α-Aminonitriles as Key Intermediates in the Synthesis of Natural Products and N-Heterocycles

Dissertation zur Erlangung des Grades

„Doktor der Naturwissenschaften“

am Fachbereich Chemie, Pharmazie und Geowissenschaften der

Johannes Gutenberg-Universität in Mainz

Julio Cesar OREJARENA PACHECO

geboren in Bucaramanga, Kolumbien

Mainz, 2018

Dekan:

1. Berichterstatter:

2. Berichterstatter:

Tag der mündlichen Prüfung:

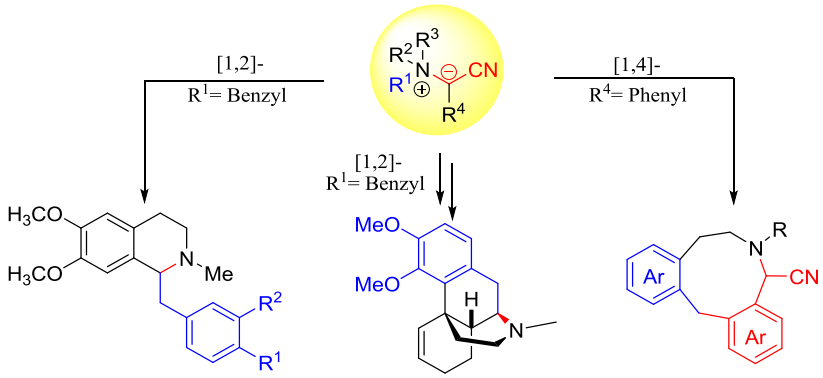
Die vorliegende Arbeit wurde im Zeitraum
von Mai 2012 bis Januar 2018
am Institut für Organische Chemie
der Johannes Gutenberg-Universität Mainz
unter Anleitung von Prof. Dr. Till OPATZ angefertigt.

To my beloved wife

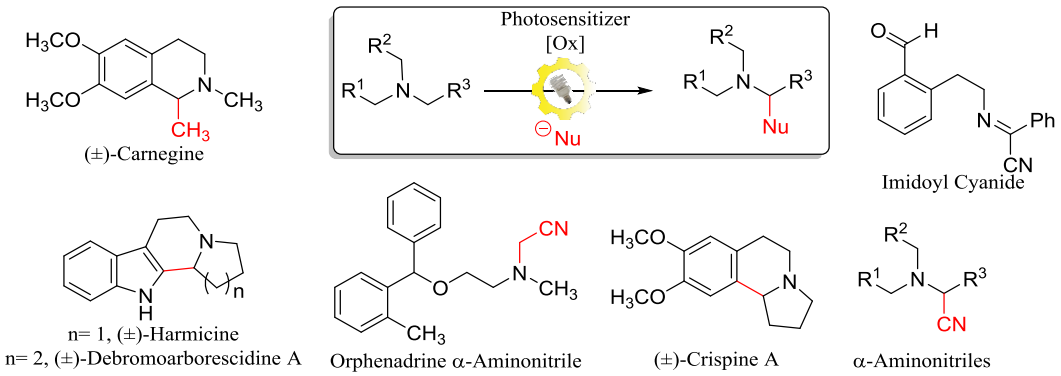
Table of Contents

Graphical Abstract

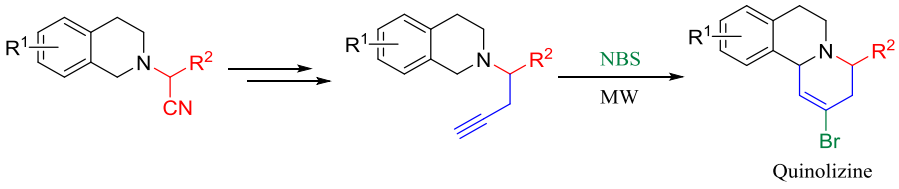
Rearrangements of Nitrile-Stabilized Ammonium Ylides



Visible Light Photocatalytic Oxidations: Synthesis and Applicatications of α-Aminonitriles



Oxidative C-H Activation / Aza PRINS Cyclization of Alkynylamines



Abstract

The aim of this investigation was to exploit the versatility of α-aminonitriles as key intermediates, to develop new methodologies for the synthesis of natural products and N-heterocycles.

The first part (Part I) of this dissertation corresponds to the rearrangement of nitrile-stabilized ammonium ylides. By this manner, benzylisoquinoline alkaloids (±)-laudanosine, (±)-laudanidine, and (±)-armepavine were successfully prepared via STEVENS rearrangement, taking advantage of their identical 1,2,3,4-tetrahydroisoquinoline core and the variable benzyl moiety. Subsequently, an unexpected ring expansion of α-ammonium nitriles resulting in dibenzo[*c,f*]azonines was investigated. This method represents the first direct ring expansion of ammonium ylides via [1,4]-rearrangement, as well as the first efficient protocol for the preparation of dibenzo[*c,f*]azonines from simple starting materials. Finally, an alternative synthetic route for the preparation of 1-veratryloctahydro-isoquinolines implementing the STEVENS rearrangement as a key step was proposed.

The second part (Part II) is focused on the reactions of tertiary amines under visible light photocatalysis. Herein, an economic and highly active catalytic system for the photocyanation of tertiary aliphatic amines, based on the use of inexpensive rose bengal, air, TMSCN, and visible light, was developed. A variety of synthetically useful α-aminonitriles were successfully prepared. Furthermore, a novel and efficient synthesis for the alkaloids (±)-crispine A, (±)-harmicine, and (±)-desbromoarborescidine A via photocyanation was described. Finally, the scope, application and mechanistic aspects of the anaerobic oxidation of tertiary amines by $BrCCl_3$ and visible light were investigated. The results showed that N-methyl-1,2,3,4-tetrahydroisoquinolines generate iminium ions as main products, while aliphatic trialkylamines with α-hydrogen are protonated. The application of this photo-oxidation method was demonstrated by intercepting the photogenerated iminium ions with GRIGNARD reagents, achieving the synthesis of (±)-carnegine, 1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline, and some cryptostylines analogous.

The third part (Part III) describes a metal-free oxidative C–H activation / aza-PRINS-type cyclization of tertiary alkynylamines. The scope of this method was demonstrated by the synthesis of ten new pyrido[2,1-a]isoquinolines obtained from alkynylamines in moderate to high yields. Due to their tricyclic framework as well as the vinyl bromide moiety, the pyrido[2,1-a]isoquinolines represent interesting building blocks for more complex organic molecules, such as natural products.

Erklärung

Hiermit erkläre ich, dass ich die vorliegende Arbeit selbstständig und ohne fremde Hilfe angefertigt habe. Es wurden nur Quellen und Hilfsmittel benutzt, die in der Arbeit angegeben sind. Ich versichere, dass alle wörtlichen und sinngemäßen Übernahmen aus anderen Werken als solche kenntlich gemacht wurden.

(Julio Cesar OREJARENA PACHECO)

Publications

- OREJARENA PACHECO, J. C.; PUSCH, S.; OPATZ, T. Metal Free Oxidative C–H Activation/Alkyne Aza-PRINS Cyclization of Homopropargyl amines. Counter Ion Induce 6-*endo-dig* Cyclization. *In preparation*.

- OREJARENA PACHECO, J. C.; NAUTH, A. M.; PUSCH, S; OPATZ, T. Oxidation of Trialkylamines by $BrCCl_3$: Scope, Applications and Mechanistic Aspects. *European Journal of Organic Chemistry* **2017**, *46*, 6966–6974.

- OREJARENA PACHECO, J. C.; LIPP, A.; NAUTH, A. M.; ACKE, F.; DIETZ, J.-P.; OPATZ, T. A Highly Active System for the Metal-Free Aerobic Photocyanation of Tertiary Amines with Visible Light: Application to the Synthesis of Tetraponerines and Crispine A. *Chemistry – A European Journal* **2016**, *22*, 5409–5415.

- LAHM, G.; OREJARENA PACHECO, J. C.; OPATZ, T. Rearrangements of Nitrile-stabilized Ammonium Ylides. *Synthesis* **2014**, *46*, 2413–2421.

- OREJARENA PACHECO, J. C.; OPATZ, T. Ring Expansion of 1,2,3,4-Tetrahydroisoquinolines to Dibenz[*c,f*]azonines. An Unexpected [1,4]-Sigmatropic Rearrangement of Nitrile-Stabilized Ammonium Ylides. *The Journal of Organic Chemistry* **2014**, *79*, 5182–5192.

- OREJARENA PACHECO, J. C.; LAHM, G.; OPATZ, T. Synthesis of Alkaloids by Stevens Rearrangement of Nitrile-Stabilized Ammonium Ylides: (±)-Laudanosine, (±)-Laudanidine, (±)-Armepavine, (±)-7-Methoxycryptopleurine, and (±)-Xylopinine. *The Journal of Organic Chemistry* **2013**, *78*, 4985–4992.

List of Abbreviations

2,4-DNPH	2,4-Dinitrophenylhydrazine
2,6-ClPyNO	2,6-Dichloropyridine *N*-oxide
Ac	Acetyl
Ar	Aryl
atm	Atmosphere
ATR	Attenuated total reflection
Bn	Benzyl
bpy	2,2′-Bipyridine
br	Broad
ca.	Circa
CFL	Compact fluorescent lamp
CNS	Central nervous system
COSY	Correlation spectroscopy
CSA	Camphorsulfonic acid
DABCO	1,4-Diazabicyclo[2.2.2]octane
DAP	*N,N'*-dimethyl-2,7-diazapyrenium
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DFT	Density functional theory
DIPEA	*N*,*N*-Diisopropylethylamine
DMA	*N*,*N*-Dimethylacetamide
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
DPEN	1,2-Diphenylethylenediamine

dtbpy	4,4'-Di-*tert*-butyl-2,2'-biyridine
EDG	Electron-donating group
ESI	Electrospray ionization
Et	Ethyl
ET	Energy transfer
et al.	*et alii*
EWG	Electron-withdrawing group
GC	Gas chromatography
HMBC	Heteronuclear multibond coherence
HMPA	Hexamethylphosphoramide
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single quantum coherence
Hz	Hertz
IC	Internal Conversion
IR	Infrared
ISC	Intersystem Crossing
KHMDS	Potassium hexamethyldisilazide
LC	Liquid chromatography
LDA	Lithium diisopropylamide
LED	Light-emitting diode
LED	Light-emitting diode
*m*CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
MS	Mass spectrometry
Ms	Mesyl
MW	Microwave

NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorsuccinimide
NMO	*N*-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser effect spectroscopy
PC	Photocatalyst
Ph	Phenyl
ppm	Parts per million
ppy	2-Phenylpyridine
Py	Pyridine
R_f	Retardation factor
rt	Room temperature
SET	Single electron transfer
TBAB	Tetrabutylammonium bromide
TBAI	Tetrabutylammonium iodide
TBSCl	*tert*-Butyldimethylsilyl chloride
TEA	Triethylamine
Tf	Triflyl; trifluoromethanesulfonyl
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl ether
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TOF	Time-of-flight
TOF	Turnover frequency
TON	Turnover number
TPAP	Tetrapropylammonium perruthenate

TPP	5,10,15,20-tetraphenyl-21*H*,23*H*-porphine
Ts	Tosyl
UV	Ultraviolet
Vis	Visible
W	Watt

General Introduction:
An Overview to α-Aminonitriles

α-Aminonitriles represent an important class of bifunctional compounds which contain an amino and a nitrile group attached to the same carbon atom (Figure 1). The discovery of α-aminonitriles took place in 1850 by the German chemist Adolph STRECKER.[1] However, it was not until 1854 that STRECKER[2] isolated and characterized the first α-aminonitriles which he named "hydrocyanoaldine".[3] Some years later, Emil ERLENMEYER proposed the structure of this "hydrocyanoaldine" and defined it as an α-aminonitrile (**1**).[4,5] Figure 1 shows the general structure of this type of compounds, as well as the simplest α-aminonitrile, aminoacetonitrile (**2**).

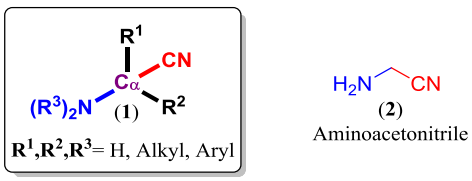


Figure 1. General structure of α-aminonitriles **1** and aminoacetonitrile (**2**).

Nowadays, α-aminonitriles have been extensively studied and represent important and adaptable building blocks in the syntheses of large and complex organic molecules.

α-Aminonitriles: From Nature to Drug Discovery

Naturally occurring α-aminonitriles are a very small but interesting group of secondary metabolites of plants, fungi, and bacteria.[6,7] For instance, tabernaelegantinines C (**3**) and D (**4**) are minor bisindole alkaloids isolated from the roots of *Tabernaemontana elegans* in which a

nitrile group is attached to the position C-3' of the isovoacangine moiety (Figure 2).[8] Two other examples of nitrile-substituted indoles are lahandinines A (**5**) and B (**6**). These *Kopsia pauciflora* alkaloids place the nitrile group at the position C-21 of their skeleton (Figure 2).[9]

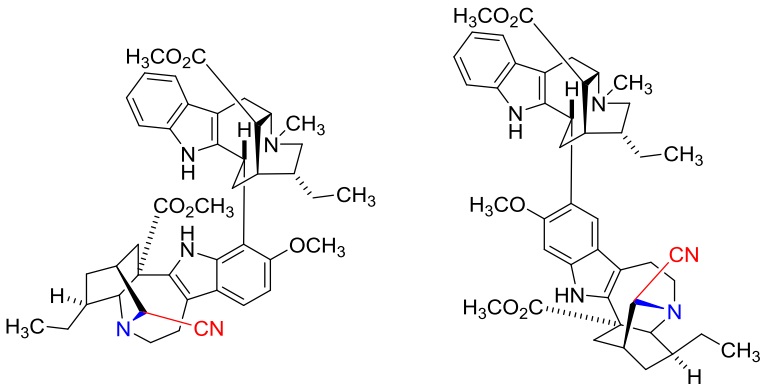


Figure 2. *Tabernaemontana elegans* and *Kopsia pauciflora* bisindole alkaloids.

The α-aminonitrile moiety can also be found in secondary metabolites of *Streptomyces*. The first α-aminonitrile isolated from *Streptomyces* (*lavendulae*) was saframycin A (**7a**).[10,11] This natural product belongs to the tetrahydroisoquinoline family of antibiotics and possesses a potent antiproliferative activity against a variety of tumor cell lines at low doses (Figure 3).[12] Remarkably, its structure resembles to the approved anticancer drug Yondelis® (**7b**).[13] Another metabolite is cyanocycline A (**8**) which exhibits antimicrobial (5 ng mL^{-1} against *Staphylococcus aureus*) and antitumor activities (Figure 3).[14] Similar to cyanocycline A is Dnacin A_1 (**9**), which also exhibits antibacterial and antitumor properties.[15]

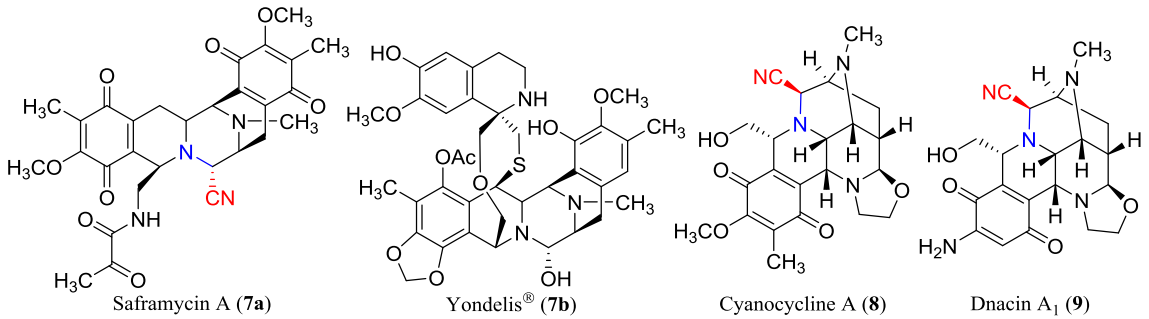


Figure 3. α-Aminonitrile isolated from *Streptomyces*.

In addition to the natural products, synthetic α-aminonitriles have also shown important and promising biological activities.[16] For example, some of the most potent reversible dipeptidyl peptidase-4 inhibitors such as vildagliptin (**10**),[17] saxagliptin (**11**),[18,19] NVP-DPP-728 (**12**),[20] and denagliptin (**13**)[21] possess an α-cyanopyrrolidine moiety in their structures (Figure 4). Other representative aminonitrile-base drugs are amphetaminil (**14**)[22,23] and odanacatib (**15**).[24] The first one is a no longer used stimulant drug for the treatment of obesity and narcolepsy, while odanacatib (**15**) is a highly effective drug in the treatment of osteoporosis and bone metastasis.

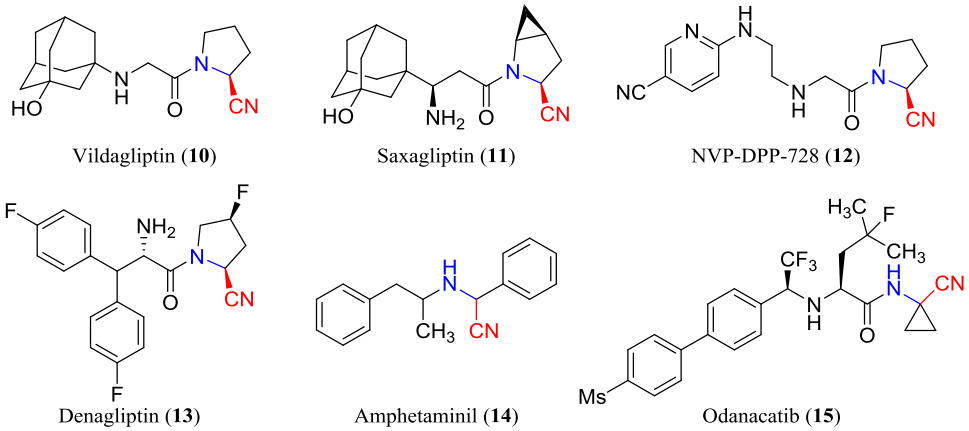
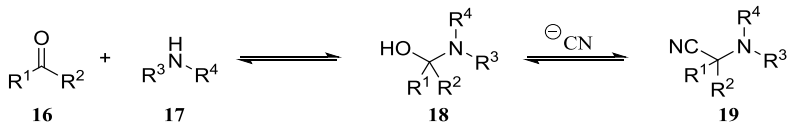


Figure 4. Biologically active α-aminonitriles.

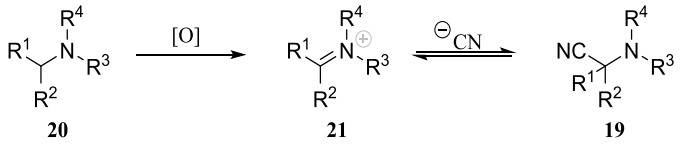
Synthetic Methods

The most known and significant method to prepare α-aminonitriles was defined by the pioneering work of Adolph STRECKER in 1850.[1,2] The reaction was described as a three-component reaction of aldehydes, aqueous ammonia, and hydrogen cyanide followed by *in situ* hydrolysis of the pre-formed α-aminonitriles to α-amino acids. Over the years, a large number of modifications such as the use of different amines and ketones as well as various cyanide sources, solvents, and catalysts have improved the outcome of the well-known STRECKER reaction (Scheme 1).[3-5,25,26] However, α-aminonitriles that contain strong electron-withdrawing groups at the α-position, and compounds with sterically hindered restrictions are not very accessible by this method.



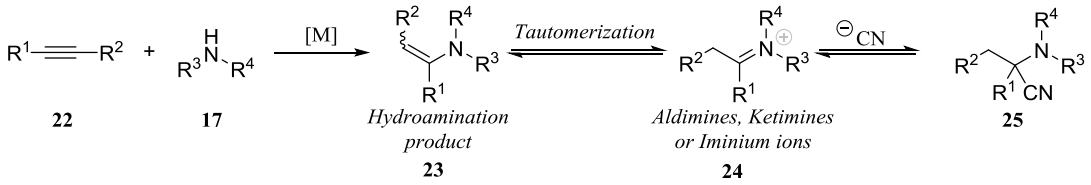
Scheme 1. STRECKER reaction.

Alternatively, α-aminonitriles can be readily obtained by oxidation of secondary and tertiary amines to their corresponding imine or iminium salts (**21**) followed by *in situ* interception with cyanide (Scheme 2).[27] For this purpose, several oxidants in combination with different metal-based and metal-free catalytic systems, as well as stoichiometric approaches have been described.[28-41]



Scheme 2. Oxidative synthesis of α-aminonitriles.

More recently, the catalytic hydroamination of alkynes has become an attractive new method for the synthesis of α-aminonitriles.[42] In this case, alkynes and amines are combined in the presence of a metal catalyst in order to form the corresponding hydroamination products. These products tautomerize to aldimines, ketimines or iminium ions which are directly trapped by cyanide (Scheme 3).[43,44]



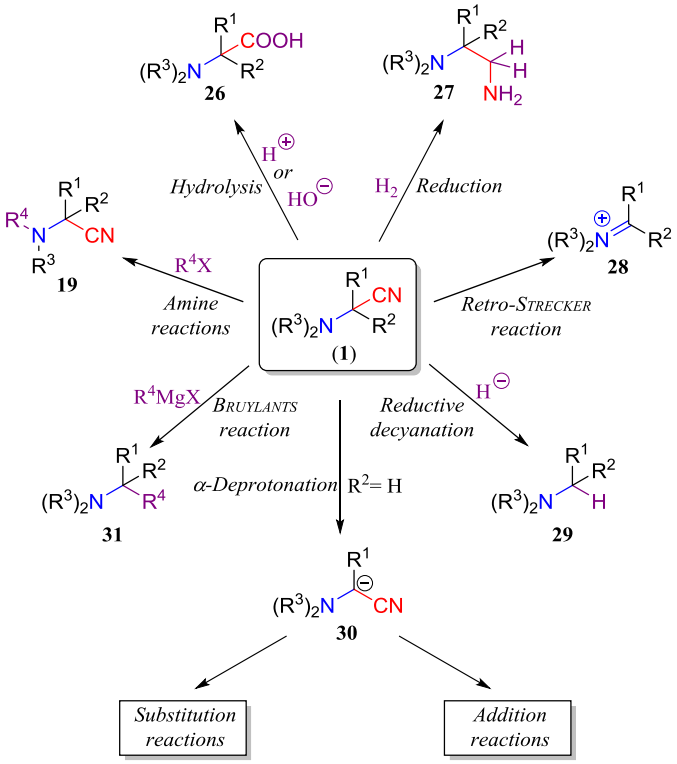
Scheme 3. Synthesis of α-aminonitriles by hydroamination.

Reactions of α-Aminonitriles

The reactivity of α-aminonitriles has been the focus of many comprehensive studies and reviews.[25,45-47] Therefore, only a general description of the chemistry of α-aminonitriles would be addressed in this section.

Due to the different reactive centers, α-aminonitriles can exhibit a broad spectrum of reaction modes. A collection of the most representative reactions of α-aminonitriles is summarized in Scheme 4. Since an amino and a nitrile group are present in their structure, α-aminonitriles can easily undergo classical amine and nitrile chemistry.[25] Historically, the hydrolysis of the nitrile function to the corresponding α-amino acid (**26**) represents one of the most important uses of α-aminonitriles.[1,48] 1,2-Diamines (**27**) are obtained by full reduction of the nitrile moiety with aluminium hydride agents or under hydrogenation conditions.[49,50] Another valuable characteristic of α-aminonitriles is the possibility to be converted into their parented imines or

iminium ions (**28**) in what is called a retro-STRECKER reaction.[46] By this manner, a hydride or a carbanion (BRUYLANTS reaction) can displace the nitrile group to furnish amines **29** and **31**, respectively.[51,52]



Scheme 4. α-Aminonitriles reactions tree.

Complementary to the masked iminium ions, the inversion in polarity of the α-carbon (*Umpolung*) represents a very important and versatile use of α-aminonitriles. For this purpose, α-aminonitriles need to bear a hydrogen in the alpha position that can be abstracted by a strong base. This carbanion (**30**) can perform further chemistry such as substitution or addition reactions.

Research Outline

The information presented above clearly shows the importance of α-aminonitriles as building blocks for more complex organic molecules. Althought α-aminonitriles have been known since 1854, their properties and dual functionality are still the focus of many research efforts. By this manner and motivated by their versatility, the aim of this investigation was to develop new methodologies using α-aminonitriles as key intermediates in the synthesis of natural products, as well as to design new methods for their preparation.

Along these lines, this doctoral dissertation has been divided in six chapters, which are distributed in three parts grouped by main topic as follows:

Part I: Rearrangements of Nitrile-Stabilized Ammonium Ylides

Chapter 1 describes the synthesis of benzylisoquinoline alkaloids (±)-laudanosine, (±)-laudanidine, and (±)-armepavine via STEVENS rearrangement.

Chapter 2 presents the synthesis of dibenzo[c,f]azonines as a result of an unexpected ring expansion of α-ammonium nitriles via [1,4]-sigmatropic rearrangement.

Chapter 3 proposes a new synthetic route for the preparation of 1-veratryloctahydroisoquinolines, implementing the STEVENS rearrangement as a key step.

Part II: Visible Light Photocatalysis: Oxidative Generation of Iminium Ions from Tertiary Amines

Chapter 4 reports the visible light photocyanation of tertiary amines and the application to the synthesis of (±)-crispine A, (±)-harmicine and (±)-desbromoarborescidine A.

Chapter 5 presents the scope, application and mechanistic aspects of the anaerobic oxidation of tertiary amines by $BrCCl_3$ and visible light.

Part III: Alkyne Aza-PRINS Cyclization

Chapter 6 describes a metal-free oxidative C–H activation / aza-PRINS-type cyclization of tertiary alkynylamines.

Part I

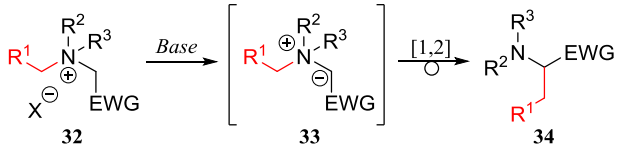
Rearrangements of Nitrile-Stabilized Ammonium Ylides

In organic chemistry, rearrangement reactions are common and highly efficient processes in which bonds are cleaved and reorganized on expenses of an energy minimum.[53] If heteroatoms are involved, the bond cleavage requires less energy and when exceeding their valency (*onium* compounds), the generation of the corresponding *onium* ylides can lead to rearrangements in a very feasible and practical fashion.[54] In the case of pnictogen ylides (e.g. phosphonium and arsonium), rearrangements are determined by how well charges are stabilized. Therefore, the energetically higher lying σ*-orbitals of the C–N bonds in ammonium ylides provide less stabilization for the negative charge on the onium center compared to phosphonium or arsonium ylides.[55] Thus, ammonium ylides are prone to undergo rearrangements to achieve a thermodynamic stabilization of the less-favorable ylide state while higher pnictogen analogous are known for intermolecular reactions such as olefinations (e.g., WITTIG reaction) or epoxide formations.[56,57]

Ammonium ylides can be generated under very mild conditions if a conjugative stabilization of the negative charge is provided (carbonyl or nitrile substituents).[58] This not only makes the ylides more accessible but also enhances the chemo- and regioselectivity of the rearrangements, favoring the ylide formation over HOFFMANN elimination. Thus, with a high anion-stabilizing capacity and the possibility to be removed tracelessly from the products, the nitrile moiety is an exceptional and particularly useful charge stabilizing group for rearrangement reactions.[59]

STEVENS Rearrangement

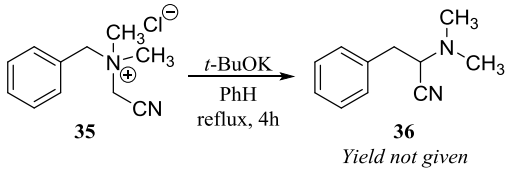
This type of rearrangement is referred to a [1,2]-shift of a migrating group from the heteroatom (in this case a nitrogen atom) of an ylide to its α-carbanion center.[60,61] In the case of ammonium salts **32**, the reaction usually involves the formation of ammonium ylides **33** via deprotonation of the salts, which further rearrange to the corresponding tertiary amines **34** (Scheme 5). Alternatively, ammonium ylides could be obtained by desilylation of ammonium salts or by the interaction of carbenes with tertiary amines.[62,63]



Scheme 5. General [1,2]-STEVENS rearrangement.

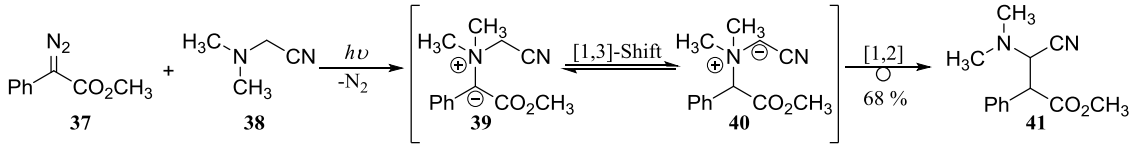
The STEVENS rearrangement is unlikely to proceed via a concerted mechanism, as this would be a symmetry-forbidden process according to the WOODWARD-HOFFMANN rules.[64] Therefore, an intramolecular homolytic cleavage-radical pair recombination process is more feasible to be involved.[65,66] This mechanistic pathway is supported by the observations on the retention of configuration of the migrating group as well as the lack of crossover products.

Regarding the STEVENS rearrangement of nitrile-stabilized ammonium ylides, only a few examples have been described.[54] The first report was made by STEVENS in 1969 and showed the rearrangement of salt **35** into amine **36** (Scheme 6).[67]



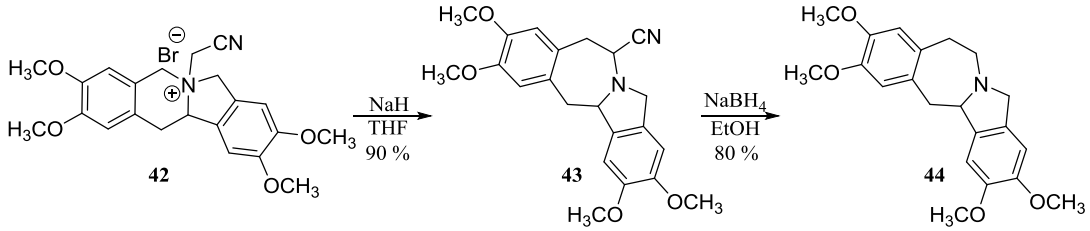
Scheme 6. First [1,2]-STEVENS rearrangement of a nitrile ammonium salt.

TOMIOKA and co-workers reported a photolysis of diazo ester **37** and reaction with *N*,*N*-dimethylaminoacetonitrile (**38**) via carbene interaction to produce ylide **39**.[68] Due to the presence of two electron-withdrawing groups, a [1,3]-proton shift takes place and generates ylide **40** which undergoes a [1,2]-Stevens rearrangement to form compound **41** in 68 % yield (Scheme 7).



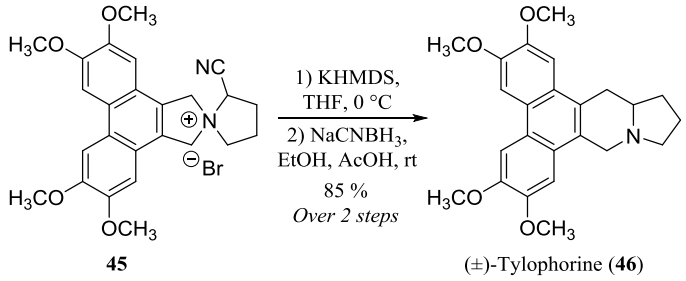
Scheme 7. Generation of a nitrile-stabilized ammonium ylide from a carbene.

Ring enlargements are valuable tools for the synthesis of pharmaceuticals and natural products. As demonstrated in 2001 by LIU and LANG,[69] nitrile-stabilized ammonium ylides are excellent synthons in the synthesis of fused benzazepines. For this purpose, N-cyanomethylammonium salt **42** was deprotonated with sodium hydride and rearranged into α-aminonitrile **43**. Further reductive decyanation of **43** gave benzazepine-isoindole **44** in 72 % yield over two steps (Scheme 8).



Scheme 8. Synthesis of benzazepine **44**.

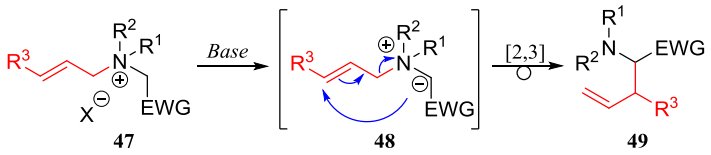
In 2012, OPATZ et al. employed the [1,2]-STEVENS rearrangement as the key step in the synthesis of the phenanthroindolizidine alkaloid (±)-tylophorine (**46**).[70] Deprotonation of spirocyclic ammonium salt **45** with KHMDS followed by reductive decyanation with $NaCNBH_3$ afforded aza-polycyclic (±)-tylophorine (**46**) in high yields (Scheme 9).



Scheme 9. Synthesis of (±)-tylophorine (**46**).

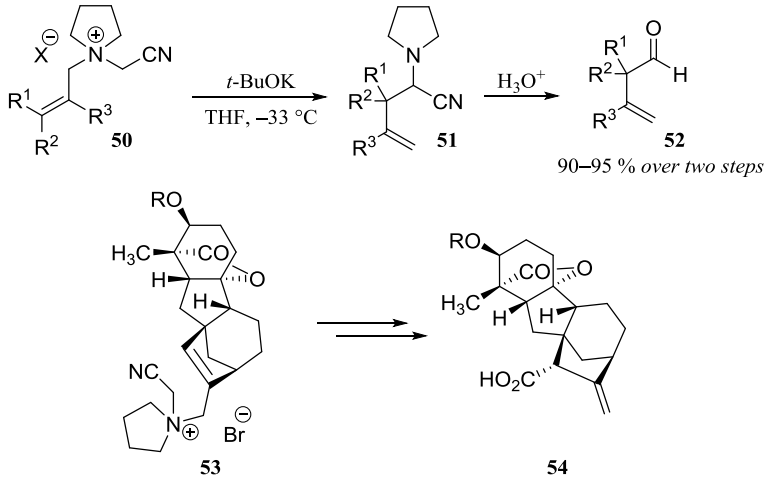
Apart from the well-known [1,2]-migration in the classical STEVENS rearrangement, STEVENS and co-workers noticed a competing reaction during mechanistic studies on N-allyl-substituted ammonium ylides.[71] This reaction was cataloged as a [2,3]-shift that often predominated over the [1,2]-shift. This migration is denominated as the [2,3]-STEVENS rearrangement and represents a symmetry-allowed process that proceeds via a concerted mechanism with a lower activation

energy than the [1,2]-shift (Scheme 10).[72,73] Rearrangements of this type are useful tools for C–C bond formation and this one, in particular, is the most widely used rearrangement of nitrile-stabilized ammonium ylides.



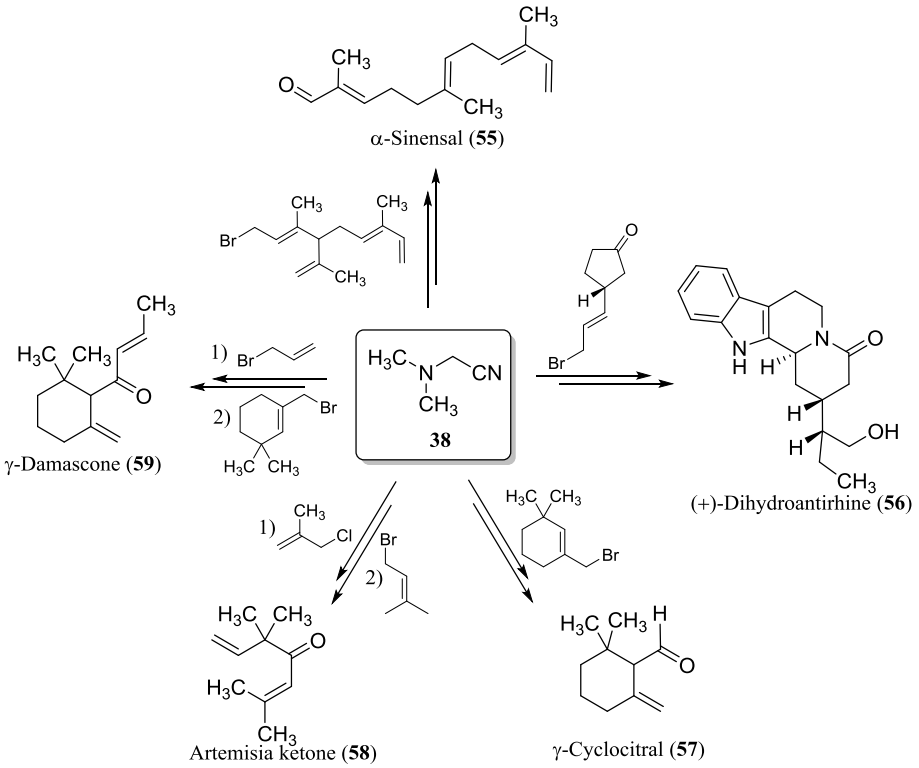
Scheme 10. General [2,3]-STEVENS rearrangement.

In 1973, MANDER and TURNER reported an important preparation of β,γ-unsaturated aldehydes via [2,3]-Stevens rearrangements of N-allyl ammonium salts **50**.[74] The ylide formation was achieved by deprotonation of the corresponding ammonium salt **50** with potassium *tert*-butoxide at –33 °C in THF. Retro-STRECKER/hydrolysis reaction of the rearranged nitriles **51** induced by oxalic acid afforded the expected unsaturated aldehydes **52**. The same authors extended this method to the synthesis of gibberellin derivatives **54** (Scheme 11).[75-77]



Scheme 11. Syntheses of β,γ-unsaturated aldehydes 52 and gibberellins **54**.

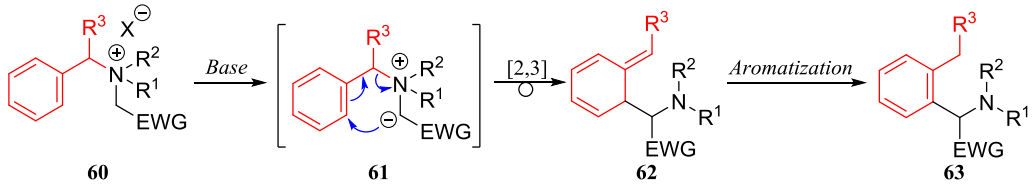
In a similar manner, some other research groups have reported the synthesis of natural products such as α-sinensal (**55**),[78] (+)-dihydroantirhine (**56**),[79] γ-cyclocitral (**57**),[80] artemisia ketone (**58**),[81] and γ-damascone (**59**).[82] In all cases, *N*,*N*-dimethylaminoacetonitrile (**38**) was used as a common alkylating substrate (Scheme 12).



Scheme 12. [2,3]-Stevens Rearrangement as a key step in the synthesis of natural products.

[2,3]-SOMMELET-HAUSER Rearrangement

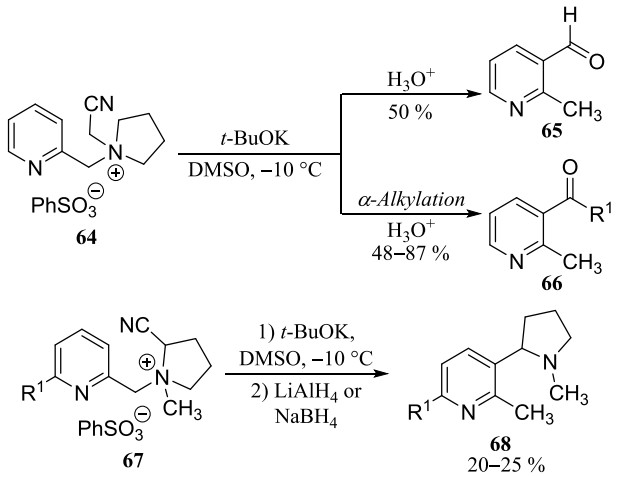
The first example of a [2,3]-sigmatropic rearrangement involving a benzylic substituent was described by SOMMELET in 1937,[83] and subsequently extended by HAUSER in 1951.[84] In this reaction, an aminoalkyl group is formally transferred to the ortho-position of the arene moiety leaving behind an alkyl substituent. The SOMMELET-HAUSER rearrangement is presumed to proceed via a suprafacial-suprafacial concerted mechanism that involves the formation of a cyclohexadiene intermediate (Scheme 13).[65,85]



Scheme 13. General SOMMELET-HAUSER rearrangement.

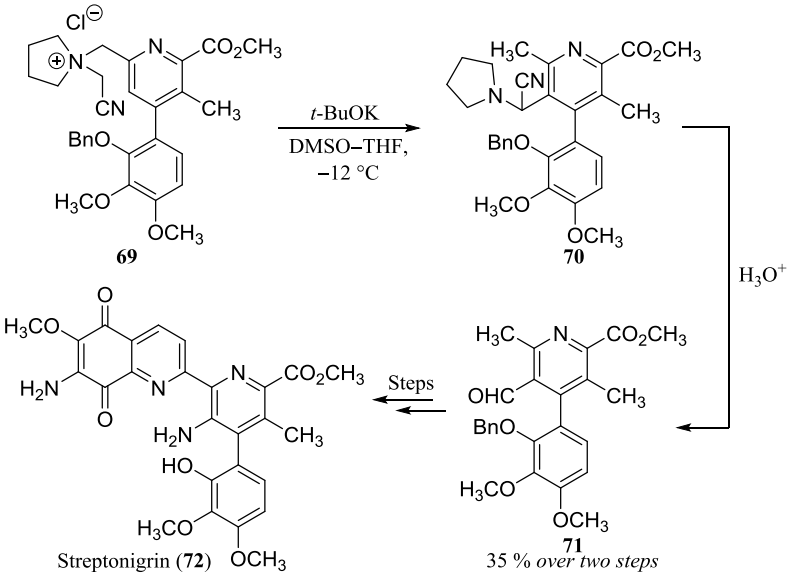
Nitrile-stabilized ammonium ylides also resulted in very useful intermediates for this sigmatropic rearrangement. As an example, SANDERS et al. described the [2,3]-migration of an α-cyanomethylpyrrolidinium salt **64** and its transformation into 3-formyl- **65** and 3-

acylpyridine **66**.[86] Along the same lines, SANDERS was also able to prepare alkyl derivatives of nicotine **68** by the rearrangement of ammonium salts **67** (Scheme 14).[87] In this case, they also observed the formation of the [1,2]-STEVENS rearrangement product when $R^1 = CH_3$ (ca. 20%).



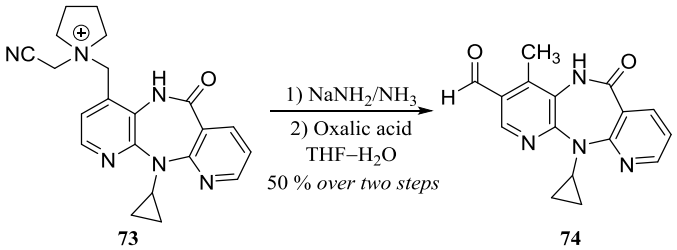
Scheme 14. Synthesis of pyridines **65**, **66**, and nicotine derivatives **68**.

In 1982, WEINREB and co-workers developed a total synthesis of the potent antitumor antibiotic streptonigrin **72**, involving the [2,3]-SOMMELET-HAUSER rearrangement as one of the steps.[88] For this purpose, pyrrolidinium salt **69** was deprotonated with potassium *tert*-butoxide and the resulting SOMMELET-HAUSER product **70** was hydrolyzed to the corresponding aldehyde **71** (Scheme 15). This aldehyde is a middle stage key precursor in the preparation route of streptonigrin **72**.



Scheme 15. Synthesis of streptonigrin **72**.

In a similar approach, KLUNDER et al. reported the preparation of a nevirapine derivative **74** via [2,3]-rearrangement of ammonium salt **73** (Scheme 16).[89] This author also detected the [1,2]-STEVENS rearrangement in 33 % yield under these reaction conditions.



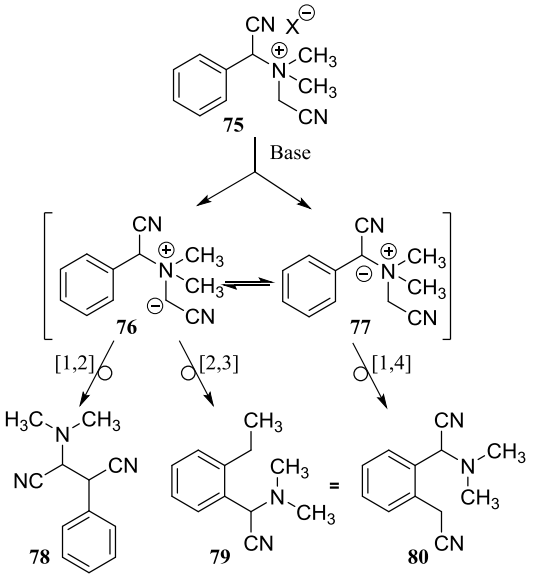
73 **74**

Scheme 16. Preparation of nevirapine derivative **74**.

Competitive [1,2]-STEVENS, [2,3]-SOMMELET-HAUSER, and [1,4]-Rearrangements

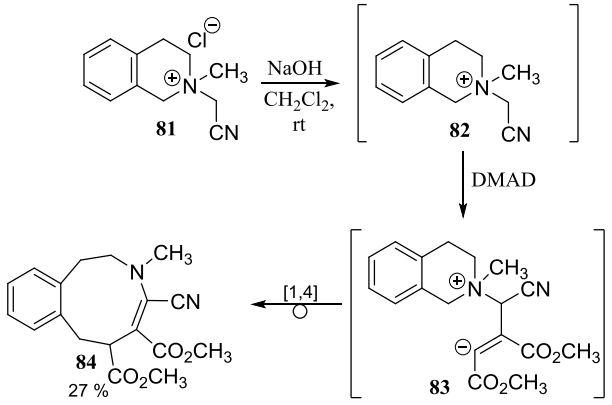
As presented before, the STEVENS and SOMMELET-HAUSER rearrangements are very well known competitive reactions. This competition could be explained based on the difference in the reaction energies as the formation of the SOMMELET-HAUSER non-aromatic intermediate is less endoergic. Thus, low temperatures favor the SOMMELET-HAUSER products while high temperatures favor the dissociative Stevens rearrangement pathway.[65]

Among these competitive reactions of ammonium ylides, there is a less frequent migration described as a [1,4]-sigmatropic rearrangement. This rarely observed rearrangement was discovered by JOŃCZYK and co-workers in the early 1990s. It was described that ylides derived from ammonium salts **75** are susceptible to undergo [1,4]-sigmatropic rearrangements in addition to the conventional [1,2]- and [2,3]-shifts.[90-93] In this case, the unusual [1,4]-migration took place when the deprotonation of ammonium salt **75** delivered two different ylides (**76** and **77**). The rearrangement of ylide **76** resulted in the formation of the STEVENS and SOMMELET-HAUSER products (**78** and **79**, respectively), while the most stable ylide **77** underwent a [1,4]-shift to compound **80** (Scheme 17). In principle, compounds **79** and **80** are identical. However, JOŃCZYK was able to prove that both pathways were operating by ^{13}C labeling experiments.[92,94] The author also described a strong dependence of the products ratio and the reaction conditions. In general, the mechanism of the reaction has been proposed to proceed in a concerted manner via 6π-electron transition state with suprafacial-suprafacial characteristics.



Scheme 17. Competitive [1,2]-STEVENS, [2,3]-SOMMELET-HAUSER, and [1,4]-rearrangement.

More recently, SOLDATOVA et al. reported an indirect [1,4]-sigmatropic rearrangement for the ring expansion of the ammonium salt **81**.[95,96] Trapping the intermediate ylide **82** with DMAD generated a new zwitterionic species **83**, which was prone to a [1,4]-rearrangement producing benzazonine **84**.



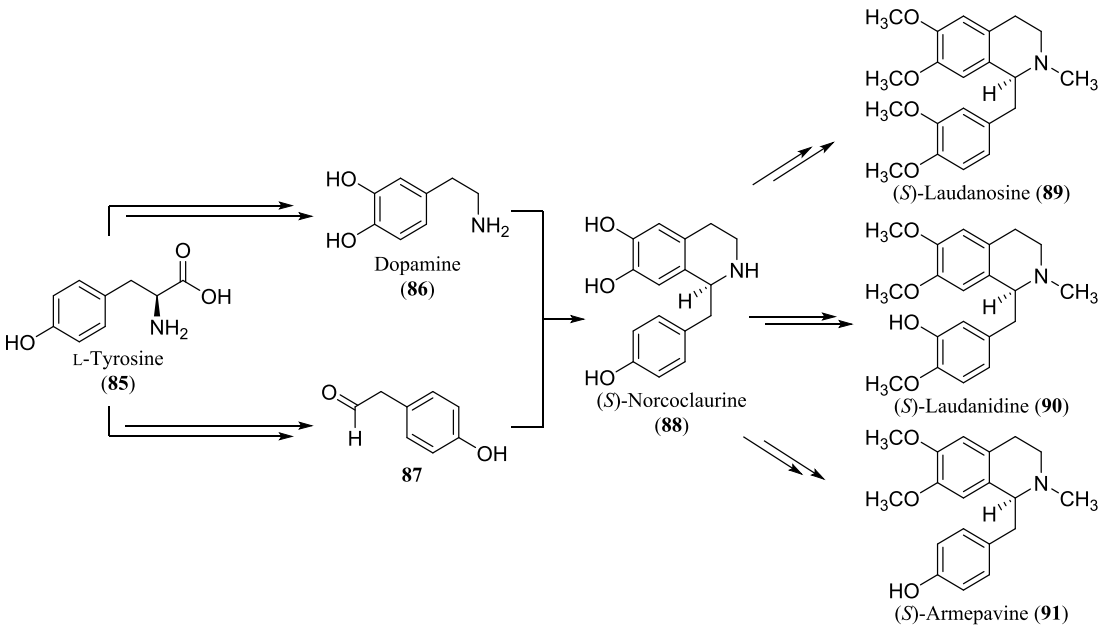
Scheme 18. Synthesis of benz[*b*]azonine **85**.

Chapter 1

Synthesis of Benzylisoquinoline Alkaloids (±)-Laudanosine, (±)-Laudanidine, and (±)-Armepavine via STEVENS Rearrangement

1.1 Introduction

Benzylisoquinoline alkaloids constitute an important and diverse group of specialized metabolites with a wide variety of pharmacological properties.[97] These alkaloids are biologically synthesized from L-tyrosine (**85**) derivatives, dopamine (**86**), and 4-hydroxyphenylacetaldehyde (**87**) via formation of (*S*)-norcoclaurine (**88**). The resulting benzylisoquinoline core of (*S*)-norcoclaurine **88** represents the scaffold from which other benzylisoquinoline alkaloids could be obtained (Scheme 19).[98]



Scheme 19. Biogenesis of benzylisoquinoline alkaloids.

For instance, opiates such as laudanosine (**89**) and laudanidine (**90**),[99] as well as the Indian lotus alkaloid armepavine[100] (**91**), are representative members possessing epileptogenic,[101] antimalarial,[102] and immunosuppressive[103] activities, respectively. More important, these

alkaloids are *in vivo* precursors of other natural occurring isoquinolines such as aporphine, protoberberine, and morphine alkaloids.[104]

1.1.1 Synthetic Approaches

In general, the synthesis of benzylisoquinoline alkaloids is commonly achieved by the classical BISCHLER-NAPIERALSKI, PICTET-SPENGLER, and POMERANZ-FRITSCH-BOBBITT reactions (Figure 5). Additional methods such as nucleophilic additions to imines (3,4-dihydroisoquinolines) and C_α-deprotonation/alkylation of tetrahydroisoquinolines have also been described.[105,106]

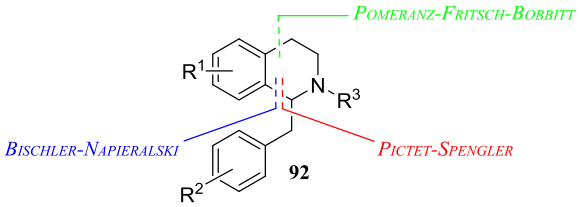
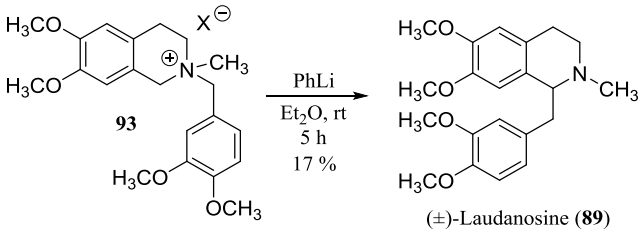


Figure 5. Classical approaches to the benzylisoquinoline alkaloids.

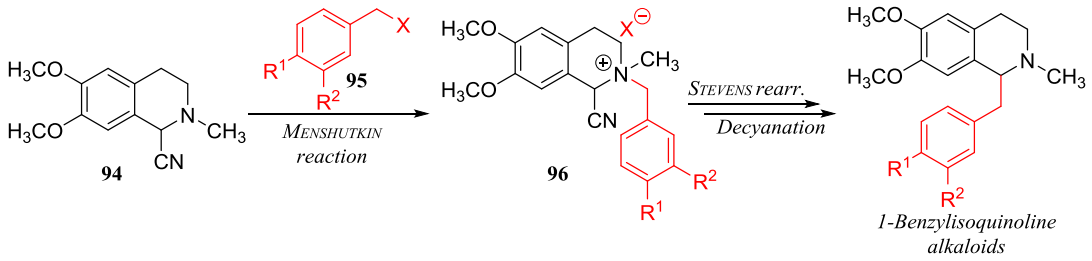
The use of rearrangements of ammonium ylides in the synthesis of benzylisoquinoline alkaloids is barely known. The first and only method involving the STEVENS rearrangement of non-stabilized ammonium ylides was reported by GRETHE et al. in 1969, producing racemic laudanosine (**89**) in 17 % yield (Scheme 20).[107] Nevertheless, harsh reaction conditions and several competition reactions were observed, resulting in low yields and poor reaction outcomes.



Scheme 20. Synthesis of (±)-laudanosine (**89**) by STEVENS rearrangement.

1.2 Aim of the Research

The STEVENS rearrangement of nitrile-stabilized ammonium ylides represent an alternative and very convenient method for the synthesis of alkaloids as demonstrated by OPATZ and co-workers on the preparation of (±)-tylophorine (**46**, see Scheme 9).[70] In order to continue with the studies on the rearrangement of nitrile-stabilized ammonium ylides and their applications, an investigation on the synthesis of benzylisoquinoline alkaloids (±)-laudanosine (**89**), (±)-laudanidine (**90**), and (±)-armepavine (**91**) was carried out (Scheme 21).



Scheme 21. Proposed synthesis of 1-benzylisoquinoline alkaloids via STEVENS rearrangement.

This reaction sequence takes advantage of the identical 1,2,3,4-tetrahydroisoquinoline core and the variable benzyl moiety of these alkaloids. Thus, α-aminonitrile **94** represents the universal synthon of the route which can be further alkylated with benzyl halides **95** in a MENSHUTKIN reaction. Deprotonation of ammonium salt **96** followed by [1,2]-STEVENS rearrangement and removal of the residual nitrile group should produce the title alkaloids.

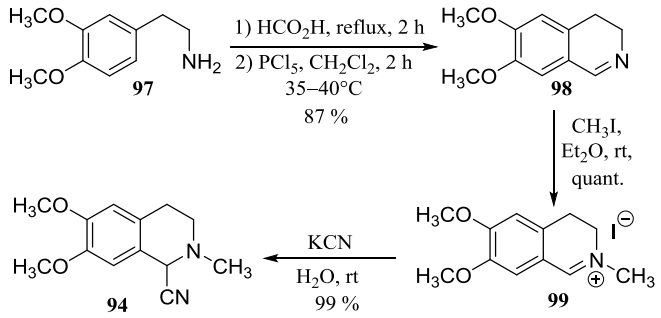
In contrast to the GRETHE approach,[107] the presence of the nitrile group in the α-position of the ammonium salt **96** allows the use of milder reaction conditions and improve the chemoselectivity of the deprotonation. By this manner, better yields and less competitive reactions are expected.

1.3 Results and Discussion

1.3.1 Preparation of the Starting Materials

1.3.1.1 Synthesis of α-Aminonitrile 94

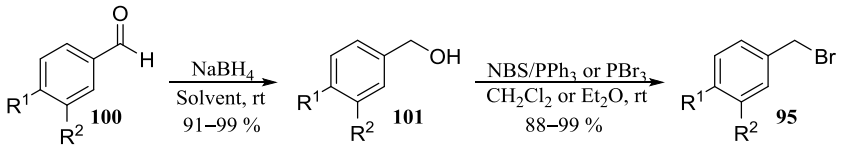
The first stage of the synthetic plan corresponds to the preparation of the universal precursor α-aminonitrile **94**. For this purpose, commercially available homoveratrylamine (**97**) was treated with formic acid and the corresponding formamide was transformed into imine **98** via BISCHLER-NAPIERALSKI cyclization. N-methylation of imine **98** using methyl iodide afforded iminium salt **99** in quantitative yield. After treatment of this compound with aqueous KCN the expected α-aminonitrile **94** was obtained in high yield (Scheme 22).



Scheme 22. Synthesis of the universal α-aminonitrile precursor **94**.

1.3.1.2 Synthesis of Benzyl Bromides 95

Benzyl bromides **95** represent an important precursor in the synthetic route since they are the carriers of the benzylic subunit present in the 1-benzylisoquinoline alkaloids. The preparation of these compounds started by reduction of the corresponding aldehydes **100** to alcohols **101** using $NaBH_4$ as reductive agent. The resulting benzylic alcohols **100** were then transformed into the expected benzyl bromides **95** in high yields via NBS/PPh_3 or PBr_3 halogenation procedures (Scheme 23).



Scheme 23. Synthesis of benzyl bromides **95**.

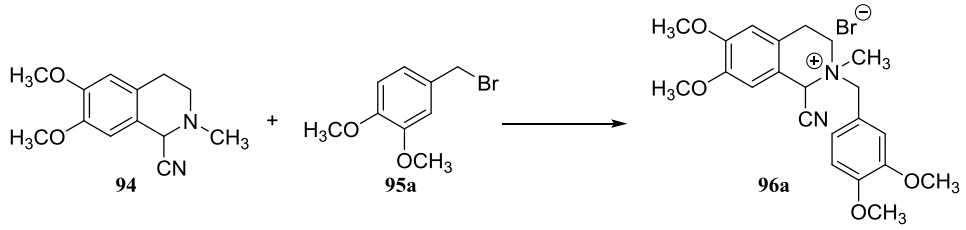
Once the starting materials were accessible, the critical steps of the synthetic route were investigated.

1.3.2 Synthesis of (±)-Laudanosine (89)

Among the desired 1-benzylisoquinoline alkaloids, (±)-laudanosine (**89**) clearly represents the simplest and most readily available benzylisoquinoline that could be obtained via STEVENS rearrangement of nitrile-stabilized ammonium ylides. Thus, laudanosine (**89**) was selected as the first alkaloid to be synthesized and also to serve as the model substrate in the construction of the other alkaloids.

The first critical step was the preparation of ammonium salt **96** via quaternization α-aminonitrile **94** with benzyl bromide **95a** (MENSHUTKIN reaction). In order to obtain the best and most efficient reaction conditions; different solvents, temperatures, amounts of alkylating agent, and reaction times were tested (Table 1).

Table 1. Optimization of the MENSHUTKIN reaction.



Entry	Eq. of Bromide 95a	Solvent	Temperature	Reaction Time	Yield (%)[a]
1	1.2	Acetone (90 mM)	rt	24 h	57
2	1.2	Acetone (90 mM)	rt	60 h	84
3	1.2	MeCN (90 mM)	rt	24 h	—[b]
4	1.2	MeCN (90 mM)	Reflux	24 h	5
5	1.2	THF (90 mM)	rt	60 h	90
6	1.2	THF (90 mM)	Reflux	24 h	65
7	1.2	THF (143 mM)	40°C	24 h	82
8	2.0	THF (143 mM)	40°C	24 h	95

[a] Isolated yield. [b] Product was not detected, only starting materials were observed

Ammonium salt **96a** was obtained in moderate to high yield, excluding the results with acetonitrile as solvent (entry 3 and 4). Among the tested conditions, THF turned out to be the best solvent for the quaternization reaction (90 % yield, entry 5) in which ammonium salt **96a** precipitated as a pale yellow solid. Further experiments revealed that increasing the temperature,

the amount of benzyl bromide **95a**, and the concentration of the mixture (entry 6, 7, and 8) led to a significant improvement in the reaction outcome. By this manner, the key precursor **96a** could be obtained in 95 % yield (entry 8) as a diastereomeric mixture in a 12 : 88 *cis*/*trans*-ratio (determined by ^{1}H NMR). It should be noted that this diastereomeric ratio was not constant during the NMR measurements process. For instance, an NMR sample freshly prepared in DMSO and directly measured afforded the above mentioned *cis*/*trans*-ratio. However, if the same sample was measured 12 h later, the ratio changed to 41 : 59 and the decomposition of the salt became notorious (Figure 6).

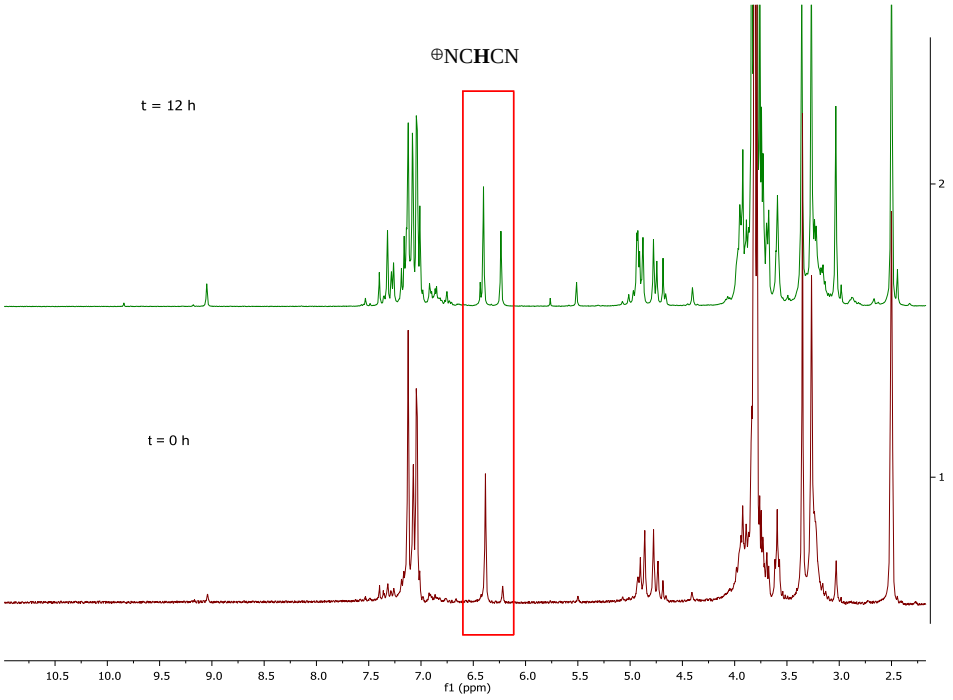
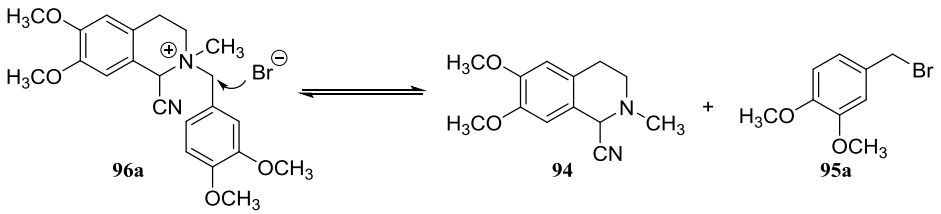


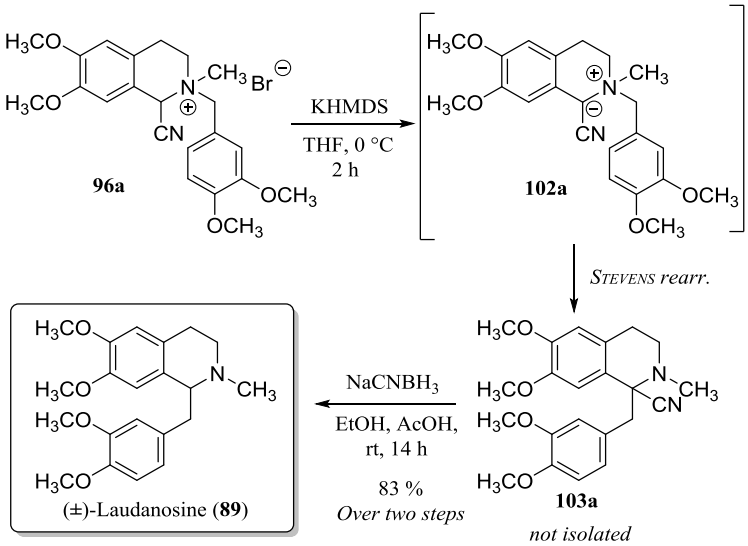
Figure 6. ^{1}H NMR experiments of ammonium salt **96a** in DMSO-d_6 over time.

This behavior could be explained by a bromide-induced nucleophilic displacement of the benzyl moiety of the ammonium salt **96a**, in which the nucleophilicity of the bromide ion is strengthened by the use of DMSO-d_6 as solvent. This process creates an equilibrium between the quaternized **96a** and the free base **94**, where the products **94** and **95a** are prone to decomposition (Scheme 24).



Scheme 24. Bromide-induced nucleophilic displacement of the benzyl moiety of the ammonium salt **96a**.

Once the preparation of ammonium salt **96a** was accomplished, the formation of the corresponding nitrile-stabilized ammonium ylide **102a** became the next synthetic target. This transformation was achieved by deprotonation of salt **96a** under the conditions reported by OPATZ and co-workers.[70] By this manner, compound **96a** was treated with KHMDS in THF at 0°C to generate the expected nitrile-stabilized ammonium ylide **102a**, which readily undergoes a STEVENS rearrangement to the α-quaternary aminonitrile **103a**. As expected, this compound is prone to the spontaneous liberation of cyanide. However, the attempt to isolate the corresponding enamines resulted in side reactions such as the oxidative cleavage of the C-1 benzylic moiety.[108] In contrast, *in situ* reduction of the crude rearrangement product **103a** with $NaCNBH_3$ at low pH values (using CH_3CO_2H) successfully afforded (±)-laudanosine **89** in 83 % yield over two steps (Scheme 25).



Scheme 25. Synthesis of (±)-laudanosine **89** by STEVENS rearrangement of nitrile-stabilized ammonium ylide **102a**.

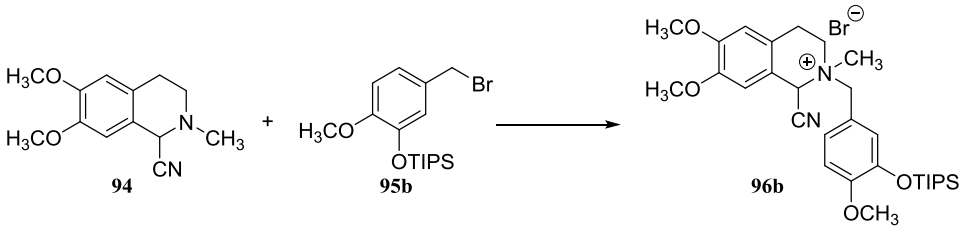
No competitive reactions such as a SOMMELET-HAUSER rearrangement, [1,4]-migration or Hofmann elimination were observed. Based on the results, it can be concluded that the designed methodology is a suitable alternative for the synthesis of (±)-laudanosine (**89**).

1.3.3 Synthesis of (±)-Laudanidine (90)

Continuing with the attempt to extend this method to other benzylisoquinolines, (±)-laudanidine (**90**) became the next synthetic target. As for (±)-laudanosine (**89**), the first stage was the preparation of ammonium salt **96b** from α-aminonitrile **94** and benzyl bromide **95b** (Table 1). In this case, benzyl bromide **95b** carries a triisopropylsilyl (TIPS) protected alcohol at position 3

that later could easily be removed to afford the characteristic hydroxy-group in (±)-laudanidine (**90**).

Table 2. Optimization of the MENSHUTKIN reaction.

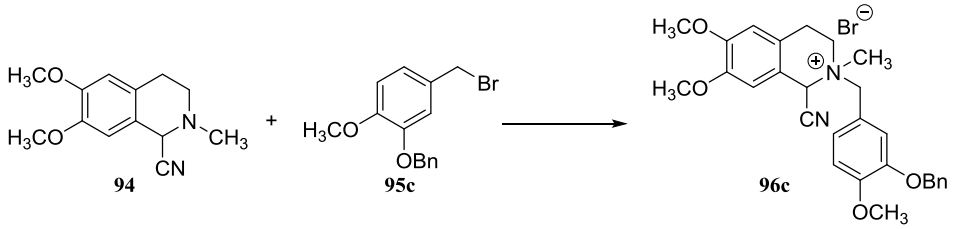


Entry	Eq. of Bromide 94b	Solvent	Temperature	Reaction Time	Yield (%)[a]
1	2.0	THF (143 mM)	40°C	48 h	85
2	1.2	THF (90 mM)	rt	6 d	53
3	1.2	Acetone (90 mM)	rt	6 d	36
4	1.2	MeCN (90 mM)	Reflux	24 h	Decomp.

[a] Isolated yield.

By applying the reaction conditions used for the preparation of **96a**, ammonium salt **96b** was obtained in 85 % yield after 2 days of heating at 40°C (entry 1). During this process, it was observed that a certain amount of α-aminonitrile **94** was transformed back into iminium ion **99** while the decomposition of benzyl bromide **95b** was taking place. Other solvents and reaction conditions were tested to avoid this decomposition (entry 2–4), however, no improvement was achieved with these modifications. Taking into consideration the low stability of benzyl bromide **95b**, a more robust and less reactive O-benzylated benzyl bromide **95c** was selected as an alternative for the quaternization reaction (Table 3).

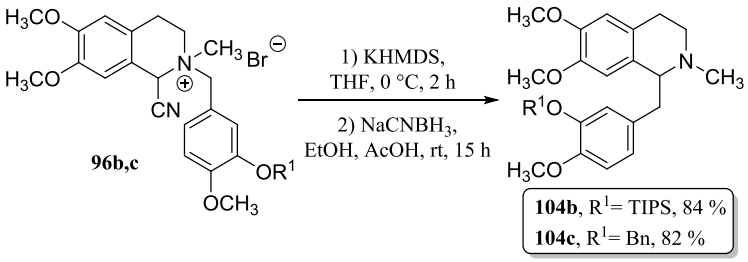
Table 3. MENSHUTKIN reaction using **95c** as alkylating agent.



Entry	Eq. of Bromide 94c	Solvent	Temperature	Reaction Time	Yield (%)[a]
1	2.0	THF (143 mM)	40°C	48 h	73
2	1.2	THF (90 mM)	rt	6 d	48

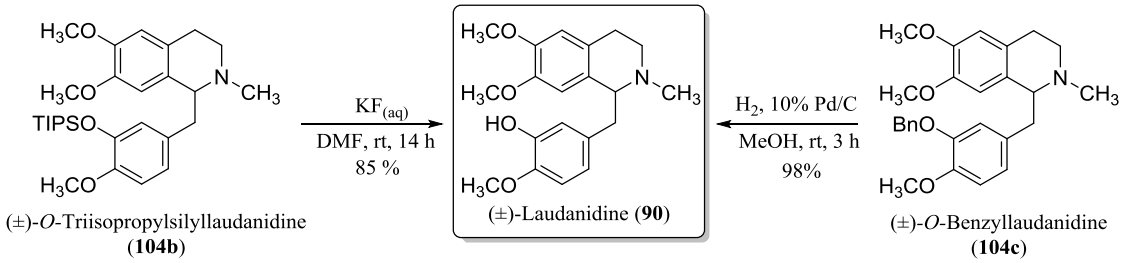
[a] Isolated yield.

Although the decomposition of the starting materials **94** and **95c** was diminished, the yields of the MENSHUTKIN reaction resulted lower than with the TIPS-protected counterpart (Table 3, entry 1 and 2). Nevertheless, in both cases the expected ammonium salts **96b** and **96c** were synthesized in moderate to high yields enabling the subsequent steps in the synthesis. Consequently, salts **96b** and **96c** were subjected to the established STEVENS rearrangement/reductive decyanation conditions which afforded (±)-*O*-(triisopropylsilyl)laudanidine **104b** and (±)-*O*-benzyllaudanidine **104c** in 84 % and 82 % yield, respectively (Scheme 26).



Scheme 26. Preparation of 1-benzyl-2-methyl-1,2,3,4-tetrahydroisoquinolines **104b** and **104c**.

With these compounds in hand, (±)-laudanidine (**90**) was easily accessed via fluoride-induced desilylation of **104b** and hydrogenolytic debenzylation of **104c** in high yields (Scheme 27).

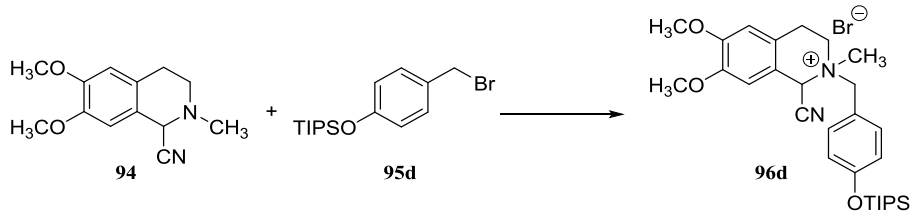


Scheme 27. Synthesis of (±)-laudanidine (**90**) from compounds **104b** and **104c**.

1.3.4 Synthesis of (±)-Armepavine (91)

Formation of salt **96d** was initially attempted by using O-TIPS benzyl bromide **95d** (Table 4).

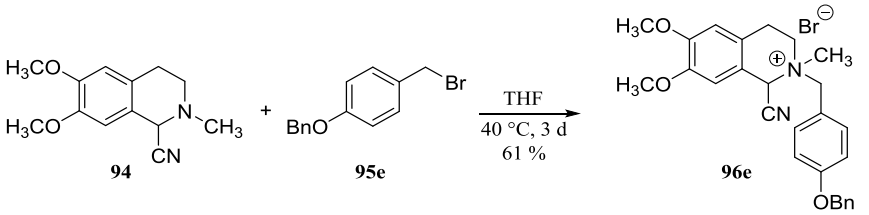
Table 4. MENSHUTKIN reaction using **95d** as alkylating agent.



Entry	Eq. of Bromide 94d	Solvent	Temperature	Reaction Time	Yield (%)
1	2.0	THF (143 mM)	40°C	48 h	Decomp.
2	1.2	THF (90 mM)	rt	6 d	Decomp.
3	1.2	Acetone (90 mM)	rt	10 d	Decomp.
4	1.2	MeCN (90 mM)	Reflux	24 h	Decomp.

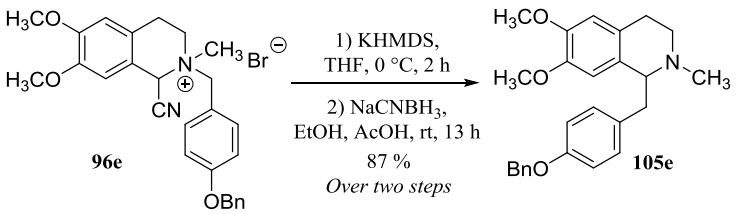
[a] Isolated yield.

Unfortunately, the expected ammonium salt **96d** was not obtained in any of the tested conditions (entry 1–4). In this case, the complete decyanation of α-aminonitrile **94** back to iminium ion **99** and fully decomposition of benzyl bromide **95d** was observed. Based on the obtained results, it was decided to test a similar benzyl bromide **95e** as alkylating agent (Scheme 28).



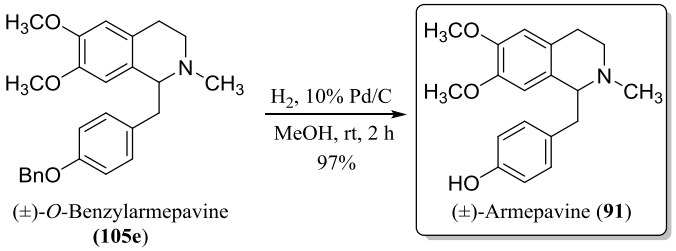
Scheme 28. Synthesis of ammonium salt **96e** from O-benzylated benzyl bromide **95c**.

By this manner, ammonium salt **96e** was obtained in 61 % yield after 3 days of reaction at 40 °C by using 2.0 equivalents of benzyl bromide **95e**. This compound was further deprotonated under the previous established STEVENS rearrangement/reductive decyanation conditions affording the expected (±)-*O*-benzylarmepavine (**105e**) in 87 % yield (Scheme 29).



Scheme 29. Synthesis of (±)-*O*-benzylarmepavine (**105e**) by STEVENS rearrangement of nitrile-stabilized ammonium ylide **95e**.

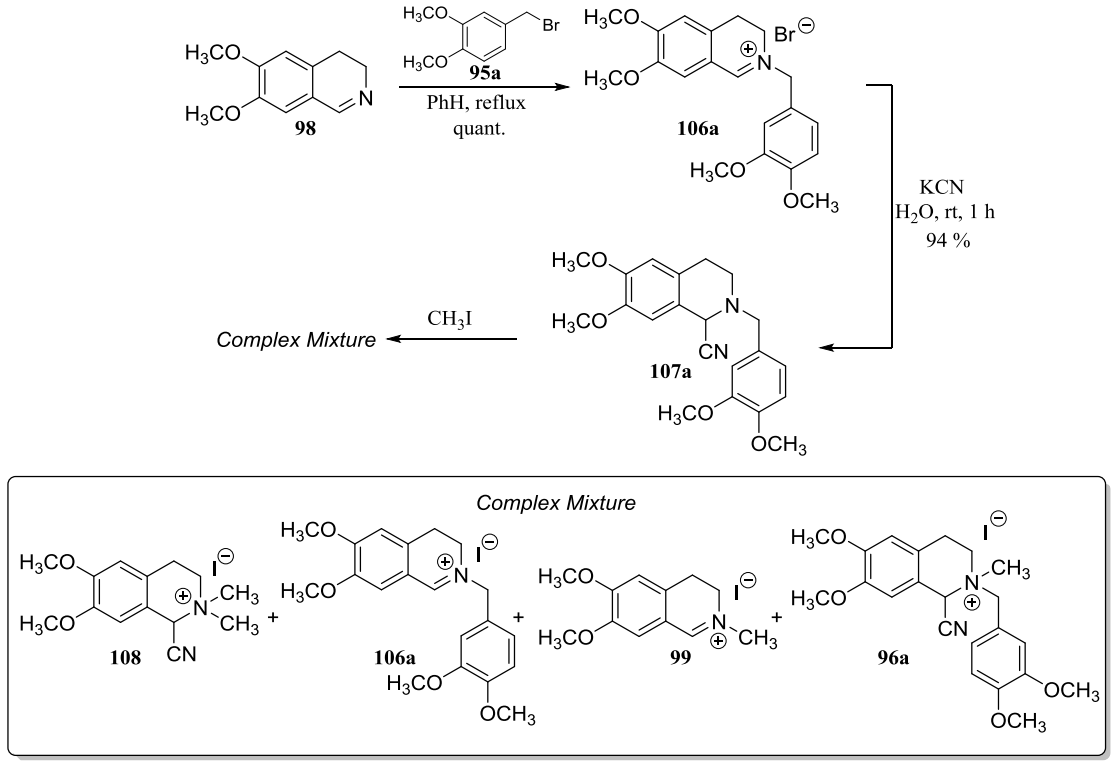
Hydrogenolytic debenzylation of (±)-*O*-benzylarmepavine (**105e**) using 10 % Pd/C and a hydrogen atmosphere gave the desired (±)-armepavine (**91**) in high yield (Scheme 30).



Scheme 30. Synthesis of **(**±**)**-armepavine (**91**).

1.3.5 Studies on an Alternative Access to Ammonium Salts 96

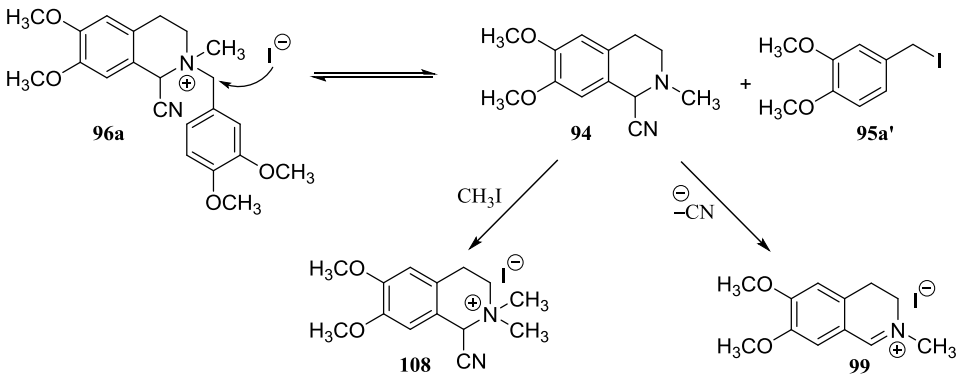
Since the critical step in the preparation of the 1-benzyl-1,2,3,4-tetrahydroisoquinoline alkaloids is the formation of the ammonium salts **96**, a potentially more convenient and efficient approach was pursued. For this purpose, ammonium salt **96a** was selected as model candidate for the study and a new strategy based on the direct benzylation of imine **98** was investigated (Scheme 31).



Scheme 31. Alternative approach to the synthesis of **96a**.

Initially, imine **98** was transformed into iminium ion **106** in high yields by alkylation with benzyl bromide **95a**. This compound was further cyanated with KCN to produce

α-aminonitrile **107a** in 94 % yield. The next step corresponded to the quaternization of the nitrogen of **107a** by N-methylation with methyl iodide. However, with different solvents and reaction conditions, an inseparable mixture of different ammonium salts (**96a**, **99**, **106a**, and **108**) was constantly obtained. The unexpected formation of the double N-methylated ammonium salt **108** revealed the importance of counterions on the ammonium salts. In this case, the formation of salt **108** could be explained via nucleophilic displacement of the benzyl moiety on salt **96a** by the iodine counterion, where α-aminonitrile **94** reacts with another molecule of methyl iodide producing **108** (Scheme 32). To avoid this nucleophilic displacement, methyl triflate was tested as methylating agent. However, the formation of triflic salt **96** was accompanied by decomposition of **107a** to iminium ion **106**.

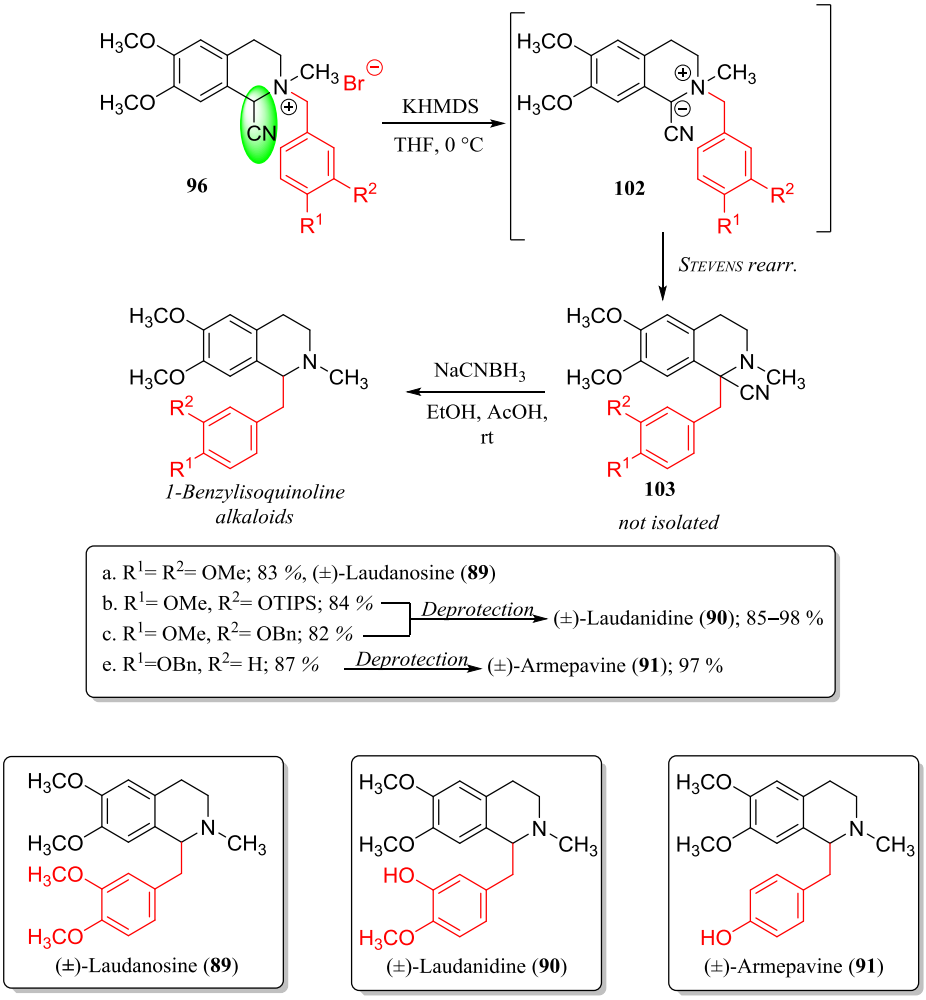


Scheme 32. Postulated formation of ammonium salt **108**.

Thus, these results show that the initially described MENSHUTKIN reaction remains the most convenient approach for the formation of salt **96a**.

1.4 Conclusions

In summary, the STEVENS rearrangement of nitrile-stabilized ammonium ylides in combination with the reductive removal of the nitrile group, proved to be a very efficient method for the synthesis of 1-benzyltetrahydroisoquinoline alkaloids (±)-laudanosine (**89**), (±)-laudanidine (**90**), and (±)-armepavine (**91**, Scheme 33).



Scheme 33. Synthesis of 1-benzylisoquinoline alkaloids via STEVENS rearrangement.

The presence of the nitrile group in the α-position of the ammonium salt **96** not only allows the unambiguous selection of the end point of the 1,2-migration but also the use of milder reaction conditions. As a consequence, no products resulting from a competing SOMMELET-HAUSER rearrangement, [1,4]-migration or HOFMANN elimination were detected. This represents a clear advantage compared to the direct deprotonation of ammonium salts where product mixtures can be observed if a thermodynamically feasible proton abstraction is possible in more than one

site.[107] Furthermore, α-ammonium-nitrile salts are easy and economical to prepare, resulting in an additional benefit over other methods such as α-stannylated or α-silylated ammonium salts.

Although the STEVENS rearrangement / reductive decyanation step works very efficiently, one limitation for this synthetic route could be found in the formation of ammonium salts **96**. It was observed that the stability and reactivity of the starting materials **95** and **94** under the reaction conditions should be carefully considered as they can have a big influence in the outcome and yield of the reaction.

Chapter 2

Unexpected Ring Expansion via [1,4]-Sigmatropic Rearrangement: Synthesis of Dibenzo[*c*,*f*]azonines.

2.1 Introduction

Medium-sized N-heterocycles (7 to 12-membered rings) are a very important group of organic compounds that occur in natural and non-natural products.[109] The most abundant and studied scaffolds of this family are carbocycles with seven- or eight-membered rings, probably due to the relative easy formation, and usefulness as synthetic intermediates and pharmaceuticals (Figure 7).[110-113]

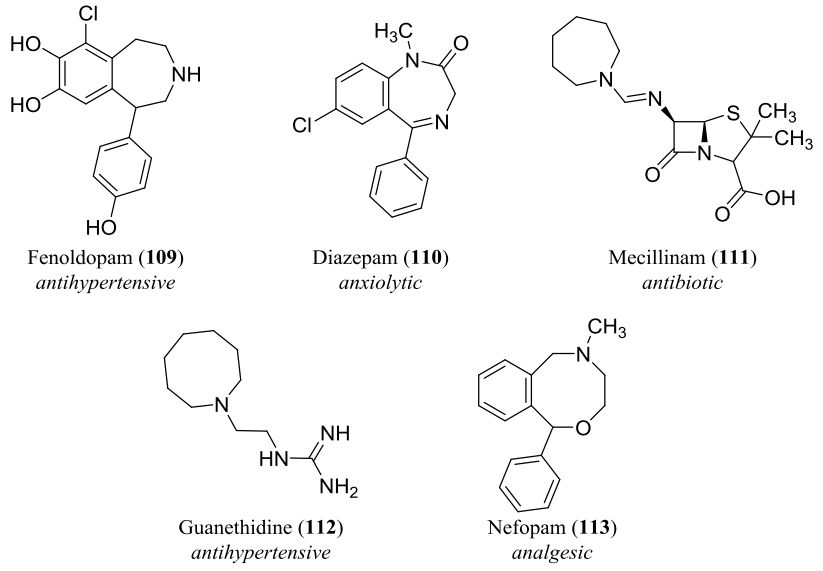


Figure 7. Biologically active azepines and azocines.

In the search for new and better drugs, larger N-heterocyclic rings such as nine-membered azonines, have caught attention as they constitute the backbone of several bioactive natural products.[109,114] For example, the very well-known anticancer drugs vinblastine (**114**) and vincristine (**115**) alkaloids,[115,116] as well as the tubulin-microtubules inhibitor rhazinilam (**116**),[117] possess an azonine subunit in their structures (Figure 8). By the same manner, the tricyclic

dibenzo[*d,f*]azonine alkaloids **117** (protostephanine, erybidine, laurifonine, bractazonine, etc.), isolated from plants of the families Menispermaceae, Leguminosae, Fumariaceae, and Papaveraceae, have shown to possess analgesic and anti-inflammatory activities, as well as anorexigenic and blood pressure effects.[114]

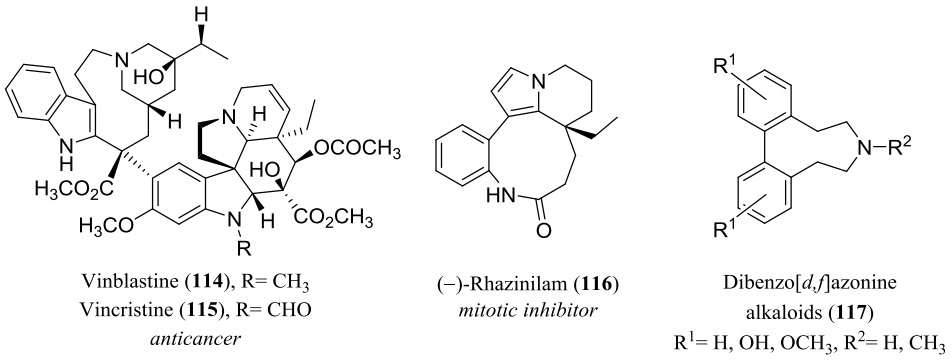


Figure 8. Naturally occurring bioactive azonines.

Analogous to the dibenzo[*d,f*]azonines, are the synthetic [*c,f*]dibenzo-annulated isomers which have also been investigated for their pharmacological properties. For instance, azonine derivatives (**118** and **119**) have shown to possess promising potential as CNS stimulants, anti-inflammatory drugs, and modulators of the NO synthase (Figure 9).[118-121] Nevertheless, dibenzo[*c,f*]azonines have been much less investigated than their naturally occurring counterparts.

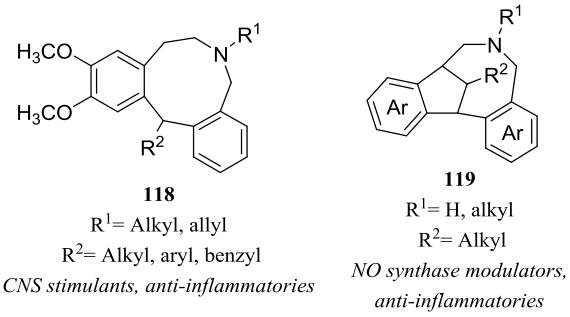
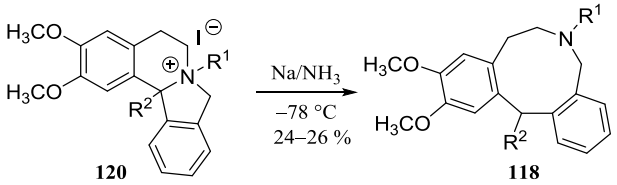


Figure 9. Dibenzo[*c,f*]azonines with potential pharmacological properties.

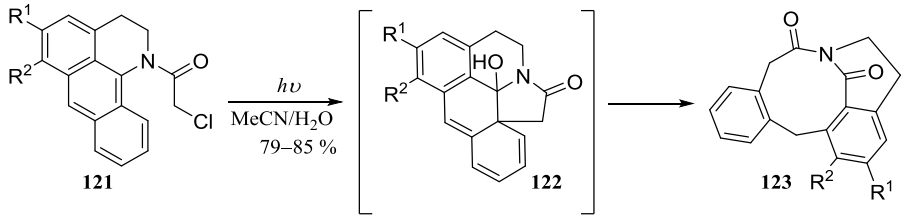
2.1.1 Synthesis of Dibenzo[*c,f*]azonines

As mentioned above, dibenzo[*c,f*]azonines have not been widely investigated, therefore the synthetic methods reported for their preparation are very limited. The first approach was described by MANNING and HOULIHAN in the early 1970's, [118,119] and illustrated the synthesis of dibenzo[*c,f*]azonines **118** from isoindolo[1,2-*a*]isoquinolinium salts **120**. For this purpose, sodium in liquid ammonia was used to reduce salt **120** and thus inducing the cleavage of the central bond between C-12b and the nitrogen (Scheme 34).



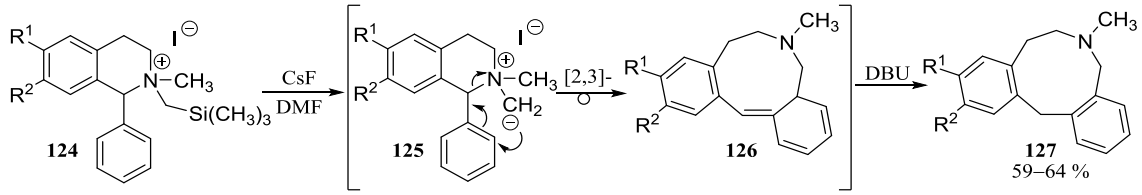
Scheme 34. Synthesis of dibenzo[*c,f*]azonines **118**.

Later, BREMNER and co-workers reported the preparation of dibenzo[*c,f*]azonines **123** via photolysis of dibenzoquinoline **121** in MeCN / H_2O using aa 400 W lamp (λ > 250 nm, Scheme 35).[122]



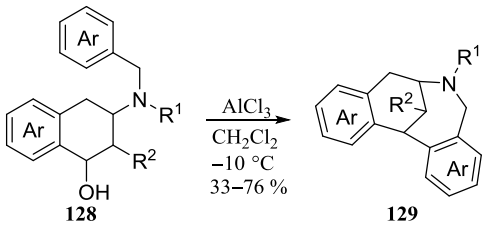
Scheme 35. Preparation of compounds **123**.

In 1992, investigating the chemical behavior of 2-methyl-2-(trimethylsilyl)-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinolinium salts **124**, SATO et al. observed that under fluoride-ion induced desilylation conditions, salts **124** afforded the corresponding methylide **125** which can undergo a SOMMELET-HAUSER rearrangement to intermediates **126**. [123] These intermediates re-aromatized in the presence of DBU to the corresponding 6-methyl-6,7,8,13-tetrahydro-5*H*-dibenzo[*c,f*]azonines (**127**, Scheme 36).



Scheme 36. Synthesis of dibenzo[*c,f*]azonines **127** via SOMMELET-HAUSER rearrangement.

The latest report on the preparation of this class of heterocycles was patented by DREUX and co-workers in 1997. They described the synthesis of dibenzo[*c*,*f*]azonines **129** by an aluminium chloride induced cyclization of hydroxytetralines **128** (Scheme 37).[120]



128 **129**

Scheme 37. Synthesis fo tetracyclic azonine **129**.

2.2 Aim of the Research

Nitrile-stabilized ammonium ylides have shown to be suitable precursors for efficient STEVENS rearrangements in the N→C-shift of benzylic substituents for the preparation of 1-benzylisoquinoline alkaloids (see Chapter 1). Motivated by these results and the potential scope of this methodology with other type of substrates, the chemical behavior of exocyclic nitrile-stabilized ammonium ylides in ring enlargements via [1,2]-STEVENS rearrangement was studied. The initial strategy was directed to the synthesis of 2-substituted benzo[*d*]azepines **131** based on the assumption that exocyclic α-ammonium nitriles **130** would undergo a [1,2]-ring expansion (Scheme 38). This hypothesis is supported by a related methodology where ester derivatives are used instead of nitriles.[124]

Scheme 38. Proposed ring enlargement approach for the synthesis of benzo[*d*]azepines (**131**).

However, as it will be described later in the results and discussion section of this chapter, α-ammonium nitriles **130** (R^3= Aryl) underwent an unexpected ring expansion to a higher ring-sized homolog; the dibenzo[*c*,*f*]azonines **132** (Figure 10).

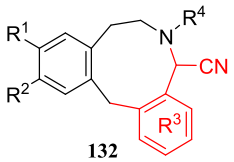


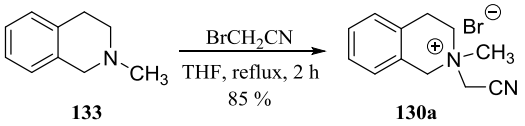
Figure 10. Unexpected dibenzo[c,f]azonines **132**.

Intrigued by these results and encourage by the lack of examples for the synthesis of this type heterocycles, the efforts of the investigation were redirected towards the optimization and preparation of dibenzo[*c*,*f*]azonines **132**.

2.3 Results and Discussion

2.3.1 Initial Observations

The investigation started by selecting the simplest α-ammonium nitrile salt **130a** as a model substrate for the deprotonation/[1,2]-migration reaction. This ammonium salt was obtained in 85 % yield by direct N-quaternization of *N*-methyl-1,2,3,4-tetrahydroisoquinoline (**133**) with commercially available bromoacetonitrile (Scheme 39).



133 **130a**

Scheme 39. Synthesis of the model substrate **130a**.

With ammonium salt **130a** in hand, the corresponding ring enlargement reaction was studied. For this purpose, salt **130a** was deprotonated with KHMDS at 0 °C to generate the expected nitrile stabilized ammonium ylide which could undergo the [1,2]-migration (Scheme 40). After 1 h of reaction, the starting material was completely consumed and two new spots appeared during TLC reaction monitoring. ^{1}H NMR analysis of the raw product showed that these compounds were obtained in a 70 : 30 ratio (Figure 11).

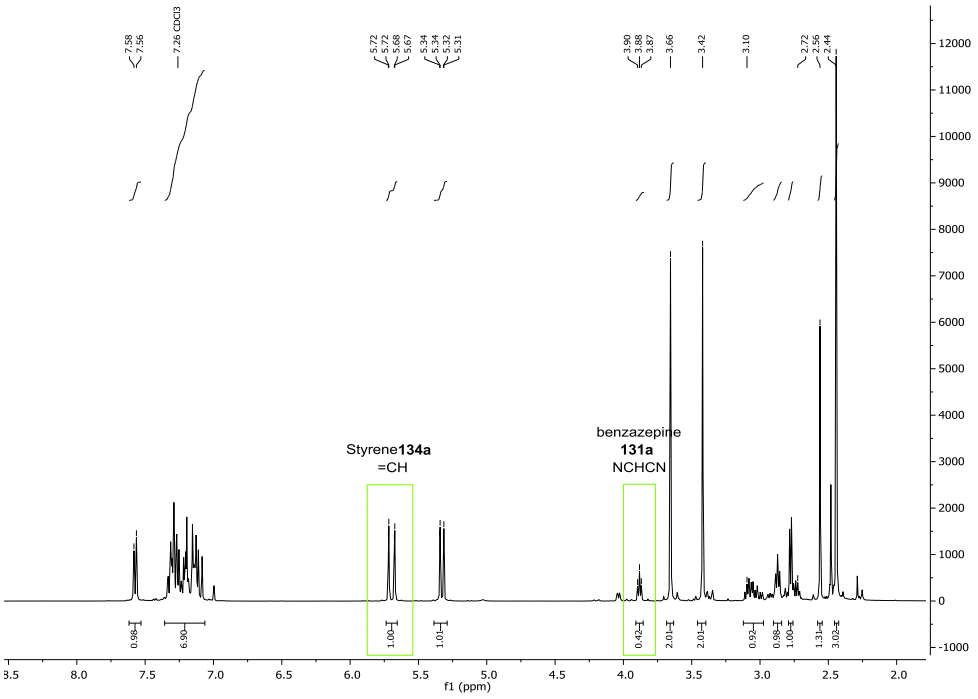
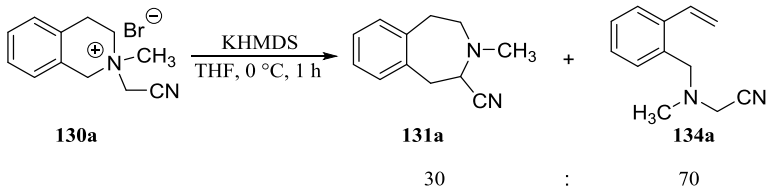


Figure 11. ^{1}H NMR analysis of the crude product from the ring expansion reaction.

The major component **134a** was identified as the product of a β-elimination (HOFMANN elimination product) while the minor component was the desired benzazepine **131a** (Scheme 40). After purification by flash chromatography, styrene **134a** was obtained in 57 % yield. SOLDATOVA and co-workers have described a similar outcome when using ammonium salt **130a** and NaH in dioxane, however, in this case, benzazepine **131a** was obtained as the main product.



Scheme 40. Reaction outcome during the ring enlargement studies.

Based on the results, it was rationalized that the chemoselectivity of the deprotonation on **130a**, could be improved if the negative charge in the intermediate ammonium ylide is stabilized by an adjacent aryl group (R^3= Aryl, salts **130**). This modification should increase the acidity of the α-C**H**CN proton and suppress the competing formation of HOFMANN elimination products.

To prove this hypothesis, a new α-ammonium nitrile salt **130b** (R^3= Ph) was chosen as a model substrate for the rearrangement reaction. The preparation of this salt was envisioned as an N-methylation of its parented α-aminonitrile **135b**, which in turn can be synthesized by two different methods: via N-alkylation of 1,2,3,4-tetrahydroisoquinoline (**136**) with 2-phenyl-2-bromoacetonitrile (**137**), or by a STRECKER reaction with benzaldehyde (**138**) and cyanide (Figure 12).

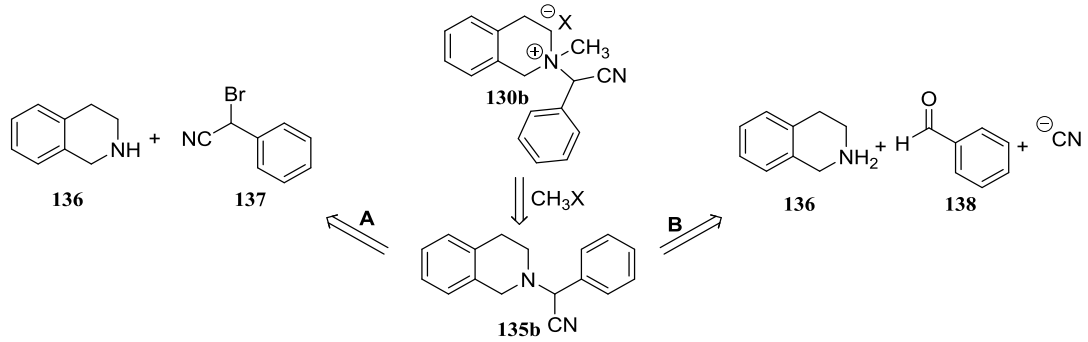
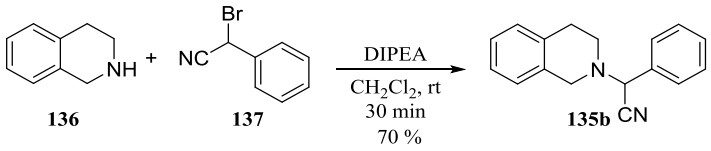


Figure 12. A synthetic approach to salt **130b**.

In an effort to establish the best method for the synthesis of α-aminonitriles **135b**, both synthetic pathways (route A and B) were followed. By this manner, α-aminonitrile **135b** was initially

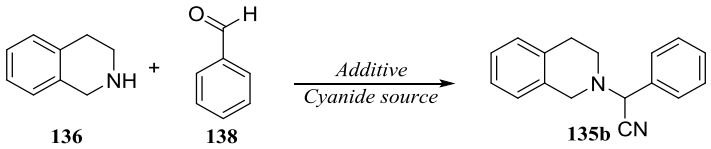
obtained in 70 % yield when 1,2,3,4-tetrahydroisoquinoline (**136**) in CH_2Cl_2 was treated with bromoacetonitrile **137** and DIPEA as base (Scheme 41).



Scheme 41. Synthesis of α-aminonitrile **135b** by N-alkylation.

With the STRECKER approach, α-aminonitrile **135b** was afforded in 83 % yield after a small optimization of the reaction conditions (Table 5). In this case, the formation of the bisulfite adduct of benzaldehyde **138** by addition of sodium bisulfite resulted very convenient for the STRECKER reaction (entry 2).[125] This modification is known as the KNOEVENAGEL-BUCHERER method and as observed, it is a better and more practical method compared with other STRECKER modifications (entry 1 and 3).[41,126,127] This approach also proved to be more efficient than the N-alkylation pathway (see Scheme 41).

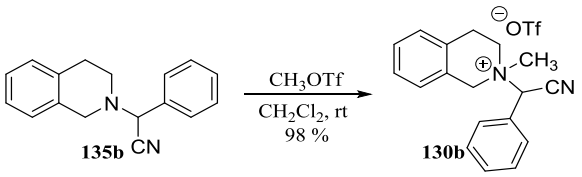
Table 5. STRECKER reaction.



Entry	Solvent	Additive	Cyanide Source	Reaction Time	Yield (%)[a]
1	MeCN	LiBr (10 mol%)	TMSCN (1.0 eq.)	24 h	66
2	H_2O/MeOH (4:1)	$NaHSO_3$ (1.0 eq.)	KCN (2.0 eq.)	18 h	83
3	THF	Ti(O*i*Pr)$_4$ (2.0 eq.)	TMSCN (1.0 eq.)	48 h	42

[a] Isolated yield

Once the preparation of α-aminonitrile **135b** was achieved in good yields, the next step corresponds to its N-methylation. Since halide anions have proved to be involved in nucleophilic N-dealkylations (see Chapter 1), methyl iodide was avoided for this transformation. Instead, methyl triflate demonstrated to be a suitable methylating agent, leading to the formation of α-ammonium nitrile salt **130b** in 98 % yield as a diastereomeric mixture in a 51 : 49 ratio (determined by ^{1}H NMR, Scheme 42).



Scheme 42. Synthesis α-ammonium nitrile salt **130b**.

With the α-ammonium nitrile salt **130b**, the investigation on the selective deprotonation as well as the [1,2]-migration was continued. Accordingly, salt **130b** was subjected to deprotonation with KHMDS in THF at 0 °C and allowed to stir over 3 h (Scheme 43). Gratifyingly, it was observed that a single product was formed (judged by TLC) and that its molecular mass matched the expected benzo[*d*]azepine **131b**. After chromatographic purification, the corresponding compound was afforded in 50 % yield. Nevertheless, when ^{1}H and ^{13}C NMR experiments of the isolated compound were conducted in $CDCl_3$, an unusual set of unresolved broad signals in the aliphatic region was observed, and one aromatic proton and two carbon resonances were missing. A very small improvement in the resolution of a couple of proton signals was achieved by using C_6D_6 instead of $CDCl_3$ (Figure 13).

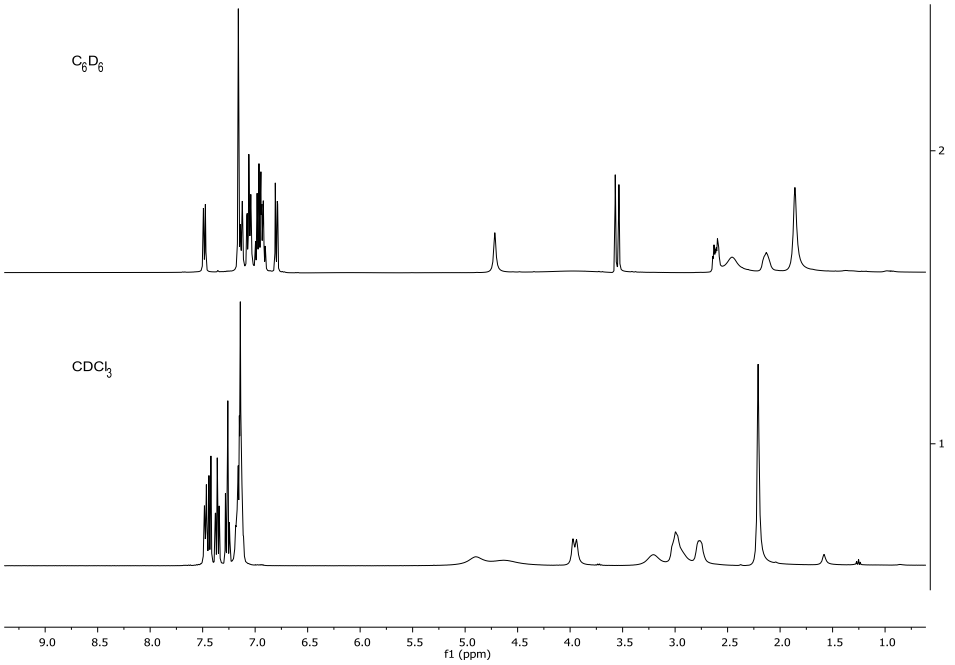


Figure 13. ^{1}H NMR of the isolated compound measured in $CDCl_3$ and C_6D_6.

Initially, this broadening was attributed to a possible slow ring flipping of the expected benzazepine **131b**, which is very unusual for 7-membered rings. To overcome this issue, a set of dynamic NMR experiments at variable temperatures were performed. As a result, an optimal

resolution of the signals was obtained at 70 °C where the ring inversion was fast enough to give sharp resonances (Figure 14).

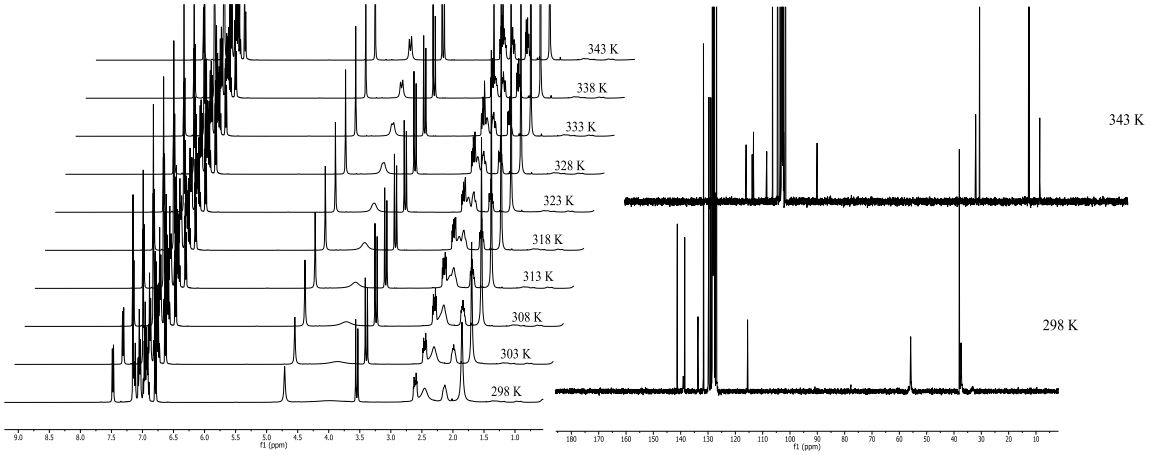
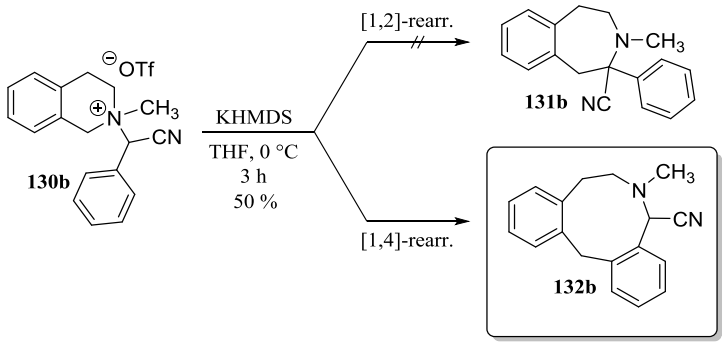


Figure 14. ^{1}H and ^{13}C spectra of the isolated compound at variable temperatures (K) in C_6D_6.

Surprisingly, after analyzing the NMR data (1D and 2D experiments at 70 °C), the isolated product was identified as a dibenzo[*c*,*f*]azonine carbonitrile **132b** and not as the expected azepine **131b** (Scheme 43). This explains the initial observation on the absence of one aromatic signal as well as the effect on the broadening of the signals, which is common on high-sized rings.[128]



Scheme 43. Unexpected formation of dibenzo[*c*,*f*]azonine **132b**.

After recrystallization from methanol, the structure of the nine-membered ring **132b** was unequivocally confirmed by X-ray crystallography (Figure 15).

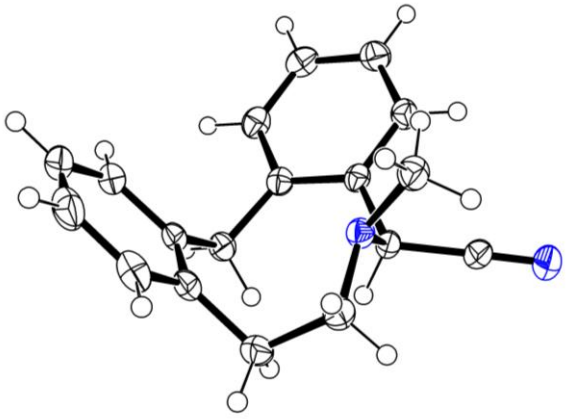
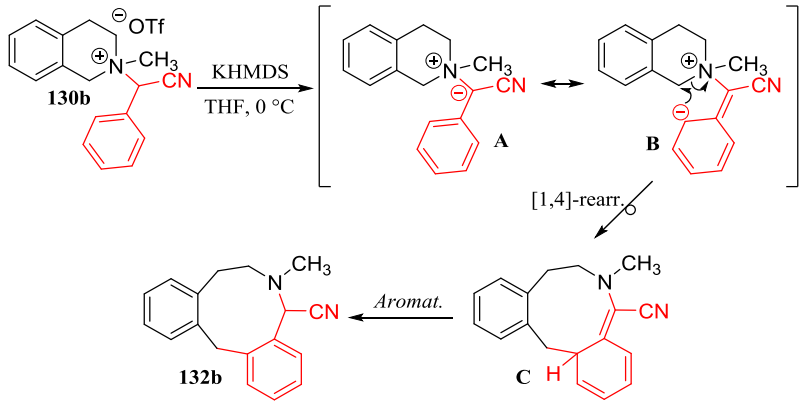


Figure 15. Crystal structure of azonine **132b** at 173 K (ORTEP, thermal ellipsoids at 50% probability).

The unexpected formation of azonine **132b** can be explained in terms of a [1,4]-sigmatropic rearrangement of the zwitterionic species **B**, derived from the corresponding nitrile-stabilized ammonium ylide **A**, followed by rearomatization of **C** (Scheme 44). Migrations of this kind have been observed on a number of occasions as a competing reaction with the [1,2]- and [2,3]-rearrangements of ammonium benzylides as well as allylic ammonium ylides.[90-93,129,130]



Scheme 44. [1,4]-Sigmatropic rearrangement of α-ammonium nitrile salt **130b**.

This [1,4]-sigmatropic rearrangement has been described as a concerted symmetry allowed and geometrically favorable process that involves a six-electron aromatic transition state with suprafacial–suprafacial characteristics.[90,91] Nevertheless, in some cases an intermolecularity of ca. 14% have been observed (e.g. acyl-stabilized ammonium ylides), suggesting that a contribution from a 1,4-coupling radical pair intermediate might occur.[130,131] In order to have further insights into the mechanism, DFT calculations were performed on this model reaction by Stefan PUSCH. As a result, a potential energy hypersurface plot from 107 discrete constrained optimizations was generated (Figure 16).

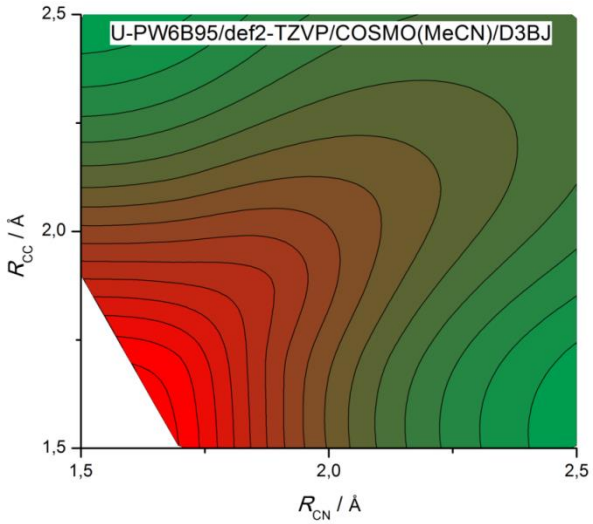


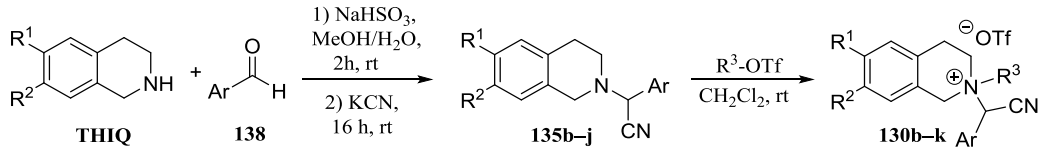
Figure 16. PES generated from 107 discrete constrained optimizations.

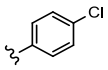
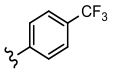
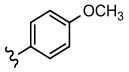
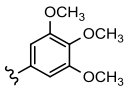
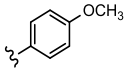
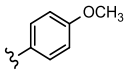
In this plot (Figure 16), red and green represent values of high and low electronic energy, while the axes (x,y) correspond to the lengths of the bonds that are forming and breaking. In this manner, it could be observed that the reaction does not involve a transition state typical for a concerted mechanism. Instead, a dissociation/recombination process seems to be operating. However, it is worth to mention that multireference characters, maybe present due to biradicaloid intermediates/transition states, were not considered in this calculation.

2.3.2 Reaction Optimization and Substrate Scope

To explore the scope of the reaction, nine new α-aminonitriles (compounds **135b–j**) were prepared according to the already used KNOEVENAGEL-BUCHERER-type STRECKER reaction of 1,2,3,4-tetrahydroisoquinoline (**136**) or 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**139**) with different benzaldehydes **138**. Derivatives containing electron withdrawing or electron donating groups were obtained in high yields (80–94%), demonstrating the wide application of this method in the preparation of α-aminonitriles (Table 6). Further quaternization of α-aminonitriles **135b–j** with alkyl triflates produced 10 new ammonium triflates **130b–k** in high yields, except for salt **130k** which was obtained in 27 % yield (entry 10). Detailed analysis of this result revealed that a by-product identified as 1,2,3,4-tetrahydroisoquinoline hydrotriflate was obtained in 70 % yield. This outcome can be due to an N-debenzylation of the α-aminonitrile **135f** induced by triflic acid which was produced by a β-elimination of the corresponding electrophilic *n*-butyl triflate.[132]

Table 6. Synthesis of α-ammonium nitrile salts **130b–k** from α-aminonitriles **135b–j**.



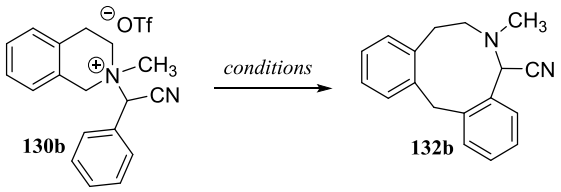
Entry	THIQ	R^1	R^2	Ar	Aminonitrile	Yield (%)[a]	R^3	Salt	Yield (%)[a]
1	**136**	H	H		**135b**	83	CH_3	**130b**	98
2	**136**	H	H		**135c**	90	CH_3	**130c**	96
3	**136**	H	H		**135d**	94[b]	CH_3	**130d**	94
4	**136**	H	H		**135e**	90	CH_3	**130e**	91
5	**136**	H	H		**135f**	93	CH_3	**130f**	99
6	**136**	H	H		**135g**	80	CH_3	**130g**	96
7	**136**	H	H		**135h**	87	CH_3	**130h**	93
8	**139**	OCH_3	OCH_3		**135i**	82	CH_3	**130i**	98
9	**139**	OCH_3	OCH_3		**135j**	84	CH_3	**130j**	99
10	**136**	H	H		**135f**	93	*n*-Bu	**130k**	27

[a] Isolated yield. [b] Used in the next step without further purification.

With the set of α-ammonium nitriles salts **130b–k** synthesized, the next stage corresponded to the optimization for the preparation of dibenz[*c*,*f*]azonines **132**. For this purpose, compound **130b** was selected again as test substrate (Table 7).

As depicted in Table 7, different bases, solvents and reaction temperatures were screened. It was found that the combination of DBU as base and acetonitrile as solvent at room temperature furnished not only the highest yields (87 %), but also the shortest reaction times (entry 4). In the cases where THF or toluene were used as solvents (entries 1–3 and 5), salt **130b** was very difficult to suspend or solubilize, causing an incomplete conversion of the starting material. Remarkably, no competing rearrangements were observed as judged by LC-MS analysis of the reaction mixtures.

Table 7. Optimization of the reaction conditions for the preparation of dibenzo[*c*,*f*]azonines **132a**.

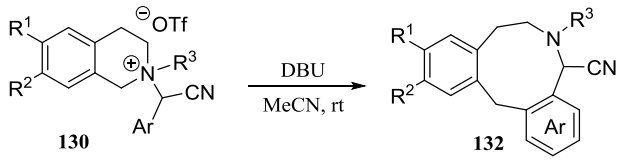


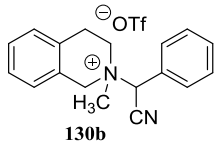
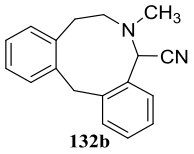
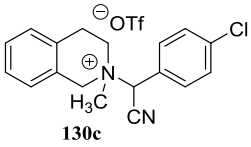
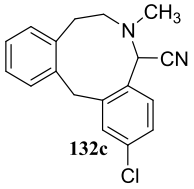
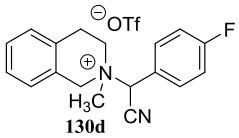
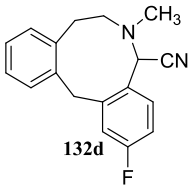
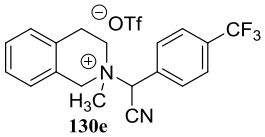
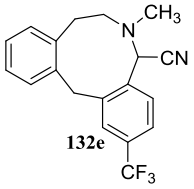
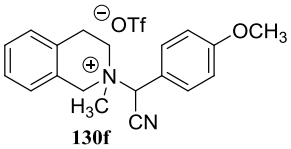
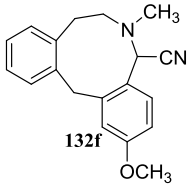
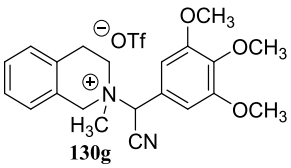
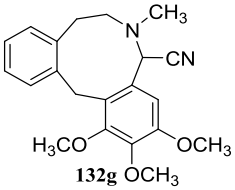
Entry	Base	Eq. of Base	Solvent	Temperature	Time (h)	Yield (%)[a]
1	KHMDS	1.2	THF	0 °C	3	50[b,c]
2	KHMDS	1.2	THF	rt	1.5	60[b,c]
3	KHMDS	1.3	PhMe	Reflux	6	65[c,d]
4	DBU	1.2	MeCN	rt	1	87[d]
5	DBU	1.2	THF	rt	15	45[c]
6	DBU	1.3	DMF	rt	1.5	77[d]
7	KOH	2	H_2O	70 °C	48	—[e]

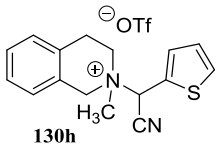
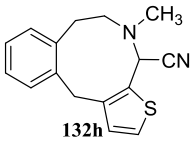
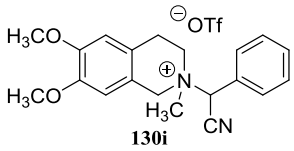
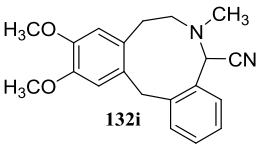
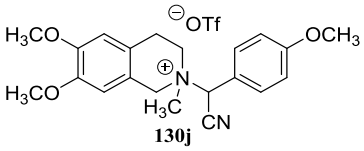
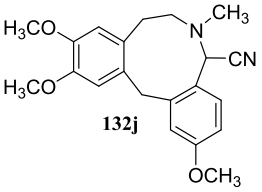
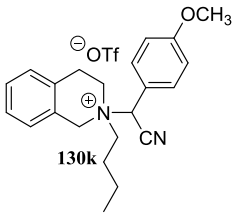
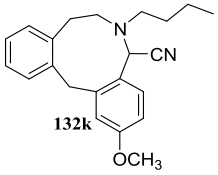
[a] Isolated yield. [b] Purification by flash chromatography. [c] Incomplete consumption of the starting material. [d] Purification by recrystallization. [e] Product was not detected, only starting material was observed.

Once the reaction conditions were optimized, compounds **130b–k** were transformed into nine new dibenzo[*c*,*f*]azonines carbonitriles **132b–k** in 78–87 % yield (Table 8). It was observed that substituents in the aryl ring directly involved in the rearrangement have a strong influence on the reaction rates but not on the outcome of the reaction. Along these lines, derivatives with electron-withdrawing groups reacted faster than derivatives with electron-donating groups.

Table 8. Preparation of dibenzo[*c*,*f*]azonines **132c–k** by [1,4]-rearrangement.



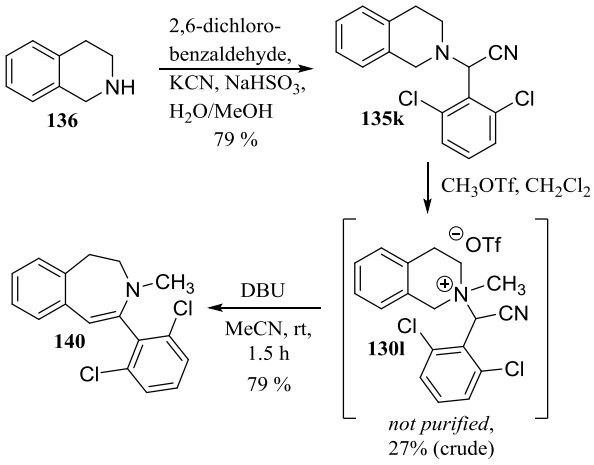
Entry	Salt	Time (h)	Product	Yield (%)[a]
1	 **130b**	1	 **132b**	87
2	 **130c**	0.67	 **132c**	84
3	 **130d**	0.67	 **132d**	85
4	 **130e**	0.5	 **132e**	89
5	 **130f**	1.5	 **132f**	81
6	 **130g**	3.7	 **132g**	87

7	 **130h**	1	 **132h**	78
8	 **130i**	1	 **132i**	84
9	 **130j**	2	 **132j**	83
10	 **130k**	1.5	 **132k**	80

[a] Isolated yield.

2.3.3 Synthesis of Benzo[*d*]azepine 140

Taking into account that the formation of the corresponding dibenzo[*c,f*]azonines **132** involved a migration of a 1,4-zwitterionic species **B** (see, Scheme 44), it was assumed that by blocking the *ortho*-positions of the aryl ring directly involved in the rearrangement, the formation of the 1,4-zwitterion could be suppressed and thus produce the initially expected benzo[*d*]azepines **131**. In order to demonstrate this, α-ammonium nitrile salt **130l** was synthesized and subjected to deprotonation with DBU (Scheme 45).



Scheme 45. Synthesis of 4-(2,6-dichlorophenyl)-3-methyl-2,3-dihydro-1H-benzo[*d*]azepine **140**.

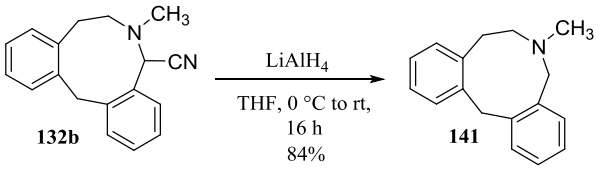
After 1.5 h, TLC showed full consumption of the starting material and the formation of two close new spots (60/40 proportion; R_{f1}= 0.67/R_{f2}=0.61, cyclohexane/EtOAc 3:2). The reaction mixture was then supported in silica gel and subjected to flash column chromatography. Surprisingly, the minor product vanished during the purification and just the major compound could be isolated and further identified as enamine **140**. These results can be explained considering that the minor product corresponded to the initial expected benzazepine carbonitrile, which under the reaction condition and during the purification underwent a dehydrodecyanation reaction to enamine **140**.

By this manner, it can be conclueded that as long as the formation of the 1,4-zwitterion **B** (see, Scheme 44) is suppressed, benzo[*d*]azepines can also be afforded from α-ammonium nitrile salts **130**.

2.3.4 Reductive decyanation of Dibenzo[*c,f*]azonine 132b

As it has been observed, dibenzo[*c,f*]azonines **132** possess an α-aminonitriles moiety remaining in their structure, which offers the opportunity for further functionalization. This possibility is

also supported by the crystal structure of azonine **132b** (see, Figure 15), which reveal that the lone pair at the pyramidal nitrogen in the ring adopt an antiperiplanar position to the nitrile group. This orientation suggests that these azonines are suitable candidates for elimination/addition reactions, such as BRUYLANTS or reductive decyanation reactions. In order to prove this rationalization, azonine **132b** was initially subjected to reaction with $NaCNBH_3$ as reducting agent, however, no decyanation was accomplished. Instead, by using a stronger reductive agent such as $LiAlH_4$, decyanated dibenzo[*c,f*]azonine **141** could be obtained in 84 % yield after 16 h (Scheme 46), which clearly illustrates the applicability of this methodology.

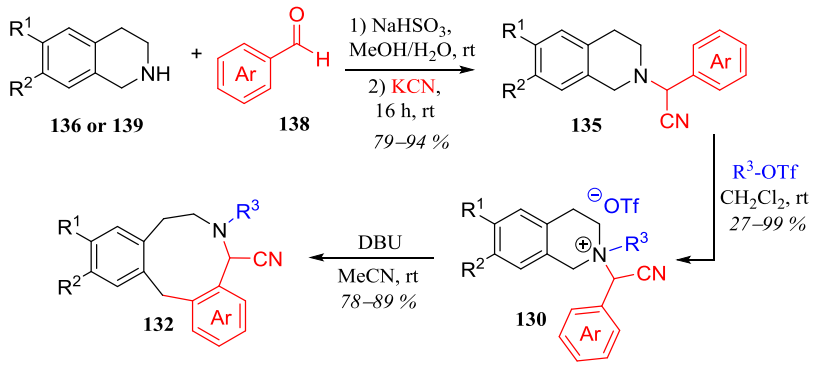


132b **141**

Scheme 46. Synthesis of 6-methyl-6,7,8,13-tetrahydro-5*H*-dibenzo[*c,f*]azonine **141** by reductive decyanation.

2.4 Conclusions

While investigating the behavior of exocyclic nitrile-stabilized ammonium ylides, a novel and broadly applicable method for the straightforward preparation of 6,7,8,13-tetrahydro-5*H*-dibenzo[*c*,*f*]azonines was found. Remarkably, this method represents the first direct ring expansion of ammonium ylides via [1,4]-rearrangement, as well as the first efficient protocol — three linear steps— for the preparation of dibenzo[*c*,*f*]azonines from simple starting materials (Scheme 47).



Scheme 47. Preparation of dibenzo[*c*,*f*]azonines **132**.

Although the outcome of the rearrangement reaction differs from what was initially expected, the introduction of aryl groups at the α-**C**–CN carbon has proved to suppress effectively the formation of HOFMANN elimination products by increasing the acidity of the α-C**H**CN proton. Furthermore, it was shown that by using 2,6-disubstituted N-benzyl groups, the reaction can be influenced to undergo the expected [1,2]-STEVENS rearrangement with formation of benzo[*d*]azepines.

Chapter 3

STEVENS Rearrangement as Key Step in the Synthesis of 1-Veratryloctahydroisoquinolines

3.1 Introduction

For centuries, natural occurring opium alkaloids (–)-morphine (**142**), (–)-codeine (**143**), and (–)-thebaine (**144**), as well as their semisynthetic analogous oxycodone (**145**) and buprenorphine (**146**), have been widely and successfully used in traditional and modern medicine as very potent analgesics for the treatment of moderate to chronic pain (Figure 17).[133-135]

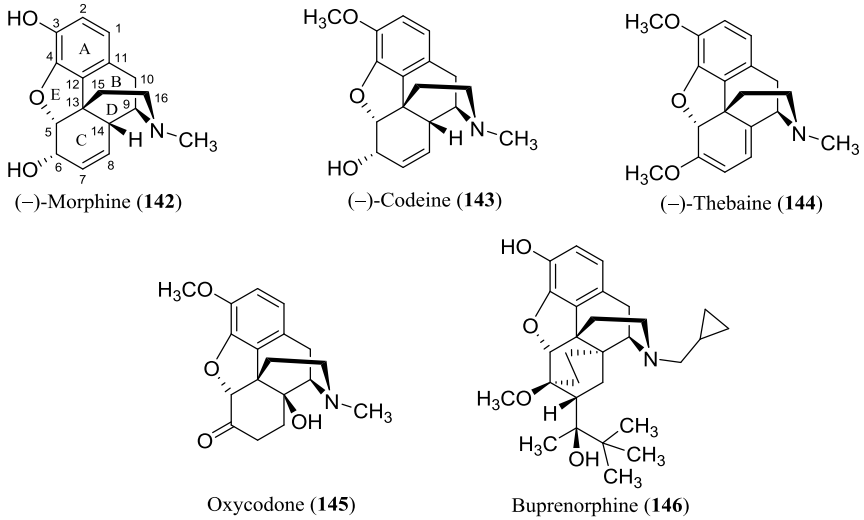


Figure 17. Morphine alkaloids and relevant semisynthetic analogous.

The biosynthesis of these morphine alkaloids in *Papaver somniferum* starts with the key intermediate (*S*)-reticuline (**147**) which arises from L-tyrosine (**85**) via (*S*)-norcoclaurine (**88**) formation. As mentioned in Chapter 1, (*S*)-norcoclaurine (**88**) is a benzyltetrahydroisoquiline alkaloid, which is also the precursor of other secondary plant metabolites, such as aporphines and protoberberines. Epimerization of (*S*)-reticuline (**147**) to the (*R*)-enantiomer takes place by oxidation to iminium ion **148** with reticuline oxidase and subsequent enantioselective reduction to (*R*)-reticuline (**149**) by dehydroreticuline reductase. Oxidative phenol coupling of (*R*)-reticuline (**149**) catalyzed by salutaridine synthase produces salutaridine (**150**). The next step corresponds to the reduction of salutaridine (**150**) by salutaridine reductase to salutaridinol (**151**),

which is then acetylated (**152**) and spontaneously cyclized to produce (–)-thebaine (**144**). Demethylation of **144** by thebaine 6-O-demethylase produces (–)-neopinone (**153**), which exists in equilibrium with its α,β-unsaturated carbonyl isomer, (–)-codeinone (**154**). The reduction of the carbonyl function by codeine reductase yields (–)-codeine (**143**), which upon demethylation finally produces (–)-morphine (**142**) (Figure 18).[136,137]

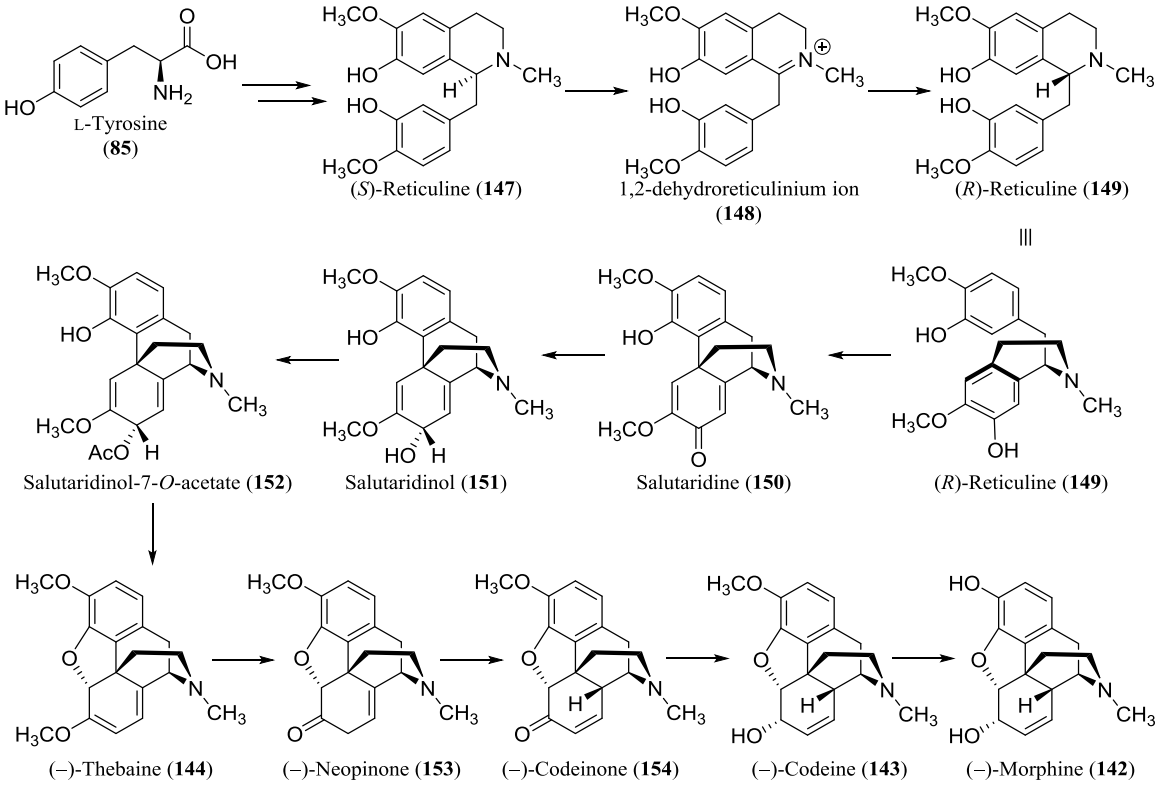


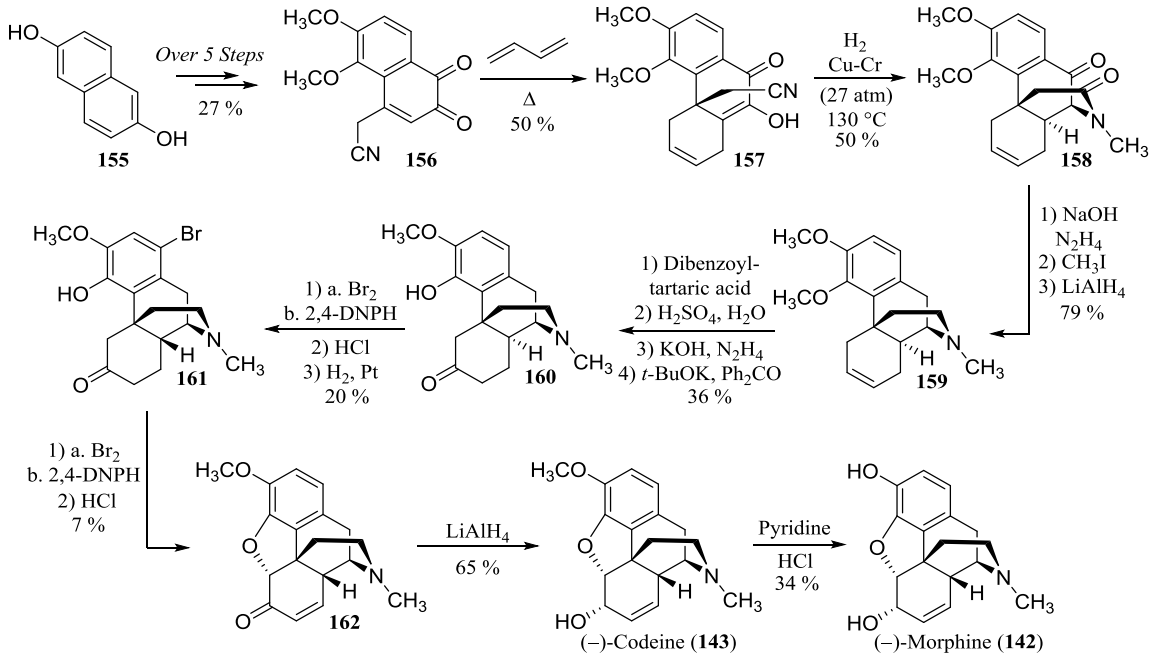
Figure 18. Biosynthesis of morphine alkaloids from (*S*)-reticuline in *papaver somniferum*.

Recent publications have confirmed that morphine alkaloids are not only produced in plants but also in mammals. This process appears to be highly similar to the pathway described in opium poppy on the basis of common intermediates.[138,139]

3.1.1 Relevant Total Syntheses of Morphine and its Derivatives

Many useful synthetic routes for the construction of morphine and its biogenetic analogous have been reported since the elucidation of its structure by ROBINSON in 1925.[133,140] GATES and co-workers reported the first synthesis of (–)-morphine (**142**), which also confirmed the structure proposed by ROBINSON. This total synthesis achieved 0.06 % yield over 31 linear steps and allowed the preparation of both morphine enantiomers by resolution of an advanced racemic intermediate.[141] The synthesis started with the construction of dienophile **156**, which was

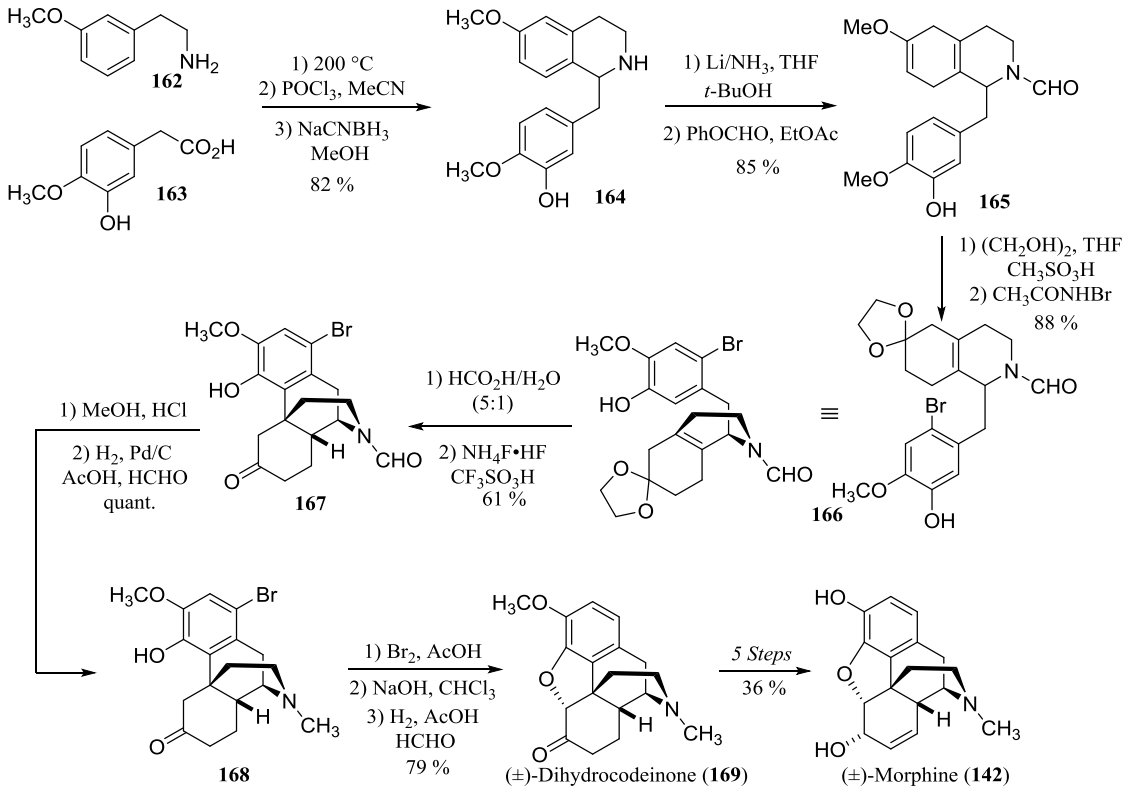
obtained over 5 steps in 27 % yield from 2,6-dihydroxynaphtalene (**155**). Dienophile **156** was then subjected to a DIELS-ALDER reaction with butadiene, followed by a reduction of the resulting enol **157** with copper chromite to amide **158**. WOLFF-KISHNER reduction, methylation, and $LiAlH_4$ reduction sequence on amide **158** afforded morphinan **159** in 79 % yield. Resolution of the racemic morphinan **159** with dibenzoyl tartrate afforded the desired isomer. Further regioselective hydration and mono-selective demethylation with hydrazine and KOH, followed by a modified OPPENAUER oxidation, yielded ketone **160**. After successive α-bromination, hydrazone formation and hydrolysis, α,β-unsaturated ketone **161** was obtained. Reduction of this ketone with $LiAlH_4$ generated codeine (**143**), which was finally demethylated with hydrochloric acid in pyridine to conclude the first total synthesis of (–)-morphine (**142**, Scheme 48).



Scheme 48. Synthesis of (–)-morphine (**142**) by GATES.

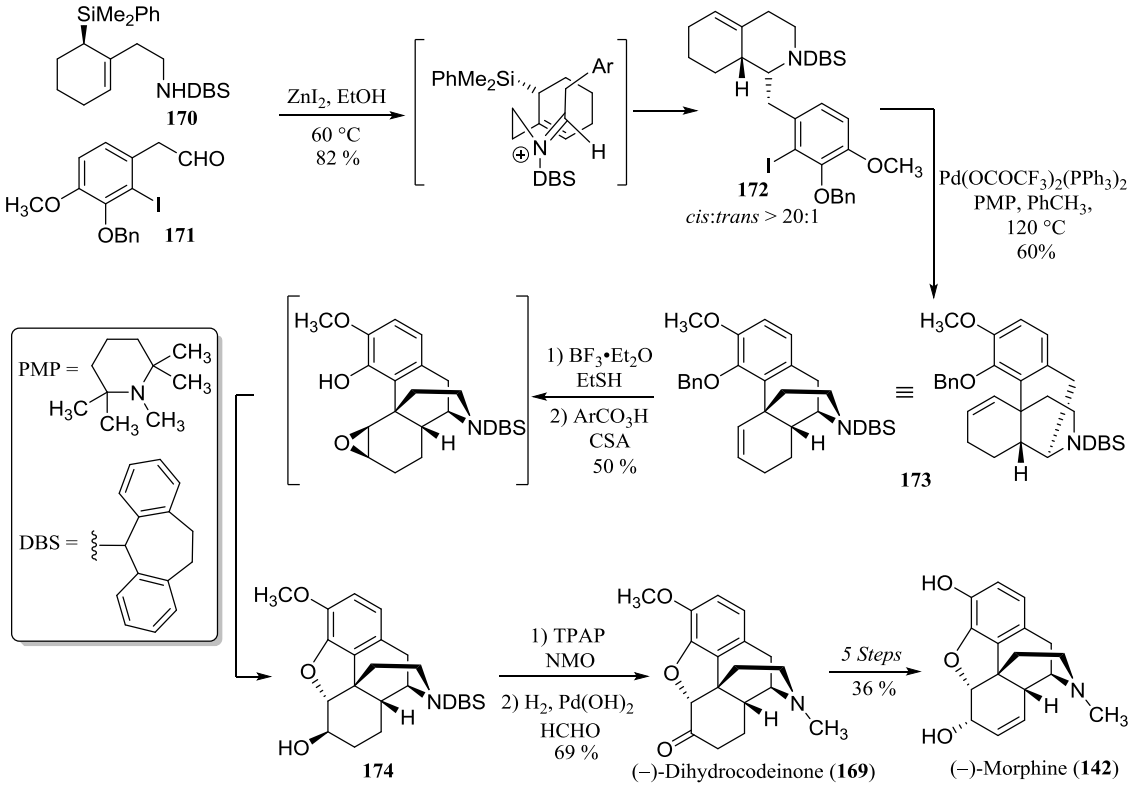
In 1980, RICE et al. reported the shortest and most efficient total synthesis of morphine (**142**) until now.[142] The route follows a biomimetic approach and delivers dihydrocodeinone in 30 % overall yield in 14 steps. The first step in this reaction sequence corresponded to a condensation between amine **162** and acid **163**, followed by a BISCHLER-NAPIERALSKI reaction in conjunction with sodium cyanoborohydride reduction to afford 1-benzyltetrahydroisoquinoline **164**. This compound was subjected to BIRCH reduction and then N-formylated with phenyl formate to produce methyl enol ether **165**. Ketalization of **165** followed by bromination of the aromatic ring afforded compound **166** in 85 %, which represents the key intermediate of this synthetic route. Subsequently, octahydroisoquinoline **166** was deprotected and then subjected to a GREWE

cyclization reaction using $NH_4F{\cdot}HF$ in triflic acid to produce morphinan **167**. Deformylation followed by reductive amination produced N-methylated morphinan **168**, which was further brominated at the ketone's α-position and then cyclized in an intramolecular etherification reaction to successfully constitute the E-ring. Removal of the residual bromide by hydrogenation reaction produced (±)-dihydrocodeinone **169** in 79 %. This compound represents a key intermediate in the formal synthesis of morphine (**142**), codeine (**143**), and thebaine (**144**, Scheme 49).



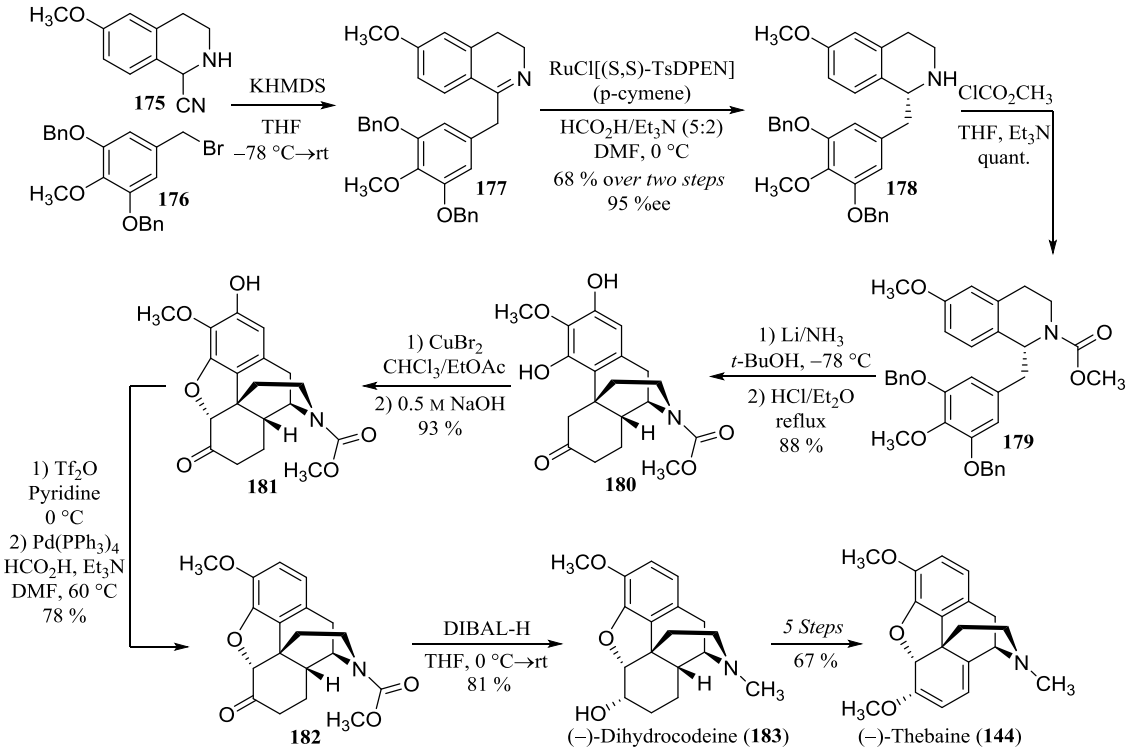
Scheme 49. Synthesis of racemic dihydrocodeinone (**169**) by RICE.

Another important example is the first enantioselective synthesis of (–)-morphine (**142**) described by OVERMAN and co-workers in 1993.[143] The key reaction began with the condensation of allylsilylamine **170** and benzaldehyde **171** followed by iminium ion-allylsilane cyclization to produce octahydroisoquinoline **172** in 82 % yield and 91 % ee. Then, compound **172** was subjected to an intramolecular HECK cyclization reaction to afford unsaturated morphinan **173**. After benzyl ether deprotection, olefin epoxidation and subsequent nucleophilic ring opening, alcohol **174** was oxidized to the ketone at C-6 and the DBS group was replaced by a methyl to deliver (–)-dihydrocodeinone (**169**). This later compound can be easily converted into (–)-morphine (**142**) over 5 steps (Scheme 50).[143]



Scheme 50. Synthesis of (–)-dihydrocodeinone (**169**) by OVERMAN.

In 2014, OPATZ and GEFFE reported the most efficient asymmetric approach to morphinan alkaloids up to date.[144] The synthesis started with the C-alkylation of α-aminonitrile **175** with benzyl bromide **176** to produce imine **177** upon spontaneous dehydrocyanation. Enantioselective reduction of this imine with RuCl[(*S*,*S*)-TsDPEN](*p*-cymene) afforded (*R*)-tetrahydroisoquinoline **178** in 68 % yield and 95 % ee over two steps. N-Acylation of this compound with methyl chloroformate produced carbamate **179**, which was further reduced and cyclized in a BIRCH reduction/GREWE cyclization procedure generating morphinan **180** in 88 % yield. The characteristic ether bridge (E ring) in compound **181** was effectively formed by α-bromination/phenoxide-nuchleophilic displacement at C-5 in 93 % yield. Finally, triflation/detriflation procedure followed by reduction of the carbonyl group with DIBAL-H furnished (–)-dihydrocodeine (**183**) in 63 % yield over three steps, which can then be easily transformed into (–)-thebaine (**144**) over 5 steps (Scheme 51).



Scheme 51. Synthesis of (–)-dihydrocodeine (**183**) by OPATZ.

More than 30 synthetic approaches towards morphine have been reported since GATES first attempt.[140] The above mentioned synthetic approaches represent just a few but very important examples, selected based on their historical relevance and their similarities with the research work herein described.

3.2 Aim of the Research

Due to their properties and applications, morphinans represent very important synthetic targets in organic chemistry. Although there are numerous reports on this field, new approaches or improvements to the existing methods are necessary in order to achieve more efficient routes than compete with the low-cost isolation of these compounds from natural sources. Motivated by these facts and with the aim of continuing the investigation on the rearrangement of nitrile stabilized ammonium ylides, a synthetic route for the preparation of 1-veratryloctahydroisoquinolines **184**, implementing the STEVENS rearrangement as a key step, was proposed. This precursor was selected since it could be converted either to the morphine intermediate dihydrodesoxycodeine-C methyl ether (**185**)[141,145] via HECK cyclization, or to morphinan **186** via GREWE cyclization.[146]

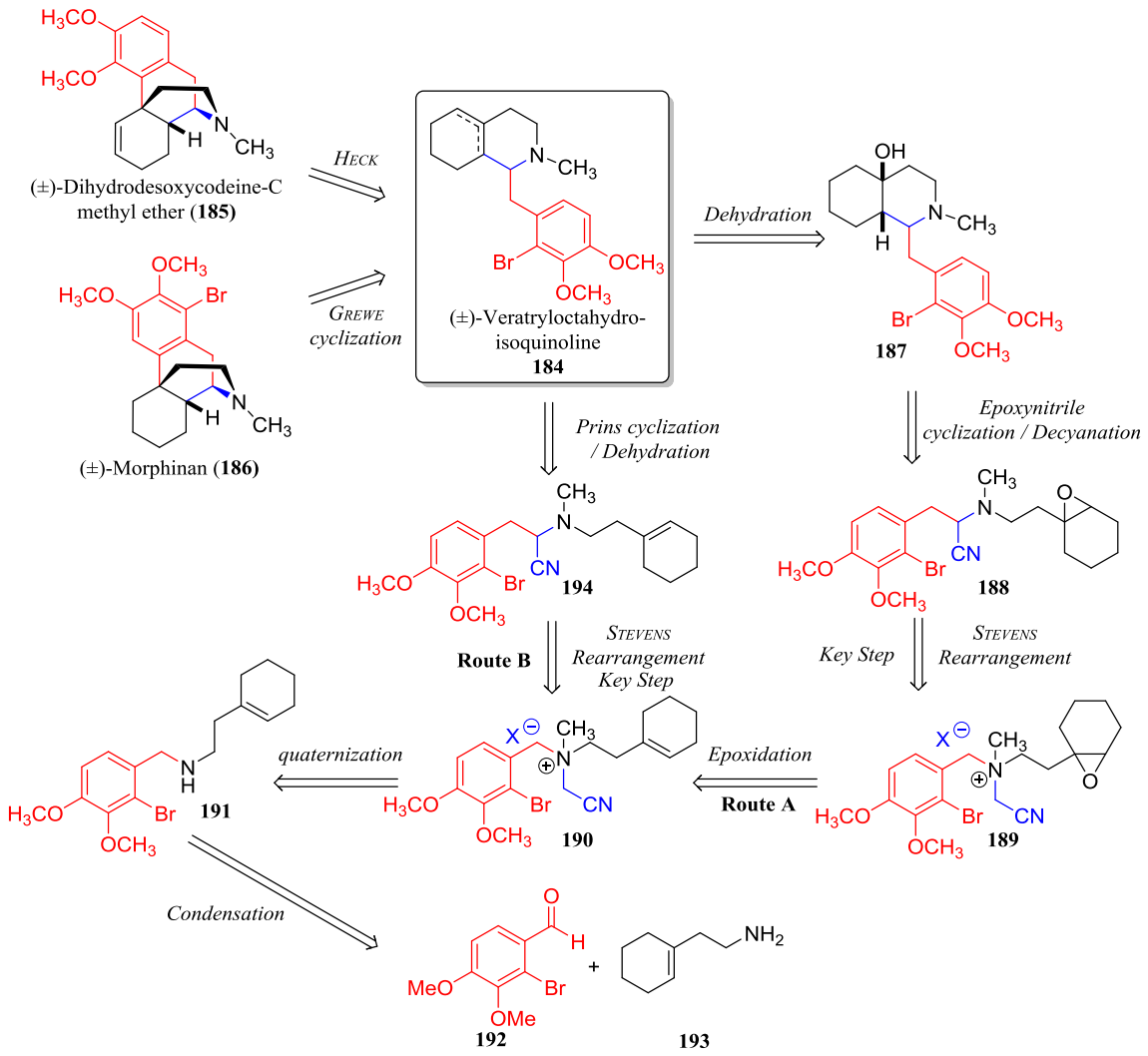


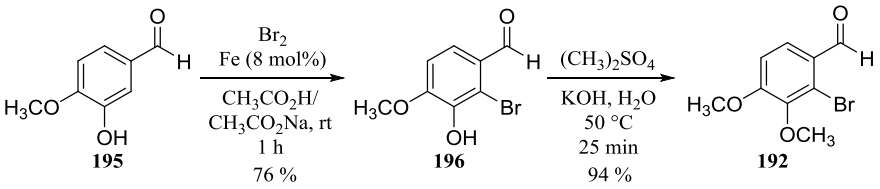
Figure 19. Retrosynthetic analysis for the preparation of 1-veratryloctahydroisoquinoline **184**.

By this manner, alcohol **187** might afford the 1-veratryloctahydroisoquinoline **184** via dehydration reaction following route A. This alcohol could be prepared in an epoxynitrile cyclization/decyanation process from α-amino nitrile **188**, which corresponds to the product of the STEVENS rearrangement of α-ammonium nitrile **189** as key step of the synthetic route. Compound **189** could be delivered by epoxidation of salt **190**, preceded by N-quaternization of amine **191** and condensation of veratraldehyde **192** and 2-(1-cyclohexenyl)ethylamine (**193**). A second approach (route B) based on a direct STEVENS rearrangement of salt **190**, followed by an Aza-PRINS cyclization/dehydration sequence of α-ammonium nitrile **194** is also proposed.

3.3 Results and Discussion

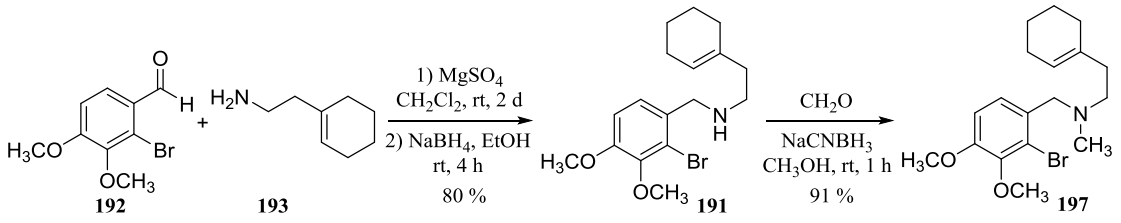
3.3.1 Synthesis of α-Ammonium Nitrile Salt 190

The synthesis of α-ammonium nitrile salt **190** began with the preparation of 2-bromoveratraldehyde (**192**). For this purpose, isovanillin (**195**) was brominated with bromine in buffered acetic acid/sodium acetate solution and iron powder (8.2 mol%) to produce 2-bromoisovanillin (**196**) in 76 % yield.[147,148] This compound was then subjected to methylation with dimethyl sulfate to afford the desired 2-bromoveratraldehyde (**192**) in 94 % yield (Scheme 52).



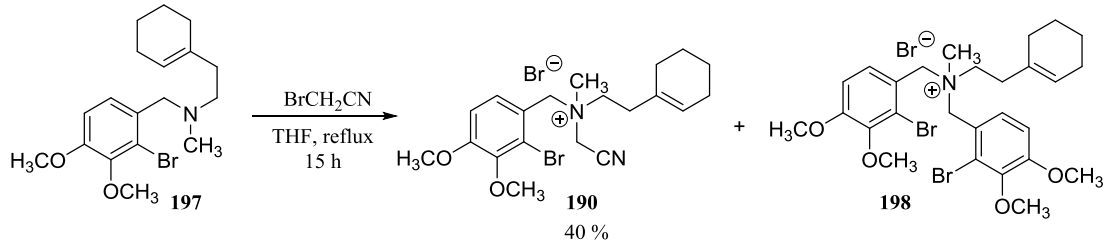
Scheme 52. Synthesis of 2-bromoveratraldehyde (**192**).

In line with the synthetic plan, 2-bromoveratraldehyde (**192**) and 2-(1-cyclohexenyl)ethylamine (**193**) were subjected to an indirect reductive amination process, delivering amine **191** in good yields.[149] Methylation of this product with formaldehyde and $NaCNBH_3$ gave N-methylamine **197** in 91 % yield (Scheme 53).



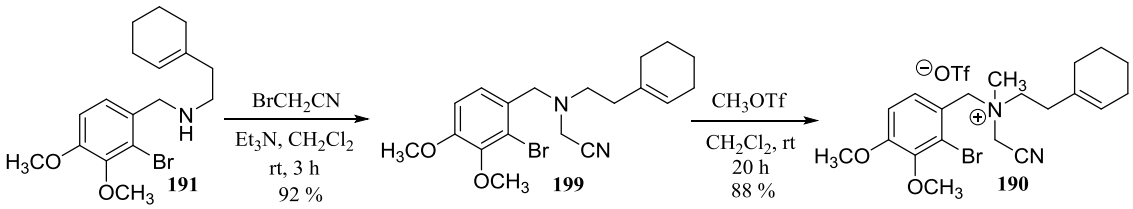
Scheme 53. Synthesis of N-methylamine **197**.

N-methylamine **197** was then treated with commercially available bromoacetonitrile in order to generate the title salt **190**. Thus, salt **190** was obtained in 40 % yield after purification by flash column chromatography. LC-MS analysis of the crude product showed that compound **190** (*m/z* = 407.1) was obtained along with a potential debenzylated salt **198** (*m/z* = 596.1). This side product might be the result of a bromide-induced debenzylation followed by reaction with the excess amine (Scheme 54).



Scheme 54. Unsatisfactory formation of salt **190**.

Aiming to avoid the formation of side product **198**, a different approach involving the N-alkylation of amine **191** with bromoacetonitrile, followed by quaternization with methyl triflate, was performed (Scheme 55).



Scheme 55. Synthesis of ammonium salt **190**.

By this manner, α-aminonitrile **199** was obtained in 92 % yield as block crystals after purification by recrystallization from n-heptane (Figure 20). The corresponding ammonium salt **190** was successfully produced in 88 % yield as a foam after purification by flash column chromatography.

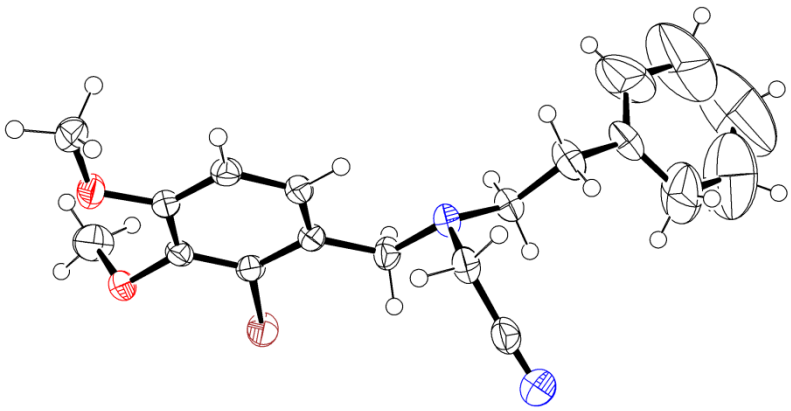
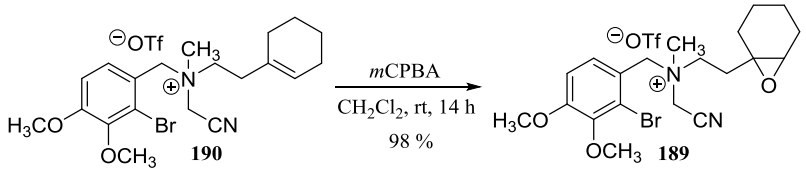


Figure 20. Crystal structure of α-aminonitrile **199** at 193 K (ORTEP, thermal ellipsoids at 50% probability).

3.3.2 Route A. STEVENS Rearrangement/Epoxynitrile Cyclization Sequence

Once ammonium salt **190** was obtained in good yields, it was transformed into epoxynitrile **189** by epoxidation with *m*-chloroperoxybenzoic acid (*m*CPBA) in dichloromethane. Remarkably, purification of epoxide **189** was easily achieved by washing the crude product with diethyl ether to afford a clean product in 98 % yield (Scheme 56). ^{1}H NMR of this epoxide showed that the compound was obtained as a mixture of diastereomers in a 54 : 46 ratio.



Scheme 56. Synthesis of epoxide **189**.

With epoxide salt **189** in hand, the next stage corresponded to the investigation on the STEVENS rearrangement of nitrile stabilize ammonium ylides as the key step of the synthetic plan. In line with these words, salt **189** was initially subjected to standard deprotonation with KHMDS in THF at 0 °C. After 2 h of stirring the reaction at 0 °C, TLC and LC-MS analysis revealed a complete conversion of the starting material and the formation of two isomeric major products. ^{1}H NMR of the crude reaction mixture showed that these two products were obtained in a 62 : 38 ratio (see Figure 21 and Table 10).

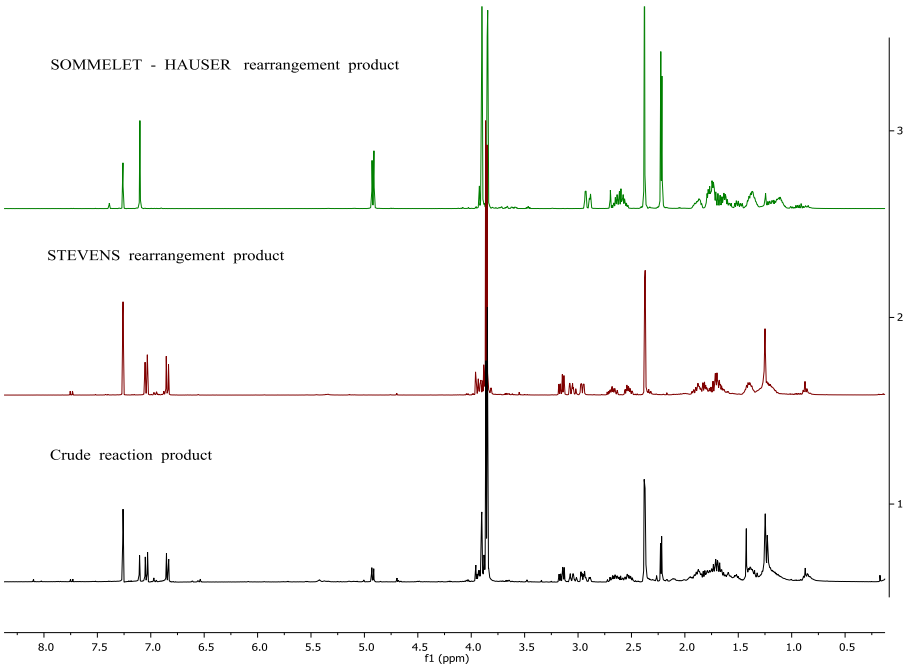
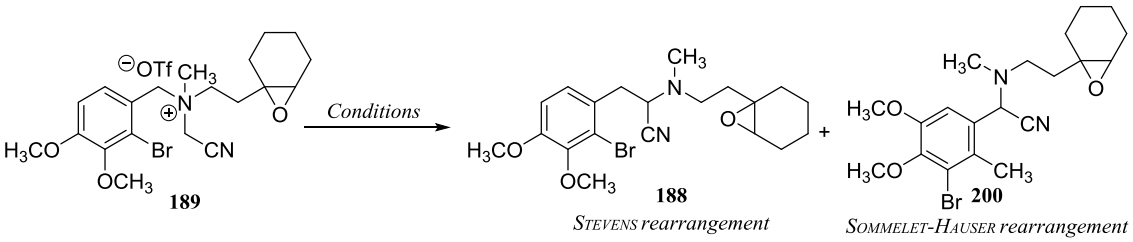


Figure 21. NMR of the rearrangement products **188** and **200**.

Purification by flash column chromatography afforded the two compounds along with several others side products that were not observed before purification (suggesting the instability of the compounds through this purification technique). After NMR analysis, the major component was identified as the expected STEVENS rearrangement adduct **188** and the minor constituent as a SOMMELET-HAUSER rearrangement product **200**. Both compounds were obtained as diastereomeric mixtures in ratios of approx. 1 : 1. The competing SOMMELET-HAUSER product **200**, although interesting, does not present any synthetic utility in this case and is hence considered as undesired. Thus, different reaction conditions were tested in order to obtain a higher product ratio towards the formation of the STEVENS rearrangement compound **188**. The results are summarized in Table 9.

Table 9. Rearrangement products of salt **189**.



Entry	Base	Eq. of Base	Solvent	Temperature	Reaction Time (min)	188/200 ratio (%)[a]
1	KHMDS	1.1	THF	0 °C	120	62 : 38[b]
2	KHMDS	1.1	THF	–20 °C→0 °C	120	28 : 72[b]
3	KHMDS	1.1	THF	rt	30	68 : 32[b]
4	KHMDS	1.1	THF	0 °C→rt	120	72 : 29[c]
5	KHMDS	1.5	THF	0 °C→rt	20	75 : 25[c]
6	KHMDS	1.1	Benzene	0 °C→Reflux	120	100 : 0[b]
7	KHMDS	1.1	Toluene	0 °C	120	—[b,d]
8	KHMDS	1.2	Toluene	rt→Reflux	60	100 : 0[b]

[a] Determined by ^{1}H NMR of the crude material. [b] A solution of KHMDS was added dropwise to a stirred solution/suspension of **189**. [c] A solution of **189** was added dropwise to a stirred solution of KHMDS. [d] Product was not detected, just starting material was observed.

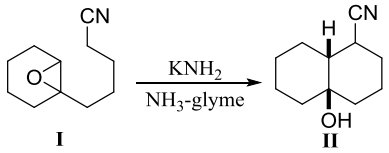
As shown in Table 9, KHMDS was used as standard base for deprotonation in all tested reactions. It was observed that by lowering the reaction temperature to –20 °C for 90 minutes and then stirring for additional 30 minutes at 0 °C, product ratio **188**/**200** changed in favor of the formation of the SOMMELET-HAUSER rearrangement product **200** (entry 2). Performing the reaction at room temperature favored the formation of the STEVENS rearrangement product **188** as the major component (entry 3). By inverting the addition mode of KHMDS/salt **189** (see

Table 9 footnote [c]) and keeping the initial temperature at 0 °C followed by gradual increased to room temperature, the formation of compound **188** was slightly improved (entry 4), however, the ratio was still not satisfactory. Similar results were observed by using 1.5 equivalents of KHMDS (entry 5). A very interesting result was obtained when benzene was used as solvent instead of THF, in combination with the initial addition mode of KHMDS/salt **189** (see Table 9 foot note [b]). By this manner, compound **188** was obtained as a sole product without detection of product **200** (entry 6). In order to enhance the solubility of KHMDS, as well as to use a less harmful solvent, benzene was replaced by toluene. It was observed that if the reaction is performed at 0 °C, the product formation does not occur (entry 7). However, if the addition of KHMDS is made at room temperature and then refluxed, STEVENS rearrangement product **188** could be obtained as the sole product (entry 8). This entry represents the best reaction conditions for the STEVENS rearrangement reaction.

In general, the results listed in Table 9 show a very interesting tendency for the transformation of ammonium salt **189** into compound **188** or **200**. For instance, it was observed that low temperatures (–20 °C) tend to favor the formation of the SOMMELET-HAUSER product **200** while high temperatures (room temperature, reflux) increased the formation of the STEVENS product **188**. Furthermore, it is important to highlight the strong influence that nonpolar solvents such as toluene and benzene had in the generation of **188** over **200**, in contrast with results obtained with THF as a polar solvent.

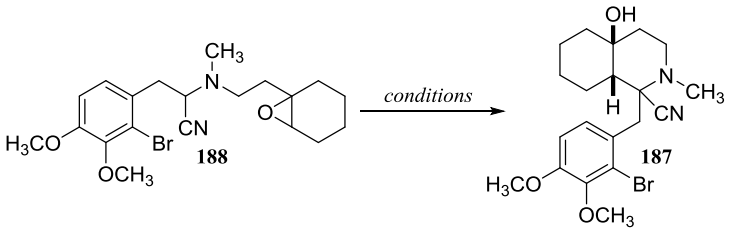
It is well known that the selectivity between STEVENS and SOMMELET-HAUSER rearrangement depends on the electronic effects of the substituents on the aromatic ring, the reaction temperatures and the choice of solvent.[85,150] For instance, when electron-donating or weak electron-withdrawing groups are present at the *para*- or *ortho*-position of the benzylic moiety, the SOMMELET-HAUSER dominates the reaction's scenario (HAMMETT constants, $\sigma_p < 0.23$). On the other hand, strong electron withdrawing groups favor the Stevens products (Hammett constants, $\sigma_p > 0.60$).[150,151] Surprisingly, in the case of ammonium salt **189**, the methoxy-group at the *para*-position of the benzylic moiety seems to have no positive influence towards the formation of the SOMMELET-HAUSER product **200**. In fact, it appears that the controllability of the reaction highly depends on the proper selection of the conditions.

Moving forward to the next synthetic step, the epoxynitrile cyclization of epoxy-α-aminonitrile **188** was investigated (Table 10). This type of cyclization was reported in 1974 by STORK and co-workers,[152] and consists in a base-induced intramolecular cyclization of a cyclohexene oxide pentanitrile (I) to a 5-hydroxydecalin-1-carbonitrile (II, Scheme 57).



Scheme 57. STORK cyclization.

Table 10. Cyclization of epoxy-α-aminonitrile **188** into 4a-hydroxydecahydroisoquinoline **187**.



Entry	Base	Eq. of Base	Solvent	Additive	Temperature	Reaction Time (h)	Product[a]
1	KHMDS	2.5	Toluene	—	Reflux	18	—[b,c]
2	KHMDS	3.0	THF	—	–78 °C→rt	48	—[b,c]
3	KHMDS	2.5	THF	—	rt	24	—[b,c]
4	KHMDS	2.5	THF	—	Reflux	18	—[b,c]
5	LDA	2.5	THF	—	–50 °C→rt	6	Decomp.[b]
6	KHMDS	2.5	Toluene	LiCl (1.1 eq.)	Reflux	18	—[b,c]
7	KHMDS	2.5	Toulene	$PdCl_2$ (10 mol%)	0 °C	24	—[b,c]
8	KHMDS	2.5	Toluene	$BF_3{\cdot}OEt_2$ (2.0 eq.)	–78 °C→rt	18	Decomp.[b]
9	KHMDS	3.0	THF	$BF_3{\cdot}OEt_2$ (3.0 eq.)	–78 °C→rt	48	Decomp.[b]
10	KHMDS	2.5	Toluene	$InBr_3$ (1.0 eq)	Reflux	48	Decomp.[b]
11	KHMDS	2.5	THF	$InBr_3$ (1.0 eq)	rt	18	Decomp.[b]
12	KHMDS	3.0	THF	TBSCl (2.0 eq.), HMPA (2.0 eq.)	–78 °C→rt	18	—[b,c]
13	KHMDS	3.0	THF	TBSCl (2.0 eq.), HMPA (2.0 eq.)	Reflux	18	Decomp.[b]

[a] Determined by ^{1}H NMR, TLC, and LC-MS of the crude material. [b] A solution of the base was added dropwise to a stirred solution of **188**. [c] Product was not detected, only starting material was observed.

Initially, compound **188** was subjected to deprotonation conditions using KHMDS, toluene or THF as a solvent at variable temperatures (entries 1–3). In these cases, no desired product was detected; only complete recovery of α-aminonitrile **188** was achieved. The use of LDA as base afforded only decomposition of the starting material, including debrominated products, proving

the unsuitability of this base for the transformation (entry 5). Taking into account that LiCl, $PdCl_2$, $BF_3{\cdot}OEt_2$, and $InBr_3$ are known to assist the epoxide ring openings under basic conditions, they were used as additives in the reaction of α-aminonitrile **188** (entries 6–11).[153,154] Unfortunately, no desired product was detected in any case. Attempts to trap the alkoxy group generated after ring opening with TBSCl also failed (entries 12–13).

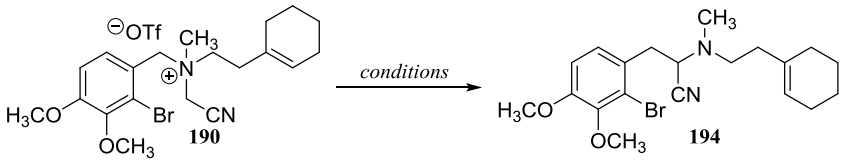
Despite the efforts, the epoxynitrile cyclization of compound **188** into **187** was not achieved. These results might be explained considering the type of substrate, where the generated carbanion and the carbon at the oxirane ring do not fulfill the specific geometry (*collinearity*) requirements to perform the corresponding S_N2 ring opening reaction (high endocyclic restrictions).[155]

3.3.3 Route B. STEVENS Rearrangement/Aza-PRINS Cyclization Sequence

Based on the inability to obtain the corresponding decahydroisoquinoline core by the epoxynitrile cyclization reaction, the focus of the investigation shifted into the alternative route B which involved a STEVENS rearrangement of ammonium salt **190** followed by its corresponding Aza-PRINS cyclization.

For this purpose, ammonium salt **190** was initially subjected to the standardized deprotonation conditions used for salt **189** (Table 11). TLC and ^{1}H NMR analysis of the crude product showed the formation of the expected STEVENS rearrangement along with some unidentified side products (entry 1). In order to improve this result, a small optimization of the reaction was performed. The best reaction conditions were obtained when solid KHMDS was added in one portion to an insolubilized mixture of salt **190** in toluene at –10 °C, followed by reflux (entry 3). By this manner, α-aminonitrile was delivered in 87 % yield (determined by ^{1}H NMR using CH_2Br_2 as internal standard). Attempts of purification of compound **190** by flash column chromatography resulted in product decomposition, as described also above for α-aminonitrile **188**. α-Aminonitrile **190** was therefore used without further purification or used in the next step without isolation.

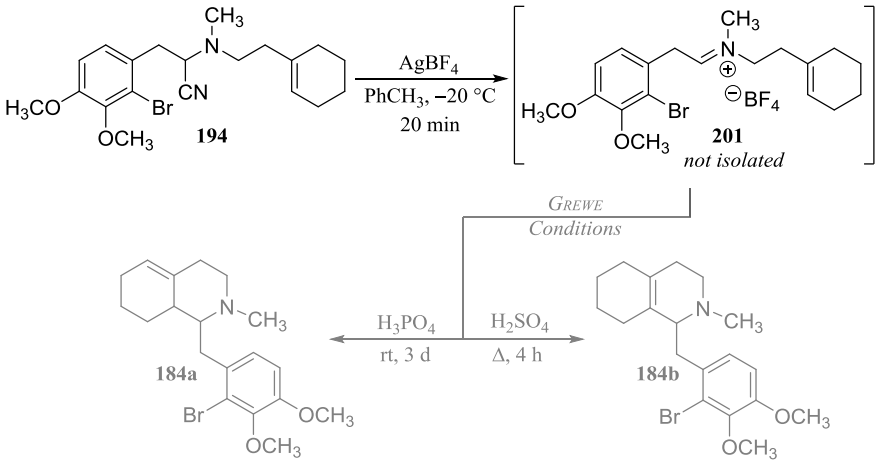
Table 11. Synthesis of α-aminonitriles **194**.



Entry	Base	Eq. of Base	Solvent	Temperature	Reaction Time (h)	Yield (%)[a]
1	KHMDS	1.2	Toluene	rt→Reflux	1	77[b]
2	KHMDS	1.2	Toluene	0 °C→Reflux	1	83[b,c]
3	KHMDS	1.2	Toluene	–10 °C→Reflux	1	87[b,c] (75)[d]

[a] Determined by 1H NMR and by using CH_2Br_2 as an internal standard. [b] A solution of KHMDS in toluene was added dropwise to an insolubilized mixture of **190** in toluene. [c] Solid KHMDS was added in one portion to an insolubilized mixture of **190** in toluene. [d] Isolated yield

After optimization, α-aminonitrile **194** was subsequently decyanated with $AgBF_4$ to produce iminium ion **201**. Isolation of this iminium salt was not attempted, however, its formation was corroborated by TLC and LC-MS reaction monitoring (Scheme 58). Iminium salt **201** represents the key intermediate for an Aza-PRINS cyclization. In fact, GREWE and co-workers have reported a seminal paper describing this type of cyclization induced by mineral acids on debrominated analogous of compound **201**. They observed that by performing the reaction in pure H_3PO_4 (80 %) at room temperature, the kinetic dehydration product **184a** (double bond at C-4a,C-5) can be afforded. On the other hand, if H_2SO_4 (50 %) is used instead and the reaction is heated (steam bath), the isomeric double bond at C4a,C8a is then obtained (Scheme 58, gray).

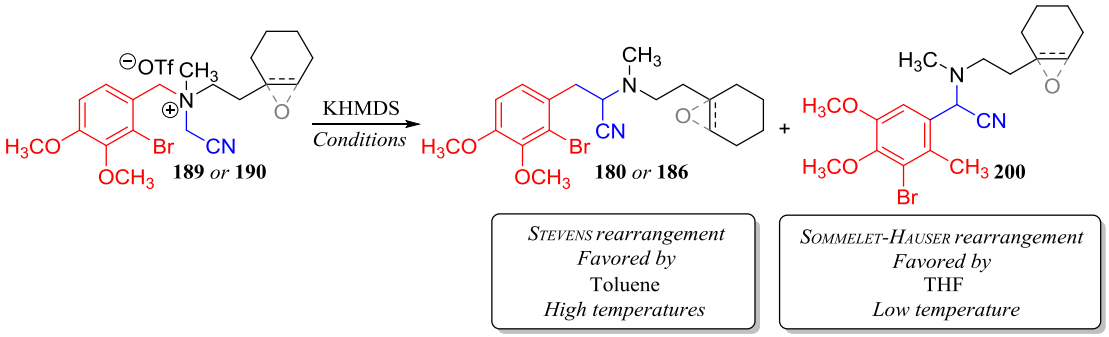


Scheme 58. Synthesis of iminium salt **201** and potential pathways through GREWE reported conditions.

A few attempts were performed based on these reported conditions; however, octahydroisoquinolines **184** were not obtained. A more detailed investigation might be necessary in order to give a final verdict about this reaction.

3.4 Conclusions

In general, it was demonstrated that the STEVENS rearrangement of nitrile-stabilized ammonium ylides is a suitable method for the synthesis of the key intermediates **188** and **194**. Furthermore, it was shown that the controllability on the rearrangement outcome highly depends on the proper selection of the reaction conditions and not only on the electronic characteristics of the migrating benzyl group. Thus, for example, THF (polar aprotic solvent) and low temperatures (–20 °C) favor the formation of the SOMMELET-HAUSER rearrangement product, while toluene (non-polar solvent) and high temperatures (reflux) favor the formation of the STEVENS rearrangement product (Scheme 59).



Scheme 59. Rearrangement outcome dependency on reaction conditions.

Although the synthesis of the octahydroisoquinolines **184** from iminium salt **201** could not be accomplished, the seminal work of GREWE and co-worker on this type of olefin-iminium cyclization clearly shows the high probability for this transformation to occur. Therefore, it would be worth to consider continuing with the investigation on this type of cyclization on substrate **201** to generate veratryloctahydroisoquinolines **184**. The further development and successful implementation of the described reaction pathway would allow the synthesis of morphinan **186** and morphine intermediate dihydrodesoxycodeine-C methyl ether (**185**).

Part II

Visible Light Photocatalysis: Oxidative Generation of Iminium Ions from Tertiary Amines

Sunlight is one of the most abundant and powerful energy sources in nature, which is used by organisms such as cyanobacteria, algae, and plants to transform carbon dioxide and water into oxygen and carbohydrates in a process called photosynthesis.[156] Although the chemical principles of photosynthesis have been known since the 19th century, it was not until 1912 that an Italian chemist named Giacomo CIAMICIAN recognized the key-importance of photochemistry for the future production of organic molecules based on the principle of light-induced chemical transformations.[157] Since this early work, many successful light-induced reactions have been developed, however their applicability compared to the classical thermally-induced reactions still remains very limited. One major problem lies on the fact that most organic molecules do not absorb photons in the visible light region (λ = 400–650 nm) and therefore, UV light (λ = 200–300 nm) has to be used to promote the chemical transformation. This represents a disadvantage since just 3 % of the solar energy that penetrates the atmosphere corresponds to UV light.[158] Moreover, UV photons are highly energetic (E = 116 kcal/mol at 250 nm), possessing enough energy to break most of the C–C, C–H, C–O bonds (E = 85, 100, 100 kcal/mol respectively), and others, thus potentially causing decomposition reactions by unselective bond breaking.[159]

To overcome this limitation, photochemists have developed an alternative method in which a photon absorbing species (photocatalyst), upon irradiation, is able to transfer the absorbed

energy to a substrate or reagent, which then performs a chemical reaction. This is denominated photocatalysis and although this is not a new concept in photochemistry, a resurgence and vast development of this field has been observed in the last decade. Much of this attention is due to the possibility of transforming visible light into chemical energy under mild conditions by catalytic amounts of readily available transition metal polypyridyl complexes, semiconductors and organic dyes.[160] More importantly, since photons from visible light are less energetic than UV photons, more selective, predictable and easy to control reactions can be achieved.

The interaction of a photocatalyst with the substrate takes place mostly by two modes of action: single electron transfer (SET) or energy transfer processes (ET, Figure 22).[161] In the first case, the photocatalyst (PC_{S0}) is first photo-excited in the ground state by an appropriate wavelength, affording an excited species PC^*_{T1}, which can act as a strong oxidant or as a strong reductant. When species PC^*_{T1} is acting as an oxidant, it can produce the reduced photocatalyst (PC_{Red}) by accepting an electron from an electron-rich substrate ($Subs_D$), which is then converted into a radical cation ($Subs_D^{\bullet\oplus}$). This radical cation can release a radical or a cationic intermediate to be used in further chemistry. The catalytic cycle is then closed when the reduced photocatalyst (PC_{Red}) donates an electron to an electron-deficient species (A) and the ground state photocatylst (PC_{S0}) is regenerated. Additionally, PC^*_{T1} can also act as a reductant by donating an electron to an electron-deficient substrate (S_A). This interaction produces the oxidized photocatalyst (PC_{Ox}) and the radical anion ($Subs_D^{\bullet\ominus}$), which can be used in further chemistry by undergoing a mesolytic cleavage and releasing a radical. The oxidized photocatalyst (PC_{Ox}) can then accept an electron from an electron-rich species (D), reestablishing the ground state photocatalyst (PC_{S0}) and completing the catalytic cycle (Figure 22a).

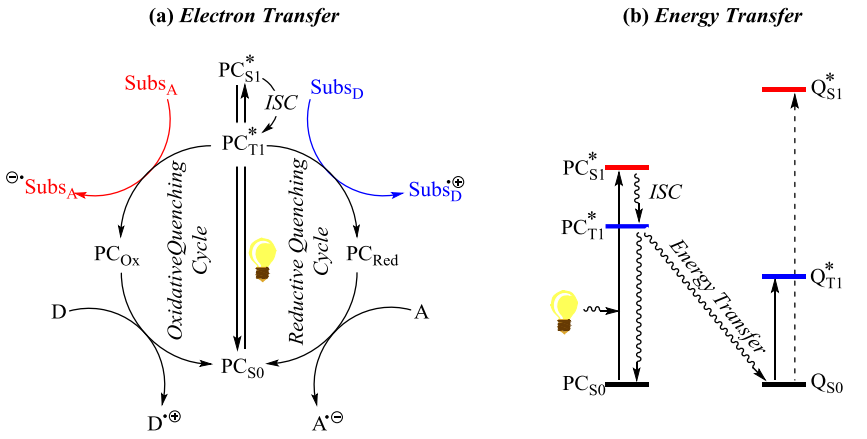


Figure 22. Photocatalysis modes of action: a) Electron transfer. b) Energy transfer.

In the case of an energy transfer process, a substrate (Q_{S0}) with a low energy triplet state is activated by the excited species PC^*_{T1} via collisional exothermic energy and spin exchange. As a result of this interaction, the PC^*_{T1} species returns to the ground state (PC_{S0}) and more importantly, the substrate gets excited to its triplet state (Q^*_{T1}). It is in this excited state that the substrate can participate in subsequent chemical reactions (Figure 22b).

Photocatalysts

The most extensively studied and widely used photocatalysts are complexes of ruthenium and iridium with polypyridyl ligands, and organic dyes (Figure 23), which are well-known for their high photocatalytic activity under irradiation with visible light.[162-164]

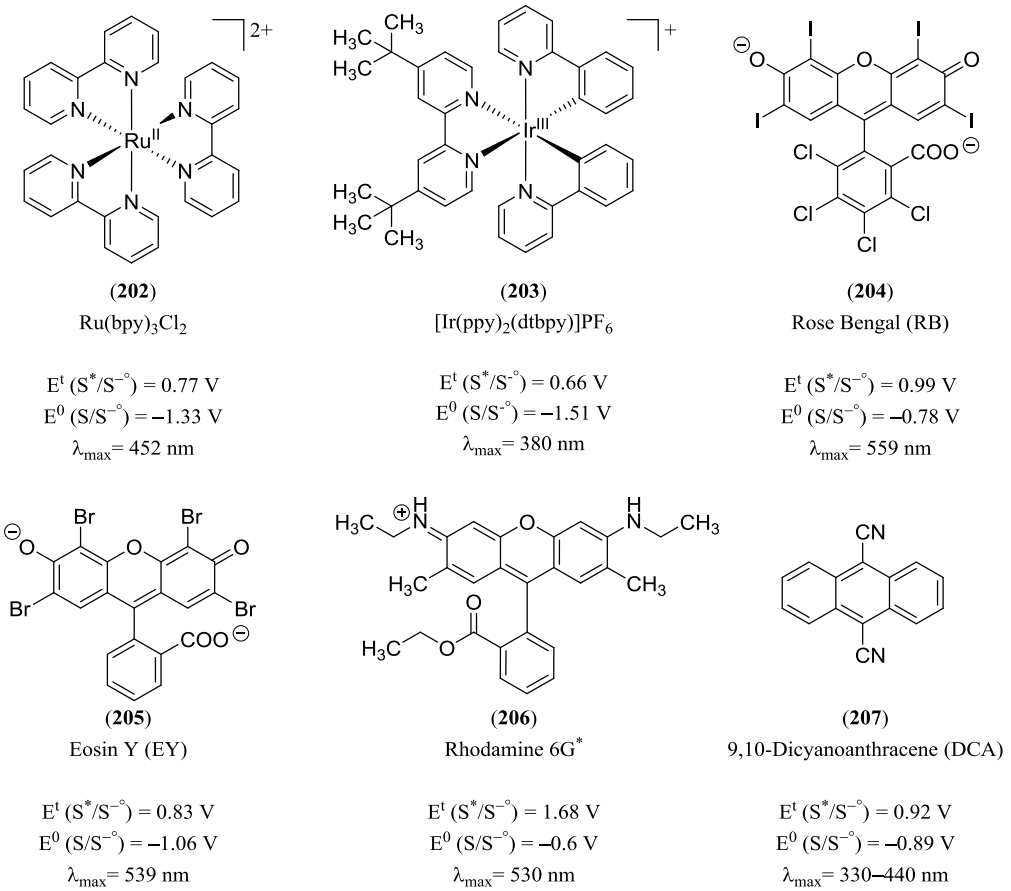


Figure 23. Photocatalysts and their redox potentials for the reductive quenching cycle in MeCN vs. SCE or NHE*.[164-167]

The mode in which a photocatalyst interacts with light can be represented in a JABLONSKI diagram (Figure 24). Upon irradiation, a singlet excited state species PC^*_{Sn} is formed by

excitation of the photocatalyst (PC_0) to the higher energy vibrational levels. This excited state species is then relaxed to the lowest vibrational level of the first singlet excited state PC^*_{S1} via internal conversion (IC). The singlet ground state PC_{S0} can be regenerated from the singlet excited state PC^*_{S1} via a spin-allowed radiative pathway (fluorescence, $h\nu_F$) or by a non-radiative pathway (K_{nr}). Additionally, PC^*_{S1} can also be deactivated by conversion to the lowest energy triplet excited state PC^*_{T1} via successive fast intersystem crossing (ISC) (spin orbital coupling). The triplet excited state is reasonably long lived, because the transition from PC^*_{T1} to the singlet ground state PC_{S0} is spin forbidden. The ground state PC_{S0} is finally regenerated by radiative deactivation (phosphorescence $h\nu_P$) or by non-radiative deactivation of the species PC^*_{T1}. In the case of a substrate being present, PC^*_{T1} could be quenched by singlet electron transfer or energy transfer processes (see Figure 22).[161]

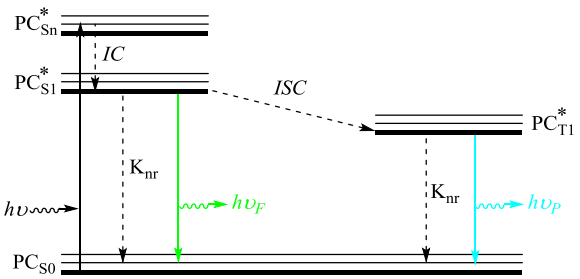
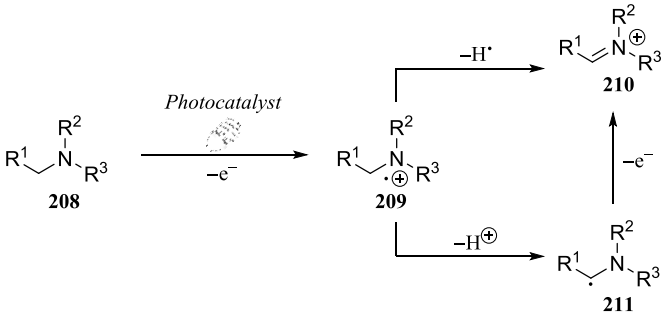


Figure 24. JABLONSKI diagram for a photocatalyst (PC).

Heavy atoms facilitate the intersystem crossing to lower excited triple states, thus enhancing the phosphorescence quantum yields.

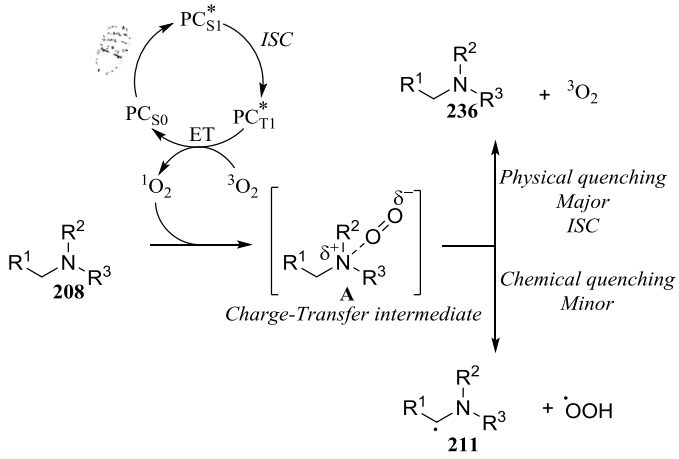
Formation of Iminium Ions

Tertiary amines (**208**) are good and very well-known electron donors which can easily undergo single electron oxidations. In photocatalysis, they usually interact with an excited photocatalyst (PC^*_{T1}) to generate a stronger reducing agent (PC_{Red}), or with an oxidized photocatalyst (PC_{Ox}) to close the oxidative catalytic cycle and deliver the ground state PC_{S0} (see Figure 22).[158,162] In both cases tertiary amines are converted to aminium radical cations **209** allowing the decrease of the bond dissociation energy of the C–H bonds as well as the pKa of the protons at the amine α-positions. Depending on the reaction conditions, radical cations **209** can undergo a hydrogen atom abstraction in the presence of good hydrogen acceptors to iminium ions **210** or can be deprotonated to α-amino radicals **211**. This radical species can undergo a second single-electron transfer, thus affording iminium ions **210** in another fashion (Scheme 60). [153,157]



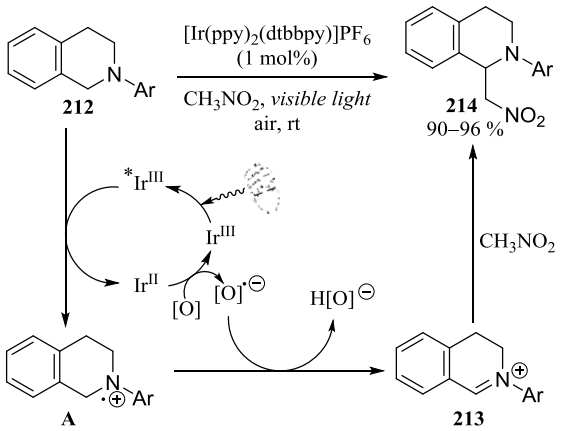
Scheme 60. Photo-oxidation of tertiary amines to iminium ions.

Another photochemical method to generate iminium ions from tertiary amines is via photosensitized singlet oxygen ($^1O_2$). In this indirect photo-oxidation, the photocatalyst initially interacts with triplet oxygen ($^3O_2$) in an energy transfer (ET) process to generated singlet oxygen ($^1O_2$). The latter species then reacts with the tertiary amine through an intermediate charge transfer complex **A** affording α-amino radical **211** which by losing an electron generates the corresponding iminium ion **210** (Scheme 61).[168,169]



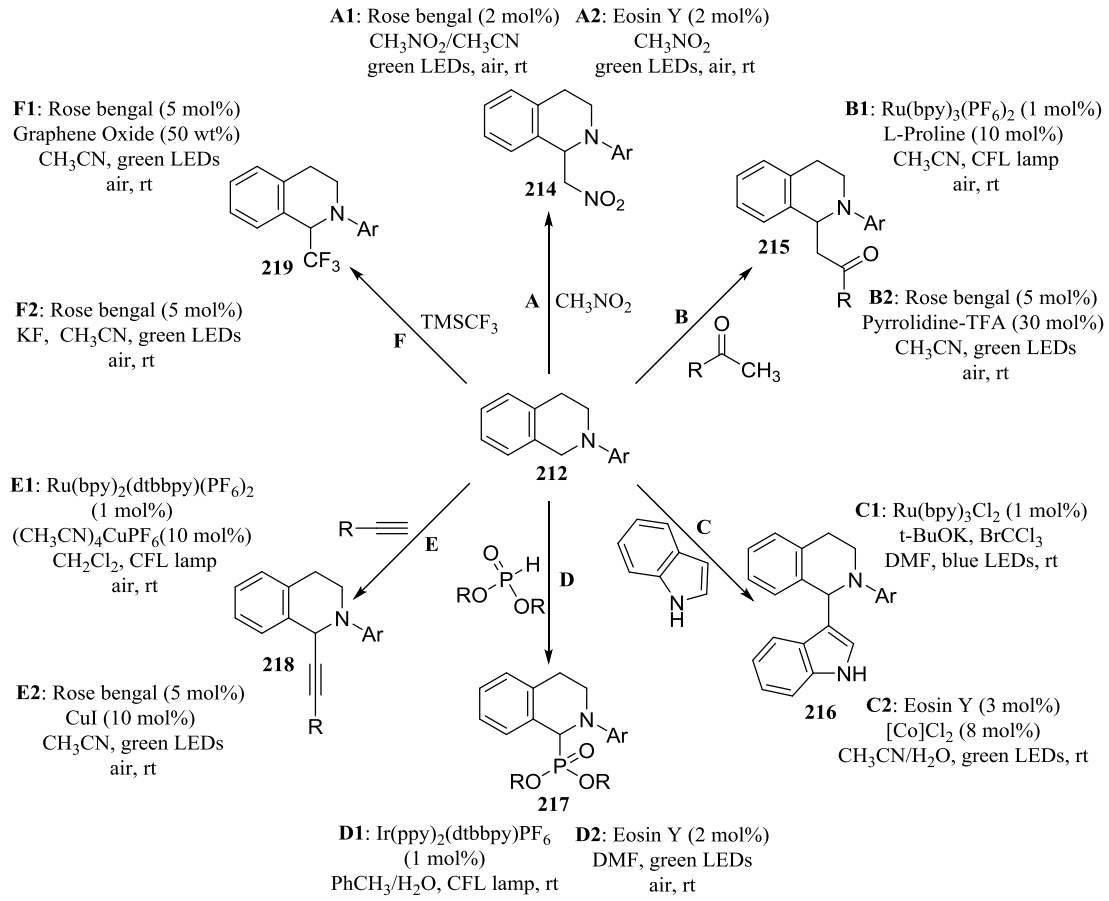
Scheme 61. Indirect photo-oxidation of tertiary amines by photosensitized singlet oxygen ($^1O_2$).

For many years, the role of tertiary amines was, with some exceptions,[170-172] mostly limited to sacrificial electron donors. It was not until early 2010, that STEPHENSON and co-workers reported the first incorporation of tertiary amines as synthetic targets in a visible light photocatalyzed aza-HENRY reaction.[173] In this case, N-aryltetrahydroisoquinolines **212** were photo-oxidized to the corresponding iminium ions **213** via SET under aerobic conditions with the excited iridium photocatalyst; $[Ir(ppy)_2(dtbbpy)]PF_6$ (**195**). Subsequently, these iminium ions were intercepted by nitromethane anions affording the expected aza-Henry products **214** (Scheme 62).



Scheme 62. Photocatalyzed aza-HENRY reaction.

After this report, several other α-functionalizations have been accomplished by using different metal complexes or organic dyes as photocatalysts. A compilation of these reactions is shown in Scheme 63.[162-164,174-176]



Scheme 63. α-Functionalization of N-aryltetrahydroisoquinolines via trapping of photo-generated iminium ions with nucleophiles.

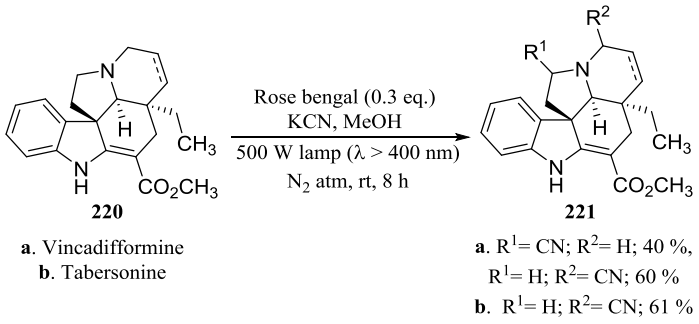
As presented above, although the visible light photo-generation of iminium ions has been investigated extensively for the use of N-aryltetrahydroisoquinolines as substrates, the application of simple tertiary aliphatic amines is rather underexploited and restricted mainly to sacrificial electron donors.

Chapter 4

Visible Light Photocyanation of Tertiary Amines: Application to the Synthesis of (±)-Crispine A, (±)-Harmicine and (±)-Desbromoarborescidine A

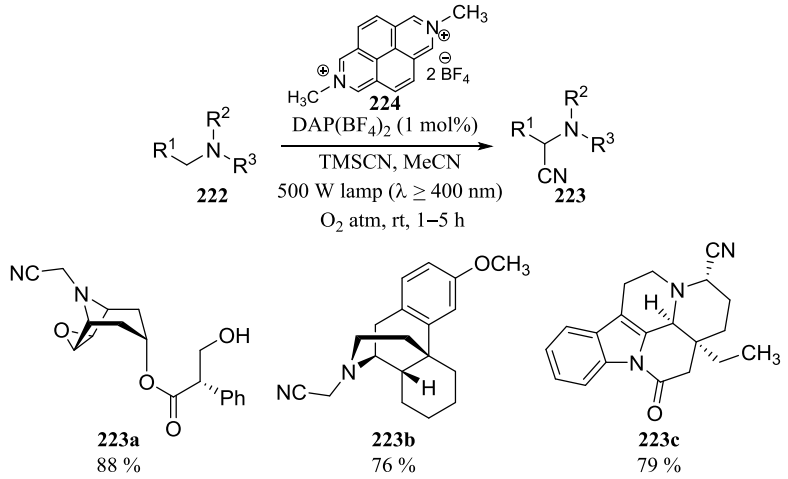
4.1 Introduction

The oxidative α-cyanation of tertiary amines represents a very efficient and straightforward method for the preparation of α-aminonitriles (see General Introduction: Synthetic Methods). Among different catalytic[29,30,33-37] and stoichiometric approaches,[38-41] visible light photocatalysis has emerged as a versatile and promising technique to achieve this transformation. One of the earliest reports on the photocyanation of tertiary amines was described in 1977 by KHUONG-HUU and co-workers.[171] They were able to transform indolizidine alkaloids **220** into α-aminonitriles **221** using rose bengal (**204**) as photocatalyst (0.3 eq.), KCN in methanol, and 8 h of irradiation with visible light (Scheme 64).



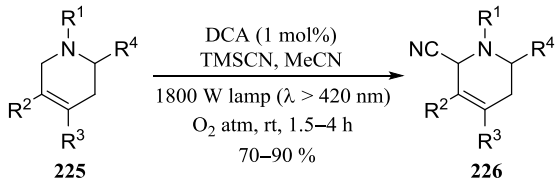
Scheme 64. Photocyanation of indolizidine alkaloids **220**.

Years later, SANTAMARIA et al. reported a very efficient photocyanation of a series of alkaloids **222** using catalytic amounts of *N,N'*-dimethyl-2,7-diazapyrenium-bis-(tetrafluoroborate) ($DAP(BF_4)_2$, **224**) as a photocatalyst.[177] In this case, TMSCN turned out to be superior to cyanide salts due to its solubility in organic solvents such as acetonitrile (Scheme 65).



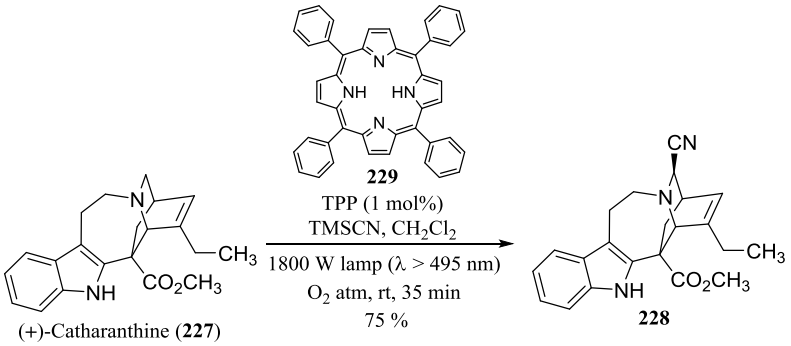
Scheme 65. Synthesis of α-aminonitriles **223** using $DAP(BF_4)_2$ (**224**) as a photocatalyst.

The same author also described that upon irradiation, N-alky-3-piperidines **225** could be transformed into endocyclic α-aminonitriles **226** in the presence of catalytic amounts of DCA (**207**) using TMSCN as cyanide source (Scheme 66).[170]



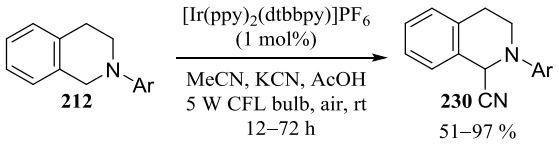
Scheme 66. Photocyanation of N-alkyl-3-piperidines **225** with DCA (**207**) as photocatalyst.

A decade later, FERROUD and co-workers showed that (+)-catharanthine (**227**), in the presence of TMSCN and a catalytic amount of 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine (TPP, **229**) produces (+)-3β-cyanocatharanthine (**228**) in high regio- and diasteroselectivities (de > 99 %).[178] Unlike the other photocyanations described above, this process thought to be mediated by singlet oxygen ($^1O_2$), which is generated by energy transfer of the excited TPP^* to the ground state oxygen molecule (Scheme 67).



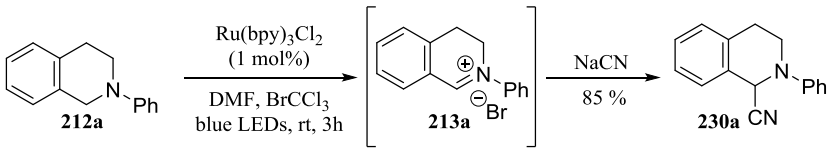
Scheme 67. α-Cyanation of catharanthine **227** induced by photosensitized singlet oxygen ($^1O_2$) with TPP (**229**).

More recently, and applying the latest advances in visible light photocatalysis, RUEPING et al. reported the aerobic α-cyanation of N-aryltetrahydroisoquinolines **212** using KCN, acetic acid, $[Ir(ppy)_2(dtbbpy)]PF_6$ (**195**) as photocatalyst (1 mol%), and a 5 W CFL bulb as source of visible light.[179] By this manner, α-aminonitriles **230** were obtained in 51–97 °% yield (Scheme 68).



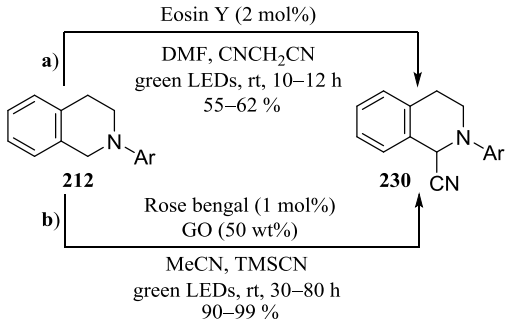
Scheme 68. RUEPING's aerobic photocyanation of N-aryltetrahydroisoquinolines **212**.

STEPHENSON and co-workers published an anaerobic two-step approach towards the preparation of *N*-phenyl-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (**230a**).[180] For this purpose, *N*-phenyl-1,2,3,4-tetrahydroisoquinoline (**212a**) was initially transformed to its iminium salt **213a** using $Ru(bpy)_3Cl_2$ (**202**) as photocatalyst (1 mol%) and $BrCCl_3$ as terminal oxidant instead of oxygen. After full conversion, the iminium salt **213a** was then converted into α-aminonitrile **230a** by addition of NaCN in the absence of irradiation (Scheme 69).



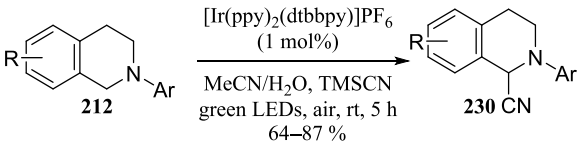
Scheme 69. STEPHENSON's anaerobic photocyanation of amine **212a**.

The use of organic dyes as metal-free counterpart in photocyanations has also been described. For instance, KÖNIG and HARI reported the use of eosin Y (**205**) as photocatalyst in the photocyanation of N-aryltetrahydroisoquinolines **212** with malononitrile as cyanide source and under irradiation with green LEDs (Scheme 70a).[181] Another metal-free catalytic system for the α-cyanation of N-arylamines **230** was developed by TAN and co-workers.[182] In this case, rose bengal (**204**, 5 mol%), graphene oxide, TMSCN and green LEDs irradiation afforded the corresponding α-aminonitriles **230** in high yields (Scheme 70b).



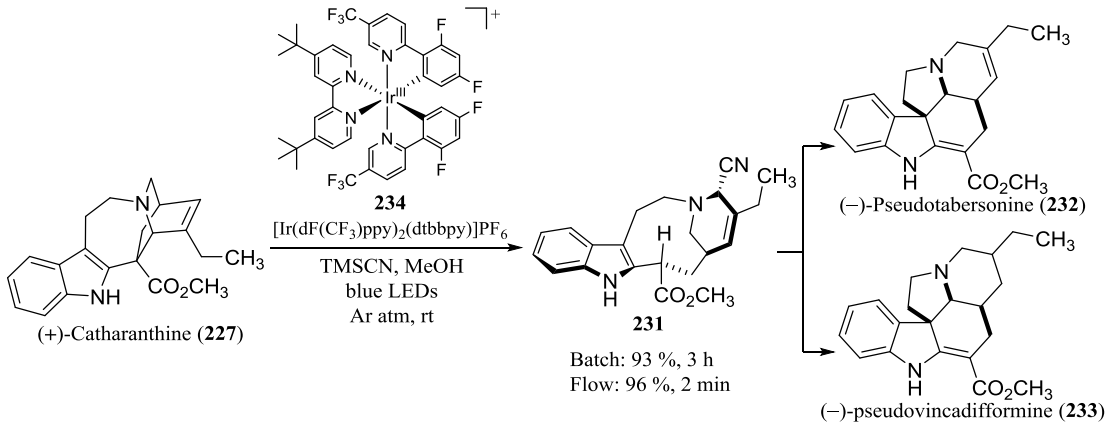
Scheme 70. Metal-free photocyanation of amines **212** catalyzed by a) eosin Y (**205**) or b) rose bengal (**204**).

To overcome the long reaction times associated with batch procedures and to increase the efficiency of light absorption, RUEPING et al. developed a continuous-flow photocyanation of the same type of substrates using green LEDs, rose bengal (5 mol%, **204**), and TMSCN in a acetonitrile/water mixture (Scheme 71).



Scheme 71. Continuous-flow photocyanation.

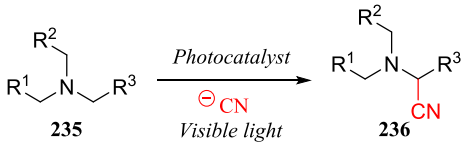
In 2014, STEPHENSON and BEATTY described a fragmentation/α-cyanation of (+)-catharanthine (**227**) in the presence of $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (**234**) and TMSCN.[183] Thus, α-aminonitrile **231** was obtained in 93 % yield after 3 h. In an attempt to improve the reaction time and the scalability, continuous-flow conditions were used allowing the generation of **231** in 96 yield after 2 minutes of residence time . The corresponding α-aminonitrile **231** was used a common intermediate in the synthesis of other natural products (Scheme 72).



Scheme 72. Fragmentation/photocyanation of (+)-catharanthine (**227**).

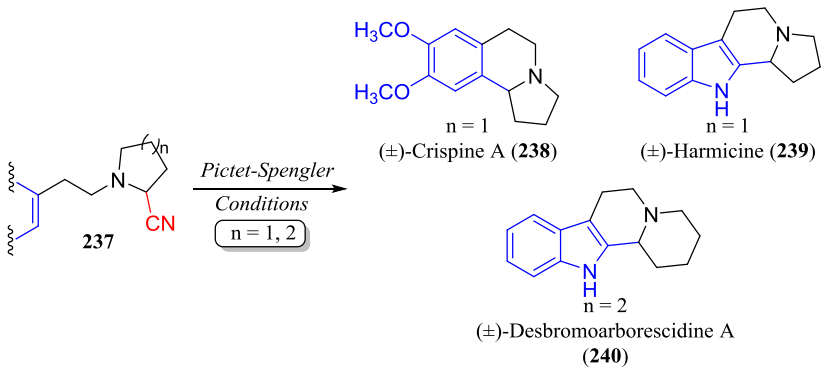
4.2 Aim of the Research

Since the resurgence of visible light photocatalysis in the last decade, the α-photocyanation of tertiary amines has evolved as a mild and selective method towards the oxidative generation of α-aminonitriles. Unfortunately, many of the reported methodologies have been often focused on α-cyanation of N-aryltetrahydroisoquinolines or N,N-dialkylanilines, leaving the use of simpler and more abundant tertiary aliphatic amines, basically unexplored. Motivated by the lack of examples, it was decided to investigate the C(sp^3)–H activation of different tertiary amines **235** as well as to develop an efficient and comprehensive photocyanation method induced by visible light (Scheme 73).



Scheme 73. Proposed photogeneration of α-aminonitriles **236**.

To show the potential applicability of the method, the photogenerated α-aminonitriles of the type **237** were tested as direct precursors of natural products such as (±)-crispine A (**238**), (±)-harmicine (**239**) and (±)-desbromoarborescidine A (**240**), via PICTET-SPENGLER cyclization.



Scheme 74. Potential application towards the synthesis of (±)-crispine A (**238**) and some tetrahydro-β-carboline alkaloids.

4.3 Results and Discussion

4.3.1 Initial Study

The investigation started with the adequate selection of the starting materials, reagents and reaction conditions for the photocyanation. Tributylamine **235a** was chosen as case study in combination with TMSCN in acetonitrile. The reaction was performed in the presence of air and using a standard 24 W household fluorescent bulb as a source of visible light. The standard setup for the reaction is displayed in Figure 25.

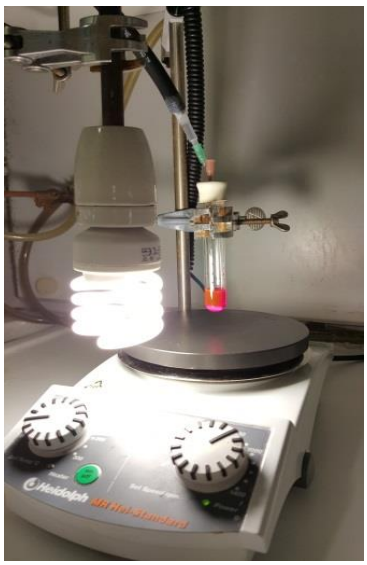
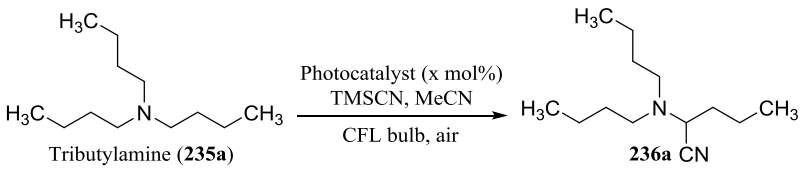


Figure 25. Typical reaction setup for the initial studies.

Table 12 shows the reaction times and yields when a series of photocatalysts were tested for the reaction system described above.

Table 12. Screening of catalyst and reaction conditions.[a]



Entry	Catalyst	MeCN volume (mL)	TMSCN (eq.)	Reaction time (h)	Yield (%)[b]
1	Eosin Y (1 mol%)	5.0	4.0	15	quant.
2	Rhodamine 6G (1 mol%)	5.0	4.0	15	72
3[c]	DCA (1 mol%)	5.0	4.0	15	42

4	Rose Bengal (1 mol%)	5.0	4.0	15	quant.
5	$[Ru(bpy)_3Cl_2]$ 6 H_2O(1 mol%)	5.0	4.0	15	57
6	Eosin Y (1 mol%)	5.0	4.0	3	79
7	Rose Bengal (1 mol%)	5.0	4.0	3	90
8	Rose Bengal (1 mol%)	2.0	2.0	2	59
9	Rose Bengal (1 mol%)	2.0	4.0	3	98
10[d]	Rose Bengal (1 mol%)	2.0	4.0	3	49
11[e]	Rose Bengal (1 mol%)	2.0	4.0	3	10
12	Rose Bengal (1 mol%)	2.5[f]	4.0 (KCN)	3	64
13[g]	Rose Bengal (1 mol%)	2.0	4.0	24	5
14	———	2.0	4.0	3	11
15	———	2.0	4.0	6	38
16	Rose Bengal (0.5 mol%)	2.0	4.0	3	90

[a] Reaction conditions: 210 μmol of tributylamine (1.0 eq.) were used. The reaction mixture was stirred and irradiated with a 24 W fluorescent household bulb at room temperature under air bubbling. [b] Determined by ^{1}H NMR spectroscopy using CH_2Br_2 as internal standard. [c] UV light (λ = 300–400 nm). [d] Air atmosphere, no bubbling. [e] Nitrogen bubbling. [f] 2.0 mL MeCN + 0.5 mL D_2O. [g] No irradiation.

The first step corresponded to the screening of different metal based as well as organic photocatalysts as shown in entries 1–5. Although the product was formed in all cases, eosin Y (**205**) and rose bengal (**204**) afforded quantitative yields after 15 h of irradiation (entries 1 and 4). These two photocatalysts were therefore chosen to continue with the optimization of the reaction conditions. Aiming to evaluate the real time needed for the conversion, the reaction was rigorously monitored by TLC until full consumption was observed. The results indicated that the reaction needs only 3 hours to undergo completion (entries 6 and 7), and that rose bengal (**204**) is a superior catalyst affording α-aminonitrile **236a** in 90 % yield. Eosin Y (**205**) on the other hand, delivered only 79 % yield. Subsequently, additional modification using rose bengal (**204**) as photocatalyst were performed in order to optimize the results further. Unsatisfactory outcomes were initially obtained when the solvent volume and the amount of TMSCN were reduced (entry 8), however, an excellent yield was obtained (98% yield by NMR) when only the volume of the solvent was reduced (2.0 mL) and the equivalents of TMSCN were left unchanged (entry 9). Thereafter, the air bubbling was suppressed and the reaction was carried out only under air atmosphere. Under these conditions the yield decreased significantly (entry 10), which is in agreement with the very low yield obtained under nitrogen atmosphere (entry 11). These observations demonstrate the importance of oxygen in the photocyanation reaction. Control experiments were also performed in the absence of light (entry 12) and catalyst (entries 14 and 15). The results showed that, although an uncatalyzed background reaction takes place, the

combination of light and rose bengal (**204**) is required to obtain good reaction rates and good yields. It was proven that KCN can be used as an alternative cyanating agent, delivering also α-aminonitrile **236a** as main product (entry 12). Nevertheless, the yield observed in this case was significantly lower than with TMSCN (entry 9). Finally, reduction of the catalyst loading to 0.5 mol% still afforded α-aminonitrile **236a** in 90 % yield after only 3 h (entry 16), indicating that even lower catalyst loadings might still be effective.

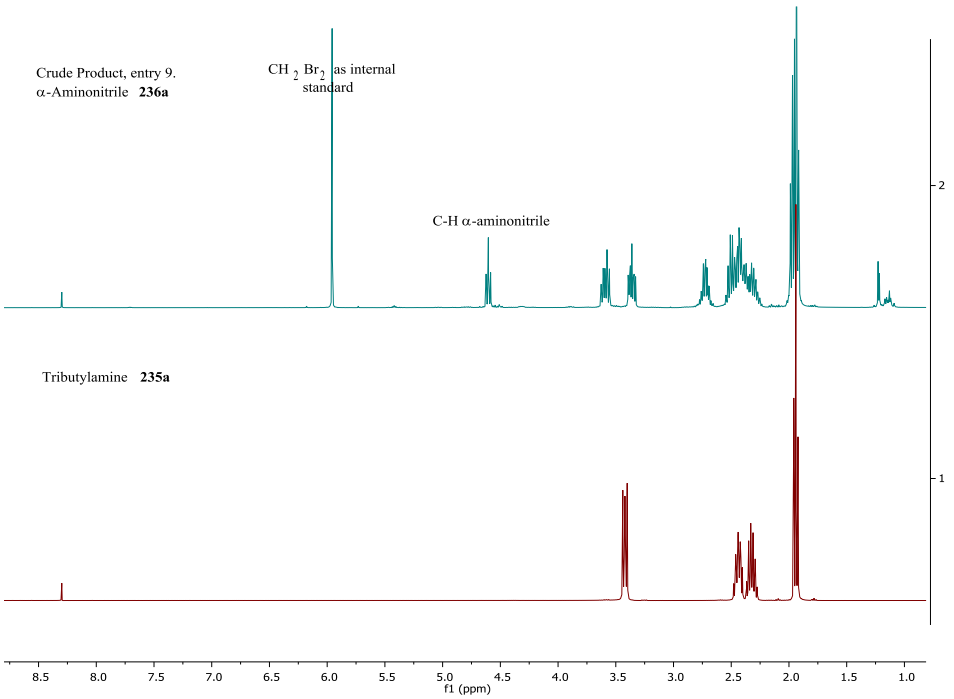


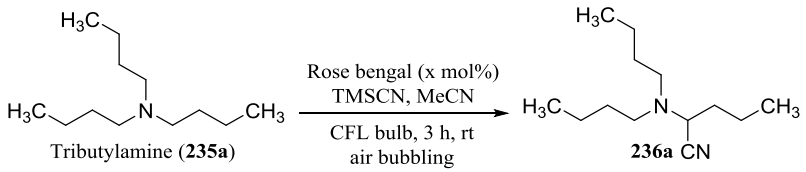
Figure 26. ^{1}H NMR spectra of the crude material obtained from entry 9. α-Aminonitrile **236a**.*

4.3.1.1 Investigation on the Catalyst Loading

Motivated by the result obtained using 0.5 mol% of photocatalyst, lower catalyst loadings were investigated. For this purpose, catalytic amounts of rose bengal (**204**) were added to the reaction mixture as stock solutions of different concentrations, which were prepared by dilution Thus, catalyst loadings of 0.1, 0.01, 0.001, 0.0001 and 0.00001 mol% were easily achieved. The results are summarized in Table 13.

* Spectra were measured in deuterated acetonitrile (CD_3CN)

Table 13. Reduction of the catalyst loading.[a]



Entry	Rose Bengal (mol%)	Average Yield (%)[b]	TON[c]	TOF (h^{-1})[d]
1	1	97.3±0.3	85.9±0.4	28.6±0.1
2	0.1	86.2±0.6	748±7	249±2
3	0.01	69.0±1.6	5760±17	1920±6
4	0.001	45.6±0.7	34267±80	11422±27
5	0.0001	24.7±1.0	133333±1100	44444±367
6	0.00001	21.7±2.3	1030000±240000	343333±80000
7	—	11.4±0.1	–	–

[a] Reaction conditions: 210 μmol of tributylamine (1.0 eq.), TMSCN (4.0 eq.) and 2.0 mL of MeCN. The reaction was stirred and irradiated under air bubbling with a 24 W fluorescent household bulb for 3 h at room temperature. Each reaction was run at least in triplicate. [b] Determined by ^{1}H NMR spectroscopy using CH_2Br_2 as internal standard. [c] TON = *n*(product)/*n*(rose bengal) after subtraction of background reaction (entry 7). [d] TOF = (*n*(product)/*n*(rose bengal))/3 h after subtraction of background reaction (entry 7).

Remarkably, loadings of 0.1 mol% (entry 2) and 0.01 mol% (entry 3) still afforded good to excellent yields (Table 13). Acceptable results were still obtained by using 0.001 mol% (entry 4) and 0.0001 mol% (entry 5) of rose bengal (**204**), with yields between 25–45% after 3 h. A TON in excess of 130,000 was achieved using a catalyst loading of 0.0001 mol% (10 ppm, entry 5), which corresponds to the lowest loading ever reported for an organic dye. The limit of the catalyst was reached at 0.00001 mol% or 0.1 ppm (entry 6, TON > 1,000,000). Although the yield dropped to 21.7%, it remained still twofold higher than the yield of the uncatalyzed background reaction (entry 7).

A graphical representation of these data shows a sigmoid growth of the yield when plotted on a semi-logarithmic scale against the catalyst loading (Figure 27). This hints towards an extensive self-quenching of the catalyst which is only minimized at low dye concentrations.[184] Nevertheless, photobleaching of the catalyst at these concentrations is restricting the full compensability of loading with reaction time.[185-187]

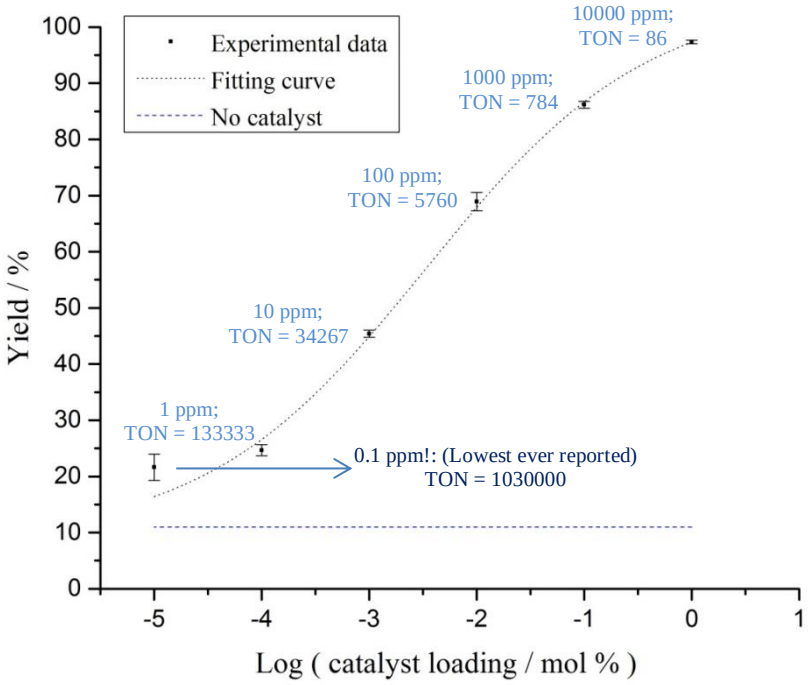


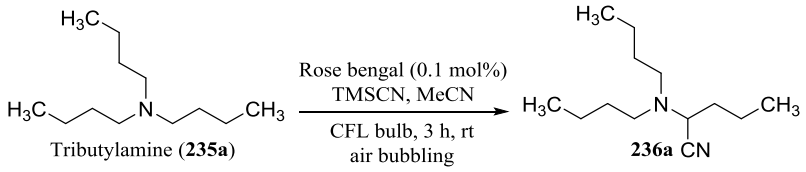
Figure 27. Yield vs catalyst loading.

Although low loadings can effectively afford the corresponding α-aminonitrile **236a**, 1 mol% of rose bengal (**204**) resulted as the optimum amount of photocatalyst to achieve the highest production rate of α-aminonitrile **236a**. An increased of the amount of rose bengal (**204** beyond 1 mol%, would probably lead to loss of efficiency by reducing the amount of photoexcited molecules of photocatalyst. This is explained by the low penetration of the light through highly concentrated solutions of dye.[188,189]

4.3.1.2 Exclusion of UV Emissions

In order to demonstrate that UV emissions from the CFL lamp did not play major role in the photocyanation, UV exclusion experiments were performed at 0.1 mol% catalyst loading.

Table 14. UV exclusion experiments.[a]



Entry	Rose Bengal (mol%)	Reaction time (h)	UV filter	Yield (%)[b]
1	0.1	1	—	79
2	0.1	1	Glass (390 nm cutoff)	60
3	0.1	1	Benzophenone (0.5 M)	66
4	0	1	Glass (390 nm cutoff)	No conversion

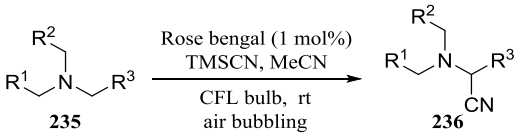
[a] Reaction conditions: 210 μmol of tributylamine (1.0 eq.), TMSCN (4.0 eq.) and 2.0 mL of MeCN. The reaction was stirred and irradiated under air bubbling with a 24 W fluorescent household bulb for 3 h at room temperature. [b] Determined by ^{1}H NMR spectroscopy using CH_2Br_2 as internal standard. [c] The glass filter was place in front of the reaction vessel. [d] A solution of benzophenone in ethanol (0.5 M) was placed in a beaker and the reaction vessel was submerged in this solution. The path length was approximately 14 mm and the distance from the fluorescent household bulb ca. 8 cm.

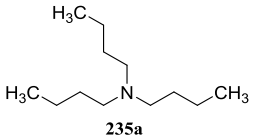
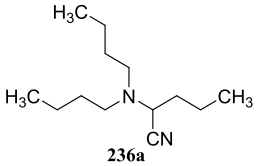
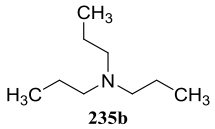
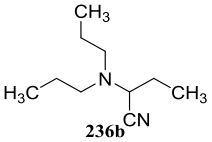
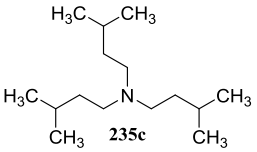
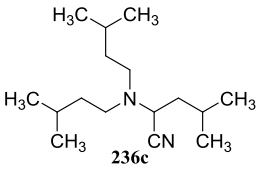
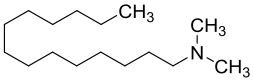
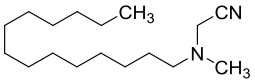
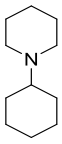
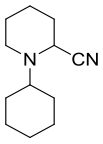
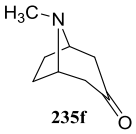
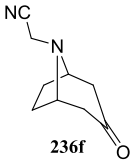
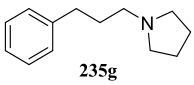
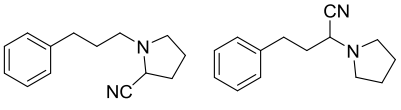
Table 14 summarizes the results obtained when a UV glass filter (390 nm cutoff) or a solution of benzophenone in ethanol (0.5 M benzophenone in ethanol, 14 mm path length) were used. Under these conditions (entry 2 and 3), only a moderate decrease in the yield could be observed compared to non-UV filtered conditions (entry 1). Therefore, it was demonstrated that the synergictic used of pure visible light and rose bengal (**204**) are the major contributors for this transformation.

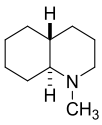
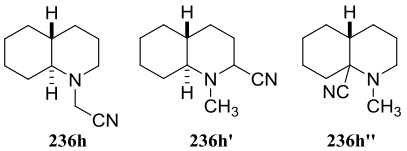
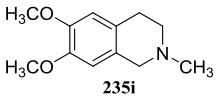
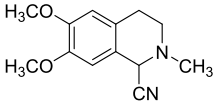
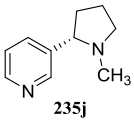
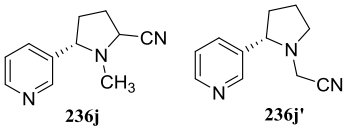
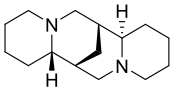
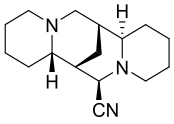
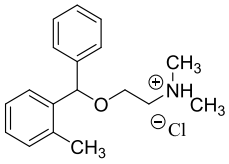
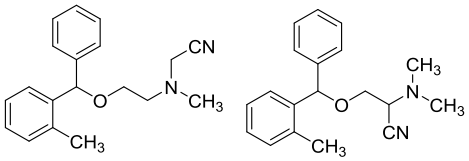
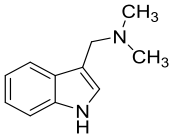
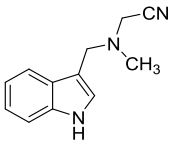
4.3.2 Scope and Limitations of the Reaction

After optimizing the reaction conditions, different tertiary aliphatic amines were subjected to the standardized conditions in order to investigate the scope and limitations of the photocyanation (Table 15).

Table 15. Reaction scope.[a]



Entry	Tertiary Amine	Time (h)	Product	Yield (%)[b]
1	 **235a**	3.0	 **236a**	89
2[c]	 **235b**	3.0	 **236b**	74
3	 **235c**	3.5	 **236c**	84
4	 **235d**	18.0	 **236d**	80
5	 **235e**	3.0	 **236e**	74
6	 **235f**	24.0	 **236f**	61
7[d]	 **235g**	3.0	 *Endo* **236g** 91 : *Exo* **236g'** 9	68

8[d]	 **235h**	4.0	 **236h** : **236h'** : **236h''** 67 : 24 : 9	82
9	 **235i**	3.0	 **236i = 94**	80
10[c]	 **235j**	3.0	 **236j** : **236j'** *diast. mix.* 55:39 : 6	89
11	 **235k**	3.0	 **236k**	52
12[c,d]	 **235l**	24.0	 **236l** : **236l'** *diast. mix.* 78 : 11:11	74
13	 **235m**	15.0	 **236m**	20
14[e]	 **235n**	24.0	——	——
15[e]	 **235o**	24.0	——	——

[a] Reaction conditions: amine (1.00 mmol, 1.0 eq.), rose bengal (10.0 μmol, 1 mol%), TMSCN (4.00 mmol, 4.0 eq.) and 8.0 mL of MeCN. The reaction was stirred and irradiated under air bubbling with a 24 W fluorescent household bulb at room temperature. [b] Isolated yield. [c] The reaction was also performed on a gram scale. [d] Product ratio determined by ^{1}H NMR spectroscopy. [e] No product was detected. Starting material was completely recovered.

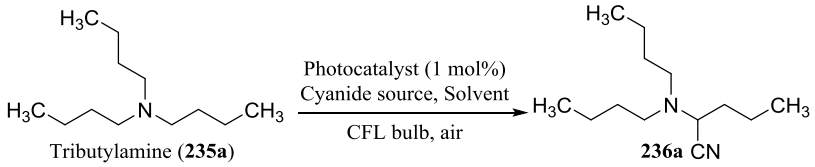
Good to excellent yields were observed in most cases, illustrating the efficiency of the photocyanation method. Longer reaction times were required for N-methyldialkylamines **235d**,**f** (entries 4 and 6), which can be explained based on the higher oxidation potentials of tertiary

amines with shorter chain length (e.g., Me_3N, +0.82 V; Et_3N, +0.79 V; nBu_3N, +0.62 V).[190] Remarkably, high regioselectivities were observed when different α-protons were available for substitution (entries 4–9). Although the reaction took place predominantly at the less hindered carbon in most cases, electronic effects also seem to play an important role.[190] This was illustrated by amine, where the substitution was primarily on the benzylic position (entry 9). Aiming to investigate the photocyanation reaction on alkaloids and pharmaceuticals, (–)-nicotine (**235j**), (+)-sparteine (**235k**), orphenadrine (**235l**), and gramine (**235m**), were selected as substrates (entries 10–13). As anticipated, similar results regarding efficiency and regioselectivity were encountered. Nevertheless, when using DABCO (**235n**), and hexamethylenetetramine (**235o**, entries 14 to 15), no reaction was observed. A potential explanation could be the violation of BREDT's rule in the formation of bridgehead iminium ions. On the other hand, DABCO is well known to act as an excellent charge transfer quencher, in particular for singlet oxygen.[191]

4.3.2.1 Potential Role of Singlet Oxygen ($^1O_2$) and Possible Involvement of a Radical chain Mechanism.

The potential involvement of $^1O_2$ in the photocyanation was investigated taking into account that singlet oxygen ($^1O_2$) is known to act as an efficient oxidizing agent for tertiary amines, and that rose bengal (**204**) is an excellent photosensitizer for the production of singlet oxygen ($^1O_2$) (Table 16).[178,192-194]

Table 16. Investigation of the involvement of singlet oxygen.[a]



Entry	Catalyst	Solvent	Cyanide Source	Additive	Air Bubbling	Yield (%)[b]
1	TPP (1 mol%)	5.0 mL of CH_2Cl_2	TMSCN	——	Yes	91
2	Rose Bengal (1 mol%)	2.0 mL of MeCN	TMSCN	——	Yes	98
3	Rose Bengal (1 mol%)	2.0 mL of MeCN	TMSCN	DABCO (1.0 eq.)	Yes	90
4[c]	Rose Bengal (1 mol%)	2.0 mL of MeCN	TMSCN	DABCO (1.0 eq.)	No	49

5[c]	Rose Bengal (1 mol%)	2.0 mL of MeCN	TMSCN	——	No	66
6[c]	Rose Bengal (1 mol%)	2.0 mL of MeCN, 0.5 mL of D_2O	KCN	NaN_3 (4.0 eq.)	No	35
7[c]	Rose Bengal (1 mol%)	2.0 mL of MeCN, 0.5 mL of D_2O	KCN	——	No	54

[a] Reaction conditions: 210 μmol of tributylamine (1.0 eq.) were used. The reaction was irradiated for 3 h with a 25 W fluorescent household bulb at room temperature. [b] Yield determined by ^{1}H NMR spectroscopy using CH_2Br_2 as internal standard. [c] The solvent was saturated with oxygen by sparging with air.

In order to corroborate the role of $^1O_2$ in the reaction, the well-known singlet oxygen ($^1O_2$) photosensitizer tetraphenylphenylporphine (TPP, **229**) was used instead of rose bengal (**204**, entry 1). The reaction smoothly generated α-aminonitrile **236a** in 91% yield after 3 h. Subsequently, the effect of physical quenchers on $^1O_2$ (ISC to $^3O_2$) was investigated. In this case, DABCO was chosen, as it is a common physical quencher for $^1O_2$ without itself undergoing any reaction (see also Table 15, entry 14).[191] Under standard reaction conditions, no inhibition was observed (entry 3). This could be due to the high concentration of oxygen in the reaction medium since air bubbling was applied. The experiment was repeated with an air-saturated solvent (sparged with air prior to irradiation) under air atmosphere during the irradiation process. Under these conditions, DABCO reduced the reaction yield from 66% to 49% (entries 4 and 5). Similar results were observed when NaN_3 was used as physical quencher, KCN as cyanating agent and rose bengal as photocatalyst (entries 6 and 7).

Although the use of physical quencher of $^1O_2$ (DABCO and NaN_3) resulted in a gradual reduction of the product yield, it did not shut down the photocyanation reaction. Therefore, it seems that the oxidation of tertiary aliphatic amines might involve a direct oxidation of the amines by the excited rose bengal as well as a singlet oxygen-mediated process (see Scheme 60 and Scheme 61).

To further investigate the photocyantion reaction, light-dark cycle, as well as radical inhibitor experiments, were performed. For this purpose, the reaction was performed under air atmosphere using tributylamine (**235a**), TMSCN, 0.5 mol% of rose bengal, 1,4-Bis(trimethylsilyl)benzene as internal standard and CD_3CN (saturated with air). The reaction was alternatingly irradiated with a 24 W CFL bulb and kept in the dark for 10 minutes intervals. Aliquots were taken at the start and after each interval, diluted with CD_3CN and subjected to ^{1}H NMR measurements. The reaction yield was determined by ^{1}H NMR spectroscopy using 4-Bis(trimethylsilyl)benzene as internal standard (Figure 28).

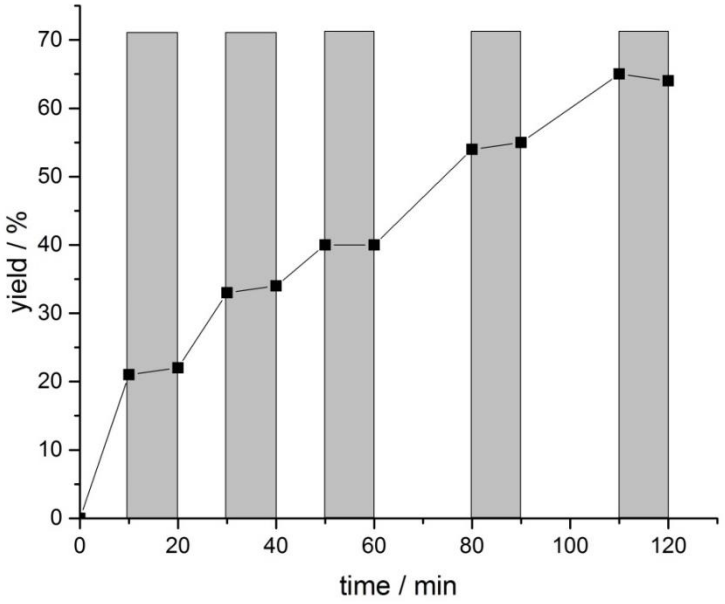
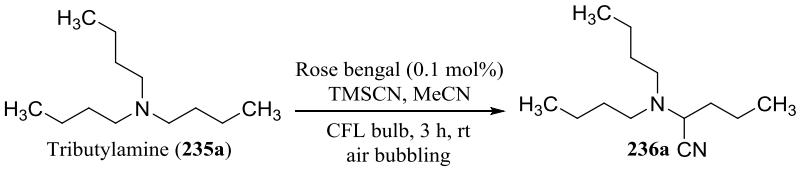


Figure 28. Light-dark cycle experiments. Reaction conditions: 210 µmol of tributylamine (1.0 eq.), TMSCN (4.0 eq.), 0.5 mol% of rose bengal, 44 µmol of 1,4-Bis(trimethylsilyl)benzene (internal standard) and 2.0 mL CD_3CN (saturated with air), were used.

The light-dark cycle experiment demonstrated that the cyanation reaction is light-dependent and does not proceed without irradiation at the time scale of the experiment. However, as YOON and co-workers[195] have recently shown, these light-dark cycle experiments are insufficient to rule out a radical chain mechanism. To observe the influence of radical inhibitors on the photocyanation, some experiments were performed in collaboration with Alexander LIPP and Alexander M. NAUTH (Table 17).

Table 17. Influence of radical inhibitors on the photocyanation.[a]



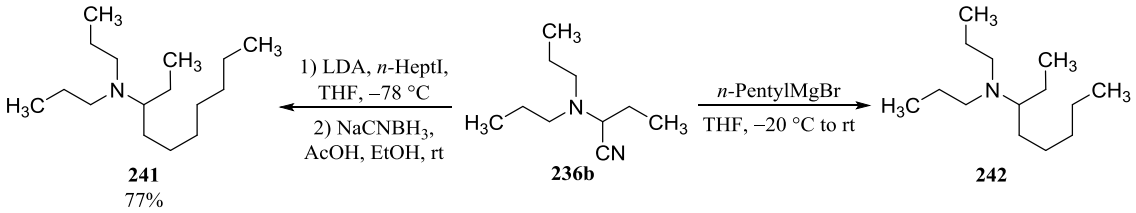
Entry	Inhibitor	mol%	Yield (%)[b]
1	—	—	45
2	BHT	1	34
3	BHT	10	6
4	I_2	1	20

[a] Reaction conditions: 210 µmol of tributylamine (1.0 eq.), TMSCN (4.0 eq.), 0.1 mol% rose bengal, 2.0 mL of MeCN and an specified amount of inhibitor. The reaction mixture was stirred and irradiated under air bubbling with a 24 W fluorescent household CFL lamp for 2 h at room temperature. [b] Yield determined by ^{1}H NMR spectroscopy using CH_2Br_2 as internal standard.

The yield of the photocyanation decreased significantly upon addition of varying amounts of radical inhibitors but the reaction did not cease completely. This outcome suggests that radical species might be intermediates in the reaction pathway. Although, the results mentioned in this section gave an insight into the species that might be involved in the reaction, they are not sufficient to draw clear mechanistic conclusions for the photocyanation.

4.3.3 Application of the Photogenerated α-Aminonitriles

To demonstrate the applicability of the photogenerated α-aminonitriles in the synthesis of new compounds and more complex molecules, 2-(dipropylamino)butanenitrile (**236b**) was selected as candidate for further derivatization. The first attempt corresponded to a one-pot C-alkylation/reductive decyanation, where α-aminonitrile **236b** was initially deprotonated by LDA at –78 °C and then alkylated with 1-iodoheptane. *In situ* reductive decyanation of the alkylated product with $NaCNBH_3$ afforded the heptyl-substituted compound **241** in 77% yield (Scheme 75 left). Consequently, another well-known reactivity mode of α-aminonitriles was investigated. Compounds **236b** was subjected to a BRUYLANTS reaction with *n*-pentylmagnesium bromide in THF at –20 °C. In this manner, pentyl-substituted amine **242** was obtained in 64% (Scheme 75 right). These examples clearly underline the synthetic potential of photocatalytic post-functionalizations of amines and alkaloids.



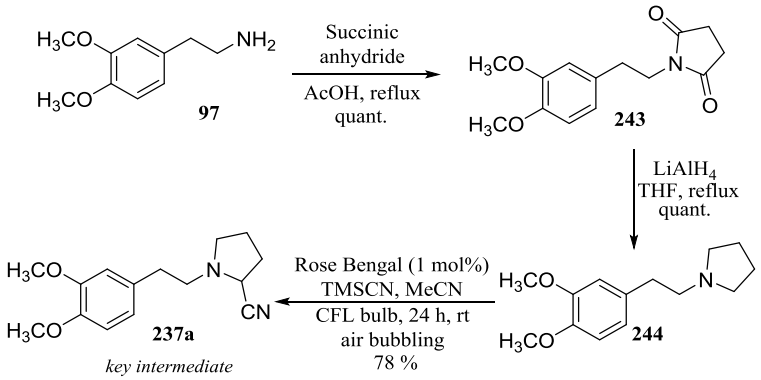
Scheme 75. One-pot C-alkylation/reductive decyanation and BRUYLANTS reaction of α-aminonitriles **236b**.

4.3.4 Application of the Obtained Method towards the Synthesis of Natural Products

To further demonstrate the direct applicability of the developed method in natural products synthesis, a total synthesis of the alkaloids (±)-crispine A (**238**), (±)-harmicine (**239**) and (±)-desbromoarborescidine A (**240**) was designed. This methodology involves the photogenerated α-aminonitriles **237** as key intermediates.

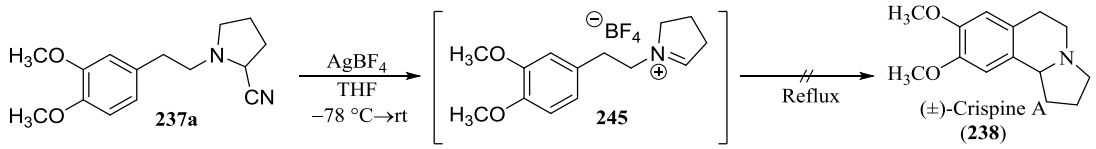
4.3.4.1 Synthesis of (±)-Crispine A (238)

Crispine A (**238**) is a tricyclic tetrahydroisoquinoline alkaloid isolated from the welted thistle, *Carduus crispus*.[196] In this section, a total synthesis of (±)-crispine A (**238**) based on the PICTET-SPENGLER cyclization of the corresponding α-aminonitrile **237a** is described (see Scheme 74). α-Aminonitrile **237a** was prepared in a 3 step procedure from commercially available homoveratrylamine (**97**). For this purpose, homoveratrylamine (**97**) was treated with succinic anhydride in acetic acid and heat at reflux for 24 h to afford succinimide **243** in quantitative yields. Reduction of this amide with $LiAlH_4$ furnished the corresponding pyrrolidine **244** also in quantitative yield. Application of the developed method for the photocyanation of tertiary amines to pyrrolidine **244**, afforded the expected α-aminonitrile **237a** in 78 % after 15 h. This compound was obtained as an inseparable mixture of the isomeric endo- and exocyclic α-aminonitriles. Unfortunately, determination of the isomeric ratio was not possible to achieve by ^{1}H NMR due to the overlapping of the signals. Based on the results from compounds **236g** (91 : 9 isomeric ratio, see Table 15, entry 7), a similar outcome for this reaction was assumed (Scheme 76).



Scheme 76. Preparation of the key intermediate α-aminonitrile **237**.

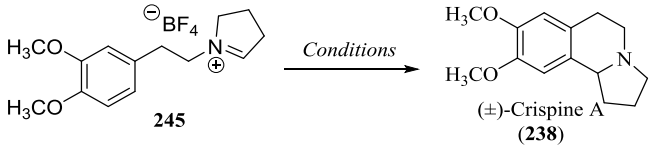
Once the preparation of α-aminonitrile **237a** was accomplished, the corresponding PICTET-SPENGLER cyclization became the next synthetic target. Initially, attempts to induce the direct cyclization by hydrolysis of α-aminonitrile **237a** via generation of an iminium ion species under acidic conditions (TFA, AcOH, and $HCl_{(aq)}$) and high temperatures (80–100 C), did not result in the product formation. Instead, the addition of $AgBF_4$ induced the formation of the intermediate iminium ion **245** (confirmed by TLC and LC-MS analysis), however, the cyclization did not proceed even after 12 h at reflux conditions (Scheme 77).



Scheme 77. Initial attempt for the synthesis of (±)-crispine A (**238**).

Considering that the PICTET-SPENGLER cyclization was not occurring, iminium salt **245** was isolated (75 % yield) and subjected to different reaction conditions in order to specifically investigate the cyclization step (Table 18).

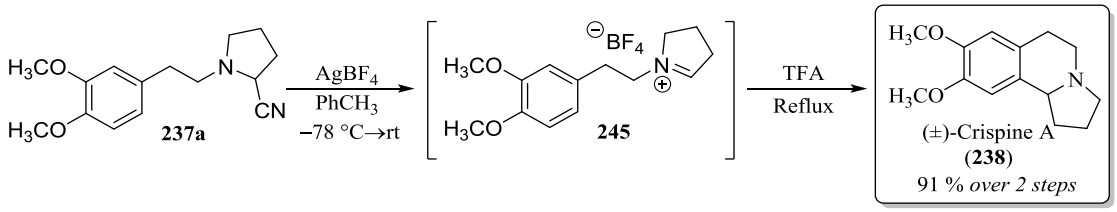
Table 18. Investigation on the PICTET-SPENGLER cyclization.



Entry	Solvent	Additive	Temperature	Reaction Time	Product
1	THF	—	Reflux	24 h	—[a]
2	Toluene	—	110 °C	24 h	—[a]
3	DMF	—	145 °C	24 h	—[a]
4	Toluene	TFA (11.0 eq.)	110 °C	24 h	(±)-crispine A (**238**)

[a] Product was not detected, only starting material was observed.

It was found that the reaction did not proceed when different solvents and temperatures were used (entries 1–3). However, when trifluoroacetic acid (TFA) was added to the reaction in toluene (entry 4), the cyclization successfully proceeded towards the generation of the expected (±)-crispine A (**238**). Applying this method, (±)-crispine A (**238**) could be obtained in 90 % yield. Aiming to improve the yield of the reaction, a one-pot procedure from α-aminonitrile **237a** was performed. Thus, *in situ* generation of iminium salt **245** with $AgBF_4$ followed by addition of TFA afforded (±)-crispine A (**238**) in 91 % yield.

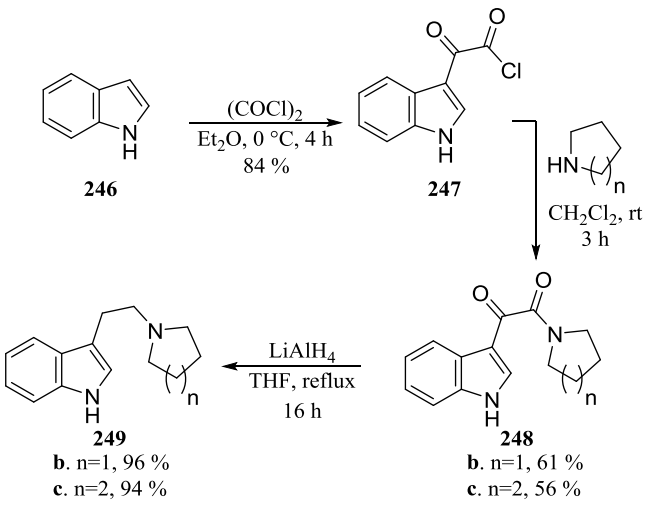


Scheme 78. One-pot synthesis of (±)-crispine A (**238**).

Based on these results, the overall yield of the natural product corresponds to 70°% starting from homoveratrylamine (**97**). Moreover, this route represents one of the shortest (four linear steps from **97**) and highest yielding syntheses of crispine A.

4.3.4.2 Synthesis of Tetrahydro-*β*-Carboline Alkaloids (±)-Harmicine (239) and (±)-Desbromoarborescidine A (240)

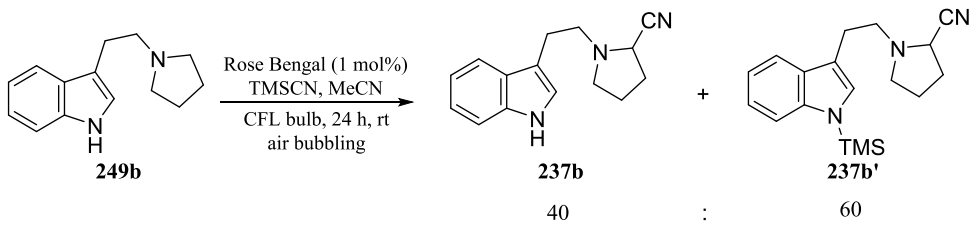
Tetrahydro-*β*-carboline alkaloids are an important class of molecules that share a common tricyclic tetrahydropyrido[3,4-*b*]indole ring structure.[197-199] Herein, the preparation of (±)-harmicine (**239**), and (±)-desbromoarborescidine A (**240**) is presented as another synthetic application of the above described photocyanation reaction. All experiments included in this section were conducted by Kristian ALT as part of his Bachelor thesis. The synthesis of these alkaloids was designed based on the use of α-aminonitriles **237** as key intermediates. For this purpose, commercially available indole (**246**) was reacted with oxalyl chloride in diethyl ether at 0°C, generating oxoacetylchloride **247** in 84 %.[200] N-acylation of compound **247** with pyrrolidine or piperidine afforded the corresponding amides **248** in 61 % and 56 % yield, respectively. Finally, reduction of these amides with $LiAlH_4$ gave amines **249** in high yields (Scheme 79).[201]



Scheme 79. Synthesis of amines **249**.

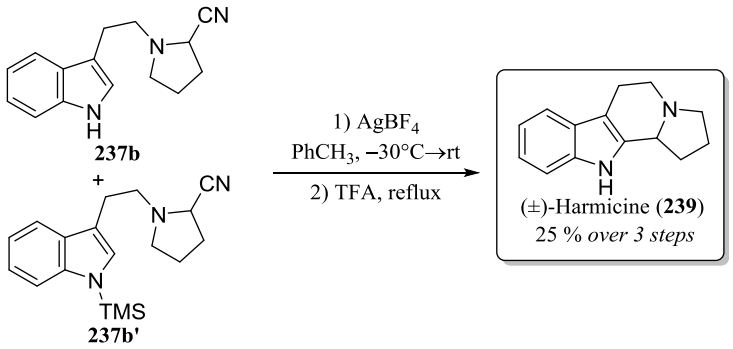
With amines **249** in hand, the preparation of α-aminonitriles **237b,c** was attempted using pyrrolidine **249b** and subjecting it to the developed photocyanation conditions for 6 h. ^{1}H NMR and LC-MS analysis of the crude product showed the formation of two different α-aminonitriles in a 60 : 40 ratio (judged by ^{1}H NMR). The major component was identified as a

dehydrogenative silylation product **237b'** while the minor product corresponded to the expected α-aminonitrile **237b** (Scheme 80). This mixture was used without separation in the next step.



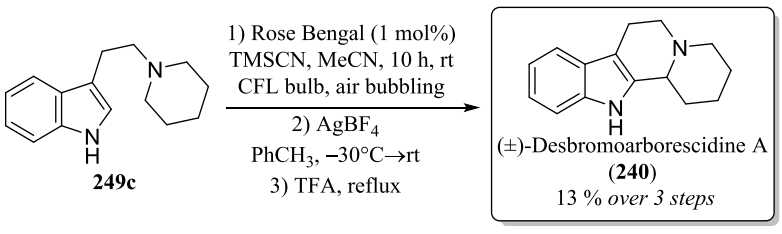
Scheme 80. Photocyanation of pyrrolidine **249b**.

Subjecting this mixture of α-aminonitriles to the same decyanation/PICTET-SPENGLER conditions used for the preparation of (±)-crispine A (**238**), the corresponding (±)-harmicine (**239**) was obtained in in 25 % yield over three steps (Scheme 81).



Scheme 81. Synthesis of (±)-harmicine (**239**).

When the same reaction sequence was applied to piperidine **249c**, (±)-desbromoarborescidine A (**240**) could be obtained in 13 % yield over three steps **249c** (Scheme 82).

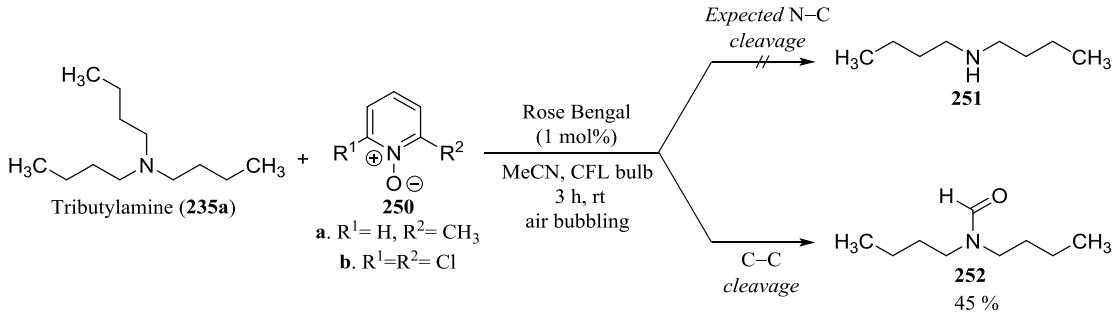


Scheme 82. Synthesis of (±)-desbromoarborescidine A (**240**).

In general, (±)-harmicine (**239**) and (±)-desbromoarborescidine A (**240**) were obtained in 12 % and 6 % overall yield, respectively, from indole (**246**).

4.3.5 Additional Findings

Aiming to explore the applicability of the photocatalytic system on other reactions different than cyanations, pyridine N-oxides **250** were selected as reagents for an oxygen atom transfer reaction with tributylamine **235a** to produce the N–C cleavage product **251**. However, using two different N-oxides and after 3 h of irradiation, a single product identified as *N*,*N*-dibutylformamide (**252**) was isolated in 45 % yield (Scheme 83). This could be explained by the formation of an enamine intermediate derived from its corresponding iminium ion, which could undergo an oxidative C–C cleavage to formamide **253** induced by singlet oxygen. Although the role of N-oxides **250** remains unclear, it is likely that they are involved in the deprotonation of the iminium ions via a highly reactive N-oxide radical anion.[202,203] Additional experiments are needed in order to understand the role of the N-oxide.



Scheme 83. Tributylamine **235a** and pyridine N-oxides **250** under photoredox conditions.

4.4 Conclusions

In summary, an economic and highly active catalytic system for the photocyanation of tertiary aliphatic amines **235** based on the use of inexpensive rose bengal (**204**), air, TMSCN, and visible light was developed. The investigation demonstrated that short reaction times can conveniently be achieved with a catalyst loading of 1 mol% but even at loadings as low as 0.1 ppm, the photoredox catalysis proceeds significantly more efficiently than the uncatalyzed reaction. Furthermore, the use of air instead of pure oxygen, halogen-free solvents, and the highly economical CFL light sources, represent clear advantages of this method.

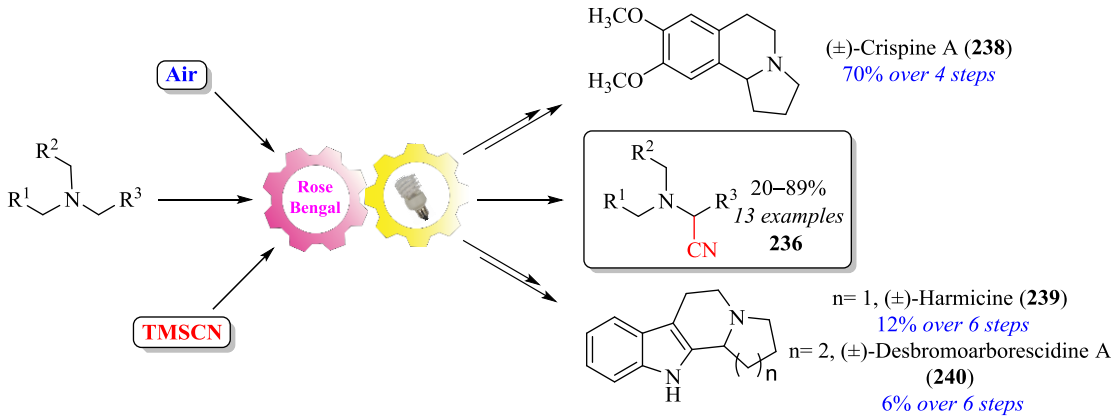


Figure 29. Highly active system for the metal-free aerobic photocyanation of tertiary amines with visible light: application to the synthesis of (±)-crispine A (**238**), (±)-harmicine (**239**), and (±)-desbromoarborescidine A (**240**).

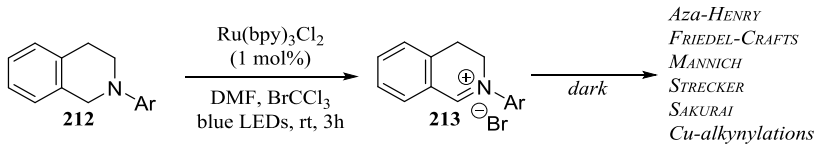
A variety of synthetically useful α-aminonitriles were prepared in moderate to high yields, and their utility for post-functionalization procedures was showcased by tri-*n*-propylamine **236b**. Furthermore, a novel and efficient synthesis for the alkaloids (±)-crispine A (**238**), (±)-harmicine (**239**), and (±)-desbromoarborescidine A (**240**) via aerial photocyanation was developed (Figure 29).

Chapter 5

Anaerobic Oxidation of Tertiary Amines by $BrCCl_3$ and Visible Light – Scope, Applications, and Mechanistic Aspects

5.1 Introduction

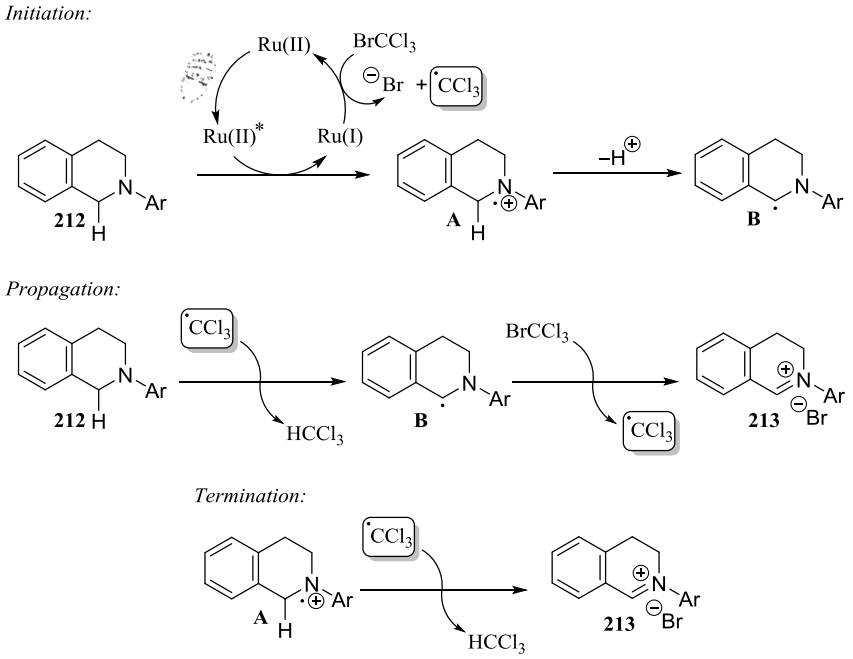
Many photocatalytic oxidations of amines rely on the use of oxygen as terminal oxidant to mediate the turnover of the photocatalyst. However, during this process, α-amino radicals can also interact with oxygen or its reactive intermediates, inducing the formation of side products such as amides and thus losing efficiency towards the generation of iminium ions. To overcome this limitation, STEPHENSON and co-workers proposed the use of alternative terminal oxidants to promote the regeneration of the photocatalyst.[204] With this aim, they attempted the corresponding photo-oxidation of N-aryltetrahydroisoquinolines **212** in the presence of $Ru(bpy)_3Cl_2$ (**202**) in DMF, finding bromotrichlormethane ($BrCCl_3$) as a suitable stoichiometric oxidant for the formation of iminium ions **213** after only 3 h.[180] These stable iminium salts were then subjected to further chemistry by adding different nucleophiles (Scheme 84).



Scheme 84. STEPHENSON's anaerobic photo-oxidation of amines **212**.

The authors suggested that the reaction probably proceeds via an efficient chain propagation process. Thus, N-aryltetrahydroisoquinoline **212** is initially oxidized by the excited photocatalyst **202** (Ru(II)*) to the corresponding amine radical cation **A**, which is further deprotonated to produce α-amino radical **B**. The reduced photocatalyst **202** (Ru(I)) is then re-oxidized by reduction of $BrCCl_3$ to trichloromethyl radical ($^{\bullet}CCl_3$). This $^{\bullet}CCl_3$ can perform a direct C–H abstraction on substrate **212**, producing another molecule of α-amino radical **B** and chloroform. The generation of chloroform was detected during the investigation. Radical **B** on the other hand is then further oxidized by another molecule of $BrCCl_3$ forming iminium salt **213** while reestablishing $^{\bullet}CCl_3$. This propagation mechanism might be favored since $BrCCl_3$ is used in

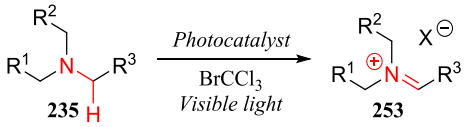
stoichiometric excess (3 eq.). Moreover, in case of a chain termination event, the photocatalyst will restore the corresponding reactive species (Scheme 85).



Scheme 85. Proposed mechanism by STEPHENSON.

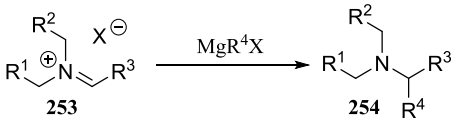
5.2 Aim of the Research

Due to their electrophilic characteristics, the development of new and efficient methods towards the generation of iminium ions continues to be of great interest in organic chemistry. Motivated by the results obtained by STEPHENSON and co-workers using $BrCCl_3$ as terminal oxidant in the photo-oxidation of N-aryltetrahydroisoquinolines **212**, it was decided to design and develop a complementary method for the generation of iminium ions **253**. In this case, the anaerobic photo-oxidation of less readily oxidized aliphatic tertiary amines **235** was investigated (Scheme 86).



Scheme 86. Proposed photo-oxidation of trialkylamines

Furthermore, an application to the synthesis of amines **254** via GRIGNARD reaction with the photogenerated iminium ions **253** was attempted (Scheme 87).



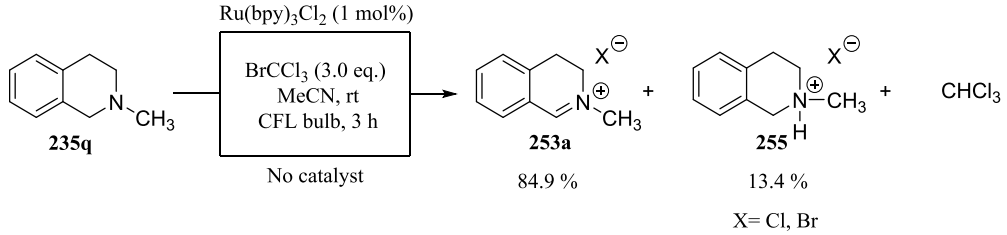
Scheme 87. GRIGNARD reaction with iminium salts **253**.

5.3 Results and Discussion

Before starting with the corresponding discussion, it should be mentioned that some of the results presented in this section were obtained in collaboration with Alexander M. NAUTH and Stefan PUSCH as part of a shared project on the study of $BrCCl_3$ as a terminal oxidant in photocatalysis.

5.3.1 Initial Study

In order to explore the potential use of $BrCCl_3$ for the anaerobic photo-oxidation of tertiary aliphatic amines, *N*-methyl-1,2,3,4-tetrahydroisoquinoline (**235q**) was selected as test substrate. The presence of this heterobicyclic system as a substructure in natural products, as well as in the well-studied N-aryltetrahydroisoquinolines **212**, makes it the ideal starting candidate for this study. In this manner, compound **235q** was initially subjected to the anaerobic photo-oxidation conditions reported by STEPHENSON and co-workers. The reaction took place under inert atmosphere (argon), using acetonitrile as solvent and a 24 W compact fluorescent light bulb as the source of visible light. Under these conditions, the expected iminium salt **253a** was formed after 3 h, along with chloroform and an unexpected by-product identified as the protonated *N*-methyl-1,2,3,4-tetrahydroisoquinoline (**255**, Scheme 88). As it is usual in catalysis, a blank reaction in the absence of $Ru(bpy)_3Cl_2$ (**202**) was carried out in order to demonstrate the need of the catalyst to promote the reaction. Interestingly, after 3 h of irradiation the color of the reaction mixture changed from colorless to amber. ^{1}H NMR analysis showed the formation of the iminium salt **253a** and chloroform as well as the protonated amine **255** in the same absolute and relative amounts as in the presence of the photocatalyst.



Scheme 88. Photogeneration of iminium salt **253a**.[†]

Intrigued by these results, some additional experiments were performed in order to gather more insights into this unexpected behavior of the reaction. Initially, it was found that under exclusion of UV light with a UV filter (0.5 M benzophenone in ethanol, 3 cm layer thickness) as well as by

[†] The yields were determined by ^{1}H NMR spectroscopy using 1,4-bis(trimethylsilyl)benzene as internal standard.

using blue LEDs (λ_{max}= 462 nm), iminium salt **253a** and amine hydrohalide **255** were again obtained without variation of the product ratio. Moreover, control experiments in the absence of light or $BrCCl_3$ were performed, confirming that no reaction takes place under these conditions (Figure 30).

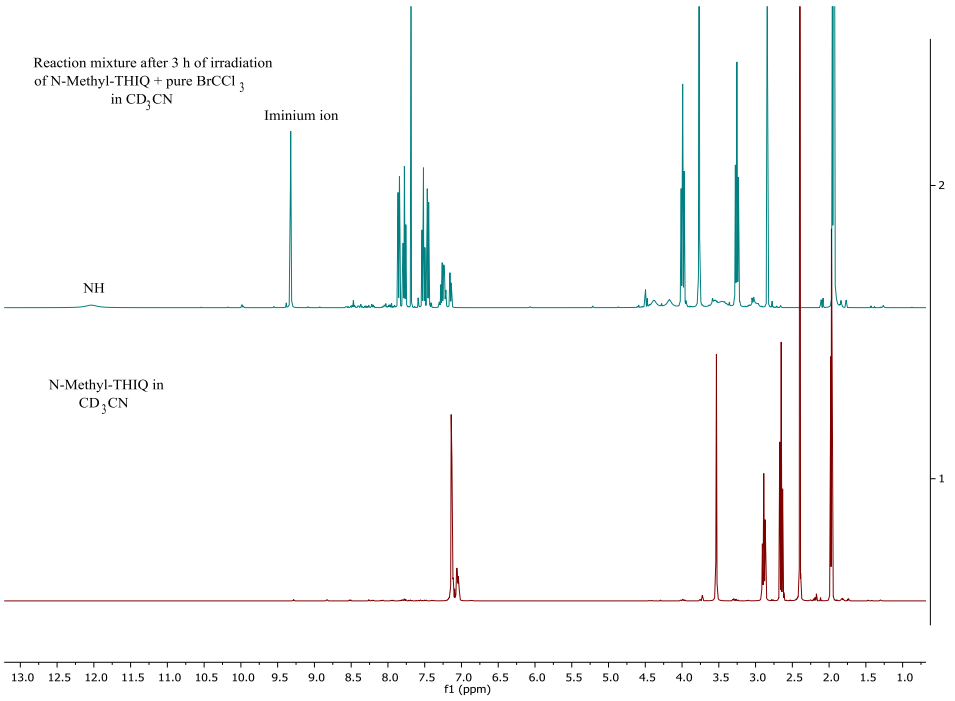


Figure 30. $BrCCl_3$ induced photo-oxidation of amine **235q**.

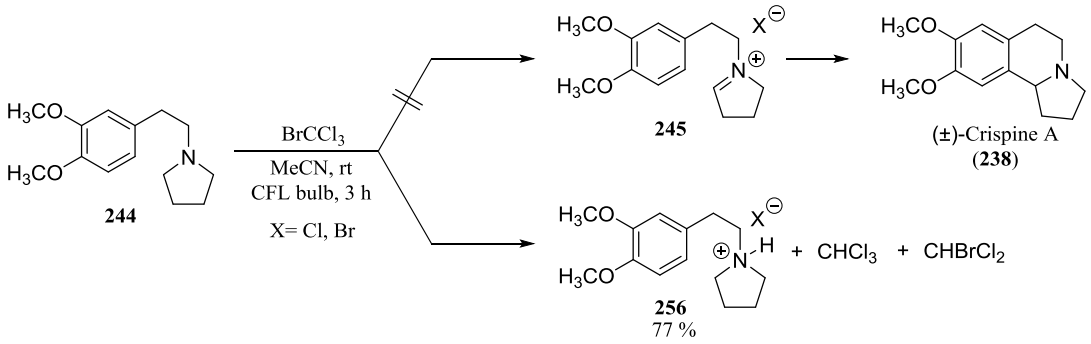
These results showed that the anaerobic reaction does not require the presence of the photocatalyst to proceed. In fact, the efficiency of the transformation did not seem to be affected by the absence of the photocatalyst. Therefore, it can be concluded that only the visible light and $BrCCl_3$ are necessary to effectively promote the photo-oxidation reaction.

During the course of this investigation, ZEITLER and co-workers reported the same observation for a catalyst free-visible light oxidation of N-aryl- and N-methyl-tetrahydroisoquinolines with polyhalomethanes.[205] Although these results regarding the generation of iminium salt **253a** are in agreement with the above mentioned observations, the formation of the side product **255** was not described.

5.3.1.1 Tertiary Aliphatic Amines + $BrCCl_3$

Aiming to define and understand the scope of the reaction, other aliphatic amines were evaluated as the substrates. Since the alkaloid (±)-crispine A (**238**) could be obtained from iminium salt

245 (also available from the corresponding α-aminonitrile **237**, see Scheme 78), pyrrolidine **244** was selected as a case study (Scheme 89).



Scheme 89. Generation of pyrrolidine hydrohalide **256**.

Nevertheless, after subjecting pyrrolidine **244** to the established reaction conditions with $BrCCl_3$, the formation of iminium salt **245** was not observed. Instead, pyrrolidine hydrohalide salt **256** was obtained in 77 % yield (determined by ^1H NMR using 1,4-bis(trimethylsilyl)benzene as internal standard) along with chloroform and bromodichloromethane Although a fraction of the pyrrolidine **244** was consumed, no other defined product was identified apart from baseline clutter during NMR reaction monitoring (Figure 31).

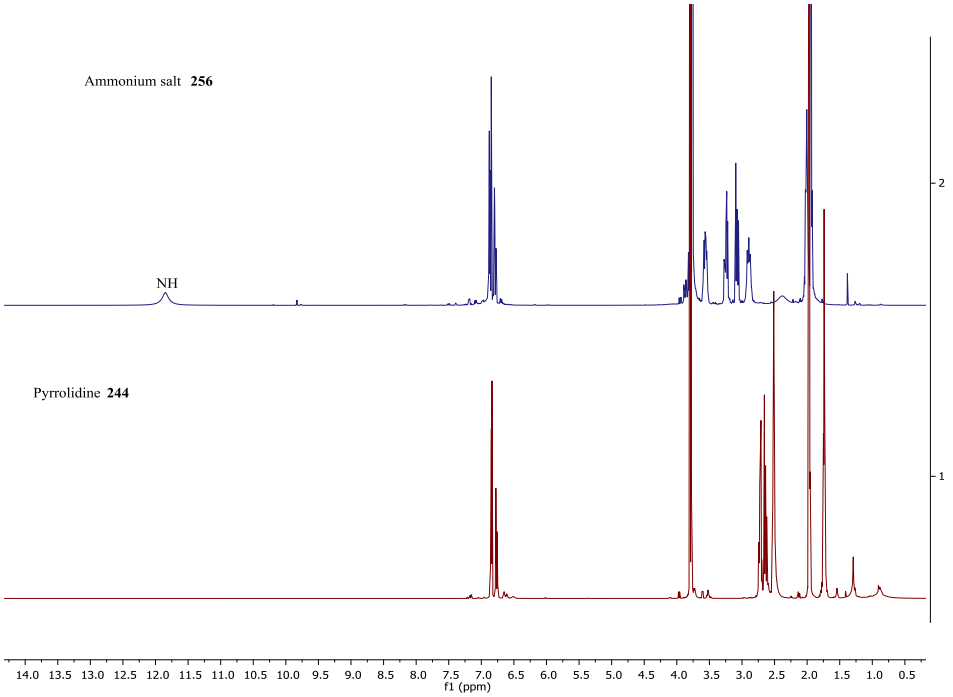
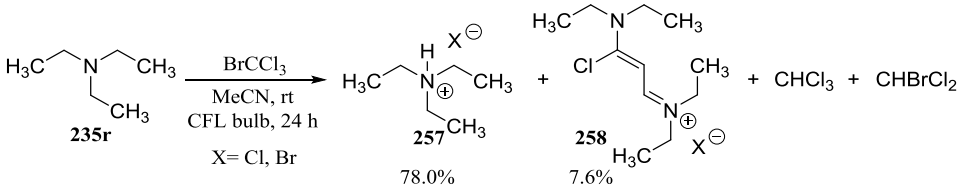


Figure 31. Formation of pyrrolidine hydrohalide **256**.‡

‡ Spectra were measured in deuterated acetonitrile (CD_3CN)

In order to evaluate if tertiary aliphatic amines other than pyrrolidine **244** would show the same behavior, the $BrCCl_3$-oxidation conditions were applied to triethylamine **235r**. The reaction mixture turned amber within minutes and once again, the amine was predominantly protonated to its hydrohalide salt **257** (Scheme 90).



Scheme 90. Formation of triethylamine hydrohalide **257** and chloro-streptocyanine **258**.

Chloroform and bromodichloromethane were also produced during the reaction. However, in this case, an additional species identified as a chlorinated *N*,*N*-diethylvinylamine derivative **258** was formed (Figure 32).

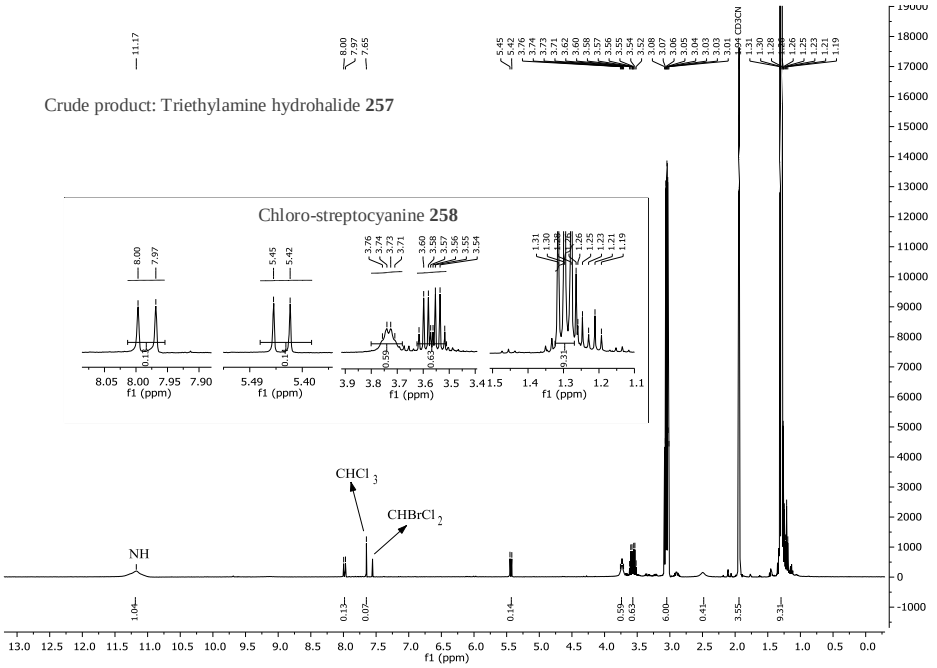


Figure 32. Formation of trimethylamine hydrohalide (**257**) and streptocyanine **258**.[§]

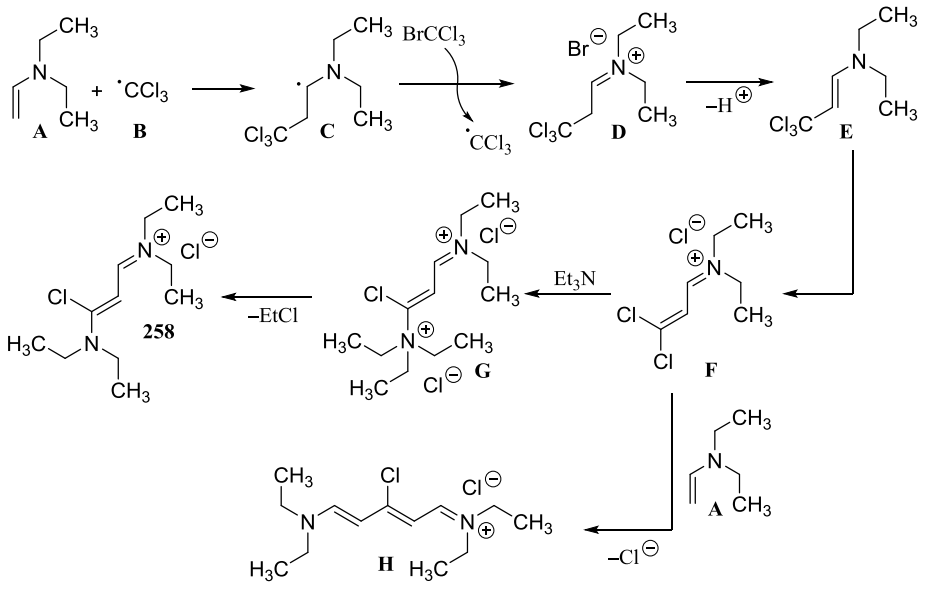
The generation of triethylamine hydrohalide (**257**) from triethylamine (**235r**), polyhalomethanes under UV-irradiation has been described by Collins,[206] Foster and Stevenson[207] already in the early 1960's. However, the yield of the reaction, as well as the nature of the co-product **258**, was not reported until recently.[208] The formation of chloro-streptocyanine **258** is in agreement with a recent publication of the BACH group, in which similar but non-chlorinated cyanines were detected as the products of the reaction of CH_2Cl_2, DIPEA, and visible light. These conjugated

[§] The spectra was measured in deuterated acetonitrile (CD_3CN)

chromophores were shown to be responsible for the amber color in a similar photo-induced reaction.[209]

In order to investigate the reaction and to dismiss the formation of hydrogen halides through hydrolysis of polyhalomethanes to phosgene or ultimately to CO_2,[210,211] the reaction was performed under a strictly inert atmosphere where moisture was rigorously excluded using a glovebox. Nevertheless, even under these conditions, the formation of the hydrohalide salt **257** took place smoothly. The next step corresponded to clarify the role of the solvent as a potential hydrogen source. Thus, NMR experiments in different deuterated or chlorinated solvents indicated that the solvent is not actively participating in the formation of hydrohalide salt. Based on these results, the only hydrogen source remaining is the amine itself, and the process might proceed through an oxidative mechanism involving the formation of cyanine **258** and homologs.**

Scheme 91 depicts a proposed mechanism for the formation of cyanine dye **258**. The process starts by the attack of the electrophilic trichloromethyl radical **B** over enamine **A** to generate radical **C**, which is then oxidized by $BrCCl_3$ to iminium salt **D**. Deprotonation of this salt yields enamine **E** which then eliminates chloride to produce the reactive vinylogous VIEHE salt **F**. This, in turn, could then react with triethylamine through addition/N-dealkylation to produce the observed streptocyanine **258** or alternatively, undergo a reaction with enamine **A** to form pentamethinecyanine **H**.

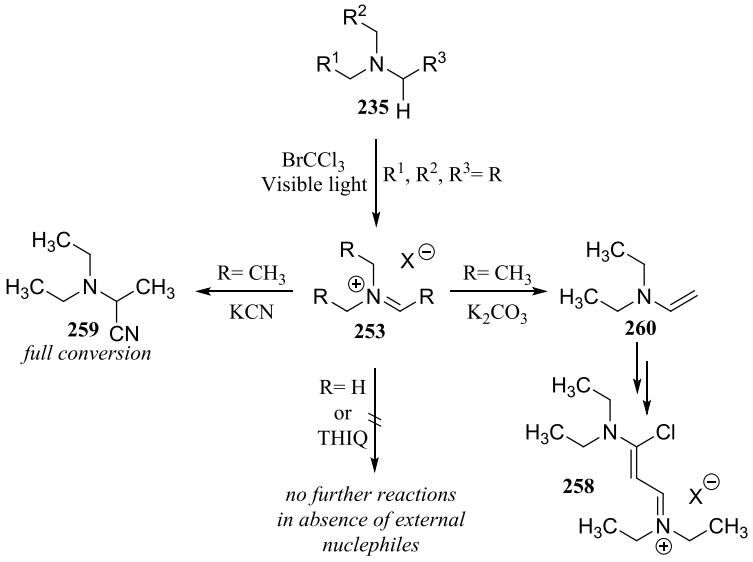


Scheme 91. Suggested formation of streptocyanine dye **258** and higher homologs.

** The experiments were carried out by Alexander M. NAUTH and Stefan PUSCH.

UV/Vis measurements of the reaction mixture showed two absorptions at 310 nm and 414 nm These values are in accordance with the values reported by BACH and co-workers for the non-halogenated trimethine and pentamethine cyanine products of DIPEA.[††209] These results also support the postulated mechanism and the formation of higher cyanine homologs (e.g. cyanine H).

In order to have further and better insights of the reaction with trialkylamines, selected trapping experiments of reactive intermediates were carried out by Alexander M. NAUTH. It was found that the addition of potassium carbonate favored the formation of the chloro-streptocyanine **258** while reducing the formation of amine hydrohalide **257** (3 : 2 ratio, respectively). In contrast, the addition of potassium cyanide resulted in the exclusive formation of α-aminonitrile **259**. These results indicate that the reaction indeed proceeds via iminium ion intermediacy. In the absence of a nucleophile, this iminium ion can be deprotonated to enamine **260** and then undergo further reactions to produce streptocyanines. An additional experiment with trimethylamine (**235s**) showed a slow conversion to its hydrohalide and a concomitant formation to its iminium salt (Scheme 92).



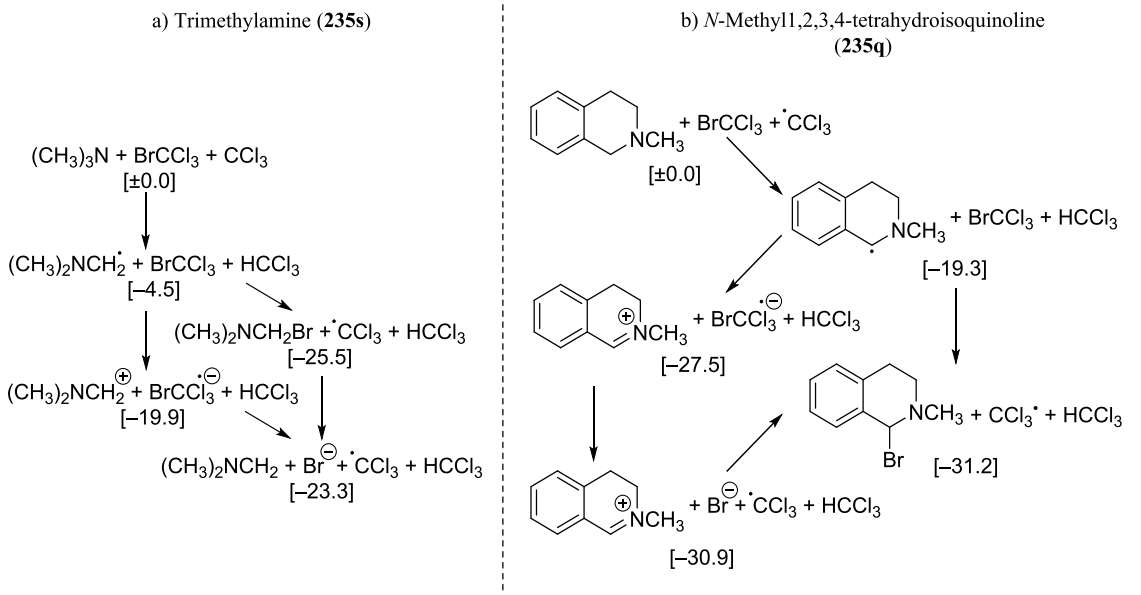
Scheme 92. Trapping experiments of reactive intermediates.

These observations also provide an explanation to the different outcome obtained when *N*-methyl-1,2,3,4-tetrahydroisoquinoline (**235q**) or tertiary aliphatic amines (**235r** and **244**) are used.

[††] UV/Vis measurements were carried out by Alexander M. NAUTH.

5.3.2 DFT Calculations

As mentioned before UV light-induced reactions between tetrahalomethanes and amines are known since the 1960's.[207,212-218] However, in this case, and as reported by ZEITLER *et al.*,[205] blue but not green light promoted the $BrCCl_3$ oxidation reaction even under rigorous exclusion of UV light. In order to understand the nature of the reaction, computational methods were carried out by Stefan PUSCH to identify the light-absorbing species and the underlying reaction mechanism. By this manner, it was found that the iminium ion formation might be proceeding through a free-radical reaction propagated by trichloromethyl radicals in which the respective steps are in all-exergonic manner (Scheme 93).



Scheme 93. Radical chain reaction via trichloromethyl radicals a) trimethylamine (**235s**) and b) *N*-methyl-1,2,3,4-tetrahydroisoquinoline (**235q**). Relative free energies given are given in kcal/mol.[‡‡]

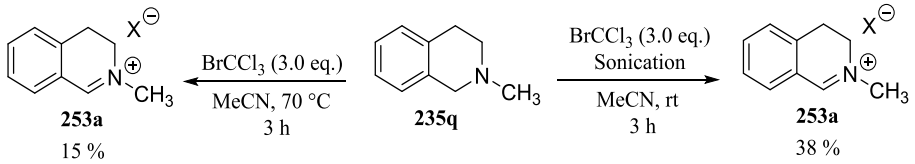
Concerning the light absorbing species, the calculations indicated that neither $BrCCl_3$ (calc: 253/226/234 nm, lit.[219]: 251 nm), amine-$BrCCl_3$ complex (calc: 297/207/215 nm) or an N-bromoammonium ion (calc: 281/272/270 nm) are able to absorb light in the visible region. The only species that can actually absorb in the visible range is molecular bromine (calc: 456/416/410 nm, lit.[220,221]: 415 nm). However, during the experiments, $BrCCl_3$ was used freshly distilled in order to avoid the potential presence of bromine as an impurity (a procedure also used by ZEITLER and co-workers). Based on these results, it is not possible to provide a

[‡‡] The calculations were performed at the UM062X/6-311++G(3df,2pd)/SMD(MeCN)//UM062X/6-311+G(2d,p)/SMD(MeCN) level of theory.

clear conclusion regarding the corresponding initiation step of the radical chain reaction as well as the role of visible light during this process.

5.3.2.1 Sonication and Thermal Induction

Fragmentation of $BrCCl_3$ to bromine and trichloromethyl radicals is known to be commonly achieved by UV light irradiation.[219] Nevertheless, ROSENTHAL and co-workers found that this type of fragmentation also occurs under sonication conditions.[222,223] Intrigued by this report, *N*-methyl-1,2,3,4-tetrahydroisoquinoline (**235q**) was subjected to oxidation with $BrCCl_3$ under sonication. Remarkably, iminium salt **253a** was obtained in 38 % yield after 3 h. Thermal induction at 70 °C also provided the corresponding salt **253a** in 15 % yield after 3 h (Scheme 94).



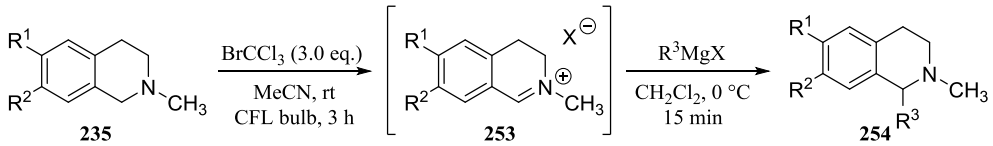
Scheme 94. Sonication and thermal induction.

Although the conversion took place, the reaction rates and yields were lower compared to its photochemical counterpart induced by visible light (85 % yield after 3 h).

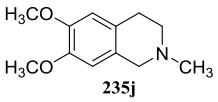
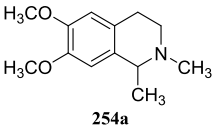
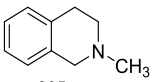
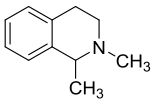
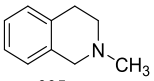
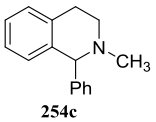
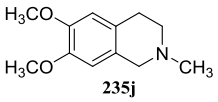
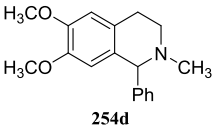
5.3.3 Application of the Anaerobic Conditions to the Synthesis of Alkaloids

The next step in the investigation corresponded to the application of the $BrCCl_3$ anaerobic oxidation conditions in the synthesis of natural products. N-methyltetrahydroisoquinoline **235q** which proved to generate a stable iminium ion **253a** was chosen as substrate to attempt the synthesis of tetrahydroisoquinoline-containing alkaloids. With this purpose, GRIGNARD reagents were used as quenching nucleophiles of the pre-formed dihydroisoquinolinium salts **253**.[224] Initial results showed that the reaction of the Grignard reagent with acetonitrile (solvent) and/or the excess of $BrCCl_3$ took place preferentially. However, when the iminium ion was pre-formed in acetonitrile, followed by solvent exchange and subsequent addition of the Grignard reagent, the reaction proved to be successful. Dichloromethane at 0 °C proved to be the best reaction conditions, giving rise to the highest yields for the addition of the organomagnesium reagent. In this fashion, (±)-carnegine[225] (**254a**), 1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline (**254b**), and some cryptostylines[226] analogous (**254c,d**) were synthesized (Table 19).

Table 19. Synthesis of (±)-carnegine (**254a**) and other 1-substituted tetrahydroisoquinolines by GRIGNARD addition.



235 253 254

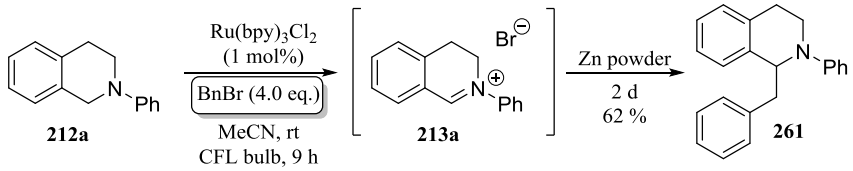
Entry	Amine	GRIGNARD reagent	Product	Yield (%)[a]
1	 235j	CH_3MgBr	 254a	73
2	 235q	CH_3MgBr	 254b	41
3	 235q	PhMgBr	 254c	50
4	 235j	PhMgBr	 254d	60

[a] Isolated yield.

5.3.4 Additional Findings

5.3.4.1 One-Pot Photocatalytic Oxidation/BARBIER-Type Reaction of Tertiary Amines

Motivated by the results obtained with $BrCCl_3$ as an alternative oxidant for the photo-oxidation of tertiary amines, it was decided to test benzyl bromide as potential photo-oxidant. Initial attempts using *N*-methyl-1,2,3,4-tetrahydroisoquinoline (**235q**) only afforded the N-quaternization product when subjected to visible light photo-oxidation conditions with $Ru(bpy)_3Cl_2$ (**202**, 1 mol%) and benzyl bromide (4.0 eq.). However, when *N*-methyl-1,2,3,4-tetrahydroisoquinoline (**212a**) was submitted to the same reaction conditions, the formation of the iminium salt **213a** was successfully achieved within 9 h (monitored by LC-MS). In order to take advantage of the excess of benzyl bromide along with the iminium salt **213a**, zinc powder was added to the reaction mixture to induce a BARBIER-type reaction.[227] Remarkably, after 2 days 1-benzyltetrahydroisoquinoline **261** was isolated in 62 % yield (Scheme 95).

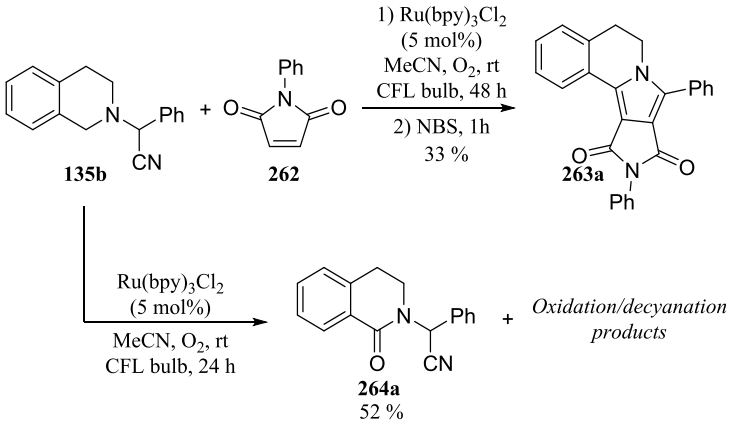


Scheme 95. One-Pot Photocatalytic Oxidation/BARBIER-Type Reaction.

Although the reaction proved to be effective, a narrow scope might be expected as only tertiary amines that do not undergo N-quaternization reactions can be used. Moreover, this also limits the used of other and more reactive benzyl bromides.

5.3.4.2 Photo-oxidation of α-Aminonitriles

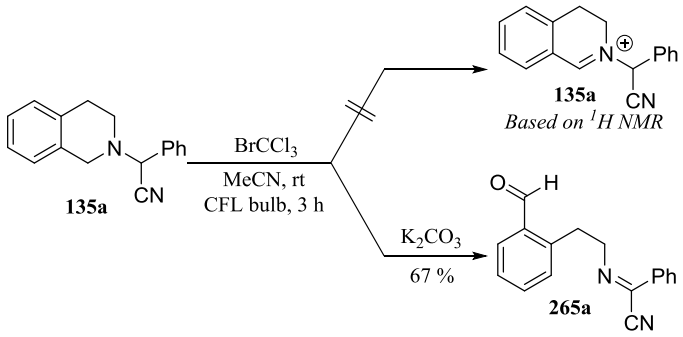
During an early stage investigation of the aerobic photo-oxidation of tertiary amines, it was observed that α-aminonitrile **135b**, in the presence of *N*-phenylmaleimide (**262**) underwent a [3+2]-dipolar cycloaddition via photogenerated azomethine ylide. In this manner, tetracyclic amine **263** was obtained in 33 % yield after oxidative aromatization with NBS.[228,229] On the other hand, when α-aminonitrile **135b** was directly subjected to the aerobic photo-oxidation conditions, amide **264a** was obtained in 52 % along with some oxidation/decyanation products (Scheme 96).



Scheme 96. Aerobic Photo-oxidation of α-aminonitrile **135b**.

In order to generate a more efficient method to oxidize α-aminonitrile **135b**, the corresponding anaerobic $BrCCl_3$ photo-oxidation reaction was attempted. However, after 72 h of irradiation, ^{1}H NMR reaction monitoring showed nothing more than a downfield shifting of the NMR signals of compound **135b**. This behavior was initially attributed to a potential formation of the corresponding amine hydrohalide. Thus, to avoid its formation, the reaction was performed in the presence of K_2CO_3. After 20 h of irradiation, an unexpected product identified as aldehyde **265a** was obtained in 67 % yield. Surprisingly, under these reaction conditions, α-aminonitrile

135b underwent not only a C–N cleavage but also an unexpected oxidation of the aminonitrile part to a corresponding imidoyl cyanide moiety (Scheme 97).

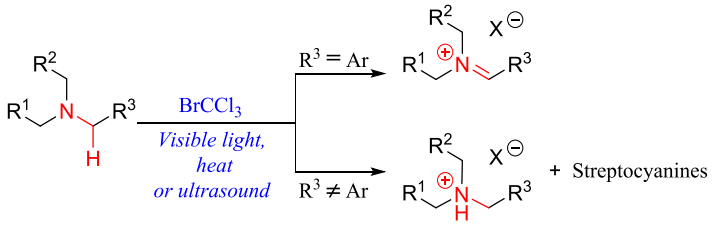


Scheme 97. Unexpected formation of imidoyl cyanide **265**.

Although these preliminary results showed that α-aminonitrile **135a** can undergo chemical transformations via photo-oxidation with $BrCCl_3$, further investigations might be necessary in order to fully understand the behavior of this reaction.

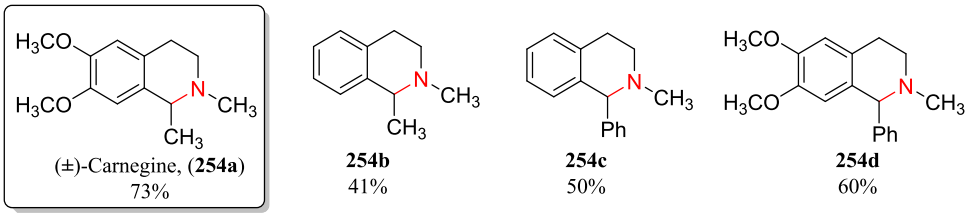
5.4 Conclusions

The anaerobic oxidation of trialkylamines with $BrCCl_3$ induced by visible light, heat or ultrasonication was investigated. The results showed that *N*-methyl-1,2,3,4-tetrahydroisoquinolines generate iminium ions as the main products, while aliphatic trialkylamines with α-hydrogen are protonated instead. Furthermore, it was shown that neither moisture nor solvent participated in the formation of hydrohalides. Therefore, the only possible hydrogen source was the amine itself as sacrificial reductant to form hydrogen halide via an oxidative mechanism involving the formation of cyanine **258** and homologs.



Scheme 98. Photo-oxidation of trialkylamines with $BrCCl_3$.

The application of this photo-oxidation method was demonstrated by intercepting the photogenerated iminium ions with GRIGNARD reagents. By this manner, the synthesis of (±)-carnegine (**254a**), 1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline (**254b**), and some cryptostylines (**254c,d**) analogous was achieved in good to moderate yields (Scheme 99).



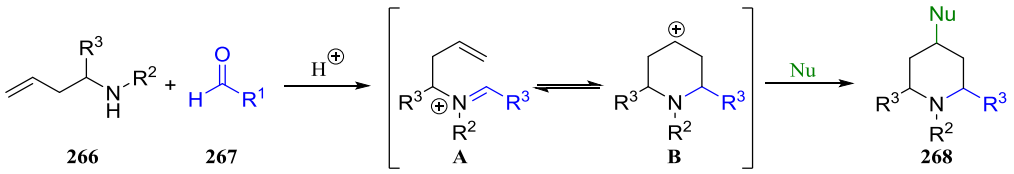
Scheme 99. Synthesized 1-substituted tetrahydroisoquinolines **254**.

DFT calculations were performed in order to understand the iminium ion formation. These results suggested a free-radical reaction propagated by trichloromethyl radicals in which the respective steps can proceed in an all-exergonic manner. Unfortunately, the initial radical generation, as well as the light absorbing species, could not be identified.

Part III

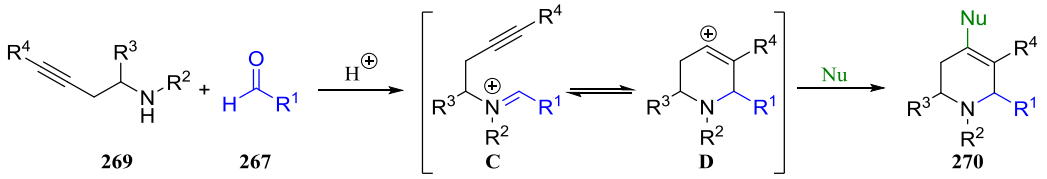
Alkyne Aza-PRINS Cyclization

Over the last decades, the PRINS cyclization reaction has become one of the fundamental tools in organic chemistry for the preparation of not only oxygen-containing heterocycles,[230,231] but also nitrogen-based analogous—aza-PRINS cyclization.[232] This successful modification usually involves the condensation of homoallylic amines **266** with aldehydes **267** under acidic conditions to produce 2,4-disubstituted piperidines **268** via an alkene-iminium ion cyclization (Scheme 100).[233-235]



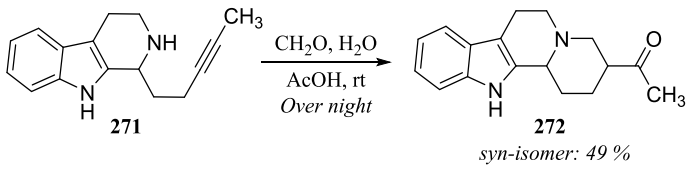
Scheme 100. Aza-PRINS cyclization.

This reaction can also be extended to alkynylamines **269** as condensation/cyclization partners of aldehydes **267**. However, cyclizations of this type are relatively scarce and less investigated than their alkene equivalent.[235,236] A major reason for this gap is that alkynes are in general less reactive than alkenes towards electrophiles such iminium ions.[236,237] This difference in reactivity has been attributed to the higher energy vinyl carbocation intermediate **D**, formed during the endocyclic closure, compared to the corresponding stable carbocation **B** (Scheme 101).[238-242]



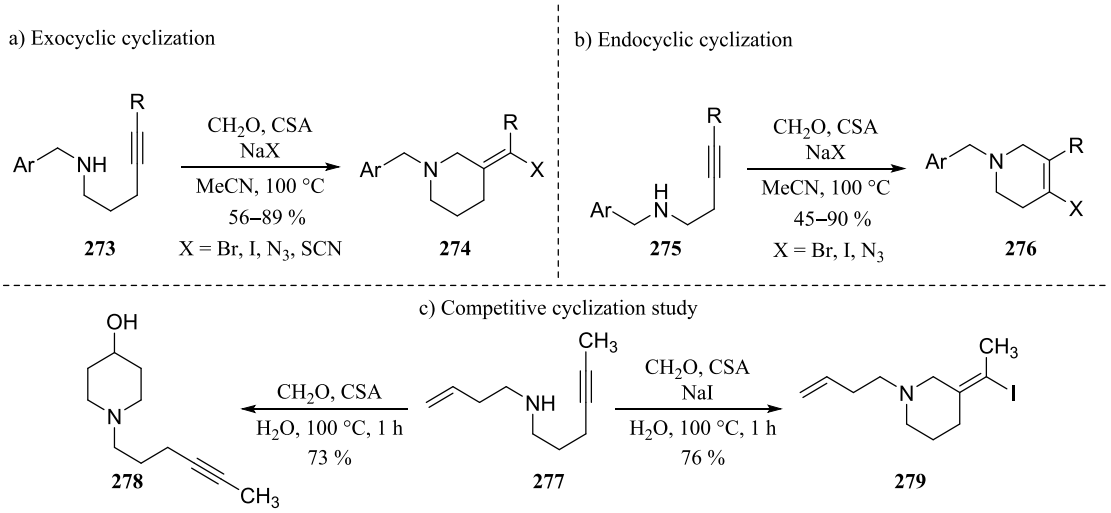
Scheme 101. Alkyne aza-PRINS cyclization.

Despite these limitations, some successful examples on the alkyne aza-Prins cyclization have been achieved. The first example of this alkyne-iminium ion cyclization was reported by WINTERFELDT et al. in late 1977.[243] In this case, tetrahydro-β-carboline **272** was prepared as a mixture of diastereomers by cyclization of 4-hexynylamine **271** and aqueous formaldehyde under acidic conditions (Scheme 102).



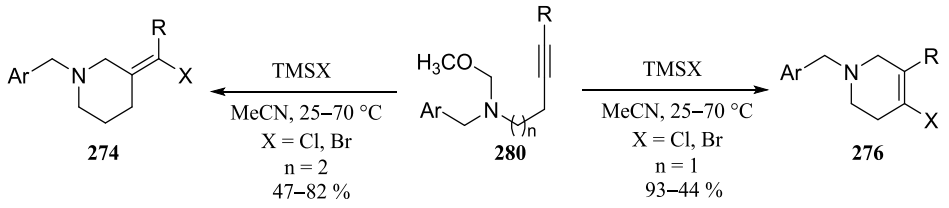
Scheme 102. Synthesis of tetrahydro-β-carboline (**272**).

Ten years later, OVERMAN and co-workers observed that 4-hexenylamines **273** and paraformaldehyde in the presence of camphorsulfonic acid (CSA) did not cyclize even when heated for 1 h at 100 °C.[244,245] However, under similar conditions but in the presence of nucleophilic anions, 3-alkylidene-piperidines **274** were formed in 56–89 %. (Scheme 103a). Moreover, while amines **273** cyclized in a *6-exo-dig* fashion, terminal and internal 3-alkynylamines **275** undertook an exclusively *6-endo-dig* pathway to compounds **276** under the influence of bromide or iodide anions (Scheme 103b). Additionally, the same author demonstrated the disposition of alkynes to cyclization in the presence of external nucleophiles when a dual alkyne/alkene-amine **277** compete as intramolecular π-nucleophiles. Thus, cyclization of amine **277** in water afforded 4-hydroxypiperidine **278** in 73 % yield while identical treatment but in the presence of NaI afforded vinyl iodide **279** in 76 % yield (Scheme 103c).



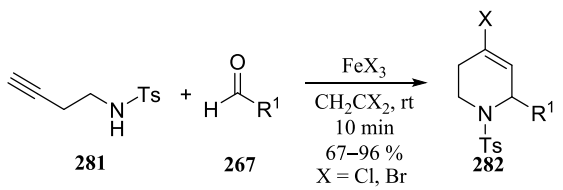
Scheme 103. OVERMAN's investigation on the nucleophile-promoted electrophilic cyclization of alkynes.

In 1996, OVERMAN and MURATA complemented the above mentioned study by developing an aprotic method that takes advantage of mixed N,O-acetals **280** as mask iminium ions and TMSX as the source of nucleophilic anions (Scheme 104).[246]



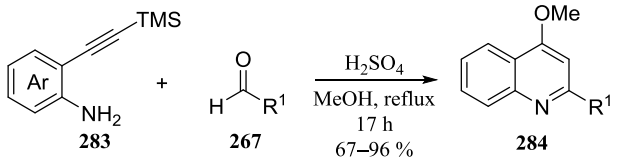
Scheme 104. N,O-acetals as mask iminium ions.

Later, PADRÓN et al. described a remarkable iron(III) halide-promoted alkyne aza-PRINS cyclization between N-tosylpropargylamines **281** and aldehydes **267**.[247] By this manner, 4-halotetrahydropyridines **282** were obtained in moderate to high yields induced by equimolar amounts of anhydrous FeX_3 (1.5 eq., Scheme 105). A catalytic modification of this method was later reported by the same author using iron(III) acetylacetonate ($Fe(acac)_3$, 7 mol%) and TMSCl (1.0 eq.).[248]



Scheme 105. Iron(III)-promoted alkyne aza-PRINS cyclization.

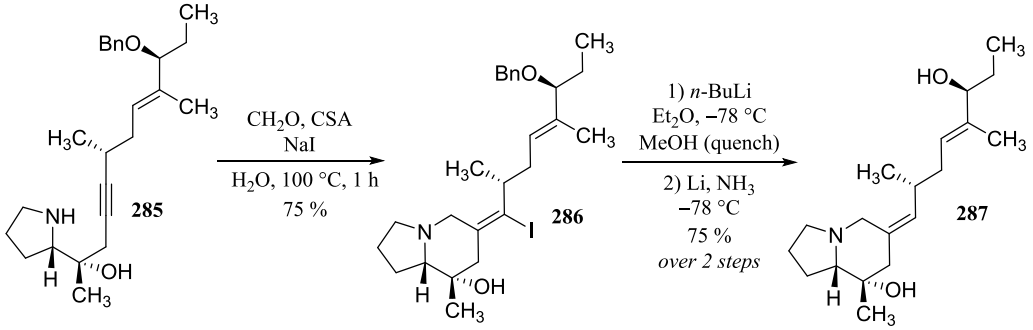
Most recently, ZHU and co-workers reported an efficient synthesis of 2-arylquinolines from alkynylanilines **283** and aromatic aldehydes **267** in the presence of sulfuric acid (Scheme 106).[249]



Scheme 106. Synthesis of 2-arylquinolines **284**.

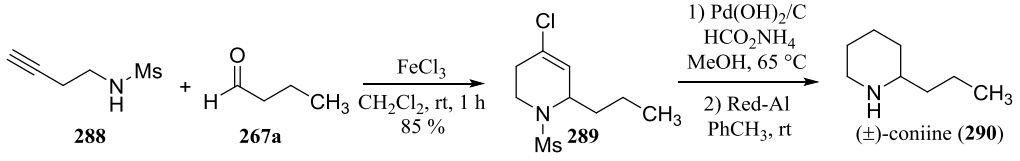
Application in Natural Products Synthesis

The utility of the alkyne aza-PRINS cyclization reaction in the natural product synthesis was firstly demonstrated by OVERMAN and SHARP with the preparation of (±)-pumiliotoxin A (287).[250] This *Dendrobates* alkaloid was obtained by applying the reaction conditions for nucleophile-induced electrophilic cyclization reported by the same authors to substrate **285** followed by deiodination with *n*-BuLi (Scheme 107).



Scheme 107. Synthesis of (±)-pumiliotoxin A (**287**).

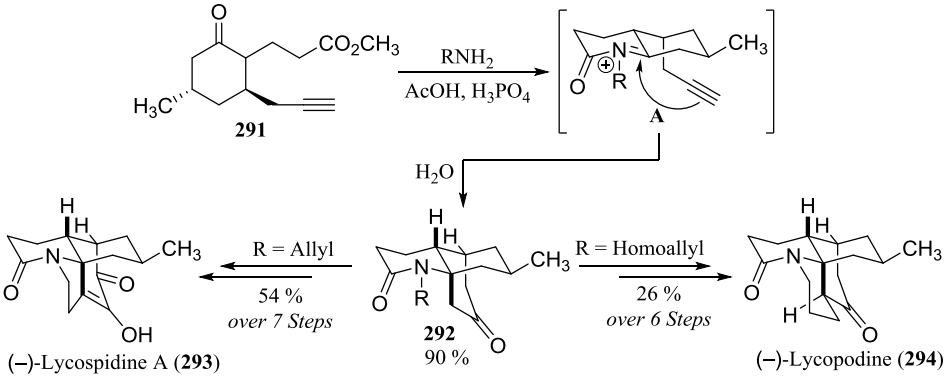
More recently, PADRÓN and co-workers applied their iron(III)-promoted cyclization method to the preparation of alkaloid (±)-coniine (**290**).[251] In this manner, stoichiometric amounts of $FeCl_3$ induced the cyclization of homoprogargylamine **288** and butanal **267a** to the corresponding tetrahydropyridine **289**. Dehydrogenation of the chlorovinyl moiety with $Pd(OH)_2/C$ and ammonium formate follow by demesylation with Red-Al afforded the expected (±)-coniine (**290**)



Scheme 108. Synthesis of (±)-coniine (**290**).

In 2016, SHE et al. reported the asymmetric total synthesis of *Lycopodium* alkaloids (–)-lycospidine A (**293**) and (–)-lycopodine (**294**) via phosphoric acid promoted alkyne aza-PRINS cyclization.[252,253] These alkaloids were prepared from intermediate **291**, which in turn was

synthesized in 5 steps from commercially available (*R*)-pulegone. Amidation/aza PRINS cyclization of compound **291** via iminium **A** afforded the corresponding tricyclic key intermediate **292** in 90 % yield. From this common intermediate, (–)-lycospidine A (**293**) was obtained in 54 % yield over 7 steps involving a late-stage oxidation followed by a reduction / oxidation sequence, while (–)-lycopodine (**294**) was afforded in 26 % yield over 6 steps, including an aldol condensation, a sequential reduction of the amide and ketone moieties and a JONES oxidation (Scheme 109).



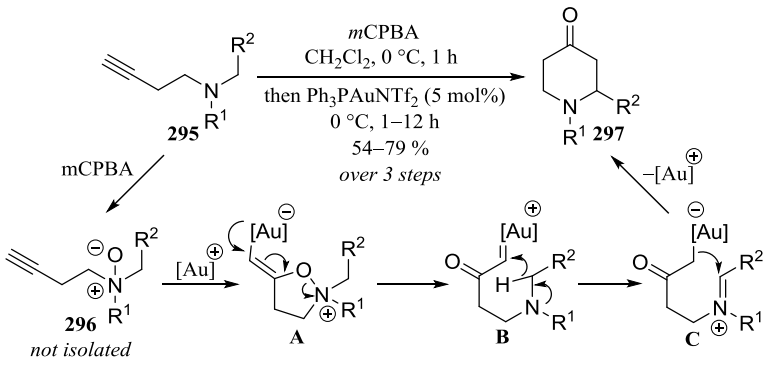
Scheme 109. Asymmetric total synthesis of *Lycopodium* alkaloids.

Chapter 6

NBS-Induced Oxidative C–H Activation / Aza-PRINS-Type Cyclization of Tertiary Alkynylamines

6.1 Introduction

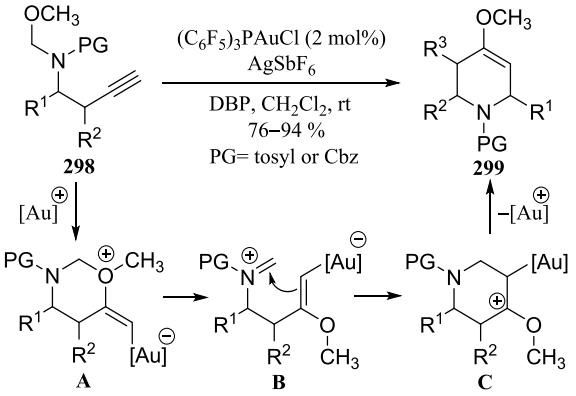
Oxidative C(sp^3)–H bond activation reaction represents an important and emerging tool in the α-functionalization of tertiary amines.[254] An unexplored but very interesting application of this C–H activation method is the preparation of nitrogen-containing six-membered rings via intramolecular cyclization of alkynes. One of the first examples was accomplished in 2009 by ZHANG and co-workers via gold(I) catalysis.[255] In this pioneering work, tertiary homopropargyl amines **295** were initially oxidized by *m*CPBA to their corresponding N-oxides **296**, which upon treatment with a catalytic amount of $Ph_3PAuNTf_2$ underwent a cyclization to the piperidin-4-ones **297**. The mechanism of the reaction was proposed to go through an initial 5-*exo*-*dig* cyclization to intermediate **A** followed by formation of a gold α-oxo carbenoid **B**. Intramolecular [1,5]-hydride shift of the N-methylene group of the carbenoid **B** afforded iminium ion **C** possessing a nucleophilic gold enolate moiety. Subsequent MANNICH-type cyclization of **C** produced the corresponding piperidin-4-ones **297** (Scheme 110).[256]



Scheme 110. Gold-catalyzed synthesis of piperidin-4-ones **297**.

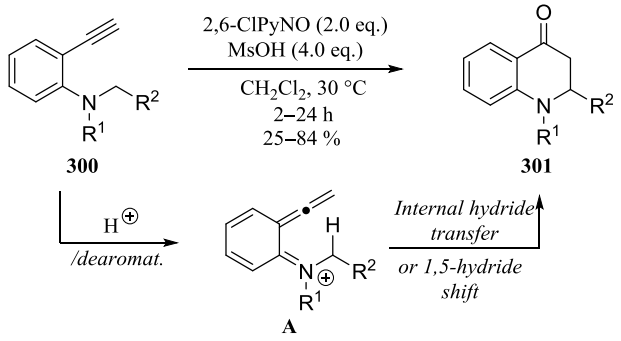
In the same year, RHEE et al. described the synthesis of 4-methoxytetrahydropyridines **299** by a formal alkyne aza-PRINS cyclization induced by gold(I).[257] For this purpose,

homopropargylamines **298** bearing a mixed N,O-acetal were subjected to cycloisomerization conditions using catalytic amounts (2 mol%) of tris-(pentafluorophenyl)phosphine gold(I) ($(C_6F_5)_3PAu\ Cl$) and 2,6-di-*tert*-butylpyridine (DBP). The authors proposed a similar mechanism as ZHANG but with an initial *6-exo-dig* cyclization to intermediate **A** (Scheme 111).



Scheme 111. Preparation of compounds **299** via gold (I) catalyzed formal alkyne aza-PRINS cyclization.

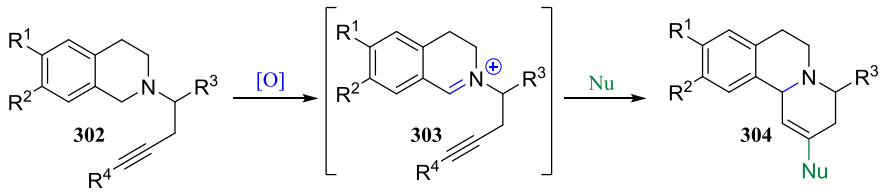
Recently, GONG and co-workers reported a metal-free oxidation/C(sp^3)–H functionalization of alkynylanilines **300** using methanesulfonic acid (MsOH, 4.0 eq.) and 2,6-dichloropyridine *N*-oxide (2,6-ClPyNO, 2.0 eq.).[258] Mechanistically, the authors proposed that the reaction started with the formation of intermediate allene **A** via protonation/dearomatization sequence, which could afford product **301** by internal hydride transfer or 1,5-hydride shift. Pyridine N-oxide was suggested as an external oxidant allowing an overall oxidative transformation to the cycloalkylketone **301** (Scheme 112).



Scheme 112. Alkynes activated by MsOH as hydride acceptors.

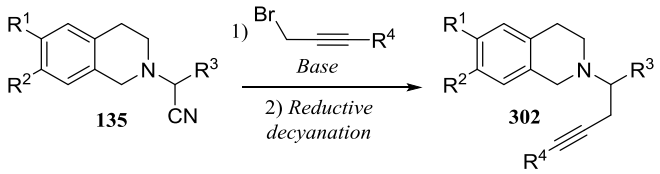
6.2 Aim of the Research

The development of new methods for the preparation of heterocyclic systems is currently an important goal in organic chemistry. For this reason and motivated by the lack of examples on oxidative C–H activation/cyclization reactions of tertiary alkynylamines, a new and alternative metal-free approach for the preparation of nitrogen-containing six-membered rings is postulated. For this purpose, it was anticipated that tertiary alkynylamines **302** could be oxidized to the corresponding iminium ions **303** and therefore undergo an intramolecular alkyne electrophilic cyclization with its alkyne moiety to generate tetrahydropyridines **304** (Scheme 113).



Scheme 113. Oxidative C–H activation/alkyne cyclization.

Furthermore, alkynylamines **302** could be obtained from α-aminonitriles **135** via C-alkylation/reductive decyanation process (Scheme 114).



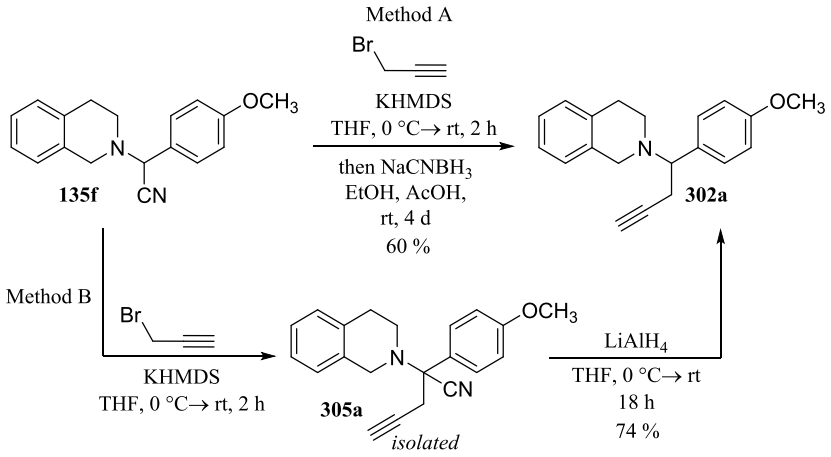
Scheme 114. Proposed alkylation/reductive decyanation process of α-aminonitriles **135**.

The selection of alkynylamines **302** as study case is based on the importance of the expected structure of the corresponding cyclization products **304**. This tricyclic framework can be found in several natural products such as tetrabenazine, emetine, berberine, protoemetinol, yohimbine, and others.[259,260]

6.3 Results and Discussion

6.3.1 Initial Observations

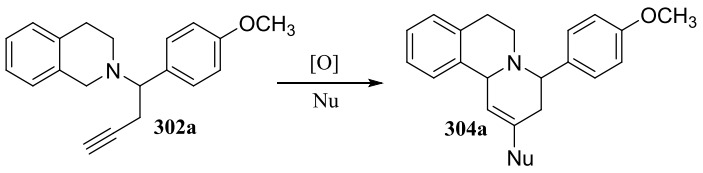
The first stage of the investigation was the selection and synthesis of homopropargylamine **302a**. This compound was chosen as the model substrate as it contains one characteristic methoxy group which could serve as an internal reference signal during ^{1}H NMR reaction monitoring to better identify conversion of the starting material and product(s) formation. Homopropargylamine **302a** was prepared from the corresponding α-aminonitrile **135f** in 60 % yield by deprotonation / C-alkylation with KHMDS and propargyl bromide, followed by *in situ* reductive decyanation with $NaCNBH_3$ and acetic acid (method A). This compound was also obtained in 74 % yield by a stepwise procedure involving the isolation of quaternary α-aminonitrile **305a** followed by reduction with $LiAlH_4$ (method B, Scheme 115).



Scheme 115. Synthesis of homopropargylamine **302a**.

As soon as compound **302a** was synthesized, the corresponding oxidation / cyclization reaction was investigated. Consequently, different reaction conditions were tested, and the results are depicted in Table 20.

Table 20. Oxidative C–H activation/alkyne cyclization.[a]



Entry	Oxidant	Catalyst	Solvent	Temperature [Ox]→[Cy][b]	Reaction Time [Ox]→[Cy][b]	Intermed.	Product
1	*m*CPBA (1.0 eq.)	$Ph_3PAuNTf_2$ (5 mol%)	CH_2Cl_2	0 °C→rt	1 h→3 d	N-oxide	—[c]
2	*m*CPBA (1.0 eq.)	$Ph_3PAuNTf_2$ (5 mol%)	DCE	0 °C→84 °C	1 h→3 d	N-oxide	—[c]
3	$BrCCl_3$ (1.1 eq.)	Visible light	MeCN	rt→rt	4 h→1 d	Iminium $Br^{\ominus}/Cl^{\ominus}$	—[c]
4	$BrCCl_3$ (1.1 eq.)	Visible light	MeCN	rt →Reflux	4 h→3 d	Iminium $Br^{\ominus}/Cl^{\ominus}$	Br **304a1** *m/z* = 370.1
5	NBS (1.1 eq.)	—	MeCN	rt →Reflux	30 min→ 1.2 d	Iminium $Br^{\ominus}$	Br **304a1** *m/z* = 370.1
6	Bobbitt's salt (1.1 eq.)	—	MeCN	rt →Reflux	30 min→ 2 d	Iminium $BF_4^{\ominus}$	—[c]
7	NCS (1.1 eq.)	—	MeCN	rt →Reflux	30 min→ 1 d	Iminium $Cl^{\ominus}$	Cl **304a2** *m/z* = 325.1

[a] The test reactions were carried out under an argon atmosphere and using dry solvents. [b] [Ox] represents the temperature/time for the oxidation step; [Cy] represents the temperature/time for the cyclization step. [c] Cyclization product was not detected.

Initially, gold catalyzed reaction conditions reported by ZHANG and co-workers[255] were tested on the substrate **302a** (entries 1 and 2). Although *m*CPBA successfully oxidized homopropargyl amine **302a** to its N-oxide (judged by TLC), gold(I) catalysis failed to give the corresponding cyclized product, even when high temperature was used. As described in chapter 5, $BrCCl_3$ has

proved to be able to oxidize N-substituted tetrahydroisoquinolines to iminium salts under the influence of visible light. Based on this and aiming to induce the alkyne cyclization by the corresponding counter ion from the iminium salt, substrate **302a** was subjected to $BrCCl_3$ oxidation conditions. As expected, $BrCCl_3$ and visible light afforded the formation of the iminium ion **303a** but without the cyclization product (entry 3). Besides the hydrohalide side product that usually accompanies this oxidation, LC-MS analysis of the reaction mixture also showed the formation of $BrCCl_3$ addition products. Interestingly, when the pre-formed iminium ion **303a** from entry 3 was heated to reflux for 3 days (entry 4), a new product with a molecular mass matching a cyclized product containing a bromine atom, was detected (LC-MS analysis). Attempts to isolate or identify this product by NMR were not possible due to the presence of several by-products. To reduce the formation of these by-products, *N*-bromosuccinimide (NBS) was tested as the oxidant. Remarkably under this condition, homopropargyl amine **302a** was exclusively oxidized to iminium bromide **303a** after 30 minutes (judge by TLC, ^{1}H NMR, and LC-MS), and then transformed to the previous observed brominated species after 2 days of refluxing (entry 5). NMR analysis of the reaction mixture confirmed the identity of this brominated species as the expected 6-*endo-dig* cyclization product **304a1**, which was formed as a mixture of diastereomers in a 60 : 40 ratio (Figure 33). The crucial role of the bromide anion as nucleophilic promoter of the alkyne electrophilic cyclization was demonstrated when BOBBITT's salt (4-acetylamino-TEMPO BF_4) was used as the stoichiometric oxidant (entry 6). In this case, the formation of the corresponding iminium salt took place; however, after heating the reaction mixture at reflux for 2 days, no cyclization product was detected. The cyclization reaction also proceeded when *N*-chlorosuccinimide (NCS) was used as oxidant, affording chlorinated product **304a2** (entry 7).

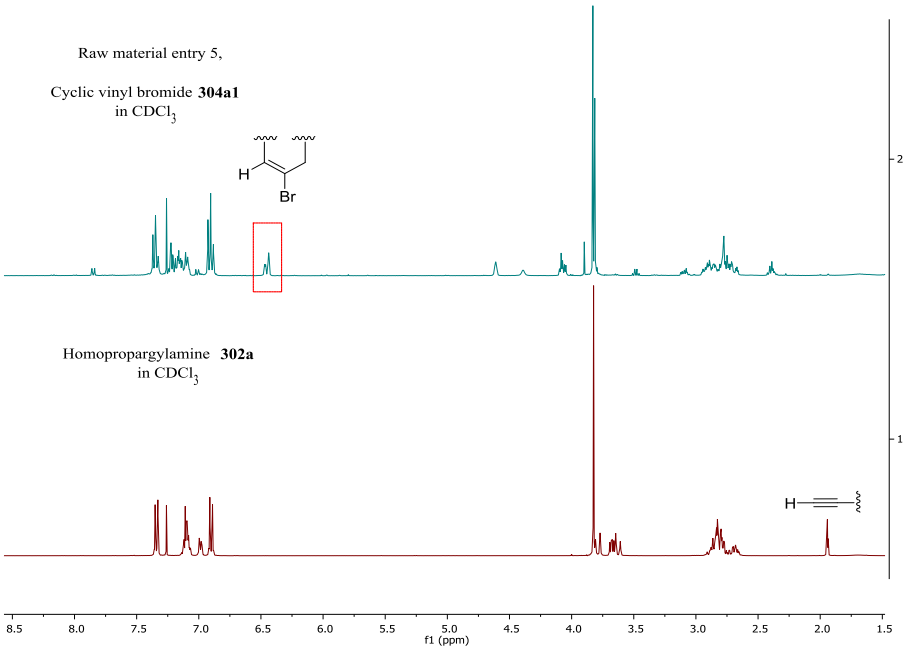
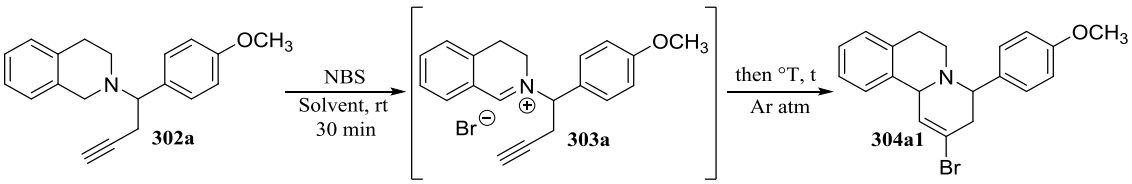


Figure 33. Formation of cyclic vinyl bromide **304a1** induced by NBS (entry 5).

6.3.2 Optimization of the Reaction Conditions

The above presented results show that the oxidative C–H activation / alkyne cyclization reaction was taking place. Therefore, different solvents, reaction times and heating sources were screened in order to improve the outcome (Table 21).

Table 21. Optimization of the oxidative C–H activation/alkyne cyclization.[a]

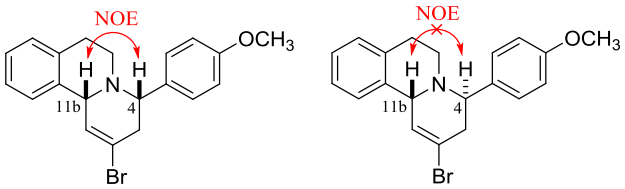


Entry	Oxidant	Solvent	Temperature	Reaction Time	Yield of 304a1(%)[a,b]
1	NBS (1.1 eq.)	MeCN	Reflux	29 h	61
2	NBS (1.1 eq.)	$CHCl_3$	66 °C	24 h	40
3	NBS (1.1 eq.)	$CHCl_3$	66 °C	3 d	88; 79[c]
4	NBS (1.1 eq.)	$CHCl_3$	120 °C (MW)[e]	20 min	91
5	NBS (1.1 eq.)	$CHCl_3$	120 °C (MW)[e]	5 min	84
6	NBS (1.1 eq.)	$CHCl_3$	120 °C (MW)[e]	15 min	94; 88[c]
7	NCS (1.1 eq.)	$CHCl_3$	120 °C (MW)[e]	15 min	30[c,d]

[a] Dry solvents were used. [b] Determined by ^{1}H NMR spectroscopy using CH_2Br_2 as internal standard. [c] Isolated yield. [d] Corresponds to only one diastereomer from compound **304a2**. [e] Microwave irradiation (MW) at 200 W.

In this manner, compound **304a1** was initially obtained in 61 % yield after 29 h at reflux in acetonitrile (entry 1). When chloroform was used as a solvent, the reaction proceeded in 40 % yield after 24 h at 66 °C (entry 2). Although the formation of the iminium salt **303a** in chloroform was slower, the reaction was cleaner than in acetonitrile (judged by ^{1}H NMR). When the reaction time was extended to 72 h at the same temperature, compound **304a1** was isolated in 79 % yield in a 60 : 40 diastereomeric ratio (entry 3). To reduce the extensive reactions times, it was decided to heat the reaction mixture at 120 °C under microwave irradiation (200 W, entries 4–6). In this fashion, the best transformation was achieved after 15 minutes of microwave irradiation, yielding compound **304a1** in 88 % yield in a 60 : 40 diastereomeric ratio (entry 6). Formation of chlorinated analog **304a2** was also attempted under the standardized conditions, however, only 30 % yield was achieved (entry 7).

From the isolated mixture on entry 6, compound **304a1** was separated in its corresponding isomeric constituents by flash column chromatography ($R_{f\text{major}}$= 0.42, $R_{f\text{minor}}$= 0.22, using a mixture of cyclohexane/EtOAc 10 : 1). The relative stereochemistry of each diastereomer was then determined by NOESY NMR. The major component was identified to possess a *cis* configuration at the C4–C11b, while the minor constituent possesses a *trans* configuration at the same carbon atoms (Figure 34). Rapid decomposition of these products was observed when exposed to light and air, therefore it was always necessary to work and store them under an inert atmosphere and in the absence of light.



major
cis-isomer **304a1**

minor
trans-isomer **304a1**

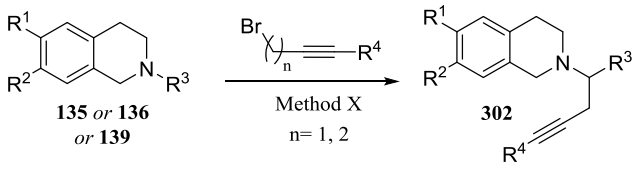
Figure 34. The relative stereochemistry of tricyclic system **304a1**.

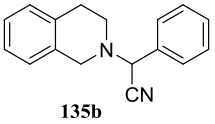
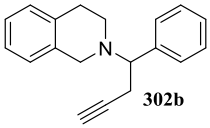
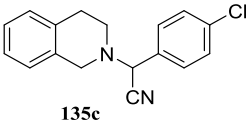
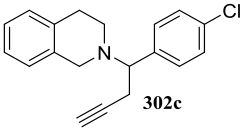
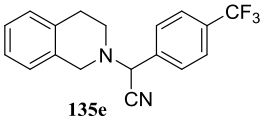
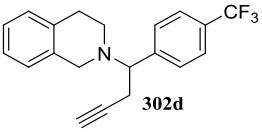
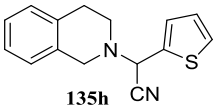
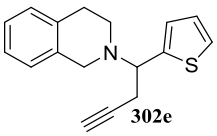
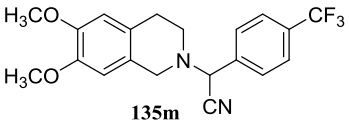
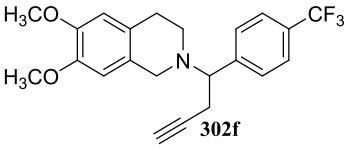
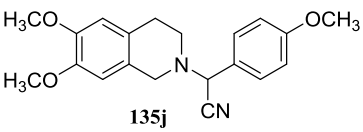
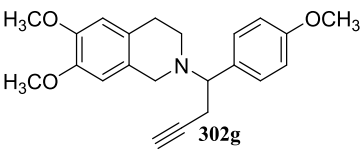
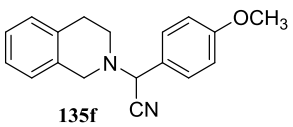
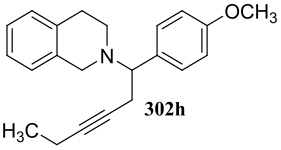
6.3.3 Reaction Scope

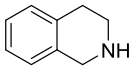
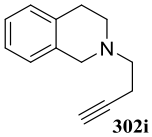
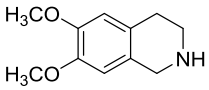
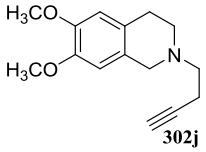
In order to investigate the scope of the reaction, ten new alkynylamines **302** were synthesized from the corresponding α-aminonitriles **135** by C-alkylation with alkynyl bromides followed by *in situ* reductive decyanation with $NaCNBH_3$ under acidic conditions (method A). In some cases, a stepwise procedure involving the isolation of quaternary α-aminonitriles **306** followed by reduction with $LiAlH_4$ was used (method B). This method afforded homopropargylamines in shorter times, however, its application to other substrates resulted in unsatisfactory results.

Unsubstituted homoprogargylamines **302** were prepared by direct N-alkylation of tetrahydroisoquinolines **136** or **139** with homopropargyl bromide (method C, Table 22).

Table 22. Synthesis of substrates **302**.



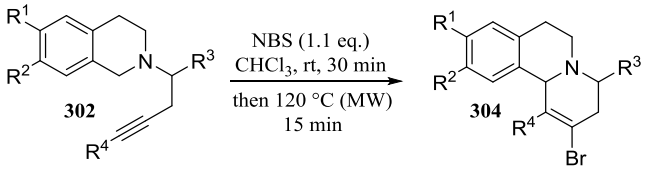
Entry	Starting Material	Alkynyl Bromide	Product	Yield (%)[a]
1	 **135b**	n=1 R^4=H	 **302b**	Method A 33
2	 **135c**	n=1 R^4=H	 **302c**	Method A 69
3	 **135e**	n=1 R^4=H	 **302d**	Method A 52
4	 **135h**	n=1 R^4=H	 **302e**	Method B 12
5	 **135m**	n=1 R^4=H	 **302f**	Method A 58
6	 **135j**	n=1 R^4=H	 **302g**	Method A 35
7	 **135f**	n=1 R^4=CH_2CH_3	 **302h**	Method A 52

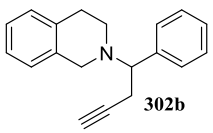
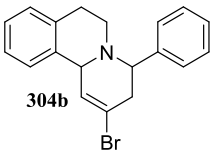
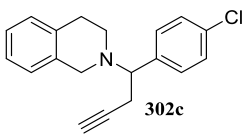
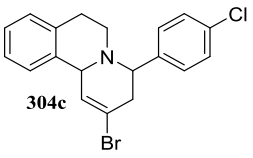
8	 **136**	n=2 R^4=H	 **302i**	Method C 81
9	 **139**	n=2 R^4=H	 **302j**	Method C 69

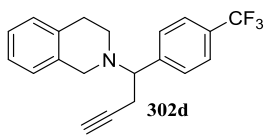
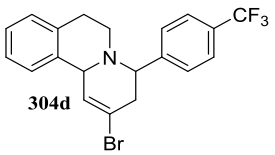
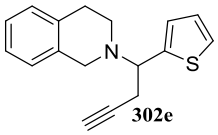
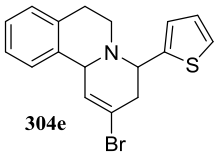
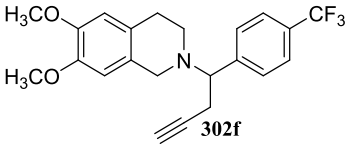
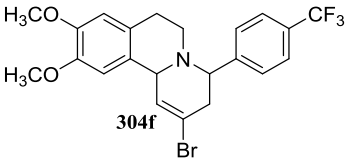
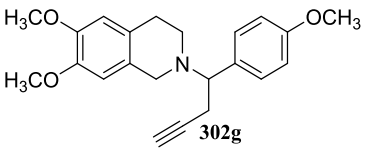
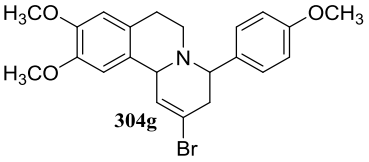
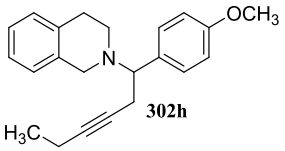
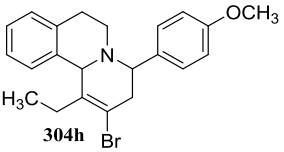
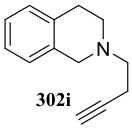
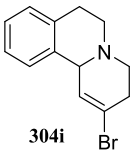
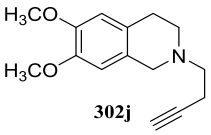
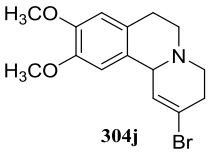
[a] Isolated yield. **Method A**: i) KHMDS, alkynyl bromide, THF, 1 h at 0 °C→1 h at rt. then $NaCNBH_3$, EtOH, AcOH, 4 days at rt; **Method B**: i) KHMDS, alkynyl bromide , THF, 1 h at 0 °C→1 h at rt. ii) $LiAlH_4$, THF, 0 °C→rt, 18 h. **Method C**: K_2CO_3, alkynyl bromide, MeCN, 24 h at rt.

Once the set of alkynylamines **302** was synthesized, the corresponding study on the scope of the oxidative C–H activation / aza-PRINS cyclization was carried out. For this purpose, alkynylamines **302** were subjected to the already optimized reaction conditions obtained for the preparation of **304a1**. In all cases, compounds **304b**–**j** were obtained as *cis/trans* diastereomeric mixtures in a 60 : 40 ratio. In most of the examples, these mixtures were separated by flash chromatography affording the respective *cis/trans*-isomers (Table 23).

Table 23. Synthesis of pyrido[2,1-*a*]isoquinolines **304** via One-pot Oxidative C–H Activation/Alkyne-Aza-Prins Cyclization.



Entry	Alkynylamines 302	MW Irradiation Time	Starting Material	Yield (%)[a]
1	 **302b**	15 min	 **304b**	73
2	 **302c**	15 min	 **304c**	78

3	 **302d**	15 min	 **304d**	92
4	 **302e**	15 min	 **304e**	86
5	 **302f**	15 min	 **304f**	18[b]
6	 **302g**	30 min	 **304g**	52
7	 **302h**	15 min	 **304h**	40[b]
8	 **302i**	15 min	 **304i**	77
9	 **302j**	30 min	 **304j**	38

[a] Isolated yield. [b] Only the *cis*-isomer could be isolated from the reaction mixture; *trans*-isomer contained unidentified impurities.

The initial oxidation of alkynylamines **302** induced by NBS proceeded very efficiently in all cases. Even more importantly, the generated iminium salts **303** reacted successfully via the expected electrophilic 6-*endo-dig* cyclization process (entries 1–9). In some cases, due to the presence of concomitant impurities, only one diastereomer was isolated (entries 5 and 7). In general, different R^3 substituents carrying electron neutral, withdrawing or donating groups resulted compatible with this transformation (entries 1–9). However, the corresponding R^1 and

R^2 substituents at the isoquinolinic ring revealed to have an influence on the efficiency of the electrophilic 6-*endo-dig* cyclization step (entries 5, 6 and 9). This could be explained based on the electrophilic character of the iminium ion involved. Thus, groups that lower the reactivity of the iminium ion (e.g donating groups) would have a negative impact for the cyclization process and vice versa. These observations indicate that the electronic characteristics of the iminium ion also play a main role during the alkyne aza-prins cyclization. Additionally, entry 8 showed that internal alkyne **302** was also able to be cyclized under the presented reaction conditions.

As in the case of compound **304a1**, all tricyclic derivatives **304** proved to be very sensitive towards exposition to light and air, therefore it was always necessary to work and storage them under inert atmosphere and in the absence/protection of light.

6.3.4 Mechanistic Proposal for the Alkyne Aza-PRINS Cyclization Step

Intrigued by the results obtained for the 6-*endo-dig* cyclization step, an investigation of the potential operating mechanism was performed.

As mentioned in the introduction of part III, it has been proposed that alkyne PRINS cyclizations reactions involve the formation of highly energetic cyclic vinyl carbocations, which then can be trapped by external nucleophiles (see Scheme 101).[238-242] Nevertheless, this assumption leaves out the involvement of the nucleophile at the initial activation step, which can have an important role as promoters of the cyclization as demonstrated by the presented results and by OVERMAN (see Scheme 103).[244]

In order to have an insight on the mechanism of the alkyne aza-PRINS cyclization, DFT calculations were carried out by Stefan PUSCH. Iminium salt **303j** was selected as the simplest model substrate for the computational methods. The relative energies obtained from these calculations are displayed in Figure 35.

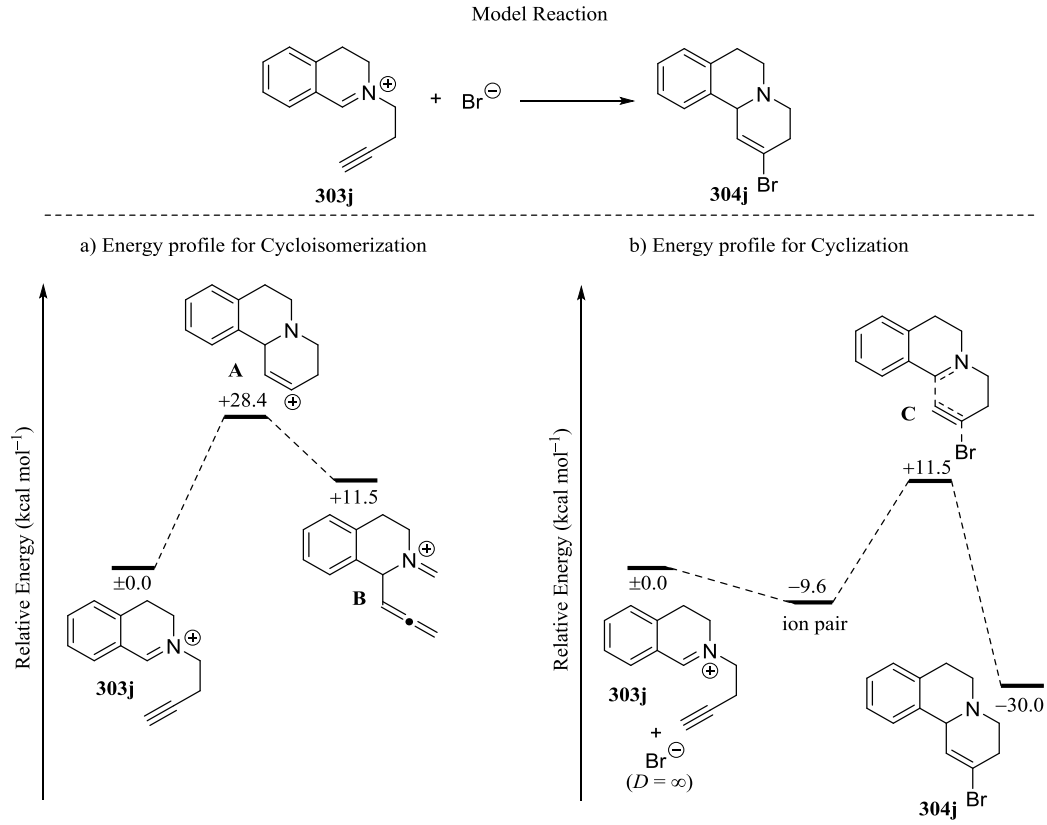


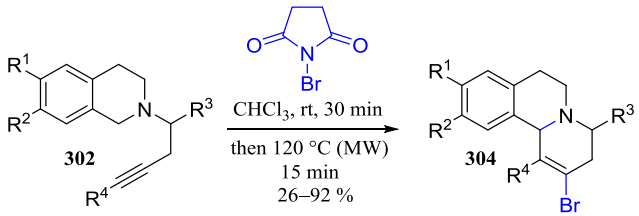
Figure 35. Energy profiles.

Figure 35a shows the calculations without involvement of a nucleophile. In this case, a stable cyclic vinyl carbocation was not located. The energy profile shows that this structure is rather a transition state between the starting material and the allene derivative via [3+3] sigmatropic rearrangement (Aza-COPE type rearrangement). Additionally, figure 35b depicts the energy profile obtained when the participation of a bromide was taken into account. The outcomes indicate that the nucleophilic addition is taking place on the triple bond in combination with the cyclization without a distinct carbocation intermediate.

These results can be suggested as a concerted termolecular addition (Ad_E3) mechanism, where the iminium ion coordinates with the triple bond to form a π-complex that is attacked by bromide. This type of mechanism has been proposed for the electrophilic hydrohalogenation of alkynes when halide ions are present.[238]

6.4 Conclusions

In summary, a novel and efficient one-pot metal-free oxidative C–H activation/aza-PRINS type cyclization of alkynylamines was developed. Remarkably, NBS was found to be the best oxidant for this transformation generating not only the iminium ion but also the nucleophilic bromide anion, which are crucial species to induce the corresponding alkyne electrophilic cyclization step. The scope of this method was demonstrated by the synthesis of ten new pyrido[2,1-*a*]isoquinolines **304** obtained from alkynylamines **302** in moderate to high yields (Scheme 116).



Scheme 116. Synthesis of new pyrido[2,1-*a*]isoquinolines **304**.

A mechanistic proposal for the alkyne aza-PRINS cyclization was described based on DFT calculations. In this manner, it was postulated that the reaction proceeds via a concerted bromide addition + electrophilic cyclization transition state without a distinct carbocation intermediate. This transition state is in accordance with a concerted termolecular addition (Ad_E3) mechanism proposed for the electrophilic hydrohalogenation of alkynes.

Furthermore, due to their tricyclic framework as well as the vinyl bromide moiety, the pyrido[2,1-*a*]isoquinolines **304** represent interesting building blocks for more complex organic molecules, such as natural products.

Part IV

Experimental Section

A General Methods

Solvents and Chemicals

Solvents and reagents were purchased from commercial suppliers (Sigma Aldrich, Alfa Aesar, TCI chemicals, ABCR ACROS organics and Fischer Scientific) and used as received unless noted otherwise. Anhydrous dichloromethane and acetonitrile were distilled under argon atmosphere from CaH_2 or P_2O_5 and collected over molecular sieves 4 Å (10 to 18 mesh, ACROS Organics). Anhydrous diethylether, toluene, and THF were distilled from sodium and benzophenone under argon atmosphere. $BrCCl_3$ was distilled under argon atmosphere, collected over molecular sieves 4 Å (10 to 18 mesh, ACROS Organics) and kept away from the light with an aluminum foil cover. The solvents used for chromatography were distilled prior to use. When necessary, the solvents were degasified using 3 freeze-pump-thaw cycles.

Reaction Conditions

Reactions under inert atmosphere

The reactions where exclusion of air and moisture was necessary were performed under argon atmosphere. In these cases, the glassware was heated three times under vacuum prior to use.

Microwave experiments

The microwave experiments were carried out using an apparatus from CEM (Discover system) at the indicated maximum temperature and power using air cooling. In these cases, special reaction vessels (10 mL or 30 mL) with Teflon-coated septa were used.

Photocatalyzed reactions

The photocatalyzed reactions were carried out using the following light sources:

- CFL lamp: *Dulux Superstar Microtwist* from Osram (220–240 V, 24 W, light output equivalent to conventional 115 W, E27, 4000 K).
- UV-A lamp: from Omnilux (230 V, 25 W, E27)
- Blue LED: from *Huey Jann Electronics Industry CO., LTD* (100 W, λmax = 462 nm, Manufacturer number: HPR40E-48K100BG).

Chromatography

Thin layer chromatography

TLC experiments were carried out on aluminum sheets coated with silica gel 60 F254 (Merck) or Macherey-Nagel aluminum oxide plates (ALOX N/UV_{254}) with defined solvent mixtures. The substances were visualized with UV-light (254 nm or 360 nm) and revealed using $KMnO_4$ reagent (solution of 5 g of Na_2CO_3 and 2 g of $KMnO_4$ in 250 mL of water).

Column chromatography

Flash chromatography was carried out using aluminium oxide (50-200 µm aluminium oxide (Acros Organics)) or silica gel (35-70 µm silica gel (Acros Organics)). Automatic flash chromatography was performed using the *Isolera One* from *Biotage*, which employs an UV-diode array detector.

NMR

NMR spectra were recorded using the following spectrometers from *Bruker* at 23°C in deuterated solvents from *Deutero* and *Sigma Aldrich*:

- Avance-III HD 300: ^{1}H NMR (300 MHz), ^{13}C NMR (75.5 MHz)
- Avance-II 400: ^{1}H NMR (400 MHz), ^{13}C NMR (100.6 MHz);
- Avance-III HD 400: ^{1}H NMR (400 MHz), ^{13}C NMR (100.6 MHz);
- Avance-III 600: ^{1}H NMR (600 MHz), ^{13}C NMR (150.6 MHz);

COSY, HSQC and HMBC measurements were performed in all spectrometers. NOESY was recorded in the Avance-III HD 400 and Avance-III 600 apparatus. The chemical shifts were referenced to the residual solvent signal ($CDCl_3$: δ H = 7.26 ppm, δ C = 77.16 ppm; DMSO-d6: δ H = 2.50 ppm, δ C = 39.52 ppm, CD_3CN δ H = 1.94 ppm, δ C = 1.32, 118.26 ppm; C_6D_6: δ H = 7.26 ppm, δ C = 128.06 ppm; $(CD_3)_2CO$: δ H = 2.05 ppm, δ C = 29.84, 206.26 ppm).[261] The evaluation and assignment of the spectra was achieved using the software *MestReNova* from *Mestrelab Research*. ^{1}H NMR data are reported as follows: chemical shift (parts per million, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sep = septet, dd = doublet of doublets, ddd = doublet of doublet of doublets dt = doublet of triplets, m = multiplet, br = broad, app = apparent), coupling constant (Hz), integration and assignment. The numbering is made according to the IUPAC name of the compounds.

Mass Spectroscopy

HPLC-ESI-MS

HPLC-ESI-MS mass spectra were recorded on a *1200 series HPLC* with UV-diode array detector and a coupled mass spectrometer (LC/MSD Trap XTC-ESI/APCI) from *Agilent*.

ESI-HRMS

ESI-HRMS spectra were recorded on Waters *Q-TOF- Ultima* III instrument from *Waters* with a dual source and a suitable external calibrant.

Infrared Spectroscopy

IR spectra were recorded on routine FTIR spectrometer (*Bruker Optics Tensor 27*) using a diamond ATR unit. The evaluation of the spectra was achieved using the software *Opus 6.5* from *Bruker*.

Crystal Structure Analysis

The crystal structure measurements were performed in a *Bruker Smart Apex CCD*. The corresponding parameteres per structure are given in the annex. The software *ORTEP-III (1.0.3)* was used for visualization.

Optical Rotation

Optical rotation of the samples was determined using a *Perkin-Elmer 241* polarimeter at $\lambda = 546$ und 578 nm with Hg-lamp.

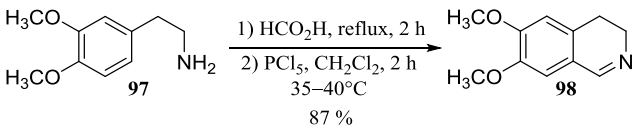
Melting Point Determination

Melting point ranges were determined with a *KSPIN* digital melting point apparatus from *Krüss*.

B Reaction Procedures: Chapter 1

B1 Synthesis of α-Aminonitrile 94

6,7-Dimethoxy-3,4-dihydroisoquinoline (98)



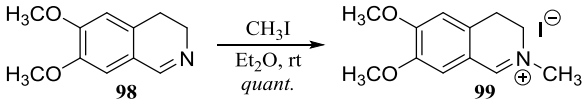
Under ice cooling, formic acid (3.48 g, 75.6 mmol) was added to 3,4-dimethoxyphenylethylamine **97** (10.0 g, 55.2 mmol). The reaction mixture was then heated to reflux over 2 h or until TLC indicated complete conversion.[262] Following the methodology of ROHLOFF and co-workers,[263] the yellow reaction mixture was cooled down and diluted with dichloromethane (10 mL). PCl_5 (12.9 g, 61.8 mmol) was then added in small portions over 90 minutes while maintaining the temperature between 35–40 °C, and the reaction mixture was stirred for additional 30 minutes at the same temperature.. The generated HCl was collected in a gas scrubber with a 1 N NaOH solution. After cooling, a mixture of ice (30 g) and hexane (10 mL) was added, and the aqueous layer was separated. The organic residue was washed with water (2 × 50 mL) and the combined aqueous layers were adjusted to pH > 12 by careful addition of NaOH (cooling). The mixture was extracted with diethyl ether (4 × 50 mL), the extracts dried over Na_2SO_4, and the solvent removed under reduced pressure to give **98** (10.5 g, 54,9 mmol, 87 %) as a yellow oil.

R_f = 0.3 (CH_2Cl_2/MeOH, 10:1)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.21 (s, 1H, H-1), 6.79 (s, 1H, H-8), 6.66 (s, 1H, H-5), 3.90, 3.88 (2s, 6H, C^6-OC**H**$_3$, C^7-OC**H**$_3$), 3.71 (t, *J* = 7.8 Hz, 2H, H-3), 2.66 (t, *J* = 7.8 Hz, 2H, H-4) ppm.

The spectroscopic data are in accordance with those reported in the literature.[262]

3,4-Dihydro-3,4-dimethoxy-2-methylisoquinolinium iodide (99)



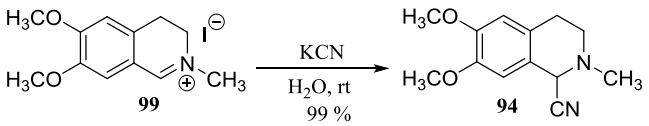
Methyl iodide (1.14 mL, 18.3 mmol) was added dropwise to a solution of compound **98** (2.01 g, 9.20 mmol) in dry diethyl ether. The reaction mixture was stirred overnight at room temperature and the precipitate filtered off and washed several times with diethyl ether. After drying *in vacuo*, compound **99** (3.05 g, 9.15 mmol, quantitative yield) was obtained as a yellow solid.

mp: 198–200 °C (dec), Lit.:[264] 200–201 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.67 (s, 1H, H-1), 7.55 (s, 1H, H-8), 6.86 (s, 1H, H-5), 4.01(t, J = 8.4 Hz, 2H, H-3), 3.98 (s, 3H, C^6-OC**H**$_3$), 3.87 (s, 3H, N-CH_3), 3.85 (s, 3H, C^7-OC**H**$_3$), 3.28 (t, J = 8.4 Hz, 2H, H-4) ppm.

The spectroscopic data are in accordance with those reported in the literature.[264]

1-Cyano-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (94)



A solution of KCN (1.76 g, 27.0 mmol) in water (5 mL) was added to a solution of the isoquinolinium salt **99** (2.09 g, 8.99 mmol) in water (20 mL). The reaction mixture was stirred overnight at room temperature and was extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with water, dried over Na_2SO_4, and the solvent was evaporated under reduced pressure to afford the compound **94** (2.06 g, 8.87 mmol, 99 %) as a yellow solid.

mp: 126–128 °C (dec), Lit.:[265] 127–128 °C.

R$_f$ = 0.22 (cyclohexane/EtOAc/Et_3N, 3:2:0.1)

IR (NaCl): $\tilde{\nu}$ = 2940, 2805, 2217, 1612, 1518, 1464, 1256, 1227, 1140, 1103, 1012 cm^{-1}.

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 6.65 (s, 1H, H-8), 6.61 (s, 1H, H-5), 4.64 (s, 1H, H-1 (NC**H**CN)), 3.86, 3.85 (2s, 6H, OC**H**$_3$), 3.02–2.92 (m, 1H, H-4a), 2.91–2.84 (m, 1H, H-3a), 2.80–2.71 (m, 1H, H-3b), 2.70 (ddd, J = 15.6, 4.2, 1.8 Hz, 1H, H-4b), 2.59 (s, 3H, NC**H**$_3$) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 149.3 (C-7), 147.9 (C-6), 126.3 (C-4a), 121.3 (C-8a), 116.8 (**C**N), 111.6 (C-5), 109.5 (C-8), 56.7 (C-1), 56.2 (O**C**H_3), 56.0 (O**C**H_3), 48.5 (C-3), 43.8 (N**C**H_3), 28.2 (C-4) ppm.

ESI-MS (*m/z*): 206.0 (100) $[M–CN]^+$.

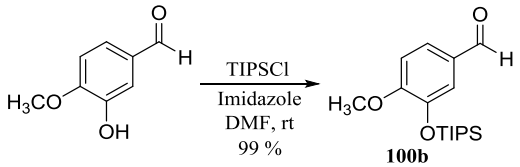
ESI-HRMS (*m/z*): calcd for $[C_{12}H_{16}NO_2]^+$ 206.1181, found 206.1183.

B2 Synthesis of Benzyl Bromides 95

General Procedure I: Preparation of TIPS-Protected Hydroxybenzaldehydes 100b and 100d

This procedure was modified based on the conditions reported by RAMACCIOTTI et al.[266] To a solution of the corresponding hydroxybenzaldehyde (1.0 eq.) and imidazole (3.5 eq.) in dry DMF (0.4 mL/mmol) was added TIPSCl (1.0 eq.) in one portion. The reaction mixture was allowed to stir at room temperature and monitored by TLC. After completion, the reaction was quenched with water and extracted with *n*-hexane (4 × 0.61 mL/mmol). The combined organic layers were washed with brine, dried over Na_2SO_4, and the solvent evaporated under reduced pressure.

4-Methoxy-3-(triisopropylsilanyloxy)benzaldehyde (100b)



100b

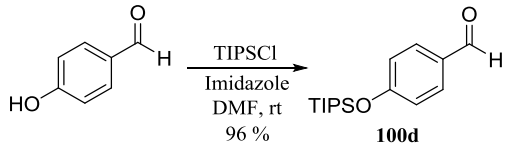
According to the general procedure I, isovanillin (2.50 g, 16.4 mmol), imidazole (3.91 g, 57.4 mmol) and TIPSCl (3.51 mL, 16.4 mmol) were dissolved in DMF (12 mL). The reaction mixture was stirred for 4.5 h (until TLC showed full conversion). After extraction, the title compound was directly obtained (5.04 g, 16.3 mmol, 99 %) as a clear oil without the need for further purification.

R_f = 0.6 (petroleum ether/EtOAc, 2:1)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.79 (s, 1H, C**H**O), 7.43 (dd, *J* = 8.2, 2.0 Hz, 1H, H-6), 7.37 (d, *J* = 2.0 Hz, 1H, H-2), 6.92 (d, *J* = 8.2 Hz, 1H, H-5), 3.86 (s, 3H, OC**H**$_3$), 1.32–1.17 (m, 3H, SiC**H**), 1.07 (d, *J* = 7.3 Hz, 18H, SiCHC**H**$_3$) ppm.

The spectroscopic data are in accordance with those reported in the literature.[266]

4-(Triisopropylsilanyloxy)benzaldehyde (100d)



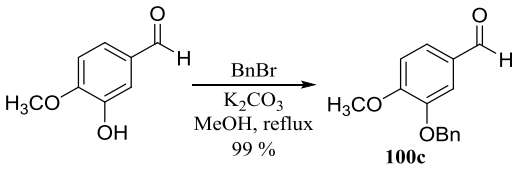
According to the general procedure I, 4-hydroxybenzaldehyde (3.00 g, 24.6 mmol), imidazole (5.86 g, 86.1 mmol) and TIPSCl (5.26 mL, 24.6 mmol) were dissolved in DMF (10 mL). The reaction mixture was stirred for 2 h (until TLC showed full conversion). After extraction, the title compound was directly obtained (6.09 g, 23.7 mmol, 96 %) as a clear oil without the need for further purification.

R_f = 0.65 (cyclohexane/EtOAc, 5:2)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.87 (s, 1H, C**H**O), 7.77 (d, *J* = 8.5 Hz, 2H, H-2, H-6), 6.97 (d, *J* = 8.5 Hz, 1H, H-3,H-5), 1.35–1.21 (m, 3H, SiC**H**), 1.10 (d, *J* = 7.1 Hz, 18H, SiCHC**H**$_3$) ppm.

The spectroscopic data are in accordance with those reported in the literature.[267]

4-Methoxy-3-(benzyloxy)benzaldehyde (100c)



This procedure was modified based on the conditions reported by SUN and SHEN.[268] A mixture of isovanillin (2.00 g, 16.0 mmol), benzyl bromide (2.30 mL, 19.2 mmol), and K_2CO_3 (2.65 g, 19.2 mmol) in methanol (40 mL) was refluxed for 4 h. After completion, the reaction mixture was filtered and the filtrate was evaporated under reduced pressure. Chloroform (20 mL) was added to the residue, and the solution was washed with water (2 × 10 mL), the organic layer was dried over Na_2SO_4 and filtered through a pad of silica gel. The solvent was evaporated under reduced pressure to afford compound **100c** as a white powder (3,86 g, 15.9 mmol, 99 %).

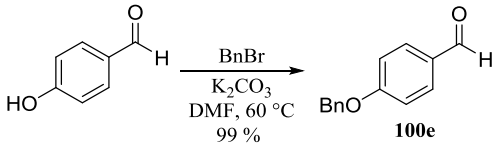
mp: 62.9–63.5 °C (dec), Lit.:[269] 63.4 °C.

R_f = 0.30 (petroleum ether/EtOAc, 3:1)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.84 (s, 1H, C**H**O), 7.50–7.47 (m, 7H, Ph-**H**, H-2, H-6), 7.00 (d, *J* = 8.8 Hz, 1H, Ph-H), 5.19 (s, 2H, OC**H**$_2$Ph), 3.96 (s, 3H, OC**H**3) ppm.

The spectroscopic data are in accordance with those reported in the literature.[268]

4-(Benzyloxy)benzaldehyde (100e)



100e

This procedure was modified based on the conditions reported by FUKUYAMA and co-workers.[270] A mixture of 4-hydroxybenzaldehyde (3.00 g, 24.6 mmol), benzyl bromide (3.2 mL, 27.1 mmol), and K_2CO_3 (4.42 g, 32.0 mmol) in DMF (40 mL) was heated at 60 °C for 4 h. After cooling, the reaction mixture was poured into water and extracted with diethyl ether (4 × 20 mL). The organic layer was washed with brine, dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The solid residue was washed with n-hexane to afford compound **100e** as a white powder (5,21 g, 24.5 mmol, 99 %).

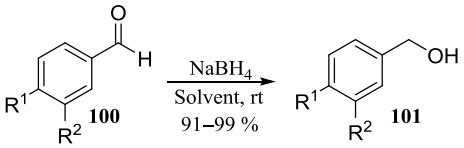
mp: 68.3–69.5 °C (dec), Lit.:[271] 71–72 °C.

R_f = 0.31 (cyclohexane/EtOAc, 5:1)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.89 (s, 1H, C**H**O), 7.84 (d, *J* = 8.7 Hz, 2H, H-2, H-6), 7.48–7.33 (m, 5H, Ph-**H**), 7.08 (d, *J* = 8.7 Hz, 2H, H-3, H-5), 5.16 (s, 2H, OC**H**$_2$Ph) ppm.

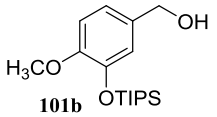
The spectroscopic data are in accordance with those reported in the literature.[270]

General Procedure II: Reduction of Benzaldehydes 100b–e



This procedure was modified based on the conditions reported by ZHOU and co-workers.[269] To a solution of **100** (1.0 eq.) in the respective solvent, $NaBH_4$ (1.2–5 eq.) was added in small portions. The reaction mixture was stir at the indicated temperature and span time. After completion, the solvent was removed under reduced pressure and the residue was rinsed up with water and then extracted with ethyl acetate (3 × 1.7 mL/mmol). The combined organic layers were washed with a saturated NH_4Cl solution, water, and brine, and then dried over Na_2SO_4. Finally the solvent was removed under reduced pressure.

4-Methoxy-3-(triisopropylsilanyloxy)benzyl alcohol (101b)



101b

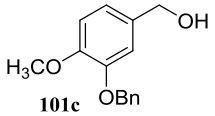
According to the general procedure II, TIPS-protected benzaldehyde **100b** (5.04 g, 16.3 mmol) was dissolved in 11 mL of ethanol and cooled to 0 °C. To this solution $NaBH_4$ (0.74 g, 19.6 mmol) was added in small portions and the reaction mixture allowed to stir at room temperature for 2 h. After extraction, the title compound was obtained (5.00 g, 16.1 mmol, 99 %) as a clear oil without further purification.

R_f = 0.80 (petroleum ether/EtOAc, 2:1)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.92–6.83 (m, 2H, H-2, H-6), 6.79 (d, J = 8.1 Hz, 1H, H-5), 4.52 (s, 2H, C**H**$_2$OH), 3.78 (s, 3H, OC**H**$_3$), 1.33–1.17 (m, 3H, SiC**H**), 1.09 (d, J = 6.9 Hz, 18H, SiCHC**H**$_3$) ppm.

The spectroscopic data are in accordance with those reported in the literature.[262]

4-Methoxy-3-(benzyloxy)benzyl alcohol (101c)



101c

According to the general procedure II, benzyl-protected benzaldehyde **100c** (3.00 g, 12.4 mmol) was dissolved in 25 mL of methanol at room temperature. To this solution, $NaBH_4$ (0.56 g, 14.9 mmol) was added in small portions and the reaction mixture allowed to stir at room temperature for 2 h. After extraction, the solvent was removed under vacuum and the residue was rinsed up with n-hexane to afford **101c** as a white powder (2,76 g, 11.3 mmol, 91 %).

mp: 69.9–71.5 °C (dec), Lit.:[269] 71–72 °C.

R_f = 0.33 (cyclohexane/EtOAc, 1:1)

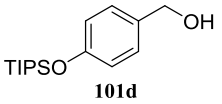
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.49–7.27 (m, 5H, Ph-**H**), 6.95 (d, J = 1.7 Hz, 1H, H-2), 6.90 (dd, J = 8.1, 1.7 Hz, 1H, H-6), 6.86 (d, J = 1.7 Hz, 1H, H-5), 5.15 (s, 2H, OC**H**$_2$Ph), 4.55 (s, 2H, C**H**$_2$OH), 3.88 (s, 3H, OC**H**$_3$) ppm.

The spectroscopic data are in accordance with those reported in the literature.[269]

4-(Triisopropylsilanyloxy)benzyl alcohol (101d)

According to the general procedure II, TIPS-protected benzaldehyde **100d** (6.59 g, 23.7 mmol) was dissolved in 20 mL of a methanol/THF mixture 1:1 and cooled to 0 °C. To this

solution $NaBH_4$ (4.48 g, 0.118 mol) was added in small portions and the reaction mixture allowed to stir at room temperature for 30 minutes. After extraction, the title compound was obtained (6.27 g, 22.3 mmol, 94 %) as a clear oil without further purification.



101d

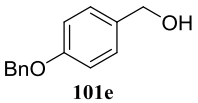
R_f = 0.39 (cyclohexane/EtOAc, 5:2)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.21 (d, *J* = 8.6 Hz, 2H, H-2, H-6), 6.86 (d, *J* = 8.6 Hz, 2H, H-3, H-5), 4.59 (s, 2H, C**H**$_2$OH), 1.34–1.18 (m, 3H, SiC**H**), 1.10 (d, *J* = 6.8 Hz, 18H, SiCHC**H**$_3$) ppm.

The spectroscopic data are in accordance with those reported in the literature.[262]

4-(Benzyloxy)benzyl alcohol (101e)

According to the general procedure II, benzyl-protected benzaldehyde **100d** (5.00 g, 23.6 mmol) was dissolved in 15 mL of a THF/H_2O mixture 4:1 and cooled to 0 °C. To this solution $NaBH_4$ (0.56 g, 14.9 mmol) was added in small portions and the reaction mixture allowed to stir at room temperature for 40 minutes. After extraction, the solvent was removed under vacuum and the residue was rinsed up with n-hexane to afford **101e** as a white solid (4,99 g, 23.3 mmol, 99 %).



101e

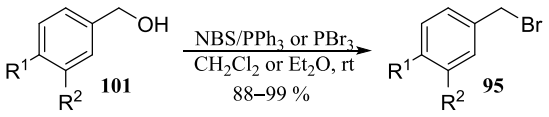
mp: 86.8–87.5 °C (dec), Lit.:[272] 86–88 °C.

R_f = 0.16 (cyclohexane/EtOAc, 5:1)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.47–7.31 (m, 5H, Ph-**H**), 6.96 (d, *J* = 8.7 Hz, 2H, H-2, H-6), 6.96 (d, *J* = 8.7 Hz, 2H, H-3, H-5), 5.06 (s, 2H, OC**H**$_2$Ph), 4.57 (s, 2H, C**H**$_2$OH) ppm.

The spectroscopic data are in accordance with those reported in the literature.[272]

General Procedure III: Conversion of alcohols 101 into bromides 95

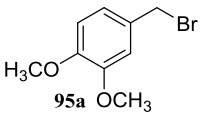


Method A: This procedure was modified based on the conditions reported by FERINGA et al.[273] Under nitrogen atmosphere, a solution of PBr_3 (1.02–1.14 eq.) in dry ether was added to a stir solution of alcohol **101a,c,e** (1.0 eq.) in dry ether at 0 °C. After the addition, the reaction mixture was allowed to stir at room temperature for an indicated period of time. The reaction mixture

was then quenched with an ice-water mixture and the layers separated. The water phase was further extracted with diethyl ether (3 × 0.83 mL/mmol) and the combined organic layers were washed with a saturated $NaHCO_3$ solution and brine. The resulting organic phase was dried over Na_2SO_4 and the solvent removed under reduced pressure.

Method B: This procedure was modified based on the conditions reported by YAMAGUCHI et al.[274] Under nitrogen atmosphere, N-bromosuccinimide (1.5 eq.) and triphenylphosphine (1,5 eq.) were added to a solution of benzyl alcohol **101b,e** (1.0 eq.) in dichloromethane or THF at 0 °C. After the addition, the reaction mixture was allowed to stir at room temperature for an indicated period of time. The mixture was poured into water and extracted with diethyl ether (3 × 9.2 mL/mmol). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The remaining brown solid was purified by filtration through a plug of silica gel (cyclohexane/EtOAc in 5:1).

3,4-Dimethoxybenzyl bromide (95a)



95a

According to the general procedure III, method A: a solution of PBr_3 (3.18 mL, 33.8 mmol) in diethyl ether (62 mL) was added to a solution of commercially available 3,4-dimethoxybenzyl alcohol **101a** (5.00 g, 29.7 mmol) dissolved in diethyl ether (62 mL) at 0 °C. The reaction mixture was stirred at room temperature for 3 h. After work up, the resulting viscous oil was cover with petroleum ether and cooled to –18 °C to give a white solid. The supernatant was decanted off and the solid dry under vacuum to afford **95a** as a white solid (6,77 g, 29.3 mmol, 98 %).

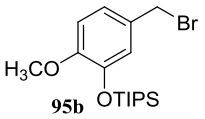
mp: 55.4–56.6 °C (dec), Lit.:[273] 55–57 °C.

R_f = 0.82 (cyclohexane/EtOAc, 1:1)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.94 (dd, *J* = 8.1, 2.1 Hz, 1H, H-6), 6.90 (dd, *J* = 2.1 Hz, 1H, H-2), 6.79 (d, *J* = 8.1 Hz, 1H, H-5), 3.88, 3.86 (2s, 6H, C^3-OC**H**$_3$, C^4-OC**H**$_3$) ppm.

The spectroscopic data are in accordance with those reported in the literature.[273]

4-Methoxy-3-(triisopropylsilanyloxy)benzyl bromide (95b)



95b

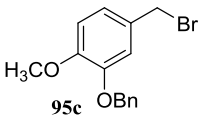
According to the general procedure III, method B: N-bromosuccinimide (0.859 g, 4.83 mmol) and triphenylphosphine (1.27 g, 4.83 mmol) were added to a solution of benzyl alcohol **101b** (1.00 g, 3.22 mmol) in dichloromethane (10 mL) at 0 °C. The reaction mixture was stirred at room temperature for 40 minutes. After purification, benzyl bromide **95b** was obtained as a clear yellow liquid (1.06 g, 2.84 mmol, 88%). To avoid decomposition the title compound was stored in THF (10 mL) with a spatula tip of $CaCO_3$.

R_f = 0.60 (cyclohexane/EtOAc, 5:1)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.98–6.87 (m, 2H, H-2, H-6), 6.77 (d, *J* = 8.8 Hz, 1H, H-5), 4.45 (s, 2H, C**H**$_2$Br), 3.80 (s, 3H, OC**H**$_3$), 1.33–1.18 (m, 3H, SiC**H**), 1.10 (d, *J* = 6.9 Hz, 18H, SiCHC**H**$_3$) ppm.

The spectroscopic data are in accordance with those reported in the literature.[262]

4-Methoxy-3-(benzyloxy)benzyl bromide (95c)



95c

According to the general procedure III, method A: a solution of PBr_3 (0.968 mL, 10.3 mmol) in diethyl ether (10 mL) was added to a solution of benzyl alcohol **101c** (2.44 g, 10.0 mmol) dissolved in diethyl ether (20 mL) at 0 °C. The reaction mixture was stirred at room temperature for 3 h. The crude product was purified by recrystallization from dichloromethane/n-heptane to afford **95c** as a white solid (2,89 g, 9.40 mmol, 94 %).

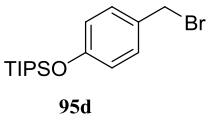
mp: 85.6–86.4 °C (dec), Lit.:[275] 86–87 °C.

R_f = 0.63 (cyclohexane/EtOAc, 1:1)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.48–7.28 (m, 5H, Ph-**H**), 6.98 (dd, *J* = 8.7, 2.1 Hz, 1H, H-6), 6.96 (d, *J* = 2.1 Hz, 1H, H-2), 6.84 (d, *J* = 2.1 Hz, 1H, H-5), 5.15 (s, 2H, OC**H**$_2$Ph), 4.55 (s, 2H, C**H**$_2$Br), 3.88 (s, 3H, OC**H**$_3$) ppm.

The spectroscopic data are in accordance with those reported in the literature.[275]

4-(Triisopropylsilanyloxy)benzyl bromide (95d)



95d

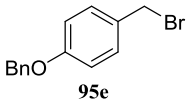
According to the general procedure III, method B: N-bromosuccinimide (1.90 g, 10.7 mmol) and triphenylphosphine (2.81 g, 10.7 mmol) were added to a solution of benzyl alcohol **101d** (2.00 g, 3.22 mmol) in THF (20 mL) at 0 °C. The reaction mixture was stirring at room temperature for 2.5 h. After purification, benzyl bromide **95d** was obtained as a clear yellow liquid (2.35 g, 6.84 mmol, 96%). To avoid decomposition, the title compound was stored in THF (10 mL) with a spatula tip of $CaCO_3$.

R_f = 0.76 (cyclohexane/EtOAc, 5:1)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.25 (d, J = 8.6 Hz, 2H, H-2, H-6), 6.83 (d, J = 8.8 Hz, 1H, H-5), 4.49 (s, 2H, C**H**$_2$Br), 1.33–1.18 (m, 3H, SiC**H**), 1.10 (d, J = 6.9 Hz, 18H, SiCHC**H**$_3$) ppm.

The spectroscopic data are in accordance with those reported in the literature. [262]

4- (benzyloxy)benzyl bromide (95e)



95e

According to the general procedure III, method A: a solution of PBr_3 (0.89 mL, 9.52 mmol) in diethyl ether (10 mL) was added to a solution of benzyl alcohol **101e** (2.00 g, 9.33 mmol) dissolved in diethyl ether (40 mL) at 0 °C. The reaction mixture was stirred at room temperature for 3 h. The crude product was purified by recrystallization from n-hexane to afford **95e** as a white solid (2.30 g, 8.30 mmol, 89 %).

mp: 81.0–81.9 °C (dec), Lit.:[276] 81–82 °C.

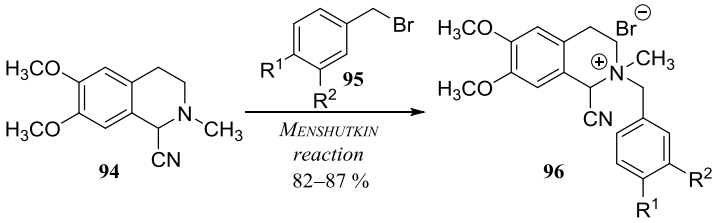
R_f = 0.28 (cyclohexane/EtOAc, 5:1)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.48–7.35 (m, 5H, Ph-**H**), 7.34 (d, J = 8.7 Hz, 2H, H-2, H-6), 6.96 (d, J = 8.7 Hz, 2H, H-3, H-5), 5.08 (s, 2H, OC**H**$_2$Ph), 4.51 (s, 2H, C**H**$_2$Br) ppm.

The spectroscopic data are in accordance with those reported in the literature. [276]

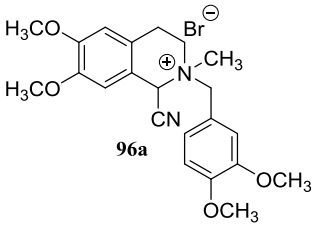
B3 Synthesis of Ammonium Salts 96

General Procedure IV: Preparation of *cis/trans*-2-Aryl-1-cyano-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolinium Salts (96)



The corresponding benzylic bromide **95** (1.0 eq.) was added to a stirred solution of α-aminonitrile **94** (2.0 eq.) in dry THF (7 mL/mmol) under nitrogen atmosphere. The mixture was heated at 40°C for 1–3 days. The precipitate formed was filtered and washed several times with THF to afford the title compounds.

cis/trans-1-Cyano-2-(3,4-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolinium bromide (96a)



The reaction was carried out during 24 h, using isoquinoline **94** (200 mg, 0.860 mmol) and bromide **95a** (397 mg, 1.72 mmol). The tetraisoquinolinium salt **96a** was obtained as a diastereomeric mixture in a 12:88 *cis/trans*-ratio (^{1}H NMR) in the form of a pale yellow solid (378 mg, 0.816 mmol, 95 %) which was used in the next step without further purification.

IR (ATR): $\tilde{\nu}$ = 2959, 2836, 2566, 1728, 1606, 1518, 1465, 1262, 1119, 817 cm^{-1}.

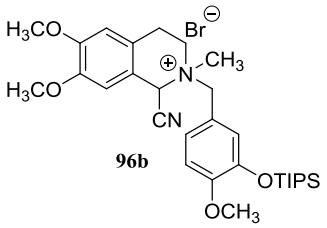
^{1}H NMR, COSY NOESY (600 MHz, DMSO-d$_6$) *trans*-**96a**:δ = 7.12 (s, 2H, H-5', H-2'), 7.06 (s, 1H, H-6'), 7.04 (s, 1H, H-5), 7.03 (s, 1H, H-8), 6.37 (s, 1H, H-1), 4.87 (d, *J* = 12.9 Hz, 1H, NC**H**$_a$Ar), 4.75 (d, *J* = 12.9 Hz, 1H, NC**H**$_b$Ar), 3.98–3.91 (m, 1H, H$_a$-3), 3.90-3.84 (m, 1H, H$_b$-3), 3.82–3.80 (3s, 9H, C$^{4'}$-OC**H**$_3$, C^6-OC**H**$_3$, C^7-OC**H**$_3$), 3.79 (s, 3H, C$^{3'}$-OC**H**$_3$), 3.26 (s, 3H, NC**H**$_3$), 3.26–3.19 (m, 2H, H-4) ppm. Characteristic signals for *cis*-**96a**: δ = 6.20 (s, 1H, H-1), 4.94 (d, *J* = 12.9 Hz, 1H, NC**H**$_a$Ar), 4.90 (d, *J* = 12.9 Hz, 1H, NC**H**$_b$Ar) ppm.

^{13}C NMR, HMBC, HSQC (150.6 MHz, DMSO-d$_6$) δ = 150.8 (C-6), 150.3 (C-4'), 148.7 (C-3'), 148.4 (C-7), 126.4 (C-2'), 122.6 (C-4$_a$), 118.1 (C-1') 116.0 (C-6'), 114.1 (C-8$_a$), 113.7 (**C**N), 112.1 (C-5), 111.8 (C-5'), 109.5 (C-8), 65.8 (N**C**H$_2$Ar), 59.3 (C-1), 56.8 (C-3), 55.8 (C^6-OMe), 55.7 (C^7-O**C**H$_3$), 55.6 (C$^{4'}$- O**C**H$_3$), 55.5 (C$^{3'}$- O**C**H$_3$), 46.2 (N**C**H$_3$), 22.5 (C-4) ppm.

ESI-MS: (*m/z*): 206.0 (100) $[M - C_{10}H_{11}NO_2]^+$, 383.1 (65) $[M]^+$, 356.2 (14.8) $[M - HCN]^+$.

ESI-HRMS: calcd for $[C_{22}H_{27}N_2O_4]^+$ 383.1971, found 383.1958.

cis/trans-1-Cyano-6,7-dimethoxy-2-(4-methoxy-3-(triisopropylsilyloxy)benzyl)-2-methyl-1,2,3,4-tetrahydroisoquinolinium bromide (96b)



96b

The reaction was carried out during 48 h, using isoquinoline **94** (200 mg, 0.860 mmol) and bromide **95b** (642 mg, 1.72 mmol). The isoquinolinium salt **96b** was obtained as a diastereomeric mixture in a *cis/trans*-ratio of 13:87 (^{1}H NMR), in the form of a pale yellow solid (442 mg, 0.730 mmol, 85 %) which was used in the next step without further purification.

IR (ATR): $\tilde{\nu}$ = 2941, 2865, 2562, 1658, 1602, 1513, 1442, 1268, 1166, 810 cm^{-1}.

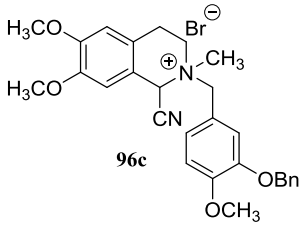
^{1}H NMR, COSY, NOESY (400 MHz, DMSO-d_6) *trans*-**96b**: δ = 7.14 (s, 2H, H-5', H-2'), 7.02 (s, 1H, H-5), 7.00 (s, 1H, H-6'), 6.99 (s, 1H, H-8), 6.37 (s, 1H, H-1), 4.86 (d, *J* = 12.8 Hz, 1H, NC**H**$_a$Ar), 4.75 (d, *J* = 12.8 Hz, 1H, NC**H**$_b$Ar), 3.99–3.89 (m, 1H, H$_a$-3), 3.88-3.81 (m, 1H, H$_b$-3), 3.81, 3.80 (2s, 6H, C$^{4'}$-OC**H**$_3$, C^6-OC**H**$_3$), 3.79 (s, 3H, C^7-OC**H**$_3$), 3.24 (s, 3H, NC**H**$_3$), 3.24–3.13 (m, 2H, H-4), 1.29–1.16 (m, 3H, SiC**H**), 1.04 (d, *J* = 7.5 Hz, 18H, SiCHC**H**$_3$) ppm. Characteristic signal of *cis*-**96b**: δ = 7.19 (s, 2H, H-5', H-2'), 6.18 (s, 1H, H-1), 4.95 (d, *J* = 12.8 Hz, 1H, NC**H**$_a$Ar) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, DMSO-d_6) δ = 152.6 (C-4'), 150.1 (C-6), 148.5 (C-7), 144.5 (C-3'), 127.3 (C-2'), 124.4 (C-6'), 122.6 (C-4$_a$), 118.1 (C-1'), 114.5 (C-8$_a$), 113.4 (**C**N), 112.6 (C-5'), 112.1 (C-5), 109.4 (C-8), 65.5 (N**C**H$_2$Ar), 59.2 (C-1), 56.7 (C-3), 55.8 (C^6-O**C**H$_3$), 55.7 (C$^{4'}$-O**C**H$_3$), 55.2 (C^7-O**C**H$_3$), 46.8 (N**C**H$_3$), 22.6 (C4), 17.8 (6C, SiCH**C**H$_3$), 12.3 (3C, Si**C**H) ppm.

ESI-MS (*m/z*): 498.3 (100) $[M - HCN]^+$, 206.0 (82) $[M - C_{18}H_{29}NO_2Si]^+$, 525.20 (39) $[M]^+$.

ESI-HRMS: calcd for $[C_{30}H_{45}N_2O_4Si]^+$ 525.3149, found 525.3156.

cis/trans-2-(3-(Benzyloxy)-4-methoxybenzyl)-1-cyano-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolinium bromide (96c)



96c

The reaction was carried out during 48 h using isoquinoline **94** (200 mg, 0.860 mmol) and bromide **95c** (528 mg, 1.72 mmol).

The isoquinolinium salt **96c** was obtained as a diastereomeric mixture in a *cis/trans*-ratio of 6:94 (^{1}H NMR) in the form of a beige solid (339 mg, 0.628 mmol, 73 %) which was used in the next step without further purification.

IR (ATR): $\tilde{\nu}$ = 2943, 2838, 2564, 1663, 1606, 1521, 1443, 1263, 1121, 815 cm^{-1}.

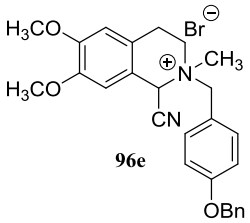
^{1}H NMR, COSY, NOESY (600 MHz, DMSO-d$_6$) *trans*-**96c**: δ = 7.45 (d, *J* = 7.5 Hz, 2H, H-2'', H-6''), 7.41 (t, *J* = 7.5 Hz, 2H, H-3'', H-5''), 7.35 (t, *J* = 7.5 Hz, 1H, H-4''), 7.17–7.11 (m, 3H, H-6', H-5', H-2'), 7.05 (s, 1H, H-5), 7.03 (s, 1H, H-8), 6.30 (s, 1H, H-1), 5.16 (d, *J* = 11.7 Hz, 1H, OC**H**$_a$Ph), 5.11 (d, *J* = 11.7 Hz, 1H, OC**H**$_b$Ph), 4.80 (d, *J* = 12.9 Hz, 1H, NC**H**$_a$Ar), 4.72 (d, *J* = 12.9 Hz, 1H, NC**H**$_b$Ar), 3.97–3.91 (m, 1H, H$_a$-3), 3.90–3.83 (m, 1H, H$_b$-3), 3.83 (s, 3H, C$^{4'}$-OC**H**$_3$), 3.82 (s, 3H, C^6-OC**H**$_3$), 3.78 (s, 3H, C^7-OC**H**$_3$), 3.21 (s, 3H, NC**H**$_3$), 3.27–3.17 (m, 2H, H-4) ppm. Characteristic signal for *cis*-**11c**: δ = 7.07 (s, 1H, H-5), 7.01 (s, 1H, H-8), 6.15 (s, 1H, H-1) ppm.

^{13}C NMR, HMBC, HSQC (150.6 MHz, DMSO-d$_6$) δ = 151.1 (C-4'), 150.3 (C-6), 148.5 (C-7), 147.7 (C-3'), 136.6 (C-1''), 128.5 (C-3'', C-5''), 128.0 (C-4''), 127.9 (C-2'', C-6''), 126.7 (C-2'), 122.6 (C-4$_a$), 117.9 (C-1'), 117.7 (C-6'), 114.1 (C-8$_a$), 113.7 (**C**N), 112.1 (C-5), 111.8 (C-5'), 109.5 (C-8), 69.8 (O**C**H$_2$Ar), 66.0 (N**C**H$_2$Ar), 59.3 (C-1), 56.8 (C-3), 55.8 (C^6-O**C**H$_3$, C^7-O**C**H$_3$), 55.7 (C$^{4'}$-O**C**H$_3$), 46.1 (N**C**H$_3$), 22.5 (C-4) ppm.

ESI-MS (*m/z*): 206.0 (100) [M – C$_{16}$H$_{15}$NO$_2$]$^+$, 432.2 (94) [M – HCN]$^+$, 559.1 (91) [M]$^+$.

ESI-HRMS: calcd for [C$_{28}$H$_{31}$N$_2$O$_4$]$^+$ 459.2284, found 459.2283.

cis/trans-2-(4-(Benzyloxy)benzyl)-1-cyano-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolinium bromide (96e)



96e

The reaction was carried out during 72 h using isoquinoline **94** (200 mg, 0.860 mmol) and bromide **95e** (528 mg, 1.72 mmol). The isoquinolinium salt **96e** was obtained as a diastereomeric mixture in a *cis/trans*-ratio of 3:97 (^{1}H-NMR) in the form of a beige solid (267 mg, 0.524 mmol, 61 %) which was used in the next step without further purification.

IR (ATR): $\tilde{\nu}$ = 2972, 2838, 2564, 1662, 1610, 1516, 1454, 1237, 1119, 811 cm^{-1}.

^{1}H NMR, COSY, NOESY (600 MHz, DMSO-d$_6$) *trans*-**96e**: δ = 7.50 (d, *J* = 8.4 Hz, 2H, H-2', H-6'), 7.47 (d, *J* = 7.5 Hz, 2H, H-2'', H-6''), 7.41 (t, *J* = 7.5 Hz, 2H, H-3'', H-5''), 7.35 (t, *J* = 7.5 Hz, 1H, H-4''), 7.18 (d, *J* = 8.4 Hz, 2H, H-3', H-5'), 7.02 (s, 1H, H-5), 6.99 (s, 1H, H-8),

6.36 (s, 1H, H-1), 5.17 (s, 2H, OC**H**$_2$Ph), 4.85 (d, *J* = 12.9 Hz, 1H, NC**H**$_a$Ar), 4.78 (d, *J* = 12.9 Hz, 1H, NC**H**$_b$Ar), 3.97–3.91 (m, 1H, H$_a$-3), 3.90–3.81 (m, 1H, H$_b$-3), 3.80 (2s, 6H, C^6-OC**H**$_3$, C^7-OC**H**$_3$), 3.23 (s, 3H, NC**H**$_3$), 3.27–3.17 (m, 2H, H-4) ppm. Characteristic signals for *cis*-**96e**: δ = 7.18 (d, *J* = 8.6 Hz, 2H, H-3', H-5'), 6.91 (s, 1H, H-5), 6.90 (s, 1H, H-8), 6.14 (s, 1H, H-1), 4.94 (d, *J* = 13.1 Hz, 1H, NC**H**$_a$Ar), 4.90 (d, *J* = 13.1 Hz, 1H, NC**H**$_b$Ar) ppm.

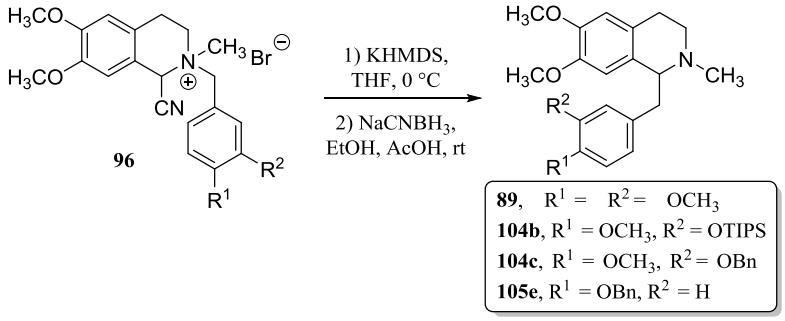
^{13}C NMR, HMBC, HSQC (150.6 MHz, DMSO-d$_6$) δ = 160.8 (C-4'), 150.6 (C-6), 148.9 (C-7), 137.1 (C-1''), 135.3 (C-2', C-6') 129.0 (C-3'', C-5''), 128.6 (C-4''), 128.3 (C-2'', C-6''), 123.0 (C-4$_a$), 118.6 (C-1'), 115.9 (C-3', C-5'), 114.5 (C-8$_a$), 114.1 (**C**N), 112.4 (C-5), 110.0 (C-8), 69.9 (O**C**H$_2$Ph), 66.4 (N**C**H$_2$Ar), 60.0 (C-1), 56.9 (C-3), 56.3 (C^6-O**C**H$_3$), 56.2 (C^7-O**C**H$_3$), 46.2 (N**C**H$_3$), 23.0 (C-4) ppm.

ESI-MS (*m/z*): 206.0 (100) [M – C$_{15}$H$_{13}$NO]$^+$, 402.2 (82) [M – HCN]$^+$, 429.1 (31) [M]$^+$.

ESI-HRMS: calcd for [C$_{27}$H$_{29}$N$_2$O$_3$]$^+$ 429.2178, found 429.2191.

B4 Synthesis of 1-Benzyltetrahydroisoquinoline Alkaloids 89–91

General Procedure V: STEVENS Rearrangement and Reductive Decyanation

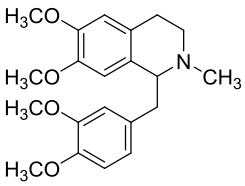


This procedure was modified based on the conditions reported by OPATZ and co-workers.[70] A solution of KHMDS (56 mg, 0.280 mmol) in dry THF (1 mL) was added to a stirred suspension of the corresponding salt **94** (0.259 mmol) in dry THF (7 mL) at 0 °C. After stirring for 1.5–3 h at this temperature, EtOH (1 mL) and NaCNBH$_3$ (57 mg, 0.91 mmol) were added and the mixture was allowed to reach room temperature. Acetic acid (85 µL, 1.5 mmol) was added dropwise and the mixture was stirred for 12 h. Saturated aqueous NaHCO$_3$ (15 mL) was added, and the product was extracted with CH$_2$Cl$_2$ (3 × 20 mL). The combined organic layers were

washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The products **89** and **104** were purified by recrystallization or column chromatography.

(±)-Laudanosine (89)

According to the general procedure and after 14 h of reaction time, compound **89** (77 mg, 0.215 mmol, 83 %) was obtained from the isoquinolinium salt **96a** (120 mg, 0.259 mmol) as a white solid after recrystallization from ethanol.


(±)-Laudanosine (**89**)

mp: 114–116 °C (dec), Lit.:[277] 114–115 °C.

$\mathbf{R}_f$ = 0.4 ($CHCl_3$/MeOH, 10:1).

IR (ATR): $\tilde{\nu}$ = 2932, 2832, 1608, 1511, 1463, 1226, 1138, 1101, 1027, 861 cm^{-1}.

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 6.74 (d, *J* = 8.1 Hz, 1H, H-5'), 6.61 (dd, *J* = 8.1, 1.9 Hz, 1H, H-6'), 6.58 (d, *J* = 1.9 Hz, 1H, H-2'), 6.54 (s, 1H, H-5), 6.03 (s, 1H, H-8), 3.82, 3.81 (2s, 6H, C^6-OCH_3, $C^{4'}$-O**C**$\mathbf{H}_3$), 3.76 (s, 3H, $C^{3'}$-O**C**$\mathbf{H}_3$), 3.68 (dd, *J* = 7.7, 4.9 Hz, 1H, H-1), 3.55 (s, 3H, C^7-O**C**$\mathbf{H}_3$), 3.19–3.13 (m, 1H, H_a-3), 3.13 (dd, *J* = 13.7, 4.9 Hz, 1H, ArC**H**$_a$), 2.87–2.69 (m, 2H, H_a-4, H_b-3), 2.75 (dd, *J* = 13.7, 7.7 Hz, 1H, ArC**H**$_b$), 2.57 (dt, *J* = 14.9, 4.0 Hz, 1H, H_b-4), 2.52 (s, 3H, NC**H**$_3$) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 148.5 (C-4'), 147.3, 147.2 (C-6, C-3'), 146.3 (C-7), 132.4 (C-1'), 129.1 (C-8_a), 125.9 (C-4_a), 121.8 (C-6'), 112.9 (C-2'), 111.1 (C-5), 111.0 (C-8), 110.9 (C-5'), 64.8 (C-1), 55.9, 55.8 (C^6-O**C**H_3, $C^{4'}$-O**C**H_3), 55.7 ($C^{3'}$-O**C**H_3), 55.5 (C^7-O**C**H_3), 46.9 (C3), 42.6 (N**C**H_3), 40.8 (Ar**C**H_2), 25.5 (C4) ppm.

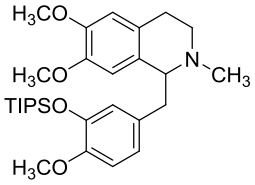
ESI-MS (*m/z*): 358.1 (100) $[M+H]^+$.

ESI-HRMS: calcd for $[C_{21}H_{28}NO_4]^+$ 358.2018, found 358.2010.

The spectroscopic data are in accordance with those reported in the literature.[278]

(±)-*O*-(Triisopropylsilyl)laudanidine (104b)

According to the general procedure and after 15 h of reaction time, compound **104b** (109 mg, 0.218 mmol, 84 %) was obtained from the isoquinolinium salt **96b** (157 mg, 0.259 mmol) as a pale yellow oil after purification by column chromatography


(±)-*O*-Triisopropylsilyllaudanidine (**104b**)

(cyclohexane/EtOAc/$HNEt_2$ = 10/3/1).

R_f = 0.60 (cyclohexane/EtOAc/$HNEt_2$, 5:3:1).

IR (ATR): $\tilde{\nu}$ = 2940, 2864, 1608, 1510, 1463, 1227, 1136, 1102, 1032, 882 cm^{-1}.

^{1}H NMR, COSY (600 MHz, $CDCl_3$) δ = 6.71 (d, *J* = 2.1 Hz, 1H, H-2'), 6.70 (d, *J* = 8.2 Hz, 1H, H-5'), 6.55 (dd, *J* = 8.2, 2.1 Hz, 1H, H-6'), 6.54 (s, 1H, H-5), 6.13 (s, 1H, H-8), 3.83 (s, 3H, C^6-OC**H**$_3$), 3.76 (s, 3H, $C^{4'}$-OC**H**$_3$), 3.62 (dd, *J* = 7.5, 4.7 Hz, 1H, H-1), 3.60 (s, 3H, C^7-OC**H**$_3$), 3.14 (ddd, *J* = 12.4, 8.7, 5.1 Hz, 1H, H_a-3), 3.07 (dd, *J* = 13.7, 4.7 Hz, 1H, ArC**H**$_a$), 2.80 (ddd, *J* = 15.9, 8.7, 5.6 Hz, 1H, H_a-4), 2.76–2.69 (m, 1H, H_b-3), 2.73 (dd, *J* = 13.7, 7.5 Hz, 1H, ArC**H**$_b$), 2.58 (dt, *J* = 15.9, 4.8 Hz, 1H, H_b-4), 2.51 (s, 3H, NC**H**$_3$), 1.26–1.17 (m, 3H, SiC**H**), 1.07 (d, *J* = 7.4 Hz, 18H, SiCHC**H**$_3$) ppm.

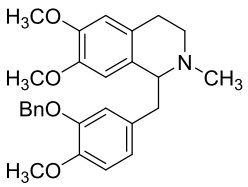
^{13}C NMR, HMBC, HSQC (150.6 MHz, $CDCl_3$) δ = 149.3 (C-4'), 147.3 (C-6), 146.5 (C-7), 145.3 (C-3'), 132.6 (C-1'), 129.6 (C-8_a), 126.1 (C-4_a), 122.8 (C-2'), 121.9 (C-5'), 111.9 (C-6'), 111.1 (C-5), 110.9 (C-8), 65.1 (C-1), 55.8, 55.7 (C^6-O**C**H$_3$, $C^{4'}$-O**C**H$_3$), 55.6 (C^7-O**C**H$_3$), 47.3 (C3), 42.9 (N**C**H$_3$), 40.6 (Ar**C**H$_2$), 25.8 (C-4), 18.0 (6C, SiCH**C**H$_3$), 13.0 (3C, SiC**H**) ppm.

ESI-MS (*m/z*): 500.2 (100) $[M+H]^+$.

ESI-HRMS: calcd for $[C_{29}H_{46}NO_4Si]^+$ 500.3196, found 500.3179.

(±)-*O*-Benzyllaudanidine (104c)

According to the general procedure and after 15 h of reaction time, compound **104c** (91.9 mg, 0.212 mmol, 82 %) was obtained from the isoquinolinium salt **96c** (140 mg, 0.259 mmol) as a white solid after recrystallization from ethanol.



(±)-*O*-Benzyllaudanidine (**104c**)

mp: 90–92 °C (dec), Lit.:[279] 90.5–91.5 °C.

R_f = 0.69 (cyclohexane/EtOAc/$HNEt_2$,5:3:1).

IR (ATR): $\tilde{\nu}$ = 2937, 2860, 1610, 1510, 1463, 1275, 1131, 1101, 1015, 863 cm^{-1}.

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.41 (d, *J* = 7.0 Hz, 2H, H-6'', H-2''), 7.34 (t, *J* = 7.3 Hz, 2H, H-5'', H-3''), 7.28 (m, 1H, H-4''), 6.77 (d, *J* = 8.1 Hz, 1H, H-5'), 6.66 (d, *J* = 2.0 Hz, 1H, H-2'), 6.60 (dd, *J* = 8.1, 2.0 Hz, 1H, H-6'), 6.54 (s, 1H, H-5), 5.99 (s, 1H, H-8), 5.07 (s, 2H, PhC**H**$_2$), 3.84, 3.83 (2s, 6H, C^6-OC**H**$_3$, $C^{4'}$-OC**H**$_3$), 3.59 (dd, *J* = 7.7, 5.1 Hz, 1H, H-1), 3.16–3.07

(m, 1H, H_a-3), 3.06 (dd, *J* = 13.7, 5.1 Hz, 1H, ArC**H**$_a$), 2.84–2.77 (m, 1H, H_a-4), 2.76–2.69 (m, 1H, H_b-3), 2.72 (dd, *J* = 13.7, 7.7 Hz, 1H, ArC**H**$_b$), 2.54 (dt, *J* = 15.6, 4.6 Hz, 1H, H_b-4), 2.48 (s, 3H, NC**H**$_3$) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 148.1 (C-4'), 147.8 (C-3'), 147.3 (C-6), 146.4 (C-7), 137.4 (C-1''), 132.5 (C-1'), 129.4 (C-4$_a$), 128.6 (C-3'', C-5''), 127.9 (C-4''), 127.4 (C-2'', C-6''), 126.1 (C-8$_a$), 122.7 (C-6'), 115.9 (C-2'), 111.7 (C-5'), 111.2 (C-5), 111.0 (C-8), 71.1 (Ph**C**H$_2$), 64.9 (C-1), 56.2, 55.9 (C^6-O**C**H$_3$, C$^{4'}$-O**C**H$_3$), 55.6 (C^7-O**C**H$_3$), 47.1 (C-3), 42.8 (N**C**H$_3$), 40.8 (Ar**C**H$_2$), 25.7 (**C**4) ppm.

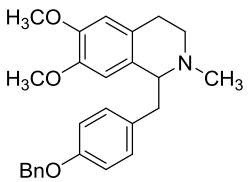
ESI-MS (*m/z*): 434.2 (100) $[M+H]^+$.

ESI-HRMS: calcd for $[C_{27}H_{32}NO_4]^+$ 434.2331, found 434.2329.

The spectroscopic data are in accordance with those reported in the literature.[279]

(±)-*O*-Benzylarmepavine (105e)

According to the general procedure and after 13 h of reaction time, compound **105e** (91 mg, 0.225 mmol, 87 %) was obtained from the isoquinolinium salt **96e** (132 mg, 0.259 mmol) as a viscous yellow oil after purification by column chromatography (cyclohexane/EtOAc/$HNEt_2$ = 10/3/1).



(±)-*O*-Benzylarmepavine (**105e**)

R$_f$ = 0.58 (cyclohexane/EtOAc/$HNEt_2$, 5:3:1).

IR (ATR): $\tilde{\nu}$ = 2926, 2858, 1612, 1511, 1463, 1250, 1101, 1066, 1015, 862 cm^{-1}.

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.44–7.35 (m, 4H, H-6'', H-5'', H-3'', H-2''), 7.34–7.29 (m, 1H, H-4''), 7.01 (d, *J* = 8.5 Hz, 2H, H-6', H-2'), 6.88 (d, *J* = 8.5 Hz, 2H, H-5', H-3'), 6.55 (s, 1H, H-5), 6.00 (s, 1H, H-8), 5.04 (s, 2H, PhC**H**$_2$), 3.83 (s, 3H, C^6-OC**H**$_3$), 3.67 (dd, *J* = 7.9, 5.0 Hz, 1H, H-1), 3.52 (s, 3H, C^7-OCH$_3$), 3.24–3.13 (m, 1H, H_a-3), 3.14 (dd, *J* = 13.7, 5.0 Hz, 1H, ArC**H**$_a$), 2.88–2.81 (m, 1H, H_a-4), 2.80–2.71 (m, 1H, H_b-3), 2.75 (dd, *J* = 13.7, 7.9 Hz, 1H, Ar-C**H**$_b$), 2.59 (dt, *J* = 15.5, 4.5 Hz, 1H, H_b-4), 2.53 (s, 3H, NC**H**$_3$) ppm.

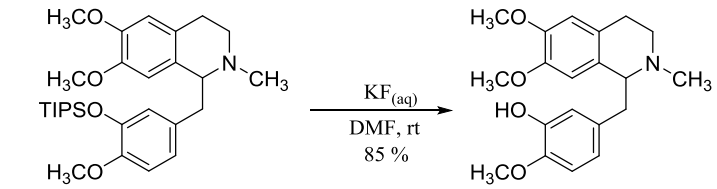
^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 157.2 (C-4'), 147.3 (C-6), 146.3 (C-7), 137.3 (C-1''), 132.3 (C-1'), 130.8 (C-6',C-2'), 129.4 (C-8$_a$), 128.7 (C-5'', C-3''), 128.0 (C-4''), 127.5 (C-6'', C-2''), 126.0 (C-4$_a$), 114.7 (C-5', C-3'), 111.2 (C-5), 111.1 (C-8), 70.1 (Ph**C**H$_2$), 65.0 (C-1), 56.0 (C^6-O**C**H$_3$), 55.6 (C^7-O**C**H$_3$), 46.9 (C-3), 42.3 (N**C**H$_3$), 40.5 (Ar**C**H$_2$), 25.6 (C-4) ppm.

ESI-MS (*m/z*): 404.2 (100) $[M+H]^+$.

ESI-HRMS: calcd for $[C_{26}H_{30}NO_3]^+$ 404.2226, found 404.2212.

(±)-Laudanidine (90)

Method A:



(±)-*O*-Triisopropylsilyllaudanidine (**104b**)

(±)-Laudanidine (**90**)

To a solution of silyl ether **104b** (90 mg, 0.18 mmol) in DMF (1 mL) was added a solution of KF (21 mg, 0.36 mmol) in water (0.1 mL). After stirring the reaction mixture overnight at room temperature, sat. aq NH_4Cl (8 mL) was added and the mixture was extracted with ethyl acetate (4 × 5 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. To remove the remaining silicon compounds, the crude material was dissolved in MeCN (3 mL) and extracted with *n*-hexane (6 mL). The MeCN-layer was concentrated *in vacuo* to afford the title compound (53 mg, 0.15 mmol, 85 %) as a white solid.

mp: 165–166 °C (dec), Lit.:[280] 164–165 °C.

$\mathbf{R}_f$ = 0.26 (cyclohexane/EtOAc/$HNEt_2$, 5:3:1).

IR (ATR): $\tilde{\nu}$ = 3437, 2937, 2835, 1610, 1510, 1463, 1253, 1131, 1015, 863 cm^{-1}.

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 6.78 (d, *J* = 2.1 Hz, 1H, H-2'), 6.72 (d, *J* = 8.2 Hz, 1H, H-5'), 6.55 (s, 1H, H-5), 6.53 (dd, *J* = 8.2, 2.1 Hz, 1H, H-6'), 6.06 (s, 1H, H-8), 3.85, 3.83 (2s, 6H, C^6-OC**H**$_3$, $C^{4'}$-OC**H**$_3$), 3.68 (dd, *J* = 7.7, 5.2 Hz, 1H, H-1), 3.57 (s, 3H, C^7-OC**H**$_3$), 3.19 (ddd, *J* = 12.5, 8.8, 5.1 Hz, 1H, H_a-3), 3.11 (dd, *J* = 13.7, 5.2 Hz, 1H, ArC**H**$_a$), 2.89–2.74 (m, 2H, H_a-4, H_b-3), 2.71 (dd, *J* = 13.7, 7.7 Hz, 1H, ArC**H**$_b$), 2.61 (dt, *J* = 15.4, 3.9 Hz, 1H, H_b-4), 2.51 (s, 3H, NC**H**$_3$) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 147.4 (C-6), 146.4 (C-7), 145.6 (C-3'), 145.1 (C-4'), 133.5 (C-1'), 129.5 (C-8$_a$), 125.8 (C-4$_a$), 121.4 (C-6'), 115.9 (C-2'), 111.2 (C-5),

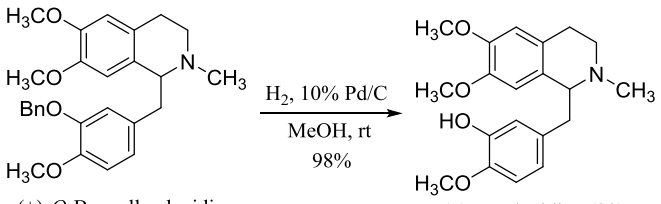
111.1 (C-8), 110.6 (C-5), 64.9 (C-1), 56.1 ($C^{4'}$-O**C**H_3), 55.9 (C^6-O**C**H_3), 55.6 (C^7-O**C**H_3), 46.8 (C-3), 42.7 (N**C**H_3), 40.9 (Ar**C**H_2), 25.4 (**C**4) ppm.

ESI-MS (*m/z*): 344.2 (100) $[M+H]^+$.

ESI-HRMS: calcd for $[C_{20}H_{26}NO_4]^+$ 344.1862, found 344.1856.

The spectroscopic data are in accordance with those reported in the literature.[281]

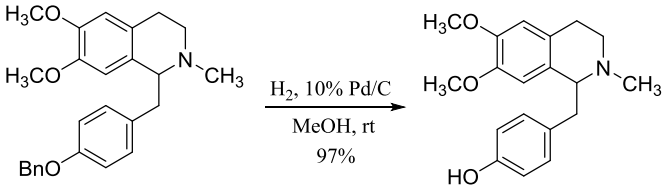
Method B:



(±)-*O*-Benzyllaudanidine (**104c**) — (±)-Laudanidine (**90**)

A mixture of benzyl ether **104c** (90 mg, 0.21 mmol) and 10% Pd/C (11 mg) in MeOH (8 mL) was stirred under a H_2-atmosphere at room temperature for 3 h. The reaction mixture was filtered through a pad of celite and the solvent was evaporated *in vacuo* to afford the title compound (71 mg, 0.207 mmol, 98 %) as a white solid. mp: 164–166 °C (dec). The spectroscopic data of the product are identical to those of the material obtained by method A.

(±)-Armepavine (91)



(±)-*O*-Benzylarmepavine (**105e**) — (±)-Armepavine (**91**)

A mixture of benzyl ether **105e** (100 mg, 0.248 mmol) and 10% Pd/C (13 mg) in MeOH (10 mL) was stirred under a H_2 atmosphere at room temperature over 2 h. The reaction mixture was filtered through a pad of celite and the solvent was evaporated *in vacuo* to afford the title compound (76 mg, 0.242 mmol, 97 %) as a white solid.

mp: 165–167 °C (dec), Lit.:[282] 166 °C.

$\mathbf{R_f}$ = 0.20 (cyclohexane/EtOAc/$HNEt_2$, 5:3:1).

IR (ATR): $\tilde{\nu}$ = 3438, 2924, 2835, 1611, 1513, 1463, 1252, 1115, 1014, 829 cm^{-1}.

^{1}H NMR, COSY (600 MHz, $CDCl_3$) δ = 6.90 (d, *J* = 8.3 Hz, 2H, H-6', H-2'), 6.63 (d, *J* = 8.3 Hz, 1H, H-5', H-3'), 6.56 (s, 1H, H-5), 6.00 (s, 1H, H-8), 3.83 (s, 3H, C^6-OC**H**$_3$), 3.71 (dd, *J* = 8.1, 5.2 Hz, 1H, H-1), 3.55 (s, 3H, C^7-OC**H**$_3$), 3.25 (ddd, *J* = 12.6, 9.4, 5.3 Hz, 1H, H_a-3), 3.13 (dd, *J* = 13.7, 5.2 Hz, 1H, ArC**H**$_a$), 2.92–2.79 (m, 2H, H_a-4, H_b-3), 2.74 (dd, *J* = 13.7, 8.1 Hz, 1H, ArC**H**$_b$), 2.62 (dt, *J* = 15.9, 5.3 Hz, 1H, H_b-4), 2.53 (s, 3H, NC**H**$_3$) ppm.

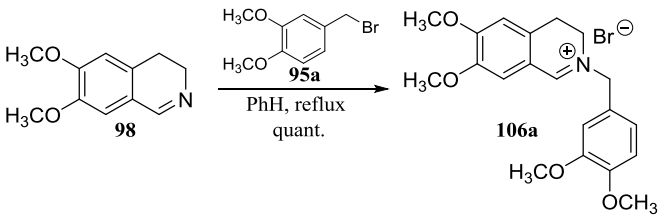
^{13}C NMR, HMBC, HSQC (150.6 MHz, $CDCl_3$) δ = 154.8 (C-4'), 147.4 (C-6), 146.4 (C-7), 131.0 (C-1'), 130.9 (C-6', C-2'), 128.8 (C-8_a), 125.3 (C-4_a), 115.5 (C-5', C-3'), 111.2 (C-8, C-5), 65.0 (C-1), 55.9 (C^6-O**C**H$_3$), 55.6 (C^7-O**C**H$_3$), 46.2 (C-3), 42.2 (N**C**H$_3$), 40.6 (Ar**C**H$_2$), 24.7 (C-4) ppm.

ESI-MS (*m/z*): 314.2 (100) $[M+H]^+$.

ESI-HRMS: calcd for $[C_{19}H_{24}NO_3]^+$ 314.1756, found: 314.1749.

B5 Studies on Alternatives Access to Ammonium Salts 96

6,7-Dimethoxy-2-veratryl-3,4-dihydro-isoquinolinium bromide (106a)



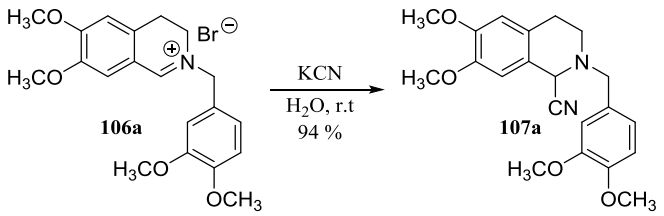
A solution of benzyl bromide **95a** (397 mg, 1.72 mmol) and imine **98** (343 mg, 1.57 mmol) in dry benzene was stirred at reflux overnight. Then, the solvent was removed under reduced pressure and the remaining solid washed with cold diethyl ether. After drying *in vacuo*, compound **106a** (663 mg, 1.57 mmol, quantitative yield) was obtained as a yellow solid.

mp: 134–137 °C (dec), Lit.:[283] 137–138 °C.

^{1}H NMR, COSY (300 MHz, DMSO-d_6) δ = 9.17 (s, 1H, H-1), 7.48 (s, 1H, H-8), 7.21 (d, *J* = 1.9 Hz, 1H, H-2'), 7.18 (s, 1H, H-5), 7.11 (dd, *J* = 8.2, 1.9 Hz, 1H, H-6'), 7.03 (d, *J* = 8.2 Hz, 1H, H-5'), 5.07 (s, 2H, NC**H**$_2$Ar), 3.92 (s, 3H, C^6-OC**H**$_3$), 3.87 (t, *J* = 8.4 Hz, 2H, H-3), 3.84 (s, 3H, C^7-OC**H**$_3$), 3.78 (s, 6H, C$^{3'}$-OC**H**$_3$, C$^{4'}$-OC**H**$_3$), 3.10 (t, *J* = 8.4 Hz, 2H, H-4) ppm.

The spectroscopic data are in accordance with those reported in the literature.[284]

1-Cyano-6,7-dimethoxy-2-veratryl-1,2,3,4-tetrahydroisoquinoline (107a)



A solution of KCN (503 mg, 27.0 mmol) in water (5 mL) was added to a solution of the isoquinolinium salt **106a** (2.09 g, 8.99 mmol) in water (20 mL). The reaction mixture was stirred for 1 h at room temperature and extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with water, dried over Na_2SO_4, and the solvent was evaporated under reduced pressure to afford the compound **107a** (0.411 g, 1.11 mmol, 94 %) as a yellow oil.

mp: 94–96 °C (dec), Lit.:[283] 98 °C.

$\mathbf{R_f}$ = 0.46 (cyclohexane/EtOAc/Et_2NH, 1:1:0.1)

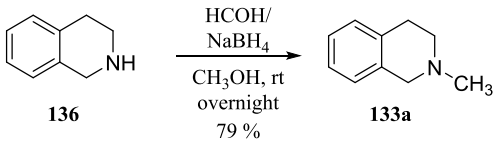
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 6.97 (dd, *J* = 8.3, 2.0 Hz, 1H, H-6‘), 6.96 (s, 1H, H-2‘), 6.85 (d, *J* = 8.3 Hz, 1H, H-5‘), 6.62 (s, 1H, H-8), 6.58 (s, 1H, H-5), 4.55 (s, 1H, H-1 (NC**H**CN)), 3.89, 3.88, 3.86, 3.83 (4s, 12H, OC$\mathbf{H_3}$), 3.85 (d, *J* = 12.8 Hz, 1H, NC$\mathbf{H}_a$Ar), 3.73 (d, *J* = 12.8 Hz, 1H, NC$\mathbf{H}_b$Ar), 3.09–2.63 (m, 4H, H-3, H-4) ppm.

The spectroscopic data are in accordance with those reported in the literature.[285]

C Reaction Procedures: Chapter 2

C1 Preparation of Compounds 130a, 133a, 134a, 139, and *n*-Butyl Triflate

N-methyl-1,2,3,4-tetrahydroisoquinoline (133a)



136 **133a**

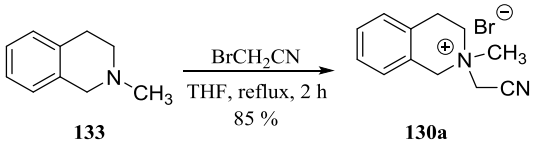
37 % aqueous formaldehyde (2.92 mL, 39.0 mmol) was added dropwise to a stir solution of commercially available 1,2,3,4-tetrahydroisoquinoline (**136**, 3.99 g, 30.0 mmol) in methanol (160 mL). The reaction mixture was stirred for 1 h at room temperature and then $NaBH_4$ (3.40 g, 90.0 mmol) was added in small portions over 5 minutes followed by stirring overnight. After this, 120 mL of methanol were removed under reduced pressure and the residue was diluted with water (50 mL). The mixture was extracted with diethyl ether (3 × 80 mL) and the combined organic layers were washed with saturated $NaHCO_3$ solution and brine, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue purified by kugelrohr distillation (T= 63–65 °C, *P*= 1.6 mbar). The title compound **133a** was obtained as a clear liquid (3.49 g, 23.7 mmol, 79 %).

$\mathbf{R}_f$ = 0.43 ($CHCl_3$/MeOH, 10:1)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.14–7.11 (m, 4H, Ph), 3.59 (s, 2H, H-1), 2.93 (t, *J* = 6.0 Hz, 2H, H-3), 2.69 (t, *J* = 6.0 Hz, 2H, H-4), 2.46 (s, 3H, NC**H$_3$**) ppm.

The spectroscopic data are in accordance with those reported in the literature.[286]

N-Cyanomethyl-*N*-methyl-1,2,3,4-tetrahydroisoquinolinium bromide (130a)



133 **130a**

Bromoacetonitrile (449 µL, 6.44 mmol) was added to a stirred solution of amine **133a** (470 mg, 3.22 mmol) in dry THF at room temperature. A few minutes after the addition, a solid started to precipitate and the reaction mixture was allowed to stir until TLC showed full conversion of the

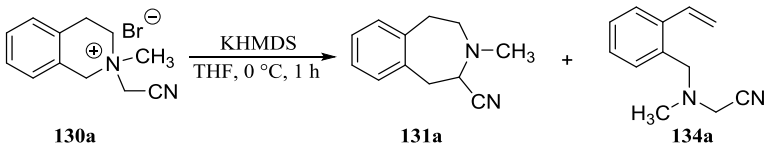
starting material. After completion, the corresponding precipitate was filtered and washed several times with THF to afford the title compound **130a** as a white solid (732 mg, 2.74 mmol, 85 %).

^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 7.41–7.23 (m, 4H, Ph), 5.12 (d, J = 16.5 Hz, 1H, C**H**$_a$CN), 5.05 (d, J = 16.5 Hz, 1H, C**H**$_b$CN), 4.83 (br. s, 2H, H-1), 4.01–3.82 (m, 2H, H-3), 3.29 (s, 3H, NC**H$_3$**), 3.32–3.13 (m, 2H, H-4) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, DMSO-d_6) δ = 129 2 (C-4a), 128.9, 128.5, 127.2 (C-5, C-6, C-7), 127.1 (C-8), 125.9 (C-8a), 111.9 (**C**N), 61.6 (C-1), 58.2 (C-3), 48.6 (N**C**H$_3$), 23.1 (C4) ppm.

The spectroscopic data are in accordance with those reported in the literature.[287]

[(2-Ethenylbenzyl)(methyl)amino]acetonitrile (134a)



130a **131a** **134a**

30 : 70

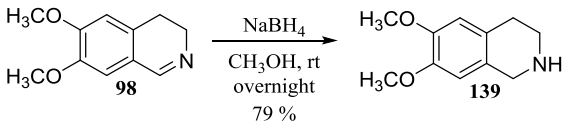
To a suspension of salt **130a** (100 mg, 374 µmol) in dry THF was added dropwise a solution of KHMDS (82.1 mg, 411 µmol) in dry THF (argon atmosphere). The reaction mixture was stirred at 0 °C for 1 h. After completion (monitored by TLC), the reaction was allowed to reach room temperature and then quenched with water. This phase was extracted with dichloromethane (3 × 10 mL) and the combined organic layers were then washed with brine, dried over Na_2SO_4 and the solvent removed under vacuum. The crude material consisted in a mixture of azepine and styrene in a 30 : 70 ratio. However, after purification by column chromatography (cyclohexane/EtOAc 6:1) compound **134a** was obtained as a yellow oil (34.0 mg, 211 µmol, 57%).

R$_f$ = 0.67 ($CHCl_3$/MeOH, 10:1)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.59 (dd, J = 7.7, 1.3 Hz, 1H, Ph-3), 7.37–7.24 (m, 3H, Ph), 7.13 (dd, J = 17.5, 11.0 Hz, 1H, C**H**=CH$_2$), 5.71 (dd, J = 17.5, 1.3 Hz, 1H, CH=C**H**$_a$), 5.34 (dd, J = 11.0 Hz, 1H, CH=C**H**$_b$), 3.67 (s, 2H, NC**H$_2$**CN), 3.44 (s, 2H, PhC**H$_2$**N), 2.46 (s, 3H, NC**H$_3$**) ppm.

The spectroscopic data are in accordance with those reported in the literature.[287]

6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline (139)



To a stirred solution of imine **98** (2.00 g, 10.5 mmol) in methanol was added $NaBH_4$ in small portions at 0 °C and over 1 h. Then, the reaction was allowed to reach room temperature and stirred overnight. After this, the methanol was removed almost until dryness and then the residue redissolved in water (20 mL) and extracted with dichloromethane (3 × 30 mL). The combined organic phases were washed with saturated $NaHCO_3$ solution and brine, and dried over Na_2SO_4. After removal of the solvent under reduce pressure, the crude product was purified by filtration through a pad of aluminium oxide (basic) (100 % EtOAc) to afford compound **139** (1.85 g, 9.57 mmol, 91 %).

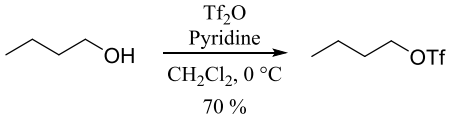
mp: 78.8–79.7 °C (dec), Lit.:[288] 79.1–80.2 °C.

$\mathbf{R}_f$ = 0.22 ($CHCl_3$/MeOH, 10:1)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.56 (s, 1H, H-8), 6.49 (s, 1H, H-5), 3.96 (s, 2H, H-1), 3.83, 3.82 (s, 6H, OC**H**$_3$), 3.15 (t, J = 6.0 Hz, 2H, H-3), 2.75 (t, J = 6.0 Hz, 2H, H-4) ppm.

The spectroscopic data are in accordance with those reported in the literature.[288]

n-Butyl triflate



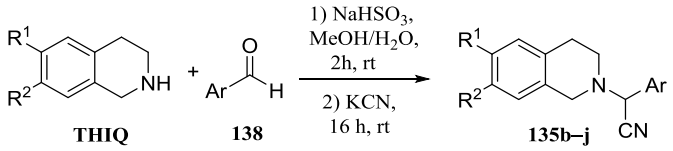
This procedure was slightly modified based on the conditions reported by FIFE et al.[289] To a stirred solution of *n*-butyl alcohol (4.94 mL, 54.0 mmol) and pyridine (4.40 mL, 54.0 mmol) in CH_2Cl_2 (100 mL) was added dropwise triflic anhydride (10.0 mL, 59.4 mmol) at 0 °C and under argon atmosphere. After stirring for 15 minutes, the reaction was quenched with an ice-water mixture and the organic layer separated. Then, this layer was washed with saturated $NaHCO_3$ solution and brine, and dried over Na_2SO_4. The solvent was then removed under vacuum to afford n-butyl triflate (7.80 g, 37.8 mmol, 70 %) as a clear but slightly purple liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.55 (t, J = 6.0 Hz, 2H, H-1), 1.87–1.76 (m, 2H, H-2), 1.52–1.41 (m, 2H, H-3), 0.97 (t, J = 7.4 Hz, 3H, C**H$_3$**) ppm.

The spectroscopic data are in accordance with those reported in the literature.[110]

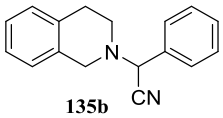
C2 Preparation of α-Aminonitriles 135b-k

General Procedure VI: One-Pot Synthesis of α-Aminonitriles 135b-k



To a turbid solution of the respective aldehyde (1.0 eq.) in water/methanol (4:1, 7 mL/mmol) was added $NaHSO_3$ (1.0 eq.) in one portion at room temperature. The reaction mixture was stirred vigorously for 2 h and then the corresponding amine (1.0 eq.) was added, followed by KCN (2.0 eq.) in one portion. The mixture turned again turbid and the stirring was continued for additional 16 h. The reaction mixture was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic layers were washed with water, brine, dried over Na_2SO_4, and filtered. The solvent was removed under reduce pressure and the crude products were either purified by recrystallization or used without further purification where indicated.

2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-2-phenylacetonitrile (135b)



Following the general procedure compound **135b** was prepared from 1,2,3,4-tetrahydroisoquinoline **136** (952 μL, 7.51 mmol), benzaldehyde (766 μL, 7.51 mmol), $NaHSO_3$ (781 mg, 7.51 mmol) and KCN (978 mg, 15.02 mmol). The crude product was recrystallized from methanol to afford the title compound (1.54 g, 6.20 mmol, 83%) as colorless crystals.

mp: 84.9–85.3 °C, Lit. [41] 77–80 °C

R_f = 0.62 (cyclohexane/EtOAc, 3:2)

IR (ATR): $\tilde{\nu}$ = 3063, 3028, 2922, 2816, 2756, 2227, 1602, 1585, 1495, 1450, 1091, 937, 740, 711 cm^{-1}.

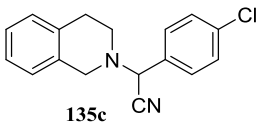
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.66–7.59 (m, 2H, H-2',6'), 7.49–7.37 (m, 3H, H-3',5', H-4'), 7.19–7.09 (m, 3H, H-5, H-6, H-7), 7.05–6.97 (m, 1H, H-8), 5.09 (s, 1H, C**H**CN), 3.82 (d, J = 14.4 Hz, 1H, H-1), 3.77 (d, J = 14.4 Hz, H-1), 3.05–2.79 (m, 4H, 2H-3, 2H-4) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 133.8 (C-4a), 133.7 (C-8a), 133.1 (C-1'), 129.1 (C-4'), 129.0 (C-3',C-5'), 128.8 (C-5), 127.9 (C-2', C-6'), 126.7 (C-8), 126.5 (C-6), 125.9 (C-7), 115.4 (**C**N), 62.3 (C–CN), 52.5 (C-1), 47.6 (C-3), 29.4 (C-4) ppm.

ESI-MS (*m/z*): 249.1 (100) $[M + H]^+$

ESI-HRMS: calcd for $[C_{17}H_{17}N_2]^+$ 249.1392, found 249.1397.

2-(4-Chlorophenyl)-2-(3,4-dihydroisoquinolin-2(1*H*)-yl)acetonitrile (135c)



135c

Following the general procedure compound **135c** was prepared from 1,2,3,4-tetrahydroisoquinoline **136** (952 µL, 7.51 mmol), *p*-chlorobenzaldehyde (1.05 g, 7.51 mmol), $NaHSO_3$ (781 mg, 7.51 mmol) and KCN (978 mg, 15.02 mmol). The crude product was recrystallized from methanol to afford the title compound (1.91 g, 6.75 mmol, 90%) as colorless crystals.

mp: 62.5–63.4 °C

$\mathbf{R}_f$ = 0.56 (cyclohexane/EtOAc, 3:2)

IR (ATR): $\tilde{\nu}$ = 3065, 3025, 2922, 2819, 2758, 2228, 1597, 1490, 1090, 1015, 937, 840, 787, 740 cm^{-1}

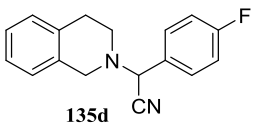
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.57 (d, *J* = 8.4 Hz, 2H, H-2',6'), 7.41 (d, *J* = 8.4 Hz, 2H, H-3',5'), 7.20–7.09 (m, 3H, H-5, H-6, H-7), 7.02–6.94 (m, 1H, H-8), 5.06 (s, 1H, C**H**CN), 3.81 (d, *J* =14.4 Hz, 1H, H-1), 3.75 (d, *J* = 14.4 Hz, 1H, H-1), 3.04–2.80 (m, 4H, 2H-3, 2H-4) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 135.3 (C-4'), 133.6 (C-4a), 133.3 (C-8a), 131.5 (C-1'), 129.4 (C-2', C-6'), 129.3 (C-3', C-5'), 128.9 (C-5), 126.7 (C-6, C-8), 126.1 (C-7), 115.0 (**C**N), 61.7 (C–CN), 52.5 (C-1''), 47.7 (C-3), 29.3 (C-4) ppm.

ESI-MS (*m/z*): 283.1 (100) $[M + H]^+$

ESI-HRMS: calcd for $[C_{17}H_{16}ClN_2]^+$ 283.1002, found 283.1008.

2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-2-(4-fluorophenyl)acetonitrile (135d)



135d

Following the general procedure compound **135d** was prepared from 1,2,3,4-tetrahydroisoquinoline **136** (952 µL, 7.51 mmol), *p*-

fluorobenzaldehyde (810 µL, 7.51 mmol), $NaHSO_3$ (781 g, 7.51 mmol) and KCN (978 mg, 15.02 mmol). The title compound (1.88 g, 7.06 mmol, 94%) was obtained as a yellow oil and was used without further purification.

R_f = 0.79 (cyclohexane/EtOAc, 3:2)

IR (ATR): $\tilde{\nu}$ = 3067, 3025, 2924, 2818, 2759, 2227, 1670, 1604, 1508, 1455, 1226, 1159, 1089, 938, 843, 785, 741 cm^{-1}

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.60 (dd, *J* = 8.7, 5.2 Hz, 2H, H-2',6'), 7.22–7.07 (m, 5H, H-3',5', H-5, H-6, H-7), 7.06–6.98 (m, 1H, H-8), 5.04 (s, 1H, C**H**CN), 3.80 (d, *J* = 14.4 Hz, 1H, H-1), 3.75 (d, *J* = 14.4 Hz, 1H, H-1), 3.09–2.74 (m, 4H, 2H-3, 2H-4) ppm.

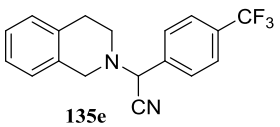
^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 163.1 (d, *J* = 248.2 Hz, C-4'), 133.7 (C-4a), 133.6 (C-8a), 129.7 (d, *J* = 8.2 Hz, 2C, C-2',6'), 129.0 (d, *J* = 3.1 Hz, C-1'), 128.8 (C-5), 126.7 (C-8), 126.6 (C-6), 126.0 (C-7), 115.9 (d, *J* = 21.7 Hz, 2C, C-3',5'), 115.3 (**C**N), 61.6 (C–CN), 52.4 (C-1), 47.6 (C-3), 29.3 (C-4) ppm.

ESI-MS (*m/z*): 267.1 (100) $[M + H]^+$

ESI-HRMS: calcd for $[C_{17}H_{16}FN_2]^+$ 267.1298, found 267.1302.

2-(3,4-Dihydroisoquinolin-2(1H)-yl)-2-(4-(trifluoromethyl)phenyl)acetonitrile (135e)

Following the general procedure compound **135e** was prepared from 1,2,3,4-tetrahydroisoquinoline **136** (952 µL, 7.51 mmol), *p*-trifluoromethylbenzaldehyde (1.03 mL, 7.51 mmol), $NaHSO_3$ (781 g, 7.51 mmol) and KCN (978 mg, 15.02 mmol). The title compound (2.15 g, 6.80 mmol, 90%) was obtained as a slightly yellow solid after purification by flash column chromatography (Isolera™ Flash Purification System, cyclohexane/EtOAc, gradient 0–28%).



135e

R_f = 0.63 (cyclohexane/EtOAc, 3:2)

IR (ATR): $\tilde{\nu}$ = 3067, 3026, 2926, 2820, 2227, 1620, 1499, 1413, 1326, 1166, 1126, 1092, 1019, 882, 753 cm^{-1}

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.78 (d, *J* = 8.3 Hz, 2H, H-2',6'), 7.70 (d, *J* = 8.3 Hz, 2H, H-3',5'), 7.22–7.11 (m, 3H, H-5, H-6, H-7), 7.06–6.97 (m, 1H, H-8), 5.12 (s, 1H, C**H**CN),

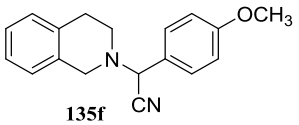
3.84 (d, *J* = 14.4 Hz, 1H, H-1), 3.77 (d, *J* = 14.4 Hz, 1H, H-1), 3.06–2.88 (m, 2H, 2H-4), 2.90–2.85 (m, 2H, 2H-3) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 137.2 (C-1'), 133.6 (C-4a), 133.4 (C-8a), 131.5 (q, *J* = 32.9 Hz, C-4'), 128.9 (C-5), 128.2 (C-2', C-6'), 126.7 (C-8), 126.6 (C-6), 126.1 (C-7), 126.0 (q, *J* = 3.8 Hz, 2C, C3',5'), 126.0 (q, *J* = 272.4, **C**F_3), 114.8 (**C**N), 61.9 (C–CN), 52.6 (C-1), 47.7 (C3), 29.3 (C-4) ppm.

ESI-MS (*m/z*): 317.1 (100) $[M + H]^+$

ESI-HRMS: calcd for $[C_{18}H_{15}F_3N_2]^+$ 317.1266, found 317.1275.

2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-2-(4-methoxyphenyl)acetonitrile (135f)



135f

Following the general procedure compound **135f** was prepared from 1,2,3,4-tetrahydroisoquinoline **136** (952 µL, 7.51 mmol), *p*-anisaldehyde (921 µL, 7.51 mmol), $NaHSO_3$ (781 g, 7.51 mmol) and KCN (978 mg, 15.02 mmol). The crude product was recrystallized from diethyl ether to afford the title compound (1.94 g, 6.97 mmol, 93%) as colorless crystals.

mp: 98.5–99.1 °C

R_f = 0.56 (cyclohexane/EtOAc, 3:2)

IR (ATR): $\tilde{\nu}$ = 3065, 3023, 2932, 2835, 2757, 2225, 1611, 1585, 1511, 1463, 1250, 1176, 1088, 1032, 937, 839, 799, 741 cm^{-1}

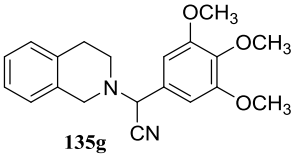
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.52 (d, *J* = 8.6 Hz, 2H, H-2',6'), 7.20–7.07 (m, 3H, H-5, H-6, H-7), 7.03–6.96 (m, 1H, H-8), 6.94 (d, *J* = 8.6 Hz, 2H, H-3',5'), 5.03 (s, 1H, C**H**CN), 3.84 (s, 3H, $C^{4'}$-OC**H**$_3$), 3.79 (d, *J* = 14.8 Hz, 1H, H-1), 3.75 (d, *J* = 14.8 Hz, 1H, H-1), 3.11–2.68 (m, 4H, 2H-3, 2H-4) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 160.3 (C-4'), 133.7 (C-4a), 133.6 (C-8a), 129.4 (C-2', C-6'), 128.9 (C-5), 126.8 (C-8), 126.6 (C-6), 126.0 (C-7), 124.8 (C-1'), 115.6 (**C**N), 114.3 (C-3', C-5'), 61.7 (C–CN), 55.5 (O**C**H_3-4'), 52.4 (C-1), 47.6 (C-3), 29.3 (C-4) ppm.

ESI-MS (*m/z*): 279.1 (100) $[M + H]^+$

ESI-HRMS: calcd for $[C_{18}H_{19}N_2O]^+$ 279.1497, found 279.1498.

2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-2-(3,4,5-trimethoxyphenyl)acetonitrile (135g)



135g

Following the general procedure compound **135g** was prepared from 1,2,3,4-tetrahydroisoquinoline **136** (952 µL, 7.51 mmol), 3,4,5-trimethoxybenzaldehyde (1.47 g, 7.51 mmol), $NaHSO_3$ (781 mg, 7.51 mmol) and KCN (978 mg, 15.02 mmol). The crude product was recrystallized from diethyl ether to afford the title compound (2.03 g, 6.00 mmol, 80%) as colorless crystals.

mp: 126.9–127.5 °C

$\mathbf{R}_f$ = 0.51 (cyclohexane/EtOAc, 3:2)

IR (ATR): $\tilde{\nu}$ = 3065, 3001, 2938, 2835, 2755, 2228, 1691, 1591, 1505, 1456, 1331, 1233, 1125, 1051, 935, 842, 741 cm^{-1}

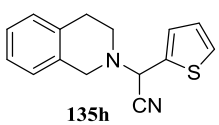
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.21–7.10 (m, 3H, H-5, H-6, H-7), 7.06–7.01 (m, 1H, H-8), 6.84 (s, 2H, H-2',6'), 5.01 (s, 1H, C**H**CN), 3.88 (s, 6H, $C^{3',5'}$-OC**H**$_3$), 3.87 (s, 3H, $C^{4'}$-OC**H**$_3$), 3.84 (d, *J* = 14.7 Hz, 1H, H-1), 3.79 (d, *J* = 14.7 Hz, 1H, H-1), 3.02–2.85 (m, 3H, 2H-3, H-4), 2.85–2.74 (m, 1H, H-4) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 153.6 (C-3', C-5'), 138.4 (C-4'), 133.8 (C-4a), 133.7 (C-8a), 128.9 (C-5), 128.7 (C-1'), 126.7 (C-8), 126.6 (C-6), 126.0 (C-7), 115.5 (**C**N), 104.7 (C-2', C-6'), 62.3 (C–CN), 61.0 ($C^{4'}$-O**C**H$_3$), 56.4 ($C^{3',5'}$-O**C**H$_3$), 52.8 (C-1), 47.3 (C-3), 29.4 (C-4) ppm.

ESI-MS (*m/z*): 206.0 (100) $[M - C_9H_{10}N]^+$, 339.1 (38) $[M + H]^+$

ESI-HRMS: calcd for $[C_{20}H_{23}N_2O_3]^+$ 339.1709, found 339.1711.

2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-2-(thiophen-2-yl)acetonitrile (135h)



135h

Following the general procedure compound **135h** was prepared from 1,2,3,4-tetrahydroisoquinoline **136** (952 µL, 7.51 mmol), 2-thiophenecarbaldehyde (702 µL, 7.51 mmol), $NaHSO_3$ (781 g, 7.51 mmol) and KCN (978 g, 15.02 mmol). The crude product was recrystallized from methanol to afford the title compound (1.66 g, 6.53 mmol, 87%) as a slightly yellow solid.

mp: 79.6–80.2 °C

R_f = 0.62 (cyclohexane/EtOAc, 3:2)

IR (ATR): $\tilde{\nu}$ = 3066, 3024, 2922, 2819, 2756, 2229, 1584, 1498, 1455, 1355, 1267, 1139, 1088, 934, 844, 739, 703 cm^{-1}

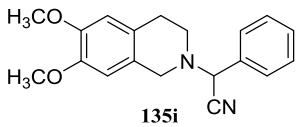
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.38 (d, *J* = 5.2 Hz, 1H, H-5'), 7.38–7.32 (m, 1H, H-3'), 7.21–7.09 (m, 3H, H-5, H-6, H-7), 7.07–6.99 (m, 2H, H-4', H-8), 5.23 (s, 1H, C**H**CN), 3.88 (t, 2H, 2H-1), 3.06–2.93 (m, 3H, 2H-3, H-4), 2.90–2.75 (m, 1H, H-4) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 137.0 (C-2'), 133.7 (C-4a), 133.2 (C-8a), 128.9 (C-5), 127.7 (C-5'), 127.5 (C-3'), 126.9 (C-4'), 126.7 (C-6, C-8), 126.1 (C-7), 114.8 (**C**N), 58.0 (C–CN), 52.7 (C-1), 47.4 (C-3), 29.3 (C-4) ppm.

ESI-MS (*m/z*): 255.1 (100) $[M + H]^+$

ESI-HRMS: calcd for $[C_{15}H_{15}N_2S]^+$ 255.0956, found 255.0957.

2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-phenylacetonitrile (135i)



135i

Following the general procedure with a subtle modification, compound **135i** was prepared from 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **139** (1.00 g, 5.17 mmol, was dissolved in 3 mL of methanol before addition), benzaldehyde (527 µL, 5.17 mmol), $NaHSO_3$ (538 mg, 5.17 mmol) and KCN (673 mg, 10.34 mmol). The crude product was recrystallized from diethyl ether to afford the title compound (1.30 g, 4.21 mmol, 82%) as colorless crystals.

mp: 101.6–102.3 °C

R_f = 0.38 (cyclohexane/EtOAc, 3:2)

IR (ATR): $\tilde{\nu}$ = 3062, 2998, 2935, 2835, 2225, 1611, 1517, 1463, 1257, 1223, 1124, 1013, 980, 855, 726, 697 cm^{-1}

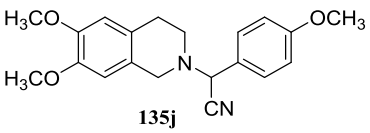
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.65–7.57 (m, 2H, H-2',6'), 7.48–7.37 (m, 3H, H-3',5', H-4'), 6.60 (s, 1H, H-5), 6.48 (s, 1H, H-8), 5.07 (s, 1H, C**H**CN), 3.84 (s, 3H, C^6-OC**H**$_3$), 3.81 (s, 3H, C^7-OC**H**$_3$), 3.72 (d, *J* = 14.0 Hz, 1H, H-1), 3.67 (d, *J* = 14.0 Hz, 1H, H-1), 2.95–2.76 (m, 4H, 2H-3, 2H-4) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 147.8 (C-6), 147.5 (C-7), 133.1 (C-1'), 129.1 (C-4'), 129.0 (C-3'), 128.0 (C-2'), 125.6 (C-4a), 125.4 (C-8a), 115.5 (**C**N), 111.5 (C-5), 109.5 (C-8), 62.3 (C–CN), 56.0 (C^6-O**C**H_3, C^7-O**C**H_3), 52.0 (C-1), 47.9 (C-3), 29.0 (C-4) ppm.

ESI-MS (*m/z*): 309.1 (100) $[M + H]^+$

ESI-HRMS: calcd for $[C_{19}H_{21}N_2O_2]^+$ 309.1603, found 309.1613.

2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-(4-methoxyphenyl)acetonitrile (135j)



135j

Following the general procedure with a subtle modification, compound **135j** was prepared from 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **139** (979 mg, 5.07 mmol, were dissolved in 3 mL of methanol before addition), anisaldehyde (622 µL, 5.07 mmol), $NaHSO_3$ (527 mg, 5.07 mmol) and KCN (660 g, 10.14 mmol). The crude product was recrystallized from diethyl ether to afford the title compound (1.44 g, 4.26 mmol, 84%) as colorless crystals.

mp: 117.3–117.7 °C

R_f = 0.39 (cyclohexane/EtOAc, 3:2)

IR (ATR): $\tilde{\nu}$ = 3059, 2999, 2935, 2836, 2226, 1611, 1585, 1511, 1463, 1250, 1223, 1175, 1123, 1030, 940, 819, 780, 733 cm^{-1}

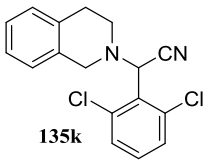
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.51 (d, *J* = 8.6 Hz, 2H, H-2', 6'), 6.94 (d, *J* = 8.8 Hz, 2H, H-3',5'), 6.60 (s, 1H, H-5), 6.48 (s, 1H, H-8), 5.01 (s, 1H, C**H**CN), 3.84 (s, 3H, C^6-OC**H**$_3$), 3.83 (s, 3H, C^7-OC**H**$_3$), 3.81 (s, 3H, $C^{4'}$-OC**H**$_3$), 3.70 (d, *J* = 14.0 Hz, 1H, H-1), 3.65 (d, *J* = 14.0 Hz, 1H, H-1), 2.99–2.71 (m, 4H, 2H-3, 2H-4) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 160.2 (C-4'), 147.8 (C-6), 147.5 (C-7), 129.3 (C-2', C-6'), 125.6 (C-4a), 125.4 (C-8a), 125.0 (C-1'), 115.7 (**C**N), 114.3 (C-3', C-5'), 111.4 (C-5), 109.5 (C-8), 61.7 (C–CN), 56.0 (C^6-O**C**H_3, C^7-O**C**H_3), 55.5 ($C^{4'}$-O**C**H_3), 51.9 (C-1), 47.8 (C-3), 28.9 (C-4) ppm

ESI-MS (*m/z*): 339.2 (100) $[M + H]^+$

ESI-HRMS: calcd for $[C_{20}H_{23}N_2O_3]^+$ 339.1709, found 339.1712.

2-(2,6-dichlorophenyl)-2-(3,4-dihydroisoquinolin-2(1H)-yl)acetonitrile (135k)



135k

Following the general procedure, compound **135k** was prepared from 1,2,3,4-tetrahydroisoquinoline (**136**, 952 µL, 7.51 mmol), 2,6-dichlorobenzaldehyde (1.31 g, 7.51 mmol), $NaHSO_3$ (781 g, 7.51 mmol) and KCN (978 mg, 15.02 mmol). The crude product (1.88 g, 5.93 mmol, 79%) was obtained as a yellow oil and was used without further purification.

R_f = 0.56 (cyclohexane/EtOAc, 3:2)

IR (ATR): $\tilde{\nu}$ = 3066, 3025, 2922, 2814, 2758, 2243, 1673, 1563, 1202, 1095, 133, 781, 749 cm^{-1}

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.43–7.38 (m, 2H, H-3',5'), 7.29 (dd, *J* = 8.8, 7.3 Hz, 1H, H-4'), 7.15–7.06 (m, 3H, H-5, H-6, H-7), 7.06–6.98 (m, 1H, H-8), 5.46 (s, 1H, C**H**CN), 3.96 (d, *J* = 14.4 Hz, 1H, H-1), 3.85 (d, *J* = 14.4 Hz, 1H, H-1), 3.13–2.86 (m, 4H, 2H-3, 2H-4) ppm.

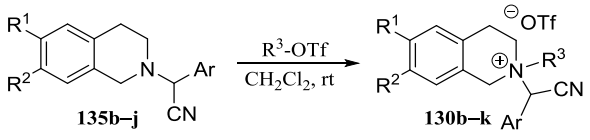
^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 136.6 (C-2', C-6'), 133.7 (C-4a), 133.5 (C-8a), 130.9 (C-4'), 129.7 (C-3', C-5'), 129.0 (C-1'), 128.8 (C-5), 126.8 (C-8), 126.6 (C-6), 126.0 (C-7), 115.5 (**C**N), 56.7 (C–CN), 52.3 (C-1), 48.4 (C-3), 29.2 (C-4) ppm.

ESI-MS (*m/z*): 317.1 (100) $[M + H]^+$

ESI-HRMS: calcd for $[C_{17}H_{15}Cl_2N_2]^+$ 317.0612, found 317.0624.

C3 Preparation of Tetrahydroisoquinolinium Salts 130b–k

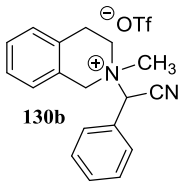
General Procedure VII: Preparation of 2-(Cyano(aryl)methyl)-2-alkyl-1,2,3,4-tetrahydroisoquinolin-2-ium Trifluoromethanesulfonate 130b–k



Alkyl triflate (1.2-2.0 eq.) was added to a stirred solution of the corresponding α-aminonitrile **135b–j** (1.0 eq.) in dry dichloromethane (6 mL). The stirring was continued at room temperature for a determined period of time (TLC monitoring). Removal of the solvent under reduce pressure

provide a crude material which was purified by flash column chromatography (Isolera™ Flash Purification System, chloroform/methanol, gradient 0–16%) to afford the title compounds.

2-(Cyano(phenyl)methyl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-2-ium trifluoromethanesulfonate (130b)



130b

According to the general procedure described above, α-aminonitrile **135b** (733 mg, 2.94 mmol) and methyl triflate (387 µL, 3.54 mmol) were allowed to react overnight in order to obtain compound **130b** as a diastereomeric mixture in a 51:49 ratio (^{1}H NMR) and in the form of a white foam (1.19 g, 2.88 mmol, 98%).

R$_f$ = 0.33 (Chloroform/methanol, 10:1)

IR (ATR): $\tilde{\nu}$ = 3060, 2934, 1588, 1459, 1253, 1224, 1155, 1029, 874, 745, 637 cm^{-1}

Major diastereomer

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.88 (d, J = 6.8 Hz, 2H, H-2',6'), 7.70–7.58 (m, 3H, H-3',5' H-4'), 7.41–7.21 (m, H-5, H-6, H-7), 7.18 (d, J = 7.6 Hz, 1H, H-8), 6.76 (s, 1H, C**H**CN), 4.88 (t, J = 14.7 Hz, 1H, H-1), 4.65 (dd, J = 14.7, 1.8 Hz, 1H, H-1), 4.09–3.97 (m, 1H, H-3), 3.94–3.86 (m, 1H, H-3), 3.39–3.25 (m, 2H, H-4), 3.28 (s, 3H, NC**H**$_3$) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 133.4 (C-4'), 132.6 (C-2', C-6'), 130.4 (C-3', C-5''), 129.9 (C-5), 129.1 (C-6), 128.5 (C-7), 128.0 (C-4a), 127.7 (C-8), 124.5 (C-8a), 123.8 (q, J = 319.6 Hz, OTf), 123.3 (C-1'), 112.8 (**C**N), 68.6 (C–CN), 60.4 (C-1), 56.4 (C-3), 44.0 (N**C**H$_3$), 23.9 (C-4) ppm.

Minor diastereomers

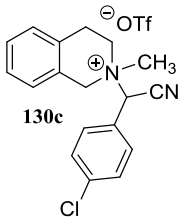
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.85 (d, J = 6.8 Hz, 2H, H-2',6'), 7.70–7.58 (m, 3H, H-3',5' H-4'), 7.41–7.21 (m, H-5, H-6, H-7), 7.15 (d, J = 7.6 Hz, 1H, H-8), 6.65 (s, 1H, C**H**CN), 4.88 (t, J = 14.7 Hz, 1H, H-1), 4.54 (dd, J = 14.7, 1.2 Hz, 1H, H-1), 4.28–4.15 (m, 1H, H-3), 3.88–3.75 (m, 1H, H-3), 3.39–3.25 (m, 2H, H-4), 3.26 (s, 3H, NC**H**$_3$) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 133.3 (C-4'), 132.5 (C-2', C-6'), 130.4 (C-3', C-5'), 129.8 (C-5), 129.2 (C-6), 128.5 (C-7), 127.9 (C-4a), 127.8 (C-8), 124.5 (C-8a), 123.8 (q, J = 319.6 Hz, OTf), 123.1 (C-1'), 112.7 (**C**N), 67.7 (C–CN), 60.2 (C-1), 57.0 (C3), 44.4 (N**C**H$_3$), 23.9 (C-4) ppm.

ESI-MS (*m/z*): 263.1 (100) $[M]^+$

ESI-HRMS: calcd for $[C_{18}H_{20}N_2]^+$ 264.1626, found 264.1617.

2-((4-Chlorophenyl)(cyano)methyl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-2-ium trifluoromethanesulfonate (130c)



130c

According to the general procedure described above, α-aminonitrile **135c** (1.00 g, 3.54 mmol) and methyl triflate (463 µL, 4.24 mmol) were allowed to react overnight in order to obtain compound **130c** as a diastereomeric mixture in a 52:48 ratio (^{1}H NMR) and in the form of a white foam (1.52 g, 3.40 mmol, 96%).

R$_f$ = 0.37 (Chloroform/methanol, 10:1)

IR (ATR): $\tilde{\nu}$ = 3057, 2933, 1596, 1495, 1251, 1156, 1028, 875, 754, 637 cm^{-1}

Major diastereomer

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = .85 (d, *J* = 8.6 Hz, 2H, H-2',6'), 7.58 (d, *J* = 8.6 Hz, 2H, H-3',5'), 7.41–7.21 (m, H-5, H-6, H-7), 7.14 (d, *J* = 7.6 Hz, 1H, H-8), 6.73 (s, 1H, C**H**CN), 4.91 (d, *J* = 14.5 Hz, 1H, H-1), 4.50 (dd, *J* = 14.5, 2.3 Hz, 1H, H-1), 4.04–3.95 (m, 1H, H-3), 3.93–3.78 (m, 1H, H-3), 3.36–3.25 (m, 2H, H-4), 3.25 (s, 3H, NC**H**$_3$) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) *Major diastereomer* δ = 140.2 (C-4'), 133.7 (C-2', C-6'), 130.7 (C-3', C-5'), 129.9 (C-5), 129.2 (C-6), 128.5 (C-7), 127.9 (C-4a), 127.8 (C-8), 124.4 (C-8a), 121.6 (C-1'), 120.6 (q, *J* = 319.7 Hz, OTf), 112.5 (**C**N), 67.0 (C–CN), 60.4 (C-1), 57.1 (C-3), 44.2 (N**C**H$_3$), 23.8 (C-4) ppm.

Minor diastereomer

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.84 (d, *J* = 8.6 Hz, 2H, H-2',6'), 7.58 (d, *J* = 8.6 Hz, 2H, H-3',5'), 7.41–7.21 (m, H-5, H-6, H-7), 7.17 (d, *J* = 7.6 Hz, 1H, H-8), 6.80 (s, 1H, C**H**CN), 4.85 (d, *J* = 14.5 Hz, 1H, H-1), 4.64 (dd, *J* = 14.5, 2.0 Hz, 1H, H-1), 4.21–4.12 (m, 1H, H-3), 3.93–3.78 (m, 1H, H-3), 3.36–3.25 (m, 2H, H-4), 3.25 (s, 3H, NC**H**$_3$) ppm.

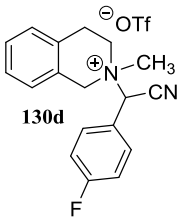
^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 140.1 (C-4'), 134.0 (C-2', C-6'), 130.7 (C-3', C-5'), 129.8 (C-5), 129.1 (C-6), 128.4 (C-7), 128.0 (C-4a), 127.9 (C-8), 124.5 (C-8a), 121.8

(C-1'), 120.6 (q, *J* = 319.7 Hz, OTf), 112.5 (**C**N), 67.8 (C–CN), 60.5 (C-1), 56.4 (C-3), 43.9 (N**C**H_3), 23.9 (C-4) ppm.

ESI-MS (*m/z*): 297.1 (100) $[M]^+$

ESI-HRMS: calcd for $[C_{18}H_{18}ClN_2]^+$ 297.1159, found 297.1164.

2-(Cyano(4-fluorophenyl)methyl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-2-ium trifluoromethanesulfonate (130d)



130d

According to the general procedure described above, α-aminonitrile **135d** (1.23 g, 4.62 mmol) and methyl triflate (606 µL, 5.54 mmol) were allowed to react overnight in order to obtain compound **130d** as a diastereomeric mixture in a 52:48 ratio (^{1}H NMR) and in the form of a slightly yellow foam (1.86 g, 4.32 mmol, 94%).

R_f = 0.37 (Chloroform/methanol, 10:1)

IR (ATR): $\tilde{\nu}$ = 3071, 2933, 1606, 1512, 1250, 1164, 1029, 845, 755, 637 cm^{-1}

Major diastereomer

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.94–7.82 (m, 2H, H-2',6'), 7.35–7.18 (m, 5H, H-5, H-6, H-7, H-3',5'), 7.11 (d, *J* = 7.5 Hz, 1H, H-8), 6.59 (s, 1H, C**H**CN), 4.84 (t, *J* = 13.9 Hz, 1H, H-1), 4.46 (dd, *J* = 13.9, 2.2 Hz, 1H, H-1), 4.15–4.05 (m, 1H, H-3), 3.98–3.75 (m, 1H, H-3), 3.35–3.23 (m, 2H, H-4), 3.17 (s, 3H, NC**H**$_3$) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 165.3 (d, *J* = 256.5 Hz, C-4'), 134.9 (d, *J* =9.3 Hz, 2C, C-2',4'), 129.7 (C-5), 129.1 (C-6), 128.3 (C-7), 128.1 (C-4a), 127.7 (C-8), 124.5 (C-8a), 120.6 (q, *J* = 319.7 Hz, OTf), 119.2 (d, *J* = 3.4 Hz, C-1'), 117.7 (d, *J* = 22.3 Hz, 2C, C-3',5''), 112.6 (**C**N), 66.9 (C–CN), 60.5 (C-1), 57.0 (C-3), 44.0 (N**C**H_3), 23.7 (C-4) ppm.

Minor diastereomers

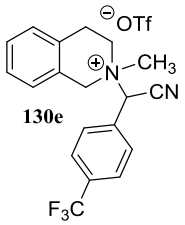
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.94–7.82 (m, 2H, H-2',6'), 7.35–7.18 (m, 5H, H-5, H-6, H-7, H-3',5'), 7.15 (d, *J* = 7.5 Hz, 1H, H-8), 6.66 (s, 1H, C**H**CN), 4.84 (t, *J* = 13.9 Hz, 1H, H-1), 4.62 (dd, *J* = 13.9, 2.3 Hz, 1H, H-1), 3.98–3.75 (m, 2H, H-3), 3.35–3.23 (m, 2H, H-4), 3.20 (s, 3H, NC**H**$_3$) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 165.3 (d, *J* = 256.5 Hz, C-4'), 134.1 (d, *J* =9.3 Hz, 2C, C-2',6'), 129.6 (C-5), 129.0 (C-6), 128.3 (C-7), 128.2 (C-4a), 127.8 (C-8), 124.6 (C-8a), 120.6 (q, *J* = 319.7 Hz, OTf), 119.3 (d, *J* = 3.4 Hz, C-1'), 117.7 (d, *J* = 22.3 Hz, 2C, C-3',5'), 112.5 (**C**N), 67.7 (C–CN), 60.6 (C-1), 56.2 (C-3), 43.8 (N**C**H_3), 23.7 (C4) ppm.

ESI-MS (*m/z*): 281.1 (100) $[M]^+$

ESI-HRMS: calcd for $[C_{18}H_{18}FN_2]^+$ 281.1454, found 281.1452.

2-(Cyano(4-(trifluoromethyl)phenyl)methyl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-2-ium trifluoromethanesulfonate (130e)



130e

According to the general procedure described above, α-aminonitrile **135e** (1.00 g, 3.16 mmol) and methyl triflate (415 µL, 3.79 mmol) were allowed to react overnight in order to obtain compound **130e** as a diastereomeric mixture in a 51:49 ratio (^{1}H NMR) and in the form of a white foam (1.38 g, 2.87 mmol, 91%).

R_f = 0.39 (Chloroform/methanol, 10:1)

IR (ATR): $\tilde{\nu}$ = 3037, 2935, 2253, 1501, 1457, 1326, 1251, 1164, 1133, 1070, 1029, 851, 756, 638 cm^{-1}

Major diastereomer

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 8.07 (d, *J* = 8.3 Hz, 2H, H-2',6'), 7.84 (d, *J* = 8.3 Hz, 2H, H-3',5'), 7.39–7.19 (m, 3H, H-5, H-6, H-7), 7.13 (d, *J* = 7.6 Hz, 1H, H-8), 6.74 (s, 1H, C**H**CN), 4.89 (t, *J* = 14.7 Hz, 1H, H-1), 4.66 (dd, *J* = 14.7, 2.4 Hz, 1H, H-1), 4.03–3.93 (m, 1H, H-3), 3.94–3.81 (m, 1H, H-3), 3.37–3.21 (m, 2H, H-4), 3.23 (s, 3H, NC**H**$_3$) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 135.0 (q, *J* = 33.1, C-4'), 133.2 (2C, C-2',6'), 129.9 (C-5), 129.1 (C-6), 128.4 (C-7), 128.0 (C-4a), 127.8 (C-8), 127.3 (q, *J* = 4.0, 2C, C-3',5'), 127.1 (C-1'), 124.4 (C-8a), 123.2 (q, *J* = 273.2 Hz, CF_3), 120.6 (q, *J* = 319.6 Hz, OTf), 112.3 (CN), 66.8 (C–CN), 60.9 (C-1), 57.4 (C-3), 44.3 (N**C**H_3), 23.8 (C-4) ppm.

Minor diastereomers

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 8.04 (d, *J* = 8.3 Hz, 2H, H-2',6'), 7.84 (d, *J* = 8.3 Hz, 2H, H-3',5'), 7.39–7.19 (m, 3H, H-5, H-6, H-7), 7.16 (d, *J* = 7.6 Hz, 1H, H-8), 6.81 (s, 1H,

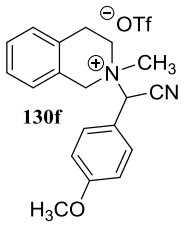
C**H**CN), 4.89 (t, *J* = 14.7 Hz, 1H, H-1), 4.51 (dd, *J* = 14.7, 2.4 Hz, 1H, H-1), 4.21–3.11 (m, 1H, H-3), 3.94–3.81 (m, 1H, H-3), 3.37–3.21 (m, 2H, H-4), 3.25 (s, 3H, NC**H**$_3$) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 135.0 (q, *J* = 33.1, C-4'), 133.3 (2C, C-2',6'), 129.8 (C-5), 129.0 (C-6), 128.3 (C-7), 127.9 (C-4a), 127.7 (C-8), 127.3 (q, *J* = 4.0, 2C, C-3',5'), 127.0 (C-1'), 124.3 (C-8a), 123.2 (q, *J* = 273.2 Hz, CF_3), 120.6 (q, *J* = 319.6 Hz, OTf), 112.2 (CN), 67.6 (C–CN), 60.8 (C-1), 57.7 (C-3), 44.1 (N**C**H$_3$), 23.8 (C-4) ppm.

ESI-MS (*m/z*): 331.2 (100) $[M]^+$

ESI-HRMS: calcd for $[C_{19}H_{18}F_3N_2]^+$ 331.1422, found 331.1431.

2-(Cyano(4-methoxyphenyl)methyl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-2-ium trifluoromethanesulfonate (130f).



130f

According to the general procedure described above, α-aminonitrile **135f** (1.00 g, 3.59 mmol) and methyl triflate (471 µL, 4.31 mmol) were allowed to react overnight in order to obtain compound **130f** as a diastereomeric mixture in a 52:48 ratio (^{1}H NMR) and in the form of a white foam (1.60 g, 3.58 mmol, 99%).

R$_f$ = 0.37 (Chloroform/methanol, 10:1)

IR (ATR): $\tilde{\nu}$ = 3041, 2938, 2844, 1609, 1515, 1254, 1157, 1028, 842, 755, 637 cm^{-1}

Major diastereomer

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.77 (d, *J* = 8.8 Hz, 2H, H-2',6'), 7.41–7.21 (m, 3H, H-5, H-6, H-7), 7.15 (d, *J* = 7.7 Hz, 1H, H-8), 6.61 (s, 1H, C**H**CN), 4.85 (t, *J* = 14.7 Hz, 1H, H-1), 4.50 (dd, *J* = 14.7, 1.6 Hz, 1H, H-1), 4.03–3.94 (m, 1H, H-3), 3.93–3.82 (m, 1H, H-3), 3.87 (s, 3H, C$^{4'}$-OC**H**$_3$), 3.35–3.24 (m, 2H, H-4), 3.25 (s, 3H, NC**H**$_3$) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 163.3 (C-4'), 134.3 (2C, C-2',6'), 129.9 (C-5), 129.2 (C-6), 128.5 (C-7), 128.1 (C-4a), 127.8 (C-8), 124.7 (C-8a), 120.7 (q, *J* = 319.3 Hz, OTf), 115.7 (2C, C-3',5'), 114.7 (C-1'), 112.9 (**C**N), 67.7 (C–CN), 59.7 (C-1), 55.9 (C-3, O**C**H$_3$-4'), 44.1 (N**C**H$_3$), 23.9 (C-4) ppm.

Minor diastereomers

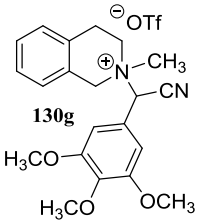
δ = 7.80 (d, *J* = 8.9 Hz, 2H, H-2',6'), 7.41–7.21 (m, 3H, H-5, H-6, H-7), 7.17 (d, *J* = 7.9 Hz, 1H, H-8), 6.71 (s, 1H, C**H**CN), 4.85 (t, *J* = 14.7 Hz, 1H, H-1), 4.60 (dd, *J* = 14.7, 1.9 Hz, 1H, H-1), 4.23–4.12 (m, 1H, H-3), 3.83–3.71 (m, 1H, H-3), 3.87 (s, 3H, $C^{4'}$-OC**H**$_3$), 3.35–3.24 (m, 2H, H-4), 3.23 (s, 3H, NC**H**$_3$) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 163.3 (C-4'), 134.1 (C-2', C-6'), 129.8 (C-5), 129.1 (C-6), 128.4 (C-7), 128.0 (C-4a), 127.9 (C-8), 124.7 (C-8a), 120.7 (q, *J* = 319.3 Hz, OTf), 115.7 (2C, C-3',5'), 114.5 (C-1'), 112.9 (**C**N), 68.5 (C–CN), 60.0 (C-1), 56.5 (C-3, $C^{4'}$-O**C**H$_3$), 43.6 (N**C**H$_3$), 24.0 (C-4) ppm.

ESI-MS (*m/z*): 293.2 (100) $[M]^+$

ESI-HRMS: calcd for $[C_{19}H_{21}N_2O]^+$ 293.1654, found 293.1653.

2-(Cyano(3,4,5-trimethoxyphenyl)methyl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-2-ium (130g)



130g

According to the general procedure described above, α-aminonitrile **135g** (500 mg, 1.47 mmol) and methyl triflate (192 µL, 4.31 mmol) were allowed to react overnight in order to obtain compound **130g** as a diastereomeric mixture in a 51:49 ratio (^{1}H NMR) and in the form of a white foam (708 mg, 1.41 mmol, 96%).

R$_f$ = 0.46 (Chloroform/methanol, 10:1)

IR (ATR): $\tilde{\nu}$ = 3058, 2943, 2843, 1593, 1508, 1466, 1246, 1126, 1028, 829, 732, 636 cm^{-1}

Major diastereomer

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.39–7.19 (m, 3H, H-5, H-6, H-7), 7.15 (t, *J* = 7.2 Hz, 1H, H-8), 7.03 (s, 2H, H-2'H-6'), 6.59 (s, 1H,C**H**CN), 4.84 (d, *J* = 14.7 Hz, 1H, H-1), 4.67 (dd, *J* = 14.7, 2.1 Hz, 1H, H-1), 4.21–4.11 (m, 1H, H-3), 4.02–3.76 (m, 1H, H-3), 3.91 (s, 6H, $C^{3',5'}$-OC**H**$_3$), 3.87 (s, 3H, $C^{4'}$-OC**H**$_3$), 3.34–3.26 (m, 2H, H-4), 3.26 (s, 3H, NC**H**$_3$) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 154.3 (C-3', C-5'), 141.8 (C-4'), 129.7 (C-5), 129.0 (C-6), 128.2 (C-7), 128.1 (C-4a), 127.8 (C-8), 124.7 (C-8a), 120.6 (q, *J* = 319.9 Hz, OTf), 118.0 (C-1'), 112.9 (**C**N), 109.8 (C-2', C-6'), 69.0 (C–CN), 61.0 ($C^{3'}$-O**C**H$_3$, $C^{5'}$-O**C**H$_3$), 60.3 (C-1), 56.8 ($C^{4'}$-O**C**H$_3$), 56.1 (C-3), 44.0 (N**C**H$_3$), 23.8 (C-4) ppm.

Minor diastereomers

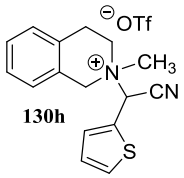
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.39–7.19 (m, 3H, H-5, H-6, H-7), 7.15 (t, *J* = 7.2 Hz, 1H, H-8), 7.07 (s, 2H, H-2',6'), 6.49 (s, 1H,C**H**CN), 4.91 (d, *J* = 14.8 Hz, 1H, H-1), 4.50 (dd, *J* = 14.8, 1.9 Hz, 1H, H-1), 4.02–3.76 (m, 2H, H-3), 3.90 (s, 6H, $C^{3',5'}$-OC**H**$_3$), 3.88 (s, 3H, $C^{4'}$-OC**H**$_3$), 3.34–3.26 (m, 2H, H-4), 3.25 (s, 3H, NC**H**$_3$) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 154.3 (C-3', C-5'), 141.8 (C-4'), 129.8 (C-5), 129.1 (C-6), 128.3 (C-7), 128.0 (C-4a), 127.7 (C-8), 124.7 (C-8a), 120.6 (q, *J* = 319.9 Hz, OTf), 117.9 (C-1'), 112.7 (**C**N), 109.8 (C-2', C-6'), 68.0 (C–CN), 61.1 ($C^{3'}$-O**C**H$_3$, $C^{5'}$-O**C**H$_3$), 60.6 (C-1), 56.9 ($C^{4'}$-OC**H**$_3$), 57.1 (C-3), 44.3 (N**C**H$_3$), 23.8 (C-4) ppm.

ESI-MS (*m/z*): 206.0 (100) $[M - C_{10}H_{13}N]^+$, 353.2 (89) $[M]^+$

ESI-HRMS: calcd for $[C_{21}H_{25}N_2O_3]^+$ 353.1865, found 353.1864.

2-(Cyano(thiophen-2-yl)methyl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-2-ium trifluoromethanesulfonate (130h)



130h

According to the general procedure described above, α-aminonitrile **135h** (501 mg, 1.97 mmol) and methyl triflate (258 µL, 2.36 mmol) were allowed to react overnight in order to obtain compound **130h** as a diastereomeric mixture in a 53:47 ratio (^{1}H NMR) and in the form of a brown foam (768 mg, 1.83 mmol, 93%).

R$_f$ = 0.43 (Chloroform/methanol, 10:1)

IR (ATR): $\tilde{\nu}$ = 3090, 2921, 1476, 1422, 1248, 1155, 1028, 845, 730, 636 cm^{-1}

Major diastereomer

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.82 (dd, *J* = 3.7, 1.2 Hz, 1H, H-5'), 7.73 (d, *J* = 1,2 Hz, 1H, H-3'), 7.38–7.20 (m, 4H, H-4', H-5, H-6, H-7), 7.13 (d, *J* = 7.6 Hz, 1H, H-8), 7.03 (s, 1H, C**H**CN), 4.94 (d, *J* = 14.9 Hz, 1H, H-1), 4.52 (dd, *J* = 14.9, 2.2 Hz, 1H, H-1), 4.03–3.81 (m, 2H, H-3), 3.43–3.25 (m, 2H, H-4), 3.27 (s, 3H, NC**H**$_3$) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 137.4 (C-5'), 133.4 (C-3'), 129.9 (C-5), 129.1 (C-6, C-4'), 128.4 (C-7), 128.2 (C-4a), 127.8 (C-8), 124.5 (C-8a), 123.4 (C-2'), 120.6 (q, *J*

= 319.8 Hz, OTf), 112.3 (**C**N), 62.9 (C–CN), 60.2 (C-1), 56.9 (C-3), 44.0 (N**C**H_3), 23.9 (C-4) ppm.

Minor diastereomers

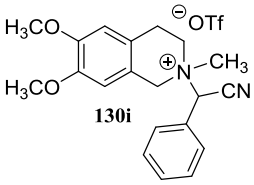
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.84 (dd, *J* = 3.7, 1.2 Hz, 1H, H-5'), 7.74 (d, *J* = 1,2 Hz, 1H, H-3'), 7.38–7.20 (m, 4H, H-4', H-5, H-6, H-7), 7.17 (d, *J* = 7.6 Hz, 1H, H-8), 7.10 (s, 1H, C**H**CN), 4.89 (d, *J* = 14.9 Hz, 1H, H-1), 4.69 (dd, *J* = 14.9, 2.2 Hz, 1H, H-1), 4.24–4.11 (m, 1H, H-3), 4.03–3.81 (m, 1H, H-3), 3.43–3.25 (m, 2H, H-4), 3.28 (s, 3H, NC**H**$_3$) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 137.7 (C-5'), 133.5 (C-3'), 129.7 (C-5), 129.2 (C-6, C-4'), 128.3 (C-7), 128.1 (C-4a), 127.8 (C-7), 124.6 (C-8a), 123.5 (C-2'), 120.6 (q, *J* = 319.8 Hz, OTf), 112.2 (**C**N), 63.7 (C–CN), 60.5 (C-1), 56.1 (C-3), 44.0 (N**C**H_3), 23.9 (C-4) ppm.

ESI-MS (*m/z*): 269.1 (100) $[M]^+$

ESI-HRMS: calcd for $[C_{16}H_{17}N_2S]^+$ 269.1112, found 269.1105.

2-(Cyano(phenyl)methyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-2-ium trifluoromethanesulfonate (130i)



130i

According to the general procedure described above, α-aminonitrile **135i** (848 mg, 2.75 mmol) and methyl triflate (361 µL, 3.30 mmol) were allowed to react overnight in order to obtain compound **130i** as a diastereomeric mixture in a 51:49 ratio (^{1}H NMR) and in the form of a slightly yellow foam (1.28 g, 2.71 mmol, 98%).

R$_f$ = 0.37 (Chloroform/methanol, 10:1)

IR (ATR): $\tilde{\nu}$ = 3061, 2940, 2841, 1613, 1521, 1461, 1252, 1157, 1119, 1028, 730, 700, 636 cm^{-1}

Major diastereomer

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.85 (d, *J* = 7.3 Hz, 2H, H-2',6'), 7.66–7.53 (m, 3H, H-3',5', H-4'), 6.86 (s, 1H, H-5), 6.63 (s, 1H, C**H**CN), 6.59 (s, 1H, H-8), 4.79 (d, *J* = 14.4 Hz, 1H, H-1), 4.54 (d, *J* = 14.4 Hz, 1H, H-1), 4.10–4.05 (m, 1H, H-3), 3.82–3.67 (m, 1H, H-3), 3.82 (s, 3H, C^6-OC**H**$_3$), 3.80 (s, 3H, C^7-OC**H**$_3$), 3.29–3.12 (m, 2H, H-4), 3.22 (s, 3H, NC**H**$_3$) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 150.0 (C-6), 149.2 (C-7), 133.2 (C-4'), 132.6 (C-2', C-6'), 130.3 (C-3','), 123.3 (C-1'), 120.6 (q, J = 319.8 Hz, OTf), 120.0 (C-4a), 116.3 (C-8a), 112.7 (**C**N), 110.9 (C-5), 109.8 (C-8), 68.5 (C–CN), 60.3 (C-1), 57.2 (C-3), 56.2 (C^6-O**C**H_3, C^7-O**C**H_3), 43.8 (N**C**H_3), 23.6 (C-4) ppm.

Minor diastereomers

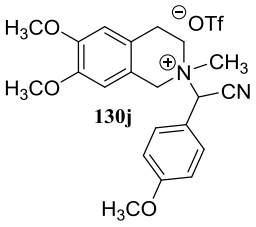
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.80 (d, J = 7.5 Hz, 2H, H-2',6'), 7.66–7.53 (m, 3H, H-3',5', H-4'), 6.68 (s, 1H, H-5), 6.58 (s, 1H, H-8), 6.52 (s, 1H, C**H**CN), 4.79 (d, J = 14.4 Hz, 1H, H-1), 4.42 (d, J = 14.4 Hz, 1H, H-1), 4.0–3.90 (m, 1H, H-3), 3.83 (s, 3H, C^6-OC**H**$_3$), 3.82–3.67 (m, 1H, H-3), 3.81 (s, 3H, C^7-OC**H**$_3$), 3.29–3.12 (m, 2H, H-4), 3.22 (s, 3H, NC**H**$_3$) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 150.1 (C-6), 149.1 (C-7), 133.2 (C-4'), 132.4 (C-2', C-6'), 130.3 (C-3', C-5'), 123.2 (C-1'), 120.6 (q, J = 319.8 Hz, OTf), 120.1 (C-4a), 116.2 (C-8a), 112.7 (**C**N), 111.0 (C-5), 109.7 (C-8), 67.4 (**C**–CN), 60.1 (C-1), 56.5 (C-3), 56.2 (C^6-O**C**H_3, C^7-O**C**H_3), 44.2 (N**C**H_3), 23.6 (C-4) ppm.

ESI-MS (*m/z*): 323.2 (100) $[M]^+$

ESI-HRMS: calcd for $[C_{20}H_{23}N_2O_2]^+$ 323.1760, found 323.1764.

2-(Cyano(4-methoxyphenyl)methyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-2-ium trifluoromethanesulfonate (130j)



130j

According to the general procedure described above, α-aminonitrile **135j** (500 mg, 1.48 mmol) and methyl triflate (194 µL, 1.77 mmol) were allowed to react overnight in order to obtain compound **130j** as a diastereomeric mixture in a 51:49 ratio (^{1}H NMR) and in the form of a white foam (650 mg, 1.47 mmol, 99%).

R$_f$ = 0.48 (Chloroform/methanol, 10:1)

IR (ATR): $\tilde{\nu}$ = 3008, 2940, 2842, 1610, 1520, 1467, 1258, 1159, 1120, 1029, 842, 811, 638 cm^{-1}

Major diastereomer

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.75 (d, *J* = 9.0 Hz, 2H, H-2',6'), 7.06 (dd, *J* = 9.0, 2.3 Hz, 2H, H-3',5'), 6.67 (s, 1H, H-5), 6.59 (s, 1H, H-8), 6.56 (s, 1H, C**H**CN), 4.78 (t, *J* = 14.5 Hz, 1H, H-1), 4.41 (d, *J* = 14.5 Hz, 1H, H-1), 4.14–4.05 (m, 1H, H-3), 3.82–3.65 (m, 1H, H-3), 3.86 (s, 3H, C^6-OC**H**$_3$), 3.85 (s, 3H, C^7-OC**H**$_3$), 3.83 (s, 3H, $C^{4'}$-OC**H**$_3$), 3.31–3.12 (m, 2H, H-4), 3.21 (s, 3H, NC**H**$_3$) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 163.2 (C-4'), 150.1 (C-6), 149.2 (C-7), 134.1 (C-2', C-6'), 120.7 (q, *J* = 319.7 Hz, OTf), 120.1 (C-4a), 116.4 (C-8a), 115.7 (C-3', C-5'), 114.6 (C-1'), 112.9 (**C**N), 111.0 (C-5), 109.7 (C-8), 67.3 (C–CN), 59.6 (C-1), 56.6 (C-3), 56.2 (C^6-O**C**H$_3$, C^7-O**C**H$_3$), 55.8 ($C^{4'}$-O**C**H$_3$), 43.9 (N**C**H$_3$), 23.6 (C-4) ppm.

Minor diastereomers

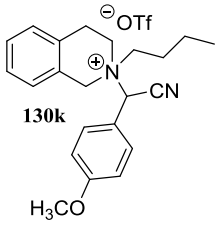
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.79 (d, *J* = 9.0 Hz, 2H, H-2',6'), 7.06 (dd, *J* = 9.0, 2.3 Hz, 2H, H-3',5'), 6.66 (s, 1H, H-5), 6.64 (s, 1H, C**H**CN), 6.52 (s, 1H, H-8), 4.78 (t, *J* = 14.5 Hz, 1H, H-1), 4.52 (dd, *J* = 14.5, 2.3 Hz, 1H, H-1), 4.00–3.87 (m, 1H, H-3), 3.82–3.65 (m, 1H, H-3), 3.86 (s, 3H, C^6-OC**H**$_3$), 3.85 (s, 3H, C^7-OC**H**$_3$), 3.83 (s, 3H, $C^{4'}$-OC**H**$_3$), 3.31–3.12 (m, 2H, H-4), 3.22 (s, 3H, NC**H**$_3$) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 163.3 (C-4'), 150.2 (C-6), 149.3 (C-7), 134.2 (C-2', C-6'), 120.7 (q, *J* = 319.7 Hz, OTf), 119.9 (C-4a), 116.5 (C-8a), 115.7 (C-3', C-5'), 114.8 (C-1'), 113.0 (**C**N), 110.9 (C-5), 109.8 (C-8), 68.3 (**C**–CN), 59.8 (C-1), 55.9 (C-3), 56.2 (C^6-O**C**H$_3$, C^7-O**C**H$_3$), 55.8 ($C^{4'}$-OC**H**$_3$), 43.5 (N**C**H$_3$), 23.7 (C-4) ppm.

ESI-MS (*m/z*): 353.2 (100) $[M]^+$

ESI-HRMS: calcd for $[C_{21}H_{25}N_2O_3]^+$ 353.1865, found 353.1864.

2-Butyl-2-(cyano(4-methoxyphenyl)methyl)-1,2,3,4-tetrahydroisoquinolin-2-ium trifluoromethanesulfonate (130k)



130k

According to the general procedure described above, α-aminonitrile **135f** (1.00 g, 3.59 mmol) and butyl triflate (1.48 g, 7.18 mmol) were allowed to react over 3 days in order to obtain compound **130k** as a diastereomeric mixture in a 52:48 ratio (^{1}H NMR) and in the form of a slightly yellow foam (463 mg, 955 μmol, 27%).

R_f = 0.41 (Chloroform/methanol, 10:1)

IR (ATR): $\tilde{\nu}$ = 3062, 2965, 2878, 2845, 1608, 1515, 1225, 1156, 1029, 838, 754, 637 cm^{-1}

Major diastereomer

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.77 (d, *J* = 8.9 Hz, 2H, H-2',6'), 7.39–7.16 (m, 4H, H-5, H-6, H-7, H-8), 7.05 (d, *J* = 8.9 Hz, 2H, H-3',5'), 6.45 (s, 1H, C**H**CN), 4.70 (d, *J* = 15.0 Hz, 1H, H-1), 4.53 (dd, *J* = 15.0, 2.1 Hz, 1H, H-1), 4.35–4.24 (m, 1H, H-3), 3.84 (s, 3H, $C^{4'}$-OC**H**$_3$), 3.76–3.54 (m, 1H, H-3), 3.48–3.14 (m, 4H, 2H-4,2H-1''), 2.18–1.85 (m, 2H,H-2''), 1.39–1.17 (m, 2H,H-3''), 0.94 (t, *J* = 7.4 Hz, 3H,H-4'') ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 163.2 (C-4'), 134.1 (C-2', C-6'), 129.7 (C-5), 129.1 (C-6), 128.5 (C-7), 128.3 (C-4a), 127.8 (C-8), 124.7 (C-8a), 120.8 (q, *J* = 319.8 Hz, OTf), 115.7 (C-3', C-5'), 114.5 (C-1'), 113.0 (**C**N), 65.2 (**C**–CN), 58.7 (C-1), 57.9 (C-1''), 55.8 ($C^{4'}$-O**C**H$_3$), 53.7 (C-3), 24.4 (C-2''), 19.8 (C-3''), 13.3 (C-4'') ppm.

Minor diastereomers

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.83 (d, *J* = 8.8 Hz, 2H, H-2',6'), 7.39–7.16 (m, 4H, H-5, H-6, H-7, H-8), 7.05 (d, *J* = 8.8 Hz, 2H, H-3',5'), 6.52 (s, 1H, C**H**CN), 4.76 (dd, *J* = 15.3, 2.4 Hz, 1H, H-1), 4.54 (d, *J* = 15.3 Hz, 1H, H-1), 4.15–4.04 (m, 1H, H-3), 3.83 (s, 3H, $C^{4'}$-OC**H**$_3$), 3.76–3.54 (m, 1H, H-3), 3.48–3.14 (m, 4H, 2H-4,2H-1''), 2.18–1.85 (m, 2H,H-2''), 1.39–1.17 (m, 2H,H-3''), 0.89 (t, *J* = 7.3 Hz, 3H,H-4'') ppm.

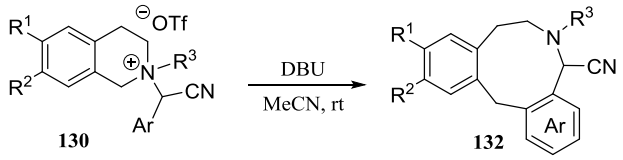
^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 163.1 (C-4'), 134.2 (C-2', C-6'), 129.6 (C-5), 128.8 (C-6), 128.4 (C-7), 128.2 (C-4a), 128.0 (C-8), 125.0 (C-8a), 120.8 (q, *J* = 319.8 Hz, OTf), 115.6 (C-3', C-5'), 114.7 (C-1'), 113.1 (**C**N), 64.8 (**C**–CN), 56.9 (C-1), 56.8 (C-1''), 55.8 ($C^{4'}$-O**C**H$_3$), 55.0 (C-3), 24.2 (C-2''), 23.8 (C-4), 20.0 (C-3''), 13.2 (C-4'') ppm.

ESI-MS (*m/z*): 335.2 (100) $[M]^+$

ESI-HRMS: calcd for $[C_{22}H_{27}N_2O]^+$ 335.2123, found 335.2126.

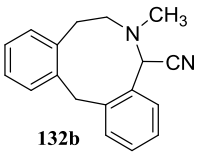
C4 Preparation of Azonines 132b-k

General Procedure VIII: Synthesis of Azonines 132b-k



DBU (1.2 eq.) was added dropwise to a stirred solution of the corresponding salt **130b-k** (1.0 eq.) in dry acetonitrile (26 mL/mmol) at room temperature. The reaction mixture was stirred for an estimated period of time (monitoring by TLC). After consumption of the starting material, acetonitrile was removed from the reaction by distillation under reduced pressure and the crude product was redissolved in dichloromethane. The organic layer was washed two times with water, and then the water layer was extracted once with dichloromethane. Combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The respective crude products were purified by recrystallization.

6-Methyl-6,7,8,13-tetrahydro-5*H*-dibenzo[*c,f*]azonine-5-carbonitrile (132b).



Following the general procedure, tetrahydroisoquinolinium salt **130b** (788 mg, 1.91 mmol) was allowed to react with DBU (342 µL, 2.29 mmol) during 1 h to obtain azonine **132b** (435 mg, 1.66 mmol, 87%) as a colorless crystalline solid after recrystallization from methanol.

mp: 125.0–126.3 °C

R_f = 0.63 (cyclohexane/EtOAc, 3:2)

IR (ATR): $\tilde{\nu}$ = 3060, 2945, 2798, 2226, 1487, 1450, 1039, 936, 808, 744, 619 cm^{-1}

^{1}H NMR, COSY (400 MHz, C_6D_6) δ = 7.48 (dd, *J* = 7.5, 1.3 Hz, 1H, H-4), 7.08 (dd, *J* = 7.6, 1.3 Hz, 1H, H-2), 7.04 (dd, *J* = 7.8, 1.6 Hz, 1H, H-12), 7.20–7.12 (m, 1H, H-1), 7.01–6.88 (m, 3H, H-3, H-10, H-11), 6.82 (dd, *J* = 7.3, 1.8 Hz, 1H, H-9), 4.73 (s, 1H, H-5), 4.16 (d, *J* = 14.0 Hz, 1H, H-13), 3.63 (d, *J* = 14.0 Hz, 1H, H-13), 2.77–2.57 (m, 2H, H-7, H-8), 2.59–2.42 (m, 1H, H-8), 2.31–2.26 (m, 1H, H-7), 1.92 (s, 3H, NC**H**$_3$) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, C_6D_6) δ = 141.4 (C-13a), 139.2 (C-12a), 138.7 (C-8a), 133.8 (C-4a), 131.7 (C-1), 129.9 (C-12), 129.8 (C-9), 129.0 (C-2), 127.8 (C-4), 127.1 (C-11),

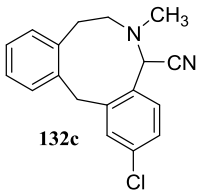
127.0 (C-10), 126.9 (C-3), 115.4 (**C**N), 57.4 (C-5), 55.9 (C-7), 38.0 (N**C**H_3), 37.8 (C-13), 33.9 (C-8) ppm.

ESI-MS (*m/z*): 263.1 (100) $[M + H]^+$

ESI-HRMS: calcd for $[C_{18}H_{19}N_2]^+$ 263.1548, found 263.1540.

2-Chloro-6-methyl-6,7,8,13-tetrahydro-5*H*-dibenzo[*c*,*f*]azonine-5-carbonitrile (132c)

Following the general procedure, tetrahydroisoquinolinium salt **130c** (100 mg, 224 μmol) was allowed to react with DBU (40 μL, 269 μmol) during 40 minutes to obtain azonine **132c** (56 mg, 189 μmol, 84%) as a colorless crystalline solid after recrystallization from methanol.



132c

mp: 165.4–166.2 °C

$\mathbf{R}_f$ = 0.63 (cyclohexane/EtOAc, 3:2)

IR (ATR): $\tilde{\nu}$ = 3058, 3015, 2945, 2849, 2801, 2227, 1568, 1482, 1143, 1042, 911, 846, 773, 754 cm^{-1}

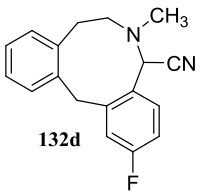
^{1}H NMR, COSY (600 MHz, C_6D_6) δ = 7.23 (d, *J* = 7.9 Hz, 2H, H-4), 7.22 (s, 1H, H-1), 6.97–6.91 (m, 2H, H-3, H-10), 6.90–6.86 (m, 2H, H-11, H-12), 6.78 (d, *J* = 7.5 Hz, 1H, H-9), 4.55 (s, 1H, H-5), 4.00 (br.s, 1H, H-13), 3.42 (d, *J* = 14.1 Hz, 1H, H-13), 2.63–2.55 (m, 2H, H-7, H-8), 2.48–2.34 (m, 1H, H-8), 2.25–2.14 (m, 1H, H-7), 1.85 (s, 3H, NC**H**$_3$) ppm.

^{13}C NMR, HMBC, HSQC (150.9 MHz, C_6D_6) δ = 143.4 (C-13a), 138.7 (C-8a), 138.3 (C-12a), 135.0 (C-2), 132.5 (C-4a), 131.9 (C-1), 130.1 (C-12), 129.9 (C-9), 129.1 (C-4), 127.4 (C-3), 127.0 (C-12), 126.9 (C-10, C-11), 115.2 (**C**N), 56.9 (C-5), 55.9 (C-7), 38.1 (N**C**H_3), 37.6 (C-13), 34.0 (C-8) ppm.

ESI-MS (*m/z*): 297.1 (100) $[M + H]^+$

ESI-HRMS: calcd for $[C_{18}H_{18}ClN_2]^+$ 297.1159, found 297.1159.

2-Fluoro-6-methyl-6,7,8,13-tetrahydro-5*H*-dibenzo[*c,f*]azonine-5-carbonitrile (132d)



132d

Following the general procedure, tetrahydroisoquinolinium salt **130d** (100 mg, 232 μmol) was allowed to react with DBU (41 μL, 278 μmol) during 40 minutes to obtain azonine **132d** (55 mg, 197 μmol, 85%) as a colorless crystalline solid after recrystallization from methanol.

mp: 164.6–165.3 °C

$\mathbf{R}_f$ = 0.61 (cyclohexane/EtOAc, 3:2)

IR (ATR): $\tilde{\nu}$ = 3059, 3015, 2945, 2848, 2802, 2227, 1612, 1589, 1493, 1450, 1246, 1121, 1040, 965, 796, 756 cm^{-1}

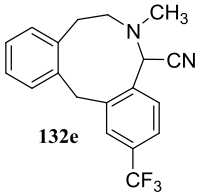
^{1}H NMR, COSY (600 MHz, C_6D_6) δ = 7.28 (dd, *J* = 8.5, 5.6 Hz, 1H, H-4), 6.98–6.92 (m, 1H, H-10), 6.92–6.86 (m, 3H, H-1, H-11, H-12), 6.79 (d, *J* = 7.3 Hz, 1H, H-9), 6.61 (td, *J* = 8.3, 2.8 Hz, 1H, H-3), 4.58 (s, 1H, H-5), 4.01 (br.s, 1H, H-13), 3.45 (d, *J* = 14.1 Hz, 1H, H-1), 2.71–2.53 (m, 2H, H-7, H-8), 2.51–2.36 (m, 1H, H-8), 2.30–2.12 (m, 1H, H-7), 1.86 (s, 3H, NC**H**$_3$) ppm.

^{13}C NMR, HMBC, HSQC (150.9 MHz, C_6D_6) δ = 163.2 (d, *J* = 247.4 Hz, C-2), 143.4 (d, *J* = 7.2 Hz, C-13a), 138.6 (C-8a), 138.2 (C-12a), 129.9(C-12), 129.8 (C-9), 129.6 (d, *J* = 3.0 Hz, C-4a), 129.2 (d, *J* = 8.7 Hz, C-4), 127.2 (C-11), 127.1 (C-10), 118.9 (d, *J* = 21.7 Hz, C-1), 115.2 (**C**N), 113.0 (d, *J* = 21.1 Hz, C-3), 56.9 (C-5), 55.6 (C-7), 37.9 (N**C**H$_3$), 37.6 (C-13), 33.8 (C-8) ppm.

ESI-MS (*m/z*): 297.1 (100) $[M + H]^+$

ESI-HRMS: calcd for $[C_{18}H_{18}FN_2]^+$ 281.1454, found 281.1459.

6-Methyl-2-(trifluoromethyl)-6,7,8,13-tetrahydro-5H-dibenzo[c,f]azonine-5-carbonitrile (132e)



132e

Following the general procedure, tetrahydroisoquinolinium salt **130e** (100 mg, 208 μmol) was allowed to react with DBU (37 μL, 250 μmol) during 30 minutes to obtain azonine **132e** (61 mg, 185 μmol, 89%) as a colorless crystalline solid after recrystallization from methanol.

mp: 171.5–172.1 °C

R_f = 0.61 (cyclohexane/EtOAc, 3:2)

IR (ATR): $\tilde{\nu}$ = 3061, 2947, 2853, 2804, 2228, 1618, 1491, 1465, 1451, 1365, 1218, 1162, 1043, 855, 800, 779 cm^{-1}

^{1}H NMR, COSY (600 MHz, C_6D_6) δ = 7.50 (s, 1H, H-1), 7.34 (d, *J* = 7.9 Hz, 1H, H-4), 7.17 (dd, *J* = 7.9, 1.7 Hz, 1H, H-3), 6.97–6.91 (m, 1H, H-10), 6.88–6.84 (m, 2H, H-11, H-12), 6.78 (d, *J* = 7.5 Hz, 1H, H-9), 4.59 (s, 1H, H-5), 4.07 (br.s, 1H, H-13), 3.47 (d, *J* = 14.2 Hz, 1H, H-13), 2.65–2.55 (m, 2H, H-7, H-8), 2.45–2.35 (m, 1H, H-8), 2.24–2.14 (m, 1H, H-7), 1.82 (s, 3H, NC**H**$_3$) ppm.

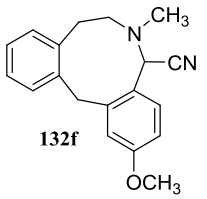
^{13}C NMR, HMBC, HSQC (150.9 MHz, C_6D_6) δ = 142.4 (C-13a), 138.5 (C-8a), 137.8 (C-12a), 137.4 (C-4a), 131.3 (q, *J* = 32.2 Hz, C-2), 129.9 (C-12), 129.8 (C-9), 128.3 (q, *J* = 3.6 Hz, C-1), 128.1 (C-4), 127.4 (C-10), 127.4 (C-11), 126.6 (q, *J* = 272.3 Hz, CF_3), 123.9 (q, *J* = 3.9 Hz, C-1), 114.7 (**C**N), 57.0 (C-5), 55.8 (C-7), 37.9 (N**C**H$_3$), 37.5 (C-13), 33.9 (C-8) ppm.

ESI-MS (*m/z*): 331.2 (100) $[M + H]^+$

ESI-HRMS: calcd for $[C_{19}H_{17}F_3N_2]^+$ 331.1422, found 331.1410.

2-Methoxy-6-methyl-6,7,8,13-tetrahydro-5*H*-dibenzo[*c*,*f*]azonine-5-carbonitrile (132f)

Following the general procedure, tetrahydroisoquinolinium salt **130f** (100 mg, 226 μmol) was allowed to react with DBU (40 μL, 271 μmol) during 1 hour and 30 minutes to obtain azonine **132f** (53 mg, 183 μmol, 81%) as a colorless crystalline solid after recrystallization from methanol.



132f

mp: 129.6–130.5 °C;

R_f = 0.61 (cyclohexane/EtOAc, 3:2)

IR (ATR): $\tilde{\nu}$ = 3058, 3014, 2944, 2838, 2798, 2227, 1613, 1578, 1495, 1253, 1037, 756 cm^{-1}

^{1}H NMR, COSY (600 MHz, C_6D_6) δ = 7.42 (d, *J* = 8.3 Hz, 1H, H-4), 7.06 (dd, *J* = 7.5, 1.5 Hz, 1H, H-12), 6.99–6.93 (m, 2H, H-1, H-11), 6.91 (td, 1H, *J* = 7.5, 1.5 Hz, 1H, H-10), 6.82 (dd, *J* = 7.5, 1.6 Hz, 1H, H-9), 6.49 (dd, *J* = 8.35, 2.7 Hz, 1H, H-3), 4.58 (s, 1H, H-5), 4.15 (br.s, 1H, H-

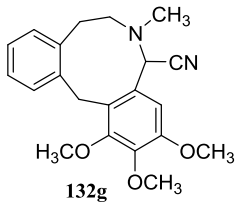
13), 3.59 (d, *J* = 14.0 Hz, 1H, H-1), 337 (s, 3H, C^2-OC**H**$_3$), 2.74–2.58 (m, 2H, H-7, H-8), 2.55–2.41 (m, 1H, H-8), 2.30–2.24 (m, 1H, H-7), 1.96 (s, 3H, NC**H**$_3$) ppm.

^{13}C NMR, HMBC, HSQC (150.9 MHz, C_6D_6) δ = 160.7 (C-2), 142.7 (C-13a), 139.2 (C-12a), 138.9 (C-8a), 130.1 (C-12), 129.8 (C-9), 128.9 (C-4), 127.2 (C-10), 127.1 (C-11), 126.3 (C-4a), 119.2 (C-1), 115.9 (**C**N), 57.0 (C-5), 55.9 (C-7), 55.2 (C^2-O**C**H$_3$), 38.1 (N**C**H$_3$), 38.0 (C-13), 34.1 (C-8) ppm.

ESI-MS (*m/z*): 293.1 (100) $[M + H]^+$

ESI-HRMS: calcd for $[C_{19}H_{21}N_2O]^+$ 293.1654, found 293.1659.

1,2,3-Trimethoxy-6-methyl-6,7,8,13-tetrahydro-5*H*-dibenzo[*c,f*]azonine-5-carbonitrile (132g)



132g

Following the general procedure, tetrahydroisoquinolinium salt **130g** (200 mg, 398 μmol) was allowed to react with DBU (71 μL, 478 μmol) during 3 hour and 45 minutes to obtain azonine **132g** (115 mg, 326 μmol, 82%) as a colorless crystalline solid after recrystallization from diethyl ether.

mp: 122.4–122.9 °C

R$_f$ = 0.54 (cyclohexane/EtOAc, 3:2)

IR (ATR): $\tilde{\nu}$ = 2942, 2836, 2799, 2226, 1600, 1490, 1404, 1332, 1117, 1033, 757 cm^{-1}

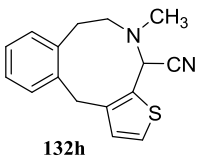
^{1}H NMR, COSY (600 MHz, C_6D_6) δ = 7.51 (d, *J* = 7.1 Hz, 1H, H-12), 7.04–6.97 (m, 2H, H-10, H-11), 6.98 (s, 1H, H-4), 6.85 (dd, *J* = 7.1, 1.9 Hz, 1H, H-9), 4.83 (s, 1H, H-5), 4.31 (d, *J* = 14.1 Hz, 1H, H-1), 3.93–3.84 (m, 1H, H-1), 3.79 (s, 3H, C^1-OC**H**$_3$), 3.73 (s, 3H, C2-OC**H**$_3$), 3.42 (s, 3H, C^3-OC**H**$_3$), 2.71 (dt, *J* = 13.0, 5.1 Hz, 1H, H-7), 2.67–2.55 (m, 2H, H-8), 2.29 (dt, *J* = 13.0, 6.4 Hz, 1H, H-7), 1.99 (s, 3H, NC**H**$_3$) ppm.

^{13}C NMR, HMBC, HSQC (150.9 MHz, $CDCl_3$) δ = 153.3 (C-1), 152.2 (C-2), 143.7 (C-3), 140.5 (C-12a), 138.7 (C-8a), 130.5 (C-12), 129.7 (C-9), 129.3 (C-13a), 127.6 (C-4a), 127.2 (C-4), 126.2 (C-11), 115.8 (**C**N), 108.4 (C-4), 60.9 (C^1-O**C**H$_3$), 60.5 (C^2-O**C**H$_3$), 57.3 (C-5), 56.0 (C-7, C^3-O**C**H$_3$), 38.4 (N**C**H$_3$), 33.5 (C-8), 28.6 (C-13) ppm.

ESI-MS (*m/z*): 353.2 (100) $[M + H]^+$

ESI-HRMS: calcd for $[C_{21}H_{25}N_2O_3]^+$ 353.1865, found 353.1864.

5-Methyl-5,6,7,12-tetrahydro-4*H*-benzo[*f*]thieno[*2,3-c*]azonine-4-carbonitrile (132h)



132h

Following the general procedure, tetrahydroisoquinolinium salt **130h** (200 mg, 478 μmol) was allowed to react with DBU (86 μL, 573 μmol) during 1 hour to obtain azonine **132h** (100 mg, 373 μmol, 78%) as a slightly violet crystalline solid after recrystallization from methanol.

mp: 134.4–135.2 °C

$\mathbf{R}_f$ = 0.54 (cyclohexane/EtOAc, 3:2)

IR (ATR): $\tilde{\nu}$ = 3059, 2945, 2911, 2849, 2799, 2227, 1539, 1464, 1117, 1087, 754, 686, 659 cm^{-1}

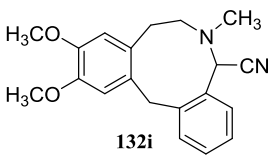
^{1}H NMR, COSY (400 MHz, C_6D_6) δ = 7.01–6.92 (m, 3H, H-9, H-10, H-11), 6.77–6.69 (m, 1H, H-8), 6.64 (d, *J* = 5.0 Hz, 1H, H-2), 6.61 (d, *J* = 5.0 Hz, 1H, H-1), 4.53 (s, 1H, H-4), 3.72 (d, *J* = 14.0 Hz, 1H), 3.66 (d, *J* = 14.2 Hz, 1H), 2.43 (dt, *J* = 12.6, 5.8 Hz, 1H, H-6), 2.36 (t, *J* = 5.5 Hz, 2H, H-7), 2.19 (dt, *J* = 12.6, 5.0 Hz, 1H, H-6), 2.08 (s, 3H, NC**H**$_3$) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, C_6D_6) δ = 140.4 (C-12a), 139.3 (C-7a), 138.3 (C-11a), 130.6 (C-11), 130.4 (C-2, C-7), 130.2 (C-2a), 127.1 (C-10), 127.0 (C-9), 116.4 (**C**N), 54.8 (C-6), 53.1 (C-4), 39.2 (N**C**H$_3$), 33.0 (C-12), 32.0 (C-7) ppm.

ESI-MS (*m/z*): 260.1 (100) $[M - CN + H_2O]^+$

ESI-HRMS: calcd for $[C_{15}H_{18}NOS]^+$ 260.1109, found 260.1099.

10,11-Dimethoxy-6-methyl-6,7,8,13-tetrahydro-5*H*-dibenzo[*c,f*]azonine-5-carbonitrile (132i)



132i

Following the general procedure, tetrahydroisoquinolinium salt **130i** (100 mg, 212 μmol) was allowed to react with DBU (38 μL, 254 μmol) during 1 hour to obtain azonine **132i** (57 mg, 178 μmol, 84%) as a colorless crystalline solid after recrystallization from methanol.

mp: 173.9–174.5 °C

$\mathbf{R}_f$ = 0.33 (cyclohexane/EtOAc, 3:2)

IR (ATR): $\tilde{\nu}$ = 2940, 2829, 2797, 2224, 1607, 1515, 1450, 1268, 1223, 1096, 743 cm^{-1}

^{1}H NMR, COSY (600 MHz, C_6D_6) δ = 7.53 (d, J = 7.5 Hz, 1H, H-4), 7.22–7.15 (m, 1H, H-1), 7.09 (td, J = 7.4, 1.4 Hz, 1H, H-2), 6.99 (td, J = 7.5, 1.5 Hz, 1H, H-3), 6.62 (s, 1H, H-12), 6.43 (s, 1H, H-9), 4.85 (s, 1H, H-5), 4.30 (d, J = 14.1 Hz, 1H, H-13), 3.63 (d, J = 14.1 Hz, 1H, H-13), 3.51 (s, 3H, C^{11}-OC**H**$_3$), 3.35 (s, 3H, C^{10}-OC**H**$_3$), 2.80–2.63 (m, 2H, H-7, H-8), 2.48–2.38 (m, 1H, H-8), 2.37–2.26 (m, 1H, H-7), 2.02 (s, 3H, NC**H**$_3$) ppm.

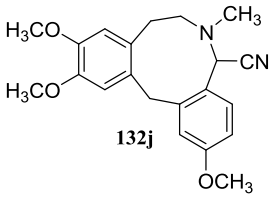
^{13}C NMR, HMBC, HSQC (150.9 MHz, C_6D_6) δ = 149.3 (C-11), 149.2 (C-10), 141.1 (C-13a), 133.4 (C-4a), 131.1 (C-1), 130.9 (C-12a), 130.7 (C-8a), 128.4 (C-2), 127.3 (C-4), 126.4 (C-3), 115.0 (**C**N), 114.8 (C-12), 114.6 (C-9), 57.1 (C-5), 56.0 (C-7), 55.7 (C^{11}-O**C**H$_3$), 55.3 (C^{10}-O**C**H$_3$), 37.6 (C-13), 37.5 (N**C**H$_3$), 33.6 (C-8) ppm.

ESI-MS (*m/z*): 323.2 (100) $[M + H]^+$

ESI-HRMS: calcd for $[C_{20}H_{23}N_2O_2]^+$ 323.1760, found 323.1765.

2,10,11-Trimethoxy-6-methyl-6,7,8,13-tetrahydro-5*H*-dibenzo[*c*,*f*]azonine-5-carbonitrile (132j)

Following the general procedure, tetrahydroisoquinolinium salt **130j** (200 mg, 452 μmol) was allowed to react with DBU (81 μL, 542 μmol) during 2 hour to obtain azonine **132j** (132 mg, 375 μmol, 83%) as a colorless crystalline solid after recrystallization from diethyl ether.



132j

mp: 143.9–144.2 °C

R$_f$ = 0.32 (cyclohexane/EtOAc, 3:2)

IR (ATR): $\tilde{\nu}$ = 2939, 2836, 2225, 1610, 1578, 1515, 1464, 1268, 1095, 1037, 735 cm^{-1}

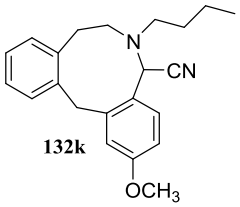
^{1}H NMR, COSY (400 MHz, C_6D_6) δ = 7.47 (d, J = 8.3 Hz, 1H, H-4), 6.97 (d, J = 2.6 Hz, 1H, H-1), 6.64 (s, 1H, H-12), 6.50 (dd, J = 8.4, 2.7 Hz, 1H, H-3), 6.42 (s, 1H, H-9), 4.82 (s, 1H, H-5), 4.31 (br.s, 1H, H-13), 3.60 (d, J = 14.1 Hz, 1H, H-13), 3.49 (s, 3H, C^{11}-OC**H**$_3$), 3.37 (s, 3H, C^2-OC**H**$_3$), 3.31 (s, 3H, C^{10}-OC**H**$_3$), 2.82–2.62 (m, 2H, H-7, H-8), 2.48–2.38 (m, 1H, H-8), 2.37–2.29 (m, 1H, H-7), 2.07 (s, 3H, NC**H**$_3$) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, C_6D_6) δ = 160.6 (C-2), 149.6 (C-11), 149.5 (C-10), 143.0 (C-13a), 131.1 (C-12a), 131.0 (C-8a), 128.9 (C-4), 126.3 (C-4a), 119.1 (C-1), 115.8 (**C**N), 115.0 (C-12), 114.8 (C-9), 110.5 (C-3), 57.1 (C-5), 56.3 (C^{11}-O**C**H$_3$), 56.0 (C^{10}-O**C**H$_3$), 55.6 (C-7), 55.0 (C^2-O**C**H$_3$), 38.1 (C-13), 38.0 (N**C**H$_3$), 34.1 (C-8) ppm.

ESI-MS (*m/z*): 353.2 (100) $[M + H]^+$

ESI-HRMS: calcd for $[C_{21}H_{25}N_2O_3]^+$ 353.1865, found 353.1850.

6-Butyl-2-methoxy-6,7,8,13-tetrahydro-5*H*-dibenzo[*c,f*]azonine-5-carbonitrile (132k)



Following the general procedure, tetrahydroisoquinolinium salt **130k** (100 mg, 206 μmol) was allowed to react with DBU (37 μL, 247 μmol) during 1 hour and 30 minutes to obtain azonine **132k** (55 mg, 165 μmol, 80%) as a colorless crystalline solid after recrystallization from methanol.

mp: 101.2–101.8 °C

$\mathbf{R}_f$ = 0.69 (cyclohexane/EtOAc, 3:2)

IR (ATR): $\tilde{\nu}$ = 3014, 2956, 2833, 2225, 1613, 1578, 1495, 1253, 1135, 1040, 754 cm^{-1}

^{1}H NMR, COSY (600 MHz, C_6D_6) δ = 7.47 (d, *J* = 8.3 Hz, 1H, H-4), 7.08 (dd, *J* = 7.2, 1.8 Hz, 1H, H-12), 7.00–6.88 (m, 3H, H-1, H-11, H-12), 6.81 (dd, *J* = 7.1, 1.9 Hz, 1H, H-10), 6.49 (dd, *J* = 8.3, 2.7 Hz, 1H, H-3), 4.72 (s, 1H, H-5), 4.11 (br.s, 1H, H-13), 3.62 (d, *J* = 13.9 Hz, 1H, H-13), 3.35 (s, 3H, C^2-OC**H**$_3$), 2.67–2.55 (m, 3H, 2H-8, H-7), 2.52–2.42 (m, 1H, H-7), 2.41–2.31 (m, 2H,H-1'), 0.98–0.58 (m, 2H,H-2'), 0.61–0.42 (m, 2H,H-3'), 0.43 (t, *J* = 7.2 Hz, 3H,H-4') ppm.

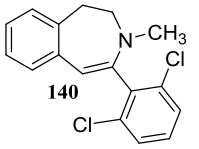
^{13}C NMR, HMBC, HSQC (150.9 MHz, C_6D_6) δ = 160.6 (C-2), 142.8 (C-13a), 139.1 (C-12a), 138.9 (C-8a), 129.8 (C-12), 129.7 (C-9), 128.7 (C-4), 126.4 (C-4a), 119.0 (C-1), 116.5 (**C**N), 110.5 (C-3), 56.6 (C-5), 55.0 (C^2-O**C**H$_3$), 52.2 (C-7), 50.1 (C-1'), 37.8 (C-13), 33.9 (C-8), 30.2 (C-2'), 19.8 (C-3'), 13.6 (C-4') ppm.

ESI-MS (*m/z*): 335.2 (100) $[M + H]^+$

ESI-HRMS: calcd for $[C_{22}H_{27}N_2O]^+$ 335.2123, found 335.2120.

C5 Synthesis of Benzo[d]azepine 140

4-(2,6-Dichlorophenyl)-3-methyl-2,3-dihydro-1*H*-benzo[*d*]azepine (140)



140

Following the same general procedure for the synthesis of dibenzo[*c,f*]azonines, tetrahydroisoquinolinium salt **130l** (200 mg, 415 μmol) was allowed to react with DBU (74 μL, 499 μmol) during 1.5 h to obtain benzazepine **140** (100 mg, 329 μmol, 79%) as a yellow oil after purification by flash column chromatography ((Isolera™ Flash Purification System, cyclohexane/EtOAc, gradient 0–18%).

$\mathbf{R}_f$ = 0.63 (cyclohexane/EtOAc, 10:1)

IR (ATR): $\tilde{\nu}$ = 3012, 2926, 2795, 1608, 1558, 1487, 1438, 1222, 775, 747 cm^{-1}

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.37 (d, *J* = 8.0 Hz, 2H, H-3', H-5'), 7.21 (dd, *J* = 8.6, 7.5 Hz, 1H, H-4'), 7.15–7.06 (m, 3H, H-6, H-7, H-8), 7.04–6.95 (m, 1H, H-9), 5.26 (s, 1H, H-1), 3.58–3.33 (m, 2H, H-4), 3.23–2.99 (m, 2H, H-5), 2.64 (s, 3H, NC**H**$_3$) ppm.

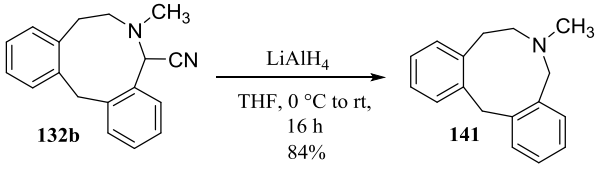
^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 142.2 (C-2), 138.9 (C-5a), 138.3 (C-9a), 137.3 (C-1'), 135.7 (C-2', C-6'), 129.7 (C-6), 129.3 (C-4'), 128.9 (C-7), 128.0 (C-3', C-5'), 126.1 (C-8), 123.4 (C-9), 104.8 (C-1), 54.3 (C-4), 41.0 (N**C**H_3), 37.2 (C-5) ppm.

ESI-MS (*m/z*): 304.1 (100) $[M + H]^+$

ESI-HRMS: calcd for $[C_{17}H_{16}NCl_2]^+$ 304.0660, found 304.0667.

C6 Reductive Decyanation of Dibenzo[c,f]azonine 132b

Synthesis of 6-methyl-6,7,8,13-tetrahydro-5*H*-dibenzo[*c,f*]azonine (141).



132b **141**

To a solution of azonine **132b** (50 mg, 190 μmol) in dry THF (3 mL) was added dropwise $LiAlH_4$ (THF solution 2M, 104 μL, 209 μmol) at 0 °C. After 10 minutes of stirring at this temperature, the mixture was allowed to reach room temperature and the stirring was continued overnight. The reaction was quenched with 10 mL of water, extracted with dichloromethane (3 ×

20 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography (cyclohexane/EtOAc 3:2) to obtain compound **141** as a slightly yellow oil (38 mg, 160 μmol, 84%).

R_f = 0.17 (cyclohexane/EtOAc, 3:2)

IR (ATR): $\tilde{\nu}$ = 3059, 3013, 2934, 2832, 2787, 1600, 1489, 1364, 1046, 741, 624 cm^{-1}

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.44 (d, *J* = 7.4 Hz, 1H, H-4), 7.31–7.21 (m, 2H, H-3, H-12), 7.19–7.02 (m, 5H, H-1, H-2, H-9, H-10, H-11), 4.26 (s, 2H, H-13), 3.50 (s, 1H, H-5), 3.07 (t, *J* = 5.7 Hz, 2H, C-8)), 2.73 (t, *J* = 5.7 Hz, 1H, H-7), 2.30 (s, 3H, NC**H**$_3$) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 141.7 (C-13a), 139.6 (C-8a, C-12a) 137.3 (C-4a), 130.7 (C-4), 130.3 (C-1), 129.9 (C-12), 129.5 (C-9), 127.7 (C-13), 126.7 (C-2), 126.5 (C-11), 126.3 (C-10), 58.1 (C-5), 57.0 (C-7), 44.3 (N**C**H$_3$), 37.4 (C-13), 32.6 (C-8) ppm.

ESI-MS (*m/z*): 238.2 (100) $[M + H]^+$

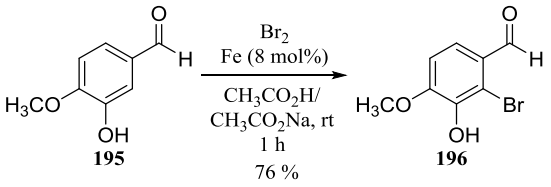
ESI-HRMS: calcd for $[C_{17}H_{20}N]^+$ 238.1596, found 238.1593.

The spectroscopic data are in accordance with those reported in the literature.[123]

D Reaction Procedures: Chapter 3

D1 Synthesis of α-Ammonium Nitrile Salt 190

2-Bromoisovanillin (196)



The title compound was prepared according to a procedure reported by FUCHS and co-workers.[147] A suspension of commercially available isovanillin (10.0 g, 65.7 mmol), powdered anhydrous sodium acetate (10.78 g, 0.131 mol), and iron powder (295 mg, 5.28 mmol) in 60 mL of glacial acetic acid under nitrogen atmosphere was treated dropwise, over 15 minutes, with a solution of bromine (3.71 mL, 72.3 mmol) in 13 mL of acetic acid. The reaction temperature rose during the course of the addition and the reaction mixture became quite thick. One hour after the completion of the addition, the reaction mixture was poured into ice water (400 mL) and the nearly colorless precipitate was collected on a filter, washed with cold water (100 mL), and air dried. Drying to constant weight under vacuum afforded compound **196** (11.3 g, 49.8 mmol, 76 %) as a grey powder.

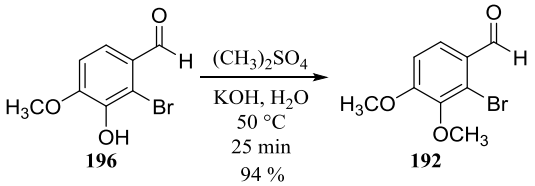
mp: 203–208 °C (dec), Lit.:[290] 206–207 °C

$\mathbf{R}_f$ = 0.89 (CH_2Cl_2/EtOAc, 9:1)

^{1}H NMR (300 MHz, DMSO-d_6) δ = 10.11 (s, 1H, C**H**O), 7.41 (d, J = 8.5 Hz, 1H, H-6), 7.14 (d, J = 8.6 Hz, 1H, H-5), 3.93 (s, 3H, C^4-OC**H**$_3$) ppm.

The spectroscopic data are in accordance with those reported in the literature.[147]

2-Bromo-3,4-dimethoxybenzaldehyde (192)



The title compound was prepared according to a procedure reported by BORCHARDT and co-workers.[291] 2-Bromoisovanillin **196** (4.99 g, 21.6 mmol) was dissolved in a solution of KOH (1.94 g, 34.6 mmol) in 35 mL of H_2O. To the bright yellow solution of 50 °C was added with vigorous stirring 3.28 mL (34.6 mmol) of dimethyl sulfate dropwise over a period of 10 minutes. After being stirred for an additional 15 minutes, the pale yellow mixture containing the solid product was cooled and filtered. The precipitate was washed twice with l N NaOH and then with H_2O. The solid was dissolved in CH_2Cl_2, and the resulting solution was washed with brine, dried (Na_2S04), and then evaporated in vacuo to dryness to give 5.00 g (20.4 mmol, 94%) of compound **192** as a yellow (clear) solid.

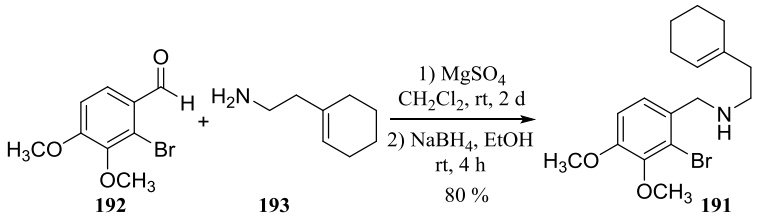
mp: 81–84 °C (dec), Lit.[291] 83–84 °C.

$\mathbf{R}_f$ = 0.89 (Cyclohexane/EtOAc, 3:2)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 10.24 (d, J = 0.8 Hz, 1H, C**H**O), 7.73 (d, J = 8.7 Hz, 1H, H-5), 6.95 (dd, J = 8.8, 0.8 Hz, 1H, H-6), 3.95 (s, 3H, OC**H**$_3$), 3.88 (s, 2H, OC**H**$_3$) ppm.

The spectroscopic data are in accordance with those reported in the literature.[291]

N-(2-bromo-3,4-dimethoxybenzyl)-2-(1-cyclohexenyl)ethylamine (191)



16.9 g of Mg_2SO_4 (0.140 mol) were added to a solution of aldehyde **192** (4.14 g, 16.9 mmol) and commercially available 2(1-cyclohexenyl)ethylamine **193** (2.82 mL, 20.3 mmol) in 56 mL of dichloromethane. This suspension was then stirred for 24 h at 40 C under nitrogen atmosphere. After this period, the Mg_2SO_4 was filtered off and washed with dichloromethane and the solvent eliminated under reduced pressure. The residue was then redissolved in 60 mL of ethanol and $NaBH_4$ (0.961 g, 25.4 mmol) was added in one-portion. Finally the mixture was stirred for 4 h at room temperature. Once the reduction was completed (TLC), the reaction mixture was concentrated under reduce pressure and to this residue treated with 80 mL of 3 N NaOH and extracted with dichloromethane (3 × 40 mL). The organic layers were then dried over Na_2SO_4 and the solvent removed under vacuum. The crude product was purified by flash column

chromatography (cyclohexane/EtOAc 3:2 + 1 % NH_4OH) to obtain compound **191** (4.79 g, 13.5 mmol, 80%) as clear liquid.

$\mathbf{R}_f$ = 0.11 (Cyclohexane/EtOAc, 3:2)

IR (ATR): $\tilde{\nu}$ = 2925, 2833, 1593, 1486, 1263, 1034, 807 cm^{-1}.

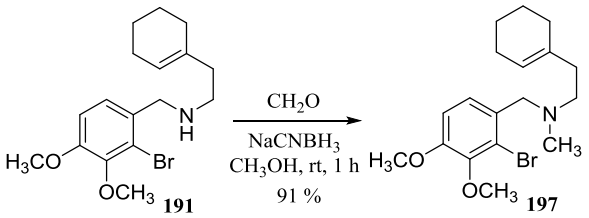
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.05 (d, *J* = 8.4 Hz, 1H, Ph-6), 6.81 (d, *J* = 8.4 Hz, 1H, Ph-5), 5.44 (br s, 1H, C=C**H**), 3.84 (s, 3H, OC**H**$_3$-Ph-4), 3.82 (s, 3H, OC**H**$_3$-Ph-3), 3.79 (s, 2H, PhC**H**$_2$N), 2.63 (t, *J* = 6.6 Hz, 2H, NC**H**$_2$), 2.13 (t, *J* = 6.6 Hz, 2H, $NCH_2C\mathbf{H}_2$), 2.00–1.91 (m, 2H, Cy-3), 1.87–1.78 (m, 2H, Cy-6), 1.62–1.47 (m, 4H, Cy-4,5) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 152.6 (Ph-4), 146.6 (Ph-3), 135.3 (**C**=CH), 132.4 (Ph-1), 125.4 (Ph-6), 123.0 (C=**C**H), 119.6 (Ph-2), 111.0 (Ph-5), 60.5 (O**C**H$_3$-Ph-3), 56.2 (O**C**H$_3$-Ph-4), 53.8 (Ph**C**H$_2$N), 46.4 (N**C**H$_2$), 38.3 ($NCH_2\mathbf{C}H_2$), 28.0 (Cy-6), 25.3 (Cy-3), 23.0 (Cy-5), 22.5 (Cy-4) ppm.

ESI-MS (*m/z*): 354.0 (100) $[C_{17}H_{25}{}^{79}BrNO_2]^+$, 356.0 (99) $[C_{17}H_{25}{}^{81}BrNO_2]^+$.

ESI-HRMS: calcd for $[C_{17}H_{25}{}^{79}BrNO_2]^+$ 354.1069, found 354.1070.

N-(2-bromo-3,4-dimethoxybenzyl)-2-(1-cyclohexenyl)-*N*-methylethylamine (197)



To a stirring solution of amine **191** (1.00 g, 2.82 mmol) and 37 % aqueous formaldehyde (1.06 mL, 14.1 mmol) in 20 mL of acetonitrile was added $NaCNBH_3$ (283 mg, 4.51 mmol) in one portion. After 15 minutes, acetic acid was added dropwise until pH ≈ 7and the mixture was continued stirring for additional 60 minutes. Once completion was achieved, the reaction was quenched with 20 mL of 2 N NaOH and extracted with dichloromethane (3 × 20 mL). The collected organic phases were washed with brine, dried over Na_2SO_4, and the solvent evaporated under reduced pressure. The crude product was purified over a pad of silica gel (cyclohexane/EtOAc 3:2) to obtain compound **197** as a clear oill (940 mg, 2.55 mmol, 91%).

$\mathbf{R}_f$ = 0.45 (Cyclohexane/EtOAc, 3:2)

IR (ATR): $\tilde{\nu}$ = 2925, 2834, 1593, 1485, 1280, 1034, 857 cm^{-1}.

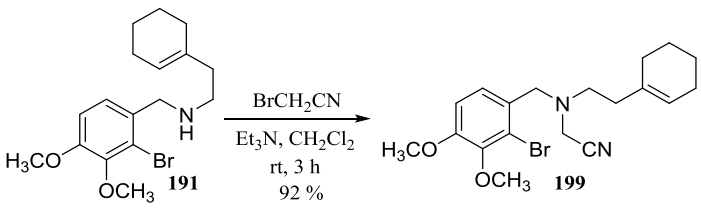
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.14 (d, *J* = 8.5 Hz, 1H, Ph-6), 6.83 (d, *J* = 8.5 Hz, 1H, Ph-5), 5.41 (s, 1H, C=C**H**), 3.85 (s, 3H, OC**H**$_3$-Ph-4), 3.83 (s, 3H, OC**H**$_3$-Ph-3), 3.52 (s, 2H, PhC**H**$_2$N), 2.55–2.47 (m, 2H, NC**H**$_2$), 2.23 (s, 3H, NC**H**$_3$), 2.16 (t, *J* = 7.9 Hz, 2H, $NCH_2C\mathbf{H}_2$), 2.01–1.91 (m, 2H, Cy-3), 1.95–1.86 (m, 2H, Cy-6), 1.62–1.47 (m, 4H, Cy-4,5) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 152.3 (Ph-4), 146.3 (Ph-3), 136.0 (**C**=CH), 131.7 (Ph-1), 125.7 (Ph-6), 121.9 (C=**C**H), 120.4 (Ph-2), 111.0 (Ph-5), 61.3 (Ph**C**H$_2$N), 60.5 (O**C**H$_3$-Ph-3), 56.6 (O**C**H$_3$-Ph-4), 56.6 (N**C**H$_2$), 42.3 (N**C**H$_3$), 36.0 ($NCH_2\mathbf{C}H_2$), 28.6 (Cy-6), 25.4 (Cy-3), 23.1 (Cy-5), 22.6 (Cy-4) ppm.

ESI-MS (*m/z*): 368.1 (96) $[C_{18}H_{27}{}^{79}BrNO_2]^+$, 370.1 (100) $[C_{18}H_{27}{}^{81}BrNO_2]^+$.

ESI-HRMS: calcd for $[C_{18}H_{27}{}^{79}BrNO_2]^+$ 368.1225, found 368.1232.

2-((2-Bromo-3,4-dimethoxybenzyl)(2-(1-cyclohexenyl)ethyl)amino)acetonitrile (199)



To a stirring solution of amine **191** (1.50 g, 4.23 mmol) and trimethylamine (498 µL, 8.46 mmol) in 30 mL of dry dichloromethane was added dropwise bromoacetonitrile (705 µL, 4.23 mmol) under nitrogen atmosphere. The reaction was stirred at room temperature until TLC showed full consumption of the starting material (ca. 3 h). After this, the reaction was quenched with 40 mL of water and extracted with dichloromethane (2 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and the solvent evaporated under reduced pressure. The crude product was purified by recrystallization from n-heptane to furnish compound **197** as white crystals (940 mg, 3.89 mmol, 91%).

mp: 73.5–74.2 °C (dec).

R$_f$ = 0.62 (Cyclohexane/EtOAc, 3:2)

IR (ATR): $\tilde{\nu}$ = 2927, 1595, 1489, 1296, 1029, 733 cm^{-1}.

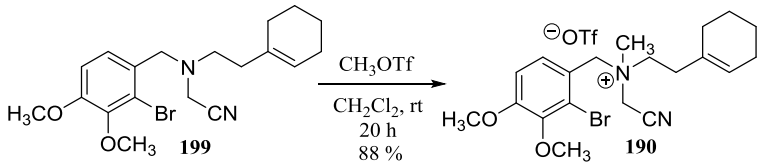
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.10 (d, J = 8.4 Hz, 1H, Ph-6), 6.84 (d, J = 8.4 Hz, 1H, Ph-5), 5.44 (s, 1H, C=C**H**), 3.87 (s, 3H, OC**H**$_3$-Ph-4), 3.85 (s, 3H, OC**H**$_3$-Ph-3), 3.72 (s, 2H, PhC**H**$_2$N), 3.49 (s, 2H, NC**H**$_2$CN), 2.71 (t_{Pseudo}, J = 7.4 Hz, 2H, NC**H**$_2$), 2.17 (t, J = 7.3 Hz, 2H, NCH$_2$C**H**$_2$), 2.01–1.93 (m, 2H, Cy-3), 1.94–1.85 (m, 2H, Cy-6), 1.65–1.48 (m, 4H, Cy-4,5) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 153.4 (Ph-4), 147.0 (Ph-3), 135.3 (**C**=CH), 129.5 (Ph-1), 126.2 (Ph-6), 122.9 (C=**C**H), 121.1 (Ph-2), 115.4 (**C**N), 111.0 (Ph-5), 60.8 (O**C**H$_3$-Ph-3), 58.3 (Ph**C**H$_2$N), 56.3 (O**C**H$_3$-Ph-4), 52.4 (N**C**H$_2$), 41.2 (N**C**H$_2$CN), 36.0 (NCH$_2$**C**H$_2$), 28.6 (Cy-6), 25.4 (Cy-3), 23.1 (Cy-5), 22.6 (Cy-4) ppm.

ESI-MS (*m/z*): 393.1 (100) $[C_{19}H_{25}{}^{79}BrN_2O_2]^+$, 395.1 (99) $[C_{19}H_{25}{}^{81}BrN_2O_2]^+$.

ESI-HRMS: calcd for $[C_{19}H_{25}{}^{79}BrN_2O_2Na]^+$ 415.0997, found 415.1001.

N-(2-Bromo-3,4-dimethoxybenzyl)-*N*-(cyanomethyl)-2-(1-cyclohexenyl)-*N*-methylethan-1-aminium trifluoromethanesulfonate (190)



Under nitrogen atmosphere, methyl triflate (306 µL, 2.79 mmol) was added to a stirred solution of the corresponding α-aminonitrile **199** (1.00 g, 2.54 mmol) in dry dichloromethane (20 mL). The stirring was continued at room temperature for a 20 h (TLC monitoring). Removal of the solvent under reduce pressure provide a crude material which was purified by flash column chromatography (Isolera™ Flash Purification System, chloroform/methanol, gradient 0–16%) to afford the title compound as a white foam (1.25 g, 2.24 mmol, 88 %).

$\mathbf{R}_f$ = 0.50 (CH_2Cl_2/EtOAc, 10:1)

IR (ATR): $\tilde{\nu}$ = 2939, 1591, 1491, 1252, 1156, 1028, 8.18, 637 cm^{-1}.

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.54 (d, J = 8.7 Hz, 1H, Ph-6), 7.05 (d, J = 8.7 Hz, 1H, Ph-5), 5.61 (s, 1H, C=C**H**), 5.00 (d, J = 13.3 Hz, 1H, PhC**H**$_a$N), 4.93 (d, J = 16.9 Hz, 1H, NC**H**$_a$CN), 4.90 (d, J = 13.3 Hz, 1H, PhC**H**$_b$N), 4.80 (d, J = 16.9 Hz, 1H, NC**H**$_b$CN), 3.94 (s, 3H, OC**H**$_3$-Ph-4), 3.87 (s, 3H, OC**H**$_3$-Ph-3), 3.83–3.73 (m, 2H, NC**H**$_a$), 3.52–3.39 (m, 2H, NC**H**$_b$), 3.27 (s, 3H, NC**H**$_3$), 2.61–2.41 (m, 2H, NCH$_2$C**H**$_2$), 2.04–1.91 (m, 4H, Cy-3,6), 1.68–1.57 (m, 2H, Cy-5), 1.59–1.48 (m, 2H, Cy-4) ppm.

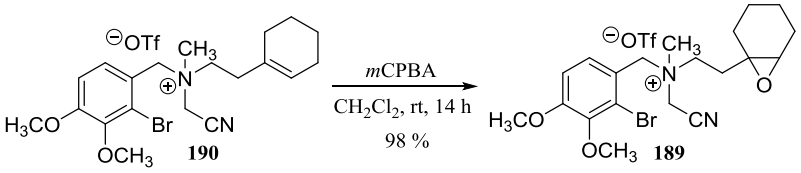
^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 156.5 (Ph-4), 147.6 (Ph-3), 131.6 (Ph-6), 130.7 (**C**=CH), 126.9 (C=**C**H), 123.5 (Ph-2), 117.8 (Ph-1), 112.3 (Ph-5), 110.8 (**C**N), 67.5 (Ph**C**H_2N), 62.6 (N**C**H_2), 60.8 (O**C**H_3-Ph-3), 56.4 (O**C**H_3-Ph-4), 49.3 (N**C**H_2CN), 48.2 (N**C**H_3), 31.1 (NCH_2**C**H_2), 28.3 (Cy-6), 25.4 (Cy-3), 22.7 (Cy-5), 22.0 (Cy-4) ppm.

ESI-MS (*m/z*): 407.1 (100) $[C_{20}H_{28}{}^{79}BrN_2O_2]^+$, 409.1 (98) $[C_{20}H_{28}{}^{81}BrN_2O_2]^+$.

ESI-HRMS: calcd for $[C_{19}H_{25}{}^{79}BrN_2O_2]^+$ 407.1334, found 407.1326.

D2 Route A. STEVENS Rearrangement/Epoxynitrile Cyclization Sequence

N-(2-Bromo-3,4-dimethoxybenzyl)-*N*-(cyanomethyl)-2-(1,2-epoxycyclohexyl)-N-methylethan-1-aminium trifluoromethanesulfonate (189)



Under nitrogen atmosphere, *m*CPBA (310 mg, 1.80 mmol) was added to a solution of the triflate salt **190** (900 mg, 1.61 mmol) in 45 mL of dry dichloromethane. After the additions, the reaction was stirred at room temperature for 14 h. Once completed (TLC), the solvent of the reaction was removed under reduced pressure affording a white solid. Rinsing this crude product with diethyl ether (3 x 30 mL) followed by removing of the residual solvent afforded epoxide **189** in 98 % yield (909 mg, 1.59 mmol) as a white sticky foam. This epoxide was isolated as mixture of diastereomers in a 54 : 46 ratio.

$\mathbf{R}_f$ = 0.35 ($CHCl_3$/methanol, 10:1)

IR (ATR): $\tilde{\nu}$ = 2943, 1591, 1491, 1255, 1158, 1029, 638 cm^{-1}

Major diastereomer

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.51 (d, *J* = 8.7 Hz, 1H, Ph-6), 7.04 (d, *J* = 8.7 Hz, 1H, Ph-5), 5.03–4.78 (m, 4H, PhC**H**$_2$N, NC**H**$_2$CN), 3.94 (s, 3H, OC**H**$_3$-Ph-4), 3.93–3.72 (m, 1H, NC**H**$_a$), 3.87 (s, 3H, OC**H**$_3$-Ph-3), 3.61–3.43 (m, 1H, NC**H**$_b$), 3.25 (s, 3H, NC**H**$_3$), 3.10–3.06 (brm, 1H, Cy-2), 2.46–2.26 (m, 1H, NCH_2C**H**$_a$), 2.15–1.87 (m, 1H, NCH_2C**H**$_b$), 1.96–1.16 (m, 8H, Cy-3,4,5,6) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 156.5 (Ph-4), 147.7 (Ph-3), 131.4 (Ph-6), 123.7 (Ph-2), 120.6 (q, *J* = 319.4 Hz, 1C, OTf), 117.7 (Ph-1), 112.3 (Ph-5), 110.8 (**C**N), 68.0 (Ph**C**H_2N), 60.8 (O**C**H_3-Ph-3), 59.9 (N**C**H_2), 59.2 (Cy-2), 57.4 (Cy-1), 56.4 (O**C**H_3-Ph-4), 49.3 (N**C**H_2CN), 48.2 (N**C**H_3), 30.8 (NCH_2**C**H_2), 27.8 (Cy-6), 24.5 (Cy-3), 19.9 (Cy-5), 19.1 (Cy-4) ppm.

Minor diastereomer

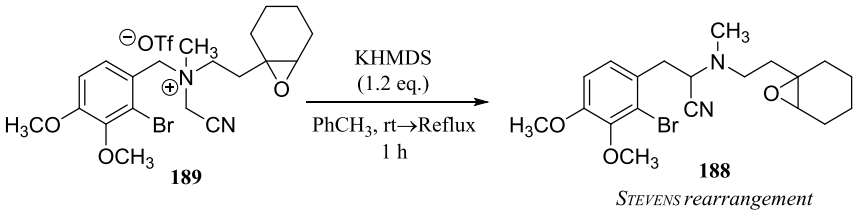
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.51 (d, *J* = 8.7 Hz, 1H, Ph-6), 7.05 (d, *J* = 8.7 Hz, 1H, Ph-5), 5.03–4.78 (m, 4H, PhC**H**$_2$N, NC**H**$_2$CN), 3.94 (s, 3H, OC**H**$_3$-Ph-4), 3.93–3.72 (m, 1H, NC**H**$_a$), 3.87 (s, 3H, OC**H**$_3$-Ph-3), 3.61–3.43 (m, 1H, NC**H**$_b$), 3.25 (s, 3H, NC**H**$_3$), 3.14–3.10 (brm, 1H, Cy-2), 2.46–2.26 (m, 1H, NCH_2C**H**$_a$), 2.15–1.87 (m, 1H, NCH_2C**H**$_b$), 1.96–1.16 (m, 8H, Cy-3,4,5,6) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 156.5 (Ph-4), 147.7 (Ph-3), 131.4 (Ph-6), 123.7 (Ph-2), 120.6 (q, *J* = 319.4 Hz, 1C, OTf), 117.7 (Ph-1), 112.3 (Ph-5), 110.8 (**C**N), 67.4 (Ph**C**H_2N), 60.8 (O**C**H_3-Ph-3), 59.9 (N**C**H_2), 58.2 (Cy-2), 57.5 (Cy-1), 56.4 (O**C**H_3-Ph-4), 49.4 (N**C**H_2CN), 48.4 (N**C**H_3), 30.3 (NCH_2**C**H_2), 28.1 (Cy-6), 24.5 (Cy-3), 19.9 (Cy-5), 19.1 (Cy-4) ppm

ESI-MS (*m/z*): 423.1 (100) $[C_{20}H_{28}{}^{79}BrN_2O_3]^+$, 425.1 (96) $[C_{20}H_{28}{}^{81}BrN_2O_3]^+$.

ESI-HRMS: calcd for $[C_{19}H_{25}{}^{79}BrN_2O_3]^+$ 423.1283, found 423.1279.

2-((2-(1,2-epoxycyclohexyl)(methyl)amino)-3-(2-bromo-3,4-dimethoxyphenyl) propanenitrile (188)



STEVENS rearrangement

Under nitrogen atmosphere, a solution of KHMDS (42.0 mg, 210 µmol) in 3 mL of toluene was added dropwise to a suspension of epoxy-salt **189** (100 mg, 174 µmol) in 10 mL of toluene at room temperature. The reaction mixture was then heated to reflux conditions for 1 h. Upon completion, the reaction was cooled and quenched with water. This aqueous phase was extracted with diethyl ether (3 x 15 mL) and the combined extracts washed with brine and dried over Na_2SO_4. Removing of the solvent under reduced pressure afforded a crude product which was purified by silica gel flash chromatography using a mixture of cyclohexane/EtOAc 6:1. In this manner, compound **188** was obtained as a yellow oil in 30 % yield (22.0 mg, 52.0 µmol) and as

a mixture of diastereomers in a 54 : 46 ratio. Nevertheless, it was observed that the product decompose upon purification by flash chromatography.

R_f = 0.31 (Cyclohexane/EtOAc, 6:1)

IR (ATR): $\tilde{\nu}$ = 2928, 1594, 11486, 1268, 103, 811 cm^{-1}

Major diastereomer

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.04 (d, *J* = 8.5 Hz, 1H, Ph-6), 6.84 (d, *J* = 8.5 Hz, 1H, Ph-5), 3.98–3.88 (m, 1H, NC**H**CN), 3.87 (s, 3H, OC**H**$_3$-Ph-4), 3.85 (s, 3H, OC**H**$_3$-Ph-3), 3.16 (dd, *J* = 13.5, 5.9 Hz, 1H, PhC**H**$_a$), 3.05 (ddd, *J* = 13.5, 9.7, 1.7 Hz, 1H, PhC**H**$_b$), 2.97 (brd, *J* = 3.4 Hz, 1H, Cy-2), 2.74–2.62 (m, 1H, NC**H**$_a$), 2.58–2.48 (m, 1H, NC**H**$_b$), 2.37 (s, 3H, NC**H**$_3$), 1.96–1.60 (m, 6H, NCH_2C**H**$_2$, Cy-2,6), 1.48–1.12 (m, 4H, Cy-4,5) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 153.1 (Ph-4), 146.8 (Ph-3), 128.0 (Ph-1), 126.8 (Ph-6), 120.3 (Ph-2), 116.7 (**C**N), 111.4 (Ph-5), 60.6 (O**C**H$_3$-Ph-3), 58.9 (Cy-1), 58.7 (Cy-2), 57.7 (NC**H**CN), 56.2 (O**C**H$_3$-Ph-4), 51.3 (N**C**H$_2$), 38.3 (N**C**H$_3$), 38.1 (Ph**C**H$_2$), 35.6 (NCH_2**C**H$_2$), 28.2 (Cy-6), 24.8 (Cy-3), 20.2 (Cy-5), 19.6 (Cy-4) ppm.

Minor diastereomer

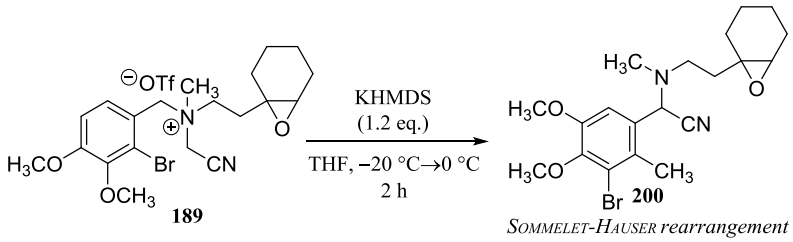
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.04 (d, *J* = 8.5 Hz, 1H, Ph-6), 6.84 (d, *J* = 8.5 Hz, 1H, Ph-5), 3.98–3.88 (m, 1H, NC**H**CN), 3.87 (s, 3H, OC**H**$_3$-Ph-4), 3.85 (s, 3H, OC**H**$_3$-Ph-3), 3.16 (dd, *J* = 13.5, 5.9 Hz, 1H, PhC**H**$_a$), 3.05 (ddd, *J* = 13.5, 9.7, 1.7 Hz, 1H, PhC**H**$_b$), 2.95 (d, *J* = 3.4 Hz, 1H, Cy-2), 2.74–2.62 (m, 1H, NC**H**$_a$), 2.58–2.48 (m, 1H, NC**H**$_b$), 2.38 (s, 3H, NC**H**$_3$), 1.96–1.60 (m, 6H, NCH_2C**H**$_2$, Cy-2,6), 1.48–1.12 (m, 4H, Cy-4,5) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 153.1 (Ph-4), 146.8 (Ph-3), 128.0 (Ph-1), 126.8 (Ph-6), 120.3 (Ph-2), 116.8 (**C**N), 111.4 (Ph-5), 60.6 (O**C**H$_3$-Ph-3), 58.9 (Cy-1), 58.6 (Cy-2), 57.9 (NC**H**CN), 56.2 (O**C**H$_3$-Ph-4), 51.4 (N**C**H$_2$), 38.4 (N**C**H$_3$), 38.2 (Ph**C**H$_2$), 35.7 (NCH_2**C**H$_2$), 28.3 (Cy-6), 24.8 (Cy-3), 20.2 (Cy-5), 19.6 (Cy-4) ppm.

ESI-MS (*m/z*): 423.1 (100) $[C_{20}H_{28}{}^{79}BrN_2O_3]^+$, 425.1 (98) $[C_{20}H_{28}{}^{81}BrN_2O_3]^+$.

ESI-HRMS: calcd for $[C_{20}H_{28}{}^{79}BrN_2O_3]^+$ 423.1283, found 423.1271.

2-((2-(1,2-epoxycyclohexyl)ethyl)(methyl)amino)-2-(3-bromo-4,5-dimethoxy-2-methylphenyl)acetonitrile (200)



Under nitrogen atmosphere, a solution of KHMDS (19.0 mg, 95.2 µmol) in 1.5 mL of THF was added dropwise to a suspension of epoxy-salt **189** (50.0 mg, 87.2 µmol) in 5 mL of THF at – 20 °C. The reaction mixture was allowed to stir at this temperature for 90 minutes and then for additional 30 minutes at 0 °C. Upon completion, the reaction was cooled and quenched with water. This aqueous phase was extracted with diethyl ether (3 x 10mL) and the combined extracts washed with brine and dried over Na_2SO_4. Removing of the solvent under reduced pressure afforded a crude product which was purified by silica gel flash chromatography using a mixture of cyclohexane/EtOAc 6:1. In this manner, compound **200** was obtained as a yellow oil in 22 % yield (8.2 mg, 19 µmol) and as a mixture of diastereomers in a 54 : 46 ratio. Nevertheless, it was observed that the product decompose upon purification by flash chromatography.

$\mathbf{R}_f$ = 0.54 (Cyclohexane/EtOAc, 3:2)

Major diastereomer

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.10 (s, Ph-6), 4.91 (s, 1H, NC**H**CN), 3.90 (s, 3H, OC**H**$_3$-Ph-5), 3.85 (s, 3H, OC**H**$_3$-Ph-4), 2.89 (brd, J = 3.4 Hz, 1H, Cy-2), 2.69–2.53 (m, 1H, NC**H**$_2$), 2.38 (s, 3H, PhC**H**$_3$), 2.23 (s, 3H, NC**H**$_3$), 1.96–1.71 (m, 2H, Cy-3), 1.83–1.45 (m, 4H, NCH$_2$C**H**$_2$, Cy-6), 1.47–1.30 (m, 2H, Cy-4), 1.26–1.06 (m, 2H, Cy-5) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 150.9 (Ph-4), 147.1 (Ph-5), 130.2 (Ph-1), 127.9 (Ph-1), 122.8 (Ph-2), 115.7 (**C**N), 112.7 (Ph-6), 61.3 (NC**H**CN), 60.6 (O**C**H$_3$-Ph-4), 58.8 (Cy-1), 58.6 (Cy-2), 56.2 (O**C**H$_3$-Ph-4), 50.2 (N**C**H$_2$), 38.1 (N**C**H$_3$), 35.8 (NCH$_2$**C**H$_2$), 27.8 (Cy-6), 24.7 (Cy-3), 20.1 (Cy-5), 19.5 (Cy-4), 18.6 (Ph**C**H$_3$) ppm.

Minor diastereomer

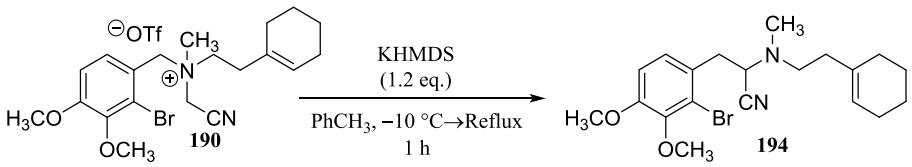
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.10 (s, Ph-6), 4.93 (s, 1H, NC**H**CN), 3.90 (s, 3H, OC**H**$_3$-Ph-5), 3.85 (s, 3H, OC**H**$_3$-Ph-4), 2.93 (brd, J = 3.4 Hz, 1H, Cy-2), 2.69–2.53 (m, 1H, NC**H**$_2$), 2.38 (s, 3H, PhC**H**$_3$), 2.22 (s, 3H, NC**H**$_3$), 1.96–1.71 (m, 2H, Cy-3), 1.83–1.45 (m, 4H, NCH$_2$C**H**$_2$, Cy-6), 1.47–1.30 (m, 2H, Cy-4), 1.26–1.06 (m, 2H, Cy-5) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 150.9 (Ph-4), 147.1 (Ph-5), 130.3 (Ph-1), 128.0 (Ph-1), 122.8 (Ph-2), 115.7 (**C**N), 112.7 (Ph-6), 61.1 (NC**H**CN), 60.6 (O**C**H$_3$-Ph-4), 58.8 (Cy-1), 58.2 (Cy-2), 56.5 (O**C**H$_3$-Ph-4), 50.2 (N**C**H$_2$), 38.1 (N**C**H$_3$), 35.3 (NCH$_2$**C**H$_2$), 28.1 (Cy-6), 24.7 (Cy-3), 20.1 (Cy-5), 19.7 (Cy-4), 18.6 (Ph**C**H$_3$) ppm.

ESI-MS (*m/z*): 423.1 (100) $[C_{20}H_{28}{}^{79}BrN_2O_3]^+$, 425.1 (98) $[C_{20}H_{28}{}^{81}BrN_2O_3]^+$.

D3 Route B. STEVENS Rearrangement/Aza-PRINS Cyclization Sequence

3-(2-bromo-3,4-dimethoxyphenyl)-2-((2-(1-cyclohexenylyl)ethyl)(methyl)amino) propanenitrile (194)



STEVENS rearrangement

Under nitrogen atmosphere, solid KHMDS (42.0 mg, 210 µmol) was added in one portion to an insolubilized mixture of salt **190** (100 mg, 174 µmol) in 10 mL of toluene at –10 °C. Rapidly, the reaction was taken directly to be heated at reflux conditions for 1 h. Upon completion, the reaction was cooled and quenched with water. The aqueous phase was extracted with toluene (2 x 10 mL) and the combined extracts washed with brine and dried over Na_2SO_4. Removal of the solvent under reduce pressure afforded a crude product which can afford the product in 87 % yield (based on quantitative ^{1}H NMR using CH_2Br_2 as internal standard). Purification of the reaction crude using silica gel flash chromatography (cyclohexane/EtOAc 8:1) afforded compound **194** in 75 % yield (54.5 mg, 134 µmol). Nevertheless, it was observed that the product decompose upon purification by flash chromatography.

$\mathbf{R}_f$ = 0.28 (Cyclohexane/EtOAc, 6:1)

IR (ATR): $\tilde{\nu}$ = 2928, 11594, 1295, 1268, 1031, 811 cm^{-1}

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.04 (d, *J* = 8.5 Hz, 1H, Ph-6), 6.84 (d, *J* = 8.5 Hz, 1H, Ph-5), 5.42 (s, 1H, C=C**H**), 3.94 (dd, *J* = 9.8, 5.8 Hz, 1H, NC**H**CN), 3.86 (s, 3H, OC**H**$_3$-Ph-4), 3.85 (s, 3H, OC**H**$_3$-Ph-3), 3.16 (dd, *J* = 13.5, 5.8 Hz, 1H, PhC**H**$_a$), 3.04 (dd, *J* = 13.5, 9.8 Hz, 1H, PhC**H**$_b$), 2.65 (ddd, *J* = 12.3, 9.0, 6.5 Hz, 1H, NC**H**$_a$), 2.50 (ddd, *J* = 12.3, 9.0, 6.0 Hz, 1H, NC**H**$_b$), 2.18–2.02 (s, 2H, , $NCH_2C\mathbf{H}_2$), 2.00–1.92 (m, 1H, Cy-3), 1.93–1.87 (m, 1H, Cy-6), 1.66–1.47 (m, 4H, Cy-4,5) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 153.0 (Ph-4), 146.9 (Ph-3), 135.3 (**C**=CH), 128.3 (Ph-1), 126.9 (Ph-6), 122.8 (C=**C**H), 120.4 (Ph-2), 117.1 (**C**N), 111.3 (Ph-5), 60.6 (O**C**H$_3$-Ph-3), 57.6 (NC**H**CN), 56.2 (O**C**H$_3$-Ph-4), 54.3 (N**C**H$_2$), 38.6 (N**C**H$_3$), 38.2 (Ph**C**H$_2$), 36.3 ($NCH_2\mathbf{C}H_2$), 28.2 (Cy-6), 25.4 (Cy-3), 23.1 (Cy-5), 22.6 (Cy-4) ppm.

ESI-MS (*m/z*): 407.1 (100) $[C_{20}H_{28}{}^{79}BrN_2O_2]^+$, 409.1 (98) $[C_{20}H_{28}{}^{81}BrN_2O_2]^+$.

ESI-HRMS: calcd for $[C_{20}H_{28}{}^{79}BrN_2O_2]^+$ 407.1334, found 407.1323.

E Reaction Procedures: Chapter 4

E1 Catalyst Screening

Screening of catalysts: general procedure

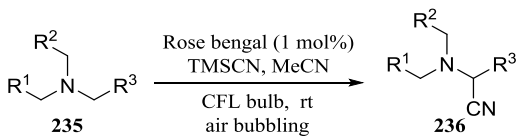
In a typical experiment, tributylamine **235a** (210 µmol, 1.0 eq.) and catalyst (1.0 mol%) were dissolved in CH_3CN (2 mL), followed by addition of TMSCN (2.0–4.0 eq.). For a specified time, the reaction was stirred and irradiated under air bubbling with a 24 W fluorescent household bulb at room temperature. The distance between the bulb and the reaction vessel (surface to surface) was approximately 8 cm. The solvent was removed under reduced pressure and a defined amount of CH_2Br_2 (NMR internal standard) was added. The mixture was dissolved in $CDCl_3$ and ^1H NMR was measured. The yield of the reaction was determined by integration of the internal standard and the product signals.

Rose bengal: studies on the catalyst loading

Rose bengal stock soluitons: In a 25 mL volumetric flask, a solution of 11.611 mg of rose bengal in CH_3CN was prepared, generating a general stock solution of 456.4 µM. Three further stock solutions of 220 µM, 7.0 µM and 224 nM were obtained by dilution of the former solution. For the loading experiments, tri-n-butylamine (1a, 210 µmol, 1.0 eq.) and different amounts of catalyst (0.1, 0.01, 0.001, 0.0001 mol% and 0.00001 mol% using the above mentioned stock solutions) were brought to a final volume of 2 mL of CH_3CN, followed by addition of TMSCN (4.0 eq.). The mixtures were stirred and irradiated under air bubbling with a 24 W fluorescent household bulb (ca. 8 cm distance to reaction vessel) at room temperature for 3 h. The solvent was removed under reduced pressure and a defined amount of CH_2Br_2 (NMR internal standard) was added. The mixture was dissolved in $CDCl_3$ and 1H NMR was measured, the yield of the reaction was determined by integration of the internal standard and the product signals.

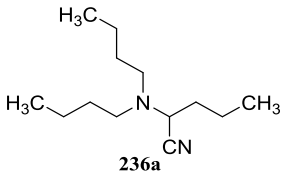
E2 Synthesis of α-Aminonitriles 236a–m

General Procedure IX: Photocyanation of Tertiary Aliphatic Amines 235



A solution of trialkylamine **235a–o** (1.0 eq.), rose bengal (1.0 mol%) and TMSCN (4.0 eq.) in CH_3CN (8 mL/mmol) was irradiated under air bubbling with a 24 W fluorescent household bulb at room temperature. Upon completion (monitored by TLC), a concentrated aqueous solution of K_2CO_3 was added and allowed to stir for an additional 10 minutes. The reaction mixture was extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was passed through a plug of aluminum oxide (basic) using CH_2Cl_2 as the eluent. In most cases, the product was used without further purification. In some cases, an additional purification step (flash chromatography) was required.

2-(Dibutylamino)pentanenitrile (236a)



236a

According to the general procedure, tributylamine **235a** (238 µL, 1.00 mmol), rose bengal (10.2 mg, 10.0 µmol) and TMSCN (502 µL, 4.00 mmol) were dissolved in CH_3CN (8 mL). The reaction mixture was stirred under air bubbling and irradiation for approximately 3 h (until TLC showed full conversion). Purification through a plug of aluminum oxide (basic) afforded the title compound (187.4 mg, 890.8 µmol, 89%) as a light yellow oil.

$\boldsymbol{R_f}$ = 0.85 (CH_2Cl_2/MeOH, 10:1) or $\boldsymbol{R_f}$ = 0.51 (cyclohexane/EtOAc, 6:1).

IR (ATR**)** υ = 2958, 2932, 2873, 2821, 2222, 1466, 1379, 1171, 1089 cm^{-1}.

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 3.58 (t, *J* = 7.7 Hz, 1H, H-2 (NC**H**CN)), 2.56 (ddd, *J* = 13.0, 8.4, 7.3 Hz, 2H, H-1'a), 2.33 (ddd, *J* = 13.0, 7.8, 4.9 Hz, 2H, H-1'b), 1.78–1.62 (m, 2H, H-3), 1.55–1.18 (m, 10H, H-4, H-2', H-3'), 0.94 (t, *J* = 7.3 Hz, 3H, H-5), 0.91 (t, *J* = 7.1 Hz, 6H, H-4') ppm.

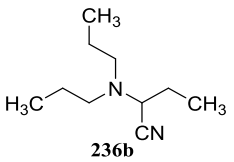
^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 118.7 (**C**N), 54.4 (C-2), 51.6 (C-1'), 34.1 (C-3), 30.3 (C-2'), 20.5 (C-3'), 19.4 (C-4), 14.1 (C-4'), 13.6 (C-5) ppm.

ESI-MS (*m/z*): 211.1 (100) $[M+H]^+$

ESI-HRMS (*m/z*): calcd for $[C_{13}H_{26}N_2Na]^+$ 233.1994, found 233.2003.

The spectroscopic data are in accordance with those reported in the literature.[32,36]

2-(Dipropylamino)butanenitrile (236b)



236b

According to the general procedure, tripropylamine **235b** (191 µL, 1.00 mmol), rose bengal (10.2 mg, 10.0 µmol) and TMSCN (502 µL, 4.00 mmol) were dissolved in CH_3CN (8 mL). The reaction mixture was stirred under air bubbling and visible light irradiation for approximately 3 h (until TLC showed full conversion). Purification through a plug of aluminum oxide (basic) afforded the title compound (125.3 mg, 744.6 µmol, 74%) as a light yellow oil. The reaction was also performed in gram scale using tripropylamine **235b** (1.91 mL, 10.0 mmol), rose bengal (101.8 mg, 100.0 µmol) and TMSCN (5.00 mL, 40.0 mmol) in CH_3CN (80 mL). The mixture was irradiated and stirred under air bubbling overnight. At this scale, compound **236b** was obtained in 71% (1.20 g, 7.10 mmol) yield.

$\boldsymbol{R_f}$ = 0.89 (CH_2Cl_2/MeOH, 10:1) or $\boldsymbol{R_f}$ = 0.56 (cyclohexane/EtOAc, 6:1).

IR (ATR) υ = 2963, 2936, 2875, 2821, 2223, 1463, 1382, 1191, 1074 cm^{-1}.

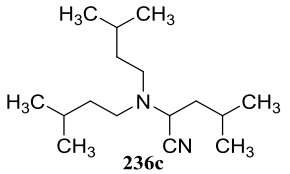
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 3.47 (t, *J* = 7.8 Hz, 1H, H-2 (NC**H**CN)), 2.50 (ddd, *J* = 13.0, 8.5, 7.6 Hz, 2H, H-1'a), 2.35 (ddd, *J* = 13.0, 8.2, 4.7 Hz, 2H, H-1'b), 1.85–1.67 (m, 2H, H-4), 1.56–1.35 (m, 4H, H-2'), 1.04 (t, *J* = 7.4 Hz, 3H, H-4), 0.89 (t, *J* = 7.3 Hz, 6H, H-3') ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 118.7 (**C**N), 56.4 (C-2), 53.8 (C-1'), 25.5 (C-3), 21.3 (C-2'), 11.8 (C-3'), 10.9 (C-4) ppm.

ESI-MS (*m/z*): 169.2 (100) $[M+H]^+$, 142.1 (6) $[M–CN]^+$; **ESI-HRMS** (*m/z*): calcd for $[C_9H_{20}N]^+$ 142.1596, found 142.1623.

The spectroscopic data are in accordance with those reported in the literature.[32,36]

2-(Diisopentylamino)-4-methylpentanenitrile (236c)



236c

According to the general procedure, triisopentylamine **235c** (292 µL, 1.00 mmol), rose bengal (10.2 mg, 10.0 µmol) and TMSCN (502 µL, 4.00 mmol) were dissolved in CH_3CN (8 mL). The reaction mixture was stirred under air bubbling and visible light irradiation for approximately 3.5 h (until TLC showed full conversion). Purification through a plug of aluminum oxide (basic) afforded the title compound (213.2 mg, 845.1 µmol, 84%) as a light yellow oil.

$\boldsymbol{R_f}$ = 0.81 (CH_2Cl_2/MeOH, 10:1) or $\boldsymbol{R_f}$ = 0.51 (cyclohexane/ EtOAc, 6:1).

IR (ATR) υ = 2956, 2930, 2870, 2826, 2222, 1468, 1368, 1170, 1095 cm^{-1}.

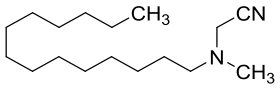
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 3.66 (t, *J* = 7.8 Hz, 1H, H-2 (NC**H**CN)), 2.61 (ddd, *J* = 13.0, 8.6, 7.8 Hz, 2H, H-1'a), 2.32 (ddd, *J* = 13.0, 7.6, 6.0 Hz, 2H, H-1'b), 1.82 (sept, *J* = 6.7 Hz, 1H, H-4), 1.67–1.53 (m, 4H, H-3, H-3'), 1.38–1.24 (m, 4H, H-2'), 0.93 (d, *J* = 6.7 Hz, 6H, H-5), 0.90 (d, *J* = 6.7 Hz, 6H, H-4'), 0.89 (d, *J* = 6.7 Hz, 6H, H-4') ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 118.8 (**C**N), 52.8 (C-2), 50.0 (C-1'), 40.8 (C-3), 37.2 (C-2'), 26.2 (C-3'), 24.8 (C-4), 23.2 (C-4'a), 22.5 (C-4'b), 22.4 (C-5), 22.2 (C-4'b) ppm.

ESI-MS (*m/z*): 253.2 (100) $[M+H]^+$; **ESI-HRMS** (*m/z*): calcd for $[C_{16}H_{33}N_2]^+$ 253.2644, found 253.2653.

The spectroscopic data are in accordance with those reported in the literature.[32,36]

2-(Methyl(tetradecyl)amino)acetonitrile (236d)



236d

According to the general procedure, *N*,*N*-dimethyltetradecylamine **235d** (241 µL, 1.00 mmol), rose bengal (10.2 mg, 10.0 µmol) and TMSCN (502 µL, 4.00 mmol) were dissolved in CH_3CN (8 mL). The reaction mixture was stirred under air bubbling and visible light irradiation for 18 h (until TLC showed full conversion). Purification was achieved first by filtration through a plug of aluminum oxide (basic) and then by flash chromatography on silica gel (*n*-pentane/Et_2O, 2:1) to afford the title compound (212.3 mg, 796.7 µmol, 80%) as a colorless oil.

$\boldsymbol{R_f}$ = 0.88 (CH_2Cl_2/MeOH, 10:1) or $\boldsymbol{R_f}$ = 0.30 (*n*-pentane/Et_2O, 2:1).

IR (ATR) υ = 2922, 2853, 2807, 1466, 1378, 1320, 1039, 861, 722 cm^{-1}.

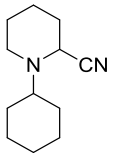
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 3.53 (s, 2H, NC**H$_2$**CN), 2.43 (t, *J* = 7.4 Hz, 2H, H-1), 2.35 (s, 3H, NC**H$_3$**), 1.44 (quint, *J* = 7.4 Hz, 2H, H-2), 1.34–1.20 (m, 22H, H-3 to H-13), 0.87 (t, *J* = 6.8 Hz, 3H, H-14) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 114.8 (**C**N), 56.0 (C-1), 45.2 (N**C**H_2CN), 42.2 (N**C**H_3), 32.1 (C-12), 29.82, 29.81, 29.79, 29.73, 29.70, 29.6, 29.5, 27.24 (C-3 to C11), 27.6 (C-2), 22.8 (C-13), 14.3 (C-14) ppm.

ESI-MS (*m/z*): 267.2 (100) $[M+H]^+$; **ESI-HRMS** (*m/z*): calcd for $[C_{17}H_{35}N_2]^+$ 267.2800, found 267.2799.

The spectroscopic data are in accordance with those reported in the literature.[32,36]

1-Cyclohexylpiperidine-2-carbonitrile (236e)



236e

According to the general procedure, 1-cyclohexylpiperidine **235e** (184 μL, 1.00 mmol), rose bengal (10.2 mg, 10.0 μmol) and TMSCN (502 μL, 4.00 mmol) were dissolved in CH_3CN (8 mL). The reaction mixture was stirred under air bubbling and visible light irradiation for approximately 3 h (until TLC showed full conversion). Purification was achieved first by filtration through a plug of aluminum oxide (basic) and then by flash chromatography on silica gel (*n*-pentane/Et_2O, 5:1) to afford the title compound (143.3 mg, 745.1 μmol, 74%) as a colorless oil.

$\boldsymbol{R_f}$ = 0.87 (CH_2Cl_2/MeOH, 10:1) or $\boldsymbol{R_f}$ = 0.54 (*n*-pentane/Et_2O, 5:1).

IR (ATR) υ = 2930, 2855, 2806, 2221, 1452, 1260, 1131, 972, 861, 849 cm^{-1}.

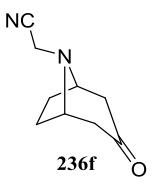
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 4.04 (t, *J* = 3.9 Hz, 1H, H-2 (NC**H**CN)), 2.94 (dt, *J* = 12.0, 3.4 Hz, 1H, H-6a), 2.40 (td, *J* = 12.0, 2.6 Hz, 1H, H-6b), 2.32 (tt, *J* = 10.4, 3.6 Hz, 1H, H-1'), 2.04–1.34 (m, 11H, H-3, H-4, H-5, H-2'a, H-3'a, H-4'a, H-5'a, H-6'a), 1.34–0.97 (m, 5H, H-2'b, H-3'b, H-4'b, H-5'b, H-6'b) ppm.

^{13}C NMR, HMBC, HSQC, H2BC (100.6 MHz, $CDCl_3$) δ = 118.6 (**C**N), 62.2 (C-1'), 49.9 (C-2), 45.9 (C-6), 30.4 (C-6'), 29.9 (C-2'), 29.8 (C-3), 26.1 (C-4'), 25.6 (C-3'), 25.5 (C-5), 25.4 (C-5'), 21.1 (C-4) ppm.

ESI-MS (*m/z*): 193.1 (100) $[M+H]^+$; **ESI-HRMS** (*m/z*): calcd for $[C_{12}H_{21}N_2]^+$ 193.1705, found 193.1705.

The spectroscopic data are in accordance with those reported in the literature.[193]

2-(3-Oxo-8-azabicyclo[3.2.1]octan-8-yl)acetonitrile (236f)



236f

According to the general procedure, tropinone **235f** (139.2 mg, 1.00 mmol), rose bengal (10.2 mg, 10.0 μmol) and TMSCN (502 μL, 4.00 mmol) were dissolved in CH_3CN (8 mL). The reaction mixture was stirred under air bubbling and visible light irradiation for 24 h (until TLC showed full conversion). Purification was achieved first by filtration through a plug of aluminum oxide (basic) and then by flash

chromatography on silica gel (cyclohexane/ EtOAc, 3:2) to afford the title compound (100.0 mg, 608.9 μmol, 61%) as a light beige solid.

mp: 64.4–64.8 °C, lit.:[32] 64.5–65.0 °C.

R_f = 0.68 (CH_2Cl_2/MeOH, 10:1) or R_f = 0.22 (cyclohexane/ EtOAc, 3:2).

IR (ATR) υ = 2941, 2895, 2246, 1703, 1450, 1350, 1156, 922, 799 cm^{-1}.

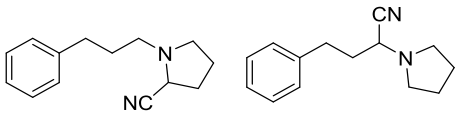
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 3.65–3.60 (m, 2H, H-1', H-5'), 3.52 (s, 2H, NC**H_2**CN), 2.68 (dd, *J* = 16.4, 4.4 Hz, 2H, H-2'a, H-4'a), 2.32–2.25 (m, 2H, H-2'b, H-4'b), 2.19–2.09 (m, 2H, H-6'a, H-7'a), 1.75–1.67 (m, 2H, H-6'b, H-7'b) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 208.1 (**C**O), 117.3 (**C**N), 59.8 (C-1', C-5'), 48.9 (C-2', C-4'), 40.3 (N**C**H_2CN), 27.6 (C-6', C-7') ppm.

ESI-MS (*m/z*): 165.0 (100) $[M+H]^+$; **ESI-HRMS** (*m/z*): calcd for $[C_9H_{13}N_2O]^+$ 165.1028, found 165.1023.

The spectroscopic data are in accordance with those reported in the literature.[32,177]

1-(3-Phenylpropyl)pyrrolidine-2-carbonitrile (236g) and its regioisomer (236g')



Endo **236g** 91 : *Exo* **236g'** 9

According to the general procedure, 1-(3-phenylpropyl)pyrrolidine **235g** (189.2 mg, 1.00 mmol), rose bengal (10.2 mg, 10.0 μmol) and TMSCN (502 μL, 4.00 mmol) were dissolved in CH_3CN (8 mL). The reaction mixture was stirred under air bubbling and visible light irradiation for 3 h (until TLC showed full conversion). Purification was achieved first by filtration through a plug of aluminum oxide (basic) and then by flash chromatography on silica gel (cyclohexane/ EtOAc, 6:1). The title compound was afforded as a colorless oil (145.5 mg, 678.9 μmol, 68%) corresponding to an isomeric mixture of the endo and exocyclic α-aminonitriles (**236g** and **236g'**) in 91:9 ratio (calculated by ^{1}H NMR) respectively.

R_f = 0.68 (CH_2Cl_2/MeOH, 10:1) or R_f = 0.65 (cyclohexane/ EtOAc, 6:1).

IR (ATR) υ = 3026, 2942, 2812, 2221, 1603, 1496, 1387, 1123, 748, 700 cm^{-1}.

Endocyclic isomer 236g:

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.32–7.27 (m, 2H, Ph-3, Ph-5), 7.24–7.15 (m, 3H, Ph-2, Ph-4, Ph-6), 3.77 (dd, *J* = 7.3, 2.9 Hz, 1H, H-2 (NC**H**CN)), 2.90 (td, *J* = 8.9, 4.7 Hz, 1H, H-5a), 2.78–2.73 (m, 1H, H-1'a), 2.68 (pseudo-t, *J* = 7.7 Hz, 2H, H-3'), 2.65–2.49 (m, 2H, H-1'b, H-5b), 2.24–2.06 (m, 2H, H-3), 2.01–1.87 (m, 2H, H-4), 1.85 (quint, *J* = 7.7 Hz, 2H, H-2') ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 141.9 (Ph-1), 128.5 (Ph-3, Ph-5), 128.4 (Ph-2, Ph-6), 126.0 (Ph-4), 118.3 (**C**N), 53.9 (C-2), 52.1 (C-1'), 51.3 (C-5) , 33.5 (C-3'), 30.2 (C-2'), 29.9 (C-3), 22.1 (C-4) ppm.

Exocyclic isomer 236g':

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.32–7.27 (m, 2H, Ph-3, Ph-5), 7.24–7.15 (m, 3H, Ph-2, Ph-4, Ph-6), 3.69 (t, *J* = 7.9 Hz, 1H, H-1' (NC**H**CN)), 2.85–2.77 (m, 2H, H-3'), 2.78–2.60 (m, 2H, H-2), 2.68–2.56 (m, 2H, H-5), 2.24–2.06 (m, 4H, H-3, H-2'), 2.01–1.87 (m, 2H, H-3') ppm.

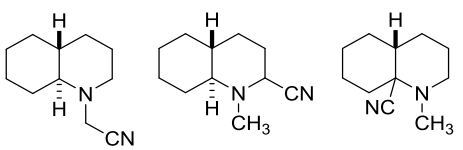
^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 140.0 (Ph-1), 128.7 (Ph-3, Ph-5), 128.6 (Ph-2, Ph-6), 126.5 (P-4h), 118.3 (**C**N), 54.4 (C-1'), 51.2 (C-5), 50.1 (C-2) , 34.2 (C-2'), 32.0 (C-3'), 23.5 (C-3), 22.1 (C-4) ppm.

ESI-MS (*m/z*): 188.0 (100) $[M–CN]^+$, 215.0 (52) $[M+H]^+$; **ESI-HRMS** (*m/z*): calcd for $[C_{14}H_{19}N_2]^+$ 215.1548, found 215.1539.

The spectroscopic data are in accordance with those reported in the literature.[41]

2-(Octahydroquinolin-1(2H)-yl)acetonitrile (236h) and its regioisomers (236h') and (236h'')

According to the general procedure, *N*-methyldecahydroquinoline **235h** (153.0 mg, 1.00 mmol), rose bengal (10.2 mg, 10.0 μmol) and TMSCN (502 μL, 4.00 mmol) were dissolved in CH_3CN (8 mL). The reaction mixture was stirred under air bubbling and visible light irradiation for 4 h (until TLC showed full conversion). Purification was achieved first by filtration through a plug of aluminum oxide (basic) and then by flash chromatography on silica gel (cyclohexane/ EtOAc, 3:2). The title compound was afforded as a



236h : **236h'** : **236h''**

67 : 24 : 9

colorless oil (146.2 mg, 820.0 μmol, 82%) corresponding to an isomeric mixture of the exocyclic isomer **236h** and its endocyclic isomers **236h'** and **236h''** in 67:24:9 ratio (calculated by ^{1}H NMR) respectively.

R_f = 0.82 (CH_2Cl_2/MeOH, 10:1) or R_f = 0.37 (cyclohexane/ EtOAc, 3:2).

IR (ATR) υ = 2925, 2856, 2802, 1447, 1242, 1167, 1141, 902, 815 cm^{-1}.

Exocyclic isomer 236h (major):

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 3.90 (d, J = 17.5 Hz, 1H, NC**H$_a$**CN), 3.35 (d, J = 17.5 Hz, 1H, NC**H$_b$**CN), 2.81–2.70 (m, 1H, H-2a), 2.56–2.42 (m, 1H, H-2b), 2.07–0.87 (m, 14H, H-3, H-4, 4a-H, H-5, H-6, H-7, H-8, 8a-H) ppm.

^{13}C NMR, DEPT-135, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 114.6 (**C**N), 64.5 (C-8a), 54.7 (C-2), 42.4 (N**C**H$_2$CN), 41.9 (C-4a), 31.9 (C-4), 25.6 (C-3), 32.7, 29.9, 25.9, 25.6 (C-5, C-6, C-7, C-8) ppm.

Endocyclic isomer 236h':

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 3.84 (t, J = 3.7 Hz, 1H, Ha (NC**H$_2$**CN)), 2.34 (s, 3H, NC**H$_3$**), (m, 14H, H-3, H-4, 4a-H, H-5, H-6, H-7, H-8, 8a-H) ppm.

^{13}C NMR, DEPT-135, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 117.2 (**C**N), 63.7 (C-8a), 56.7 (C-2), 41.6 (C-4a), 40.5 (N**C**H$_3$), 32.3, 30.1, 28.8, 28.3, 25.8, 25.6 (C-3, C-4, C-5, C-6, C-7, C-8) ppm.

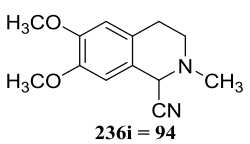
Endocyclic isomer 236h'' (minor):

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 2.81–2.70 (m, 1H, H-2a), 2.56–2.42 (m, 1H, H-2b), 2.26 (dt, J = 13.0, 3.3 Hz, 1H, H-8), 2.34 (s, 3H, NC**H$_3$**), (m, 12H, H-3, H-4, 4a-H, H-5, H-6, H-7, H-8) ppm.

^{13}C NMR, DEPT-135, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 117.4 (**C**N), 66.8 (C-8a), 53.5 (C-2), 44.4 (C-4a), 39.3 (N**C**H$_3$) , 32.4 (C-8), 30.2, 29.0, 25.4, 25.2, 23.5 (C-3, C-4, C-5, C-6, C-7) ppm.

ESI-MS (*m/z*): 179.0 (100) $[M+H]^+$; **ESI-HRMS** (*m/z*): calcd for $[C_{11}H_{19}N_2]^+$ 179.1548, found 179.1550.

1-Cyano-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (236i)



236i = 94

According to the general procedure, 6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline **235i** (207.3 mg, 1.00 mmol), rose bengal (10.2 mg, 10 μmol) and TMSCN (502 μL, 4.00 mmol) were dissolved in CH_3CN (8 mL). The reaction mixture was stirred under air bubbling and visible light irradiation for 3 h (until TLC showed full conversion). Purification through a plug of aluminum oxide (basic) afforded the title compound (185.8 mg, 799.9 μmol, 80%) as a light yellow solid.

mp: 126.0–126.4 °C, Lit.:[292] 126–128 °C.

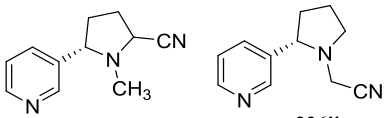
$\boldsymbol{R_f}$ = 0.84 (CH_2Cl_2/MeOH/Et_3N, 10:1:0.1) or $\boldsymbol{R_f}$ = 0.22 (cyclohexane/ EtOAc /Et_3N, 3:2:0.1).

IR (ATR) υ = 2937, 2804, 1702, 1612, 1518, 1256, 1226, 1139, 1011, 833, 771 cm^{-1}.

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 6.65 (s, 1H, H-8), 6.61 (s, 1H, H-5), 4.64 (s, 1H, H-1 (NC**H**CN)), 3.86, 3.85 (2s, 6H, OC**H$_3$**), 3.02–2.92 (m, 1H, H-4a), 2.91–2.84 (m, 1H, H-3a), 2.80–2.71 (m, 1H, H-3b), 2.70 (ddd, *J* = 15.6, 4.2, 1.8 Hz, 1H, H-4b), 2.59 (s, 3H, NC**H$_3$**) ppm.

The spectroscopic data are in accordance with those reported in the literature and with those obtained for compound **94**.[265,292]

5'-Cyanonicotine (236j) and regioisomer (236j')



236j **236j'**

diast. mix.

55:39 : 6

According to the general procedure, (–)-nicotine **235j** (162.2 mg, 1.00 mmol), rose bengal (10.2 mg, 10.0 μmol) and TMSCN (502 μL, 4.00 mmol) were dissolved in CH_3CN (8 mL). The reaction mixture was stirred under air bubbling and visible light irradiation for 3 h (until TLC showed full conversion). Purification was achieved first by filtration through a plug of aluminum oxide (basic) and then by flash chromatography on silica gel (EtOAc, 100%). The title compound was obtained as a light yellow oil (166.3 mg, 888.8 μmol, 89%) corresponding to the mixture of endocyclic diasteromers **236j** and the exocyclic regioisomer **236j'** in 55:39:6 ratio (calculated by ^{1}H NMR).

$\boldsymbol{R_f}$ = 0.80 (CH_2Cl_2/MeOH, 10:1) or $\boldsymbol{R_f}$ = 0.35 (EtOAc, 100%).

IR (ATR) υ = 2952, 2796, 2243, 2224, 1578, 1430, 1047, 1026, 809, 716 cm^{-1}.

Major endocyclic diastereomer 236j:

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 8.52 (d, J = 1.8 Hz, 1H, Py-2), 8.54 (dd, J = 8.6, 2.0 Hz, 1H, Py-6), 7.64 (dt, J = 7.8, 2.0 Hz, 1H, Py-4) 7.32–7.25 (m, 1H, Py-5), 4.14 (d, J = 7.8 Hz, 1H, H-2 (NC**H**CN)), 3.57 (d, J = 8.0 Hz, 1H, H-5), 2.52–2.08 (m, 3H, H-3, H-4a), 2.29 (s, 3H, N**C**H_3), 1.93–1.69 (m, 1H, H-4b) ppm.

^{13}C NMR, DEPT-135, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 149.3 (Py-2), 149.2 (Py-6), 135.0 (Py-4), 137.5 (Py-3), 123.8 (Py-5), 117.5 (**C**N), 65.2 (C-5), 56.8 (C-2), 36.6 (N**C**H_3), 33.2 (C-4), 28.5 (C-3) ppm.

Minor endocyclic diastereomer 236j:

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 8.52 (d, J = 1.8 Hz, 1H, Py-2), 8.54 (dd, J = 8.6, 2.0 Hz, 1H, Py-6), 7.73 (dt, J = 7.8, 2.0 Hz, 1H, Py-4) 7.32–7.25 (m, 1H, Py-5), 3.37 (t, J = 7.9 Hz, 1H, H-5), 3.36 (d, J = 7.7 Hz, 1H, H-2 (NC**H**CN)), 2.52–2.08 (m, 3H, H-3, H-4a), 2.31 (s, 3H, N**C**H_3), 1.93–1.69 (m, 1H, H-4b) ppm.

^{13}C NMR, DEPT-135, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 149.4 (Py-2), 149.3 (Py-6), 134.5 (Py-4), 137.0 (Py-3), 123.9 (Py-5), 120.2 (**C**N), 68.1 (C-5), 55.9 (C-2), 38.9 (N**C**H_3), 34.2 (C-4), 28.7 (C-3) ppm.

Exocyclic isomer 236j':

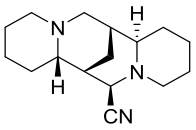
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 8.60–8.44 (m, 2H, Py-2, Py-6), 7.76–7.58 (m, 1H, Py-4) 7.32–7.25 (m, 1H, Py-5), 3.62–3.60 (m, 1H, H-5), 3.59 (d, J = 17.3 Hz, 1H, NC**H$_a$**CN), 3.31 (d, J = 17.3 Hz, 1H, NC**H$_b$**CN), 3.21 (td, J = 8.4, 3.0 Hz, 1H, H-2a), 2.75 (q, J = 8.8 Hz, H-2b), 2.05–2.08 (m, 2H, H-4), 2.08–1.91 (m, 2H, H-3) ppm.

^{13}C NMR, DEPT-135, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 149.4 (Py-2), 149.3 (Py-6), 135.2 (Py-4), 136.9 (Py-3), 123.8 (Py-5), 114.8 (**C**N), 64.4 (C-5), 52.7 (C-2), 39.9 (N**C**H_2CN), 35.1 (C-4), 22.6 (C-3) ppm.

ESI-MS (*m/z*): 188.0 (100) $[M+H]^+$; **ESI-HRMS** (*m/z*): calcd for $[C_{11}H_{14}N_3]^+$ 188.1188, found 188.1192.

The spectroscopic data are in accordance with those reported in the literature.[182,293,294]

(+)-17β-Cyanosparteine (236k)



236k

According to the general procedure, (+)-sparteine **235k** (234.4 mg, 1.00 mmol), rose bengal (10.2 mg, 10 μmol) and TMSCN (502 μL, 4.00 mmol) were dissolved in CH_3CN (8 mL). The reaction mixture was stirred under air bubbling and visible light irradiation for 3 h. Purification by flash chromatography on basic aluminum oxide (cyclohexane/EtOAc, 6:1) afforded the title compound (134.0 mg, 516.6 μmol, 52%) as a light yellow oil.

$[\boldsymbol{a}]_{\boldsymbol{D}}^{\boldsymbol{26}}$ = +39° (c = 1.0, $CHCl_3$), lit. for **(–)-17β-Cyanosparteine**:[172] $[a]_D^{20}$ = –33° (c = 1.0, $CHCl_3$).

$\boldsymbol{R_f}$ = 0.59 (cyclohexane/EtOAc, 6:1 on basic aluminum oxide TLC plates).

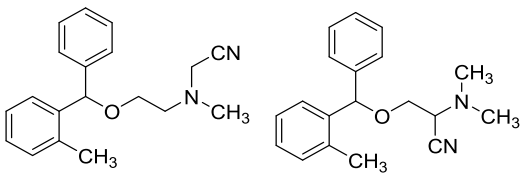
IR (ATR) υ = 2926, 2855, 2801, 2763, 2237, 1464, 1443, 1144 cm^{-1}.

^{1}H NMR, COSY, NOESY (600 MHz, $CDCl_3$) δ = 3.37 (d, *J* = 3.5 Hz, 1H, H-17 (NC**H**CN)), 3.36 (dt, *J* = 11.1, 3.3 Hz, 1H, H-15a), 2.66 (ddt, *J* = 11.6, 4.0, 1.9 Hz, 1H, H-2a), 2.46 (dt, *J* = 11.2, 2.4 Hz, 1H, H-10a), 2.21–2.13 (m, 2H, H-7, H-8a), 2.04–1.98 (m, 3H, H-10b, H-11, H-15b), 1.96 (td, *J* = 11.6, 2.9 Hz, 1H, H-2b), 1.84 (dt, *J* = 11.6, 2.4 Hz, 1H, H-6), 1.78–1.17 (m, 13H, H-3, H-4, H-5, H-9, H-12, H-13, H-14), 1.13 (dt, *J* = 11.9, 2.4 Hz, 1H, H-8b) ppm.

^{13}C NMR, HMBC, HSQC, H2BC (150.9 MHz, $CDCl_3$) δ = 122.1 (**C**N), 64.9 (C-6), 64.0 (C-11), 61.4 (C-10), 55.8 (C-2), 54.1 (C-15), 53.2 (C-17), 40.4 (C-7), 35.6 (C-9), 34.8 (C-12), 29.2 (C-5), 26.1 (C-8), 25.9, 25.7, 24.9, 24.4 (C-3, C-4, C-13, C-14) ppm.

ESI-MS (*m/z*): 260.2 (100) $[M–CN]^+$; **ESI-HRMS** (*m/z*): calcd for $[C_{16}H_{26}N_3]^+$ 260. 2127, found 260.2123.

2-(Methyl(2-(phenyl(2-methylphenyl)methoxy)ethyl)amino)acetonitrile (2l) and its regioisomer (2l')



236l : **236l'**

78 : 11:11

diast. mix.

Orphenadrine hydrochloride **235l** (305.9 mg, 1.00 mmol) was dissolved in water (4 mL) and the resulting solution was basified to pH = 14 with a 2 M NaOH solution. After 30 min of stirring, the oil-water dispersion was extracted with CH_2Cl_2 (3 x 10 mL), the combine organic layers were dried

over Na_2SO_4 and the solvent eliminated under reduce pressure. Cyanation of the remaining oil was performed according to the general procedure using rose bengal (10.2 mg, 10.0 μmol) and TMSCN (502 μL, 4.00 mmol) in CH_3CN (8 mL). The reaction mixture was stirred under air bubbling and visible light irradiation for approximately 24 h (until TLC showed full conversion). Purification was achieved first by filtration through a plug of aluminum oxide (basic) and then by flash chromatography on silica gel (cyclohexane/EtOAc, 3:1). The title compound was afforded as a colorless oil (200.0 mg, 742.0 μmol, 74%) corresponding to a mixture of regioisomers **236l** and **236l'** in a 78:22 ratio (calculated by ^{1}H NMR). The reaction was also performed in gram scale starting from orphenadrine hydrochloride **235l** (2.00 g, 6.54 mmol), rose bengal (66.0 mg, 65.0 μmol) and TMSCN (3.30 mL, 26.2 mmol) in 52 mL CH_3CN. The reaction mixture was irradiated and stirred under air bubbling for 2 d. At this scale it was possible to obtain compound **236l** and **236l'** in 52% (1.00 g, 3.40 mmol) yield.

$\boldsymbol{R_f}$ = 0.90 (CH_2Cl_2/MeOH, 10:1) or $\boldsymbol{R_f}$ = 0.13 (cyclohexane/EtOAc, 6:1).

IR (ATR) υ = 3027, 2984, 2868, 2794, 2237, 1677, 1452, 1075, 756, 700 cm^{-1}.

Major Isomer (236l):

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.46 (dd, J = 7.5, 1.7 Hz, 1H, Ph-6), 7.36–7.26 (m, 5H, Ph-2',Ph-3', Ph-4', Ph-5', Ph-6'), 7.30–7.09 (m, 3H, Ph-3, Ph-4, Ph-5), 5.52 (s, 1H, OC**H**Ph), 3.63 (s, 1H, NC**H$_2$**CN), 3.61–3.57 (m, 2H, H-2), 2.76 (t, J = 5.2 Hz, 2H, H-1), 2.41 (s, 3H, NC**H$_3$**), 2.26 (s, 3H, Ph-2) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 140.9 (Ph-1'), 139.6 (Ph-1), 135.9 (Ph-2), 130.7 (Ph-3), 128.5 (Ph-3', Ph-5'), 127.7, 127.6 (Ph-4, Ph-2', Ph-4', Ph-6'), 127.0 (Ph-6), 126.2 (Ph-5), 115.0 (**C**N), 81.5 (O**C**HPh), 67.4 (C-2), 55.4 (C-1), 45.8 (N**C**H$_2$CN), 43.1 (NCH$_3$**)**, 19.6 (CH_3–Ph-2) ppm.

Minor isomer (236l', diasteromeric mixture 1:1):

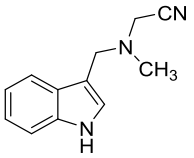
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.45–7.42 (m, 1H, Ph-6), 7.36–7.26 (m, 5H, Ph-2',Ph-3', Ph-4', Ph-5', Ph-6'), 7.30–7.09 (m, 3H, Ph-3, Ph-4, Ph-5), 5.62, 5,60 (2s, 1H, OC**H**Ph), 3.85–3.79 (m, 1H, H-1 (NC**H**CN)), 3.77–3.63 (m, 2H, H-2), 2.33 (s, 6H, NC**H$_3$**), 2.27 (s, 3H, Ph-2) ppm.

^{13}C NMR, DEPT-135, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 140.2 (Ph-1'), 138.7 (Ph-1), 136.1 (Ph-2), 130.9 (Ph-3), 128.6 (Ph-3', Ph-5'), 128.0, 127.9 (Ph-4, Ph-2', Ph-4', Ph-6'), 127.2

(Ph-6), 126.3 (Ph-5), 115.0 (**C**N), 82.1 (O**C**HPh), 68.3 (C-2), 59.1 (C-1), 45.8 (N**C**H_2CN), 42.7 (N(**C**H_3)$_2$**)**, 19.6 (CH_3–Ph-2) ppm.

ESI-MS (*m/z*): 181.0 (100) [M-$C_{14}H_{13}$]$^+$, 317.1 (11) [M+Na]$^+$; **ESI-HRMS** (*m/z*): calcd for [$C_{16}H_{22}N_2Na$]$^+$ 317.1630, found 317.1621.

2-(((1H-Indol-3-yl)methyl)(methyl)amino)acetonitrile (236m)



236m

According to the general procedure, gramine **235m** (174.2 mg, 1.00 mmol), rose bengal (10.2 mg, 10 μmol), and TMSCN (502 μL, 4.00 mmol) were dissolved in CH_3CN (8 mL). The reaction mixture was stirred under air bubbling and visible light irradiation for 15 h (until TLC showed full conversion). Purification was achieved first by filtration through a plug of aluminum oxide (basic) and then by flash chromatography on silica gel (CH_2Cl_2/MeOH, 20:1) to afford the title compound (40.4 mg, 202 μmol, 20%) as a light yellow oil.

$\boldsymbol{R_f}$ = 0.60 (CH_2Cl_2/MeOH, 10:1).

IR (ATR) υ = 3404, 2949, 2788, 2220, 1664, 1456, 1338, 1010, 842, 740 cm^{-1}.

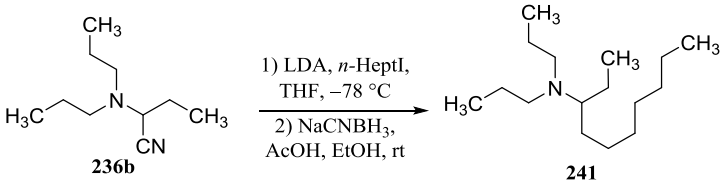
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 8.17 (s, 1H, N**H**), 7.74 (d, *J* = 8.0 Hz, 1H, H-4), 7.38 (dt, *J* = 8.0, 1.1 Hz, 1H, H-7), 7.23 (ddd, *J* = 8.0, 7.0, 0.9 Hz, 1H, H-6), 7.18 (d, *J* = 2.5 Hz, 1H, H-2), 7.15 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H, H-5), 3.81 (s, 2H, 1'), 3.46 (s, 2H, NC**H$_2$**CN), 2.50 (s, 3H, NC**H$_3$**) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 136.6 (C-7a), 127.3 (C-3a), 124.2 (C-2), 122.6 (C-6), 120.0 (C-5), 119.6 (C-4), 115.0 (**C**N), 111.9 (C-3), 111.3 (C-7), 51.3 (C-1'), 43.8 (N**C**H_2CN), 42.5 (N**C**H_3) ppm.

ESI-MS (*m/z*): 173.0 (100) [M-CN]$^+$; **ESI-HRMS** (*m/z*): calcd for [$C_{11}H_{13}N_2$]$^+$ 173.1079, found 173.1086.

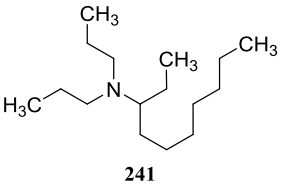
E3 Derivatization of α-Aminonitriles

General procedure X: One-Pot C-Alkylation/Reductive Decyanation of α-aminonitriles



The corresponding α-aminonitrile (1.0 eq.) was dissolved in dry THF (7 mL/mmol) under nitrogen atmosphere and the resulting solution was cooled to –78 °C. At this temperature LDA 2 M or 1.5 M (1.0 eq.) was added dropwise and the orange mixture was stirred for 10 minutes. The reaction was warmed up to –30 °C for 10 minutes and after this period was cooled again to –78 °C. A solution of 1-heptyl iodide (1.0 eq.) in dry THF (3.5 mL/mmol) was added dropwise to the reaction mixture. After the reaction had finished (according to TLC), the temperature was increased to 0 °C and then ethanol (1.7 mL/mmol), $NaCNBH_3$ (1.0–3.0 eq.) and acetic acid (339 μL/mmol) were added successively. The solution was allowed to warm to room temperature and stirred for the indicated time. The mixture was quenched with a concentrated $NaHCO_3$ solution followed by extraction (Et_2O or EtOAc, 3 x 20 mL). The organic phases were washed with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by filtration on a plug of aluminium oxide (basic) or by flash chromatography on silica gel.

N,*N*-dipropyldecan-3-amine (241)



Following the general procedure described above, compound **241** was synthesized from α-aminonitrile **236b** (100.0 mg, 594.2 μmol), LDA 2 M (295 μL, 594.2 μmol) and heptyl iodide (134 mg, 594.2 μmol). The reaction was stirred for 2 h at –78 °C and then warmed to 0 °C followed by addition of ethanol (1 mL), $NaCNBH_3$ (111.2 mg, 1.77 mmol) and acetic acid (200 μL). The mixture was allowed to reach room temperature and stirred overnight. Filtration over a pad of aluminium oxide (basic) using cyclohexane as eluent afforded the title compound (110.0 mg, 456 μmol, 77%) as a colorless oil.

$\boldsymbol{R_f}$ = 0.40 (cyclohexane/EtOAc, 20:1) or $\boldsymbol{R_f}$ = 0.66 (cyclohexane, 100% on basic aluminum oxide TLC plates).

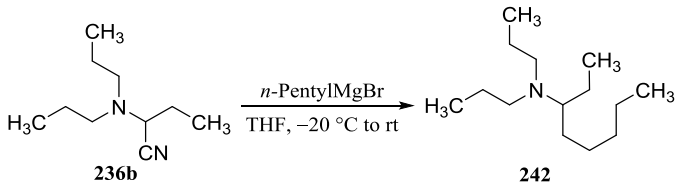
IR (ATR) υ = 2956, 2926, 2855, 1662, 1378, 1191, 999, 723 cm^{-1}.

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 2.30 (t, *J* = 7.3 Hz, 4H, H-1'), 2.36–2.19 (m, 1H, H-3), 1.46–1.13 (m, 18H, H-2, H-4, H-5, H-6, H-7, H-8, H-9, H-10, H-2'), 0.88 (t, *J* = 6.9 Hz, 6H, H-1, H-10), 0.85 (t, *J* = 7.4 Hz, 6H, H-3') ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 62.1 (C-3), 52.4 (C-1'), 32.1 (C-8), 30.3, 30.1, 29.6, 27.7 (C-4, C-5, C-6, C-7), 23.3 (C-2), 22.9 (C-9), 22.7 (C-2'), 14.3 (C-10), 12.4 (C-1), 12.1 (C-3') ppm.

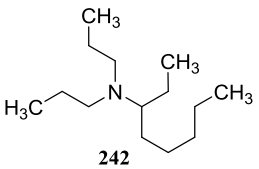
ESI-MS (*m/z*): 242.2 (100) $[M+H]^+$; **ESI-HRMS** (*m/z*): calcd for $[C_{16}H_{36}N]^+$ 242.2848, found 242.2847.

General procedure XI: Bruylants Reaction



In a typical procedure, the selected α-aminonitrile (1.0 eq.) was dissolved in dry THF and cooled to –20 °C. *n*-Pentylmagnesium bromide 2 M (2.1–2.5 eq.) was then added dropwise and the reaction mixture was allowed to stir for 2–3 h at the same temperature. After this period of time, the reaction was warmed to room temperature and stirred for additional 1–2 h. The reaction was quenched by addition of a saturated NH_4Cl, followed by extraction with Et_2O or EtOAc (4 x 20 mL). The combined organic phases were washed with $NaHCO_3$ solution, brine and dried over Na_2SO_4. The solvent was evaporated in vacuo and the crude product was purified by filtration on a plug of aluminium oxide (basic) or by flash chromatography on silica gel.

N,N-dipropyloctan-3-amine (242)



α-Aminonitrile **236b** (100.0 mg, 594.2 μmol) and *n*-pentylmagnesium bromide 2 M (297 μL, 594.2 μmol) were allowed to react as stated in the general procedure described above. The reaction was stirred for 2 h at –20 °C and then at room temperature for an additional hour. Filtration over a pad of aluminium oxide (basic) using cyclohexane as eluent afforded the title compound (80.3 mg, 376.3 μmol, 64%) as a colorless oil.

R_f = 0.55 (cyclohexane/EtOAc, 20:1).

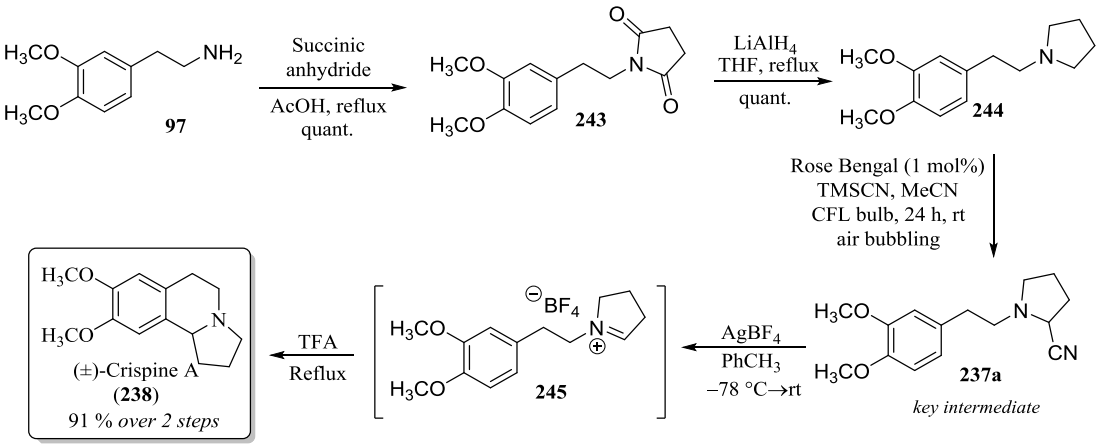
IR (ATR) υ = 2956, 2928, 2858, 1464, 1378, 1188, 1078, 1001 cm^{-1}.

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 2.31 (t, *J* = 7.2 Hz, 4H, H-1'), 2.36–2.22 (m, 1H, H-3), 1.53–1.07 (m, 14H, H-2, H-4, H-5, H-6, H-7, H-8, H-2'), 0.85 (t, *J* = 7.4 Hz, 6H, H-3'), 0.89 (t, *J* = 7.1 Hz, 3H, H-1), 0.88 (t, *J* = 7.4 Hz, 3H, H-8) ppm.

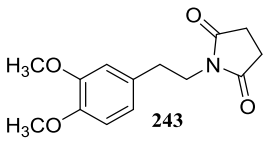
^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 62.2 (C-3), 52.4 (C-1'), 32.4 (C-6), 30.3, 27.4 (C-4, C-5), 23.3 (C-2), 22.9 (C-7), 22.7 (C-2), 14.3 (C-8), 12.4 (C-1), 12.1 (C-3') ppm.

ESI-MS (*m/z*): 214.2 (100) $[M+H]^+$; **ESI-HRMS** (*m/z*): calcd for $[C_{14}H_{32}N]^+$ 214.2535, found 214.2540.

E4 Total Synthesis of (±) Crispine A



***N*-[2-(3,4-Dimethoxyphenyl)ethyl]succinimide (243)**



The title compound was prepared by a modified procedure of Lete et al.[295] A solution of homoveratrylamine **97** (6.00 g, 33.1 mmol) and succinic anhydride (6.00 g, 59.6 mmol) in glacial acetic acid (70 mL) was refluxed for 24 h. After this period, the reaction was cooled and the acetic acid was evaporated under reduced pressure. The crude product was then recrystallized from MeOH yielding colorless crystals (6.86 g, 26.1 mmol). The residual product from the mother liquor was purified by flash chromatography (CH_2Cl_2/MeOH, 10:1) affording another crop of the product (1.70 g). In total, 8.60 g of product were obtained (quantitative yield).

mp: 128.5–129.7 °C, lit.:[295] 124–125 °C.

R_f = 0.73 (CH_2Cl_2/MeOH, 10:1).

IR (ATR) υ = 2942, 2834, 1772, 1509, 1397, 1234, 1154, 1024, 815 cm^{-1}.

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 6.79–6.71 (m, 3H, Ph-2, Ph-5, Ph-6), 3.86 3.83 (2s, 6H, OC**H$_3$**), 3.73–3.68 (m, 2H, H-1'), 2.89–2.72 (m, 2H, H-2'), 2.64 (s, 4H, H-2, H-3) ppm.

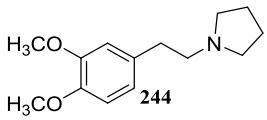
^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 177.1 (N**C**O, C-2, C-5), 148.9, 147.81 (Ph-3, Ph-4), 130.3 (Ph-1), 120.9 (Ph-6), 112.0 (Ph-2), 111.3 (Ph-5), 56.0(O**C**H$_3$), 55.9 (O**C**H$_3$), 40.1 (C-1'), 33.2 (C-2'), 28.2 (C-3, C-4) ppm.

ESI-MS (*m/z*): 264.1 (100) $[M+H]^+$

ESI-HRMS (*m/z*): calcd for $[C_{14}H_{17}NO_4Na]^+$ 286.1055, found 286.1054.

The spectroscopic data are in accordance with those reported in the literature.[295]

1-(3,4-Dimethoxyphenethyl)pyrrolidine (244)



Under nitrogen atmosphere, succinimide **243** (6.00 g, 22.8 mmol, 1.0 eq.) was dissolved in dry THF (100 mL) and $LiAlH_4$ (3.46 g, 91.2 mmol, 4.0 eq.) was added in small portions at –20 °C. When the addition was complete, the reaction was allowed to reach room temperature and then refluxed for 20 h. After completion, the reaction was cooled slowly; first to room temperature and then to –20 °C. At this point, water (3.6 mL) was carefully added dropwise followed by NaOH solution (15%, 6 mL) and water (1 mL). The mixture was diluted with diethyl ether (60 mL) and allowed to stir overnight at room temperature. The resulting suspension was treated with a saturated sodium tartrate solution (200 mL) and the biphasic mixture was extracted with diethyl ether (3 x 200 mL). The combined organic phases were washed with a saturated $NaHCO_3$ solution, brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford the crude product (5.30 g, 22.7 mmol, quantitative) as light yellow oil. The compound was used without further purification based on its ^{1}H NMR.

R_f = 0.34 (CH_2Cl_2/MeOH, 10:1).

IR (ATR) υ = 2982, 2834, 1690, 1512, 1397, 1195, 1233, 1019, 761 cm^{-1}.

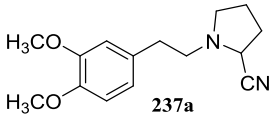
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 6.81–6.69 (m, 3H, Ph-2, Ph-5, Ph-6,), 3.85 (s, 3H, OC**H$_3$**), 3.83 (s, 3H, OC**H$_3$**), 2.81–2.72 (m, 2H, H-2'), 2.70–2.61 (m, 2H, H-1'), 2.59–2.51 (m, 4H, H-2, H-5), 1.84–1.70 (m, 4H, H-3, H-4) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 148.8, 147.3 (Ph-3, Ph-4), 133.2 (Ph-1), 120.5 (Ph-6), 112.0 (Ph-2), 111.2 (Ph-5), 58.6 (C-1'), 55.9 (O**C**H_3), 55.8 (O**C**H_3), 54.3 (C-2, C-5), 35.5 (C-2'), 23.5 (C-3, C-4) ppm.

ESI-MS (*m/z*): 236.1 (100) $[M+H]^+$

ESI-HRMS (*m/z*): calcd for $[C_{14}H_{22}NO_2]^+$ 236.1651, found 236.1641.

1-(3,4-Dimethoxyphenethyl)pyrrolidine-2-carbonitrile (237a)



237a

According to the general procedure for photocyanations, pyrrolidine **244** (2.00 g, 8.50 mmol), rose bengal (86.5 mg, 85.0 µmol) and TMSCN (4.26 mL, 33.9 mmol) were dissolved in CH_3CN (60 mL). The reaction mixture was stirred under air bubbling and visible light irradiation for 15 h (monitored by TLC). Purification through a plug of aluminum oxide (basic) afforded the title compound (1.72 g, 6.60 mmol, 78%) as a light yellow oil. It is worth to mention that the title compound was obtained as an isomeric mixture of the endo and exocyclic α-aminonitriles. However, determination of its isomeric ratio was not possible to achieve by ^{1}H NMR. Therefore, based on the results from compound **236g** (91:9 isomeric ratio) we assumed the same outcome for this reaction.

$\boldsymbol{R_f}$ = 0.87 (CH_2Cl_2/MeOH, 10:1) or $\boldsymbol{R_f}$ = 0.26 (cyclohexane/EtOAc, 1:1).

IR (ATR) υ = 2952, 2832, 1608, 1516, 1262, 1237, 1157, 1142, 1028 cm^{-1}.

Endocyclic isomer (237):

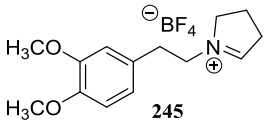
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 6.84–6.71 (m, 3H, Ph-2, Ph-5, Ph-6), 3.86, 3.83 (2s, 6H, OC**H$_3$**), 3.81 (dd, *J* = 7.3, 3.0 Hz, 1H, H-2 (NC**H**CN)), 3.03–2.90 (m, 2H, H-5a, H-1'a), 2.85–2.73 (m, 3H, H-1'b, H-2'), 2.60 (td, *J* = 9.0, 7.3 Hz, 1H, H-5'b), 2.23–2.07 (m, 2H, H-3), 2.04–1.82 (m, 2H, H-4) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 149.0, 147.6 (Ph-3, Ph-4), 132.2 (Ph-1), 120.6 (Ph-6), 118.2 (**C**N), 112.0 (Ph-2), 111.4 (Ph-5), 56.0 (O**C**H_3), 55.9 (O**C**H_3), 54.5 (C-1'), 53.9 (C-2), 51.5 (C-5), 34.9 (C-2'), 29.8 (C-3), 22.0 (C-4) ppm.

ESI-MS (*m/z*): 234.0 (100) $[M - CN]^+$, 261.1 (29) $[M+CN]^+$

ESI-HRMS (*m/z*): calcd for $[C_{15}H_{21}N_2O_2]^+$ 261.1603, found 261.1590.

1-(3,4-Dimethoxyphenethyl)-3,4-dihydro-2H-pyrrol-1-ium tetrafluoroborate (245)



245

To a solution of α-aminonitrile **237a** (200.0 mg, 768.0 µmol, 1.0 eq.) in dry THF (15 mL), $AgBF_4$ (299 mg, 1.54 mmol, 2.0 eq.) was added in one portion at –78 °C. The mixture was stirred for 15 min and then warmed to room temperature. The brown precipitate was decanted and washed with THF (2 x 10 mL) to eliminate the excess of $AgBF_4$. The residue was washed with acetone (3 x 10 mL), in order to separate the product from AgCN. After filtration, the acetone was removed under reduced pressure to afford the title compound (185.0 mg, 576.1 µmol, 75%) as brown paste.

$\boldsymbol{R_f}$ = 0.40 (CH_2Cl_2/MeOH, 10:1).

IR (ATR) υ = 2966, 2895, 2841, 1685, 1592, 1263, 1261, 1061, 1025 cm^{-1}.

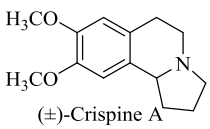
^{1}H NMR, COSY (400 MHz, $(CD_3)_2CO$) δ = 8.77 (s, 1H, H-2), 7.01 (d, *J* = 2.0 Hz, 1H, Ph-2), 6.90 (d, *J* = 8.2 Hz, 1H, Ph-5), 6.85 (dd, *J* = 8.2, 2.0 Hz, 1H, Ph-6), 4.42–4.29 (m, 4H, H-1', H-5), 3.79, 3.78 (2s, 6H, OCH_3), 3.28 (br. t, *J* = 7.3 Hz, 2H, H-3), 3.20 (t, *J* = 7.4 Hz, 2H, H-2'), 2.41 (quint, *J* = 8.0 Hz, 2H, H-4) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $(CD_3)_2CO$) δ = 182.5 (C-2), 150.7 (Ph-3), 149.6 (Ph-4), 129.8 (Ph-1), 121.8 (Ph-6), 113.5 (Ph-2), 113.0 (Ph-5), 60.0 (C-5), 56.1 (OCH_3), 56.0 (C-1'), 36.7 (C-3), 33.4 (C-2'), 20.5 (C-4) ppm.

ESI-MS (*m/z*): 234.0 (100) $[M+H]^+$

ESI-HRMS (*m/z*): calcd for $[C_{14}H_{20}NO_2]^+$ 234.1494, found 286.1493.

(±)-Crispine A



(±)-Crispine A
(**238**)

One Pot procedure: To a solution of α-aminonitrile **237a** (100.0 mg, 384.1 µmol, 1.0 eq.) in dry toluene (7.5 mL), $AgBF_4$ (149.6 mg, 768.5 µmol, 2.0 eq.) was added in one portion at –78 °C. The mixture was stirred for 10 min and then warmed to room temperature. TFA (329 µL, 4.20 mmol, 11.0 eq.) was added and the reaction was refluxed for 24 h. After cooling, the mixture was basified with 2 M NaOH solution and then extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent was evaporated under reduce pressure. The resulting crude product was purified through a plug of aluminum oxide (basic) (100% CH_2Cl_2 to CH_2Cl_2/MeOH 10:1) affording (±)-Crispine A (81.1 mg, 347.6 µmol, 91%) as a slightly brownish solid.

mp: 86.6–87.5 °C, lit.:[296] 86–88 °C.

R_f = 0.25 (CH_2Cl_2/MeOH, 10:1).

IR (ATR) υ = 2935, 2787, 1609, 1509, 1375, 1252, 1212, 1012, 854, 764 cm^{-1}.

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 6.60 (s, 1H, H-7), 6.56 (s, 1H, H-10), 3.84 (2s, 6H,OC**H$_3$**), 3.42 (t, *J* = 8.1 Hz, 1H, 10b-H), 3.17 (ddd, *J* = 11.2, 6.2, 2.9 Hz, 1H, H-5a), 3.07 (ddd, *J* = 9.3, 8.1, 3.9 Hz, 1H, H-3a), 3.05–2.96 (m, 1H, H-6a), 2.73 (dt, *J* = 16.2, 3.7 Hz, 1H, H-6b), 2.63 (ddd, *J* = 11.3, 10.2, 4.8 Hz, 1H, H-5b), 2.55 (td, *J* = 8.9, 7.6 Hz, 1H, H-3b), 2.32 (dddd, *J* = 11.8, 9.3, 6.9, 3.7 Hz, 1H, H-1a), 2.01–1.78 (m, 2H, H-2), 1.71 (dddd, *J* = 11.8, 10.6, 9.4, 7.1 Hz, 1H, H-1b) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 147.5, 147.3 (C-8, C-9), 131.1 (C-10a), 126.4 (C-6a), 111.5 (C-7), 109.0 (C-10), 63.1 (C-10b), 56.1 (O**C**H$_3$), 56.0 (O**C**H$_3$), 53.3 (C-3), 48.5 (C-5), 30.6 (C-1), 28.2 (C-6), 22.4 (C-2) ppm.

ESI-MS (*m/z*): 234.0 (100) $[M+H]^+$

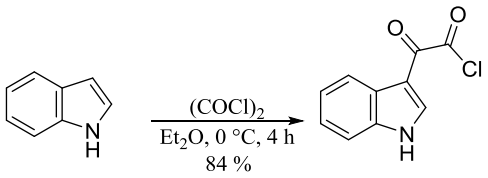
ESI-HRMS (*m/z*): calcd for $[C_{14}H_{20}NO_2]^+$ 234.1494, found 286.1493.

The spectroscopic data are in accordance with those reported in the literature.[296,297]

NOTE: Its was also possible to obtain (±)-crispine A from iminium ion **245** in a two-step procedure in 90% yield by using TFA and toluene under reflux.

E5 Synthesis of Tetrahydro-β-Carboline Alkaloids (±)-Harmicine (239) and (±)-Desbromoarborescidine A (240)

Synthesis of 2-(1H-Indol-3-yl)-2-oxoacetylchloride (247)



246 **247**

The title compound was prepared by a modified procedure of J. DENIS and co-workers.[298] Oxalylchloride (4.4 mL, 51.5 mmol) was added dropwise at 0°C to a solution of indol **246** (5.0 g, 42.7 mmol) in 85mL of dry diethylether. After 3h at 0°C, the reaction mixture was stirred for 1h at room temperature. The obtained solid was filtered under vacuum and washed with cold diethylether. The title compound was obtained as a yellow solid (35.9 mmol, 84 %) and was used in the next step without further purification.

mp: 130.0–133.6 °C (dec), Lit.:[299] 135 °C.

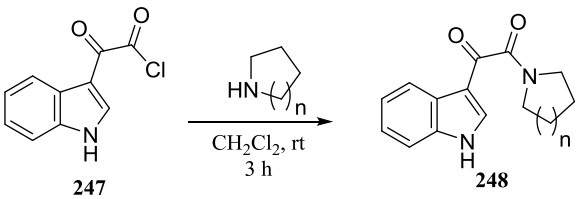
Rf: 0.56 (Cyclohexane/EtOAc = 3:2).

IR (ATR): $\tilde{\nu}$ = 3213, 3020, 1782, 1616, 1427, 981, 745, 724 cm^{-1}.

1H-NMR (300 MHz, $CDCl_3$) δ = 12.42 (s, 1H, N**H**), 8.41 (d, J = 3.2 Hz, H-2), 8.21–8.14 (m, 1H, H-4), 7.58–7.52 (m, 1H, H-7), 7.33–7.23 (m, 2H, H-5, H-6) ppm.

The spectroscopic data are in accordance with those reported in the literature. [300]

General Procedure XII: Synthesis of 3-Indolamide (248)



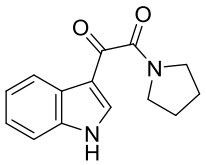
247 **248**

Compound **248b,c** were prepared according to a procedure of PÉREZ et al.[301] Oxoacetylchloride compound **247** (1.0 eq.) was suspended in dichloromethane under nitrogen atmosphere, followed

by dropwise addition of the corresponding amine (3.0 – 4.0 eq.) under cooling. After the reaction mixture was stirred for 3 h at room temperature, it was dissolved in water and extracted with dichloromethane. Finally the solvent was evaporated under reduced pressure.

Synthesis of 1-(1H-Indol-3-yl)-2-(pyrrolidin-1-yl)ethan-1,2-dione (248b)

According to the general procedure, 2-(1H-Indol-3-yl)-2-oxoacetylchloride **247** (1.0 g, 4.8 mmol), pyrrolidine (1.6 mL, 19.3 mmol) were dissolved in 20 mL of dichloromethane. The title compound was recrystallized in ethanol affording 705 mg of yellow crystals (2.9 mmol, 60 %).


248b

mp: 178.5–181.8 °C, Lit.: [302] 195–197 °C

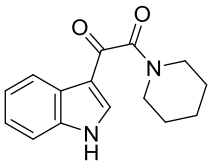
IR (ATR): $\tilde{\nu}$ = 3154, 3052, 2975, 2927, 2874, 1611, 1435, 1243, 1156, 748 cm^{-1}.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 12.28 (s, 1H, N**H**), 8,18 (s, 1H, Ind-2), 8.15–8.09 (m, 1H, Ind-4), 7.56–7.49 (m, 1H, Ind-7), 7.32–7.21 (m, 2H, Ind-5, Ind-6), 3.49 (t, *J* = 6.8 Hz, 2H, H-2), 3.39 (t, *J* = 6.8 Hz, 2H, H-5), 2.51 (dt, *J* = 7.2, 3.3 Hz, 4H, H-3, H-4) ppm.

The spectroscopic data are in accordance with those reported in the literature.[301]

1-(1*H*-Indol-3-yl)-2-(piperidin-1-yl)ethan-1,2-dione (248c)

According to the general procedure, 2-(1H-Indol-3-yl)-2-oxoacetylchloride **247** (3.7 g, 18.0 mmol), Piperidine (5.2 mL, 53.0 mmol) were dissolved in 25 mL of dichloromethane. The title compound was recrystallized in ethanol affording 2.6 mg of yellow crystals (10.1 mmol, 56 %).


248c

mp: 178.5–181.8 °C, Lit.:[303] 182–185 °C.

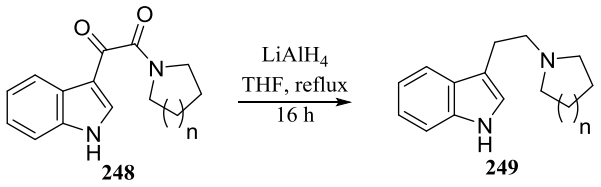
R_f: 0.49 (CH_2Cl_2/MeOH = 10:1).

IR (ATR): $\tilde{\nu}$ = 3155, 3054, 2938, 2858, 1606, 1497, 1433, 1242, 1128, 735, 639 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 10.25 (s, 1H, N**H**), 8.29 (d, *J* = 7.8 Hz, 1H, Ind-4), 7.68 (d, *J* = 3.3 Hz, 1H, Ind-2), 7.33 (dt, *J* = 7.8, 1.0 Hz, 1H, Ind-7), 7.33–7.20 (m, 2H, Ind-5, Ind-6), 3.67 (t, *J* = 5.4 Hz, 2H, H-2), 3.39 (t, *J* = 5.4 Hz, 2H, H-6), 1.70–1.61 (m, 4H, H-3, H-5), 1.53 (p, *J* = 5.4 Hz, 2H, H-4) ppm.

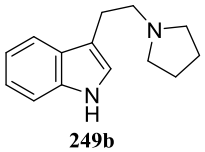
The spectroscopic data are in accordance with those reported in the literature.[303]

General Procedure XIII: Synthesis of 3-Indolamines (249)



Compounds **249b,c** were prepared according to a procedure of PÉREZ et al.[301] The corresponding starting indolamine **248b**,**c** (1.0 eq.) was added portionsweise at 0°C to a suspension of $LiAlH_4$ (4.0 eq.) in THF. The reaction was allowed to stirr under reflux during 16h, followed by quenching at room temperature with excess of $Na_2SO_4 \cdot 10\ H_2O$. The obtained solid was filtered under vacuum and washed with diethylether.

3-(2-Pyrrolidin-1-yl)ethyl)-1*H*-indol (249b)



According to the general procedure, 1-(1H-Indol-3-yl)-2-(pyrrolidin-1-yl)ethan-1,2-dione **248b** (500 mg, 2.1 mmol, 1.0 eq.) and $LiAlH_4$ (331 mg, 8.7 mmol, 4.0 eq.) were dissolved in 15 mL THF. The title compound was obtained as colorless crystals (425 mg, 2.0 mmol, 96 %).

mp: 98.7–102.3 °C, Lit.;[304] 109–110 °C.

R_f: 0.21 (CH_2Cl_2/MeOH = 10:1).

IR (ATR): $\tilde{\nu}$ = 3414, 3055, 2930, 2877, 2805, 1456, 1351, 1230, 1110, 736 cm^{-1}.

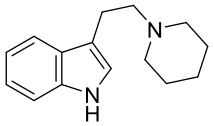
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.21 (s, 1H, N**H**), 7.62 (ds, *J* = 7.7, 1.2 Hz, 1H, Ind-4), 7.35 (dt, *J* = 8.1, 1.3 Hz, 1H, Ind-7), 7.18 (td, *J* = 8.1, 1.2 Hz, 1H, Ind-6), 7.12 (td, *J* = 7.4, 1.2 Hz, 1H, Ind-5), 7.03 (d, *J* = 2.2 Hz, 1H, Ind-2), 3.11 – 3.01 (m, H-1`), 2.92–2.83 (m, 2H, H-2`), 2.76– 2.67 (m, 4H, H-2, H-5), 1.91– 1.82 (m, 4H, H-3, H-4) ppm.

^{13}C-NMR, HSQC, HMBC (75.5 MHz, $CDCl_3$): δ = 136.4 (Ind-7a), 127.5 (Ind-3a), 122.1 (Ind-6), 121.8 (Ind-2), 119.4 (Ind-5), 118.9 (Ind-4), 114.1 (Ind-3), 111.3 (Ind-7), 57.2 (C-2`), 54.4 (C-2, C-5), 24.9 (C-1`), 23.6 (C-3, C-4) ppm.

HR-MS: *m*/*z* calcd for $[C_{14}H_{19}N_2]^+$: 215.1548, found: 215,1551

The spectroscopic data are in accordance with those reported in the literature.[301]

3-(2-Piperidin-1-yl)ethyl)-1*H*-indol (249c)


249c

According to the general procedure, 1-(1H-Indol-3-yl)-2-(piperidin-1-yl)ethan-1,2-dione **248c** (2.0 g, 7.8 mmol, 1.0 eq.) and $LiAlH_4$ (1.3 g, 32.9 mmol, 4.2 eq.) were dissolved in 20 mL THF. The title compound was obtained as colorless crystals (1.7 g, 7.3 mmol, 94 %).

mp: 143.5–147.8 °C, Lit.: [305] 151–152 °C.

R_f: 024 (CH_2Cl_2/MeOH = 10:1).

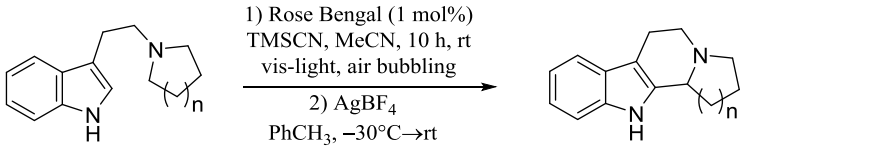
IR (ATR): $\tilde{\nu}$ = 3414, 2931, 2853, 1455, 1352, 1104, 735 cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.08 (s, 1H, N**H**), 7.63 (d, *J* = 7.8 Hz, 1H, Ind-4), 7.35 (dd, *J* = 7.8, 1.1 Hz, 1H, Ind-7), 7.19 (td, *J* = 7.8, 1.2 Hz, 1H, Ind-6), 7.11 (td, *J* = 7.8, 1.1 Hz, 1H, Ind-5), 7.02 (d, *J* = 2.4 Hz, 1H, Ind-2), 3.04–2.96 (m, 2H, H-1`), 2.73–2.66 (m, 2H, H-2`), 2.60–2.46 (m, 4H, H-2, H-6), 1.74–1.58(m, 4H, H-3, H-5), 1.56–1.40 (m, 2H, H-4) ppm.

^{13}C-NMR, HSQC, HMBC (75.5 MHz, $CDCl_3$): δ = 136.5 (Ind-7a), 127.5 (Ind-3a), 121.9 (Ind-6), 121.5 (Ind-2), 119.2 (Ind-5), 118.9 (Ind-4), 114.5 (Ind-3), 111.1 (Ind-7), 60.1 (C-2`), 54.6 (C-2, C-6), 25.9 (C-3, C-5), 24.4 (C-4), 22.8 (C-1`) ppm.

HR-MS: *m/z* calcd for $[C_{15}H_{21}N_2]^+$: 229.1705, found: 229.1705

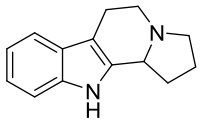
General procedure XIV: Photocyanation and Cyclization Reaction



The photocyanation reaction was performed according to the general procedure described in section E4. The obtained α-aminonitriles were used without further purification in the cyclization reactions. By this manner, the corresponding α-aminonitriles (1.0 eq.) were dissolved in toluene and cooled down to -20°C. Subsequenly, $AgBF_4$ (2.0 eq.) was added to the reaction mixture. After stirring 10 min at -20°C, TFA (11.0 – 20.0 eq.) was added at room temperature and then heated at 108°C during 16 h. The reaction was quenched with a concentrated solution of NH_4OH or a 2 molar solution of NaOH until a pH of around 11 was obtained. The reaction

mixture was finally extracted with EtOAc, washed with a solution of NaCl and dried over Na_2SO_4. The solvent was evaporated under reduced pressure.

Synthesis of (±)-Harmicine (239)


(±)-Harmicine (**239**)

According to the general procedure, 3-(2-Pyrrolidin-1-yl)ethyl)-1H-indol (**249b**) (100 mg, 0.5 mmol, 1 eq.), Rose Bengal (5.0 mg, 1 mol%) und TMSCN (235 µL, 1,9 mmol, 4 eq.) were dissolved in 4 mL of acetonitrile. The reaction mixture was filtered over a patch of Al_2O_3 (100% CH_2Cl_2) to eliminate the residual rose bengal. The product was used without further purification in the next step. For the cyclization reaction, α-aminonitrile **237b** (51 mg, 0.2 mmol, 1.0 eq.), $AgBF_4$ (83 mg, 0.42 mmol, 2.0 eq.) and TFA (270 µL, 17.0 eq.) were dissolved in 5 mL of toluene. After purification using flash chromatography (CH_2Cl_2/MeOH = 20:1), the title compound was obtained as an orange solid (24mg, 0.1 mmol, 25 % from **249b**).

mp: 167.4–169.7 °C, Lit.: [306] 173 °C.

R_f: 0.24 (CH_2Cl_2/MeOH = 10:0.1).

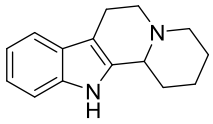
IR (ATR): $\tilde{\nu}$ = 3054, 2922, 2872, 2849, 1450, 1326, 737 cm^{-1}.

^{1}H-NMR, COSY (300 MHz, $CDCl_3$): δ = 7.94 (s, 1H, N**H**), 7.48 (dd *J* = 7.1, 1.3 Hz, 1H, H-7), 7.32 (dd, *J* = 7.1, 1.5 Hz, 1H, H-10), 7.14 (td, *J* = 7.1, 1.3 Hz, 1H, H-9), 7.09 (td, *J* = 7.1, 1.5 Hz, 1H, H-8), 4,32–4.19 (m, 1H, H-11b), 3.33 (ddd, *J* = 12.6, 5.3, 2.5 Hz, 1H, H-5), 3.10 (td, *J* = 12.6, 4,6 Hz, 1H, H-), 3.02–2.83 (m, 3H, H-6, H-3), 2.68 (ddt, *J* = 15.6, 4.7, 2.5 Hz, 1H, H-6), 2.35–2.25 (m, 1H, H-1), 2.02–1.76 (m, 3H, H-1, H-2) ppm.

^{13}C-NMR, HSQC, HMBC (75.5 MHz, CDCl3): δ = 136.1 (C-10a), 135.0 (C-11a), 127.4 (C-6b), 121.7 (C-9), 119.6 (C-10), 118.3 (C-7), 110.9 (C-8), 107.8 (C-6a), 57.2 (C-11b), 49.5 (C-3), 46.1 (C-5), 29.6 (C-1), 23.5 (C-2), 17.9 (C-6) ppm.

HR-MS: *m/z* calculated for $[C_{14}H_{17}N_2]$+: 213.1392, found: 213.1395

Synthesis of (±)-Debromarborescidin A (240)



(±)-Desbromoarborescidine A (**240**)

According to the general procedure, 3-(2-Piperidin-1-yl)ethyl)-1H-indol (**249c**) (228 mg, 1.0 mmol, 1 eq.), Rose Bengal (10.0 mg, 1 mol%) und TMSCN (502 µL, 4.0 mmol, 4 eq.) were dissolved in 6.5 mL of acetonitrile. The reaction mixture was filtered over a patch of Al_2O_3 (100% CH_2Cl_2) to eliminate the residual rose bengal. The product was used without further purification in the next step. For the cyclization reaction, the corresponding α-aminonitrile (145 mg, 0.6 mmol, 1.0 eq.), $AgBF_4$ (236 mg, 1.2 mmol, 2.1 eq.) and TFA (500 µL, 6.5 mmol, 11.0 eq.) were dissolved in 12 mL of toluene. After purification using a patch of Al_2O_3 (Cyclohexane/EtOAc = 1:1), the title compound was obtained as an orange solid (30mg, 0.1 mmol, 13 % from **249c**).

mp: 139.4–142.1 °C, Lit.: [307] 150–152 °C.

R_f: 0.49 (Cyclohexane/EtOAc = 1:1).

IR (ATR): $\tilde{\nu}$ = 3413, 3055, 2933, 2852, 2806, 2755, 1464, 1364, 1321, 1250, 1110, 737 cm^{-1}.

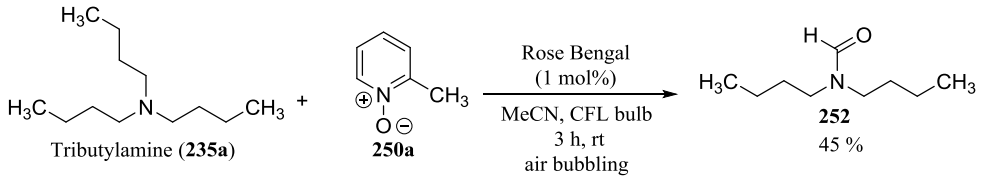
^{1}H-NMR, COSY (300 MHz, $CDCl_3$): δ = 7.81 (s, 1H, N-H), 7.47 (dd, *J* = 7.1, 1.2 Hz, 1H, H-8), 7.31 (dd, *J* = 7.0, 1.2 Hz, 1H, H-11), 7.13 (td, *J* = 7.1, 1.3 Hz, 1H, H-10), 7.08 (td, *J* = 7.1, 1.2 Hz, 1H, H-7), 3.26 (d, *J* = 10.2 Hz, 1H, H-12b), 3.16–2.98 (m, 3H, H-4, H-6, H-7), 2.81–2.61 (m, 2H, H-6, H-7), 2.40 (td, *J* = 11.3, 4.3 Hz, 1H, H-4), 2.12–2.03 (m, 1H, H-1), 1.93–1.38 (m, 5H, H-1, H-2, H-3) ppm.

^{13}C-NMR, HSQC, HMBC (75.5 MHz, $CDCl_3$): δ = 136.0 (C-11a), 134.9 (C-12a), 127.5 (C-7b), 121.3 (C-10), 119.4 (C-9), 118.1 (C-8), 110.8 (C-11), 108.1 (C-7a), 60.2 (C-12b), 55.7 (C-4), 53.5 (C-6), 29.9 (C-1), 25.7, 24.3 (C-2,C-3), 21.5 (C-7) ppm.

HR-MS: *m*/*z* calculated for $[C_{15}H_{19}N_2]^+$: 227.1548, found: 227.1539

E6 Additional Findings

Synthesis of N,N-dibutylformamide (252)



A solution of tributylamine **235a** (38.9 mg, 210 µmol) and pyridine N-oxide **250a** (91.6 mg, 839 mg) in 2 mL of CH_3CN was subjected to visible light irradiation in the presence of rose bengal (2.1 mg, 1 mol%) and under air bubbling at room temperature. Upon completion (monitored by TLC), the reaction mixture was treated with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and solvent was evaporated under reduced pressure producing a crude product. Purification through a plug of aluminum oxide (basic) afforded the title compound (15.0 mg, 95.3 µmol, 45 %) as a colorless oil.

$\boldsymbol{R_f}$ = 0.83 (CH_2Cl_2/MeOH, 10:1)

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 8.02 (s, 1H, C**H**O), 3.27 (t, *J* = 7.3 Hz, 2H, C**H$_2$**N), 3.18 (t, *J* = 7.2 Hz, 2H, C**H$_2$**N), 1.57–1.43 (m, 4H, C**H$_2$**), 1.36–1.24 (m, 4H, C**H$_2$**), 0.92 (t, *J* = 7.3 Hz, 3H, C**H$_3$**), 0.91 (t, *J* = 7.3 Hz, 3H, C**H$_3$**) ppm.

The spectroscopic data are in accordance with those reported in the literature.[308]

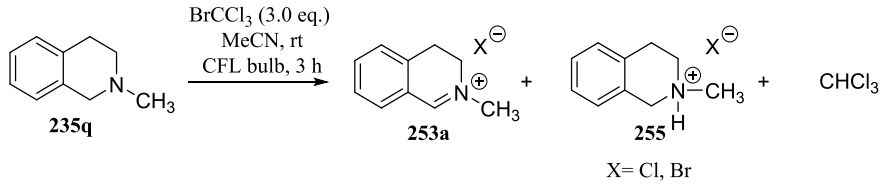
F Reaction Procedures: Chapter 5

F1 Photogeneration of Iminium salts

General Procedure XV: Oxidation of N-methyltetrahydroisoquinolines by Bromotrichloromethane.

In a pre-dried Schlenk tube and under argon atmosphere, *N*-methyl-1,2,3,4-tetrahydroisoquinoline **235q** (1.0 equiv) and $BrCCl_3$ (3.0 equiv) were dissolved in dry acetonitrile. After this, the reaction mixture was degassed with argon by three freeze-vacuum-thaw cycles. The mixture was then stirred and irradiated (24 W CFL lamp) for the indicated time span at room temperature. Once the reaction was complete (TLC monitoring), the product was either isolated and identified, or used in a continuous stepwise procedure.

Synthesis of *N*-methyl-3,4-dihydroisoquinolin-2-ium halide (253a) and *N*-methyl-1,2,3,4-tetrahydroisoquinoline hydrohalide (255)



In a YOUNG NMR tube and according to the general procedure, *N*-methyl-1,2,3,4-tetrahydroisoquinoline **235q** (20.0 mg, 0.136 mmol) and $BrCCl_3$ (40.2 µL, 0.408 mmol) were dissolved in 0.5 mL of deuterated acetonitrile. The reaction mixture was irradiated under visible light at room temperature for 3 h. In order to determine the yield of the reaction by NMR, 1,4-bis(trimethylsilyl)benzene was added as internal standard. A mixture of iminium ion **253a** and hydrohalide **255** inseparable by column chromatography was observed.

R_f = 0.13 ($CHCl_3$/MeOH, 10 : 1)

Iminium salt 253a: 84.9% NMR yield

^{1}H NMR, COSY (400 MHz, CD_3CN) δ = 9.26 (s, 1H, H-1), 7.84 (dd, *J* = 7.6, 1.3 Hz, 1H, H-8), 7.78 (td, *J* = 7.6, 1.3 Hz, 1H, H-6), 7.56–7.49 (m, 1H, H-7), 7.45 (d, *J* = 7.6 Hz, 1H, H-5), 3.99 (t, *J* = 8.1 Hz, 2H, H-3), 3.76 (s, 3H, NC**H**$_3$), 3.25 (t, *J* = 8.1 Hz, 2H, H-4) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, CD_3CN) δ = 167.8 (C-1), 138.8 (C-7), 137.2 (C-4a), 134.4 (C-8), 129.7 (C-5), 129.4 (C-6), 125.6 (C-8a), 51.0 (C-3), 28.9 (N**C**H$_3$), 25.5 (C-4) ppm.

ESI-MS (*m/z*): 146.1 (100) $[M + H]^+$.

The spectroscopic data are in accordance with those reported in the literature.[205,309]

Hydrohalide 255: 13.4% NMR yield

^{1}H NMR, COSY (400 MHz, CD_3CN) δ = 12.39 (s, 1H, N**H**), 7.32–7.20 (m, 3H, H-6, H-7, H-8), 7.14 (d, *J* = 6.8 Hz, 1H, H-5), 4.38 (dd, *J* = 15.6, 3.4 Hz, 1H, H-1a), 4.38 (dd, *J* = 15.6, 8.3 Hz, 1H, H-1b), 3.60–3.52 (m, 1H, H-3a), 3.51–3.49 (m, 1H, H-4a), 3.32–3.18 (m, 1H, H-3b), 3.04–2.96 (m, 1H, H-4b), 2.83 (d, *J* = 4.9 Hz, 3H, NC**H**$_3$) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 132.2 (C-4a), 129.3, 127.8 (C-6 & C-7), 129.1 (C-8a), 128.9 (C-8), 127.5 (C-5), 54.5 (C-1), 51.4 (C-3), 42.9 (N**C**H$_3$), 26.0 (C-4) ppm.

ESI-MS (*m/z*): 148.1 (100) $[M + H]^+$.

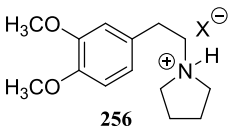
The spectroscopic data are in accordance with those reported in the literature.[310]

F2 Photochemical Reaction of Aliphatic Trialkylamines and Bromotrichloromethane

General Procedure XVI:

In a pre-dried Schlenk tube and under argon atmosphere, trialkylamine (1.0 equiv) and $BrCCl_3$ (3.0 equiv) were dissolved in dry acetonitrile. After this, the reaction mixture was degassed with argon by three freeze-vacuum-thaw cycles. The mixture was then stirred and irradiated (24 W household CFL bulb) for the indicated time span at room temperature.

1-(3,4-Dimethoxyphenethyl)pyrrolidine hydrohalide (256)



256

In a valved Young NMR tube and according to the general procedure, 1-(3,4-dimethoxyphenethyl)pyrrolidine **244** (20.0 mg, 85.0 μmol) and $BrCCl_3$ (25.1 μL, 0.255 mmol) were dissolved in 0.5 mL of CD_3CN. The reaction mixture was irradiated under visible light at room temperature for 3 h. In order to determine the yield of the reaction by NMR, CH_2Br_2 (10 mg) was added as an internal standard. Compound **256** was obtained in 77 % yield.

IR (ATR) $\tilde{\nu}$ = 2955, 2688, 2596, 1515, 1260, 1236, 1141, 1023 cm^{-1}.

^{1}H NMR, COSY (400 MHz, CD_3CN) δ = 11.28 (s, 1H, N**H**), 6.88 (d, *J* = 2.0 Hz, 1H, Ph-2), 6.85 (d, *J* = 8.2 Hz, 1H, Ph-5), 6.79 (dd, *J* = 8.2, 2.0 Hz, 1H, H-6), 3.79 (s, 3H, OC**H**$_3$–Ph-3), 3.76 (s, 3H, OC**H**$_3$–Ph-4), 3.63–3.54 (m, 2H, H-2a, H-5a), 3.31–3.23 (m, 2H, H-1'), 3.10–3.03 (m, 2H, H-1'), 2.98–2.86 (m, 2H, H-2b, H-5b), 2.09–1.97 (m, 4H, 2H-3, 2H-4) ppm.

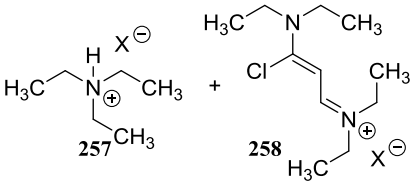
^{13}C NMR, HMBC, HSQC (100.6 MHz, CD_3CN) δ = 150.2 (Ph-3), 149.1 (Ph-4), 130.5 (Ph-1), 121.7 (Ph-6), 113.4 (Ph-2), 112.8 (Ph-5), 56.8 (C-1'), 56.3 (2xO**C**H$_3$), 54.3 (C-2, C-5), 32.0 (C-2'), 24.1(C-3, C-4) ppm.

ESI-MS (*m/z*): 236.2 (100) $[C_{14}H_{22}NO_2]^+$

ESI-HRMS (*m/z*): calcd for $[C_{14}H_{22}NO_2]^+$ 236.1661, found 236.1648.

Triethylamine hydrohalide (257) and chloro-streptocyanine dye (258)

In a Young NMR tube and according to the general procedure III, triethylamine **235r** (10.0 mg, 98.8 μmol) and $BrCCl_3$ (29.2 μL, 0.296 mmol) were dissolved in 0.5 mL of deuterated acetonitrile. The reaction mixture was irradiated with a 24 W CFL lamp at room temperature for 24 h. After monitoring the reaction by ^{1}H NMR, triethylamine **235r** was predominantly converted in triethylamine hydrohalide **257** and chloro-streptocyanine dye **258** in 91 : 9 ratio, respectively.



Hydrohalide (**257**): 78.0% NMR yield

^{1}H NMR, COSY (400 MHz, CD_3CN) δ = 11.17 (s, 1H, NH), 3.05 (qd, *J* = 7.3, 4.9 Hz, 6H, NCH_2), 1.30 (t, *J* = 7.3 Hz, 9H, NCH_2CH_3) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 46.6 (NCH_2), 8.9 (NCH_2CH_3) ppm.

ESI-MS (*m/z*): 102.6 (100) $[C_6H_{16}N]^+$.

Chloro-streptocyanine dye (**258**): 7.6 % NMR yield

^{1}H NMR, COSY (400 MHz, CD_3CN) δ = 7.98 (d, *J* = 11.3 Hz, 1H, H-1), 5.44 (d, *J* = 11.3 Hz, 1H, H-2), 3.80–3.67 (m, 4H, NCH_2), 3.59 (q, *J* = 7.3 Hz, 2H, $^{\oplus}NCH_2$), 3.54 (q, *J* = 7.2 Hz, 2H, $^{\oplus}NCH_2$), 1.34–1.18 (m, 12H, 4xCH_3).

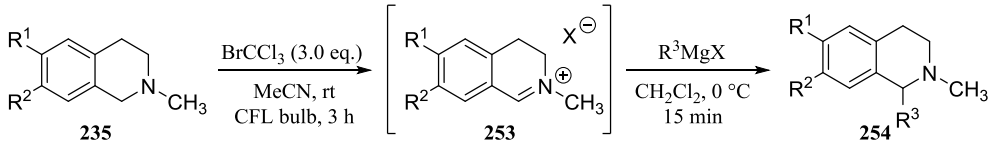
^{13}C NMR, HMBC, HSQC (100.6 MHz, CD_3CN) δ = 160.9 (C-1), 158.7 (C-3), 88.4 (C-2), 53.4, 45.4 ($^{\oplus}N(CH_2)_2$), 43.2 ($N(CH_2)_2$), 14.5, 12.3, 11.4 (4xCH_3) ppm.

ESI-MS (*m/z*): 217.3 (100) $[C_{11}H_{22}{}^{35}ClN_2]^+$, 219.0 (35) $[C_{11}H_{22}{}^{37}ClN_2]^+$.

ESI-HRMS: calcd for $[C_{11}H_{22}{}^{35}ClN_2]^+$ 217.1471, found: 217.1459. Calcud for $[C_{11}H_{22}{}^{37}ClN_2]^+$: 19.1442, found: 219.1437

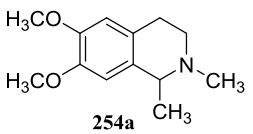
F3 Iminium Ions as Traps for Grignard Reagents

General Procedure XVII: Synthesis of 1-Substituted Tetrahydroisoquinolines 254



Iminium salts **253** were prepared according to the general procedure described in section F1. All volatiles were removed under reduced pressure and the organic residue was redissolved in dry dichloromethane (under argon atmosphere). The reaction mixture was then cooled to 0 °C and the Grignard reagent (2.0 equiv.) was added dropwise over 5 minutes. Once this period was complete, the mixture was allowed to reach room temperature. The mixture was quenched by slow addition of a saturated solution of NH_4Cl, followed by dilution with water and extraction with dichloromethane (3 x 5 mL). The combined organic phases were washed with $NaHCO_3$ solution, brine and dried over Na_2SO_4. The solvent was evaporated in vacuo and the crude product was purified by flash chromatography on silica gel.

(±)-Carnegine (254a).



According to the general procedure mentioned in section F1, 6,7-dimethoxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline **235j** (50.0 mg, 0.241 mmol) and $BrCCl_3$ (71.2 µL, 0.723 mmol) were dissolved in 2 mL of acetonitrile. The reaction mixture was stirred at room temperature and irradiated under visible light for 3 h. Subsequently, following general procedure mentioned above, the organic residue was redissolved in 2 mL of dry dichloromethane and methylmagnesium bromide (3 m in THF, 160 µL, 0.482 mmol) was added. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH/NH_4OH 90 : 9 :1) to afford the title compound (39.0 mg, 0.176 mmol, 73 %) as a light yellow oil.

$\boldsymbol{R_f}$ = 0.48 (CH_2Cl_2/MeOH, 10 : 1).

IR (ATR) $\tilde{\nu}$ = 2934, 2786, 1513, 1256, 1216, 1146, 1057 cm^{-1}.

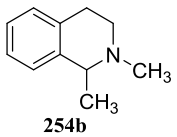
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 6.58 (s, 1H, H-8), 6.56 (s, 1H, H-5), 3.84(2s, 6H, OC**H**$_3$-6, OC**H**$_3$-7), 3.57 (q, *J* = 6.6 Hz, 1H, H-1), 3.04 (ddd, *J* = 11.7, 6.6, 5.1 Hz, 1H, H-3a), 2.87–2.69 (m, 2H, H-4), 2.65 (ddd, *J* = 11.7, 6.9, 5.0 Hz, 1H, H-3b), 2.48 (s, 3H, NC**H**$_3$), 1.39 (d, *J* = 6.6 Hz, 3H, NCHC**H**$_3$) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 147.4 (C-6), 147.3 (C-7), 131.4 (C-8a), 125.9 (C-4a), 111.3 (C-5), 110.0 (C-8), 58.8 (C-1), 56.1, 55.9 (O**C**H$_3$-6, O**C**H$_3$-7), 48.9 (C-3), 42.9 (N**C**H$_3$), 27.4 (C-4), 19.9 (NCH**C**H$_3$) ppm.

ESI-MS (*m/z*): 222.2 (100) $[M + H]^+$.

The spectroscopic data are in accordance with those reported in the literature.[311]

1,2-Dimethyl-1,2,3,4-tetrahydroisoquinoline (254b)



254b

According to the general procedure mentioned in section F1, *N*-methyl-1,2,3,4-tetrahydroisoquinoline **235q** (35.5 mg, 0.241 mmol) and $BrCCl_3$ (71.2 µL, 0.723 mmol) were dissolved in 2 mL of acetonitrile. The reaction mixture was stirred at room temperature and irradiated under visible light for 3 h. Subsequently, following general procedure mentioned above, the organic residue was redissolved in 2 mL of dry dichloromethane and methylmagnesium bromide (3 m in THF, 160 µL, 0.482 mmol) was added. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 10 : 1) to afford 16 mg of the title compound (89 % pure) as a volatile light yellow liquid (14.2 mg, 88.3 µmol, 37 %).

R_f = 0.30 (CH_2Cl_2/MeOH, 10 : 1).

IR (ATR) $\tilde{\nu}$ = 2928, 2784, 1709, 1461, 1077, 758, 732 cm^{-1}.

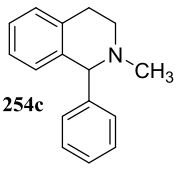
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.20–7.04 (m, 4H, H-5, H-6, H-7, H-8), 3.69 (q, *J* = 6.6 Hz, 1H, H-1), 3.09 (ddd, *J* = 12.0, 6.6, 5.1 Hz, 1H, H-3a), 2.97–2.81 (m, 2H, H-4), 2.71 (ddd, *J* = 12.0, 7.1, 5.0 Hz, 1H, H-3b), 2.52 (s, 3H, NC**H**$_3$), 1.44 (d, *J* = 6.6 Hz, 3H, NCHC**H**$_3$) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 139.2 (C-8a), 133.6 (C-4a), 128.9 (C-5), 127.0 (C-8), 126.2 (C-6), 126.1 (C-7), 59.2 (C-1), 48.9 (C-3), 42.7 (N**C**H$_3$), 27.8 (C-4), 19.8 (NCH**C**H$_3$) ppm.

ESI-MS (*m/z*): 162.1 (100) $[M + H]^+$.

The spectroscopic data are in accordance with those reported in the literature.[312]

N-Methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (254c).



254c

According to the general procedure mentioned in section F1, *N*-methyl-1,2,3,4-tetrahydroisoquinoline **235q** (35.5 mg, 0.241 mmol) and $BrCCl_3$ (71.2 µL, 0.723 mmol) were dissolved in 2 mL of acetonitrile. The reaction mixture was stirred at room temperature and irradiated under visible light for 3 h. Subsequently, following general procedure mentioned above, the organic residue was redissolved in 2 mL of dry dichloromethane and phenylmagnesium bromide (1 m in THF, 482 µL, 0.482 mmol) was added. The crude product was purified by flash chromatography on silica gel (cyclohexane/EtOAc, 10 : 1) to afford the title compound (26.7 mg, 0.119 mmol, 50 %) as a light yellow oil.

$\boldsymbol{R_f}$ = 0.50 (cyclohexane/EtOAc, 6 : 1).

IR (ATR) $\tilde{\nu}$ = 2921, 2782, 1492, 1450, 1067, 739, 699 cm^{-1}.

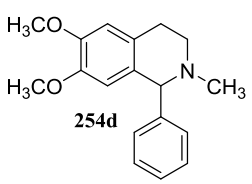
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.34–7.20 (m, 5H, 2H-2', 2H-3', H-4'), 7.13–7.04 (m, 2H, H-5, H-6), 6.96 (td, *J* = 7.3, 1.9 Hz, 1H, H-7), 6.61 (d, *J* = 7.8 Hz, 1H, H-8), 4.22 (s, 1H, H-1), 3.26 (ddd, *J* = 16.3, 11.1, 5.5 Hz, 1H, H-4a), 3.11 (ddd, *J* = 11.4, 5.5, 2.8 Hz, 1H, H-3a), 2.81 (dt, *J* = 16.3, 3.4 Hz, 1H, H-4b), 2.62 (td, *J* = 11.4, 3.8 Hz, 1H, H-3b), 2.22 (s, 3H, NCH_3) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 144.1 (C-1'), 138.7 (C-8a), 134.4 (C-4a), 129.8 (2C-2'), 128.7 (C-8), 128.4 (C-5, 2C-3'), 127.4 (C-4'), 126.1 (C-6), 125.8 (C-7), 71.7 (C-1), 52.5 (C-3), 44.5 (NCH_3), 29.7 (C-4) ppm.

ESI-MS (*m/z*): 224.1 (100) $[M + H]^+$.

The spectroscopic data are in accordance with those reported in the literature.[224]

6,7-Dimethoxy-*N*-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (254d).



254d

According to the general procedure mentioned in section F1, 6,7-dimethoxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline **235j** (50.0 mg, 0.241 mmol) and $BrCCl_3$ (71.2 µL, 0.723 mmol) were dissolved in 2 mL of acetonitrile. The reaction mixture was stirred at room temperature and irradiated under visible light for 3 h. Subsequently, following general procedure mentioned above, the organic residue was redissolved in 2 mL of dry dichloromethane and phenylmagnesium bromide (1 m in THF, 482 µL, 0.482 mmol) was added. The crude product

was purified by flash chromatography on silica gel (CH_2Cl_2 100% grad. to CH_2Cl_2/MeOH, 10 : 1) to afford the title compound (41.0 mg, 0.145 mmol, 60 %) as a light yellow oil.

$\boldsymbol{R_f}$ = 0.63 (CH_2Cl_2/MeOH, 10 : 1).

IR (ATR) $\tilde{\nu}$ = 2945, 2784, 1611, 1254, 1217, 727, 701 cm^{-1}.

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.37–7.20 (m, 5H, 2H-2', 2H-3', H-4'), 6.60 (s, 1H, H-5), 6.09 (s, 1H, H-8), 4.18 (s, 1H, H-1), 3.85 (s, 3H, OC**H**$_3$-6), 3.56 (s, 3H, OC**H**$_3$-7), 3.18 (dddt, *J* = 15.5, 10.4, 5.4, 1.23 Hz, 1H, H-4a), 3.10 (ddd, *J* = 11.4, 5.4, 2.8 Hz, 1H, H-3a), 2.74 (dt, *J* = 15.5, 3.4 Hz, 1H, H-4b), 2.61 (td, *J* = 10.8, 4.0 Hz, 1H, H-3b), 2.24 (s, 3H, NC**H**$_3$) ppm.

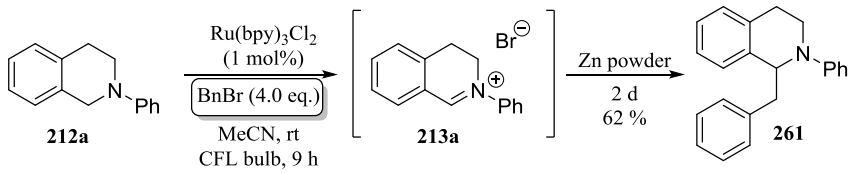
^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 147.3 (C-6), 147.0 (C-7), 144.0 (C-1'), 130.5 (C-8a), 129.6 (2C-2'), 128.3 (2C-3'), 126.7 (C-4a), 127.3 (C-4'), 111.6 (C-8), 110.9 (C-5), 71.2 (C-1), 55.9 (O**C**H$_3$-6, O**C**H$_3$-7), 52.4 (C-3), 44.4 (N**C**H$_3$), 29.1 (C-4) ppm.

ESI-MS (*m/z*): 284.2 (100) $[M + H]^+$.

The spectroscopic data are in accordance with those reported in the literature.[224]

F4 Additional Findings

One-Pot Photocatalytic Oxidation/Barbier-Type Reaction–Synthesis of Compound 261



Under argon atmosphere, a solution of amine **212a** (203 mg, 970 mmol), $Ru(bpy)_3Cl_2$ (7.6 mg, 1 mol%), and benzyl bromide (451µL, 3.88 mmol), in 10 mL of MeCN was irradiated with visible light (CFL lamp 24 W) for 9 h at room temperature. After consumption of the starting material (confirmed by TLC), the irradiation was removed and then zinc powder (317 mg, 4.85 mmol) was added to the mixture at 0 °C. Once added the reaction was allowed to stir for 2 d at room temperature. The reaction was then poured into a saturated $NaHCO_3$, extracted with dichloromethane (4 x 20 mL) and the organic layers dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford a crude product which was purified by silica gel

flash chromatography (cyclohexane/EtOAc 50:1). In this manner, 180 mg of 1-benzyltetrahydroisoquinoline **261** (601 µmol, 62 %) were obtained in the form of a clear oil.

R_f = 0.63 (Cyclohexane/EtOAc, 40 : 1).

IR (ATR) $\tilde{\nu}$ = 3025, 1597, 1502, 748, 697 cm^{-1}.

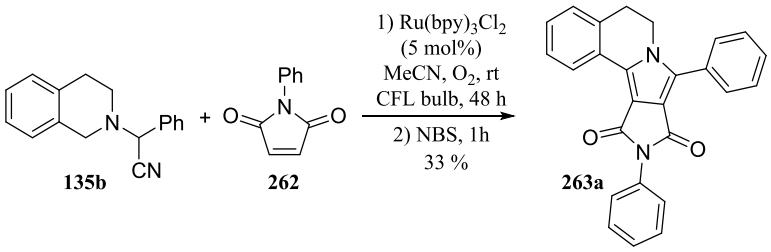
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.22–7.12 (m, 7H, ArH), 7.09–6.99 (m, 3H, ArH), 6.86 (d, J = 8.2 Hz, 2H, ArH), 6.74 (t, J = 7.6 Hz, 2H, ArH), 4.91 (Pseudo-t, J = 6.4 Hz, 1H, H-1), 3.72–3.61 (m, 1H,C**H**$_2$), 3.60–3.50 (m, 1H, C**H**$_2$), 3.33–3.22 (m, 1H, C**H**$_2$), 3.07–2.94 (m, 2H, C**H**$_2$), 2.82–2.68 (m, 1H, C**H**$_2$) ppm.

ESI-MS (*m/z*): 300.0 (100) $[M + H]^+$.

The spectroscopic data are in accordance with those reported in the literature.[313]

Photo-oxidation of α-Aminonitriles

Synthesis of Compound 263a



A solution of α-aminonitrile **135b** (89.0 mg, 358µmol), $Ru(bpy)_3Cl_2$ (12 mg, 5 mol%) and *N*-phenylmaleimide (52 mg, 300 mmol), in 3 mL of MeCN was irradiated with visible light (CFL lamp 24 W) for 48 h at rt and under an oxygen atmosphere. After this period, the irradiation was removed and then NBS (317 mg, 4.85 mmol) was added to induce the oxidative aromatization. The reaction was then poured into a saturated $NaHCO_3$ and extracted with dichloromethane (4 x 20 mL). The extracts were washed with brine, dried over Na_2SO_4, and the solvent removed under reduced pressure. The corresponding crude was then purified by silica gel flash chromatography (cyclohexane/EtOAc 10:1). In this manner, 46.4 mg of the title compound **263a** (119 µmol, 33 %) were obtained in the form of a yellow gum.

R_f = 0.48 (Cyclohexane/EtOAc, 3 : 2).

IR (ATR) $\tilde{\nu}$ = 3063, 1746, 1701, 1383, 1332, 1149, 771 cm^{-1}.

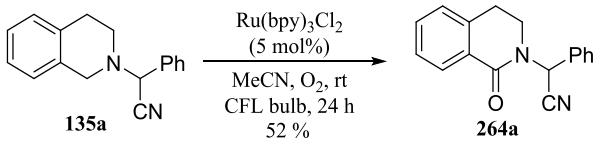
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 8.57 (dd, J = 7.8, 1.3 Hz, 1H, Ph-H), 7.71–7.64 (m, 2H, Ph-H), 7.56–7.39 (m, 8H, Ph-H), 7.39–7.29 (m, 2H, Ph-H), 7.29–7.26 (m, 1H, Ph-H), 4.29 (t, J = 6.7 Hz, 2H, C**H**$_2$N), 3.14 (t, J = 6.7 Hz, 2H, PhC**H**$_2$CH$_2$N) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 163.8 (**C**=O), 163.7 (**C**=O), 133.1, 132.9, 129.6, 129.5, 129.4, 128.97, 128.9, 128.2, 128.2, 127.7, 127.5, 127.5, 127.1, 126.8, 118.1, 115.6 (22 C-Ar), 132.0 (C-4a), 130.5 (C-11c),43.3 (**C**H$_2$N), 29.3 (Ph**C**H$_2$CH$_2$N) ppm.

ESI-MS (*m/z*): 391.4 (100) $[M + H]^+$

ESI-HRMS: calcd for $[C_{26}H_{19}N_2O_2]^+$ 391.1447, found 391.1452.

Formation of Amide 264a as By-product



When applying the above mentioned conditions to α-aminonitrile **135b** (20.0 mg, 80.5 µmol), $Ru(bpy)_3Cl_2$ (3.1 mg, 5 mol%) but in the absence of *N*-phenylmaleimide, compound **264a** was obtained in 52 % yield as a clear oil (10.4 mg, 42.2 µmol).

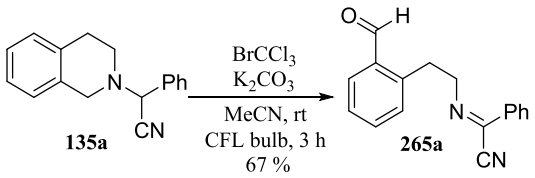
R_f = 0.15 (Cyclohexane/EtOAc, 10 : 1).

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 8.15 (dd, J = 7.8, 1.4 Hz, 1H, H-8), 7.56–7.36 (m, 7H, H-6, 7, 2', 3', 4', 5', 6'), 7.25 (s, 1H, NC**H**CN), 7.19 (dd, J = 7.5, 1.2 Hz, 1H, H-8), 3.68 (ddd, J = 12.0, 8.6, 5.0 Hz, 1H, H-3a), 3.30 (ddd, J = 12.0, 7.5, 5.2 Hz, 1H, H-3b), 3.30 (ddd, J = 16.0, 7.5, 5.0 Hz, 1H, H-4a), 2.96–2.84(m, 1H,H-4b) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 164.3 (C-1, **C**=O), 138.2 (C-4a), 132.9, 127.5 (C-6, C-7) 132.2 (C-1') 129.5 (C-4), 129.4 (C-3), 129.1 (C-8), 128.1 (C-8a), 127.4 (C-5), 127.3 (C-2', C-6'), 116.4 (**C**N), 48.5 (NC**H**CN), 42.35 (C-3), 28.0 (C-4) ppm.

ESI-MS (*m/z*): 263.1 (100) $[M+H]^+$

Formation of Imidoyl Cyanide 265a



If the reaction conditions for the visible light $BrCCl_3$ photo-oxidation conditions are applied to α-aminonitrile **135b** (20.0 mg, 80.5 µmol), in the presence of K_3CO_3 (22.0 mg, 159 µmol) compound **265a** was obtained in 67 % yield as a clear yellow oil (14.0 mg, 56.8 µmol).

$\boldsymbol{R_f}$ = 0.57 (Cyclohexane/EtOAc, 3 : 2).

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 10.30 (s, PhC**H**O), 7.96–7.92 (m, 2H, Ph–H-2, Ph–H-6), 7.87 (dd, *J* = 7.6, 1.5 Hz, 1H, PhCHO–H-6), 7.58–7.51 (m, 2H, PhCHO–H-4, Ph–H-4), 7.51–7.43 (m, 3H, PhCHO–H-5, Ph–H-3,5), 7.36 (dd, *J* = 7.6, 1.3 Hz, 1H, PhCHO–H-3), 4.27 (t, *J* = 6.8 Hz, 2H, C**H$_2$**N), 3.59 (t, *J* = 6.8 Hz, 2H, PhC**H$_2$**CH$_2$N), ppm.

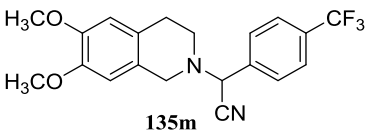
^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 193.4 (PhC**H**O), 142.4 (N=**C**CN), 141.34 (PhCHO–C-2), 134.4 (PhCHO–C-1), 133.9 (PhCHO–C-4), 133.4 (Ph–C-1), 133.2 (PhCHO–C-6), 132.4 (Ph–C-4), 132.1 (PhCHO–C-3), 129.0 (Ph–C-3), 127.7 (Ph–C-2), 127.5 (PhCHO–C-5), 109.6 (**C**N), 59.7 (**C**H$_2$N), 33.5 (PhCH$_2$CH$_2$N) ppm.

ESI-MS (*m/z*): 263.1 (100) $[M + H]^+$

G Reaction Procedures: Chapter 6

G1 Preparation of α-Aminonitrile 135m

2-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2-(4-(trifluoromethyl)phenyl)acetonitrile (135m)



135m

Following the general procedure VI, described in section C2, compound **135m** was prepared from 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **139** (1.45 g, 5.07 mmol, were dissolved in 4 mL of methanol before addition), *p*-trifluoromethylbenzaldehyde (1.03 mL, 7.51 mmol), $NaHSO_3$ (781 mg, 7.51 mmol), and KCN (980 g, 15.1 mmol). The crude product was recrystallized from diethyl ether to afford the title compound (2.30 g, 6.11 mmol, 81%) as colorless crystals.

mp: 142.1–142.6 °C

R_f = 0.46 (cyclohexane/EtOAc, 3:2)

IR (ATR): $\tilde{\nu}$ = 3002, 2938, 2837, 1614, 1518, 1324, 1122, 1067, 731 cm^{-1}

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.76 (d, *J* = 8.6 Hz, 2H, H-2', H-6'), 7.69 (d, *J* = 8.3 Hz, 2H, H-3', H-5'), 6.61 (s, 1H, H-8), 6.48 (s, 1H, H-5), 5.11 (s, 1H, C**H**CN), 3.85 (s, 3H, C^6-OC**H**$_3$), 3.82 (s, 3H, C^7-OC**H**$_3$), 3.73 (d, *J* = 13.9 Hz, 1H, H-1a), 3.66 (d, *J* = 13.9 Hz, 1H, H-1b), 2.97–2.78 (m, 4H, H-3, H-4) ppm.

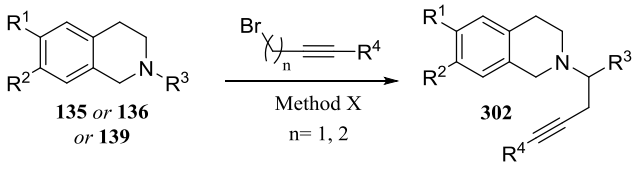
^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 148.0 (C-6), 147.6 (C-7), 137.2 (C-1'), 131.5 (q, *J* = 32.7 Hz), 128.4 (C-2', C-6'), 126.0 (q, *J* = 3.7 Hz, C-3'), 125.4 (C-8a), 125.1 (C-4a), 123.9 (q, *J* = 272.3 Hz, CF_3), 114.9 (**C**N), 111.5 (C-8), 109.4 (C-5), 62.0 (**C**–CN), 56.1 (C^6-O**C**H$_3$, C^7-O**C**H$_3$), 52.1 (C-1), 48.0 (C-3), 29.0 (C-4) ppm.

ESI-MS (*m/z*): 377.2 (100) $[M + H]^+$

ESI-HRMS: calcd for $[C_{20}H_{19}N_2O_3F_3Na]^+$ 399.1296, found 399.1302.

G1 Synthesis of Alkynyl Amines 302

General Procedures XVIII:



Method A: to a cold (0 C) solution of the corresponding α-aminonitrile **135** (1.0 eq.) in dry THF (8.5 mL/mmol) was added solid KHMDS (1.2 eq.) in small portions and over a period of 5 min and then allowed to stirred for additional 5 minutes. After this period, alkynyl bromide (1.5 eq.) was added dropwise to the deprotonated α-aminonitrile and the reaction was permitted to stir initially at 0 °C for 1 h and then an additional 1 °h at room temperature. Once the C-alkylation was completed, EtOH (3.4 mL/mmol) and acetic acid (3 eq.) were added to the reaction mixture. Then solid $NaCNBH_3$ (16.0 eq.) was added in portions (4.0 eq./day) distributed over 4 days (until TLC showed full conversion). The pH of the reaction was kept acidic (ca. 3–5) by addition of acetic acid in order to speed up and enhance the process. After completion, the reaction was poured in a $NaHCO_3$ saturated solution and the layers were stirred for 10 minutes. The biphasic system was then extracted 3 times with diethyl ether and the combined organic layers were washed with brine and dried over Na_2SO_4. Removal of the solvent under reduce pressure provide a crude material which was purified by automated flash column chromatography (Isolera™ Flash Purification System) to afford the title compounds.

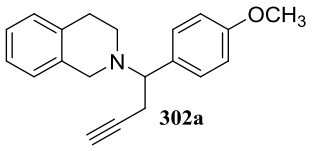
Method B: This procedure initially follows the same procedure described above for the C-alkylation of -aminonitrile **135**. However, in this case, the reductive decyanation process is not performed via one-pot procedure.[§§] In this manner, upon completion of the C-alkylation, the reaction mixture is quenched with water and extracted 3 times with diethyl ether. The combined organic layers were washed brine, dried over Na_2SO_4, and the solvent removed under reduce pressure. The provided crude product is then redissolved in THF followed by addition of solid $LiAlH_4$ (2.0 eq) at 0 °C. The reaction mixture was then allowed to warm up to room temperature and stirred 18 h. Once completed, the reaction was quenched by addition of $Na_2SO_4 \cdot 10\ H_2O$ (excess) was added at room temperature. The obtained solid was filtered under vacuum and washed with several times diethyl ether. Evaporation of the ether afforded a crude material

[§§] Attempts to perform the reductive decyanation process in a one-pot fashion resulted in the no generation of the expected alkynyl amine **302**.

which was purified by automated flash column chromatography (Isolera™ Flash Purification System) to afford the title compounds.[***]

Method C: to a suspension of the corresponding tetrahydroisoquinoline **136** or **134** (1.0 eq.) and K_2CO_3 (448 mg, 3.24 mmol) in acetonitrile (3.38 mL/mmol) at room temperature was added dropwise 4-bromo-1-butyne (426µL, 3.20 mmol). The reaction mixture was then stirred for 24 h at the same temperature. After completion, the solid was filtered off and washed several times with acetonitrile. The acetonitrile solution is then evaporated under reduce pressure to afford a crude product which was purified by automated flash column chromatography (Isolera™ Flash Purification System) to afford the title compounds.

2-(1-(4-Methoxyphenyl)but-3-yn-1-yl)-1,2,3,4-tetrahydroisoquinoline (302a)



302a

Following method A, α-aminonitrile **135a** (821 mg, 2.95 mmol), KHMDS (647 mg, 3.24 mmol), propargyl bromide (500 µL, 4.47 mmol, 80 % in toluene), and $NaCNBH_3$ (741 mg, 11.8 mmol) were dissolved in THF (25 mL) in synergy with EtOH (10 mL) and AcOH (500 µL). The title compound (636 mg, 2.18 mmol, 74 %) was obtained as a pale yellow solid after purification by flash column chromatography (Isolera™ Flash Purification System, cyclohexane/EtOAc, gradient 0–28%). Applying method B, homopropargylamine **302a** was obtained in 74% (636 mg, 2.18 mmol)

mp: 58.3–60.0°C

$\mathbf{R_f}$ = 0.26 (Cyclohexane/EtOAc, 6:1)

IR (ATR): $\tilde{\nu}$ = 3290, 2915, 2118, 1610, 1511, 1247, 1035, 808 cm^{-1}

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.34 (d, *J* = 8.6 Hz, 2H, H-2',6'), 7.14–7.06 (m, 3H, H-5,6,7), 6.99 (d, *J* = 8.3 Hz, 1H, H-8), 6.90 (d, *J* = 8.6 Hz, 2H, H-3',6'), 3.82 (s, 3H, $C^{4'}$-OC**H**$_3$), 3.79 (d, *J* = 14.8 Hz, 1H, H-1a), 3.68 (dd, *J* = 8.2, 4.9 Hz, 1H, NC**H**Ph), 3.63 (d, *J* = 14.8 Hz, 1H, H-1b), 2.92–2.74 (m, 6H, H-3, H-4, C**H**$_2$C≡), 1.94 (t, *J* = 2.6 Hz, 1H, C≡C**H**) ppm.

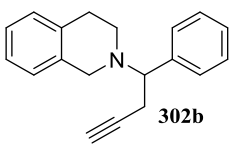
^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 158.91 (C-4'), 134.9 (C-8a), 134.5 (C-4a), 132.5 (C-1'), 129.3 (C-2', C-6'), 128.8 (C-5), 126.7 (C-8), 126.0 (C-6), 125.5 (C-7), 113.5 (C-3', C-5'), 81.9 (**C**≡CH), 70.4 (C≡**C**H), 67.1 (N**C**HPh), 55.2 (O**C**H$_3$-4'), 53.4 (C-1), 47.8 (C-3), 29.2 (C-4) ppm.

[***] This method did not work with substrates **135** wearing electron withdrawing groups at the aryl moiety.

ESI-MS (*m/z*): 292.2 (100) $[M]^+$

ESI-HRMS: calcd for $[C_{20}H_{22}NO]^+$ 292.1701, found 292.1708.

2-(1-Phenylbut-3-yn-1-yl)-1,2,3,4-tetrahydroisoquinoline (302b)



302b

Following method A, α-aminonitrile **135b** (733 mg, 2.95 mmol), KHMDS (647 mg, 3.24 mmol), propargyl bromide (500 µL, 4.47 mmol, 80 % in toluene), and $NaCNBH_3$ (741 mg, 11.8 mmol) were dissolved in THF (25 mL) in synergy with EtOH (10 mL) and AcOH (500 µL). The title compound (253 mg, 968 µmol, 33 %) was obtained as a pale yellow solid after purification by flash column chromatography (Isolera™ Flash Purification System, cyclohexane/EtOAc, gradient 0–10%).

mp: 33.9–45.0°C

$\mathbf{R}_f$ = 0.48 (Cyclohexane/EtOAc, 6:1)

IR (ATR): $\tilde{\nu}$ = 3292, 2917, 2753, 2119, 1495, 1453, 742, 702 cm^{-1}

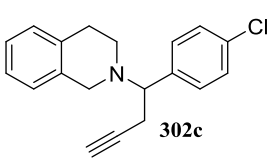
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.43 (dd, *J* = 8.3, 1.3 Hz, 2H, H-2',6'), 7.39–7.34 (m, 2H, H-3',5'), 7.349–7.30 (m, 2H, H-4'), 7.14–7.06 (m, 3H, H-5,6,7), 6.99 (d, *J* = 8.2 Hz, 1H, H-8), 3.82 (d, *J* = 14.7 Hz, 1H, H-1a), 3.71 (dd, *J* = 7.9, 5.1 Hz, 1H, NC**H**Ph), 3.64 (d, *J* = 14.7 Hz, 1H, H-1b), 2.99–2.63 (m, 6H, H-3, H-4, C$\mathbf{H}_2$C≡), 1.94 (t, *J* = 2.7 Hz, 1H, C≡C**H**) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 140.7 (C-1'), 135.0 (C-8a), 134.6 (C-4a), 128.8 (C-4'), 128.38 (C-2', C-6'), 128.34 (C-3', C-5'), 127.7 (C-5), 126.9 (C-8), 126.2 (C-6), 125.7 (C-7), 81.8 (**C**≡CH), 70.6 (C≡**C**H), 68.0 (N**C**HPh), 53.6 (C-1), 48.0 (C-3), 29.4 (C-4) ppm.

ESI-MS (*m/z*): 262.2 (100) $[M]^+$

ESI-HRMS: calcd for $[C_{19}H_{202}N]^+$ 262.1596, found 262.1596.

2-(1-(4-Chlorophenyl)but-3-yn-1-yl)-1,2,3,4-tetrahydroisoquinoline (302c)



302c

Following method A, α-aminonitrile **135c** (834 mg, 2.95 mmol), KHMDS (647 mg, 3.24 mmol), propargyl bromide (500 µL, 4.47 mmol, 80 % in toluene), and $NaCNBH_3$ (741 mg, 11.8 mmol) were dissolved in THF (25 mL) in synergy with EtOH (10 mL) and AcOH (500 µL). The title compound (600 mg, 2.03 mmol, 69 %) was obtained as a pale yellow solid after purification by flash column chromatography (Isolera™ Flash Purification System, cyclohexane/EtOAc, gradient 0–10%).

mp: 69.8–70.2°C

$\mathbf{R}_f$ = 0.33 (Cyclohexane/EtOAc, 20:1)

IR (ATR): $\tilde{\nu}$ = 3330, 2918, 2803, 2118, 1591, 1489, 1090, 744 cm^{-1}

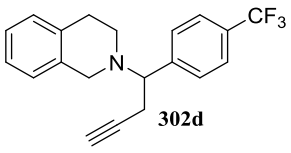
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.38 (d, *J* = 8.5 Hz, 2H, H-2',6'), 7.33 (d, *J* = 8.5 Hz, 2H, H-3',5'), 7.14–7.08 (m, 3H, H-5,6,7), 6.98 (d, *J* = 8.3 Hz, 1H, H-8), 3.79 (d, *J* = 14.7 Hz, 1H, H-1a), 3.66 (dd, *J* = 8.1, 4.7 Hz, 1H, NC**H**Ph), 3.62 (d, *J* = 14.7 Hz, 1H, H-1b), 2.91–2.66 (m, 6H, H-3, H-4, C$\mathbf{H}_2$C≡), 1.94 (t, *J* = 2.7 Hz, 1H, C≡C**H**) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 139.47 (C-1'), 134.7 (C-8a), 134.6 (C-4a), 133.31 (C-4'), 129.70 (C-2', C-6'), 128.8 (C-5), 128.5 (C-3', C-5'), 126.8 (C-8), 126.3 (C-6), 125.8 (C-7), 81.3 (**C**≡CH), 71.0 (C≡**C**H), 67.2 (N**C**HPh), 53.5 (C-1), 48.0 (C-3), 29.3 (C-4) ppm.

ESI-MS (*m/z*): 296.2 (100) $[C_{19}H_{19}{}^{35}ClN]^+$, 298.1 (36) $[C_{19}H_{19}{}^{37}ClN]^+$.

ESI-HRMS: calcd for $[C_{19}H_{19}{}^{35}ClN]^+$ 296.1206, found 296.1216.

2-(1-(4-(Trifluoromethyl)phenyl)but-3-yn-1-yl)-1,2,3,4-tetrahydroisoquinoline (135d)



302d

Following method A, α-aminonitrile **135d** (933 mg, 2.95 mmol), KHMDS (647 mg, 3.24 mmol), propargyl bromide (500 µL, 4.47 mmol, 80 % in toluene), and $NaCNBH_3$ (741 mg, 11.8 mmol) were dissolved in THF (25 mL) in synergy with EtOH (10 mL) and

AcOH (500 µL). The title compound (501 mg, 1.52 mmol, 52%) was obtained as a white solid after purification by flash column chromatography (Isolera™ Flash Purification System, cyclohexane/EtOAc, gradient 0–10%).

mp: 52.5–53.2°C

$\mathbf{R}_f$ = 0.26 (Cyclohexane/EtOAc, 20:1)

IR (ATR): $\tilde{\nu}$ = 3306, 2803, 1618, 1322, 1118, 1067, 742 cm^{-1}

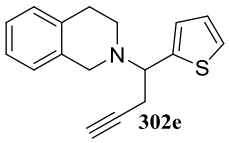
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.62 (d, *J* = 8.4 Hz, 2H, H-3',5'), 7.57 (d, *J* = 8.4 Hz, 2H, H-2',6'), 7.18–7.06 (m, 3H, H-5,6,7), 6.99 (d, *J* = 8.3 Hz, 1H, H-8), 3.83 (d, *J* = 14.6 Hz, 1H, H-1a), 3.74 (dd, *J* = 7.8, 4.8 Hz, 1H, NC**H**Ph), 3.63 (d, *J* = 14.6 Hz, 1H, H-1b), 3.04–2.20 (m, 6H, H-3, H-4, C$\mathbf{H}_2$C≡), 1.95 (t, *J* = 2.7 Hz, 1H, C≡C**H**) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 145.2 (C-1'), 134.6 (C-8a), 134.5 (C-4a), 129.9 (q, *J* = 32.5 Hz, C-4'), 128.8 (C-5), 128.7 (C-2', C-6'), 126.8 (C-8), 126.4 (C-6), 125.7 (C-7), 125.3 (q, *J* = 3.7 Hz, C-3', C-5'), 124.4 (q, *J* = 272.0, **C**F_3), 81.0 (**C**≡CH), 71.3 (C≡**C**H), 67.5 (N**C**HPh), 53.5 (C-1), 48.2 (C-3), 29.3 (C-4) ppm.

ESI-MS (*m/z*): 330.2 (100) $[M + H]^+$

ESI-HRMS: calcd for $[C_{20}H_{19}F_3N]^+$ 330.1470, found 330.1473.

2-(1-(Thiophen-2-yl)but-3-yn-1-yl)-1,2,3,4-tetrahydroisoquinoline (302e)†††



302e

Following method B, compound **302e** was prepared from α-aminonitrile **135h** (600 mg, 2.36 mmol), KHMDS (518 mg, 2.60 mmol), propargyl bromide (400 µL, 3.58 mmol, 80 % in toluene), and $LiAlH_4$ (179 mg, 4.72 mmol) in THF (25 mL). The title compound (75.7 mg, 283 µmol, 12 %) was obtained as a yellow viscous oil after purification by flash column chromatography (Isolera™ Flash Purification System, cyclohexane/EtOAc, gradient 0–5%).

$\mathbf{R}_f$ = 0.20 (Cyclohexane/EtOAc, 20:1)

IR (ATR): $\tilde{\nu}$ = 3289, 2917, 2804, 2118, 1497, 1132, 742, 702 cm^{-1}

††† Compound **302e** was not possible to be obtained by method A.

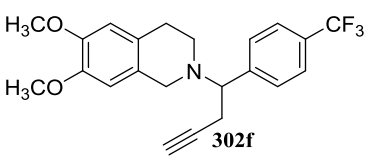
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.26 (dd, *J* = 4.9, 1.3 Hz, 1H, H-5'), 7.13–7.08 (m, 3H, H-5,6,7), 7.09–7.06 (m, 1H, H-8), 7.02–6.98 (m, 1H, H-3',4'), 4.22 (dd, *J* = 8.2, 5.3 Hz, 1H, NC**H**Ph), 3.88 (d, *J* = 14.6 Hz, 1H, H-1a), 3.77 (d, *J* = 14.6 Hz, 1H, H-1b), 2.94–2.73 (m, 6H, H-3, H-4, C$\mathbf{H}_2$C≡), 2.03 (t, *J* = 2.7 Hz, 1H, C≡C**H**) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 144.06 (C-2'), 134.9 (C-8a), 134.6 (C-4a), 128.2 (C-5), 125.7 (C-7), 126.1 (C-6), 125.0(C-5'), 81.7 (**C**≡CH), 70.9 (C≡**C**H), 63.18 (N**C**HPh), 52.5 (C-1), 47.1 (C-3), 29.6 (C-4) ppm.

ESI-MS (*m/z*): 268.1 (100) $[M + H]^+$

ESI-HRMS: calcd for $[C_{17}H_{18}NS]^+$ 268.1160, found 268.1165.

6,7-Dimethoxy-2-(1-(4-(trifluoromethyl)phenyl)but-3-yn-1-yl)-1,2,3,4-tetrahydroisoquinoline (135f)



302f

Following method A, α-aminonitrile **135m** (1.11 g, 2.95 mmol), KHMDS (647 mg, 3.24 mmol), propargyl bromide (500 µL, 4.47 mmol, 80 % in toluene), and $NaCNBH_3$ (741 mg, 11.8 mmol) were dissolved in THF (25 mL) in synergy with EtOH (10 mL) and AcOH (500 µL). The title compound (669 mg, 1.72 mmol, 58%) was obtained as a clear viscous oil after purification by flash column chromatography (Isolera™ Flash Purification System, cyclohexane/EtOAc, gradient 0–28%).

$\mathbf{R}_f$ = 0.44 (Cyclohexane/EtOAc, 3:2)

IR (ATR): $\tilde{\nu}$ = 3298, 2836, 1616, 1518, 1325, 1125, 854 cm^{-1}

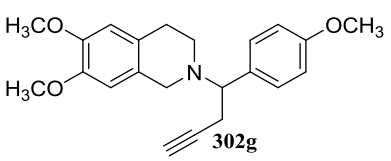
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.62 (d, *J* = 8.3 Hz, 2H, H-3',5'), 7.57 (d, *J* = 8.3 Hz, 2H, H-2',6'), 6.58 (s, 1H, H-5), 6.48 (s, 1H, H-8), 3.84 (s, 3H, C^6-OC$\mathbf{H}_3$), 3.81 (s, 3H, C^7-OC$\mathbf{H}_3$), 3.76–3.70 (m, 2H, H-1a, NC**H**Ph), 3.55 (d, *J* = 14.2 Hz, 1H, H-1b), 2.90–2.65 (m, 6H, H-3, H-4, C$\mathbf{H}_2$C≡), 1.95 (t, *J* = 2.7 Hz, 1H, C≡C**H**) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 147.7 (C-6), 147.4 (C-7), 145.3 (C-1'), 129.9 (q, *J* = 32.0 Hz, C-4'), 128.7 (C-2', C-6'), 126.3 (C-8a), 126.4 (C-4a), 125.3 (q, *J* = 3.7 Hz, C-3', C-5'), 124.0 (q, *J* = 269.7, **C**F_3), 111.4 (C-5), 109.6 (C-8), 80.9 (**C**≡CH), 71.3 (C≡**C**H), 67.4 (N**C**HPh), 56.0 (C^6-O**C**H_3, C^7-O**C**H_3), 53.2 (C-1), 48.3 (C-3), 28.6 (C-4) ppm.

ESI-MS (*m/z*): 390.2 (100) $[M + H]^+$

ESI-HRMS: calcd for $[C_{22}H_{23}F_3NO_2]^+$ 390.1681, found 390.1687.

6,7-Dimethoxy-2-(1-(4-methoxyphenyl)but-3-yn-1-yl)-1,2,3,4-tetrahydroisoquinoline (302g)



302g

Following method A, α-aminonitrile **135j** (998 mg, 2.95 mmol), KHMDS (647 mg, 3.24 mmol), propargyl bromide (500 µL, 4.47 mmol, 80 % in toluene), and $NaCNBH_3$ (741 mg, 11.8 mmol) were dissolved in THF (25 mL) in synergy with EtOH (10 mL) and AcOH (500 µL). The title compound (363 mg, 1.03 mmol, 35 %) was obtained as a pale yellow viscous oil after purification by flash column chromatography (Isolera™ Flash Purification System, cyclohexane/EtOAc, gradient 0–28%).

$\mathbf{R}_f$ = 0.44 (Cyclohexane/EtOAc, 3:2)

IR (ATR): $\tilde{\nu}$ = 3285, 2834, 1610, 1515, 1251, 1127 cm^{-1}

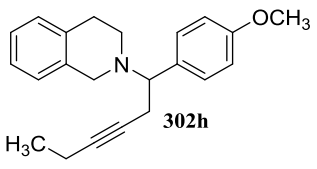
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.334 (d, *J* = 8.7 Hz, 2H, H-2',6'), 6.89 (d, *J* = 8.7 Hz, 2H, H-3',6'), 6.57 (s, 1H, H-5), 6.48 (s, 1H, H-8), 3.83 (s, 3H, C^6-OC**H**$_3$), 3.82 (s, 3H, $C^{4'}$-OC**H**$_3$), 3.81 (s, 3H, C^7-OC**H**$_3$), 3.69 (d, *J* = 14.4 Hz, 1H, H-1a), 3.64 (dd, *J* = 7.8, 3.1 Hz, 1H, NC**H**Ph), 3.54 (d, *J* = 14.4 Hz, 1H, H-1b), 2.92–2.54 (m, 6H, H-3, H-4, C**H**$_2$C≡), 1.94 (t, *J* = 2.6 Hz, 1H, C≡C**H**) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 159.1 (C-4'), 147.6 (C-6), 147.3 (C-7), 132.8 (C-1'), 129.4 (C-2', C-6'), 126.7 (C-8a), 126.4 (C-4a), 113.5 (C-3', C-5'), 111.4 (C-5), 109.7 (C-8), 82.0 (**C**≡CH), 70.6 (C≡**C**H), 67.3 (N**C**HPh), 56.0 (C^6-O**C**H$_3$, C^7-O**C**H$_3$), 55.3 (O**C**H$_3$-4'), 53.2 (C-1), 48.1 (C-3), 28.9 (C-4) ppm.

ESI-MS (*m/z*): 352.3 (100) $[M]^+$

ESI-HRMS: calcd for $[C_{22}H_{26}NO_3]^+$ 352.1913, found 352.1915.

2-(1-(4-Methoxyphenyl)hex-3-yn-1-yl)-1,2,3,4-tetrahydroisoquinoline (302h)



302h

Following method A, α-aminonitrile **135a** (821 mg, 2.95 mmol), KHMDS (647 mg, 3.24 mmol), 1-bromo-2-pentyne (451 µL, 4.42 mmol), and $NaCNBH_3$ (741 mg, 11.8 mmol) were dissolved in THF (25 mL) in synergy with EtOH (10 mL) and AcOH (500 µL). The title compound (494 mg, 1.55 mmol, 52 %) was obtained as a pale yellow oil after

purification by flash column chromatography (Isolera™ Flash Purification System, cyclohexane/EtOAc, gradient 0–7%, 7–16%).

R_f = 0.39 (Cyclohexane/EtOAc, 6:1)

IR (ATR): $\tilde{\nu}$ = 2915, 2118, 1609, 1511, 1246, 1036, 743 cm^{-1}

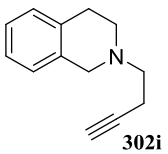
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.33 (d, *J* = 8.6 Hz, 2H, H-2',6'), 7.13–7.04 (m, 3H, H-5,6,7), 6.98 (d, *J* = 8.0 Hz, 1H, H-8), 6.88 (d, *J* = 8.6 Hz, 2H, H-3',6'), 3.82 (s, 3H, $C^{4'}$-OC**H**$_3$), 3.79 (d, *J* = 14.9 Hz, 1H, H-1a), 3.63 (d, *J* = 14.9 Hz, 1H, H-1b), 3.59 (dd, *J* = 8.3, 4.9 Hz, 1H, NC**H**Ph), 2.97–2.55 (m, 6H, H-3, H-4, C**H**$_2$C≡), 2.07 (qt, *J* = 7.5, 2.4 Hz, 2H, C≡C**H$_2$**CH_3), 1.02 (t, *J* = 7.5 Hz, 3H, C≡CH_2C**H$_3$**) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 158.8 (C-4'), 135.2 (C-8a), 134.7 (C-4a), 133.6 (C-1'), 129.4 (C-2', C-6'), 128.7 (C-5), 126.9 (C-8), 126.3 (C-6), 125.6 (C-7), 113.5 (C-3', C-5'), 84.1 (C≡**C**H_2CH_3), 77.0 (**C**≡CH_2CH_3), 67.9 (N**C**HPh), 55.5 (O**C**H_3-4'), 53.7 (C-1), 48.1 (C-3), 29.4 (C-4), 24.1 (C**H$_2$**C≡), 14.3 (C≡CH_2**C**H_3), 12.6 (C≡**C**H_2CH_3)ppm.

ESI-MS (*m/z*): 320.3 (100) $[M]^+$

ESI-HRMS: calcd for $[C_{22}H_{26}NO]^+$ 320.2014, found 320.2020.

2-(But-3-yn-1-yl)-1,2,3,4-tetrahydroisoquinoline (302i)



302i

According to method C, compound **302i** was prepared from 1,2,3,4-tetrahydroisoquinoline (**136**, 393 mg, 2.95 mmol), 4-bromo-1-butyne (304 µL, 3.25 mmol), and K_2CO_3 (448 mg, 3.24 mmol) in MeCN (10 mL). The title compound (444 mg, 2.40 mmol, 81 %) was obtained as a clear viscous oil after purification by flash column chromatography (Isolera™ Flash Purification System, cyclohexane/EtOAc, gradient 0–80%).

R_f = 0.51 (Cyclohexane/EtOAc, 3:2)

IR (ATR): $\tilde{\nu}$ = 3294, 2919, 2806, 2118, 1498, 1134, 1097, 934, 741, 637 cm^{-1}

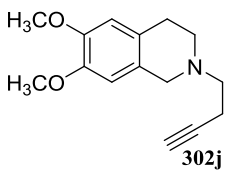
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.16–7.08 (m, 3H, H-5,6,7), 7.05–7.00 (m, 1H, H-8), 3.69 (s, 2H, H-1), 2.91 (pseudo-t, *J* = 5.9 Hz, 2H, H-4), 2.80 (d, *J* = 12.3 Hz, 2H, H-3), 2.79 (d, *J* = 14.8 Hz, 2H, NC**H$_2$**CH_2), 2.50 (td, *J* = 6.8, 2.7 Hz, 2H, NCH_2C**H$_2$**C≡), 2.01 (t, *J* = 2.7 Hz, 1H, C≡C**H**) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 134.6 (C-8a), 134.2 (C-4a), 128.8 (C-5), 126.7 (C-8), 126.3, 125.8 (C-6, C-7), 82.8 (**C**≡CH), 69.3 (C≡**C**H), 56.8 (N**C**H_2CH_2), 55.8 (C-1), 50.8 (C-3), 29.1 (C-4) 17.3 (NCH_2**C**H_2C≡) ppm.

ESI-MS (*m/z*): 186.0 (100) $[M + H]^+$

ESI-HRMS: calcd for $[C_{13}H_{16}N]^+$ 186.1283, found 186.1274.

2-(But-3-yn-1-yl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (302j)



302j

According to method C, compound **302j** was prepared from 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**139**, 570 mg, 2.95 mmol), 4-bromo-1-butyne (304 µL, 3.25 mmol), and K_2CO_3 (448 mg, 3.24 mmol) in MeCN (10 mL). The title compound (500 mg, 2.04 mmol, 69 %) was obtained as a pale yellow solid after purification by flash column chromatography (Isolera™ Flash Purification System, cyclohexane/EtOAc, gradient 0–80%).

mp: 61.2–65.9°C

$\mathbf{R}_f$ = 0.24 (Cyclohexane/EtOAc, 3:2)

IR (ATR): $\tilde{\nu}$ = 3284, 2935, 2834, 2118, 1610, 1517, 1227, 1131 cm^{-1}

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 6.92 (s, 1H, H-5), 6.85 (s, 1H, H-8), 4.17 (s, 3H, C^6-OC**H**$_3$), 4.16 (s, 3H, C^7-OC**H**$_3$), 3.69 (s, 2H, H-1), 3.20–3.13 (m, 2H, NC**H$_2$**CH_2), 3.13–3.07 (m, 4H, H-3,4), 2.83 (td, *J* = 7.6, 2.6 Hz, 2H, NCH_2C**H$_2$**C≡), 2.34 (t, *J* = 2.7 Hz, 1H, C≡C**H**) ppm.

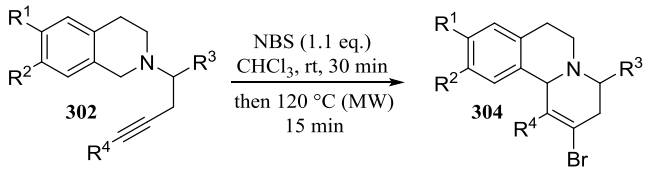
^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 147.7 (C-6), 147.4 (C-7), 126.2 (C-8a), 126.0 (C-4a), 111.4 (C-5), 109.5 (C-8), 82.8 (**C**≡CH), 69.3 (C≡**C**H), 55.7 (C-3), 56.0 (C^6-O**C**H_3, C^7-O**C**H_3), 55.4 (C-1), 50.8 (N**C**H_2CH_2), 28.5 (C-4) 17.3 (NCH_2**C**H_2C≡) ppm.

ESI-MS (*m/z*): 246.1 (100) $[M + H]^+$

ESI-HRMS: calcd for $[C_{15}H_{20}NO_2]^+$ 246.1494, found 246.1500.

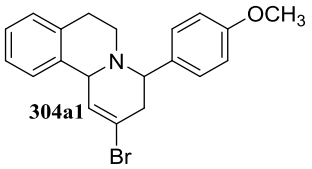
G1 Synthesis of Pyrido[2,1-*a*]isoquinolines 304

General Procedures XIX: One-Pot Oxidative C–H Activation / Aza PRINS Cyclization of Alkynylamines 302



In a microwave vessel and under argon atmosphere, solid *N*-bromosuccinimide (1.1 equiv) was added in one portion to a solution of the corresponding alkynylamine **302** (1.0 eq.) in dry $CHCl_3$. The reaction vessel was purge with argon and sealed with a Teflon septum, and allowed to stir for 30 minutes at room temperature (iminium ion formation, monitored by TLC). After this, the reaction mixture was heated at 120 C under microwave irradiation (200 W) for an indicated time span. Upon completion, the reaction mixture was transferred to a round bottom flask and the solvent was evaporated under reduced pressure. The afforded crude product was then purified by manual or automated flash column chromatography (Isolera™ Flash Purification System) to afford the title compounds.

2-Bromo-4-(4-methoxyphenyl)-3,6,7,11b-tetrahydro-4H-pyrido[2,1-a]isoquinoline (304a1)



Following the general procedure XIX, compound **304a1** was prepared from alkynylamine **302a** (100 mg, 343 μmol) and NBS (68.0 mg, 382 μmol) using $CHCl_3$ (10 mL) as solvent. After 30 minutes of stirring at room temperature, the mixture was then heated up to 120 C for 15 minutes via microwave irradiation. The title compound was obtained as a diastereomeric mixture in *cis/trans*-ratio 60 : 40 (^{1}H NMR of the crude product), which was separated by flash column chromatography (Isolera™ Flash Purification System, cyclohexane/EtOAc, gradient 2–10%). By this manner, 81.0 mg and 30.0 mg of the *cis*- and *trans*-isomers were isolated respectivetly (111 mg, 299 μmol, 88 % overall). The compounds were observed to undergo rapid decomposition when exposed to light and air.

IR (ATR): $\tilde{\nu}$ = 2834, 1641, 1511, 1246, 1147, 1028, 728 cm^{-1}

ESI-MS (*m/z*): 370.1 (99) $[C_{20}H_{21}{}^{79}BrNO]^+$, 372.0 (100) $[C_{20}H_{21}{}^{81}BrNO]^+$.

ESI-HRMS: calcd for $[C_{20}H_{21}{}^{79}BrNO]^+$ 370.0807, found 370.0815.

Cis-isomer (major)

Appereance: viscous yellow oil (turn black upon exposure to air and light!)

$\mathbf{R}_f$ = 0.40 (Cyclohexane/EtOAc, 10:1)

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.37 (d, *J* = 8.5 Hz, 2H, H-2',6'), 7.25–7.15 (m, 3H, H-9,10,11), 7.10 (d, *J* = 7.0 Hz, 1H, H-8), 6.92 (d, *J* = 8.5 Hz, 2H, H-3',6'), 6.43 (br s, 1H, H-1), 4.63 (br s, 1H, H-11b), 4.09 (dd, *J* = 10.7, 3.3 Hz, 1H, H-4), 3.83 (s, 3H, C$^{4'}$-OC**H**$_3$), 3.01–2.84 (m, 1H, H-3a), 2.82–2.74 (m, 3H, H-6a, H-7), 2.70 (dt, *J* = 17.4, 3.3 Hz, 1H, H-3b), 2.41 (br s, 1H, H-6b) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 159.2 (C-4'), 136.0 (C-11a), 135.3 (C-7a), 132.9 (C-1'), 130.4 (C-1), 129.3 (C-8), 128.9 (C-2', C-6'), 126.8, 126.2, 125.9 (C-9, C-10, C-11), 120.1 (C-2), 114.1 (C-3', C-5'), 63.6 (C-4), 63.1 (C-11b), 55.4 (O**C**H$_3$-4'), 41.8 (C-6), 38.5 (C-3), 29.8 (C-7) ppm.

Trans-isomer (minor)

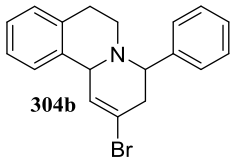
Appereance: viscous light dark oil (turn black upon exposure to air and light!)

$\mathbf{R}_f$ = 0.22 (Cyclohexane/EtOAc, 10:1)

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.35 (d, *J* = 8.4 Hz, 2H, H-2',6'), 7.20–7.11 (m, 3H, H-9,10,11), 7.09 (d, *J* = 8.3 Hz, 1H, H-8), 6.90 (d, *J* = 8.4 Hz, 2H, H-3',6'), 6.47 (dt, *J* = 3.2, 1.5 Hz, 1H, H-1), 4.42 (br s, 1H, H-11b), 4.09 (t, *J* = 5.2 Hz, 1H, H-4), 3.84 (s, 3H, C$^{4'}$-OC**H**$_3$), 3.15–3.05 (m, 1H, H-6a), 2.98–2.79 (m, 4H, H-3, H-6b, H-7a), 2.72 (dt, *J* = 10.7, 4.8 Hz, 1H, H-7b) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 159.2 (C-4'), 136.0 (C-11a), 134.4 (C-7a), 132.1 (C-1'), 130.3 (C-1), 129.3 (C-8, C-2', C-6'), 126.8, 126.6, 126.4 (C-9, C-10, C-11), 119.6 (C-2), 114.0 (C-3', C-5'), 60.0 (C-4), 57.1 (C-11b), 55.4 (O**C**H$_3$-4'), 46.7 (C-6), 38.6 (C-3), 27.0 (C-7) ppm.

2-Bromo-4-phenyl-3,6,7,11b-tetrahydro-4H-pyrido[2,1-a]isoquinoline (304b)



Following the general procedure XIX, compound **304b** was prepared from alkynylamine **302b** (100 mg, 383 μmol) and NBS (74.4 mg, 418 μmol) using $CHCl_3$ (10 mL) as solvent. After 30 minutes of stirring at room temperature, the mixture was then heated up to 120 C for 15 minutes via microwave irradiation. The title compound was obtained as a diastereomeric mixture in *cis/trans*-ratio 60 : 40 (^{1}H NMR of the crude product), which was separated by flash column chromatography (cyclohexane/EtOAc, 50 : 1). By this manner, 57.0 mg and 38.0 mg of the *cis*- and *trans*-isomers were isolated respectivetly (95.0 mg, 279 μmol, 73 % overall). The compounds were observed to undergo rapid decomposition when exposed to light and air.

IR (ATR): $\tilde{\nu}$ = 2921, 2834, 1642, 1490, 1147, 1090, 736, 699 cm^{-1}

ESI-MS (*m/z*): 340.4 (93) $[C_{19}H_{19}{}^{79}BrN]^+$, 341.9 (100) $[C_{19}H_{19}{}^{81}BrN]^+$.

ESI-HRMS: calcd for $[C_{20}H_{21}{}^{79}BrNO]^+$ 340.0701, found 340.0693.

Cis-isomer (major)

Appereance: viscous yellow oil (turn black upon exposure to air and light!)

$\mathbf{R_f}$ = 0.41 (Cyclohexane/EtOAc, 20:1)

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.51 (d, *J* = 7.6 Hz, 2H, H-2',6'), 7.42 (t, *J* = 7.6 Hz, 2H, H-3',5'), 7.38–7.33 (m, 1H, H-4'), 7.25–7.18 (m, 3H, H-9,10,11), 7.13 (d, *J* = 6.9 Hz, 1H, H-8), 6.47 (s, 1H, H-1), 4.71 (br s, 1H, H-11b), 4.19 (br s, 1H, H-4), 3.05–2.99 (m, 1H, H-3a), 2.89–2.69 (m, 4H, H-3b, H-6a, H-7), 2.48 (br s, 1H, H-6b) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 140.6 (C-1'), 135.9 (C-11a), 135.2 (C-7a), 130.4 (C-1), 129.3 (C-8), 128.8 (C-3', C-4', C-5'), 127.8 (C-2', C.-6'), 126.9, 126.3, 126.0 (C-9, C-10, C-11), 119.9 (C-2), 64.1 (C-4), 63.0 (C-11b), 42.0 (C-6), 38.5 (C-3), 29.6 (C-7) ppm.

Trans-isomer (minor)

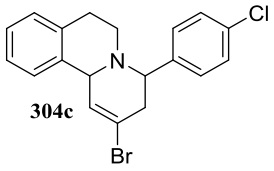
Appereance: viscous brown oil (turn black upon exposure to air and light!)

$\mathbf{R_f}$ = 0.19 (Cyclohexane/EtOAc, 20:1)

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.42 (d, *J* = 7.1 Hz, 2H, H-2',6'), 7.36 (t, *J* = 7.4 Hz, 2H, H-3',5'), 7.35–7.26 (m, 1H, H-4'), 7.25–7.18 (m, 3H, H-9,10,11), 7.13 (d, *J* = 6.9 Hz, 1H, H-8), 6.47 (s, 1H, H-1), 4.71 (br s, 1H, H-11b), 4.19 (br s, 1H, H-4), 3.05–2.99 (m, 1H, H-3a), 2.89–2.69 (m, 4H, H-3b, H-6a, H-7), 2.48 (br s, 1H, H-6b) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 140.3 (C-1'), 135.7 (C-11a), 135.6 (C-7a), 130.5 (C-1), 129.3 (C-8), 128.6, 128.2 (C-3', C-4', C-5'), 127.8 (C-2', C.-6'), 126.9, 126.6, 126.4 (C-9, C-10, C-11), 119.5 (C-2), 61.2 (C-4), 57.1 (C-11b), 46.9 (C-6), 38.5 (C-3), 27.1 (C-7) ppm.

2-Bromo-4-(4-chlorophenyl)-3,6,7,11b-tetrahydro-4H-pyrido[2,1-a]isoquinoline (304c)



304c

Following the general procedure XIX, compound **304c** was prepared from alkynylamine **302b** (100 mg, 338 μmol) and NBS (66.0 mg, 371 μmol) using $CHCl_3$ (10 mL) as solvent. After 30 minutes of stirring at room temperature, the mixture was then heated up to 120 C for 15 minutes via microwave irradiation. The title compound was obtained as a diastereomeric mixture in *cis/trans*-ratio 60 : 40 (^{1}H NMR of the crude product), which was separated by flash column chromatography (Isolera™ Flash Purification System, cyclohexane/EtOAc, gradient 0–5%). By this manner, 59.0 mg and 40.0 mg of the *cis*- and *trans*-isomers were isolated respectivetly (99.0 mg, 264 μmol, 78 % overall). The compounds were observed to undergo rapid decomposition when exposed to light and air.

IR (ATR): $\tilde{\nu}$ = 2921, 2832, 1642, 1490, 1110, 767, 735 cm^{-1}

ESI-MS (*m/z*): 374.4 (68) $[C_{19}H_{19}{}^{79}Br^{35}ClN]^+$, 376.0 (100) $[C_{19}H_{19}{}^{81}Br^{35}ClN]^+$.

ESI-HRMS: calcd for $[C_{19}H_{19}{}^{79}Br^{35}ClN]^+$ 374.0311, found 374.0322.

Cis-isomer (major)

Appereance: viscous yellow oil (turn black upon exposure to air and light!)

$\mathbf{R_f}$ = 0.46 (Cyclohexane/EtOAc, 20:1)

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.41 (d, *J* = 8.5 Hz, 2H, H-2',6'), 7.35 (d, *J* = 8.5 Hz, 2H, H-3',5'), 7.24–7.15 (m, 3H, H-9,10,11), 7.11(d, *J* = 7.1 Hz, 1H, H-8), 6.43 (br s, 1H, H-1),

4.66 (br s, 1H, H-11b), 4.13 (dd, *J* = 10.9, 4.2 Hz,1H, H-4), 2.95–2.82 (m, 1H, H-3a), 2.81–2.66 (m, 4H, H-3b, H-6a, H-7), 2.49–2.32 (m, 4H, H-6b) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 139.5 (C-1'), 135.9 (C-11a), 135.1 (C-7a), 133.5 (C-4'), 130.6 (C-1), 129.3 (C-8), 129.0 (C-2', C-6'), 128.9 (C-3', C-5'), 126.9, 126.3, 126.0 (C-9, C-10, C-11), 119.5 (C-2), 63.2 (C-4), 62.9 (C-11b), 41.6 (C-6), 37.8 (C-3), 29.7 (C-7) ppm.

Trans-isomer (minor)

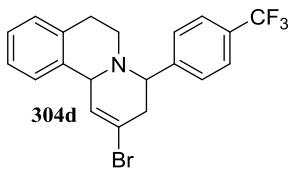
Appereance: viscous brown oil (turn black upon exposure to air and light!)

R_f = 0.22 (Cyclohexane/EtOAc, 20:1)

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.37 (d, *J* = 8.6 Hz, 2H, H-2',6'), 7.33 (d, *J* = 8.8 Hz, 2H, H-3',5'), 7.20–7.11 (m, 3H, H-9,10,11), 7.10 (d, *J* = 8.5 Hz, 1H, H-8), 6.45 (dt, *J* = 3.1, 1.5 Hz, 1H,1H, H-1), 4.32 (br s, 1H, H-11b), 4.11 (t, *J* = 5.0 Hz,1H, H-4), 3.15–3.00 (m, 1H, H-6a), 3.01–2.67 (m, 5H, H-3, H-6b, H-7) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 138.7 (C-1'), 135.7 (C-11a), 134.2 (C-7a), 133.4 (C-4'), 130.7 (C-1), 129.5 (C-2', C-6'), 129.3 (C-8), 128.8 (C-3', C-5'), 126.9, 126.7, 126.4 (C-9, C-10, C-11), 118.9 (C-2), 60.7 (C-4), 56.9 (C-11b), 46.8 (C-6), 37.7 (C-3), 29.3 (C-7) ppm.

2-Bromo-4-(4-(trifluoromethyl)phenyl)-3,6,7,11b-tetrahydro-4H-pyrido[2,1-a]isoquinoline (304d)



304d

Following the general procedure XIX, compound **304d** was prepared from alkynylamine **302d** (100 mg, 304 μmol) and NBS (59.0 mg, 331 μmol) using $CHCl_3$ (10 mL) as solvent. After 30 minutes of stirring at room temperature, the mixture was then heated up to 120 C for 15 minutes via microwave irradiation. The title compound was obtained as a diastereomeric mixture in *cis/trans*-ratio 60 : 40 (^{1}H NMR of the crude product), which was separated by flash column chromatography (cyclohexane/EtOAc, 20 : 1). By this manner, 71.0 mg and 42.0 mg of the *cis*- and *trans*-isomers were isolated respectivetly (114 mg, 279 μmol, 92 % overall). The compounds were observed to undergo rapid decomposition when exposed to light and air.

IR (ATR): $\tilde{\nu}$ = 2921, 2832, 1642, 1322, 1667, 1017, 732 cm^{-1}

ESI-MS (*m/z*): 408.4 (92) $[C_{20}H_{28}{}^{79}BrF_3N]^+$, 409.9 (100) $[C_{20}H_{28}{}^{81}BrF_3N]^+$.

ESI-HRMS: calcd for $[C_{20}H_{28}{}^{79}BrF_3N]^+$ 408.0575, found 408.0577.

Cis-isomer (major)

Appereance: viscous brown oil (turn black upon exposure to air and light!)

$\mathbf{R}_f$ = 0.43 (Cyclohexane/EtOAc, 20:1)

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.65 (d, *J* = 8.4 Hz, 2H, H-3',5'), 7.61 (d, *J* = 8.4 Hz, 2H, H-2',6'), 7.26–7.15 (m, 3H, H-9,10,11), 7.12(d, *J* = 7.1 Hz, 1H, H-8), 6.44 (s, 1H, H-1), 4.71 (br s, 1H, H-11b), 4.23 (d, *J* = 10.9 Hz,1H, H-4), 3.02–2.68 (m, 5H, H-3, H-6a, H-7), 2.41 (br s, 1H, H-6b) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 145.0 (C-1'), 135.7 (C-11a), 135.0 (C-7a), 130.8 (C-1), 130.0 (q, *J* = 33.7 Hz, C-4'),129.3 (C-8), 128.0 (C-2', C-6'), 127.0, 126.4, 126.0 (C-9, C-10, C-11), 125.7 (q, *J* = 3.8 Hz, C-3', C-5'), 124.2 (q, *J* = 272.0, **C**F_3), 119.2 (C-2), 63.4 (C-4), 62.9 (C-11b), 41.8 (C-6), 37.6 (C-3), 29.6 (C-7) ppm.

Trans-isomer (minor)

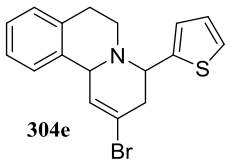
Appereance: viscous dark oil (turn black upon exposure to air and light!)

$\mathbf{R}_f$ = 0.17 (Cyclohexane/EtOAc, 20:1)

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.63 (d, *J* = 8.1 Hz, 2H, H-3',5'), 7.56 (d, *J* = 8.1 Hz, 2H, H-2',6'), 7.21–7.05 (m, 4H, H-8,9,10,11), 6.44 (dt, *J* = 3.4, 1.8 Hz, 1H, H-1), 4.33 (br s, 1H, H-11b), 4.20 (t, *J* = 5.0 Hz,1H, H-4), 3.10 (ddd, *J* = 11.6, 6.5, 4.8 Hz, 1H, H-6a), 3.03–2.71 (m, 5H, H-3, H-6b, H-7) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 144. 4 (C-1'), 135.8 (C-11a), 134.4 (C-7a), 130.9 (C-1), 130.0 (q, *J* = 36.0 Hz, C-4'),129.3 (C-8), 128.5 (C-2', C-6'), 126.9, 126.8, 126.6 (C-9, C-10, C-11), 125.7 (q, *J* = 3.53 Hz, C-3', C-5'), 124.1 (q, *J* = 272.0, **C**F_3), 118.8 (C-2), 61.1 (C-4), 56.9 (C-11b), 47.0 (C-6), 37.4 (C-3), 27.4 (C-7) ppm.

2-Bromo-4-(thiophen-2-yl)-3,6,7,11b-tetrahydro-4H-pyrido[2,1-a]isoquinoline (304e)



304e

Following the general procedure XIX, compound **304e** was prepared from alkynylamine **302e** (63 mg, 236 μmol) and NBS (45.0 mg, 253 μmol) using $CHCl_3$ (7 mL) as solvent. After 30 minutes of stirring at room temperature, the mixture was then heated up to 120 C for 15 minutes via microwave irradiation. The title compound was obtained as a diastereomeric mixture in *cis/trans*-ratio 60 : 40 (^{1}H NMR of the crude product), which was separated by flash column chromatography (cyclohexane/EtOAc, 30 : 1). By this manner, 47.0 mg and 21.0 mg of the *cis*- and *trans*-isomers were isolated respectivetly (68 mg, 279 μmol, 92 % overall). The compounds were observed to undergo rapid decomposition when exposed to light and air.

IR (ATR): $\tilde{\nu}$ = 2921, 2834, 1639, 1493, 1020, 768, 741, 702 cm^{-1}

ESI-MS (*m/z*): 346.7 (67) $[C_{17}H_{17}{}^{79}BrN^{32}S]^+$, 348.1 (100) $[C_{17}H_{17}{}^{81}BrN^{34}S]^+$.

ESI-HRMS: calcd for $[C_{17}H_{17}{}^{79}BrN^{32}S]^+$ 346.0265, found 346.0274.

Cis-isomer (major)

Appereance: viscous yellow oil (turn brown upon exposure to air and light!)

$\mathbf{R}_f$ = 0.34 (Cyclohexane/EtOAc, 30:1)

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.36–7.32 (m, 1H, H-5'), 7.29–7.15 (m, 3H, H-9,10,11), 7.17–7.10 (m, 1H, H-8), 7.06–6.99 (m, 2H, H-3', 5'), 6.33 (dd, *J* = 3.29, 1.80 Hz, 1H, H-1), 4.85 (br s, 1H, H-11b), 4.55 (dd, *J* = 10.5, 4.1 Hz, 1H, H-4), 3.03–2.89 (m, 2H, H-3a, H-7a), 2.84 (dddd, *J* = 17.3, 4.6, 3.1, 1.3 Hz, 1H, H-3b), 2.81–2.66 (m, 3H, H-7b, H-6) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 141.5 (C-1'), 136.0 (C-11a), 135.4 (C-7a), 131.4 (C-1), 129.2 (C-8), 126.9, 126.6, 126.4 (C-9, C-10, C-11, C-3', C-4'), 125.6 (C-5'), 118.5 (C-2), 62.1 (C-11b), 59.6 (C-4), 39.2 (C-6), 35.9 (C-3), 29.8 (C-7) ppm.

Trans-isomer (minor)

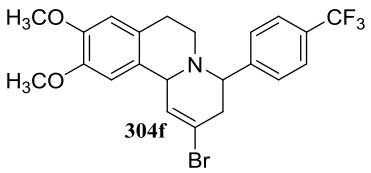
Appereance: viscous brown oil (turn black upon exposure to air and light!)

$\mathbf{R}_f$ = 0.19 (Cyclohexane/EtOAc, 30:1)

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.28 (dd, *J* = 5.1, 1.20 Hz, 1H, H-5'), 7.21–7.07 (m, 4H, H-8, 9, 10, 11), 7.04 (d, *J* = 3.3 Hz, 1H, H-3'), 6.99 (dd, *J* = 5.1, 3.3 Hz, 1H, H-4'), 6.39 (td, *J* = 2.4, 1.30 Hz, 1H, H-1), 4.46 (dd, , *J* = 6.0, 2.4 Hz, 1H, H-4), 4.41 (br s, 1H, H-11b), 3.17–2.79 (m, 6H, H-3, H-6, 7) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 143.4 (C-1'), 135.8 (C-11a), 134.6 (C-7a), 130.6 (C-1), 129.3 (C-8), 126.6, 126.5, 126.4, 126.3 (C-9, C-10, C-11, C-4'), 125.5 (C-3'), 125.4 (C-5'), 118.5 (C-2), 58.8 (C-4), 56.3 (C-11b), 47.2 (C-6), 37.7 (C-3), 28.9 (C-7) ppm.

2-Bromo-9,10-dimethoxy-4-(4-(trifluoromethyl)phenyl)-3,6,7,11b-tetrahydro-4H-pyrido[2,1-a]isoquinoline (304f)



304f

Following the general procedure XIX, compound **304f** was prepared from alkynylamine **302f** (100 mg, 257 μmol) and NBS (50.3 mg, 283 μmol) using $CHCl_3$ (10 mL) as solvent. After 30 minutes of stirring at room temperature, the mixture was then heated up to 120 C for 15 minutes via microwave irradiation. The title compound was obtained as a diastereomeric mixture in *cis/trans*-ratio 60 : 40 (^{1}H NMR of the crude product), which was separated by flash column chromatography (cyclohexane/EtOAc, 6 : 1). By this manner, 22.0 mg and 10.0 mg of the *cis*- and *trans*-isomers were isolated respectivetly. The *trans*-isomer was not considered for the calculation of the overall yield as it contained impurities (22.0 mg, 279 μmol, 92 % overall). The compounds were observed to undergo rapid decomposition when exposed to light and air.

IR (ATR): $\tilde{\nu}$ = 2935, 2835, 1640, 1515, 1323, 1067, 730 cm^{-1}

ESI-MS (*m/z*): 468.4 (91) $[C_{22}H_{22}{}^{79}BrF_3NO_2]^+$, 470.0 (100) $[C_{22}H_{22}{}^{81}BrF_3NO_2]^+$.

ESI-HRMS: calcd for $[C_{20}H_{28}{}^{79}BrF_3N]^+$ 468.0786, found 468.0779.

Cis-isomer (major)

Appereance: viscous brown oil (turn black upon exposure to air and light!)

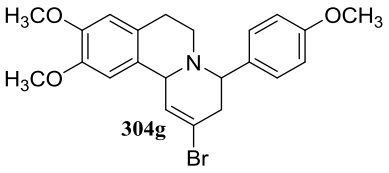
$\mathbf{R_f}$ = 0.22 (Cyclohexane/EtOAc, 6:1)

Cis-isomer (major)

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.65 (s, 4H, H-2', 3', 5', 6'), 6.68 (s, 1H, H-11), 6.59 (s, 1H, H-8), 6.38 (br s, 1H, H-1), 4.72 (br s, 1H, H-11b), 4.31 (br s, 1H, H-4), 3.90 (s, 3H, C^{9}-OC**H**$_3$), 3.85 (s, 3H, C^{10}-OC**H**$_3$), 3.06–2.37 (m, 6H, H-3, 6, 7) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 148.3, 148.0 (C-10, C-9), 145.0 (C-1'), 130.6 (C-1), 130.0 (C-4'), 128.2 (C-2', C-6'), 127.2 (C-11a), 127.0 (C-7a), 125.8 (q, J = 3.51 Hz, C-3', C-5'), 124.2 (q, J = 272.2 Hz, **C**F_3-4'), 119.0 (C-2), 111.7 (C-8), 109.0 (C-11), 63.2 (C-4), 62.3 (C-11b), 56.3, 56.1 (C^{10}-O**C**H_3, C^{19}-O**C**H_3), 41.4 (C-6), 37.1 (C-3), 29.3 (C-7) ppm.

2-Bromo-9,10-dimethoxy-4-(4-methoxyphenyl)-3,6,7,11b-tetrahydro-4H-pyrido[2,1-a]isoquinoline (304g)



304g

Following the general procedure XIX, compound **304g** was prepared from alkynylamine **302g** (100 mg, 284 μmol) and NBS (55.7 mg, 313 μmol) using $CHCl_3$ (10 mL) as solvent. After 30 minutes of stirring at room temperature, the mixture was then heated up to 120 C for 30 minutes via microwave irradiation. The title compound was obtained as a diastereomeric mixture in *cis/trans*-ratio 60 : 40 (^{1}H NMR of the crude product), which was separated by flash column chromatography (cyclohexane/EtOAc, 3 : 1). By this manner, 41.0 mg and 23.0 mg of the *cis*- and *trans*-isomers were isolated respectivetly (64 mg, 149 μmol, 52 % overall). The compounds were observed to undergo rapid decomposition when exposed to light and air.

IR (ATR): $\tilde{\nu}$ = 2834, 1641, 1511, 1246, 1147, 1028, 728 cm^{-1}

ESI-MS (*m/z*): 430.5 (90) $[C_{22}H_{25}{}^{79}BrNO_3]^+$, 432.0 (100) $[C_{22}H_{25}{}^{81}BrNO_3]^+$.

ESI-HRMS: calcd for $[C_{22}H_{25}{}^{79}BrNO_3]^+$ 430.1018, found 430.1026.

Cis-isomer (major)

Appereance: viscous yellow oil (turn black upon exposure to air and light!)

$\mathbf{R}_f$ = 0.20 (Cyclohexane/EtOAc, 3:1)

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.40 (br s, 2H, H-2', 6'), 6.92 (d, J = 8.7 Hz, 2H, H-3', 5'), 6.68 (s, 1H, H-11), 6.57 (s, 1H, H-8), 6.37 (br s, 1H, H-1), 4.64 (br s, 1H, H-11b), 4.16 (br

s, 1H, H-4), 3.91 (s, 3H, C^9-OC**H**$_3$), 3.86 (s, 3H, C^{10}-OC**H**$_3$), 3.85 (s, 3H, $C^{4'}$-OC**H**$_3$), 3.08–2.32 (m, 6H, H-3, 6, 7) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 159.4 (C-4'), 148.0, 147.7 (C-9, C-10), 132.6 (C-1'), 130.2 (C-1), 128.9 (C-2', C-6'), 127.6 (C-11a), 127.2 (C-7a), 119.8 (C-2), 114.0 (C-3', C-5'), 111.5 (C-8), 108.8 (C-11), 63.3 (C-4), 62.5 (C-11b), 56.1, 55.9 (C^9-O**C**H$_3$, C^{10}-O**C**H$_3$)), 55.3 ($C^{4'}$-O**C**H$_3$), 41.4 (C-6), 37.9 (C-3), 29.3 (C-7) ppm.

Trans-isomer (minor)

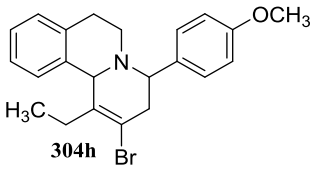
Appereance: viscous yellow oil (turn black upon exposure to air and light!)

R$_f$ = 0.09 (Cyclohexane/EtOAc, 3:1)

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.37 (d, *J* = 8.2 Hz, 2H, H-2', 6'), 6.90 (d, *J* = 8.2 Hz, 2H, H-3', 5'), 6.58, 6.57 (s, 2H, H-11, H-8), 6.43 (dt, *J* = 3.4, 1.7, Hz, 1H, H-1), 4.37 (br s, 1H, H-11b), 4.10 (t, *J* = 5.3 Hz, 1H, H-4), 3.84 (s, 6H, C^9-OC**H**$_3$, C^{10}-OC**H**$_3$), 3.81 (s, 3H, $C^{4'}$-OC**H**$_3$), 3.09 (dt, *J* = 11.1, 5.3 Hz, 1H, H-6b), 2.99–2.72 (m, 4H, H-3, H-6a, H-7b), 2.66 (dt, *J* = 16.3, 5.6 Hz, 1H, H-7b)ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 159.3 (C-4'), 148.0, 147.9 (C-9, C-10), 132.8 (C-1'), 130.0 (C-1), 129.4 (C-2', C-6'), 127.4 (C-11a), 127.3 (C-7a), 119.6 (C-2), 114.1 (C-3', C-5'), 111.7 (C-8), 109.6 (C-11), 60.7 (C-4), 56.8 (C-11b), 56.2, 56.0 (C^9-O**C**H$_3$, C^{10}-O**C**H$_3$), 55.4 ($C^{4'}$-O**C**H$_3$), 46.8 (C-6), 38.4 (C-3), 29.5 (C-7) ppm.

2-Bromo-1-ethyl-4-(4-methoxyphenyl)-3,6,7,11b-tetrahydro-4H-pyrido[2,1-a]isoquinoline (304h)



304h

Following the general procedure XIX, compound **304h** was prepared from alkynylamine **302h** (100 mg, 313 μmol) and NBS (61.3 mg, 344 μmol) using $CHCl_3$ (10 mL) as solvent. After 30 minutes of stirring at room temperature, the mixture was then heated up to 120 C for 15 minutes via microwave irradiation. The title compound was obtained as a diastereomeric mixture in *cis/trans*-ratio 60 : 40 (^{1}H NMR of the crude product), which was separated by flash column chromatography (cyclohexane/EtOAc, 20 : 1). By this manner, 50.0 mg and 30.0 mg of the *cis*- and *trans*-isomers were isolated respectivetly. The *trans*-isomer was not considered for the calculation of the overall yield as it contained impurities (50.0 mg,

126 μmol, 40 % overall). The compounds were observed to undergo rapid decomposition when exposed to light and air.

IR (ATR): $\tilde{\nu}$ = 2964, 2835, 1638, 1511, 1138, 745 cm^{-1}

ESI-MS (*m/z*): 398.5 (95) $[C_{22}H_{25}{}^{79}BrNO]^+$, 400.0 (100) $[C_{22}H_{25}{}^{81}BrNO]^+$.

ESI-HRMS: calcd for $[C_{22}H_{25}{}^{79}BrNO]^+$ 398.1120, found 398.1108.

Cis-isomer (major)

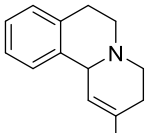
Appereance: viscous yellow oil (turn black upon exposure to air and light!)

$\mathbf{R}_f$ = 0.34 (Cyclohexane/EtOAc, 20:1)

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.42 (d, *J* = 8.8 Hz, 2H, H-2', 6'), 7.27–7.12 (m, 3H, H-9, 10, 11), 7.10 (dd, *J* = 7.4, 1.7 Hz, 1H, H-8), 6.89 (d, *J* = 8.8 Hz, 2H, H-3', 5'), 4.94 (br s, 1H, H-11b), 4.45 (dd, *J* = 10.9, 3.4 Hz, 1H, H-4), 3.81 (s, 3H, $C^{4'}$-OC**H**$_3$), 3.16–3.04 (m, 1H, H-3a), 2.95–2.56 (m, 5H, H-3b, H-6, H-7), 2.32 (q, *J* = 7.4 Hz, 2H, C**H**$_2$$CH_3$), 0.65 (t, *J* = 7.4 Hz, 3H, CH_2C**H**$_3$) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 159.0 (C-4'), 138.2 (C-1), 135.8 (C-7a), 135.1 (C-11a), 131.8 (C-1'), 129.1 (C-8), 128.7 (C-2', C-6'), 129.3, 127.4, 125.2 (C-9, C-10, C-11), 118.1 (C-2), 113.9 (C-3', C-5'), 64.7 (C-11b), 61.2 (C-4), 55.4 ($C^{4'}$-O**C**H_3), 37.8 (C-6), 36.4 (C-3), 29.0 (C-7), 26.9 (**C**H_2CH_3), 12.1 (CH_2**C**H_3) ppm.

2-Bromo-3,6,7,11b-tetrahydro-4H-pyrido[2,1-a]isoquinoline (304i)



304i

Following the general procedure XIX, compound **304i** was prepared from alkynylamine **302i** (100 mg, 540 μmol) and NBS (107 mg, 601 μmol) using $CHCl_3$ (10 mL) as solvent. After 30 minutes of stirring at room temperature, the mixture was then heated up to 120 C for 15 minutes via microwave irradiation. The title compound (110 mg, 416 μmol, 77 %) was obtained as a yellow oil after purification by flash column chromatography (cyclohexane/EtOAc, 3:1). The compound was observed to undergo rapid decomposition when exposed to light and air.

$\mathbf{R}_f$ = 0.29 (Cyclohexane/EtOAc, 3:2)

IR (ATR): $\tilde{\nu}$ = 2922, 1640, 736 cm^{-1}

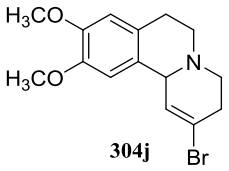
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.24–7.13 (m, 3H, H-9, 10, 11), 7.14–7.08 (m, 1H, H-8), 6.38 (br s, 1H, H-1), 4.39 (br s, 1H, H-11b), 3.19–2.70 (m, 7H, H-3a, H-4, H-6, H-7), 2.48–2.39 (m, 1H, H-3b) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 135.3 (C-11a), 134.1 (C-7a), 129.9 (C-1), 129.2 (C-8), 126.8, 126.3, 125.7 (C-9, C-10, C-11), 120.5 (C-2), 60.9 (C-11b), 51.9, 48.1 (C-4, C-6), 32.9 (C-3) 28.7 (C-7) ppm.

ESI-MS (*m/z*): 264.4 (92) $[C_{13}H_{15}{}^{79}BrN]^+$, 266.0 (100) $[C_{13}H_{15}{}^{81}BrN]^+$.

ESI-HRMS: calcd for $[C_{13}H_{15}{}^{79}BrN]^+$ 264.0388, found 264.0381.

2-Bromo-9,10-dimethoxy-3,6,7,11b-tetrahydro-4H-pyrido[2,1-a]isoquinoline (304j)



304j

Following the general procedure XIX, compound **304i** was prepared from alkynylamine **302i** (100 mg, 408 μmol) and NBS (80.0 mg, 494 μmol) using $CHCl_3$ (10 mL) as solvent. After 30 minutes of stirring at room temperature, the mixture was then heated up to 120 C for 30 minutes via microwave irradiation. The title compound (50 mg, 154 μmol, 38 %) was obtained as a yellow oil after purification by flash column chromatography (100 % EtOAc). The compound was observed to undergo rapid decomposition when exposed to light and air.

$\mathbf{R}_f$ = 0.22 (Cyclohexane/EtOAc, 3:2)

IR (ATR): $\tilde{\nu}$ = 2922, 1640, 736 cm^{-1}

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.24–7.13 (m, 3H, H-9, 10, 11), 7.14–7.08 (m, 1H, H-8), 6.38 (br s, 1H, H-1), 4.39 (br s, 1H, H-11b), 3.19–2.70 (m, 7H, H-3a, H-4, H-6, H-7), 2.48–2.39 (m, 1H, H-3b) ppm.

^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 135.3 (C-11a), 134.1 (C-7a), 129.9 (C-1), 129.2 (C-8), 126.8, 126.3, 125.7 (C-9, C-10, C-11), 120.5 (C-2), 60.9 (C-11b), 51.9, 48.1 (C-4, C-6), 32.9 (C-3) 28.7 (C-7) ppm.

ESI-MS (*m/z*): 324.4 (92) $[C_{15}H_{19}{}^{79}BrNO_2]^+$, 326.0 (100) $[C_{15}H_{19}{}^{81}BrNO_2]^+$.

ESI-HRMS: calcd for $[C_{15}H_{19}{}^{79}BrNO_2]^+$ 324.0599, found 324.0588.

References

[1] STRECKER, A. *Liebigs Ann.* **1850**, *75*, 27–45.

[2] STRECKER, A. *Liebigs Ann.* **1854**, *91*, 349–351.

[3] STRECKER, A. *Philos. Mag.* **1854**, *8*, 326–327.

[4] SIGEL, O.; ERLENMEYER, E. *Liebigs Ann.* **1875**, *177*, 111–144.

[5] PASSAVANT, S. C.; ERLENMEYER, E. *Liebigs Ann.* **1880**, *200*, 120–138.

[6] LEGRAS, J. L.; CHUZEL, G.; ARNAUD, A.; GALZY, P. *World J. Microbiol. Biotechnol.* **1990**, *6*, 83–108.

[7] F. FLEMING, F. *Nat. Prod. Rep.* **1999**, *16*, 597–606.

[8] DANIELI, B.; PALMISANO, G.; GABETTA, B.; MARTINELLI, E. M. *J. Chem. Soc., Perkin Trans. 1* **1980**, 601–606.

[9] KAM, T.-S.; YOGANATHAN, K. *Phytochemistry* **1997**, *46*, 785–787.

[10] ARAI, T.; TAKAHASHI, K.; KUBO, A. *J. Antibiot.* **1977**, *30*, 1015–1018.

[11] ARAI, T.; TAKAHASHI, K.; NAKAHARA, S.; KUBO, A. *Experientia* **1980**, *36*, 1025–1027.

[12] ISHIGURO, K.; SAKIYAMA, S.; TAKAHASHI, K.; ARAI, T. *Biochemistry* **1978**, *17*, 2545–2550.

[13] CUEVAS, C.; FRANCESCH, A. *Nat. Prod. Rep.* **2009**, *26*, 322–337.

[14] HAYASHI, T.; NOTO, T.; NAWATA, Y.; OKAZAKI, H.; SAWADA, M.; ANDO, K. *J. Antibiot.* **1982**, *35*, 771–777.

[15] HIDA, T.; MUROI, M.; TANIDA, S.; HARADA, S. *J. Antibiot.* **1994**, *47*, 917–921.

[16] FLEMING, F. F.; YAO, L.; RAVIKUMAR, P. C.; FUNK, L.; SHOOK, B. C. *J. Med. Chem.* **2010**, *53*, 7902–7917.

[17] HE, H.; TRAN, P.; YIN, H.; SMITH, H.; BATARD, Y.; WANG, L.; EINOLF, H.; GU, H.; MANGOLD, J. B.; FISCHER, V.; HOWARD, D. *Drug Metab. Dispos.* **2009**, *37*, 536–544.

[18] DHILLON, S.; WEBER, J. *Drugs* **2009**, *69*, 2103–2114.

[19] DEACON, C. F.; HOLST, J. J. *Adv. Ther.* **2009**, *26*, 488–499.

[20] WILLAND, N.; JOOSSENS, J.; GESQUIÈRE, J.-C.; TARTAR, A. L.; EVANS, D. M.; ROE, M. B. *Tetrahedron* **2002**, *58*, 5741–5746.

[21] DENG, G.; YE, D.; LI, Y.; HE, L.; ZHOU, Y.; WANG, J.; LI, J.; JIANG, H.; LIU, H. *Tetrahedron* **2008**, *64*, 10512–10516.

[22] KLOSA, J. *J. Prakt. Chem.* **1963**, *20*, 275–278.

[23] HARRIS, L. S. *Drug Alcohol Depend.* **1986**, *17*, 107–118.

[24] GAUTHIER, J. Y.; CHAURET, N.; CROMLISH, W.; DESMARAIS, S.; DUONG, L. T.; FALGUEYRET, J.-P.; KIMMEL, D. B.; LAMONTAGNE, S.; LÉGER, S.; LERICHE, T.; LI, C. S.; MASSÉ, F.; MCKAY, D. J.; NICOLL-GRIFFITH, D. A.; OBALLA, R. M.; PALMER, J. T.; PERCIVAL, M. D.; RIENDEAU, D.; ROBICHAUD, J.; RODAN, G. A.; RODAN, S. B.; SETO, C.; THÉRIEN, M.; TRUONG, V.-L.; VENUTI, M. C.; WESOLOWSKI, G.; YOUNG, R. N.; ZAMBONI, R.; BLACK, W. C. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 923–928.

[25] YU, M. S.; VASILIY, A. B.; VLADIMIR, S. M. *Russ. Chem. Rev.* **1989**, *58*, 148–162.

[26] KURTI, L.; CZAKO, B. In *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier Science: **2005**, 446–447.

[27] NORTH, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4126–4128.

[28] BARTON, D. H. R.; BILLION, A.; BOIVIN, J. *Tetrahedron Lett.* **1985**, *26*, 1229–1232.

[29] MURAHASHI, S.-I.; KOMIYA, N.; TERAI, H.; NAKAE, T. *J. Am. Chem. Soc.* **2003**, *125*, 15312–15313.

[30] MURAHASHI, S.-I.; NAKAE, T.; TERAI, H.; KOMIYA, N. *J. Am. Chem. Soc.* **2008**, *130*, 11005–11012.

[31] CHEN, B.; WANG, L.; GAO, S. *ACS Catalysis* **2015**, *5*, 5851–5876.

[32] WAGNER, A.; OFIAL, A. R. *J. Org. Chem.* **2015**, *80*, 2848–2854.

[33] NAUTH, A. M.; OTTO, N.; OPATZ, T. *Adv. Synth. Catal.* **2015**, *357*, 3424–3428.

[34] SINGHAL, S.; JAIN, S. L.; SAIN, B. *Adv. Synth. Catal.* **2010**, *352*, 1338–1344.

[35] SINGHAL, S.; JAIN, S. L.; SAIN, B. *Chem. Commun.* **2009**, 2371–2372.

[36] WAGNER, A.; HAN, W.; MAYER, P.; OFIAL, A. R. *Adv. Synth. Catal.* **2013**, *355*, 3058–3070.

[37] ZHANG, Y.; PENG, H.; ZHANG, M.; CHENG, Y.; ZHU, C. *Chem. Commun.* **2011**, *47*, 2354–2356.

[38] SHU, X.-Z.; XIA, X.-F.; YANG, Y.-F.; JI, K.-G.; LIU, X.-Y.; LIANG, Y.-M. *J. Org. Chem.* **2009**, *74*, 7464–7469.

[39] TAJIMA, T.; NAKAJIMA, A. *J. Am. Chem. Soc.* **2008**, *130*, 10496–10497.

[40] ALLEN, J. M.; LAMBERT, T. H. *J. Am. Chem. Soc.* **2011**, *133*, 1260–1262.

[41] MA, L.; CHEN, W.; SEIDEL, D. *J. Am. Chem. Soc.* **2012**, *134*, 15305–15308.

[42] SEVERIN, R.; DOYE, S. *Chem. Soc. Rev.* **2007**, *36*, 1407–1420.

[43] LEE, A. V.; SCHAFER, L. L. *Synlett* **2006**, *2006*, 2973–2976.

[44] HAMACHI, Y.; KATANO, M.; OGIWARA, Y.; SAKAI, N. *Org. Lett.* **2016**, *18*, 1634–1637.

[45] OPATZ, T. *Synthesis* **2009**, *2009*, 1941–1959.

[46] ENDERS, D.; SHILVOCK, J. P. *Chem. Soc. Rev.* **2000**, *29*, 359–373.

[47] OTTO, N.; OPATZ, T. *Chem. Eur. J.* **2014**, *20*, 13064–13077.

[48] CAI, X.-H.; XIE, B. *ARKIVOC* **2014**, *1*, 205–248.

[49] FREIFELDER, M.; HASBROUCK, R. B. *J. Am. Chem. Soc.* **1960**, *82*, 696–698.

[50] RAJAGOPALAN, P.; ADVANI, B. G. *Tetrahedron Lett.* **1965**, *6*, 2197–2200.

[51] MATTALIA, J.-M.; MARCHI-DELAPIERRE, C.; HAZIMEH, H.; CHANON, M. *ARKIVOC* **2006**, 90–118.

[52] BRUYLANTS, P. *Bull. Soc. Chim. de Belg* **1924**, *33*, 467–478.

[53] BRUCKNER, R. In *Organic Mechanisms: Reactions, Stereochemistry and Synthesis*; Harmata, M., Ed.; Springer Berlin-Heidelberg: Germany, **2010**, 595–642.

[54] CLARK, J. S. *Nitrogen, Oxygen, and Sulfur Ylide Chemistry: A Practical Approach in Chemistry*; Oxford University Press: United States, **2002**.

[55] SWEENEY, J. B. *Chem. Soc. Rev.* **2009**, *38*, 1027–1038.

[56] AGGARWAL, V. K.; HARVEY, J. N.; ROBIETTE, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 5468–5471.

[57] PINE, S. H. In *Organic Reactions*; John Wiley & Sons, Inc.: **2004**; Vol. *18*, 403–452.

[58] ALBRIGHT, J. D. *Tetrahedron* **1983**, *39*, 3207–3233.

[59] LAHM, G.; OREJARENA PACHECO, J. C.; OPATZ, T. *Synthesis* **2014**, *46*, 2413–2421.

[60] CLAYDEN, J.; DONNARD, M.; LEFRANC, J.; TETLOW, D. J. *Chem. Commun.* **2011**, *47*, 4624–4639.

[61] WANG, Z. In *Comprehensive Organic Name Reactions and Reagents*; John Wiley & Sons, Inc.: **2010**; Vol. *3*, 2668–2672.

[62] VEDEJS, E.; WEST, F. G. *Chem. Rev.* **1986**, *86*, 941–955.

[63] NIKOLAEV, V. A.; KOROBITSYNA, I. *Zh. Vses Khim. Ova.* **1979**, *24*, 496–505.

[64] WOODWARD, R. B.; HOFFMANN, R. *J. Am. Chem. Soc.* **1965**, *87*, 2511–2513.

[65] GHIGO, G.; CAGNINA, S.; MARANZANA, A.; TONACHINI, G. *J. Org. Chem.* **2010**, *75*, 3608–3617.

[66] OLLIS, W. D.; REY, M.; SUTHERLAND, I. O.; CLOSS, G. L. *J. Chem. Soc., Chem. Commun.* **1975**, 543–545.

[67] PATON, J. M.; PAUSON, P. L.; STEVENS, T. S. *J. Chem. Soc. C* **1969**, 2130–2131.

[68] TOMIOKA, H.; SUZUKI, K. *Tetrahedron Lett.* **1989**, *30*, 6353–6356.

[69] LIU, Y.; LIANG, X. *Chin. Chem. Lett.* **2001**, *12*, 7–10.

[70] LAHM, G.; STOYE, A.; OPATZ, T. *J. Org. Chem.* **2012**, *77*, 6620–6623.

[71] MILLARD, B. J.; STEVENS, T. S. *J. Chem. Soc. (Resumed)* **1963**, 3397–3403.

[72] MAGESWARAN, S.; OLLIS, W. D.; SUTHERLAND, I. O. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1953–1962.

[73] RAUTENSTRAUCH, V. *Helv. Chim. Acta* **1972**, *55*, 2233–2241.

[74] MANDER, L. N.; TURNER, J. V. *J. Org. Chem.* **1973**, *38*, 2915–2916.

[75] MANDER, L.; TURNER, J.; COOMBE, B. *Aust. J. Chem.* **1974**, *27*, 1985–2000.

[76] COSSEY, A.; MANDER, L.; TURNER, J. *Aust. J. Chem.* **1980**, *33*, 2061–2069.

[77] MANDER, L. N.; TURNER, J. V.; TWITCHIN, B. *Tetrahedron Lett.* **1981**, *22*, 3017–3020.

[78] BUCHI, G.; WUEST, H. *J. Am. Chem. Soc.* **1974**, *96*, 7573–7574.

[79] KAMETANI, T.; SUZUKI, T.; SATO, E.; NISHIMURA, M.; UNNO, K. *J. Chem. Soc., Chem. Commun.* **1982**, 1201–1203.

[80] STELLA, L. *Tetrahedron Lett.* **1984**, *25*, 3457–3458.

[81] STELLA, L.; AMROLLAH-MADJDABADI, A. *Synth. Commun.* **1984**, *14*, 1141–1147.

[82] AMROLLAH-MADJDABADI, A.; STELLA, L. *Bull. Soc. Chim. Fr.* **1987**, 350–354.

[83] SOMMELET, M. *CR Acad. Sci., Paris* **1937**, *205*, 56–58.

[84] KANTOR, S. W.; HAUSER, C. R. *J. Am. Chem. Soc.* **1951**, *73*, 4122–4131.

[85] WANG, Z. In *Comprehensive Organic Name Reactions and Reagents*; John Wiley & Sons, Inc.: **2010**; Vol. *3*, 2620–2624.

[86] SANDERS, E. B.; SECOR, H. V.; SEEMAN, J. I. *J. Org. Chem.* **1976**, *41*, 2658–2659.

[87] SANDERS, E. B.; SECOR, H. V.; SEEMAN, J. I. *J. Org. Chem.* **1978**, *43*, 324–330.

[88] WEINREB, S. M.; BASHA, F. Z.; HIBINO, S.; KHATRI, N. A.; KIM, D.; PYE, W. E.; WU, T. T. *J. Am. Chem. Soc.* **1982**, *104*, 536–544.

[89] KLUNDER, J. M. *J. Heterocycl. Chem.* **1995**, *32*, 1687–1691.

[90] JOŃCZYK, A.; LIPIAK, D.; SIENKIEWICZ, K. *Synlett* **1991**, *1991*, 493–496.

[91] JOŃCZYK, A.; LIPIAK, D. *J. Org. Chem.* **1991**, *56*, 6933–6937.

[92] ZDROJEWSKI, T.; JOŃCZYK, A. *Tetrahedron Lett.* **1995**, *36*, 1355–1358.

[93] JOŃCZYK, A.; ZDROJEWSKI, T.; GRZYWACA, P.; BALCERZAK, P. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2919–2923.

[94] ZDROJEWSKI, T.; JOŃCZYK, A. *J. Org. Chem.* **1998**, *63*, 452–457.

[95] SOLDATENKOV, A. T.; SOLDATOVA, S. A.; SULEIMANOV, R. R.; KOLYADINA, N. M.; KHRUSTALEV, V. N. *Chem. Heterocycl. Compd. (N. Y., NY, U. S.)* **2010**, *46*, 245–247.

[96] SOLDATENKOV, A. T.; SOLDATOVA, S. A.; MAMYRBEKOVA-BEKRO, J. A.; GIMRANOVA, G. S.; MALKOVA, A. V.; POLYANSKII, K. B.; KOLYADINA, N. M.; KHRUSTALEV, V. N. *Chem. Heterocycl. Compd. (N. Y., NY, U. S.)* **2012**, *48*, 1332–1339.

[97] CORDELL, G. A. *The Alkaloids: Chemistry and Biology*; Academic Press, **2001**.

[98] HAN, X.; LAMSHÖFT, M.; GROBE, N.; REN, X.; FIST, A. J.; KUTCHAN, T. M.; SPITELLER, M.; ZENK, M. H. *Phytochemistry* **2010**, *71*, 1305–1312.

[99] GLASBY, J. *Encyclopedia of the Alkaloids:*; Springer US, **2012**; Vol. *2*.

[100] TOMITA, M.; WATANABE, Y.; FURUKAWA, H. *Yakugaku Zasshi* **1961**, *81*, 1644–1647.

[101] KATZ, Y.; WEIZMAN, A.; PICK, C. G.; PASTERNAK, G. W.; LIU, L.; FONIA, O.; GAVISH, M. *Brain Res.* **1994**, *646*, 235–241.

[102] KANOKMEDHAKUL, S.; KANOKMEDHAKUL, K.; LEKPHROM, R. *J. Nat. Prod.* **2007**, *70*, 1536–1538.

[103] LIU, C.-P.; KUO, Y.-C.; SHEN, C.-C.; WU, M.-H.; LIAO, J.-F.; LIN, Y.-L.; CHEN, C.-F.; TSAI, W.-J. *J. Leukocyte Biol.* **2007**, *81*, 1276–1286.

[104] BENTLEY, K. W.; ROBINSON, R. *The Isoquinoline Alkaloids: A Course in Organic Chemistry*; Elsevier Science, **2014**.

[105] MAURICE, S. In *The Isoquinoline Alkaloids Chemistry and Pharmacology*; Elsevier: **1972**; Vol. *25*, 44–89.

[106] BLANK, N.; OPATZ, T. *J. Org. Chem.* **2011**, *76*, 9777–9784.

[107] GRETHE, G.; LEE, H. L.; USKOKOVIĆ, M. R. *Tetrahedron Lett.* **1969**, *10*, 1937–1940.

[108] VENKOV, A. P.; IVANOV, I. I. *Tetrahedron* **1996**, *52*, 12299–12308.

[109] EVANS, P. A.; HOLMES, B. *Tetrahedron* **1991**, *47*, 9131–9166.

[110] OLIVER, W. C. J.; NUTTALL, G. A.; CHERRY, K. J.; DECKER, P. A.; BOWER, T.; ERETH, M. H. *Anesthesia & Analgesia* **2006**, *103*, 833–840.

[111] CALCATERRA, N. E.; BARROW, J. C. *ACS Chem. Neurosci.* **2014**, *5*, 253–260.

[112] NEU, H. C. *Pharmacother.* **1985**, *5*, 1–10.

[113] COHEN, A.; HERNANDEZ, C. M. *J. Int. Med. Res.* **1976**, *4*, 138–143.

[114] CASTEDO, L.; DOMINGUEZ, D. *The Alkaloids: Chemistry and Pharmacology* **1989**, *35*, 177–214.

[115] KONITS, P. H.; AISNER, J.; VAN ECHO, D. A.; LICHTENFELD, K.; WIERNIK, P. H. *Cancer* **1981**, *48*, 1295–1298.

[116] IQBAL, Z.; NASIR, H. *Studies in natural products chemistry* **1994**, *14*, 805–805.

[117] DAVID, B.; SÉVENET, T.; THOISON, O.; AWANG, K.; PAÏS, M.; WRIGHT, M.; GUÉNARD, D. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2155–2158.

[118] HOULIHAN, W. J.; MANNING, R. E.; Sandoz-Wander, Inc. . **1970**, 8 pp.

[119] HOULIHAN, W. J.; MANNING, R. E.; Sandoz-Wander, Inc. . **1972**, 8 pp.

[120] NALLET, J. P.; MEGARD, A. L.; DREUX, J.; Laboratoires Hoechst, Fr. . **1997**, 49 pp.

[121] NADELSON, J.; HOULIHAN, W. J.; Google Patents: **1976**.

[122] BREMNER, J. B.; JATURONRUSMEE, W.; ENGELHARDT, L. M.; WHITE, A. H. *Tetrahedron Lett.* **1989**, *30*, 3213–3216.

[123] SATO, Y.; SHIRAI, N.; MACHIDA, Y.; ITO, E.; YASUI, T.; KURONO, Y.; HATANO, K. *J. Org. Chem.* **1992**, *57*, 6711–6716.

[124] VALPUESTA, M.; ARIZA, M.; DÍAZ, A.; SUAU, R. *Eur. J. Org. Chem.* **2010**, *2010*, 4393–4401.

[125] FLEMING, A. A.; AKZO NV, Neth. . **1993**, 3 pp.

[126] SURESH, A. S.; SANDHU, J. S. *Synth. Commun.* **2008**, *38*, 3655–3661.

[127] KUMPATY, H. J.; BHATTACHARYYA, S. *Synthesis* **2005**, *2005*, 2205–2209.

[128] QADIR, M.; COBB, J.; SHELDRAKE, P. W.; WHITTALL, N.; WHITE, A. J. P.; HII, K. K.; HORTON, P. N.; HURSTHOUSE, M. B. *J. Org. Chem.* **2005**, *70*, 1552–1557.

[129] JEMISON, R. W.; OLLIS, W. D. *J. Chem. Soc., Chem. Commun.* **1969**, 294–295.

[130] CHANTRAPROMMA, K.; OLLIS, W. D.; SUTHERLAND, I. O. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1049–1061.

[131] OLLIS, W. D.; SUTHERLAND, I. O.; THEBTARANONTH, Y. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1981–1993.

[132] JUNG, M. E.; KOCH, P. *Tetrahedron Lett.* **2011**, *52*, 6051–6054.

[133] LEVY, J. V.; FREYE, E. *Opioids in Medicine: A Comprehensive Review on the Mode of Action and the Use of Analgesics in Different Clinical Pain States*; Springer Netherlands, **2008**.

[134] AMIRKIA, V.; HEINRICH, M. *Phytochemistry Letters* **2014**, *10*, xlviii–liii.

[135] ROYER, R. J. *Ann Anesthesiol Fr* **1978**, *19*, 326–332.

[136] NOVAK, B. H.; HUDLICKY, T.; REED, J. W.; MULZER, J.; TRAUNER, D. *Curr. Org. Chem.* **2000**, *4*, 343–362.

[137] FOSSATI, E.; NARCROSS, L.; EKINS, A.; FALGUEYRET, J.-P.; MARTIN, V. J. J. *PLoS One* **2015**, *10*, e0124459.

[138] BOETTCHER, C.; FELLERMEIER, M.; BOETTCHER, C.; DRÄGER, B.; ZENK, M. H. *Proc. Natl. Acad. Sci. U. S. A.* **2005**, *102*, 8495–8500.

[139] LAUX-BIEHLMANN, A.; MOUHEICHE, J.; VÉRIÈPE, J.; GOUMON, Y. *Neuroscience* **2013**, *233*, 95–117.

[140] ZEZULA, J.; HUDLICKY, T. *Synlett* **2005**, *2005*, 388–405.

[141] GATES, M.; TSCHUDI, G. *J. Am. Chem. Soc.* **1956**, *78*, 1380–1393.

[142] RICE, K. C. *J. Org. Chem.* **1980**, *45*, 3135–3137.

[143] HONG, C. Y.; KADO, N.; OVERMAN, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 11028–11029.

[144] GEFFE, M.; OPATZ, T. *Org. Lett.* **2014**, *16*, 5282–5285.

[145] VARGHESE, V.; HUDLICKY, T. *Synlett* **2013**, *24*, 369–374.

[146] GREWE, R.; MONDON, A.; NOLTE, E. *Liebigs Ann.* **1949**, *564*, 161–198.

[147] TOTH, J. E.; HAMANN, P. R.; FUCHS, P. L. *J. Org. Chem.* **1988**, *53*, 4694–4708.

[148] HAZLET, S. E.; BROTHERTON, R. J. *J. Org. Chem.* **1962**, *27*, 3253–3256.

[149] KLEIN, J. E. M. N.; MULLER-BUNZ, H.; EVANS, P. *Org. Biomol. Chem.* **2009**, *7*, 986–995.

[150] KURTI, L.; CZAKO, B. In *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier Science: **2005**, 422–423.

[151] TANAKA, T.; SHIRAI, N.; SUGIMORI, J.; SATO, Y. *J. Org. Chem.* **1992**, *57*, 5034–5036.

[152] STORK, G.; CAMA, L. D.; COULSON, D. R. *J. Am. Chem. Soc.* **1974**, *96*, 5268–5270.

[153] LUJÁN-MONTELONGO, J. A.; ÁVILA-ZÁRRAGA, J. G. *Tetrahedron Lett.* **2010**, *51*, 2232–2236.

[154] POSNER, G. H.; MAXWELL, J. P.; KAHRAMAN, M. *J. Org. Chem.* **2003**, *68*, 3049–3054.

[155] BRUCKNER, R.; ZETTLMEIER, W.; WENDER, P.; HARMATA, M. *Organic Mechanisms: Reactions, Stereochemistry and Synthesis*; Springer Berlin Heidelberg, **2010**.

[156] KERFELD, C. A.; KROGMANN, D. W. *Annu. Rev. Plant. Biol.* **1998**, *49*, 397–425.

[157] CIAMICIAN, G. *Science* **1912**, *36*, 385–394.

[158] SCHULTZ, D. M.; YOON, T. P. *Science* **2014**, *343*, 1239176, 1239171-1239178.

[159] KAGAN, J. *Organic Photochemistry: Principles and Applications*; Elsevier Science, **2012**.

[160] KÖNIG, B. *Eur. J. Org. Chem.* **2017**, *2017*, 1979–1981.

[161] SAHOO, B. *Visible Light Photocatalyzed Redox-Neutral Organic Reactions and Synthesis of Novel Metal-Organic Frameworks*; Springer International Publishing, **2016**.

[162] PRIER, C. K.; RANKIC, D. A.; MACMILLAN, D. W. C. *Chem. Rev.* **2013**, *113*, 5322–5363.

[163] SHAW, M. H.; TWILTON, J.; MACMILLAN, D. W. C. *J. Org. Chem.* **2016**, *81*, 6898–6926.

[164] ROMERO, N. A.; NICEWICZ, D. A. *Chem. Rev.* **2016**, *116*, 10075–10166.

[165] HARI, D. P.; KONIG, B. *Chem. Commun.* **2014**, *50*, 6688–6699.

[166] RECKENTHÄLER, M.; GRIESBECK, A. G. *Adv. Synth. Catal.* **2013**, *355*, 2727–2744.

[167] FAN, K. l.; GUO, Z. k.; GENG, Z. g.; GE, J.; JIANG, S. l.; HU, J. h.; ZHANG, Q. *Chin. J. Chem. Phys.* **2013**, *26*, 252–258.

[168] BACIOCCHI, E.; DEL GIACCO, T.; LAPI, A. *Helv. Chim. Acta* **2006**, *89*, 2273–2280.

[169] YOUNG, R. H.; MARTIN, R. L.; FERIOZI, D.; BREWER, D.; KAYSER, R. *Photochem. Photobiol.* **1973**, *17*, 233–244.

[170] SANTAMARIA, J.; KADDACHI, M. T. *Synlett* **1991**, *1991*, 739-740.

[171] SANTAMARIA, J.; HERLEM, D.; KHUONG-HUU, F. *Tetrahedron* **1977**, *33*, 2389–2392.

[172] SANTAMARIA, J.; KHUONG-HUU, F. *Tetrahedron* **1978**, *34*, 1523–1528.

[173] CONDIE, A. G.; GONZÁLEZ-GÓMEZ, J. C.; STEPHENSON, C. R. J. *J. Am. Chem. Soc.* **2010**, *132*, 1464–1465.

[174] SHI, L.; XIA, W. *Chem. Soc. Rev.* **2012**, *41*, 7687–7697.

[175] XI, Y.; YI, H.; LEI, A. *Org. Biomol. Chem.* **2013**, *11*, 2387–2403.

[176] HU, J.; WANG, J.; NGUYEN, T. H.; ZHENG, N. *Beilstein J. Org. Chem.* **2013**, *9*, 1977–2001.

[177] SANTAMARIA, J.; KADDACHI, M. T.; RIGAUDY, J. *Tetrahedron Lett.* **1990**, *31*, 4735–4738.

[178] COCQUET, G.; ROOL, P.; FERROUD, C. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2277–2281.

[179] RUEPING, M.; ZHU, S.; KOENIGS, R. M. *Chem. Commun.* **2011**, *47*, 12709–12711.

[180] FREEMAN, D. B.; FURST, L.; CONDIE, A. G.; STEPHENSON, C. R. J. *Org. Lett.* **2012**, *14*, 94–97.

[181] HARI, D. P.; KÖNIG, B. *Org. Lett.* **2011**, *13*, 3852–3855.

[182] PAN, Y.; WANG, S.; KEE, C. W.; DUBUISSON, E.; YANG, Y.; LOH, K. P.; TAN, C.-H. *Green Chem.* **2011**, *13*, 3341–3344.

[183] BEATTY, J. W.; STEPHENSON, C. R. J. *J. Am. Chem. Soc.* **2014**, *136*, 10270–10273.

[184] LUDVIKOVA, L.; FRIS, P.; HEGER, D.; SEBEJ, P.; WIRZ, J.; KLAN, P. *Phys. Chem. Chem. Phys.* **2016**, *18*, 16266–16273.

[185] DEROSA, M. C.; CRUTCHLEY, R. J. *Coord. Chem. Rev.* **2002**, *233–234*, 351–371.

[186] BARTHOLOMEW, R. F.; DAVIDSON, R. S. *J. Chem. Soc. C* **1971**, 2347–2351.

[187] ZAKRZEWSKI, A.; NECKERS, D. C. *Tetrahedron* **1987**, *43*, 4507–4512.

[188] COLMENARES, J. C.; XU, Y. J. *Heterogeneous Photocatalysis: From Fundamentals to Green Applications*; Springer Berlin Heidelberg, **2015**.

[189] NOËL, T. *Organometallic Flow Chemistry*; Springer International Publishing, **2016**.

[190] GRIESBECK, A.; OELGEMOLLER, M.; GHETTI, F.; EDITORS *CRC Handbook Of Organic Photochemistry And Photobiology, Third Edition, Volume 1*; CRC Press, **2012**.

[191] OUANNES, C.; WILSON, T. *J. Am. Chem. Soc.* **1968**, *90*, 6527–6528.

[192] FERROUD, C.; ROOL, P.; SANTAMARIA, J. *Tetrahedron Lett.* **1998**, *39*, 9423–9426.

[193] COCQUET, G.; FERROUD, C.; SIMON, P.; TABERNA, P.-L. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1147–1153.

[194] USHAKOV, D. B.; GILMORE, K.; KOPETZKI, D.; MCQUADE, D. T.; SEEBERGER, P. H. *Angew. Chem., Int. Ed.* **2014**, *53*, 557–561.

[195] CISMESIA, M. A.; YOON, T. P. *Chem. Sci.* **2015**, *6*, 5426-5434.

[196] ZHANG, Q.; TU, G.; ZHAO, Y.; CHENG, T. *Tetrahedron* **2002**, *58*, 6795–6798.

[197] BUCKHOLTZ, N. S. *Life Sci.* **1980**, *27*, 893–903.

[198] AIRAKSINEN, M. M.; KARI, I. *Medical biology* **1981**, *59*, 190–211.

[199] KAWASHIMA, Y.; HORIGUCHI, A.; TAGUCHI, M.; TUYUKI, Y.; KARASAWA, Y.; ARAKI, H.; HATAYAMA, K. *Chem. Pharm. Bull.* **1995**, *43*, 783–787.

[200] GUINCHARD, X.; VALLÉE, Y.; DENIS, J.-N. *Org. Lett.* **2007**, *9*, 3761–3764.

[201] PÉREZ, E. G.; CASSELS, B. K.; EIBL, C.; GÜNDISCH, D. *Bioorg. Med. Chem.* **2012**, *20*, 3719–3727.

[202] ANDO, W.; SAIKI, T.; MIGITA, T. *J. Am. Chem. Soc.* **1975**, *97*, 5028–5029.

[203] SAKO, M.; SHIMADA, K.; HIROTA, K.; MAKI, Y. *J. Am. Chem. Soc.* **1986**, *108*, 6039–6041.

[204] FURST, L.; STEPHENSON, C. R. J. In *From C-H to C-C Bonds: Cross-Dehydrogenative-Coupling*; The Royal Society of Chemistry: **2015**, 219–253.

[205] FRANZ, J. F.; KRAUS, W. B.; ZEITLER, K. *Chem. Commun.* **2015**, *51*, 8280–8283.

[206] COLLINS, R. F. *Chem. Ind. (London, U. K.)* **1957**, 704.

[207] STEVENSON, D. P.; COPPINGER, G. M. *J. Am. Chem. Soc.* **1962**, *84*, 149–152.

[208] SCHROTH, W.; JAHN, U.; STRÖHL, D. *Chem. Ber.* **1994**, *127*, 2013-2022.

[209] BÖHM, A.; BACH, T. *Chem. Eur. J.* **2016**, *22*, 15921–15928.

[210] BHOWMICK, M.; SEMMENS, M. J. *Water Res.* **1994**, *28*, 2407–2415.

[211] EBERSON, L.; EKSTROEM, M. *Acta Chem. Scand.* **1989**, *43*, 86–92.

[212] LAUTENBERGER, W. J.; JONES, E. N.; MILLER, J. G. *J. Am. Chem. Soc.* **1968**, *90*, 1110–1115.

[213] BIASELLE, C. J.; MILLER, J. G. *J. Am. Chem. Soc.* **1974**, *96*, 3813–3816.

[214] MARKARIAN, S. A.; FISCHER, H. *J. Chem. Soc., Chem. Commun.* **1979**, 1055–1056.

[215] BLACKSTOCK, S. C.; LORAND, J. P.; KOCHI, J. K. *J. Org. Chem.* **1987**, *52*, 1451–1460.

[216] ERRABALSELLS, R.; FRASCA, A. *Aust. J. Chem.* **1988**, *41*, 103–110.

[217] EBERSON, L.; EKSTRÖM, M. *Acta Chem. Scand.* **1989**, *43*, 86–92.

[218] LAZAREVA, N. F.; VAKUL'SKAYA, T. I.; LAZAREV, I. M. *J. Phys. Org. Chem.* **2009**, *22*, 144-154.

[219] SIDEBOTTOM, H. W.; TEDDER, J. M.; WALTON, J. C. *J. Chem. Soc. Faraday Trans.* **1969**, *65*, 755–762.

[220] MILNE, J. *Polyhedron* **1985**, *4*, 65–68.

[221] CHINA, H.; OKADA, Y.; OGINO, H. *J. Phys. Org. Chem.* **2016**, *29*, 84–91.

[222] ROSENTHAL, I.; MOSSOBA, M. M.; RIESZ, P. *Journal of Magnetic Resonance (1969)* **1981**, *45*, 359–361.

[223] KIMURA, T.; FUJITA, M.; SOHMIYA, H.; ANDO, T. *J. Org. Chem.* **1998**, *63*, 6719–6720.

[224] BARHAM, J. P.; JOHN, M. P.; MURPHY, J. A. *Beilstein J. Org. Chem.* **2014**, *10*, 2981–2988.

[225] BRACCA, A. B. J.; KAUFMAN, T. S. *Tetrahedron* **2004**, *60*, 10575–10610.

[226] BROSSI, A.; TEITEL, S. *Helv. Chim. Acta* **1971**, *54*, 1564–1571.

[227] SHONO, T.; HAMAGUCHI, H.; SASAKI, M.; FUJITA, S.; NAGAMI, K. *J. Org. Chem.* **1983**, *48*, 1621–1628.

[228] RUEPING, M.; LEONORI, D.; POISSON, T. *Chem. Commun.* **2011**, *47*, 9615–9617.

[229] VILA, C.; LAU, J.; RUEPING, M. *Beilstein J. Org. Chem.* **2014**, *10*, 1233–1238.

[230] CLARKE, P. A.; SANTOS, S. *Eur. J. Org. Chem.* **2006**, *2006*, 2045–2053.

[231] HAN, X.; PEH, G.; FLOREANCIG, P. E. *Eur. J. Org. Chem.* **2013**, *2013*, 1193–1208.

[232] DOBBS, A. P.; GUESNE, S. J. J.; PARKER, R. J.; SKIDMORE, J.; STEPHENSON, R. A.; HURSTHOUSE, M. B. *Org. Biomol. Chem.* **2010**, *8*, 1064–1080.

[233] OLIER, C.; KAAFARANI, M.; GASTALDI, S.; BERTRAND, M. P. *Tetrahedron* **2010**, *66*, 413–445.

[234] M. PASTOR, I.; YUS, M. *Curr. Org. Chem.* **2012**, *16*, 1277–1312.

[235] SUBBA REDDY, B. V.; NAIR, P. N.; ANTONY, A.; LALLI, C.; GRÉE, R. *Eur. J. Org. Chem.* **2017**, *2017*, 1805–1819.

[236] YATES, K.; SCHMID, G. H.; REGULSKI, T. W.; GARRATT, D. G.; LEUNG, H.-W.; MCDONALD, R. *J. Am. Chem. Soc.* **1973**, *95*, 160–165.

[237] STROZIER, R. W.; CARAMELLA, P.; HOUK, K. N. *J. Am. Chem. Soc.* **1979**, *101*, 1340–1343.

[238] CAREY, F. A.; SUNDBERG, R. J. *Advanced Organic Chemistry: Part A: Structure and Mechanisms*; Springer US, **2007**.

[239] ANH, N. T.; NGUYÊN, T. A. *Frontier Orbitals: A Practical Manual*; Wiley, **2007**.

[240] GILMORE, K.; ALABUGIN, I. V. *Chem. Rev.* **2011**, *111*, 6513–6556.

[241] MIRANDA, P. O.; RAMÍREZ, M. A.; MARTÍN, V. S.; PADRÓN, J. I. *Chem. Eur. J.* **2008**, *14*, 6260–6268.

[242] MARYANOFF, B. E.; ZHANG, H.-C.; COHEN, J. H.; TURCHI, I. J.; MARYANOFF, C. A. *Chem. Rev.* **2004**, *104*, 1431–1628.

[243] AHMAD, V. U.; FEUERHERD, K.-H.; WINTERFELDT, E. *Chem. Ber.* **1977**, *110*, 3624–3635.

[244] OVERMAN, L. E.; SHARP, M. J. *J. Am. Chem. Soc.* **1988**, *110*, 612–614.

[245] OVERMAN, L. E.; SARKAR, A. K. *Tetrahedron Lett.* **1992**, *33*, 4103–4106.

[246] MURATA, Y.; OVERMAN, L. E. *Heterocycles* **1996**, *2*, 549–553.

[247] CARBALLO, R. M.; RAMÍREZ, M. A.; RODRÍGUEZ, M. L.; MARTÍN, V. S.; PADRÓN, J. I. *Org. Lett.* **2006**, *8*, 3837–3840.

[248] MIRANDA, P. O.; CARBALLO, R. M.; MARTÍN, V. S.; PADRÓN, J. I. *Org. Lett.* **2009**, *11*, 357–360.

[249] WANG, Y.; PENG, C.; LIU, L.; ZHAO, J.; SU, L.; ZHU, Q. *Tetrahedron Lett.* **2009**, *50*, 2261–2265.

[250] OVERMAN, L. E.; SHARP, M. J. *Tetrahedron Lett.* **1988**, *29*, 901–904.

[251] CARBALLO, R. M.; VALDOMIR, G.; PURINO, M.; MARTÍN, V. S.; PADRÓN, J. I. *Eur. J. Org. Chem.* **2010**, *2010*, 2304–2313.

[252] MA, D.; ZHONG, Z.; LIU, Z.; ZHANG, M.; XU, S.; XU, D.; SONG, D.; XIE, X.; SHE, X. *Org. Lett.* **2016**, *18*, 4328–4331.

[253] XU, S.; ZHANG, J.; MA, D.; XU, D.; XIE, X.; SHE, X. *Org. Lett.* **2016**, *18*, 4682–4685.

[254] YU, J. Q.; SHI, Z. *C-H Activation*; Springer Berlin Heidelberg, **2010**.

[255] CUI, L.; PENG, Y.; ZHANG, L. *J. Am. Chem. Soc.* **2009**, *131*, 8394–8395.

[256] NOEY, E. L.; LUO, Y.; ZHANG, L.; HOUK, K. N. *J. Am. Chem. Soc.* **2012**, *134*, 1078–1084.

[257] KIM, C.; BAE, H. J.; LEE, J. H.; JEONG, W.; KIM, H.; SAMPATH, V.; RHEE, Y. H. *J. Am. Chem. Soc.* **2009**, *131*, 14660–14661.

[258] CHEN, D.-F.; HAN, Z.-Y.; HE, Y.-P.; YU, J.; GONG, L.-Z. *Angew. Chem., Int. Ed.* **2012**, *51*, 12307–12310.

[259] MORENO, L.; CABEDO, N.; BOULANGÉ, A.; PÁRRAGA, J.; GALÁN, A.; LELEU, S.; SANZ, M.-J.; CORTES, D.; FRANCK, X. *Eur. J. Med. Chem.* **2013**, *69*, 69–76.

[260] KANG, Y.; CHEN, W.; BREUGST, M.; SEIDEL, D. *J. Org. Chem.* **2015**, *80*, 9628–9640.

[261] FULMER, G. R.; MILLER, A. J. M.; SHERDEN, N. H.; GOTTLIEB, H. E.; NUDELMAN, A.; STOLTZ, B. M.; BERCAW, J. E.; GOLDBERG, K. I. *Organometallics* **2010**, *29*, 2176–2179.

[262] WERNER, F.; BLANK, N.; OPATZ, T. *Eur. J. Org. Chem.* **2007**, *2007*, 3911–3915.

[263] ROHLOFF, J. C.; DYSON, N. H.; GARDNER, J. O.; ALFREDSON, T. V.; SPARACINO, M. L.; ROBINSON III, J. *J. Org. Chem.* **1993**, *58*, 1935–1938.

[264] TAYLOR, A. M.; SCHREIBER, S. L. *Org. Lett.* **2006**, *8*, 143–146.

[265] PYMAN, F. L. *J. Chem. Soc., Trans.*, **1909**, *95*, 1266–1275.

[266] RAMACCIOTTI, A.; FIASCHI, R.; NAPOLITANO, E. *J. Org. Chem.* **1996**, *61*, 5371–5374.

[267] ISCHAY, M. A.; LU, Z.; YOON, T. P. *J. Am. Chem. Soc.* **2010**, *132*, 8572–8574.

[268] SHEN, L.; SUN, D. *Tetrahedron Lett.* **2011**, *52*, 4570–4574.

[269] YANG, P.-Y.; ZHOU, Y.-G. *Tetrahedron: Asymmetry* **2004**, *15*, 1145–1149.

[270] KUROSAWA, W.; KAN, T.; FUKUYAMA, T. *J. Am. Chem. Soc.* **2003**, *125*, 8112–8113.

[271] WARD, R. S.; COOKS, R. G.; WILLIAMS, D. H. *J. Am. Chem. Soc.* **1969**, *91*, 2727–2732.

[272] SHAIKH, N. S.; JUNGE, K.; BELLER, M. *Org. Lett.* **2007**, *9*, 5429–5432.

[273] VAN OEVEREN, A.; JANSEN, J. F.; FERINGA, B. L. *J. Org. Chem.* **1994**, *59*, 5999–6007.

[274] YAMAGUCHI, S.; TSUCHIDA, N.; MIYAZAWA, M.; HIRAI, Y. *J. Org. Chem.* **2005**, *70*, 7505–7511.

[275] MEYERS, A.; GUILES, J. *Heterocycles* **1989**, *28*, 295–301.

[276] KASHDAN, D. S.; SCHWARTZ, J. A.; RAPOPORT, H. *J. Org. Chem.* **1982**, *47*, 2638–2643.

[277] CAVA, M. P.; AFZALI, A. *J. Org. Chem.* **1975**, *40*, 1553–1556.

[278] LANGHALS, E.; LANGHALS, H.; RÜCHARDT, C. *Chem. Ber.* **1984**, *117*, 1436–1454.

[279] MILLER, L.; STERMITZ, F.; FALCK, J. *J. Am. Chem. Soc.* **1973**, *95*, 2651–2656.

[280] KUCK, A.; FRYDMAN, B. *J. Org. Chem.* **1961**, *26*, 5253–5254.

[281] HARA, H.; HASHIMOTO, F.; HOSINO, O.; UMEZAWA, B. *Chem. Pharm. Bull.* **1986**, *34*, 1946–1949.

[282] MARION, L.; LEMAY, L.; PORTELANCE, V. *J. Org. Chem.* **1950**, *15*, 216–220.

[283] HAWORTH, R. D.; PERKIN, W. H.; RANKIN, J. *J. Chem. Soc., Trans.*, **1925**, *127*, 1444–1448.

[284] KIPARISSIDES, Z.; FICHTNER, R. H.; POPLAWSKI, J.; NALLIAH, B. C.; MACLEAN, D. B. *Can. J. Chem.* **1980**, *58*, 2770–2779.

[285] SUAU, R.; POSADAS, N.; SILVA, M. V.; VALPUESTA, M. *Phytochemistry* **1998**, *49*, 2551–2555.

[286] LOCHER, C.; PEERZADA, N. *J. Chem. Soc., Perkin Trans. 1* **1999**, 179–184.

[287] SOLDATENKOV, A. T.; SOLDATOVA, S. A.; MAMYRBEKOVA-BEKRO, J. A.; GIMRANOVA, G. S.; MALKOVA, A. V.; POLYANSKII, K. B.; KOLYADINA, N. M.; KHRUSTALEV, V. N. *Chem. Heterocycl. Compd. (N. Y., NY, U. S.)* **2012**, *48*, 1332-1339.

[288] LAHM, G.; OPATZ, T. *Org. Lett.* **2014**, *16*, 4201–4203.

[289] FIFE, W. K.; RANGANATHAN, P.; ZELDIN, M. *J. Org. Chem.* **1990**, *55*, 5610–5613.

[290] CHENG, B.; ZHANG, S.; ZHU, L.; ZHANG, J.; LI, Q.; SHAN, A.; HE, L. *Synthesis* **2009**, *2009*, 2501–2504.

[291] SINHABABU, A. K.; BORCHARDT, R. T. *J. Org. Chem.* **1983**, *48*, 2356–2360.

[292] OREJARENA PACHECO, J. C.; LAHM, G.; OPATZ, T. *J. Org. Chem.* **2013**, *78*, 4985–4992.

[293] KEM, W. R.; SOTI, F.; ROUCHAUD, A.; XING, H.; LINDSTROM, J.; ANDRUD, K. M.; University of Florida Research Foundation, Inc., USA . **2012**, 88pp.

[294] NGUYEN TRONG, L.; GRUENKE, L. D.; CASTAGNOLI, N. *J. Med. Chem.* **1976**, *19*, 1168–1169.

[295] COLLADO, M. I.; MANTECA, I.; SOTOMAYOR, N.; VILLA, M.-J.; LETE, E. *J. Org. Chem.* **1997**, *62*, 2080–2092.

[296] HUANG, H.; JI, X.; WU, W.; JIANG, H. *Chem. Commun.* **2013**, *49*, 3351–3353.

[297] DHANASEKARAN, S.; BISAI, V.; UNHALE, R. A.; SUNEJA, A.; SINGH, V. K. *Org. Lett.* **2014**, *16*, 6068–6071.

[298] GUINCHARD, X.; VALLÉE, Y.; DENIS, J.-N. *Org. Lett.* **2007**, *9*, 3761-3764.

[299] SHAW, K. N. F.; MCMILLAN, A.; GUDMUNDSON, A. G.; ARMSTRONG, M. D. *J. Org. Chem.* **1958**, *23*, 1171-1178.

[300] AUBRY, C.; WILSON, A. J.; EMMERSON, D.; MURPHY, E.; CHAN, Y. Y.; DICKENS, M. P.; GARCÍA, M. D.; JENKINS, P. R.; MAHALE, S.; CHAUDHURI, B. *Bioorg. Med. Chem.* **2009**, *17*, 6073-6084.

[301] PÉREZ, E. G.; CASSELS, B. K.; EIBL, C.; GÜNDISCH, D. *Bioorg. Med. Chem. Lett.* **2012**, *20*, 3719-3727.

[302] MIR, F.; SHAFI, S.; ZAMAN, M. S.; KALIA, N. P.; RAJPUT, V. S.; MULAKAYALA, C.; MULAKAYALA, N.; KHAN, I. A.; ALAM, M. S. *European Journal of Medicinal Chemistry* **2014**, *76*, 274-283.

[303] MIELCZAREK, M.; THOMAS, R. V.; MAC, C.; KANDEMIR, H.; YANG, C.-G.; BHADBHADE, M.; BLACK, D. S.; GRIFFITH, R.; LEWIS, P. J.; KUMAR, N. *Bioorg. Med. Chem. Lett.* **2015**, *23*, 1763-1775.

[304] STORK, G.; HILL, R. K. *J. Am. Chem. Soc.* **1957**, *79*, 495-500.

[305] GRIBBLE, G. W. *J. Org. Chem.* **1972**, *37*, 1833-1835.

[306] PAKHARE, D. S.; KUSURKAR, R. S. *Tetrahedron Lett.* **2015**, *56*, 6012-6015.

[307] HOEFGEN, B.; DECKER, M.; MOHR, P.; SCHRAMM, A. M.; ROSTOM, S. A. F.; EL-SUBBAGH, H.; SCHWEIKERT, P. M.; RUDOLF, D. R.; KASSACK, M. U.; LEHMANN, J. *J. Med. Chem.* **2006**, *49*, 7760-7769.

[308] ORTEGA, N.; RICHTER, C.; GLORIUS, F. *Org. Lett.* **2013**, *15*, 1776–1779.

[309] HANQUET, G. M.; LUSINCHI, X.; MILLIET, P. *Tetrahedron* **1993**, *49*, 423–438.

[310] TSAREV, V. N.; MORIOKA, Y.; CANER, J.; WANG, Q.; USHIMARU, R.; KUDO, A.; NAKA, H.; SAITO, S. *Org. Lett.* **2015**, *17*, 2530–2533.

[311] BROOKS, D. J.; DOWELL, D. S.; MINTER, D. E.; VILLARREAL, M. C. *J. Org. Chem.* **1984**, *49*, 130–133.

[312] DUNSMORE, C. J.; CARR, R.; FLEMING, T.; TURNER, N. J. *J. Am. Chem. Soc.* **2006**, *128*, 2224–2225.

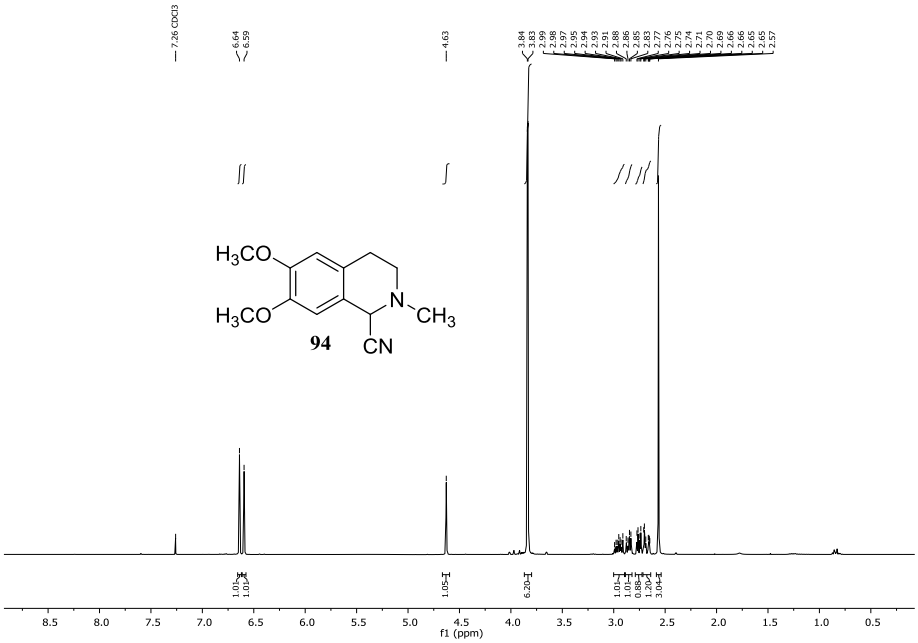
[313] WANG, T.; SCHREMPP, M.; BERNDHÄUSER, A.; SCHIEMANN, O.; MENCHE, D. *Org. Lett.* **2015**, *17*, 3982–3985.

Apendix A: NMR Spectra

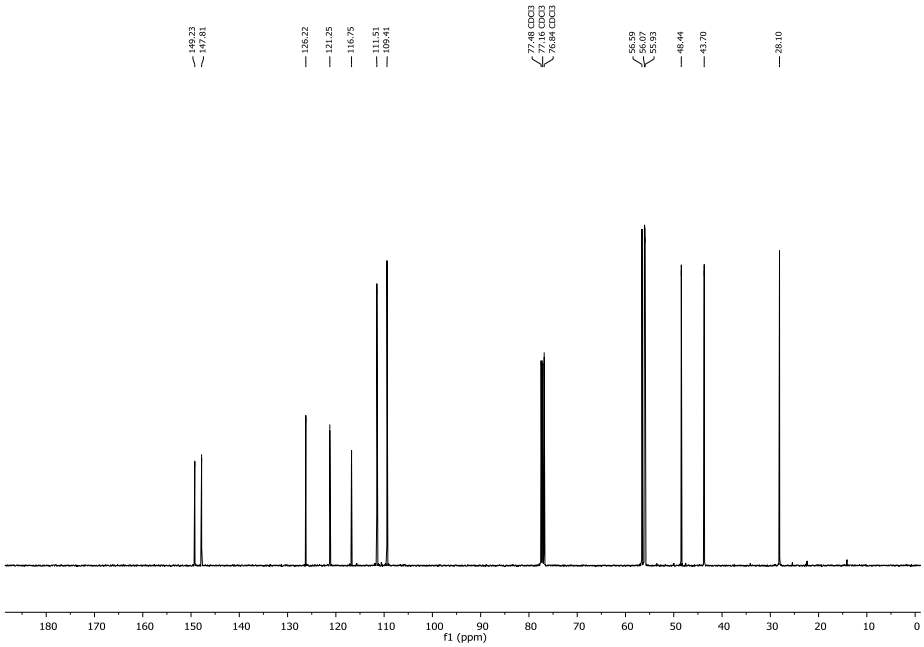
In the following section, ^{1}H and ^{13}C NMR spectra of selected compounds are presented.

Chapter 1

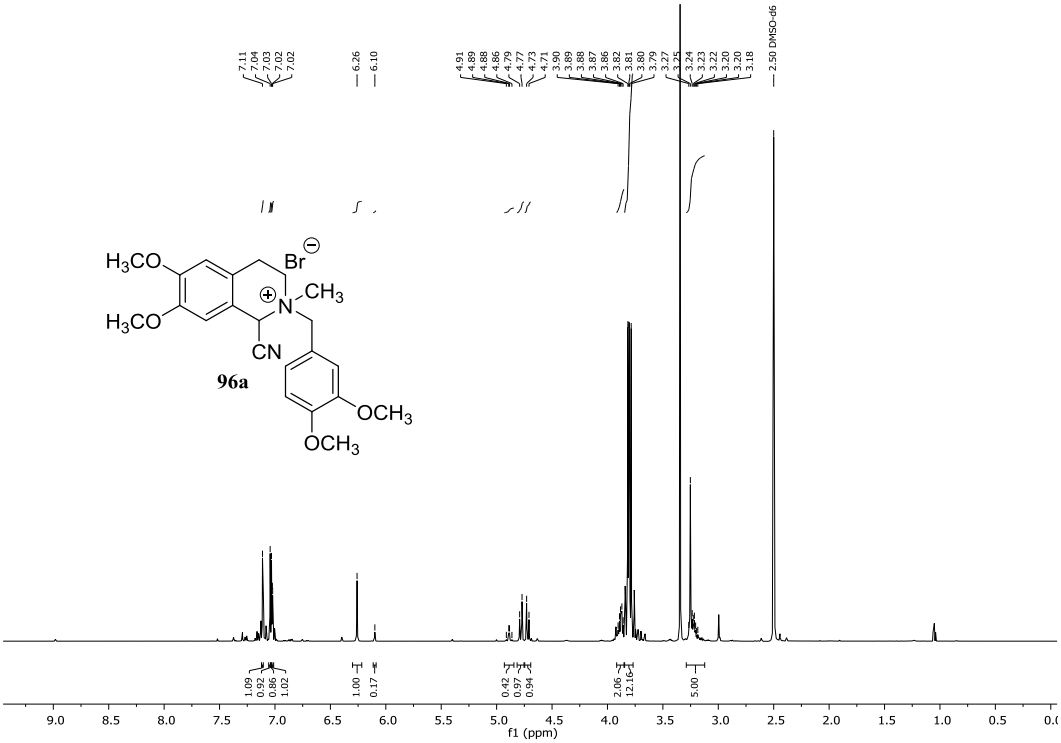
For this chapter a few sample spectra are depicted. The remaining spectra can be found in the *Journal of Organic Chemistry* under the following DOI: 10.1021/jo400659n.



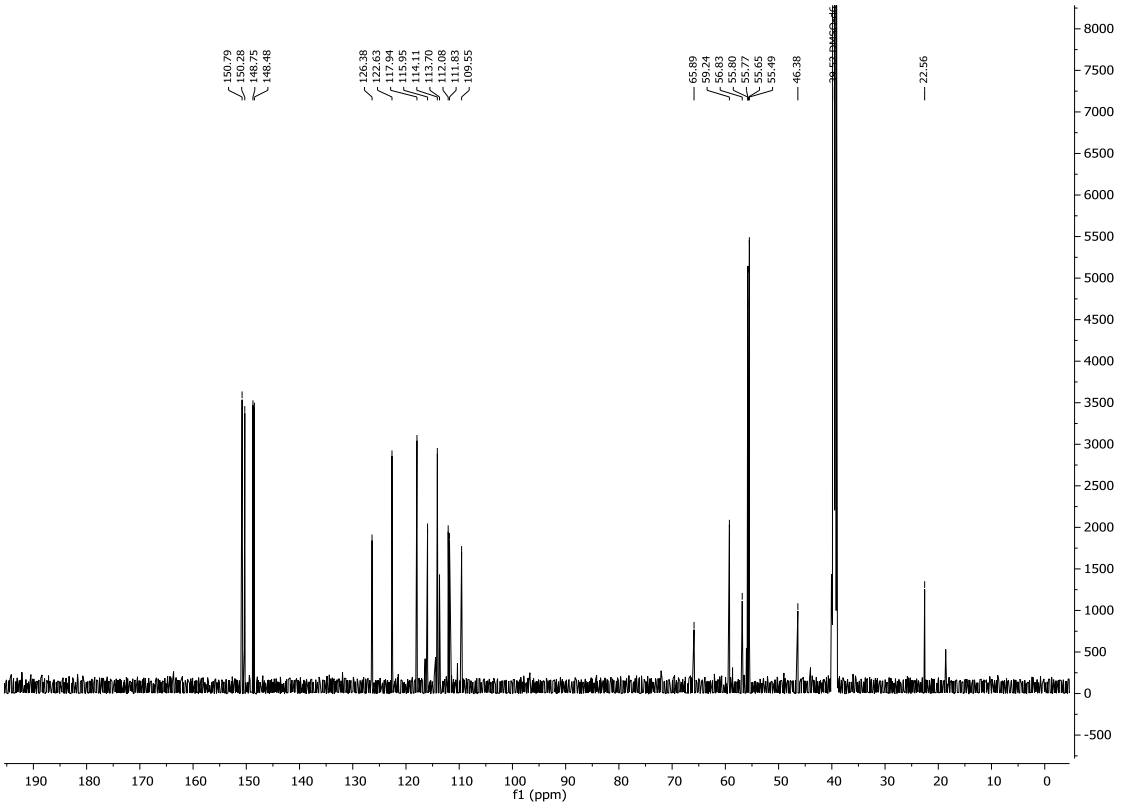
^{1}H NMR (400 MHz, $CDCl_3$) of compound **94**.



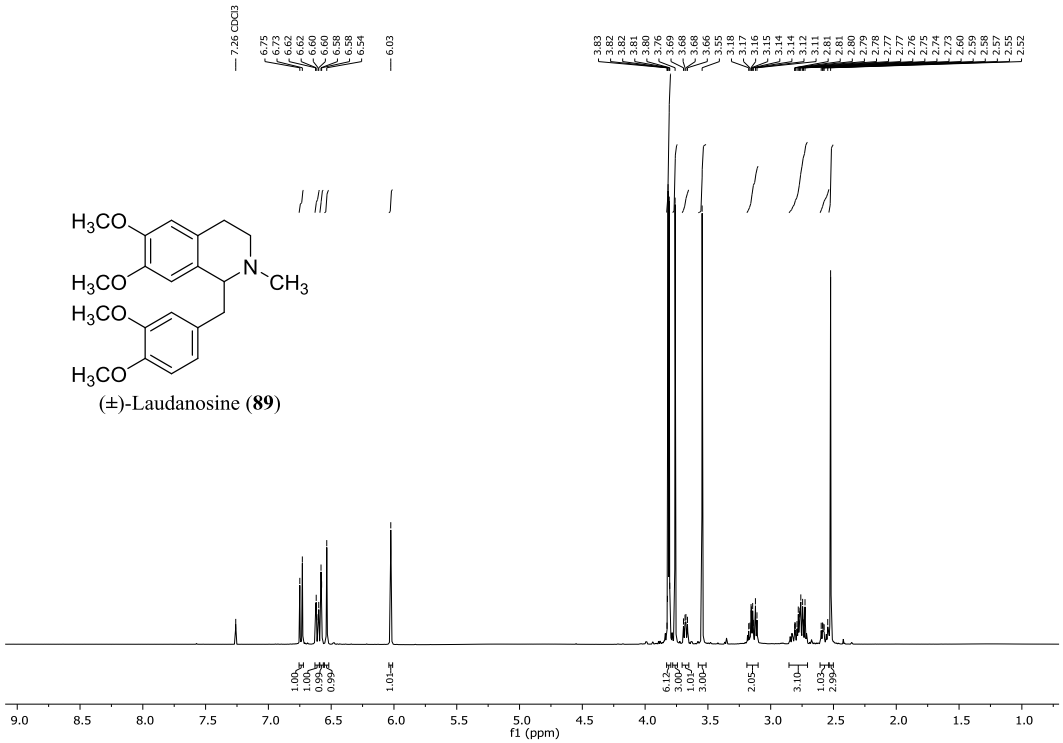
^{13}C NMR (100.6 MHz, $CDCl_3$) of compound **94**.



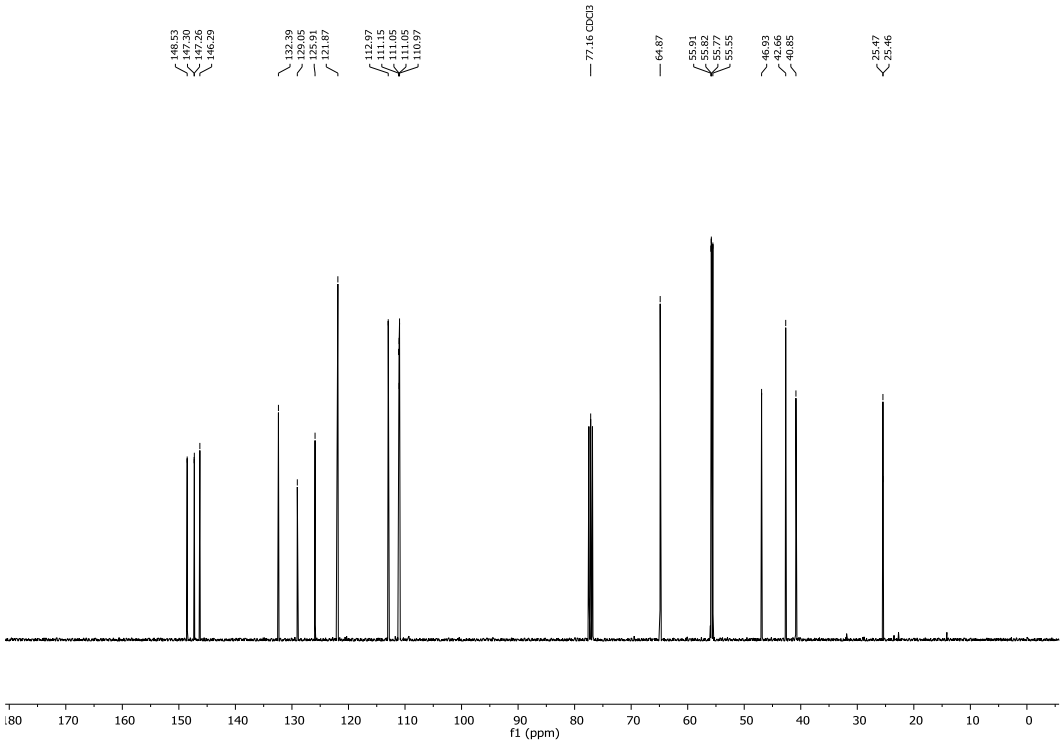
^{1}H NMR (600 MHz, DMSO-d_6) of compound **96a**.



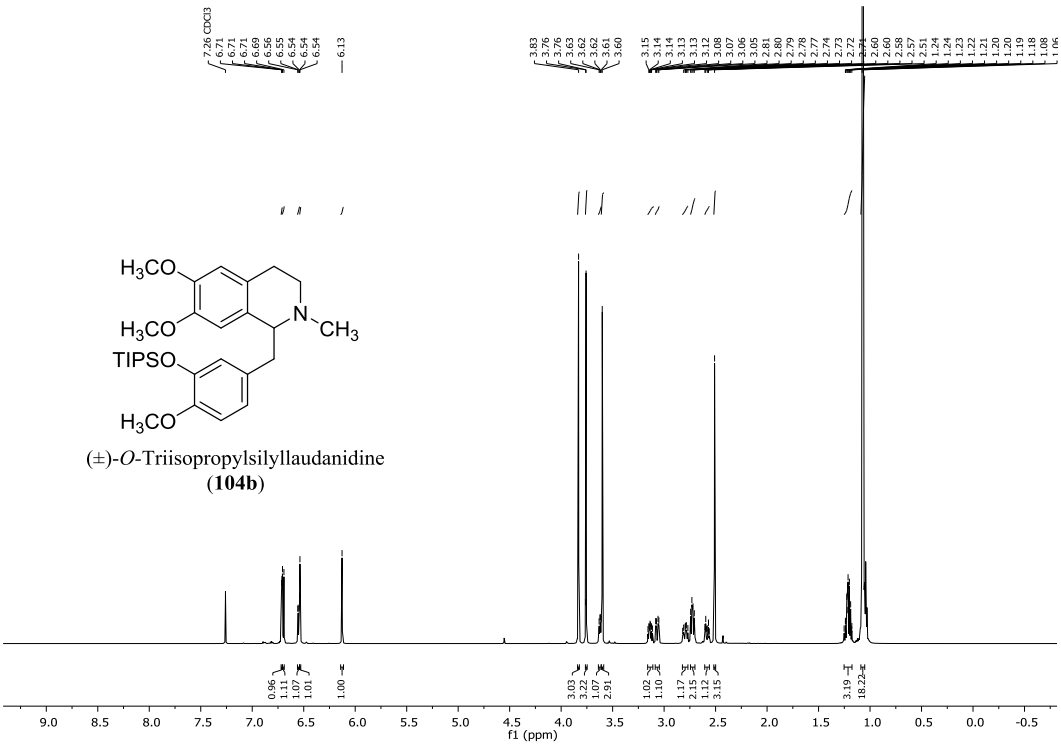
^{13}C NMR (150.9 MHz, DMSO-d_6) of compound **96a**.



^{1}H NMR (400 MHz, $CDCl_3$) of compound **89**.

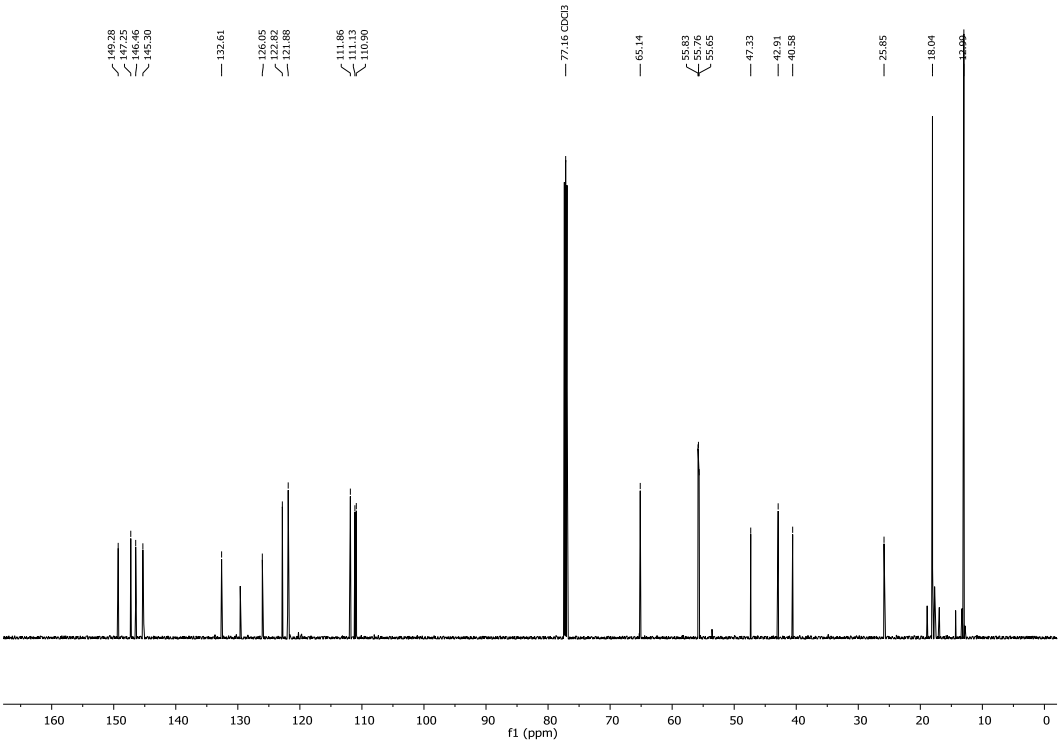


^{13}C NMR (100.6 MHz, $CDCl_3$) of compound **89**.

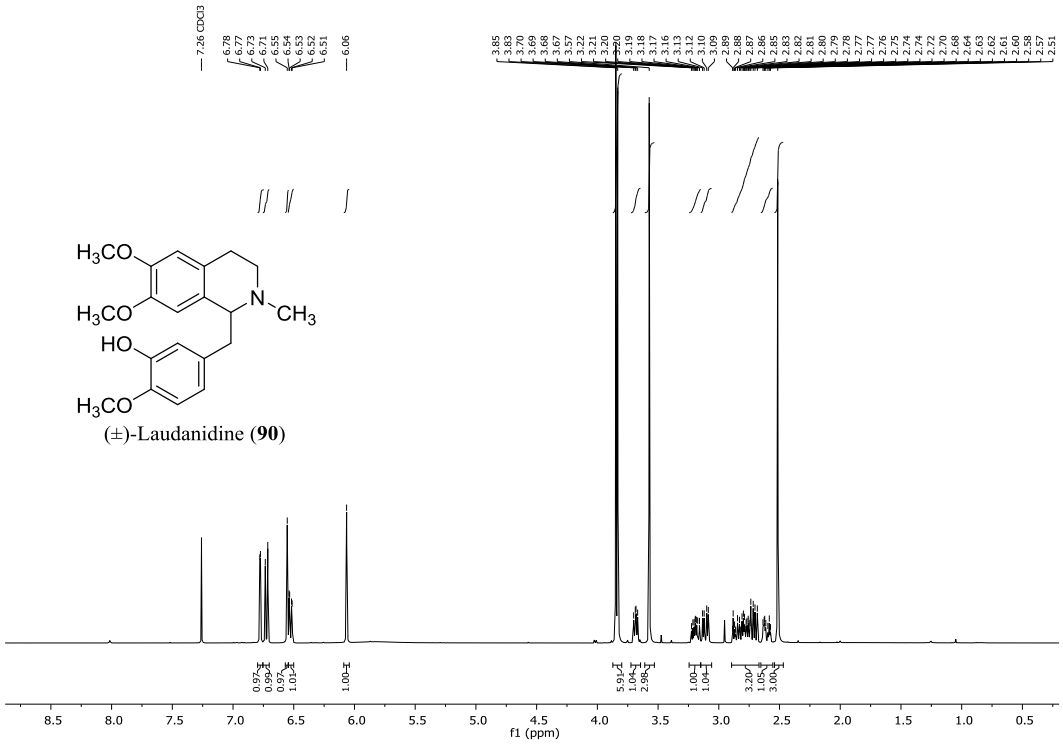


(±)-*O*-Triisopropylsilyllaudanidine
(**104b**)

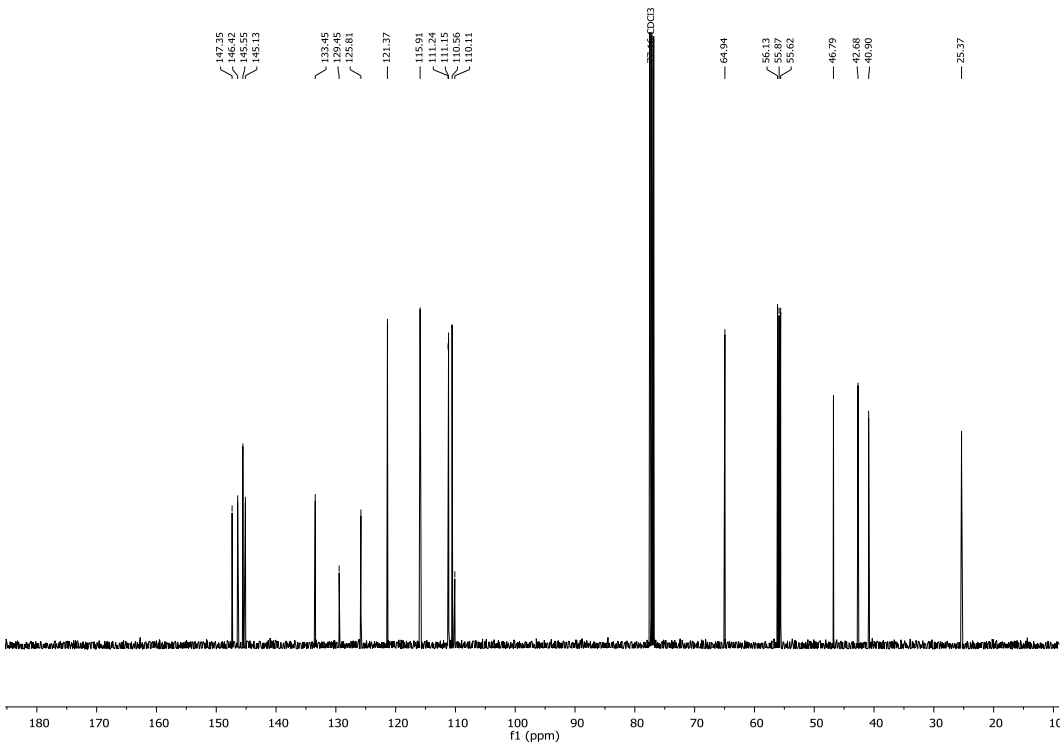
^{1}H NMR (400 MHz, $CDCl_3$) of compound **104b**.



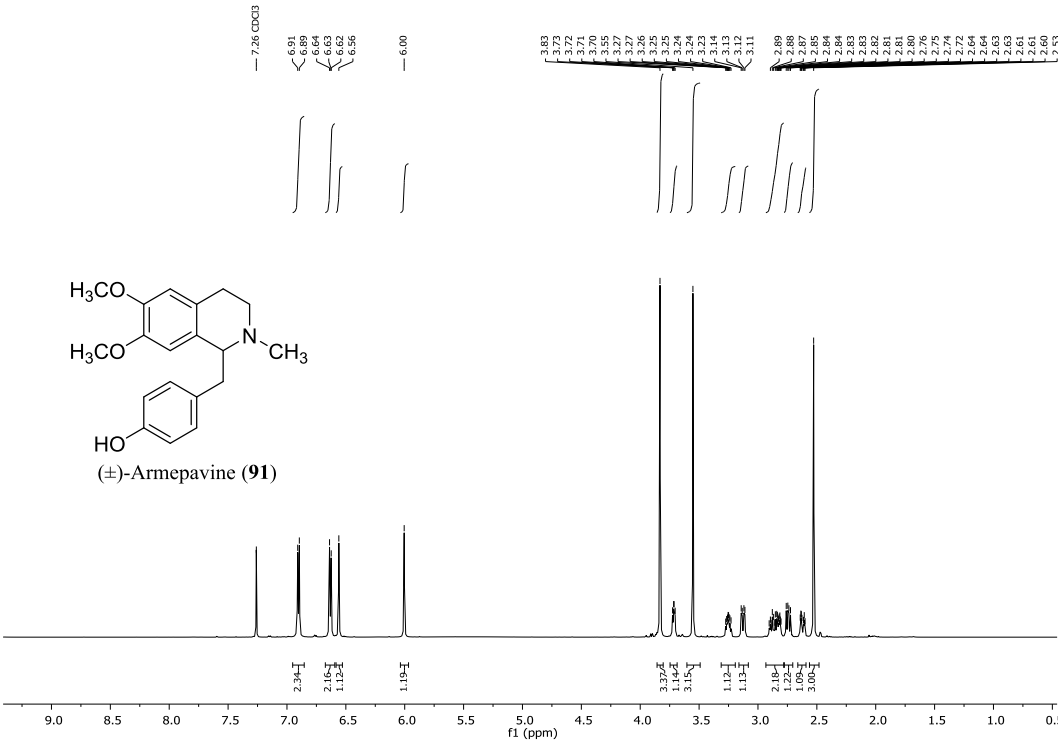
^{13}C NMR (100.6 MHz, $CDCl_3$) of compound **104b**.



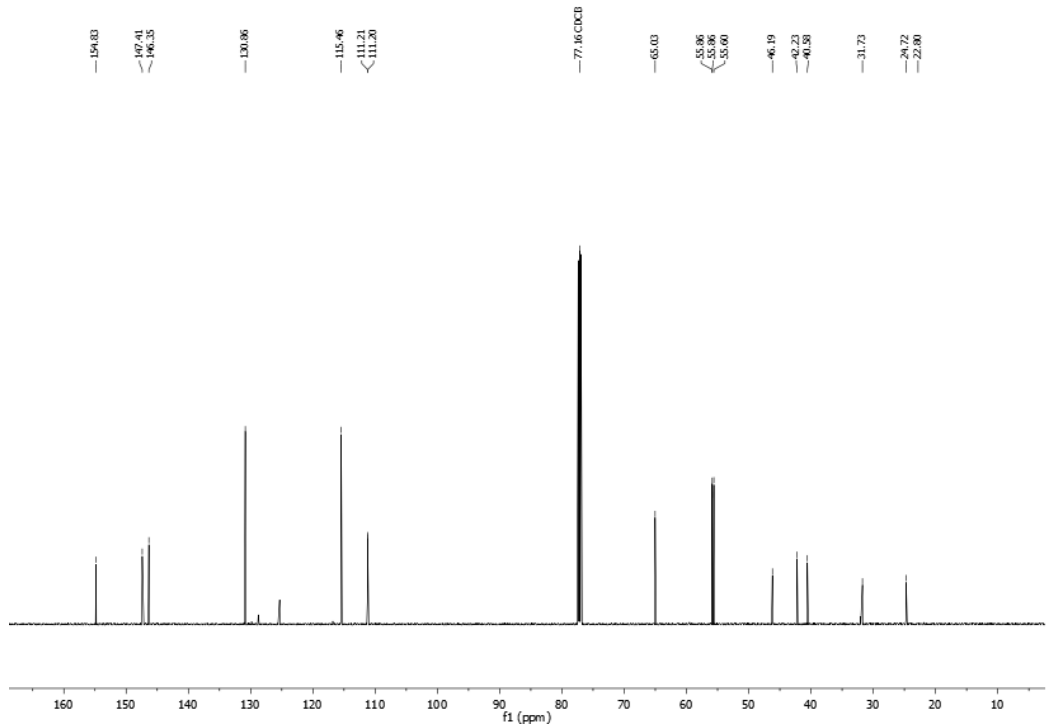
^{1}H NMR (400 MHz, $CDCl_3$) of compound **90**.



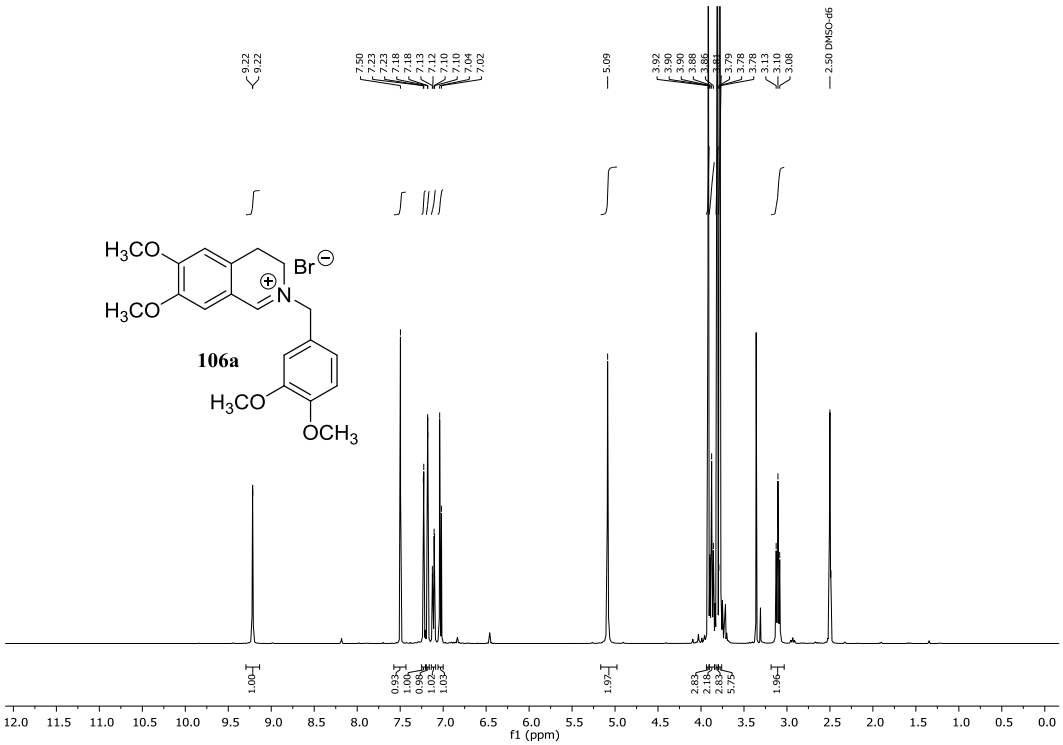
^{13}C NMR (100.6 MHz, $CDCl_3$) of compound **90**.



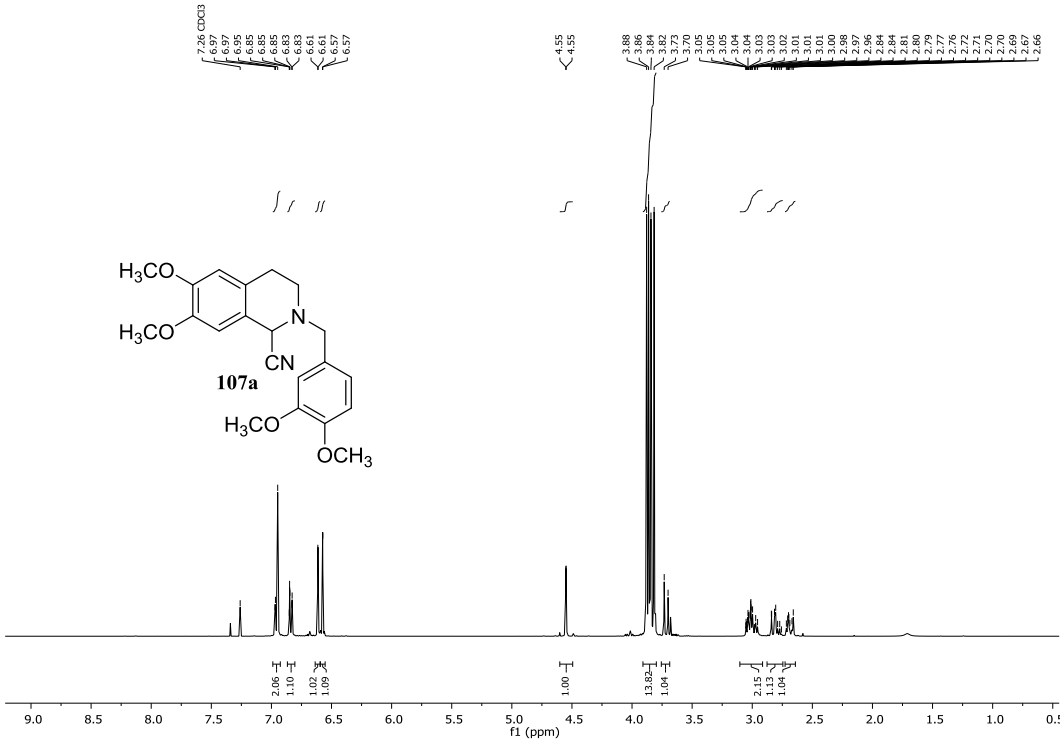
^{1}H NMR (600 MHz, $CDCl_3$) of compound **91**.



^{13}C NMR (150.9 MHz, $CDCl_3$) of compound **91**.



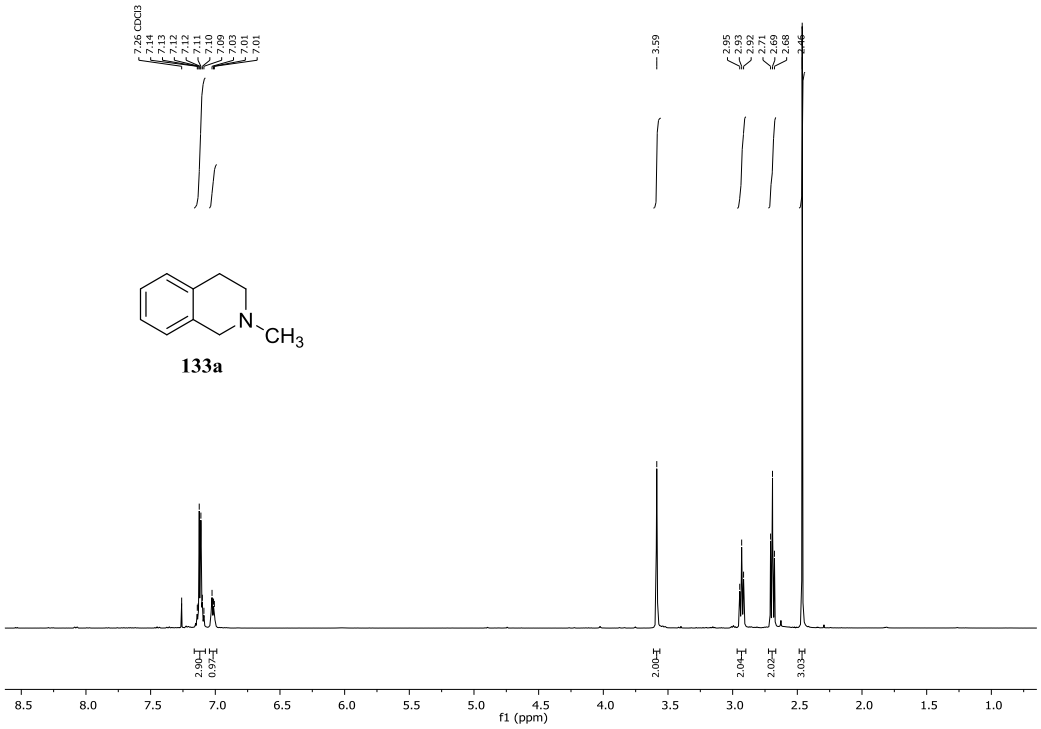
^{1}H NMR (400 MHz, $CDCl_3$) of compound **106a**.



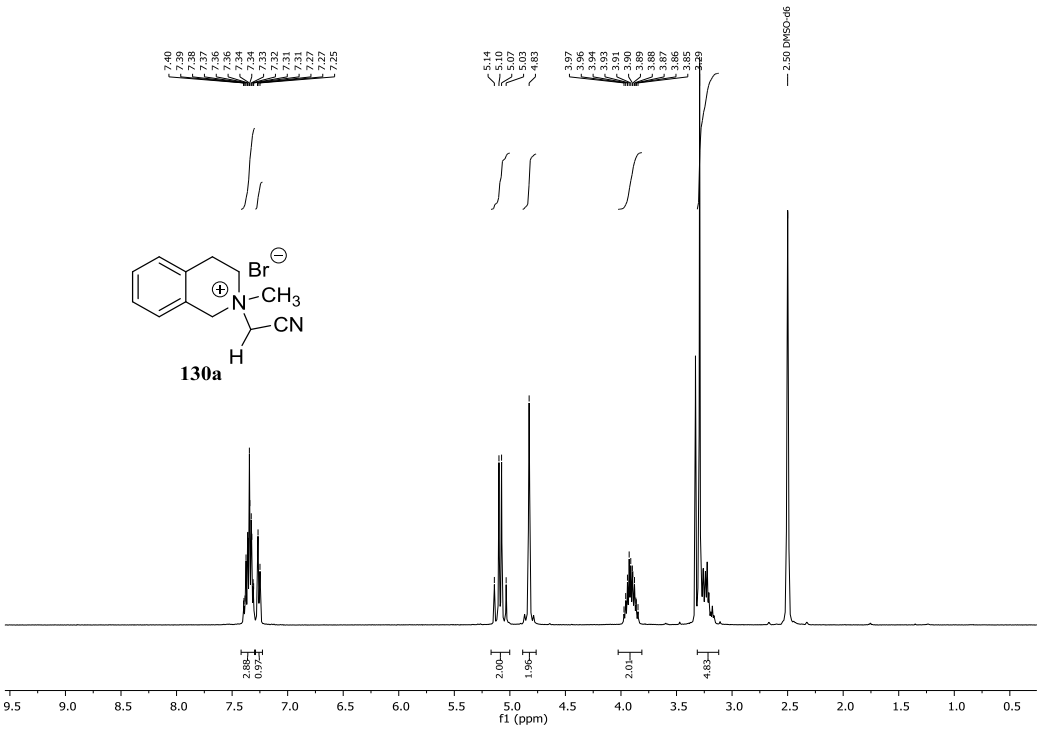
^{1}H NMR (400 MHz, $CDCl_3$) of compound **107a**.

Chapter 2

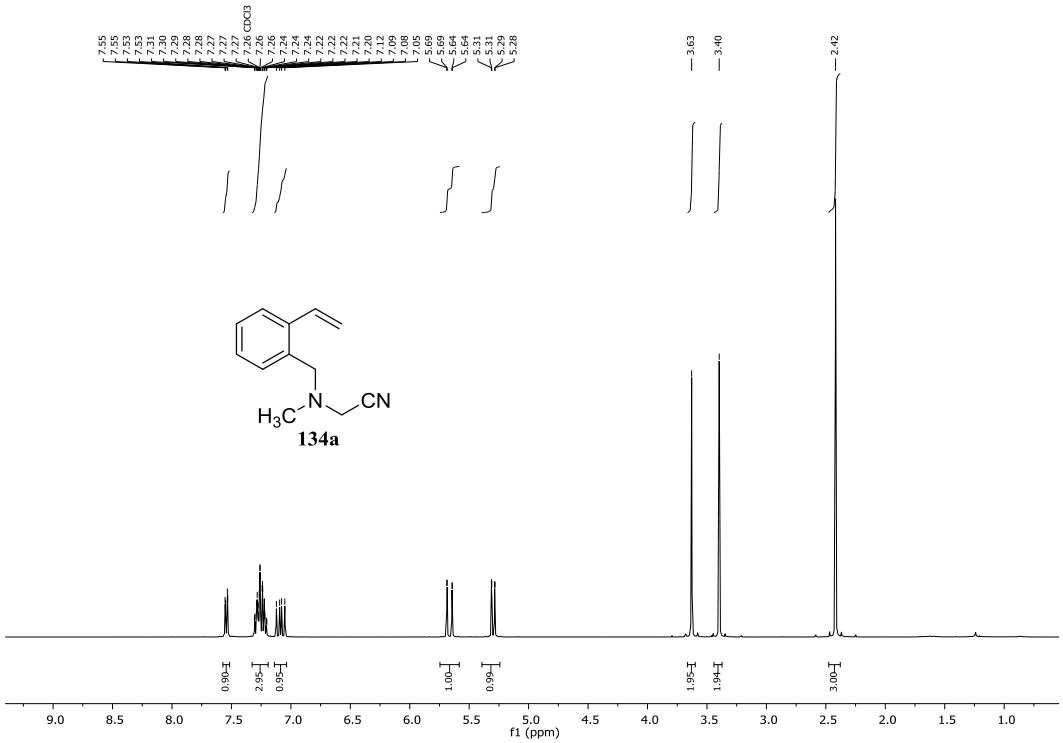
For this chapter a few sample spectra are depicted. The remaining spectra can be found in the *Journal of Organic Chemistry* under the following DOI: 10.1021/jo500749x.



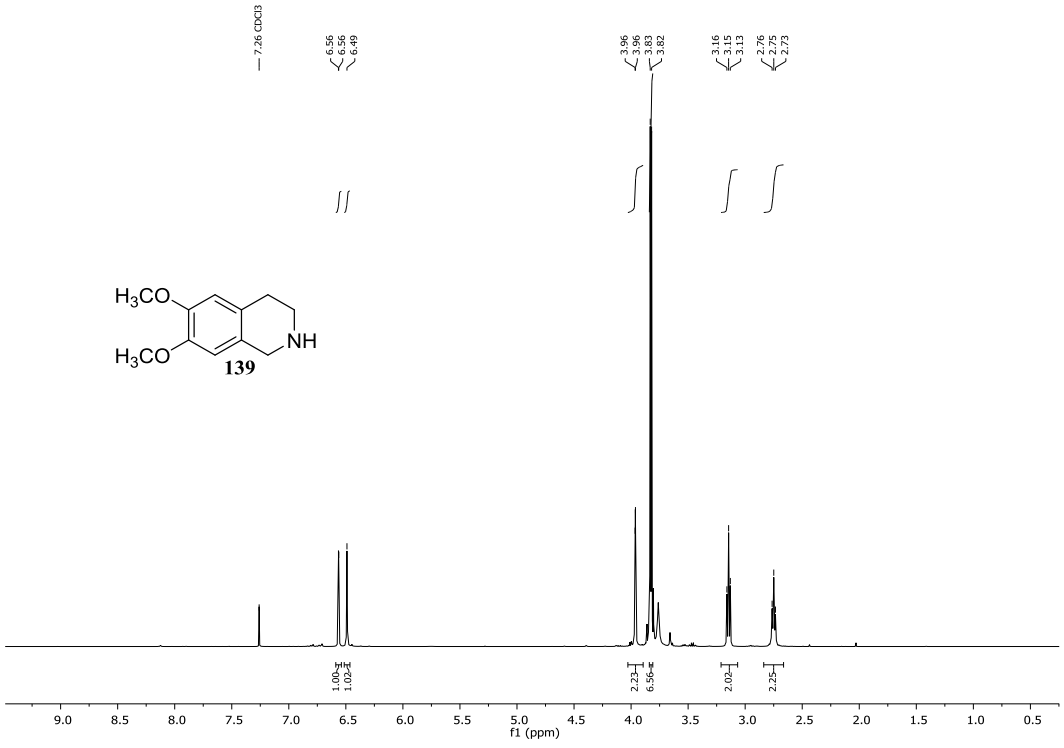
^{1}H NMR (400 MHz, $CDCl_3$) of compound **133a**.



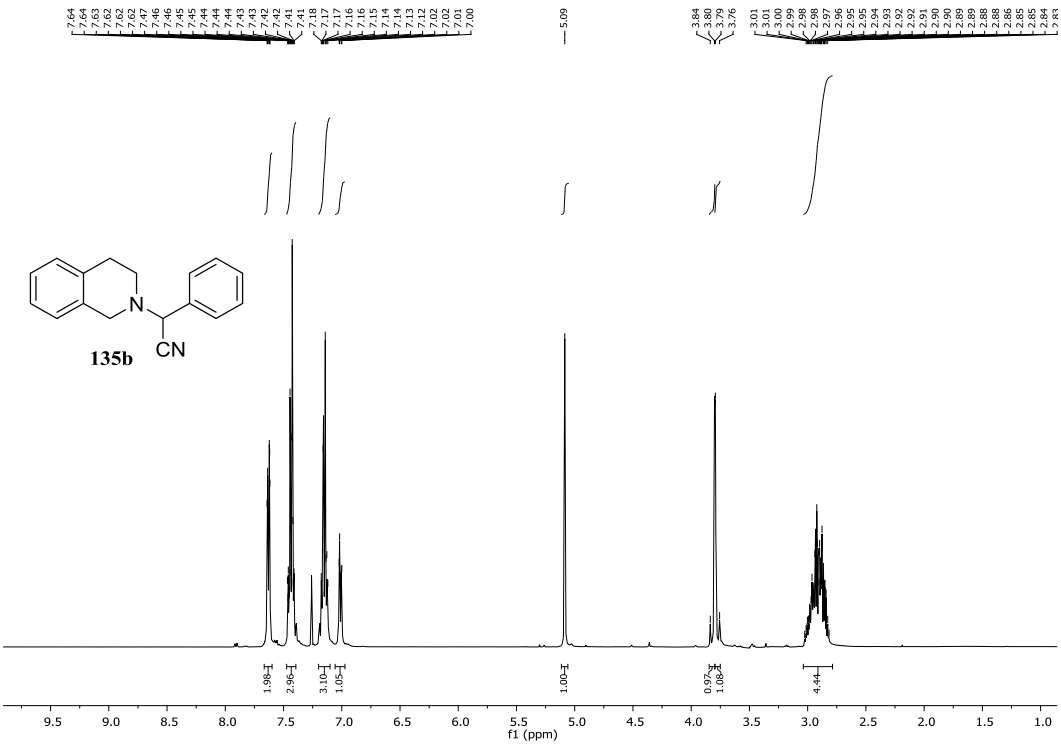
^{1}H NMR (400 MHz, $CDCl_3$) of compound **130a**.



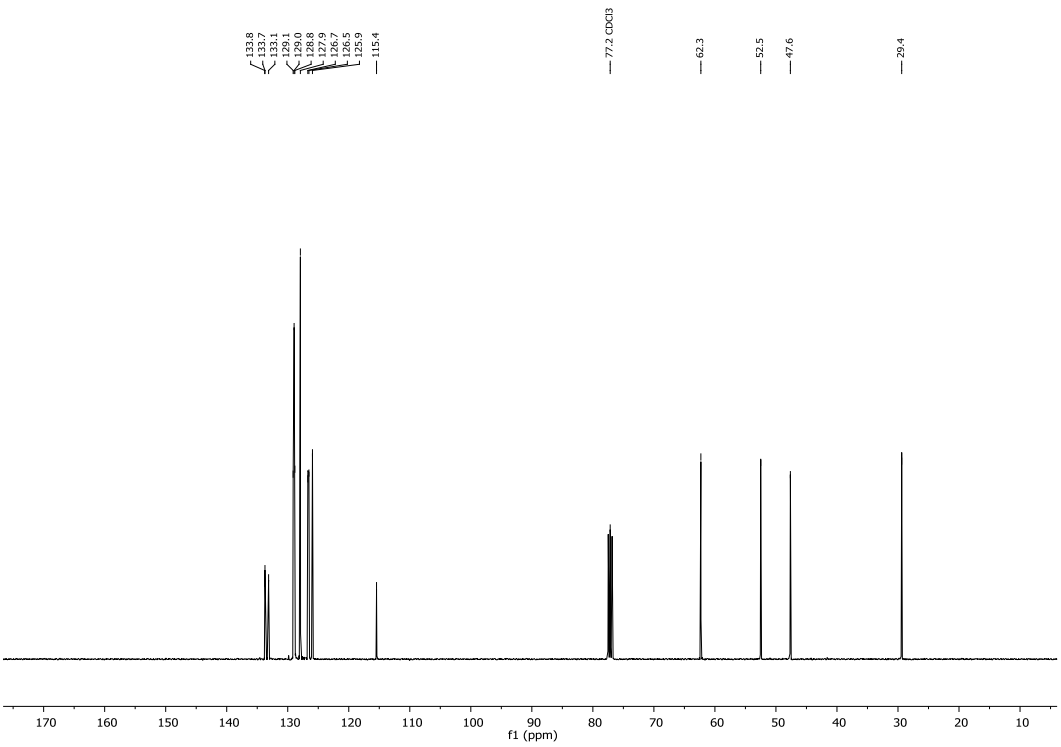
^{1}H NMR (400 MHz, $CDCl_3$) of compound **134a**.



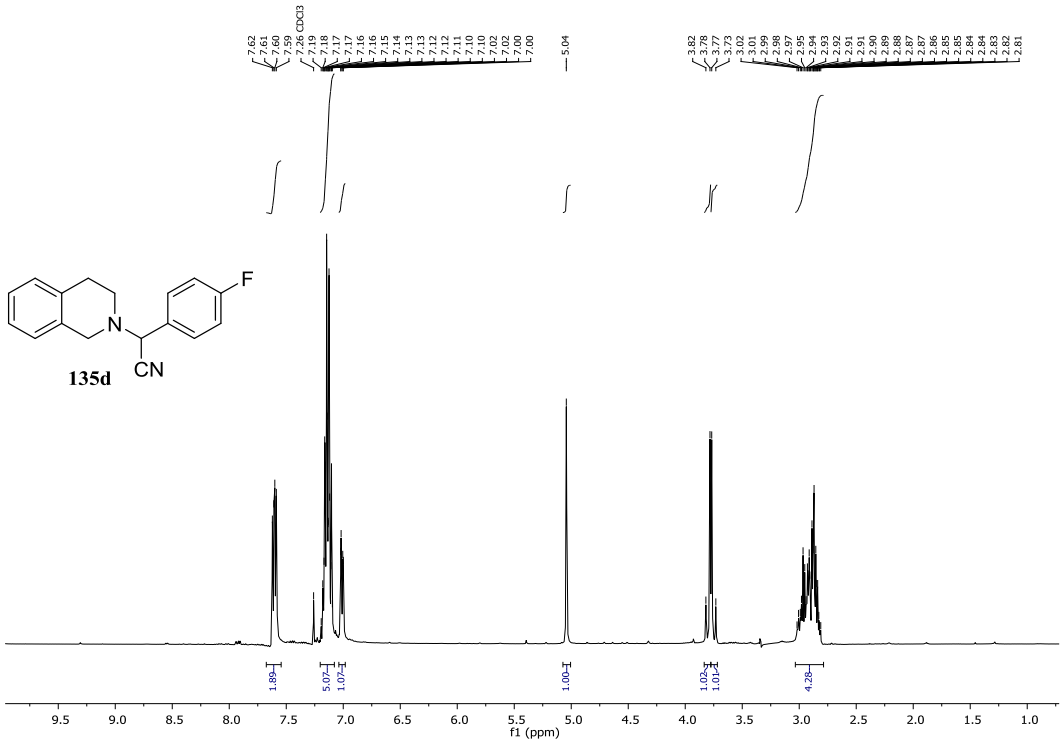
^{1}H NMR (400 MHz, $CDCl_3$) of compound **139**.



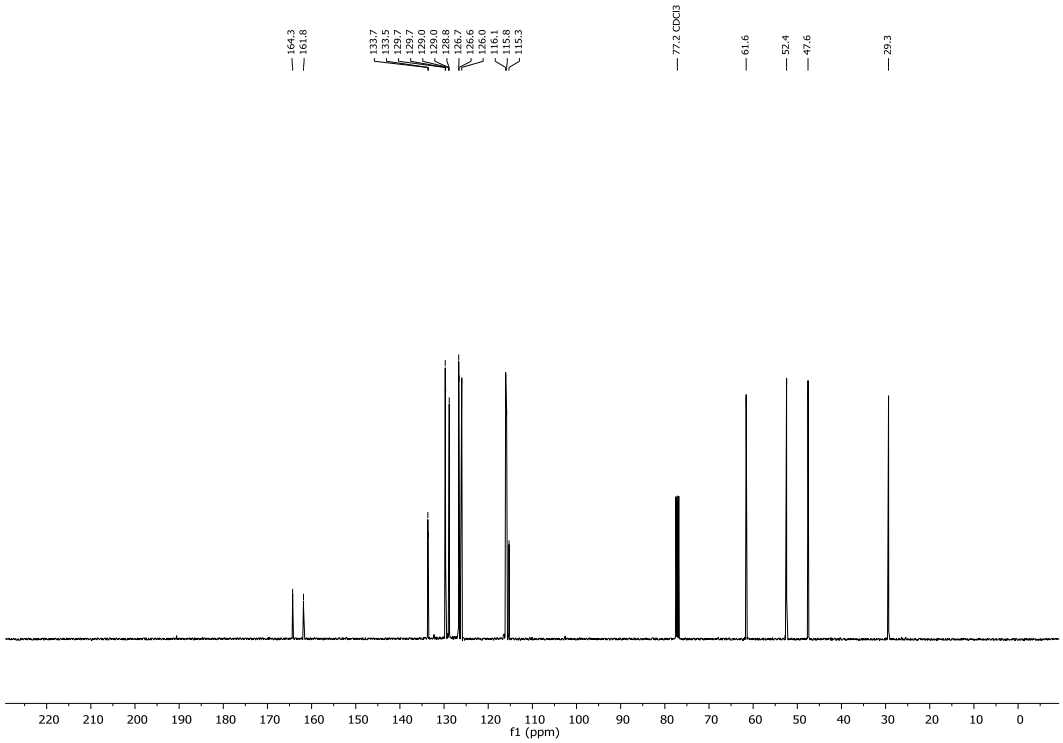
^{1}H NMR (400 MHz, $CDCl_3$) of compound **135b**.



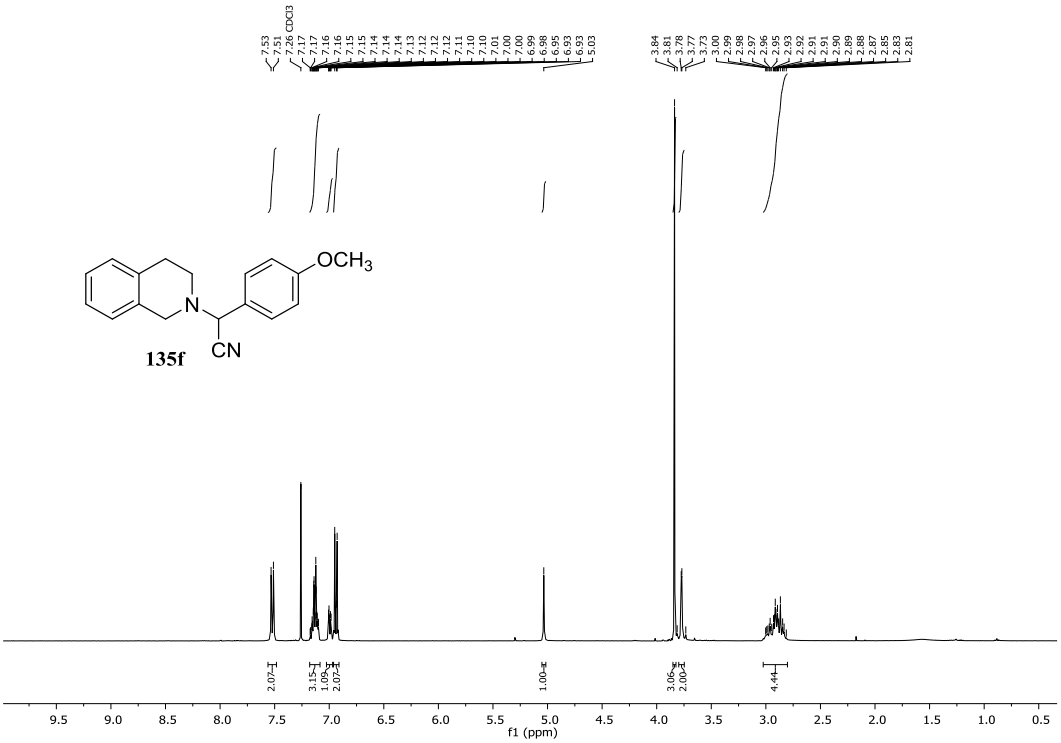
^{13}C NMR (100.6 MHz, $CDCl_3$) of compound **135b**.



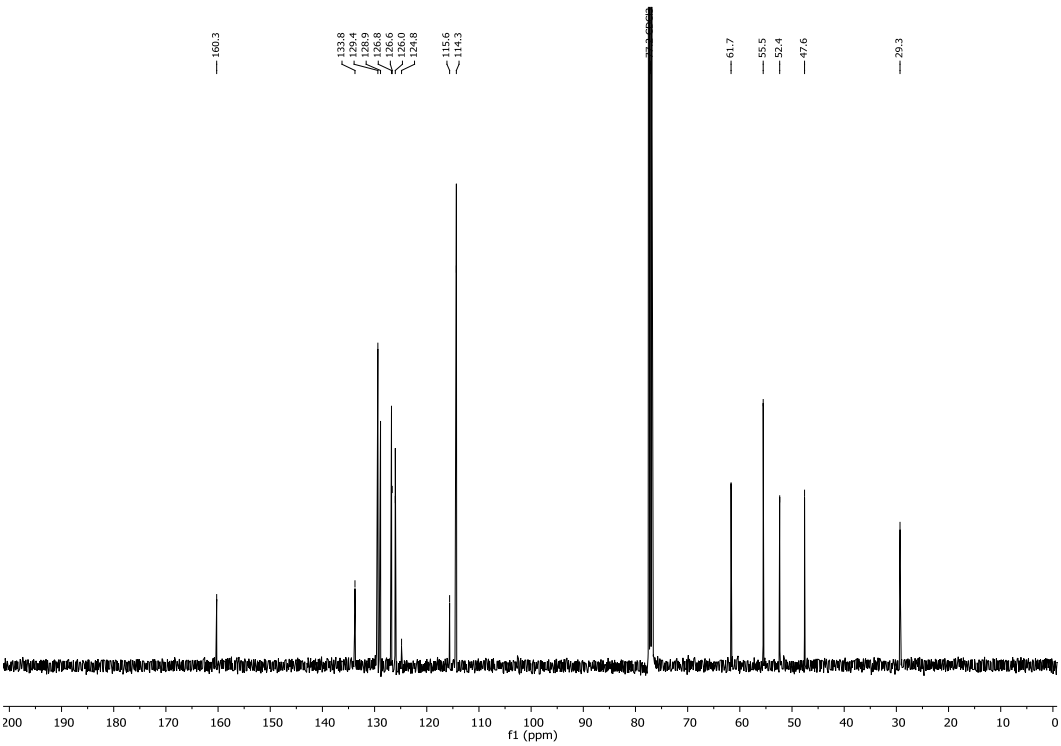
^{1}H NMR (400 MHz, $CDCl_3$) of compound **135d**.



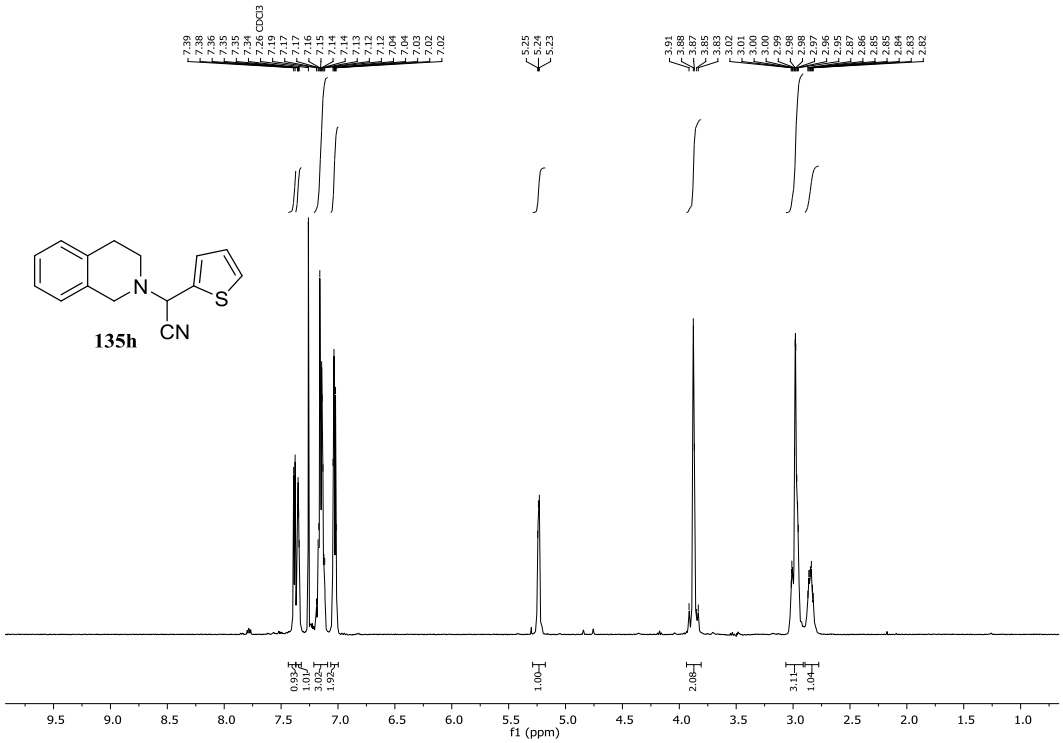
^{13}C NMR (100.6 MHz, $CDCl_3$) of compound **135d**.



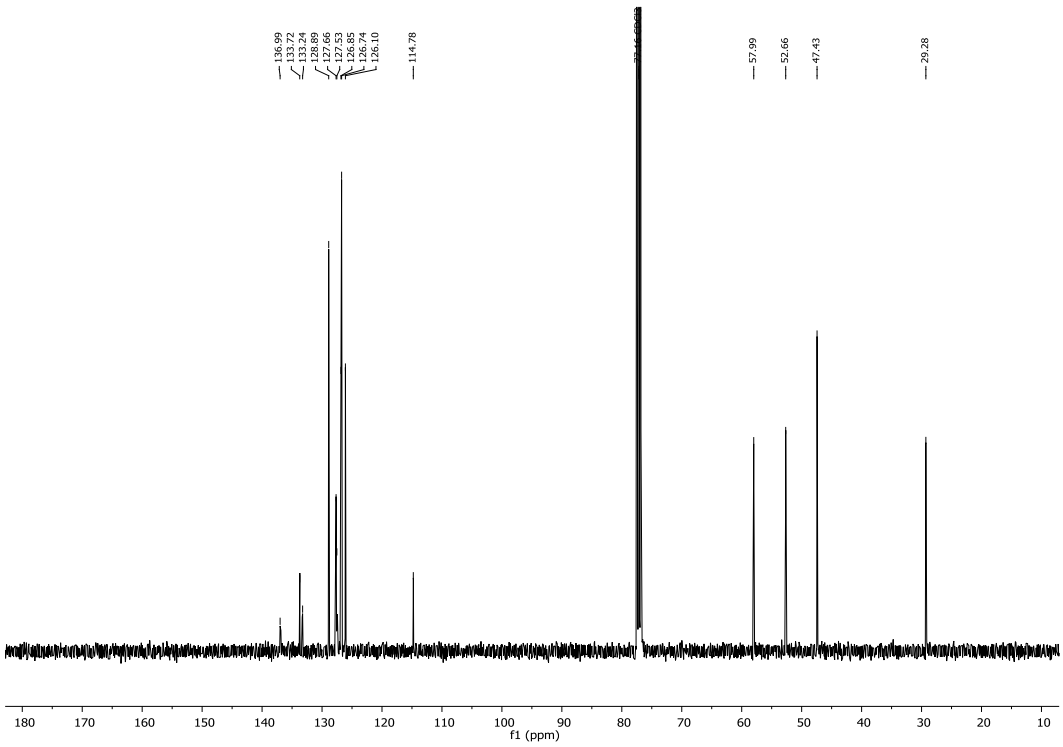
^{1}H NMR (400 MHz, $CDCl_3$) of compound **135f**.



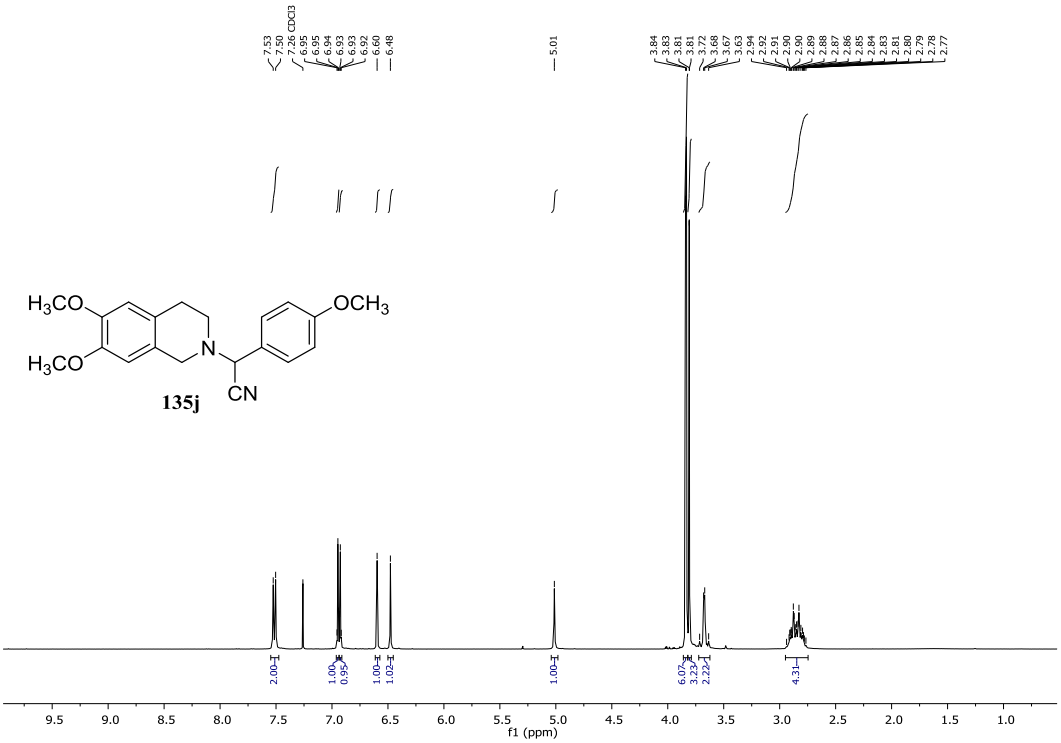
^{13}C NMR (100.6 MHz, $CDCl_3$) of compound **135f**.



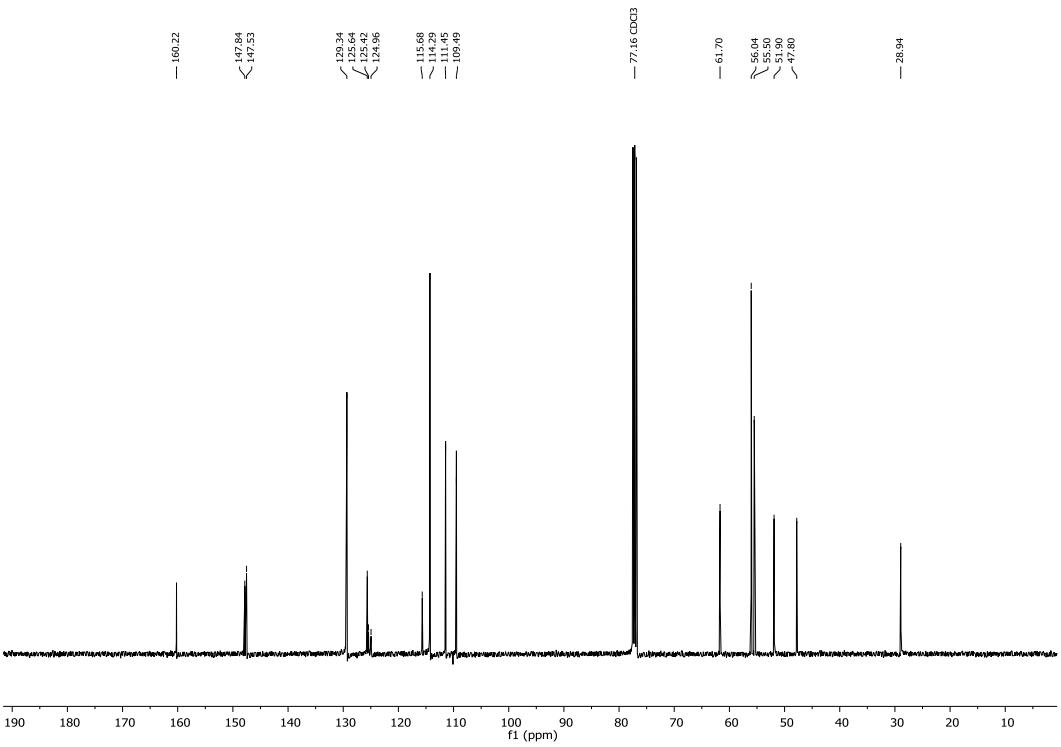
^{1}H NMR (400 MHz, $CDCl_3$) of compound **135h**.



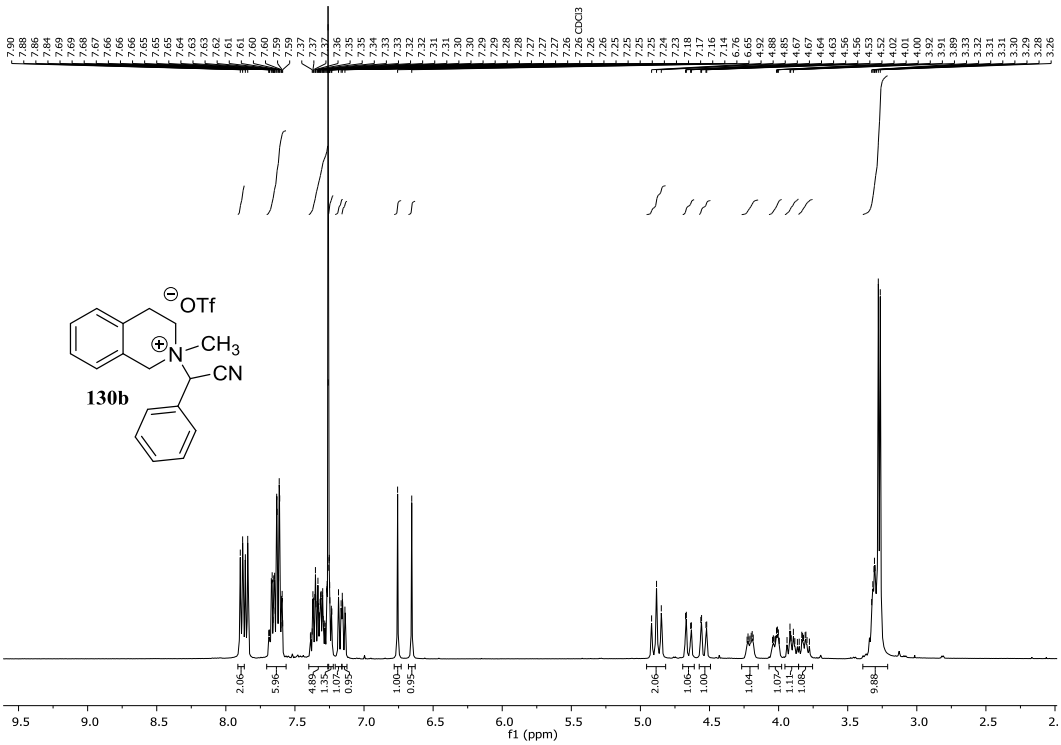
^{13}C NMR (100.6 MHz, $CDCl_3$) of compound **135h**.



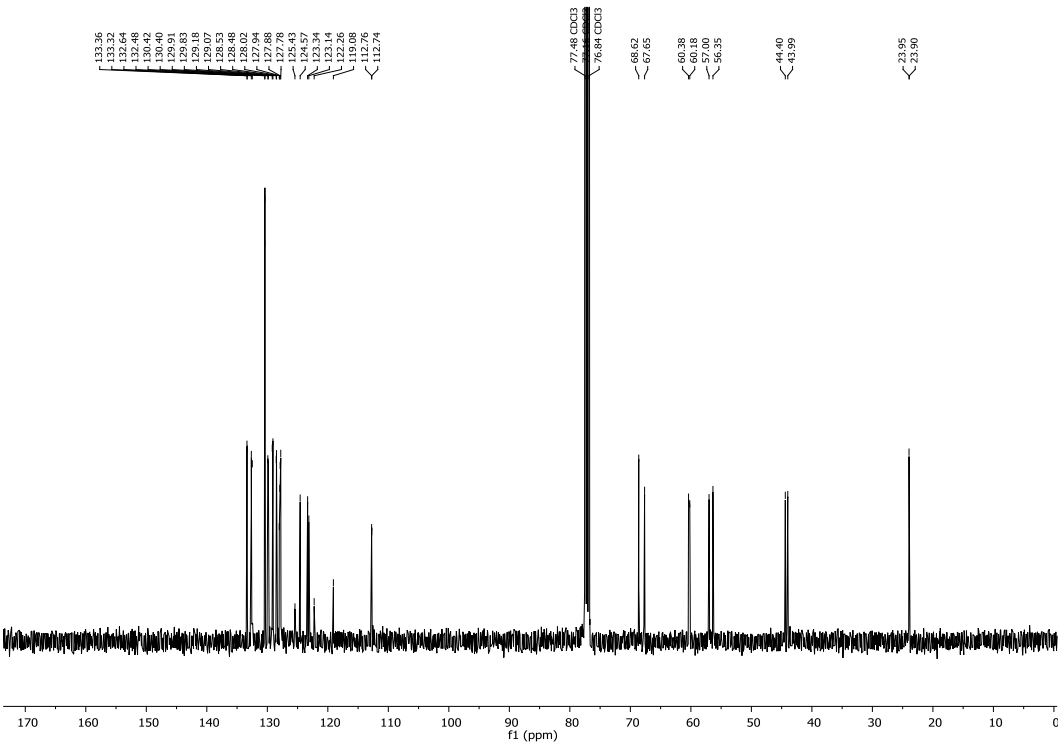
^{1}H NMR (400 MHz, $CDCl_3$) of compound **135j**.



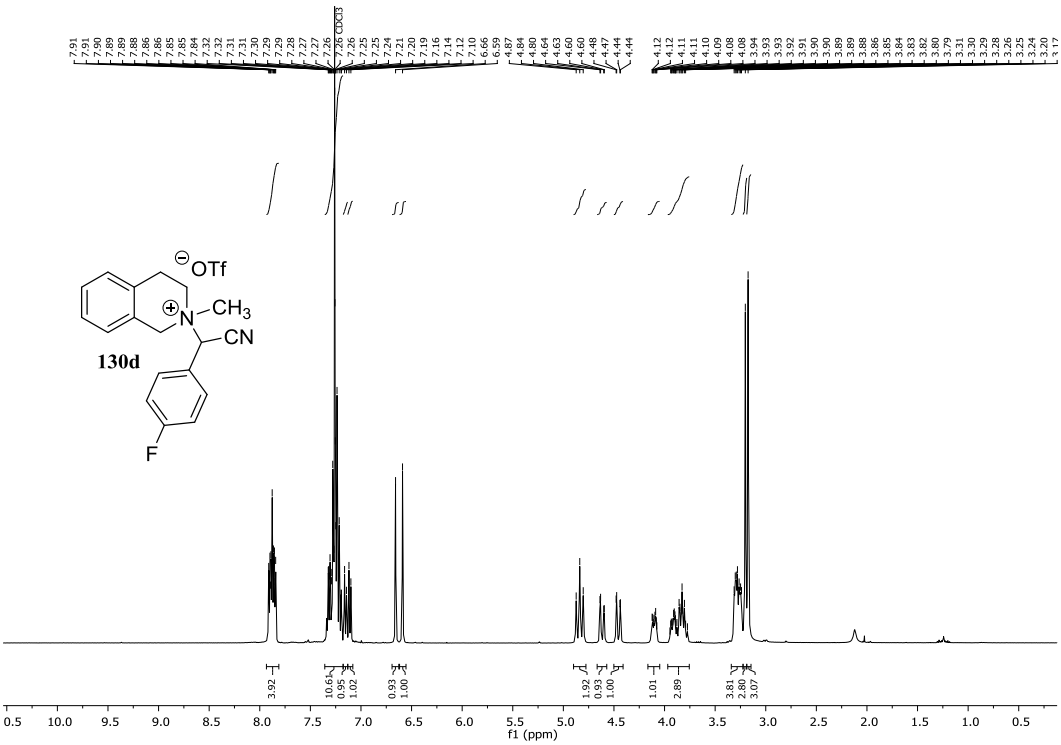
^{13}C NMR (100.6 MHz, $CDCl_3$) of compound **135j**.



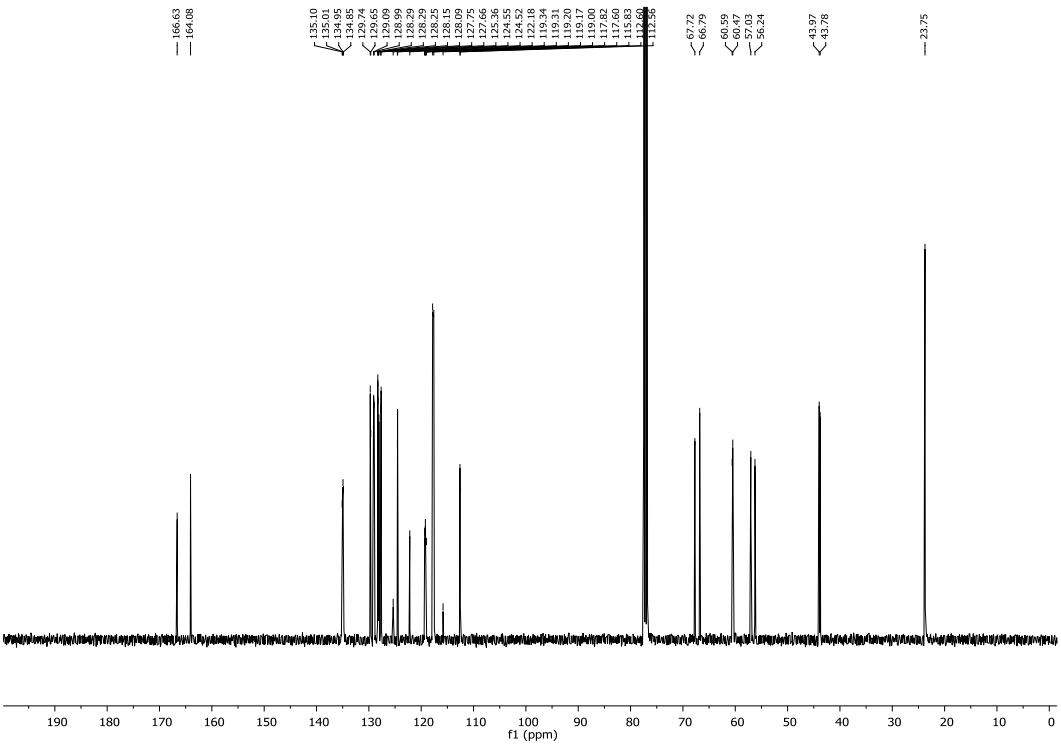
^{1}H NMR (400 MHz, $CDCl_3$) of compound **130b**.



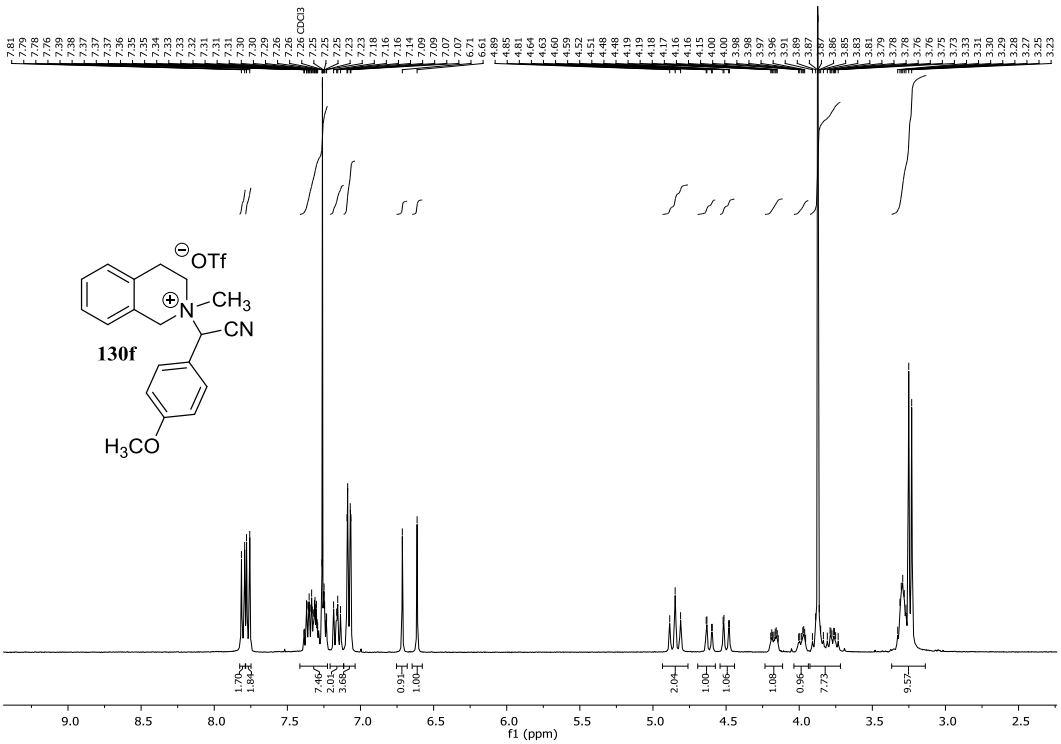
^{13}C NMR (100.6 MHz, $CDCl_3$) of compound **130b**.



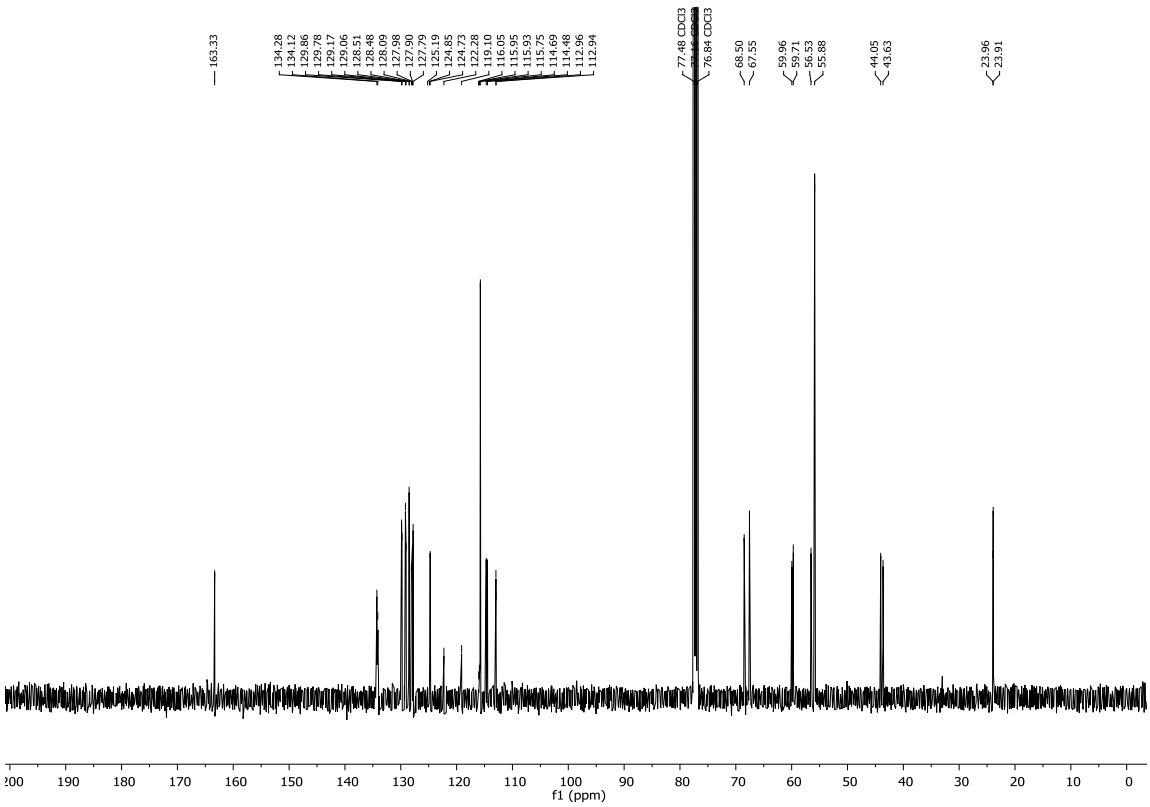
^{1}H NMR (400 MHz, $CDCl_3$) of compound **130d**.



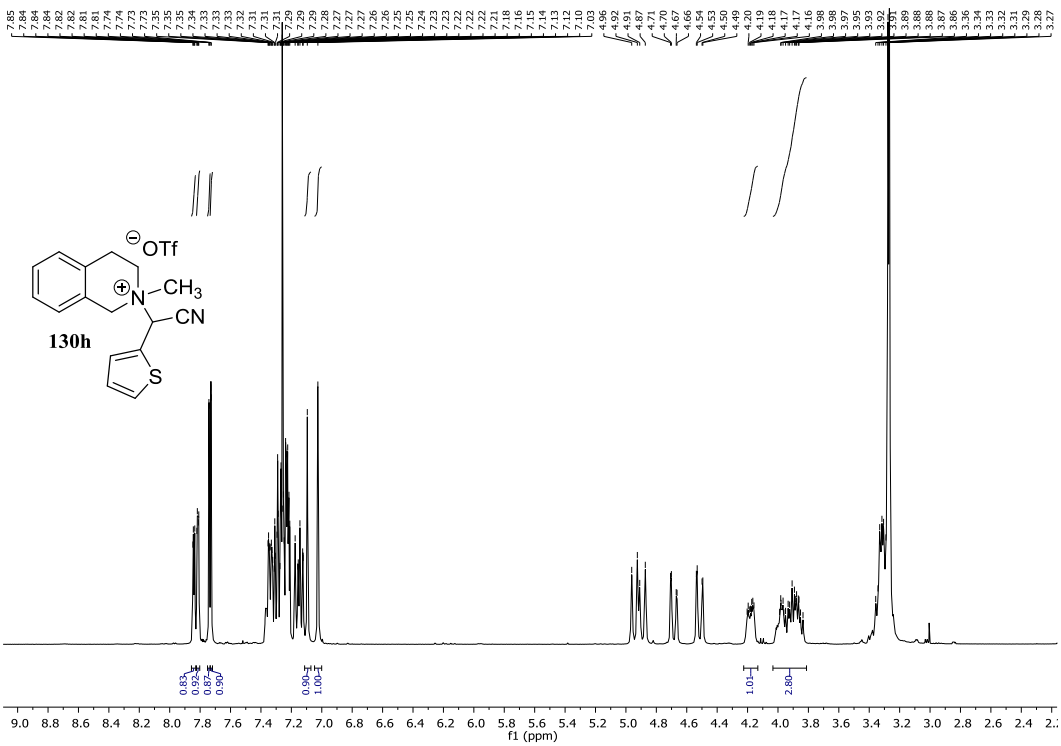
^{13}C NMR (100.6 MHz, $CDCl_3$) of compound **130d**.



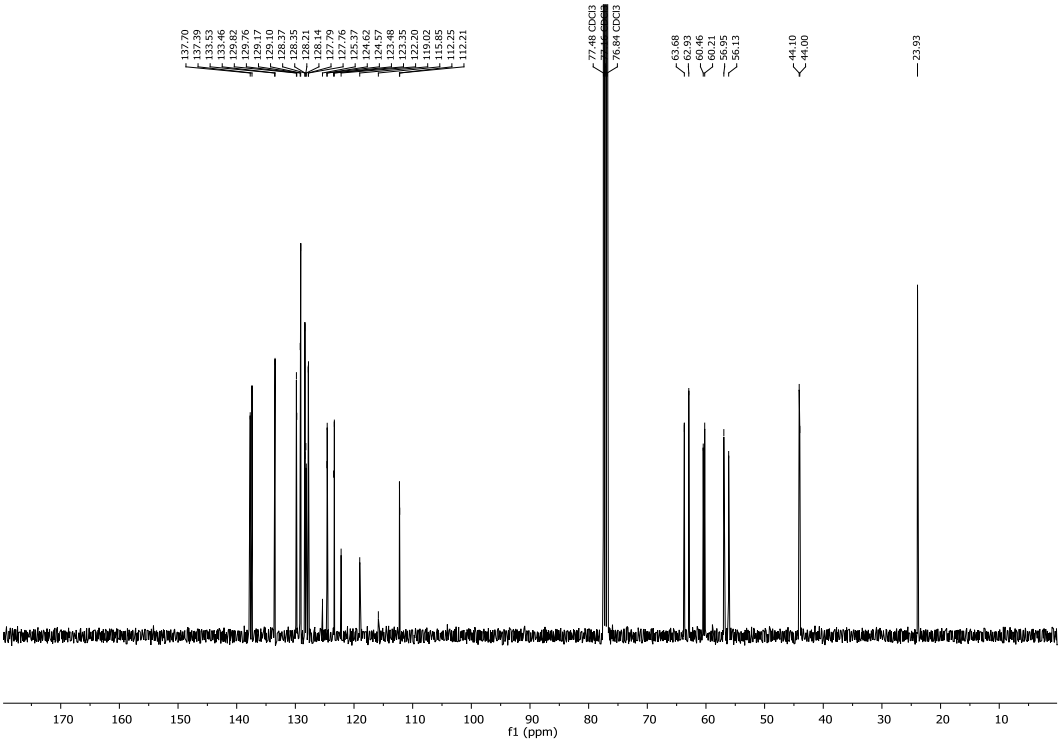
^{1}H NMR (400 MHz, $CDCl_3$) of compound **130f**.



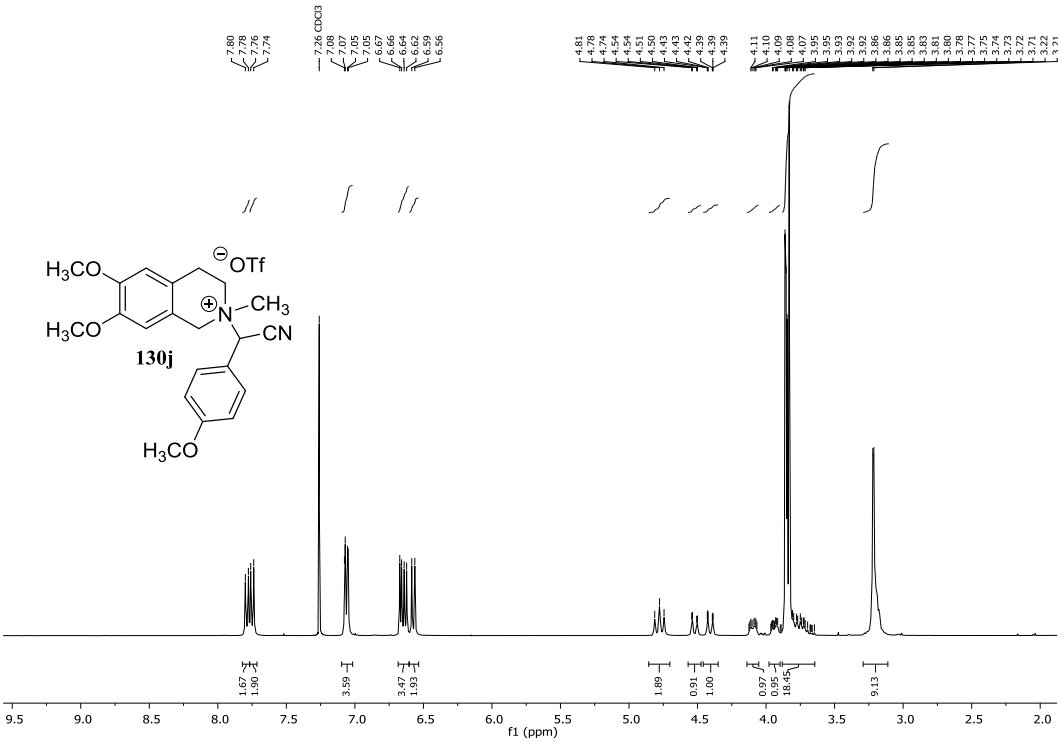
^{13}C NMR (100.6 MHz, $CDCl_3$) of compound **130f**.



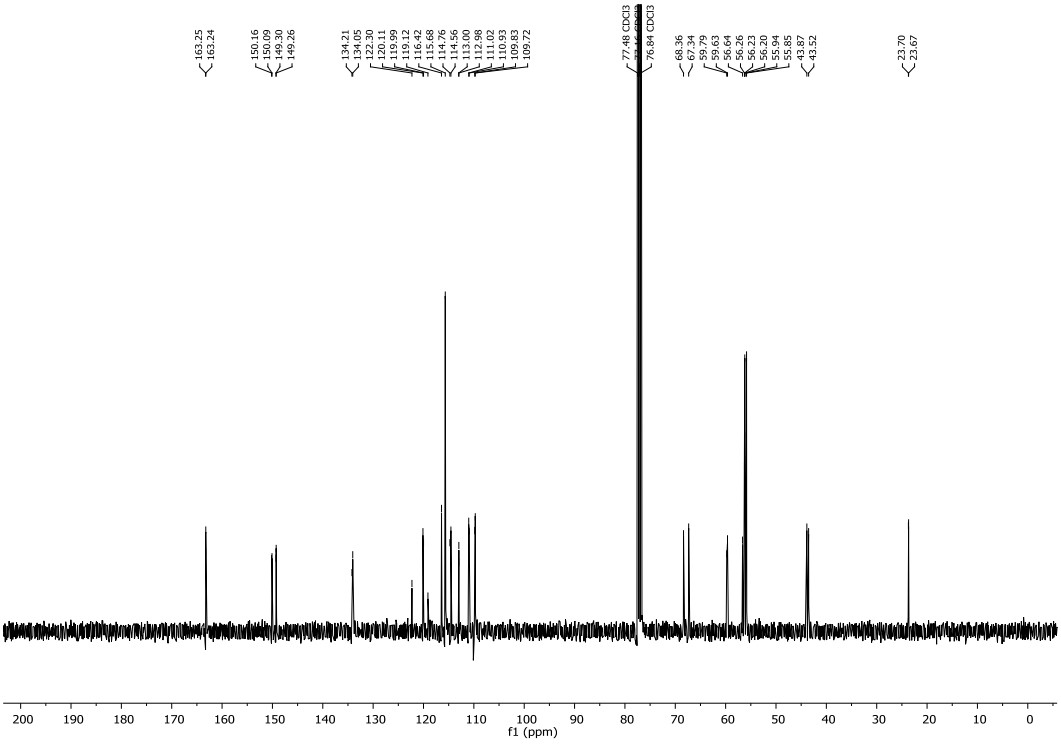
^{1}H NMR (400 MHz, $CDCl_3$) of compound **130h**.



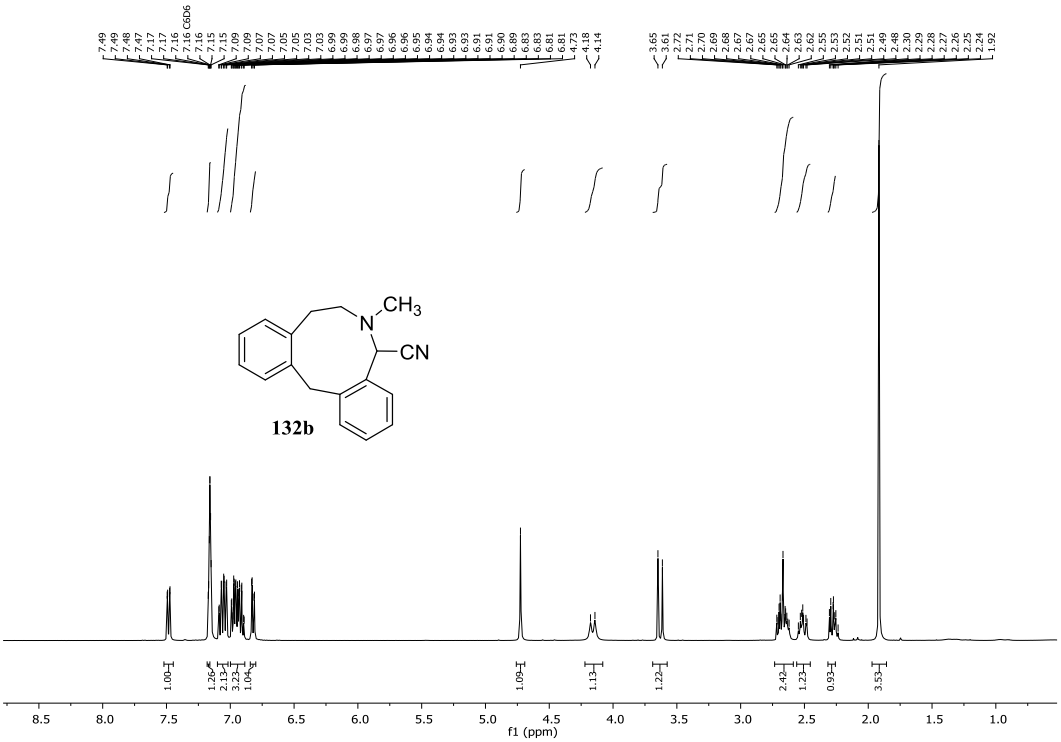
^{13}C NMR (100.6 MHz, $CDCl_3$) of compound **130h**.



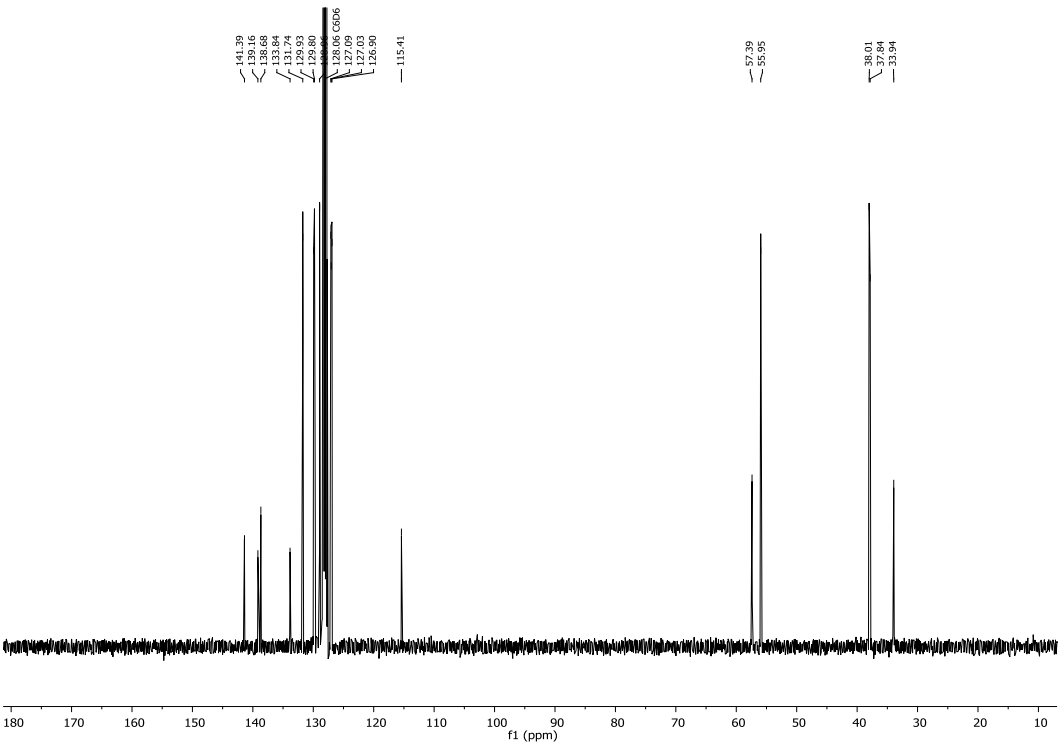
^{1}H NMR (400 MHz, $CDCl_3$) of compound **130j**.



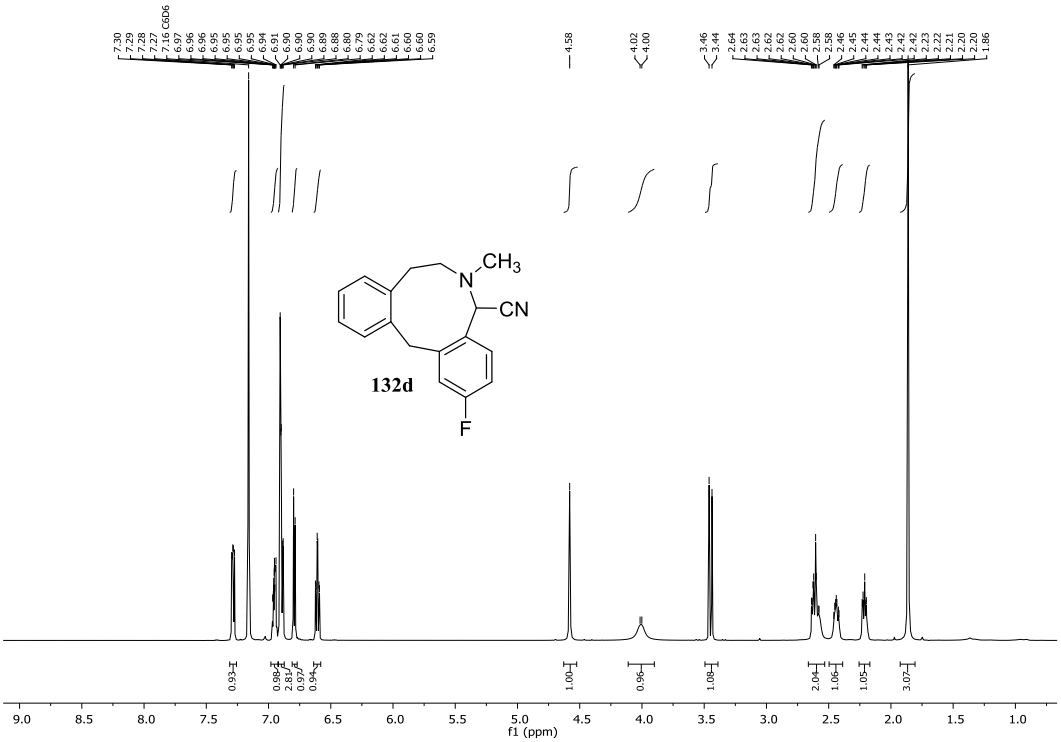
^{13}C NMR (100.6 MHz, $CDCl_3$) of compound **130j**.



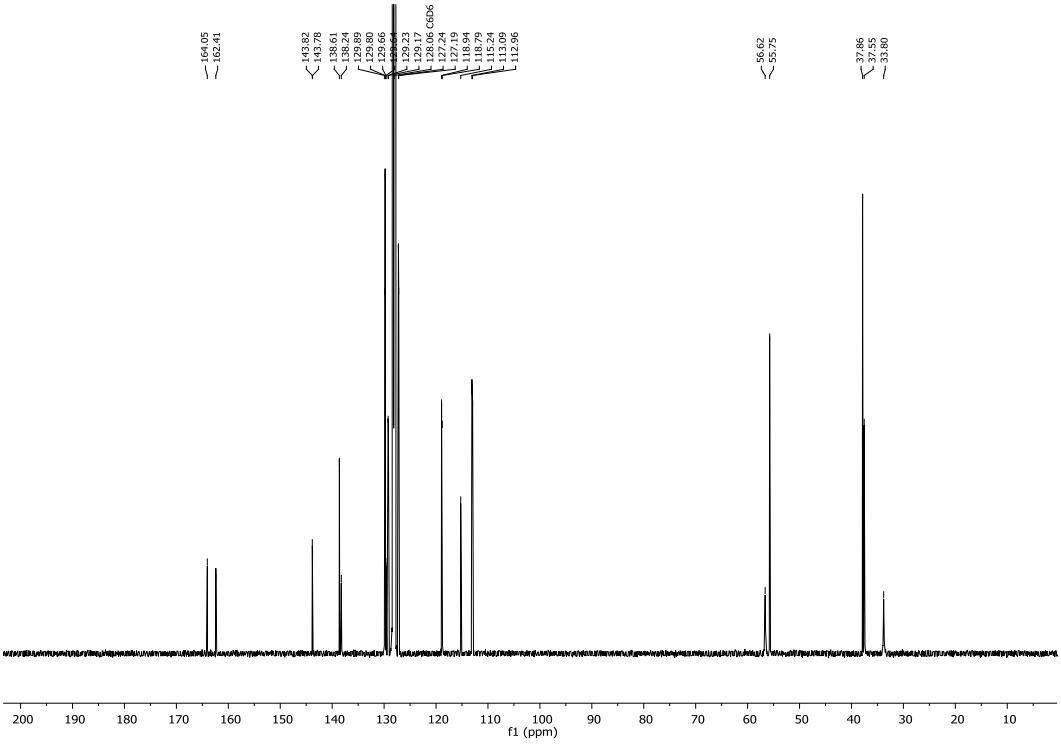
^{1}H NMR (400 MHz, C_6D_6) of compound **132b**.



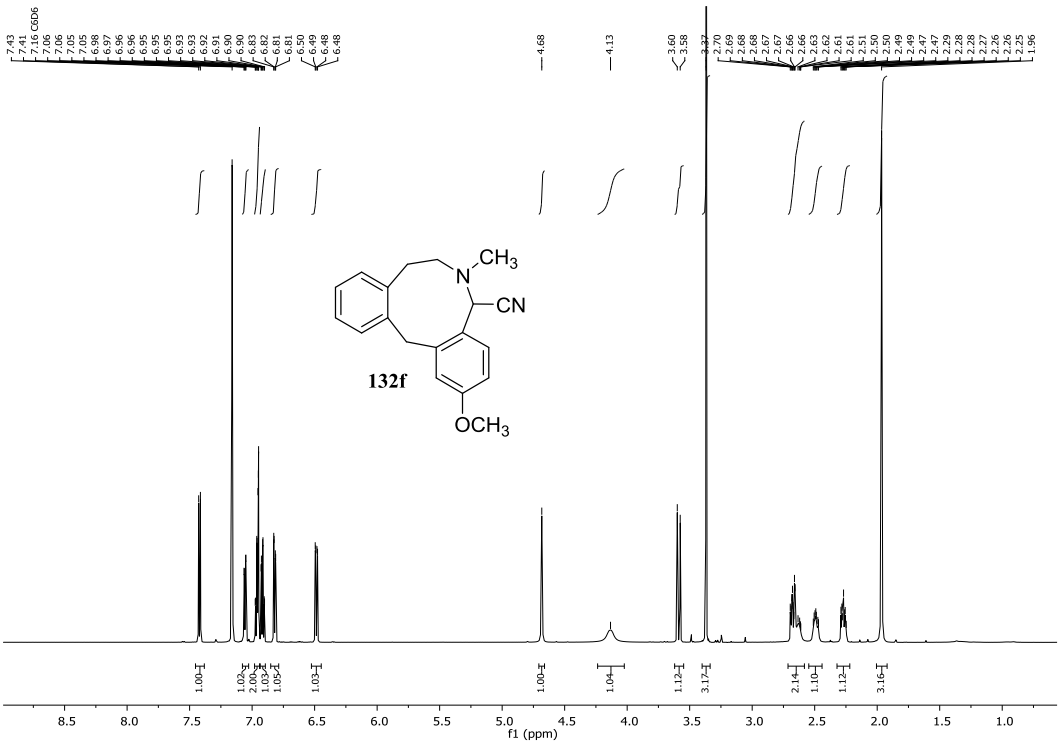
^{13}C NMR (100.6 MHz, C_6D_6) of compound **132b**.



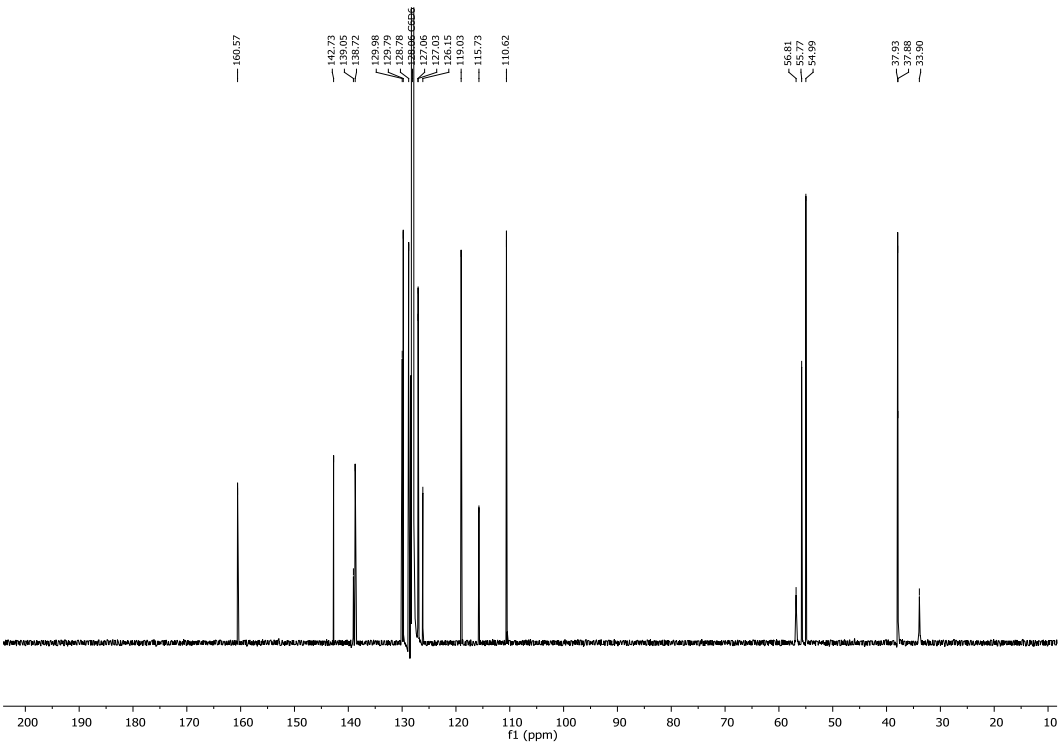
^{1}H NMR (600 MHz, C_6D_6) of compound **132d**.



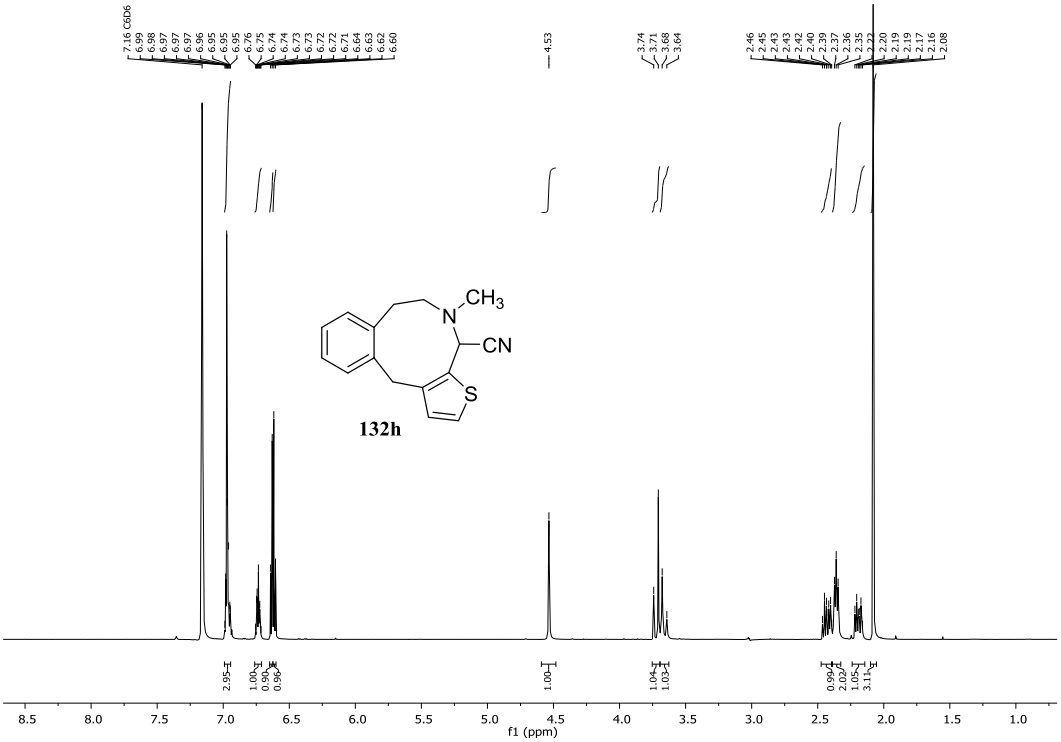
^{13}C NMR (150.9 MHz, C_6D_6) of compound **132d**.



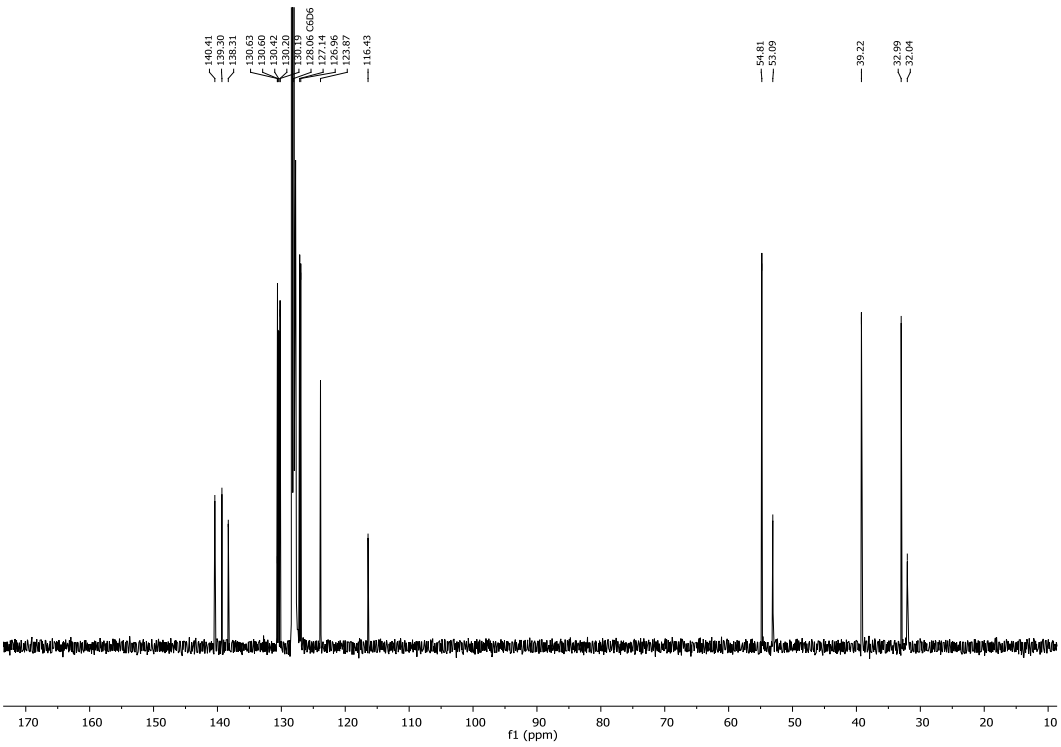
^{1}H NMR (600 MHz, C_6D_6) of compound **132f**.



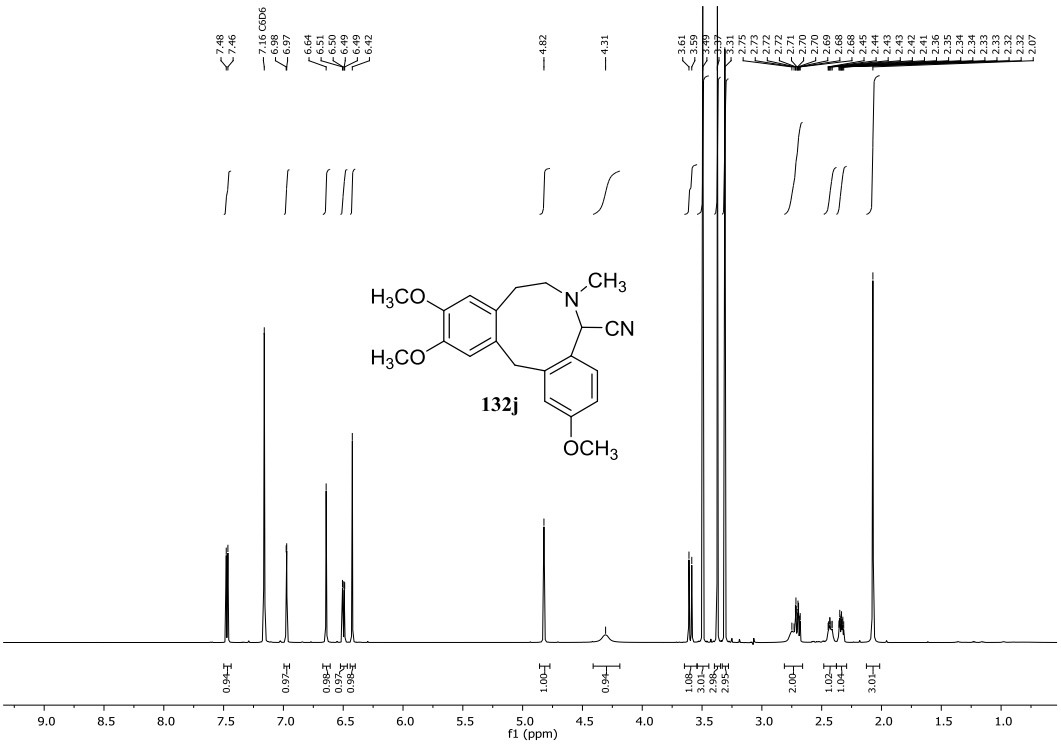
^{13}C NMR (150.9 MHz, C_6D_6) of compound **132f**.



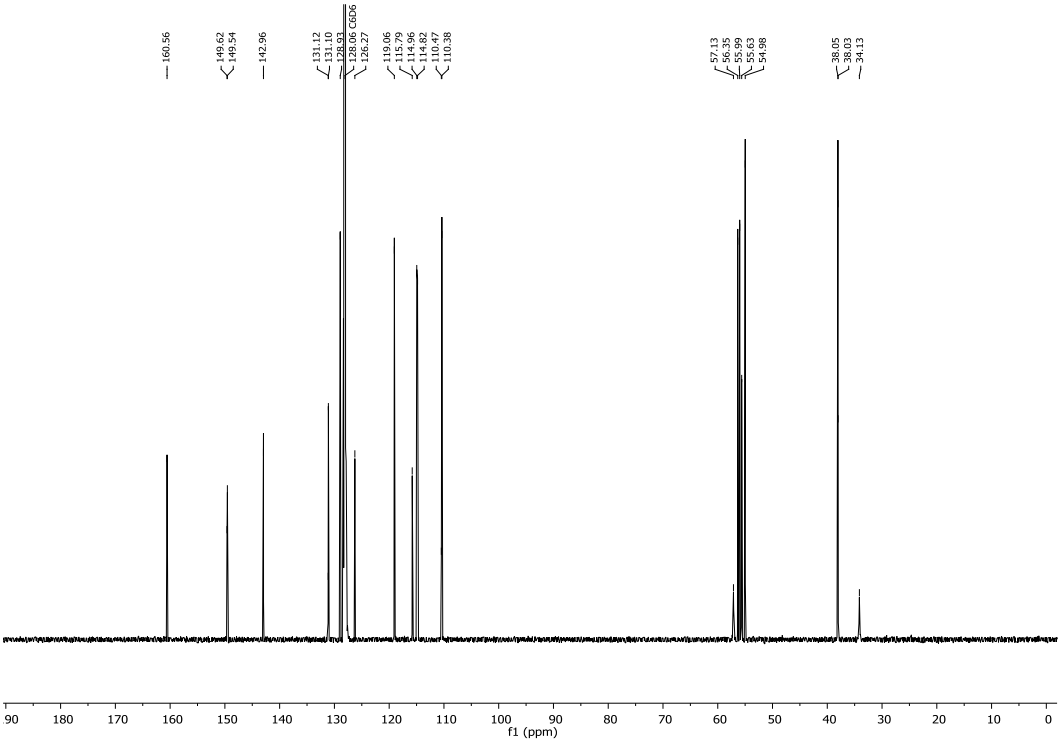
^{1}H NMR (400 MHz, C_6D_6) of compound **132h**.



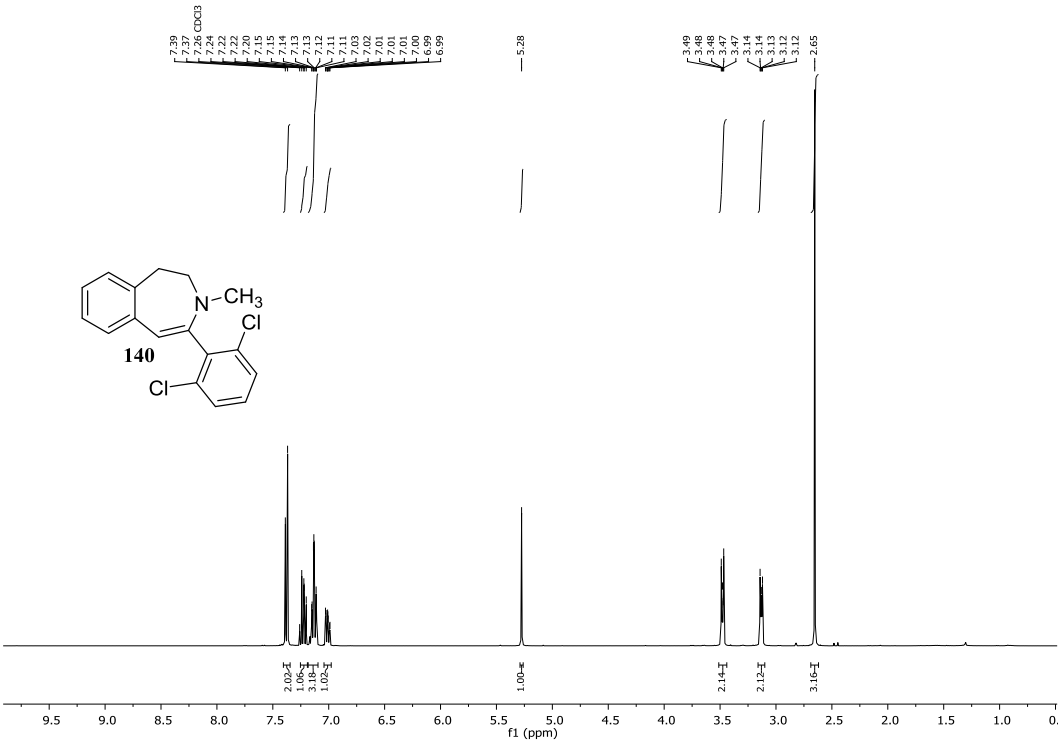
^{13}C NMR (150.9 MHz, C_6D_6) of compound **132f**.



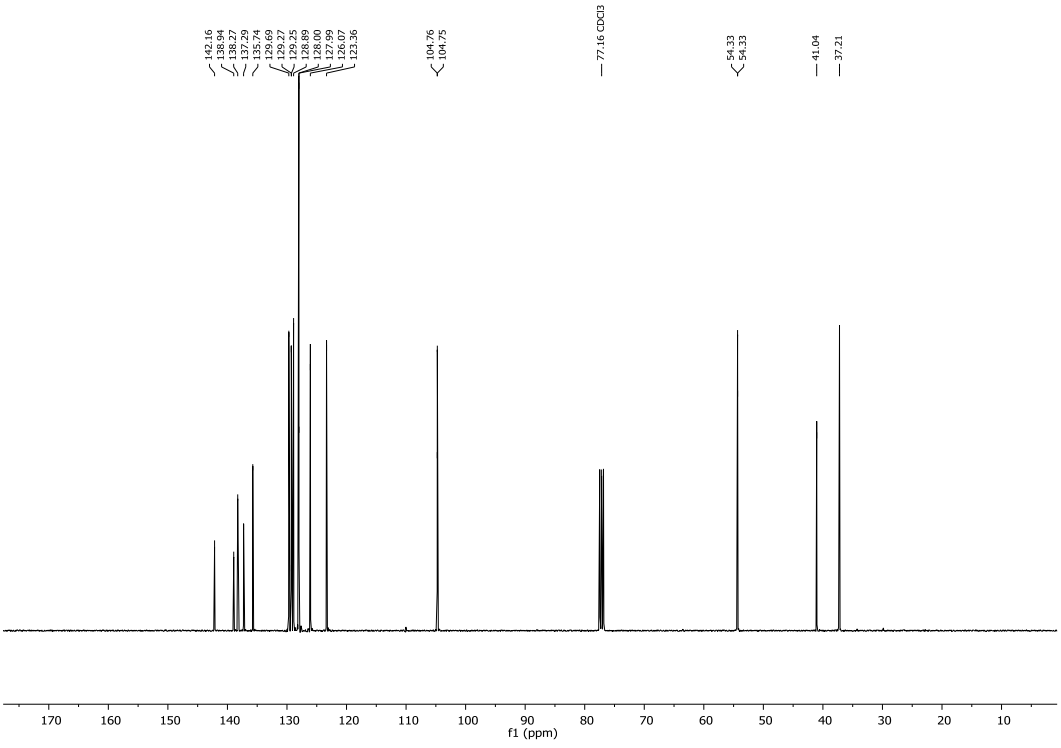
^{1}H NMR (600 MHz, C_6D_6) of compound **132j**.



^{13}C NMR (150.9 MHz, C_6D_6) of compound **132j**.

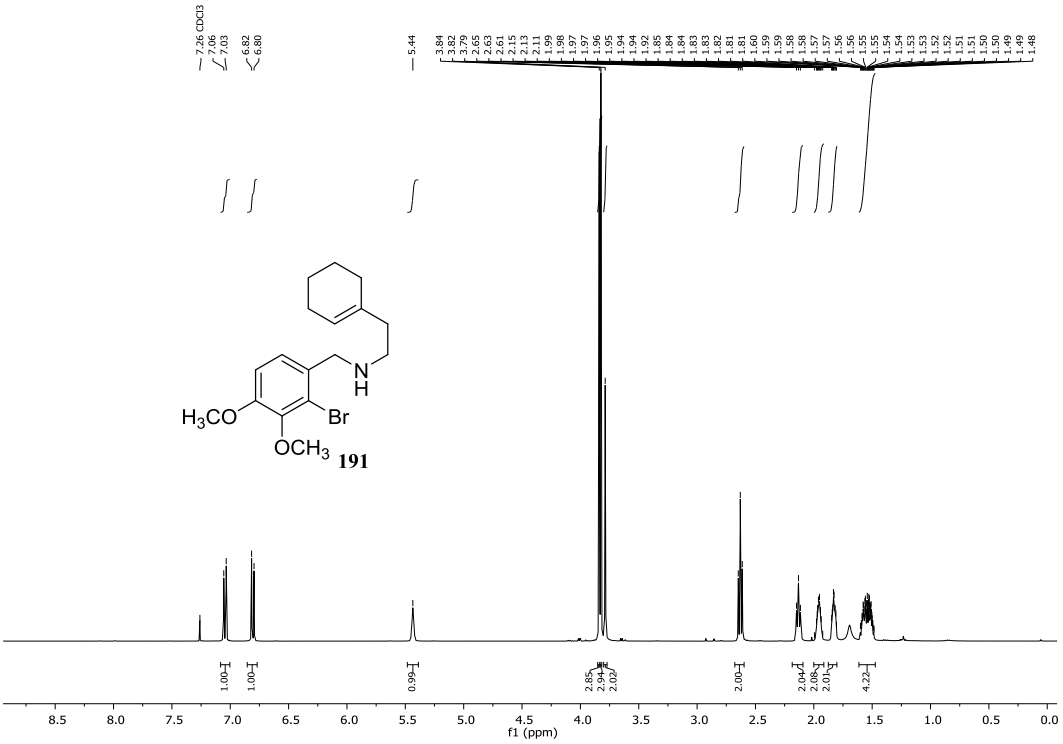


^{1}H NMR (400 MHz, $CDCl_3$) of compound **140**.

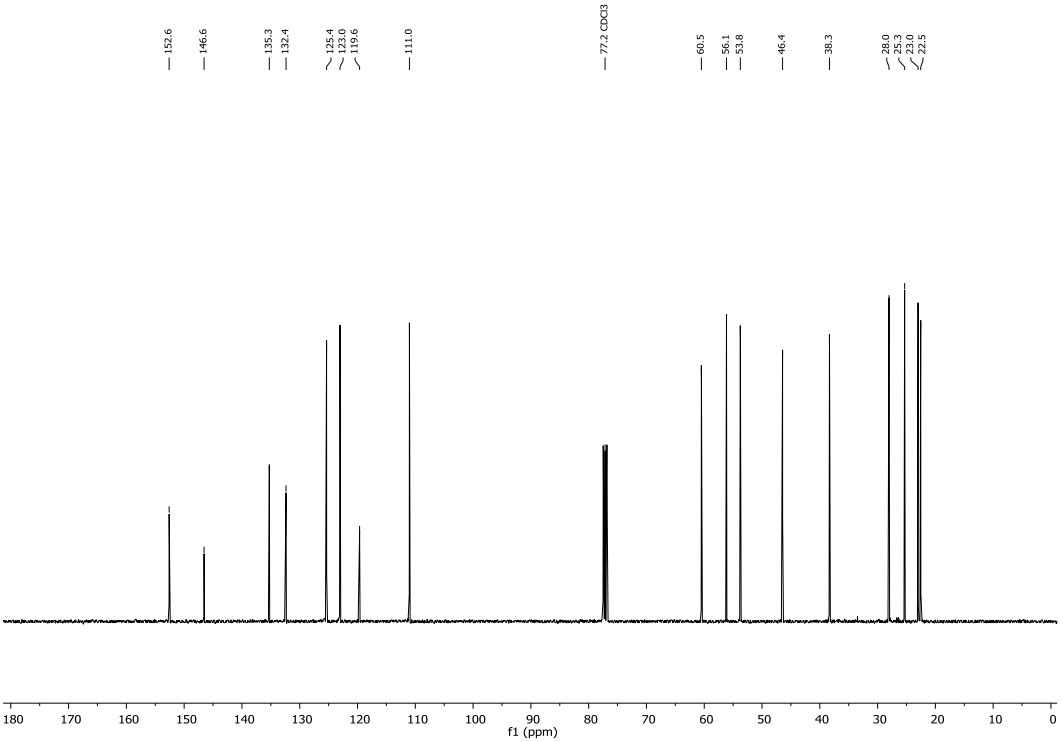


^{13}C NMR (100.6 MHz, $CDCl_3$) of compound **140**.

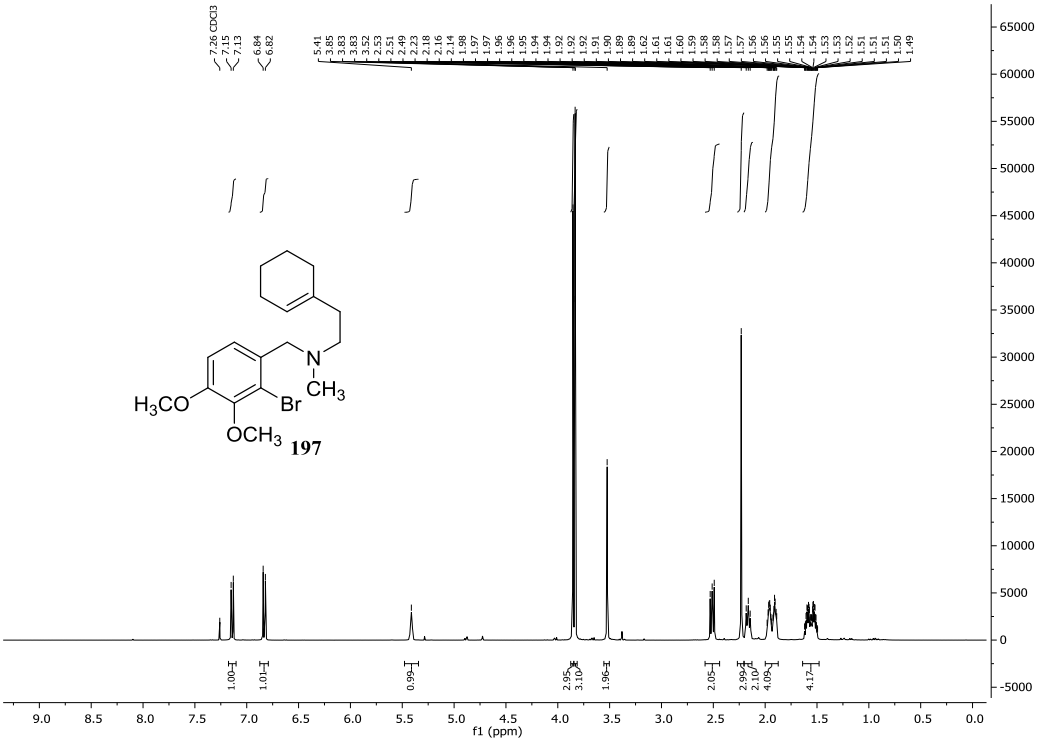
Chapter 3



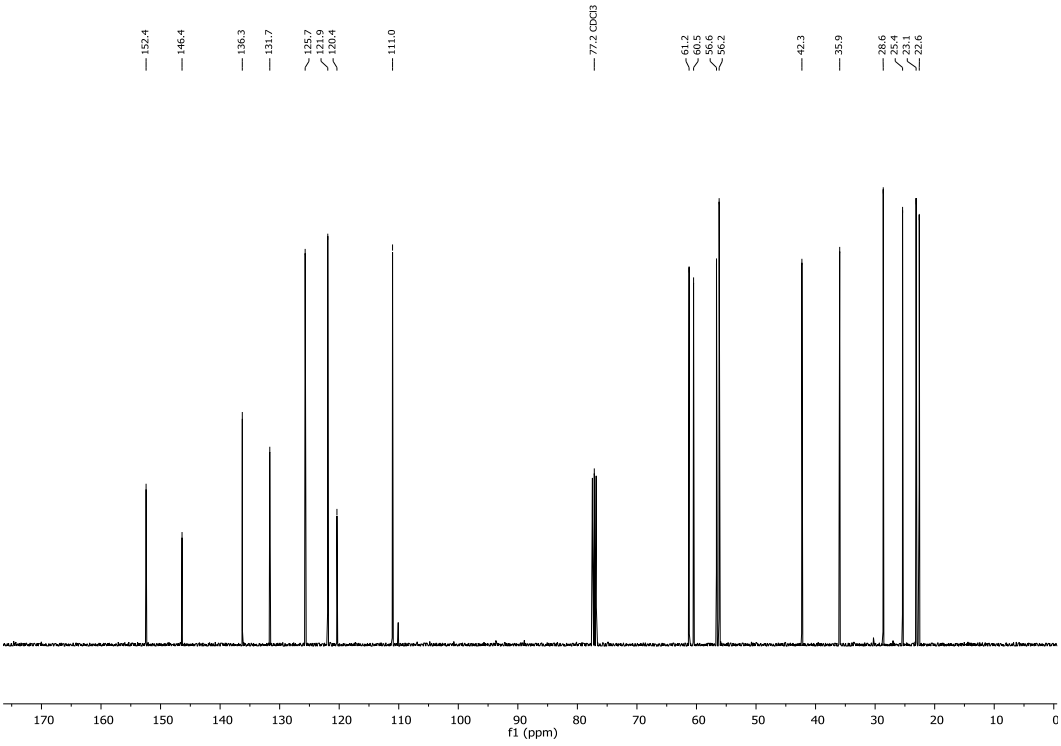
^{1}H NMR (400 MHz, $CDCl_3$) of compound **191**.



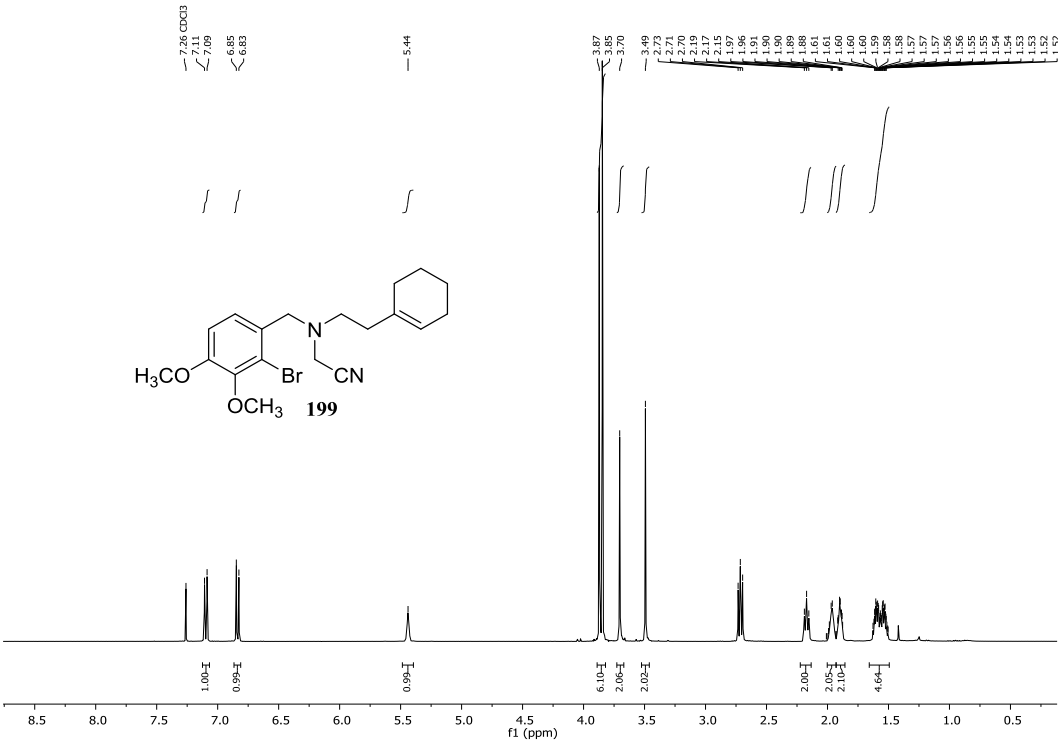
^{13}C NMR (100.6 MHz, $CDCl_3$) of compound **191**.



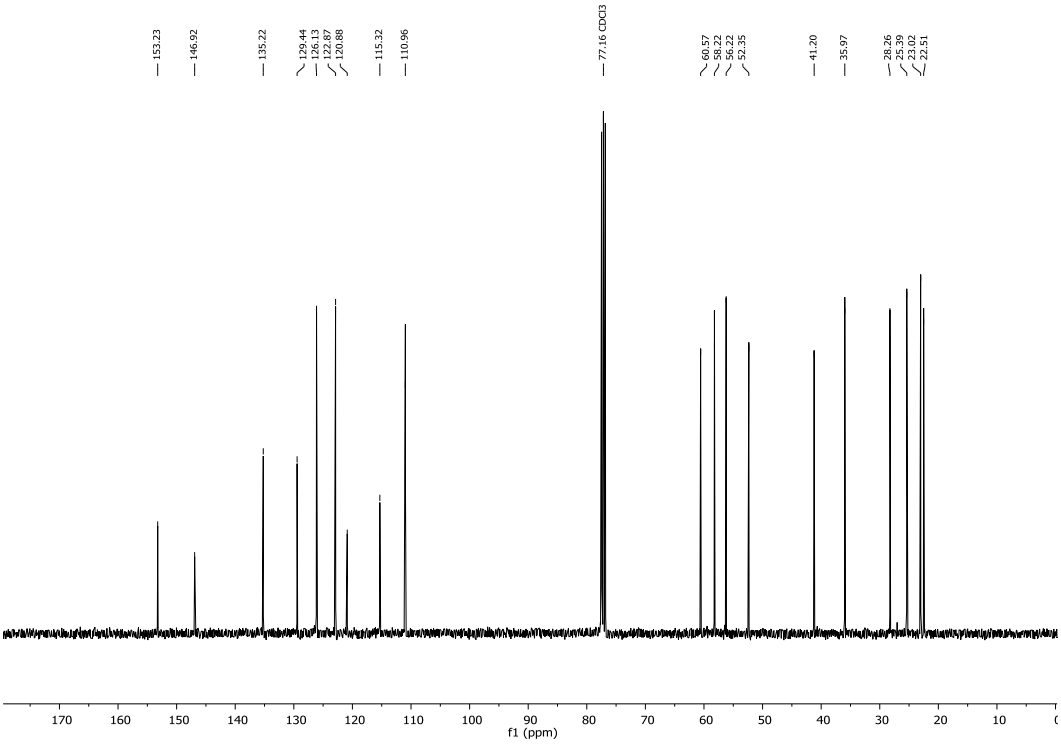
^{1}H NMR (400 MHz, $CDCl_3$) of compound **197**.



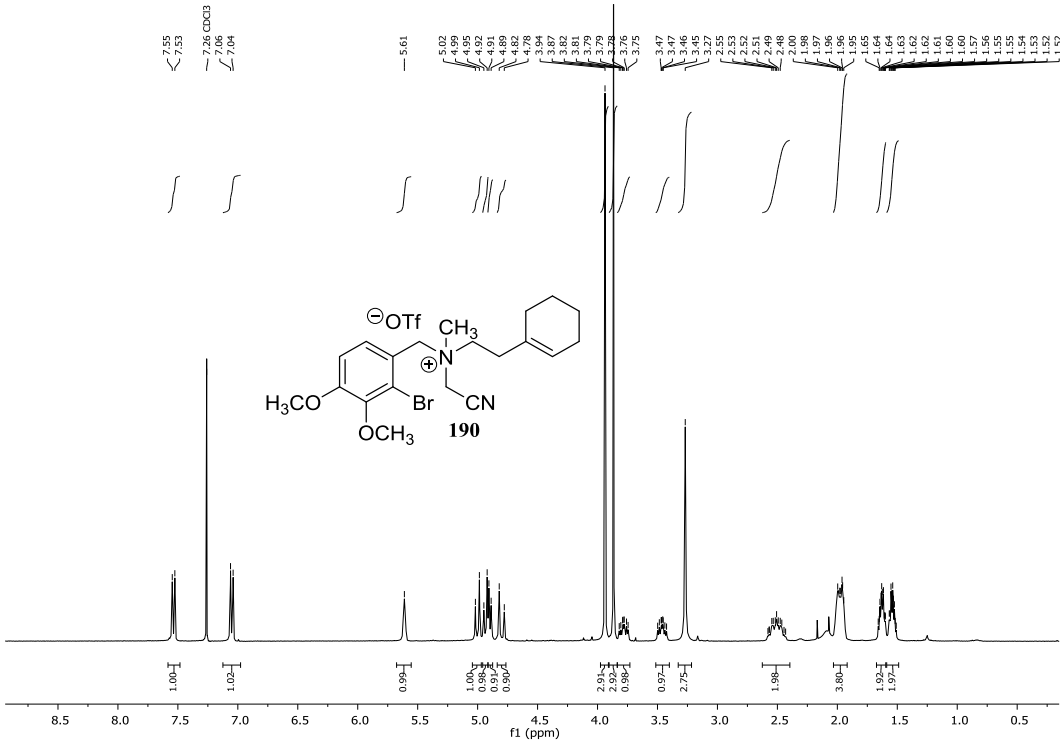
^{13}C NMR (100.6 MHz, $CDCl_3$) of compound **197**.



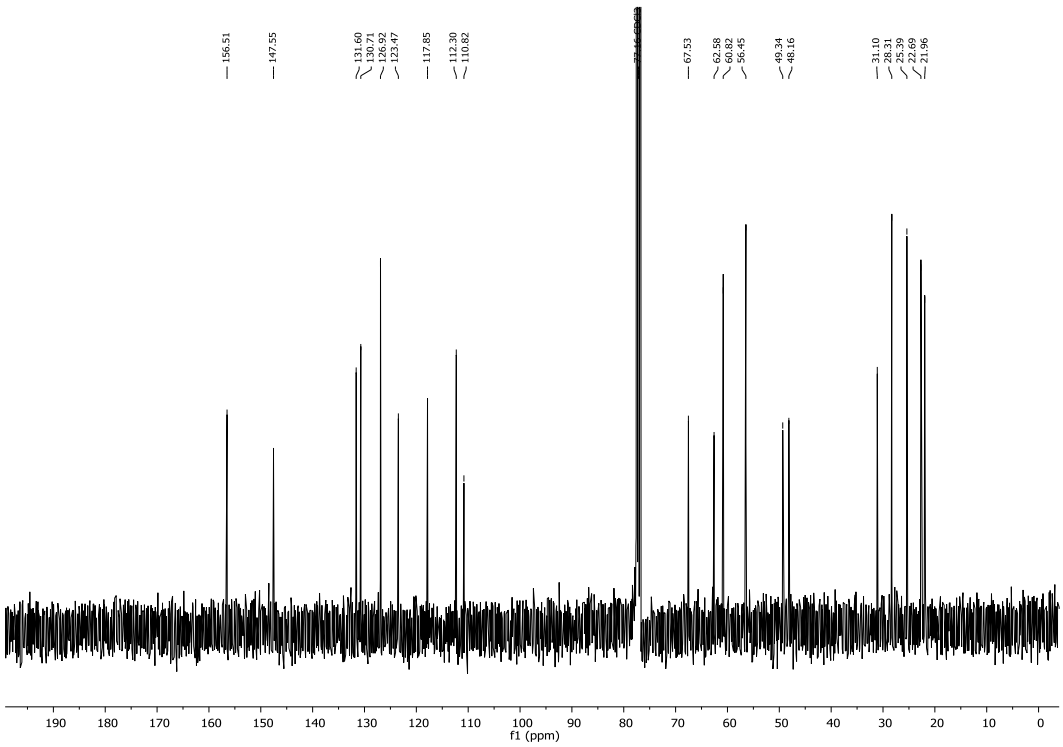
^{1}H NMR (400 MHz, $CDCl_3$) of compound **199**.



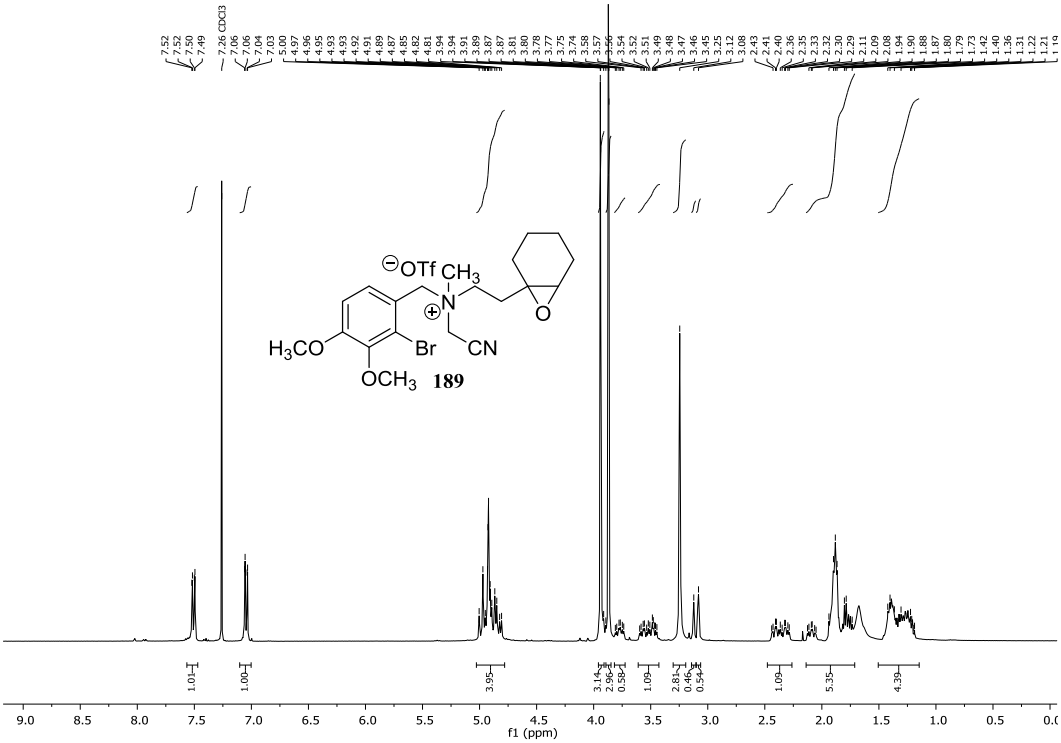
^{13}C NMR (100.6 MHz, $CDCl_3$) of compound **199**.



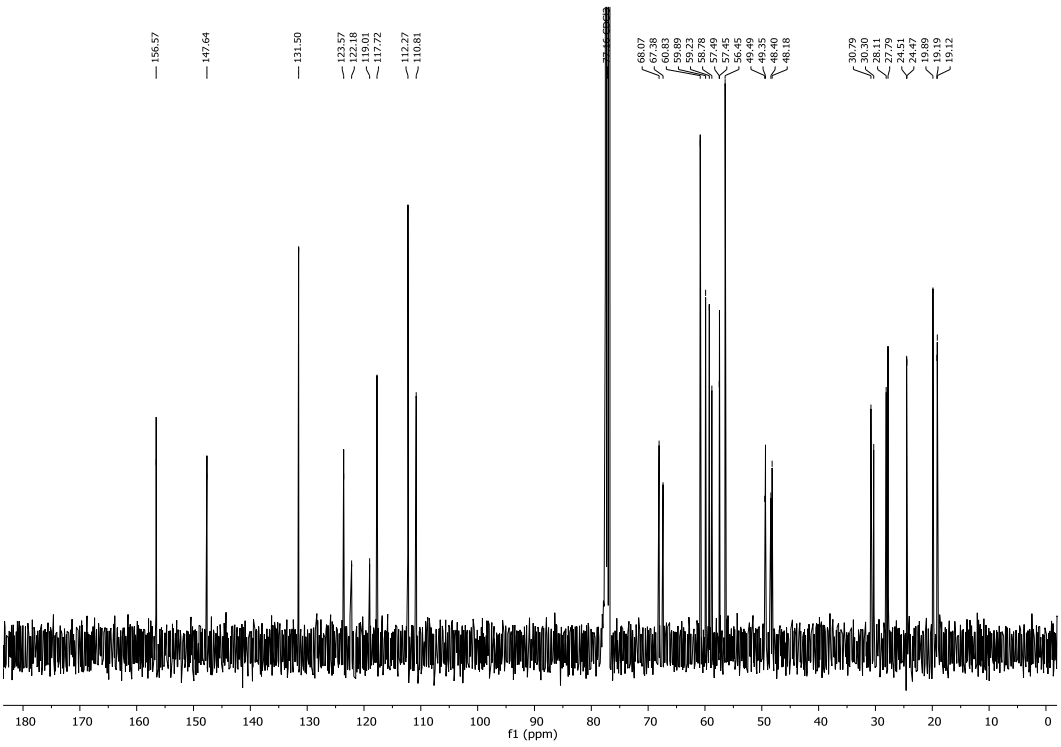
^{1}H NMR (400 MHz, $CDCl_3$) of compound **190**.



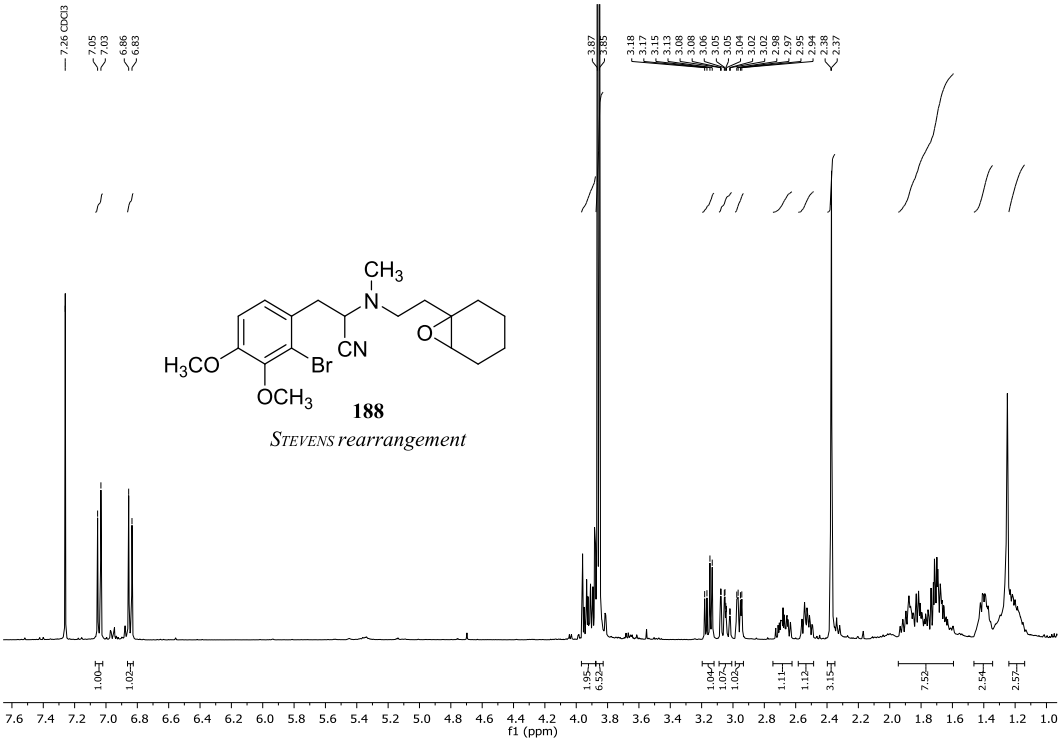
^{13}C NMR (100.6 MHz, $CDCl_3$) of compound **190**.



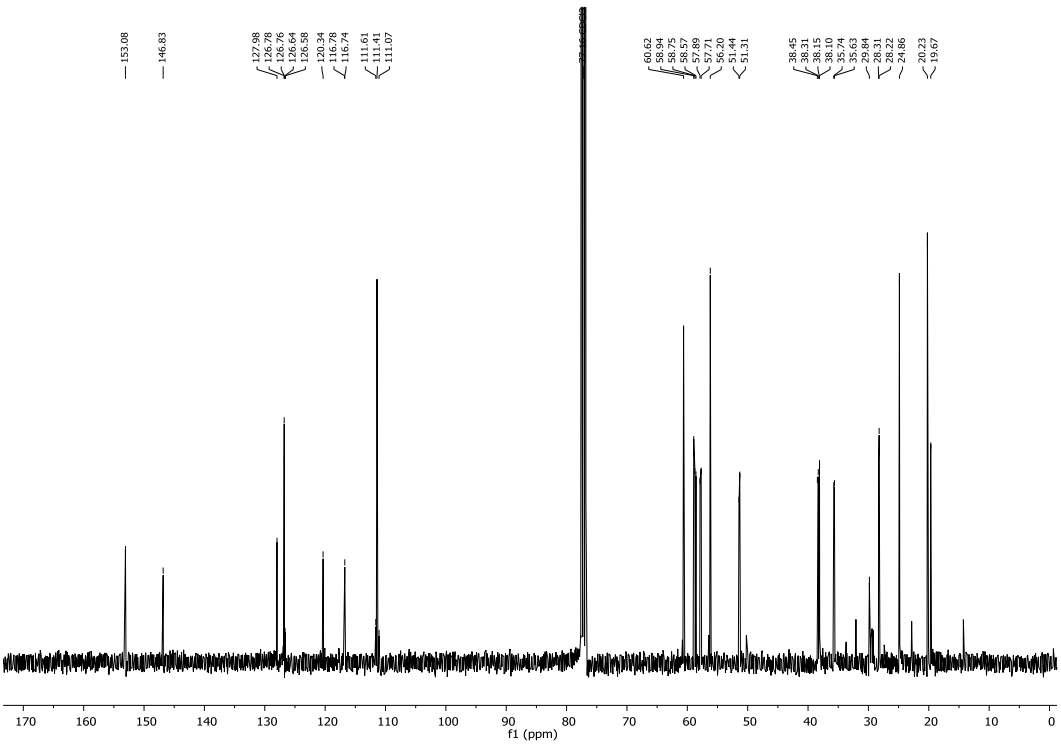
^{1}H NMR (400 MHz, $CDCl_3$) of compound **189**.



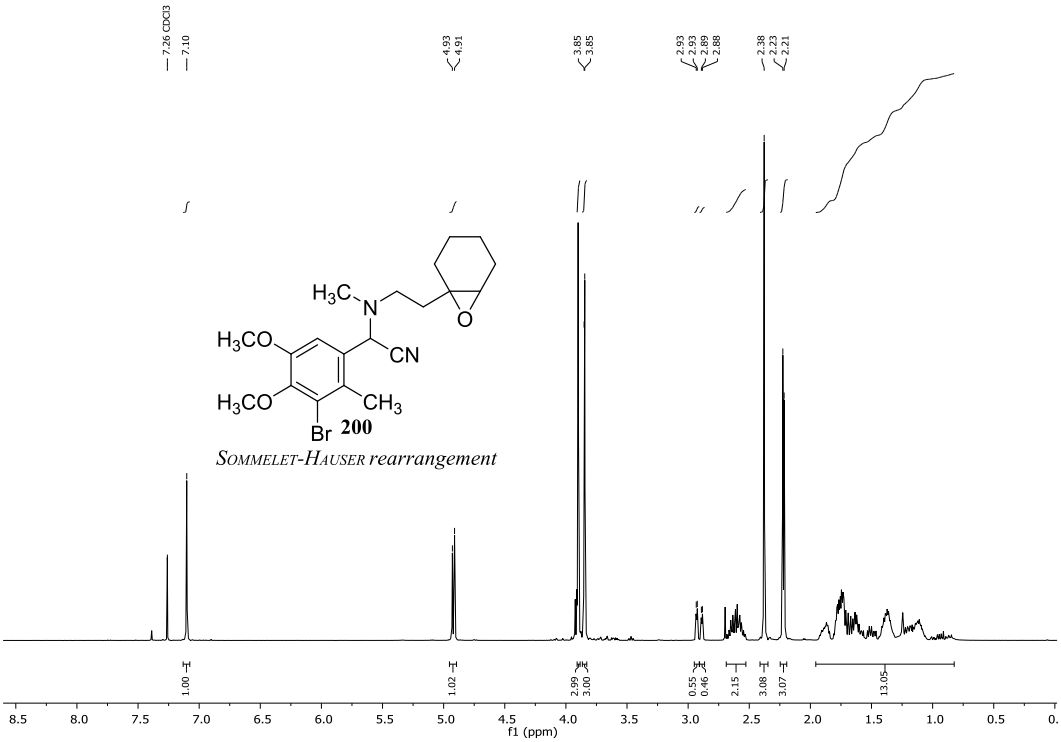
^{13}C NMR (100.6 MHz, $CDCl_3$) of compound **189**.



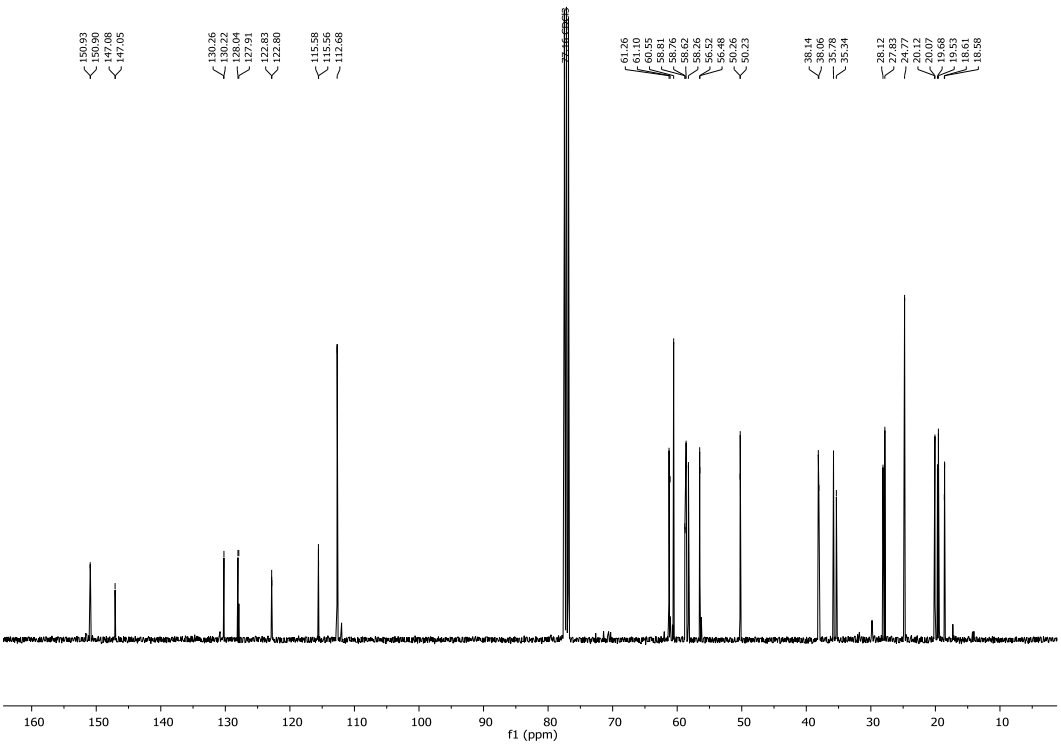
^{1}H NMR (400 MHz, $CDCl_3$) of compound **188** along with some decomposition products.



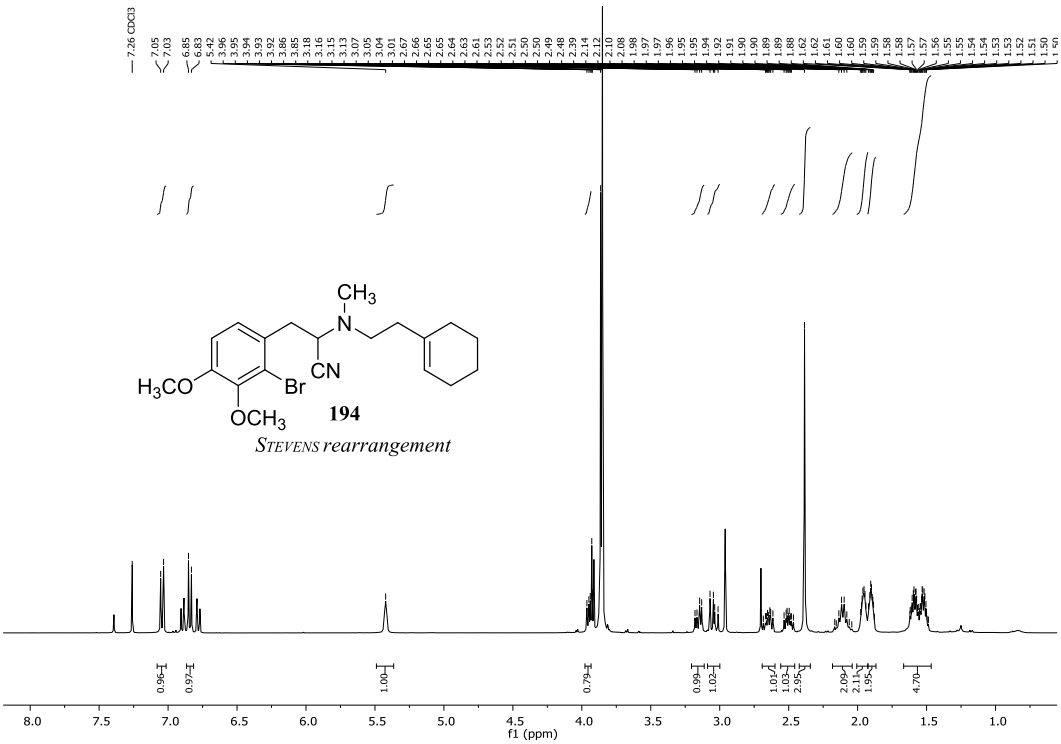
^{13}C NMR (100.6 MHz, $CDCl_3$) compound **188** along with some decomposition products.



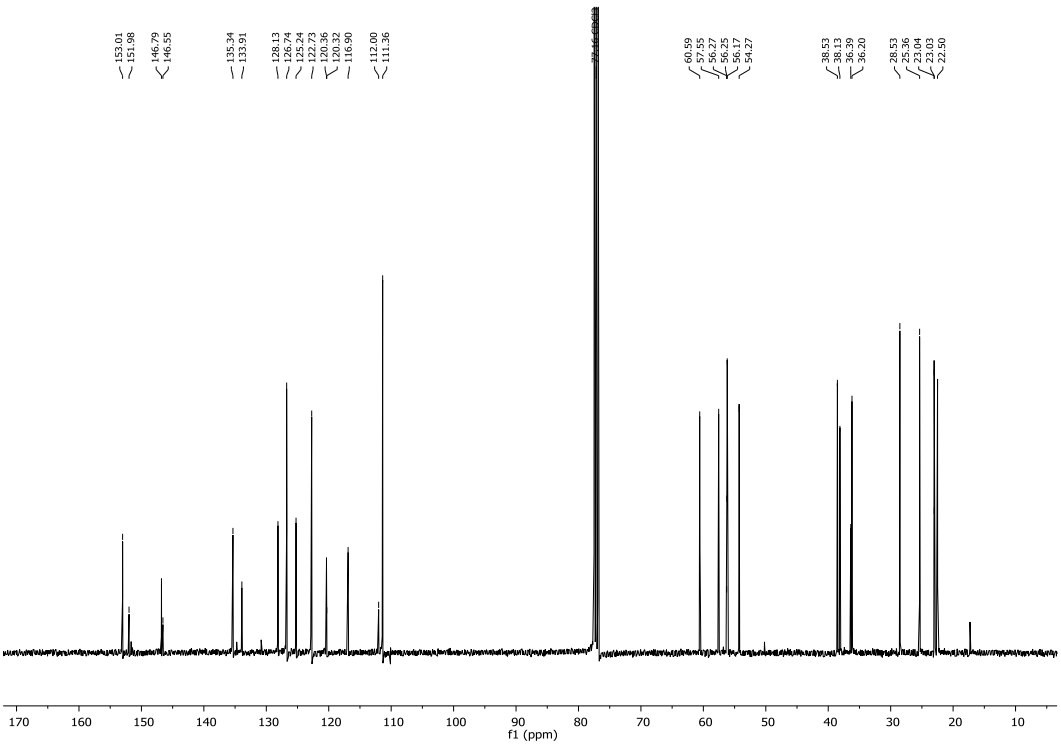
^{1}H NMR (400 MHz, $CDCl_3$) of compound **200** along with some decomposition products.



^{13}C NMR (100.6 MHz, $CDCl_3$) compound **200** along with some decomposition products.



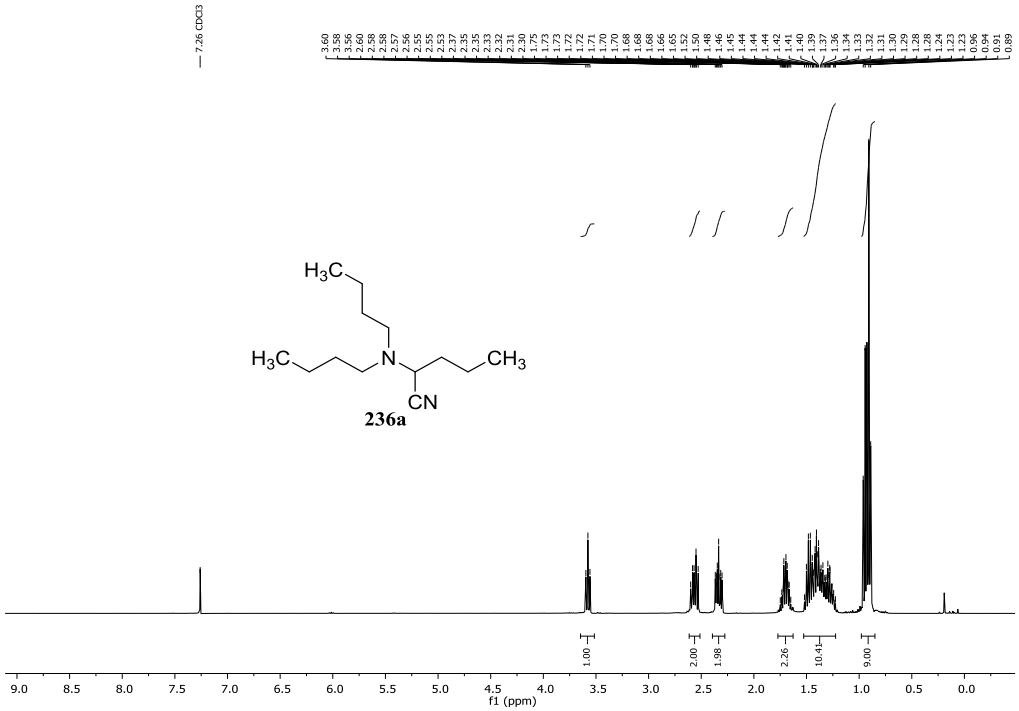
^{1}H NMR (400 MHz, $CDCl_3$) of compound **194** along with some decomposition products.



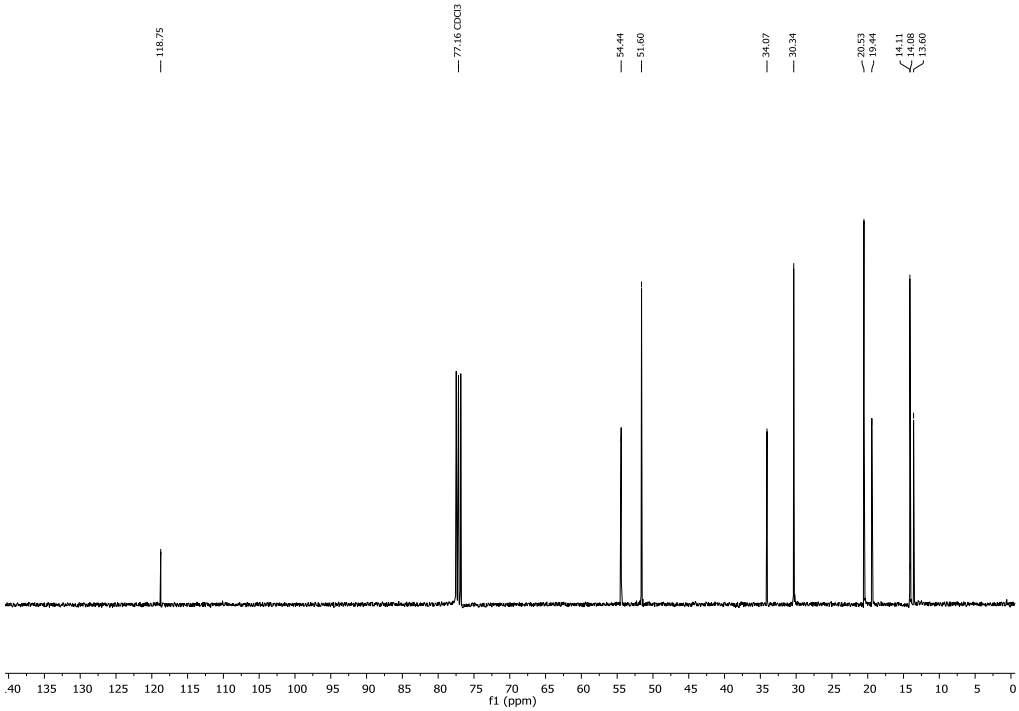
^{13}C NMR (100.6 MHz, $CDCl_3$) of compound **194** along with some decomposition products.

Chapter 4

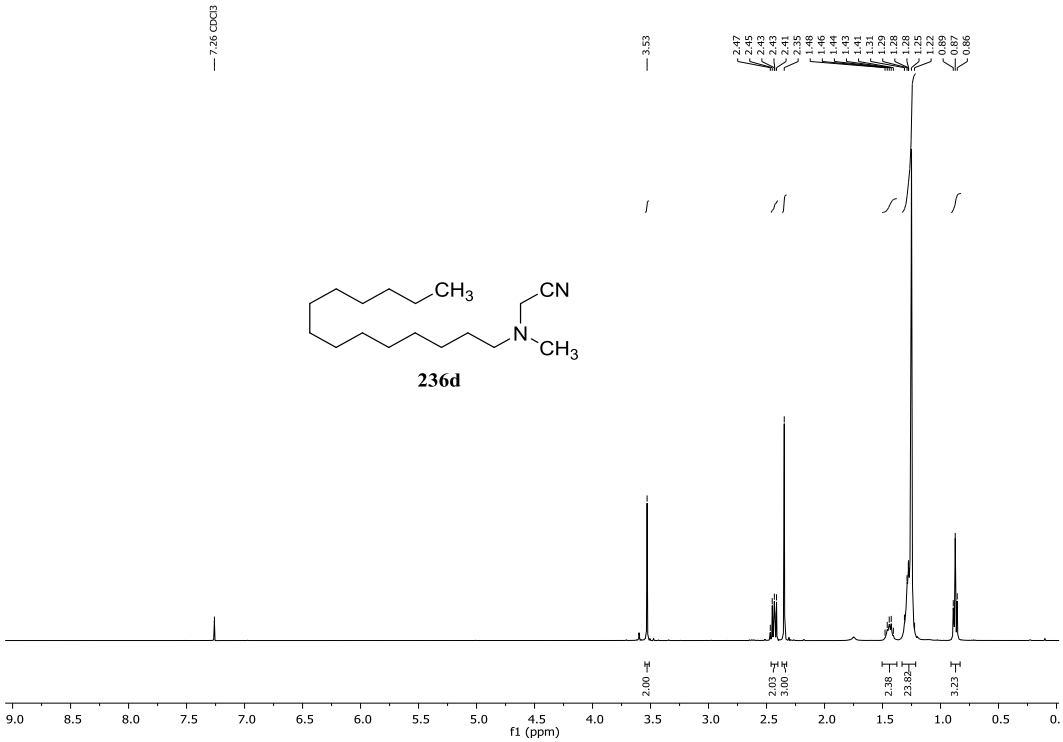
For this chapter a few sample spectra are depicted. The remaining spectra can be found in the *Chemistry a European Journal* under the following DOI: 10.1002/chem.201504845



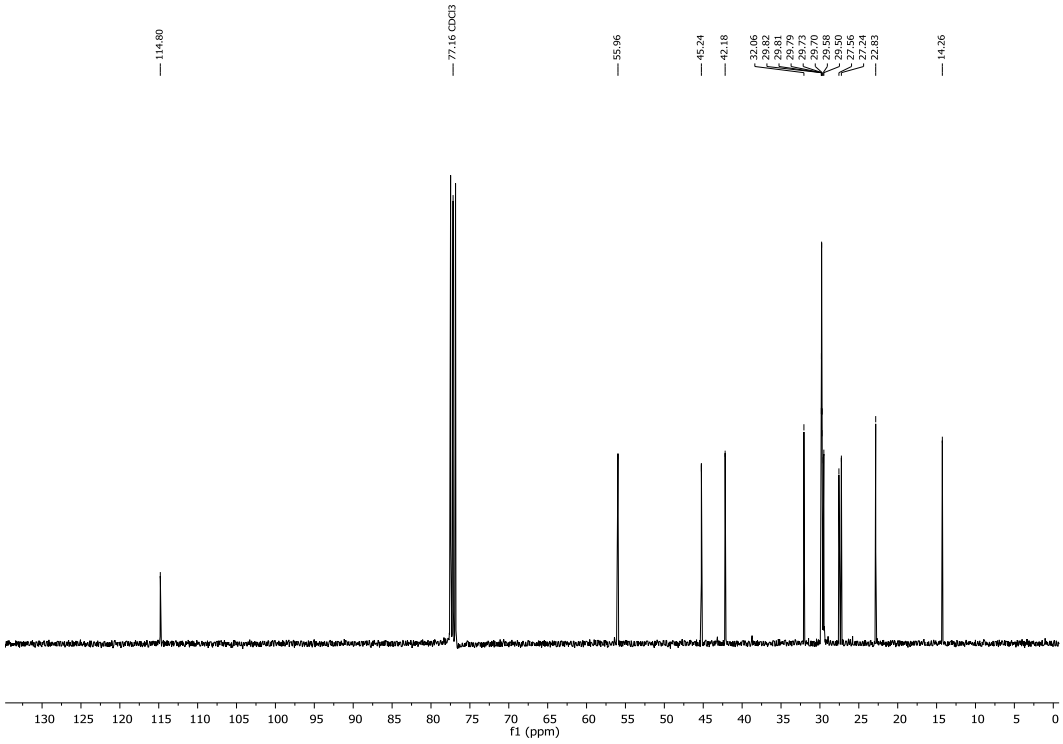
^{1}H NMR (400 MHz, $CDCl_3$) of compound **236a**.



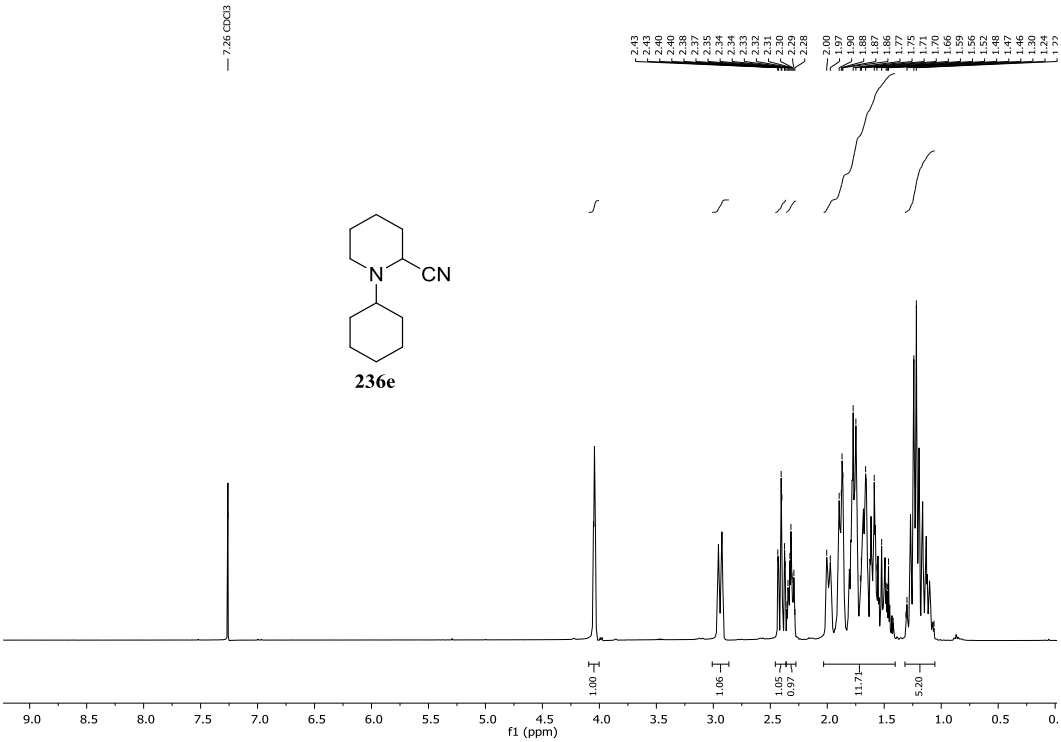
^{13}C NMR (100.6 MHz, $CDCl_3$) of compound **236a**.



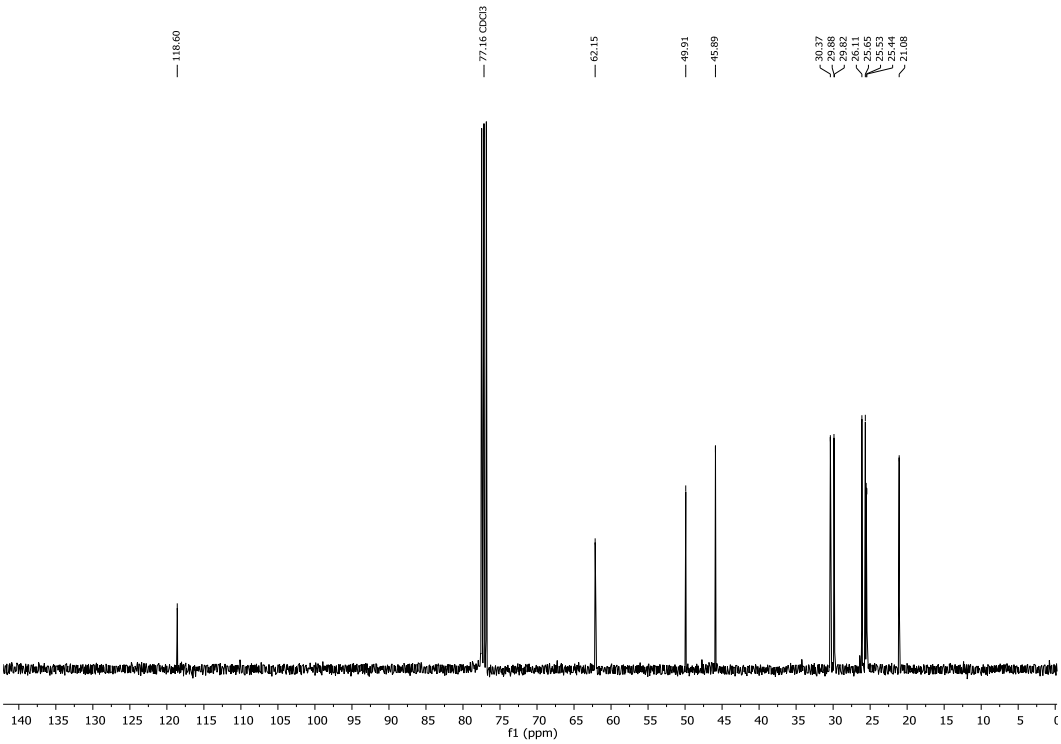
^{1}H NMR (400 MHz, $CDCl_3$) of compound **236d**.



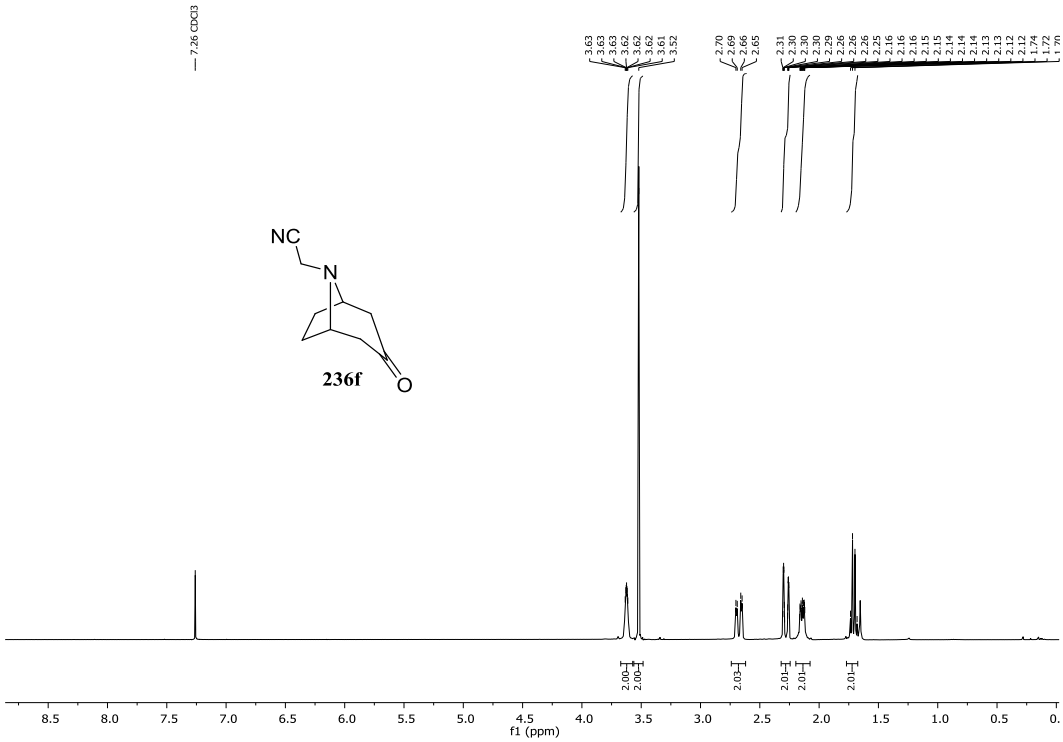
^{13}C NMR (100.6 MHz, $CDCl_3$) of compound **236d**.



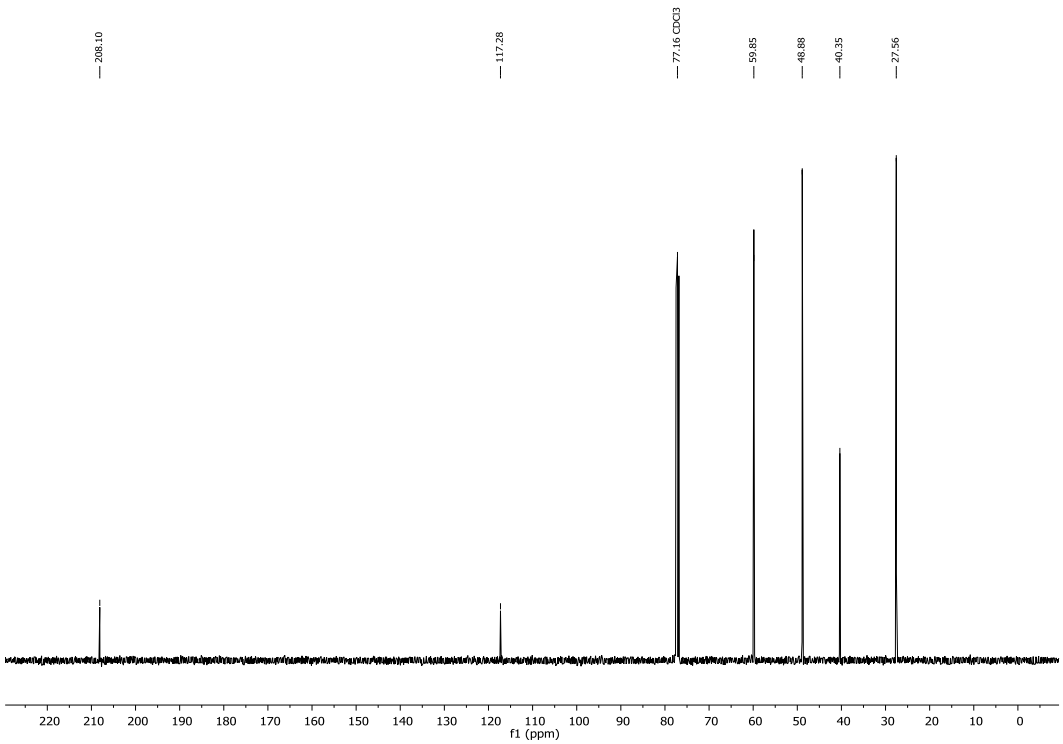
^{1}H NMR (400 MHz, $CDCl_3$) of compound **236e**.



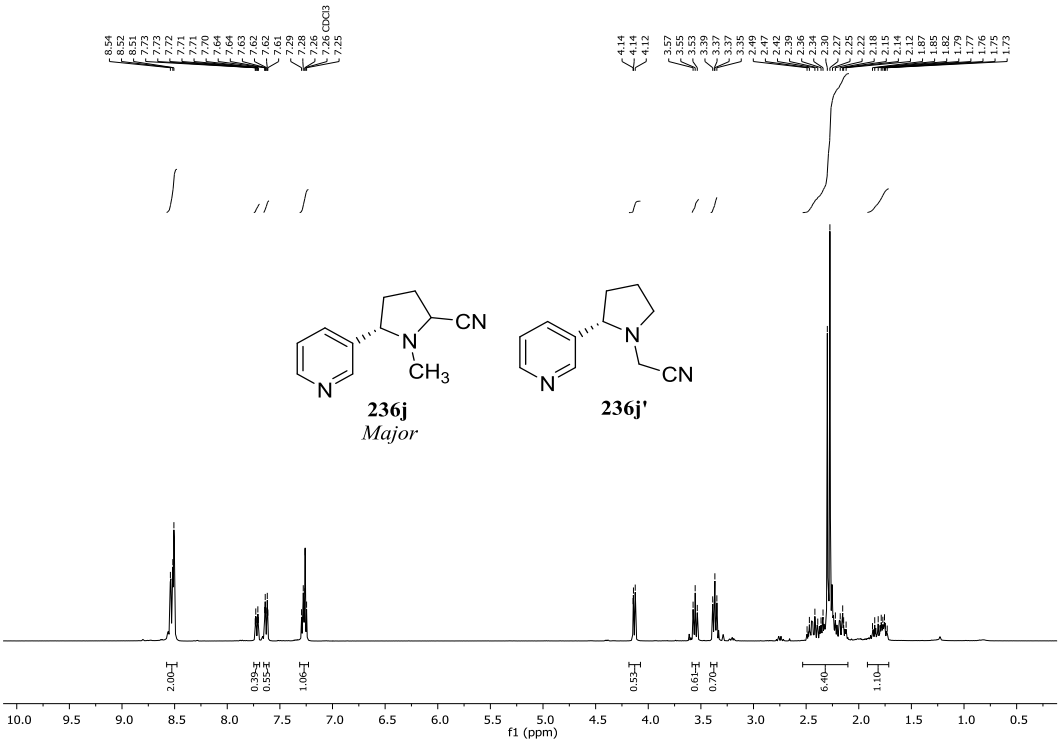
^{13}C NMR (100.6 MHz, $CDCl_3$) of compound **236e**.



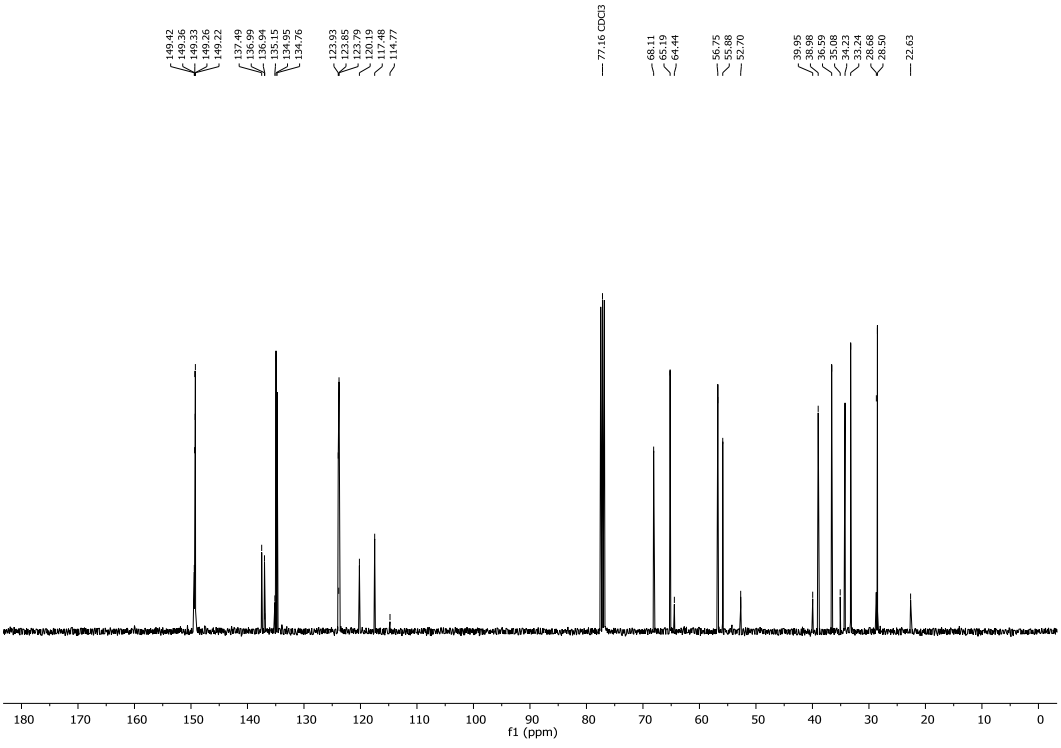
^{1}H NMR (400 MHz, $CDCl_3$) of compound **236f**.



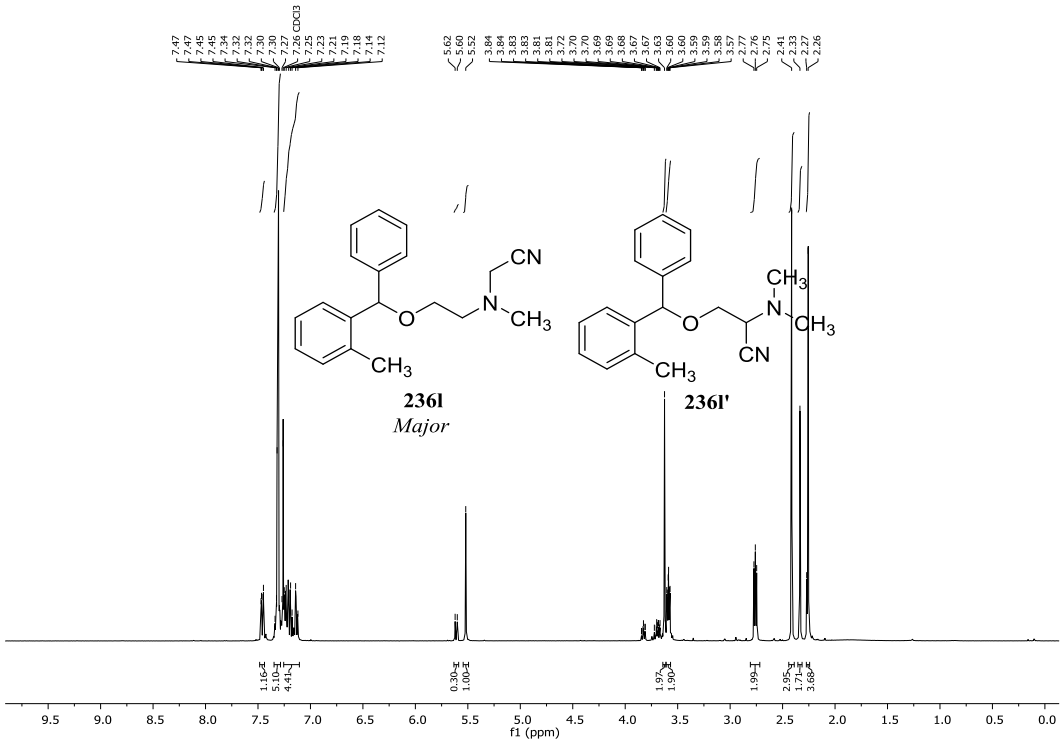
^{13}C NMR (100.6 MHz, $CDCl_3$) of compound **236f**.



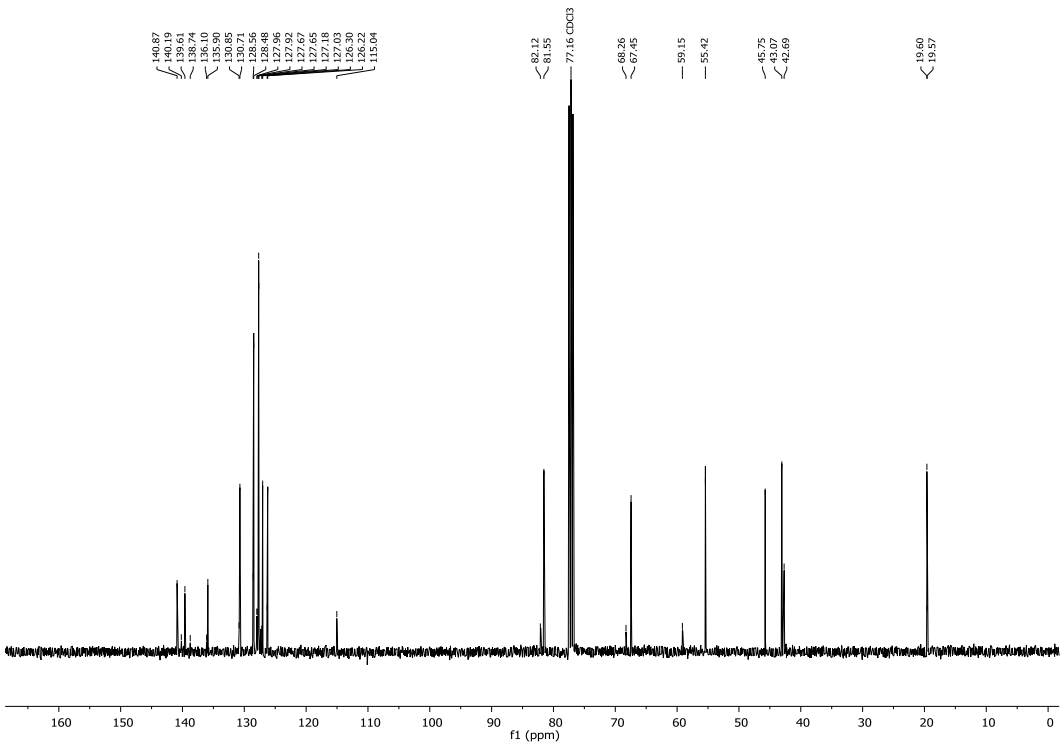
^{1}H NMR (400 MHz, $CDCl_3$) of compounds **236j** and **236j'**.



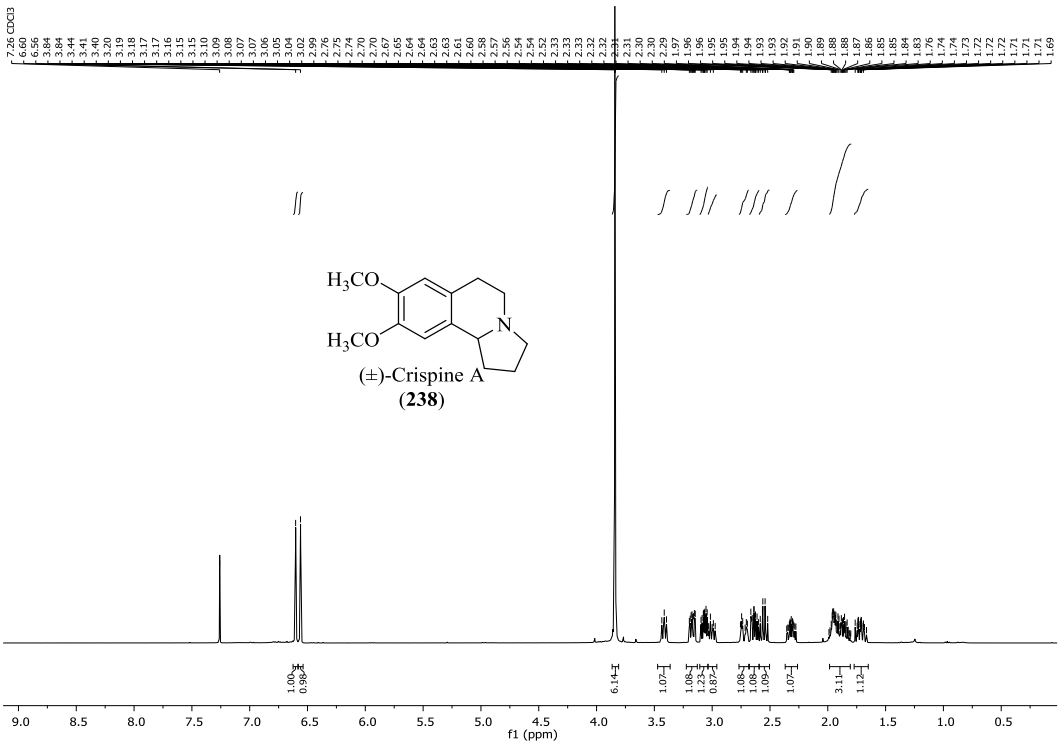
^{13}C NMR (100.6 MHz, $CDCl_3$) of compounds **236j** and **236j'**.



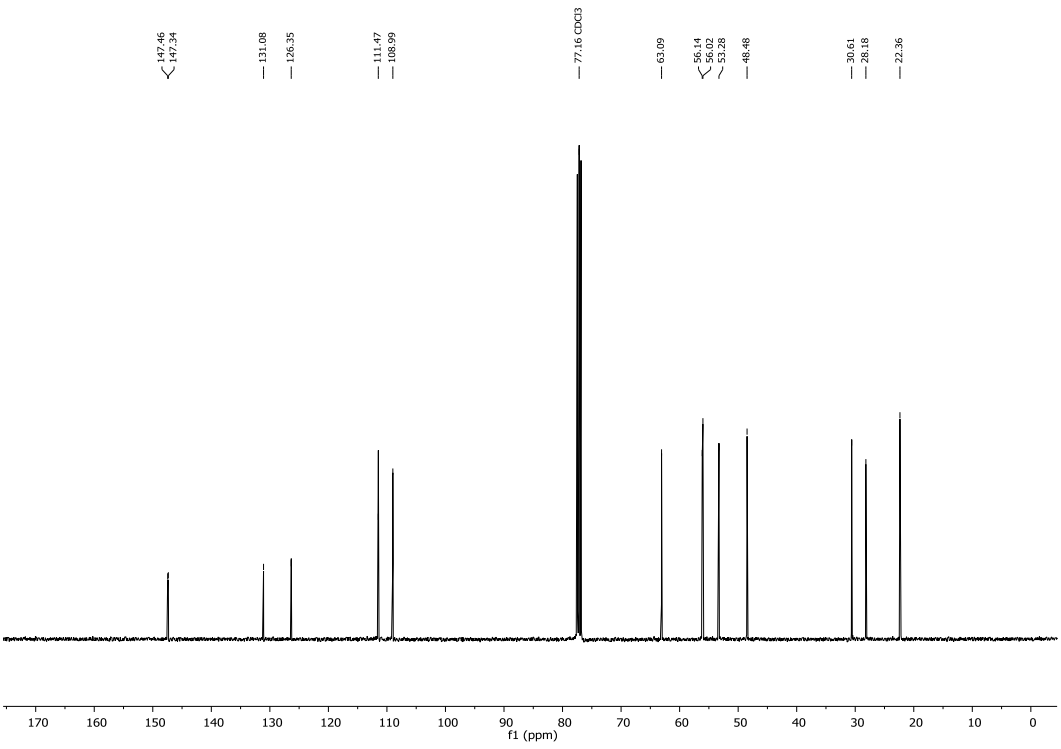
^{1}H NMR (400 MHz, $CDCl_3$) of compounds **236l** and **236l'**.



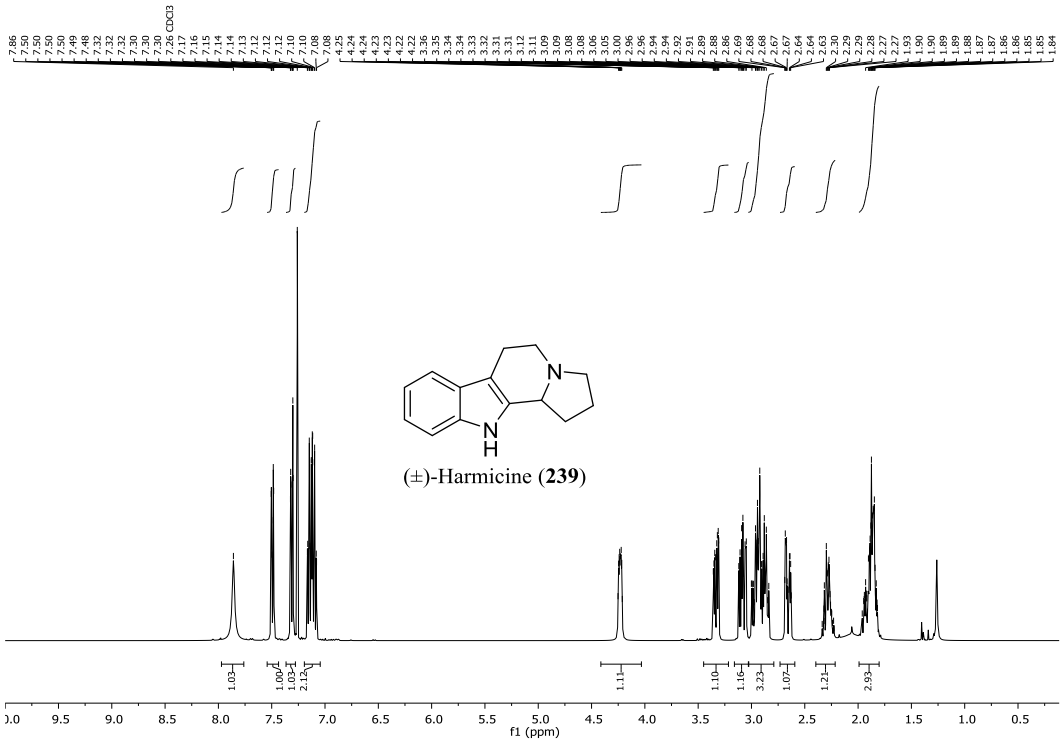
^{13}C NMR (100.6 MHz, $CDCl_3$) of compounds **236l** and **236l'**.



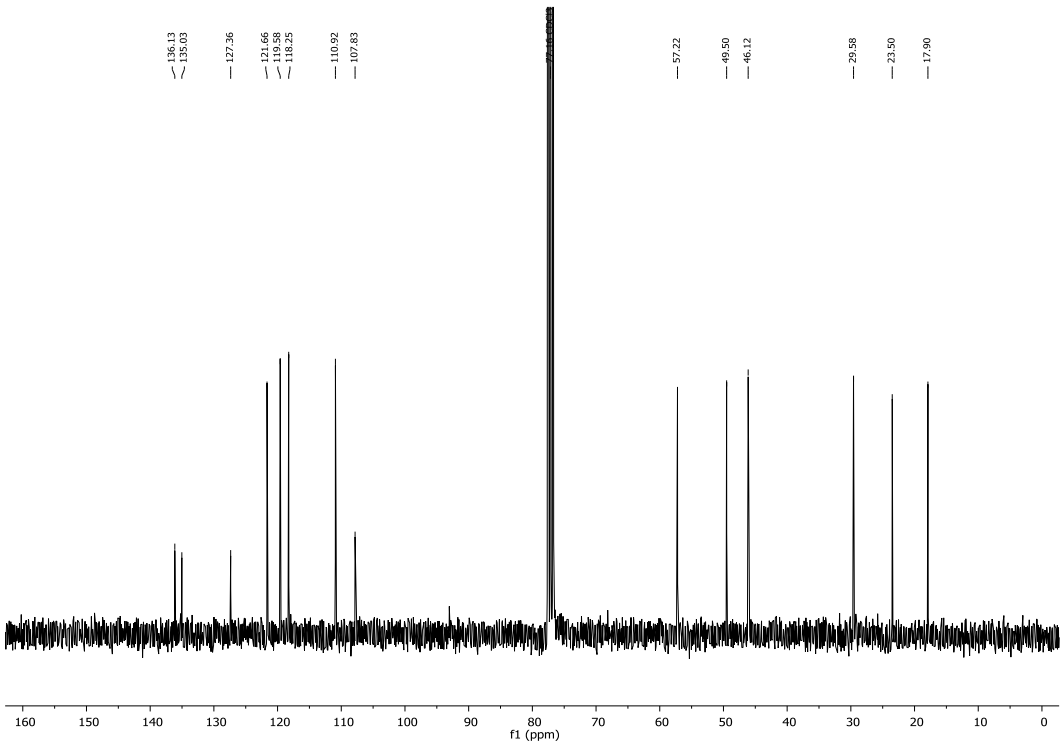
^{1}H NMR (400 MHz, $CDCl_3$) of compound **238**.



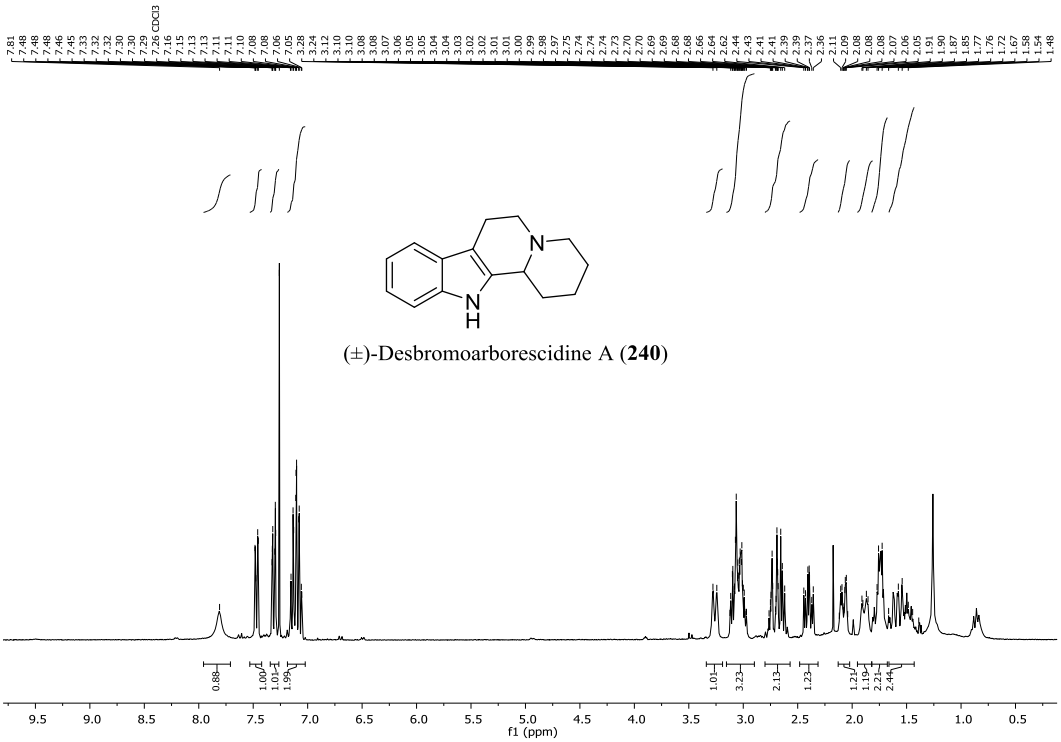
^{13}C NMR (100.6 MHz, $CDCl_3$) of compound **238**.



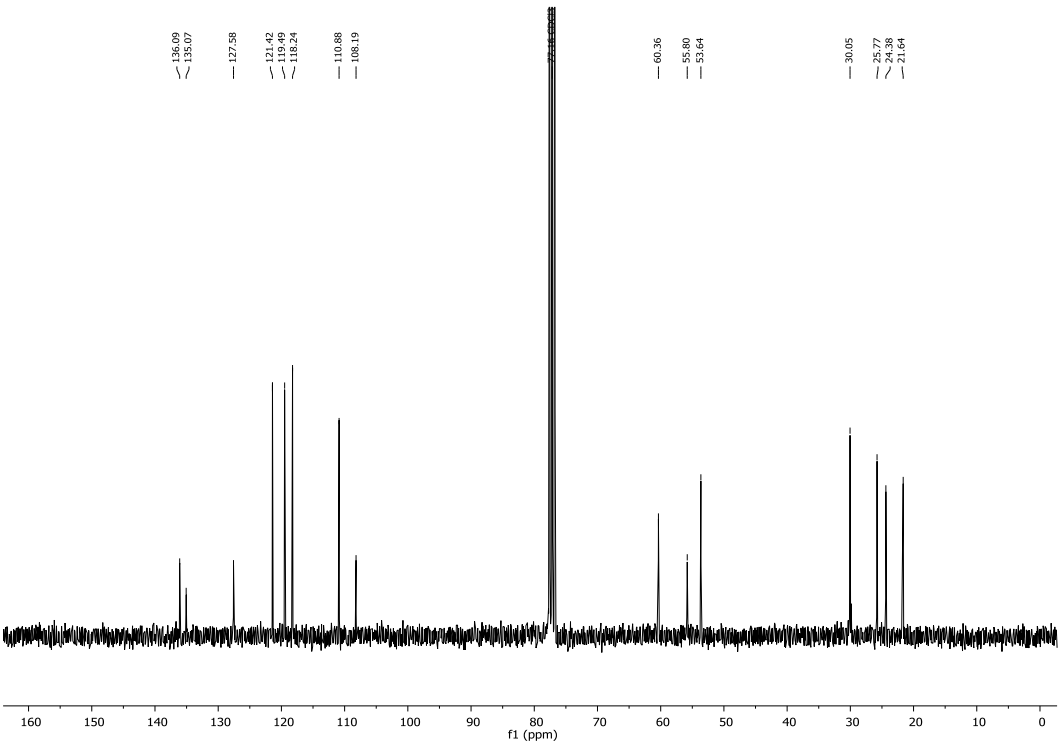
^{1}H NMR (300 MHz, $CDCl_3$) of compound **239**.



^{13}C NMR (75.5 MHz, $CDCl_3$) of compound **239**.



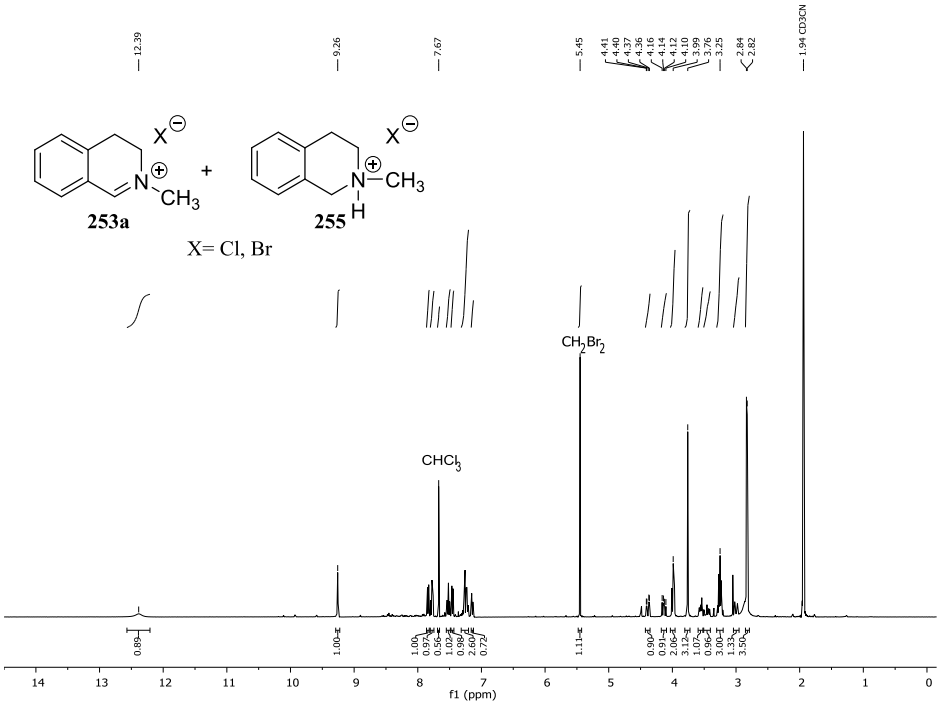
^{1}H NMR (300 MHz, $CDCl_3$) of compound **240**.



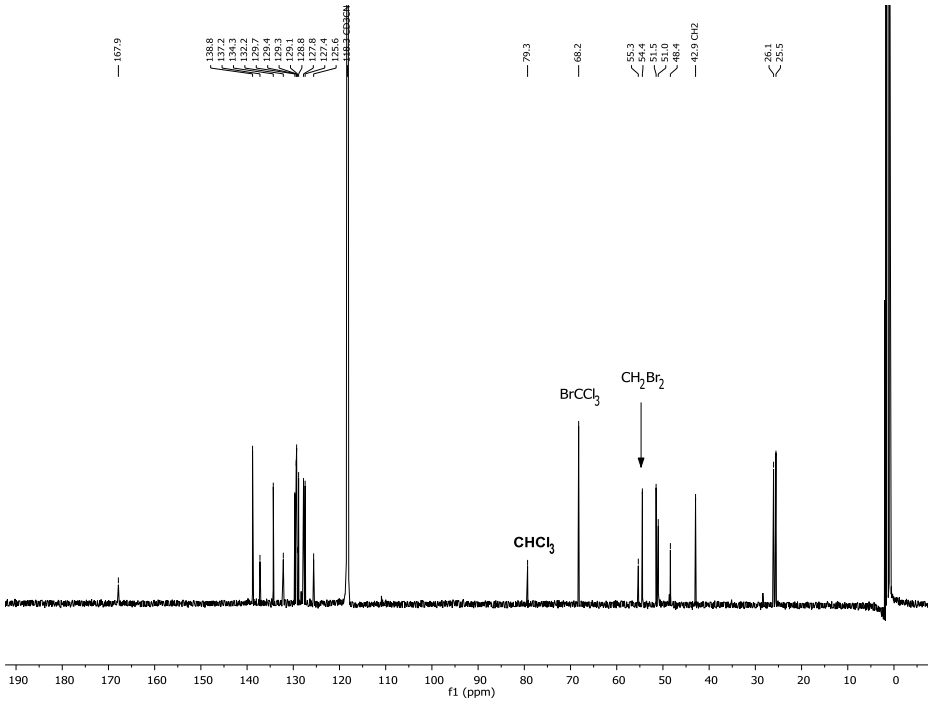
^{13}C NMR (75.5 MHz, $CDCl_3$) of compound **240**.

Chapter 5

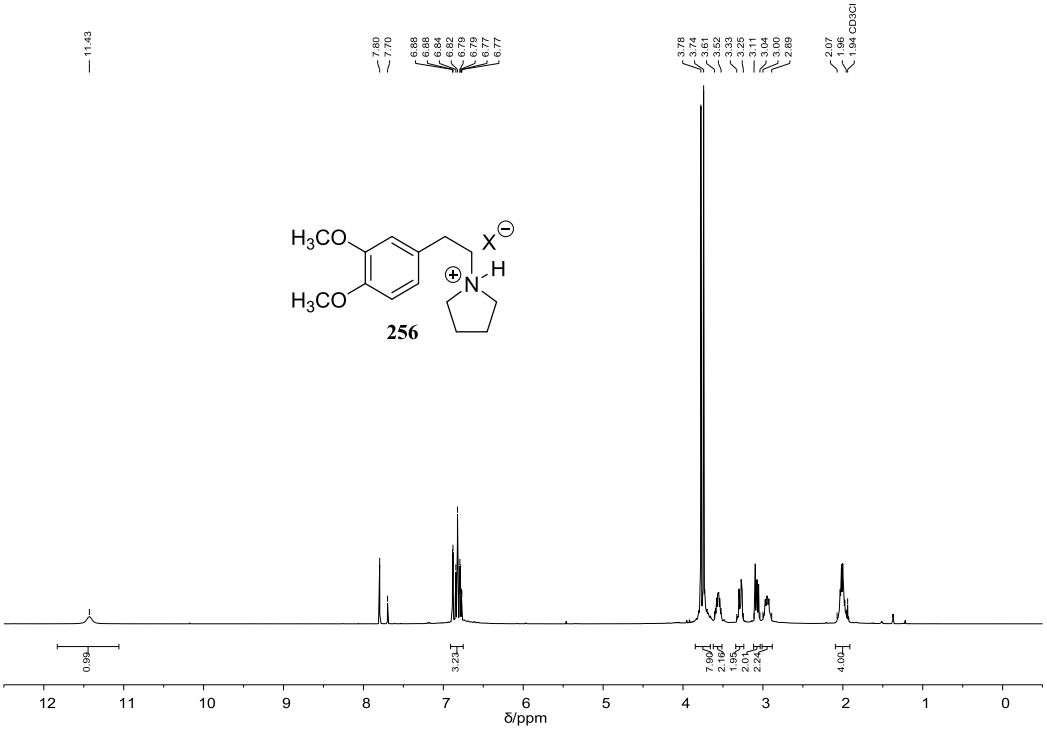
The depicted spectra can be also found in the *European Journal of Organic Chemistry* under the following DOI: 10.1002/ejoc.201701320



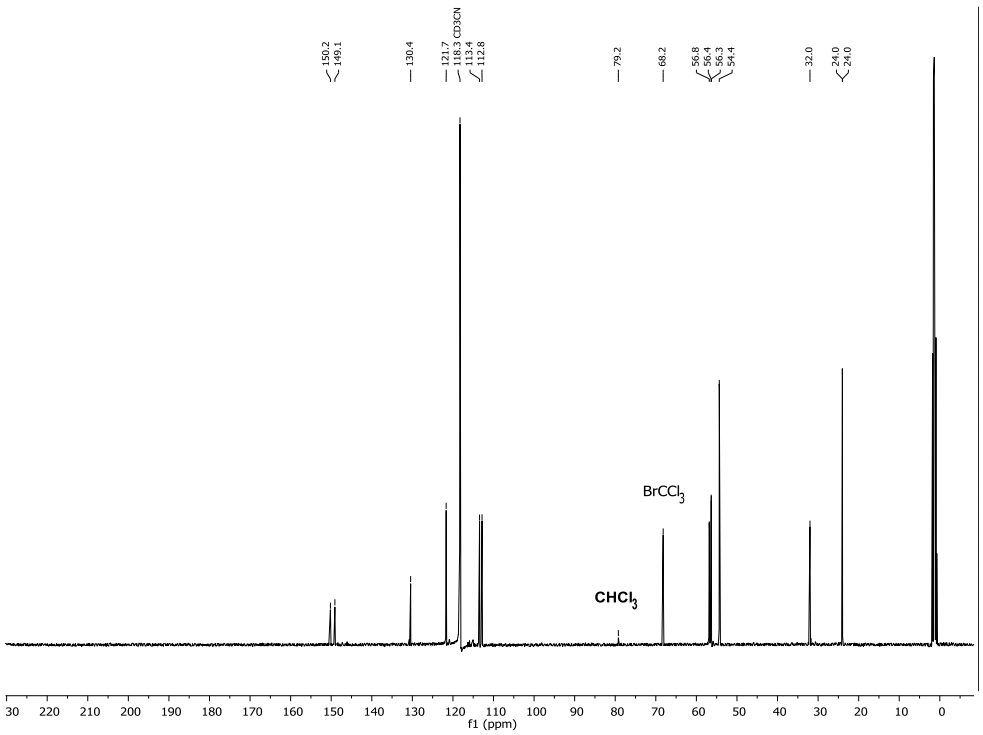
^{1}H NMR (400 MHz, CD_3CN) of compounds **253a** and **255**.



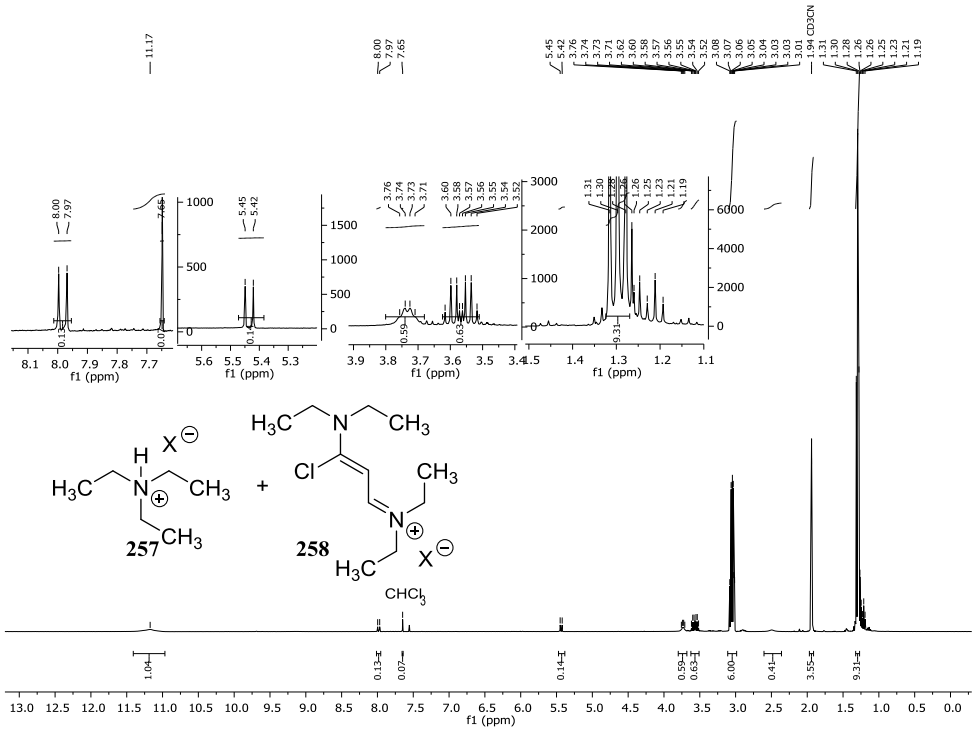
^{13}C NMR (100.6 MHz, CD_3CN) of compounds **253a** and **255**.



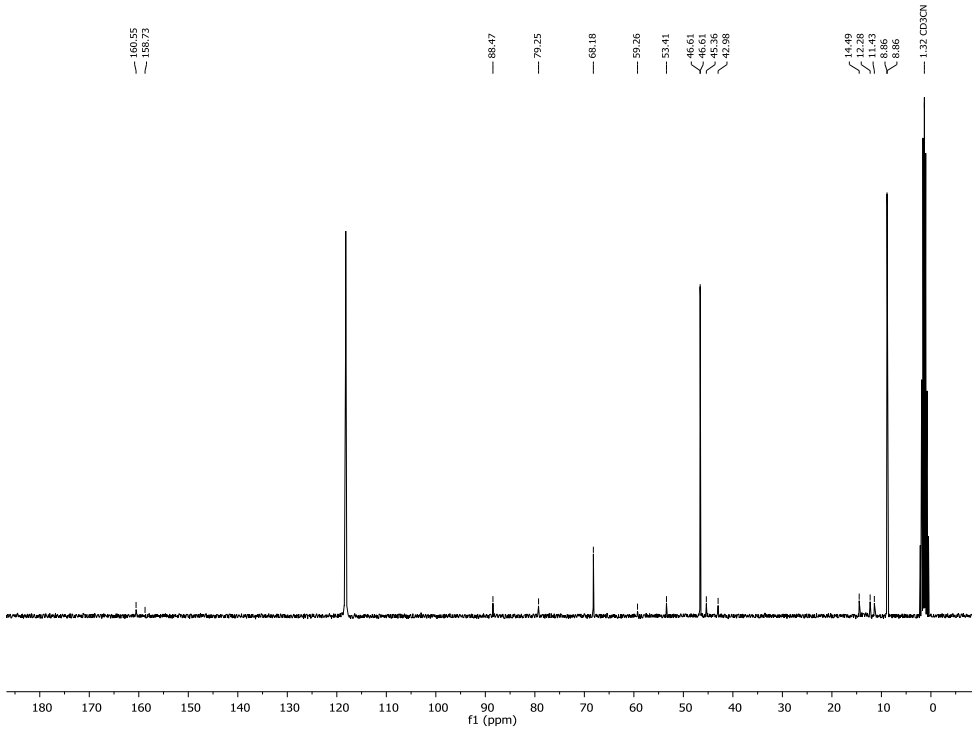
^{1}H NMR (400 MHz, $CDCl_3$) of compound **256**.



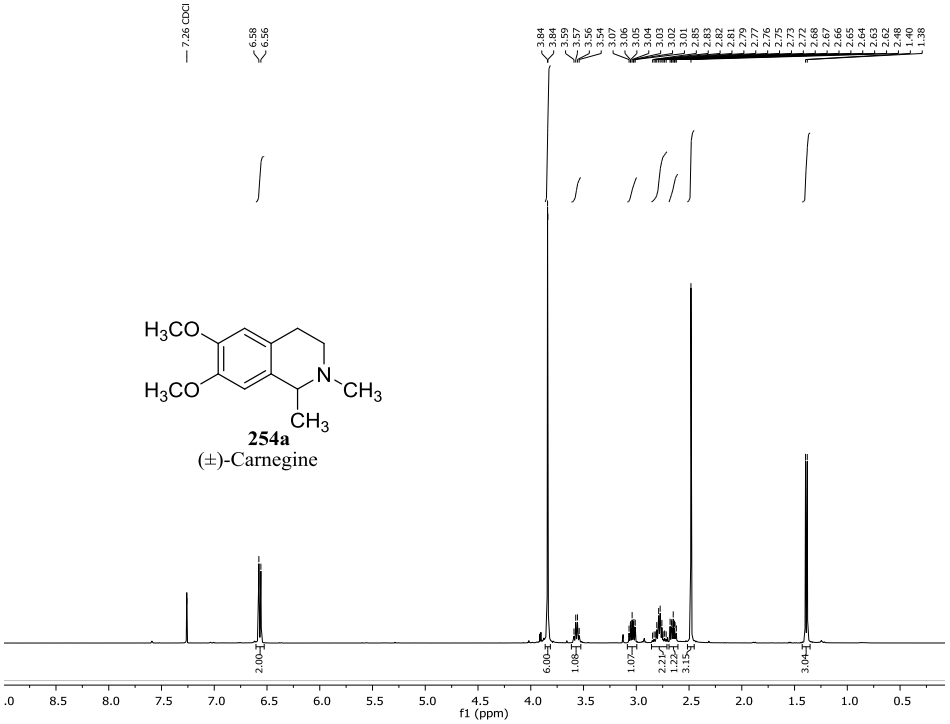
^{13}C NMR (100.6 MHz, $CDCl_3$) of compound **256**.



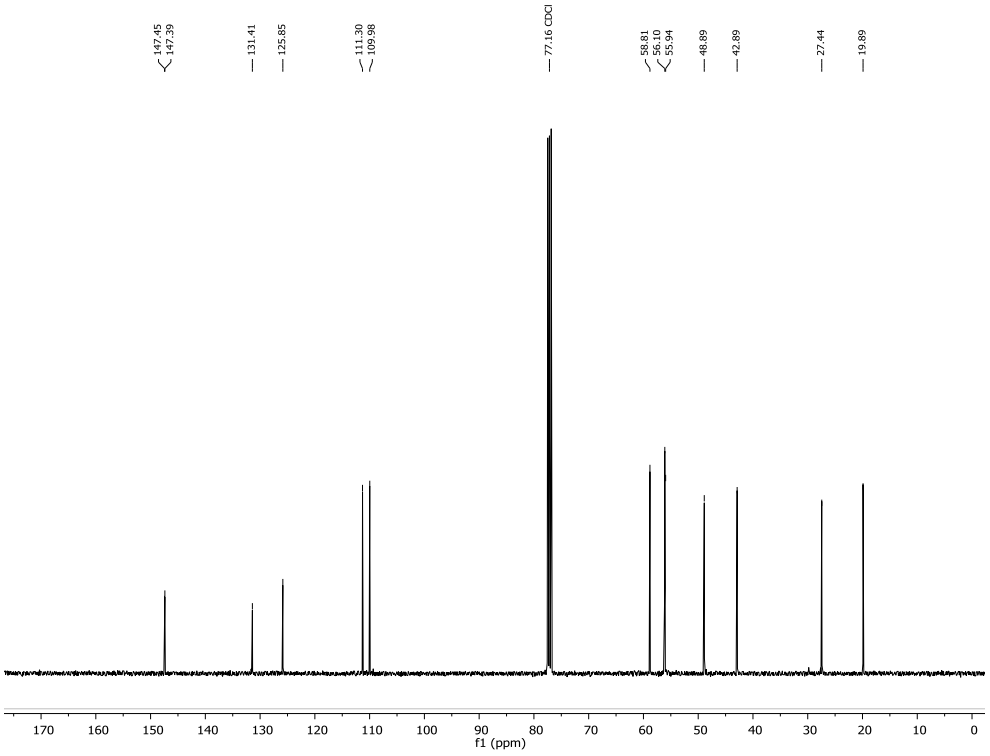
^{1}H NMR (400 MHz, $CDCl_3$) of compounds **257** and **258**.



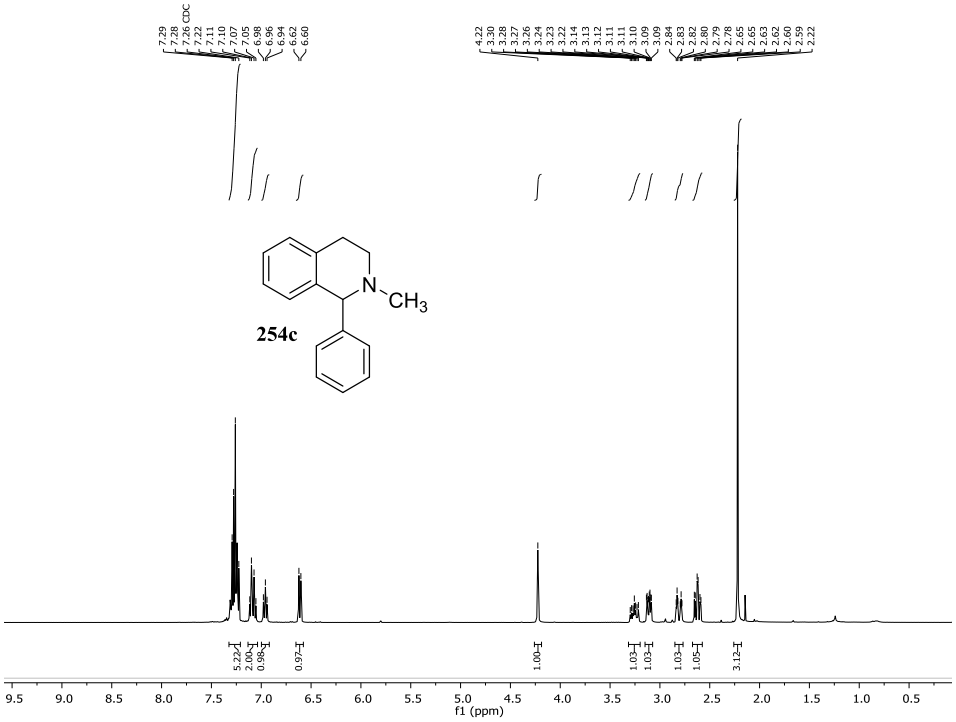
^{13}C NMR (100.6 MHz, $CDCl_3$) of compounds **257** and **258**.



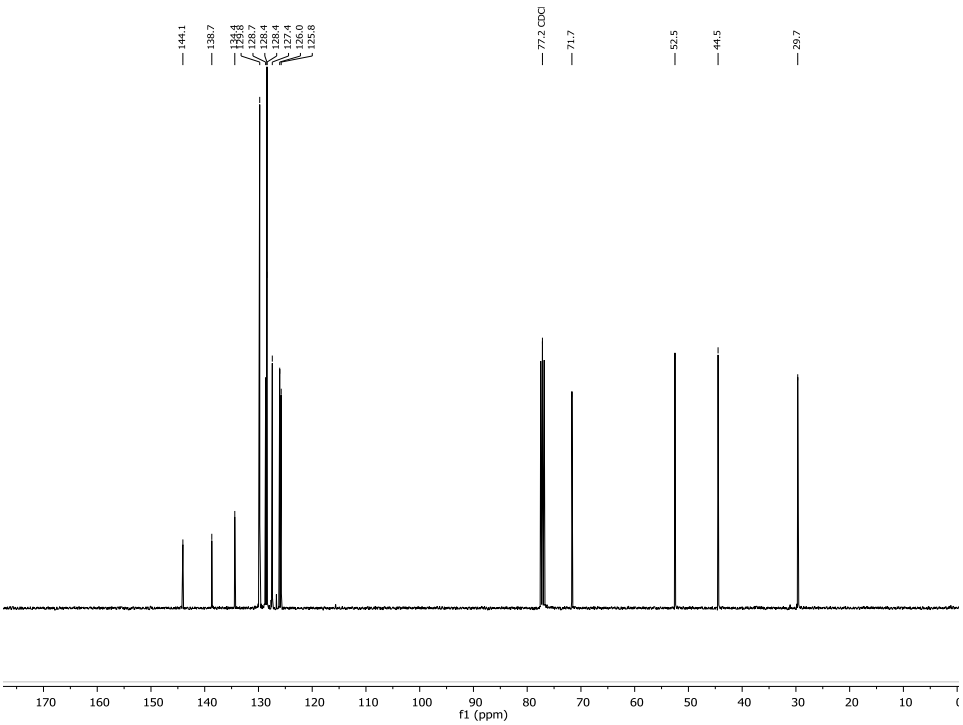
^{1}H NMR (400 MHz, $CDCl_3$) of compound **254a**.



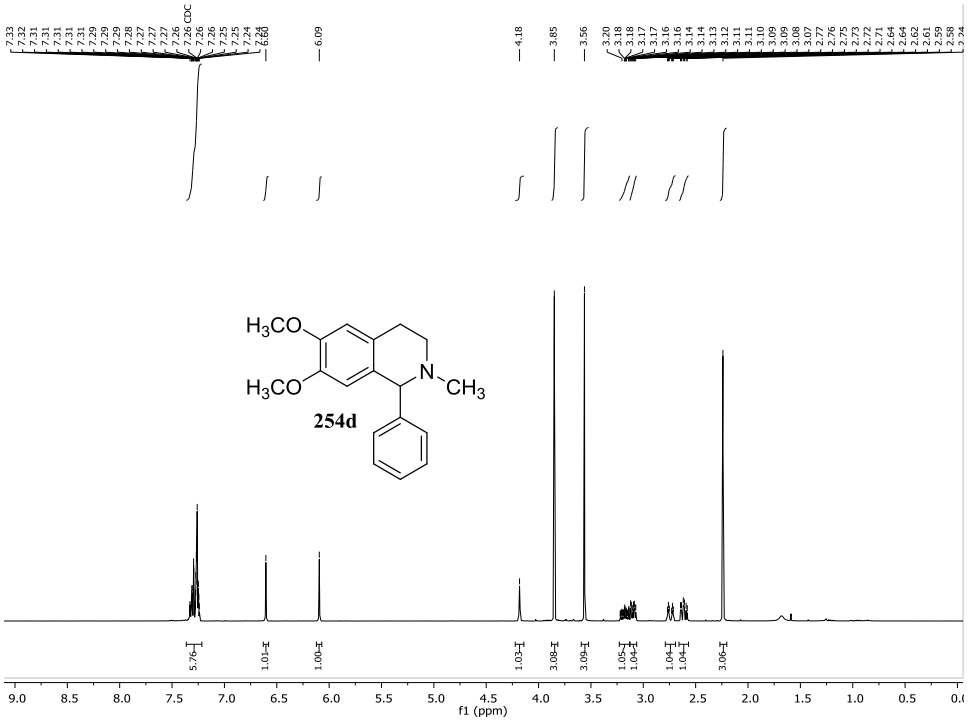
^{13}C NMR (100.6 MHz, $CDCl_3$) of compound **254a**.



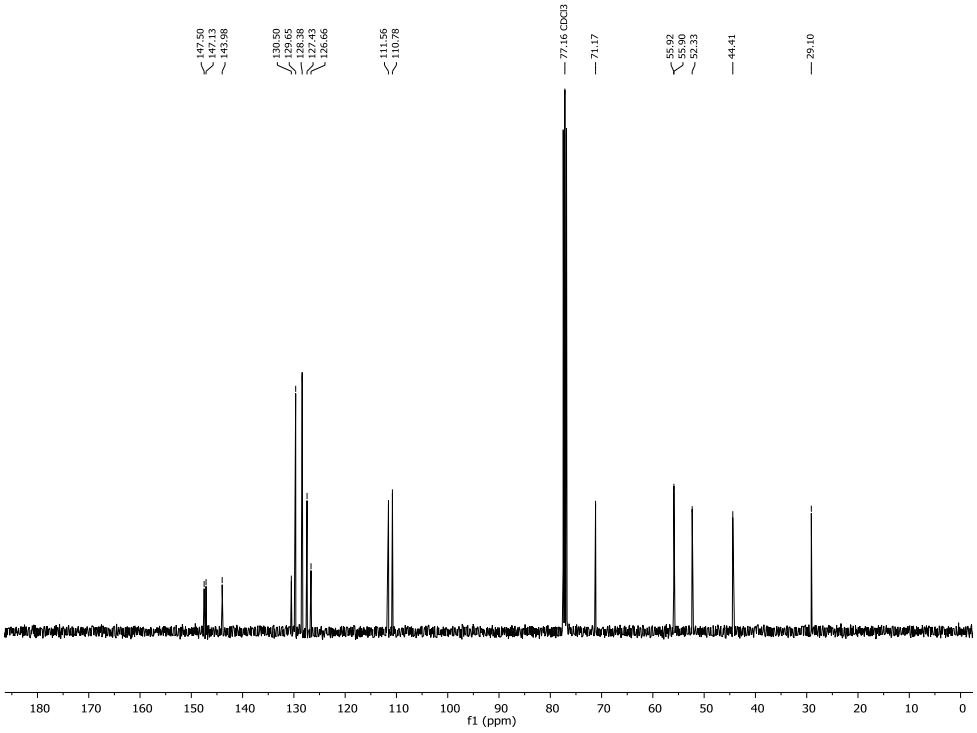
^{1}H NMR (400 MHz, $CDCl_3$) of compound **254c**.



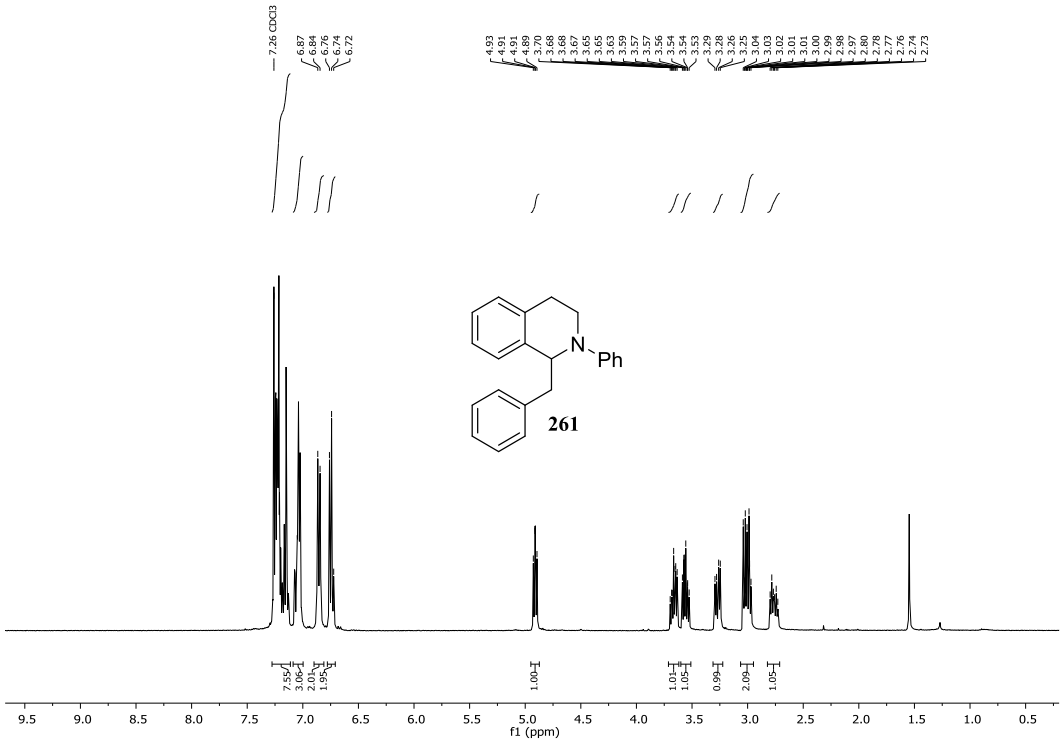
^{13}C NMR (100.6 MHz, $CDCl_3$) of compound **254c**.



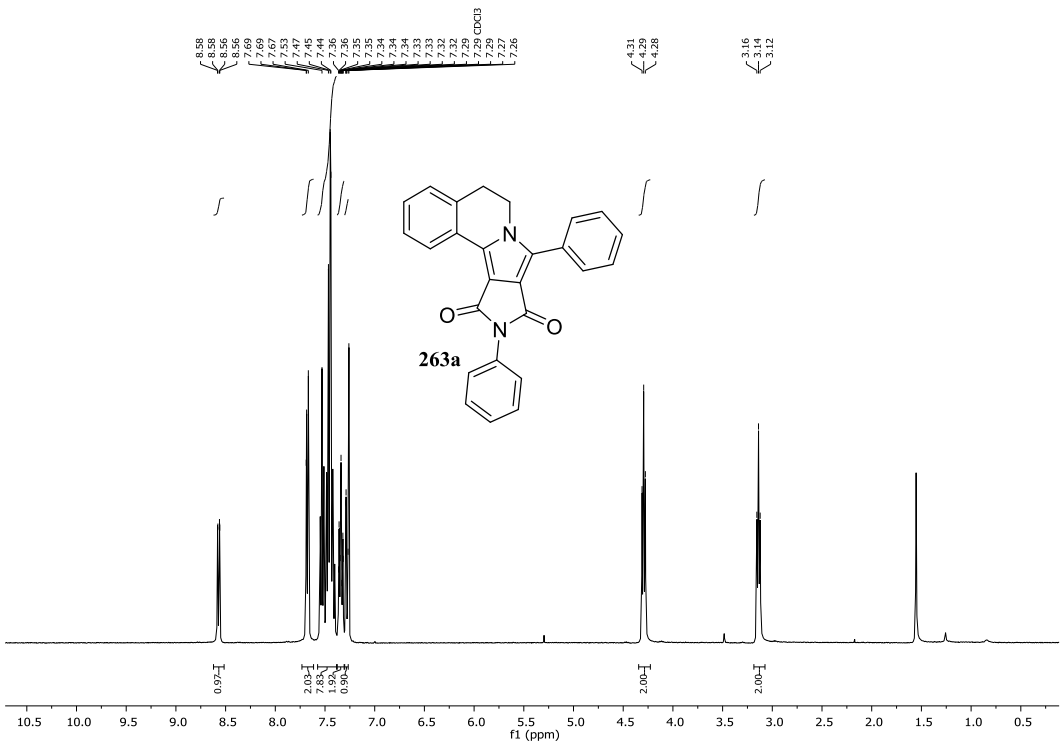
^{1}H NMR (400 MHz, $CDCl_3$) of compound 2**54d**.



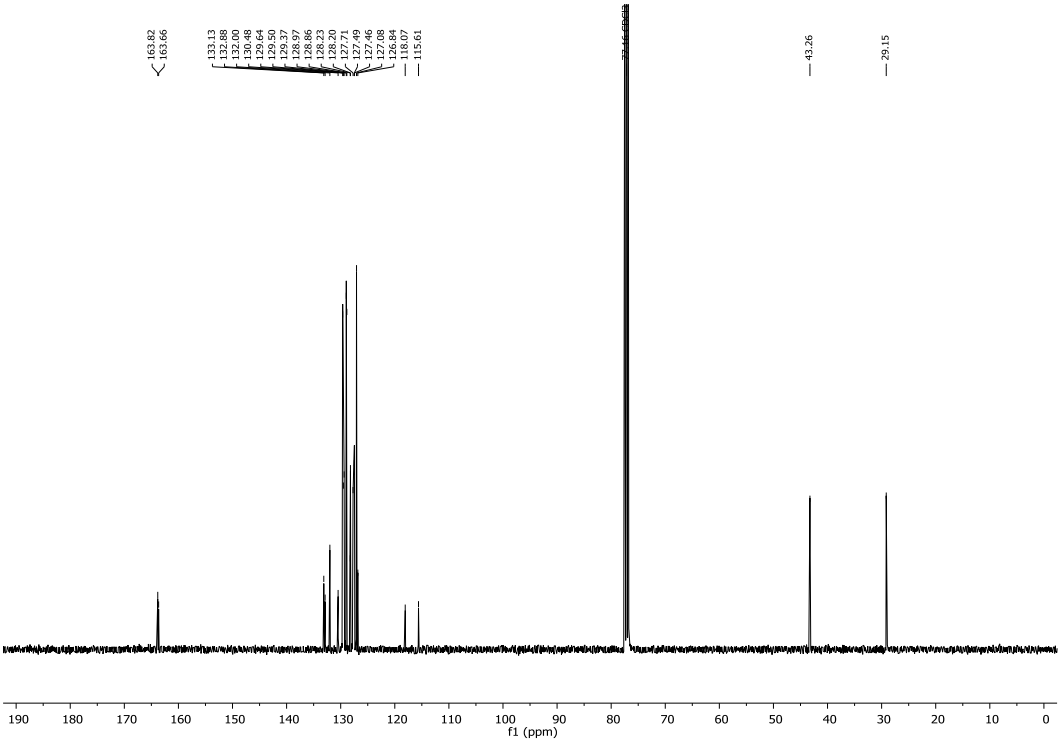
^{13}C NMR (100.6 MHz, $CDCl_3$) of compound **254d**.



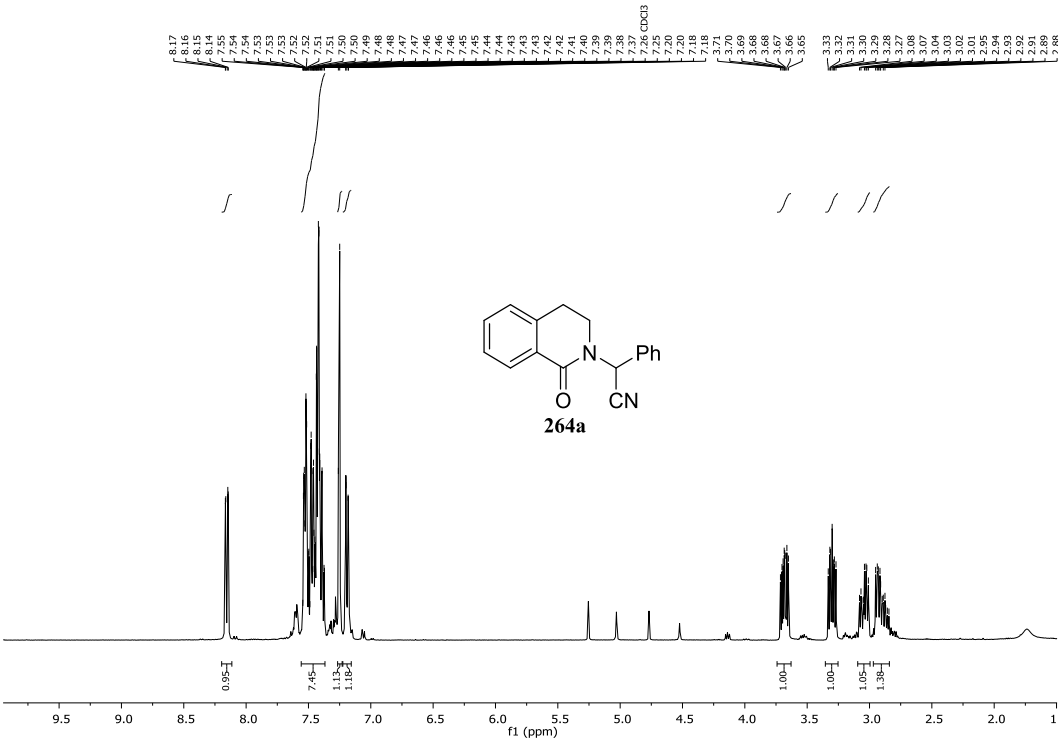
^{1}H NMR (400 MHz, $CDCl_3$) of compound **261**.



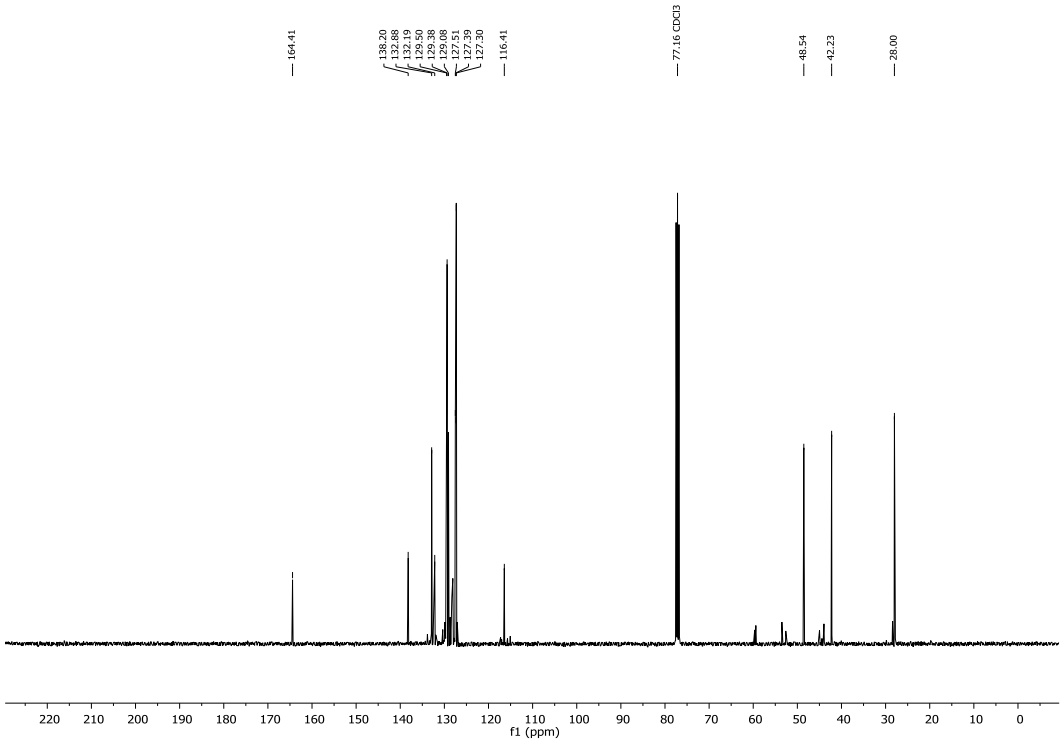
^{1}H NMR (400 MHz, $CDCl_3$) of compound **263a**.



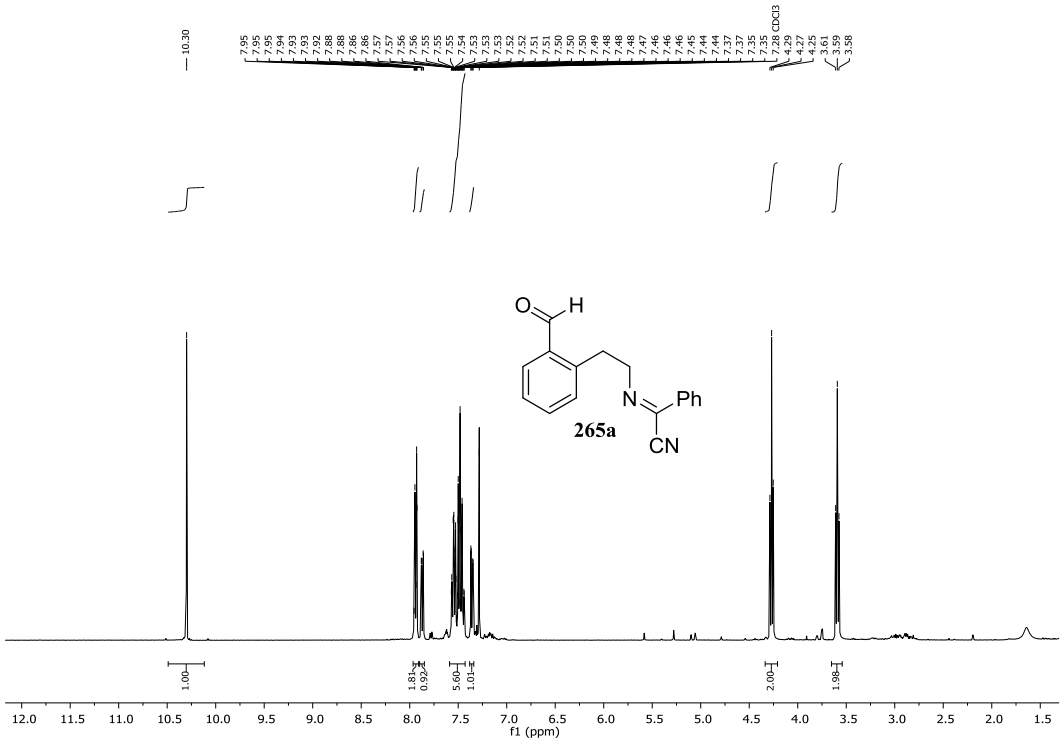
^{13}C NMR (100.6 MHz, $CDCl_3$) of compound **263a**.



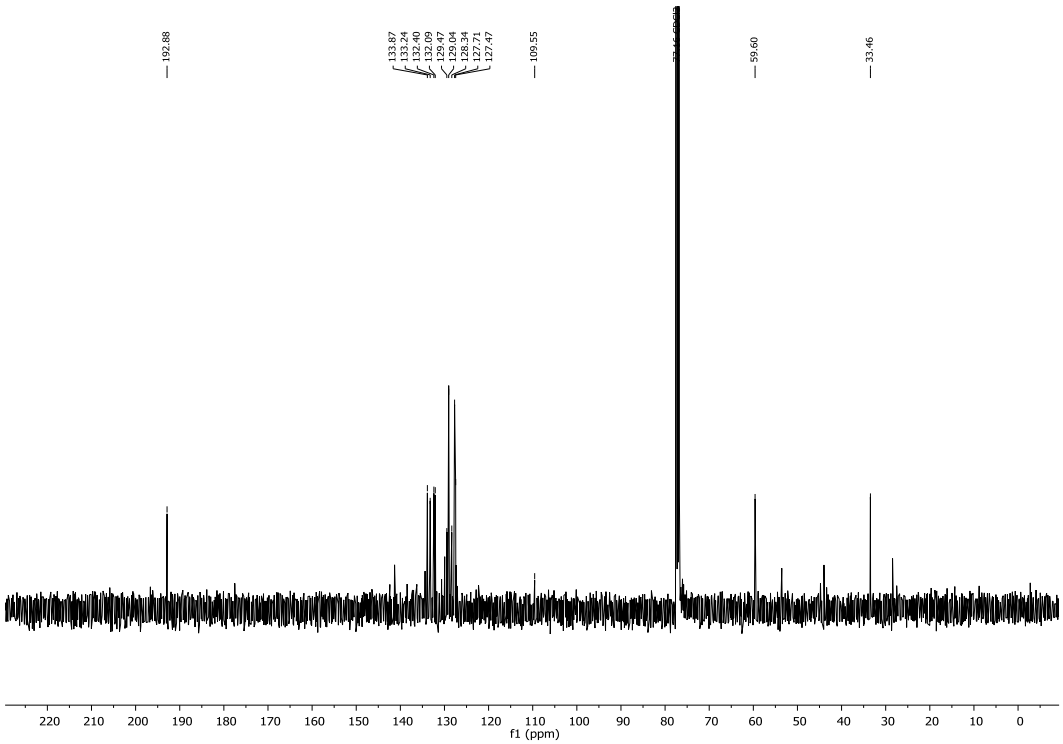
^{1}H NMR (400 MHz, $CDCl_3$) of compound **264a**.



^{13}C NMR (100.6 MHz, $CDCl_3$) of compound **264a**.

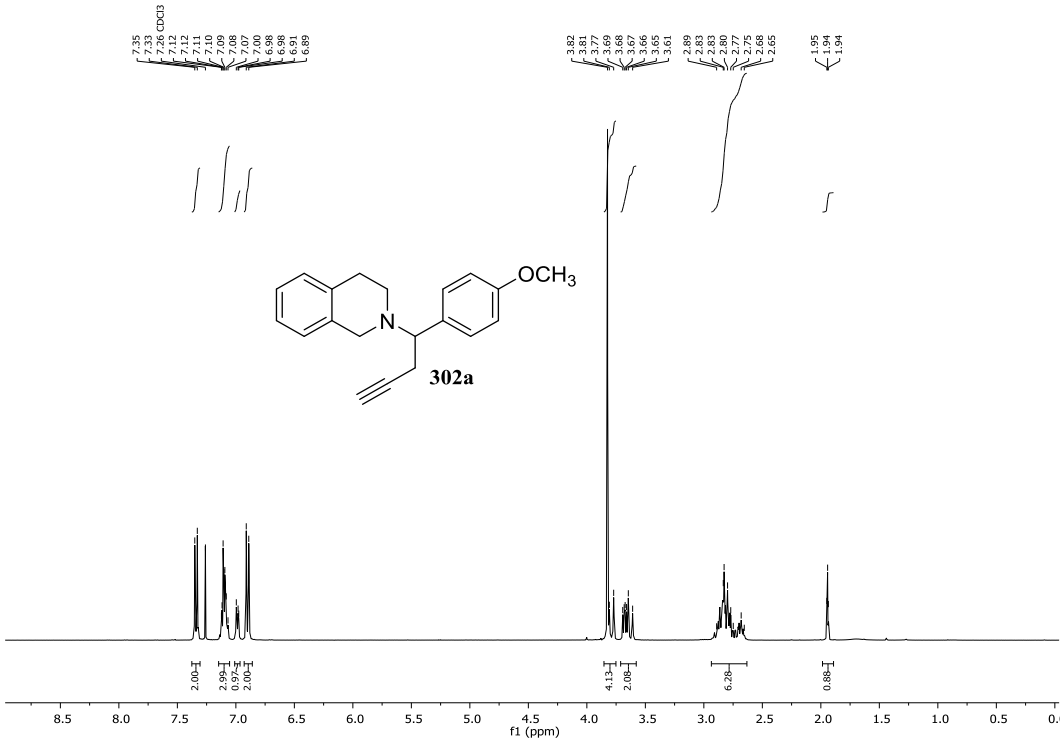


^{1}H NMR (400 MHz, $CDCl_3$) of compound **265a**.

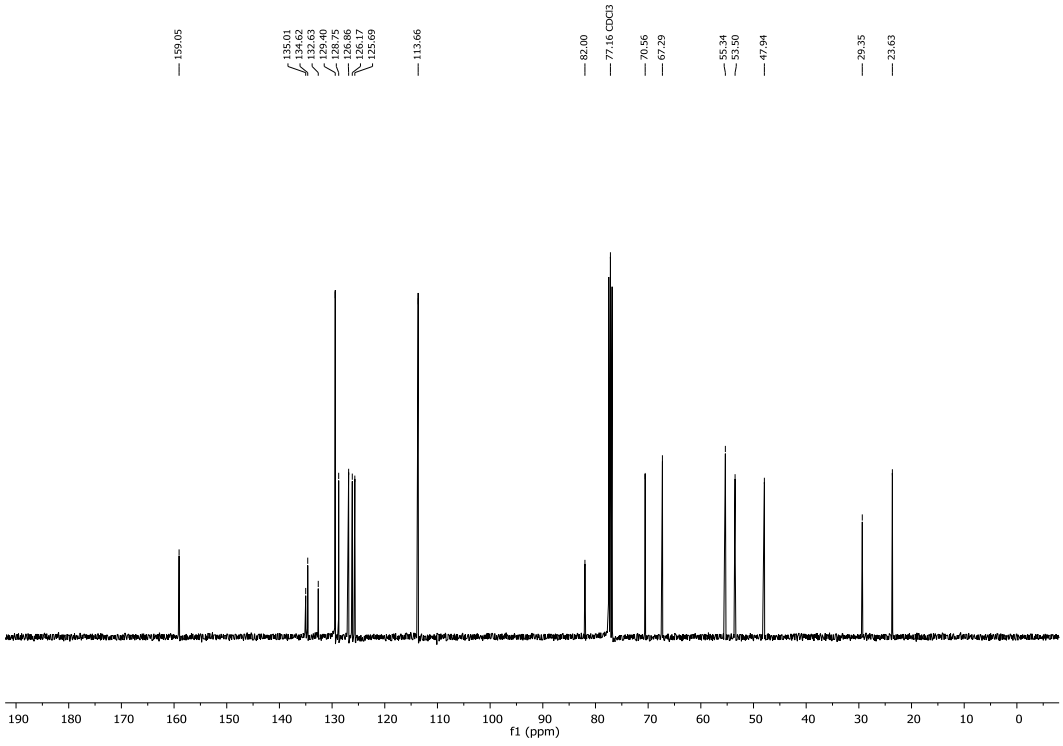


^{13}C NMR (100.6 MHz, $CDCl_3$) of compound **265a**.

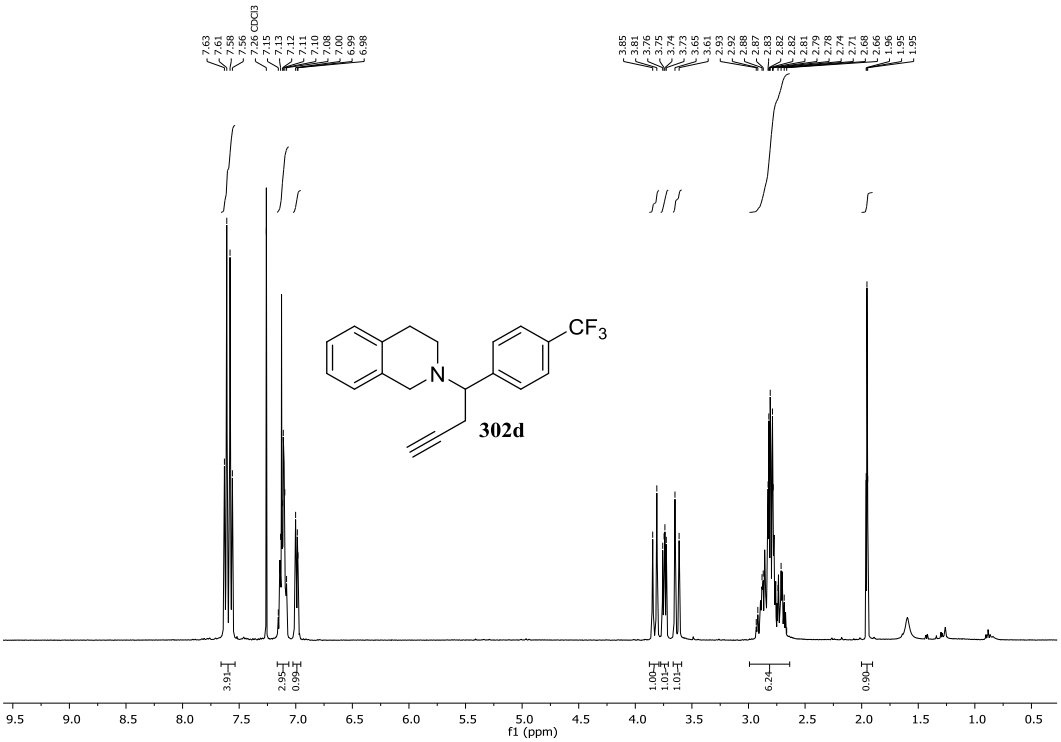
Chapter 6



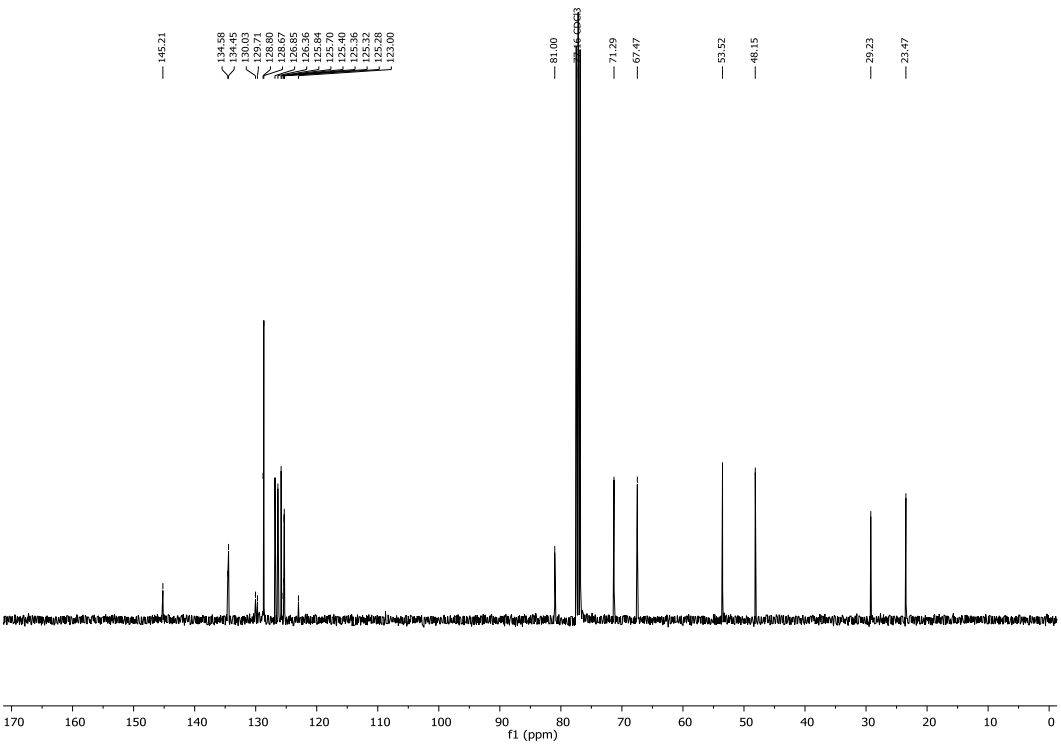
^{1}H NMR (400 MHz, $CDCl_3$) of compound **302a**.



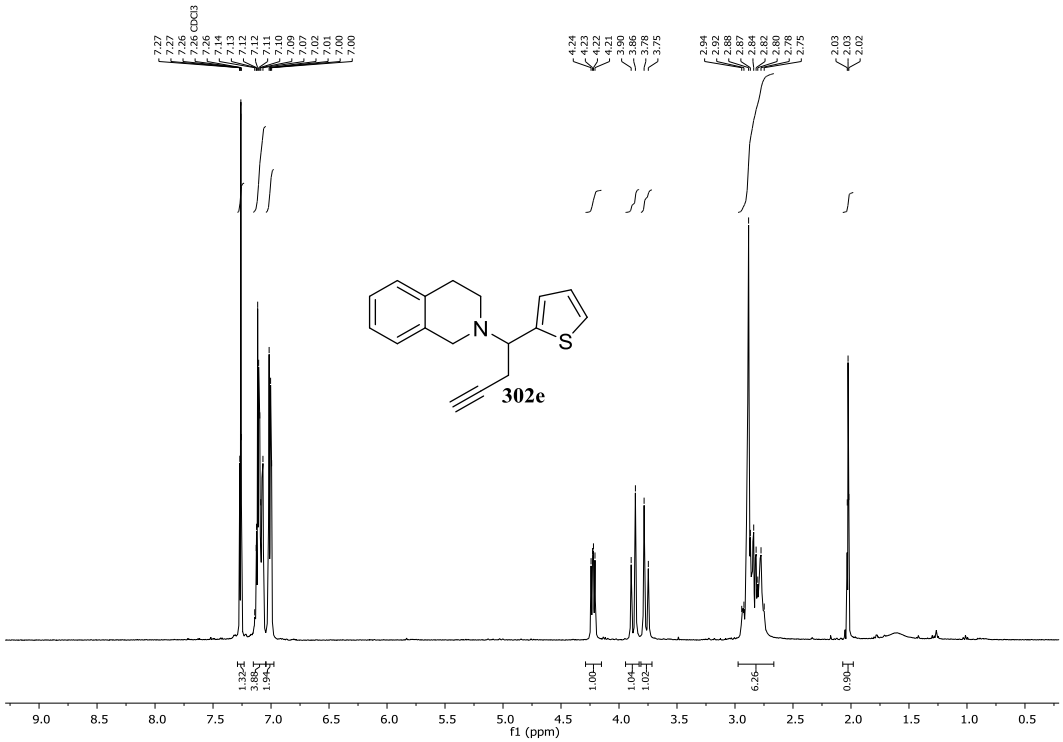
^{13}C NMR (100.6 MHz, $CDCl_3$) of compound **302a**.



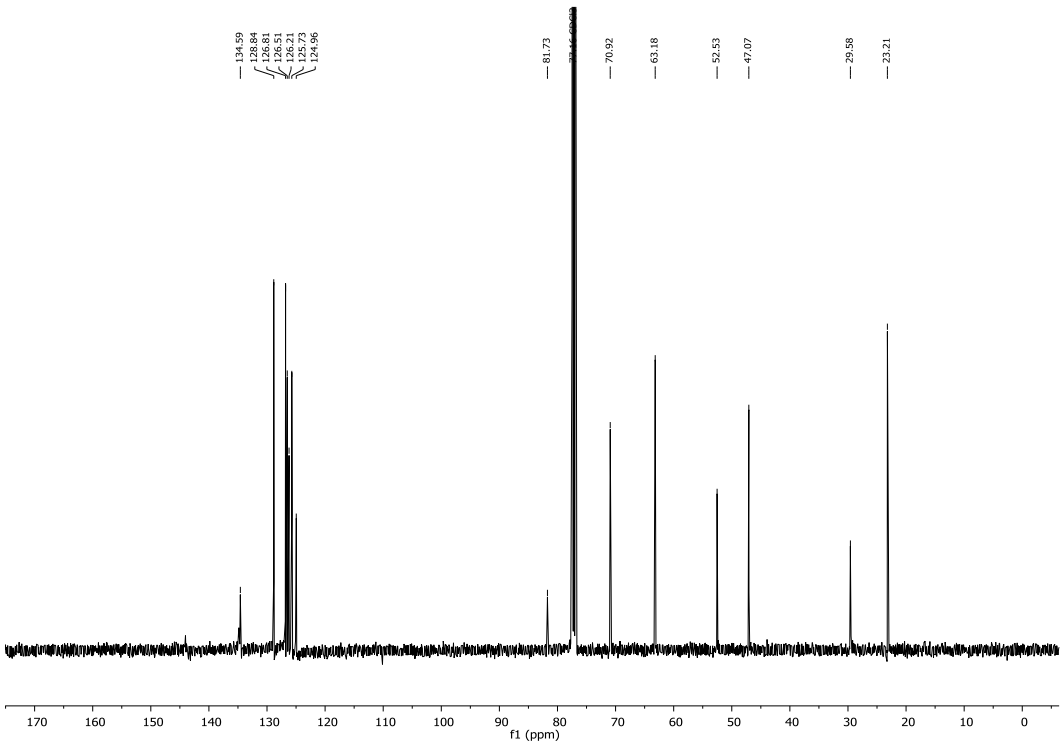
^{1}H NMR (400 MHz, $CDCl_3$) of compound **302d**.



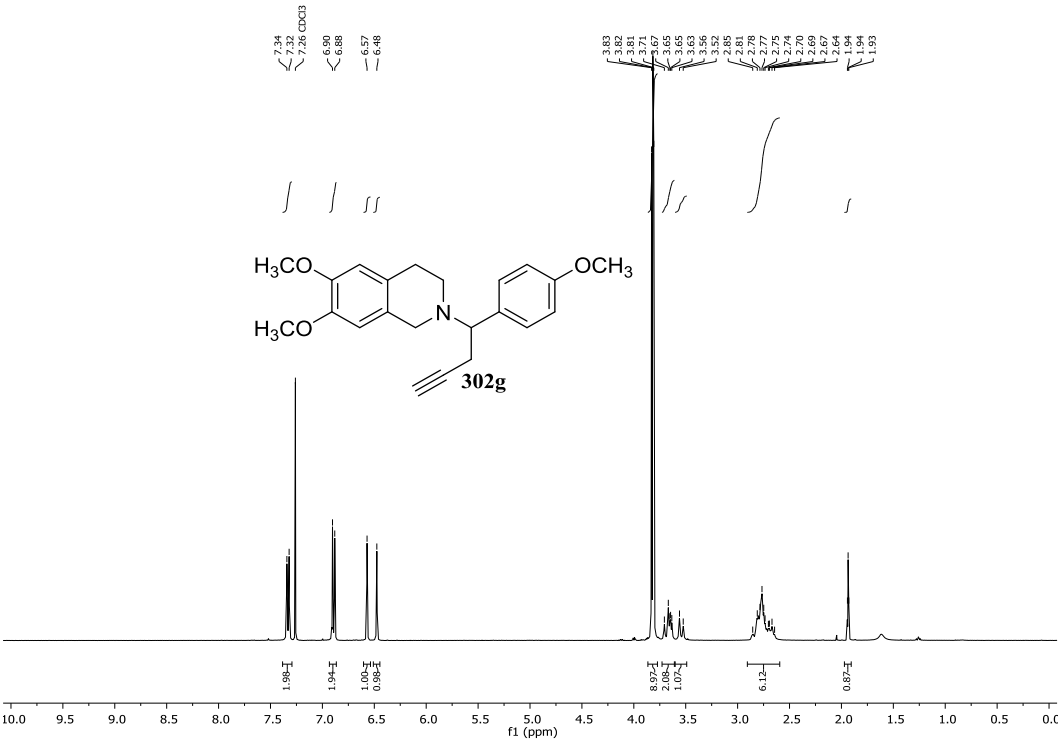
^{13}C NMR (100.6 MHz, $CDCl_3$) of compound **302d**.



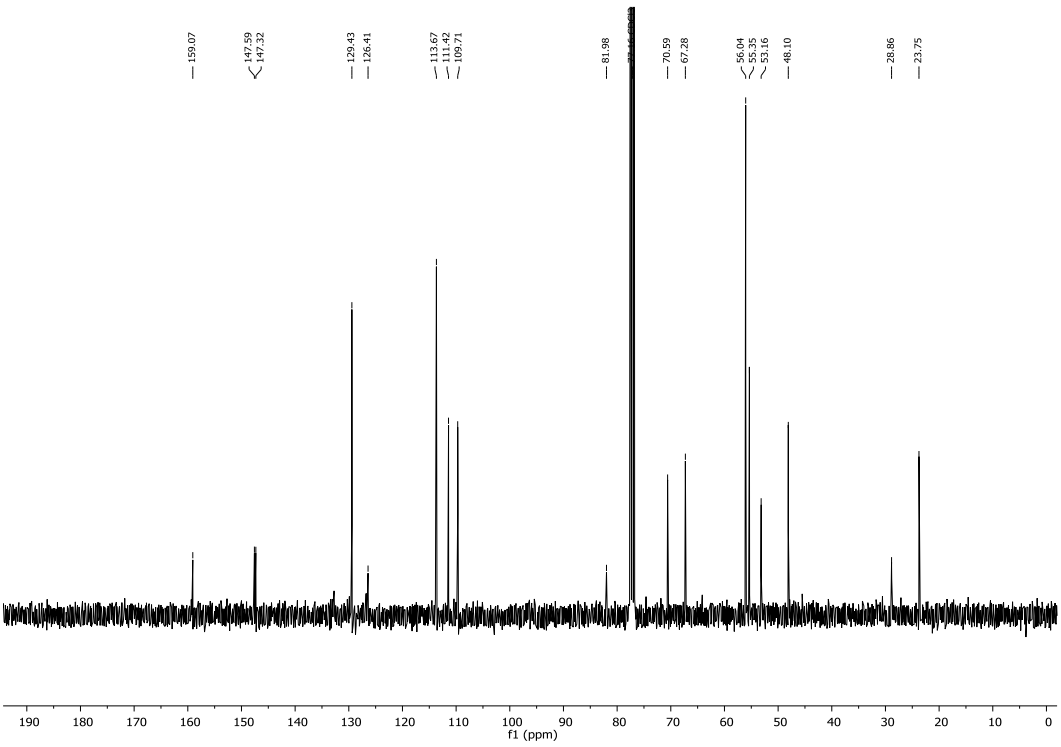
^{1}H NMR (400 MHz, $CDCl_3$) of compound **302e**.



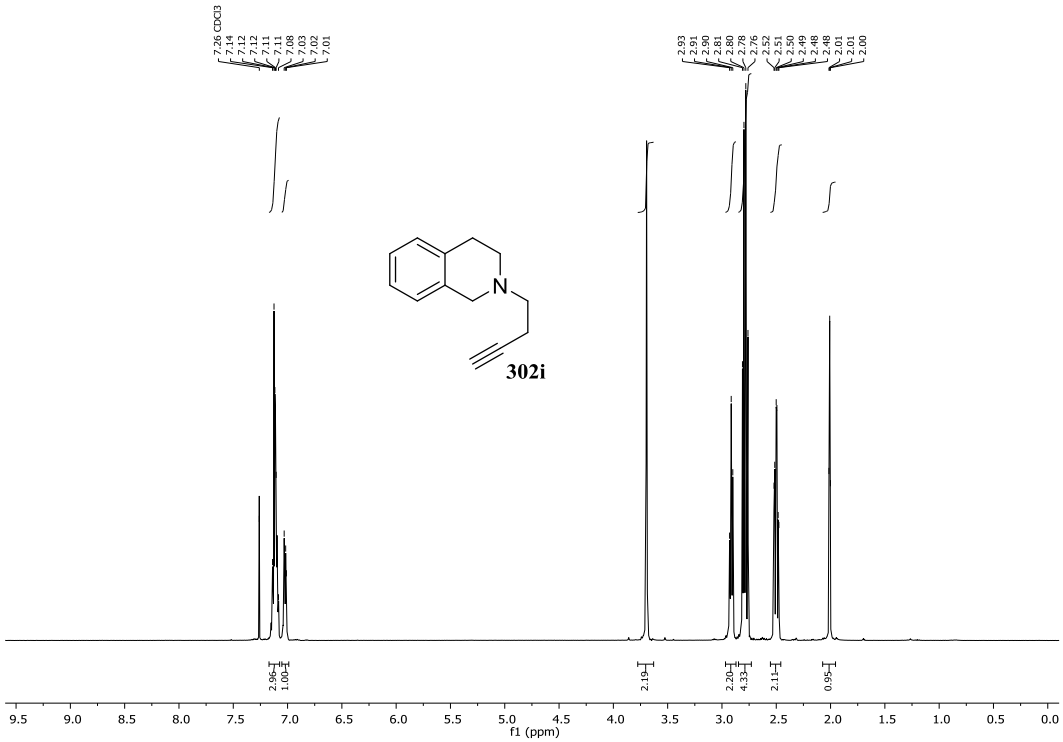
^{13}C NMR (100.6 MHz, $CDCl_3$) of compound **302e**.



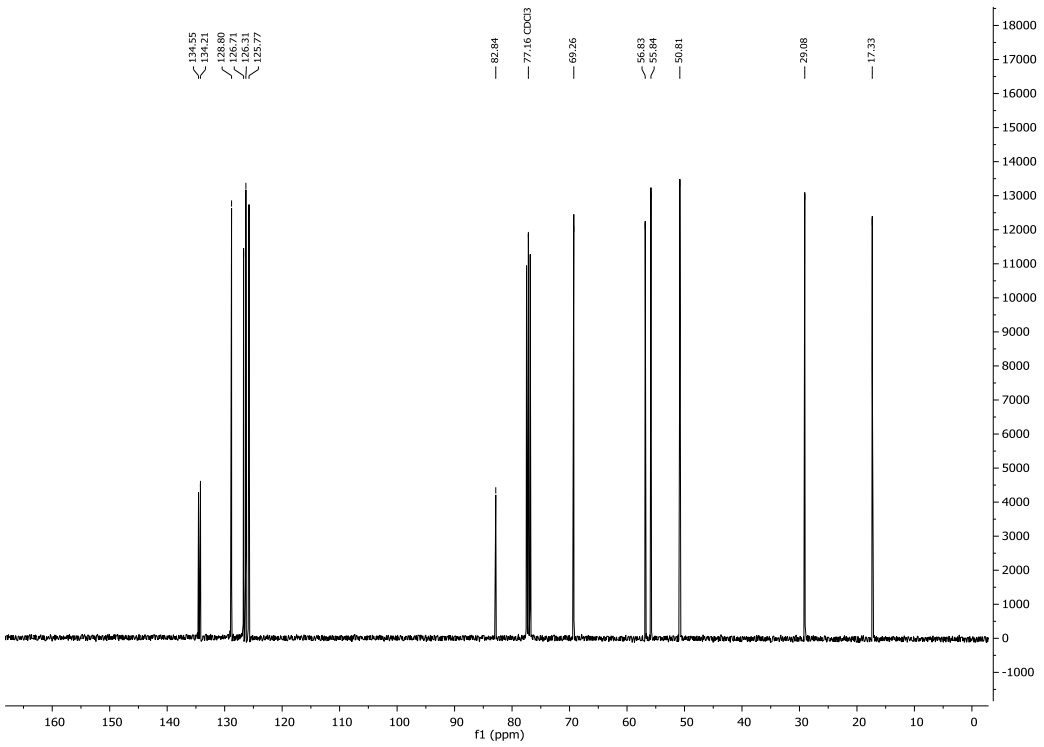
^{1}H NMR (400 MHz, $CDCl_3$) of compound **302g**.



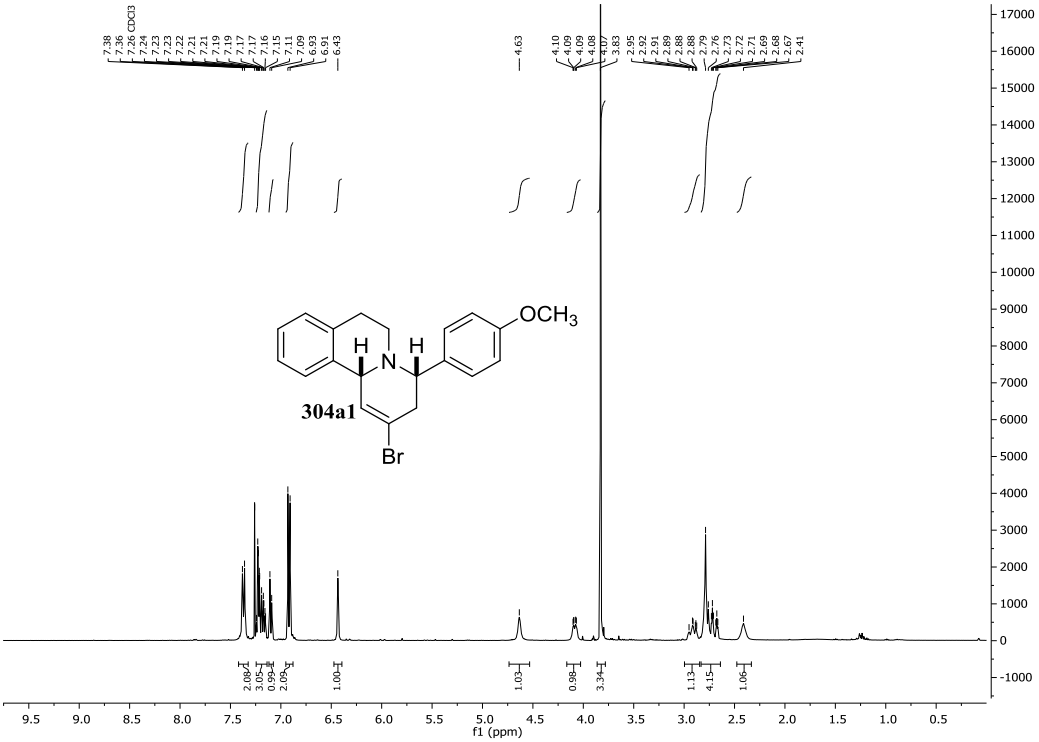
^{13}C NMR (100.6 MHz, $CDCl_3$) of compound **302g**.



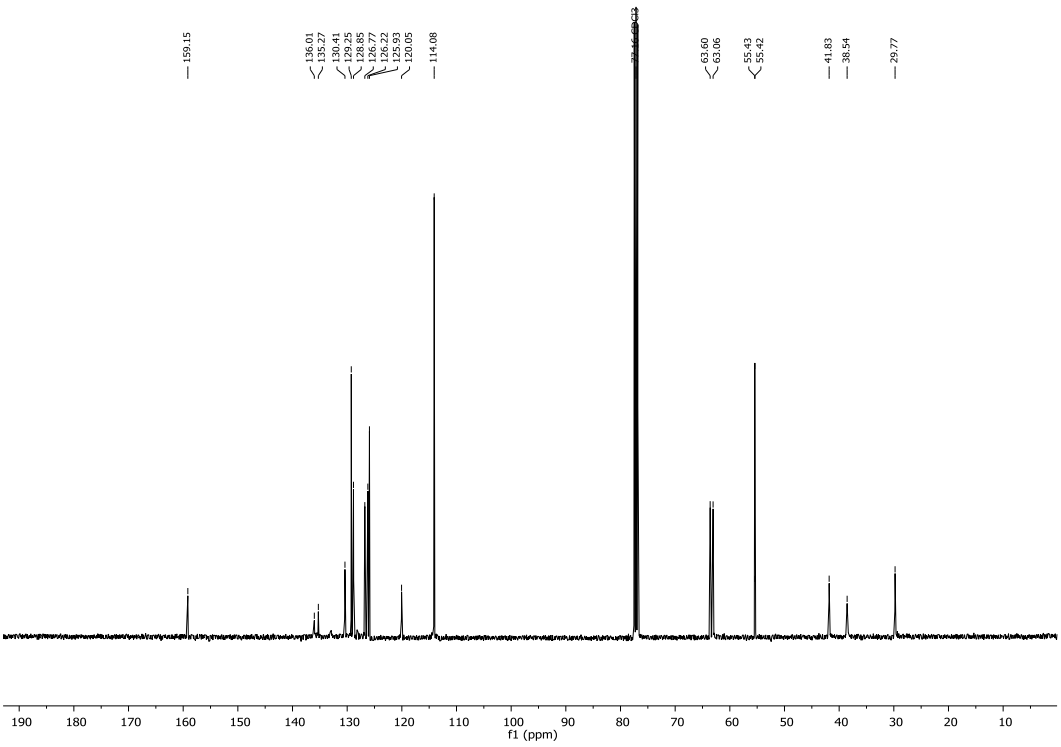
^{1}H NMR (400 MHz, $CDCl_3$) of compound **302a**.



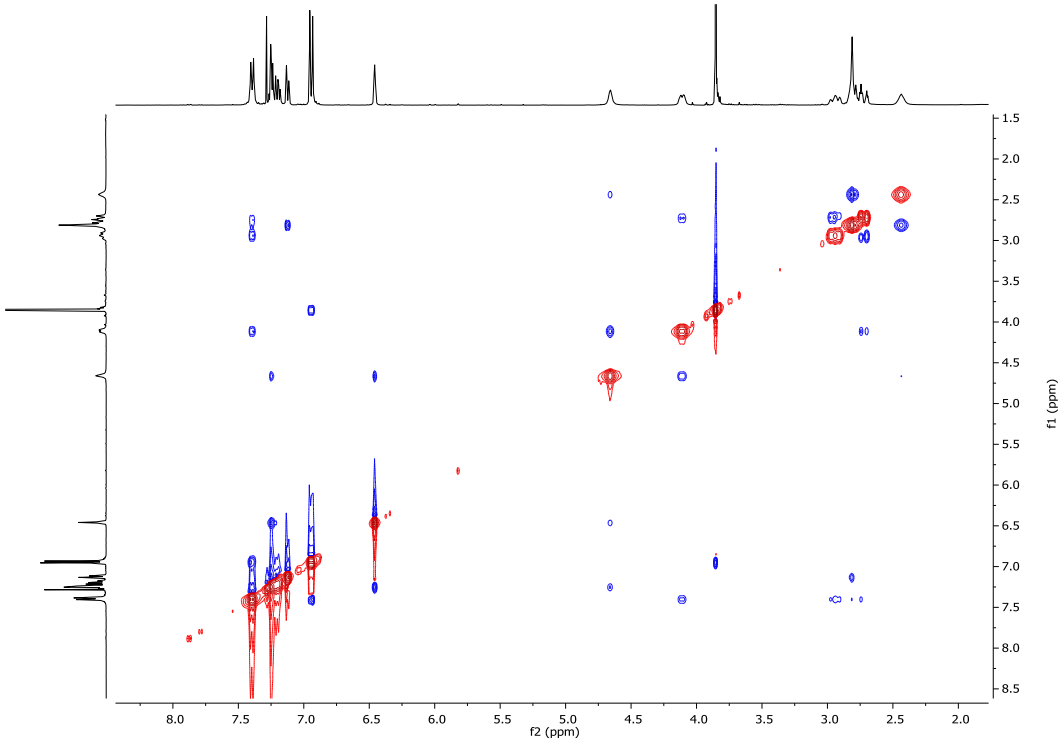
^{13}C NMR (100.6 MHz, $CDCl_3$) of compound **302a**.



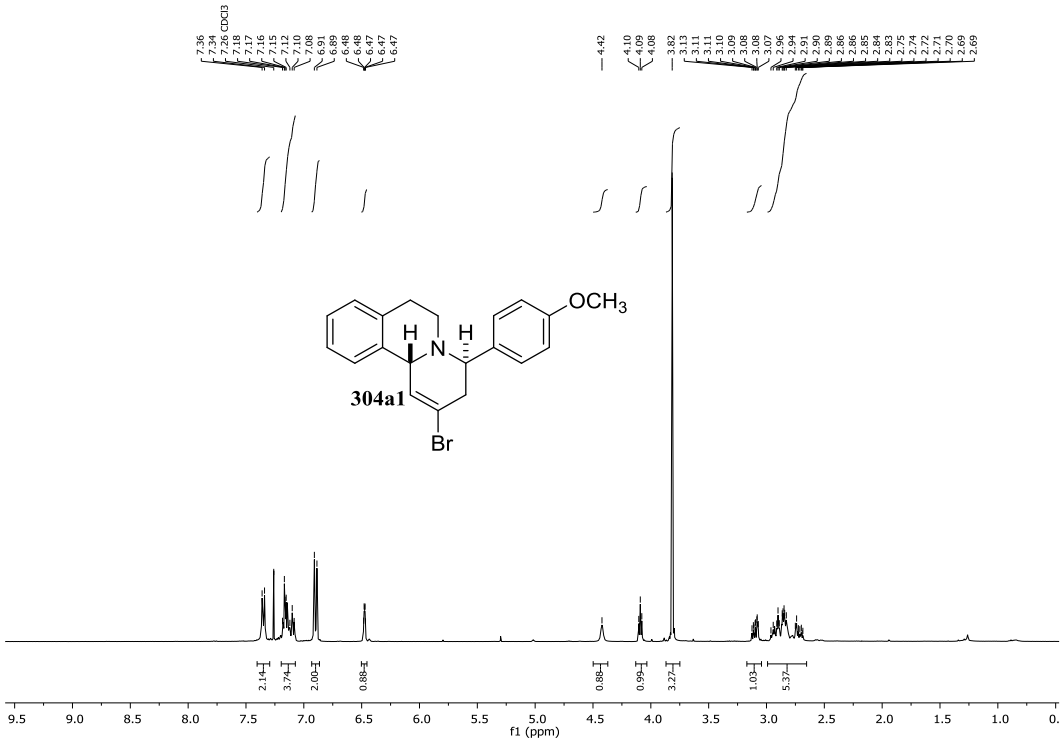
^{1}H NMR (400 MHz, $CDCl_3$) of *cis*-isomer **304a1**.



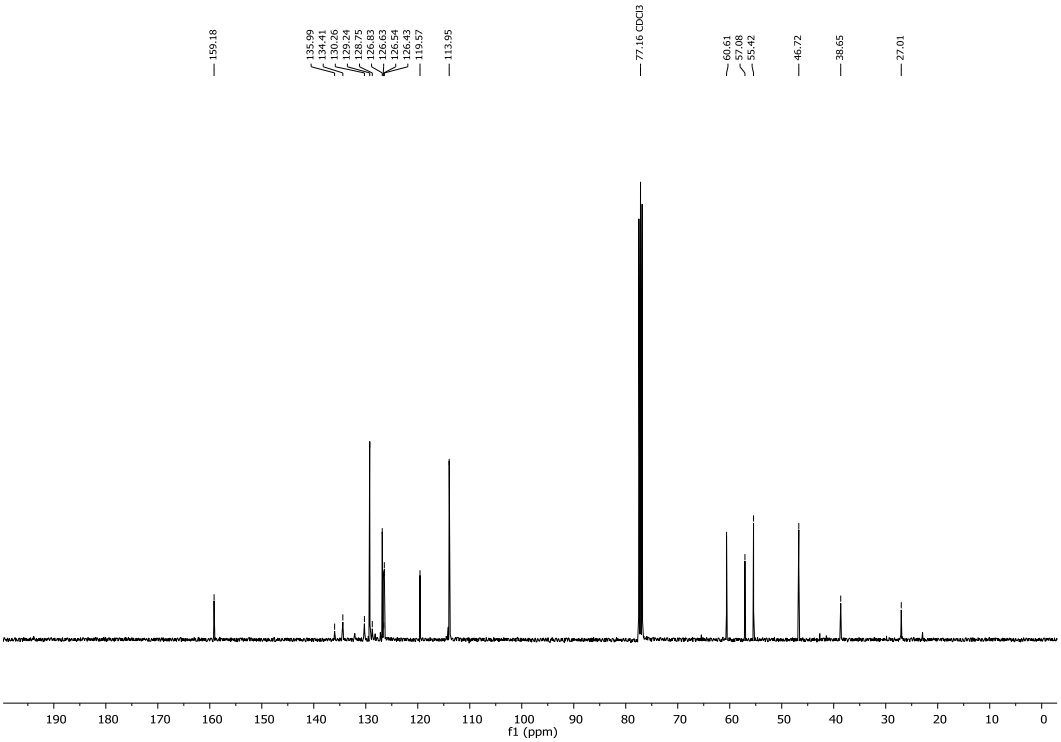
^{13}C NMR (100.6 MHz, $CDCl_3$) of *cis*-isomer **304a1**.



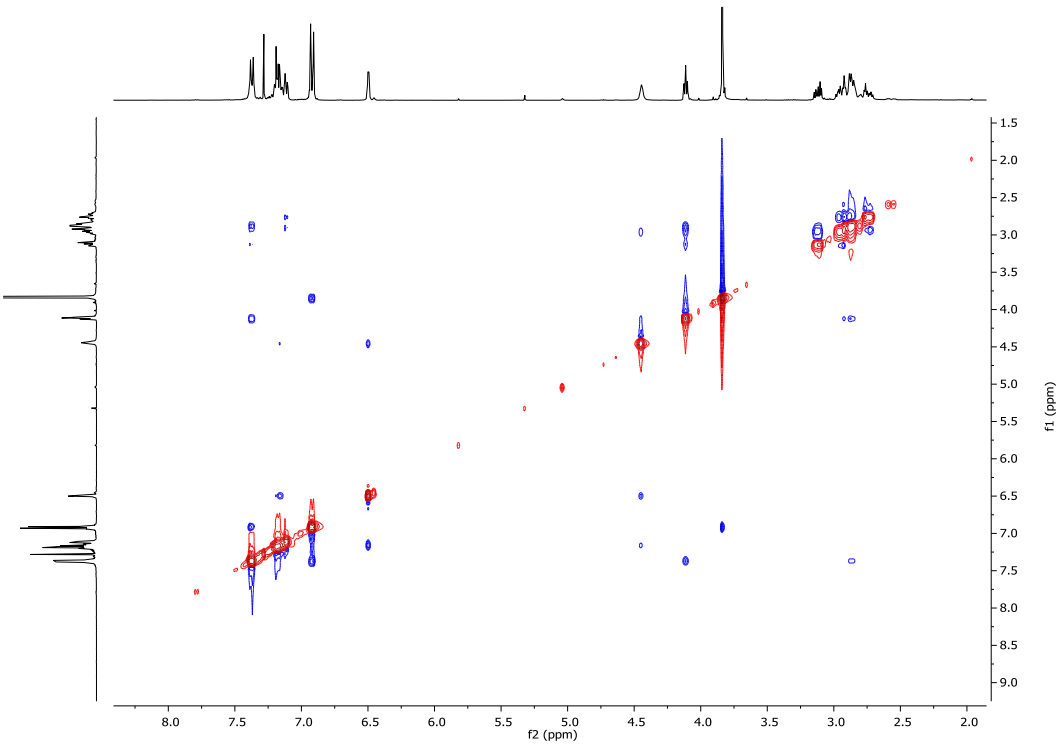
NOESY of *cis*-isomer **304a1**.



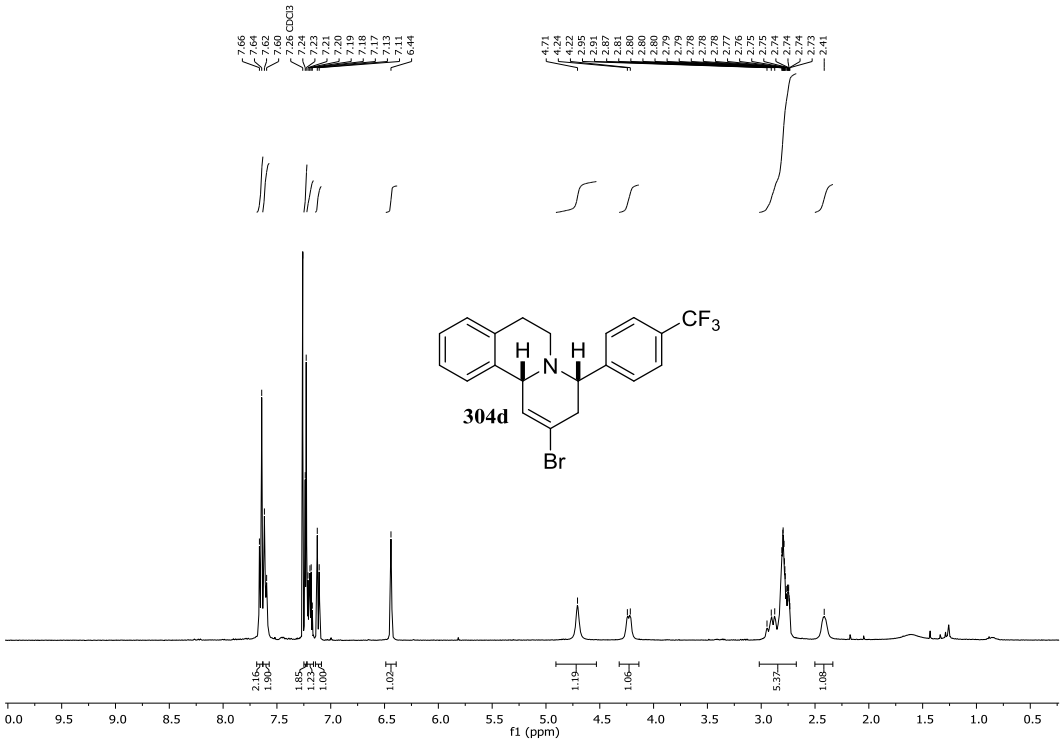
^{1}H NMR (400 MHz, $CDCl_3$) of *trans*-isomer **304a1**.



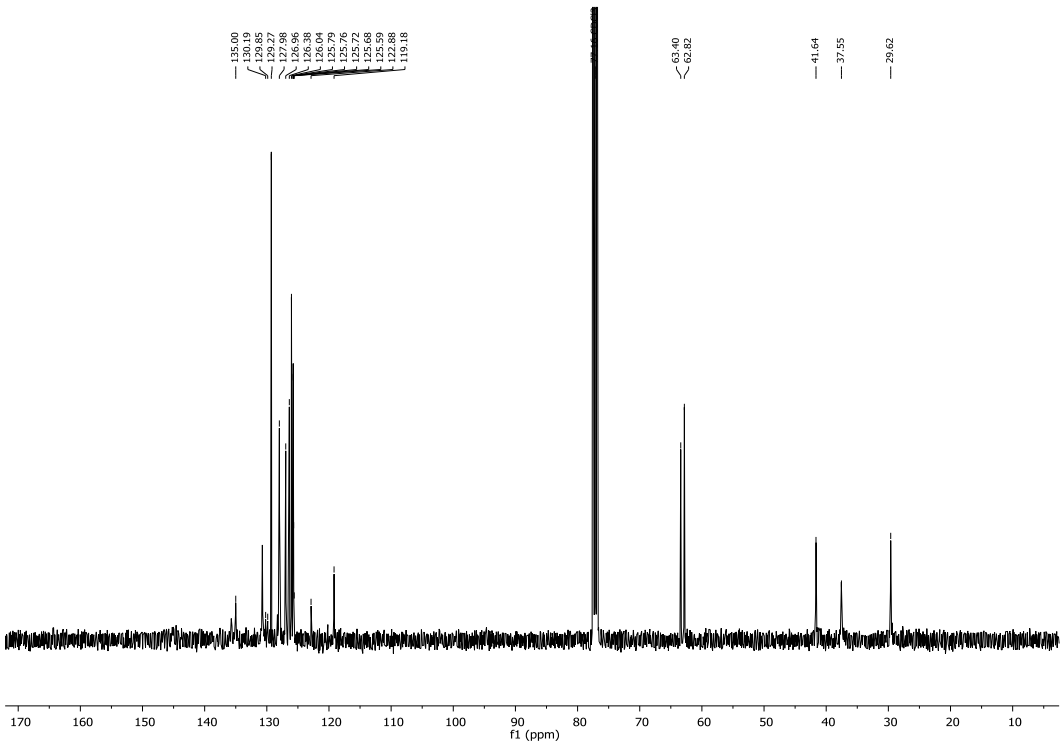
^{13}C NMR (100.6 MHz, $CDCl_3$) of *trans*-isomer **304a1**.



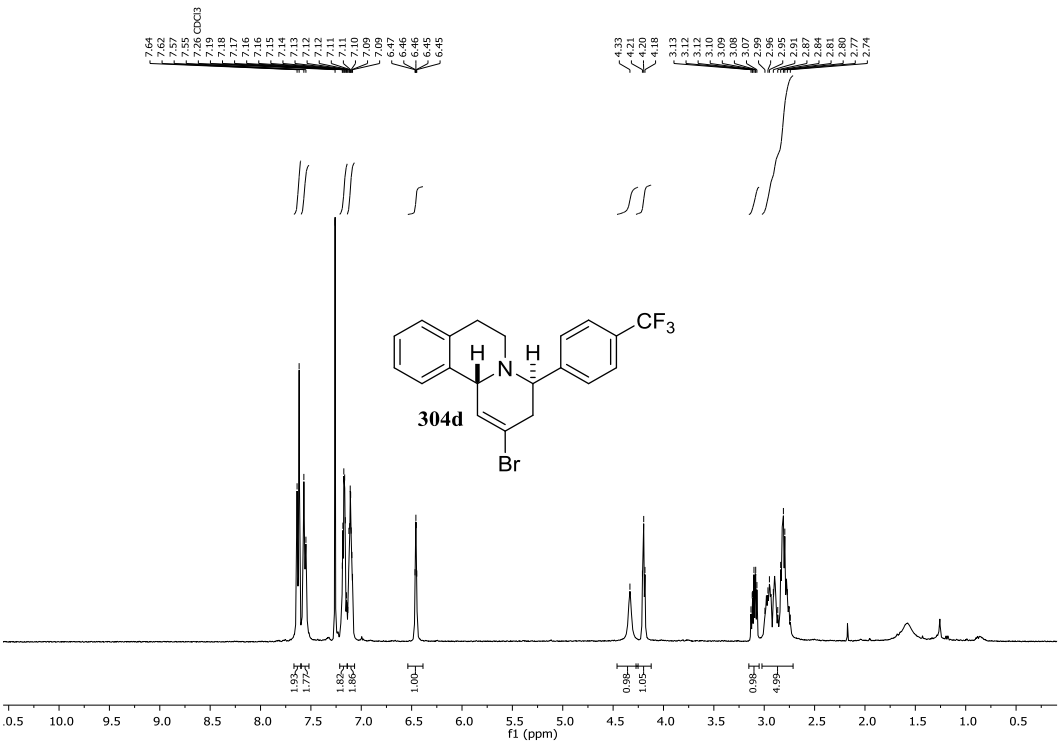
NOESY of *trans*-isomer **304a1**.



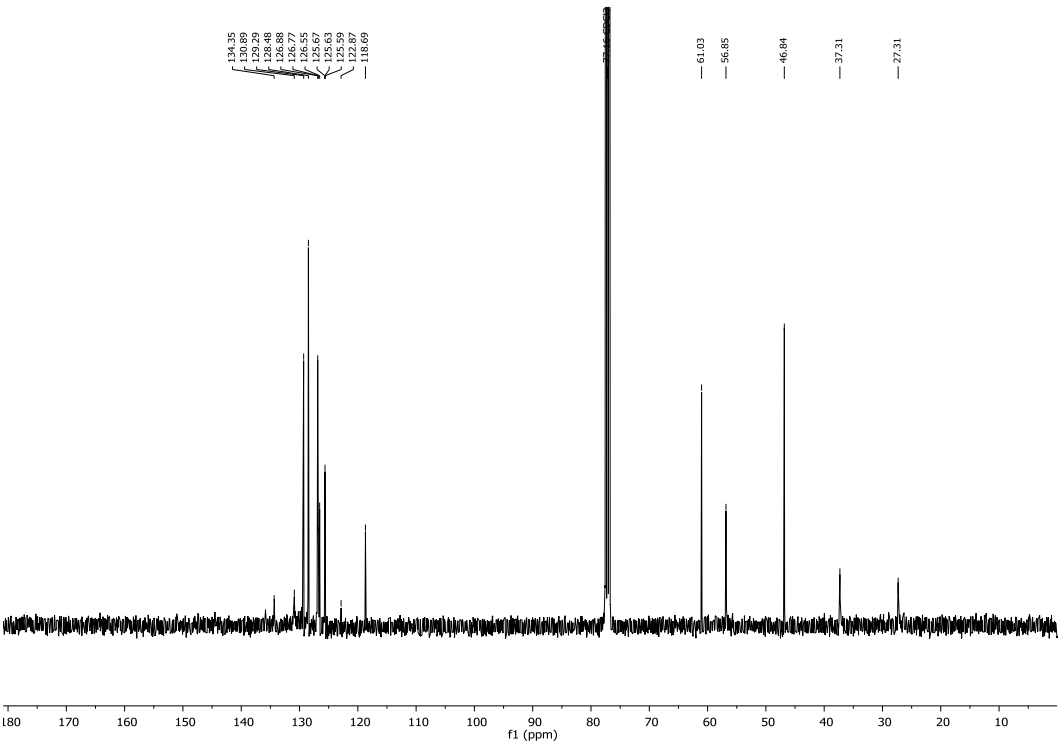
^{1}H NMR (400 MHz, $CDCl_3$) of *cis*-isomer **304d**.



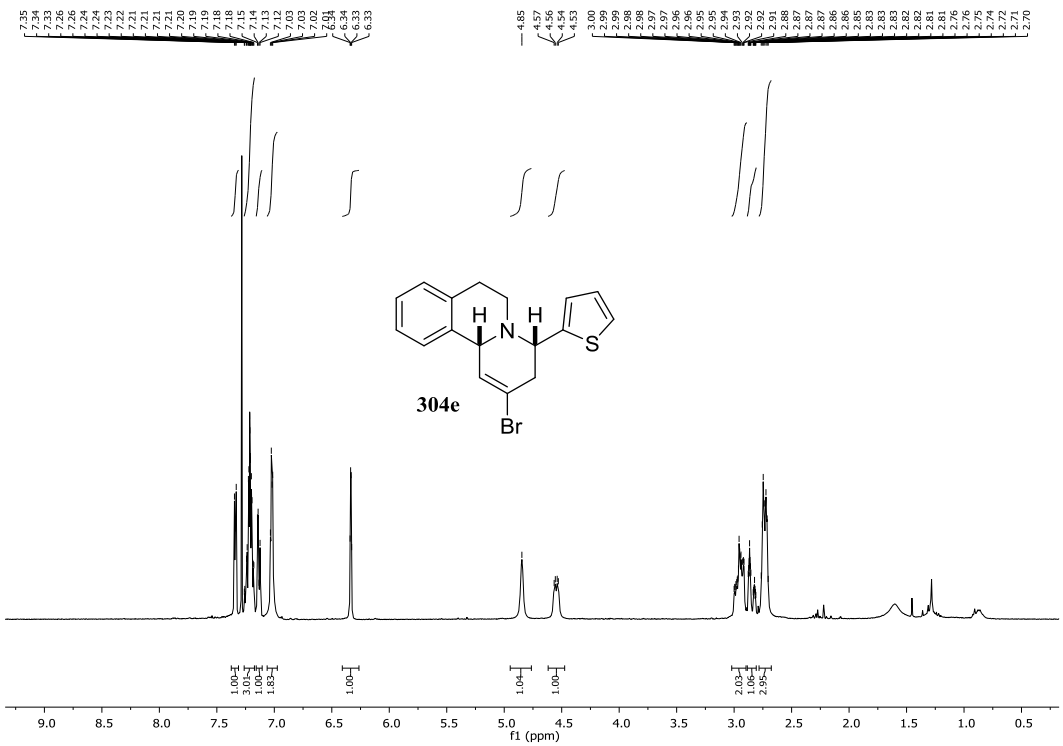
^{13}C NMR (100.6 MHz, $CDCl_3$) of *cis*-isomer **304d**.



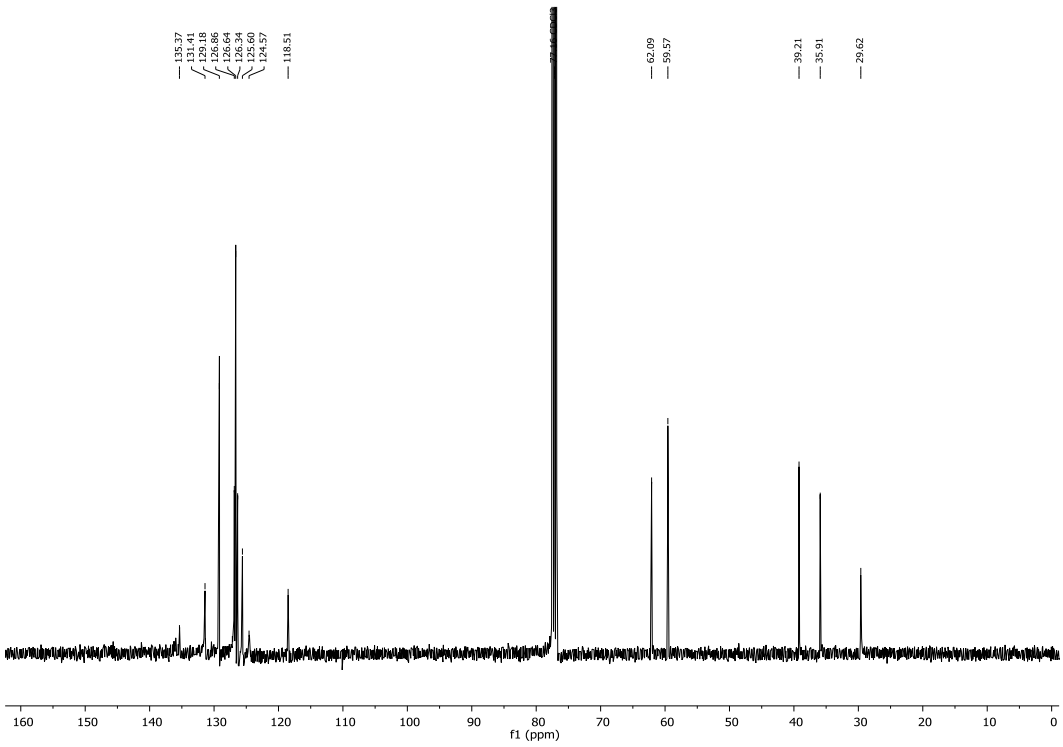
^{1}H NMR (400 MHz, $CDCl_3$) of *trans*-isomer **304d**.



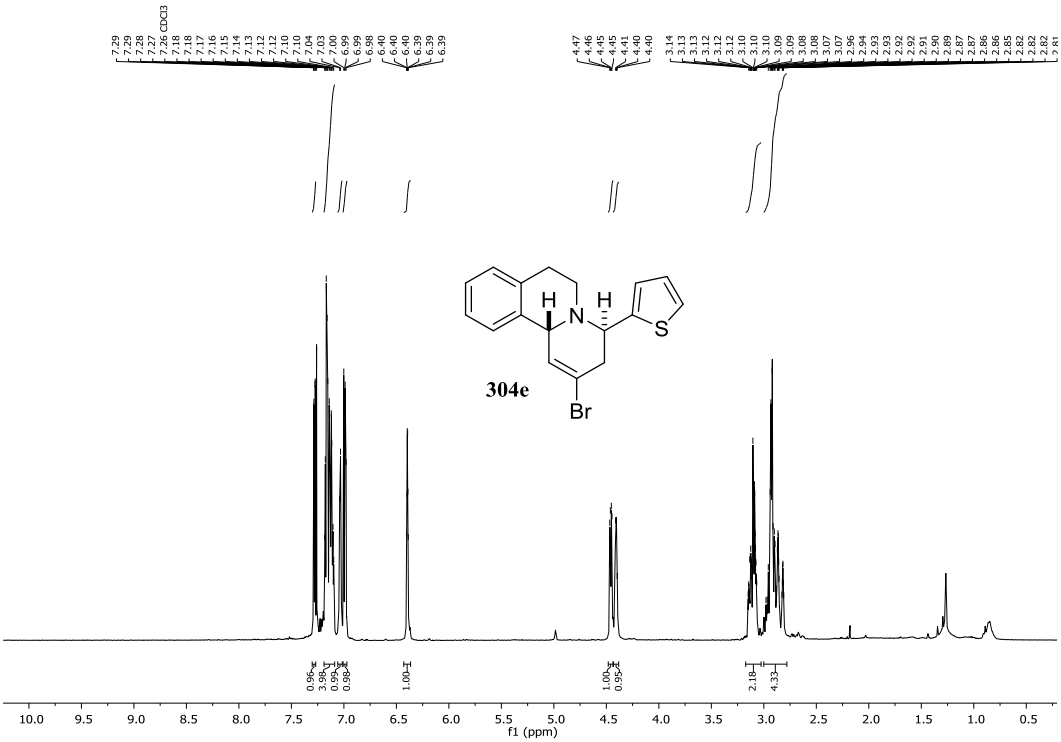
^{13}C NMR (100.6 MHz, $CDCl_3$) of *trans*-isomer **304d**.



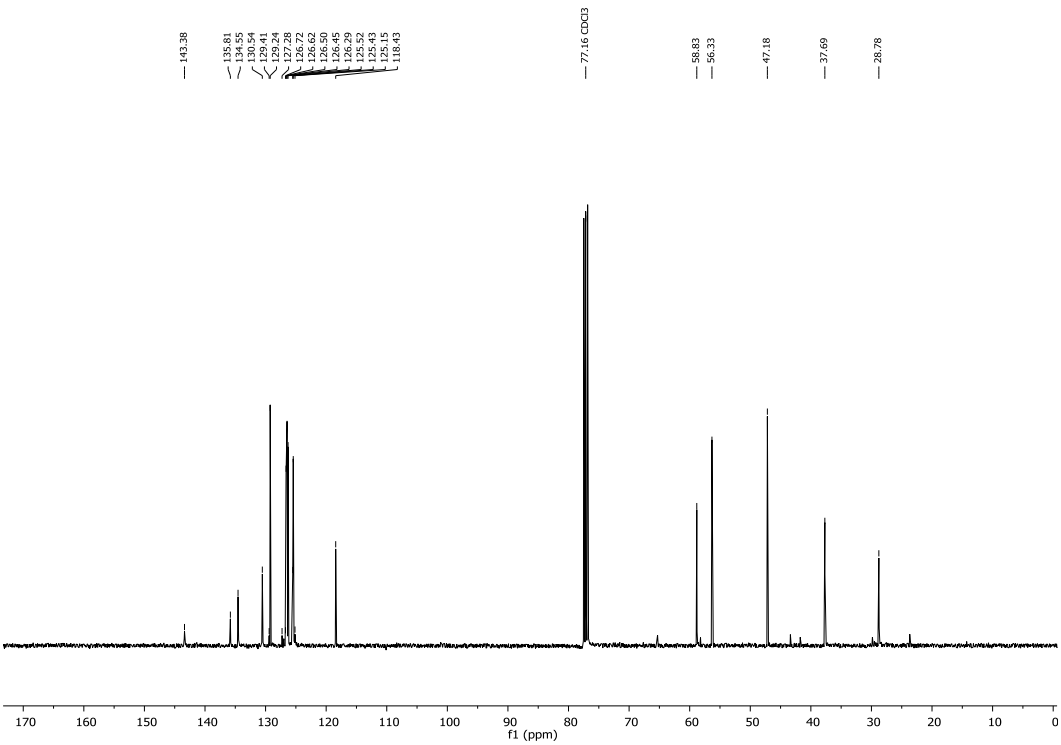
^{1}H NMR (400 MHz, $CDCl_3$) of *cis*-isomer **304e**.



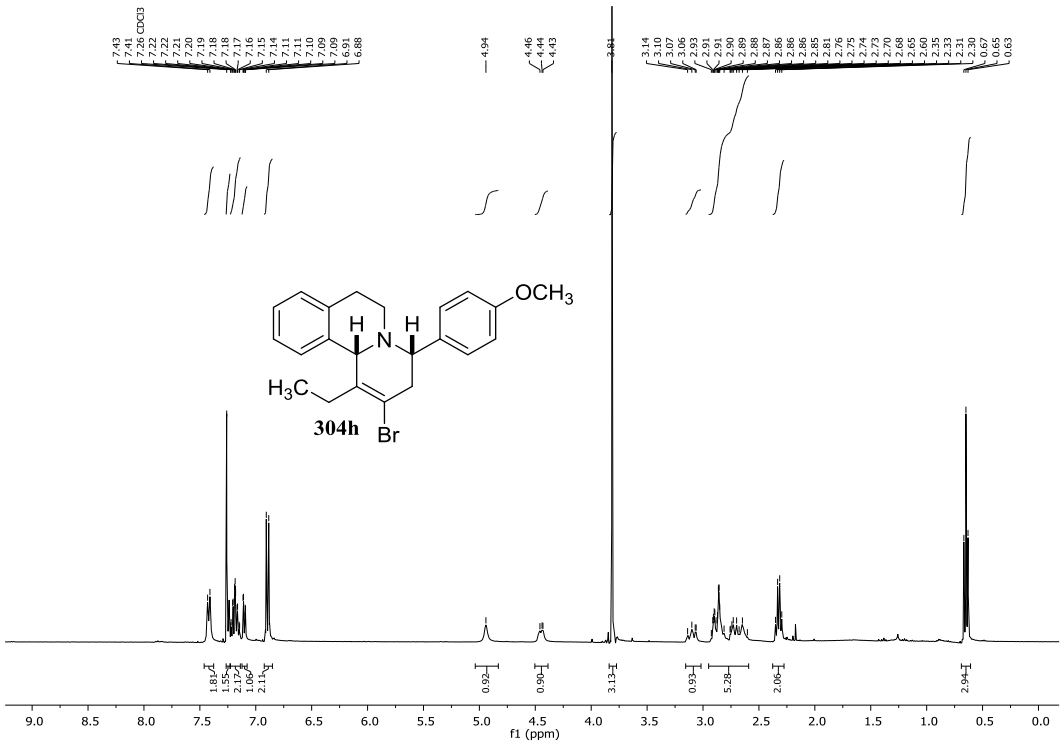
^{13}C NMR (100.6 MHz, $CDCl_3$) of *cis*-isomer **304e**.



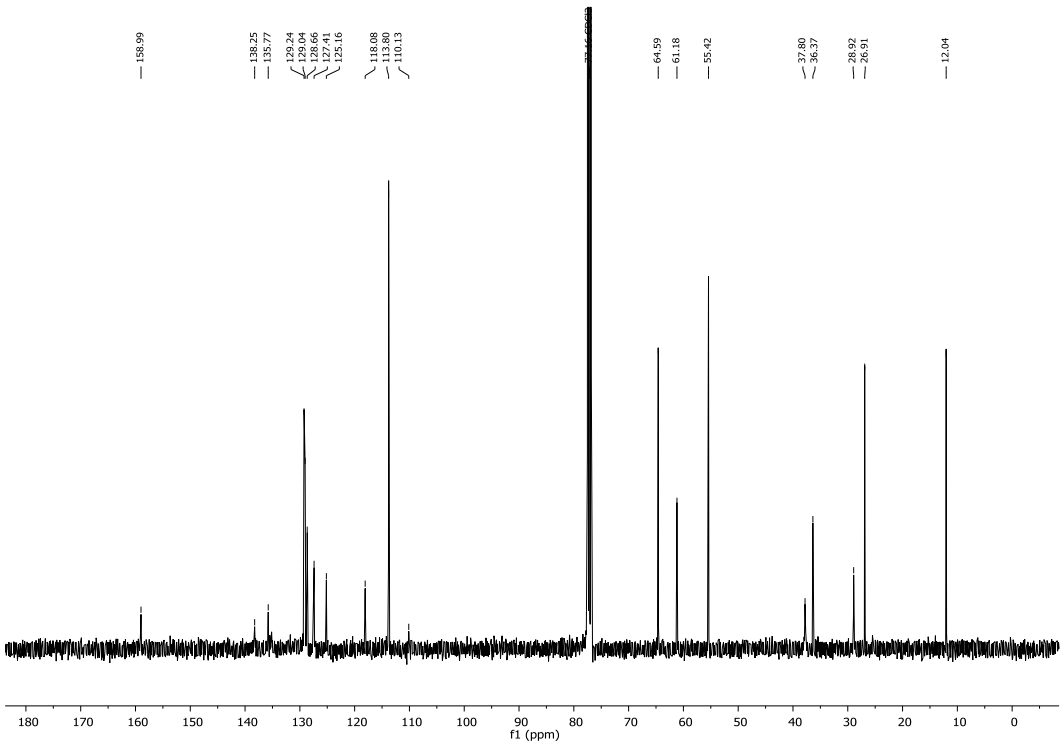
^{1}H NMR (400 MHz, $CDCl_3$) of *trans*-isomer **304e**.



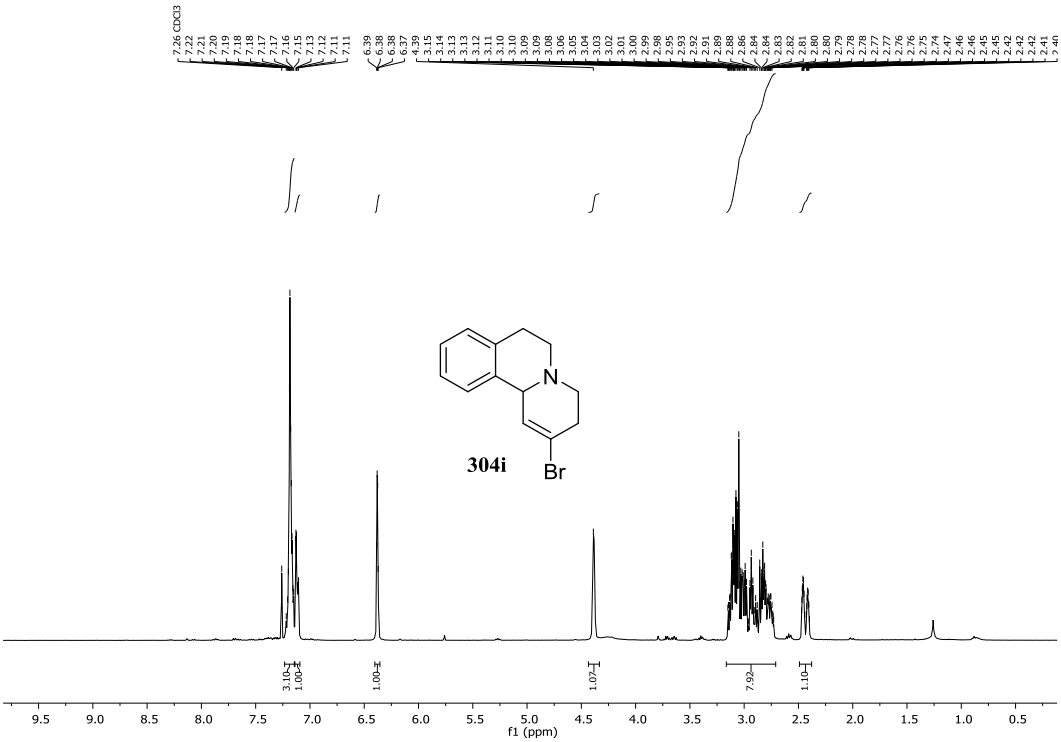
^{13}C NMR (100.6 MHz, $CDCl_3$) of *trans*-isomer **304e**.



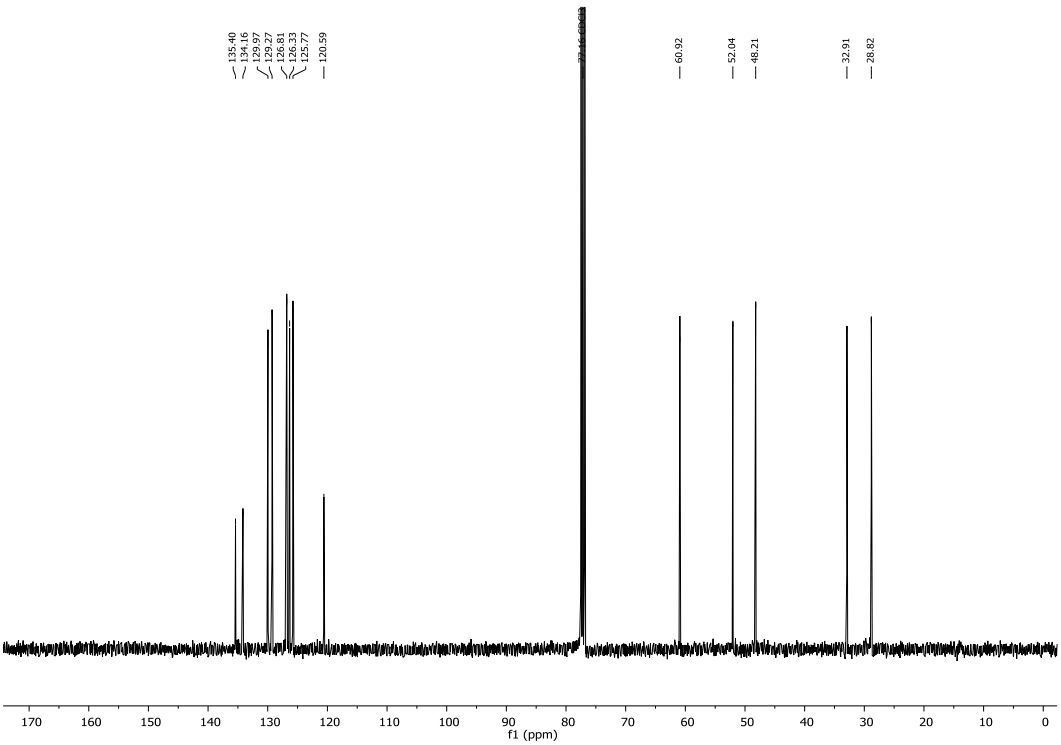
^{1}H NMR (400 MHz, $CDCl_3$) of *cis*-isomer **304h**.



^{13}C NMR (100.6 MHz, $CDCl_3$) of *cis*-isomer **304h**.



^{1}H NMR (400 MHz, $CDCl_3$) of compound **304i**.



^{13}C NMR (100.6 MHz, $CDCl_3$) of compound **304i**.

Apendix B: X-Ray Data

Crystal data for compound **132b**

formula	$C_{18}H_{18}N_2$		
molecular weight	262.4 $gmol^{-1}$		
absorption	$\mu = 0.07\ mm^{-1}$		
crystal size	0.23 x 0.5 x 0.5 mm^3 colourless plate		
space group	P -1 (triclinic)		
lattice parameters	a = 9.067(2)Å	α = 112.775(4)°	
(calculate from	b = 9.430(2)Å	ß = 98.136(4)°	
4965 reflections with	c = 9.859(2)Å	γ = 107.001(4)°	
2.3° < θ < 27.8°)	V = 711.6(4)$Å^3$	z = 2	F(000) = 280
temperature	-100°C		
density	$d_{xray} = 1.224\ gcm^{-3}$		

data collection

diffractometer	Smart CCD
radiation	Mo-K_α graphit monochromator
scan type	ω-scans
scan – width	0.5°
scan range	2° ≤ θ < 28°
	-11 ≤ h ≤ 11 -12 ≤ k ≤ 12 -12 ≤ l ≤ 12
number of reflections:	
measured	8795
unique	3365 (R_{int} = 0.0236)
observed	3015 ($\|F\|/\sigma(F) > 4.0$)

data correction, structure solution and refinement

corrections	Lorentz and polarisation correction.
Structure solution	Program: SIR-97 (Direct methods)
refinement	Program: SHELXL-97 (full matrix). 182 refined parameters, weighting scheme: $w=1/[\sigma^2(F_o^2) + (0.0552*P)^2+0.18*P]$ with $(Max(F_o^2,0)+2*F_c^2)/3$. H-atoms at calculated positions and refined with isotropic displacement parameters, non H- atoms refined anisotropically.
R-values	wR2 = 0.1087 (R1 = 0.0414 for observed reflections, 0.0459 for all reflections)
goodness of fit	S = 1.049
maximum deviation of parameters	0.001 * e.s.d
maximum peak height in diff. Fourier synthesis	0.23, -0.26 $eÅ^{-3}$

final coordinates and equivalent displacement parameters (Å^2)
$U_{äq}= (1/3)*\sum\sum_{ij}a_i^* a_j^* \mathbf{a}_i\mathbf{a}_j$

Atom	X	Y	Z	U_{eq}
C1	0.0784(1)	0.1290(1)	0.1891(1)	0.0244(4)
C2	0.1762(1)	0.2720(1)	0.1616(1)	0.0221(4)
C3	0.1034(1)	0.3756(1)	0.1381(1)	0.0271(4)
C4	0.1891(1)	0.5146(1)	0.1226(1)	0.0295(4)
C5	0.3503(1)	0.5519(1)	0.1282(1)	0.0295(4)
C6	0.4237(1)	0.4469(1)	0.1458(1)	0.0258(4)
C7	0.3390(1)	0.3079(1)	0.1621(1)	0.0215(4)
C8	0.4223(1)	0.1991(1)	0.1908(1)	0.0219(4)
N9	0.4711(1)	0.2455(1)	0.3545(1)	0.0226(3)
C10	0.4559(1)	0.1055(1)	0.3894(1)	0.0289(5)
C11	0.2780(1)	-0.0007(1)	0.3568(1)	0.0290(4)
C12	0.1900(1)	0.1072(1)	0.4334(1)	0.0254(4)
C13	0.2020(1)	0.1514(2)	0.5884(1)	0.0338(5)
C14	0.1294(2)	0.2543(2)	0.6686(1)	0.0396(5)
C15	0.0412(2)	0.3136(2)	0.5933(2)	0.0385(5)
C16	0.0275(1)	0.2707(1)	0.4396(1)	0.0310(5)
C17	0.1020(1)	0.1694(1)	0.3580(1)	0.0235(4)
C18	0.5596(1)	0.2000(1)	0.1219(1)	0.0264(4)
N19	0.6676(1)	0.1999(1)	0.0745(1)	0.0363(4)
C20	0.6237(1)	0.3876(1)	0.4409(1)	0.0279(4)

anisotropic displacement parameters

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C1	0.0174(4)	0.0233(5)	0.0269(5)	0.0050(4)	0.0044(4)	0.0086(4)
C2	0.0210(5)	0.0233(5)	0.0175(4)	0.0072(4)	0.0043(3)	0.0062(4)
C3	0.0235(5)	0.0321(6)	0.0248(5)	0.0125(4)	0.0051(4)	0.0112(4)
C4	0.0358(6)	0.0318(6)	0.0258(5)	0.0182(5)	0.0079(4)	0.0142(4)
C5	0.0371(6)	0.0287(5)	0.0272(5)	0.0127(5)	0.0128(4)	0.0157(4)
C6	0.0259(5)	0.0286(5)	0.0244(5)	0.0102(4)	0.0111(4)	0.0124(4)
C7	0.0221(5)	0.0233(5)	0.0173(4)	0.0093(4)	0.0065(3)	0.0069(4)
C8	0.0194(4)	0.0218(5)	0.0235(5)	0.0083(4)	0.0086(4)	0.0082(4)
N9	0.0210(4)	0.0238(4)	0.0238(4)	0.0087(3)	0.0069(3)	0.0112(3)
C10	0.0267(5)	0.0321(6)	0.0376(6)	0.0157(4)	0.0118(4)	0.0210(5)
C11	0.0293(5)	0.0259(5)	0.0370(6)	0.0115(4)	0.0115(4)	0.0180(5)
C12	0.0202(5)	0.0227(5)	0.0298(5)	0.0031(4)	0.0084(4)	0.0117(4)
C13	0.0276(5)	0.0372(6)	0.0318(6)	0.0029(5)	0.0078(4)	0.0182(5)
C14	0.0388(6)	0.0385(7)	0.0279(6)	0.0006(5)	0.0158(5)	0.0098(5)
C15	0.0405(7)	0.0290(6)	0.0425(7)	0.0092(5)	0.0269(6)	0.0106(5)
C16	0.0276(5)	0.0269(5)	0.0409(6)	0.0098(4)	0.0179(5)	0.0152(5)
C17	0.0185(4)	0.0197(5)	0.0276(5)	0.0026(4)	0.0089(4)	0.0088(4)
C18	0.0260(5)	0.0241(5)	0.0274(5)	0.0105(4)	0.0100(4)	0.0086(4)
N19	0.0313(5)	0.0339(5)	0.0427(6)	0.0134(4)	0.0192(4)	0.0127(4)
C20	0.0224(5)	0.0286(5)	0.0268(5)	0.0081(4)	0.0051(4)	0.0086(4)

final coordinates and isotropic displacement parameters (Å^2) for H- atoms

Atom	X	Y	Z	U_{iso}
H1A	-0.03723	0.09575	0.13972	0.0292
H1B	0.10820	0.03253	0.13846	0.0292
H3	-0.00736	0.35064	0.13268	0.0325
H4	0.13717	0.58389	0.10813	0.0354
H5	0.40995	0.64804	0.12000	0.0354
H6	0.53322	0.47038	0.14679	0.0309
H8	0.34093	0.08229	0.13835	0.0263
H10A	0.51314	0.14809	0.49891	0.0347
H10B	0.50702	0.03553	0.32629	0.0347
H11A	0.22573	-0.06104	0.24451	0.0347
H11B	0.27137	-0.08408	0.39566	0.0347
H13	0.26123	0.10987	0.64013	0.0405
H14	0.14025	0.28385	0.77421	0.0476
H15	-0.00971	0.38334	0.64691	0.0462
H16	-0.03398	0.31110	0.38850	0.0373
H20A	0.63956	0.42314	0.55114	0.0418
H20B	0.62167	0.47935	0.41792	0.0418
H20C	0.71232	0.35553	0.41147	0.0418

Crystal data for compound **199**

formula	$C_{19}H_{25}BrN_2O_2$
molecular weight	393.32 $gmol^{-1}$
absorption	μ = 2.17 mm^{-1} correction with 6 crystal faces
transmission	t_{min} = 0.3249, t_{max} = 0.5817
crystal size	0.26 x 0.45 x 0.70 mm^3 colourless block
space group	P $2_1/c$ (monoclinic)
lattice parameters	a = 13.2821(9)Å
(calculate from	b = 12.5739(5)Å ß = 104.670(5)°
14253 reflections with	c = 11.7859(7)Å
2.6° < θ < 28.4°)	V = 1904.2(2)$Å^3$ z = 4 F(000) = 816
temperature	-80°C
density	d_{xray} = 1.372 gcm^{-3}

data collection

diffractometer	STOE IPDS 2T
radiation	Mo-K_α Graphitmonochromator
Scan – type	ω scans
Scan – width	1°
scan range	2° ≤ θ < 28°
	-17 ≤ h ≤ 16 -16 ≤ k ≤ 16 -15 ≤ l ≤ 15
number of reflections:	
measured	13014
unique	4595 (R_{int} = 0.0558)
observed	3570 (|F|/σ(F) > 4.0)

data correction, structure solution and refinement

corrections	Lorentz and polarisation correction.
Structure solution	Program: SIR-97 (Direct methods)
refinement	Program: SHELXL-97 (full matrix). 219 refined parameters, weighting scheme: $w=1/[\sigma^2(F_o^2) + (0.0502*P)^2+0.85*P]$ with $(Max(F_o^2,0)+2*F_c^2)/3$. H-atoms at calculated positions and refined with isotropic displacement parameters, non H- atoms refined anisotropically.
R-values	wR2 = 0.1017 (R1=0.0399 for observed reflections, 0.0573 for all reflections)
goodness of fit	S = 1.021
maximum deviation of parameters	0.001 * e.s.d
maximum peak height in diff. Fourier synthesis	0.30,-0.66 e$Å^{-3}$
remark	cyclohexene is disorderd

final coordinates and equivalent displacement parameters (Å^2)
$U_{äq}= (1/3)*\sum\sum_{ij}a_i^* a_j^* \mathbf{a}_i\mathbf{a}_j$

Atom	X	Y	Z	U_{eq}
BR1	0.25905(2)	0.57754(2)	0.62802(2)	0.04007(9)
C1	0.1564(2)	0.4157(2)	0.4684(2)	0.0282(7)
C2	0.0827(2)	0.3366(2)	0.4357(2)	0.0293(7)
C3	0.0145(2)	0.3094(2)	0.5031(2)	0.0303(7)
C4	0.0206(2)	0.3622(2)	0.6081(2)	0.0289(7)
C5	0.0932(2)	0.4434(2)	0.6430(2)	0.0280(7)
C6	0.1596(2)	0.4685(2)	0.5737(2)	0.0284(7)
O7	-0.0418(2)	0.3427(1)	0.6821(2)	0.0378(6)
C8	-0.1126(2)	0.2553(2)	0.6543(2)	0.0388(8)
O9	0.0970(1)	0.4991(1)	0.7446(1)	0.0332(5)
C10	0.1573(3)	0.4491(3)	0.8476(2)	0.058(1)
C11	0.2345(2)	0.4427(2)	0.3986(2)	0.0333(8)
N12	0.2151(2)	0.3845(2)	0.2869(2)	0.0319(6)
C13	0.1325(2)	0.4339(2)	0.1979(2)	0.0364(8)
C14	0.1638(2)	0.5356(2)	0.1521(2)	0.0422(9)
N15	0.1912(3)	0.6117(2)	0.1164(3)	0.063(1)
C16	0.3117(2)	0.3692(2)	0.2502(2)	0.0351(8)
C17	0.2974(2)	0.2950(3)	0.1453(3)	0.0479(10)
C18	0.3999(2)	0.2737(3)	0.1162(3)	0.0471(10)
C19	0.4321(4)	0.3498(5)	0.0424(5)	0.100(2)
C20	0.5402(6)	0.3331(9)	0.0258(8)	0.177(5)
C21	0.5811(7)	0.237(1)	0.044(1)	0.240(9)
C22	0.5586(8)	0.1667(10)	0.1241(9)	0.199(6)
C23	0.4554(5)	0.1871(4)	0.1544(5)	0.110(2)

anisotropic displacement parameters

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
BR1	0.0465(2)	0.0385(1)	0.0366(2)	-0.0143(1)	0.0130(1)	-0.0094(1)
C1	0.034(1)	0.026(1)	0.025(1)	0.0029(9)	0.0082(9)	0.0015(8)
C2	0.036(1)	0.027(1)	0.026(1)	0.0006(9)	0.0091(9)	-0.0018(8)
C3	0.035(1)	0.025(1)	0.031(1)	-0.0021(9)	0.0078(10)	-0.0014(9)
C4	0.033(1)	0.027(1)	0.028(1)	0.0041(9)	0.0104(9)	0.0029(8)
C5	0.036(1)	0.0238(10)	0.024(1)	0.0039(9)	0.0072(9)	-0.0018(8)
C6	0.034(1)	0.0239(10)	0.027(1)	-0.0001(9)	0.0063(9)	0.0008(8)
O7	0.045(1)	0.0376(9)	0.0372(9)	-0.0100(8)	0.0216(8)	-0.0048(7)
C8	0.040(1)	0.037(1)	0.042(1)	-0.007(1)	0.016(1)	0.001(1)
O9	0.045(1)	0.0308(8)	0.0264(8)	0.0007(7)	0.0131(7)	-0.0047(6)
C10	0.091(3)	0.051(2)	0.026(1)	0.008(2)	0.004(1)	0.000(1)
C11	0.038(1)	0.038(1)	0.026(1)	-0.005(1)	0.0109(10)	-0.0033(9)
N12	0.032(1)	0.037(1)	0.0277(10)	0.0016(8)	0.0107(8)	-0.0033(8)
C13	0.037(1)	0.045(1)	0.030(1)	0.004(1)	0.012(1)	-0.004(1)
C14	0.052(2)	0.048(2)	0.028(1)	0.014(1)	0.013(1)	0.000(1)

N15	0.098(2)	0.050(1)	0.048(2)	0.015(2)	0.031(2)	0.010(1)
C16	0.033(1)	0.039(1)	0.035(1)	0.001(1)	0.011(1)	-0.006(1)
C17	0.043(2)	0.054(2)	0.050(2)	-0.004(1)	0.020(1)	-0.021(1)
C18	0.042(1)	0.055(2)	0.044(2)	0.011(1)	0.010(1)	-0.019(1)
C19	0.074(3)	0.141(5)	0.103(4)	0.011(3)	0.058(3)	0.007(3)
C20	0.100(5)	0.28(1)	0.184(8)	-0.018(6)	0.100(6)	-0.010(8)
Atom	U_{11} U_{23}	U_{22}	U_{33}	U_{12}	U_{13}	
C21	0.080(5)	0.32(2)	0.34(2)	0.037(8)	0.096(9)	-0.14(1)
C22	0.153(9)	0.25(1)	0.180(9)	0.161(9)	0.019(6)	-0.023(8)
C23	0.109(4)	0.090(3)	0.127(4)	0.057(3)	0.019(3)	-0.010(3)

final coordinates and isotropic displacement parameters ($Å^2$) for H- atoms

Atom	X	Y	Z	U_{iso}
H2	0.07842	0.29940	0.36448	0.0352
H3	-0.03592	0.25508	0.47753	0.0364
H8A	-0.16140	0.26749	0.57779	0.058
H8B	-0.15141	0.24885	0.71452	0.058
H8C	-0.07368	0.18953	0.65155	0.058
H10A	0.12103	0.38545	0.86434	0.087
H10B	0.16749	0.49855	0.91379	0.087
H10C	0.22516	0.42880	0.83566	0.087
H11A	0.23159	0.52002	0.38239	0.0400
H11B	0.30536	0.42571	0.44632	0.0400
H13A	0.07258	0.44762	0.23154	0.0437
H13B	0.10930	0.38366	0.13183	0.0437
H16A	0.36563	0.33961	0.31654	0.0421
H16B	0.33665	0.43912	0.22972	0.0421
H17A	0.26709	0.22696	0.16307	0.057
H17B	0.24820	0.32741	0.07663	0.057
H19A	0.42900	0.42154	0.07607	0.120
H19B	0.38183	0.34844	-0.03552	0.120
H20A	0.53889	0.35367	-0.05565	0.213
H20B	0.58773	0.38291	0.07856	0.213
H21A	0.65759	0.24605	0.06641	0.29
H21B	0.56353	0.19983	-0.03239	0.29
H22A	0.61513	0.17003	0.19713	0.238
H22B	0.55761	0.09372	0.09234	0.238
H23	0.43037	0.13722	0.20125	0.133