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Development of Chiral Gold(III)-complexes and Studies of Their Catalytic Activity

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Norwegian University of Science and Technology
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The illustration on the cover depicts the crystal structure of gold(III)-complex **10**

I hereby declare that the work presented in this master's thesis was conducted individually and in accordance with the regulations of the master's degree program at Norwegian University of Science and Technology. The work was conducted from January 2018 to June 2018.

Trondheim, June 18th, 2018

Elise Østrem

Preface

The presented work was carried out at the Department of Chemistry at the Norwegian University of Science and Technology in the spring of 2018.

I am very grateful to my supervisor, professor Anne Fiksdahl, for the motivation, inspiration and guidance you have given me this year. I also want to thank my co-supervisor, Ph.D candidate Ann Christin Reiersølmoen, who has been a great help in the lab and during the writing process. Both of my supervisors are always in a good mood and willing to help, which is greatly appreciated. An extra thanks goes to Ph.D candidate Helgi Freyr Jónsson, for his uplifting spirit in the lab and his willingness to help when asked.

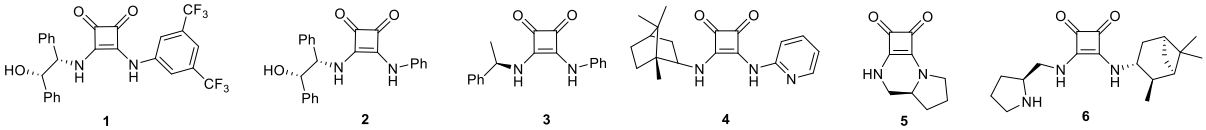
I would also like to thank Susana Villa Gonzalez and Julie Asmussen for all their help with MS analyses, and Torunn Margareta Melø for always being available to help with NMR. I am also grateful to Roger Aarvik for his quick procurement of solvents and his friendly attitude. I would also like to thank Sigurd Øien-Ødegaard at UiO for his willingness to run X-ray crystallography on my compounds.

Finally, I would like to thank my friends, family and fellow students for making my last year fun and memorable.

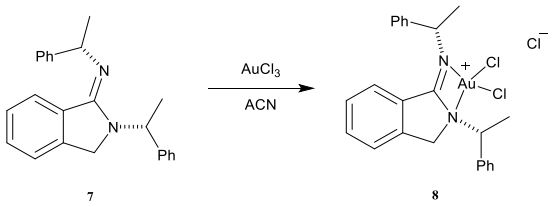
Abstract

The purpose of this master project was to synthesise chiral ligands and coordinate these to gold(III), thereby developing novel chiral gold(III)-complexes. These complexes were then used as gold-catalysts in cyclopropanation reactions in which their catalytic activity and their enantioselectivity could be measured.

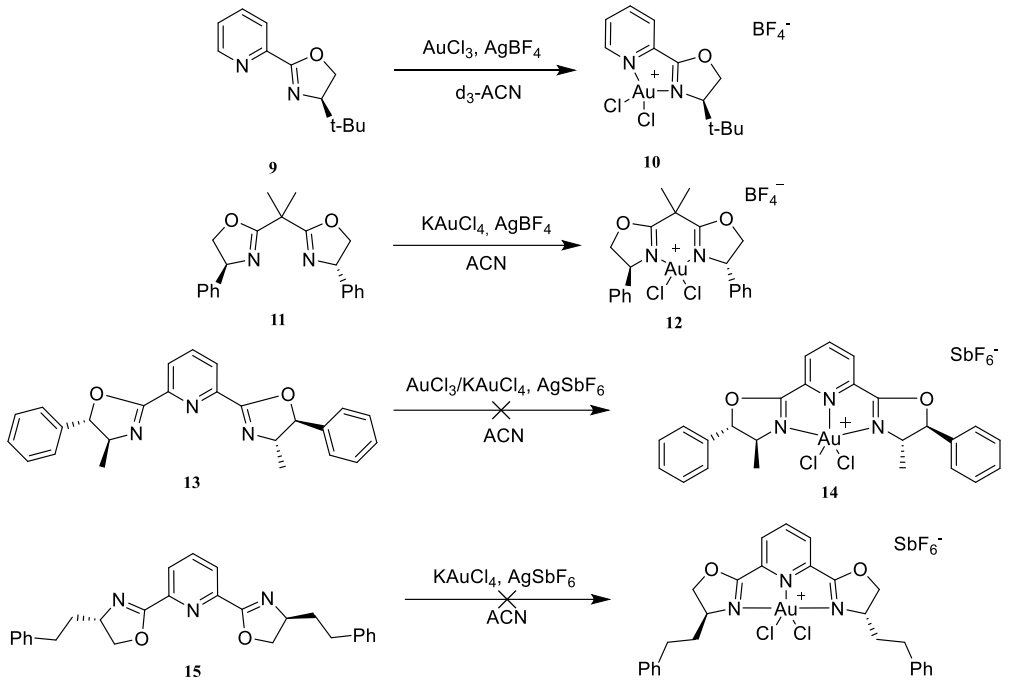
Six different squaramide ligands (**1**-**6**) were synthesised by the addition of different amines to squaric ethyl ester, resulting in yields varying from 7% to 68%. Gold(III)-coordination of squaramides **1**-**6** was unsuccessful, mostly due to the insolubility of squaramides **1**-**3** and the low yields of **5** and **6**. Gold(III)-coordination of squaramide **4** only resulted in protonation of the aminopyridine nitrogen and a $AuCl_4^-$ counterion (**4**[$AuCl_4$]).



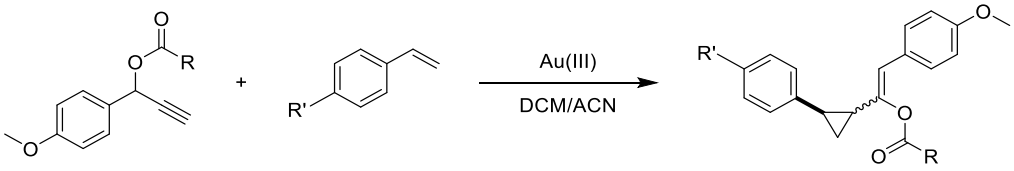
After the failure of creating gold(III)-complexes of squaramides, iminoisoindoline **7** was synthesised (94%) and subsequent gold(III)-coordination resulted in iminoisoindoline-Au(III)-complex **8** (94%).



Gold(III)-coordination to several commercially available oxazoline-based ligands were also attempted. Gold(III)-complex **10** was successfully coordinated and crystallized (63%), and the structure was confirmed by X-ray crystallography. Gold(III)-complex **12** had already been developed during the pre-master project and was repeated here (22%). Gold(III)-coordination of oxazoline-based ligand **13** resulted in a mixture of gold(III)-complex **14** and several other products. Complex **14** was attempted isolated from the mixture, without success. Gold(III)-coordination of oxazoline-based ligand **15** resulted in a complex mixture which did not contain the wanted gold(III)-complex.



The catalytic ability of the successful gold(III)-complexes **8**, **10** and **12**, the mixture containing gold(III)-complex **14** and the squaramide **4**[$AuCl_4$]-salt were tested in cyclopropanation reaction of propargyl esters **17a-b** with vinyl substrates **18a-b**, affording the cyclopropanation products **19a-c** in 63-89% yield, with different *cis:trans* ratios.



17a: R = *t*-Bu
17b: R = CH_3

18a: R' = H
18b: R' = OMe

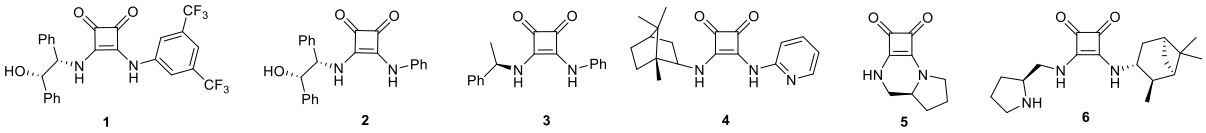
19a: R = *t*-Bu, R' = H
19b: R = CH_3, R' = H
19c: R = *t*-Bu, R' = OMe

Enantioselectivity of cyclopropanation products *trans*-**19a**, *cis*-**19a** and *trans*-**19b** catalysed by gold(III)-complexes **8**-**12** were tested by chiral HPLC, but none of the products showed any enantiomeric excess.

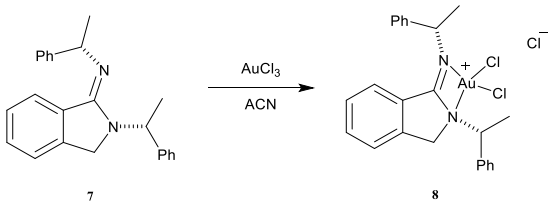
Sammendrag

Målet med denne masteroppgaven var å syntetisere kirale ligander og koordinere disse til gull(III), og dermed utvikle nye kirale gull(III)-komplekser. Disse kompleksene var så brukt som gullkatalysatorer i syklopropaneringsreaksjoner slik at deres katalytiske evne og deres enantioselektivitet kunne måles.

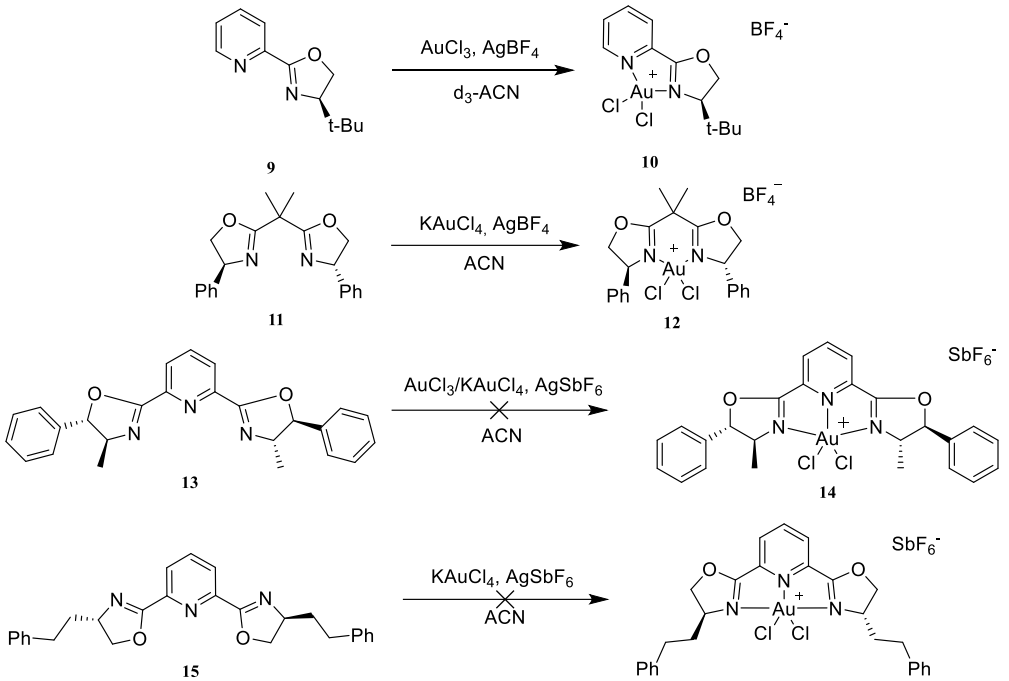
Seks ulike «squaramid» ligander (**1**-**6**) ble syntetisert ved addisjon av forskjellige aminer til kvadratisk etylester, som resulterte i utbytter fra 7% til 68%. Gull(III)-koordinering av squaramide **1**-**6**- var mislykket, hovedsakelig på grunn av uløseligheten til squaramid **1**-**3** og de lave utbyttene av **5** og **6**. Gull(III)-koordinering av squaramid **4** resulterte kun i protonering av aminopyridin-gruppen og $AuCl_4^-$ som motion (**4**[$AuCl_4$]).



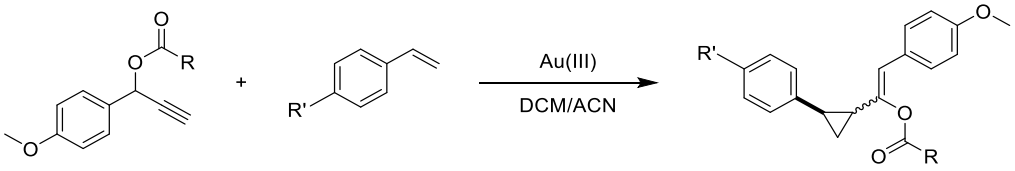
Etter de mislykkede forsøkene på å lage gull(III)-komplekser av squaramidene, ble iminoisoindolin **7** syntetisert (94%) og påfølgende gull(III)-koordinasjon resulterte i gull(III)-kompleks **8** (94%).



Gull(III)-koordinering til flere kommersielt tilgjengelige oxazolinbaserte ligander ble også prøvd. Koordinering og krystallisering av gull(III)-kompleks **10** var vellykket (63%) og strukturen ble bekreftet ved røntgenkrystallografi. Under fordypningsprosjektet ble gull(III)-kompleks **12** utviklet, og det ble gjentatt her (22%). Gull(III)-koordinering til den oxazolinbaserte liganden **13** resulterte i en blanding av gull(III)-kompleks **14** og andre produkter. Isolering av kompleks **14** ble prøvd uten suksess. Koordinering av gull(III) til den oxazolinbaserte liganden **15** resulterte i en kompleks blanding som ikke inneholdt det ønskede gull(III)-komplekset.



De katalytiske evnene til gull(III)-kompleksene **8**, **10** og **12**, blandingen av gull(III)-kompleks **14** og squaramid-saltet **4**[$AuCl_4^-$] ble testet i syklopropaneringsreaksjoner av propargylester **17a-b** med vinylsubstrat **18a-b**, som gav syklopropaneringsproduktene **19a-c** i 63-89% utbytte, med forskjellige *cis*:*trans* forhold.



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17b: R = CH_3

18a: R' = H
18b: R' = OMe

19a: R = *t*-Bu, R' = H
19b: R = CH_3, R' = H
19c: R = *t*-Bu, R' = OMe

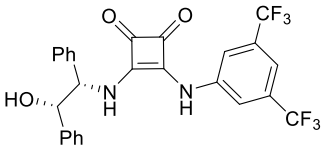
Enantioselektivitet av syklopropaneringsproduktene *trans*-**19a**, *cis*-**19a** og *trans*-**19b**, katalysert av gull(III)-kompleksene **8-12**, ble testet med kiral HPLC, men ingen av produktene viste noe enantiomerisk overskudd.

Abbreviations

Ac	Acetyl
ACN	Acetonitrile
d_3-ACN	Deuterated acetonitrile
Ar	Aryl
ASAP	Atmospheric Solids Analysis Probe
BF_4	Tetrafluoroborate
Box	Bis(oxazoline)
$CDCl_3$	Deuterated chloroform
cm^{-1}	Wave number, reciprocal centimetre
Conc.	Concentrated
COSY	Correlated Spectroscopy
CSP	Chiral Stationary Phase
δ	Chemical shift [ppm]
DCM	Dichloromethane
d_2-DCM	Deuterated dichoromethane
d	Doublet (NMR)
dd	Doublet of doublets (NMR)
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
d_4-DMSO	Deuterated dimethyl sulfoxide
%ee	Enantiomeric excess
equiv.	Equivalent
et al.	Et alia (and others)
Et_3N	Triethylamine
EtOAc	Ethyl acetate
GC	Gas Chromatography
HMBC	Heteronuclear Multi Bond Correlation
HPLC	High Performance Liquid Chromatography
HR	High Resolution (MS)
hrs	Hours
HSQC	Heteronuclear Single Quantum Coherence
Hz	Hertz

IR	Infrared Spectroscopy
J	Coupling constant [Hz]
M^+	Molecular ion
m	Multiplett (NMR)
Me	Methyl
MeOH	Methanol
min	Minutes
mL	Millilitres
mmol	Millimoles
MS	Mass Spectroscopy
m/z	Mass per charge
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
Nu	Nucleophile
obsd	Observed
Ph	Phenyl
ppm	Parts per million
R_f	Retention factor (TLC)
rx	Reaction
s	Singlet (NMR)
SbF_6	Hexafluoroantimonate
t	Triplet (NMR)
t-Bu	*tert*-Butyl
Bu_4N	Tetrabutylammonium
Tf_2N	Bistriflimide
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl

Numbered compounds



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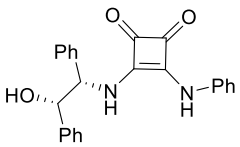

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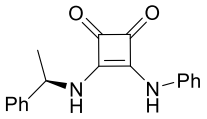

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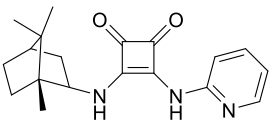

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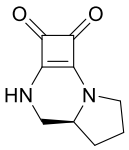

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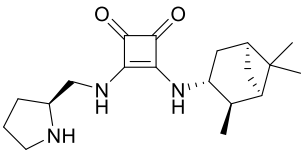

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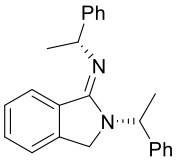

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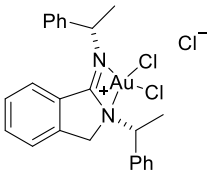

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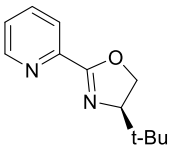

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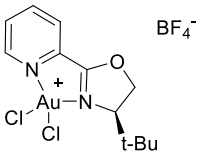

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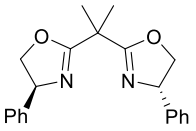

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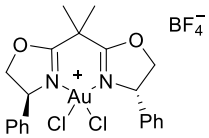

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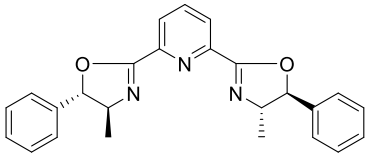

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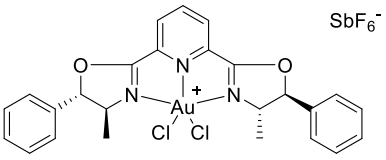

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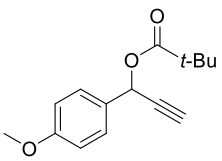

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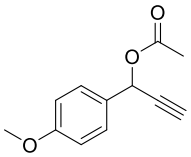

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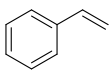

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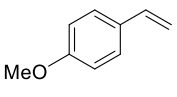

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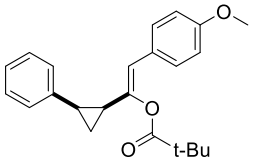
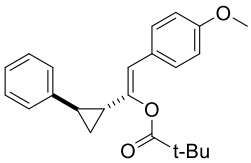
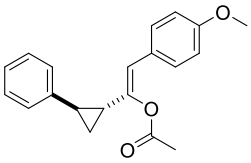


***cis*-19a**



***trans*-19a**



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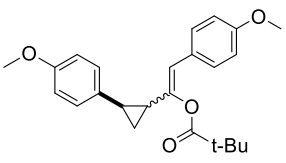


19c

Table of Contents

1 Introduction

The last decade the interest in gold-chemistry has increased exponentially, but the focus has primarily been on the development of new gold(I)-catalysed reactions and the discovery of new gold(I)-ligated complexes. Catalysis with gold(III) has been limited, and mainly focused on ligand-free gold(III)-species.[1] The square-planar geometry of gold(III), compared to the linear geometry of gold(I), is suspected to be the cause of the successful enantioselective cycloisomerization of 1,5-enynes with a gold(III)-catalyst.[2] Development of enantioselective catalysts are of great interest, especially to the pharmaceutical industry, since two isomers might have completely different properties. All the pharmaceutical activity may reside in one isomer and the other may have a qualitatively different effect, an antagonistic effect or might even be toxic.[3]

During my pre-master project[4], novel bis-oxazoline(BOX)-Au(III)-complexes were developed with different counterions (Figure 1). Gold(III)-complex A was found in a 42% yield, gold(III)-complex B in a 31% yield and gold(III)-complex C in a 55% yield.

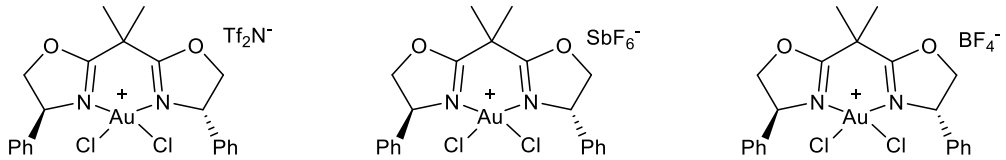


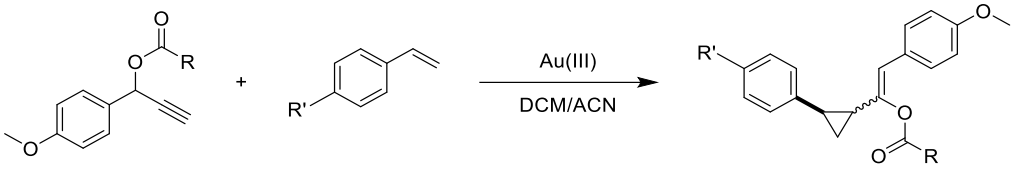
Figure 1: BOX-Ph-Au(III) complexes, with bistriflimide (Tf_2N^-), h*exafluoroantimonate (SbF_6^-) and* t*etrafluoroborate (BF_4^-) as counterions, developed during the pre-master project.*

The catalytic ability of these BOX-Au(III)-complexes was tested in several cyclopropanation reactions, due to the exceptional ability of gold to activate C-C multiple bonds to nucleophilic attack.[5] Alkynes are among the most versatile substrates in gold chemistry, and the reactive and easily accessible propargyl esters are of interest to several research groups.[6] Gold(III)-complexes A-C were used as catalysts in reactions between propargyl esters and styrene and the conversion times and *cis*:*trans* ratios at conversion and after 24 hours were recorded. Isolation of the *cis*-products were also performed, and isomerization of these products with gold(III)-complex B as catalyst were recorded.

Some of the results from the pre-master project and from the corresponding work of colleague Ann Christin Reiersølmoen is soon to be published (Appendix A)[1]. Additional results are offered in a poster presented at Organisk Kjemisk Vintermøte 2018 (Organic chemistry

wintermeeting) (Appendix B). It was found that Box-Au(III)-catalysts were superior to gold(I)-catalysts, ligand-free gold(III)-species and other Au(III)-complexes developed at combined fast cyclopropanation and in-situ *cis*-to-*trans* vinylcyclopropyl isomerization.[1]

After the success of these BOX-Au(III)-complexes, further studies are required to find and develop other ligands with successful coordination to gold(III) and perhaps develop an enantioselective catalyst. In this project several squaramide-, iminoisoindoline- and oxazoline-ligands were prepared and attempted coordinated to gold(III). The catalytic ability of the successful gold(III)-complexes was then tested in cyclopropanation reactions of propargyl ester and vinyl substrates, resulting in diastereomeric products (Scheme 1).



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*Scheme 1: Gold(III) catalysed cyclopropanation reaction of propargyl esters **17a-b** and vinyl substrates **18a-b** resulting in vinylcyclopropyl **19a-c**.*

The potential enantioselectivity of the cyclopropanation products formed with different gold(III)-catalyst were assessed by chiral HPLC.

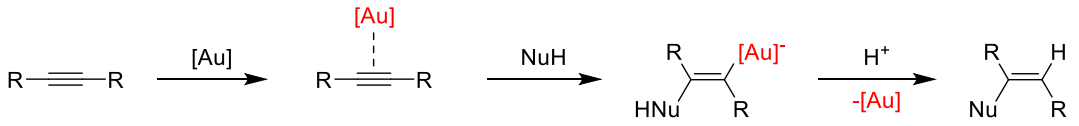
2 Theory

2.1 Gold as catalyst

As a noble metal, gold has low reactivity which allows it to occur in nature in free elemental form, as nuggets or grains. This low reactivity comes from the highly positive normal potential of gold.[7] Gold was long thought to be too expensive and inert, and was therefore seldom used in synthesis.[8] This is evident from the lack of reports before 1970. Then there were a few reports on the use of gold as catalyst, but none of them showed gold to be superior to other catalysts. This perception of gold started to change, however, when in 1973 Bond et al.[9] reported the hydrogenation of olefins over supported gold catalysts.[10] This was the start of a new "gold-rush", although it did not pick up until two decades later. A report from Teles in the BASF laboratories released in 1998 triggered the research in homogeneous catalysis by gold compounds.[11]

In the presence of organic substrates, there are three different oxidation states for gold, Au(0), Au(I) and Au(III), where Au(I) and Au(III) dominate its chemistry.[7] Gold(I) has a linear geometry which places the active reaction site away from possible chiral information, and this is a challenge in the development of enantioselective transformations. A solution to this problem could be the use of ligated gold(III), which has a square-planar geometry with four coordination sites.[2] This may allow for more selective reactions due to the proximity of the ligand to the reaction centre.[1]

Gold(I)-complexes has in recent years been used as catalysts in several organic reactions because of gold's ability to activate C-C multiple bonds toward nucleophilic attack.[5] Theoretically, the gold catalyst interacts with the π-system of the C-C multiple bond, forming an intermediate, and then a nucleophile attacks *anti* to gold resulting in a vinyl gold species. Protodemetallation then liberates the addition product by the regeneration of the gold-catalyst (Scheme 2).[7]



Scheme 2: Gold catalyzed nucleophilic addition to alkyne.

2.2 Ligands

2.2.1 Oxazoline

Gold(III) has low toxicity and an environmentally benign nature, but relies on ligands for stabilization.[12] Ligands containing chiral oxazoline rings are one of the most used ligands for asymmetric catalysis because of its applicability in several transformations, its modular nature and because it is easily accessible.[13] Most oxazoline-based ligands derive from chiral amino alcohols and the close proximity of the chiral carbon to the coordinating nitrogen results in a direct influence of the stereochemical outcome of the reaction.[14]

The first oxazoline-based ligand in asymmetric catalysis was reported in 1986, and since then ligands with one, two or more oxazoline rings have been reported as successful asymmetric catalysts.[14] Pyridinyl oxazolines (PyOX) (R = *i*-Pr, Bn, Ph) have successfully been coordinated to gold(III), and the complexes were reported to be air- and moisture-stable yellow solids, insoluble in chlorinated solvents but soluble in highly polar solvents like acetone and acetonitrile (Figure 2b).[13] Bis(oxazoline) (BOX) ligands have two asymmetric carbons which results in a complex with chiral and achiral isomers. BOX-ligands with a one carbon spacer between the oxazoline rings are most common (Figure 2c).[15] A BOX-Au(III)-complex was first synthesised for investigations of its thermal properties.[16] Further studies by the Fiksdahl group tested the catalytic abilities of two novel box-Au(III)-complexes in cyclopropanation reactions with alkenes.[1]

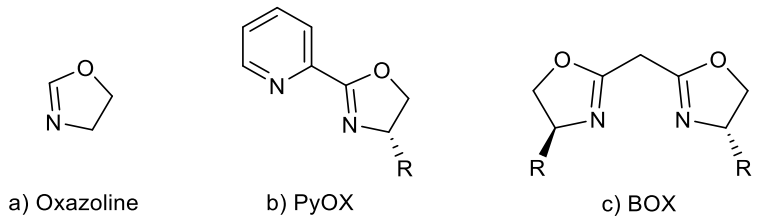
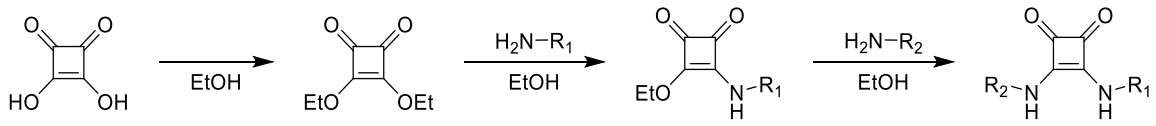


Figure 2: a) Oxazoline structure b) oxazoline ligand pyridinyl oxazoline (PyOX) c) oxazoline ligand bis(oxazoline)(BOX) linked by CH_2.

Gold-complexes like these are catalytic alternatives to $AuCl_3$, since they are less sensitive in air and moisture, and can be applied in a larger variety of solvents in precise quantities.[11] Some problems have been reported however, where the gold-complexes were mixtures of the desired counter-ion (X^-) and $AuCl_4^-$ instead of purely the desired counter-ion (X^-).[13]

2.2.2 Squaramides

Squaramides are other ligands with potential for gold-coordination. Squaramides originate from square acid, an aromatic compound with unique characteristics. Square acid has acidic hydroxyl groups which can be replaced by various functional groups, for example amines, which leads to the convenient preparation of versatile chiral ligands (Scheme 3).[17]



Scheme 3: Formation of squaramides from reaction of squaric ester with primary amines.

The rigid ring moiety of the squaramide provides an environment suitable for chiral additions, and have been used in a variety of reactions, such as organocatalysis, due to its properties. Xie et. al. demonstrated that the asymmetric synthesis of enantiomerically pure secondary alcohols is possible from reduction of prochiral ketones by borane in the presence of a catalytical amount of squaric acid aminoalcohols.[17] This enantioselective borane reduction was further conducted with chiral squaric acid camphor aminoalcohols as catalyst.[18] Furthermore, an estradiol based squaramide ligand was successfully coordinated to different transition metals, palladium, nickel and zinc, and the estrongen receptor binding affinities of the complexes were tested.[19] The coordination of gold to squaramides has, to the best of our knowledge, not yet been attempted.

2.2.3 Imines

Gold(III) has also been reported to coordinate to the salen ligand and used as catalyst during synthesis of ketones through hydration of alkynes[20]. Chiral salen has also been coordinated to manganese, chromium, cobalt and aluminium, providing catalysts with the ability to epoxidize olefins with a high level of enantioselectivity, among other reactions. Some chiral salen-complexes are privileged catalysts, meaning that it is enantioselective over a wide range of different reactions.[21] These results encouraged colleague Helgi Freyr Jónsson in the Fiksdahl Group, to coordinate both the salen ligand and a chiral salen ligand to gold(III) (Figure 3).[22]

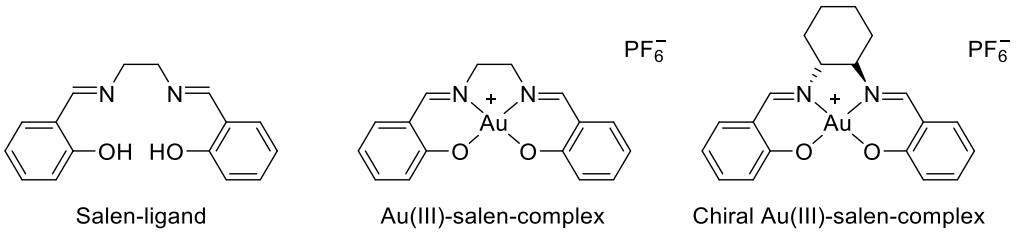
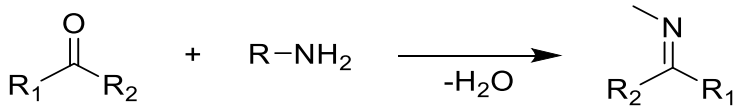


Figure 3: Structure of the salen ligand, and the gold(III)-salen-complex and the chiral gold(III)-salen-complex developed by Helgi Freyr Jónsson.

The successful gold-coordination of salen gives reason to think that other imines might also have this ability. Imines are synthesized by the condensation of aldehyde or ketone and a primary amine (Scheme 4).[23]



Scheme 4: Synthesis of imine by condensation of aldehyde/ketone and primary amine.

Diimines have reached a certain popularity as ligands due to their steric and electronic tunability, and the ease with which they are synthesized. The most common synthetic method of producing diimines are similar to what is shown in Scheme 4, but starting with a dialdehyde or -ketone.[24] Three types of diimines, called α-, β- and γ-diimines are shown in Figure 4.

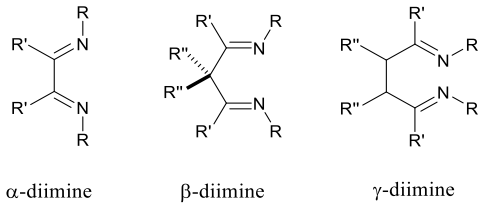
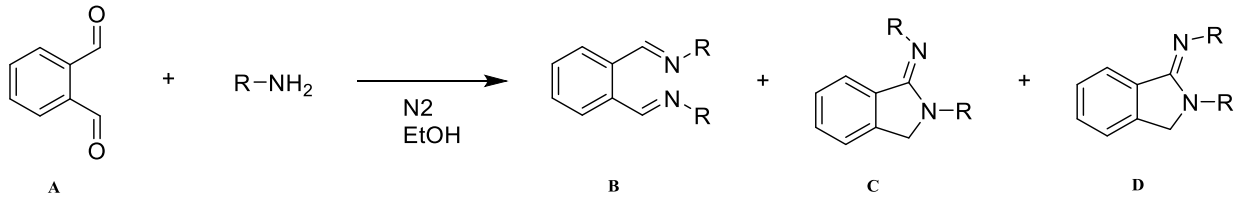


Figure 4: Chemical structure of α -, β- and γ-diimines.

α-Diimines have been successfully coordinated to Ni(II) and Pd(II), first reported by Brookhart, who used the complexes in olefinpolymerization.[25] β-Diimines have also been successfully

coordinated to Pd(II)[26] and Ni(II), and it was found that the complexes catalyses Heck, Suzuki and Hiyama coupling reactions.[27] Unlike the easy synthesis of α- and β-diimines, γ-diimines have proved more difficult and have yielded different results.



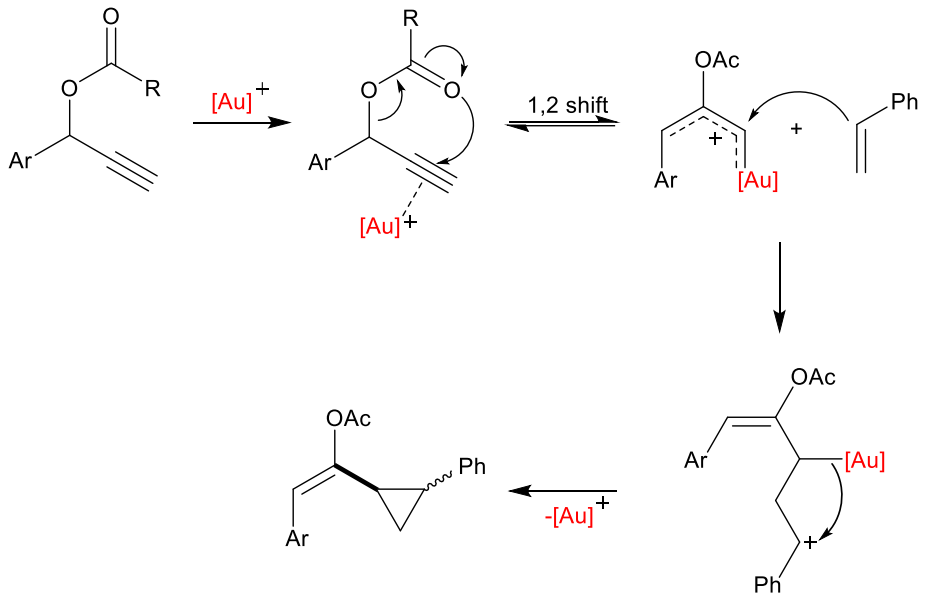
*Scheme 5: Reaction between phthaldialdehyde (**A**) and a primary amine yielding three different products, γ-diimine, (E)-iminoisoindoline (**C**) and (Z)-iminoisoindoline (**D**).*

In 2008, attempts to synthesize a γ-diimine from a simple diketone was prevented when the only result was a pyrrol product. A second attempt using phthaldialdehyde (**A**), which should prevent pyrrole formation because of its containment, resulted in an iminoisoindoline (**C/D**), not diimine (**B**) (Scheme 5).[24] This result was not surprising as it had also been reported in 2004, proved by x-ray analysis.[28] The same group did further research on the subject in 2005, and found that different amines gave different products, but the most common was iminoisoindoline (**C**/**D**), either in (*E*)- or (*Z*)-form.[29] In 2007, however, it was found that by the use of a catalytic amount of formic acid with phthaldialdehyde (**A**) and amine, γ-diimine (**B**) was indeed the product. The γ-diimine (**B**) was then found to successfully coordinate to Co(III), Fe(III) and Cr(III).[30] These findings are relevant for this project (see chapter 3.2).

2.3 Cyclopropanation

Cyclopropane is a basic structural element in several compounds found in nature. Although unsubstituted cyclopropane is achiral, chirality is often found in substituted cyclopropane. A lot of the synthetic effort in recent years has been to find an enantioselective synthesis of cyclopropane.[31]

Propargylic esters have been applied extensively in nucleophilic addition of terminal alkynes with gold catalysis. Propargylic esters are easily accessible and have a tendency to undergo 1,2- and 1,3- acyl migration, creating gold-carbene and allene, respectively.[32] Whether 1,2- or 1,3 migration occurs depend on the ligand, substrate and reaction conditions. Terminal propargyl esters undergo 1,2-migration while non-terminal undergo 1,3-migration. The three species, the propargyl ester, 1,2- and 1,3- migration products, are in rapid equilibrium, which could lead to different stable products.[5] Cyclopropanation occurs after a 1,2 acyl migration of terminal propargylic ester, and then a [1+2] cycloaddition with a vinyl substrate, resulting in vinylcyclopropyl, normally as *cis*/*trans* mixtures (Scheme 6).[1]

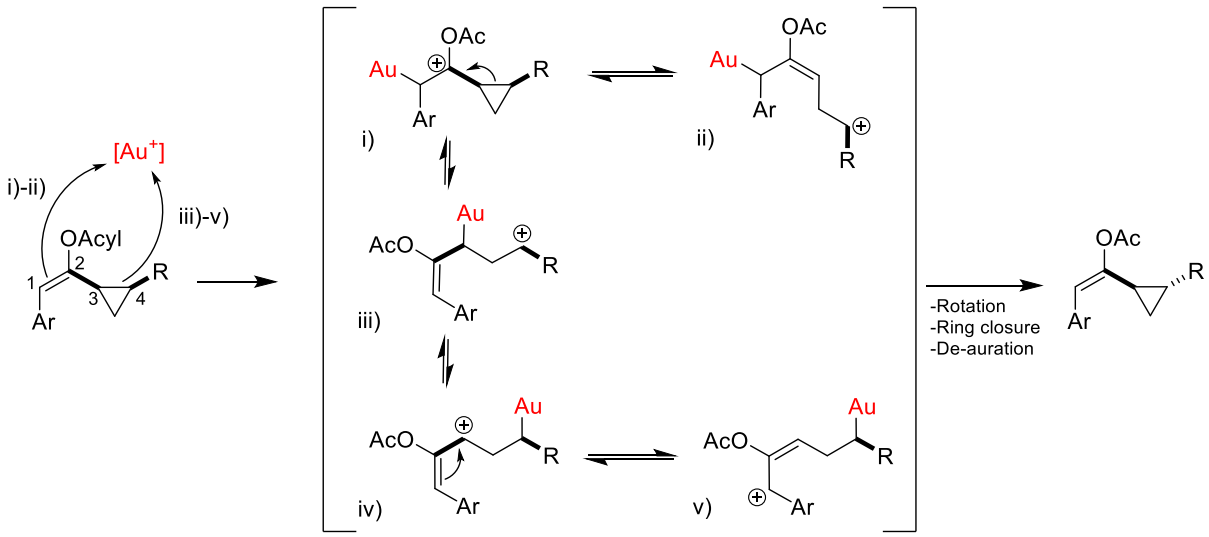


Scheme 6: Gold-catalyzed activation of propargyl ester and subsequent alkene cyclopropanation.

The cyclopropanation reactions with styrene or other alkenes have previously showed to favour *cis*-isomer compared to *trans*. This is contributed to the lower energy of the *cis*-transition state, and the stabilizing π-π interactions which occur only in *cis*-cyclopropane.[33] It has also been widely accepted that steric interactions are the cause of the favoured *cis*-selectivity, called the cyclopropanation stereoselectivity model.[34] This model was recently disputed when it was found, by the Fiksdahl group, that electronic properties of the substrate, choice of gold(I)- or

gold(III)- catalyst and reaction time affected the stereoselective outcome, more than steric interactions.[1]

By the formation of vinylcyclopropane, it has been reported that the favoured *cis*-product will undergo in-situ isomerization to *trans*-vinylcyclopropane in the presence of a gold-catalysts. Isolation of the *cis*-products ensures even faster isomerization by a gold(III)-catalyst. The isomerization is proposed to proceed by gold-catalyzed ring opening through intermediates i-v (Scheme 7). First the Au moiety attaches to the *cis*-product at C1, C3 or C4, giving intermediates i/ii, iii, or iv/v, respectively. Bond-rotation, de-auration and ring-closure then follows, resulting in the *trans*-product.[1]



Scheme 7: Gold-catalyzed isomerization of cis-vinylcyclopropane.

To monitor the conversion of a cyclopropanation reaction and the subsequent *cis*-to-*trans* isomerization, the reactions were performed as ^{1}H NMR experiments. The reactants are added to an NMR-tube, and a catalyst is added immediately before the first ^{1}H NMR spectrum is recorded. Several ^{1}H NMR spectra can then be executed consecutively to pinpoint the exact time of full conversion. The reaction can then be followed further to record the *cis*:*trans* ratio over time.

2.4 Enantiomeric separation

The cyclopropanation diastereometric products (Scheme 6) are formed as enantiomers, meaning that for both the *cis*- and *trans*-products there are two possible stereoisomers which are mirror images of each other. Many biological and pharmaceutical drugs contain chiral compounds, and the physiological properties of two enantiomers of these compounds may differ. This biological enantioselectivity was first discovered by Louis Pasteur in 1858, and since then the research into the preparation of individual enantiomers have become more and more important.[35]

The most common methods of separating two enantiomers in a sample is the use of a chiral stationary phase (CSP) in high performance liquid chromatography (HPLC) or gas chromatography (GC). The degree to which one enantiomer is in excess compared to the other is given in enantiomeric excess (%ee), in which 0% ee means equal amount of both enantiomers, and 100% ee means an enantiomerically pure sample.[36]

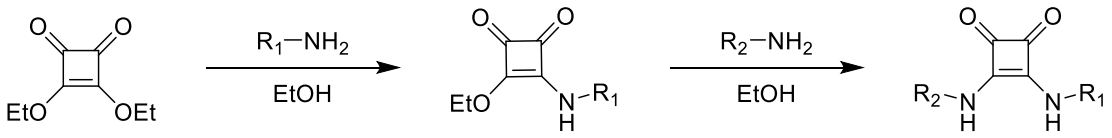
For polar or non-volatile compounds, a great number of CSP's for HPLC have been developed, and they can be separated into two types; optically active small molecules and optically active polymers, immobilized or coated on a support surface. Polysaccharide-based CSPs are the most common chiral phases used today. Although polysaccharides, like cellulose and amylose, can discriminate between enantiomers, they are not good enough to be used as a CPS. By derivatization of the polymers however, their abilities improve. Phenylcarbamates are common derivatives of polysaccharides, and different substituents on the phenyl group can influence the recognition abilities of the derivatives. Electron-donating substituents and electron-withdrawing substituents affect the resolution differently, while polar substituents may interact with the racemates non-enantioselectively and cause little to no resolution at all.[35]

The resolution depends on which enantiomer forms the most stable connection with the chiral compound on the CSP and will thus be more retained than the other. The composition, pH and temperature of the mobile phase also affect the enantioselectivity.[35] Both utilization similar to normal-phase HPLC and reversed-phase HPLC are applicable in the separation of enantiomers.[37] Polysaccharide CPSs are commercially available as immobilized or coated on a support surface. Coated CPSs is limited to a selected number of solvents, alkane/alcohol mixtures in normal-phase HPLC and water/acetonitrile mixtures in reverse-phase HPLC. Many of the other commonly used solvents in HPLC might destroy the chiral stationary phase. Immobilized CPSs have been developed to overcome these challenges.[38]

3 Results and Discussion

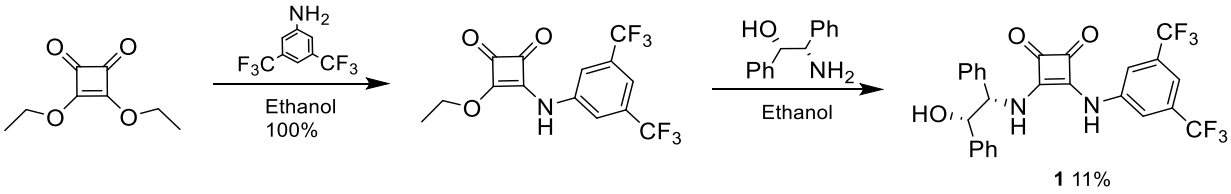
3.1 Synthesis of squaramide ligands

Syntheses of different squaramides were performed following a literary procedure[19], by adding different primary amines to squaric ethyl ester in ethanol and stirred until completion. Non-symmetric target products were prepared by a step-wise procedure (Scheme 8).



Scheme 8: General synthesis of squaramide from squaric ethyl ester reacted with two primary amines.

Following the procedure shown in Scheme 8, six novel squaramides were synthesized. These reactions were executed as screening studies where the priority was the syntheses of as many different squaramides as possible and not optimizing of the procedures. Studies of generating higher yields were therefore not prioritized.



*Scheme 9: Step-wise synthesis of squaramide **1** from squaric ethyl ester, 3,5-bis(trifluoromethyl) aniline and (1S,2S)-2-amino-1,2-diphenylethan-1-ol.*

Squaramide **1** was synthesized by first adding 3,5-bis(trifluoromethyl) aniline to squaric ethyl ester in ethanol and stirring for ten days (Scheme 9). The long reaction time is due to the strong electron withdrawing properties of the CF_3-groups on the aniline. After ten days ^{1}H NMR showed full conversion and no purification was needed, and the second amine, (1*S*,2*S*)-2-amino-1,2-diphenylethan-1-ol, was added dropwise. White precipitate was visible immediately, and after one hour ^{1}H NMR showed full conversion. Since the product was no longer soluble, it was filtrated and washed thoroughly with ethanol, giving 13.8 mg (11%) of squaramide **1**.

Despite the full conversion achieved in both steps of the synthesis, a low yield was achieved. This might be caused by the filtration and washing where the product might have been more soluble in ethanol than first thought, and product might have been lost. The product was not soluble in anything but DMF and DMSO.

The structure of squaramide **1** with ^{1}H and ^{13}C NMR shifts are given in Figure 5.

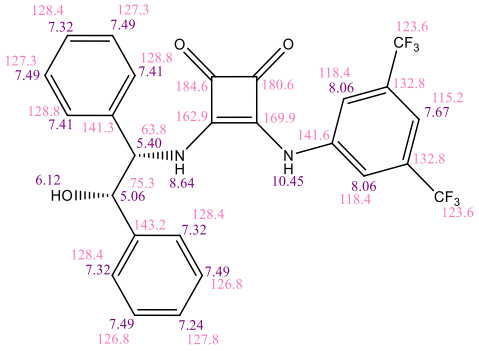
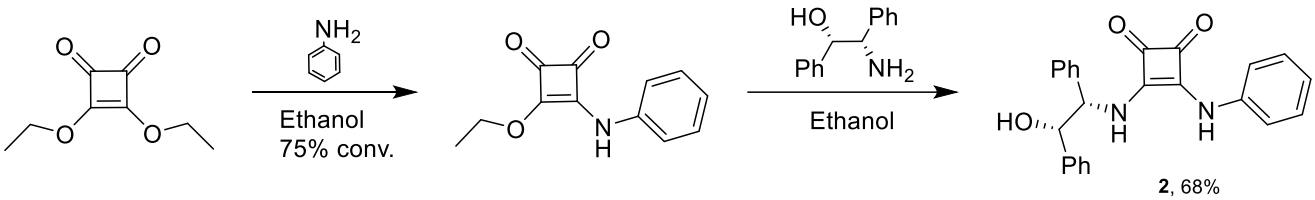


*Figure 5: Squaramide **1** with accompanying ^{1}H and ^{13}C NMR shifts in d_6-DMSO.*



*Scheme 10: Step-wise synthesis of squaramide **2** from squaric ethyl ester, aniline and (1S,2S)-2-amino-1,2-diphenylethan-1-ol.*

Squaramide **2** was synthesized according to Scheme 10, by adding aniline to squaric ethyl ester and stirring for five days. After five days there was a conversion of 75%, which was only four percentage points higher than after four days. Therefore, the reaction was stopped and extracted with water to remove the residual amine and squaric ester. (1*S*,2*S*)-2-Amino-1,2-diphenylethan-1-ol was then added dropwise, and ^{1}H NMR showed full conversion after one hour. The product was washed with ethanol, giving 68% yield of squaramide **2**. The same insolubility problem was present for this product, and it was only soluble in DMF and DMSO. The structure of squaramide **2** with ^{1}H and ^{13}C NMR shifts are given in Figure 6.

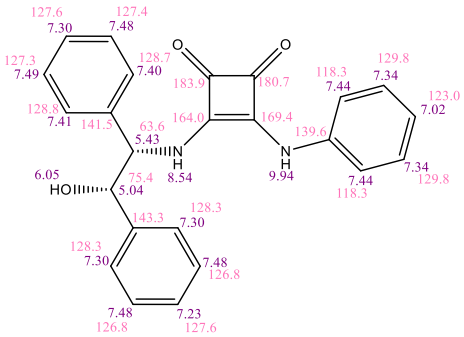
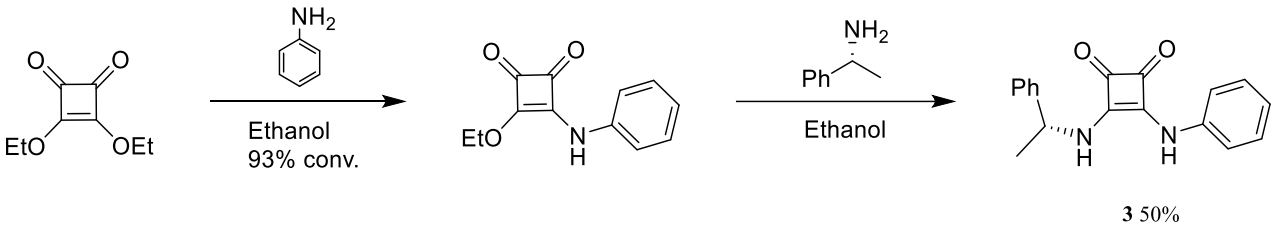


*Figure 6: Squaramide **2** with accompanying ^{1}H and ^{13}C NMR shifts in in d_6-DMSO.*

Compared to the ^{1}H NMR shifts of squaramide **1**, the shifts of squaramide **2** are lower on the aniline due to the electron withdrawing property of the CF_3-groups in squaramide **1** which shifts a proton signal downfield.



*Scheme 11: Step-wise synthesis of squaramide **3** from squaric ethyl ester, aniline and (R)-1-phenylethan-1-amine.*

The next squaramide synthesizes was squaramide **3**, shown in Scheme 11. Similarly to squaramide **2**, aniline was added to squaric ethyl ester dropwise, but in this case 93% conversion was unexpectedly obtained after one day, for unknown reasons. The reaction was stirred overnight, and then (*R*)-1-phenylethan-1-amine was added dropwise. The mixture turned at once from pale yellow to white and precipitate was visible. The product was no longer soluble in ethanol, and it was tried to filtrate the product off, but small particles went through the filter paper. Thus, the product was instead washed with ethanol, giving 34.5 mg (50%) of squaramide **3** as a white solid. The structure of squaramide **3** with ^{1}H and ^{13}C NMR shifts are given in Figure 7.

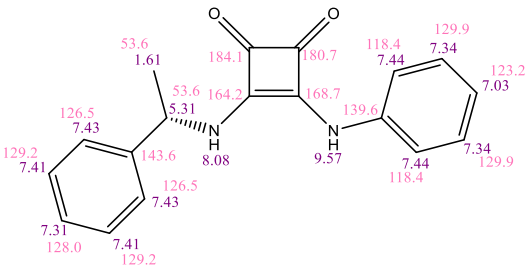
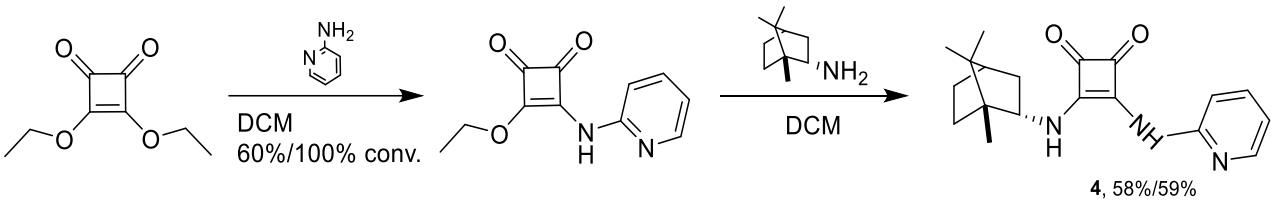


*Figure 7: Squaramide **3** with accompanying ^{1}H and ^{13}C NMR shifts in in d_6-DMSO.*



*Scheme 12: Step-wise synthesis of squaramide **4** from squaric ethyl ester, 2-aminopyridine and (R)-(+)-bornylamine.*

Squaramide **4** was challenging to synthesize from squaric ethyl ester, particularly the initial introduction of the electron deficient 2-aminopyridine. The first-step reaction was attempted in ethanol like the rest of the squaramide reactions, but after two days of essentially no conversion, the solvent was changed to dichloromethane (DCM), and two drops of triethyl amine was added, as previously reported.[19] Two days later the reaction had reached 60% conversion but unfortunately the DCM had evaporated. There was also a small amount of amine left, so half of the original amount of 2-aminopyridine and DCM was again added to the reaction mixture. The next day there was little improvement and the mixture was extracted with water to remove the residual amine. To remove the excess squaric ester the product was dissolved in ethyl acetate and left in the freezer overnight for precipitation. This was unsuccessful, and the product was purified by column chromatography. (*R*)-(+)-Bornylamine was added dropwise to the intermediate and ^{1}H NMR showed full conversion after two hours. The product was washed with ethanol, giving 58% yield of squaramide **4**.

This two-step synthesis was repeated in larger scale, this time in DCM and heated to 40 °C to speed up the reaction. The heat had apparently the opposite effect, as after one week only 44 % conversion had been achieved. The heat was turned off and after two days ^{1}H NMR showed full conversion. (*R*)-(+)-Bornylamine was added dropwise to the intermediate and ^{1}H NMR showed full conversion after two hours. The product was purified on a column, giving 59 % yield of squaramide **4** as a pale-yellow powder. The structure of squaramide **4** with ^{1}H and ^{13}C NMR shifts are given in Figure 8.

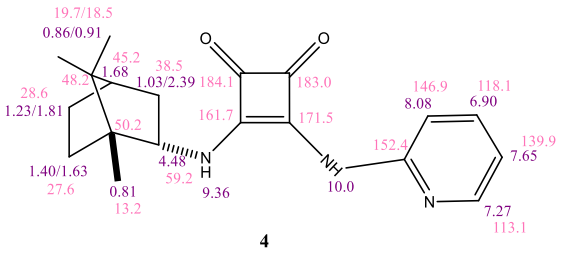
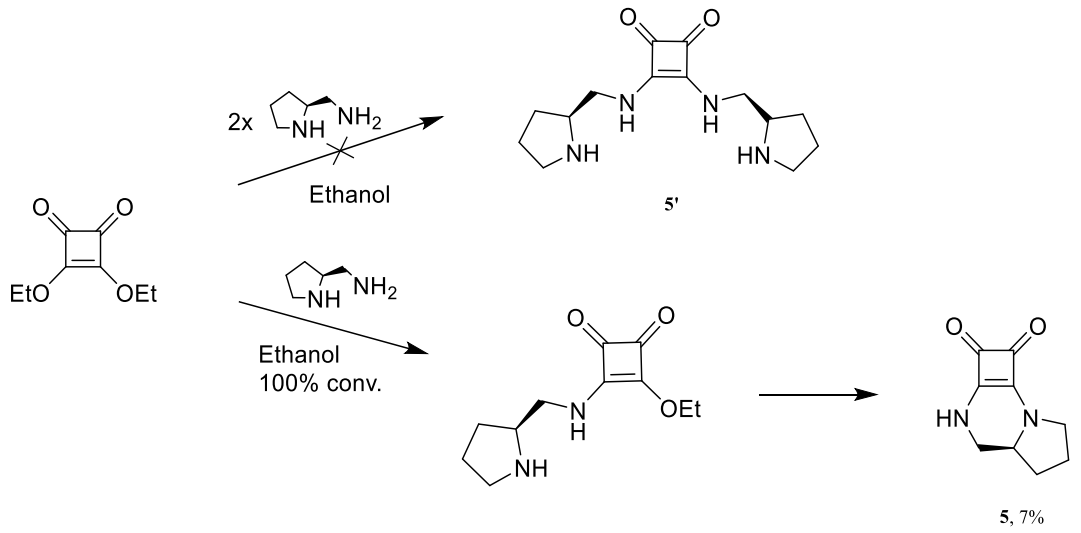
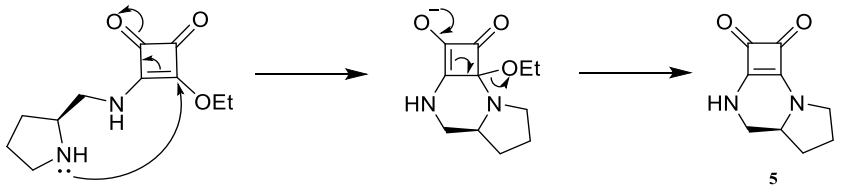


*Figure 8: Squaramide **4** with accompanying ^{1}H and ^{13}C NMR shifts in in d_2-DCM.*



*Scheme 13: Synthesis of squaramide **5** from squaric ethyl ester and (S)-(+)-2-(aminomethyl)pyrrolidine. Synthesis of squareamide **5'** with two equivalents of (S)-(+)-2-(aminomethyl)pyrrolidine was unsuccessful.*

The heterocyclic piperazine squaramide **5** was unexpectedly formed in attempts to make the monosubstituted squaramide by adding (*S*)-(+)-2-(aminomethyl)pyrrolidine to squaric ethyl ester. Purification of the product by silica-gel column chromatography provided two products, both in a very small amounts. The first product to elude might be monosubstituted squaramide, but the ^{1}H NMR was complex. The second product was first thought to be the disubstituted squaramide **5'** (Scheme 13). However, the different cyclic product **5** was formed in a low yield of only 8%. The formation of squaramide **5** prompted a second reaction with 2 equivalents of (*S*)-(+)-2-(aminomethyl)pyrrolidine to develop squaramide **5'**, but this proved to be just as ineffective as the previous reaction, with only 5.4 mg (7%) of product **5** after purification by silica-gel column chromatography. Because of the symmetric nature of the disubstituted squaramide **5'**, based on ^{1}H NMR it was not possible to distinguish between this product **5'** and squaramide **5**. MS, however, only detected a product with mass 179, which may correspond to squaramide **5** with an additional hydrogen. It therefore seems like that after the formation of monosubstitued amine, the pyrrolidine nitrogen attacks the remaining ethoxy group and forms a six-membered piperazine ring (Scheme 14).



*Scheme 14: Mechanism of the heterocyclic piperazine squaramide **5**.*

The structure of squaramide **5** including ^{1}H and ^{13}C NMR shifts are given in Figure 9.

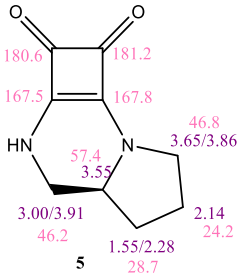
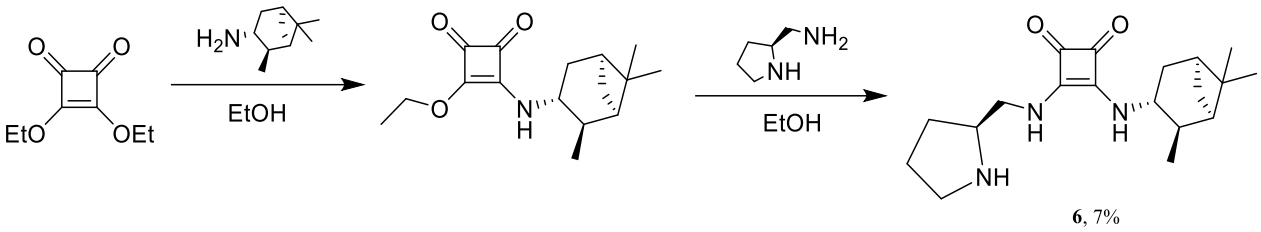


*Figure 9: Squaramide **5** with accompanying ^{1}H and ^{13}C NMR shifts in in d-$CDCl_3$.*



*Scheme 15: Step-wise synthesis of squaramide **6** from squaric ethyl ester, (1R,2R,3R,5S)-(−)-isopinocampheyl amine and (S)-(+)-2-(aminomethyl)pyrrolidine.*

Squaramide **6** was the intended product when squaramide **5** was unexpectedly obtained. Since the primary addition of (*S*)-(+)-2-(aminomethyl)pyrrolidine did not work, it was decided to introduce (1*R*,2*R*,3*R*,5*S*)-(−)-isopinocampheyl amine first (Scheme 15). When all the amine was consumed, the ^{1}H NMR was a bit messy and purification on silica-column was desired, but the product was not soluble in ethyl acetate nor methanol. Therefore, the second amine, (*S*)-(+)-2-(aminomethyl)pyrrolidine, was added directly to the mixture. The final product was still not completely soluble in methanol, but eluted partly on TLC using 100:5 DCM:MeOH as eluent, even if there was still some product stuck on the baseline. Purification by column chromatography started with 5 % methanol in DCM, but as the elution progressed the eluent was changed to 20 % methanol, and finally to 100 % methanol to get all the product from the column. As with squaramide **5** there was very little product in all the fractions, and eventually, only a yield of 5.2 mg (7%) of squaramide **6** was achieved. The structure of squaramide **6** with ^{1}H and ^{13}C NMR shifts are given in Figure 10.

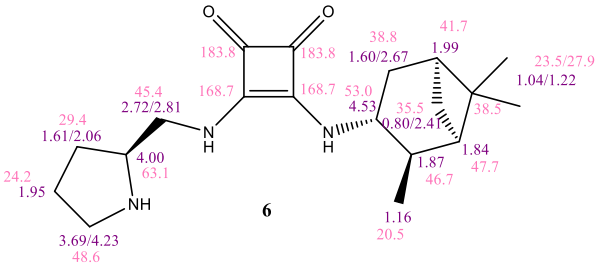
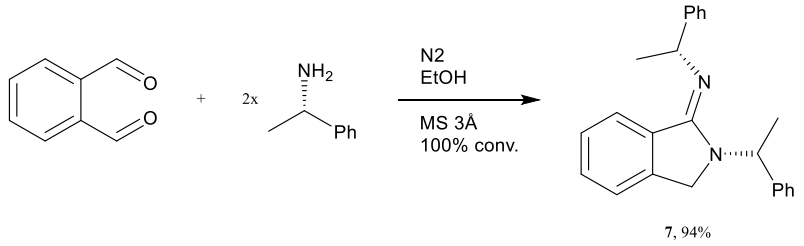


*Figure 10: Squaramide **6** with accompanying ^{1}H and ^{13}C NMR shifts in in d-$CDCl_3$.*

3.2 Synthesis of imine ligands

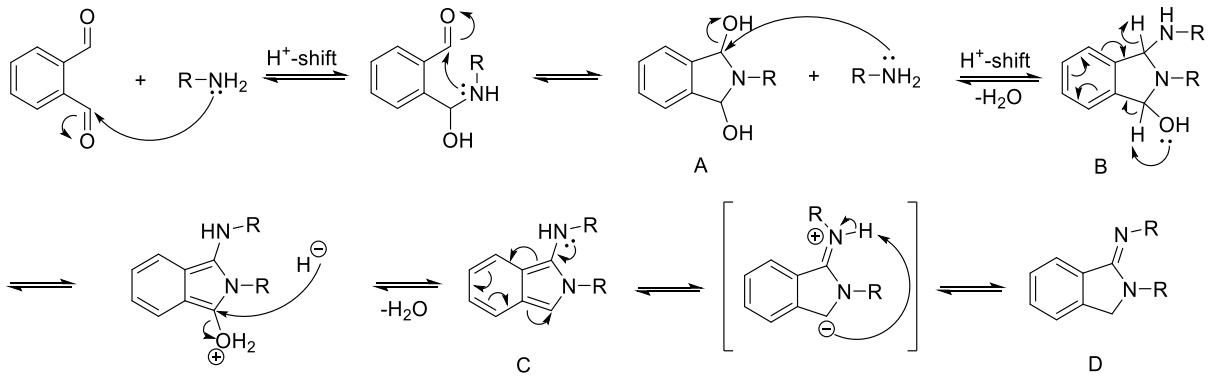
Syntheses of imines were done according to a literary procedure[29], by adding two equivalents of (*R*)-(+)-α-methylbenzylamine to phthaldialdehyde in ethanol under a nitrogen atmosphere (Scheme 16).



*Scheme 16: Synthesis of iminoisoindoline **7** from phthaldialdehyde and two equivalents of (R)-(+)-α-methylbenzylamine.*

The reaction was stirred for an hour until ^{1}H NMR showed full conversion. Purification was not necessary, and the solvent was removed under reduced pressure, which resulted in a 94% yield. It was assumed that this reaction would produce a γ-diimine product, but it was later found that it was iminoisoindoline **7**.

Formation of iminoisoindolines occurs by amine addition to phthaldialdehyde followed by ring-closing, giving 1,3-dihydroxyisoindoline (A) (Scheme 17). Condensation of A with a second mole of amine, affords a 1-amino-3-isoindolinol intermediate (B). Dehydration gives aminoisoindole (C) which quickly tautomerizes to iminoisoindolines (D).[29]



Scheme 17: Mechanism for synthesis of iminoisoindoline (D) by addition of amine to phthaldialdehyde.

Product **7** was very unstable, having degraded to a mixture of products after few hours in deuterated acetonitrile (d_3-ACN). The original product was still present, in addition to several others, which might be a result of hydrolysis of the iminoisoindoline.

The first indication of a different product than expected was the absence of two imine protons with ^{1}H NMR shifts at 9 ppm. HSQC of the product also showed that the two protons at 4.20

ppm and 4.51 ppm were a CH_2-group because they are both on the same carbon and the signals were green. In ^{1}H-^{13}C HSQC, CH and CH_3 protons have blue signals, while CH_2 protons have green. IR confirmed the presence of an imine-group, with a strong signal at 1644 cm^{-1}.

Characterization of iminoisoindoline **7** were performed by ^{1}H NMR, ^{13}C NMR, ^{1}H-^{1}H COSY, ^{1}H-^{13}C HSQC and ^{1}H-^{13}C HMBC. Figure 11b shows iminoisoindoline **7** with ^{1}H and ^{13}C NMR shifts, and Figure 11a shows selected proton-proton (pink) and carbon-carbon (purple) correlations between both protonated and quaternary carbons on iminoisoindoline **7**.

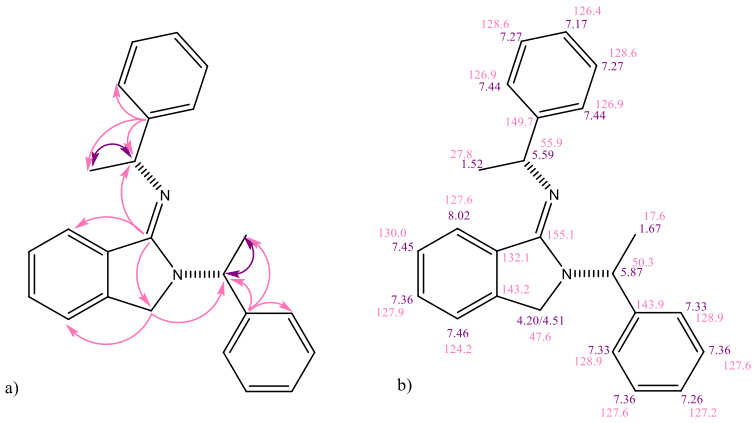
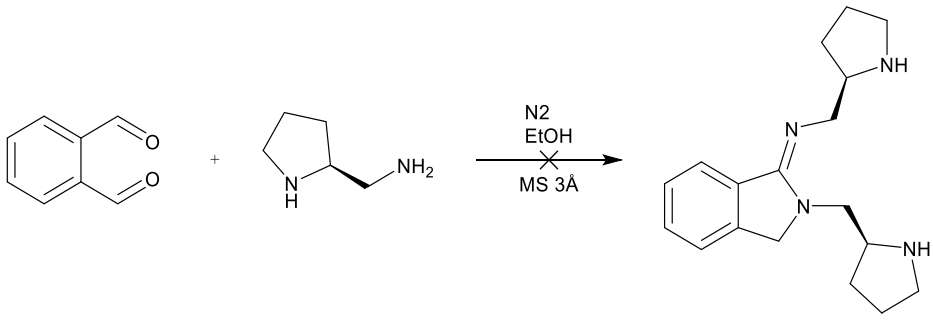


Figure 11: a) Structure of iminoisoindoline 7 with arrows showing selected proton-proton (purple) and carbon-carbon (pink) correlations. b) Structure of iminoisoindoline 7 with accompanying ^{1}H and ^{13}C NMR shifts in d_3-ACN.

The fact that this reaction resulted in an iminoisoindoline and not a γ-diimine is confirmed by literature[29], since diimines are produced when formic acid is used in a catalytic amount, as presented in the theory (Section 2).



Scheme 18: Failed synthesis of (E)-N,2-bis(((S)-pyrrolidin-2-yl)methyl)isoindolin-1-imine from phthaldialdehyde and two equivalents of (S)-(+)-2-(aminomethyl)pyrrolidine.

To verify that iminoisoindoline was the product for all amines used in this reaction, phthaldialdehyde was then reacted with (*S*)-(+)-2-(aminomethyl)pyrrolidine under the same reaction conditions, as seen in Scheme 18. The result was a complex mixture which degraded in solution after less than 12 hours. To see if the complex mixture was a result of degrading after evaporation, the reaction was repeated in *d*-ACN to avoid evaporation. The ^{1}H NMR

spectrum remained the same, and it could then be concluded that the product was indeed this intricate. Purification on column chromatography was therefore the next step, but the product did not elute on silica TLC plates, not even in 100% methanol. Therefore, alumina TLC plates were tried, which eluted the product mixture using an eluent of 1% MeOH in DCM. The product was then purified on an alumina column, but the results were unsatisfying. The product was dark green before purification, which separated into several colours with different retention times. The product divided into five coloured sections, first two yellow, then a turquoise, a green and another yellow. None of the sections were visible in UV-light, therefore ^{1}H NMR was done for one sample of each colour (Figure 12).

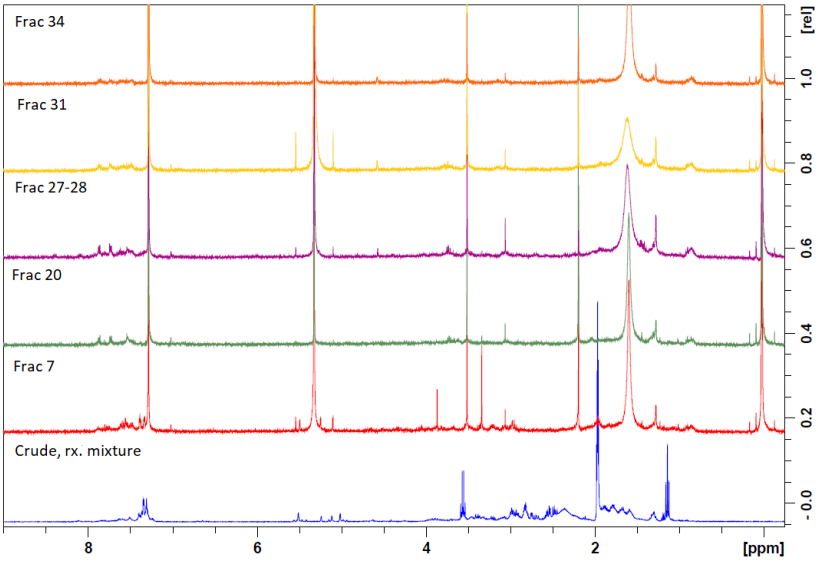


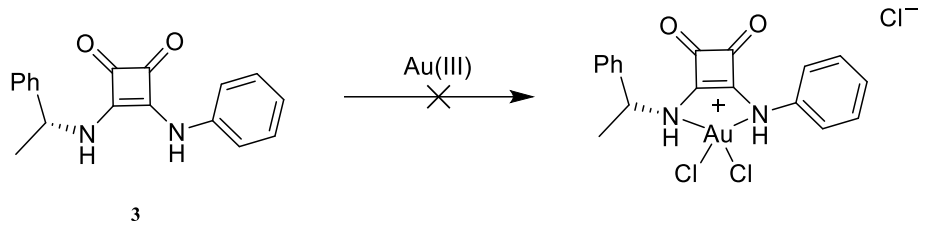
Figure 12: ^{1}H NMR spectra from the attempted synthesis of (E)-N,2-bis(((S)-pyrrolidin-2-yl)methyl)isoindolin-1-imine. From the bottom and up, crude product before purification on column chromatography, and the fractions 7, 20, 27-28, 31 and 34 after purification on column chromatography.

The wanted product of an iminoisoindoline would give four prominent protons in the aromatic region, since there were no aromatic protons on the amine. This was not true for any of the fractions, although fraction 20 was the most promising because this fraction had the most separation between the signals in the aromatic region. MS was taken of this sample, but results did not correspond with the wanted iminoisoindoline, so synthesis of more suitable ligands for gold coordination was prioritized in favour of solving this complex reaction mixture.

3.3 Au(III)-complexes

When coordinating a ligand to gold, one wishes to see a definite shift of the signals in ^{1}H NMR spectra compared to the ligand. Often the shift is significantly to the left, meaning the protons are more deshielded by the presence of gold. Both $KAuCl_4$ and $AuCl_3$ can be used as a source of gold(III), although $KAuCl_4$ has been found to be more stable.

3.3.1 Squaramide ligands



3

*Scheme 19: Attempted coordination of squaramide **3** to gold(III).*

Squaramide **3** was the first squaramide attempted to coordinate to gold(III) (Scheme 19). Several attempts were made after the first resulted in black precipitate of decomposed gold. A summary of the four coordination attempts to squaramide **3** can be seen in Table 1.

*Table 1: Summary of attempts at coordinating squaramide **3** to gold(III) with different solvents, gold chlorides, salts and temperatures. The color of the solution, time stirred and whether the coordination worked is also presented.*

Attempt	Solvent	Gold	Salt	Temp.	Colour	Time	Coordination
1	DMF	$AuCl_3$	$AgSbF_6$	25 °C	Black	30 min	No
2	DMF	$KAuCl_4$	-	25 °C	Yellow	4 days	No
3	ACN	$KAuCl_4$	-	65 °C	Yellow	3 days	No
4	DCM/EtOH	$KAuCl_4$	$(Bu_4N)PF_4$	25 °C	Yellow	2 days	No

Coordination of squaramide **3** to gold(III) was first attempted using $AuCl_3$ in DMF, which turned the mixture brown. Form previous experiences, ACN and DCM have shown to be favourable solvents for coordination to gold, probably due to good solubility and stability of the gold(III) salt and the formed gold complexes. However, the poor solubility of squaramide **3** in all solvents except for DMF and DMSO, limits the possibilities. DMF seems to be a less ideal solvent for coordination since the brown colour of the solvent can imply that some of the gold salt has decomposed. When the silver salt $AgSbF_6$ was added the mixture turned black from precipitate of decomposed gold, indicating the attempt had failed. Coordination using $KAuCl_4$ was attempted instead, since it has proved to be a milder and more stable source of gold than $AuCl_3$ in previous studies. The silver salt was also left out since it is only used to

exchange the counter ion and is not necessary for coordination. This second attempt resulted in a yellow mixture, demonstrating the higher stability of $KAuCl_4$ compared to $AuCl_3$, but after four days the ^1H NMR spectra of squaramide **3** and the coordination attempt were still equal (Figure 13, spectra i and ii).

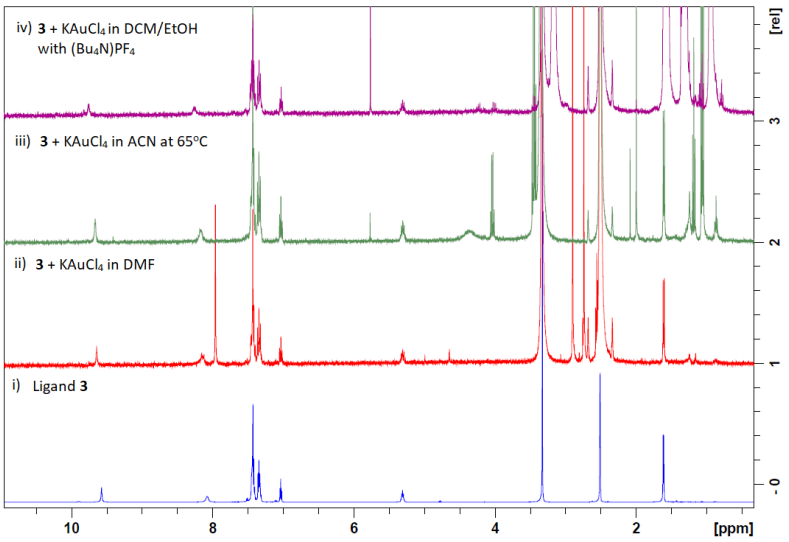
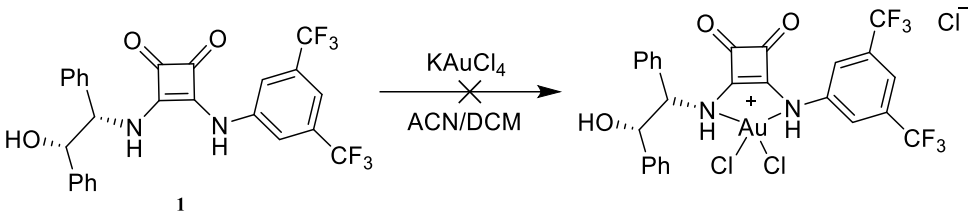


*Figure 13: ^1H NMR spectra of squaramide **3** (i), the coordination attempt of squaramide **3** with $KAuCl_4$ in DMF after stirring 4 days (ii), the coordination attempt of squaramide **3** with $KAuCl_4$ in ACN at 65 °C after stirring 3 days (iii) and the coordination attempt of squaramide **3** with $KAuCl_4$ in DCM/EtOH with $(Bu_4N)PF_4$ after stirring 2 days.*

Since DMF is not an ideal solvent in these types of reactions, attempt 3 used ACN instead and raised the temperature to 65 °C to help the squaramide to dissolve. The dissolution was partly successful, but after three days there was still no indication of coordination to gold (Figure 13, spectrum iii).

The final attempt involved tetrabutylammonium (Bu_4N) salt of tetrachloroaurate ($AuCl_4$). This compound was synthesized in-situ by the addition of $(Bu_4N)PF_4$ to $KAuCl_4$ in the presence of squaramide **3**. This resulted in the formation of $(Bu_4N)AuCl_4$, which has previously been reported to be a more efficient source of gold(III) in coordination reactions, at least compared to $HAuCl_4$[39]. In this case, the mixture was stirred for two days with no indication of gold coordination (Figure 13, spectrum vi).



*Scheme 20: Attempted coordination of squaramide **1** to gold(III).*

After the failure to coordinate gold to squaramide **3** with 4 different methods, coordination of squaramides **1** was only tried once, with $KAuCl_4$ in a DCM/ACN solvent mixture (Scheme 20). The solubility of squaramide **3** in this mixture was poor, although good enough for a portion of the product to dissolve. The reaction stirred for one week, with no change in ^1H NMR from squaramide **1** (Figure 14).

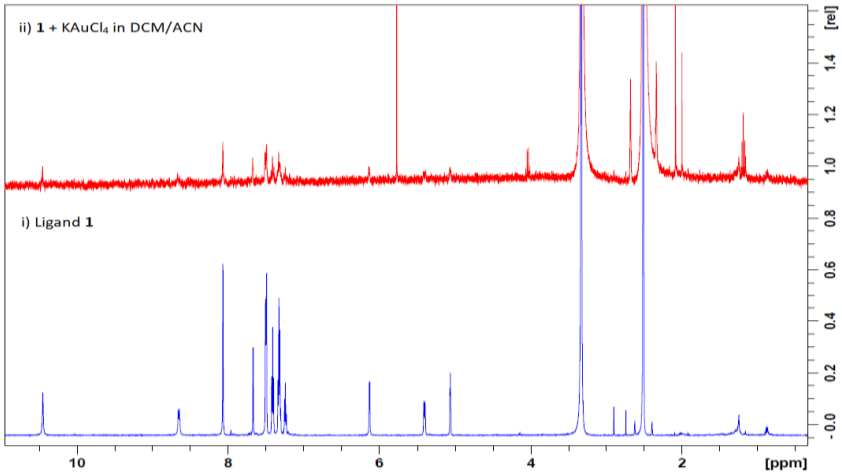
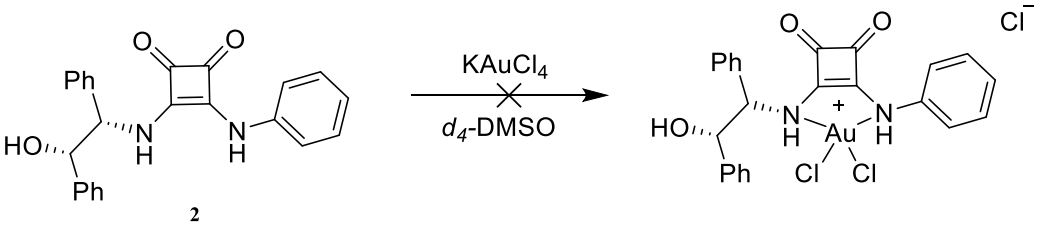


*Figure 14: ^1H NMR spectra of squaramide **1** (i) and the coordination attempt of squaramide **1** with $KAuCl_4$ in DCM/ACN after 1 week (ii).*



*Scheme 21: Attempted coordination of squaramide **2** to gold(III).*

Coordination of squaramide **2** to gold(III) was also only tried once with $KAuCl_4$ in d_4-DMSO due to solubility issues in other solvents. After stirring for two days, no change to the ^1H NMR spectrum of squaramide **2** had occurred (Figure 15).

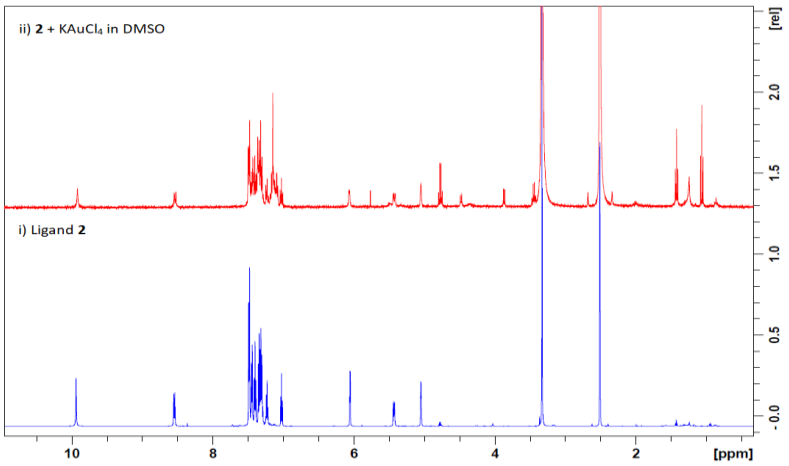
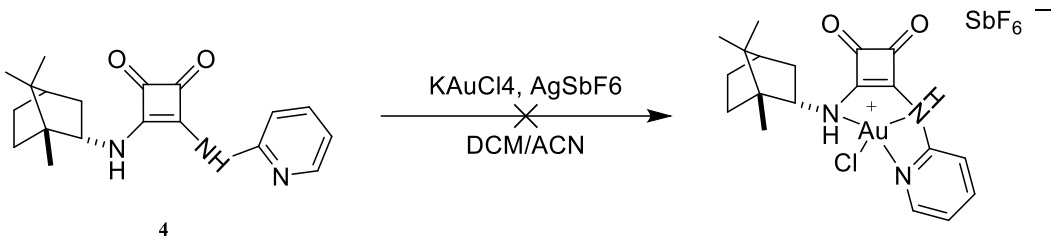


*Figure 15: ^{1}H NMR spectra of squaramide **2** (i) and the coordination attempt of squaramide **1** with $KAuCl_4$ in d_4-DMSO after 2 days (ii).*

Caused mainly by solubility problems of squaramide **1-3** in the preferred solvents DCM or ACN, none of these squaramides were successfully coordinated to gold(III). Even though other solvents, even with low solubility, and different gold(III)-sources were attempted coordination of the squaramides was not achieved, due to some extent by decomposition of gold.



*Scheme 22: Attempted coordination of squaramide **4** to gold(III) with $KAuCl_4$ as gold source and $AgSbF_6$ as silver salt in a DCM/ACN mixture.*

The attempted coordination of gold(III) to squaramide **4** (Scheme 22) was first thought to be successful, because of the small shift of several of the signals in ^{1}H NMR, and because the product after coordination successfully catalysed a cyclopropanation reaction which requires gold to react. Squaramide **4** was not soluble in ACN and therefore DCM was used as solvent for the ligand and ACN for the gold source and silver salt. After stirring overnight there was some black precipitate, but that was most likely silver chloride or excess silver. ^{1}H NMR showed a slight change in the shifts of some of the signals, especially of the aminopyridine protons from 7 ppm to 8.5 ppm, which were shifted a bit to the left. Figure 16 shows the ^{1}H NMR spectra of the ligand (i) compared to the first coordination attempt (ii) with the accompanying crystals (iii).

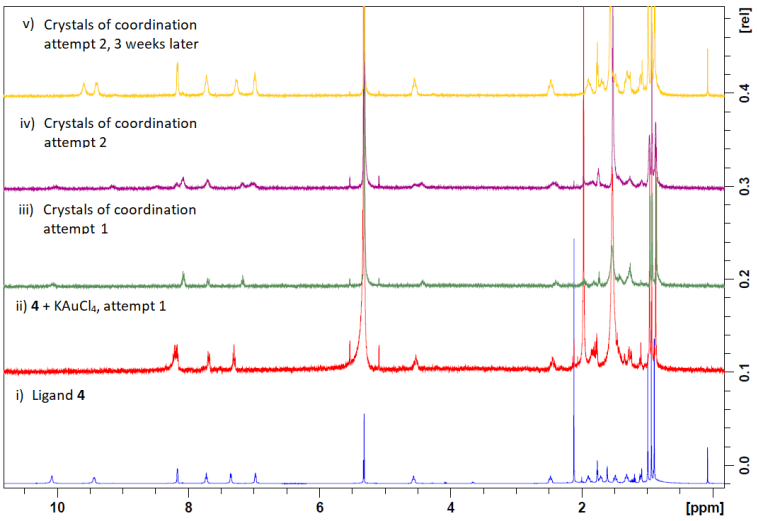


*Figure 16: ^{1}H NMR spectra of the ligand squaramide **4** (i), after the first coordination attempt of squaramide **4** with $KAuCl_4$ (ii), crystals from the first coordination attempt (iii), crystals of the second coordination attempt (iv), and crystals of the second coordination attempt after three weeks in the freezer (v).*

As seen in Figure 16, the change in the ^{1}H NMR shifts of the signals is minor and requires careful examination to detect. One can also see a slight change from the sample of the coordination reaction (ii) and the crystalline product (iii). A second coordination attempt was done in a larger scale, and crystallization of the product gave ^{1}H NMR spectrum iv) in Figure 16. It appears that there are remains of uncoordinated ligand in the second coordination product. After 3 weeks in crystalline form stored in the freezer, the second coordination product appears to have reverted to the uncoordinated state (i). Indeed, the only difference between spectra i) and v) are the NH-protons above 9 ppm.

X-Ray crystallography of the crystals shown in spectrum v) confirmed that they were indeed just the squaramide **4**, as seen in Figure 17.

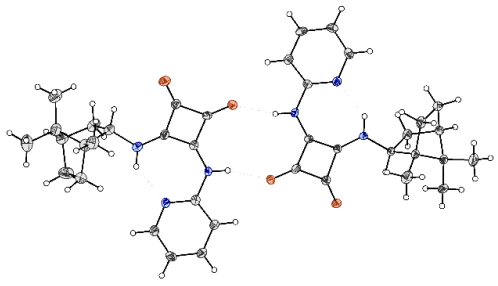


*Figure 17: Structure of the crystals of the second coordination attempt of squaramide **4** three weeks after they were made, found by X-ray crystallography.*

The results from the x-ray crystallography might indicate that no coordination of squaramide **4** took place at all, but there is also a chance that the coordination product reverted back to the ligand. ^{1}H NMR spectrum iv) was not taken straight after crystallization, meaning it might not show a halfway done crystallization, but that the reversion back to squaramide **4** had already

started and it is only finished by the time the second ^{1}H NMR was taken (v). This theory might be supported by the fact that the second crystals (iv) was used as a catalyst in cyclopropanation reaction between propargyl ester **17a** and styrene (**18a**). The cyclopropanation reactions are discussed in chapter 3.4.

Research of the possible coordination of squaramide **4** was continued by colleague Ann Christin Reiersølmoen in the Fiksdahl group. Similar ^{1}H NMR spectrum as ii) shown in Figure 16 were attained, and crystals from this product were sent for X-ray crystallography. From these results shown in Figure 18, it is evident that crystallization has not taken place, but the nitrogen on the aminopyridine has been protonated and $AuCl_4^-$ acts as counterion.

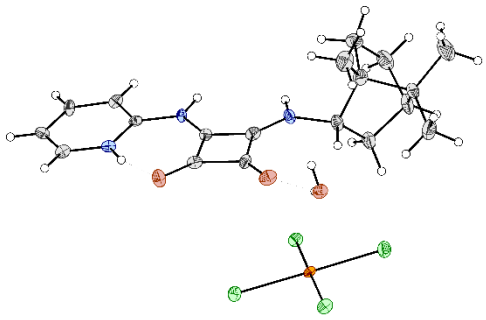
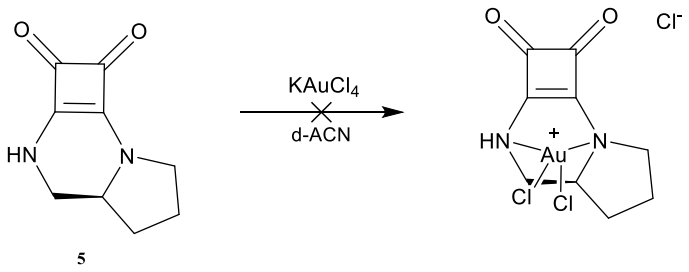


*Figure 18: Structure of the crystals of the attempted coordination of squaramide **4**, courtesy of Ann Christin Reiersølmoen, found by X-ray crystallography.*

It can be assumed that the same result has happened here, based on the similarity of the ^{1}H NMR spectra. As seen in Figure 16, it is also only the aminopyridine protons which are affected by the presence of gold. The fact that the products seem to revert to the ligand makes sense since all it takes is deprotonation of the ligand. The successful cyclopropanation reactions are also explained by the presence of $AuCl_4^-$ as counterion in the product, which acts as a source for the active $Au(III)Cl_3$ catalyst.

It can therefore be concluded that gold(III)-coordination of squaramide **4** was not successful, but the reaction resulted in a protonation of the aminopyridine nitrogen with $AuCl_4^-$ as counterion.



5

*Scheme 23: Attempted coordination of squaramide **5** to gold(III) with $KAuCl_4$ as gold source in d_3-ACN.*

Squaramide **5** proved to be difficult to synthesize, resulting in only 0.8 mg. This meant that the entirety of the squaramide had to be used in the coordination attempt to gold (Scheme 23). This was unfortunate since coordination reaction was done in d_3-ACN to avoid the necessity of removing the solvent under reduced pressure. This meant that the ligand, squaramide **5** in deuterated chloroform (d-$CDCl_3$), and the possible coordination product had ^{1}H NMR spectra in different solvents, and therefore they were difficult to compare. The two ^{1}H NMR spectra are shown in Figure 19.

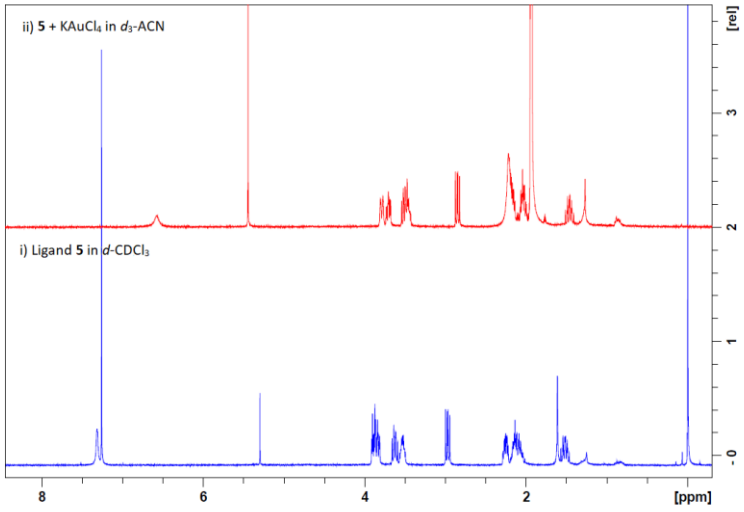
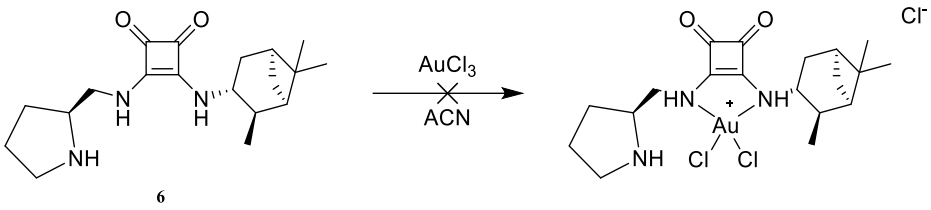


*Figure 19: ^{1}H NMR spectra of the ligand squaramide **5** (i) in d-$CDCl_3$ and the product after an attempted coordination of the ligand with $KAuCl_4$ in d_3-ACN (ii).*

As seen in Figure 19 there is a subtle change in the signals from 1.5 ppm to 4 ppm, where most of them have shifted to the left with around 0.12 ppm. This is a smaller change than usually shown at Au(III) coordination of a ligand and could easily be the result of the different solvents used. Therefore, it is assumed that gold(III)-coordination of squaramide **5** was unsuccessful.



*Scheme 24: Attempted gold coordination of squaramide **6** to gold (III) with $AuCl_3$ as gold source in ACN.*

The synthesis of squaramide **6** also produced small amounts of product, only 5.3 mg. Therefore, the attempted coordination of gold(III) to squaramide **6** also used all the available product (Scheme 24). After one day of stirring in ACN, the mixture had become cloudy and the product was no longer soluble in chloroform, indicating that some change had occurred. The ^{1}H NMR of the ligand and the attempted coordination product are shown in Figure 20.

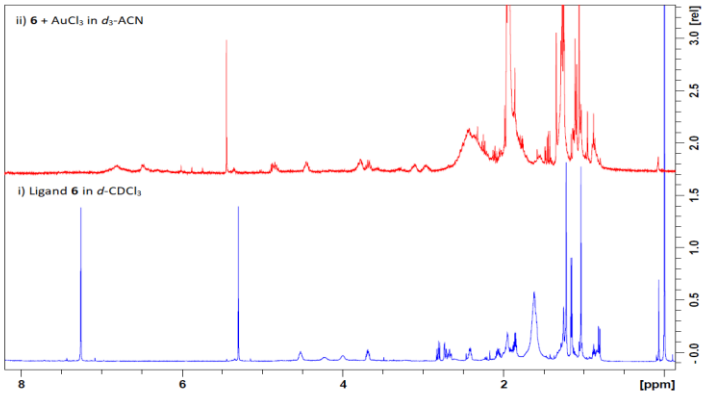
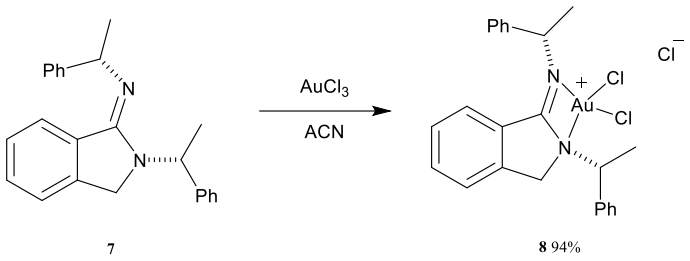


*Figure 20: ^{1}H NMR spectra of the ligand squaramide **6** in d-$CDCl_3$ (i) and the product after an attempted coordination of squaramide **6** with $AuCl_3$ in d_3-ACN (ii).*

The ligand is dissolved in *d*-$CDCl_3$ while the attempted coordination product is dissolved in d_3-ACN. This poses the same problem as with squaramide **5**, that the spectra are difficult to compare. The four protons associated with nitrogen, with signals from 3.5 ppm to 4.5 ppm in the ligand, have shifted in the attempted coordination product with 0.32 ppm as the largest change. The two leftmost protons, at 4.22 ppm and 4.55 ppm in the ligand, have shifted left to 4.44 ppm and 4.84 ppm respectively. The other two protons, at 3.69 ppm and 4.00 ppm in the ligand, have shifted right to 3.67 ppm and 3.78 ppm respectively. The other protons in the structure are harder to compare because the signal for acetonitrile is in the way, and the spectra for the attempted coordination product is generally less clear. The three methyl groups are especially hard to identify caused by several other signals in that region and a poor baseline. These observations, especially the insolubility of the attempted coordination product in chloroform, may indicate that the coordination was successful, but it may also just be a result of the different solvents. One would also expect a larger shift to the left than indicated in Figure 20 during a successful gold-coordination.

3.3.2 Iminoisoindoline ligand



*Scheme 25: Coordination of gold(III) to iminoisoindoline **7**, resulting in the gold(III)-complex **8**.*

The success of coordination of iminoisoindoline **7** is uncertain, although at the first drop of $KAuCl_4$ the solution turned stark purple and the ^1H NMR of the product showed a distinct difference from the ligand, as shown in Figure 21.

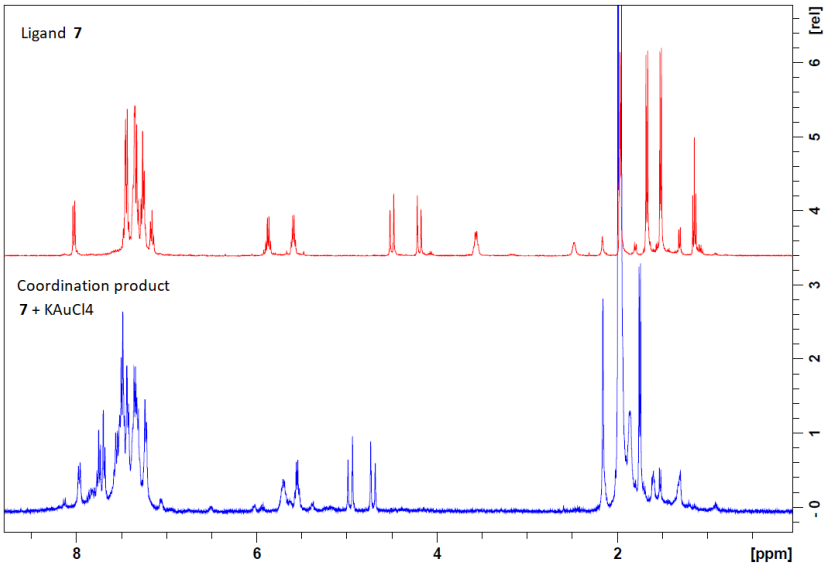


*Figure 21: ^1H NMR spectra of the ligand iminoisoindoline **7** compared to the product after coordination of iminoisoindoline **7** with $KAuCl_4$ in d_3-ACN.*

The largest difference between the ^1H NMR spectra of the coordination product and iminoisoindoline **7** is the shift of the CH_2-protons. They were originally at 4.18-4.53 ppm, but shifted left to 4.68-4.99 ppm after coordination, a change of about 0.5 ppm. The CH_3-protons have also shifted left, one from 1.52 ppm to 1.74 ppm. The other has presumably shifted behind the acetonitrile signal. The difference between the aromatic protons are less clear, but there is an apparent change with the entire aromatic portion having shifted to the left, except for the proton originally at 8.02 ppm which is at 7.97 ppm after coordination. The CH-protons have also shifted with 0.17 ppm and 0.04 ppm to the right.

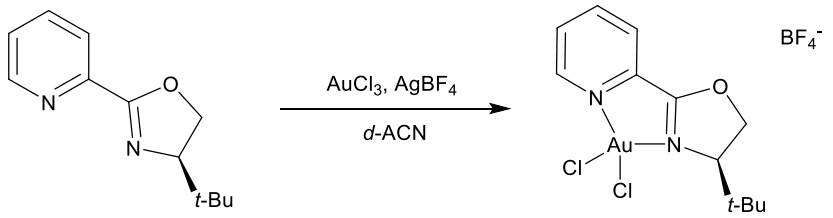
Crystallization of the product was attempted by vapor diffusion of *n*-pentane in DCM, but this was unsuccessful, even after several attempts. Slow diffusion of *n*-pentane in ACN was then tried, which resulted in tiny crystals. *n*-Pentane and ACN are immiscible, and therefore the crystals only appeared in the interface between the two solvents. X-ray crystallography was attempted on the crystals, but they were unfortunately too small and disordered to find the structure. Other crystallization attempts provided the same result.

Because of the difficulty with crystallizing the product, to check for catalytic activity an in-situ cyclopropanation reaction was performed. First, iminoisoindoline **7** was synthesized in ethanol, and a sample was extracted, dried and dissolved in 0.5 mL d_3-ACN and ^{1}H NMR showed full conversion after 17 minutes. 1 equivalent of $AuCl_3$ in 0.1 mL d_3-ACN was then added directly to the NMR-tube, and ^{1}H NMR showed full conversion to the assumed coordination product **8** after 10 minutes, in a 94% yield. An ^{1}H NMR experiment of cyclopropanation of propargyl ester **17a** and styrene (**18a**) was then prepared. 5 mol% of product **8** was then added and the reaction was followed by ^{1}H NMR. The experiment was successful, indicating that the product was indeed gold-complex **8**. An ^{1}H NMR experiment of the same cyclopropanation reaction with $AuCl_3$ as catalyst, giving different results, was also performed to verify that it was not uncoordinated gold in the iminoisoindoline solution that was catalyzing the reaction. Complete discussion of these cyclopropanation reactions can be found in chapter 3.4.

Mass spectroscopy (MS) of product **8** only indicated the presence of iminoisoindoline **7**. At first it was thought that the product had been left in solvent too long before the sample was run, and another batch of product **8** was made. Still only iminoisoindoline **7** was found. The large change in ^{1}H NMR shifts between iminoisoindoline **7** and the coordination product **8**, and the effective cyclopropanation reaction with product **8** as catalyst, indicate that the gold-coordination was successful. The unsatisfactory results from MS might be due to instability of the product in solvent, and it might also not handle the stress of the spectroscopy method, even though the most delicate method, electron spray, was used.

3.3.3 Oxazoline-based ligands

Oxazolinebased ligands were developed during my pre-master project[4] and have also been reported to be catalytically active.[1] The oxazoline-based ligands used in this section were commercially available.



9 **10** 63%

*Scheme 26: Coordination of gold(III) to oxazoline ligand **9** with $AuCl_3$ and the silver salt $AgBF_4$, providing gold(III)-complex **10**.*

Formation of gold-complex **10** by coordination of gold(III) to oxazoline ligand **9** was successful (Scheme 26). Coordination occurred immediately after addition of $AuCl_3$, and AgCl precipitated instantly at addition of $AgBF_4$. ^{1}H NMR shows that the proton signals of crystallized gold(III)-complex **10** have shifted significantly to the left of the corresponding ligand protons (Figure 22).

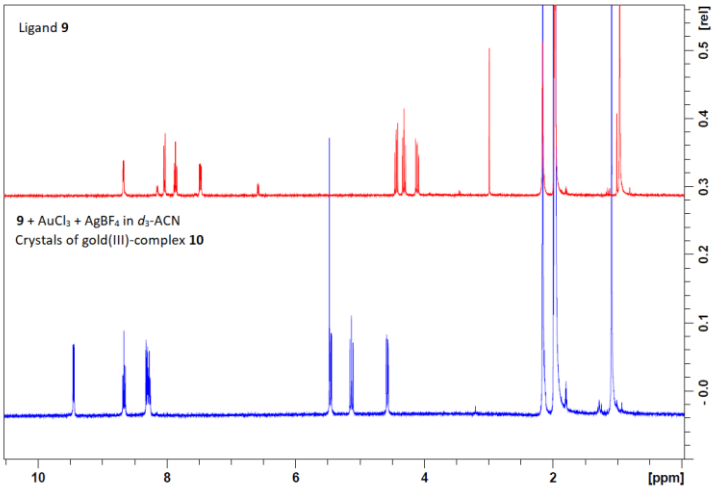


*Figure 22: ^{1}H NMR spectrum of crystals of gold(III)-complex **10** compared to the ^{1}H NMR spectrum of ligand **9**.*

The successful crystallization of the product was simple, with crystals appearing within an hour by vapor diffusion of *n*-pentane in DCM, with a 63% yield of gold(III)-complex **10**. The crystal structure of gold-catalyst **10**, found by X-ray crystallography, is shown in Figure 23. MS also confirmed the structure by finding a mass of 401.0934 corresponding to gold(III)-complex **10** missing the two chloride-atoms.

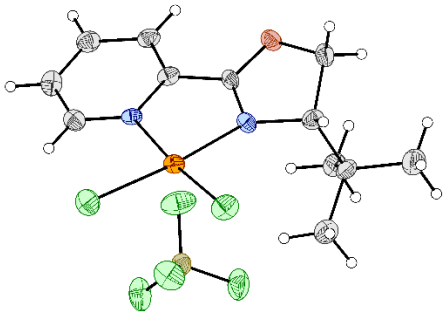
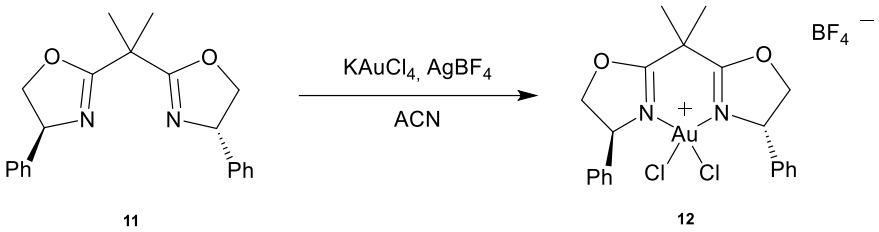


*Figure 23: Crystal structure of gold-complex **10** obtained by X-ray crystallography.*



Gold(III)-complex **12** was first synthesized during the pre-master project[4] and was repeated here to perform further studies on the cyclopropanation reaction. Gold(III)-coordination of oxazoline ligand **11** occurred overnight, and the product was crystallized by slow diffusion of *n*-pentane in DCM, affording 22% of gold(III)-complex **12**. The difference in the ^{1}H NMR spectra of oxazoline ligand **11** and the crystallized gold(III)-complex **12** is shown in Figure 24. Coordination was successful, evident by the shift of the oxazoline protons significantly to the left.

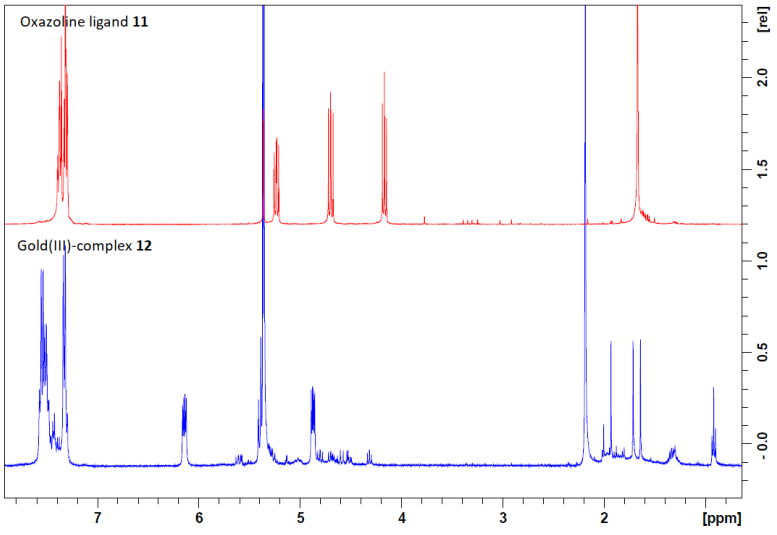
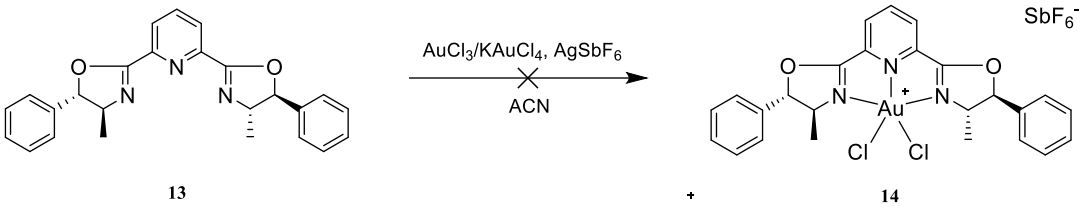


*Figure 24: ^{1}H NMR spectrum of crystals of gold(III)-complex **12** compared to the ^{1}H NMR spectrum of ligand **11**.*

Gold(III)-complex **12** but with SbF_6^- as counterion was reported in the article by the Fiksdahl group, where it was tested in cyclopropanation reactions (Appendix A)[1].



*Scheme 27: Unsuccessful coordination of oxazoline ligand **13** to form the gold-complex **14**.*

The gold(III)-coordination of oxazoline ligand **13** proved to be more difficult than first imagined. To easily check if there was any possibility of gold to coordinate to the ligand, the reaction was done as an NMR-experiment with $AuCl_3$. This resulted in a mixture of products containing the starting material and one or more other products. The reaction was then done in a larger laboratory scale where the mixture was stirred for three hours and then crystallized. Figure 25 shows the ^{1}H NMR spectra of the product in the reaction mixture after three hours (i), the product after crystallization (ii) and the ligand, oxazoline **13** (iii), all in d_3-ACN.

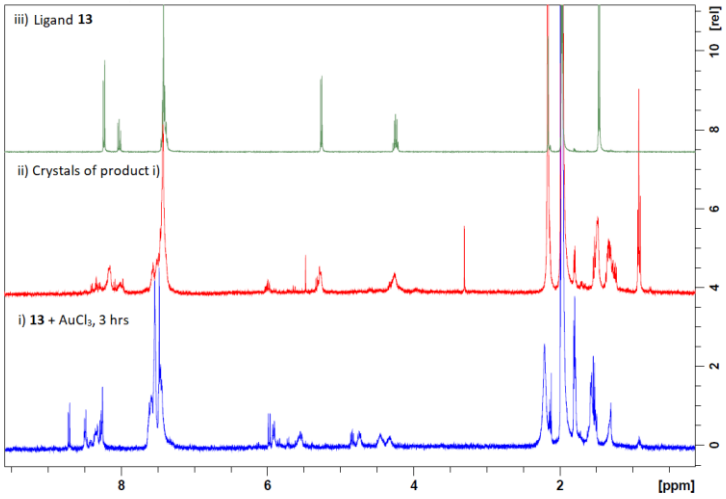


*Figure 25: ^{1}H NMR spectra of the attempted formation of gold-complex **14** after three hours (i), crystals formed from the same attempt (ii) and oxazoline ligand **13** (iii).*

Spectrum i) in Figure 25 indicates that some reaction has occurred because none of the signals from the ligand is present. There rather seems to be a mixture of products. Crystallization was done to purify the product and perhaps isolate the correct coordination product. This was not successful since spectrum ii) indicates that the product has reverted to ligand **13**, with some other products. MS of the crystals provided both ligand **13** with an additional H^+, and the coordinated product **14** without chloride. A cyclopropanation reaction of propargyl ester **17a** and styrene (**18a**), with product **14** as catalyst, stirred overnight and resulted in a *cis:trans* ratio of 84:16 of cyclopropanation product **19a**. These results show that there is a catalytically

active component in the product and prompted the following attempts at separating gold-complex **14** from the rest of the products in the solution. The cyclopropanation reactions are discussed further in chapter 3.4.

The coordination reaction was attempted again and instead of filtrating through celite to remove precipitated AgCl, which might affect the product, the filtration was done with a double filter paper. This did not help, and the crystals formed had the same ^{1}H NMR spectrum as spectrum ii) in Figure 25.

A third attempt used $KAuCl_4$ instead of $AuCl_3$, which by ^{1}H NMR seemed to give the wanted product **14** after stirring for 40 minutes (Figure 26, i), because all signals have shifted to the left to some degree, indicating successful coordination to gold. The product was then added LiCl to remove any excess silver and filtrated with double filter paper. A second ^{1}H NMR was taken of the product to follow the reaction all the way to pinpoint the exact point where the product degraded. This was proven to be a good idea, because, as seen by spectrum ii) in Figure 26, the product had degraded into several products, although not back to the ligand. After extraction with water, on the other hand, the product had partly reverted to the ligand (Figure 26, iii). These results prove that the mixture does not tolerate any workup, even filtration.

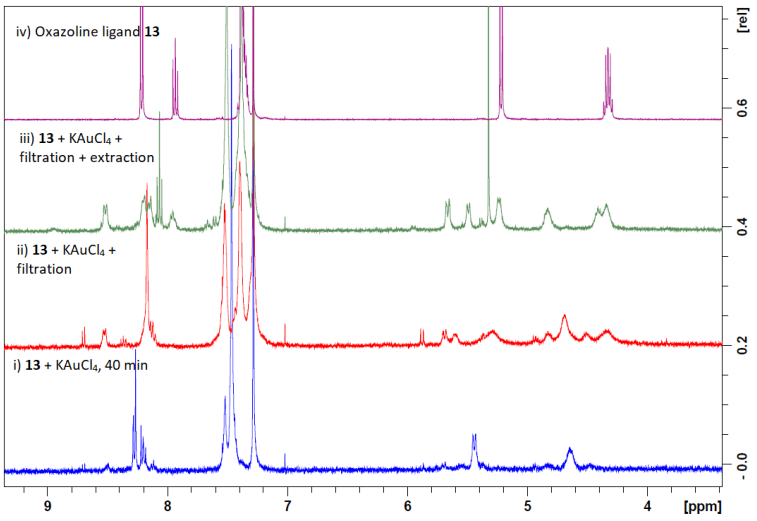


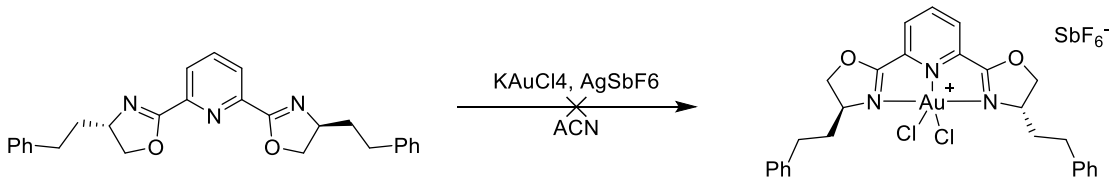
*Figure 26: ^{1}H NMR spectra of the product after attempted formation of gold-complex **14** after 40 minutes (i), after filtration of the same product (ii), after extraction of the product (iii) and the oxazoline ligand **13** (iv).*

Next, coordination of oxazoline **13** was tried again with $KAuCl_4$ which stirred overnight. and the results were the same as after the extraction of the previous experiment (Figure 26, iii). Even if the result was not as desired, purification of the mixture was attempted by precipitation of biproducts in DCM. To avoid filtration, AgCl was removed from the mixture

by pipetting the solvent and product off. The solvent was then removed under reduced pressure and the product was dissolved in DCM to see if any precipitation occurred. It did, and the mixture was filtrated, but ^{1}H NMR was still like spectrum iii) (Figure 16).

Intending to follow the same careful procedure for work-up on a reaction mixture containing the right product from the start (Figure 26, i), a sample was taken after 40 minutes stirring, but the result showed a mixture of products. This was a disappointment since stirring for 40 minutes had previously been successful in getting the wanted product. The reaction was tried again, this time a sample was taken after 20 minutes, yielding a product like spectrum i) (Figure 26). The solvent and the product were then pipetted off carefully to remove precipitated AgCl from the product before the solvent was removed under reduced pressure and the product dissolved in DCM. Precipitation occurred and ^{1}H NMR was taken of both the DCM phase and the precipitate. Instead of providing a purified product, the DCM phase showed an NMR equal to spectrum iii) (Figure 26). The ^{1}H NMR of the precipitate showed nothing but solvents.

One final experiment was conducted, with the attempted coordination taking place in deuterated DCM to avoid the work-up and then possibly crystallize straight from the reaction mixture. Coordination had not been attempted in DCM previously, and it was unsuccessful since an ^{1}H NMR after 15 minutes showed a more complex mixture than ever. Because of this low stability of the gold-complex during handling the hope of coordinating oxazoline **14** to gold(III) was abandoned.



15

*Scheme 28: Unsuccessful gold(III)-coordination of oxazoline ligand **15**.*

The attempt at coordinating gold(III) to oxazoline ligand **15** (Scheme 28) resulted in a complex mixture after stirring overnight. The mixture was then filtrated and extracted with water. The ^{1}H NMR spectrum of the product after stirring overnight (i) and after extraction (ii), compared to the oxazoline ligand **15** (iii), are shown in Figure 27.

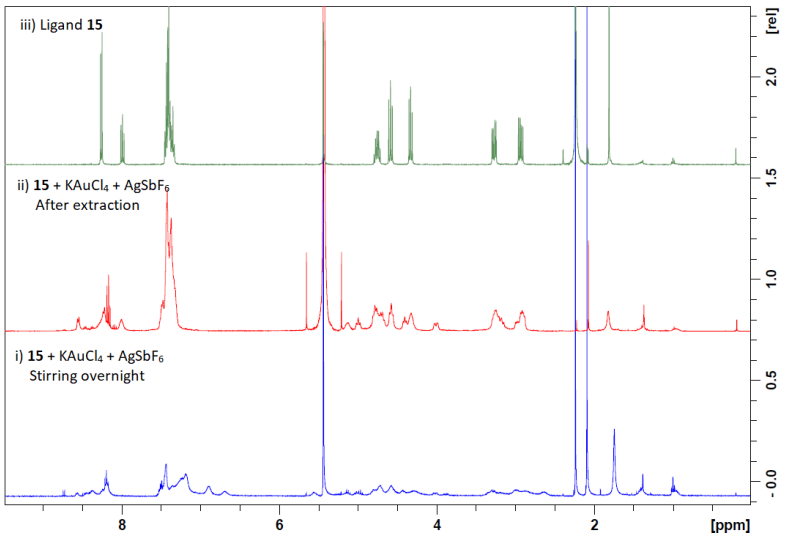


*Figure 27: ^{1}H NMR spectra of the product after attempted gold(III)-coordination of oxazoline ligand **15** after stirring overnight (i), after extraction of the same product (ii) and the oxazoline ligand **15** (iii).*

The ^{1}H NMR spectrum after the extraction is cleaner than the product in the reaction mixture. Other than this, it appears to be the uncoordinated ligand and some impurities in the product. Therefore, the coordination of oxazoline ligand **15** was deemed unsuccessful.

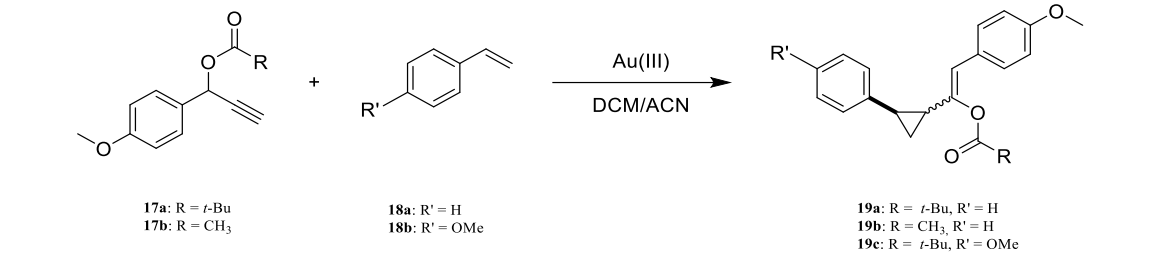
Although gold(III)-coordination of oxazoline-based ligands have previously been successful, these results show that this is not the case for all of them. It appears that pyridinyl-monooxazoline ligands (**9**) are better at coordinating to gold(III) than pyridinyl-bisoxazoline ligands (**13**/**15**).

There are three categories of promising Au-complexes. A: A complex which crystallizes where structure is confirmed by X-ray, ^{1}H NMR show coordination, MS show Au-ligand-ion and which is catalytically active; B: a complex where ^{1}H NMR show coordination, MS show Au-ligand-ion and which is catalytically active; C: a complex where ^{1}H NMR show coordination and which is catalytically active. Gold(III)-complex **10** is a category A catalyst, gold(III)-complexes **12** and **14** are category B catalysts and gold(III)complex **8** is a category C catalyst.

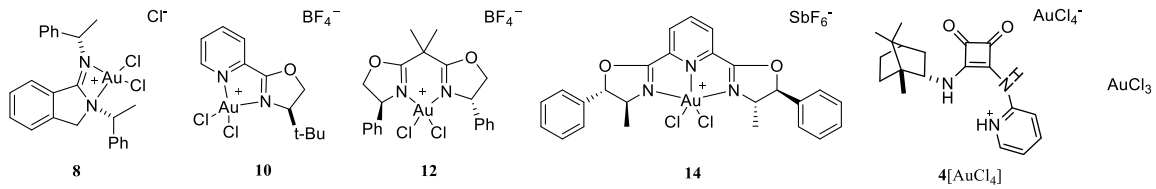
3.4 Cyclopropanation reactions

Cyclopropanation reaction have been used in the Fiksdahl group to test gold(III)-complexes for catalytic activity.[1] In the present project, gold(III) catalysed cyclopropanation of propargyl esters **17a-b**, synthesised in the pre-master project[4], and vinyl substrates **18a-b** were studied (Table 2).

Table 2: Studies on stereoselective cyclopropanation. [a]



Au(III):



Entry	Substrates	Gold(III)-complex	Prod	Solvent	*Cis:trans* ratio[c] (Time, full conversion)/Yield[d]	*Cis:trans* ratio[c] (Time)/Yield[d]
1	**17a + 18a**	**8**	**19a**	d_3-ACN	79:21 (15 min)	23:77 (24 hrs)/85%
2	**17a + 18a**	$AuCl_3$	**19a**	d_3-ACN	40:60 (<6 min)	9:91 (3 hrs)
3	**17a + 18a**	**10**	**19a**	d_3-ACN	11:89 (<6 min)	6:94 (30 min)/65%
4[b]	**17a + 18a**	**10**	**19a**	ACN	84:16 (<25 min)/63%	-
5[b]	**17a + 18a**	**10**	**19a**	ACN	6:94 (<10 min)	-
6[b]	**17a + 18a**	**12**	**19a**	DCM	53:47 (<15 min)	6:94 (24 hrs)/81%
7	**17a + 18a**	**14**	**19a**	d_2-DCM	88:12 (3 hrs)	88:12 (23 hrs)
8	**17b + 18a**	**10**	**19b**	d_3-ACN	38:62 (13 min)	27:73 (23 hrs)
9	**17b + 18a**	**12**	**19b**	d_2-DCM	-	10:90 (24 hrs)/63%
10	**17a + 18a**	**4[$AuCl_4$]**	**19a**	d_2-DCM	88:12 (6 hrs)	88:12 (23 hrs)
11	**17a + 18b**	**4[$AuCl_4$]**	**19c**	d_2-DCM	57:43 (12 min)	57:43 (18 hrs)/89%

[a] The general reactions were performed in NMR tubes; **17a,b** (5 mg, 1 equiv) and **18a,b** (4 equiv.) in deuterated solvent, added Au(III)-catalyst (5 mol%) and the reactions were monitored by ^{1}H NMR; [b] Laboratory scale reactions; **17a,b** (10 mg, 1 equiv) and **18a,b** (4 equiv.) in ACN, added Au(III)-catalyst (5 mol%); [c] *Cis:trans* ratios were determined by ^{1}H NMR spectroscopy of the crude reaction mixture; [d] Isolated yield after purification by column chromatography.

The cyclopropanation with iminoisoindoline gold(III)-complex **8** as catalyst (entry 1) had to be done in ACN, instead of in DCM as is most commonly used. This was because the reaction was done with catalyst **8** generated in situ because of the low stability of iminoisoindoline **7**. Iminoisoindoline **7** was first synthesized in d_3-ACN and then the exact amount of $AuCl_3$ was added directly to the NMR-tube. ^{1}H NMR showed full conversion of iminoisoindoline **7** to gold(III)-complex **8** after 10 minutes, as discussed in chapter 3.3.2. Part of this solution (5 mol%) was then added to a second NMR-tube containing propargyl ester **17a** and vinyl substrate **18a**, and the cyclopropanation was followed by ^{1}H NMR. The reaction reached full conversion after 15 minutes, with a 79:21 *cis:trans* ratio, and 24 hours later the product had undergone in-situ *cis*-to-*trans* isomerization into a 23:77 *cis:trans* ratio. Purification of the product by column chromatography provided 85% yield of **19a**. Compared with gold(III)-catalysts **10** and **12** (entries 3 and 6), which gave full conversion in less than 6 and 15 minutes, respectively, gold(III)-complex **8** seems to be a less activated catalyst with a lower capacity for in-situ *cis*-to-*trans* isomerization.

Since the synthesis of gold(III)-complex **8** was not entirely certain, caused by the lack of X-ray crystallography and MS only finding iminoisoindoline **7**, the cyclopropanation reaction was also performed with $AuCl_3$ as catalyst in ACN (entry 2). This was done to make sure that it was not uncoordinated gold(III) in the solution which catalysed the reaction in entry 1. The reaction resulted in a 40:60 *cis:trans* ratio at full conversion after less than 6 minutes, and a 9:91 *cis:trans* ratio after 3 hours. This result is quite different from previously reported[1], which found that this cyclopropanation reaction with $AuCl_3$ as catalyst in DCM reached full conversion after 30 minutes with a 55:45 *cis:trans* ratio, and that no isomerization was observed after 24 hours. It was concluded that $AuCl_3$ gave low reproducibility and was unstable in DCM, evident by the immediate formation of black precipitate of decomposed gold.[1] It appears that $AuCl_3$ has a much higher stability in ACN, as seen from the lower conversion time, the occurrence of isomerization and the lack of black precipitate. The cyclopropanation reaction catalysed by $AuCl_3$ was repeated once to confirm the results since they deviated from previous results.

These results show that $AuCl_3$ catalyses the cyclopropanation reaction faster than gold(III)-complex **8** in ACN, and in-situ isomerization of product **19a** also occurs at a higher rate. From this it can be concluded, with as much certainty as possible in these circumstances, that gold(III)-complex **8** was indeed prepared.

The ^{1}H NMR experiment of cyclopropanation reaction of propargyl ester **17a** and vinyl substrate **18a** catalysed by pyridinyl-oxazoline gold(III)-complex **10** resulted in full conversion in less than 6 minutes with a 11:89 *cis:trans* ratio (entry 3). Purification of the product by column chromatography provided 65% yield of **19a**. This high preference to *trans*-isomer from the start is unusual in this cyclopropanation reaction, as the largest amount of *trans*-isomer at full conversion is previously reported to be 50%.[1] This surprising result might be due to the solvent, which in this case was ACN instead of DCM, because gold(III)-complex **10** has a poor solubility in DCM. This means that if the *trans*-isomer is desired, gold(III)-complex **10** in ACN is hitherto the best catalyst because of its high amount of *trans*-**19a** in a very short amount of time.

The same reaction was repeated in a larger laboratory scale and in a lower concentration (entry 4). This resulted in 84:16 *cis:trans* ratio after 25 minutes, which was a welcome surprise since this allowed the purification of the product to *cis*-**19a** for HPLC studies in 63% yield. The reaction was again repeated in laboratory scale, but with the same concentration of propargyl ester **17** as in the NMR-experiment to see if the *cis:trans* ratios would now correspond. This resulted in a 6:94 *cis:trans* ratio after 10 minutes (entry 5), which is the same result as after 30 minutes during the NMR-experiment in entry 3. The higher amount of *trans*-product after lesser time is caused by the stirring occurring in the laboratory experiment compared to the ^{1}H NMR experiment. These results prove that the stereochemical outcome of cyclopropanation reactions can be controlled by concentration, in addition to the gold(III)-catalyst used and time stirred.

Gold(III)-catalyst **12** was first synthesised during the pre-master project, and there it was used in a study of the activity of the catalyst in different analogous cyclopropanation reactions.[4] The cyclopropanation reaction of propargyl ester **17a** and vinyl **18a** was repeated here, which resulted in full conversion after less than 15 minutes with a 53:47 *cis:trans* ratio, and a 6:94 *cis:trans* ratio after 24 hours (entry 6). Purification of the product by column chromatography provided 81% yield of **19a**. This result is the same as reported in the accepted article by the Fiksdahl group given in Appendix A, which used gold(III)-catalyst **12** but with SbF_6^- as counterion instead of BF_4^-. Gold(III)-complexes with different counterions have been found to give corresponding results, although their ^{1}H NMR spectra are slightly different.[1]

The gold(III)-complex **14** was unstable and it was not possible to isolate the pure complex from the reaction mixture. MS, however, proved that complex **14** was present. Therefore, the gold(III)-complex **14** solution was used when the catalytic ability of the complex was tested.

The cyclopropanation reaction (**17a** + **18a**) resulted in full conversion to product **19a** after 3 hours, with a *cis:trans* ratio of 88:12, with no isomerization occurring afterwards (entry 7). This result indicates that gold(III)-complex **14** is a less active catalyst than the rest of the catalysts in this section. That is to be expected since the catalyst is a mixture of at least the uncoordinated ligand and the gold(III)-complex **14**, meaning the loading of gold(III) was lower than 5 mol%.

Gold(III)-catalyst **10** was also tested in the cyclopropanation reaction of propargyl acetate **17b** and vinyl substrate **18a** (Entry 8). This reaction was also conducted in ACN, which resulted in full conversion in 13 minutes. The increased conversion time compared to propargyl pivaloyl ester **17a** (Entry 3) is expected, because propargyl acetate **17b** has previously proven to have a lower reactivity than propargyl ester **17a**.[1] At full conversion the *cis*:*trans* ratio was at 38:62, which is quite different from previous studies of this cyclopropanation reaction which gave a 92:18 *cis*:*trans* ratio with gold(III)-complex **10** with SbF_6^- as counterion.[1] This again proves that gold(III)-complex **10** favours fast formation of *trans*-isomers. However, the subsequent in-situ isomerization was slow compared to gold(III)-complex **10** with SbF_6^- as counterion, reaching only a 27:73 *cis*:*trans* ratio after 23 hours, compared to a 10:90 *cis*:*trans* ratio.

The cyclopropanation reaction of propargyl ester **17b** and vinyl substrate **18a** was also tested with gold(III)-complex **12**, which was done to see how long time was necessary to give as much *trans*-isomer as possible. This was found to be 23 hours, when the reaction had reached a 10:90 *cis*:*trans* ratio (Entry 9), which is equal to the results found with gold(III)-catalyst **12** but with SbF_6^- as counterion instead of BF_4^-. Purification of the product by column chromatography provided 63% yield of product **19b**.

The coordination of gold(III) to squaramide **4** was unsuccessful, but indications show that protonation of squaramide **4** and $AuCl_4^-$ as counterion occurred. Before this was realized, cyclopropanation reactions were run with the suspected gold(III)-coordinated squaramide **4**, as a way of testing if gold was present and therefore if coordination would occur.

Cyclopropanation of propargyl ester **17a** and vinyl **18a** with the **4**[$AuCl_4$]-salt reached full conversion to product **19a** in 6 hours with 88:12 *cis*:*trans* ratio (Entry 10). For gold(III) to be catalytically active, the presence of $[Au]^+$ is required. In this situation, to acquire the active $AuCl_3$ catalyst, HCl must be removed from the protonated squaramide **4** and $AuCl_4^-$. For this reason, it comes as no surprise that this cyclopropanation reaction is much slower than with other catalysts. Within 23 hours no isomerization was detected, which is in accordance with cyclopropanation reactions previously reported catalysed with $AuCl_3$ in DCM.[1]

The **4**[$AuCl_4$]-salt was also used in a cyclopropanation reaction between propargyl ester **17a** and vinyl substrate **18b** (Entry 11). Vinyl substrate **18b** has a methoxy group which is electron rich and activating and decreases the reaction time and full conversion was reached at 12 minutes, with a *cis*:*trans* ratio of 57:43. No isomerization was observed. Purification of the product by column chromatography provided 89% yield of **19c**.

3.5 Studies on enantioselectivity

Chiral HPLC is used to separate and quantify enantiomers in a sample, and the degree to which one enantiomer is in excess compared to the other is given in enantiomeric excess (%ee). A chiral HPLC column, Chiralpak AD, with amylose tris (3,5-dimethylphenylcarbamate) coated on 10µm silica-gel was used to analyse possible enantioselectivity in formation of cyclopropanation products **19a-b**. Successful enantiomeric separation of similar cyclopropanation products was previously reported with 2-propanol in hexane as eluent[34], therefore this solvent combination was used in a gradient scouting run. After the gradient testing, 10% 2-propanol in hexane was used to separate the enantiomers of *trans*-**19a**, but separation was insufficient. Thereby, 5% 2-propanol was attempted and resulted in sufficient baseline separation. This solvent mixture was used as eluent for enantiomeric HPLC separation of cyclopropyl products *trans*-**19a-b** and *cis*-**19a** synthesised with gold(III)-catalysts **8**¸**10** and **12** (Table 3).

*Table 3: Chiral HPLC analysis of cyclopropanation products **19a-b**, obtained by catalysis with gold(III)-complexes **8**, **10** and **12**.*

Entry	**Cyclopropanation product**	**Gold(III)-complex**	**Retention, t_R (min)**	**Ratio of enantiomers**	**Enantiomeric excess**
1	***trans*-**19a	**8**	13.0:14.2	48:52	0-4%
2	***trans*-**19a	**10**	12.5:13.1	53:47	0-6%
3	***trans*-**19b	**12**	12.7:13.8	49:51	0-2%
4	***cis*-**19a	**10**	10.3:12.1	50:50	0%

The results show that the retention times vary for identical samples (e.g. entries 1 and 2). The *cis*-isomer elutes first (approx.10 and 12 min) and the *trans*-isomers follow closely behind (approx. 13 and 14 min). The measured values for the enantiomer ratio are expected to show some uncertainty. Unfortunately, none of the gold(III)-complexes seem to give enantioselective cyclopropanation reactions, even if a low %ee was indicated for the reaction with gold(III)-catalyst **10** (entry 2).

4 Conclusion

The purpose of this master project was to synthesise chiral ligands and coordinate these to gold(III), thereby developing novel chiral gold(III)-complexes. These complexes were then used as gold-catalysts in cyclopropanation reactions in which their catalytic activity and their enantioselectivity could be measured.

Several squaramide ligands were synthesised from square ethyl ester and then coordination of gold(III) to the ligands was attempted. Squaramide **1** was synthesised (11%) and attempted coordinated to gold(III) using $KAuCl_4$ as gold(III)-source. No coordination was observed, mostly because of the low solubility of the ligand. The same result was observed with squaramide **2** which was synthesised (68%) and unsuccessfully coordinated to gold(III). Several attempts were made to coordinate squaramide **3** (50% yield) to gold(III), but none yielded successful results. Squaramide **4** was synthesised twice (58%/59%), but coordination provided only protonation of the aminopyridine nitrogen and $AuCl_4^-$ as counterion, giving a **4**[$AuCl_4^-$]-salt. Squaramide **5** was synthesised in a very low yield (7%) and as a result the ^{1}H NMR spectra of the ligand and the attempted coordination product were dissolved in different solvents. This made for difficult comparison, but it was concluded that the coordination of gold(III) to squaramide **5** was unsuccessful. The same problem was present in the gold(III)-coordination of squaramide **6** which also had a very low yield (7%), and coordination was deemed unsuccessful.

After the failure to coordinate gold(III) to the squaramides, iminoisoindoline **7** was synthesised (94%) from addition of (*R*)-(+)-α-methylbenzylamine to phthaldialdehyde. Gold(III)-complex **8** was made by addition of $AuCl_3$ to ligand **7** (94%). Although crystallization of the gold-complex afforded too small and disordered crystals for X-ray crystallography, the cyclopropanation of propargyl ester **17a** and styrene (**18a**) indicated the successful development of gold(III)-complex **8**, along with clear identification by ^{1}H NMR.

Gold(III)-coordination to several commercially available oxazoline-based ligands were also attempted. Gold(III)-complex **10** was successfully coordinated and crystallized (63%), and the structure was confirmed by X-ray crystallography. Gold(III)-complex **12** had already been developed during the pre-master project and was repeated here (22%). Gold(III)-coordination of oxazoline-based ligand **13** resulted in a mixture of gold(III)-complex **14** and several other products. Complex **14** was attempted isolated from the mixture, without success. Gold(III)-

coordination of oxazoline-base ligand **15** resulted in a complex mixture which seem to not contain the wanted gold(III)-complex.

The catalytic ability of the successful gold(III)-complexes **8**, **10** and **12**, the mixture containing gold(III)-complex **14** and the squaramide **4**[$AuCl_4$]-salt were tested in cyclopropanation reaction of propargyl esters **17a-b** with vinyl substrates **18a-b**, affording the cyclopropanation products **19a-c** in different *cis:trans* ratios. Gold(III)-complex **8** was found to catalyse the reaction of propargyl ester **17a** and styrene (**18a**) to product **19a** (85 %) in a 79:21 *cis:trans* ratio after 15 minutes, and after 23 hours in-situ isomerization afforded a 23:77 *cis:trans* ratio. Gold(III)-complex **8** was found to be the least catalytically active catalyst of the gold(III)-complexes developed, with the exception of gold(III)-catalyst **14** which was not properly isolated from its reaction mixture.

Gold(III)-complex **10** catalysed the same reaction (**17a** + **18a**) to a 11:89 *cis:trans* ratio of product **19a** (65%) in less than 5 minutes. Lower concentration of propargyl ester **17a** resulted in a 84:16 *cis:trans* ratio of product **19a**, proving that the stereochemical outcome of cyclopropanation reactions can be controlled by the concentration of the substrates. Catalyst **10** was also tested in the cyclopropanation reaction of propargyl acetate **17b** and vinyl substrate **18a** giving product **19b**. At full conversion (13 min) the *cis*:*trans* ratio was at 38:62, and compared to previously reported results, this proves that gold(III)-complex **10** favours fast formation of *trans*-isomers.

Cyclopropanation reaction (**17a** + **18a**) catalysed by gold(III)-complex **12** resulted in full conversion to product **19a** (81%) in less than 15 minutes with a 53:47 *cis:trans* ratio, and a 6:94 *cis:trans* ratio after 24 hours. Gold(III)-complex **12** was also used as catalyst in reaction of propargyl acetate **17b** and vinyl substrate **18a** giving a 10:90 *cis*:*trans* ratio of product **19b** (63%) after 23 hours. These results are the same as reported previously with gold(III)-catalyst **12** but with SbF_6^- as counterion instead of BF_4^-.

Since gold(III)-complex **14** was not isolated from its reaction mixture, the cyclopropanation reaction (**17a** + **18a**) did not reach full conversion until after 3 hours, with a *cis:trans* ratio of 88:12 of product **19a**. No in-situ isomerisation occurred.

Although the **4**[$AuCl_4$]-salt was not a gold(III)-coordinated complex, cyclopropanation reactions with propargyl ester **17a** and vinyl substrates **18a-b** were tested with the **4**[$AuCl_4$]-salt as catalyst. The reactions reached full conversion to products **19a** and **19c** in 3 hours and 12 minutes, respectively. No in-situ isomerisation occurred in either reaction.

The enantioselectivity of cyclopropyl products *trans*-**19a-b** and *cis*-**19a** synthesised with gold(III)-catalysts **8**¸**10** and **12** were tested by chiral HPLC, but no enantiomeric excess was found.

5 Further Work

During this master's thesis two novel gold(III)-complexes (**8** and **10**) were developed which successfully catalysed different cyclopropanation reactions. Further work would be the development of new catalytically active gold(III)-complexes, and to test for their enantioselectivity.

Although the gold(III)-coordination of squaramides was unsuccessful, squaramide **4** was the most promising. To avoid the protonation of the aminopyridine nitrogen, the coordination could be tested in presence of a base. This might make the coordination of gold(III) to the squaramide possible.

New ligands could also be developed and attempted to coordinate to gold(III). Cyclams are 14-membered tetraamine macrocycles which have been proved to bind strongly to transition metals and could therefore be of interest (Figure 28a). The increased stability of metal complexes of macrocyclic ligands compared to noncyclic ligands is called the macrocyclic effect. These cyclam-complexes have been proven to be catalytically active, although they are not chiral and therefore not suited for enantioselective studies.[40] Recently, however, studies on the preparation of chiral non-racemic analogues of cyclam have been reported, and these macrocycles could prove to be useful in asymmetric catalysis (Figure 28b).[41]

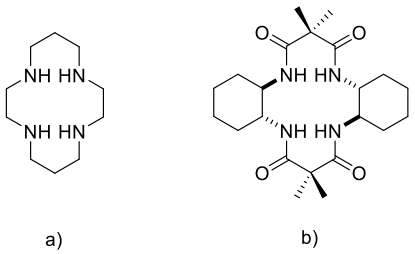
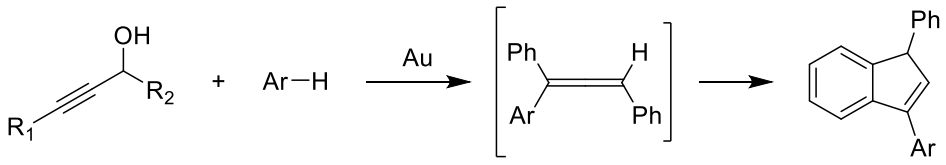


Figure 28: a) Structure of cyclam b) Example of a chiral cyclam derivative.

Except the development of novel gold(III)-complexes, new methods of testing the catalytic ability of both old and new complexes could be developed. Nucleophilic reactions of aromatic compounds with propargylic alcohols have been reported to be catalysed by gold (Scheme 29). This resulted in a dehydrative Friedel-Crafts reaction and Nazarov cyclisation sequence, providing 1,3-diarylindenes.[42]



Scheme 29: Gold-catalysed reaction of aromatic compounds with propargylic alcohols, resulting in

These types of reactions could be an alternative to the cyclopropanation reactions to test for catalytic abilities in both old and new gold(III)-complexes.

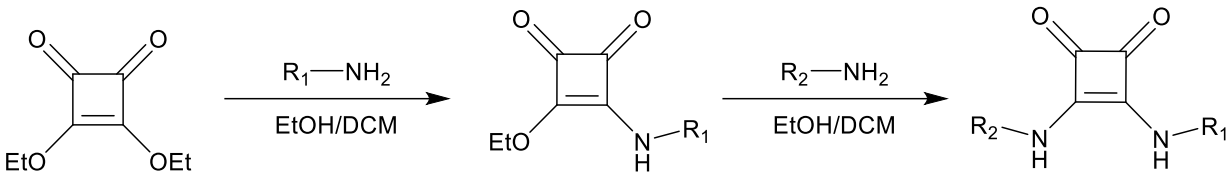
6 Experimental

The following reactions were all synthesized using commercially available reagents and solvent purchased from Sigma Aldrich without further purification. Thin layer chromatography (TLC) were conducted with silica-gel 60 F_{245} or aluminium oxide 60 F_{245} on aluminium plates and developed by UV-light (245 nm). Column chromatography was performed with Merck silica-gel 60 (0.040-0.063 mm) or aluminium oxide 90 (0.063-0.200 mm). ^{1}H and ^{13}C NMR spectra were recorded by a Bruker Avance instrument operating at 400 or 600 MHz for proton and 100 or 150 for carbon. Chemical shifts are expressed in ppm (δ) downfield from tetramethylsilane (TMS) as an internal standard. Accurate mass determination in positive and negative mode was performed on a "Synapt G2-S" Q-TOF instrument from Water TM. Samples were ionized by an ASAP probe (APCI) or ESI probe. No chromatographic separation was used before the mass analysis. Calculated exact mass and spectra processing was done by Waters TM Software Masslynx V4.1 SCN871. Infrared absorption (IR) spectra were recorded with a Bruker Alpha FT-IR spectrometer using OPUS V7 software to analyze the spectra. A Stuart automatic melting point SMP40 was used to determine melting points. HPLC analyses were performed on an Agilent 1100-series instrument with a G1379A Degasser, G1311A Quatpump, G1313A ALC autosampler and G1315D Agilent detector. Detection was done at 254 nm, and the software was Agilent Chemstation. A Chiralpak AD, with amylose tris (3,5-dimethylphenylcarbamate) coated on 10µm silica-gel column (250 x 4.6 mm ID) was used with a flow of 1 mL/min. Single crystal X-ray data was acquired using Bruker D8 Venture single crystal diffractometer. 3-circle goniometer, Cu and Mo InCoatec microfocus X-ray sources, Photon 100 detector. Oxford Cryosystems Cryostream plus low temperature attachment (80 – 500 K). The APEX suite was used for data collection and processing.

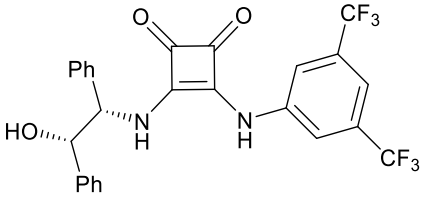
6.1 Synthesis of ligands

6.1.1 Synthesis of squaramides **1**-**6**

General procedure A



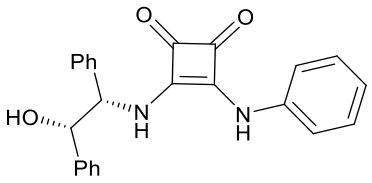
To a solution of 3,4-diethoxycyclobut-3-ene-1,2-dione in ethanol or DCM, an amine (1 equiv.) in ethanol or DCM was added dropwise. The mixture was stirred until TLC or ^{1}H NMR showed full conversion. The procedure was repeated with a second amine in ethanol or DCM. If necessary, the product was extracted with water to remove excess amine. When the product was insoluble in EtOAc and MeOH, it was thoroughly washed with ethanol to remove residual starting material. Otherwise, the crude product was purified by silica-gel or alumina column chromatography.



1

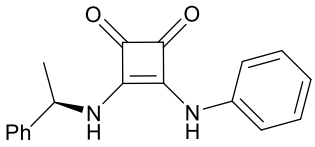
3-((3,5-Bis(trifluoromethyl)phenyl)amino)-4-(((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)amino)cyclobut-3-ene-1,2-dione: Following General Procedure A, 3,4-diethoxycyclobut-3-ene-1,2-dione (40 mg, 0.235 mmol) in ethanol was added 3,5-bis(trifluoromethyl)aniline (53.4 mg, 0.235 mmol) in ethanol dropwise over 30 minutes. The mixture was stirred for 10 days until ^{1}H NMR showed full conversion. (1*S*,2*S*)-2-Amino-1,2-diphenylethan-1-ol (55.1 mg, 0.259 mmol) dissolved in ethanol (0.5 ml) and triethylamine (0.18 ml) was then added to the mixture dropwise over 30 minutes. White precipitate occurred, and the mixture was stirred for 1 hour until ^{1}H NMR showed full conversion. The product was filtered off and washed thoroughly with ethanol, which gave 13.8 mg (0.026 mmol, 11%) of squaramide **1** as a white solid. ^{1}H NMR ($(CD3)_2SO$, 600 MHz): δ = 10.44 (s, 1H), 8.63 (d, *J* = 9.7, 1H), 8.06 (s, 2H), 7.66 (s, 1H), 7.48-7.50 (m, 4H), 7.40 (t, *J* = 7.4, 2H), 7.30-7.34 (m, 3 H), 7.24 (t, *J* = 7.3, 1H), 6.11 (d, *J* = 4.4, 1H), 5.40 (d, *J* = 9.1, 1H), 5.06 (s, 1H);

^{1}H NMR correspond to previously reported data.[43]



2

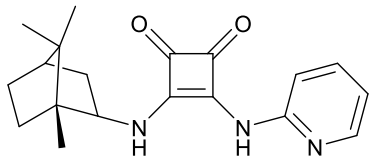
3-(((1*S*,2*S*)-2-Hydroxy-1,2-diphenylethyl)amino)-4-(phenylamino)cyclobut-3-ene-1,2-dione: Following General Procedure A, 3,4-diethoxycyclobut-3-ene-1,2-dione (40 mg, 0.235 mmol) in ethanol was added aniline (21.9 mg, 0.235 mmol) dissolved in ethanol dropwise over 30 minutes. The mixture was stirred for 5 days until ^{1}H NMR showed 75 % conversion. The solvent was removed under reduced pressure, dissolved in DCM and extracted with water. (1*S*,2*S*)-2-Amino-1,2-diphenylethan-1-ol (51.2 mg, 0.24 mmol) was added dropwise to the intermediate dissolved in ethanol (3.5 mL), and the mixture was stirred for 1 hour until ^{1}H NMR showed full conversion. The product was washed thoroughly with ethanol, which gave 61.7 mg (0.161 mmol, 68%) of squaramide **2** as a white solid, mp. 256.3-266.3 ^{o}C. ^{1}H NMR ((CD3)$_2$SO, 600 MHz): δ = 9.94 (s, 1H), 8.54 (d, *J* = 9.9, 1H), 7.48 (d, *J* = 5.5, 4H). 7.44 (d, *J* = 7.9, 2H), 7.40 (t, *J* = 7.5, 2H), 7.33-7.35 (m, 2H), 7.29-7.7.32 (m, 3H), 7.23 (t, *J* = 7.2, 1H), 7.02 (t, *J* = 4.4, 1H), 6.05 (d, *J* = 4.4, 1H), 5.43 (d, *J* = 7.8, 1H), 5.04 (t, *J* = 3.0, 1H); ^{13}C NMR ((CD3)$_2$SO, 150 MHz): δ = 183.9, 180.7, 169.4, 154.0, 143.3, 141.5, 139.6, 129.8 (2C), 128.7 (2C), 128.3 (2C), 127.6 (2C), 127.4 (2C), 126.8 (2C), 123.0, 118.3 (2C), 75.4, 63.6; IR (thin film, cm^{-1}): 3441, 3167, 2959, 1799, 1647, 1540, 1443, 1001, 755, 697; HRMS (ASAP, m/z): found 385.1553 (calc. $C_{24}H_{21}N_2O_3$, 385.1552 $[M+H]^+$).



3

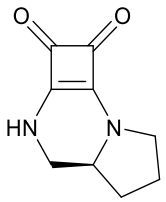
(*R*)-3-(Phenylamino)-4-((1-phenylethyl)amino)cyclobut-3-ene-1,2-dione: Following General Procedure A, 3,4-diethoxycyclobut-3-ene-1,2-dione (40 mg, 0.235 mmol) in ethanol was added aniline (21.9 mg, 0.235 mmol) in ethanol dropwise over 30 minutes. The mixture was stirred for 2 days until ^{1}H NMR showed full conversion. (*R*)-1-Phenylethan-1-amine (28.5 mg, 0.235 mmol) in ethanol was added dropwise, resulting in formation of white precipitate. The mixture stirred for 1 hour, and then the product was washed with ethanol, resulting in 34.6 mg (0.118 mmol, 50%) of squaramide **3** as a white solid, mp. 292.0-294.9 ^{o}C. ^{1}H NMR ((CD3)$_2$SO, 600 MHz): δ = 9.57 (s, 1H), 8.08 (s, 1H), 7.40-7.44 (m, 6H), 7.31-7.36 (t, *J* = 7.5, 3H), 7.03 (t, *J* = 7.2, 1 H), 5.30 (t, *J* = 6.6, 1H), 1.61 (d, *J* = 6.9, 3H); ^{13}C NMR ((CD3)$_2$SO,

150 MHz): δ = 184.1, 180.7, 168.7, 164.2, 143.6, 139.4, 129.8 (2C), 129.2 (2C), 128.0, 126.5 (2C), 123.2, 118.4 (2C), 53.6, 23.5; IR (thin film, cm^{-1}): 3162, 2980, 1794, 1660, 1556, 1461, 751, 657; HRMS (ASAP, m/z): found 293.1287 (calc. $C_{18}H_{17}N_2O_2$, 293.1290 $[M+H]^+$).



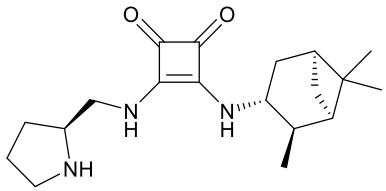
4

3-(Pyridin-2-ylamino)-4-(((1*R*,2*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)amino)cyclobut-3-ene-1,2-dione: Following General Procedure A, 3,4-diethoxycyclobut-3-ene-1,2-dione (100 mg, 0.588 mmol) in DCM was added 2-aminopyridin (55.3 mg, 0.588 mmol) in DCM dropwise. Ten drops of triethylamine were also added, and the mixture was stirred for 7 days at 40 °C, which resulted in only 29 % conversion. The heating was turned off and the mixture stirred for 4 days, when ^{1}H NMR showed full conversion. (*R*)-(+)-Bornylamine (91 mg, 0.595 mmol) in DCM was added to the mixture and stirred for 2 hours. The solvent was evaporated under reduced pressure and the crude product was purified by silica-gel column chromatography (100:2.5 DCM:MeOH, R_f = 0.22), giving 113 mg (0.345 mmol, 59%) of squaramide **4** as a pale yellow powder, mp. 280.9-284.1 °C. ^{1}H NMR (CD_2Cl_2, 600 MHz): δ = 10.00 (s, 1H), 9.36 (d, *J* = 9.1, 1H), 8.08 (d, *J* = 4.1, 1H), 7.65 (t, *J* = 7.3, 1H), 7.27 (d, *J* = 8.1, 1H), 6.90 (t, *J* = 5.8, 1H), 4.48 (t, *J* = 9.7, 1H), 2.37-2.42 (m, 1H), 1.80-1.84 (m, 1H), 1.68 (t, *J* = 4.5, 1H), 1.60-1.65 (m, 1H), 1.38-1.43 (m, 1H), 1.21-1.26 (m, 1H), 1.00-1.03 (m, 1H), 0.91 (s, 3H), 0.86 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (CD_2Cl_2, 150 MHz): δ = 184.1, 183.0, 171.5, 161.7, 152.4, 146.9, 139.9, 118.1, 113.1, 59.2, 50.2, 48.2, 45.2, 38.5, 28.6, 27.6, 19.7, 18.5, 13.2; IR (thin film, cm^{-1}): 3179, 2952, 1798, 1693, 1600, 1564, 1477, 1375, 1247, 766; HRMS (ASAP, m/z): found 326.1866 (calc. $C_{19}H_{24}N_3O_2$, 326.1869 $[M+H]^+$).



5

3,4-Bis((((*S*)-pyrrolidin-2-yl)methyl)amino)cyclobut-3-ene-1,2-dione: Following General Procedure A, (*S*)-(+)-2-(aminomethyl)pyrrolidine (59 mg, 0.588 mmol) in ethanol was added dropwise to a solution of squaric ethyl ester (50 mg, 0.294 mmol) in ethanol (1 mL). The solution was stirred overnight until ^{1}H NMR showed full conversion of the squaric ethyl ester. The solvent was evaporated under reduced pressure and the crude product was purified by silica-gel column chromatography (100:5 DCM:MeOH, R_f = 0.17), which gave 5.4 mg (0.0124 mmol, 7 %) of squaramide **5** as a yellow-brown oil. ^{1}H NMR ($CDCl_3$ 400 MHz): δ = 3.89-3.94 (m, 1H), 3.84-87 (m, 1H), 3.62-3.69 (m, 1H), 3.52-3.59 (m, 1H), 2.97-3.02 (dd, *J* = 8.4, 11.9 1H), 2.25-2.32 (m, 1H), 2.07-2.20 (m, 2H), 1.49-1.59 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 181.2, 180.6, 167.8, 167.5, 57.4, 46.8, 46.2, 28.7, 24.2; IR (thin film, cm^{-1}): 3200, 2931, 1667, 1613, 1556, 1465, 1329, 1301, 812, 664; HRMS (ASAP, m/z): found 179.0816 (calc. $C_9H_{11}N_2O_2$, 179.0821 $[M+H]^+$).

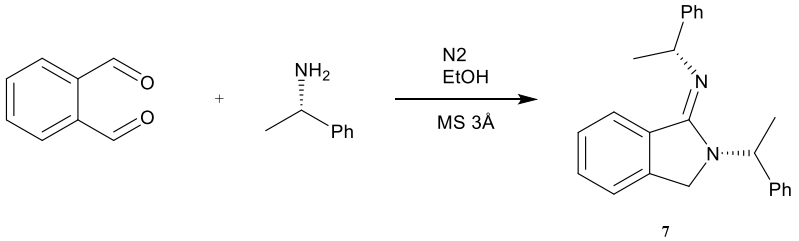


6

3-((((*S*)-Pyrrolidin-2-yl)methyl)amino)-4-(((1R,2R,3R,5S)-2,6,6-trimethylbicyclo[3.1.1] heptan-3-yl)amino)cyclobut-3-ene-1,2-dione: Following General Procedure A, (1*R*,2*R*,3*R*,5*S*)-(−)-isopinocampheyl amine (36 mg, 0.24 mmol) in ethanol (1mL) was added dropwise over 15 minutes to squaric ethyl ester (40 mg, 0.24 mmol) in ethanol (1 mL). The mixture was stirred for 7 hours until TLC indicated full conversion. (*S*)-(+)-2-(Aminomethyl)pyrrolidine (25 mg, 0.25 mmol) was added to the intermediary product in ethanol (5 mL). The mixture was stirred for 6 hours until ^{1}H NMR showed full conversion. The solvent was evaporated under reduced pressure and the crude product was purified by silica-gel column chromatography (100:5 DCM:MeOH, R_f = 60). This gave 5.2 mg (0.02 mmol, 8%) of squaramide **6** as a white powder, mp. 237.8-239.1 °C. ^{1}H NMR ($CDCl_3$ 600

MHz): δ = 4.52-4.53 (m, 1H), 4.23 (s, 1H), 4.00 (s, 1H), 3.69 (p, *J* = 7.2, 12.3, 1H), 2.81 (dd, *J* = 9.9, 12.9, 1H), 2.72 (dd, *J* = 3.5, 13.4, 1H), 2.65-2.69 (m, 1H), 2.40-2.43 (m, 1H), 2.04-2.09 (m, 1H), 1.98-2.00 (m, 1H), 1.95-1.96 (m, 2H), 1.86-1.89 (m, 1H), 1.83-1.85 (m, 1H), 1.61-1.62 (m, 1H), 1.59-1.60 (m, 1H), 1.22 (s, 3H), 1.16 (d, *J* = 7.6, 3H), 1.04 (s, 3H), 0.80 (d, *J* = 9.9, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 183.8 (2C), 168.7 (2C), 63.1, 53.0, 48.6, 47.7, 46.7, 45.4, 41.7, 38.8, 38.5, 35.5, 29.4, 27.9, 24.2, 23.5, 20.5; IR (thin film, cm^{-1}): 3210, 2919, 1790, 1667, 1565, 1520, 1455, 1353; HRMS (ASAP, m/z): found 332.2340 (calc. $C_{19}H_{30}N_3O_2$, 332.2338 $[M+H]^+$);

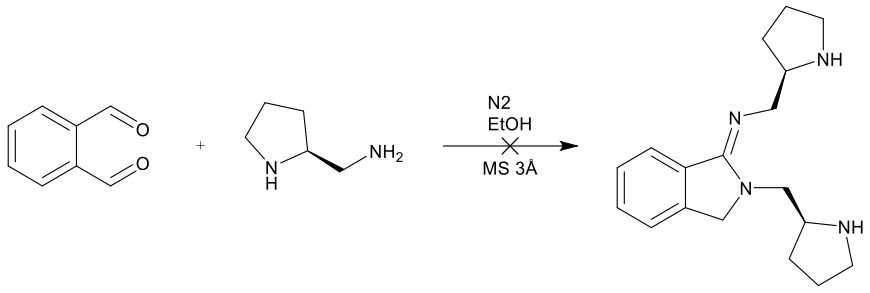
6.1.2 Iminoisoindolines



7

(*E*)-N,2-Bis((*R*)-1-phenylethyl)isoindolin-1-imine: (*R*)-(+)-α-Methylbenzylamine (90 mg, 0,7455 mmol) was added to phthaldialdehyd (50 mg, 0.373 mmol) in ethanol (3 mL) and the mixture was stirred for 1 hour until ^{1}H NMR showed full conversion. The solvent was removed by reduced pressure, which resulted in 119 mg (0,350 mmol, 94%) of the iminoisoindolin **7** as a dark orange oil. ^{1}H NMR (CD_3CN 600 MHz): δ = 8.02 (d, *J* = 7.7, 1H), 7.47-7.48 (m, 1H), 7.46 (s, 1H), 7.44 (d, *J* = 7.4, 2H), 7.36-7.38 (m, 3H), 7.31-7.35 (m, 2H), 7.27-7.28 (m, 2H), 7.24-7.26 (m, 1H), 7.16 (t, *J* = 7.1, 1H), 5.87 (q, *J* = 7.2, 14.47 Hz, 1H), 5.59 (q, *J* = 6.4, 12.86 Hz, 1H), 4.51 (d, *J* = 16.9, 1H), 4.20 (d, J = 16.9, 1H), 1.67 (d, *J* = 7.1, 3H), 1.52 (d, *J* = 6.6, 3H); ^{13}C NMR (CD_3CN, 150 MHz): δ = 155.1, 149.7, 143.9, 143.2, 132.2, 130.0, 128.9 (2C), 128.6 (2 C), 127.9, 127.6 (2 C), 127.2, 126.9 (2 C), 126.7, 126.4, 124.2, 55.9, 50.3, 47.6, 27.8, 17.6; ; IR (thin film, cm^{-1}): 3371, 2971, 1644, 1449, 1376, 1028, 760, 699; HRMS (ASAP, m/z): found 341.2018 (calc. $C_{24}H_{25}N_2$, 341.2018 $[M+H]^+$).

6.1.2.1 Attempted imine



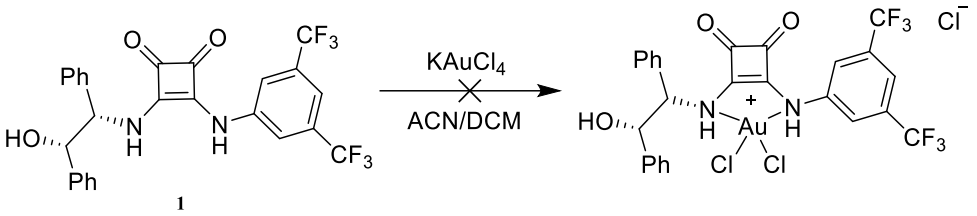
(*Z*)-N,2-Bis(((*S*)-pyrrolidin-2-yl)methyl)isoindolin-1-imine was attempted synthesized by following the same procedure as for iminoisoindoline **7**. (*S*)-(+)-2-(Aminomethyl)pyrrolidine (45 mg, 0.447 mmol, 2 equiv.) in ethanol (1 mL) to a solution of phthaldialdehyd (30 mg, 0.224 mmol) in ethanol (5 mL). The mixture stirred for 1.5 hours until ^{1}H NMR showed full consumption of phthalaldehyde. The solvent was evaporated under reduced pressure and the crude product was purified on alumina column chromatography (100:1 DCM:MeOH). Purification gave no discernible product in either of the five fractions.

6.2 Synthesis of gold(III)-complexes

General Procedure B

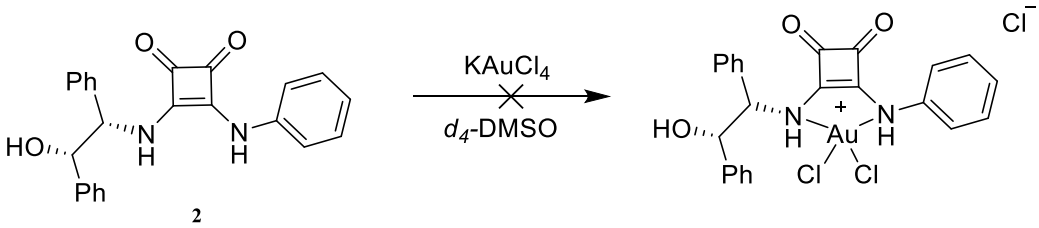
An acetonitrile solution of ligand **1**-**8** and an acetonitrile solution of $KAuCl_4$ or $AuCl_3$ (1 equiv.) were mixed. If necessary, a solution of the appropriate silver salt, AgX, (1 equiv.) in acetonitrile was added. The solution was stirred until ^{1}H NMR showed full conversion, before a small amount (approx. 10 mg) of lithium chloride was added. The solution was filtered through a short plug of celite and the solvent was removed under reduced pressure. The residue was extracted with DCM, and washed several times with water, dried over anhydrous sodium, filtered and the solvent was removed under reduced pressure. The gold-complexes were purified by crystallization or precipitation.

6.2.1 Unsuccessful gold(III)-coordination to squaramides **1**-**6**



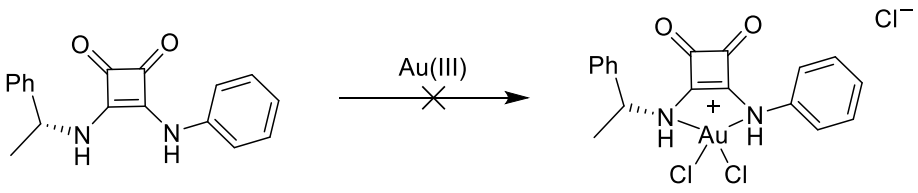
1

Following General Procedure B, squaramide **1** (4.3 mg, 0.008 mmol), partly dissolved in DCM (6 mL) and ACN (3 mL), was added $KAuCl_4$ (3.4 mg, 0.009 mmol) in ACN (2 mL). The mixture was stirred for 4 days with no indication of coordination of gold by ^{1}H NMR.



2

Following General Procedure B, squaramide **2** (5.3 mg, 0.014 mmol) dissolved in d_4-DMSO (2 mL), was added $KAuCl_4$ (5.2 mg, 0.0014 mmol) in 2 mL ACN. The mixture was stirred for 2 days with no indication of coordination of gold by ^{1}H NMR.



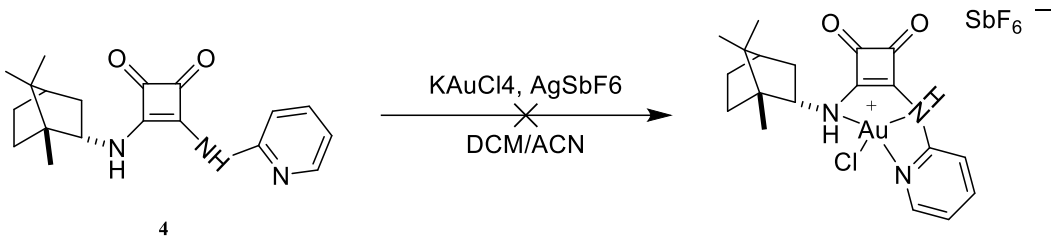
3

Following General Procedure B, squaramide **3** (4.9 mg, 0.015 mmol) was dissolved in DMF (1 mL), before $AuCl_3$ (5 mg, 0.025 mmol) in DMF (0.5 mL) was added, causing the transparent mixture to turn brown. $AgSbF_6$ (8.6 mg, 0.025 mmol, 1.5 eq) dissolved in DMF (0.5 mL) was subsequently added, causing the formation of black precipitate. ^{1}H NMR of the solution indicated no coordination to gold.

The reaction was attempted again using $KAuCl_4$ (5.6 mg, 0.015 mmol) instead of $AuCl_3$, and no silver salt. The mixture turned yellow at the addition of gold and was stirred for 4 days with no indication of coordination of gold.

Third, squaramide **3** (7.1 mg, 0.024 mmol) was attempted dissolved in ACN (5 mL) at 65 °C. Despite the poor solubility, $KAuCl_4$ (10 mg, 0.027 mmol) dissolved in ACN (1 mL) was added and the mixture stirred at 65 °C for 3 days, with no indication of coordination of gold.

Finally, squaramide **3** (4.8 mg, 0.016 mmol) dissolved in DCM (3 mL) and EtOH (1.5 mL) was added $KAuCl_4$ (6.8 mg, 0.018 mmol) dissolved in DCM (1 mL) and EtOH (0.5 mL). Subsequently, tetrabutyl ammonium hexafluoro phosphate (3.8 mg, 0.098 mmol) dissolved in EtOH (1 mL) was added and the mixture was stirred for 2 days with no indication of coordination of gold.



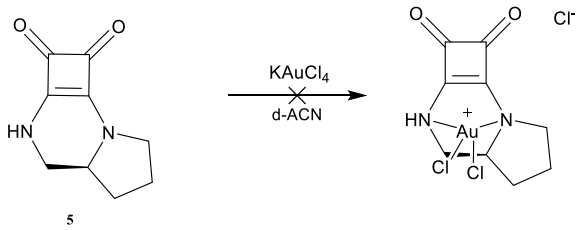
4

Following General Procedure B, to a solution of squaramide **4** (3.5 mg, 0.011 mmol) dissolved in DCM (6 mL), $KAuCl_4$ (4.3 mg, 0.011 mmol) in ACN (3 mL) was added and the mixture was stirred for a few minutes before $AgSbF_6$ (3.8 mg, 0.011 mmol) in ACN (3 mL) was added. The mixture was stirred overnight, and ^1H NMR seemed to indicate some coordination to gold.

The reaction was repeated in a larger scale, with a mixture of squaramide **4** (20 mg, 0.061 mmol) dissolved in DCM (2 mL), $KAuCl_4$ (23.3 mg, 0.062 mmol) in ACN (1.5 mL) and $AgSbF_6$ (21.1 mg, 0.061 mmol) in ACN (1.5 mL) was stirred for 1.5 hours. The mixture turned green after 10 minutes, and some black precipitate developed over time. Filtration and extraction followed, and then crystallization in DCM and *n*-pentane, giving 14.4 mg of yellow solid believed to be coordinated product.

The reaction was again repeated, with squaramide **4** (60.0 mg, 0.183 mmol) dissolved in DCM (5 mL), $KAuCl_4$ (69.6 mg, 0.184 mmol) in ACN (2 mL) and $AgSbF_6$ (63.0 mg, 0.183 mmol) in ACN (2 mL) stirred for 1 hour. The product was dark green with some black precipitate. Workup and crystallization gave 44.7 mg of a yellow solid.

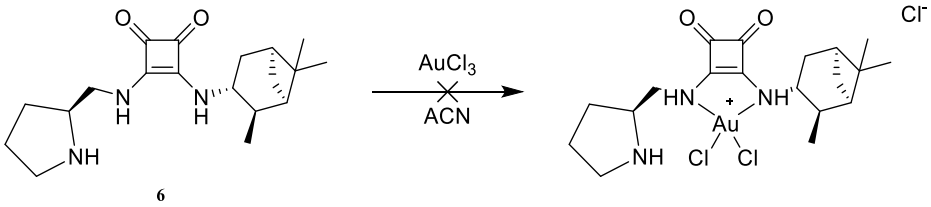
Finally, the reaction was repeated one last time, with squaramide **4** (11.5 mg, 0.035 mmol) in DCM (1 mL) and ACN (3.5 mL), $KAuCl_4$ (14.0 mg, 0.037 mmol) in ACN (1 mL) and $AgSbF_6$ (12.2 mg, 0.036 mmol) in ACN (1 mL). The mixture was stirred for 4 hours, until it was green and with some black precipitate. Workup and crystallization gave 11.6 mg of a yellow solid.



5

Following General Procedure B, a small amount of squaramide **5** (0.8 mg, 0.002 mmol) was mixed with $KAuCl_4$ (1.6 mg, 0.004 mmol) dissolved in d_3-ACN (0.5 mL), although the squaramide was not very soluble. The mixture was stirred for 6 hours, after which ^{1}H NMR showed possible coordination.

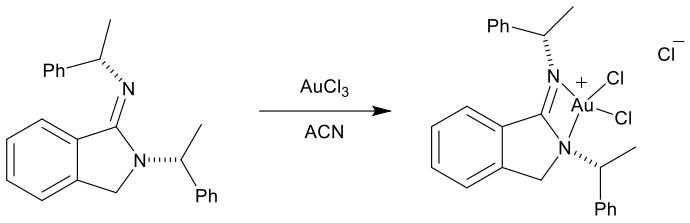
A second coordination attempt consisted of squaramide **5** (5.4 mg, 0.019 mmol) in ACN (1 mL), was added $AuCl_3$ (5.9 mg, 0.019 mmol) in ACN (1 mL). The mixture turned brown straight away and evaporation of the solvent under reduced pressure gave a black, insoluble solid.



6

Following General Procedure B, to a solution of squaramide **6** (4.9 mg, 0.015 mmol) dissolved in DCM (1 mL), $AuCl_3$ (4.5 mg, 0.015 mmol) in ACN (1 mL) was added and the mixture was stirred for 1 day. ^{1}H NMR was inconclusive.

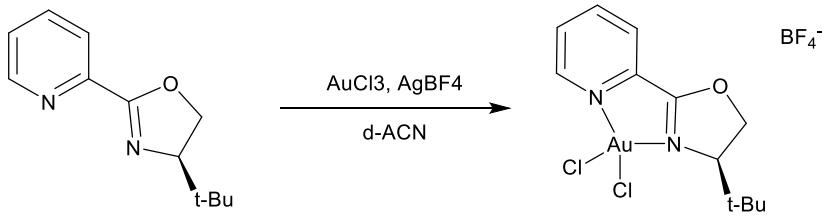
6.2.2 Gold(III)-coordination of iminoisoindoline **7**



7 8

Gold (III)-complex (**8**): Following General Procedure B, iminoisoindoline **7** (12.1 mg, 0.036 mmol) in *d*-ACN (0.5 mL) was added $AuCl_3$ (11 mg, 0.036 mmol) in *d*-ACN (0.15 mL). The reaction was stirred for 10 minutes, when ^{1}H NMR showed full conversion. Purification by crystallization by slow diffusion of *n*-pentane in ACN was attempted, but only resulted in a few tiny crystals in the interphase of the two solvents. The solvent was then removed under reduced pressure, giving 20.2 mg (0.033 mmol, 94%) of gold(III)-complex **8** as a pale purple oil. ^{1}H NMR (CD_3CN 600 MHz): δ = 7.97 (d, *J* = 7.6, 1H), 7.75 (t, *J* = 7.6, 1H), 7.70 (d, *J* = 7.5, 1H), 7.53-7.56 (m, 1H), 7.49-7.50 (m, 2H), 7.47-7.48 (m, 1H), 7.43-7.44 (m, 2H), 7.35-7.37 (m, 2H), 7.30-7.33 (m, 1H), 7.23-7.25 (m, 2H), 5.72 (m, 1H), 5.55 (q, *J* = 7.2, 13.6, 1H), 4.97 (d, *J* = 19.9, 1H), 4.72 (d, *J* = 20.3, 1H), 1.87-1.90 (m, 3H), 1.75 (d, *J* = 6.8, 3H); ^{13}C NMR (CD_3CN, 150 MHz): δ = 161.1, 144.5, 142.2, 138.6, 134.3, 129.9 (2C), 129.6 (2C), 129.5, 129.4, 128.5, 127.9, 127.5 (2C), 127.1, 126.0 (2C), 124.3, 55.4 (2C), 53.9, 24.0, 18.9; HRMS(ASAP, m/z): $[M+H]^+$ not found.

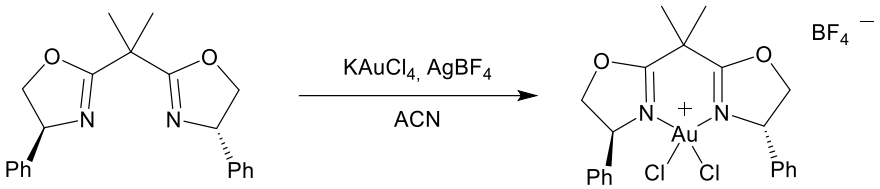
6.2.3 Gold(III)-coordination of oxazoline-based ligands **10**-**12**



9 10

Gold(III) complex (**10**): Following General Procedure B, (*R*)-4-(*tert*-butyl)-2-(pyridin-2-yl)-4,5-dihydrooxazole (10.1 mg, 0,049 mmol) (**9**) in d_3-ACN (0.5 mL) was added $AuCl_3$ (14.8 mg, 0.049 mmol) in d_3-ACN (1 mL) and $AgBF_4$ (9.7 mg, 0,050 mmol) in d_3-ACN (1 mL). At the first drop of $AgBF_4$ white precipitate emerged. The mixture was stirred for 15 minutes until ^{1}H NMR showed full conversion. The white precipitate of AgCl was removed before the crude was extracted with water and was crystallized by vapor diffusion of *n*-pentane in a DCM solution of the product which gave 14.8 mg (0.031 mmol, 63 %) of product **10** as pale yellow

solid. ^{1}H NMR (CD_3CN 600 MHz): δ = 9.45 (d, *J* = 5.6, 1H), 8.67 (t, *J* = 7.6, 1H), 8.32 (d, *J* = 7.6, 1H), 8.28 (t, *J* = 6.4, 1H), 5.46 (dd, *J* = 2.6, 7.5, 1H), 5.14 (t, *J* = 9.4, 1H), 4.57 (dd, *J* = 2.5, 8.9, 1H), 1.09 (s, 9H); ^{13}C NMR (CD_3CN, 150 MHz): δ = 177.2, 149.9, 147.2, 141.2, 134.3, 131.0, 79.7, 72.9, 36.5, 25.7 (3C); HRMS (ASAP, m/z): found 401.0934 (calc. $C_{12}H_{16}N_2OAu$, 401.0928 $[M\text{-}Cl_2]^+$).

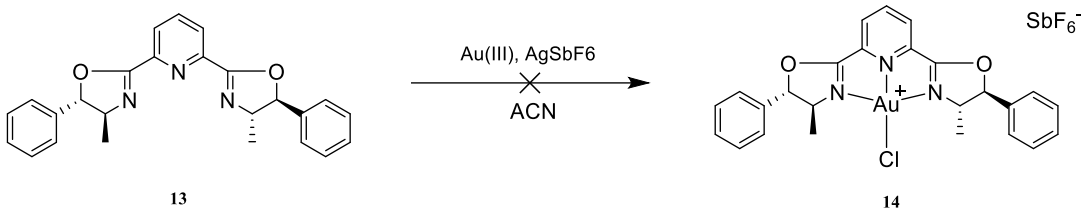


11 **12**

Gold-complex (**12**): Following General Procedure B, 2,2′-isopropylidenebis[(4S)-4-phenyl-2-oxazoline] (**11**) (58 mg, 0.17 mmol) was reacted with KAuCl4 (64 mg, 0.17 mmol) and $Ag[BF_4]$ (53 mg, 0.27 mmol) in ACN (5 mL). The product after extraction was a yellow oil which was crystallized from a slow diffusion of n-pentane in a DCM solution of the product which gave 31 mg (0.037 mmol, 22 %) of product **12** as yellow crystals. 1H NMR (CD_2Cl_2, 400 MHz): δ = 7.50-7.57 (m, 6H), 7.30-7.34 (m, 4H), 6.14 (dd, *J* = 4.9, 10.0, 2H), 5.39 (t, *J* = 9.7, 18.8, 2H), 4.9 (dd, *J* = 4.9, 9.3, 2H), 2.19 (s, 6H).

^{1}H NMR spectrum correspond to previously reported data.[1]

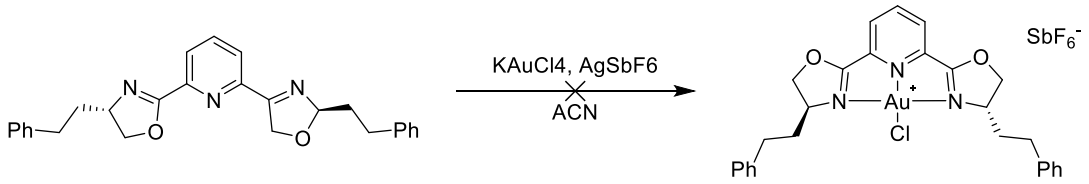
6.2.4 Unsuccessful gold(III)-coordination of oxazoline-based ligands **14**-**16**



13 14

Following General Procedure B, 2,6-bis((4S,5S)-4-methyl-5-phenyl-4,5-dihydrooxazol-2-yl)pyridine (20.9 mg, 0.053 mmol) in ACN (3 mL) was added $AuCl_3$ (15.6 mg, 0.052 mmol) in ACN (3 mL) and $AgSbF_6$ (18 mg, 0.052 mmol) in ACN (3 mL) and stirred for 30 minutes when ^1H NMR showed full conversion. The product was filtrated, extracted with water, and crystallized from a slow diffusion of n-pentane in a DCM solution of the product, but ^1H NMR showed some reversion back to the starting material. Several attempts were made to separate gold(III)-complex **14** from the oxazoline ligand **13**, but with no success.

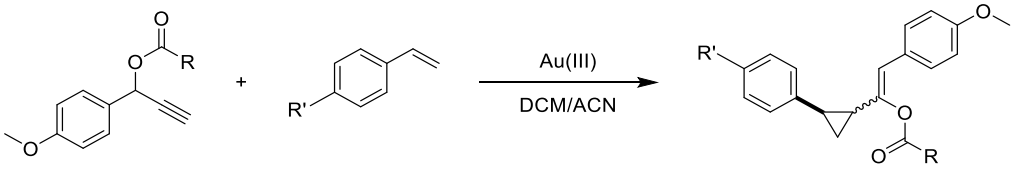
HRMS (ASAP, m/z): found 594.1457 (calc. $C_{25}H_{23}N_3O_2Au$, 594.1456 $[M\text{-}Cl]^+$)



15

Following General Procedure B, 2,6-bis((S)-4,5-dihydro-4-phenethyloxazol-2-yl)pyridine (**15**) (15.4 mg, 0.036 mmol) in ACN (2mL) was added $KAuCl_4$ (13.5 mg, 0.036 mmol) in ACN (1 mL) and $AgSbF_6$ (12.3 mg, 0.036 mmol) in ACN (1 mL). The mixture was stirred overnight, after which ^1H NMR was inconclusive, and the mixture was filtrated and extracted with water to purify the sample. The purification was partly successful, but no coordination product was visible on ^1H NMR.

6.3 Cyclopropanation reactions

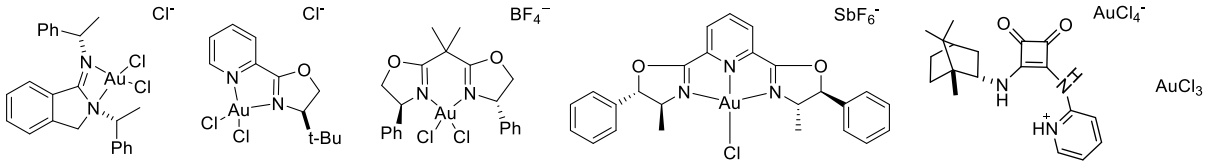


17a: R = *t*-Bu
17b: R = CH_3

18a: R' = H
18b: R' = OMe

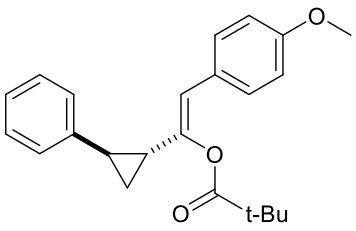
19a: R = *t*-Bu, R' = H
19b: R = CH_3, R' = H
19c: R = *t*-Bu, R' = OMe

Au(III):



8 **10** **12** **14** **4**[$AuCl_4$]

Propargyl ester **17a** and **17b** were synthesised during the pre-master project and the vinyl substrates **18a** and **18b** were commercially available. Cyclopropanation products **19a** and **19b** were synthesised several times using different gold(III)-catalysts. Enantiomeric excess was measured for some of the cyclopropanation products by chiral HPLC.

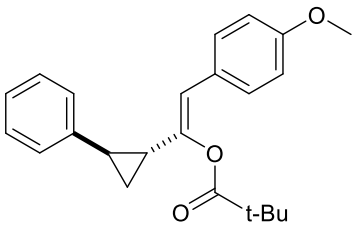


trans-**19a**

(Z)-2-(4-methoxyphenyl)-1-((1R,2R)-2-phenylcyclopropyl)vinyl pivalate:

1-(4-methoxyphenyl)prop-2-yn-1-yl pivalate (5 mg, 0.020 mmol), styrene (8.5 mg, 0.082 mmol) and gold(III)-complex **8** (0.7 mg, 0.001 mmol, 5 mol%) were mixed in *d*-ACN (0.6 mL). An ^{1}H NMR experiment was conducted for 42 hours, when the reaction had reached a 23:77 *cis:trans* ratio of cyclopropanation product **19a**. The product was purified by silica-gel column chromatography (10:1 *n*-pentane:EtOAc, R_f = 0.32). This gave 5.8 mg (0.017 mmol, 85 %) of cyclopropanation product **19a** as a yellow liquid. ^{1}H NMR (CD_2Cl_2, 400 MHz): δ = 7.25-7.30 (m, 4H), 7.15-7.18 (m, 1H), 7.11 (d, *J* = 7.5, 2H), 6.82 (d, *J* = 8.5, 2H), 6.08 (s, 1H), 3.78 (s, 3H), 2.16-2.21 (m, 1H), 1.90-1.95 (m, 1H), 1.28-1.33 (m, 1H), 1.26 (s, 9H), 1.20-1.24 (m, 1H); %ee determined by HPLC (Chiralpak AD Column, 2-propanol:hexane = 5:100 (1ml/min), isomer 1 13.0 min, isomer 2 14.2 min): 0% ee.

^{1}H NMR spectrum correspond to previously reported data.[1]

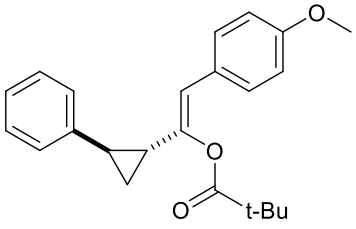


trans-**19a**

(Z)-2-(4-methoxyphenyl)-1-((1R,2R)-2-phenylcyclopropyl)vinyl pivalate:

1-(4-methoxyphenyl)prop-2-yn-1-yl pivalate (5 mg, 0.020 mmol), styrene (8.5 mg, 0.082 mmol) and gold(III)-complex **10** (0.6 mg, 0.001 mmol, 5 mol%) were mixed in *d*-ACN (0.5 mL). An ^{1}H NMR experiment was conducted for 30 minutes, when the reaction had reached a 6:94 *cis:trans* ratio of cyclopropanation product **19a**. The product was purified by silica-gel column chromatography (10:1 *n*-pentane:EtOAc, R_f = 0.25). This gave 4.5 mg (0.013 mmol, 65 %) of cyclopropanation product **19a** as a yellow liquid. ^{1}H NMR (CD_2Cl_2, 400 MHz): δ = 7.25-7.30 (m, 4H), 7.15-7.18 (m, 1H), 7.11 (d, *J* = 7.5, 2H), 6.82 (d, *J* = 8.5, 2H), 6.09 (s, 1H), 3.78 (s, 3H), 2.16-2.27 (m, 1H), 1.90-1.95 (m, 1H), 1.28-1.33 (m, 1H), 1.26 (s, 9H), 1.20-1.24 (m, 1H); %ee determined by HPLC (Chiralpak AD Column, 2-propanol:hexane = 5:100 (1ml/min), isomer 1 12.5 min, isomer 2 13.1 min): 0% ee.

^{1}H NMR spectrum correspond to previously reported data.[1]



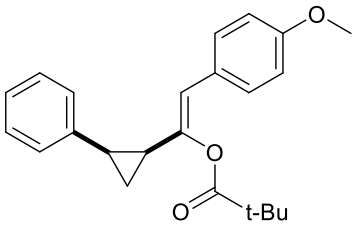
trans-**19a**

(Z)-2-(4-methoxyphenyl)-1-((1R,2R)-2-phenylcyclopropyl)vinyl pivalate:

1-(4-methoxyphenyl)prop-2-yn-1-yl pivalate (20 mg, 0.081 mmol), styrene (34 mg, 0.325 mmol) and gold(III)-complex **12** (3.4 mg, 0.004 mmol, 5 mol%) were mixed in DCM. The mixture stirred for 18 hours when ^{1}H NMR showed full completion and the reaction had reached a 6:94 *cis:trans* ratio of cyclopropanation product **19a**. The product was purified by silica-gel column chromatography (10:1 *n*-pentane:EtOAc, R_f = 0.33). This gave 23 mg (0.065 mmol, 81 %) of cyclopropanation product **19a** as a yellow liquid. ^{1}H NMR (CD_2Cl_2, 400 MHz): δ = 7.25-

7.30 (m, 4H), 7.15-7.18 (m, 1H), 7.11 (d, *J* = 7.5, 2H), 6.82 (d, *J* = 8.5, 2H), 6.09 (s, 1H), 3.78 (s, 3H), 2.16-2.27 (m, 1H), 1.90-1.95 (m, 1H), 1.28-1.33 (m, 1H), 1.26 (s, 9H), 1.20-1.24 (m, 1H).

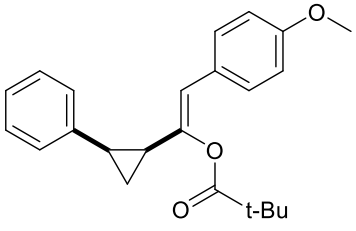
^{1}H NMR spectrum correspond to previously reported data.[1]



cis-**19a**

(Z)-2-(4-methoxyphenyl)-1-((1S,2R)-2-phenylcyclopropyl)vinyl pivalate:
1-(4-methoxyphenyl)prop-2-yn-1-yl pivalate (10 mg, 0.0406 mmol), styrene (16.9 mg, 0.162 mmol) and gold(III)-complex **10** (1.2 mg, 0.002 mmol, 5 mol%) were mixed in ACN (2 mL). The mixture was stirred for 30 minutes when ^{1}H NMR showed full completion and a 84:16 *cis*:*trans* ratio of cyclopropanation product **19a**. The product was purified by silica-gel column chromatography (10:1 *n*-pentane:EtOAc, R_f = 0.33). This gave 8.9 mg (0.025 mmol, 63 %) of cyclopropanation product **19a** as a yellow liquid. ^{1}H NMR (CD_2Cl_2, 400 MHz): δ = 7.17-7.29 (m, 5H), 7.09-7.11 (m, 2H), 6.77-6.79 (m, 2H), 5.94 (s, 1H), 3.78 (s, 3H), 2.29-2.40 (m, 2H), 1.30-1.41 (m, 2H), 1.15 (s, 9H); %ee determined by HPLC (Chiralpak AD Column, 2-propanol:hexane = 5:100 (1ml/min), isomer 1 10.3 min, isomer 2 12.1 min): 0% ee.

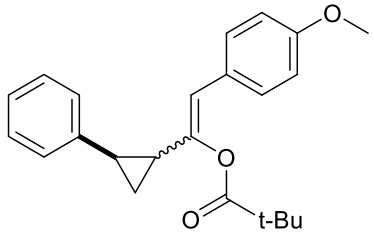
^{1}H NMR spectrum correspond to previously reported data.[1]



cis-**19a**

(Z)-2-(4-methoxyphenyl)-1-((1S,2R)-2-phenylcyclopropyl)vinyl pivalate:
1-(4-methoxyphenyl)prop-2-yn-1-yl pivalate (5.2 mg, 0.021 mmol), styrene (8.5 mg, 0.081 mmol) and gold(III)-complex **14** (0.9 mg, 0.001 mmol, 5 mol%) were mixed in *d*-DCM (0.5 mL). An ^{1}H NMR experiment was conducted for 23 hours, when the reaction had reached a 88:12 *cis:trans* ratio of cyclopropanation product **19a**. The product was not purified by silica-

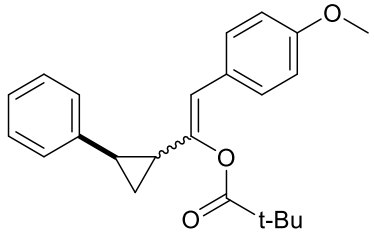
gel column chromatography, but the ^{1}H NMR spectrum correspond to previously reported data.[1]



19a

(R)-2-(4-methoxyphenyl)-1-(2-phenylcyclopropyl)vinyl pivalate:

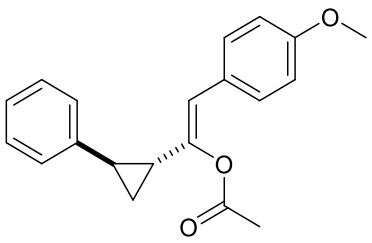
1-(4-methoxyphenyl)prop-2-yn-1-yl pivalate (5 mg, 0.02 mmol), styrene (8.5 mg, 0.081 mmol) and gold(III)-salt **4**[$AuCl_4$] (0.9 mg, 0.001 mmol, 5 mol%) were mixed in d_2-DCM (0.5 mL). An ^{1}H NMR experiment was conducted for 18 hours, when the reaction had reached a 57:43 *cis:trans* ratio of cyclopropanation product **19a**. The product was not purified by silica-gel column chromatography, but the ^{1}H NMR spectrum correspond to previously reported data.[1]



19a

(R)-2-(4-methoxyphenyl)-1-(2-phenylcyclopropyl)vinyl pivalate:

1-(4-methoxyphenyl)prop-2-yn-1-yl pivalate (5 mg, 0.02 mmol), styrene (8.5 mg, 0.081 mmol) and $AuCl_3$ (0.3 mg, 0.001 mmol, 5 mol%) were mixed in d_3-ACN (0.5 mL). An ^{1}H NMR experiment was conducted for 3 hours, when the reaction had reached a 9:91 *cis:trans* ratio of cyclopropanation product **19a**. The product was not purified by silica-gel column chromatography, but the ^{1}H NMR spectrum correspond to previously reported data.[1]

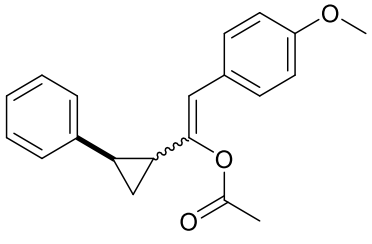


trans-**19b**

(Z)-2-(4-methoxyphenyl)-1-((1R,2R)-2-phenylcyclopropyl)vinyl acetate:

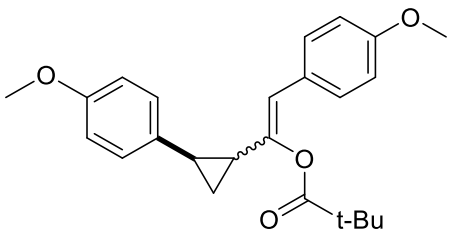
1-(4-methoxyphenyl)prop-2-yn-1-yl acetate (20 mg, 0.098 mmol), styrene (40.8 mg, 0.392 mmol) and gold(III)-complex **12** (4.1 mg, 0.005 mmol, 5 mol%) were mixed in DCM. The mixture stirred for 23 hours when ^{1}H NMR showed full completion and the reaction had reached a 10:90 *cis:trans* ratio of cyclopropanation product **19b**. The product was purified by silica-gel column chromatography (10:1 *n*-pentane:EtOAc, R_f = 0.23). This gave 19 mg (0.062 mmol, 63 %) of cyclopropanation product **19b** as a yellow liquid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.29-7.34 (m, 4H), 7.19-7.23 (m, 1H),7.13-7.15 (m, 2H), 6.87 (d, *J* = 8.8, 2H), 6.06 (s, 1H), 3.28 (s, 3H), 2.24-2.27 (m, 1H), 2.22 (s, 3H), 1.96-2.01 (m, 1H), 1.34-1.39 (m, 1H), 2.25-2.30 (m, 1H); %ee determined by HPLC (Chiralpak AD Column, 2-propanol:hexane = 5:100 (1ml/min), isomer 1 12.7 min, isomer 2 13.8 min): 0% ee.

^{1}H NMR spectrum correspond to previously reported data.[1]



19b

(R)-2-(4-methoxyphenyl)-1-(2-phenylcyclopropyl)vinyl acetate: 1-(4-methoxyphenyl)prop-2-yn-1-yl acetate (5.2 mg, 0.025 mmol), styrene (10.1 mg, 0.970 mmol) and gold(III)-complex **10** (7 mg, 0.001 mmol, 5 mol%) were mixed in *d*-ACN. An ^{1}H NMR experiment was conducted for 23 hours, when the reaction had reached a 27:73 *cis:trans* ratio of cyclopropanation product **19b**. The product was not purified by silica-gel column chromatography, but the ^{1}H NMR spectrum correspond to previously reported data.[1]



19c

(R)-2-(4-methoxyphenyl)-1-(2-(4-methoxyphenyl)cyclopropyl)vinyl pivalate:

1-(4-methoxyphenyl)prop-2-yn-1-yl pivalate (30.8 mg, 0.125 mmol), 1-methoxy-4-vinylbenzene (65.4 mg, 0.487 mmol) and gold(III)-salt **4**[$AuCl_4$] (0.5 mg, 0.006 mmol, 5 mol%) were mixed in DCM (5 mL). The mixture was stirred for 30 minutes when ^{1}H NMR showed full completion and a 53:47 *cis*:*trans* ratio of cyclopropanation product **19c**. The product was purified by silica-gel column chromatography (10:1 *n*-pentane:EtOAc, R_f = 0.24). This gave 42.1 mg (0.111 mmol, 89 %) of cyclopropanation product **19c** as a yellow liquid. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.28 (ap. d, *J* = 8.9, 2H, *trans*), 7.11 (d, J =8.7, 2H, *cis*), 7.06 (d, J = 6.2, 2H, *cis*), 7.05 (d, J = 6.2, 2H, *trans*), 6.81 (dd, J = 8.7,1.6, 4H, *trans*), 6.78 (m, 2H, *cis*), 6.74 (m, 2H, *cis*), 6.06 (s, 1H, *trans*), 5.88 (s, 1H, *cis*), 3.79 (s, 3H, *trans*), 3.78 (s, 3H, *trans*), 3.77 (s, 3H, *cis*), 3.76 (s, 3H, *cis*), 2.27 (d, J = 6.2, 1H, *cis*), 2.25 (d, J = 6.3, 1H, *cis*), 2.18-2.13 (m, 1H, *trans*), 1.91-1.86 (m, 1H, *trans*), 1.32-1.30 (m, 1H, *cis*), 1.27 (s, 9H, *trans*), 1.24-1.22 (m, 1H, *trans*), 1.20-1.18 (m, 1H, *cis*), 1.17-1.14 (m, 1H, *trans*), 1.12 (s, 9H, *cis*).

^{1}H NMR spectrum correspond to previously reported data.[1]

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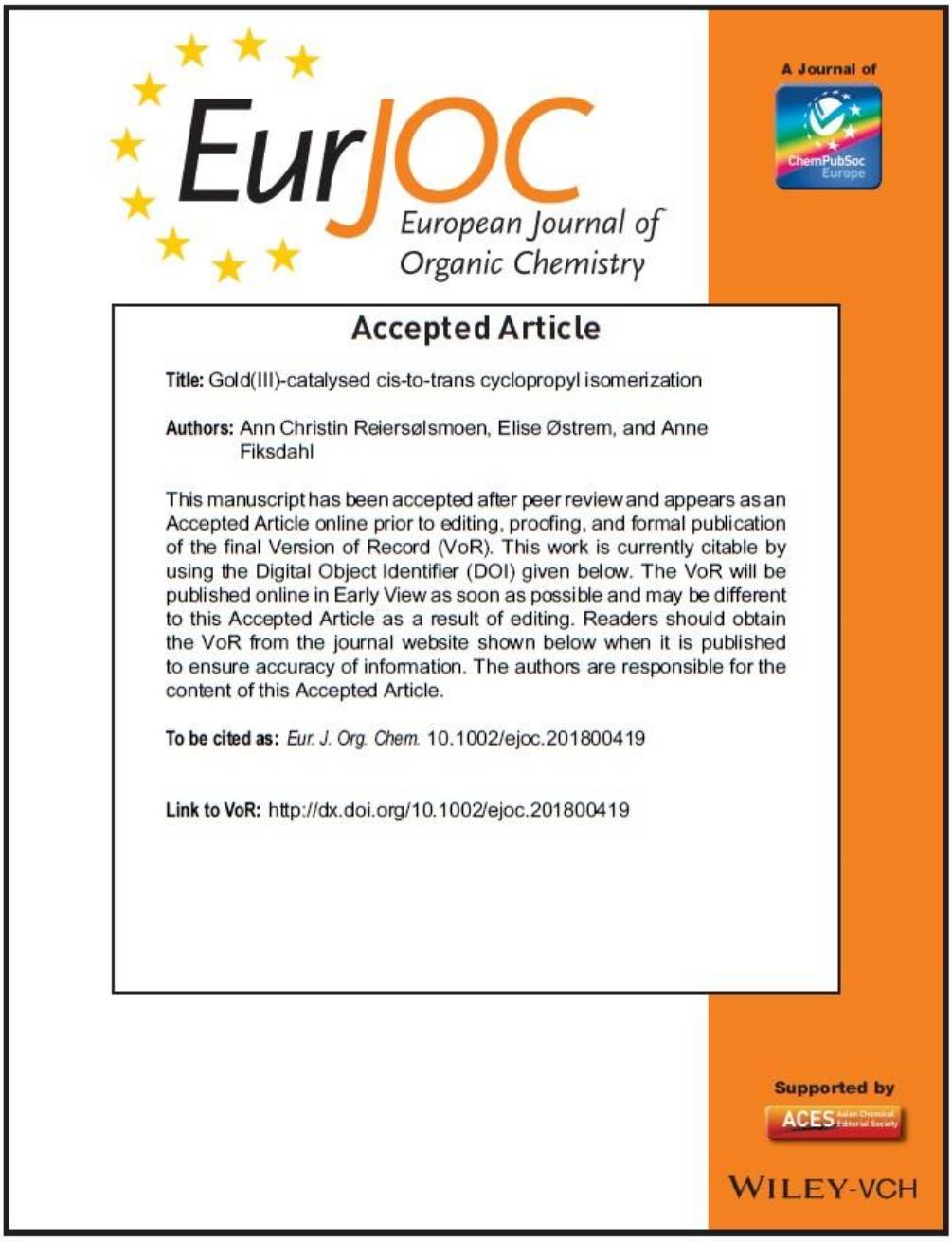
Appendix A Accepted Article



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Accepted Article

Title: Gold(III)-catalysed cis-to-trans cyclopropyl isomerization

Authors: Ann Christin Reiersølsmoen, Elise Østrem, and Anne Fiksdahl

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FULL PAPER

Gold(III)-catalysed *cis*-to-*trans* cyclopropyl isomerization

Ann Christin Reiersølmoen,[a] Elise Østrem[a] and Anne Fiksdahl*[a]

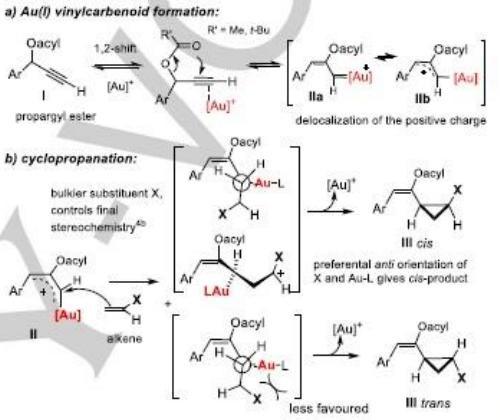
Abstract: Novel chiral gold(III) complexes, based on bisoxazoline (BOX) and 2-pyridyl-(-)menthol ligands, were prepared and characterised (X-ray), and their catalytic properties in cyclopropanation reactions of propargyl esters with alkenes were explored. The BOX-Au(III) catalysts gave excellent results for fast cyclopropanation and subsequent in situ *cis*-to-*trans* vinylcyclopropyl isomerization. Au(I) and Au(III) catalytic species showed different abilities to tune the reactions and transform the initially formed *cis* into the isomerized *trans* product. The appropriate choice of gold(I) or gold(III) complexes enabled highly stereoselective formation of *cis* or *trans* products (up to 99% dr), in high yields (63-98%). The pure *cis* isomers were used in isomerization studies, showing that rapid *cis*-to-*trans* isomerization took place at r.t. in the presence of BOX-Au(III) catalysts.

Introduction

The intensive development of gold chemistry the last decade has mainly focussed on the discovery and understanding of new gold(I)-catalysed reactions as well as the introduction of a variety of ligands for construction of new gold(I)-ligated complexes. Gold(III) catalysts opened the field of gold catalysis in organic synthesis.[1] However, gold(III) catalysts have not found widespread usage in later years, and with some exceptions,[2,3] the Au(III) complexes have mainly been limited to ligand-free, less stable gold(III)-species, typically $AuCl_3$ or K/Na/H($AuCl_4$). In contrast to the linear coordination mode of gold(I) catalysts, the ligated gold(III) complexes are square planar complexes, having four coordination sites. This may provide easier steric control, due to the proximity of the ligand to the reaction centre, which can allow for more selective reactions. Gold(III) catalyses many of the same reactions as gold(I), but may also be unreactive or exhibit quite different properties in many transformations.

Gold-catalysed cyclopropanation has emerged as a powerful method and provides complementarity to traditional metal-catalysed cyclopropanation systems. Gold vinyl carbenoids have been proposed as reactive intermediates in olefin cyclopropanations and have been generated by many methods.[4]

The propargyl ester - gold approach, based on gold-catalysed activation of propargyl esters, has been applied in a variety of cycloaddition reactions[5] (including cyclopropanation) as the easily accessible propargylic ester entity constitutes a convenient synthetic equivalent to an α-diazoketone for cyclopropanation processes. Terminal propargyl esters (**I**, Scheme 1) tend to undergo Au(I)-catalysed 1,2-acyloxy migration, analogous to Ru-catalysed[6a,b] rearrangements, affording gold vinylcarbenoid intermediates (**II**). These intermediates may undergo cyclopropanation with alkenes to give rise to vinylcyclopropyl products (**III**), normally obtained as *cis*/*trans* mixtures.[6]



Scheme 1. Au(I)-catalysed cyclopropanation, including a stereochemical model.[4b]

In general, reported successful gold-catalysed alkene cyclopropanations starting from propargyl esters have been performed with Au(I) complexes with e.g. phosphine or NHC ligands.[7] Some very few exceptions are known that apply Au(III) complexes, such as $AuCl_3$.[8]

Our earlier work employing propargyl esters **I** as gold vinylcarbenoid precursors in cyclopropanation reactions with alkenes (Scheme 1a,b) directly connected to a heteroatoms (X=NR,R' or OR,R')[6f,9a] provided highly functionalized vinylcyclopropyl derivatives **III** in up to 99% diastereoselectivity. Our previous cycloaddition studies of propargyl acetals,[6f,9] were based on Au(I) catalysis, as Au(III) salts mostly were shown to be unreactive.[9b-d,f,g] This is in accordance with other gold-catalysed cyclopropanation studies with varied substrates, but always performed with standard Au(I) catalysts.[6]

In light of these results, further exploration focussed on the ability of different gold catalytic species to stereoselectively afford *cis* or *trans* vinylcyclopropyl products. Our comparative studies, including the use of novel ligated gold(III) complexes, $AuCl_3$ and Pic-Au(III) as well as the JohnPhosAu(I) catalyst, are discussed below.

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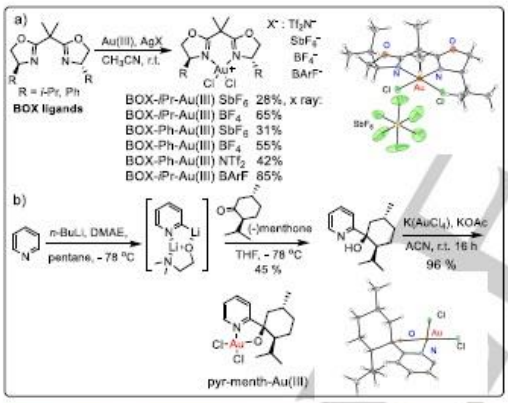
Supporting information is available on the WWW under https://doi.org .....

Results and Discussion

Preparation of chiral Au(III)-ligated catalysts.

Butyl-bisoxazoline-Au(III)$_T$ (BOX-*n*-Bu-Au(III))$_T$ complexes$_T$ have been prepared for investigation of thermal properties of such ionic liquids.[10a] According to this method, two new chiral *i*-Pr and phenyl bisoxazoline-Au(III) complexes were prepared for application in the present study on Au(III)-catalysed cyclopropanation. The crystalline BOX-*i*-Pr-Au(III) and BOX-Ph-Au(III) complexes were obtained from the respective BOX ligands and $K(AuCl_4)$ (in 28-65% yields, Scheme 2a). Different counterions, Tf_2N^-, SbF_6^-, BF_4^- and $BArF^-$ were introduced by the appropriate silver or sodium[10b] salts.

Another chiral 2-pyridyl-mentholate-Au(III) complex was prepared in 96% yield by base treatment and complexation of 2-pyridyl-menthol to $K(AuCl_4)$ (Scheme 1b).[3a] The pyr-menth ligand was prepared by enantioselective addition of lithiated pyridine to (-)-menthone.[11] The bis-pyridine by-product formation was challenging, and optimization of reaction conditions (e.g. reactant equivalents, temperature, additives) allowed isolation of moderate yields of the ligand (45% from a 1:3:6:12 equiv mixture of menthone-pyridine-DMAE-BuLi).



Scheme 2. Preparation of Au(III)-ligated complexes, including single-crystal X-ray structures; a) cationic BOX-Au(III) catalysts; b) pyridine-(-)-mentholate-Au(III) catalyst.

Cyclopropanation and cis-to-trans isomerization.

Most *cis/trans* ratios reported for propargyl cyclopropanation[6] are given as fixed values, characteristic for the actual product and reaction. Based on a previously postulated stereoselectivity model, dominating *cis*-selectivity is proposed to be consistent with an interaction of the olefin substituent with the ligated metal to disfavour the formation of the *trans*-cyclopropane[4b] (Scheme 1b). Thus, the steric interaction between the gold(I) ligand and the bulkier X-substituent on the vinyl substrate was suggested to preferentially give an *anti* orientation in the transition state to afford the main *cis* product. Our previous results with heteroatom-alkene cyclopropanations[6f,9a] showed that the *cis/trans* product ratios varied, depending on the bulkiness, but stereoselectivity was also clearly affected by the electronic properties of the alkenes.

Our present studies confirm the importance of the electronic nature of substrates, but also show that the properties and the catalytic activity of Au(I)/Au(III) catalysts are much more important and predominant for the steroselectivity of the reactions than the steric nature of the propargyl **1** and alkene **2** substrates. The results show that a more complex situation controls the stereochemical outcome of propargyl cyclopropanations, as particularly Au(III) catalysts may activate for in situ *cis*-to-*trans* isomerization in the course of cyclopropanation reactions. Thus, the stereoselective outcome of the reactions strongly depended on the specific performance of the applied gold catalyst. As a result, stereoselectivity could be tuned by appropriate reaction time.

A recent cyclopropanation study[12] has reported that slow *cis*-to-*trans* isomerization takes place during the progress of a similar cyclopropanation in the presence of a JohnPhosAu(I) catalyst, as shown by the moderate *cis/trans* isomerization; increasing the amount of *trans* isomer from 10% to 62 % by heating (75 ^{0}C) for nearly a week.

In our present study, the impact of the applied Au catalyst on the obtained stereoselectivity in cyclopropanation of terminal propargyl esters (**1a**,**b**,**c**) and alkenes **2a-c** and **2'a**,**b** (Table 1) was explored. The reactions were carried out as NMR experiments without stirring, affording longer reaction times than normal reactions performed in lab-scale, as shown by comparison with Table 2. The catalytic activity of the new Au(III)-complexes were compared to the simple $AuCl_3$ and the commercially available Pic-Au(III) salts, as well as the frequently used JohnPhosAu(I) catalysts. Despite the chiral nature of the new Au(III) catalysts, no enantioselectivity was observed, and racemic cyclopropyl products were obtained (HPLC).

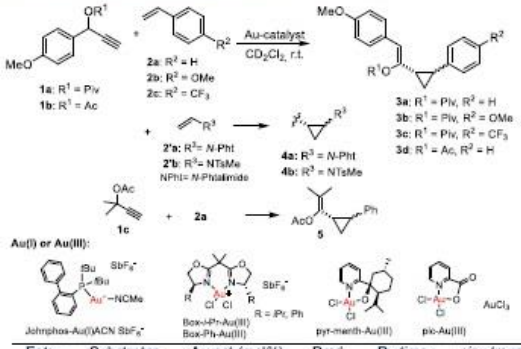
Most interestingly, the ability of BOX-Au(III) complexes to both afford fast cyclopropanation, and strongly activate for *cis*-to-*trans* isomerization was observed. Full conversion of propargyl pivaloyl ester **1a** into *cis/trans* mixtures of cyclopropyl products **3a** and **3b** was seen in the reaction with styrenes **2a**,**b** in the presence of 1-5 mol% BOX-*i*-Pr-Au(III)SbF_6 in less than 5 min (entries 1,3,7,8). With increased reaction times, a larger amount of the *trans* isomer evolved (up to 99% for **3a** in 24 h; entry 1) in the presence of 5 mol% Au(III) complex. The BOX-Ph-Au(III) catalyst afforded correspondingly 94% *trans* (entry 2). Lower catalyst loading (1 mol%) slowed down the *cis*-to-*trans* isomerization (86% *trans* **3a** in 2 d; entry 3). Propargyl acetate **1b** seemed to be slightly less reactive for both the cyclization and isomerization of product **3d** (entry 10). A marginally lower tendency for isomerization was seen for the electron-deficient *p*-CF_3 product **3c** (91% *trans* in 24 h, entry 9). A more complex situation was observed for electron-rich dimethoxy product **3b**, as shown by a competing rearrangement into cyclopentenyl products[9a] (entries 7,8). The BOX-Au(III) complexes with BF_4^- and NTf_2^- anions (Scheme 2a) gave corresponding results as the BOX-Au(III) SbF_6^- complexes (Table 1).

The pyr-menth-Au(III) complex inefficiently afforded cyclopropanation (2 h, entry 4) and isomerization (16% *trans*-**3a**

10.1002/ejoc.201800419

in 24 h), while the JohnPhos-Au(I) catalyst (5 mol%) gave fast cyclopropanation, but was less effective for isomerization (70% *trans* in 2d, entry 5). The $AuCl_3$ salt activated for a fast cyclization into a *cis*/*trans* mixture of product **3a**. However, the disadvantage with $AuCl_3$ is the low reproducibility and instability, as shown by the immediate formation of a dark gold precipitate, but generally, no subsequent isomerization took place (entry 6).

Table 1. Studies on stereoselective cyclopropanation.[a]



Entry	Substrates	Au cat (mol%)	Prod	Rx-time	*cis* : *trans* ratio
1	**1a + 2a**	BOX-*i*-Pr-Au(III)SbF_6 (5)	**3a**	< 5 min[b] 30 min 24 h	50 : 50 25 : 75 1 : 99
2	**1a + 2a**	BOX-Ph-Au(III)SbF_6 (5)	**3a**	< 15min[b] 24h	53 :47 6 : 94
3	**1a + 2a**	BOX-*i*-Pr-Au(III)SbF_6 (1)	**3a**	< 5 min[b] 19 h 2 d	88 : 12 65 : 35 14 : 86
4	**1a + 2a**	pyr-menth-Au(III) (5)	**3a**	2 h[b] 24 h	88 : 12 84 : 16
5	**1a + 2a**	JohnPhos-Au(I)ACN (5)	**3a**	< 5 min[b] 9 h 2d	95 : 5 67 : 23 30 : 70
6	**1a + 2a**	$AuCl_3$ (5)	**3a**	30 min[b] 24 h	55 : 45 55 : 45
7	**1a + 2b**	BOX-*i*-Pr-Au(III)SbF_6 (5)	**3b**	< 5 min[b] 30 min 24 h	45 : 55 27 : 73 17 : 83[c]
8	**1a + 2b**	BOX-*i*-Pr-Au(III)SbF_6 (1)	**3b**	< 5 min[b] 24 h	50 : 50 44 : 56[c]
9	**1a + 2c**	BOX-*i*-Pr-Au(III)SbF_6 (5)	**3c**	< 5 min[b] 24 h	76 : 24 9 : 91
10	**1b + 2a**	BOX-Ph-Au(III)SbF_6 (5)	**3d**	10 min[b] 24 h	92 : 18 10 : 90
11	**1a + 2'a**	BOX-*i*-Pr-Au(III)SbF_6 (5)	**4a**	12 h[b] 24 h	86 : 14 82 : 18
12	**1a + 2'b**	BOX-*i*-Pr-Au(III)SbF_6 (5)	**4b**	< 5 min[b]	1 : 99
13	**1a + 2'b**	BOX-*i*-Pr-Au(III)SbF_6 (1)	**4b**	15 min[b]	1 : 99
14	**1a + 2'b**	JohnPhos-Au(I)ACN (5)	**4b**	< 5 min [b]	1 : 99
15	**1c + 2a**	BOX-*i*-Pr-Au(III)SbF_6 (5)	**5**	1h [b] 24 h	85 : 15 85 : 15
16	**1c + 2a**	pyr-menth-Au(III) (5	**5**	1h [b] 24 h	90 : 10 90 : 10
17	**1c + 2a**	JohnPhos-Au(I)ACN (5)	**5**	5 min [b] 24 h	95 : 5 95 : 5

[a] The general reactions were performed in NMR tubes; **1a,b** (5 mg, 1 equiv.) and vinyl substrate **2a-c** (4 equiv.) in *d*-DCM (0.6 mL) added Au catalyst (1 or 5 mol-%) in *d*-DCM and monitored by ^{1}H NMR; [b] full conversion of propargyl substrate; [c] rearranged cyclopentenyl product[6a] was also formed.

Alkenes connected to N-heteroatom functionalities were tested as well. The electron-deficient *N*-phtalimide-alkene **2'a** slowly afforded cyclization product **4a**, but no further isomerization took place in the presence of BOX-*i*-Pr-Au(III) (12-24 h, 18% *trans* entry 11). In contrast, the NTsMe-alkene **2'b** is activated for immediate cyclization into product **4b** with both Au(I) and Au(III) catalysts (1-5 mol%, entries 12-14). This reaction does not appear to be controlled by the *cis*-stereoselective model[4b] (Scheme 1b). In contrary to all the alkenes above, the reaction of NTsMe-alkene **2'b** seems to follow a selective direct *trans*-cyclization pathway, as no traces of the *cis* isomer were observed.

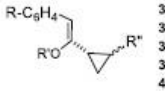
The dimethylpropargyl substrate **1c** readily afforded 85 – 95% *cis*-cyclopropylpropenyl product **5** (5 min - 1h, entries 15-17), but no further isomerization took place in the presence of any gold catalyst.

Selective preparation of cis and trans cyclopropyl products

As shown above, the appropriate choice of gold(I) or gold(III) complexes allows for the highly stereoselective formation of *cis* or *trans* products (up to 99% dr). To demonstrate the potential of the selective methods, a number of *cis* and *trans* isomers of cyclopropyl products **3** and **4** were prepared in high yields (in general 63-92%) from the appropriate propargyl esters and alkenes by applying the JohnPhosAu(I)(MeCN)SbF_6 and BOX-Au(III) catalysts, respectively (Table 2). Due to stirring, most reactions, even for *trans* preparation, were faster than the NMR experiments shown in Table 1.

Samples of >99% purity of *cis* isomers were further prepared to be used in *cis*-to-*trans* isomerization studies below (Table 3).

Table 2. Stereoselective preparation of *cis* or *trans* cyclopropyl products from appropriate substrates, according to Table 1.[a,b]



3a: R = 4-OMe; R'= Piv; R" = Ph
3b: R = 4-OMe R' = Piv, R" = 4-OMe-C_6H_4
3c: R = 4-OMe R' = Piv, R" = 4-CF_3-C_6H_4
3d: R = 4-OMe R' = Ac, R" = Ph
3f: R = 4-CF_3 R' = Piv, R" = Ph
4a: R = 4-OMe, R' = Piv, R" = *N*-Pht
4b: R = 4-OMe, R' = Piv, R" = *N*TsMe

product	*cis* isomer[a] *cis*:*trans* ratio	yield	*trans* isomer[b] *cis*:*trans* ratio	yield
3a	96:4	64 %	>99 % *trans*	76 %
3b	98:2	79 %		
3c	98:2	72 %		
3d	90:10	79 %	10 : 90[d]	63%
3f	>99 % *cis*	14 %	15 :85	98%
4a	>99 % *cis*[c]	92%		
4b			>99 % *trans*	75 %

[a] Approx. 0.1 mmol substrates and JohnPhosAu(I)(MeCN)SbF_6 (5 mol%) in DCM; stirred at r.t. 3-15 min; [b] Approx. 0.1 mmol substrates and BOX-Au(III) (5 mol%) in DCM; stirred at r.t. 15-60 min; [c] 24 h reaction time; [d] 1 h reaction time.

10.1002/ejoc.201800419

Cis-to-*trans* isomerization

The gold-catalysed isomerizations of pure *cis* products **3a-d** and **4a** (Table 2) into the corresponding *trans* diastereomers were monitored by ^{1}H NMR (Table 3). For all substances **3a** (entries 1-4), **3b** (entry 10), **3c** (entry 14) and **3d** (entries 19-20), the BOX catalysts afforded faster isomerization (5 min - 5h) than the other tested catalysts.

Table 3. *Cis*-to-*trans* isomerization studies.[a]

Entry	Cis compound[a],[b]	Au catalyst (5 mol%)	time	*cis*:*trans* ratio
1	**3a**	BOX-*i*-Pr-Au(III)-SbF_6	2h	**1:99**
2	**3a**	BOX-*i*-Pr-Au(III)-SbF_6 (1mol%)	3 h	**3 : 97**
3	**3a**	BOX-Ph -Au(III)-SbF_6	2 h	**5 : 95**
4	**3a**	BOX-Ph -Au(III)-SbF_6 (1 mol%)	5 h	**5 : 95**
5	**3a**	$AuCl_3$	1 d	35 :65
6	**3a**	$AuCl_3$ (1 mol%)	1 d	11 : 89
7	**3a**	pyr-menth-Au(III)	8 h	15 : 85
8	**3a**	Pic-Au(III)	5 h	**4 : 96**
9	**3a**	JohnPhos-Au(I)	24 h	**4 : 96**
10	**3b**	BOX-*i*-Pr-Au(III)-SbF_6	5 min	**4 :96**[c]
11	**3b**	pyr-menth-Au(III)	5 min	**4:96**[c]
12	**3b**	$AuCl_3$	17 h	78:22
13	**3b**	JohnPhos-Au(I)	5 min	-[d]
14	**3c**	BOX-*i*-Pr-Au(III)-SbF_6	3 h	5 :95
15	**3c**	JohnPhos-Au(I)	4 d	**1:99**
16	**3c**	pyr-menth-Au(III)	5 h 4 d	90:10 **1:99**
17	**3c**	$AuCl_3$	3 h	**5:95**
18	**3c**	Pic-Au(III)	1 d 4 d	22:78 18:82
19	**3d**	BOX-*i*-Pr-Au(III)-SbF_6	4 h	**2:98**
20	**3d**	BOX-Ph-Au(III)-SbF_6	2 h	**5 : 95**
21	**3d**	pyr-menth-Au(III)	2 d	**5 : 95**
22	**3d**	$AuCl_3$	8 h	15 : 85
23	**3d**	JohnPhos-Au(I)	1 d	**4 : 96**
24	**4a**	BOX-*i*-Pr-Au(III)-SbF_6	2 d	67 : 33
25	**4a**	BOX-*i*-Pr-Au(III)-BArF	2 h 2 d	83 : 17 60 : 40
26	**5**[e]	BOX-*i*-Pr-Au(III)-SbF_6	1 d	95 : 5
27	**5**[e]	JohnPhos-Au(I)	1 d	95 : 5

[a] The *cis*-product (>99% purity) (5 mg, 1 equiv.) was dissolved in *d*-DCM (0.6 mL) in a NMR tube and added the gold-catalyst (1 or 5 mol%) dissolved in *d*-DCM. The reaction progress at r.t. was monitored by ^{1}H NMR; [b] Samples of >99% *cis* purity were prepared according to Table 2; [c] minor amounts of rearranged cyclopentenyl product[9a] was observed; [d] rearranged cyclopentenyl product[9a] was mainly formed; [e] Sample **5**; 95 : 5 *cis* : *trans*, was prepared according to Table 1, entry 17.

The pyr-menth-Au(III) and the JohnPhos-Au(I) complexes also activated for isomerization, but to a lower extent (85-96% trans-**3a**, 8-24 h, entries 7,9). Results with $AuCl_3$ were not reproducible, as discussed above (entries 5,6). Spontaneous and selective BOX-Au(III)-catalysed isomerization was seen for the electron-rich substrate **3b** (96% *trans*, 5 min, entry 10), in contrast to the rearranged cyclopentenyl product[9a] mainly afforded with JohnPhos-Au(I) (entry 13). In general, the isomerization reactions of the electron-deficient *cis* isomer of CF_3 product **3c** (entry 14-18) as well as the acetate **3d** (entry 19-23) were slower than **3a** and **3b**.

The electron-deficient N-pht product **4a** gave only partial isomerization with the BOX-*i*-Pr-Au(III)-SbF_6 complex (33% *trans*, 2d, entry 24). The BOX-*i*-Pr-Au(III)-BArF was slightly more efficient (40% *trans*, 2 d, entry 25), demonstrating the reported positive effect[10b] of counter-anion exchange with the more weakly coordinating BArF anion. Previously, JohnPhosAu(I) (10 mol%) has been reported[12] to afford slow and moderate isomerization of similar *cis* N-phtalimide- and aryl-cyclopropyl structures into 69-87% *trans* product by heating (75 °C) for 1-2 weeks. The cyclopropylpropenyl product **5**, prepared from dimethylpropargyl substrate **1c**, failed to undergo isomerization by any gold catalyst (entries 26,27).

The *cis* isomer of NTsMe product **4b** was not accessible for isomerization studies, as this isomer was not observed during cyclopropanation, explained by a possible direct *trans*-cyclization pathway.

Proposed cis-to-trans isomerization pathways.

The observed *cis*-to-*trans* isomerization of vinyl-cyclopropyl products (**III**, Scheme 3) is proposed to proceed by Au-catalysed ring-opening through intermediates i-v (Scheme 3). In the first step, the Au moiety attaches to the substrate at C1, C3 or C4, giving intermediates i/ii, iii and iv/v, respectively. Finally, the *trans*-cyclopropyl product may be formed after bond rotation and ring re-closure.

The ability of cyclopropyl moieties to undergo Au-catalysed ring opening has previously been illustrated in several studies, either as substrates or as proposed intermediates in Au-catalysed transformations.[13] Alkynylcyclopropanes are known to undergo Au-catalysed nucleophilic ring opening.[14] Ring expansions are also known to take place by C-C bond migration by Au-catalysed cyclopropyl ring opening and ring closure into larger ring systems,[6a,15] such as cyclobutane products.[16] Au-catalysed cycloisomerization of enynes may proceed through cyclopropyl-gold-carbene interemediates and ring opening by nucleophilic attack or rearrangements.[15b,17]

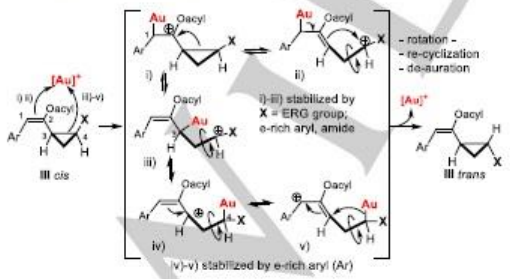
In contrast to our previous observations using propargyl substrates[9f] and heteroatom-alkenes, a step-wise mechanism has been suggested[15e] for ring expansion of *cis*-cyclopropyl intermediates (**III**) into cyclopentadienes. The process involves Au-vinyl activation by Au-coordination to C1, cyclopropyl ring opening (intermediates i)-ii); Scheme 3) and final ring closure to give the *trans*-product. A second mechanism for a related Au-catalysed vinylcyclopropyl (X = *N*-phtalimide or aryl) *cis*-*trans* isomerization has also previously been elucidated, involving intermediates iv)-v) (Scheme 3).[12]

10.1002/ejoc.201800419

In the present study, the total electronic properties of the *cis* product seem to control its general ability to undergo isomerization. However, our products **3,4** have both electron-rich and electron-deficient functionalities, some originating from the alkene substrates **2** and **2'** (X, Scheme 3). A more multifaceted situation for the *cis-trans* isomerization is therefore proposed for the vinylcyclopropyl derivatives **3,4** (**III**, Scheme 3), where the substrates can undergo isomerization through different pathways, influenced by the stabilization of the intermediate cationic Au complexes i-v. In general, the stabilities of these complexes are proposed to be dependent on the electronic natures of the substrates. Hence, the isomerization pathways may differ, as different intermediates have different stabilization capacities. This may explain the variation in ability to undergo isomerization, as different pathways are unlikely to have transition state complexes of the same stability. Consequently, one pathway will have a lower energy requirement than the others.

The presently studied aryl-vinylcyclopropyl ester products **3**, **4** (**III** in Scheme 3) contain the activating 4-OMe-phenyl-propargyl group. Such structures are proposed, to readily undergo isomerization through the stabilized allylic and benzylic carbocations (iv-v, Scheme 3), obtained by ring cleavage by Au-connection to C4. In contrast, the corresponding alkyl product **5** does not contain an analogous stabilizing group, explaining its negligible ability for isomerization (entries 26 and 27, Table 3). Electron-deficient *cis* products with additional EWG, such as **4a** (X= Npht) may also follow the iv)-v) isomerization pathway, but are overall observed to be too deactivated to undergo efficient isomerization (entries 24 and 25, Table 3).

However, *cis* products with X = ERG may favour isomerization through the alternative cationic Au intermediates i)-iii) (Scheme 3), formed by ring cleavage by allylic Au-connection to C1/C3. These intermediates are likely to be favoured due to stabilization of the positive charge by electron-rich aryl-cyclopropyl groups, as observed for **3b** (entries 10 and 11, Table 3). In particular, the X = NTsMe group would allow strong iminium stabilization of intermediates ii) and iii), which may explain the immediate cyclopropanation into the NTsMe *trans*-product **4b**, by a direct *trans* cyclization pathway (entries 12-14, Table 1).



Scheme 3. Possible intermediates in *cis*-to-*trans* vinylcyclopropyl isomerization.

Conclusions

In contrast to the established cyclopropanation stereoselectivity model,[4b] which explains the favoured *cis*-selectivity by steric interactions, we have shown that a more complex situation controls the stereochemistry of propargyl cyclopropanation reactions. The present results demonstrate that the stereoselective outcome is mostly affected by the electronic properties of substrates as well as the choice of Au(I) or Au(III) catalyst, and finally, the reaction time as well as the bulkiness of substrates.

Our studies show that BOX-Au(III) catalysts are superior to the other tested catalysts for combined fast cyclopropanation and subsequent in situ *cis*-to-*trans* vinylcyclopropyl isomerization. In the presence of BOX-Au(III) complexes, rapid and complete in situ isomerizations from initially formed *cis* (>99%) into *trans* (>99%) isomers may take place at r.t. during cyclopropanation reactions. As a consequence, the proper choice of Au(I) or Au(III) catalyst allowed highly stereoselective formation of either *cis* or *trans* products, respectively, in up to 99% dr, and facilitated isolation of pure *cis* or *trans* isomers in high yields (63-98%).

To the best of our knowledge, the present study for the first time proves the BOX-Au(III) effect on propargyl cyclopropanation, affording complete in situ *cis*-to-*trans* isomerization. The BOX-Au(III) complexes represent an interesting group of Au(III) catalysts with specific and unique properties. Further studies on comparable complexes are in progress in our laboratories.

ASSOCIATED CONTENT

Supporting Information (see footnote on the first page of this article). Characterization of compounds and copies of ^{1}H, ^{13}C NMR spectra are available free of charge at www..... Crystallographic data; Cambridge Crystallographic Data Centre; BOX-*i*Pr-Au(III)SbF_6 and pyr-menth-Au(III) complexes; CCDC ID: 1828155 and 1828159.

Experimental Section

General. Commercial grade reagents were used as received. Dry solvents were collected from a solvent-purification system. All reactions were monitored by thin-layer chromatography (TLC) using silica gel 60 F254 (0.25-mm thickness) or by ^{1}H-NMR. Flash chromatography was carried out using silica gel 60 (0.040-0.063 mm). High Throughput Flash Purification (HPFP) was performed on pre-packed cartridges. ^{1}H and ^{13}C NMR spectra were recorded using a 400 or 600 MHz spectrometer. Chemical shifts are reported in ppm (δ) relative to tetramethylsilane (TMS) or *d*-DCM. Coupling constants (*J*) are reported in Hertz (Hz). The attributions of the chemical shifts were determined using COSY, HSQC and HMBC NMR experiments. The identification the *cis-trans*-diastereomers of products **3** was based on NOESY 2D NMR experiments. Accurate mass determination in either positive or negative mode was performed with a "Synapt G2-S" Q-TOF instrument from

Waters. Samples were ionised with an ASAP probe, and no chromatographic separation was used before the mass analysis. IR spectra were obtained using a Bruker Alpha FT-IR spectrometer using OPUS V7 software to analyze the spectra. Single crystal X-ray data was acquired using a Bruker D8 Venture diffractometer with the APEX3 suit, integrated with SAINT V9.32B, solved with XT and refined with XL using Olex2 as GUI. The cif files were edited with encipher 1.4 and molecular graphics were produced with Mercury 3.8. CCDC- ID 1828159 (BOX-Au(III)) and 1828155 (pyr-menth-Au(III)) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Propargyl esters **1a**[18a], **1b/1d**[18b] and **1c**[18c] were prepared according to literature procedures.

General method A for preparation of BOX-Au(III)-complexes[10a]

The *R,S*-BOX-ligand (1 equiv.) and K($AuCl_4$) (1 equiv.) were mixed in acetonitrile. A solution of the appropriate silver salt (1.5 equiv.) in acetonitrile was added. The solution was stirred in the dark for one day, before a small amount of lithium chloride was added. The solution was filtered through a short plug of celite and the solvent was removed under reduced pressure. The residue was extracted with DCM, and washed several times with water, dried over anhydrous Na_2SO_4 and filtered before the solvent was removed under reduced pressure. The gold-complexes were purified by crystallization or precipitation as described for each complex.

BOX-i-Pr-Au(III)-SbF$_6$ The title compound was prepared as described in Method A above from (4*S*,4'*S*)-2,2'-(propane-2,2-diyl)bis(4-isopropyl-4,5-dihydrooxazole) (38 mg, 0.143 mmol), K($AuCl_4$) (53 mg, 0.140 mmol) and $AgSbF_6$ (71 mg, 0.207 mmol) in acetonitrile (10 mL). The product was purified by precipitation from acetone in DCM over night to give the product as a pale yellow powder, 30 mg (28%, 0.039 mmol), after drying. ^{1}H NMR ($(CD_3)_2CO$, 600 MHz) δ: 5.16 (dd, J = 9.7,2.9, 2H), 5.09 (dt, J = 9.2,2.8, 2H), 4.89 (t, J = 9.4, 2H), 2.52 (dhep, J = 20.9,14.0,7.0,2.6 , 2H), 1.99 (s, 6H), 0.99 (d, J = 7.0, 6H), 0.90 (d, J = 6.9, 6H); ^{13}C NMR (CD_2Cl_2), 150 MHz) δ : 174.2 (2C), 72.0 (2C), 70.7 (2C), 42.2, 30.0 (2C), 26.0 (2C), 17.8 (2C), 13.5 (2C); HRMS (APCI/ASAP, m/z): found 529.1543 (calcd. $C_{16}H_{29}N_2O_3ClAu$, 529.1532, [M+MeO-Cl]$^+$). X-ray: CCDC ID 1828159.

BOX-i-Pr -Au(III)-BF$_4$ The title compound was prepared as described in Method A above from (4*S*,4'*S*)-2,2'-(propane-2,2-diyl)bis(4-isopropyl-4,5-dihydrooxazole) (36 mg, 0.135 mmol), K($AuCl_4$) (57 mg, 0.151 mmol) and $AgBF_4$ (52 mg, 0.267 mmol) in acetonitrile (10 mL). The product was purified by precipitation from DCM against *n*-pentane over night to give the product as a yellow powder, 54 mg (65%, 0.087 mmol), after drying. ^{1}H NMR (CD_2Cl_2, 400 MHz) δ: 5.03 (dt, J = 8.9,3.0, 2H), 4.86-4.77 (m, 4H), 2.62 (dp, J = 13.9,6.9,2.7, 2H), 1.86 (s, 6H), 1.00 (d, J = 7.1, 6H), 0.88 (d, J = 6.8, 6H); ^{13}C NMR (CD_2Cl_2), 100 MHz) δ: 174.4 (2C), 71.8 (2C), 70.7 (2C), 42.1, 29.9 (2C), 25.6 (2C), 17.9 (2C), 13.3 (2C); HRMS (APCI/ASAP, m/z): found 525.2030 (calcd. $C_{17}H_{32}N_2O_4Au$, 525.2028, [M+2MeO-2Cl]$^+$).

BOX-Ph -Au(II)-SbF$_6$ The title compound was prepared as described in Method A above from (*S,S*)-2,2'-isopropylidenebis(4-phenyl-2-oxazoline) (58 mg, 0.17 mmol), K$AuCl_4$ (65 mg, 0.17 mmol) and $AgSbF_6$ (93 mg, 0.27 mmol) in acetonitrile (20 mL). The crude product was purified by precipitation from DCM against *n*-pentane to give the product as a yellow powder, 45 mg (31%, 0.053 mmol), after drying. ^{1}H NMR (CD_2Cl_2, 400 MHz) δ: 7.18-7.45 (m, 10H), 5.18 (dd, J = 10.1,7.7, 1H), 4.87-4.92 (m, 1H), 4.67 (dd, J = 10.1,8.8, 1H), 4.48 (dd, J = 12.2,11.0, 1H), 4.38 (dd, J = 12.2,4.4, 1H), 4.19 (dd, J = 8.7,7.8, 1H), 1.59 (s, 3H), 1.52 (s, 3H); ^{13}C NMR (CD_2Cl_2, 150 MHz) δ: 172.4, 172.12, 140.4, 133.5, 130.1 (2C), 129.6 (2C), 128.6 (2C), 127.9 (2C), 126.9 (2C), 76.3, 68.8, 66.6, 59.1, 45.1, 22.9, 22.4; HRMS (APCI/ASAP, m/z): found 531.1357 (calcd. $C_{21}H_{22}N_2O_2Au$, 531.1347, [M-Cl2]$^+$).

BOX-Ph -Au(III)-Tf$_2$N The title compound was prepared as described in Method A above from 2,2'-isopropylidenebis[(4*S*)-4-phenyl-2-oxazoline] (58 mg, 0.17 mmol), K$AuCl_4$ (65 mg, 0.17 mmol) and $AgTf_2N$ (110 mg, 0.28 mmol) in acetonitrile (20 mL). Removal of solvent under reduced pressure gave the product as a yellow powder, 63 mg (42%, 0.071 mmol). Recrystallization was not necessary. ^{1}H NMR (CD_2Cl_2, 400 MHz) δ: 7.45-7.12 (m, 10H), 5.18 (dd, J = 10.1,7.7, 1H), 4.92-4.86 (m, 1H), 4.67 (dd, J = 10.1,8.9, 1H), 4.48 (t, J =10.9, 1H), 4.38 (dd, J = 12.2,4.5, 1H), 4.19 (t, J = 8.5, 1H), 1.59 (s, 3H), 1.52 (s, 3H); ^{13}C NMR (CD_2Cl_2, 150 MHz) δ: 172.4, 172.1, 140.4, 133.5, 130.1 (2C), 129.6 (2C), 128.6 (2C), 127.9 (2C), 126.9 (2C), 76.3, 68.8, 66.6, 59.1, 45.1, 22.9, 22.4; HRMS (APCI/ASAP, m/z): found 531.1357 (calcd. $C_{21}H_{22}N_2O_2Au$, 531.1347, [M-Cl2]$^+$).

BOX-Ph -Au(III)-BF$_4$ The title compound was prepared as described in Method A above from, 2,2'-isopropylidenebis[(4S)-4-phenyl-2-oxazoline] (54 mg, 0.16 mmol), K$AuCl_4$ (66 mg, 0.17 mmol) and $AgBF_4$ (55 mg, 0.28 mmol) in acetonitrile (20 mL). The product after extraction was a yellow oil which was crystallized by slow diffusion of *n*-pentane in a DCM solution of the product, to give 61 mg (55%, 0.089 mmol) of the product as yellow crystals. ^{1}H NMR (CD_2Cl_2, 400 MHz) δ: 7.40-7.18 (m, 10H), 5.18 (dd, J = 10.2,7.9, 1H), 4.94-4.84 (m, 1H), 4.67 (dd, J = 10.1,8.7, 1H), 4.48 (dd, J = 12.2,10.9, 1H), 4.38 (dd, J = 8.2,4.6, 1H), 4.19 (dd, J = 8.6,7.8, 1H), 1.59 (s, 3H), 1.52 (s, 3H); ^{13}C NMR (CD_2Cl_2, 150 MHz): δ: 175.6 (2C), 129.8 (4C), 128.6 (2C), 127.9 (4C), 126.7 (2C), 80.1 (2C), 69.3 (2C), 45.1, 26.1 (2C); HRMS (APCI/ASAP, m/z): found 531.1356 (calcd. $C_{21}H_{22}N_2O_2Au$, 531.1347, [M-Cl2]$^+$).

BOX-i-Pr -Au(III)-BArF The title compound was prepared based on Method A above from (4*S*,4'*S*)-2,2'-(propane-2,2-diyl)bis(4-isopropyl-4,5-dihydrooxazole) (20 mg, 0.077 mmol), $AuCl_3$ (23 mg, 0.077 mmol) and NaBArF (63 mg, 0.071 mmol) in acetonitrile (10 mL). No additional purification after extracting was necessary, yielding the product as a yellow powder, 91.3 mg (85%, 0.065 mmol), after drying. ^{1}H NMR (CD_2Cl_2, 400 MHz) δ: 7.72-7.71 (m, 8H), 5.56 (s, 4H), 5.03 (dt, J = 9.2,2.9, 2H), 4.84 (dd, J = 9.7,3.3, 2H), 4.67 (t, J = 9.5, 2H), 2.57 (dp, J = 13.9,6.9,2.6, 2H), 1.81 (s, 6H), 0.99 (d, J = 7.1, 6H), 0.80 (d, J = 7.0, 6H); ^{13}C NMR (CD_2Cl_2), 100 MHz) δ: 174.8 (2C), 162.1 (q, J = 49.5, 8C), 135.2 (8C), 129.2 (q, J = 31.5, 4C), 125.0 (q, J = 272.2, 8C), 117.9 (q, J = 4.6, 4C), 71.4 (2C), 71.1 (2C), 42.6, 30.5 (2C), 26.3 (2C), 17.9 (2C), 13.6 (2C); HRMS (APCI/ASAP, m/z): found 529.1539 (calcd. $C_{16}H_{29}N_2O_3ClAu$, 529.1532, [M+MeO-Cl]$^+$)

2-Pyridyl-mentholate-Au(III) complex

2-Pyridyl-menthol ligand; (1S,2S,5R)-2-isopropyl-5-methyl-1-(pyridin-2-yl)cyclohexan-1-ol. The pyr-menth-ligand was prepared from a 1:3:6:12 equiv. mixture of menthone:pyridine: DMAE:BuLi by optimizing a literature method.[11b] DMAE (0.98 mL, 9.72 mmol) in pentane (10 mL) was added to *n*-BuLi (10 mL, 2M, 20.0 mmol) at 0 °C. The reaction mixture was cooled to -78 °C before pyridine (0.39 mL, 4.82 mmol) in pentane (5 mL) was added. After stirring for 1 hour, (-)-menthone (0.28 mL, 1.61 mmol) in THF (5 mL) was added dropwise over 15 minutes. The reaction mixture was stirred for 2 hours before quenching with sat. NH_4Cl (aq., 15 ml). The water phase was extracted with diethyl ether (3 x 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and solvent removed *in vacuum*. The crude product was purified with silica-gel column chromatography (DCM:*n*-pentane, 1:1, R_f= 0.15) to yield the product as a colorless oil, 168 mg (45%, 0.72 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.52-8.51 (m, 1H), 7.70 (td, J = 7.6,1.7, 1H), 7.35-7.33 (m, 1H), 7.18 (ddd, J = 7.32,4.9,0.9, 1H), 5.2 (br s, 1H), 2.03-1.94 (m, 1H), 1.91-1.87 (m, 1H), 1.74-1.63 (m, 3H), 1.58-1.53 (m, 1H), 1.35 (t, J = 12.3, 1H), 1.23-1.16 (m, 1H), 1.10-1.07 (m, 1H), 0.89 (d, J = 6.6, 3H), 0.83 (d, J = 6.9, 3H), 0.67 (d, J = 7.0, 3H). The ^{1}H NMR shifts are in accordance with partly characterized product previously reported.[11b]

2-Pyridyl-mentholate-Au(III). (*1R,2R,5S*)-2-Isopropyl-5-methyl-1-(pyridin-2-yl)cyclohexan-1-ol (7 mg, 0.03 mmol) was dissolved in acetonitrile (0.8 mL) and aqueous KOAc (0.03 mL, 1M, 0.03 mmol) was added. After stirring for 15 min, $K(AuCl_4)$ (11 mg, 0.03 mmol) in water (0.8 mL) was added to the reaction mixture. The mixture was stirred over night before water (2 mL) was added and extracted with DCM (3 x 1 mL). The combined organic phases were removed *in vacuum*. The product was purified by precipitation from DCM in *n*-pentane to give the pyr-menth-Au(III) complex as an orange powder, 14 mg (96%, 0.03 mmol). ^{1}H NMR (400 MHz, CD_2Cl_2,) δ: 9.18 (dd, J = 6.1,1.2, 1H), 8.08 (td, J = 7.7,1.5, 1H), 7.55 (ddd, J = 6.1,1.5, 1H), 7.38 (dd, J = 8.1,1.5, 1H), 2.06-1.98 (m, 2H), 1.88-1.83 (m, 1H), 1.71-1.57 (m, 4H), 1.29-1.22 (m, 1H), 1.04-1.02 (m, 1H), 1.00 (d, J = 6.7, 3H), 0.91 (d, J = 6.5, 3H), 0.81 (d, J = 6.9, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2,) δ: 146.5, 142.6, 125.3, 123.8, 96.4, 54.3, 54.0, 51.4, 35.0, 29.4, 28.3, 23.8, 22.1, 21.3, 19.5; IR (neat, cm-1): 2945, 1594, 1470, 1293, 1117, 1018, 951, 769, 743, 644; HRMS (APCI/ASAP+, m/z): found 500.0823 (calcd. $C_{15}H_{23}NOCl_2Au$, 500.0822 [M+H]$^+$). X-ray: CCDC ID 1828155.

General method for cyclopropanation and in situ cis-to-trans isomerization

The propargyl ester **1** (5 mg, 1 equiv.) and vinyl derivative **2** (4 equiv.) was dissolved in *d*-DCM (0.6 mL) and added the gold-catalyst (1 or 5 mol%) dissolved in *d*-DCM. The reaction progress was monitored by ^{1}H NMR every 2 min for the first 20 minutes, and then at 30 minutes, 1 h, 2 h, 3 h, 5 h, 8 h, 24 h. The results are presented in Table 1.

General method B for preparation of cis-isomers

The propargyl ester (1 equiv.) and the vinyl derivative (4 equiv.) was dissolved in DCM before JohnPhos Au(MeCN)SbF6 (0.05 equiv.) dissolved in DCM was added. The reaction mixture was stirred at r.t. for 5-60 min, before the reaction was quenched with triethylamine. The solvent was removed in vacuum, before the crude oil was purified directly by silica-gel column chromatography to give *cis* isomer below in 64-98% yield. Samples of >99% pure *cis* isomer were further prepared by flash chromatography for *cis*-to-*trans* isomerization studies.

***Cis-(Z)*-2-(4-methoxyphenyl)-1-(2-phenylcyclopropyl)vinyl pivalate (3a).** Compound **3a** was prepared as described in Method B above, starting with propargyl ester **1a** (28 mg, 0.114 mmol), styrene **2a** (51 mg, 0.490 mmol) and JohnPhos Au(MeCN)SbF_6 (5 mg, 0.006 mmol). The crude oil was purified by silica-gel column chromatography (*n*-pentane:EtOAc, 10:1, R_f = 0.11), affording 26 mg (64%, 0.073 mmol, 96:4 *cis*:*trans*-ratio) of **3a** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.23-7.15 (m, 5H), 7.05 (d, J = 8.9, 2H), 6.73 (d, J = 8.9, 2H), 5.91 (s, 1H), 3.75 (s, 3H), 2.38-2.28 (m, 2H), 1.38-1-32 (m, 1H), 1.30-1.25 (m, 1H), 1.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.0, 158.4, 145.5, 138.4, 129.7 (2C), 128.2 (2C), 127.8 (2C), 126.9, 126.0, 118.4, 113.4 (2C), 55.2, 38.8, 27.0 (3C), 23.6, 23.0, 11.3; IR (neat, cm^{-1}): 2968, 2836, 1737, 1606, 1509, 1247, 1120, 1030, 825, 698; HRMS (ASAP+, m/z): found 350.1878 (calcd. $C_{23}H_{26}O_3$, 350.1882 [M$^+$+]).

Cis-(Z)-2-(4-methoxyphenyl)-1-(2-(4-methoxyphenyl)cyclopropyl)vinyl pivalate (3b). Compound **3b** was prepared as described in Method B above, starting with propargyl ester **1a** (27 mg, 0.110 mmol), 1-methoxy-4-vinylbenzene **2b** (66 mg, 0.489 mmol) and JohnPhos Au(MeCN)SbF_6 (4 mg, 0.006 mmol). The crude oil was purified by silica-gel column chromatography (*n*-pentane:EtOAc, 10:1, R_f = 0.14). This gave the 33 mg (79%, 0.087 mmol, 98:2 *cis*:*trans*-ratio) of **3b** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.11 (d, J = 8.7, 2H), 7.06 (d, J = 8.8, 2H), 6.78 (d, J = 8.8, 2H), 6.74 (d, J = 8.9, 2H), 5.88 (s, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 2.27 (d, J = 6.2, 1H), 2.25 (d, J = 6.4, 1H), 1.34-1.28 (m, 1H), 1.19 (q, J = 6.2,5.6, 1H), 1.12 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.1, 158.4, 158.0, 145.7, 130.3, 129.7 (2C), 129.3 (2C), 127.0, 118.1, 113.4 (2C), 113.3 (2C), 55.3, 55.2, 38.9, 27.1 (3C), 23.1, 22.4, 11.1; IR (neat, cm^{-1}): 3334, 2947, 2899, 1396, 1181, 1144, 1118, 999, 800; HRMS (ASAP+, m/z): found 380.1988 (calcd. $C_{24}H_{28}O_4$, 380.1983 [M$^+$+]).

***Cis- (Z)*-2-(4-methoxyphenyl)-1-(2-(4-(trifluoromethyl)phenyl)cyclopropyl)vinyl pivalate (3c).** Compound **3c** was prepared as described in Method B above, starting with propargyl ester **1a** (28 mg, 0.106 mmol), 1-(trifluoromethyl)-4-vinylbenzene **2c** (54 mg, 0.406 mmol) and JohnPhos Au(MeCN)SbF_6 (3 mg, 0.004 mmol). The crude oil was purified by silica-gel column chromatography (*n*-pentane:EtOAc, 10:1, R_f = 0.14). This gave the 32 mg (72%, 0.076 mmol, 98:2 *cis*:*trans*-ratio) of **3c** as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.51 (d, J = 8.2, 2H), 7.31 (d, J = 8.2, 2H), 7.08 (d, J = 8.8, 2H), 6.78 (d, J = 8.8, 2H), 5.98 (s, 1H), 3.79 (s, 3H), 2.50-2.46 (m, 1H), 2.38-2.34 (m, 1H), 1.48-1.44 (m, 1H), 1.34 (q, J=6.1,5.9, 1H), 1.10 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 175.9, 158.7, 144.7, 143.0, 129.7 (2C), 128.3 (2C), 128.2 (q, J = 32.3), 126.5, 124.6 (q, J=3.5, 2C), 124.4 (q, J = 271.3), 119.0, 113.6 (2C), 55.2, 38.8, 27.0 (3C), 24.3, 22.8, 12.1; IR (neat, cm^{-1}): 2975, 1742, 1512, 1327,

1252, 1123, 844; HRMS (ASAP+, m/z): found 418.1756 (calcd. $C_{24}H_{25}O_3F_3$, 418.1750 [M⁺+]).

***Cis-(Z)*-2-(4-methoxyphenyl)-1-(2-phenylcyclopropyl)vinyl acetate (3d).** Compound **3d** was prepared as described in Method B above, starting with propargyl ester **1b** (30 mg, 0.147 mmol), styrene **2a** (61 mg, 0.588 mmol) and JohnPhos Au(MeCN)SbF_6 (6 mg, 0.008 mmol). The crude oil was purified by silica-gel column chromatography (*n*-pentane:EtOAc, 10:1, R_f = 0.15). This gave the 36 mg (79%, 0.117 mmol, 90:10 *cis:trans*-ratio) of **3d** as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.24-7.19 (m, 4H), 7.17-7.15 (m, 1H), 7.07 (d, J = 8.6, 2H), 6.75 (d, J = 8.9, 2H), 5.83 (s, 1H), 3.76 (s, 3H), 2.37-2.30 (m, 2H), 3.03 (s, 3H), 1.38-1.34 (m, 1H), 1.31-1.29 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 168.7, 158.5, 145.2, 138.2, 129.5 (2C), 128.4 (2C), 127.8 (2C), 126.9, 126.0, 117.9, 113.7 (2C), 55.2, 23.7, 23.5, 21.0, 11.0; IR (neat, cm^{-1}): 3027, 2932, 2836, 1749, 1606, 1509, 1366, 1248, 1201, 1147, 1029, 833, 699; HRMS (APCI/ASAP, m/z): found 249.1274 (calcd. $C_{18}H_{17}O$, 249.1279, [M-CH_3CO-H_2O+H].

***Cis-(Z)*-1-(2-phenylcyclopropyl)-2-(4-(trifluoromethyl)phenyl)vinyl pivalate (3f).** Compound **3f** was prepared as described in Method B above, starting with propargyl ester **1c** (19 mg, 0.07 mmol), styrene **2a** (29 mg, 0.28 mmol) and JohnPhos gold-catalyst (3 mg, 0.004 mmol). The crude product purified by silica-gel column chromatography (10:1, *n*-pentan:EtOAc, R_f = 0.14). This gave 3.8 mg (14 %, 0.01 mmol) of pure *cis*-**3f**. ^{1}H NMR (CD_2Cl_2, 600 MHz): δ = 7.45-7.17 (m, 9H), 5.95 (s, 1H), 2.43-2.31 (m, 2H), 1.42-1.34 (m, 2H), 1.09 (s, 9H); ^{13}C NMR (CD_2Cl_2, 150 MHz) δ: 175.8, 148.8, 137.8, 129.9, 128.7 (q, J = 32.2), 128.5, (2C), 128.3 (2C), 127.8 (2C), 126.8, 124.9 (q, J = 3.7, 2C), 123.7 (q, J = 272.3), 117.5, 38.9, 26.9 (3C), 23.4 (2C), 11.0; IR (neat, cm^{-1}): 2927, 2930, 1744, 1324, 1122, 1067, 699; HRMS (APCI/ASAP, m/z): found 389.1721 (calcd. $C_{23}H_{24}O_2F_3$, 389.1728, [M+H]⁺).

***Cis-(Z)*-1-(2-(1,3-dioxoisoindolin-2-yl)cyclopropyl)-2-(4-methoxyphenyl)vinyl pivalate (4a).** Compound **4a** was prepared as described in Method B above, starting with propargyl ester **1a** (21 mg, 0.085 mmol), N-Vinylphthalimide **2'a** (48 mg, 0.277 mmol) and JohnPhos Au(MeCN)SbF_6 (5 mg, 0.006 mmol). The crude oil was purified by silica-gel column chromatography (*n*-pentane:EtOAc, 10:1, R_f = 0.06). This gave the 33 mg (92%, 0.079 mmol, 99:1 *cis:trans*-ratio) of **4a** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.80 (dd, J = 5.5,3.1, 2H), 7.67 (dd, J = 5.4,3.0, 2H), 7.05 (ap. d, J = 8.9, 2H), 6.68 (ap. d, J = 8.9, 2H), 6.02 (s, 1H), 3.72 (s, 3H), 3.07-3.03 (m, 1H), 2.26-2.22 (m, 1H), 2.12-2.07 (m, 1H), 1.52-1.46 (m, 1H), 1.18 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.0, 168.8 (2C), 158.5, 143.2, 134.0 (2C), 131.7 (2C), 129.6 (2C), 126.6, 123.1 (2C), 118.1, 113.4 (2C), 55.1, 39.0, 28.4, 27.1 (3C), 21.2, 8.3 ; IR (neat, cm^{-1}): 2972, 1716, 1512, 1395, 1250, 1119, 723; HRMS (APCI/ASAP, m/z): found 419.1719 (calcd. $C_{25}H_{25}NO_5$, 419.1733, [M⁺+].

***Cis-2-methyl-1-(2-phenylcyclopropyl)prop-1-en-1-yl acetate* (5).**[4q] Compound **5** was prepared as described in Method B above, starting with propargyl ester **1c** (27 mg, 0.085 mmol), styrene **2a** (75 mg, 0.716 mmol) and JohnPhos Au(MeCN)SbF_6 (8.7 mg, 0.011 mmol). The crude oil was purified by silica-gel column chromatography (*n*-pentane:EtOAc, 10:1, R_f = 0.35). This gave 21 mg (41%, 0.091 mmol, 95:5 *cis:trans*-ratio) of **5** as a colorless oil. The spectroscopic data corresponds with that reported previously.[4q]

General method C for preparation of trans-isomers.

The propargyl ester (1 equiv.) and the vinyl derivative (4 equiv.) was dissolved in DCM before BOX-Au(III)-X (0.05 equiv.) dissolved in DCM was added. The reaction mixture was stirred at r.t. for 15 min - 23 h, before the solvent was removed in vacuum. The crude oil was purified directly by silica-gel column chromatography.

***Trans-(Z)*-2-(4-methoxyphenyl)-1-(2-phenylcyclopropyl)vinyl pivalate (3a).** Compound **3a** was prepared as described in Method C above, starting with propargyl ester 1a (25 mg, 0.101 mmol), styrene 2a (54 mg, 0.522 mmol) and BOX-*i*-Pr-Au(III)SbF_6 (3 mg, 0.004 mmol). The crude oil was purified by silica-gel column chromatography (*n*-pentane:EtOAc, 10:1, Rf = 0.13). This gave the 27 mg (76%, 0.077 mmol, 1:99 cis:trans-ratio) of 3a as a colorless oil. ^{1}H NMR (400 MHz, CDCl3) δ: 7.29-7.25 (m, 4H), 7.17 (dt, J = 7.4,1.2, 1H), 7.12-7.10 (m, 2H), 6.83-6.80 (m, 2H), 6.07 (s, 1H), 3.79 (s, 3H), 2.22 (m, 1H), 1.99-1.94 (m, 1H), 1.32-1.20 (m, 2H), 1.26 (s, 9H); ^{13}C NMR (100 MHz, CDCl3) δ: 175.9, 158.5, 147.4, 141.6, 129.6 (2C), 128.4 (2C), 127.0, 126.1 (2C), 125.9, 115.2, 113.6 (2C), 55.2, 39.1, 27.2 (3C), 26.7, 24.0, 14.5; IR (neat, cm-1): 2968, 2836, 1737, 1606, 1509, 1247, 1120, 1030, 825, 698; HRMS (ASAP+, m/z): found 350.1875 (calcd. C23H26O3, 350.1882, [M•]+).

***Trans*-(Z)-2-(4-methoxyphenyl)-1-(2-phenylcyclopropyl)vinyl acetate (3d).** Compound **3d** was prepared as described in Method C above, starting with propargyl ester **1b** (20 mg, 0.098 mmol), styrene **2a** (41 mg, 0.392 mmol) and BOX-Ph-Au(III)BF_4 (4 mg, 0.005 mmol). The crude oil was purified by silica-gel column chromatography (*n*-pentane:EtOAc, 10:1, R_f = 0.21). This gave the 19 mg (63%, 0.062 mmol, 6:94 *cis:trans*-ratio) of **3d** as a colorless oil.^{1}H NMR (CD_2Cl_2, 600 MHz) δ: 7.22 (d, J = 8.6, 2H) , 7.17 (d, J = 7.8, 2H), 7.09-7.06 (m, 1H) , 7.03 (ap. d, J = 7.9, 2H), 6.75 (d, J = 7.1 Hz, 2H) , 5.93 (s, 1H) , 3.70 (s, 3H), 2.13-2.10 (m, 1H), 2.09 (s, 3H), 1.85-1.82 (m, 1H), 1.26-1.23 (m, 1H), 1.18-1.14 (m, 1H); ^{13}C NMR (CD_2Cl_2, 150 MHz) δ: 168.4, 158.7, 147.3, 141.7, 129.2 (2C), 128.3 (2C), 127.0 (2C), 125.9 (2C), 114.3, 113.9 (2C), 55.1, 26.8, 24.1, 20.9, 14.5; IR (neat, cm^{-1}): 3028, 2933, 2836, 1749, 1606, 1509, 1366, 1248, 1201, 1147, 1029, 833, 699. HRMS (APCI/ASAP, m/z): found 249.1275 (calcd. $C_{18}H_{17}O$, 350.1882, [M-CH_3CO-H_2O+H]).

***Trans-(Z)*-1-(2-phenylcyclopropyl)-2-(4-(trifluoromethyl)phenyl)vinyl pivalate (3f).** Compound **3f** was prepared as described in Method C above, starting with propargyl ester **1d** (20 mg, 0.070 mmol), styrene **2a** (29 mg, 0.281 mmol) and BOX-Ph-Au(III)Tf_2N (3 mg, 0.004 mmol). The product was purified by silica-gel column chromatography (10:1, *n*-pentane:EtOAc, R_f = 0.15), which gave 22 mg (98 %, 0.075 mmol, 15:85 *cis:trans*-ratio) of product **3f**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.56 (d, J = 8.3, 2H), 7.45 (d, J = 8.3, 2H), 7.18-7.14 (m, 3H), 7.03-7.00 (m, 2H), 6.25 (s, 1H), 2.54-2.42 (m, 2H), 1.40-1.36 (m, 1H), 1.18 (s, 9H), 1.16-

1.12 (m, 1H); ^{13}C NMR (CD_2Cl_2, 150 MHz): δ: 176.7, 149.0, 137.7, 129.1, 128.9 (2C), 128.6 (q, J = 32.3), 127.8 (2C), 127.7 (2C), 126.0, 124.9 (q, J = 3.3, 2C), 124.3 (q, J = 272.0), 120.4, 38.9, 27.0 (3C), 25.0, 22.0, 12.3; IR (neat, cm^{-1}): 2927, 2930, 1744, 1324, 1122, 1067, 699; HRMS (APCI/ASAP, m/z): found 389.1723 (calcd. $C_{23}H_{24}O_2F_3$, 389.1728, [M+H]$^+$).

***Trans-(Z)*-1-(2-((N,4-dimethylphenyl)sulfonamido)cyclopropyl)-2-(4-methoxyphenyl)vinyl pivalate (4b).** Compound **4b** was prepared as described in Method C above starting with propargyl ester **1a** (23 mg, 0.093 mmol), N,4-dimethyl-N-vinylbenzenesulfonamide **2'b** (66 mg, 0.312 mmol) and BOX-*i*-Pr-Au(III)SbF_6 (2.5 mg, 0.003 mmol). The reaction was stirred for 5 min before the solvent was removed *in vacuum*. The crude oil was purified by silica-gel column chromatography (*n*-pentane:EtOAc, 10:1, R_f = 0.09). This gave the 38 mg (75%, 0.083 mmol, <1:>99 *cis*:*trans*-ratio) of **4b** as a colorless oil. ^{1}H NMR (400 MHz, CD_2Cl_2) δ: 7.44 (d, J = 8.3, 2H), 7.17 (d, J = 7.8, 2H), 6.90 (ap. d, J = 8.5, 2H), 6.77 (ap. d, J = 8.7, 2H), 5.42 (q, J = 4.3,2.8, 1H), 4.59 (dt, J = 8.7,5.5, 1H), 3.89-3.87 (m, 1H), 3.79 (s, 3H), 2.88 (2, 3H), 2.54 (ddt, J = 16.7,5.4,2.5, 1H), 2.39 (s, 3H), 2.17 (ddt, J = 16.7,5.4,2.2, 1H), 1.53 (s, 9H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ: 175.7, 158.8, 150.4, 143.1, 136.6, 131.7, 129.5 (2C), 129.0 (2C), 126.9 (2C), 113.8 (2C), 112.0, 63.8, 55.2, 51.3, 38.6, 30.7, 29.0, 26.4 (3C), 21.2 ; IR (neat, cm^{-1}): 2973, 2936, 1746, 1512, 1341, 1247, 1180, 1157, 1116; HRMS (ASAP+, m/z): found 457.1924 (calcd. $C_{25}H_{31}NO_5S$ 457.1923 [M$^+$]).

Minor amounts of pure *trans* **3b** and *trans* **3c** were purified by flash chromatography (*n*-pentane:EtOAc, 10:1) from diastereomeric mixtures for NMR and HRMS characterization:

***Trans-(Z)*-2-(4-methoxyphenyl)-1-(2-(4-methoxyphenyl)cyclopropyl)vinyl pivalate (3b).** ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.28 (ap. d, J = 8.9, 2H), 7.05 (ap. d, J = 8.5, 2H), 6.81 (dd, J = 7.9,1.7, 4H), 6.06 (s, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 2.17-2.12 (m, 1H), 1.91-1.81 (m, 1H), 1.26 (s, 9H), 1.24-1.22 (m, 1H), 1.18-1.13 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.9, 158.5, 158.0, 147.6, 133.5, 129.6 (2C), 127.2 (2C), 127.1, 114.9, 113.8 (2C), 113.6 (2C), 55.3, 55.2, 39.1, 27.2 (3C), 26.2, 23.3, 14.1; IR (neat, cm^{-1}): 3334, 2947, 2899, 1396, 1181, 1144, 1118, 999, 800; HRMS (ASAP+, m/z): found 380.1983 (calcd. $C_{24}H_{28}O_4$ 380.1988 [M$^+$+]).

***Trans-((Z)*-2-(4-methoxyphenyl)-1-(2-(4-(trifluoromethyl)phenyl)cyclopropyl)vinyl pivalate (3c).** ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.52 (d, J = 8.2, 2H), 7.28 (d, J = 8.6, 2H), 7.20 (d, J = 8.2, 2H), 6.82 (d, J = 8.8, 2H), 6.08 (s, 1H), 3.01 (s, 3H), 2.26-2.21 (m, 1H), 2.03-1.98 (m, 1H), 1.41-1.36 (m, 1H), 1.32-1.27 (m, 1H), 1.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.9, 158.7, 146.7, 145.9, 129.6 (2C), 128.2 (q, J = 32.9), 126.8, 126.2 (2C), 125.3 (q, J = 4.1, 2C), 124.3 (q, J = 271.3), 115.6, 113.7 (2C), 55.2, 39.1, 27.3, 27.2 (3C), 23.9, 15.0; IR (neat, cm^{-1}): 2975, 1742, 1512, 1327, 1252, 1123, 844; HRMS (ASAP+, m/z): found 418.1749 (calcd. $C_{24}H_{25}O_3F_3$ 418.1756 [M$^+$+]).

General procedure for separate cis-to-trans isomerization studies

Isolated *cis*-product (5 mg, 1 equiv.) was dissolved in *d*-DCM (0.6 mL) and added the gold-catalyst (1 or 5 mol%) dissolved in *d*-DCM. The reaction progress was monitored by ^{1}H NMR every 2 min for the first 20 minutes, and then at 30 minutes, 1 hour, 2 hours, 3 hours, 5 hours, 8 hours, 24 hours, 48 hours and 72 hours after the gold-catalyst was added. Some reactions were quenched earlier, dependent on the reactivity of the catalyst. The results are presented in Table 3.

Keywords: BOX-Au(III) catalysts; stereoselective propargyl cyclopropanation; *cis*-to-*trans* isomerization

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Entry for Table of Content

FULL PAPER

Gold(III)-catalysed *cis*-to-*trans* cyclopropyl isomerization

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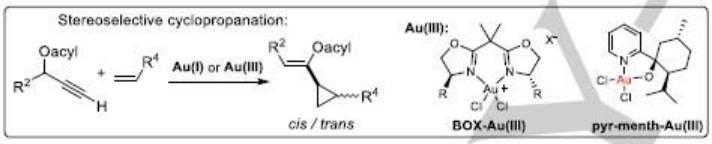

The strong ability of BOX-Au(III) catalysts for combined fast propargyl cyclopropanation and subsequent in situ *cis*-to-*trans* isomerization is reported. Au(I) or Au(III) catalysts selectively provided pure *cis* or *trans* products, respectively, and isolated *cis* isomers were shown to rapidly isomerize into *trans* products in the presence of BOX-Au(III) catalysts.

Key topic:
Au(III) catalysed cyclopropyl isomerization

Appendix B Poster

Gold-catalyzed *cis-trans* cyclopropanation

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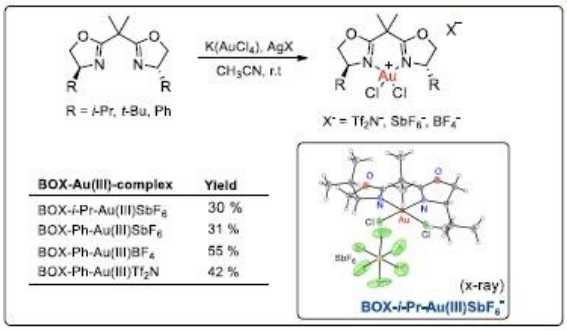
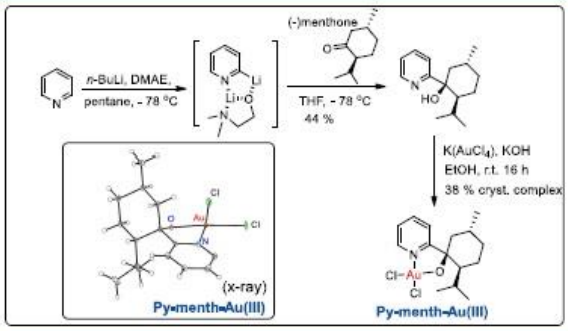
Background

- **Gold(I)** complexes have dominated the development of gold catalysts.
- **Gold(III)** complexes have got less attention in organic synthesis[1], mostly limited to unstable, ligand-free species, typically $AuCl_3$ and $K(AuCl_4)$.
- Based on our earlier studies on gold(I) catalyzed cyclopropanations[2-3], we are currently exploring the ability of novel **gold(III)** complexes to afford stereoselective *cis/trans* cyclopropanation.

Preparation of novel chiral Au(III) complexes

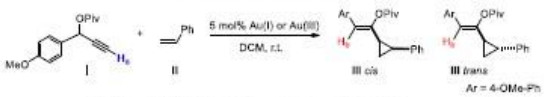


BOX-Au(III)-complex	Yield
BOX-*i*-Pr-Au(III)SbF_6	30 %
BOX-Ph-Au(III)SbF_6	31 %
BOX-Ph-Au(III)BF_4	55 %
BOX-Ph-Au(III)Tf_2N	42 %



Cyclopropanation

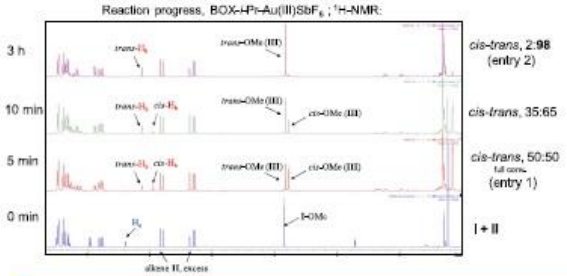
Stereoselectivity studies



Entry	Au-Catalyst [5 mol%]	Time (full conv.)	*cis/trans* ratio
1	BOX-*i*-Pr-Au(III)SbF_6	5 min	50 : 50
2		2 h	2 : **98**
3	JohnPhos Au[(MeCN)SbF_6	5 min	**98** :2
4		2 h	96 :5
5		4 d	2 : **98**

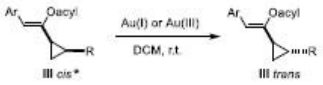
⇒ Au(III)-complexes show higher cyclopropation reactivity and *cis*-to-*trans* isomerization ability than Au(I)-complexes.

Reaction progress, BOX-*i*-Ph-Au(III)SbF_6 ; ^{1}H-NMR:



Cis-to-*trans* isomerization studies

⇒ Proper choice of Au(**I**)-catalyst and reaction conditions enable isolation of pure *cis** for further *cis*-to-*trans* isomerization studies:



Ar	acyl	R	Au-catalyst [5 mol%]	Time	*cis/trans* ratio
4-OMe-Ph	Piv	Ph	**BOX-*i*-Pr-Au(III)SbF_6**	**5 min**	**50 : 50**
				2 h	**1 : 99**
4-OMe-Ph	Piv	Ph	**BOX-*i*-Pr-Au(III)SbF_6 [1mol%]**	**5 min**	**17 : 83**
				3 h	3 : **97**
4-OMe-Ph	Piv	Ph	**BOX-Ph-Au(III)SbF_6**	**2 h**	**5 : 95**
4-OMe-Ph	Piv	Ph	**BOX-Ph-Au(III)SbF_6 [1 mol%]**	**5 h**	**6 : 94**
4-OMe-Ph	Piv	Ph	Py-menth-Au(III)	8 h	4 : 96
4-OMe-Ph	Piv	Ph	Pic-Au(III) (unstable)	5 h	4 : 96
4-OMe-Ph	Piv	Ph	JohnPhos Au(I)(MeCN)SbF_6	48 h	9 : 91
4-OMe-Ph	Piv	Ph	$AuCl_3$	24 h	35 : 65
4-CF_3-Ph	Piv	Ph	BOX-Ph-Au(III)SbF_6	10 h	97 : 3
4-OMe-Ph	Piv	4-OMe-Ph	**BOX-*i*-Pr-Au(III)SbF_6**	**5 min**	**5 : 95**
4-OMe-Ph	Piv	4-CF_3-Ph	**BOX-*i*-Pr-Au(III)SbF_6**	**3 h**	**5 : 95**
4-OMe-Ph	Ac	Ph	**BOX-*i*-Pr-Au(III)SbF_6**	**4 h**	**2 : 98**
4-OMe-Ph	Ac	Ph	**BOX-Ph-Au(III)SbF_6 [1 mol%]**	**5 h**	**5 : 95**
4-OMe-Ph	Ac	Ph	JohnPhos Au(I)(MeCN)SbF_6	24 h	4 : 96
4-OMe-Ph	Ac	Ph	$AuCl_3$	8 h	15 : 85

* Isolated according to entry 3

⇒ **BOX-Au(III) catalysts** show exceptional capacity for *cis*-to-*trans* isomerization.

Conclusion

The present study shows that:

⇒ **Application of appropriate gold(I) or gold(III) catalysts allows stereoselective *cis* or *trans* cyclopropanation (up to 99% dr);**

⇒ **Box-Au(III) catalysts show exceptional capacity for *cis*-to-*trans* isomerization (in < 5 min for e-rich vinylcyclopropanes).**

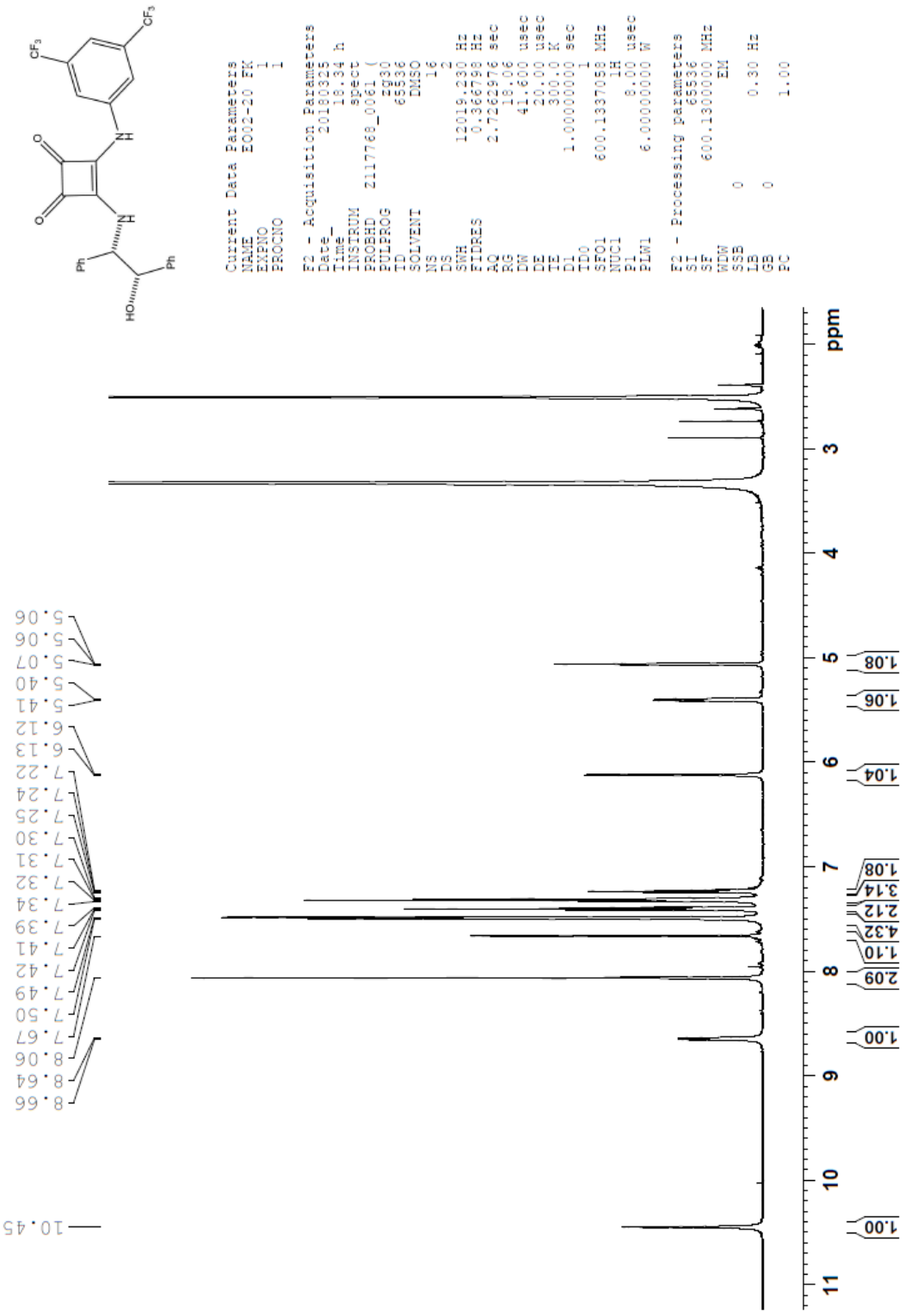
References

1. Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180-3211;
2. Sperger, C. A.; Tungen, J. E.; Fiksdahl, A. *Eur J. Org. Chem.* **2011**, 3719;
3. Sperger, C. A.; Tungen, J. E.; Fiksdahl, A. *Org. Letters* **2009**, *11*, 2449.

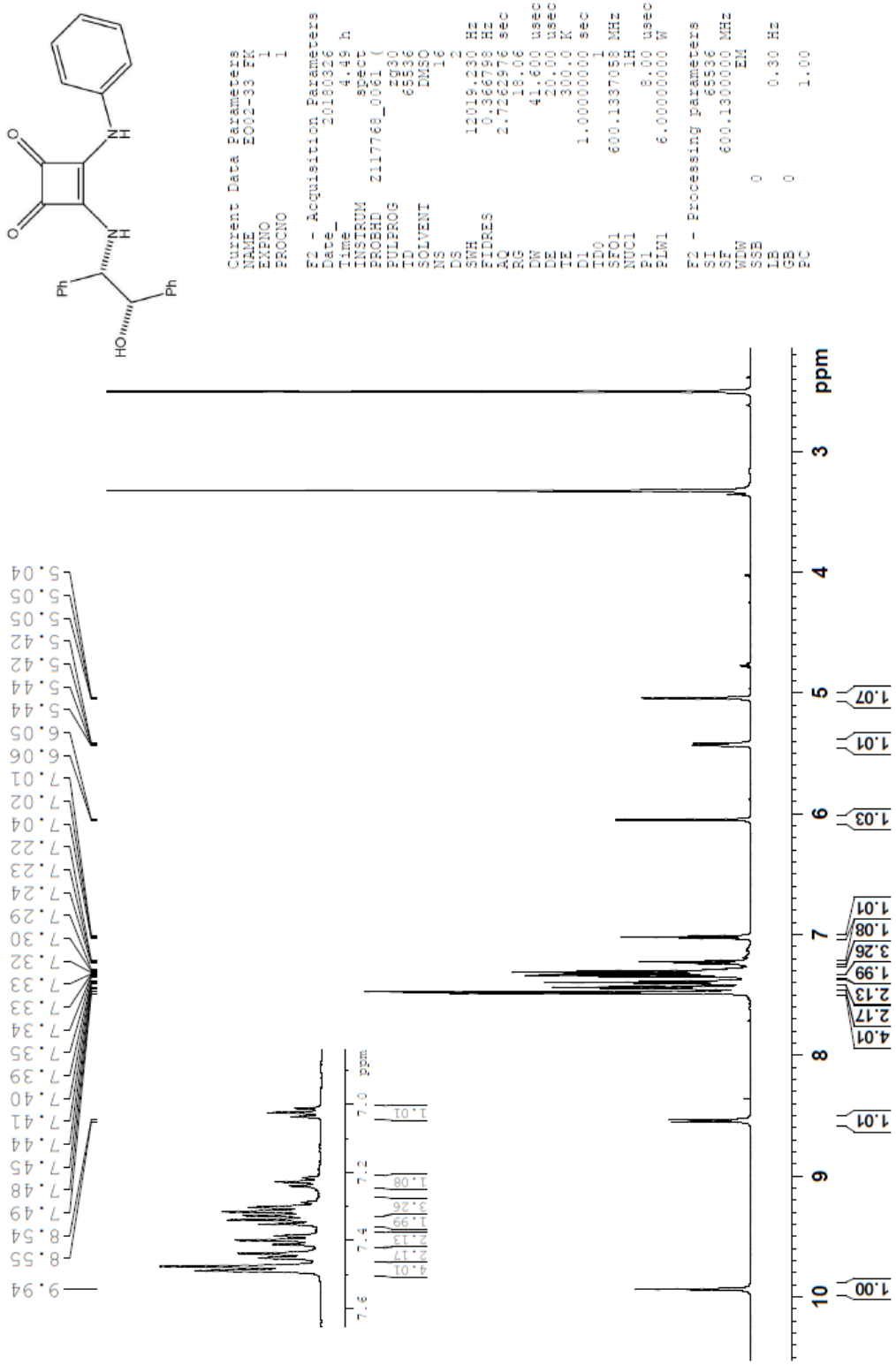
Acknowledgements

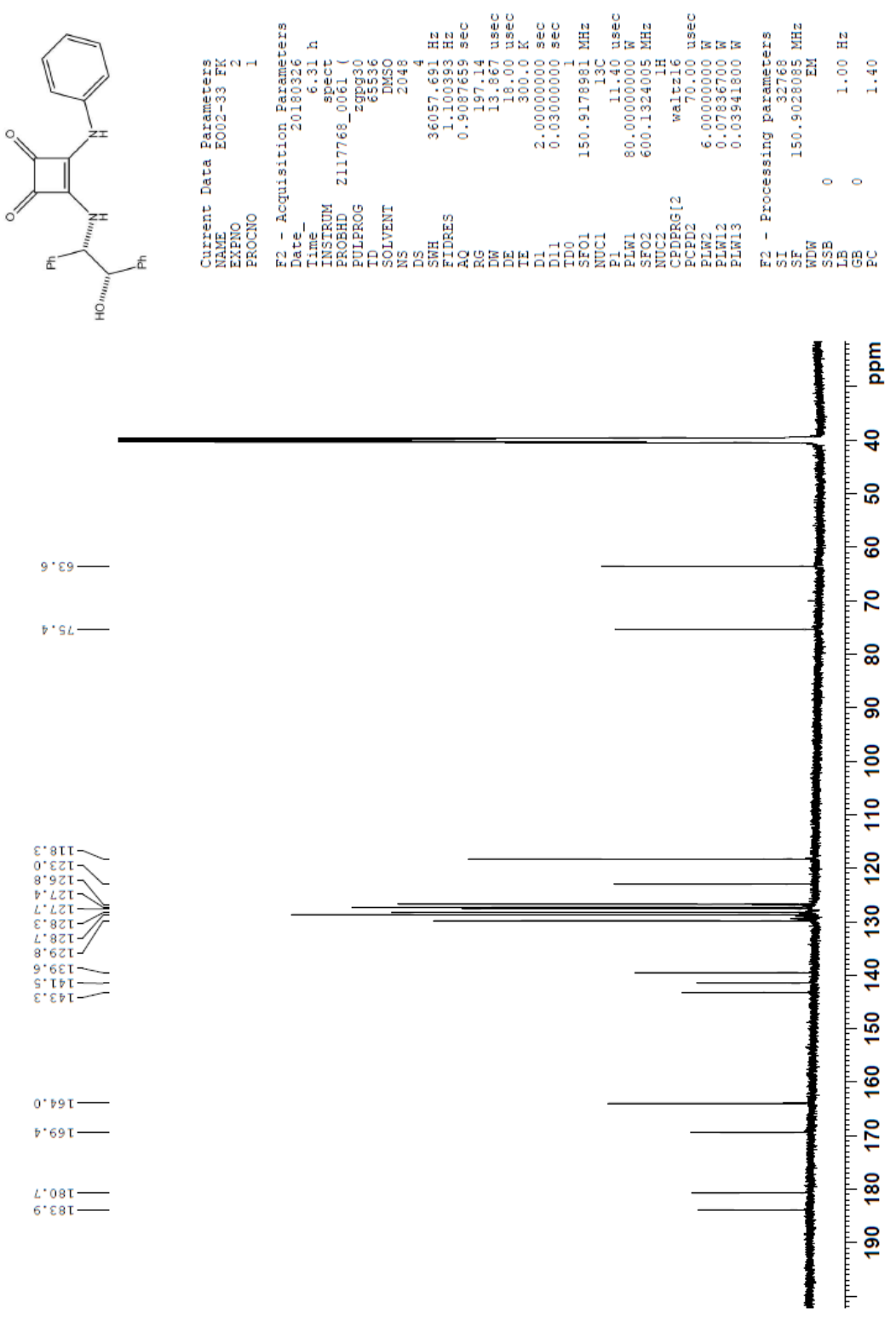
This project is supported by the Department of Chemistry, Norwegian University of Science and Technology. FOK is gratefully acknowledged for its financial support in the form of travel stipend for this conference.

Appendix C Squaramide **1**



Appendix D Squaramide **2**

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PROCNO 1
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PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 2048
DS 4
SWH 36057.691 Hz
FIDRES 1.100393 Hz
AQ 0.9087659 sec
RG 197.14
DW 13.867 usec
DE 18.00 usec
TE 300.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 150.9178981 MHz
NUC1 13C
P1 11.40 usec
PLW1 80.00000000 W
SFO2 600.1324005 MHz
NUC2 1H
CPDPRG2 waltz16
PCPD2 70.00 usec
PLW2 6.00000000 W
PLW12 0.07836700 W
PLW13 0.03941800 W
F2 - Processing parameters
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SF 150.9028085 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
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75.4
118.3
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126.8
127.4
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129.8
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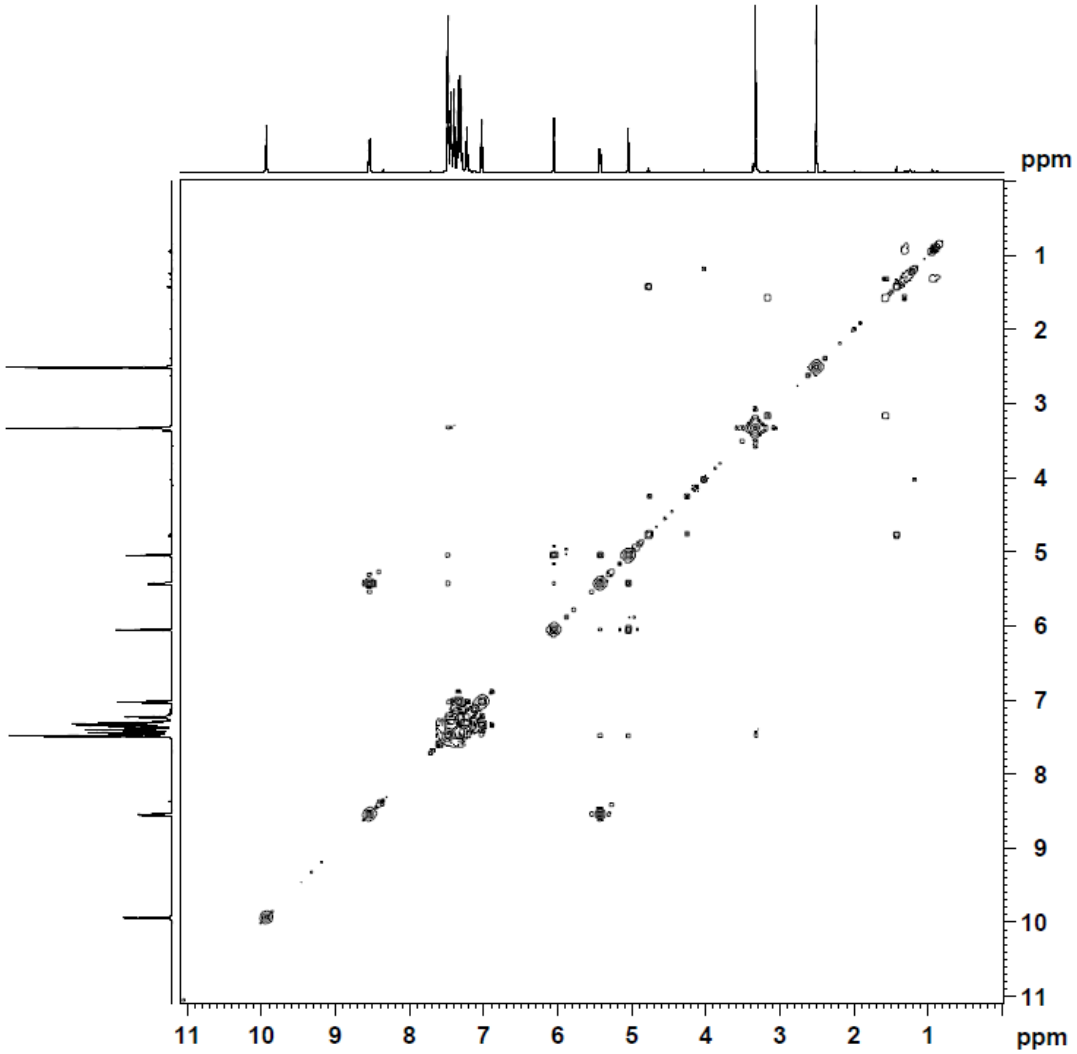
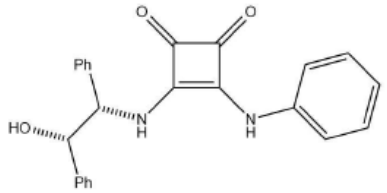
183.9
ppm

XVII



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PROCNO                        1

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PULPROG                  zg30
TD                      65536
SOLVENT                  DMSO
NS                          16
DS                           2
SWH                 12019.230 Hz
FIDRES                0.366798 Hz
AQ                    2.7262976 sec
RG                        18.06
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DE                       20.00 usec
TE                       300.0 K
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TD0                           1
SFO1               600.1337058 MHz
NUC1                         1H
P1                        8.00 usec
PLW1                6.00000000 W

F2 - Processing parameters
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LB                        0.30 Hz
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PC                        1.00
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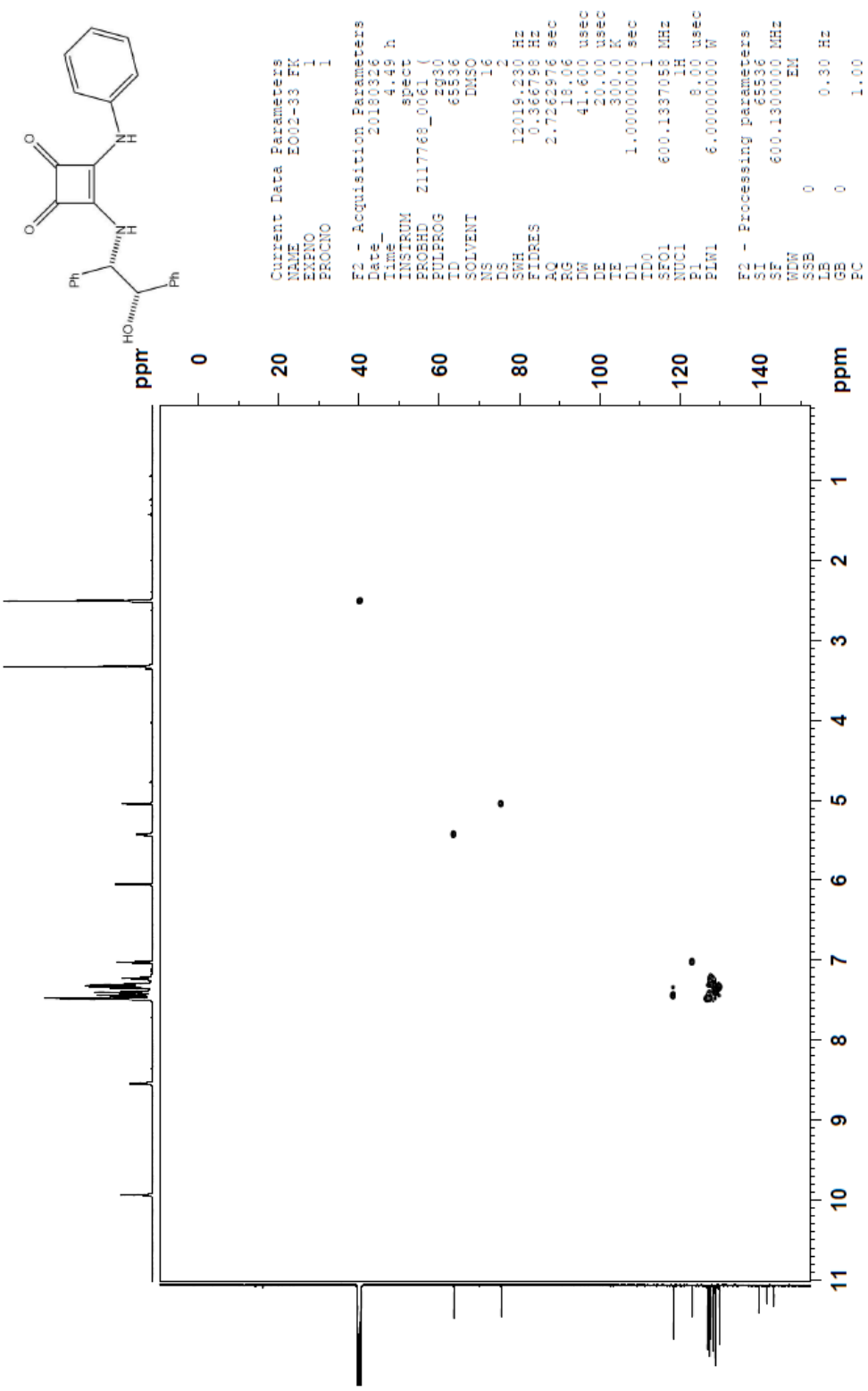
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PROCNO 1
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SOLVENT DMSO
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DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 2.7262976 sec
RG 18.06
DW 41.600 usec
DE 20.00 usec
TE 300.0 K
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PLW1 6.00000000 W
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SSB 0
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GB 0
PC 1.00
ppm
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80
100
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140
ppm
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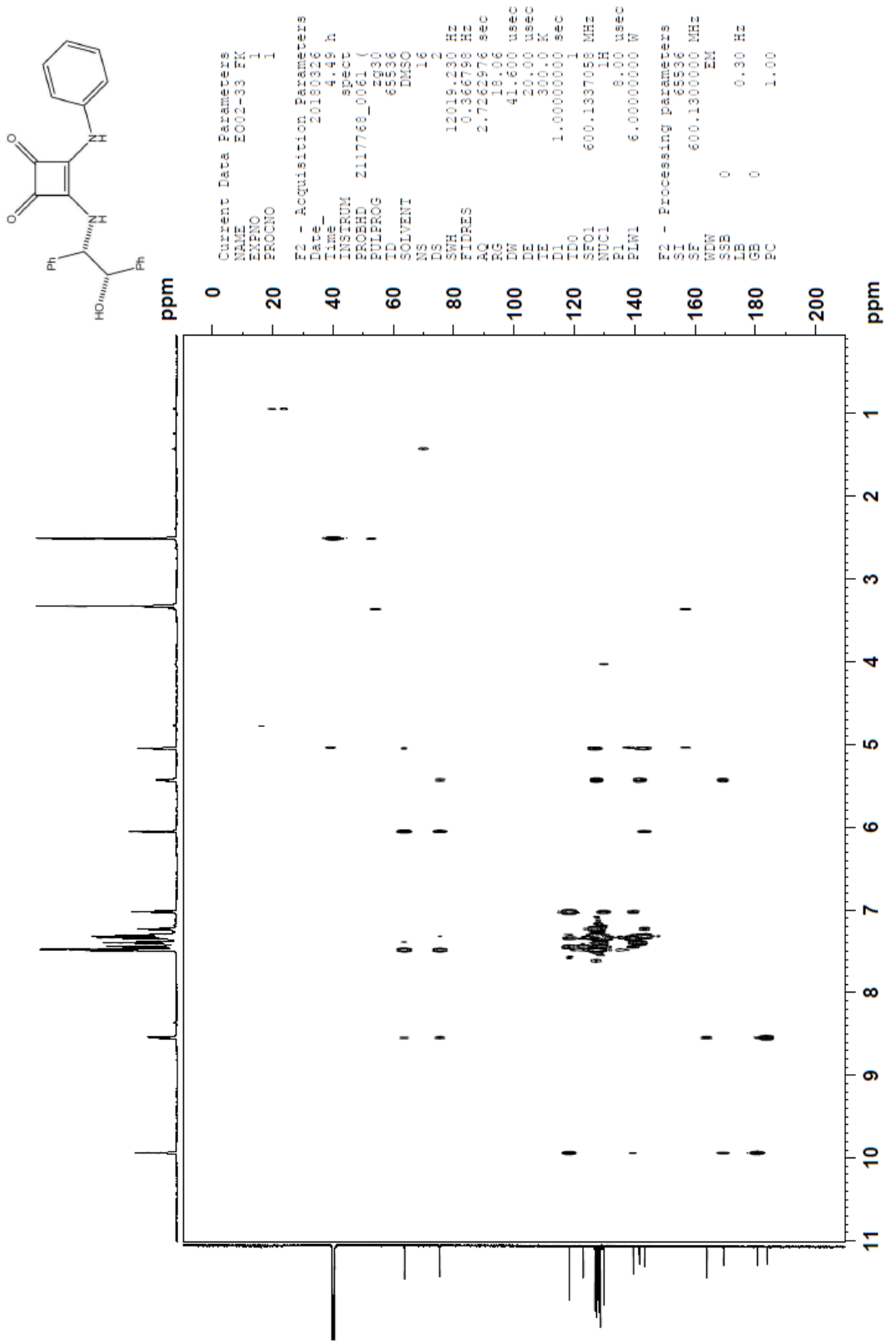
N
H
Ph
Ph
HO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TD 65536
SOLVENT DMSO
NS 16
DS 2
SWH 12019.230 Hz
FIDRES 0.367798 Hz
AQ 2.7262976 sec
RG 18.06
DW 41.600 usec
DE 20.00 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1
SFO1 600.1337058 MHz
NUC1 1H
P1 8.00 usec
PLW1 6.00000000 W
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PC 1.00
ppm
ppm

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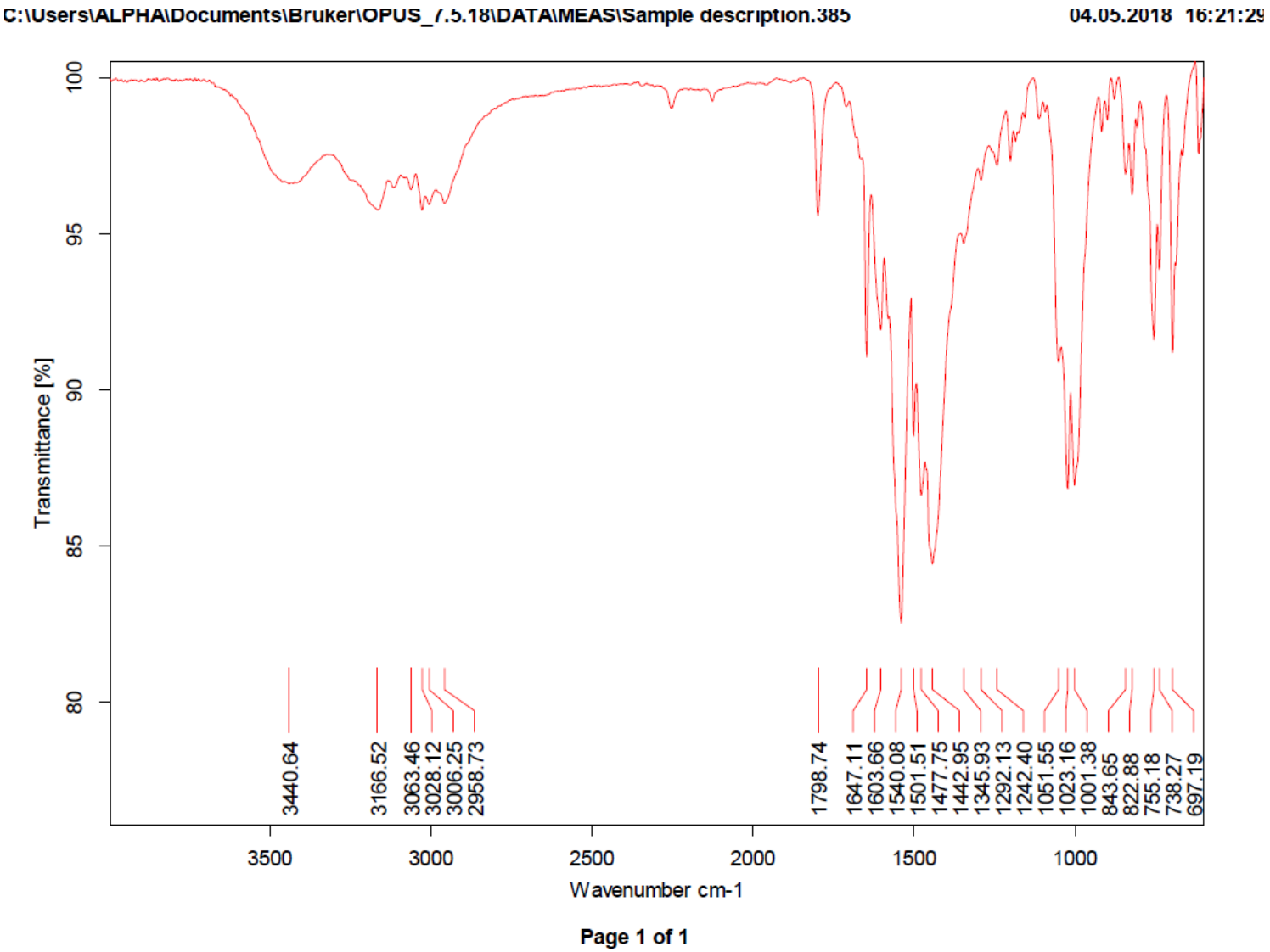
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1001.38
843.65
822.88
755.18
738.27
697.19
3500
3000
2500
2000
1500
1000
Wavenumber cm-1
Page 1 of 1

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 2.0 PPM / DBE: min = -100.0, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
5273 formula(e) evaluated with 5 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-10 O: 0-20 Na: 0-1
2018-209 214 (4.169) AM2 (Ar,35000.0,0.00,0.00); Cm (212:217)
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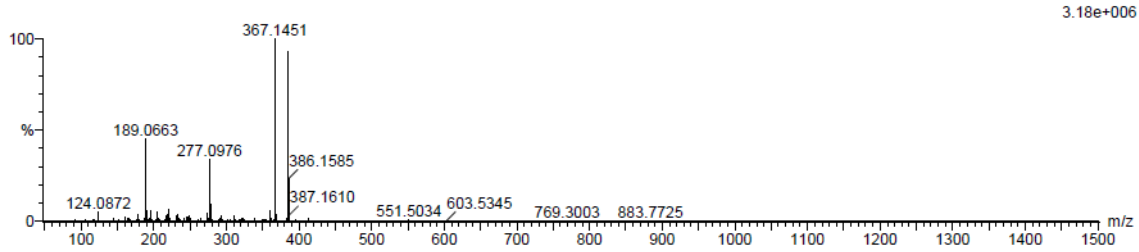

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Maximum:		5000.0	2.0	100.0				
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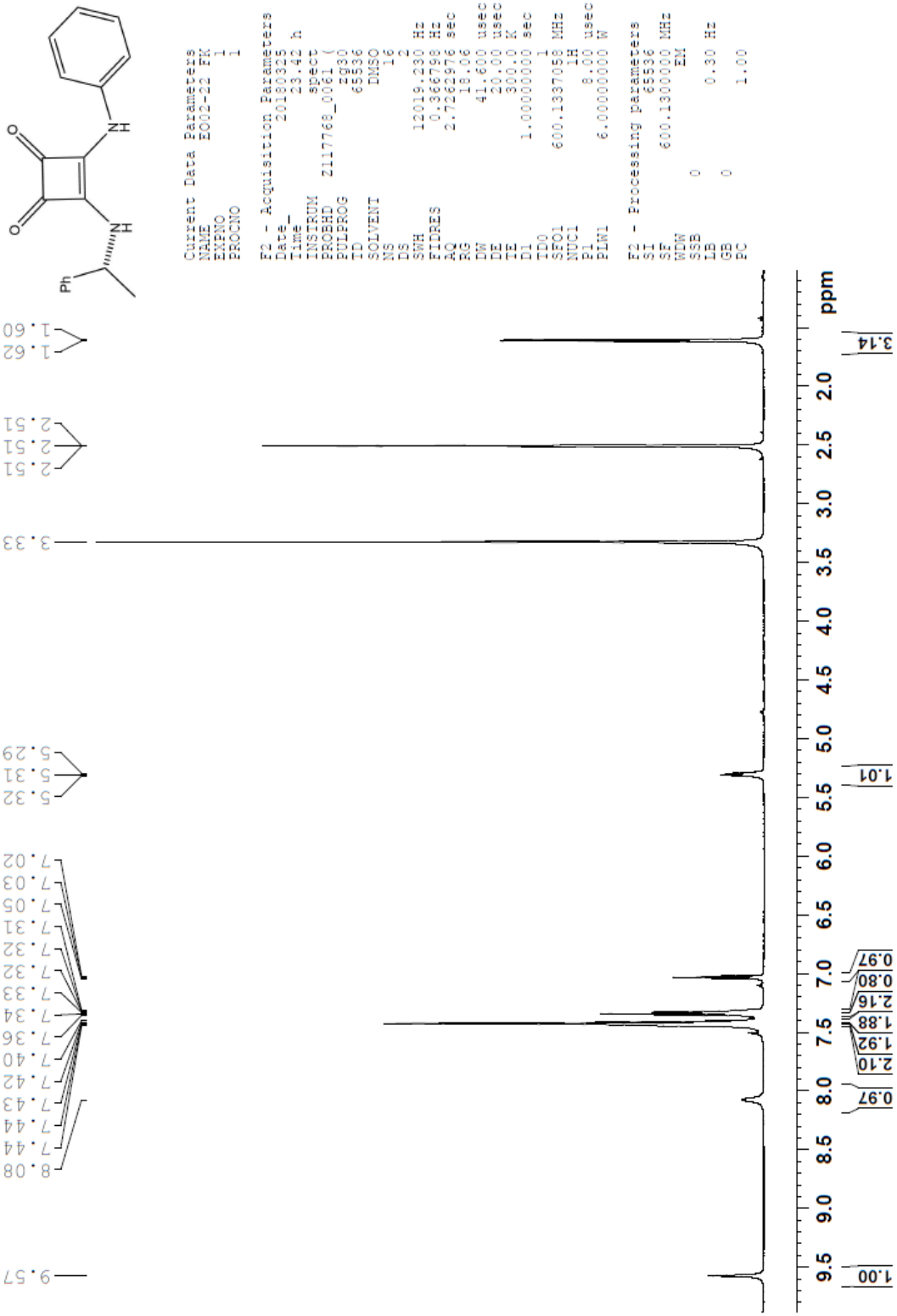
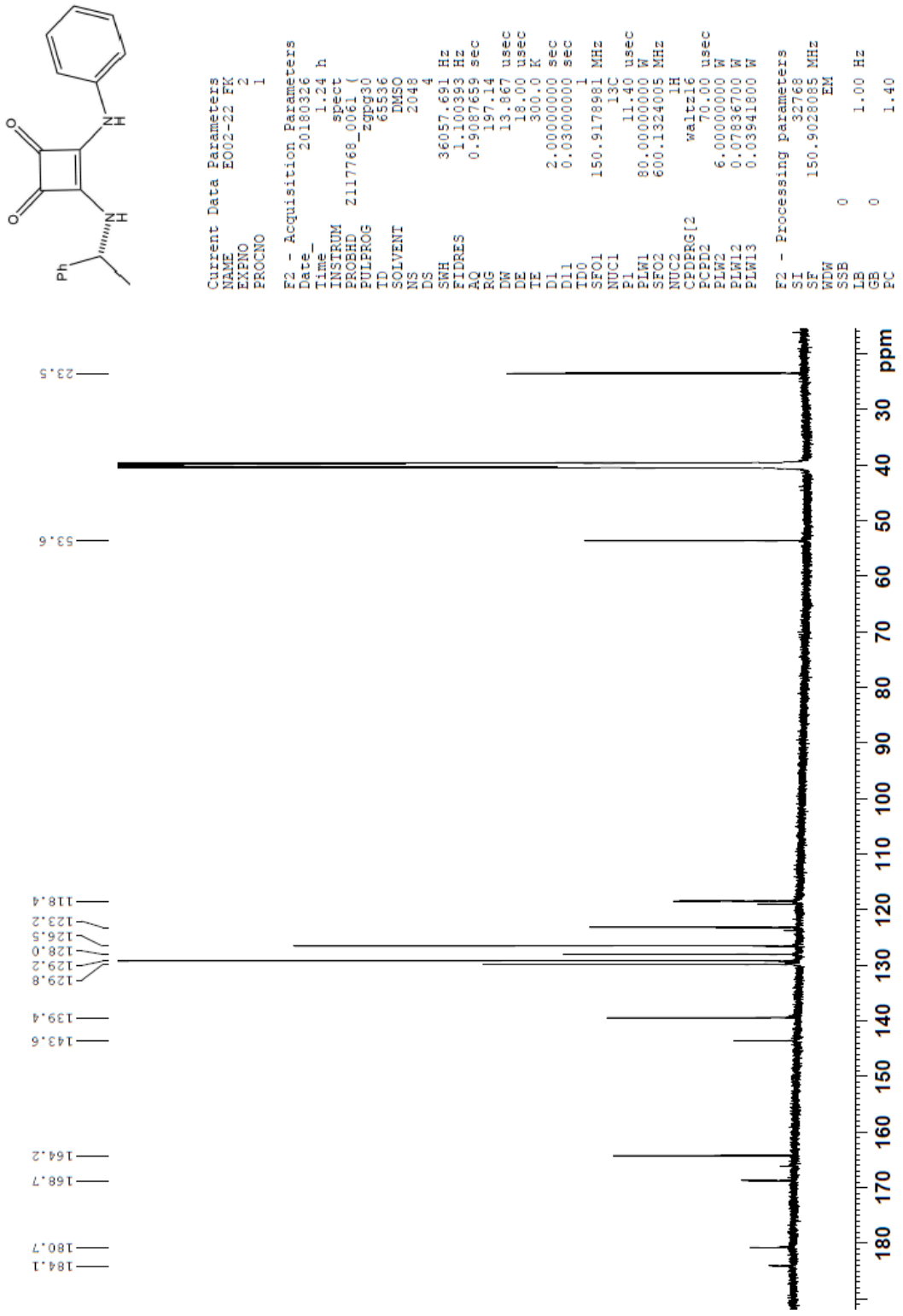
	385.1552	0.1	0.3	15.5	1235.6	0.002	99.78	C24 H21 N2 O3
	385.1557	-0.4	-1.0	-2.5	1245.0	9.424	0.01	C11 H29 O14
	385.1547	0.6	1.6	-0.5	1246.4	10.809	0.00	C10 H26 N4 O10 Na
	385.1560	-0.7	-1.8	4.5	1244.8	9.214	0.01	C11 H22 N8 O6 Na

Appendix E Squaramide **3**

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SOLVENT DMSO
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RG 197.14
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DE 18.00 usec
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D11 0.03000000 sec
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SFO1 150.9178981 MHz
NUC1 13C
P1 11.40 usec
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SFO2 600.1324005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 70.00 usec
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PLW12 0.07836700 W
PLW13 0.03941800 W
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N
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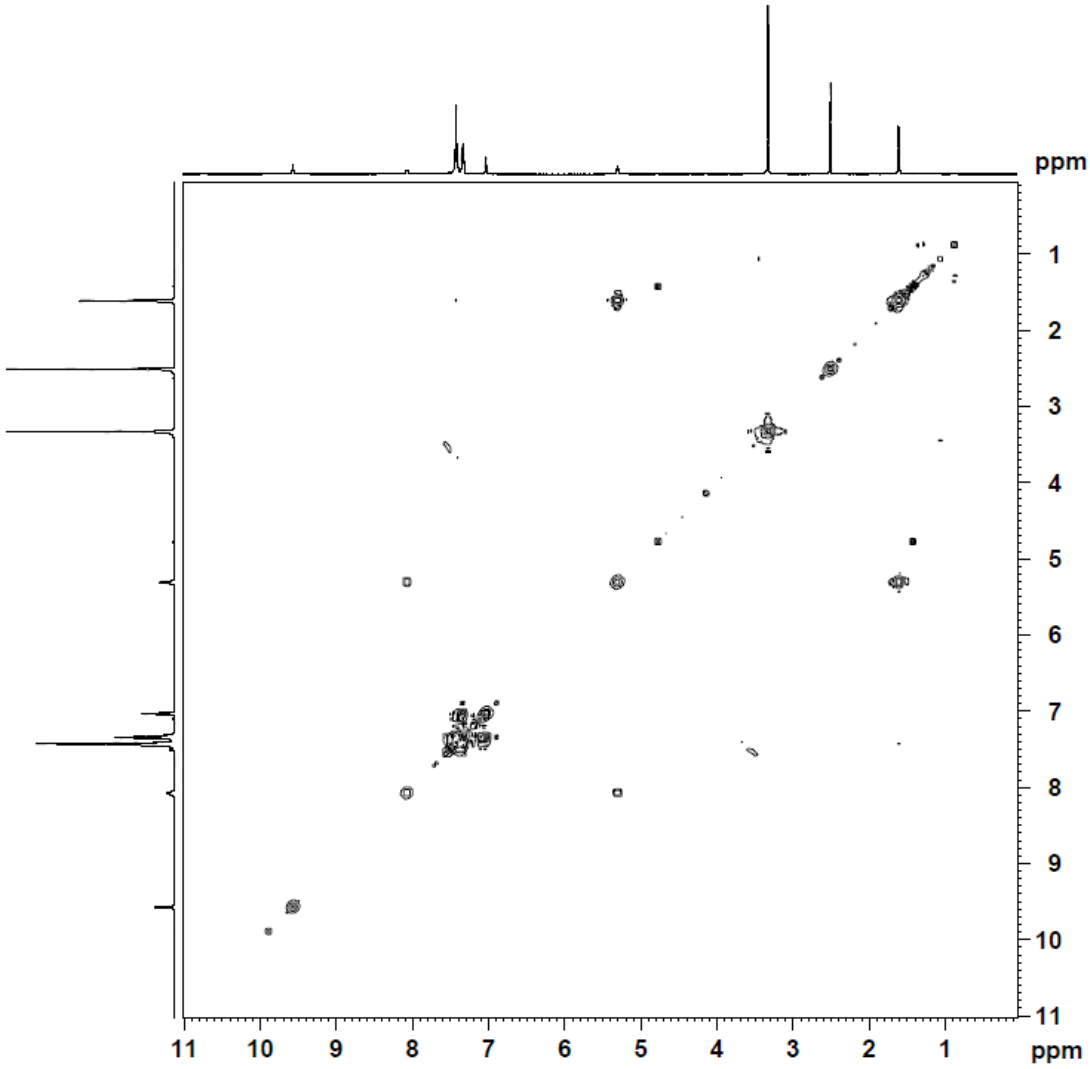

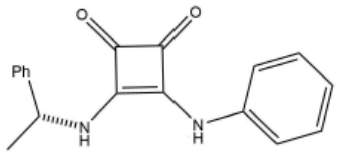


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TD                 65536
SOLVENT             DMSO
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FIDRES         0.366798 Hz
AQ            2.7262976 sec
RG                 18.06
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TE                300.0 K
D1           1.00000000 sec
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NUC1                  1H
P1                 8.00 usec
PLW1         6.00000000 W

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WDW                   EM
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LB                 0.30 Hz
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PC                 1.00
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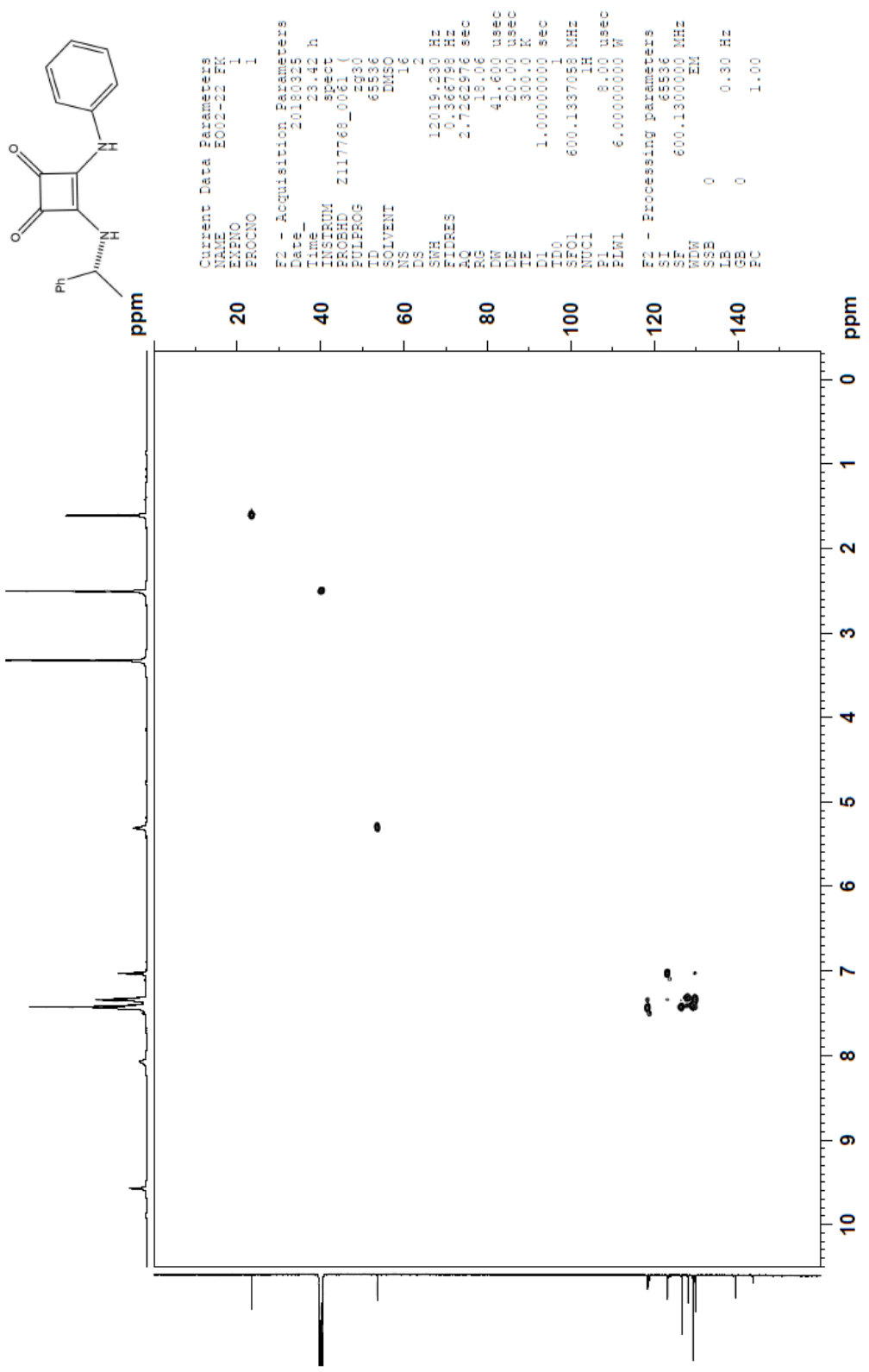
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SOLVENT DMSO
NS 16
DS 2
SWH 12019.230 Hz
FIDRES 0.183679 Hz
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RG 18.06
DW 41.600 usec
DE 20.00 usec
TE 300.0 K
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D0 0.00003000 sec
SFO1 600.1337058 MHz
NUC1 1H
P1 8.00 usec
PLW1 6.00000000 W
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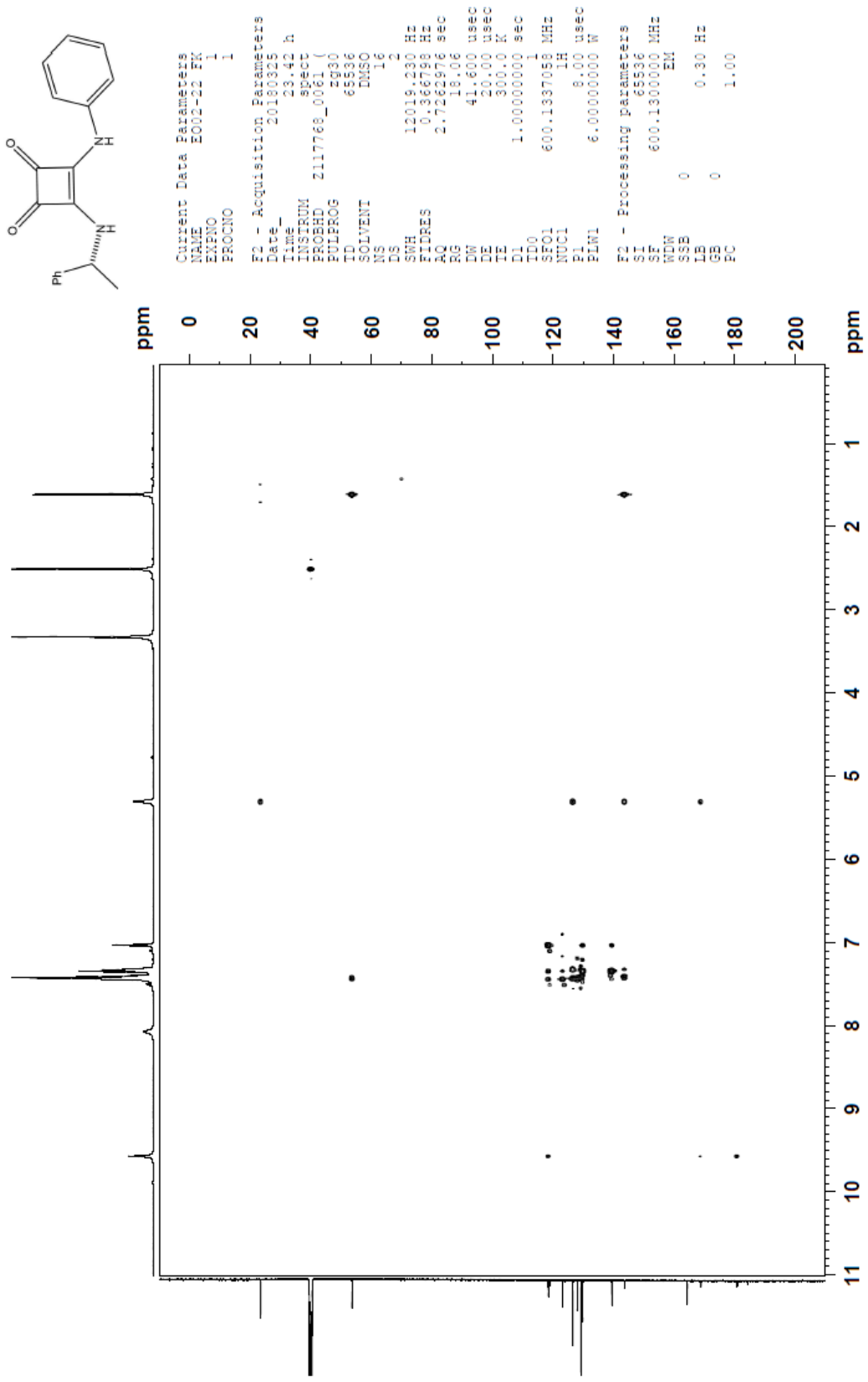
Ph
ppm
ppm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EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
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PULPROG zg30
TD 65536
SOLVENT DMSO
NS 16
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 2.7262976 sec
RG 18.06
DW 41.600 usec
DE 20.00 usec
TE 300.0 K
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TD0 1
SFO1 600.1337058 MHz
NUC1 1H
P1 8.00 usec
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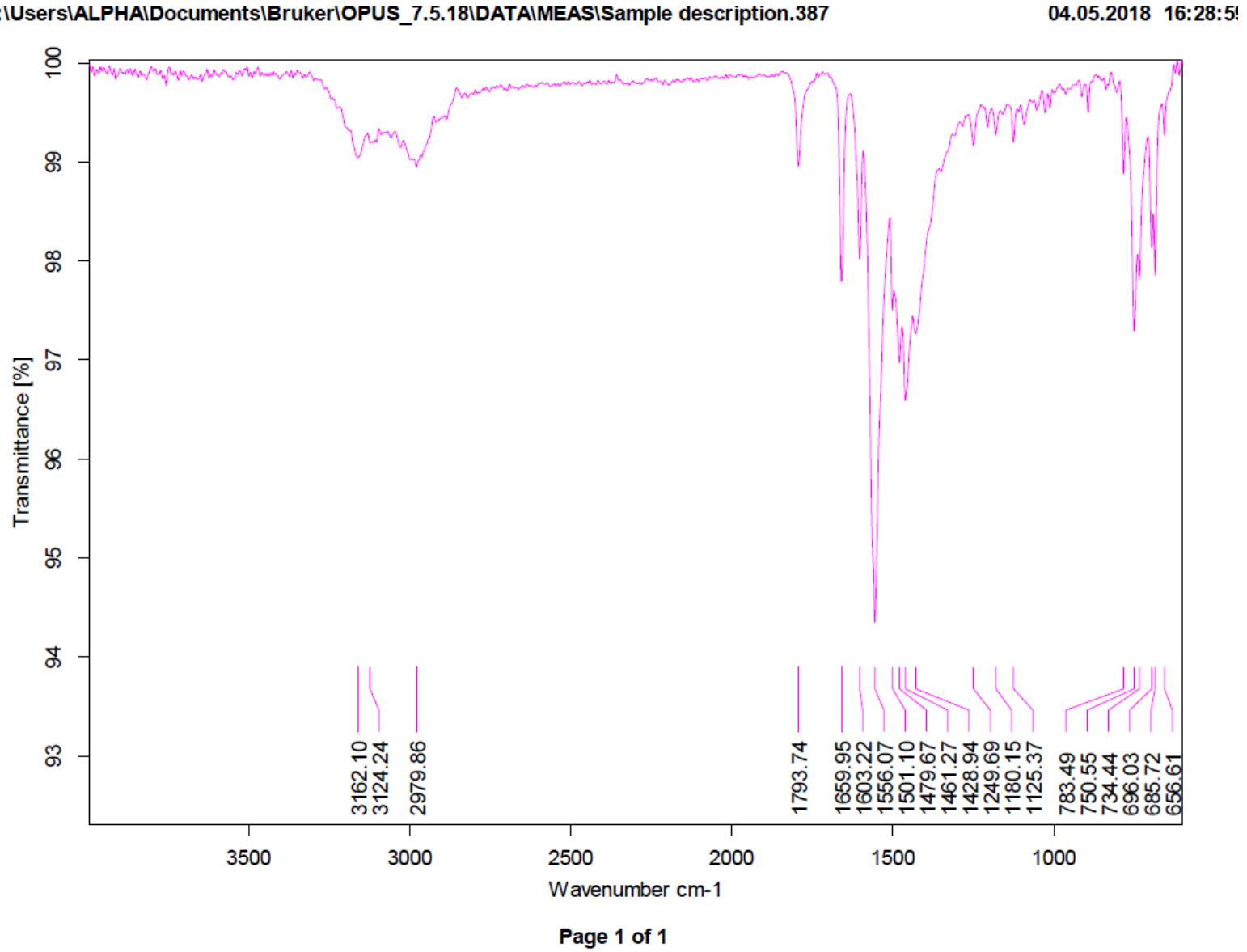
PC 1.00
ppm
ppm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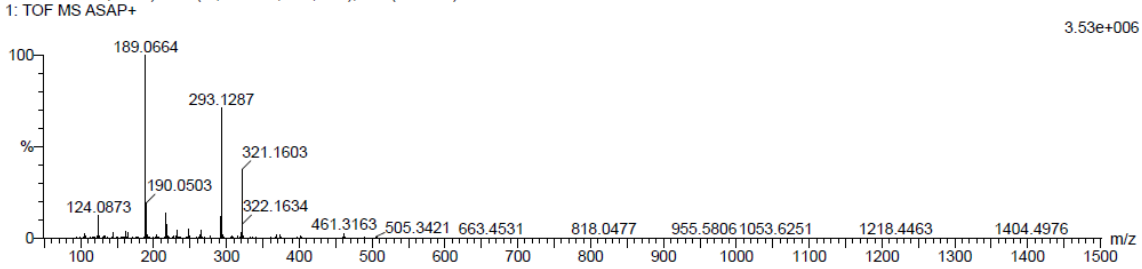
1501.10
1479.67
1461.27
1428.94
1249.69
1180.15
1125.37
783.49
750.55
734.44
696.03
685.72
656.61
3500
3000
2500
2000
1500
1000
Wavenumber cm-1
Page 1 of 1

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 2.0 PPM / DBE: min = -100.0, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
2983 formula(e) evaluated with 3 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-10 O: 0-20 Na: 0-1
2018-208 168 (3.273) AM2 (Ar,35000.0,0.00,0.00); Cm (165:170)
1: TOF MS ASAP+



Minimum:				-100.0				
Maximum:		5000.0	2.0	100.0				
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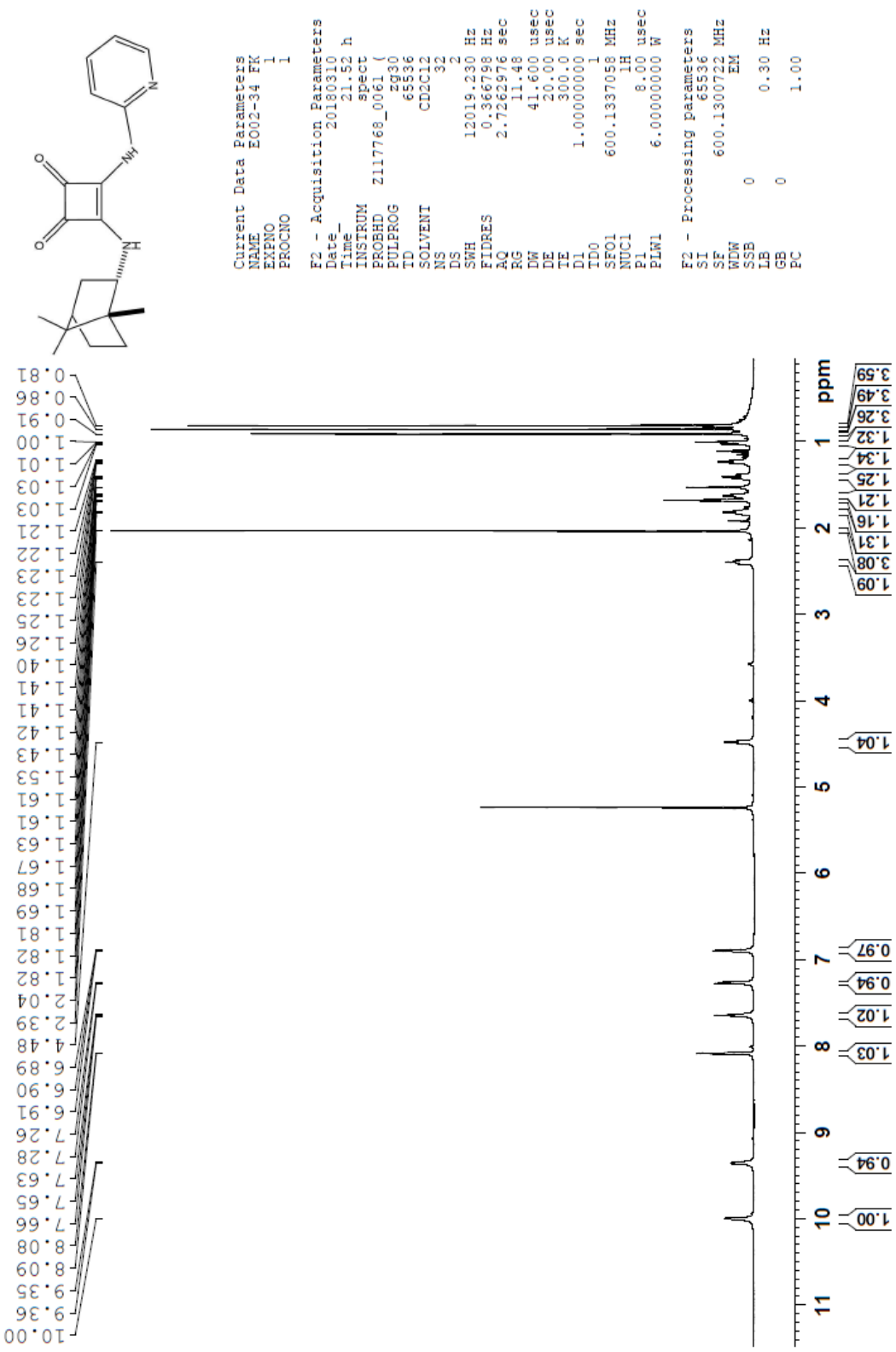
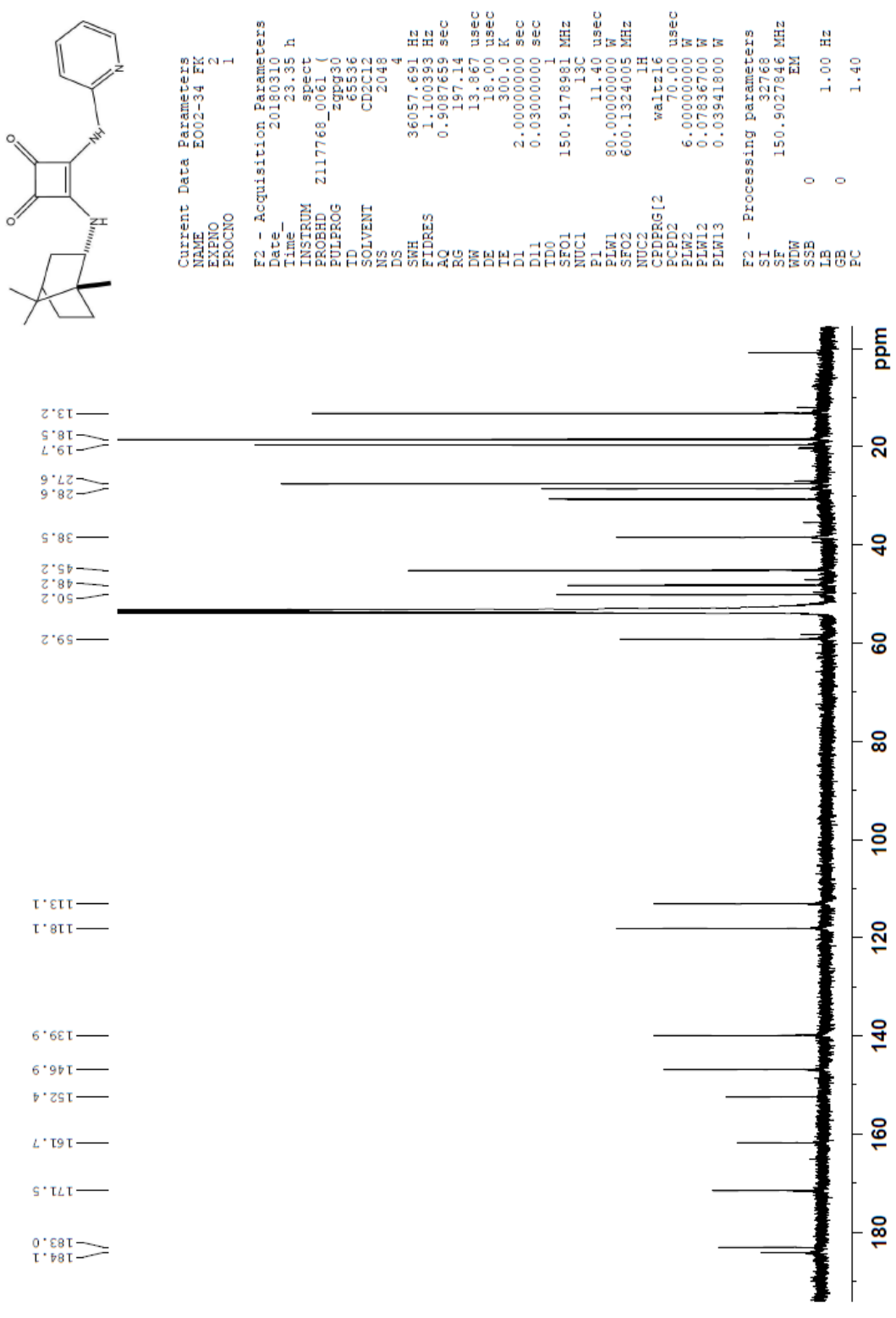
	293.1284	0.3	1.0	-4.5	1506.1	12.588	0.00	C4 H22 N4 O9 Na
	293.1282	0.5	1.7	-0.5	1509.2	15.605	0.00	C2 H17 N10 O7

Appendix F Squaramide **4**

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NS 2048
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FIDRES 1.100393 Hz
AQ 0.9087659 sec
RG 197.14
DW 13.867 usec
DE 18.00 usec
TE 300.0 K
D1 2.00000000 sec
D11 0.03000000 sec
ID0 1
SFO1 150.9178981 MHz
NUC1 13C
P1 11.40 usec
PLW1 80.00000000 W
SFO2 600.1324005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 70.00 usec
PLW2 6.00000000 W
PLW12 0.07836700 W
PLW13 0.03941800 W
F2 - Processing parameters
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LB 1.00 Hz
GB 0
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146.9
152.4
161.7
171.5
183.0
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ppm
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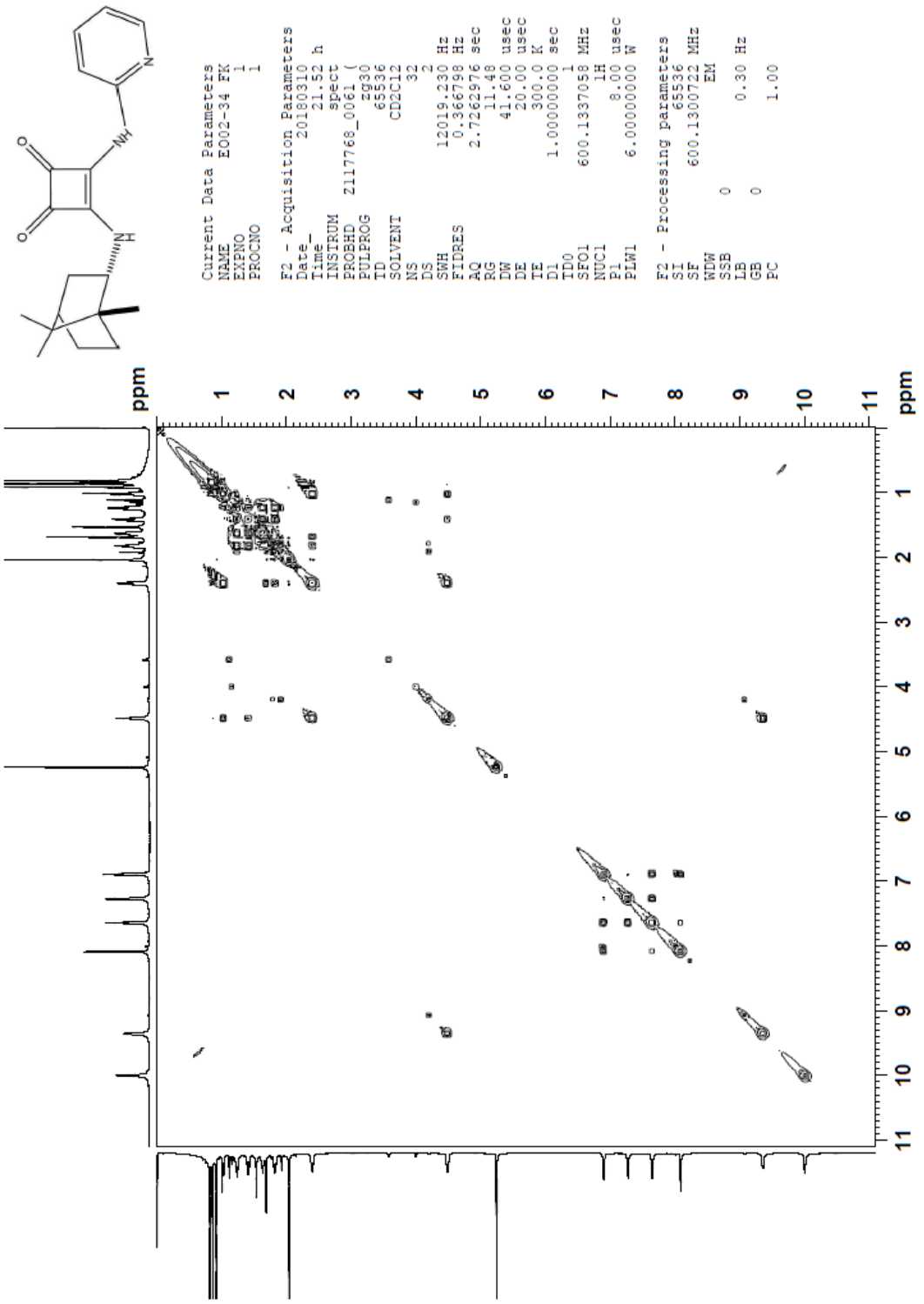
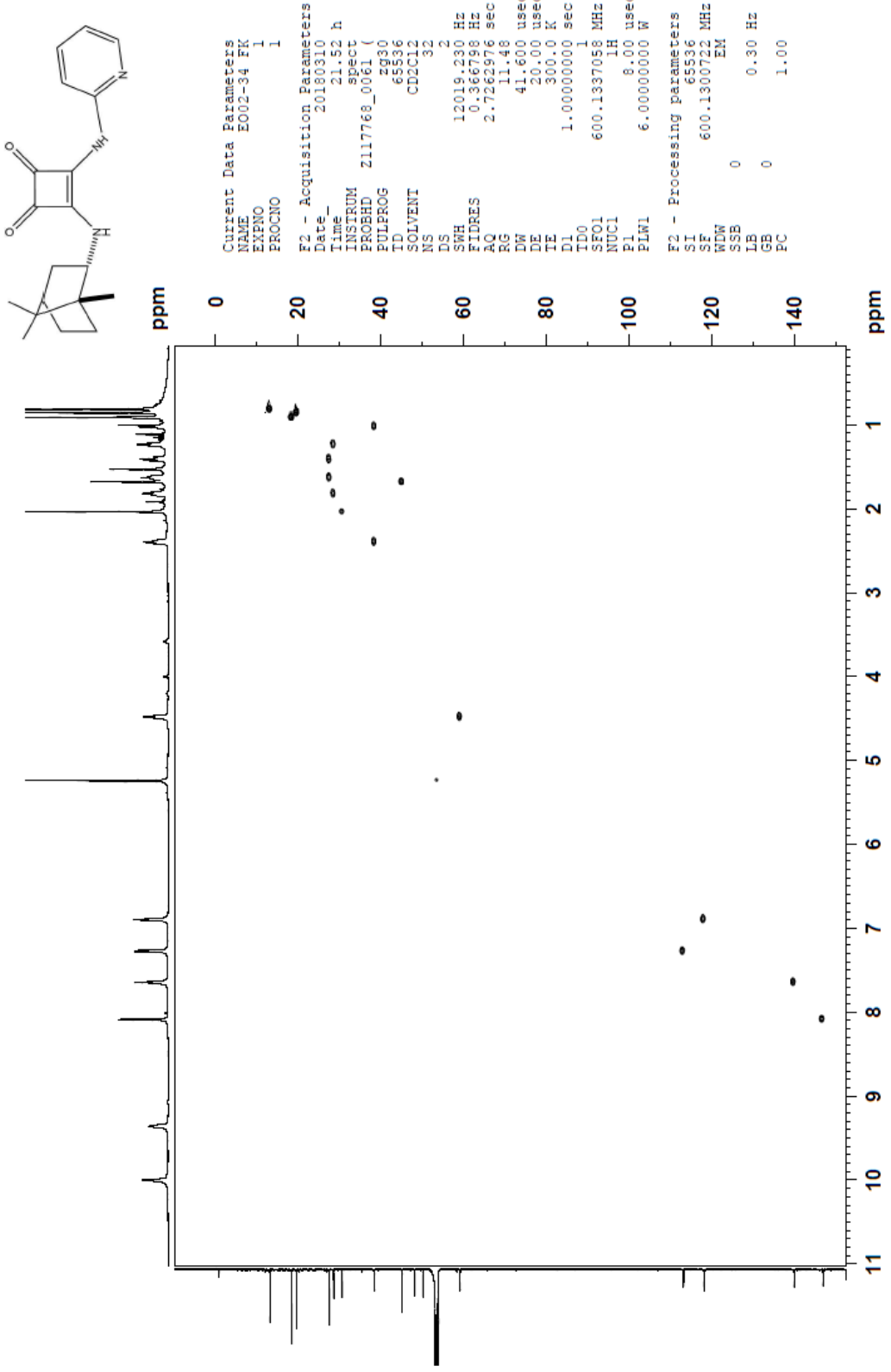
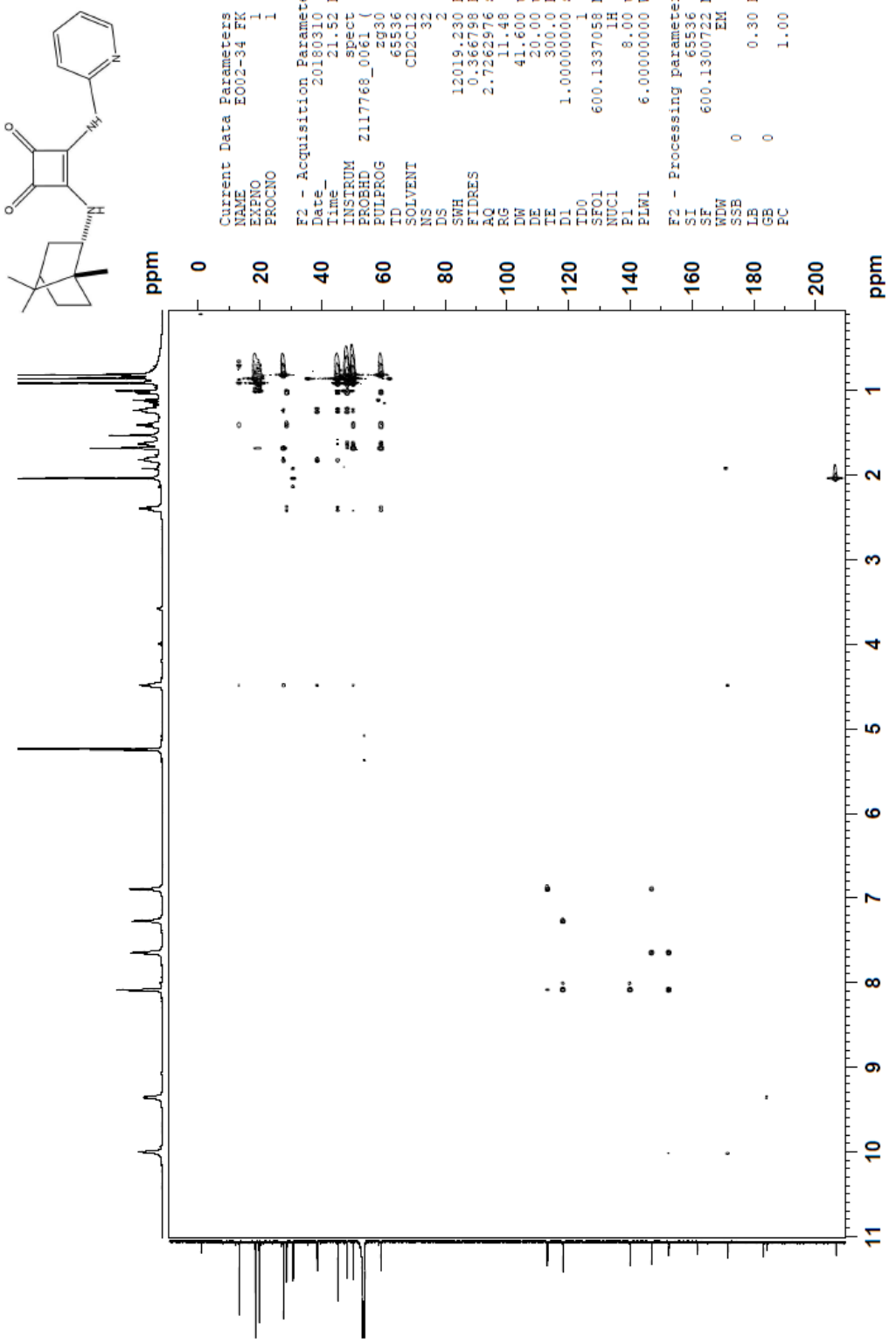
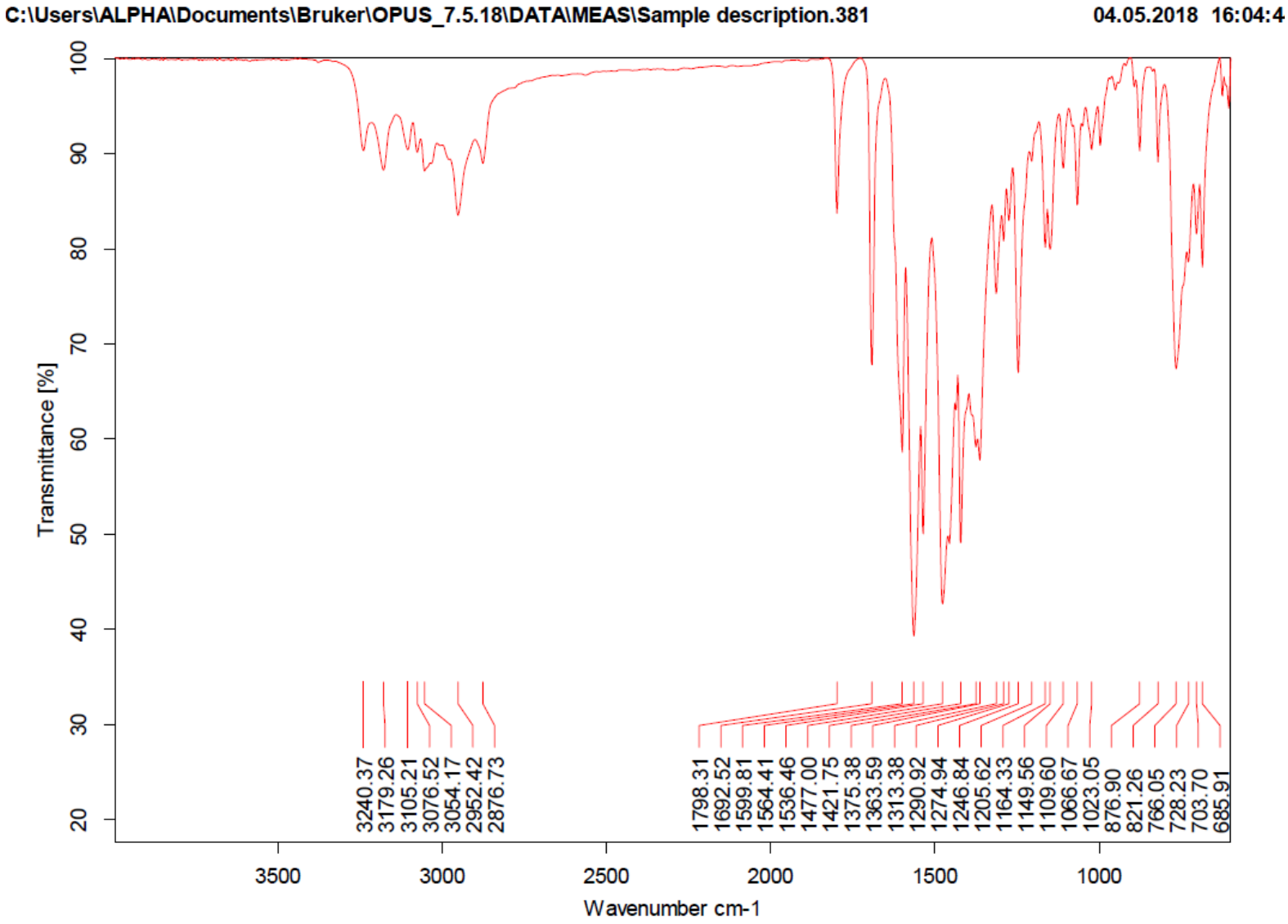
40
60
80
100
120
140
160
180


Current Data Parameters
NAME EO02-34 FK
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20180310
Time_ 21.52 h
INSTRUM spect
PROBHD Z117768_0061 (
PULPROG zg30
TD 65536
SOLVENT CD2C12
NS 32
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 2.7262976 sec
RG 11.48
DW 41.600 usec
DE 20.00 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1
SFO1 600.13370058 MHz
NUC1 1H
P1 8.00 usec
PLW1 6.00000000 W
F2 - Processing parameters
SI 65536
SF 600.13007722 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
ppm
ppm


Current Data Parameters
NAME EO02-34 FK
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20180310
Time 21.52 h
INSTRUM spect
PROBHD Z117768_0061 (
PULPROG zg30
TD 65536
SOLVENT CD2Cl2
NS 32
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 2.7262976 sec
RG 11.48
DW 41.600 usec
DE 20.00 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1
SFO1 600.1337058 MHz
NUC1 1H
P1 8.00 usec
PLW1 6.00000000 W
F2 - Processing parameters
SI 65536
SF 600.1300722 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
ppm
0
20
40
60
80
100
120
140
ppm
1
2
3
4
5
6
7
8
9
10
11


Current Data Parameters
NAME E002-34 FK
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20180310
Time 21.52 h
INSTRUM spect
PROBHD Z117768_0061 (
PULPROG zg30
TD 65536
SOLVENT CD2Cl2
NS 32
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 2.7262976 sec
RG 11.48
DW 41.600 usec
DE 20.00 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1
SFO1 600.1337058 MHz
NUC1 1H
P1 8.00 usec
PLW1 6.00000000 W
F2 - Processing parameters
SI 65536
SF 600.1300722 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
ppm
ppm


C:\Users\ALPHA\Documents\Bruker\OPUS_7.5.18\DATA\MEAS\Sample description.381
04.05.2018 16:04:4
Transmittance [%]
100
90
80
70
60
50
40
30
20
3500
3000
2500
2000
1500
1000
Wavenumber cm-1
3240.37
3179.26
3105.21
3076.52
3054.17
2952.42
2876.73
1798.31
1692.52
1599.81
1564.41
1536.46
1477.00
1421.75
1375.38
1363.59
1313.38
1290.92
1274.94
1246.84
1205.62
1164.33
1149.56
1109.60
1066.67
1023.05
876.90
821.26
766.05
728.23
703.70
685.91
Page 1 of 1

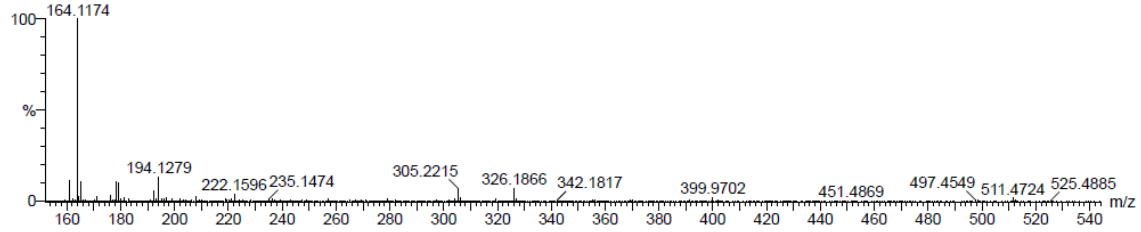
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 2.0 PPM / DBE: min = -100.0, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
2688 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-10 O: 0-20 I: 0-1

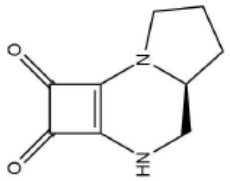
2018-203 59 (1.173) AM2 (Ar,35000.0,0.00,0.00); Cm (57:59)
1: TOF MS ASAP+

6.08e+004

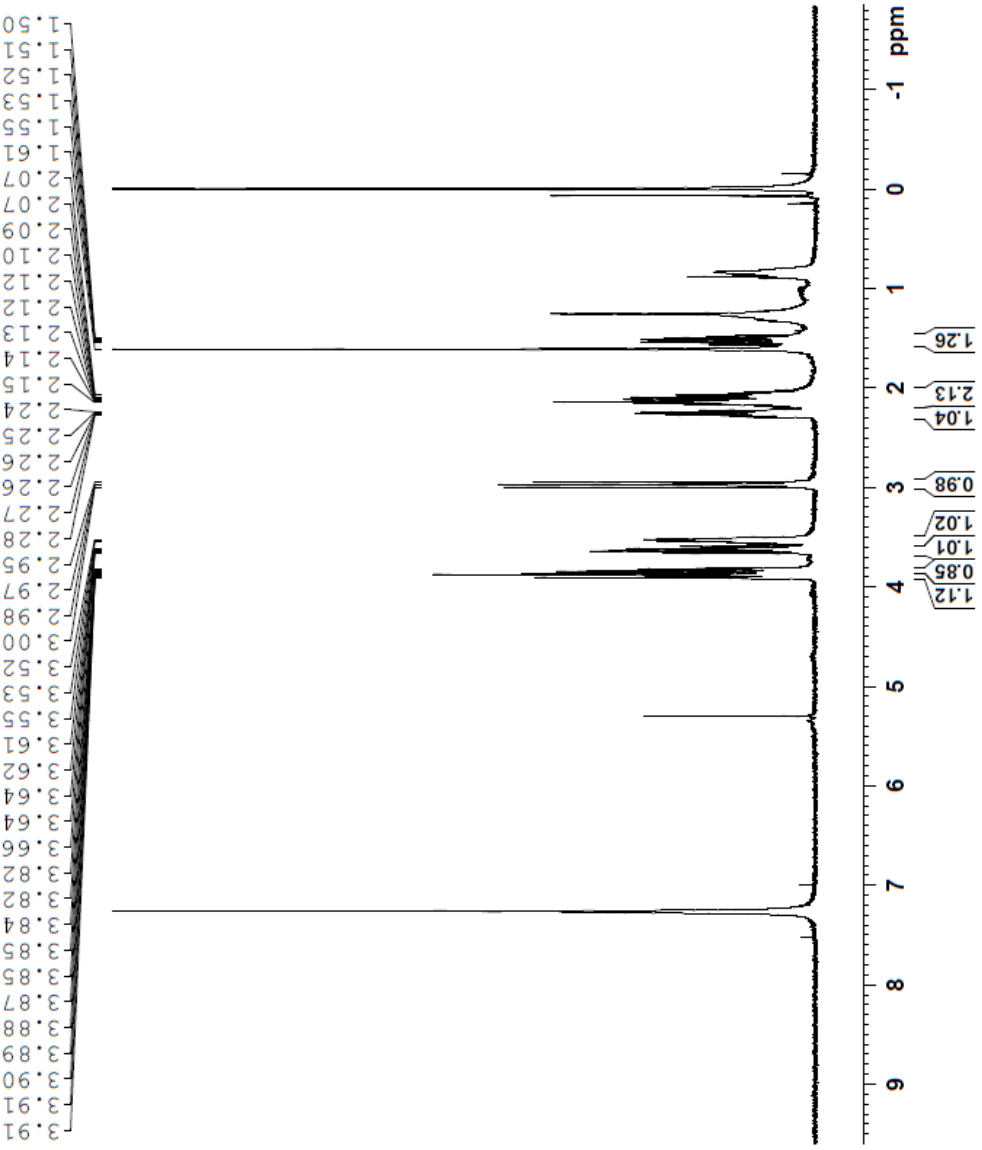


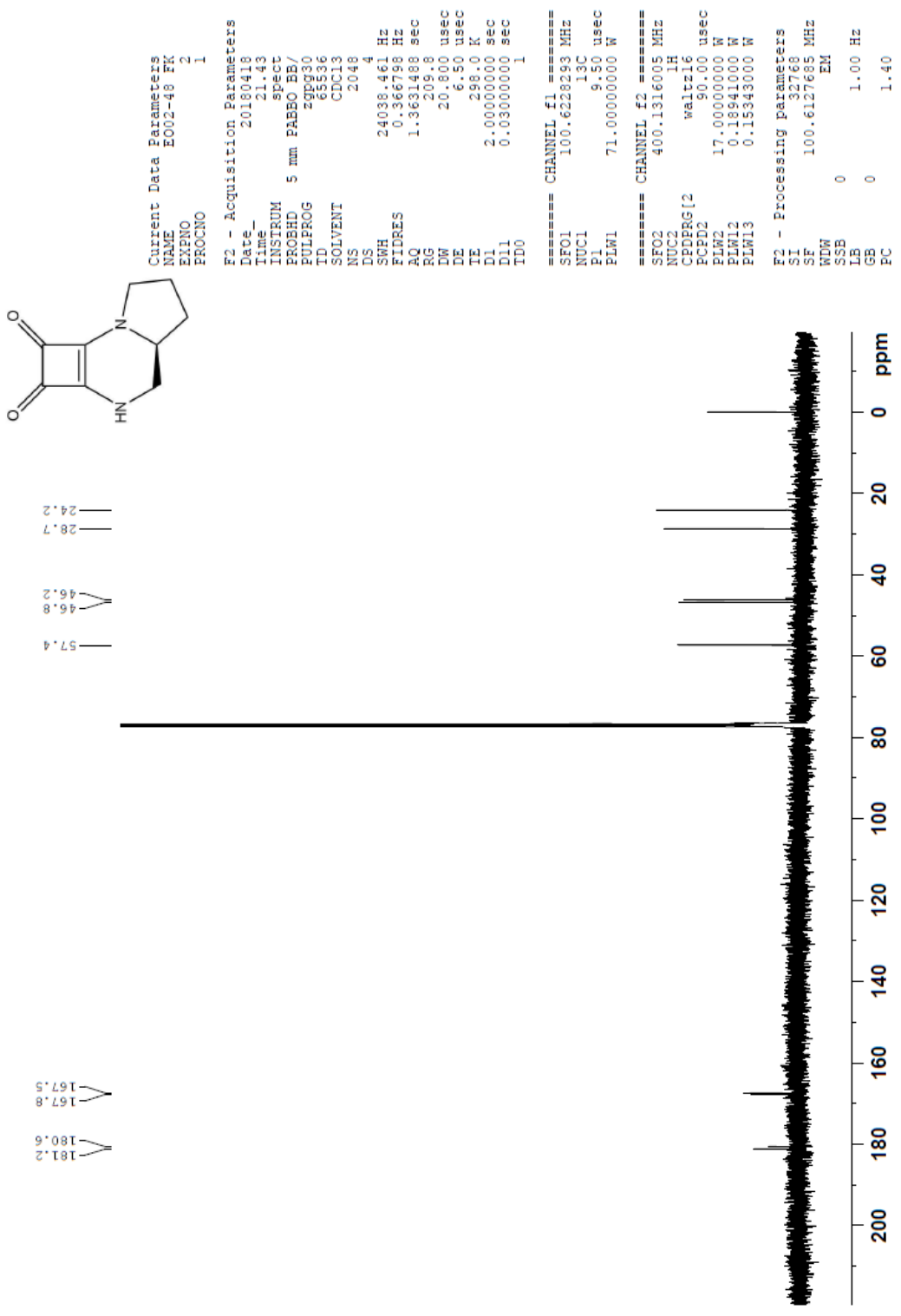
Minimum:				-100.0				
Maximum:		5000.0	2.0	100.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
326.1866	326.1869	-0.3	-0.9	9.5	204.6	n/a	n/a	C19 H24 N3 O2

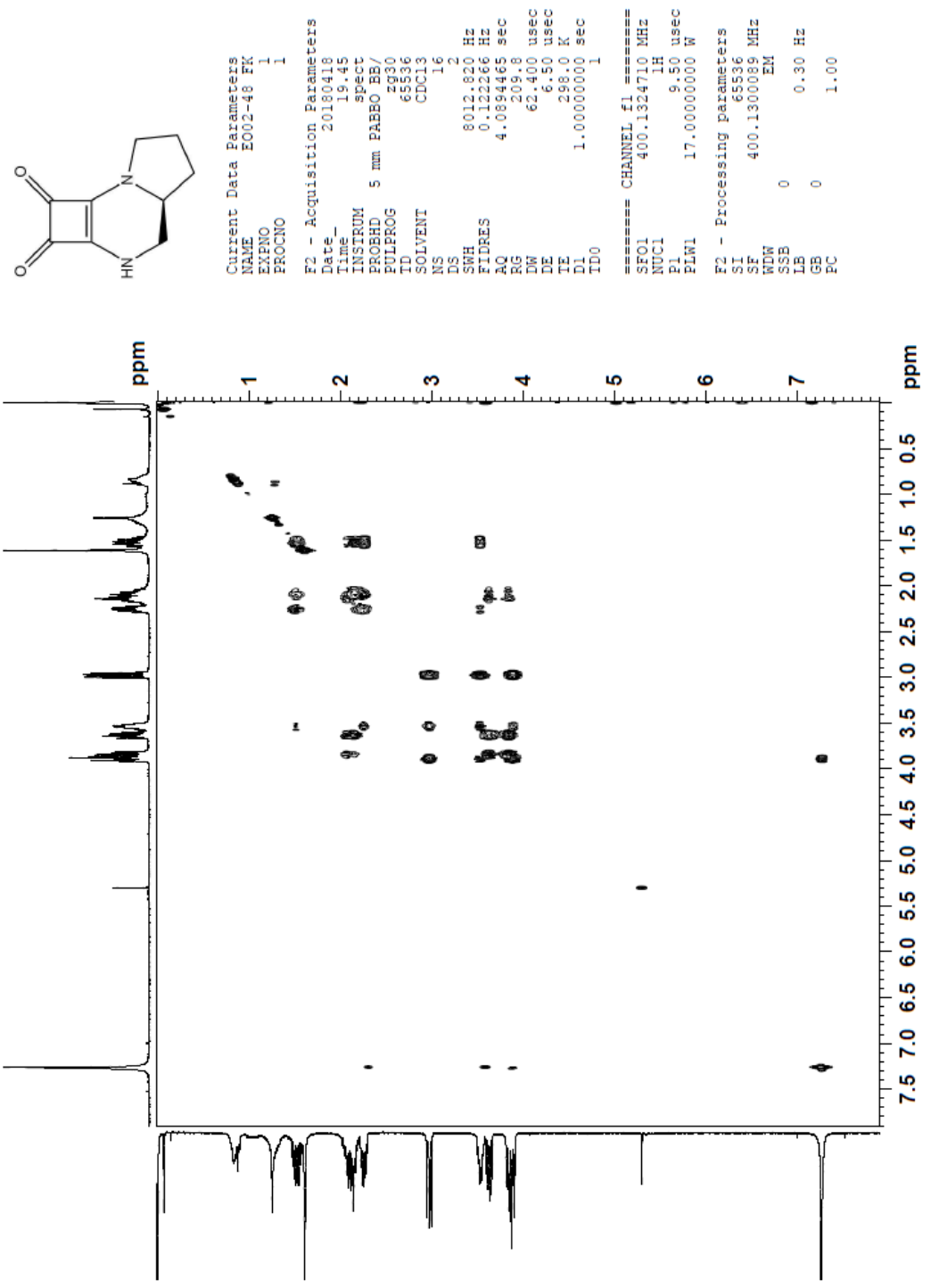
Appendix G Squaramide **5**



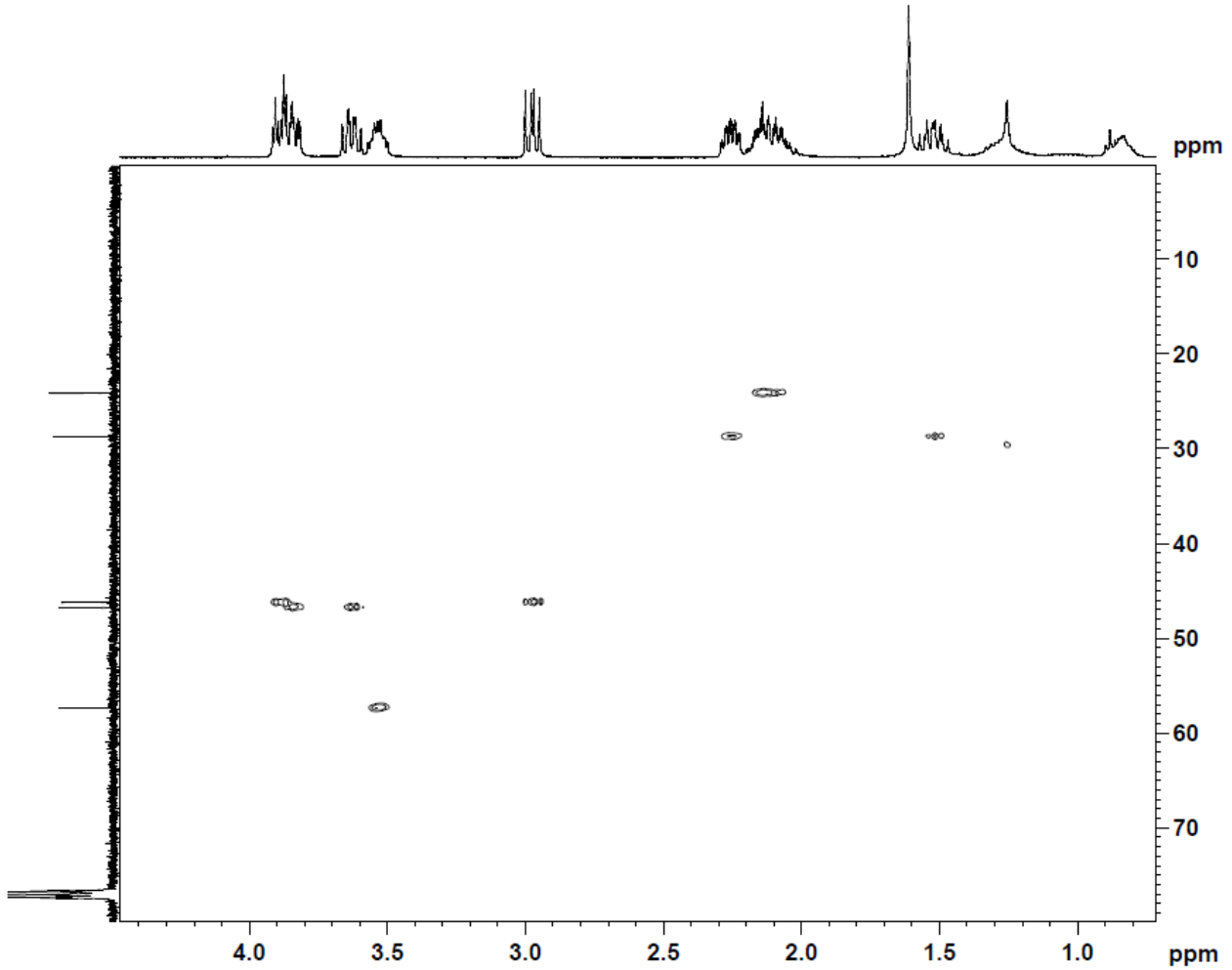

```
Current Data Parameters
NAME       EO02-48 EK
EXPNO             1
PROCNO            1

F2 - Acquisition Parameters
Date_        20180418
Time              19.45
INSTRUM           spect
PROBHD   5 mm PABBO BB/
PULPROG           zg30
TD               65536
SOLVENT          CDCl3
NS                  16
DS                   2
SWH           8012.820 Hz
FIDRES        0.122266 Hz
AQ            4.0894465 sec
RG                209.8
DW               62.400 usec
DE                6.50 usec
TE                298.0 K
D1            1.00000000 sec
TD0                  1

======== CHANNEL f1 ========
SFO1         400.1324710 MHz
NUC1               1H
P1                9.50 usec
PLW1        17.00000000 W

F2 - Processing parameters
SI               65536
SF          400.1300089 MHz
WDW                EM
SSB                0
LB                 0.30 Hz
GB                 0
PC                 1.00
```

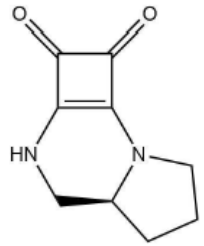



Current Data Parameters
NAME E002-48 FK
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20180418
Time_ 21.43
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 2048
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631488 sec
RG 209.8
DW 20.800 usec
DE 6.50 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 100.6228283 MHz
NUC1 13C
P1 9.50 usec
PLW1 71.00000000 W
======== CHANNEL f2 ========
SFO2 400.1316005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 17.00000000 W
PLW12 0.18941000 W
PLW13 0.15343000 W
F2 - Processing parameters
SI 32768
SF 100.6127685 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
O
O
N
HN
24.2
28.7
46.8
46.2
57.4
167.8
167.5
180.6
181.2
200
180
160
140
120
100
80
60
40
20
0
ppm

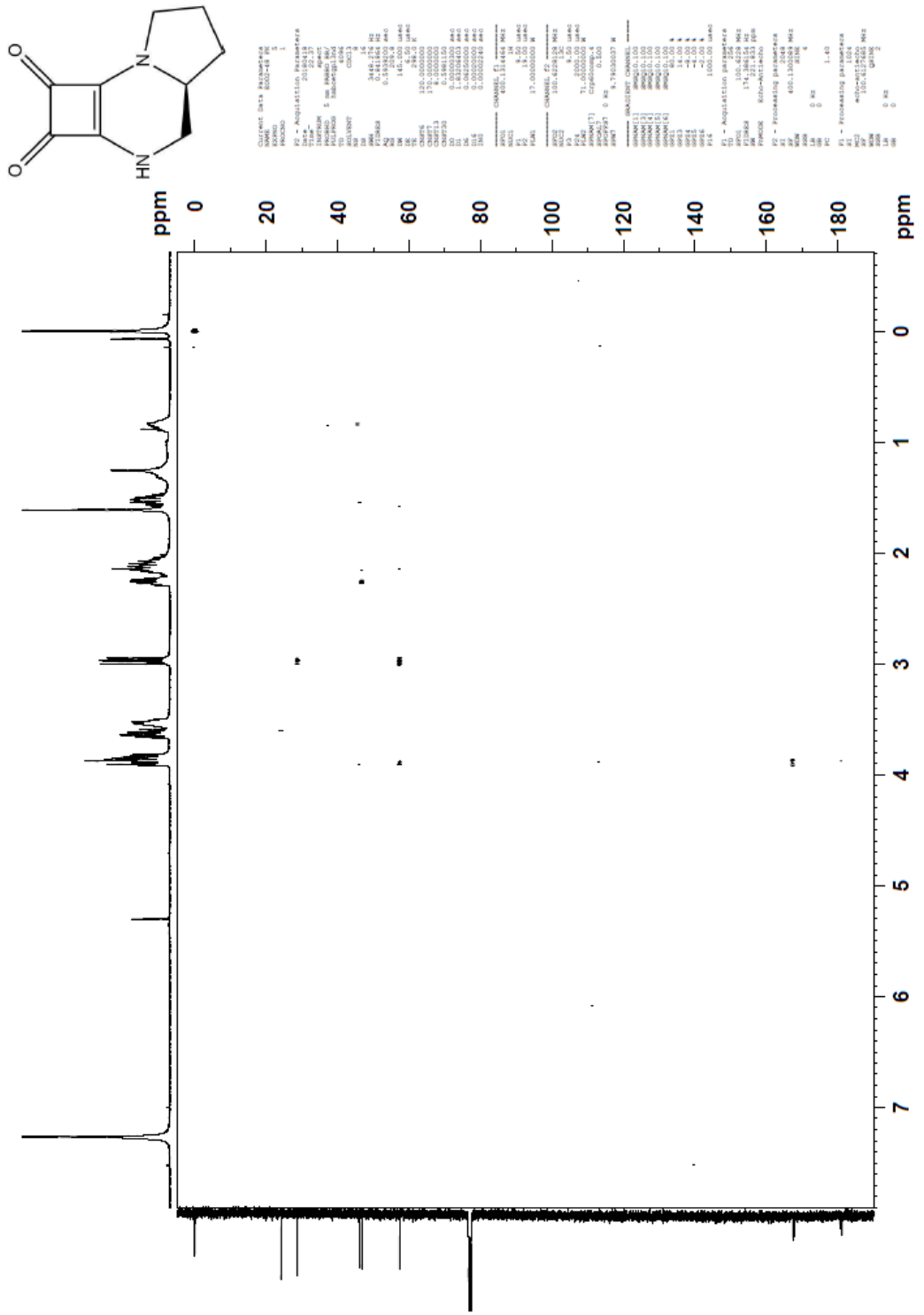

Current Data Parameters
NAME E002-48 FK
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20100418
Time 19.45
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894465 sec
RG 209.8
DW 62.400 usec
DE 6.50 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.1324710 MHz
NUC1 1H
P1 9.50 usec
PLW1 17.00000000 W
F2 - Processing parameters
SI 65536
SF 400.1300089 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
O
O
N
HN
ppm
1
2
3
4
5
6
7
ppm
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5

XIXXX

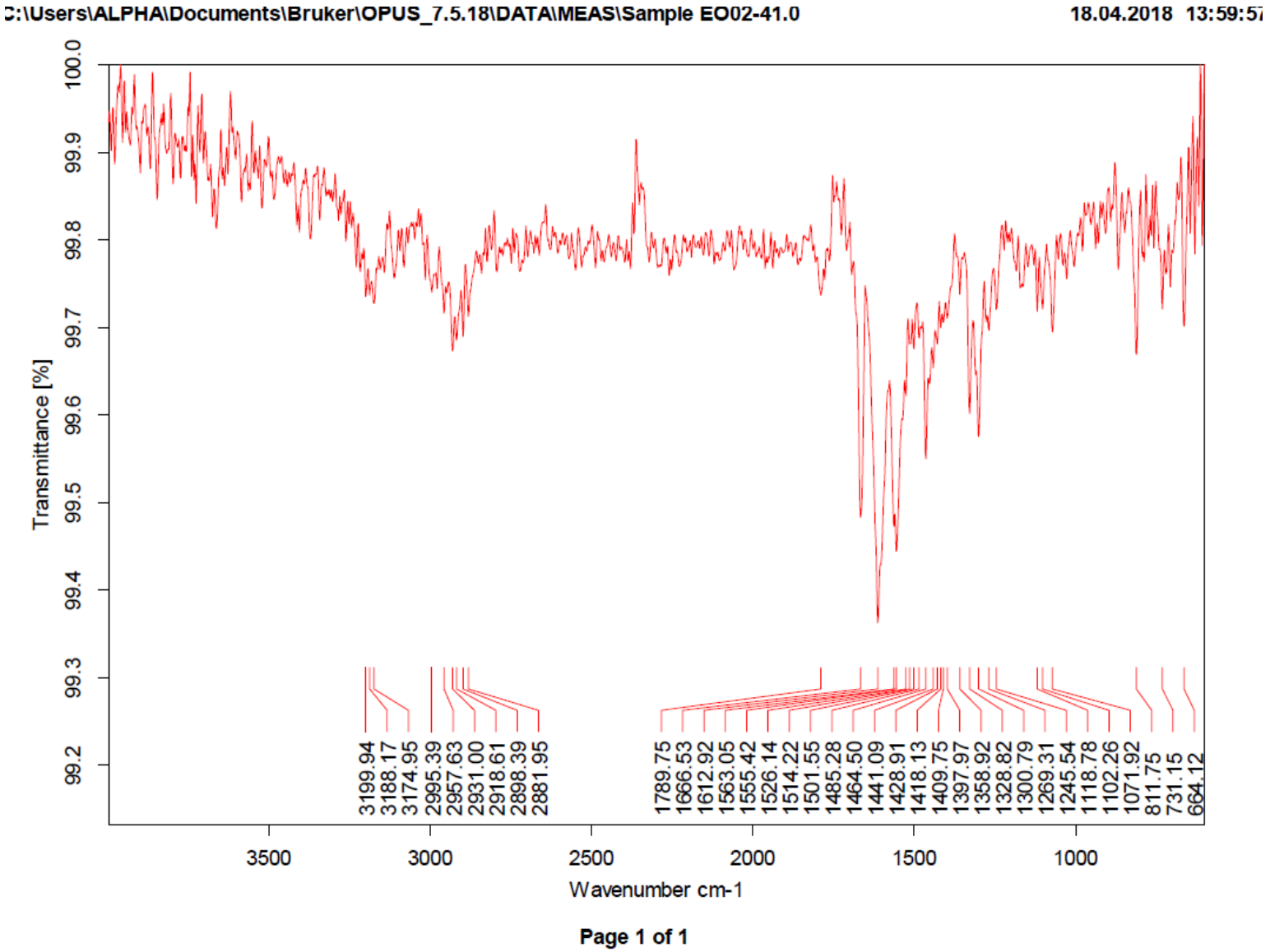





```
Current Data Parameters
NAME          EO02-48 FK
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20180418
Time               19.45
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8012.820 Hz
FIDRES          0.122266 Hz
AQ              4.0894465 sec
RG                 209.8
DW                62.400 usec
DE                 6.50 usec
TE                298.0 K
D1             1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         400.1324710 MHz
NUC1                   1H
P1                  9.50 usec
PLW1        17.00000000 W

F2 - Processing parameters
SI                 65536
SF           400.1300089 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```


O
O
N
HN
ppm
0
20
40
60
80
100
120
140
160
180
ppm
0
1
2
3
4
5
6
7

ITX

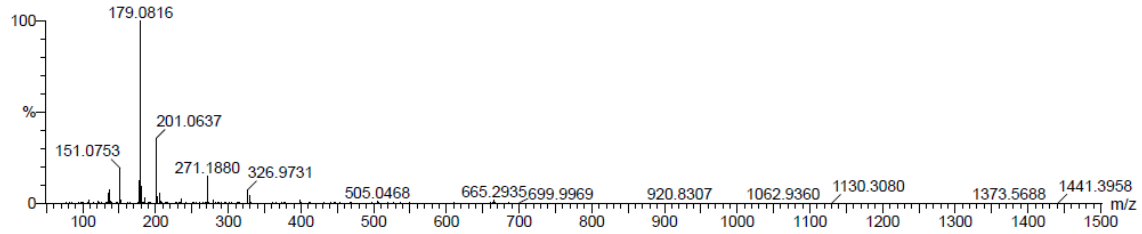

C:\Users\ALPHA\Documents\Bruker\OPUS_7.5.18\DATA\MEAS\Sample EO02-41.0
18.04.2018 13:59:57
Transmittance [%]
100.0
99.9
99.8
99.7
99.6
99.5
99.4
99.3
99.2
3199.94
3188.17
3174.95
2995.39
2957.63
2931.00
2918.61
2898.39
2881.95
1789.75
1666.53
1612.92
1563.05
1555.42
1526.14
1514.22
1501.55
1485.28
1464.50
1441.09
1428.91
1418.13
1409.75
1397.97
1358.92
1328.82
1300.79
1269.31
1245.54
1118.78
1102.26
1071.92
811.75
731.15
664.12
3500
3000
2500
2000
1500
1000
Wavenumber cm-1
Page 1 of 1

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

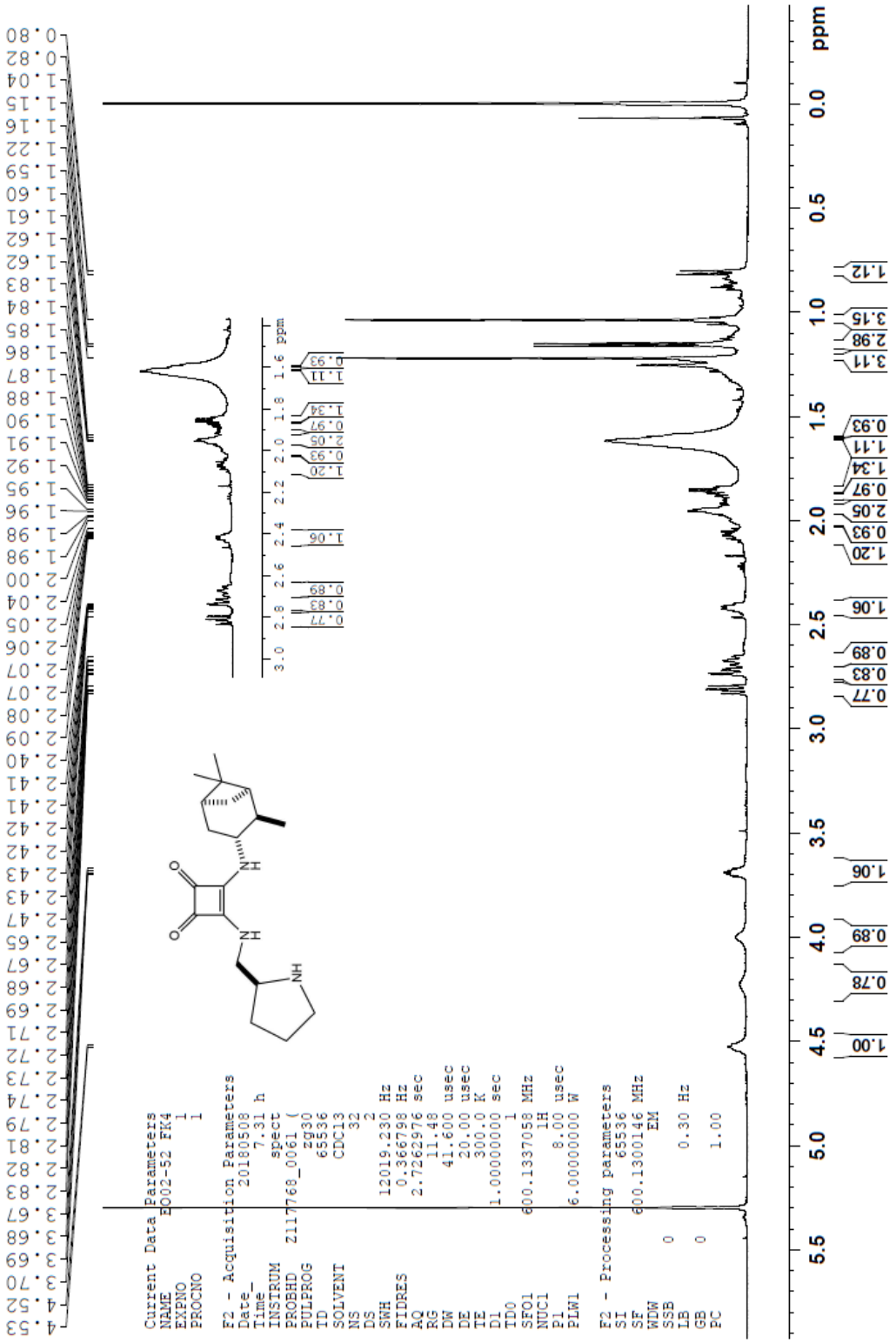
Monoisotopic Mass, Even Electron Ions
187 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-4 O: 0-20 Na: 0-1
2018-206 77 (0.734) AM2 (Ar,35000.0,0.00,0.00); Cm (76:77)
1: TOF MS ES+

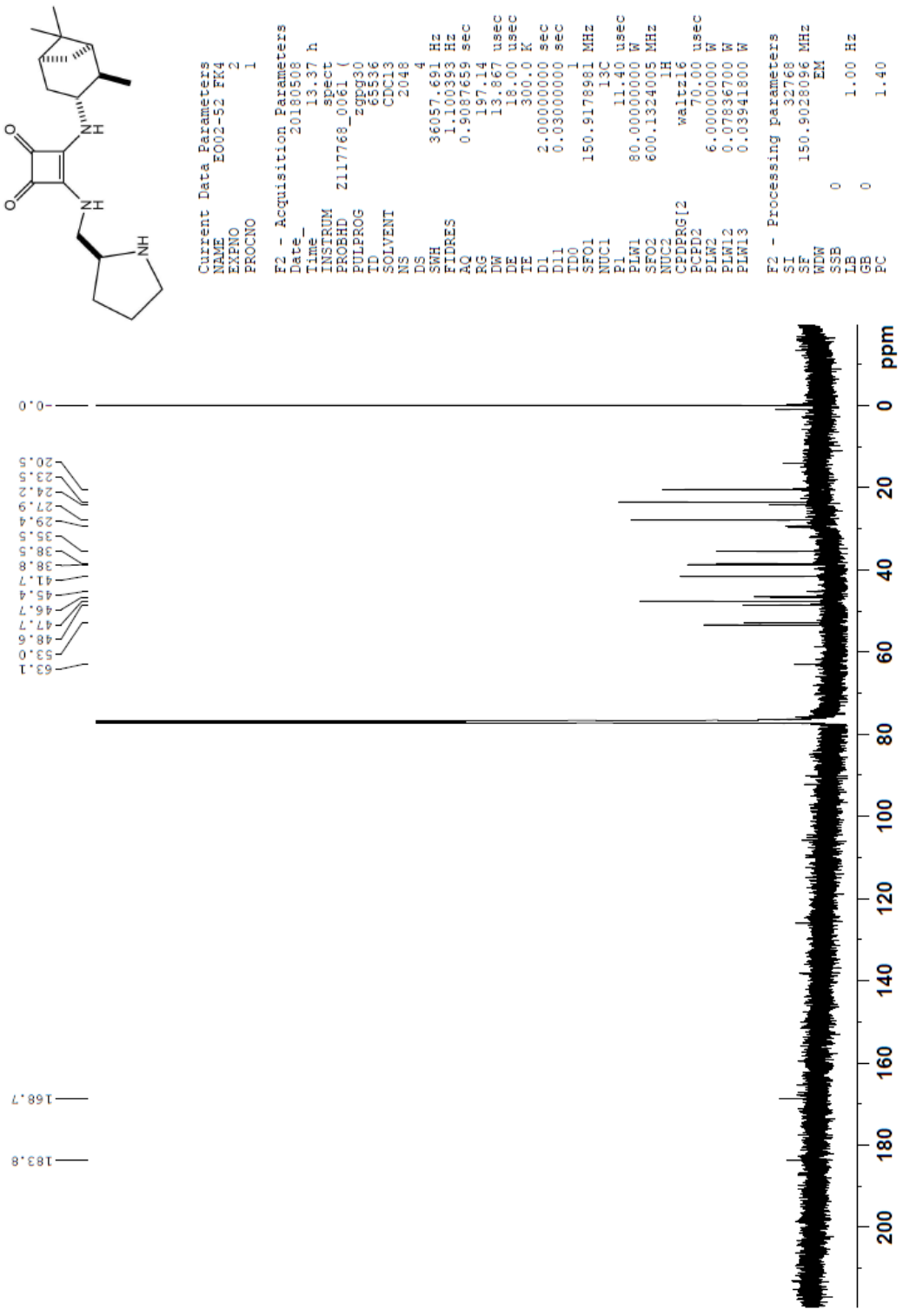
8.22e+005

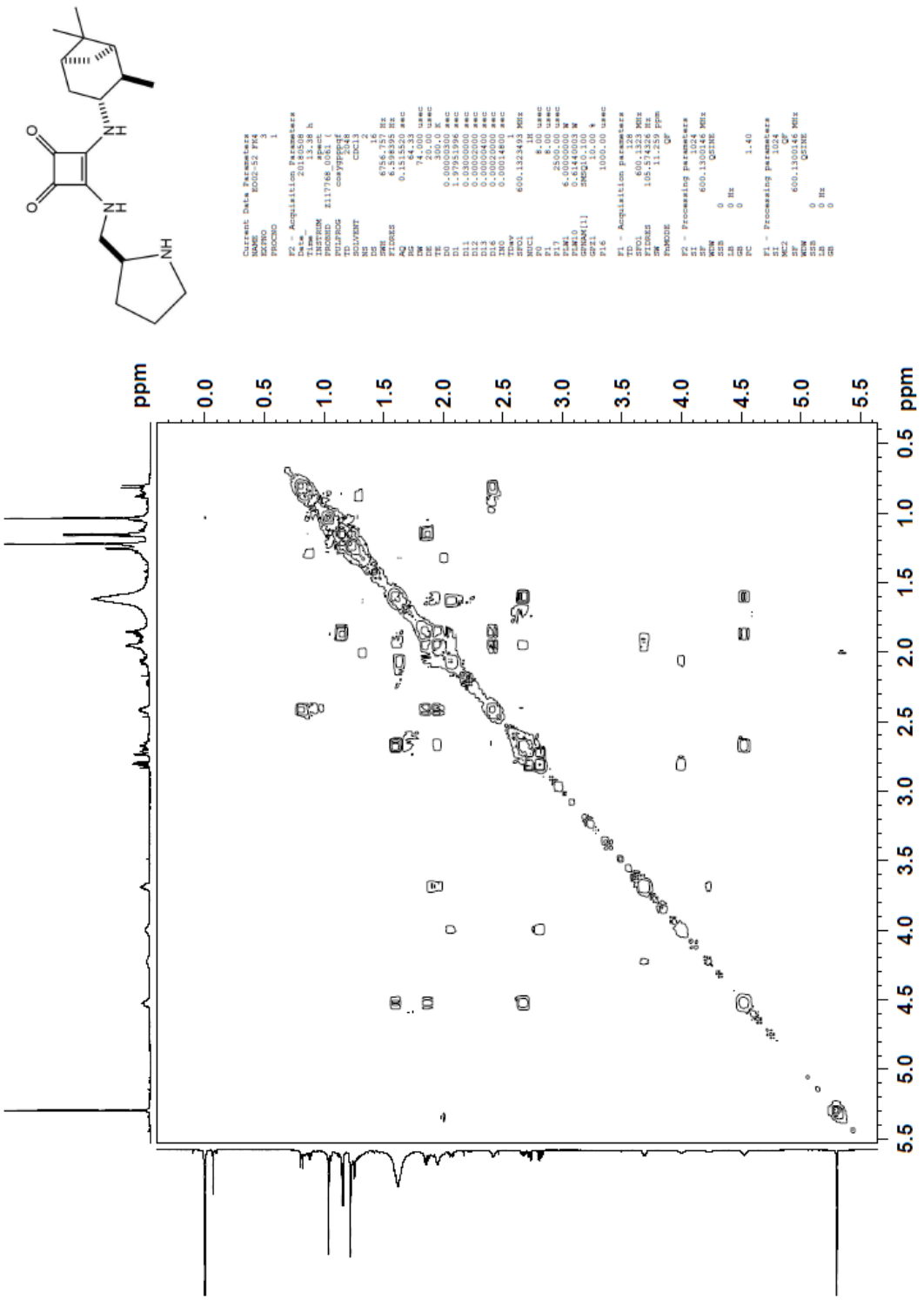


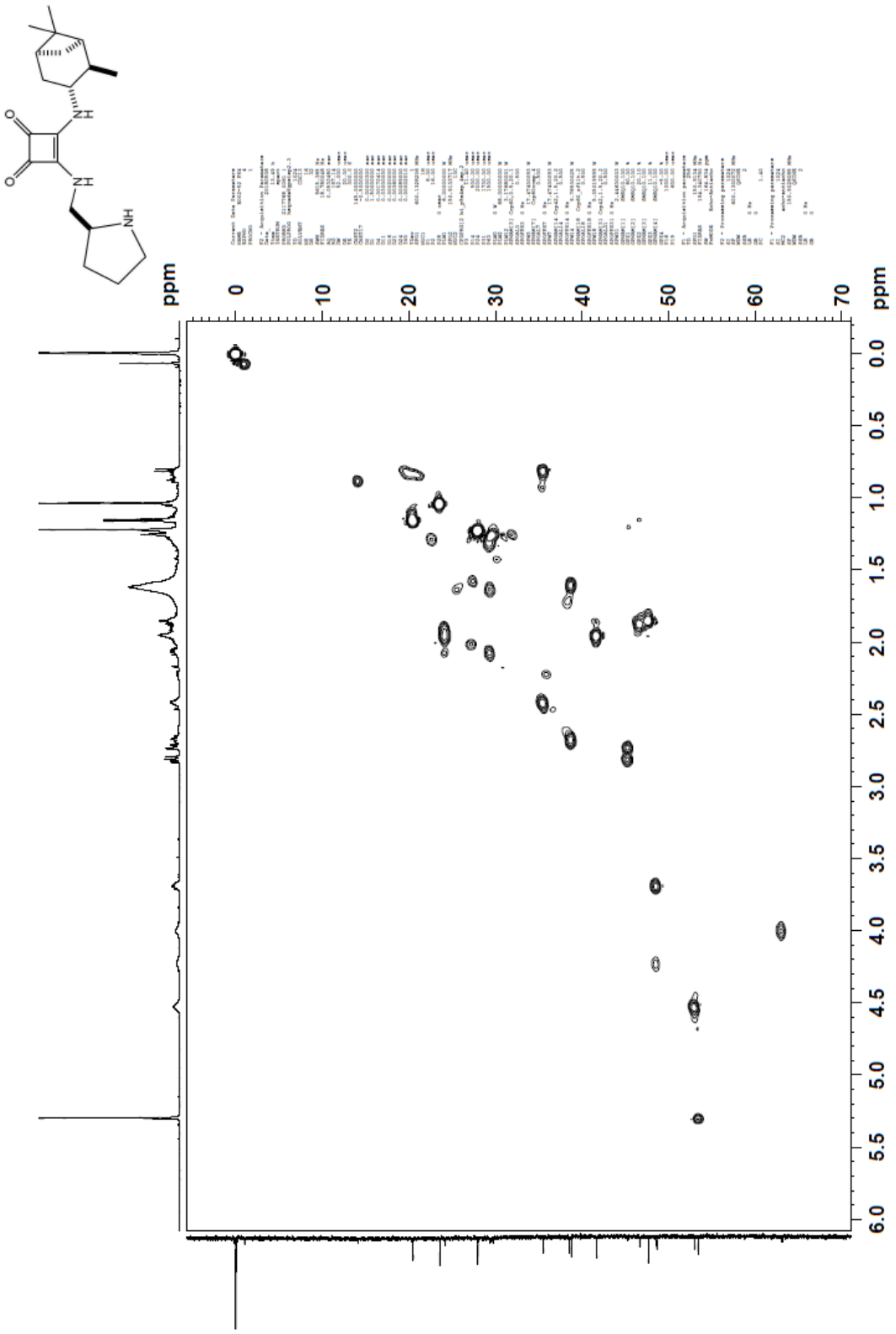
Minimum:				-1.5				
Maximum:		5.0	10.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
179.0816	179.0821	-0.5	-2.8	5.5	1560.6	n/a	n/a	C9 H11 N2 O2

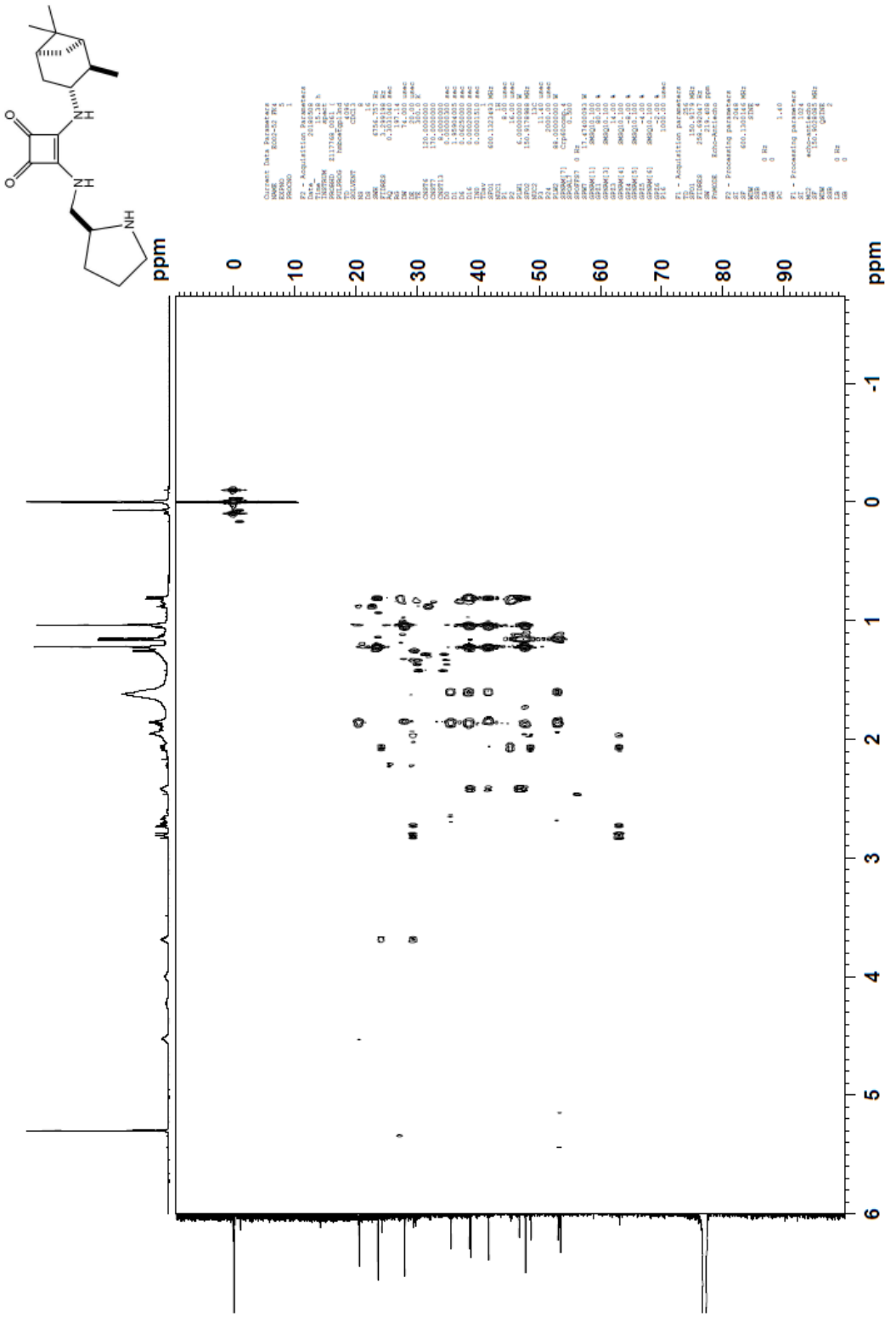
Appendix H Squaramide **6**

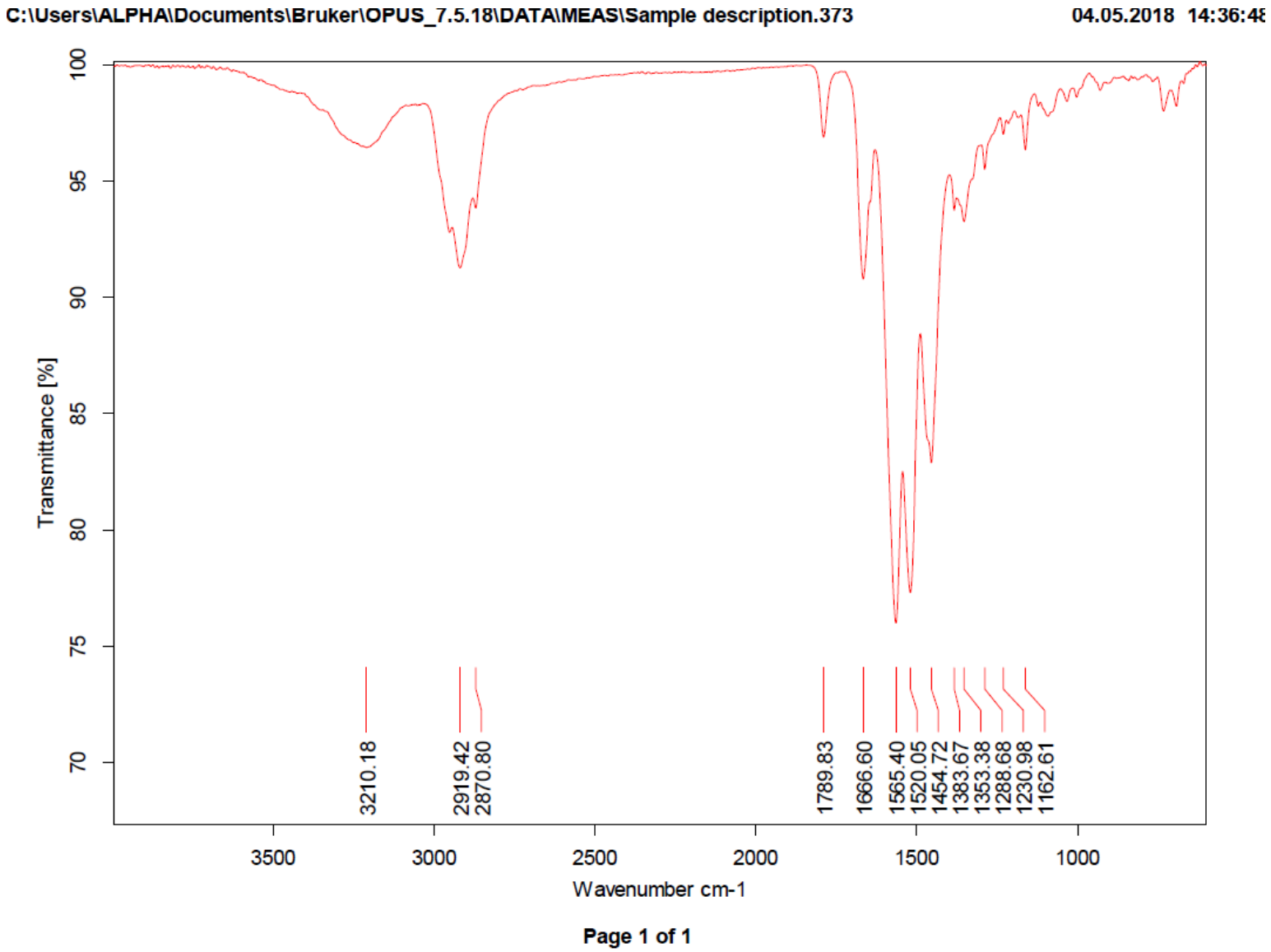



Current Data Parameters
NAME EO02-52 FK4
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20180508
Time 13.37 h
INSTRUM spect
PROBHD Z117768_0061 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 2048
DS 4
SWH 36057.691 Hz
FIDRES 1.100393 Hz
AQ 0.9087659 sec
RG 197.14
DW 13.867 usec
DE 18.00 usec
TE 300.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 150.9178981 MHz
NUC1 13C
P1 11.40 usec
PLW1 80.00000000 W
SFO2 600.1324005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 70.00 usec
PLW2 6.00000000 W
PLW12 0.07836700 W
PLW13 0.03941800 W
F2 - Processing parameters
SI 32768
SF 150.9028096 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
ppm
0
20
40
60
80
100
120
140
160
180
200
0.0
20.5
23.5
24.2
27.9
29.4
35.5
38.5
38.8
41.7
45.4
46.7
47.7
48.6
53.0
63.1
168.7
183.8


ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5


ppm
0
10
20
30
40
50
60
70
ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0




C:\Users\ALPHA\Documents\Bruker\OPUS_7.5.18\DATA\MEAS\Sample description.373
04.05.2018 14:36:48
Transmittance [%]
100
95
90
85
80
75
70
3210.18
2919.42
2870.80
1789.83
1666.60
1565.40
1520.05
1454.72
1383.67
1353.38
1288.68
1230.98
1162.61
3500
3000
2500
2000
1500
1000
Wavenumber cm-1
Page 1 of 1

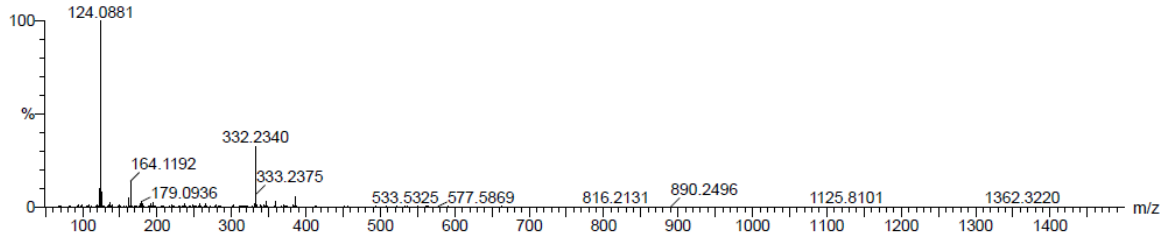
Elemental Composition Report **Page 1**

Single Mass Analysis

Tolerance = 3.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

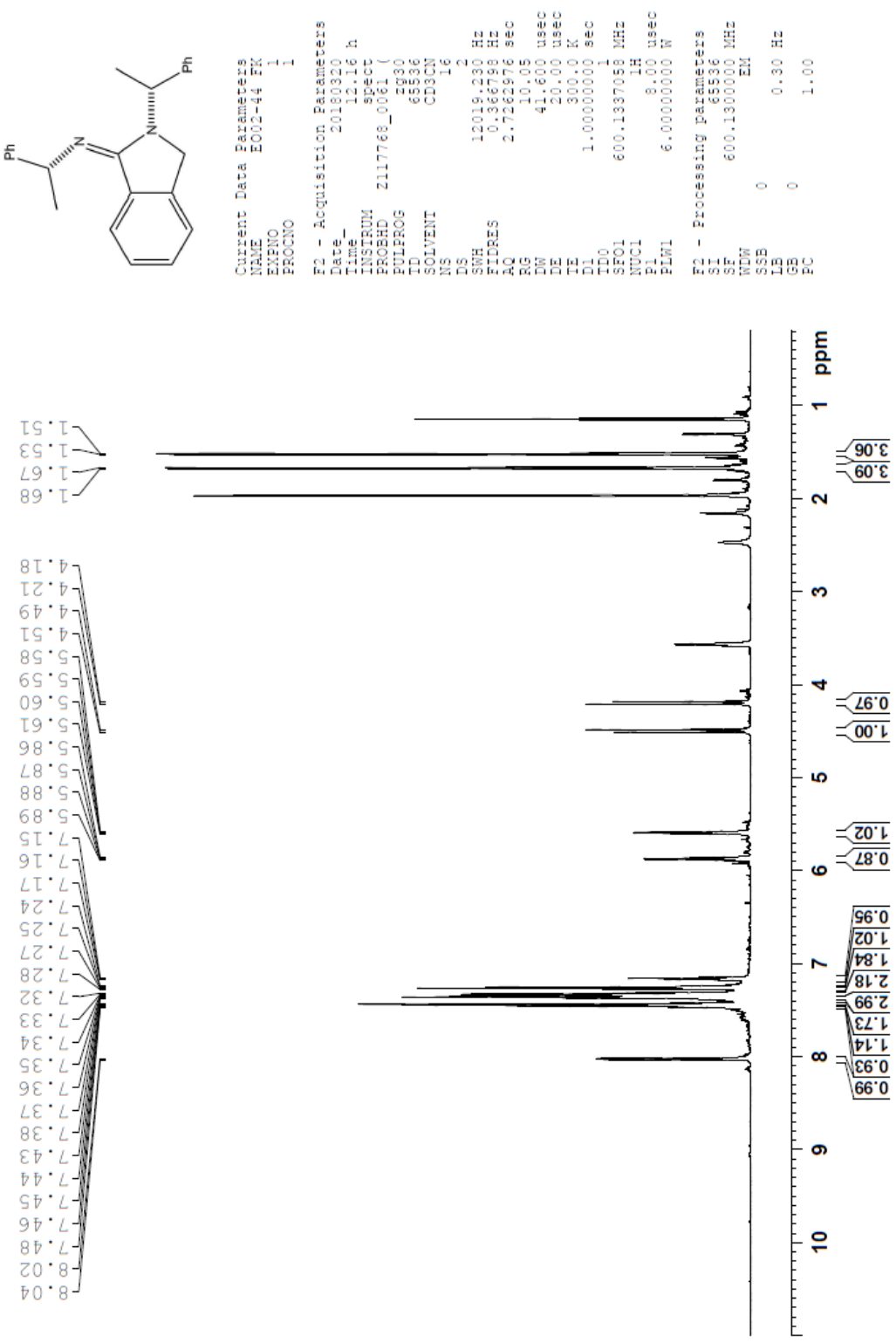
Monoisotopic Mass, Even Electron Ions
1820 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-10 O: 0-20 S: 0-4
2018-262 126 (2.464) AM2 (Ar,35000.0,0.00,0.00); Cm (118:126)
1: TOF MS ASAP+

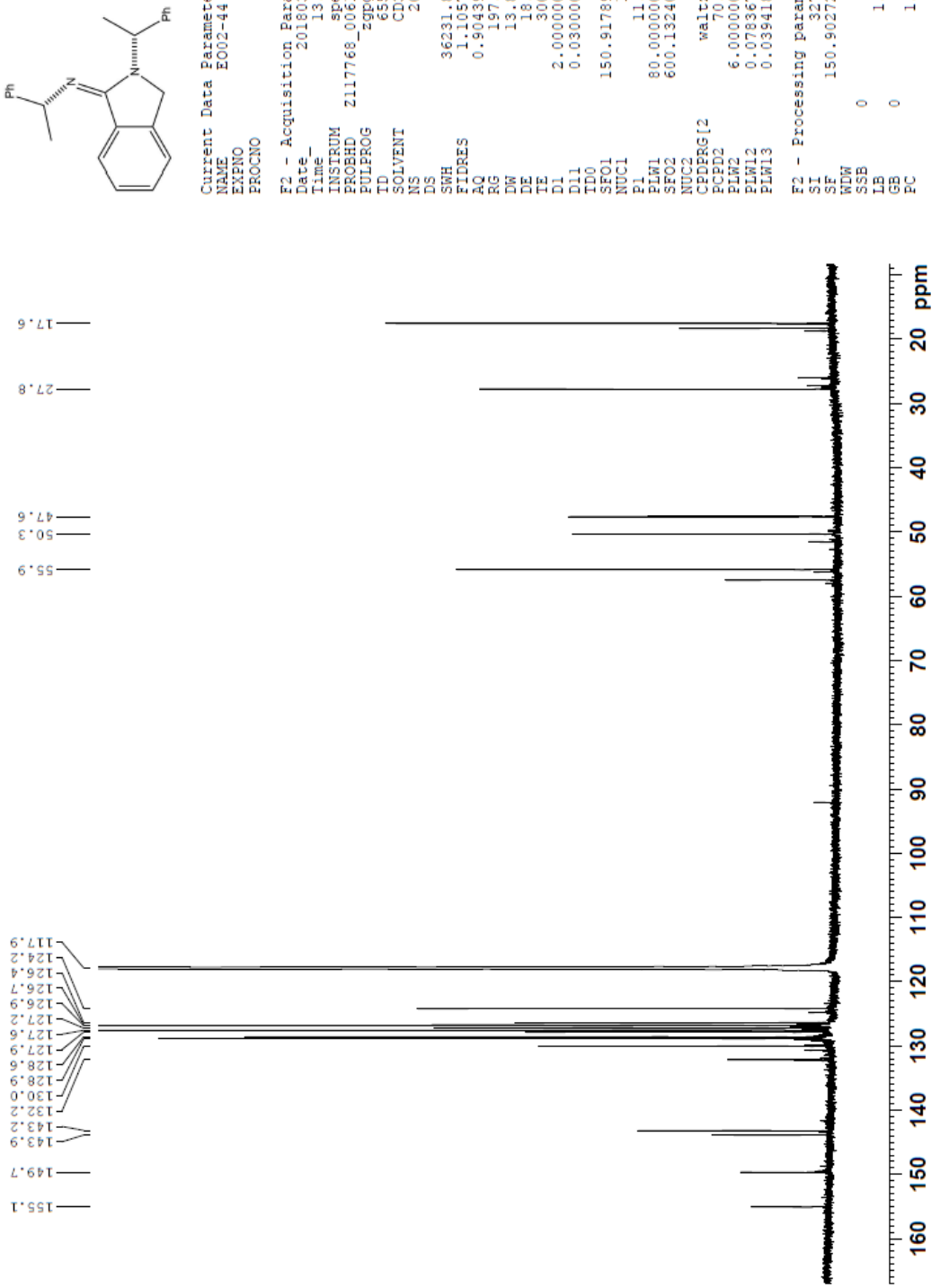
2.71e+005



Minimum:				-1.5				
Maximum:		5000.0	3.0	100.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
332.2340	332.2338	0.2	0.6	6.5	727.3	0.000	100.00	C19 H30 N3 O2
	332.2345	-0.5	-1.5	2.5	739.0	11.735	0.00	C12 H30 N9 S

Appendix I Iminoisoindoline **7**




Ph
N
N
Ph
Current Data Parameters
NAME EO02-44 FK
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20180320
Time_ 13.58 h
INSTRUM spect
PROBHD Z117768_0061 (
PULPROG zgpg30
TD 65536
SOLVENT CD3CN
NS 2048
DS 4
SWH 36231.883 Hz
FIDRES 1.105709 Hz
AQ 0.9043968 sec
RG 197.14
DW 13.800 usec
DE 18.00 usec
TE 300.0 K
D1 2.00000000 sec
D11 0.03000000 sec
ID0 1
SFO1 150.9178988 MHz
NUC1 13C
P1 11.40 usec
PLW1 80.00000000 W
SFO2 600.1324005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 70.00 usec
PLW2 6.00000000 W
PLW12 0.07836700 W
PLW13 0.03941800 W
F2 - Processing parameters
SI 32768
SF 150.9027209 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
17.6
27.8
47.6
50.3
55.9
117.9
124.2
126.4
126.7
126.9
127.2
127.6
127.9
128.6
128.9
130.0
132.2
143.2
143.9
149.7
155.1
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
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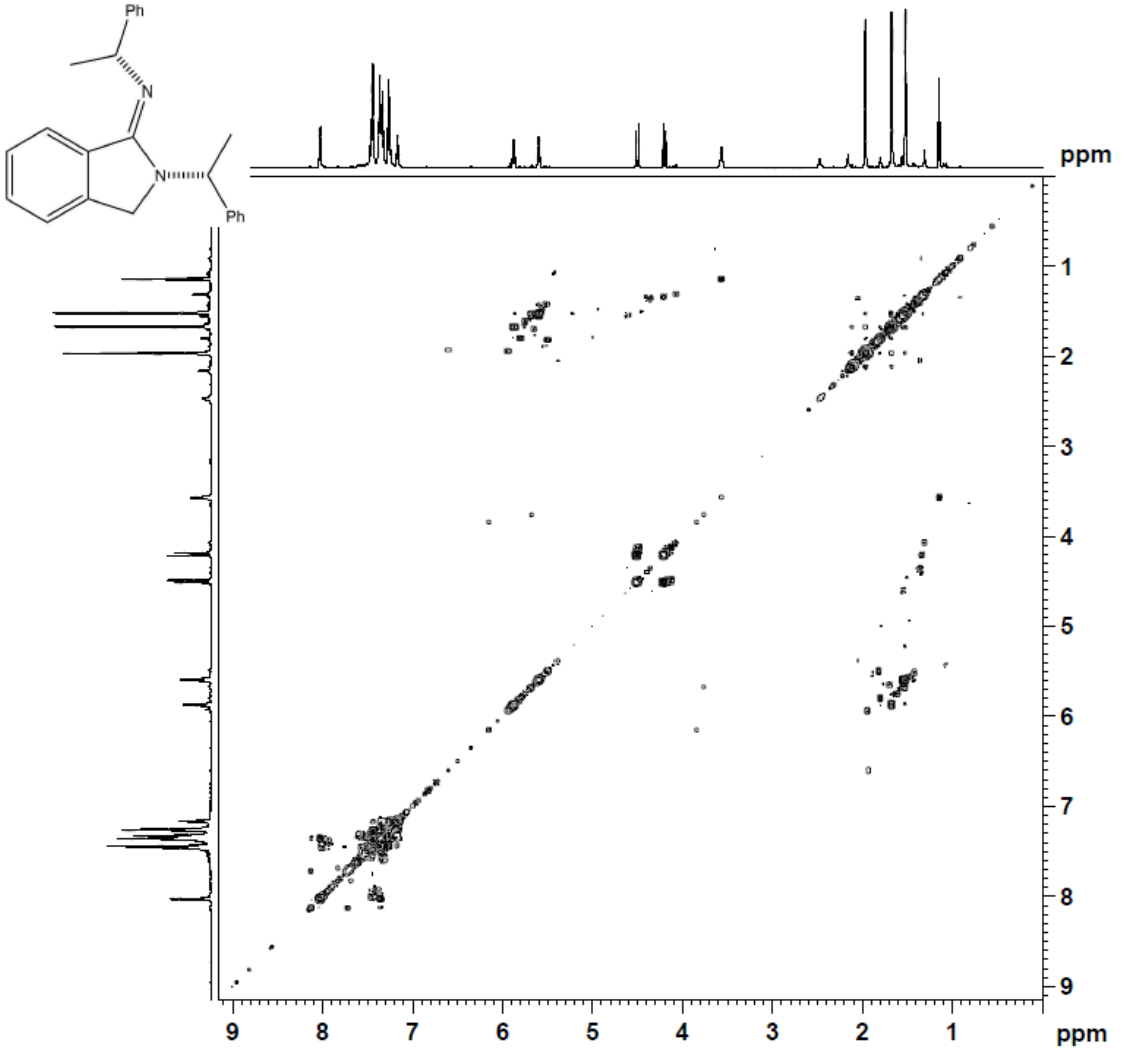


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EXPNO                        3
PROCNO                       1

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Time               20.10 h
INSTRUM                spect
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PULPROG          cosygpppqf
TD                       2048
SOLVENT                  CD3CN
NS                           2
DS                          16
SWH                5494.505 Hz
FIDRES             5.365728 Hz
AQ                 0.1863680 sec
RG                      64.33
DW                     91.000 usec
DE                      20.00 usec
TE                     300.0 K
D0                 0.00000300 sec
D1                 1.94470406 sec
D11                0.03000000 sec
D12                0.00002000 sec
D13                0.00000400 sec
D16                0.00020000 sec
IN0                0.00018200 sec
TDav                         1
SFO1              600.1327448 MHz
NUC1                       1H
P0                      8.00 usec
P1                      8.00 usec
P17                  2500.00 usec
PLW1               6.00000000 W
PLW10              0.61440002 W
GPNAM[1]          SMSQ10.100
GPZ1                   10.00 %
P16                 1000.00 usec

F1 - Acquisition parameters
TD                         128
SFO1                600.1327 MHz
FIDRES             86.861646 Hz
SW                     9.155 ppm
FnMODE                    QF

F2 - Processing parameters
SI                        1024
SF                600.1300000 MHz
WDW                     QSINE
SSB                 0
LB                  0 Hz
GB                  0
PC                       1.40

F1 - Processing parameters
SI                        1024
NC1                         QF
SF                600.1300000 MHz
WDW                     QSINE
SSB                 0
LB                  0 Hz
GB                  0
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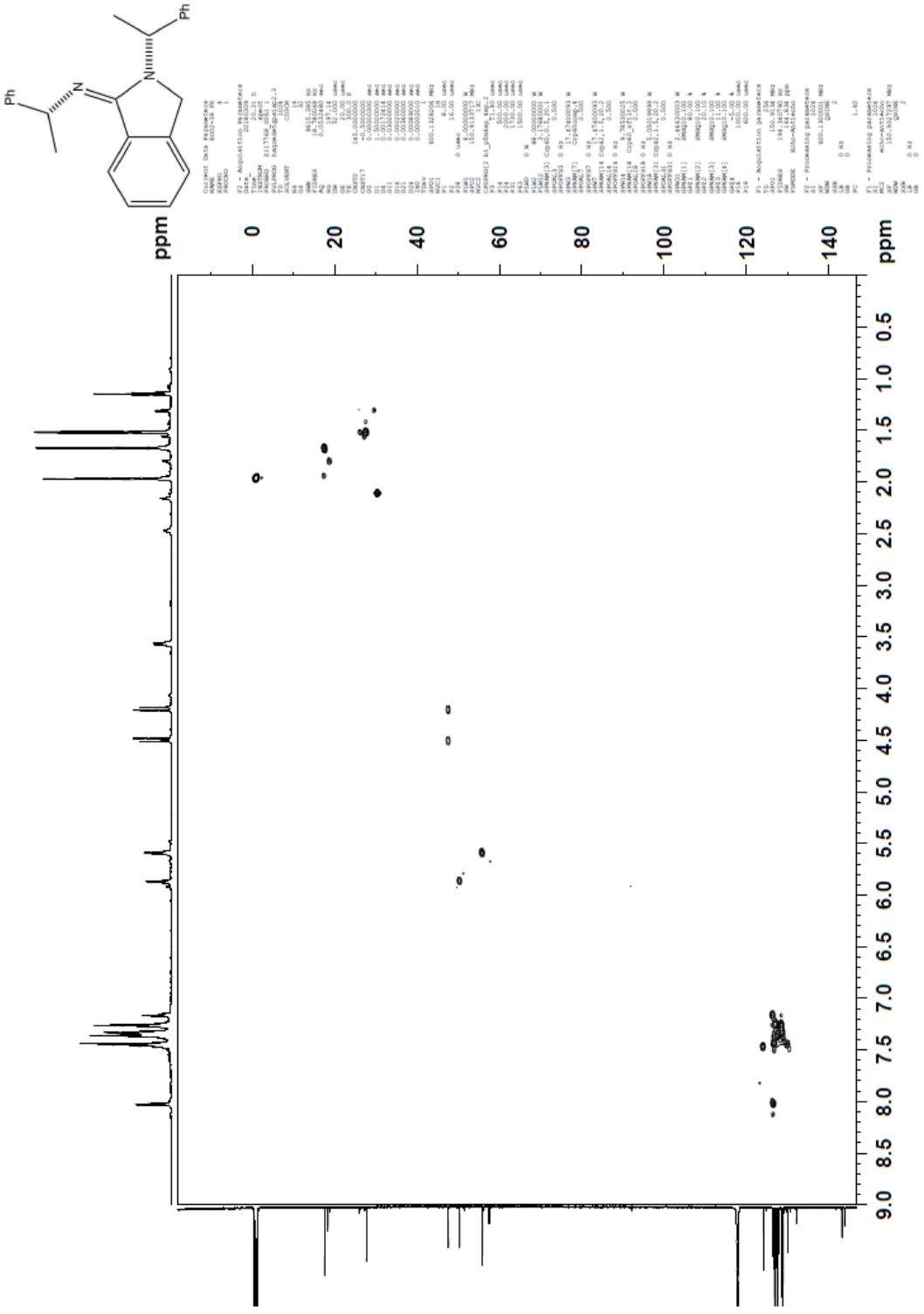
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N
Ph
ppm
0
20
40
60
80
100
120
140
ppm
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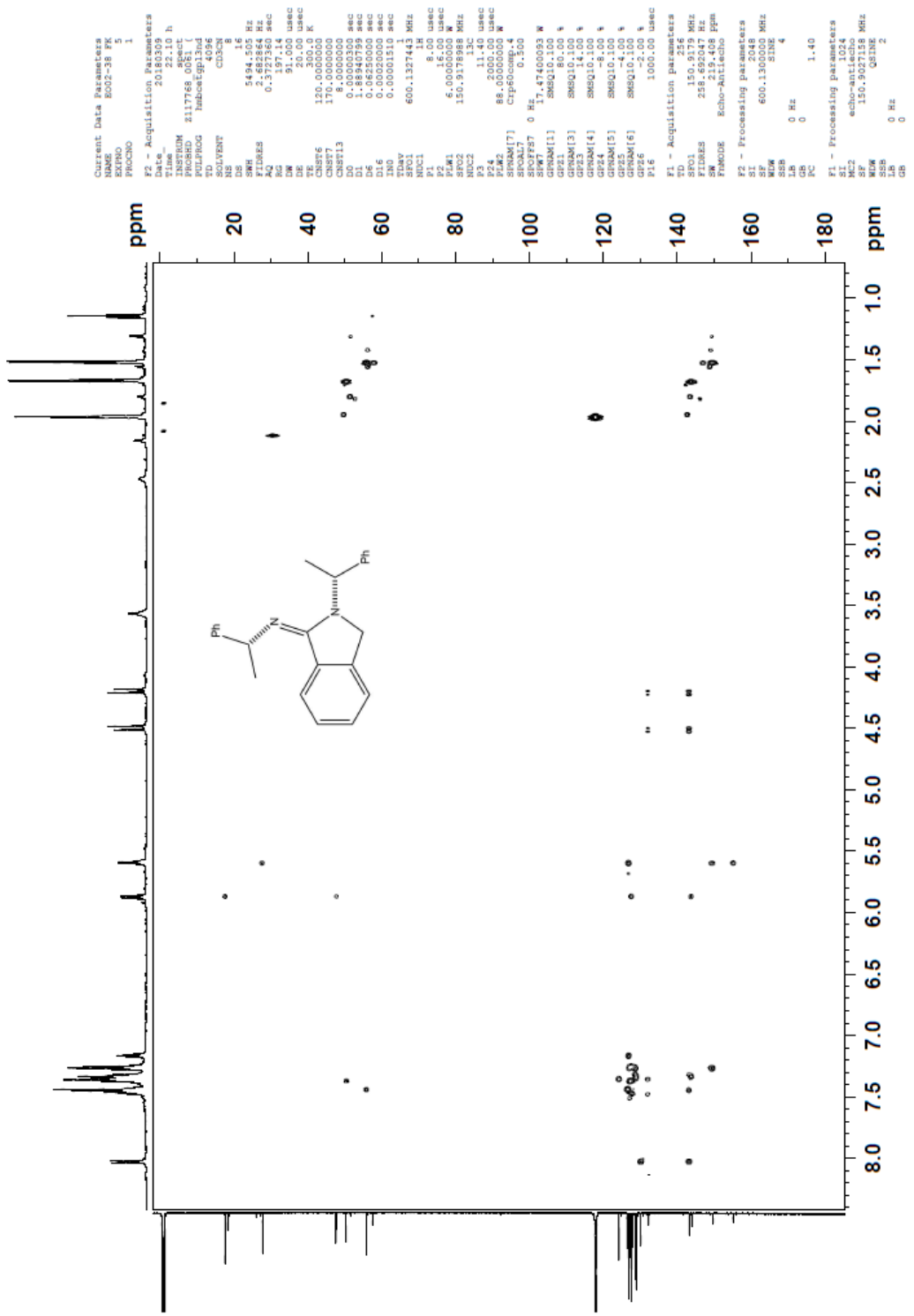
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0


ppm
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40
60
80
100
120
140
160
180
ppm
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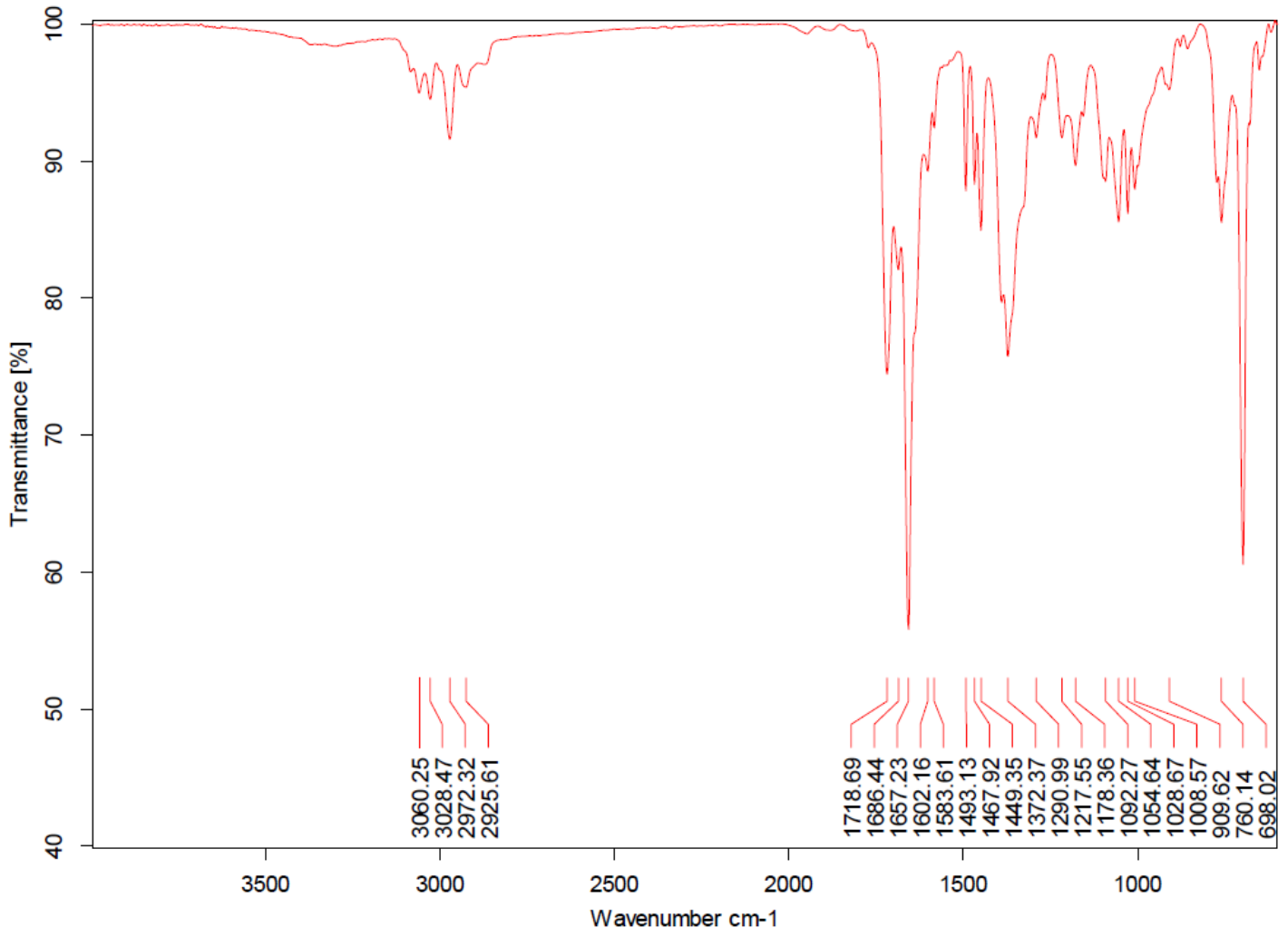
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
Ph
N
N
Ph

C:\Users\ALPHA\Documents\Bruker\OPUS_7.5.18\DATA\MEAS\Sample description.382 04.05.2018 16:09:35



Elemental Composition Report **Page 1**

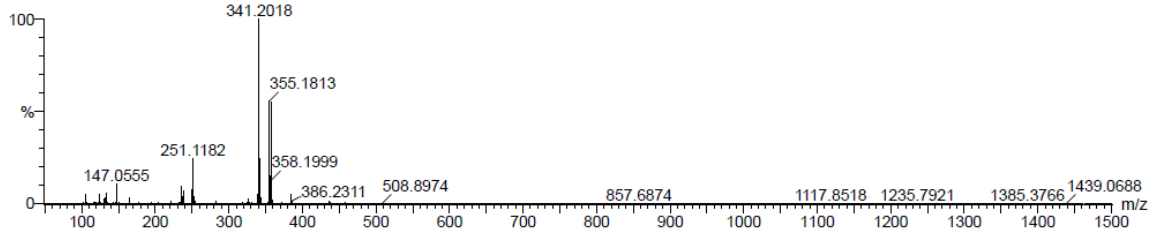
Single Mass Analysis

Tolerance = 3.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
797 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-10 O: 0-50 I: 0-1

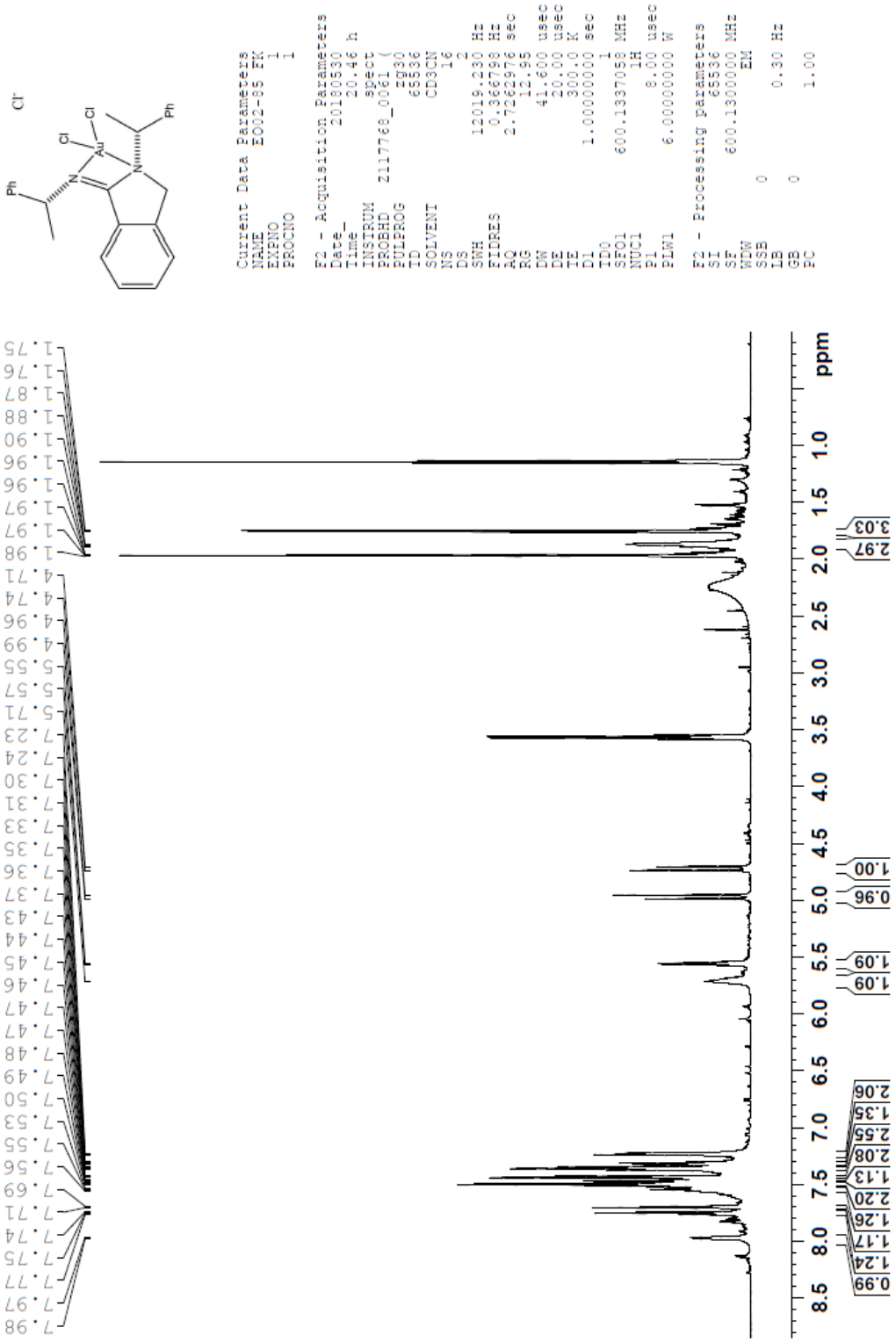
2018-97 39 (0.775) AM2 (Ar,35000.0,0.00,0.00); Cm (38:40)
1: TOF MS ASAP+

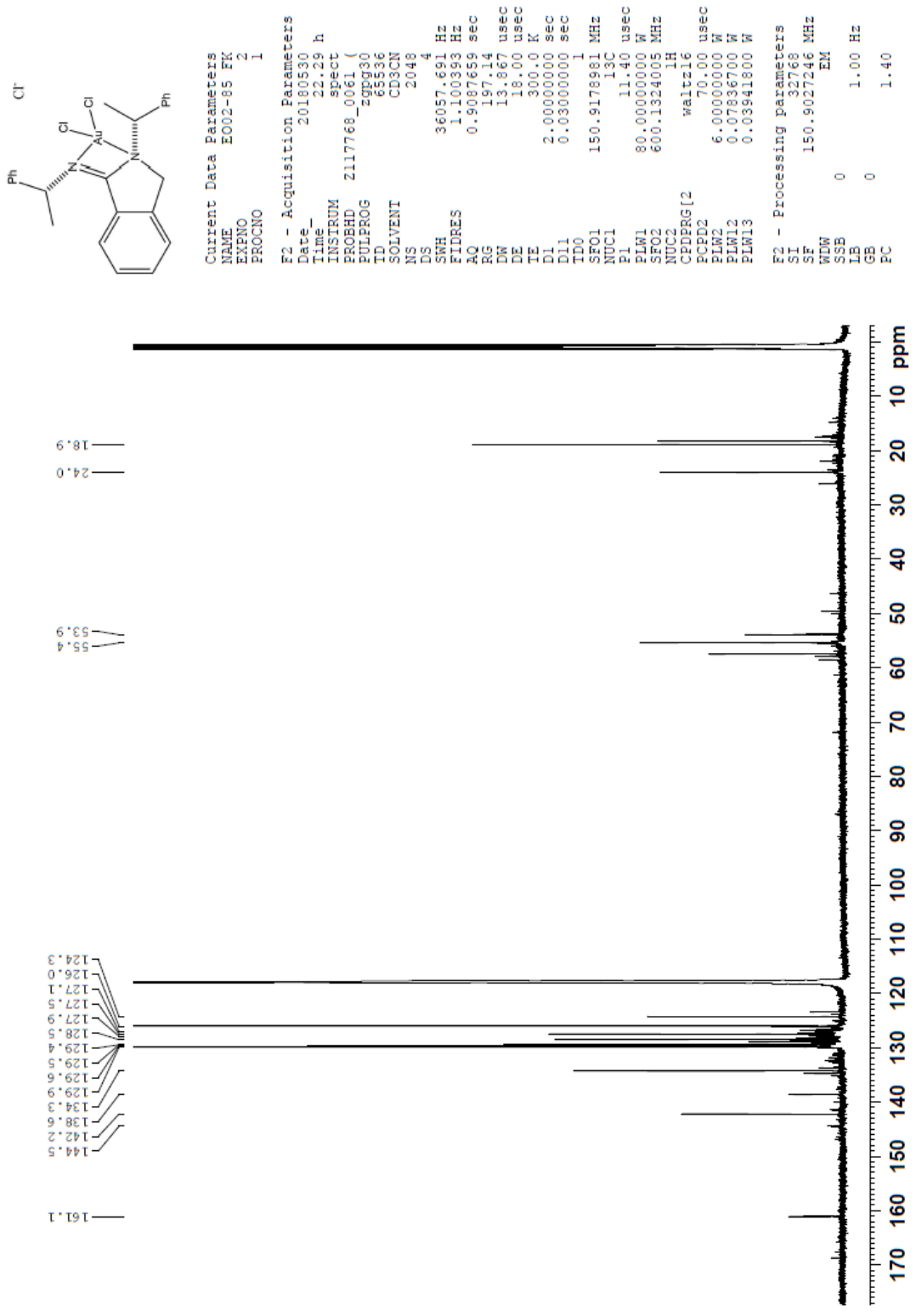
3.96e+006



Minimum:				-1.5				
Maximum:		5.0	3.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
341.2018	341.2018	0.0	0.0	13.5	1399.5	0.000	100.00	C24 H25 N2
	341.2009	0.9	2.6	1.5	1412.5	12.999	0.00	C8 H25 N10 O5

Appendix J Gold(III)-complex **8**

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Ph
Cl
Cl
Au
N
N
Ph
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EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
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Time 22.29 h
INSTRUM spect
PROBHD Z117768_0061 (
PULPROG zgpg30
TD 65536
SOLVENT CD3CN
NS 2048
DS 4
SWH 36057.691 Hz
FIDRES 1.100393 Hz
AQ 0.9087659 sec
RG 197.14
DW 13.867 usec
DE 18.00 usec
TE 300.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 150.9178981 MHz
NUC1 13C
P1 11.40 usec
PLW1 80.00000000 W
SFO2 600.1324005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 70.00 usec
PLW2 6.00000000 W
PLW12 0.07836700 W
PLW13 0.03941800 W
F2 - Processing parameters
SI 32768
SF 150.9027246 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
18.9
24.0
53.9
55.4
124.3
126.0
127.1
127.5
127.9
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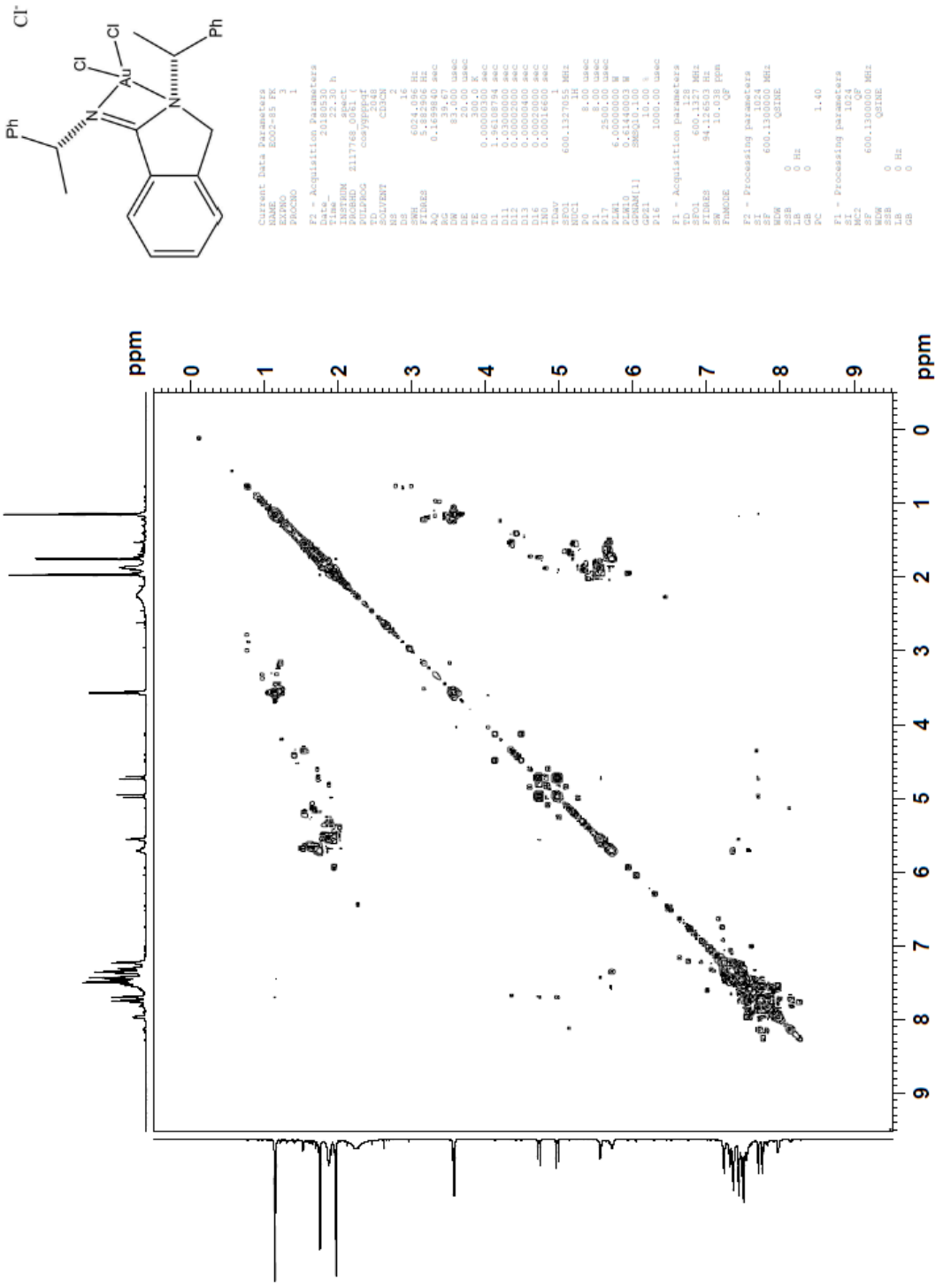
129.4
129.5
129.6
129.9
134.3
138.6
142.2
144.5
161.1
ppm


Cl⁻
Ph
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Cl
Au
Cl
N
Ph
ppm
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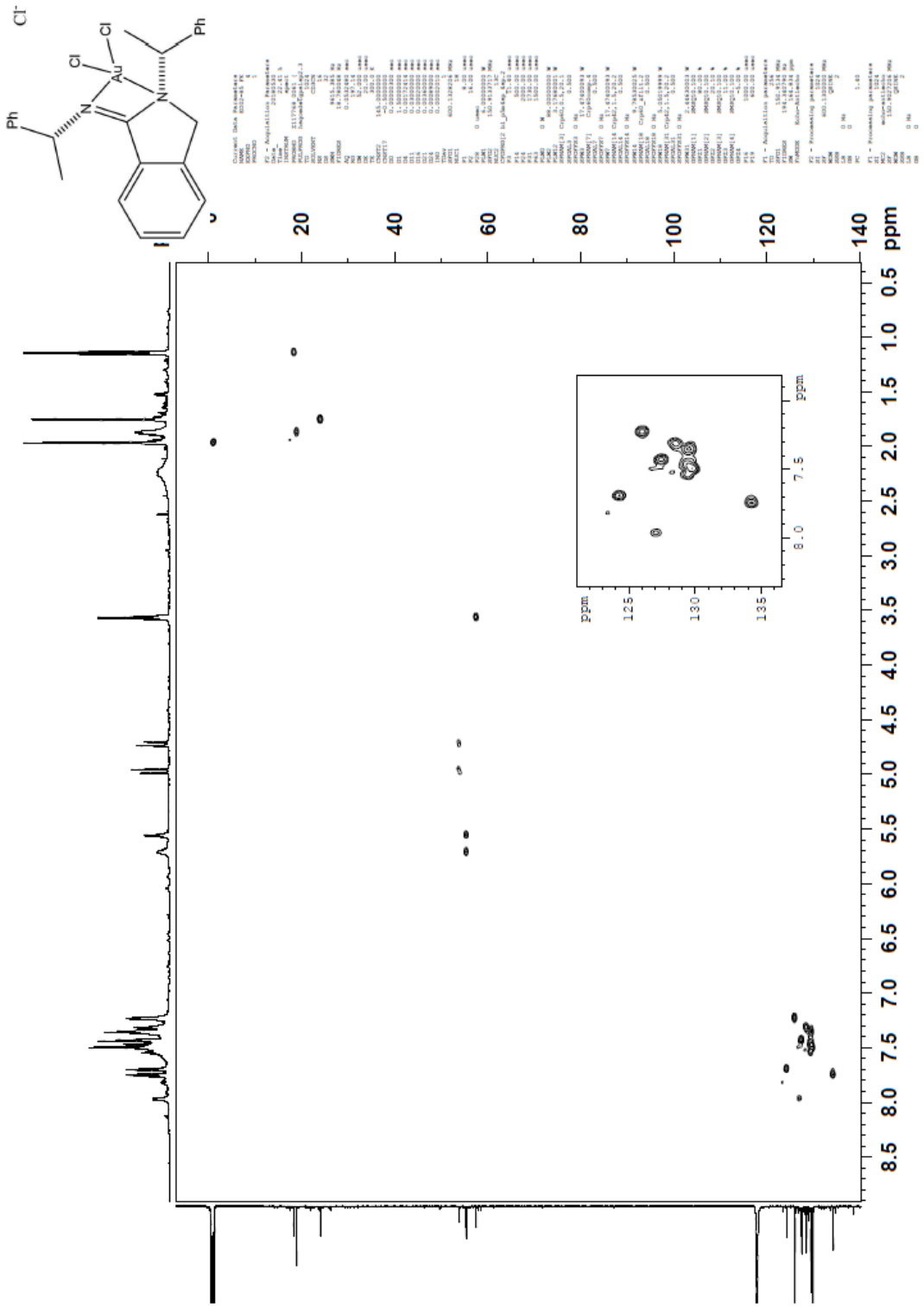
2
3
4
5
6
7
8
9
ppm


Cl⁻
Ph
N
Cl
Au
Cl
N
Ph
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40
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80
100
120
140
ppm
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1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
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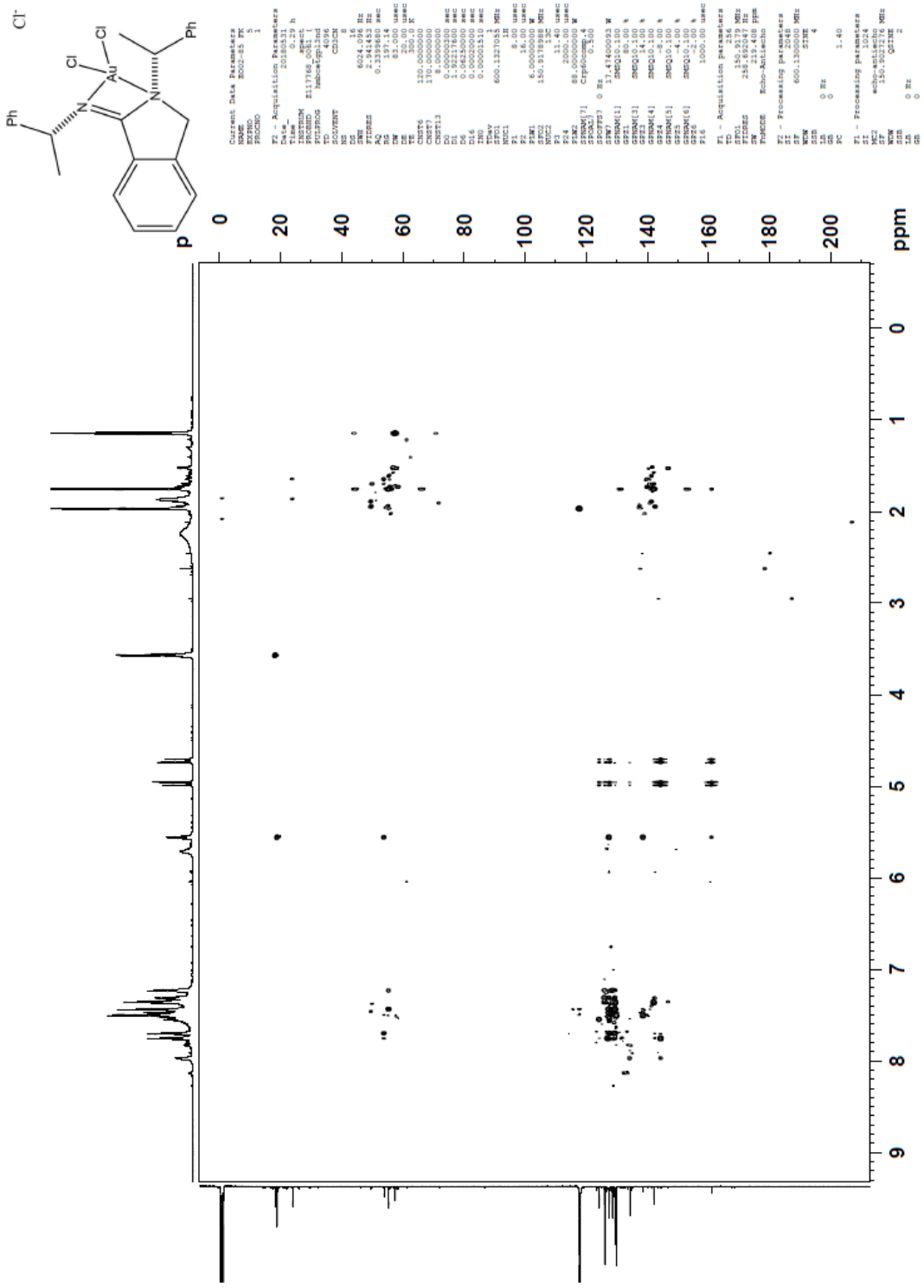
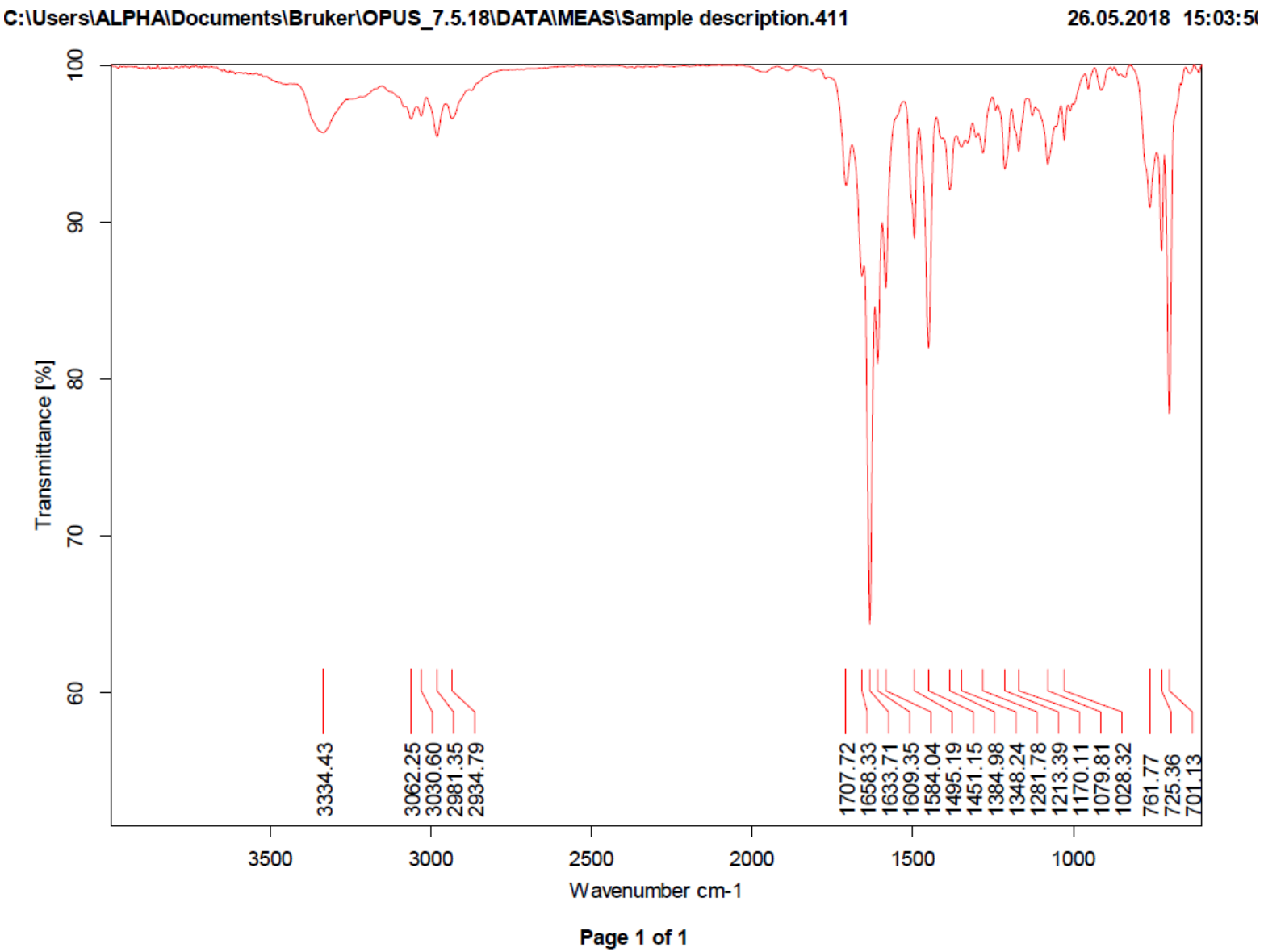
6.5
7.0
7.5
8.0
8.5
ppm
7.5
8.0
ppm
125
130
135


Cl⁻
Ph
N
Cl
Au
Cl
N
Ph
ppm


C:\Users\ALPHA\Documents\Bruker\OPUS_7.5.18\DATA\MEAS\Sample description.411
26.05.2018 15:03:5(
Transmittance [%]
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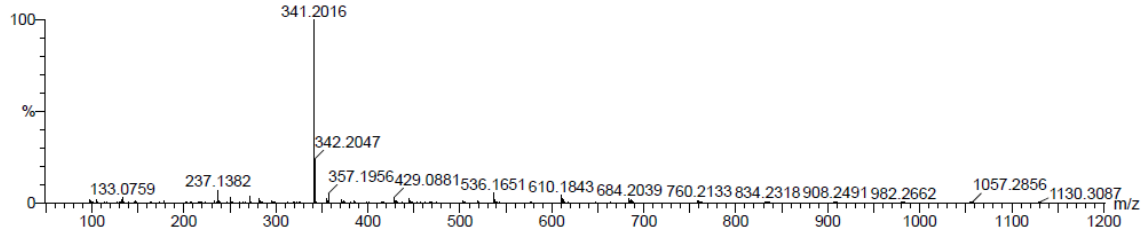
90
80
70
60
3334.43
3062.25
3030.60
2981.35
2934.79
1707.72
1658.33
1633.71
1609.35
1584.04
1495.19
1451.15
1384.98
1348.24
1281.78
1213.39
1170.11
1079.81
1028.32
761.77
725.36
701.13
3500
3000
2500
2000
1500
1000
Wavenumber cm-1
Page 1 of 1

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 2.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

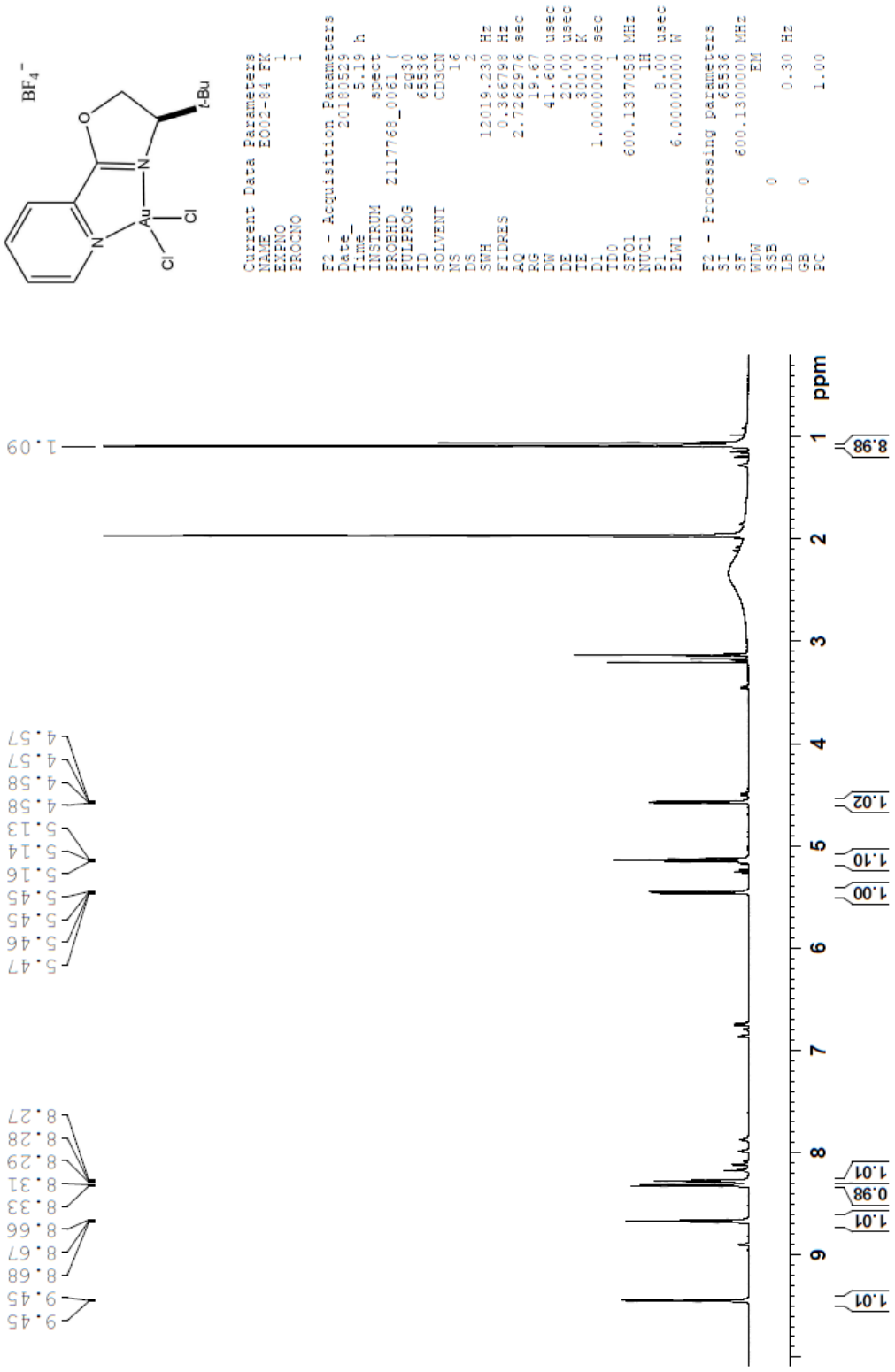
Monoisotopic Mass, Even Electron Ions
1065 formula(e) evaluated with 2 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-10 O: 0-20 Na: 0-1
2018 329POS 41 (0.767) AM2 (Ar,35000.0,0.00,0.00); Cm (41:43)
1: TOF MS ES+

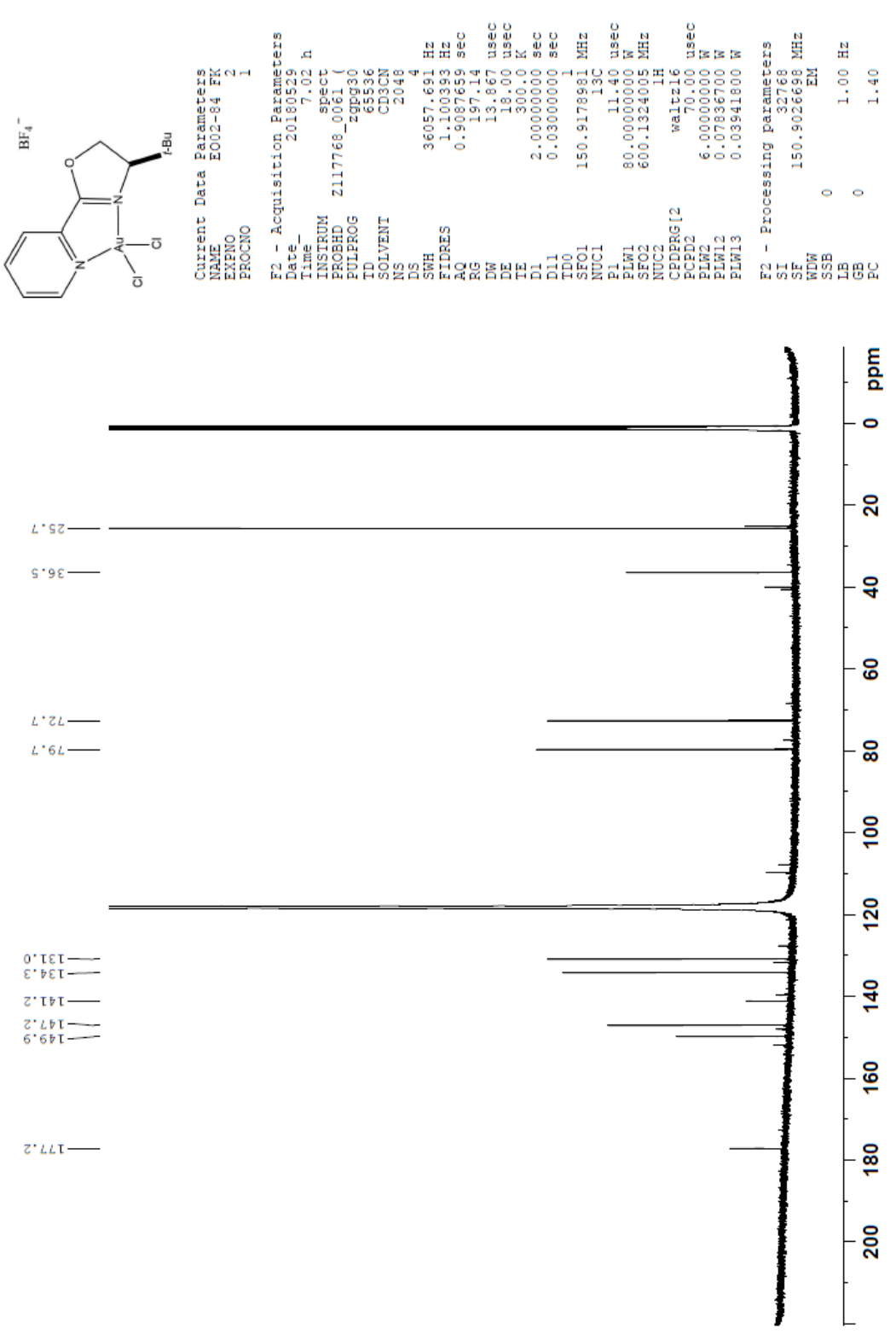
8.02e+005



Minimum:				-1.5				
Maximum:		5.0	2.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
341.2016	341.2018	-0.2	-0.6	13.5	1190.6	0.000	99.99	C24 H25 N2
	341.2009	0.7	2.1	1.5	1199.7	9.076	0.01	C8 H25 N10 O5

Appendix K Gold(III)-complex **10**

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Au
Cl
Cl
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PROCNO 1
F2 - Acquisition Parameters
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Time 7.02 h
INSTRUM spect
PROBHD Z117768_0061 (
PULPROG zgpg30
TD 65536
SOLVENT CD3CN
NS 2048
DS 4
SWH 36057.691 Hz
FIDRES 1.100393 Hz
AQ 0.90876659 sec
RG 197.14
DW 13.867 usec
DE 18.00 usec
TE 300.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 150.9170981 MHz
NUC1 13C
P1 11.40 usec
PLW1 80.00000000 W
SFO2 600.1324005 MHz
NUC2 1H
CPDPRG12 waltz16
PCPD2 70.00 usec
PLW2 6.00000000 W
PLW12 0.07836700 W
PLW13 0.03941800 W
F2 - Processing parameters
SI 32768
SF 150.9026698 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
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36.5
72.7
79.7
131.0
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149.9
177.2
ppm
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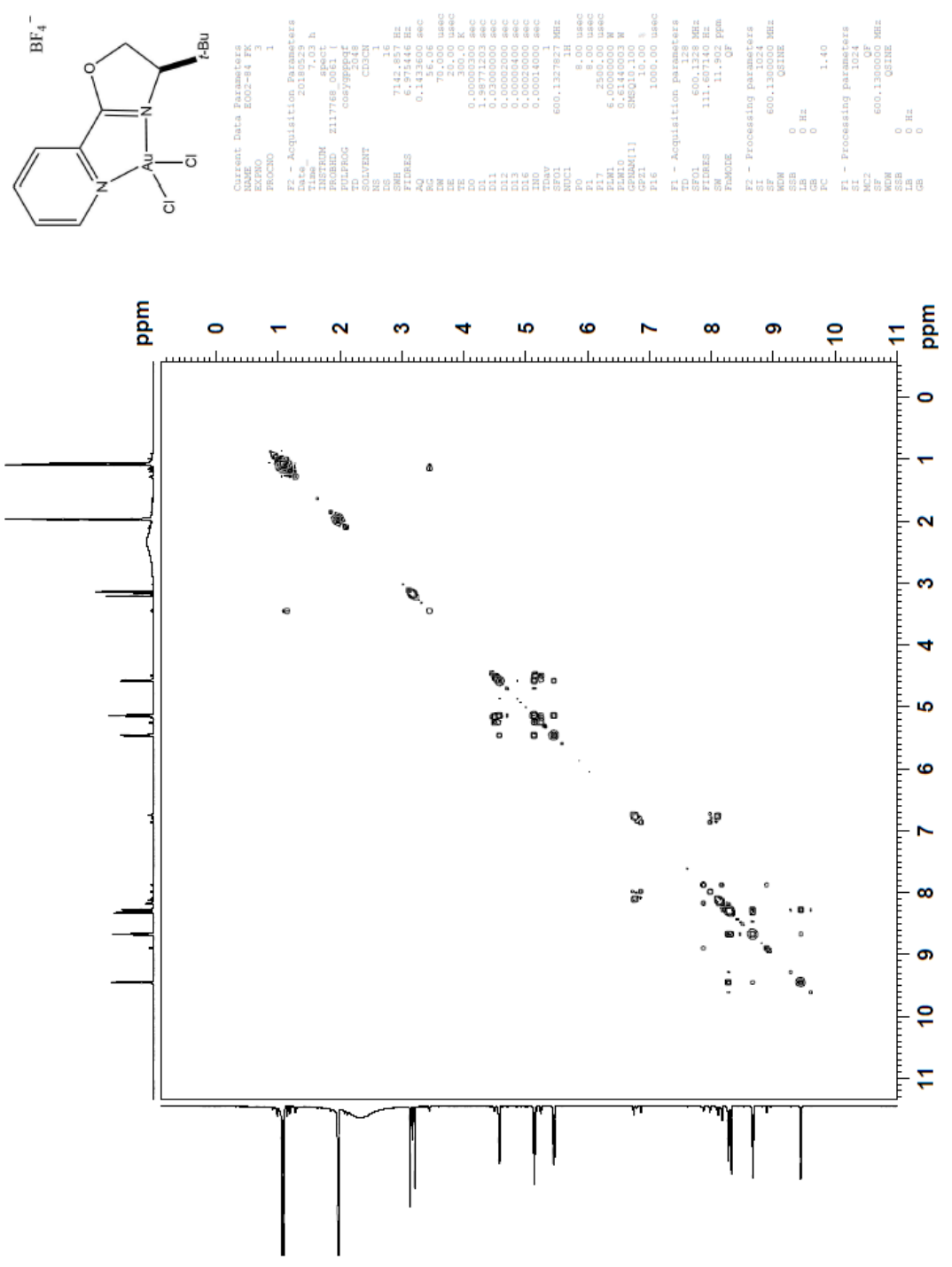
60
80
100
120
140
160
180
200


BF4 -
t-Bu
O
N
Au
Cl
Cl
N
ppm
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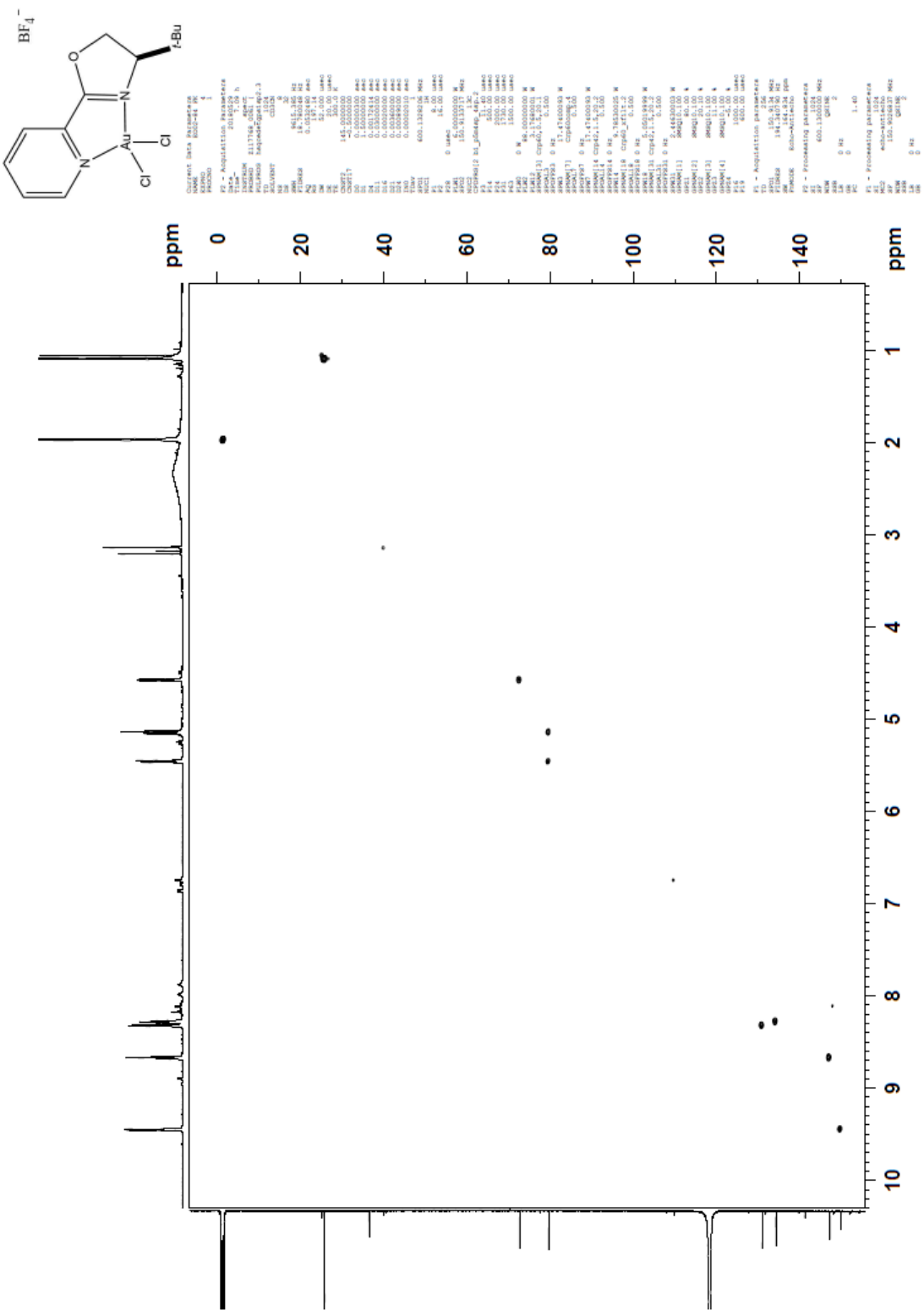
2
3
4
5
6
7
8
9
10
11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t-Bu
Au
Cl
Cl
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ppm
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80
100
120
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ppm
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2
3
4
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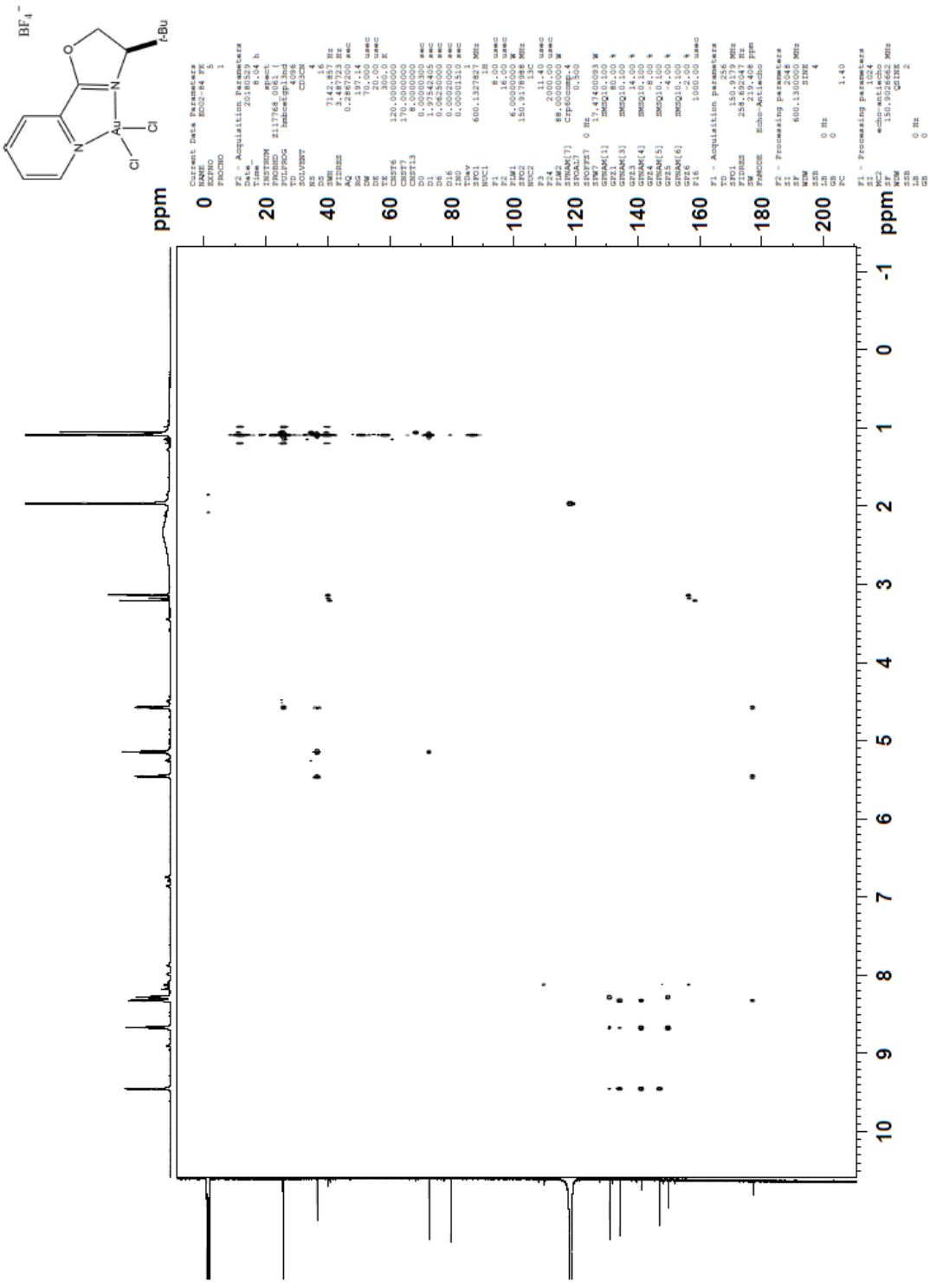
10


BF4−
t-Bu
O
N
Au
Cl
Cl
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ppm
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40
60
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180
200
ppm
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2
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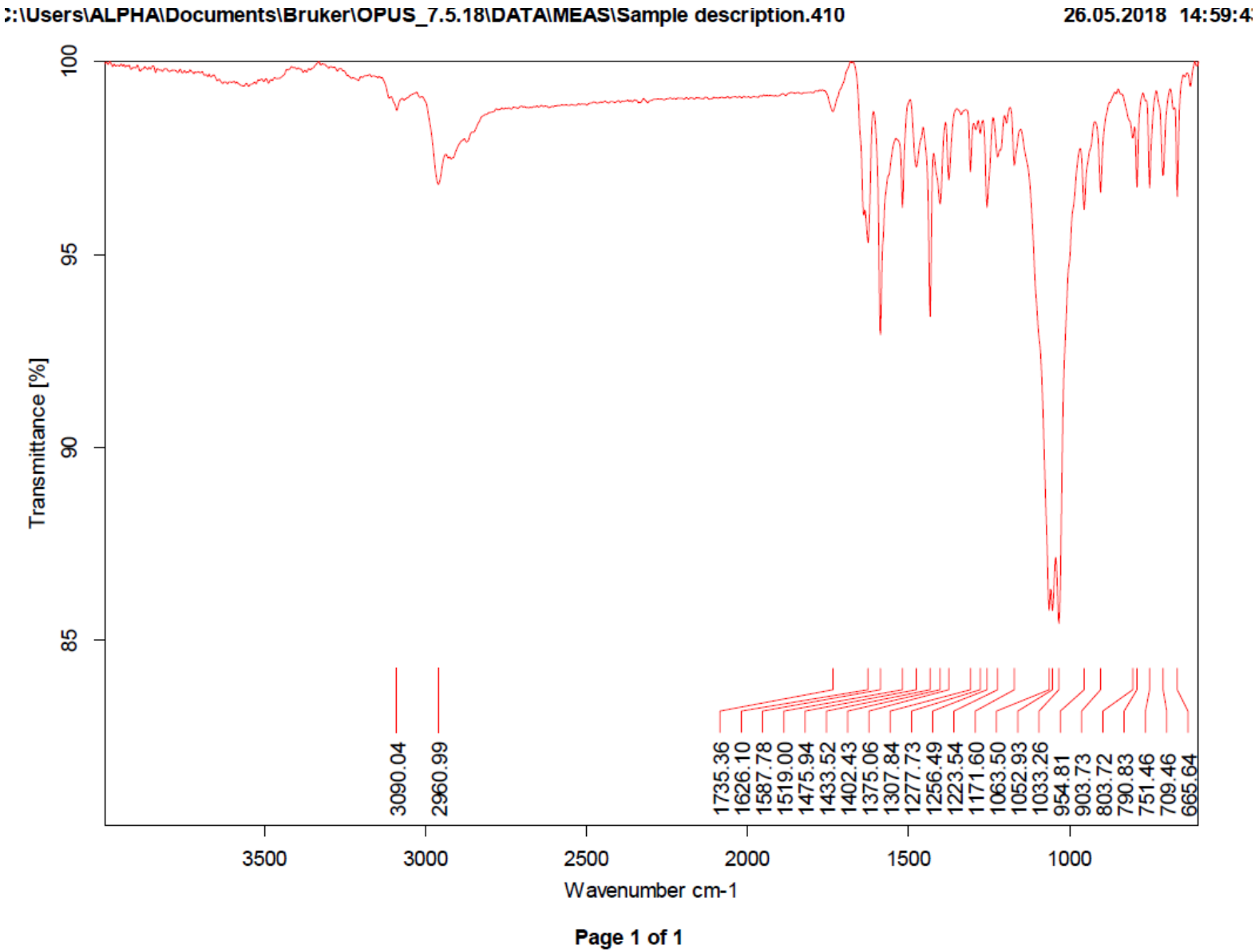
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26.05.2018 14:59:4
Transmittance [%]
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90
85
3090.04
2960.99
1735.36
1626.10
1587.78
1519.00
1475.94
1433.52
1402.43
1375.06
1307.84
1277.73
1256.49
1223.54
1171.60
1063.50
1052.93
1033.26
954.81
903.73
803.72
790.83
751.46
709.46
665.64
3500
3000
2500
2000
1500
1000
Wavenumber cm-1
Page 1 of 1

Elemental Composition Report

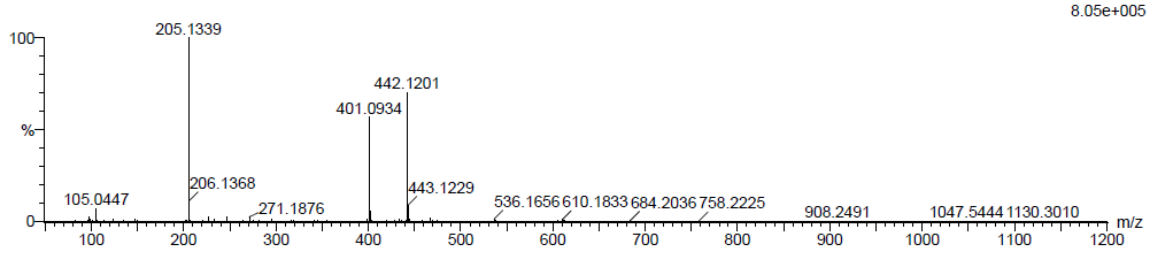
Single Mass Analysis

Tolerance = 3.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
968 formula(e) evaluated with 5 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-4 O: 0-20 Na: 0-1 Au: 0-1

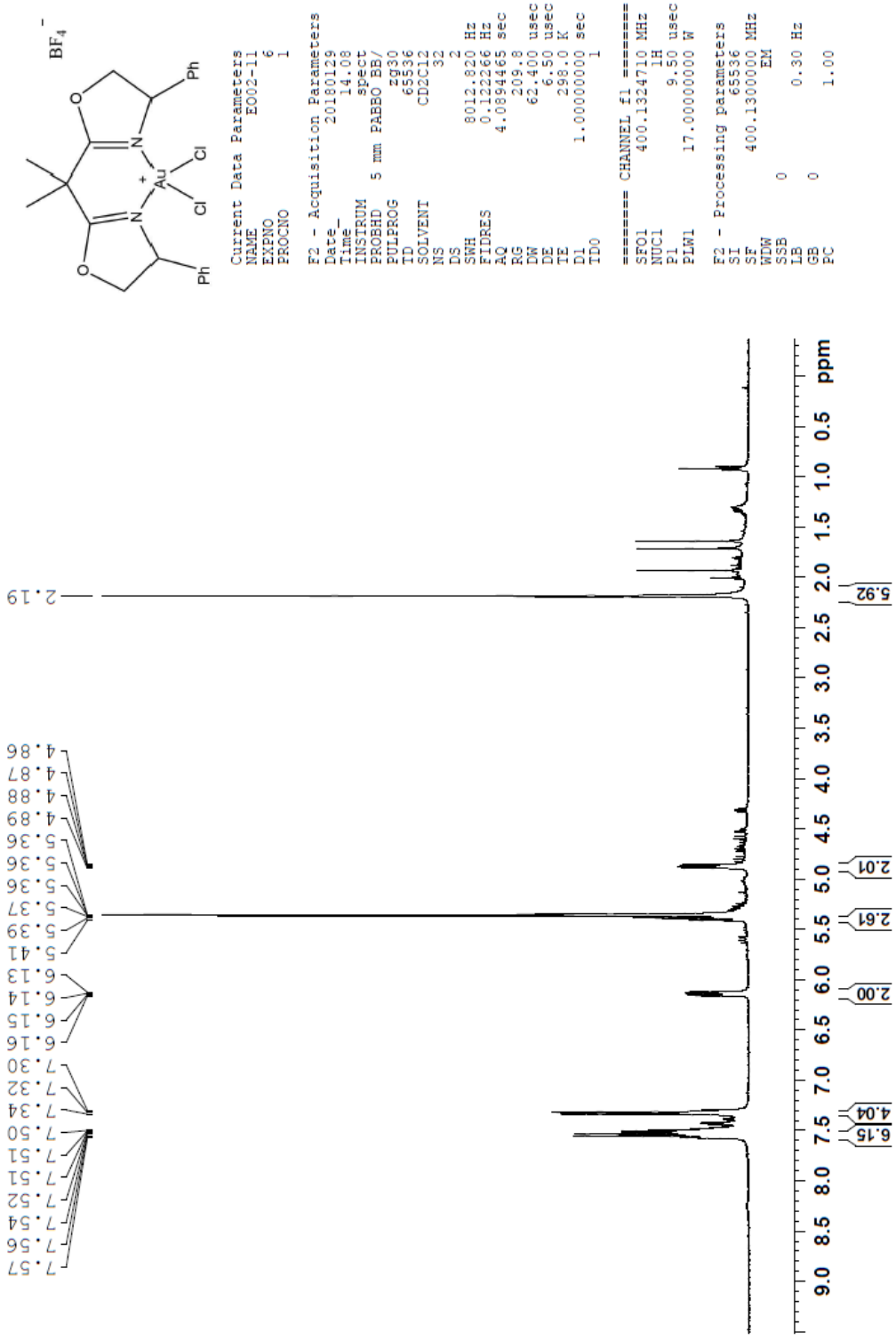
2018 330POS 41 (0.767) AM2 (Ar,35000.0,0.00,0.00); Cm (40:41)
1: TOF MS ES+

8.05e+005

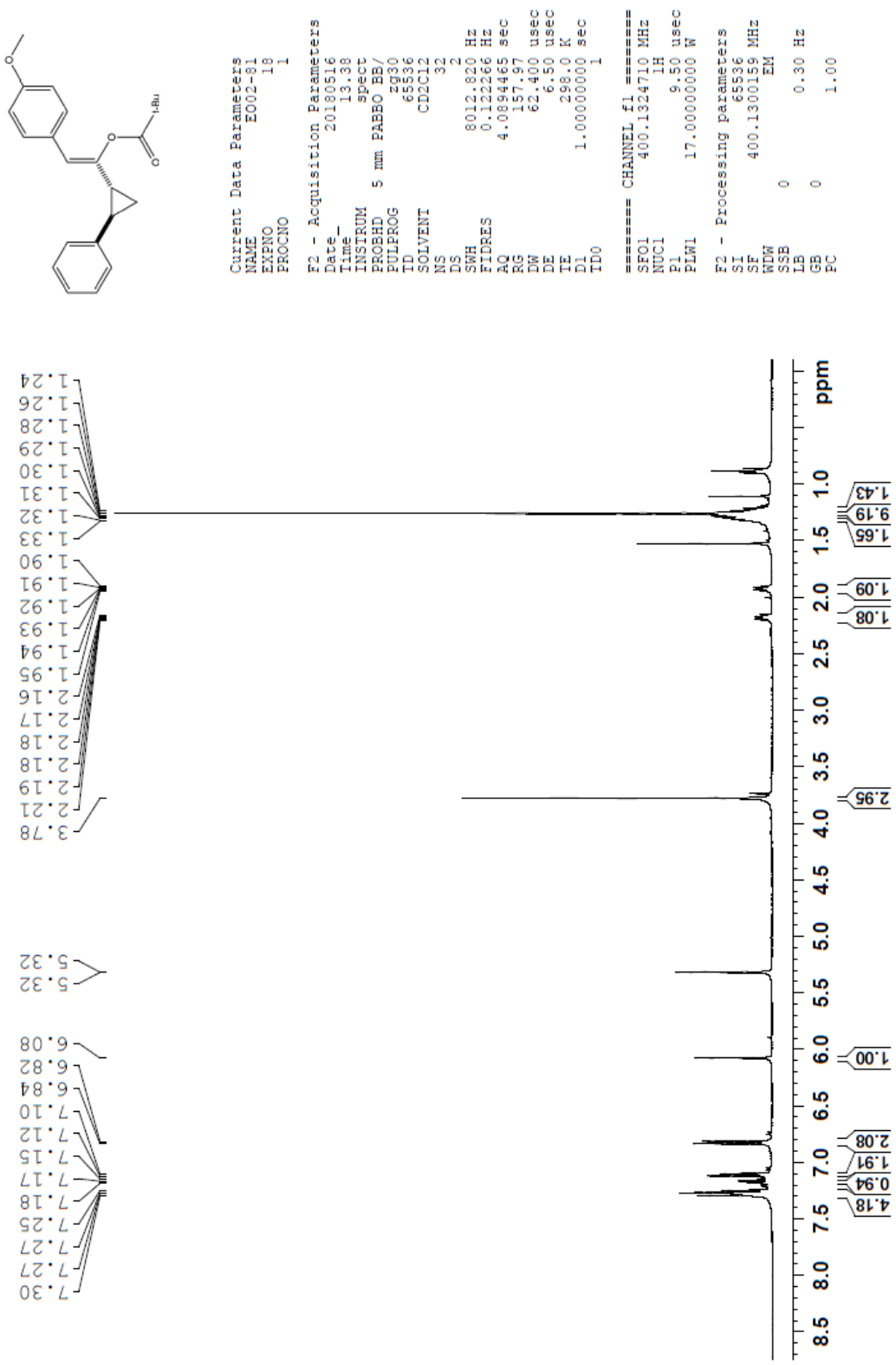


Minimum:				-1.5				
Maximum:		5.0	3.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
401.0934	401.0928	0.6	1.5	6.5	962.3	0.024	97.64	C12 H16 N2 O Au
	401.0945	-1.1	-2.7	8.5	966.9	4.679	0.93	C14 H17 N4 O10
	401.0931	0.3	0.7	3.5	967.4	5.183	0.56	C13 H21 O14
	401.0942	-0.8	-2.0	22.5	967.4	5.207	0.55	C29 H14 O Na
	401.0926	0.8	2.0	21.5	968.0	5.723	0.33	C26 H13 N2 O3

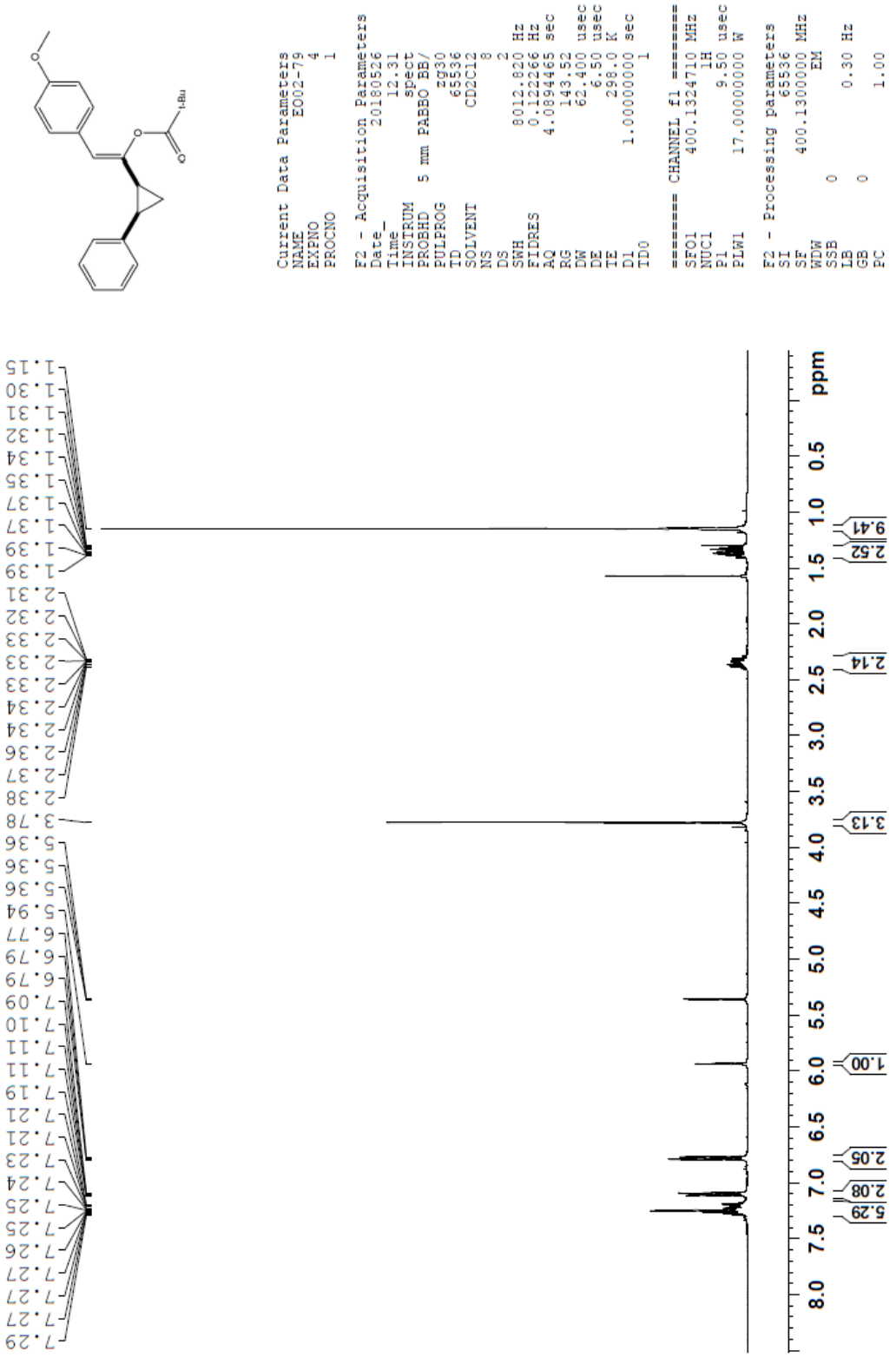
Appendix L Gold(III)-complex **12**



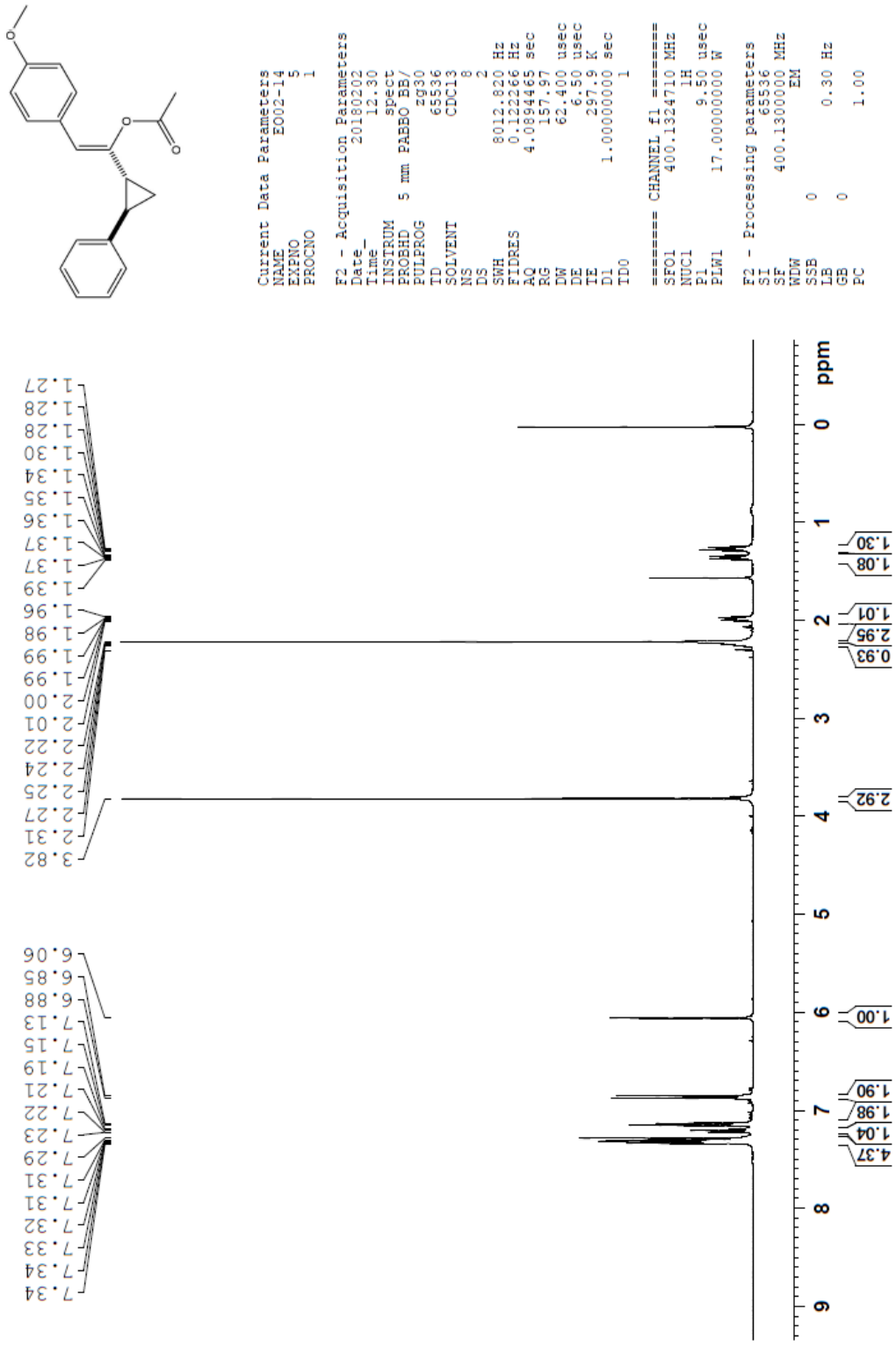
Appendix M *Trans*-**19a**



Appendix N *Cis*-**19a**



Appendix O *Trans*-**19b**



Appendix P **19c**