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Synthesis of chiral 2-azabicycloalkane derivatives and their application in asymmetric synthesis

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Ph.D. Thesis

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"*Think, think, think*."

Winnie the Pooh
in Disney's "*The book of Pooh*",
based on *"Winnie-the-Pooh"* by A. A. Milne

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- Wojaczyńska, E.; **Steppeler, F.**, Pochodne (1S,4S,5R)-2-((S)-1-fenyloetylo)-4-(1H-1,2,3-triazol-1-ylo)-2-azabicyklo[3.2.1]oktanu lub 1S,4R,5R)-2-((S)-1-fenyloetylo)-4-(1H-1,2,3-triazol-1-ylo)-2-azabicyklo[3.2.1]oktanu oraz sposób ich wytwarzania, PL241225B1, 2022.
- **Steppeler, F.**; Wojaczyńska, E., Triazole o symetrii C2 i C3 - pochodne (1S,4R,5R)-2-((S)-1-fenyloetylo)-2-azabicyklo[3.2.1]okt-anu lub (1S,4S,5R)-2-((S)-1-fenyloetylo)-2-azabicyklo[3.2.1]oktanu oraz sposób ich wytwarzania, PL241235B1, 2022.
- **Steppeler, F.**; Wojaczyńska, E., Epimeryczne bicykliczne dihalogenoalkany i epimeryczne alkiny oparte na szkielecie 2-azabicykloalkanowym oraz sposób wytwarzania epimerycznych alkinów opartych na szkielecie 2-azabicykloalkanowym, application nr P.434219; 05.06.2020.

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- **Steppeler, F.**, Wojaczyńska, E., Synthesis of New chiral Triazoles based on 2-azabicycloalkanes, VI Konferncja Związki biologicznie czynne: aktywność, struktura, synteza, 2019, Białystok, Poster.
- **Steppeler, F.**, Wojaczyńska, E., The development of a triazole-bearing modular system based on 2-azabicycloalkanes, 5th Symposium on Asymmetric Synthesis, 2019, Warsaw, Poster.

- **Steppeler, F.**, Wojaczyńska, E., Synthesis of novel 2-Azabicycloalkane thioureas, XXII International Symposium “Advances in the Chemistry of Heteroorganic Compounds", 2019, Łódż, Poster.
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Abstract

The thesis is devoted to the stereoselective synthesis of 2-azanorborane derivatives. The bicyclic system was obtained in the asymmetric *aza*-Diels-Alder cycloaddition. The DA-products were in turn modified giving a set of 2-azabicyclo[2.2.1]heptanes and 2-azabicyclo[3.2.1]octanes, and a series of triazole and thiourea derivatives were prepared. During the preparation of the compounds diverse aspects were considered, including substitution, various linkers and functional groups towards multifunctional complex compounds and multivalency in the approach towards calix[4]arene based thiourea organocatalysts. Application of chosen triazoles yielded one characterized palladium(II) complex alongside valuable insight in the formation of possible square-planar complexes with triazole functionalized 2-azabicycloalkanes. The thiourea derivatives were designed analogously to previously successful bifunctional organocatalysts with chiral moieties based on proline or *Cinchona* alkaloids. The substitution of the chiral backbone by the intrinsically chiral 2-azabicycloalkane yielded numerous novel thiourea organocatalysts. The obtained catalysts were used in model Michael-addition reactions. The addition of dimethyl malonate to β-nitrostyrene was catalyzed with up to 67% *ee*, whilst the addition of cyclohexanone to the latter nitro-vinyl compound yielded enantiomeric excesses of up to 96%. All triazoles and a selection of the derived thioureas were tested for their biological activity in broad scope of biological tests including satisfying initial results. The triazoles were tested as antiproliferative agents against various malicious cancer cell lines, accompanied by a structure-activity study. Chosen triazoles and thioureas exhibited also a promising behavior as antiviral and antifungal agents.

Streszczenie

Praca doktorska poświęcona jest stereoselektywnej syntezie pochodnych 2-azanorboranu. Podstawowy układ bicykliczny otrzymany został na drodze asymetrycznej cykloaddycji aza-Dielsa-Aldera. Produkty DA były następnie modyfikowane, dając zbiór 2-azabicyklo[2.2.1]heptanów i -2-azabicyklo[3.2.1]oktanów, w tym pochodnych triazolowych i tiomocznikowych. Podczas planowania syntez skupiano się na apektach takich, jak miesce podstawienia, rodzaj łącznika oraz różnorodność grup funkcyjnych, mając na uwadze możliwość tworzenia związków kompleksowych oraz wielofunkcyjnych organokatalizatorów tiomocznikowych opartych na kaliks[4]arenie. W wyniku zastosowania wybranych triazoli otrzymano jeden scharakteryzowany kompleks palladu(II), uzyskano również cenny wgląd w możliwość tworzenia płaskokwadratowych kompleksów z 2-azabicykloalkanami funkcjonalizowanymi triazolami. Pochodne tiomocznikowe zostały zaprojektowane analogicznie do stosowanych wcześniej z powodzeniem bifunkcyjnych organokatalizatorów opartych na prolinie lub alkaloidach drzewa chinowego. W wyniku zastąpienia tych układów przez wewnętrznie chiralny 2-azabicykloalkan otrzymano wiele nowych organokatalizatorów tiomocznikowych. Zostały one wykorzystane w modelowych reakcjach addycji Michaela. Addycja malonianu dimetylu do β-nitrostyrenu zachodziła z enancjoselektywnością do 67% ee, natomiast addycja cykloheksanonu do tego samego alkenu dawała nadmiar enancjomeryczny do 96%. Wszystkie triazole oraz wybrane pochodne tiomocznikowe zostały przebadane pod kątem ich aktywności biologicznej w szerokim spektrum testów biologicznych, a wstępne wyniki były interesujące. Triazole badano jako środki antyproliferacyjne wobec różnych złośliwych linii komórek nowotworowych, z określeniem zależności między strukturą i aktywnością. Wybrane triazole i tiomoczniki wykazały również obiecującą aktywność jako środki przeciwwirusowe i grzybobójcze.

List of Abbreviations

Ac	acetyl
Ar	aryl
API	active pharmaceutical ingredient
aq.	aqueous
Aza-DA	aza-Diels Alder reaction
BA	Brönsted acid
9-BBN	9-borabicyclo[3.3.1]nonane
BHT	butylhydroxytoluene
Boc	tert-butoxycarbonyl
BSA	bis(trimethylsilyl)acetamide
Bu	butyl
Bz	benzoyl
Bn	benzyl
Cbz	carboxybenzyl
CD	circular dichroism
cod	cycloocta-1,5-diene
CpH	cyclopentadiene
CuAAc	Copper-Catalyzed Azide–Alkyne cycloaddition
Cy	cyclohexyl
DA	Diels-Alder reaction
DACH	1,2-Diaminocyclohexane
dba	dibenzylideneacetone
DBAD	di-*tert*-butyl azadicarboxylate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	N,N'-dicyclohexylcarbodiimide
DCM	dichloromethane
DCU	1,3-Dicyclohexyl urea
DCE	dichloroethane
de	diasteromeric excess
DEA	diethanolamine
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIPEA	diisopropylethylamine
DFT	discrete function-theory calculation
DMAP	4-dimethylaminopyridine
DMF	N, N-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
DPPA	diphenylphosphoryl azide
dr	diasteromeric ratio

E^+	electrophile
E_A	activation energy
ECD	electronic circular dichroism
EDG	electron donating group
ee	enantiomeric excess
er	enantiomeric ratio
Et	ethyl
EWG	electron withdrawing group
HFIP	1,1,1,3,3,3-hexafluoroisopropanol
HMDS	hexamethyldisilylazide, $(Si(CH_3)_3)_2N$-
HRMS	high resolution mass spectrometry
Cat.	catalyst
L	ligand
LA	Lewis acid
LG	leaving group
M	metal
MAGL	monoacylglycerol lipase
Me	methyl
MeLi	methyl lithium
MLL	mixed-lineage leukemia
MS	mass spectrometry
Ms	mesyl, $-SO_2Me$
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
Nu	nucleophile
NS5A	nonstructural protein 5A
OPNB	*p*-nitrobenzoyloxy group, $4\text{-}NO_2C_6H_4\text{-}COO$-
OTf	triflate group, CF_3SO_3-
PG	protective group
Ph	phenyl
Ph*H*	phenyl-hydrogen
Ph*C*	phenyl-carbon
PIFA	phenyliodine bis(trifluoroacetate), (bis(trifluoroacetoxy)iodo)benzene
PMPI	*p*-maleimidophenyl isocyanate
Pr	propyl
Py	pyridine
quart.	quaternary
R	any type of group
rac.	racemate
rt	room temperature
SI	selectivity index
TBS	*tert*-butyldimethylsilyl, $((CH_3)_3C)(CH_3)_2Si$-

TBDPS	*tert*-butyldiphenylsilyl, $((CH_3)_3C)(Ph)_2Si$-
TBHP	*tert*-butyl hydroperoxide
TES	triethylsilane, Et_3Si-
Tf	trifluoromethyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl group, $(Me_3C)Me_2Si$-
TS	transition state
Ts	tosyl
wrt	with respect to
wt%	weight percent
X, Y, Z	various groups

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1 Introduction and Goal of the Work

"*Science, my lad, is made up of mistakes,*
but they are mistakes which it is useful to make,
because they lead little by little to the truth."

Jules Verne,
A Journey to the Center of the Earth

In organic chemistry selectivity, particularly stereoselectivity, is one of the biggest challenges posed to scientists. The synthesis of selected stereoisomeric compounds and their application is deeply intertwined with nature – stereoselectivity and chirality influence everything down to life itself. It is not surprising, that a series of Nobel prizes were awarded in recognition of the field:[1,2] 1969 Barton and Hassel were awarded "*for their contributions to the development of the concept of conformation and its application in chemistry"*, 1975 Cornforth "*for his work on the stereochemistry of enzyme-catalyzed reactions*" and Prelog *"for his research into the stereochemistry of organic molecules and reactions"*, 1987 Cram, Lehn and Pedersen *"for their development and use of molecules with structure-specific interactions of high selectivity"*, 2001 Knowles and Noyori *"for their work on chirally catalysed hydrogenation reactions"* and Sharpless *"for his work on chirally catalysed oxidation reactions"* together with the recent Nobel prize in 2021 of List and MacMillan *"for the development of asymmetric organocatalysis"*. Reading the explanations for the awarded prizes gives parallelly a short mental stroll through the great development modern stereochemistry has taken. With the advances in chemistry the demand for chiral pure and active compounds has risen tremendously. The search for chiral compounds is unbroken due to the interest of industry, *e.g.* pharmaceutical or fine chemicals; these chemicals are applied as active pharmaceutical ingredients, ligands or catalysts in asymmetric reactions.

For some time, our research group has worked on the stereoselective synthesis of azabicycloalkane derivatives. Besides 2-azabicyclo[2.2.1]heptanes (2-azanorbornanes), explored in biological and catalytic applications, more recent research concentrates on their ring expanded homologues, 2-azabicyclo[3.2.1]octanes. These intrinsically chiral systems can be treated as bicyclic analogues of nitrogen-containing cyclic compounds, such as pyrrolidine, piperidine or azepane, and with appropriate functionalization they can serve as analogues of amino acids or alkaloids. The synthesis of 2-azanorbornene by *aza*-DA reaction is well established, and two isolated diastereomers may be subjected to further modifications.

The main aim of the thesis was the stereoselective synthesis of novel 2-azabicycloalkanes, and the development of new routes towards complex multifunctional systems, their characterization, and the application of these bicyclic amino acid/alkaloid analogues as possible ligands, organocatalysts and as biologically active compounds.

The field of 2-azabicyclic ligands is especially well researched towards hydrogenation reaction, particularly coordinated to iridium, ruthenium and copper. Only a few publications attempted the application of 2-azabicycloalkane derivatives as organocatalysts. Both fields, ligands and organocatalysts, are interwoven with the field of biological activity.

Two structural motifs, triazoles and thioureas were chosen as the target functionalities explored within this dissertation. Both structures exhibiting great bonding qualities are known to be potent ligands, especially thioureas well established for their organocatalytic properties and the biorthogonal 1,2,3-triazole group is often successfully applied in ligation and as a fragment of biologically active compounds. Manifold amino acids and alkaloids were bound with them forming compounds with great potential and many desired qualities, which lead to the initial thought of combining those two structural motifs with 2-azabicycloalkanes as analogues of natural structural motifs such as *e.g.* proline, tropane or quinuclidine in *Cinchona* alkaloids. Upon establishment of suitable routes towards various bicyclic substrates a variety of triazoles and thioureas were synthesized and fully characterized. Those multifunctional molecules are in turn valuable materials for many applications: triazoles were tested in ligation and for their biological activities and thioureas for their organocatalytic properties and biological activity as well.

2 Theoretical Part

2.1 Stereoselective synthesis

An inherent aspect of chemistry, and in particular organic chemistry, is the selectivity of reactions. Often students learn in early stages, that certain reactions give certain products, but this is only part of the truth. A simple change in the conditions might give rise to other products or complex mixtures may be received ultimately. Often, a reaction can produce not only one, but two or even more products which may differ in various ways. In organic chemistry, this means that reactions can be controlled, and products may be received depending on reaction type, reaction conditions or catalysts, to name only a few. The importance of stereochemistry can additionally be pointed out: the structure on a microscopic level influences properties on the macroscopic level. The inherent properties of chemical compounds are therefore dependent not only on constitution, but on configuration and conformation as well. Generally, there are four main categories of selectivity: chemo-, regio-, diastereo- and enantioselectivity (Figure 1). Their general influence on reactions will be a constant companion within this whole doctoral thesis and will appear, mentioned or not mentioned all over it. The influence will be ubiquitous in planning, execution of syntheses, as well as for the purpose of all synthesized compounds.

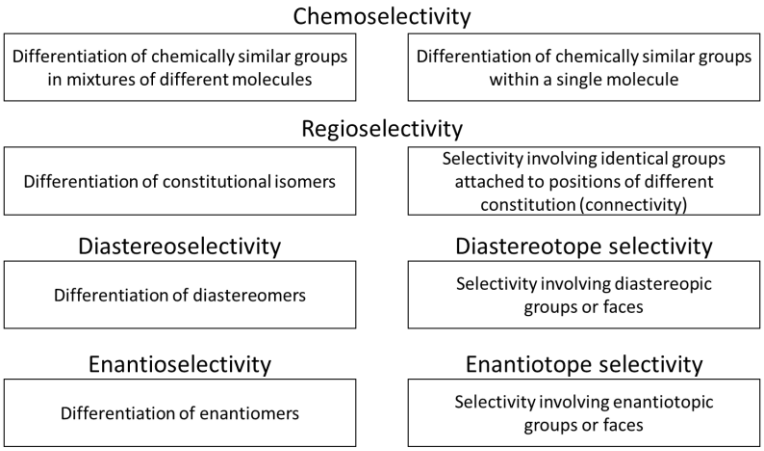


Figure 1 Types of selectivity in reaction (reproduced from Poppe et al.[2] page 129).

Chemoselectivity is by definition of the "Golden Book" of IUPAC[3] the preferential reaction of a chemical reagent with certain functional groups. High chemoselectivity is observed if a reaction only occurs with limited numbers of different groups. This happens due to careful choice of the right chemical compounds and reactions on the way to complex structures, keeping in mind the chemoselectivity of reactants and the groups that might need protection in certain steps. A step deeper into the careful choice of reactants is regioselectivity. It is defined as the preferential direction a reaction may go in cases of bond making or breaking, in particular at certain positions in a molecule over other positions.[3] If one chooses a reactant carefully there might still be two groups with different locations in the molecule and when only one of them reacts – a complete regioselectivity is possible and favorable.
Chemoselectivity and regioselectivity are the backbone of classical organic chemistry; powerful tools to generate a plethora of compounds but limited to produce generally only racemates (a set of enantiomers), or mixtures of diastereomers (Figure 2).

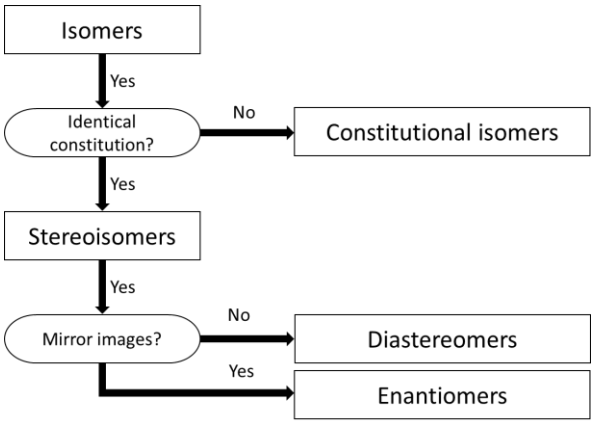


Figure 2 Differentiation between isomers (reproduced from Poppe et al.[2] page 26).

With a deeper knowledge and understanding of biochemical processes a greater desire for enantiomerically pure compounds rose, since certain enantiomers have preferable properties, others might be harmful – Thalidomide can serve as an example.[4] Organic chemists had to come up with powerful methodologies to introduce such selectivity during the synthesis.

The synthesis of the racemate and separation of the enantiomers is one possibility, however for more efficient synthesis other methods were developed. Approaches include the use of compounds from a "*chiral pool*" offering already chiral building blocks applicable for further reaction. Nature itself offers a variety of chiral compounds:[5] amino acids[6], sugars[7], and plenty of metabolites such as alkaloids[8], to name a few. Chiral auxiliaries might be used in the synthesis as well[9] – it is the application of chiral compounds in at least equimolar amounts to help transferring a desired stereogenic element or block the possibility of receiving the undesired. Chiral, natural and synthetically received compounds may be used to induce chirality during the reaction, transferring desired properties. Other very potent methods include catalysis by chiral metal complexes. Only very small amount of a catalyst is typically necessary for a highly selective reaction. However, downsides for that application are possible metal contamination of the product, expensive materials and usually stringent, often air-free, conditions. A variety of metals are highly toxic and even the smallest amounts of them might hassle with any possible positive outcome of medicinal treatments. For such applications, this methodology is limited to a handful of easily removable and mostly non-toxic metals. Instead, organocatalysis has been significantly developed in the past decades and receives more and more attention.

2.2 Nitrogen-containing heterocycles

The abundance of elemental nitrogen on earth often leads to the misconception of a general abundance of bio-available nitrogen. In many ecosystems nitrogen is in fact a limiting factor for primary production, since nitrogen gas cannot be transformed easily into biologically available forms (until the industrial applied Haber-Bosch process). However, it plays a major role in many metabolic pathways. The sheer quantity of amino acids, proteins, nitrogen bases in the nucleic acids, as well as alkaloids in nature with various cyclic moieties is another proof for its importance. Nitrogen containing heterocycles, but especially non-aromatic heterocycles (important for this chapter) are typically a part of a complex biological system. Among them, aziridine, azetidine, pyrrolidine, piperidine, azepane and azocane, to name the smallest (Figure 3).

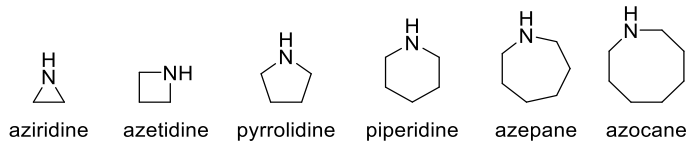


Figure 3 Smallest single nitrogen-containing non-aromatic heterocycles.

An often-cited article from 2014 puts the importance of nitrogen-containing heterocycles in a better perspective. Solely concentrating on the American market, it is analyzing the FDA approved pharmaceuticals considering nitrogen heterocycles (Figure 4).[10] The paper not only gives a deeper insight into the distribution and use of cyclic nitrogen compounds but also states, that a staggering number of 910, 84% of all unique FDA approved drugs, contain at least one nitrogen atom. 640 (59%) of all unique approved drugs contain at least one nitrogen heterocycle; both, aromatic and non-aromatic heterocycles can be found among the biologically highly active compounds.

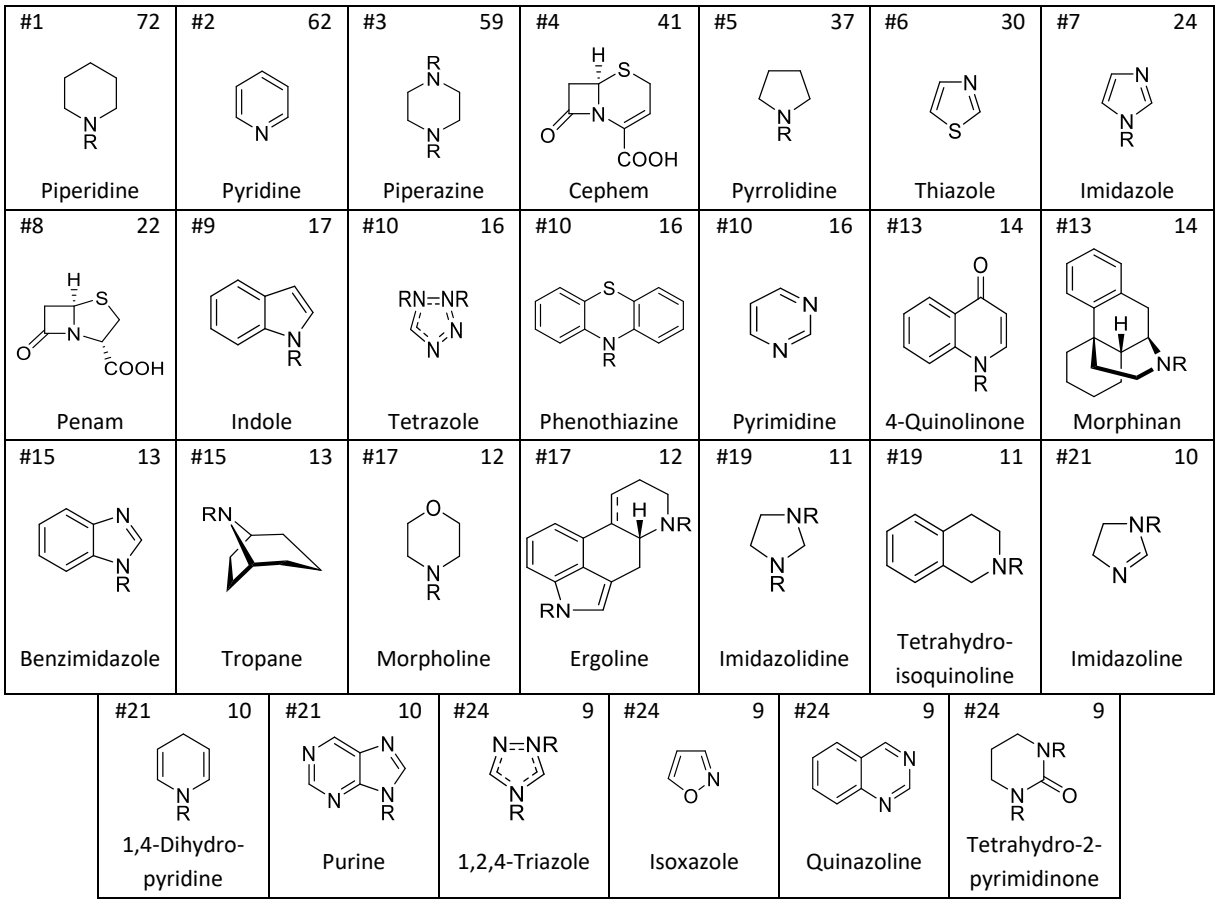


Figure 4 Top 27 most frequent nitrogen containing heterocycles in US FDA approved drugs, with the number of drugs 2014 (reproduced from Njardarson et al. 2014[10]).

Five- and six-membered cycles are especially prominent, but also four- and seven-membered cyclic nitrogen compounds can be found. For this dissertation bridged and polycyclic structures are of special interest (Figure 5). Whilst polycyclic structures may contain aromatic structures, they are typically absent in bridged aza-cycles where the bridge is at least containing one atom ("azabicyclo[X.Y.Z]", with $Z \geq 1$). This originates from the strain associated with bridge formation and the tetrahedral character this poses upon the compound, together with the definition of aromatic systems as planar to ensure efficient π-conjugation. Both, natural and synthetic sources are available and readily usable as building

blocks for the synthesis of biologically active compounds, but they are also used as reagents, chiral auxiliaries, ligands and organocatalysts.

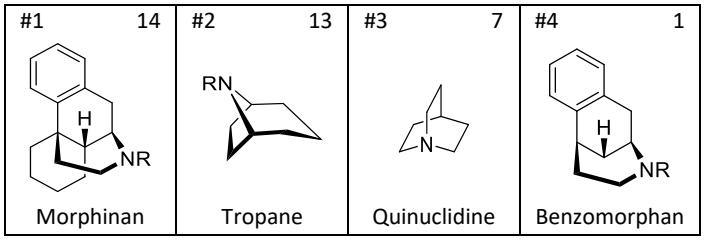


Figure 5 The four most common aza-polycyclic moieties of the form azabicyclo[X.Y.Z], with Z ≥ 1 in US FDA approved drugs with the number of drugs 2014 (reproduced from Njardarson et al. 2014[10]).

2.2.1 Natural polycyclic sources

The origin of nitrogen containing polycycles, bridged and fused ones, is various. Biologically, they are metabolic products – alkaloids – originating from amino-acids, from which they inherit chirality. Synthetically many starting materials may be used, however, amino-acids and alkaloids themselves are still prime material with already fixed stereocenters. They are therefore very interesting and an often-used resource of chiral nitrogen cycles, building blocks for the synthesis of chiral nitrogen cycles or inspiration for synthetic approaches of analogues.

Using nature's various materials, easily available units and mimicking them is one major field of chemistry. As such amino acids are one of the most important set of chiral compounds in nature – building blocks of proteins, alkaloids and part of many metabolic pathways. In nature there is an abundance of amino acids and the access to these cheap, renewable sources of chirality makes them a prime starting point for organic synthesis, their vast history is therefore not surprising. The sheer amount of applications as building blocks,[6,11–14] chiral auxiliaries[9,15,16] or in organocatalysis[17] seem to be non-ending. Amino acids contain various cyclic structures and structures prone to be converted into nitrogen containing cyclic systems (Figure 6).

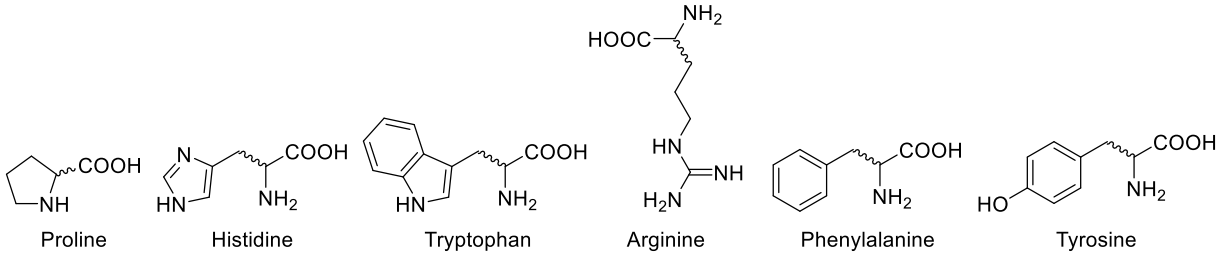
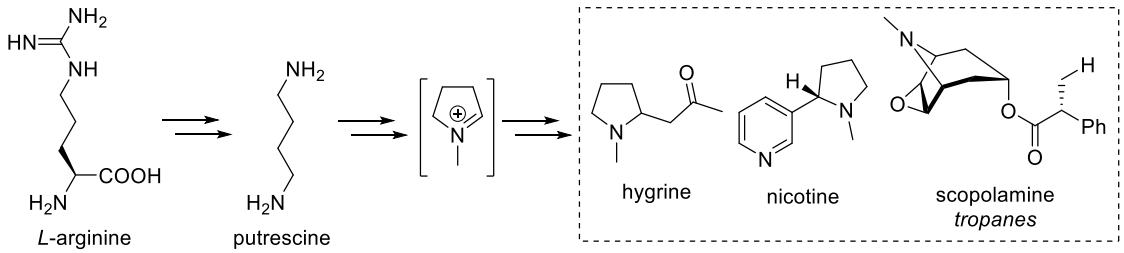


Figure 6 Examples of six canonical amino acids with nitrogen containing cycles or the ability of forming easily accessible polycyclic nitrogen-containing systems.

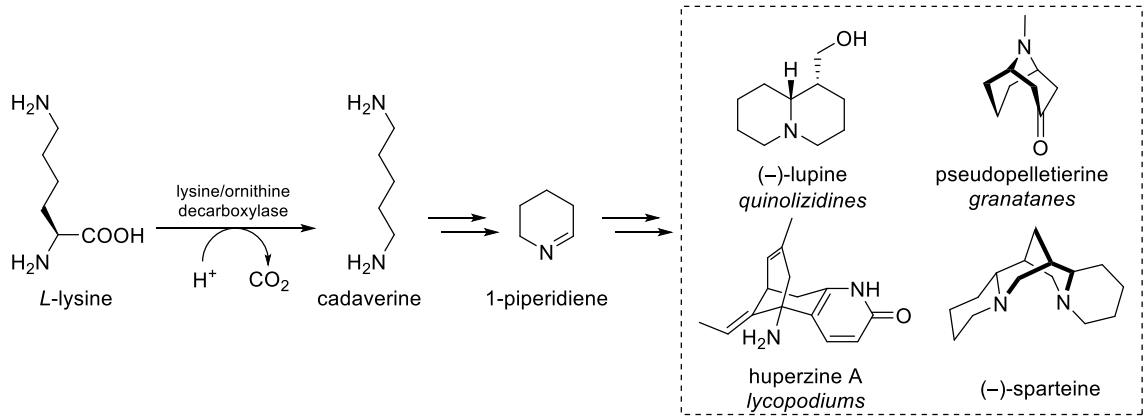
Many metabolic pathways are explored of which the synthesis of alkaloids is a major part. Various paper dealt already with the subject.[6,18–20] Enzymes are highly chemo- and regiospecific and powerful tools in biosynthesis. Starting from the set of mere amino acids a plethora of compounds can be received. The following paragraph is based on the excellent review of B. Lichman on scaffold forming steps in the alkaloid biosynthesis.[20]

As precursors for major alkaloid classes the simple polyamines putrescine and cadaverine are readily received via biosynthetical routes. For example, two routes starting from arginine yield putrescine: either by arginase removing urea, followed by decarboxylation by ornithine decarboxylase or by

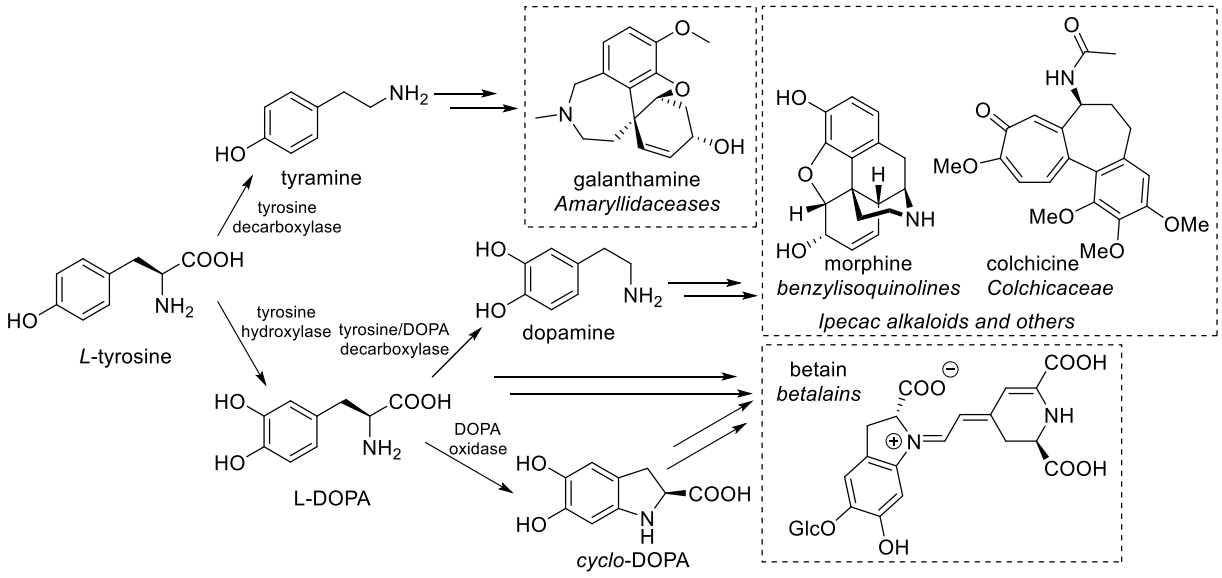
decarboxylation by arginine decarboxylase followed by agmatine iminohydrolase forming *N*-carbamoylputrescine and hydrolysis using *N*-carbamoylputrescine aminohydrolase. The formed putrescine then in turn may be further used in the synthesis of hygrine and nicotine type of alkaloids, as well as for tropane type of alkaloids, such as scopolamine (Scheme 1). Similarly, lysine is transformed by simple lysine or ornithine decarboxylase to cadaverine, which in turn is converted to 1-piperidiene, a precursor of quinolizindes, granatanes, lycopodium alkaloids as well as sparteine (Scheme 2).



Scheme 1 Putrescine, biosynthetically received from L-arginine and examples of alkaloids derived from it.[20]



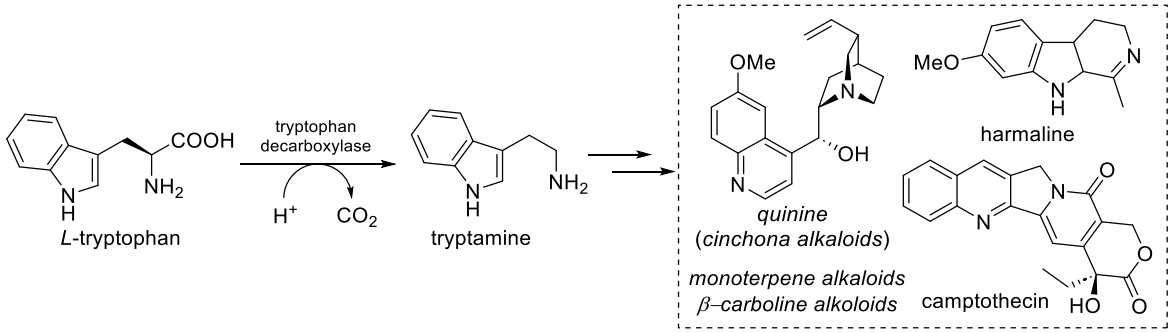
Scheme 2 Cadaverine, biosynthetically received from lysine, and examples of alkaloids derived from it.[20]



Scheme 3 Biosynthetic route to various alkaloids from L-tyrosine.[20]

Both, L-tyrosine and L-tryptophan are readily transformed by tyrosine decarboxylase and tryptophan decarboxylase to yield the corresponding amines - tyramine and tryptamine, respectively. Parallelly, L-tyrosine can be transformed into L-DOPA, which in turn can be transformed into dopamine and *cyclo*-

DOPA. Ultimately, L-tyrosine is a precursor for various alkaloid families including Amayllidaceases, Benzylisoqunolines, Colchicaceaes, Ipecac alkaloids and betains (Scheme 3). L-tryptophan on the other hand is a precursor for Monoterpene, β-Carboline and Cinchona alkaloids (Scheme 4).



Scheme 4 Biosynthesis of tryptamine from tryptophan, and derived alkaloids.[20]

As biosynthetically received from just a relatively small number of canonical amino acids the alkaloid family consists of circa 20 000 very heterogeneous members. Various polycyclic nitrogen structures can be found among them and application of them can be found all over life sciences (Figure 7).

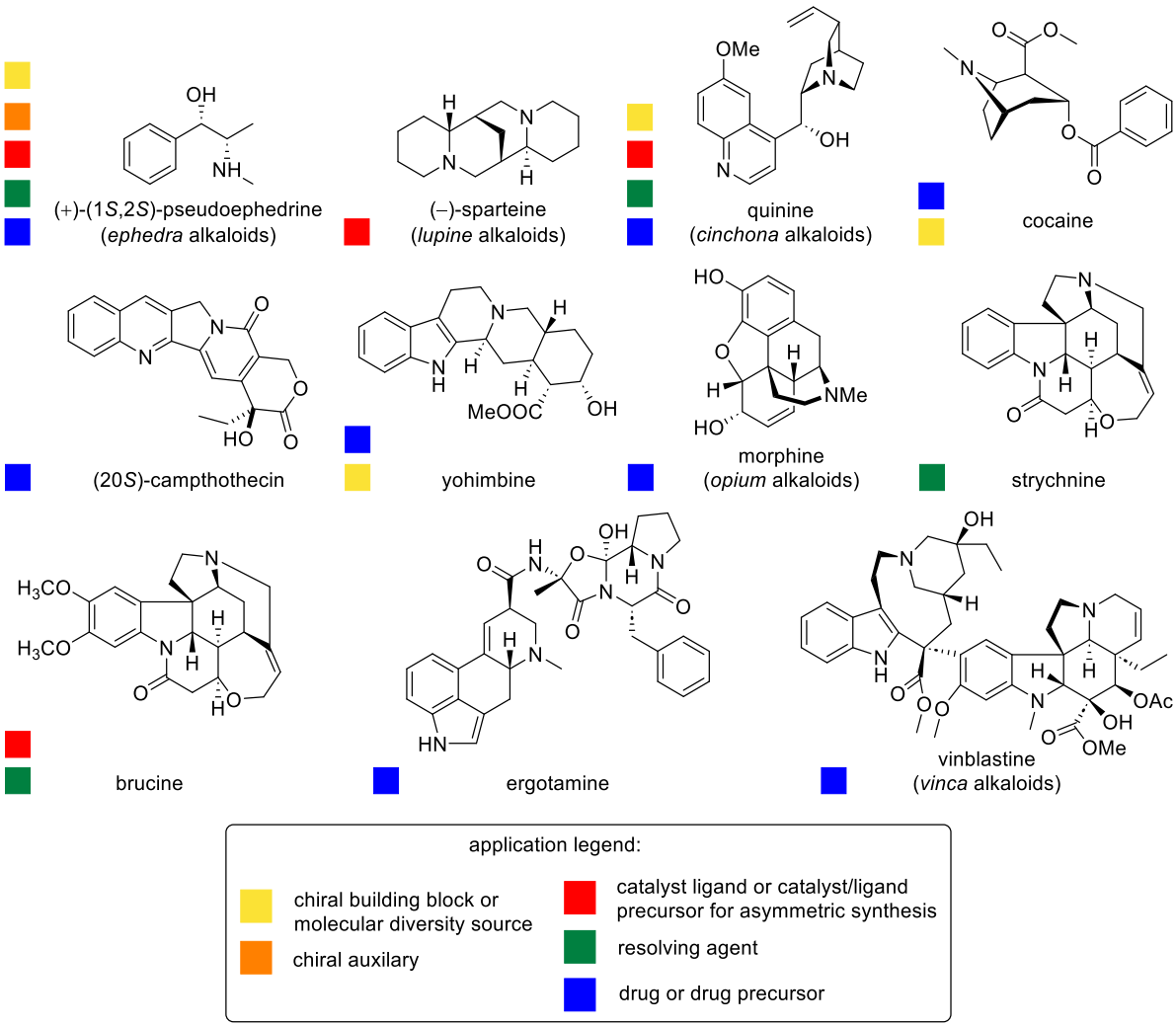
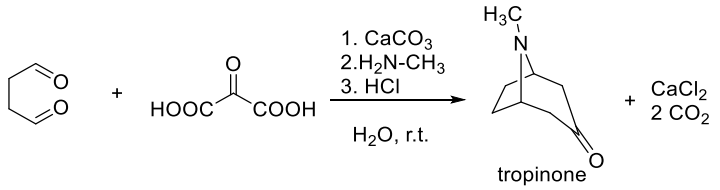


Figure 7 Various example alkaloids together with their application (adapted from Kacprzak, 2022).[8]

2.2.2 Synthetic methods for the preparation of polycyclic structures

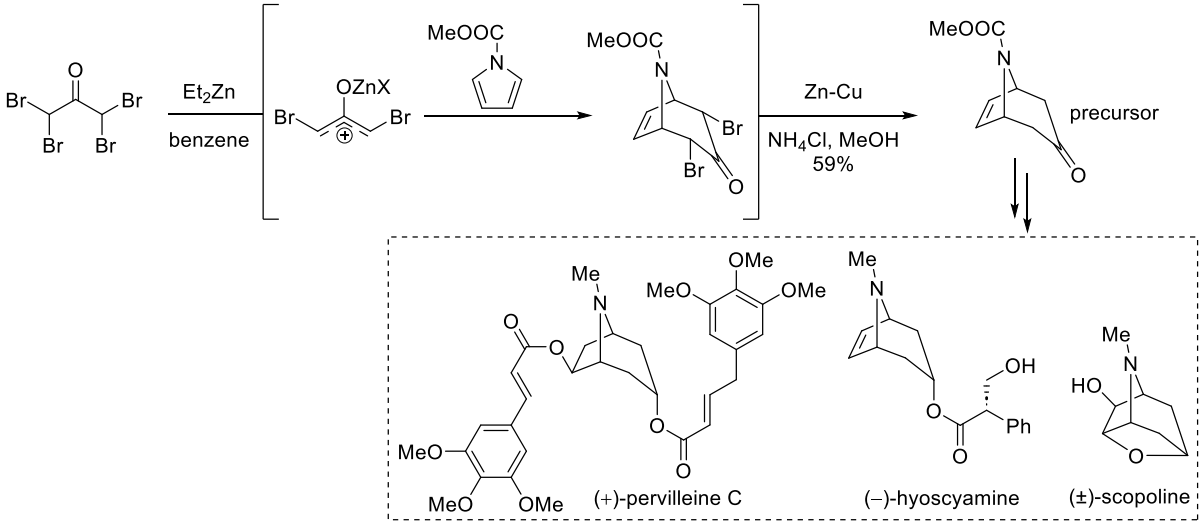
There is an endless interest in natural products and compounds. Their biological activities and other possible applications are widely investigated. It is estimated, that in developing countries plant-based drugs contribute to as much as 80% of all medicines, while developed countries still depend on one fourth of their drugs with natural origin. However, their accessibility is limited by availability of plants and by extensive isolation procedures.[21] Total synthesis is therefore a desired tool, not only to investigate natural products, but also for the determination of stereocenters, as well as for the synthesis of analogues. Of special interest for this work are the key-steps for the formation of nitrogen-containing bridged structures.

An early example of the preparation of a major building block moiety is the total synthesis of tropinone in a one-pot tandem reaction by Robinson in 1917 (Scheme 5).[22] After salt formation of acetone dicarboxylic acid methylamine reacts in a condensation with the dialdehyde, followed by a second condensation step – the **bridge construction step**. Decarboxylation of the intermediate by hydrochloric acid yields tropinone. The synthesis's simplicity and biomimetic approach makes it one of the classical total syntheses.[21] Over the years vast improvements of the reaction could be achieved and conditions were changed to implement different functional groups in the final product.[19,23]



Scheme 5 Robinson's one-pot tropinone synthesis from succindialdehyde, methylamine and acetone dicarboxylic acid including the formation of a bicyclic moiety.[22]

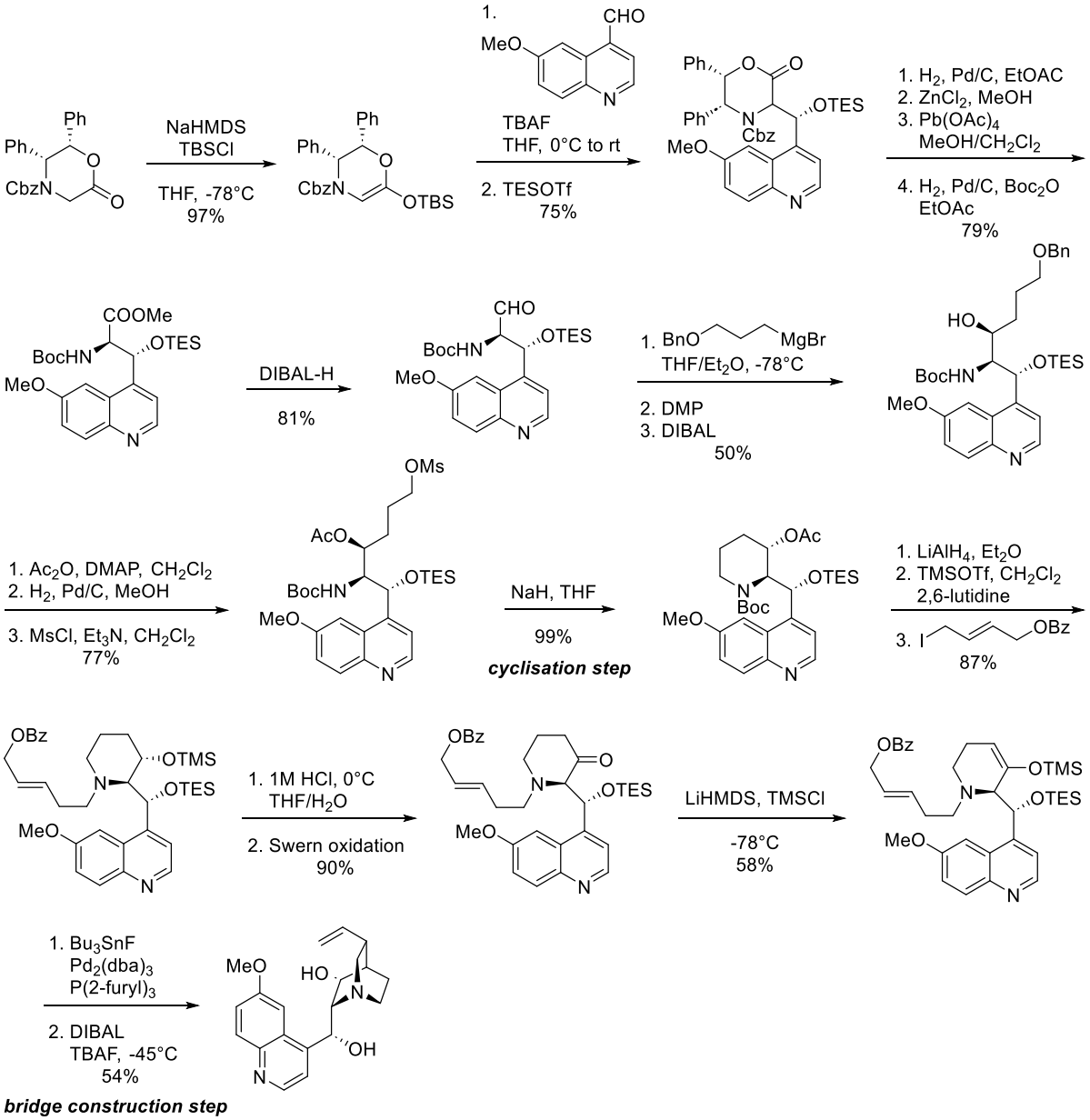
Another interesting approach towards tropane alkaloids is a [4+3]-cycloaddition including pyrroles.[24] A variety of natural products can be received from a single precursor, set in an one pot, two step synthesis (Scheme 6).[25–28] 1,1,3,3-tetrabromoacetone is activated by an organozinc compound, followed by the addition a suitable pyrrole derivative. After the [4+3] cycloaddition the nortropinone precursor can be easily received after debromination as *meso* intermediate. Various synthetic routes



Scheme 6 [4+3]-cycloaddition towards nortropinone precursor and natural products received from it. [25–28] (adapted from Chiu et al.[24])

from this precursor have been reported yielding (±)-scopoline,[27] (–)-hyoscyamine,[25] and (+)-pervilleine C.[28]

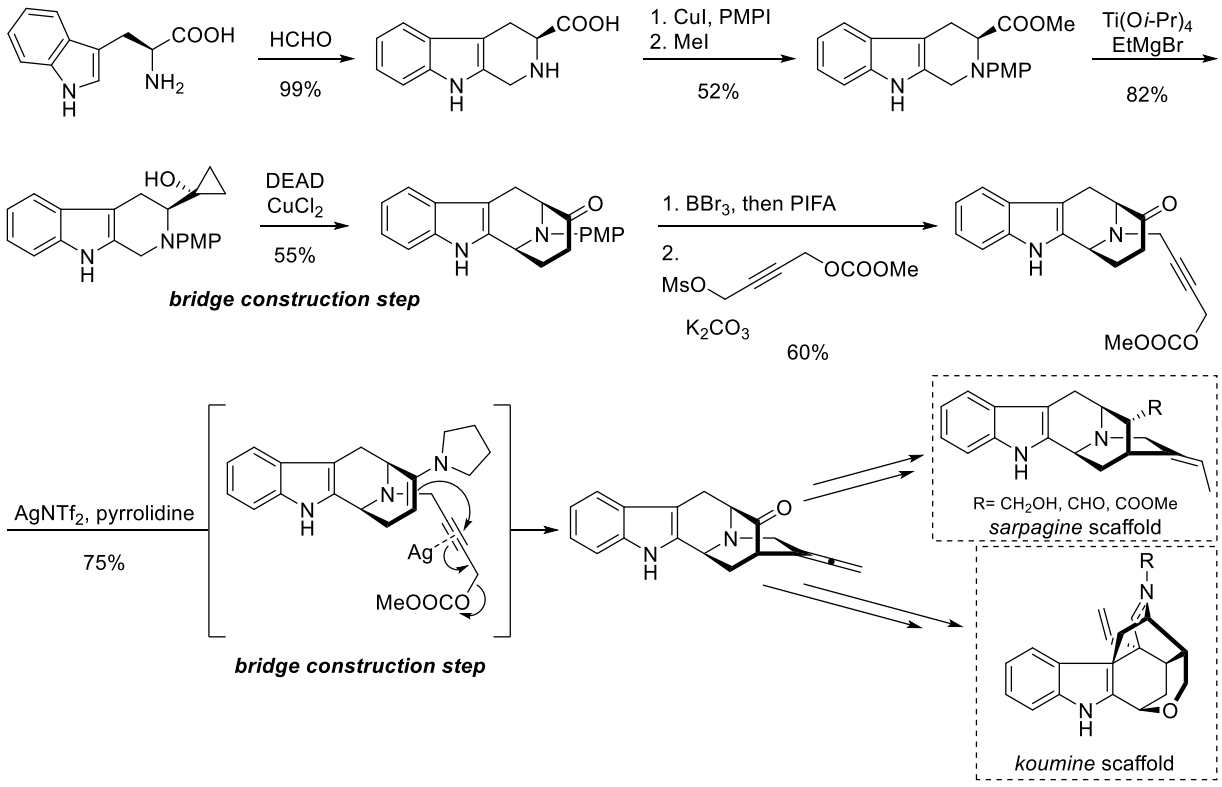
The quinuclidine moiety present in, among others, cinchona, sarpagine and koumine alkaloids is considered to be an important bridged structure. In the biosynthesis it is formed starting from L-tryptophane.[29] A simple literature research reveals many independent total syntheses of (+)- and (–)-quinine,[30–39] with the earliest by Woodward et al. in 1945 [30] and the first entirely stereoselective synthetic route published just in 2001 by Stork et al.[32,33] Still, further attempts on the total synthesis of quinine were conducted. Reading the formerly mentioned syntheses[30–39] reveals interesting insight in the development of organic chemistry and the continues application of new methodologies within the stereochemical syntheses. By the huge number of different approaches and the everlasting revision of synthetic routes up to now the importance of this class of alkaloids and the challenge of their preparation are demonstrated continuously. The chosen method for the synthesis of 7-



Scheme 7 Total synthesis of the quinine analogue 7-hydroxyquinine including the formation of a chiral bicyclic moiety from commercially available starting material. [39]

hydroxyquinine, is not the most recent methodology (Scheme 7),[39] yet it is chosen for a couple of reasons: the protocol is elegant, including amino acids as chiral auxiliaries, and the use of orthogonal protection groups to direct the selectivity. The synthesis starts from chiral, commercially available (+)-(2*S*,3*R*)-6-oxo-2,3-diphenylmorpholines – an amino acid protected with a chiral auxiliary. Especially in the ***cyclization steps*** the synthesis applies orthogonal protection groups on different alcohols: mesyl (Ms) and triethylsilane (TES) in the cyclization step, as well as benzoyl (Bz), trimethylsilyl (TMS) and TES in the ***bridge construction step***, followed by final deprotection of TES yielding the product. Through the proactive choice of reaction sequence and chiral auxiliary, the desired stereochemistry could be achieved. The final product was received with reasonable yield and with very high stereoselectivity.

Amino acids, canonical ones and non-canonical ones, are of great interest for the synthesis of complex structures and pharmaceuticals.[40] Another approach toward quinuclidine derivatives starts from L-tryptophane (Scheme 8),[41] similarly to the beforehand mentioned biosyntheses of *e.g.* Cinchona, monoterpene and β-carboline alkaloids (Scheme 4). After a first cyclization step with the help of formaldehyde the use and preservation of the amino acid stereocenter becomes essential for all further steps towards optically pure compounds. In the course of the ***first bridge construction step*** the given stereocenter dictates the highly stereocontrolled reaction path by cyclopropane ring opening. The ***second bridge construction step*** is in turn influenced by the conformation; with the use of pyrrolidine base an enamine structure is formed, which then reacts intramolecularly with a silver(I)-activated alkyne. The allene moiety in the quinuclidine intermediate was used in the total synthesis of five distinctive sarpagine alkaloids and three koumine alkaloids.



Scheme 8 Synthesis of important quinuclidine-containing intermediate of the total synthesis of *sarpagine* and *koumine* alkaloids.[41]

2.2.3 Synthesis of artificial nitrogen polycycles

2-Azanorbornane structures are intrinsically chiral (Figure 8),[42] in contrast to the naturally available bicyclic moieties in tropane alkaloids or quinuclidine. As all bridged bicyclic structures they are more rigid than their monocyclic pendants, *e.g.* pyrrolidine, piperidine, azepane (Figure 9). This makes them interesting building blocks for the substitution of monocyclic analogues.

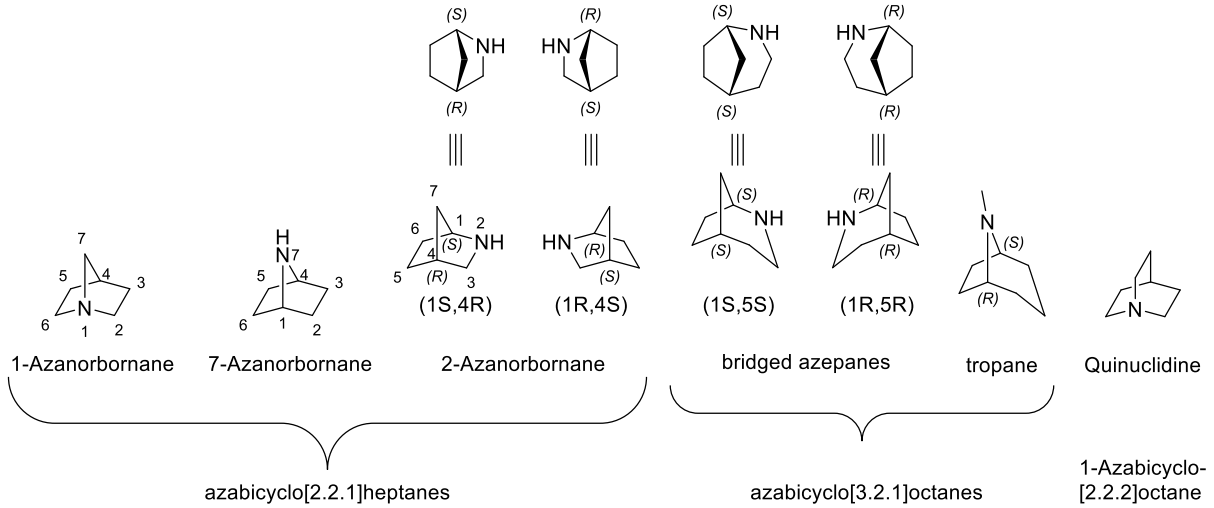


Figure 8 2-Azabicyclo[2.2.1]heptane and 2-azabicyclo[3.2.1]octane enantiomers and artificial and natural bicyclic structures.

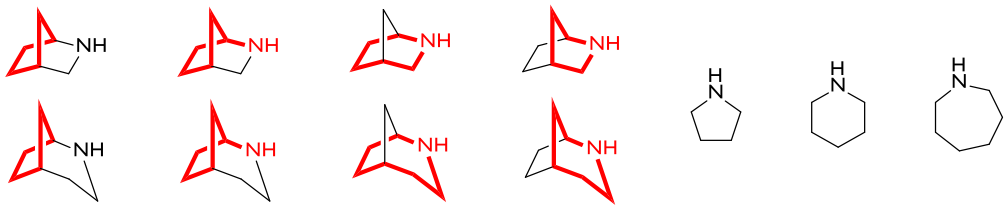
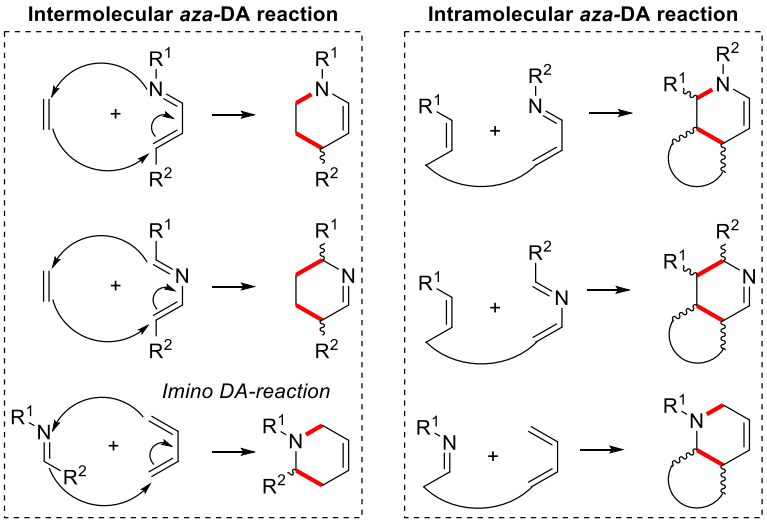


Figure 9 2-Azabicyclo[2.2.1]heptane and 2-azabicyclo [3.2.1]octane as analogues of pyrrolidine, piperidine and azepane.

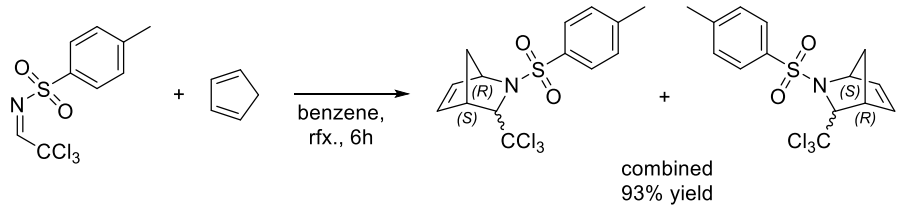
Among other reactions,[43] cycloadditions are powerful instruments in the synthesis of interesting bicyclic complex structures.[44–46] First described in 1928 by two German chemists - Otto Diels and Kurt Alder,[47] the name bearing reaction has become one of the most used, versatile and efficient cycloaddition reactions to set in a single reaction step conveniently up to four stereocenters in a regio-



Scheme 9 Overview of aza-DA reaction (adapted from Xu et al.[54]).

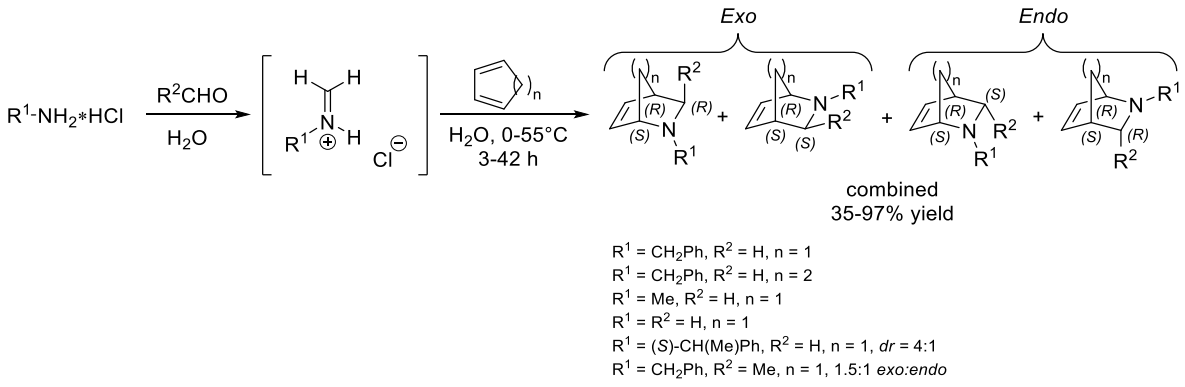
and stereoselective manner.[2,48–52] It's nitrogen counterpart, the *aza*-DA reaction,[53–55] is widely used and probably the easiest and most powerful method to synthesize 2-azanorbornane structures. Generally, consisting of conjugated diene and dienophile the *aza*-DA reaction may include the nitrogen both, in diene or in dienophile (Scheme 9).

Imines and Schiff bases have a long history in the Diels-Alder reaction and were used as early as 1943, briefly mentioned by Alder.[56] Various publications and efforts have been made since then applying various nitrogen-containing compounds, both as dienophiles and as dienes.[57,58] Only a couple of years after the first application of imines in a DA reaction a method for the synthesis of 2-azanorbornenes was published by Kresze and Albrecht.[59,60] The reaction of 4-methyl-*N*-(2,2,2-trichloroethylidene)-benzenesulfonamide with cyclopentadiene in refluxed benzene yielded 93% of racemic 2-aza-bicyclo[2.2.1]heptane (Scheme 10).



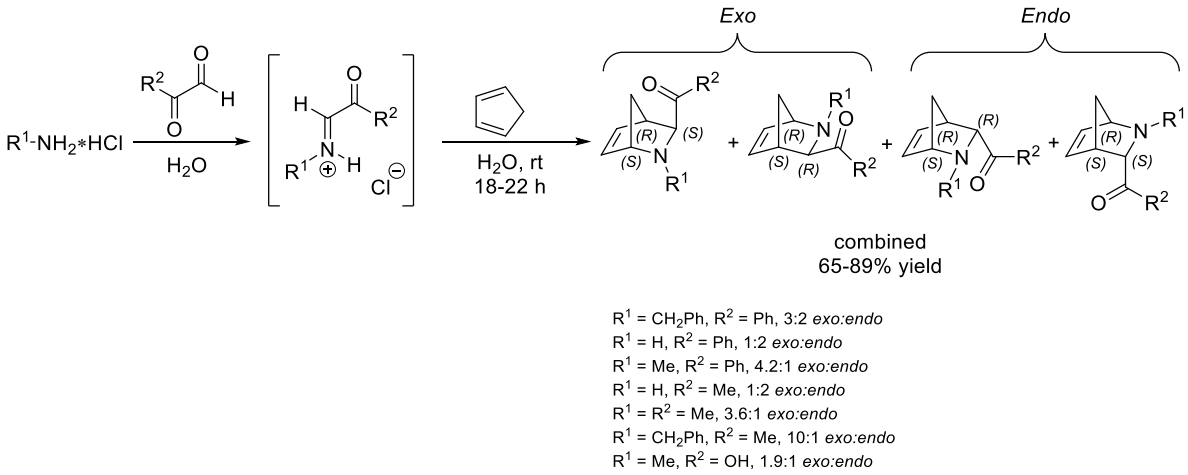
Scheme 10 First synthesis of 2-azanorbornanes.[59]

It took roughly another 20 years for further meaningful development in the field of the synthesis of 2-azanorbornanes, when Grieco *et al*. worked on the *aza*-DA reaction of cyclopentadiene and cyclohexa-1,3-diene.[61–63] First attempts in 1985[61] gave a set of six reactions conducted in water at various temperatures (Scheme 11); two are interesting from stereoselectivity point of view. The first four cycloadditions produce no *exo* and *endo* epimers (there are two hydrogen atoms at position 3), but two enantiomers - (1*S,*4*R*) and (1*R,*4*S*)-2-azanorbornene. The last reaction produced also the sets of *exo* and *endo* forms*,* yielding a total of four products in two sets of enantiomers. The most interesting cycloaddition employs the chiral auxiliary (*S*)-phenylethylamine in the imine formation. This is directly reflected in the stereochemistry of the formed 2-azanorbornene (4:1 ratio of (1*R,*4*S*):(1*S,*4*R*)).



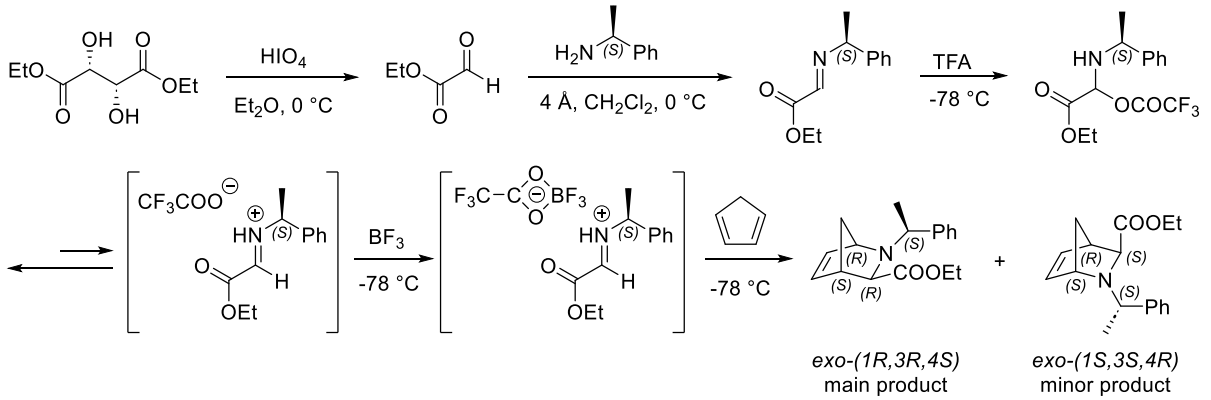
Scheme 11 First aza-DA reaction of iminium salts with dienes to generate aza-bicycloalkanes.[61]

The second paper by Grieco *et al*. published a year later was focused on the tuning of *exo*:*endo* ratio (Scheme 12).[62] It employed activated aldehydes, which in turn were converted into imines applying ammonium chloride or methylammonium chloride. The reactions were conducted in water with only slightly varying duration times. *Exo* and *endo* were formed as racemates – a downside for any biomimetic application and exchange of monocycles with the more rigid bicyclic structures.



Scheme 12 Aza-Diels Alder reaction of activated aldehyde-derived imines.

The topic of more stereoselective synthesis of 2-azabicyclo[2.2.1]heptene was taken on by Stella *et al*.[64] A vast analysis of the received products made it possible to synthesize certain diastereomers stereoselective, depending on the use of chiral auxiliary.[62,65–69] Using (*S*)-phenylethylamine (1*R*,4*S*)-product can be received as a major isomer (Scheme 13),[64–66,69] while (*R*)-phenylethylamine favors (1*S*,4*R*)-2-azanorbornene. Later, various attempts of the exploration of the mechanism were conducted; interesting excerpts of those studies include the importance of Lewis acid catalytic system and the resulting non-concerted tandem Mannich-Michael type of reaction, as well as studies on the applied solvent systems towards more environmentally friendly and even biphasic systems.[70–75]



Scheme 13 Synthesis and mechanism of the TFA/BF_3-catalyzed aza-DA reaction forming 2-azabicyclo[2.2.1]heptenes.[64,69]

The Diels-Alder reaction itself, applying also to *aza*-DA, produces two pairs of epimers. The *exo*:*endo* ratio is dependent on the reaction conditions: at room temperature the thermodynamic *endo* products are favored, whilst at lower temperature the kinetic *exo* products are prevailing. Depending on *si*-face attack (diene is above the dienophile) or *re*-face attack (diene is below the dienophile) two *exo* products and two *endo* products are possible (Figure 10). Achiral dienes and especially dienophiles will produce two sets of enantiomers. To omit this problem, the chiral auxiliary, either (*S*) or (*R*), was introduced. Two factors influence the reaction greatly: the low temperature increases the *exo* products and the stereochemistry of the chiral auxiliary favors *re*-face attacks over *si*-face attacks. The two *exo* products are diastereomers, but also pseudo enantiomers (differing only in the stereocenter of the chiral auxiliary). Since diastereomers differ by physical properties, they may be simply separated using achiral column chromatography on silica gel. This founding was first noticed by Grieco *et al*.[61], but

Stella *et al.*[64] first applied its full potential, being able to produce the full set of all 4 diastereomers using (*S*)- and (*R*)-phenylethylamine. The methodology is very helpful and straightforward yielding stereochemically pure compounds which then may be modified. The conditions applied in the *aza*-DA in Scheme 13 are trimmed for a maximum output of *exo*-(1*R*,3*R*,4*S*)-product as major diastereomer by the use of the Lewis acid catalytic system, as well as the temperature set to -78 °C favoring the kinetic product.

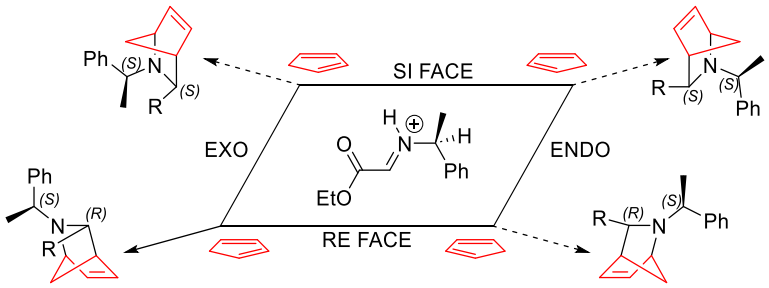
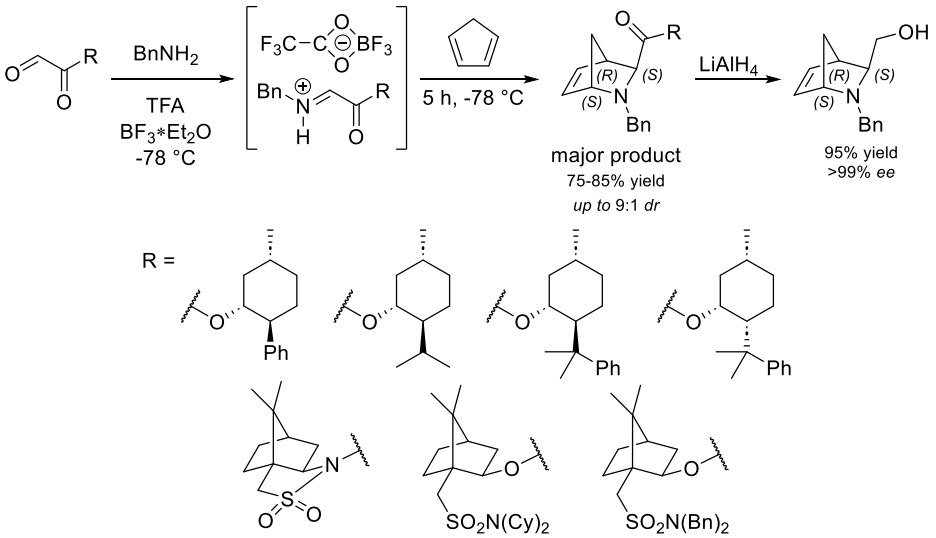


Figure 10 All possible diastereomers of the Aza-Diels-Alder reaction with indication of main and minor product pathways applying (*S*)-phenylethylamine; (*R*)-auxiliary yields the opposing set (reproduced from Stella et al.[64]).

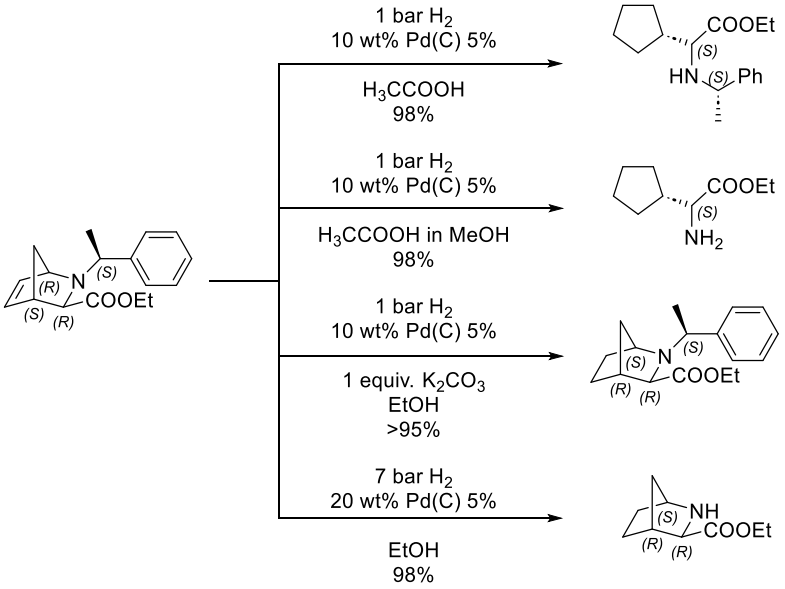
Besides the application of chiral phenylethylamine other stereoselective methodologies were applied in the synthesis of 2-azanorbornene structures. A good overview can be found in a 2015 review by Wojaczyńska et al. on 2-azanorbornenes;[42] various stereoselective,[76–82] chiral auxiliary[83–89] and metal-catalyzed[90–92] *aza*-DA methodologies were addressed, as well as competing [4+2]- and [3+2]-cycloaddition and multistep protocols. The application of chiral auxiliaries can be seen in Scheme 14.[83–88] Besides the use of different auxiliaries the interesting difference to the previously published methodology is the use of chiral auxiliary in the activated aldehyde, rather than using a chiral amine. Various chiral auxiliaries, such as menthol, Corey's menthol derivative, Oppoltzer's camphorsultam or other camphor-based chiral auxiliaries were applied.



Scheme 14 Application of various chiral auxiliaries during the stereoselective synthesis of 2-azabicyclo[2.2.1]heptanes followed by removal of the auxiliary.[83–88]

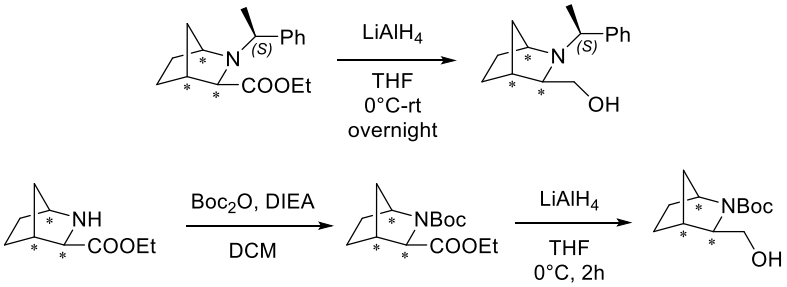
Mechanistically, the DA reaction is reversible. Stella et al.[64] conducted experiments on the retro-DA reaction of the 2-azabicyclo[2.2.1]heptenes, concluding that at 100 °C the reaction is swiftly carried out. To omit such behavior at high temperatures and over time, the unsaturated cycloadducts can be

easily reduced.[93–95] Various hydrogenation conditions were applied and depending on the aim various products may be received (Scheme 15). Valuable α-amino ester building blocks may be produced by the hydrogenation in either pure acetic acid or in an acetic acid/methanol solvent mixture. Omitting the acidic media hydrogenations in ethanol yielded 2-azanorbornanes, either with reduced double bond, or with the removal of the phenylethyl substituent on the nitrogen depending on the conditions (with or without potassium carbonate and the applied hydrogen pressure). It has to be pointed out, that upon reduction the configurations of bridgehead stereocenters changes due to CIP rules.



Scheme 15 Various possible hydrogenation products of chiral 2-azanorbornene.[93–95]

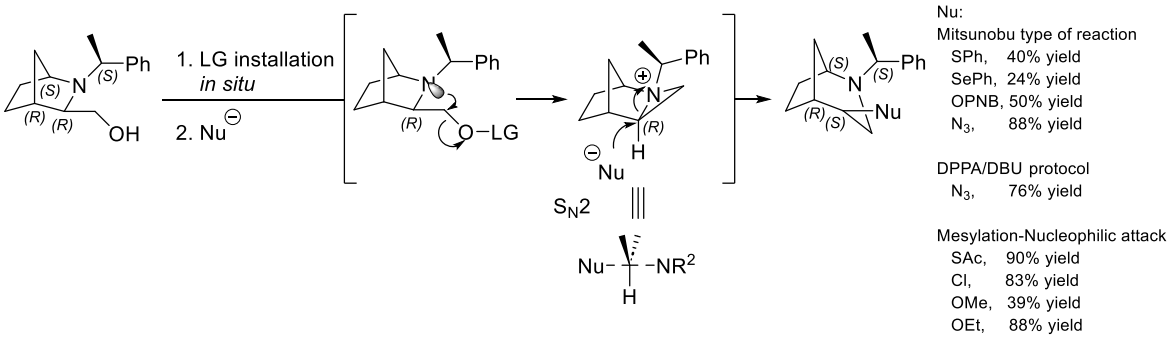
The ring expansion of β-amino alcohols is a powerful tool in stereoselective synthesis.[96] Well known for its application in the stereoselective transformation of prolinol derivatives it may be applied to piperidines as well, such as in the synthesis of tropane alkaloid analogues (formal 8-azabicyclo[3.2.1]octanes) from 2-azabicyclo[2.2.1]heptane alcohols, which are readily available (Scheme 16).[93,97,98]



Scheme 16 Reduction of 2-azanorbornane esters to alcohols. [93,97,98]

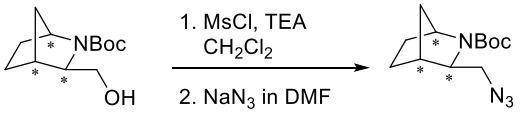
Gore *et al.* firstly encountered the ring expansion of the 2-azanorbornane skeleton upon nucleophilic substitution,[99] later Wojaczyńska *et al.* explored this possibility applying various nucleophiles, leaving groups and reaction methodologies.[100–102] The *N*-phenylethyl-substituted bicyclic alcohols can be converted in S_N2-type reactions expanding the ring by one carbon, with inversion of the stereocenter (Scheme 17). Former (1*S*,3*R*,4*R*)-2-azabicyclo[2.2.1]heptanes yield (1*S*,4*S*,5*R*)-2-azabicyclo[3.2.1]octanes, with the functional group still facing "up"; analogue pseudo-enantiomeric

(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.1]heptanes yield (1*R*,4*R*,5*S*)-2-azabicyclo[3.2.1]octanes. The ring expansion proceeds through an aziridinium intermediate (the proposed mechanism was supported by DFT calculations) and was proven by X-Ray structure analysis and 2D NMR measurements of the formed products. Clear indications were found to distinguish between 2-azabicyclo[2.2.1]heptane and 2-azabicyclo[3.2.1]octane structures through differences in their ^{1}H-NMR spectra.



Scheme 17 Nucleophilic substitution reaction of the S_N2-type leading to 2-azabicyclo[3.2.1]octanes via ring expansion.[99–102]

As expected, the ring expansion was relying on the +I effect of the nitrogen substituent as previously observed for monocyclic ring expansions.[96] However, literature research came short on examples of nucleophilic substitution reactions of Boc protected 2-azanorbornane alcohols, just one example is given in a patent by Gilead Sciences Inc.[103] Upon installation of mesyl leaving group on the alcohol, nucleophilic substitution gave an exchange of hydroxyl group with azide without ring expansion from 2-azabicyclo[2.2.1]heptane to 2-azabicyclo[3.2.1]octane (Scheme 18).



Scheme 18 Nucleophilic substitution of Boc-protected 2-azanorbornane alcohol.[103]

The possibilities for the modification of the alcohol based on 2-azabicyclo[2.2.1]heptane to 2-azabicyclo[3.2.1]octane structures, depending on the substituent on the nitrogen within the heterocycles are manifold. Both structures are easily accessible as rigid, intrinsically chiral building blocks for various applications and as analogues of monocyclic nitrogen-containing moieties.

2.3 Applications of nitrogen heterocycles with focus on 2-azabicycloalkanes

There is a plethora of various cyclic and bicyclic nitrogen compounds and their application is deeply incorporated in stereoselective synthesis, as well as in biologically active compounds. A couple of examples presented in this section are chosen to show the structural diversity and miscellaneous application and activities (Figure 11). Wherever it is possible 2-azabicycloalkane examples are especially pointed out in the sub-sections to indicate their importance in depth.

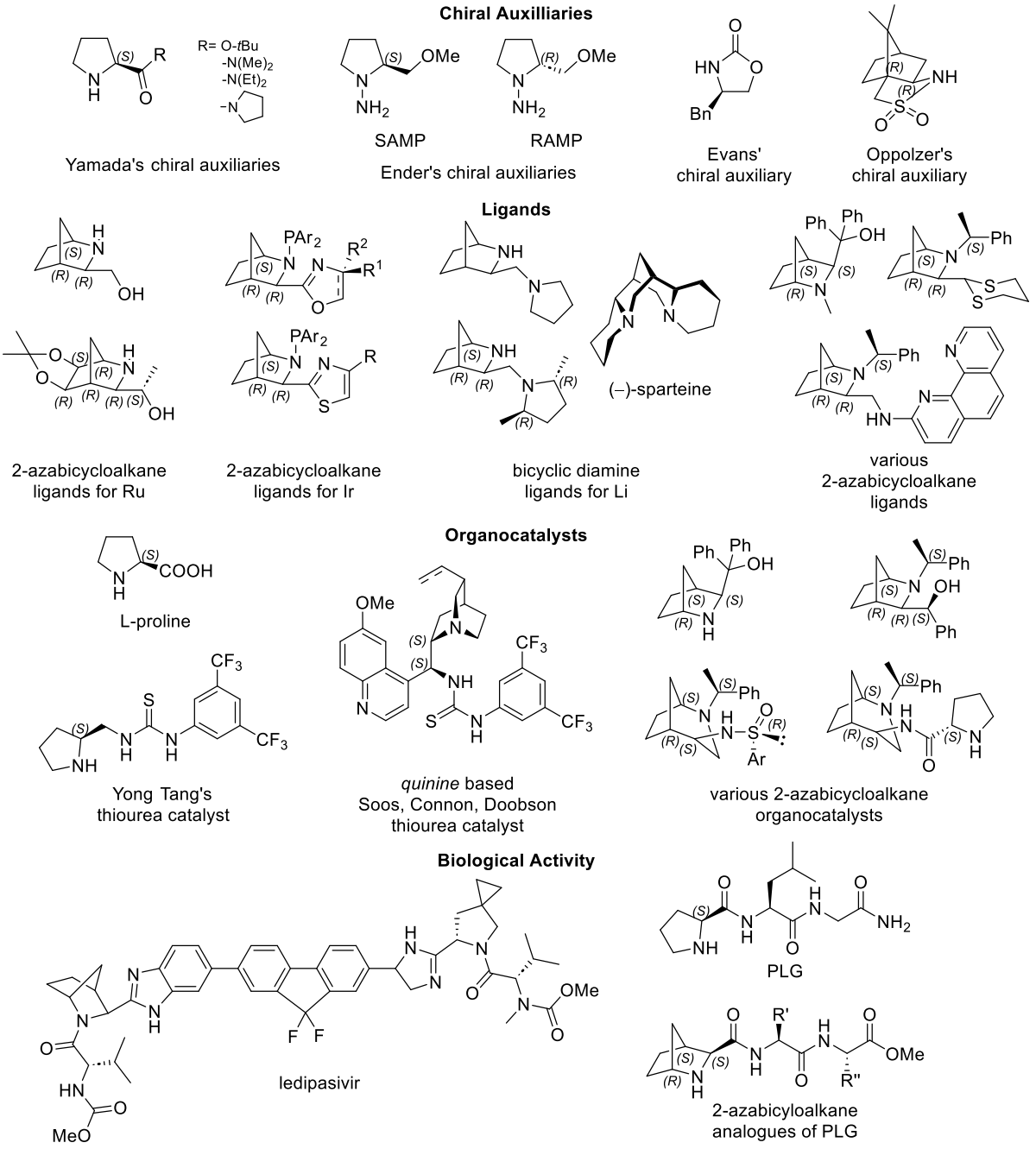


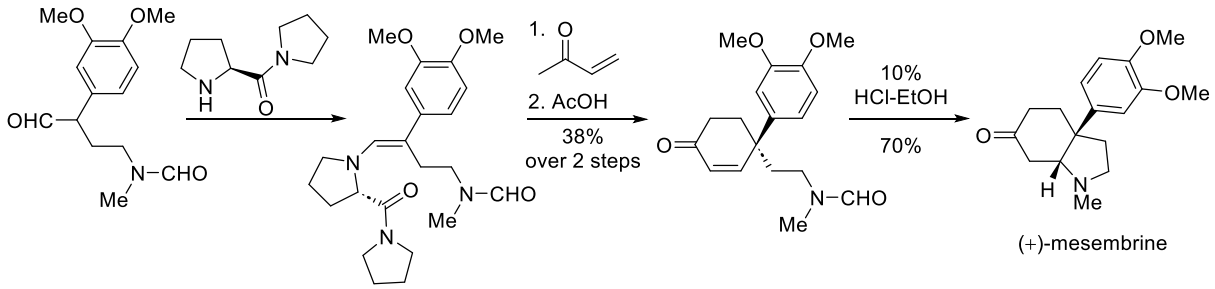
Figure 11 Various nitrogen heterocycles and their application.

2.3.1 Chiral auxiliaries

Chiral auxiliaries are, as the name suggests, helping agents in organic chemistry.[7–9,15,16] For a long time they have dominated the organic chemistry methodologies to produce stereoselective products. They may be used when substrate molecules have enantiotopic faces or groups which then in turn can be tuned. Besides pushing reactions into certain directions chiral auxiliaries form diastereomers. A plethora of auxiliaries have been discovered from nature and synthetically developed, providing many examples of highly stereoselective reactions. If, however, stereoselectivity is poor or insufficient, separations of the diastereomers comes easy with simple purification methods, such as column chromatography, but also repeated crystallization or distillation.

Yamada's chiral auxiliaries

For the development of new methodologies, a first glance is probably always taken at nature. In 1969 Yamada et al. firstly reported the application of L-proline in the development of asymmetric alkylation reactions.[104,105] His group published various auxiliaries received from the chiral amino acid proline and applied them. The chiral auxiliary forms enamines which then in turn dictates the favorable product of the alkylation reaction. Many examples, such as the presented synthesis by Yamada from 1971, include cyclization, for which the methodology has become well known (Scheme 19).[106] Condensation gave an enamine which then reacted in a stereoselective way with Michael acceptors, and the addition of acetic acid resulted in the formation of the first ring. After all stereocenters were set by the chiral auxiliary, yet another condensation yields (+)-mesembrine. Comparison with experimental data, including NMR, IR, TLC and optically rotation of naturally occurring (–)-mesembrine led to the conclusion of a successful total synthesis.

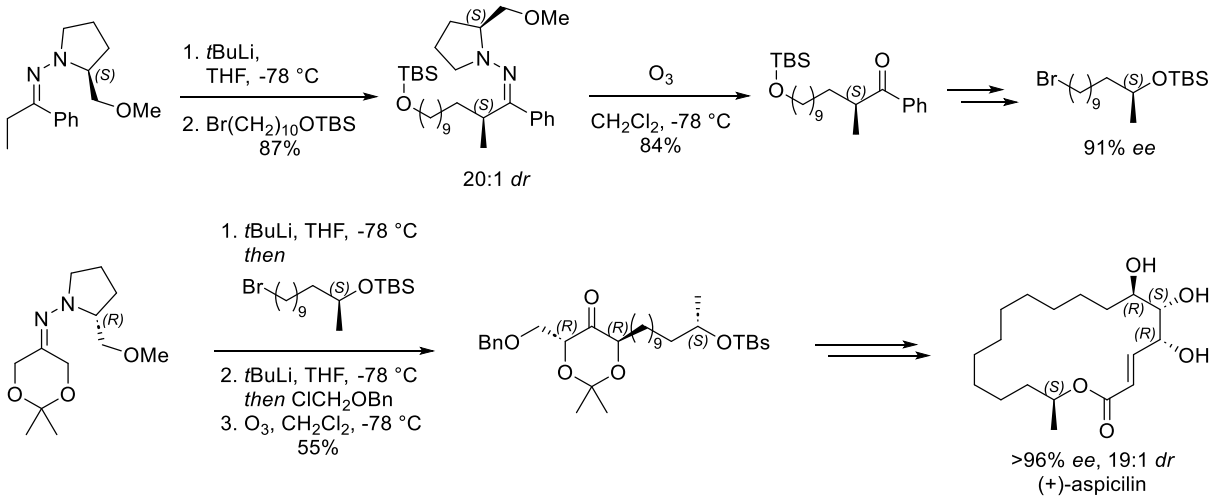


Scheme 19 Application of Yamada's L-proline derived chiral auxiliary in the total synthesis of (+)-mesembrine.[106]

Ender's chiral auxiliaries

Another set of amino acid-derived chiral auxiliaries were developed by Ender *et al.*[107–112] Both (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP)[107,109] and the (*R*)-enantiomer RAMP[108] were described in 1976. Whilst SAMP is derived from L-proline, RAMP is obtained from (*R*)-glutamic acid. Similarly to Yamada's type (enamines), Ender's chiral auxiliaries (hydrazones) react by forming a carbon-nitrogen bond. Often, the hydrazones can be used without further purification; they are reasonably stable under purification conditions and can be stored at low temperatures under inert atmosphere. Their use in asymmetric alkylation reaction is well known and still an often-used methodology in asymmetric synthesis.[113]

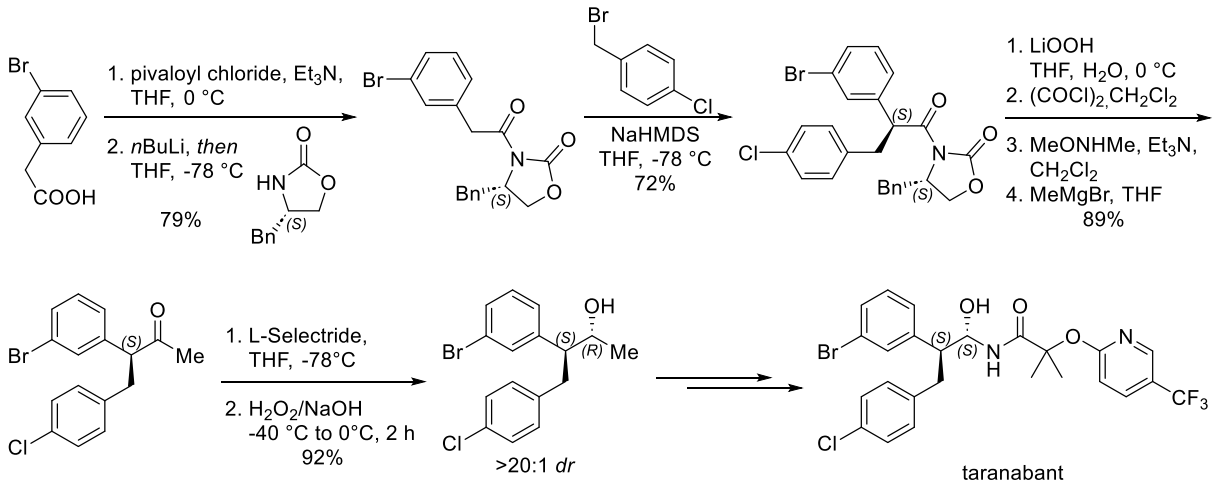
As a proof of concept and advanced possibilities offered by the commercially available chiral auxiliaries SAMP and RAMP, Ender's group published the total synthesis of the 18-membered cyclic ester (+)-aspicilin (Scheme 20).[114] All stereocenters can be set by the use of relatively simple hydrazone starting materials incorporating either SAMP or RAMP for the installation of (*S*)- or (*R*)-stereogenic centers, respectively. The clever introduction of two (*R*) 1,3-hydroxy stereocenters by RAMP is particularly interesting. Conveniently the reaction first yields a singly substituted intermediate, which then in turn can be reacted a second time, followed by oxidation. Further transformation yielded the desired macrocycle with an excellent enantiomeric excess and diastereomeric ratio. The methodology has been developed into a potent way of installing (1*S*,3*S*) or (1*R*,3*R*)- *trans* stereocenters and is used efficiently in many total syntheses (for more examples see[113,115–117]).



Scheme 20 Synthesis of (+)-aspicilin by setting the stereocenters conveniently with the help of SAMP and RAMP.[114]

Evans' oxazolidine auxiliaries

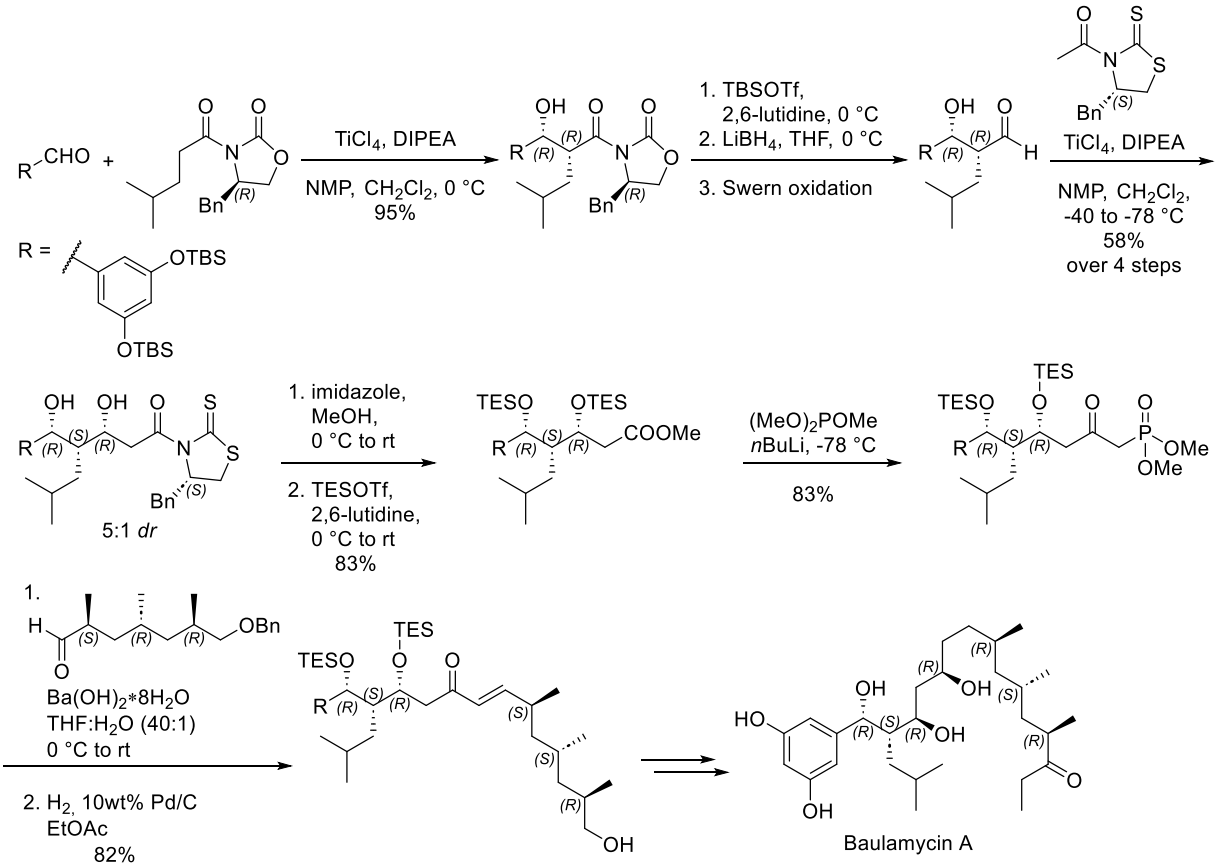
Another widely used chiral auxiliary is Evans' oxazolidine.[9,118–120] First applied in an aldol condensation reaction in 1981 it found vast use in asymmetric total syntheses.[121] Among others, it is used in alkylation, aldol, intra-molecular DA and 1,4 addition reaction. Major investigations were conducted on aldol reactions; often various metals, lithium, titanium or zirconium, but also boron found application.[122,123] Other examples included the asymmetric alkylation of enones, such as the total synthesis of taranabant by Lee *et al.* published in 2007, an cannabinoid-1 receptor inverse agonist as a potential drug candidate (Scheme 21).[124] Upon coupling of the acetic acid derivative with oxazolidine the chiral precursor could be received. A following alkylation of the enolate proceeded in a stereoselective manner due to the installed chiral auxiliary. Lithium hydroperoxide conveniently removed the oxazolidine in 92% yield leaving the chiral carboxylic acid, which was in turn transformed to the Weinreb amide, followed by Grignard reaction yielding a chiral ketone. The second stereocenter was installed using the diastereoselective reduction by L-Selectride, followed by H_2O_2/NaOH oxidation. With all stereocenters set in the previous steps, further transformations yielded taranabant. Unfortunately, the publication did not give any further insight into the stereoselectivity, besides the diastereomeric ratio of the intermediate alcohol. It was stated, that in the NMR were no recognizable



Scheme 21 Synthesis of taranabant with asymmetric key steps including Evans' chiral auxiliary.[124]

peaks of other diastereomers. The yield of every step towards the precursor do suggest high stereoselectivities and good separability of the diastereomers.

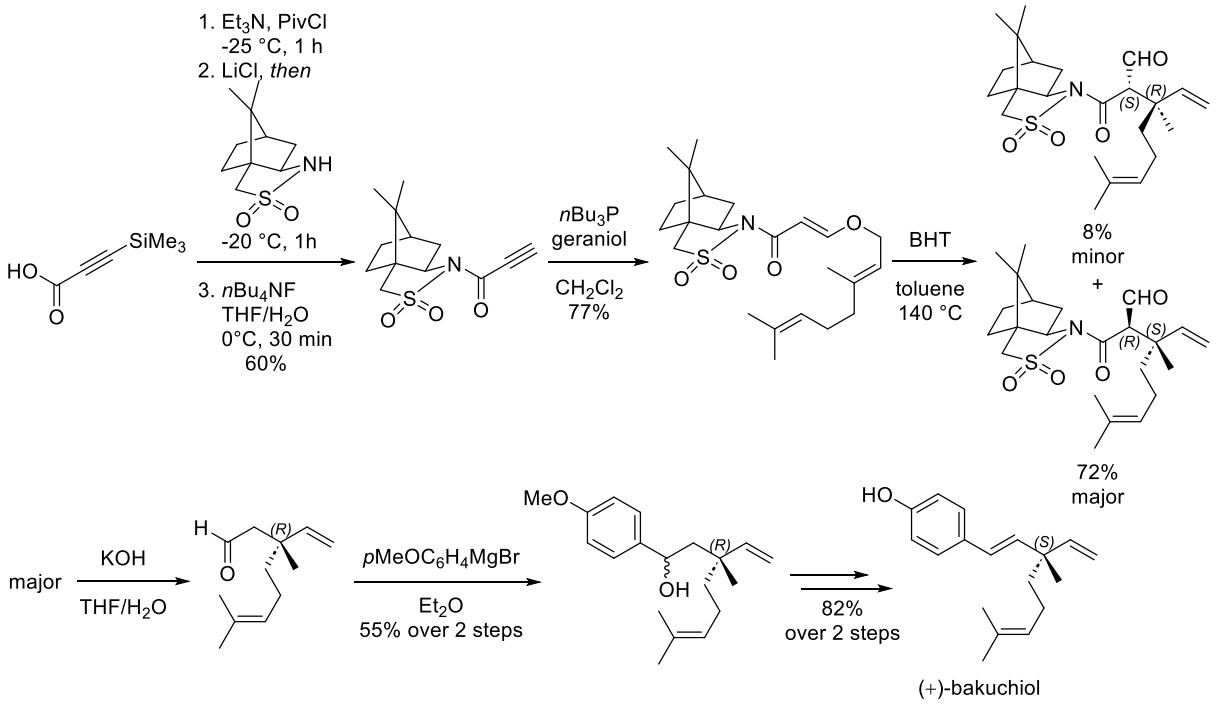
Another, more recent total synthesis was towards Baulamycin A; Evans' auxiliary, alongside a further developed chiral thiazolidinethione auxiliary were used (Scheme 22).[125] Application of them by Crimmins *et al.* and use of the Lewis acid titanium tetrachloride became a powerful method in the stereoselective synthesis.[120,126–128] Nearly all stereocenters, including the *trans*-1,3-methyl centers in the substrate of the Horner-Wadsworth-Emmons olefination were installed using chiral auxiliaries, either by Crimmins aldol reaction or by Evans methylation.



Scheme 22 Synthesis of Baulamycin A by the application of chiral oxazolidine and thiazolidinethione auxiliaries.[125]

Oppolzer's chiral auxiliary

Among other chiral auxiliaires Oppolzer's was already briefly mentioned during the synthesis of 2-azabicyclo[2.2.1]heptanes (Scheme 14). Resorting to chiral natural products, Oppolzer developed (1*R*)-(+)-2,10-camphorsultam and its enantiomer.[129] Both sultams, nowadays commercially available, proved to be useful for diverse transformations.[130–133] One recent example is the synthesis of (+)-bakuchiol by Takao *et al.* (Scheme 23)[134] During Claisen rearrangement in toluene and butylhydroxytoluene at 140 °C in a pressure vial the auxiliary affected the rearrangement yielding an asymmetric outcome. Without the auxiliary diastereomeric ratio is 1:1 and racemates are formed. Therefore, separation of the diastereomers with camphorsultam auxiliary proceeded easily, and the isolated chiral fractions were then further reacted. Upon the basic deprotection and Grignard reaction (+)-bakuchiol product was received in two more steps.



Scheme 23 Synthesis of (+)-bakuchiol using Oppolzer's camphorsultam auxiliary.[134]

Being for long time nearly the only methodology of introducing stereocenters, chiral auxiliary approach can be illustrated by other applications, but discussing all of them lies beyond the scope of this section. The examples shown were chosen due to their nature of incorporating nitrogen atom into rings and their wide scope, being able to influence a broad variety of reaction types. Many other interesting examples do exist,[9,15,16,135] and proved to be complementary to the presented chiral auxiliaries in many cases offering a plethora of possibilities, which can be applied in the stereoselective synthesis. Unfortunately, there are also some disadvantages of auxiliaries, which should be mentioned. Besides often being expensive, their need to be used in stoichiometric quantities and removed at later stages increases waste and lowers the overall yields. This approach is thus time consuming, and unfavorable from the economic and environmental points of view. The drawbacks of this classical method gave rise to the development of new methodologies - catalysis with metal complexes and organocatalysis.

2.3.2 Chiral complexes with nitrogen containing ligands

Ligands, in general, are anions or neutral compounds coordinating to metal ions in a complex ion. Historically, appropriate achiral ligands were used to modulate the energy levels of the metal center, making it suitable for catalysis. With the emerging need of stereochemically pure compounds as pharmaceuticals, various methodologies have arisen, one of which is the development of chiral ligands for asymmetric catalytic reactions. However, not only catalytic reactions are dependent on ligands, but also stoichiometric reactions. To introduce those two modes of action various reaction types with cyclic nitrogen-containing ligands are chosen.

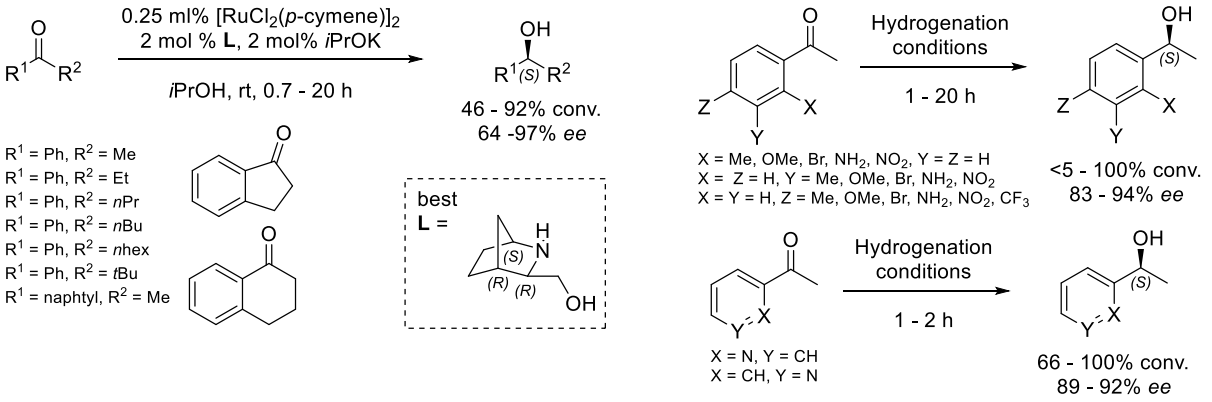
Asymmetric hydrogenation with 2-azabicyclo[2.2.1]heptane ligands

Asymmetric transfer hydrogenation rejoiced a great interest at the beginning of this century.[136] Many different metals and ligands were applied to optimize the reaction outcomes. A prominent nature-derived example is the application of β-amino alcohols in the ruthenium(II)-catalyzed asymmetric

transfer hydrogenation.[137] Structures of ligands used in this reaction became an inspiration for the application of their analogues in other catalytic processes.

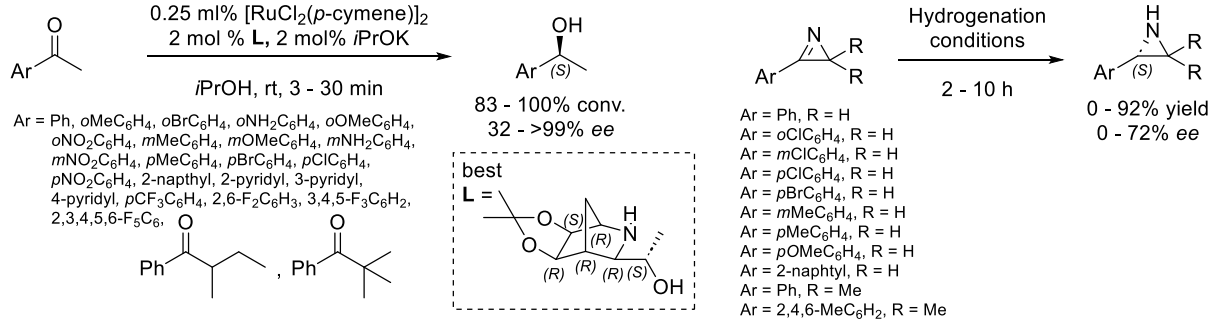
An extraordinary example of synthetic bicyclic nitrogen-containing compounds in catalysis are the sets of various ligands based on 2-azabicycloalkanes developed by the group of Andersson. Their pioneering work brought a great interest for this class of compounds and their possible applications. Many different approaches were tested by the group and later on adapted by other research teams. The first publication, that appeared in 1998, was dedicated to the comparison of L-prolinol and the simple bicyclic β-amino alcohol ((1*S*,3*R*,4*R*)-2-azabicyclo[2.2.1]heptan-3-yl)methanol (Scheme 24, left).[138] To the surprise of the authors and contraceptive to chemical sense not only did the (*S*)-prolinol-catalyzed reaction have poor conversion (16%) and enantiomeric excess (8%), but the bicyclic (*R*)-amino alcohol (92% yield, 95% *ee*) led to the same (*S*)-enantiomer. Later on, many theoretical studies and optimizations substantiated the results obtained with the use of bicyclic ligands.[139,140]

In the same year Andersson and co-workers developed various new β-amino alcohols and applied them with a limited success as ligands in borane reduction.[141] Two years later the group presented a work applying the previously developed ligands together with new ones. They further broadened the substrate scope. Again, good to very good conversions and enantiomeric excesses could be observed, however, the novel ligands did not improve the results of the previously successful "simple" ligand and the information drawn from the publication remains the scope, together with tendencies for further investigations (Scheme 24, right): more steric hindrance is counterproductive for both yield and enantiomeric excess.[142]



Scheme 24 Application of bicyclic β-amino alcohol in the ruthenium(II)-catalyzed transfer hydrogenation of various ketones.[138,142]

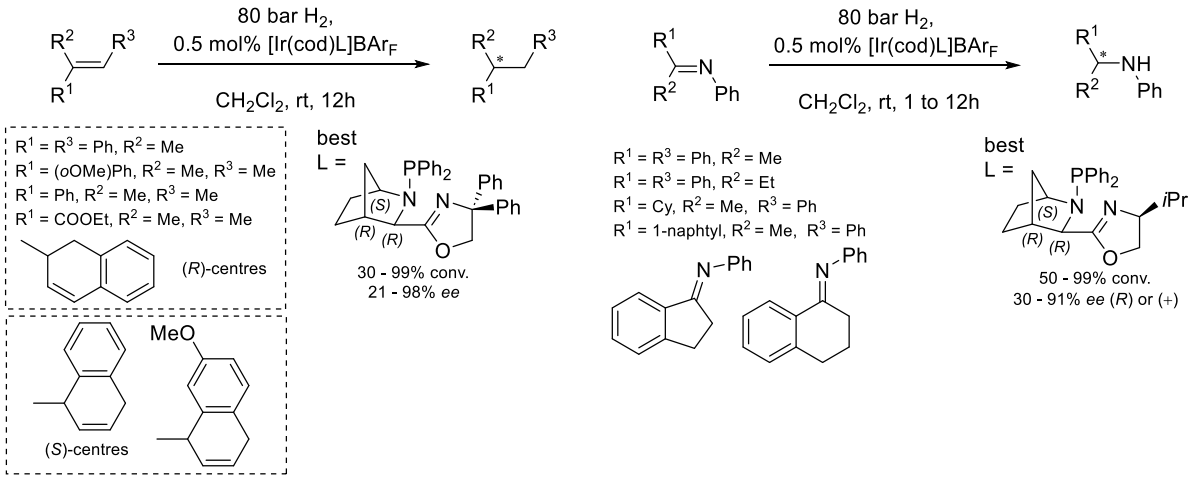
On the continuous search for improved ligands with better substrate scopes and tolerances, including electron withdrawing substituents, which were vastly problematic previously, a new set of ligands was synthesized, of which the best one can be seen in Scheme 25.[140,143,144] Except of one example (1-(perfluorophenyl)ethan-1-one, 32% *ee*), all received enantiomeric excesses for the asymmetric hydrogenation of various ketones were very good to excellent, together with very high conversion rates, generally above 90%.[140,143] Applying the same ligand with similar asymmetric hydrogenation conditions to prochiral azirines gave enantiomerically enriched chiral aziridines; however, while conversions remained mostly good (just one example below 72% yield) enantiomeric excesses were moderately good with only up to 72% *ee*.[144]



Scheme 25 Bicyclic β-amino alcohol ligand with additional stereocenters applied in the ruthenium(II)-catalyzed transfer hydrogenation with various ketones and application in hydrogenation of azirines to chiral aziridines. [140,143,144]

First applications of 2-azanorbonane-based ligands in the iridium-catalyzed hydrogenation gave rather poor results. Application of chiral sulfides and sulfoxides only gave enantiomeric excess of up to 63% for the asymmetric transfer hydrogenation of acetophenone.[98] By 2004 the first oxazoline-based ligands were developed, however, in the asymmetric transfer hydrogenation with iridium rather poor results were achieved again.[145] A breakthrough in research was achieved, once the group of Andersson developed their platform towards Crabtree catalyst analogues.[146] Especially, Pfaltz's utilization of phosphine-oxazoline ligands in the iridium-catalyzed hydrogenation of imines[147] led to an accelerated development, which did not stop until today. Because of the lack of very comprehensive reviews on this matter after 2015,[42] the following part includes all references the author found on the subject of the 2-azabicyclo[2.2.1]heptane skeleton used as ligands in iridium-catalyzed asymmetric hydrogenations. However, reviews partly covering the subject may be found.[148–155]

Initial studies were performed on alkenes and imines.[156,157] Both, alkenes and imines could be efficiently hydrogenated using the described protocols with up to 99% conversion and up to 98% and 91% enantiomeric excess, respectively (Scheme 26). However, the biggest drawback is steric hindrance, from which both conversion and enantiomeric excesses are suffering. In addition, Lewis bases such as the formed products (amines) are known to be inhibitors of phosphorous-nitrogen-based ligands in the hydrogenation.



Scheme 26 Iridium-catalyzed hydrogenation of various alkenes and imines with the help of 2-azanorbonane-phosphine-oxazoline ligands. [156,157]

Further development of ligands led to the introduction of phosphine-thiazoline based ones. At first unselective in the hydrogenation of enamines in 2008 they have developed to be equally powerful

ligands to the oxazoline analogues.[158] All further developed ligands, up to date, are based on a phosphine moiety, which generally moderates reactivity and on a coordinating nitrogen-containing moiety – oxazoline or thiazoline, which modulates selectivity (Figure 12).[159] All Crabtree-type iridium catalysts can be received in their crystalline form and are stable at room temperature under inert atmosphere. An exemplary structure of the [Ir(cod)L]BAr_F salt can be seen in Figure 13.

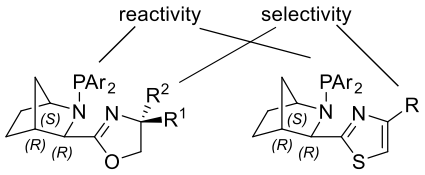


Figure 12 General structure of 2-azabicyclo[2.2.1]heptane ligands with phosphine-oxazoline/thiazoline functionalization and proposition of structure/activity relationship in ligands.[159]

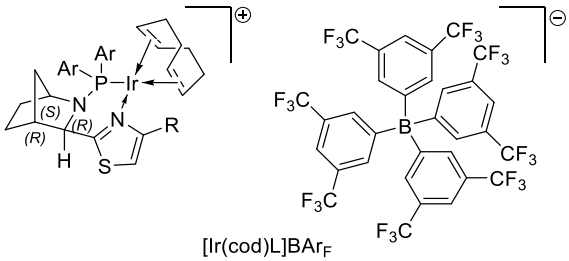
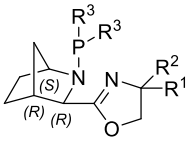


Figure 13 Example of Crabtree-type iridium complex with 2-azabicyclo[2.2.1]heptane-phosphine-thiazoline ligand.

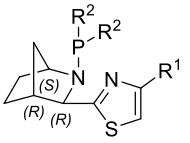
The scope of application was developed along the way of ligand development. Many diversely substituted alkenes can be successfully hydrogenated, which include α,β-unsaturated ester,[160] allylic alcohols,[161] trisubstituted enones,[162] enamides and amides,[163] divinyl carbinols and carbamides,[164] chiral sulfones,[165,166] enol-phosphinates,[167,168] fluorinated alkenes,[169–172] and others (Scheme 27).[173–183] Further publications addressed kinetic resolution methodologies[154,184,185] and application in total synthesis[154,166]

Over the years the applications and substrate scopes of 2-azabicyclo[2.2.1]heptane based phosphine-oxazoline/thiazoline ligands were investigated in more detail. Various relationships of activities and substituents in either complexing moiety were revealed and overall very efficient sets of catalysts for relatively simple hydrogenation conditions were developed. Except for stated examples the conditions were similar: reaction at room temperature in dichloromethane with low catalyst loadings and reaction times in the range of several minutes up to 72 hours. The only drawback included occasionally very high hydrogen pressures - practically not available in some laboratories. Conversions were in general excellent and resulting isolated yields good to very good – nearly all steric hindrances could be overcome with a change of ligand. The same can be stated for the enantiomeric excesses, which were only in some examples poor and in the broad majority of cases excellent.

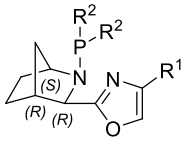
The examples of thiazoline-based ligands **H** and **ent-H** are interesting to mention. Both could be efficiently used in hydrogenation reaction of fluorinated vinyl alcohols offering access to both enantiomeric products. Further investigations showed that ligand **H** yielded one specific enantiomer if used in an iridium-catalyzed asymmetric hydrogenation of *Z*-fluoro-alkenes and the opposite enantiomer upon conversion of the *E* isomer. *Vice versa*, **ent-H** offered a powerful methodology complementary to its enantiomer enabling a chemist to apply either of them to achieve the desired outcome.



A R^1 = *i*Pr, R^2 = H, R^3 = *o*Tol
B R^1 = R^2 = Ph, R^3 = *o*Tol
C R^1 = *t*Bu, R^2 = H, R^3 = *o*Tol
D R^1 = *t*Bu, R^2 = H, R^3 = Ph
E R^1 = *i*Pr, R^2 = H, R^3 = 2,4-diMeC_6H_3
F R^1 = iPr, R^2 = H, R^3 = Ph
G R^1 = iPr, R^2 = H, R^3 = *o*EtPh

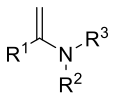


H R^1 = Ph, R^2 = *o*Tol
I R^1 = Ph, R^2 = *i*Pr
J R^1 = Ph, R^2 = *i*Pr
K R^1 = Ph, R^2 = Cy

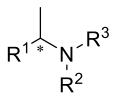


L R^1 = Ph, R^2 = *o*Tol

general conditions
5 - 100 bar H_2
0.5 - 2.0 mol% [Ir(cod)**L**]BAr_F
CH_2Cl_2, rt, 3 min - 24 h

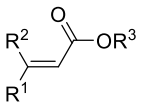


Ligand **A**
conditions

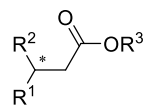


10 examples
66 - >99% *conv.*
0 - 87% *ee*

Ref. 158

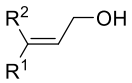


Ligands **A, B, H**
conditions

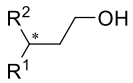


30 examples
>99% *conv.*
85 - >99% *ee*

Ref. 160

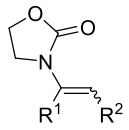


Ligands **C, D, H, ent-H**
conditions

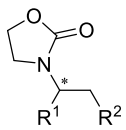


21 examples
92 - 99%
82 - 99% *ee*

Ref. 161

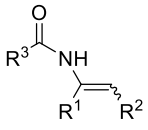


Ligands **H, ent-H, ent-L**
conditions

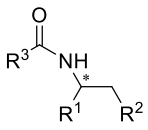


Z/E - Mixture

one enantiomer
25 examples
80 - 99%
87 - 99% *ee*



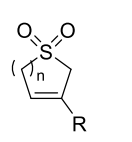
Ligand **ent-H**
conditions



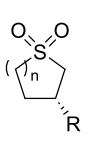
Z/E - Mixture

one enantiomer
4 examples
quant. *conv.*
90 - 98% *ee*

Ref. 163



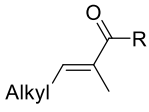
Ligand **H**
conditions



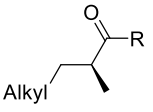
n = 1-3

9 examples
43 - >99% *conv.*
85 - 93% *ee*

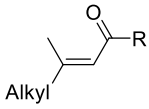
Ref. 165, 166



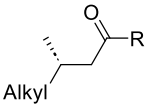
Ligands **E, I**
conditions



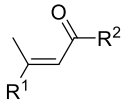
7 examples
74 - 99%
94 - 99% *ee*



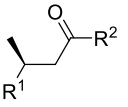
Ligands **E, I**
conditions



6 examples
72 - 99%
88 - 96% *ee*

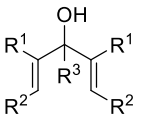


Ligand **ent-H**
conditions

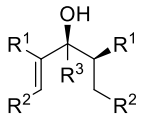


5 examples
89 - 99%
94 - 99% *ee*

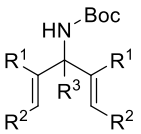
Ref. 162



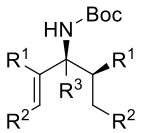
1- 6 bar H_2
0.5 - 1 mol%
[Ir(cod)**ent-H**]BAr_F
10 mol% K_2CO_3,
toluene rt
10 - 60 min



26 examples
68 - 96%
95 - 99% *ee*
>20:1 *dr*

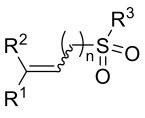


1- 6 bar H_2
0.5 - 1 mol%
[Ir(cod)**ent-H**]BAr_F
10 mol% K_2CO_3,
toluene rt
10 - 60 min



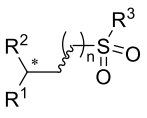
8 examples
77 - 91%
97 - 99% *ee*
19:1 - >20:1 *dr*

Ref. 164

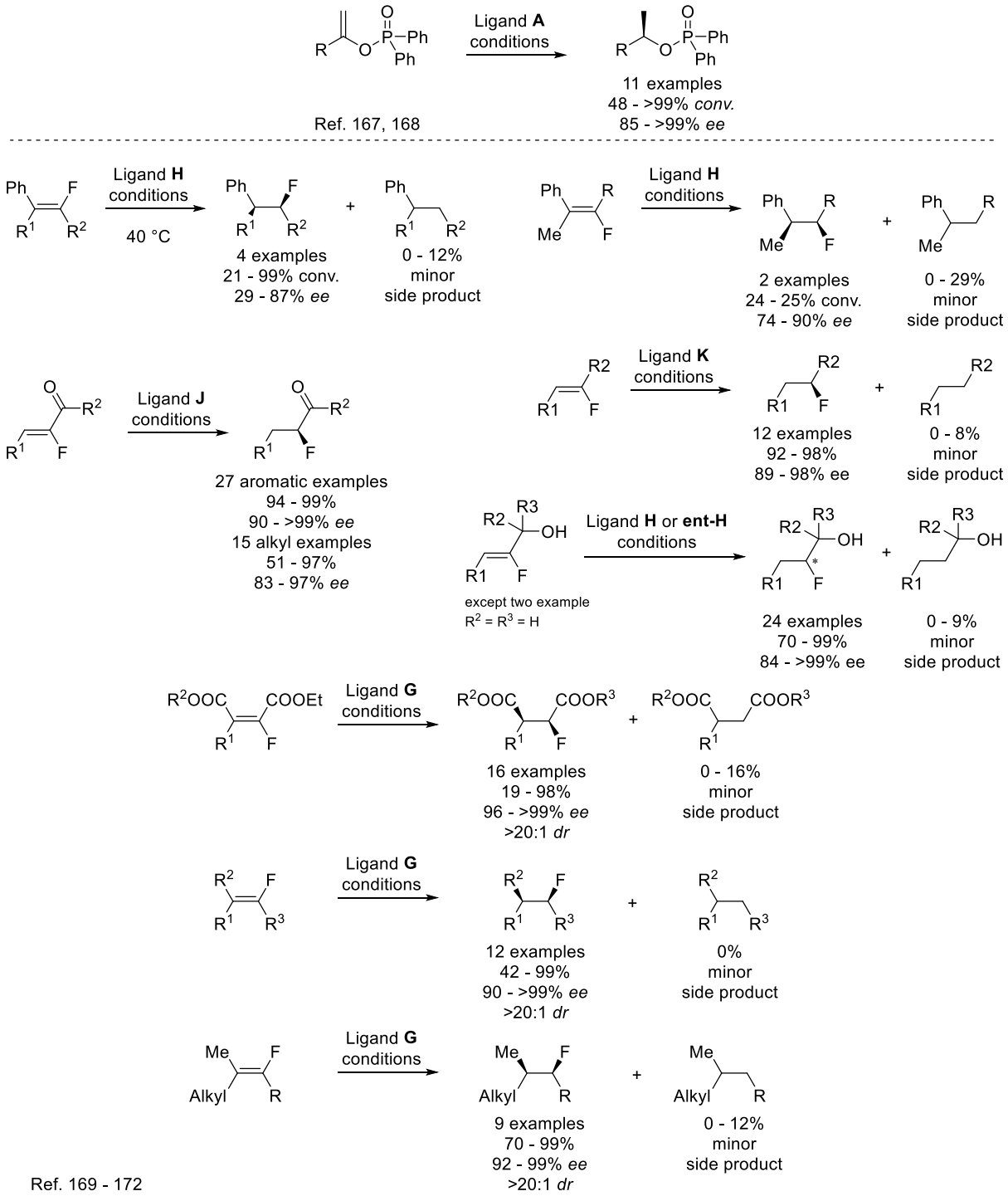


n = 0 - 2

Ligand **H**
conditions



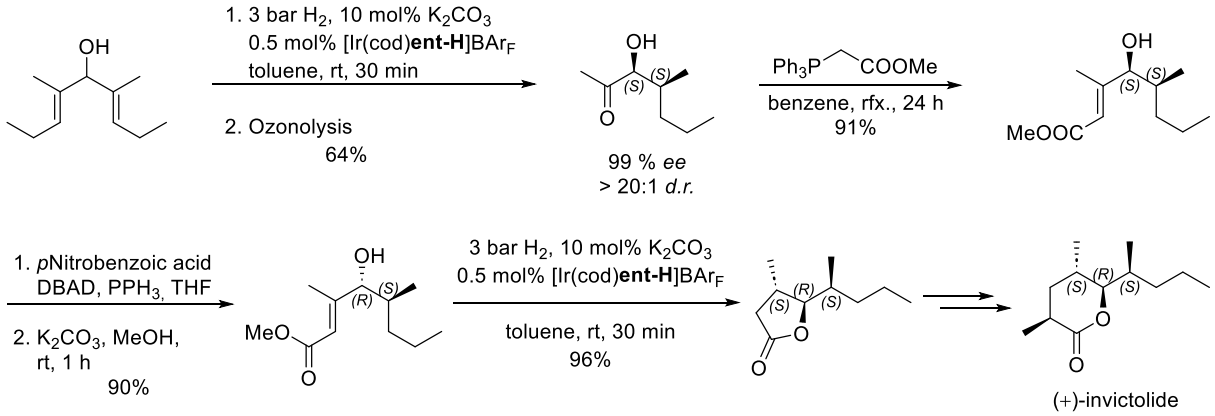
39 *E* examples
0 - >99% *conv.*
14 - 99% *ee*
9 *Z* examples
0 - >99% *conv.*
88 - 97% *ee*



Scheme 27 Overview of 2-azabicyclo[2.2.1]heptane ligands and scope of application in iridium-catalyzed asymmetric hydrogenation.[158,160–172]

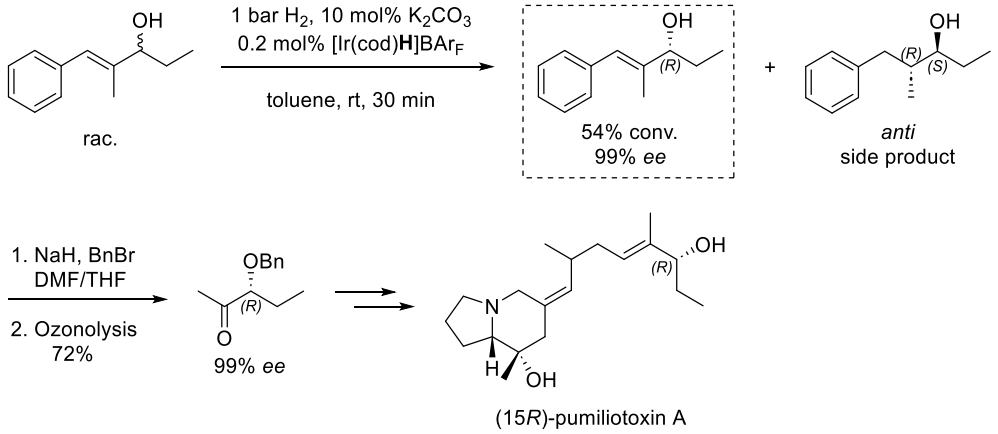
The continuous efforts of Andersson's group provided a plethora of ligands (including not only 2-azabicyclo[2.2.1]heptanes). The versatility of the catalysts can be seen in two chosen examples of formal total syntheses (Scheme 28 and Scheme 29).[154] Using the formerly developed methodology of asymmetric hydrogenation of divinyl alcohols with ligand **ent-H** (Scheme 27)[164] the prochiral starting material could be efficiently hydrogenated. Follow-up ozonolysis gave the α-hydroxy ketone in good yields with excellent enantiomeric and diastereomeric excess. The *cis*-product was then reacted in a Wittig type of transformation and a following Mitsunobu reaction of the hydroxy group inverted the stereocenter. Following reduction gave the *trans*-diastereomer. The same hydrogenation conditions,

previously used, do not only cause reduction of the α,β-unsaturated ester, but also initiate a stereoselective intramolecular transesterification. Further transformations yielding (+)-invictolide were previously published by Ziegler *et al.*[186]



Scheme 28 Formal total synthesis of (+)-invictolide by two asymmetric hydrogenations using a bicyclic ligand.[154,186]

In another example ligand **H** was applied in a kinetic resolution (Scheme 29). Whilst the (*S*)-vinyl alcohol is efficiently reduced by the catalytic system, the (*R*)-enantiomer remains completely unreacted (99% *ee*). Upon separation the alcohol was protected and ozonolysis gave the protected α-hydroxyketone with a retained stereocenter. Further formerly published transformation give (15*R*)-pumiliotoxin A.[187] The chiral precursor was synthesized in a simple and short two step procedure opposing to the formerly used 7 step synthesis from glycidol.



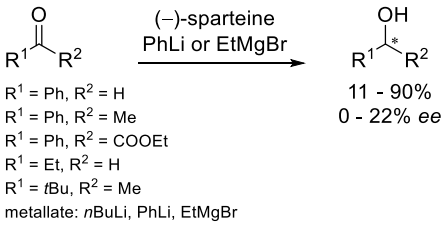
Scheme 29 Kinetic resolution of a racemic vinyl alcohol in the synthesis of a chiral precursor for the formal total synthesis of (15*R*)-pumiliotoxin A.[154,187]

Asymmetric deprotonation-substitution reactions with cyclic diamines

Unlike chiral auxiliaries, ligands generally are external sources of chirality within a reaction, which do not necessarily bond to the substrates, but to the reactive center. Historically, coordinating solvents, such as THF, DME or TMEDA improved the reactivity of lithium in reactions. By introducing chiral ethereal and amino ligands the coordination of the metal center could be altered (in competition with the solvent), reactivity remained good, but asymmetry was introduced into the reaction.

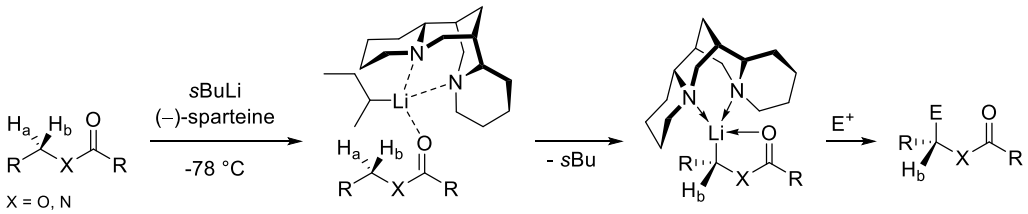
The application of the natural alkaloid sparteine (especially the more abundant (−)-sparteine) in lithiation reaction was primarily investigated and the first application was published in 1968 by Nozaki, Toraya, and co-workers.[188] Attempts of the asymmetric addition of *n*-BuLi to benzaldehyde employing

(–)-sparteine as a ligand gave the product in high yields, however, chiral induction was rather poor (6% *ee*). Three years later, a study on the scope employed, besides two other carbonyl compounds, also phenyl lithium and the Grignard compound ethyl magnesium bromide.[189] All organometallic compounds reacted yielding chiral alcohols, however, chiral induction was poor (up to 22% *ee* 5% yield) (Scheme 30).



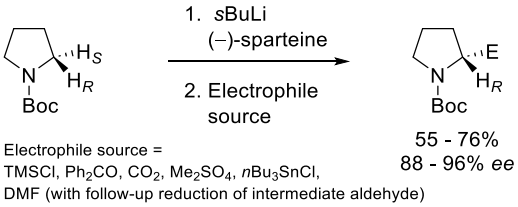
Scheme 30 First application of the cyclic diamine (–)-sparteine in asymmetric lithiation and Grignard reaction.[188,189]

While the additions of organometallic compounds to aldehydes or ketones were not very stereoselective, deprotonation reactions applying (–)-sparteine as a base proved to be.[190] Continuous efforts, among others by Strohmann *et al*.[191–193] and Beak *et al*.,[194–196] explored the conformers of sparteine theoretically, together with NMR and crystallography studies and the scope. Deprotonation of a carbonyl moiety coordinated to lithium proceeds stereoselectively under temperature control, followed by stereoretentive trapping with an electrophile (Scheme 31).[197,198]



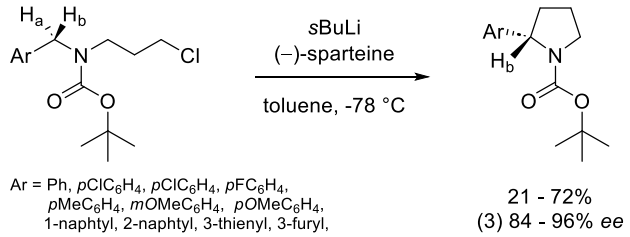
Scheme 31 Ligation of lithium by (–)-sparteine during the stereoselective deprotonation with a following electrophilic substitution (reproduced from Aggarwal et al.).[197,198]

Good yields and very good enantiomeric excesses could be achieved in the stereoselective deprotonation-electrophilic substitution of *N*-Boc protected pyrrolidines (Scheme 32).[195,199] Generally, the reactions were conducted in diethyl ether at -78 °C for the deprotonation, while a subsequent electrophilic substitution was performed after reaching room temperature. Lithium complexes are stable at -78 °C and become reactive at higher temperature. Understandably, best enantiomeric excess results can be achieved by applying stoichiometric amounts of sparteine in the reaction. However, the reaction is still asymmetric (with lower *ee*) when applying substoichiometric amounts of the ligand. Separation of sparteines from the reaction mixture is easily afforded by extraction: products usually stay in the organic phase, while sparteine is soluble in water and can be recovered by acid/base treatment.



Scheme 32 Stereoselective deprotonation/electrophilic substitution example of lithium with sparteine as ligand.[195,199]

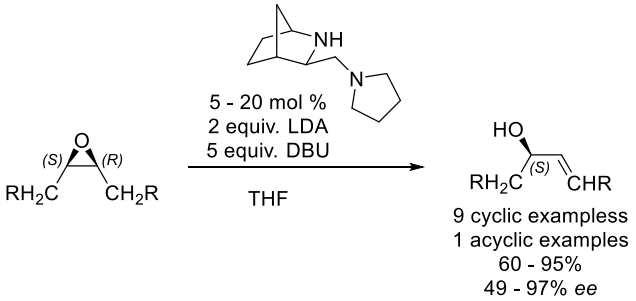
Among other examples, the intramolecular lithium-mediated cyclization of *N*-Boc-protected amines forming stereoselectivly pyrrolidines is of interest.[196] Mediated by lithium and (–)-sparteine the reaction is a great methodology for cyclization because due to the carbamate the *N*-Boc protected amine is forming alongside stereoselectivity a strong regioselectivity is given. Besides one example applying *para*-methoxyphenyl as aryl moiety (42% yield, 3% *ee*) all enantiomeric excesses were good to excellent.



Scheme 33 Intramolecular lithium-mediated stereoselective cyclization.[196]

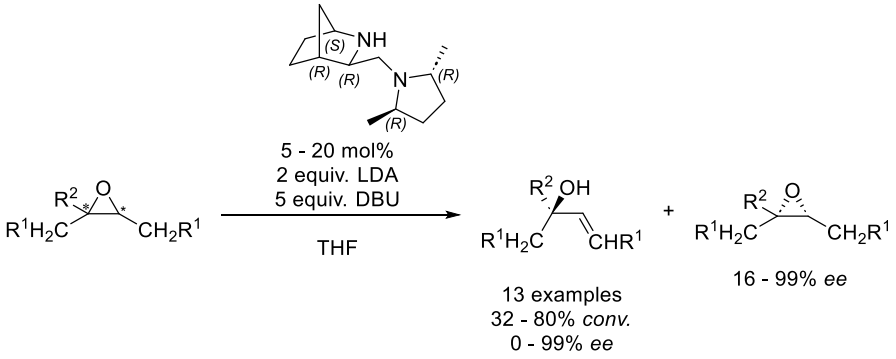
Various further asymmetric reactions with 2-azabicyclo[2.2.1]heptane ligands

Various lithium-catalyzed epoxide ring opening reactions were conducted applying bicyclic diamines. The group of Andersson was the sole research team with contributions toward the development of catalysts and investigation of the scope. A set of ten substrates was tested with different conditions and various ligand loadings, together with tests of the influence of solvent and theoretical investigations (Scheme 34).[80,200–203] The same catalyst was applied in the kinetic resolution of racemic epoxide mixtures with mediocre conversions and good enantiomeric excess.[204]



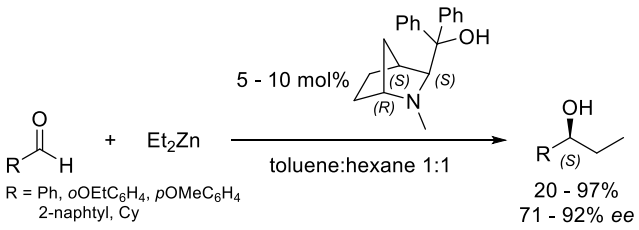
Scheme 34 Asymmetric epoxide ring opening with bicyclic diamine ligands.[80,200–203]

The development of new catalysts led to the optimal ligand for the asymmetric epoxide ring opening,[205] which, in turn, was also very successful in the kinetic resolution of racemic epoxides leaving unreacted epoxides with general very good to excellent enantiomeric excess (Scheme 35).[206]

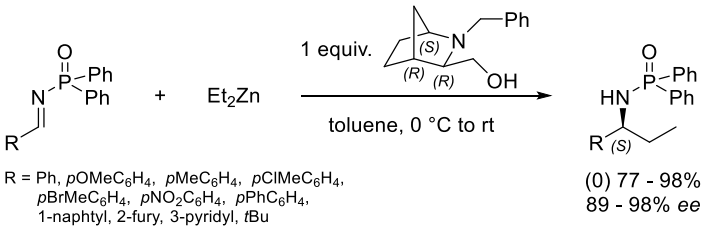


Scheme 35 Kinetic resolution of racemic epoxides by a chiral bicyclic diamine. [202,204–206]

The groups of Hongo and Andersson worked on the 2-azabicyclo[2.2.1]heptane-promoted addition of diethylzinc to aldehydes and imines (phosphinyl imines). A set of various γ–amino alcohols was obtained and tested. Hongo (Scheme 36)[93,207] and Andersson (Scheme 37)[95,208,209] parallelly applied similar ligands with good to very good yields and good to very good enantiomeric excess. Whilst Hongo reacted various aldehydes, the group of Andersson applied the 2-azanorbornane based ligands on phophinyl imines. Both groups received (*S*)-enantiomers, which is surprising given the opposite configuration of catalysts and might be explained by the bulky substituent on Hongo's catalyst and by using different substrates.



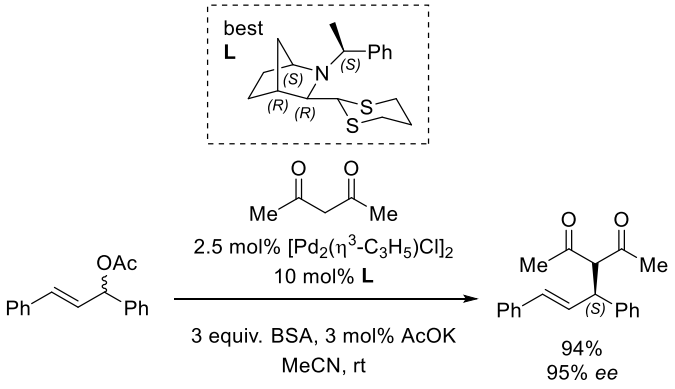
Scheme 36 Addition of Et_2Zn to various aldehydes with bicyclic ligands by Hongo *et al.*[93,207]



Scheme 37 Asymmetric addition of Et_2Zn to phosphinyl imines with bicyclic ligands by Andersson *et al.*[95,208,209]

A couple of applications of chiral 2-azabicyclo[2.2.1]heptanes as ligands were reported by Wojaczyńska *et al.* The asymmetric reactions included palladium-catalyzed Tsuji-Trost alkylation reaction,[101] copper-catalyzed Henry reaction[100] and zinc-catalyzed aldol reaction.[210]

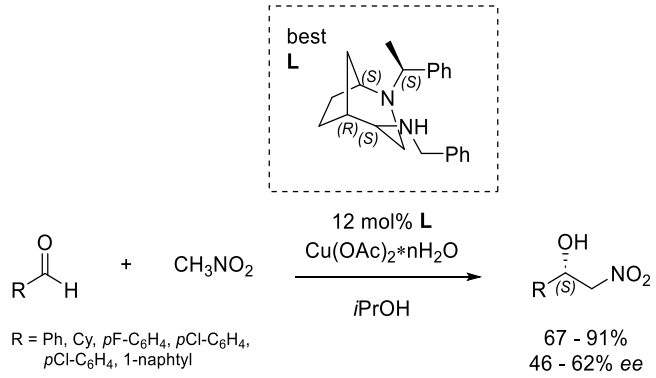
For the application in a palladium-catalyzed alkylation reaction a set of eight N,X-ligands was synthesized, where X is either nitrogen, sulfur or selenium.[101] The best ligand was incorporating a dithiane moiety. Although initial testing was very promising with very high yields and enantiomeric excess, no further attempts on the asymmetric Tsuji-Trost reaction were published (Scheme 38).



Scheme 38 Asymmetric palladium-catalyzed Tsuji-Trost alkylation with the help of bicyclic ligands.[101]

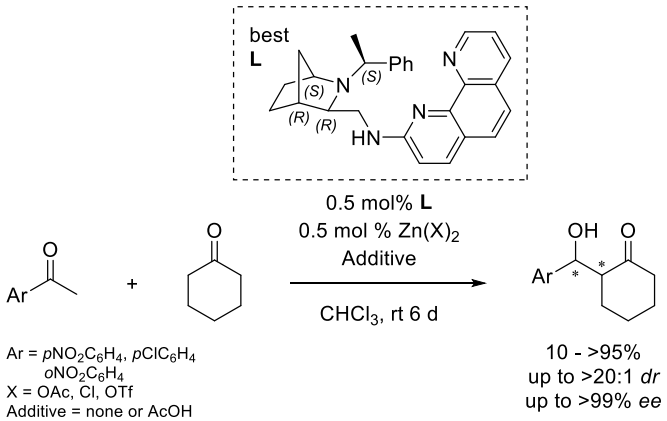
A set of nine *N,N*-chelating ligands, including one chiral tertiary amine unit together with a second primary, secondary or tertiary unit, was prepared and tested in the Henry reaction of various aldehydes

with nitromethane (Scheme 39).[101] The reaction proceeded with good to very good yield, chiral induction, however, was rather mediocre. The structures, at first mistakenly identified as a (1*S*,3*R*,4*R*)-2-azabicyclo[2.2.1]heptane derivatives were later identified as ring-expanded (1*S*,4*S*,5*R*)-2-azabicyclo[3.2.1]octanes.[102] Further, the stereochemistry of the claimed *endo*-epimer was found to be the pseudo-enantiomer ((1*R*,4*R*,5*S*)-2-azabicyclo[3.2.1]octane derivative), rather, then the epimer. Either way, the opposite chiral induction upon the application of the pseudoenantiomer of the best ligand was particularly interesting; higher yields were accompanied by the decrease of the enantiomeric excess.



Scheme 39 Asymmetric copper-catalyzed Henry reaction with bicyclic ligands.[100]

The most recent attempt on applying 2-azabicycloalkanes as ligands in asymmetric reactions was published by the group of Wojaczyńska in 2016 with a zinc-catalyzed aldol reaction (Scheme 40).[210] The best ligand was an 1,10-anthryl-functionalized 2-azabicyclo[2.2.1]heptane, however, either the yields were limited, while enantiomeric and diastereomeric excess were good or reasonable yields were accompanied with poor asymmetric inductions, which also appeared to be substrate dependent. The publication unfortunately was not followed-up and remains therefore preliminary.



Scheme 40 Asymmetric zinc-catalyzed Aldol reaction with the help of bicyclic ligands.[210]

2.3.3 Organocatalysis

Many different strategies are available for the enantioselective synthesis. In addition to the previously reviewed methodologies of chiral auxiliaries and the use of chiral ligands in metal catalysis, organocatalysis is a powerful alternative with many advantages.[211,212] Besides relatively low toxicity of the organocatalysts, compared with toxic heavy metals, this class of compounds offers great opportunities; often they are even compared to enzymes, natural organocatalysts. They are

inexpensive and rather easy to prepare, simple to apply, often available as both enantiomers and stable in air and water. To support the great interest in organocatalysis and stereoselective synthesis in organic chemistry the number of documents accessible with the keywords “stereoselective synthesis” and “organocatalysis” using the Scopus.com website is shown in Figure 14. The interest in organocatalysts and stereoselective synthesis remains very high, although the rise stagnated and even sunk a bit.

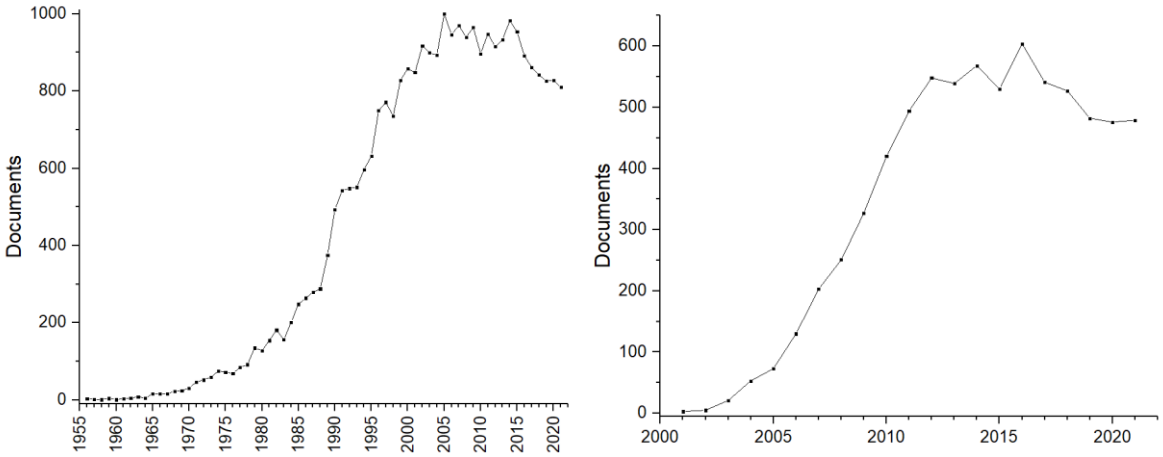


Figure 14 Graphs of number of documents including the keywords “Stereoselective Synthesis” (left; total number of documents 29808) and “Organocatalysis” (right; total number of documents 7505) on the Scopus website accessed on the 02.12.2022.

From proline and cinchona alkaloid organocatalyst to the rapid development of new organocatalysts

Due to the interest of pharma industry in the stereoselective synthesis of pharmaceuticals many new methodologies were developed to cope with this need. In contrast to simple catalysts bifunctional catalysts activate or interact with two partners of a reaction. The outstanding idea behind using two moieties within one catalyst, one for each substrate, offers new possibilities in directing reactions before not fathomed. While monofunctional catalyst may produce chiral products the scope of bifunctional catalysts is much more broadened and their application in asymmetric reactions are beneficial. Generally, all bifunctional catalysts consist of three necessary building blocks/moieties, two of which are the functionalities interacting with the substrates and a chiral backbone fixing the functionalities in a three-dimensional space (Figure 15).

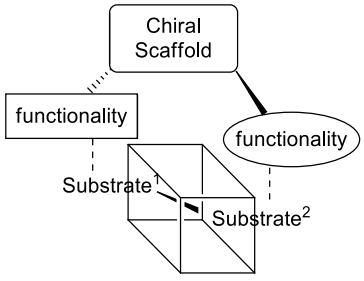
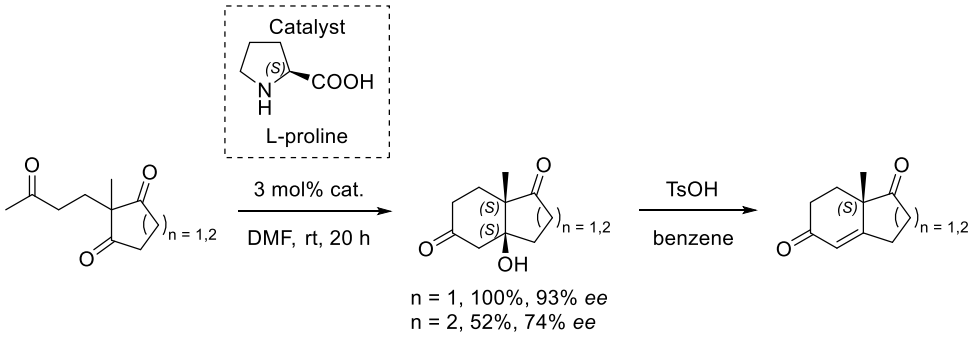


Figure 15 Schematic picture of chiral bifunctional catalysts with the reaction space.

L-Proline, bearing amine and carboxylic acid functionalities, enables effective aminocatalysis of Lewis base-type iminium and enamine-based catalysis.[213] Early on examples of L-proline, bearing amine and carboxylic acid functionality being used as bifunctional organocatalysts were published in the beginning of the 1970s by two independent industrial research groups. Both groups started from the

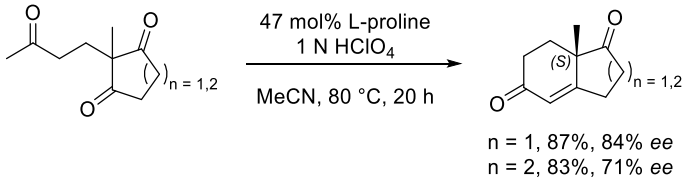
same Michael-addition of vinyl ketones and cyclic 1,3-diketones. A following intramolecular cyclization was in both cases catalyzed by L-proline, and dehydration catalyzed by acids.

In a patent application from 1970, granted in 1971, a two-step procedure was described and later on published in an scientific journal by Hajos and Parrish.[214,215] Initial research was targeting the stereoselective synthesis of the steroid precursors known as Wieland-Miescher ketones and used low organocatalytic loadings installing the stereocenters with up to 93% *ee* and a quantitative yield (Scheme 41).



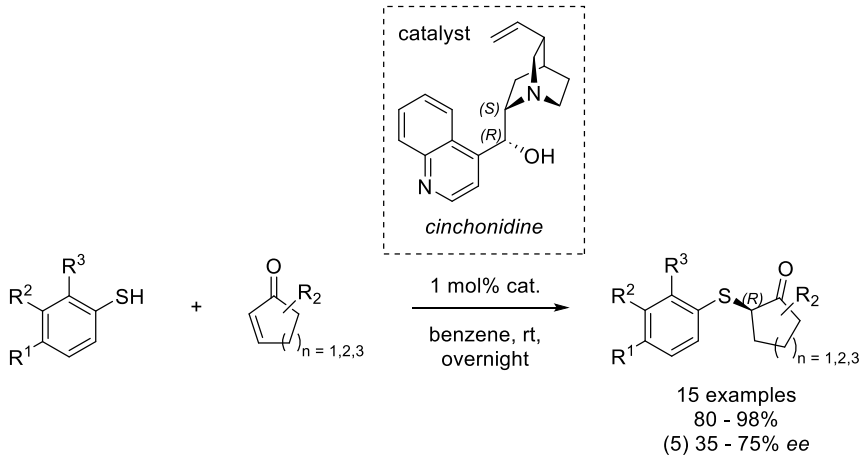
Scheme 41 First example of L-proline being applied as organocatalyst in the stereoselective synthesis of steroid precursors.[214,215]

The second industrial group of Eder, Wiechert and Sauer patented a similar procedure in 1971 applying L-proline and acid in a one-pot procedure under reflux for 20 hours (Scheme 42).[216,217] The reaction did yield good enantiomeric excesses, however, the organocatalyst was used in half-stoichiometric amount. The publication included the use of other chiral amino acids as organocatalysts, together with various solvents, acids and different temperatures. The authors further stated that the application of D-proline resulted in the formation of the (*R*)-enantiomer (75% yield, 67% *ee*).



Scheme 42 Early one-pot intramolecular cyclization/dehydration catalyzed by L-proline/perchloric acid.[216,217]

Similar approach of applying existing natural products as bifunctional organocatalysts in asymmetric reaction were published by Hiemstra and Wynberg in 1981, they used various *Cinchona* alkaloids (and two ephidrines) in the *thio*-Michael reaction (Scheme 43).[218] Best initial results could be achieved using cinchonidine producing (except one example) exclusively (*R*)-enantiomers. Yields were generally good to excellent and enantiomeric excess mediocre to good. Investigations on the influence of solvent and initial mechanistic considerations were conducted as well. Overall results were notable enough to pursue further scope and functionalization of the abundant natural compounds.



Scheme 43 First application of alkaloids as organocatalysts in the *thio*-Michael reaction.[218]

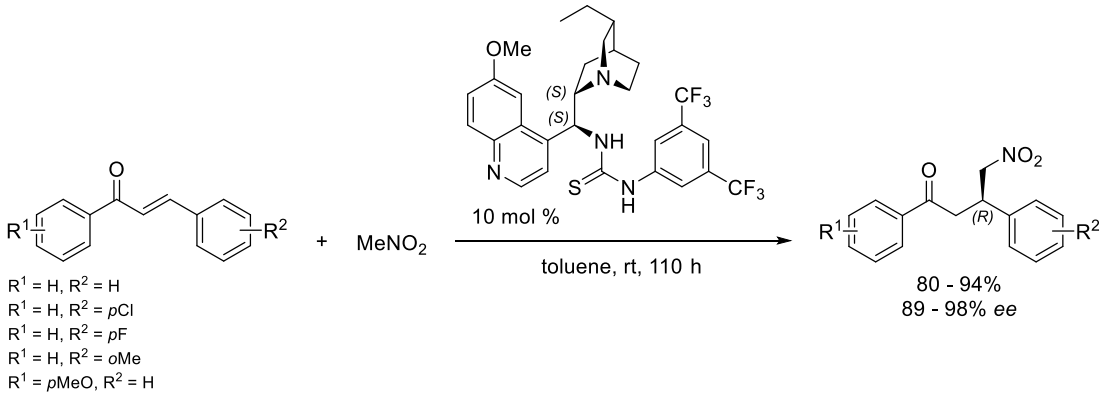
In spite of promising results organocatalysis remained a niche subject in organic chemistry until the beginning of the 21st century.[219] The interest in natural products rose, accompanied by intense testing and modification of newly found organocatalysts pushing forward the fast-rising field of stereochemistry. Previously investigated amino acids proved once again to be powerful molecules for asymmetric transformations like aldol reaction.[220] The development of organocatalysts changed fast from purely natural compounds to optimized natural compounds modifying one of the two functionalities of the bifunctional organocatalysts introducing and modulating reactivities and selectivities with *e.g.* urea or thiourea-hydrogen bond-donor moieties.[221] Good examples of those implementation are both, Cinchona alkaloids[222–225] and pyrrolidine;[226] the cyclic amine remained one functionality and an artificial group was generally added producing new potentially powerful organocatalysts. Development did, however, include all types of chiral backbones, such as carbohydrate,[227] DACH-based catalysts[228,229] or also compounds basing on axial chirality.[230]

Over the years various modes of catalysis were identified[231]: enamine catalysis, as previously shown with proline,[213,220,232,233] hydrogen-bonding catalysis,[234–236] iminium catalysis,[237] singly occupied molecular orbital-catalysis (SOMO)[238] and counterion catalysis.[239,240] The perhaps greatest breakthrough of organocatalysis was the development of generic modes of catalysis. Every of the previously mentioned catalytic modes can be used in a generic mode. As the name suggests they are able to activate not only very specific substrates, but many different substrates – directing and participating in many reactions with a multitude of compounds in a highly selective manner. Combination of functionalities in bifunctional catalysts adds another great modifiable feature.

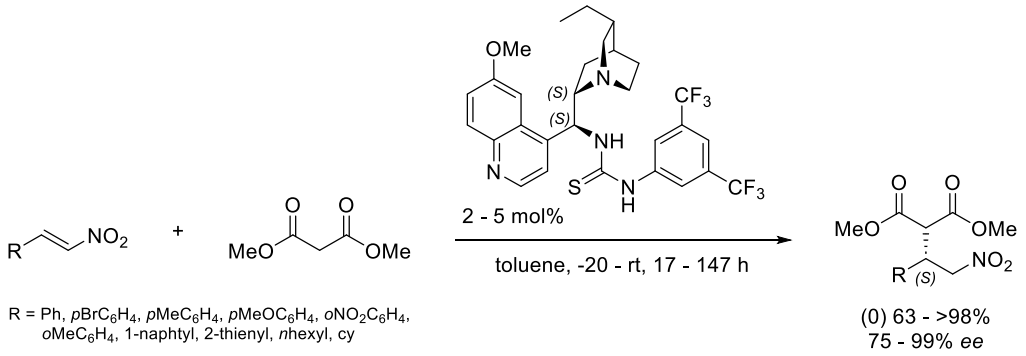
One of those features enjoying increased interest in the recent two decades are hydrogen bonding bifunctional thiourea catalysts.[17,221,241] Various renowned scientists developed a diversity of catalysts. Jacobsen's chiral Schiff's base organocatalyst for the highly enantioselective Strecker reaction[242] and Takemoto's organocatalyst for the asymmetric Michael and *aza*-Henry reaction[229] both are based on 1,2-DACH as chiral moiety.

In 2005 Soos, Connon and Doobson introduced Cinchona alkaloids as chiral backbone for the asymmetric induction in addition reactions. The hydroquinine derivative appeared to be the best *Cinchona*-thiourea catalyst, proven also in independent studies. The group of Soos applied the (8*S*,9*S*)-alkaloid in the addition reaction of nitromethane to various chalcones (Scheme 44).[225] The reaction proceeded with good to very good yields and enantiomeric excesses. The same excellent yields were

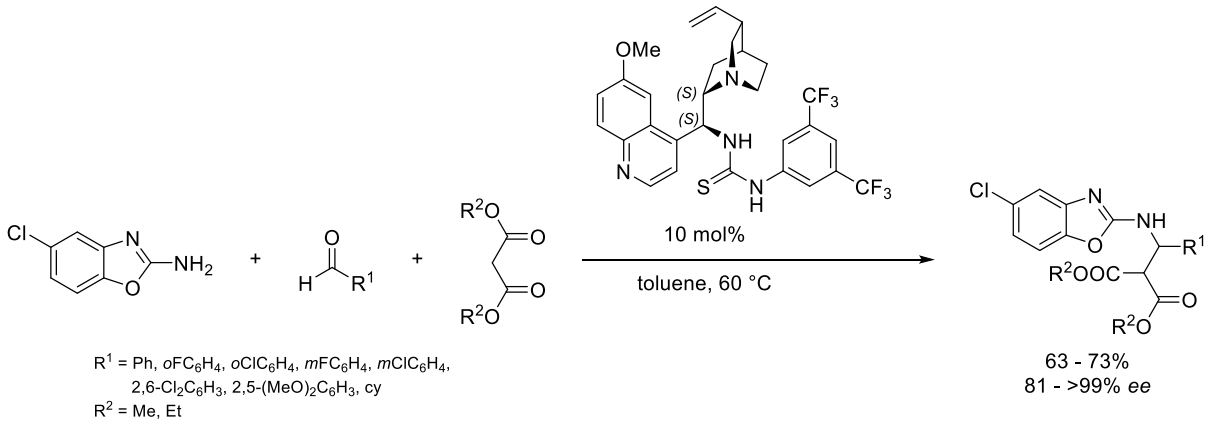
achieved in the somewhat similar Michael reaction of malonates and nitroolefines published by the group of Connon (Scheme 45).[243]. Both groups concluded that toluene was the best solvent for high stereoselectivity of the organocatalysts. Lower temperatures favored higher enantiomeric excesses. The reaction proceeded with such a success, that both number of citations and further application show the importance of the found catalysts. Quinine-based organocatalysts are widely applied, also in asymmetric multicomponent reactions, such as the Mannich reaction of benzoxazoles with aldehydes and dialkyl malonates proceeding with good yields and good to excellent enantiomeric excesses (Scheme 46).[244,245]



Scheme 44 Asymmetric addition of nitromethane to various chalcones catalyzed by a bifunctional Cinchona alkaloid organocatalyst.[225]

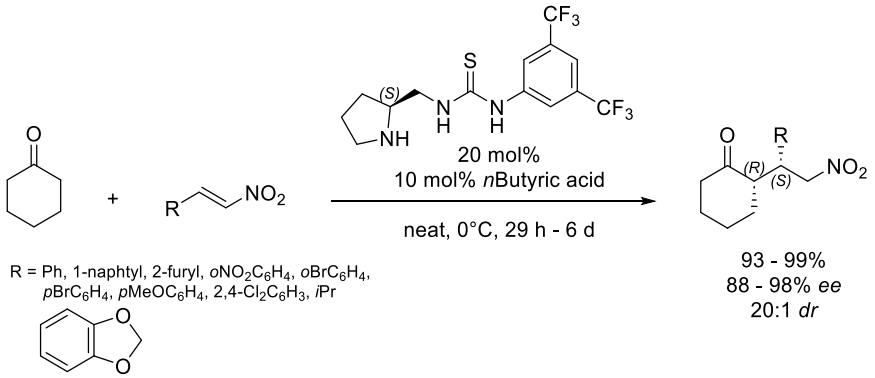


Scheme 45 Asymmetric Michael addition of dimethyl malonate to nitroolefines catalyzed by a Cinchona alkaloid organocatalyst.[243]



Scheme 46 Asymmetric multicomponent Mannich-type reaction catalyzed by a quinine thiourea organocatalyst.[244,245]

It is noticeable, that all presented thiourea organocatalysts bear a 3,5-triflouromethyl-substituted phenyl ring. The extremely electron withdrawing group is used to activate the thiourea moiety to produce more efficient hydrogen bonds.[221] The same thiourea-substituted phenyl moiety, together with a chiral pyrrolidine (L-proline derived) was an efficient bifunctional organocatalyst introduced by Tang and co-workers.[226] Together with acid additive the neat Michael reaction of cyclohexanone with various nitroolefins was efficiently catalyzed giving high to quantitative yields, always excellent diastereomeric ratios and very high to near perfect enantiomeric excesses. Both cyclic and bicyclic structures proved to be excellent chiral moieties for organocatalysts (Scheme 47).

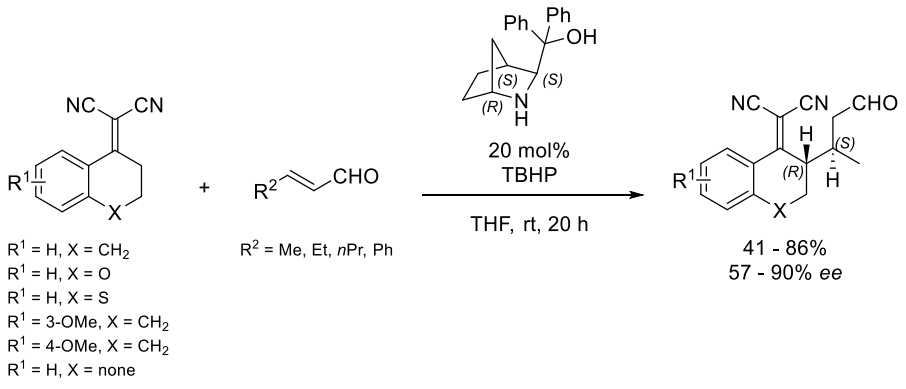


Scheme 47 Michael addition of cyclohexanone to nitrooolefins catalyzed by L-proline-derived bifunctional thiourea organocatalyst.[226]

2-Azabicylcoalkanes as organocatalysts

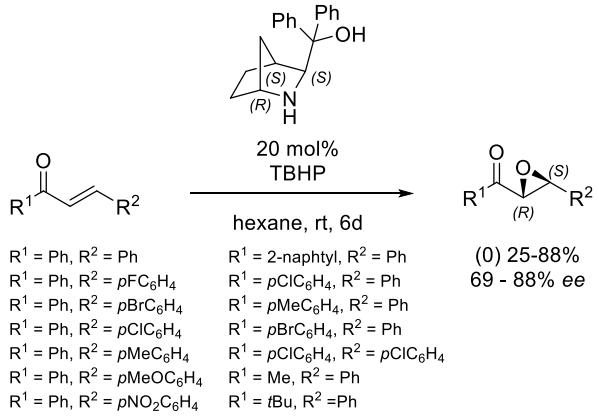
Although similarities with cinchona alkaloids and pyrrolidine-based organocatalysts are obvious, not many 2-azabicycloalkanes were applied as organocatalysts. The quantity of very good examples of ligands, however, indicate that a lot of potential lies within the rigid structural moiety.

The group of Loh applied bicyclic γ-amino alcohols for the catalysis of vinylogous Michael addition and epoxidation reaction. Similar ligands were previously applied in the addition of diethylzinc to aldehydes. Five new organocatalysts were applied in Michael additions with good yields and enantioselectivities (in some cases 99% *ee* after recrystallization, Scheme 48). Various conditions were tested including temperature, solvent and reaction time. The secondary amine moiety was crucial to enable the catalytic induction proceeding through an enamine activation. Experiments with a similar pyrrolidine catalyst indicated that the rigidity of the ring is essential in the chiral induction in the reaction.



Scheme 48 Asymmetric Michael addition catalyzed by bicyclic γ-amino alcohols.[246]

The optimal organocatalyst was used for the epoxidation of various α,β–unsaturated ketones (Scheme 49).[247] Good yields and good to very good enantiomeric excesses were achieved. Temperature did not affect the reaction; however, the prolonged time was necessary to achieve good yields, with consistent enantiomeric excesses.



Scheme 49 Organocatalytic epoxidation of α,β–unsaturated ketones catalyzed by a bicyclic amino alcohol.[247]

Eight years after the first use of the amino alcohol organocatalyst the group of Nakano came back to this class of organocatalysts. Application of already published compounds were accompanied by two novel catalysts in the enantioselective aldol reaction of indole-2,3-dione with cyclohexanone under acidic conditions (Figure 16).[248] Neither of the used organocatalysts produced high enantiomeric excess. The previously used catalyst (first one in Figure 16) was the best with 40:60 *syn:anti* ratio and 38 and 30% enantiomeric excess, respectively. Experiments with different substituted indole-2,3-diones did not yield better results.

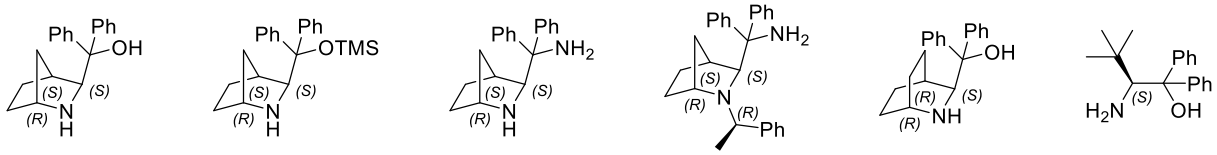
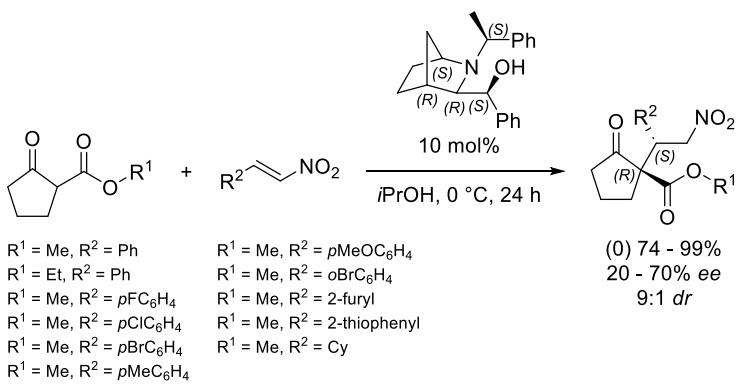


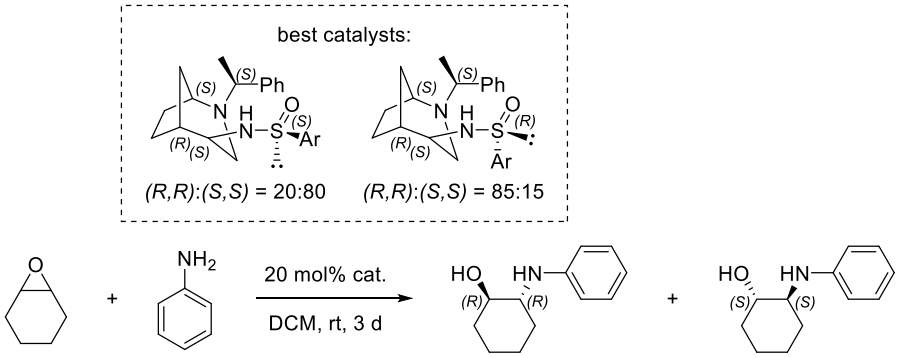
Figure 16 Various new bicyclic catalysts used in aldol reactions by Nakano *et al.*[248]

The same group applied a chiral 2-azanorbornane-based amino alcohol in asymmetric Michael reactions of various β-keto esters and nitroolefins (Scheme 50).[249] Good diastereomeric ratios around 9:1 were achieved, together with good to excellent yields and moderate chiral induction. Alongside various novel organocatalysts the reaction conditions were varied, including temperature and solvents, and the experimental studies were supported by DFT calculations.



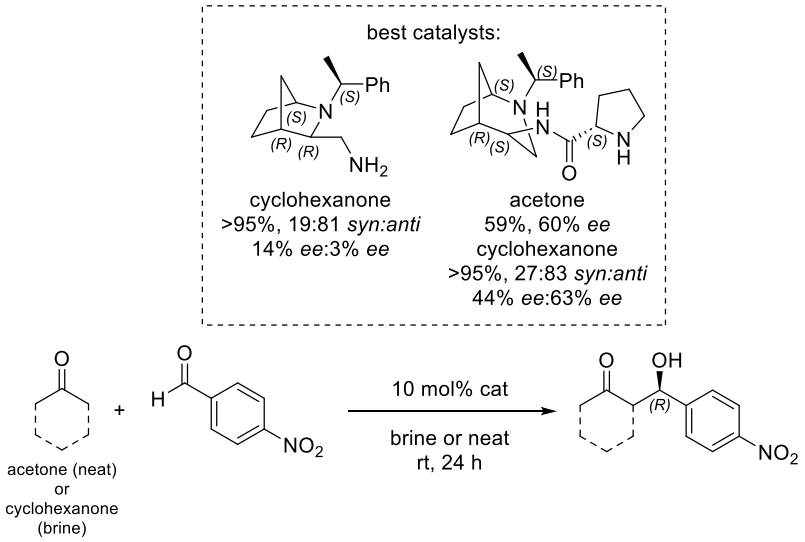
Scheme 50 Asymmetric Michael addition catalyzed by a chiral bicyclic amino alcohol.[249]

The group of Wojaczyńska, who previously worked on aspects of the stereoselective synthesis of 2-azabicycloalkanes and their applications as ligands enriched the scope by further organocatalysts and reaction types. An asymmetric epoxide ring opening was investigated, catalyzed by various non-racemic sulfinamides (Scheme 51).[250] The asymmetric reaction of cyclohexene oxide and aniline was successfully influenced by the organocatalysts with 4:1 and 6:1 diastereomeric ratios. Unfortunately, experimental data did not include yields nor conversion; crude reaction mixture was analyzed for the stereochemical determination. The application of quinine-derived sulfinamides was tested as a comparison to the more efficient 2-azabicyclo[3.2.1]octane-based ones. A clear origin of chiral induction can be found in the application of (*S*) and (*R*)-sulfur stereocenter yielding the opposing *trans*-products.



Scheme 51 Epoxide ring opening reaction, catalyzed by chiral sulfinamide organoocatalysts.[250]

Chiral diamines and amine-amide bifunctional organocatalysts were tested in the asymmetric aldol reaction by reacting acetone (neat) or cyclohexanone (in chloroform or brine) with *para*-benzaldehyde (Scheme 52).[251] Various catalysts were tested in the publication, and generally the results were better using brine as solvent. While diastereomeric induction was good, enantiomeric excess was mediocre.



Scheme 52 Asymmetric aldol reaction, catalyzed by various bifunctional bicyclic organocatalysts.[251]

2.3.4 Biological activity

Cyclic nitrogen structures are vastly employed as biologically active compounds (Figure 4 and Figure 5). The proline ring, tropane- or quinuclidine bicyclic system are proven to be important structures in pharmaceuticals.[10,13,252–254] Besides natural available aza-bicyclic structures the exchange of proline or

piperidine with the more rigid and intrinsically chiral 2-azanorbornanes proved to be a valid option.[255,256] 2-Azabicycloalkanes are themselves biologically active moieties which in cooperation with other functional groups become interesting for pharmaceutical applications.[42]

Early examples of bicyclic analogues were the analogues of meperidine and arecoline, in which the cyclic nitrogen-containing structure is exchanged by a bicyclic one (Figure 17). In case of the analgesic drug meperidine to the replacement with the more rigid system increased both activity and toxicity for the (5*R*)-diastereomer and did not change activity and toxicity of the (5*S*)-diastereomer.[255] The muscarinic agonist arecoline's bicyclic analogues were prepared in the group of Pombo-Villar and tested for their cholinergic properties, however, their activity was only traded with a better selectivity.[256]

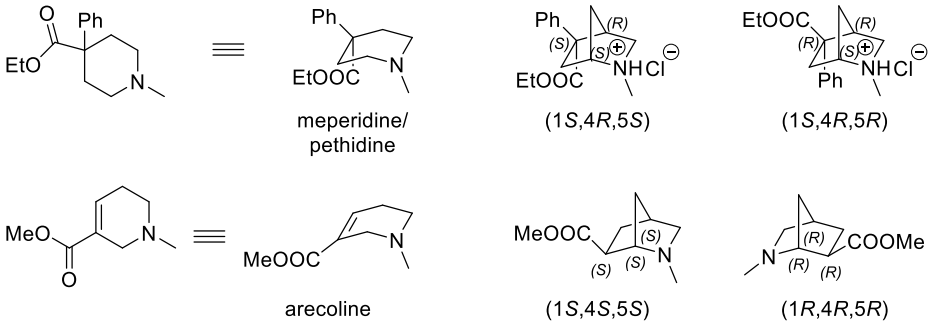


Figure 17 Biologically active bicyclic meperidine and arecoline analogues. [255,256]

More recent examples of the proline exchange are the synthesis and evaluation of L-proline-L-leucylglycinamide (PLG) analogue synthesis conducted in the group of Rodiguez-Borges (Figure 18).[97] In a straightforward synthesis enantiomerically pure peptidomimetics could be received and tested on their D_2 receptor binding activity. The same methodology of exchanging proline by 2-azanorbornane moieties was applied in vasopressin receptor antagonist,[257] Glypromate analogues with prolyl and pipecolyl surrogates,[258] KRAS inhibitor probings,[259] PAD-4 inhibitors[260,261] or Janus Kinase.[262]

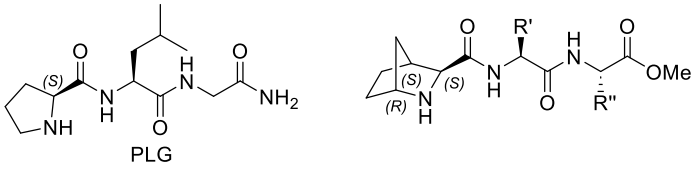


Figure 18 2-Azabicyclo alkane analogue of PLG.[97]

Dipeptidyl peptidase 4 (DDP-4) inhibitors were targeted by the groups of Schiöth and Trukhan. Promising results were found, with high selectivity for DPP-4. In particular, the structure-activity relationship of the bicyclic structures was investigated and compared with 2-substituted pyrrolidines (Figure 19).[263]

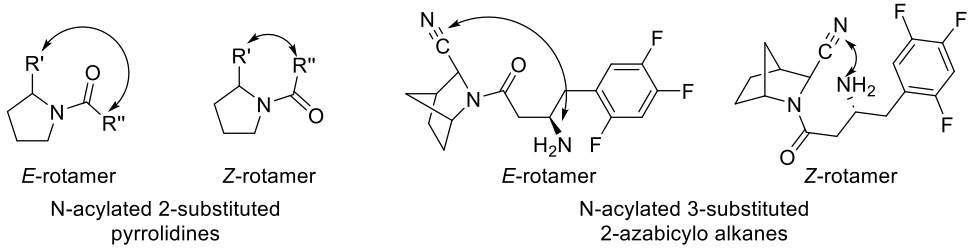


Figure 19 Pyrrolidine and 2-azabicycloalkane analogue rotamers as DPP-4 inhibitors.[263]

Among the biologically active compounds incorporating 2-azabicycloalkanes ledipasivir is the most prominent and most successful (Figure 20).[264] The hepatitis C (HCV) API which was developed as NS5A inhibitor was proven to be very efficient in the treatment. Many further developments on the implementation and probing to inhibit NS5A were conducted as well.[265–268]

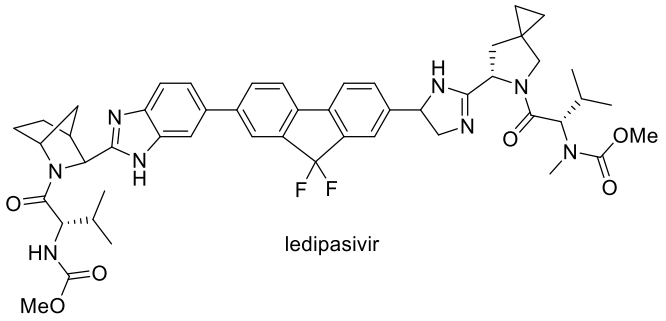


Figure 20 Ledipasavir.

Two other recently patented drug candidates including 2-azabicycloalkane moieties show the structural and applicational diversity (Figure 21). A menin-MLL inhibitor exhibits promising antileukemia activity,[269] whilst the bicyclic rigid 2-azabicycloalkane skeleton was used as a linker in the drug candidate to treat prophylaxis of neuroinflammation inhibiting MAGL.[270]

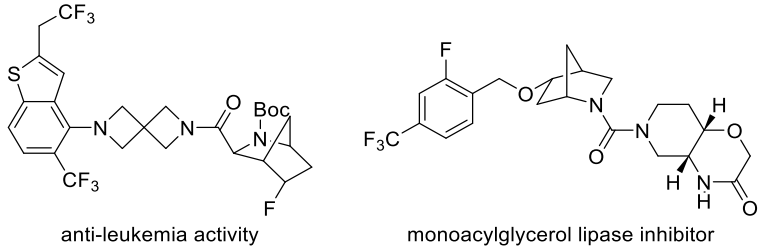


Figure 21 Recently patented drug candidates incorporating 2-azabicyclo[2.2.1]heptane moieties.[269,270]

The group of Wojaczyńska published several papers on various biological activities of small molecules, such as polyamines[271] and sulfonamides incorporating bicyclic nitrogen compounds.[272,273] The tested polyamines exhibited antiproliferative action, however, they were less efficient than *cis*-platin. The sulfonamides were tested also for their antiproliferative activities, which were found to be good. Selectivity indices (SI) were good with up to 3.1.[272] Various novel sulfonamides were tested later for their anticancer and their antiviral activities were good with an SI of up to 40.3. Interesting features of the studies included the use of 2-azabicyclo[2.2.1]heptanes and -[3.2.1]octanes. Biological activity surveys were generally only applying the former, *i.e.* 2-azanorbornane structure, and not the tropane ring analogue, whereas 2-azabicyclo[3.2.1]octanes remained vastly uninvestigated.

3 Scientific Work

The Thesis's goal was the development of novel routes towards variously applicable substrates for the synthesis of complex bicyclic molecular structures derived from 2-azabicyclo[2.2.1]heptanes and 2-azabicyclo[3.2.1]octanes, especially towards triazoles and thioureas (Figure 22). Both structural motifs have had a great impact in various fields, such as ligands, functionality in mono- and bifunctional organocatalysts, and in biological activity assays. This work is therefore focused on the synthesis of bicyclic compounds and later on their tests in the aforementioned applications.

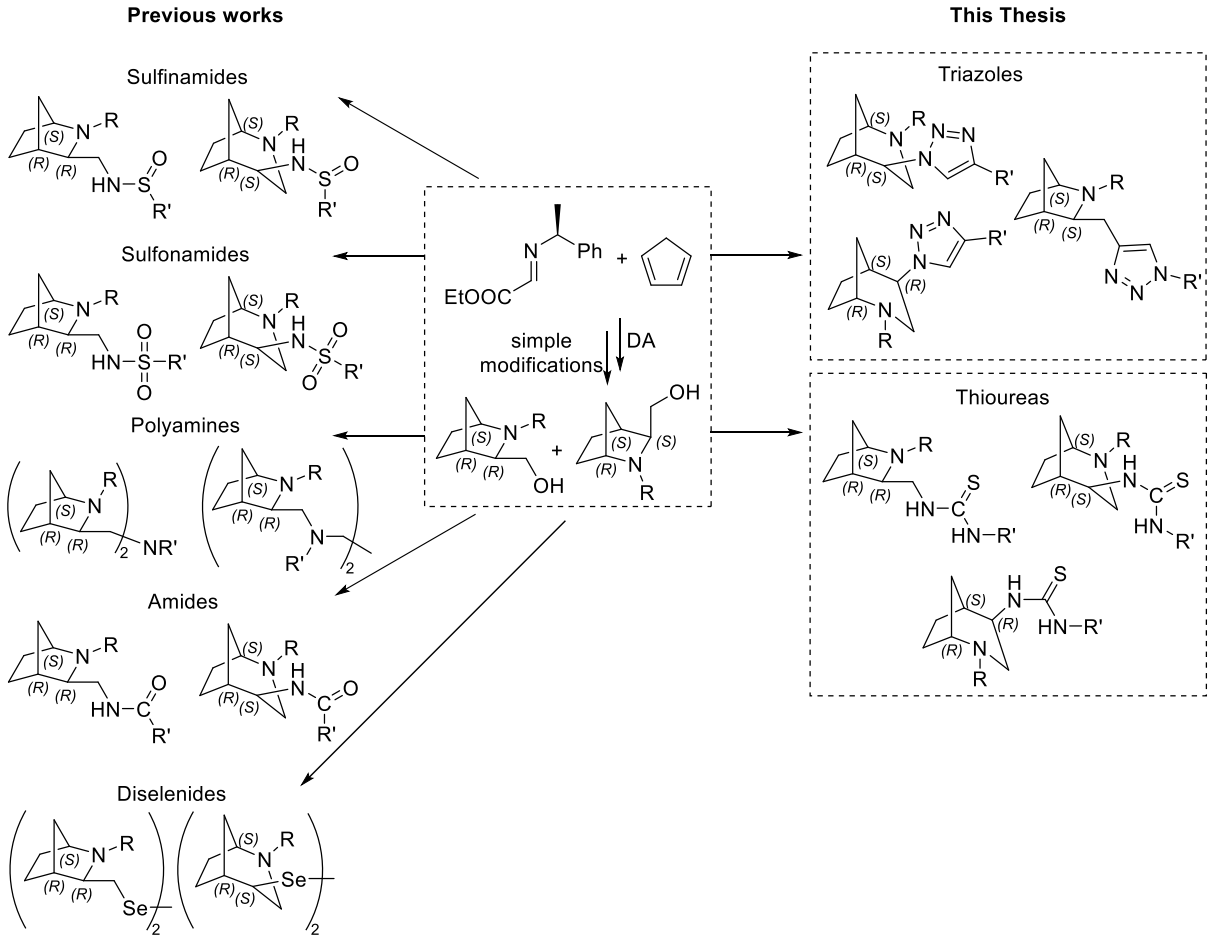


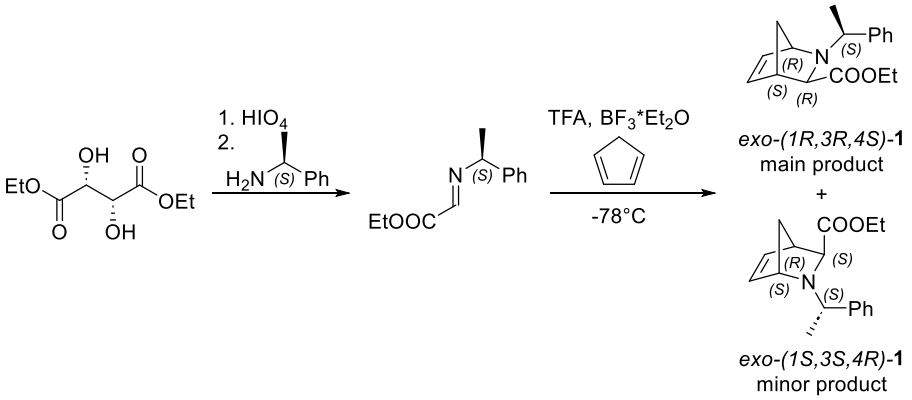
Figure 22 Previous work of the author's research group and his contributions.

3.1 Asymmetric synthesis of functionalized 2-azabicycloalkanes

3.1.1 Aza-Diels-Alder reaction towards 2-azabicyclo[2.2.1]heptanes

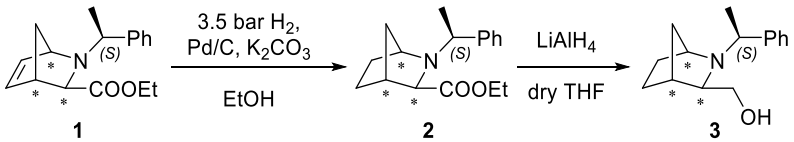
The synthesis and stereoselective installation of three stereocenters within the presented *aza*-DA reaction is a powerful methodology to yield 2-azabicycloalkane structures. Commercially available (+)-diethyl L-tartrate was oxidized using periodic acid in diethyl ether yielding two equivalents of ethyl glyoxylate, followed by a condensation reaction with chiral (*S*)-(−)-1-phenylethylamine forming the dienophile for the following *aza*-Diels-Alder reaction. The reaction was conducted using trifluoroacetic acid, the Lewis acid trifluoroborane and cyclopentadiene as diene, as previously discussed in detail (Section 2.2.3). The reaction was conducted in dichloromethane at -78°C to shift the reaction to the kinetically more stable *exo* products and *endo* is mostly avoided. Due to the application of the chiral auxiliary the products formed are the two possible *exo* diastereomers, the major product *exo*-

(1*R*,3*R*,4*S*)-**1** and the minor product of the reaction *exo*-(1*S*,3*S*,4*R*)-**1** (Scheme 53, more detail in Scheme 13).[69] As it is depictured in Figure 10, a set of four products is theoretically possible, whereas only two products are formed in any meaningful amount, which are pseudoenantiomerical to one another; the only common stereocenter is present in the chiral auxiliary. Often both diastereomers are used in the following parts, however generally (1*R*,3*R*,4*S*)-**1** was used to establish synthetic routes first and for optimization, while (1*S*,3*S*,4*R*)-**1** was used on a smaller scale, after trials being conducted.
Outgoing from an error in the 2015 review article on 2-azanorbornanes[42] initially the stereochemistry of the minor product was wrongfully assigned as *endo*-(1*R*,3*S*,4*S*)-2-azabicyclo[2.2.1]heptane (X-Ray structure and crystallographic data of *exo*-(1*S*,3*S*,4*R*)-2-azabicyclo[2.2.1]heptane **1** in the Appendix A.1). All structures in this thesis are corrected in aspect of that mistake.



Scheme 53 Aza-Diels-Alder reaction producing one set of pseudoenantiomers.[69]

To avoid the possible retro-Diels-Alder reaction, the double bond in **1** is reduced by hydrogenation. Generally, a high-pressure apparatus and a hydrogen generator is used, though the reaction also proceeds at atmospheric hydrogen pressure from a balloon under similar conditions. Palladium on carbon is applied as a catalyst together with potassium carbonate in dry ethanol and substrate **1** reacted with hydrogen at 3.5 bars (see Scheme 15).[93,94] The following ester **2** can then be efficiently transformed using lithium aluminum hydride into the corresponding alcohol **3**, which is a valuable precursor for many reactions (Scheme 54). Both diastereomers can be received by this protocol.



Scheme 54 Synthesis of bicyclic alcohols **3**.[69,93,94]

3.1.2 Towards the synthesis of triazoles

Biologically active compounds and catalysts or ligands are having some common characteristics, both interact through their functionalities with substrates, groups or pockets, either creating or filling gaps with their designed properties, *e.g.* bonding capabilities, electron density, etc. It is not surprising that catalysts might exhibit biological activities and biologically active compounds exhibit catalytic or ligation properties (Figure 23). Triazoles are great bioisosteres and peptidomimetics and this offers a broad space of application making them great targets and modified with various functionalities a broad chemical space/ many application may be tackled (Figure 24).[274–277]

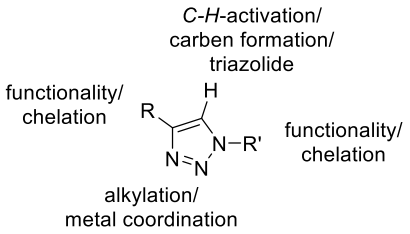


Figure 23 Various active sides and possible substitutions of 1,2,3-triazoles.[274–277]

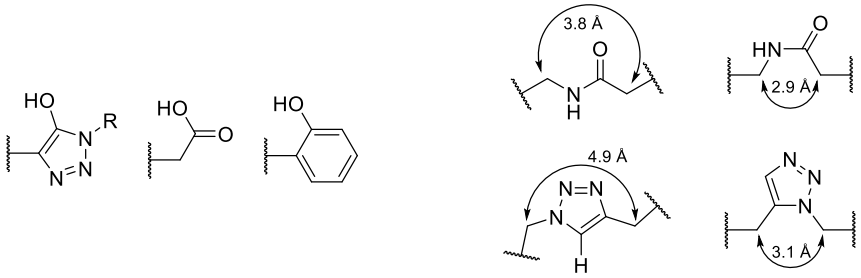
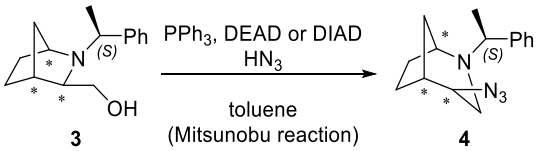


Figure 24 1,2,3-Triazoles as bioisosteres (left) and peptidomimetics (right). [274–277]

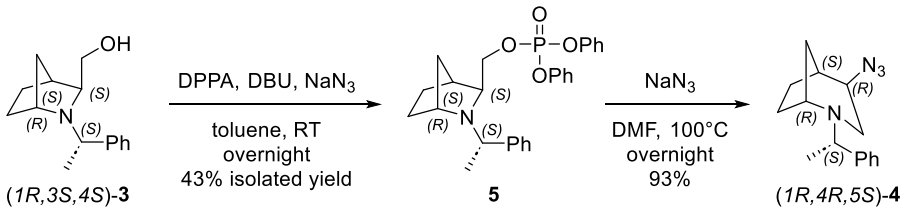
Synthesis of 4-azido-2-((S)-1-phenylethyl)-2-azabicyclo[3.2.1]octanes

Both diastereomers ((1*S*,4*S*,5*R*)-**4** and (1*R*,4*R*,5*S*)-**4**) can be synthesized in a one-step transformation in a Mitsunobu type of nucleophilic substitution from alcohols **3** (Scheme 55, mechanism in Scheme 17).[99,100,102] The reaction protocol includes the addition of triphenylphosphine, which together with an appropriate azodicarboxylate generates a phosphonium ion, which in turn binds with the alcohol activating it as a leaving group. Through an aziridinium intermediate, the ring expanded products, *i.e.* both diasteromers **4** can be received.[102] Proof of the ring expanded structure of both diastereomers **4** and the correctness of configuration assignment of its stereocenters may be found in the X-ray structure of their triazole derivatives shown in the appendix A.1.



Scheme 55 Mitsunobu reaction to synthesize bicyclic azides proceeding with ring expansion.[100,102]

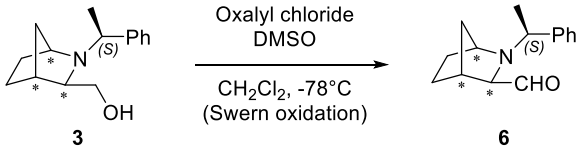
Another methodology of synthesizing bicyclic azides is the use of DBU together with DPPA as source of azide. Published for the transformation of (1*S,*3*R*,4*R*)-**3** to (1*S,*4*S*,5*R*)-**4** the same conditions, with the exception of addition of two equivalent sodium azide, were applied for the transformation of (1*R,*3*S*,4*S*)-**3** at room temperature (Scheme 56).[102] However, the reaction did not proceed, but stopped at the phosphoryl stage, as proven by MS- and NMR-analyses. The intermediate was stable enough to be efficiently purified by flash column chromatography and could then be transformed into the corresponding ring-expended (1*R,*4*R*,5*S*)-**4** by reacting it with sodium azide in DMF at 100°C. The literature procedure of the standard reaction with DPPA and DBU includes the transformation at 100°C.[278] Generally, azidations were conducted with the Mitsunobu protocol, however, applies the very toxic hydrazoic acid as source of azide; the reaction with DPPA and DBU yields similar results with significantly less harmful reactants.



Scheme 56 Azide synthesis using DBU and DPPA with isolatable diphenyl phosphate.

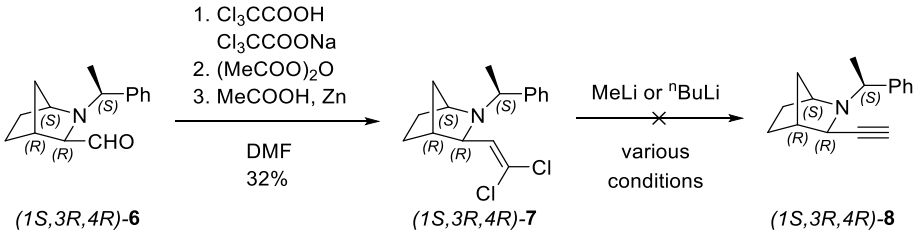
Synthesis of 3-ethynyl-2-((S)-1-phenylethyl)-2-azabicyclo[2.2.1]heptanes

Whilst the synthesis of bicyclic azides **4** is known, the bicyclic terminal alkyne, which could be also applied in the preparation of the corresponding triazoles, remained to be synthesized. For this purpose, two approaches which included C-C-bond formation were chosen: a non-Wittig approach including a vinyl dichloride-intermediate[279,280] and a Wittig-type reaction procedure forming a vinyl dibromide-intermediate.[280–283] Both reactions start from aldehydes known in literature.[200,208,284] To synthesize them, Swern oxidation was chosen as a good stereoretentive methodology. The chiral pure alcohols **3** were reacted with oxalyl chloride and DMSO in dichloromethane at -78°C (Scheme 57).[203,208,285] Both, (1*S*,3R,4*R*)-**6** and (1*R*,3*S*,4*S*)-**6**, diastereomers could be received in proper amounts for further transformations.



Scheme 57 Swern oxidation of bicyclic alcohols 3 to bicyclic aldehydes **6.**[203,208,284,285]

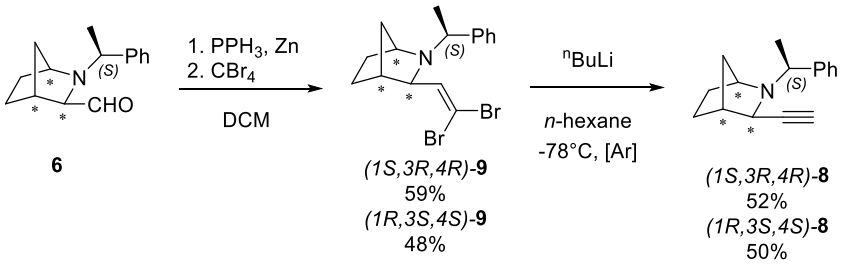
A first attempt to receive terminal alkynes was undertaken with the more abundant aldehyde (1*S*,3R,4*R*)-**6** (Scheme 58). The reaction sequence included trichloromethyl anions generated by decarboxylation, forming trichloromethyl carbinols.[286] Addition of acetic anhydride acetylated the alcohol intermediate, which then in turn was converted into vinyl dichloride (1*S*,3*R*,4*R*)-**7**. Several attempts to reduce the dichlorovinyl compound to the alkyne **8** were unsuccessful; various conditions and reducing agents were tried but mostly unreacted substrate **7** was recovered in each case.



Scheme 58 Non-Wittig-type reaction approach to bicyclic terminal alkynes **8** using a vinyl dichloride intermediate. [279,280]

To overcome the issue of lack of desired reactivity of (1*S*,3*R*,4*R*)-**7**, another attempt was made on the same aldehyde (1*S*,3R,4*R*)-**6.** The Corey-Fuchs reaction sequence was applied, successful as a one-pot methodology earlier applied by Abbott Laboratories on *N*-Boc protected bicyclic analogues.[281,283] In the first reaction step a triphenylphosphine-dibromomethylene ylide species was formed which was then converted in a Wittig reaction to the dibromovinyl derivative (1*S*,3*R*,4*R*)-**9**. The vinyl species was in turn easily reduced by *n*-BuLi in hexane at -78°C yielding pure (1*S*,3*R*,4*R*)-**8**. Attempts with the

diastereomeric aldehyde (1*R*,3*S*,4*S*)-**6** were equally successful in receiving the terminal alkyne (Scheme 59).

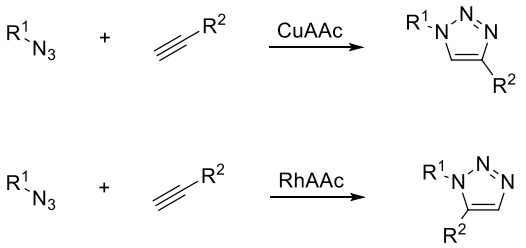


Scheme 59 Corey-Fuchs reaction for the synthesis of bicyclic terminal alkynes **8** using a vinyl dibromide intermediate.[280–283]

Although the Corey-Fuchs reaction sequence is the better-known procedure of the synthesis of terminal alkynes from aldehydes at first the non-Wittig type of reaction was applied. The key idea was to use less sterically hindered substrates and the excellent reported yields on cyclic saturated compounds, which are often used as models for transformation of bridged bicyclic compounds. Compounds **8** and **9** were easily accessible and differ only by their halogens. The dibromovinyl compounds **9** are reduced more easily as bromide is a better leaving group compared with chloride and the dichlorovinyl compound **7**. This becomes especially apparent considering the various attempts of eliminating dichloroalkene **7**, even doubling the reactive lithium species. Besides the obvious non-reactivity of the vinyl compound with the used methyl lithium and *n*-butyl lithium, an important reason of the failing reaction can be excluded: a wrong molarity of the used lithium compound, which was not titrated prior usage. The successful reaction of dibromoalkenes **9**, together with the complete lack of starting product in the crude reaction mixture proofs a sufficient quality of the used chemicals.

Synthesis of 1,2,3-triazoles

The synthesis of 1,2,3-triazoles is relatively easy and well researched. Two regioselective main routes are known and used predominantly, the copper(I)-catalyzed azide alkyne cycloaddition – CuAAc, producing 1,4-substituted 1,2,3-triazoles, and the ruthenium(I)-catalyzed version, RuAAC, yielding a 1,5-substituted product (Scheme 60). Both mechanisms are examples of so-called “click”-reaction.

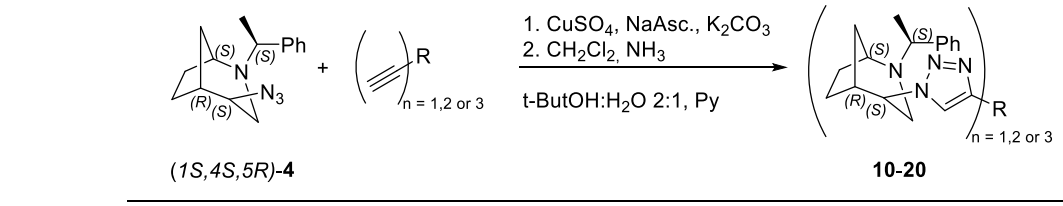


Scheme 60 General schemes of CuAAc and RhAAc reactions.[277]

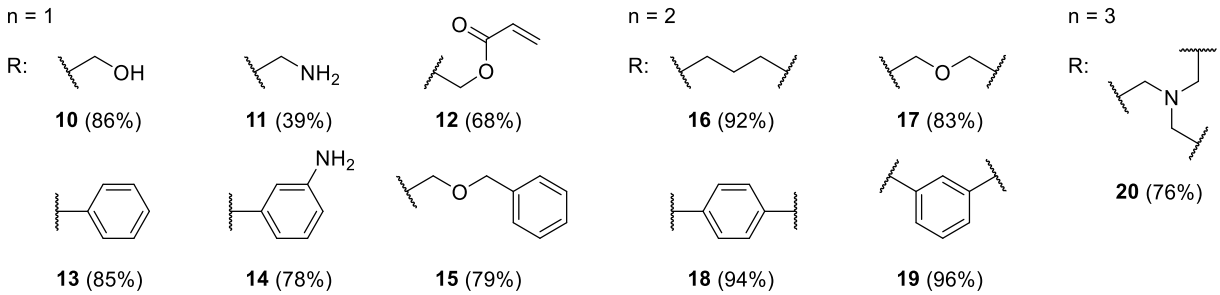
Both azides **4** and alkynes **8** were used together with commercial and non-commercial complementary reactants to synthesize a vast set of different triazoles. Most of the synthesized triazoles are, however, based on azides **4** and only a few compounds containing (1*S*,3*R*,4*R*)-**8** were synthesized as a proof of concept.

For the synthesis both optically pure azides (1*S,*4*S*,5*R*)-**4** or (1*R,*4*R*,5*S*)-**4** were used. They were reacted with commercially available alkynes, which were either mono-, di- or in one case trimeric offering the introduction of C_2 and C_3 symmetries in triazoles **10**-**30** (Scheme 61 and Scheme 62).[280,287–289]

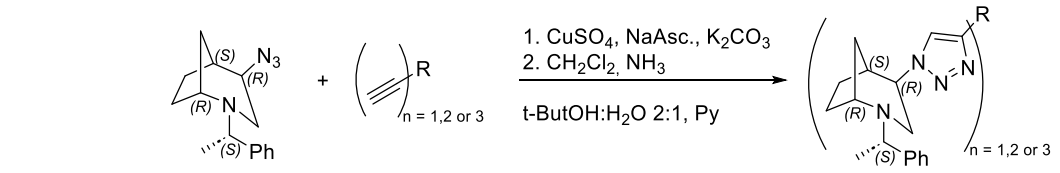
Copper(II)sulfate was reduced *in situ* to the reactive Cu(I) species by sodium ascorbate. After the reaction the remaining copper was removed from the reaction mixture by the addition of sodium sulfide solution. The highly insoluble copper(II)sulfide is precipitated and can be filtered off easily. Purifications were usually conducted by column chromatography on silica with various ratio of dichloromethane to methanol. However, a bigger scale reaction showed that recrystallization from methanol is also a potent method in some cases; still, column chromatography of the remaining reaction mixture was necessary to increase the overall yield. It must be pointed out that the click reactions proceeded with such a good conversion, that only one product was received in each case; complex mixtures with various singly or doubly reacted starting materials (used for C_2- and C_3-symmetrical triazoles) were not isolated.



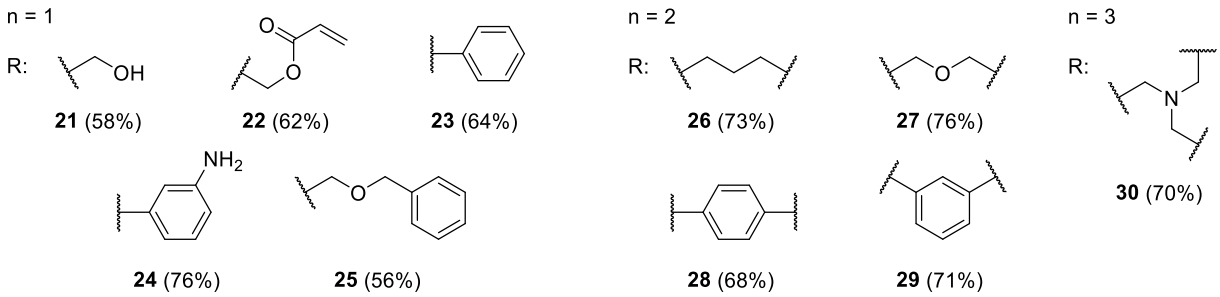
(*1S,4S,5R*)-**4** **10-20**



Scheme 61 Synthesis and overview of C_1-, C_2- and C_3-symmetrical triazole-(1*S*,4*S*,5*R*) 2-azabicyclo[3.2.1]octenes **10**-**20**.[287–289]



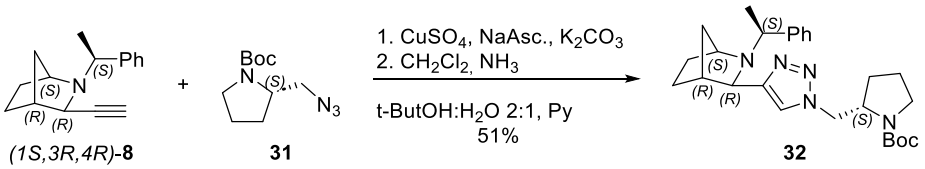
(*1R,4R,5S*)-**4** **21-30**



Scheme 62 Synthesis and overview of C_1-, C_2- and C_3-symmetrical triazole-(1*R*,4*R*,5*S*) 2-azabicyclo[3.2.1]octenes **21**-**30**.[287–289]

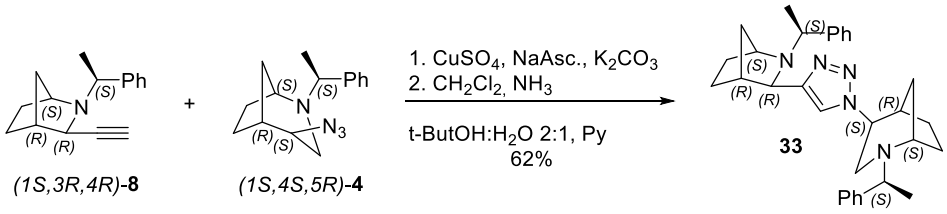
With bicyclic alkyne (1*S*,3*R*,4*R*)-**8** in hand, it was applied in two click reactions.[280] The first reaction included alkyne and an *N*-Boc-protected pyrrolidine azide **21**, easily accessible by standard Mitsunobu reaction from *N*-Boc-L-prolinol (Scheme 63). Similarly, the reaction in Scheme 64 proceeded

incorporating two bicyclic moieties in the final product, 2-azabicyclo[2.2.1]heptane and 2-azabicyclo-[3.2.1.]octane, by applying both bicyclic components, alkyne **8** and azide (1*S*,4*S*,5*R*)-**4**.



(1S,3R,4R)-**8** **31** **32**

Scheme 63 CuAAC reaction of bicyclic alkyne with a cyclic nitrogen-containing azide.[280]



(1S,3R,4R)-**8** *(1S,4S,5R)*-**4** **33**

Scheme 64 CuAAc reaction of bicyclic alkyne and bicyclic azide.[280]

Further analysis of the structure of **32** was conducted.[280] The Boc protecting group directs the compound to form conformers, of which two rotamers are the main distinctive ones (see ^{1}H- and ^{13}C-NMR spectra). A single crystal of **32** was investigated using X-ray diffraction and the obtained structure can be seen in Figure 25; the crystallographic data can be found in the appendix A.1. The R factor was, however, 24.3% which might be explained by a poor quality of the received single crystal. It led to further investigations including chiroptical methods supported by quantum chemical simulations conducted by Dr. Marcin Górecki, whose results are published along others[280] and will be paraphrased to some extent in the upcoming paragraph.

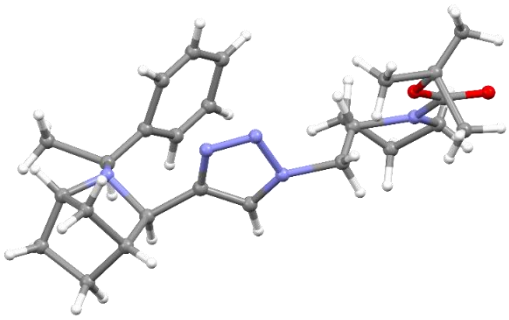


Figure 25 X-ray structure of **32**.[280]

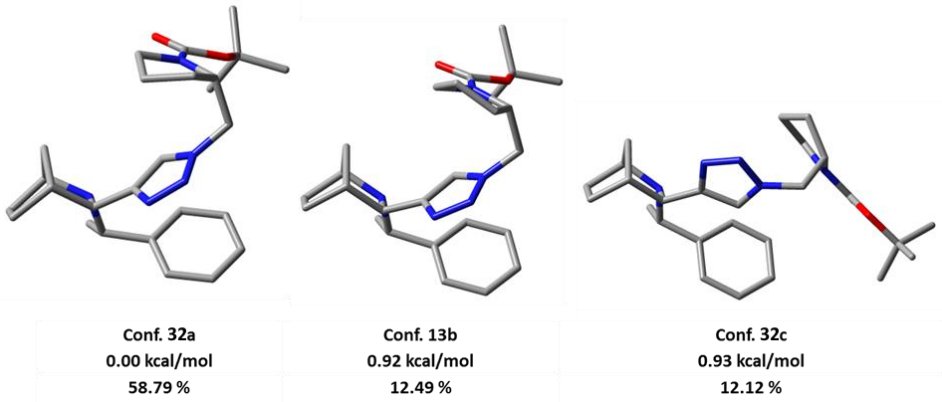


Figure 26 Three most populated conformers of **32** calculated by DFT method using wB97X-D/6-311+G(d,p) basis set.[280]

DFT analyses led to six conformers of **32** within the range of 1.5 kcal/mol, whereas the three most abundant (highest population in %) can be found in Figure 26. Only small differences in the pyrrolidine ring can be seen between conformer **32a** and **32b**, whereas **32c** is obviously different.

A good methodology to determine absolute configurations is carrying out quantum chemical calculation supported experimental studies such as ECD-, UV-spectroscopy and optical rotation studies.[290–296] ECD- and UV spectra of compound **32** at room temperature were measured together with its calculated TD-DFT simulations performed at the CAM-B3LYP/def2-TZVP level of theory basing on the previously calculated and optimized six conformers (Figure 27).

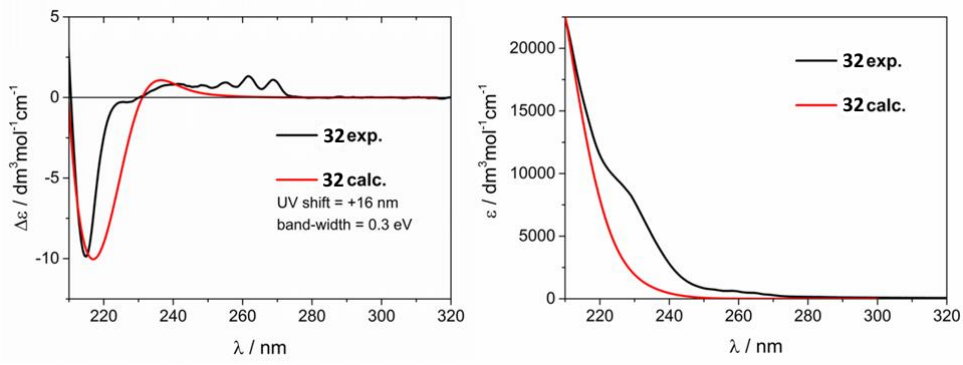
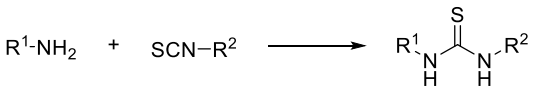


Figure 27 Comparison of experimental ECD (left) and UV (right) spectra with calculated ones.[280]

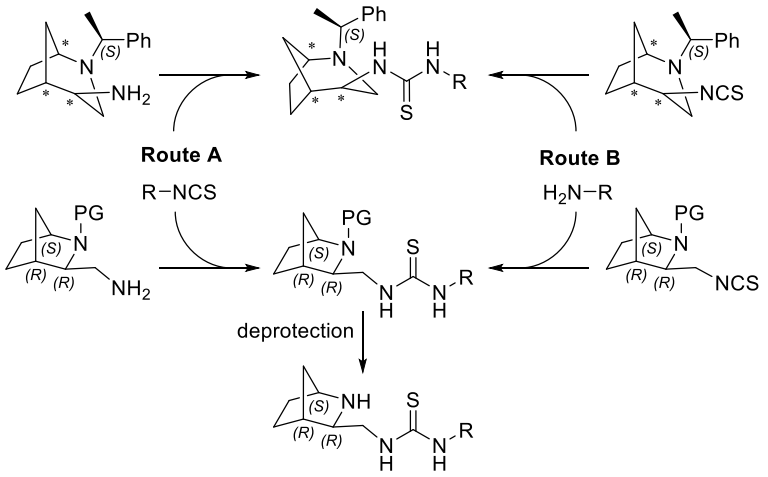
Another independent confirmation of the equilibrium between the six most abundant conformers is the quantum chemical calculation of optical rotation. Particularly for rotamers it is a good methodology to further support the absolute configuration.[296–298] Various different sets were used for the calculation and can be found in the paper, together with deeper insight in the quantum chemical calculations. Altogether, experimental and theoretical analysis led to the absolute configuration and unambiguous assignment of **32**.

3.1.3 Towards the synthesis of thioureas

A lot of different thiourea organocatalysts have been already prepared (Section 2.3.3). Most of them incorporate three units: two functionalities, a hydrogen bonding thiourea moiety together with a second reversible binding or coordinating moiety are connected over the third chiral unit – the backbone. Depending on the configuration of the second binding/coordinating moiety various catalytic states and substrate scopes may be tackled. In the approach described in this dissertation the thiourea unit is connected over a chiral bicyclic backbone with a secondary or tertiary amine offering possibilities of chiral base or enamine catalytic activations. The structures may be achieved by reacting bicyclic amines or isothiocyanates in condensation reactions with their complementary partner, isothiocyanate or amine, respectively (Scheme 65 and Scheme 66).[221]



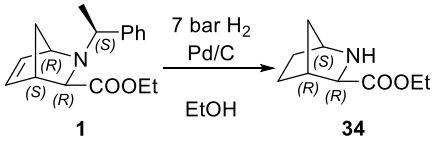
Scheme 65 Condensation of amines and isothiocyanates yielding thioureas.[221]



Scheme 66 Conceptual idea of introducing bicyclic moiety in thioureas together with secondary and tertiary amine functionality.

Synthesis of 2-azabicyclo[2.2.1]heptane thioureas

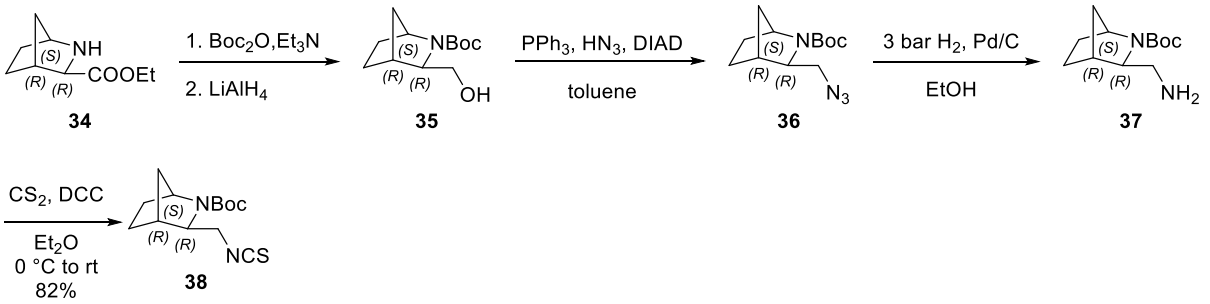
As Andersson's group extensively described, the change in conditions during hydrogenation reactions has a great impact on the reaction outcome (Scheme 15).[95,138] Omitting the addition of potassium carbonate and the increase of hydrogen pressure, as well as duration of the reaction (in opposite to the reduction in Scheme 54) leads to **34** (Scheme 67). The reaction has two purposes: reduction of the double bond, and therefore prohibition of the retro-DA reaction and the removal of the methyl benzyl chiral auxiliary in quantitative yields.



Scheme 67 Reduction of double bond and hydrogenative removal of methyl benzyl group.[95,138]

Upon protection of the secondary nitrogen with the electron withdrawing *tert*-butyloxycarbonyl (BOC) protecting group the conversions towards enantiopure 2-azabicyclo[2.2.1]heptane amines and isothiocyanates were conducted in general as before for 2-azabicyclo[3.2.1]octanes (Scheme 68).[97,98,299] Reduction of *N*-Boc protected ester by $LiAlH_4$ yielded the alcohol **35**.[93,103] Opposing to the reduction to alcohol **3** (Scheme 54) the alcohol is not dropped into a solution of $LiAlH_4$ in THF, but a cooled solution of $LiAlH_4$ (~1 M) is added dropwise to a stirred solution of **intermediate-35**. Additionally, the reaction time was reduced to only 3 hours to omit side reactions. The following Mitsunobu type S_N2 reaction yielded, as described earlier (Scheme 18), 2-azabicyclo[2.2.1]heptane product **36**. This is due to the electron withdrawing character of the protection group, which prevents the formation of the aziridinium ion-intermediate as Gore[99] and Wojaczyńska described.[100,102] Subsequently, there are two possibilities to reduce the azide to amine functionality yielding **37**, as for the bridged azepanes **4**. Either reflux in methanol with triphenylphosphine or hydrogenation can be performed. The latter methodology yields a crude product, which often may be used without any further purification.[95,97,98,103,300,301] Reaction of **37** with an excess of carbon disulfide and equimolar DCC yields 2-azabicyclo[2.2.1]heptane isothiocyanate **38** in good yields after fast and simple purification.[302] Compounds **35-37**, as well as their enantiomers, are known in literature.[103] Generally, a mixture of two rotamers is observed in solution, which originates from the hindrance of rotation around the nitrogen-

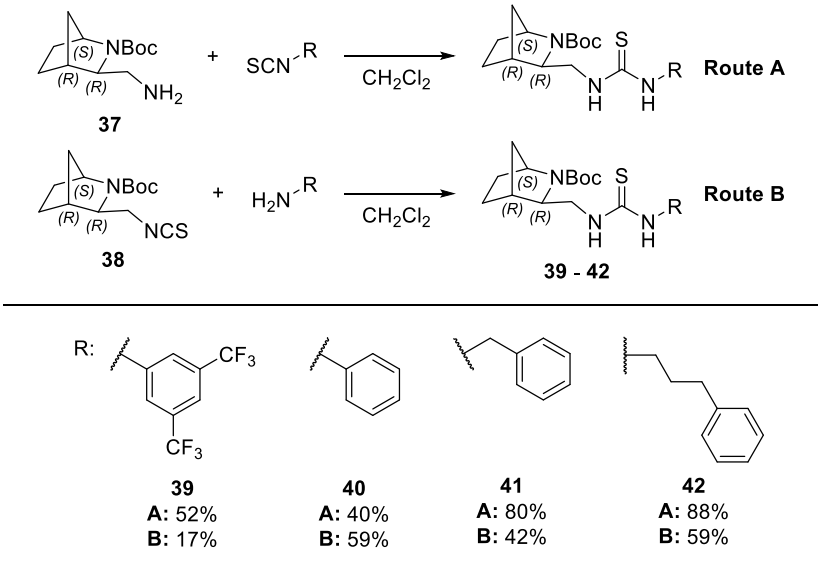
carbon bond of *N*-Boc due to the protection group. Whilst ^{1}H-NMR spectra generally become harder to interpret due to splitting and overlap of signals, ^{13}C-NMR spectra and two-dimensional spectra usually resolve such issues.



Scheme 68 Synthesis of 2-azabicyclo[2.2.1]heptane amines and isothiocyanates.[95,97,98,103,283,300–303]

As shown in Scheme 66, the bicyclic moiety may be introduced during the condensation of amine and isothiocyanate towards thiourea as a part of both reaction partners. Amine **37** was reacted with a couple of isothiocyanates, which are either commercially available or were synthesized similarly to the bicyclic isothiocyanate **38** by reacting commercially available amines with an excess of carbon disulfide and equimolar amounts of DCC.[302]

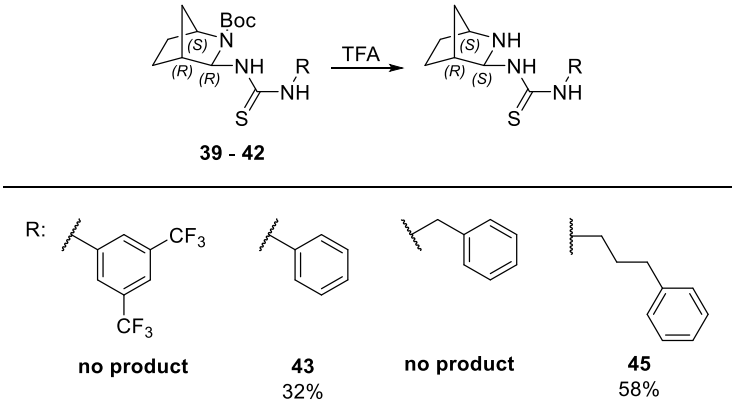
The condensation conditions yielding thioureas are relatively simple and mild, besides the use of argon flushed round bottom flasks and dry dichloromethane or chloroform no precautions were taken. The reaction partners were generally used in equimolar amounts, however, a small increase (up to 1.2 equiv.) of less valuable reaction partner improved the yields. A set of four thioureas **39**–**42** was synthesized, applying various groups, with the focus on the incorporation of thiourea activating groups, as well as different linker lengths to the aromatic unit (Scheme 69). Both routes were used, to compare their reactivities for further bigger batch reactions. Yields were generally good to very good and generally higher in **Route A**, applying a bicyclic amine. Especially **39**, synthesized by **Route B** is only produced in 17% yield. Due to the electron withdrawing character of the trifluoromethyl groups on the aromatic unit, which deactivate the amine. Besides higher yields, achieved by **Route A** the total step count of the synthesis of the organocatalysts is lower making this approach more favorable (amine **37**



Scheme 69 Synthesis of 2-azabicyclo[2.2.1]heptane thioureas.

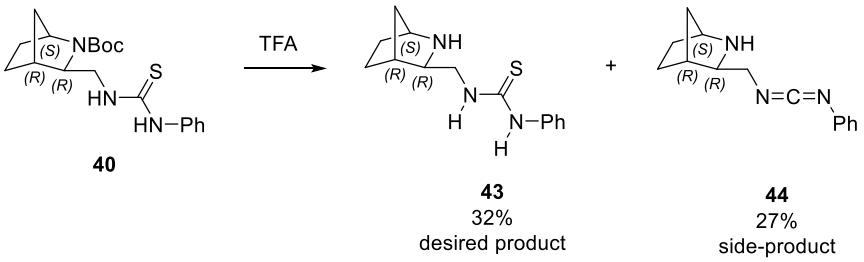
may be used and is not transformed to **38**). The easier the synthesis of the catalysts, the better they can be received by the community of chemists.

To receive the final pyrrolidine-based analogues the Boc protection must be removed, which usually is achieved by treatment with trifluoroacetic acid (Scheme 70). Standard conditions, 3 mL of an 1:1 mixture of trifluoroacetic acid per 1.2 mmol of *N*-Boc protection, were applied and the reaction was monitored by TLC, followed by rendering the reaction mixture basic by aqueous ammonia solution. Only two desired products could be received, **43** and **45**, however, all reaction mixtures developed a distinctive smell of some sulfur containing compounds.



Scheme 70 Deprotection attempts of **39** - **42**.

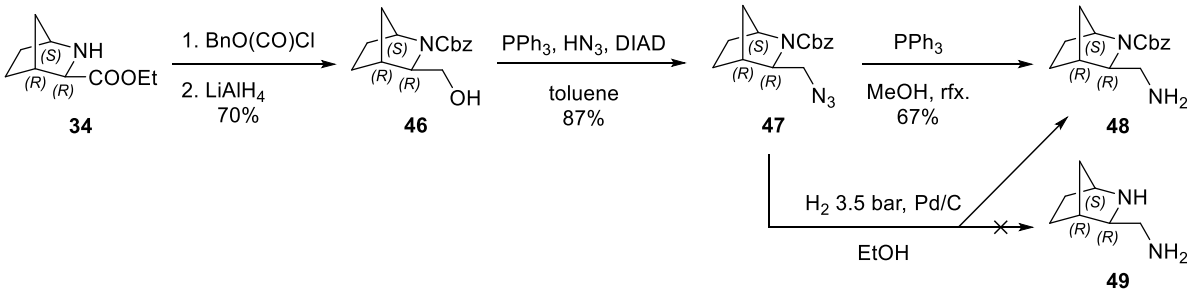
During the purification of **43**, a side product (**44**) could be isolated in comparably high yields (Scheme 71). The carbodiimide was identified by NMR spectra analysis and high-resolution mass spectrometry, proving unambiguously the structure of this compound. Precedents can be found in the literature of 1,3-substituted thioureas converted into carbodiimides by base or acid catalysis. As a side-product in a set of reactions carbonyl sulfide is received, which might be the explanation for the distinctive smell.[304–306] Another possibility is the acid catalyzed formation of hydrogen sulfide which is applied in pharmacotherapy studies.[307,308] Both side-products are known for their distinctive pervasive smell.



Scheme 71 Deprotection of **40** yielding **43** and a side-product **44**.

Another approach towards secondary amine-thiourea bifunctional catalysts based on 2-azabicyclo[2.2.1]heptanes applied benzyl carbamate (Cbz) as protecting group (Scheme 72). Upon reaction of bicyclic secondary amine **34** with benzyl chloroformate[309] the protected ester is reduced similarly to *N*-Boc bicyclic intermediate during the synthesis of **46** by dropping a solution of dissolved lithium aluminium hydride in the ester solution.[93] Mitsunobu reaction yielded **47** without ring expansion due to the electron withdrawing effect of the Cbz protecting group. The following reduction may be afforded with triphenylphosphine with good yields.[100,102,103,300,301] Various different conditions were applied to remove the protecting group, which is normally readily cleft under hydrogenation

conditions, but due to faster hydrogenation of the azide the palladium catalyst is mildly poisoned by the formed amine. The deprotection is prohibited leading not to **49**, but to **48** instead. Reaction of **48** with isothiocyanates gave the expected thioureas, which are, however, of no greater interest and therefore will not be described. They could not be reduced due to the non-reversible poisoning of the palladium catalyst by sulfur.

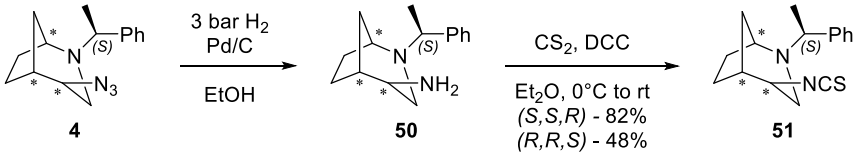


Scheme 72 Synthesis of N-Cbz protected amine.[93,100,102,103,300,301,309]

Synthesis of 2-azabicyclo[3.2.1]octane thioureas

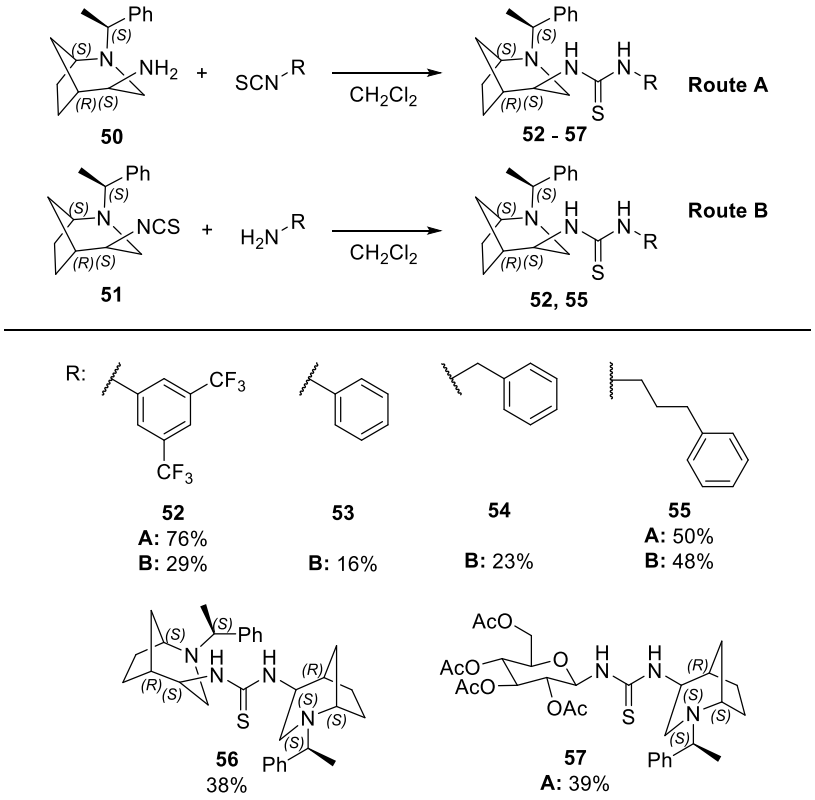
From the chiral pure azides **4** both pseudoenantiomers, amines (1*S*,4*S*,5*R*)-**50** and (1*R*,4*R*,5*S*)-**50** can be obtained. To yield the amines **50** two protocols, reduction by triphenylphosphine[102] and palladium-catalyzed hydrogenation were applied, however, the latter proved to be a more convenient protocol giving often quantitative yields without further purification necessary.

For the synthesis of isothiocyanates various synthetical methodologies are available. Reacting amines **50** with carbon disulfide and equimolar amounts of DCC in diethyl ether was the chosen method, again.[302] By-product dicyclohexyl thiourea is easily filtered off and product isothiocyanates **51** can be achieved after purification in good to very good yields (Scheme 73). It might be worth considering reacting the known 4-chloro-2-((S)-1-phenylethyl)-2-azabicyclo[3.2.1]octane[310] with potassium isothiocyanate, however, such attempts were not conducted given the well-established route.



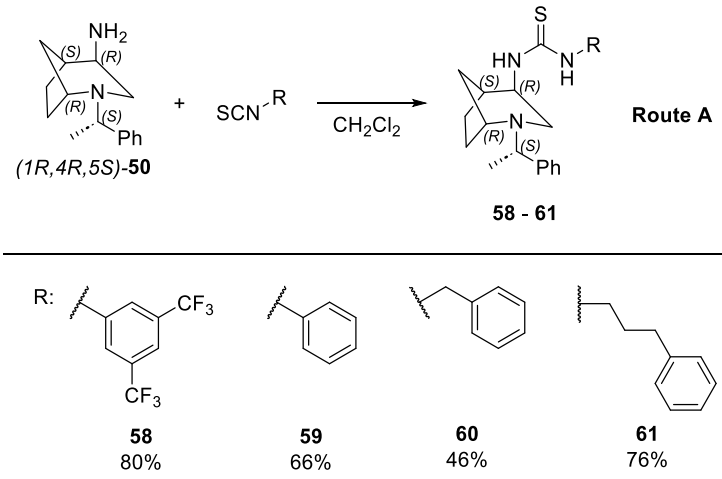
Scheme 73 Synthesis of 2-azabicyclo[3.2.1]octane amines and isothiocyanates.[102,302]

Either amines **50** or isothiocyanates **51** were applied in the synthesis of a set of thioureas in good to very good yields. Thioureas **52**–**55** were synthesized in cooperation with mgr inż. Dominika Iwan (**Route B** was conducted by her) and the author of this thesis synthesized compounds **52** and **55** applying **Route A** after initial tests in asymmetric reactions. Additionally, one thiourea with a C_2-symmetry **56** and a saccharide-based organocatalyst **57**,[227] were received in mediocre yields (Scheme 74). As the general tendency was already revealed during the synthesis of *N*-Boc protected thioureas **39**–**42**, and again proven by the yields of **52**–**55**, the preferential route is **A**.



Scheme 74 Synthesis of (1*S*,4*S*,5*R*)-2-azabicyclo[3.2.1]octane thioureas.

As a consequence of the earlier findings solely **Route A** was applied for the synthesis with the much rarer pseudoenantiomeric starting material (1*R*,4*R*,5*S*)-**50**. A similar set to **39** to **42** and **52** to **55** was synthesized in good yields: thioureas **58** – **61** (Scheme 75).



Scheme 75 Synthesis of (1*R*,4*R*,5*S*)-2-azabicyclo[3.2.1]octane thioureas.

Synthesis of calix[4]arene and complex clusters

In cooperation with two French research groups, the group of Alberto Marra (IBBM University of Montpellier) and Marie-Christine Scherrmann (ICCMO University Paris-Saclay) and in collaboration with Dominika Iwan, attempts towards the application of calix[4]arenes as backbone for multivalent compounds were conducted. The French research groups already had experience in working with the calixarene scaffold[311–314] and they were used efficiently in the synthesis of various

organocatalysts,[241,315–319] but also used with triazoles in chemosensors,[320] or for biological delivery systems and clusters,[311–314] to name a few examples.

Among others, modifications of calixarenes with thioureas were envisaged. Especially calix[4]arenes are of interest, due the relatively easy synthesis and the commercial availability of precursors.[321–323] Conformationally, calix[4]arene exists in various forms (Figure 28).[324,325] Depending on the substitution of the hydroxy groups and substituents R the conformation may be fixed or free to rotate. Conformational changes are also dependent on other factors, mainly temperature. For the purpose of clean conformations, it was fixed to be in cone conformation (Figure 29). This may be achieved by the attachment of substituents on the lower rim which induce a steric hindrance, big enough to prevent rotations.

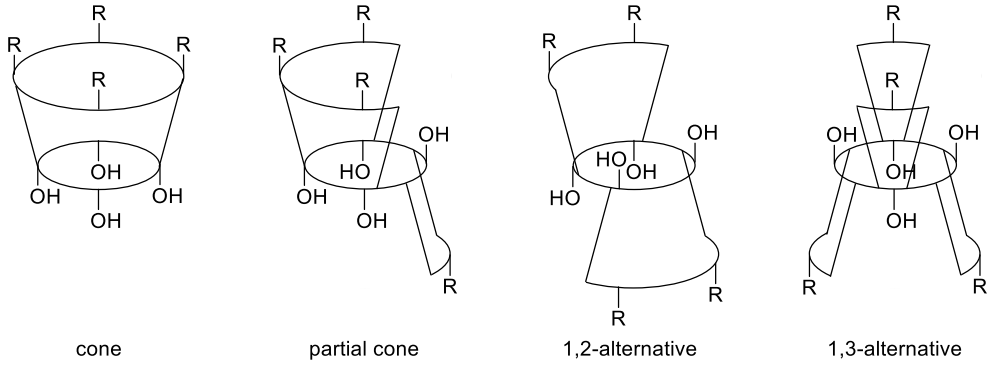


Figure 28 The four possible conformations of calix[4]arene .[324,325]

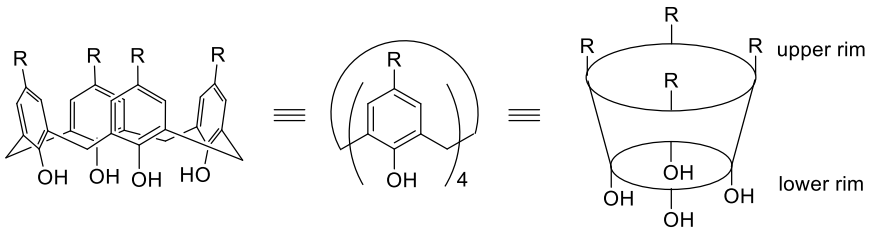
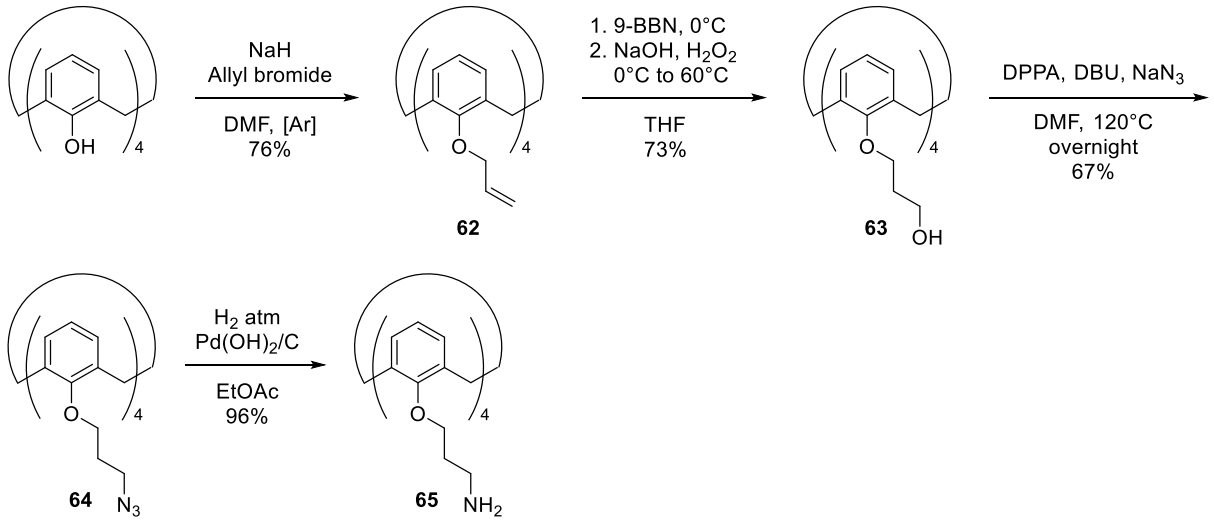


Figure 29 Three possible representations of the cone conformation.

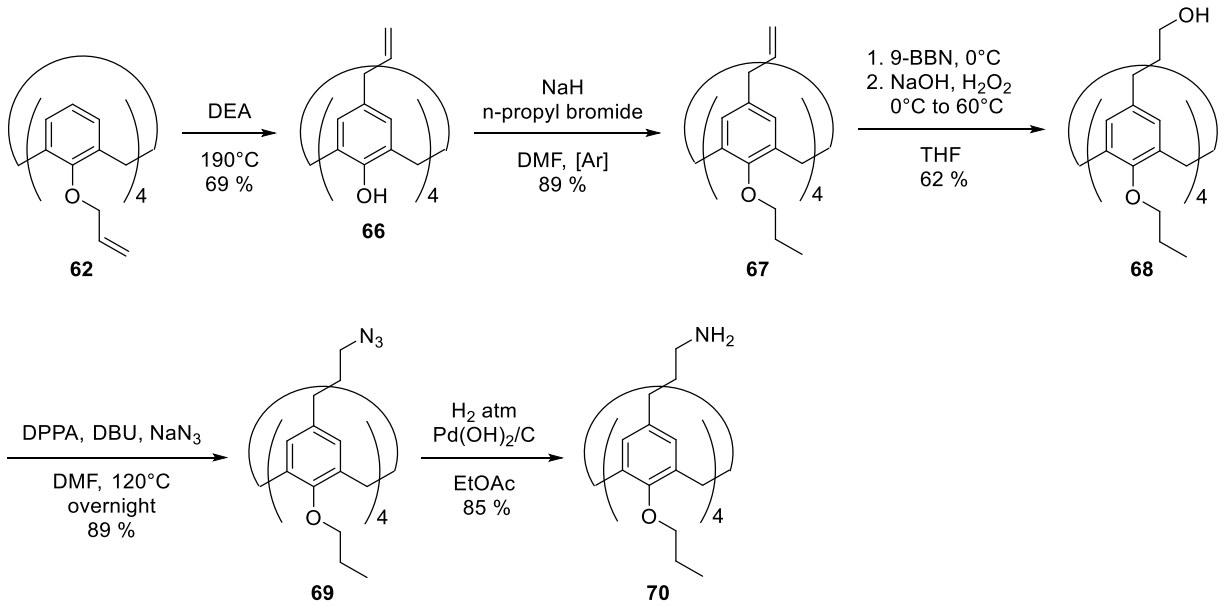
Transformations of calix[4]arenes need to be complete to omit working with complexly substituted mixtures. A good reactivity and rather simple reaction should be used intending the full transformation of starting materials. The synthesis of various calix[4]arene backbones was targeted. Besides lower rim functionalization of the hydroxy groups the upper rim may be functionalized, as well as upper and lower rim at the same time. The challenge for a full transformation rises, as the normality of the solution rises with more functional groups to be reacted simultaneously.

The synthesis of the lower rim derivatives starts from commercially available calix[4]arene-25,26,27,28-tetraol (Scheme 76). Tetraallyl derivative **62** was received by reacting the hydroxy groups with allyl bromide and a strong base.[321] Follow-up hydroboration-oxidation procedure yields tetraol derivative **63**, its azidation with DPPA, DBU and sodium azide yielded lower rim tetraazide calix[4]arene **64**.[313] Simple hydrogenation led to amine **65**, thus readily available for further transformation towards possible thioureas.[314] Purification of the calix[4]arenes was possible by flash column chromatography, but often the best methodology was trituration with various hot solvents due to the low solubility, which often became problematic during purification by chromatography.



Scheme 76 Lower rim calix[4]arene route towards tetra-amine derivative **65**.[313,314,321]

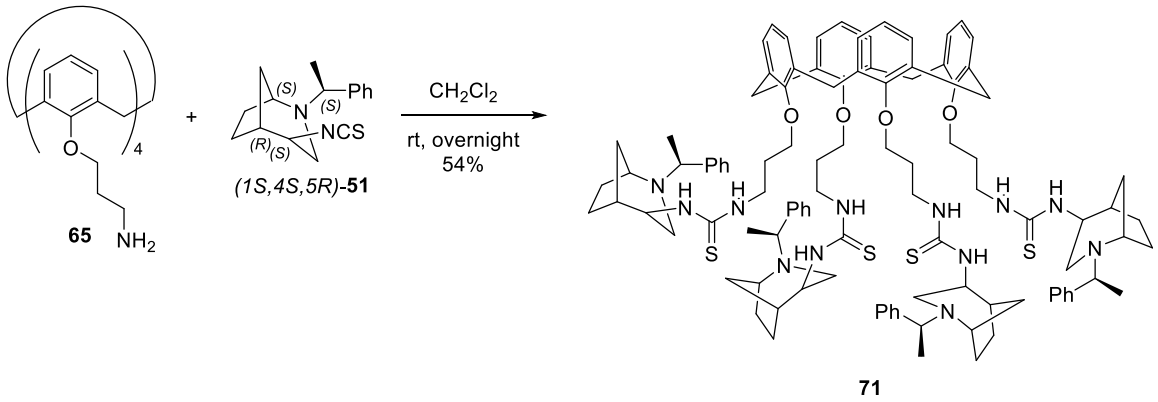
The second approach targeted the synthesis of upper rim amines (Scheme 77). The route, known until the stage of tetraazides,[313] is a challenging one. From earlier synthesized tetra-allyl derivative **62** an atypical Claisen rearrangement (*para*, not *meta* transfer of the substituent) gives **66**.[323] Special attention must be given to the reaction time, as the terminal alkene is prone to an irreversible rearrangement at high temperatures to the thermodynamically more stable form. Furthermore, **66** may change its conformation due rotational changes of its structure (Figure 28). As the hydroxy groups on the lower rim are not posing especially big sterical hindrance upon the calix[4]arene they need to be functionalized quickly to guarantee a single conformer of the product. This may be attained, like previously, by substituting the hydroxy groups.[311] Hydroboration/oxidation,[311] followed by azidation gave upper rim tetra-azide calix[4]arene **69**.[312] A subsequent hydrogenation yielded the novel upper rim amine **70**.



Scheme 77 Upper rim calix[4]arene route towards tetra-amine derivative **70**.[311–313,323]

Calix[4]arene derivatives **65** were reacted under typical thiourea forming conditions. The tetra-amine was easily soluble in dichloromethane and readily reacted with the bicyclic isothiocyanate **51** (only the

more abundant (1*S*,4*S*,5*R*)-diastereomer was applied) yielding the cluster **71** in 54% yield after purification with Sephadex® LH-20 (Scheme 78).



Scheme 78 Synthesis of multivalent calix[4]arene thiourea with bicyclic moiety.

Analysis of the tetrathiourea **71** posed a challenge. Even though complex chiral molecules, such as sugars have been connected in clusters with calix[4]arenes,[311,313] the product is not easily analyzed due to the complex hydrogen bonding capabilities of the thiourea units. Already posing certain problems during the analysis of the analogous mono-thiourea compounds **52**-**55** the degree of conformational freedom the system has, together with the various intramolecular interactions resulted in very broad peaks in the ^{1}H- and ^{13}C-NMR (Figure 30 and Figure 31). Measurement of spectra, in various solvents, deuterated chloroform, methanol and DMSO together with different NMR instruments (400, 500 and 600 MHz) were conducted to improve the resolution and omit hydrogen bondings. Further variable temperature experiments and cryoprobe carbon NMR spectra, together with MALDI-TOF and ESI-TOF mass spectrometry gave a set of data proving the structure and purity of the substance.

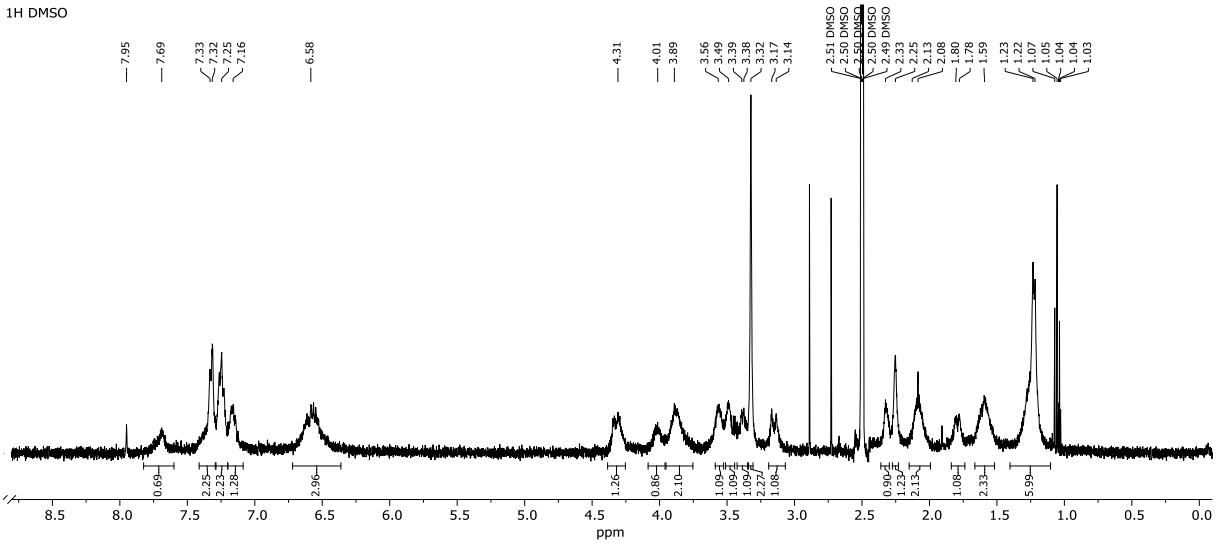


Figure 30 ^{1}H-NMR (400 MHz, d6-DMSO, 296K) spectra of calix[4]arene tetrathiourea **71**

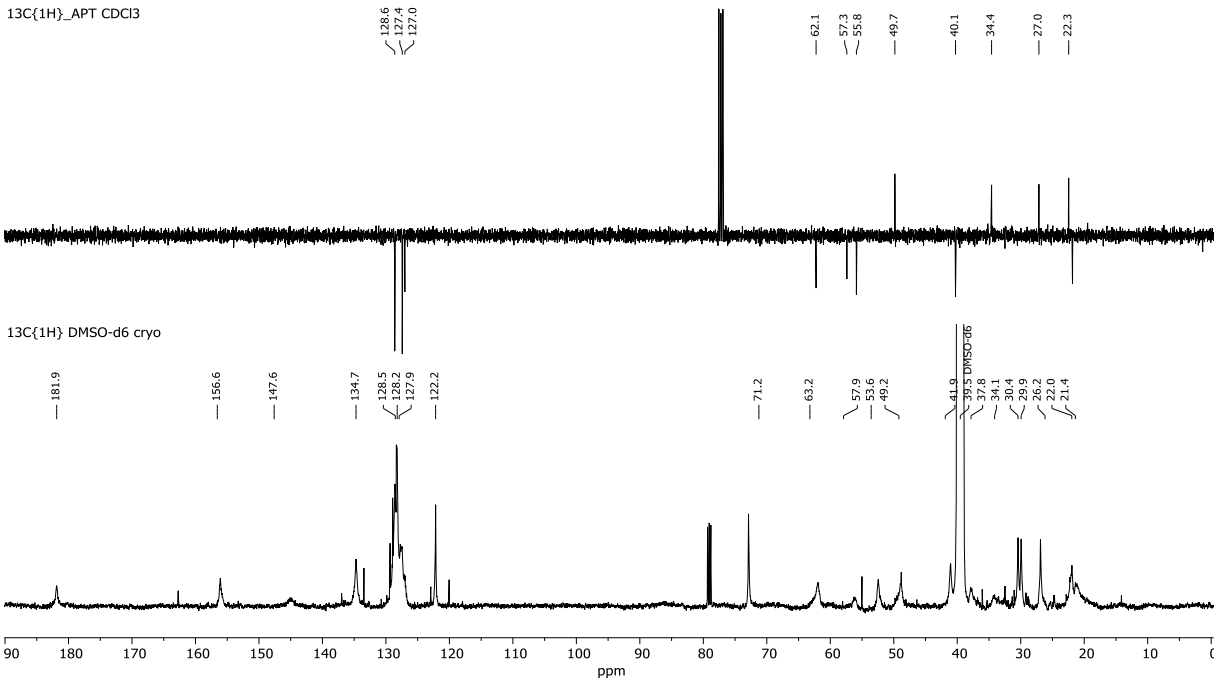
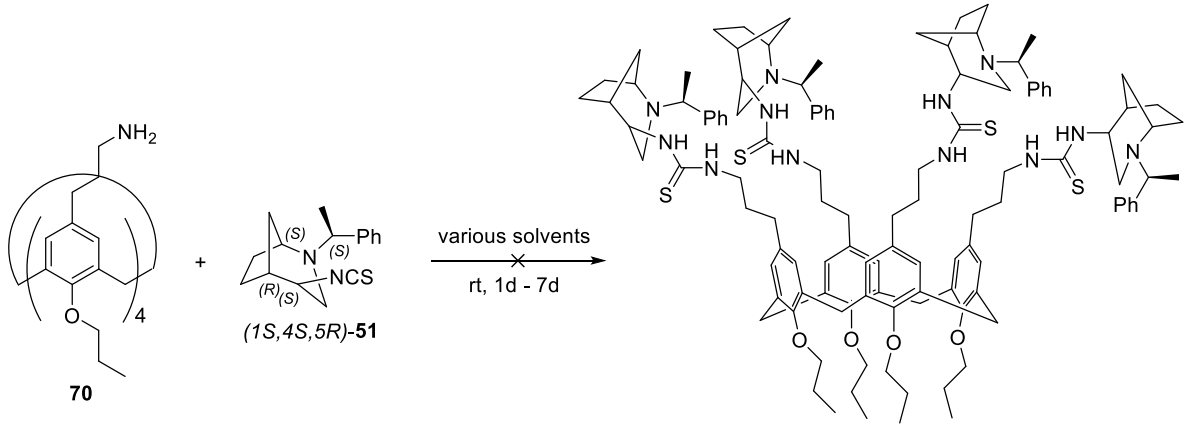


Figure 31 ^{13}C-NMR spectra (proton decoupled – 126 MHz, d6-DMSO, 300K and APT – 101 MHz, $CDCl_3$, 298 K) of calix[4]arene tetrathiourea **71**

A second approach towards calixarene thioureas was undertaken by reacting amine **70** with (1*S*,4*S*,5*R*)-**51** (Scheme 79). Unfortunately, the solubility of **70** was very low in various solvents, such as dichloromethane, chloroform, diethyl ether, toluene, acetone or acetonitrile. Suspicions of the substrate being present in its salt form were refuted by the lack of solubility in water. Further treatment with 1 M sodium hydroxide and extraction did not resolve the issue. Only alcohols, such as methanol, ethanol and isopropanol were able to dissolve the tetraamine, whereas the simple addition reaction did not proceed. Attempts of reacting substrate **70** in dichloromethane and toluene as emulsions did not proceed. High-resolution mass spectrometry indicated starting material and only singly substituted upper rim calix[4]arene. Cleaned by Sephadex® LH-20 gave a complex mixture cleaned of unreacted isothiocyanate substrate **51**, which was recovered.



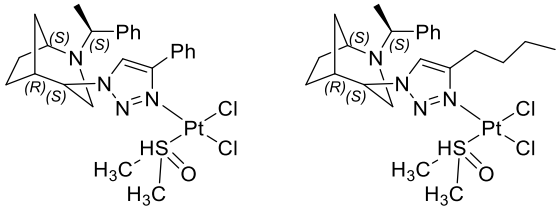
Scheme 79 Attempted synthesis of upper rim tetra-thiourea calix[4]arene.

A more recent reaction was conducted in DMF under the same conditions. Upon purified on Sephadex® LH-20 an off-white solid was yielded. Initial characterization by ^{1}H-NMR and HRMS gave promising

results, but further analyses are pending. A more detailed description in this thesis was therefore omitted due to the lack of comprehensive data.

3.2 Formation of complexes

In an initial cooperation with the group of Iwona Łakomska (University of Toruń) two planar triazole-platinum(II) complexes were synthesized for the application as anti-cancer agent (Figure 32, no experimental data available to the author). Starting material for the synthesis are triazole **13** and an *n*-butyl substituted triazole prepared in the research group the author is a member of.[288] Independent investigations towards the synthesis of complexes with palladium(II) salts were conducted to receive initial insight into square-planar complexes formed by bicyclo-alkane triazole compounds.



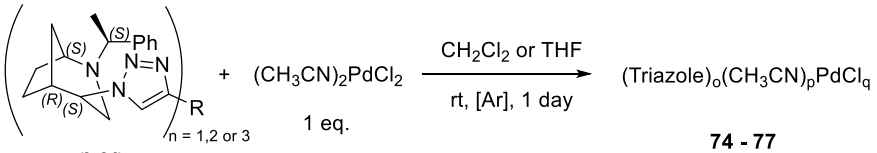
72 **73**

Figure 32 Two triazole-platinum(II) complexes for the possible application as anticancer compound.

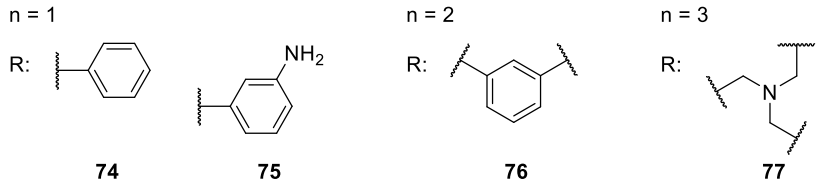
As palladium(II) forms square planar complexes, such as platinum(II) and due to lower, but still high costs of the starting material initial investigations were limited to a set of different expectedly good ligands (Scheme 80). For a better solubility in organic solvents, $PdCl_2$ was initially transformed to the solvated $(MeCN)_2PdCl_2$ by refluxing $PdCl_2$ in acetonitrile and recrystallizing it from a mixture of acetonitrile and hexane.[326] In adapted literature procedures,[327,328] the palladium substrate was stirred in dichloromethane or tetrahydrofuran with various equivalents of triazoles **13**, **14**, **19** and **20** at room temperature under argon atmosphere for one day. Initial analyses were conducted by mass spectrometry (Appendix A.3). The solid, but not crystalline products were analyzed, however, in all but one case the majority of the crude mixture consisted of starting materials. Mass peaks, associated with the product were clearly visible, but purification, by either crystallization with various solvents or column chromatography most often did not yield any meaningful result.

74 and **75** could be synthesized, however, they were never successfully isolated. Mass spectrometry, only as an indication, shows, that the complexes **74** are much more likely to form than **75**, as for the more positive character of the amine on the benzene ring. The preferential complex, if the palladium center was saturated with bonding partner, was two triazole-ligands, which exchanged the solvating acetonitrile ligands. It was surprising, that in turn a dimeric triazole **76** did not complex the palladium at all. No indications in the spectra could be found.

The one, outstanding result could be achieved by complexing palladium with the trimeric triazole **20**. Product **77** (Figure 33) could be received with 50% isolated yield after column chromatography. The success of the synthesis might be found in the more flexible linker within the trimeric triazole ligand **20**, rather than the rigid benzene structure in **19**.



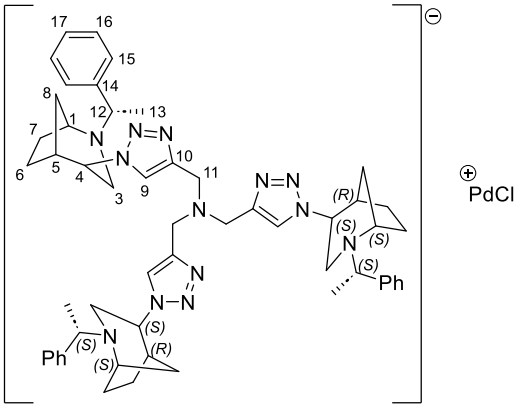
n eq.
13, 14, 19, 20



74 **75** **76** **77**

Input	Equivalents	complex formula (by HRMS)	Isolated yield
74-1	1	(**13**)$PdCl_2$ and (**13**)$_2PdCl_2$	-
74-2	2	(**13**)$_2PdCl_2$	-
74-3	3	(**14**)$_2PdCl_2$	-
75-1	1	(**14**)$PdCl_2$	-
75-2	2	(**14**)$_2PdCl_2$	-
76	1	No product	-
77	1	(**20**)PdCl	50 %

Scheme 80 Triazole-palladium(II)-complex synthesis trials.



77

Figure 33 Proposed structure of the complex **77**.

Crystallization attempts were not successful, but NMR analysis could give an initial insight into the structure of the square-planar complex (Figure 34). A first glance at the carbon-13 spectra reveals a complex spectrum, compared with the spectra of **20** (Figure 35), which is very easy to analyze. Each carbon has a different chemical shift and therefore a different chemical environment. For ease of description the numbering of the atoms is only applied for one of the three bicyclic subunits of the trimer (Figure 33).

Broader peaks make the analysis of the ^{1}H-NMR harder, however, a fast insight may be found by the chemical shift of the protons attached at positions 9 of **77** - 7.86, 8.99 and 9.14 ppm, compared to 8.29 ppm for the shift of all three protons on 9-C in triazole **20**. This clearly shows an influence of the complex, where two protons are shifted to higher frequencies and one to lower frequencies. The downfield shift originates in the deshielding effect of the palladium towards the triazole, indicating

two complexing triazoles, whilst the upfield shift originates from a shielding effect and a further distance from the complex center. The complexing properties of the trimer are strong enough, that it successfully competes not only with the solvating ligands, but also with the chlorides, effectively losing one proton to exist as anion. Computational analysis might be necessary to locate the preferential position for the negative charge. Additional indication for the aforementioned hypothesis is the general NMR spectral pattern in the midfield, where a clear separation between two signals and a third one (combining to three hydrogens per position, as for **20**) showing a deeper separation between units bound directly in the complex and the third free unit. Additionally, the molecular peak of complex **77** and the characteristic palladium isotopic pattern may be found in the mass spectrum (Figure 36).

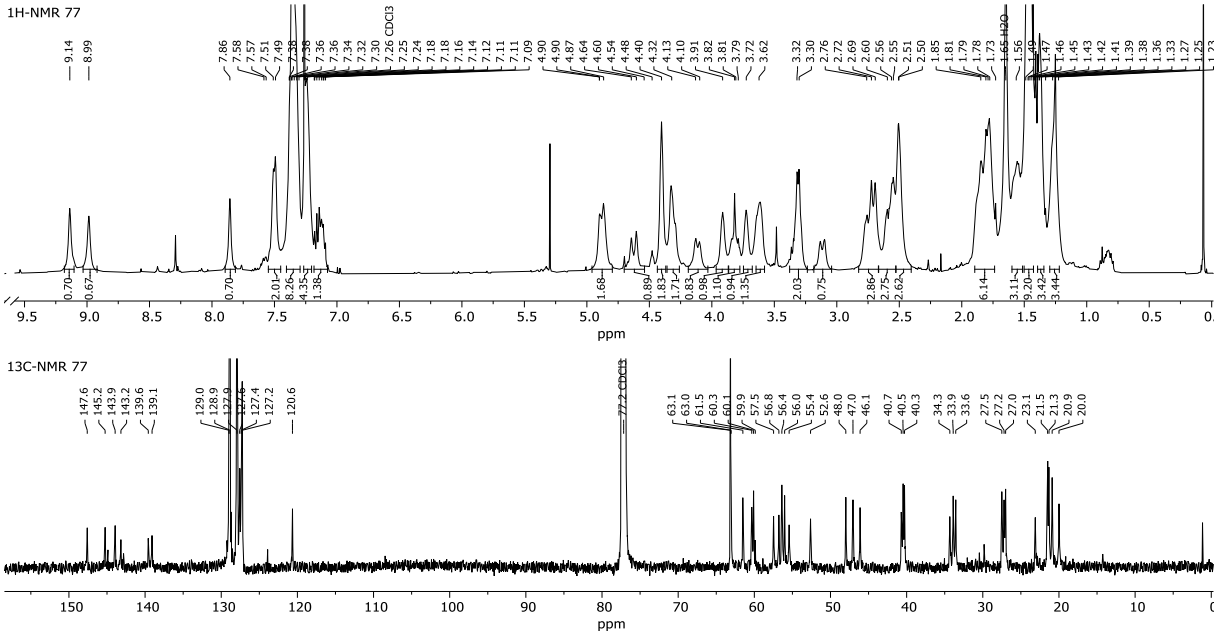


Figure 34 ^{1}H and ^{13}C-NMR spectra of triazole-palladium-complex **77**

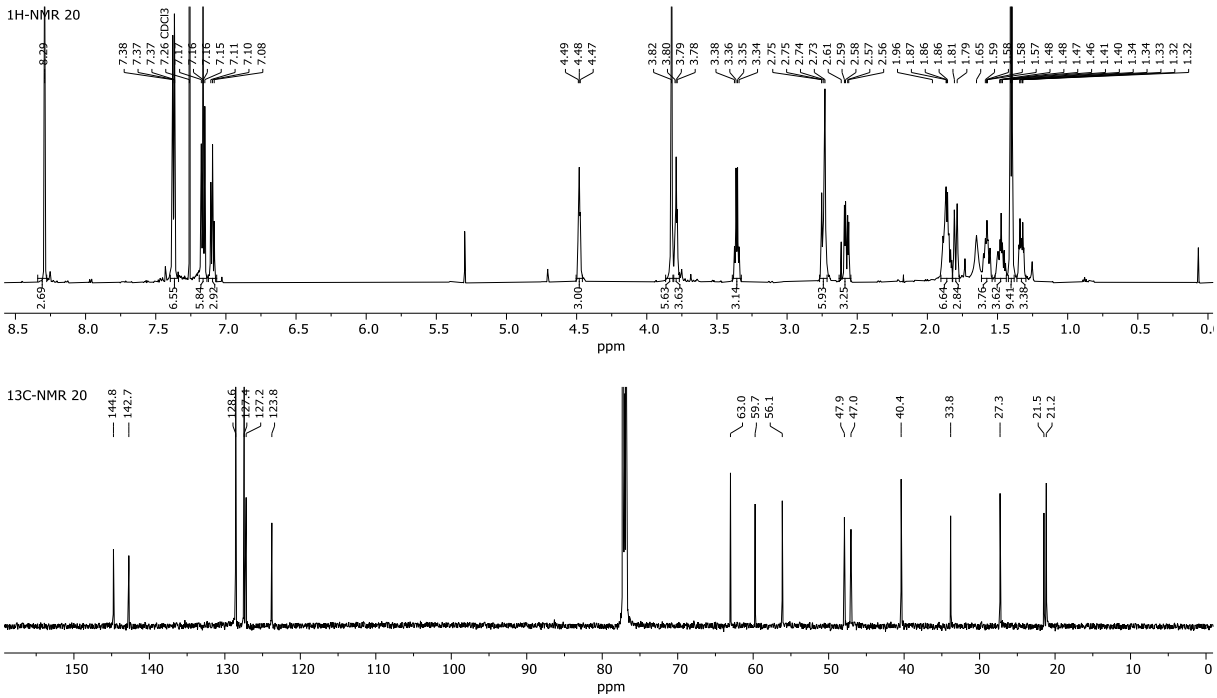


Figure 35 ^{1}H and ^{13}C-NMR spectra of triazole **20**

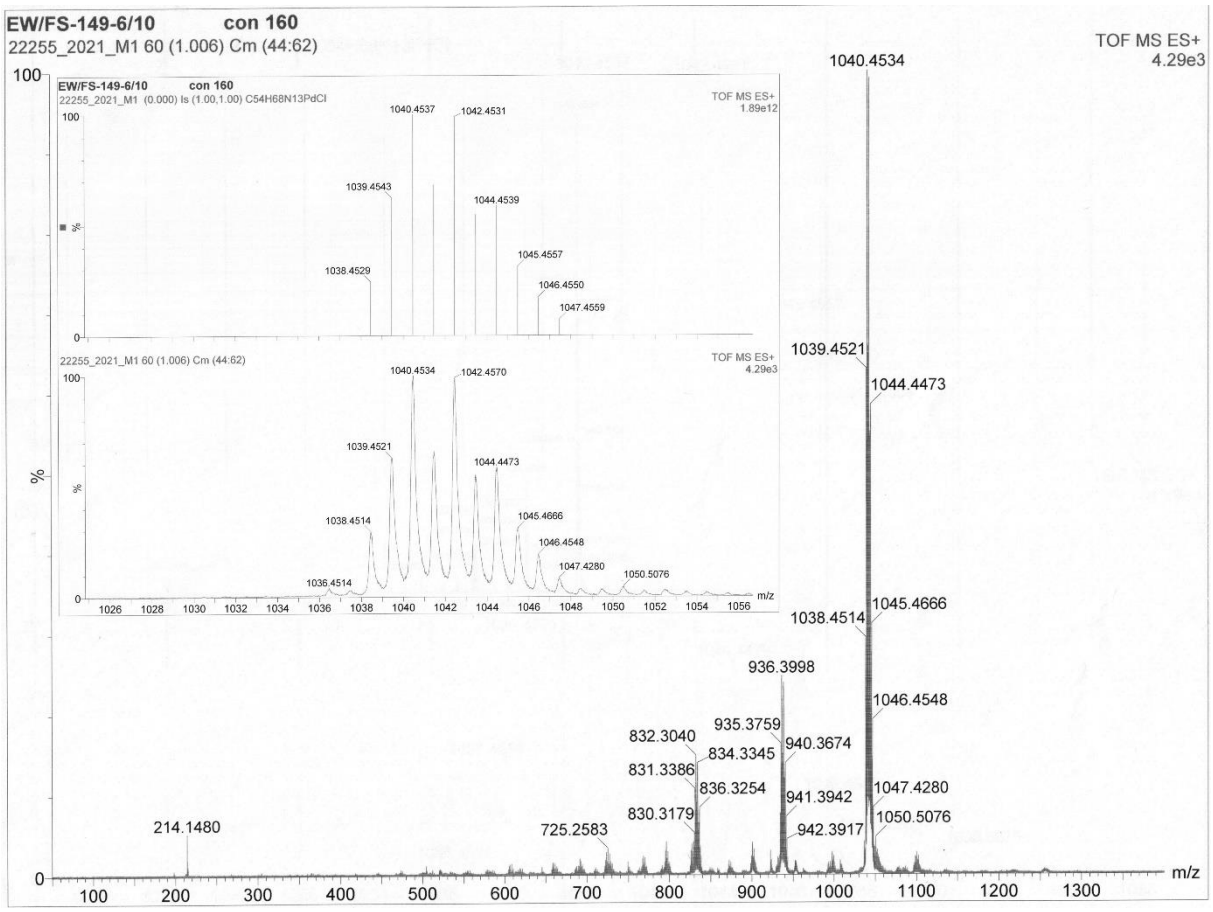
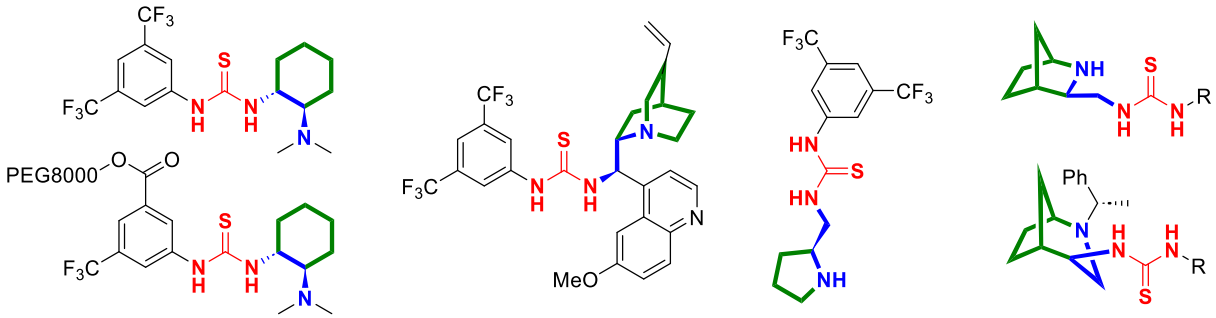


Figure 36 High resolution mass spectrum of triazole-palladium-complex **77**

3.3 Chiral induction in asymmetric reactions

As described earlier, thioureas are useful functionalities for bifunctional organocatalysts. The combination of hydrogen-donor moiety with a second functionality bound by a chiral backbone especially gained momentum at the brink of the 21st century. The design of the bicyclic organocatalysts in the previous synthesis of thioureas was tailored to a couple of qualities to become analogues of already successfully applied catalysts, such as Takemoto's DACH-based,[229] Soos', Connon's and Dobson's *Cinchona*-based[225,329,330] and Yong Tang's pyrrolidine (proline-derived)[226] thiourea organocatalyst (Figure 37). All mentioned catalysts were successfully applied in various asymmetric Michael-addition reactions in reactions of malonates or ketones/aldehydes (cyclic and non-cyclic) with nitroalkenes and the focus of the upcoming catalytic attempts is similar.



Takemoto's and PEG-bound Thiourea organocatalyst | Soos's, Connon and Dobson's Thiourea organocatalyst | Yong Tang's Thiourea organocatalyst | This thesis' approach

Figure 37 Three successfully applied thiourea organocatalysts compared to the structure developed during this thesis.[225,226,229,329,330]

The shown structures share certain features, the thiourea moiety is connected by two bonds (both σ) with the second amine functionality. Either tertiary or secondary amines may be used, depending on the intended use and form of activation mechanism (Figure 38). Takemoto's and Soos', Connon's and Dobson's thiourea catalysts were developed as combination of hydrogen donor moiety and chiral base to activate the substrates and bring them into favorable chiral proximity to react substrates in Michael-additions in asymmetric manner. Yong Tang's pyrrolidine-based catalyst reacts similar to proline with an enamine intermediate.

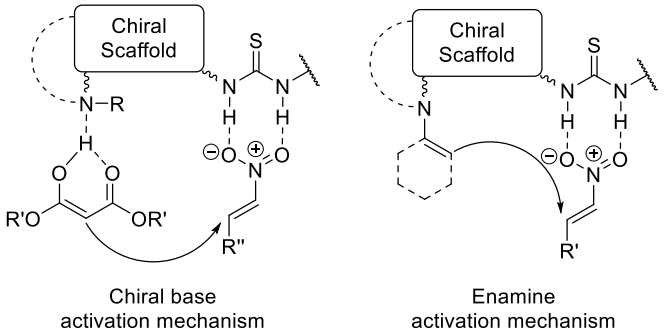


Figure 38 Modes of activation during Michael addition catalyzed by bifunctional thiourea organocatalysts.

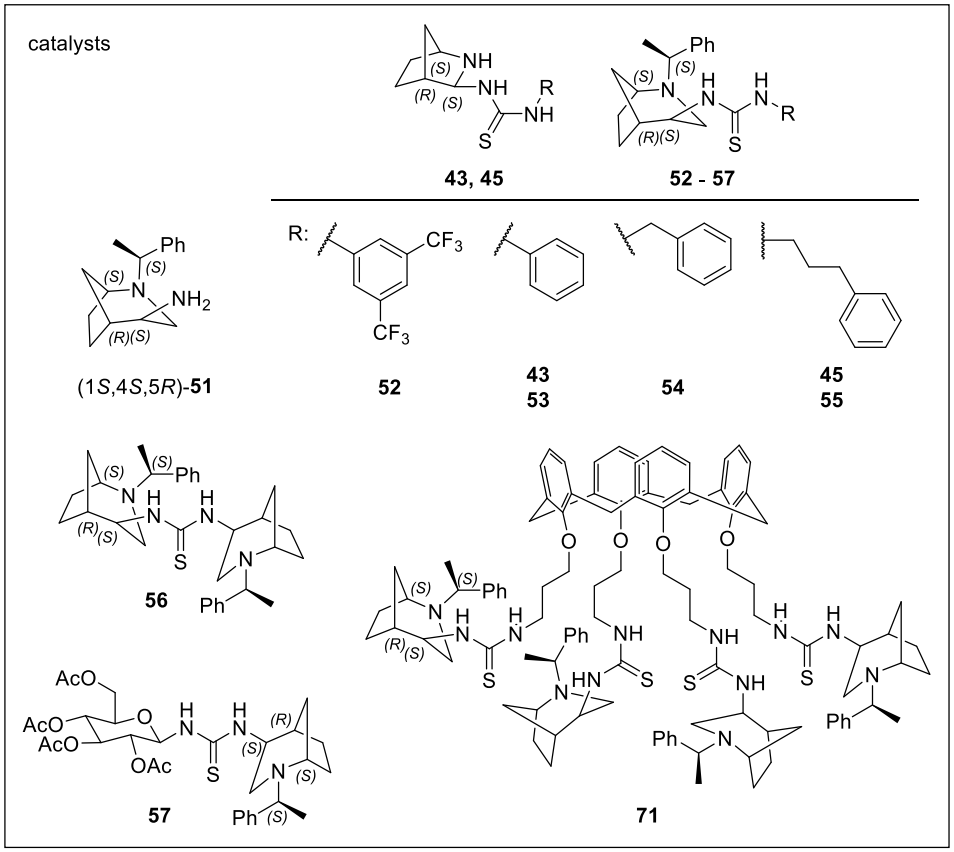
Another feature many of the existing thiourea organocatalysts have in common is the 3,5-bis(trifluoromethyl)benzyl substituent. It is not only an electron withdrawing moiety, which activates the thiourea efficiently, but it is also involved in the Lewis-basic binding with an *ortho*-CH coordination.[331]

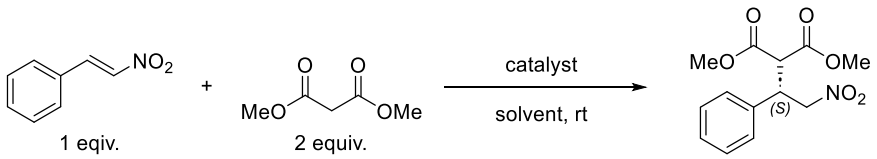
Among others, the 3,5-bis(trifluoromethyl)benzyl-substituent was used during the synthesis of a set of bicyclic organocatalysts (**52**, **58**). Other incorporated groups are a phenyl ring (**43**, **53**, **59**), a benzyl group (**54**, **60**) and a phenylpropyl one (**45**, **55**, **61**). These groups were incorporated to get a first insight into the reactivity and chirality transfer during the asymmetric reactions. This is especially interesting considering the tetravalent organocatalyst **71**, which is based on calix[4]arenes and may be described as analogue of the monovalent **55**. Further syntheses included a C_2-symmetrical bicyclic thiourea **56** and, in accordance with - Ma Jun-An's chiral tertiary amine thiourea catalyst based on saccharides one bicyclic analogue **57**.[227,332] Three different chiral backbones were used, whereas two are pseudoenantiomeric to each other: (1*S*,4*S*,5*R*)-2-azabicyclo[3.2.1]octane (**52-57**,**71**) and (1*R*,4*R*,5*S*)-2-azabicyclo[3.2.1]octane (**58-61**), together with (1*S*,3*S*,4*R*)-2-azabicyclo[2.2.1]heptane (**43**,**45**).

In the upcoming section two Michael additions were tested to assess the initial efficiency of the synthesized organocatalysts: the reaction of dimethylmalonate to β-nitrostyrene and the addition of cyclohexanone to the same alkene.[225,226,229,329,330] Initially, reaction mixtures were purified by column chromatography before being analyzed for their enantiomeric excesses, but the majority of them were tested before purification. This is not only due to the simplicity and often efficient separation of the enantiomers from other substances in the crude mixture during the high-performance liquid chromatography analysis, but foremost because of the possible altering the results by self-disproportionation of the enantiomers. This effect often occurs during the application of processes such as purification procedures.[333] Well known for crystallization, all types of purifications, *e.g.* column chromatography, precipitation, evaporation or distillation, among others, may greatly influence the enantiomeric excess and lead to inaccurate results.

During the addition of dimethylmalonate to β-nitrostyrene, (1*S*,3*S*,4*R*)-2-azabicyclo[2.2.1]heptanes (**43**,**45**) and (1*S*,4*S*,5*R*)-2-azabicyclo[3.2.1]octanes (**51-57**,**71**) were applied. leading preferentially to (*S*) enantiomers of the adduct (Table 1). No chiral induction was observed for **43** and **45** and very little for the chiral bicyclic diamine **51** (4% *ee*). Comparing **52**-**55**, thiourea **52** was the most active and best in the induction of chirality (67% *ee* and 98% conversion). The descending conversions from **52** to **55** is in accordance with the electron withdrawing -I effect of the substituents and additionally proves the importance of the substituents. The best results and highest conversions were achieved with **52**, whose 3,5-bis(trifluoromethyl)benzyl substituent activated the thiourea. Catalysts **53**-**55** do not differ much in their asymmetric induction (42%, 54% and 48% *ee*, respectively) from the chiral bicyclic alkane-thiourea catalytic system. Good conversions, with mediocre chiral induction were achieved by the C_2-symmetrical thiourea **56**, and low yields and poor enantiomeric excesses by the saccharide-based catalyst **57**. Calix[4]arene-tetravalent thiourea organocatalyst **71** was designed to check the influence of more catalytic centers within one molecule. It is an analogue to catalyst **55** and should be compared with it if it is coming to its activity; as it includes four catalytic centers it was applied in lower catalytic loading to have equal normality of catalytic units (2.5 mol%, in contrast to **55** 10 mol%). Whilst the chiral induction of **71** was greater than the one of **55** (57% > 48% *ee*), its activity was limited (31% < 66% conversion).

Table 1 Catalyst screening of (1*S*,3*S*,4*R*)-2-azabicyclo[2.2.1]heptane and (1*S*,4*S*,5*R*)-2-azabicyclo[3.2.1]octane catalysts.





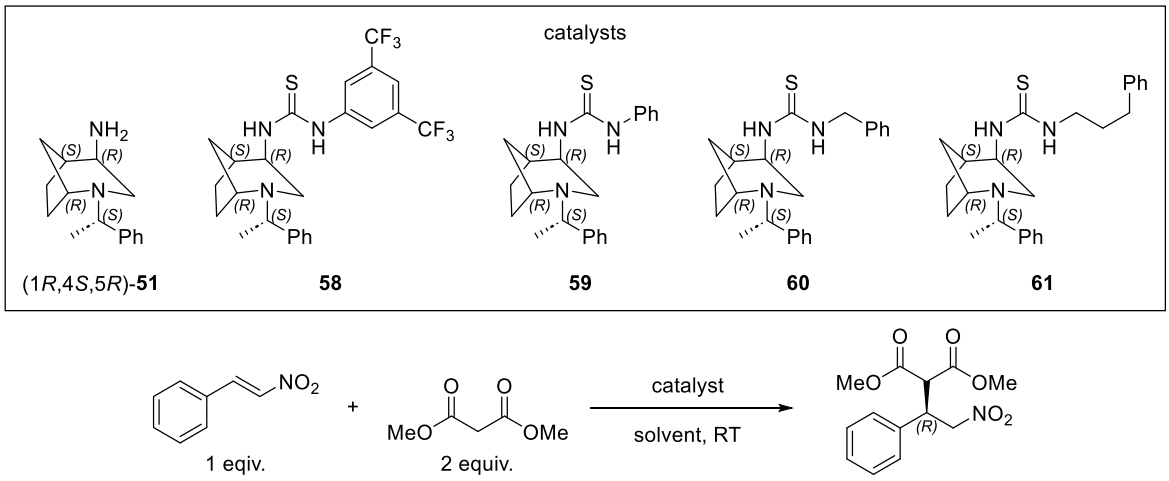
Catalyst	Loading [mol%]	Solvent	Time	*ee* [%][1]	conv. [%][2]
43	10	DCM	3d	0	82[3]
45	10	DCM	3d	0	82[3]
(1*S*,4*S*,5*R*)-51	10	DCM	3d	4	55[3]
52	10	DCM	1d	67	98
53	10	DCM	1d	42	73
54	10	DCM	1d	54	70
55	10	DCM	1d	48	66
56	10	DCM	1d	53	81
57	10	DCM	1d	26	19
71	2.5	DCM	3d	57	31

All reactions were carried out at room temperature in 0.125 mmol scale; [1)]all *ee* values were determined from crude reaction mixtures on either Chiralpak® AD-H or Chiralpak® IA columns with 80:20, 90:10 or 95:5 *n*-hexane:isopropanol eluent if not differently stated; [2]conversions were determined by ^{1}H-NMR; [3)]isolated yield.

The pseudoenantiomers (1*S*,4*S*,5*R*)-2-azabicyclo[3.2.1]octanes (**51, 58-61**) induced the opposing stereocenter in the Michael-addition product (Table 2). Amine (1*R*,4*R*,5*S*)-**51** was, as its (1*S*,4*S*,5*R*)-**51** counterpart, not efficient in transferring chirality. Again, the catalyst with the 3,5-bis(trifluoromethyl)benzyl substituent was found to be the most efficient regarding the conversion

(75%) and was among the two best catalysts for the chiral induction (51% *ee*). No general tendency can be determined with the received results of organocatalysts **59**-**61**

Table 2 Catalyst screening of (1*R*,4*R*,5*S*)-2-azabicyclo[3.2.1]octane organocatalysts.

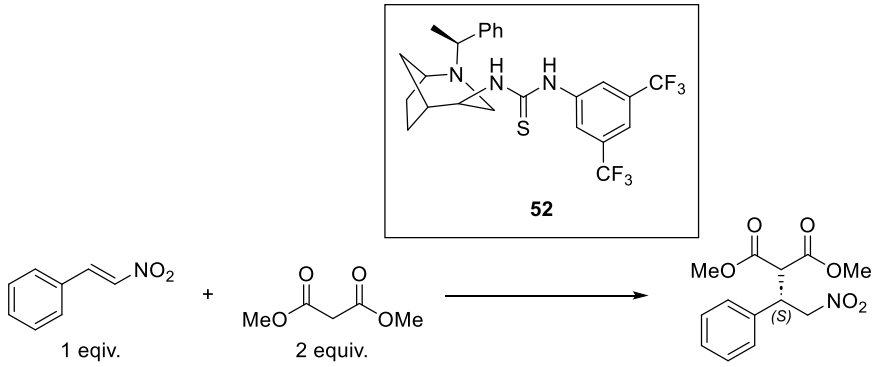


Catalyst	Loading [mol%]	Solvent	Time	*ee* [%][1]	conv. [%][2]
(1*R*,4*R*,5*S*)-51	10	DCM	3d	2	48[3]
58	10	DCM	1d	51	75
59	10	DCM	1d	-	traces
60	10	DCM	1d	42	5
61	10	DCM	1d	51	42

All reactions were carried out at room temperature in 0.125 mmol scale; [1)]all *ee* values were determined from crude reaction mixtures on either Chiralpak® AD-H or Chiralpak® IA columns with 80:20, 90:10 or 95:5 *n*-hexane:isopropanol eluent; [2]conversions were determined by [1]H-NMR; [3)]isolated yield.

Upon initial tests optimization attempts were conducted with the best organocatalyst **52** (Table 3). The catalyst, received from the more abundant *aza*-DA product *exo*-(1*R*,3*R*,4*S*)-**1**, was applied under various reaction conditions. Tests with 5 mol%, 10 mol% and 20 mol% catalyst loadings were conducted; the conversion remained high (97%, 98% and >99%, respectively), but the enantiomeric excess was affected (48% *ee* for 5 mol%, 67% for 10 mol% and 74% *ee* for 20 mol%). Other tests included the reaction mixture to be stirred at 3 °C and -20 °C compared with the same loading (10 mol%) at room temperature the *ee* rose at lower temperatures to 71%, but the conversion rate suffered (83% and 79% respectively). Introduction of acid additives, often used as co-catalysts in Michael-addition reaction,[334] proved to be highly counterproductive. Both, salicylic acid and benzoic acid additives (10 mol%) only yielded traces of product. Solvent tests were conducted including acetonitrile, THF, toluene and DMSO. Some good results for the enantiomeric excess and some very good conversion rates were found (best: 63% *ee*, 95% conversion in toluene), however, none of which exceeded the initial results applying **52** in dichloromethane.

Table 3 Optimization of the conditions for the best catalyst **52**.



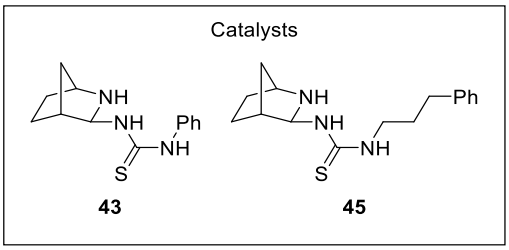
Catalyst	Loading [mol%]	Solvent	T [°C]	Time	*ee* [%][1]	conv. [%][2]
52	5	DCM	RT	1d	48	97
52	10	DCM	RT	1d	67	98
52	20	DCM	RT	1d	74	>99
52	10	DCM	3	1d	71	83
52	10	DCM	- 20	1d	71	79
52	10[3]	DCM	RT	1d	-	traces
52	10[4]	DCM	RT	1d	-	traces
52	10	MeCN	RT	1d	57	92
52	10	THF	RT	1d	57	48
52	10	Toluene	RT	1d	63	95[5]
52	10	DMSO	RT	1d	-	0

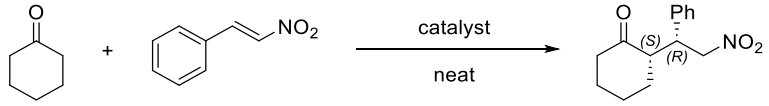
All reactions were carried out at room temperature in 0.125 mmol scale; [1)]all *ee* values were determined from crude reaction mixtures on either Chiralpak® AD-H or Chiralpak® IA columns with 80:20, 90:10 or 95:5 *n*-hexane:isopropanol eluent; [2]conversions were determined by [1]H-NMR, [3)]addition of 0.1 mol% salicylic acid, [4)] addition of 0.1 mol% benzoic acid, [5)]isolated yield.

A clear chiral induction can be seen for the developed catalysts. Some very good conversion rates were achieved and good enantiomeric excesses. The application of both pseudoenantiomeric thioureas offers the possibility inducing (*S*) and (*R*)-stereocenters in the Michael-addition products, as it is observed for pseudoenantiomeric *Cinchona* alkaloids.[225,329,330]

Catalysts **43** and **45** are capable to function as chiral base and as enamine in the catalytic substrate activation. The asymmetric Michael-addition reaction of ketones or aldehydes with nitroalkenes is therefore a long-used test reaction to assess chiral induction and activity of organocatalysts and was applied for Yong Tang's earlier mentioned L-proline-based thiourea catalyst [226] The same reaction of cyclohexane and β-nitrostyrene was chosen to initially assess the two received secondary amine/thiourea catalysts. Two sets of tests were conducted with 10 mol% loading of catalysts at either room temperature or 2 °C for one or three days, respectively. Best enantiomeric excess results were achieved for catalyst **45** at 2 °C after three days (96% *ee*), however, at room temperature the *ee* was not significantly worse (93%). A prolongation of the reaction time increased the conversion from 19% for one day reaction time to 29%. Either way no significant increase of the conversion rate could be achieved, leaving the catalyst as a highly stereoselective, but not active one which is why no further tests were conducted.

Table 4 Michael addition of cyclohexanone and β-nitrostyrene catalyzed by (1*S*,3*S*,4*R*)-2-azabicyclo[2.2.1]heptane catalysts





Catalyst	Loading [mol%]	T	Time	*ee* [%][1]	conv. [%][2]
43	10	RT	1d	-	traces
45	10	RT	1d	93	19
43	10	2 °C	3d	0	traces
45	10	2 °C	3d	96	29

All reactions were carried out at room temperature in 0.125 mmol scale; [1]all *ee* values were determined from crude reaction mixtures on Chiralpak® IH columns with 90:10 *n*-hexane:isopropanol eluent; stereochemistry determined according to the literature reference[335] [2]conversions were determined by ^{1}H-NMR

3.4 Biological activities of chosen chiral 2-azabicycloalkanes

The exchange of monocyclic nitrogen containing cycles, such as pyrrolidine, piperidine or azepane for their more rigid bicyclic analogues is a well-known methodology in the development of biological active compounds.[255,256] However, also natural existing moieties, such as tropane or quinuclidine structures are important pharmaceutically active building blocks.[10,13,252–254] It is therefore a promising approach for the development of new biologically active compounds to resort to a mix of combining known active moieties together and test them for various application in a broader biological space. Combination with triazoles or with thioureas was not only conducted to develop possible ligands and catalysts, but also for the application in biological assays.[221,275,277,336–340] A set of different tests, including antiproliferative activity, cytotoxicity, antiviral, antibacterial and antifungal activity were conducted with different cooperating parties.

All synthesized triazoles, including (1*S*,4*S*,5*R*)- and (1*R*,4*R*,5*S*)-2-azabicyclo[3.2.1]octane derivatives (Figure 39 and Figure 40, respectively) and 2-azabicyclo[2.2.1]heptanes (Figure 41) were applied in comprehensive antiproliferative testing[287] and some chosen examples of mono-, di- and trivalent triazoles were tested in a broader scope, together with the thioureas presented in Figure 42. The application of 2-azabicyclo[3.2.1]octanes was especially interesting, since the majority of existing research applied 2-azabicyclo[2.2.1]heptanes and comprehensive tests of octanes were not yet conducted.

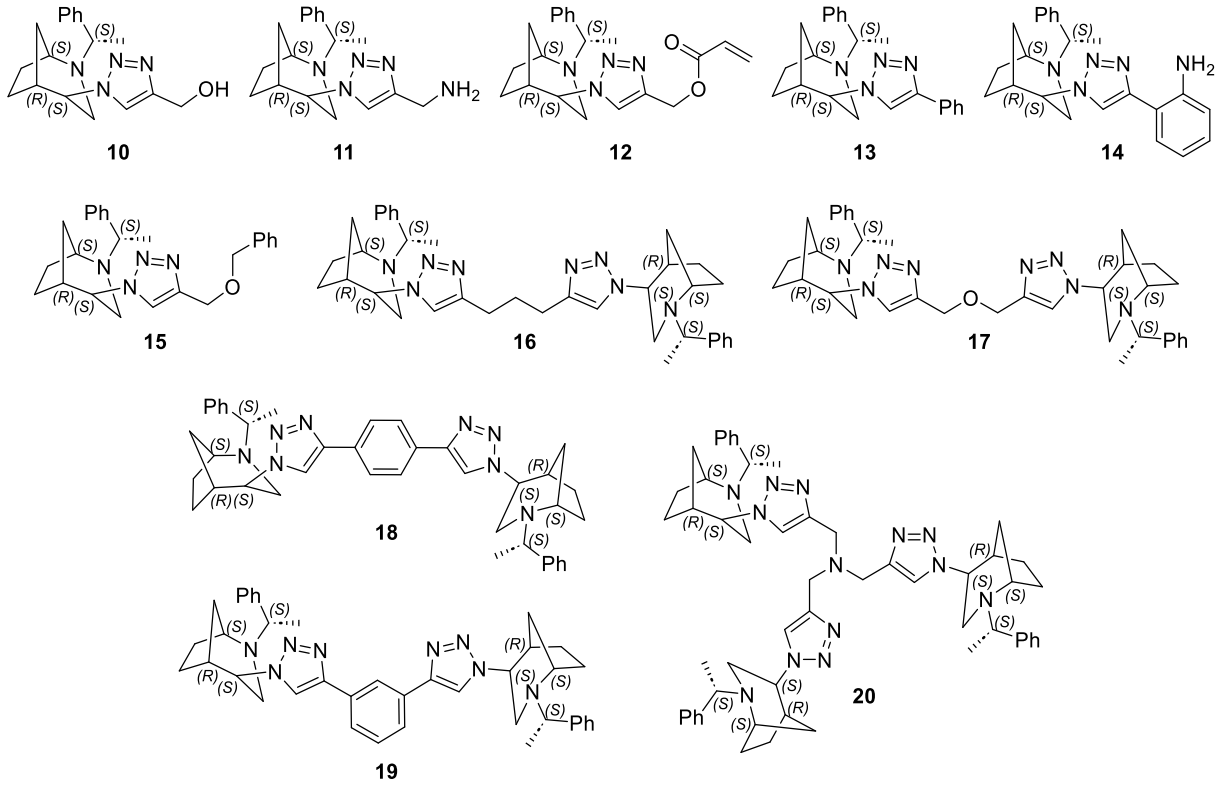


Figure 39 (1*S*,4*S*,5*R*)-2-azabicyclo[3.2.1]octane derivatives applied in biological activity testing.

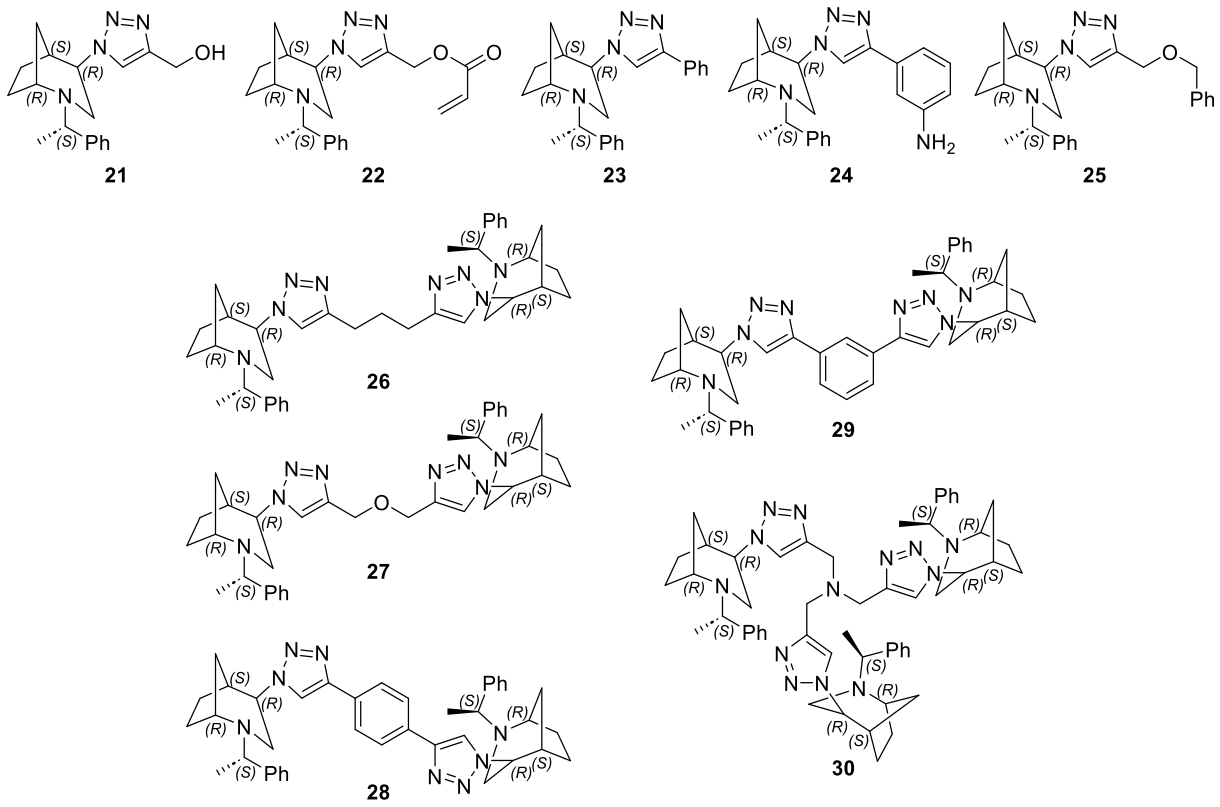


Figure 40 (1*R*,4*R*,5*S*)-2-azabicyclo[3.2.1]octane-triazoles applied in biological activity testing.

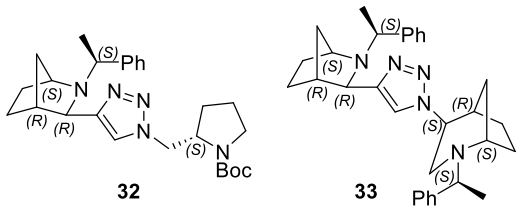


Figure 41 (1*S*,4*R*,5*R*)-2-azabicyclo[2.2.1]heptane-triazoles applied in biological activity testing.

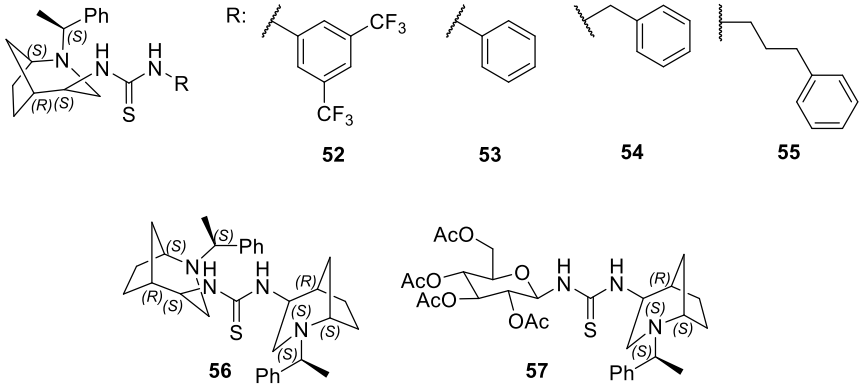


Figure 42 (1*S*,4*S*,5*R*)-2-azabicyclo[3.2.1]octane-thioureas applied in biological activity testing.

3.3.1 Antiproliferative activity

Tests on HS294T, MIA-PaCa-2 and NCl-H1581

In a cooperation with the group of Joanna Wietrzyk (Hirszfeld Institute of Immunology and Experimental Therapy, Polish Academy of Science, Wrocław) tests on the antiproliferative activity (the suppression of cell growth) were conducted for compounds **10**-**33**. Three human cancer cell lines, melanoma Hs294T, pancreatic MIA PaCa-2 and lung NCI-H1581 cancer, were tested and their cytotoxicity against normal cell lines was evaluated by normal murine fibroblasts cell line BALB/3T3 clone A31. Activities were compared to *cis*-platin (Table 5). The following description and structure activity discussion is based on a publication by the author from 2021.[287]

A couple of triazoles expressed lower IC_{50} values than the known cancer treatment *cis*-platin for cell line NCI-H1581 (as low as 2.4 µM for compound **20**, compared to 7.3 µM for *cis*-platin; eight triazoles with better activity and significantly better SI). Overall, the results on this cell line were good, especially in light of the selectivity index which is an indicator for a more selective treatment.

The biological effects of the applied triazoles were systematically less good for pancreas cancer cell line MIA PaCa-2. The best result, again compound **20,** was about half as active compared to *cis*-platin, but still exhibits much better selectivity, if compared with the toxicity towards normal murine fibroblasts cell line BALB/3T3. Better results were noted against melanoma cell line Hs294T, with four compounds **12**, **16**, **26** and **27** in the range of 9.5 to 13.7 µM compared to 1.3 µM for *cis*-platin. Unfortunately, they are toxic towards BALB/3T3.

Literature offers various criteria of selectivity. Certain margins must be applied for a preliminary classification. Some compounds exhibit high toxicities towards malicious cell lines, but also towards normal cells, which would be counterproductive. There is no omnipotent guideline, however, some approaches describe SI of two to three as good.[341,342] Given, that a total of twelve SI values are >3, whereas the majority is even above 6 and go as high as 9 and 9.5, the results may be considered very promising.

Table 5 Antiproliferative activity of triazoles

Compound	IC_{50} [µM]				SI
	Hs294T	MIA PaCa-2	NCI-H1581	BALB3T3	
Cisplatin	1.30±0.50	12.63±3.13	7.27±2.83	1.83±0.70	0.3
10	na[1]	na	na	na	-
11	88.53±9.41	99.90±4.46	11.27±1.25	94.44±1.89	8
12	9.52±2.51	87.73±1.66	7.91±1.20	1.75±0.76	0.2
14	74.54±14.94	84.42±1.04	30.76±3.51	77.08±1.10	2.5
15	73.81±10.11	79.12±0.5	15.48±0.12	61.46±3.28	4
16	10.35±3.39	40.19±1.60	4.20±0.36	11.85±5.03	3
17	32.42±7.83	51.47±1.60	6.00±0.86	44.40±7.50	7
18[2]	77.26±9.50	na	20.91±15.20	na	-
19[2]	na	na	53.93±5.07	na	-
20	20.83±5.02	25.67±0.26	2.44±0.07	23.08±2.72	9.5
21	na	na	72.34±33.99	na	-
22	72.8±9.71	86.31±0.35	18.77±4.45	28.54±22.68	1.5
24	65.87±8.30	76.95±1.98	7.39±1.15	52.69±6.16	7
25	70.88±5.86	76.47±4.37	8.52±1.39	50.03±3.25	6
26[2]	9.71±3.08	37.58±5.51	4.40±0.61	26.72±4.76	6
27	13.65±2.31	44.91±3.69	4.88±0.41	46.06±11.29	9
28[2]	58.82±4.07	111.47±9.55	6.87±1.46	59.5±11.71	9
29	na	na	na	na	-
30	29.13±1.36	31.84±2.31	3.27±0.42	27.65±3.24	8.5
32[2]	92.58±21.97	90.28±0.69	77.57±8.68	na	-
33	57.01±13.64	63.01±7.29	6.25±1.37	39.40±4.86	6

[1]not active (IC_{50} > 100 µM), [2]poor or no solvability in DMSO. The IC_{50} value defined as the concentration of a compound which inhibited cell proliferation in 50%. The SI (Selectivity Index) was calculated for each compound using the formula: SI = IC_{50} for normal cell line BALB/3T3/ IC_{50} for NCI-H1581 human lung cancer cell line. The beneficial SI > 1.0 indicates a compound with efficacy against tumor cells greater than the toxicity against normal cells.

The only systematic notable results can be found for lung cancer cell line NCI-H1581, on which the upcoming structure-activity-analysis is based. During the synthesis of the triazoles a couple of aspects were covered and found to have an impact on their activity: the number of triazole units, the stereochemistry of the bicyclic units, the type of 2-azabicycloalkane and the substituent or linker. A general dependence on each of those aspects could be found and will be discussed.

Whilst the most active compound **20** has (1*S*,4*S*,5*R*)-stereochemistry the overall activity was better for the (1*R*,4*R*,5*S*)-2-azabicyclo[3.2.1]octane derivatives. The tendencies show that by the increase of the number of 2-azabicycloalkane-triazole moieties the activity rises as well. For each set of stereochemically different triazoles **10**–**20** and **21**–**30** ((1*S*,4*S*,5*R*)- and (1*R*,4*R*,5*S*)-derivatives, respectively) the trimeric triazoles **20** (2.44 µM) and **30** (3.27 µM) were the most active ones. Monomeric triazoles exhibited lower activities, with a stepwise rise through dimeric to trimeric units. This clearly shows the activity of the compounds to originate from azabicycloalkanes and/or triazoles. The influence of the bicyclic part can further be manifested by comparing compounds **10**-**20** with **32** and **33**. Both of the latter compounds possess (1*S*,3*S*,4*R*)-2-azabicyclo[2.2.1]heptane units, but **33** also includes a (1*S*,4*S*,5*R*)-2-azabicyclo[3.2.1]octane one. Activities differ vastly; whilst **32** has an IC_{50} value of 77.57 µM the addition of the tropane analogue in **33** gave rise of its activity of 6.25 µM.

Differences within the groups of monomeric and dimeric triazoles could be found. Their influence may lay within a couple of reasons: type of substitution, electron density, aromatic character, and in case of linkers also a degree of freedom and distance between the active units. Generally, more rigid structures, such as benzene-linked C_2-symmetrical compounds **18**, **19**, **28** and **29** exhibit lower antiproliferative activities (with exception of **28**, 6.87 µM). But their disadvantage does not only lay within possibly low IC_{50} values, but also their problematic solubility which pose significant issues on the way towards pharmaceuticals. On the counter side, more flexible assemblies, such as propyl or ether linked **16**,**17** and **26**,**27** exhibit higher activities (4.20 µM, 6.00 µM and 4.40 µM, 4.88 µM) and less restrictions in their solubility making them better options for further investigations given also their good SI. The same positive effect also applies for the flexible trimeric **20** and **30**.

Tests on HeLa and A549

In cooperation with the group of Agnieszka Olejniczak (Institute of Medical Biology, Polish Academy of Science, Łódź) tests on the cytotoxicity of two human cancer cell lines, namely cervic adenocarcinoma HeLA and lung carcinoma A549 were conducted. Further the cytotoxicity against non-cancer cell lines, namely Vero (*Cercopithecus aethiops* normal kidney cells), LLC-MK2 (*Macaca mulatta* normal kidney cells), and MRC-5 (human lung normal fibroblasts) was tested. The tested compounds, triazoles **13**, **14**, **19** and **20** and thioureas **52**–**57**, all possessed the same (1*S*,4*S*,5*R*)-2-azabicyclo[3.2.1]octane moiety. Some good results were achieved, including CC_{50} values of as low as 2.70 µM for cervic adenocarcinoma HeLA and 3.33 µM against lung carcinoma A549 for **52**; unfortunately, this thiourea is also the most toxic compound against all checked three normal cell lines. Two other thioureas, **55** and **56**, exhibited good cytotoxicities. Unfortunately, all promising compounds were toxic against normal cell lines Vero, LLC-MK2 and MRC-5 cells.

Table 6 Toxicity tests of various bicyclic compounds against HeLA and A549 cancer cell lines.

	CC_{50} [µM]				
Compound	**HeLa**	**A549**	**Vero**	**LLC-MK2**	**MRC-5**
13	75.33 ± 8.08	71.33 ± 2.08	28.27 ± 0.23	6.07 ± 0.231	76.50 ± 9.58
14	37.50 ± 4.95	69.67 ± 9.50	7.17 ± 1.04	6.57 ± 0.21	81.67 ± 3.51
19	79.33 ± 10.07	>1000	10.33 ± 1.53	7.70 ± 1.01	>1000
20	76.50 ± 2.12	118.50 ± 6.26	>1000	50.75 ± 1.77	>1000
52	2.70 ± 0.10	3.33 ± 0.06	3.23 ± 0.15	1.53 ± 0.12	6.27 ± 1.66
53	20.93 ± 2.90	27.80 ± 1.22	22.83 ± 0.29	24.40 ± 1.20	27.33 ± 2.52
54	14.93 ± 1.29	17.70 ± 0.99	22.83 ± 5.58	18.60 ± 1.97	18.07 ± 2.25
55	4.07 ± 0.23	9.30 ± 1.08	6.27 ± 0.92	4.77 ± 0.74	6.67 ± 1.22
56	5.33 ± 0.61	28.67 ± 1.15	17.6 ± 2.09	4.23 ± 0.25	6.53 ± 1.17
57	139.33 ± 3.06	194.00 ± 8.49	117.5 ± 10.61	190.67 ± 9.81	259.33 ± 8.08

Tests on HT29 and PC3

In a cooperation with the group of Wessjohann (Leibniz-Institute für Pflanzenbiochemie, Halle, Germany) tests on the antiproliferative activity (CV – cell growth assay) and cell viability assay (MTT) were conducted applying bicycloalkane-based triazoles **13**, **14**, **19** and **20** and thioureas **52**–**57** (Table 7). The human colon cancer HT29 and prostate cancer PC3 cell lines were investigated and tested

compared with the pharmaceutical Digitonin. The assays were normed against a control medium which was set as 100%, as growth and viability were not impacted.

Overall, the impact of all tested (1*S*,4*S*,5*R*)-2-azabicyclo[3.2.1]octane-based compounds was very limited. The best results were achieved by thiourea **54**, which inhibited the cell viability of the colon cancer cell line HT29 slightly, as well as their cell growth. Unfortunately, none of the given results encourages any further investigation into these cell lines.

Table 7 Cell viability (MTT) and cell growth (CV) assays of various bicyclic compounds against HT29 and PC3

		HT29		PC3	
Compound	Conc [µM]	MTT[1] [% of control]	CV[2] [% of control]	MTT[1] [% of control]	CV[2] [% of control]
D[3]	0.1	-0.4 ± 7.2	-0.3 ± 10.7	-0.3 ± 6.5	-0.1 ± 11.1
C[4]	0	100.0 ± 7.9	100.0 ± 8.4	100 ± 9.1	100 ± 7.1
13	0.01	124.3 ± 7.2	92.7 ± 3.7	93.3 ± 5.9	96.8 ± 5.0
	10	152.7 ± 7.6	84.8 ± 9.7	102.3 ± 9.4	97.6 ± 5.1
14	0.01	109.6 ± 10.6	95.9 ± 2.9	98.2 ± 3.1	99.3 ± 4.3
	10	144.5 ± 8.9	100.7 ± 3.9	98.8 ± 2.4	96.7 ± 1.3
19	0.01	88.2 ± 10.6	92.5 ± 2.0	100.6 ± 2.2	93.3 ± 3.1
	10	146.4 ± 3.3	95.2 ± 10.2	113.1 ± 4.0	79.2 ± 45.3
20	0.01	90.0 ± 14.3	99.7 ± 4.0	96.0 ± 3.5	109.1 ± 3.9
	10	144.0 ± 4.1	95.9 ± 2.3	100.3 ± 1.6	104.0 ± 3.6
52	0.01	117.1 ± 6.4	86.2 ± 3.4	93.9 ± 2.6	95.8 ± 3.2
	10	138.0 ± 6.6	94.5 ± 4.4	109.9 ± 5.9	96.2 ± 3.0
53	0.01	63.6 ± 4.9	105.1 ± 3.8	101.3 ± 2.5	81.6 ± 6.7
	10	116.6 ± 22.7	107.4 ± 3.9	109.3 ± 6.3	81.0 ± 3.1
54	0.01	72.3 ± 9.6	89.4 ± 4.9	110.0 ± 7.1	103.7 ± 9.8
	10	74.1 ± 4.9	75.0 ± 8.5	110.7 ± 3.7	91.5 ± 5.1
55	0.01	111.8 ± 7.1	94.0 ± 4.9	91.2 ± 6.1	109.0 ± 8.8
	10	134.7 ± 8.9	97.1 ± 10.8	108.3 ± 3.7	113.0 ± 7.6
56	0.01	103.2 ± 10.1	92.8 ± 5.5	104.2 ± 4.7	105.6 ± 5.7
	10	100.4 ± 15.9	76.1 ± 7.7	92.6 ± 1.2	101.3 ± 3.6
57	0.01	99.7 ± 4.0	96.3 ± 7.8	90.7 ± 3.2	88.9 ± 8.0
	10	127.9 ± 5.3	103.4 ± 3.9	92.2 ± 7.5	80.0 ± 5.5

[1)]MTT = cell viability assay, [2)]CV = cell growth assay, [3]D = Digitonin, 125µg/mL, [4)]C = Control (Medium)

3.3.2 Antiviral activity

In cooperation with the group of A. Olejniczak (Institute of Medical Biology, Polish Academy of Science, Łódź) antiviral activity tests on five viruses, herpes simplex virus HSV-1, human parainfluenza virus HPIV-3, human adenovirus AdV5, Human cytomegalovirus HCMV and encephalomyocarditis virus EMCV were conducted. Four triazoles including mono-, di- and trimeric **13**, **14**, **19** and **20** and seven thioureas **52**–**57** were tested. Promising results were achieved, although the data set given is often inconclusive (Table 8). Values are often presented without proper standard deviation, making it difficult to correctly assess the true impact of those values; the initial analysis is, however, possible.

Special attention may be given to the thioureas **52**, **55** which have IC_{50} values of below 10 µM for all tested virus variants. Many good to very good results were found for HPIV-3 with six from ten tested compounds with low IC_{50} values. Again, **52** and **55** were good with >1.53 µM and 1.70 µM, respectively.

Considering the SI and the earlier established threshold of two to three as promising, **53** and **55** seem interesting with SI of 2.18 and 2.81 with respect to HPIV-3, respectively. Further investigation and more certain antiviral data are necessary for definite assessment of the compounds.

Table 8 Antiviral activity tests of various 2-azabicycloalkanes against HSV-1, HPIV-3, AdV5, HCMV and EMCV

	Antiviral activity IC_{50} [µM]					
Compound	**HSV-1**	**HPIV-3**	**AdV5**	**HCMV**	**EMCV**	**SI**
13	>28.27	>6.07	>75.33	>76.50	>71.33	ND
14	>7.17	>6.57	>37.50	>81.67	>69.67	ND
19	>10.33	>7.7	>79.33	>1000	>1000	ND[b]
20	>1000	>50.75	>50.75	>1000	>118.50	ND
52	>3.23	>1.53	>2.70	>6.27	>3.33	ND
53	>22.83	11.15 ± 0.13	>20.93	>27.33	>27.80	2.18 (HPIV-3)
54	>22.83	>18.60	>14.93	>18.07	>17.70	ND
55	>6.27	1.70 ± 0.26	>4.07	>6.67	>9.30	2.81 (HPIV-3);
56	>17.60	>4.23	>5.33	>6.53	>28.67	ND
57	>117.5	176.00 ± 8.00	75.67 ± 5.51	>259.33	>194.00	1.08 (HPIV-3) 1.84 (ADV-5)

[a] Selectivity index (SI) = CC_{50}/IC_{50}.; [b] ND = not determined

3.3.3 Antibacterial activity

In a cooperation with the group of L. Wessjohann (Leibniz-Institute für Pflanzenbiochemie, Halle, Germany) antibacterial activity studies on two basic strains, *A. fischeri* and *B. subtilis* were conducted applying the same triazoles **13**, **14**, **19** and **20** and thioureas **52**–**57** as already tested (Table 9). The activities were compared with the antibacterial impact of the known broad spectrum antibiotic API chloramphenicol. The antibacterial properties of the tested compounds can be clearly divided in two groups: the rather inactive triazoles **13**, **14**, **19** and **20** and the active thioureas **52** – **56** (with the exception of the saccharide-azabicycloalkane thiourea **57**). Especially against *Aliivibrio fischeri*, a gram-negative bacteria, the activities were consistently high, above 90% inhibition at 100 µM concentration compared with the control. Compounds **55** and **56** have an advantage against the known antibacterial drug: after just one hour at the higher concentrations. Unfortunately, the inhibition drastically dropped with smaller concentration (1 µM).

Comparing the obtained values for the inhibition of *Bacillus subtilis*, a gram-positive bacteria, with the activity of the antibiotic three very good results could be found. Tests for a lower concentration of 1 µM of chloramphenicol were not conducted by the cooperation partners; conclusions on the concentration dependency of chloramphenicol and the three active thioureas **52**, **55** and **56** could not be drawn.

Overall, especially compounds **55** and **56** stood out (at 100 µM concentration). And the pursue of 2-azabicyclo[3.2.1]octane-thioureas as antibiotics might be worth considering, if not for earlier cytotoxic behavior against non-malicious cell lines. Calculations and deeper investigations into SI could procure remedy on that.

Table 9 Antibacterial activity against A. fisheri and B. subtilis.

		Aliivibrio fischeri [% inhibition]		*Bacillus subtilis* [% inhibition]
Compound	**conc. [µM]**	**t = 1h**	**t = 24h**	**t = 20h**
Chloramphenicol	1	-7.59 ± 1.84	96.18 ± 0.55	-
	100	-31.43 ± 1.66	99.97 ± 0.00	99 ± 0
13	1	8.38 ± 2.01	-27.93 ± 10.61	35 ± 12
	100	10.41 ± 1.91	37.49 ± 4.69	18 ± 16
14	1	6.78 ± 3.87	-13.19 ± 23.20	50 ±10
	100	41.62 ± 6.04	65.65 ± 3.06	-2 ± 13
19	1	1.46 ± 1.82	-21.25 ± 16.27	15 ± 10
	100	-1.22 ± 1.17	-49.88 ± 16.87	27 ± 17
20	1	0.77 ± 1.88	7.48 ± 15.95	28 ± 14
	100	2.17 ± 2.30	-74.22 ± 11.88	1 ± 15
52	1	-11.99 ± 3.02	18.61 ± 12.40	53 ±9
	100	28.67 ± 2.69	95.2 ± 0.68	101 ± 1
53	1	6.06 ± 2.56	-33.16 ± 9.03	11 ± 4
	100	-10.47 ± 1.47	99.58 ± 0.73	-66 ± 29
54	1	3.00 ± 2.16	-25.81 ± 6.90	33 ±28
	100	29.19 ± 16.52	95.29 ± 4.73	-23 ± 16
55	1	4.09 ± 3.31	-46.99 ± 7.57	29 ± 6
	100	93.53 ± 5.25	97.57 ± 0.85	95 ± 3
56	1	3.06 ± 2.02	-24.86 ± 6.49	14 ± 11
	100	99.31 ± 0.58	99.91 ± 0.19	100 ± 1
57	1	9.26 ± 4.66	-55.28 ± 31.52	5 ± 21
	100	10.86 ± 3.13	-16.91 ± 22.24	25 ± 30

Tests were evaluated towards a control sample. Negative values might indicate accelerated growth.

3.3.4 Antifungal activity

The cooperation with the group of L. Wessjohann (Leibniz-Institute für Pflanzenbiochemie, Halle, Germany) yielded a broad spectrum of results against three fungal cell lines, *S. tritici*, *B. cinerea* and *P. infestans*. The assay was conducted applying four triazoles (**13**, **14**, **19** and **20**) and six thioureas (**52** – **57**). Comparison of their inhibition in percent is given by the application of the fungicides epoxiconazole (for *S. tritici* and *B. cinerea*) and terbinafine, for (*P. infestans*). Some good results were found against *S. tricitici* and *B. cinerea*, but overall good to very good results were achieved by triazoles and thioureas likewise against the fungal stem *P.infestans.*

Again, the best results were achieved by the thioureas **55** and **56** likewise, however, only with the higher concentration of 125 µM applied. Against the oomycete *Phytophthora infestans* a total of eight of the ten tested compounds had above 80% of inhibition and seven had even better activity at lower concentration compared with the known antifungal agent Terbinafine. The best antifungal agent was **55** with 98.91% inhibition at 125 µM concentration and 96.82% at 42 µM. As all the tested fungi are infecting plants. Their application has to be tailored for the application as fungicide for crops. Former toxicities against human cell lines have less of an impact on the evaluation.

Table 10 Antifungal activity against *S. tritici*, *B. cinerea* and *P. infestans*.

Compound	Conc.[µM]	*S. tritici* Inhibition [%]	*B. cinerea* Inhibition [%]	*P. infestans* Inhibition [%]
Epoxiconazole	125	97.71 ± 0.32	96.92 ± 1.98	-
	42	99.28 ± 0.21	100.30 ± 0.44	-
Terbinafine	125	-	-	97.65 ± 0.94
	42	-	-	11.72 ± 1.32
13	125	24.34 ± 9.95	57.28 ± 12.28	56.02 ± 7.79
	42	27.90 ± 16.45	50.49 ± 5.64	87.90 ± 2.80
14	125	-2.25 ± 14.31	78.16 ± 5.31	89.10 ± 3.09
	42	-23.03 ± 4.52	47.20 ± 4.19	6.98 ± 3.77
19	125	-33.39 ± 13.37	-33.34 ± 18.22	6.10 ± 0.91
	42	-5.26 ± 9.23	8.69 ± 9.16	4.10 ± 1.52
20	125	-62.07 ± 14.89	-36.30 ± 8.73	94.24 ± 2.38
	42	-27.06 ± 3.52	7.26 ± 14.71	94.44 ± 2.41
52	125	86.80 ± 4.5	20.9 ± 12.4	96.1 ± 0.4
	42	50.60 ± 14.80	34 ± 13	88.0 ± 12.6
53	125	58.8 ± 9.5	49.6 ± 14.5	94.3 ± 1.5
	42		38.8 ± 10.7	83.7 ± 2.6
54	125	32.4 ± 10	49.3 ± 9.5	93.1 ± 2.5
	42	27.80 ± 4.60	40.4 ± 5.4	87.2 ± 1.6
55	125	108.36 ± 2.22	96.25 ± 3.37	98.91 ± 0.34
	42	22.52 ± 19.70	44.40 ± 10.33	96.82 ± 0.46
56	125	99.3 ± 1.4	82.1 ± 5.7	93.5 ± 2.8
	42	58.00 ± 7.80	48.1 ± 5.7	84.3 ± 3.0
57	125	45.18 ± 14.64	25.25 ± 9.25	10.24 ± 3.45
	42	0.64 ± 23.47	5.61 ± 23.57	0.69 ± 2.11

3.3.5 Anthelmintic activity

With the help of the group of L. Wessjohann (Leibniz-Institute für Pflanzenbiochemie, Halle, Germany) initial results on possible anthelmintic activities of triazoles **13**, **14**, **19** and **20** and thioureas **52**–**57** were received. The antiparasitic properties of the ten bicyclic derivatives were tested against *Caenorhabditis elegans* (Table 11) and evaluated compared to the known pharmaceutical Ivermectin. Overall, no significant activity could be observed, the highest activity was given by **55** with mere 7.22%, compared to 96.47%to the existing drug. It is therefore of no interest to further investigate any deeper into the matter of application as anthelmintic agent.

Table 11 Anthelmintic assay against *C. elegans*.

Compound	Activity [%]
2% DMSO	2,27 ± 3,21
Ivermectin	96,47 ± 2,50
13	1,45 ± 1,04
14	0,00 ± 0,00
19	2,95 ± 2,24
20	4,70 ± 2,06
52	3,14 ± 2,33
53	0,00 ± 0,00
54	4,92 ± 1,94
55	7,22 ± 2,67
56	1,23 ± 1,74
57	3,36 ± 1,33

4 Discussion and Summary

Various novel 2-azabicyclo[2.2.1]heptane and 2-azabicyclo[3.2.1]octane-based triazoles and thioureas were synthesized. The synthesis of known compounds, as well as the development of new routes applying established methodologies led to the synthesis of various new substrates for the synthesis of multifunctional triazole and thiourea derivatives. Building on known bicyclic azides a set of triazoles was synthesized by CuAAC "click" reaction. The Corey-Fuchs methodology led to two pseudo-enantiomeric bicyclic alkynes (through a dibromovinyl intermediate) which in turn could be applied in the preparation of further triazoles. For the synthesis of thioureas, the condensation of amine and isothiocyanate derivatives was chosen. Bicyclic amines and three bicyclic isothiocyanates were reacted with various complimentary partners modulating the inductive effect on the catalytic center and adjusting linker lengths. A set of protected 2-azabicyclo[2.2.1]heptane and 2-azabicyclo[3.2.1]octane derivatives were synthesized and attempts of deprotection of the heptane-thiourea derivatives were partially successfully carried out and side-products were analyzed. Attempts to overcome the issue were conducted in using another protecting group (Cbz); a full set of novel protected 2-azabicyclo[2.2.1]heptane precursors was synthesized, which may find application whereas the deprotection conditions of other protecting groups are too harsh. Further, two calix[4]arene derivatives were obtained for the purpose of development of multivalent organocatalysts. In addition to known lower-rim tetra-amines a novel upper-rim calix[4]arene was successfully synthesized. Both tetra-amines were applied in the condensation reaction with bicyclic 2-azabicyclo[3.2.1]octane isothiocyanates to form tetra-thiourea clusters. Whereas lower-rim tetra-thiourea **71** was successfully synthesized, the upper-rim thiourea could not be obtained (with a full characterization) due to solubility issues of the starting material, which might have been overcome by conducting the reaction in DMF.

The 2-azabicycloalkane products were tested in various applications. Four triazoles were applied in the synthesis of square-planar palladium(II) complexes. One product **77** could be isolated successfully with 50% yield and the remaining attempts provided some insight into the possible complexation of palladium(II) by various bicyclic triazoles. Triazole **20** ligand shown clear indications of anionic character in the complex and could successfully chelate palladium as a tridendate ligand, competing with the solvent and chloride ligands likewise. Application of other non-rigid, non-aromatic dimeric triazoles may be promising, such as compounds **16, 17, 26, 27**. Furthermore, the initial idea of complexing platinum(II) may be tackled again: similarly to *cis*-platin the square-planar complexes are promising targets for modification and optimization for their anti-cancer properties.

The thioureas were applied in asymmetric model Michael-addition reactions and gave good to very good enantiomeric excesses and up to very good conversion rates. The addition of dimethyl malonate to β-nitrostyrene was efficiently catalyzed by the thiourea catalysts (up to 74% *ee* and >99% conversion for **52**) and it was possible to control the stereochemical outcome by application of either (1*S*,4*S*,5*R*)- or (1*R*,4*R*,5*S*)-2-azabicyclo[3.2.1]octane-thioureas (**52-57,71** or **58-61**, respectively), whereas the best results for the opposite (*R*)-stereochemistry of the product was achieved by the pseudo-enantiomer **58** (51% *ee*, 75% conversion). The conversion rates of both compounds are good, which proves their activity and sufficient basicity of the amines, however, enantiomeric excesses are at best good and not sufficient enough to be considered for practical applications.

What might be an issue is the relatively big, sterically hindering substituent on the basic nitrogen atom which additionally includes an independent stereocenter inhibiting a clear transition state. Compared to the DACH-based Takemoto catalyst the basicity is similar, but the steric hindrance significantly higher. The removal of the chiral methylbenzyl substituent proved to be problematic, as at suitable stages, such as azide or amine stage of precursors the hydrogenation does not proceed completely due to the mild amine-poisoning. Other possibilities for future transformation might include the removal of the methylbenzyl substituent by hydrogenation after *aza*-DA cycloaddition (products **2**) and a following non-reversible methylation of the amine. Tests on the nucleophilic substitution and accompanying possible ring-expansion are necessary, but the +I effect of the alkyl group should allow the aziridinium ion formation followed by substitution accompanied by ring expansion. This procedure would have the advantage, that formerly pseudo-enantiomeric products (after removal of the only identical stereogenic center) would become enantiomers and asymmetric reaction should proceed with the opposite stereochemical outcome and better enantiomeric excesses.

In the second model reaction, the Michael addition of cyclohexanone to β-nitrostyrene, two secondary amine organocatalysts were applied. The best results were achieved for **45**, while the conversion was low (up to 29%), the enantiomeric excesses were very good (up to 96% *ee*). The main problem of the reaction was the lack of the activation from the 3,5-di(flouromethyl)benzene substituent, as for **52** and **58**. Deprotection reaction, however, never yielded the targeted product **42**, because of a competing desulfiration side-reaction and this problem has never been fully overcome.

All synthesized triazoles and part of thioureas were applied in biological activity assays. The triazoles were comprehensively tested as anti-cancer drugs and a chosen set of triazoles and thioureas were applied in broad spectrum tests in frame of various international cooperations. Tests on their antiproliferative, antiviral, antibacterial, antifungal and anthelmintic activity were conducted.

Antiproliferative activity assays of the triazoles were conducted and a structure-activity analysis accompanied the good results, especially against the lung cancer cell line NCI-H1581. *Cis*-platin exceeding results and significantly much better selectivity indices could be found for the bicyclic triazole derivatives, whereas a tendency in activity increase from monomeric, to dimeric and trimeric could be observed. The best results were observed for **20**, which also exhibited good antiproliferative activity against pancreas cancer cell line MIA PaCa-2 together with a significant lower toxicity against murine normal fibroblast BALB/3T3 clone A31 compared to *cis*-platin. Similar results with slightly less activity for both cancer cell lines were found for the trimeric pseudo-enantiomer **30**.

The broad scope tests of various selected triazoles and thioureas gave insight into promising biological activities worth pursuing. Toxicity tests against cervic adenocarcinoma HeLA and lung caricnoma A549 cancer cell lines revealed good activity for some thioureas (**53, 55, 56**), however, accompanied by very high toxicities against three chosen non-cancer normal cell lines. Assays against colon cancer and prostate cancer were unsatisfactory. Antiviral tests against five chosen virus variants are promising, especially in light of some derived SI. Generally good results against human parainfluenza virus HPIV-3 were achieved, by triazole and thiourea samples likewise. Best results were found for thioureas **52** and **55**, which both exhibited antiviral activities against all five tested variants and its calculated SI of 2.81 against HPIV-3 is a good initial result. Tests against gram-positive and gram-negative bacteria stems, *B. subtilis* and *A. fischeri*, respectively, were to some extend favorable. High concentration of some thioureas were successful against both, with **55** and **56** exhibiting the overall best activities. They also

demonstrated the fastest antibacterial response against *A. fischeri* with high inhibition after already one hour and high inhibition against *B. subtilis*, comparably good as the control drug. Antifungal activity tests revealed overall very high inhibition of *P. infestans* at high and low concentrations for a variety of both triazole and thiourea derivatives, exceeding the antifungal agent Terbinafine. Some good results against *S. tritici* and *B. cinerea* at higher concentration by **55** and **56** were found. Anthelmintic activity tests revealed very low impact on the chosen parasite.
All conducted tests gave an initial insight into possible biological applications of the applied triazoles and thioureas. Some good results were collected against viruses, which, however, need to be further investigated concerning their toxicities against normal cell lines. The most promising results were achieved as antifungal agent. For this application, toxicities against human cell lines are to some extent negligible. The overall most active compound was **55**, exhibiting some anti-cancer, good antiviral, good antibacterial and excellent antifungal activities. The biological activity tests add to the understanding of biological activity exhibited by the tropane alkaloid analogues 2-azabicyclo[3.2.1]octane, especially in contrast to the majority of previous collected data which was focused on 2-azabicyclo[2.2.1]heptane derivatives.

The results of the presented thesis, up to the date of submission include among others published information from two research articles and two patents, and insight into the subject from two review papers and one book chapter. It includes the successful synthesis of numerous new and fully characterized (published and not yet published) compounds, products and analyzed intermediates or side-products, bearing 2-azabicyclo[2.2.1]heptane or 2-azabicyclo[3.2.1]octane units. Among them, 23 novel triazoles and 16 new thiourea derivatives were synthesized, together with 15 novel precursors or side-products. The final products were then applied successfully in various ways, including the complexation of palladium(II), asymmetric model Michael addition reaction and broad biological activity tests (antiproliferative, antiviral, antibacterial, antifungal and anthelmintic activity). Critical discussion of the results indicate future possibilities and inspirations laying the groundwork for further investigations on the promising skeleton of 2-azabicycloalkanes.

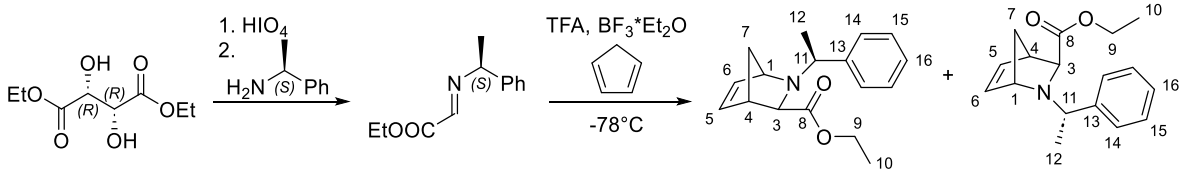
5 Experimental data

General information

All reagents were acquired from Merck and were used without further purifications. Column chromatography was performed on silica gel 60 (70-230 mesh) and Sephadex® LH-20 and flash column chromatography on silica gel 60 (230-400 mesh). Thin layer chromatography was conducted on precoated plates (Silica gel 60, with fluorescent indicator 254 nm). Wherever concentrations of starting materials in solvents were mentioned the Molarity M was calculated as following: $M\ \left[\frac{mol}{L}\right] = \frac{n}{V}$ with V is volume of solvent and is therefore by design only an approximation. NMR spectra were, if not otherwise stated, measured on Jeol 400yh and Bruker Avance II 600 instruments. ^{1}H-NMR spectra were measured at 400 and 600 MHz, and ^{13}C-NMR spectra at 100 and 151 MHz, respectively. If not otherwise stated, the experiments were conducted at 298 K and in deuterated solvents ($CDCl_3$, CD_3OD and d6-DMSO, indicated in the description of the spectra), whose residual peaks were used for calibration. All numbering of the products in the upcoming experimental data are not correct by IUPAC standards and are only applied for assignment reasons; wherever possible assignments were given. High resolution mass spectra were collected using Waters LCT Premier XE TOF instrument with electrospray ionization, if not otherwise mentioned. Optical rotations were measured using an Optical Activity Ltd. Model AA-5 automatic polarimeter. Infrared spectra in the range of 500 – 4000 cm^{-1} were recorded using a Perkin Elmer 2000 FTIR spectrophotometer. Melting points were determined on the Schmelzpunkt Bestimmer Apotec apparatus using standard open capillary. Elementary analyses were conducted with a vario EL cube from Elementar. HPLC analyses were conducted on an Agilent 1260 Infinity II with 4.6 x 250 mm chiral columns from Daicel (indications of the column at the spectra).

5.1 2-Azabicycloalkanes

Ethyl-2-((S)-1-phenylethyl)-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylates **1**



exo-(1R,3R,4S)-**1**
main product

exo-(1S,3S,4R)-**1**
minor product

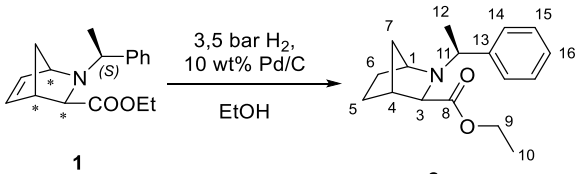
A synthesis was typically conducted in a one tenth scale of the literature method.[69] Diethyl L-tartarte (8.00 g, 0.039 mmol, 0.50 equiv.) was dissolved in Et_2O (100 mL, 0.39 M) and cooled to 0 °C. Periodic acid (8.84 g, 0.039 mmol, 0.50 equiv.) was then added portionwise over a period of 30 min and the reaction mixture was allowed to reach room temperature and stirred for additional 30 min. The liquid phase was then decantated, the solid was washed with Et_2O and combined organic phases were concentrated under reduced pressure. The formed ethyl glyoxylate was transferred into a three-neck round bottom flask equipped with a mechanical stirrer, dissolved in CH_2Cl_2 (120 mL, 0.65 M), and 4 Å molecular sieves (approximately 40 g) were added. The reaction mixture was cooled by an ice bath and (*S*)-phenylethylamine (10 mL, 0.078 mmol, 1.00 equiv.) was added dropwise and stirred for 1 to 2 h. The reaction mixture was cooled to -78°C with a cryostat and in roughly 10 min intervals trifluoroacetic

acid (6.0 mL, 0.078 mmol, 1.00 equiv.), boron trifluoride diethyl etherate (10.0 mL, 0.078 mmol, 1.00 equiv.) and freshly distilled cyclopentadiene (7.8 mL, 0.093 mmol, 1.2 equiv.) were added. The reaction was stirred overnight, quenched by aq. Na_2CO_3, extracted by CH_2Cl_2 (3x 75 mL) and the combined organic phases concentrated under reduced pressure. The crude was purified by column chromatography (SiO_2, 35x4 cm, 90:10 hexane:EtOAc) yielding the two diastereomers, major *exo*-(1*R*,3*R*,4*S*)-**1** and minor *exo*-(1*S*,3S,4*R*)-**1** as colourless to slightly yellow oils. Comparable yields to the literature could be achieved with up to 63% combined yield.
All recorded spectroscopic data matched previously reported ones.

Ethyl (1R,3R,4S)-2-((S)-1-phenylethyl)-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate **1**
^{1}H-NMR: (400 MHz, $CDCl_3$) δ 7.29 – 7.24 (m, 2H, 2x PhH), 7.22 – 7.18 (m, 2H, 2x PhH), 7.17 – 7.12 (m, 1H, *p*-PhH), 6.39-6.40 (m, 1H, C=CH), 6.24 – 6.26 (m, 1H, C=CH), 4.29-4.27 (m, 1H, C3H), 3.85 – 3.73 (m, 2H, $C9H_2$), 3.01 (m, 1H, C11H), 2.88 – 2.85 (m, 1H, C1H), 2.18 (m, 1H, C4H), 2.08 (m, 1H, $C7H_a$),1.38-1.41 (m, 4H, $C7H_b$, $C12H_3$), 0.92 (t, *J* = 6.8 Hz, $C10H_3$) ppm.

Ethyl (1S,3S,4R)-2-((S)-1-phenylethyl)-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate **1**
^{1}H-NMR: (400 MHz, $CDCl_3$) δ 7.56 – 7.29 (m, 4H, 4x PhH), 7.28 – 7.24 (m, 1H, *p*-PhH), 6.41 – 6.39 (m, 1H, C=CH), 6.02 – 6.01 (m, 1H, C=CH), 4.26 – 4.20 (m, 2H), 3.52 (s, 1H), 3.08 – 3.00 (m, 2H), 2.48 – 2.44 (m, 1H), 1.90 –1.86 (m, 1H), 1.33 – 1.15 (m, 7H) ppm.
Crystals formed in the fridge over time. X-Ray structure was measured to prove the structure unambiguously.

Ethyl-2-((S)-1-phenylethyl)-2-azabicyclo[2.2.1]heptane-3-carboxylate **2**



According to literature,[94] a standard reduction of the double bond was conducted with the separated fractions of (1*R*,3*R*,4*S*)-**1** and (1*S*,3*S*,4*R*)-**1** individually yielding (1*S*,3*R*,4*R*)-**2** and (1*R*,3*S*,4*S*)-**2**, respectively. The weighed fractions of *aza*-DA-products were dissolved in absolute EtOH and 10 % Pd/C (10 wt%) and K_2CO_3 (1.00 equiv.) was added. The reaction was put into a hydrogen generator, three times purged and set to react at 3.5 bar H_2 pressure. Pressure loss could be observed and roughly be calculated according to the used starting material. Reaction times varied between two and five hours, after filtration through celite the solvent was removed under reduced pressure and completeness of the reduction was controlled by ^{1}H-NMR. The reaction yield was usually quantitative, and no further purification was necessary.
Some recorded spectroscopic data did not match previously reported ones. Comments concerning the observed differences are provided.

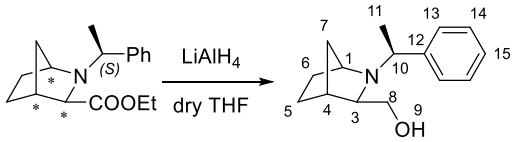
Ethyl (1S,3R,4R)-2-((S)-1-phenylethyl)-2-azabicyclo[2.2.1]heptane-3-carboxylate **2**
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.28 (m, 2H, 2x PhH), 7.25 – 7.19 (m, 2H, 2x PhH), 7.19 – 7.13 (m, 1H, *p*-PhH), 3.77 – 3.74 (m, 1H, C4H), 3.72 – 3.69 (m, 2H, $C9H_2$), 3.50 (q, *J* = 6.4 Hz, 1H, C11H), 2.54 (s,

1H, C3H), 2.31 – 2.24 (m, 1H, C1H), 2.17 – 2.06 (m, 1H, $C7H_a$), 2.05 – 1.93 (m, 1H, $C5H_a$), 1.70 – 1.60 (m, 1H, $C6H_a$), 1.46 – 1.35 (m, 2H, $C5H_b$, $C6H_b$), 1.34 (d, *J* = 6.6 Hz, 3H, $C12H_3$), 1.31 – 1.26 (m, 1H, $C7H_b$), 0.91 (t, *J* = 7.1 Hz, 3H, $C10H_3$) ppm. In the published data[94] some errors must have occurred while integrating the spectra (2 protons too much), which are corrected in the data given here; chemical shifts are concordant with the reported values.

Ethyl (1R,3S,4S)-2-((S)-1-phenylethyl)-2-azabicyclo[2.2.1]heptane-3-carboxylate **2**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (m, 2H, 2x PhH), 7.33 – 7.27 (m, 2H, 2x PhH), 7.25 – 7.19 (m, 1H, *p*-PhH), 3.70 (q, *J* = 7.0 Hz, 2H, $C9H_2$), 3.58 (d, *J* = 6.6 Hz, 1H, C11H), 3.46 (s, 1H), 3.04 (m, 1H), 2.85 (d, *J* = 11.2 Hz, 1H), 2.52 – 2.46 (m, 1H), 1.94 – 1.80 (m, 2H), 1.67 – 1.53 (m, 1H), 1.44 – 1.34 (m, 1H), 1.27 (d, *J* = 6.6 Hz, 3H, $C12H_3$), 1.23 – 1.20 (t, *J* = 7.0 Hz, 3H, $C10H_3$), 1.19 – 1.06 (m, 2H) ppm.

(2-((S)-1-phenylethyl)-2-azabicyclo[2.2.1]heptan-3-yl)methanol **3**



2 **3**

According to literature,[93,100] a standard reduction of ester to alcohol was conducted as following: to a stirred solution of $LiAlH_4$ (2.30 equiv.) in dry THF (0.8 M) at 0 °C a solution of diastereomerically pure **2** (1.00 equiv.) in THF (0.1 M) was added dropwise. The cooling was removed and the reaction mixture was stirred overnight at room temperature, quenched by 10 wt% aq. NaOH breaking the emulsion and precipitating white hygroscopic LiOH. Upon filtration through a pad of celite the filtrate was dried with Na_2SO_4 and concentrated under vacuum. Opposing literature procedure generally no further purification was necessary and the yields were quantitative, if it became necessary, column chromatography was applied (SiO_2, 83.3:16.7 to 75:25 hexane:EtOAc).
All recorded spectroscopic data matched previously reported ones.

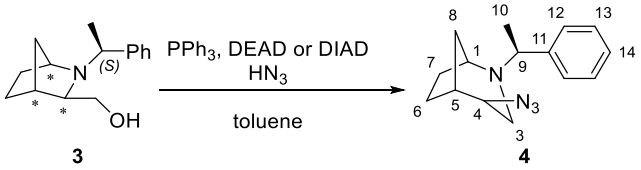
((1S,3R,4R)-2-((S)-1-phenylethyl)-2-azabicyclo[2.2.1]heptan-3-yl)methanol **3**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.16 (m, 5H, 5x PhH), 3.77 – 3.69 (m, 1H, OH), 3.65 – 3.60 (m, 1H, C4H), 3.50 (q, *J* = 6.5 Hz, 1H, C10H), 2.73 (dd, *J* = 10.5, 2.0 Hz, 1H, C3H), 2.29 (dd, *J* = 10.5, 6.1 Hz, 1H, $C8H_a$), 2.12 (dd, *J* = 4.1, 2.1 Hz, 1H, C1H), 2.05 (dd, *J* = 6.1, 2.3 Hz, 1H, $C8H_b$), 1.97 (m, 1H, $C5H_a$), 1.85 – 1.82 (m, 1H, $C7H_a$), 1.59 (m, 1H, $C6H_a$), 1.40 – 1.34 (m, 1H, $C5H_b$), 1.33 (d, *J* = 6.6 Hz, 3H, $C11H_3$), 1.31 – 1.21 (m, 1H, $C6H_b$), 1.21 – 1.15 (m, 1H, $C7H_b$) ppm.

((1R,3S,4S)-2-((S)-1-phenylethyl)-2-azabicyclo[2.2.1]heptan-3-yl)methanol **3**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.26 (m, 4H, 4x PhH), 7.26 – 7.17 (m, 1H, *p*-PhH), 3.67 (q, *J* = 6.6 Hz, 1H, C10H), 3.54 (dd, *J* = 10.2, 6.7 Hz, 1H, $C8H_a$), 3.47 (dd, *J* = 10.2, 2.4 Hz, 1H, $C8H_b$), 3.01 – 2.95 (m, 1H), 2.38 (dd, *J* = 6.7, 2.4 Hz, 1H), 2.27 (dd, *J* = 4.1, 2.1 Hz, 1H), 1.93 (dddd, *J* = 13.4, 9.2, 4.5, 2.5 Hz, 1H), 1.88 – 1.81 (m, 1H), 1.81 – 1.73 (m, 1H), 1.57 (tt, *J* = 12.2, 4.4 Hz, 1H), 1.32 (d, *J* = 6.4 Hz, 3H, $C11H_3$), 1.31 – 1.18 (m, 1H), 1.18 – 1.09 (m, 1H), 1.09 – 1.03 (m, 1H) ppm.

4-azido-2-((S)-1-phenylethyl)-2-azabicyclo[3.2.1]octane **4**

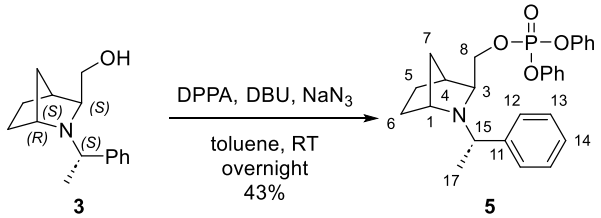


According to literature,[100,102] a general synthesis of azides **4** was conducted by dissolving diasteriomerically pure alcohols **3** (1.00 equiv.) and triphenylphosphine (PPh_3, 1.30 equiv.) in toluene (0.13 M) at 0 °C, followed by addition of hydrazoic acid (1 M in toluene, 1.3 equiv.) in one portion and the dropwise addition of either DEAD (40% in toluene, 1.50 equiv.) or DIAD (40% in toluene, 1.50 equiv.). The reaction was allowed to reach room temperature and stirred overnight before it was quenched by the addition of aq. NaOH (10 wt%) to basify the solution. Upon extraction (3 times with CH_2Cl_2) the organic phase was concentrated under reduced pressure. To remove the majority of triphenylphosphine oxide side product, the crude mixture was dissolved in 1:1 hexane:Et_2O and the undissolved side product was filtered off. Purification was achieved by column chromatography (SiO_2, 90:10 to 83.3:16.7 hexane:EtOAc).
All recorded spectroscopic data matched previously reported ones.

(1S,4S,5R)-4-azido-2-((S)-1-phenylethyl)-2-azabicyclo[3.2.1]octane **4**
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.26 (m, 4H, 4x PhH), 7.25 – 7.18 (m, 1H, *p*-PhH), 3.60 (t, *J* = 5.0 Hz, 1H, C1H), 3.36 (q, *J* = 6.6 Hz, 1H, C9H), 3.27 (tt, *J* = 3.7, 1.7 Hz, 1H, C4H), 2.56 (dd, *J* = 13.4, 1.3 Hz, 1H, $C3H_a$), 2.34 (q, *J* = 5.3, 4.4 Hz, 1H, C5H), 2.24 (dd, *J* = 13.3, 3.7 Hz, 1H, $C3H_b$), 2.18 – 2.07 (m, 1H, $C8H_a$), 1.84 – 1.66 (m, 2H, $C6H_a$, $C7H_a$), 1.48 – 1.38 (m, 1H, $C6H_b$), 1.36 (m, 1H, $C7H_b$), 1.33 (d, *J* = 6.6 Hz, 3H, $C10H_3$), 1.31 – 1.24 (m, 1H, $C8H_b$) ppm.

(1R,4R,5S)-4-azido-2-((S)-1-phenylethyl)-2-azabicyclo[3.2.1]octane **4**
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.26 (m, 4H, 4x PhH), 7.24 – 7.17 (m, 1H, *p*-PhH), 3.43 – 3.33 (m, 2H, C4H, C9H), 3.08 – 3.00 (m, 2H, C1H, $C3H_a$), 2.45 (dd, *J* = 13.0, 3.7 Hz, 1H, $C3H_b$), 2.39 – 2.31 (m, 1H, C5H), 1.98 (dd, *J* = 11.5, 2.8 Hz, 1H, $C8H_a$), 1.82 – 1.73 (m, 1H, $C7H_a$), 1.73 – 1.63 (m, 1H, $C6H_a$), 1.39 – 1.31 (m, 1H, $C6H_b$), 1.31 – 1.19 (m, 1H, $C7H_b$), 1.26 (d, *J* = 6.7 Hz, 3H, $C10H_3$), 1.12 (dtd, *J* = 11.3, 4.7, 1.8 Hz, 1H, $C8H_b$) ppm.

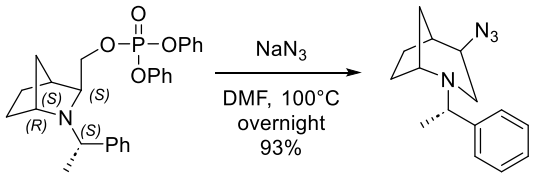
Diphenyl (((1R,3S,4S)-2-((S)-1-phenylethyl)-2-azabicyclo[2.2.1]heptan-3-yl)methyl) phosphate **5**



To a solution of (1*R*,3*S*,4*S*)-**3** (1.155 g, 5.00 mmol, 1.00 equiv.) in toluene (10 mL, 0.5 M) sodium azide (0.650 g, 10.00 mmol, 2.00 equiv.) was introduced under argon atmosphere. DPPA (1.62 mL, 7.50 mmol, 1.50 equiv.) followed by DBU (1.12 mL, 7.50 mmol, 1.50 equiv.) were added dropwise at 0 °C. After 15 min. the cooling was removed and the reaction mixture was stirred overnight. It was then diluted with H_2O (15 mL) and extracted with CH_2Cl_2 (2x 15 mL). The combined organic phases

were dried over Na_2SO_4 and the solvent was removed under reduced pressure. Flash column chromatography (SiO_2, 15x4.5 cm, 90:10 to 75:25 *c*-Hex:EtOAc) yielded 983 mg (2.12 mmol, 43% yield) of colourless needles. Analyses concentrated only on the identification of the intermediate product, without full characterisation; all experimental data are presented.

^{1}H-NMR: (400 MHz, $CDCl_3$) δ 7.35 (m, 4H, 4x PhH), 7.29 – 7.24 (m, 8H, 8x PhH), 7.20 (m 3H, 3x *p*-PhH), 4.15 (ddd, *J* = 10.0, 6.5, 3.4 Hz, 1H), 3.88 (q, *J* = 9.9 Hz, 1H), 3.59 (q, *J* = 6.4 Hz, 1H, C9), 2.88 (s, 1H), 2.47 (dd, *J* = 9.8, 3.3 Hz, 1H), 2.35 (d, *J* = 4.0 Hz, 1H), 1.93 – 1.82 (m, 1H, C6H_a), 1.61 (d, *J* = 7.5 Hz, 1H, C7H_a), 1.54 (dt, *J* = 12.2, 4.4 Hz, 1H, C5H_a), 1.29 (d, *J* = 6.5 Hz, 3H, C10H_3), 1.25 – 1.16 (m, 1H, C6H_b), 1.13 – 1.02 (m, 2H, C5H_b, C7H_b) ppm. **MS (m/z):** (ESI-TOF): calculated for $C_{27}H_{30}NO_4P$ $[M+H]^+$: 464.20, found 464.20.

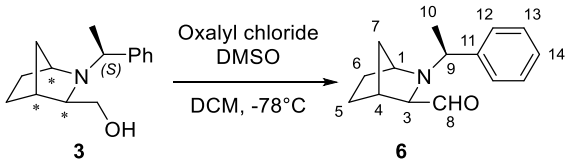


5 *(1R,4R,5S)*-**4**

To a solution of bicyclic phosphate **5** (100 mg, 0.22 mmol, 1.00 equiv.) in DMF (1.0 mL, 0.22 M) sodium azide (112 mg, 1.72 mmol, 7.8 equiv.) was added. The reaction mixture was heated to 100°C and stirred overnight under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (SiO_2, 15x1 cm, 83.3:16.7 *c*-Hex:EtOAc) yielding 56 mg azide (1*R*,4*R*,5*S*)-**4** (0.21 mmol, 93 %) as yellowish crystals.

All recorded spectroscopic data matched previously reported ones above.

2-((S)-1-phenylethyl)-2-azabicyclo[2.2.1]heptane-3-carbaldehyde **6**



3 **6**

According to literature,[208] a standard synthesis of aldehydes **6** was conducted by adding oxalyl chloride (1.10 equiv.) in dry CH_2Cl_2 (0.4 M) to a solution of DMSO (2.4 equiv.) in CH_2Cl_2 (8 M) at -78 °C over 5 min. The reaction was stirred for 10 additional minutes, followed by the addition of a solution of diasteromerically pure alcohol **3** (1.00 equiv.) in CH_2Cl_2 (3 M) over 5 min. After an additional stirring for 15 min an excess of Et_3N (3.50 equiv.) was added over 5 min, before the reaction mixture was left to reach room temperature. After the addition of water (3.5 mL/mmol substrate) the mixture was extracted by CH_2Cl_2 (3x 1.75 mL/mmol substrate). Combined organic phases were washed by brine, dried over Na_2SO_4 and concentrated under vacuum. Column chromatography (SiO_2, 83.3:16.7 hexane:EtOAc) yielded aldehydes **6**. Yields varied vastly between 29 and 88%; the reference yield is 92%.

All recorded spectroscopic data matched previously reported ones.

(1S,3R,4R)-2-((S)-1-phenylethyl)-2-azabicyclo[2.2.1]heptane-3-carbaldehyde **6**

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (d, *J* = 3.1 Hz, 1H, CHO), 7.38 – 7.26 (m, 4H, 4x PhH), 7.26 – 7.18 (m, 1H, *p*-PhH), 3.81 (dd, *J* = 2.7, 1.6 Hz, 1H, C4H), 3.55 (q, *J* = 6.4 Hz, 1H, C9H), 2.47 – 2.40 (m, 2H, C1H,

C3H), 2.05 (dddd, *J* = 13.3, 9.0, 4.7, 2.5 Hz, 1H, C5H$_a$), 1.77 – 1.72 (m, 1H, C7H$_a$), 1 .72 – 1.61 (m, 1H, C6H$_a$), 1.55 – 1.37 (m, 2H, C5H$_b$, C6H$_b$), 1.42 (d, *J* = 6.4 Hz, 3H, C10H$_3$), 1.37 – 1.33 (m, 1H, C7H$_b$) ppm.

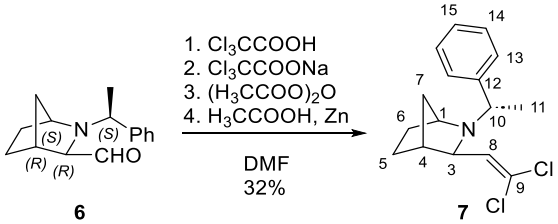
(1R,3S,4S)-2-((S)-1-phenylethyl)-2-azabicyclo[2.2.1]heptane-3-carbaldehyde **6**

Aldehyde (1*R*,3*S*,4*S*)-**6** was previously used in publications, but described as a different stereoisomer. All received experimental data, including ^{1}H-, ^{13}C-NMR and HRMS are enclosed.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (d, *J* = 3.1 Hz, 1H, CHO), 7.42 – 7.28 (m, 4H, 4x PhH), 7.28 – 7.20 (m, 1H, *p*-PhH), 3.65 (q, *J* = 6.4 Hz, 1H, C9H), 3.12 (tt, *J* = 1.8, 0.8 Hz, 1H, C4H), 2.68 (d, *J* = 2.9 Hz, 1H, C3H), 2.57 (dd, *J* = 4.1, 2.0 Hz, 1H, C1H), 1.93 (dddd, *J* = 13.6, 9.3, 4.9, 2.4 Hz, 1H, C5H$_a$), 1.68 (ddt, *J* = 9.6, 4.3, 2.3 Hz, 1H, C7H$_a$), 1.61 (dt, *J* = 12.4, 4.4 Hz, 1H, C6H$_a$), 1.46 – 1.36 (m, 1H, C5H$_b$), 1.23 (d, *J* = 6.4 Hz, 3H, C10H$_3$), 1.26 – 1.14 (m, 2H, C6H$_b$, C7H$_b$) ppm.**^{13}C NMR** (101 MHz, $CDCl_3$) δ = 206.0 (CHO), 145.3(C11), 128.5 (2x PhC), 127.5 (2x PhC), 127.1 (*p*-PhC), 74.4 (C3), 59.9 (C9), 59.0 (C4), 42.8 (C1), 36.7 (C7), 29.3 (C6), 24.7 (C5), 23.1 (C10) ppm. **HRMS (m/z):** (ESI-TOF) calculated for $C_{15}H_{19}NO$ $[M+H]^+$ 230.1545; found 230.1542.

5.2 Towards 2-azabicycloalkane alkynes

(1S,3R,4R)-3-(2,2-dichlorovinyl)-2-((S)-1-phenylethyl)-2-azabicyclo[2.2.1]heptane **7**

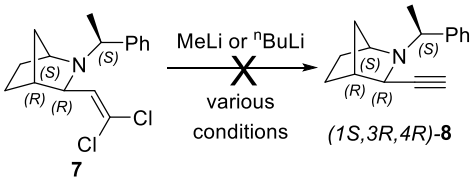


6 **7**

According to literature,[279] to a stirred solution of aldehyde (1*S*,3*R*,4*R*)-**6** (1.295 g, 5.65 mmol, 1.00 equiv.) and trichloroacetic acid (1.41 g, 8.6 mmol, 1.50 equiv.) in DMF (37 mL, 0.15 M) at room temperature sodium trichloroacetate (1.57 g, 8.65 mmol, 1.55 equiv.) was added portionwise. After 2 h, when the CO_2 evolution was finished, the solution was cooled to 0 °C and acetic anhydride (1.07 mL, 11.34 mmol, 2.00 equiv.) was added dropwise. The reaction mixture was stirred for 1 h to reach room temperature. Then, concentrated acetic acid (5.3 mL, 0.94 mL/mmol substrate) and zinc powder (0.80 g, 12.24 mmol, 2.17 equiv.) were added. The reaction mixture was stirred at 60 °C overnight. After cooling to room temperature, the reaction mixture was extracted with *n*-hexane, washed with water and the crude product was recrystallized using an *n*-hexane/ethyl acetate mixture yielding 421 mg (1.42 mmol, 27 %) white needles.

^{1}H-NMR: (400 MHz, $CDCl_3$) δ 7.34 – 7.16 (m, 5H, 5x PhH), 5.42 (d, *J* = 8.3 Hz, 1H, C8H), 3.68 – 3.62 (m, 1H, C4H), 3.52 (q, *J* = 6.4 Hz, 1H, C10H), 2.71 (d, *J* = 8.3 Hz, 1H, C3H), 2.06 (dd, *J* = 4.1, 1.9 Hz, 1H, C1H), 1.98 (ddt, *J* = 13.3, 10.9, 4.4 Hz, 1H, C5H$_a$), 1.77 – 1.68 (m, 1H, C7H$_a$), 1.69 – 1.57 (m, 1H, C6H$_a$), 1.44 – 1.31 (m, 3H, C5H$_b$, C6H$_b$, C7H$_b$), 1.30 (d, *J* = 6.4 Hz, 3H, C11H$_3$) ppm. **^{13}C-NMR:** (101 MHz, $CDCl_3$) δ = 145.2 (C12), 135.0 (C8), 128.1 (2x PhC), 128.1 (2x PhC), 127.3 (*p*-pPhC), 117.2 (C9), 68.2 (C3), 60.9 (C10), 58.5 (C4), 43.8 (C1), 36.2 (C7), 29.4 (C6), 23.2 (C11), 22.4 (C5) ppm. **HRMS (m/z):** (ESI-TOF) calculated for $C_{16}H_{19}NCl_2$ $[M+H]^+$ 296.0973; found 296.0970. **IR (ϑ_{max}/cm^{-1}, KBr):** 3065, 2959, 2876, 1613, 1490, 1455, 1445, 1365, 1311, 1188, 1099, 1080, 955. $[\alpha]_D^{25}$**:** -12.5 (c = 0.48, CH_2Cl_2). **mp:** 129-135 °C.

*Elimination approaches towards (1S,3R,4R)-8 from (1S,3R,4R)-***7**



Attempt 1

According to literature,[279] the dihalogenalkene (1*S*,3*R*,4*R*)-**7** (421 mg, 1.42 mmol, 1 equiv.) was dissolved in dry THF (3 mL, 0.5 M) and cooled to -20 °C. MeLi (1.07 mL, 1.6 M in hexanes, 1.71 mmol, 1.20 equiv.) was added dropwise and the reaction mixture was allowed to reach room temperature and stirred for 1 h, before being quenched by saturated aq. NH_4Cl (3 mL), extracted by hexanes (3x3 mL), dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography (SiO_2, 25x2 cm, 90:10 hexanes:EtOAc) yielding no product, but recovering 378 mg of starting material **7** indicating no reaction.

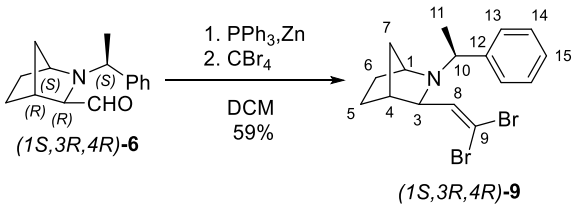
Attempt 2

According to the modified literature protocol,[279] the dihalogenalkene (1*S*,3*R*,4*R*)-**7** (538 mg, 1.82 mmol, 1 equiv.) was dissolved in dry THF (5 mL, 0.3 M) and cooled to -20 °C. *n*-BuLi (0.9 mL, 2.5 M in hexanes, 2.18 mmol, 1.20 equiv.) was added dropwise and the reaction mixture was allowed to reach room temperature and stirred for 1 h, before being quenched by saturated aq. NH_4Cl (5 mL), extracted by hexanes (3x 5 mL), dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography (SiO_2, 25x2 cm, 90:10 hexanes:EtOAc) yielding no product, but recovering 487 mg of starting material **7** indicating no reaction.

Attempt 3

According to the modified literature protocol,[279] the dihalogenalkene (1*S*,3*R*,4*R*)-**7** (487 mg, 1.64 mmol, 1 equiv.) was dissolved in dry n-hexane (5 mL, 0.3 M) and cooled to -78 °C. *n*-BuLi (1.64 mL, 2.5 M in hexanes, 4.10 mmol, 2.50 equiv.) was added dropwise, the reaction mixture was kept stirring for 3 h, allowed to reach room temperature and stirred for an additional 1 h, before being quenched by saturated aq. NH_4Cl (5 mL), extracted by hexanes (3x 5 mL), dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography (SiO_2, 25x2 cm, 90:10 hexanes:EtOAc) yielding no product, but recovering 487 mg of starting material **7** indicating no reaction.

(1S,3R,4R)-3-(2,2-dibromovinyl)-2-((S)-1-phenylethyl)-2-azabicyclo[2.2.1]heptane **9**

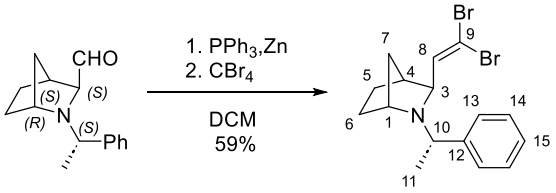


According to literature,[281,282] triphenylphosphine (4.70 g, 17.9 mmol, 4.00 equiv.) was added in one portion to a stirred suspension of zinc (1.18 g, 18.0 mmol, 4.00 equiv.) in dry CH_2Cl_2 (50 mL) under

argon atmosphere. The reaction mixture was cooled to 0 °C using an ice bath and carbon tetrabromide (3.18 g, 9.6 mmol, 2 equiv.) dissolved in CH_2Cl_2 (7 mL, 1.4 M) was added dropwise. Aldehyde (1*S*,3*R*,4*R*)-**6** (1.02 g, 4.5 mmol, 1.00 equiv.) in CH_2Cl_2 (10 mL, 0.45 M) was then added dropwise and the reaction mixture was left to reach room temperature and was stirred overnight. The solution was extracted with CH_2Cl_2 (3x 10 mL), washed with brine (10 mL) and the combined organic phases were dried over $MgSO_4$. The crude was purified by column chromatography (SiO_2, 25x2 cm 83.3:16.7 hexane:EtOAc) yielding 1.00 g (2.60 mmol, 58 %) of red crystals.

^{1}H-NMR: (601 MHz, $CDCl_3$) δ 7.30 – 7.19 (m, 5H, 5x PhH), 5.96 (d, *J* = 7.8 Hz, 1H, C8H), 3.68 – 3.64 (m, 1H, C4H), 3.52 (q, *J* = 6.5 Hz, 1H, C10H), 2.61 (d, *J* = 7.8 Hz, 1H, C3H), 2.09 (d, *J* = 4.4 Hz, 1H, C1H), 1.96 (qt, *J* = 6.9, 4.5 Hz, 1H, $C5H_a$), 1.72 (dt, *J* = 9.8, 2.1 Hz, 1H, $C7H_a$), 1.64 (dt, *J* = 14.7, 4.4 Hz, 1H, $C6H_a$), 1.42 – 1.34 (m, 2H, $C5H_b$, $C6H_b$), 1.33 – 1.28 (m, 1H, $C7H_b$), 1.30 (d, *J* = 6.4 Hz, 3H, $C11H_3$) ppm. **^{13}C-NMR:** (151 MHz, $CDCl_3$) δ = 145.1 (C12), 143.6 (C8), 128.2 (4x PhC), 127.4 (*p*-PhC), 85.6 (C9), 71.1 (C3), 60.9 (C10), 58.5 (C4), 43.7 (C1), 36.3 (C7), 29.5 (C6), 23.1 (C11), 22.4 (C5) ppm. **HRMS (m/z):** (ESI-TOF) calculated for $C_{16}H_{19}NBr_2$ $[M+H]^+$ 383.9962; found 383.9960. **IR (ϑ_{max}/cm^{-1}, KBr):** 3064, 3024, 2968, 2870, 1604, 1490, 1453, 1364, 1310, 1188, 1162, 1094, 942. **$[\alpha]_D^{25}$:** +7.7° (c = 0.52, CH_2Cl_2). **mp:** 133-138°C.

(1R,3S,4S)-3-(2,2-dibromovinyl)-2-((S)-1-phenylethyl)-2-azabicyclo[2.2.1]heptane **9**



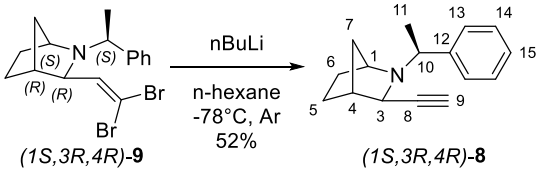
(1R,3S,4S)-**6** *(1R,3S,4S)*-**9**

According to literature,[281,282] triphenylphosphine (3.55 g, 13.6 mmol, 4.00 equiv.) was added in one portion to a stirred suspension of zinc (0.89 g, 13.6 mmol, 4.00 equiv.) in dry CH_2Cl_2 (30 mL) under argon atmosphere. The reaction mixture was cooled to 0 °C using an ice bath and carbon tetrabromide (2.28 g, 6.8 mmol, 2.00 equiv.) dissolved in CH_2Cl_2 (5 mL, 1.36 M) was added dropwise. Aldehyde (1R,3S,4S)-**6** (780 mg, 3.4 mmol, 1.00 equiv.) in CH_2Cl_2 (10 mL, 0.3 M) was then added dropwise and the reaction mixture was left to reach room temperature and stirred for 21 h. The solution was extracted with CH_2Cl_2 (3x 10 mL), washed with brine (10 mL)and the combined organic phases were dried over $MgSO_4$. The crude product obtained after removal of solvent was purified by column chromatography (SiO_2, 25x2 cm, 83.3:17.6 hexanes:EtOAc yielding 632 mg (1.64 mmol, 48 % yield) of a solidifying red oil.

^{1}H-NMR: (400 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 4H, 4x PhH), 7.25 – 7.16 (m, 1H, *p*-PhH), 6.61 (d, *J* = 7.5 Hz, 1H, C8H), 3.62 (q, *J* = 6.4 Hz, 1H, C10H), 3.02 – 2.96 (m, 1H, C4H), 2.90 (d, *J* = 7.5 Hz, 1H, C3H), 2.30 – 2.24 (m, 1H, C1H), 1.92 – 1.80 (m, 1H, $C5H_a$), 1.73 – 1.66 (m, 1H, $C7H_a$), 1.58 (tt, *J* = 12.2, 4.4 Hz, 1H, $C6H_a$), 1.40 (dddt, *J* = 11.9, 9.2, 4.6, 2.3 Hz, 1H), 1.24 (d, *J* = 6.4 Hz, 3H, $C11H_3$), 1.15 (d, *J* = 9.6, 1H, $C7H_b$), 1.13 – 1.04 (m, 1H) ppm. **^{13}C-NMR:** (101 MHz, $CDCl_3$) δ = 146.0 (C12), 144.9 (C8), 128.4 (2x PhC), 127.4 (2x PhC), 126.9 (*p*-PhC), 85.5 (98), 69.8 (C3), 60.2 (C10), 59.2 (C4), 44.6 (C1), 36.3 (C7), 29.5 (C6), 24.5 (C11), 22.6 (C5) ppm. **HRMS (m/z):** (ESI-TOF) calculated for $C_{16}H_{19}NBr_2$ $[M+H]^+$ 383.9962; found

383.9965. **IR (ϑ_{max}/cm^{-1}, KBr):** 3063, 3027, 2963, 2870, 1604, 1491, 1453, 1304, 1191, 1079, 1016, 954, 858. $[\alpha]_D^{25}$**:** +5.4° (c=0.61, CH_2Cl_2).

(1S,3R,4R)-3-ethynyl-2-((S)-1-phenylethyl)-2-azabicyclo[2.2.1]heptane **8**

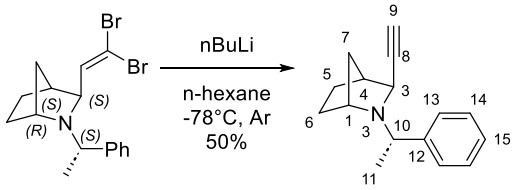


(1S,3R,4R)-**9** *(1S,3R,4R)*-**8**

According to literature,[281,282] to a mechanically stirred solution of dibromoalkene (1*S*,3*R*,4*R*)-**9** (1.00 g, 3.5 mmol, 1 equiv.) in *n*-hexane (90 mL, 0.05 M) at -78 °C under argon *n*-BuLi (3.5 mL, 2.5 M in hexanes, 8.8 mmol, 2.50 equiv.) was added dropwise. After 3.5 h the reaction was allowed to reach room temperature, quenched by water (50 mL), extracted using *n*-hexane (3x 50 mL) and the combined organic layers were dried over $MgSO_4$. The crude was concentrated under reduced pressure and purified by column chromatography (SiO_2, 25x3 cm, 90:10 hexane:EtOAc) yielding 413 mg (1.83 mmol, 52 % yield) of a colorless oil.

^{1}H-NMR: (400 MHz, $CDCl_3$) δ 7.45 – 7.38 (m, 2H, 2x PhH), 7.33 – 7.26 (m, 2H, 2x PhH), 7.26 – 7.20 (m, 1H, *p*-PhH), 3.71 – 3.65 (m, 1H, C4H), 3.49 (q, *J* = 6.4 Hz, 1H, C10H), 2.70 – 2.65 (m, 1H, C3H), 2.36 – 2.29 (m, 1H, C1H), 2.13 – 2.02 (m, 1H, C7H$_a$), 2.04 – 1.93 (m, 1H, C5H$_a$), 1.88 (d, *J* = 2.0 Hz, 1H, C9H), 1.69 – 1.57 (m, 1H, C6H$_a$), 1.46 – 1.35 (m, 2H, C5H$_b$. C7H$_b$), 1.33 (d, *J* = 6.4 Hz, 3H, C11H$_3$), 1.31 – 1.23 (m, 1H, C7H$_b$) ppm. **^{13}C-NMR:** ^{13}C NMR (101 MHz, $CDCl_3$) δ = 144.9 (C12), 128.5 (2x PhC), 128.1 (2x PhC), 127.3 (*p*-PhC), 86.8 (C8), 68.9 (C3), 61.8, 59.3, 58.6 (C4), 45.2 (C1), 36.9 (C7), 28.3 (C6), 23.4 (C11), 22.8 (C5) ppm. **HRMS (m/z):** (ESI-TOF) calculated for $C_{16}H_{19}N$ $[M+H]^+$ 226.1596; found 226.1595. **IR (ϑ_{max}/cm^{-1}, KBr):** 3307, 2972, 2871, 1493, 1454, 1370, 1303, 1164, 1058, 1024, 8301 760. $[\alpha]_D^{25}$**:** +7.0° (c 1.06, CH_2Cl_2).

(1R,3S,4S)-3-ethynyl-2-((S)-1-phenylethyl)-2-azabicyclo[2.2.1]heptane **8**



(1R,3S,4S)-**9** *(1R,3S,4S)*-**8**

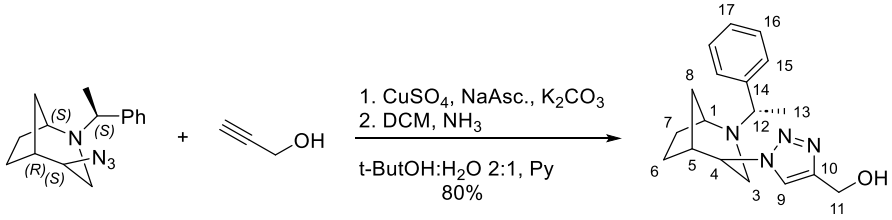
According to literature,[281,282] to a mechanically stirred solution of dibromoalkene (1*R*,3*S*,4*S*)-**9** (558 mg, 2 mmol, 1.00 equiv.) in *n*-hexane (60 mL, 0.03 M) at -78°C under argon *n*-BuLI (2.5 mL, 2.5 M in hexanes, 5.0 mmol, 2.50 equiv was added dropwise. After 3 h the reaction was led to reach room, quenched by the addition of water (30 mL) extracted by *n*-hexane (3x 30 mL) and the combined organic layers were dried over $MgSO_4$. After the crude was concentrated under vacuum it was purified by column chromatography (SiO_2, 25x2 cm, 90:10 hexane:EtOAc) yielding 220 mg (0.98 mmol, 50 % yield) of a yellowish solid.

^{1}H-NMR: (400 MHz, $CDCl_3$) δ 7.40 – 7.31 (m, 2H, 2x PhH), 7.35 – 7.25 (m, 2H, 2x PhH), 7.27 – 7.17 (m, 1H, *p*-PhH), 3.57 (q, *J* = 6.4 Hz, 1H, C10H), 3.06 – 3.00 (m, 1H, C4H), 2.87 (d, *J* = 2.4 Hz, 1H, C3H), 2.46 (d, *J* = 4.3 Hz, 1H, C1H), 2.32 (d, *J* = 2.1 Hz, 1H, C9H), 2.00 – 1.91 (m, 1H, C7H$_a$), 1.82 (dddd, *J* = 13.3, 9.2,

4.5, 2.4 Hz, 1H, C5H$_a$), 1.56 (tt, *J* = 12.4, 4.4 Hz, 1H, C6H$_a$), 1.45 (d, *J* = 6.4 Hz, 3H, C11H$_3$), 1.38 – 1.24 (m, 1H, C5H$_b$), 1.25 – 1.17 (m, 1H, C7H$_b$), 1.09 (tdd, *J* = 12.4, 4.7, 2.8 Hz, 1H, C6H$_b$) ppm. **^{13}C-NMR:** (101 MHz, $CDCl_3$) δ = 145.5 (C12), 128.4 (2x PhC), 127.6 (2x PhC), 126.9 (*p*-PhC), 88.1 (C9), 69.6 (C3), 61.3, 58.9, 58.4 (C4), 45.8 (C1), 36.8 (C7), 28.9 (C6), 24.7 (C11), 22.7 (C5) ppm. **HRMS (m/z):** (ESI-TOF) calculated for $C_{16}H_{19}N$ $[M+H]^+$ 226.1596; found 226.1589. **IR (ϑ_{max}/cm^{-1}, KBr):** 3307, 2972, 2871, 1491, 1453, 1373, 1304, 1162, 1114, 1079, 1028, 828. **$[\alpha]_D^{25}$:** +5.6 (c 1.04, CH_2Cl_2). **mp:** 72-75 °C.

5.3 (1*S*,4*S*,5*R*)-2-azabicyclo[3.2.1]octane triazoles

1-((1S,4S,5R)-2-((S)-1-phenylethyl)-2-azabicyclo[3.2.1]octan-4-yl)-1H-1,2,3-triazol-4-yl)methanol **10**

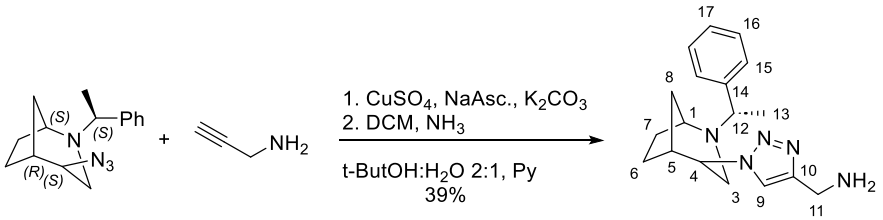


(1S,4S,5R)-**4** *(1S,4S,5R)*-**10**

According to literature,[343] azide (1*S*,4*S*,5*R*)-**4** (288 mg, 1.12 mmol, 1.00 equiv.) and propargyl alcohol (71 mg, 1.27 mmol, 1.13 equiv.) were dissolved in *t*-ButOH:water (2:1, 3 mL, 0.3 M) together with pyridine (0.20 mL). Subsequently $CuSO_4 \cdot 5H_2O$ (72 mg, 0.29 mmol, 0.26 equiv.), sodium ascorbate (123 mg, 0.62 mmol, 0.55 equiv.) and potassium carbonate (135 mg, 0.98 mmol, 0.87 equiv.) were added. The mixture was stirred overnight, before CH_2Cl_2 (5 mL) and aq. NH_3 (25 %, 0.5 mL) were added and the mixture was stirred for another night and quenched by sat. sodium sulfide nonahydrate (0.2 mL). After stirring the quenched solution for another 5 min. the reaction mixture was filtered through a pad of silica, washed by $CHCl_3$:MeOH (50 mL, 90:10). The filtrate was concentrated under reduced pressure and purified by column chromatography (SiO_2, 25x2 cm 95:5 to 90:10 $CHCl_3$:MeOH) yielding 280 mg (0.90 mmol, 80%) of a yellow oil.

^{1}H-NMR: (601 MHz, $CDCl_3$) δ 7.99 (s, 1H, C9H), 7.31 (d, *J* = 6.9 Hz, 4H, 4x PhH), 7.25 – 7.19 (m, 1H, C16H), 4.76 (s, 2H, C11H$_2$), 4.41 (t, *J* = 4.6 Hz, 1H, C4H), 3.76 (t, *J* = 5.1 Hz, 1H, C1H), 3.40 – 3.30 (m, 1H, C12H), 3.06 (br. s, 1H, OH), 2.73 – 2.69 (m, 1H, C5H), 2.69 – 2.66 (m, 1H, C3H$_a$), 2.62 – 2.55 (m, 1H, C3H$_b$), 1.89 – 1.82 (m, 2H, C6H$_a$, C7H$_a$), 1.64 – 1.59 (m, 1H, C8H$_a$), 1.59 – 1.52 (m, 1H, C6H$_b$), 1.51 – 1.45 (m, 1H, C7H$_b$), 1.38 (d, *J* = 6.7 Hz, 3H, C13H$_3$), 1.32 – 1.27 (m, 1H, C8H$_b$) ppm. **^{13}C-NMR:** (151 MHz, $CDCl_3$) δ = 146.5 (C14), 144.7 (C10), 128.7 (2x C15), 127.5 (C16), 127.4 (2x C14), 122.0 (C9), 66.0 (C11), 63.1 (C12), 59.8 (C4), 56.3 (C1), 47.8 (C3), 40.4 (C5), 33.8 (C8), 27.2 (C6), 21.7 (C7), 21.1 (C13) ppm. **HRMS (m/z):** (ESI-TOF): calculated for $C_{18}H_{24}N_4O_2$ $[M+H]^+$: 313.2029, found 313.2023. **Elementary analysis:** calculated C 69.20, H 7.74, N 17.93; found C 68.97, H 7.72, N 17.69. **IR (ϑ_{max}/cm^{-1}, neat):** 3435. 3061, 2925, 2868, 1667, 1600, 1492, 1453, 1347, 1212, 1058, 779, 704, 549. **$[\alpha]_D^{25}$:** +108.8° (c=0.68, CH_2Cl_2).

(1-((1S,4S,5R)-2-((S)-1-phenylethyl)-2-azabicyclo[3.2.1]octan-4-yl)-1H-1,2,3-triazol-4-yl)methanamine **11**

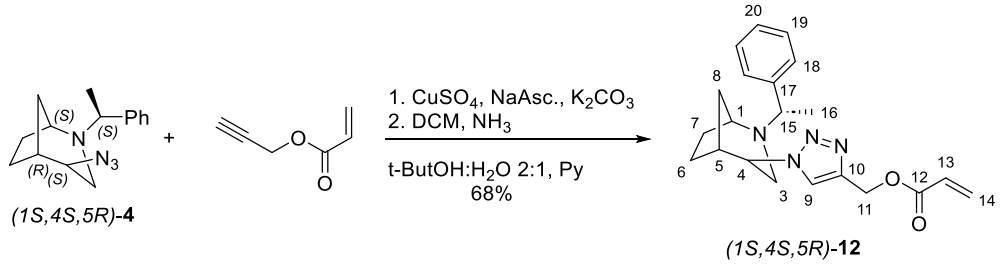


(1S,4S,5R)-**4** *(1S,4S,5R)*-**11**

According to literature,[343] Azide (1*S*,4*S*,5*R*)-**4** (263 mg, 1.03 mmol, 1.00 equiv.) and propargyl amine (58 mg, 1.07 mmol, 1.04 equiv.) were reacted in similar manner as previously for **10** yielding 124 mg (0.40 mmol, 39%) of an orange oil.

^{1}H-NMR: (400 MHz, $CDCl_3$) δ 7.92 (s, 1H, C9H), 7.37 – 7.26 (m, 4H, 4xPhH), 7.25 – 7.14 (m, 1H, C17H), 4.43 – 4.36 (m, 1H, C4H), 4.06 – 3.90 (m, 2H, $C11H_2$), 3.75 (t, *J* = 4.7 Hz, 1H, C1H), 3.34 (q, *J* = 6.7 Hz, 1H, C12H), 2.73 – 2.68 (m, 1H, C5H), 2.67 (d, *J* = 14.2 Hz, 1H, $C3H_a$), 2.56 (dd, *J* = 13.8, 4.7 Hz, 1H, $C3H_b$), 2.45 (s, 2H, NH_2), 1.91 – 1.77 (m, 2H, $C6H_a$, $C7H_a$), 1.62 (dt, *J* = 11.9, 1.9 Hz, 1H, $C8H_a$), 1.58 – 1.51 (m, 1H, $C6H_b$), 1.52 – 1.41 (m, 1H, $C7H_b$), 1.38 (d, *J* = 6.7 Hz, 3H, $C13H_3$), 1.33 – 1.24 (m, 1H, $C8H_b$) ppm. **^{13}C-NMR:** (101 MHz, $CDCl_3$) δ = 147.6 (C10), 144.9 (C14), 128.7 (2x C16), 127.5 (C17), 127.4 (2x C15), 121.1 (C9), 63.0 (C12), 59.8 (C4), 56.2 (C1), 47.9 (C3), 40.4 (C5), 33.8 (C8), 27.3 (C6), 25.5 (C11), 21.7 (C7), 21.1 (C13) ppm. **HRMS (m/z):** (ESI-TOF) calculated for $C_{18}H_{25}N_5$ $[M+H]^+$ 312.2188; found 312.2190. **Elementary analysis:** calculated C 69.42, H 8.09, N 22.49; found C 69.56, H 8.17, N 22.10. **IR (ϑ_{max}/cm^1, neat):** 3148, 2933, 2868, 2824, 1658, 1492, 1452, 1346, 1212, 1133, 1046, 956, 779, 704. $[\alpha]_D^{25}$**:** +128.0° (c 0.25, CH_2Cl_2).

(1-((1S,4S,5R)-2-((S)-1-phenylethyl)-2-azabicyclo[3.2.1]octan-4-yl)-1H-1,2,3-triazol-4-yl)methyl acrylate **12**



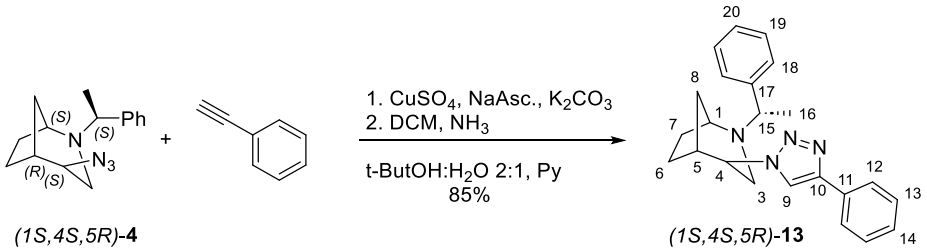
(1S,4S,5R)-**4** *(1S,4S,5R)*-**12**

According to literature,[343] Azide (1*S*,4*S*,5*R*)-**4** (256 mg, 1.00 mmol, 1.00 equiv.) and propargyl acrylate (110 mg, 1.00 mmol, 1.00 equiv.) were reacted in similar manner as previously for **10** yielding 250 mg (0.68 mmol, 68%) of an orange solid.

^{1}H-NMR: (400 MHz, $CDCl_3$) δ 8.12 (s, 1H, C9H), 7.36 – 7.27 (m, 4H, 4x PhH), 7.22 (m, 1H, C20H), 6.48 (dd, *J* = 17.3, 1.7 Hz, 1H, $C14H_{trans}$), 6.18 (dd, *J* = 17.3, 10.5 Hz, 1H, C13H), 5.88 (dd, *J* = 10.5, 1.6 Hz, 1H, $C14H_{cisf}$), 5.36 (d, *J* = 12.7 Hz, 1H, $C11H_a$), 5.26 (d, *J* = 12.7 Hz, 1H, $C11H_b$), 4.43 (t, *J* = 4.4 Hz, 1H, C4H), 3.77 (t, *J* = 5.0 Hz, 1H, C1H), 3.34 (q, *J* = 6.6 Hz, 1H, C15H), 2.70 (m, 1H, C5H), 2.65 (d, *J* = 13.8 Hz, 1H, $C3H_a$), 2.55 (dd, *J* = 13.7, 4.7 Hz, 1H, $C3H_b$), 1.86 (m, 2H, $C6H_a$, $C7H_b$), 1.64 – 1.56 (m, 1H, $C8H_a$), 1.60 – 1.49 (m, 1H, $C6H_b$), 1.53 – 1.41 (m, 1H, $C7H_b$), 1.39 (d, *J* = 6.6 Hz, 3H, $C16H_3$), 1.31 (m, 1H, $C8H_b$) ppm. **^{13}C-NMR:** (101 MHz, $CDCl_3$) δ = 166.0 (C12), 144.8 (C17), 141.6 (C10), 131.4(C14), 128.8 (2xC19), 128.3

(C13), 127.4 (C20), 127.4 (2xC18), 124.1 (C9), 63.0 (C15), 59.8 (C4), 58.0 (C11), 56.1 (C1), 47.9 (C3), 40.3 (C5), 33.8 (C8), 27.2 (C6), 21.5 (C7), 21.2 (C16) ppm. **HRMS (m/z):** (ESI-TOF): calculated for $C_{21}H_{26}N_4O_2$ 367.2134; found 367.2130. **Elementary analysis:** calculated C 68.83, H 7.15, N 15.29; found C 68.71, H 7.17, N 15.14. **IR (ϑ_{max}/cm^{-1}, KBr):** 3148, 2959, 2830, 1973, 1726, 1629, 1492, 1453, 1413, 1376, 1337, 1292, 1182, 1132, 1097, 1058, 1049, 982, 925, 815, 773, 708, 546. $[\alpha]_D^{25}$**:** +114.3° (c 0.51, CH_2Cl_2).

(1S,4S,5R)-4-(4-benzyl-1H-1,2,3-triazol-1-yl)-2-((S)-1-phenylethyl)-2-azabicyclo[3.2.1]octane **13**

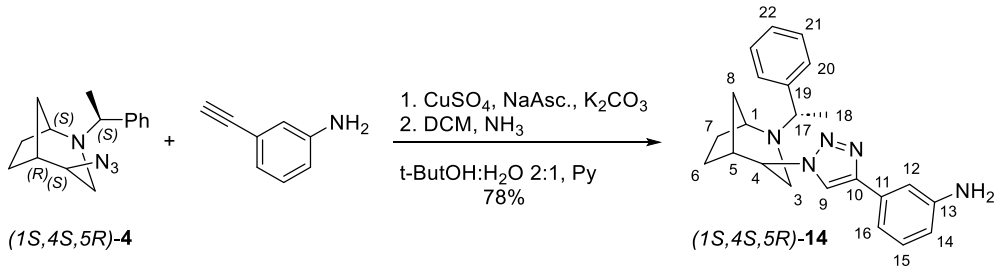


(1S,4S,5R)-**4** *(1S,4S,5R)*-**13**

According to literature,[343] Azide (1*S*,4*S*,5*R*)-**4** (326 mg, 1.27 mmol, 1.00 equiv.) and phenylacetylene (130 mg, 1.27 mmol, 1.00 equiv.) were reacted in similar manner as previously for **10** yielding 386 mg (1.08 mmol, 85%) of colourless crystals.

^{1}H-NMR: (601 MHz, $CDCl_3$) δ 8.23 (s, 1H, C9H), 7.84 (dd, *J* = 8.2, 1.4 Hz, 2H, 2x C12H), 7.46 (dd, *J* = 8.8, 6.9 Hz, 2H, 2x C13H), 7.42 – 7.39 (m, 2H, 2x C19H), 7.39 – 7.35 (m, 2H, 2x C18H), 7.35 – 7.32 (m, 1H, C14H), 7.28 – 7.25 (m, 1H, C20H), 4.48 – 4.43 (m, 1H, C4H), 3.81 (t, *J* = 5.0 Hz, 1H, C1H), 3.37 (q, *J* = 6.6 Hz, 1H, C15H), 2.81 (q, *J* = 4.4 Hz, 1H, C5H), 2.75 (dd, *J* = 13.8, 1.1 Hz, 1H, $C3H_a$), 2.63 (dd, *J* = 13.8, 4.7 Hz, 1H, $C3H_b$), 1.94 – 1.85 (m, 2H, $C6H_a$, $C7H_b$), 1.66 (d, *J* = 12.2 Hz, 1H, $C8H_a$), 1.64 – 1.57 (m, 1H, $C6H_b$), 1.57 – 1.47 (m, 1H, $C7H_b$), 1.42 (d, *J* = 6.6 Hz, 3H, $C16H_3$), 1.37 – 1.31 (m, 1H, $C8H_b$) ppm. **^{13}C-NMR:** (151 MHz, $CDCl_3$) δ = 146.5 (C10), 145.2 (C17), 131.4 (C11), 128.9 (2x C13), 128.7 (2x C18), 127.9 (C14), 127.6 (C20), 127.4 (2x C19), 125.7 (2xC12), 120.2 (C9), 63.1 (C15), 59.7 (C4), 56.1 (C1), 48.1 (C3), 40.4 (C5), 33.9 (C8), 27.3 (C6), 21.7 (C7), 21.2 (C16) ppm. **HRMS (m/z):** (ESI-TOF) calculated for $C_{23}H_{26}N_4$ $[M+H]^+$ 359.2236; found 359.2229. **IR (ϑ_{max}/cm^{-1}, KBr):** 3150, 3023, 2959, 2810, 1609, 1492, 1452, 1370, 1339, 1229, 1211, 1129, 1073, 1059, 955. $[\alpha]_D^{25}$**:** +264° (c = 0.48, CH_2Cl_2)

3-(1-((1S,4S,5R)-2-((S)-1-phenylethyl)-2-azabicyclo[3.2.1]octan-4-yl)-1H-1,2,3-triazol-4-yl)aniline **14**



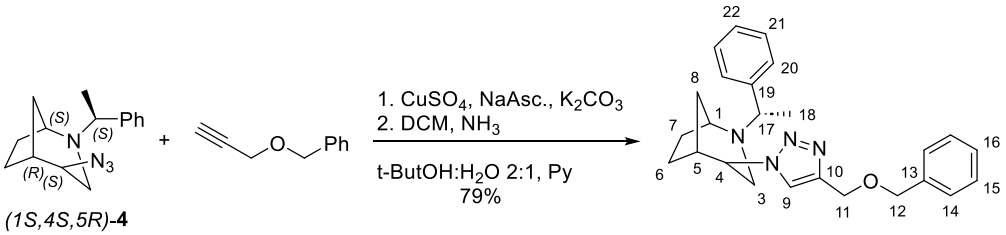
(1S,4S,5R)-**4** *(1S,4S,5R)*-**14**

According to literature,[343] Azide (1*S*,4*S*,5*R*)-**4** (263 mg, 1.03 mmol, 1.03 equiv.) and 3-ethynylaniline (138 mg, 1.18 mmol, 1.15 equiv.) were reacted in similar manner as previously for **10** yielding 300 mg (0.80 mmol, 78%) of off-white crystals.

^{1}H-NMR: (601 MHz, $CDCl_3$) δ 8.19 (s, 1H, C9H), 7.41 – 7.38 (m, 2H, 2x C20H), 7.37 – 7.32 (m, 2H, 2x C21H), 7.28 (m, 1H, C12H), 7.26 (m, 1H, C15H), 7.26 – 7.21 (m, 1H, C22H), 7.15 – 7.11 (m, 1H, C16H), 6.67 (ddd, *J* = 7.9, 2.4, 1.0 Hz, 1H, C14H), 4.44 (t, *J* = 4.3 Hz, 1H, C4H), 3.80 (t, *J* = 4.9 Hz, 1H, C1H), 3.76

(s, 2H, NH_2), 3.37 (q, *J* = 6.7 Hz, 1H, C17H), 2.80 (q, *J* = 4.3 Hz, 1H, C5H), 2.74 (d, *J* = 13.8 Hz, 1H, $C3H_a$), 2.62 (dd, *J* = 13.8, 4.7 Hz, 1H, $C3H_b$), 1.93 – 1.84 (m, 2H, $C6H_a$, $C7H_a$), 1.65 (d, *J* = 12.4 Hz, 1H, $C8H_a$), 1.63 – 1.57 (m, 1H, $C6H_b$), 1.55 – 1.47 (m, 1H, $C7H_b$), 1.42 (d, *J* = 6.6 Hz, 3H, $C18H_3$), 1.36 – 1.30 (m, 1H, $C8H_b$) ppm. **^{13}C-NMR:** (151 MHz, $CDCl_3$) δ = 147.0 (C11), 146.6 (C10), 145.2 (C19), 132.3 (C13), 129.8 (C122), 128.8 (2x C21), 127.6 (C15), 127.5 (2x C20), 120.3 (C9), 116.1 (C16), 114.7(C14), 112.3 (C12), 63.1 (C17), 59.7 (C4), 56.1 (C1), 48.1 (C3), 40.4 (C5), 33.9 (C8), 27.3 (C6), 21.8 (C7), 21.2 (C18) ppm. **HRMS (m/z):** (ESI-TOF) calculated for $C_{23}H_{27}N_5$ $[M+H]^+$ 374.2345; found 374.2344. **Elementary analysis:** calculated C 73.96, H 7.29, N 18.75; found C 73.75, H 7.47, N 18.43. **IR (ϑ_{max}/cm^{-1}, KBr):** 3351, 3223, 3142, 2934, 2820, 1613, 1590, 1491, 1452, 1363, 1349, 1280, 1225, 1132, 1057, 956, 874, 780, 703, 548. $[\alpha]_D^{25}$**:** +247.5° (c 0.56, CH_2Cl_2).

(1S,4S,5R)-4-(4-((benzyloxy)methyl)-1H-1,2,3-triazol-1-yl)-2-((S)-1-phenylethyl)-2-azabicyclo[3.2.1]octane **15**

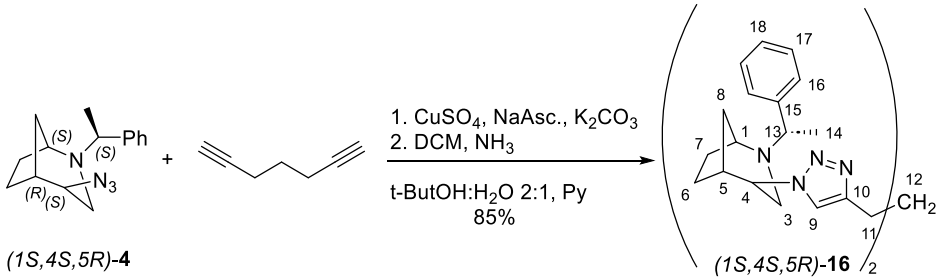


(1S,4S,5R)-**4** *(1S,4S,5R)*-**15**

According to literature,[343] Azide (1*S*,4*S*,5*R*)-**4** (279 mg, 1.09 mmol, 1.00 equiv.) and benzyl propargylether (145 mg, 1.10 mmol, 1.01 equiv.) were reacted in similar manner as previously for **10** yielding 346 mg (0.86 mmol, 79%) of a yellow oil.

^{1}H-NMR: (400 MHz, $CDCl_3$) δ 7.95 (s, 1H, C9), 7.34 – 7.27 (m, 4H, 4x PhH), 7.26 – 7.15 (m, 5H, 5x PhH), 7.14 – 7.09 (m, 1H, *p*-PhH), 4.62 (d, *J* = 3.2 Hz, 2H, $C11H_2$), 4.54 (s, 2H, $C12H_2$), 4.35 (t, *J* = 4.4 Hz, 1H, C4H), 3.69 (t, *J* = 5.0 Hz, 1H, C1H), 3.27 (q, *J* = 6.6 Hz, 1H, C17H), 2.69 – 2.63 (m, 1H, C5H), 2.63 – 2.56 (m, 1H, $C3H_a$), 2.49 (dd, *J* = 13.7, 4.7 Hz, 1H, $C3H_b$), 1.85 – 1.73 (m, 2H, $C6H_a$, $C7H_a$), 1.58 – 1.52 (m, 1H, $C8H_a$), 1.52 – 1.43 (m, 1H, $C6H_b$), 1.43 – 1.33 (m, 1H, $C7H_b$), 1.31 (d, *J* = 6.6 Hz, 3H, $C18H_3$), 1.24 (m, 1H, $C8H_b$) ppm. **^{13}C-NMR:** (101 MHz, $CDCl_3$) δ = 144.9 (*q*PhC), 143.8 (*q*Ph-C), 138.2 (C10), 128.7 (2x PhC), 128.5 (2x PhC), 128.0 (2x PhC), 127.8 (*p*-PhC), 127.4 (*p*-PhC), 127.3 (2x PhC), 122.8 (C9), 72.4 (C12), 64.0 (C11), 63.0 (C17), 59.7 (C4), 56.1 (C1), 47.9 (C3), 40.4 (C5), 33.8 (C8), 27.2 (C6), 21.6 (C7), 21.2 (C18) ppm. **HRMS (m/z):** (ESI-TOF) calculated for $C_{25}H_{30}N_4O_2$ $[M+H]^+$ 403.2498; found 403.2490. **Elementary analysis:** calculated C 74.59, H 7.51, N 13.92; found C 74.26, H 7.80, N 14.14. **IR (ϑ_{max}/cm^{-1}, KBr):** 3147, 2953, 2866, 2097, 1684, 1600, 1492, 1453, 1347, 1094, 1046, 778, 737, 702. $[\alpha]_D^{25}$**:** +83.6° (c 0.55, CH_2Cl_2).

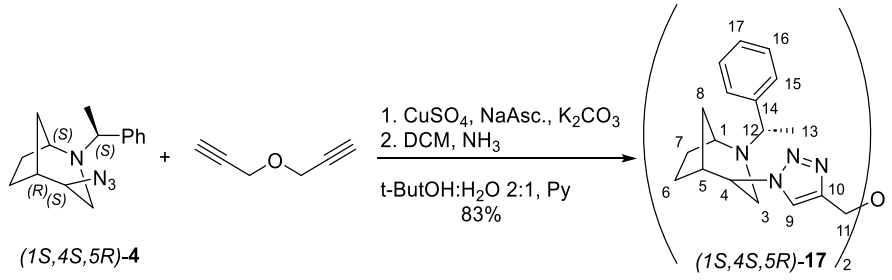
1,3-Bis-(1-((1S,4S,5R)-2-((S)-1-phenylethyl)-2-azabicyclo[3.2.1]octan-4-yl)-1H-1,2,3-triazol-4-yl) propane **16**



According to literature,[343] Azide (1*S*,4*S*,5*R*)-**4** (264 mg, 1.03 mmol, 1.00 equiv.) and hepta-1,6-diyne (51 mg, 0.55 mmol, 0.53 equiv.) were reacted in similar manner as previously for **10** yielding 284 mg (0.47 mmol, 85 %) of a white solid.

^{1}H-NMR: (400 MHz, $CDCl_3$) δ 7.83 (s, 2H, 2x C9H), 7.36 – 7.23 (m, 8H, 8x PhH), 7.22 – 7.13 (m, 2H, 2x C18H), 4.45 – 4.37 (m, 2H, 2x C4H), 3.77 (t, *J* = 5.0 Hz, 2H, 2x C1H), 3.34 (q, *J* = 6.8 Hz, 2H, 2x C13H), 2.81 (td, *J* = 7.3, 3.1 Hz, 4H, 2x $C11H_2$), 2.72 (q, *J* = 4.0 Hz, 2H, 2x C5H), 2.68 (d, *J* = 13.4 Hz, 2H, 2x $C3H_a$), 2.56 (dd, *J* = 13.5, 4.8 Hz, 2H, 2x $C3H_b$), 2.07 (p, *J* = 7.7 Hz, 2H, $C12H_2$), 1.92 – 1.78 (m, 4H, 2x $C6H_a$, 2x $C7H_a$), 1.65 (d, *J* = 12.2 Hz, 2H, 2x $C8H_a$), 1.61 – 1.53 (m, 2H, 2x $C6H_b$), 1.53 – 1.42 (m, 2H, 2x $7H_b$), 1.39 (d, *J* = 6.7 Hz, 6H, 2x $C14H_3$), 1.35 – 1.26 (m, 2H, 2x $C8H_b$) ppm. **^{13}C-NMR:** (101 MHz, $CDCl_3$) δ = 146.4 (2x C9), 145.0 (2x C15), 128.7 (4x C17), 127.5 (2x C18), 127.4 (4x C16), 121.1 (2x C10), 63.1 (2x C13), 59.6 (2x C4), 56.2 (2x C1), 48.0 (2x C3), 40.5 (2x C5), 33.9 (2x C8), 29.3 (C12), 27.3 (2x C6), 25.5 (2xC11), 21.6 (2x C7), 21.2 (2x C14) ppm. **HRMS (m/z):** (ESI-TOF) calculated for $C_{37}H_{48}N_8$ $[M+H]^+$ 605.4080; found 605.4084. **Elementary analysis:** calculated C 73.47, H 8.00, N 18.53; found C 73.12, H 8.27, N 18.26. **IR (ϑ_{max}/cm^{-1}, KBr):** 3144, 2936, 2865, 2820, 1683, 1548, 1492, 1442, 1347, 1211, 1132, 1046, 955, 761, 703, 548. $[\alpha]_D^{25}$**:** +121.1° (c 0.83, CH_2Cl_2).

(1S,1'S,4S,4'S,5R,5'R)-4,4'-(4,4'-(oxybis(methylene))bis(1H-1,2,3-triazole-4,1-diyl))bis(2-((S)-1-phenylethyl)-2-azabicyclo[3.2.1]octane) **17**

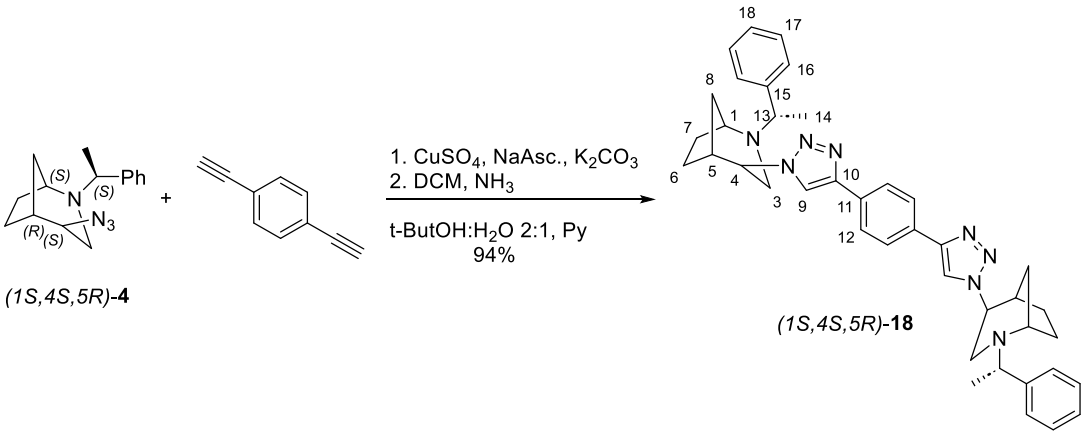


According to literature,[343] Azide (1*S*,4*S*,5*R*)-**4** (249 mg, 0.97 mmol, 1.00 equiv.) and propargyl ether (65 mg, 0.69 mmol, 0.71 equiv.) were reacted in similar manner as previously for **10** yielding 244 mg (0.40 mmol, 83%) of a yellow solid.

^{1}H-NMR: (400 MHz, $CDCl_3$) δ 8.09 (s, 2H, 2x C9H), 7.37 – 7.23 (m, 8H, 8x PhH), 7.23 – 7.14 (m, 2H, 2x C17H), 4.72 (d, *J* = 4.4 Hz, 4H, 2x $C11H_2$), 4.44 (t, *J* = 4.5 Hz, 2H, 2x C4H), 3.77 (t, *J* = 5.2 Hz, 2H, 2x C1H), 3.36 (q, *J* = 7.3 Hz, 2H, 2x C12H), 2.77 – 2.66 (m, 4H, 1, 2x $C3H_a$), 2.63 – 2.53 (m, 2H, 2x $C3H_b$), 1.90 – 1.82 (m, 4H, 2x $C6H_a$, 2x $C7H_a$), 1.66 (d, *J* = 12.7 Hz, 2H, 2x $C8H_a$), 1.59 – 1.53 (m, 2H, 2x $C7H_b$), 1.53 – 1.44 (m, 2H, 2x $6H_b$), 1.39 (d, *J* = 6.6 Hz, 6H, 2x $C13H_3$), 1.34 – 1.25 (m, 2H, 2x$8H_b$) ppm. **^{13}C-NMR:** (101

MHz, $CDCl_3$) δ = 149.9 (2x C10), 144.7 (2x C14), 128.7 (4x C16), 127.5 (2x C17), 127.4 (4x C15), 123.1 (2x C9), 63.7 (2x C11), 63.1 (2x C12), 59.8 (2x C4), 56.3 (2x C1), 47.9 (2x C3), 40.4 (2x C5), 33.8 (2x C8), 27.3 (2x C6), 21.7 (2x C7), 21.1 (2x C13) ppm. **HRMS (m/z):** (ESI-TOF) calculated for $C_{36}H_{46}N_8O$ $[M+H]^+$ 607.3873; found 607.3885. **Elementary analysis:** calculated C 71.26, H 7.64, N 18.47; found C 71.52, H 7.76, N 18.21. **IR (ϑ_{max}/cm^{-1}, KBr):** 3145, 2965, 2866, 2820, 1684, 1599, 1492, 1452, 1346, 1225, 1132, 1093, 1046, 956, 778, 703. $[\alpha]_D^{25}$**:** +118.9° (c 0.61, CH_2Cl_2).

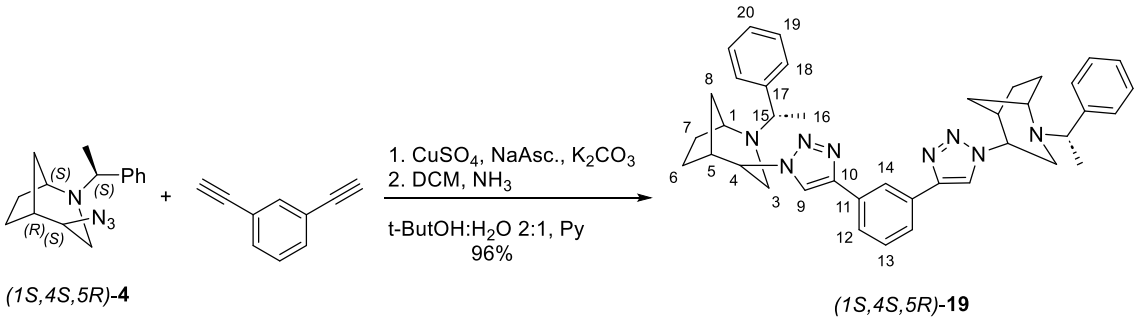
1,4-Bis-(1-((1S,4S,5R)-2-((S)-1-phenylethyl)-2-azabicyclo[3.2.1]octan-4-yl)-1H-1,2,3-triazol-4-yl) benzene **18**



According to literature,[343] Azide (1*S*,4*S*,5*R*)-**4** (263 mg, 1.03 mmol, 1.00 equiv.) and 1,4-diethynylbenzene (63 mg, 0.50 mmol, 0.49 equiv.) were reacted in similar manner as previously for **10** yielding 301 mg (0.47 mmol, 94 %) of an off-white solid.

^{1}H-NMR: (400 MHz, $CDCl_3$) δ 8.19 (s, 2H, 2x C9H), 7.85 (s, 4H, 4x C12H), 7.36 – 7.28 (m, 8H, 8x PhH), 7.22 – 7.19 (m, 2H, 2x C18H), 4.38 (d, *J* = 4.6 Hz, 2H, 2x C4H), 3.75 (t, *J* = 5.1 Hz, 2H, 2x C1H), 3.30 (q, *J* = 6.7 Hz, 2H, 2x C13H), 2.79 – 2.72 (m, 2H, 2x C5H), 2.69 (d, *J* = 13.6 Hz, 2H, 2x $C3H_a$), 2.57 (dd, *J* = 13.8, 4.7 Hz, 2H, 2x $C3H_b$), 1.89 – 1.77 (m, 4H, 2x $C6H_a$, 2x $C7H_a$), 1.61 (d, *J* = 12.4 Hz, 2H, 2x $C8H_a$), 1.57 – 1.50 (m, 2H, 2x $C6H_b$), 1.50 – 1.40 (m, 2H, 2x $C7H_b$), 1.36 (d, *J* = 6.6 Hz, 6H, 2x $C14H_3$), 1.28 – 1.23 (m, 2H, 2x $C8H_b$) ppm. **^{13}C-NMR:** (101 MHz, $CDCl_3$) δ = 146.2 (2x C10), 145.3 (2x C15), 130.7 (2x C11), 128.8 (4x C17), 127.7 (2x C18), 127.5 (4x C16), 126.0 (4x C12), 120.3 (2x C9), 63.1 (2x C13), 59.7 (2x C4), 56.0 (2x C1), 48.2 (2x C3), 40.4 (2x C5), 33.9 (2x C8), 27.3 (2x C6), 21.7 (2x C7), 21.2 (2x C14) ppm. **HRMS (m/z):** (ESI-TOF) calculated for $C_{40}H_{46}N_8$ $[M+H]^+$; found 639.3921. **Elementary analysis:** calculated C 75.20, H 7.26, N 17.54; found C 74.87, H 7.43, N 17.22. **IR (ϑ_{max}/cm^{-1}, KBr):** 3141, 2966, 2866, 28220, 2096, 1682, 1491, 1452, 1348, 1225,, 1132, 1057, 956. $[\alpha]_D^{25}$**:** +321.3° (c 0.39, CH_2Cl_2)

1,3-Bis-(1-((1S,4S,5R)-2-((S)-1-phenylethyl)-2-azabicyclo[3.2.1]octan-4-yl)-1H-1,2,3-triazol-4-yl) benzene **19**

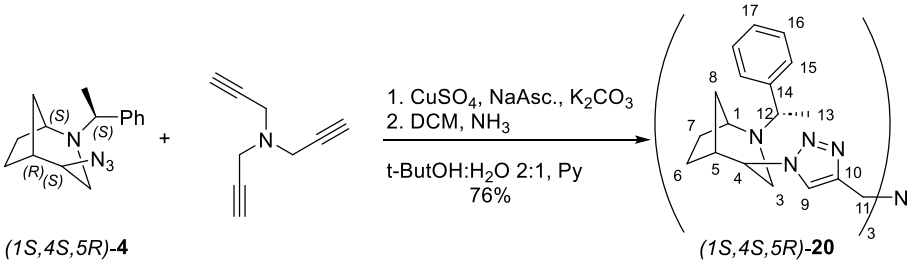


(1S,4S,5R)-**4** *(1S,4S,5R)*-**19**

According to literature,[343] Azide (1*S*,4*S*,5*R*)-**4** (256 mg, 1.00 mmol, 1.00 equiv.) and 1,3 diethynylbenzene (76 mg, 0.60 mmol, 0.60 equiv.) were reacted in similar manner as previously for **10** yielding 307 mg (0.48 mmol, 96%) of a yellow solid.

^{1}H-NMR: (400 MHz, $CDCl_3$) δ 8.36 (s, 2H, 2x C9H), 7.83 (dd, *J* = 7.7, 1.8 Hz, 2H, 2x C12H), 7.45 – 7.39 (m, 4x C18H, 4x C19H), 7.33 – 7.20 (m, 4H, 2x C20H, C13H, C14H), 4.48 (t, *J* = 4.4 Hz, 2H, 2x C4H), 3.82 (t, *J* = 5.0 Hz, 2H, 2x C1H), 3.37 (q, *J* = 6.7 Hz, 2H, 2x C15H), 2.86 – 2.80 (m, 2H, 2x C5H), 2.80 – 2.70 (m, 2H, 2x $C3H_a$), 2.68 – 2.59 (m, 2H, 2x $C3H_b$), 1.97 – 1.83 (m, 4H, 2x $C6H_a$, 2x $C7H_a$), 1.70 (d, *J* = 12.4 Hz, 2H, 2x $C8H_a$), 1.63 (ddd, *J* = 11.3, 4.7, 2.5 Hz, 2H, 2x $C6H_b$), 1.56 – 1.46 (m, 2H, 2x $C7H_b$), 1.42 (d, *J* = 6.7 Hz, 6H, 2x $C16H_3$), 1.39 – 1.34 (m, 2H, 2x $C8H_b$) ppm. **^{13}C-NMR:** (101 MHz, $CDCl_3$) δ = 146.4 (2x C10), 145.1 (2x C17), 131.9 (PhC), 129.4 (PhC), 128.9 (4x C19), 127.7 (2x C20), 127.4 (4x C18), 124.9 (2x C9), 122.7 (PhC), 120.5 (2x C12), 63.1 (2x C15), 59.8 (2x C4), 56.1 (2x C1), 48.1 (2x C3), 40.4 (2x C5), 33.9 (2x C8), 27.3 (2x C6), 21.7 (2x C7), 21.2 (2x C16) ppm. One PhC peak is accounting for 2 carbons (C10), but cannot be distinguished. **HRMS (m/z):** (ESI-TOF) calculated for $C_{40}H_{46}N_8$ $[M+H]^+$ 639.3924; found 639.3920. **Elementary analysis:** calculated C 75.20, H 7.26, N 17.54; found C 74.94, H 7.51, N 17.31. **IR (ϑ_{max}/cm^{-1}, KBr):** 3140, 2953, 2866, 2820, 1683, 1616, 1492, 1452, 1347, 1226, 1132, 1057, 778. $[\alpha]_D^{25}$**:** +307.9° (c 0.93, CH_2Cl_2).

N,N,N-tri((1-((1S,4S,5R)-2-((S)-1-phenylethyl)-2-azabicyclo[3.2.1]octan-4-yl)-1H-1,2,3-triazol-4-yl)methyl) amine **20**



(1S,4S,5R)-**4** *(1S,4S,5R)*-**20**

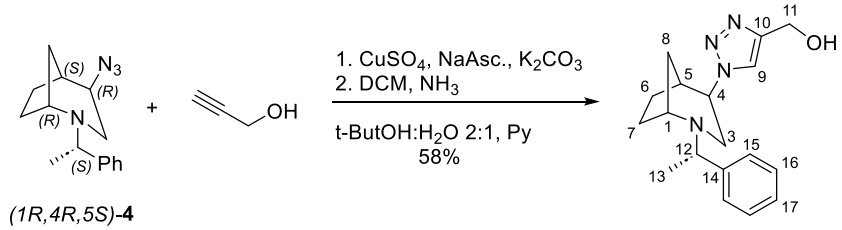
According to literature,[343] Azide (1*S*,4*S*,5*R*)-**4** (257 mg, 1.00 mmol, 1.00 equiv.) and tripropargylamine (43 mg, 0.33 mmol, 0.33 equiv.) were reacted in similar manner as previously for **10** yielding 222 mg (0.25 mmol, 76%) of white crystals.

^{1}H-NMR: (601 MHz, $CDCl_3$) δ 8.29 (s, 3H, 3x C9H), 7.39 – 7.35 (m, 6H, 6x C15H), 7.16 (t, J = 7.4 Hz, 6H, 6x C16H), 7.12 – 7.07 (m, 3H, 3x C17), 4.48 (t, J = 4.4 Hz, 3H, 3x C4H), 3.82 (s, 6H, 3x $C11H_2$), 3.79 (t, J = 4.7 Hz, 3H, 3x C1H), 3.36 (q, J = 6.7 Hz, 3H, 3x 12H), 2.77 – 2.73 (m, 3H, 3x C5H), 2.73 – 2.71 (m, 3H, 3x

$C3H_a$), 2.63 – 2.55 (m, 3H, 3x $C3H_b$), 1.90 – 1.83 (m, 6H, 3x $C6H_a$, 3x $C7H_a$), 1.80 (d, J = 11.8 Hz, 3H, 3x $C8H_a$), 1.60 – 1.55 (m, 3H, 3x $C6H_b$), 1.51 – 1.44 (m, 3H, 3x $C7H_b$), 1.40 (d, J = 6.6 Hz, 9H, 3x $C13H_3$), 1.36 – 1.30 (m, 3H, 3x $C8H_b$) ppm. **^{13}C-NMR:** (151 MHz, $CDCl_3$) δ = 144.8 (3xC14), 142.7 (3x C10), 128.6 (6x C16), 127.4 (6x C15), 127.2 (3x C17), 123.8 (3x C9), 63.0 (3x C12), 59.7 (3x C4), 56.1 (3x C1), 47.9 (3x C3), 47.0 (3x C11), 40.4 (3x C5), 33.8 (3x C8), 27.3 (3x C6), 21.5 (3x C7), 21.2 (3x C13) ppm. **HRMS (m/z):** (ESI-TOF) calculated for $C_{54}H_{69}N_{13}$ $[M+H]^+$ 900.5877; found 900.5876. **Elementary analysis:** calculated C 72.05, H 7.73, N 20.23; found C 72.32, H 7.46, N 20.11. **IR (ϑ_{max}/cm^{-1}, KBr):** 3143, 2953, 2867, 2821, 1650, 1492, 1452, 1335, 1211, 1132, 1045, 956, 759. $[\alpha]_D^{25}$**:** +233.3° (c 0.06, CH_2Cl_2).

5.4 (1*R*,4*R*,5*S*)-2-azabicyclo[3.2.1]octane triazoles and substrates

(1-((1R,4R,5S)-2-((S)-1-phenylethyl)-2-azabicyclo[3.2.1]octan-4-yl)-1H-1,2,3-triazol-4-yl)methanol **21**

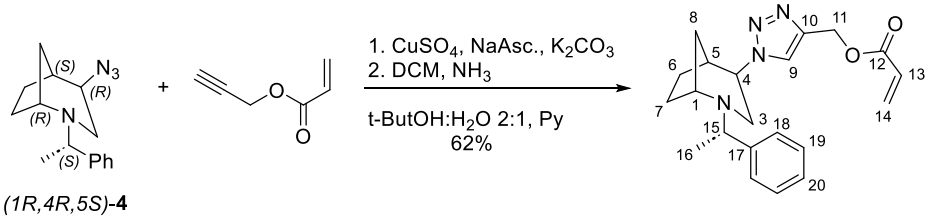


(1R,4R,5S)-**4** *(1R,4R,5S)*-**21**

According to literature,[343] Azide (1*R*,4*R*,5S)-**4** (257 mg, 1.00 mmol, 1.00 equiv.) and propargyl alcohol (67 mg, 1.20 mmol, 1.20 equiv.) were reacted in similar manner as previously for **10** yielding 182 mg (0.90 mmol, 58%) of a yellow solid.

^{1}H-NMR: (400 MHz, $CDDCl_3$) δ 8.33 (s, 1H, C9H), 7.37 – 7.31 (m, 4H, 4x PhH), 7.30 – 7.22 (m, 1H, C17H), 4.86 (d, *J* = 5.5 Hz, 2H, $C11H_2$), 4.66 – 4.59 (m, 1H, C4H), 3.47 (q, *J* = 6.6 Hz, 1H, C12H), 3.27 (d, *J* = 12.7 Hz, 1H, $C3H_a$), 3.16 (t, *J* = 5.0 Hz, 1H, C1H), 2.82 (dd, *J* = 13.1, 4.8 Hz, 1H, $C3H_b$), 2.78 (s, 1H, OH), 2.67 (q, *J* = 4.6 Hz, 1H, C5H), 1.92 – 1.83 (m, 1H, $C7H_a$), 1.82 – 1.74 (m, 1H, $C6H_a$), 1.63 – 1.56 (m, 1H, $C6H_b$), 1.54 – 1.48 (m, 1H, $C8H_a$), 1.32 (d, *J* = 6.6 Hz, 3H, $C13H_3$), 1.39 – 1.24 (m, 1H, $C7H_b$), 1.14 – 1.05 (m, 1H, $C8H_b$) ppm. **^{13}C-NMR:** (101 MHz, $CDDCl_3$) δ = 146.5 (C10), 145.3 (C14), 128.7 (2x C16), 127.4 (2x C15), 127.2 (C17), 122.0 (C10), 62.2 (C12), 60.0 (C4), 57.5 (C1), 56.8 (C11), 46.5 (C3), 40.4 (C5), 33.5 (C8), 27.2 (C6), 21.8 (C7), 21.8 (C13) ppm. **HRMS (m/z):** (ESI-TOF) calculated for $C_{18}H_{24}N_4O$ $[M+H]^+$ 313.2029; found 313.2021. **Elementary analysis:** calculated C 69.20, H 7.74, N 17.93; found C 69.07, H 8.01, N 17.61. **IR (ϑ_{max}/cm^{-1}, KBr):** 3144, 2968, 2868, 1722, 1492, 1452, 1343, 1224, 1119, 1054, 1019, 953, 766, 702. $[\alpha]_D^{25}$**:** +28.6° (c 0.21, CH_2Cl_2).

(1-((1S,4R,5R)-2-((S)-1-phenylethyl)-2-azabicyclo[3.2.1]octan-4-yl)-1H-1,2,3-triazol-4-yl)methyl acrylate **22**

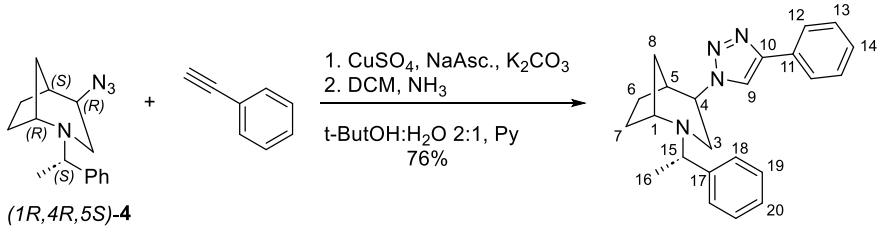


(1R,4R,5S)-**4** *(1R,4R,5S)*-**22**

According to literature,[343] Azide (1*R*,4*R*,5*S*)-**4** (269 mg, 1.05 mmol, 1.00 equiv.) and propargyl acrylate (122 mg, 1.11 mmol, 1.06 equiv) were reacted in similar manner as previously for **10** yielding 239 mg (0.65 mmol, 62%) of an orange solid.

^{1}H-NMR: (400 MHz, $CDCl_3$) δ 8.43 (s, 1H, C9H), 7.39 – 7.32 (m, 4H, 4x PhH), 7.31 – 7.23 (m, 1H, C20H), 6.48 (dd, *J* = 17.3, 1.5 Hz, 1H, $C14H_{trans}$), 6.18 (dd, *J* = 17.3, 10.4 Hz, 1H, C13H), 5.87 (dd, *J* = 10.5, 1.5 Hz, 1H, $C14H_{cis}$), 5.37 (d, *J* = 1.7 Hz, 2H, $C11H_2$), 4.63 (t, *J* = 4.4 Hz, 1H, C4H), 3.48 (q, *J* = 6.6 Hz, 1H, C15H), 3.26 (d, *J* = 13.1 Hz, 1H, $C3H_a$), 3.16 (t, *J* = 4.8 Hz, 1H, C1H), 2.83 (dd, *J* = 13.1, 4.7 Hz, 1H, $C3H_b$), 2.75 – 2.64 (m, 1H, C5H), 1.92 – 1.83 (m, 1H, $C7H_a$), 1.83 – 1.74 (m, 1H, $C6H_a$), 1.64 – 1.52 (m, 1H, $C6H_b$), 1.49 (dd, *J* = 12.1, 2.4 Hz, 1H, $C8H_a$), 1.41 – 1.34 (m, 1H, $C7H_b$), 1.32 (d, *J* = 6.6 Hz, 3H, $C16H_3$), 1.14 – 1.04 (m, 1H, $C8H_b$) ppm. **^{13}C-NMR:** (101 MHz, $CDCl_3$) δ = 166.1 (C17), 145.3 (C13), 141.8 (C9), 131.4 (C19), 128.7 (2xC15), 128.3 (C18), 127.4 (2xC14), 127.2 (C16), 124.1 (C8), 62.1 (C11), 59.9 (C7), 58.2 (C10), 57.5 (C4), 46.4 (C6), 40.3 (C1), 33.5 (C5), 27.2 (C2), 21.9 (C3), 21.8 (C12) ppm. **HRMS (m/z):** (ESI-TOF) calculated for $C_{21}H_{27}N_4O_2$ $[M+H]^+$ 367.2134; found 367.2125. **Elementary analysis:** calculated C 68.83, H 7.15, N 15.29; found C 68.47, H 7.37, N 15.21. **IR (ϑ_{max}/cm^{-1}, KBr):** 3148, 2964, 2869, 1726, 1634, 1492, 1452, 1407, 1268, 1183, 1047, 954, 770, 702. $[\alpha]_D^{25}$**:** +12.1° (c 0.52, CH_2Cl_2).

(1R,4R,5S)-4-(4-phenyl-1H-1,2,3-triazol-1-yl)-2-((S)-1-phenylethyl)-2-azabicyclo[3.2.1]octane **23**

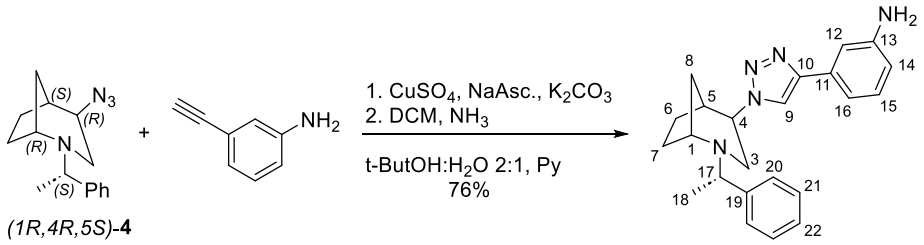


(1R,4R,5S)-**4** *(1R,4R,5S)*-**23**

According to literature,[343] Azide (1*R*,4*R*,5*S*)-**4** (256 mg, 1.00 mmol, 1.00 equiv.) and phenyl acetylene (102 mg, 1.00 mmol, 1.00 equiv.) were reacted in similar manner as previously for **10** yielding 230 mg (0.64 mmol, 64%) of white crystals.

^{1}H-NMR: (400 MHz, $CDCl_3$) δ 8.55 (s, 1H, C9H), 7.92 – 7.85 (m, 2H, 2x C12H), 7.51 – 7.45 (m, 2H, 2x PhH), 7.37 (d, *J* = 5.0 Hz, 4x PhH), 7.36 – 7.33 (m, 1H, *p*-PhH), 7.32 – 7.26 (m, 1H, *p*-PhH), 4.66 (t, *J* = 4.4 Hz, 1H, C4H), 3.55 (q, *J* = 6.6 Hz, 1H, C15H), 3.31 (dd, *J* = 13.1, 1.1 Hz, 1H, $C3H_a$), 3.22 (t, *J* = 5.0 Hz, 1H, C1H), 2.89 (dd, *J* = 13.1, 4.7 Hz, 1H, $C3H_{b)}$, 2.75 (q, *J* = 4.2 Hz, 1H, C5H), 1.97 – 1.77 (m, 2H, $C6H_a$, $C7H_a$), 1.64 (d, *J* = 6.4 Hz, 1H, $C8H_a$), 1.59 (m, 1H, $C6H_b$), 1.45 – 1.29 (m, 1H, $C7H_b$), 1.37 (d, *J* = 6.7 Hz, 3H, $C16H_3$), 1.14 (m, 1H, $C8H_b$) ppm. **^{13}C-NMR:** (101 MHz, $CDCl_3$) δ = 146.8 (C10), 145.2 (C17), 131.3 (C11), 129.0 (2x C13), 128.8 (2x C19), 128.0 (C14), 127.5 (2x *o*-PhC), 127.3 (C20), 125.9 (2x *o*-PhC), 120.0 (C9), 62.2 (C15), 59.9 (C4), 57.9 (C1), 46.2 (C3), 40.4 (C5), 33.6 (C8), 27.2 (C6), 22.2 (C7), 21.4 (C16) ppm. **HRMS (m/z):** (ESI-TOF) calculated for $C_{23}H_{26}N_4$ $[M+H]^+$ 359.2236; found 359.2231. **IR (ϑ_{max}/cm^{-1}, KBr):** 3131, 3061, 2929, 2851, 1483, 1452, 1364, 1225, 1126, 1053, 771, 699. $[\alpha]_D^{25}$**:** +86.2° (c = 0.55, CH_2Cl_2)

3-(1-((1R,4R,5S)-2-((S)-1-phenylethyl)-2-azabicyclo[3.2.1]octan-4-yl)-1H-1,2,3-triazol-4-yl)aniline **24**

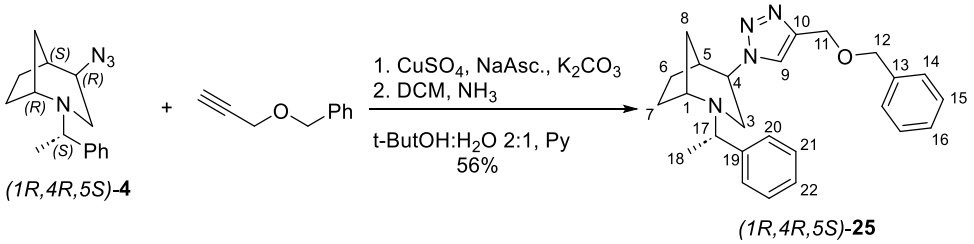


(1R,4R,5S)-**4** *(1R,4R,5S)*-**24**

According to literature,[343] Azide (1*R*,4*R*,5*S*)-**4** (257 mg, 1.00 mmol, 1.00 equiv.) and 3-ethynylaniline (130 mg, 1.11 mmol, 1.11 equiv.) were reacted in similar manner as previously for **10** yielding 283 mg (0.76 mmol, 76%) of off-white crystals.

^{1}H-NMR: (400 MHz, $CDCl_3$) δ 8.62 (s, 2H, NH_2), 8.51 (s, 1H, C9), 7.67 (tt, *J* = 7.6, 1.8 Hz, 1H, C15H), 7.37 – 7.35 (m, 3H, 3x PhH), 7.33 – 7.30 (m, 1H, PhH), 7.29 – 7.24 (m, 2H, 2x PhH), 7.22 – 7.18 (m, 1H, PhH), 6.72 – 6.63 (m, 1H, C14H), 4.65 (t, *J* = 4.4 Hz, 1H, C4H), 3.54 (q, *J* = 6.6 Hz, 1H, C17H), 3.30 (d, *J* = 13.1 Hz, 1H, $C3H_a$), 3.21 (t, *J* = 5.0 Hz, 1H, C1H), 2.88 (dd, *J* = 13.2, 4.7 Hz, 1H, $C3H_b$), 2.73 (q, *J* = 4.4 Hz, 1H, C5H), 1.96 – 1.86 (m, 1H, $C7H_a$), 1.86 – 1.76 (m, 1H, $C6H_a$), 1.62 (q, *J* = 5.0, 4.0 Hz, 1H, $C6H_b$), 1.60 – 1.52 (m, 1H, $C8H_a$), 1.44 – 1.28 (m, 1H, $C7H_b$), 1.36 (d, *J* = 6.7 Hz, 3H, $C18H_3$), 1.18 – 1.07 (m, 1H, $C8H_b$) ppm. **^{13}C-NMR:** (101 MHz, $CDCl_3$) δ = 150.0 (C11), 147.0 (C19), 146.9 (C10), 132.2 (C15), 129.9 (C22), 128.8 (2x C21), 127.5 (2x C20), 127.3 (C13), 120.1 (C9), 116.2 (C12), 114.8 (C14), 112.4 (C16), 62.2 (C17), 59.9 (C4), 57.8 (C1), 46.3 (C3), 40.4 (C5), 33.5 (C8), 27.2 (C6), 22.1 (C7), 21.4 (C18) ppm. **HRMS (m/z):** (ESI-TOF) calculated for $C_{23}H_{27}N_5$ $[M+H]^+$ 374.2345; found 374.2343. **Elementary analysis:** calculated C 73.96, H 7.29, N 18.75; found C 74.15, H 7.17, N 18.40. **IR (ϑ_{max}/cm^{-1}, KBr):** 3351, 3138, 2958, 2822, 1610, 1591, 1484, 1351, 1281, 1224, 1138, 1055, 874, 791. **$[\alpha]_D^{25}$:** +102.4° (c 0.42, CH_2Cl_2).

(1R,4R,5S)-4-(4-((benzyloxy)methyl)-1H-1,2,3-triazol-1-yl)-2-((S)-1-phenylethyl)-2-azabicyclo[3.2.1]octane **25**



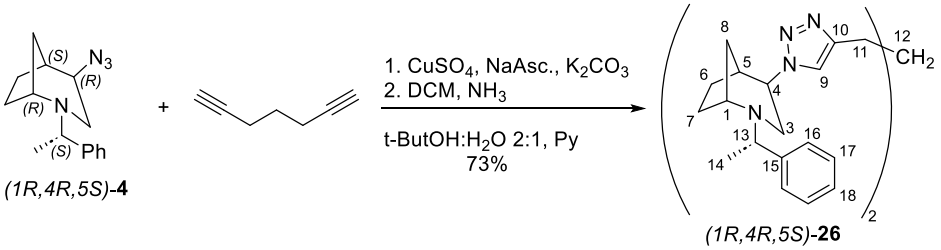
(1R,4R,5S)-**4** *(1R,4R,5S)*-**25**

According to literature,[343] Azide (1*R*,4*R*,5*S*)-**4** (261 mg, 1.02 mmol, 1.00 equiv.) and benzyl propargylether (137 mg, 1.04 mmol, 1.02 equiv.) were reacted in similar manner as previously for **10** yielding 231 mg (0.57 mmol, 56%) of an orange oil.

^{1}H-NMR: (400 MHz, $CDCl_3$) δ 8.36 (s, 1H, C9), 7.45 – 7.23 (m, 10H, 10x PhH), 4.77 (s, 2H, $C12H_2$), 4.67 (s, 2H, $C11H_2$), 4.63 (t, *J* = 4.3 Hz, 1H, C4H), 3.47 (q, *J* = 6.7 Hz, 1H, C17H), 3.32 – 3.24 (m, 1H, $C3H_a$), 3.21 – 3.12 (m, 1H, C1H), 2.83 (dd, *J* = 13.1, 4.7 Hz, 1H, $C3H_b$), 2.68 (q, *J* = 4.1 Hz, 1H, C5H), 1.94 – 1.84 (m, 1H, $C7H_a$), 1.84 – 1.74 (m, 1H, $C6H_a$), 1.59 (ddd, *J* = 9.0, 4.3, 2.4 Hz, 1H, $C6H_b$), 1.56 – 1.50 (m, 1H, $C8H_a$), 1.46 – 1.21 (m, 1H, $C7H_b$), 1.32 (d, *J* = 6.6 Hz, 3H, $C18H_3$), 1.14 – 1.04 (m, 1H, $C8H_b$) ppm. **^{13}C-NMR:** (101 MHz, CCl_3) δ = 145.3 (*q*PhC), 144.1 (*q*PhC), 138.2 (C10), 128.7 (2x PhC), 128.6 (2x PhC), 128.0 (2x PhC), 127.8(*p*-PhC), 127.4 (2x PhC), 127.2 (*p*-PhC), 122.9 (C9), 72.5 (C12), 63.9 (C11), 62.1 (C17),

59.9 (C4), 57.5 (C1), 46.5 (C3), 40.4 (C5), 33.5 (C8), 27.2 (C6), 21.9 (C7), 21.8 (C18) ppm. **HRMS (m/z):** (ESI-TOF) $C_{25}H_{30}N_4O$ $[M+H]^+$ 403.2420; found 403.2454. **Elementary analysis:** calculated for C 74.59, H 7.51, N 13.92; found C 74.32, H 7.57, N 14.33. **IR (ϑ_{max}/cm^{-1}, KBr):** 3141, 2968, 2866, 1720, 1600, 1493, 1452, 1343, 1226, 1098, 1046, 953, 737, 700. $[\alpha]_D^{25}$**:** +25.1° (c 0.47, CH_2Cl_2).

1,3-Bis-(1-((1R,4R,5S)-2-((S)-1-phenylethyl)-2-azabicyclo[3.2.1]octan-4-yl)-1H-1,2,3-triazol-4-yl) propane **26**

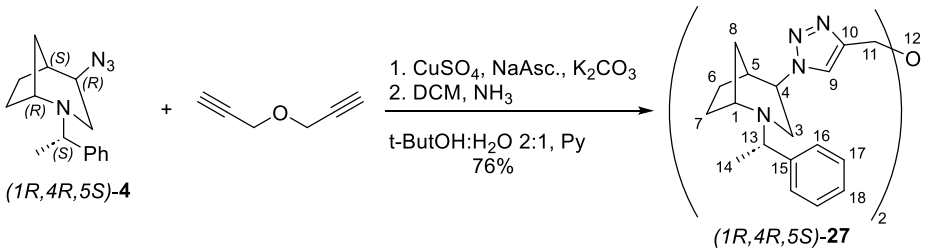


(1R,4R,5S)-**4** *(1R,4R,5S)*-**26**

According to literature,[343] Azide (1*R*,4*R*,5*S*)-**4** (272 mg, 1.06 mmol, 1.00 equiv.) and hepta-1,6-diyne (50 mg, 0.54 mmol, 0.51 equiv.) were reacted in similar manner as previously for **10** yielding 234 mg (0.39 mmol, 73 %) of an off-white solid.

^{1}H-NMR: (400 MHz, $CDCl_3$) δ 8.12 (s, 2H, 2x C9H), 7.35 – 7.32 (m, 8H, 8x PhH), 7.26 – 7.20 (m, 2H, 2x C18H), 4.60 (t, *J* = 4.4 Hz, 2H, 2x C4H), 3.47 (q, *J* = 6.7 Hz, 2H, 2x C13H), 3.26 (d, *J* = 13.0 Hz, 2H, 2x $C3H_a$), 3.16 (t, *J* = 5.0 Hz, 2H, 2x C1H), 2.91 (t, *J* = 7.6 Hz, 4H, 2x $C11H_2$), 2.81 (dd, *J* = 13.0, 4.6 Hz, 2H, 2x $C3H_b$), 2.67 (q, *J* = 4.2 Hz, 2H, 2x C5H), 2.24 – 2.12 (m, 2H, $C12H_2$), 1.95 – 1.84 (m, 2H, 2x $C7H_a$), 1.78 (m, 2H, 2x $C6H_a$), 1.62 – 1.53 (m, 4H, 2x $C6H_b$, 2x $C8H_a$), 1.37 – 1.27 (m, 2H, 2x $C7H_b$), 1.32 (d, *J* = 6.7 Hz, 6H, 2x $C14H_3$), 1.14 – 1.04 (m, 2H, 2x $C8H_b$) ppm. **^{13}C-NMR:** (101 MHz, $CDCl_3$) δ = 146.7 (2x C10), 145.3 (2x C15), 128.7 (4x C17), 127.5 (4x C16), 127.2 (2x C18), 121.2 (2x C9), 62.2 (2x C13), 59.8 (2x C4), 57.6 (2x C1), 46.5 (2x C3), 40.5 (2x C5), 33.6 (2x C8), 29.8 (C12), 27.2 (2x C6), 25.6 (2x C11), 21.9 (2x C7), 21.7 (2x C14) ppm. **HRMS (m/z):** (ESI-TOF) calculated for $C_{37}H_{48}N_8$ $[M+H]^+$ 605.4080; found 605.4088. **Elementary analysis:** calculated C 73.47, H 8.00, N 18.53; found C 73.56, H 8.30, N 18.14. **IR (ϑ_{max}/cm^{-1}, KBr):** 3140, 2935, 2866, 2820, 2095, 1546, 1492, 1452, 1343, 1213, 1136, 1047, 953, 761, 701, 550. $[\alpha]_D^{25}$**:** +46.7° (c 0.46, CH_2Cl_2).

(1R,1'R,4R,4'R,5S,5'S)-4,4'-(4,4'-(oxybis(methylene))bis(1H-1,2,3-triazole-4,1-diyl))bis(2-((S)-1-phenylethyl)-2-azabicyclo[3.2.1]octane) **27**

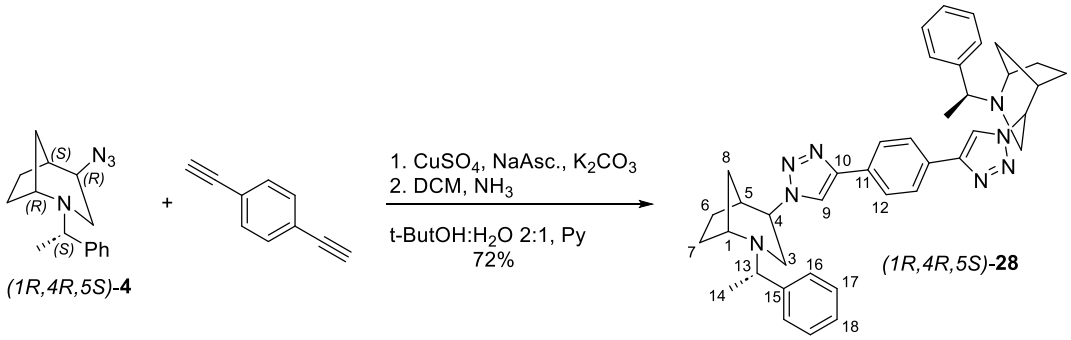


(1R,4R,5S)-**4** *(1R,4R,5S)*-**27**

According to literature,[343] Azide (1*R*,4*R*,5*S*)-**4** (262 mg, 1.02 mmol, 1.00 equiv.) and propargyl ether (52 mg, 0.55 mmol, 0.54 equiv.) were reacted in similar manner as previously for **10** yielding 235 mg (0.39 mmol, 76%) of an off-white solid.

^{1}H-NMR: (400 MHz, $CDCl_3$) δ 8.40 (s, 2H, 2x C9H), 7.36 – 7.32 (m, 8H, 8x PhH), 7.28 – 7.22 (m, 2H, 2x C16H), 4.88 – 4.78 (m, 4H, 2x C11H_2), 4.63 (t, *J* = 4.4 Hz, 2H, 2xC4H), 3.46 (q, *J* = 6.6 Hz, 2H, 2x C12H), 3.28 (d, *J* = 13.1 Hz, 2H, 2x C3H_a), 3.16 (t, *J* = 5.0 Hz, 2H, 2x C1H), 2.82 (dd, *J* = 13.1, 4.6 Hz, 2H, 2x C3H_b), 2.72 – 2.65 (m, 2H, 2x C5H), 1.92 – 1.83 (m, 2H, 2x C7H_a), 1.82 – 1.74 (m, 2H, 2x 6H_a), 1.60 – 1.50 (m, 4H, 2x C6H_b, 2x C8H_a), 1.31 (d, *J* = 6.6 Hz, 6H, 2x C13H_3), 1.37 – 1.25 (m, 2H, 2x C7H_b), 1.13 – 1.05 (m, 2H, 2x C8H_b) ppm. **^{13}C-NMR:** (101 MHz, $CDCl_3$) δ = 145.2 (2x C14), 143.5 (2x C10), 128.7 (4x C16), 127.5 (4x C15), 127.2 (2x C17), 123.3 (2x C9), 63.7 (2x C11), 62.2 (2x C12), 60.0 (2x C4), 57.4 (2x C1), 46.6 (2x C3), 40.4 (2x C5), 33.5 (2x C8), 27.2 (2x C6), 21.9 (2x C7), 21.8 (2x C13) ppm. **HRMS (m/z):** (ESI-TOF) calculated for $C_{36}H_{46}N_8O$ $[M+H]^+$ 607.3873; found 607.3866. **Elementary analysis:** calculated C 71.26, H 7.64, N 18.47; found C 71.45, H 7.84, N 18.32. **IR (ϑ_{max}/cm^{-1}, KBr):** 3140, 2967, 2867, 2820, 2095, 1683, 1492, 1452, 1343, 1226, 1118, 1098, 1077, 1046, 953, 760. $[\alpha]_D^{25}$**:** +23.5° (c 0.37, CH_2Cl_2).

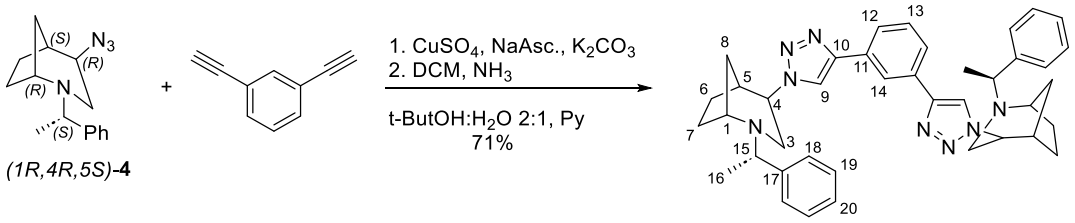
1,4-Bis-(1-((1R,4R,5S)-2-((S)-1-phenylethyl)-2-azabicyclo[3.2.1]octan-4-yl)-1H-1,2,3-triazol-4-yl) benzene **28**



According to literature,[343] Azide (1*R*,4*R*,5*S*)-**4** (272 mg, 1.06 mmol, 1.00 equiv.) and 1,4-diethynylbenzene (70 mg, 0.56 mmol, 0.52 equiv.) were reacted in similar manner as previously for **10** yielding 239 mg (0.38 mmol, 72%) of an off-white solid.

^{1}H-NMR: (400 MHz, $CDCl_3$) δ 8.58 (s, 2H, 2x C9H), 7.95 (d, *J* = 31.8 Hz, 4H, 4x C12H), 7.44 – 7.35 (m, 8H, 8x PhH), 7.31 – 7.26 (m, 2H, 2x C18H), 4.67 (t, *J* = 4.3 Hz, 2H, 2x C4H), 3.58 (q, *J* = 6.6 Hz, 2H, 2x C13H), 3.32 (d, *J* = 12.4 Hz, 2H, 2x C3H_a), 3.25 (t, *J* = 4.8 Hz, 2H, 2x C1H), 2.91 (dd, *J* = 13.3, 4.6 Hz, 2H, 2x C3H_b), 2.80 – 2.71 (m, 2H, 2x C5H), 1.96 – 1.88 (m, 2H, 2x C6H_a), 1.86 – 1.79 (m, 2H, 2x C7H_a), 1.68 – 1.56 (m, 4H, 2x C6H_b, 2x C8H_a), 1.50 – 1.31 (m, 2H, 2x C7H_b), 1.40 (d, *J* = 6.7 Hz, 6H, 2x C14H_3), 1.21 – 1.11 (m, 2H, 2x C8H_b) ppm. **^{13}C-NMR:** ^{13}C NMR (101 MHz, $CDCl_3$) δ = 146.5 (2x C10), 145.1 (2x C15), 130.8 (2x C11), 128.8 (4x C17), 127.5 (4x C16), 127.3 (2x C18), 126.2 (4x C12), 120.1 (2x C9), 62.2 (2x C13), 59.9 (2x C4), 58.0 (2x C1), 46.1 (2x C3), 40.4 (2x C5), 33.6 (2x C8), 27.2 (2x C6), 22.3 (2x C7), 21.2 (2x C14) ppm. **HRMS (m/z):** (ESI-TOF) calculated for $C_{40}H_{46}N_8$ $[M+H]^+$ 639.3924; found 639.3937. **Elementary analysis:** calculated C 75.20, H 7.26, N 17.54; found C 75.52, H 7.13, N 17.25. **IR (ϑ_{max}/cm^{-1}, KBr):** 3136, 2966, 2867, 2821, 1722, 1492, 1451, 1345, 1225, 1054, 761. $[\alpha]_D^{25}$**:** +106.2° (c 0.37, CH_2Cl_2).

1,3-Bis-(1-((1R,4R,5S)-2-((S)-1-phenylethyl)-2-azabicyclo[3.2.1]octan-4-yl)-1H-1,2,3-triazol-4-yl) benzene **29**

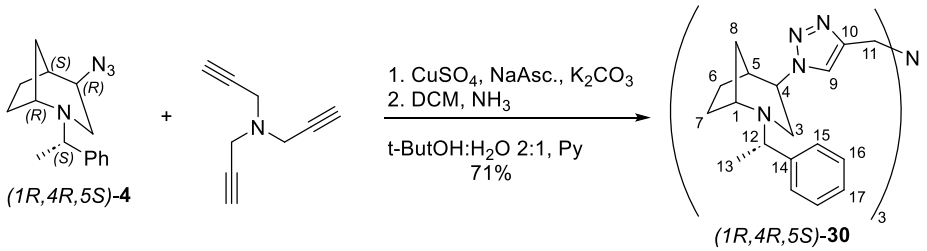


(1R,4R,5S)-**4** *(1R,4R,5S)*-**29**

According to literature,[343] (1*R*,4*R*,5*S*)-**4** (270 mg, 1.05 mmol, 1.00 equiv.) and propargyl alcohol (70 mg, 0.56 mmol, 0.53 equiv.) were reacted in similar manner as previously for **10** yielding 239 mg (0.37 mmol, 71%) of white crystals.

^{1}H-NMR: (400 MHz, $CDCl_3$) δ 8.60 (s, 2H, 2x C9H), 7.88 (dd, *J* = 7.7, 1.8 Hz, 2H, 2x C12H), 7.40 – 7.36 (m, 8H, 4x C18H, 4x C19H), 7.30 – 7.20 (m, 4H, 2x C20H, C13H, C14H), 4.68 (t, *J* = 4.4 Hz, 2H, 2x C4H), 3.55 (q, *J* = 6.6 Hz, 2H, 2x C15H), 3.33 (d, *J* = 13.3 Hz, 2H, 2x $C3H_a$), 3.25 (t, *J* = 4.9 Hz, 2H, 2x C1H), 2.90 (dd, *J* = 13.1, 4.6 Hz, 2H, 2x $C3H_b$), 2.77 (d, *J* = 6.1 Hz, 2H, 2x C5H), 1.94 – 1.80 (m, 4H, 2x $C6H_a$, 2x $C7H_a$), 1.69 (d, *J* = 19.9 Hz, 2H, 2x $C8H_a$), 1.62 (d, *J* = 3.7 Hz, 2H, 2x $C6H_b$), 1.45 – 1.38 (m, 2H, 2x $C7H_b$), 1.36 (d, *J* = 6.7 Hz, 6H, 2x $C16H_3$), 1.16 (dtd, *J* = 12.2, 4.5, 1.5 Hz, 2H, 2x $C8H_b$) ppm. **^{13}C-NMR:** (101 MHz, $CDCl_3$) δ = 146.7 (2x C9), 145.0 (2x C13), 132.0 (PhC), 129.5 (PhC), 128.8 (4x C15), 127.5 (2x C14), 127.3 (2x C16), 125.5 (2x C8), 123.2 (PhC), 120.3 (2x C17), 62.3 (2x C11), 60.0 (2x C7), 57.8 (2x C4), 46.2 (2x C6), 40.5 (2x C1), 33.7 (2x C5), 27.2 (2x C2), 22.3 (2x C3), 21.1 (2x C12) ppm. One PhC peak is accounting for 2 carbons (C10), but cannot be distinguished. **HRMS (m/z):** (ESI-TOF) calculated for $C_{40}H_{46}N_8$ $[M+H]^+$ 639.3924; found 639.3939. **Elementary analysis:** calculated C 75.20, H 7.26, N 17.54; found C 75.02, H 7.29, N 17.43. **IR (ϑ_{max}/cm^{-1}, KBr):** 3136, 2967, 2867, 2822,, 2095, 1616, 1492, 1452, 1344, 1226, 1137, 1054, 953. $[\alpha]_D^{25}$**:** +72.1° (c 0.43, CH_2Cl_2).

N,N,N-tri((1-((1R,4R,5S)-2-((S)-1-phenylethyl)-2-azabicyclo[3.2.1]octan-4-yl)-1H-1,2,3-triazol-4-yl)methyl) amine **30**



(1R,4R,5S)-**4** *(1R,4R,5S)*-**30**

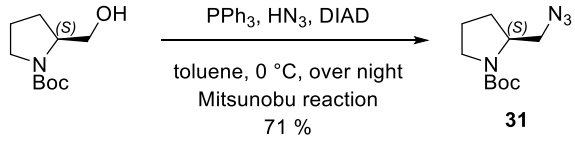
According to literature,[343] Azide (1*R*,4*R*,5*S*)-**4** (258 mg, 1.01 mmol, 1.00 equiv.) and tripropargylamine (49 mg, 0.37 mmol, 0.37 equiv.) were reacted in similar manner as previously for **10** yielding 213 mg (0.24 mmol, 71%) of slightly yellow crystals.

^{1}H-NMR: (400 MHz, $CDCl_3$) δ 8.61 (m, 3H, 3x C9H), 7.24 – 7.33 (m, 12H, 12x PhH), 7.21 – 7.18 (m, 3H, 3x *p*-PhH), 4.63 (dt, *J* = 6.6, 2.9 Hz, 3H, 3x C4H), 4.06 – 3.81 (m, 6H, 3x $C11H_2$), 3.49 – 3.42 (m, 3H, 3x C12H), 3.37 (d, *J* = 13.0 Hz, 3H, 3x $C3H_a$), 3.17 (t, *J* = 4.9 Hz, 3H, 3x C1H), 2.86 – 2.77 (m, 3H, 3x $C3H_b$), 2.75 – 2.67 (m, 3H, 3x C5H), 1.91 – 1.78 (m, 6H, 3x $C6H_a$, 3x $C7H_a$), 1.63 (d, *J* = 11.6 Hz, 3H, 3x $C8H_a$), 1.60 – 1.54 (m, 3H, 3x $C6H_b$), 1.48 (m, 3H, 3x $C7H_b$), 1.35 (d, *J* = 6.6 Hz, 9H, 3x $C13H_3$), 1.13 – 1.06 (m,

3H, C8H$_b$) ppm. **^{13}C-NMR:** (101 MHz, $CDCl_3$) δ = 145.5 (3x C14), 142.7 (3x C9), 128.7(6x C15), 127.7 (6x C14), 127.5 (3x C16), 123.7 (3x C9), 62.2 (3x C12), 59.9 (3x C4), 57.3 (3x C1), 47.1 (3x C11), 46.6 (3x C3), 40.5 (3x C5), 33.6 (3x C8), 27.3 (3x C6), 22.0 (3x C7), 21.7 (3x C13) ppm. **HRMS (m/z):** (ESI-TOF) calculated for $C_{54}H_{69}N_{13}$ $[M+H]^+$ 900.5877; found 900.5879. **Elementary analysis:** calculated C 72.05, H 7.73, N 20.23; found C 71.77, H 8.05, N 19.91. **IR (ϑ_{max}/cm^{-1}, KBr):** 3140, 2965, 2866, 2821, 1721, 1644, 1492, 1452, 1335, 1262, 1098, 1045, 801, 702. **$[\alpha]_D^{25}$:** +35.6° (c 0.43, CH_2Cl_2).

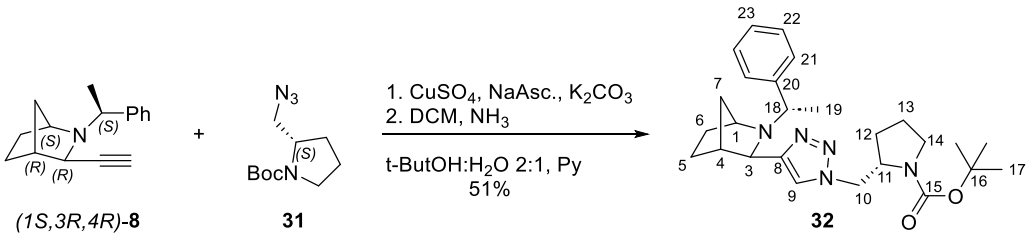
5.5 Towards (1*S*,3*R*,4*R*)-2-azabicyclo[2.2.1]heptane triazoles

tert-butyl (S)-2-(azidomethyl)pyrrolidine-1-carboxylate **31**



According to a previously applied literature procedure,[100,102] to a solution of *N*-Boc-L-prolinol (1.006 g, 5.00 mmol, 1.00 equiv.), triphenylphosphine (1.443 g, 5.5 mmol, 1.10 equiv.) in toluene (0.25 M) hydrazoic acid (1.0 M in toluene, 5.5 mL, 5.5 mmol, 1.1 equiv.) was added in one portion. Following, a solution of DIAD (0.1 M in toluene 1.10 mL, 5.50 mmol. 1.10 equiv.) was dropped in under stirring at 0 °C. The reaction mixture was left to reach room temperature and was stirred overnight, before it was quenched by the addition of aq. NaOH (10 wt%) to basify the solution. Upon extraction by CH_2Cl_2 (3 times) the organic phase was concentrated under reduced pressure. To remove the majority of triphenylphosphine oxide side product the crude product was dissolved in 1:1 hexane:Et_2O and the undissolved side product was filtered off. Purification was achieved by column chromatography (SiO_2, 75:25 hexane:EtOAc) yielding 799 mg (3.53 mmol, 71%) of a yellowish oil.
All recorded spectroscopic data matched previously reported ones.
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.03 – 3.82 (m, 1H), 3.63 – 3.23 (m, 4H), 2.06 – 1.76 (m, 4H), 1.47 (s, 9H) ppm. As a mixture of two conformers.

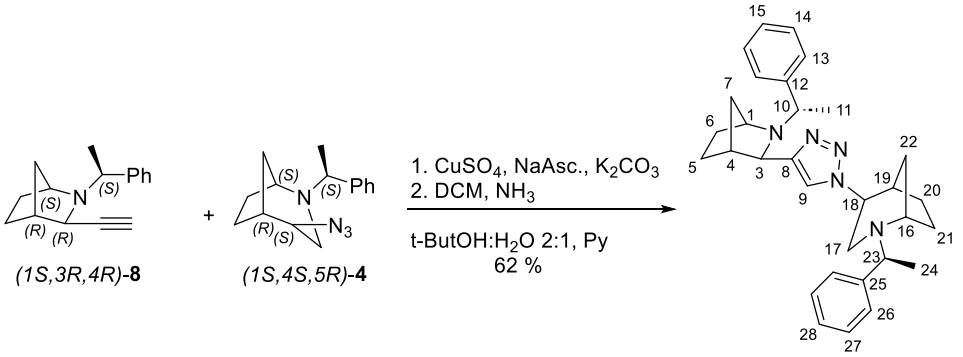
(2S)-tert-butyl 2-((4-((1S,3R,4R)-2-((S)-1-phenylethyl)-2-azabicyclo[2.2.1]heptan-3-yl)-1H-1,2,3-triazol-1-yl)-methyl)pyrrolidine-1-carboxylate **32**



According to literature,[343] azide **31** and (0.11 g, 0.50 mmol, 1.00 equiv.) and alkyne (1*S*,3*R*,4*R*)-**8** (0.11 g, 0.50 mmol, 1.00 equiv.) were reacted in similar manner as previously for **10**. The crude was purified by column chromatography (SiO_2, 25x2 cm 75:25 hexane:EtOAc) yielding 115 mg (0.26 mmol, 52%) of a yellow solid.
^{1}H-NMR (601 MHz, $CDCl_3$, 283 K) δ 7.31 (s, 1H, C9H), 7.24 – 7.19 (m, 2H. 2x PhH), 7.10 – 7.04 (m, 2H, 2x PhH), 7.03 – 6.97 (m, 1H, C23H), 4.35 (dd, *J* = 13.5, 2.9 Hz, 1H), 4.32 – 4.23 (m, 1H), 3.94 (tt, *J* = 8.0, 3.2 Hz, 1H), 3.80 – 3.72 (m, 1H), 3.59 (dd, *J* = 6.6, 4.7 Hz, 1H), 3.36 (d, *J* = 12.9 Hz, 1H), 3.32 – 3.25 (m,

1H), 3.14 (ddd, *J* = 11.2, 7.7, 3.5 Hz, 1H), 2.28 (dd, *J* = 48.3, 4.3 Hz, 1H), 2.09 (tdd, *J* = 13.2, 4.5, 2.5 Hz, 1H), 1.81 – 1.67 (m, 5H, C5H_a, C6H_a, C7H_a), 1.61 (s, 3H), 1.57 (s, 6H, 29, 30, 31), 1.55 – 1.45 (m, 3H, C6H_b, C7H_b), 1.40 (d, *J* = 6.5 Hz, 3H, C19H_3), 1.34 – 1.26 (m, 1H, C7H_b). Mixture of two conformers. Wherever possible assignments were added. **^{13}C-NMR** (151 MHz, $CDCl_3$, 283 K) δ = 154.7, 154.2, 153.9, 153.5, 145.3 and 145.0 (C20), 128.5, 128.4, 127.7, 127.6, 126.7 (23), 122.6 and 121.7 (C9), 80.2 and 79.9 (C16), 65.1 and 65.1 (C18), 61.3, 61.2, 58.6, 58.5, 57.2, 57.2, 51.8, 50.7, 47.0, 46.7, 45.1, 44.9, 35.5, 35.1, 29.1, 28.9, 28.7, 28.6, 28.6, 28.0, 23.3, 22.6, 22.5, 22.3, 22.2 ppm. Mixture of two conformers. Wherever possible assignments were added. **HRMS (m/z):** (ESI-TOF) calculated for $C_{26}H_{37}N_5O$ $[M+H]^+$ 452.3026; found 452.3026. **Elementary analysis:** calculated C 69.15, H 8.26, N 15.51; found C 68.93, H 8.48, N 15.25. **IR (ϑ_{max}/cm^{-1}, KBr):** 3426, 2968, 2931, 2869, 2770, 1697, 1455, 1397, 1365, 1174, 1118, 1051, 762. $[\alpha]_D^{25}$**:** +44.8° (c 0.23, CH_2Cl_2).

(1S,4S,5R)-2-((S)-1-phenylethyl)-4-(4-((1S,3S,4R)-2-((S)-1-phenylethyl)-2-azabicyclo[2.2.1]heptan-3-yl)-1H 1,2,3-triazol-1-yl)-2-azabicyclo[3.2.1]octane **33**



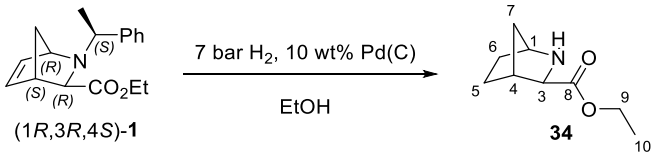
(1S,3R,4R)-**8** *(1S,4S,5R)*-**4** **33**

According to literature,[343] azide (1*S*,4*S*,4*R*)-**4** and (0.15 g, 0.60 mmol, 1.00 equiv.) and alkyne (1*S*,3*R*,4*R*)-**8** (0.13 g, 0.50 mmol, 1.00 equiv.) were reacted in similar manner as previously for **10**. The crude was purified by column chromatography (SiO_2, 25x2 cm 75:25 hexane:EtOAc) yielding 177 mg (0.37 mmol, 62%) of an orange oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H, C8H), 7.45 – 7.39 (m, 2H, 2x PhH), 7.38 – 7.32 (m, 2H, 2x PhH), 7.30 – 7.22 (m, 3H, 2x PhH, *p*-PhH), 7.04 – 6.98 (m, 2H, 2x PhH), 6.98 – 6.90 (m, 1H, *p*-PhH), 4.18 (s, 1H, CH), 3.82 (m, 2H, 2x CH), 3.63 (q, *J* = 6.6 Hz, 1H, CH), 3.36 (q, *J* = 6.7 Hz, 1H, CH), 2.61 – 2.43 (m, 3H, 3x CH), 2.18 – 2.06 (m, 2H, 2x CH), 1.91 – 1.74 (m, 3H, 3x CH), 1.72 – 1.61 (m, 2H, 2x CH), 1.56 – 1.47 (m, 5H, 5x CH), 1.45 (d, *J* = 6.6 Hz, 3H, CH_3), 1.43 (d, *J* = 6.6 Hz, 3H, CH_3), 1.29 – 1.24 (m, 2H, 2x CH) ppm. Wherever possible assignments were added. **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 152.4 (C8), 145.4 (*q*-PhC), 145.4 (*q*-PhC), 128.7 (2x PhC), 128.3 (2x PhC), 127.8 (2x PhC), 127.5 (2x PhC), 127.4 (*p*-PhC), 126.7 (*p*-PhC), 121.7 (C9), 65.4, 63.1, 61.5, 59.2, 58.6, 56.0, 48.1, 45.4, 40.3, 35.4, 33.9, 28.9, 27.3, 23.1, 22.8, 21.6, 21.5 ppm. Wherever possible assignments were added. **HRMS (m/z):** (ESI-TOF) calculated for $C_{31}H_{40}N_5$ $[M+H]^+$ 482.3280; found 482.3280. **Elementary analysis:** calculated C 77.30, H 8.16, N 14.54; found C 77.06, H 8.38, N 14.24. **IR (ϑ_{max}/cm^{-1}, KBr):** 3435, 2967, 2868, 2788, 1492, 1453, 1359, 1348, 1258, 1210, 1165, 1133, 1104, 142, 761. $[\alpha]_D^{25}$**:** +127.4° (c 0.33, CH_2Cl_2).

6.6 Various *N*-Boc protected 2-azabicycloalkanes and substrates

ethyl (1S,3R,4R)-2-azabicyclo[2.2.1]heptane-3-carboxylate **34**



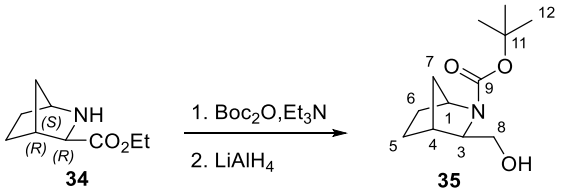
(1*R*,3*R*,4*S*)-**1** **34**

According to literature,[95,283,300,303] a standard reduction of the double bond/hydrogenation of the amine was conducted with chiral pure ester (1*R*,3*R*,4*S*)-**1**. The weighed fractions of *aza*-DA-product (1.00 equiv.) were dissolved in absolute ethanol (with varying concentrations 0.5–3 M) and 10 % Pd/C (10 wt%) as catalyst. The reaction was placed into a hydrogen generator, three times purged and set to react at 7 bar H_2 pressure. Pressure loss could be observed and roughly be calculated according to the used starting material. Generally, the reaction was left overnight, filtered through celite and concentrated under reduced pressure. Completeness of the reaction was controlled by ^{1}H-NMR. The reaction yield was usually quantitative, no further purification was necessary. The product was then directly transformed.

All recorded spectroscopic data matched previously reported ones.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.17 (q, *J* = 7.1 Hz, 2H, C9H_2), 3.56 (s, 1H, C4H), 3.34 (s, 1H, C1H), 2.65 – 2.60 (m, 1H, C3H), 2.28 (s, 1H, NH), 1.70 – 1.35 (m, 5H, 2x C5H, 2x C6H, C7H_a), 1.27 (t, *J* = 7.1 Hz, 3H, C10H_3), 1.26 – 1.22 (m, 1H, C7H_b) ppm.

tert-butyl (1S,3R,4R)-3-(hydroxymethyl)-2-azabicyclo[2.2.1]heptane-2-carboxylate **35**



34 **35**

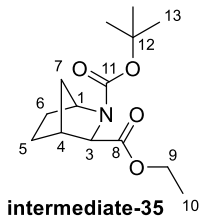
According to literature,[97,98,103,300,301] a standard *N*-Boc protection was conducted by dissolving ester **34** (1.00 equiv.) in dry CH_2Cl_2 (with varying concentrations, 0.2–0.5 M) and follow-up addition of triethylamine (2.00 equiv.) and di-*tert*-butyl dicarbonate (Boc_2O, 1.50 equiv.) at 0 °C until the cease of carbon dioxide development. The reaction was led to reach room temperature and stirred overnight. Upon concentration under reduced pressure the dry reaction mixture was dissolved in EtOAc and washed by aq. $NaHCO_3$ solution and brine. The organic phase was dried with Na_2SO_4 and solvent was removed under reduced pressure. The reaction proceeded generally quantitatively and the *N*-Boc protected bicyclic intermediate-**25** was used without further purification.

To a stirred solution of intermediate-**25** (1.00 equiv.) in THF (0.5 – 1 M) at 0 °C an emulsion of $LiAlH_4$ (1 M in THF, 2.3 equiv.) is added slowly dropwise and the reaction mixture was kept stirring for 2-3 h. The reaction was quenched by aq. NaOH (10 wt%), filtered through a pad of celite, dried over Na_2SO_4 and concentrated giving the alcohol as a colourless oil, usually with 90–99 % yield.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.09 (tt, *J* = 2.1, 1.2 Hz, 1H, C3H), 3.56 (d, *J* = 6.1 Hz, 2H, C8H_2), 3.43 (br s, 1H, OH), 3.42 (t, *J* = 6.3 Hz, 1H, C1H), 2.34 – 2.28 (m, 1H, C4H), 1.74 – 1.69 (m, 1H, C7H_a), 1.63 – 1.55 (m, 2H, C5H_a, C6H_a), 1.45 (s, 9H, 3x C12H_3), 1.47 – 1.38 (m, 2H, C5H_b, C6H_b), 1.24 (ddd, *J* = 10.1 Hz, 1H,

C7H$_b$) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 80.4 (C11), 67.3, 66.7, 58.0, 39.9, 35.8, 29.8, 28.6 (3x C12), 28.0 ppm. C9=O not visible.

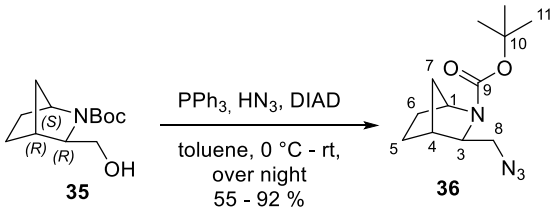
2-(tert-butyl) 3-ethyl (1S,3R,4R)-2-azabicyclo[2.2.1]heptane-2,3-dicarboxylate intermediate-**35**



intermediate-35

^{1}H-NMR (601 MHz, $CDCl_3$) δ (4.37 and 4.24 td)(*J* = 2.3, 1.1 Hz, 1H, C3H), , 4.23 – 4.10 (m, 2H, C9H$_2$), (3.84 and 3.73)(s, 1H, C1H), 2.71 – 2.66 (m, 1H, C4H), 1.97 – 1.90 (m, 1H, C7H$_a$), 1.79 – 1.73 (m, 1H), 1.69 – 1.60 (m, 2H), 1.57 – 1.49 (m, 1H), (1.48 and 1.41)(s, 9H, 3x C13H$_3$), 1.30 – 1.26 (m, 4H, C7H$_b$, C10H$_3$) ppm. As a mixture of two rotamers.

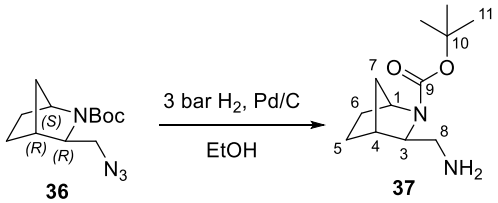
tert-butyl (1S,3R,4R)-3-(azidomethyl)-2-azabicyclo[2.2.1]heptane-2-carboxylate **36**



According to literature,[100,102,103,300,301] alcohol **35** (1.00 equiv.) and triphenylphosphine (PPh_3, 1.30 equiv.) were dissolved in toluene (0.1–0.3 M) at 0 °C, followed by addition of hydrazoic acid (1 M in toluene, 1.3 equiv.) in one portion and the dropwise addition of either DEAD (40% in toluene, 1.50 equiv.) or DIAD (40% in toluene, 1.5 equiv.). The reaction was allowed to reach room temperature and stirred overnight, before it was quenched by the addition of aq. NaOH (10 wt%) to basify the solution. Upon extraction by CH_2Cl_2 (3 times) the organic phase was concentrated under reduced pressure. To remove the majority of triphenylphosphine oxide side product the crude product was dissolved in 1:1 hexane:Et_2O and the undissolved side product was filtered off. Purification was achieved by column chromatography (SiO_2, 90:10 to 83.3:16.7 hexane:EtOAc). Yields were between 55 and 92 %.

Most of the recorded spectroscopic data matched previously reported ones. In the published description there was one proton too much for the chiral backbone in the area between 1 and 2 ppm. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 4.20 – 4.02 (m, 1H, C3H), 3.64 – 3.46 (m, 1H, C8H$_a$), 3.42 – 3.21 (m, 1H, C8H$_b$), 3.10 – 2.91 (m, 1H, C4H), 2.48 (d, *J* = 4.6 Hz, 1H, C1H), 1.78 – 1.65 (m, 3H, C5H$_a$, C6H$_a$, C7H$_a$), 1.64 – 1.55 (m, 2H, C5H$_b$, C6H$_b$), 1.45 (s, 9H, 3x C11H$_3$), 1.26 (dd, *J* = 9.6, 2.4 Hz, 1H, C7H$_b$) ppm. As a mixture of two rotamers.

tert-butyl (1S,3R,4R)-3-(aminomethyl)-2-azabicyclo[2.2.1]heptane-2-carboxylate **37**



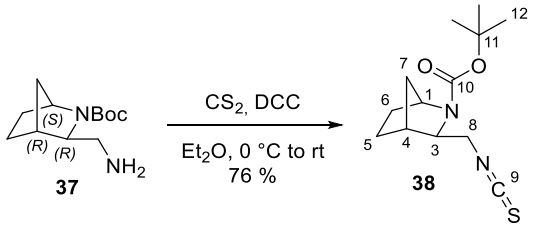
According to literature,[95,283,300,301,303] to a solution of azide **36** in absolute ethanol (varying conenctration, 0.3 – 2 M) Pd/C (10 wt%) as catalyst. The reaction was put into a hydrogen generator,

three times purged and set to react at 3.5 bar H_2 pressure. Pressure loss could not be observed properly due to released N_2 in the process. The reaction proceeds within 2-3 hours before being filtered through celite and concentrated under reduced pressure. The reaction yield was usually quantitative, no further purification was in most cases necessary, if it became necessary usually a short silica column was prepared (SiO_2, 10 cm height, 90:10 CH_2Cl_2:MeOH).

All recorded spectroscopic data matched previously reported ones.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.03 (s, 1H, C3H), 3.27 – 3.02 (m, 1H, C1H), 2.88 (dd, *J* = 12.9, 6.0 Hz, 1H, C8H$_a$), 2.63 – 2.44 (m, 1H, C8H$_b$), 2.44 – 2.36 (m, 1H, C4H), 2.02 (s, 2H, NH_2), 1.76 – 1.65 (m, 2H, C7H$_a$, CH), 1.65 – 1.53 (m, 2H, 2x CH), 1.44 (s, 9H,C11H$_3$), 1.43 – 1.33 (m, 1H, CH), 1.26 – 1.19 (m, 1H, C7H$_b$) ppm. As a mixture of two rotamers.

tert-butyl (1S,3R,4R)-3-(isothiocyanatomethyl)-2-azabicyclo[2.2.1]heptane-2-carboxylate **38**

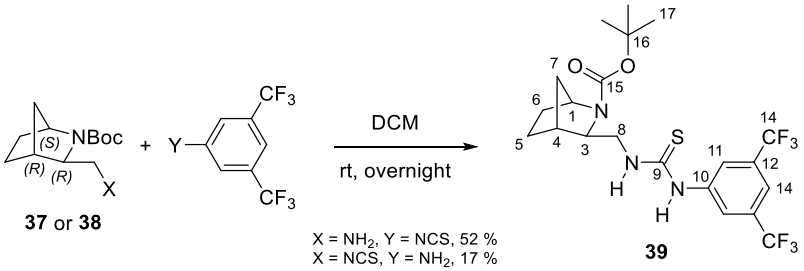


In accordance with literature procedure,[302] to a solution of DCC (1.280 mg, 6.20 mmol, 1.00 equiv.) and CS_2 (2.4 mL, 39.7mmol, 6.4 equiv.) in Et_2O (50 mL, 0.1 M) at -10 °C (NaCl/ice) was added the bicyclic amine **37** (1.40 mg, 6.20 mmol, 1.00 equiv.). The reaction kept stirring and led to reach room temperature and kept stirred overnight. After filtering off the precipitate the filtrate was concentrated under reduced pressure and purified by column chromatography (SiO_2, 25x3 cm, 90:10 hexane:EtOAc) yielding 1.368 g (5.10 mmol, 82 %) of a colourless oil.

^{1}H-NMR (601 MHz, 283 K, $CDCl_3$) δ 4.10 (d, *J* = 62.5 Hz, 1H, C3H), 3.77 (ddd, *J* = 75.6, 14.0, 3.6 Hz, 1H, C8H$_a$), 3.41 (ddd, *J* = 59.8, 9.5, 3.5 Hz, 1H, C8H$_b$), 3.30 (ddd, *J* = 13.8, 9.5, 7.3 Hz, 1H, C1H), 2.56 (dd, *J* = 12.9, 5.0 Hz, 1H, C4H), 1.82 – 1.71 (m, 2H, C7H$_a$, CH), 1.68 (d, *J* = 9.0 Hz, 1H, CH), 1.64 – 1.52 (m, 2H, 2x CH), 1.44 (d, *J* = 6.4 Hz, 9H, 3x C12H$_3$), 1.30 (dd, *J* = 9.8, 4.0 Hz, 1H, C7H$_b$) ppm. As a mix of two rotamers. **^{13}C-NMR** (151 MHz, 283 K, $CDCl_3$) δ = 155.1 and 154.3 (C9), 130.7 and 130.5 (C10), 80.4 and 80.1 (C11), 62.9 and 62.7, 58.0 and 57.2, 46.4 and 45.8, 39.8 and 39.2, 34.7 and 33.9, 30.1 and 29.6, 28.6 (3x C12), 27.5 and 27.5 ppm. As a mix of two rotamers. **HRMS (m/z):** (ESI-TOF) calculated for $C_{13}H_{20}N_2O_2S$ $[M+Na]^+$ 291.1143; found 291.1137. **IR (ϑ_{max}/cm^{-1}, KBr):** 2994, 2974, 2869, 2207, 2122, 1674, 1457, 1394, 1252, 1187, 1100, 1080, 951, 793, 702.

6.7 *N*-Boc protected 2-azabicycloalkane thioureas

tert-butyl (1S,3R,4R)-3-((3-(3,5-bis(trifluoromethyl)phenyl)thioureido)methyl)-2-azabicyclo[2.2.1]-heptane-2-carboxylate **39**

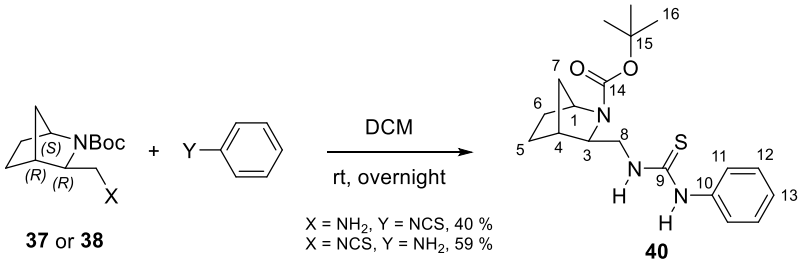


A solution of bicyclic amine **37** (0.224 g, 1.00 mmol, 1.00 equiv.) and commercially available 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene (0.274 g, 1.00 mmol, 1.00 equiv.) was stirred in $CHCl_3$ (4 mL, 0.25 M) at room temperature overnight. After concentrating under vacuum the crude was purified by column chromatography (SiO_2, 25x2 cm, 75:25 hexane:EtOAc) yielding 0.260 g (0.52 mmol, 52 %) of a white solid.

Alternatively, a solution of bicyclic isothiocyanate **38** (134 mg, 0.50 mmol, 1.00 equiv.) and commercially available 3,5-bis(trifluoromethyl)aniline (115 mg, 0.50 mmol, 1.00 equiv.) was stirred in CH_2Cl_2 (2 mL, 0.25 M) at room temperature overnight. After concentrating under vacuum the crude was purified by column chromatography yielding 42 mg (0.08 mmol, 17 %) of an white solid. Spectroscopic data of both products matched.

^{1}H-NMR (601 MHz, $CDCl_3$) δ 10.58 (s, 1H, NH), 8.72 (2x s, 1H, C14H), 8.03 – 7.55 (m, 2H, 2x C11H), 4.03 (2x s, 1H, C3H), 3.87 – 3.55 (m, 1H, C8H$_a$), 3.47 – 2.91 (m, 2H, C1H,C8H$_b$), 2.43 (2x s, 1H, C4H), 1.76 – 1.63 (m, 3H, C5H$_a$, C6H$_a$, C7H$_a$), 1.60 – 1.54 (m, 1H, CH), 1.46 (m, 6H, 6H of 3x C17H$_3$), 1.39 – 1.33 (m, 1H, CH), 1.32 – 1.27 (m, 1H, C7H$_b$), 1.25 – 1.19 (m, 3H, 3H of 3x C17H$_3$) ppm. One NH is missing or could not be assigned. **^{13}C-NMR** (151 MHz, $CDCl_3$) δ = 180.7 and 180.0 (C9), 157.5 and 155.4 (C15), 142.9 and 139.3 (C10), 132.7 and 131.2 (q, *J* = 33.7 Hz, 2x C14), 125.1 and 123.3 (2x C11), 119.5 and 117.6 (C16), 81.5 and 80.6 (2x C14), 63.9 and 62.9 (C1), 58.4 and 56.9 (C3), 52.8 and 46.5 (C8), 41.4 and 40.8 (C4), 35.5 and 35.3 (C7), 30.0 and 29.7 (C5), 28.3 and 28.1 (3x C17), 27.5 and 27.4 (6) ppm. 2x C12 is missing. As a mixture of two rotamer. **HRMS (m/z):** (ESI-TOF) calculated for $C_{21}H_{25}N_3F_6O_2S$ $[M+H]^+$ 498.1650, $[M+Na]^+$ 520.1469; found 498.1643, 520.1490. **IR (ϑ_{max}/cm^{-1}, KBr):** 3435, 3286, 2979, 1663, 1592, 1477, 1425, 1381, 1280, 1174, 1131. $[\alpha]_D^{23}$**:** +46° (c = 0.48, CH_2Cl_2), **mp:** 121-123 °C.

tert-butyl (1S,3R,4R)-3-((3-phenylthioureido)methyl)-2-azabicyclo[2.2.1]heptane-2-carboxylate **40**



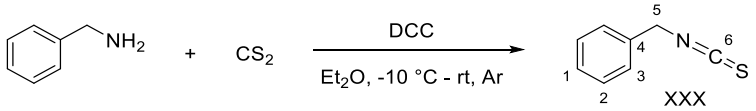
A solution of bicyclic amine **37** (0.224 g, 1.00 mmol, 1.00 equiv.) and isothiocyanatobenzene (0.140 g, 1.00 mmol, 1.00 equiv.) was stirred in $CHCl_3$ (4 mL, 0.25 M) at room temperature overnight. After

concentrating under vacuum the crude was purified by column chromatography (SiO_2, 25x2 cm, 75:25 hexane:EtOAc) yielding 0.146 g (0.40 mmol, 40 %) of an off-white solid.

Alternatively, a solution of bicyclic isocyanate **38** (268 mg, 1.00 mmol, 1.00 equiv.) and aniline (99 mg, 1.00 mmol, 1.00 equiv.) was stirred in $CHCl_3$ (5 mL, 0.2 M) at room temperature overnight. After concentrating under vacuum the crude was purified by column chromatography yielding 212 mg (0.59 mmol, 59 %) of a white solid. Spectroscopic data of both products matched.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H, NH), 7.66 (s, 1H, NH), 7.38 (t, *J* = 7.7 Hz, 2H, 2x PhH), 7.29 – 7.19 (m, 3H, 2x PhH, *p*PhH), 3.99 (s, 1H, C3H), 3.86 (d, *J* = 9.6 Hz, 1H, $C8H_a$), 3.36 (s, 2H, C1H, $C8H_b$), 2.37 (d, *J* = 4.1 Hz, 1H, C4H), 1.81 (d, *J* = 10.4 Hz, 1H, $C6H_a$), 1.72 – 1.60 (m, 1H, CH), 1.60 – 1.48 (m, 2H, 2x CH), 1.48 – 1.40 (m, 1H, CH), 1.39 – 1.33 (m, 1H, $C7H_b$), 1.27 (s, 9H, 3x $C16H_3$) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 180.8 (C9), 157.2 (C14), 136.3 (C10), 129.8 (2x PhC), 127.1 (C13), 126.1 (2x PhC), 80.3 (C15), 63.0 (C1), 58.3 (C3), 52.9 (C8), 41.0 (C4), 35.7 (C5), 29.8, 28.4 (3x C16), 27.6 ppm. **HRMS (m/z):** (ESI-TOF) calculated for $C_{19}H_{27}N_3O_2S$ $[M+H]^+$ 362.1902; found 362.1903. **IR (ϑ_{max}/cm^{-1}, KBr):** 3278, 3187, 2976, 1929, 1677, 1538, 1398, 1365, 1246, 1168, 1084, 970, 739. **$[\alpha]_D^{25}$:** +19° (c = 0.16, CH_2Cl_2). **mp:** 185.2°C.

(isothiocyanatomethyl)benzene

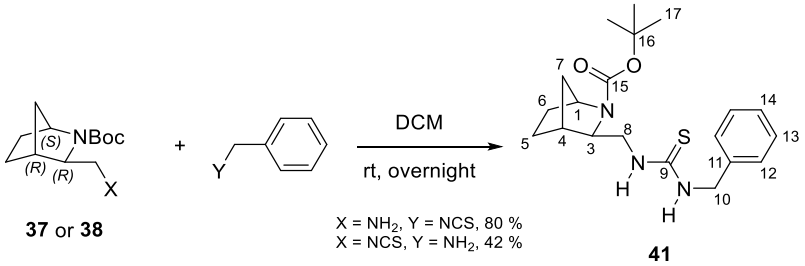


According to literature,[302] to a solution of DCC (3.09 g, 15.00 mmol, 1.00 equiv.) and CS_2 (6 mL, 99.00 mmol, 6.6 equiv.) in Et_2O (50 mL, 0.3 M) at -10 °C (NaCl/ice) was added benzyl amine (1.68 g, 15.00 mmol, 1.00 equiv.). The reaction kept stirring and led to reach room temperature and kept stirred overnight. After filtering off the precipitate the filtrate was concentrated under reduced pressure and purified by column chromatography (SiO_2, 25x3 cm, 75:25 hexane:EtOAc) yielding 1.527 g (10.25 mmol, 68 %) of a colourless oil.

All recorded spectroscopic data matched previously reported ones.[344]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.38 (m, 2H, 2x PhH), 7.38 – 7.29 (m, 3H, 2x PhH, *p*-PhH), 4.72 (s, 2H, $C5H_2$) ppm.

tert-butyl (1S,3R,4R)-3-((3-benzylthioureido)methyl)-2-azabicyclo[2.2.1]heptane-2-carboxylate **41**

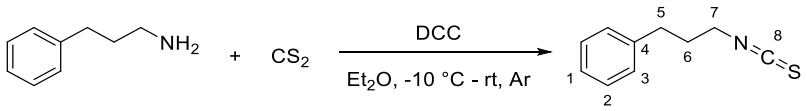


A solution of bicyclic amine **37** (0.224 g, 1.00 mmol, 1.00 equiv.) and (isothiocyanatomethyl)benzene (0.149 g, 1.00 mmol, 1.00 equiv.) in $CHCl_3$ (4 mL, 0.25 M) was stirred at room temperature overnight. After concentrating under vacuum the crude was purified by column chromatography (SiO_2, 25x2 cm, 75:25 hexane:EtOAc) yielding 0.301 g (0.80 mmol, 80%) of white crystals.

Alternatively, a solution of bicyclic isocyanate **38** (268 mg, 1.00 mmol, 1.00 equiv.) and benzylamine (107 mg, 1.00 mmol, 1.00 equiv.) in $CHCl_3$ (5 mL, 0.2 M) was stirred at room temperature overnight. After concentrating under vacuum the crude was purified by column chromatography yielding 159 mg (0.42 mmol, 42%) of off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.30 (m, 4H, 4x PhH), 7.30 – 7.26 (m, 1H, *p*PhH), 4.82 – 4.32 (br s, 2H, C10H_2), 4.05 (s, 1H, C3H), 3.48 – 3.33 (m, 2H, C1H, C8H_a), 2.40 (s, 1H, C4H), 1.89 – 1.77 (m, 1H, CH), 1.76 – 1.63 (m, 2H, 2x CH), 1.63 – 1.50 (m, 3H, 3x CH), 1.40 (s, 9H, 3x C17H_3), 1.34 – 1.26 (m, 2H, C7H_b, CH) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 181.1 (C9), 136.8 (C15), 128.8 (2x PhC), 128.2 (2x PhC), 127.8 (*p*PhC), 81.2 (C16), 63.2 (C1), 58.2 (C3), 52.1 (C8), 47.9 (C10), 40.9 (C4), 35.5 (C7), 30.0, 28.5 (3x C17), 27.6 ppm. Quartenerary phenyl carbon not visible. **HRMS (m/z):** (ESI-TOF) calculated for $C_{20}H_{29}N_3O_2S$ $[M+H]^+$ 376.2059, $[M+Na]^+$ 398.1878; found 376.2059, 398.1830. **IR (ϑ_{max}/cm^{-1}, KBr):** 3282, 3086, 2974, 2880, 1664, 1567, 1415, 1364, 1245, 1167, 1129, 1102, 698. $[\alpha]_D^{25}$**:** +15° (c = 0.78, CH_2Cl_2). **mp:** 138.1 – 139.7 °C.

(3-isothiocyanatopropyl)benzene

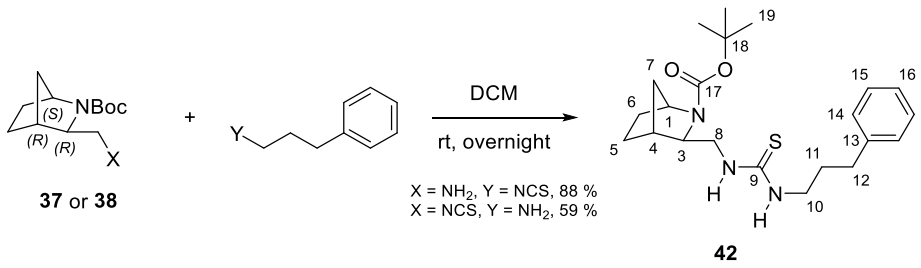


According to literature,[302] to a solution of DCC (3.09 g, 15.00 mmol, 1.00 equiv.) and CS_2 (6 mL, 99.00 mmol, 6.6 equiv.) in Et_2O (50 mL, 0.3 M) at -10 °C (NaCl/ice) was added 3-phenylpropyl amine (2.03 g, 15.00 mmol, 1.00 equiv.). The reaction was allowed to reach room temperature and stirred overnight. After filtering off the precipitate the filtrate was concentrated under reduced pressure and purified by column chromatography (SiO_2, 25x3 cm, 90:10 hexane:EtOAc) yielding 2.410 g (13.60 mmol, 91 %) of a colourless oil.

All recorded spectroscopic data matched previously reported ones.[345]

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 2H, 2x PhH), 7.25 – 7.21 (m, 1H, *p*-PhH), 7.21 – 7.15 (m, 2H, 2x PhH), 3.50 (t, *J* = 6.5 Hz, 2H, C7H_2), 2.76 (t, *J* = 7.4 Hz, 2H, C5H_2), 2.02 (dq, *J* = 8.4, 6.6 Hz, 2H, C6H_2) ppm.

tert-butyl (1S,3R,4R)-3-((3-(3-phenylpropyl)thioureido)methyl)-2-azabicyclo[2.2.1]heptane-2-carboxylate **42**



42

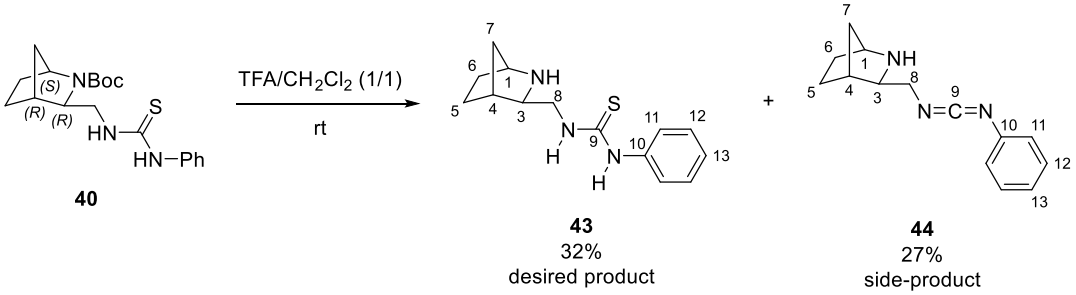
A solution of bicyclic amine **37** (0.226 g, 1.00 mmol, 1.00 equiv.) and (3-isothiocyanatopropyl)benzene (0.190 g, 1.00 mmol, 1.00 equiv.) in $CHCl_3$ (4 mL, 0.25 M) was stirred overnight at room temperature. After concentrating under vacuum the crude was purified by column chromatography (SiO_2, 25x2 cm, 75:25 hexane:EtOAc) yielding 0.165 g (0.88 mmol, 88%) of an slightly yellowish oil.

Alternatively, a solution of bicyclic isocyanate **38** (268 mg, 1.00 mmol, 1.00 equiv.) and 3-phenylpropan-1-amine (140 mg, 1.00 mmol, 1.00 equiv.) in $CHCl_3$ (5 mL, 0.2 M) was stirred overnight at room temperature. After concentrating under vacuum the crude was purified by column chromatography yielding 355 mg (0.59 mmol, 59 %) of slightly yellowish oil. Spectroscopic data of both products matched.

^{1}H-NMR (601 MHz, $CDCl_3$) δ 8.26 (s, 1H, NH), 7.34 – 7.26 (m, 2H, 2x PhH), 7.25 – 7.12 (m, 3H, 2x PhH, *p*PhH), 6.05 (s, 1H, NH), 4.08 (s, 1H, C3H), 3.78 (s, 1H, CH), 3.50 (s, 1H, CH), 3.38 (dd, *J* = 14.1, 7.9 Hz, 2H, CH_2), 3.28 (s, 1H, CH), 2.72 (dt, *J* = 8.3, 3.5 Hz, 2H, CH_2), 2.43 – 2.39 (m, 1H, CH), 1.97 (s, 3H, C7H$_a$, C11H$_2$), 1.77 – 1.70 (m, 1H, CH), 1.67 – 1.54 (m, 2H, 2x CH), 1.47 (s, 9H, 3x C19H$_3$), 1.44 (s, 1H, CH), 1.33 (d, *J* = 10.2 Hz, 1H, C7H$_b$) ppm. **^{13}C-NMR** (151 MHz, $CDCl_3$) δ = 180.9 (C9), 138.3 (C17), 128.5 (4x PhC), 126.1 (*p*PhC)), 80.6 (C18), 63.2 (C3), 58.5, 57.7, 52.6 (C8), 45.9, 42.9, 40.9 (C4), 35.5 (C7), 33.2, 30.4, 30.0, 28.6 (3x C19), 27.6 ppm. **HRMS (m/z):** (ESI-TOF) calculated for $C_{22}H_{33}N_3O_2S$ $[M+H]^+$ 404.2372; found 404.2366. **IR (ϑ_{max}/cm^{-1}, film):** 3282, 2973, 1664, 1567, 1415, 1364, 1245, 1167, 1129, 1102, 879, 758. $[\alpha]_D^{25}$**:** +23° (c = 0.16, CH_2Cl_2).

5.8 Deprotected 2-azabicycloalkanes thioureas and side products

1-((1S,3R,4R)-2-azabicyclo[2.2.1]heptan-3-ylmethyl)-3-phenylthiourea **43**



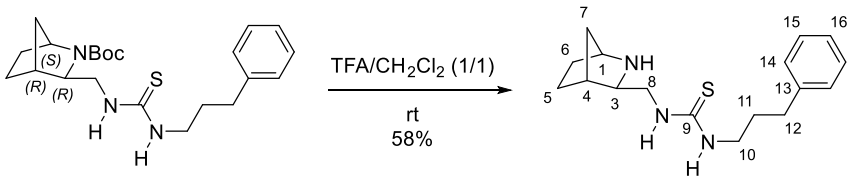
N-Boc protected thiourea **40** (292 mg, 0.81 mmol) was dissolved in a mixture of TFA:CH_2Cl_2 (1:1, 2 mL, 3 mL for each 1.2 mmol) and the reaction was stirred at rt until TLC indicated a complete consumption of starting material. The reaction mixture was rendered basic with aq. NH_3 (30 %) and extracted by CH_2Cl_2 (3x 3 mL) before the combined organic layers were dried over Na_2SO_4 and crude product was concentrated under vacuum. Purification by chromatography was conducted on an CombiFlash companion (SiO_2, 20g, 83.3:16.7 to 20:80 hexane:EtOAc) yielding 67 mg (0.26 mmol, 32%) of yellowish wax like product. A side product (**44**) could be isolated: 50 mg (0.22 mmol, 27%). During the extraction the characteristic smell of hydrogen sulfide was perceptible.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H, bicyclic-NH), 7.42 (d, *J* = 8.1 Hz, 2H, 2x PhH), 7.38 – 7.30 (m, 2H, 2x PhH), 7.22 – 7.14 (m, 1H, *p*PhH), 4.01 – 3.83 (m, 1H, C3H), 3.81 – 3.71 (m, 1H, C8H$_a$), 3.51 (s, 1H, C8H$_b$), 3.34 – 3.20 (m, 1H, C1H), 2.32 (s, 1H), 2.01 – 1.87 (m, 1H, C4H), 1.72 – 1.55 (m, 3H), 1.57 – 1.35 (m, 3H) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 181.8 (C9), 138.0 (C10), 129.2 (2x PhC), 126.1 (*p*PhC), 124.5 (2x PHC), 64.1 (C1), 56.6 (3), 46.6 (C8), 38.9 (C4), 35.6 (7), 28.2, 27.2 ppm. **HRMS (m/z):** (ESIC-TOF) calculated for $C_{14}H_{19}N_3S$ $[M+H]^+$ 262.1378; found 262.1372. **IR (ϑ_{max}/cm^{-1}, KBr):** 2965, 1675, 1539, 1497, 1351, 1319, 1257, 1201, 1172, 1129, 1027, 697. $[\alpha]_D^{25}$**:** +80° (c = 0.52, CH_2Cl_2).

N-(((1S,3R,4R)-2-azabicyclo[2.2.1]heptan-3-yl)methyl)-N-phenylmethanediimine **44**

^{1}H-NMR (400 MHz, $CDCl_3$) δ 12.04 (d, *J* = 422.3 Hz, 1H, NH), 7.40 – 7.29 (m, 4H, 4x PhH), 7.20 – 7.09 (m, 1H, *p*PhH), 3.95 – 3.85 (m, 2H, $C8H_2$), 3.79 (br s, 1H, C3H), 3.31 – 3.20 (m, 1H, C1H), 2.50 (d, *J* = 4.3 Hz, 1H, C4H), 1.76 – 1.59 (m, 2H, 2x CH), 1.59 – 1.45 (m, 3H, 3x CH), 1.43 – 1.34 (m, 1H, $C7H_b$) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 162.1 (C9), 136.5 (C10), 129.6 (2x PhC), 125.6 (*p*PhC), 121.3 (2x PhC), 65.9 (C1), 61.8 (C3), 48.5 (C8), 41.4 (C4), 35.6 (C7), 27.6, 27.2 ppm. **HRMS (m/z):** (ESI-TOF) calculated for $C_{14}H_{16}N_3$ $[M+H]^+$ 228.1501; found 228.1292.

1-((1S,3R,4R)-2-azabicyclo[2.2.1]heptan-3-ylmethyl)-3-(3-phenylpropyl)thiourea **45**



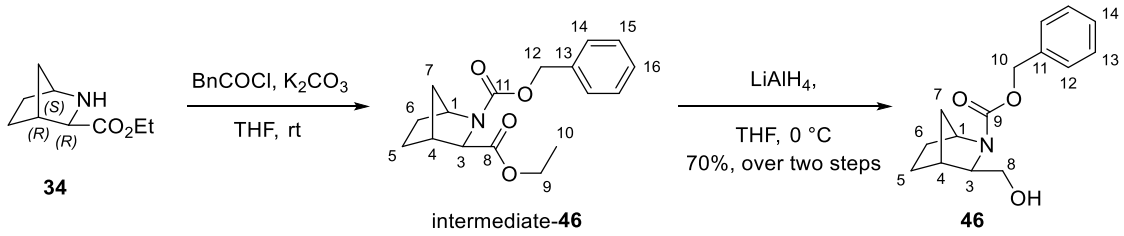
42 **45**

N-Boc protected thiourea **42** (316 mg, 0.78 mmol) was dissolved in a mixture of TFA/CH_2Cl_2 (1/1, 2 mL, 3 mL for each 1.2 mmol) and the reaction was stirred at rt until TLC indicated a complete consumption of starting material. The reaction mixture was rendered basic with aq. NH_3 (30 %) and extracted by CH_2Cl_2 (3x 3 mL) before the combined organic layers were dried over Na_2SO_4 and crude product was concentrated under vacuum. Purification by chromatography was conducted on an CombiFlash companion (SiO_2, 20g, 1:99 to 5:95 MeOH:CH_2Cl_2) yielding 140 mg (0.45 mmol, 58%) of yellowish wax like product. During the extraction the characteristic smell of hydrogen sulfide was perceptible. Despite the smell no side product was isolated.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.34 (d, *J* = 87.4 Hz, 1H, NH), 7.97 (d, *J* = 181.6 Hz, 1H, NH), 7.29 – 7.24 (m, 2H, 2x PhH), 7.21 – 7.12 (m, 3H, 2x PhH, *p*PhH), 4.24 – 4.11 (m, 1H, C3H), 4.01 (s, 1H, CH), 3.56 (s, 1H, CH), 3.42 (s, 3H, CH, CH_2), 2.68 – 2.60 (m, 2H, $C12H_2$), 2.44 (s, 1H, CH), 2.17 (s, 1H, CH), 1.98 – 1.91 (m, 1H, CH), 1.91 – 1.82 (m, 2H, CH_2), 1.65 (s, 2H, 2x CH), 1.60 (d, *J* = 11.0 Hz, 1H, CH), 1.54 (d, *J* = 11.5 Hz, 1H, $C7H_b$) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 171.4 (C9), 141.5 (C13), 128.6 (2x PhC), 128.5 (2x PHC), 126.1 (*p*PhC), 66.1 (C1), 58.1 (C3), 45.1 (C8), 38.5 (C4, CH_2), 35.6 (C7), 33.1 (CH_2), 30.8 (CH_2), 27.5, 25.7 ppm. **HRMS (m/z):** (ESI-TOF) calculated for $C_{17}H_{25}N_3S$ $[M+H]^+$ 304.1848; found 304.1846. **IR (ϑ_{max}/cm^{-1}, KBr):** 3283, 3006, 2973, 2880, 1664, 1567, 1415, 1245, 1167, 1129, 1102, 879, 698. $[\alpha]_D^{25}$**:** +13° (c = 0.83, CH_2Cl_2).

5.9 Various *N*-Cbz protected 2-azabicycloalkanes.

benzyl (1S,3R,4R)-3-(hydroxymethyl)-2-azabicyclo[2.2.1]heptane-2-carboxylate **46**



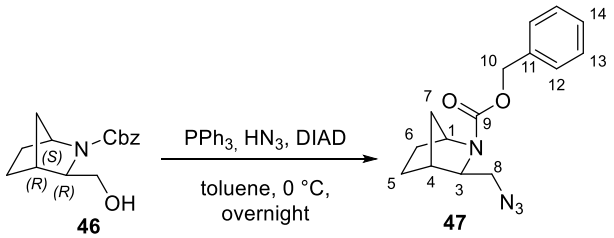
In a modified literature procedure,[93,309] ester **34** (1.848 g, 10.92 mmol, 1.00 equiv.) and K_2CO_3 (4.50 g, 32.80 mmol, 3.00 equiv.) were stirred in THF (80 mL, 0.14 M). Benzyl chloroformate (1.9 mL, 13.1 mmol, 1.20 equiv.) was dropped in by syringe at room temperature. The reaction was kept stirring for 1 hour at that temperature, before water was added (15 mL) and the mixture was stirred for another hour. Upon addition of water (100 mL) the reaction mixture was extracted by EtOAc (3x 50 mL). Combined organic phases were dried over Na_2SO_4 and concentrated under vacuum. Crude product was then directly proceeded (some spectral data were collected). The protected ester intermediate was dropped into a stirred solution of $LiAlH_4$ (0.62 g, 16.3 mmol, 1.37 equiv.) in THF (40 mL, 0.5 M solution of $LiAlH_4$) at 0 °C and stirred for 3 hours, before the reaction was quenched by the addition of aq. NaOH (10 % wt). Upon filtration the organic phase was dried over Na_2SO_4, concentrated and purified by column chromatography (SiO_2, 25x3 cm, 83.3:16.7 hexane:EtOAc) yielding 1.995 g (7.6 mmol, 70 %, over two steps) of a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.26 (m, 5H, 5x PhH), 5.11 (d, *J* = 1.8 Hz, 2H, C10H_2), 4.19 (s, 1H, OH), 4.11 (t, *J* = 5.2 Hz, 1H, C3H), 3.63 – 3.53 (m, 2H, C8H_2), 3.54 – 3.44 (m, 1H, C1H), 2.35 – 2.28 (m, 1H, C4H), 1.75 – 1.62 (m, 3H, C5H_a, C6H_a, C7H_a), 1.59 (dt, *J* = 6.7, 1.4 Hz, 1H, CH), 1.47 – 1.38 (m, 1H, CH), 1.28 – 1.23 (m, 1H, C7H_b) ppm. **^{13}C-NMR** (101 MHz,$CDCl_3$) δ = 157.6 (C11), 136.6 (C9), 128.6, 128.2 (C14), 127.9, 67.4, 67.3, 67.1, 57.9, 39.8, 35.9, 30.1, 28.0 ppm. **HRMS (m/z):** (ESI-TOF) calculated for $C_{15}H_{19}NO_3$ $[M+Na]^+$ 284.1263; found 284.1268. **IR (ϑ_{max}/cm^{-1}, film):** 3419, 3032, 2953, 2874, 1699, 1498, 1455, 1417, 1358, 1317, 1101, 1046, 698. $[\alpha]_D^{25}$**:** +69 (c = 0.82, CH_2Cl_2).

*2-benzyl 3-ethyl (1S,3R,4R)-2-azabicyclo[2.2.1]heptane-2,3-dicarboxylate intermediate-***46**

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.26 (m, 5H, 5x PhH), 5.21 – 4.98 (m, 2H, C12H_2), 4.44 – 4.32 (m, 1H, C3H), 4.24 – 4.13 (m, 1H, C9H_a), 4.17 – 3.96 (m, 1H, C9H_b), 3.85 (d, *J* = 23.4 Hz, 1H, C1H), 2.74 – 2.67 (m, 1H, C4H), 1.95 (d, *J* = 9.9, 1H, C7H_a), 1.75 (ddd, *J* = 13.9, 7.8, 4.4 Hz, 2H, 2x CH), 1.68 – 1.58 (m, 2H, 2x CH), 1.51 (dtd, *J* = 13.9, 7.3, 3.6 Hz, 1H, CH), 1.32 – 1.23 (m, 3H, C7H_b, 2x H of C17H_3), 1.15 (t, *J* = 7.1 Hz, 1H, 1x H of C17H_3) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 171.0 and 170.8 (C8), 154.8 and 153.9 (C13), 136.9 and 136.8 (C11), 128.6 and 128.5, 128.1 and 127.9, 128.0 and 127.7, 67.1 and 66.8, 64.7 and 64.5, 61.2 and 61.1, 57.5 and 57.1, 42.7 and 42.0, 35.5 and 34.8, 30.8 and 30.3, 28.0 and 27.8, 14.3 and 14.2 (C10) ppm. **HRMS (m/z):** (ESI-TOF) calculated for $C_{17}H_{21}NO_4$ $[M+H]^+$ 304.1549, $[M+Na]^+$ 326.1368; found 304.1540, 326.1340.

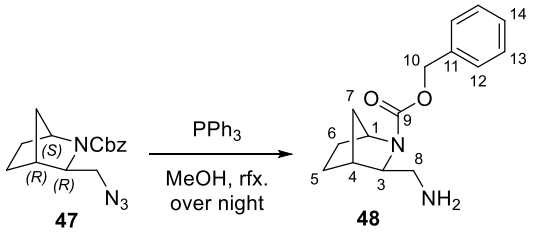
benzyl (1S,3R,4R)-3-(azidomethyl)-2-azabicyclo[2.2.1]heptane-2-carboxylate **47**



According to literature,[100,102,103,300,301] alcohol **46** (0.371 g, 1.42 mmol, 1.00 equiv.) and triphenylphosphine (0.485 g, 1.85 mmol, 1.30 equiv.) were dissolved in toluene (7 mL, 0.2 M) at 0 °C, followed by addition of hydrazoic acid (1 M in toluene, 1.85 mL, 1.85 mmol, 1.3 equiv.) in one portion and the dropwise addition of DIAD (0.42 mL, 2.13 mmol, 1.5 equiv.) in toluene (7 mL). The reaction was allowed to reach room temperature and stirred overnight, before it was quenched by the addition of aq. NaOH (10 wt%) to basify the solution. Upon extraction by CH_2Cl_2 (3x 7 mL) the organic phase was dried by Na_2SO_4 and concentrated under reduced pressure. To remove the majority of triphenylphosphine oxide side product the crude mixture was dissolved in 1:1 hexane:Et_2O and the undissolved side product was filtered off. Purification was achieved by column chromatography (SiO_2, 25x2 cm, 75:25 hexane:EtOAc) yielding 355 mg (1.24 mmol, 87%) of a slightly yellowish oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.28 (m, 5H, 5x PhH), 5.13 (s, 2H, C10H_2), 4.21 (d, *J* = 14.4 Hz, 1H, C3H), 3.59 (ddd, *J* = 57.6, 12.1, 3.7 Hz, 1H, C8H_a), 3.41 (ddd, *J* = 31.3, 9.4, 3.8 Hz, 1H, C8H_b), 3.06 (ddd, *J* = 32.9, 12.4, 9.2 Hz, 1H, C4H), 2.53 (d, *J* = 4.6 Hz, 1H, C1H), 1.84 – 1.64 (m, 3H, C5H_a, C6H_a, C7H_a), 1.61 (d, *J* = 7.0 Hz, 1H, CH), 1.48 – 1.37 (m, 1H, CH), 1.31 (d, *J* = 10.4 Hz, 1H, C7H_b) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 155.6 and 155.0 (C11), 136.9 and 136.7 (C9), 128.7and 128.6, 128.4, 128.2, 128.1, 128.0, 67.0 and 66.9, 63.4 and 63.0, 57.8 and 57.6, 52.7 and 51.8, 40.1 and 39.4, 34.8 and 34.0, 30.5 and 29.8, 27.6 and 27.5 ppm. Mixture of two rotamers. **HRMS (m/z):** (ESI-TOF) calculated for $C_{15}H_{18}N_4O_2$ $[M+H]^+$ 287.1508, $[M+Na]^+$ 309.1328; found 287.1515, 309.1329.

benzyl (1S,3R,4R)-3-(aminomethyl)-2-azabicyclo[2.2.1]heptane-2-carboxylate **48**



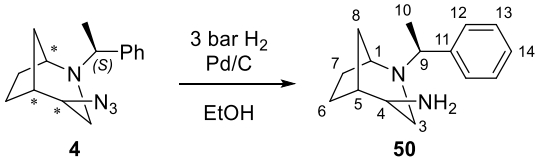
In an adapted literature method,[102] azide **47** (0.630 mg, 2.20 mmol, 1.00 equiv.) was dissolved in methanol (24 mL, 0.1 M). Upon addition of triphenylphosphine (0.757 g, 2.90 mmol, 1.31 equiv.) the reaction mixture was stirred under reflux overnight. To remove the majority of triphenylphosphine oxide side product the crude mixture was dissolved in 1:1 hexane:Et_2O and the undissolved side product was filtered off. Purification was achieved by column chromatography (SiO_2, 10x2 cm, 90:10 CH_2Cl_2:MeOH) yielding 382 mg (1.47 mmol, 67 %) of a slightly yellowish oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 5H, 5x PhH), 5.19 – 5.02 (m, 2H, C10H_2), 4.23 – 4.16 (m, 1H, C3H), 3.38 – 3.17 (m, 1H, C8H_a), 2.93 (td, *J* = 12.2, 11.3, 5.1 Hz, 1H, C1H), 2.68 (dd, *J* = 12.9, 6.6 Hz, 1H, C8H_b), 2.56 (s, 2H, NH_2), 2.52 – 2.41 (m, 1H, C4H), 1.80 – 1.61 (m, 3H, C5H_a, C6H_a, C7H_a), 1.58 (dt, *J*

= 7.5, 1.8 Hz, 1H, CH), 1.49 – 1.33 (m, 1H, CH), 1.33 – 1.23 (m, 1H, C7H_b) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 156.6 and 155.4 (C11), 137.0 and 136.9 (9), 128.6, 128.1, 127.9, 67.1 and 67.0, 66.8 and 66.8, 57.9 and 57.5, 45.2 and 45.0, 39.7 and 39.6, 35.1 and 34.1, 30.4 and 29.9 and 27.7 ppm. Mix of two rotamers. **HRMS (m/z):** (ESI-TOF) calculated for $C_{15}H_{20}N_2O_2$ $[M+H]^+$ 261.1603; found 261.1608. **IR (ϑ_{max}/cm^{-1}, film):** 3356, 3031, 2953, 1694, 1455, 1412, 1356, 1316, 1113, 777, 739, 698. $[\alpha]_D^{25}$**:** +0.57 (c = 0.48, CH_2Cl_2).

5.10 2-azabicyclo[3.2.1]octane substrates for the thiourea synthesis

2-((S)-1-phenylethyl)-2-azabicyclo[3.2.1]octan-4-amine **50**

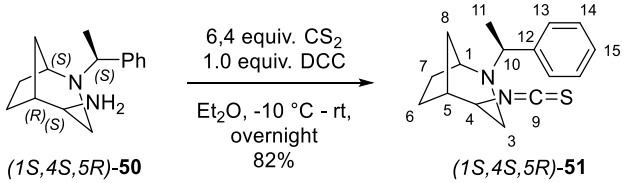


In contrast to literature procedure reducing the azide applying triphenylphosphine,[102] a general procedure of reduction was conducted by stirring a solution of azide **4** in absolute ethanol (0.2 – 1.5 M) and Pd/C (10 wt%) under hydrogen atmosphere (3.0 bar). Amines **50** were generally received quantitatively as colourless to slightly yellowish oils.
All recorded spectroscopic data matched previously reported ones.

*(1S,4S,5R)-2-((S)-1-phenylethyl)-2-azabicyclo[3.2.1]octan-4-amine **50***
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.23 (m, 4H, 4x PhH), 7.24 – 7.15 (m, 1H, *p*-PhH), 3.55 (t, *J* = 4.9 Hz, 1H, C1H), 3.33 (q, *J* = 6.7 Hz, 1H, C9H), 2.57 (q, *J* = 3.8 Hz, 1H, C5H), 2.24 (d, *J* = 2.9 Hz, 1H, C3H_a), 2.14 (dt, *J* = 6.1, 4.3 Hz, 1H, C4H), 2.02 (d, *J* = 11.8 Hz, 1H, C3H_b), 1.75 – 1.66 (m, 3H, C6H_a, C7H_a, C8H_a), 1.341.37 – 1.32 (m, 1H, CH_b), 1.31 (d, *J* = 6.6 Hz, 3H, C10H_3), 1.30 – 1.26 (m, 1H, CH_b), 1.26 – 1.21 (m, 1H, C8H_b) ppm. NH_2 protons were not visible.

*(1R,4R,5S)-2-((S)-1-phenylethyl)-2-azabicyclo[3.2.1]octan-4-amine **50***
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.26 (m, 4H, 4x PhH), 7.25 – 7.16 (m, 1H, *p*-PhH), 3.33 (q, *J* = 6.7 Hz, 1H, C9H), 3.08 (dd, *J* = 13.4, 3.8 Hz, 1H, C3H_a), 2.94 (q, *J* = 4.9 Hz, 1H, C1H), 2.79 – 2.73 (m, 1H, C5H), 2.47 (d, *J* = 13.3 Hz, 1H, C3H_b), 2.41 (dd, *J* = 11.5, 3.7 Hz, 1H, C4H), 2.22 – 2.06 (m, 2H, NH_2), 1.87 (dt, *J* = 11.8, 2.4 Hz, 1H, C8H_a), 1.79 – 1.57 (m, 2H, C6H_a, C7H_a), 1.36 – 1.12 (m, 2H, C6H_b, C7H_b), 1.22 (d, *J* = 6.6 Hz, 3H, C10H_3), 1.06 – 0.98 (m, 1H, C8H_b) ppm.

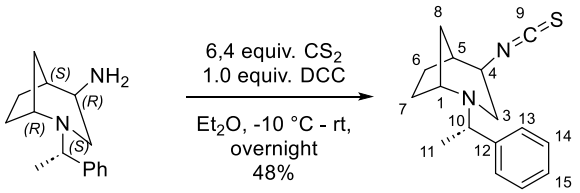
(1S,4S,5R)-4-isothiocyanato-2-((S)-1-phenylethyl)-2-azabicyclo[3.2.1]octane **51**



In accordance with literature procedure,[302] to a solution of DCC (1.40 g, 6.77 mmol, 1.00 equiv.) and CS_2 (2.6 mL, 43.3 mmol, 6.4 equiv.) in Et_2O (70 mL, 0.1 M) at -10 °C (NaCl/ice) the bicyclic amine **(1*S*,4*S*,5*R*)-50** was added (1.56 g, 6.77 mmol, 1.00 equiv.). The reaction was allowed to reach room

temperature and kept stirred overnight. After filtering off the precipitate the filtrate was concentrated under reduced pressure and purified by column chromatography (SiO_2, 25x3 cm, 83.3:16.7 hexane:EtOAc) yielding 1.510 g (5.54 mmol, 82%) of a slightly reddish oil solidifying in the refrigerator. **^{1}H-NMR** (601 MHz, $CDCl_3$) δ 7.35 – 7.30 (m, 2H, 2x C13H), 7.30 – 7.26 (m, 2H, 2x C14H), 7.22 – 7.17 (m, 1H, *p*-PhH), 3.59 (t, *J* = 5.0 Hz, 1H, C1H), 3.37 (q, *J* = 6.6 Hz, 1H, C10H), 3.35 (t, *J* = 3.9 Hz, 1H, C4H), 2.63 (d, *J* = 13.0 Hz, 1H, $C3H_a$), 2.46 – 2.40 (m, 1H, C5H), 2.25 (dd, *J* = 13.0, 3.6 Hz, 1H, $C3H_b$), 2.13 (dd, *J* = 11.9, 2.6 Hz, 1H, $C8H_a$), 1.73 – 1.64 (m, 2H, $C6H_a$, $C7H_a$), 1.45 – 1.38 (m, 1H, $C7H_b$), 1.38 – 1.33 (m, 1H, $C6H_b$), 1.29 (d, *J* = 6.6 Hz, 3H, $C11H_3$), 1.28 – 1.23 (m, 1H, $C8H_b$) ppm. **^{13}C-NMR** (151 MHz, $CDCl_3$) δ = 145.3 (C12), 131.2 (C9), 128.6 (2x C14), 127.4 (2x C13), 127.0 (C15), 62.1 (C10), 57.3 (C4), 55.7 (C1), 49.7 (C3), 40.1 (C5), 34.5 (C8), 27.0 (C6), 22.3 (C7), 21.7 (C11) ppm. **HRMS (ESI-TOF):** *m/z* $[M+H]^+$ calcd for $(C_{16}H_{20}N_2S)^+$ 273.1425; found 273.1429. **IR (KBr): cm^{-1}** 3053, 2928, 2111, 1685, 1628, 1453, 1342, 1135, 957, 701. $[\alpha]_D^{25}$**:** +124° (c 0.82, CH_2Cl_2). **mp:** 47.3 °C.

(1S,4R,5R)-4-isothiocyanato-2-((S)-1-phenylethyl)-2-azabicyclo[3.2.1]octane **51**



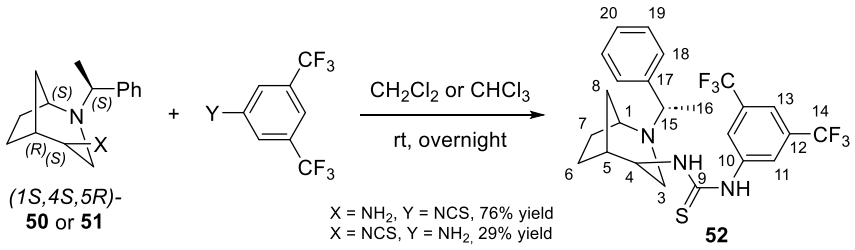
(1R,4R,5S)-**50** *(1R,4R,5S)*-**51**

In accordance with literature procedure,[302] to a solution of DCC (206 mg, 1.00 mmol, 1.00 equiv.) and CS_2 (0.4 mL, 6.6 mmol, 6.6 equiv.) in Et_2O (10 mL, 0.1 M) at -10 °C (NaCl/ice) the bicyclic amine **(1*R*,4*R*,5*S*)-50** was added (230 mg, 1.00 mmol, 1.00 equiv.). The reaction kept stirring and led to reach room temperature and kept stirred overnight. After filtering off the precipitate the filtrate was concentrated under reduced pressure and purified by column chromatography (SiO_2, 25x3 cm, 83.3:16.7 hexane:EtOAc) yielding 130 mg (0.48 mmol, 48%) of a colourless oil.

^{1}H-NMR (601 MHz, $CDCl_3$) δ 7.39 – 7.34 (m, 2H, 2x C13H), 7.35 – 7.26 (m, 2H,2x C14H), 7.26 – 7.19 (m, 1H, C15H), 3.54 (tt, *J* = 3.7, 1.5 Hz, 1H, C4H), 3.46 (q, *J* = 6.7 Hz, 1H, C10H), 3.10 (s, 1H, C1H), 3.09 – 3.03 (m, 1H, $C3H_a$), 2.49 (dd, *J* = 12.5, 3.6 Hz, 1H, $C3H_b$), 2.47 (q, *J* = 4.6 Hz, 1H, C5), 2.04 (ddt, *J* = 11.9, 2.1, 1.2 Hz, 1H, $C8H_a$), 1.77 – 1.73 (m, 1H, $C7H_a$), 1.73 – 1.68 (m, 1H, $C6H_a$), 1.35 – 1.32 (m, 1H, $C7H_b$), 1.31 – 1.29 (m, 1H, $C6H_b$), 1.26 (d, *J* = 6.7 Hz, 3H, $C11H_3$), 1.22 – 1.14 (m, 1H, $C8H_b$) ppm. **^{13}C-NMR** (151 MHz, $CDCl_3$) δ = 146.0 (C12), 131.6 (C9), 128.5 (2x C14), 127.6 (2x C13), 126.9 (C15), 61.6 (10), 57.5 (C4), 57.2 (C1), 48.2 (C3), 40.2 (C5), 33.9 (C8), 26.9 (C6), 22.5 (C7), 22.0 (C11) ppm. **HRMS (m/z):** (ESI-TOF) calculated for $C_{16}H_{20}N_2S$ $[M+H]^+$ 273.1425; found 273.1425. **IR (ϑ_{max}/cm^{-1}, KBr):** 3025, 2931, 2856, 2118, 1691, 1451, 1339, 1141, 954, 767, 702 ppm. $[\alpha]_D^{25}$**:** + 30° (c 0.43, CH_2Cl_2).

5.11 (1*S*,4*S*,5*R*)-2-azabicyclo[3.2.1]octane thioureas

1-(3,5-bis(trifluoromethyl)phenyl)-3-((1S,4S,5R)-2-((S)-1-phenylethyl)-2-azabicyclo[3.2.1]octan-4-yl)thiourea **52**

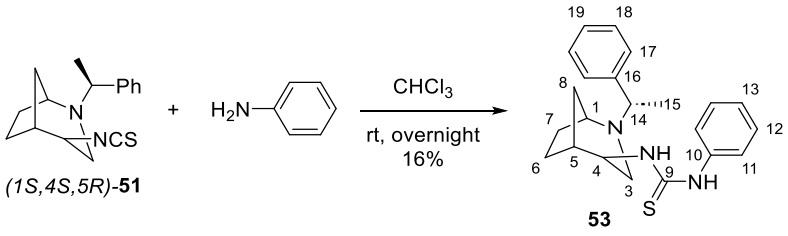


A solution of bicyclic amine **50** (0.691 g, 3.0 mmol, 1.00 equiv.) and 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene (0.814 g, 3.0 mmol, 1.00 equiv.) in CH_2Cl_2 (6 mL, 0.5 M) was stirred overnight at room temperature. After concentrating under vacuum the crude was purified by column chromatography (SiO_2, 25x2 cm, 75:25 hexane:EtOAc) yielding 1.140 g (2.30 mmol, 76%) of an off-white solid.

Alternatively, a solution of bicyclic isothiocyanate **51** (0.314 g, 1.36 mmol, 1.00 equiv.) and 1-amino-3,5-bis(trifluoromethyl)benzene (0.25 mL, 1.36 mmol, 1.00 equiv.) in $CHCl_3$ (15 mL, 0.1 M) was stirred overnight at room temperature. After concentrating under vacuum the crude was purified by column chromatography yielding 0.195 g (0.39 mmol, 29%) of an off-white solid. Spectroscopic data of both products matched.

^{1}H NMR (601 MHz, $CDCl_3$) δ 8.66 – 8.16 (br, 1H, NH), 7.80 (s, 3H, 2x C11H, C13H), 7.20 – 7.12 (m, 1H, C20H), 7.12 – 7.05 (m, 2H, 2x PhH), 6.95 (s, 2H, 2x Ph*H*), 6.88 – 6.52 (br, 1H, NH), 4.11 (s, 1H, C4H), 3.61 (dd, *J* = 14.5, 3.9 Hz, 1H, C1H), 3.32 (s, 1H, C15H), 2.70 (s, 1H, C5H), 2.39 (d, *J* = 11.4 Hz, 1H, $C3H_a$), 2.21 (s, 1H, $C3H_b$), 1.81 – 1.58 (m, 3H, $C6H_a$, $C7H_a$, $C8H_a$), 1.52 – 1.35 (m, 3H, $C6H_b$, $C7H_b$, $C8H_b$), 1.33 – 1.20 (m, 3H, $C16H_3$) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 178.8 (C9), 145.0 (C17), 138.4 (C10), 132.9 (2x C12), 128.4 (2x Ph*C*), 127.2 (C20), 127.0 (2x Ph*C*), 124.2 (2x C11), 122.9 (q, *J* = 273, 2x C14), 119.5 (17), 61.3 (C15), 56.4 (C1), 54.4 (C4), 49.4 (C3), 37.3 (C5), 35.2 (C8), 27.0 (C6), 22.1 (C7), 20.7 (C16) ppm. **HRMS (m/z):** (ESI-TOF) calculated for $C_{24}H_{25}N_3F_6S$ $[M+H]^+$ 502.1752; found 502.1753. **IR (ϑ_{max}/cm^{-1}, KBr):** 3280, 3030, 2956, 2870, 1526, 1473, 1384, 1278, 1179, 1134, 701. $[\alpha]_D^{23}$: +44° (c 0,44, CH_2Cl_2). **mp:** 74.2 – 76.3 °C

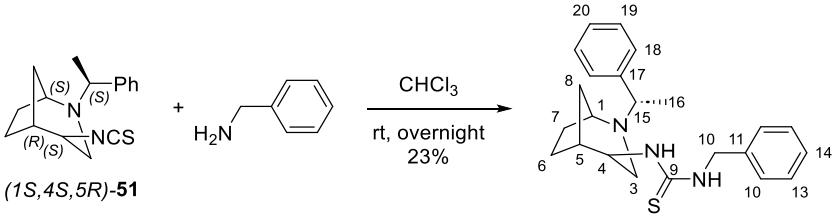
1-phenyl-3-((1S,4S,5R)-2-((S)-1-phenylethyl)-2-azabicyclo[3.2.1]octan-4-yl)thiourea **53**



A solution of bicyclic isothiocyanate **51** (0.250 g, 0.92 mmol, 1.00 equiv.) and aniline (0.08 mL, 0.92 mmol, 1.00 equiv.) in $CHCl_3$ (10 mL, 0.1 M) was stirred overnight at room temperature. After concentrating under vacuum the crude was purified by column chromatography (SiO_2, 20x2 cm, 50:50 hexane:EtOAc) yielding 0.054g (0.15 mmol, 16%) of an off-white solid.

^{1}H NMR (601 MHz, $CDCl_3$) δ 7.60 (s, 1H, NH), 7.49 (t, *J* = 7.9 Hz, 2H, 2x Ph*H*), 7.36 (t, *J* = 7.4 Hz, 1H, *p*Ph*H*), 7.17 (d, *J* = 7.5 Hz, 2H, 2x Ph*H*), 7.13 – 7.05 (m, 3H, 2x Ph*H*, *p*Ph*H*), 6.91 – 6.87 (m, 2H, 2x Ph*H*), 6.58 (s, 1H, NH), 4.01 (s, 1H, C4H), 3.42 (t, *J* = 5.2 Hz, 1H, C1H), 3.18 (q, *J* = 6.4 Hz, 1H, C14H), 2.67 (q, *J* = 4.6 Hz, 1H, C5H), 2.28 (dd, *J* = 12.7, 3.7 Hz, 1H, $C3H_a$), 2.12 – 2.06 (m, 1H, $C3H_b$), 1.68 – 1.60 (m, 2H, $C6H_a$, $C7H_a$), 1.48 (d, *J* = 8.8 Hz, 1H, $C8H_a$), 1.37 – 1.29 (m, 2H, $C6H_b$, $C7H_b$), 1.25 – 1.18 (m, 1H, $C8H_b$), 1.17 – 1.09 (m, 3H, $C15H_3$) ppm. ^{13}C-NMR (151 MHz, $CDCl_3$) δ = 178.4 (C9), 145.4 (*q*Ph*C*), 136.2 (*q*Ph*C*), 130.2 (2x Ph*C*), 128.3 (2x Ph*C*), 127.4 (*p*Ph*C*), 126.9 ((2x Ph*C*, *p*Ph*C*), 125.4 (2x Ph*C*), 62.0 (C14), 55.8 (C1), 54.2 (C4), 49.3 (C3), 37.4 (C5), 35.2 (C8), 27.1 (C6), 22.0 (C7), 21.0 (C15) ppm. **HRMS (m/z):** (ESI-TOF) calculated for $C_{22}H_{27}N_3S$ $[M+H]^+$ 366.2004; found 366.1999. **IR (ϑ_{max}/cm^{-1}, KBr):** 3370, 3194, 3026, 2951, 2864, 1596, 1525, 1496, 1451, 1297, 1245, 700. $[\alpha]_D^{23}$**:** +74° (c 0,35, CH_2Cl_2). **mp:** 60.3 - 62.8 °C

1-benzyl-3-((1S,4S,5R)-2-((S)-1-phenylethyl)-2-azabicyclo[3.2.1]octan-4-yl)thiourea **54**

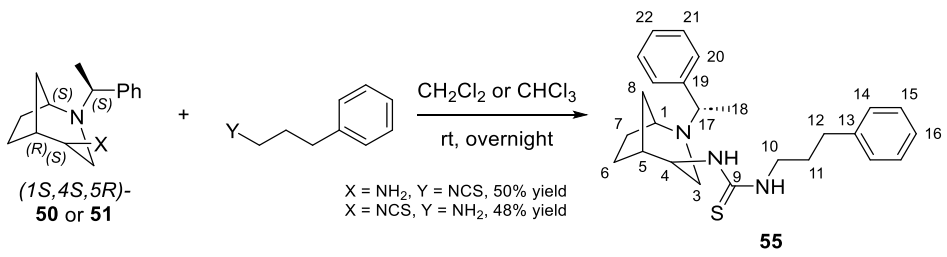


(1S,4S,5R)-**51** **54**

A solution of bicyclic isothiocyanate **51** (0.250 g, 0.92 mmol, 1.00 equiv.) and benzylamine (0.10 mL, 0.92 mmol, 1.00 equiv.) in $CHCl_3$ (10 mL, 0.1 M) was stirred overnight at room temperature. After concentrating under vacuum the crude was purified by column chromatography (SiO_2, 20x2 cm, 50:50 hexane:EtOAc) yielding 0.078g (0.21 mmol, 23%) of an off-white solid.

^{1}H-NMR (601 MHz, $CDCl_3$) δ 7.37 – 7.22 (m, 5H, 5x PhH), 7.21 – 7.00 (m, 5H, 5x PhH), 6.32 (d, *J* = 86.9 Hz, 2H, 2x NH), 4.67 – 4.20 (m, 2H, $C10H_2$), 4.17 – 3.69 (m, 1H, C4H), 3.53 – 3.38 (m, 1H, C1H), 3.34 – 3.17 (m, 1H, C15H), 2.53 – 2.42 (m, 1H, $C3H_a$), 2.34 – 2.26 (m, 1H, C5H), 2.26 – 2.14 (m, 1H, $C3H_b$), 1.65 – 1.56 (m, 2H, $C8H_a$, CH), 1.48 – 1.34 (m, 1H, CH), 1.35 – 1.26 (m, 2H, 2x CH), 1.25 – 1.17 (m, 3H, $C16H_3$), 1.17 – 1.09 (m, 1H, C8H) ppm. All signals are broad and coupling patterns cannot be confidently identified. **^{13}C-NMR** (151 MHz, $CDCl_3$) δ = 180.3 (C9), 144.2 (*q*PhC), 136.3 (*q*PhC), 129.1 (2x PhC), 128.6 (2x PhC), 128.1 (*p*PhC), 127.6 (2x PhC), 127.4 (2x PhC, *p*PhC), 62.5 (C15), 56.5 (C1), 53.9 (C4), 49.1 (C10), 48.1 (C3), 37.9 (C5), 34.6 (C8), 27.2 (C6), 22.2 (C7), 20.9 (C16) ppm. **HRMS (m/z):** (ESI-TOF) calculated for $C_{23}H_{29}N_3S$ $[M+H]^+$ 380.2160; found 380.2160. **IR (ϑ_{max}/cm^{-1}, KBr):** 3257, 3059, 3027, 2931, 2864, 1535, 1494, 1452, 1344, 1296, 1217, 1110, 1028. $[\alpha]_D^{23}$**:** +28° (c 0,37, CH_2Cl_2). **mp:** 65.4 - 67.3 °C

1-((1S,4S,5R)-2-((S)-1-phenylethyl)-2-azabicyclo[3.2.1]octan-4-yl)-3-(3-phenylpropyl)thiourea **55**



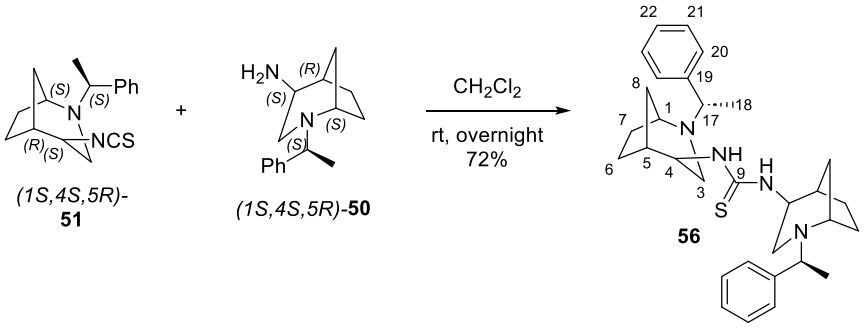
(1S,4S,5R)-**50** or **51** **55**

A solution of bicyclic amine **50** (0.703 g, 3.1 mmol, 1.00 equiv.) and 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene (0.814 g, 3.0 mmol, 0.97 equiv.) in CH_2Cl_2 (6 mL, 0.5 M) was stirred

overnight at room temperature. After concentrating under vacuum the crude was purified by column chromatography (SiO_2, 25x2 cm, 75:25 hexane:EtOAc) yielding 0.612 g (1.50 mmol, 50%) of an off-white solid.

Alternatively, a solution of bicyclic isothiocyanate **51** (0.250 g, 0.92 mmol, 1.00 equiv.) and 3-phenyl-1-propylamine (1.02 mL, 0.92 mmol, 1.00 equiv.) in $CHCl_3$ (10 mL, 0.1 M) was stirred overnight at room temperature. After concentrating under vacuum the crude was purified by column chromatography yielding 0.180 g (0.44 mmol, 48%) of an off-white solid. Spectroscopic data of both products matched. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (t, *J* = 7.5 Hz, 2H, 2x Ph*H*), 7.19 – 7.08 (m, 8H, 8x Ph*H*), 6.16 (s, 1H, NH), 6.04 (s, 1H,NH), 4.28 – 3.59 (br, 1H, C4H), 3.52 (t, *J* = 5.0 Hz, 1H, C1H), 3.39 – 3.12 (m, 3H, C16H, CH_2), 2.64 (t, *J* = 7.6 Hz, 2H, CH_2), 2.50 (s, 1H, C5H), 2.29 (dd, *J* = 12.9, 3.7 Hz, 1H, $C3H_a$), 2.20 (d, *J* = 12.5 Hz, 1H, $C3H_b$), 1.87 (p, *J* = 7.1 Hz, 2H, $C11H_2$), 1.72 (d, *J* = 11.5 Hz, 1H, $C8H_a$), 1.62 (m, 2H, $C6H_a$, $C7H_a$), 1.33 (m, 2H, $C6H_b$, $C7H_b$), 1.24 (d, *J* = 6.6 Hz, 3H, $C18H_3$), 1.22 – 1.14 (m, 1H, $C8H_b$) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 180.4 (C9), 144.8 (*q*Ph*C*), 140.0 (*q*Ph*C*), 128.7 (2x Ph*C*), 128.6 (2x Ph*C*), 128.5 (2x Ph*C*), 127.3 (2x Ph*C, p*Ph*C*), 126.3 (*p*Ph*C*), 62.4 (C17), 56.4 (C1), 53.6 (C4), 49.2 (C3), 43.2 (C10), 37.9 (C5), 34.9 (C8), 33.3, 30.4, 27.2 (C6), 22.1 (C7), 21.1 (C18) ppm. **HRMS (m/z):** (ESI-TOF) calculated for $C_{25}H_{33}N_3S$ $[M+H]^+$ 408.2473; found 408.2476. **IR (ϑ_{max}/cm^{-1}, KBr):** 3305, 3210, 3054, 2938, 2833, 1562, 1526, 1452, 1346, 1304, 1216, 1128, 1033, 951, 737. $[\alpha]_D^{23}$: +38° (c 0,40, CH_2Cl_2). **mp**: 96.7-98.1°C.

1,3-bis((1S,4S,5R)-2-((S)-1-phenylethyl)-2-azabicyclo[3.2.1]octan-4-yl)thiourea **56**



A solution of bicyclic amine **50** (0.230 g, 1.00 mmol, 1.00 equiv.) and bicyclic isothiocyanate **51** (0.272 g, 1.00 mmol, 1.00 equiv.) in CH_2Cl_2 (2 mL, 0.5 M) was stirred overnight at room temperature. After concentrating under vacuum the crude was purified by column chromatography (SiO_2, 25x2 cm, 83.3:16.7 to 75:25 hexane:EtOAc) yielding 0.360 g (0.72 mmol, 72%) of a solidifying oil.

^{1}H-NMR (601 MHz, $CDCl_3$) δ 7.23 (s, 8H, 8x PhH), 7.19 (s, 2H, 2x PhH), 6.08 (s, 2H, 2x NH), 3.83 (br s, 2H, 2x C4H), 3.57 (s, 2H, 2x C1H), 3.32 (s, 2H, 2x C17H), 2.61 (s, 2H, 2x CH), 2.42 – 2.31 (m, 2H, 2x CH), 2.18 (s, 2H, 2x CH), 1.72 (s, 6H, 2x $C6H_a$, 2x $C7H_a$, 2x $C8H_a$), 1.41 (s, 4H, 2x $C6H_b$, 2x $C7H_b$), 1.37 – 1.25 (m, 6H, 2x $C18H_3$), 1.25 – 1.09 (m, 2H, 2x $C8H_b$) ppm. **^{13}C-NMR** (151 MHz, $CDCl_3$) δ = 178.5 (C9), 144.5 (C19), 128.6 (2x PhC), 126.2 (2x PhC, *p*PhC), 62.3 (C17), 57.1 (C1), 53.2 (C4), 49.2 (C3), 37.9 (C5), 35.0 (C8), 27.1 (C7), 22.2 (C6), 20.9 (C18) ppm. **HRMS (m/z):** (ESI-TOF) calculated for $C_{31}H_{42}N_4S$ $[M+H]^+$ 503.3208; found 503.3201. **IR (ϑ_{max}/cm^{-1}, KBr):** 3058, 3026, 2949, 2864, 1526, 1474, 1452, 1372, 1255, 1216, 1134, 1090, 1043, 953. $[\alpha]_D^{25}$**:** +77° (c = 0.40, CH_2Cl_2). **mp:** 91.3-93.0 °C.

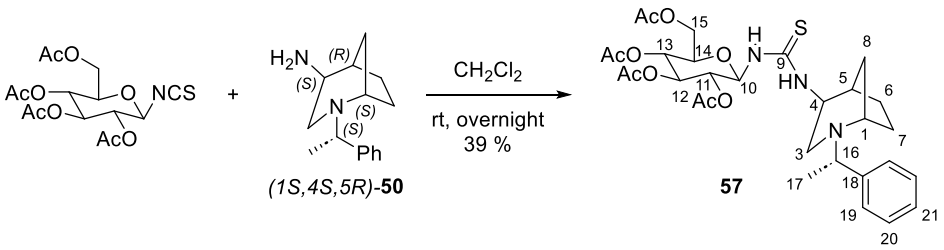
2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl isothiocyanate

According to literature procedure,[346,347] a solution of sugar bromide (1.00g, 2.43 mmol, 1.00 equiv.) was dissolved in acetonitrile (50 mL, 0.05 M) together with potassium isothiocyanate (0.47 g, 4.86 mmol, 2.00 equiv.), tetra(*n*-butyl)ammonium bromide (0.78 g, 2.43 mmol, 1.00 equiv.) and molecular sieves (4 Å, 1.50 g). The reaction mixture was then refluxed for 3 hours, before it was allowed to reach room temperature and stirred for another 2 hours. Upon addition of water (30 mL) and extraction with CH_2Cl_2 (3x 20 mL) the combined organic phases were dried with $NaSO_4$ and concentrated under vacuum. Purification by column chromatography (SiO_2, 25x2 cm, 60:40 hexane:EtOAc) gave 370 mg (0.95 mmol, 39%) of a white solid.

All recorded spectroscopic data matched previously reported ones.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.25 – 5.16 (m, 1H, C3H), 5.15 – 5.05 (m, 2H, C2H, C4H), 5.02 (d, *J* = 8.4 Hz, 1H, C1H), 4.24 (dd, *J* = 12.5, 4.9 Hz, 1H, C6H$_a$), 4.14 (dd, *J* = 12.4, 2.3 Hz, 1H, C6H$_b$), 3.74 (ddd, *J* = 10.2, 4.8, 2.3 Hz, 1H, C5H), 2.10 (d, *J* = 1.1 Hz, 6H, 2x CH_3CO), 2.03 (s, 3H, CH_3CO), 2.02 (s, 3H, CH_3CO) ppm.

2,3,4,6-tetra-O-acetyl-1-(3-((1S,4S,5R)-2-((S)-1-phenylethyl)-2-azabicyclo[3.2.1]octan-4-yl)thioureido) β-D-glucopyranose **57**



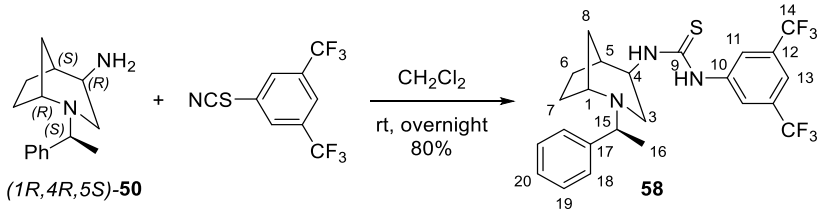
A solution of bicyclic amine **50** (0.115 g, 0.50 mmol, 1.00 equiv.) and 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl isothiocyanate (0.195 g, 0.50 mmol, 1.00 equiv.) in CH_2Cl_2 (1 mL, 0.5 M) was stirred overnight at room temperature. After concentrating under vacuum the crude was purified by column chromatography (SiO_2, 25x2 cm, 95:5 CH_2Cl_2:MeOH) yielding 0.100 g (0.16 mmol, 39%) of a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.17 (m, 5H, 5x PhH), 6.69 (s, 1H, NH), 6.48 (d, *J* = 7.3 Hz, 1H, NH), 5.86 – 5.58 (m, 1H, *sugar*-CH), 5.35 (t, *J* = 9.4 Hz, 1H, *sugar*-CH), 5.14 – 5.05 (m, 1H, *sugar*-CH), 4.98 (t, *J* = 9.6 Hz, 1H, *sugar*-CH), 4.40 – 4.32 (m, 1H, *sugar*-CH), 4.18 (s, 1H, C4H), 4.13 – 4.07 (m, 1H, *sugar*-CH), 3.85 (ddd, *J* = 10.1, 4.3, 2.3 Hz, 1H, *sugar*-CH), 3.59 (t, *J* = 4.7 Hz, 1H, C1H), 3.36 (q, *J* = 6.6 Hz, 1H, C16H), 2.56 (s, 1H, C5H), 2.40 – 2.32 (m, 1H, C3H$_a$), 2.33 – 2.25 (m, 1H, C3H$_b$), 2.10 – 1.92 (m, 12H, 4x *Ac*-CH_3), 1.79 – 1.63 (m, 3H, C6H$_a$, C7H$_a$, C8H$_a$), 1.46 – 1.27 (m, 3H, C6H$_a$, C7H$_a$, C8H$_a$), 1.32 (d, *J* = 6.7 Hz, 3H, C17H$_3$) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 181.9 (C9), 171.5 (C=O), 170.8 (C=O), 170.0 (C=O), 169.9 (C=O), 144.9 (C18), 128.6 (2x PhC), 127.4 (2x PhC), 127.1 (C21), 82.7 (*sugar*-C), 73.3 (*sugar*-C), 72.9 (*sugar*-C), 70.9 (*sugar*-C), 68.4 (*sugar*-C), 62.4 (C16), 61.7 (*sugar*-C), , 56.4 (C1), 53.8 (C4), 49.2 (C3), 37.5 (C5), 35.0 (C8), 27.2 (C6), 22.0 (C7), 21.1 (C17), 20.9 (A*c*-CH_3), 20.8 (A*c*-CH_3), 20.7 (A*c*-CH_3), 20.7 (A*c*-CH_3) ppm. **HRMS (m/z):** (ESI-TOF) calculated for $C_{30}H_{41}N_3O_9S$ $[M+H]^+$ 620.2642; found

620.2635. **IR (ϑ_{max}/cm^{-1}, KBr):** 3331, 3108, 2956, 1752, 1539, 1366, 1277, 1069, 1038, 702. $[\alpha]_D^{25}$**:** +25° (c = 0.38, CH_2Cl_2). **mp:** 104.5–105.7 °C.

5.12 (1*R*,4*R*,5*S*)-2-azabicyclo[3.2.1]octane thioureas

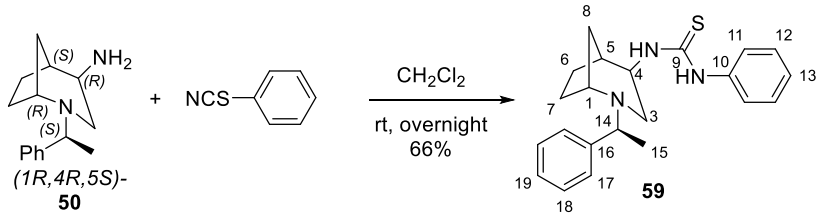
1-(3,5-bis(trifluoromethyl)phenyl)-3-((1R,4R,5S)-2-((S)-1-phenylethyl)-2-azabicyclo[3.2.1]octan-4-yl)thiourea **58**



A solution of bicyclic amine (1*R*,4*R*,5*S*)-**50** (0.123 g, 0.53 mmol, 1.00 equiv.) and 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene (0.189 g, 0.70 mmol, 1.32 equiv.) in CH_2Cl_2 (1 mL, 0.5 M) was stirredovernight at room temperature. After concentrating under vacuum the crude was purified by column chromatography (SiO_2, 15x2 cm, 75:25 hexane:EtOAc) yielding 0.201 g (0.40 mmol, 80%) of a white solid.

^{1}H-NMR (400 MHz, CD_3OD) δ 8.29 (s, 2H, 2x C11H), 7.64 (s, 1H, C13H), 7.36 – 7.29 (m, 4H, 4x PhH), 7.25 – 7.18 (m, 1H, *p*-PhH), 4.32 (s, 1H, C4H), 3.43 (q, *J* = 6.8 Hz, 1H, C15H), 3.07 (t, *J* = 5.2 Hz, 1H, C1H), 3.03 (d, *J* = 12.4 Hz, 1H, C3H_a), 2.61 (dd, *J* = 12.5, 4.1 Hz, 1H, C3H_b), 2.56 (q, *J* = 5.3 Hz, 1H, C5H), 1.93 – 1.82 (m, 1H, CH), 1.82 – 1.75 (m, 1H, C8H_a), 1.75 – 1.66 (m, 1H, CH), 1.51 – 1.40 (m, 1H, CH), 1.28 (d, *J* = 6.7 Hz, 3H, C16H_3), 1.26 – 1.15 (m, 2H, C8H_b, CH) ppm. Both NH protons are invisible due to the solvent. **^{13}C-NMR** (101 MHz, CD_3OD) δ = 181.3 (C9), 146.8 (C17), 143.3 (2x C12), 132.7 (q, *J* = 33.3 Hz, 2x C14), 129.5 (2x PhC), 128.5 (2x PhC), 128.0 (C20), 126.1 (C10), 123.2 (2x C11), 117.6 (C13), 63.3 (C15), 58.5, 54.8, 38.9, 34.9, 28.1, 22.4, 22.2 ppm. One carbon peak is overlapping with the solvent peaks. **HRMS (m/z):** (ESI-TOF) calculated for $C_{24}H_{25}F_6N_3S$ $[M+H]^+$ 502.1752; found 502.1758. **IR (ϑ_{max}/cm^{-1}, KBr):** 3005, 2922, 2852, 1663, 1519, 1470, 1384, 1279, 1179, 1130. $[\alpha]_D^{25}$**:** +56° (c = 0.70, CH_2Cl_2). **mp:** 69.6–71.3 °C.

1-phenyl-3-((1R,4R,5S)-2-((S)-1-phenylethyl)-2-azabicyclo[3.2.1]octan-4-yl)thiourea **59**

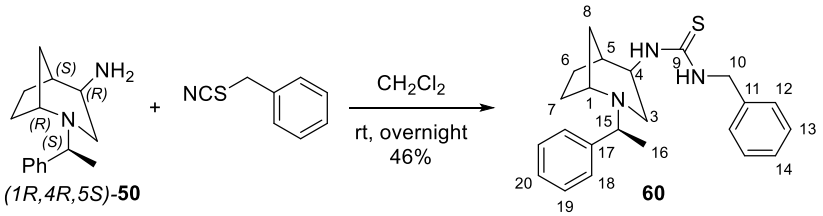


A solution of bicyclic amine (1*R*,4*R*,5*S*)-**50** (0.115 g, 0.50 mmol, 1.00 equiv.) and isothiocyanatobenzene (0.081 g, 0.60 mmol, 1.20 equiv.) in CH_2Cl_2 (1 mL, 0.5 M) was stirred overnight at room temperature. After concentrating under vacuum the crude was purified by column chromatography (SiO_2, 15x2 cm, 83.3:16.7 hexane:EtOAc) yielding 0.122 g (0.33 mmol, 66%) of a white solid.

^{1}H-NMR (601 MHz, $CDCl_3$) δ 7.78 (s, 1H, NH), 7.52 (t, *J* = 7.9 Hz, 2H, 2x PhH), 7.39 (d, *J* = 7.5 Hz, 1H, PhH), 7.32 (d, *J* = 7.8 Hz, 2H, 2x PhH), 7.21 (dt, *J* = 14.4, 6.8 Hz, 3H, 3x PhH), 7.05 (d, *J* = 7.6 Hz, 2H, 2x

PhH), 6.91 (d, *J* = 14.6 Hz, 1H, NH), 4.28 (s, 1H, C4H), 3.36 (q, *J* = 6.6 Hz, 1H, C14H), 2.93 (t, *J* = 5.1 Hz, 1H, C1H), 2.74 (d, *J* = 13.4 Hz, 1H, $C3H_a$), 2.65 (q, *J* = 4.6 Hz, 1H, C5H), 2.58 (dd, *J* = 12.2, 3.6 Hz, 1H, $C3H_b$), 1.76 – 1.63 (m, 2H, 2x CH), 1.47 – 1.35 (m, 2H, 2x CH), 1.29 – 1.23 (m, 1H, CH), 1.12 (d, *J* = 6.7 Hz, 3H, $C15H_3$), 1.07 (dt, *J* = 12.1, 4.6 Hz, 1H, $C8H_b$) ppm. **^{13}C-NMR** (151 MHz, $CDCl_3$) δ = 179.1 (C9), 146.0 (C16), 136.7 (C10), 130.3 (2x PhC), 128.4 (2x PhC), 127.3 (*p*PhC), 127.3 (2x PhC), 126.9 (*p*PhC), 125.5 (2x PhC), 61.5 (C14), 57.9 (C1), 54.3 (C4), 47.7 (C3), 37.7 (C5), 34.9 (C8), 27.1 (C6), 22.5, 21.8 ppm. **HRMS (m/z):** (ESI-TOF) calculated for $C_{22}H_{27}N_3S$ $[M+H]^+$ 366.2004; found 366.2003. **IR (ϑ_{max}/cm^{-1}, KBr):** 3026, 2954, 2866, 1597, 1526, 1497, 1451, 1317, 1245, 700. $[\alpha]_D^{25}$**:** +64° (c = 0.35, CH_2Cl_2). **mp:** 68.3–70.1 °C.

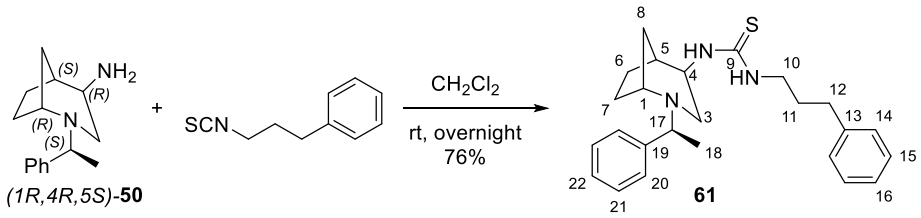
1-benzyl-3-((1R,4R,5S)-2-((S)-1-phenylethyl)-2-azabicyclo[3.2.1]octan-4-yl)thiourea **60**



A solution of bicyclic amine (1*R*,4*R*,5*S*)-**50** (0.115 g, 0.50 mmol, 1.00 equiv.) and (thiocyanatomethyl)benzene (90 mg, 0.60 mmol, 1.20 equiv.) in CH_2Cl_2 (1 mL, 0.5 M) was stirred overnight at room temperature. After concentrating under vacuum the crude was purified by column chromatography (SiO_2, 15x2 cm, 83.3:16.7 hexane:EtOAc) yielding 0.089 g (0.23 mmol, 46%) of an off-white solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.38 (m, 4H, 4x PhH), 7.32 – 7.22 (m, 4H, 4x PhH), 7.19 – 7.13 (m, 2H, 2x PhH), 6.80 (s, 1H, NH), 6.46 (s, 1H, NH), 4.59 (br s, 2H, $C10H_2$), 4.25 – 3.98 (br s, 1H, C4H), 3.31 (q, *J* = 6.7 Hz, 1H, C15H), 2.92 (t, *J* = 5.0 Hz, 1H, C1H), 2.72 (s, 1H, $C3H_a$), 2.56 – 2.44 (m, 2H, C5H, $C3H_b$), 1.75 – 1.56 (m, 2H, 2x CH), 1.39 – 1.31 (m, 1H, CH), 1.28 – 1.23 (m, 1H, CH), 1.22 – 1.16 (m, 1H, CH), 1.12 (d, *J* = 6.7 Hz, 3H, $C16H_3$), 1.06 – 0.94 (m, 1H, $C8H_b$) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 180.3 (C9), 145.6 (C17), 136.7 (C11), 129.2 (2x PhC), 128.5 (2x PhC), 128.1 (*p*PhC), 127.4 (4x PhC), 127.0 (*p*PhC), 61.7 (C15), 57.4 (C1), 54.2 (C4), 47.9 (C3, C10), 37.9 (C5), 34.2 (C8), 27.1 (C6), 21.8, 21.8 ppm. **HRMS (m/z):** (ESI-TOF) calculated for $C_{23}H_{29}N_3S$ $[M+H]^+$ 380.2160; found 380.2169. **IR (ϑ_{max}/cm^{-1}, KBr):** 3060, 2928, 2864, 1538, 1452, 1253, 1221, 1135, 700. $[\alpha]_D^{25}$**:** +22° (c = 0.84, CH_2Cl_2). **mp:** 73.4–74.5 °C.

1-((1R,4R,5S)-2-((S)-1-phenylethyl)-2-azabicyclo[3.2.1]octan-4-yl)-3-(3-phenylpropyl)thiourea **61**

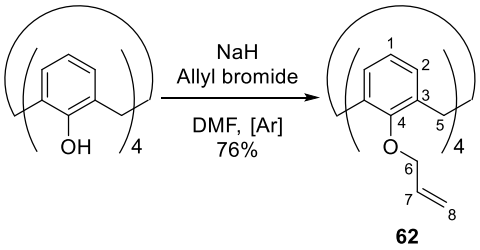


A solution of bicyclic amine (1*R*,4*R*,5*S*)-**50** (0.115 g, 0.50 mmol, 1.00 equiv.) and (3-isothiocyanatopropyl)benzene (0.106 g, 0.60 mmol, 1.20 equiv.) in CH_2Cl_2 (1 mL, 0.5 M) was stirredovernight at room temperature. After concentrating under vacuum the crude was purified by column chromatography (SiO_2, 15x2 cm, 83.3:16.7 to 75:25 hexane:EtOAc) yielding 0.156 g (0.38 mmol, 76%) of a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.26 (m, 6H, 6x PhH), 7.24 – 7.19 (m, 4H, 4x PhH), 6.36 (s, 1H, NH), 6.18 – 5.80 (m, 1H, NH), 3.40 (q, *J* = 6.6 Hz, 1H, C17H), 3.50 – 3.36 (m, 1H, C4H) , 3.04 (t, *J* = 5.0 Hz, 1H, C1H), 2.80 (d, *J* = 12.3 Hz, 1H, $C3H_a$), 2.75 (t, *J* = 7.5 Hz, 2H, $C12H_2$), 2.58 – 2.50 (m, 1H, $C3H_b$), 2.52 – 2.40 (m, 1H, C5H), 2.00 (p, *J* = 7.2 Hz, 2H, $C11H_2$), 1.72 – 1.58 (m, 3H, $C6H_a$, $C7H_a$, $C8H_a$), 1.42 – 1.35 (m, 1H, $C7H_b$), 1.33 – 1.28 (m, 1H, $C6H_b$), 1.27 – 1.25 (m, 2H, $C10H_2$), 1.23 (d, *J* = 6.5 Hz, 3H, $C18H_3$), 1.16 – 1.07 (m, 1H, $C8H_b$) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 180.1 (C9), 145.5 (C19), 140.9 (C13), 128.8 (2x PhC), 128.6 (2x PhC), 128.5 (2x PhC), 127.4 (2x PhC), 127.1 (*p*PhC), 126.4 (*p*PhC), 61.9 (C17), 57.7 (C1), 53.8 (C4), 47.8 (C3), 38.0 (C5), 34.6 (C8), 33.4 (C12), 30.6 (C11), 29.8 (C10), 27.1 (C7), 22.0 (C6), 21.5 (C18) ppm. **HRMS (m/z):** (ESI-TOF) calculated for $C_{25}H_{33}N_3S$ $[M+H]^+$ 408.2473; found 408.2473. **IR (ϑ_{max}/cm^{-1}, KBr):** 3024, 2928, 2861, 1533, 1495, 1452, 1334, 1235, 11300, 1029, 749, 700. $[\alpha]_D^{25}$**:** +6 (c = 2.02, CH_2Cl_2).

5.13 Calix[4]arene derivatives

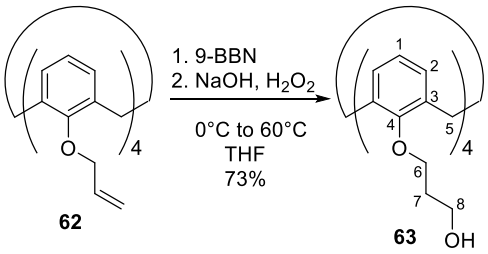
25,26,27,28-Tetraallyloxycalix[4]arene **62**



62

According to literature,[321] calix[4]arene (2.122 g, 5.00 mmol, 1.00 equiv.) was dissolved in dry DMF (20 mL, 0.25 M) and sodium hydride (60 wt% in mineral oil, 1.600 g, 40.00 mmol, 8.00 equiv.) was added slowly under temperature control before allyl bromide (2.59 mL, 30.00 mmol, 6.00 equiv.) was added dropwise and the reaction mixture was kept stirring for three hours, before the reaction was quenched by the addition of a few drops of methanol. Addition of water (50 mL) and extraction by diethyl ether (3x 100 mL) was followed by drying of the combined organic phase and concentration under vacuum. Trituration by methanol (3 times) yielded 2.193 g (3.90 mmol, 76%) of a white solid.
All recorded spectroscopic data matched previously reported ones.
^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.68 – 6.62 (m, 8H, 8x C2H), 6.62 – 6.55 (m, 4H, 4x C1H), 6.35 (ddt, *J* = 17.3, 10.3, 6.3 Hz, 4H, 4x C7H), 5.25 (dq, *J* = 17.2, 1.5 Hz, 4H, 4x $C8H_{trans}$), 5.18 (ddt, *J* = 10.3, 1.9, 1.0 Hz, 4H, 4x $C8H_{cis}$), 4.47 (dt, *J* = 6.4, 1.2 Hz, 8H, 4x $C8H_2$), 4.42 (d, *J* = 13.3 Hz, 4H, 4x $C5H_a$), 3.16 (d, *J* = 13.4 Hz, 4H, 4x $C5H_b$) ppm.

25,26,27,28-Tetrakis(3-hydroxypropoxy)calix[4]arene **63**

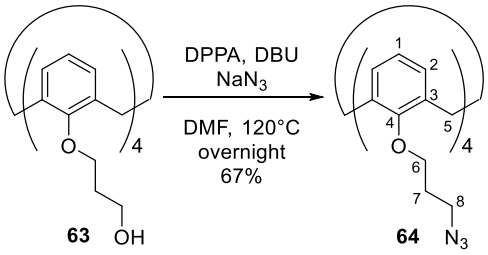


According to literature,[313] 25,26,27,28-tetraallyloxycalix[4]arene **62** (0.585 g, 1.00 mmol, 1.00 equiv.) was dissolved in THF (5 mL, 0.2 M) and a solution of 9-BBN (0.5 M in THF, 24 mL, 12.00 mmol, 12.00 equiv.) was added dropwise at 0 °C. The reaction mixture was allowed to reach room temperature and was stirred for 1.5 h before the solution was again cooled to 0 °C and aq. NaOH (10 M, 0.75 mL) was added slowly followed by aq. hydrogen peroxide (35%, 1.9 mL). The ice bath was removed and the reaction mixture was stirred for 30 min before being heated to 60 °C for another 1.5 h. After being cooled to room temperature the reaction mixture was diluted by phosphate buffer (pH = 7, 1 M, 25 mL) the organic solvent was removed under reduced pressure and the residue extracted by CH_2Cl_2 (2x 50 mL). No further purification was needed.

All recorded spectroscopic data matched previously reported ones.

^{1}H-NMR (400 MHz, CD_3OD) δ 6.60 (d, *J* = 8.0 Hz, 8H, 8x C2H), 6.57 – 6.51 (m, 4H, 4x C1H), 4.46 (d, *J* = 13.2 Hz, 4H, 4x $C5H_a$), 4.02 (t, *J* = 7.1 Hz, 8H, 4x $C6H_2$), 3.79 (t, *J* = 6.4 Hz, 8H, 4x $C8H_2$), 3.16 (d, *J* = 13.4 Hz, 4H, 4x $C5H_b$), 2.23 – 2.12 (m, 8H, 4x $C7H_2$) ppm.

25,26,27,28-Tetrakis(3-azidopropoxy)calix[4]arene **64**

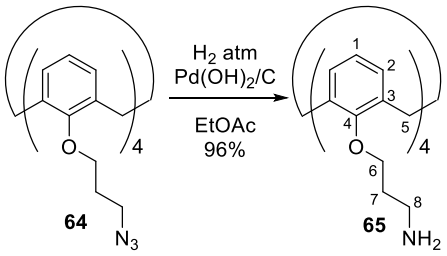


According to literature,[313] alcohol **63** (280 mg, 0.43 mmol, 1.00 equiv.) and sodium azide (233 mg, 3.44 mmol, 8.00 equiv.) were dissolved in DMF (4 mL, 0.1 M) and DPPA (0.55 mL, 2.58 mmol, 6.00 equiv.) and DBU (0.26 mL, 1.72 mL, 4.00 equiv.) were added successively and the reaction mixture was stirred overnight at 120 °C. After being cooled to room temperature the solvent was evaporated, diluted by diethyl ether (100 mL) washed by water (2x 10 mL) and the organic phase was dried over $MgSO_4$, before being concentrated. The crude product was recrystallized from methanol yielding 218 mg (0.29 mmol, 67%) of off-white crystals.

All recorded spectroscopic data matched previously reported ones.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.64 – 6.57 (m, 12H, 12x PhH), 4.33 (d, *J* = 13.5 Hz, 4H, 4x $C5H_a$), 3.97 (t, *J* = 7.0 Hz, 8H, 4x $C6H_2$), 3.52 (t, *J* = 6.7 Hz, 8H, 4x $C8H_2$), 3.21 (d, *J* = 13.5 Hz, 4H, 4x $C5H_b$), 2.16 (p, *J* = 6.9 Hz, 8H, $C7H_2$) ppm.

25,26,27,28-Tetrakis(3-aminopropoxy)calix[4]arene **65**

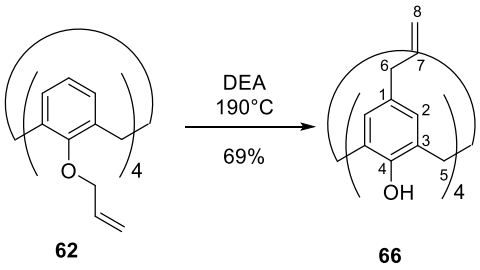


According to literature,[314] a solution of azide **64** (185 mg, 0.24 mmol, 1.00 equiv.) and $Pd(OH)_2/C$ (95 mg, 50 wt%) in EtOAc (4 mL, 0.25 M) was 3 times degassed under vacuum and refilled by hydrogen before being left for 4 hours under hydrogen atmosphere (H_2 filled balloon). The reaction mixture was filtered through a pad of cotton, washed by methanol and the solvent was removed under reduced pressure yielding quantitatively 156 mg (0.24 mmol, 100%) of a white solid.

All recorded spectroscopic data matched previously reported ones.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.69 – 6.58 (m, 12H, 12x PhH), 4.36 (d, *J* = 13.4 Hz, 4H, 4x C5H_a), 4.00 (t, *J* = 7.0 Hz, 8H, 4x C6H_2), 3.63 – 3.47 (m, 8H, 4x C8H_2), 3.24 (d, *J* = 13.5 Hz, 4H, 4x C5H_b), 2.20 (q, *J* = 6.9 Hz, 8H, 4x C7H_2) ppm. NH_2 protons are not visible.

5,11,17,23-Tetraallyl-25,26,27,28-tetrahydroxycalix[4]arene **66**

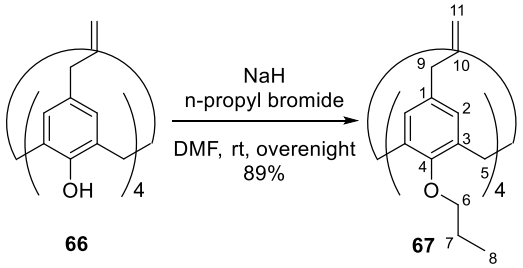


According to literature,[323] calixarene derivative **62** (585 mg, 1.00 mmol) was dissolved in DEA (10 mL, 0.1 M) and refluxed for 2 hours under argon atmosphere. The reaction mixture was cooled to room temperature, before being poured into ice water (80 mL); addition of concentrated hydrochloric acid (80 mL) precipitated the product. The solid was triturated by hot ethanol and gave 405 mg (0.69 mmol, 69 %) of a slightly brownish solid.

All recorded spectroscopic data matched previously reported ones.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.16 (s, 4H, 4x OH), 6.85 (s, 8H, 8x PhH), 5.87 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 4H, 4x C7H), 5.09 – 4.99 (m, 8H, 4x C8H_a, 4x C8H_b), 4.21 (s, 4H, 4x C5H_a), 3.46 (s, 4H, 4x C5H_b), 3.19 (dt, *J* = 6.8, 1.5 Hz, 8H, 4x C6H_2) ppm.

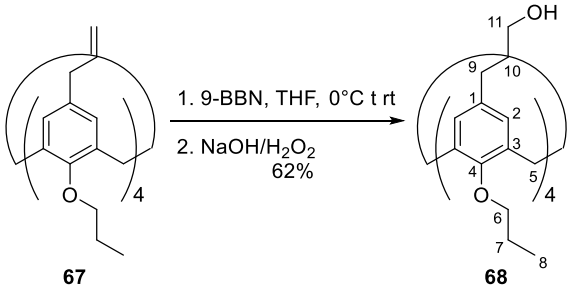
5,11,17,23-Tetrakis(3-hydroxypropyl)-25,26,27,28-tetra-propoxy-calix[4]arene **67**



According to literature,[311] to a solution of calixarene derivative **66** (400 mg, 0.68 mmol, 1.00 equiv.) in DMF (7 mL, 0.1 M) sodium hydride (60 wt% in mineral oil, 219 mg, 5.47 mmol, 8.00 equiv.) was added slowly under temperature control (keeping the reaction mixture below 40 °C) before bromopropane (0.5 mL, 5.47 mmol, 8.00 equiv.) was added dropwise. The reaction mixture was stirred overnight at room temperature before it was quenched by the addition of phosphate buffer (pH = 7, 1 M, 25 mL) and extracted by CH_2Cl_2 (2x 50 mL). Combined organic phases were dried using $MgSO_4$ and the crude product was concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, 15x3 cm, 90:10 cyclohexane:EtOAc) gave 507 mg (0.67 mmol, 99%) of a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.47 (s, 8H, 8x PhH), 5.81 (ddt, *J* = 16.7, 10.1, 6.5 Hz, 4H, 4x C10H), 4.96 (ddd, *J* = 10.1, 2.3, 1.1 Hz, 4H, 4x C11H_{cis}), 4.91 (dq, *J* = 17.0, 1.7 Hz, 4H, 4x C11H_{trans}), 4.40 (d, *J* = 13.0 Hz, 4H, 4x C5H_a), 3.86 – 3.72 (m, 8H, 4x C6H_2), 3.14 – 3.03 (m, 12H, 4x C5H_b, 4x C9H_2), 2.01 – 1.87 (m, 8H, 4x C7H_2), 0.99 (t, *J* = 7.5 Hz, 12H, 4x C8H_3) ppm.

5,11,17,23-Tetrakis(3-hydroxypropyl)-25,26,27,28-tetra- propoxy-calix[4]arene **68**



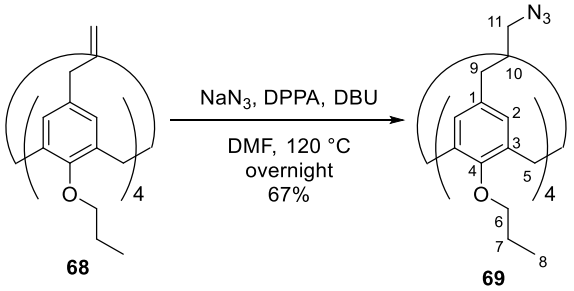
According to literature,[311] the calix[4]arene derivative **67** (507 mg, 0.67mmol, 1.00 equiv.) was dissolved in THF (4 mL, 0.17 M) and a solution of 9-BBN (0.5 M in THF, 16.1 mL, 8.04 mmol, 12.00 equiv.) was added dropwise at 0 °C. The reaction mixture was allowed to reach room temperature and was stirred for 1.5 h before the solution was again cooled to 0 °C and aq. NaOH (10 M, 0.51 mL) was added slowly followed by aq. hydrogen peroxide (35%, 1.3 mL). The ice bath was removed and the reaction mixture was stirred for 30 min before being heated to 60 °C for another 1.5 h. After being cooled to room temperature the reaction mixture was diluted by phosphate buffer (pH = 7, 1 M, 25 mL) the organic solvent was removed under reduced pressure and the residue was extracted with CH_2Cl_2 (3x 15 mL). The crude product was washed with cyclohexane and recrystallized from MeCN yielding 340 mg (0.41 mmol, 62%) of white crystals.

All recorded spectroscopic data matched previously reported ones.

^{1}H-NMR (400 MHz, CD_3OD) δ 6.49 (s, 8H, 8x PhH), 4.41 (d, *J* = 12.9 Hz, 4H, 4x C5H_a), 3.82 (t, *J* = 7.4 Hz, 8H, 4x C11H_2), 3.48 (t, *J* = 6.5 Hz, 8H, 4x C6H_2), 3.06 (d, *J* = 13.0 Hz, 4H, 4x C5H_b), 2.34 (t, *J* = 7.7 Hz, 8H,

4x $C9H_2$), 1.97 (p, *J* = 7.5 Hz, 8H, 4x $C7H_2$), 1.67 – 1.59 (m, 8H, 4x $C10H_2$), 1.02 (t, *J* = 7.5 Hz, 12H, 4x $C8H_3$) ppm.

5,11,17,23-Tetrakis(3-azidopropyl)-25,26,27,28-tetrapropoxy- calix[4]arene **69**

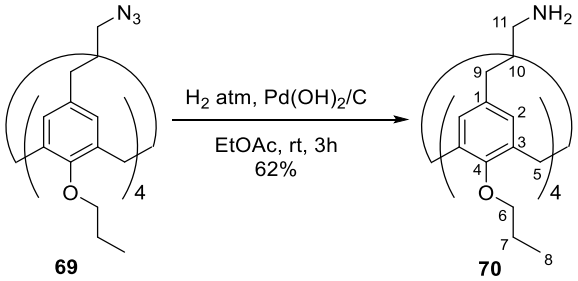


According to literature,[312] tetrol **68** (334 mg, 0.41 mmol, 1.00 equiv.) and sodium azide (210 mg, 3.24 mmol, 8.00 equiv.) were dissolved in DMF (4 mL, 0.1 M) DPPA (0.52 mL, 2.43 mmol, 6.00 equiv.) and DBU (0.24 mL, 1.62 mL, 4.00 equiv.) were added successively and the reaction mixture was stirred at 120 °C overnight. After being cooled to room temperature the solvent was evaporated, diluted by diethyl ether (100 mL), washed by water (2x 10 mL) and the organic phase was dried over $MgSO_4$, before being concentrated. The crude product was recrystallized from methanol yielding 218 mg (0.29 mmol, 67%) of off-white crystals.

All recorded spectroscopic data matched previously reported ones.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.45 (s, 8H, 8x PhH), 4.39 (d, *J* = 13.0 Hz, 4H, 4x $C5H_a$), 3.86 – 3.77 (m, 8H, 4x $C6H_2$), 3.16 (t, *J* = 6.8 Hz, 8H, 4x $C11H_2$), 3.06 (d, *J* = 13.1 Hz, 4H, 3x $C5H_b$), 2.37 (dd, *J* = 8.2, 6.7 Hz, 8H, 4x $C9H_2$), 1.99 – 1.88 (m, 8H, 4x $C7H_2$), 1.71 (dq, *J* = 8.4, 6.8 Hz, 8H, $C10H_2$), 0.98 (t, *J* = 7.5 Hz, 12H, 3x $C8H_3$) ppm.

5,11,17,23-Tetrakis(3-aminopropyl)-25,26,27,28-tetrapropoxy- calix[4]arene **70**

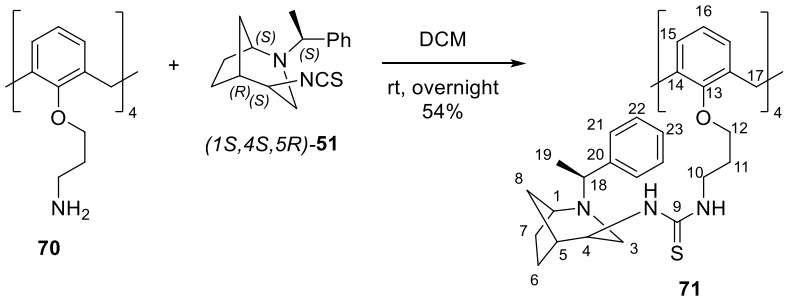


In a modified literature procedure,[314] a solution of azide **69** (248 mg, 0.26 mmol, 1.00 equiv.) and $Pd(OH)_2/C$ (130 mg, 50 wt%) in EtOAc (4 mL, 0.25 M) was 3 times degassed under vacuum and refilled by hydrogen before being left for 4 hours under hydrogen atmosphere (H_2 filled balloon). The reaction mixture was filtered through a pad of cotton and through Florisil®, before being washed by methanol. The solvent was removed under reduced pressure yielding quantitatively 135 mg (0.16 mmol, 62%) of a white solid.

^{1}H-NMR (400 MHz, CD_3OD) δ 6.49 (s, 8H, 8x PhH), 4.42 (d, *J* = 13.0 Hz, 4H, 4x $C5H_a$), 3.82 (t, *J* = 7.4 Hz, 8H, 4x $C6H_2$), 3.06 (d, *J* = 13.0 Hz, 4H, 4x $C5H_b$), 2.55 (t, *J* = 7.1 Hz, 8H, 2x $C11H_2$), 2.31 (t, *J* = 7.6 Hz, 8H, 4x $C9H_2$), 1.95 (q, *J* = 7.5 Hz, 8H, 2x $C7H_2$), 1.59 (p, *J* = 7.5 Hz, 8H, 2x $C10H_2$), 1.02 (t, *J* = 7.5 Hz, 12H, 4x $C8H_3$) ppm. NH_2-protons are not visible in the chosen solvent. **^{13}C-NMR** (101 MHz, MeOD) δ = 154.5

(C), 134.9 (C), 134.5 (C), 127.8 (CH), 76.5 (CH_2), 40.7 (CH_2), 34.4 (CH_2), 32.4 (CH_2), 30.6 (CH_2), 23.1 (CH_2), 9.5 (CH_3). **MS (m/z):** (ESI-micrOTOF-Q) calculated for $C_{52}H_{76}N_4O_4$ $[M+H]^+$ 821.59, $[M+2H]^{2+}$ 411.30, $[M+3H]^{3+}$ 274.20; found 821.60, 411.30, 274.54.

25,26,27,28-Tetrakis{3-{(S)-1-phenylethyl)-2-azabicyclo[3.2.1]octan-4-yl)thioureido}propoxy}-calix[4]arene **71**

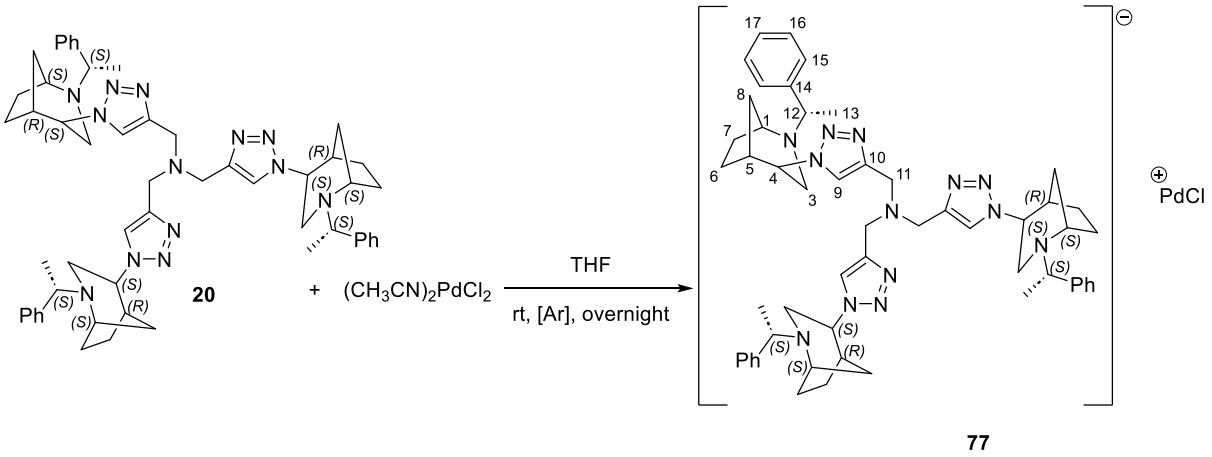


A solution of tetraamine **70** (41 mg, 0.062 mmol, 1.00 equiv.) and bicyclic isothiocyanate (1*S*,5*S*,5*R*)-**51** (81 mg, 0.298 mmol, 4.81 equiv.) was stirred in CH_2Cl_2 (0.8 mL, 0.37 M with respect to isothiocyanate) at room temperature overnight. After concentrating under vacuum the crude was purified by column chromatography (Sephadex® LH-20, 45x2 cm, 50:50 CH_2Cl_2:MeOH) yielding 58 mg (0.066 mmol, 54%) of a slightly reddish solid.

^{1}H-NMR (400 MHz, DMSO-D_6) δ 7.69 (s, 4H), 7.32 (d, *J* = 6.6 Hz, 8H, 8x PhH), 7.25 (s, 8H, 8x PhH), 7.16 (s, 4H, 4x *p*PhH), 6.58 (s, 12H, 12x *calix*-PhH), 4.31 (s, 4H), 4.01 (s, 4H), 3.89 (s, 8H), 3.56 (s, 4H), 3.49 (s, 4H), 3.38 (d, *J* = 6.1 Hz, 4H), 3.32 (s, 8H), 3.15 (d, *J* = 13.3 Hz, 4H), 2.33 (s, 4H), 2.25 (s, 4H), 2.13 (s, 8H), 1.79 (d, *J* = 10.5 Hz, 4H, 4x $C8H_a$), 1.59 (s, 8H, 4x $C6H_a$, 4x $C7H_a$), 1.23 (d, *J* = 6.1 Hz, 24H, 4x $C6H_b$, 4x $C7H_b$, 4x $C8H_b$, 4x $C19H_3$) ppm. **^{13}C-NMR** (126 MHz, cryo-probe, DMSO-D_6) δ = 181.9 (C9), 156.6 (C20), 147.6, 134.7, 128.5, 128.2, 127.9, 122.2, 71.2, 63.2 (C18), 57.9 (C1), 53.6 (C4), 49.2 (C3), 41.9, 37.8 (C5), 34.1 (C8), 30.4, 29.9, 26.2 (C7), 22.0 (C6), 21.4 (C19) ppm. **HRMS (m/z):** (ESI-TOF) calculated for $C_{104}H_{132}N_{12}O_4S_4$ $[M+H]^+$ 1742.9486, $[M+2H]^{2+}$ 871.9782; found 1742.9470, 871.9741, (MALDI-TOF, DHB matrix) found 1742.9. **IR (ϑ_{max}/cm^{-1}):** Literature usually does not present IR-spectra of calixarenes. $[\alpha]_D^{25}$**:** +26° (c = 0.41, CH_2Cl_2).**mp:** As for previous literature the melting point of the product could not be determined, being above the instrument's maximum temperature

5.14 Synthesis of complexes

[N,N,N-tri((1-((1S,4S,5R)-2-((S)-1-phenylethyl)-2-azabicyclo[3.2.1]octan-4-yl)-1H-1,2,3-triazol-4-yl)methyl) amine]palladium(II)chloride **77**



77

According to literature,[328] to a stirred solution of bis(acetonitrile)palladium dichloride (52 mg, 0.2 mmol, 1 equiv.) in THF (2 mL, 0.1 M) at room temperature under argon atmosphere triazole **20** (180 mg, 0.2 mml, 1 equiv.) was added and the reaction mixture was kept stirring overnight. Upon evaporation of the solvent column chromatography (SiO_2, 25x1.5 cm, 95:5 CH_2Cl_2:MeOH) yielded 109 mg (0.10 mmol, 50%) of a yellowish solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.14 (s, 1H, C9H), 8.99 (s, 1H, C9H), 7.86 (s, 1H, C9H), 7.55 – 7.45 (m, 2H), 7.40 – 7.29 (m, 8H), 7.24 (s, 4H), 7.18 – 7.08 (m, 1H), 4.88 (d, *J* = 13.1 Hz, 2H), 4.62 (d, *J* = 16.3 Hz, 1H), 4.40 (s, 2H), 4.36 – 4.26 (m, 2H), 4.11 (d, *J* = 13.3 Hz, 1H), 3.91 (s, 1H), 3.87 – 3.78 (m, 1H), 3.72 (s, 1H), 3.62 (s, 1H), 3.31 (d, *J* = 7.0 Hz, 2H), 3.12 (d, *J* = 13.9 Hz, 1H), 2.83 – 2.67 (m, 3H), 2.65 – 2.54 (m, 2H), 2.54 – 2.40 (m, 3H), 1.90 – 1.74 (m, 6H), 1.65 (s, 3H), 1.60 – 1.51 (m, 3H), 1.50 – 1.43 (m, 9H), 1.39 – 1.34 (m, 3H), 1.30 – 1.22 (m, 3H) ppm. **^{13}C-NMR** (151 MHz, $CDCl_3$) δ (147.6, 145.2, 143.9), (143.2, 139.6, 139.1), (129.0, 128.9), (127.9, 127.6, 127.4), 127.2, 120.6, (63.1, 63.0), (61.5, 60.3, 60.1), 59.9, 57.5, 56.8, 56.4, 56.0, 55.4, 52.6, (48.0, 47.0, 46.1), (40.7, 40.5, 40.3), (34.3, 33.9, 33.6), (27.5, 27.2, 27.0), 23.1, 21.5, 21.3, 20.9, 20.0 ppm. Wherever possible groupings were assigned. **HRMS (m/z):** (ESI-TOF) calculated for $C_{54}H_{68}N_{13}PdCl$ $[M+H]^+$ 1040.4537; found 104.4534.

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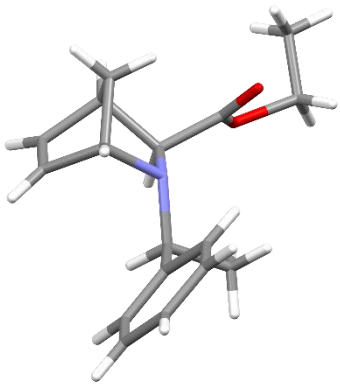
Appendix

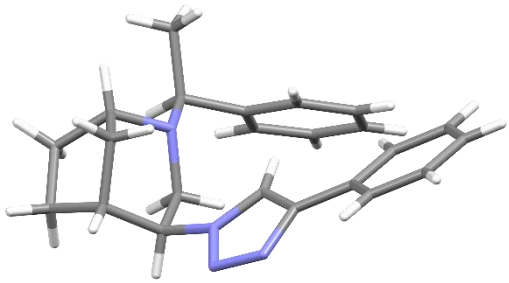
A.1 Crystallographic data

Crystallographic data of (1*S*,3*S*,4*R*)-**1**



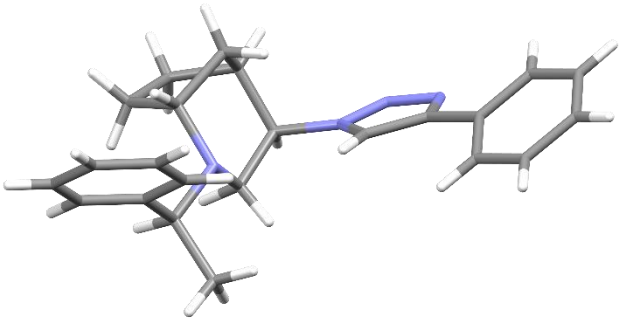
Molecular formula	$C_{17}H_{21}NO_2$
Molar mass	451.61
Temperature	283-303 K
Crystallographic system	Orthorhombic
Space group	P $2_12_12_1$
Cell length	a 9.0572 Å b 11.9521 Å c 14.2289 Å
Cell angles	α 90°, β 90°, γ 90°
Cell volume	1540.31 Å^3
Z	4
R-factor	6.11 %
Packing coefficient	0.64993
Density	1.170 g/cm^3

Crystallographic data of (*1S,4S,5R*)-**13**



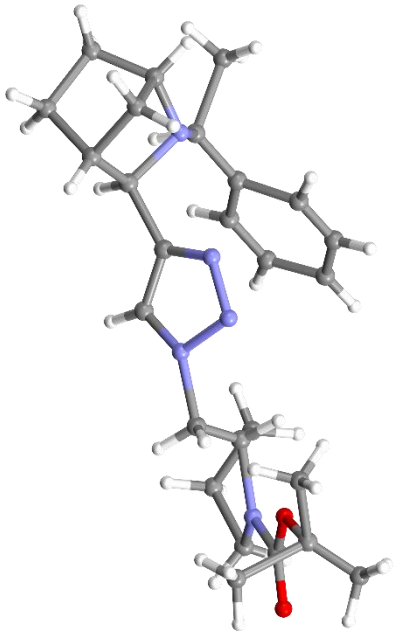
Molecular formula	$C_{23}H_{26}N_4$
Molar mass	451.61
Temperature	283-303 K
Crystallographic system	Orthorhombic
Space group	P $2_12_12_1$
Cell length	a 6.0494 Å b 16.1424 Å c 19.8521 Å
Cell angles	α 90°, β 90°, γ 90°
Cell volume	1938.58 Å^3
Z	4
R-factor	3.78 %
Packing coefficient	0.67405
Density	1.228 g/cm^3

Crystallographic data of (*1R,4R,5S*)-**23**



Molecular formula	$C_{23}H_{26}N_4$
Molar mass	451.61
Temperature	283-303 K
Crystallographic system	Orthorhombic
Space group	P $2_12_12_1$
Cell length	a 9.2139 Å b 11.5802 Å c 19.1678 Å
Cell angles	α 90°, β 90°, γ 90°
Cell volume	2045.18 Å^3
Z	4
R-factor	3.79 %
Packing coefficient	0.639249
Density	1.164 g/cm^3

Crystallographic data of **32**

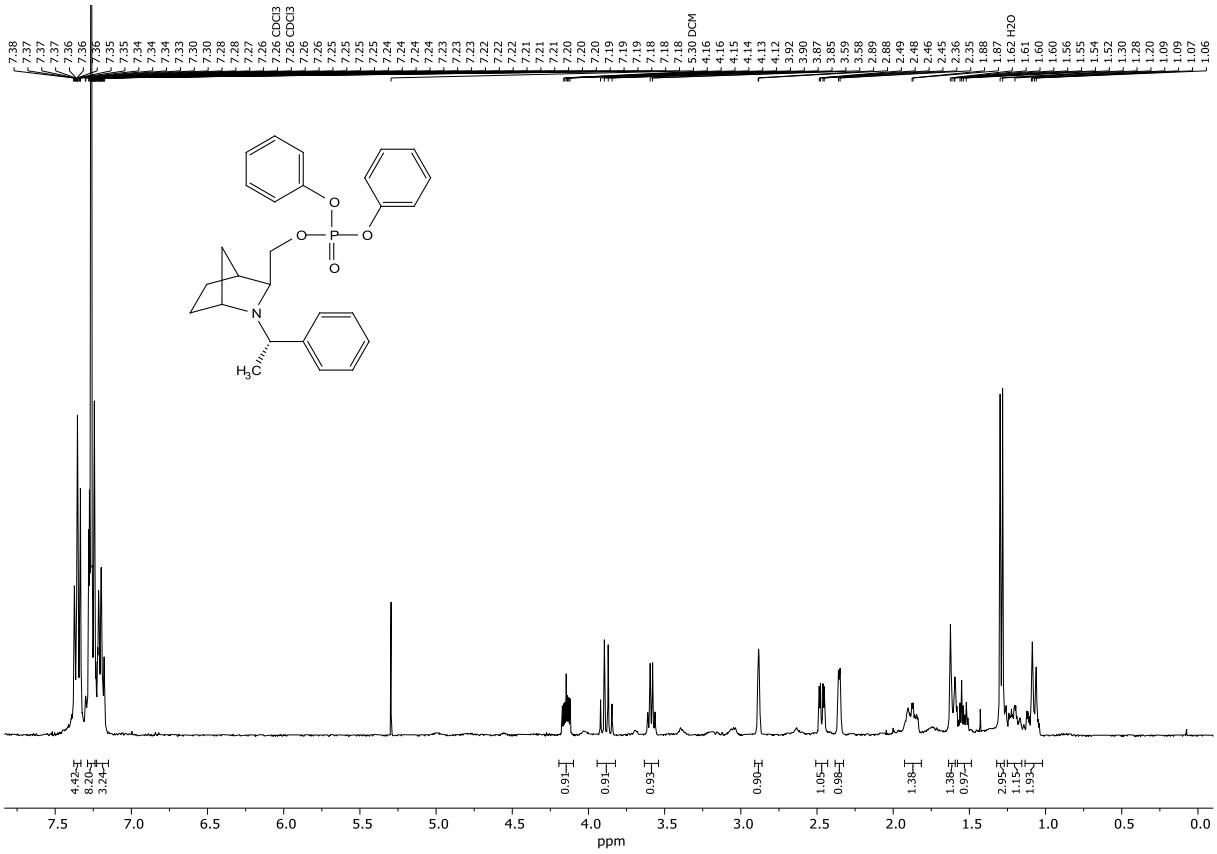


Molecular formula	$C_{26}H_{37}N_5O_2$
Molar mass	451.61
Temperature	100 K
Crystallographic system	Monoclinic
Space group	I2
Cell length	a 20.380 Å b 5.7379 Å c 21.825 Å
Cell angles	α 90°, β 104.53°, γ 90°
Cell volume	2470.55 Å^3
Z	4
R-factor	24.32 %
Packing coefficient	0.665831
Density	1.214 g/cm^3

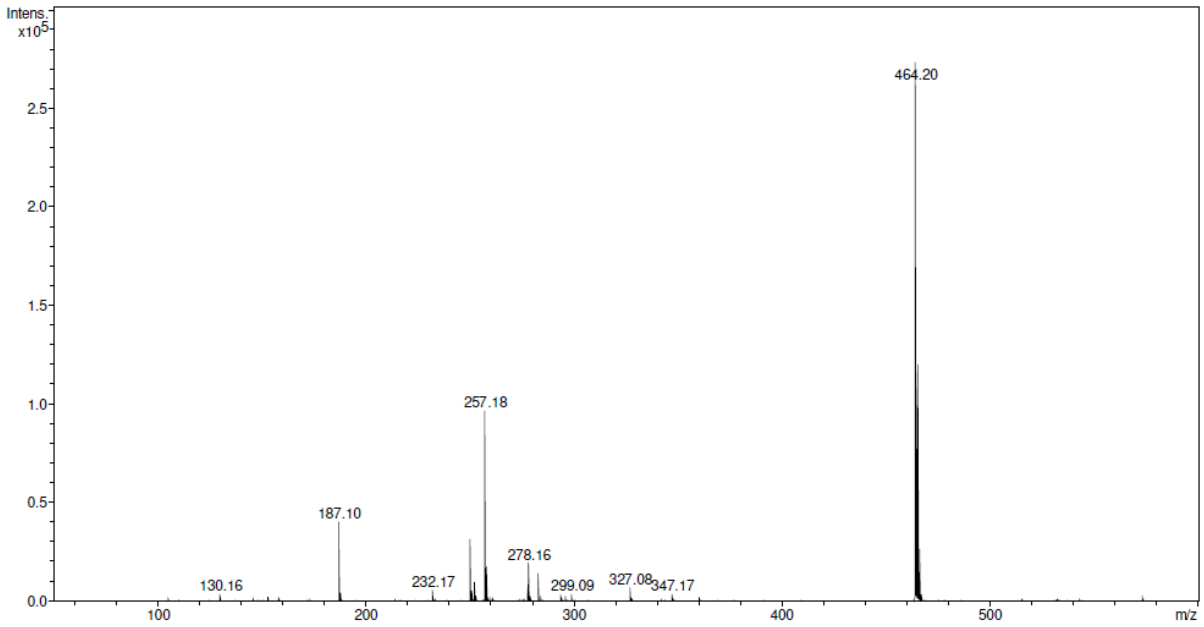
The structure may be found on the Cambridge data base under CCDC-2020530

A.2 NMR spectra

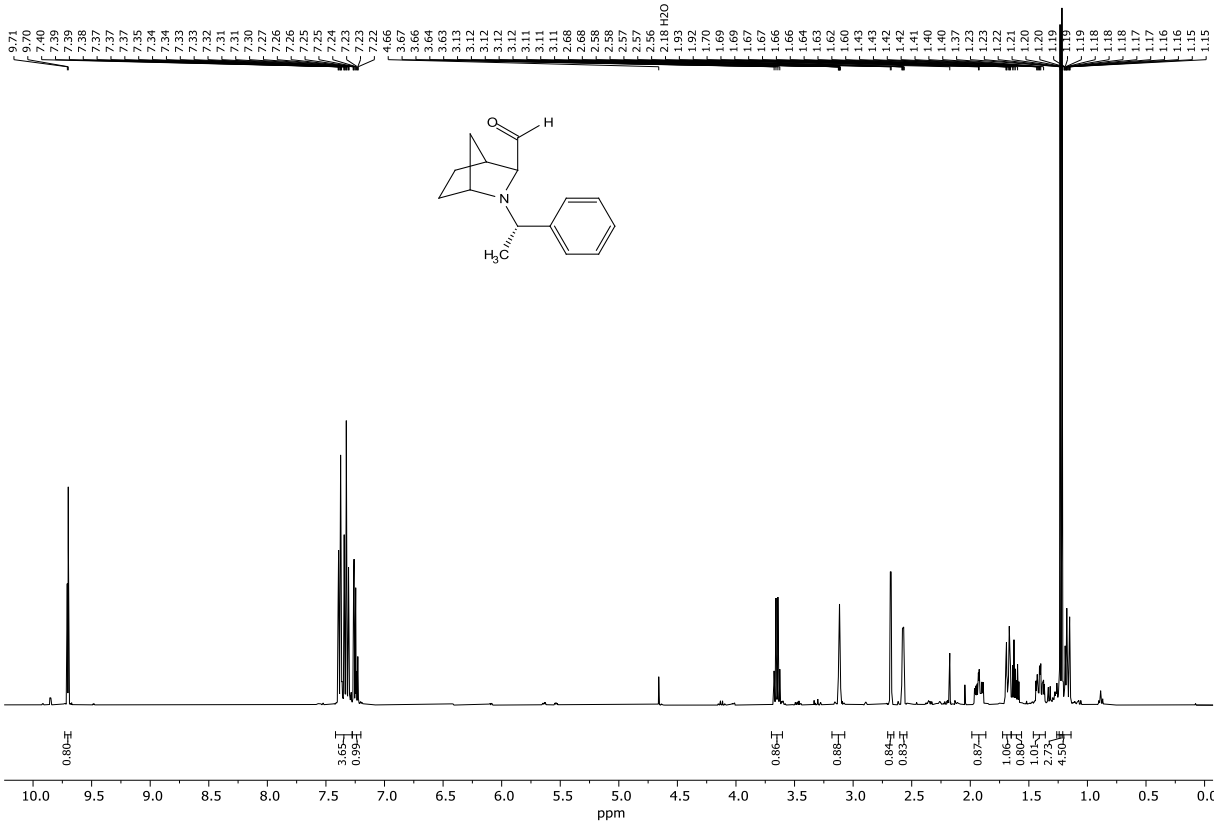
^{1}H-NMR (400 MHz, $CDCl_3$) of **5**



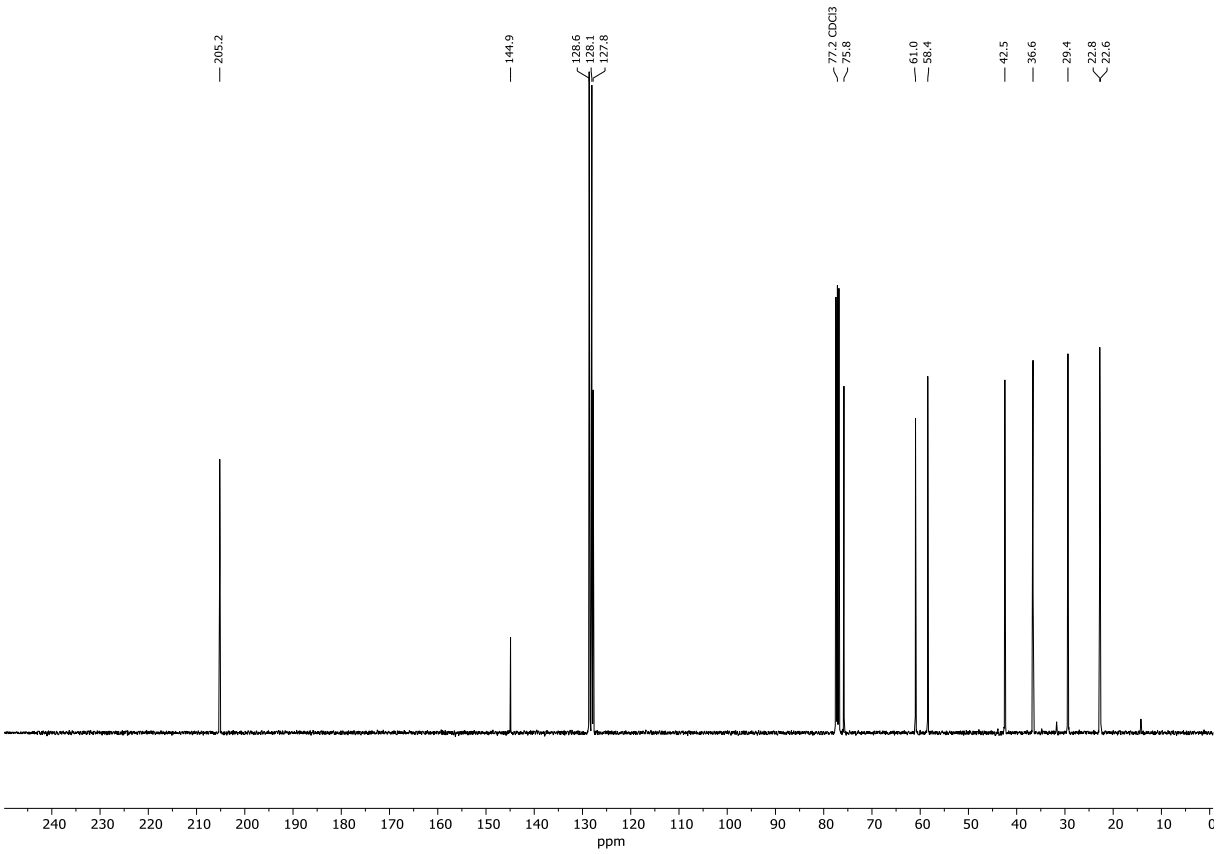
Mass spectrum (ESI-TOF) of **5**



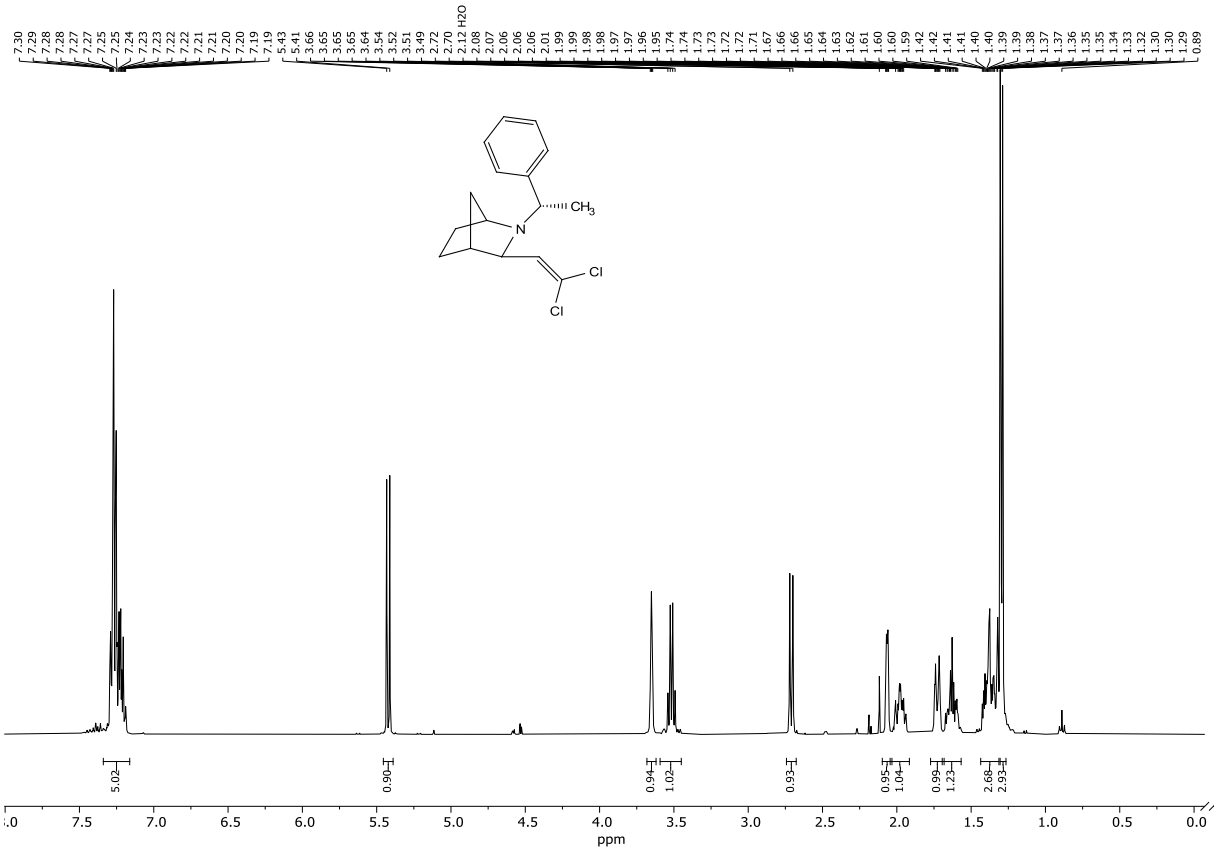
^{1}H-NMR (400 MHz, $CDCl_3$) of (1*R*,4*S*,4*S*)-**6**



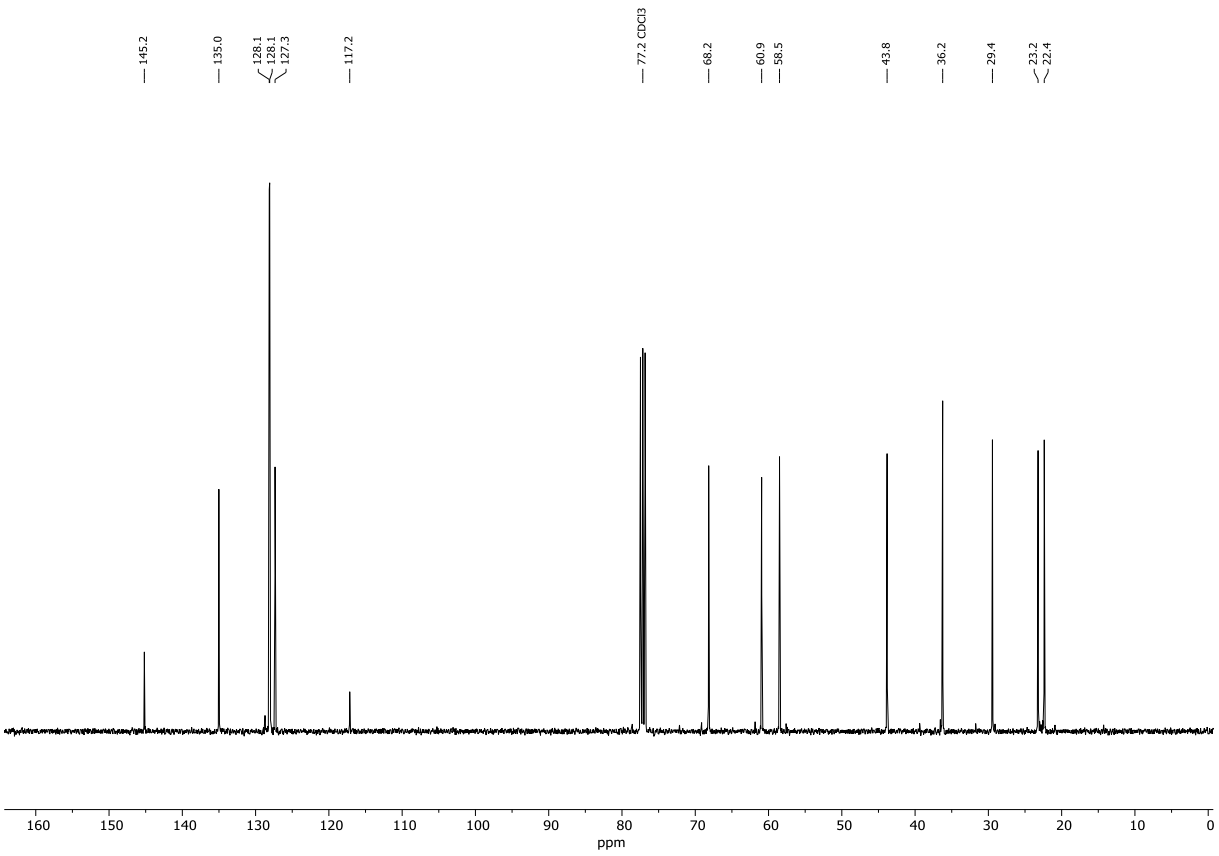
^{13}C-NMR (101 MHz, $CDCl_3$) of (1*R*,4*S*,4*S*)-**6**



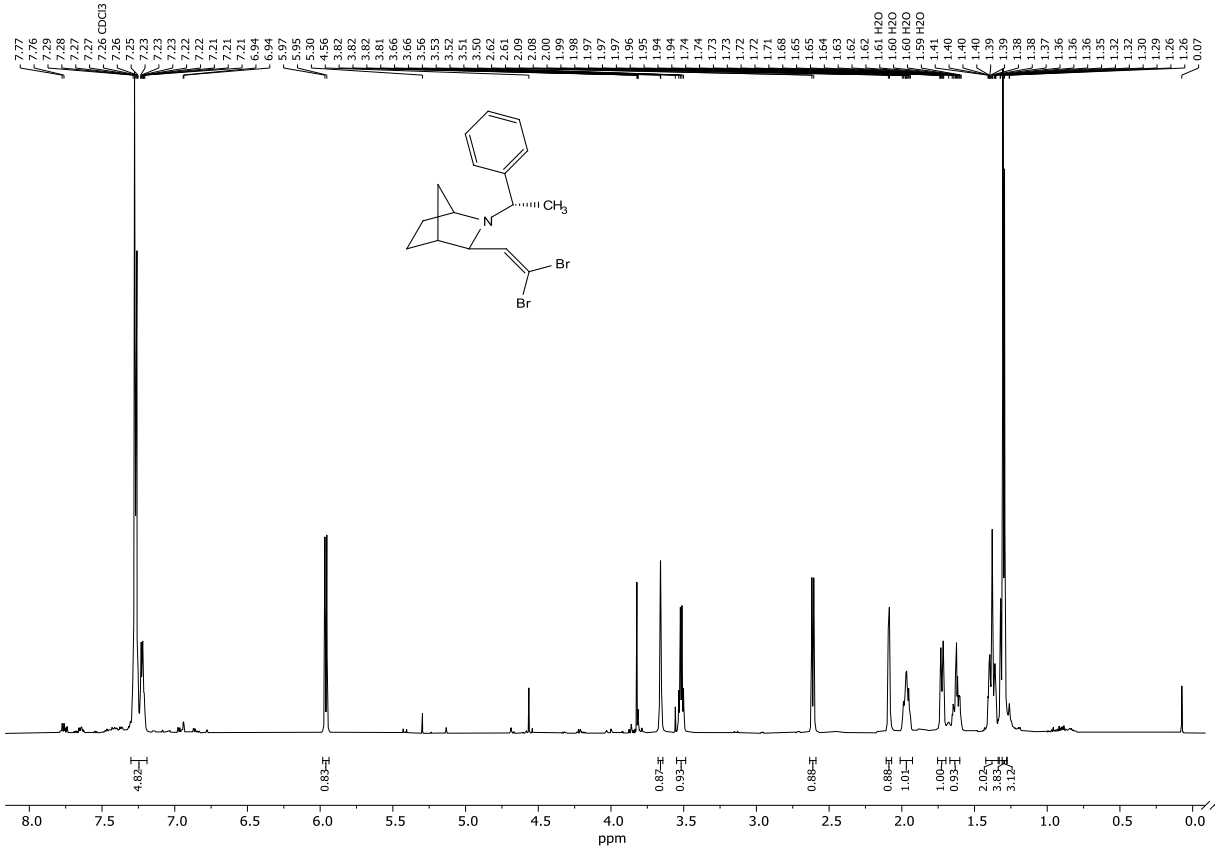
^{1}H-NMR (400 MHz, $CDCl_3$) of **7**



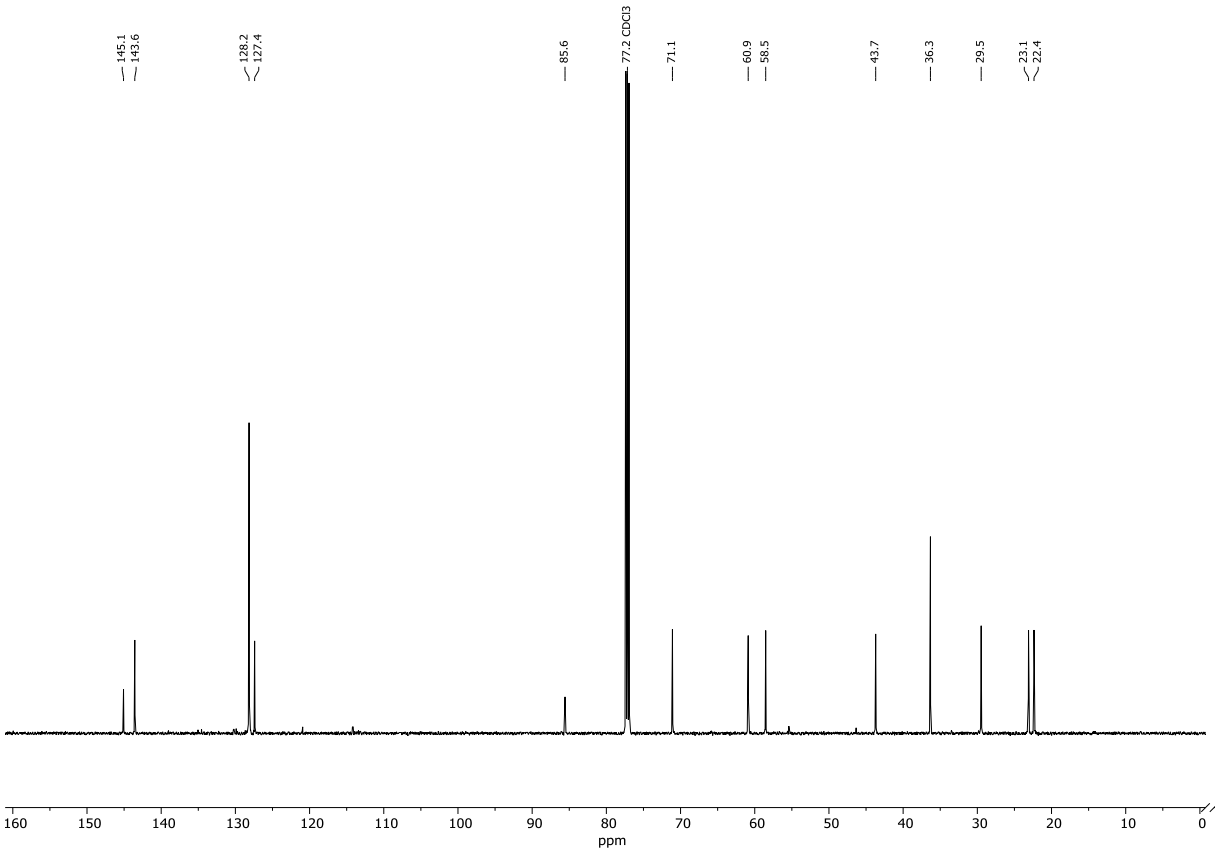
^{13}C-NMR (101 MHz, $CDCl_3$) of **7**



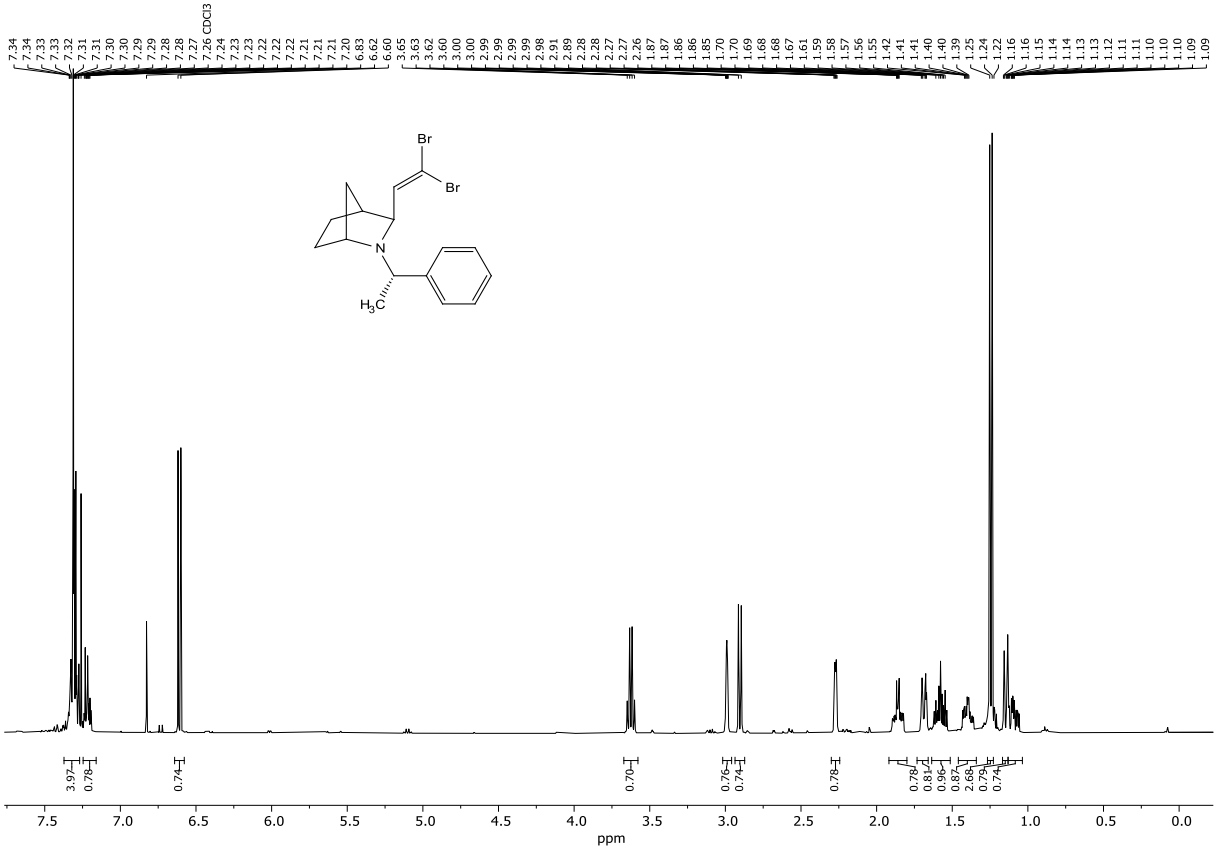
^{1}H-NMR (601 MHz, $CDCl_3$) of (1*S*,3*R*,4*R*)-**9**



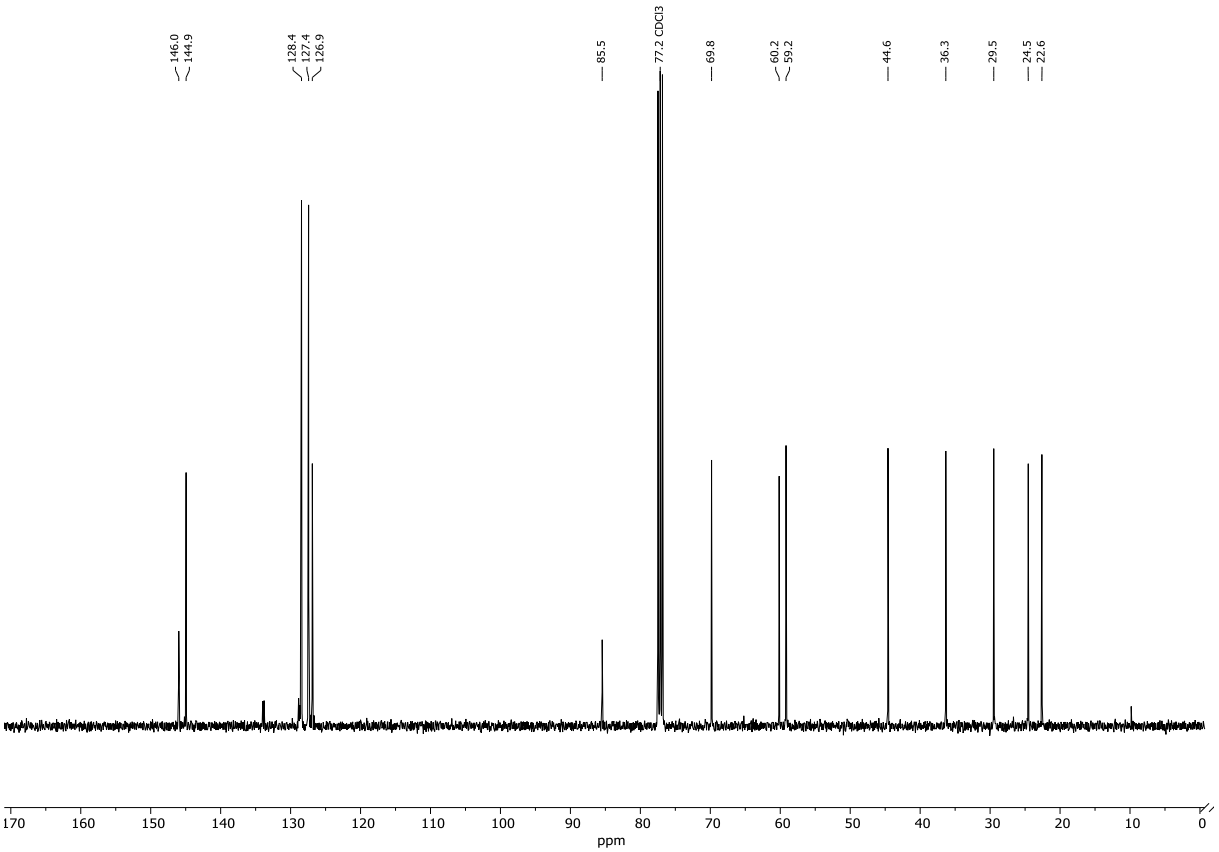
^{13}C-NMR (151 MHz, $CDCl_3$) of (1*S*,3*R*,4*R*)-**9**



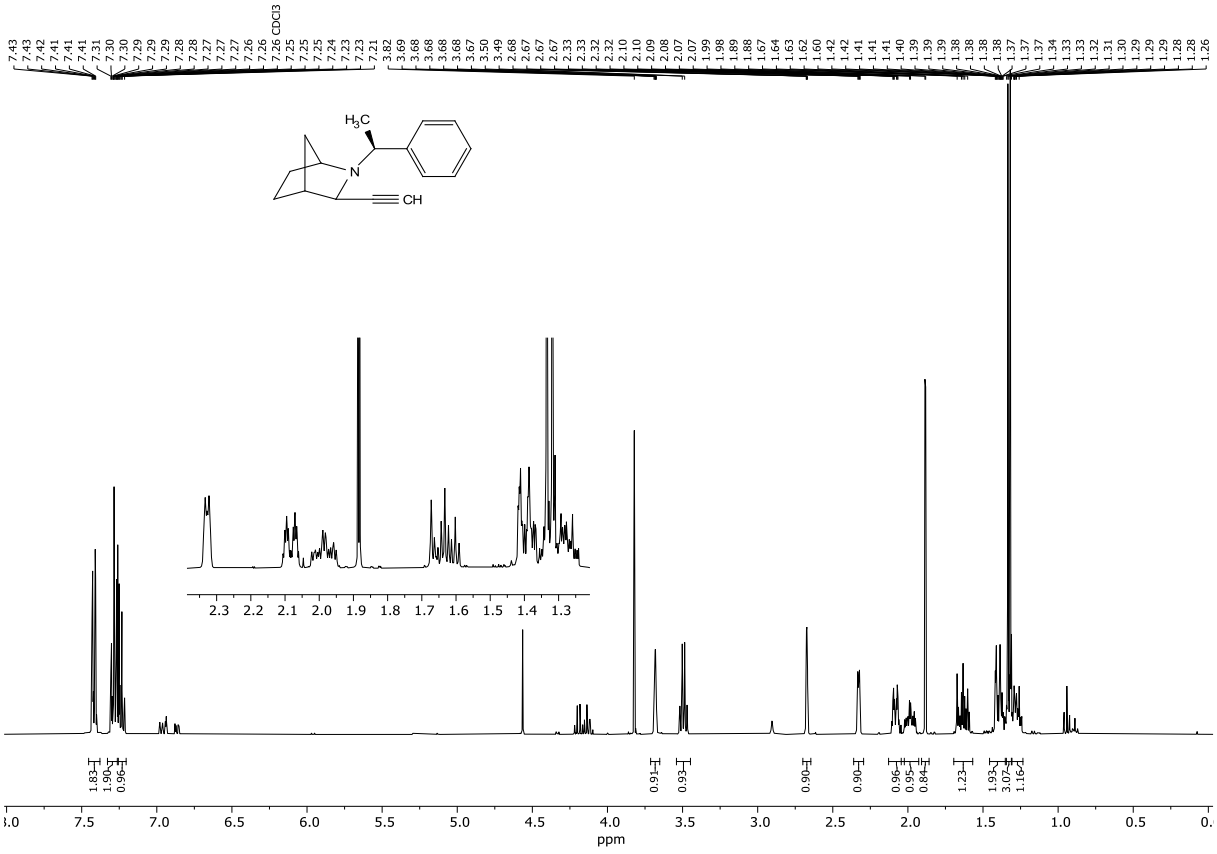
^{1}H-NMR (400 MHz, $CDCl_3$) of (1*R*,3*S*,4*S*)-**9**



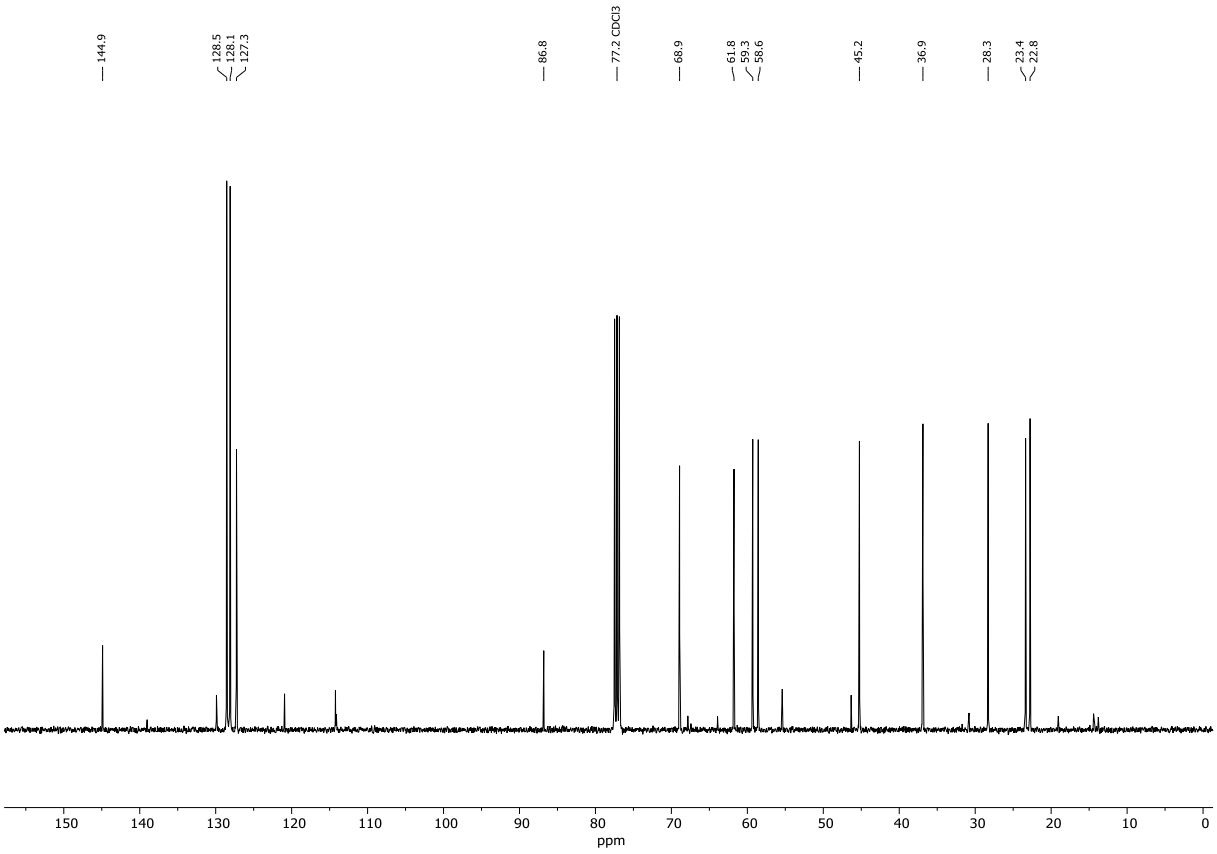
^{13}C-NMR (101 MHz, $CDCl_3$) of (1*R*,3*S*,4*S*)-**9**



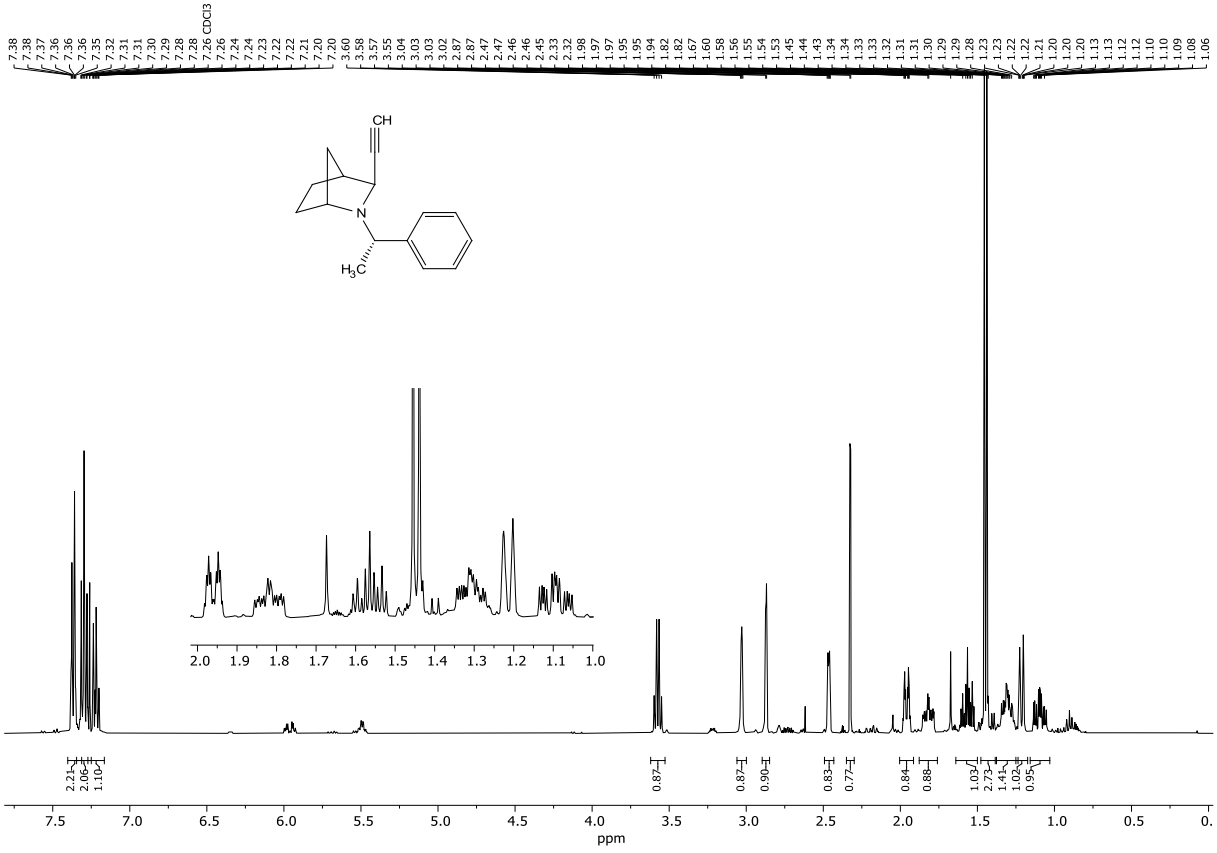
^{1}H-NMR (400 MHz, $CDCl_3$) of (1*S*,3*R*,4*R*)-**8**



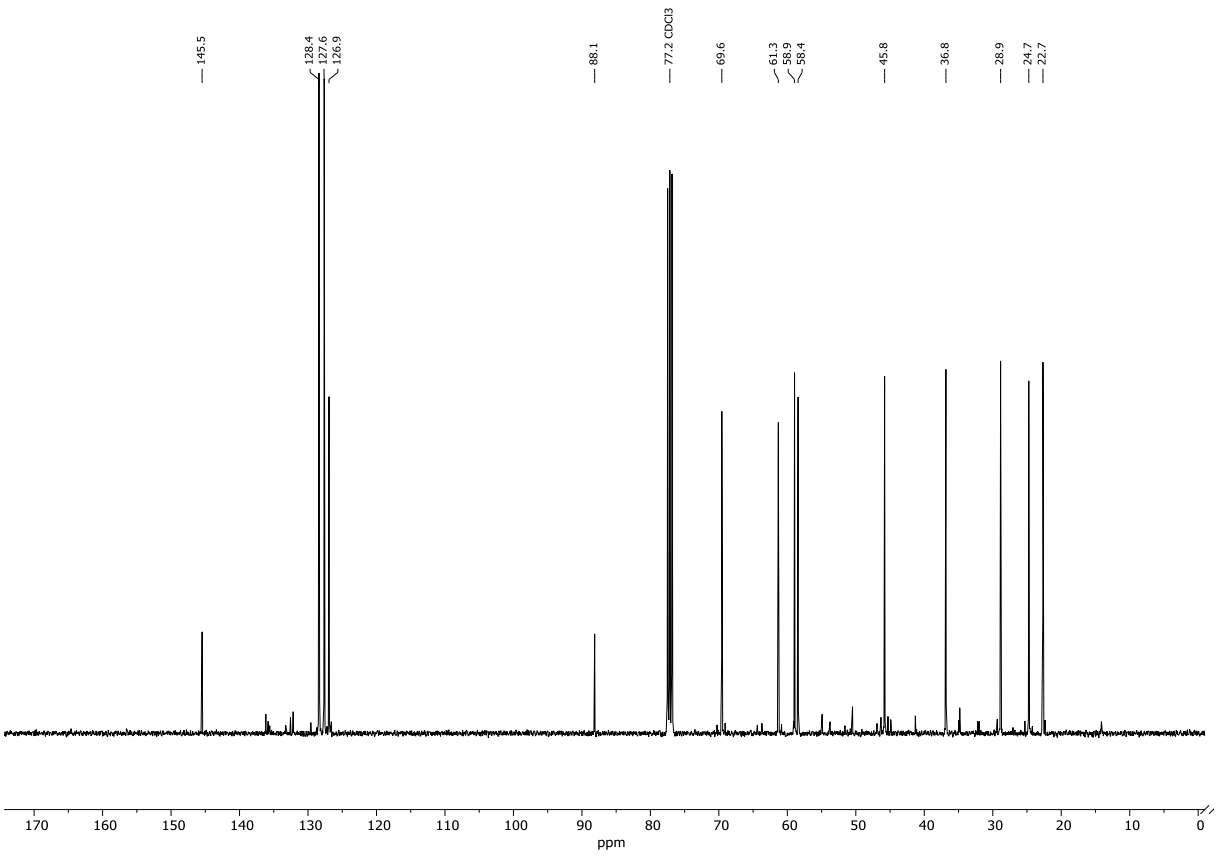
^{13}C-NMR (101 MHz, $CDCl_3$) of (1*S*,3*R*,4*R*)-**8**



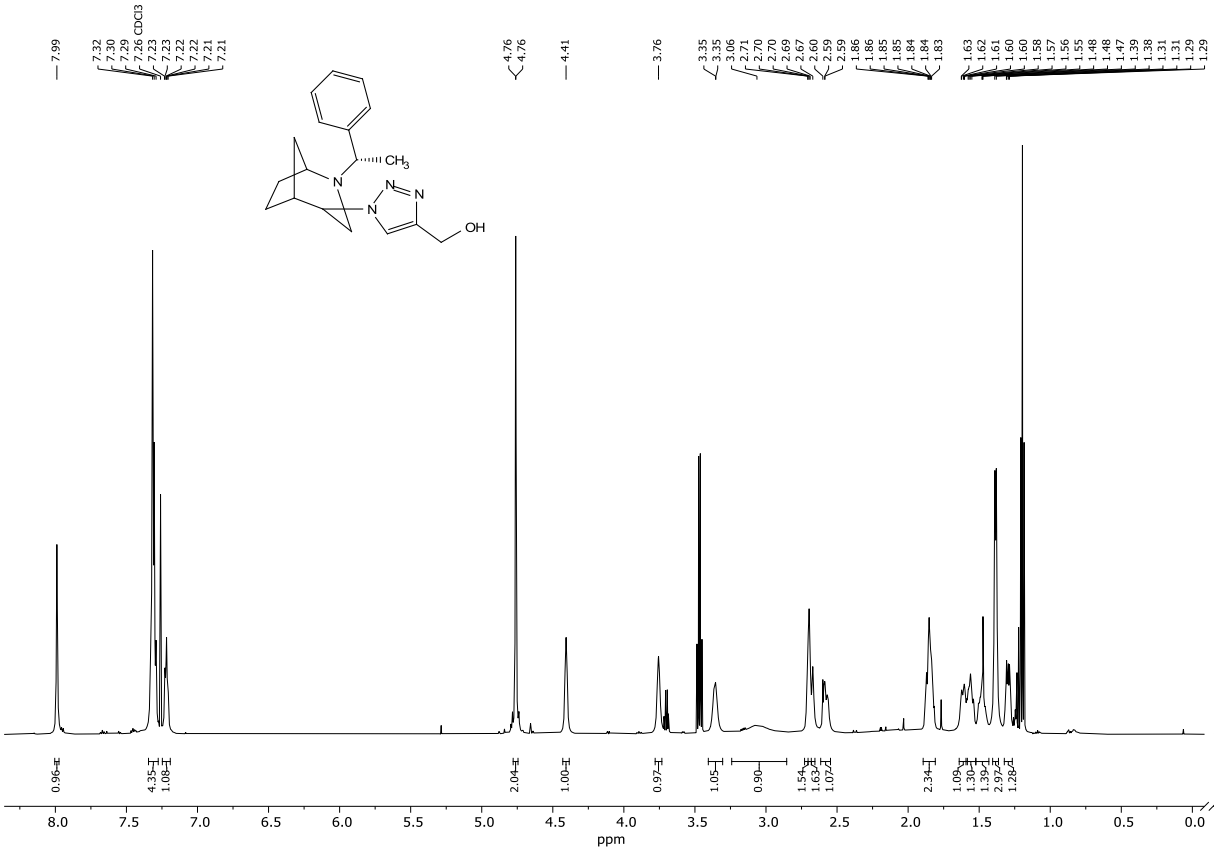
^{1}H-NMR (400 MHz, $CDCl_3$) of (1*R*,3*S*,4*S*)-**8**



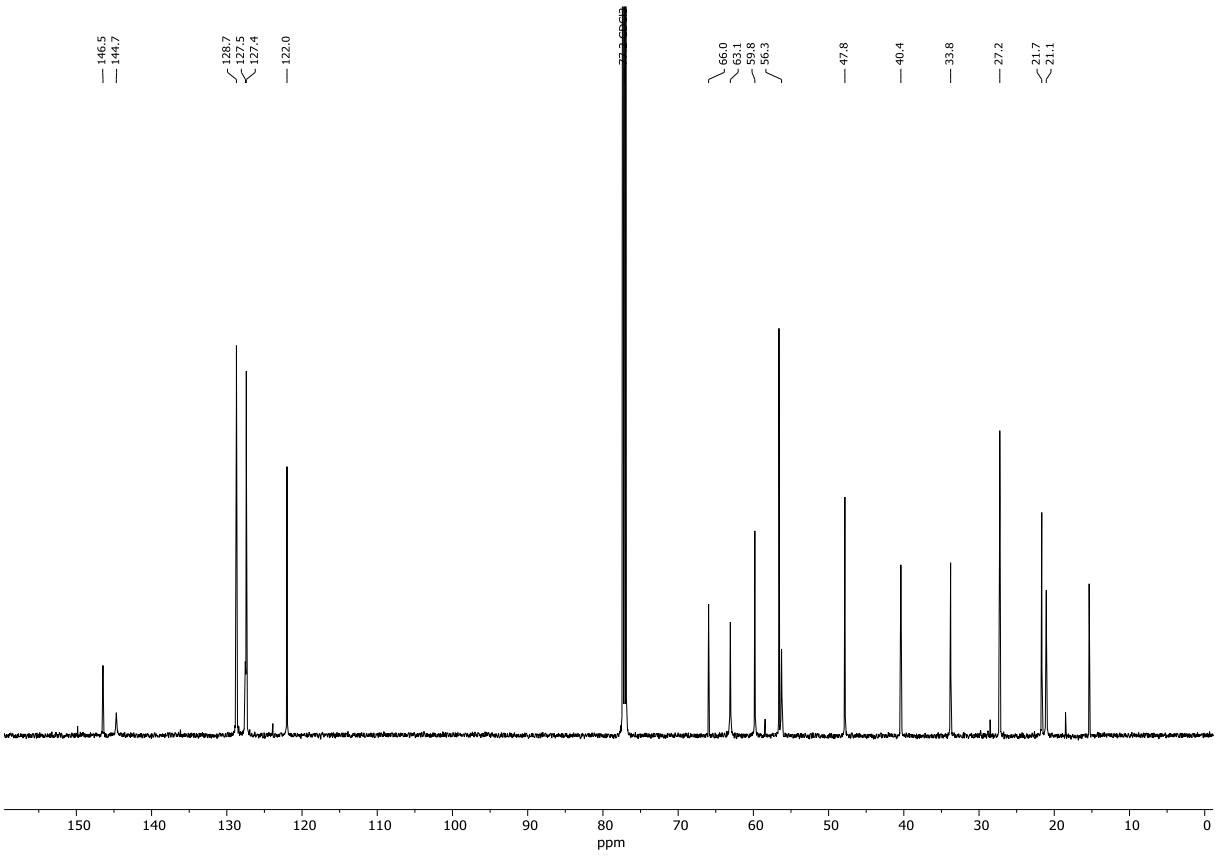
^{13}C-NMR (101 MHz, $CDCl_3$) of (1*R*,3*S*,4*S*)-**8**



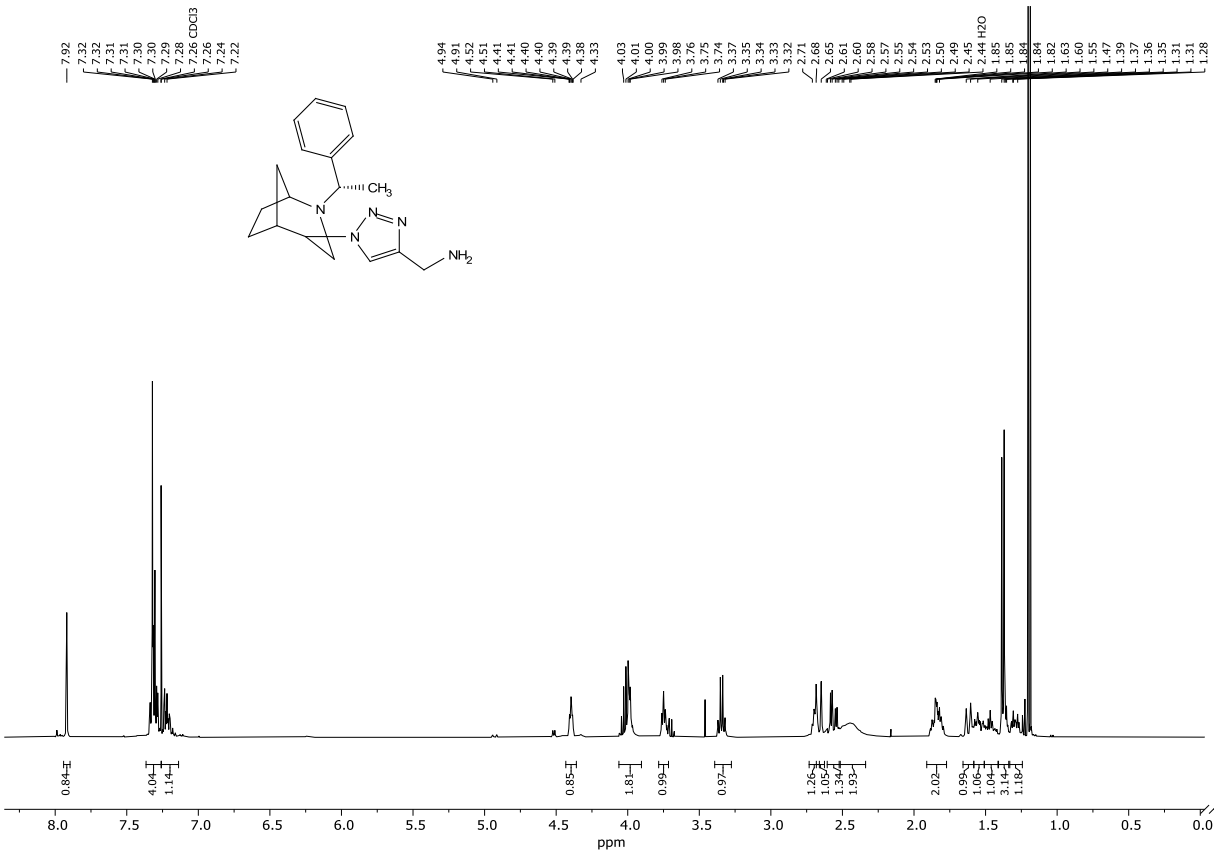
^{1}H-NMR (600 MHz, $CDCl_3$) of **10**



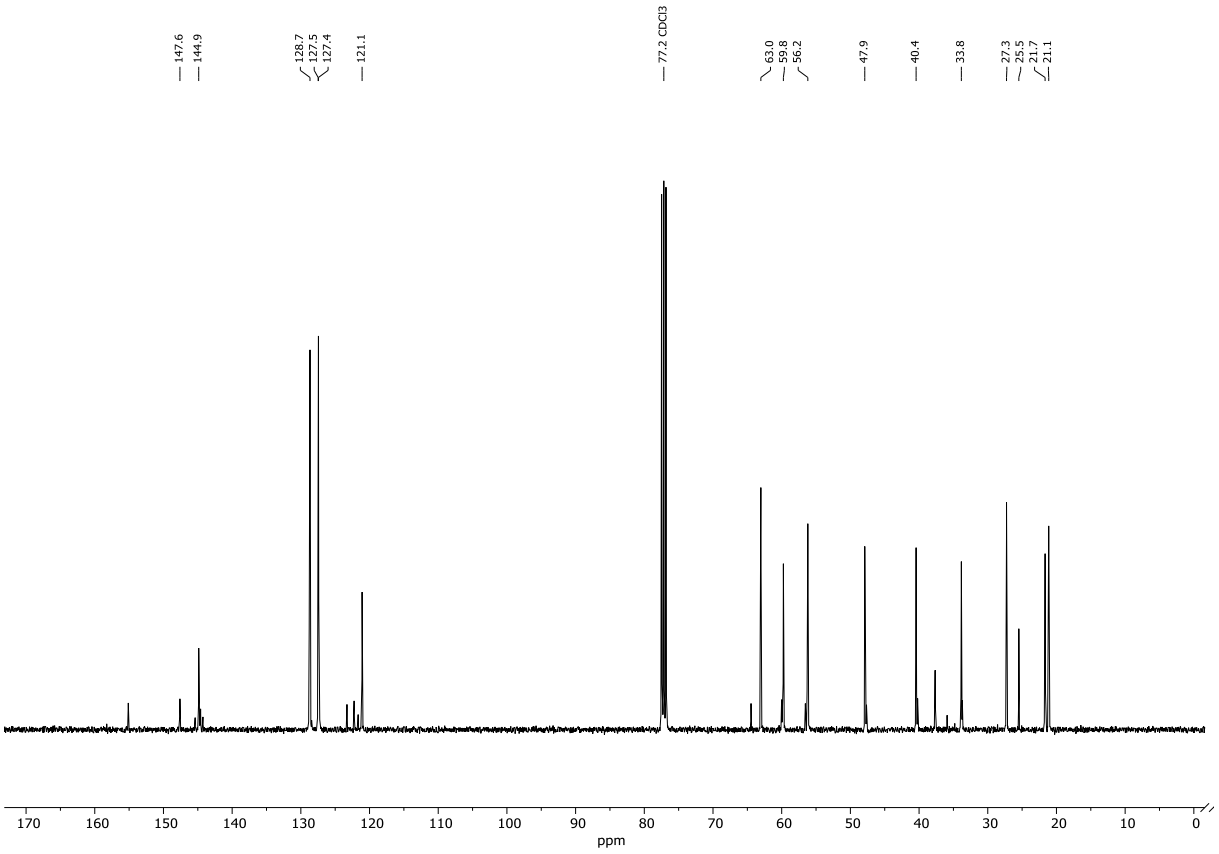
^{13}C-NMR (151 MHz, $CDCl_3$) of **10**



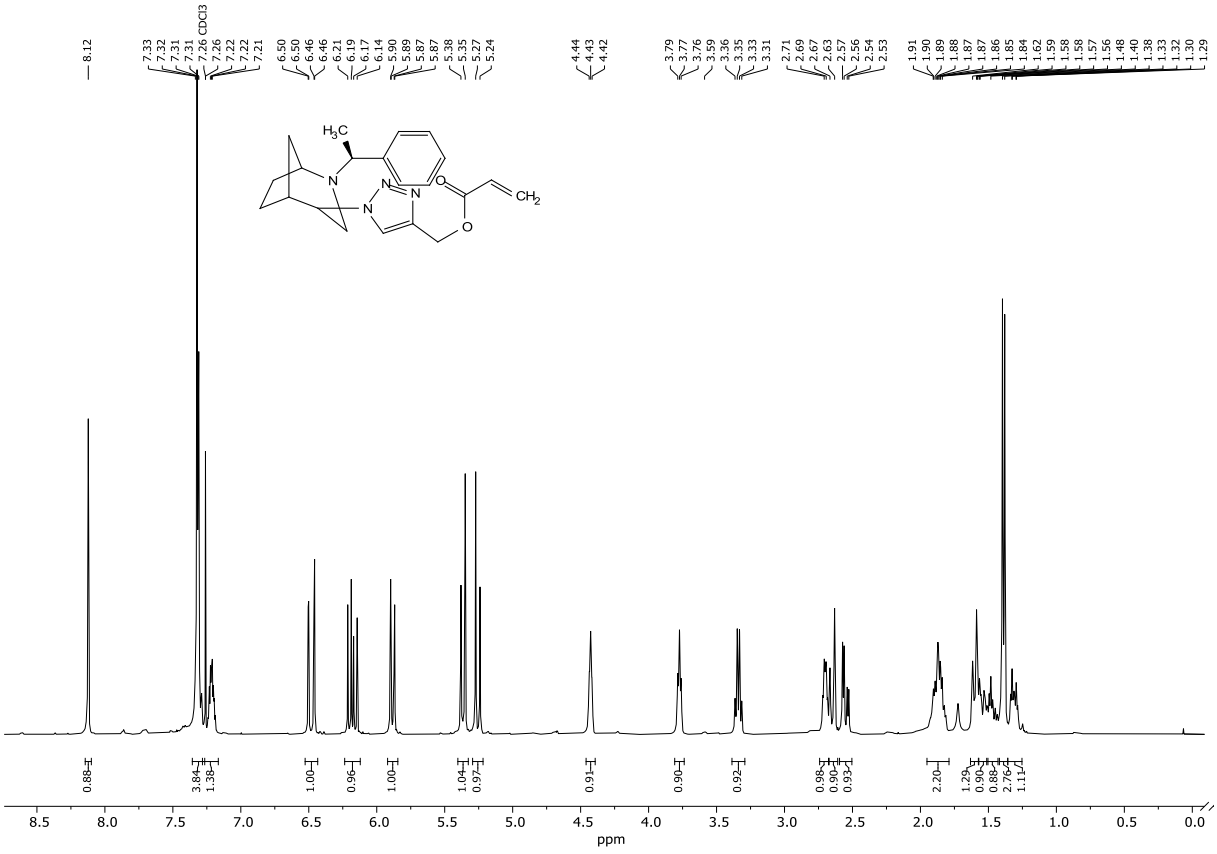
^{1}H-NMR (400 MHz, $CDCl_3$) of **11**



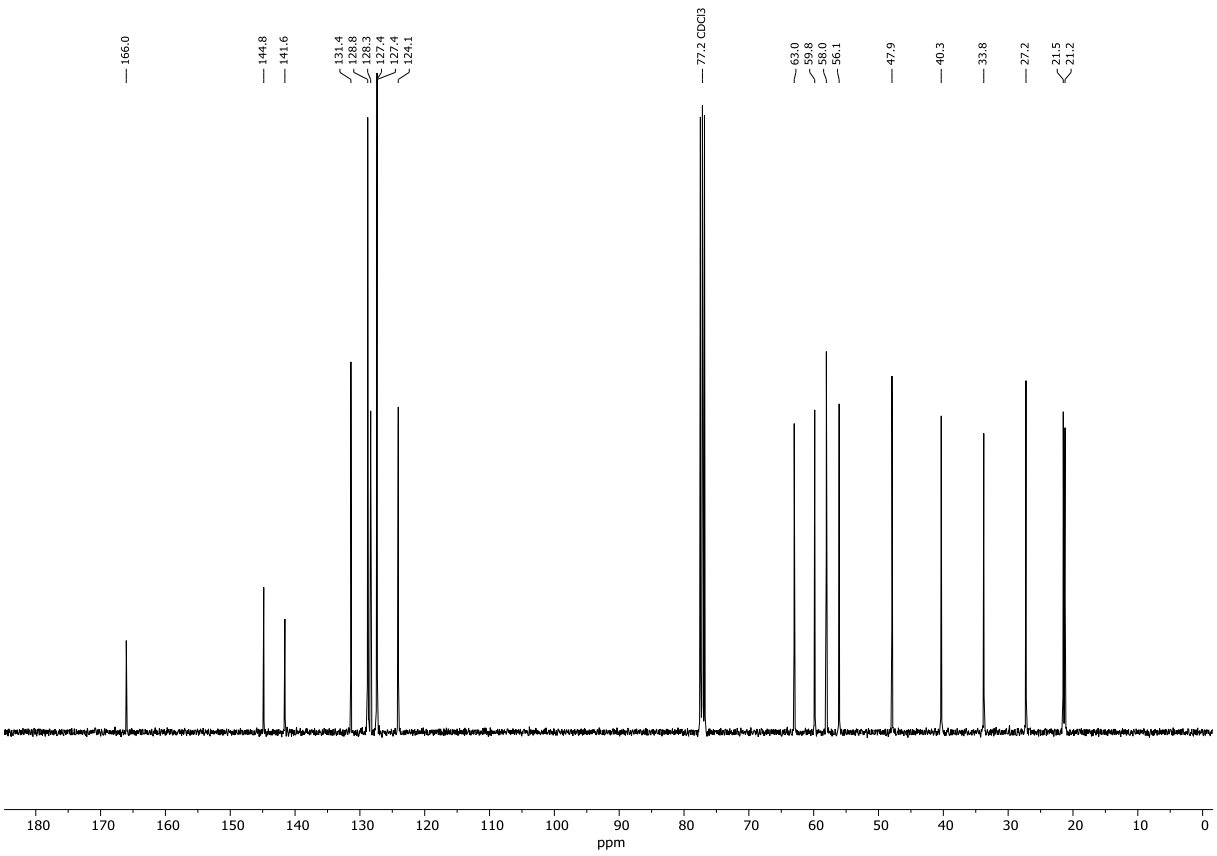
^{13}C-NMR (100 MHz, $CDCl_3$) of **11**



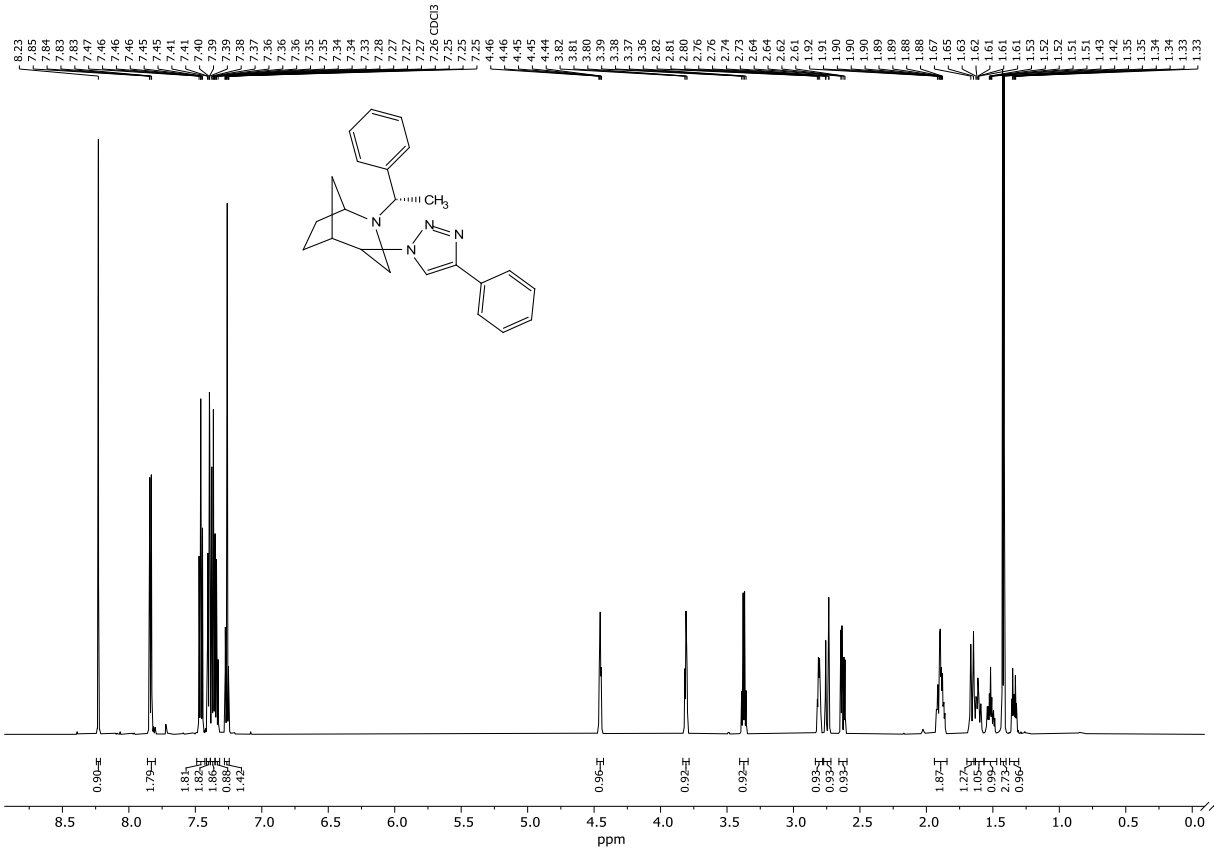
^{1}H-NMR (400 MHz, $CDCl_3$) of **12**



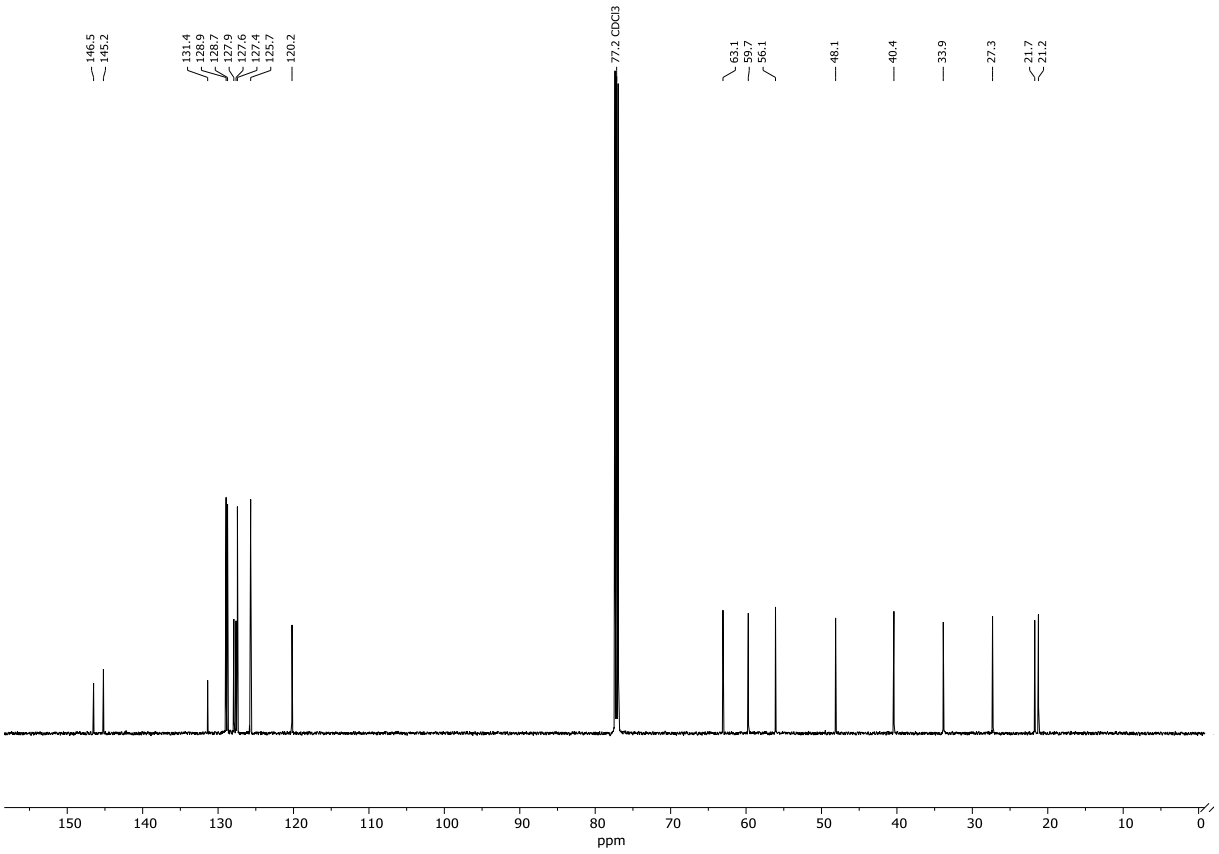
^{13}C-NMR (100 MHz, $CDCl_3$) of **12**



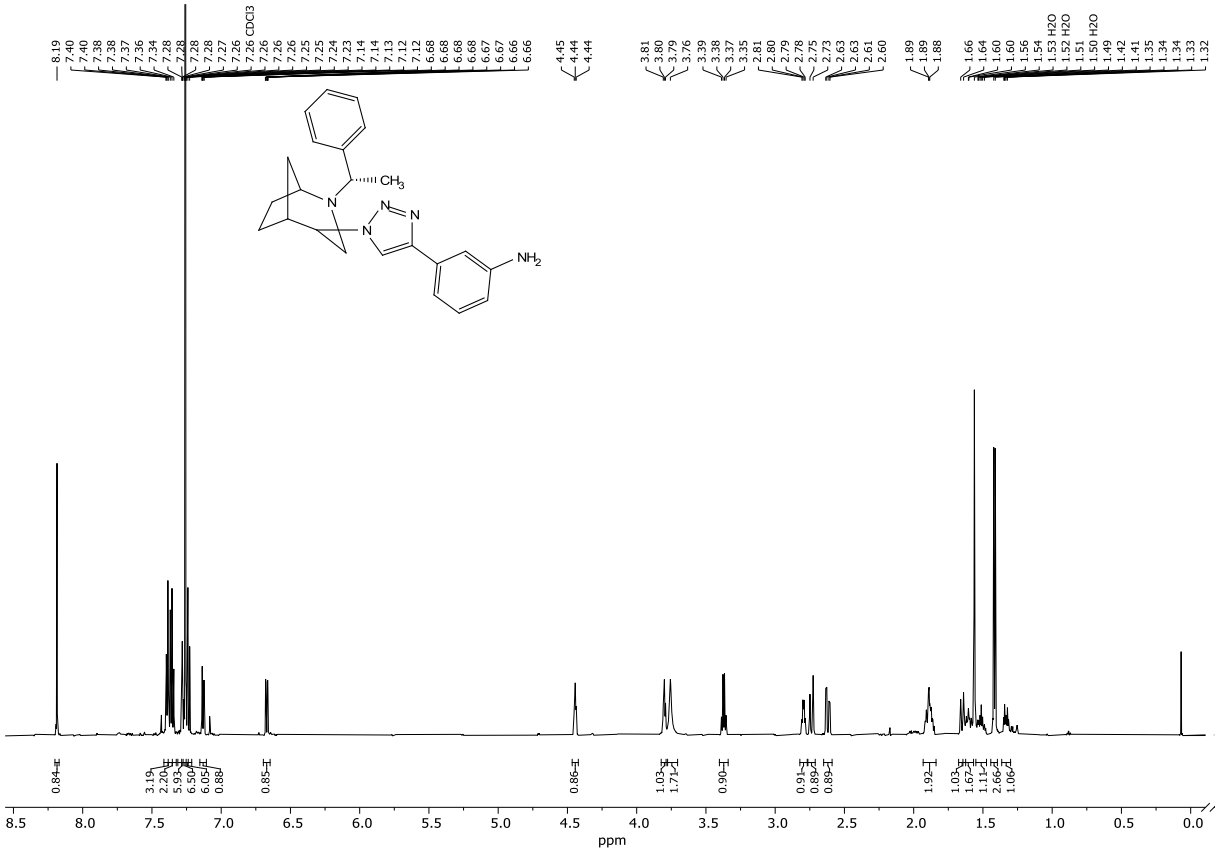
^{1}H-NMR (600 MHz, $CDCl_3$) of **13**



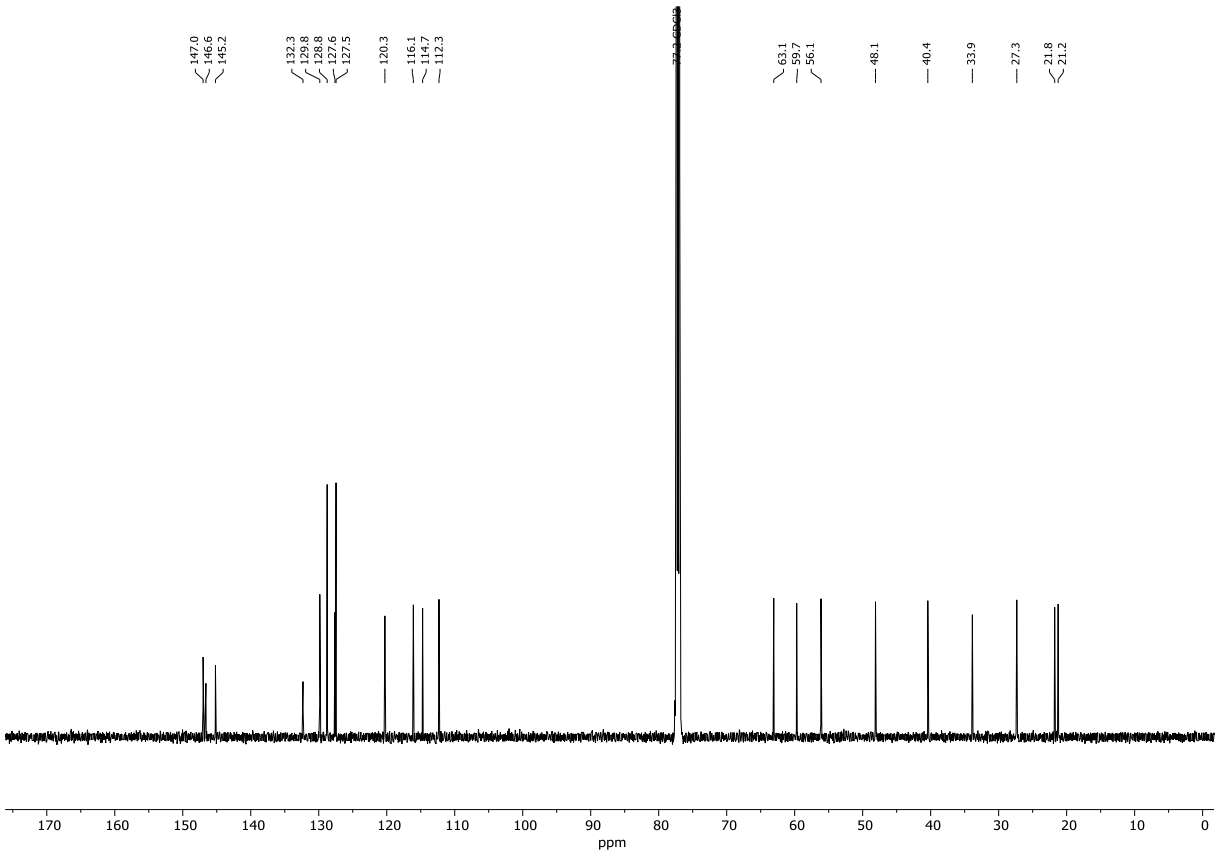
^{13}C-NMR (151 MHz, $CDCl_3$) of **13**



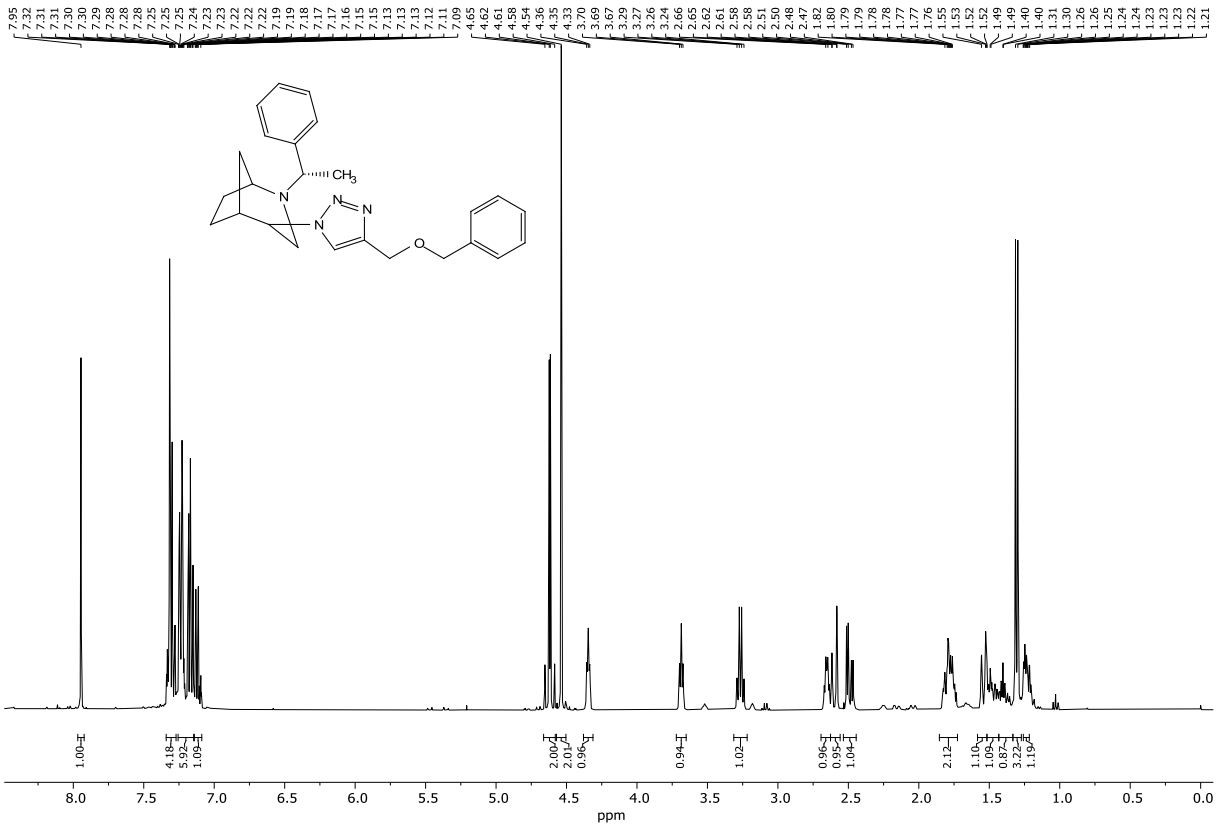
^{1}H-NMR (600 MHz, $CDCl_3$) of **14**



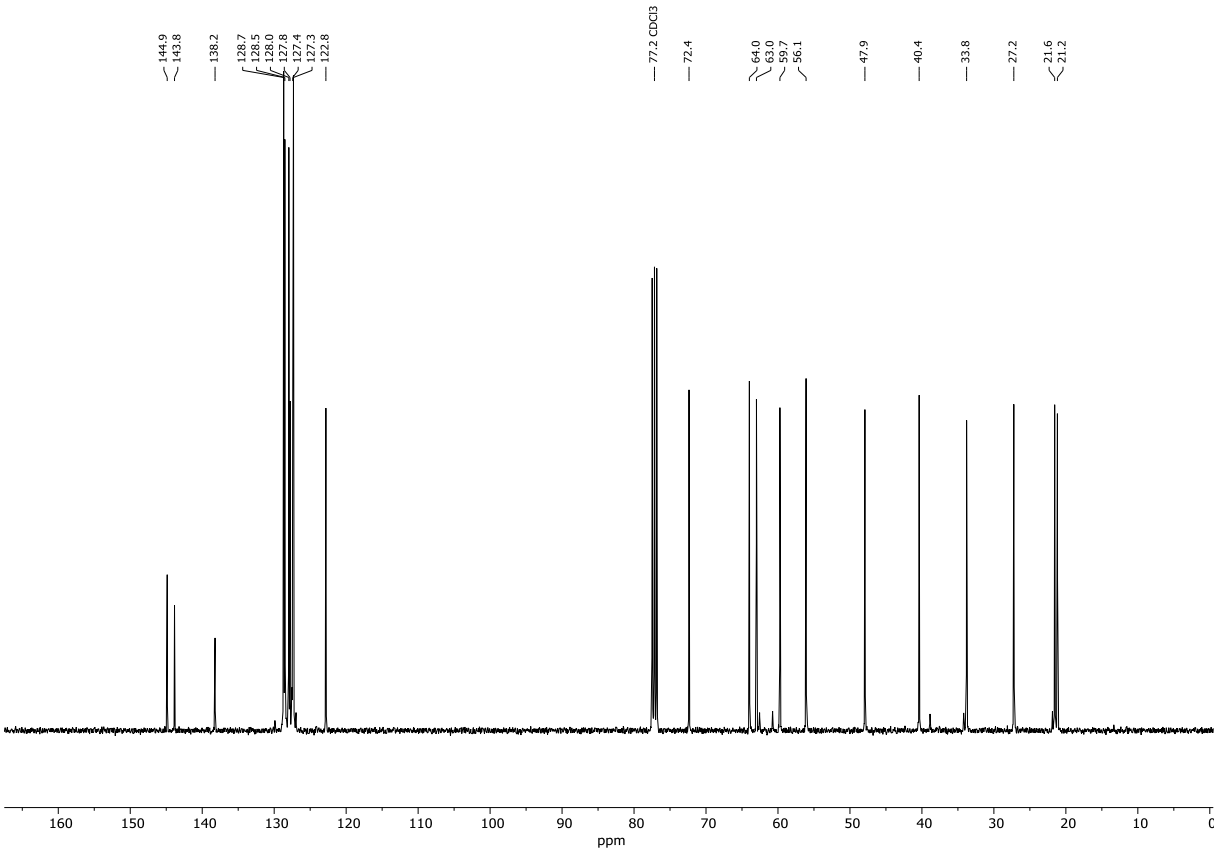
^{13}C-NMR (151 MHz, $CDCl_3$) of **14**



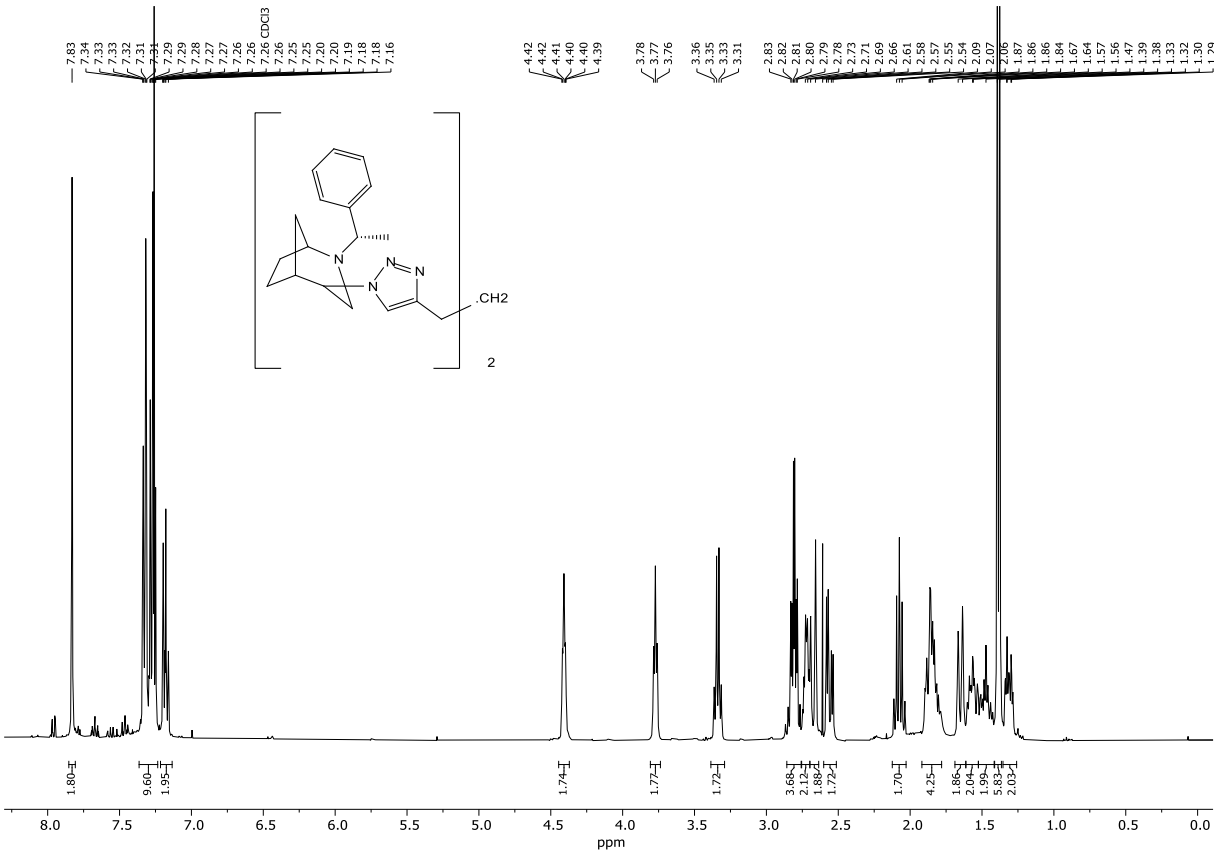
^{1}H-NMR (400 MHz, $CDCl_3$) of **15**



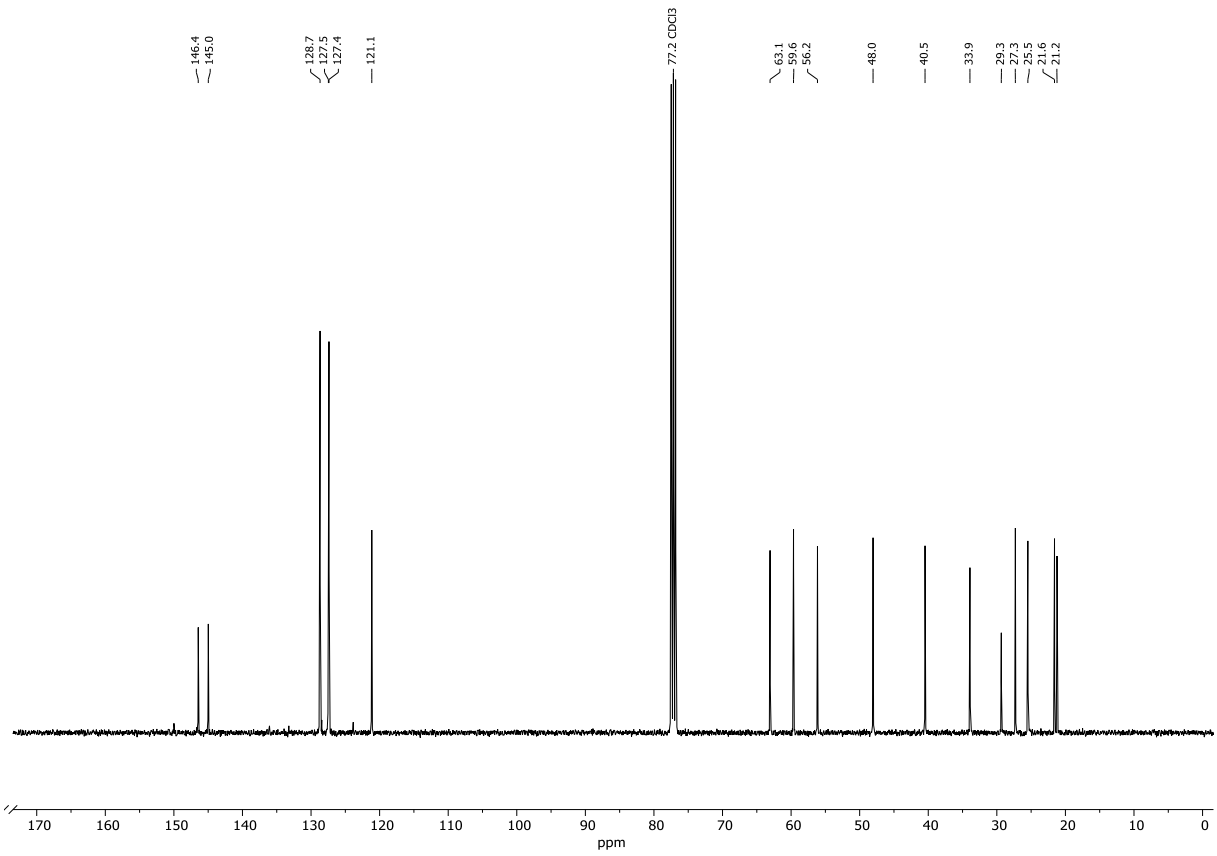
^{13}C-NMR (100 MHz, $CDCl_3$) of **15**



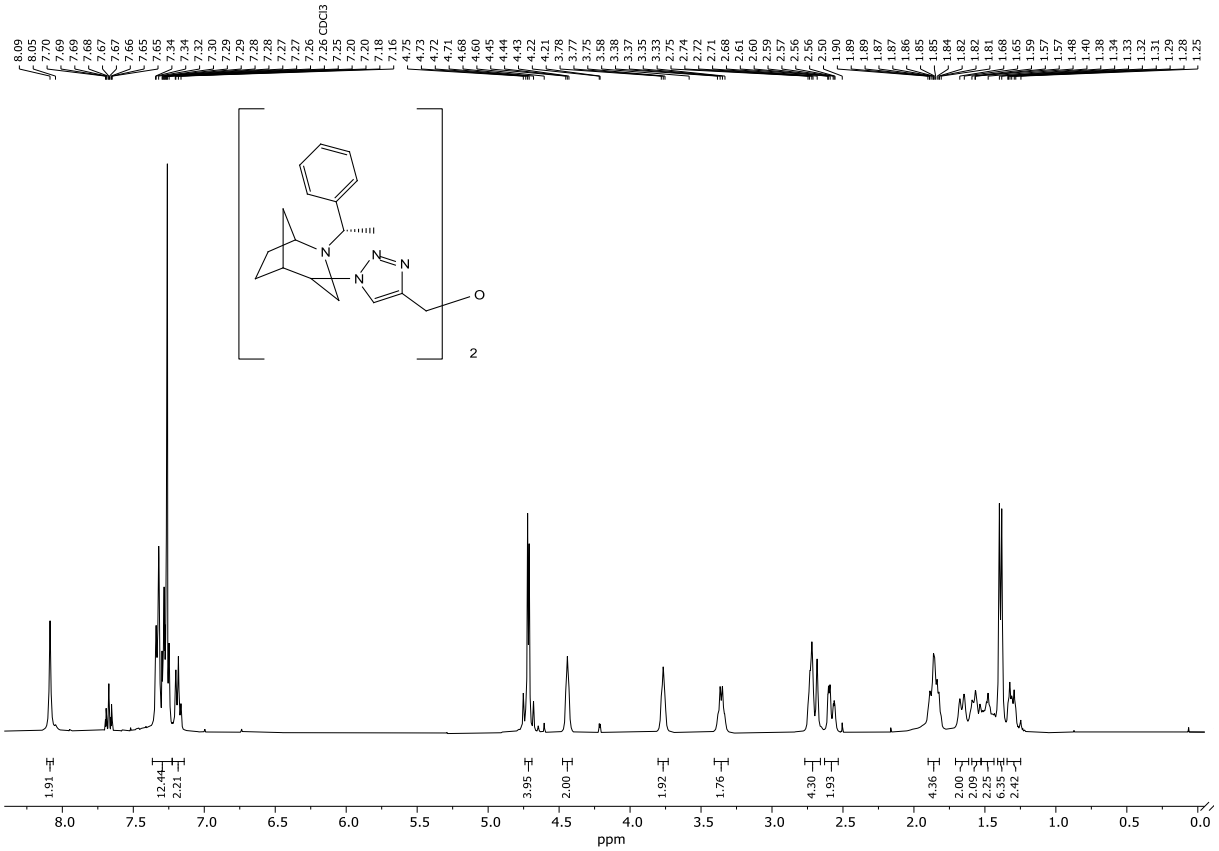
^{1}H-NMR (400 MHz, $CDCl_3$) of **16**



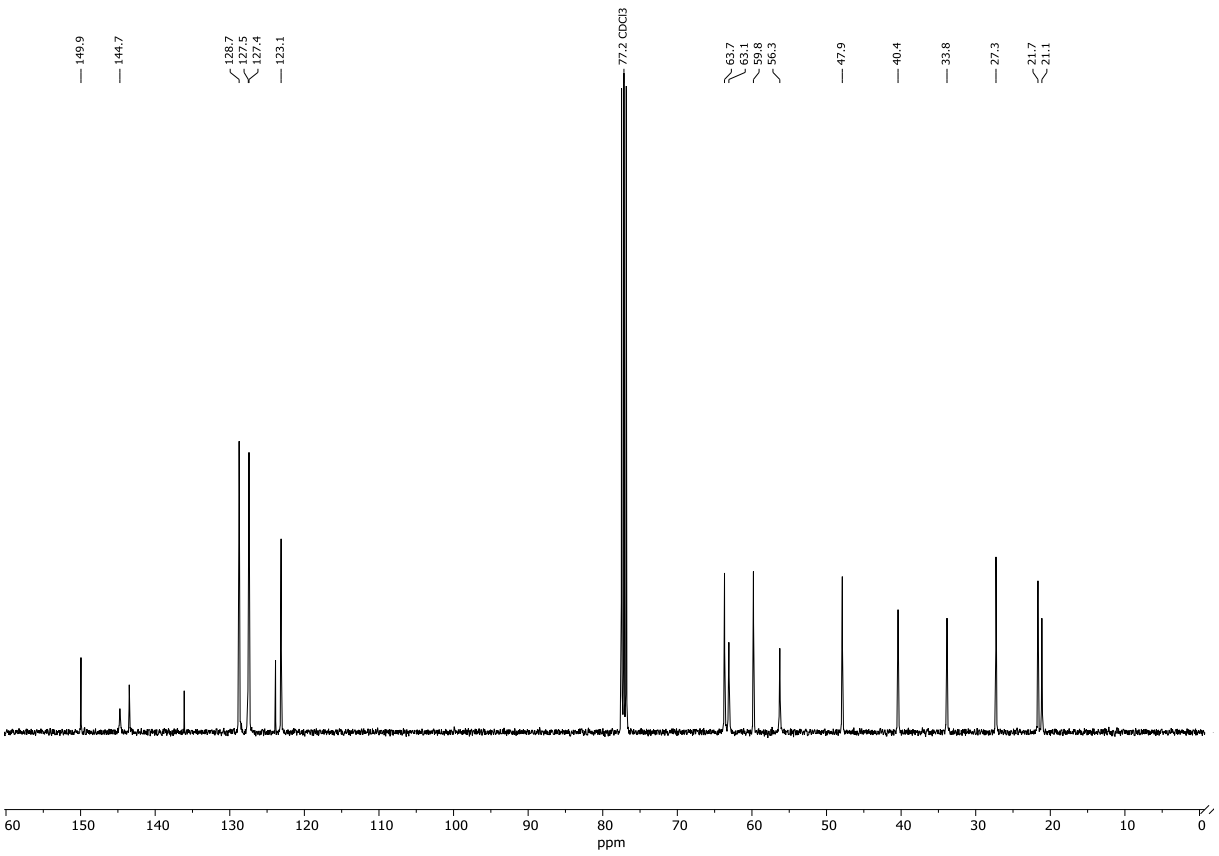
^{13}C-NMR (100 MHz, CDCl3) of **16**



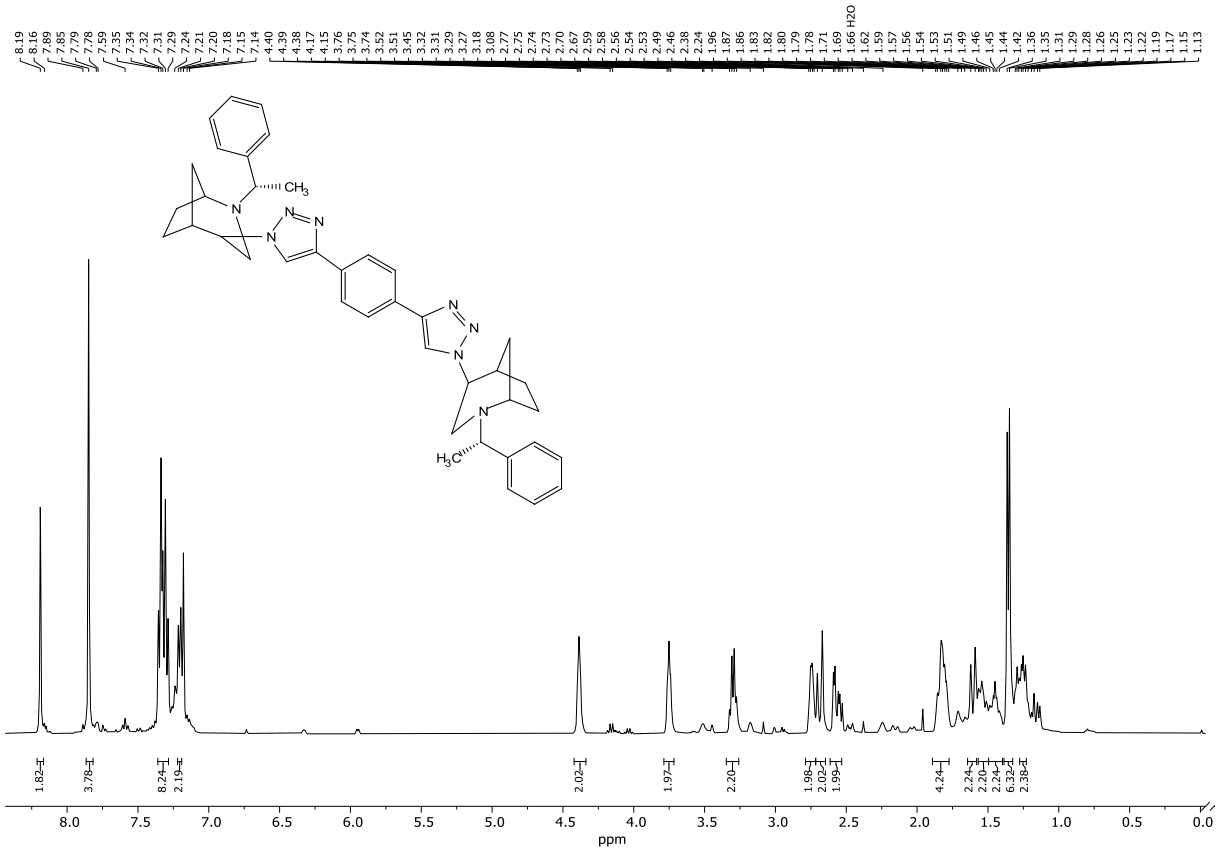
^{1}H-NMR (400 MHz, $CDCl_3$) of **17**



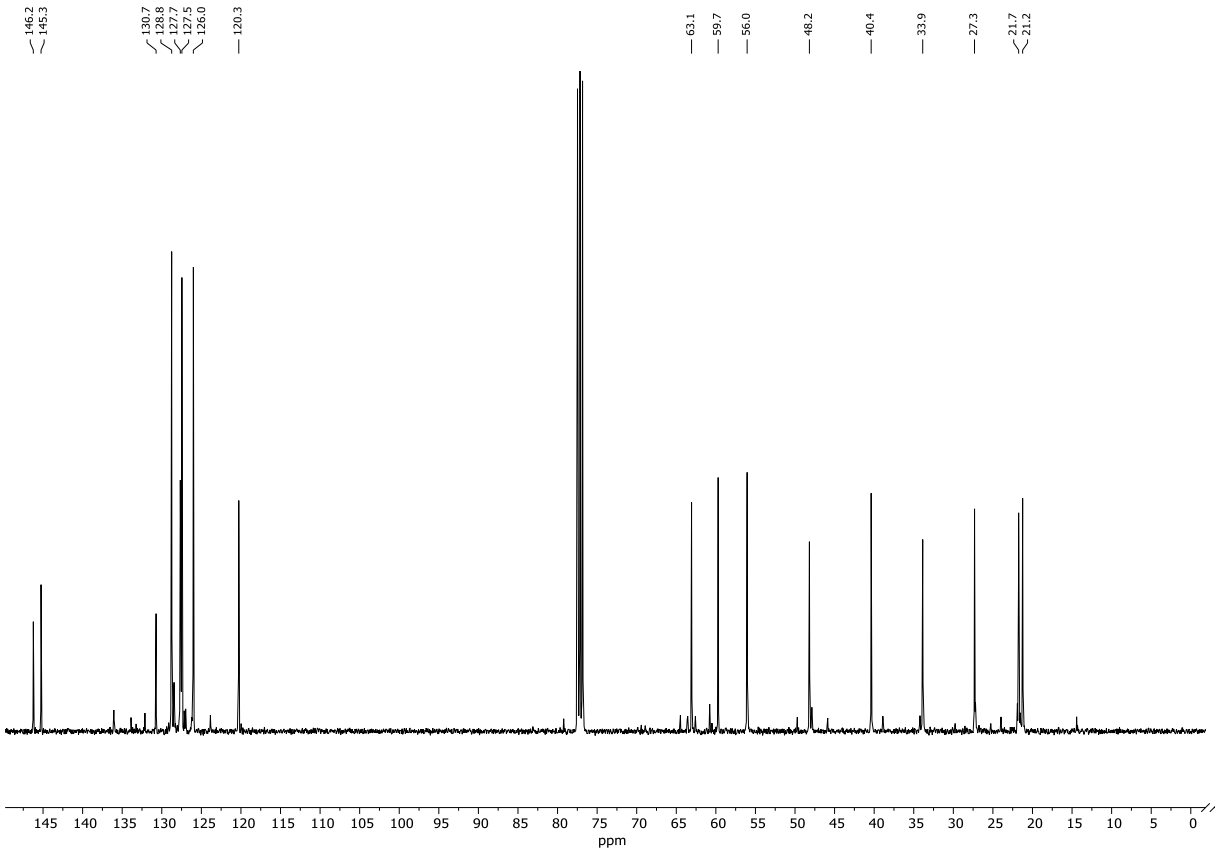
^{13}C-NMR (100 MHz, $CDCl_3$) of **17**



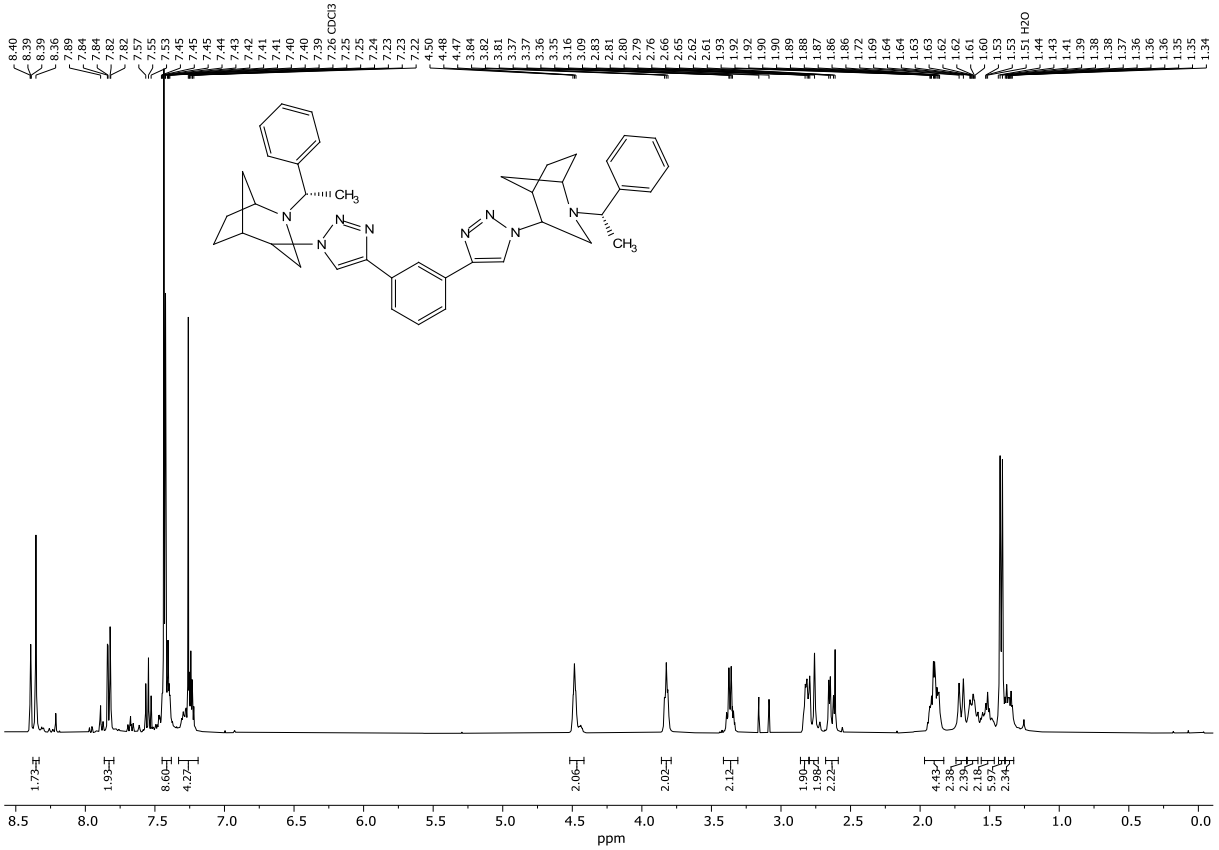
^{1}H-NMR (400 MHz, $CDCl_3$) of **18**



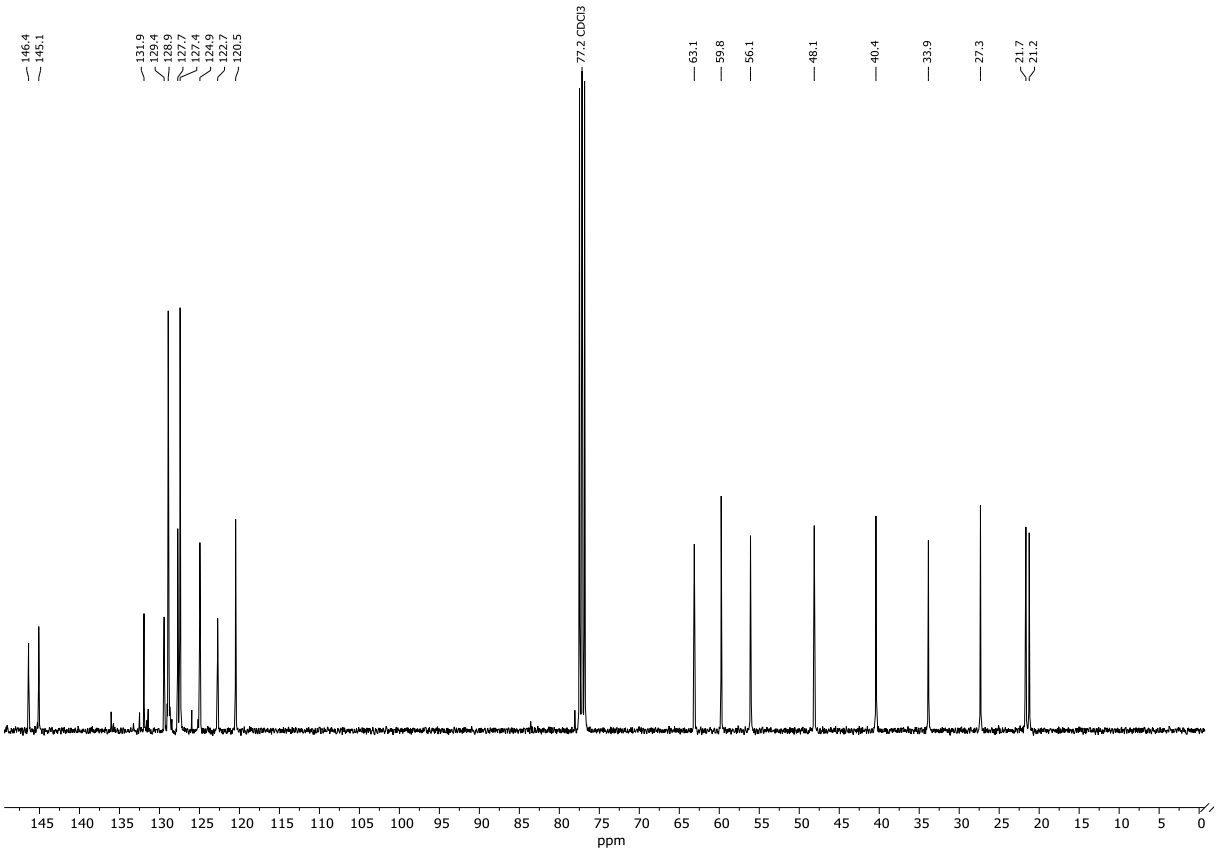
^{13}C-NMR (100 MHz, $CDCl_3$) of **18**



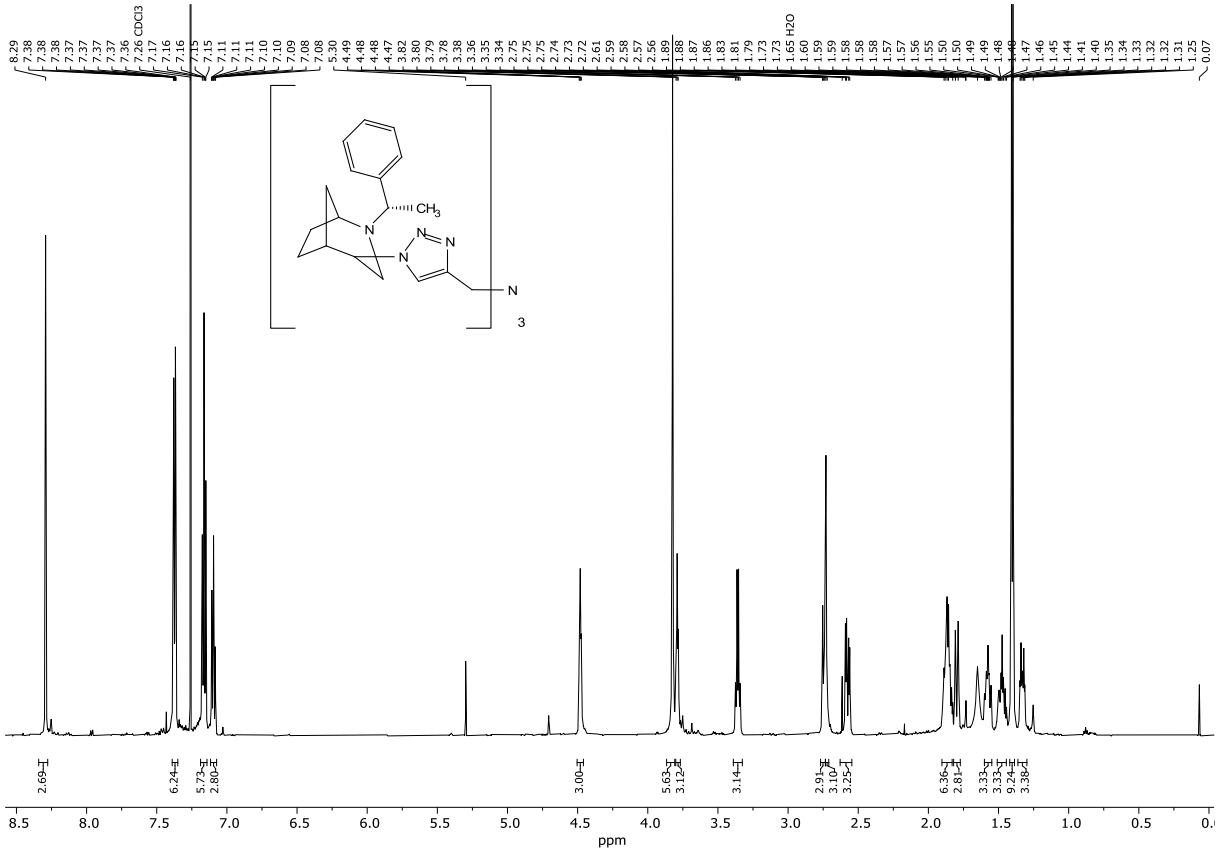
^{1}H-NMR (400 MHz, $CDCl_3$) of **19**



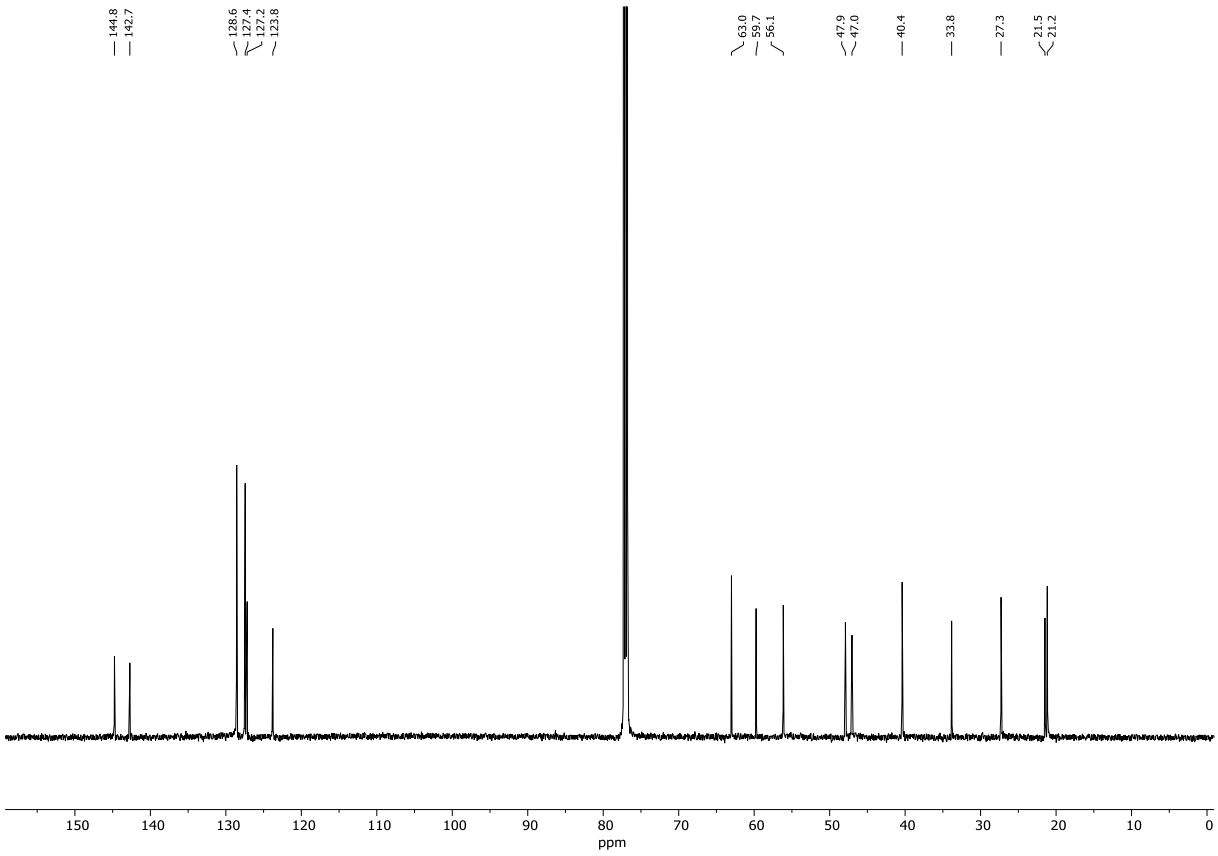
^{13}C-NMR (100 MHz, $CDCl_3$) of **19**



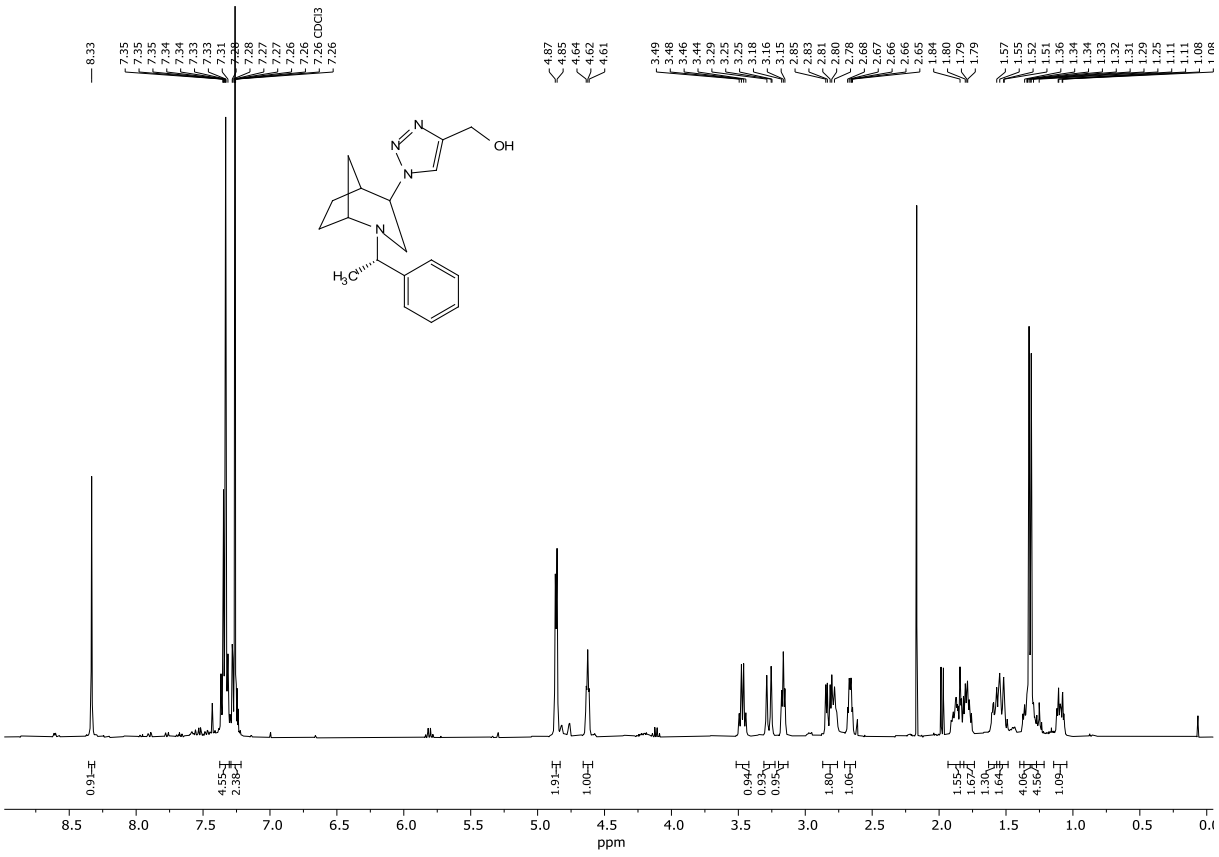
^{1}H-NMR (600 MHz, $CDCl_3$) of **20**



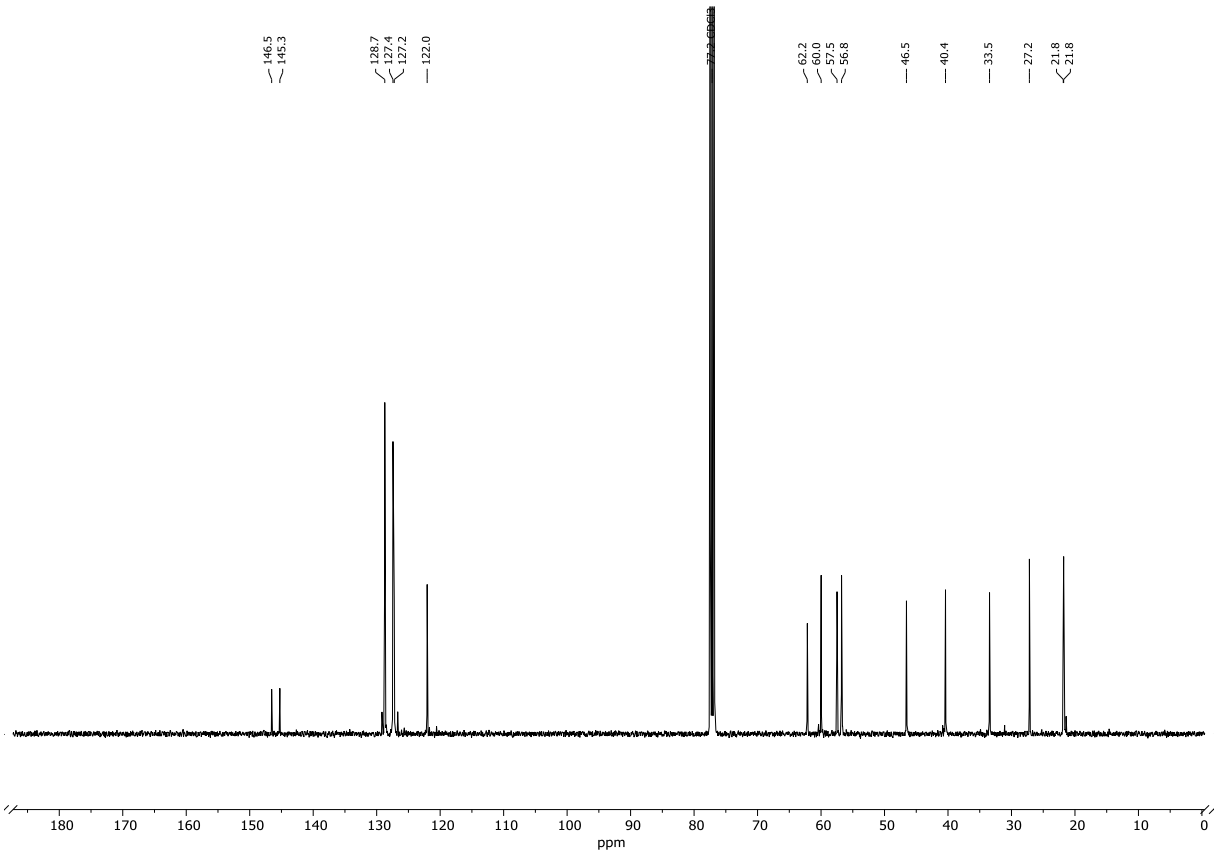
^{13}C-NMR (151 MHz, $CDCl_3$) of **20**



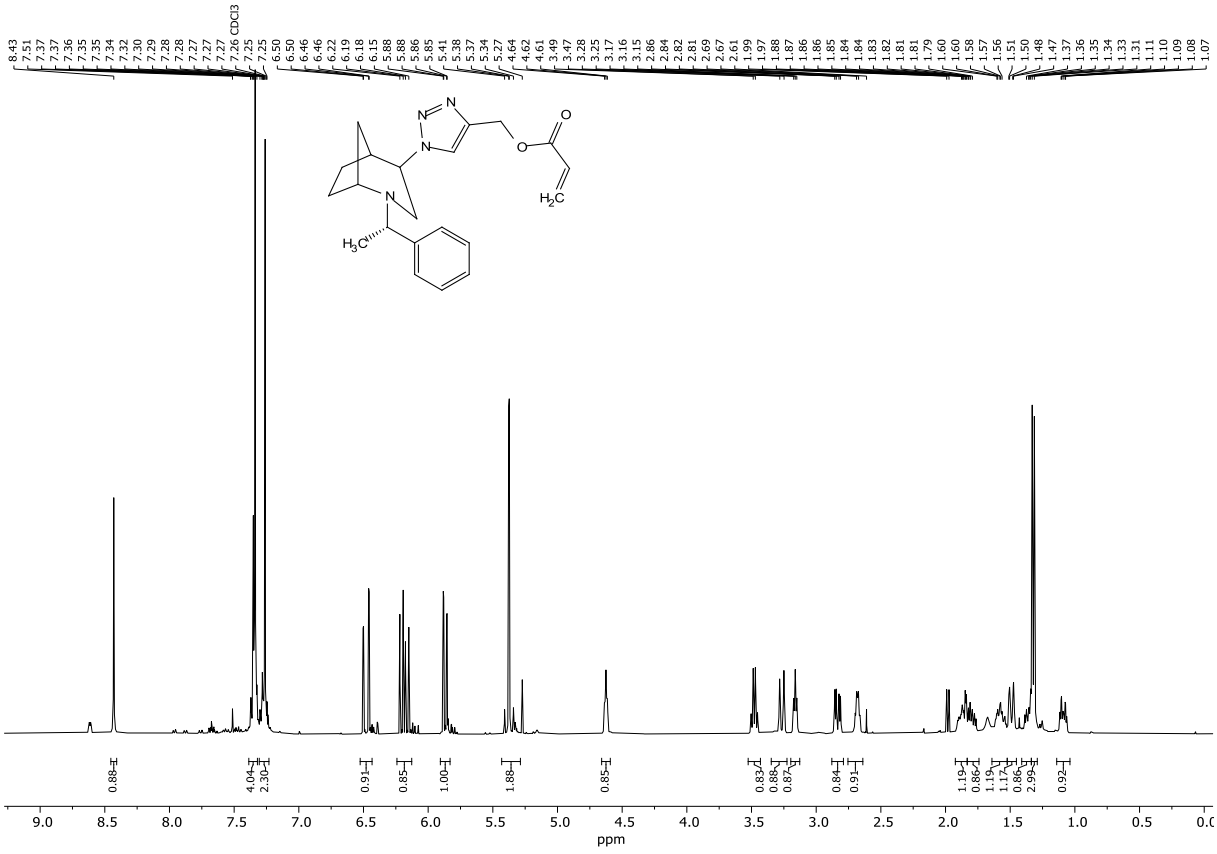
^{1}H-NMR (400 MHz, $CDCl_3$) of **21**



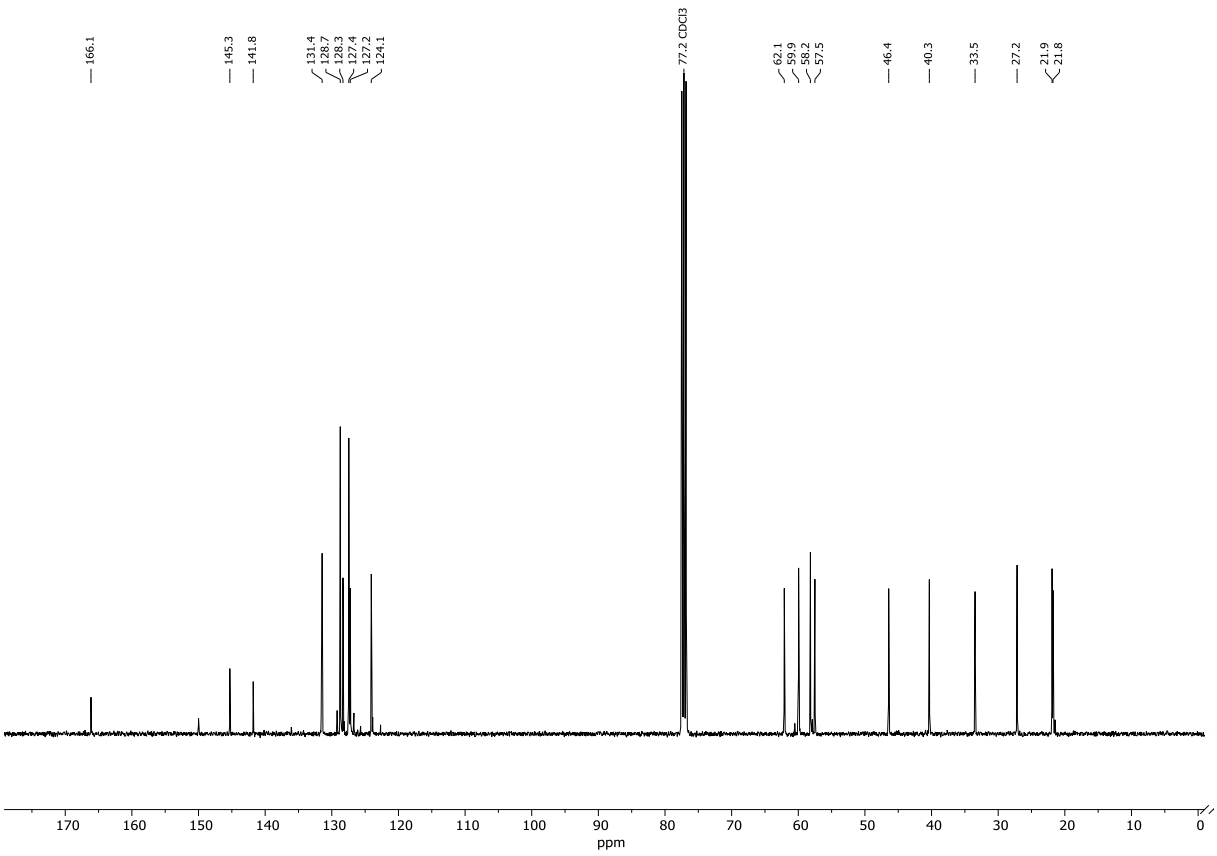
^{13}C-NMR (100 MHz, $CDCl_3$) of **21**



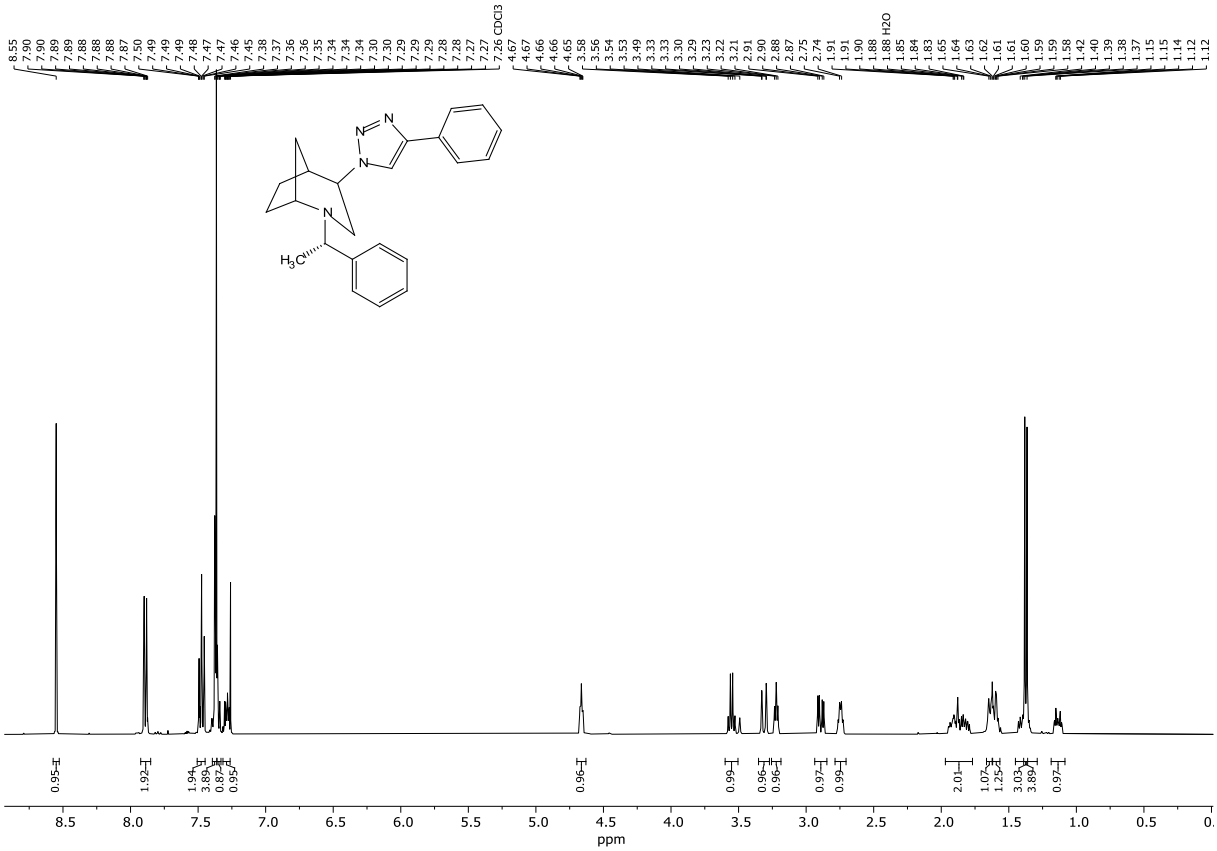
^{1}H-NMR (400 MHz, $CDCl_3$) of **22**



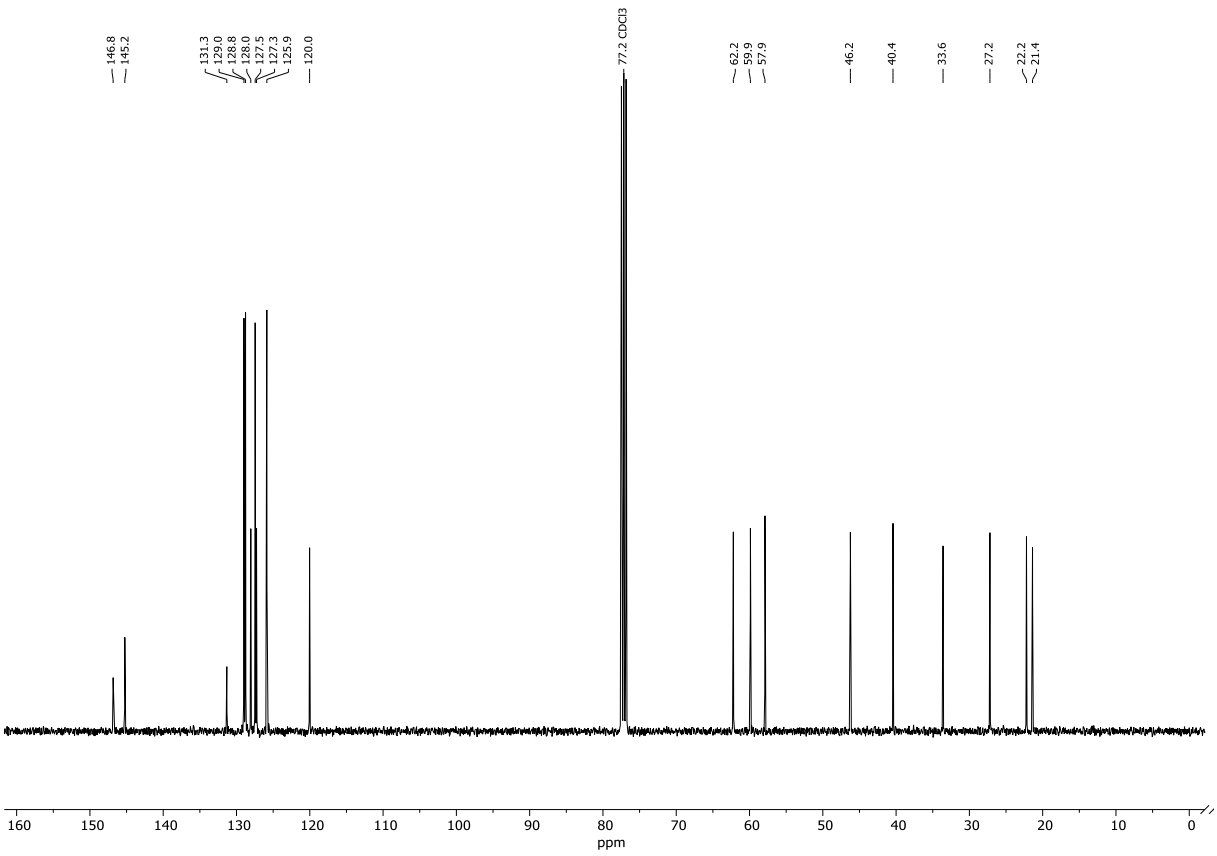
^{13}C-NMR (100 MHz, $CDCl_3$) of **22**



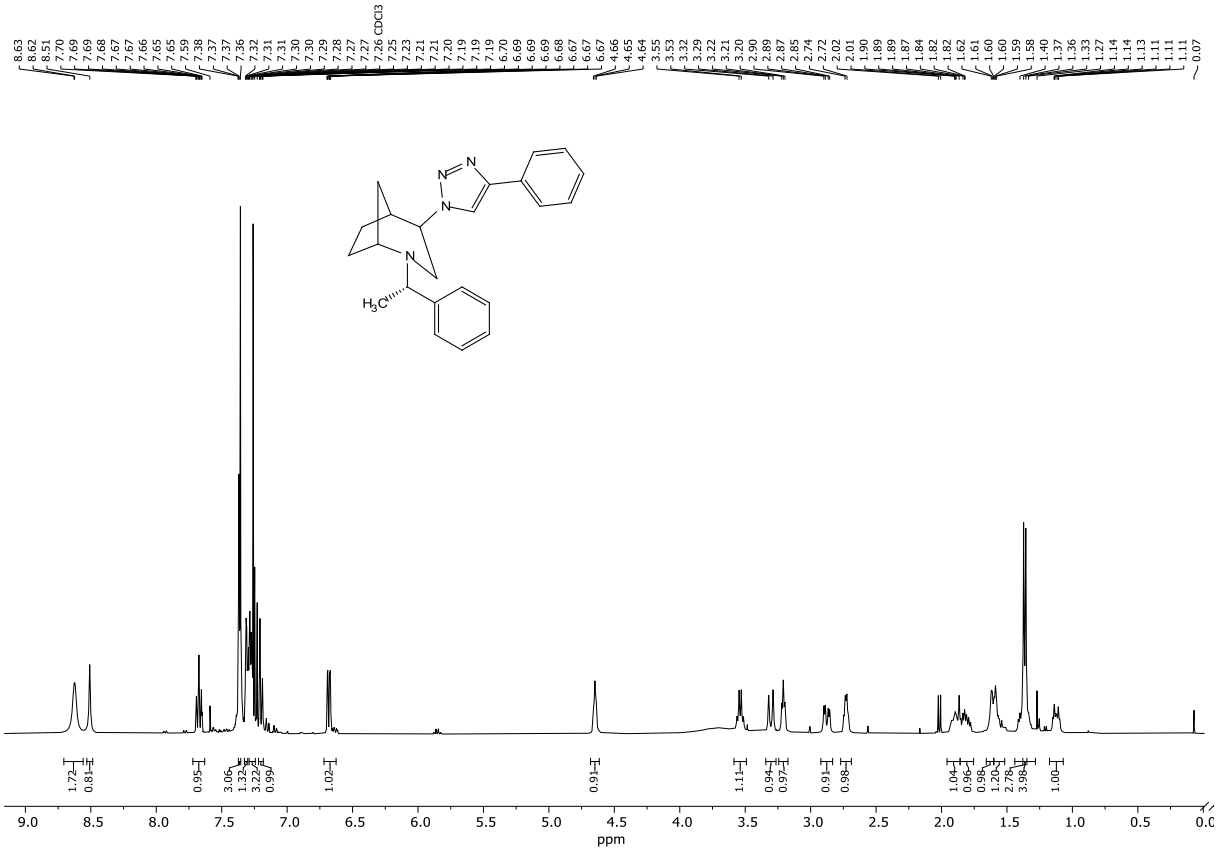
^{1}H-NMR (400 MHz, $CDCl_3$) of **23**



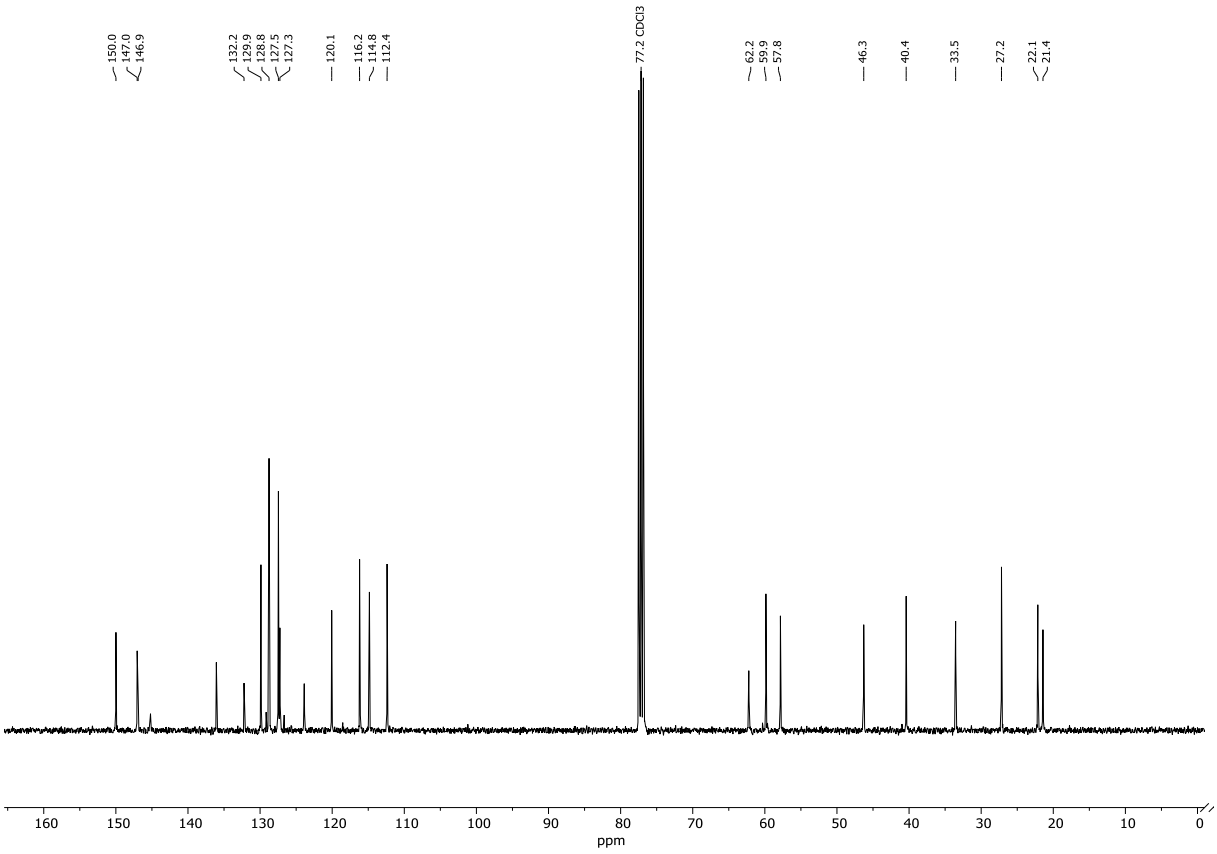
^{13}C-NMR (100 MHz, $CDCl_3$) of **23**



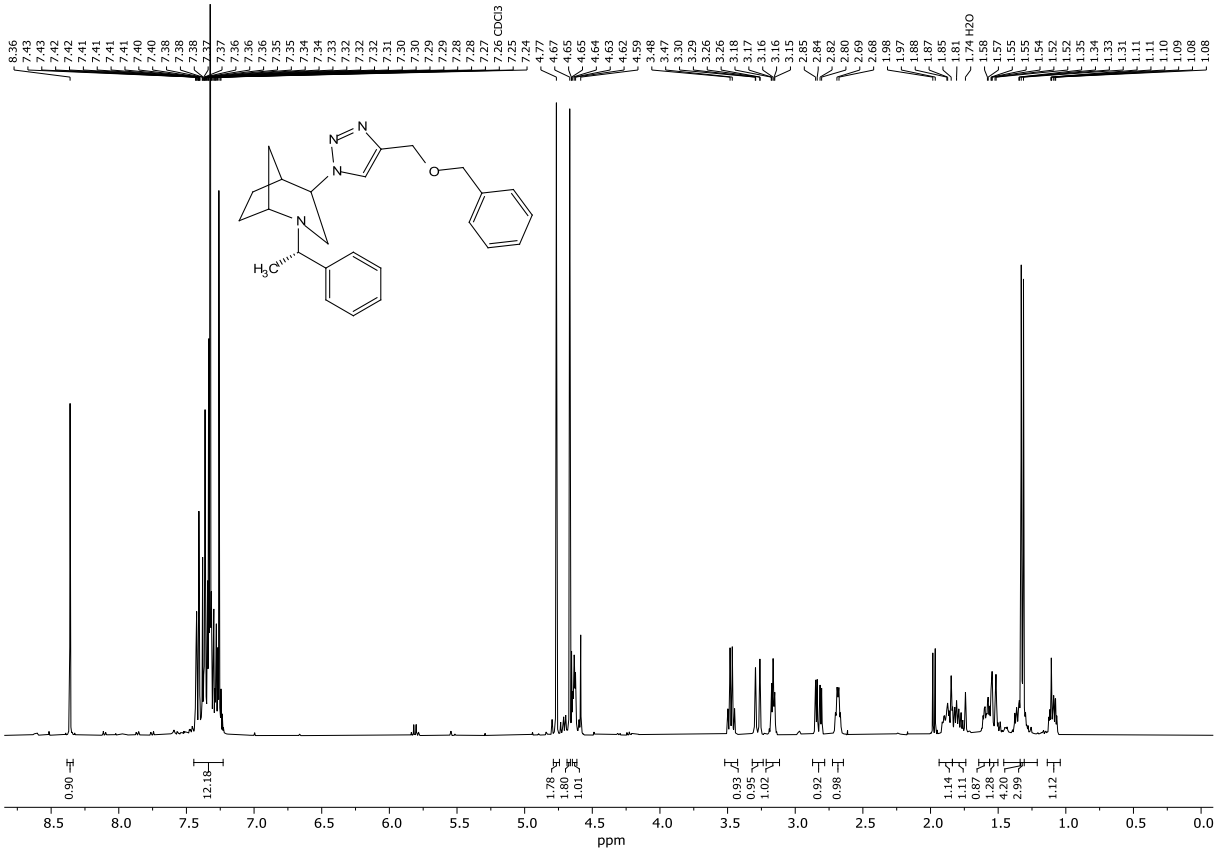
^{1}H-NMR (400 MHz, $CDCl_3$) of **24**



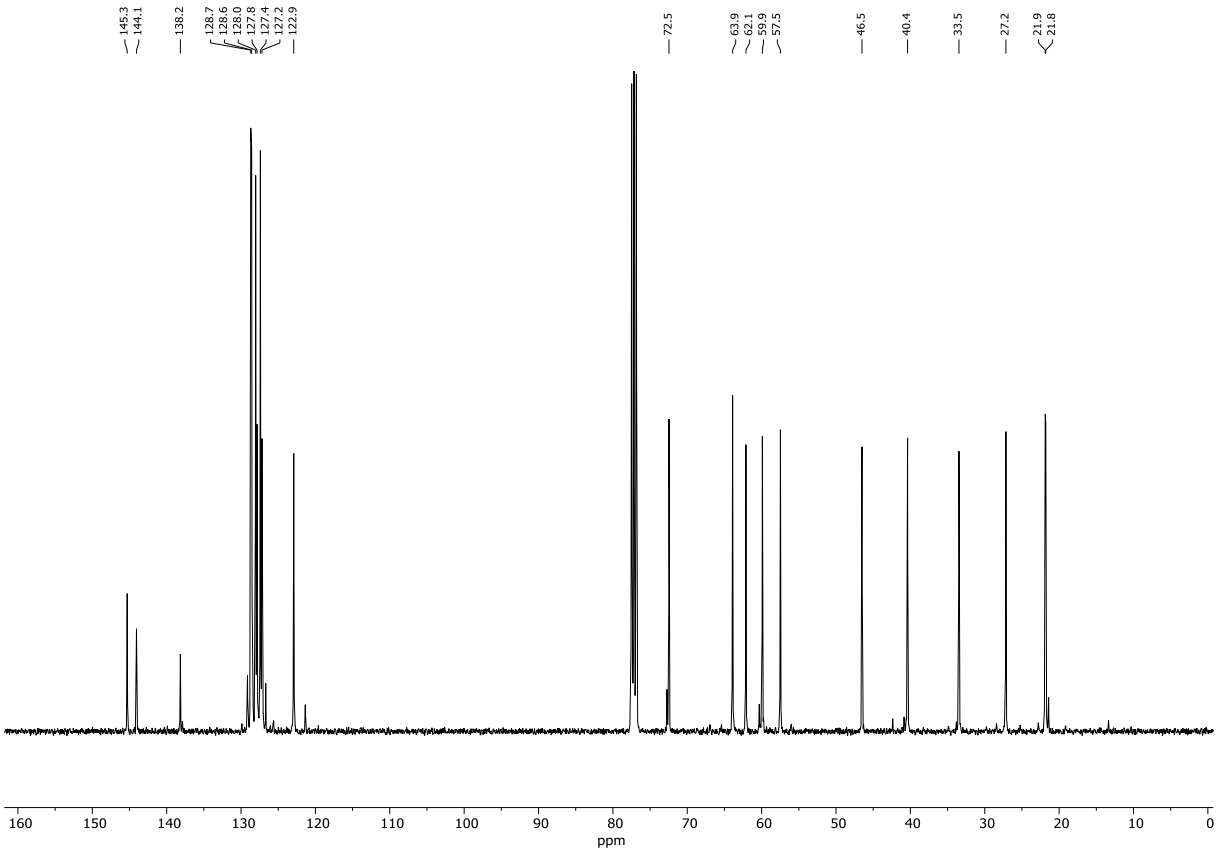
^{13}C-NMR (100 MHz, $CDCl_3$) of **24**



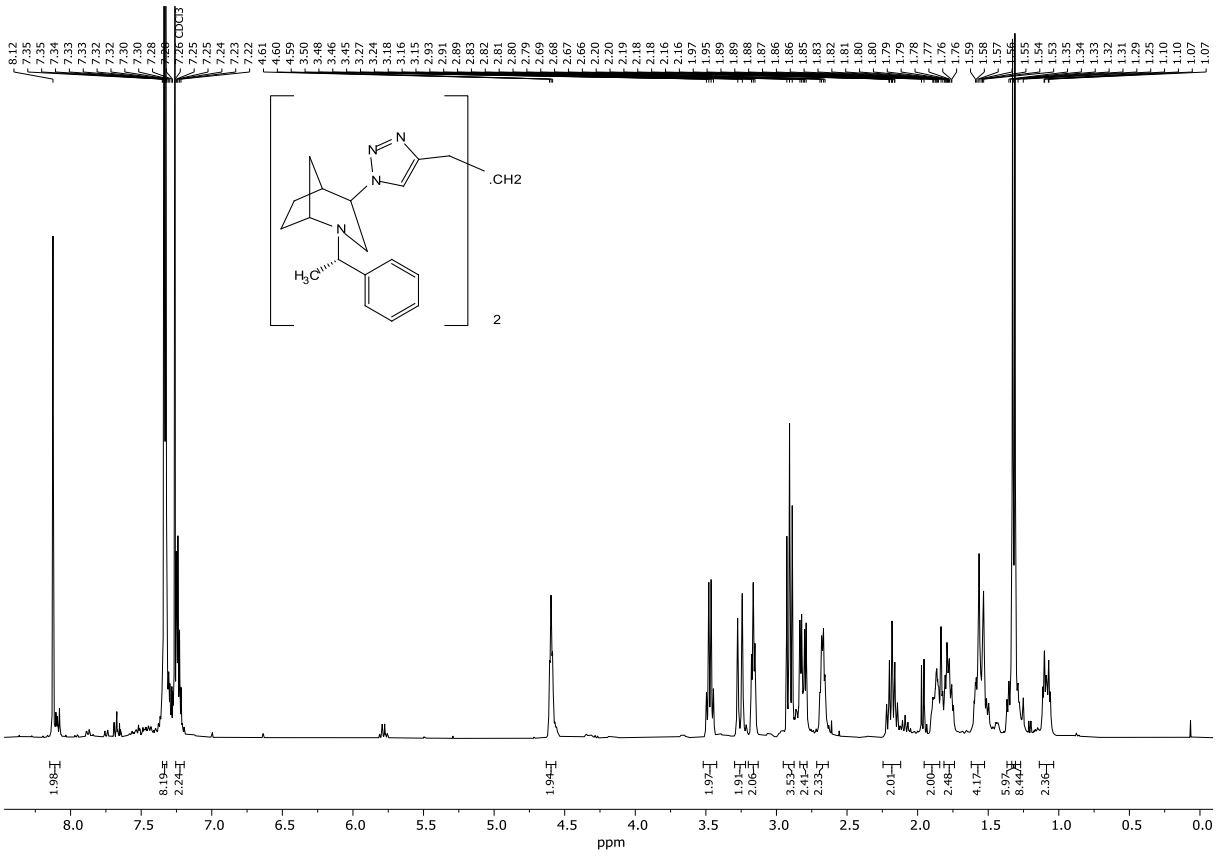
^{1}H-NMR (400 MHz, $CDCl_3$) of **25**



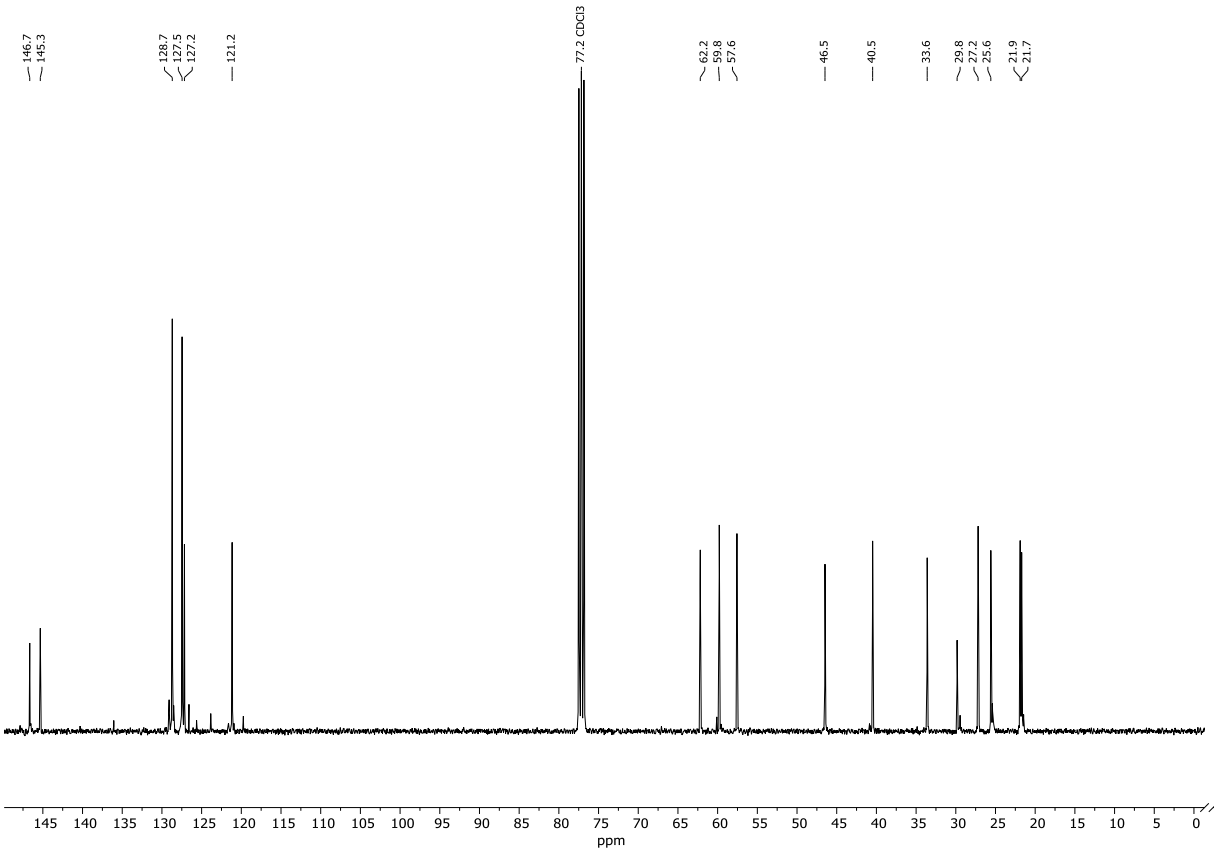
^{13}C-NMR (100 MHz, $CDCl_3$) of **25**



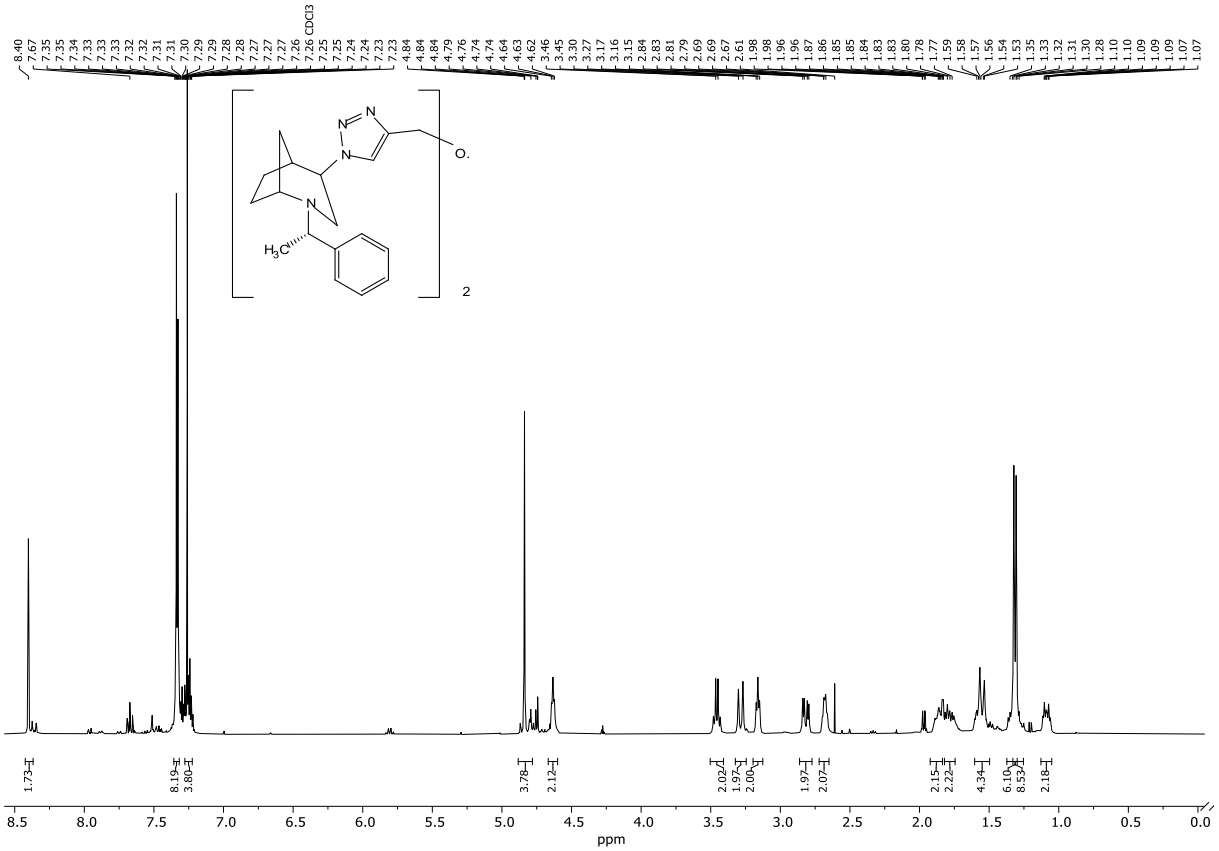
^{1}H-NMR (400 MHz, $CDCl_3$) of **26**



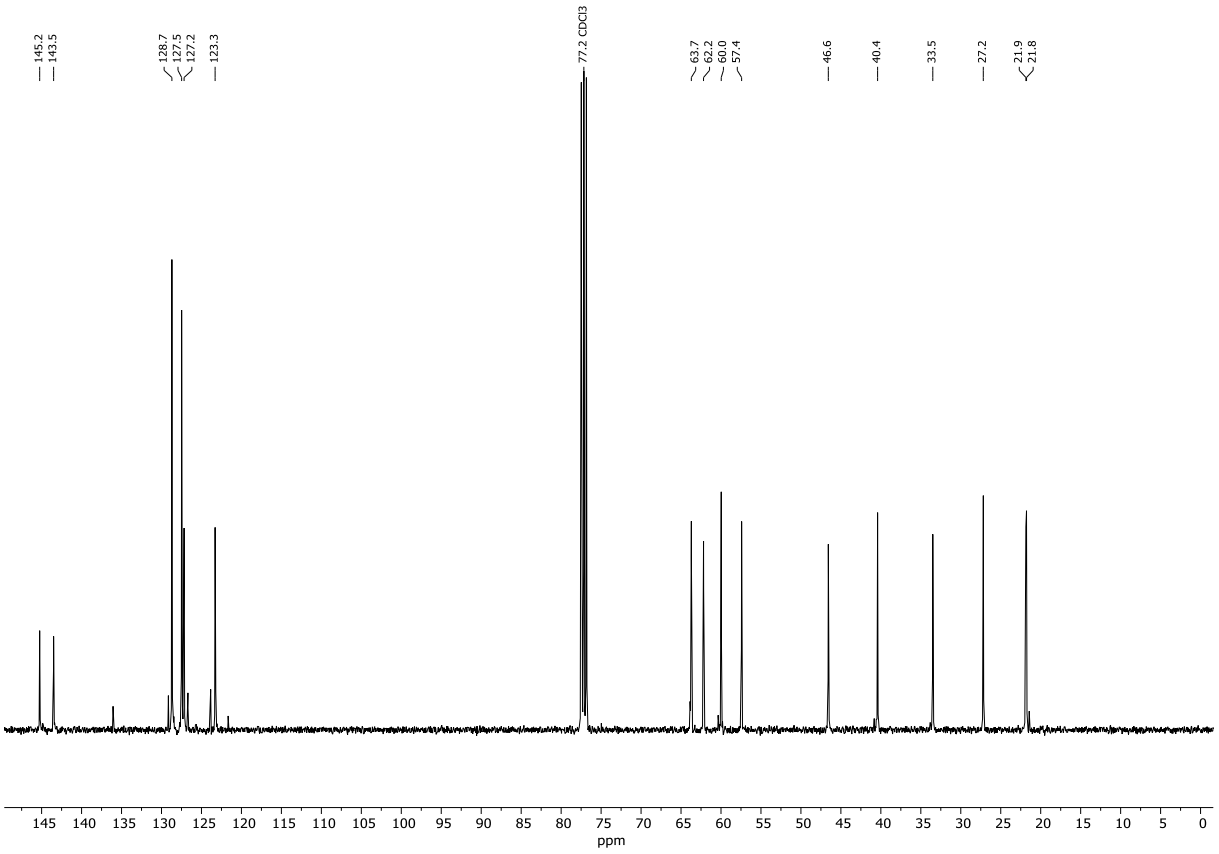
^{13}C-NMR (100 MHz, $CDCl_3$) of **26**



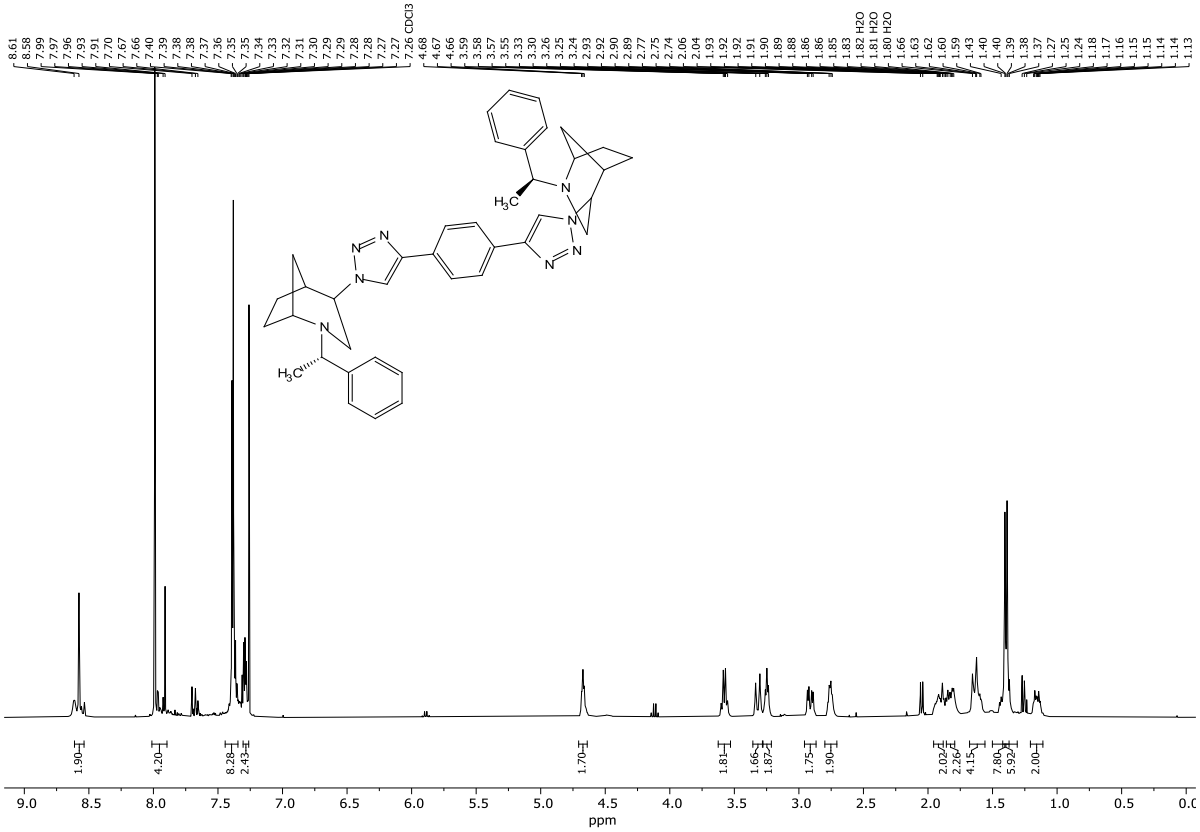
^{1}H-NMR (400 MHz, $CDCl_3$) of **27**



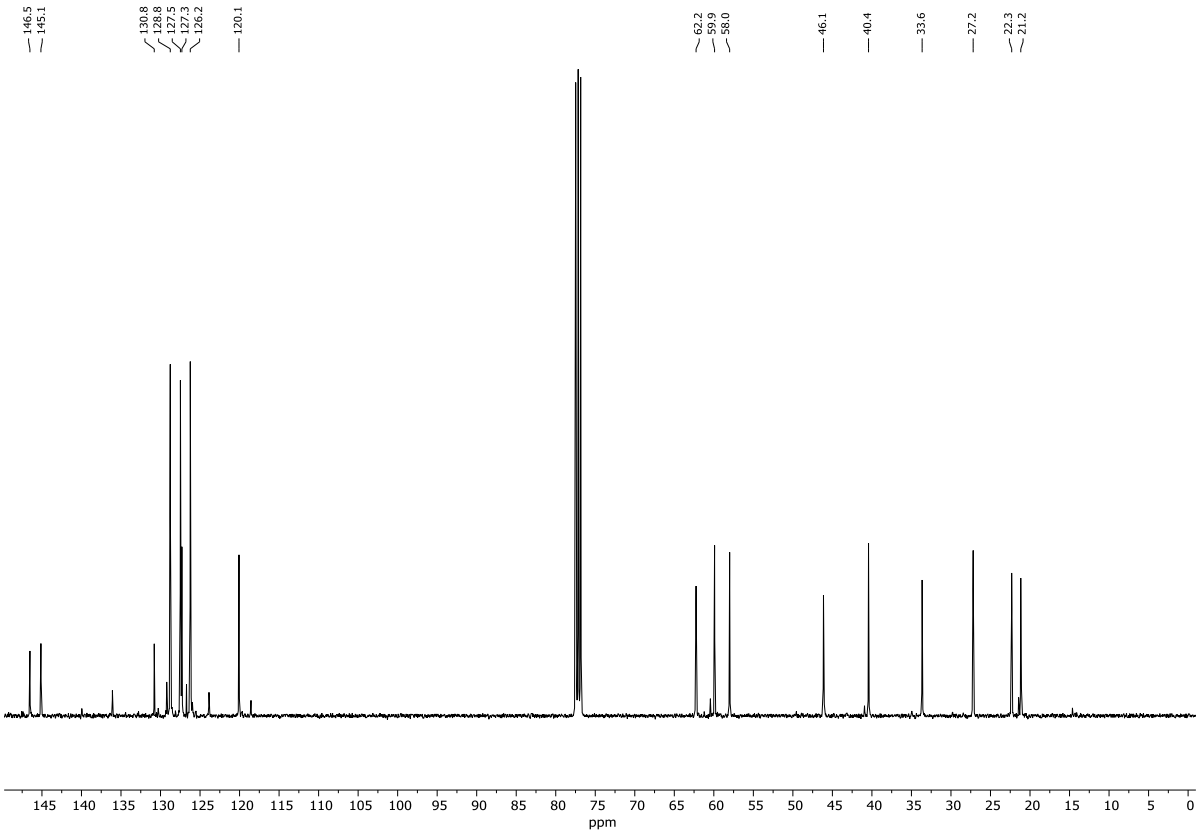
^{13}C-NMR (100 MHz, $CDCl_3$) of **27**



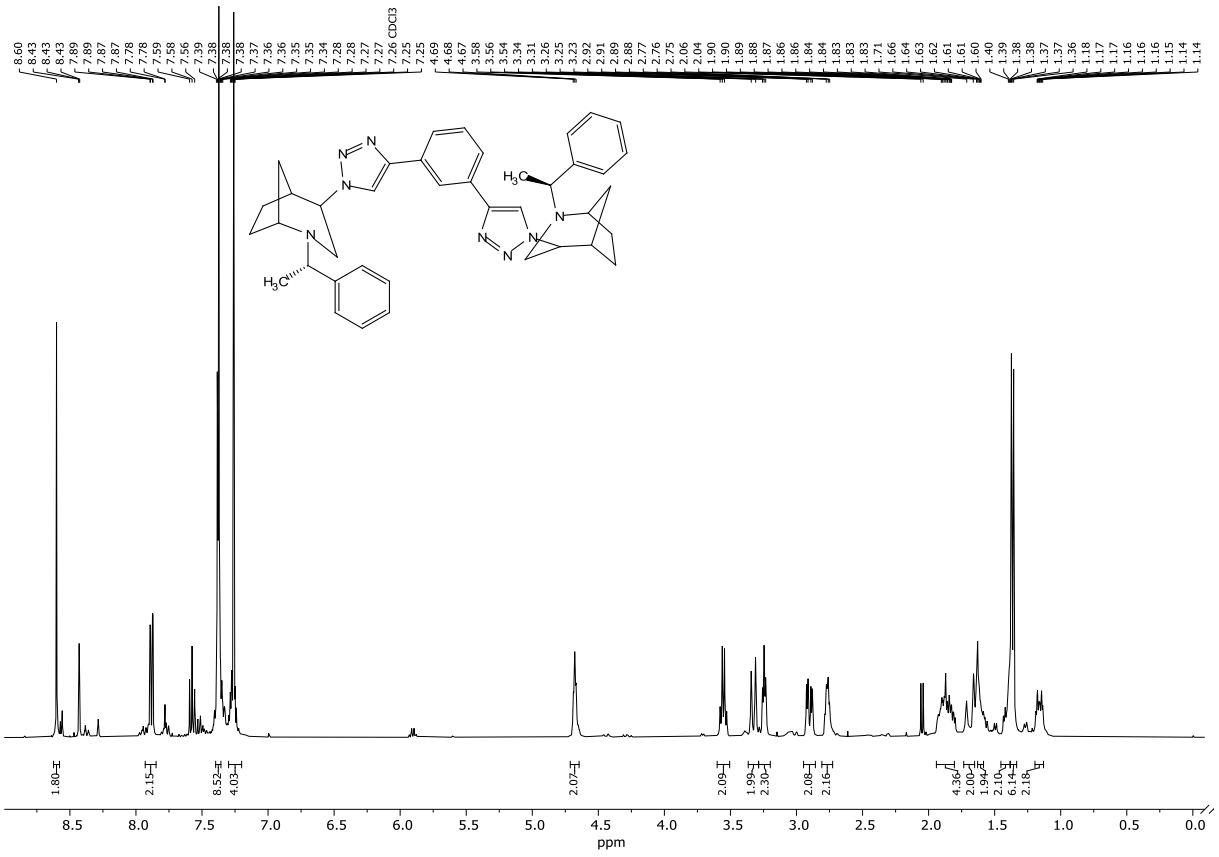
^{1}H-NMR (400 MHz, $CDCl_3$) of **28**



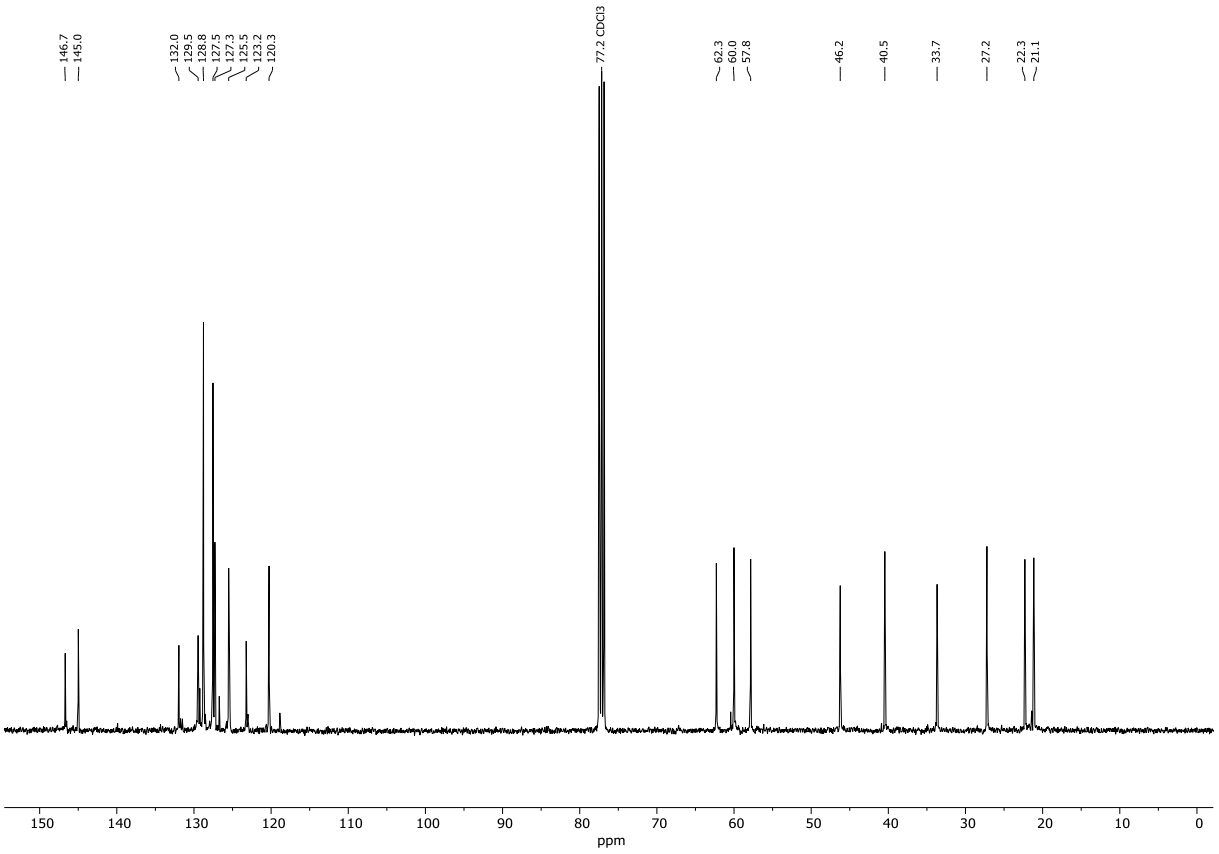
^{13}C-NMR (100 MHz, $CDCl_3$) of **28**



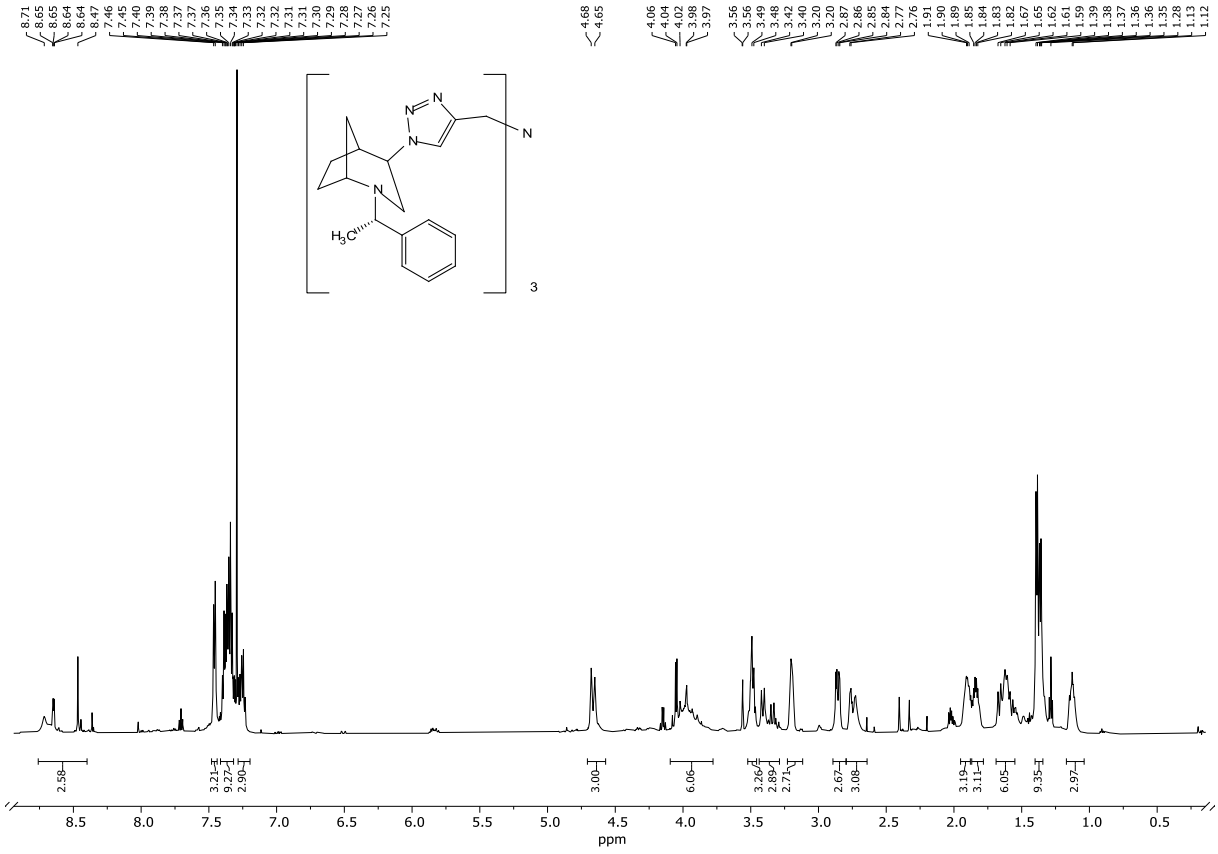
^{1}H-NMR (400 MHz, $CDCl_3$) of **29**



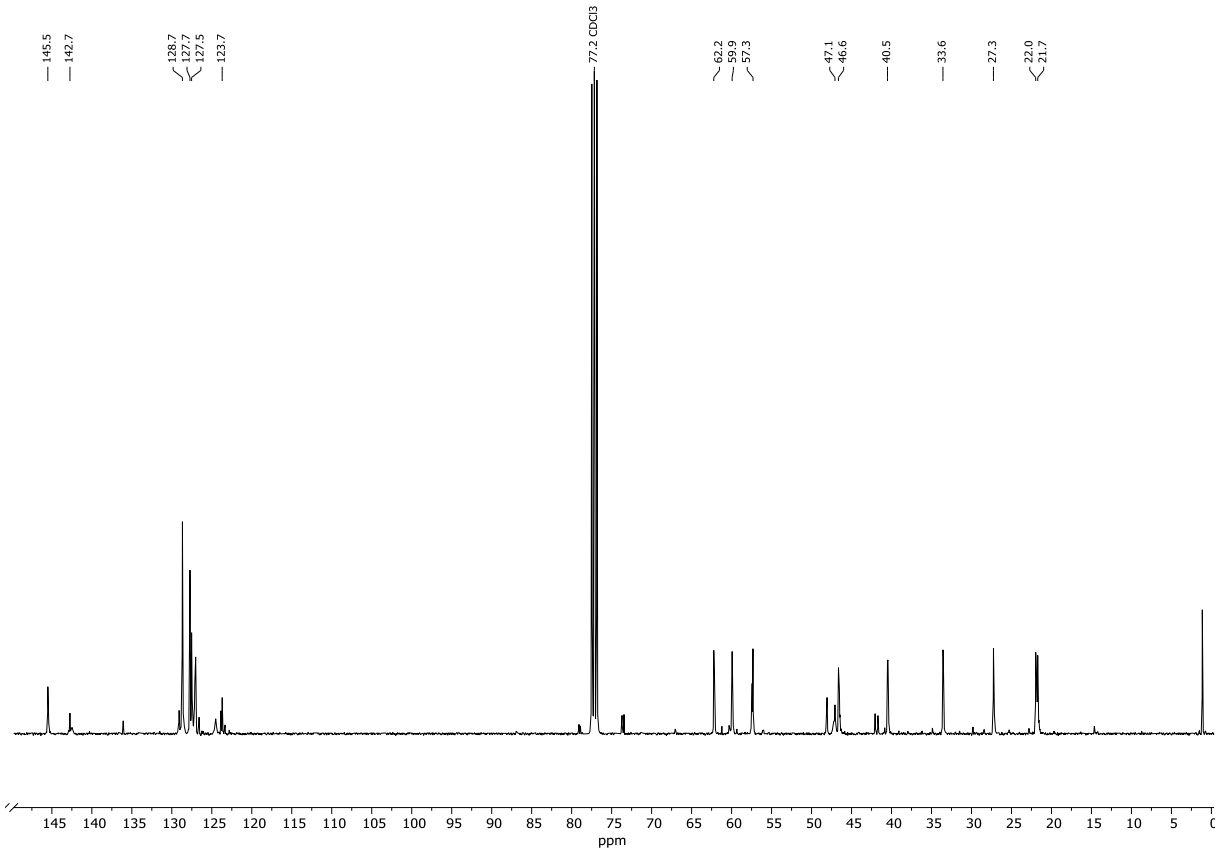
^{13}C-NMR (100 MHz, $CDCl_3$) of **29**



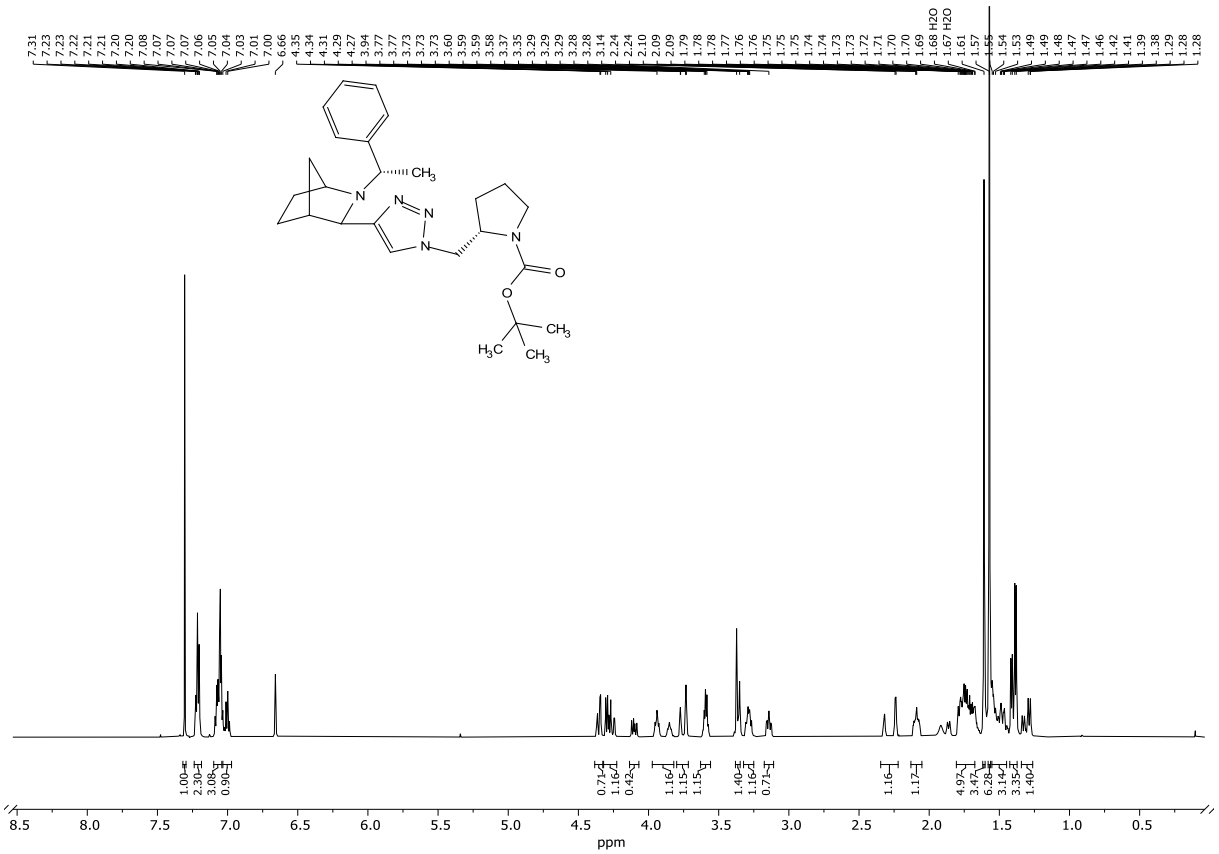
^{1}H-NMR (400 MHz, $CDCl_3$) of **30**



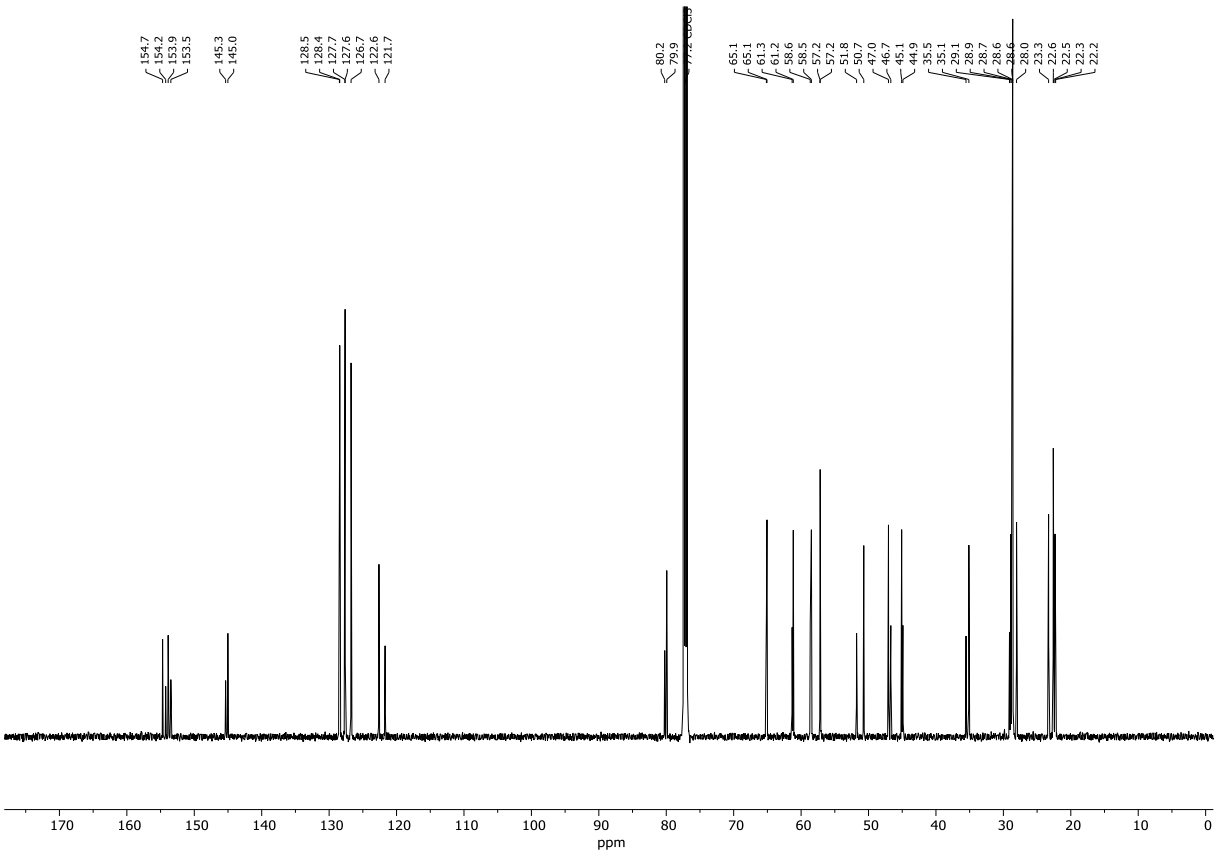
^{13}C-NMR (100 MHz, $CDCl_3$) of **30**



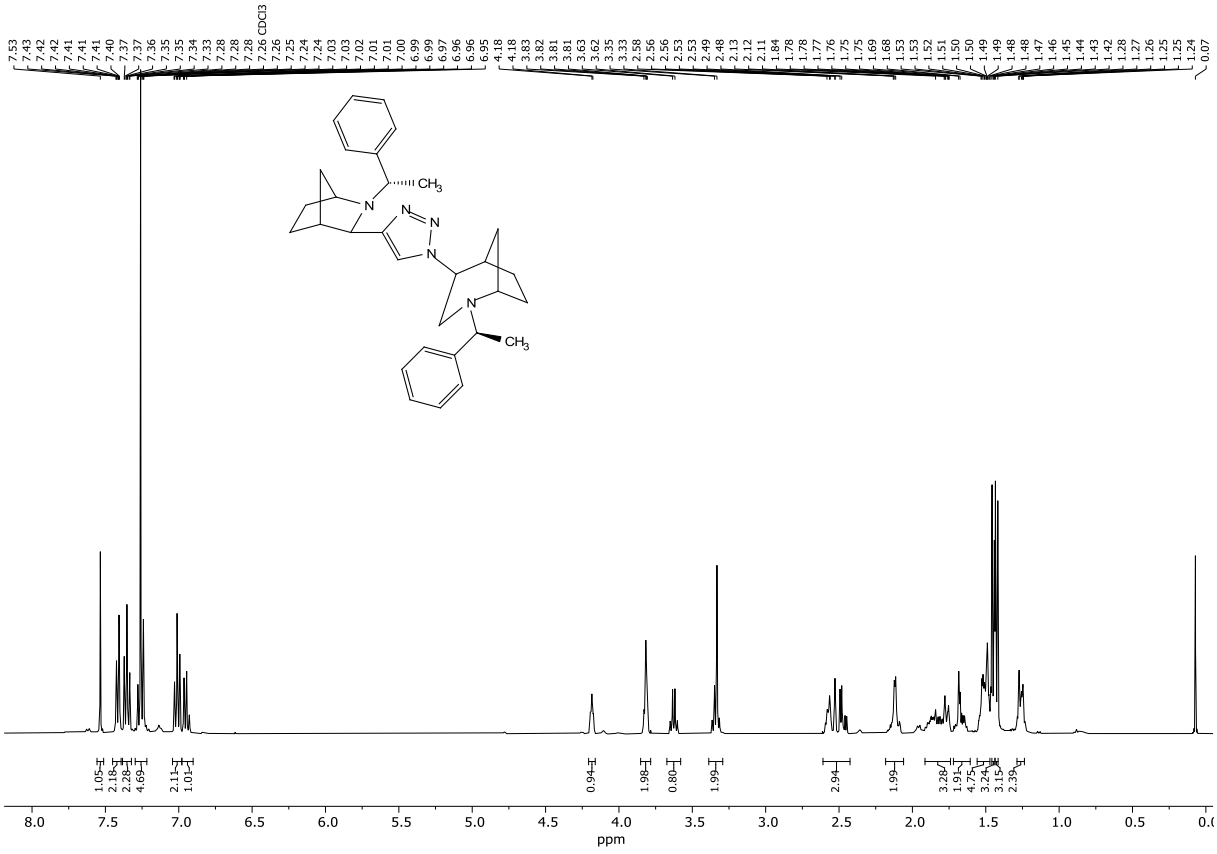
^{1}H-NMR (600 MHz, $CDCl_3$) of **32**



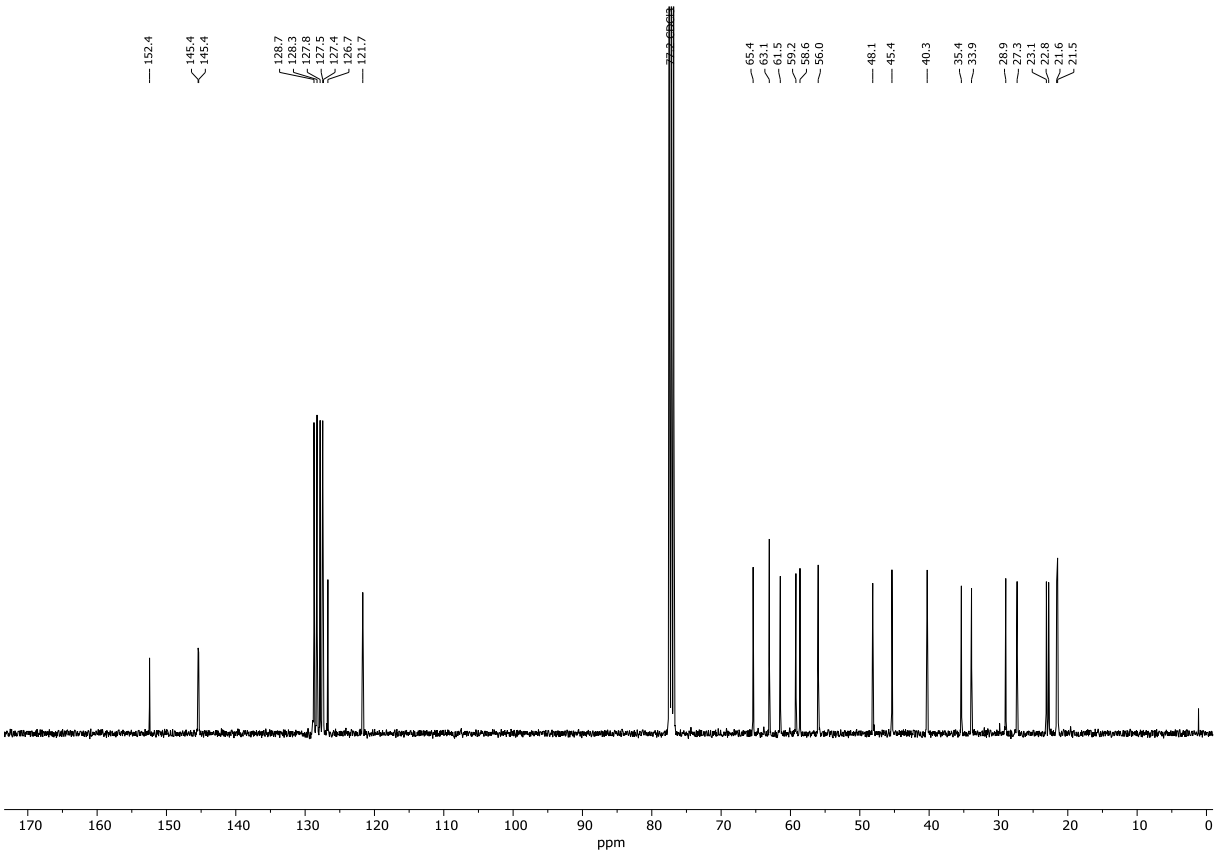
^{13}C-NMR (151 MHz, $CDCl_3$) of **32**



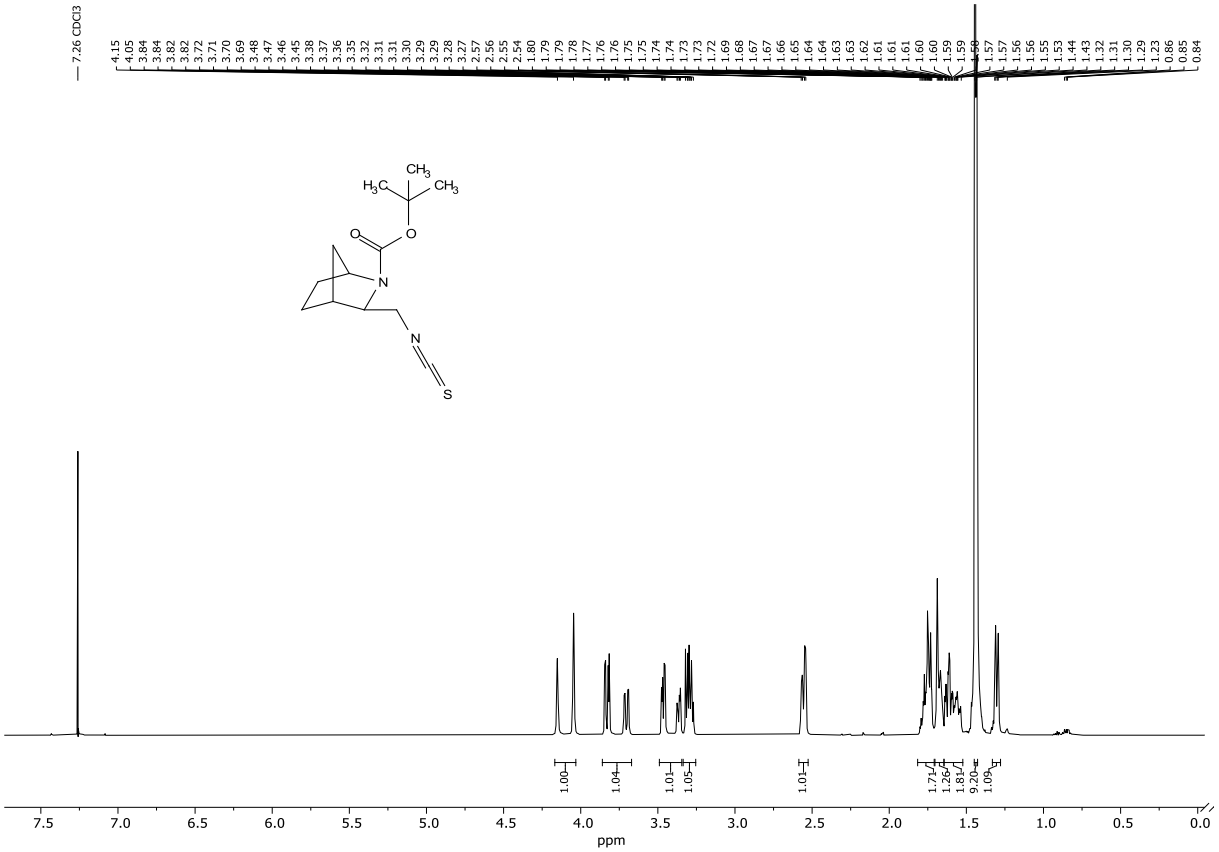
^{1}H-NMR (400 MHz, $CDCl_3$) of **33**



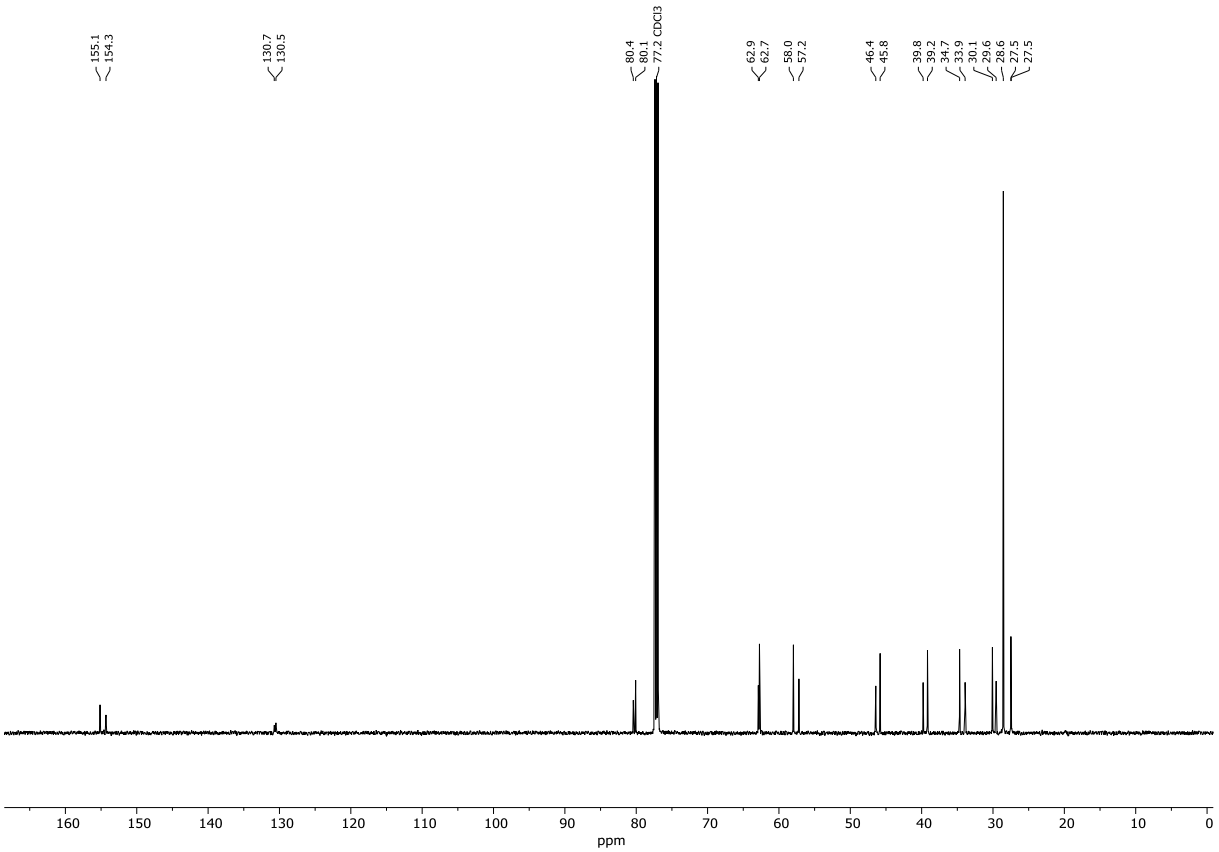
^{13}C-NMR (100 MHz, $CDCl_3$) of **33**



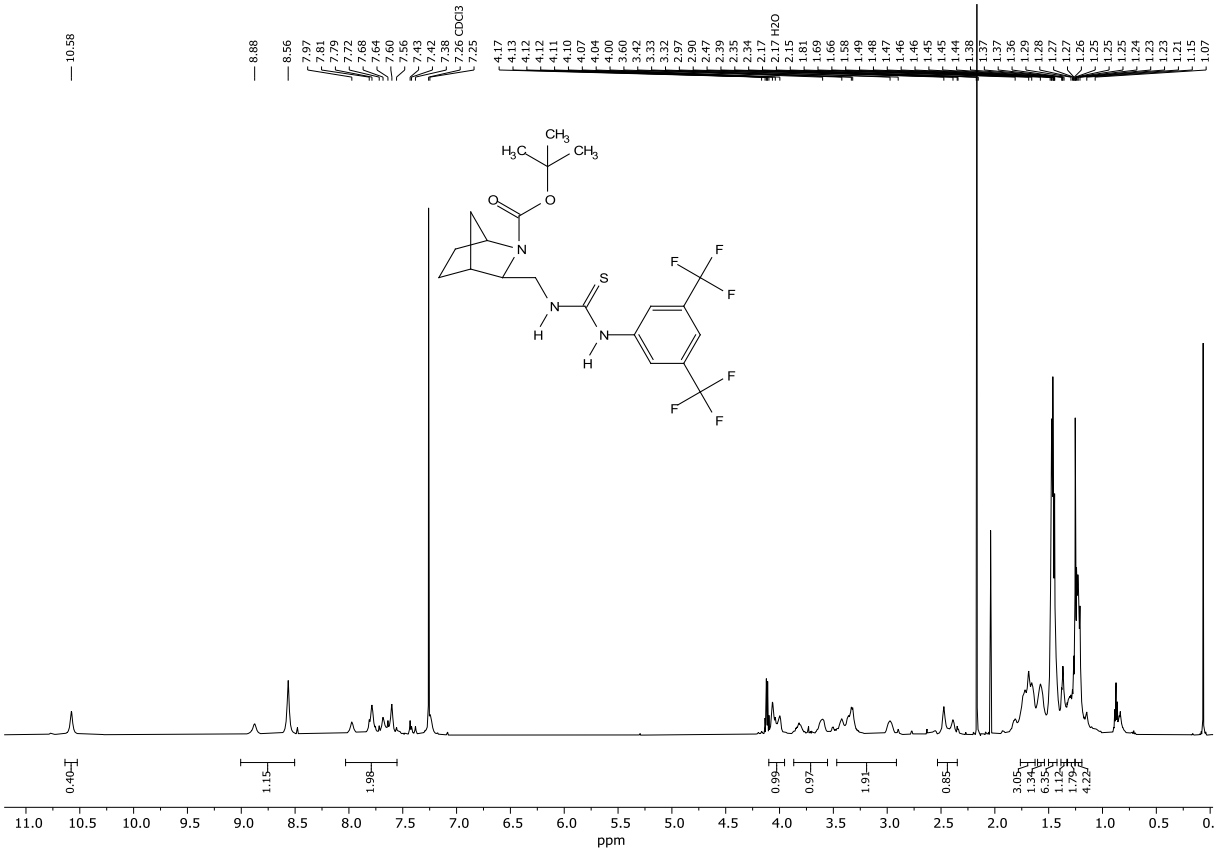
^{1}H-NMR (600 MHz, 283 K, $CDCl_3$) of **38**



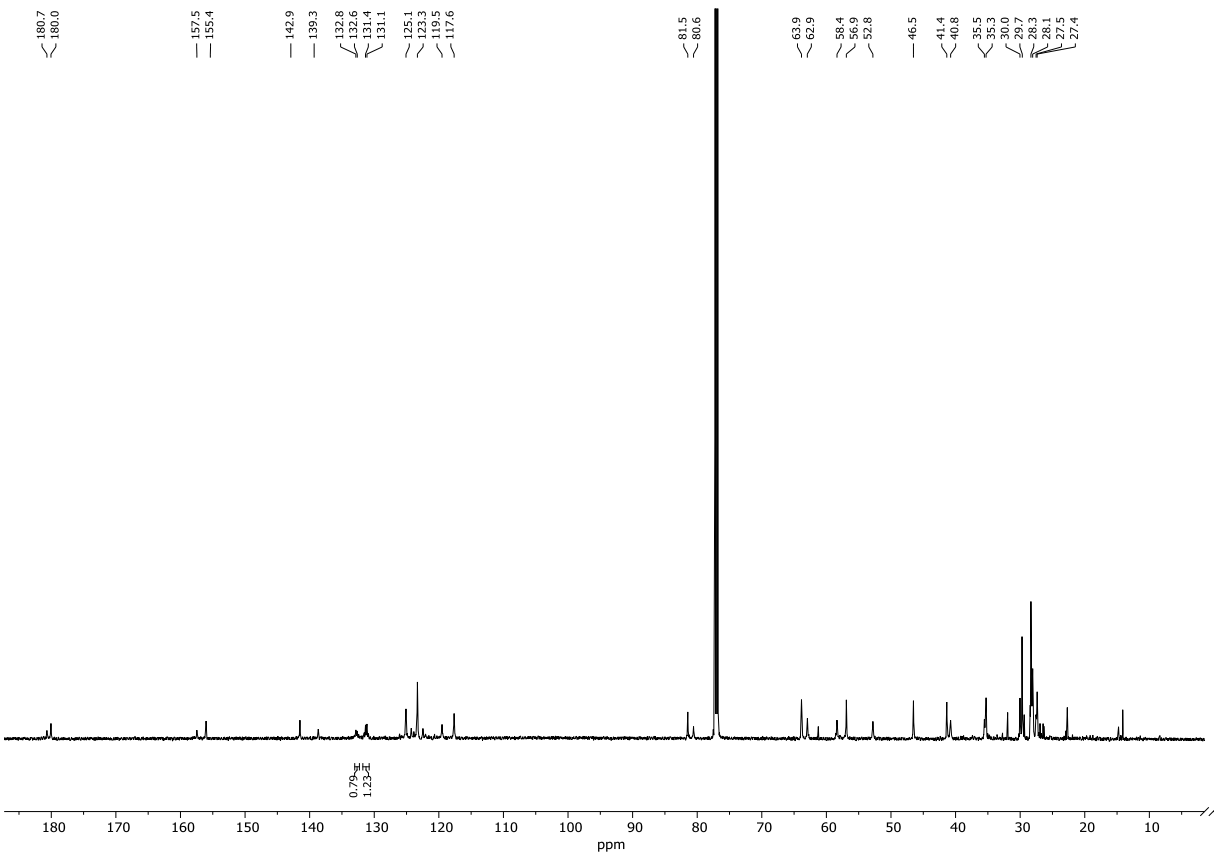
^{13}C-NMR (151 MHz, 283 K, $CDCl_3$) of **38**



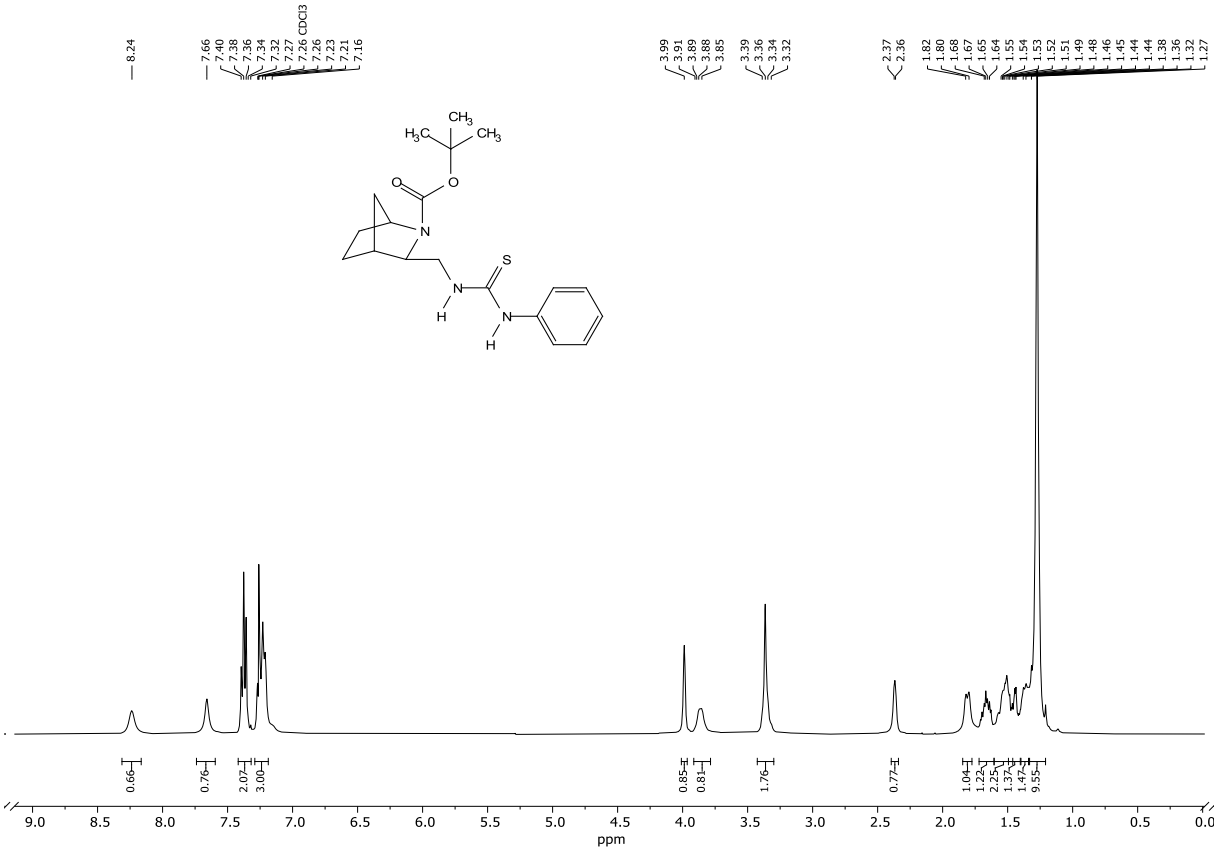
^{1}H-NMR (600 MHz, $CDCl_3$) of **39**



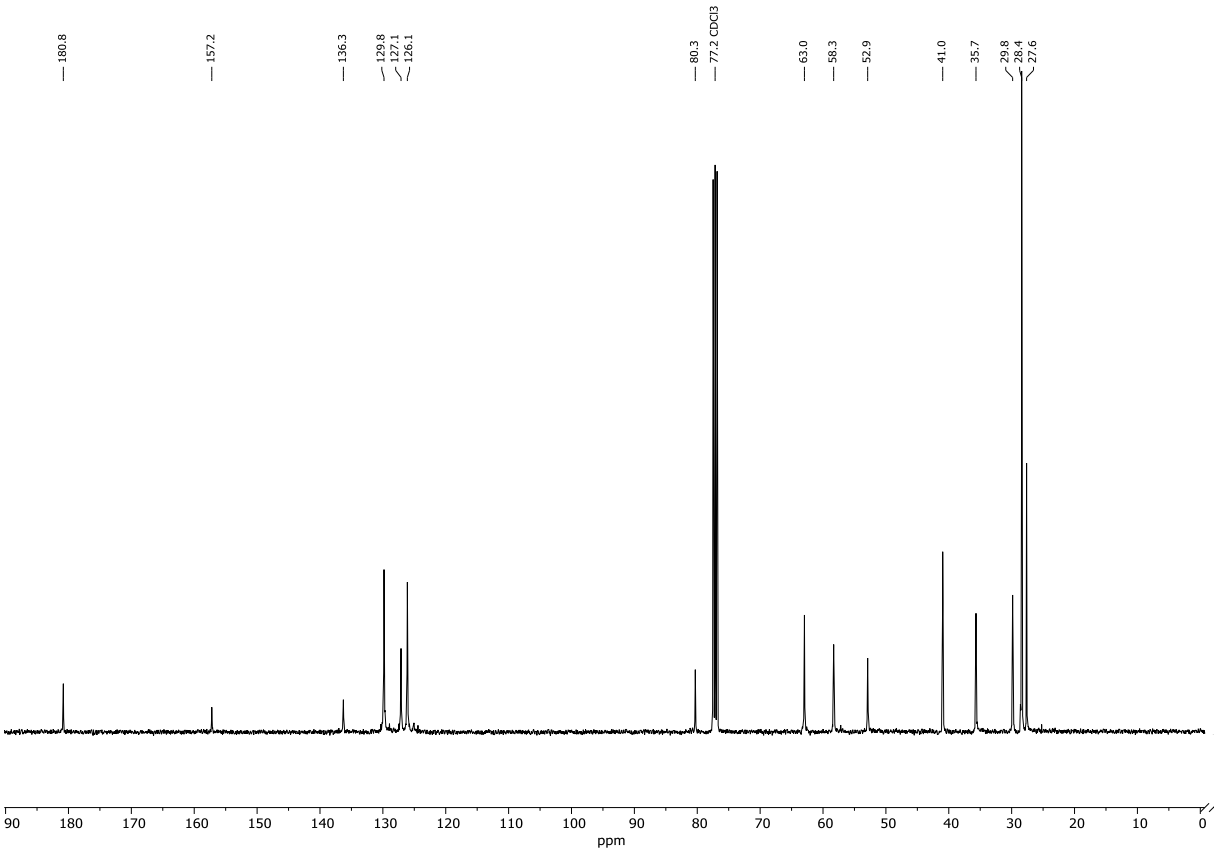
^{13}C-NMR (151 MHz, $CDCl_3$) of **39**



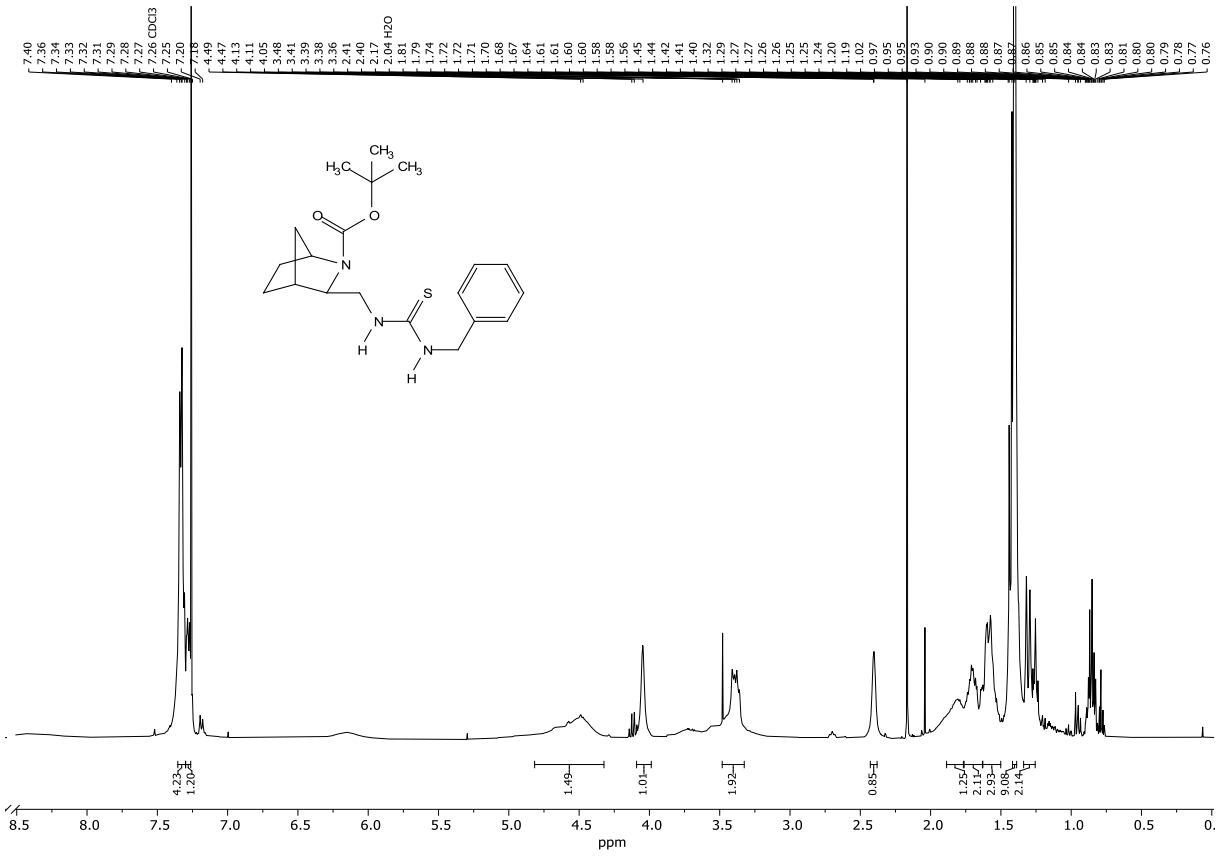
^{1}H-NMR (400 MHz, $CDCl_3$) of **40**



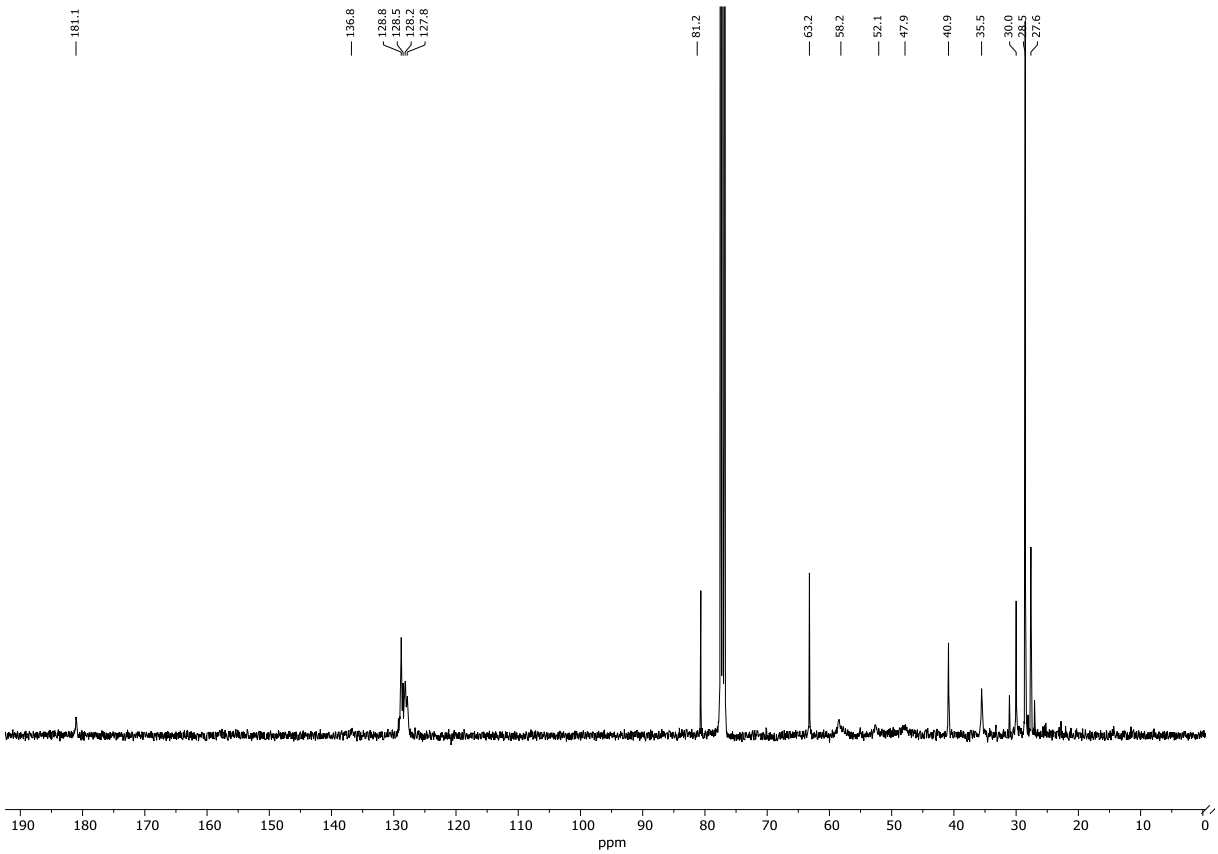
^{13}C-NMR (100 MHz, $CDCl_3$) of **40**



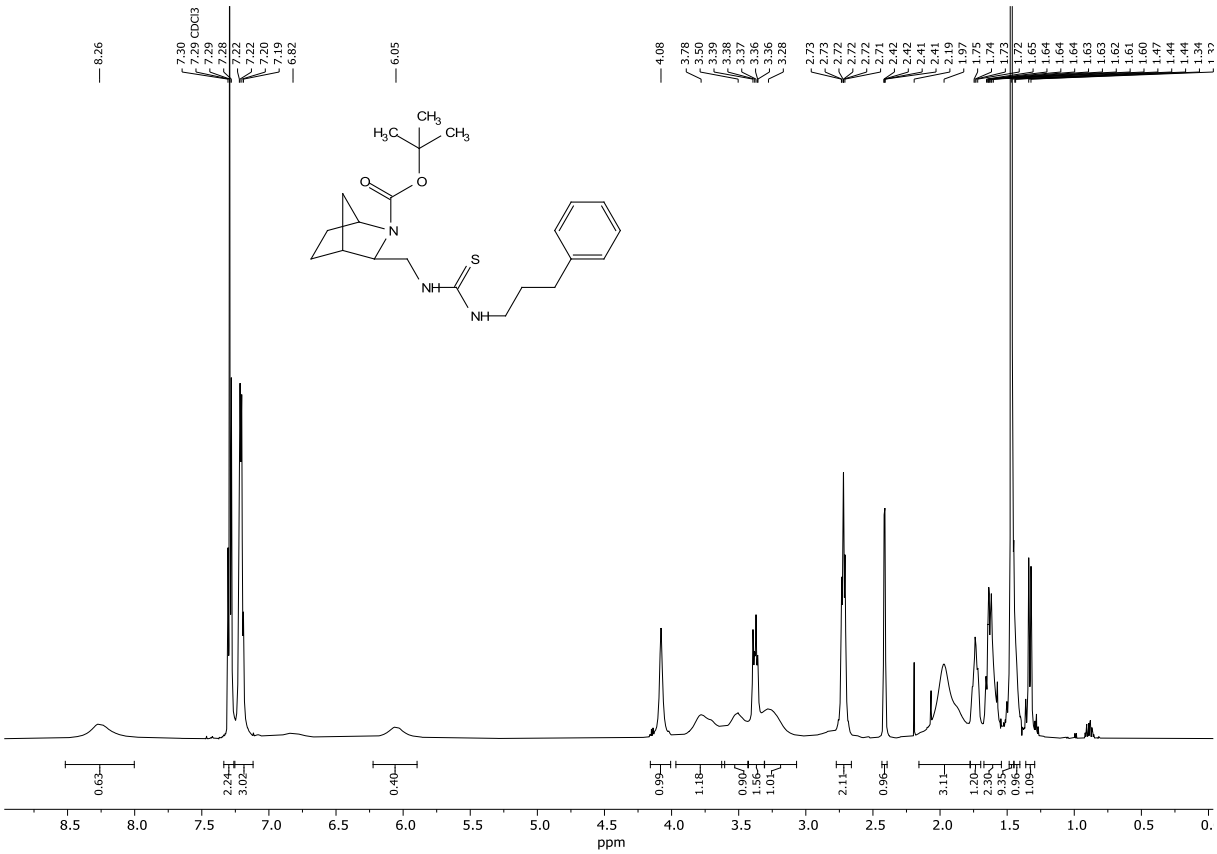
^{1}H-NMR (400 MHz, $CDCl_3$) of **41**



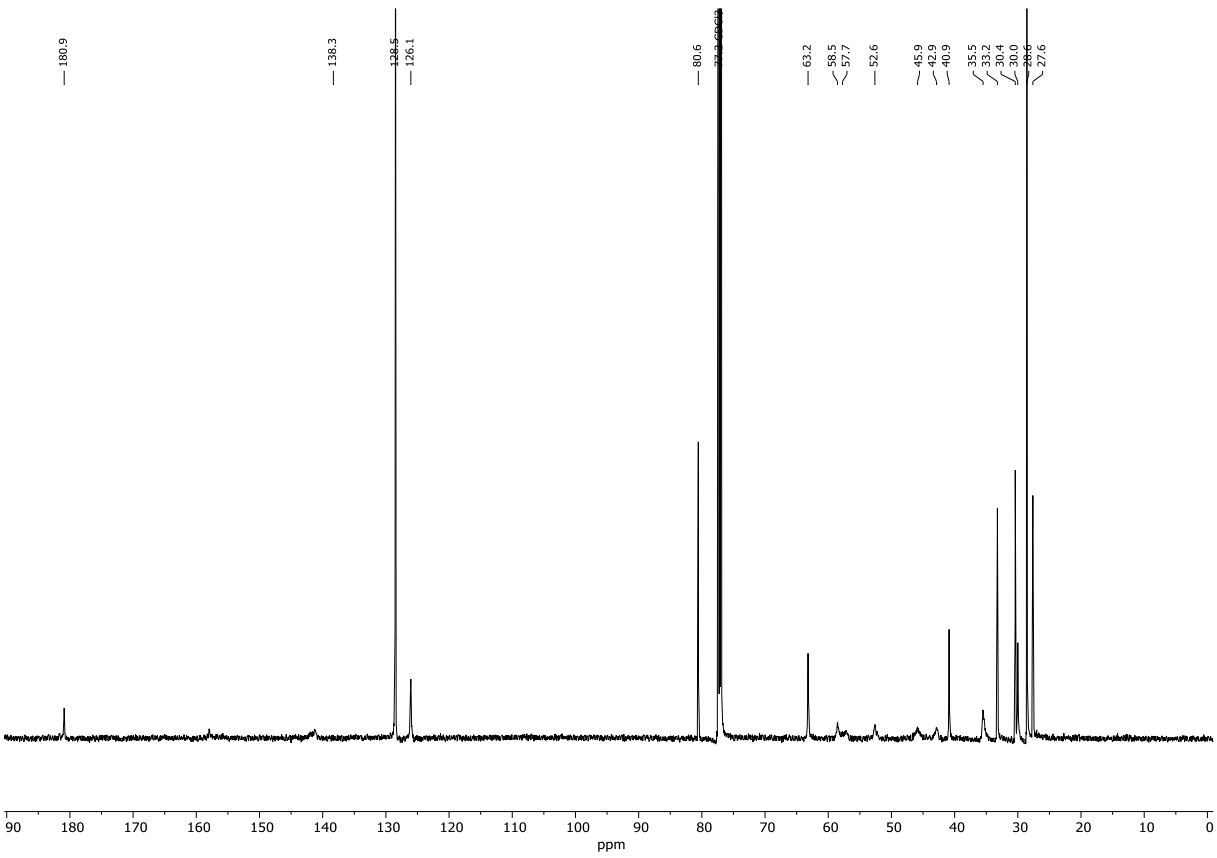
^{13}C-NMR (100 MHz, $CDCl_3$) of **41**



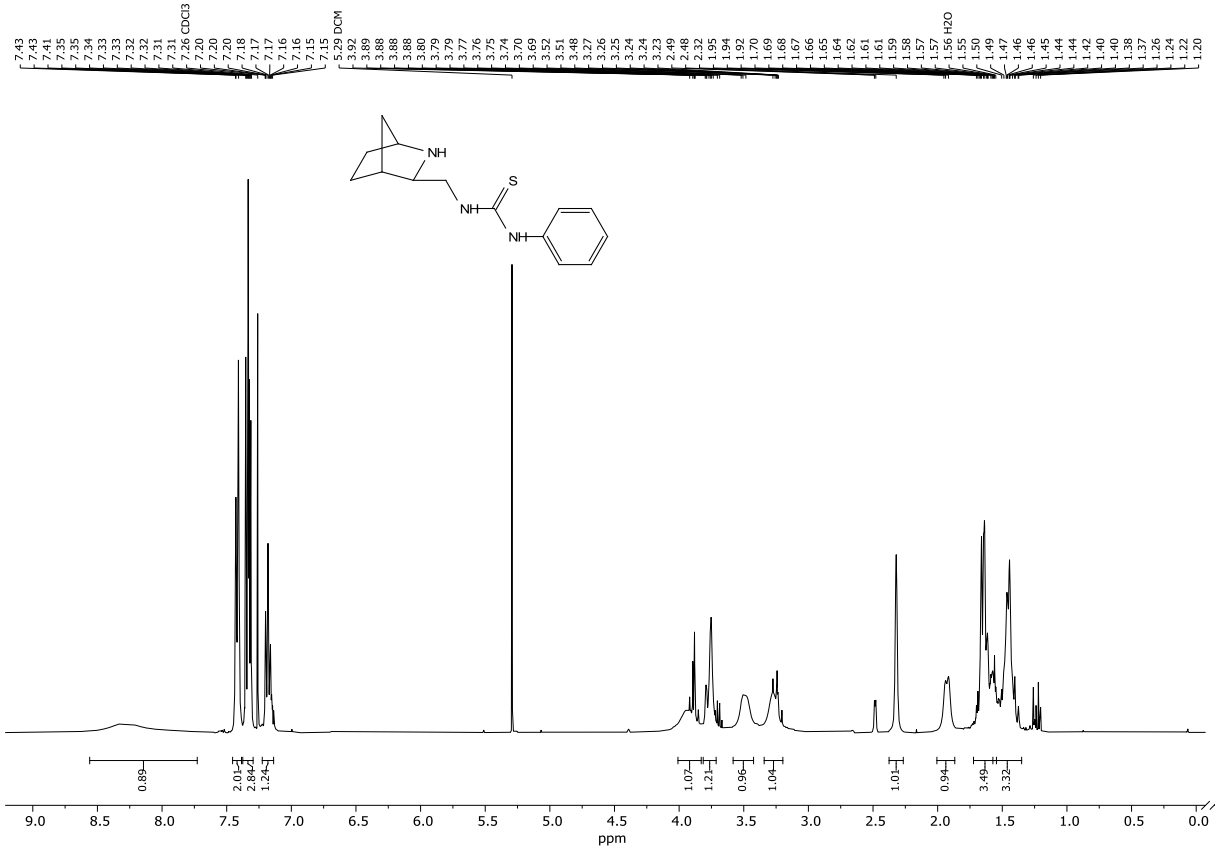
^{1}H-NMR (400 MHz, $CDCl_3$) of **42**



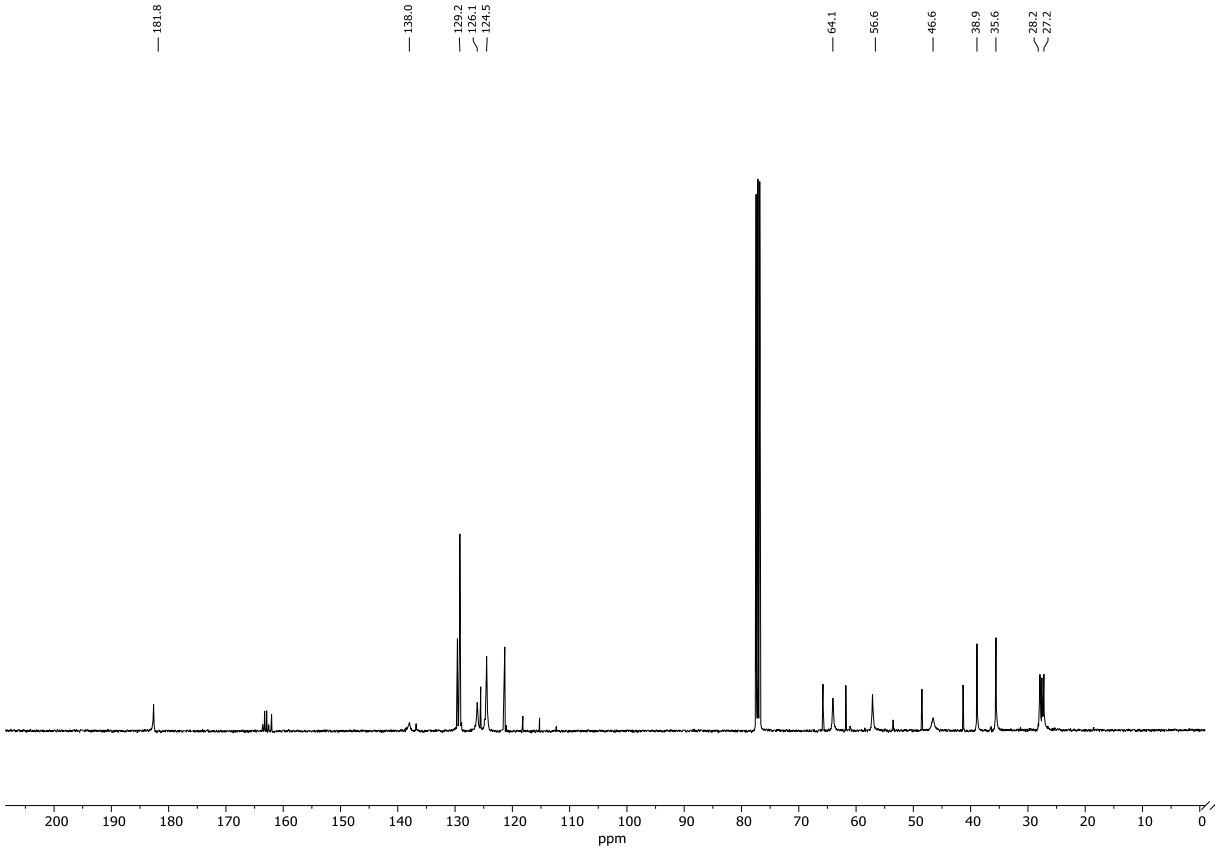
^{13}C-NMR (100 MHz, $CDCl_3$) of **42**



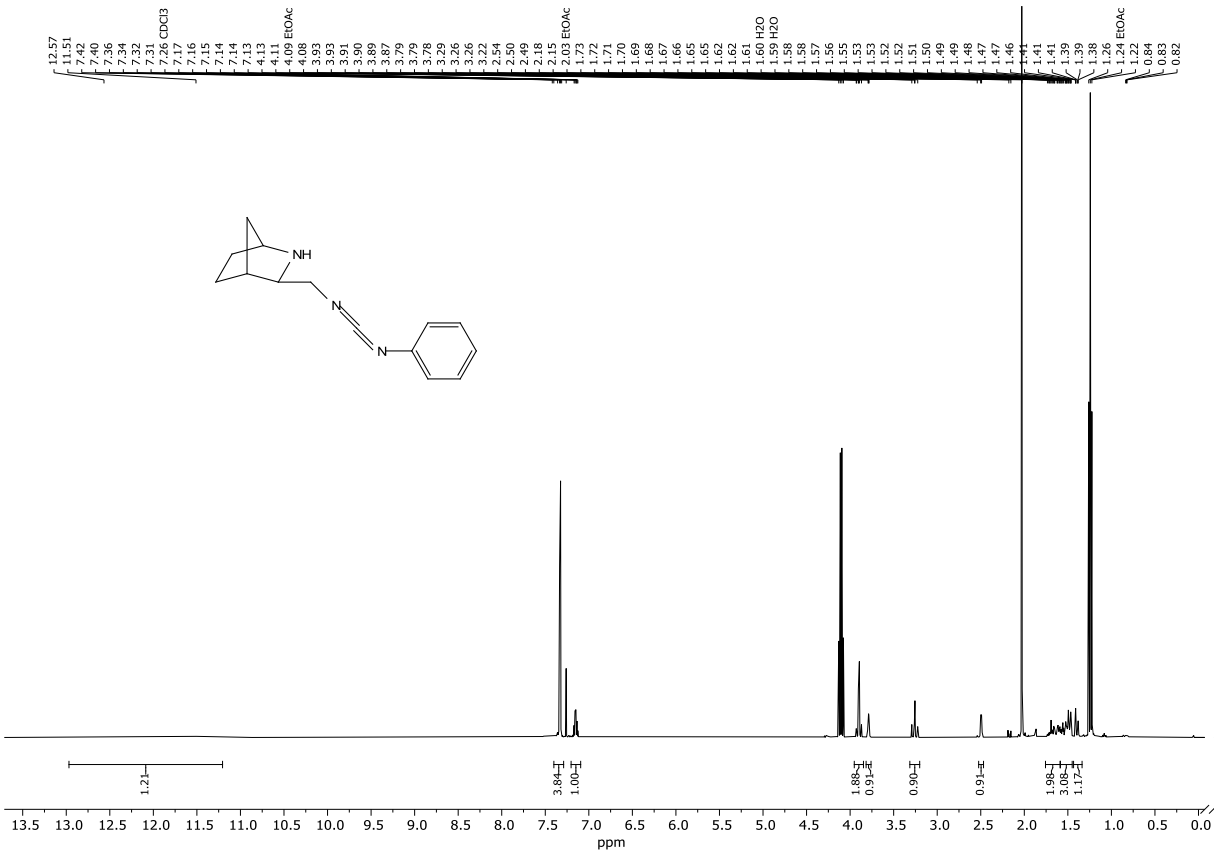
^{1}H-NMR (400 MHz, $CDCl_3$) of **43**



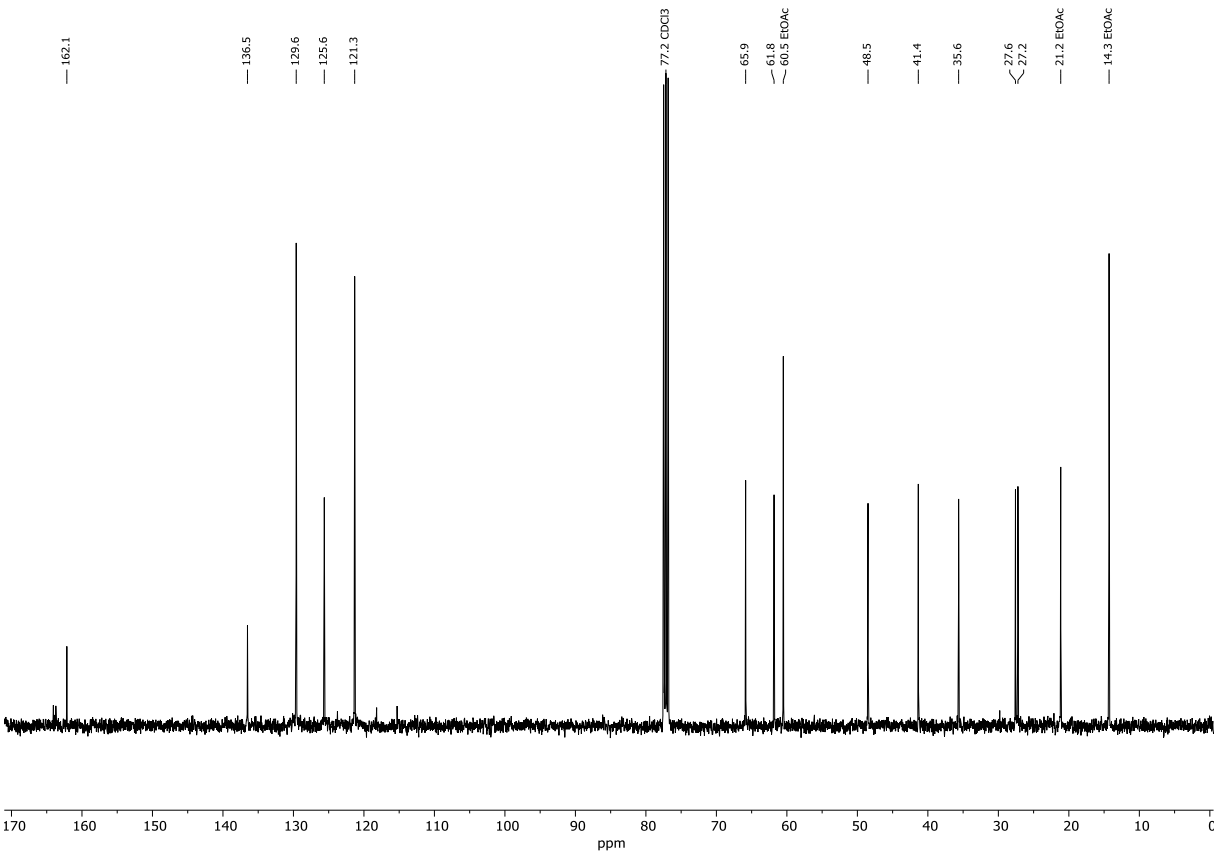
^{13}C-NMR (100 MHz, $CDCl_3$) of **43**



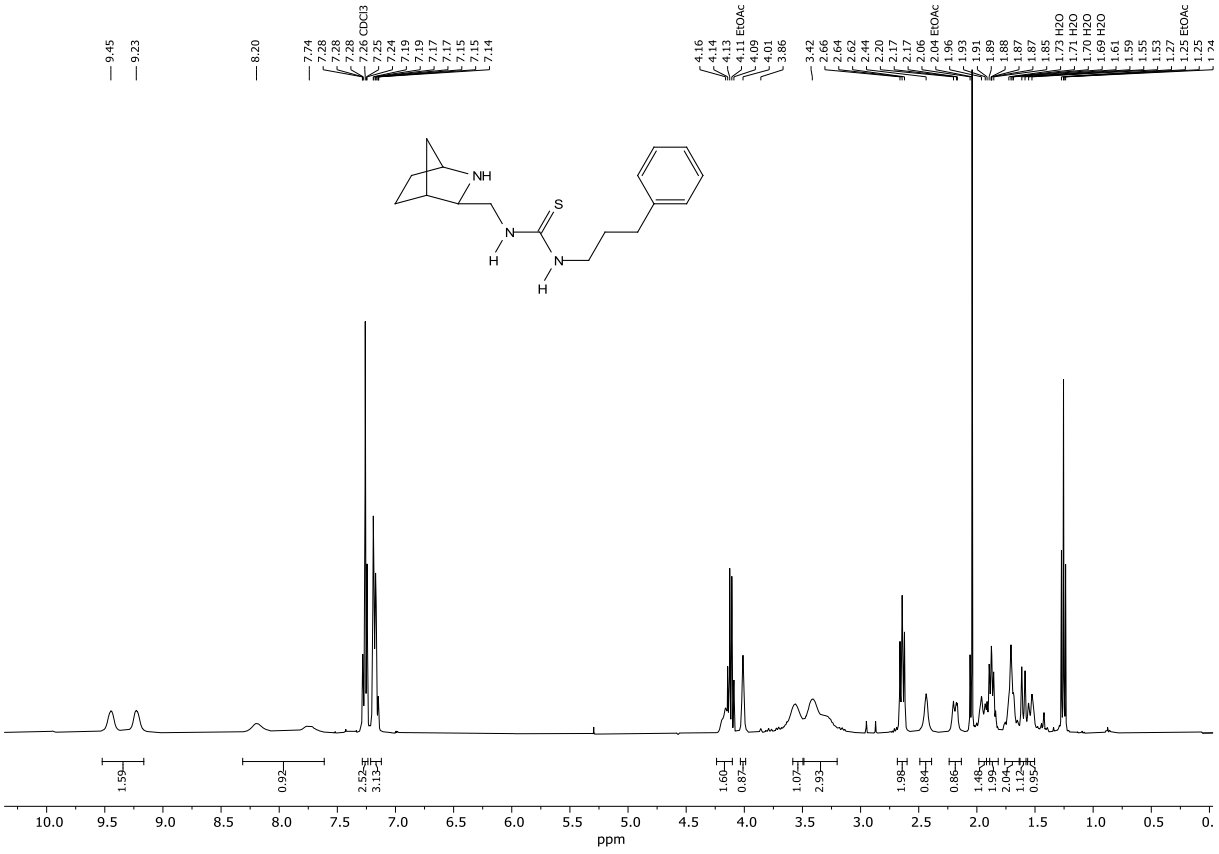
^{1}H-NMR (400 MHz, $CDCl_3$) of **44**



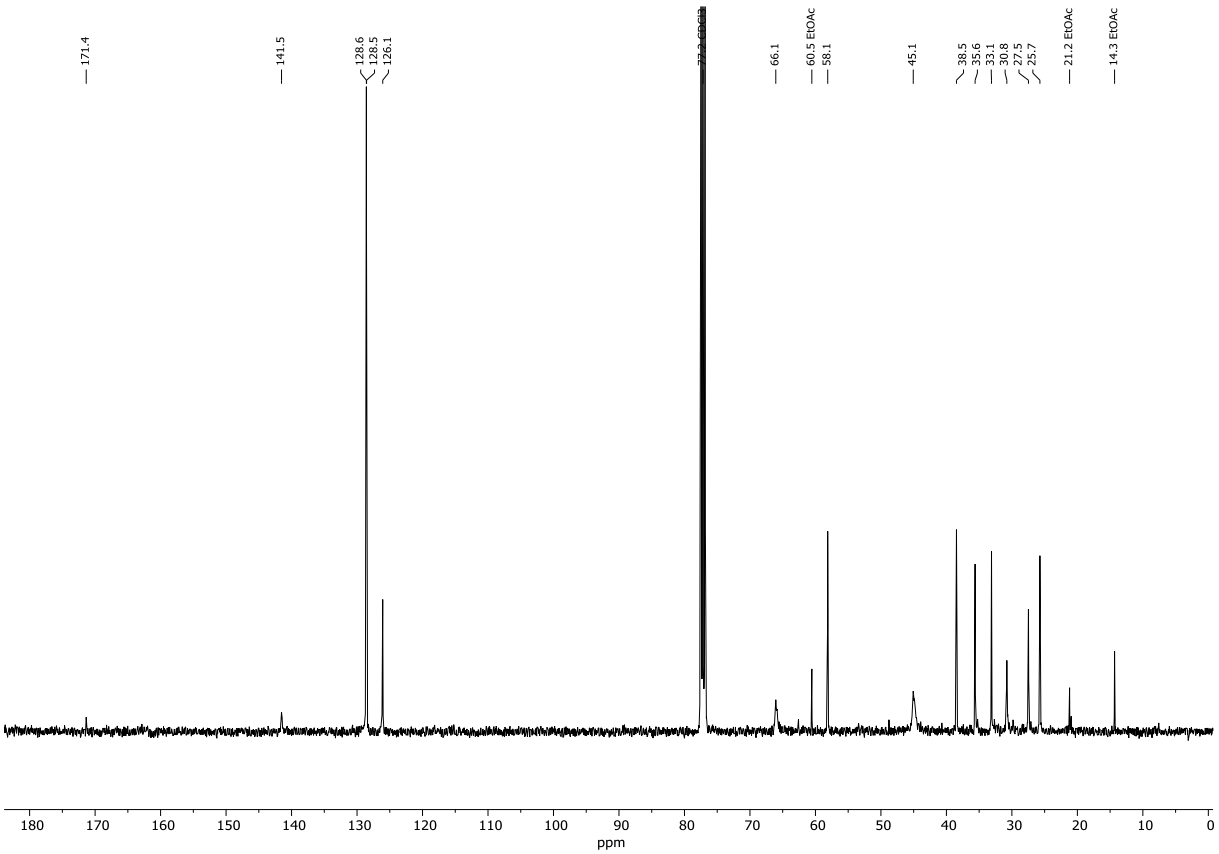
^{13}C-NMR (100 MHz, $CDCl_3$) of **44**



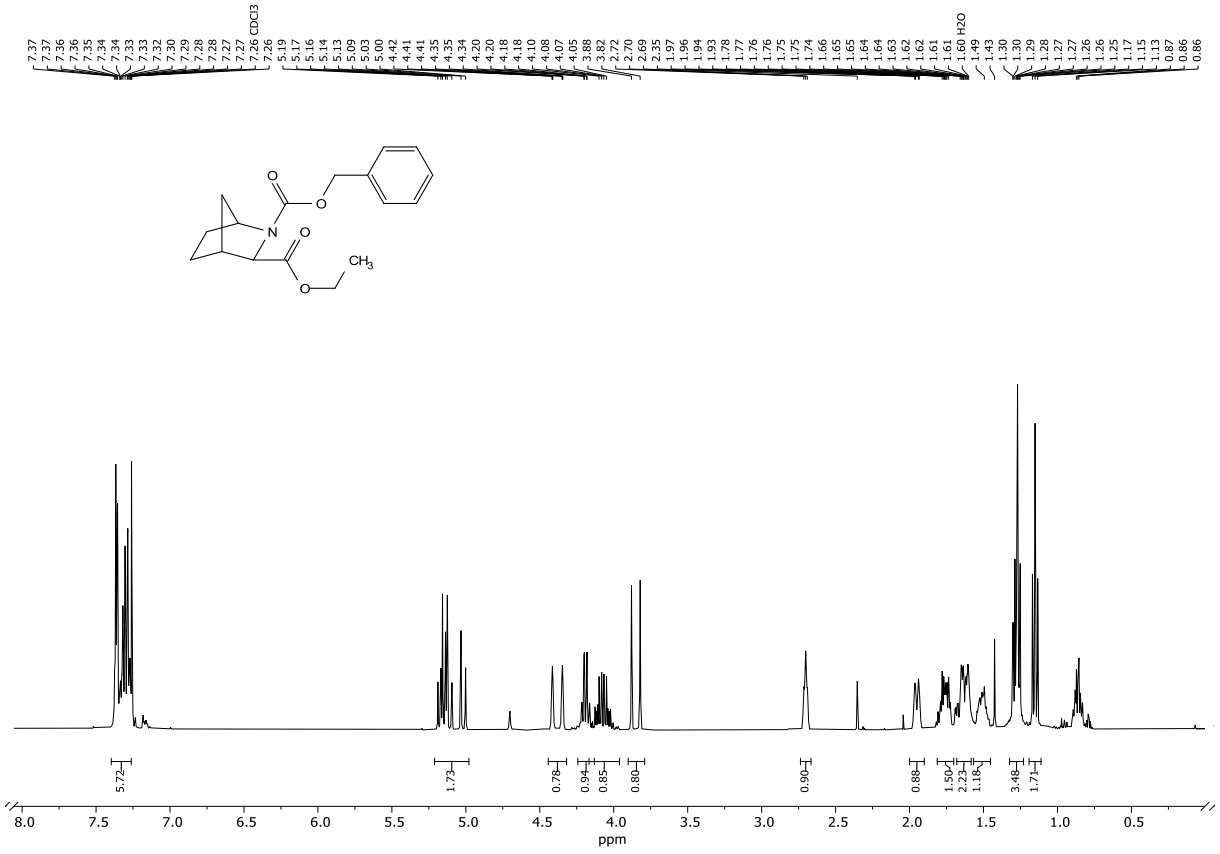
^{1}H-NMR (400 MHz, $CDCl_3$) of **45**



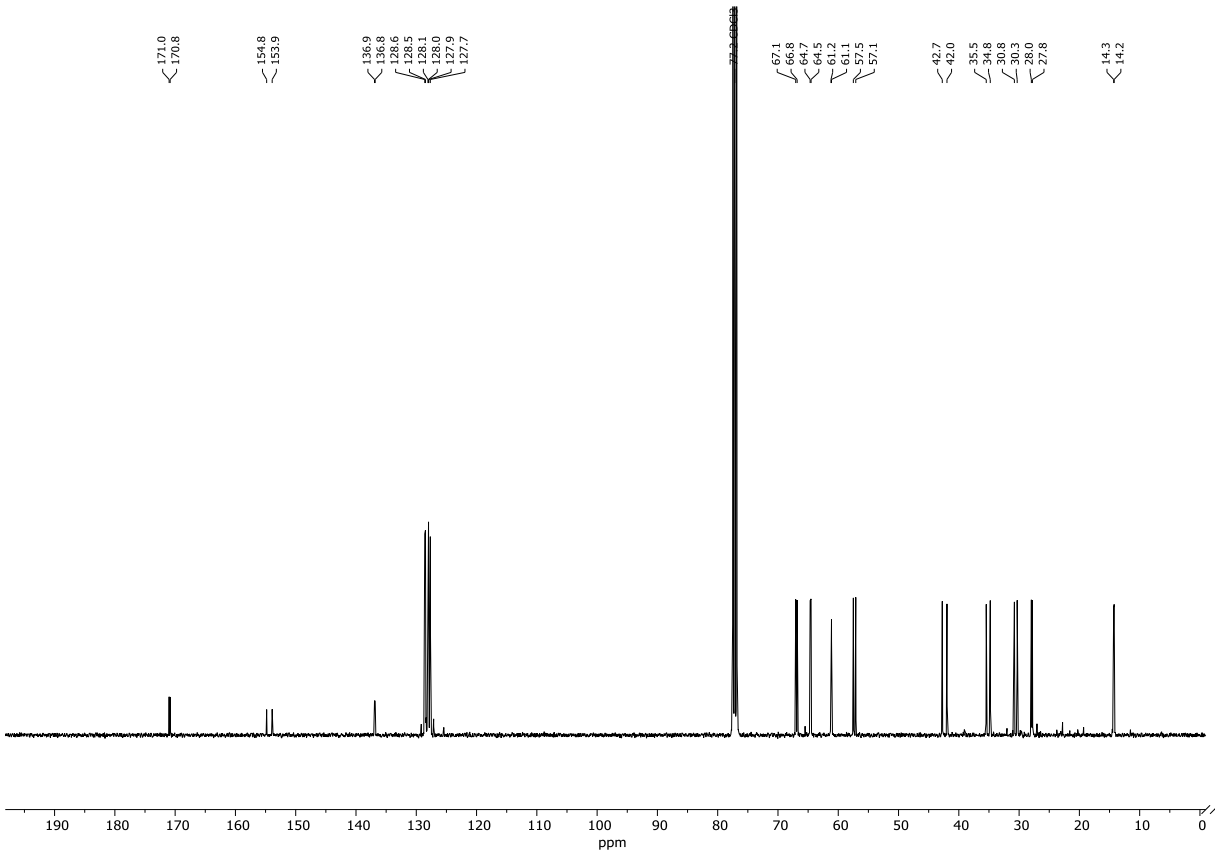
^{13}C-NMR (100 MHz, $CDCl_3$) of **45**



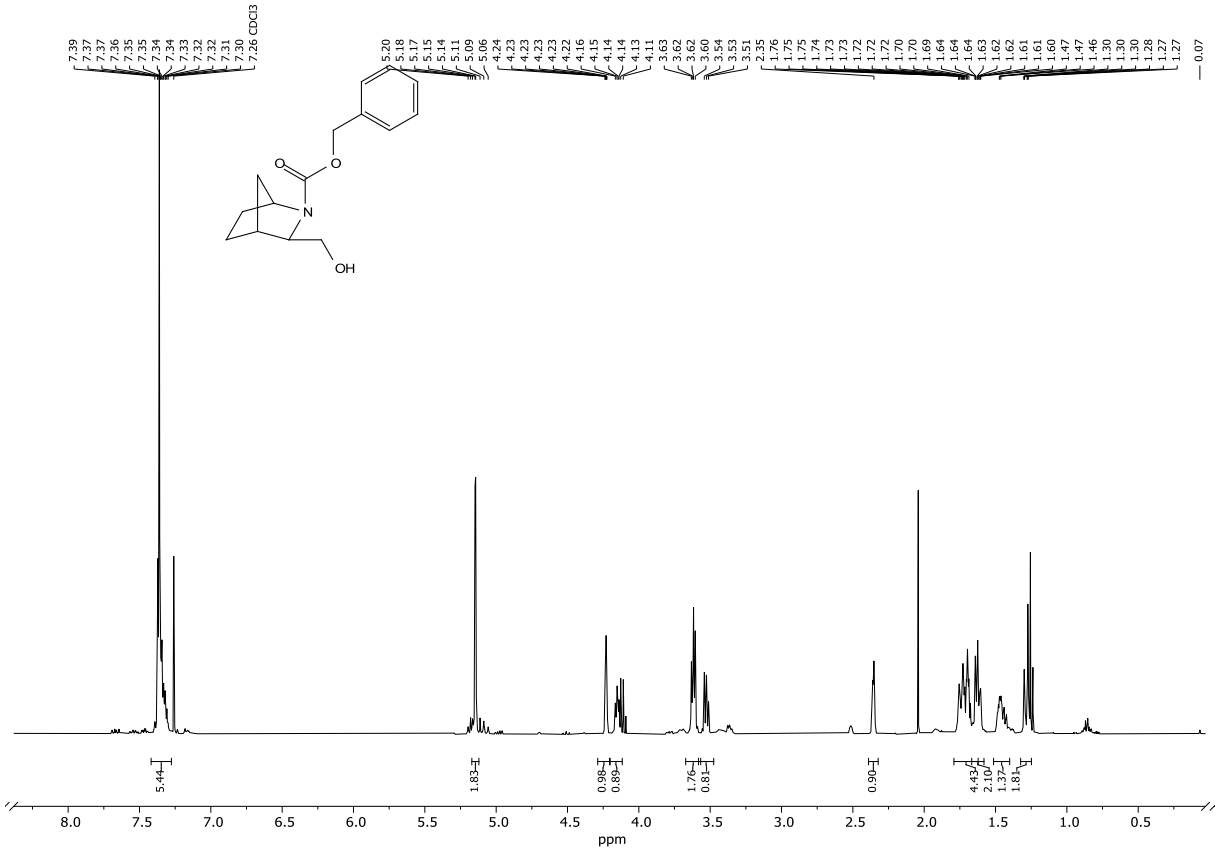
^{1}H-NMR (400 MHz, $CDCl_3$) of intermediate-**46**



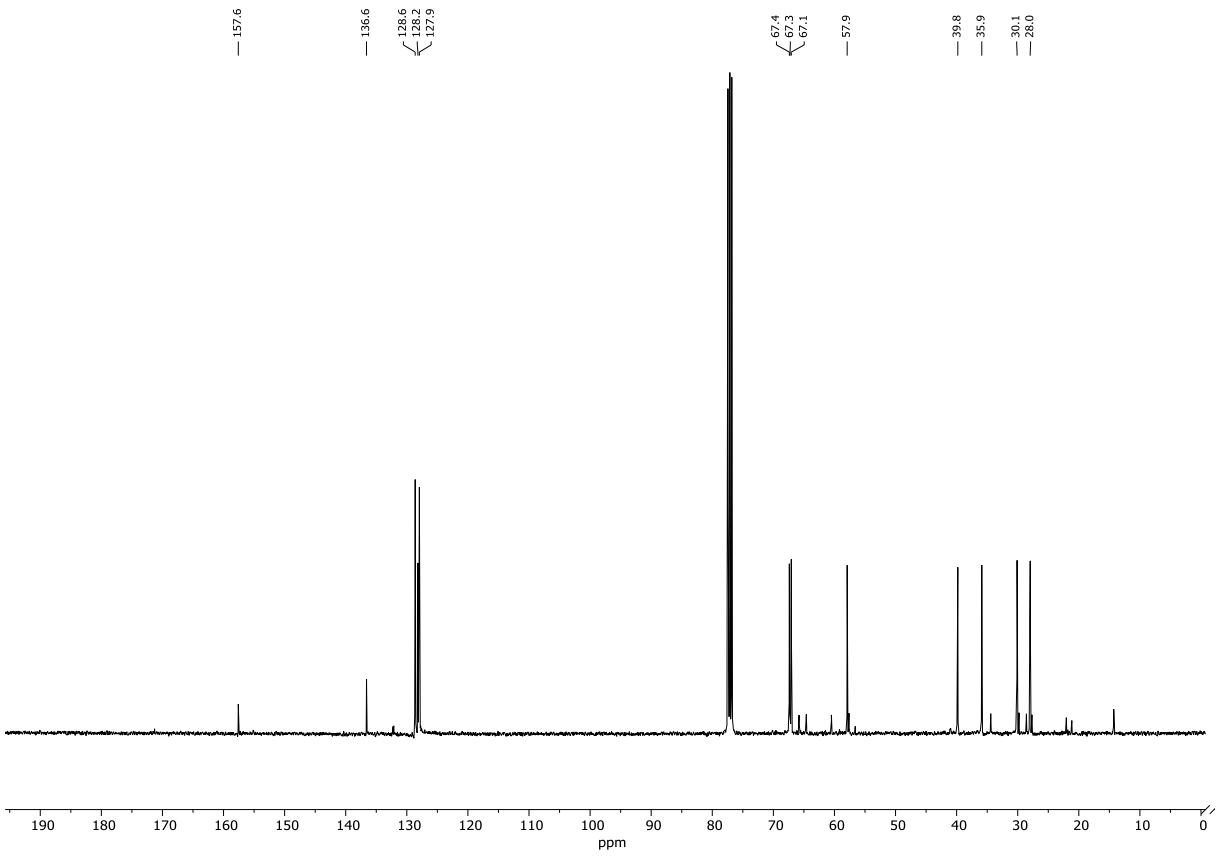
^{13}C-NMR (100 MHz, $CDCl_3$) of intermediate-**46**



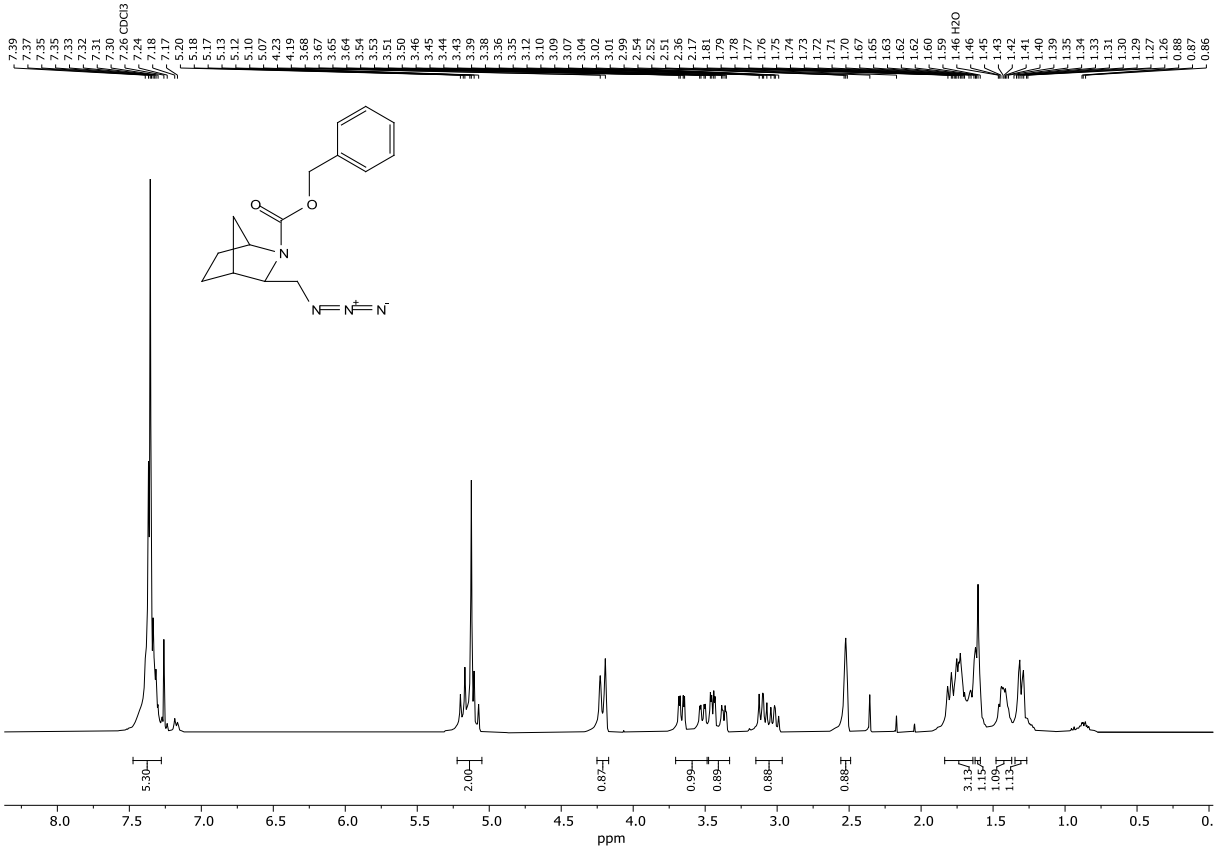
^{1}H-NMR (400 MHz, $CDCl_3$) of **46**



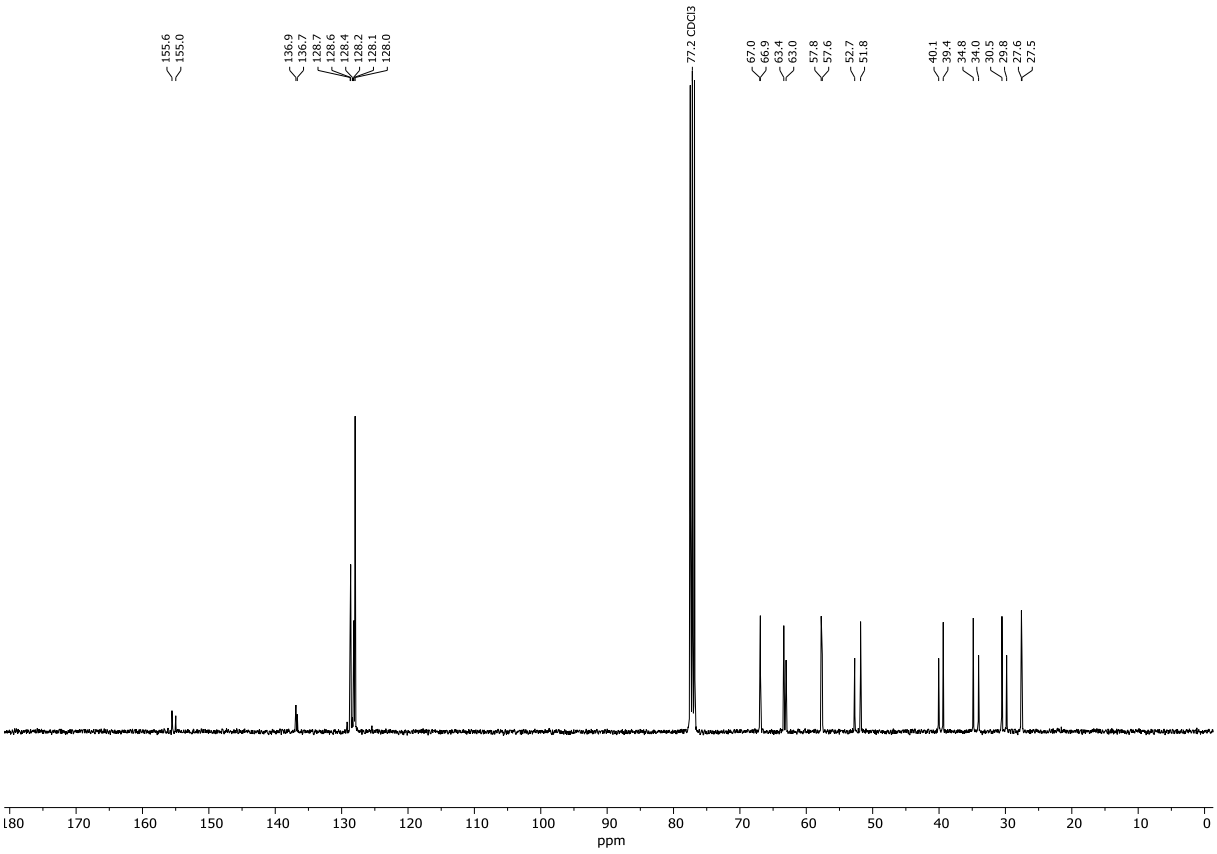
^{13}C-NMR (100 MHz, $CDCl_3$) of **46**



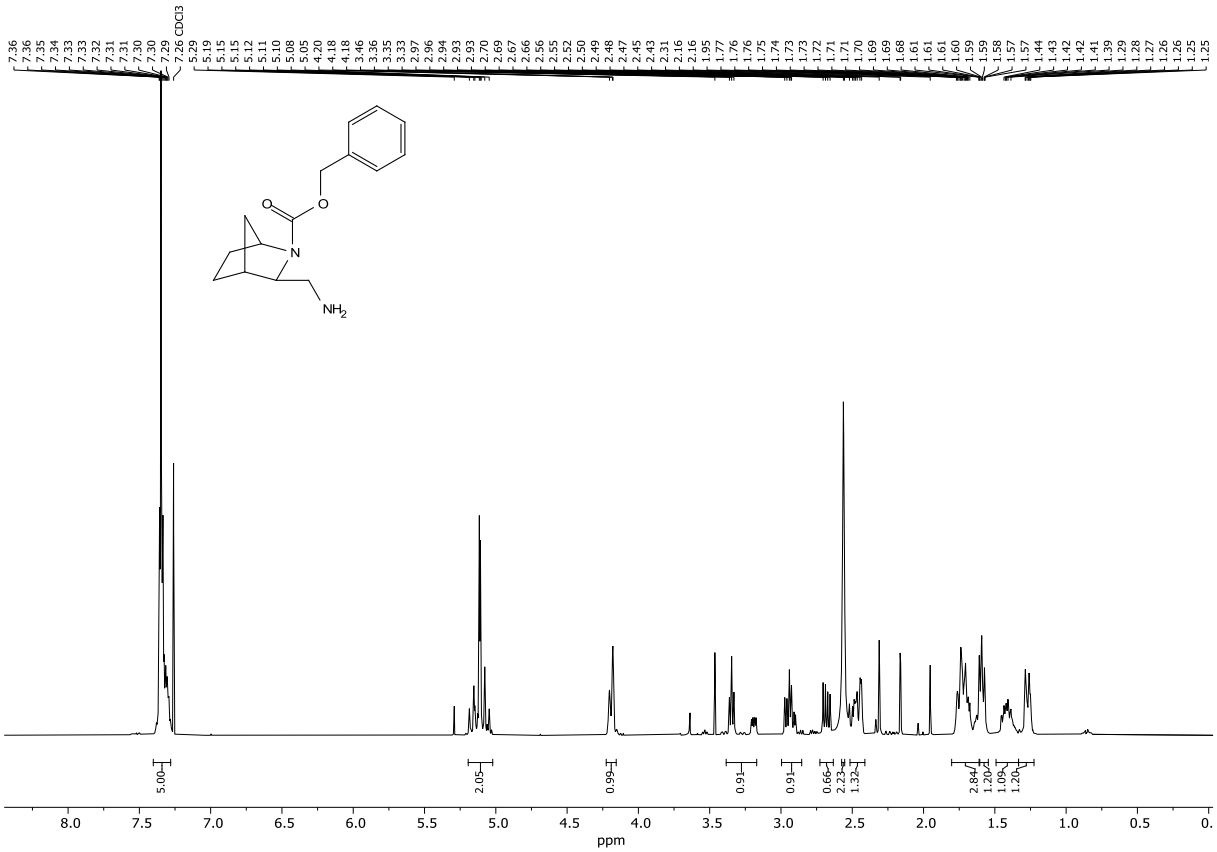
^{1}H-NMR (400 MHz, $CDCl_3$) of **47**



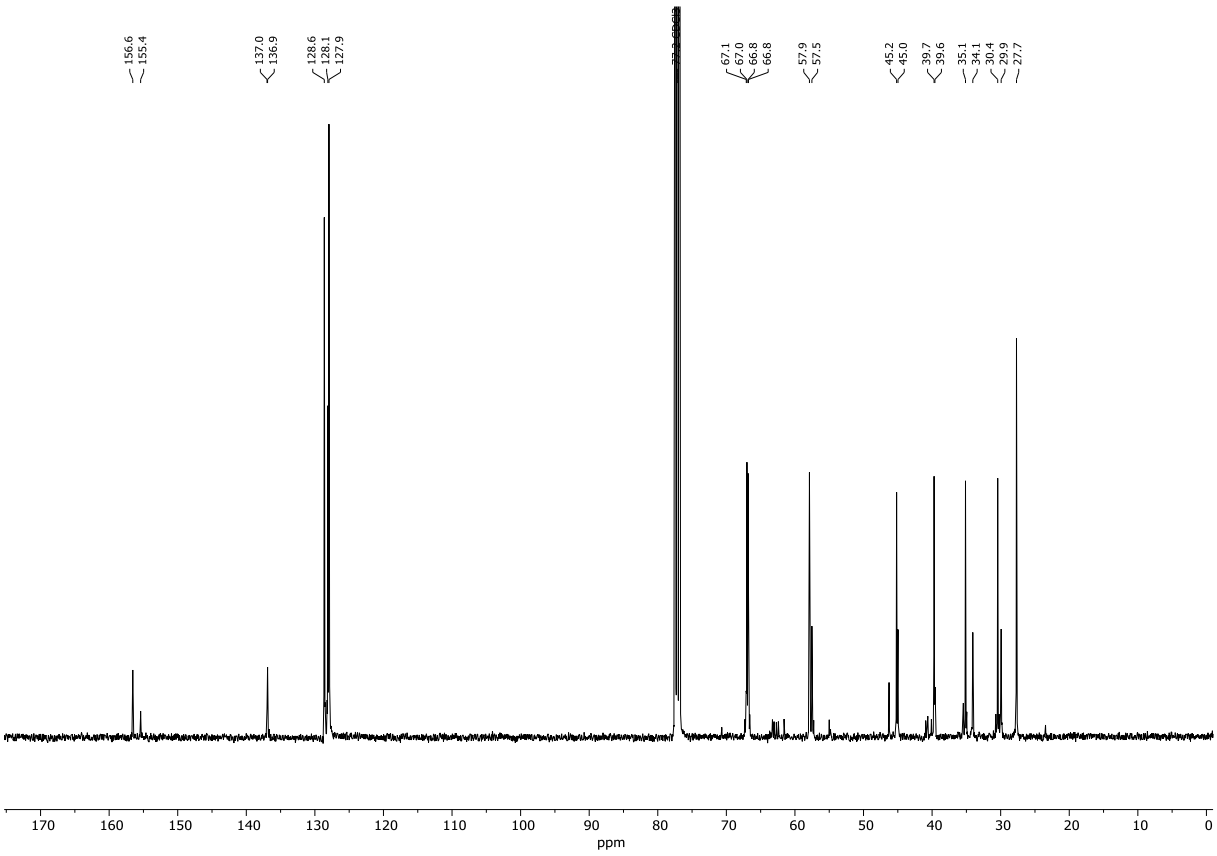
^{13}C-NMR (100 MHz, $CDCl_3$) of **47**



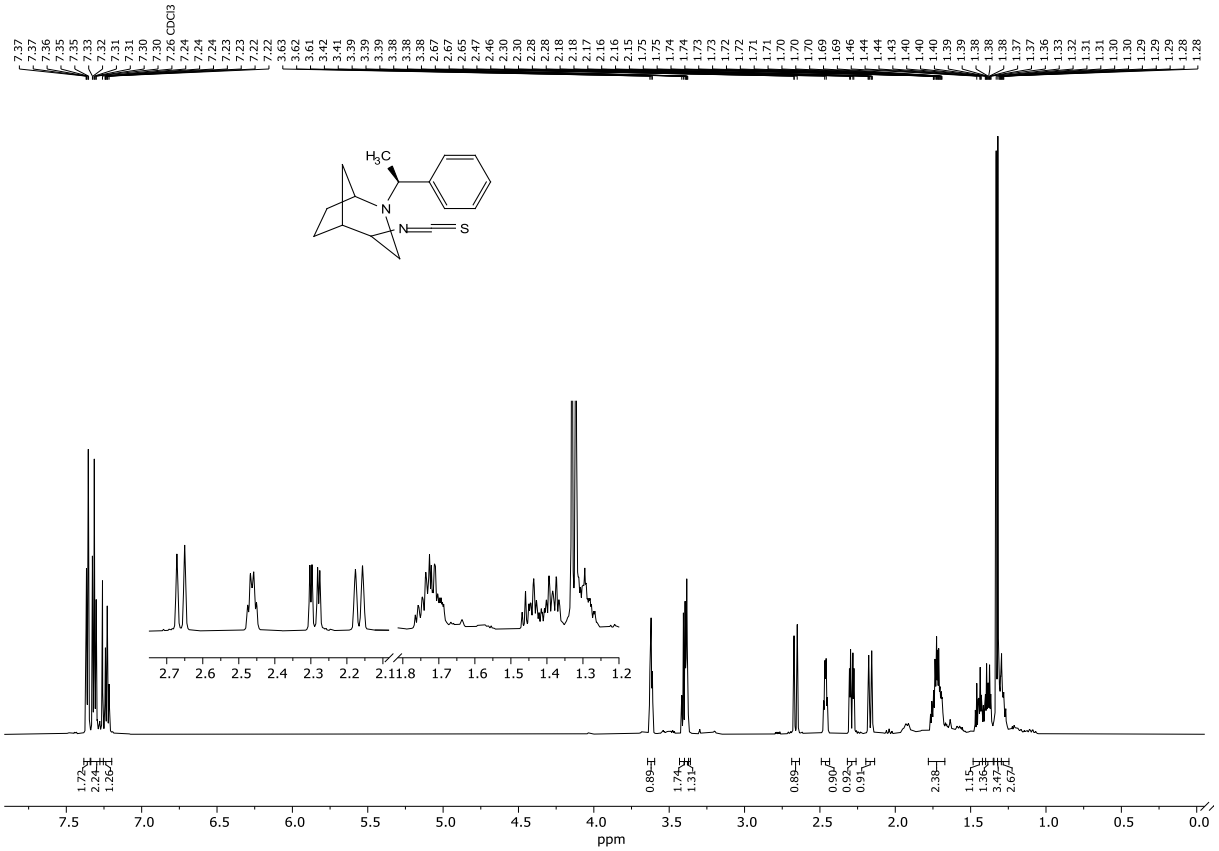
^{1}H-NMR (400 MHz, $CDCl_3$) of **48**



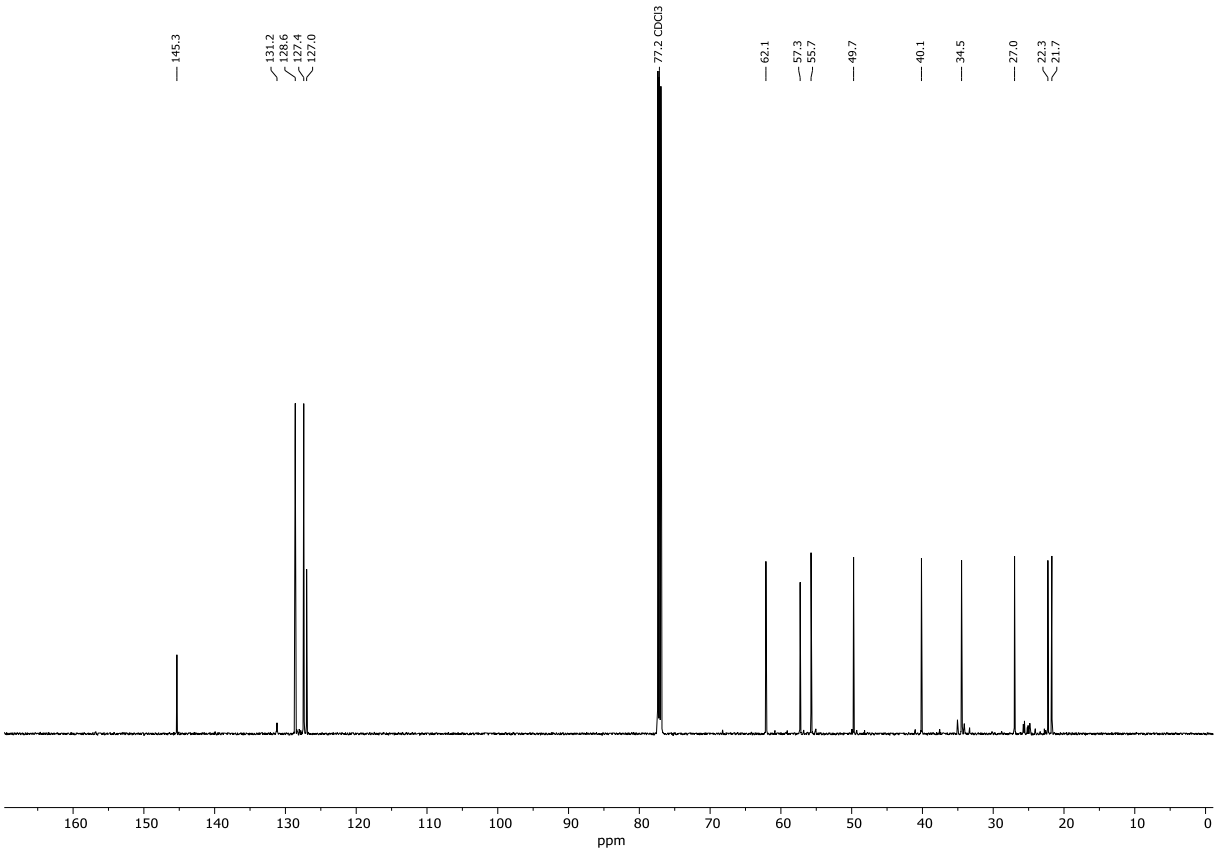
^{13}C-NMR (100 MHz, $CDCl_3$) of **48**



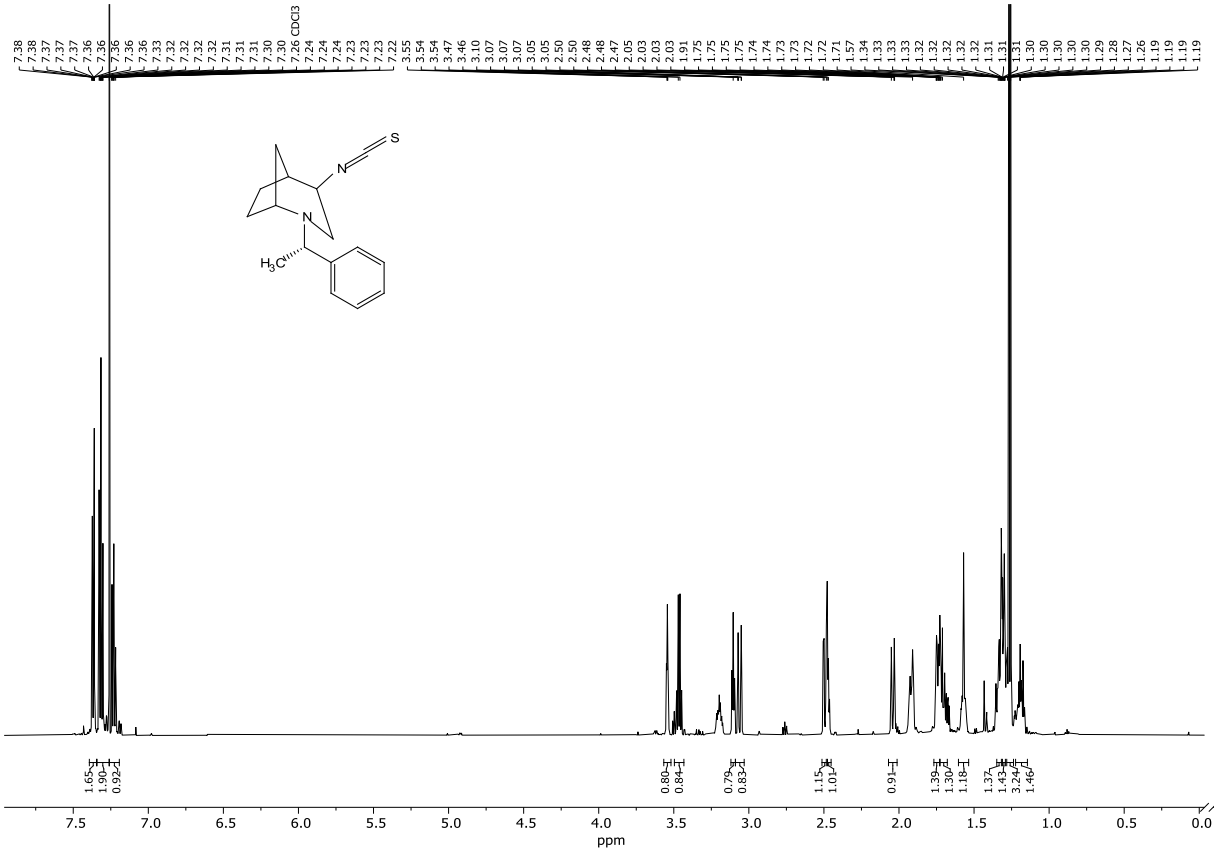
^{1}H-NMR (600 MHz, $CDCl_3$) of (1*S*,4*S*,5*R*)-**51**



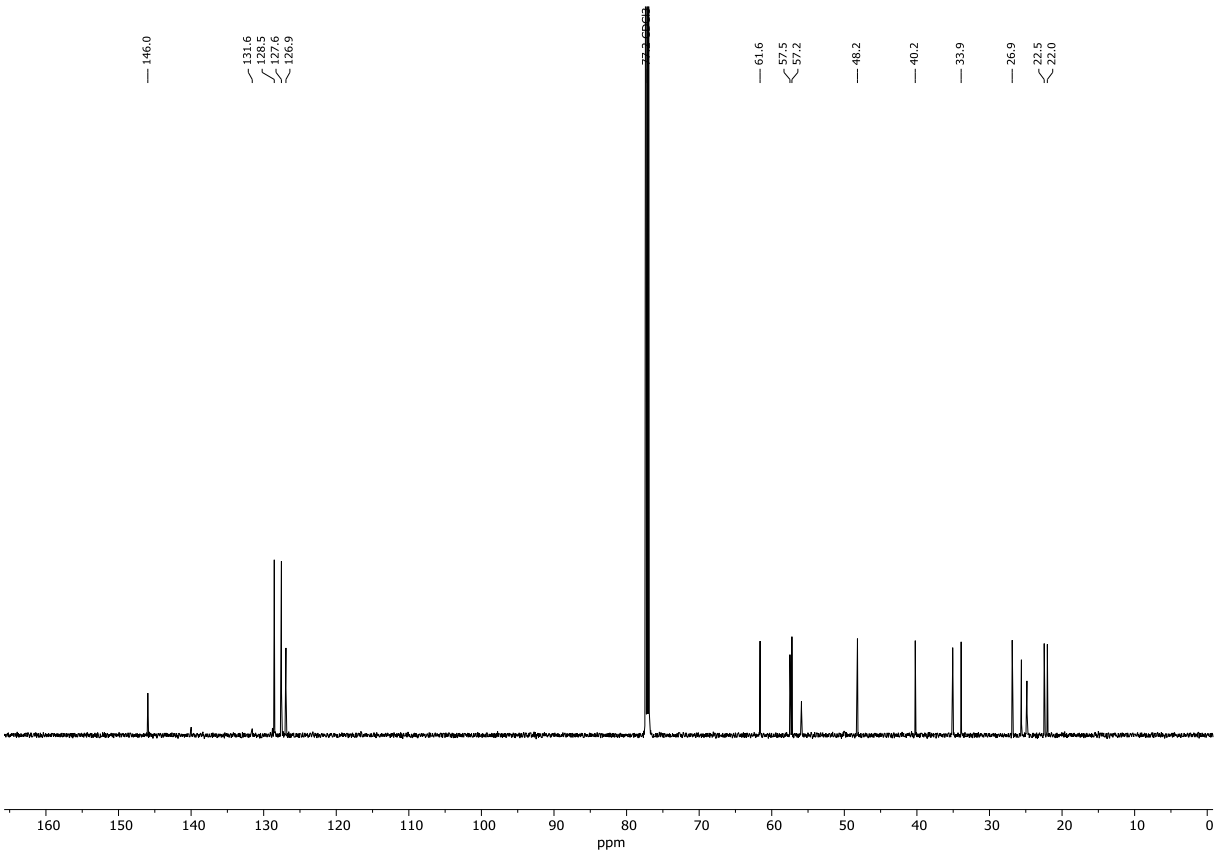
^{13}C-NMR (151 MHz, $CDCl_3$) of (1*S*,4*S*,5*R*)-**51**



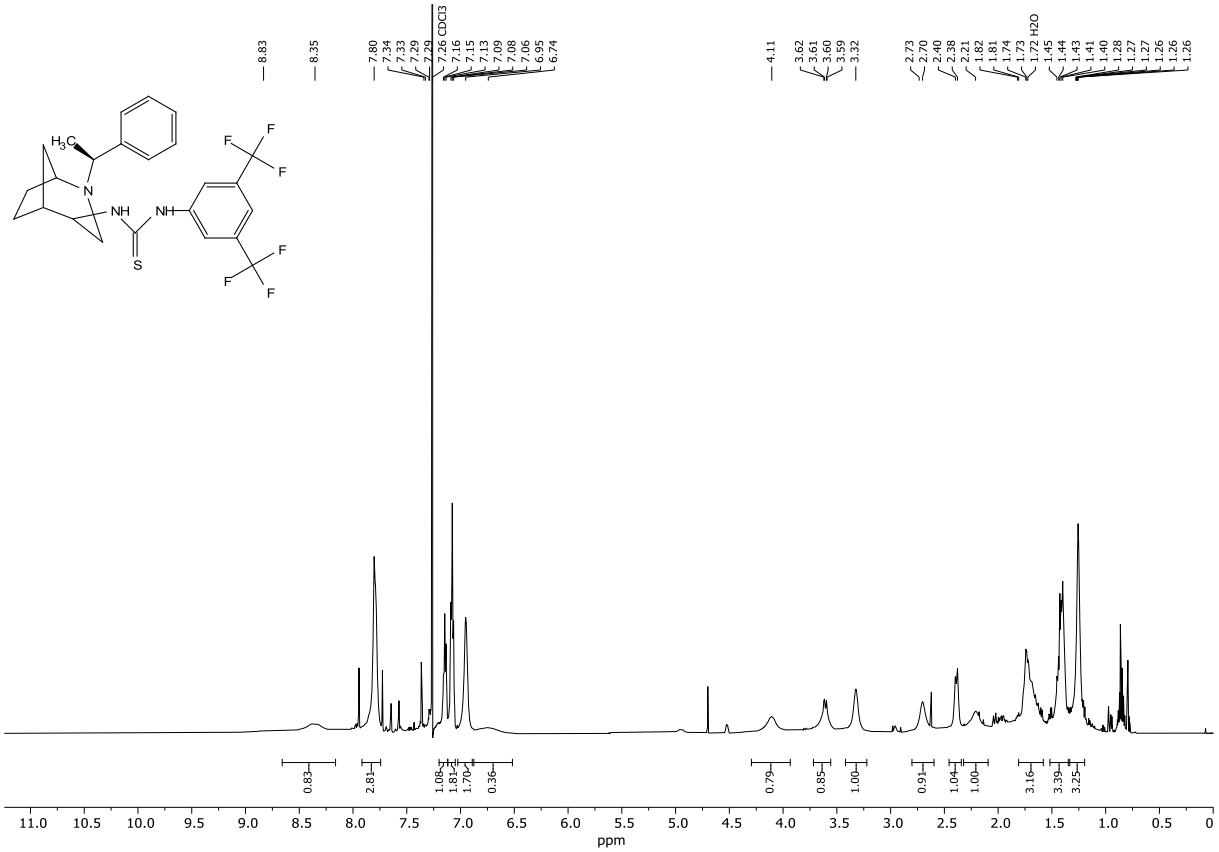
^{1}H-NMR (400 MHz, $CDCl_3$) of (1*R*,4*R*,5*S*)-**51**



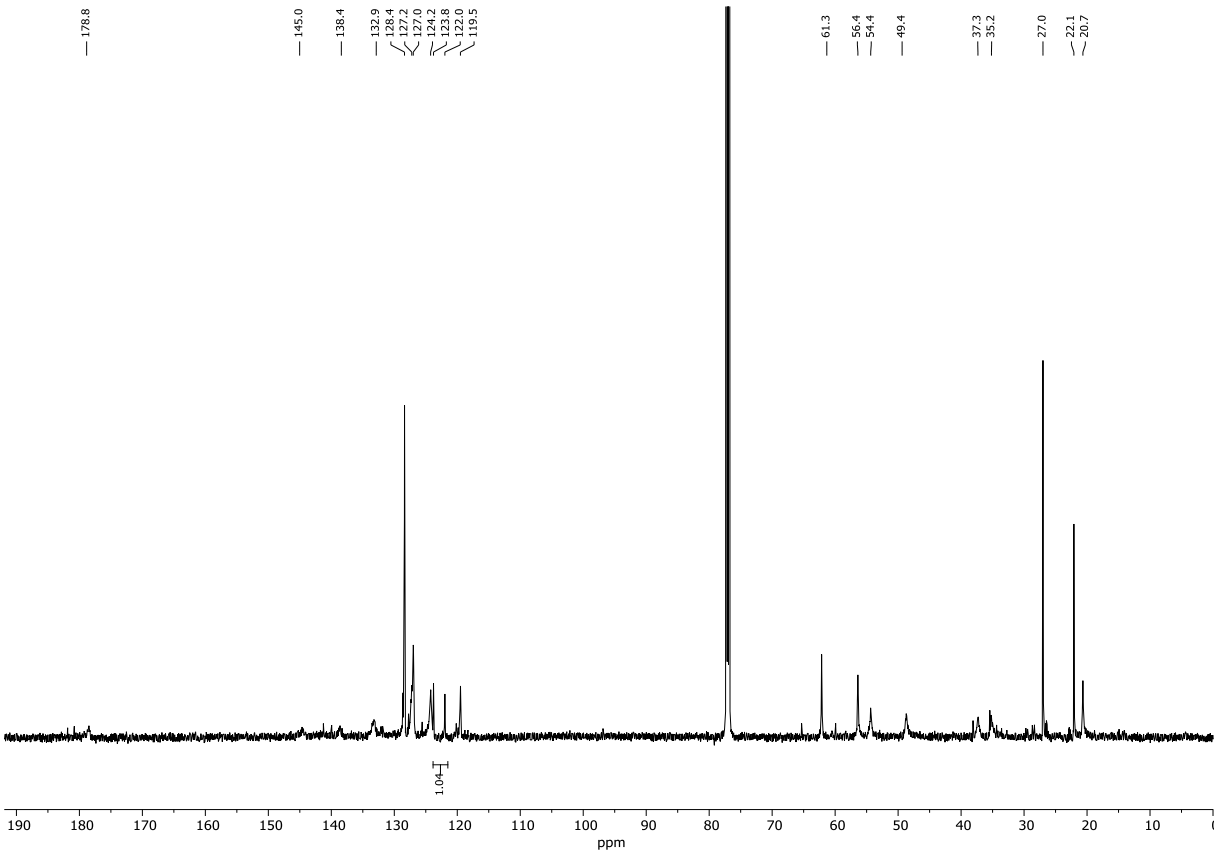
^{13}C-NMR (101 MHz, $CDCl_3$) of (1*R*,4*R*,5*S*)-**51**



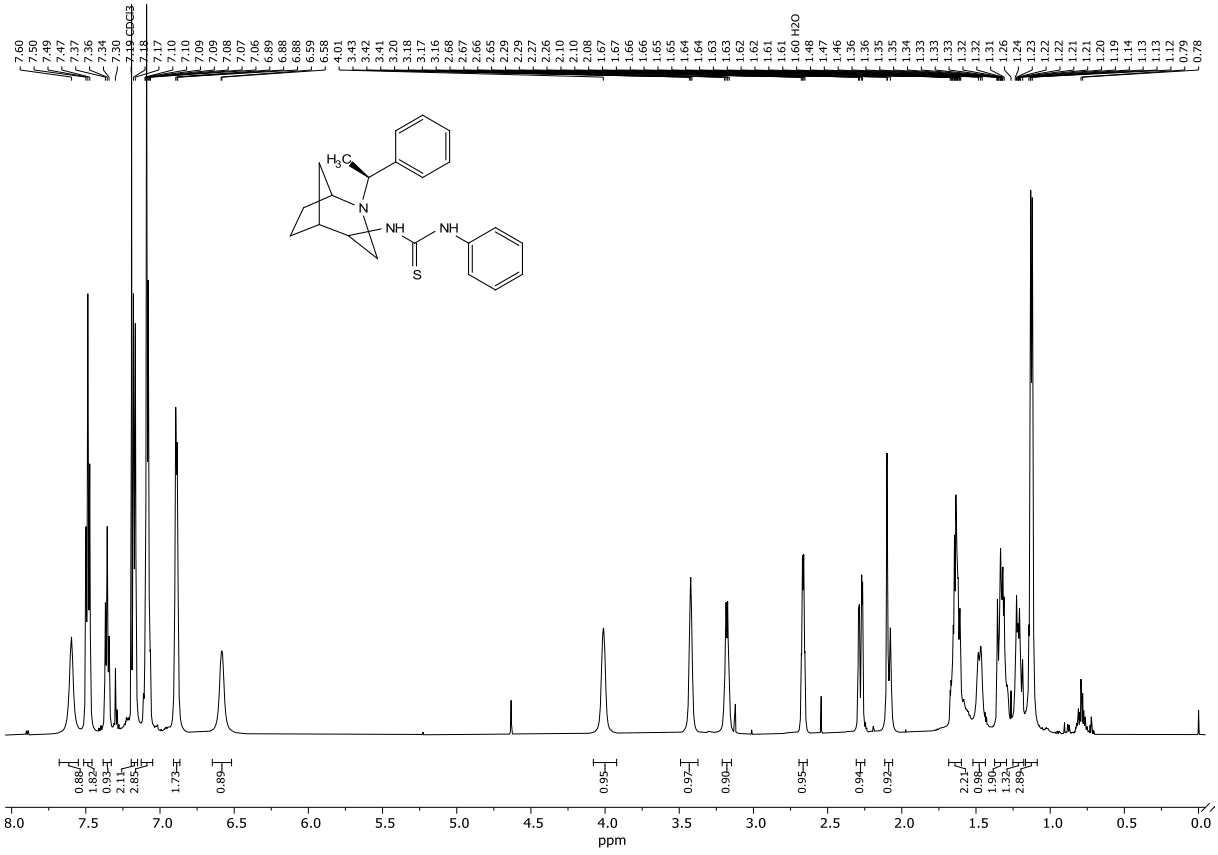
^{1}H-NMR (600 MHz, $CDCl_3$) of **52**



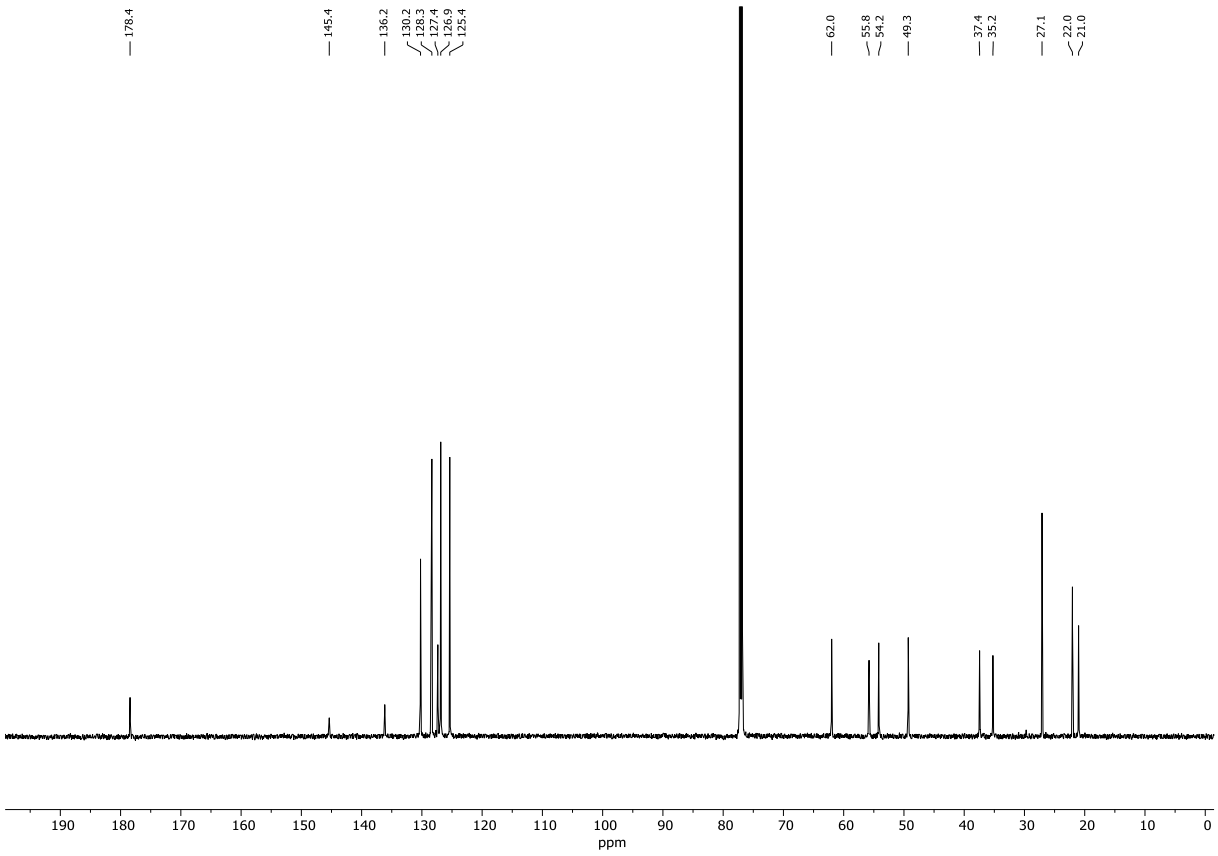
^{13}C-NMR (151 MHz, $CDCl_3$) of **52**



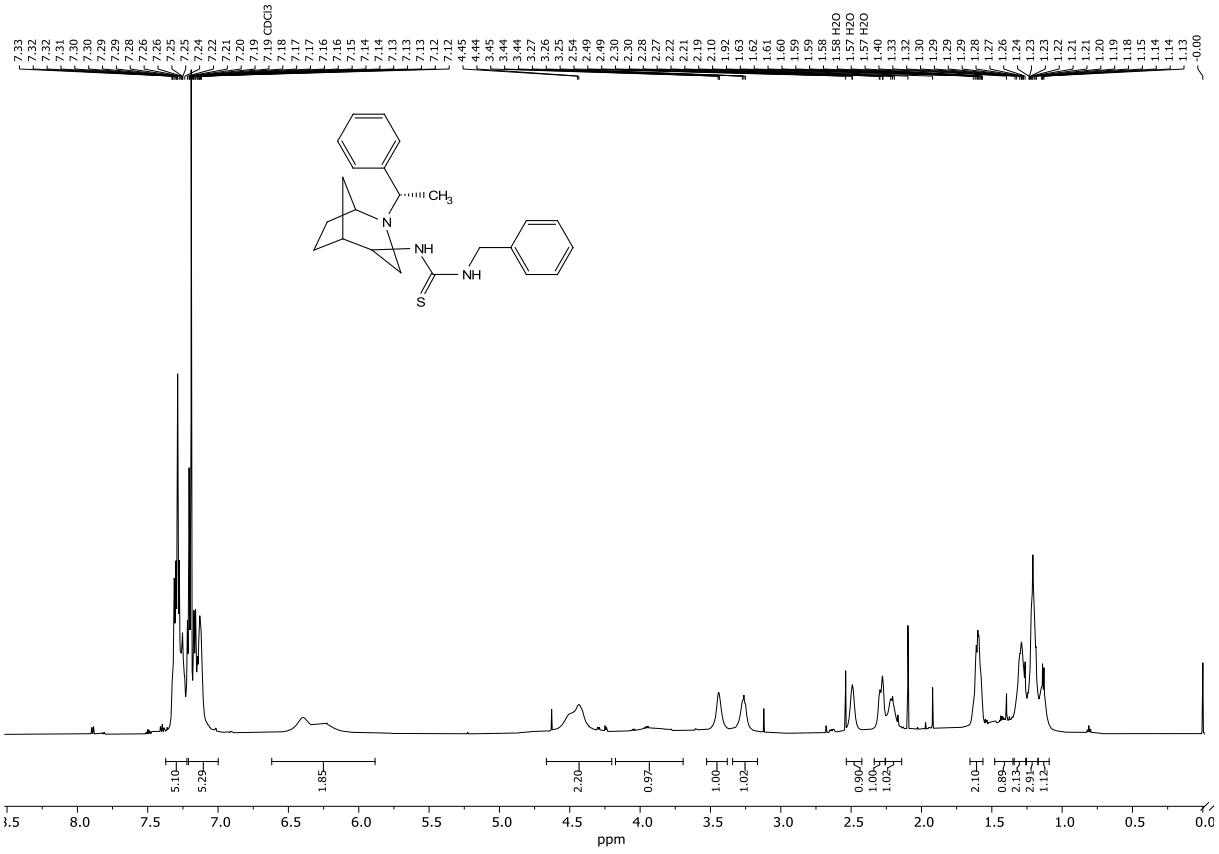
^{1}H-NMR (400 MHz, $CDCl_3$) of **53**



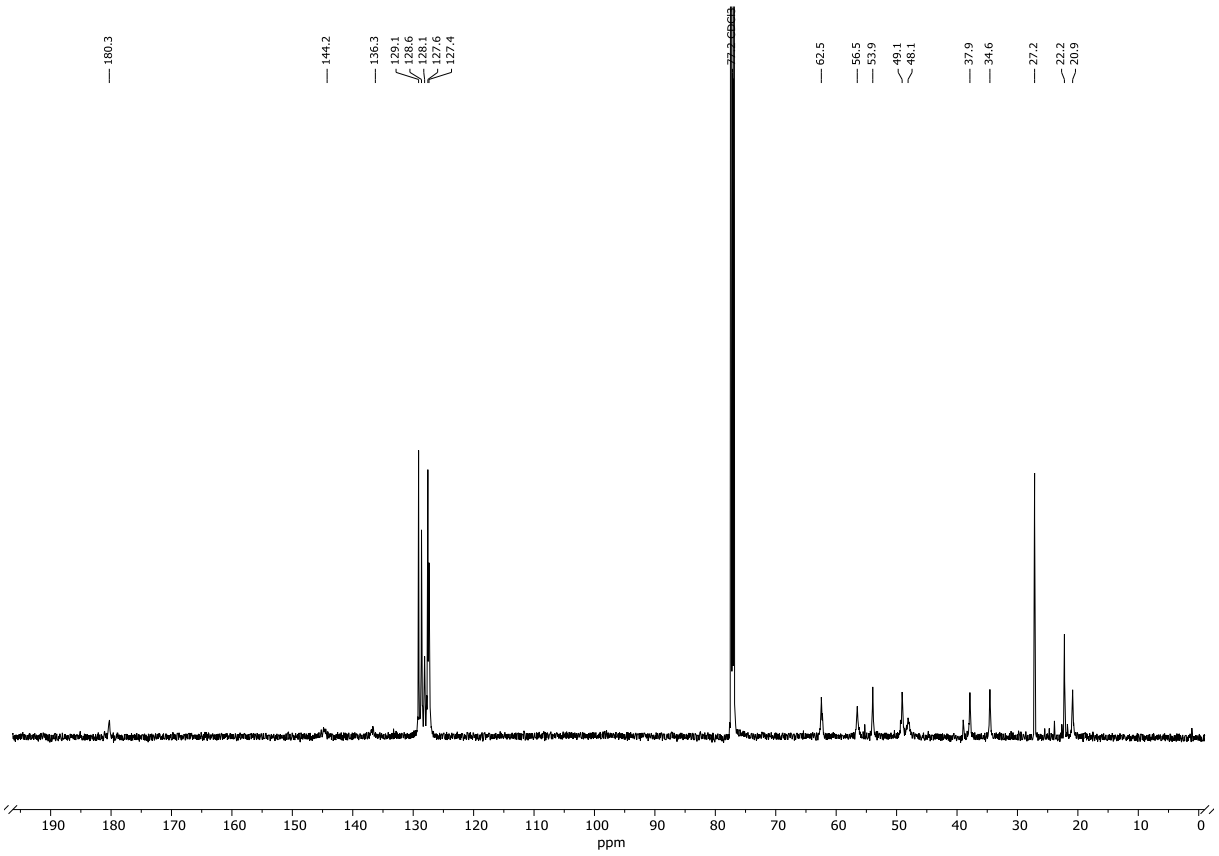
^{13}C-NMR (100 MHz, $CDCl_3$) of **53**



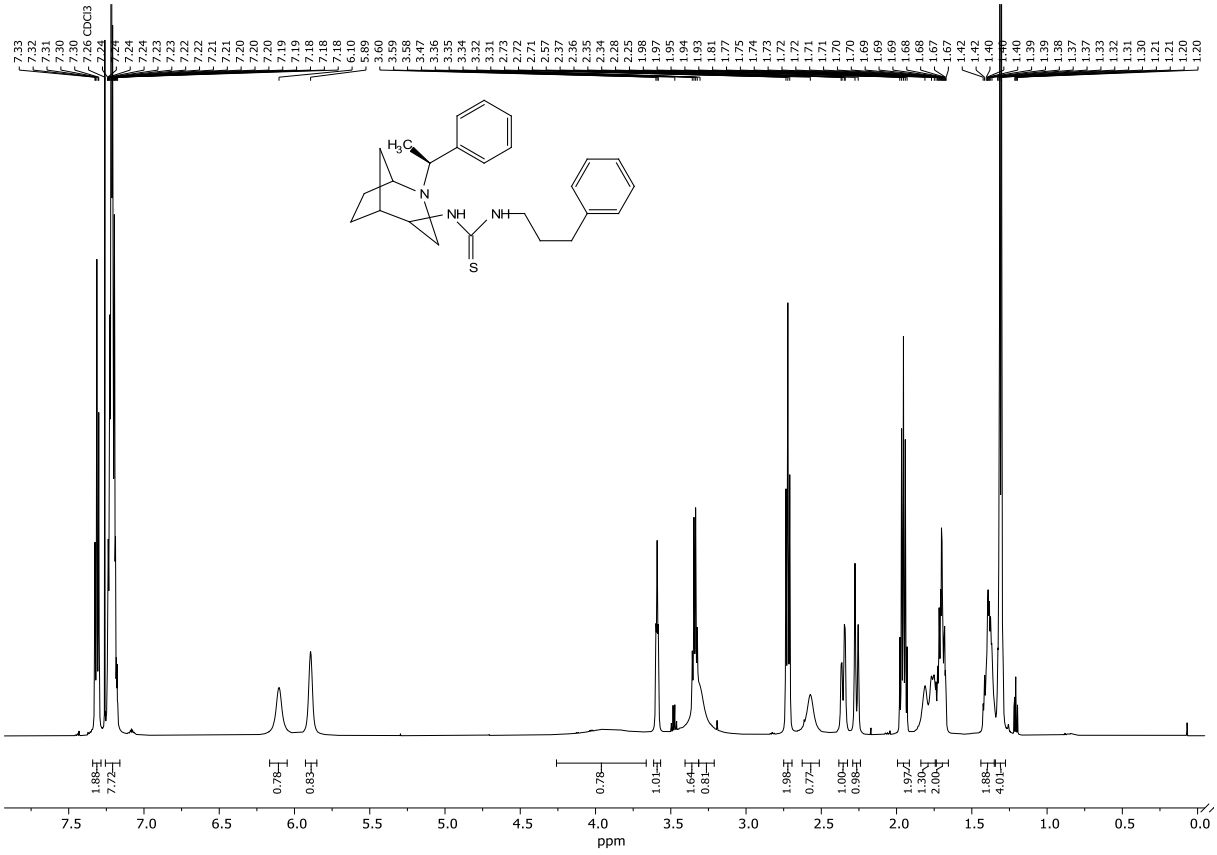
^{1}H-NMR (400 MHz, $CDCl_3$) of **54**



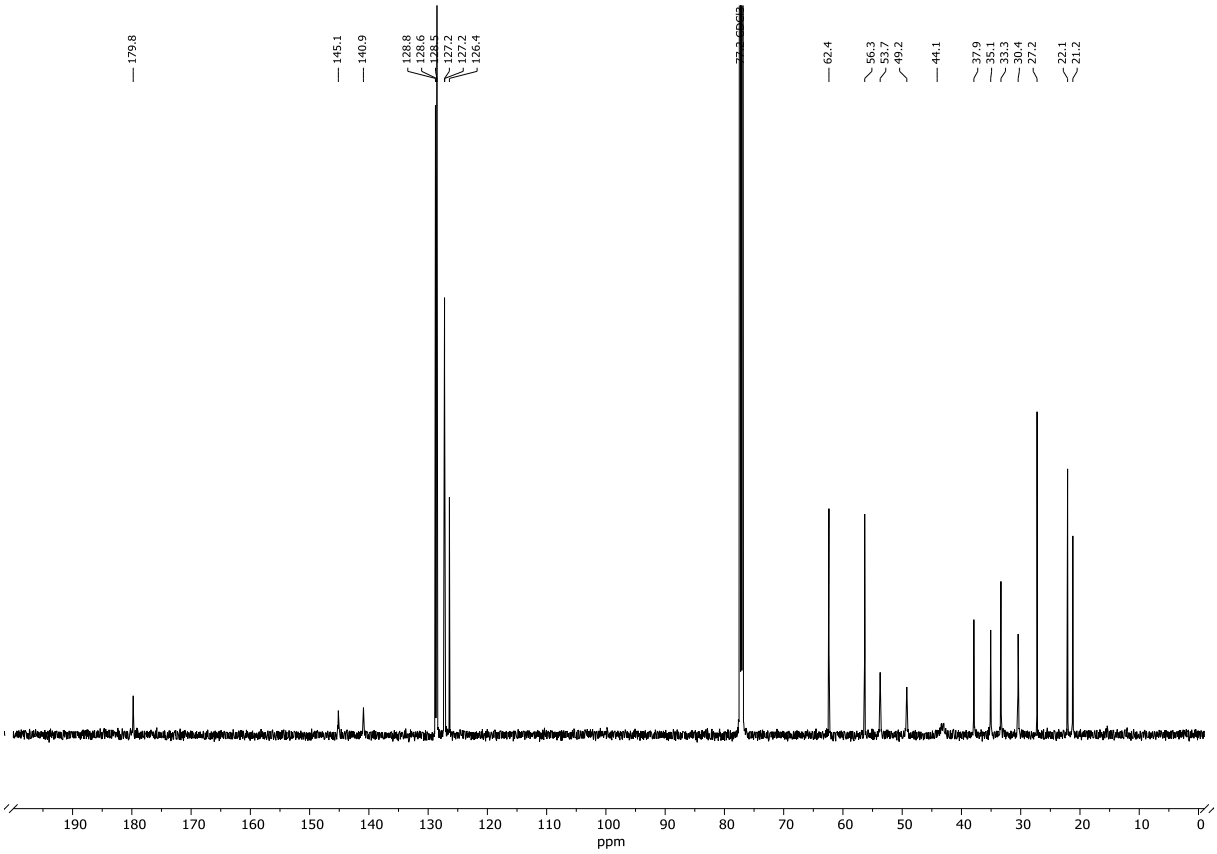
^{13}C-NMR (100 MHz, $CDCl_3$) of **54**



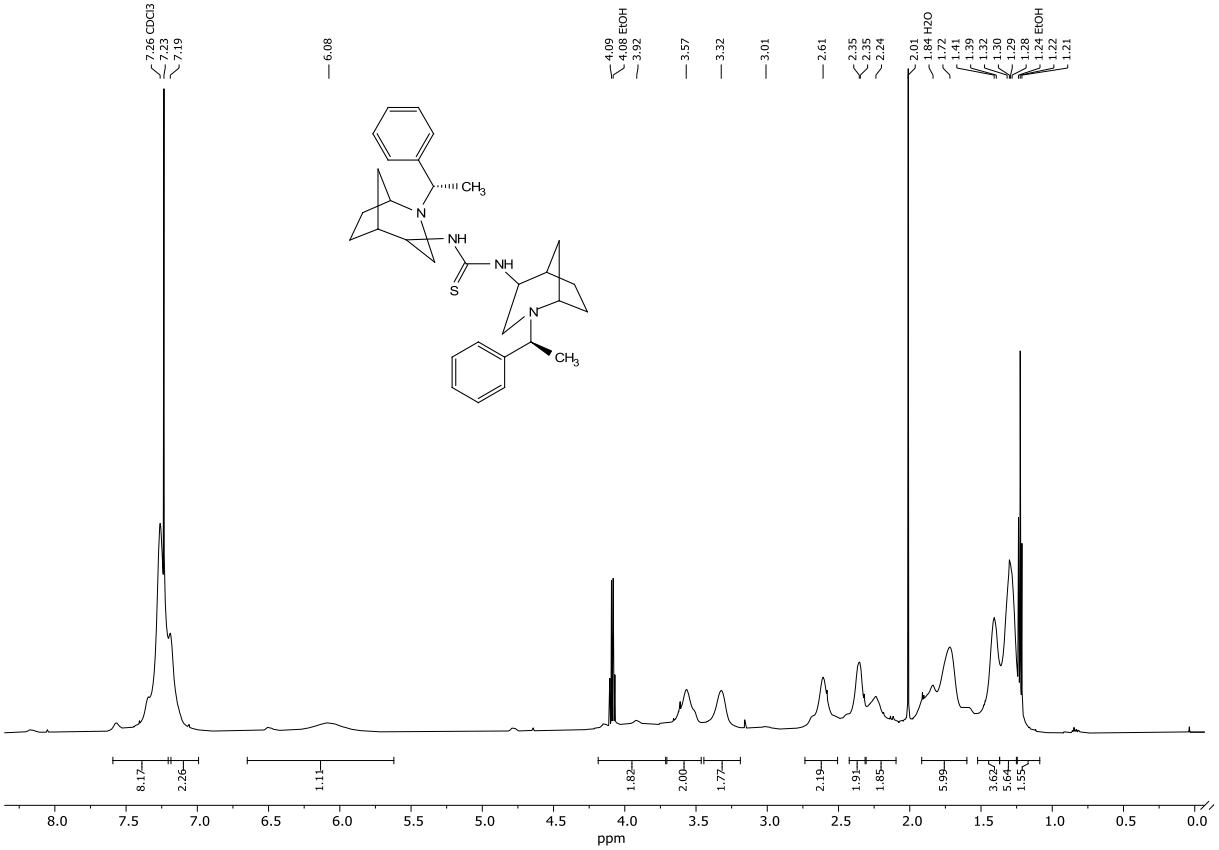
^{1}H-NMR (400 MHz, $CDCl_3$) of **55**



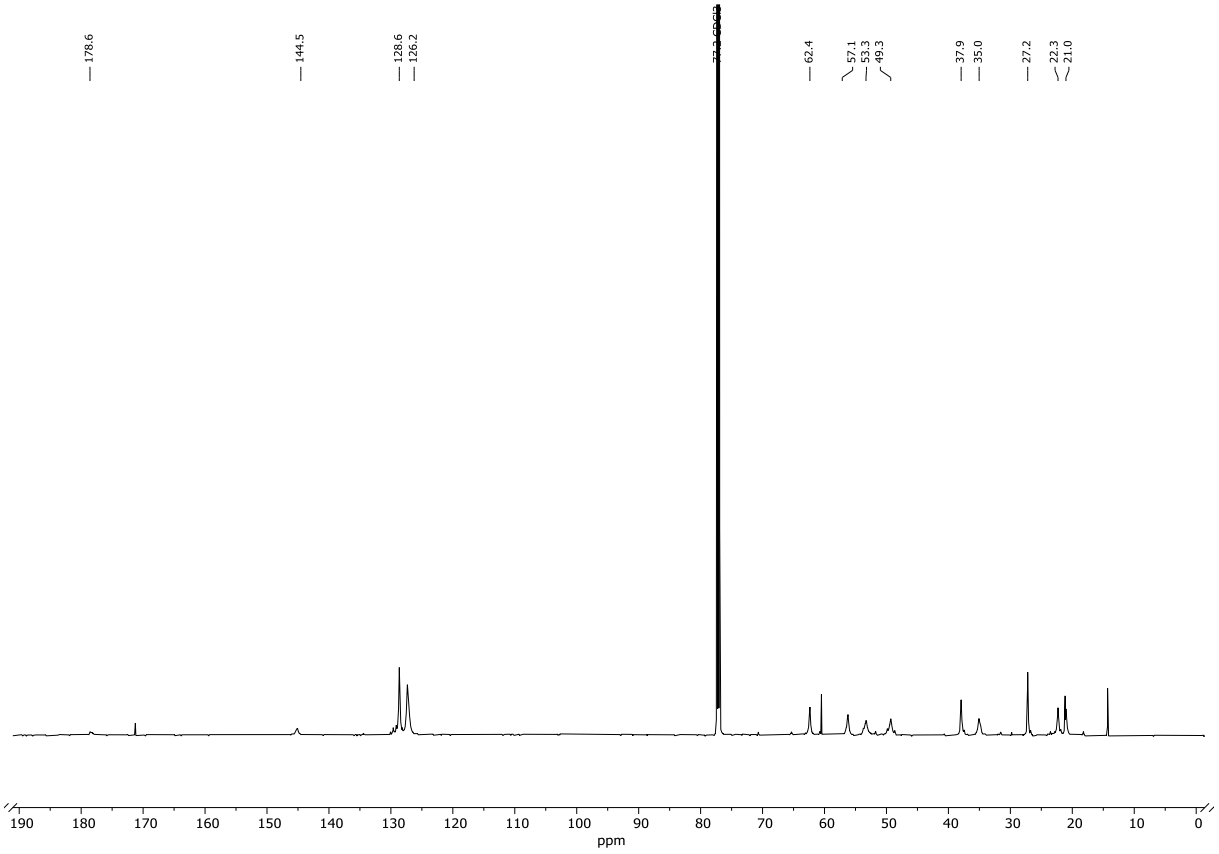
^{13}C-NMR (100 MHz, $CDCl_3$) of **55**



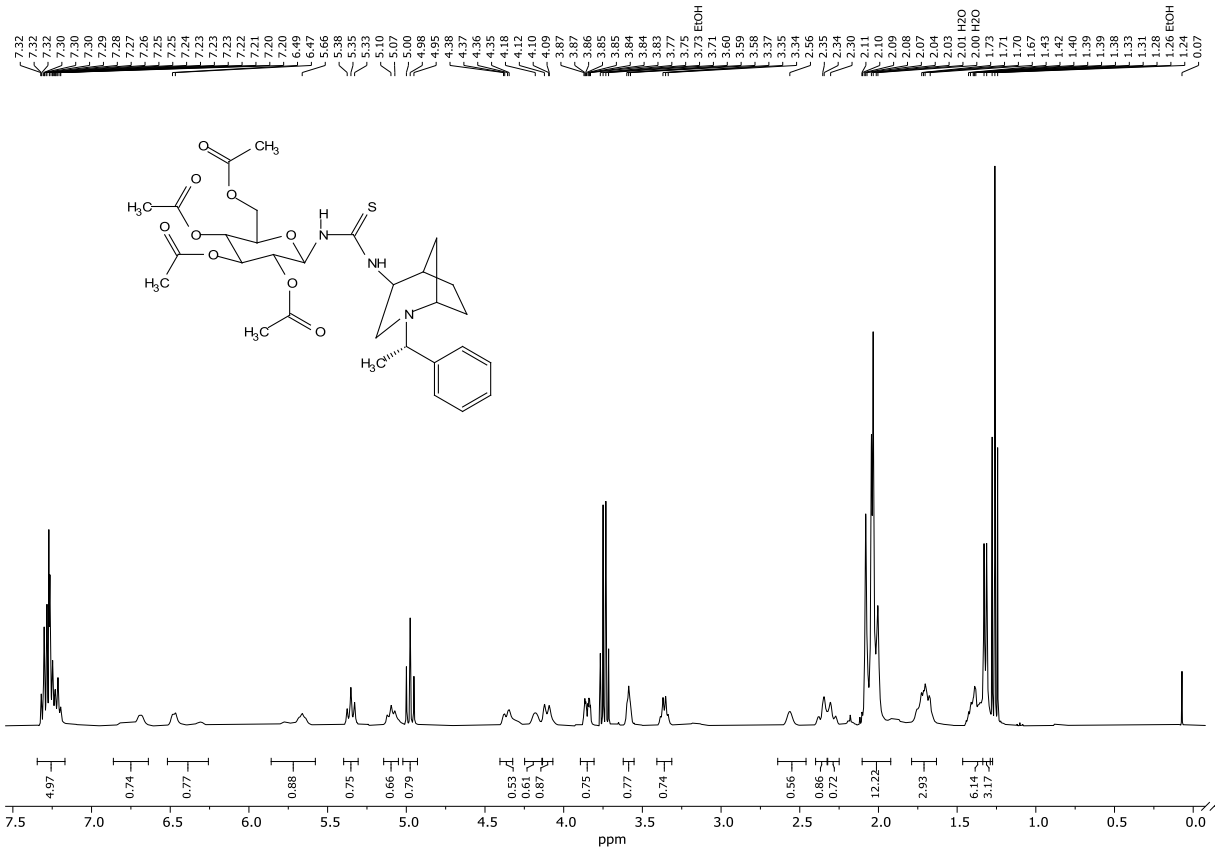
^{1}H-NMR (400 MHz, $CDCl_3$) of **56**



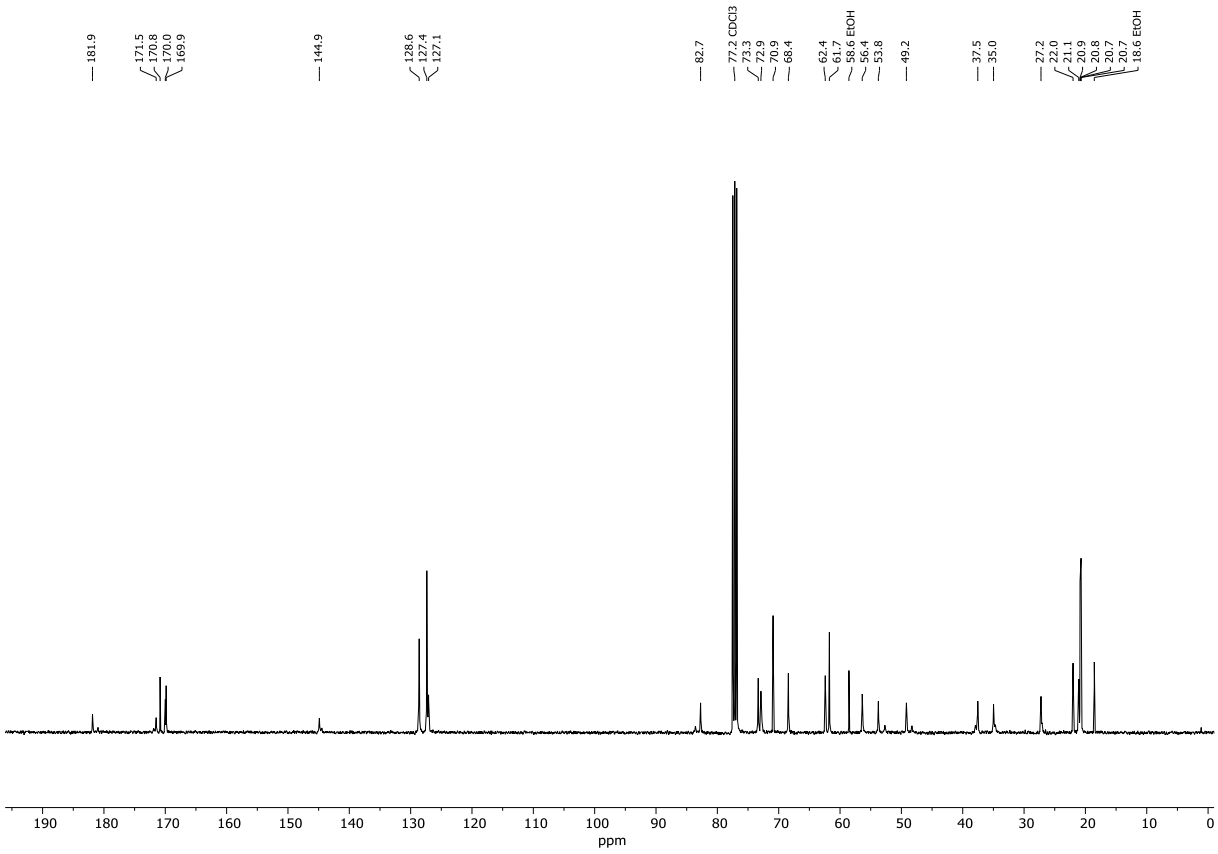
^{13}C-NMR (100 MHz, $CDCl_3$) of **56**



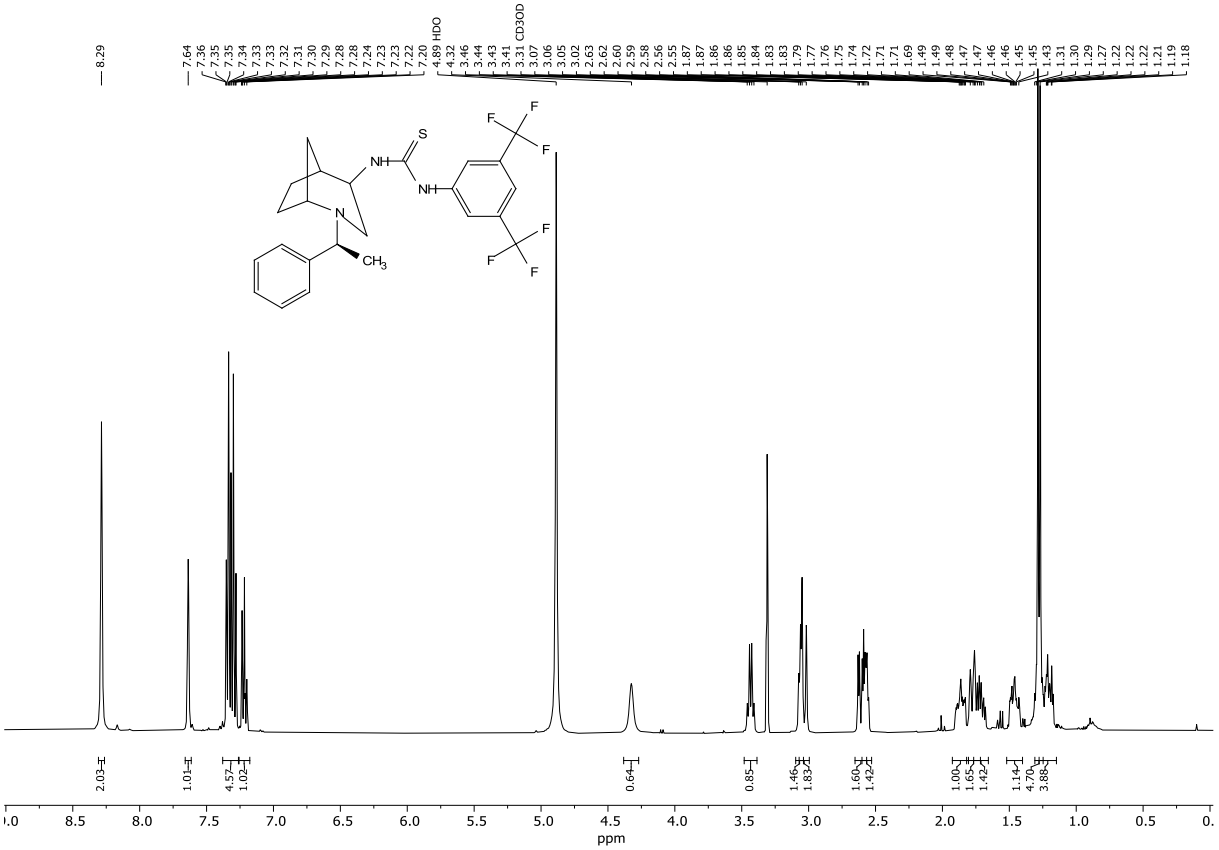
^{1}H-NMR (400 MHz, $CDCl_3$) of **57**



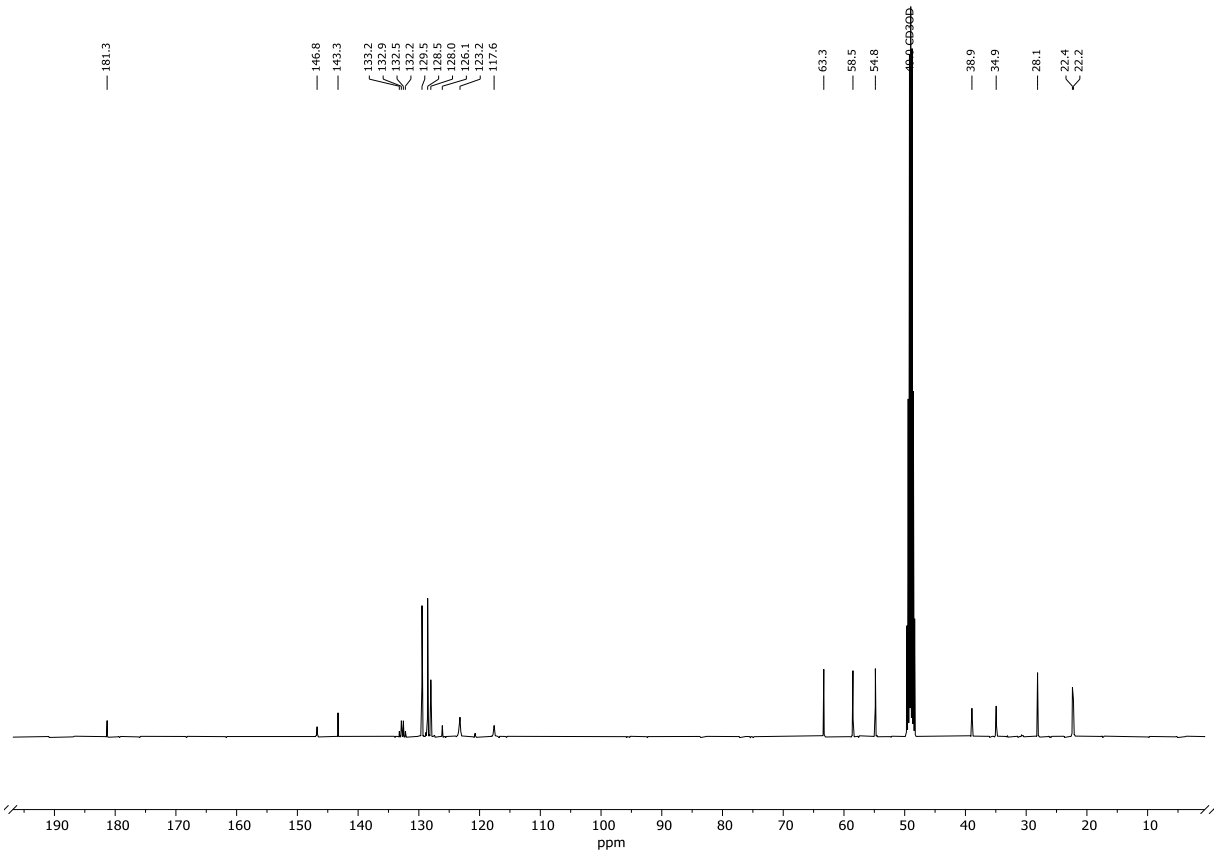
^{13}C-NMR (100 MHz, $CDCl_3$) of **57**



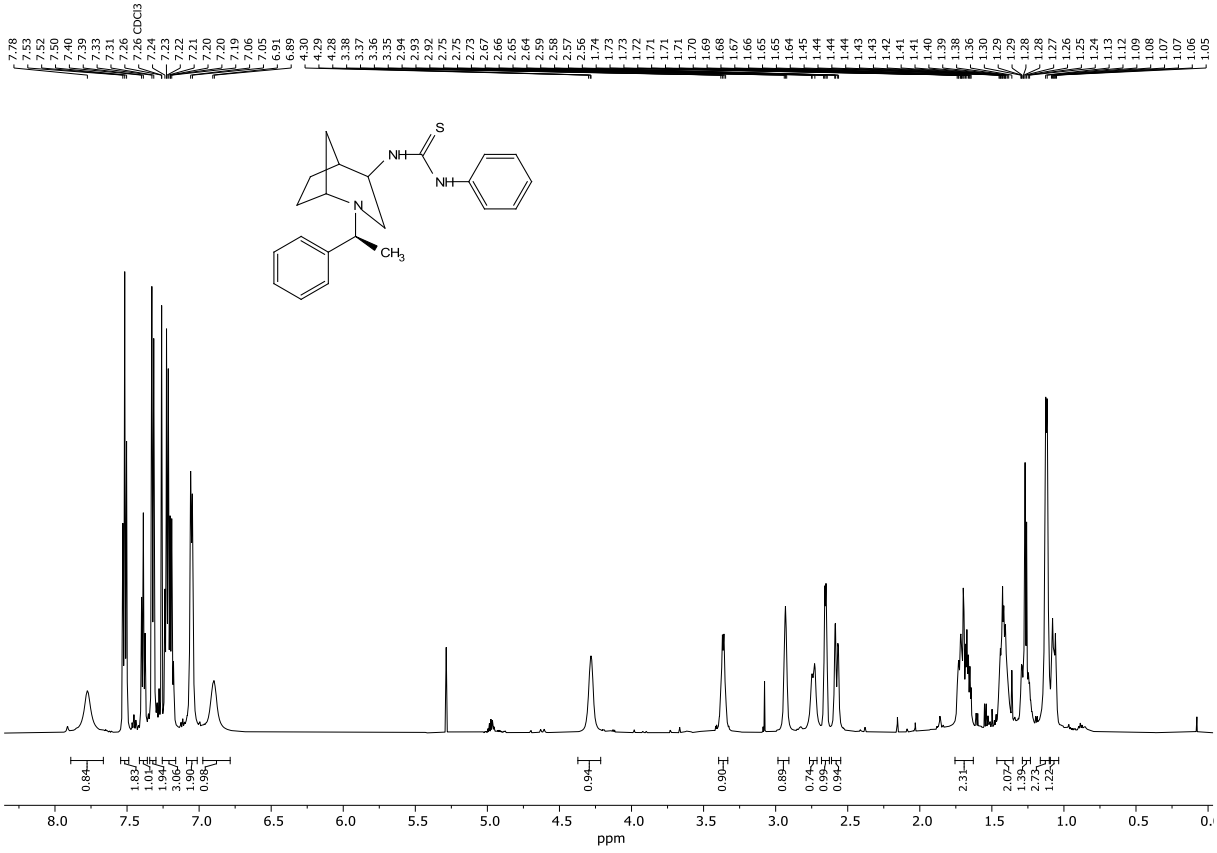
^{1}H-NMR (400 MHz, $CDCl_3$) of **58**



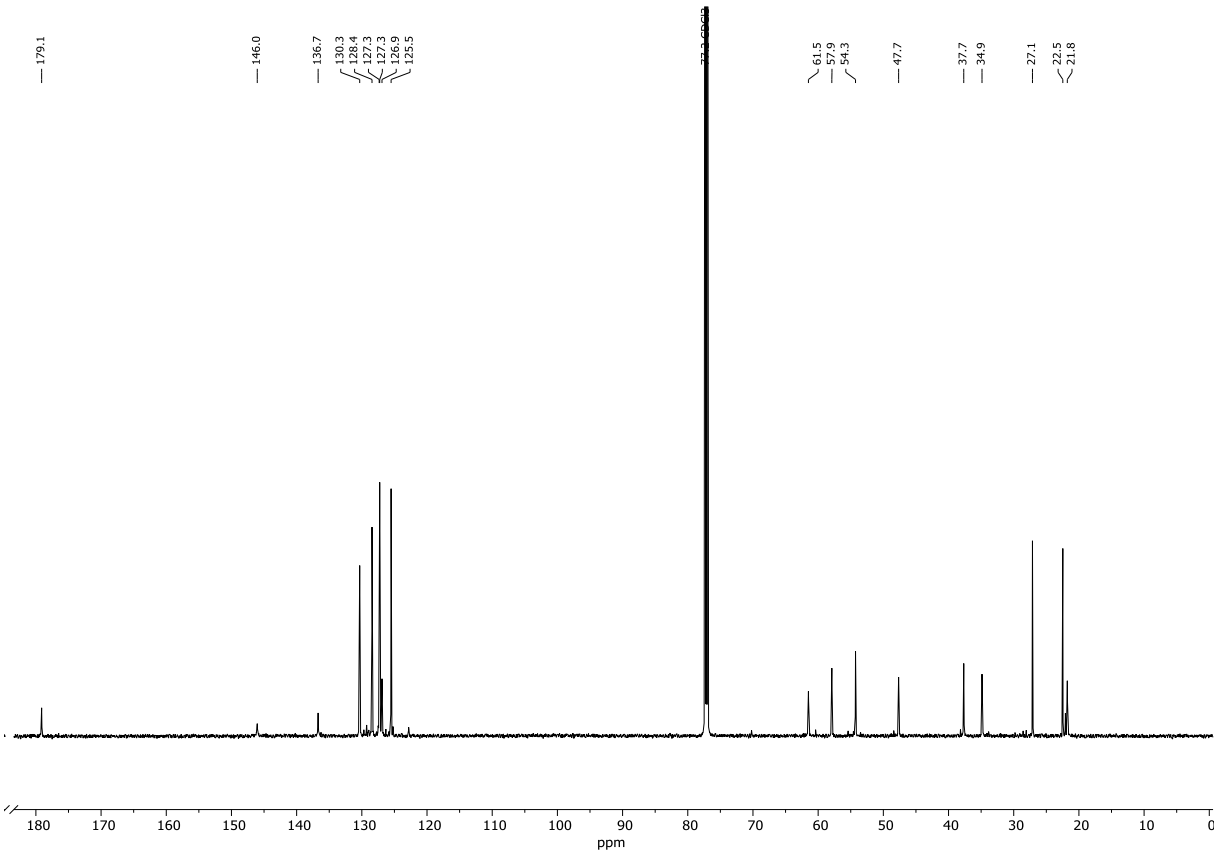
^{13}C-NMR (100 MHz, $CDCl_3$) of **58**



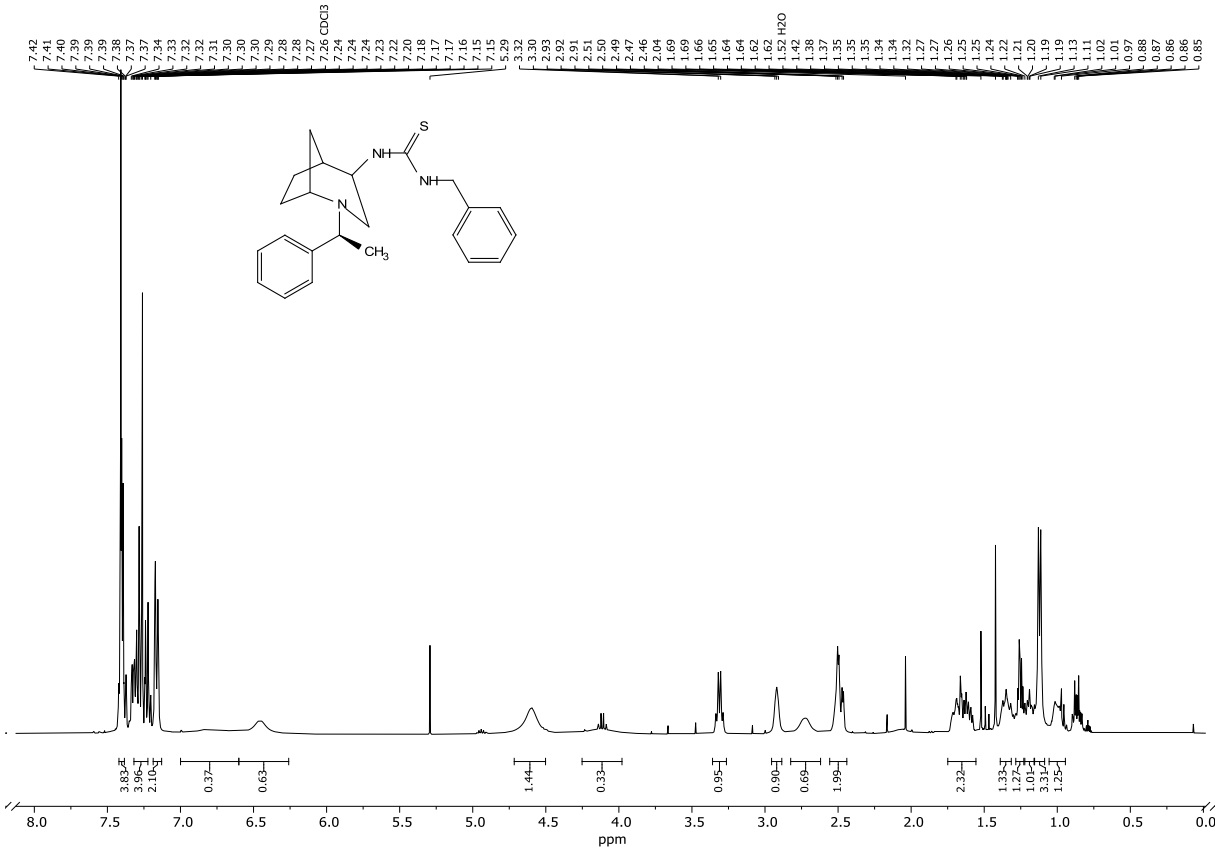
^{1}H-NMR (400 MHz, $CDCl_3$) of **59**



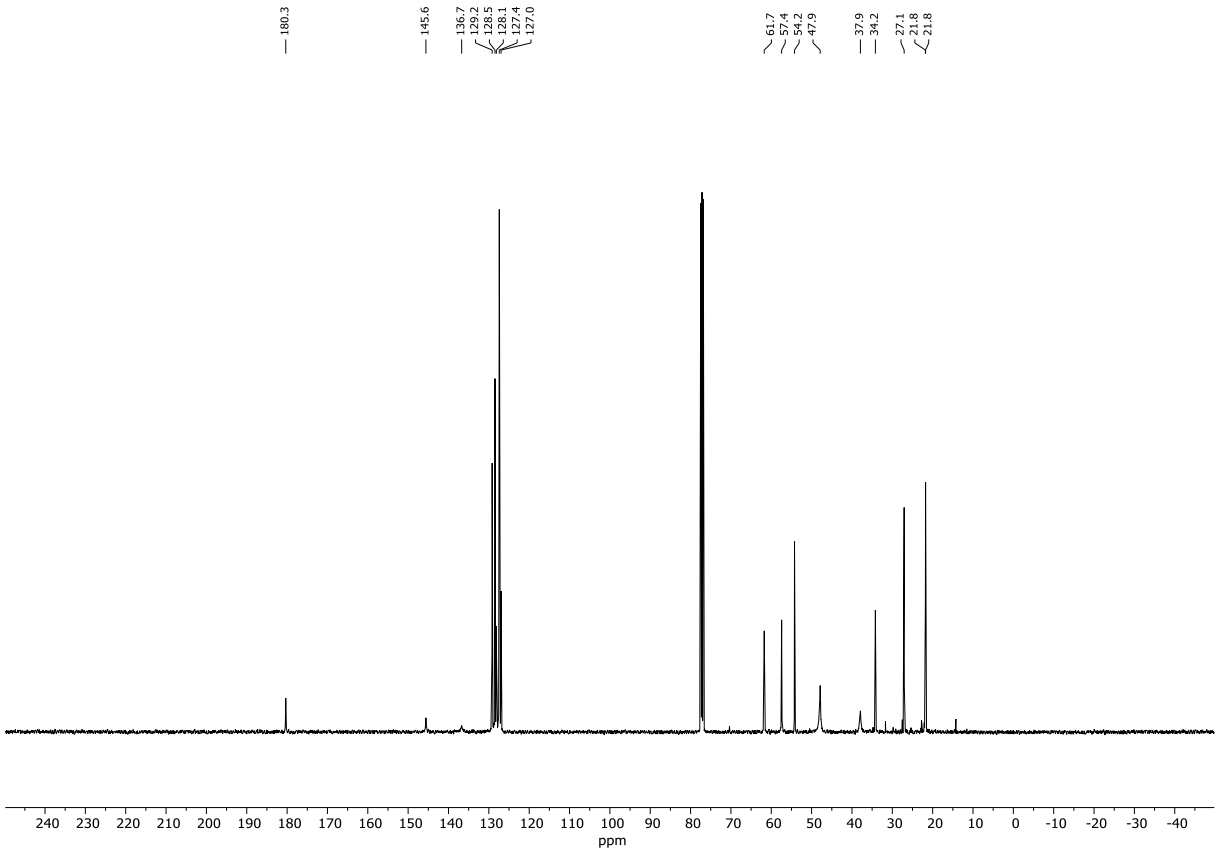
^{13}C-NMR (100 MHz, $CDCl_3$) of **59**



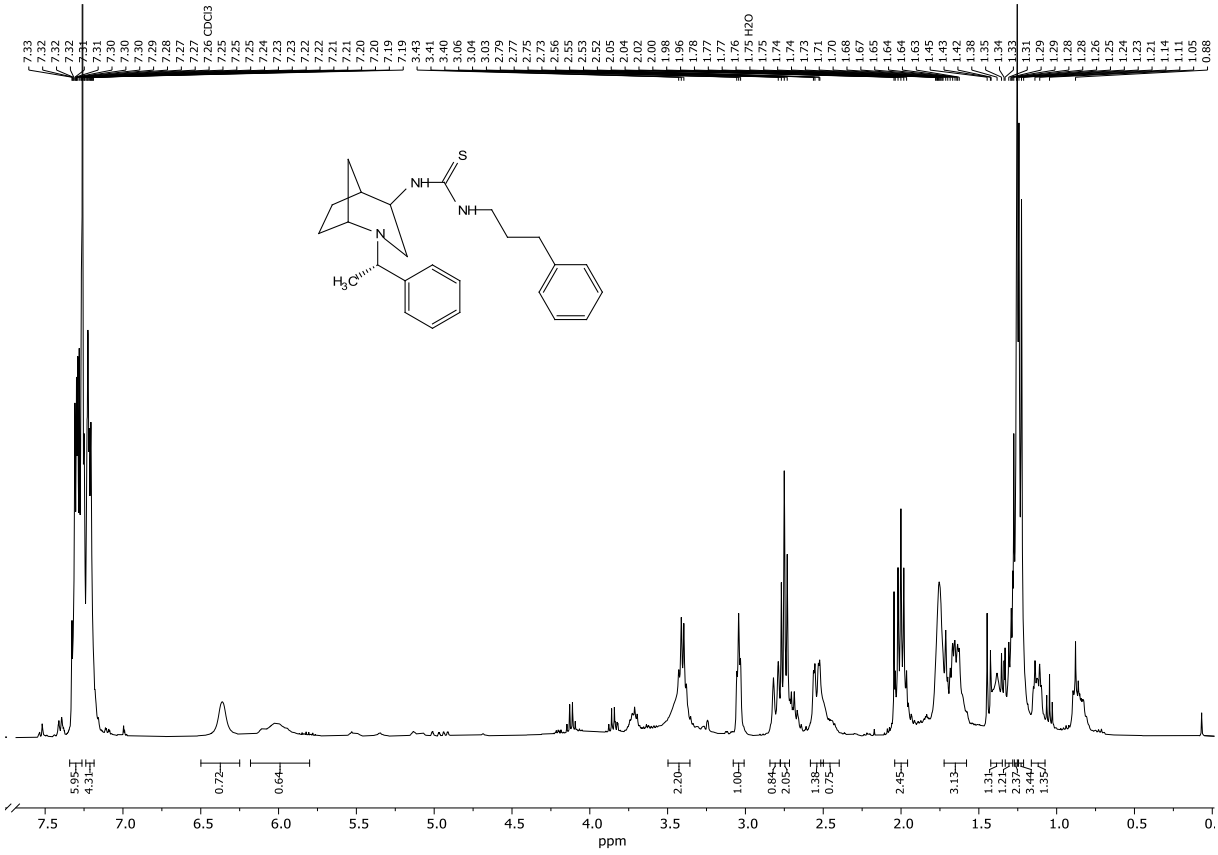
^{1}H-NMR (400 MHz, $CDCl_3$) of **60**



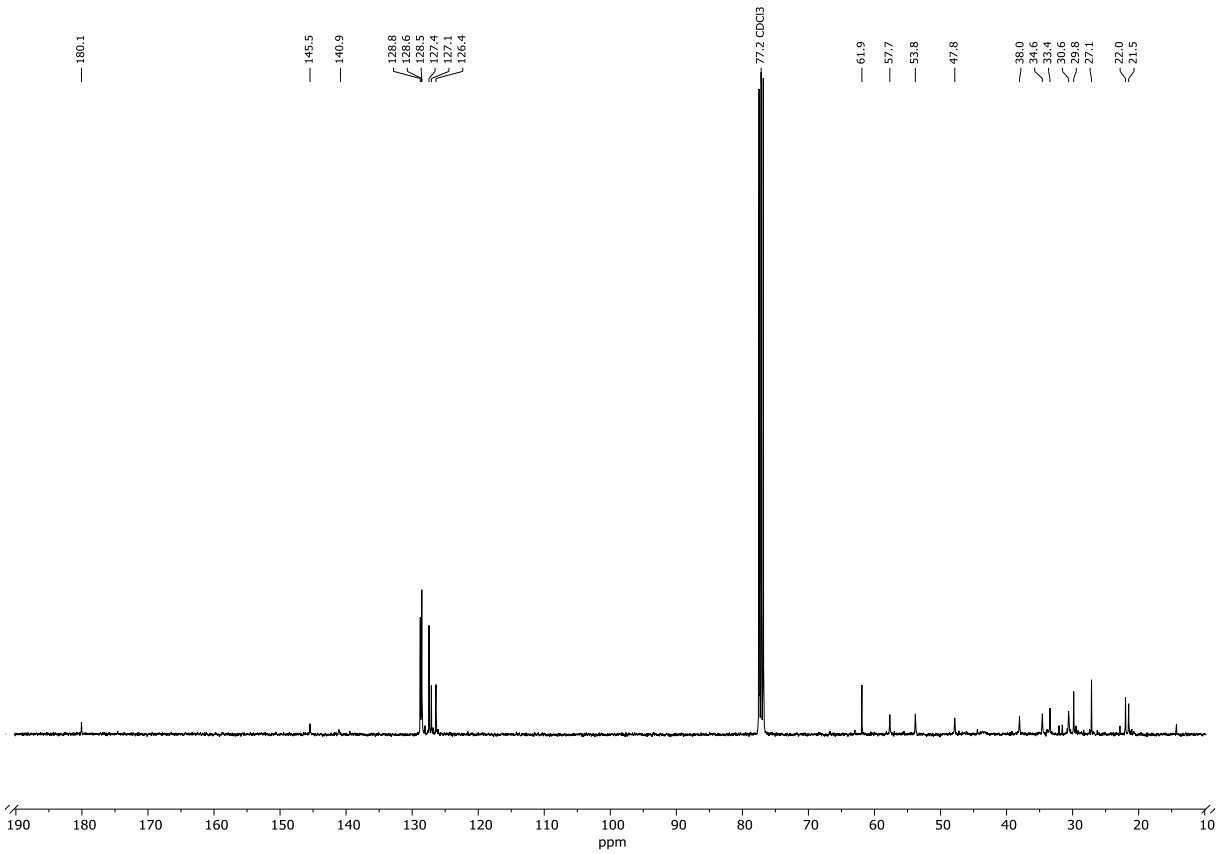
^{13}C-NMR (100 MHz, $CDCl_3$) of **60**



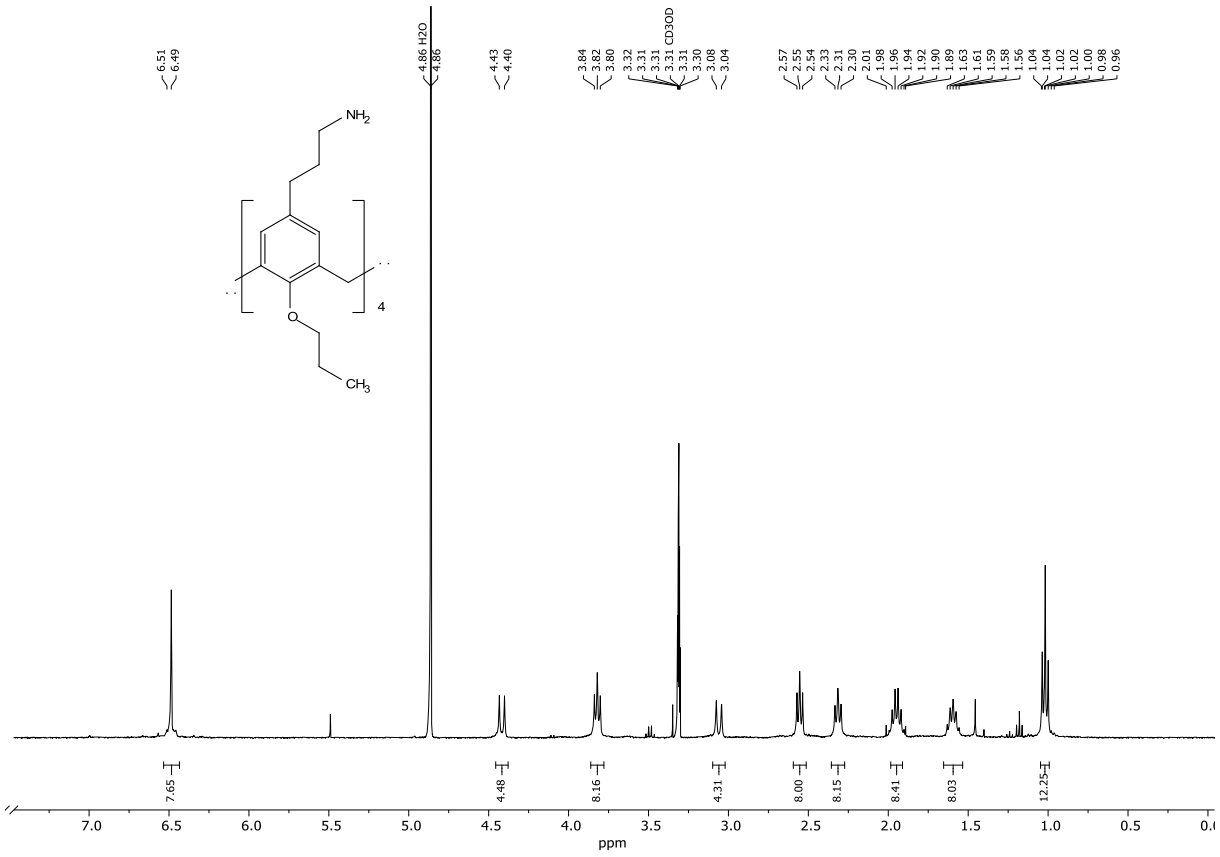
^{1}H-NMR (400 MHz, $CDCl_3$) of **61**



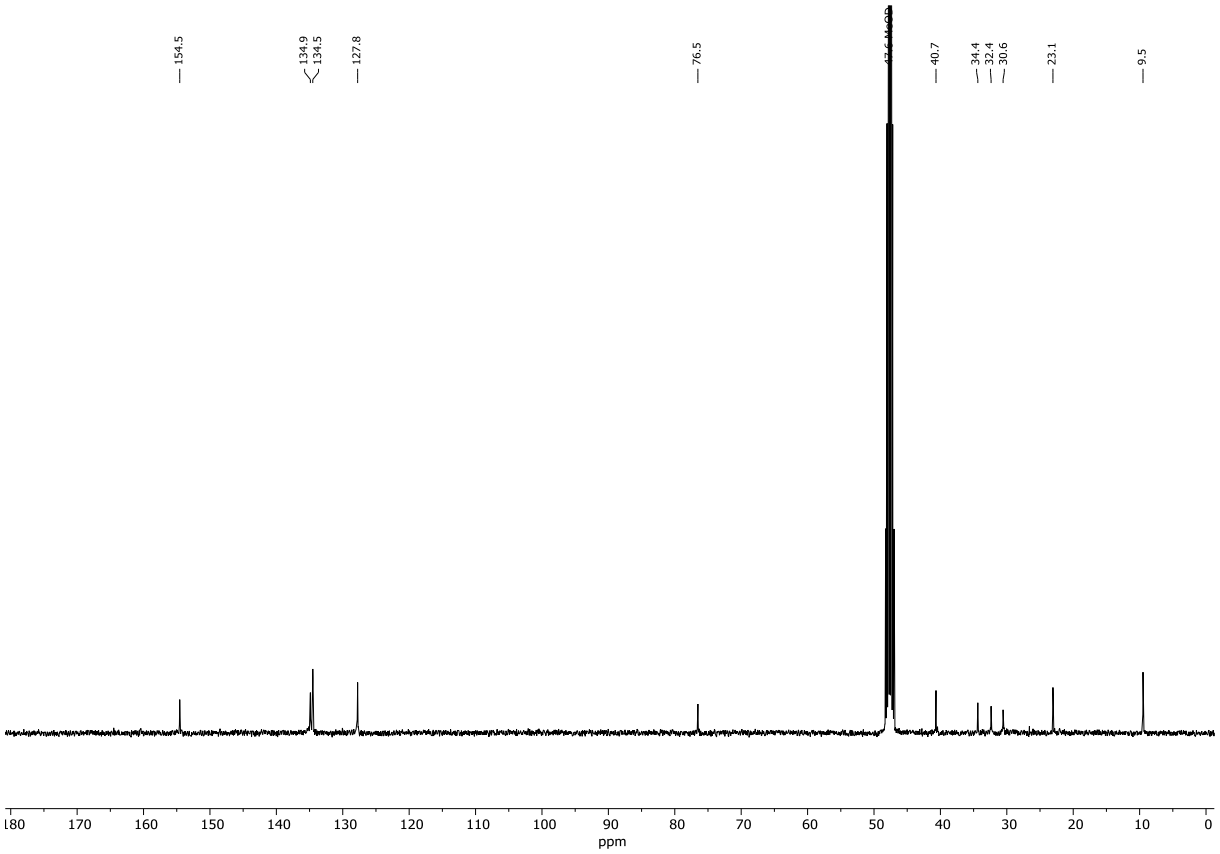
^{13}C-NMR (100 MHz, $CDCl_3$) of **61**



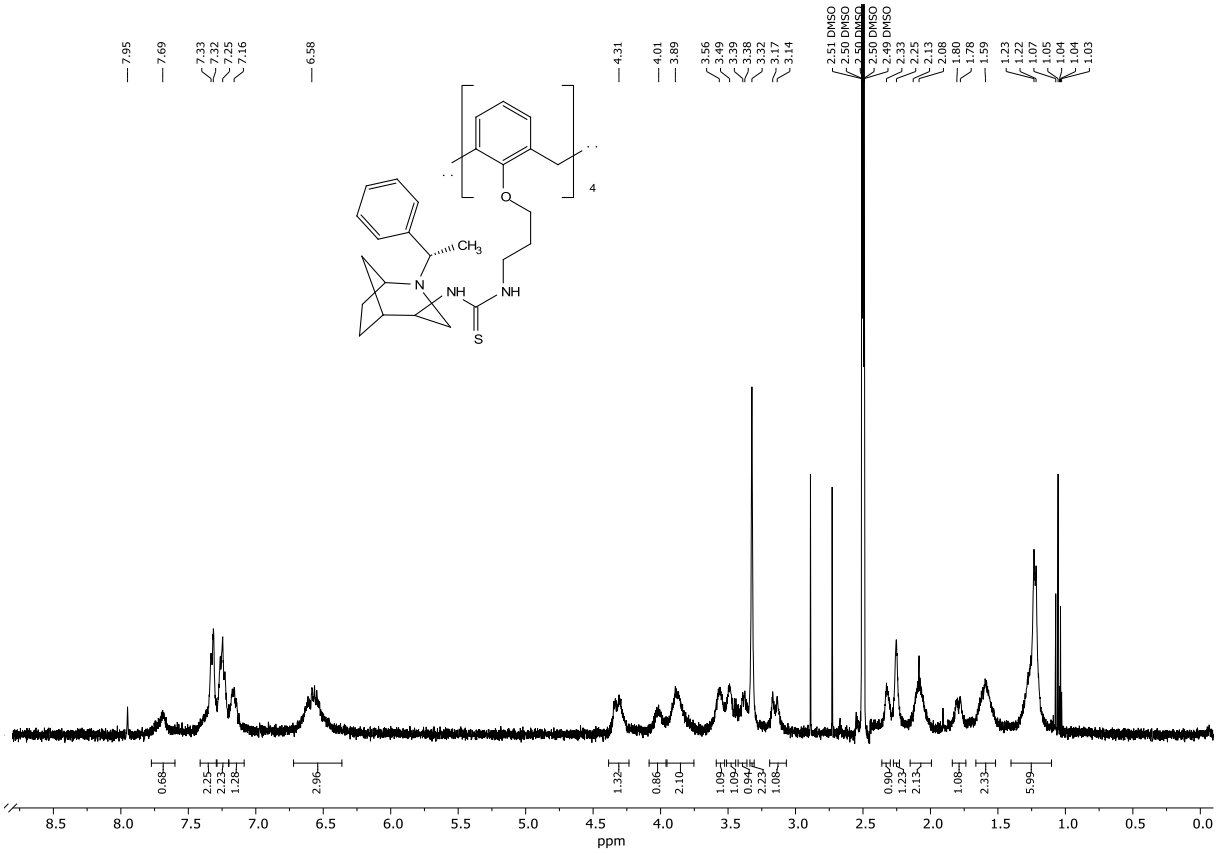
^{1}H-NMR (400 MHz, CD_3OD) of **70**



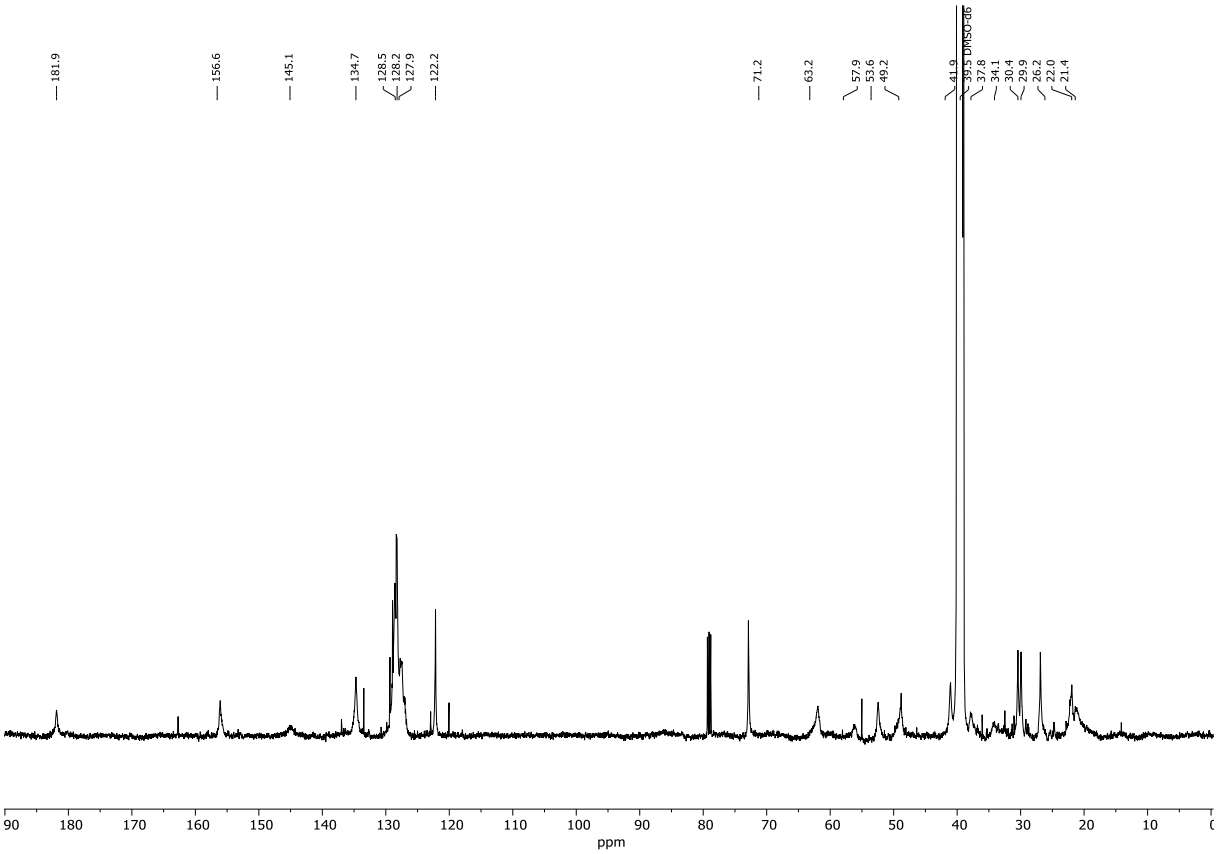
^{13}C-NMR (100 MHz, CD_3OD) of **70**



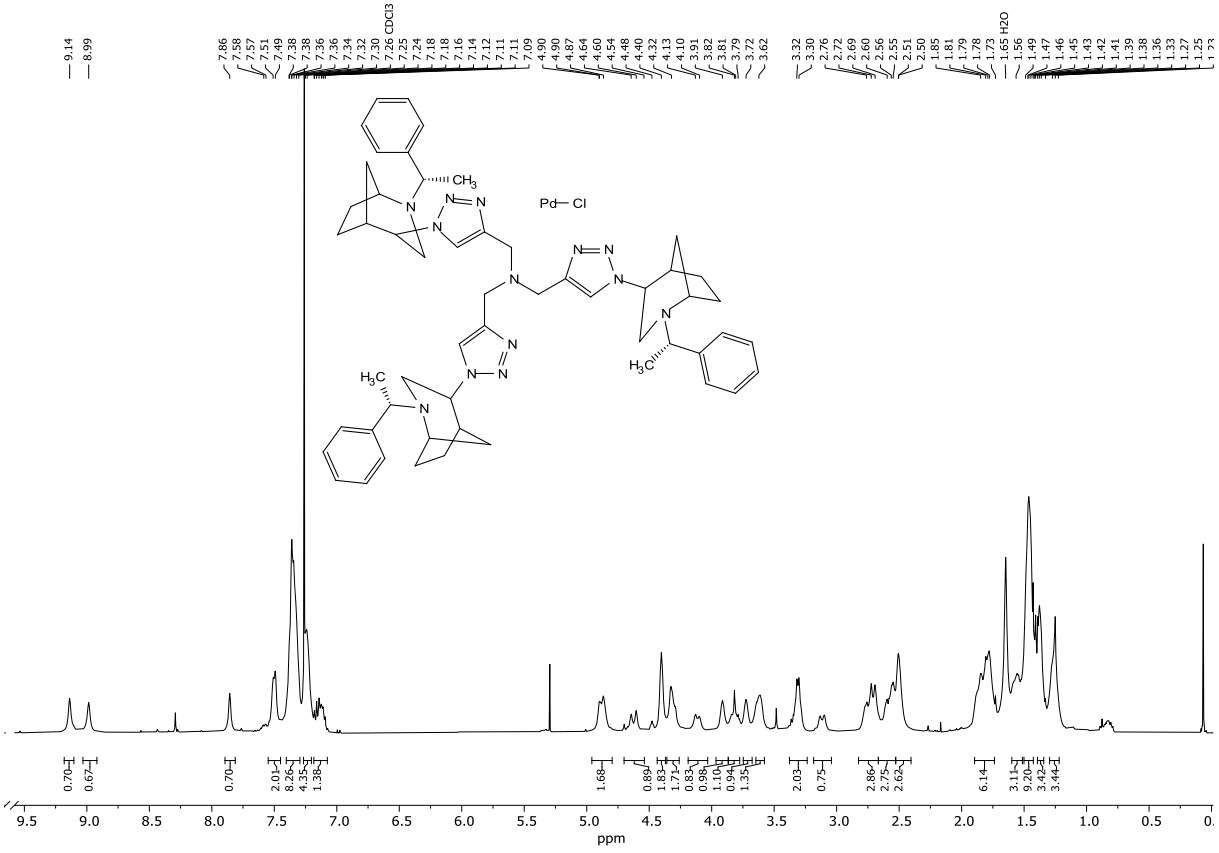
^{1}H-NMR (400 MHz, DMSO-*D*6) of **71**



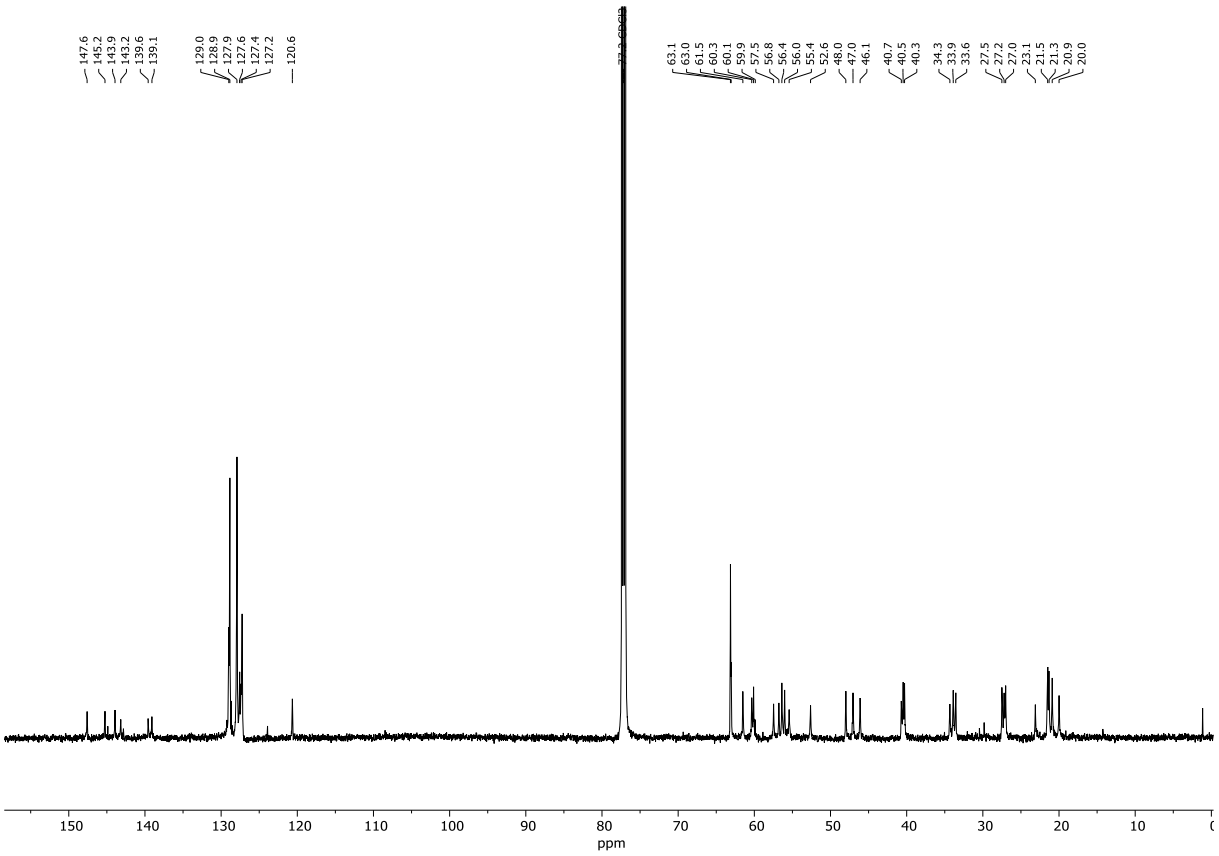
^{13}C-NMR (126 MHz, cryo probe, DMSO-D_6) of **71**



^{1}H-NMR (400 MHz, $CDCl_3$) of **77**

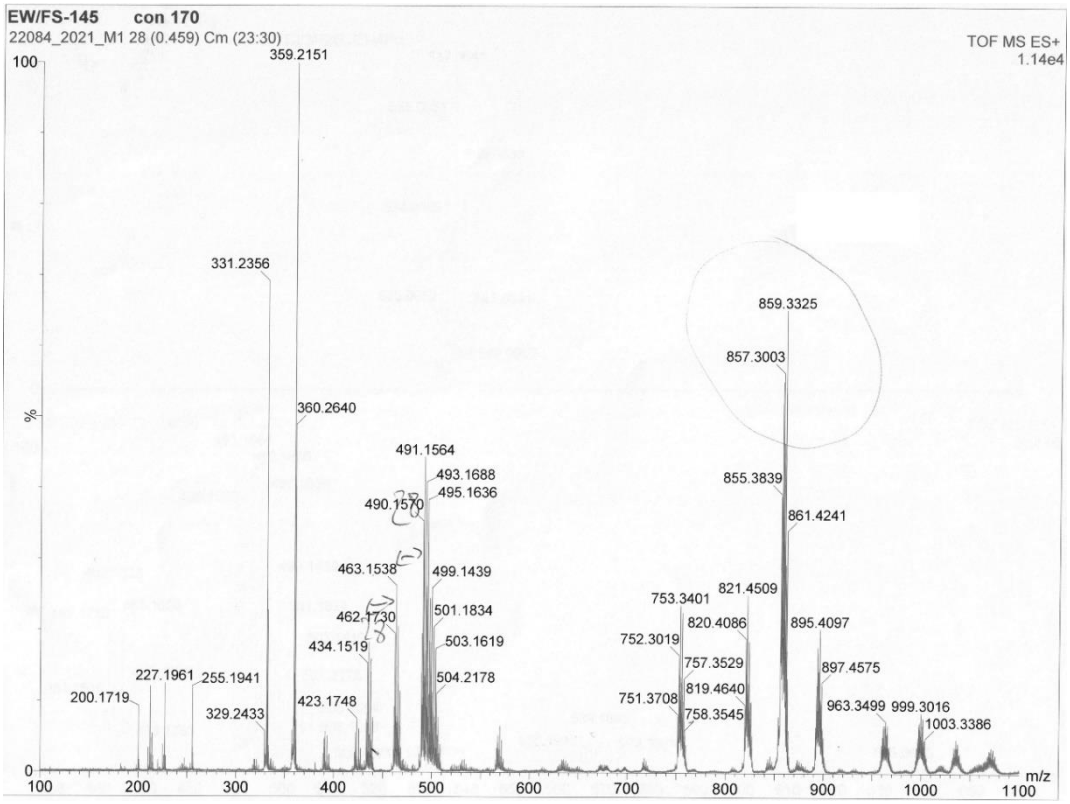


^{13}C-NMR (100 MHz, $CDCl_3$) of **77**

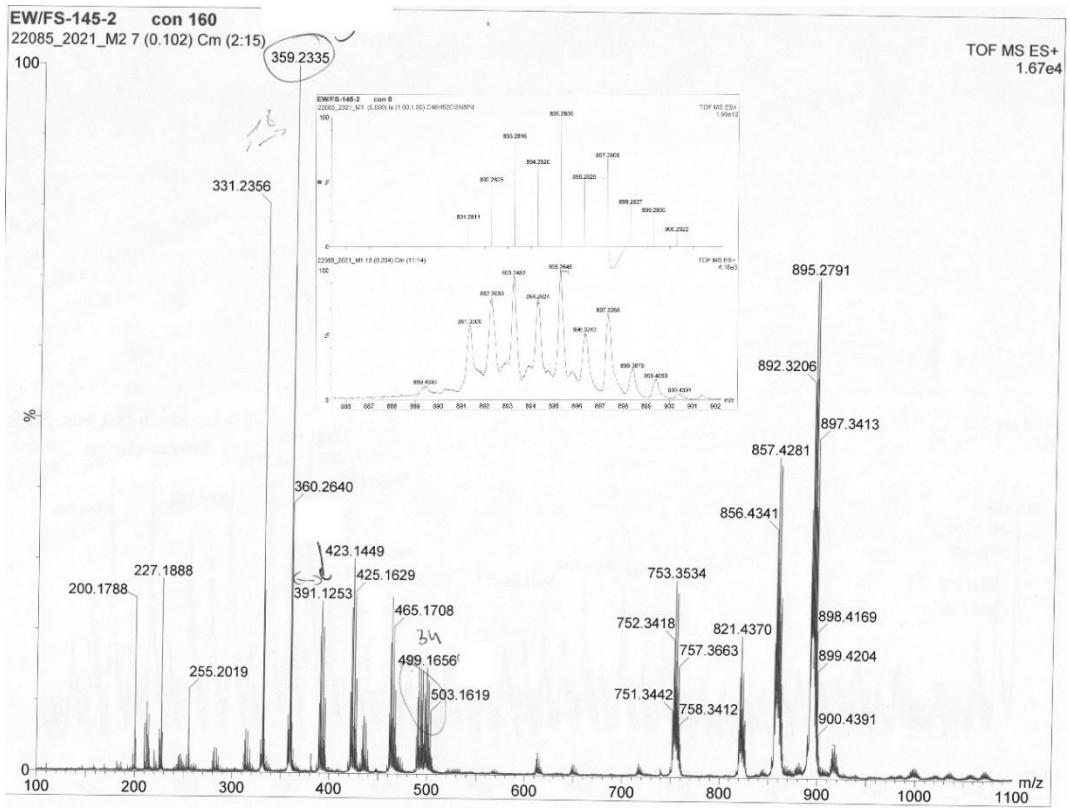


A.3 High resolution mass spectra of triazole-palladium complexes

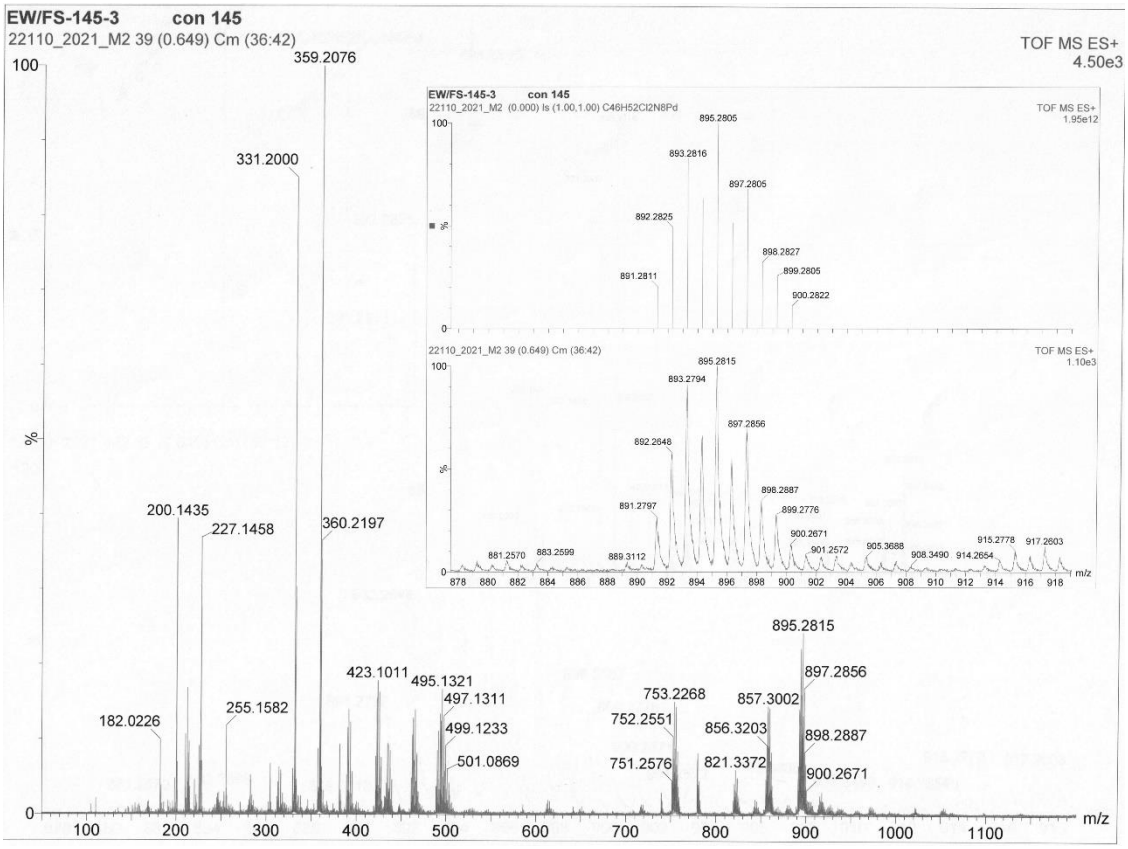
High-resolution mass spectrum of **74-1**



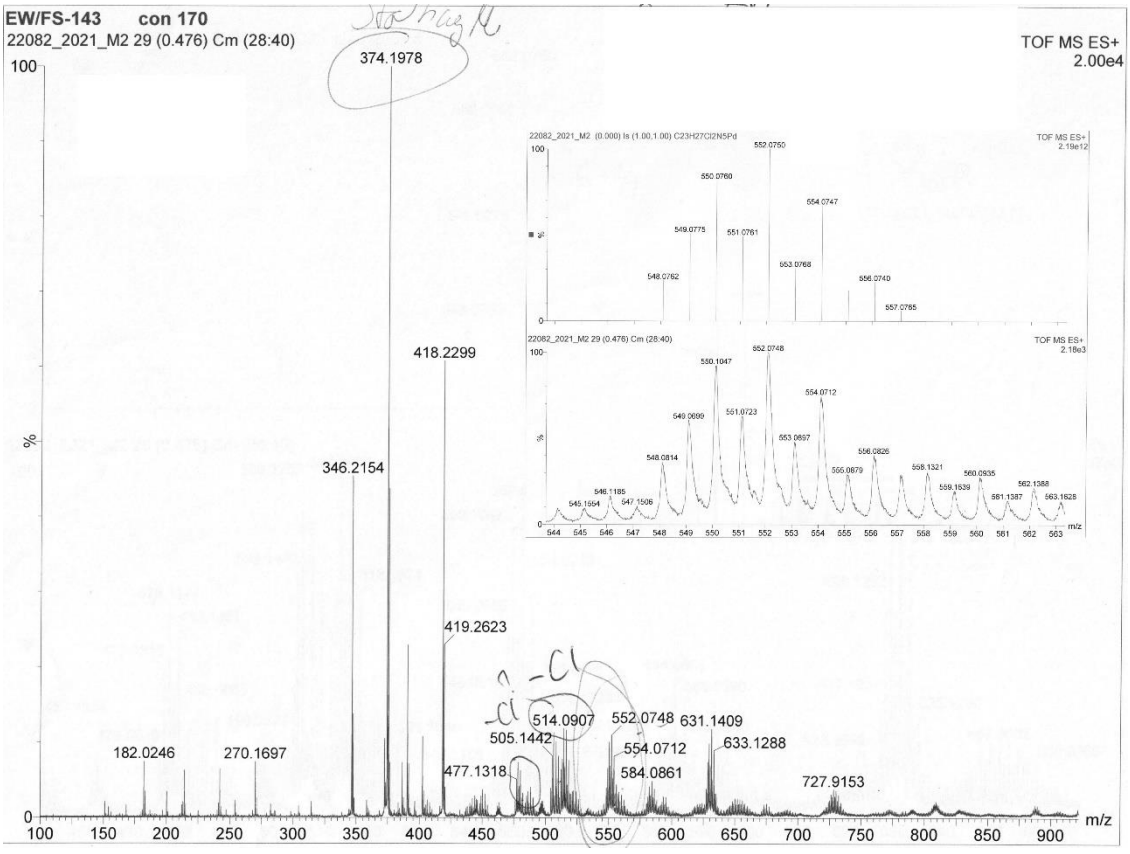
High-resolution mass spectrum of **74-2**



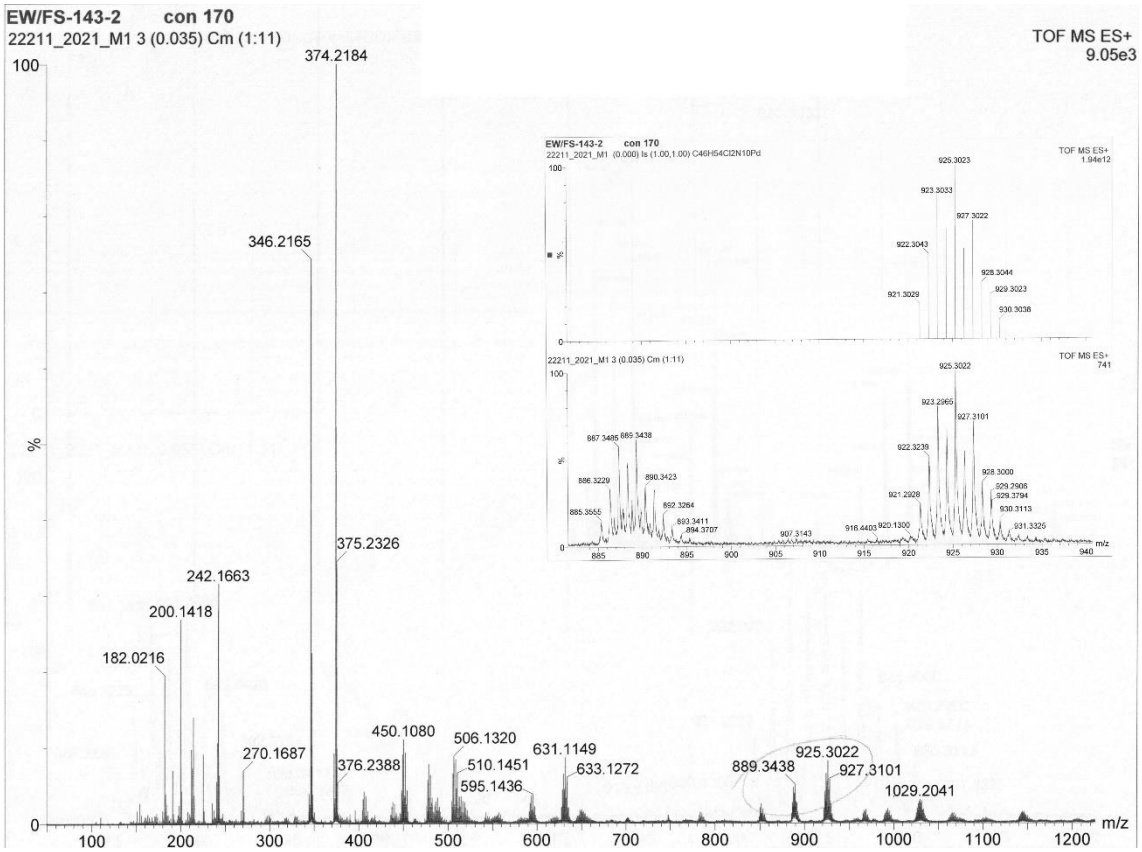
High-resolution mass spectrum of **74-3**



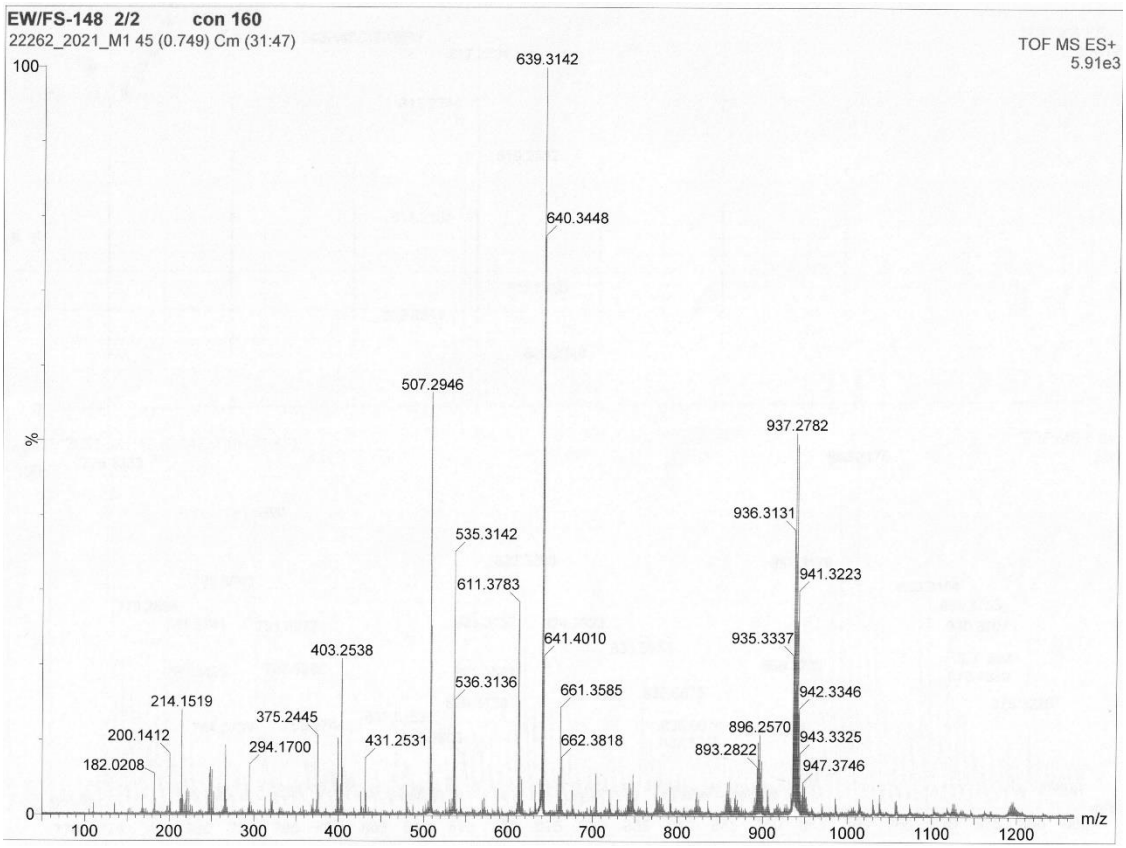
High-resolution mass spectrum of **75-1**



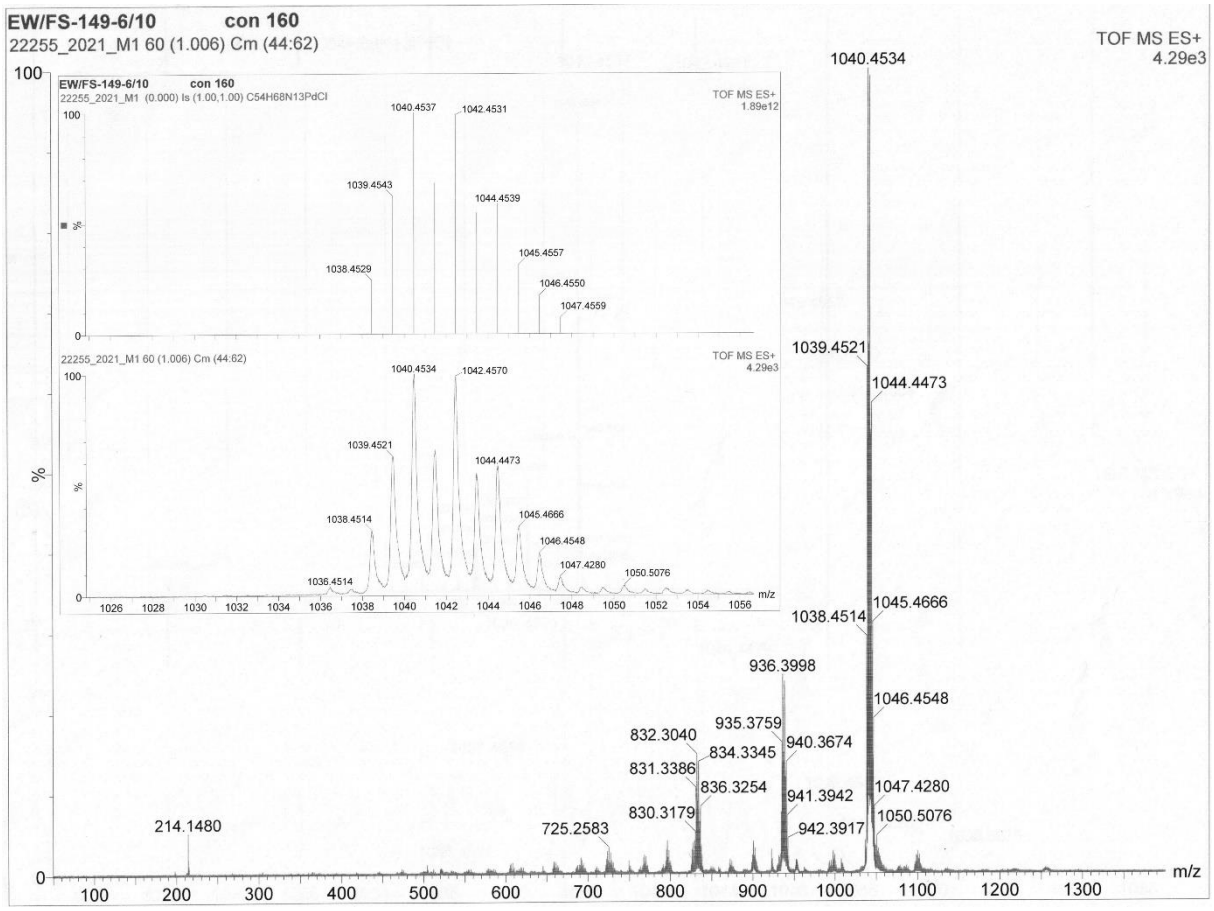
High-resolution mass spectrum of **75-2**



High-resolution mass spectrum of **76**



High-resolution mass spectrum of **77**

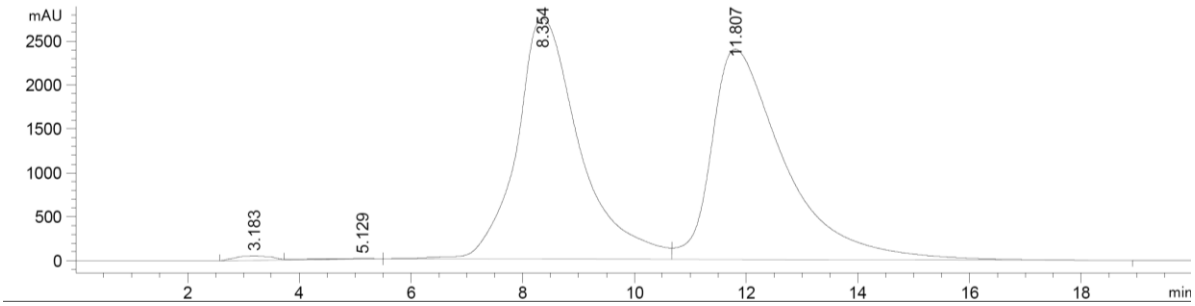


A.4 Selected HPLC chromatograms

A.4.1 Asymmetric Michael addition of dimethyl malonate to β-nitrostyrene

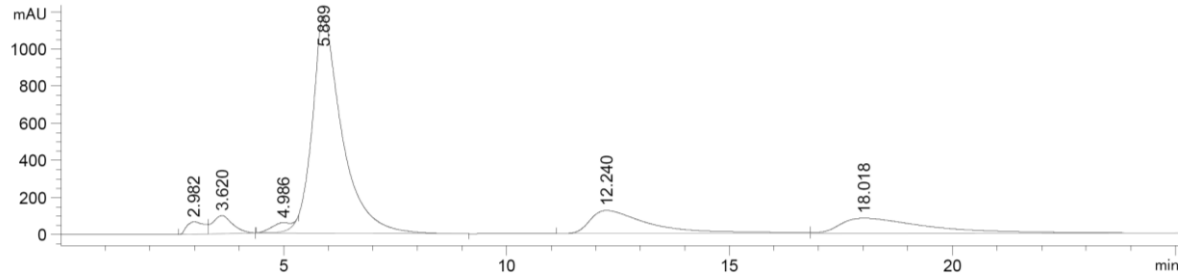
Racemic mixtures

50 mol% TEA in CH_2Cl_2 at RT, Chiralpak® IA (5 µM, 4.6 x 250 mm), 80:20 *n*-hexane:isopropanol, 1 mL/min, 210 nm.



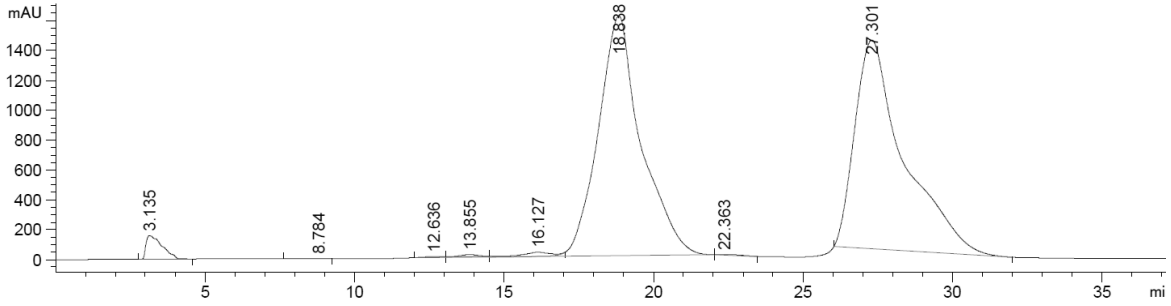
Retention time	Height [mAU]	Area [mAU*s]	Area %
8.354	2736.51	214218	49.7
11.807	2394.21	217135	50.3

50 mol% TEA in CH_2Cl_2 at RT, Chiralpak® IA (5 µM, 4.6 x 250 mm), 90:10 *n*-hexane:isopropanol, 1 mL/min, 210 nm.



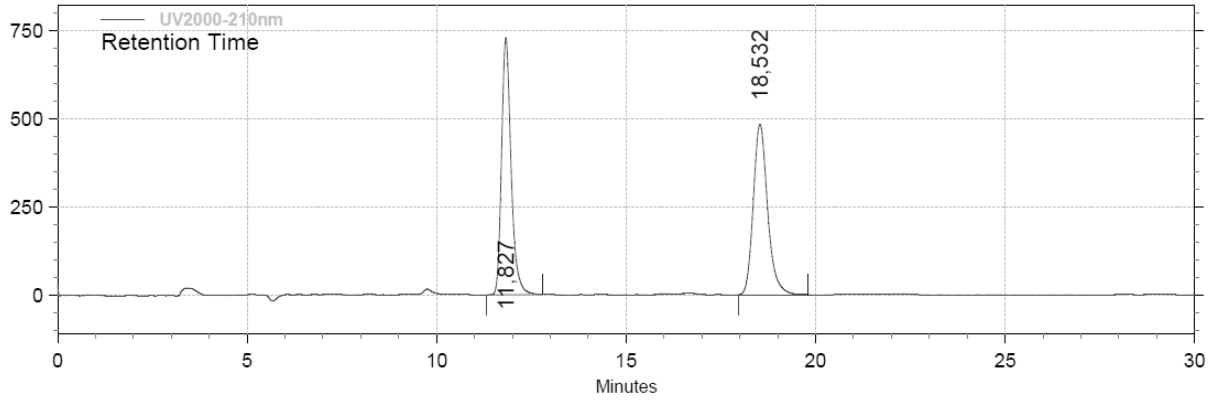
Retention time	Height [mAU]	Area [mAU*s]	Area %
12.240	123.49	11473.6	51.24
18.018	80.84	10917.3	48.76

50 mol% TEA in CH_2Cl_2 at RT, Chiralpak® IA (5 µM, 4.6 x 250 mm), 95:5 *n*-hexane:isopropanol, 1 mL/min, 210 nm.



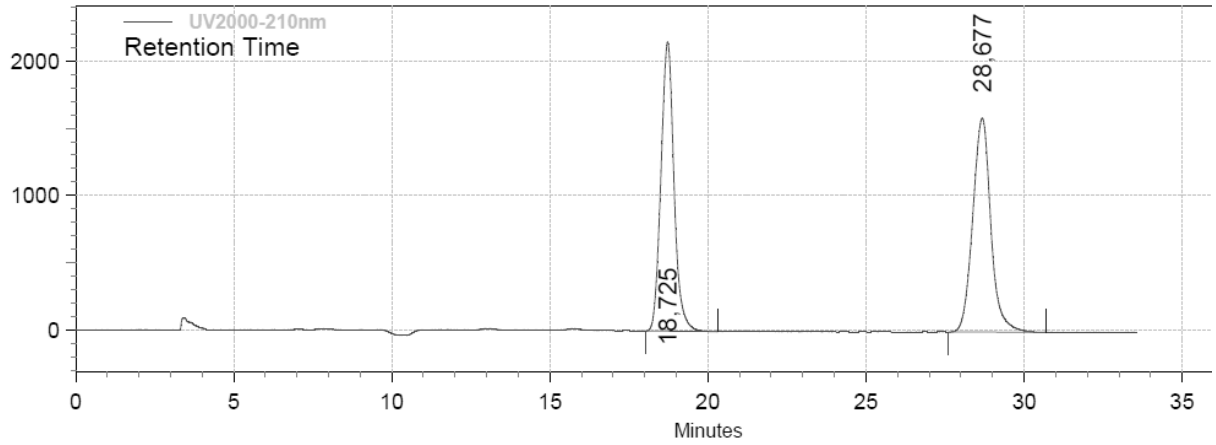
Retention time	Height [mAU]	Area [mAU*s]	Area %
18.838	1605.61	159758	50.12
27.301	1397.47	158969	49.88

50 mol% TEA in CH_2Cl_2 at RT, Chiralpak® AD-H (5 µM, 4.6 x 250 mm), 90:10 *n*-hexane:isopropanol, 1 mL/min, 210 nm.



Retention time	Height [mAU]	Area [mAU*s]	Area %
11.827	728.19	1269.26	50.03
18.532	483.01	1267.85	49.97

50 mol% TEA in CH_2Cl_2 at RT, Chiralpak® AD-H (5 µM, 4.6 x 250 mm), 95:5 *n*-hexane:isopropanol, 1 mL/min, 210 nm.

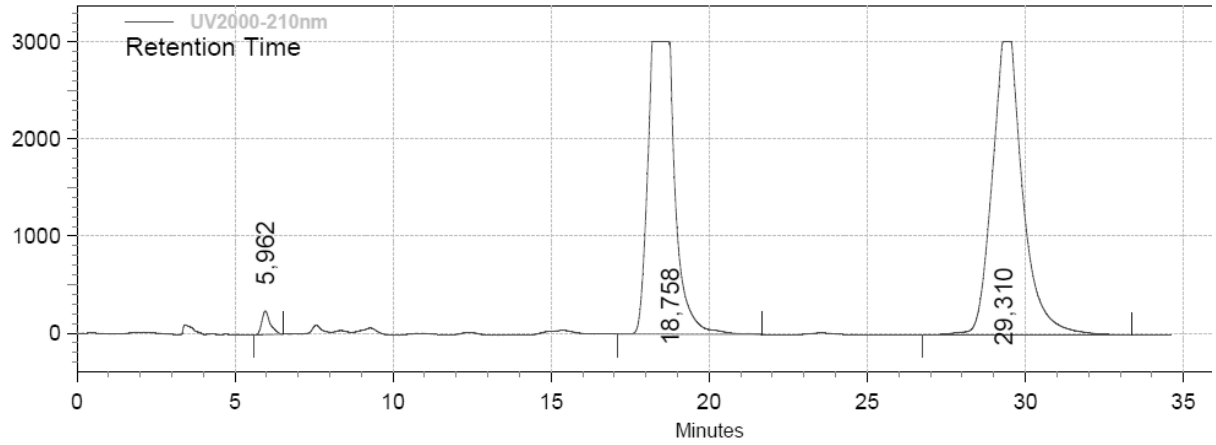


Retention time	Height [mAU]	Area [mAU*s]	Area %
18.725	2150.00	6182.15	49.41
28.677	1591.14	6328.74	50.59

Catalyst screening of (1*S*,3*S*,4*R*)-2-azabicyclo[2.2.1]heptane and (1*S*,4*S*,5*R*)-2-azabicyclo[3.2.1]octane catalysts.

Catalyst **43**

10 mol% **43** in CH_2Cl_2 at RT, Chiralpak® AD-H (5 µM, 4.6 x 250 mm), 95:5 *n*-hexane:isopropanol, 1 mL/min, 210 nm.

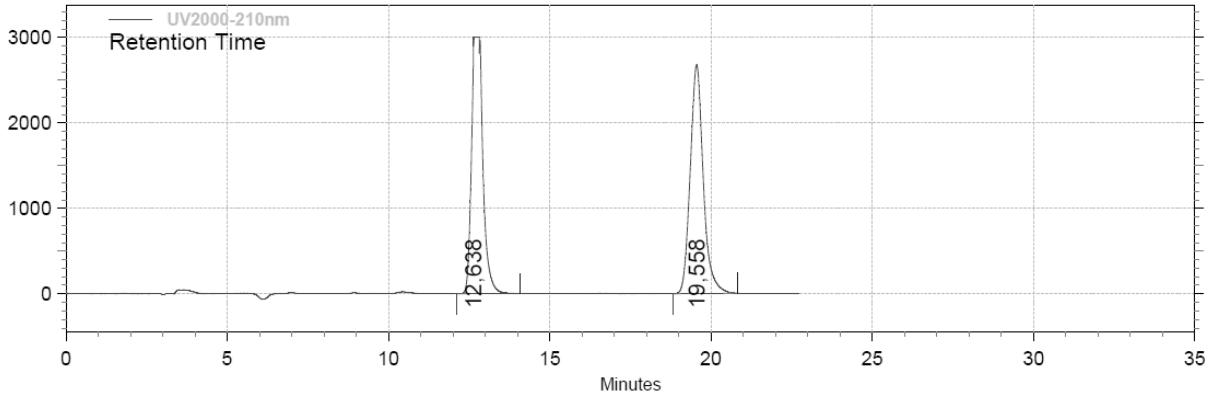


Retention time	Height [mAU]	Area [mAU*s]	Area %
18.758	3011.10	18054.78	46.73
29.310	3018.96	20581.66	53.27

Detector reached its maximum, however, the results could not be sufficient

Catalyst **45**

10 mol% **45** in CH_2Cl_2 at RT, Chiralpak® AD-H (5 µM, 4.6 x 250 mm), 90:10 *n*-hexane:isopropanol, 1 mL/min, 210 nm.

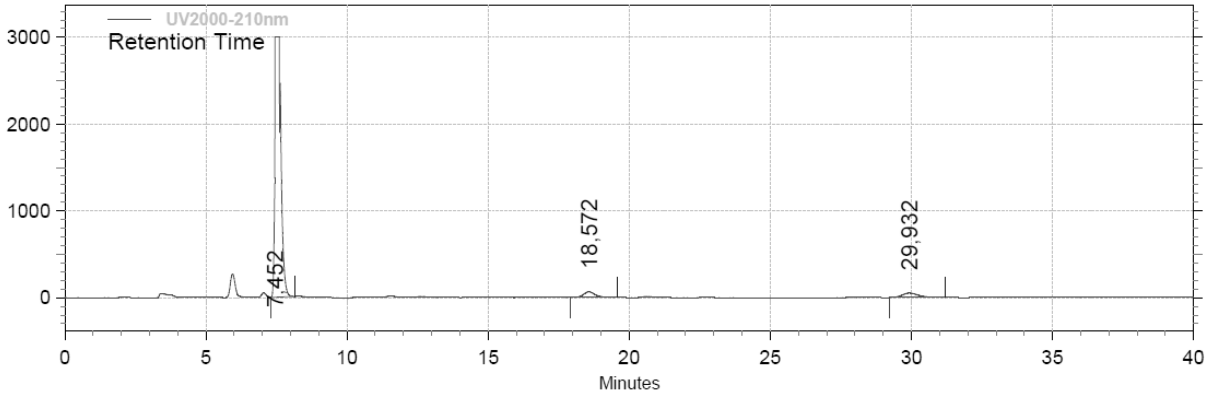


Retention time	Height [mAU]	Area [mAU*s]	Area %
12.638	2997.29	7404.36	49.53
19.558	2676.40	7543.52	50.47

Detector reached its maximum, however, the results could not be sufficient

Catalyst (1*S*,4*S*,5*R*)-**51**

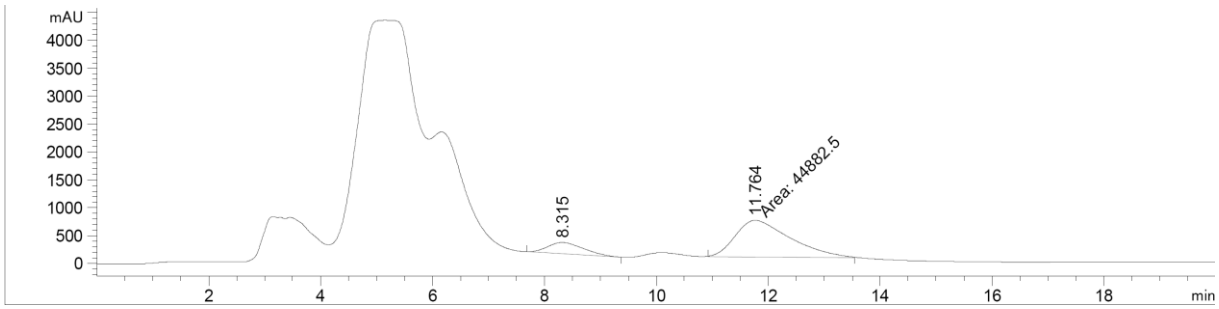
10 mol% (1*S*,4*S*,5*R*)-**51** in CH_2Cl_2 at RT, Chiralpak® AD-H (5 µM, 4.6 x 250 mm), 95:5 *n*-hexane:isopropanol, 1 mL/min, 210 nm.



Retention time	Height [mAU]	Area [mAU*s]	Area %
18.572	65.70	192.43	48.15
29.932	50.88	207.22	51.85

Catalyst **52**

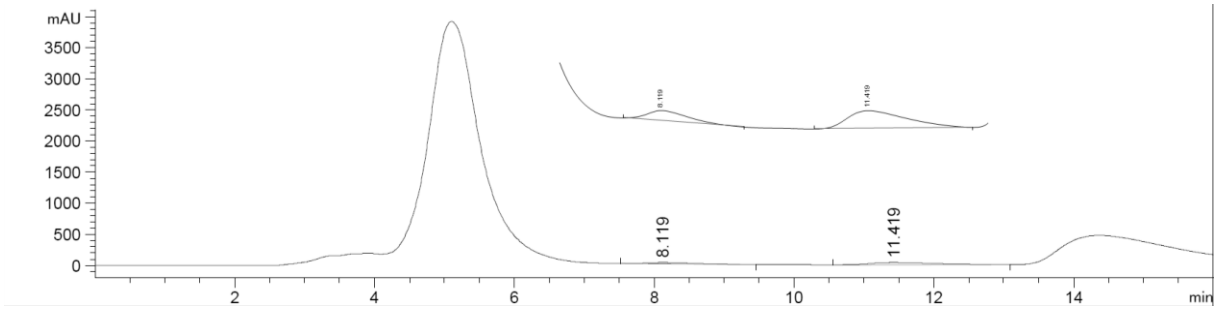
10 mol% **52** in CH_2Cl_2 at RT, Chiralpak® IA (5 µM, 4.6 x 250 mm), 80:20 *n*-hexane:isopropanol, 1 mL/min, 210 nm.



Retention time	Height [mAU]	Area [mAU*s]	Area %
8.315	202.28	8927.3	16.59
11.764	655.25	44882.5	83.41

Catalyst **53**

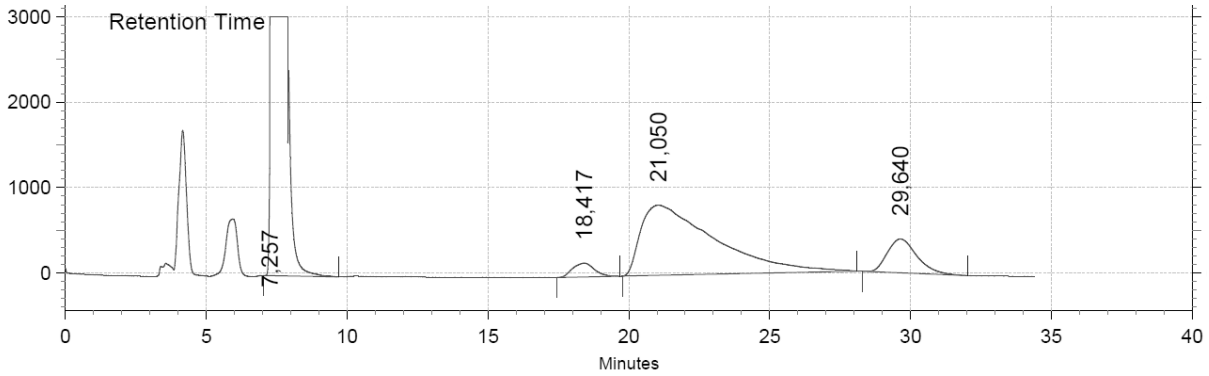
10 mol% **53** in CH_2Cl_2 at RT, Chiralpak® IA (5 µM, 4.6 x 250 mm), 80:20 *n*-hexane:isopropanol, 1 mL/min, 210 nm.



Retention time	Height [mAU]	Area [mAU*s]	Area %
8.119	19.06	893.23	29.13
11.419	33.00	2172.61	70.87

Catalyst **54**

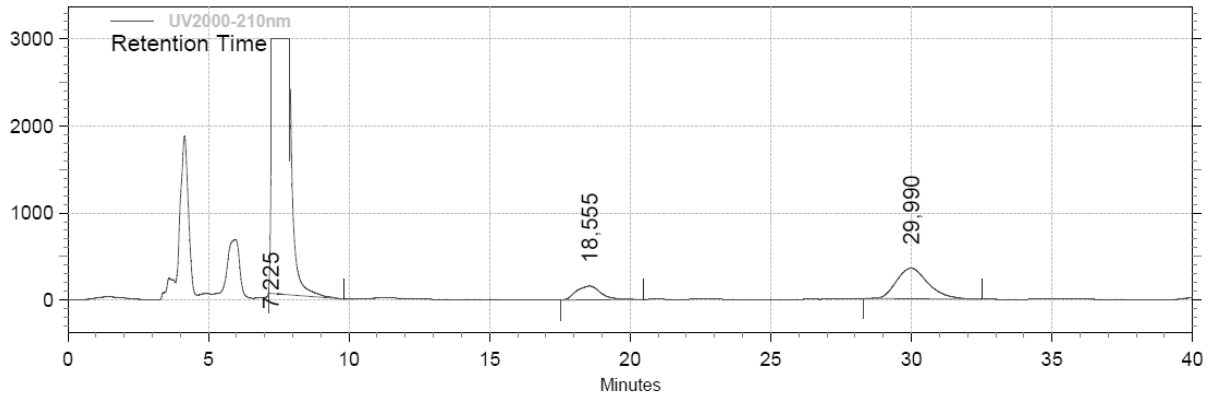
10 mol% **54** in CH_2Cl_2 at RT, Chiralpak® AD-H (5 µM, 4.6 x 250 mm), 95:5 *n*-hexane:isopropanol, 1 mL/min, 210 nm.



Retention time	Height [mAU]	Area [mAU*s)	Area %
18.417	161.67	868.05	23.16
29.640	395.93	2880.7	76.84

Catalyst **55**

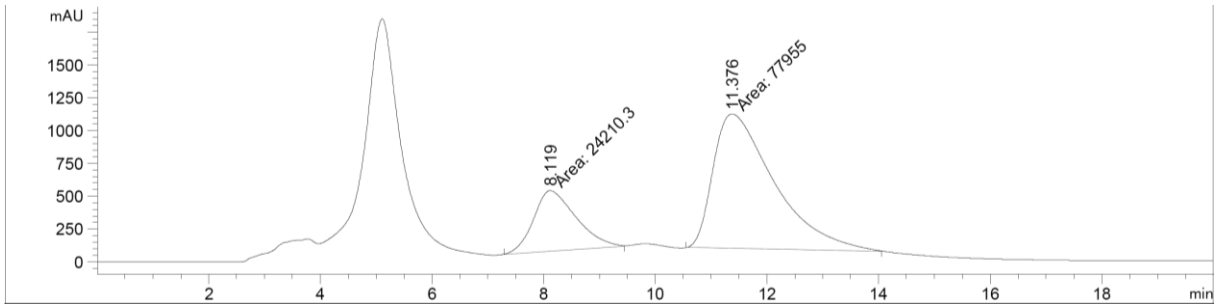
10 mol% **55** in CH_2Cl_2 at RT, Chiralpak® AD-H(5 µM, 4.6 x 250 mm), 95:5 *n*-hexane:isopropanol, 1 mL/min, 210 nm.



Retention time	Height [mAU]	Area [mAU*s)	Area %
18.555	158.33	963.49	26.01
29.990	350.87	2740.38	73.99

Catalyst **56**

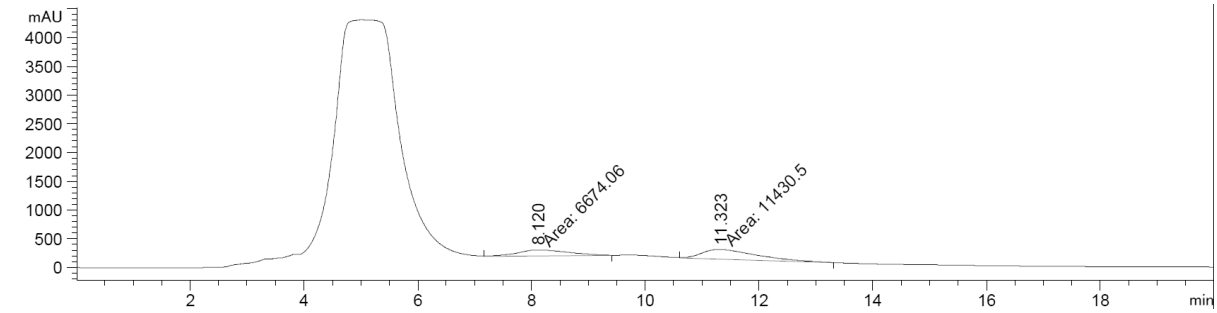
10 mol% **56** in CH_2Cl_2 at RT, Chiralpak® IA (5 µM, 4.6 x 250 mm), 80:20 *n*-hexane:isopropanol, 1 mL/min, 210 nm.



Retention time	Height [mAU]	Area [mAU*s)	Area %
8.119	459.72	24210.3	23.70
11.376	1023.84	77955.0	76.30

Catalyst **57**

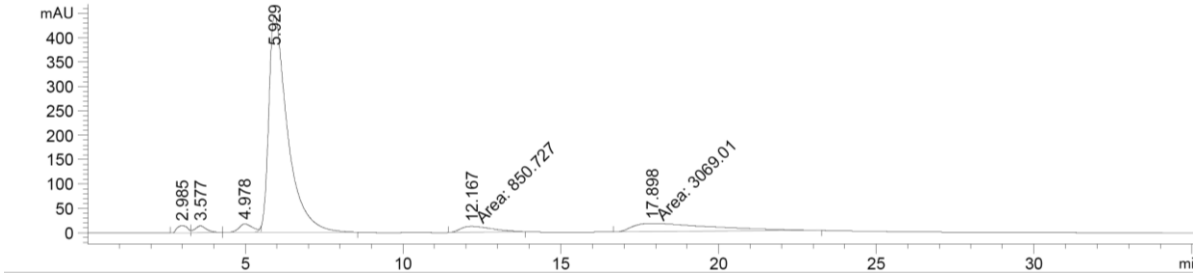
10 mol% **57** in CH_2Cl_2 at RT, Chiralpak® IA (5 µM, 4.6 x 250 mm), 80:20 *n*-hexane:isopropanol, 1 mL/min, 210 nm.



Retention time	Height [mAU]	Area [mAU*s)	Area %
8.120	104.71	6674.1	36.86
11.323	167.57	11430.5	63.14

Catalyst **71**

5 mol% **54** in CH_2Cl_2 at RT, Chiralpak® IA (5 µM, 4.6 x 250 mm), 90:10 *n*-hexane:isopropanol, 1 mL/min, 210 nm.

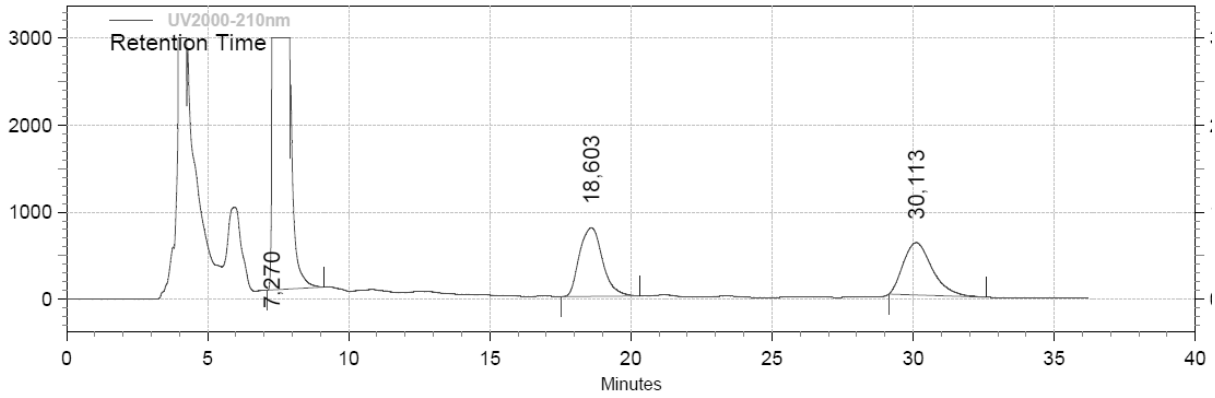


Retention time	Height [mAU]	Area [mAU*s)	Area %
12.167	12.12	850.73	21.70
17.898	16.91	3069.01	78.30

Catalyst screening of (1*R*,4*R*,5*S*)-2-azabicyclo[3.2.1]octane catalysts.

Catalyst (1*R*,4*R*,5*S*)-**51**

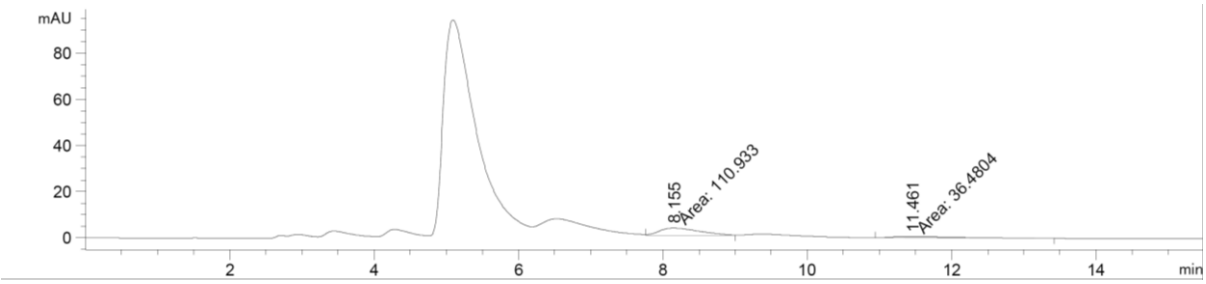
10 mol% (1*R*,4*R*,5*S*)-**51** in CH_2Cl_2 at RT, Chiralpak® AD-H (5 µM, 4.6 x 250 mm), 95:5 *n*-hexane:isopropanol, 1 mL/min, 210 nm.



Retention time	Height [mAU]	Area [mAU*s]	Area %
18.603	789.37	4489.83	51.18
30.113	602.19	4293.41	48.82

Catalyst **58**

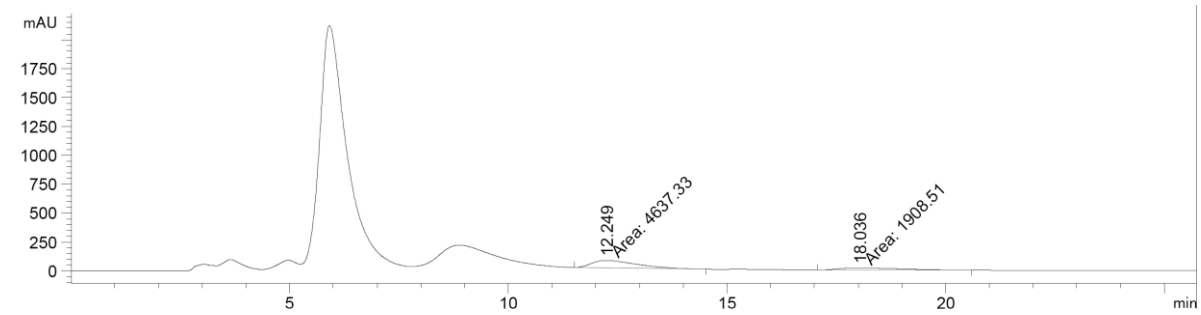
10 mol% **58** in CH_2Cl_2 at RT, Chiralpak® IA (5 µM, 4.6 x 250 mm), 80:20 *n*-hexane:isopropanol, 1 mL/min, 210 nm.



Retention time	Height [mAU]	Area [mAU*s]	Area %
8.155	2.96	110.93	75.25
11.461	0.60	36.48	24.75

Catalyst **60**

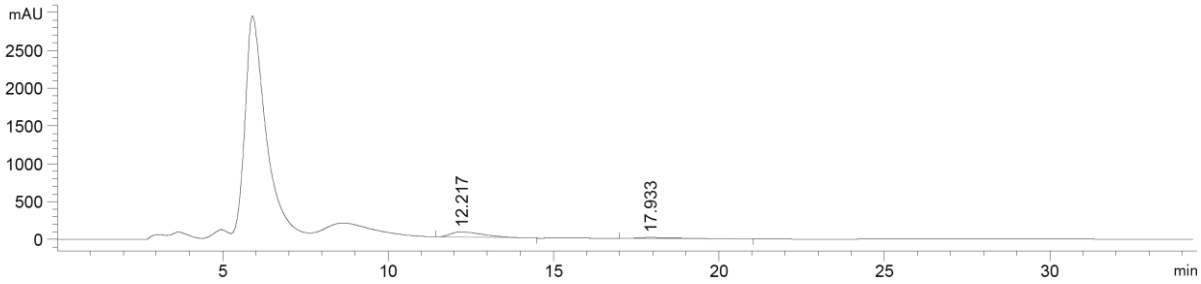
10 mol% **60** in CH_2Cl_2 at RT, Chiralpak® IA (5 µM, 4.6 x 250 mm), 90:10 *n*-hexane:isopropanol, 1 mL/min, 210 nm.



Retention time	Height [mAU]	Area [mAU*s)	Area %
8.249	64.06	4637.33	70.84
18.036	18.55	1908.51	29.16

Catalyst **61**

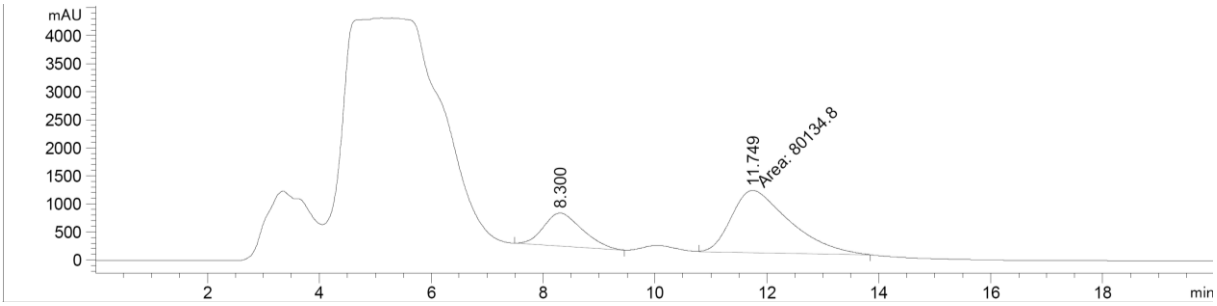
10 mol% **61** in CH_2Cl_2 at RT, Chiralpak® IA (5 µM, 4.6 x 250 mm), 90:10 *n*-hexane:isopropanol, 1 mL/min, 210 nm.



Retention time	Height [mAU]	Area [mAU*s)	Area %
12.217	69.78	4996.69	75.68
18.036	15.64	1605.45	24.32

Catalyst **52**, 5 mol% catalyst loading

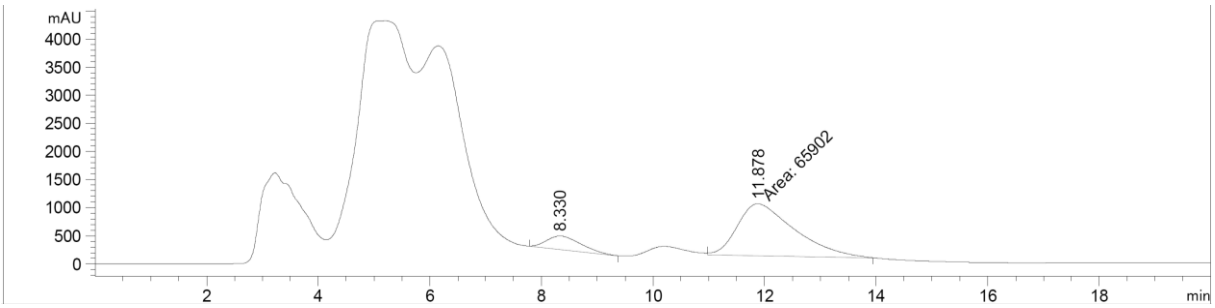
5 mol% **52** in CH_2Cl_2 at RT, Chiralpak® IA (5 µM, 4.6 x 250 mm), 80:20 *n*-hexane:isopropanol, 1 mL/min, 210 nm.



Retention time	Height [mAU]	Area [mAU*s)	Area %
8.300	586.18	27918.6	25.84
11.749	1108.83	80134.8	74.16

Catalyst **52**, 20 mol% catalyst loading

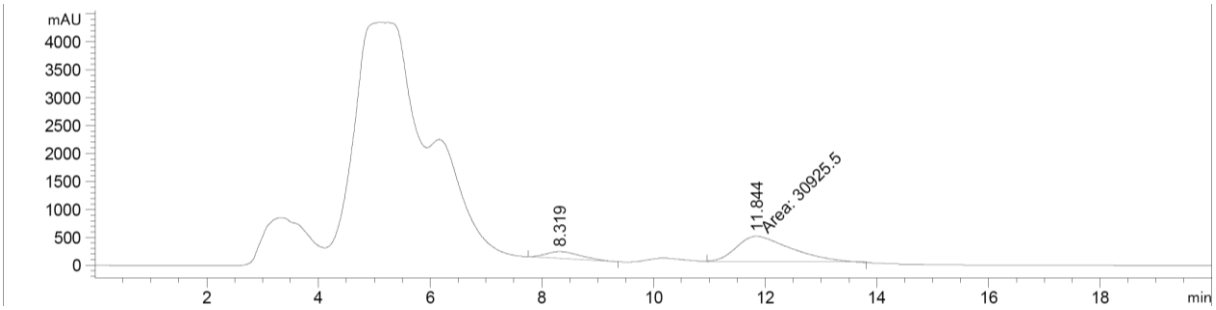
20 mol% **52** in CH_2Cl_2 at RT, Chiralpak® IA (5 µM, 4.6 x 250 mm), 80:20 *n*-hexane:isopropanol, 1 mL/min, 210 nm.



Retention time	Height [mAU]	Area [mAU*s]	Area %
8.330	238.701	10062.9	13.25
11.878	923.76	65902.0	86.75

Catalyst **52**, 2 °C reaction temperature

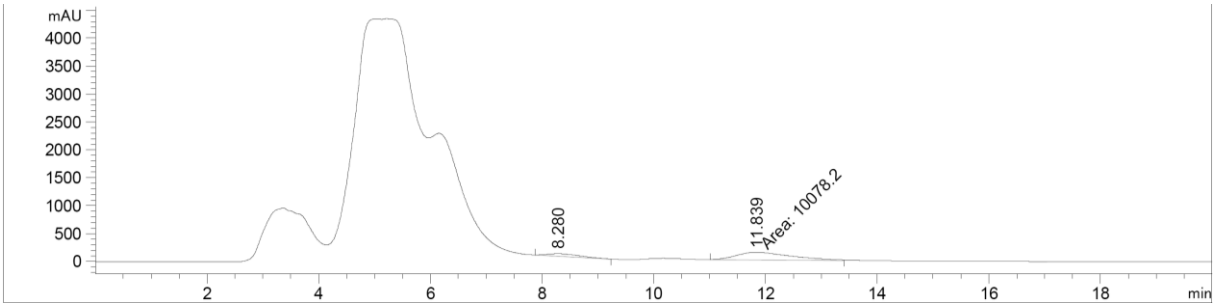
10 mol% **52** in CH_2Cl_2 at 2 °C, Chiralpak® IA (5 µM, 4.6 x 250 mm), 80:20 *n*-hexane:isopropanol, 1 mL/min, 210 nm.



Retention time	Height [mAU]	Area [mAU*s]	Area %
8.319	121.92	5248.7	14.51
11.844	455.55	30925.5	85.49

Catalyst **52**, -20 °C reaction temperature

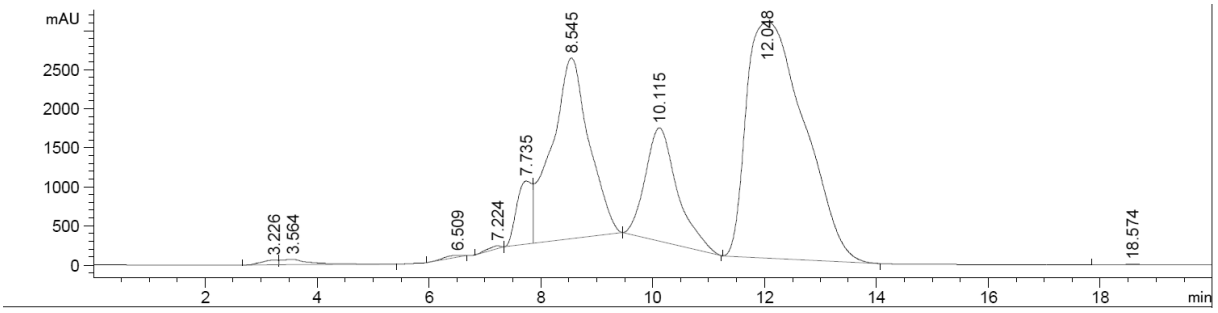
10 mol% **52** in CH_2Cl_2 at -20 °C, Chiralpak® IA (5 µM, 4.6 x 250 mm), 80:20 *n*-hexane:isopropanol, 1 mL/min, 210 nm.



Retention time	Height [mAU]	Area [mAU*s)	Area %
8.280	43.36	1743.4	14.75
11.839	141.40	10078.2	85.25

Catalyst **52**, in acetonitrile

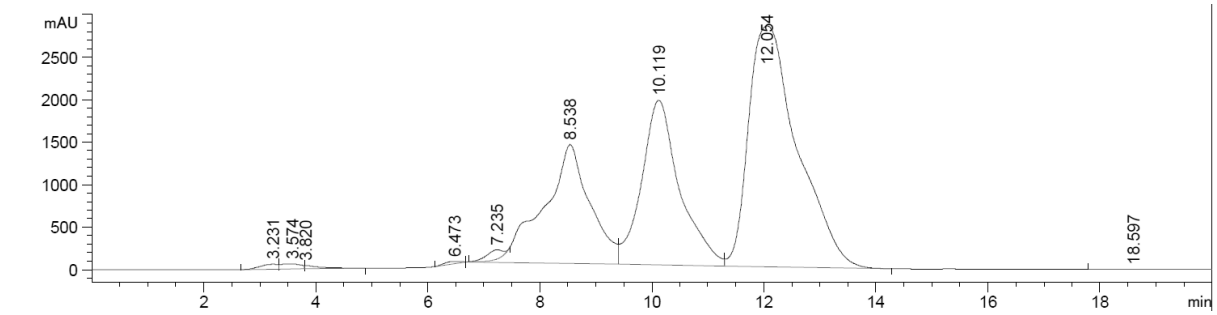
10 mol% **52** in MeCN at RT, Chiralpak® IA (5 µM, 4.6 x 250 mm), 80:20 *n*-hexane:isopropanol, 1 mL/min, 210 nm.



Retention time	Height [mAU]	Area [mAU*s)	Area %
8.545	2313.91	108163	33.21
12.048	3022.82	217527	66.79

Catalyst **52**, in tetrahydrofuran

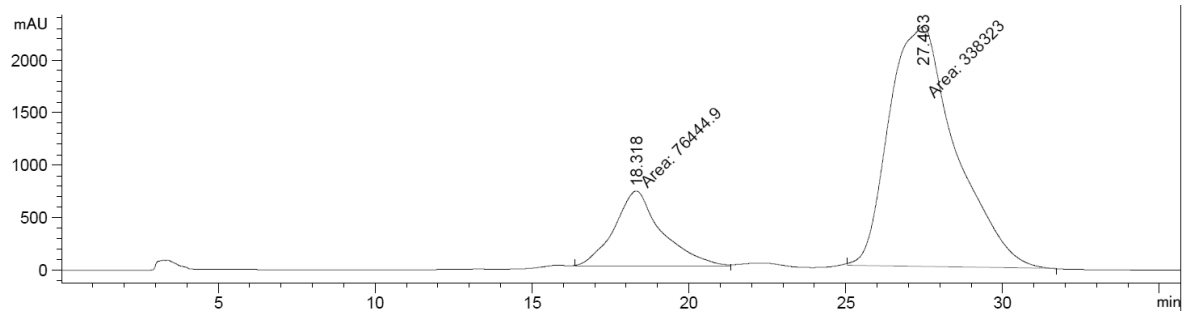
10 mol% **52** in THF at RT, Chiralpak® IA (5 µM, 4.6 x 250 mm), 80:20 *n*-hexane:isopropanol, 1 mL/min, 210 nm.



Retention time	Height [mAU]	Area [mAU*s)	Area %
8.538	1400.23	1743.4	33.06
12.054	2835.57	10078.2	66.94

Catalyst **52**, in toluene

10 mol% **52** in toluene at RT, Chiralpak® IA (5 µM, 4.6 x 250 mm), 95:5 *n*-hexane:isopropanol, 1 mL/min, 210 nm.

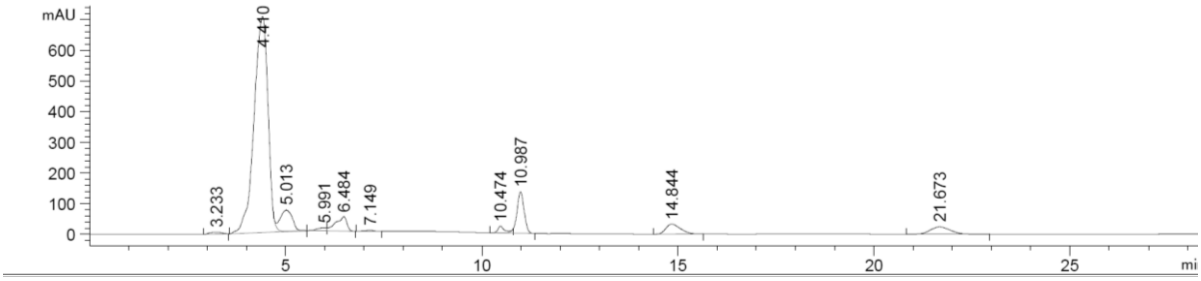


Retention time	Height [mAU]	Area [mAU*s]	Area %
18.318	717.49	76445	18.43
27.463	2282.39	338323	81.57

A.4.2 Michael addition of cyclohexanone and β-nitrostyrene by (1*S*,3*S*,4*R*)-2-azabicyclo[2.2.1]heptane catalysts

Racemic mixture

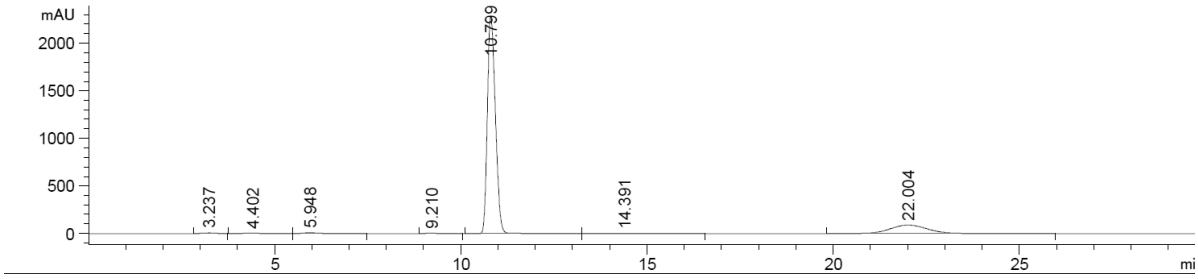
50 mol% piperidine in CH_2Cl_2 at RT, Chiralpak® IH (5 µM, 4.6 x 250 mm), 90:10 *n*-hexane:isopropanol, 1 mL/min, 238 nm.



Retention time	Height [mAU]	Area [mAU*s]	Area %
14.844	32.26	834.13	49.6
21.673	23.94	846.45	50.4

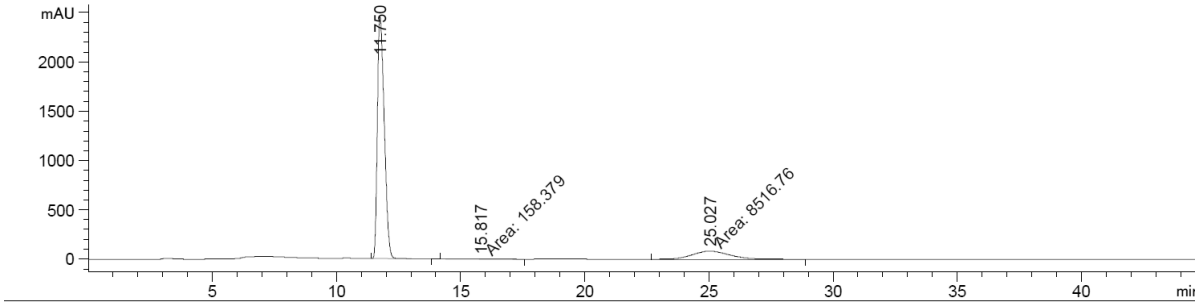
Catalyst **45**

10 mol% **45** in CH_2Cl_2 at RT, Chiralpak® IH (5 µM, 4.6 x 250 mm), 90:10 *n*-hexane:isopropanol, 1 mL/min, 238 nm.



Retention time	Height [mAU]	Area [mAU*s)	Area %
14.391	1.84	222.12	3.4
22.004	89.33	6322.22	96.6

10 mol% **45** in CH_2Cl_2 at 2 °C, Chiralpak® IH (5 µM, 4.6 x 250 mm), 90:10 *n*-hexane:isopropanol, 1 mL/min, 238 nm.



Retention time	Height [mAU]	Area [mAU*s)	Area %
15.817	1.24	158.38	1.8
24.027	81.19	8516.76	98.2