*-disposition in the molecule.

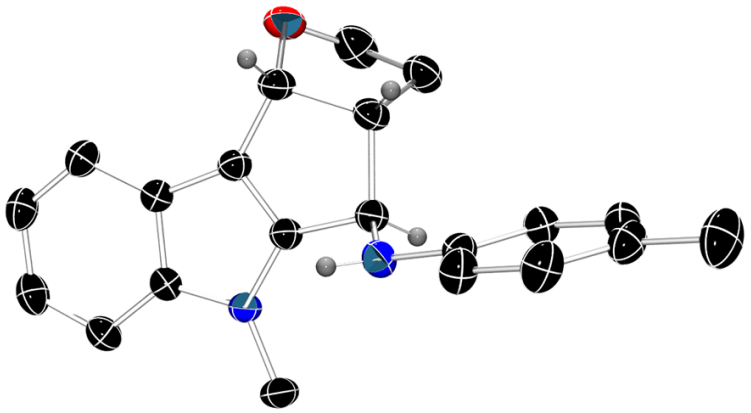
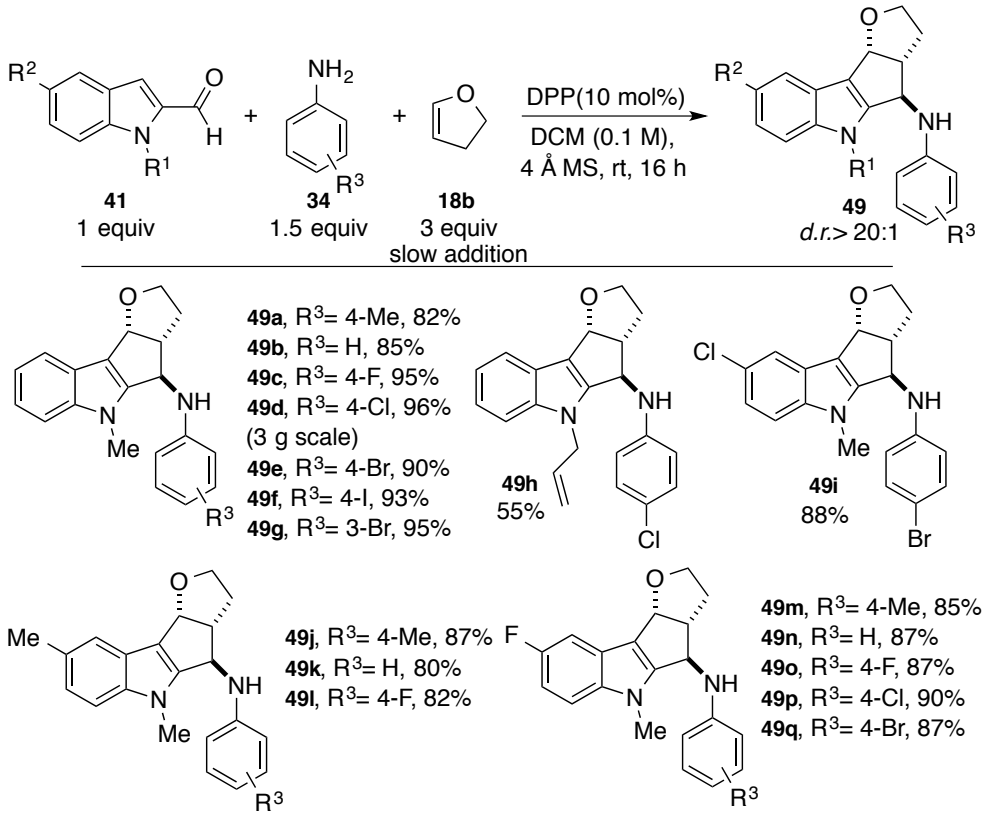


Figure 2.4 ORTEP representation of the structure of the hexahydrofurocyclopenta[1,2-*b*]indole derivative **49a** determined by single crystal X-ray diffraction techniques.

2.2.A.3 Scope of the reaction: Synthesis of Cyclopenta[*b*]indole Derivatives

With optimal conditions in hand (see **Table 2.1**, **Entry 9**), the scope of the reaction was investigated by probing changes to the starting materials (**Scheme 2.1**). The study began with the use of different aniline derivatives **34**. The process showed to be very efficient when simple aniline was used (**49b**, 85%) and also when a set of para-substituted aniline derivatives **34** were employed (**49c-f**, 82-96%). But, formation of the corresponding product **49** was not observed when 4-methoxyaniline was used. Moreover, meta-substituted anilines were appropriate substrates (**49g**, 95%). Unfortunately, the desired compounds could not be obtained with ortho-substituted anilines **34**. Regarding to the indole-2-carbaldehyde counterpart **41**, apart from a methyl group at the nitrogen, other substituents such as an allyl group were also successfully used although in this case the yield was slightly lower (**49h**, 55%). The indole ring could also be decorated with halogens (F, Cl) and a methyl group without any negative influence on the

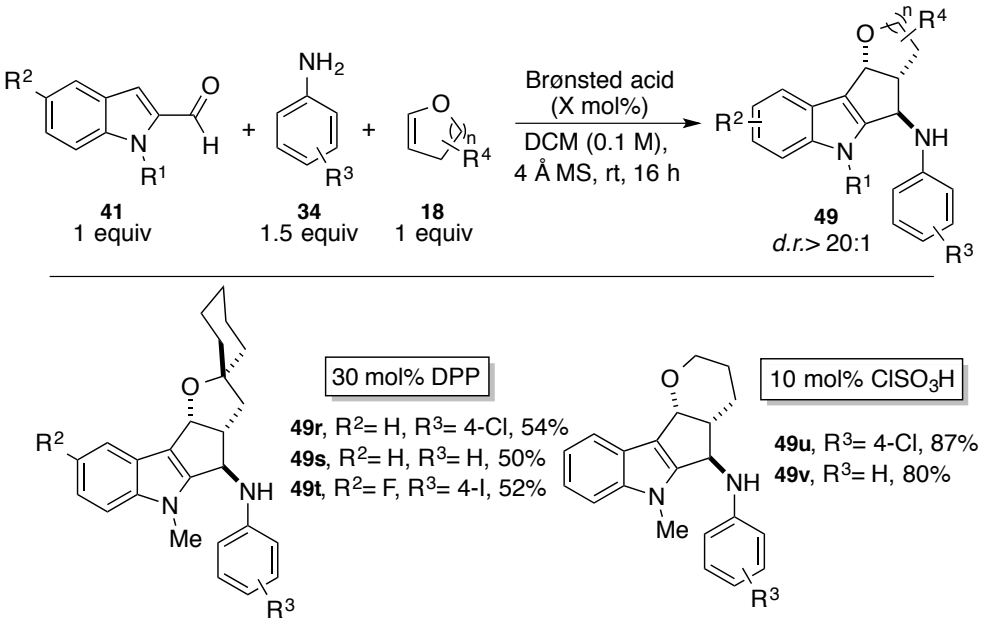
isolated yield of the corresponding compounds (**49i-q**, 80–90%). Furthermore, it was verified that the reaction could be performed on a gram scale and thus, 3.0 grams of **49d** were easily prepared in one batch without problems.



Scheme 2.6 Multicomponent synthesis of hexahydrofurocyclopenta[*b*]indole derivatives.

The proposed anti-Povarov process not only worked with 2,3-dihydrofuran **18b** and therefore other enol ethers **18** such as substituted furan derivatives and 3,4-dihydro-2*H*-pyran could be used (**Scheme 2.7**). However, in these particular cases the optimal conditions previously found were slightly modified and slow addition of the enol ether **18** counterpart did not show better results. In this way, compounds **49r-t** derived from spirocyclic enol ethers **18** could be synthesised in moderate yields (50-54%) by the use of DPP as Brønsted acid. However, the amount of catalyst had to be increased to 30 mol%. For 3,4-dihydro-2*H*-pyran the use of chlorosulfonic acid as catalyst gave the best results, and thus, the corresponding hexahydro-2*H*-pyrano[2',3':3,4]cyclopenta[1,2-*b*]indole derivatives **49u-v** could be isolated in very good yield (80 and 87% respectively) and as single diastereoisomers. Unfortunately, when the reaction was performed using enol ethers such as 5-methyl-2,3-dihydrofuran, butyl vinyl ether, 6-methoxy-3,4-dihydro-2*H*-pyran or benzofuran, formation of the corresponding

cyclopenta[*b*]indole derivatives could not be observed in the crude of the reaction mixture, being the unreacted preformed imine the only product observed.



Scheme 2.7 Multicomponent synthesis of cyclopenta[*b*]indole derivatives **49**: extension of the scope to the use of other enol ether derivatives **18**.

The structure and relative configuration of the stereogenic centres of the hexahydro-2*H*-pyrano[2',3':3,4]cyclopenta[1,2-*b*]indole derivative **49v** was determined by single crystal X-ray diffraction analysis techniques (**Figure 2.5**). Therefore, as it is shown in the ORTEP representation the arylamino group and the tetrahydropyran ring are placed in *trans*-disposition in the molecule, showing an analogous disposition to the one observed for the hexahydrofuro[2',3':3,4]cyclopenta-[1,2-*b*]indole derivative **49a**.

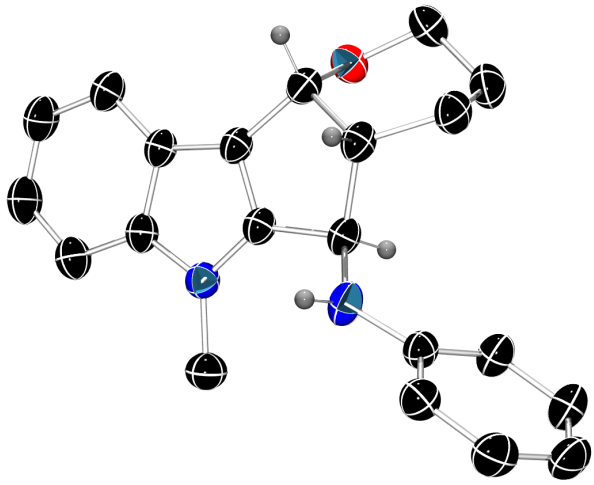
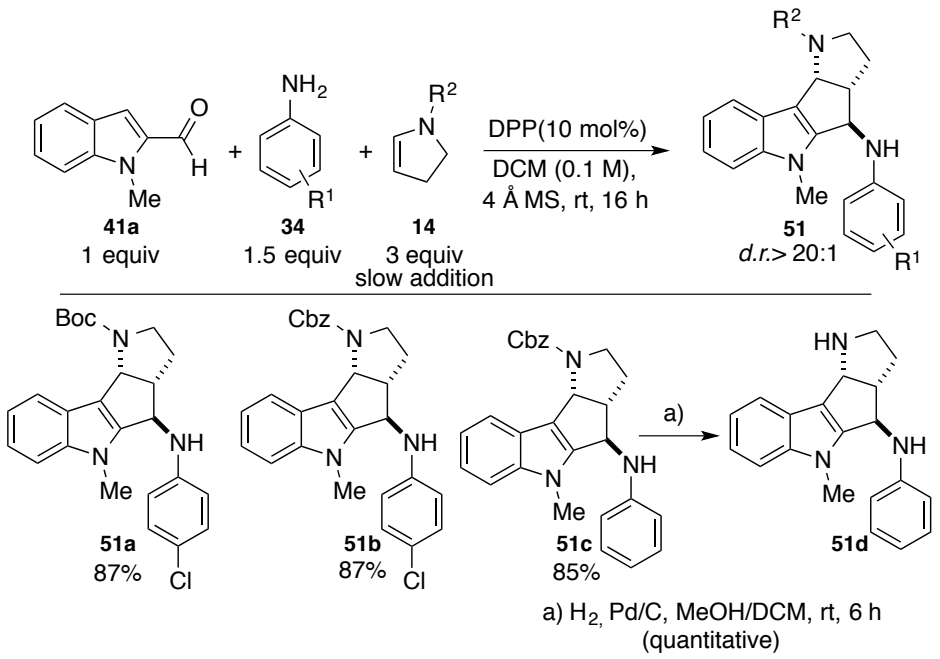


Figure 2.5 ORTEP representation of the structure of the hexahydro-2*H*-pyrano[2',3':3,4]cyclopenta[1,2-*b*]indole derivative **49v** determined by single crystal X-ray diffraction techniques.

Interestingly, enamine derivatives **14** could also be employed as the electron-rich counterpart of the process instead of enol ethers **18**. Therefore, the hexahydro-1*H*-pyrrolo[2',3':3,4]cyclopenta[1,2-*b*]indole derivatives **51** bearing a Boc or Cbz protecting group at the pyrrolidine moiety of the molecule were isolated in high yield (85-87%, **Scheme 2.8**). Furthermore, the corresponding Cbz-protected derivative **51c** could be quantitatively deprotected by simple hydrogenolysis to get the corresponding derivate **51d** (**Scheme 2.8**).

Figure 2.6 shows the ^{1}H–NMR spectrum of **51b** in C_6D_6 at room temperature (298 K) where it is easy to distinguish doubled signals presumably due to the presence of rotamers. Moreover, the corresponding ^{1}H–NMR spectrum in C_6D_6 at 343 K shows the coalescence of signals (coalescence temperature) and confirms our hypothesis regarding the presence of two rotamers at room temperature.

It should be remarked that in all the cases compounds **49** and **51** were basically formed as single diastereoisomers (*d.r.*> 20:1) as evidenced by the ^{1}H–NMR spectra of the crude product mixtures. Furthermore, formation of the hexahydrofuro[3,2-*c*]quinoline derivatives **50** coming from the alternative Povarov [4+2] pathway was not observed at an appreciable extent.



Scheme 2.8 Multicomponent synthesis of hexahydropyrrolocyclopenta[1,2-*b*]indole derivatives **51**: extension of the scope to the use of *N*-protected 2,3-dihydropyrrole derivatives **14**.

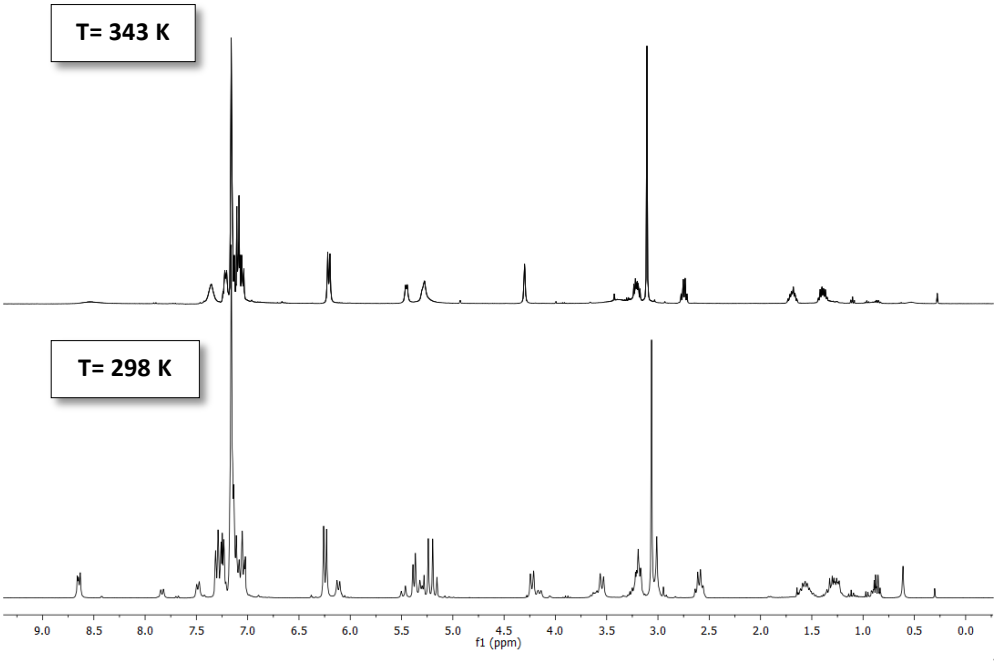
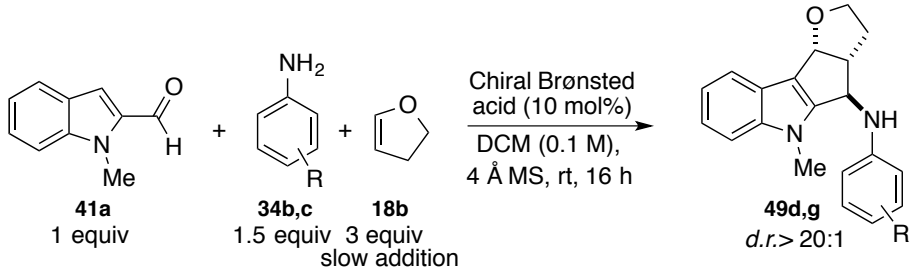


Figure 2.6 ^{1}H–NMR of the derivative **51c** in C_6D_6 at room temperature (298 K) and at coalescence temperature (343 K).

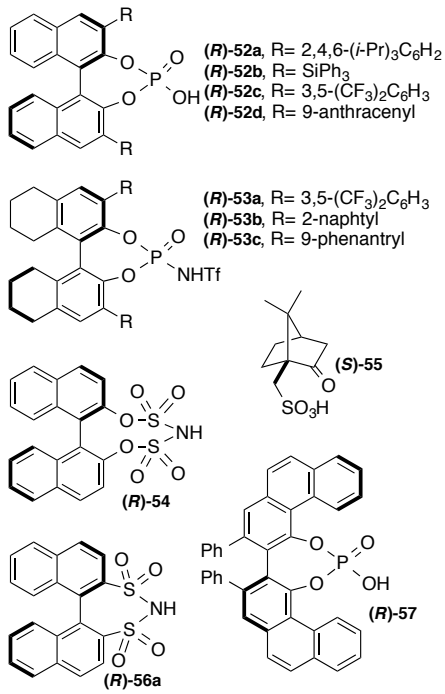
2.2.A.4 Enantioselective Version: Preliminary Studies

In order to further evaluate the scope of the new anti-Povarov reaction, some attempts to develop an enantioselective version were performed by using some selected chiral Brønsted acids as catalysts. A model reaction using 1-methyl-1*H*-indole-2-carbaldehyde **41a**, 4-chloroaniline **34b** and 2,4-dihydrofuran **18b** was investigated and the results are shown in **Table 2.2**.

Table 2.2 Screening of chiral Brønsted acids.



Entry	R	Chiral HB	Yield [%][a]	*e.r.*[b]
1	4-Cl	(*R*)-**52a**	–[c]	–
2	4-Cl	(*R*)-**52b**	–[c]	–
3	4-Cl	(*R*)-**52c**	84	54:46
4	4-Cl	(*R*)-**52d**	75	39:61
5	4-Cl	(*R*)-**53a**	78	58:42
6	4-Cl	(*R*)-**53b**	75	55:45
7	4-Cl	(*R*)-**53c**	84	54:46
8	4-Cl	(*R*)-**54**	–[c]	–
9	4-Cl	(*R*)-**55**	–[c]	–
10	4-Cl	(*R*)-**56a**	82	67:33
11	4-Cl	(*R*)-**57**	90	72:28
12	3-Br	(*R*)-**57**	95	82:18[d]



[a] Isolated yield after chromatography. [b] Determined by HPLC analysis. [c] Unreacted preformed imine was mainly observed in the crude reaction mixture. [d] Absolute configuration could not be determined.

Chiral (*R*)-BINOL-derived phosphoric acids **(*R*)-52a,b** were not appropriate catalysts and the unreacted imine was recovered (**Table 2.2**, **Entries 1 and 2**). With catalysts **(*R*)-52c,d** the corresponding product was formed in high yield but the enantiomeric excess was very low (**Table 2.2**, **Entries 3 and 4**). Similar results were obtained by the use of (*R*)-H_8-BINOL-derived *N*-triflyl phosphoramides **(*R*)-53a-c** as the process showed to be efficient in terms of chemical yield but the enantioselectivity was low (**Table 2.2**, **Entries 5–7**). Neither the (*R*)-BINOL-derived disulfurylimide **(*R*)-54** nor (+)-camphor sulfonic acid **(*R*)-55** were appropriate catalysts because formation of product **49d** was not observed and the unreacted *in situ* preformed imine was recovered (**Table 2.2**, **Entries 8 and 9**). However, a promising 67:33 enantiomeric ratio was observed with the chiral disulfonimide **(*R*)-56a** (**Table 2.2**, **Entry 10**). The best result was obtained with (*R*)-VAPOL phosphoric acid **(*R*)-57**. Thus, product **49d** could be isolated in excellent yield, as single diastereoisomer and with an enantiomeric ratio of 72:28 (**Table 2.2**, **Entry 11**). Moreover, when the reaction was performed using 3-bromoaniline **34c** instead of 4-chloroaniline **34b**, the enantiomeric ratio of the isolated derivative **(+)-49g** could be improved to 82:18 (**Table 2.2**, **Entry 12**), a very promising result for a future deeper study of this enantiomeric version of the new anti-Povarov reaction.

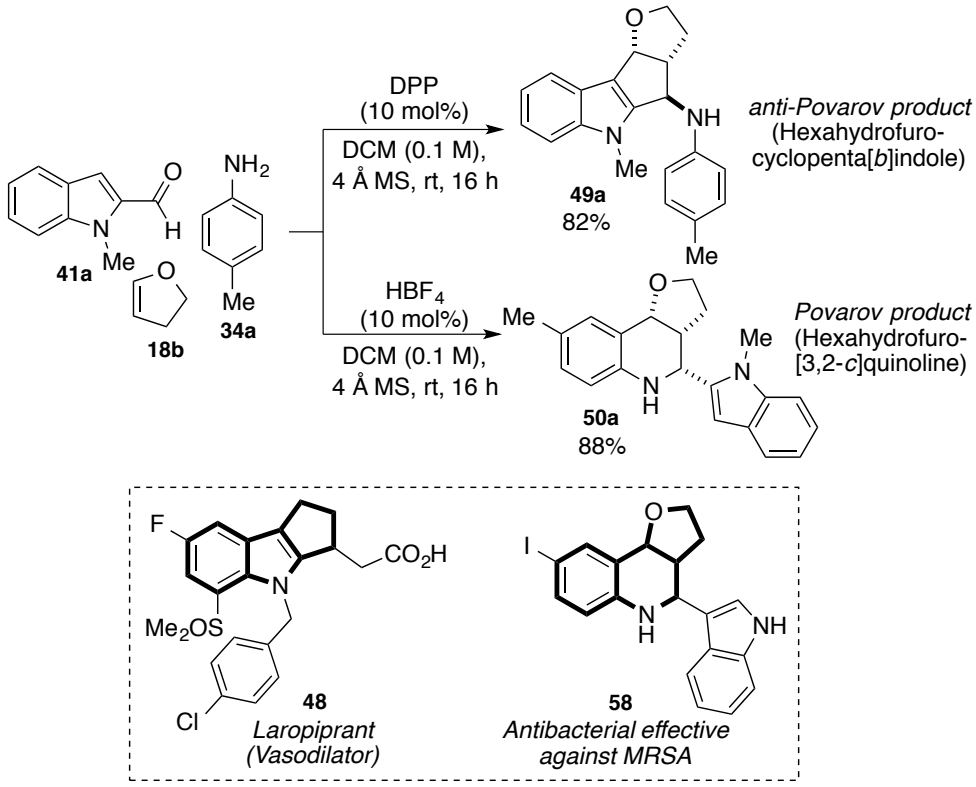
2.2.A.5 Chemodivergent Multicomponent Process: Anion-Controlled Switch of Selectivity

As described in the General Introduction of this thesis, multicomponent reactions are recognised useful processes in synthetic organic chemistry (see **Section 1.4.3.2**, General Introduction). Furthermore, in last years, Diversity Oriented Synthesis (DOS) has appeared as a new paradigm for developing large collections of structurally diverse small molecules as probes to investigate biological pathways. However, the efficient synthesis of structurally diverse compounds involving multicomponent processes within the field of Diversity Oriented Synthesis remains a challenge to synthetic chemists.

Clear examples of how structurally very different products can be obtained from a set of identical starting materials by the action of different enzymes can be found in Nature. As an attempt to imitate Nature, one of the current challenges in catalysis is to get different products from the same set of starting materials just using different catalysts.

In this context, and looking at the optimisation study of our three component coupling reaction of 1-methyl-1*H*-indole-2-carbaldehyde **41a**, 4-methylaniline **34a** and 2,3-dihydrofuran **18b** (see **Table 2.1**), it was considered that this process could be tuned to get the hexahydrofuro[3,2-*c*]quinoline derivative

49a or the hexahydrofurocyclopenta[1,2-*b*]indole derivative **50a** by the simple change of the acid catalyst (HBF_4 or DPP) (**Scheme 2.9**). Thus, by the appropriate election of the Brønsted acid, a chemodivergent multicomponent Brønsted-acid catalysed reaction of three simple starting materials, an indole-2-carbaldehyde **41**, an aniline **34** and an enol ether **18**, could be developed.[184] The prevalence of the cyclopenta[*b*]indole core in natural products and pharmaceuticals has been shown in the previous section (see **Figure 2.3**). Furthermore, the alternative hexahydrofuro[3,2-*c*]quinoline core is also found in several interesting compounds (**Scheme 2.9**).

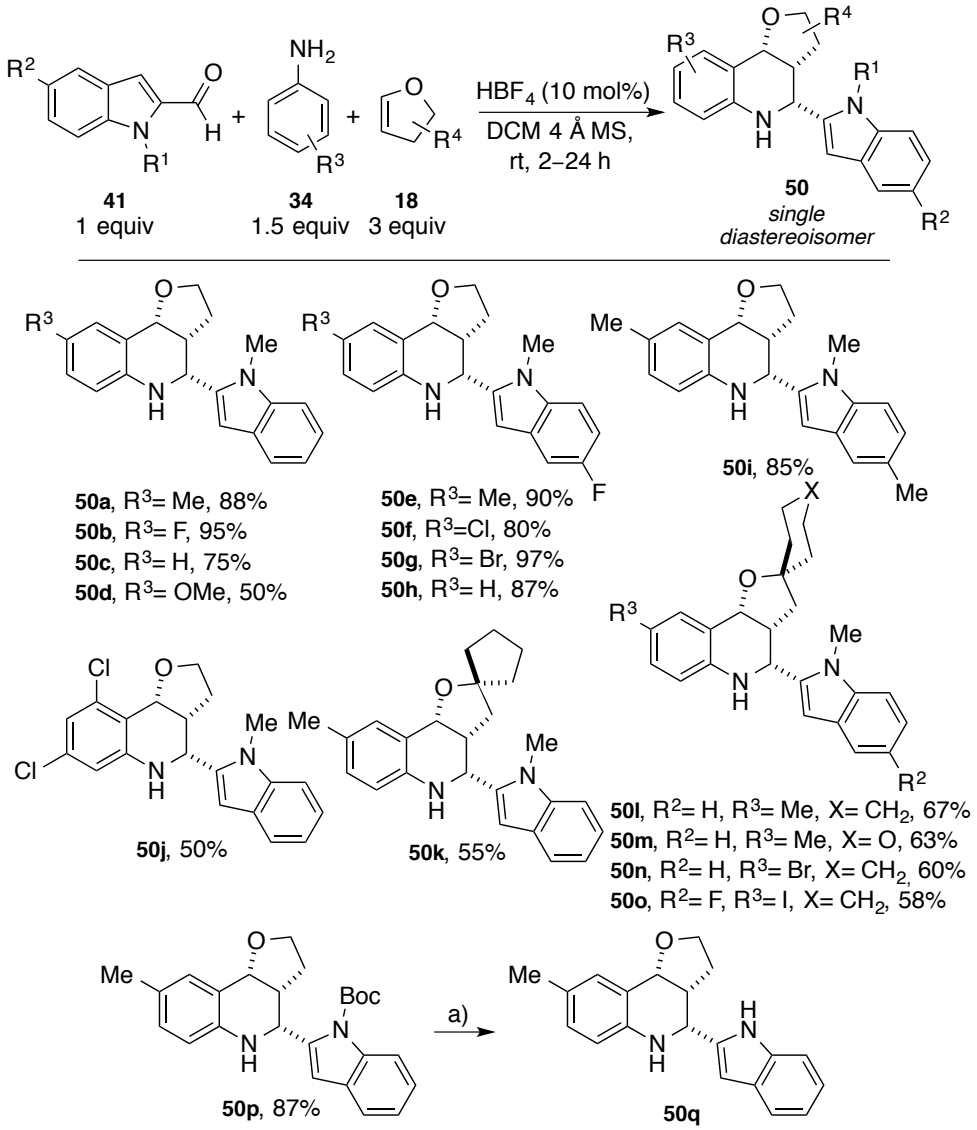


Scheme 2.9 Chemodivergent multicomponent process.

With all this in mind, once the study of the scope of the new [3+2] anti-Povarov reaction was covered, it was decided to investigate if the conventional [4+2] Povarov process was also a general reaction. Thus, the same set of starting

[184] For some examples of switchable MCRs, see: a) H.-G. Cheng, C.-B. Chen, F. Tan, N.-J. Chang, J.-R. Chen, W.-J. Xiao*, Eur. J. Org. Chem.,* **2010**, 4976. b) V. A. Chebanov, V. E. Saraev, S. V. Shishkina, O. V. Shishkin, V. I. Musatov, S. M. Desenko, *Eur. J. Org. Chem.,* **2012**, 5515. c) M. V. Murlykina, Y. I. Sakhno, S. M. Desenko, I. S. Konovalova, O. V. Shishkin, D. A. Sysoiev, M. N. Kornet, V. A. Chebanov, *Tetrahedron*, **2013**, *69*, 9261. d) Y. Wang, F. Zhao, Y. Chi, W. X. Zhang, Z. Xi, *J. Org. Chem.* **2014**, *79*, 11146.

materials, indole-2-carbaldehydes **41**, anilines **34** and 2,3-dihydrofuran derivatives **18** were reacted in the presence of 10 mol% of tetrafluoroboric acid (HBF_4) (**Scheme 2.10**).



Scheme 2.10 Multicomponent synthesis of hexahydrofuro[3,2-*c*]quinoline derivatives 50.

Pleasingly, the reaction was general, and thus, a series of hexahydrofuro[3,2-*c*]quinoline derivatives **50** could be easily synthesised. The process showed to be efficient with the use of electron-poor and neutral anilines (**50a-c**, 75–95%) and moderate yields were obtained in the case of the electron-rich 4-methoxyaniline (**50d**, 50%) and when 3,5-disubtituted anilines where used

(**50j**, 50%). Moreover, the indole moiety could be decorated with halogens (**50e-h**, 80–97%) and methyl groups (**50i**, 85%), and a series of alkyl-substituted 2,3-dihydrofuran derivatives showed to be appropriate starting materials as well (**50l-o**, 58-67%).

Additionally, the *N*-Boc protected derivative **50p** could be synthesised in very good yield (87%) and afterwards, it could be easily and quantitatively deprotected under basic conditions, affording the interesting derivative **50q** pretty similar to the antibacterial effective against MRSA **58** shown in **Scheme 2.9**.

It should be noted that the Povarov reaction was totally diastereoselective and compounds **50** were always isolated as *endo* isomers. The structure and relative configuration of the stereogenic centres of **50a** was determined by one-dimensional and two-dimensional NMR experiments (**Figure 2.7**). The doublet centred at 5.21 ppm (d, *J*= 8.0 Hz) was assigned to $\mathbf{H_a}$, the doublet centred at 4.26 ppm (d, *J*= 2.7 Hz) was assigned to $\mathbf{H_b}$ and the apparent triple doublet of doublets centred at 2.57 ppm was assigned to $\mathbf{H_c}$. The value of the coupling constant between $\mathbf{H_b}$ and $\mathbf{H_c}$ (*J*= 2.7 Hz) enabled the assignment of a relative gauche *cis*-disposition between $\mathbf{H_b}$ and $\mathbf{H_c}$. Thus, it has been reported that in similar systems a coupling constant value around 3 Hz corresponds to a *cis*-disposition (usually these isomers are called *endo*). However, a higher coupling constant value (*J*> 6 Hz) would indicate a trans disposition between $\mathbf{H_b}$ and $\mathbf{H_c}$ (*exo* isomer). Moreover, the value of the coupling constant between $\mathbf{H_a}$ and $\mathbf{H_c}$ (*J*= 8.0 Hz) is also consistent with the expected cis fusion between the furan and the tetrahydroquinoline moiety.

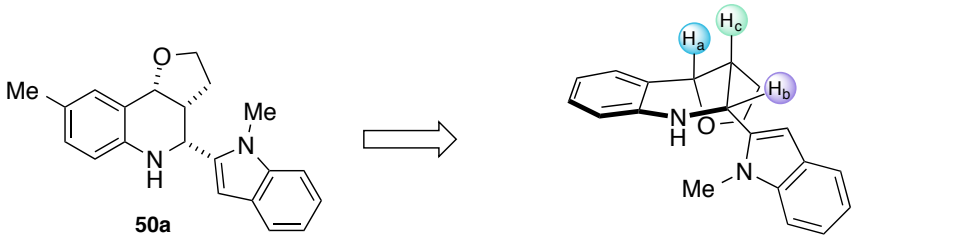


Figure 2.7 Determination of the relative configuration of **50a** through ^{1}H–NMR experiment.

Remarkably, formation of the corresponding hexahydrofurocyclopenta[1,2-*b*]indole derivatives **49** was not observed at appreciable extent in any of the experiments performed with HBF_4 as catalyst. This demonstrates the chemodivergence of the process as hexahydrofuro[3,2-*c*]quinolines **50** are

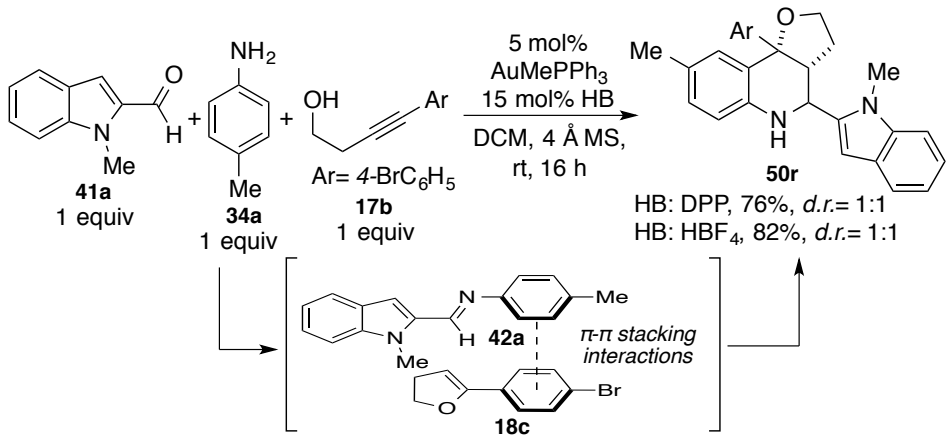
exclusively obtained with HBF_4 as catalyst and cyclopenta[*b*]indoles **49** are exclusively obtained with DPP.

2.2.A.6 Attempts to Develop a Multicomponent Cascade Process Involving a Hydroalkoxylation Reaction

Considering the experience of our research group in the development of cascade processes involving the *in situ* generation of enol ethers **18** through a hydroalkoxylation reaction of an alkyne, it was thought that the formal [3+2]-carbocyclisation and the formal [4+2]-cycloaddition reactions previously described could be performed through similar cascade processes where the enol ether was *in situ* generated. To this end, a binary catalytic system including a metallic complex and a Brønsted acid would be required. On the one hand, the metallic complex would promote the *in situ* formation of the enol ether through a hydroalkoxylation process of an alkynol derivative **17** and on the other hand, the Brønsted acid would promote the *in situ* generation of the corresponding *N*-arylimine **42** and also the subsequent formal [3+2]-carbocyclisation or [4+2]-cycloaddition processes.

To test the feasibility of these proposed cascade reactions, 1-methyl-1*H*-indole-2-carbaldehyde **41a**, 4-methylaniline **34a** and 4-(4-bromophenyl)but-3-yn-1-ol **17b** were chosen as model reagents. The catalytic system consisted in a combination of 5 mol% of $AuMePPh_3$ and 15 mol% of an acid (DPP or HBF_4). Under these reaction conditions, formation of the corresponding hexahydrofuro[3,2-*c*]quinoline derivative **50r** as mixture of diastereoisomers (*d.r.*= 1:1) and coming from the formal [4+2] Povarov reaction, was observed independently of the acid used (**Scheme 2.11**). Particularly surprising was the result obtained in the presence of DPP because with this acid we had previously observed, with preformed enol ethers **18**, that hexahydrofurocyclopenta[1,2-*b*]indole derivatives were exclusively obtained and formation of the hexahydrofuro[3,2-*c*]quinoline derivatives was not detected (see **Section 2.2.A.2**). At first sight, the most relevant difference between the present reaction and those previously developed is that the enol ether *in situ* generated through a cycloisomerisation reaction is substituted at C2 position whereas the commercially available enol ethers previously used were unsubstituted at that position. With all this in mind, the exclusive formation of the hexahydrofuro[3,2-*c*]quinoline in the above commented cascade reaction independently of the Brønsted acid used might be tentatively explained by the presence of π-π-stacking interactions between the aromatic ring coming from the aniline **34** and the aromatic ring of the *in situ* formed enol ether **18c**. As recently

reported, this interaction could favour the Povarov formal [4+2]-cycloaddition reaction over the alternative anti-Povarov [3+2]-carbocyclisation process.[185]



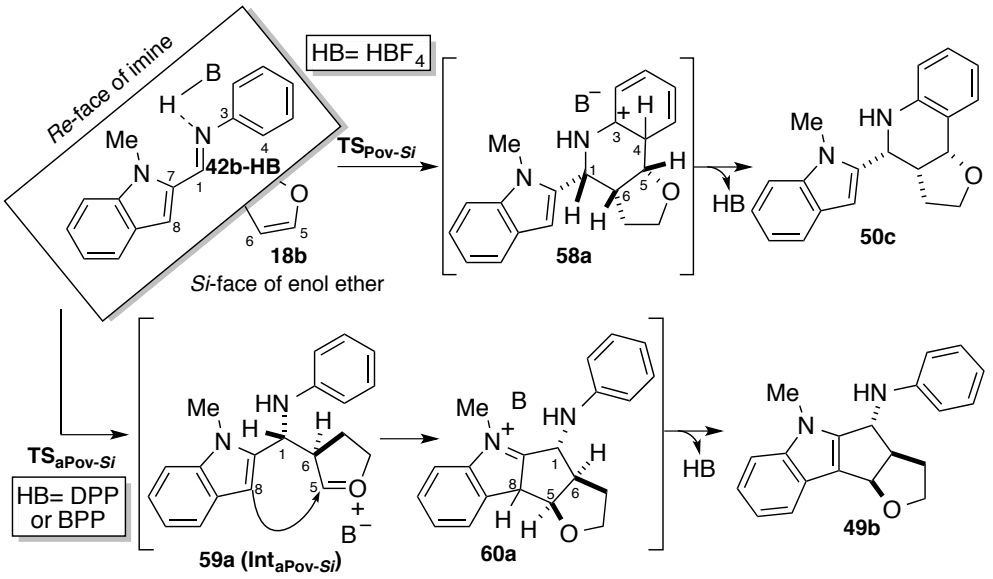
Scheme 2.11 Attempts to develop multicomponent cascade processes involving a hydroalkoxylation reaction.

2.2.A.7 Mechanistic and Computational Studies

From the mechanistic point of view the chemo-divergent multicomponent process previously described is also very interesting. In this context, it is very important to note that attending to the stereochemistry of products **49** and **50**, both compounds proceed from the same approach of the enol ether to the *in situ* formed imine **42** (**Scheme 2.12**). This approach implies the combination of the *Re*-face of the activated imine **42-HB** and the *Si*-face of 2,3-dihydrofuran **18b** (or the reverse relative topicities).

To further understand the mechanistic details of the processes computational studies (DFT calculations) on the Povarov [4+2]-cycloaddition reaction and the anti-Povarov [3+2]-carbocyclisation process were performed in collaboration with Dr. Adán B. González Pérez, Prof. Dr. Rosana Álvarez and Prof. Dr. Ángel Rodríguez de Lera from the Department of Organic Chemistry (University of Vigo, Spain). Moreover, a study of the stereoselectivity of the process was also developed.

[185] This proposed π-π interaction has been observed in a Povarov reaction developed in our research group, see ref. 154, General Introduction.



Scheme 2.12 Mechanistic considerations for the chemodivergent process.

The selected model reactions for the calculations are shown in **Scheme 2.12** and imply a Povarov pathway to afford **50c** with HBF_4 and an anti- Povarov pathway to give **49b** with biphenylphosphate (BPP, a conformationally-restricted DPP), where **42b**-HB denotes the species formed upon activation of the imine by coordination to the Brønsted acid HB (HBF_4 or BPP). Calculations were performed with Gaussian 09[186] using the dispersion-corrected wB97XD functional.[187]

The Povarov reaction between the imine **42b-HBF_4** complex and **18b** to give **58a** (a direct precursor of **50c**) was characterised as an asynchronous concerted process, in agreement with similar cycloadditions previously reported in which 2,3-dihydrofuran **18b** was used as dienophile.[154] The asynchronicity of the cycloaddition reaction can be noted on the forming C-C bond lengths at the transition structure (*Si* face, 2.00 and 3.05 Å; *Re* face, 2.06 and 3.06 Å; for C_1-C_6 and C_4-C_5 bonds, respectively, see **Figure 2.8**), which indicate the formation of the C_4-C_5 bond after C_1-C_6 bond is almost complete. The high asynchronicity is due to distortion of the unsymmetrical diene, as shown in the $C_1NC_3C_4$ dihedral angles in **Figure 2.8**, and the impact of catalyst coordination.[188]

[186] M. J. Frisch, Gaussian 09, revision A1, Gaussian, Inc., Wallingford, CT, **2009.**

[187] J.-D. Chai, M. Head-Gordon, *Phys. Chem. Chem. Phys.*, **2008**, *10*, 6615. For an overview of dispersion-corrected DFT methods in the description of aromatic interactions, see: S. Ehrlich, J. Moellmann, S. Grimme, *Acc. Chem. Res.*, **2013**, *46*, 916.

[188] E. Clot, *Eur. J. Inorg. Chem.,* **2009**, 2319.

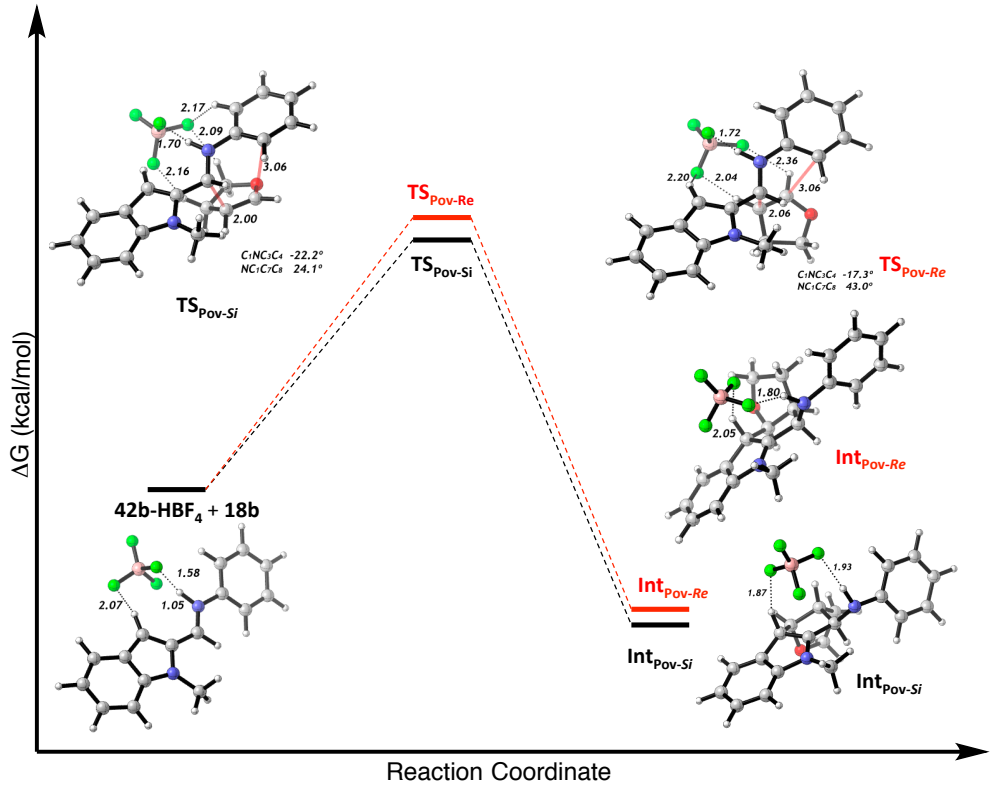


Figure 2.8 Energy profile and representative structures corresponding to the Povarov reaction catalysed by HBF_4 between imine **42b** and dihydrofuran **18b** computed at the wB97XD/6-31G* level in gas phase. Relevant atom distances (in Å) and dihedral angles are shown.

The difference in activation free energies between **TS$_{Pov-Si}$** (12.3 kcal/mol, **Table 2.3**) and **TS$_{Pov-Re}$** (13.1 kcal/mol, **Table 2.3**), in favor of the former, which is in line with the stereoselectivity experimentally observed, could in part be ascribed to the stronger C-H…F intermolecular interactions in **TS$_{Pov-Si}$** (some of them are shown in **Figure 2.8**).[189] In fact, the interactions involving the approach though the *Si*-face of **18b** are more stabilising than those through the *Re*-face as reflected by the more negative electronic energy of the transition state (-3.2 and -2.3 kcal/mol respectively, see **Table 2.3**).[190]

[189] a) J. D. Dunitz, R. Taylor, *Chem. Eur. J.,* **1997**, *3*, 89. b) R. S. Rathore, N. S. Karthiekeyan, Y. Alekhya, K. Sathiyanarayanan, P. G. Aravindan, *J. Chem. Sci.,* **2011**, *123*, 403. c) C. Bissantz; B. Kuhn; M. Stahl, *J. Med. Chem.,* **2010**, *53*, 5061.

[190] The negative electronic energies for the HBF_4-catalysed Povarov pathway relative to the components are consistent with the strenghtening of electrostatic interactions between the imine **42b-HBF$_4$** complex and **18b** as reaction progresses towards the transition state, as often observed in strongly polarised reactions: a) F. M. Bickelhaupt, *J. Comput. Chem.*, **1999**, *20*, 114. b) J. DeChancie, O. Acevedo, J. D. Evanseck, *J. Am. Chem. Soc.*, **2004**, *126*, 6043.

Table 2.3 Calculated activation energies (kcal/mol) for HBF_4-promoted Povarov pathway.[a]

HBF_4-Povarov Pathway		
Structures	**ΔE_{act}**[b]	**ΔG_{act}**
$TS_{Pov\text{-}Si}$	**-3.2**	***12.3***
$Prod_{Pov\text{-}Si}$	-23.4	-6.5
$TS_{Pov\text{-}Re}$	-2.3	13.1
$Prod_{Pov\text{-}Re}$	-23.8	-6.3

[a] Energies (in kcal/mol) were computed at the wB97XD/6-31G* level in gas phase. The activation energies refer to the difference between the energies of the transition structure and the sum of energies of starting **18b** and imine **42b-HBF_4** complex. [b] Electronic energies including zero-point correction.

The biphenylphosphoric acid-catalysed anti-Povarov pathway was characterized by IRC analysis as a stepwise process proceeding through the oxocarbenium ion intermediate **59a** formed through a Mannich-type reaction, which is then nucleophilically trapped by the electron-rich indole in a Friedel-Crafts type process to give **60a** and finally **49b** after a rearomatisation process (see **Scheme 2.12**). In this case, the BPPO-H and N_{imine}-H bond distances (1.51 and 1.09 Å, respectively) in the initial **42b-BPP** complex suggest that the reaction proceeds via ion pairing and the π-π interactions previously observed observed in related systems,[154] do not play an important role.[191] The anti-Povarov transition states are slightly more retarded than those of the corresponding Povarov reaction catalysed by HBF_4 for the same facial interaction, as shown by the forming C_1-C_6 bond distances (BPP-*Si* face, 2.00 Å; BPP-*Re* face, 1.84 Å; Figure 1). In contrast to the compact transition structures (negative electronic energies, **Table 2.3**) found for the HBF_4-promoted Povarov reaction and characteristic of concerted mechanisms, those derived from the reaction catalysed by BPP are rather loose (positive electronic energies, **Table 2.4**). Also, oxocarbenium ion intermediate **59a** seems to be stabilised not only by the interaction of the hydrogen at carbon-2 of **18b** and BPP (1.69 Å) but also by the negative π-cloud of the indole ring. Similarly to the Povarov reaction catalysed by HBF_4 shown before, in the carbocyclisation promoted by BPP, the approach of the **42b-BPP** complex to the *Si*-face of **18b** proved to be energetically favoured over the alternative approach through the *Re*-

[191] Previous studies have revelead the contribution of two posible interactions, termed ion-pairing and hydrogen bonding between N_{imines} and acids, depending on the nature of the imine substituents: a) M. Fleischmann, D. Drettwan, E. Sugiono, M. Rueping; R. M. Gschwind, *Angew. Chem. Int. Ed.* **2011**, *50*, 6364. b) R. Appel, S. Chelli, T. Tokuyasu, K. Troshin, H. Mayr, *J. Am. Chem. Soc.,* **2013**, *135*, 6579. c) D. Parmar, E. Sugiono, S. Raja, M. Rueping, *Chem. Rev*., **2014**, *114*, 9047.

face of **18b** (18.7 and 22.8 kcal/mol respectively, **Figure 2.9** and **Table 2.4**)[14] in agreement with the experimental results.

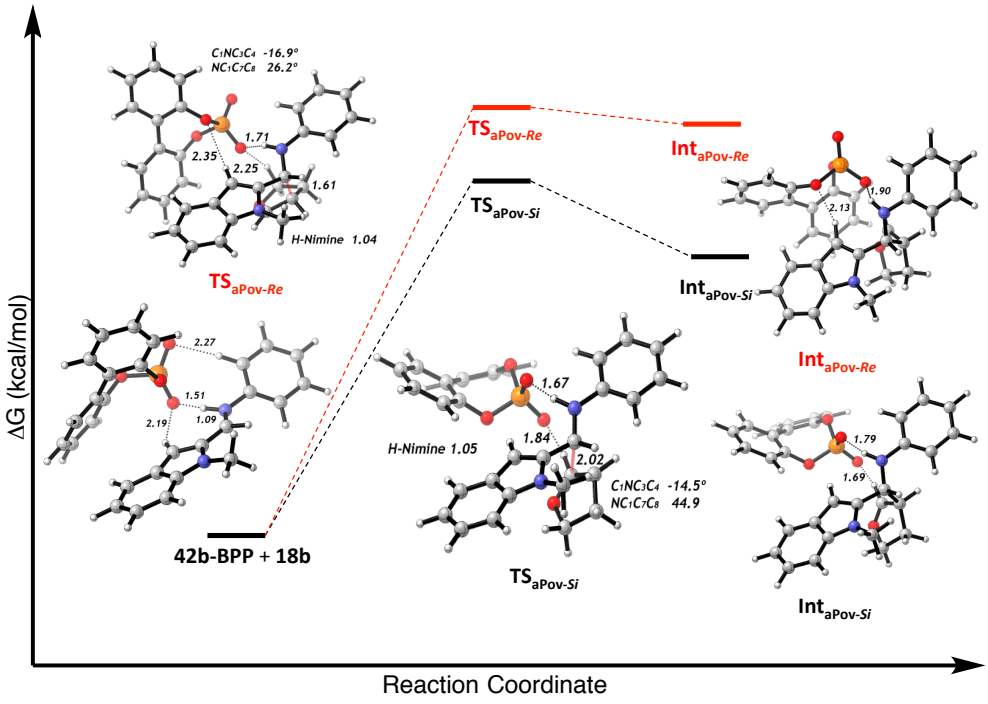


Figure 2.9 Energy profile and representative structures corresponding to the anti-Povarov reaction catalysed by BPP between imine **42b** and dihydrofuran **18b** computed at the wB97XD/6-31G* level in gas phase. Relevant atom distances (in Å) and dihedral angles are shown.

Table 2.4 Calculated activation energies (kcal/mol) for BPP-promoted anti-Povarov pathway.[a]

BPP-Anti-Povarov Pathway

Structures	ΔE_{act} [b]	ΔG_{act}
$TS_{aPov\text{-}Si}$	**4.3**	***18.7***
$Int_{aPov\text{-}Si}$	0.9	14.3
$TS_{aPov\text{-}Re}$	7.9	22.8
$Int_{aPov\text{-}Re}$	8.2	22.1

[a] Energies (in kcal/mol) were computed at the wB97XD/6-31G* level in gas phase. The activation energies refer to the difference between the energies of the structure and the sum of energies of the starting **18b** and imine **42b-BPP** complex [b] Electronic energies including zero-point correction.

As a conclusion, these computational studies suggest that the Povarov reaction is preferential when HBF_4 is used as catalyst because the strong interactions F-H and its acidity favour the formation of a highly polarised **42b-HBF_4** complex that behaves as a very good electron-poor diene in inverse electron-demand concerted [4+2] cycloadditions. Moreover, these F-H interactions also favour the formation of compact transition states typical of concerted mechanisms. On the other hand, when a less acidic and fluorine-free acid catalyst such as DPP is used, the concerted Povarov reaction becomes less favoured. In contrast, when this acid is used, the oxocarbenium ion intermediate **59a** is particularly stabilised mainly by the indole moiety and thus, the stepwise anti-Povarov reaction becomes the preferred pathway.

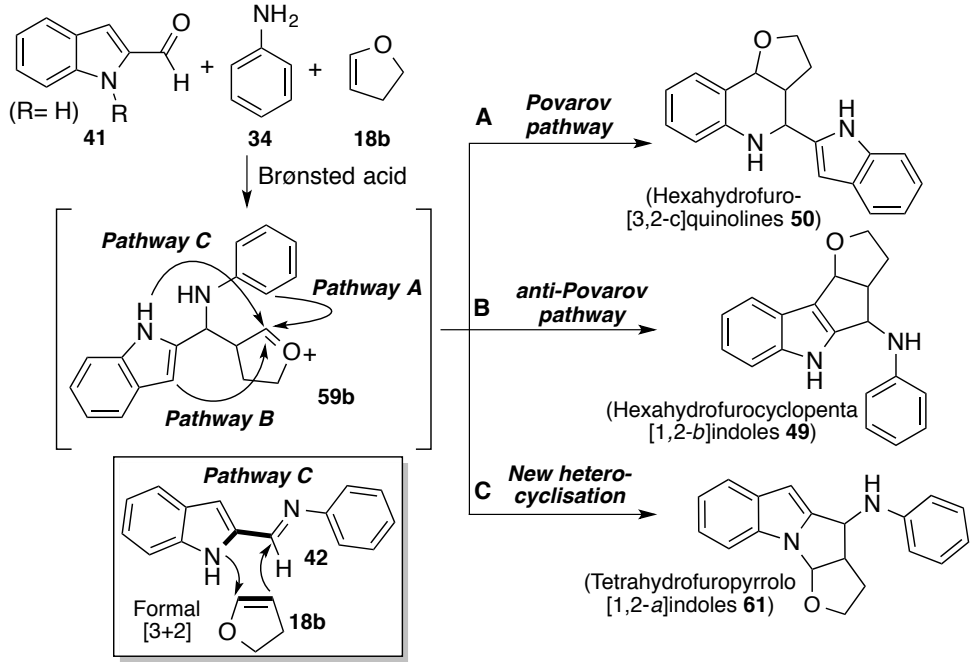
Part B

Enantioselective [3+2]-Heterocyclisation of 1H-Indol-2-carbaldehyde Imines and Enol Ethers. Asymmetric Synthesis of Tetrahydrofuropyrrolo[1,2-a]indole Derivatives

2.2.B Results and Discussion. Part B

2.2.B.1 Objective

The development of a new [3+2] anti-Povarov carbocyclisation was described in the previous sections of this thesis. Also, a chemodivergent synthesis of hexahydrofuro[3,2-*c*]quinoline derivatives **50** or hexahydrofurocyclopenta[1,2-*b*]indoles **49** depending on the acid catalyst employed was described. However, in all these previous reactions, the 1*H*-indole-2-carbaldehyde derivatives **41** used were always substituted at the nitrogen. In this context, it was thought on the possibility of studying the reaction using 1*H*-indole-2-carbaldehydes derivatives **41** (R= H) as starting materials (i.e. *N*-unsubstituted indole-2-carbaldehyde derivatives). In this new situation, once the oxonium intermediate **59b** is formed, there might be three different reaction pathways, the Povarov and anti-Povarov processes previously described and a new heterocyclisation (**Scheme 2.13**).



Scheme 2.13 Study with 1*H*-indole-2-carbaldehydes derivatives: possible reaction pathways.

These three possible pathways derive from the same intermediate **59b** formed by the addition of the enol ether **18b** to the *in situ* formed imine. Pathway A would afford hexahydrofuro[3,2-*c*]quinoline derivatives **50** through a conventional Povarov reaction. Pathway B would led to the formation of hexahydrofurocyclopenta[1,2-*b*]indole derivatives **49** through an anti-Povarov

reaction and finally, a new alternative pathway C would imply the nucleophilic addition of the unprotected nitrogen of the indole to form tetrahydrofuropyrrolo[1,2-*a*]indole derivatives **61**. This product can also be seen as derived from a formal [3+2]-heterocyclisation reaction between the *in situ* formed imine **42** and the enol ether **18b**.

It should be noted that the pyrrolo[1,2-*a*]indole tricyclic core, available through the proposed formal [3+2]-heterocyclisation reaction, is a key structural motif found in a variety of biologically active natural products and pharmaceutical compounds.[192] Some representative examples are shown in **Figure 2.10**. For example, mitomycin C **62** exhibits potent antibacterial and antitumoral activity, and is now used as an anticancer drug in the treatment of certain cancers.[193] The indole alkaloid flinderole B[194] **65** has shown selective antimalarial properties and, recently, another pyrroloindole natural product, isatisine A **63**, has generated much interest among synthetic chemists as its acetonide derivative was found to exhibit cytotoxicity against C8166 and anti-HIV activity.[195] Moreover, other non-natural molecules such as the HCV NSB5 polymerase inhibitor **64** has been used in the treatment of hepatitis C infection.

[192] a) L. Hao, Y. Pan, T. Wang, M. Lin, L. Chen, Z.-P. Zhan, *Adv. Synth. Catal.*, **2010**, *352*, 3215. b) R. Kakadiya, H. Dong, P.-C. Lee, N. Kapuriya, X. Zhang, T.-C. Chou, T.-C. Lee, K. Kapuriya, A. Shah, T.-L. Su, *Bioorg. Med. Chem.*, **2009**, *17*, 5614. c) M. Tanaka, S. Sagawa, J.-I. Hoshi, F. Shimoma, K. Yasue, M. Ubukata, T. Ikemoto, Y. Hase, M. Takahashi, T. Sasase, N. Ueda, M. Matsushita, T. Inaba, *Bioorg. Med. Chem.*, **2006**, *14*, 5781.

[193] a) U. Galm, M. H. Hager, S. G. V. Lanen, J. Ju, J. S. Thorson, B. Shen, *Chem. Rev.*, **2005**, *105*, 739. b) W. A. Remers, R. T. Dorr, in *Alkaloids: Chemical and Biological Perspectives*, ed. S. W. Pelletier, John Wiley & Sons, New York, **1988**, vol. 6. c) S. J. Danishefsky, J. M. Schkeryantz, *Synlett*, **1995**, 475.

[194] a) L. S. Fernandez, M. F. Jobling, K. T. Andrews, V. M. Avery, *Phytother. Res.*, **2008**, *22*, 1409. b) L. S. Fernandez, M. S. Buchanan, A. R. Carroll, Y. J. Feng, R. J. Quinn, V. M. Avery, *Org. Lett.*, **2009**, *11*, 329. c) L. S. Fernandez, M. L. Sykes, K. T. Andrews, V. M. Avery, *Int. J. Antimicrob. Agents*, **2010**, *36*, 275. d) D. H. Dethe, R. D. Erande, A. Ranjan, *J. Am. Chem. Soc.*, **2011**, *133*, 2864. e) R. M. Zeldin, F. D. Toste, *Chem. Sci.*, **2011**, 2, 1706. f) R. Vallakati, J. A. May, *J. Am. Chem. Soc.*, **2012**, *134*, 6936.

[195] J.-F. Liu, Z.-Y Jiang, R.-R Wang, Y.-T Zeng, J.-J Chen, X.-M. Zhang, Y.-B. Ma, *Org. Lett.*, **2007**, *9*, 4127.

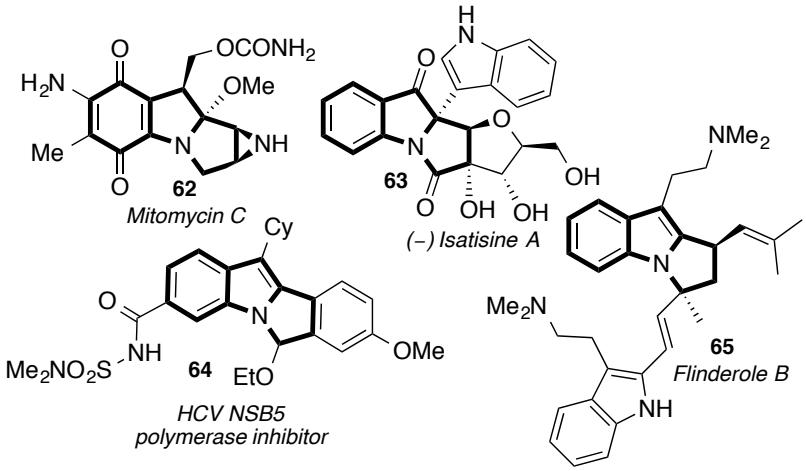


Figure 2.10 Natural products and bioactive molecules containing a pyrrolo[1,2-*a*]indole core.

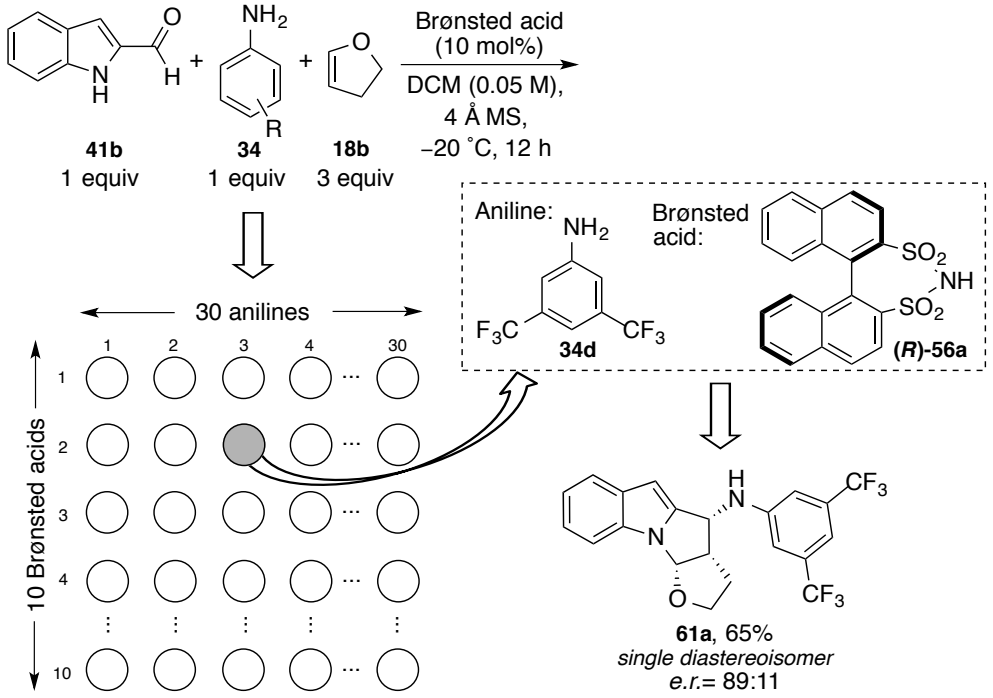
In this context, the objective was the study of the behaviour of 1*H*-indole-2-carboxaldehyde derivatives **41** in multicomponent reactions with anilines **34** and enol ethers **18**. Particularly, we wanted to evaluate if these reactions proceeded through the conventional Povarov pathway, through the new anti-Povarov pathway described in the previous section, or if a new [3+2]-heterocyclisation reaction could be developed (see **Scheme 2.13**).

2.2.B.2 Preliminary Studies and Optimisation of the Reaction Conditions

Studies began with the use of 1*H*-indole-2-carbaldehyde **41b**, 4-methylaniline **34a** and 2,3-dihydrofuran **18b** under the previously found optimised Povarov (with HBF_4 as catalyst) or anti-Povarov reaction conditions (with DPP as catalyst). However, formation of the expected tetrahydroquinoline or cyclopenta[*b*]indoles was not observed and neither traces of the proposed new pyrrolo[1,2-*a*]indole derivative could be detected. Although several parameters of these model reaction were varied, evolution of the *in situ* formed imine derivative was never observed.

However, convinced by the opportunities that these reagents could offer, we initiated a detailed and systematic investigation on the reactivity of *N*-unsubstituted 1*H*-indole-2-carboxaldehydes following a high-throughput experimentation model (**Scheme 2.14**). The selected model substrates were 1*H*-indole-2-carboxaldehyde **41b** and 2,3-dihydrofuran **18b**. Therefore, a survey of more than 30 differently substituted commercially available aniline derivatives **34** with different electronic properties (electron-rich, neutral and electron-poor)

along with different substitution patterns (ortho-, meta- and para-substituted, 3,5-disubstituted and 2,6-disubstituted) and more than 10 achiral and chiral Brønsted acids (including carboxylic, phosphoric and sulfonic acids between others) were tested in dichloromethane as solvent at –20 °C. Remarkably, just a unique catalyst/aniline combination provided a positive result after 12 hours. This combination included the 3,5-bis(trifluoromethyl)aniline **34d** and, surprisingly, the disulfonimide derivative **(*R*)-56a** as the Brønsted acid. None of the other experiments showed evident evolution of the corresponding *in situ* formed imine derivative. Pleasantly, the product of this highly specific reaction was shown to be (3a*S*,4*R*,10a*S*)-*N*-(3,5-bis(trifluoromethyl)phenyl)-2,3,3a,10a-tetrahydro-4*H*-furo[3',2':4,5]pyrrolo[1,2-*a*]indol-4-amine **61a**. Interestingly, this compound was formed as a single diastereoisomer and more importantly, the enantioselectivity of this new reaction was very high (*e.r.*= 89:11). It should also be noted that this transformation was also totally chemoselective because formation other possible products such as the corresponding hexahydrofuro[3,2-*c*]quinoline **50** (see **Scheme 2.13**, pathway A) or hexahydrofurocyclopenta[1,2-*b*]indole **49** (see **Scheme 2.13**, pathway B) was not observed at any extension.

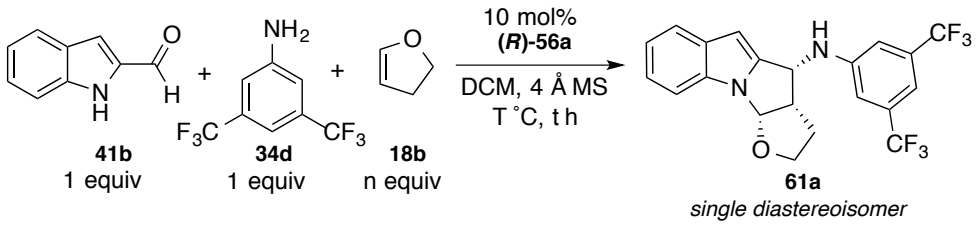


Scheme 2.14 Screening of aniline derivatives **34** and Brønsted acids.

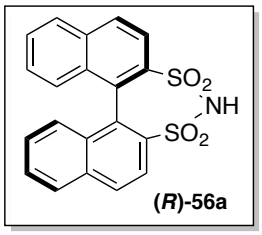
At this point, an additional optimisation of the reaction conditions was performed (**Table 2.5**, **Entries 2-4**). Thus, it was observed that better results were obtained by stirring the reaction mixture for longer reaction times (24 hours) at

–50 °C. Thus, the desired tetrahydrofuropyrrolo[1,2-*a*]indole **61a** was isolated in 72% yield, as single diastereoisomer and in 93:7 enantiomeric ratio (**Table 2.5**, **Entry 3**). Delightfully, this result could be further improved and finally, compound **61a** could be isolated in excellent yield (90%) and very good enantiomeric ratio (95:5) by performing the reaction at –70 °C and using 5 equivalents of the enol ether counterpart **18b** (**Table 2.5**, **Entry 4**).

Table 2.5 Preliminary results and optimisation of the reaction conditions.



Entry[a]	Equiv of 18b (n)	T (°C)	t (h)	Yield [%][b]	*e.r.*[c]
1	3	–20	12	65	89:11
2	3	–30	12	68	89:11
3	3	–50	24	72	93:7
4	5	–70	72	90	95:5



[a] Imine preformed at room temperature for 30 minutes. Then, 2,3-dihydrofuran **18b** was added at T. [b] Isolated yield after chromatography. [c] Determined by HPLC analysis. [d] Complex mixture of unidentified compounds.

The structure and absolute configuration of the stereogenic centres of the tetrahydropyrrolo[1,2-*a*]indole derivative **61a** were determined by single crystal X-ray diffraction analysis techniques. Therefore, as shown in the ORTEP representation in **Figure 2.11**, considering the pyrrolo[1,2-*a*]indole skeleton, the arylamino group and the tetrahydrofuran ring are placed in *cis*-disposition in the molecule.

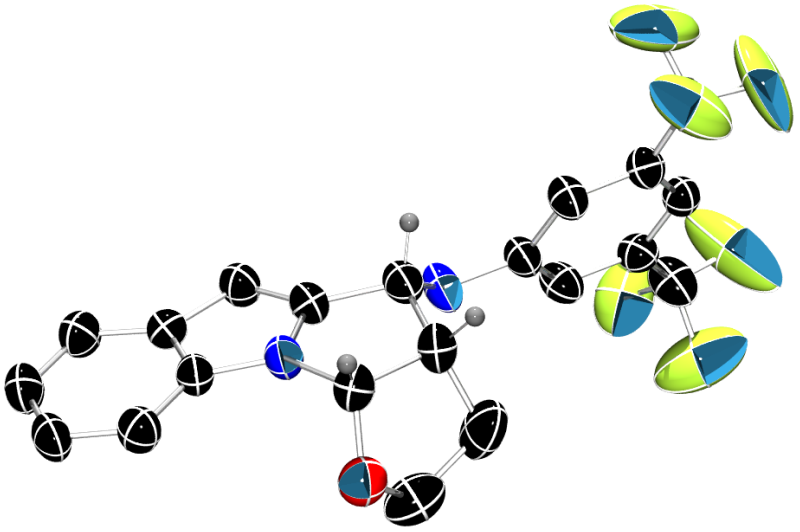
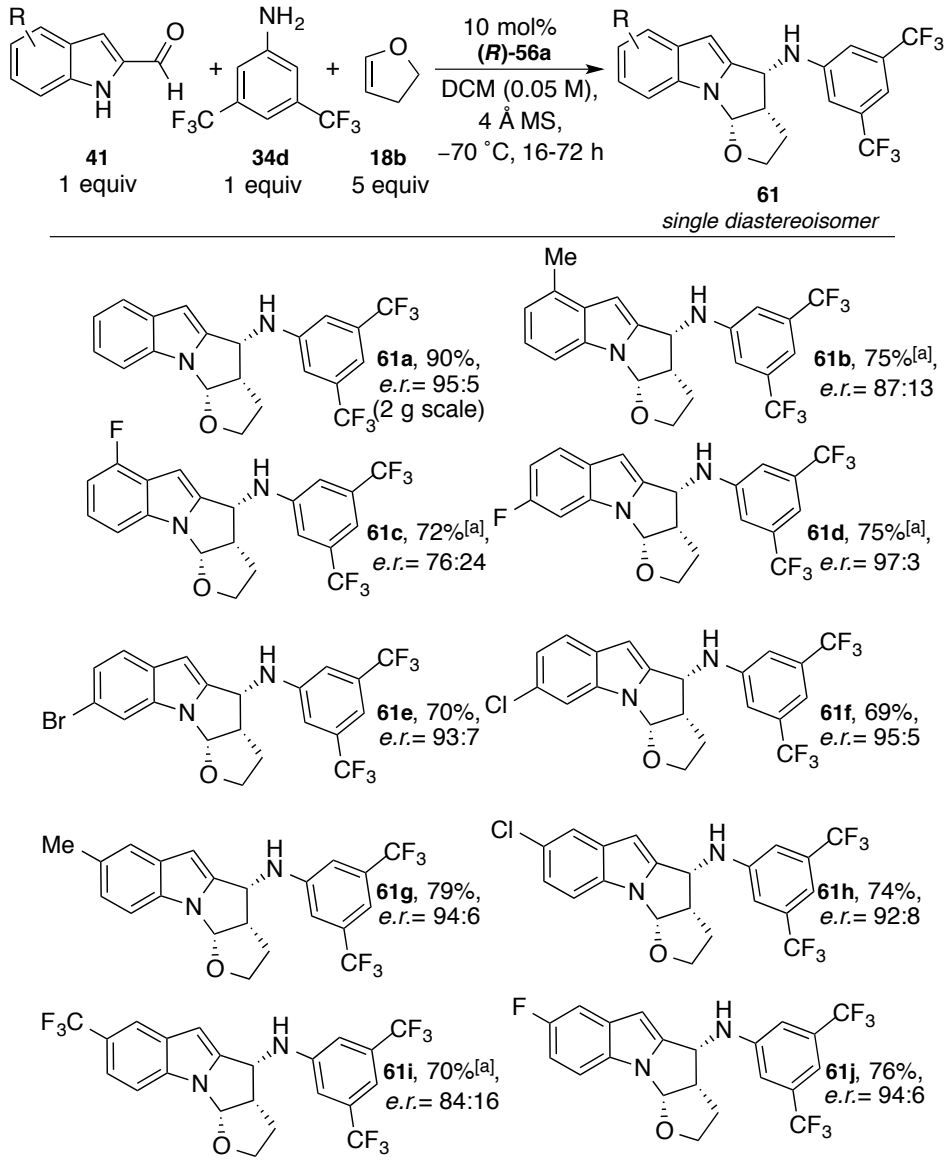


Figure 2.11 ORTEP representation of the structure of the pyrrolo[1,2-*a*] derivative **61a** determined by single crystal X-ray diffraction techniques.

2.2.B.3 Scope of the reaction: Synthesis of Pyrrolo[1,2-*a*] Derivatives

At this point, the study of the scope of the reaction was investigated. Firstly, a series of 1*H*-indole-2-carbaldehyde derivatives **41** was reacted with 3,5-bis(trifluoromethyl)aniline **34d** and 2,3-dihydrofuran **18b** under the previously optimised conditions (**Table 2.5**, **Entry 5**). The corresponding tetrahydrofuropyrrolo[1,2-*a*]indole derivatives **61** could be easily synthesised in good yields (**61a-j**, 69–90%) and enantiomeric ratios up to 97:3 (**Scheme 2.15**). As a limitation, 1*H*-indole-2-carbaldehyde derivatives **41** bearing the electron-donating methoxy group at different positions did not afford the desired compounds **61**, and the unreacted imine derivative was recovered under several reaction conditions. Moreover, 3-subtituted 1*H*-indole-2-carbaldehydes **41** were not appropriate substrates, and with the use of 7-substituted 1*H*-indole-2-carbaldehydes **41** the corresponding tetrahydrofuropyrrolo[1,2-*a*]indole derivatives **61** were just observed in the crude reaction mixture as traces and with very low enantiomeric ratio.



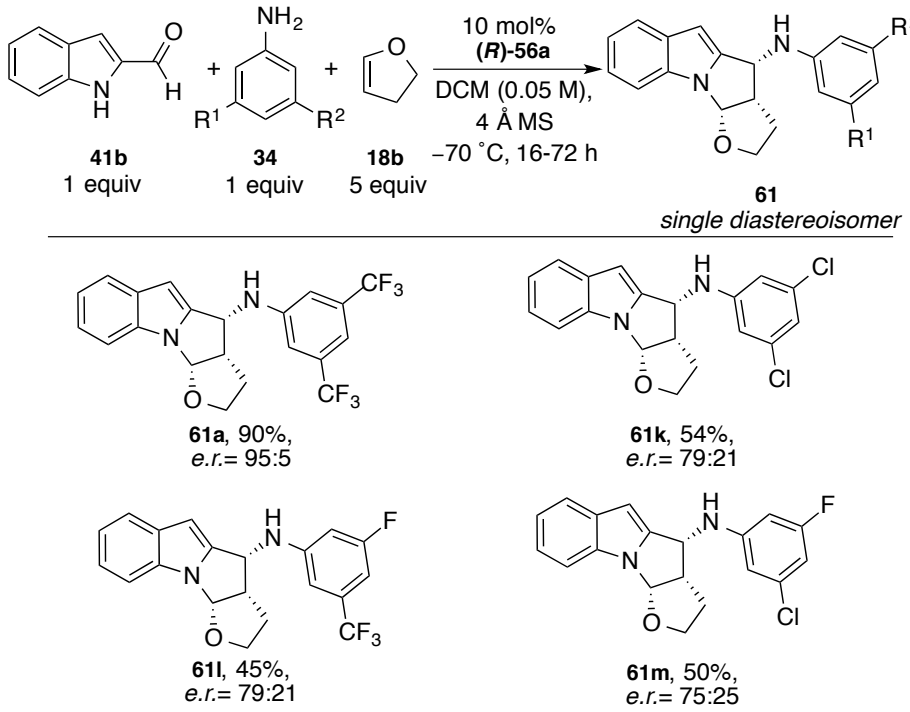
[a] PhF/DCM (1:1) was used as solvent (the aldehyde counterparts were unsoluble in DCM).

Scheme 2.15 Scope of the reaction regarding the aldehyde counterpart **41**.

Interestingly, it was also verified that the reaction could be performed on a gram scale and thus, 2.0 grams of **61a** were easily prepared in one batch without any loss in the chemical yield or enantiomeric excess. It is also important to remark that the chiral catalyst **(*R*)-56a** could be easily recovered at the end of the process and reused in subsequent reactions after an acidification process.

As shown in our initial screening (see **Scheme 2.14**) the reaction was limited to the use of 3,5-bis(trifluoromethyl)aniline **34d**. However, a more detailed study

showed that some other particular halogen-containing 3,5-disubtituted anilines **34** gave the desired tetrahydrofuropyrrolo[1,2-*a*]indole derivatives **61** (**Scheme 2.16**). However, in these cases the yields and enantiomeric ratios were lower than those observed for similar reactions performed with 3,5-bis(trifluoromethyl)aniline.



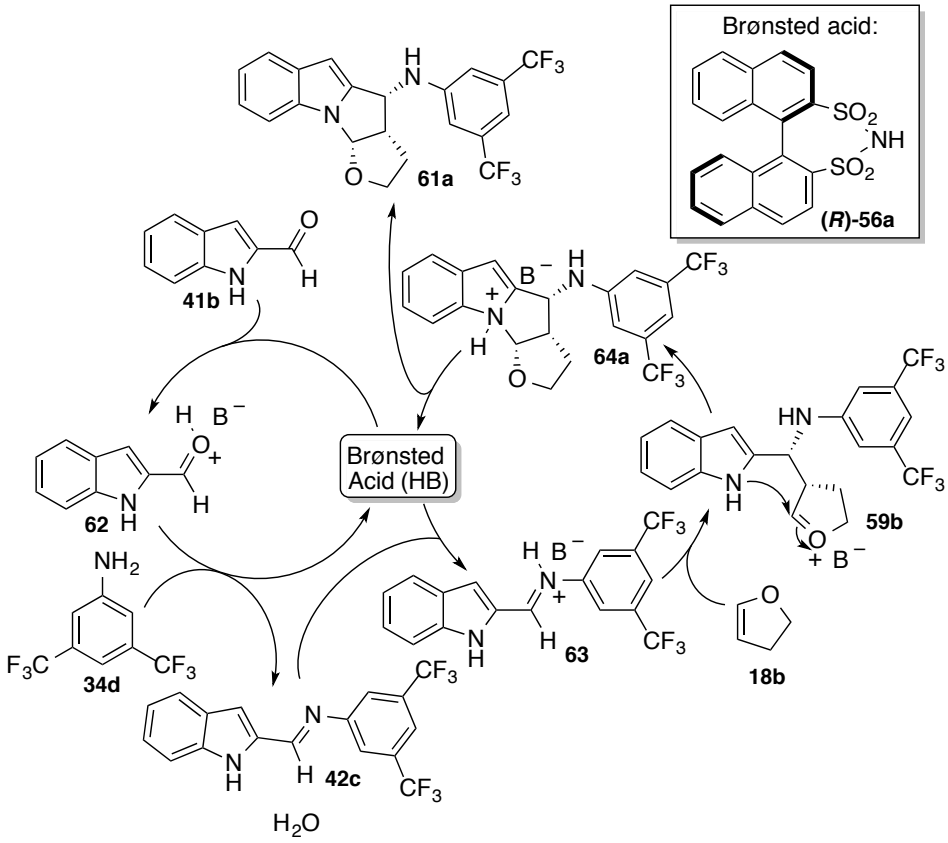
Scheme 2.16 Scope of the reaction regarding the aniline counterpart **34**.

Regarding the enol ether counterpart, a deep investigation was performed in order to expand its scope. Unfortunately, the reaction showed to be restricted to the use of 2,3-dihydrofuran **18b**. When other enol ethers, enamines or simple olefin derivatives were used, formation of the desired products was not observed, and the *in situ* formed imine was recovered unreacted in all cases and under several reaction conditions.

2.2.B.4 Mechanistic Proposal

Formation of tetrahydrofuropyrrolo[1,2-*a*]indole derivatives **61** could be explained by a self-relay Brønsted acid-catalysed mechanism, that is outlined in the following **Scheme 2.17** and explains the particular formation of **61a**. The first catalytic cycle implies the simple condensation of the 1*H*-indole-2-carbaldehyde **41b** and aniline **34d** to generate the imine **42** that enters the second catalytic cycle to form the activated iminium species **63**. At this point the nucleophilic attack of the 2,3-dihydrofuran **18b** would lead to the oxonium cation intermediate **59b**. The

subsequent intramolecular nucleophilic addition of the nitrogen of the indole moiety to the oxonium would give the intermediate **64a**. Finally, a deprotonation step would close the catalytic cycle, affording the tetrahydrofuropyrrolo[1,2-*a*]indole derivative **61a** and releasing the Brønsted acid catalyst.



Scheme 2.17 Mechanistic proposal: self-relay catalytic cycle.

2.2.B.5 Computational Studies

It should be reminded that the new reaction here described is particularly effective if 3,5-bis(trifluoromethyl)aniline is used as the aniline counterpart and the disulfonimide X is used as catalyst. This seems to indicate that some specific interactions should be established between this acid and the imines formed by condensation of the corresponding aldehydes and 3,5-bis(trifluoromethyl)aniline.

In order to understand the mechanism and the enantioselectivity observed in the new [3+2]-heterocyclisation process, computational studies (DFT calculations) were again performed in collaboration with Dr. Adán B. González Pérez, Prof. Dr. Rosana Álvarez and Prof. Dr. Ángel Rodríguez de Lera from the Department of Organic Chemistry (University of Vigo, Spain).

Thus, the key steps of the mechanism shown in **Scheme 2.17**, which are the coordination of the catalyst **(*R*)-56a** to the imine **42c** to give complex **63** and the subsequent reaction of these species with 2,3-dihydrofurane **18b** (also denoted as DHF along the discussion), were computed at the wB97XD-PCM(CH_2Cl_2)/6-31G*//wB97XD/6-31G* level[187] of theory using Gaussian 09.[186] It should be noted that the addition of 2,3-dihydrofurane **18b** to complex **63** is the stereodetermining step of the mechanism.

Initially, the formation of adduct **63** by coordination of catalyst **(*R*)-56a** to the imine **42c** was investigated. This study revealed that a network of interactions is established between both components in addition to the expected formation of a hydrogen bond between the nitrogen of the imine and the N-H of the chiral disulfonimide **(*R*)-56a (Figure 2.12)**.

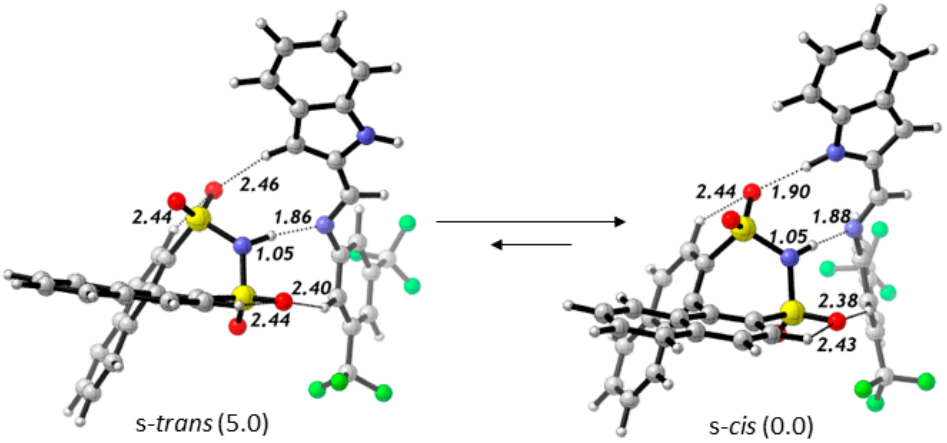


Figure 2.12 Representation of the conformational equilibrium of the starting complex **63** computed at the wB97XD-PCM(CH_2Cl_2)/6-31G*//wB97XD/6-31G* level. Relevant atom distances (in Å) are shown.

A conformational search revealed the preference of the complex **63** to adopt an **s-*cis*** conformation (note that **s-*cis*** and **s-*trans*** refer to the orientation of the N-H of the indole with respect to the nitrogen of the imine). In this conformation, the indole N-H is also engaged in hydrogen bonding with one of the oxygen atoms of the disulfonimide (ca. 1.90 Å).[196] This interaction is not possible in the **s-*trans*** conformation, where a less significant interaction between an oxygen

[196] This type of interaction between the NH of indole and an organo-catalyst, has been previously proposed, see: a) X. Li, D. Chen, H. Gu, X. Lin, *Chem. Commun.,* **2014**, *50*, 7538. b) X. Tian, N. Hofmann, P. Melchiorre, *Angew. Chem. Int. Ed.,* **2014**, *53*, 2997. c) L. M. Overvoorde, M. N. Grayson, Y. Luo, J. M. Goodman, *J. Org. Chem.,* **2015**, *80*, 2634.

atom of the disulfonimide and the hydrogen of the carbon at 3-position of the indole (2.46 Å) is established. In both conformers of the starting complex **63**, the dihedral angle between the naphthyl groups of the disulfonimide (s-*cis*: –67.6°; s-*trans*: –67.0°) freezes due to the interactions established the hydrogen atoms at 3- and 3'-positions of the binaphthyl moiety and an oxygen atom of each SO_2-groups (around 2.44 Å). These interactions restrict the disulfonimide conformational space.[197] Also, hydrogen-bonding interactions of polar aromatic C-H bonds from the 3,5-bis(trifluoromethyl)phenyl moiety with Lewis basic sites of **(*R*)-56a** (2.40 and 2.38 Å to **s-*trans*** and **s-*cis*** respectively) are established. These C-H….O hydrogen-bonding interactions are known to be important in molecular conformation, molecular recognition processes and the stabilisation of complexes.[198] As a result of all the above interactions, the **63-s-*cis*** complex shows a higher stability (ca. 5 kcal/mol), greater polarity and tendency to engage in π-π interactions than the alternative **63-s-*trans*** counterpart.[199] The N-H-N bond distances at the catalytic center [$S(O)_2$N-H 1.05 Å; $S(O)_2$NH----N_{imine} 1.88 Å] indicate that adduct **63** is better described as a neutral complex, rather than as an iminium disulfonimide ion pair.

Next, the reaction of the **(*R*)-56a-imine** complex **63** and 2,3-dihydrofuran **18b** (DHF) was computationally studied. Firstly, it was recognised that this reaction followed an stepwise mechanism to form an oxonium intermediate **59b** that is easily captured by the nitrogen of the indole to give **64** and finally, the pirrolo[1,2-*a*]indole **61a**. As this Mannich-type addition of dihydrofuran **18b** to complex **63** is the stereodetermining step, all approaches through the *Re* and *Si* faces of imine of the complex **63** and dihydrofuran **18b** to give the four possible stereoisomers of **59b** were analysed. Upon interaction of 2,3-dihydrofuran **18b** with complex **63** several changes were noticed. First, to allow the formation of the new carbon-carbon bond and pyramidalisation of the initial imine trigonal center, the indole ring undergoes a slight displacement that weakens the stabilising interaction between the hydrogen of the N-H of the indole and an oxygen atom of one of the SO_2-groups of the catalyst. Instead, the N-H of the indole interacts with the nitrogen atom of the sulfonamide, which is undergoing a transition to a disulfonimide anion. Therefore, as reaction progresses the effective acidity of the

[197] M. Treskow, J. Neudörfl, R. Giernoth, *Eur. J. Org. Chem.* **2009**, 3693-3697.

[198] R. Vargas, J. Garza, D. A. Dixon, B. P. Hay, *J. Am. Chem. Soc.* **2000**, *122*, 4750-4755.

[199] a) X. Li, H. Deng, B. Zhang, J. Li, L. Zhang, S. Luo, J.-P. Cheng, *Chem. Eur. J.*, **2010**, *16*, 450. b) K. M. Lippert, K. Hof, D. Gerbig, D. Ley, H. Hausmann, S. Guenther, P. R. Schreiner, *Eur. J. Org. Chem.*, **2012**, 5919. c) G. Jakab, C. Tancon, Z. Zhang, K. M. Lippert, P. R. Schreiner, *Org. Lett.*, **2012**, *14*, 1724. d) B. Zhu, W. Zhang, R. Lee, Z. Han, W. Yang, D. Tan, K.-W. Huang, Z. Jiang, *Angew. Chem. Int. Ed.*, **2013**, *52*, 6666.

catalyst is increased and the initial **(*R*)-56a**/**imine 42c** neutral complex **63-s-*cis*** shifts to an iminium disulfonimide ion pair form in all four stereoisomeric transition structures (see **Table 2.6** and **Figure 2.13**).

Table 2.6 Computed activation energies (kcal/mol) for the Mannich-type addition of dihydrofuran **18b** (DHF) to complex **63-s-*cis*** through the different faces of both reagents.[a]

Structures	$\Delta\Delta G^{\#}$
$TS_{Re\ imine\text{-}Re\ DHF}$	***0.0***
$TS_{Re\ imine\text{-}Si\ DHF}$	9.0
$TS_{Si\ imine\text{-}Re\ DHF}$	6.0
$TS_{Si\ imine\text{-}Si\ DHF}$	4.7

[a]Energies (in kcal/mol) were computed at the wB97XD-PCM(CH_2Cl_2)/6-31G*//wB97XD/6-31G* level. [c]Relative activation energies.

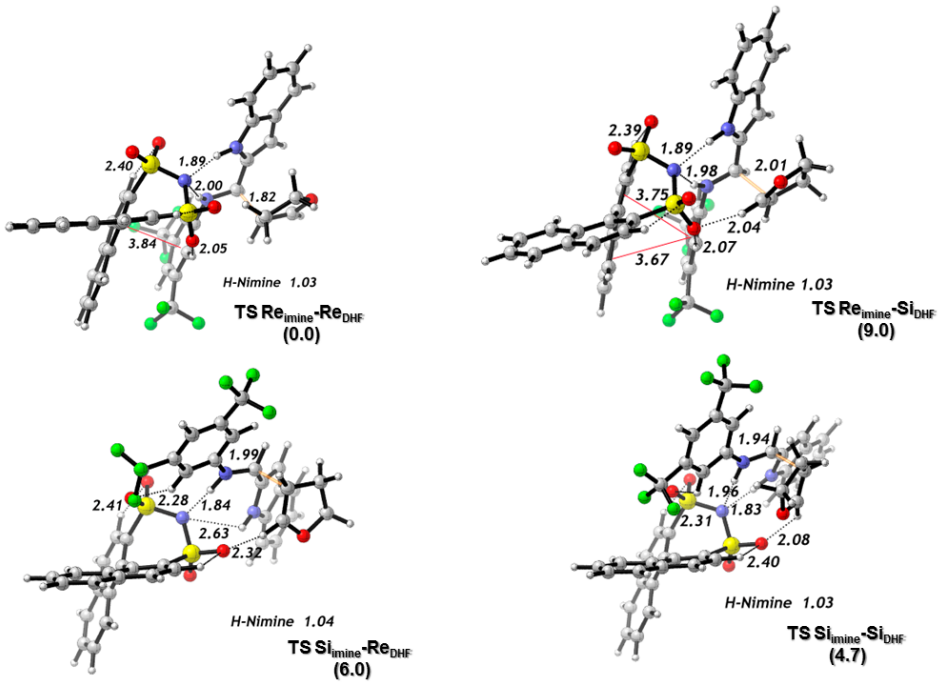


Figure 2.13 Representation of the transition structures corresponding to the reaction of dihydrofuran **18b** (DHF) with complex **63-s-*cis*** computed at the wB97XD-PCM(CH_2Cl_2)/6-31G*//wB97XD/6-31G* level. Relevant atom distances (in Å) are shown.

$TS_{Re\ imine\text{-}Re\ DHF}$ was computed to be energetically favoured, in agreement with the experimental results. Analysis of the H---N_{imine} (1.03 Å) and N-SO_2---H (2.00 Å) bond lenghts at this transition structure confirmed the bond reorganisation at the interacting core atoms. $TS_{Re\ imine\text{-}Re\ DHF}$ is the more retarded of the computed

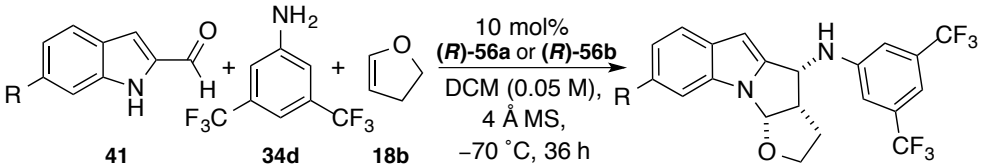
transition states (the distance for the incipient new carbon-carbon bond is 1.82 Å in **TS*Re* imine-*Re* DHF** but longer, 1.94-2.01 Å, in the other transition states). The greater strength of the C-H….O hydrogen-bonding interaction established between an aromatic C-H bond of the 3,5-bis(trifluoromethyl)phenyl moiety and an oxygen atom of one of the SO_2-groups (2.05 Å) along with the stabilising π-π interactions observed between the 3,5-bis(trifluoromethyl)phenyl group and one of the naphthyl groups (parallel-displaced or PD arrangement) further contribute to lower its energy relative to the alternative transition states. In particular, transition states involving the ***Si*imine** face do not exhibit the stabilising π-π interactions of the 3,5-trifluoromethylphenyl and the proximal benzene ring of the binaphthyl catalyst.[200] On the contrary, destabilising T-shaped interactions between the electronegative CF_3 group and a proximal benzene ring of the binaphthyl catalyst are observed.

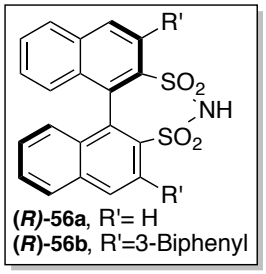
2.2.B.6 Switch of Enantioselectivity

This new reaction is also remarkable in the context of disulfonimide-catalysed asymmetric reactions. Thus, as previously outlined in the General Introduction of this thesis, chiral disulfonimide derived catalyst have been mainly used in the context of silylium Lewis acid promoted reactions. However, in our reaction, catalyst **(*R*)-56a** behaves as a conventional Brønsted acid catalyst. Another remarkable feature of our reaction is the high enantioselectivity observed by using the simplest 3,3'-unsubstituted disulfonimide **(*R*)-56a**. Usually, high enantioselectivities are obtained, only, when aromatic substituents are placed at those positions of the binaphthyl group. In this context, we have also tried our reaction with the disulfonimide derivative **(*R*)-56b** containing 3-biphenyl groups at 3- and 3'-positions (**Table 2.4**). Reactions with this catalyst were also very efficient and the corresponding tetrahydrofuropyrrolo[1,2-*a*]indole derivatives **61a** and **61d** could be isolated in high yield and enantioselectivity. But surprisingly, the major enantiomer is the opposite of the one obtained with the simple catalyst **(*R*)-56a**.

Table 2.7 Switch of enantioselectivity.

[200] a) P. Hobza, H. L. Selzle, E. W. Schlab, *J. Phys. Chem.*, **1996**, *100*, 18790. b) K. S. Kim, P. Tarakeshwar, J. Y. Lee, *Chem. Rev.*, **2000**, *100,* 4145. c) E. A. Meyer, R. K. Castellano, F. Diederich, *Angew. Chem. Int. Ed.*, **2003**, *42*, 1210. d) L. M Salonen, M. Ellermann, F. Diederich, *Angew. Chem. Int. Ed*., **2011**, 50, 4808. e) S. E. Wheeler, *Acc. Chem. Res.*, **2013**, *46*, 1029.





Entry	Chiral HB	R	Yield [%][a]	*e.r.*[b]
1	**(*R*)-56a**	H	90	95:5
2	**(*R*)-56b**	H	90	8:92
3	**(*R*)-56a**	F	75	97:3
4	**(*R*)-56b**	F	75	8:92

[a] Isolated yield after chromatography.

[b] Determined by HPLC analysis.

Usually, to achieve the reversal of enantioselectivity of a reaction requires the change of the absolute configuration of the catalyst. However, in the above commented examples both catalysts **(*R*)-56a** and **(*R*)-56b** are of the same configuration. Thus, these reactions are atypical examples of reversal of enantioselectivity achieved by a simple structural modification of the catalyst without altering its absolute configuration.[201] Thus, interestingly, in our case the switch of enantioselectivity can be accomplished by the conventional method using both enantiomers of the same catalyst (i.e. **(*R*)-56a** / **(*S*)-56a**) or alternatively, by using two closely related catalysts with the same absolute configuration (i.e. **(*R*)-56a** / **(*R*)-56b**).

2.2.B.7 Derivatisation Reactions of Tetrahydrofuropyrrolo[1,2-*a*]indole Compounds

To further demonstrate the utility of the new asymmetric multicomponent reactions here described, tetrahydrofuropyrrolo[1,2-*a*]indole derivatives **61** were easily transformed into some other valuable products.

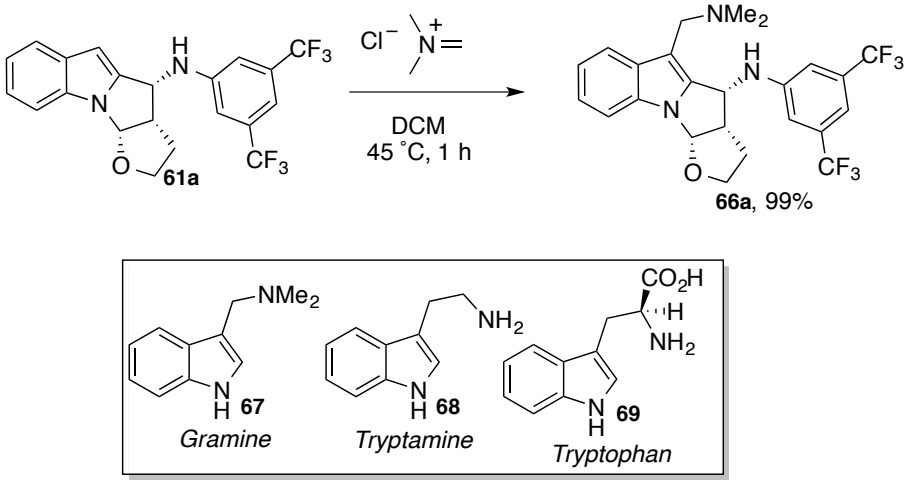
Thus, bromination at C-3 position of the indole was efficiently achieved by reaction of the tetrahydrofuropyrrolo[1,2-*a*]indole derivative **61a** with *N*-bromosuccinimide (NBS) in DMF at room temperature for 2 hours. Thus, the chiral

[201] For a review of complete reversal of enantioselectivity using a single chiral source, see: T. Tanaka, M. Hayashi, *Synthesis*, **2008**, 3361.

brominated compound **65a** was isolated in excellent chemical yield (**Scheme 2.18**). The presence of a bromine atom in **65a** offers multiple opportunities for further transformations.

Scheme 2.18 Bromination at the C-3 position of the indole moiety of **61a**.

Moreover, derivative **61a** was treated with the iminium ion electrophile known as "Eschenmoser's salt" in dichoromethane at 45 °C for one hour to quantitatively give the product **66a** via a Mannich-type reaction (**Scheme 2.19**).

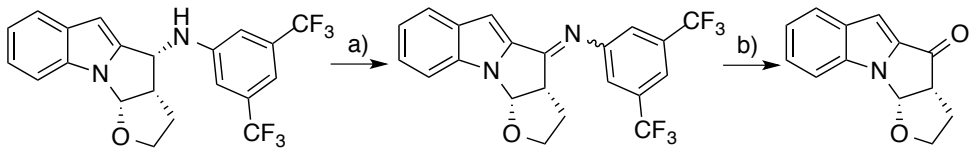


Scheme 2.19 Reaction with iminium ions.

This new derivative **66a** contains a gramine moiety **67**, a naturally occurring indole alkaloid present in several plant species that also serves as starting material in many synthesis of the essential amino acid tryptophan **69**.[202]

Finally, derivative **61a** was reacted with the oxidant 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in benzene at room temperature for 5 hours to get the corresponding imine **70a** in a quantitative yield as mixture of isomers (5:1). Subsequently, imine **70a** was easily hydrolysed to afford the corresponding chiral furopyrrolo[1,2-*a*]indol-4-one derivative **71a** (**Scheme 2.20**).

[202] J. A. Joule, G. F. Smith, *Heterocyclic Chemistry*, 4th ed., Blackwell Science, Oxford, **2000**.



61a **70a** **71a**

a) DDQ (1.2 equiv.), benzene (0.04 M), rt, 5 h, quantitative
b) AcOH (20 equiv.), THF/H_2O (1:1), 80˚C, 16 h, quantitative

Scheme 2.20 Synthesis of furopyrrolo[1,2-*a*]indol-4-one derivative **71b** by removal of the aryl amino group.

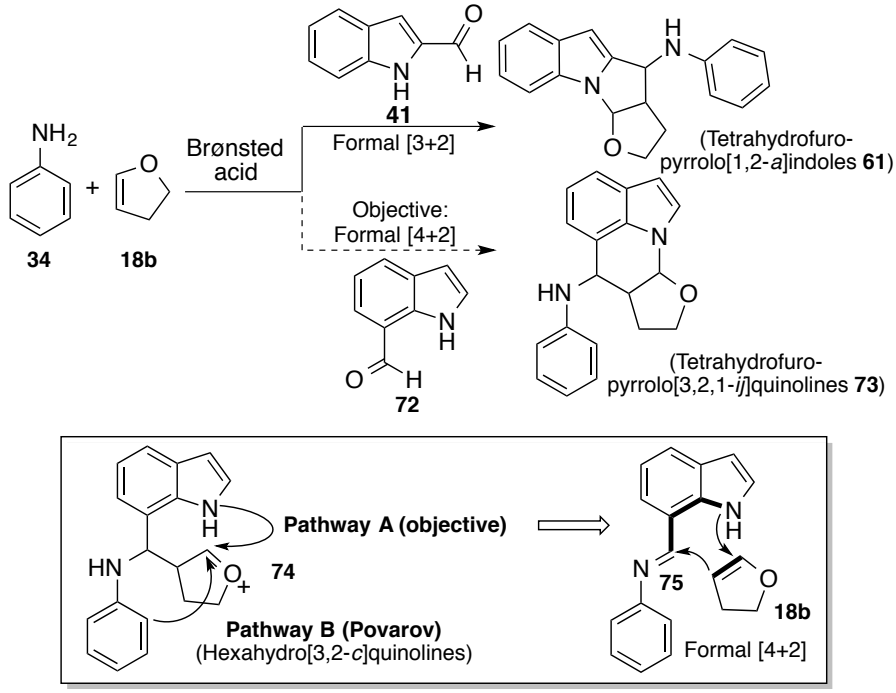
Part C

Stereoselective [4+2]-Heterocyclisation of 1H-Indol-7-carbaldehyde Imines and Electron-Rich Alkenes. Synthesis of Pyrrolo[3,2,1-ij]quinoline Derivatives

2.2.C.1 Results and Discussion. Part C

2.2.C.1 Objective

In the previous section it has been shown that the nitrogen atom present in 1*H*-indole-2-carbaldehyde derivatives **41** was involved in the nucleophilic trapping of the oxonium intermediate **59b** (see **Scheme 2.13**) to afford tetrahydrofuropyrrolo[1,2-*a*]indole derivatives **61** via a formal [3+2]-heterocyclisation reaction. Once this reactivity pathway was demonstrated, the use of 1*H*-indole-7-carbaldehydes **72** instead of 1*H*-indole-2-carbaldehydes **41** was considered. Thus, in this case, after the *in situ* generation of the *N*-arylimine derivative **75** and its reaction with an enol ether **18b**, the oxonium intermediate **74** would be generated. This cationic species could evolve by the nucleophilic attack of the nitrogen atom to afford interesting tetrahydrofuropyrrolo[3,2,1-*ij*]quinoline derivatives **73** (**Scheme 2.21**).



Scheme 2.21 Objective.

It should be noted that this new process represents a formal [4+2]-heterocyclisation reaction between the *N*-arylimine **75** and the enol ether **18b**, and that the alternative [4+2] Povarov reaction to give hexahydrofuro[3,2-c]quinoline derivatives is also conceivable (pathway B, **Scheme 2.21**).

The pyrrolo[3,2,1-*ij*]quinoline structural unit is found in numerous pharmaceuticals and natural products. Extensive studies have demonstrated that pyrrolo[3,2,1-*ij*]quinolines are lead candidates for fungicides against rice blast disease, and they are also potential candidates for treatments of other diseases. For example, derivative **76** (**Figure 2.14**) possesses good anticonvulsant properties and **78** (**Figure 2.14**) has been reported to be highly potent agonists at 5-HT_{2c} (5-hydroxytryptamine) with selectivity over 5-HT_{2a} isoform for the prophylactic management of epilepsy and obesity. In addition, it has been reported in numerous patents that pyrrolo[3,2,1-*ij*]quinoline is a promising skeleton in drug development. This system is present at the core of the lilolidine **79** alkaloids (**Figure 2.14**), which have been explored as therapeutics, fungicides and moreover, pyrrolo[3,2,1-*ij*]quinoline derivatives are used as red-light-emitting dopants in organic light-emitting diodes (OLEDs) (**77**, **Figure 2.14**).[203]

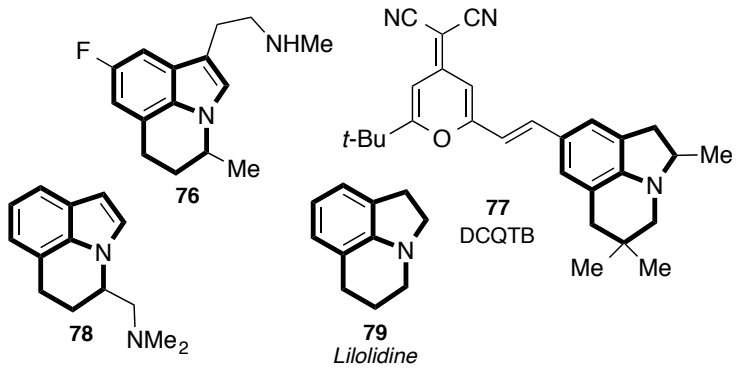


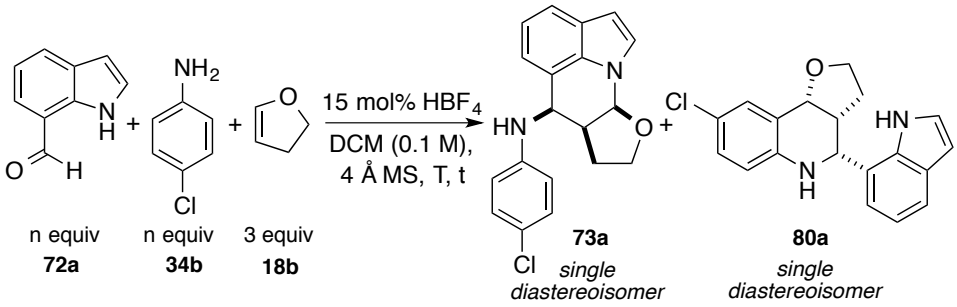
Figure 2.14 Bioactive molecules and alkaloids containing a pyrrolo[3,2,1-*ij*]quinoline core.

[203] Y.-S. Yao, Q.-X. Zhou, X.-S. Wang, Y. Wang, B.-W. Zhang, *Adv. Funct. Mater.*, **2007**, *17*, 93. a) J. L. Stanton, M. H. Ackerman, *J. Med. Chem.*, **1983**, *26*, 986. b) R. S. Al-awar, J. E. Ray, K. A. Hecker, J. Huang, P. P. Waid, C. Shih, H. B. Brooks, C. D. Spencer, S. A. Watkins, B. R. Patel, N. B. Stamm, C. A. Ogg, R. M. Schultz, E. L. Considine, M. M. Faul, K. A. Sullivan, S. P. Kolis, J. L. Grutsch, S. Joseph, *Bioorg. Med. Chem. Lett.*, **2004**, *14*, 3217. c) G. Zhu, S. E. Conner, X. Zhou, H.-K. Chan, C. Shih, T. A. Engler, R. S. Al-awar, H. B. Brooks, S. A. Watkins, C. D. Spencer, R. M. Schultz, J. A. Dempsey, E. L. Considine, B. R. Patel, C. A. Ogg, V. Vasudevan, M. L. Lytle, *Bioorg. Med. Chem. Lett.*, **2004**, *14*, 3057. d) R. J. Bass, R. C. Koch, H. C. Richards, J. E. Thorpe, *J. Agric. Food Chem.*, **1981**, *29*, 576. e) D. Paris, M. Cottin, P. Demonchaux, G. Augert, P. Dupassieux, P. Lenoir, M. J. Peck and D. J. Jasserand, *J. Med. Chem.*, **1995**, *38*, 669. f) M. Isaac, A. Slassi, A. O'Brien, L. Edwards, N. MacLean, D. Bueschkens, D. K. H. Lee, K. McCallum, I. D. Lannoy, L. Demchyshyn, R. Kamboj, *Bioorg. Med. Chem. Lett.*, **2000**, *10*, 919. H. Rapoport, J. R. Tretter, *J. Am. Chem. Soc.*, **1958**, *80*, 5574.

2.2.C.2 Preliminary Studies and Optimisation of the Reaction Conditions

To test the feasibility of the proposed reaction, 1*H*-indole-7-carbaldehyde **72a**, 4-chloroaniline **34b** and 2,3-dihydrofuran **18b** were selected as model starting materials and HBF_4 was chosen as the Brønsted acid catalyst (**Table 2.8**).[204]

Table 2.8 Preliminary studies and Optimisation of the Reaction Conditions.



Entry	Equiv. 72a (n)	Equiv. 34b (n)	Imine[a] t (min)	T (°C)	t (h)	Prod. [b] (73a:80a)	Conv. [%][c] (yield)
1	1	1	30	rt	3	–	–[e]
2	1	1	30	0	12	–	–[e]
3	1	1	30	–20	20	2.4:1	81
4	1	1.5	30	–20	20	2.5:1	26
5	1.5	1	30	–20	20	2.4:1	56
6	1	1	60	–30	20	3:1	91 (68%)
7	1	1	120	–30	24	5:1	97 (80%)[e]

[a] Imine preformed at room temperature for t min. Then 2,3-dihydrofurane **18b** was added at T. [b] Ratio determined by ^{1}H–NMR analysis of the crude reaction mixture. [c] Conversion determined by ^{1}H–NMR analysis of the crude reaction mixture by comparison with 1*H*-indole-7-carbaldehyde **72a**. [d] Complex mixture of unidentified compounds [e] 3% of preformed imine was observed by ^{1}H–NMR analysis of the crude reaction mixture, but any 1*H*-indole-7-carbaldehyde was present.

Thus, the initial experiments were performed by reacting 1*H*-indole-7-carbaldehyde **72a** and 4-chloroaniline **34b** with 15 mol% of HBF_4 in dichloromethane as solvent in the presence of 4 Å MS at room temperature. After

[204] For some preliminary studies, see: Raquel Fontaneda López, *Trabajo Fin de Máster*, Universidad de Oviedo, **2014**.

30 minutes of stirring at room temperature the reaction mixture was set at the selected temperature, 2,3-dihydrofuran **18b** (3 equiv) was added and the consumption of the imine was followed by TLC.

First experiments were devoted to find an appropriate temperature of reaction and in this regard it was observed that temperatures above –20 °C were not appropriate because formation of mixtures of unidentified compounds were observed (**Table 2.8**, **Entries 1 and 2**). However, at –20 °C it was possible to observe the generation of a mixture of just two products, (6*R**,6a*S**,9a*S**)-*N*-(4-chlorophenyl)-6a,7,8,9a-tetrahydro-6*H*-furo[2,3-*b*]pyrrolo[3,2,1-*ij*]quinolin-6-amine **73a** and (3a*R**,4*R**,9b*R**)-8-chloro-4-(1*H*-indol-7-yl)-2,3,3a,4,5,9b-hexahydrofuro[3,2-*c*]quinoline **80** in a 2.4:1 ratio (**Table 2.8**, **Entry 3**). Interestingly, the tetrahydrofuropyrrolo[3,2,1-*ij*]quinoline **73a** is the product coming from the proposed new formal [4+2]-heterocyclisation reaction between the *N*-arylimine **75a** and the enol ether **18b** while the hexahydrofuro[3,2-*c*]quinoline derivative **80** is the result of a conventional Povarov reaction. After this initial promising result, a study to improve the conversion of the reaction was performed. In this regard, nor the use of an excess of the aniline **34b** or an excess of the aldehyde **72a** led to better results (**Table 2.8**, **Entries 4 and 5**). However, extending the reaction time of the imine formation reaction from 30 minutes to 2 hours had a positive effect not only on the conversion (up to 97%) but also on the selectivity of the process as the ratio of products **73a**/**80a** was improved up to 5:1 (**Table 2.8**, **Entries 6 and 7**). Finally, some experiments were carried out with other Brønsted acids as catalysts (PTSA, DNBSA, DPP, etc). However, only positive results were achieved with HBF_4. Thus, the fully optimised conditions implied the reaction of 1*H*-indole-7-carbaldehyde **72a** and 4-chloroaniline **34b** with 15 mol% of HBF_4 in dichloromethane as solvent in the presence of 4 Å MS at room temperature for 2 hours. After cooling the mixture to –30 °C, 2,3-dihydrofuran **18b** (3 equiv) was added and the reaction was stirred for 24 hours at this temperature. Under these conditions, tetrahydrofuropyrrolo[3,2,1-*ij*]quinoline **73a** could be isolated as a single diastereoisomer in 80% yield (**Table 2.8**, **Entry 7**).

The structure and relative configuration of the stereogenic centres of (6*R**,6a*S**,9a*S**)-*N*-(4-chlorophenyl)-6a,7,8,9a-tetrahydro-6*H*-furo[2,3-*b*]pyrrolo[3,2,1-*ij*]quinolin-6-amine **73a** was determined by single crystal X-ray diffraction analysis techniques (**Figure 2.15**). Therefore, as shown in the ORTEP representation, considering the pyrroloquinoline skeleton, the arylamino group and the tetrahydrofuran ring are placed in *cis*-disposition. Moreover, a *cis*-fusion between the tetrahydrofuran ring and the quinoline moiety is also observed.

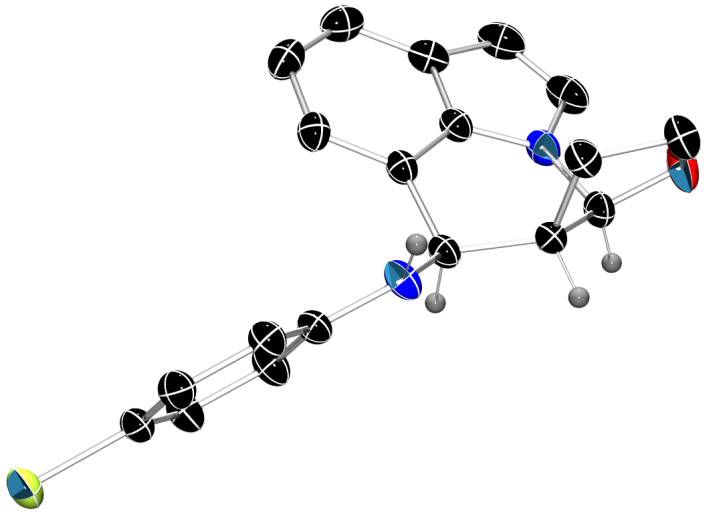


Figure 2.15 ORTEP representation of the structure of the tetrahydro-6*H*-furo[2,3-*b*]pyrrolo[3,2,1-*ij*]quinoline derivative **73a** determined by single crystal X-ray diffraction techniques.

Additionally, the structure and relative configuration of the stereogenic centres of the hexahydrofuro[3,2-*c*]quinoline derivative **80a** derived from the Povarov reaction were determined by one- and two-dimensional NMR experiments (**Figure 2.16**).

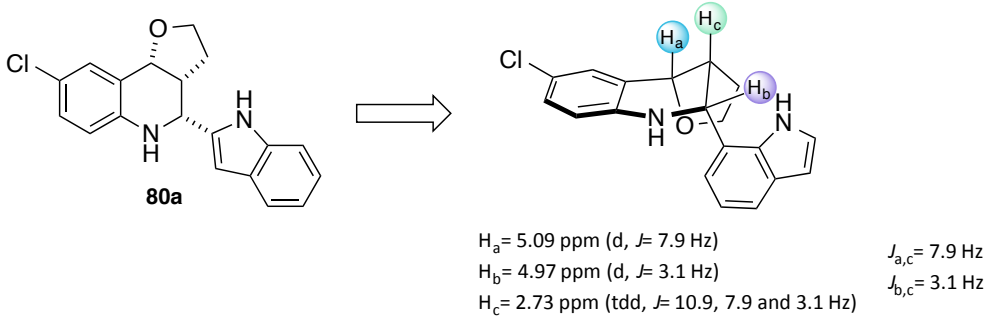
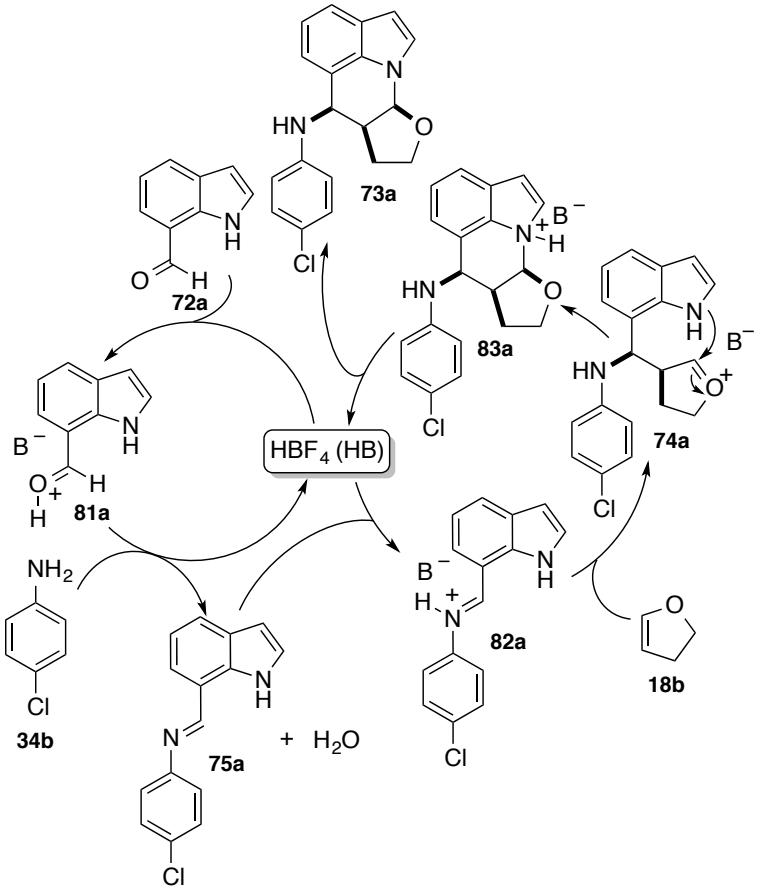


Figure 2.16 Determination of the relative configuration of **80a** through ^{1}H–NMR experiment.

The doublet centred at 5.09 ppm (d, *J*= 7.9 Hz) was assigned to $\mathbf{H_a}$, the doublet centred at 4.97 ppm (d, *J*= 3.1 Hz) was assigned to $\mathbf{H_b}$ and the triple doublet of doublet centred at 2.73 ppm was assigned to $\mathbf{H_c}$. The value of the coupling constant between $\mathbf{H_b}$ and $\mathbf{H_c}$ (*J*= 3.1 Hz) enabled the assignment of a relative gauche *cis*-disposition between $\mathbf{H_b}$ and $\mathbf{H_c}$ and the value of the coupling constant between $\mathbf{H_a}$ and $\mathbf{H_c}$ (*J*= 8.0 Hz) is also consistent with the expected *cis*-

fusion between the furan ring and the quinoline moiety of the molecule, as previously observed for the Povarov derivative **50a** (see **Figure 2.7**).

The mechanism proposed to explain the formation of the tetrahydrofuropyrrolo[3,2,1-*ij*]quinoline derivative **73a** is shown in **Scheme 2.22** and involves a self-relay catalytic process very similar to that previously described in **section 2.2.B.4** for the synthesis of **61a** (see **Scheme 2.17**). Thus, condensation of the 1*H*-indole-7-carbaldehyde **72a** and the aniline **34b** affords the imine **75a**, that enters the second catalytic cycle to form the activated iminium species **82a**. Subsequently, the nucleophilic attack of the 2,3-dihydrofuran **18b** would lead to the oxonium cation intermediate **74a**. The intramolecular nucleophilic addition of the nitrogen of the indole moiety to the oxonium would give rise to the intermediate **83a**. Finally, a deprotonation step would close the catalytic cycle, affording the tetrahydrofuropyrrolo[3,2,1-*ij*]quinoline derivative **73a** and releasing the Brønsted acid catalyst.

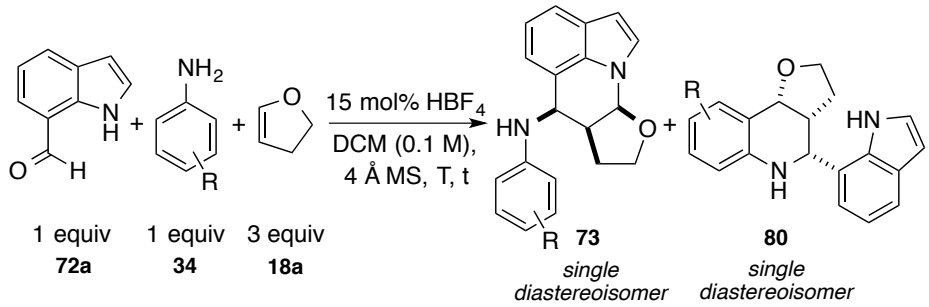


Scheme 2.22 Proposed catalytic cycle for the formation of the derivative **73a**: self-relay catalytic cycle.

2.2.C.3 Scope of the Reaction: Synthesis of Pyrrolo[3,2,1-*ij*]quinoline Derivatives

With optimal conditions in hand for the synthesis of the tetrahydrofuropyrrolo[3,2,1-*ij*]quinoline derivative **73a**, the study of the scope of the multicomponent process was next studied. Firstly, a set of anilines **34** with different electronic properties was tested (**Table 2.9**). It should be noted that almost every aniline attempted needed an optimisation of the reaction conditions.

Table 2.9 Influence of the electronic properties of the aniline **34**.



Entry[a]	R	T (°C)	t (h)	Prod. [b] (73:80)	Conv. [%][c] (yield) [d]
1	4-MeO	0	12	1:1	67 (32%)
2	H	0	16	2:1	95 (60%)
3	4-Cl	–30	24	5:1	97 (80%)
4	4-CF_3	–50	9	1:0	85 (80%)
5	3-CF_3	–50	9	1:0	87 (83%)
6	3,5-$(Cl)_2$	–50	42	1:0	95 (90%)
7	3,5-$(CF_3)_2$	–70	48	1:0	>99 (96%)

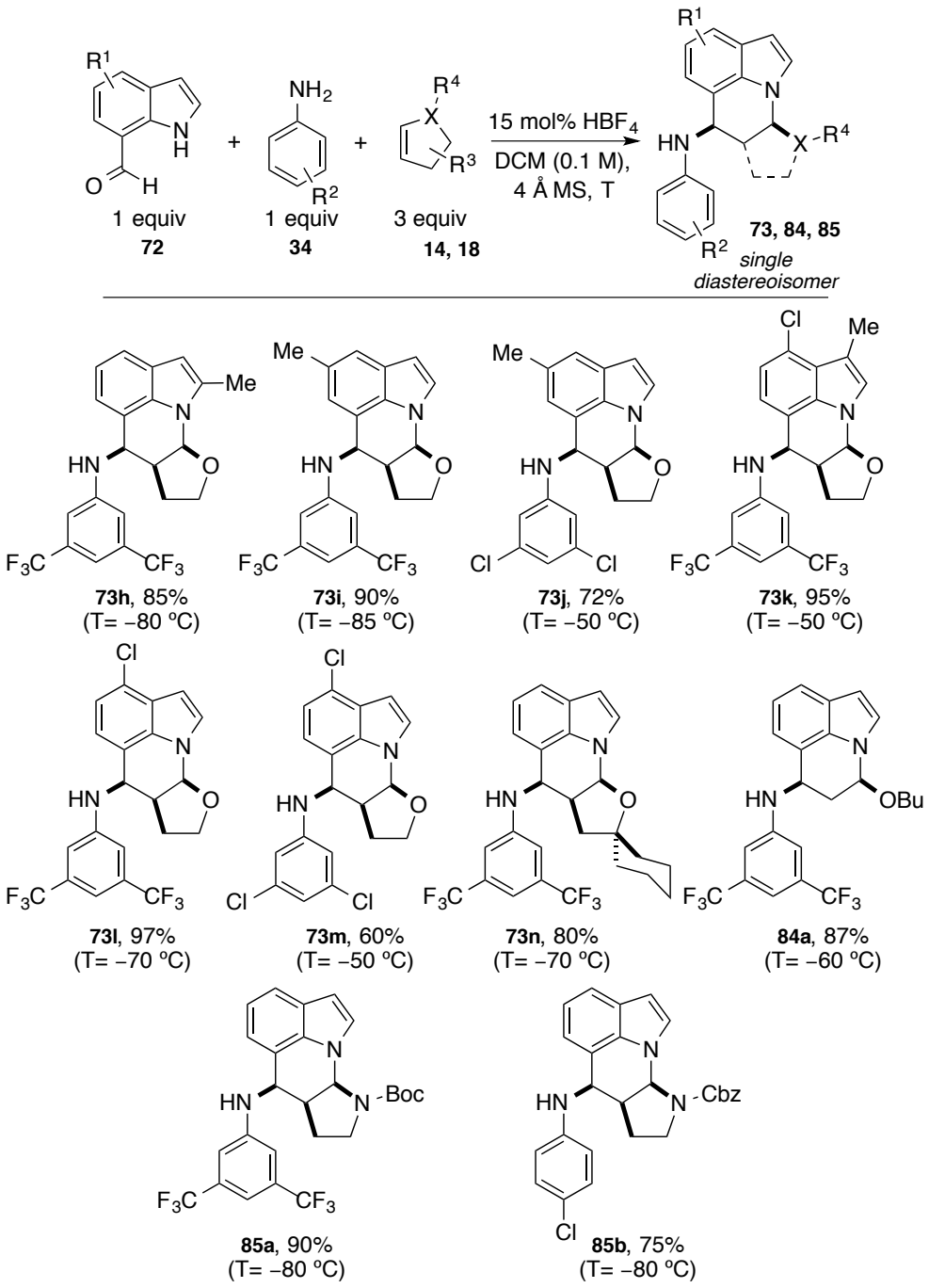
[a] Imine preformed at room temperature for 2 hours. Then 2,3-dihydrofurane **18b** was added at T. [b] Ratio determined by ^{1}H–NMR analysis of the crude reaction mixture. [c] Conversion determined by ^{1}H–NMR analysis of the crude reaction mixture. [d] Isolated yield of compound **73** after chromatography.

As shown, when the electron-donating methoxy group was decorating the aniline counterpart **34**, best results were obtained when the reaction was performed at 0 °C for 12 hours. However, the conversion was low (67%) and formation of a 1:1 mixture of compounds **73b** and **80b** was observed. Thus, the desired compound **73b** was isolated in low yield (32%) (**Table 2.9**, **Entry 1**). This

result could not be further improved. The use of neutral aniline gave better results in terms of conversion and selectivity (95% and 2:1 mixture of **73b** and **80b**) and then, the corresponding tetrahydrofuropyrrolo[3,2,1-*ij*]quinoline derivative **73b** could be isolated in 60% yield (**Table 2.9**, **Entry 2**). As previously described for our model reaction, the use of 4-chloroaniline **34b** afforded the desired compound in 80% isolated yield with good selectivity (5:1, **73a**/**80a**) (**Table 2.9**, **Entry 3**). Interestingly, the use of 4-(trifluoromethyl)aniline allowed the exclusive formation of the corresponding tetrahydrofuropyrrolo[3,2,1-*ij*]quinoline derivatives **73d** in very good yield when the reaction was performed at –50 °C. Under these conditions formation of the corresponding "undesired" hexahydrofuro[3,2-*c*]quinoline derivative **80** was completely avoided (**Table 2.9**, **Entry 4**). Similar results were obtained by the use of 3-(trifluoromethyl)aniline (**Table 2.9**, **Entry 5**). The process also showed to be highly efficient when 3,5-dichloro- or 3,5-bis(trifluoromethyl)-anilines were used. Again, in these particular examples, the desired compounds were exclusively obtained and isolated in excellent yields (**Table 2.9**, **Entries 6 and 7**). Summarising, tetrahydrofuropyrrolo[3,2,1-*ij*]quinoline derivatives **73** seemed to be efficiently and exclusively formed when relatively electron-poor aniline derivatives are used.

The scope of the process was further investigated by probing changes in the 1*H*-indole-7-carbaldehyde **72a** and the enol ether counterpart **18b** previously used (**Scheme 2.23**). Thus, when the electron-poor 3,5-dichloroaniline and 3,5-bis(trifluoromethyl)aniline were reacted with a series of 3, 4, 5 and 6-substituted 1*H*-indole-7-carbaldehyde derivatives **72** using 2,3-dihydrofuran **18b** as the enol ether counterpart, the corresponding tetrahydrofuropyrrolo[3,2,1-*ij*]quinolines **72h-m** were formed and isolated in good to excellent yields (60-97%). Interestingly, the reaction worked not only with 2,3-dihydrofuran **18b** as the enol ether counterpart but also with substituted cyclic enol ethers **18** (**73n**, 80%). Moreover, the use of linear enol ethers such as butyl vinyl ether was also allowed (**84a**, 87%). Finally, some reactions were attempted with *N*-protected enamine derivatives **14** instead of enol ethers **18**. As shown, these reagents were appropriate starting materials, and thus, compounds **85a** and **85b** were isolated in high yields as mixtures of rotamers (75-90%).

It should be remarked that in all the cases shown in **Scheme 2.23** compounds **73**, **84** and **85** were formed as single diastereoisomers as evidenced by the ^{1}H–NMR spectra of the crude of the reaction mixtures. Moreover, formation of the hexahydrofuro[3,2-*c*]quinoline derivatives **80** coming from the alternative Povarov [4+2] pathway was not observed.



Scheme 2.23 Scope of the reaction. Synthesis of pyrrolo[3,2,1-*ij*]quinolone derivatives.

The relative configuration of the stereogenic centres of (4*S**,6*R**)-*N*-(3,5-bis(trifluoromethyl)phenyl)-4-butoxy-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-6-amine **84a** was determined by one- and two-dimensional NMR experiments (**Figure 2.17**). The singlet centred at 6.88 ppm was assigned to $\mathbf{H_a}$, the apparent

triplet centred at 4.71 ppm (app. t, *J*= 2.8 Hz) was assingned to **H_b**, the double doublet of doublets centred at 4.41 ppm (ddd, *J*= 10.1, 4.2 and 2.2 Hz) was assigned to **H_c**, the doublet triplets centred at 3.09 (dt, *J*= 8.8 and 6.1 Hz), 2.83 (dt, *J*= 8.8 and 6.1 Hz) and 2.19 ppm (dt, *J*= 14.1 and 2.2 Hz) were assigned to **H_d**, **H_e** and **H_f** respectively, and the double doublet of doublets centred at 1.43 ppm (ddd, *J*= 14.1, 4.2 and 3.5 Hz) was assigned to **H_g**. The value of the coupling constants between **H_b** and **H_f** ($J_{ec,ec}$≈ 2.5 Hz), **H_b** and **H_g** ($J_{ec,ax}$≈ 3.0 Hz), **H_c** and **H_f** ($J_{ec,ec}$= 2.2 Hz), **H_c** and **H_g** ($J_{ec,ax}$= 4.2 Hz), suggested the pseudo-ecuatorial position of **H_c** and **H_b** in the molecule due to the absence of any axial-axial coupling constant value. Moreover the cross-peak signals arising from protons close in space observed in the NOESY two-dimensional NMR experiment between **H_a** and **H_f** (in blue in **Figure 2.17**) and also between **H_f** and **H_d** or **H_e** (in blue in **Figure 2.17**) showed that the aryl-amino group, **H_f** and the butoxy group are placed in *cis*-disposition in the same plane of the molecule.

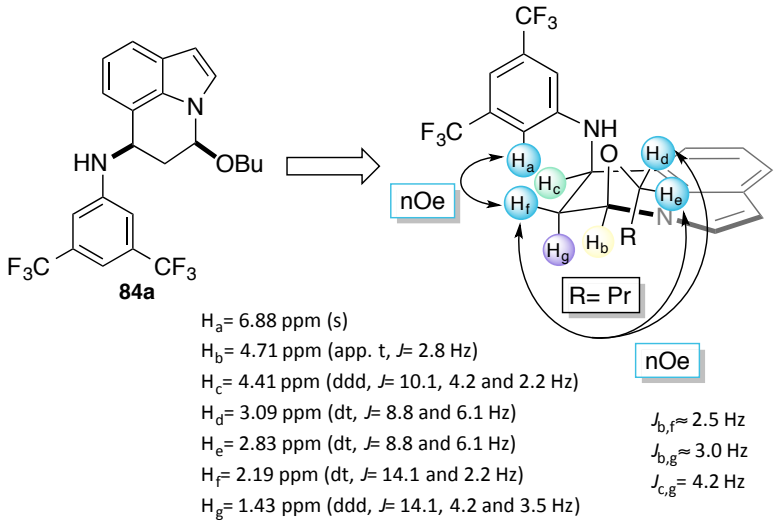


Figure 2.17 Determination of the relative configuration of **84a** through ^{1}H-NMR and NOESY experiments.

Figure 2.18 shows the ^{1}H–NMR spectrum in C_6D_6 at room temperature (298 K) of **85b** where it is easy to distinguish doubled signals. This suggests again the presence of rotamers at this temperature. Moreover, the corresponding ^{1}H–NMR spectrum in C_6D_6 at 353 K shows the coalescence of signals (coalescence temperature) and confirms our hypothesis regarding the presence of two rotamers at room temperature.

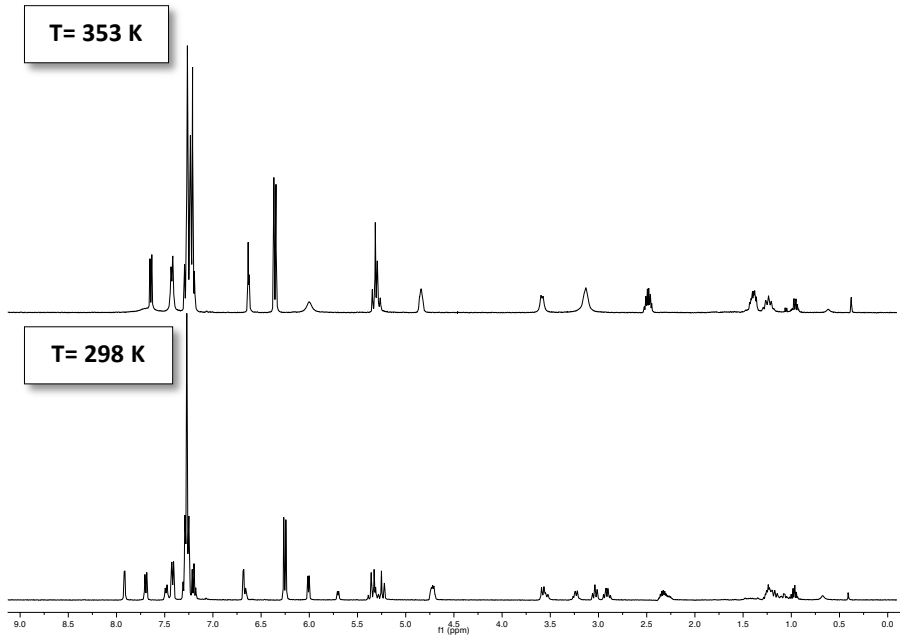


Figure 2.18 ^{1}H–NMR in C_6D_6 at room temperature (298 K) and coalescence temperature (353 K) of the derivative **85b**.

2.3 Summary

In summary, in Chapter 2, new one-pot Brønsted acid-catalysed multicomponent coupling reactions of indolecarbaldehyde derivatives, anilines and electron rich alkenes to afford interesting indole-containing heterocyclic compounds have been described (**Scheme 2.24**).

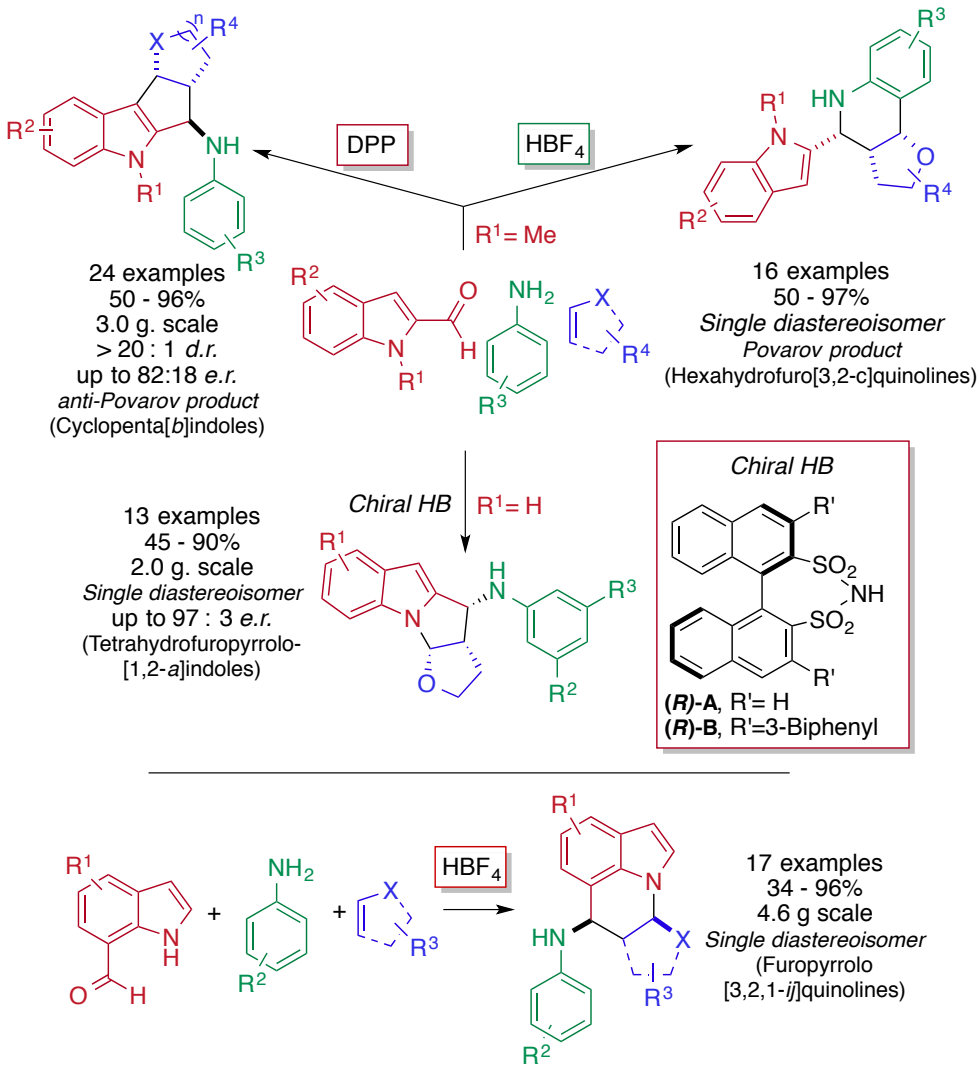
In Part A, an alternative reaction pathway to the well established formal [4+2]-cycloaddition reaction of *N*-arylimines and electron-rich alkenes (Povarov reaction) has been described. This chemo-, regio-, and diastereoselective multicomponent coupling reaction of *N*-substituted 1*H*-indole-2-carbaldehydes, anilines and electron-rich alkenes supposes a new method to obtain cyclopenta[1,2-*b*]indole derivatives. This acid-catalysed reaction, which may be performed at a gram scale, has been termed as an "anti-Povarov reaction" and proceeds through an unprecedented formal [3+2]-carbocyclisation reaction between an *in situ* formed *N*-aryl imine and an electron-rich alkene. Preliminary studies on the asymmetric version of this reaction have demonstrated its viability and an enantiomeric ratio of 82:18 has been achieved on a model reaction using as catalyst a chiral Brønsted acid derived from phosphoric acid.

Additionally, it has been described that the multicomponent coupling process can be divergently directed through the conventional Povarov pathway to

achieve hexahydrofuro[3,2-*c*]quinolines or through the new "anti-Povarov" pathway to get hexahydrofurocyclopenta[1,2-*b*]indoles by appropriate choice of the Brønsted acid-catalyst under otherwise similar reaction conditions. A computational study about these processes has been performed and it has been found that the Povarov reaction can be described as a concerted [4+2]-cycloaddition, whereas the new anti-Povarov is best conceived as a stepwise Mannich/Friedel-Crafts cascade reaction through an oxocarbenium ion intermediate.

In Part B, a new diastereo- and enantioselective multicomponent reaction of *N*-unsubstituted 1*H*-indole-2-carbaldehydes, anilines and enol ethers to give chiral tetrahydrofuropyrrolo[1,2-*a*]indole derivatives has been described. It has been found that the efficiency of this reaction is highly dependent on the structure of the aniline derivative and the catalyst. In fact, the reaction only was very effective when 3,5-bis(trifluoromethyl)aniline was used as the aniline counterpart and a binaphthyl-based chiral disulfonimide was used as catalyst. This new reaction can be understood as a formal [3+2]-heterocyclisation reaction of the *in situ* formed *N*-aryl imine and the enol ether. Remarkably, in this reaction the chiral disulfonimide behaves as a typical Brønsted acid catalyst. Moreover, high enantioselectivities (up to 97:3 *e.r.*) were achieved by the use of a simple 3,3'-unsubstituted binaphthyl-based chiral disulfonimide and interestingly, a switch of enantioselectivity was observed when a binaphthyl-based chiral disulfonimide with the same absolute configuration but substituted with biphenyl groups at 3- and 3'-positions. The reaction could be easily performed at gram scale and the catalyst could be recovered and reused.

In Part C, a multicomponent Brønsted acid-catalysed reaction of *N*-unsubstituted 1*H*-indole-7-carbaldehydes, anilines and electron-rich alkenes to give pyrrolo[3,2,1-*ij*]quinoline derivatives has been described. This new formal [4+2]-heterocyclisation reaction of the *in situ* formed *N*-aryl imine and the electron-rich alkene is highly efficient when relatively electron-poor aniline derivatives are used and gram scale synthesis could also be performed.



Scheme 2.24 Summary.

Conclusions

Conclusions

In Chapter 1 of this thesis, new cascade reactions promoted by a binary catalytic systems consisting in a mixture of a platinum (II) or (IV) metallic complex and a Brønsted acid are described. These new processes allow the synthesis of pyrrolidine derivatives and may be framed in the context of "one-pot" catalysis. These reactions are clear examples of the efficiency of orthogonal-relay catalysis for the synthesis of complex molecules from simple starting materials. These reactions proceed through an initial platinum-promoted cycloisomerisation reaction of the *N*-Boc alkynamine to afford a *N*-Boc enamine that in the presence of the Brønsted acid generates an iminium species. This cationic intermediate reacts with a nucleophile present in the reaction media to give a new cationic species that is trapped by the Boc group of the starting alkynamine.

Specifically, the results obtained when the external nucleophiles were alkenes and alkynes are shown in Part A of Chapter 1. The new reactions described allow the synthesis of bicyclic compounds with a pyrroloxazinone core. However, when the alkyne counterpart used was a propargylsilane derivative, the reaction evolved through a different way and the formation of bicyclic compounds with an exo-cyclic double bond but lacking the silyl group was observed.

In Part B of the chapter, a new cascade reaction of *N*-Boc alkynamines and alkynol derivatives to give furopyrroloxazinone derivatives in a stereoselective way is described. This reaction implies a double cycloisomerisation to afford *N*-Boc enamines and enol ethers and the subsequent heterodimerisation process of these intermediates. Thus, this process supposes the *in situ* generation and selective heterocoupling of two different electron-rich alkenes. This type of heterodimerisation reactions had not precedents in the literature. It should be remarked the complete chemoselectivity observed in this process in the sense that products coming from homocoupling reactions of the same electron rich alkene intermediate are not observed. However, in the absence of the starting alkynol, the corresponding pyrroloxazinones derived from the homocoupling of two *N*-Boc alkynamines are obtained.

In Chapter 2, new Brønsted acid catalysed coupling reactions of indolecarbaldehydes, anilines and electron-rich alkenes to give different indole-containing heterocyclic compounds are described. These new processes are also clear examples of one-pot catalytic processes in which two different catalytic reactions are promoted by the Brønsted acid in a consecutive manner.

The results of the above commented multicomponent reaction for the particular case of *N*-substituted indole-2-carbaldehydes are shown in Part A of this chapter. More precisely, a new reaction alternative to the well-established formal [4+2]-cycloaddition reaction of *N*-aryl imines and electron-rich alkenes (the Povarov reaction) is described. The novel process can be understood as a formal [3+2]-carbocyclisation between the *in situ* generated *N*-aryl imine and the electron-rich alkene. This reaction, termed as an "anti-Povarov reaction", leads to cyclopenta[*b*]indole derivatives in a chemo-, regio- and diastereoselective way. Preliminary studies on the asymmetric version of this process demonstrated its viability. Additionally, it has been described that the multicomponent coupling process can be divergently directed through the conventional Povarov pathway or through the new "anti-Povarov" one by appropriate choice of the Brønsted acid catalyst. Computational studies about these processes have shown that the Povarov reaction can be described as a concerted process, whereas the new anti-Povarov is best conceived as a stepwise (Mannich/Friedel-Crafts) cascade reaction through an oxocarbenium ion intermediate.

In Part B, a new diastereo- and enantioselective multicomponent reaction of *N*-unsubstituted indole-2-carbaldehydes, anilines and enol ethers is described. This process, catalysed by a chiral disulfonimide derivative, leads to tetrahydrofuropyrrolo[1,2-*a*]indole derivatives with high enantiomeric excess. It has been observed that the efficiency of this reaction is highly dependent on the structure of the starting aniline derivative and the catalyst. This new reaction can be understood as a formal [3+2]-heterocyclisation reaction of the *in situ* formed *N*-aryl imine and the enol ether.

Finally, in Part C a multicomponent Brønsted acid-catalysed reaction of *N*-unsubstituted indole-7-carbaldehydes, anilines and electron-rich alkenes to give pyrrolo[3,2,1-*ij*]quinoline derivatives has been developed. This new formal [4+2]-heterocyclisation reaction of the *in situ* formed *N*-aryl imine and the electron-rich alkene is highly efficient when relatively electron-poor aniline derivatives are used.

Conclusiones
(en Español)

Conclusiones (en Español)

En el Capítulo 1 de esta Memoria se describen nuevas reacciones en cascada promovidas por un sistema catalítico binario que consta de un complejo metálico de platino(II) o (IV) y un ácido de Brønsted. Estas reacciones dan lugar a derivados de pirrolidina y pueden ser encuadradas en el contexto de la catálisis "one-pot". Así, estas reacciones son claros ejemplos de la eficiencia de la catálisis ortogonal para la síntesis de moléculas complejas a partir de materiales sencillos. Estas reacciones transcurren a través de un mecanismo en el que el complejo de platino promueve la cicloisomerización de una *N*-Boc alquinamina para generar un intermedio de tipo enamina. Dicho intermedio evoluciona hacia la formación de un intermedio de tipo iminio en presencia del catalizador ácido de Brønsted. Este intermedio catiónico es atrapado por un nucleófilo presente en el medio de reacción (alqueno, alquino, enol éter o enamida) y finalmente, el grupo Boc de la alquinamina inicial atrapa la nueva especie catiónica generada.

Concretamente, en la Parte A del capítulo se muestran los resultados obtenidos cuando los nucleófilos externos empleados fueron alquenos o alquinos. Estas nuevas reacciones permiten obtener compuestos bicíclicos con estructura de pirroloxazinona. Cuando el alquino utilizado fue propargiltrimetilsilano la reacción evolucionó de una forma diferente dando lugar a productos que carecen grupo trimetilsililo y que contienen un doble enlace exocíclico.

En la Parte B de este capítulo se describe un nuevo proceso en cascada a partir de *N*-Boc alquinaminas y alquinoles para dar, de manera totalmente estereoselectiva, compuestos heterocíclicos con estructura de furopirroloxazinona. Esta reacción implica una doble cicloisomerización que da lugar a una *N*-Boc enamina y un enol éter y una posterior heterodimerización de estos dos alquenos. Además este proceso representa la generación *in situ* y posterior heteroacoplamiento selectivo de dos alquenos electrónicamente ricos. Este tipo de reacciones de dimerización de alquenos carecía de antecedentes bibliográficos. Es destacable la completa quimioselectividad de este proceso referente a la ausencia de productos resultantes de procesos de homoacoplamiento de dos alquenos iguales. Sin embargo, cuando la reacción se lleva a cabo en ausencia del alquinol, se obtiene el correspondiente producto de homoacoplamiento de dos moléculas de la *N*-Boc alquinamina inicial.

En el Capítulo 2 se muestran nuevos procesos de acoplamiento multicomponente catalizados por ácidos de Brønsted. En concreto se presentan reacciones entre indolcarbaldehídos, anilinas y alquenos electrónicamente ricos que dan lugar de manera eficiente a compuestos heterocíclicos derivados de indol.

Estas nuevas reacciones también son claros ejemplos de procesos catalíticos "one-pot" en los que el ácido de Brønsted es capaz de promover dos procesos catalíticos de manera consecutiva.

En la Parte A de este capítulo se describen los resultados de la reacción multicomponente arriba señalada en la que se usan indol-2-carbaldehídos sustituidos en el átomo de nitrógeno. Así, se ha descubierto una nueva reacción alternativa a la conocida cicloadición formal [4+2] entre iminas aromáticas y alquenos electrónicamente ricos (reacción de Povarov). Este nuevo proceso se entiende como una carbociclación formal [3+2] entre la imina aromática generada *in situ* y el alqueno electrónicamente rico. Esta reacción, que se ha denominado "reacción anti-Povarov" da lugar a derivados de ciclopenta[*b*]indol de manera quimio-, regio- y diastereoselectiva. Estudios preliminares de la versión asimétrica demuestran su viabilidad. Además, esta nueva reacción multicomponente puede ser dirigida hacia la vía Povarov o hacia la nueva vía "anti-Povarov" en función del ácido de Brønsted utilizado. Los estudios computacionales que se han llevado a cabo demuestran que la reacción de Povarov transcurre a través de un proceso concertado, mientras que la nueva reacción "anti-Povarov" transcurre a través de un proceso en cascada por pasos (Mannich/Friedel-Crafts) a través de un intermedio de tipo catiónico.

En la Parte B de este capítulo se presenta una nueva reacción multicomponente diastereo- y enantioselectiva de indol-2-carbaldehídos sin sustituyentes en el átomo de nitrógeno, anilinas y enol éteres. Esta reacción, catalizada por una disulfonimida quiral, da lugar a derivados de tetrahidrofuropirrolo[1,2-*a*]indol con elevados excesos enantioméricos. Se ha observado que la eficiencia de la reacción depende de la estructura de la anilina empleada y del catalizador. Estudios computacionales apoyan estos resultados experimentales. Este nuevo proceso puede entenderse como una heterociclación formal [3+2] entre la imina aromática generada *in situ* y el enol éter.

Finalmente, en la Parte C del capítulo se muestra un proceso multicomponente catalizado por un ácido de Brønsted que implica la reacción de indol-7-carbaldehídos sin sustituyentes en el átomo de nitrógeno, anilinas y alquenos electrónicamente ricos. Esta nueva reacción da lugar a derivados de pirrolo[3,2,1-*ij*]quinolina de manera totalmente diastereoselectiva. Este proceso supone una nueva reacción de heterociclación formal [4+2] entre la imina aromática generada *in situ* y el alqueno. Además se ha comprobado que el proceso es altamente eficiente cuando se utilizan anilinas sustituidas con átomos o grupos que retiran densidad de carga.

Experimental Part

General Information

- **Reactions**

All reactions were carried out using oven dried glassware and RR98030 Carousel Reaction Station™ from Radleys Discovery Technologies, under an atmosphere of argon (99.999%), unless otherwise stated, and monitored by TLC.

Low temperature reactions were performed using Dewar flask with a chilled mixture of liquid nitrogen and acetone or 2-propanol. Longer low temperature reactions were carried out in a chilled Dewar flask filled with acetone under controlled temperature using a Julabo® F70 ultra-low refrigerated circulator.

High temperature reactions were performed using hot plate/oil bath apparatus with internal temperature control.

Commercially available starting materials and reagents were purchased at the highest commercial quality and used without further purification. Those that required chemical manipulation were prepared according to the methods reported in the literature and purified by standard procedures.[205]

Solvents

All anhydrous solvents were dried and deoxygenated with a PureSolv® column before use except for the case of dichloromethane that was dried by standard techniques and freshly distilled from calcium hydride.[205]

Chromatography

All flash chromatography was carried out using dry packed 60 silica gel (230-240 mesh, Merck, Scharlau) under a positive pressure of air.

Thin layer chromatography (TLC) was carried out on Merck Kieselgel 60 PF254 0.2 mm plates. Visualisation was accomplished using ultra violet light (λ= 254 nm) and chemical staining with solutions of vanilline in ethanol containing sulfuric acid or acidic potassium permanganate as appropriate heating the TLC after the immersion.

[205] D. D. Perrin, W. L. F. Armarego, *Purification of Laboratory Chemicals*, Pergamon Press, Oxford, **1997**.

- **Data Collection**

Nuclear Magnetic Resonance (NMR)

^{1}H–NMR spectra were recorded on a Bruker AV-600 (600 MHz), Bruker AV-400 (400 MHz), Bruker AV-300 (300 MHz) or Bruker DPX-300 (300 MHz). Chemical shifts (δ) are reported in parts per million (ppm) and quoted to the nearest 0.01 ppm relative to the residual solvent (chloroform δ: 7.26, benzene δ: 7.16, dichloromethane δ: 5.32, acetone δ: 2.05, dimethylsulfoxide δ: 2.50).

^{13}C–NMR spectra were recorded on a Bruker AV-400 (100 MHz), Bruker AV-300 (75 MHz) or Bruker DPX-300 (75 MHz) with complete proton decoupling. Chemical shifts (δ) are reported in parts per million (ppm) and quoted to the nearest 0.1 ppm relative to the residual deuterated solvent ($CDCl_3$ δ: 77.2, C_6D_6 δ: 128.6, CD_2Cl_2 δ: 54.0, acetone-d_6 δ: 29.8, dimethylsulfoxide-d_6 δ: 39.5).

^{19}F–NMR spectra were recorded on a Bruker AV-300 (75 MHz) or Bruker DPX-300 (75 MHz) with complete proton decoupling. Chemical shifts (δ) are quoted in parts per million (ppm) and quoted to the nearest 0.1 ppm.

Two-dimensional NMR experiments (COSY, HSQC, HMBC, NOESY) were recorded on a Bruker AV-600 (600 MHz), Bruker AV-400 (400 MHz), Bruker AV-300 (300 MHz) or Bruker DPX-300 (300 MHz).

The temperature of the acquisition of the NMR spectra was 298 ± 3K unless otherwise stated.

Coupling constants (*J*) are corrected and quoted to the nearest 0.1 Hz. The following abbreviations are used to indicate the multiplicity of the signals: s= singlet, d= doublet, dd= double doublet, dt= double triplet, ddd= double doublet of doublets, dddd= doublet of doublet of doublet of doublets, t= triplet, td= triplet of doublets, ttd= triple triplet of doublets, tdt= triple doublet of triplets, ddt= double doublet of triplets, q= quartet, quintuplet, br= broad, m= multiplet.

Data are reported as follows: ^{1}H–NMR: chemical shift (multiplicity, coupling constant *J* in Hz, number of protons and assignment); ^{13}C–NMR: chemical shift (for fluorine-containing molecules: multiplicity, coupling constant *J* in Hz) and ^{19}F–NMR: chemical shift.

High-Resolution Mass Spectrometry (HRMS)

High-resolution mass spectrometry was carried out on a Finnigan-Mat 95 spectrometer at the Mass Spectrometry Service at the University of Burgos (Spain).

High-Performance Liquid Chromarography (HPLC)

Chiral HPLC analyses were performed using a Waters 2695 Alliance LC Module 1 Plus with V-UV detector instrument. Daicel chiral-packed columns IA, IC, ODH and ADH were used.

Optical Rotation and Melting Point

Optical rotations were measured using a 2 mL cell with a 1 dm path length on an Autopol IV Rudolph Research Analytical polarimeter at 589 nm, and are reported as $[\alpha]^{T}_{D}$ (concentration in grams/mL solvent).

Melting points (m.p.) were recorded using a Gallenkamp melting point apparatus and are reported uncorrected.

Chapter 1

Part A

- **Synthesis of *N*-Boc Alkynamine Derivatives 7**

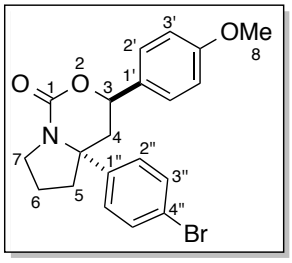
N-Boc alkynamine derivatives 7 were prepared according to the methods reported in the literature[206] and purified by standard procedures.

Section 1.A.2.1

- **General Procedure for the Synthesis of Hexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one Derivatives 11a-d**

The corresponding *N*-Boc alkynamine derivative **7** (0.2 mmol) and $PtCl_4$ (5 mol%) were placed in a glass reaction tube equipped with a magnetic stirring bar under argon atmosphere. Then, dry dichloromethane (2 mL) and the corresponding freshly distilled alkene derivative **3a,b** (2 equiv, 0.4 mmol) were added. The solution was cooled to 0 °C and freshly distilled triflic acid (10 mol%) was added. The mixture was allowed to warm to room temperature and was kept at this temperature during 40 hours. Finally, the reaction was filtered through a pad of Celite eluting with ethyl acetate, the solvent was removed under vacuum and the resulting crude was purified by flash column chromatography on silica gel using diethyl ether or ethyl acetate as eluent to give pure **11a-d**.

(3*R,4a*R**)-4a-(4-Bromophenyl)-3-(4-methoxyphenyl)hexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (11a)**



Light yellow oil

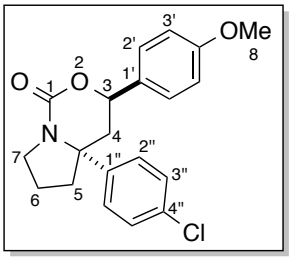
R_f = 0.22 (diethyl ether)

Isolated yield: 55%

[206] a) J. R. Dunetz, R. L. Danheiser, *J. Am. Chem. Soc.*, **2005**, *127*, 5776. b) K. Sonogashir, Y. Tohda, N. Hagihara. *Tetrahedron Lett.*, **1975**, 4467. c) H. Wu, Y.-P. He, L.-Z. Gonga, *Adv. Synth. Catal.*, **2012**, *354*, 975.

^{1}H–NMR (400 MHz, $CDCl_3$)	δ: 7.56 (d, *J*= 8.5 Hz, 2H, $H_{3''}$), 7.22 (d, *J*= 8.5 Hz, 2H, $H_{2''}$), 7.18 (d, *J*= 8.7 Hz, 2H, $H_{2'}$), 6.85 (d, *J*= 8.7 Hz, 2H, $H_{3'}$), 4.76 (dd, *J*= 12.0, 2.3 Hz, 1H, H_3), 3.91 – 3.77 (m, 1H, H_{7A}), 3.80 (s, 3H, H_8), 3.71 – 3.61 (m, 1H, H_{7B}), 2.59 (dd, *J*= 13.6, 2.3 Hz, 1H, H_{4A}), 2.47 – 2.34 (m, 1H, H_{5A}), 2.11 (dd, *J*= 13.6, 12.0 Hz, 1H, H_{4B}), 2.06 – 1.83 (m, 2H, H_{5B} and H_{6A}). 1.67 – 1.45 (m, 1H, H_{6B}).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 159.8, 153.5, 142.8, 132.1, 130.8, 127.6, 127.4, 121.9, 114.0, 76.0, 67.1, 55.4, 47.1, 43.9, 42.1, 31.1, 21.0.
HRMS (70 eV, IE)	Calculated for $[C_{20}H_{20}BrNO_3]^+$: 401.0621, found 401.0621.

(3*R,4a*R**)-4a-(4-Chlorophenyl)-3-(4-methoxyphenyl)hexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (11b)**



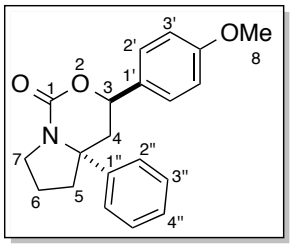
Light yellow oil

R_f = 0.35 (diethyl ether)

Isolated yield: 52%

^{1}H–NMR (400 MHz, $CDCl_3$)	δ: 7.39 (d, *J*= 8.5 Hz, 2H, $H_{3''}$), 7.25 (d, *J*= 8.5 Hz, 2H, $H_{2''}$), 7.16 (d, *J*= 8.7 Hz, 2H, $H_{2'}$), 6.83 (d, *J*= 8.7 Hz, 2H, $H_{3'}$), 4.74 (dd, *J*= 11.9, 2.4 Hz, 1H, H_3), 3.89 – 3.74 (m, 1H, H_{7A}), 3.77 (s, 3H, H_8), 3.69 – 3.59 (m, 1H, H_{7B}), 2.58 (dd, *J*= 13.7, 2.4 Hz, 1H, H_{4A}), 2.44 – 2.33 (m, 1H, H_{5A}), 2.09 (dd, *J*= 13.7, 11.9 Hz, 1H, H_{4B}), 2.04 – 1.85 (m, 2H, H_{5B} and H_{6A}), 1.63 – 1.45 (m, 1H, H_{6B}).
^{13}C–NMR ($CDCl_3$)	δ: 159.8, 153.5, 142.2, 133.8, 130.8, 129.2, 127.4, 127.2, 114.0, 76.0, 67.0, 55.4, 47.1, 43.9, 42.1, 21.0.
HRMS (70 eV, IE)	Calculated for $[C_{20}H_{20}ClNO_3]^+$: 357.1126, found 357.1124.

(3*R,4a*R**)-3-(4-Methoxyphenyl)-4a-phenylhexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one 11c).**



Light yellow oil

R_f = 0.35 (diethyl ether)

Isolated yield: 48%

^{1}H–NMR
(300 MHz, $CDCl_3$)

δ: 7.45 – 7.37 (m, 2H, $H_{3''}$), 7.36 – 7.28 (m, 3H, $H_{2''}$ and $H_{4''}$), 7.16 (d, *J*= 8.7 Hz, 2H, $H_{2'}$), 6.82 (d, *J*= 8.7 Hz, 2H, $H_{3'}$), 4.76 (dd, *J*= 11.9, 2.4 Hz, 1H, H_3), 3.89 – 3.77 (m, 1H, H_{7A}), 3.77 (s, 3H, H_8), 3.71 – 3.60 (m, 1H, H_{7B}), 2.63 (dd, *J*= 13.5, 2.4 Hz, 1H, H_{4A}), 2.44 (dd, *J*= 11.1, 6.1 Hz, 1H, H_{5A}), 2.08 (dd, *J*= 13.5, 11.9 Hz, 1H, H_{4B}), 2.05 – 1.84 (m, 2H, H_{5B} and H_{6A}), 1.69 – 1.44 (m, 1H, H_{6B}).

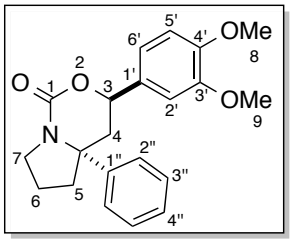
^{13}C–NMR
(75 MHz, $CDCl_3$)

δ: 159.7, 153.6, 143.5, 131.1, 129.0, 127.7, 127.4, 125.7, 113.9, 76.0, 67.3, 55.4, 47.0, 44.1, 42.1, 21.0.

HRMS
(70 eV, IE)

Calculated for $[C_{20}H_{21}NO_3]^+$: 323.1516, found 323.1512.

(3*R,4a*R**)-3-(3,4-Dimethoxyphenyl)-4a-phenylhexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (11d)**



Light yellow oil

R_f = 0.60 (ethyl acetate)

Isolated yield: 56%

^{1}H–NMR
(300 MHz, $CDCl_3$)

δ: 7.45 – 7.37 (m, 2H, $H_{3''}$), 7.36 – 7.27 (m, 3H, $H_{2''}$ and $H_{4''}$), 6.85 – 6.66 (m, 3H, $H_{2'}$, $H_{5'}$, and $H_{6'}$), 4.75 (dd, *J*= 11.9, 2.2 Hz, 1H, H_3), 3.84 and 3.83 (2s, 6H, H_8 and H_9), 3.64 – 3.60 (m, 2H, H_7), 2.63 (dd, *J*= 13.5, 2.5 Hz, 1H, H_{4A}), 2.43 (dd, *J*= 11.1, 6.2 Hz, 1H, H_{5A}), 2.09 (dd, *J*= 13.5, 11.8 Hz, 1H, H_{4B}), 2.07 – 1.85 (m, 2H, H_{5B} and H_{6A}), 1.65 – 1.42 (m, 1H, H_{6B}).

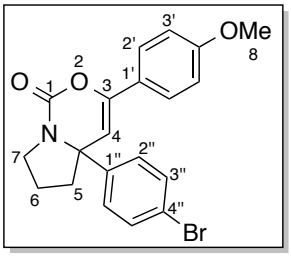
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 153.6, 149.1, 143.4, 131.5, 128.9, 127.7, 125.6, 118.4, 110.8, 109.2, 76.2, 67.2, 56.1, 56.0, 47.0, 44.0, 42.1, 21.0.
HRMS (70 eV, IE)	Calculated for $[C_{21}H_{23}NO_4]^+$: 353.1622, found 353.1626.

Section 1.A.2.2

- **General Procedure for the Synthesis of Tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one Derivatives 11e-r**

The corresponding *N*-Boc alkynamine derivative **7** (0.2 mmol) and $PtMe_2(COD)$ (5 mol%) were placed in a glass reaction tube equipped with a magnetic stirring bar under argon atmosphere. Then, dry dichloromethane (2 mL) and the corresponding freshly distilled alkyne derivative **3c,d** (2 equiv, 0.4 mmol) were added. The solution was cooled to –10 °C and freshly distilled triflic acid (10 mol%) was added. The mixture was kept at this temperature during 12-24 hours. Finally, the reaction was filtered through a pad of celite eluting with ethyl acetate, the solvent was removed under vacuum and the resulting crude was purified by flash column chromatography on silica gel using mixtures of hexanes and diethyl ether as eluent to give pure **11e-r**.

4a-(4-Bromophenyl)-3-(4-methoxyphenyl)-4a,5,6,7-tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (11e)



Light brown solid

mp= 173 – 175 °C

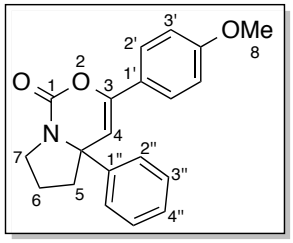
R_f= 0.20 (hexane:diethyl ether, 1:2)

Isolated yield: 90%

^{1}H–NMR (300 MHz, $CDCl_3$)	δ: 7.5 (d, *J*= 8.9 Hz, 2H, $H_{2'}$), 7.5 (d, *J*= 8.6 Hz, 2H, $H_{3'}$), 7.17 (d, *J*= 8.6, 2H, $H_{2''}$), 6.84 (d, *J*= 8.9 Hz, 2H, $H_{3'}$), 5.82 (s, 1H, H_4), 3.88 (dt, *J*= 11.4, 9.9 Hz, 1H, H_{7A}), 3.80 (s, 3H, H_8), 3.61 (ddd, *J*= 11.4, 9.9, 2.3 Hz, 1H, H_{7B}), 2.52 (dd, *J*= 12.0, 6.8 Hz, 1H, H_{5A}), 2.15 (td, *J*= 12.0, 7.6 Hz, 1H, H_{5B}), 2.02 – 1.88 (m, 1H, H_{6A}), 1.61 (ttd, *J*= 12.0, 9.7, 6.8 Hz, 1H, H_{6B}).

^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 161.0, 150.6, 147.6, 143.4, 132.5, 126.9, 126.5, 124.3, 121.7, 114.3, 101.9, 67.4, 55.8, 46.5, 40.5, 20.7.
HRMS (70 eV, IE)	Calculated for $[C_{20}H_{18}BrNO_3]^+$: 399.0465, found 399.0472.

3-(4-Methoxyphenyl)-4a-phenyl-4a,5,6,7-tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (11f)



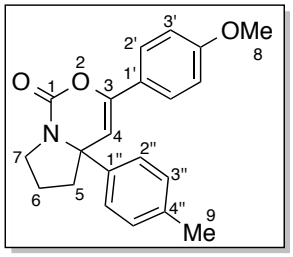
Light brown foam

R_f = 0.30 (hexane:diethyl ether, 1:2)

Isolated yield: 89%

^{1}H–NMR (300 MHz, $CDCl_3$)	δ: 7.53 (d, *J*= 8.9 Hz, 2H, $H_{2'}$), 7.40 – 7.22 (m, 5H, H_{Ph}), 6.84 (d, *J*= 8.9 Hz, 2H, $H_{3'}$), 5.87 (s, 1H, H_4), 3.88 (dt, *J*= 11.4, 8.8 Hz, 1H, H_{7A}), 3.79 (s, 3H, H_8), 3.64 (ddd, *J*= 11.4, 10.0, 2.4 Hz, 1H, H_{7B}), 2.57 (dd, *J*= 12.0, 6.7 Hz, 1H, H_{5A}), 2.15 (td, *J*= 12.0, 7.6 Hz, 1H, H_{5B}), 2.00 – 1.87 (m, 1H, H_{6A}), 1.71 – 1.54 (m, 1H, H_{6B}).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 160.5, 150.5, 147.0, 143.9, 129.1, 127.5, 126.5, 124.4, 124.3, 113.9, 102.2, 67.4, 55.4, 46.2, 40.2, 20.3.
HRMS (70 eV, IE)	Calculated for $[C_{20}H_{19}NO_3]^+$: 321.1359, found 321.1369.

3-(4-Methoxyphenyl)-4a-(*p*-tolyl)-4a,5,6,7-tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (11g)



Brown solid

mp= 170 – 172 °C

R_f= 0.20 (hexane:diethyl ether, 1:2)

Isolated yield: 92%

^{1}H–NMR
(300 MHz, $CDCl_3$)

δ: 7.5 (d, *J*= 8.9 Hz, 2H, $H_{2'}$), 7.23 – 7.13 (m, 4H, $H_{2''}$ and $H_{3''}$), 6.83 (d, *J*= 8.9 Hz, 2H, $H_{3'}$), 5.85 (s, 1H, H_4), 3.87 (dt, *J*= 11.4, 8.7 Hz, 1H, H_{7A}), 3.79 (s, 3H, H_8), 3.62 (ddd, *J*= 11.4, 10.0, 2.4 Hz, 1H, H_{7B}), 2.55 (dd, *J*= 12.0, 6.6 Hz, 1H, H_{5A}), 2.32 (s, 3H, H_9), 2.12 (td, *J*= 12.0, 7.6 Hz, 1H, H_{5B}), 2.00 – 1.86 (m, 1H, H_{6A}), 1.71 – 1.53 (m, 1H, H_{6B}).

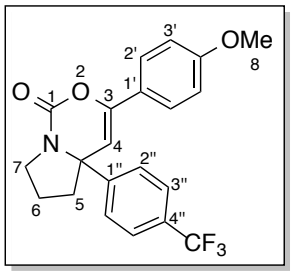
^{13}C–NMR
(75 MHz, $CDCl_3$)

δ: 160.5, 150.5, 146.7, 140.9, 137.2, 129.7, 126.5, 124.3, 113.8, 102.4, 67.1, 55.4, 46.1, 40.1, 21.1, 20.2.

HRMS
(70 eV, IE)

Calculated for $[C_{21}H_{21}NO_3]^+$: 335.1516 found 335.1522.

3-(4-Methoxyphenyl)-4a-(4-(trifluoromethyl)phenyl)-4a,5,6,7-tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (11h)



Brown oil

R_f= 0.20 (hexane:diethyl ether, 1:2)

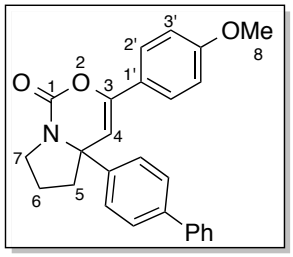
Isolated yield: 85%

^{1}H–NMR
(300 MHz, $CDCl_3$)

δ: 7.62 (d, *J*= 8.1 Hz, 2H, $H_{3''}$), 7.52 (d, *J*= 8.9 Hz, 2H, $H_{2'}$), 7.42 (d, *J*= 8.1 Hz, 2H, $H_{2''}$), 6.84 (d, *J*= 8.9 Hz, 2H, $H_{3'}$), 5.87 (s, 1H, H_4), 3.90 (dt, *J*= 11.6, 8.8 Hz, 1H, H_{7A}), 3.79 (s, 3H, H_8), 3.65 (ddd, *J*= 11.6, 9.9, 2.3 Hz, 1H, H_{7B}), 2.56 (dd, *J*= 12.1, 6.6 Hz, 1H, H_{5A}), 2.21 (td, *J*= 12.1, 7.5 Hz, 1H, H_{5B}), 2.05 – 1.91 (m, 1H, H_{6A}), 1.69 – 1.49 (m, 1H, H_{6B}).

^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 160.8, 150.3, 148.0, 147.7, 129.8 (q, $J_{C\text{-}F}$= 32.7 Hz), 126.6, 126.1 (q, $J_{C\text{-}F}$= 3.9 Hz), 124.8, 124.1 (q, $J_{C\text{-}F}$= 274.0 Hz), 113.9, 101.3, 67.3, 55.4, 46.3, 40.3, 20.3.
^{19}F–NMR (282 MHz, $CDCl_3$)	δ: -62.5.
HRMS (70 eV, IE)	Calculated for $[C_{21}H_{18}F_3NO_3]^+$: 389.1233, found 389.1241.

4a-([1,1'-Biphenyl]-4-yl)-3-(4-methoxyphenyl)-4a,5,6,7-tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (11i)



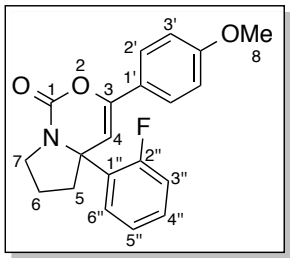
Brown oil

R_f = 0.10 (hexane:diethyl ether, 1:2)

Isolated yield: 90%

^{1}H–NMR (300 MHz, $CDCl_3$)	δ: 7.62 – 7.52 (m, 6H, $H_{2'}$ and H_{biph}), 7.47 – 7.31 (m, 5H, H_{biph}), 6.85 (d, *J*= 8.9 Hz, 2H, $H_{3'}$), 5.91 (s, 1H, H_4), 3.92 (dt, *J*= 11.4, 8.7 Hz, 1H, H_{7A}), 3.79 (s, 3H, H_8), 3.68 (ddd, *J*= 11.4, 9.9, 2.4 Hz, 1H, H_{7B}), 2.61 (dd, *J*= 12.0, 6.5 Hz, 1H, H_{5A}), 2.18 (td, *J*= 12.0, 7.6 Hz, 1H, H_{5B}), 2.04 – 1.91 (m, 1H, H_{6A}), 1.80 – 1.60 (m, 1H, H_{6B}).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 160.5, 150.5, 147.0, 142.9, 140.4, 128.9, 127.8, 127.5, 127.1, 126.5, 124.9, 124.2, 113.9, 102.1, 67.2, 55.4, 46.2, 40.2, 20.3.
HRMS (70 eV, IE)	Calculated for $[C_{26}H_{23}NO_3]^+$: 397.1672, found 397.1674.

4a-(2-Fluorophenyl)-3-(4-methoxyphenyl)-4a,5,6,7-tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (11j)



Brown solid

mp= 108 – 110 °C

R_f= 0.40 (hexane:diethyl ether, 1:2)

Isolated yield: 82%

^{1}H–NMR
(300 MHz, $CDCl_3$)

δ: 7.55 (d, *J*= 8.9 Hz, 2H, $H_{2'}$), 7.31 – 7.02 (m, 4H, $H_{3''}$, $H_{4''}$, $H_{5''}$ and $H_{6''}$), 6.85 (d, *J*= 8.9 Hz, 2H, $H_{3'}$), 6,16 (d, J_{H-F}= 4.1 Hz, 1H, H_4), 3.94 – 3,80 (m, 1H, H_{7A}), 3. 80 (s, 3H, H_8), 3.72 (ddd, *J*= 11.8, 9.7, 2.3 Hz, 1H, H_{7B}), 2.64 (dd, *J*= 12.0, 7.6 Hz, 1H, H_{5A}), 2.18 (td, *J*= 12.0, 7.5 Hz, 1H, H_{5B}), 2.04 – 1.90 (m, 1H, H_{6A}), 1.70 – 1.51 (m, 1H, H_{6B}).

^{13}C–NMR
(75 MHz, $CDCl_3$)

δ: 160.6, 158.8 (d, J_{C-F}= 245.3 Hz), 150.6, 148.0, 130.8 (d, J_{C-F}= 12.9 Hz), 129.5 (d, J_{C-F}= 8.4 Hz), 126.6, , 126.1 (d, J_{C-F}= 4.2 Hz), 124.5 (d, J_{C-F}= 3.4 Hz), 124.2, 116.7 (d, J_{C-F}= 22.3 Hz), 113.9, 100.6 (d, J_{C-F}= 4.9 Hz), 65.7 (d, J_{C-F}= 3.0 Hz), 55.4, 46.6, 39.5 (d, J_{C-F}= 3.3 Hz), 20.7.

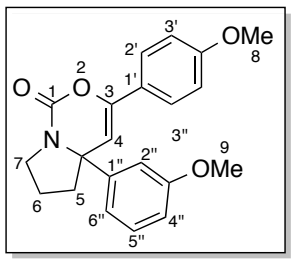
^{19}F–NMR
(282 MHz, $CDCl_3$)

δ: -113.0.

HRMS
(70 eV, IE)

Calculated for $[C_{20}H_{18}FNO_3]^+$: 339.1265, found 339.1276.

4a-(3-Methoxyphenyl)-3-(4-methoxyphenyl)-4a,5,6,7-tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (11k)



Light brown solid

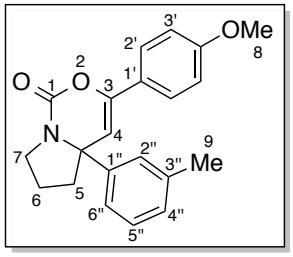
mp= 130 – 132 °C

R_f= 0.13 (hexane:diethyl ether, 1:2)

Isolated yield: 96%

^{1}H–NMR (300 MHz, $CDCl_3$)	δ: 7.52 (d, *J*= 8.9 Hz, 2H, $H_{2'}$), 7.28 (t, *J*= 7.9 Hz, 1H, $H_{5''}$), 6.91 – 6.75 (m, 3H, $H_{2''}$, $H_{4''}$ y $H_{6''}$), 6.83 (d, *J*= 8.9 Hz, 2H, $H_{3'}$), 5.85 (s, 1H, H_4), 3.90 (dt, *J*= 11.5, 9.0 Hz, 1H, H_{7A}), 3.79 and 3.78 (2 s, 6H, H_8 and H_9), 3.64 (ddd, *J*= 11.5, 10.0, 2.3 Hz, 1H, H_{7B}), 2.55 (dd, *J*= 12.0, 6.5 Hz, 1H, H_{5A}), 2.12 (td, *J*= 12.0, 7.5 Hz, 1H, H_{5B}), 1.99 – 1.82 (m, 1H, H_{6A}), 1.72 – 1.53 (m, 1H, H_{6B}).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 160.5, 160.1, 150.4, 146.9, 145.6, 130.1, 126.5, 124.2, 116.7, 113.8, 112.0, 110.8, 102.0, 67.3, 55.4, 46.2, 40.2, 20.2.
HRMS (70 eV, IE)	Calculated for $[C_{21}H_{21}NO_4]^+$: 351.1465, found 351.1482.

3-(4-Methoxyphenyl)-4a-(*m*-tolyl)-4a,5,6,7-tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (11l)



Light brown solid

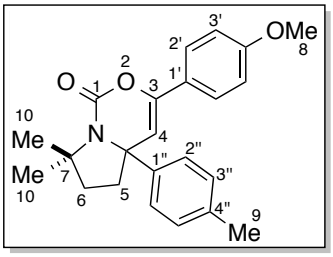
mp= 127 – 129 °C

R_f = 0.18 (hexane:diethyl ether, 1:2)

Isolated yield: 95%

^{1}H–NMR (300 MHz, $CDCl_3$)	δ: 7.53 (d, *J*= 8.9 Hz, 2H, $H_{2'}$), 7.25 (dd, *J*= 8.4, 8.3 Hz, 1H, $H_{5''}$), 7.12 – 7.03 (m, 3H, $H_{2''}$, $H_{4''}$ and $H_{6''}$), 6.84 (d, *J*= 8.9 Hz, 2H, $H_{3'}$), 5.86 (s, 1H, H_4), 3.88 (dt, *J*= 11.4, 8.7 Hz, 1H, H_{7A}), 3. 79 (s, 3H, H_8), 3.63 (ddd, *J*= 11.4, 10.0, 2.4 Hz, 1H, H_{7B}), 2.56 (dd, *J*= 12.0, 6.5 Hz, 1H, H_{5A}), 2.35 (s, 3H, H_9), 2.13 (td, *J*= 12.0, 6.5 Hz, 1H, H_{5B}), 1.99 – 1.86 (m, 1H, H_{6A}), 1.62 (ttd, *J*= 12.0, 9.7, 6.7 Hz, 1H, H_{6B}).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 160.5, 150.5, 146.7, 143.8, 138.8, 128.9, 128.2, 126.5, 125.0, 124.3, 121.4, 113.8, 102.3, 67.3, 55.4, 46.2, 40.2, 21.7, 20.2.
HRMS (70 eV, IE)	Calculated for $[C_{21}H_{21}NO_3]^+$: 335.1516, found 335.1520.

3-(4-Methoxyphenyl)-7,7-dimethyl-4a-(*p*-tolyl)-4a,5,6,7-tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (11m)



Yellow foam

R_f = 0.23 (hexane:diethyl ether, 2:1)

Isolated yield: 95%

^{1}H–NMR
(300 MHz, $CDCl_3$)

δ: 7.51 (d, *J*= 8.9 Hz, 2H, $H_{2'}$), 7.24 (d, *J*= 8.3 Hz, 2H, $H_{2''}$), 7.15 (d, *J*= 8.3 Hz, 2H, $H_{3''}$), 6.82 (d, *J*= 8.9 Hz, 2H, $H_{3'}$), 5.86 (s, 1H, H_4), 3.78 (s, 3H, H_8), 2.51 (dd, *J*= 12.1, 5.7 Hz, 1H, H_{5A}), 2.35 – 2.18 (m, 1H, H_{5B}), 2.31 (s, 3H, H_9), 1.81 – 1.58 (m, 2H, H_6), 1.66 and 1.50 (2 s, 6H, H_{10}).

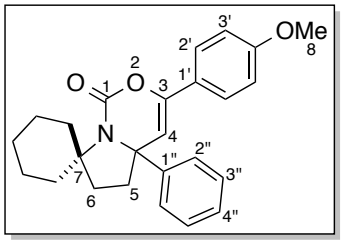
^{13}C–NMR
(75 MHz, $CDCl_3$)

δ: 160.4, 149.8, 147.5, 142.0, 137.0, 129.5, 126.4, 124.5, 124.4, 113.8, 104.6, 68.4, 63.5, 55.4, 37.7, 37.1, 27.4, 25.6, 21.0.

HRMS
(70 eV, IE)

Calculated for $[C_{23}H_{25}NO_3]^+$: 363.1829, found 363.1833.

3'-(4-Methoxyphenyl)-4a'-phenyl-4a',5'-dihydro-1'*H*,6'*H*-spiro[cyclohexane-1,7'-pyrrolo[1,2-*c*][1,3]oxazin]-1'-one (11n)



Light brown solid

mp= 138 – 140 °C

R_f = 0.60 (hexane:diethyl ether, 1:2)

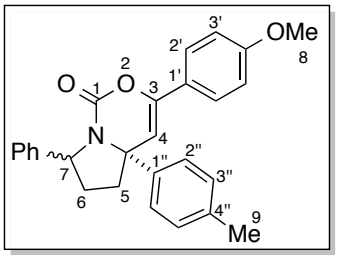
Isolated yield: 98%

^{1}H–NMR
(300 MHz, $CDCl_3$)

δ: 7.52 (d, *J*= 8.9 Hz, 2H, $H_{2'}$), 7.41 – 7.30 (m, 4H, $H_{2''}$ and $H_{3''}$), 7.27 – 7.20 (m, 1H, $H_{4''}$), 6.83 (d, *J*= 8.9 Hz, 2H, $H_{3'}$), 5.87 (s, 1H, H_4), 3.78 (s, 3H, H_8), 2.92 (td, *J*=13.0, 3.8 Hz, 1H, H_{Cy}), 6.61 – 2.45 (m, 2H, H_{5A} and H_{Cy}), 2.26 – 2.07 (m, 2H, H_{5B} and H_{Cy}), 1.88 – 1.05 (m, 9H, H_6 and H_{Cy}).

^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 160.4, 149.6, 147.5, 145.1, 128.8, 127.2, 126.4, 124.7, 124.3, 113.8, 104.5, 68.0, 67.8, 55.4, 37.2, 36.2, 32.1, 31.0, 24.9, 24.8, 23.9.
HRMS (70 eV, IE)	Calculated for $[C_{25}H_{27}NO_3]^+$: 389.1985, found 389.1989.

3-(4-Methoxyphenyl)-7-phenyl-4a-(*p*-tolyl)-4a,5,6,7-tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (11o)[207]



Mixture of diastereoisomers 3:1

Brown oil

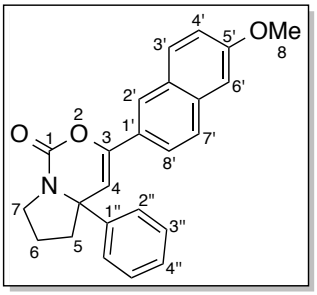
R_f = 0.18 (hexane:diethyl ether, 1:2)

Isolated yield: 88%

^{1}H–NMR (300 MHz, $CDCl_3$)	δ: 7.62 (d, *J*= 8.8 Hz, 2H, $H_{2'\ major\ diast}$), 7.58 (d, *J*= 8.9 Hz, 2H, $H_{2'\ minor\ diast}$), 7.41 – 7.11 (m, 18H, $H_{2''\ major\ and\ minor\ diast}$, $H_{3''\ major\ and\ minor\ diast}$, $H_{Ph\ major\ and\ minor\ diast}$), 6.90 (d, *J*= 8.8 Hz, 2H, $H_{3'\ major\ diast}$), 6.88 (d, *J*= 8.9 Hz, 2H, $H_{3'\ minor\ diast}$), 6.27 (s, 1H, $H_{4\ major\ diast}$), 5.74 (s, 1H, $H_{4\ minor\ diast}$), 5.29 (d, *J*= 9.1 Hz, 1H, $H_{7\ major\ diast}$), 5.20 (dd, *J*= 9.9, 7.7 Hz, 1H, $H_{7\ minor\ diast}$), 3.83 (s, 3H, $H_{8\ major\ diast}$), 3.82 (s, 3H, $H_{8\ minor\ diast}$), 2.98 (dd, *J*= 12.3, 5.9 Hz, 1H, $H_{5A\ minor\ diast}$), 2.59 – 2.15 (m, 3H, $H_{5B\ minor\ diast}$, $H_{6A\ major\ and\ minor\ diast}$), 2.37 (s, 3H, H_9), 2.03 – 1.84 (m, 1H, $H_{6B\ minor\ diast}$), 1.78 (dd, *J*= 12.4, 6.4 Hz, 1H, $H_{6B\ major\ diast}$).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ (major diast): 160.5, 150.3, 148.8, 142.1, 141.8, 137.1, 129.6, 128.8, 127.3, 126.5, 125.5, 124.1, 113.8, 103.7, 67.5, 61.6, 55.4, 37.3, 31.2, 21.0 δ (minor diast): 160.5, 151.1, 145.5, 141.5, 140.8, 137.5, 129.6, 128.2, 127.1, 126.5, 125.8, 124.1, 113.8, 103.7, 68.6, 64.9, 55.4, 37.8, 31.2, 21.0.
HRMS (70 eV, IE)	Calculated for $[C_{27}H_{25}NO_3]^+$: 411.1834, found 411.1837.

[207] Relative configuration could not be determined.

3-(6-Methoxynaphthalen-2-yl)-4a-phenyl-4a,5,6,7-tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (11p)



Brown solid

mp= 137 – 139 °C

R_f = 0.33 (hexane:diethyl ether, 1:2)

Isolated yield: 85%

^{1}H–NMR
(300 MHz, $CDCl_3$)

δ: 8.10 (d, *J*= 2.0 Hz, 1H, $H_{2'}$), 7.73 (d, *J*= 8.9 Hz, 1H, $H_{3'}$), 7.66 (d, *J*= 8.7 Hz, 1H, $H_{7'}$), 7.56 (dd, *J*= 8.7, 2.0 Hz, 1H, $H_{8'}$), 7.42 – 7.31 (m, 4H, $H_{2''}$ and $H_{3''}$), 7.30 – 7.23 (m, 1H, $H_{4''}$), 7.14 (dd, *J*= 8.9, 2.4 Hz, 1H, $H_{4'}$), 7.08 (d, *J*= 2.4 Hz, 1H, $H_{6'}$), 6.08 (s, 1H, H_4), 3.92 (dt, *J*= 11.5, 8.8 Hz, 1H, H_{7A}), 3.89 (s, 3H, H_8), 3.67 (ddd, *J*= 11.5, 10.0, 2.3 Hz, 1H, H_{7B}), 2.60 (dd, *J*= 12.0, 6.6 Hz, 1H, H_{5A}), 2.18 (td, *J*= 12.0, 7.6 Hz, 1H, H_{5B}), 2.02 – 1.88 (m, 1H, H_{6A}), 1.74 – 1.55 (m, 1H, H_{6B}).

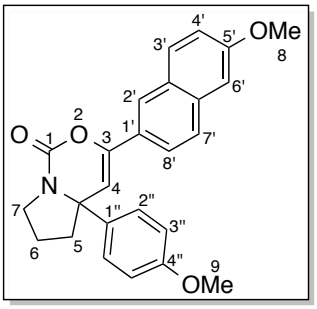
^{13}C–NMR
(75 MHz, $CDCl_3$)

δ: 158.5, 150.5, 147.1, 143.7, 134.9, 130.2, 129.1, 128.5, 127.5, 127.0, 126.6, 124.6, 124.4, 122.7, 119.4, 105.8, 103.6, 67.4, 55.4, 46.2, 40.2, 20.3.

HRMS
(70 eV, IE)

Calculated for $[C_{24}H_{21}NO_3]^+$: 371.1516, found 371.1522.

3-(6-Methoxynaphthalen-2-yl)-4a-(4-methoxyphenyl)-4a,5,6,7-tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (11q)



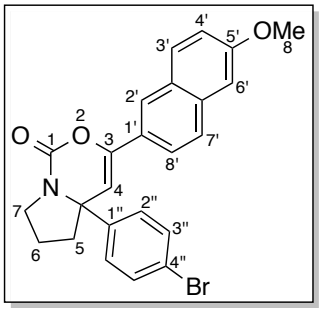
Brown foam

R_f = 0.25 (hexane:diethyl ether, 1:2)

Isolated yield: 82%

^{1}H–NMR (300 MHz, $CDCl_3$)	δ: 8.10 (d, *J*= 2.0 Hz, 1H, $H_{2'}$), 7.73 (d, *J*= 8.9 Hz, 1H, $H_{3'}$), 7.66 (d, *J*= 8.7 Hz, 1H, $H_{7'}$), 7.56 (dd, *J*= 8.7, 2.0 Hz, 1H, $H_{8'}$), 7.25 (d, *J*= 8.8 Hz, 2H, $H_{2''}$), 7.14 (dd, *J*= 8.9, 2.4 Hz, 1H, $H_{4'}$), 7.08 (d, *J*= 2.4 Hz, 1H, $H_{6'}$), 6.90 (d, *J*= 8.8 Hz, 2H, $H_{3''}$), 6.05 (s, 1H, H_4), 3.90 (dt, *J*= 11.4, 8.6 Hz, 1H, H_{7A}), 3.90 (s, 3H, H_8), 3.78 (s, 3H, H_9), 3.64 (ddd, *J*= 11.4, 9.8, 2.2 Hz, 1H, H_{7B}), 2.58 (dd, *J*= 12.0, 6.6 Hz, 1H, H_{5A}), 2.16 (td, *J*= 12.0, 7.6 Hz, 1H, H_{5B}), 2.03 – 1.88 (m, 1H, H_{6A}), 1.75 – 1.57 (m, 1H, H_{6B}).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 159.0, 158.5, 150.5, 146.8, 135.8, 134.9, 130.2, 128.6, 127.0, 126.7, 125.7, 124.6, 122.8, 119.4, 114.4, 105.8, 103.8, 67.0, 55.4, 46.1, 40.0, 20.3.
HRMS (70 eV, IE)	Calculated for $[C_{25}H_{23}NO_4]^+$: 401.1622, found 401.1628.

4a-(4-Bromophenyl)-3-(6-methoxynaphthalen-2-yl)-4a,5,6,7-tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (11r)



Brown solid

mp= 130 – 132 °C

R_f= 0.30 (hexane:diethyl ether, 1:2)

Isolated yield: 95%

^{1}H–NMR (300 MHz, $CDCl_3$)	δ: 8.10 (d, *J*= 2.0 Hz, 1H, $H_{2'}$), 7.73 (d, *J*= 8.9 Hz, 1H, $H_{3'}$), 7.66 (d, *J*= 8.7 Hz, 1H, $H_{7'}$), 7.56 (dd, *J*= 8.7, 2.0 Hz, 1H, $H_{8'}$), 7.49 (d, *J*= 8.6 Hz, 2H, $H_{3''}$), 7.20 (d, *J*= 8.6 Hz, 2H, $H_{2''}$), 7.14 (dd, *J*= 8.9, 2.4 Hz, 1H, $H_{4'}$), 7.08 (d, *J*= 2.4 Hz, 1H, $H_{6'}$), 6.03 (s, 1H, H_4), 3.90 (dt, *J*= 11.5, 9.5 Hz, 1H, H_{7A}), 3.89 (s, 3H, H_8), 3.64 (ddd, *J*= 11.5, 9.5, 2.3 Hz, 1H, H_{7B}), 2.53 (dd, *J*= 12.0, 6.5 Hz, 1H, H_{5A}), 2.17 (td, *J*= 12.0, 7.5 Hz, 1H, H_{5B}), 2.03 – 1.89 (m, 1H, H_{6A}), 1.62 (ttd, *J*= 12.0, 9.5, 6.5 Hz, 1H, H_{6B}).

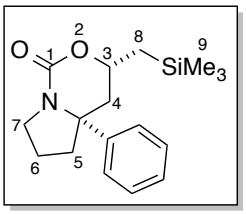
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 158.5, 150.3, 147.5, 142.9, 135.0, 132.2, 130.2, 128.5, 127.1, 126.3, 126.2, 124.7, 122.7, 121.5, 119.5, 105.8, 102.9, 67.1, 55.4, 46.2, 40.1, 20.2.
HRMS (70 eV, IE)	Calculated for $[C_{24}H_{20}BrNO_3]^+$: 449.0621, found 449.0628.

Section 1.A.2.3

- **General Procedure for the Synthesis of Silicon-Containing Hexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one Derivatives 11s-y**

The corresponding *N*-Boc alkynamine derivative **7** (0.2 mmol) and $PtCl_4$ (5 mol%) were placed in a glass reaction tube equipped with a magnetic stirring bar under argon atmosphere. Then, dry dichloromethane (10 mL) and allyltrimethylsilane (10 equiv, 2 mmol) were added. The solution was cooled to –10 °C and triflic acid (10 mol%) was added. The mixture was kept at this temperature during 72 h. Finally, the reaction was filtered through a pad of Celite eluting with ethyl acetate, the solvent was removed under vacuum and the resulting crude was purified by flash column chromatography on silica gel using diethyl ether as eluent to give pure **11s-y.**[208]

(3*S,4a*R**)-4a-Phenyl-3-((trimethylsilyl)methyl)hexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (11s)**



Light yellow oil

R_f = 0.43 (diethyl ether)

Isolated yield (major diast): 72%

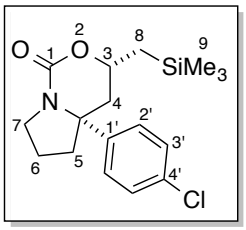
^{1}H–NMR (300 MHz, $CDCl_3$)

δ: 7.38 – 7.31 (m, 2H, $H_{3'}$), 7.29 – 7.21 (m, 3H, $H_{2'}$ and $H_{4'}$), 4.47 (tt, *J*= 7.9, 5.2 Hz, 1H, H_3), 3.79 (dt, *J*= 11.3, 8.7 Hz, 1H, H_{7A}), 3.56 (app. td, *J*= 10.6, 2.2 Hz, 1H, H_{7B}), 2.40 – 2.32 (m, 3H, H_4 and H_{5A}), 1.94 (td, *J*= 11.9, 7.7 Hz, 1H, H_{5B}), 1.89 – 1.79 (m, 1H, H_{6A}), 1.55 – 1.40 (m, 1H, H_{6B}), 0.74 (dd, *J*= 14.6, 7.9 Hz, 1H, H_{8A}), 0.44 (dd, *J*= 14.6, 7.9 Hz, 1H, H_{8B}), –0.06 (s, 9H, H_9).

[208] In some cases minor diastereoisomer could not be characterised.

^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 154.5, 145.0, 128.9, 127.3, 125.2, 75.1, 66.2, 46.4, 42.7, 42.2, 23.8, 20.5, –0.9.
HRMS (70 eV, IE)	Calculated for $[C_{17}H_{25}NO_2Si]^+$: 303.1649, found 303.1654.

(3*S,4a*R**)-4a-(4-Chlorophenyl)-3-((trimethylsilyl)methyl)hexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (11t)**



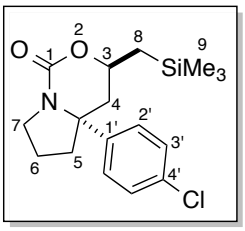
Brown oil

R_f = 0.43 (diethyl ether)

Isolated yield (major diast): 54%

^{1}H–NMR (400 MHz, $CDCl_3$)	δ: 7.33 (d, *J*= 8.6 Hz, 2H, $H_{3'}$), 7.18 (d, *J*= 8.6 Hz, 2H, $H_{2'}$), 4.46 (tt, *J*= 7.9, 5.3 Hz, 1H, H_3), 3.79 (dt, *J*= 11.5, 8.6 Hz, 1H, H_{7A}), 3.52 (ddd, *J*= 11.5, 9.8, 2.4 Hz, 1H, H_{7B}), 2.40 – 2.26 (m, 3H, H_4 and H_{5A}), 2.00 – 1.79 (m, 2H, H_{5B} and H_{6A}), 1.55 – 1.37 (m, 1H, H_{6B}), 0.78 (dd, *J*= 14.6, 7.9 Hz, 1H, H_{8A}), 0.48 (dd, *J*= 14.6, 7.9 Hz, 1H, H_{8B}), –0.03 (s, 9H, H_9).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 154.4, 143.6, 133.2, 129.0, 126.7, 75.0, 65.9, 46.4, 42.7, 42.1, 23.9, 20.4, –0.9.
HRMS (70 eV, IE)	Calculated for $[C_{17}H_{24}ClNO_2Si]^+$: 337.1259, found 337.1262.

(3*R,4a*R**)-4a-(4-Chlorophenyl)-3-((trimethylsilyl)methyl)hexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (*diast*-11t)**



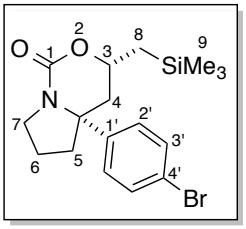
Brown oil

R_f = 0.41 (diethyl ether)

Isolated yield (minor diast): 54%

^{1}H–NMR (400 MHz, $CDCl_3$)	δ: 7.34 (d, *J*= 8.6 Hz, 2H, $H_{3'}$), 7.18 (d, *J*= 8.6 Hz, 2H, $H_{2'}$), 3.90 (dddd, *J*= 11.3, 8.8, 6.0, 2.0 Hz, 1H, H_3), 3.76 (td, *J*= 10.8, 7.6 Hz, 1H, H_{7A}), 3.56 (t, *J*= 10.8 Hz, 1H, H_{7B}), 2.40 (dd, *J*= 13.5, 2.0 Hz, 1H, H_{4A}), 2.34 (dd, *J*= 11.0, 6.3 Hz, 1H, H_{5A}), 1.95 – 1.82 (m, 2H, H_{5B} and H_{6A}), 1.75 (dd, *J*= 13.5, 11.3 Hz, 1H H_{4B}), 1.59 – 1.31 (m, 1H, H_{6B}), 1.11 (dd, *J*= 14.5, 6.0 Hz, 1H, H_{8A}), 0.86 (dd, 14.5, 8.8 Hz, 1H, H_{8B}), –0.08 (s, 9H, H_9).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 153.7, 142.4, 133.4, 128.8, 127.0, 73.5, 66.9, 46.7, 43.8, 41.8, 23.9, 20.9, –0.9.
HRMS (70 eV, IE)	Calculated for $[C_{17}H_{24}ClNO_2Si]^+$: 337.1259, found 337.1256.

(3*S,4a*R**)-4a-(4-Bromophenyl)-3-((trimethylsilyl)methyl)hexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (11u)**



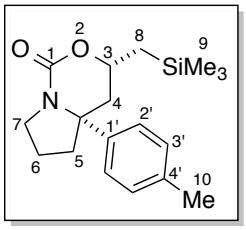
Brown oil

R_f = 0.33 (diethyl ether)

Isolated yield (major diast): 49%

^{1}H–NMR (300 MHz, C_6D_6)	δ: 7.17 (d, *J*= 8.5 Hz, 2H, $H_{3'}$), 6.66 (d, *J*= 8.5 Hz, 2H, $H_{2'}$), 4.16 – 4.05 (m, 1H, H_3), 3.70 (dt, *J*= 11.8, 8.5 Hz, 1H, H_{7A}), 3.29 (ddd, *J*= 11.8, 9.7, 2.3 Hz, 1H, H_{7B}), 1.71 (dd, *J*= 5.6, 1.4 Hz, 2H, H_4), 1.64 – 1.54 (m, 1H, H_{5A}), 1.31 – 1.11 (m, 2H, H_{5B} and H_{6A}), 1.00 – 0.81 (m, 1H, H_{6B}), 0.63 (dd, *J*= 14.6, 9.2 Hz, 1H, H_{8A}), 0.24 (dd, *J*= 14.6, 6.3 Hz, 1H, H_{8B}), –0.02 (s, 9H, H_9).
^{13}C–NMR (75 MHz, C_6D_6)	δ: 153.2, 144.8, 131.7, 126.9, 120.8, 73.7, 65.4, 46.0, 42.9, 41.1, 23.6, 20.0, –1.2.
HRMS (70 eV, IE)	Calculated for $[C_{17}H_{24}BrNO_2Si]^+$: 381.0754, found 381.0745.

(3*S,4a*R**)-4a-(*p*-Tolyl)-3-((trimethylsilyl)methyl)hexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (11v)**



Brown oil

R_f = 0.43 (diethyl ether)

Isolated yield (major diast): 50%

^{1}H–NMR
(300 MHz, $CDCl_3$)

δ: 7.15 (d, *J*= 8.5 Hz, 2H, $H_{2'}$), 7.10 (d, *J*= 8.5 Hz, 2H, $H_{3'}$), 4.45 (tt, *J*= 7.9, 5.2 Hz, 1H, H_3), 3.78 (dt, *J*= 11.4, 8.6 Hz, 1H, H_{7A}), 3.53 (ddd, *J*= 11.4, 9.5, 2.1 Hz, 1H, H_{7B}), 2.37 – 2.28 (m, 3H, H_4 and H_{5A}), 2.33 (s, 3H, H_{10}), 1.98 – 1.75 (m, 2H, H_{5B} and H_{6A}), 1.57 – 1.38 (m, 1H, H_{6B}), 0.78 (dd, *J*= 14.6, 7.9 Hz, 1H, H_{8A}), 0.47 (dd, *J*= 14.6, 7.9 Hz, 1H, H_{8B}), –0.05 (s, 9H, H_9).

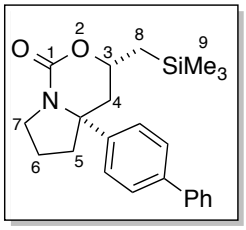
^{13}C–NMR
(75 MHz, $CDCl_3$)

δ: 154.4, 141.8, 136.8, 129.3, 125.0, 75.0, 65.8, 46.2, 42.6, 41.9, 23.6, 20.9, 20.3, –1.0.

HRMS
(70 eV, IE)

Calculated for $[C_{18}H_{27}NO_2Si]^+$: 317.1806, found 317.1815.

(3*S,4a*R**)-4a-([1,1'-Biphenyl]-4-yl)-3-((trimethylsilyl)methyl)hexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (11w)**



Brown oil

R_f = 0.33 (diethyl ether)

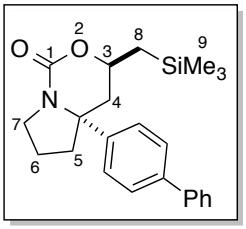
Isolated yield (major diast): 63%

^{1}H–NMR
(300 MHz, $CDCl_3$)

δ: 7.63 – 7.53 (m, 4H, H_{BiPh}), 7.50 – 7.40 (m, 2H, H_{BiPh}), 7.39 – 7.28 (m, 3H, H_{BiPh}), 4.49 (tt, *J*= 7.9, 5.2 Hz, 1H, H_3), 3.82 (dt, *J*= 11.3, 8.6 Hz, 1H, H_{7A}), 3.59 (ddd, *J*= 11.3, 9.7, 2.3 Hz, 1H, H_{7B}), 2.46 – 2.32 (m, 3H, H_4 and H_{5A}), 2.06 – 1.80 (m, 2H, H_{5B} and H_{6A}), 1.68 – 1.44 (m, 1H, H_{6B}), 0.82 (dd, *J*= 14.6, 7.9 Hz, 1H, H_{8A}), 0.52 (dd, *J*= 14.6, 7.9 Hz, 1H, H_{8B}), –0.04 (s, 9H, H_9).

^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 154.5, 144.0, 140.5, 140.3, 129.0, 127.6, 127.5, 127.2, 125.7, 75.2, 66.1, 46.4, 42.7, 42.1, 23.8, 20.5, –0.9.
HRMS (70 eV, IE)	Calculated for $[C_{23}H_{29}NO_2Si]^+$: 379.1962, found 379.1966.

(3*R,4a*R**)-4a-([1,1'-Biphenyl]-4-yl)-3-((trimethylsilyl)methyl)hexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (*diast*-11w)**



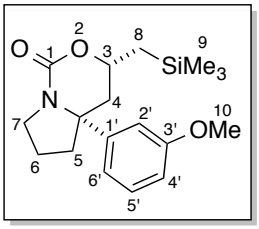
Brown oil

R_f = 0.40 (diethyl ether)

Isolated yield (minor diast): 25%

^{1}H–NMR (300 MHz, $CDCl_3$)	δ: 7.64 – 7.54 (m, 4H, H_{Ar}), 7.50 – 7.41 (m, 2H, H_{Ar}), 7.40 – 7.27 (m, 3H, H_{Ar}), 3.98 (dddd, *J*= 11.5, 8.8, 5.9, 2.0 Hz, 1H, H_3), 3.78 (td, *J*= 11.2, 7.8 Hz, 1H, H_{7A}), 3.61 (app. t, *J*= 10.6 Hz, 1H, H_{7B}), 2.48 (dd, *J*= 13.5, 2.0 Hz, 1H, H_{4A}), 2.46 – 2.36 (m, 1H, H_{5A}), 2.00 – 1.83 (m, 2H, H_{5B} and H_{6A}), 1.77 (dd, *J*= 13.5, 11.5 Hz, 1H, H_{4B}), 1.69 – 1.46 (m, 1H, H_{6B}), 1.13 (dd, *J*= 14.4, 5.9 Hz, 1H, H_{8A}), 0.86 (dd, *J*= 14.4, 8.8 Hz, 1H, H_{8B}), –0.07 (s, 9H, H_9).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 154.0, 143.0, 140.4, 129.0, 127.7, 127.4, 127.2, 126.1, 73.7, 67.2, 46.9, 44.1, 41.9, 24.1, 21.1, –0.8.
HRMS (70 eV, IE)	Calculated for $[C_{23}H_{29}NO_2Si]^+$: 379.1962, found 379.1966.

(3*S,4a*R**)-4a-(3-Methoxyphenyl)-3-((trimethylsilyl)methyl)hexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (11x)**



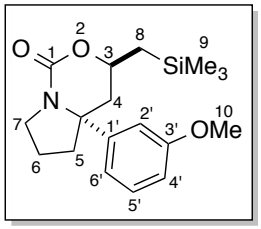
Yellow oil

R_f = 0.35 (diethyl ether)

Isolated yield (major diast): 55%

^{1}H–NMR (300 MHz, $CDCl_3$)	δ: 7.31 – 7.22 (m, 1H, $H_{2'}$), 6.86 – 6.73 (m, 3H, $H_{4'}$, $H_{5'}$ and $H_{6'}$), 4.53 – 4.41 (m, 1H, H_3), 3.86 – 3.71 (m, 1H, H_{7A}), 3.81 (s, 3H, H_{10}), 3.63 – 3.44 (m, 1H, H_{7B}), 2.41 – 2.28 (m, 3H, H_4 and H_{5A}), 1.99 – 1.75 (m, 2H, H_{5B} and H_{6A}), 1.66 – 1.40 (m, 1H, H_{6B}), 0.80 (ddd, *J*= 14.6, 7.9, 2.0 Hz, 1H, H_{8A}), 0.50 (ddd, *J*= 14.6, 7.9, 2.0 Hz, 1H, H_{8B}), –0.04 (br s, 9H, H_9).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 160.1, 154.4, 146.8, 129.9, 117.6, 112.2, 111.5, 110.1, 75.1, 66.2, 55.5, 46.5, 42.6, 42.2, 23.7, 20.5, –0.9.
HRMS (70 eV, IE)	Calculated for $[C_{18}H_{27}NO_3Si]^+$: 333.1755, found 333.1757.

(3*R,4a*R**)-4a-(3-Methoxyphenyl)-3-((trimethylsilyl)methyl)hexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (*diast*-11x)**



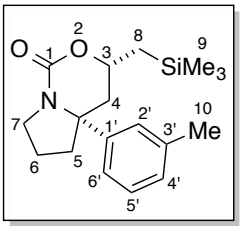
Yellow oil

R_f= 0.33 (diethyl ether)

Isolated yield (minor diast): 25%

^{1}H–NMR (300 MHz, $CDCl_3$)	δ: 7.28 (t, *J*= 7.9 Hz, 1H, $H_{5'}$), 6.84 – 6.72 (m, 3H, $H_{2'}$, $H_{4'}$ and $H_{6'}$), 3.95 (dddd, *J*= 11.3, 8.9, 5.9, 2.0 Hz, 1H, H_3), 3.81 (s, 3H, H_{10}), 3.74 (td, *J*= 11.1, 7.7 Hz, 1H, H_{7A}), 3.63 – 3.52 (m, 1H, H_{7B}), 2.45 (dd, *J*= 13.4, 2.0 Hz, 1H, H_{4A}), 2.37 (dd, *J*= 10.9, 6.6 Hz, 1H, H_{5A}), 1.94 – 1.79 (m, 2H, H_{5B} and H_{6A}), 1.71 (dd, *J*= 13.4, 11.3 Hz, 1H, H_{4B}), 1.62 – 1.41 (m, 1H, H_{6B}), 1.11 (dd, *J*= 14.4, 5.9 Hz, 1H, H_{8A}), 0.86 (dd, 14.4, 8.9 Hz, 1H, H_{8B}), –0.08 (m, 9H, H_9).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 159.9, 154.0, 145.9, 129.9, 118.0, 112.3, 112.2, 73.7, 67.4, 55.5, 46.9, 44.0, 41.9, 24.0, 21.1, –0.8.
HRMS (70 eV, IE)	Calculated for $[C_{18}H_{27}NO_3Si]^+$: 333.1755, found 333.1757.

(3*S,4a*R**)-4a-(*m*-Tolyl)-3-((trimethylsilyl)methyl)hexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (11y)**



Yellow oil

R_f = 0.38 (diethyl ether)

Isolated yield (major diast): 45%

^{1}H–NMR
(300 MHz, $CDCl_3$)

δ: 7.23 (t, *J*= 7.9 Hz, 1H, $H_{5'}$), 7.10 – 6.97 (m, 3H, $H_{4'}$, $H_{5'}$ and $H_{6'}$), 4.46 (tt, *J*= 7.9, 5.2 Hz, 1H, H_3), 3.78 (dt, *J*= 11.4, 8.5 Hz, 1H, H_{7A}), 3.55 (ddd, 11.4, 9.5, 2.0 Hz, 1H, H_{7B}), 2.39 – 2.30 (m, 3H, H_4 and H_{5A}), 2.35 (s, 3H, H_{10}), 1.99 – 1.76 (m, 2H, H_{5B} and H_{6A}), 1.57 – 1.38 (m, 1H, H_{6B}), 0.77 (dd, *J*= 14.5, 7.9 Hz, 1H, H_{8A}), 0.47 (dd, *J*= 14.5, 7.9 Hz, 1H, H_{8B}), -0.05 (s, 9H, H_9).

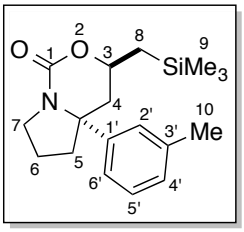
^{13}C–NMR
(75 MHz, $CDCl_3$)

δ: 154.5, 144.8, 138.5, 128.7, 128.0, 125.8, 122.3, 77.4, 66.1, 46.3, 42.7, 42.1, 23.7, 21.7, 20.5, -0.9.

HRMS
(70 eV, IE)

Calculated for $[C_{18}H_{27}NO_2Si]^+$: 317.1806, found 317.1814.

(3*R,4a*R**)-4a-(*m*-Tolyl)-3-((trimethylsilyl)methyl)hexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (*diast*-11y)**



Yellow oil

R_f = 0.45 (diethyl ether)

Isolated yield (minor diast): 44%

^{1}H–NMR
(300 MHz, $CDCl_3$)

δ: 7.24 (t, *J*= 7.9 Hz, 1H, $H_{5'}$), 7.12 – 6.96 (m, 3H, $H_{2'}$, $H_{4'}$ and $H_{6'}$), 3.97 – 3.84 (m, 1H, H_3), 3.74 (td, *J*= 11.1, 7.7 Hz, 1H, H_{7A}), 3.57 (app. t, *J*= 10.1 Hz, 1H, H_{7B}), 2.49 – 2.28 (m, 2H, H_{4A} and H_{5A}), 2.35 (s, 3H, H_{10}), 1.95 – 1.78 (m, 2H, H_{5B} and H_{6A}), 1.77 – 1.65 (m, 1H, H_{4B}), 1.58 – 1.41 (m, 1H, H_{6B}), 1.10 (dd, *J*= 14.4, 5.9 Hz, 1H, H_{8A}), 0.86 (dd, *J*= 14.4, 8.9 Hz, 1H, H_{8B}), -0.09 (s, 9H, H_9).

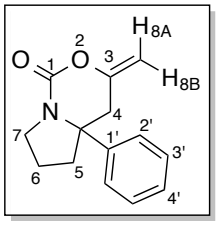
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 154.0, 143.9, 138.4, 128.6, 128.3, 126.3, 122.7, 73.7, 67.3, 46.9, 44.1, 41.9, 24.0, 21.7, 21.1, -0.8.
HRMS (70 eV, IE)	Calculated for $[C_{18}H_{27}NO_2Si]^+$: 317.1806, found 317.1809.

Section 1.A.2.4

- **General Procedure for the Synthesis of 3-Methylene-hexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one Derivatives 14**

The corresponding *N*-Boc alkynamine derivative **7** (0.2 mmol) and $PtCl_4$ (5 mol%) were placed in a glass reaction tube equipped with a magnetic stirring bar under argon atmosphere. Then, dry dichloromethane (6 mL), trimethylpropargylsilane (2.5 equiv, 0.5 mmol) and 3 µL of H_2O (0.5 equiv, 0.1 mmol) were added. The solution was cooled to –10 °C and freshly distilled triflic acid (10 mol%) was added. The mixture was kept at this temperature during 36 hours. Then, the reaction was filtered through a pad of Celite eluting with ethyl acetate, the solvent was removed under vacuum and the resulting crude was purified by flash column chromatography on silica gel using diethyl ether as eluent to give pure **14**.

3-Methylene-4a-phenylhexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (14a)



Light brown solid

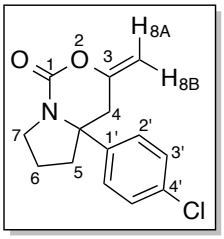
mp= 134 – 136 °C

R_f = 0.45 (diethyl ether)

Isolated yield: 96%

^{1}H–NMR (300 MHz, $CDCl_3$)	δ: 7.38 – 7.22 (m, 3H, $H_{3'}$ and $H_{4'}$), 7.15 (d, *J*= 7.3 Hz, 2H, $H_{2'}$), 4.45 (s, 1H, H_{8A}), 3.89 (s, 1H, H_{8B}), 3.79 – 3.61 (m, 2H, H_7), 3.03 (d, *J*= 13.8 Hz, 1H, H_{4A}), 2.60 (d, *J*= 13.8 Hz, 1H, H_{4B}), 2.45 (dd, *J*= 12.0, 6.3 Hz, 1H, H_{5A}), 2.08 – 1.84 (m, 2H, H_{5B} and H_{6A}), 1.68 – 1.48 (m, 1H, H_{6B}).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 150.8, 150.6, 142.1, 128.7, 127.6, 125.1, 94.1, 66.6, 47.0, 41.7, 41.1, 21.1
HRMS (70 eV, IE)	Calculated for $[C_{14}H_{15}NO_2]^+$: 229.1097, found 229.1104.

4a-(4-Chlorophenyl)-3-methylenehexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (14b)



Light brown foam

R_f = 0.38 (diethyl ether)

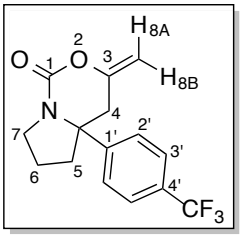
Isolated yield: 90%

^{1}H–NMR (400 MHz, $CDCl_3$): δ: 7.31 (d, *J*= 8.5 Hz, 2H, $H_{3'}$), 7.10 (d, *J*= 8.5 Hz, 2H, $H_{2'}$), 4.47 (s, 1H, H_{8A}), 3.91 (t, *J*= 1.8 Hz, 1H, H_{8B}), 3.77 – 3.60 (m, 2H, H_7), 2.98 (d, *J*= 13.9 Hz, 1H, H_{4A}), 2.60 (dt, *J*= 13.9, 1.8 Hz, 1H, H_{4B}), 2.41 (dd, *J*= 11.9, 6.3 Hz, 1H, H_{5A}), 2.07 – 1.88 (m, 2H, H_{5B} and H_{6A}), 1.64 – 1.49 (m, 1H, H_{6B}).

^{13}C–NMR (75 MHz, $CDCl_3$): δ: 150.4, 140.8, 133.6, 129.0, 126.7, 94.5, 66.3, 47.0, 41.6, 40.9, 21.1.

HRMS (70 eV, IE): Calculated for $[C_{14}H_{14}ClNO_2]^+$: 263.0708, found 263.0712.

3-Methylene-4a-(4-(trifluoromethyl)phenyl)hexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (14c)



Light brown foam

R_f = 0.30 (diethyl ether)

Isolated yield: 70%

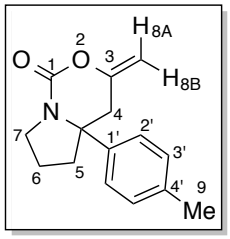
^{1}H–NMR (300 MHz, $CDCl_3$): δ: 7.61 (d, *J*= 8.2 Hz, 2H, $H_{3'}$), 7.30 (d, *J*= 8.2 Hz, 2H, $H_{2'}$), 4.48 (s, 1H, H_{8A}), 3.92 (t, *J*= 1.8 Hz, 1H, H_{8B}), 3.82 – 3.62 (m, 2H, H_7), 3.04 (d, *J*= 13.9 Hz, 1H, H_{4A}), 2.65 (dt, *J*= 13.9, 1.8 Hz, 1H, H_{4B}), 2.46 (dd, *J*= 11.9, 6.3 Hz, 1H, H_{5A}), 2.17 – 1.89 (m, 2H, H_{5B} and H_{6A}), 1.67 – 1.47 (m, 1H, H_{6B}).

^{13}C–NMR (75 MHz, $CDCl_3$): δ: 150.4, 150.2, 146.4, 130.1 (q, $J_{C\text{-}F}$= 33.0 Hz), 125.9 (q, $J_{C\text{-}F}$= 3.7 Hz), 125.8, 122.2, 94.7, 66.6, 47.1, 41.7, 40.9, 21.2.

^{19}F–NMR (282 MHz, $CDCl_3$): δ: –62.6.

HRMS (70 eV, IE)	Calculated for $[C_{15}H_{14}F_3NO_2]^+$: 297,0971, found 297,0974.

3-Methylene-4a-(*p*-tolyl)hexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (14d)



Light brown solid

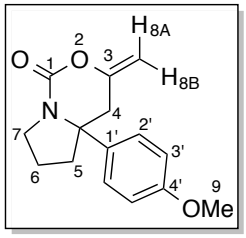
mp= 138 – 140 °C

R_f = 0.40 (diethyl ether)

Isolated yield: 86%

^{1}H–NMR (300 MHz, $CDCl_3$)	δ: 7.14 (d, *J*= 8.1 Hz, 2H, $H_{2'}$), 7.04 (d, *J*= 8.1 Hz, 2H, $H_{3'}$), 4.46 (s, 1H, H_{8A}), 3.90 (t, *J*= 1.7 Hz, 1H, H_{8B}), 3.77 – 3.62 (m, 2H, H_7), 3.01 (d, *J*= 13.8 Hz, 1H, H_{4A}), 2.58 (dt, *J*= 13.8, 1.7 Hz, 1H, H_{4B}), 2.42 (dd, *J*= 11.8, 6.1 Hz, 1H, H_{5A}), 2.32 (s, 3H, H_9), 2.04 – 1.85 (m, 2H, H_{5B} and H_{6A}), 1.66 – 1.51 (m, 1H, H_{6B}).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 150.9, 150.6, 139.1, 137.3, 129.4, 125.1, 94.1, 66.4, 47.0, 41.7, 41.1, 21.1, 21.1.
HRMS (70 eV, IE)	Calculated for $[C_{15}H_{17}NO_2]^+$: 243.1254, found 243.1257.

4a-(4-Methoxyphenyl)-3-methylenehexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (14e)



Brown oil

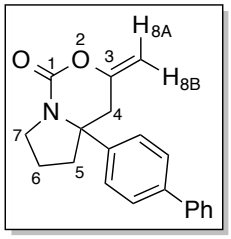
R_f = 0.40 (diethyl ether)

Isolated yield: 40%

^{1}H–NMR (300 MHz, $CDCl_3$)	δ: 7.07 (d, *J*= 8.8 Hz, 2H, $H_{2'}$), 6.85 (d, *J*= 8.8 Hz, 2H, $H_{3'}$), 4.47 (s, 1H, H_{8A}), 3.91 (t, *J*= 1.7 Hz, 1H, H_{8B}), 3.79 (s, 3H, H_9), 3.77 – 3.60 (m, 2H, H_7), 2.99 (d, *J*= 13.7 Hz, 1H, H_{4A}), 2.58 (dt, *J*= 13.7, 1.7 Hz, 1H, H_{4B}), 2.41 (dd, *J*= 11.2, 6.2 Hz, 1H, H_{5A}), 2.06 – 1.84 (m, 2H, H_{5B} and H_{6A}), 1.67 – 1.53 (m, 1H, H_{6B}).

^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 159.0, 151.0, 150.6, 134.0, 126.4, 114.1, 94.1, 66.2, 55.4, 47.0, 41.8, 41.2, 21.2.
HRMS (70 eV, IE)	Calculated for $[C_{15}H_{17}NO_3]^+$: 259.1203, found 259.1203.

4a-([1,1'-Biphenyl]-4-yl)-3-methylenehexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (14f)



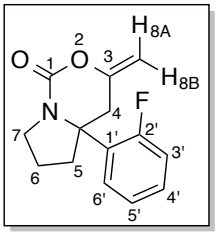
Yellow foam

R_f = 0.50 (diethyl ether)

Isolated yield: 81%

^{1}H–NMR (300 MHz, $CDCl_3$)	δ: 7.61 – 7.53 (m, 4H, H_{BiPh}), 7.49 – 7.31 (m, 3H, H_{BiPh}), 7.27 – 7.19 (m, 2H, H_{BiPh}), 4.50 (s, 1H, H_{8A}), 3.95 (t, *J*= 1.6 Hz, 1H, H_{8B}), 3.82 – 3.65 (m, 2H, H_7), 3.08 (d, *J*= 13.8 Hz, 1H, H_{4A}), 2.64 (dt, *J*= 13.8, 1.6 Hz, 1H, H_{4B}), 2.49 (dd, *J*= 11.6, 6.2 Hz, 1H, H_{5A}), 2.11 – 1.88 (m, 2H, H_{5B} and H_{6A}), 1.74 – 1.55 (m, 1H, H_{6B}).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 150.6, 150.5, 141.0, 140.4, 140.2, 128.8, 127.5, 127.3, 127.0, 125.6, 94.2, 66.4, 46.9, 41.6, 40.9, 21.1.
HRMS (70 eV, IE)	Calculated for $[C_{20}H_{19}NO_2]^+$: 305.1410, found 305.1419.

4a-(2-Fluorophenyl)-3-methylenehexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (14g)



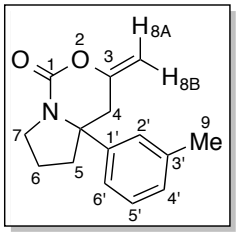
Light brown foam

R_f = 0.40 (diethyl ether)

Isolated yield: 61%

^{1}H–NMR (300 MHz, $CDCl_3$)	δ: 7.33 – 7.24 (m, 1H, $H_{3'}$), 7.14 – 7.00 (m, 3H, $H_{4'}$, $H_{5'}$ and $H_{6'}$), 4.45 (s, 1H, H_{8A}), 3.97 (t, *J*= 1.7 Hz, 1H, H_{8B}), 3.81 – 3.62 (m, 2H, H_7), 3.34 (d, *J*= 14.1 Hz, 1H, H_{4A}), 2.65 – 2.54 (m, 1H, H_{5A}), 2.53 (dt, *J*= 14.1, 1.7 Hz, 1H, H_{4B}), 2.08 – 1.88 (m, 2H, H_{5B} and H_{6A}), 1.69 – 1.49 (m, 1H, H_{6B}).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 158.8 (d, $J_{C\text{-}F}$= 245.4 Hz), 151.1, 150.5, 130.1 (d, $J_{C\text{-}F}$= 8.5 Hz), 128.8 (d, $J_{C\text{-}F}$= 12.0 Hz), 128.5 (d, $J_{C\text{-}F}$= 3.6 Hz), 124.3 (d, $J_{C\text{-}F}$= 3.5 Hz), 116.7 (d, $J_{C\text{-}F}$= 22.5 Hz), 94.2, 65.1 (d, $J_{C\text{-}F}$= 2.8 Hz), 47.2, 40.0 (d, $J_{C\text{-}F}$= 3.4 Hz), 38.7 (d, $J_{C\text{-}F}$= 5.1 Hz), 21.5.
^{19}F–NMR (282 MHz, $CDCl_3$)	δ: –112.8.
HRMS (70 eV, IE)	Calculated for $[C_{14}H_{14}FNO_2]^+$: 247.1003, found 247.1009.

3-Methylene-4a-(*m*-tolyl)hexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (14h)



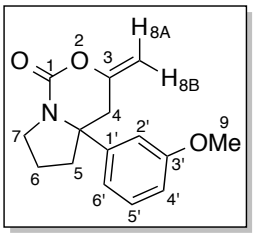
White foam

R_f = 0.38 (diethyl ether)

Isolated yield: 66%

^{1}H–NMR (300 MHz, $CDCl_3$)	δ: 7.22 (t, *J*= 7.4 Hz, 1H, $H_{5'}$), 7.07 (d, *J*= 7.4 Hz, 1H, $H_{6'}$), 6.95 (d, *J*= 7.4 Hz, 1H, $H_{4'}$), 6.94 (s, 1H, $H_{2'}$), 4.46 (s, 1H, H_{8A}), 3.91 (t, *J*= 1.7 Hz, 1H, H_{8B}), 3.79 – 3.61 (m, 2H, H_7), 3.03 (d, *J*= 13.7 Hz, 1H, H_{4A}), 2.59 (dt, *J*= 13.7, 1.8 Hz, 1H, H_{4B}), 2.44 (dd, *J*= 11.7, 6.7 Hz, 1H, H_{5A}), 2.34 (s, 3H, H_9), 2.07 – 1.84 (m, 2H, H_{5B} and H_{6A}), 1.71 – 1.49 (m, 1H, H_{6B}).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 150.9, 150.6, 142.1, 138.4, 128.6, 128.4, 125.8, 122.3, 94.1, 66.6, 47.0, 41.8, 41.1, 21.8, 21.2
HRMS (70 eV, IE)	Calculated for $[C_{15}H_{17}NO_2]^+$: 243.1254, found 243.1255.

4a-(3-Methoxyphenyl)-3-methylenehexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (14i)



Light brown solid

mp= 99 – 101 °C

R_f = 0.30 (diethyl ether)

Isolated yield: 85%

^{1}H–NMR
(300 MHz, $CDCl_3$)

δ: 7.26 (t, *J*= 8.0 Hz, 1H, $H_{5'}$), 6.79 (ddd, *J*= 8.0, 2.1, 0.9 Hz, 1H, $H_{6'}$), 6.74 (ddd, *J*= 8.0, 2.1, 0.9 Hz, 1H, $H_{4'}$), 6.68 (t, *J*= 2.1 Hz, 1H, $H_{2'}$), 4.46 (s, 1H, H_{8A}), 3.92 (t, *J*= 1.8 Hz, 1H, H_{8B}), 3.79 (s, 3H, H_9), 3.78 – 3.61 (m, 2H, H_7), 3.03 (d, *J*= 13.7 Hz, 1H, H_{4A}), 2.58 (dt, *J*= 13.7, 1.8 Hz, 1H, H_{4B}), 2.44 (dd, *J*= 11.8, 6.6 Hz, 1H, H_{5A}), 2.05 – 1.84 (m, 2H, H_{5B} and H_{6A}), 1.70 – 1.50 (m, 1H, H_{6B}).

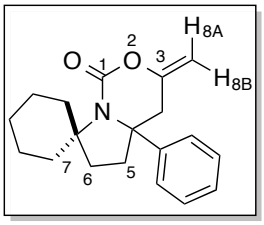
^{13}C–NMR
(75 MHz, $CDCl_3$)

δ: 159.9, 150.8, 150.5, 144.0, 129.8, 117.5, 112.1, 111.9, 94.2, 66.6, 55.4, 47.0, 41.8, 41.0, 21.2.

HRMS
(70 eV, IE)

Calculated for $[C_{15}H_{17}NO_3]^+$: 259.1203, found 259.1205.

3'-Methylene-4a'-phenyltetrahydro-1'*H*,3'*H*-spiro[cyclohexane-1,7'-pyrrolo[1,2-*c*][1,3]oxazin]-1'-one (14j)



Light brown foam

R_f = 0.45 (hexane:diethyl ether, 1:1)

Isolated yield: 45%

^{1}H–NMR
(300 MHz, $CDCl_3$)

δ: 7.40 – 7.21 (m, 5H, H_{Ph}), 4.36 (t, *J*= 1.4 Hz, 1H, H_{8A}), 3.79 (t, *J*= 1.8 Hz, 1H, H_{8B}), 2.97 (d, *J*= 13.9 Hz, 1H, H_{4A}), 3.01 – 2.82 (m 1H, H_{Cy}), 2.56 (dt, *J*= 13.8, 1.8 Hz, 1H, H_{4B}), 2.68 – 2.50 (m 1H, H_{Cy}), 2.49 – 2.38 (m, 1H, H_{5A}), 2.20 – 2.00 (m, 2H, H_{5B} and H_{6A}), 1.84 – 1.10 (m, 9H, H_{6B} and H_{Cy}).

^{13}C–NMR
(75 MHz, $CDCl_3$)

δ: 151.0, 149.1, 142.6, 128.5, 127.5, 125.6, 92.5, 68.3, 68.0, 42.9, 38.6, 35.9, 31.9, 30.6, 24.9, 24.7, 24.2.

HRMS (70 eV, IE)	Calculated for $[C_{19}H_{23}NO_2]^+$: 297.1723, found 297.1726.

Part B

- **Synthesis of *N*-Boc Alkynamines 7, Alkynols 17 and Enol Ether 18a**

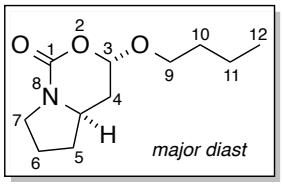
N-Boc alkynamines **7** and alkynol derivatives **17** and enol ether **18a** were prepared according to the methods reported in the literature[206a,] and purified by standard procedures.

Sections 1.B.2.1, 1.B.2.2 and 1.B.2.3

- **General Procedure for the Synthesis of 3-Butoxyhexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one derivative 11aa**

The corresponding *tert*-butyl-2,3-dihydro-1*H*-pyrrole-1-carboxylate **14c** (0.2 mmol) and butylvinylether **3f** (0.2 mmol) were placed in a glass reaction tube under argon atmosphere. Then, dry dichloromethane (2 mL) was added. The solution was cooled to 0 °C and triflic acid (5 mol%) was added. The mixture was allowed to warm to room temperature and was kept at this temperature during 8 hours. Then, the reaction was filtered through a pad of Celite, the solvent was removed under vacuum and the resulting crude was purified by flash column chromatography on silica gel using mixtures of hexane and ethyl acetate as eluent to give pure **11aa** in 82% isolated yield and as mixture of diastereoisomers (*d.r.*= 6:1).

(3*S,4a*R**)-3-Butoxyhexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (11aa)**



Mixture of diastereoisomers 6:1

Colourless oil

R_f = 0.24 (ethyl acetate)

Isolated yield: 82%

^{1}H– NMR
(300 MHz, C_6D_6)

δ: 4.97 (dd, *J*= 2.8, 1.7 Hz, 1H, $H_{3\ mayor\ diast}$), 4.88 (dd, *J*= 9.5, 3.0 Hz, 1H, $H_{3\ minor\ diast}$), 4.07 (dt, *J*= 9.4, 6.6 Hz, 1H, $H_{9A\ minor\ diast}$), 3.92 (dt, *J*= 9.4, 6.6 Hz, 1H, $H_{9A\ mayor\ diast}$), 3.60 – 3.48 (m, 2H, H_7), 3.45 – 3.32 (m, 2H, H_{4a}, H_{9B}), 1.72 (dddd, *J*= 13.2, 5.7, 4.0, 1.8 Hz, 1H, H_{4A}), 1.64 – 0.75 (m, 9H, H_{4B}, H_5, H_6, H_{10}, H_{11}), 0.91 (t, *J*= 7.42 Hz, 3H, H_{12}).

^{13}C–NMR (100 MHz, $CDCl_3$)	δ: 152.1, 151.5, 100.9, 98.7, 69.5, 68.9, 68.9, 53.5, 51.8, 46.5, 46.2, 34.7, 33.3, 33.2, 33.1, 33.0, 31.6, 28.5, 23.2, 22.8, 19.3, 13.9.
HRMS (70 eV, IE)	Calculated for $[C_{11}H_{19}NO_3]^+$: 213.1365, found 213.1363.

- **General Procedures for the Synthesis of 3a-Phenyloctahydro-5*H*-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin-5-one 20a**

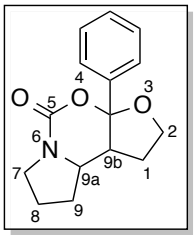
Procedure A:

The corresponding *tert*-butyl-2,3-dihydro-1*H*-pyrrole-1-carboxylate **14c** (0.2 mmol) and 5-phenyl-2,3-dihydrofurane **18a** (0.2 mmol) were placed in a glass reaction tube under argon atmosphere. Then, dry dichloromethane (2 mL) was added. The solution was cooled to 0 °C and triflic acid (5 mol%) was added. The mixture was allowed to warm to room temperature and was kept at this temperature during 16 hours. Then, the reaction was filtered through a pad of Celite, the solvent was removed under vacuum and the resulting crude was purified by flash column chromatography on silica gel using ethyl acetate as eluent to give pure **20a** in 55% isolated yield and as mixture of diastereoisomers (*d.r.*= 1:1).

Procedure B:

The corresponding *tert*-butyl-2,3-dihydro-1*H*-pyrrole-1-carboxylate **14c** (0.2 mmol), the alkynol derivative **17a** (0.2 mmol) and $PtMe_2$(cod) (5 mol%) were placed in a glass reaction tube under argon atmosphere. Then, dry dichloromethane (2 mL) was added. The solution was cooled to 0 °C and triflic acid (10 mol%) was added. The mixture was allowed to warm to room temperature and was kept at this temperature during 16 hours. Then, the reaction was filtered through a pad of Celite, the solvent was removed under vacuum and the resulting crude was purified by flash column chromatography on silica gel using ethyl acetate as eluent to give pure **20a** in 52% isolated yield and as mixture of diastereoisomers (*d.r.*= 1:1).

3a-Phenyloctahydro-5*H*-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin-5-one (20a)



Mixture of diastereoisomers 1:1

Colourless oil

R_f = 0.28 (ethyl acetate)

Isolated yield: 55% (Proc. A) and 52% (Proc. B)

^{1}H–NMR (300 MHz, $CDCl_3$)	δ: 7.39 – 7.34 (m, 4H), 7.28 – 7.18 (m, 6H), 4.11 (app. q, *J*= 7.5 Hz, 1H), 3.92 (app. quintuplet, *J*= 8.0 Hz, 2H), 3.83 (td, *J*= 8.2, 5.8 Hz, 2H), 3.71 – 3.64 (m, 3H), 3,52 (m, 3H), 3.43 (dd, *J*= 9.8, 3.1 Hz, 1H), 2.42 (q, *J*= 9.4 Hz, 1H), 2.27 – 2.13 (m, 2H), 2.10 – 2.01 (m, 3H), 1.92 – 1.79 (m, 4H), 1.75 – 1.66 (m, 4H), 1.35 – 1.29 (m, 2H).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 152.1, 146.0, 129.2, 128.6, 127.6, 126.2, 112.0, 85.8, 68.5, 67.8, 54.4, 47.0, 46.3, 37.2, 25.9, 25.1, 23.6.
HRMS (70 eV, IE)	Calculated for $[C_{15}H_{16}NO_3]^+$: 258.1125, found 258.1128.

- **General Procedures for the Synthesis of 5*H*-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin-5-one Derivative 20b**

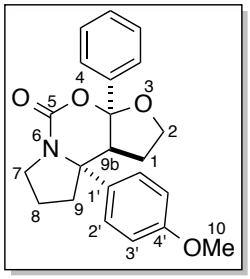
Procedure A:

The corresponding *N*-Boc alkynamine derivative **7c** (0.2 mmol), 5-phenyl-2,3-dihydrofurane **18a** (0.2 mmol) and $PtMe_2$(cod) (5 mol%) were placed in a glass reaction tube under argon atmosphere. Then, dry dichloromethane (2 mL) was added. The solution was cooled to 0 °C and triflic acid (10 mol%) was added. The mixture was allowed to warm to room temperature and was kept at this temperature during 16 hours. Then, the reaction was filtered through a pad of Celite, the solvent was removed under vacuum and the resulting crude was purified by flash column chromatography on silica gel using ethyl acetate as eluent to give pure **20b** in 54% isolated yield and as single diastereoisomer.

Procedure B:

The corresponding *N*-Boc alkynamine derivative **7c** (0.2 mmol), alkynol derivative **17a** (0.2 mmol) and $PtMe_2(cod)$ (5 mol%) were placed in a glass reaction tube under argon atmosphere. Then, dry dichloromethane (2 mL) was added. The solution was cooled to 0 °C and triflic acid (10 mol%) was added. The mixture was allowed to warm to room temperature and was kept at this temperature during 16 hours. Then, the reaction was filtered through a pad of Celite, the solvent was removed under vacuum and the resulting crude was purified by flash column chromatography on silica gel using ethyl acetate as eluent to give pure **20b** in 50% isolated yield and as single diastereoisomer.

(3a*S,9a*R**,9b*S**)-9a-(4-Methoxyphenyl)-3a-phenyloctahydro-5*H*-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin-5-one (20b)**



White foam

R_f = 0.35 (ethyl acetate)

Isolated yield: 54% (Proc. A) and 50% (Proc. B)

^{1}H–NMR
(300 MHz, $CDCl_3$)

δ: 7.10 – 6.88 (m, 5H, H_{Ph}), 6.77 (d, *J*= 8.8 Hz, 2H, $H_{2'}$), 6.47 (d, *J*= 8.8 Hz, 2H, $H_{3'}$), 4.28 (td, *J*= 8.8, 4.4 Hz, 1H, H_{2A}), 4.23 (app. q, *J*= 8.7 Hz, 1H, H_{2B}), 3.88 – 3.71 (m, 2H, H_7), 3.67 (s, 3H, H_{10}), 3.46 (dd, *J*= 10.6, 8.8 Hz, 1H, H_{9b}), 2.50 (dddd, *J*= 12.1, 8.8, 7.5, 4.4 Hz, 1H, H_{1A}), 2.23 – 2.07 (m, 3H, H_{1B} and H_9), 1.96 – 1.79 (m, 1H, H_{8A}), 1.73 – 1.50 (m, 1H, H_{8B}).

^{13}C–NMR
(75 MHz, $CDCl_3$)

δ: 158.6, 152.1, 138.8, 134.2, 127.7, 127.4, 126.7, 126.0, 113.5, 111.5, 67.2, 66.6, 55.4, 52.8, 47.6, 40.4, 27.0, 20.6.

HRMS
(70 eV, IE)

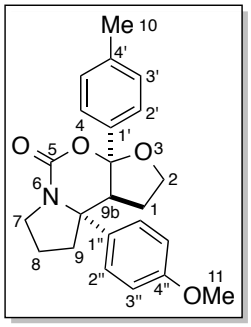
Calculated for $[C_{22}H_{23}NO_4]^+$: 365.1627, found 365.1626.

Sections 1.B.2.4, 1.B.2.5 and 1.B.2.6

- **General Procedure for the Synthesis of 5*H*-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin-5-one Derivatives 20d-al**

The corresponding *N*-Boc alkynamine derivative **7** (0.2 mmol), alkynol derivative **17** (0.2 mmol) and $PtMe_2(cod)$ (5 mol%) were placed in a glass reaction tube under argon atmosphere. Then, dry dichloromethane (2 mL) was added. The solution was cooled to 0 °C and triflic acid (10 mol%) was added. The mixture was allowed to warm to room temperature and was kept at this temperature during 16 hours. Then, the reaction was filtered through a pad of Celite, the solvent was removed under vacuum and the resulting crude was purified by flash column chromatography on silica gel using mixtures of hexane and ethyl acetate as eluent to give pure **20d-al** as single diastereoisomers.

(3a*S,9a*R**,9b*S**)-9a-(4-Methoxyphenyl)-3a-(*p*-tolyl)octahydro-5*H*-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin-5-one (20d)**



White foam

R_f = 0.30 (ethyl acetate)

Isolated yield: 78%

^{1}H–NMR
(300 MHz, $CDCl_3$)

δ: 6.83 (d, *J*= 8.2 Hz, 2H, $H_{2'}$), 6.72 (d, *J*= 8.8 Hz, 2H, $H_{2''}$), 6.70 (d, *J*= 8.2 Hz, 2H, $H_{3'}$), 6.43 (d, *J*= 8.8 Hz, 2H, $H_{3''}$), 4.29 – 4.11 (m, 2H, H_2), 3.81 – 3.65 (m, 2H, H_7), 3.63 (s, 3H, H_{11}), 3.38 (dd, *J*= 10.7, 8.6 Hz, 1H, H_{9b}), 2.44 (dddd, *J*= 12.4, 8.7, 7.4, 4.3 Hz, 1H, H_{1A}), 2.15 – 2.02 (m, 3H, H_{1B} and H_9), 2.13 (s, 3H, H_{10}), 1.91 – 1.79 (m, 1H, H_{8A}), 1.67 – 1.50 (m, 1H, H_{8B}).

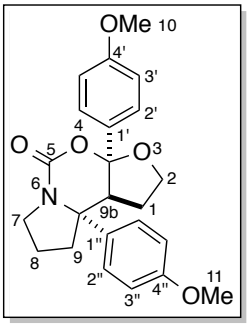
^{13}C–NMR
(75 MHz, $CDCl_3$)

δ: 158.5, 152.1, 137.1, 135.7, 134.3, 128.0, 126.6, 125.8, 113.4, 111.5, 67.0, 66.5, 55.4, 52.6, 47.5, 40.2, 26.8, 20.9, 20.6.

HRMS
(70 eV, IE)

Calculated for $[C_{23}H_{25}NO_4]^+$: 379.1784, found 379.1784.

(3a*S,9a*R**,9b*S**)-3a,9a-Bis(4-methoxyphenyl)octahydro-5*H*-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin-5-one (20e)**



White foam

R_f = 0.32 (ethyl acetate)

Isolated yield: 90%

^{1}H–NMR
(300 MHz, $CDCl_3$)

δ: 6.87 (d, *J*= 8.8 Hz, 2H, $H_{2'}$), 6.73 (d, *J*= 8.8 Hz, 2H, $H_{2''}$), 6.47 (d, *J*= 8.8 Hz, 2H, $H_{3''}$), 6.43 (d, *J*= 8.8 Hz, 2H, $H_{3'}$), 4.23 (td, *J*= 8.7, 4.3 Hz, 1H, H_{2A}), 4.18 (app. q, *J*= 8.5 Hz, 1H, H_{2B}), 3.85 – 3.62 (m, 2H, H_7), 3.65 (s, 6H, H_{10} and H_{11}), 3.37 (dd, *J*= 10.8, 8.9 Hz, 1H, H_{9b}), 2.42 (dddd, *J*= 12.3, 8.7, 7.4, 4.3 Hz, 1H, H_{1A}), 2.16 – 2.02 (m, 3H, H_{1B} and H_9), 1.90 – 1.79 (m, 1H, H_{8A}), 1.66 – 1.49 (m, 1H, H_{8B}).

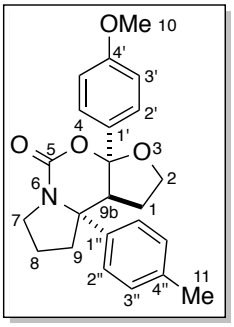
^{13}C–NMR
(75 MHz, $CDCl_3$)

δ: 159.0, 158.5, 152.2, 134.3, 130.8, 127.3, 126.6, 113.5, 112.9, 111.6, 66.9, 66.6, 55.4, 55.3, 52.6, 47.5, 40.3, 26.8, 20.6.

HRMS
(70 eV, IE)

Calculated for $[C_{23}H_{25}NO_5]^+$: 395.1733, found 395.1733.

(3a*S,9a*R**,9b*S**)-3a-(4-Methoxyphenyl)-9a-(*p*-tolyl)octahydro-5*H*-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin-5-one (20f)**



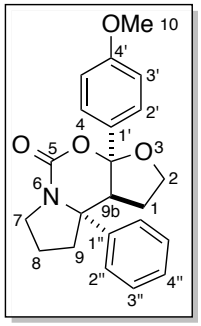
White foam

R_f = 0.42 (ethyl acetate)

Isolated yield: 78%

^{1}H–NMR (300 MHz, $CDCl_3$)	δ: 6.84 (d, *J*= 8.9 Hz, 2H, $H_{2'}$), 6.75 (d, *J*= 8.5 Hz, 2H, $H_{2''}$), 6.70 (d, *J*= 8.5 Hz, 2H, $H_{3''}$), 6.40 (d, *J*= 8.9 Hz, 2H, $H_{3'}$), 4.21 (td, *J*= 9.0, 4.1 Hz, 1H, H_{2A}), 4.19 (app. q, *J*= 8.8 Hz, 1H, H_{2B}), 3.76 (ddd, *J*= 11.0, 9.2, 1.8 Hz, 1H, H_{7A}), 3.72 (td, *J*= 11.0, 7.5 Hz, 1H, H_{7B}), 3.63 (s, 3H, H_{10}), 3.38 (dd, *J*=10.6, 8.8 Hz, 1H, H_{9b}), 2.44 (dddd, *J*= 12.3, 8.7, 7.6, 4.1 Hz, 1H, H_{1A}), 2.16 – 2.02 (m, 3H, H_9 and H_{1B}), 2.13 (s, 3H, H_{11}), 1.92 – 1.77 (m, 1H, H_{8A}), 1.65 – 1.48 (m, 1H, H_{8B}).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 159.0, 152.1, 139.3, 136.5, 130.8, 128.6, 127.3, 125.4, 112.7, 111.5, 66.8, 66.7, 55.3, 52.5, 47.5, 40.3, 26.8, 20.7, 20.6.
HRMS (70 eV, IE)	Calculated for $[C_{23}H_{25}NO_4]^+$: 379.1784, found 379.1786.

(3a*S,9a*R**,9b*S**)-3a-(4-Methoxyphenyl)-9a-phenyloctahydro-5*H*-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin-5-one (20g)**



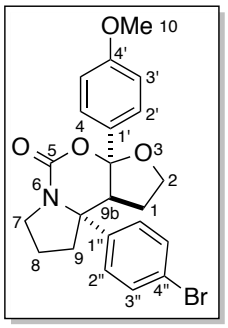
White foam

R_f= 0.35 (ethyl acetate)

Isolated yield: 80%

^{1}H–NMR (300 MHz, $CDCl_3$)	δ: 6.98 – 6.90 (m, 3H, $H_{4''}$ and $H_{2''}$), 6.88 – 6.81 (m, 4H, $H_{2'}$ and $H_{3''}$), 6.39 (d, *J*= 8.8 Hz, 2H, $H_{3'}$), 4.21 (td, *J*= 8.9, 4.3 Hz, 1H, H_{2A}), 4.16 (app. q, *J*= 8.7 Hz, 1H, H_{2B}), 3.85 – 3.66 (m, 2H, H_7), 3.61 (s, 3H, H_{10}), 3.41 (dd, *J*= 10.7, 8.8 Hz, 1H, H_{9b}), 2.45 (dddd, *J*= 12.4, 8.7, 7.4, 4.3 Hz, 1H, H_{1A}), 2.16 – 2.02 (m, 3H, H_{1B} and H_9), 1.88 – 1.77 (m, 1H, H_{8A}), 1.61 – 1.44 (m, 1H, H_{8B}).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 158.9, 152.1, 142.2, 130.6, 128.0, 127.2, 126.9, 125.4, 112.8, 111.5, 67.0, 66.8, 55.2, 52.2, 47.5, 40.4, 26.9, 20.5.
HRMS (70 eV, IE)	Calculated for $[C_{22}H_{23}NO_4]^+$: 365.1627, found 365.1628.

(3a*S,9a*R**,9b*S**)-9a-(4-Bromophenyl)-3a-(4-methoxyphenyl)octahydro-5*H*-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin-5-one (20h)**



White foam

R_f = 0.35 (ethyl acetate)

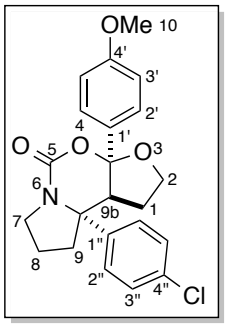
Isolated yield: 78%

^{1}H–NMR (300 MHz, $CDCl_3$): δ: 7.06 (d, *J*= 8.5 Hz, 2H, $H_{3''}$), 6.85 (d, *J*= 8.9 Hz, 2H, $H_{2'}$), 6.71 (d, *J*= 8.5 Hz, 2H, $H_{2''}$), 6.45 (d, *J*= 8.9 Hz, 2H, $H_{3'}$), 4.24 – 4.15 (m, 2H, H_2), 3.82 – 3.66 (m, 2H, H_7), 3.70 (s, 3H, H_{10}), 3.34 (dd, *J*= 10.7, 8.8 Hz, 1H, H_{9b}), 2.46 (dddd, *J*= 12.1, 8.8, 6.9, 4.8 Hz, 1H, H_{1A}), 2.17 – 2.01 (m, 3H, H_{1B} and H_9), 1.93 – 1.81 (m, 1H, H_{8A}), 1.62 – 1.45 (m, 1H, H_{8B}).

^{13}C–NMR (75 MHz, $CDCl_3$): δ: 159.3, 151.9, 141.6, 131.0, 130.2, 127.3, 127.2, 120.8, 112.9, 111.4, 66.9, 66.6, 55.4, 52.4, 47.6, 40.1, 26.6, 20.5.

HRMS (70 eV, IE): Calculated for $[C_{22}H_{22}BrNO_4]^+$: 443.0732, found 443.0732.

(3a*S,9a*R**,9b*S**)-9a-(4-Chlorophenyl)-3a-(4-methoxyphenyl)octahydro-5*H*-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin-5-one (20i)**



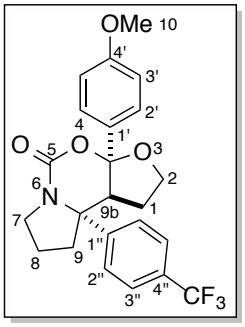
White foam

R_f = 0.28 (ethyl acetate)

Isolated yield: 80%

^{1}H–NMR (600 MHz, $CDCl_3$)	δ: 6.90 (d, *J*= 8.5 Hz, 2H, $H_{3''}$), 6.85 (d, *J*= 8.8 Hz, 2H, $H_{2'}$), 6.76 (d, *J*= 8.5 Hz, 2H, $H_{2''}$), 6.44 (d, *J*= 8.8 Hz, 2H, $H_{3'}$), 4.17 (td, *J*= 9.0, 4.1 Hz, 1H, H_{2A}), 4.18 (app. q, *J*= 8.8 Hz, 1H, H_{2B}), 3.77 (ddd, *J*= 11.0, 9.2, 1.8 Hz, 1H, H_{7A}), 3.70 (td, *J*= 11.0, 7.5 Hz, 1H, H_{7B}), 3.67 (s, 3H, H_{10}), 3.34 (dd, *J*= 10.7, 8.7 Hz, 1H, H_{9b}), 2.45 (dddd, *J*= 12.3, 8.7, 7.6, 4.1 Hz, 1H, H_{1A}), 2.14 – 2.03 (m, 3H, H_9 and H_{1B}), 1.86 (dtt, *J*= 12.7, 7.5, 1.8 Hz, 1H, H_{8A}), 1.53 (dtdd, *J*= 12.7, 10.5, 9.2, 6.6 Hz, 1H, H_{8B}).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 159.3, 152.0, 141.1, 132.8, 130.3, 128.1, 127.3, 127.0, 113.0, 111.4, 66.9, 66.6, 55.4, 52.5, 47.6, 40.2, 26.7, 20.5.
HRMS (70 eV, IE)	Calculated for $[C_{22}H_{22}ClNO_4]^+$: 399.1237, found 399.1239.

(3a*S,9a*R**,9b*S**)-3a-(4-Methoxyphenyl)-9a-(4(trifluoromethyl)phenyl)-octahydro-5*H*-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin-5-one (20j)**



White foam

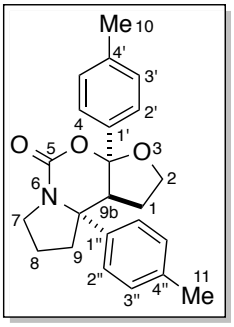
R_f= 0.30 (ethyl acetate)

Isolated yield: 25%

^{1}H–NMR (300 MHz, $CDCl_3$)	δ: 7.22 (d, *J*= 8.0 Hz, 2H, $H_{3''}$), 6.99 (d, *J*= 8.0 Hz, 2H, $H_{2''}$), 6.85 (d, *J*= 8.8 Hz, 2H, $H_{2'}$), 6.40 (d, *J*= 8.8 Hz, 2H, $H_{3'}$), 4.25 (td, *J*= 9.0, 4.1 Hz, 1H, H_{2A}), 4.23 (app. q, *J*= 8.8 Hz, 1H, H_{2B}), 3.81 (ddd, *J*= 11.0, 9.2, 1.8 Hz, 1H, H_{7A}), 3.76 (td, *J*= 11.0, 7.5 Hz, 1H, H_{7B}), 3.62 (s, 3H, H_{10}), 3.40 (dd, *J*= 10.7, 8.8 Hz, 1H, H_{9b}), 2.50 (dddd, *J*= 12.3, 8.7, 7.6, 4.1 Hz, 1H, H_{1A}), 2.24 – 2.06 (m, 3H, H_9 and H_{1B}), 1.96 – 1.86 (m, 1H, H_{8A}), 1.54 (dtdd, *J*= 12.7, 10.5, 9.2, 6.6 Hz, 1H, H_{8B}).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 159.4, 152.0, 146.6, 129.9, 129.4 (q, $J_{C\text{-}F}$= 33.1 Hz), 127.3, 126.1, 125.1, 125.0, 123.9 (q, $J_{C\text{-}F}$= 271.0 Hz) 113.0, 111.4, 66.9, 66.9, 55.1, 52.4, 47.7, 40.3, 26.7, 20.6.

^{19}F–NMR (282 MHz, $CDCl_3$)	δ: –62.8.
HRMS (70 eV, IE)	Calculated for $[C_{23}H_{22}F_3NO_4]^+$: 433.1495, found 433.1499.

(3a*S,9a*R**,9b*S**)-3a,9a-Di-*p*-tolyloctahydro-5*H*-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin-5-one (20k)**



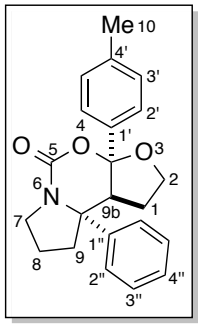
White foam

R_f = 0.33 (ethyl acetate)

Isolated yield: 50%

^{1}H–NMR (300 MHz, $CDCl_3$)	δ: 6.81 (d, *J*= 8.3 Hz, 2H, $H_{2'}$), 6.74 – 6.66 (m, 6H, $H_{3'}$, $H_{3''}$ and $H_{2''}$), 4.23 (td, *J*= 8.7, 4.3 Hz, 1H, H_{2A}), 4.18 (app. q, *J*= 8.8 Hz, 1H, H_{2B}), 3.82 – 3.72 (m, 1H, H_{7A}), 3.70 (td, *J*= 11.2, 7.6 Hz, 1H, H_{7B}), 3.40 (dd, *J*= 10.7, 8.7 Hz, 1H, H_{9b}), 2.43 (dddd, *J*= 12.5, 8.4, 7.6, 4.3 Hz, 1H, H_{1A}), 2.16 – 2.03 (m, 3H, H_{1B} and H_9), 2.13 and 2.12 (2s, 6H, H_{10} and H_{11}), 1.88 – 1.78 (m, 1H, H_{8A}), 1.64 – 1.47 (m, 1H, H_{8B}).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 152.3, 139.1, 137.3, 136.7, 135.6, 128.6, 127.9, 125.9, 125.4, 111.7, 67.1, 66.8, 52.6, 47.5, 40.2, 26.8, 20.9, 20.7, 20.6.
HRMS (70 eV, IE)	Calculated for $[C_{23}H_{25}NO_3]^+$: 363.1829, found 363.1829.

(3a*S,9a*R**,9b*S**)-9a-Phenyl-3a-(*p*-tolyl)octahydro-5*H*-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin-5-one (20l)**



White foam

R_f = 0.45 (ethyl acetate)

Isolated yield: 70%

^{1}H–NMR
(300 MHz, $CDCl_3$)

δ: 6.95 – 6.89 (m, 3H, $H_{4''}$ and $H_{2''}$), 6.86 – 6.81 (m, 4H, $H_{3''}$ and $H_{2'}$), 6.67 (d, *J*= 8.2 Hz, 2H, $H_{3'}$), 4.24 (td, *J*= 8.7, 4.2 Hz, 1H, H_{2A}), 4.19 (app. q, *J*= 8.6 Hz, 1H, H_{2B}), 3.83 – 3.75 (m, 1H, H_{7A}), 3.73 (td, *J*= 11.2, 7.3 Hz, 1H, H_{7B}), 3.45 (dd, *J*=10.7, 8.7 Hz, 1H, H_{9b}), 2.47 (dddd, *J*= 12.4, 8.7, 7.4, 4.3 Hz, 1H, H_{1A}), 2.19 – 2.03 (m, 3H, H_{1B}, H_9), 2.11 (s, 3H, H_{10}), 1.90 – 1.80 (m, 1H, H_{8A}), 1.63 – 1.46 (m, 1H, H_{8B}).

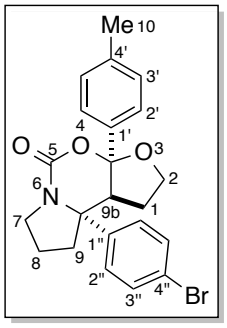
^{13}C–NMR
(75 MHz, $CDCl_3$)

δ: 152.2, 142.2, 137.4, 135.5, 128.0, 128.0, 126.8, 125.8, 125.5, 111.5, 67.0, 52.4, 47.5, 40.5, 27.0, 21.0, 20.6

HRMS
(70 eV, IE)

Calculated for $[C_{22}H_{23}NO_3]^+$: 349.1678, found 349.1678.

(3a*S,9a*R**,9b*S**)-9a-(4-Bromophenyl)-3a-(*p*-tolyl)octahydro-5*H*-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin-5-one (20m)**



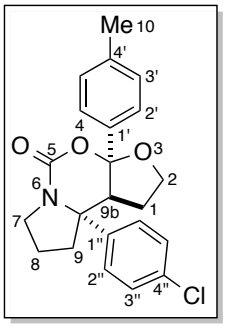
White foam

R_f = 0.38 (ethyl acetate)

Isolated yield: 65%

^{1}H–NMR (300 MHz, $CDCl_3$)	δ: 7.03 (d, *J*=8.5 Hz, 2H, $H_{2'}$), 6.83 (d, *J*= 8.4 Hz, 2H, $H_{3''}$), 6.74 (d, *J*= 8.4 Hz, 2H, $H_{2''}$), 6.69 (d, *J*=8.5 Hz, 2H, $H_{3'}$), 4.23 (td, *J*= 8.9, 4.3 Hz, 1H, H_{2A}), 4.19 (app. q, *J*= 8.8 Hz, 1H, H_{2B}), 3.81 – 3.72 (m, 1H, H_{7A}), 3.71 (td, *J*= 11.4, 7.0 Hz, 1H, H_{7B}), 3.35 (dd, *J*=10.7, 8.7 Hz, 1H, H_{9b}), 2.45 (dddd, *J*= 12.4, 8.7, 7.6, 4.3 Hz, 1H, H_{1A}), 2.20 (s, 3H, H_{10}), 2.17 – 2.02 (m, 3H, H_{1B} and H_9), 1.93 – 1.82 (m, 1H, H_{8A}), 1.62 – 1.45 (m, 1H, H_{8B}).
^{13}C–NMR ($CDCl_3$)	δ: 151.9, 141.3, 138.0, 135.0, 130.9, 128.2, 127.2, 125.8, 121.0, 111.3, 66.9, 66.6, 52.3, 47.5, 40.0, 26.6, 20.9, 20.5.
HRMS (70 eV, IE)	Calculated for $[C_{22}H_{22}BrNO_3]^+$: 427,0778, found 427,0774.

(3a*S,9a*R**,9b*S**)-9a-(4-Chlorophenyl)-3a-(*p*-tolyl)octahydro-5*H*-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin-5-one (20n)**



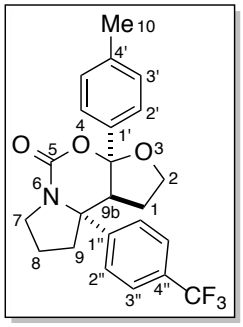
White foam

R_f = 0.35 (ethyl acetate)

Isolated yield: 62%

^{1}H–NMR (300 MHz, $CDCl_3$)	δ: 6.89 (d, *J*= 8.7 Hz, 2H, $H_{3''}$), 6.84 (d, *J*= 8.2 Hz, 2H, $H_{2'}$), 6.76 (d, *J*= 8.7 Hz, 2H, $H_{2''}$), 6.74 (d, *J*= 8.2 Hz, 2H, $H_{3'}$), 4.25 (td, *J*= 8.9, 4.4 Hz, 1H, H_{2A}), 4.21 (app. q, *J*= 8.8 Hz, 1H, H_{2B}), 3.81 – 3.73 (m, 1H, H_{7A}), 3.72 (td, *J*= 11.7, 7.0 Hz, 1H, H_{7B}), 3.37 (dd, *J*= 10.8, 8.7 Hz, 1H, H_{9b}), 2.46 (dddd, *J*= 12.5, 8.7, 7.2, 4.4 Hz, 1H, H_{1A}), 2.18 (s, 3H, H_{10}), 2.17 – 2.03 (m, 3H, H_{1B} and H_9), 1.93 – 1.82 (m, 1H, H_{8A}), 1.62 – 1.45 (m, 1H, H_{8B}).
^{13}C–NMR ($CDCl_3$)	δ: 152.0, 140.9, 138.0, 135.1, 133.0, 128.3, 128.0, 127.0, 125.9, 111.4, 67.0, 66.6, 52.5, 47.6, 40.2, 26.7, 21.0, 20.6.
HRMS (70 eV, IE)	Calculated for $[C_{22}H_{22}ClNO_3]^+$: 383.1283, found 383.1287.

(3a*S,9a*R**,9b*S**)-3a-(*p*-Tolyl)-9a-(4-(trifluoromethyl)phenyl)octahydro-5*H*-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin-5-one (20o)**



White foam

R_f = 0.35 (ethyl acetate)

Isolated yield: 62%

^{1}H–NMR
(300 MHz, $CDCl_3$)

δ: 7.17 (d, *J*= 8.1 Hz, 2H, $H_{2''}$), 6.97 (d, *J*= 8.1 Hz, 2H, $H_{3''}$), 6.82 (d, *J*= 8.2 Hz, 2H, $H_{3'}$), 6.68 (d, *J*= 8.2 Hz, 2H, $H_{2'}$), 4.28 (td, *J*= 8.8, 4.3 Hz, 1H, H_{2A}), 4.23 (apparent q, *J*= 8.7 Hz, 1H, H_{2B}), 3.85 – 3.78 (m, 1H, H_{7A}), 3.76 (td, *J*= 11.4, 6.7 Hz, 1H, H_{7B}), 3.41 (dd, *J*= 10.8, 8.8 Hz, 1H, H_{9b}), 2.50 (dddd, *J*= 12.3, 8.8, 7.1, 4.4 Hz, 1H, H_{1A}), 2.24 – 2.07 (m, 3H, H_{1B}, H_9), 2.11 (s, 3H, H_{10}), 1.96 – 1.86 (m, 1H, H_{8A}), 1.63 – 1.48 (m, 1H, H_{8B}).

^{13}C–NMR
(75 MHz, $CDCl_3$)

δ: 152.0, 146.5, 138.1, 134.8, 129.3 ($J_{C\text{-}F}$= 31.9 Hz), 128.3, 126.1, 125.90, 125.0, 125.0, 123.9 ($J_{C\text{-}F}$= 272.6 Hz), 111.4, 67.0, 66.9, 52.4, 47.7, 40.3, 26.6, 20.7, 20.6

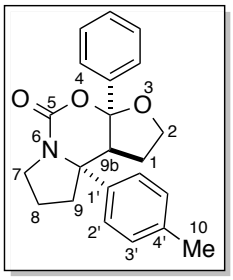
^{19}F–NMR
(282 MHz, $CDCl_3$)

δ: –62.8.

HRMS
(70 eV, IE)

Calculated for $[C_{23}H_{22}F_3NO_3]^+$: 417.1546, found 417.1548.

(3a*S,9a*R**,9b*S**)-3a-Phenyl-9a-(*p*-tolyl)octahydro-5*H*-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin-5-one (20p)**



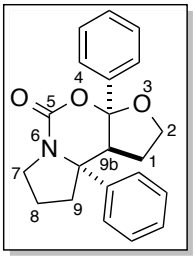
White foam

R_f = 0.38 (ethyl acetate)

Isolated yield: 48%

^{1}H–NMR (300 MHz, $CDCl_3$)	δ: 6.99 – 6.86 (m, 5H, H_{Ph}), 6.72 (br s, 4H, $H_{3'}$ and $H_{2'}$), 4.26 (td, *J*= 8.8, 4.3 Hz, 1H, H_{2A}), 4.23 (app. q, *J*= 8.7 Hz, 1H, H_{2B}), 3.82 (ddd, *J*= 11.2, 9.8, 1.8 Hz, 1H, H_{7A}), 3.72 (td, *J*= 11.2, 7.4 Hz, 1H, H_{7B}), 3.46 (dd, *J*= 10.6, 8.8 Hz, 1H, H_{9b}), 2.48 (dddd, *J*= 12.4, 8.8, 7.5, 4.4 Hz, 1H, H_{1A}), 2.21 – 2.05 (m, 3H, H_{1B} and H_9), 2.12 (s, 3H, H_{10}), 1.91 – 1.81 (m, 1H, H_{8A}), 1.68 – 1.50 (m, 1H, H_{8B}).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 152.1, 139.1, 138.7, 136.8, 128.7, 127.5, 127.4, 126.0, 125.5, 111.5, 67.2, 66.8, 52.8, 47.6, 40.4, 27.0, 20.8, 20.6.
HRMS (70 eV, IE)	Calculated for $[C_{22}H_{23}NO_3]^+$: 349.1672, found 349.1677.

(3a*S,9a*R**,9b*S**)-3a,9a-Diphenyloctahydro-5*H*-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin-5-one (20q)**



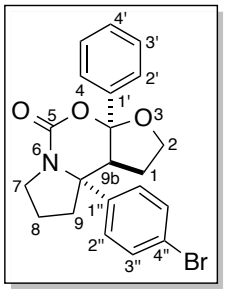
White foam

R_f = 0.38 (ethyl acetate)

Isolated yield: 40%

^{1}H–NMR (300 MHz, $CDCl_3$)	δ: 6.99 – 6.84 (m, 10H, H_{Ph}), 4.27 (td, *J*= 8.9, 4.3 Hz, 1H, H_{2A}), 4.23 (app. q, *J*= 8.6 Hz, 1H, H_{2B}), 3.88 – 3.76 (m, 1H, H_{7A}), 3.74 (td, *J*= 11.1, 7.1 Hz, 1H, H_{7B}), 3.49 (dd, *J*= 10.6, 8.8 Hz, 1H, H_{9b}), 2.48 (dddd, *J*= 12.4, 8.8, 7.5, 4.4 Hz, 1H, H_{1A}), 2.22 – 2.07 (m, 3H, H_{1B} and H_9), 1.91 – 1.81 (m, 1H, H_{8A}), 1.65 – 1.47 (m, 1H, H_{8B}).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 152.1, 142.1, 138.6, 128.1, 127.8, 127.4, 127.1, 125.9, 125.5, 111.4, 67.1, 67.0, 52.5, 47.6, 40.5, 27.1, 20.6.
HRMS (70 eV, IE)	Calculated for $[C_{21}H_{21}NO_3]^+$: 335.1516, found 335.1519.

(3a*S,9a*R**,9b*S**)-9a-(4-Bromophenyl)-3a-phenyloctahydro-5*H*-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin-5-one (20r)**



White foam

R_f = 0.30 (ethyl acetate)

Isolated yield: 45%

^{1}H–NMR
(300 MHz, $CDCl_3$)

δ: 7.08 – 7.01 (m, 1H, $H_{4'}$), 7.04 (d, *J*= 8.6 Hz, 2H, $H_{3''}$), 6.99 – 6.92 (m, 4H, $H_{3'}$ and $H_{2'}$), 6.72 (d, *J*= 8.6 Hz, 2H, $H_{2''}$), 4.27 (td, *J*= 8.9, 4.5 Hz, 1H, H_{2A}), 4.23 (app. q, *J*= 8.8 Hz, 1H, H_{2B}), 3.89 – 3.76 (m, 1H, H_{7A}), 3.73 (td, *J*= 11.3, 7.2 Hz, 1H, H_{7B}), 3.42 (dd, *J*= 10.6, 8.8 Hz, 1H, H_{9b}), 2.49 (dddd, *J*= 12.4, 8.7, 7.2, 4.7 Hz, 1H, H_{1A}), 2.22 – 2.06 (m, 3H, H_{1B} and H_9), 1.94 – 1.84 (m, 1H, H_{8A}), 1.64 – 1.49 (m, 1H, H_{8B}).

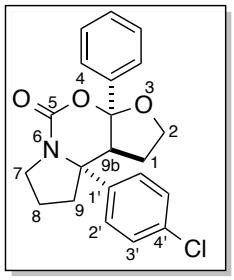
^{13}C–NMR
(75 MHz, $CDCl_3$)

δ: 152.0, 141.4, 138.2, 131.1, 128.0, 127.7, 127.3, 126.0, 121.2, 111.4, 67.2, 66.7, 52.7, 47.7, 40.3, 26.9, 20.6.

HRMS
(70 eV, IE)

Calculated for $[C_{21}H_{20}BrNO_3]^+$: 413.0621, found 413.0626.

(3a*S,9a*R**,9b*S**)-9a-(4-Chlorophenyl)-3a-phenyloctahydro-5*H*-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin-5-one (20s)**



White foam

R_f = 0.30 (ethyl acetate)

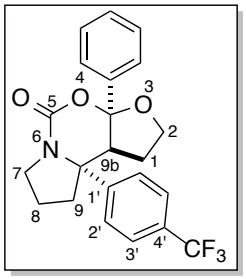
Isolated yield: 45%

^{1}H–NMR
(300 MHz, $CDCl_3$)

δ: 7.07 – 6.94 (m, 5H, H_{Ph}), 6.9 (d, *J*= 8.7 Hz, 2H, $H_{3'}$), 6.78 (d, *J*= 8.7 Hz, 2H, $H_{2'}$), 4.27 (td, *J*= 8.9, 4.5 Hz, 1H, H_{2A}), 4.23 (app. q, *J*= 8.8 Hz, 1H, H_{2B}), 3.84 – 3.76 (m, 1H, H_{7A}), 3.74 (td, *J*= 11.3, 7.2 Hz, 1H, H_{7B}), 3.43 (dd, *J*= 10.7, 8.8 Hz, 1H, H_{9b}), 2.48 (dddd, *J*= 12.5, 8.9, 7.2, 4.5 Hz, 1H, H_{1A}), 2.21 – 2.03 (m, 3H, H_{1B} and H_9), 1.97 – 1.83 (m, 1H, H_{8A}), 1.70 – 1.47 (m, 1H, H_{8B}).

^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 151.9, 140.9, 138.3, 133.1, 128.1, 128.0, 127.7, 127.0, 126.0, 111.4, 67.2, 66.7, 52.7, 47.7, 40.4, 26.9, 20.6.
HRMS (70 eV, IE)	Calculated for $[C_{21}H_{20}ClNO_3]^+$: 369.1126, found 369.1122.

(3a*S,9a*R**,9b*S**)-3a-Phenyl-9a-(4-(trifluoromethyl)phenyl)octahydro-5*H*-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin-5-one (20t)**



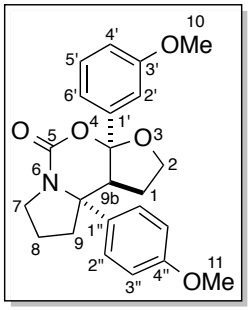
White foam

R_f = 0.40 (ethyl acetate)

Isolated yield: 10%

^{1}H–NMR (300 MHz, $CDCl_3$)	δ: 7.19 (d, *J*= 8.1 Hz, 2H, $H_{3'}$), 7.00 – 6.87 (m, 7H, $H_{2'}$ and H_{Ph}), 4.30 (td, *J*= 8.9, 4.6 Hz, 1H, H_{2A}), 4.26 (app. q, *J*= 8.8 Hz, 1H, H_{2B}), 3.88 – 3.78 (m, 1H, H_{7A}), 3.77 (td, *J*= 11.2, 7.1 Hz, 1H, H_{7B}), 3.46 (dd, *J*= 10.7, 8.8 Hz, 1H, H_{9b}), 2.53 (dddd, *J*= 12.4, 8.8, 7.1, 4.8 Hz, 1H, H_{1A}), 2.26 – 2.09 (m, 3H, H_{1B} and H_9), 1.97 – 1.87 (m, 1H, H_{8A}), 1.68 – 1.47 (m, 1H, H_{8B}).
^{19}F–NMR (282 MHz, $CDCl_3$)	δ: –62.8.
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 151.9, 146.4, 138.0, 129.4 (q, $J_{C\text{-}F}$= 33.1 Hz), 128.2, 127.7, 126.1, 125.9, 125.1, 125.0, 123.9 (q, $J_{C\text{-}F}$= 271.0 Hz), 111.3, 67.2, 66.9, 52.6, 47.7, 40.4, 29.9, 26.8, 20.6.
HRMS (70 eV, IE)	Calculated for $[C_{22}H_{20}F_3NO_3]^+$: 403.1390, found 403.1393.

(3a*S,9a*R**,9b*S**)-3a-(3-Methoxyphenyl)-9a-(4-methoxyphenyl)octahydro-5*H*-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin-5-one (20u)**



White foam

R_f = 0.32 (ethyl acetate)

Isolated yield: 78%

^{1}H–NMR
(400 MHz, $CDCl_3$)

δ: 6.89 (t, *J*= 8.0 Hz, 1H, $H_{5'}$), 6.77 (d, *J*= 8.7 Hz, 2H, $H_{2''}$), 6.62 (ddd, *J*= 8.0, 2.2, 0.8 Hz, 1H, $H_{6'}$), 6.52 (ddd, *J*= 8.0, 2.2, 0.8 Hz, 1H, $H_{4'}$), 6.48 (d, *J* = 8.7 Hz, 2H, $H_{3''}$), 6.46 (t, *J* = 2.2 Hz, 1H, $H_{2'}$), 4.25 (td, *J*= 9.0, 4.3 Hz, 1H, H_{2A}), 4.22 (app. q, *J*= 8.7 Hz, 1H, H_{2B}), 3.87 – 3.78 (m, 1H, H_{7A}), 3.72 (td, *J*= 11.2, 7.6 Hz, 1H, H_{7B}), 3.67 and 3.63 (2s, 6H, H_{10} and H_{11}), 3.44 (dd, *J*= 10.5, 8.8 Hz, 1H, H_{9b}), 2.46 (dddd, *J*= 12.3, 8.6, 7.7, 4.2 Hz, 1H, H_{1A}), 2.16 – 2.05 (m, 3H, H_{1B} and H_9), 1.91 – 1.83 (m, 1H, H_{8A}), 1.68 – 1.55 (m, 1H, H_{8B}).

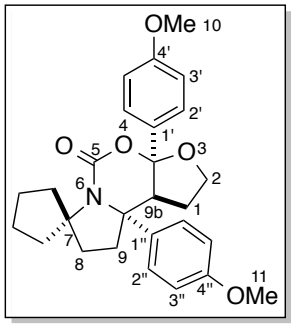
^{13}C–NMR
(75 MHz, $CDCl_3$)

δ: 158.7, 158.6, 152.0, 140.4, 134.2, 128.6, 126.7, 118.4, 113.5, 113.5, 111.9, 111.4, 67.2, 66.6, 55.4, 55.2, 53.0, 47.6, 40.3, 27.0, 20.6.

HRMS
(70 eV, IE)

Calculated for $[C_{23}H_{25}NO_5]^+$: 395.1733, found 395.1734.

(3a'*S,9a'*R**,9b'*S**)-3a',9a'-Bis(4-methoxyphenyl)hexahydro-5'*H*,8'*H*-spiro[cyclopentane-1,7'-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin]-5'-one (20v)**



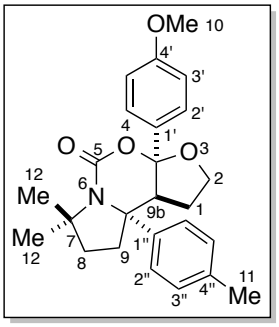
White foam

R_f = 0.56 (hexane:ethyl acetate, 1:2).

Isolated yield: 68%

^{1}H–NMR (400 MHz, $CDCl_3$)	δ: 6.84 (d, *J*= 8.4 Hz, 2H, $H_{2''}$), 6.83 (d, *J*= 8.9 Hz, 2H, $H_{2'}$), 6.49 (d, *J*= 8.4 Hz, 2H, $H_{3''}$), 6.43 (d, *J*= 8.9 Hz, 2H, $H_{3'}$), 4.18 (t, *J*= 7.3 Hz, 2H, H_2), 3.67 and 3.66 (2s, 6H, H_{10} and H_{11}), 3.38 (t, *J*= 9.4 Hz, 1H, H_{9b}), 3.12 – 3.02 (m, 1H, H_{8A}), 2.52 – 2.36 (m, 2H, H_{1A} and H_{9A}), 2.20 – 1.99 (m, 3H, H_{1B} and $H_{Cyclopent}$), 1.97 – 1.86 (m, 2H, $H_{Cyclopent}$), 1.76 – 1.45 (m, 6H, H_{8B}, H_{9B} and $H_{Cyclopent}$).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 158.7, 158.6, 150.6, 134.5, 131.8, 127.2, 127.2, 113.4, 112.7, 111.4, 72.5, 68.3, 67.0, 55.4, 55.3, 53.6, 38.0, 37.1, 36.4, 35.3, 27.2, 24.7.
HRMS (70 eV, IE)	Calculated for $[C_{27}H_{31}NO_5]^+$: 449.2202, found 449.2202.

(3a*S,9a*R**,9b*S**)-3a-(4-Methoxyphenyl)-7,7-dimethyl-9a-(*p*-tolyl)octahydro-5*H*-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin-5-one (20w)**



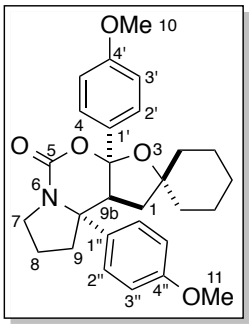
White foam

R_f = 0.33 (hexane:ethyl acetate, 1:1).

Isolated yield: 78%

^{1}H–NMR (300 MHz, $CDCl_3$)	δ: 6.87 (d, *J*= 8.0 Hz, 2H, $H_{2''}$), 6.84 (d, *J*= 8.9 Hz, 2H, $H_{2'}$), 6.76 (d, *J*= 8.0 Hz, 2H, $H_{3''}$), 6.40 (d, *J*= 8.9 Hz, 2H, $H_{3'}$), 4.20 (td, *J*= 9.0, 4.7 Hz, 1H, H_{2A}), 4.15 (app. q, *J*= 8.7 Hz, 1H, H_{2B}), 3.65 (s, 3H, H_{10}), 3.34 (t, *J*= 9.5 Hz, 1H, H_{9b}), 2.48 (dddd, *J*= 12.4, 9.1, 7.7, 4.7 Hz, 1H, H_{1A}), 2.26 – 2.16 (m, 2H, H_9), 2.14 (s, 3H, H_{11}), 2.02 (dddd, *J*= 12.4, 7.0, 5.8, 1.4 Hz, 1H, H_{1B}), 1.75 (s, 3H, H_{12}), 1.67 – 1.56 (m, 2H, H_8), 1.54 (s, 3H, H_{12}).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 158.8, 150.9, 139.6, 136.7, 131.6, 128.5, 127.2, 126.2, 112.6, 111.4, 69.5, 66.9, 63.1, 55.3, 53.4, 37.2, 37.0, 27.6, 27.1, 24.6, 20.7.
HRMS (70 eV, IE)	Calculated for $[C_{25}H_{29}NO_4]^+$: 407.2097, found 407.2098.

(3a'*S,9a'*R**,9b'*S**)-3a',9a'-Bis(4-methoxyphenyl)hexahydro-1'*H*,5'*H*-spiro[cyclohexane-1,2'-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin]-5'-one (20x)**



White foam

R_f = 0.30 (hexane:ethyl acetate, 1:2).

Isolated yield: 68%

^{1}H–NMR
(300 MHz, $CDCl_3$)

δ: 6.87 (d, *J*= 8.8 Hz, 2H, $H_{3'}$), 6.72 (d, *J*= 8.8 Hz, 2H, $H_{3''}$), 6.43 (d, *J*= 8.8 Hz, 2H, $H_{2''}$), 6.41 (d, *J*= 8.8 Hz, 2H, $H_{2'}$), 3.82 – 3.72 (m, 1H, H_{7A}), 3.71 (td, *J*= 11.3, 7.1 Hz, 1H, H_{7B}), 3.63 (2s, 6H, H_{10} and H_{11}), 3.42 (dd, *J*= 11.9, 8.1 Hz, 1H, H_{9b}), 2.32 (dd, *J*= 12.5, 8.1 Hz, 1H, H_{1A}), 2.05 – 1.98 (m, 2H, H_{1B}, H_{9A}), 1.88 – 1.31 (m, 13H, H_8, H_{9B} and H_{Cy}).

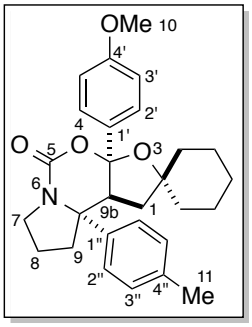
^{13}C–NMR
(75 MHz, $CDCl_3$)

δ: 158.8, 158.4, 152.1, 134.4, 131.2, 127.5, 126.6, 113.3, 112.8, 111.4, 83.8, 66.4, 55.3, 55.3, 52.2, 47.5, 40.0, 38.0, 37.9, 25.2, 23.8, 23.5, 20.5.

HRMS
(70 eV, IE)

Calculated for $[C_{28}H_{33}NO_5]^+$: 463.2359, found 463.2359.

(3a'*S,9a'*R**,9b'*S**)-3a'-(4-Methoxyphenyl)-9a'-(*p*-tolyl)hexahydro-1'*H*,5'*H*-spiro[cyclohexane-1,2'-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin]-5'-one (20y)**



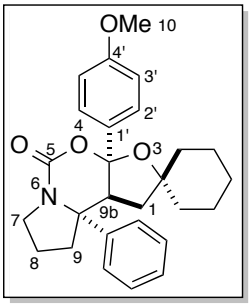
White foam

R_f = 0.58 (hexane:ethyl acetate, 1:2).

Isolated yield: 65%

^{1}H–NMR (300 MHz, $CDCl_3$)	δ: 6.89 (d, *J*= 8.8 Hz, 2H, $H_{2'}$), 6.74 (br s, 4H, $H_{3''}$ and $H_{2''}$), 6.41 (d, *J*= 8.8 Hz, 2H, $H_{3'}$), 3.85 – 3.76 (m, 1H, H_{7A}), 3.75 (td, *J*= 11.1, 7.1 Hz, 1H, H_{7B}), 3.66 (s, 3H, H_{10}), 3.48 (dd, *J*= 11.9, 8.2 Hz, 1H, H_{9b}), 2.36 (dd, *J*= 12.4, 8.2 Hz, 1H, H_{1A}), 2.14 (s, 3H, H_{11}), 2.10 – 2.03 (m, 2H, H_{1B}, H_{9A}), 1.90 – 1.34 (m, 13H, H_8, H_{9B} and H_{Cy}).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 159.0, 152.2, 139.4, 136.4, 131.1, 128.6, 127.6, 125.5, 112.7, 111.5, 83.8, 66.7, 55.3, 52.2, 47.6, 40.1, 40.0, 38.0, 38.0, 25.2, 23.8, 23.6, 20.7, 20.5.
HRMS (70 eV, IE)	Calculated for $[C_{28}H_{33}NO_4]^+$: 447.2410, found 447.2409.

(3a'*S,9a'*R**,*9b'S**)-3a'-(4-Methoxyphenyl)-9a'-phenylhexahydro-1'*H*,5'*H*-spiro[cyclohexane-1,2'-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin]-5'-one (20z)**



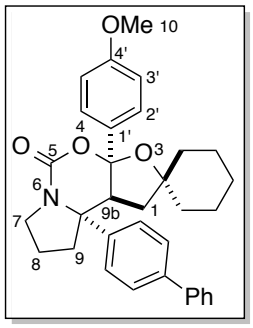
White foam

R_f = 0.55 (hexane:ethyl acetate, 1:2).

Isolated yield: 45%

^{1}H–NMR (300 MHz, $CDCl_3$)	δ: 6.97 – 6.83 (m, 5H, H_{Ph}), 6.89 (d, *J*= 9.0 Hz, 2H, $H_{2'}$), 6.40 (d, *J*= 9.0 Hz, 2H, $H_{3'}$), 3.83 – 3.75 (m, 1H, H_{7A}), 3.75 (td, *J*= 11.3, 6.7 Hz, 1H, H_{7B}), 3.64 (s, 3H, H_{10}), 3.49 (dd, *J*= 11.9, 8.1 Hz, 1H, H_{9b}), 2.36 (dd, *J*= 12.5, 8.1 Hz, 1H, H_{1A}), 2.09 – 2.03 (m, 2H, H_{1B} and H_{9A}), 1.88 – 1.32 (m, 13H, H_8, H_{9B} and H_{Cy}).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 158.9, 152.2, 142.4, 131.0, 128.0, 127.6, 126.9, 125.5, 112.9, 111.4, 83.8, 66.9, 55.4, 51.9, 47.6, 40.3, 40.0, 38.1, 25.3, 23.8, 23.6, 20.5.
HRMS (70 eV, IE)	Calculated for $[C_{27}H_{31}NO_4]^+$: 433.2248, found 433.2249.

(3a'*S,9a'*R**,9b'*S**)-9a'-([1,1'-Biphenyl]-4-yl)-3a'-(4-methoxyphenyl)hexahydro-1'*H*,5'*H*-spiro[cyclohexane-1,2'-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin]-5'-one (20aa)**



White foam

R_f = 0.53 (hexane:ethyl acetate, 1:2).

Isolated yield: 50%

^{1}H–NMR (300 MHz, $CDCl_3$)

δ: 7.43 – 7.28 (m, 5H, H_{BiPh}), 7.12 (d, *J*= 8.8 Hz, 2H, $H_{2'}$), 6.93 – 6.86 (m, 4H, H_{BiPh}), 6.37 (d, *J*= 8.8 Hz, 2H, $H_{3'}$), 3.91 – 3.79 (m, 1H, H_{7A}), 3.77 (td, *J*= 11.1, 7.3 Hz, 1H, H_{7B}), 3.52 (dd, *J*= 11.9, 8.2 Hz, 1H, H_{9b}), 3.44 (s, 3H, H_{10}), 2.37 (dd, *J*= 12.5, 8.2 Hz, 1H, H_{1A}), 2.17 – 2.04 (m, 2H, H_{1B} and H_{9A}), 1.94 – 1.32 (m, 13H, H_8, H_{9B} and H_{Cy}).

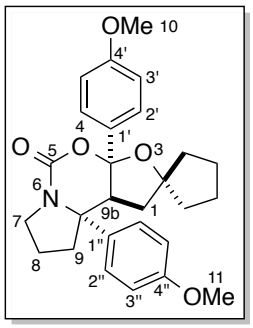
^{13}C–NMR ($CDCl_3$)

δ: 158.9, 152.1, 141.3, 140.6, 140.0, 130.8, 128.7, 127.5, 127.3, 127.0, 126.6, 125.9, 112.6, 111.4, 83.8, 66.7, 55.0, 52.2, 47.6, 39.9, 39.9, 38.0, 37.8, 25.1, 23.7, 23.5, 20.5.

HRMS (70 eV, IE)

Calculated for $[C_{33}H_{35}NO_4]^+$: 509,2561, found 509,2567.

(3a'*S,9a'*R**,9b'*S**)-3a',9a'-bis(4-methoxyphenyl)hexahydro-1'*H*,5'*H*-spiro[cyclopentane-1,2'-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin]-5'-one (20ab)**



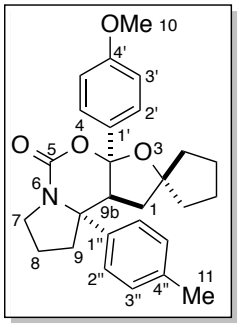
White foam

R_f = 0.53 (hexane:ethyl acetate, 1:2).

Isolated yield: 72%

^{1}H–NMR (300 MHz, $CDCl_3$)	δ: 6.88 (d, *J*= 9.0 Hz, 2H, $H_{2'}$), 6.73 (d, *J*= 8.9 Hz, 2H, $H_{2''}$), 6.43 (d, *J*= 8.9, Hz, 2H, $H_{3''}$), 6.42 (d, *J*= 9.0 Hz, 2H, $H_{3'}$), 3.78 – 3.68 (m, 2H, H_7), 3.64 and 3.63 (2 s, 6H, H_{10}, H_{11}), 3.44 (dd, *J*= 12.0, 8.1 Hz, 1H, H_{9b}), 2.38 (dd, *J*= 12.5, 8.1 Hz, 1H, H_{1A}) 2.17 – 1.94 (m, 5H, H_{1B} and H_9, $H_{Cyclopent}$), 1.86 – 1.48 (m, 8H, H_8 and $H_{Cyclopent}$).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 158.9, 158.4, 152.2, 134.4, 131.1, 127.4, 126.6, 113.4, 112.8, 111.5, 91.8, 66.5, 55.3, 55.3, 52.9, 47.5, 40.8, 40.1, 38.0, 23.9, 23.7, 20.5.
HRMS (70 eV, IE)	Calculated for $[C_{27}H_{31}NO_5]^+$: 449.2202, found 449.2205.

(3a'*S,9a'*R**,9b'*S**)-3a'-(4-Methoxyphenyl)-9a'-(*p*-tolyl)hexahydro-1'*H*,5'*H*-spiro[cyclopentane-1,2'-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin]-5'-one (20ac)**



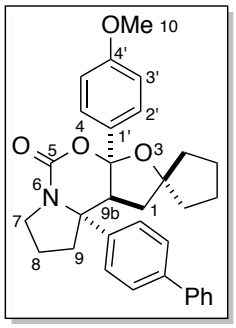
White foam

R_f = 0.38 (hexane:ethyl acetate, 1:2).

Isolated yield: 70%

^{1}H–NMR (300 MHz, $CDCl_3$)	δ: 6.87 (d, *J*= 8.9 Hz, 2H, $H_{2'}$), 6.71 (br s, 4H, $H_{3''}$ and $H_{2''}$), 6.39 (d, *J*= 8.9 Hz, 2H, $H_{3'}$), 3.81 – 3.73 (m, 1H, H_{7A}), 3.72 (td, *J*= 11.2, 7.0 Hz, 1H, H_{7B}), 3.63 (s, 3H, H_{10}), 3.47 (dd, *J*= 11.9, 8.1 Hz, 1H, H_{9b}), 2.39 (dd, *J*= 12.5, 8.1 Hz, 1H, H_{1A}) 2.16 – 1.99 (m, 5H, H_{1B}, H_9, and $H_{Cyclopent}$), 2.12 (s, 3H, H_{11}), 1.86 – 1.48 (m ,8H, H_8 and $H_{Cyclopent}$).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 159.0, 152.2, 139.4, 136.4, 131.1, 128.5, 127.5, 125.5, 112.7, 111.5, 91.7, 66.7, 55.3, 52.9, 47.5, 40.8, 40.1, 40.1, 38.0, 23.9, 23.7, 20.7, 20.5.
HRMS (70 eV, IE)	Calculated for $[C_{27}H_{31}NO_4]^+$: 433.2253, found 433.2254.

(3a'*S,9a'*R**,9b'*S**)-9a'-([1,1'-biphenyl]-4-yl)-3a'-(4-methoxyphenyl)hexahydro-1'*H*,5'*H*-spiro[cyclopentane-1,2'-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin]-5'-one (20ad)**



White foam

R_f = 0.33 (hexane:ethyl acetate, 1:2).

Isolated yield: 66%

^{1}H–NMR
(300 MHz, $CDCl_3$)

δ: 7.57 – 7.28 (m, 5H, H_{BiPh}), 7.12 (d, *J*= 8.8 Hz, 2H, $H_{2'}$), 7.00 – 6.81 (m, 4H, H_{BiPh}), 6.37 (d, *J*= 8.8 Hz, 2H, $H_{3'}$), 3.87 – 3.80 (m, 1H, H_{7A}), 3.77 (td, *J*= 11.2, 7.3 Hz, 1H, H_{7B}), 3.54 (dd, *J*= 11.9, 8.1 Hz, 1H, H_{9b}), 3.44 (s, 3H, H_{10}), 2.43 (dd, *J*= 12.5, 8.1 Hz, 1H, H_{1A}), 2.27 – 1.97 (m, 5H, H_{1B}, H_9 and $H_{Cyclopent}$), 1.95 – 1.55 (m, 8H, H_8 and $H_{Cyclopent}$).

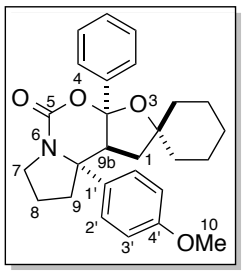
^{13}C–NMR
(75 MHz, $CDCl_3$)

δ: 159.1, 152.2, 141.4, 140.7, 140.1, 130.9, 128.8, 127.5, 127.4, 127.1, 126.7, 126.0, 112.8, 111.6, 91.9, 66.8, 55.1, 53.0, 47.7, 40.8, 40.1, 40.0, 38.0, 24.0, 23.7, 20.6.

HRMS
(70 eV, IE)

Calculated for $[C_{32}H_{33}NO_4]^+$: 495.2410, found 495.2411.

(3a'*S,9a'*R**,9b'*S**)-9a'-(4-Methoxyphenyl)-3a'-phenylhexahydro-1'*H*,5'*H*-spiro[cyclohexane-1,2'-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin]-5'-one (20ae)**



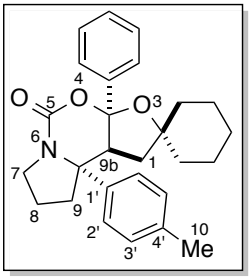
White foam

R_f = 0.36 (hexane:ethyl acetate, 1:2).

Isolated yield: 58%

^{1}H–NMR (300 MHz, $CDCl_3$)	δ: 7.01 – 6.86 (m, 5H, H_{Ph}), 6.72 (d, *J*= 8.8 Hz, 2H, $H_{2'}$), 6.41 (d, *J*= 8.8 Hz, 2H, $H_{3'}$), 3.81 – 3.73 (m, 1H, H_{7A}), 3.72 (td, *J*= 11.1, 7.1 Hz, 1H, H_{7B}), 3.62 (s, 3H, H_{10}), 3.49 (dd, *J*= 11.9, 8.2 Hz, 1H, H_{9b}), 2.35 (dd, *J*= 12.5, 8.2 Hz, 1H, H_{1A}), 2.07 – 1.97 (m, 2H, H_{1B} and H_{9A}), 1.88 – 1.30 (m, 13H, H_8, H_{9B} and H_{Cy}).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 158.4, 152.1, 139.0, 134.2, 127.5, 127.3, 126.7, 126.3, 113.4, 111.5, 84.2, 66.5, 55.4, 52.3, 47.6, 40.1, 40.0, 38.0, 38.0, 25.2, 23.8, 23.6, 20.5.
HRMS (70 eV, IE)	Calculated for $[C_{27}H_{31}NO_4]^+$: 433.2253, found 433.2252.

(3a'*S,9a'*R**,9b'*S**)-3a'-Phenyl-9a'-(*p*-tolyl)hexahydro-1'*H*,5'*H*-spiro[cyclohexane-1,2'-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin]-5'-one (20af)**



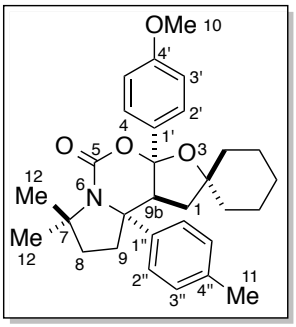
White foam

R_f = 0.38 (hexane:ethyl acetate, 1:2).

Isolated yield: 55%

^{1}H–NMR (300 MHz, $CDCl_3$)	δ: 6.98 – 6.83 (m, 5H, H_{Ph}), 6.72 – 6.65 (m, 4H, $H_{3'}$, $H_{2'}$), 3.79 (ddd, *J*= 11.3, 9.4, 2.0 Hz, 1H, H_{7A}), 3.72 (td, *J*= 11.3, 7.2 Hz, 1H, H_{7B}), 3.51 (dd, *J*= 11.9, 8.2 Hz, 1H, H_{9b}), 2.36 (dd, *J*= 12.5, 8.2 Hz, 1H, H_{1A}), 2.08 (s, 3H, H_{10}), 2.07 – 2.02 (m, 2H, H_{1B} and H_{9A}), 1.88 – 1.31 (m, 13H, H_8, H_{9B} and H_{Cy}).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 152.1, 139.1, 138.9, 136.6, 128.5, 127.3, 127.2, 126.3, 125.5, 111.5, 84.2, 66.7, 52.3, 47.6, 40.1, 40.0, 38.0, 25.2, 23.8, 23.6, 20.7, 20.5.
HRMS (70 eV, IE)	Calculated for $[C_{27}H_{31}NO_3]^+$: 417.2304, found 417.2306.

(3a'*S,9a'*R**,9b'*S**)-3a'-(4-Methoxyphenyl)-7',7'-dimethyl-9a'-(*p*-tolyl)hexahydro-1'*H*,5'*H*-spiro[cyclohexane-1,2'-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin]-5'-one (20ag)**



White foam

R_f = 0.28 (hexane:ethyl acetate, 3:1).

Isolated yield: 55%

^{1}H–NMR
(300 MHz, $CDCl_3$)

δ: 6.86 (d, *J*= 8.8 Hz, 2H, $H_{2'}$), 6.72 (br s, 4H, $H_{2''}$ and $H_{3''}$), 6.37 (d, *J*= 8.8 Hz, 2H, $H_{3'}$), 3.64 (s, 3H, H_{10}), 3.41 (dd, *J*= 11.3, 8.7 Hz, 1H, H_{9b}), 2.38 (dd, *J*= 12.4, 8.7 Hz, 1H, H_{1A}), 2.19 – 2.07 (m, 1H, H_{1B}), 2.11 (s, 3H, H_{11}), 1.98 – 1.86 (m, 2H, H_9), 1.81 – 1.31 (m, 12H, H_8 and H_{Cy}), 1.76 and 1.53 (2s, 6H, H_{12}).

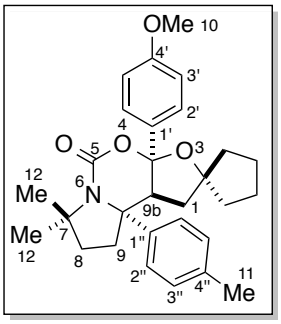
^{13}C–NMR
(75 MHz, $CDCl_3$)

δ: 158.5, 158.5, 150.6, 134.6, 132.1, 127.6, 112.6, 111.5, 83.7, 72.5, 68.3, 55.4, 55.3, 53.3, 40.1, 38.3, 38.3, 37.7, 37.1, 36.5, 35.3, 25.3, 24.9, 24.8, 23.8, 23.6.

HRMS
(70 eV, IE)

Calculated for $[C_{30}H_{37}NO_4]^+$: 475.2723, found 475.2721.

(3a'*S,9a'*R**,9b'*S**)-3a'-(4-Methoxyphenyl)-7',7'-dimethyl-9a'-(*p*-tolyl)hexahydro-1'*H*,5'*H*-spiro[cyclopentane-1,2'-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin]-5'-one (20ah)**



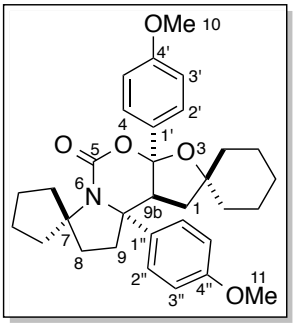
White foam

R_f = 0.28 (hexane:ethyl acetate, 3:1).

Isolated yield: 69%

^{1}H–NMR (300 MHz, $CDCl_3$)	δ: 6.89 (d, *J*= 8.8 Hz, 2H, $H_{2'}$), 6.88 (d, *J*= 8.0 Hz, 2H, $H_{2''}$), 6.74 (d, *J*= 8.0 Hz, 2H, $H_{3''}$), 6.40 (d, *J*= 8.8 Hz, 2H, $H_{3'}$), 3.66 (s, 3H, H_{10}), 3.45 (dd, *J*= 11.3, 8.6 Hz, 1H, H_{9b}), 2.47 (dd, *J*= 12.6, 8.6 Hz, 1H, H_{1A}), 2.25 – 1.96 (m, 5H, H_{1B}, H_9 and $H_{Cyclopent}$), 2.23 (s, 3H, H_{11}), 1.83 – 1.53 (m, 8H, H_8 and $H_{Cyclopent}$), 1.77 and 1.55 (2s, 6H, H_{12}).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 158.7, 150.9, 139.6, 136.5, 131.9, 128.4, 127.5, 126.2, 112.5, 111.4, 91.5, 69.4, 63.1, 55.3, 53.7, 40.8, 40.2, 38.6, 37.0, 36.9, 27.2, 24.5, 24.0, 23.7, 20.7.
HRMS (70 eV, IE)	Calculated for $[C_{29}H_{35}NO_4]^+$: 461.2566, found 461.2566.

(3a'*S,9a'*R**,9b'*S**)-3a',9a'-Bis(4-methoxyphenyl)tetrahydro-1'*H*,5'*H*,8'*H*-dispiro[cyclohexane-1,2'-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazine-7',1''-cyclopentan]-5'-one (20ai)**



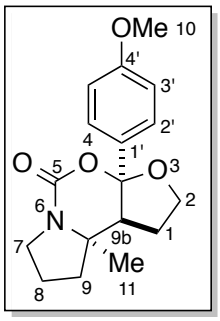
White foam

R_f = 0.26 (hexane:ethyl acetate, 3:1).

Isolated yield: 68%

^{1}H–NMR (300 MHz, $CDCl_3$)	δ: 6.85 (d, *J*= 8.8 Hz, 4H, $H_{2'}$ and $H_{2''}$), 6.40 (d, *J*= 8.8 Hz, 4H, $H_{3'}$ and $H_{3''}$), 3.66 and 3.65 (2s, 6H, H_{10} and H_{11}), 3.46 (dd, *J*= 11.3, 8.9 Hz, 1H, H_{9b}), 3.15 – 3.02 (m, 1H, H_{8A}), 2.51 – 2.38 (m, 1H, H_{9A}), 2.35 (dd, *J*= 12.7, 8.9 Hz, 1H, H_{1A}), 2.13 – 1.35 (m, 21H, H_{1B}, H_{8B}, H_{9B}, H_{Cy} and $H_{Cyclopent}$).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 158.5, 158.5, 150.6, 134.6, 132.1, 127.6, 112.6, 111.5, 83.7, 72.5, 68.3, 55.4, 55.3, 53.3, 40.1, 38.3, 38.3, 37.7, 37.1, 36.5, 35.3, 25.3, 24.9, 24.8, 23.8, 23.6.
HRMS (70 eV, IE)	Calculated for $[C_{32}H_{39}NO_5]^+$: 517.2828, found 517.2825.

(3a*S,9a*R**,9b*S**)-3a-(4-Methoxyphenyl)-9a-methyloctahydro-5*H*-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin-5-one (20aj)**



White foam

R_f = 0.28 (ethyl acetate).

Isolated yield: 92%

^{1}H–NMR
(300 MHz, $CDCl_3$)

δ: 7.47 (d, *J*= 8.8 Hz, 2H, $H_{2'}$), 6.88 (d, *J*= 8.8 Hz, 2H, $H_{3'}$), 4.18 (td, *J*= 9.1, 4.5 Hz, 1H, H_{2A}), 4.12 (td, *J*= 9.1, 4.2 Hz, 1H, H_{2B}), 3.80 (s, 3H, H_{10}), 3.64 (dt, *J*= 11.5, 8.2 Hz, 1H, H_{7A}), 3.60 (dt, *J*= 11.5, 5.0 Hz, 1H, H_{7B}), 2.98 (dd, *J*= 10.6, 8.9 Hz, 1H, H_{9b}), 2.27 (dtd, *J*= 11.5, 8.9, 4.5 Hz, 1H, H_{1A}), 2.02 – 1.91 (m, 3H, H_{1B} and H_8), 1.84 (dd, *J*= 11.3, 7.3 Hz, 1H, H_{9A}), 1.79 – 1.72 (m, 1H, H_{9B}), 0.86 (s, 3H, H_{11}).

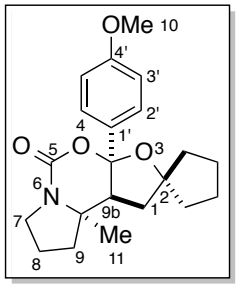
^{13}C–NMR
(75 MHz, $CDCl_3$)

δ: 160.0, 151.5, 132.5, 113.8, 111.2, 67.0, 60.5, 55.4, 52.0, 46.7, 38.2, 26.8, 26.1, 21.3.

HRMS
(70 eV, IE)

Calculated for $[C_{17}H_{21}NO_4]^+$: 303.1465, found 303.1465.

(3a'*S,9a'*R**,9b'*S**)-3a'-(4-Methoxyphenyl)-9a'-methylhexahydro-1'*H*,5'*H*-spiro[cyclopentane-1,2'-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin]-5'-one (20ak)**



White foam

R_f = 0.25 (hexane:ethyl acetate, 1:2).

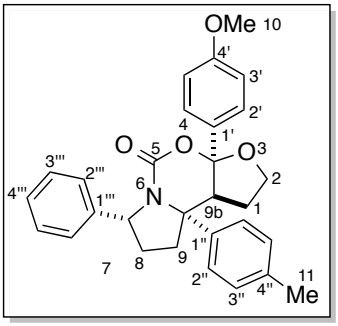
Isolated yield: 90%

^{1}H–NMR
(300 MHz, $CDCl_3$)

δ: 7.44 (d, *J*= 8.8 Hz, 2H, $H_{2'}$), 6.87 (d, *J*= 8.8 Hz, 2H, $H_{3'}$), 3.79 (s, 3H, H_{10}), 3.70 – 3.53 (m, 2H, H_7), 3.03 (dd, *J*= 12.1, 8.0 Hz, 1H, H_{9b}), 2.21 (dd, *J*= 12.5, 8.0 Hz, 1H, H_{1A}), 2.12 – 1.55 (m, 13H, H_{1B}, H_8, H_9 and $H_{Cyclopent}$) 0.86 (s, 3H, H_{11}).

^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 159.9, 151.5, 132.8, 127.6, 113.8, 111.1, 91.9, 60.3, 55.4, 52.4, 46.6, 40.6, 40.1, 38.0, 25.9, 24.0, 23.7, 21.1.
HRMS (70 eV, IE)	Calculated for $[C_{21}H_{27}NO_4]^+$: 357.1940, found 357.1942.

(3a*S,7*R**,9a*R**,9b*S**)-3a-(4-Methoxyphenyl)-7-phenyl-9a-(*p*-tolyl)octahydro-5*H*-furo[3,2-*e*]pyrrolo[1,2-*c*][1,3]oxazin-5-one (20al)**



White foam

R_f = 0.25 (hexane:ethyl acetate, 1:2).

Isolated yield: 92%

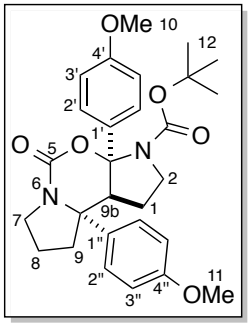
^{1}H–NMR (600 MHz, $CDCl_3$)	δ: 7.42 (dd, *J*= 7.2, 1.3 Hz, 2H, $H_{2'''}$), 7.30 (t, *J*= 7.2 Hz, 2H, $H_{3'''}$), 7.25 (tt, *J*= 7.2, 1.3 Hz, 1H, $H_{4'''}$), 6.91 (d, *J*= 7.9 Hz, 2H, $H_{2''}$), 6.90 (d, *J*= 8.9 Hz, 2H, $H_{2'}$), 6.73 (d, *J*= 7.9 Hz, 2H, $H_{3''}$), 6.43 (d, *J*= 8.9 Hz, 2H, $H_{3'}$), 5.07 (dd, *J*= 10.5, 6.9 Hz, 1H, H_7), 4.23 (td, *J*= 8.9, 3.6 Hz, 1H, H_{2A}), 4.15 (app. q, *J*= 8.4 Hz, 1H, H_{2B}), 3.67 (s, 3H, H_{10}), 3.37 (dd, *J*= 10.9, 8.7 Hz, 1H, H_{9b}), 2.55 – 2.47 (m, 2H, H_{1A} and H_{9A}), 2.33 (td, *J*= 12.3, 6.7 Hz, 1H, H_{9B}), 2.28 – 2.24 (m, 1H, H_{8A}), 2.21 – 2.16 (m, 1H, H_{1B}), 2.14 (s, 3H, H_{11}), 1.81 (tdd, *J*= 12.6, 10.5, 6.4 Hz, 1H, H_{8B}).
^{13}C–NMR (100 MHz, $CDCl_3$)	δ: 159.3, 153.4, 140.8, 139.4, 136.7, 130.0, 128.4, 128.4, 128.3, 127.6, 127.2, 126.7, 112.9, 111.2, 68.6, 66.3, 65.7, 55.4, 52.9, 39.7, 30.8, 27.2, 20.8.
HRMS (70 eV, IE)	Calculated for $[C_{29}H_{29}NO_4]^+$: 455.2097, found 455.2099.

Sections 1.B.2.8

- **General Procedure for the Synthesis of 5-Oxooctahydro-3*H*,5*H*-dipyrrolo[1,2-*c*:3',2'-*e*][1,3]oxazine Derivatives 24**

The corresponding *N*-Boc alkynamine derivative **7** (0.4 mmol) and $PtMe_2(cod)$ (5 mol%) were placed in a glass reaction tube under argon atmosphere. Then, dry dichloromethane (4 mL) was added. The solution was cooled to 0 °C and triflic acid (10 mol%) was added. The mixture was allowed to warm to room temperature and was kept at this temperature during 16 hours. Then, the reaction was filtered through a pad of Celite, the solvent was removed under vacuum and the resulting crude was purified by flash column chromatography on silica gel using ethyl acetate as eluent to give pure **24** as single diastereoisomers.

***tert*-Butyl (3a*S**,9a*R**,9b*S**)-3a,9a-bis(4-methoxyphenyl)-5-oxooctahydro-3*H*,5*H*-dipyrrolo[1,2-*c*:3',2'-*e*][1,3]oxazine-3-carboxylate (24a)**



White foam

R_f = 0.50 (ethyl acetate)

Isolated yield: 90%

^{1}H–NMR
(300 MHz, $CDCl_3$)

δ: 6.74 (d, *J*= 9.0 Hz, 2H, $H_{2'}$), 6.68 (d, *J*= 8.8 Hz, 2H, $H_{2''}$), 6.45 (d, *J*= 8.8 Hz, 2H, $H_{3''}$), 6.38 (d, *J*= 9.0 Hz, 2H, $H_{3'}$), 3.87 – 3.76 (m, 2H, H_{2A} and H_{7A}), 3.67 and 3.65 (2 s, 6H, H_{10} and H_{11}), 3.76 – 3.57 (m, 2H, H_{2B} and H_{7B}), 3.41 (dd, *J*= 12.8, 6.7 Hz, 1H, H_{9b}), 2.25 (dt, *J*= 12.8, 6.7 Hz, 1H, H_{1A}), 2.11 (td, *J*= 12.2, 6.8 Hz, 1H, H_{9A}), 2.00 – 1.88 (m, 2H, H_{1B}, H_{9B}), 1.88 – 1.86 (m, 1H, H_{8A}), 1.65 – 1.46 (m, 1H, H_{8B}), 0.99 (br s, 9H, H_{12}).

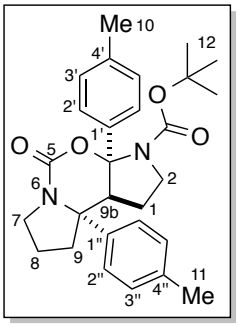
^{13}C–NMR
(75 MHz, $CDCl_3$)

δ: 158.3, 158.1, 153.1, 151.8, 134.5, 126.5, 113.4, 112.7, 97.5, 80.5, 66.5, 55.5, 55.3, 47.8, 46.2, 39.7, 27.9, 24.2, 20.2.

HRMS
(70 eV, IE)

Calculated for $[C_{28}H_{34}N_2O_6]^+$: 494.2417, found 494.2419.

tert-Butyl (3a*S,9a*R**,9b*S**)-5-oxo-3a,9a-di-*p*-tolyloctahydro-3*H*,5*H*-dipyrrolo[1,2-*c*:3',2'-*e*][1,3]oxazine-3-carboxylate (24b)**



White foam

R_f = 0.60 (ethyl acetate)

Isolated yield: 86%

^{1}H–NMR
(300 MHz, $CDCl_3$)

δ: 6.67 (d, *J*= 8.6 Hz, 2H, $H_{2'}$), 6.64 (d, *J*= 8.6 Hz, 2H, $H_{2''}$), 6.59 (d, *J*= 8.6 Hz, 4H, $H_{3'}$ and $H_{3''}$), 3.88 – 3.75 (m, 2H, H_{2A} and H_{7A}), 3.68 (td, *J*= 10.4, 7.6 Hz, 1H, H_{7B}), 3.61 (td, *J*= 11.0, 6.6 Hz, 1H, H_{2B}), 3.42 (dd, *J*= 12.9, 6.5 Hz, 1H, H_{9b}), 2.24 (dt, *J*= 12.7, 6.5 Hz, 1H, H_{1A}), 2.12 and 2.10 (2s, 6H, H_{10} and H_{11}), 2.08 (td, *J*= 12.2, 6.7 Hz, 1H, H_{9A}), 1.97 –1.88 (m, 2H, H_{1B} and H_{9B}), 1.79 (dt, *J*= 12.7, 6.7 Hz, 1H, H_{8A}), 1.61 – 1.44 (m, 1H, H_{8B}), 0.92 (br s, 9H, H_{12}).

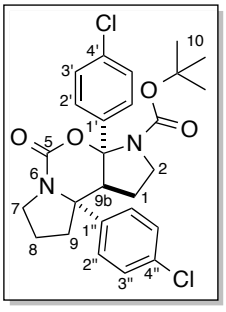
^{13}C–NMR
(75 MHz, $CDCl_3$)

δ: 151.8, 139.3, 138.7, 136.4, 135.9, 128.4, 127.6, 125.3, 97.5, 80.5, 66.7, 55.4, 47.7, 46.2, 39.7, 27.8, 24.2, 20.8, 20.7, 20.2.

HRMS
(70 eV, IE)

Calculated for $[C_{28}H_{34}N_2O_4]^+$: 462.2519, found 462.2517.

tert-Butyl (3a*S,9a*R**,9b*S**)-3a,9a-bis(4-chlorophenyl)-5-oxooctahydro-3*H*,5*H*-dipyrrolo[1,2-*c*:3',2'-*e*][1,3]oxazine-3-carboxylate (24c)**



White foam

R_f = 0.40 (ethyl acetate)

Isolated yield: 78%

^{1}H–NMR (300 MHz, $CDCl_3$)	δ: 6.93 (d, *J*= 8.1 Hz, 2H, $H_{2'}$), 6.86 (d, *J*= 8.7 Hz, 2H, $H_{2''}$), 6.77 (d, *J*= 8.7 Hz, 2H, $H_{3''}$), 6.71 (d, *J*= 8.1 Hz, 2H, $H_{3'}$), 3.83 (app. q, *J*= 10.6 Hz, 2H, H_{2A} and H_{7A}), 3.70 (td, *J*= 10.8, 7.3 Hz, 1H, H_{7B}), 3.62 (td, *J*= 10.9, 6.9 Hz, 1H, H_{2B}), 3.39 (dd, *J*= 12.7, 6.6 Hz, 1H, H_{9b}), 2.28 (dt, *J*= 12.9, 6.6 Hz, 1H, H_{1A}), 2.13 (td, *J*= 12.3, 6.8 Hz, 1H, H_{9A}), 2.03 – 1.80 (m, 3H, H_{1B}, H_{8A} and H_{9B}), 1.67 – 1.43 (m, 1H, H_{8B}), 0.97 (br s, 9H, H_{10}).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 151.3, 140.9, 140.4, 133.3, 132.9, 128.2, 127.4, 126.9, 96.9, 81.1, 66.6, 55.6, 47.9, 46.2, 39.7, 27.9, 24.2, 20.2
HRMS (70 eV, IE)	Calculated for $[C_{26}H_{28}Cl_2N_2O_4]^+$: 502.1426, found 502.1424.

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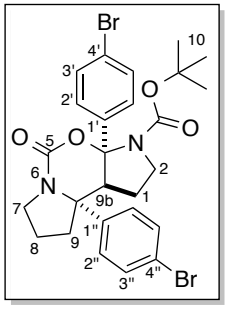
tert-Butyl (3a*S,9a*R**,9b*S**)-3a,9a-bis(4-bromophenyl)-5-oxooctahydro-3*H*,5*H*-dipyrrolo[1,2-*c*:3',2'-*e*][1,3]oxazine-3-carboxylate (24d)**



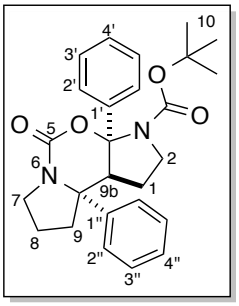
White foam

R_f = 0.45 (ethyl acetate)

Isolated yield: 74%

^{1}H–NMR (300 MHz, $CDCl_3$)	δ: 7.09 (d, *J*= 8.1 Hz, 2H, $H_{2'}$), 7.03 (d, *J*= 8.8 Hz, 2H, $H_{2''}$), 6.71 (d, *J*= 8.8 Hz, 2H, $H_{3''}$), 6.64 (d, *J*= 8.1 Hz, 2H, $H_{3'}$), 3.83 (app. q, *J*= 10.2 Hz, 2H, H_{2A}, H_{7A}), 3.69 (td, *J*= 11.0, 7.3 Hz, 1H, H_{7B}), 3.62 (td, *J*= 11.2, 6.9 Hz, 1H, H_{2B}), 3.38 (dd, *J*= 12.7, 6.7 Hz, 1H, H_{9b}), 2.28 (dt, *J*= 13.0, 6.7 Hz, 1H, H_{1A}), 2.12 (td, *J*= 12.3, 6.9 Hz, 1H, H_{9A}), 2.02 – 1.76 (m, 3H, H_{1B}, H_{8A} and H_{9B}), 1.68 – 1.44 (m, 1H, H_{8B}), 0.97 (br s, 9H, H_{10}).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 151.3, 141.3, 140.9, 131.1, 130.4, 127.2, 121.3, 120.9, 96.9, 81.1, 66.7, 55.4, 47.9, 46.2, 39.6, 27.9, 24.1, 20.2.
HRMS (70 eV, IE)	Calculated for $[C_{26}H_{28}Br_2N_2O_4]^+$: 590.0410, found 590.0412.

tert-Butyl (3a*S,9a*R**,9b*S**)-5-oxo-3a,9a-diphenyloctahydro-3*H*,5*H*-dipyrrolo[1,2-*c*:3',2'-*e*][1,3]oxazine-3-carboxylate (24e)**



White foam

R_f = 0.60 (ethyl acetate)

Isolated yield: 80%

^{1}H–NMR
(300 MHz, $CDCl_3$)

δ: 6.92 –6.87 (m, 4H, $H_{3'}$ and $H_{3''}$), 6.85 –6.77 (m, 6H, $H_{4'}$, $H_{4''}$, $H_{2'}$, $H_{2''}$), 3.89 – 3.79 (m, 2H, H_{2A} and H_{7A}), 3.72 (td, *J*= 10.9, 7.4 Hz, 1H, H_{7B}), 3.64 (td, *J*= 10.9, 6.7 Hz, 1H, H_{2B}), 3.51 (dd, *J*= 12.9, 6.7 Hz, 1H, H_{9b}), 2.29 (dt, *J*= 12.3, 6.7 Hz, 1H, H_{1A}), 2.14 (td, *J*= 12.2, 6.8 Hz, 1H, H_{9A}), 2.06 – 1.90 (m, 2H, H_{1B} and H_{9B}), 1.81 (dt, *J*= 12.7, 6.7 Hz, 1H, H_{8A}), 1.60 – 1.43 (m, 1H, H_{8B}), 0.91 (br s, 9H, H_{10}).

^{13}C–NMR
(75 MHz, $CDCl_3$)

δ: 151.8, 142.2, 141.9, 127.9, 127.2, 126.9, 126.6, 125.4, 97.4, 80.7, 67.0, 55.4, 47.8, 46.3, 40.0, 27.8, 24.4, 20.2.

HRMS
(70 eV, IE)

Calculated for $[C_{26}H_{30}N_2O_4]^+$: 434.2206, found 434.2205.

Chapter 2

Part A

- **Synthesis of Indole-2-carbaldehydes 41 and Substituted 2,3-dihydrofuran Derivatives 18**

Non commercially available 1*H*-indole-2-carbaldehyde derivatives **41**[209] and substituted 2,3-dihydrofuran derivatives **18**[210] were prepared according to the methods reported in the literature and purified by standard procedures.

Section 2.2.A.3

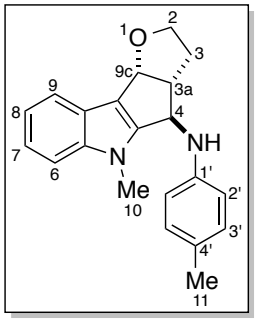
- **General Procedure for the Synthesis of the Hexahydrofurocyclopenta[1,2-*b*]indole Derivatives 49a-q**

The corresponding 1*H*-indole-2-carbaldehyde derivative **41** (0.2 mmol), aniline **34** (1.5 equiv, 0.3 mmol), diphenyl phosphate (10 mol%) and 4 Å powder molecular sieves (50 mg) were placed in a glass reaction tube equipped with a magnetic stirring bar under argon atmosphere. Then, dichloromethane (2 mL) was added at 0 °C. The mixture was allowed to warm to room temperature and stirred at this temperature for 1 hour. Then, 2,3-dihydrofuran **18b** (3 equiv, 0.6 mmol, in 2 mL of dichloromethane) was added at room temperature over 5 hours via syringe pump. The reaction was kept at this temperature for additional 12 hours. Finally, the resulting slurry was filtered through a pad of basic alumina eluting with ethyl acetate, the solvent was removed under vacuum and the crude was purified by flash column chromatography on silica gel using mixtures of hexane and diethyl ether as eluent to give pure **49a-q**.

[209] Y.-F. Yang, L.-H. Li, Y.-T. He, J.-Y. Luo, Y.-M. Liang, *Tetrahedron*, **2014**, *70*, 702.

[210] a) C. Shu, M.-Q. Liu, Y.-Z. Sun, L.-W. Ye, *Organic Letters*, **2012**, *14*, 4958. b) B. M. Trost, Y. H. Rhee, *J. Am. Chem. Soc.*, **2003**, *125*, 7482.

(3a*R,4*R**,9c*R**)-5-Methyl-*N*-(*p*-tolyl)-2,3,3a,4,5,9c-hexahydrofuro[2',3':3,4]cyclopenta[1,2-*b*]indol-4-amine (49a)**



Brown solid

mp= 143 – 145 °C

R_f= 0.33 (hexane:diethyl ether, 2:1).

Isolated yield: 82%

^{1}H–NMR
(300 MHz, C_6D_6)

δ: 7.96 (dd, *J*= 6.7, 1.4 Hz, 1H, H_9), 7.22 (td, *J*= 6.7, 1.4 Hz, 1H, H_7), 7.21 (td, *J*= 6.7, 1.4 Hz, 1H, H_8), 7.06 (dd, *J*= 6.7, 1.4 Hz, 1H, H_6), 7.03 (d, *J*= 8.4 Hz, 2H, $H_{3'}$), 6.45 (d, *J*= 8.4 Hz, 2H, $H_{2'}$), 5.76 (dd, *J*= 6.5, 1.4 Hz, 1H, H_{9c}), 4.52 (d, *J*= 8.5 Hz, 1H, H_4), 3.70 (ddd, *J*= 8.5, 6.9, 4.5 Hz, 1H, H_{2A}), 3.56 (td, *J*= 8.5, 6.0 Hz, 1H, H_{2B}), 3.09 (s, 3H, H_{10}), 3.04 (br s, 1H, NH), 2.95 – 2.87 (m, 1H, H_{3a}), 2.22 (s, 3H, H_{11}), 1.86 (dddd, *J*= 12.3, 9.8, 8.5, 6.9 Hz, 1H, H_{3A}), 1.53 (ddt, *J*= 12.3, 6.0, 4.5 Hz, 1H, H_{3B}).

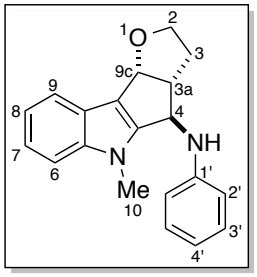
^{13}C–NMR
(75 MHz, C_6D_6)

δ: 145.3, 145.0, 143.3, 130.2, 127.2, 124.2, 122.3, 120.5, 120.4, 119.9, 114.5, 110.0, 80.7, 66.8, 59.4, 57.0, 33.8, 30.0, 20.6.

HRMS
(70 eV, IE)

Calculated for $[C_{21}H_{22}N_2O]^+$: 318.1727 found 318.1737.

(3a*R,4*R**,9c*R**)-5-Methyl-*N*-phenyl-2,3,3a,4,5,9c-hexahydrofuro[2',3':3,4]cyclopenta[1,2-*b*]indol-4-amine (49b)**



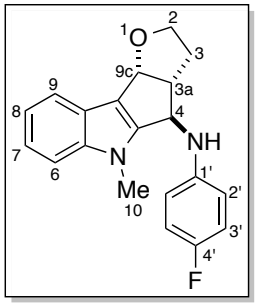
Brown oil

R_f= 0.18 (hexane:diethyl ether, 2:1).

Isolated yield: 85%

^{1}H–NMR (300 MHz, C_6D_6)	δ: 7.96 (dd, *J*= 7.0, 1.7 Hz, 1H, H_9), 7.39 – 7.29 (m, 4H, H_7, H_8 and $H_{3'}$), 7.05 (dd, *J*= 7.0, 1.7 Hz, 1H, H_6), 6.80 (t, *J*= 7.3 Hz, 1H, $H_{4'}$), 6.47 (d, *J*= 7.3 Hz, 2H, $H_{2'}$), 5.75 (dd, *J*= 6.5, 1.6 Hz, 1H, H_{9c}), 4.49 (d, *J*= 8.4 Hz, 1H, H_4), 3.68 (ddd, *J*= 8.5, 6.9, 4.5 Hz, 1H, H_{2A}), 3.55 (td, *J*= 8.5, 6.0 Hz, 1H, H_{2B}), 3.13 (app. d, *J*= 9.6 Hz, 1H, NH), 3.05 (s, 3H, H_{10}), 2.89 – 2.80 (m, 1H, H_{3a}), 1.83 (dddd, *J*= 12.2, 9.8, 8.1, 6.9 Hz, 1H, H_{3A}), 1.56 – 1.45 (m, 1H, H_{3B}).
^{13}C–NMR (75 MHz, C_6D_6)	δ: 147.5, 144.7, 143.3, 129.7, 124.2, 122.3, 120.5, 120.4, 120.0, 118.3, 114.1, 110.0, 80.7, 66.9, 60.0, 57.1, 33.7, 29.9.
HRMS (70 eV, IE)	Calculated for $[C_{20}H_{20}N_2O]^+$: 304.1570, found 304.1577.

(3a*R,4*R**,9c*R**)-*N*-(4-Fluorophenyl)-5-methyl-2,3,3a,4,5,9c-hexahydrofuro[2',3':3,4]cyclopenta[1,2-*b*]indol-4-amine (49c)**



Yellow foam

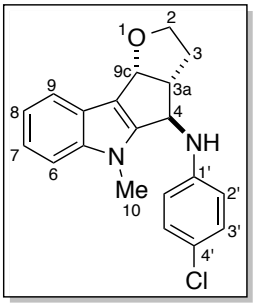
R_f= 0.23 (hexane:diethyl ether, 2:1).

Isolated yield: 95%

^{1}H–NMR (300 MHz, C_6D_6)	δ: 7.94 (dd, *J*= 6.9, 1.7 Hz, 1H, H_9), 7.28 – 7.18 (m, 2H, H_7 and H_8), 7.06 (d, *J*= 7.0 Hz, 1H, H_6), 6.87 (t, $J_{H\text{-}F}$= 8.7, *J*= 8.7 Hz, 2H, $H_{3'}$), 6.21 (dd, *J*= 8.7 Hz, $J_{H\text{-}F}$= 4.4 Hz, 2H, $H_{2'}$), 5.72 (dd, *J*= 6.5, 1.6 Hz, 1H, H_{9c}), 4.34 (d, *J*= 9.3 Hz, 1H, H_4), 3.68 (ddd, *J*= 8.5, 6.9, 4.6 Hz, 1H, H_{2A}), 3.54 (td, *J*= 8.5, 6.0 Hz, 1H, H_{2B}), 3.07 (s, 3H, H_{10}), 2.96 (d, *J*= 9.7 Hz, 1H, NH), 2.80 – 2.73 (m, 1H, H_{3a}), 1.78 (dddd, *J*= 12.3, 9.7, 8.5, 6.9 Hz, 1H, H_{3A}), 1.47 – 1.38 (m, 1H, H_{3B}).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 156.3 (d, $J_{C\text{-}F}$= 236.0 Hz), 144.9, 143.2, 142.9, 123.1, 122.3, 120.2, 119.8, 119.2, 116.1 (d, $J_{C\text{-}F}$= 22.3 Hz), 114.9 (d, $J_{C\text{-}F}$= 7.4 Hz), 110.0, 80.6, 67.2, 59.8, 56.6, 33.6, 30.7.

^{19}F–NMR (282 MHz, $CDCl_3$)	δ: –127.1
HRMS (70 eV, IE)	Calculated for $[C_{20}H_{19}FN_2O]^+$: 322.1476 found 322.1484.

(3a*R,4*R**,9c*R**)-*N*-(4-Chlorophenyl)-5-methyl-2,3,3a,4,5,9c-hexahydrofuro[2',3':3,4]cyclopenta[1,2-*b*]indol-4-amine (49d)**



Brown solid

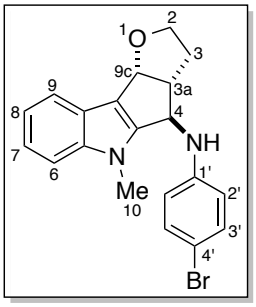
mp= 185 – 187 °C

R_f= 0.20 (hexane:diethyl ether, 2:1).

Isolated yield: 96%

^{1}H–NMR (300 MHz, C_6D_6)	δ: 7.94 (d, *J*= 7.4 Hz, 1H, H_9), 7.28 – 7.18 (m, 2H, H_7 and H_8), 7.13 (d, *J*= 8.9 Hz, 2H, $H_{3'}$), 7.06 (d, *J*= 7.8 Hz, 1H, H_6), 6.17 (d, *J*= 8.9 Hz, 2H, $H_{2'}$), 5.72 (dd, *J*= 6.5, 1.6 Hz, 1H, H_{9c}), 4.31 (d, *J*= 8.9 Hz, 1H, H_4), 3.69 (ddd, *J*= 8.6, 6.9, 4.6 Hz, 1H, H_{2A}), 3.53 (td, *J*= 8.6, 6.0 Hz, 1H, H_{2B}), 3.02 (s, 3H, H_{10}), 3.00 (s, 1H, NH), 2.76 – 2.69 (m, 1H, H_{3a}), 1.77 (dddd, *J*= 12.3, 9.7, 8.6, 6.9 Hz, 1H, H_{3A}), 1.45 – 1.36 (m, 1H, H_{3B}).
^{13}C–NMR (75 MHz, C_6D_6)	δ: 145.9, 144.3, 143.3, 129.6, 124.1, 122.9, 122.5, 120.6, 120.4, 120.1, 115.2, 110.0, 80.6, 66.8, 59.0, 56.8, 33.6, 29.8.
HRMS (70 eV, IE)	Calculated for $[C_{20}H_{19}ClN_2O]^+$: 338.1180, found 338.1187.

(3a*R,4*R**,9c*R**)-*N*-(4-Bromophenyl)-5-methyl-2,3,3a,4,5,9c-hexahydrofuro[2',3':3,4]cyclopenta[1,2-*b*]indol-4-amine (49e)**



Light brown solid

mp= 185 – 187 °C

R_f= 0.20 (hexane:diethyl ether, 2:1).

Isolated yield: 90%

^{1}H–NMR (300 MHz, C_6D_6)

δ: 7.94 (d, *J*= 7.4 Hz, 1H, H_9), 7.28 – 7.18 (m, 2H, H_7 and H_8), 7.26 (d, *J*= 8.8 Hz, 2H, $H_{3'}$), 7.06 (d, *J*= 7.8 Hz, 1H, H_6), 6.11 (d, *J*= 8.8 Hz, 2H, $H_{2'}$), 5.72 (dd, *J*= 6.5, 1.6 Hz, 1H, H_{9c}), 4.30 (d, *J*= 9.7 Hz, 1H, H_4), 3.69 (ddd, *J*= 8.7, 6.9, 4.5 Hz, 1H, H_{2A}), 3.53 (td, *J*= 8.7, 6.0 Hz, 1H, H_{2B}), 3.01 (s, 3H, H_{10}), 2.99 (d, *J*= 9.7 Hz, 1H, NH), 2.75 – 2.68 (m, 1H, H_{3a}), 1.77 (dddd, *J*= 12.3, 9.8, 8.7, 6.9 Hz, 1H, H_{3A}), 1.40 (ddt, *J*= 12.3, 5.8, 4.5 Hz, 1H, H_{3B}).

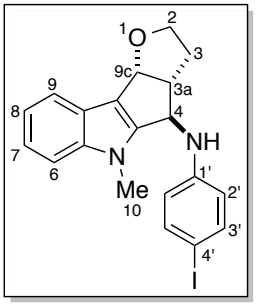
^{13}C–NMR (75 MHz, C_6D_6)

δ: 146.3, 144.2, 143.3, 132.5, 124.1, 122.5, 120.6, 120.4, 120.1, 115.6, 110.0, 80.6, 66.8, 58.9, 56.8, 33.6, 29.8.

HRMS (70 eV, IE)

Calculated for $[C_{20}H_{19}BrN_2O]^+$: 382.0675, found 382.0681.

(3a*R,4*R**,9c*R**)-*N*-(4-Iodophenyl)-5-methyl-2,3,3a,4,5,9c-hexahydrofuro[2',3':3,4]cyclopenta[1,2-*b*]indol-4-amine (49f)**



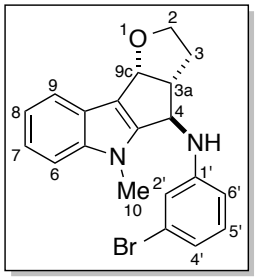
Light brown foam

R_f= 0.20 (hexane:diethyl ether, 2:1).

Isolated yield: 93%

^{1}H–NMR (300 MHz, C_6D_6)	δ: 7.94 (d, *J*= 7.4 Hz, 1H, H_9), 7.42 (d, *J*= 8.7 Hz, 2H, $H_{3'}$), 7.28 – 7.18 (m, 2H, H_7 and H_8), 7.05 (d, *J*= 7.8 Hz, 1H, H_6), 6.01 (d, *J*= 8.7 Hz, 2H, $H_{2'}$), 5.72 (dd, *J*= 6.4, 1.6 Hz, 1H, H_{9c}), 4.29 (d, *J*= 9.8 Hz, 1H, H_4), 3.69 (ddd, *J*= 8.7, 6.9, 4.5 Hz, 1H, H_{2A}), 3.53 (td, *J*= 8.7, 6.0 Hz, 1H, H_{2B}), 3.00 (s, 3H, H_{10}), 2.97 (br s, 1H, NH), 2.75 – 2.67 (m, 1H, H_{3a}), 1.77 (dddd, *J*= 12.3, 9.8, 8.7, 6.9 Hz, 1H, H_{3A}), 1.44 – 1.33 (m, 1H, H_{3B}).
^{13}C–NMR (75 MHz, C_6D_6)	δ: 146.9, 144.2, 143.3, 138.3, 124.1, 122.5, 120.6, 120.4, 120.2, 116.2, 110.0, 80.6, 66.8, 58.7, 56.9, 33.6, 29.8.
HRMS (70 eV, IE)	Calculated for $[C_{20}H_{19}IN_2O]^+$: 430.0537, found 430.0537.

(3a*R,4*R**,9c*R**)-*N*-(3-Bromophenyl)-5-methyl-2,3,3a,4,5,9c-hexahydrofuro[2',3':3,4]cyclopenta[1,2-*b*]indol-4-amine (49g)**



White solid

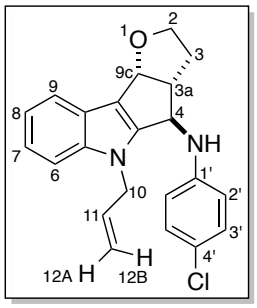
mp= 140 – 142 °C

R_f= 0.30 (hexane:diethyl ether, 2:1).

Isolated yield: 95%

^{1}H–NMR (300 MHz, C_6D_6)	δ: 7.92 (dd, *J*= 7.3, 1.3 Hz, 1H, H_9), 7.27 – 7.19 (m, 2H, H_7 and H_8), 7.05 (dd, *J*= 7.3, 1.3 Hz, 1H, H_6), 6.91 (d, *J*= 7.9 Hz, 1H, $H_{4'}$), 6.80 (t, *J*= 7.9 Hz, 1H, $H_{5'}$), 6.66 (t, *J*= 2.1 Hz, 1H, $H_{2'}$), 6.20 (dd, *J*= 7.9, 2.4 Hz, 1H, $H_{6'}$), 5.68 (dd, *J*= 6.5, 1.4 Hz, 1H, H_{9c}), 4.29 (d, *J*= 9.5 Hz, 1H, H_4), 3.65 (ddd, *J*= 8.5, 7.0, 4.8 Hz, 1H, H_{2A}), 3.49 (td, *J*= 8.5, 6.0 Hz, 1H, H_{2B}), 3.09 (d, *J*= 9.5 Hz, 1H, NH), 3.00 (s, 3H, H_{10}), 2.68 (app. dtd, *J*= 12.2, 4.6, 1.4 Hz, 1H, H_{3a}), 1.84 – 1.71 (m, 1H, H_{3A}), 1.30 – 1.35 (m, 1H, H_{3B}).
^{13}C–NMR (75 MHz, C_6D_6)	δ: 148.7, 144.0, 143.2, 130.9, 124.0, 123.9, 122.5, 121.0, 120.6, 120.4, 120.2, 116.9, 112.4, 110.0, 80.6, 66.9, 58.6, 56.9, 33.6, 29.8.
HRMS (70 eV, IE)	Calculated for $[C_{20}H_{19}BrN_2O]^+$: 382.0675, found 382.0684.

(3a*R,4*R**,9c*R**)-5-Allyl-*N*-(4-chlorophenyl)-2,3,3a,4,5,9c-hexahydrofuro[2',3':3,4]cyclopenta[1,2-*b*]indol-4-amine (49h)**



Yellow foam

R_f = 0.23 (hexane:diethyl ether, 2:1).

Isolated yield: 55%

^{1}H–NMR
(300 MHz, C_6D_6)

δ: 7.93 (dd, *J*= 6.6, 2.3 Hz, 1H, H_9), 7.25 – 7.09 (m, 3H, H_7, H_8 and H_6), 7.13 (d, *J*= 8.8 Hz, 2H, $H_{3'}$), 6.20 (d, *J*= 8.8 Hz, 2H, $H_{2'}$), 5.72 (dt, *J*= 6.5, 1.9 Hz, 1H, H_{9c}), 5.52 (ddt, *J*= 17.2, 10.3, 5.1 Hz, 1H, H_{11}), 4.81 (dd, *J*= 10.3, 1.5 Hz, 1H, H_{12A}), 4.61 (dd, *J*= 17.2, 1.5 Hz, 1H, H_{12B}), 4.39 (d, *J*= 9.3 Hz, 1H, H_4), 4.26 – 4.08 (m, 2H, H_{10}), 3.67 (ddd, *J*= 8.7, 6.9, 4.4 Hz, 1H, H_{2A}), 3.51 (td, *J*= 8.7, 5.9 Hz, 1H, H_{2B}), 3.24 (d, *J*= 9.3 Hz, 1H, NH), 2.80 – 2.73 (m, 1H, H_{3a}), 1.77 (dddd, *J*= 12.3, 9.7, 8.2, 6.9 Hz, 1H, H_{3A}), 1.45 – 1.36 (m, 1H, H_{3B}).

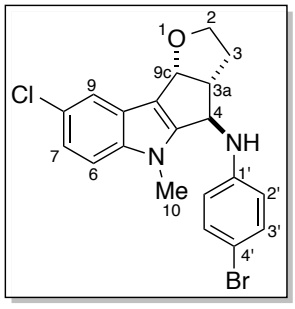
^{13}C–NMR
(75 MHz, C_6D_6)

δ: 145.9, 144.1, 142.7, 134.0, 129.6, 124.2, 122.9, 122.6, 120.7, 120.5, 120.5, 116.1, 115.0, 110.6, 80.6, 66.9, 59.1, 57.0, 46.3, 33.6.

HRMS
(70 eV, IE)

Calculated for $[C_{22}H_{21}ClN_2O]^+$: 364.1342 found 364.1337.

(3a*R,4*R**,9c*R**)-*N*-(4-Bromophenyl)-8-chloro-5-methyl-2,3,3a,4,5,9c-hexahydrofuro[2',3':3,4]cyclopenta[1,2-*b*]indol-4-amine (49i)**



Brown solid

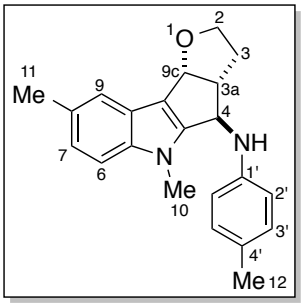
mp= 242 – 244 °C

R_f = 0.30 (hexane:diethyl ether, 2:1).

Isolated yield: 88%

^{1}H–NMR (300 MHz, acetone-d_6)	δ: 7.52 (d, *J*= 2.1 Hz, 1H, H_9), 7.40 (d, *J*= 8.8 Hz, 1H, H_6), 7.30 (d, *J*= 8.8 Hz, 2H, $H_{3'}$), 7.17 (dd, *J*= 8.8, 2.1 Hz, 1H, H_7), 6.76 (d, *J*= 8.8 Hz, 2H, $H_{2'}$), 5.64 (br s, 1H, NH), 5.61 (dd, *J*= 6.5, 1.1 Hz, 1H, H_{9c}), 5.03 (d, *J*= 8.9 Hz, 1H, H_4), 3.77 (ddd, *J*= 8.4, 6.9, 4.5 Hz, 1H, H_{2A}), 3.72 (s, 3H, H_{10}), 3.57 (td, *J*= 8.4, 6.0, 1H, H_{2B}), 3.25 – 3.13 (m, 1H, H_{3a}), 2.26 – 2.13 (m, 1H, H_{3A}), 2.07 – 1.98 (m, 1H, H_{3B}).
^{13}C–NMR (75 MHz, acetone-d_6)	δ: 148.1, 142.2, 132.8, 125.9, 125.3, 122.4, 119.6, 119.4, 116.3, 112.4, 109.0, 80.8, 67.4, 59.4, 57.8, 34.0, 31.0.
HRMS (70 eV, IE)	Calculated for $[C_{20}H_{18}BrClN_2O]^+$: 416.0286, found 416.0295.

(3a*R,4*R**,9c*R**)-5,8-Dimethyl-*N*-(*p*-tolyl)-2,3,3a,4,5,9c-hexahydrofuro[2',3':3,4]cyclopenta[1,2-*b*]indol-4-amine (49j)**



Brown solid

mp= 153 – 155 °C

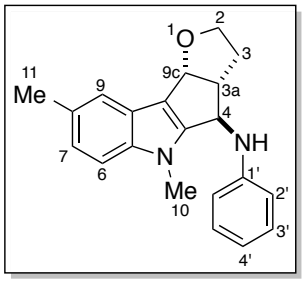
R_f= 0.30 (hexane:diethyl ether, 2:1).

Isolated yield: 87%

^{1}H–NMR (300 MHz, acetone-d_6)	δ: 7.33 (d, *J*= 1.5 Hz, 1H, H_9), 7.23 (d, *J*= 8.4 Hz, 1H, H_6), 7.01 (dd, *J*= 8.4, 1.5 Hz, 1H, H_7), 6.99 (d, *J*= 8.3 Hz, 2H, $H_{2'}$), 6.70 (d, *J*= 8.3 Hz, 2H, $H_{3'}$), 5.59 (dd, *J*= 6.4, 1.4 Hz, 1H, H_{9c}), 5.06 (d, *J*= 8.9 Hz, 1H, NH), 4.94 (d, *J*= 8.0 Hz, 1H, H_4), 3.74 (ddd, *J*= 8.5, 6.9, 4.4 Hz, 1H, H_{2A}), 3.66 (s, 3H, H_{10}), 3.56 (td, *J*= 8.5, 6.0 Hz, 1H, H_{2B}), 3.21 – 3.13 (m, 1H, H_{3a}), 2.41 and 2.22 (2 s, 6H, H_{11} and H_{12}), 2.13 – 2.08 (m, 1H, H_{3A}), 2.02 – 1.93 (m, 1H, H_{3B}).
^{13}C–NMR (75 MHz, acetone-d_6)	δ: 146.8, 146.6, 142.1, 130.5, 129.2, 126.6, 124.6, 123.7, 119.8, 119.0, 114.7, 110.4, 81.0, 67.0, 59.8, 57.7, 34.1, 21.6, 20.5.

HRMS (70 eV, IE)	Calculated for $[C_{22}H_{24}N_2O]^+$: 332.1883, found 332.1889.

(3a*R,4*R**,9c*R**)-5,8-Dimethyl-*N*-phenyl-2,3,3a,4,5,9c-hexahydrofuro[2',3':3,4]cyclopenta[1,2-*b*]indol-4-amine (49k)**



Brown solid

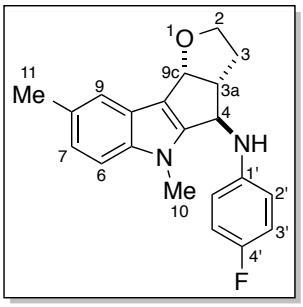
mp= 164 – 166 °C

R_f = 0.48 (hexane:diethyl ether, 2:1).

Isolated yield: 80%

^{1}H–NMR (300 MHz, C_6D_6)	δ: 7.73 (s, 1H, H_9), 7.21 (dd, *J*= 8.6, 7.3 Hz, 2H, $H_{3'}$), 7.11 (dd, *J*= 8.5, 1.5 Hz, 1H, H_7), 7.00 (d, *J*= 8.5 Hz, 1H, H_6), 6.80 (t, *J*= 7.3 Hz, 1H, $H_{4'}$), 6.48 (d, *J*= 8.6 Hz, 2H, $H_{2'}$), 5.75 (dd, *J*= 6.5, 1.8 Hz, 1H, H_{9c}), 4.50 (br s, 1H, H_4), 3.69 (ddd, *J*= 8.6, 6.9, 4.5 Hz, 1H, H_{2A}), 3.56 (td, *J*= 8.6, 6.0 Hz, 1H, H_{2B}), 3.23 (br s, 1H, NH), 3.07 (s, 3H, H_{10}), 2.90 – 2.82 (m, 1H, H_{3a}), 2.40 (s, 3H, H_{11}), 1.90 – 1.78 (m, 1H, H_{3A}), 1.55 – 1.47 (m, 1H, H_{3B}).
^{13}C–NMR (75 MHz, C_6D_6)	δ: 147.6, 144.9, 141.8, 129.7, 129.4, 124.4, 123.8, 120.4, 119.5, 118.3, 114.1, 109.7, 80.7, 66.8, 59.0, 57.1, 33.8, 29.9, 21.7.
HRMS (70 eV, IE)	Calculated for $[C_{21}H_{22}N_2O]^+$: 318.1727, found 318.1736.

(3a*R,4*R**,9c*R**)-*N*-(4-Fluorophenyl)-5,8-dimethyl-2,3,3a,4,5,9c-hexahydrofuro[2',3':3,4]cyclopenta[1,2-*b*]indol-4-amine (49l)**



Brown solid

mp= 174 – 176 °C

R_f= 0.30 (hexane:diethyl ether, 2:1).

Isolated yield: 82%

^{1}H–NMR
(300 MHz, C_6D_6)

δ: 7.73 (d, *J*= 1.7 Hz, 1H, H_9), 7.12 (dd, *J*= 8.4, 1.5 Hz, 1H, H_7), 7.01 (d, *J*= 8.4 Hz, 1H, H_6), 6.87 (t, J_{H-F}= 8.9 Hz, *J*= 8.9 Hz, 2H, $H_{3'}$), 6.22 (dd, *J*= 8.9 Hz, J_{H-F}= 4.4 Hz, 2H, $H_{2'}$), 5.73 (dd, *J*= 6.5, 1.5 Hz, 1H, H_{9c}), 4.35 (br s, 1H, H_4), 3.70 (ddd, *J*= 8.5, 6.8, 4.4 Hz, 1H, H_{2A}), 3.56 (td, *J*= 8.5, 6.0 Hz, 1H, H_{2B}), 3.08 (s, 3H, H_{10}), 3.02 (br s, 1H, NH), 2.82 – 2.73 (m, 1H, H_{3a}), 2.40 (s, 3H, H_{11}), 1.87 – 1.73 (m, 1H, H_{3A}), 1.49 – 1.39 (m, 1H, H_{3B}).

^{13}C–NMR
(75 MHz, C_6D_6)

δ: 156.6 (d, J_{C-F}= 235.15 Hz), 144.7, 143.8, 141.8, 129.5, 124.3, 123.9, 120.4, 119.5, 116.1 (d, J_{C-F}= 22.3 Hz), 115.0 (d, J_{C-F}= 7.13 Hz), 109.7, 80.7, 66.8, 59.6, 56.8, 33.7, 29.9, 21.7.

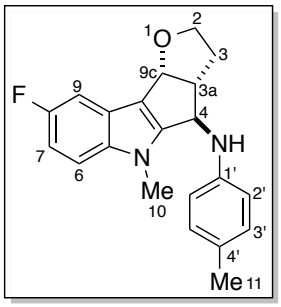
^{19}F–NMR
(282 MHz, $CDCl_3$)

δ: –123.3.

HRMS
(70 eV, IE)

Calculated for $[C_{21}H_{21}FN_2O]^+$: 336.1632, found 336.1632.

(3a*R,4*R**,9c*R**)-8-Fluoro-5-methyl-*N*-(*p*-tolyl)-2,3,3a,4,5,9c-hexahydrofuro[2',3':3,4]cyclopenta[1,2-*b*]indol-4-amine (49m)**



Light brown solid

mp= 151 – 153 °C

R_f = 0.28 (hexane:diethyl ether, 2:1).

Isolated yield: 85%

^{1}H–NMR
(300 MHz, C_6D_6)

δ: 7.60 (dd, $J_{H\text{-}F}$= 9.4 Hz, J= 2.5 Hz, 1H, H_9), 7.03 (d, J= 8.4 Hz, 2H, $H_{2'}$), 6.98 (td, $J_{H\text{-}F}$= 9.0 Hz, J= 9.0, 2.8 Hz, 1H, H_7), 6.73 (dd, J= 9.0 Hz, $J_{H\text{-}F}$= 4.3 Hz, 1H, H_6), 6.45 (d, J= 8.4 Hz, 2H, $H_{3'}$), 5.60 (dd, J= 6.5, 1.5 Hz, 1H, H_{9c}), 4.47 (br s, 1H, H_4), 3.65 (ddd, J= 8.7, 6.9, 4.6 Hz, 1H, H_{2A}), 3.51 (td, J= 8.7, 5.9 Hz, 1H, H_{2B}), 3.06 (br s, 1H, NH), 3.00 (s, 3H, H_{10}), 2.89 – 2.82 (m, 1H, H_{3a}), 2.22 (s, 3H, H_{11}), 1.83 (dddd, J= 12.3, 9.7, 8.7, 6.9 Hz, 1H, H_{3A}), 1.54 – 1.45 (m, 1H, H_{3B}).

^{13}C–NMR
(75 MHz, C_6D_6)

δ: 158.8 (d, $J_{C\text{-}F}$= 235.2 Hz), 146.8, 145.2, 139.7, 130.3, 127.4, 124.3 (d, $J_{C\text{-}F}$= 10.0), 119.7 (d, $J_{C\text{-}F}$= 4.6 Hz), 114.5, 110.6 (d, $J_{C\text{-}F}$= 9.6 Hz), 110.3 (d, $J_{C\text{-}F}$= 26.0 Hz), 110.2, 80.3, 66.9, 59.4, 56.9, 33.8, 30.0, 20.6.

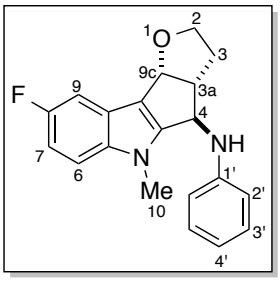
^{19}F–NMR
(282 MHz, $CDCl_3$)

δ: –123.6.

HRMS
(70 eV, IE)

Calculated for $[C_{21}H_{21}FN_2O]^+$: 336.1632, found 336.1639.

(3a*R,4*R**,9c*R**)-8-Fluoro-5-methyl-*N*-phenyl-2,3,3a,4,5,9c-hexahydrofuro[2',3':3,4]cyclopenta[1,2-*b*]indol-4-amine (49n)**



Light brown solid

mp= 130 – 132 °C

R_f= 0.28 (hexane:diethyl ether, 2:1).

Isolated yield: 87%

^{1}H–NMR
(300 MHz, C_6D_6)

δ: 7.59 (dd, $J_{H\text{-}F}$= 9.4 Hz, J= 2.5 Hz, 1H, H_9), 7.21 (dd, J= 8.5, 7.2 Hz, 2H, $H_{3'}$), 6.97 (td, $J_{H\text{-}F}$= 9.0 Hz, J= 9.0, 2.6 Hz, 1H, H_7), 6.81 (t, J= 7.2 Hz, 1H, $H_{4'}$), 6.73 (dd, J= 9.0 Hz, $J_{H\text{-}F}$= 4.3 Hz, 1H, H_6), 6.50 – 6.47 (m, 2H, $H_{2'}$), 5.57 (d, J= 6.5 Hz, 1H, H_{9c}), 4.45 (s, 1H, H_4), 3.63 (ddd, J= 8.6, 6.8, 4.6 Hz, 1H, H_{2A}), 3.50 (td, J= 8.6, 6.0 Hz, 1H, H_{2B}), 3.21 (br s, 1H, NH), 3.02 (s, 3H, H_{10}), 2.83 – 2.76 (m, 1H, H_{3a}), 1.80 (dddd, J= 12.3, 9.7, 8.6, 6.8 Hz, 1H, H_{3A}), 1.53 – 1.42 (m, 1H, H_{3B}).

^{13}C–NMR
(75 MHz, C_6D_6)

δ: 158.8 (d, $J_{C\text{-}F}$= 235.3 Hz), 147.4, 146.6, 139.7, 129.8, 124.2 (d, $J_{C\text{-}F}$= 10.4 Hz), 119.8 (d, $J_{C\text{-}F}$= 4.5 Hz), 118.5, 114.2, 110.6 (d, $J_{C\text{-}F}$= 10.0 Hz), 110.3 (d, $J_{C\text{-}F}$= 26.7 Hz), 105.4 (d, $J_{C\text{-}F}$= 23.9 Hz), 80.3, 66.9, 59.0, 57.0, 33.7, 30.0.

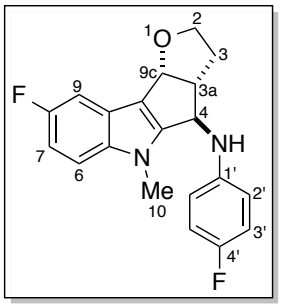
^{19}F–NMR
(282 MHz, $CDCl_3$)

δ: –123.6.

HRMS
(70 eV, IE)

Calculated for $[C_{20}H_{19}FN_2O]^+$: 322.1476 found 322.1478.

(3a*R,4*R**,9c*R**)-8-Fluoro-*N*-(4-fluorophenyl)-5-methyl-2,3,3a,4,5,9c-hexahydrofuro[2',3':3,4]cyclopenta[1,2-*b*]indol-4-amine (49o)**



Light brown solid

mp= 175– 177 °C

R_f = 0.20 (hexane:diethyl ether, 2:1).

Isolated yield: 87%

^{1}H–NMR
(300 MHz, C_6D_6)

δ: 7.60 (dd, $J_{H\text{-}F}$= 9.3 Hz, J= 2.5 Hz, 1H, H_9), 6.99 (td, $J_{H\text{-}F}$= 9.0 Hz, J= 9.0, 2.6 Hz, 1H, H_7), 6.87 (t, J= 8.9 Hz, 2H, $H_{3'}$), 6.74 (dd, J= 9.0 Hz, $J_{H\text{-}F}$= 4.2 Hz, 1H, H_6), 6.20 (dd, J= 8.9 Hz, $J_{H\text{-}F}$= 4.3 Hz, 2H, $H_{2'}$), 5.58 (dd, J= 6.5, 1.5 Hz, 1H, H_{9c}), 4.29 (br s, 1H, H_4), 3.65 (ddd, J= 8.7, 6.9, 4.6 Hz, 1H, H_{2A}), 3.50 (td, J= 8.7, 6.0 Hz, 1H, H_{2B}), 2.90 (br s, NH) 2.97 (s, 3H, H_{10}), 2.75 – 2.68 (m, 1H, H_{3a}), 1.76 (dddd, J= 12.3, 9.8, 8.7, 6.9 Hz, 1H, H_{3A}), 1.45 – 1.36 (m, 1H, H_{3B}).

^{13}C–NMR
(75 MHz, C_6D_6)

δ: 158.9 (d, $J_{C\text{-}F}$= 231.15 Hz), 156.6 (d, $J_{C\text{-}F}$= 235.4 Hz), 146.3, 143.6, 139.7, 124.2 (d, $J_{C\text{-}F}$= 10.5 Hz), 119.9 (d, $J_{C\text{-}F}$= 4.7 Hz), 116.2 (d, $J_{C\text{-}F}$= 22.2 Hz), 110.6, 110.4 (d, $J_{C\text{-}F}$= 16.8 Hz), 105.5 (d, $J_{C\text{-}F}$= 23.9 Hz), 80.3, 66.9, 59.5, 56.7, 33.7, 30.0.

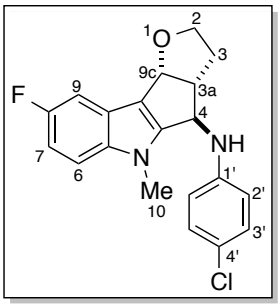
^{19}F–NMR
(282 MHz, $CDCl_3$)

δ: –126.7, –123.4.

HRMS
(70 eV, IE)

Calculated for $[C_{20}H_{18}F_2N_2O]^+$: 340.1382, found 340.1378.

(3a*R,4*R**,9c*R**)-8-*N*-(4-Chlorophenyl)-8-fluoro-5-methyl-2,3,3a,4,5,9c-hexahydrofuro[2',3':3,4]cyclopenta[1,2-*b*]indol-4-amine (49p)**



Brown solid

mp= 194– 196 °C

R_f= 0.20 (hexane:diethyl ether, 2:1).

Isolated yield: 90%

^{1}H–NMR
(300 MHz, C_6D_6)

δ: 7.60 (dd, $J_{H\text{-}F}$= 9.3 Hz, J= 2.5 Hz, 1H, H_9), 7.14 (d, J= 8.8 Hz, 2H, $H_{3'}$), 6.99 (td, $J_{H\text{-}F}$= 9.0 Hz, J= 9.0, 2.6 Hz, 1H, H_7), 6.73 (dd, J= 9.0 Hz, $J_{H\text{-}F}$= 4.2 Hz, 1H, H_6), 6.16 (d, J= 8.8 Hz, 2H, $H_{2'}$), 5.57 (dd, J= 6.5, 1.5 Hz, 1H, H_{9c}), 4.26 (d, J= 8.8 Hz, 1H, H_4), 3.65 (ddd, J= 8.7, 6.9, 4.6 Hz, 1H, H_{2A}), 3.49 (td, J= 8.7, 6.0 Hz, 1H, H_{2B}), 2.95 (br s, 1H, NH), 2.92 (s, 3H, H_{10}), 2.71 – 2.63 (m, 1H, H_{3a}), 1.75 (dddd, J= 12.3, 9.7, 8.7, 6.9 Hz, 1H, H_{3A}), 1.42 – 1.33 (m, 1H, H_{3B}).

^{13}C–NMR
(75 MHz, acetone-d_6)

δ: 158.9 (d, $J_{C\text{-}F}$= 233.1 Hz), 148.3, 147.7, 140.4, 129.9, 124.5 (d, $J_{C\text{-}F}$= 10.2 Hz), 122.0, 119.8 (d, $J_{C\text{-}F}$= 4.8 Hz), 115.7, 111.8 (d, $J_{C\text{-}F}$= 10.1 Hz), 110.2 (d, $J_{C\text{-}F}$= 25.9 Hz), 104.9 (d, $J_{C\text{-}F}$= 23.8 Hz), 80.8, 67.3, 59.4, 57.7, 34.0, 31.0.

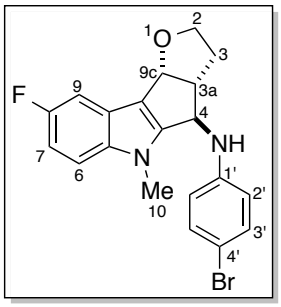
^{19}F–NMR
(282 MHz, $CDCl_3$)

δ: –123.3.

HRMS
(70 eV, IE)

Calculated for $[C_{20}H_{18}ClFN_2O]^+$: 356.1086, found 356.1088.

(3a*R,4*R**,9c*R**)-*N*-(4-Bromophenyl)-8-fluoro-5-methyl-2,3,3a,4,5,9c-hexahydrofuro[2',3':3,4]cyclopenta[1,2-*b*]indol-4-amine (49q)**



Light brown solid

mp= 225– 227 °C

R_f= 0.28 (hexane:diethyl ether, 2:1).

Isolated yield: 87%

^{1}H–NMR (300 MHz, C_6D_6)

δ: 7.60 (dd, $J_{H\text{-}F}$= 9.3 Hz, *J*= 2.5 Hz, 1H, H_9), 7.26 (d, *J*= 8.8 Hz, 2H, $H_{3'}$), 6.99 (td, $J_{H\text{-}F}$= 9.0 Hz, *J*= 9.0, 2.5 Hz, 1H, H_7), 6.73 (dd, *J*= 9.0 Hz, *J*= 4.2 Hz, 1H, H_6), 6.10 (d, *J*= 8.8 Hz, 2H, $H_{2'}$), 5.57 (dd, *J*= 6.5, 1.6 Hz, 1H, H_{9c}), 4.24 (d, *J*= 9.4 Hz, 1H, H_4), 3.65 (ddd, *J*= 8.6, 6.9, 4.6 Hz, 1H, H_{2A}), 3.48 (td, *J*= 8.6, 5.9 Hz, 1H, H_{2B}), 2.95 (br s, 1H, NH), 2.91 (s, 3H, H_{10}), 2.70 – 2.62 (m, 1H, H_{3a}), 1.80 – 1.68 (m, 1H, H_{3A}), 1.41 – 1.32 (m, 1H, H_{3B}).

^{13}C–NMR (75 MHz, acetone-d_6)

δ: 158.9 (d, $J_{C\text{-}F}$= 232.5 Hz), 148.3, 148.1, 140.4, 132.8, 124.5 (d, $J_{C\text{-}F}$= 10.1 Hz), 116.3, 111.8 (d, $J_{C\text{-}F}$= 9.7 Hz), 110.3 (d, $J_{C\text{-}F}$= 26.0 Hz), 109.0, 104.9 (d, $J_{C\text{-}F}$= 23.8 Hz), 80.9, 67.3, 59.4, 57.7, 34.0, 31.0.

^{19}F–NMR (282 MHz, $CDCl_3$)

δ: –123.3.

HRMS (70 eV, IE)

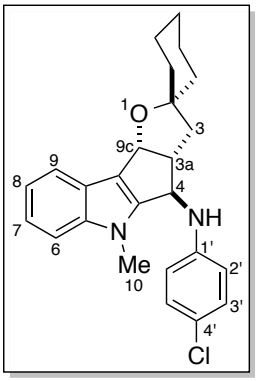
Calculated for $[C_{20}H_{18}BrFN_2O]^+$: 400.0581, found 400.0586.

- **General Procedure for the Synthesis of the Cyclopenta[*b*]indole Derivatives 49r-t**

The corresponding 1-methyl-1*H*-indole-2-carbaldehydederivative **41** (0.2 mmol), aniline **34** (1.5 equiv, 0.3 mmol), diphenyl phosphate (30 mol%) and 4 Å powder molecular sieves (50 mg) were placed in a glass reaction tube equipped with a magnetic stirring bar under argon atmosphere. Then, dichloromethane (2 mL) was added at 0 °C. The mixture was allowed to warm to room temperature and stirred at this temperature for 1 hour. Then, 1-oxaspiro[4.5]dec-2-ene (3 equiv, 0.6 mmol) was added at room temperature. The reaction was kept at this temperature for additional 12 hours. Finally, the resulting slurry was filtered

through a pad of basic alumina eluting with ethyl acetate, the solvent was removed under vacuum and the crude was purified by flash column chromatography on silica gel using mixtures of hexane and diethyl ether as eluent to give pure **49r-t**.

(3a'*R,4'*R**,9c'*R**)-*N*-(4-Chlorophenyl)-5'-methyl-3a',4',5',9c'-tetrahydro-3'*H*-spiro[cyclohexane-1,2'-furo[2',3':3,4]cyclopenta[1,2-*b*]indol]-4'-amine (49r)**



Brown solid

mp= 156– 158 °C

R_f= 0.40 (hexane:diethyl ether, 4:1).

Isolated yield: 54%

^{1}H–NMR
(300 MHz, C_6D_6)

δ: 7.95 (dd, *J*= 6.8, 1.3 Hz, 1H, H_9), 7.27 – 7.17 (m, 2H, H_7 and H_8), 7.17 (d, *J*= 8.7 Hz, 2H, $H_{3'}$), 7.05 (dd, *J*= 7.2, 1.3 Hz, 1H, H_6), 6.25 (d, *J*= 8.7 Hz, 2H, $H_{2'}$), 5.70 (dd, *J*= 6.9, 1.7 Hz, 1H, H_{9c}), 4.44 (d, *J*= 9.5 Hz, 1H, H_4), 3.12 (d, *J*= 9.5 Hz, 1H, NH), 3.03 (s, 3H, H_{10}), 3.02 – 2.94 (m, 1H, H_{3a}), 2.06 (dd, *J*= 12.1, 9.5 Hz, 1H, H_{3A}), 1.84 – 1.22 (m, 11H, H_{3B} and H_{Cy}).

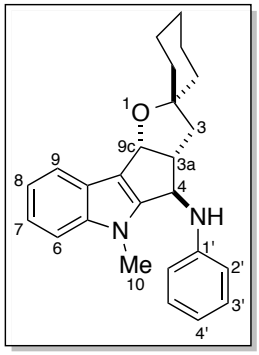
^{13}C–NMR
(75 MHz, C_6D_6)

δ: 146.0, 143.1, 142.7, 129.6, 124.1, 122.9, 122.5, 122.4, 120.5, 115.0, 110.0, 84.8, 79.2, 59.0, 57.2, 43.9, 38.8, 35.9, 29.8, 26.2, 24.1, 23.7.

HRMS
(70 eV, IE)

Calculated for $[C_{25}H_{27}ClN_2O]^+$: 406.1806, found 406.1811.

(3a'*R,4'*R**,9c'*R**)-5'-Methyl-*N*-phenyl-3a',4',5',9c'-tetrahydro-3'*H*-spiro[cyclohexane-1,2'-furo[2',3':3,4]cyclopenta[1,2-*b*]indol]-4'-amine (49s)**



Brown solid

mp= 179– 181 °C

R_f = 0.40 (hexane:diethyl ether, 4:1).

Isolated yield: 50%

^{1}H–NMR
(300 MHz, C_6D_6)

δ: 7.95 (dd, *J*= 6.8, 1.5 Hz, 1H, H_9), 7.27 – 7.18 (m, 4H, H_7, H_8, and $H_{3'}$), 7.04 (dd, *J*= 7.2, 1.5 Hz, 1H, H_6), 6.82 (t, *J*= 7.4 Hz, 1H, $H_{4'}$), 6.55 (d, *J*= 7.4 Hz, 2H, $H_{2'}$), 5.72 (dd, *J*= 6.9, 1.7 Hz, 1H, H_{9c}), 4.62 (d, *J*= 8.1 Hz, 1H, H_4), 3.27 (app. d, *J*= 8.9 Hz, 1H, NH), 3.16 – 3.05 (m, 1H, H_{3a}), 3.06 (s, 3H, H_{10}), 2.12 (dd, *J*= 12.1, 9.5 Hz, 1H, H_{3A}), 1.80 – 1.20 (m, 11H, H_{3B} and H_{Cy}).

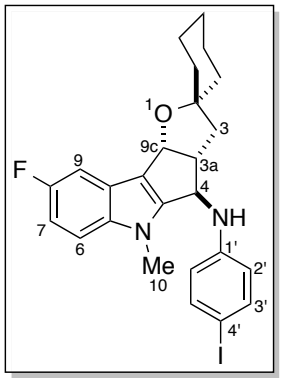
^{13}C–NMR
(75 MHz, C_6D_6)

δ: 147.6, 143.2, 143.1, 129.8, 124.2, 122.5, 122.2, 120.5, 120.4, 118.3, 114.0, 110.0, 84.7, 79.2, 59.0, 57.4, 43.9, 38.8, 35.9, 29.8, 26.3, 24.1, 23.7.

HRMS
(70 eV, IE)

Calculated for $[C_{25}H_{28}N_2O]^+$: 372.2196, found 372.2200.

(3a'*R,4'*R**,9c'*R**)-8'-Fluoro-*N*-(4-iodophenyl)-5'-methyl-3a',4',5',9c'-tetrahydro-3'*H*-spiro[cyclohexane-1,2'-furo[2',3':3,4]cyclopenta[1,2-*b*]indol]-4'-amine (49t)**



Brown oil

R_f = 0.50 (hexane:diethyl ether, 2:1).

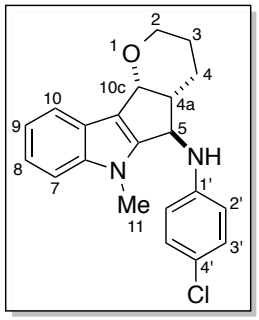
Isolated yield: 52%

^{1}H–NMR (300 MHz, C_6D_6)	δ: 7.60 (dd, $J_{H\text{-}F}$= 9.4 Hz, *J*= 2.5 Hz, 1H, H_9), 7.46 (d, *J*= 8.6 Hz, 2H, $H_{3'}$), 6.97 (td, *J*= 9.0 Hz, $J_{H\text{-}F}$= 2.5 Hz, 1H, H_7), 6.72 (dd, *J*= 9.0 Hz, $J_{H\text{-}F}$= 4.2 Hz, 1H, H_6), 6.09 (d, *J*= 8.6 Hz, 2H, $H_{2'}$), 5.56 (dd, *J*= 6.9, 1.6 Hz, 1H, H_{9c}), 4.37 (d, *J*= 9.5 Hz, 1H, H_4), 3.07 (d, *J*= 9.5 Hz, 1H, NH), 2.96 – 2.87 (m, 1H, H_{3a}), 2.92 (s, 3H, H_{10}), 2.02 (dd, *J*= 12.2, 9.4 Hz, 1H, H_{3A}), 1.83 – 1.20 (m, 11H, H_{3B} and H_{Cy}).
^{19}F–NMR (282 MHz, $CDCl_3$)	δ: –123.5.
^{13}C–NMR (75 MHz, C_6D_6)	δ: 158.8 (d, $J_{C\text{-}F}$= 235.0 Hz), 146.8, 144.5, 139.5, 138.41, 124.2 (d, $J_{C\text{-}F}$= 10.2 Hz), 122.4 (d, $J_{C\text{-}F}$= 4.8 Hz), 116.1, 110.6, 110.4 (d, $J_{C\text{-}F}$= 16.7 Hz), 105.6 (d, $J_{C\text{-}F}$= 23.9 Hz), 84.8, 79.1, 78.8, 58.8, 57.2, 43.9, 38.7, 35.8, 29.9, 26.2, 24.1, 23.6.
HRMS (70 eV, IE)	Calculated for $[C_{25}H_{26}FIN_2O]^+$: 516.1068, found 516.1066.

- **General Procedure for the Synthesis of the Cyclopenta[*b*]indole Derivatives 49u-v**

The corresponding 1-methyl-1*H*-indole-2-carbaldehyde derivative **41** (0.2 mmol), aniline **34** (1.5 equiv, 0.3 mmol) and 4 Å powder molecular sieves (50 mg) were placed in a glass reaction tube equipped with a magnetic stirring bar under argon atmosphere. Then, dichloromethane (2 mL) was added, the slurry was cooled to 0 °C and and $ClSO_3H$ (10 mol%) was added. The mixture was allowed to warm to room temperature and stirred at this temperature for 1 hour. Then, 2,3-dihydro-2*H*-pyran (3 equiv, 0.6 mmol) was added at room temperature. The reaction was kept at this temperature for additional 12 hours. Finally, the resulting slurry was filtered through a pad of basic alumina eluting with ethyl acetate, the solvent was removed under vacuum and the crude was purified by flash column chromatography on silica gel using mixtures of hexane and diethyl ether as eluent to give pure **49u-v**.

(4a*R,5*R**,10c*R**)-*N*-(4-Chlorophenyl)-6-methyl-3,4,4a,5,6,10c-hexahydro-2*H*-pyrano[2',3':3,4]cyclopenta[1,2-*b*]indol-5-amine (49u)**



Brown solid

mp= 172– 174 °C

R_f = 0.20 (hexane:diethyl ether, 2:1).

Isolated yield: 87%

^{1}H–NMR
(300 MHz, acetone-d_6)

δ: 7.50 (d, *J*= 7.8 Hz, 1H, H_{10}), 7.34 (d, *J*= 8.1 Hz, 1H, H_7), 7.17 – 7.11 (m, 1H, H_8), 7.14 (d, *J*= 8.8 Hz, 2H, $H_{2'}$), 7.09 – 7.03 (m, 1H, H_9), 6.81 (d, *J*= 8.8 Hz, 2H, $H_{3'}$), 5.50 (d, *J*= 9.2 Hz, 1H, NH), 5.07 (dd, *J*= 9.2, 6.7 Hz, 1H, H_5), 5.03 (d, *J*= 4.8 Hz, 1H, H_{10c}), 3.77 – 3.70 (m, 1H, H_{2A}), 3.64 (s, 3H, H_{11}), 3.50 (ddd, *J*= 11.1, 9.7, 3.0 Hz, 1H, H_{2B}), 2.66 – 2.59 (m, 1H, H_{4a}), 1.99 – 1.83 (m, 2H, H_3), 1.79 – 1.62 (m, 1H, H_{4A}), 1.58 – 1.46 (m, 1H, H_{4B}).

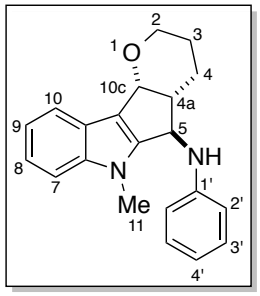
^{13}C–NMR
(75 MHz, acetone-d_6)

δ: 148.5, 142.5, 129.9, 124.7, 121.9, 121.6, 120.4, 119.9, 119.7, 115.2, 110.7, 74.0, 65.3, 56.1, 51.6, 30.7, 24.4, 23.2.

HRMS
(70 eV, IE)

Calculated for $[C_{21}H_{21}ClN_2O]^+$: 352.1337, found 352.1339.

(4a*R,5*R**,10c*R**)-6-Methyl-*N*-phenyl-3,4,4a,5,6,10c-hexahydro-2*H*-pyrano[2',3':3,4]cyclopenta[1,2-*b*]indol-5-amine (49v)**



Brown solid

mp= 164– 166 °C

R_f = 0.18 (hexane:diethyl ether, 2:1).

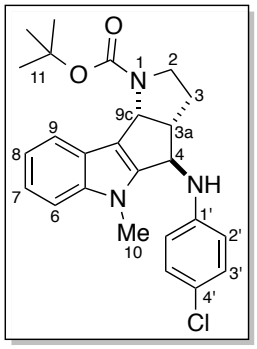
Isolated yield: 87%

^{1}H–NMR (300 MHz, C_6D_6)	δ: 7.95 – 7.87 (m, 1H, H_{10}), 7.27 – 7.21 (m, 2H, H_8 and H_9), 7.12 (d, *J*= 8.0 Hz, 2H, $H_{3'}$), 7.08 – 7.02 (m, 1H, H_7), 6.73 (app. t, *J*= 7.3 Hz, 1H, $H_{4'}$), 6.42 (d, *J*= 8.0 Hz, 2H, $H_{2'}$), 5.06 (d, *J*= 4.7 Hz, 1H, H_{10c}), 4.73 (app. t, *J*= 7.1 Hz, 1H, H_5), 3.82 – 3.71 (m, 1H, H_{2A}), 3.44 – 3.32 (m, 1H, H_{2B}), 3.04 (s, 4H, H_{11} and NH), 2.26 (app. quintuplet, *J*= 5.2 Hz, 1H, H_{4a}), 1.77 – 1.13 (m, 4H, H_3 and H_4).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 147.6, 147.5, 141.8, 129.7, 123.3, 121.6, 120.2, 119.3, 118.9, 118.0, 113.4, 109.9, 73.5, 65.3, 55.5, 51.6, 30.6, 23.8, 22.5.
HRMS (70 eV, IE)	Calculated for $[C_{21}H_{22}N_2O]^+$: 318.1727, found 318.1731.

- **General Procedure for the Synthesis of the Hexahydropyrrolocyclopenta[*b*]indole Derivatives 51a-c**

The corresponding 1-methyl-1*H*-indole-2-carbaldehydederivative **41** (0.2 mmol), aniline **34** (1.5 equiv, 0.3 mmol), diphenyl phosphate (10 mol%) and 4 Å powder molecular sieves (50 mg) were placed in a glass reaction tube equipped with a magnetic stirring bar under argon atmosphere. Then, dichloromethane (2 mL) was added at 0 °C. The mixture was allowed to warm to room temperature and stirred at this temperature for 1 hour. Then, the *N*-protected 2,3-dihydropyrrole derivative **14** (3 equiv, 0.6 mmol, in 2 mL of dichloromethane) was added at room temperature over 5 hours via syringe pump. The reaction was kept at this temperature for additional 12 hours. Finally, the resulting slurry was filtered through a pad of basic alumina eluting with ethyl acetate, the solvent was removed under vacuum and the crude was purified by flash column chromatography on silica gel using mixtures of hexane and diethyl ether as eluent to give pure **51a-c**.

tert-Butyl (3a*R,4*R**,9c*R**)-4-((4-chlorophenyl)amino)-5-methyl-2,3,3a,4,5,9c-hexahydro-1*H*-pyrrolo[2',3':3,4]cyclopenta[1,2-*b*]indole-1-carboxylate (51a)**



Mixture of rotamers at room temperature

Brown solid

mp= 210 – 212 °C

R_f = 0.20 (hexane:diethyl ether, 2:1).

Isolated yield: 87%

^{1}H–NMR
(300 MHz, C_6D_6)

δ: 8.76 (d, *J*= 6.7 Hz, 1H, $H_{9\ major\ rota.}$), 8.35 (d, *J*= 6.7 Hz, 1H, $H_{9\ minor\ rota.}$), 7.44 – 7.31 (m, 2H, H_7 and $H_{8\ major\ and\ minor\ rota.}$), 7.26 (d, *J*= 8.3 Hz, 2H, $H_{3'\ major\ and\ minor\ rota.}$), 7.16 (d, *J*= 7.6 Hz, 1H, $H_{6\ major\ and\ minor\ rota.}$), 6.35 (d, *J*= 8.3 Hz, 2H, $H_{2'\ major\ rota.}$), 6.24 (d, *J*= 8.3 Hz, 2H, $H_{2'\ minor\ rota.}$), 5.50 (d, *J*= 7.0 Hz, 1H, $H_{9c\ major\ and\ minor\ rota.}$), 4.35 (d, *J*= 8.7 Hz, 1H, $H_{4\ major\ rota.}$), 4.24 (d, *J*= 8.2 Hz, 1H, $H_{4\ minor\ rota.}$), 3.68 – 3.77 (m, 1H, $NH_{\ minor\ rota.}$), 3.55 (app. d, *J*= 9.5 Hz, 1H, $NH_{\ major\ rota.}$), 3.43 – 3.24 (m, 2H, $H_{2\ major\ and\ minor\ rota.}$), 3.18 (s, 3H, $H_{10\ major\ rota.}$), 3.14 (s, 3H, $H_{10\ minor\ rota.}$), 2.73 (app. q, *J*= 7.8 Hz, 1H, $H_{3a\ major\ and\ minor\ rota.}$), 1.88 – 1.59 (m, 1H, $H_{3A\ major\ and\ minor\ rota.}$), 1.83 (s, 9H, $H_{11\ minor\ rota.}$), 1.65 (s, 9H, $H_{11\ major\ rota.}$), 1.53 – 1.28 (m, 1H, $H_{3B\ major\ and\ minor\ rota.}$).

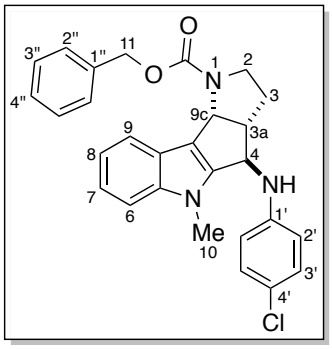
^{13}C–NMR
(75 MHz, C_6D_6)

δ (major rota.): 154.7, 146.1, 143.0, 142.6, 129.6, 124.4, 123.0, 122.7, 122.5, 122.2, 120.5, 114.9, 109.6, 78.9, 60.2, 57.5, 54.6, 46.1, 30.8, 29.9, 28.7.

HRMS
(70 eV, IE)

Calculated for $[C_{25}H_{28}ClN_3O_2]^+$: 437.1865, found 437.1878.

Benzyl (3a*R,4*R**,9c*R**)-4-((4-chlorophenyl)amino)-5-methyl-2,3,3a,4,5,9c-hexahydro-1*H*-pyrrolo[2',3':3,4]cyclopenta[1,2-*b*]indole-1-carboxylate (51b)**



Mixture of rotamers at room temperature

Brown solid

mp= 196 – 198 °C

R_f = 0.20 (hexane:diethyl ether, 2:1).

Isolated yield: 87%

^{1}H–NMR
(300 MHz, C_6D_6)

δ: 8.66 – 8.63 (m, 1H, $H_{9\ major\ rota.}$), 7.83 (d, *J*= 7.9 Hz, 1H, $H_{9\ minor\ rota.}$), 7.48 (d, *J*= 7.4 Hz, 2H, $H_{2''\ minor\ rota.}$), 7.31 – 7.02 (m, 10H, H_6, H_7, H_8, $H_{3'}$, $H_{3''}$, $H_{4''\ major\ and\ minor\ rota.}$, $H_{2''\ major\ rota.}$), 6.25 (d, *J*= 8.7 Hz, 2H, $H_{2'\ major\ rota.}$), 6.12 (d, *J*= 8.7 Hz, 2H, $H_{2'\ minor\ rota.}$), 5.48 (d, *J*= 12.0 Hz, 1H, $H_{11A\ minor\ rota.}$), 5.34 (d, *J*= 12.6 Hz, 1H, $H_{11B\ minor\ rota.}$), 5.38 (d, *J*= 7.3 Hz, 1H, $H_{9c\ major\ and\ minor\ rota.}$), 5.26 (d, *J*= 12.5 Hz, 1H, $H_{11A\ major\ rota.}$), 5.18 (d, *J*= 12.5 Hz, 1H, $H_{11B\ major\ rota.}$), 4.23 (d, *J*= 9.1 Hz, 1H, $H_{4\ major\ rota.}$), 4.15 (d, *J*= 9.2 Hz, 1H, $H_{4\ minor\ rota.}$), 3.67 – 3.57 (m, $NH_{\ minor\ rota.}$), 3.55 (app. d, *J*= 9.6 Hz, 1H, $NH_{\ major\ rota.}$), 3.30 – 3.12 (m, 2H, $H_{2\ major\ and\ minor\ rota.}$), 3.06 (s, 3H, $H_{10\ major\ rota.}$), 3.01 (s, 3H, $H_{10\ minor\ rota.}$), 2.65 – 2.53 (m, 1H, $H_{3a\ major\ and\ minor\ rota.}$), 1.64 – 1.16 (m, 2H, $H_{3\ major\ and\ minor\ rota.}$).

^{13}C–NMR
(75 MHz, C_6D_6)

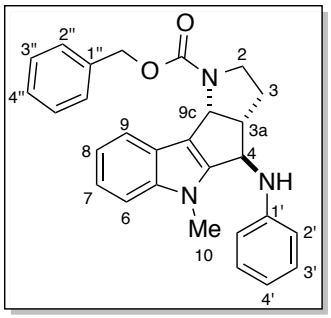
δ (major rota): 155.2, 146.1, 143.0, 142.7, 137.9, 129.6, 128.3, 124.3, 122.9, 122.8, 122.6, 121.8, 120.5, 114.9, 109.6, 66.9, 60.8, 57.3, 54.6, 46.0, 30.6, 29.9.

δ (minor rota): 154.9, 145.8, 143.1, 142.9, 137.7, 129.1, 128.3, 124.2, 122.3, 122.0, 121.3, 120.7, 120.5, 114.9, 109.8, 67.3, 60.1, 57.1, 56.0, 46.6, 32.0, 29.6

HRMS
(70 eV, IE)

Calculated for $[C_{28}H_{26}ClN_3O_2]^+$: 471.1708, found 471.1718.

tert-Butyl (3a*R,4*R**,9c*R**)-5-Methyl-4-(phenylamino)-2,3,3a,4,5,9c-hexahydro-1*H*-pyrrolo[2',3':3,4]cyclopenta[1,2-*b*]indole-1-carboxylate (51c)**



Mixture of rotamers at room temperature

Brown oil

R_f = 0.13 (hexane:diethyl ether, 2:1)

Isolated yield: 85%

^{1}H–NMR
(300 MHz, CD_2Cl_2)

δ: 7.95 (d, *J*= 8.0 Hz, 2H, $H_{2'' \text{ minor rota.}}$), 7.59 – 7.16 (m, 8H, $H_{3' \text{ major and minor rota}}$, $H_{4'' \text{ major and minor rota}}$, $H_{6 \text{ major and minor rota}}$, $H_{7 \text{ major and minor rota}}$, $H_{8 \text{ major and minor rota}}$, $H_{9 \text{ major and minor rota}}$ and $H_{2'' \text{ major rota}}$, $H_{3'' \text{ major rota}}$), 7.11 (app. t, *J*= 7.5 Hz, 2H, $H_{3'' \text{ minor rota}}$), 6.78 (t, *J*= 7.5 Hz, 1H, $H_{4' \text{ major and minor rota}}$), 6.72 (d, *J*= 7.5 Hz, 2H, $H_{2' \text{ major and minor rota}}$), 5.57 (d, *J*= 7.0 Hz, 1H, $H_{9c \text{ minor rota}}$), 5.49 (d, *J*=7.0 Hz, 1H, $H_{9c \text{ major rota}}$), 5.41 (d, *J*= 12.0 Hz, 1H, $H_{11A \text{ minor rota}}$), 5.32 (d, *J*= 12.0 Hz, 1H, $H_{11B \text{ minor rota}}$), 5.22 (br s, 2H, $H_{11 \text{ major rota}}$), 4.89 (br s, 1H, $H_{4 \text{ major and minor rota}}$), 4.10 (br s, 1H, $NH_{\text{ major rota}}$), 4.02 (br s, 1H, $NH_{\text{ minor rota}}$), 3.69 (s, 3H, $H_{10 \text{ major and minor rota}}$), 3.64 – 3.27 (m, 3H, H_2 and $H_{3a \text{ major and minor rota}}$), 2.45 – 2.24 (m, 1H, $H_{3A \text{ major and minor rota}}$), 2.06 – 1.88 (m, 1H, $H_{3B \text{ major and minor rota}}$).

^{13}C–NMR
(C_6D_6)

δ (rota major): 155.5, 147.6, 144.2, 143.0, 138.0, 130.0, 129.0, 128.9, 128.3, 128.3, 122.3, 122.2, 121.3, 121.0, 120.1, 118.5, 114.1, 110.2, 110.0, 67.1, 61.0, 57.9, 55.3, 46.5, 31.2, 30.9.

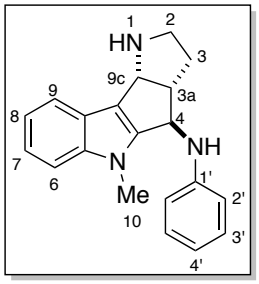
HRMS
(70 eV, IE)

Calculated for $[C_{28}H_{27}N_3O_2]^+$: 437.2098, found 437.2095.

- **General Procedure for the Synthesis of the Hexahydropyrrolocyclopenta[*b*]indole Derivative 51d.**

A oven dried flask equipped with a magnetic stirring bar was charged with palladium on carbon (5% w/w) and to this flask was added a solution of compound **51c** (0.17 mmol) in MeOH:DCM (9:1, 5 mL). The system was purged with hydrogen (3 x vacuum/hydrogen cycle) and the mixture was stirred under one atmosphere of hydrogen at room temperature until complete consumption of the starting material (6 hours), after which time it was filtered through a pad of celite eluting with dichloromethane. Finally, the solvent was removed under vacuum to give **51d**.

(3a*S,4*R**,9c*R**)-5-Methyl-*N*-phenyl-2,3,3a,4,5,9c-hexahydro-1*H*-pyrrolo[2',3':3,4]cyclopenta[1,2-*b*]indol-4-amine (51d)**



Brown oil

R_f = 0.20 (hexane:diethyl ether, 2:1)

Isolated yield: >99%

^{1}H–NMR (300 MHz, DMSO-d_6)

δ: 7.73 (d, *J*= 7.8 Hz, 1H, H_9), 7.49 (d, *J*= 8.2 Hz, 1H, H_6), 7.23 (app. t, *J*= 7.6 Hz, 1H, H_7), 7.19 – 7.08 (m, 3H, $H_{3'}$ and H_8) 6.71 (d, *J*= 8.1 Hz, 2H, $H_{2'}$), 6.62 (t, *J*= 7.2 Hz, 1H, $H_{4'}$), 6.20 (d, *J*= 8.8 Hz, 1H, NH_{Ar}), 5.20 (d, *J*= 7.2 Hz, 1H, H_{9c}), 5.09 (d, *J*= 8.8 Hz, 1H, H_4), 3.67 (s, 3H, H_{10}), 3.59 – 3.00 (m, 3H, H_{3a} and H_2), 2.44 – 2.25 (m, 1H, H_{3A}), 2.15 – 1.99 (m, 1H, H_{3B}).

^{13}C–NMR (75 MHz, DMSO-d_6)

δ: 147.6, 145.0, 142.3, 129.1, 122.4, 121.9, 119.7, 119.6, 116.7, 113.2, 112.7, 110.5, 60.3, 57.3, 56.0, 45.1, 30.5, 30.2.

HRMS (70 eV, IE)

Calculated for $[C_{20}H_{21}N_3]^+$: 303.1730, found 303.1734.

Section 2.2.A.4

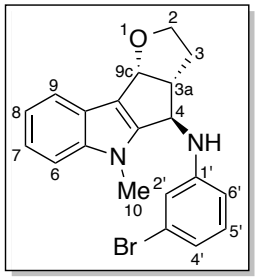
- **General Procedure for the Synthesis of the Cyclopenta[*b*]indole Derivative (+)-49g**[211]

1-Methyl-1*H*-indole-2-carbaldehydederivative **41a** (0.2 mmol), 3-bromoaniline **34c** (1.5 equiv, 0.3 mmol), (*R*)-(–)-VAPOL hydrogenphosphate (10 mol%) and 4 Å powder molecular sieves (50 mg) were placed in a glass reaction tube equipped with a magnetic stirring bar under argon atmosphere. Then, dichloromethane (2 mL) was added at 0 °C. The mixture was allowed to warm to room temperature and stirred at this temperature for 1 hour. Then, 2,3-dihydrofuran **18b** (3 equiv, 0.6 mmol, in 2 mL of dichloromethane) was added at room temperature over 5 hours via syringe pump. The reaction was kept at this temperature for additional 12 hours. Finally, the resulting slurry was filtered through a pad of basic alumina eluting with ethyl acetate, the solvent was removed under vacuum and the crude was purified by flash column chromatography on silica gel using mixtures of hexane and diethyl ether as eluent to give pure pure **(+)-49g** as a mixture of enantiomers (*e.r.* = 82:18).

Non commercially available chiral Brønsted acids used in section 2.2.A.4 were prepared according to the methods reported in the literature and purified by standard procedures.

[211] Absolute configuration could not be determined. The representation shown was arbitrary chosen.

(3a*R*,4*R*,9c*R*)-*N*-(3-Bromophenyl)-5-methyl-2,3,3a,4,5,9c-hexahydrofuro[2',3':3,4]cyclopenta[1,2-*b*]indol-4-amine ((+)-49g)



White solid

mp= 140 – 142 °C

R_f = 0.30 (hexane:diethyl ether, 2:1)

$[\alpha]^{16}_{D}$= +100° (*c* 0.5, DCM)

Isolated yield: 95%

^{1}H–NMR
(300 MHz, C_6D_6)

δ: 7.92 (dd, *J*= 7.3, 1.3 Hz, 1H, H_9), 7.27 – 7.19 (m, 2H, H_7 and H_8), 7.05 (dd, *J*= 7.3, 1.3 Hz, 1H, H_6), 6.91 (d, *J*= 7.9 Hz, 1H, $H_{4'}$), 6.80 (t, *J*= 7.9 Hz, 1H, $H_{5'}$), 6.66 (t, *J*= 2.1 Hz, 1H, $H_{2'}$), 6.20 (dd, *J*= 7.9, 2.4 Hz, 1H, $H_{6'}$), 5.68 (dd, *J*= 6.5, 1.4 Hz, 1H, H_{9c}), 4.29 (d, *J*= 9.5 Hz, 1H, H_4), 3.65 (ddd, *J*= 8.5, 7.0, 4.8 Hz, 1H, H_{2A}), 3.49 (td, *J*= 8.5, 6.0 Hz, 1H, H_{2B}), 3.09 (d, *J*= 9.5 Hz, 1H, NH), 3.00 (s, 3H, H_{10}), 2.68 (app. dtd, *J*= 12.2, 4.6, 1.4 Hz, 1H, H_{3a}), 1.84 – 1.71 (m, 1H, H_{3A}), 1.30 – 1.35 (m, 1H, H_{3B}).

^{13}C–NMR
(75 MHz, C_6D_6)

δ: 148.7, 144.0, 143.2, 130.9, 124.0, 123.9, 122.5, 121.0, 120.6, 120.4, 120.2, 116.9, 112.4, 110.0, 80.6, 66.9, 58.6, 56.9, 33.6, 29.8.

HRMS
(70 eV, IE)

Calculated for $[C_{20}H_{19}BrN_2O]^+$: 382.0675, found 382.0684.

HPLC

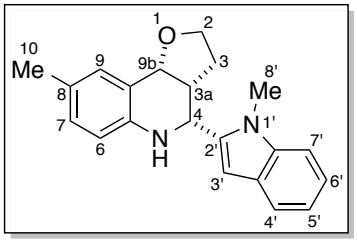
Daicel CHIRALPAK ODH (250 x 4.6 mm)
Hexane:*i*PrOH= 90:10, 0.6 mL/min, λ_{max}= 221.3 nm,
t_R (major)= 50.6 min, t_R (minor)= 91.5 min

Section 2.2.A.5

- **General Procedure for the Synthesis of the Tetrahydroquinoline Derivatives 50a-p**

The corresponding 1*H*-indole-2-carbaldehyde derivative **41** (0.2 mmol), aniline **34** (1 equiv, 0.2 mmol) and 4 Å powder molecular sieves (50 mg), were placed in a glass reaction tube equipped with a magnetic stirring bar under argon atmosphere. Then, dichloromethane (2 mL) was added. The slurry was cooled to 0 °C and HBF_4 (10 mol%) was added. The mixture was allowed to warm to room temperature and stirred at this temperature for 1 hour. Then, the 2,3-dihydrofuran derivative **18** (3 equiv, 0.6 mmol) was added at room temperature (except in the case of **50g** that it was added at 0 °C). The reaction was kept at this temperature followed by TLC until total consumption of the starting material (the *in situ* generated imine derivative, 2-16 hours). Finally the resulting slurry was filtered through a pad of basic alumina eluting with ethyl acetate, the solvent was removed under vacuum and the crude was purified by flash column chromatography on silica gel using mixtures of hexane and diethyl ether as eluent to give pure **50a-p**.

(3a*R,4*R**,9b*R**)-8-Methyl-4-(1-methyl-1*H*-indol-2-yl)-2,3,3a,4,5,9b-hexahydrofuro[3,2-*c*]quinoline (50a)**



Yellow solid

mp= 140 – 142 °C

R_f = 0.30 (hexane:diethyl ether, 2:1)

Isolated yield: 88%

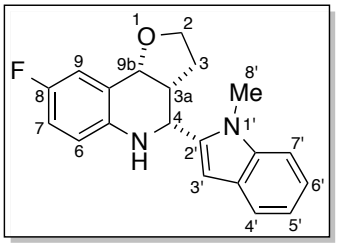
^{1}H–NMR

(300 MHz, C_6D_6)

δ: 7.72 (dd, *J*= 7.8, 1.5 Hz, 1H, $H_{7'}$), 7.48 (br s, 1H, H_9), 7.32 – 7.23 (m, 2H, $H_{5'}$ and $H_{6'}$), 7.11 (d, *J*= 7.6 Hz, 1H, $H_{4'}$), 6.88 (dd, *J*= 8.1, 2.0 Hz, 1H, H_7), 6.51 (s, 1H, $H_{3'}$), 6.32 (d, *J*= 8.1 Hz, 1H, H_6), 5.21 (d, *J*= 7.8 Hz, 1H, H_{9b}), 4.26 (d, *J*= 2.7 Hz, 1H, H_4), 3.74 (td, *J*= 8.6, 4.2 Hz, 1H, H_{2A}), 3.62 (app. q, *J*= 7.9 Hz, 1H, H_{2B}), 3.28 (br s, 1H, NH), 2.94 (s, 3H, $H_{8'}$), 2.52 – 2.42 (m, 1H, H_{3a}), 2.27 – 2.14 (m, 1H, H_{3A}), 2.20 (s, 3H, H_{10}), 1.35 – 1.25 (m, 1H, H_{3B}).

^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 142.9, 140.6, 137.7, 130.5, 129.4, 128.9, 127.6, 122.8, 121.6, 120.6, 119.8, 115.2, 109.1, 99.4, 75.9, 66.8, 51.2, 43.5, 30.0, 25.3, 20.7.
HRMS (70 eV, IE)	Calculated for $[C_{21}H_{22}N_2O]^+$: 318.1727 found 318.1731.

(3a*R,4*R**,9b*R**)-8-Fluoro-4-(1-methyl-1*H*-indol-2-yl)-2,3,3a,4,5,9b-hexahydrofuro[3,2-*c*]quinoline (50b)**



Yellow solid

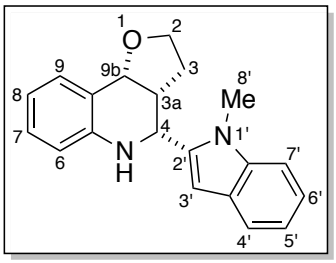
mp= 210 – 212 °C

R_f= 0.20 (hexane:diethyl ether, 2:1)

Isolated yield: 95%

^{1}H–NMR (300 MHz, C_6D_6)	δ: 7.73 – 7.70 (m, 1H, $H_{7'}$), 7.37 (dd, $J_{H\text{-}F}$= 9.1 Hz, J= 2.9 Hz, 1H, H_9), 7.33 – 7.23 (m, 2H, $H_{5'}$, $H_{6'}$), 7.13 – 7.10 (m, 1H, $H_{4'}$), 6.73 (td, $J_{H\text{-}F}$= 8.8 Hz, J= 8.8, 2.9 Hz, 1H, H_7), 6.46 (s, 1H, $H_{3'}$), 6.08 (dd, J= 8.8 Hz, $J_{H\text{-}F}$= 4.6 Hz, 1H, H_6), 4.96 (d, J =7.7 Hz, 1H, H_{9b}), 4.14 (d, J =2.7 Hz, 1H, H_4), 3.63 (td, J= 8.5, 4.2 Hz, 1H, H_{2A}), 3.55 (app. q, J= 8.2 Hz, 1H, H_{2B}), 3.17 (br s, 1H, NH), 2.94 (s, 3H, $H_{8'}$), 2.40 – 2.30 (m, 1H, H_{3a}), 2.14 – 2.00 (m, 1H, H_{3A}), 1.28 – 1.17 (m, 1H, H_{3B}).
^{13}C–NMR (75 MHz, C_6D_6)	δ: 157.3 (d, $J_{C\text{-}F}$= 236.8 Hz), 141.2, 140.3, 138.1, 128.3, 124.7 (d, $J_{C\text{-}F}$= 6.1 Hz), 121.9, 121.0, 120.3, 116.5 (d, $J_{C\text{-}F}$= 21.8 Hz), 116.1 (d, $J_{C\text{-}F}$= 7.0 Hz), 115.6 (d, $J_{C\text{-}F}$= 22.8 Hz), 109.3, 99.9, 75.5, 66.6, 50.4, 43.1, 29.2, 24.9.
^{19}F–NMR (282 MHz, C_6D_6)	δ: –125.0.
HRMS (70 eV, IE)	Calculated for $[C_{20}H_{19}FN_2O]^+$: 322.1476 found 322.1484.

(3a*R,4*R**,9b*R**)-4-(1-Methyl-1*H*-indol-2-yl)-2,3,3a,4,5,9b-hexahydrofuro[3,2-*c*]quinoline (50c)**



Yellow solid

mp= 152 – 154 °C

R_f = 0.20 (hexane:diethyl ether, 2:1)

Isolated yield: 75%

^{1}H–NMR
(300 MHz, C_6D_6)

δ: 7.71 (dd, *J*= 7.8, 1.5 Hz, 1H, $H_{7'}$), 7.63 (d, *J*= 7.8 Hz, 1H, H_9), 7.32 – 7.22 (m, 2H, $H_{5'}$ and $H_{6'}$), 7.11 (d, *J*= 7.8 Hz, 1H, $H_{4'}$), 7.05 (td, *J*= 7.8, 1.5 Hz, 1H, H_7), 6.85 (td, *J*= 7.8, 1.2 Hz, 1H, H_8), 6.48 (s, 1H, $H_{3'}$), 6.36 (dd, *J*= 7.8, 1.2 Hz, 1H, H_6), 5.17 (d, *J*= 7.8 Hz, 1H, H_{9b}), 4.25 (d, *J*= 2.8 Hz, 1H, H_4), 3.69 (td, *J*= 8.5, 4.1 Hz, 1H, H_{2A}), 3.59 (app. q, *J*= 7.9 Hz, 1H, H_{2B}), 3.38 (br s, 1H, NH), 2.94 (s, 3H, $H_{8'}$), 2.48 – 2.39 (m, 1H, H_{3a}), 2.22 – 2.09 (m, 1H, H_{3A}), 1.32 – 1.21 (m, 1H, H_{3B}).

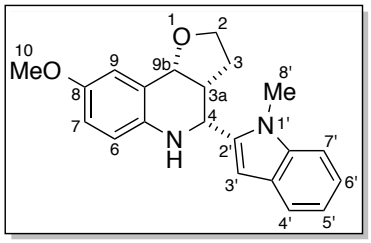
^{13}C–NMR
(75 MHz, C_6D_6)

δ: 145.2, 140.5, 138.1, 130.7, 128.6, 128.3, 123.4, 121.8, 121.0, 120.2, 119.7, 115.2, 109.3, 99.8, 75.8, 66.5, 50.4, 43.4, 29.2, 25.2.

HRMS
(70 eV, IE)

Calculated for $[C_{20}H_{20}N_2O]^+$: 304.1570, found 304.1579.

(3a*R,4*R**,9b*R**)-8-Methoxy-4-(1-methyl-1*H*-indol-2-yl)-2,3,3a,4,5,9b-hexahydrofuro[3,2-*c*]quinoline (50d)**



Yellow solid

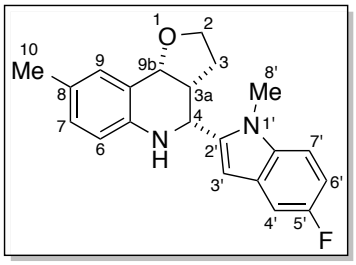
mp= 176 – 178 °C

R_f = 0.13 (hexane:diethyl ether, 1:1)

Isolated yield: 50%

^{1}H–NMR (300 MHz, C_6D_6)	δ: 7.73 (d, *J*= 7.4 Hz, 1H, $H_{7'}$), 7.33 – 7.23 (m, 3H, $H_{5'}$, $H_{6'}$ and H_9), 7.12 (d, *J*= 7.6 Hz, 1H, $H_{4'}$), 6.82 (dd, *J*= 8.7, 2.9 Hz, 1H, H_7), 6.54 (s, 1H, $H_{3'}$), 6.30 (d, *J*= 8.7 Hz, 1H, H_6), 5.19 (d, *J*= 7.7 Hz, 1H, H_{9b}), 4.25 (d, *J*= 2.6 Hz, 1H, H_4), 3.74 (td, *J*= 8.7, 4.3 Hz, 1H, H_{2A}), 3.62 (app. q, *J*= 7.9 Hz, 1H, H_{2B}), 3.43 (s, 3H, H_{10}), 3.16 (br s, 1H, NH), 2.97 (s, 3H, $H_{8'}$), 2.52 – 2.43 (m, 1H, H_{3a}), 2.28 – 2.15 (m, 1H, H_{3A}), 1.37 – 1.26 (m, 1H, H_{3B}).
^{13}C–NMR (75 MHz, C_6D_6)	δ: 154.1, 140.7, 139.1, 138.1, 124.2, 121.8, 121.0, 120.2, 116.6, 116.2, 114.3, 109.2, 99.9, 76.2, 66.6, 55.3, 50.8, 43.5, 29.3, 25.0.
HRMS (70 eV, IE)	Calculated for $[C_{21}H_{22}N_2O_2]^+$: 334.1676, found 334.1678.

(3a*R,4*R**,9b*R**)-4-(5-Fluoro-1-methyl-1*H*-indol-2-yl)-8-methyl-2,3,3a,4,5,9b-hexahydrofuro[3,2-*c*]quinoline (50e)**



White solid

mp= 206 – 208 °C

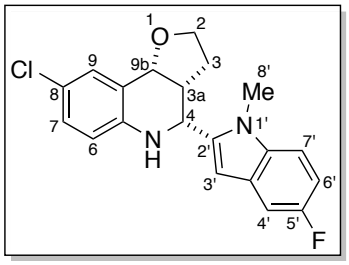
R_f= 0.28 (hexane:diethyl ether, 1:1)

Isolated yield: 90%

^{1}H–NMR (300 MHz, C_6D_6)	δ: 7.47 (d, *J*= 2.0 Hz, 1H, H_9), 7.37 (dd, $J_{H\text{-}F}$= 9.4 Hz, *J*= 2.5 Hz, 1H, $H_{4'}$), 7.02 (td, $J_{H\text{-}F}$= 9.1 Hz, *J*= 9.1, 2.5 Hz, 1H, $H_{6'}$), 6.89 (dd, *J*= 8.1, 2.0 Hz, 1H, H_7), 6.79 (dd, *J*= 9.0 Hz, $J_{H\text{-}F}$= 4.3 Hz, 1H, $H_{7'}$), 6.34 (d, *J*= 8.1 Hz, 1H, H_6), 6.33 (s, 1H, $H_{3'}$), 5.20 (d, *J*= 7.8 Hz, 1H, H_{9b}), 4.18 (d, *J*= 2.7 Hz, 1H, H_4), 3.73 (td, *J*= 8.7, 4.2 Hz, 1H, H_{2A}), 3.61 (app. q, *J*= 7.9 Hz, 1H, H_{2B}), 3.22 (br s, 1H, NH), 2.84 (s, 3H, $H_{8'}$), 2.46 – 2.37 (m, 1H, H_{3a}), 2.22 – 2.11 (m, 1H, H_{3A}), 2.20 (s, 3H, H_{10}), 1.31 – 1.20 (m, 1H, H_{3B}).

^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 158.7 (d, $J_{C\text{-}F}$= 233.8 Hz), 142.8, 142.4, 134.6, 131.1, 129.4, 123.3, 115.3, 109.0 (d, $J_{C\text{-}F}$= 26.1 Hz), 109.8 (d, $J_{C\text{-}F}$= 9.6 Hz), 105.8 (d, $J_{C\text{-}F}$= 23.2 Hz), 99.8 (d, $J_{C\text{-}F}$= 4.5 Hz), 75.9, 66.5, 50.7, 43.4, 29.3, 25.1, 20.8.
^{19}F–NMR (282 MHz, C_6D_6)	δ: –124.6.
HRMS (70 eV, IE)	Calculated for $[C_{21}H_{21}FN_2O]^+$: 336.1632, found 336.1634.

(3a*R,4*R**,9b*R**)-8-Chloro-4-(5-fluoro-1-methyl-1*H*-indol-2-yl)-2,3,3a,4,5,9b-hexahydrofuro[3,2-*c*]quinoline (50f)**



Yellow solid

mp= 190 – 208 °C

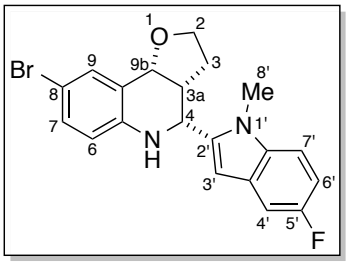
R_f= 0.18 (hexane:diethyl ether, 2:1)

Isolated yield: 80%

^{1}H–NMR (300 MHz, C_6D_6)	δ: 7.65 (d, *J*= 2.5 Hz, 1H, H_9), 7.36 (dd, $J_{H\text{-}F}$= 9.4 Hz, *J*= 2.5 Hz, 1H, $H_{4'}$), 7.05 (td, $J_{H\text{-}F}$= 9.0 Hz, *J*= 9.0, 2.5 Hz, 1H, $H_{6'}$), 7.00 (dd, *J*= 8.6, 2.5 Hz, 1H, H_7), 6.79 (dd, *J*= 9.0 Hz, $J_{H\text{-}F}$= 4.3 Hz, 1H, $H_{7'}$), 6.24 (s, 1H, $H_{3'}$), 6.05 (d, *J*= 8.6 Hz, 1H, H_6), 4.92 (d, *J*= 7.6 Hz, 1H, H_{9b}), 4.05 (d, *J*= 2.8 Hz, 1H, H_4), 3.59 (td, *J*= 8.6, 4.2 Hz, 1H, H_{2A}), 3.51 (app. q, *J*= 8.2 Hz, 1H, H_{2B}), 3.15 (br s, 1H, NH), 2.83 (s, 3H, $H_{8'}$), 2.31 – 2.22 (m, 1H, H_{3a}), 2.02 – 1.89 (m, 1H, H_{3A}), 1.21 – 1.09 (m, 1H, H_{3B}).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 158.8 (d, $J_{C\text{-}F}$= 234.3 Hz), 143.3, 141.8, 134.5, 130.3, 128.6, 128.4, 124.8, 124.3, 116.4, 110.1 (d, $J_{C\text{-}F}$= 33.1 Hz), 109.9 (d, $J_{C\text{-}F}$= 2.5 Hz), 105.8 (d, $J_{C\text{-}F}$= 23.5 Hz), 99.8 (d, $J_{C\text{-}F}$= 4.5 Hz), 75.1, 66.5, 50.1, 42.8, 29.3, 24.8.
^{19}F–NMR (282 MHz, C_6D_6)	δ: –124.3.

HRMS (70 eV, IE)	Calculated for $[C_{20}H_{18}ClFN_2O]^+$: 356.1086, found 356.1092.

(3a*R,4*R**,9b*R**)-8-Bromo-4-(5-fluoro-1-methyl-1*H*-indol-2-yl)-2,3,3a,4,5,9b-hexahydrofuro[3,2-*c*]quinoline (50g)**



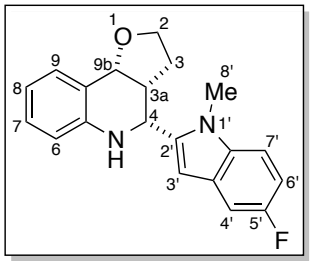
Yellow foam

R_f = 0.23 (hexane:diethyl ether, 2:1)

Isolated yield: 97%

^{1}H–NMR (300 MHz, C_6D_6)	δ: 7.80 (d, *J*= 2.3 Hz, 1H, H_9), 7.36 (dd, J_{H-F}= 9.4 Hz, *J*= 2.5 Hz, 1H, $H_{4'}$), 7.13 (dd, *J*= 8.5, 2.3 Hz, 1H, H_7), 7.03 (td, J_{H-F}= 9.0 Hz, *J*= 9.0, 2.5 Hz, 1H, $H_{6'}$), 6.79 (dd, *J*= 9.0 Hz, J_{H-F}= 4.3 Hz, 1H, $H_{7'}$), 6.22 (s, 1H, $H_{3'}$), 5.99 (d, *J*= 8.5 Hz, 1H, H_6), 4.90 (d, *J*= 7.6 Hz, 1H, H_{9b}), 4.04 (d, *J*= 2.8 Hz, 1H, H_4), 3.58 (td, *J*= 8.7, 4.0 Hz, 1H, H_{2A}), 3.49 (app. q, *J*= 8.0 Hz, 1H, H_{2B}), 3.13 (br s, 1H, NH), 2.81 (s, 3H, $H_{8'}$), 2.30 – 2.20 (m, 1H, H_{3a}), 2.02 – 1.85 (m, 1H, H_{3A}), 1.21 – 1.09 (m, 1H, H_{3B}).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 158.8 (d, J_{C-F}= 234.4 Hz), 143.7, 141.7, 134.5, 133.3, 131.4, 125.3, 116.8, 111.4, 110.0 (d, J_{C-F}= 34.4 Hz), 109.9, 105.8 (d, J_{C-F}= 23.1 Hz), 99.8 (d, J_{C-F}= 4.5 Hz), 75.0, 66.5, 50.0, 42.8, 29.3, 24.8.
^{19}F–NMR (282 MHz, C_6D_6)	δ: –124.3.
HRMS (70 eV, IE)	Calculated for $[C_{20}H_{18}BrFN_2O]^+$: 400.0581, found 400.0572.

(3a*R,4*R**,9b*R**)-4-(5-Fluoro-1-methyl-1*H*-indol-2-yl)-2,3,3a,4,5,9b-hexahydrofuro[3,2-*c*]quinoline (50h)**



Light yellow solid

mp= 188 – 190 °C

R_f = 0.13 (hexane:diethyl ether, 2:1)

Isolated yield: 87%

^{1}H–NMR
(300 MHz, C_6D_6)

δ: 7.64 (d, *J*= 7.4 Hz, 1H, H_9), 7.36 (dd, $J_{H\text{-}F}$= 9.4 Hz, *J*= 2.5 Hz, 1H, $H_{4'}$), 7.08 – 7.02 (m, 1H, H_7), 7.02 (td, $J_{H\text{-}F}$=9.0 Hz, *J*= 9.0, 2.5 Hz, 1H, $H_{6'}$), 6.86 (td, *J*= 7.4, 1.1 Hz, 1H, H_8), 6.79 (dd, *J*= 9.0 Hz, $J_{H\text{-}F}$= 4.2 Hz, 1H, $H_{7'}$), 6.37 (dd, *J*= 8.0, 1.1 Hz, 1H, H_6), 6.30 (s, 1H, $H_{3'}$), 5.16 (d, *J*= 7.7 Hz, 1H, H_{9b}), 4.17 (d, *J*= 2.8 Hz, 1H, H_4), 3.70 (td, *J*= 8.7, 4.2 Hz, 1H, H_{2A}), 3.59 (app. q, *J*= 7.9 Hz, 1H, H_{2B}), 3.29 (br s, 1H, NH), 2.84 (s, 3H, $H_{8'}$), 2.43 – 2.34 (m, 1H, H_{3a}), 2.17 – 2.04 (m, 1H, H_{3A}), 1.28 – 1.18 (m, 1H, H_{3B}).

^{13}C–NMR
(75 MHz, $CDCl_3$)

δ: 158.7 (d, $J_{C\text{-}F}$= 234.1 Hz), 145.1, 142.2, 134.6, 130.7, 128.6, 128.4, 123.4, 119.8, 115.2, 109.9 (d, $J_{C\text{-}F}$= 26.5 Hz), 109.8 (d, $J_{C\text{-}F}$= 9.7 Hz), 105.8 (d, $J_{C\text{-}F}$= 23.3 Hz), 99.8 (d, $J_{C\text{-}F}$= 4.5 Hz), 75.7, 66.5, 50.4, 43.3, 29.3, 25.1.

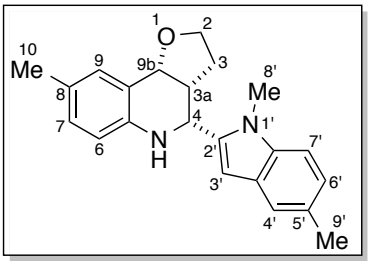
^{19}F–NMR
(282 MHz, C_6D_6)

δ: –124.5.

HRMS
(70 eV, IE)

Calculated for $[C_{20}H_{19}FN_2O]^+$: 322.1476, found 322.1476.

(3a*R,4*R**,9b*R**)-4-(1,5-Dimethyl-1*H*-indol-2-yl)-8-methyl-2,3,3a,4,5,9b-hexahydrofuro[3,2-*c*]quinoline (50i)**



Light yellow solid

mp= 190 – 192 °C

R_f = 0.25 (hexane:diethyl ether, 2:1)

Isolated yield: 85%

^{1}H–NMR
(300 MHz, C_6D_6)

δ: 7.52 (d, *J*= 1.5 Hz, 1H, $H_{4'}$), 7.47 (d, *J*= 2.0 Hz, 1H, H_9), 7.15 (dd, *J*= 8.4, 1.5 Hz, 1H, $H_{6'}$), 7.06 (d, *J*= 8.4 Hz, 1H, $H_{7'}$), 6.88 (dd, *J*= 8.1, 2.0 Hz, 1H, H_7), 6.50 (s, 1H, $H_{3'}$), 6.32 (d, *J*= 8.1 Hz, 1H, H_6), 5.21 (d, *J* =7.8 Hz, 1H, H_{9b}), 4.28 (d, *J* = 2.7 Hz, 1H, H_4), 3.74 (td, *J*= 8.6, 4.2 Hz, 1H, H_{2A}), 3.61 (app. q, *J*= 7.9 Hz, 1H, H_{2B}), 3.33 (br s, 1H, NH), 2.97 (s, 3H, $H_{8'}$), 2.53 – 2.43 (m, 1H, H_{3a}), 2.48 (s, 3H, $H_{9'}$), 2.30 – 2.17 (m, 1H, H_{3A}), 2.20 (s, 3H, H_{10}), 1.39 – 1.27 (m, 1H, H_{3B}).

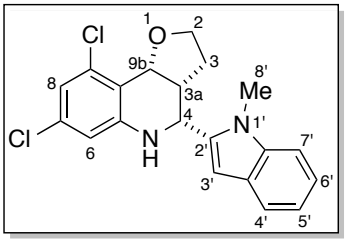
^{13}C–NMR
(75 MHz, $CDCl_3$)

δ: 143.0, 140.8, 136.6, 131.1, 129.3, 128.9, 128.6, 127.8, 123.4, 123.3, 120.8, 115.3, 109.0, 99.3, 75.9, 66.5, 50.7, 43.6, 29.3, 25.2, 21.7, 20.8.

HRMS
(70 eV, IE)

Calculated for $[C_{22}H_{24}N_2O]^+$: 332.1883, found 332.1888.

(3a*R,4*R**,9b*R**)-7,9-Dichloro-4-(1-methyl-1*H*-indol-2-yl)-2,3,3a,4,5,9b-hexahydrofuro[3,2-*c*]quinoline (50j)**



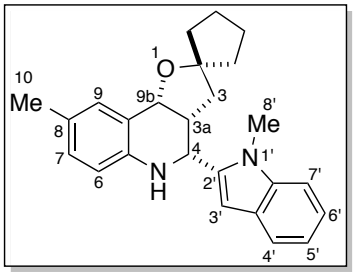
Yellow foam

R_f = 0.20 (hexane:diethyl ether, 2:1)

Isolated yield: 50%

^{1}H–NMR (300 MHz, C_6D_6)	δ: 7.82 (d, *J*= 7.4 Hz, 1H, $H_{7'}$), 7.44 – 7.33 (m, 2H, $H_{5'}$ and $H_{6'}$), 7.21 (d, *J*= 7.4 Hz, 1H, $H_{4'}$), 7.02 (d, *J*= 2.0 Hz, 1H, H_8), 6.45 (s, 1H, $H_{3'}$), 6.16 (d, *J*= 2.0 Hz, 1H, H_6), 5.39 (d, *J*= 8.6 Hz, 1H, H_{9b}), 4.03 (d, *J*= 3.0 Hz, 1H, H_4), 3.73 (td, *J*= 8.3, 4.0 Hz, 1H, H_{2A}), 3.57 (td, *J*= 8.3, 6.6 Hz, 1H, H_{2B}), 3.34 (br s, 1H, NH), 3.00 (s, 3H, $H_{8'}$), 2.54 – 2.44 (m, 1H, H_{3a}), 2.16 (ddt, *J*= 12.3, 9.5, 8.3 Hz, 1H, H_{3A}), 1.27 (dddd, *J*= 12.4, 8.3, 6.6, 4.0 Hz, 1H, H_{3B}).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 148.4, 139.2, 138.1, 138.1, 134.3, 122.1, 121.0, 120.6, 120.4, 113.9, 109.3, 99.9, 73.6, 66.8, 51.2, 43.7, 29.3, 26.2.
HRMS (70 eV, IE)	Calculated for $[C_{20}H_{18}Cl_2N_2O]^+$: 372.0791, found 372.0798.

(3a'*R,4'*R**,9b'*R**)-8'-Methyl-4'-(1-methyl-1*H*-indol-2-yl)-3a',4',5',9b'-tetrahydro-3'*H*-spiro[cyclopentane-1,2'-furo[3,2-*c*]quinoline] (50k)**



Yellow foam

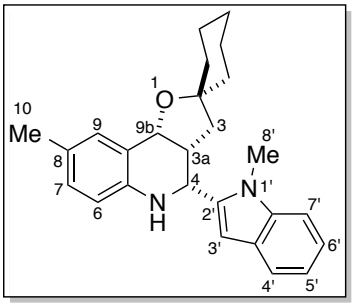
R_f = 0.35 (hexane:diethyl ether, 3:1)

Isolated yield: 55%

^{1}H–NMR (300 MHz, C_6D_6)	δ: 7.74 (dd, *J*= 7.4, 1.6 Hz, 1H, $H_{7'}$), 7.45 (s, 1H, H_9), 7.32 – 7.23 (m, 2H, $H_{5'}$ and $H_{6'}$), 7.12 (app. d, *J*= 7.4 Hz, 1H, $H_{4'}$), 6.88 (d, *J*= 8.0 Hz, 1H, H_7), 6.59 (s, 1H, $H_{3'}$), 6.35 (d, *J*= 8.0 Hz, 1H, H_6), 5.21 (d, *J*= 8.1 Hz, 1H, H_{9b}), 4.28 (d, *J*= 3.0 Hz, 1H, H_4), 3.35 (br s, 1H, NH), 2.98 (s, 3H, $H_{8'}$), 2.80 – 2.70 (m, 1H, H_{3a}), 2.43 (app. t, *J*= 12.0 Hz, 1H, H_{3A}), 2.19 (s, 3H, H_{10}), 1.92 – 1.20 (m, 9H, H_{3B} and $H_{Cyclopent}$).

^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 142.6, 140.8, 138.1, 131.3, 129.1, 124.5, 121.7, 120.9, 120.2, 115.5, 109.3, 99.9, 91.1, 75.5, 51.2, 44.2, 39.2, 39.5, 36.0, 29.3, 24.4, 24.1, 20.8.
HRMS (70 eV, IE)	Calculated for $[C_{25}H_{28}N_2O]^+$: 372.2196, found 372.2205.

(3a'*R,4'*R**,9b'*R**)-8'-Methyl-4'-(1-methyl-1*H*-indol-2-yl)-3a',4',5',9b'-tetrahydro-3'*H*-spiro[cyclohexane-1,2'-furo[3,2-*c*]quinoline] (50l)**



Light yellow solid

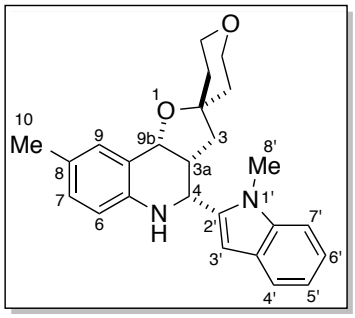
mp= 190 – 192 °C

R_f = 0.35 (hexane:diethyl ether, 3:1)

Isolated yield: 67%

^{1}H–NMR (300 MHz, C_6D_6)	δ: 7.73 (d, *J*= 7.0 Hz, 1H, $H_{7'}$), 7.51 (d, *J*= 2.0 Hz, 1H, H_9), 7.31 – 7.21 (m, 2H, $H_{5'}$ and $H_{6'}$), 7.11 (d, *J*= 7.3 Hz, 1H, $H_{4'}$), 6.88 (dd, *J*= 8.1, 2.0 Hz, 1H, H_7), 6.60 (br s, 1H, $H_{3'}$), 6.35 (d, *J*= 8.1 Hz, 1H, H_6), 5.25 (d, *J*= 7.7 Hz, 1H, H_{9b}), 4.30 (d, *J*= 2.7 Hz, 1H, H_4), 3.36 (br s, 1H, NH), 2.99 (s, 3H, $H_{8'}$), 2.19 (app. t, *J*= 11.8 Hz, 1H, H_{3A}), 2.74 (dtd, *J*= 10.9, 7.7, 2.7 Hz, 1H, H_{3a}), 2.22 (s, 3H, H_{10}), 1.51 – 0.89 (m, 11H, H_{3B} and H_{Cy}).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 142.0, 140.9, 138.1, 131.1, 129.0, 125.0, 121.7, 120.9, 120.2, 115.3, 109.3, 99.9, 82.9, 75.5, 50.7, 43.3, 40.5, 38.8, 35.9, 29.3, 25.9, 24.1, 24.1, 20.9.
HRMS (70 eV, IE)	Calculated for $[C_{26}H_{30}N_2O]^+$: 386.2353, found 386.2358.

(3a*R,4*R**,9b*R**)-8-Methyl-4-(1-methyl-1*H*-indol-2-yl)-2',3a,3',4,5,5',6',9b-octahydro-3*H*-spiro[furo[3,2-*c*]quinoline-2,4'-pyran] (50m)**



Yellow solid

mp= 226 – 228 °C

R_f = 0.20 (hexane:diethyl ether, 2:1)

Isolated yield: 63%

^{1}H–NMR
(300 MHz, C_6D_6)

δ: 7.77 – 6.73 (m, 1H, $H_{7'}$), 7.44 (d, *J*= 2.0 Hz, 1H, H_9), 7.33 – 7.24 (m, 2H, $H_{5'}$ and $H_{6'}$), 7.11 (d, *J*= 8.0 Hz, 1H, $H_{4'}$), 6.88 (dd, *J*= 8.1, 2.0 Hz, 1H, H_7), 6.56 (s, 1H, $H_{3'}$), 6.32 (d, *J*= 8.1 Hz, 1H, H_6), 5.19 (d, *J*= 7.8 Hz, 1H, H_{9b}), 4.26 (d, *J*= 2.7 Hz, 1H, H_4), 3.93 – 3.76 (m, 2H, H_{11A}), 3.50 – 3.36 (m, 2H, H_{11B}), 3.31 (br s, 1H, NH), 2.98 (s, 3H, $H_{8'}$), 2.65 (dtd, *J*= 11.0, 8.0, 2.7 Hz, 1H, H_{3a}), 2.20 (s, 3H, H_{12}), 2.14 (app. t, *J*= 12.0 Hz, 1H, H_{3A}), 1.60 – 1.26 (m, 5H, H_{3B}, H_{10}).

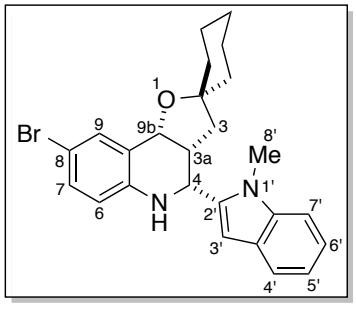
^{13}C–NMR
(75 MHz, $CDCl_3$)

δ: 141.7, 140.3, 137.8, 130.7, 128.9, 124.3, 121.6, 120.7, 120.1, 115.1, 109.1, 99.7, 79.7, 75.3, 65.2, 65.0, 50.3, 42.8, 40.1, 38.9, 35.9, 29.0, 20.6.

HRMS
(70 eV, IE)

Calculated for $[C_{25}H_{28}N_2O_2]^+$: 388.2145, found 388.2151.

(3a'*R,4'*R**,9b'*R**)-8'-Bromo-4'-(1-methyl-1*H*-indol-2-yl)-3a',4',5',9b'-tetrahydro-3'*H*-spiro[cyclohexane-1,2'-furo[3,2-*c*]quinoline] (50n)**



Yellow solid

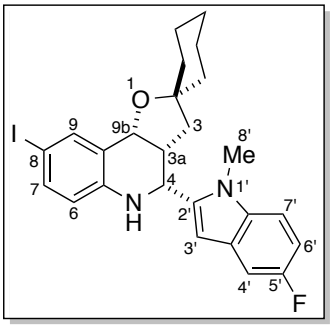
mp= 202 – 204 °C

R_f = 0.35 (hexane:diethyl ether, 3:1)

Isolated yield: 60%

^{1}H–NMR (300 MHz, C_6D_6)	δ: 7.85 (d, *J*= 2.3 Hz, 1H, H_9), 7.74 – 7.70 (m, 1H, $H_{7'}$), 7.32 – 7.22 (m, 2H, $H_{5'}$ and $H_{6'}$), 7.14 – 7.09 (m, 2H, $H_{4'}$ and H_7), 6.49 (s, 1H, $H_{3'}$), 6.00 (d, *J*= 8.5 Hz, 1H, H_6), 4.97 (d, *J*= 7.6 Hz, 1H, H_{9b}), 4.16 (d, *J*= 2.7 Hz, 1H, H_4), 3.26 (br s, 1H, NH), 2.96 (s, 3H, $H_{8'}$), 2.64 – 2.54 (m, 1H, H_{3a}), 1.98 (app. t, *J*= 12.1 Hz, 1H, H_{3A}), 1.68 – 1.06 (m, 11H, H_{3B} and H_{Cy}).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 142.9, 140.1, 138.1, 133.3, 131.1, 127.0, 121.9, 121.0, 120.3, 116.7, 111.1, 109.4, 99.9, 83.3, 74.7, 50.0, 42.6, 40.5, 38.7, 35.8, 29.3, 25.8, 24.0, 23.9.
HRMS (70 eV, IE)	Calculated for $[C_{25}H_{27}BrN_2O]^+$: 450.1301, found 450.1308.

(3a'*R,4'*R**,9b'*R**)-4'-(5-Fluoro-1-methyl-1*H*-indol-2-yl)-8'-iodo-3a',4',5',9b'-tetrahydro-3'*H*-spiro[cyclohexane-1,2'-furo[3,2-*c*]quinoline] (50o)**



Brown foam

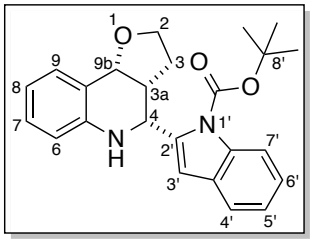
R_f = 0.30 (hexane:diethyl ether, 2:1)

Isolated yield: 58%

^{1}H–NMR (300 MHz, C_6D_6)	δ: 8.03 (d, *J*= 2.0 Hz, 1H, H_9), 7.38 (dd, $J_{H\text{-}F}$= 9.4 Hz, *J*= 2.5 Hz, 1H, $H_{4'}$), 7.31 (dd, *J*= 8.5, 2.0 Hz, 1H, H_7), 7.02 (app. td, $J_{H\text{-}F}$= 9.1 Hz, *J*= 9.1, 2.5 Hz, 1H, $H_{6'}$), 6.77 (dd, *J*= 8.9, 4.3 Hz, 1H, $H_{7'}$), 6.28 (s, 1H, $H_{3'}$), 5.90 (d, *J*= 8.5 Hz, 1H, H_6), 4.94 (d, *J*= 7.5 Hz, 1H, H_{9b}), 4.06 (d, *J*= 2.8 Hz, 1H, H_4), 3.15 (s, 1H, NH), 2.83 (s, 3H, $H_{8'}$), 2.57 – 2.47 (m, 1H, H_{3a}), 1.93 (app. t, *J*= 12.0 Hz, 1H, H_{3A}), 1.70 – 1.05 (m, 10H, H_{Cy}), 1.36 (dd, *J*= 12.5, 8.0 Hz, 1H, H_{3B}).

^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 158.8 (d, $J_{C\text{-}F}$= 234.4 Hz), 143.3, 141.8, 139.3, 136.9, 134.5, 117.2, 110.1, 110.1 (d, $J_{C\text{-}F}$= 26.9 Hz), 105.8 (d, $J_{C\text{-}F}$= 23.2 Hz), 99.8 (d, $J_{C\text{-}F}$= 4.7 Hz), 83.2, 80.5, 74.6, 49.9, 42.5, 40.4, 38.8, 35.8, 29.3, 25.7, 23.9, 23.9.
^{19}F–NMR (282 MHz, C_6D_6)	δ: –124.3.
HRMS (70 eV, IE)	Calculated for $[C_{25}H_{26}FIN_2O]^+$: 516.1068, found 516.1082.

***tert*-Butyl 2-((3a*R**,4*R**,9b*R**)-2,3,3a,4,5,9b-hexahydrofuro[3,2-*c*]quinolin-4-yl)-1*H*-indole-1-carboxylate (50p)**



Yellow solid

mp= 176 – 178 °C

R_f= 0.50 (hexane:diethyl ether, 2:1)

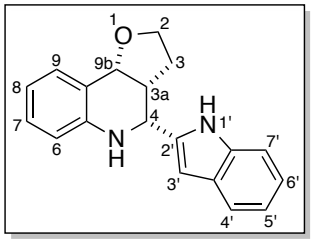
Isolated yield: 87%

^{1}H–NMR (300 MHz, C_6D_6)	δ: 8.46 (d, *J*= 8.2 Hz, 1H, $H_{7'}$), 7.49 (d, *J*= 7.6 Hz, 1H, $H_{4'}$), 7.45 (d, *J*= 2.0 Hz, 1H, H_9), 7.34 – 7.29 (m, 1H, $H_{6'}$), 7.26 – 7.20 (m, 1H, $H_{5'}$), 6.90 (dd, *J*= 8.1, 2.0 Hz, 1H, H_7), 6.65 (s, 1H, $H_{3'}$), 6.40 (d, *J*= 8.1 Hz, 1H, H_6), 5.39 (d, *J*= 7.7 Hz, 1H, H_{9b}), 5.24 (d, *J*= 2.6 Hz, 1H, H_4), 3.77 (td, *J*= 8.7, 4.0 Hz, 1H, H_{2A}), 3.65 (app. q, *J*= 8.0 Hz, 1H, H_{2B}), 3.26 (s, 1H, NH), 3.21 – 3.11 (m, 1H, H_{3a}), 2.24 – 2.11 (m, 1H, H_{3A}), 2.18 (s, 3H, H_{10}), 1.37 (s, 9H, $H_{8'}$), 1.31 – 1.21 (m, 1H, H_{3B}).
^{13}C–NMR ($CDCl_3$)	δ: 150.5, 143.1, 142.9, 137.4, 131.2, 129.7, 129.2, 124.4, 123.7, 123.4, 120.8, 116.5, 115.4, 108.1, 84.1, 76.0, 66.5, 52.3, 42.8, 30.0, 25.1, 20.7.
HRMS (70 eV, IE)	Calculated for $[C_{25}H_{28}N_2O_3]^+$: 404.2094, found 404.2101.

- **General Procedure for the Synthesis of the Hexahydrofuro[3,2-*c*]quinoline Derivative 50q**

A glass reaction tube equipped with a magnetic stirring bar was charged with a solution of K_2CO_3 (3 equiv, 0.54 mmol) in methanol:water (3:1, 2 mL) and the *N*-Boc derivative **50p** (0.17 mmol). The reaction mixture was heated under reflux until the substrate was consumed followed by TLC (6 hours). Then, the reaction mixture was diluted with water (10 mL), extracted with ethyl acetate (3 x 10 mL), dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under vaccum to give pure **50q**.

(3a*R,4*R**,9b*R**)-4-(1*H*-Indol-2-yl)-2,3,3a,4,5,9b-hexahydrofuro[3,2-*c*]quinoline (50q)**



Brown foam

Isolated yield: >99%

^{1}H–NMR
(300 MHz, C_6D_6)

δ: 7.94 (br s, 1H, $H_{1'}$), 7.72 – 7.65 (m, 1H, $H_{7'}$), 7.43 (d, *J*= 2.0 Hz, 1H, H_9), 7.25 – 7.17 (m, 2H, $H_{5'}$ and $H_{6'}$), 7.14 – 7.07 (m, 1H, $H_{4'}$), 6.86 (dd, *J*= 8.1, 2.0 Hz, 1H, H_7), 6.30 (d, *J*= 2.1 Hz, 1H, $H_{3'}$), 6.27 (d, *J*= 8.1 Hz, 1H, H_6), 5.02 (d, *J*= 7.4 Hz, 1H, H_{9b}), 4.21 (d, *J*= 3.8 Hz, 1H, H_4), 3.59 (td, *J*= 8.7, 4.1 Hz, 1H, H_{2A}), 3.50 (app. q, *J*= 8.1 Hz, 1H, H_{2B}), 3.26 (br s, 1H, H_5), 2.47 – 2.35 (m, 1H, H_{3a}), 2.16 (s, 3H, H_{10}), 1.95 – 1.76 (m, 1H, H_{3A}), 1.35 – 1.17 (m, 1H, H_{3B}).

^{13}C–NMR
(75 MHz, $CDCl_3$)

δ: 142.1, 139.6, 136.5, 131.3, 129.6, 128.7, 128.5, 122.4, 122.1, 120.7, 120.4, 115.5, 111.3, 100.6, 75.7, 66.4, 51.8, 43.8, 26.1, 20.7.

HRMS
(70 eV, IE)

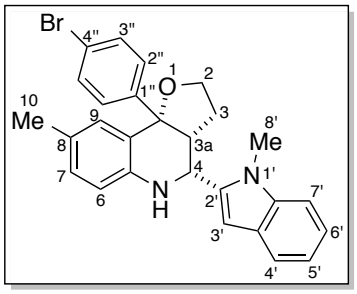
Calculated for $[C_{20}H_{20}N_2O]^+$: 304.1570, found 304.1579.

Section 2.2.A.6

- **General Procedure for the Synthesis of the Hexahydrofuro[3,2-*c*]quinoline Derivatives 50r**

1-Methyl-1*H*-indole-2-carbaldehyde **41a** (0.2 mmol), 4-methylaniline **34a** (1 equiv, 0.2 mmol) and 4 Å powder molecular sieves (50 mg), were placed in a glass reaction tube equipped with a magnetic stirring bar under argon atmosphere. Then, dichloromethane (2 mL) was added. The slurry was cooled to 0 °C and HBF_4 (10 mol%) or DPP (10 mol%) was added. The mixture was allowed to warm to room temperature and stirred at this temperature for 1 hour. Then, $AuMePPh_3$ (5 mol%) and 4-(4-bromophenyl)but-3-yn-1-ol **17b** (1 equiv, 0.2 mmol) were added at room temperature. The reaction was kept at this temperature followed by TLC until total consumption of the starting material (*in situ* generated imine derivative 16 hours). Finally the resulting slurry was filtered through a pad of basic alumina eluting with ethyl acetate, the solvent was removed under vacuum and the crude was purified by flash column chromatography on silica gel using mixtures of hexane and diethyl ether as eluent to give pure **50r** and ***diast*-50r**.

(3a*R,4*R**,9b*S**)-9b-(4-Bromophenyl)-8-methyl-4-(1-methyl-1*H*-indol-2-yl)-2,3,3a,4,5,9b-hexahydrofuro[3,2-*c*]quinoline (50r)**



Brown foam

Isolated yield: 38% (DPP) and 41% (HBF_4)

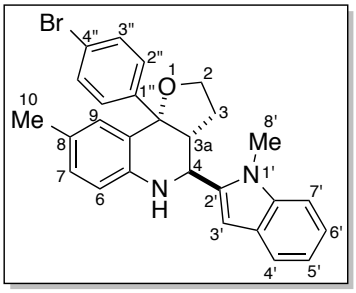
^{1}H–NMR

(300 MHz, C_6D_6)

δ: 7.75 – 7.68 (m, 1H, $H_{7'}$), 7.36 (d, *J*= 8.8 Hz, 2H, $H_{2''}$), 7.30 (d, *J*= 8.8 Hz, 2H, $H_{3''}$), 7.26 – 7.21 (m, 3H, H_9, $H_{5'}$ and $H_{6'}$), 7.03 – 6.98 (m, 1H, $H_{4'}$), 6.91 (dd, *J*= 8.2, 2.1 Hz, 1H, H_7), 6.40 (d, *J* = 8.2 Hz, 1H, H_6), 6.51 (s, 1H, $H_{3'}$), 4.36 (d, *J* = 2.3 Hz, 1H, H_4), 3.82 – 3.69 (m, 2H, H_2), 3.43 (br. s, 1H, NH), 2.66 (s, 3H, $H_{8'}$), 2.34 – 2.19 (m, 1H, H_{3A}), 2.18 – 2.03 (m, 1H, H_{3a}), 2.07 (s, 3H, H_{10}), 1.50 – 1.35 (m, 1H, H_{3B}).

^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 148.1, 142.5, 140.2, 138.1, 131.3, 130.9, 129.8, 129.1, 128.8, 124.0, 121.9, 121.5, 120.9, 120.2, 115.1, 109.2, 99.6, 84.4, 66.3, 52.1, 48.1, 28.8, 26.0, 20.7.
HRMS (70 eV, IE)	Calculated for $[C_{27}H_{25}BrN_2O]^+$ 472.1145, found 472.1142.

(3a*R,4*S**,9b*S**)-9b-(4-Bromophenyl)-8-methyl-4-(1-methyl-1*H*-indol-2-yl)-2,3,3a,4,5,9b-hexahydrofuro[3,2-*c*]quinoline (*diast*-50r)**



Brown foam

Isolated yield: 38% (DPP) and 41% (HBF_4)

^{1}H–NMR (300 MHz, C_6D_6)	δ: 7.78 – 7.73 (m, 1H, $H_{7'}$), 7.35 – 7.22 (m, 4H, $H_{5'}$, $H_{6'}$ and $H_{2''}$), 7.22 – 7.17 (d, *J*= 9.0 Hz, 2H, $H_{3''}$), 7.13 – 7.08 (m, 1H, $H_{4'}$) 7.06 (d, *J*= 2.2 Hz, 1H, H_9), 6.82 (dd, *J*= 8.8, 2.2 Hz, 1H, H_7), 6.33 (d, *J* = 8.8 Hz, 1H, H_6), 6.30 (s, 1H, $H_{3'}$), 3.71 (d, *J* = 12.5 Hz, 1H, H_4), 3.53 (dd, *J*= 10.8, 2.0 Hz, 1H, H_{2A}), 3.51 (d, *J*= 10.8 Hz, 1H, H_{2B}), 3.22 (s, 1H, NH), 2.80 (s, 3H, $H_{8'}$), 2.43 (dd, *J* = 12.5, 6.8 Hz, 1H, H_{3a}), 1.52 (s, 3H, H_{10}), 1.14 – 1.00 (m, 1H, H_{3A}), 0.98 – 0.86 (m, 1H, H_{3B}).
^{13}C–NMR (75 MHz, $CDCl_3$)	δ: 147.4, 142.8, 138.9, 138.7, 132.1, 131.5, 129.3, 128.7, 127.0, 122.2, 121.1, 120.8, 120.4, 115.4, 109.5, 102.5, 85.4, 65.2, 52.3, 51.7, 30.2, 28.2, 20.6.
HRMS (70 eV, IE)	Calculated for $[C_{27}H_{25}BrN_2O]^+$ 472.1145, found 472.1142.

Part B

- **Synthesis of 1*H*-Indole-2-carbaldehyde Derivatives 41**

Non commercially available 1*H*-indole-2-carbaldehyde derivatives **41** were prepared according to the methods reported in the literature and purified by standard procedures.

Non commercially available chiral Brønsted acids used in section 2.2.A.4 were prepared according to the methods reported in the literature and purified by standard procedures.

Section 2.2.B.3 and 2.2.B.4

- **General Procedure for the Synthesis of the Pyrrolo[1,2-*a*] Derivatives 61**

The corresponding 1*H*-indole-2-carbaldehyde derivative **41** (0.1 mmol), aniline **34** (1 equiv, 0.1 mmol), chiral disulfonimide **(*R*)-56a** or **(*R*)-56b** (10 mol%) and 4 Å powder molecular sieves (50 mg) were placed in a glass reaction tube equipped with a magnetic stirring bar under argon atmosphere. Then, dichloromethane[212] (2 mL) was added at 0 °C. The mixture was allowed to warm to room temperature and stirred at this temperature for 1 hour. Then, the preformed imine was cooled to –70°C and 2,3-dihydrofuran **18b** (3 equiv, 0.6 mmol) was added. The reaction was kept at this temperature followed by TLC until total consumption of the starting material (*in situ* generated imine derivative, 16-72 hours). Finally, the resulting slurry was filtered through a pad of basic alumina eluting with ethyl acetate, the solvent was removed under vacuum and the crude was purified by flash column chromatography on silica gel using mixtures of hexane and diethyl ether as eluent to give pure **61a-m**.

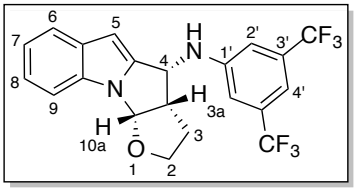
Racemic compounds **61** used to determine the enantiomeric excess by HPLC were prepared following the same procedure using the corresponding racemic catalyst **56a** prepared from the corresponding racemic BINOL.

[212] A Fluorobenzene:dichoromethane (1:1) mixture was used as solvent for compounds **61b**, **61c** and **61i**.

- **General Procedure for the Synthesis of the Pyrrolo[1,2-*a*] Derivative 61a Recovering the Chiral Brønsted Acid**

1*H*-indole-2-carbaldehyde **41b** (5.2 mmol), aniline **34d** (1 equiv, 5.2 mmol), chiral disulfonimide **(*R*)-56a** (10 mol%) and 4 Å powder molecular sieves (1,3 g) were placed in a schlenk tube equipped with a magnetic stirring bar under argon atmosphere. Then, dichloromethane (30 mL) was added at 0 °C. The mixture was allowed to warm to room temperature and stirred at this temperature for 1 hour. Then, the preformed imine was cooled to –70°C and 2,3-dihydrofuran **XX** (3 equiv, 15.6 mmol) was added. The reaction was kept at this temperature followed by TLC until total consumption of the starting material (*in situ* generated imine derivative, 72 hours). Finally, the resulting slurry was filtered through a pad of silica gel eluting with 250 mL of hexane:diethyl ether (1:1) (fraction 1) and then the remaining cake was eluted with 250 mL ethyl acetate:methanol (10:1) (fraction 2). The solvent of fraction 1 was removed under vacuum and the crude was purified by flash column chromatography on silica gel using mixtures of hexane and diethyl ether as eluent to give pure **61a** (2 g). The solvent of fraction 2 was removed under vacuum recovering the catalyst of the reaction that could be reused after acidification (a chloroform solution of the catalyst was washed with HCl 6 N three times, then the solvent was removed under vacuum and moisture was removed by distillation as an azeotrope with toluene).

(3a*S*,4*R*,10a*S*)-*N*-(3,5-Bis(trifluoromethyl)phenyl)-2,3,3a,10a-tetrahydro-4*H*-furo[3',2':4,5]pyrrolo[1,2-*a*]indol-4-amine (61a)



Yellow solid

mp= 165 – 167 °C

R_f= 0.40 (hexane:diethyl ether, 2:1)

e.r.= 95:5, $[\alpha]^{20}_{D}$= +20° (*c* 0.4, DCM)

Isolated yield: 90%

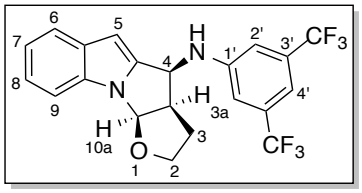
^{1}H–NMR

(300 MHz, C_6D_6)

δ: 7.76 – 7.68 (m, 2H, H_6 and H_9), 7.31 – 7.22 (m, 3H, H_7, H_8 and $H_{4'}$), 6.44 (d, *J*= 1.5 Hz, 2H, $H_{2'}$), 6.16 (s, 1H, H_5), 5.79 (d, *J*= 5.7 Hz, 1H, H_{10a}), 4.13 (app. t, *J*= 7.0 Hz, 1H, H_4), 3.84 (d, *J*= 6.6 Hz, 1H, NH), 3.50 (ddd, *J*= 8.8, 7.4, 2.7 Hz, 1H, H_{2A}), 3.00 (ddd, *J*= 10.2, 8.8, 6.2 Hz, 1H, H_{2B}), 2.70 (dddd, *J*= 11.0, 7.8, 5.7, 3.2 Hz, 1H, H_{3a}), 1.21 – 0.99 (m, 2H, H_3).

^{13}C–NMR (75 MHz, C_6D_6)	δ: 147.6, 141.9, 134.0, 132.9 (q, $J_{C\text{-}F}$= 32.7 Hz), 132.4, 124.2 (q, $J_{C\text{-}F}$= 271.9 Hz), 122.6, 121.5, 121.4, 112.1, 111.4, 110.9, 94.2, 90.4, 67.8, 51.5, 50.0, 26.1.
^{19}F–NMR (282 MHz, C_6D_6)	δ: –62.6.
HRMS (70 eV, IE)	Calculated for $[C_{21}H_{16}F_6N_2O]^+$: 426.1161 found 426.1165.
HPLC	Daicel CHIRALPAK ODH (250 x 4.6 mm) Hexane:*i*PrOH= 90:10, 0.2 mL/min λ_{max}= 215.4 nm t_R (minor)= 61.4 min, t_R (major)= 91.5 min

(3a*R*,4*S*,10a*R*)-*N*-(3,5-Bis(trifluoromethyl)phenyl)-2,3,3a,10a-tetrahydro-4*H*-furo[3',2':4,5]pyrrolo[1,2-*a*]indol-4-amine (*ent*-61a)



Yellow solid

mp= 165 – 167 °C

R_f= 0.40 (hexane:diethyl ether, 2:1)

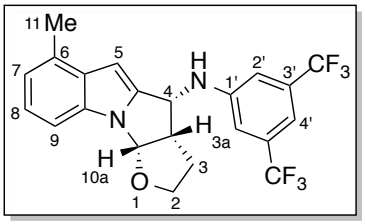
e.r.= 8:92, $[\alpha]^{17}_D$= –18° (*c* 0.4, DCM)

Isolated yield: 90%

^{1}H–NMR (300 MHz, C_6D_6)	δ: 7.76 – 7.68 (m, 2H, H_6 and H_9), 7.31 – 7.22 (m, 3H, H_7, H_8 and $H_{4'}$), 6.44 (d, *J*= 1.5 Hz, 2H, $H_{2'}$), 6.16 (s, 1H, H_5), 5.79 (d, *J*= 5.7 Hz, 1H, H_{10a}), 4.13 (app. t, *J*= 7.0 Hz, 1H, H_4), 3.84 (d, *J*= 6.6 Hz, 1H, NH), 3.50 (ddd, *J*= 8.8, 7.4, 2.7 Hz, 1H, H_{2A}), 3.00 (ddd, *J*= 10.2, 8.8, 6.2 Hz, 1H, H_{2B}), 2.70 (dddd, *J*= 11.0, 7.8, 5.7, 3.2 Hz, 1H, H_{3a}), 1.21 – 0.99 (m, 2H, H_3).
^{13}C–NMR (75 MHz, C_6D_6)	δ: 147.6, 141.9, 134.0, 132.9 (q, $J_{C\text{-}F}$= 32.7 Hz), 132.4, 124.2 (q, $J_{C\text{-}F}$= 271.9 Hz), 122.6, 121.5, 121.4, 112.1, 111.4, 110.9, 94.2, 90.4, 67.8, 51.5, 50.0, 26.1.
^{19}F–NMR (282 MHz, C_6D_6)	δ: –62.6.

HRMS (70 eV, IE)	Calculated for $[C_{21}H_{16}F_6N_2O]^+$: 426.1161 found 426.1165.
HPLC	Daicel CHIRALPAK ODH (250 x 4.6 mm) Hexane:*i*PrOH= 90:10, 0.2 mL/min λ_{max}= 215.4 nm t_R (major)= 61.4 min, t_R (minor)= 91.5 min

(3a*S*,4*R*,10a*S*)-*N*-(3,5-Bis(trifluoromethyl)phenyl)-6-methyl-2,3,3a,10a-tetrahydro-4*H*-furo[3',2':4,5]pyrrolo[1,2-*a*]indol-4-amine (61b)



Brown solid

mp= 190 – 192 °C

R_f= 0.48 (hexane:diethyl ether, 2:1)

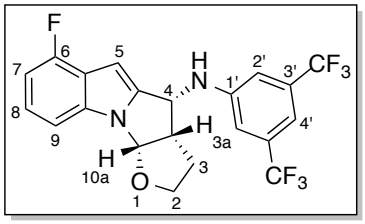
e.r.= 87:13, $[\alpha]^{20}_D$= −37° (*c* 0.075, DCM)

Isolated yield: 75%

^{1}H–NMR (300 MHz, C_6D_6)	δ: 7.57 (dd, *J*= 8.2, 0.6 Hz, 1H, H_9), 7.22 (dd, *J*= 8.2, 7.2 Hz, 1H, H_8), 7.16 (s, 1H, $H_{4'}$), 7.06 (app. dt, *J*= 7.2, 0.9 Hz, 1H, H_7), 6.53 (s, 2H, $H_{2'}$), 6.16 (app. t, *J*= 1.0 Hz, 1H, H_5), 5.79 (d, *J*= 5.7 Hz, 1H, H_{10a}), 4.21 – 4.15 (m, 1H, H_4), 3.93 (d, *J*= 6.4 Hz, 1H, NH), 3.52 (ddd, *J*= 8.7, 7.3, 2.6 Hz, 1H, H_{2A}), 3.00 (ddd, *J*= 10.3, 8.7, 6.1 Hz, 1H, H_{2B}), 2.79 – 2.67 (m, 1H, H_{3a}), 2.58 (s, 3H, H_{11}), 1.25 – 1.06 (m, 2H, H_3).
^{13}C–NMR (75 MHz, C_6D_6)	δ: 147.8, 141.4, 133.9, 133.0 (q, $J_{C\text{-}F}$= 32.8 Hz), 132.1, 130.5, 124.3 (q, $J_{C\text{-}F}$= 273.9 Hz), 122.7, 121.5, 112.1 (d, $J_{C\text{-}F}$= 2.9 Hz), 110.9, 109.1, 92.6, 90.5, 67.8, 51.6, 50.1, 26.1, 19.0.
^{19}F–NMR (282 MHz, C_6D_6)	δ: −62.7.
HRMS (70 eV, IE)	Calculated for $[C_{22}H_{18}F_6N_2O]^+$: 440.1318, found 440.1323.

HPLC	Daicel CHIRALPAK ODH (250 x 4.6 mm) Hexane:*i*PrOH= 90:10, 0.2 mL/min λ_{max}= 217.8 nm t_R (minor)= 37.5 min, t_R (major)= 49.9 min

(3a*S*,4*R*,10a*S*)-*N*-(3,5-Bis(trifluoromethyl)phenyl)-6-fluoro-2,3,3a,10a-tetrahydro-4*H*-furo[3',2':4,5]pyrrolo[1,2-*a*]indol-4-amine (61c)



Light brown solid

mp= 94 – 96 °C

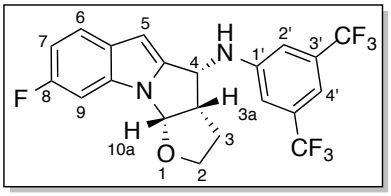
R_f= 0.43 (hexane:diethyl ether, 2:1)

e.r.= 76:24, $[\alpha]^{20}_D$= +96° (*c* 0.075, DCM)

Isolated yield: 72%

^{1}H–NMR (300 MHz, C_6D_6)	δ: 7.40 (d, *J*= 8.1 Hz, 1H, H_9), 7.29 (s, 1H, $H_{4'}$), 7.01 (td, *J*= 8.1 Hz, $J_{H\text{-}F}$= 5.2 Hz, 1H, H_8), 6.91 (dd, $J_{H\text{-}F}$= 9.6 Hz, *J*= 8.1 Hz, 1H, H_7), 6.43 (s, 2H, $H_{2'}$), 6.34 (s, 1H, H_5), 5.70 (d, *J*= 5.7 Hz, 1H, H_{10a}), 4.03 (app. t, *J*= 7.2 Hz, 1H, H_4), 3.77 (d, *J*= 6.5 Hz, 1H, NH), 3.48 (ddd, *J*= 8.8, 7.5, 2.8 Hz, 1H, H_{2A}), 3.02 – 2.90 (m, 1H, H_{2B}), 2.74 – 2.62 (m, 1H, H_{3a}), 1.20 – 0.97 (m, 2H, H_3).
^{13}C–NMR (75 MHz, C_6D_6)	δ: 156.7 (d, *J*= 246.9 Hz), 147.2, 141.8, 134.4 (d, *J*= 11.0 Hz), 132.6 (q, *J*= 33.0 Hz), 123.8 (q, 273.9 Hz), 122.8 (d, *J*= 7.5 Hz), 111.9, 110.8, 90.2, 90.1, 67.7, 51.0, 49.9, 25.7.
^{19}F–NMR (282 MHz, C_6D_6)	δ: –62.8, –121.8.
HRMS (70 eV, IE)	Calculated for $[C_{21}H_{15}F_7N_2O]^+$: 444.1067, found 444.1078.
HPLC	Daicel CHIRALPAK IA (250 x 4.6 mm) Hexane:*i*PrOH= 90:10, 0.2 mL/min λ_{max}= 215.1 nm t_R (minor)= 25.0 min, t_R (major)= 27.4 min

(3a*S*,4*R*,10a*S*)-*N*-(3,5-Bis(trifluoromethyl)phenyl)-8-fluoro-2,3,3a,10a-tetrahydro-4*H*-furo[3',2':4,5]pyrrolo[1,2-*a*]indol-4-amine (61d)



Yellow solid

mp= 143 – 145 °C

R_f = 0.48 (hexane:diethyl ether, 2:1)

e.r.= 97:3, $[\alpha]^{20}_D$= +19° (*c* 0.5, DCM)

Isolated yield: 75%

^{1}H–NMR
(300 MHz, C_6D_6)

δ: 7.45 – 7.38 (m, 2H, H_6 and H_9), 7.30 (s, 1H, $H_{4'}$), 7.00 (ddd, $J_{H\text{-}F}$= 9.6 Hz, *J*= 8.8, 2.4 Hz, 1H, H_7), 6.45 (s, 2H, $H_{2'}$), 6.05 (s, 1H, H_5), 5.63 (d, *J*= 5.7 Hz, 1H, H_{10a}), 4.09 (app. t, *J*= 7.3 Hz, 1H, H_4), 3.81 (d, *J*= 6.7 Hz, 1H, NH), 3.47 (ddd, *J*= 8.8, 7.4, 2.8 Hz, 1H, H_{2A}), 2.95 (ddd, *J*= 10.2, 8.8, 6.2 Hz, 1H, H_{2B}), 2.68 (dddd, *J*= 11.2, 7.8, 5.7, 3.3 Hz, 1H, H_{3a}), 1.19 – 0.98 (m, 2H, H_3).

^{13}C–NMR
(75 MHz, C_6D_6)

δ: 160.3 (d, $J_{C\text{-}F}$= 238.9 Hz), 147.6, 142.5, 142.4, 132.9 (q, $J_{C\text{-}F}$= 32.9 Hz), 132.2, 132.1, 130.3, 124.2 (q, $J_{C\text{-}F}$= 272.0 Hz), 122.3 (d, $J_{C\text{-}F}$= 10.1 Hz), 112.1, 111.0, 110.0 (d, $J_{C\text{-}F}$= 24.6 Hz), 97.9 (d, $J_{C\text{-}F}$= 26.4 Hz), 94.3, 90.2, 67.9, 51.4, 50.0, 26.0.

^{19}F–NMR
(282 MHz, C_6D_6)

δ: –62.7, –119.7.

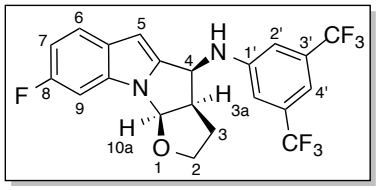
HRMS
(70 eV, IE)

Calculated for $[C_{21}H_{15}F_7N_2O]^+$: 444.1067, found : 444.1063.

HPLC

Daicel CHIRALPAK ODH (250 x 4.6 mm)
Hexane:*i*PrOH= 90:10, 0.2 mL/min
λ_{max}= 214.3 nm
t_R (minor)= 29.8 min, t_R (major)= 45.3 min

(3a*R*,4*S*,10a*R*)-*N*-(3,5-Bis(trifluoromethyl)phenyl)-8-fluoro-2,3,3a,10a-tetrahydro-4*H*-furo[3',2':4,5]pyrrolo[1,2-*a*]indol-4-amine (*ent*-61d)



Yellow solid

mp= 143 – 145 °C

R_f= 0.48 (hexane:diethyl ether, 2:1)

e.r.= 97:3, $[\alpha]^{20}_{D}$= –19° (*c* 0.5, DCM)

Isolated yield: 75%

^{1}H–NMR
(300 MHz, C_6D_6)

δ: 7.45 – 7.38 (m, 2H, H_6 and H_9), 7.30 (s, 1H, $H_{4'}$), 7.00 (ddd, J_{H-F}= 9.6 Hz, *J*= 8.8, 2.4 Hz, 1H, H_7), 6.45 (s, 2H, $H_{2'}$), 6.05 (s, 1H, H_5), 5.63 (d, *J*= 5.7 Hz, 1H, H_{10a}), 4.09 (app. t, *J*= 7.3 Hz, 1H, H_4), 3.81 (d, *J*= 6.7 Hz, 1H, NH), 3.47 (ddd, *J*= 8.8, 7.4, 2.8 Hz, 1H, H_{2A}), 2.95 (ddd, *J*= 10.2, 8.8, 6.2 Hz, 1H, H_{2B}), 2.68 (dddd, *J*= 11.2, 7.8, 5.7, 3.3 Hz, 1H, H_{3a}), 1.19 – 0.98 (m, 2H, H_3).

^{13}C–NMR
(75 MHz, C_6D_6)

δ: 160.3 (d, J_{C-F}= 238.9 Hz), 147.6, 142.5, 142.4, 132.9 (q, J_{C-F}= 32.9 Hz), 132.2, 132.1, 130.3, 124.2 (q, J_{C-F}= 272.0 Hz), 122.3 (d, J_{C-F}= 10.1 Hz), 112.1, 111.0, 110.0 (d, J_{C-F}= 24.6 Hz), 97.9 (d, J_{C-F}= 26.4 Hz), 94.3, 90.2, 67.9, 51.4, 50.0, 26.0.

^{19}F–NMR
(282 MHz, C_6D_6)

δ: –62.7, –119.7.

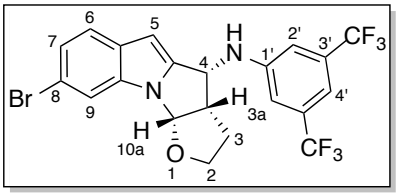
HRMS
(70 eV, IE)

Calculated for $[C_{21}H_{15}F_7N_2O]^+$: 444.1067, found : 444.1063.

HPLC

Daicel CHIRALPAK ODH (250 x 4.6 mm)
Hexane:*i*PrOH= 90:10, 0.2 mL/min
λ_{max}= 214.3 nm
t_R (minor)= 29.9 min, t_R (major)= 46.2 min

(3a*S*,4*R*,10a*S*)-*N*-(3,5-Bis(trifluoromethyl)phenyl)-8-bromo-2,3,3a,10a-tetrahydro-4*H*-furo[3',2':4,5]pyrrolo[1,2-*a*]indol-4-amine (61e)



Yellow solid

mp= 215– 217 °C

R_f = 0.60 (hexane:diethyl ether, 2:1)

e.r.= 93:7, $[\alpha]^{20}_{D}$= +74° (*c* 0.5, DCM)

Isolated yield: 70%

^{1}H–NMR
(300 MHz, C_6D_6)

δ: 7.93 – 7.91 (m, 1H, H_9), 7.63 – 7.29 (m, 3H, H_6, H_7, and $H_{4'}$), 6.47 (d, *J*= 1.9 Hz, 2H, $H_{2'}$), 6.00 (s, 1H, H_5), 5.61 (d, *J*= 5.7 Hz, 1H, H_{10a}), 4.06 (app. t, *J*= 7.3 Hz, 1H, H_4), 3.80 (d, *J*= 6.8 Hz, 1H, NH), 3.46 (ddd, *J*= 8.8, 7.3, 2.9 Hz, 1H, H_{2A}), 2.96 – 2.83 (m, 1H, H_{2B}), 2.74 – 2.63 (m, 1H, H_{3a}), 1.20 – 0.88 (m, 2H, H_3).

^{13}C–NMR
(75 MHz, C_6D_6)

δ: 147.5, 142.6, 133.0, 133.0 (q, $J_{C\text{-}F}$= 32.6 Hz), 132.6, 124.5, 124.2 (q, $J_{C\text{-}F}$= 273.0 Hz), 122.7, 116.0, 114.4, 112.2, 111.1, 94.3, 90.3, 67.9, 51.3, 49.9, 25.9.

^{19}F–NMR
(282 MHz, C_6D_6)

δ: –62.7.

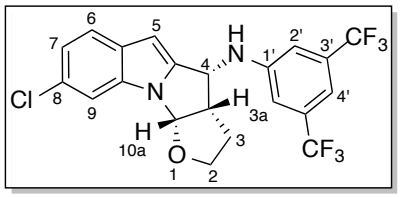
HRMS
(70 eV, IE)

Calculated for $[C_{21}H_{15}BrF_6N_2O]^+$: 504.0266, found: 504.0265.

HPLC

Daicel CHIRALPAK IC (250 x 4.6 mm)
Hexane:*i*PrOH= 97:3, 0.2 mL/min
λ_{max}= 223.7 nm
t_R (minor)= 29.8 min, t_R (major)= 43.3 min

(3a*S*,4*R*,10a*S*)-*N*-(3,5-Bis(trifluoromethyl)phenyl)-8-chloro-2,3,3a,10a-tetrahydro-4*H*-furo[3',2':4,5]pyrrolo[1,2-*a*]indol-4-amine (61f)



Yellow foam

R_f = 0.40 (hexane:diethyl ether, 2:1)

e.r.= 95:5, $[\alpha]^{19}_{D}$= +33° (*c* 0.25, DCM)

Isolated yield: 69%

^{1}H–NMR
(300 MHz, C_6D_6)

δ: 7.77 (d, *J*= 1.9 Hz, 1H, H_9), 7.38 (d, *J*= 8.6 Hz, 1H, H_6), 7.30 (s, 1H, $H_{4'}$), 7.23 (dd, *J*= 8.6, 1.9 Hz, 1H, H_7), 6.45 (s, 2H, $H_{2'}$), 6.01 (s, 1H, H_5), 5.62 (d, *J*= 5.7 Hz, 1H, H_{10a}), 4.06 (app. t, *J*= 7.3 Hz, 1H, H_4), 3.80 (d, *J*= 6.8 Hz, 1H, NH), 3.46 (ddd, *J*= 8.8, 7.4, 2.9 Hz, 1H, H_{2A}), 2.91 (ddd, *J*= 10.0, 8.8, 6.3 Hz, 1H, H_{2B}), 2.67 (dddd, *J*= 9.2, 7.8, 5.7, 3.4 Hz, 1H, H_{3a}), 1.16 – 0.97 (m, 2H, H_3).

^{13}C–NMR
(75 MHz, C_6D_6)

δ: 147.5, 142.7, 132.9 (q, $J_{C\text{-}F}$= 32.8 Hz), 132.6, 132.3, 124.2 (q, $J_{C\text{-}F}$= 272.7 Hz), 122.3, 122.0, 112.2, 111.5, 111.1, 94.3, 90.3, 67.9, 51.3, 50.0, 25.9.

^{19}F–NMR
(282 MHz, C_6D_6)

δ: –62.7.

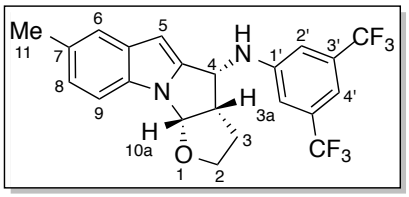
HRMS
(70 eV, IE)

Calculated for $[C_{21}H_{15}ClF_6N_2O]^+$: 460,0772, found: 460.0778.

HPLC

Daicel CHIRALPAK ODH (250 x 4.6 mm)
Hexane:*i*PrOH= 97:3, 0.2 mL/min
λ_{max}= 222.5 nm
t_R (minor)= 28.4 min, t_R (major)= 42.0 min

(3a*S*,4*R*,10a*S*)-*N*-(3,5-Bis(trifluoromethyl)phenyl)-7-methyl-2,3,3a,10a-tetrahydro-4*H*-furo[3',2':4,5]pyrrolo[1,2-*a*]indol-4-amine (61g)



Yellow oil

R_f = 0.50 (hexane:diethyl ether, 2:1)

e.r.= 94:6, $[\alpha]^{26}_{D}$= +16° (*c* 0.5, DCM)

Isolated yield: 79%

^{1}H–NMR
(300 MHz, C_6D_6)

δ: 7.63 (d, *J*= 8.3 Hz, 1H, H_9), 7.52 (s, 1H, H_6), 7.29 (s, 1H, $H_{4'}$), 7.10 (dd, *J*= 8.3, 1.6 Hz, 1H, H_8), 6.46 (s, 2H, $H_{2'}$), 6.13 (s, 1H, H_5), 5.80 (d, *J*= 5.6 Hz, 1H, H_{10a}), 4.15 (app. t, *J*= 7.2 Hz, 1H, H_4), 3.92 (d, *J*= 6.4 Hz, 1H, NH), 3.52 (ddd, *J*= 8.8, 7.4, 2.8 Hz, 1H, H_{2A}), 3.02 (ddd, *J*= 10.1, 8.8, 6.2 Hz, 1H, H_{2B}), 2.76 – 2.66 (m, 1H, H_{3a}), 2.43 (s, 3H, H_{11}), 1.22 – 1.02 (m, 2H, H_3).

^{13}C–NMR
(75 MHz, C_6D_6)

δ: 147.7, 142.0, 134.4, 132.9 (q, $J_{C\text{-}F}$= 32.7 Hz), 130.9, 130.3, 124.2 (q, $J_{C\text{-}F}$= 272.8 Hz), 124.1, 121.3, 112.1, 111.0, 110.8, 93.8, 90.4, 67.8, 51.5, 50.0, 26.1, 21.8.

^{19}F–NMR
(282 MHz, C_6D_6)

δ: –62.7.

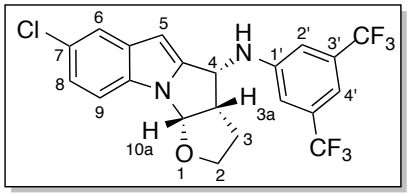
HRMS
(70 eV, IE)

Calculated for $[C_{22}H_{18}F_6N_2O]^+$: 440.1318, found 440.1326.

HPLC

Daicel CHIRALPAK ODH (250 x 4.6 mm)
Hexane:*i*PrOH= 95:5, 0.2 mL/min
λ_{max}= 206.0 nm
t_R (minor)= 39.1 min, t_R (major)= 46.4 min

(3a*S*,4*R*,10a*S*)-*N*-(3,5-Bis(trifluoromethyl)phenyl)-7-chloro-2,3,3a,10a-tetrahydro-4*H*-furo[3',2':4,5]pyrrolo[1,2-*a*]indol-4-amine (61h)



Yellow solid

mp= 123 – 125 °C

R_f = 0.40 (hexane:diethyl ether, 2:1)

e.r.= 92:8, $[\alpha]^{26}_{D}$= +28° (*c* 0.4, DCM)

Isolated yield: 74%

^{1}H–NMR
(300 MHz, C_6D_6)

δ: 7.68 (d, *J*= 2.0 Hz, 1H, H_6), 7.38 (d, *J*= 8.6 Hz, 1H, H_9), 7.30 (s, 1H, $H_{4'}$), 7.22 (dd, *J*= 8.6, 2.0 Hz, 1H, H_8), 6.47 (s, 2H, $H_{2'}$), 5.94 (s , 1H, H_5), 5.65 (d, *J*= 5.7 Hz, 1H, H_{10a}), 4.08 (app. t, *J*= 7.4 Hz, 1H, H_4), 3.84 (d, *J*= 6.6 Hz, 1H, NH), 3.48 (ddd, *J*= 8.8, 7.4, 2.8 Hz, 1H, H_{2A}), 2.94 (ddd, *J*= 10.1, 8.8, 6.2 Hz, 1H, H_{2B}), 2.70 (dddd, *J*= 11.0, 7.8, 5.7, 3.2 Hz, 1H, H_{3a}), 1.21 – 0.99 (m, 2H, H_3).

^{13}C–NMR
(75 MHz, C_6D_6)

δ: 147.5, 143.3, 134.8, 133.0 (q, $J_{C\text{-}F}$= 32.9 Hz), 130.6, 127.1, 124.2 (q, $J_{C\text{-}F}$= 273.0 Hz), 122.8, 121.0, 112.3, 112.2, 111.1, 94.0, 90.4, 67.9, 51.4, 50.0, 26.0.

^{19}F–NMR
(282 MHz, C_6D_6)

δ: –62.7.

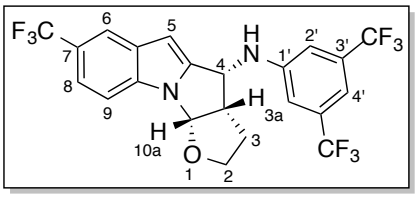
HRMS
(70 eV, IE)

Calculated for $[C_{21}H_{15}ClF_6N_2O]^+$: 460.0772, found 460.0776.

HPLC

Daicel CHIRALPAK ODH (250 x 4.6 mm)
Hexane:*i*PrOH= 90:10, 0.2 mL/min
λ_{max}= 225.7 nm
t_R (minor)= 41.2 min, t_R (major)= 50.4 min

(3a*S*,4*R*,10a*S*)-*N*-(3,5-Bis(trifluoromethyl)phenyl)-7-(trifluoromethyl)-2,3,3a,10a-tetrahydro-4*H*-furo[3',2':4,5]pyrrolo[1,2-*a*]indol-4-amine (61i)



Yellow oil

R_f = 0.48 (hexane:diethyl ether, 2:1)

e.r.= 84:16, $[\alpha]^{20}_D$= +18° (*c* 0.5, DCM)

Isolated yield: 70%

^{1}H–NMR
(300 MHz, C_6D_6)

δ: 8.01 (s, 1H, H_9), 7.52 – 7.45 (m, 2H, H_6 y H_8), 7.32 (s, 1H, $H_{4'}$), 6.49 (s, 2H, $H_{2'}$), 6.06 (s, 1H, H_5), 5.68 (d, *J*= 5.7 Hz, 1H, H_{10a}), 4.10 (app. t, *J*= 7.4 Hz, 1H, H_4), 3.86 (d, *J*= 6.6 Hz, 1H, NH), 3.49 (ddd, *J*= 8.8, 7.4, 3.0 Hz, 1H, H_{2A}), 2.94 (ddd, *J*= 10.0, 8.9, 6.2 Hz, 1H, H_{2B}), 2.78 – 2.68 (m, 1H, H_{3a}), 1.20 – 0.99 (m, 2H, H_3).

^{13}C–NMR
(75 MHz, C_6D_6)

δ: 147.5, 143.8, 133.5, 133.1, 133.0 (q, $J_{C\text{-}F}$= 32.8 Hz), 124.4, 124.2 (q, $J_{C\text{-}F}$= 272.8 Hz), 123.7 (q, $J_{C\text{-}F}$= 31.6 Hz), 119.2, 112.2, 111.6, 111.2, 95.1, 90.4, 68.0, 51.4, 50.0, 25.9.

^{19}F–NMR
(282 MHz, C_6D_6)

δ: –59.8, –62.7.

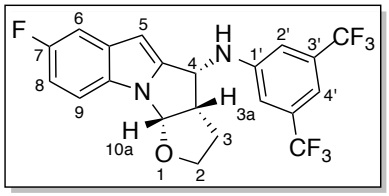
HRMS
(70 eV, IE)

Calculated for $[C_{22}H_{15}F_9N_2O]^+$: 494.1035, found 494.1038.

HPLC

Daicel CHIRALPAK ODH (250 x 4.6 mm)
Hexane:*i*PrOH= 90:10, 0.2 mL/min
λ_{max}= 222.5 nm
t_R (minor)= 29.1 min, t_R (major)= 32.9 min

(3a*S*,4*R*,10a*S*)-*N*-(3,5-Bis(trifluoromethyl)phenyl)-7-fluoro-2,3,3a,10a-tetrahydro-4*H*-furo[3',2':4,5]pyrrolo[1,2-*a*]indol-4-amine (61j)



Yellow oil

R_f = 0.40 (hexane:diethyl ether, 2:1)

e.r.= 94:6, $[\alpha]^{24}_{D}$= +6° (*c* 0.5, DCM)

Isolated yield: 76%

^{1}H–NMR
(300 MHz, C_6D_6)

δ: 7.41 (dd, *J*= 8.9 Hz, $J_{H\text{-}F}$= 4.5 Hz, 1H, H_9), 7.35 (dd, $J_{H\text{-}F}$= 9.6 Hz, *J*= 2.4 Hz, 1H, H_6), 7.31 (s, 1H, $H_{4'}$), 6.98 (app. td, $J_{H\text{-}F}$= 9.1 Hz, *J*= 2.5 Hz, 1H, H_8), 6.49 (s, 2H, $H_{2'}$), 6.00 (s, 1H, H_5), 5.70 (d, *J*= 5.7 Hz, 1H, H_{10a}), 4.11 (app. t, *J*= 7.3 Hz, 1H, H_4), 3.87 (d, *J*= 6.6 Hz, 1H, NH), 3.50 (ddd, *J*= 8.8, 7.3, 2.8 Hz, 1H, H_{2A}), 2.97 (ddd, *J*= 10.2, 8.9, 6.2 Hz, 1H, H_{2B}), 2.72 (dddd, *J*= 11.2, 7.8, 5.7, 3.2 Hz, 1H, H_{3a}), 1.21 – 0.99 (m, 2H, H_3).

^{13}C–NMR
(75 MHz, C_6D_6)

δ: 159.2 (d, $J_{C\text{-}F}$= 235.6 Hz), 147.6, 143.7, 134.3, 134.2, 133.5 (q, $J_{C\text{-}F}$= 32.8 Hz), 124.2 (q, $J_{C\text{-}F}$= 273.5 Hz), 112.2, 112.0 (d, $J_{C\text{-}F}$= 10.2 Hz), 111.1, 110.8 (d, $J_{C\text{-}F}$= 26.6 Hz), 106.5 (d, $J_{C\text{-}F}$= 23.6 Hz), 94.4 (d, $J_{C\text{-}F}$= 4.4 Hz), 90.5, 67.9, 51.5, 50.0, 26.0.

^{19}F–NMR
(282 MHz, C_6D_6)

δ: –62.7, –122.6.

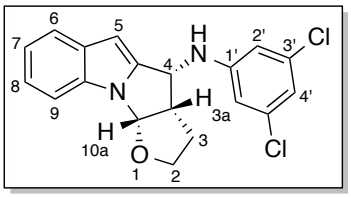
HRMS
(70 eV, IE)

Calculated for $[C_{21}H_{15}F_7N_2O]^+$: 444.1067, found 444.1072.

HPLC

Daicel CHIRALPAK ODH (250 x 4.6 mm)
Hexane:*i*PrOH= 90:10, 0.2 mL/min
λ_{max}= 208.4 nm
t_R (minor)= 36.8 min, t_R (major)= 44.0 min

(3a*S*,4*R*,10a*S*)-*N*-(3,5-Dichlorophenyl)-2,3,3a,10a-tetrahydro-4*H*-furo[3',2':4,5]pyrrolo[1,2-*a*]indol-4-amine (61k)



Yellow oil

R_f = 0.40 (hexane:diethyl ether, 2:1)

e.r.= 79:21, $[\alpha]^{20}_D$= –15° (*c* 0.5, DCM)

Isolated yield: 54%

^{1}H–NMR
(300 MHz, acetone-d_6)

δ: 7.55 (d, *J*= 7.6 Hz, 1H, H_6), 7.48 (d, *J*= 8.1 Hz, 1H, H_9), 7.08 (t, *J*= 7.6 Hz, 1H, H_7), 7.15 (t, *J*= 8.1 Hz, 1H, H_8), 6.87 (d, *J*= 1.8 Hz, 2H, $H_{2'}$), 6.74 (t, *J*= 1.8 Hz, 1H, $H_{4'}$), 6.41 (d, *J*= 5.7 Hz, 1H, H_{10a}), 6.27 (s, 1H, H_5), 6.26 (d, *J*= 7.9 Hz, 1H, NH), 5.28 (td, *J*= 7.9, 1.4 Hz, 1H, H_4), 4.12 – 4.02 (m, 1H, H_{3a}), 3.95 (ddd, *J*= 8.7, 7.5, 2.7 Hz, 1H, H_{2A}), 3.66 (ddd, *J*= 10.4, 8.7, 6.1 Hz, 1H, H_{2B}), 2.10 – 1.84 (m, 2H, H_3).

^{13}C–NMR
(75 MHz, acetone-d_6)

δ: 150.9, 143.9, 136.2, 134.6, 132.7, 122.0, 121.5, 121.0, 117.0, 111.8, 111.5, 94.4, 91.0, 68.4, 52.2, 50.9, 27.2.

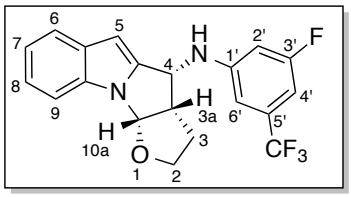
HRMS
(70 eV, IE)

Calculated for $[C_{19}H_{16}Cl_2N_2O]^+$: 358.0634, found: 358.0644.

HPLC

Daicel CHIRALPAK IC (250 x 4.6 mm)
Hexane:*i*PrOH= 90:10, 0.2 mL/min
λ_{max}= 221.3 nm
t_R (minor)= 31.8 min, t_R (major)= 37.3 min

(3a*S*,4*R*,10a*S*)-*N*-(3-Fluoro-5-(trifluoromethyl)phenyl)-2,3,3a,10a-tetrahydro-4*H*-furo[3',2':4,5]pyrrolo[1,2-*a*]indol-4-amine (61l)



Yellow oil

R_f = 0.40 (hexane:diethyl ether, 2:1)

e.r.= 79:21, $[\alpha]^{21}_D$= +14° (*c* 0.5, DCM)

Isolated yield: 45%

^{1}H–NMR
(300 MHz, C_6D_6)

δ: 7.74 – 7.66 (m, 2H, H_6 and H_9), 7.29 – 7.20 (m, 2H, H_7 and H_8), 6.67 (dt, $J_{H\text{-}F}$= 8.5 Hz, *J*= 2.1 Hz, 1H, $H_{4'}$), 6.22 (s, 1H, $H_{6'}$), 6.14 (s, 1H, H_5), 5.93 (dt, $J_{H\text{-}F}$= 10.9 Hz, *J*= 2.1 Hz, 1H, $H_{2'}$), 5.77 (d, *J*= 5.7 Hz, 1H, H_{10a}), 4.19 (app. t, *J*= 7.2 Hz, 1H, H_4), 3.83 (d, *J*= 6.6 Hz, 1H, NH), 3.51 (ddd, *J*= 8.8, 7.2, 2.5 Hz, 1H, H_{2A}), 2.99 (ddd, *J*= 10.4, 8.8, 6.0 Hz, 1H, H_{2B}), 2.68 (dddd, *J*= 10.3, 8.2, 5.7, 2.9 Hz, 1H, H_{3a}), 1.29 – 1.03 (m, 2H, H_3).

^{13}C–NMR
(75 MHz, C_6D_6)

δ: 164.3 (d, $J_{C\text{-}F}$= 245.0 Hz), 149.0 (d, $J_{C\text{-}F}$= 11.1 Hz), 142.1, 134.0, 133.4 (dd, $J_{C\text{-}F}$= 32.2, 10.2 Hz), 132.4, 122.5, 121.5, 121.3, 111.4, 105.9, 102.3 (d, $J_{C\text{-}F}$= 25.4 Hz), 101.7 (dq, $J_{C\text{-}F}$= 25.6, 3.6 Hz), 94.2, 90.3, 67.9, 51.6, 50.1.

^{19}F–NMR
(282 MHz, C_6D_6)

δ: –62.5, –109.8.

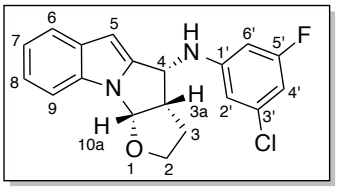
HRMS
(70 eV, IE)

Calculated for $[C_{20}H_{16}F_4N_2O]^+$: 376.1193, found: 376.1197.

HPLC

Daicel CHIRALPAK IC (250 x 4.6 mm)
Hexane:*i*PrOH= 97:3, 0.2 mL/min
λ_{max}= 216.6 nm
t_R (minor)= 31.1 min, t_R (major)= 49.8 min

(3a*S*,4*R*,10a*S*)-*N*-(3-Chloro-5-fluorophenyl)-2,3,3a,10a-tetrahydro-4*H*-furo[3',2':4,5]pyrrolo[1,2-*a*]indol-4-amine (61m)



Yellow oil

R_f = 0.50 (hexane:diethyl ether, 2:1)

e.r.= 75:25, $[\alpha]^{20}_D$= +32° (*c* 0.25, DCM)

Isolated yield: 45%

^{1}H–NMR
(300 MHz, C_6D_6 C_6D_6)

δ: 7.72 – 7.66 (m, 2H, H_6 and H_9), 7.28 – 7.20 (m, 2H, H_7 and H_8), 6.49 (dt, $J_{H\text{-}F}$=8.6 Hz, *J*= 2.0 Hz, 1H, $H_{3'}$), 6.12 (s, 1H, H_5), 6.03 – 6.00 (m, 1H, $H_{4'}$), 5.80 (dt, $J_{H\text{-}F}$= 10.9 Hz, *J*= 2.3 Hz, 1H, $H_{2'}$), 5.75 (d, *J*= 5.7 Hz, 1H, H_{10a}), 4.23 (ddd, *J*= 8.0, 6.6, 1.3 Hz, 1H, H_4), 3.76 (d, *J*= 6.7 Hz, 1H, NH), 3.51 (ddd, *J*= 8.7, 7.6, 2.5 Hz, 1H, H_{2A}), 2.99 (ddd, *J*= 10.3, 8.7, 5.9 Hz, 1H, H_{2B}), 2.73 – 2.63 (m, 1H, H_{3a}), 1.38 – 1.08 (m, 2H, H_3).

^{13}C–NMR
(75 MHz, C_6D_6)

δ: 164.5 (d, $J_{C\text{-}F}$= 245.5 Hz), 149.1 (d, $J_{C\text{-}F}$= 12.0 Hz), 142.3, 136.2 (d, $J_{C\text{-}F}$= 13.6 Hz), 134.1, 132.5, 122.4, 121.5, 121.2, 111.4, 109.1 (d, $J_{C\text{-}F}$= 2.4 Hz), 105.6 (d, $J_{C\text{-}F}$= 25.5 Hz), 98.3 (d, $J_{C\text{-}F}$= 25.5 Hz), 94.1, 90.3, 67.9, 51.6, 50.2, 26.2.

^{19}F–NMR
(282 MHz, C_6D_6)

δ: –110.6.

HRMS
(70 eV, IE)

Calculated for $[C_{19}H_{16}ClFN_2O]^+$: 342.0930, found: 342.0938.

HPLC

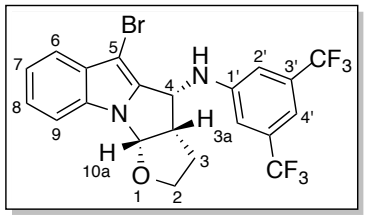
Daicel CHIRALPAK IC (250 x 4.6 mm)
Hexane:*i*PrOH= 90:10, 0.2 mL/min
λ_{max}= 216.6 nm
t_R (minor)= 32.2 min, t_R (major)= 37.1 min

Section 2.2.B.5

- **General Procedure for the Synthesis of the 5-Bromo-pyrrolo[1,2-*a*] Derivative 65a**

(3a*S*,4*R*,10a*S*)-*N*-(3,5-Bis(trifluoromethyl)phenyl)-2,3,3a,10a-tetrahydro-4*H*-furo[3',2':4,5]pyrrolo[1,2-*a*]indol-4-amine (**65a**) (0.1 mmol) was placed in a glass reaction tube equipped with a magnetic stirring bar under argon atmosphere. Then, dry DMF (2 mL) was added and the mixture was cooled to 0 °C and *N*-bromo succinimide (1.1 equiv, 0.11 mmol) was added at this temperature, the mixture was allowed to warm to room temperature and stirred at this temperature 2 hours. Finally, the resulting mixture was diluted with ethyl acetate (15 mL), washed with brine (10 mL), dried over Na_2SO_4 and filtered. The solvent was removed under vacuum and the crude was purified by flash column chromatography on silica gel using hexane:diethyl ether (2:1) as eluent to give pure **65a**.[213]

(3a*S*,4*R*,10a*S*)-*N*-(3,5-Bis(trifluoromethyl)phenyl)-5-bromo-2,3,3a,10a-tetrahydro-4*H*-furo[3',2':4,5]pyrrolo[1,2-*a*]indol-4-amine (65a)



Yellow solid

mp= 60 – 62°C

R_f = 0.40 (hexane:diethyl ether, 2:1)

$[\alpha]^{19}_D$= –11° (*c* 0.5, DCM)

Isolated yield: 95%

^{1}H–NMR
(300 MHz, C_6D_6)

δ: 7.76 – 7.69 and 7.60 – 7.53 (2 m, 2H, H_6 and H_9), 7.30 (s, 1H, $H_{4'}$), 7.23 – 7.17 (m, 2H, H_7 and H_8), 6.55 (s, 2H, $H_{2'}$), 5.62 (d, *J*= 5.8 Hz, 1H, H_{10a}), 4.04 – 3.92 (m, 2H, H_{3a} and NH), 3.50 (ddd, *J*= 8.8, 7.5, 2.4 Hz, 1H, H_{2A}), 3.00 (ddd, *J*= 10.5, 8.8, 5.9 Hz, 1H, H_{2B}), 2.71 – 2.60 (m, 1H, H_{3a}), 1.22 – 0.97 (m, 2H, H_3).

^{13}C–NMR
(75 MHz, C_6D_6)

δ: 147.8, 138.2, 133.0 (q, $J_{C\text{-}F}$=32.7 Hz), 132.5, 132.0, 124.2 (q, $J_{C\text{-}F}$= 271.7 Hz), 123.7, 122.1, 119.7, 112.2, 111.4, 111.3, 90.6, 83.7, 68.1, 51.4, 50.3, 26.1.

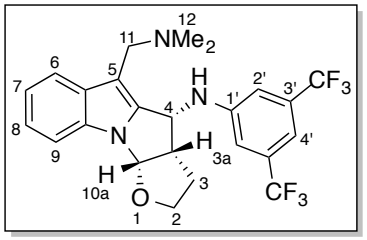
[213] A. Ghosh, L. M. Stanley, *Chem. Commun.*, **2014**, *50*, 2765.

^{19}F–NMR (282 MHz, C_6D_6)	δ: –62.7.
HRMS (70 eV, IE)	Calculated for $[C_{21}H_{15}BrF_6N_2O]^+$: 504.0266, found: 504.0268.

- **General Procedure for the Synthesis of the 5-((Dimethylamino)methyl)-pyrrolo[1,2-*a*] Derivative 66a**

(3a*S*,4*R*,10a*S*)-*N*-(3,5-Bis(trifluoromethyl)phenyl)-2,3,3a,10a-tetrahydro-4*H*-furo[3',2':4,5]pyrrolo[1,2-*a*]indol-4-amine (**61a**) (0.1 mmol) was placed in a glass reaction tube equipped with a magnetic stirring bar under argon atmosphere. Then, dichloromethane (2 mL) and dimethylmethylideneammonium chloride (Eschenmosher's salt) (3.3 equiv, 0.33 mmol) was added at room temperature. The mixture was heated at reflux and stirred at this temperature followed by TLC until total consumption of the starting material (1.5 hours). Then, triethylamine (3.3 equiv, 0.33 mmol) and water (6 mL) were added at room temperature. Finally, the resulting mixture was extracted with ethyl acetate (3 x 10 mL), the organic layer was dried over Na_2SO_4 and the solvent was removed under vacuum to give **66a** in 99% yield.[214]

(3a*S*,4*R*,10a*S*)-*N*-(3,5-Bis(trifluoromethyl)phenyl)-5-((dimethylamino)methyl)-2,3,3a,10a-tetrahydro-4*H*-furo[3',2':4,5]pyrrolo[1,2-*a*]indol-4-amine (66a)



Yellow oil

$[\alpha]^{19}_D$= +6° (*c* 0.5, DCM)

Isolated yield: 99%

[214] E. R. Abbey, L. N. Zakharov, and S.-Y. Liu, *J. Am. Chem. Soc.*, **2010**, *132*, 16340.

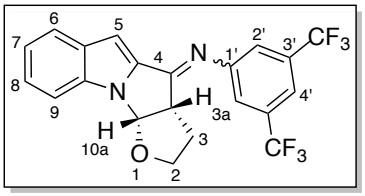
^{1}H–NMR (300 MHz, C_6D_6)	δ: 8.44 (s, 1H, NH), 7.70 – 7.63 and 7.56 – 7.48 (2m, 2H, H_6 and H_9), 7.37 (s, 1H, $H_{4'}$), 7.27 – 7.18 (m, 2H, H_7 and H_8), 6.92 (s, 2H, $H_{2'}$), 5.95 (d, *J*= 5.4 Hz, 1H, H_{10a}), 4.15 (d, *J*= 7.7 Hz, 1H, H_4), 3.51 (ddd, *J*= 8.9, 7.7, 2.2 Hz, 1H, H_{2A}), 3.43 (d, *J*= 13.0 Hz, 1H, H_{11A}), 2.97 (d, *J*= 13.0 Hz, 1H, H_{11B}), 2.98 – 2.80 (m, 2H, H_{2B} and H_{3a}), 1.87 (s, 6H, H_{12}), 1.66 – 1.55 (m, 1H, H_{3A}), 1.24 (dtd, *J*= 12.7, 10.4, 7.7 Hz, 1H, H_{3B}).
^{13}C–NMR (75 MHz, C_6D_6)	δ: 149.8, 141.0, 134.1, 133.0 (q, $J_{C\text{-}F}$= 32.4 Hz), 131.5, 124.4 (q, $J_{C\text{-}F}$= 274.0 Hz), 122.1, 121.0, 118.7, 112.4, 111.6, 110.3, 105.1, 91.2, 67.7, 52.9, 52.5, 51.4, 44.4, 25.8
^{19}F–NMR (282 MHz, C_6D_6)	δ: –62.8.
HRMS (70 eV, IE)	Calculated for $[C_{24}H_{23}F_6N_3O]^+$: 483.1740, found: 483.1745.

- **General Procedure for the Synthesis of the Pyrrolo[1,2-*a*]indol-4-imine Derivative 70a**

(3a*S*,4*R*,10a*S*)-*N*-(3,5-Bis(trifluoromethyl)phenyl)-2,3,3a,10a-tetrahydro-4*H*-furo[3',2':4,5]pyrrolo[1,2-*a*]indol-4-amine (**61a**) (0.1 mmol) was placed in a glass reaction tube equipped with a magnetic stirring bar under argon atmosphere. Then, benzene (2.5 mL) and DDQ (1.1 equiv, 0.11 mmol) were added at room temperature. The mixture was stirred at this temperature followed by TLC until total consumption of the starting material (5 hours). Then, ethyl acetate (10 mL) was added and the mixture was washed with aqueous NaOH solution (0.5 M) (3 x 10 mL). Finally, the organic layer was dried over Na_2SO_4, the solvent was removed under vacuum and the crude was purified by flash column chromatography on silica gel using hexane:diethyl ether (2:1) as eluent to give pure **70a** as mixture of two stereoisomers (5:1) in >99% yield.[215]

[215] L. Strekowski, M. T. Cegla, D. B. Harden, S.-B. Kong, *J. Org. Chem.*, **1989**, *54*, 2464.

(3a*S*,10a*S*)-*N*-(3,5-Bis(trifluoromethyl)phenyl)-2,3,3a,10a-tetrahydro-4*H*-furo[3',2':4,5]pyrrolo[1,2-*a*]indol-4-imine (70a)



Yellow oil

R_f = 0.18 (hexane:diethyl ether, 2:1)

$[\alpha]^{20}_D$ = +86° (*c* 0.5, DCM)

Isolated yield: 99%

^{1}H–NMR
(300 MHz, C_6D_6)

δ: (major isomer): 7.78 (s, 1H, $H_{4'}$), 7.55 (s, 2H, $H_{2'}$), 7.32 (dt, *J*= 8.1, 1.0 Hz, 1H, H_9), 7.27 – 7.19 (m, 2H, H_6 and H_8), 7.05 (td, *J*= 8.1, 1.0 Hz, 1H, H_7), 5.83 (d, *J*= 5.5 Hz, 1H, H_{10a}) 5.82 (s, 1H, H_5), 3.61 (td, *J*= 9.2, 1.0 Hz, 1H, H_{2A}), 3.52 (ddd, *J*= 9.9, 5.5, 1.2 Hz, 1H, H_{3a}), 3.10 (ddd, *J* = 12.0, 9.2, 5.1 Hz, 1H, H_{2B}), 2.10 (br dd, *J*= 12.0, 5.1 Hz, 1H, H_{3A}), 1.86 (app tdd, *J* = 12.0, 9.9, 7.7 Hz, 1H, H_{3B}).

^{13}C–NMR
(75 MHz, C_6D_6)

δ (major isomer): 165.4, 154.3, 134.0, 133.3 (q, $J_{C\text{-}F}$= 33.2 Hz), 133.3, 132.3, 125.8, 124.1 (q, $J_{C\text{-}F}$= 272.4 Hz), 123.6, 122.4, 117.8, 111.6, 101.3, 87.2, 66.7, 54.8, 32.7.

^{19}F–NMR
(282 MHz, C_6D_6)

δ: –62.5.

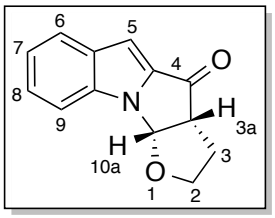
HRMS
(70 eV, IE)

Calculated for $[C_{21}H_{14}F_6N_2O]^+$: 424.1005, found: 424.0991.

- **General Procedure for the Synthesis of the Pyrrolo[1,2-*a*]indol-4-one Derivative 71a**

(3a*S*,10a*S*)-*N*-(3,5-Bis(trifluoromethyl)phenyl)-2,3,3a,10a-tetrahydro-4*H*-furo[3',2':4,5]pyrrolo[1,2-*a*]indol-4-imine (**70a**) (0.1 mmol) was placed in a glass reaction tube equipped with a magnetic stirring bar. Then, THF:H_2O (3 mL) and acetic acid (2 equiv, 0.2 mmol) were added at room temperature. The mixture was heated at 80 °C and stirred at this temperature 16 hours. Then, THF was removed under vacuum, water was added (5 mL) and the resulting mixture was extracted with ethyl acetate (3 x 10 mL). Finally, the organic layer was dried over Na_2SO_4, filtered, the solvent was removed under vacuum and the crude was purified by flash column chromatography on silica gel using hexane:diethyl ether (1:1) as eluent to give pure **71a** in >99% yield.

(3a*R*,10a*S*)-2,3,3a,10a-Tetrahydro-4*H*-furo[3',2':4,5]pyrrolo[1,2-*a*]indol-4-one (71a)



Yellow oil

R_f = 0.28 (hexane:diethyl ether, 1:1)

$[\alpha]^{19}_D$= +99° (*c* 0.5, DCM)

Isolated yield: 99%

^{1}H–NMR (300 MHz, C_6D_6)	δ: 7.52 (dt, *J*= 8.2, 1.0 Hz, 1H, H_9), 7.48 (dq, *J*= 8.2, 1.0 Hz, 1H, H_6), 7.18 (td, *J*= 8.2, 1.0 Hz, 1H, H_8), 7.04 (td, *J*= 8.2, 1.0 Hz, 1H, H_7), 6.89 (d, *J*= 1.0 Hz, 1H, H_5), 5.61 (d, *J*= 5.4 Hz, 1H, H_{10a}), 3.35 (app. t, *J*= 8.9 Hz, 1H, H_{2A}), 2.95 – 2.85 (m, 2H, H_{2B} and H_{3a}), 1.83 (br dd, *J*= 12.8, 5.2 Hz, 1H, H_{3A}), 1.54 – 1.38 (m, 1H, H_{3B}).
^{13}C–NMR (75 MHz, C_6D_6)	δ: 192.3, 136.7, 135.0, 133.4, 125.8, 124.3, 122.3, 112.0, 99.3, 86.6, 66.7, 56.1, 30.2.
HRMS (70 eV, IE)	Calculated for $[C_{13}H_{11}NO_2]^+$: 213.0784, found: 213.0781.

Part C

- **Synthesis of 1*H*-Indole-7-carbaldehyde Derivatives 72 and Enol Ethers 18**

Non commercially available 1*H*-indole-7-carbaldehyde derivatives **72**[216] and substituted 2,3-dihydrofuran derivatives **18b** were prepared according to the methods reported in the literature and purified by standard procedures.

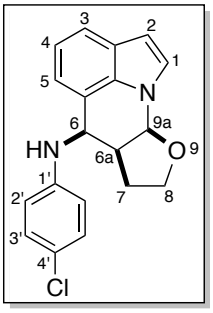
Section 2.2.C.3

- **General Procedure for the Synthesis of the Pyrrolo[3,2,1-*ij*]quinoline Derivatives 73, 84 and 85**

The corresponding 1*H*-indole-7-carbaldehyde derivative **72** (0.2 mmol), aniline **34** (1 equiv, 0.2 mmol) and 4 Å powder molecular sieves (50 mg) were placed in a glass reaction tube equipped with a magnetic stirring bar under argon atmosphere. Then, dichloromethane (2 mL) was added, the slurry was cooled to 0 °C and HBF_4 (15 mol%) was added. The mixture was allowed to warm to room temperature and stirred at this temperature for 2 hours. Then, the mixture was cooled to the corresponding temperature (see **Section 2.2.C.3**, Results and Discussion) and the corresponding enol ether **18**, butyl vinyl ether or *N*-protected enamine derivative **14** (3 equiv, 0.6 mmol) was added. The reaction was kept at the corresponding temperature followed by TLC until total consumption of the starting material (*in situ* generated imine derivative 9-72 hours). Finally, the resulting slurry was filtered through a pad of basic alumina (except for the case of compounds **85a** and **85b** where silica gel was used) eluting with ethyl acetate, the solvent was removed under vacuum and the crude was purified by flash column chromatography on silica gel using mixtures of hexane and diethyl ether as eluent to give pure **73**, **84** and **85**.

[216] a) A. Dobbs, *J. Org. Chem.*, **2001**, *66,* 638. b) M. P. Moyer, J. F. Shiurba, H. Rapoport, *J . Org. Chem.*, **1986**, *51*, 5106.

(6*R,6a*S**,9a*S**)-*N*-(4-Chlorophenyl)-6a,7,8,9a-tetrahydro-6*H*-furo[2,3-*b*]pyrrolo[3,2,1-*ij*]quinolin-6-amine (73a)**



White solid

mp= 192 – 194 °C

R_f = 0.61 (hexane:diethyl ether, 2:1)

Isolated yield: 80%

^{1}H–NMR (300 MHz, C_6D_6)

δ: 7.59 (d, *J*= 7.6 Hz, 1H, H_3), 7.26 (d, *J*= 3.2 Hz, 1H, H_1), 7.23 – 7.15 (m, 2H, H_6 and H_7), 7.13 (d, *J*= 8.9 Hz, 2H, $H_{3'}$), 6.58 (d, *J*= 3.2 Hz, 1H, H_2), 6.14 (d, *J*= 8.9 Hz, 2H, $H_{2'}$), 5.53 (d, *J*= 5.2 Hz, 1H, H_{9a}), 4.73 (br s, 1H, H_6), 3.50 (q, *J*= 8.3 Hz, 1H, H_{8A}), 3.46 – 3.37 (m, 2H, H_{8b} and NH), 2.58 (ddt, *J*= 10.6, 8.6, 5.1 Hz, 1H, H_{6a}), 1.28 – 1.05 (m, 2H, H_7).

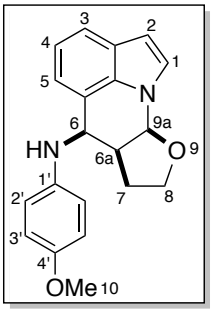
^{13}C–NMR (75 MHz, C_6D_6)

δ: 146.2, 133.4, 129.7, 126.7, 124.1, 123.0, 120.7, 120.3, 120.2, 118.0, 115.0, 104.0, 85.3, 67.1, 50.3, 43.6, 24.2.

HRMS (70 eV, IE)

Calculated for $[C_{19}H_{17}ClN_2O]^+$: 324.1024, found: 324.1033.

(6*R,6a*S**,9a*S**)-*N*-(4-Methoxyphenyl)-6a,7,8,9a-tetrahydro-6*H*-furo[2,3-*b*]pyrrolo[3,2,1-*ij*]quinolin-6-amine (73b)**



White solid

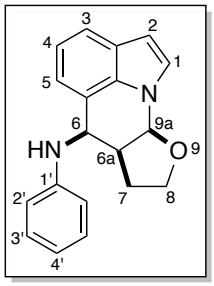
mp= 197 – 199 °C

R_f = 0.40 (hexane:diethyl ether, 2:1)

Isolated yield: 32%

^{1}H–NMR (300 MHz, acetone-d_6)	δ: 7.43 (dt, *J*= 8.0, 1.1 Hz, 1H, H_8), 7.30 (d, *J*= 3.1 Hz, 1H, H_1), 7.25 (dt, *J*= 7.3, 1.1 Hz, 1H, H_5), 7.02 (dd, *J*= 8.0, 7.3 Hz, 1H, H_4), 6.95 (d, *J*= 9.0 Hz, 2H, $H_{2'}$), 6.83 (d, *J*= 9.0 Hz, 2H, $H_{3'}$), 6.52 (d, *J*= 3.1 Hz, 1H, H_2), 6.18 (d, *J*= 5.3 Hz, 1H, H_{9a}), 5.50 (dd, *J*= 10.2, 5.0 Hz, 1H, H_6), 4.88 (d, *J*= 10.2 Hz, 1H, NH), 3.94 (q, *J*= 8.3 Hz, 1H, H_{8A}), 3.74 (s, 3H, H_{10}), 3.61 (ddd, *J*= 9.8, 8.3, 3.9 Hz, 1H, H_{8B}), 3.32 (ddt, *J*= 10.7, 8.8, 5.0 Hz, 1H, H_{6a}), 2.10 – 1.96 (m, 1H, H_{7A}), 1.65 – 1.48 (m, 1H, H_{7B}).
^{13}C–NMR (75 MHz, acetone-d_6)	δ: 146.2, 133.4, 129.7, 126.7, 124.1, 123.0, 120.7, 120.3, 120.2, 118.0, 115.0, 104.0, 85.3, 67.1, 50.3, 43.6, 24.2.
HRMS (70 eV, IE)	Calculated for $[C_{20}H_{20}N_2O_2]^+$: 320.1519, found: 320.1526.

(6*R,6a*S**,9a*S**)-*N*-Phenyl-6a,7,8,9a-tetrahydro-6*H*-furo[2,3-*b*]pyrrolo[3,2,1-*ij*]quinolin-6-amine (73c)**



White solid

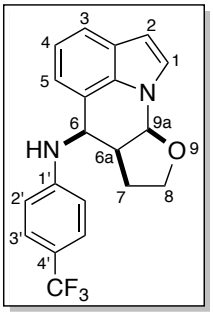
mp= 159 – 161 °C

R_f = 0.55 (hexane:diethyl ether, 2:1)

Isolated yield: 60%

^{1}H–NMR (300 MHz, C_6D_6)	δ: 7.59 (d, *J*= 7.9 Hz, 1H, H_3), 7.32 (d, *J*= 7.2 Hz, 1H, H_5), 7.25 (d, *J*= 3.2 Hz, 1H, H_1), 7.23 – 7.14 (m, 3H, H_4 and $H_{3'}$), 6.81 (t, *J*= 7.3 Hz, 1H, $H_{4'}$), 6.58 (d, *J*= 3.2 Hz, 1H, H_2), 6.49 (d, *J*= 7.9 Hz, 2H, $H_{2'}$), 5.52 (d, *J*= 5.0 Hz, 1H, H_{9a}), 4.94 (dd, *J*= 9.2, 5.0 Hz, 1H, H_6), 3.59 (d, *J*= 9.1 Hz, 1H, NH), 3.46 (q, *J*= 8.2 Hz, 1H, H_{8A}), 3.45 – 3.36 (m, 1H, H_{8B}), 2.73 (ddt, *J*= 10.5, 8.5, 5.0 Hz, 1H, H_{6a}), 1.34 –1.05 (m, 2H, H_7).
^{13}C–NMR (75 MHz, C_6D_6)	δ: 147.7, 133.5, 129.8, 126.7, 124.0, 120.7, 120.7, 120.1, 118.5, 118.1, 114.0, 103.9, 85.4, 67.1, 50.2, 43.8, 24.2.
HRMS (70 eV, IE)	Calculated for $[C_{19}H_{18}N_2O]^+$: 290.1414, found: 290.1424.

(6*R,6a*S**,9a*S**)-*N*-(4-(Trifluoromethyl)phenyl)-6a,7,8,9a-tetrahydro-6*H*-furo[2,3-*b*]pyrrolo[3,2,1-*ij*]quinolin-6-amine (73d)**



Yellow solid

mp= 164 – 166 °C

R_f = 0.45 (hexane:diethyl ether, 2:1)

Isolated yield: 80%

^{1}H–NMR
(300 MHz, C_6D_6)

δ: 7.59 (d, *J*= 7.6 Hz,1H, H_3), 7.41 (d, *J*= 8.4 Hz, 2H, $H_{3'}$), 7.25 (d, *J*= 3.2 Hz, 1H, H_1), 7.18 – 7.08 (m, 2H, H_6 and H_7), 6.58 (d, *J*= 3.2 Hz, 1H, H_2), 6.14 (d, *J*= 8.4 Hz, 2H, $H_{2'}$), 5.51 (d, *J*= 5.2 Hz, 1H, H_{9a}), 4.73 (dd, *J*= 9.6, 4.9 Hz, 1H, H_6), 3.73 (d, *J*= 9.6 Hz, 1H, NH), 3.50 (q, *J*= 8.3 Hz, 1H, H_{8A}), 3.42 (app. td, *J*= 8.6, 4.1 Hz, 1H, H_{8b}), 2.52 (ddt, *J*= 10.5, 8.8, 5.1 Hz,1H, H_{6a}), 1.25 – 1.01 (m, 2H, H_7).

^{13}C–NMR
(75 MHz, C_6D_6)

δ: 150.2, 133.3, 127.7 (q, $J_{C\text{-}F}$= 272.7 Hz), 127.3 – 127.0 (m), 126.8, 124.2, 120.7, 120.5, 119.8 (q, $J_{C\text{-}F}$= 32.3 Hz), 119.7, 117.9, 112.8, 104.1, 85.2, 67.1, 49.7, 43.5, 24.3.

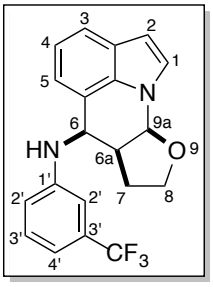
^{19}F–NMR
(282 MHz, C_6D_6)

δ: –60.4.

HRMS
(70 eV, IE)

Calculated for $[C_{20}H_{17}F_3N_2O]^+$: 358.1287, found: 358.1292.

(6*R,6a*S**,9a*S**)-*N*-(3-(Trifluoromethyl)phenyl)-6a,7,8,9a-tetrahydro-6*H*-furo[2,3-*b*]pyrrolo[3,2,1-*ij*]quinolin-6-amine (73e)**



Yellow solid

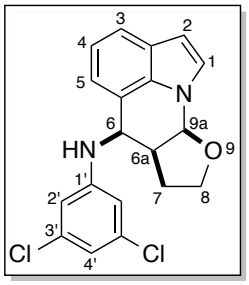
mp= 170 – 172°C

R_f = 0.33 (hexane:diethyl ether, 4:1)

Isolated yield: 83%

^{1}H–NMR (300 MHz, C_6D_6)	δ: 7.63 – 7.55 (m, 1H, H_3), 7.24 (d, *J*= 3.2 Hz, 1H, H_1), 7. 19 – 7.12 (m, 2H, H_4 and H_5), 7.02 – 6.92 (m, 2H, $H_{5'}$ and $H_{6'}$), 6.72 (br s, 1H, $H_{2'}$), 6.58 (d, *J*= 3.2 Hz, 1H, H_2), 6.36 – 6.28 (m, 1H, $H_{4'}$), 5.44 (d, *J*= 5.0 Hz, 1H, H_{9a}), 4.71 (dd, *J*= 9.7, 5.0 Hz, 1H, H_6), 3.61 (d, *J*= 9.7 Hz, 1H, NH), 3.46 (q, *J*= 8.3 Hz, 1H, H_{8A}), 3.41 (app. td, *J*= 8.6, 4.8 Hz, 1H, H_{8B}), 2.54 (ddt, *J*= 10.5, 8.8, 5.0 Hz, 1H, H_{6a}), 1.25 – 1.03 (m, 2H, H_7).
^{13}C–NMR (75 MHz, C_6D_6)	δ: 147.9, 133.3, 132.1 (q, $J_{C\text{-}F}$= 31.5 Hz), 130.3, 126.7, 125.3 (q, $J_{C\text{-}F}$= 272.4 Hz), 124.1, 120.7, 120.4, 119.8, 117.9, 116.2, 114.8 – 114.3 (m), 110.3 – 109.9 (m), 104.0, 85.2, 67.1, 49.9, 43.5, 24.4.
^{19}F–NMR (282 MHz, C_6D_6)	δ: –62.1.
HRMS (70 eV, IE)	Calculated for $[C_{20}H_{17}F_3N_2O]^+$: 358.1287, found: 358.1297.

(6*R,6a*S**,9a*S**)-*N*-(3,5-Dichlorophenyl)-6a,7,8,9a-tetrahydro-6*H*-furo[2,3-*b*]pyrrolo[3,2,1-*ij*]quinolin-6-amine (73f)**



White solid

mp= 220 – 222 °C

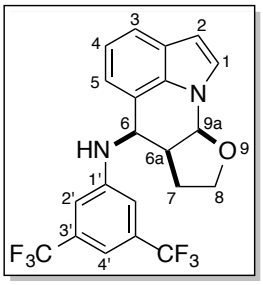
R_f= 0.56 (hexane:diethyl ether, 2:1)

Isolated yield: 90%

^{1}H–NMR (300 MHz, C_6D_6)	δ: 7.57 (d, *J*= 8.1 Hz, 1H, H_3), 7.22 (d, *J*= 3.2 Hz, 1H, H_1), 7.14 (app. t, *J*= 7.7 Hz, 1H, H_4), 7.06 (d, *J*= 7.1 Hz, 1H, H_5), 6.79 (t, *J*= 1.8 Hz, 1H, $H_{4'}$), 6.57 (d, *J*= 3.2 Hz, 1H, H_2), 6.20 (d, *J*= 1.8 Hz, 2H, $H_{2'}$), 5.37 (d, *J*= 5.2 Hz, 1H, H_{9a}), 4.47 (dd, *J*= 9.8, 5.2 Hz, 1H, H_6), 3.50 (d, *J*= 9.8 Hz, 1H, NH), 3.48 (q, *J*= 8.3 Hz, 1H, H_{8A}), 3.45 – 3.35 (m, 1H, H_{8B}), 2.41 (ddt, *J*= 10.5, 8.6, 5.2 Hz, 1H, H_{6a}), 1.21 – 1.00 (m, 2H, H_4).

^{13}C–NMR (75 MHz, C_6D_6)	δ: 149.4, 136.2, 133.2, 126.7, 124.2, 120.6, 120.4, 119.5, 117.9, 117.8, 111.8, 104.0, 85.1, 67.0, 49.9, 43.4, 24.4.
HRMS (70 eV, IE)	Calculated for $[C_{19}H_{16}Cl_2N_2O]^+$: 358.0634, found: 358.0632.

(6*R,6a*S**,9a*S**)-*N*-(3,5-Bis(trifluoromethyl)phenyl)-6a,7,8,9a-tetrahydro-6*H*-furo[2,3-*b*]pyrrolo[3,2,1-*ij*]quinolin-6-amine (73g)**



White solid

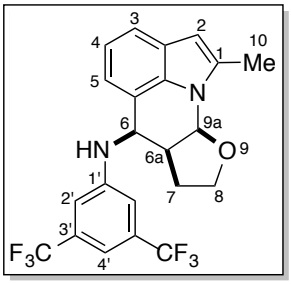
mp= 212 – 214 °C

R_f = 0.50 (hexane:diethyl ether, 2:1)

Isolated yield: 96%

^{1}H–NMR (300 MHz, C_6D_6)	δ: 7.59 (d, *J*= 7.9 Hz, 1H, H_3), 7.31 (s, 1H, $H_{4'}$), 7.22 (d, *J*= 3.2 Hz, 1H, H_1), 7.15 (app. t, *J*= 7.6 Hz, 1H, H_4), 6.99 (d, *J*= 7.3 Hz, 1H, H_5), 6.62 (s, 2H, $H_{2'}$), 6.57 (d, *J*= 3.2 Hz, 1H, H_2), 5.33 (d, *J*= 5.0 Hz, 1H, H_{9a}), 4.49 (dd, *J*= 9.6, 5.0 Hz, 1H, H_6), 3.69 (d, *J*= 9.6 Hz, 1H, NH), 3.48 (q, *J*= 8.3 Hz, 1H, H_{3A}), 3.42 (td, *J*= 8.3, 5.5 Hz, 1H, H_{8B}), 2.39 (ddt, *J*= 10.2, 9.1, 5.0 Hz, 1H, H_{6a}), 1.18 – 1.03 (m, 2H, H_7).
^{13}C–NMR (75 MHz, C_6D_6)	δ: 148.5, 133.2, 133.1 (q, $J_{C\text{-}F}$= 32.7 Hz), 126.8, 124,2 (q, $J_{C\text{-}F}$= 272.7 Hz), 124.2, 120.6, 120.5, 119,0 117.8, 112.5, 111.4 – 110.5 (m), 104.1, 85.1, 67.0, 49.8, 43.3, 24.5.
^{19}F–NMR (282 MHz, C_6D_6)	δ: –62.6.
HRMS (70 eV, IE)	Calculated for $[C_{21}H_{16}F_6N_2O]^+$: 426.1161, found: 426.1152.

(6*R,6a*S**,9a*S**)-*N*-(3,5-Bis(trifluoromethyl)phenyl)-1-methyl-6a,7,8,9a-tetrahydro-6*H*-furo[2,3-*b*]pyrrolo[3,2,1-*ij*]quinolin-6-amine(73h)**



Yellow solid

mp= 198 – 200 °C

R_f = 0.55 (hexane:diethyl ether, 2:1)

Isolated yield: 85%

^{1}H–NMR
(300 MHz, C_6D_6)

δ: 7.55 (d, *J*= 7.9 Hz, 1H, H_3), 7.30 (s, 1H, $H_{4'}$), 7.15 (app. t, *J*= 7.6 Hz, 1H, H_4), 6.96 (d, *J*= 7.2 Hz, 1H, H_5), 6.62 (s, 2H, $H_{2'}$), 6.31 (d, *J*= 1.3 Hz, 1H, H_2), 5.23 (d, *J*= 5.4 Hz, 1H, H_{9a}), 4.47 (dd, *J*= 9.6, 4.9 Hz, 1H, H_6), 3.79 (d, *J*= 9.6 Hz, 1H, NH), 3.40 (q, *J*= 8.3 Hz, 1H, H_{8A}), 3.35 (td, *J*= 8.3, 5.0 Hz, 1H, H_{8B}), 2.46 (s, 3H, H_{10}), 2.46 – 2.33 (m, 1H, H_{6a}), 1.18 – 1.03 (m, 2H, H_7).

^{13}C–NMR
(75 MHz, C_6D_6)

δ: 148.5, 136.8, 133.8, 133.0 (q, $J_{C\text{-}F}$= 32.5 Hz), 127.0, 124.3 (q, $J_{C\text{-}F}$= 272.5 Hz), 120.5, 119.5, 118.6, 116.7, 112.7 – 112.3 (m), 110.9 – 110.5 (m), 102.4, 84.4, 66.5, 49.9, 43.3, 25.1, 13.3.

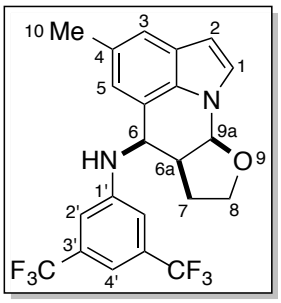
^{19}F–NMR
(282 MHz, C_6D_6)

δ: –62.6.

HRMS
(70 eV, IE)

Calculated for $[C_{22}H_{18}F_6N_2O]^+$: 440.1318, found: 440.1329.

(6*R,6a*S**,9a*S**)-*N*-(3,5-Bis(trifluoromethyl)phenyl)-4-methyl-6a,7,8,9a-tetrahydro-6*H*-furo[2,3-*b*]pyrrolo[3,2,1-*ij*]quinolin-6-amine (73i)**



Yellow solid

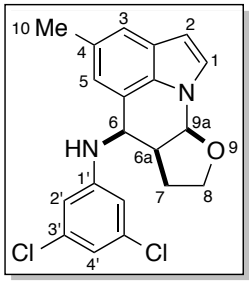
mp= 202 – 204 °C

R_f = 0.48 (hexane:diethyl ether, 4:1)

Isolated yield: 90%

^{1}H–NMR (300 MHz, C_6D_6)	δ: 7.59 (d, *J*= 7.9 Hz, 1H, H_3), 7.31 (s, 1H, $H_{4'}$), 7.22 (d, *J*= 3.2 Hz, 1H, H_1), 7.15 (app. t, *J*= 7.6 Hz, 1H, H_4), 6.99 (d, *J*= 7.3 Hz, 1H, H_5), 6.62 (s, 2H, $H_{2'}$), 6.57 (d, *J*= 3.2 Hz, 1H, H_2), 5.33 (d, *J*= 5.0 Hz, 1H, H_{9a}), 4.49 (dd, *J*= 9.6, 5.0 Hz, 1H, H_6), 3.69 (d, *J*= 9.6 Hz, 1H, NH), 3.48 (q, *J*= 8.3 Hz, 1H, H_{3A}), 3.42 (td, *J*= 8.3, 5.5 Hz, 1H, H_{8B}), 2.47 (s, 3H, H_{10}), 2.39 (ddt, *J*= 10.2, 9.1, 5.0 Hz, 1H, H_{6a}), 1.18 – 1.03 (m, 2H, H_7).
^{13}C–NMR (75 MHz, C_6D_6)	δ: 148.4, 133.1 (q, $J_{C\text{-}F}$= 32.8 Hz), 131.7, 129.5, 127.1, 124.3, 124.2 (q, $J_{C\text{-}F}$= 273.3 Hz), 120.3, 119.3, 118.6, 112.7 – 112.25 (m), 110.9 – 110.6 (m), 103.6, 85.0, 67.0, 49.8, 43.3, 24.6, 22.0.
^{19}F–NMR (282 MHz, C_6D_6)	δ: –62.6.
HRMS (70 eV, IE)	Calculated for $[C_{22}H_{19}F_6N_2O]^+$: 440.1318, found: 440.1326.

(6*R,6a*S**,9a*S**)-*N*-(3,5-Dichlorophenyl)-4-methyl-6a,7,8,9a-tetrahydro-6*H*-furo[2,3-*b*]pyrrolo[3,2,1-*ij*]quinolin-6-amine (73j)**



Yellow solid

mp= 198 – 200 °C

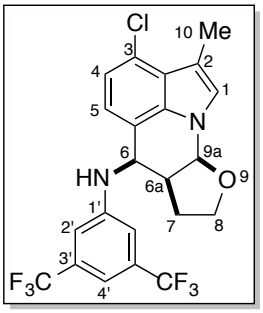
R_f = 0.25 (hexane:diethyl ether, 2:1)

Isolated yield: 72%

^{1}H–NMR (300 MHz, C_6D_6)	δ: 7.34 (s, 1H, H_3), 7.22 (d, *J*= 3.2 Hz, 1H, H_1), 6.97 (s, 1H, H_5), 6.78 (t, *J*= 1.8 Hz, 1H, $H_{4'}$), 6.53 (d, *J*= 3.2 Hz, 1H, H_2), 6.21 (d, *J*= 1.8 Hz, 2H, $H_{2'}$), 5.37 (d, *J*= 5.0 Hz, 1H, H_{9a}), 4.51 (dd, *J*= 9.7, 5.0 Hz, 1H, H_6), 3.52 (d, *J*= 9.7 Hz, 1H, NH), 3.48 (q, *J*= 8.3 Hz, 1H, H_{8A}), 3.47 – 3.37 (m, 1H, H_{8B}), 2.45 (s, 3H, H_{10}), 2.43 (ddt, *J*= 10.5, 8.6, 5.0 Hz, 1H, H_{6a}), 1.21 – 1.00 (m, 2H, H_7).
^{13}C–NMR (75 MHz, C_6D_6)	δ: 149.3, 136.2, 131.8, 127.0, 124.2, 120.1, 119.3, 119.1, 117.9, 111.7, 103.5, 85.1, 67.0, 49.9, 43.5, 24.5, 22.1.

HRMS (70 eV, IE)	Calculated for $[C_{22}H_{18}F_6N_2O]^+$: 372.0791, found: 372.0792.

(6*R,6a*S**,9a*S**)-*N*-(3,5-Bis(trifluoromethyl)phenyl)-3-chloro-2-methyl-6a,7,8,9a-tetrahydro-6*H*-furo[2,3-*b*]pyrrolo[3,2,1-*ij*]quinolin-6-amine (73k)



White solid

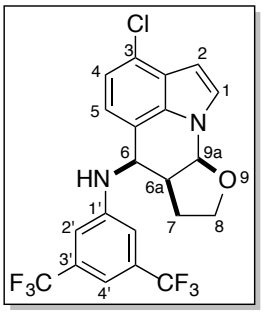
mp= 222 – 224 °C

R_f = 0.55 (hexane:diethyl ether, 2:1)

Isolated yield: 95%

^{1}H–NMR (300 MHz, C_6D_6)	δ: 7.31 (s, 1H, $H_{4'}$), 7.12 (d, *J*= 7.6 Hz, 1H, H_4), 6.88 (s, 1H, H_1), 6.71 (d, *J*= 7.6 Hz, 1H, H_5), 6.58 (s, 2H, $H_{2'}$), 5.24 (d, *J*= 5.0 Hz, 1H, H_{9a}), 4.34 (dd, *J*= 9.7, 5.0 Hz, 1H, H_6), 3.52 (d, *J*= 9.7 Hz, 1H, NH), 3.47 (q, *J*= 8.3 Hz, 1H, H_{8A}), 3.38 (app. td, *J*= 8.7, 4.3 Hz, 1H, H_{8B}), 2.61 (s, 3H, H_{10}), 2.33 (ddt, *J*= 10.4, 8.7, 5.0 Hz, 1H, H_{6a}), 1.15 – 0.91 (m, 2H, H_7).
^{13}C–NMR (75 MHz, C_6D_6)	δ: 148.2, 134.6, 133.1 (q, $J_{C\text{-}F}$= 32.8 Hz), 126.7, 124.5 (q, $J_{C\text{-}F}$= 273.2 Hz), 123.8, 123.3, 120.4, 118.7, 117.7, 114.2, 112.6 – 112.4 (m), 111.1 – 110.8 (m), 85.0, 66.9, 49.4, 43.0, 24.4, 12.2.
^{19}F–NMR (282 MHz, C_6D_6)	δ: –62.6.
HRMS (70 eV, IE)	Calculated for $[C_{22}H_{17}ClF_6N_2O]^+$: 474.0928, found: 474.0929.

(6*R,6a*S**,9a*S**)-*N*-(3,5-Bis(trifluoromethyl)phenyl)-3-chloro-6a,7,8,9a-tetrahydro-6*H*-furo[2,3-*b*]pyrrolo[3,2,1-*ij*]quinolin-6-amine (73l)**



White solid

mp= 196 – 198 °C

R_f= 0.60 (hexane:diethyl ether, 2:1)

Isolated yield: 97%

^{1}H–NMR
(300 MHz, C_6D_6)

δ: 7.33 (s, 1H, $H_{4'}$), 7.17 (d, *J*= 7.6 Hz, 1H, H_4), 7.11 (d, *J*= 3.3 Hz, 1H, H_1), 6.77 (d, *J*= 3.3 Hz, 1H, H_2), 6.75 (d, *J*= 7.6 Hz, 1H, H_5), 6.60 (s, 2H; $H_{2'}$), 5.23 (d, *J*= 4.9 Hz, 1H, H_{9a}), 4.37 (dd, *J*= 9.7, 4.9 Hz, 1H, H_6), 3.54 (d, *J*= 9.7 Hz, 1H, NH), 3.46 (q, *J*= 8.3 Hz, 1H, H_{8A}), 3.37 (app. td, *J*= 9.3, 3.7 Hz, 1H, H_{8B}), 2.33 (ddt, *J*= 10.5, 8.6, 4.9 Hz, 1H, H_{6a}), 1.15 – 0.86 (m, 2H, H_7).

^{13}C–NMR
(75 MHz, C_6D_6)

δ: 148.2, 133.6, 133.1 (q, $J_{C\text{-}F}$ = 32.8), 125.8, 125.5, 125.0, 124.3 (q, $J_{C\text{-}F}$ = 273.2) 120.2, 118.7, 117.8, 112.6 – 112.4 (m), 111.2 – 110.9 (m), 102.7, 85.2, 67.1, 49.5, 43.1, 24.3.

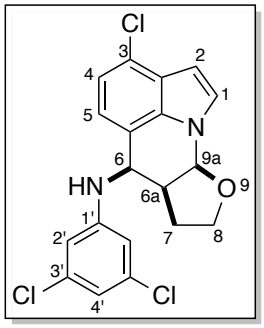
^{19}F–NMR
(282 MHz, C_6D_6)

δ: –62.6.

HRMS
(70 eV, IE)

Calculated for $[C_{21}H_{15}ClF_6N_2O]^+$: 460.0772, found: 460.0780.

(6*R,6a*S**,9a*S**)-3-Chloro-*N*-(3,5-dichlorophenyl)-6a,7,8,9a-tetrahydro-6*H*-furo[2,3-*b*]pyrrolo[3,2,1-*ij*]quinolin-6-amine (73m)**



White solid

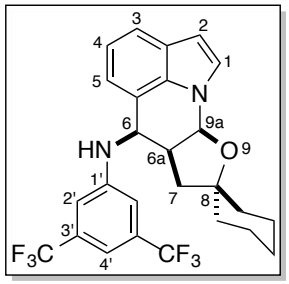
mp= 199 – 201 °C

R_f= 0.30 (hexane:diethyl ether, 3:1)

Isolated yield: 60%

^{1}H–NMR (300 MHz, C_6D_6)	δ: 7.15 (d, *J*= 7.6 Hz, 1H, H_4), 7.10 (d, *J*= 3.2 Hz, 1H, H_1), 6.79 (d, *J*= 7.6 Hz, 1H, H_5), 6.78 (d, *J*= 1.8 Hz, 1H, $H_{4'}$), 6.76 (d, *J*= 3.2 Hz, 1H, H_2), 6.17 (d, *J*= 1.8 Hz, 2H, $H_{2'}$), 5.25 (d, *J*= 5.0 Hz, 1H, H_{9a}), 4.33 (dd, *J*= 9.7, 5.0 Hz, 1H, H_6), 3.44 (q, *J*= 8.2 Hz, 1H, H_{8A}), 3.38 – 3.29 (m, 1H, H_{8B}), 3.34 (d, *J*= 9.7 Hz, 1H, NH), 2.33 (ddt, *J*= 10.8, 8.7, 5.0 Hz, 1H, H_{6a}), 1.15 – 1.03 (m, 1H, H_{7A}), 0.99 – 0.84 (m, 1H, H_{7B}).
^{13}C–NMR (75 MHz, C_6D_6)	δ: 149.0, 136.2, 133.6, 125.6, 125.4, 124.9, 120.2, 118.8, 118.3, 118.2, 111.8, 102.7, 85.3, 67.1, 49.5, 43.2, 24.1.
HRMS (70 eV, IE)	Calculated for $[C_{19}H_{15}Cl_3N_2O]^+$: 392.0244, found: 392.0253 .

(6'*R,6a'*S**,9a'*S**)-*N*-(3,5-Bis(trifluoromethyl)phenyl)-6a',9a'-dihydro-6'*H*,7'*H*-spiro[cyclohexane-1,8'-furo[2,3-*b*]pyrrolo[3,2,1-*ij*]quinolin]-6'-amine (73n)**



White solid

mp= 191 – 193 °C

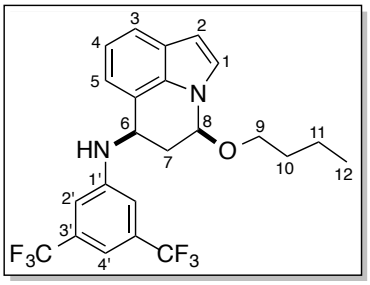
R_f = 0.43 (hexane:diethyl ether, 8:1)

Isolated yield: 80%

^{1}H–NMR (300 MHz, C_6D_6)	δ: 7.59 (d, *J*= 7.9 Hz, 1H, H_3), 7.30 (s, 1H, $H_{4'}$), 7.26 (d, *J*= 3.2 Hz, 1H, H_1), 7.14 (app. t, *J*= 7.8 Hz, 1H, H_4), 6.98 (d, *J*= 7.1 Hz, 1H, H_5), 6.72 (s, 2H, $H_{2'}$), 6.57 (d, *J*= 3.2 Hz, 1H, H_2), 5.40 (d, *J*= 5.0 Hz, 1H, H_{9a}), 4.53 (dd, *J*= 9.6, 5.0 Hz, 1H, H_6), 3.74 (d, *J*= 9.6 Hz, 1H, NH), 2.69 (ddt, *J*= 12.9, 8.2, 5.0 Hz, 1H, H_{6a}), 1.66 – 0.78 (m, 12H, H_7 and H_{Cy}).
^{13}C–NMR (75 MHz, C_6D_6)	δ: 148.6, 133.12 (q, $J_{C\text{-}F}$= 32.6 Hz), 132.8, 126.8, 124.4 (q, $J_{C\text{-}F}$= 272.6 Hz), 124.3, 120.6, 120.5, 119.1, 117.6, 112.5 – 112.1 (m), 111.0 – 110.6 (m), 103.7, 85.0, 49.9, 43.2, 39.7, 38.6, 36.3, 25.5, 23.9, 23.8.

^{19}F–NMR (282 MHz, C_6D_6)	δ: –62.6.
HRMS (70 eV, IE)	Calculated for $[C_{26}H_{24}F_6N_2O]^+$: 494.1787, found: 494.1792.

(4*S,6*R**)-*N*-(3,5-Bis(trifluoromethyl)phenyl)-4-butoxy-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-6-amine (84a)**



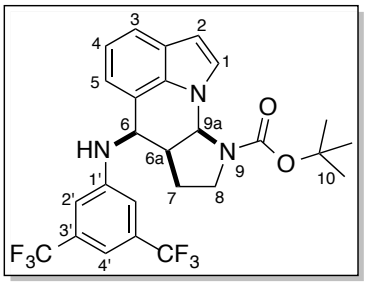
Yellow oil

R_f = 0.63 (hexane:diethyl ether, 4:1)

Isolated yield: 87%

^{1}H–NMR (300 MHz, C_6D_6)	δ: 7.59 (dd, *J*= 7.5, 1.5 Hz, 1H, H_3), 7.25 (s, 1H, $H_{4'}$), 7.21 – 7.10 (m, 2H, H_4 and H_5), 6.82 (s, 2H, $H_{2'}$), 6.76 and 6.49 (2 d, *J*= 3.2 Hz, 2H, H_1 and H_2), 4.84 (d, *J*= 10.1 Hz, 1H, NH), 4.71 (t, *J*=2.8 Hz, 1H, H_8), 4.41 (ddd, *J*= 10.1, 4.2, 2.2 Hz, 1H, H_6), 3.09 (dt, *J*= 8.8, 6.1 Hz, 1H, H_{9A}), 2.83 (dt, *J*= 8.8, 6.1 Hz, 1H, H_{9B}), 2.19 (dt, *J*= 14.1, 2.2 Hz, 1H, H_{7A}), 1.43 (ddd, *J*= 14.1, 4.2, 3.5 Hz, 1H, H_{7B}), 1.14 – 0.91 (m, 4H, H_{10} and H_{11}), 0.72 (t, *J*= 7.1 Hz, 3H, H_{12}).
^{13}C–NMR (75 MHz, C_6D_6)	δ: 148.4, 132.8 (q, $J_{C\text{-}F}$= 32.6 Hz), 132.7, 126.6, 124.4 (q, $J_{C\text{-}F}$= 273.7 Hz), 121.5, 121.3, 120.9, 120.7, 113.0, 112.9, 110.3 –109.8 (m), 102.8, 82.6, 68.6, 46.2, 32.3, 31.7, 19.5, 13.8.
^{19}F–NMR (282 MHz, C_6D_6)	δ: –62.7.
HRMS (70 eV, IE)	Calculated for $[C_{23}H_{22}F_6N_2O]^+$: 456.1631, found: 456.1633.

tert-Butyl (6*R,6a*S**,9a*S**)-6-((3,5-bis(trifluoromethyl)phenyl)amino)-6a,7,8,9a-tetrahydrodipyrrolo[2,3-*b*:3',2',1'-*ij*]quinoline-9(6*H*)-carboxylate (85a)**



Mixture of rotamers at room temperature

R_f = 0.48 (hexane:diethyl ether, 2:1)

Isolated yield: 90%

^{1}H–NMR
(300 MHz, C_6D_6)

δ: 7.87 (d, *J*= 3.3 Hz, 1H, $H_{1\ major\ rota}$), 7.66 – 7.54 (m, 2H, $H_{3\ major\ and\ minor\ rota}$ and $H_{1\ minor\ rota}$), 7.31 (s, 2H, $H_{4'\ major\ and\ minor\ rota}$), 7.19 – 7.09 (m, 1H, $H_{4\ major\ and\ minor\ rota}$), 6.98 (d, *J*= 7.2 Hz, 1H, $H_{5\ major\ and\ minor\ rota}$), 6.67 (d, *J*= 3.3 Hz, 1H, $H_{2\ minor\ rota}$), 6.62 (s, 2H, $H_{2'\ major\ and\ minor\ rota}$), 6.60 (d, *J*= 3.3 Hz, 1H, $H_{2\ major\ rota}$), 5.78 (d, *J*= 5.6 Hz, 1H, $H_{9a\ major\ rota}$), 5.60 (d, *J*= 5.6 Hz, 1H, $H_{9a\ minor\ rota}$), 4.43 (dd, *J*= 9.6, 5.1 Hz, 1H, $H_{6\ minor\ rota}$), 4.37 (dd, *J*= 9.6, 5.1 Hz, 1H, $H_{6\ major\ rota}$), 3.69 (d, *J*= 9.6 Hz, 1H, $NH_{\ major\ rota}$), 3.63 (d, *J*= 9.6 Hz, 1H, $NH_{\ minor\ rota}$), 3.20 – 3.08 and 2.96 – 2.72 (2m, 2H, $H_{8\ major\ and\ minor\ rota}$), 2.14 – 1.91 (m, 1H, $H_{6a\ major\ and\ minor\ rota}$), 1.54 (s, 9H, $H_{10\ minor\ rota}$), 1.50 (s, 9H, $H_{10\ major\ rota}$), 1.22 – 0.99 (m, 2H, $H_{7\ major\ and\ minor\ rota}$).

^{13}C–NMR
(75 MHz, C_6D_6)

δ (major rota): 154.9, 148.3, 132.8 (q, $J_{C\text{-}F}$= 32.1 Hz), 132.7, 126.4, 126.0, 124.4, 123.4 (q, $J_{C\text{-}F}$= 272.7 Hz), 120.3, 120.0, 118.4, 117.0, 112.2, 110.7 – 110.3 (m), 103.5, 80.0, 67.8, 49.4, 49.3, 41.4, 28.2, 23.9.

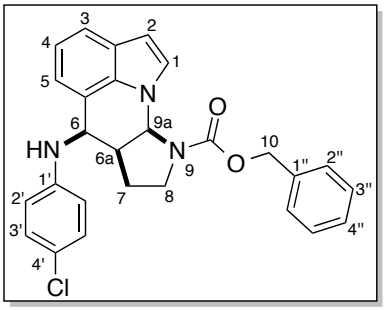
^{19}F–NMR
(282 MHz, C_6D_6)

δ: –62.5.

HRMS
(70 eV, IE)

Calculated for $[C_{26}H_{25}F_6N_3O_2]^+$: 525.1845, found: 525.1848.

Benzyl (6*R,6a*S**,9a*S**)-6-((4-Chlorophenyl)amino)-6a,7,8,9a-tetrahydrodipyrrolo[2,3-*b*:3',2',1'-*ij*]quinoline-9(6*H*)-carboxylate (85q)**



Mixture of rotamers at room temperature

R_f = 0.30 (hexane:diethyl ether, 2:1)

Isolated yield: 75%

^{1}H–NMR
(300 MHz, C_6D_6)

δ: 7.82 (d, *J*= 3.3 Hz, 1H, $H_{1\ major\ rota}$), 7.59 (d, *J*= 7.3 Hz, 1H, $H_{3\ major\ and\ minor\ rota}$), 7.40 – 7.05 (m, 10H, $H_{1\ minor\ rota}$ and H_4, H_5, $H_{3'}$, $H_{2''}$, $H_{3''}$, $H_{4''\ major\ and\ minor\ rota}$), 6.58 (d, *J*= 3.2 Hz, 1H, $H_{2\ major\ rota}$), 6.55 (d, *J*= 3.2 Hz, 1H, $H_{2\ minor\ rota}$), 6.13 (d, *J*= 8.2 Hz, 2H, $H_{2'\ major\ and\ minor\ rota}$), 5.90 (d, *J*= 5.6 Hz, 1H, $H_{9a\ major\ rota}$), 5.56 (d, *J*= 5.2 Hz, 1H, $H_{9a\ minor\ rota}$), 5.27 (d, *J*= 12.0 Hz, 1H, $H_{10A\ minor\ rota}$), 5.24 (d, *J*= 12.2 Hz, 1H, $H_{10A\ major\ rota}$), 5.18 (d, *J*= 12.2 Hz, 1H, $H_{10B\ minor\ rota}$), 5.12 (d, *J*= 12.2 Hz, 1H, $H_{10B\ major\ rota}$), 4.65 – 4.54 (m, 1H, $H_{6\ major\ and\ minor\ rota}$), 3.46 (d, *J*= 10.1 Hz, 1H, $NH_{\ major\ rota}$), 3.42 (d, *J*= 10.1 Hz, 1H, $NH_{\ minor\ rota}$), 3.17 – 3.04 (m, 2H, $H_{8\ minor\ rota}$), 2.98 – 2.87 (m, 1H, $H_{8A\ major\ rota}$), 2.85 – 2.72 (m, 1H, $H_{8B\ major\ rota}$), 2.28 – 2.08 (m, 1H, $H_{6a\ major\ and\ minor\ rota}$), 1.21 – 0.79 (m, 2H, $H_{7\ major\ and\ minor\ rota}$).

^{13}C–NMR
(75 MHz, C_6D_6)

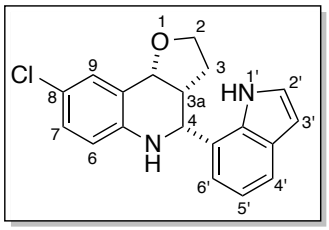
δ (major rota): 155.8, 146.0, 137.1, 133.0, 129.7, 128.8, 128.5, 126.6, 126.0, 123.0, 120.5, 120.3, 119.8, 117.4, 115.0, 103.8, 68.6, 67.5, 49.8, 44.8, 41.6, 23.7.

HRMS
(70 eV, IE)

Calculated for $[C_{27}H_{24}ClN_3O_2]^+$: 457.1552, found: 457.1558.

- Characterisation data of compound **80a**

(3a*R,4*R**,9b*R**)-8-Chloro-4-(1*H*-indol-7-yl)-2,3,3a,4,5,9b-hexahydrofuro[3,2-*c*]quinoline (80a)**



White solid

mp= 215 – 219 °C

R_f= 0.79 (hexane:diethyl ether, 2:1)

Isolated yield: 16%

^{1}H–NMR
(300 MHz, DMSO-d_6)

δ: 11.08 (br s, 1H, $H_{1'}$),7.38 (d, *J* = 7.5 Hz, 1H, $H_{4'}$), 7.24 (t, *J* = 2.9 Hz, 1H, $H_{2'}$), 7.19 (d, *J* = 7.5 Hz, 1H, $H_{6'}$), 7.04 (d, *J* = 2.5 Hz, 1H, H_9), 6.92 (t, *J* = 7.5 Hz, 1H, $H_{5'}$), 6.91 (dd, *J* = 8.7, 2.5 Hz, 1H; H_7), 6.66 (d, *J* = 8.7 Hz, 1H, H_6), 6.35 (dd, *J* = 2.9, 1.7 Hz, 1H, $H_{3'}$), 5.99 (br s, 1H, H_5), 5.09 (d, *J* = 7.9 Hz, 1H, H_{9b}), 4.97 (d, *J* = 3.1 Hz, 1H, H_4), 3.53 (dt, *J* = 8.8, 3.5 Hz, 1H, H_{2A}), 3.47 (td, *J* = 8.4, 6,9 Hz, 1H, H_{2B}), 2.86 (tdd, *J* = 10.9, 7.9, 3.1 Hz, 1H, H_{3a}), 1.98 – 1.78 (m, 1H, H_{3B}), 1.20 – 1.05 (m, 1H, H_{3A}).

^{13}C–NMR
(75 MHz, DMSO-d_6)

δ: 145.1, 133.2, 128.9, 128.0, 127.6, 125.4, 125.2, 124.0, 120.6, 119.11, 119.0, 118.0, 116.9, 101.6, 74.7, 66.1, 52.0, 42.7, 25.8.

HRMS
(70 eV, IE)

Calculated for $[C_{19}H_{17}ClN_2O]^+$: 324,1024, found: 324.1022.