Dissertation zur Erlangung des Doktorgrades
der Fakultät für Chemie und Pharmazie
der Ludwig-Maximilians-Universität München

Stereoselective functionalization of azetidines

Von

Muhammad Shahbaz

aus

Rawalpindi, Pakistan

2025

Erklärung

Diese Dissertation wurde im Sinne von § 7 der Promotionsordnung vom 28. November 2011 von Prof. Dr. Dorian Didier betreut.

Eidesstattliche Versicherung

Diese Dissertation wurde eigenständig und ohne unerlaubte Hilfe erarbeitet.

München, den 12-05-2025

……

Muhammad Shahbaz

Dissertation eingereicht am:	07-04-2025
1. Gutachter:	Prof. Dr. Dorian Didier
2. Gutachter:	Prof. Dr. Konstantin Karaghiosoff
Mündliche Prüfung am:	06-05-2025

Dedication

I would like to dedicate this thesis to Allah and Holy Prophet Muhammad (S.A.W)

Acknowledgements

Firstly, all praises be to Allah Almighty for blessing me with understanding, strength, and courage to accomplish this work successfully. Nothing would have been possible without His grace and may the blessings be on Holy Prophet Hazrat Muhammad (PBUH).

I owe my gratitude to my Ph.D. supervisor Prof. Dr. Dorian Didier for encouragement, support, guidance and for providing his precious time to accomplish this research work on time.

In addition, I am deeply thankful to the Punjab Educational Endowment Fund (PEEF) for the scholarship they have provided throughout my degree.

I am grateful to my second reviewer Prof. Dr. Konstantin Karaghiosoff for his precious time and support. I am also thankful to my examiners Prof. Dr. Oliver Trapp, Prof. Dr. Andrea Rentmeister, Prof. Dr. Anne Schütz, Prof. Dr. Thomas M. Klapötke.

I appreciate the facilities provided by LMU which enabled me to finish my work on time. I am also grateful to my research group, faculty members, analytical department, and staff.

Furthermore, I would like to express my acknowledgment to my intern, Yasser Alhayani. He performed well in the laboratory and played a crucial role in completing the tasks shown in this thesis.

Finally, I pay heartfelt thanks to my parents and siblings for their love and efforts, enabling me to pursue my dreams. Also, I am very grateful to my beloved daughter Abeeha Fatima and my wife, Iqra Shahbaz, for providing me motivation and assistance all the time.

Parts of this Ph.D. Thesis have been published:

1. **M. Shahbaz** and Dorian Didier. Stereoselective electrophilic trapping at the alpha position of 3-arylated azetidines. (In preparation)

2. F. Trauner, F. Reiners, K.-E. Apaloo-Messan, B. Nißl, **M. Shahbaz**, et al.,"Strain-release arylations for the bis-functionalization of azetidines," Chemical Communications, vol. 58, no. 15, pp. 2564-2567, 2022.

3. F. Trauner, **M. Shahbaz**, Dorian Didier, "How the cube works," November 2021, Newsletter Chemistry 69(11):72-75.

Abstract

The synthesis of functionalized azetidine molecules has been and will continue to be crucial in advancing organic chemistry, as azetidine frameworks are among the most valuable structural motifs present in natural products and commercialized drugs. Due to this, the area of synthetic organic chemistry is continuously striving to develop innovative techniques that surpass previous generations in terms of cost and sustainability. The fundamental purpose of this thesis is to meet the ongoing demand for the creation of supplementary techniques and alternatives. Therefore, this work presents the diastereoselective approach for the synthesis of the functionalized azetidine molecules under several conditions. Initially, a range of techniques were employed to develop effective and widely recognized procedures for synthesizing fundamental 3-arylated azetidine compounds using various Grignard reagents. At last, established various approaches to achieve α-lithiation followed by electrophile trapping of 3-arylated N-protected azetidine and further applications to peptide formation. Also, selective 3-arylated azetidine intermediates can be formed through strain-release approach by adding nucleophilic organometallic species to in situ produced azabicyclobutanes. For the N-arylation of the resultant azetidines, single pot methods were further developed using Buchwald-Hartwig couplings or S_NAr reactions.

List of Abbreviations

Boc	tert-butoxycarbonyl
Botc	tert-butoxythiocarbonyl
ABB	1-azabicyclo[1.1.0]butane
DCM	dichloromethane
s-Bu	sec-Butyl
n-Bu	butyl
t-Bu	tert-butyl
°C	Degree Celsius
dr	diastereomeric ratio
DMSO	dimethyl sulfoxide
Et_3N	triethylamine
eq.	equivalents
h	hour (s)
g	gram (g)
LDA	lithium diisopropylamide
Piv	pivaloyl
NMR	nuclear magnetic resonance
IR	infrared
PG	protecting group
Py	pyridine
rt	room temperature
THF	tetrahydrofuran
TMEDA	N,N,N,N-tetramethylethylenediamine
R_f	retardation factor
DG	directing groups
HRMS	high resolution mass spectrometry
ATR	attenuated total reflectance
cm^{-1}	wavenumber
δ	chemical shift
DMF	dimethylformamide
E	electrophile

ee	enantiomeric excess
er	enantiomeric ratio
Het	heteroaryl
GC	gas chromatography
MP	melting point
M	molar
MeLi	methyllithium
mmol	millimole
MS	mass spectrometry
n-BuLi	n-butyllithium
s-BuLi	sec-butyllithium
Ph	phenyl
ppm	parts per million
R	organic substituent
SM	starting material
t-BuLi	tert-butyllithium
TLC	thin layer chromatography
mol%	equiv.10^2
TMSCl	trimethylsilyl
PG	protecting groups
EWG	electron withdrawing group
EDG	electron donating group

Table of Contents

ACKNOWLEDGEMENT……IV

ABSTRACT……VI

ABBREVIATIONS……..VII

A. INTRODUCTION.....1

1 Organometallic Chemistry.....1

1.1 Oxidative Insertion.....2

1.2 Halogen-Metal Exchange Reactions.....2

1.3 Transmetalation.....3

1.4 Deprotonation of Alkynes.....4

1.5 Deprotonation of aromatic ring (Ortholithiation).....4

2 Azetidines.....5

2.1 Synthesis of azetidines.....6

2.2 α-Lithiation of azetidines.....7

2.3 Activation/Electrophilic substitution of azetidines.....8

2.4 Removal of N-thiopivaloyl group.....11

2.5 Alpha-Lithiation/Electrophilic substitution of N-thiopivaloylazetidin-3-ol.....11

2.6 Deprotection of 2-Substituted N-thiopivaloylazetidin-3-ol.....12

2.7 Electrophilic trapping/Deprotection of N-Botc azetidine.....13

2.8 Enantioselective α-electrophilic substitution of N-Botc-azetidine.....15

2.9 2, 3-disubstituted azetidines.....16

2.10 Carbon-Carbon bond formation of azetidines.....18

2.11 Carbon-Nitrogen bond formation.....24

3 Objectives.....27

B. Results and Discussion.....30

1 Stereoselective approach for the electrophilic α-substitution of 3-arylated azetidines 30

1.1 Introduction 30

1.2 Optimization and Scope of the lithiation/electrophilic trapping of azetidines 33

1.3 Stereoselectivity of 3-arylated azetidines upon electrophilic incorporation 37

1.4 Competition between stereochemistry of electrophilic substituted azetidines 43

2 Bis-arylation of azetidines by means of strain release approach 45

2.1 Introduction 45

2.2 Optimization and scope for the strain release bis-arylation of azetidines 46

3 Conclusion 54

C. Experimental Section 57

3 General Considerations 57

4 General Procedures 58

4.1 Synthesis of Aryl Grignard Reagents 58

4.2 Synthesis of 3-substituted azetidines 58

4.3 Preparation of O-(tert-butyl) 3-pheylazetidine-1-carbothioate 59

4.4 Preparation of N-thiopivaloyl 3-arylated azetidines 59

4.5 Lithiation-electrophilic substitution 60

5 Preparation and Characterization of compounds 61

6 NMR Spectra 91

7 Single Crystal X-Ray Diffraction 170

D. References 174

List of Schemes

Scheme 1. Mechanism for the oxidative addition of magnesium into carbon-halogen bonds. 2

Scheme 2. A typical halogen-metal exchange reaction. 3

Scheme 3. The general transmetalation reaction. 3

Scheme 4. The general reaction for the deprotonation of alkyne [30]. 4

Scheme 5. Reaction for the ortholithiation of aromatic ring [31]. 5

Scheme 6. Examples of biologically active drugs and natural substances including azetidine. 6

Scheme 7. Strain-released driven synthesis of azetidines using ABB. 7

Scheme 8. First reported examples of α-lithiated azetidines. 7

Scheme 9. Presents preparation, lithiation, and electrophilic trapping of N-thiopivalamide **5**. The yields provided are specifically for the product that has been separated. [a]100% D, determined by ^{1}H NMR and GC-MS. [b]Main diastereomers. [c]Isolated as methyl ester after reacting with $TMSCHN_2$. DMAP = 4-dimethylaminopyridine, py = pyridine, and Piv = pivaloyl. 9

Scheme 10. N-thiopivaloyl azetidine **5** undergoes an asymmetric lithiation-methylation sequence. . 10

Scheme 11. Removal and transformation of the N-thiopivaloyl group 11

Scheme 12. Electrophilic incorporation into N-thiopivaloylazetidin-3-ol **13**. The yields mentioned are specifically for the product that has been separated. [a]Ratio of cis/trans isomers is indicated, with the dominant diastereoisomer being depicted. The major diastereoisomer displayed has a cis/trans ratio[c]. [b]Mixture of epimers at the side chain carbinol, with the major diastereoisomer being depicted. 12

Scheme 13. Preparation, lithiation, and electrophilic trapping N-Botc azetidine **16**. **17g** is deprotected using TFA. The yields mentioned are specifically for the product that has been separated. [a]95 % D, determined by mass spectrometry. [b]dr (70:30), and the dominant diastereomer is displayed. [c]1.0 equivalent of s-BuLi was used. 14

Scheme 14. The lithiated N-Botc-azetidine **16** undergoes enantioselective α-electrophilic substitution. 15

Scheme 15. The reaction involves the use of Pd(0) to facilitate cross coupling and transmetalation with CuCN·2LiCl of organozinc species **31** generated from azetidine. [a]Reaction is conducted at room

temperature. The organozinc species **32** can easily undergo transmetalation with CuCN·2LiCl in THF. Upon reaction with allyl bromide, it produces azetidine **35** with a moderate yield. 19

Scheme 16. Methods utilizing nickel to produce 3-aryl azetidines. [a]$NiCl_2$.glyme(10 mol%), 4-ethylpirydine (50 mol%), phenanthroline (20 mol%), MeOH (0.2 M). [b]NiI_2 (10 mol%), $NaBF_4$ (50 mol%), Mn (2 eq.), di-tBu-bipyridine (10 mol%), DMA (0.2 M), 4-ethylpyridine (1 eq.), Mn (2 eq.), and $MgCl_2$ (1 eq.). 20

Scheme 17. Iron- and cobalt-facilitated arylation of azetidines. [a][cat.] = $CoCl_2$ (5 mol%). [b][cat.] = $FeCl_2$ (10 mol%). Ts = Tosyl. 22

Scheme 18. Involves Rueping's azetidine cross-coupling using Grignard reagents and synthetic application of pharmaceutical importance. 23

Scheme 19. General reaction for the formation of Pd catalyzed C-N bond. 25

Scheme 20. Sketch of the Buchwald-Hartwig amination catalytic cycle. 26

Scheme 21. Formation of 3-arylated azetidines using Grignard reagents. 27

Scheme 22. Substitution of protecting groups on 3-arylated azetidines. 27

Scheme 23. α-lithiation/electrophilic substitution 3-arylated N-protected azetidines using various conditions and electrophiles. 28

Scheme 24. Nucleophilic aromatic substitutions (S_NAr) of 3-arylated azetidines. 29

Scheme 25. C-N bond formation of 3-arylazetidines via Buchwald–Hartwig coupling. 29

Scheme 26. Comparison among previous and current work for α-lithiation/electrophilic substitution of azetidines. 32

Scheme 27. Synthesis of N-protected 3-subsituted azetidines using Botc and tPiv groups. 34

Scheme 28. Possible stereoisomers of N-protected 2,3-disubsituted azetidine 36

Scheme 29. α-lithiation/electrophilic trapping of 3-arylated N-tPiv protected azetidines using various electrophiles. 42

Scheme 30. Metal-catalyzed asymmetric reduction for the diastereoselective synthesis of novel α-amino acids [153]. 43

Scheme 31. Diastereoselective synthesis of novel α-aminoacids using tPiv, **58m-58p** (51 to 87 %) and Botc, **60d** (19 %), respectively. 44

Scheme 32. Synthesis of peptide chains via functionalized 2-azetidinecarboxylic acid. 44

Scheme 33. Synthetic approach to 1,3-bisfunctionalized azetidines. 46

Scheme 34. Issues related with the reported conditions for the bis-functionalization of azetidines. .. 47

Scheme 35. Establishing conditions for the strain-release reaction with aryl-magnesium reagents. .. 48

Scheme 36. Nucleophilic aromatic substitutions (S_NAr) of 3-arylated azetidines. 49

Scheme 37. Buchwald–Hartwig coupling of 3-arylazetidines. [a] x = 1 mol%, [b] x = 2 mol%, [c] x = 3 mol%. 51

Scheme 38. One-pot ring-opening/Buchwald–Hartwig coupling sequence of 3-arylated azetidines. [a] x = 3 mol%, [b] x = 4 mol%, [c] x = 5 mol%. 53

Scheme 39. Electrophilic trapping at 2 position of N-protected functionalized azetidines. 54

Scheme 40. Comparison of the yield and diastereomeric ratio among 3-arylated N protected azetidines containing electrophiles (Deuterium oxide and TMSCl). 55

Scheme 41. Strain release approach for the bis-arylation of azetidines. 55

List of Tables

Table 1. Optimization of α-lithiation/electrophilic substitution at 3-arylated N-protected azetidines. 35

Table 2. Scope of Electrophilic Incorporation into 3-Arylated N-Botc azetidines.....38

Table 3. Optimization of conditions for Buchwald–Hartwig couplings of azetidines.....50

List of Figures

Figure 1. Displays the favourable deprotonation side opposite to R^1 group due to steric hindrance. 28

Figure 2. Strain-release reagents use for medicinal discovery.....30

Figure 3. Major trans-diastereomer observed for 2,3-disubstituted azetidine as revealed by X-ray diffraction technique. 37

A. INTRODUCTION

1 Organometallic Chemistry

Organometallic compounds are chemical compounds that have at least one bond between a carbon atom and a metal or metalloid atom, such as boron, silicon, or tin. While the first synthesis of organometallic compounds documented back to the 18th century, their widespread use was popularized by Victor Grignard's groundbreaking research on organomagnesium compounds in 1900 [1], for which he was awarded the Nobel Prize in 1912. Over a century later, several compounds with C-M bonds have been synthesized and examined, containing a broad range of earth alkaline, alkaline and transition metals, as well as exhibiting significant structural variability on the organic counterpart [2-5].

The attractiveness of organometallic compounds lies in the intrinsic polarization of the C-M bond, which can be best understood through the difference in electronegativity between the two atoms. Carbon atom shows electronegativity value of 2.55 on the Pauling scale, the carbon atom exhibits more electronegativity compared to any known metal or metalloid, therefore generally it acts as a nucleophile when bonded to a metal. The ionic character of the C-M bond increases as the difference between the two atoms becomes larger leading to a more reactive species. Due to this, organolithium compounds are extremely reactive substances that can even behave as nucleophiles for ethereal solvents at ambient temperature but they have a little tolerance for functional groups [6]. On the other hand, Grignard reagents exhibit lesser reactivity compared to organolithium compounds and can be kept in ethereal solvents at a room temperature, however they have a higher tolerance for functional groups [7].

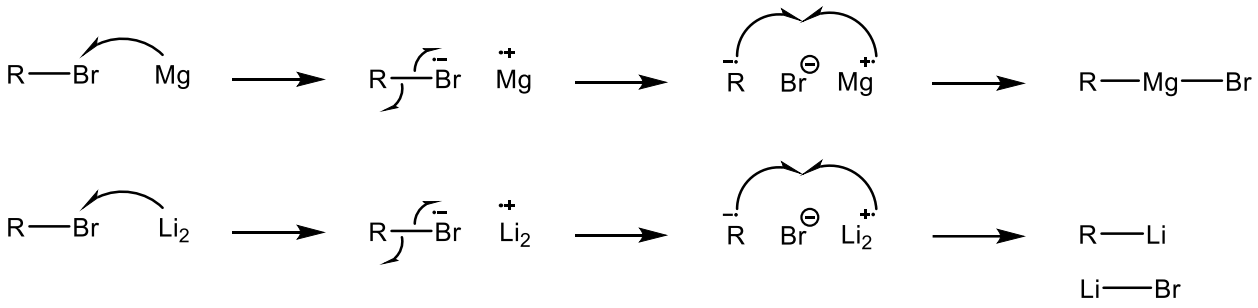
Moreover, when the hybridization of the organometallic species is altered, further tendencies for tolerance and reactivity can be detected. Typically, the reactivity of organometallic compounds rises as we go from C_{sp}-M to C_{sp^3}-M species, because the stabilization of the nucleophilic carbon atom from the nuclei decreases as the p-orbital character increases [8]. Various methods can be employed to access organometallic species such as oxidative insertion, halogen-metal exchange, transmetalation, deprotonation of alkynes and deprotonation of aromatic ring (ortholithiation) as described in the next paragraphs of my thesis.

1.1 Oxidative Insertion

In the late 19th century, Frankland [9] and Grignard [1] developed the first general approach for creating organometallic reagents. This process involves the introduction of a metal, such as lithium [10], zinc [9], or magnesium [1], into a carbon-halogen bond through oxidative insertion. In the case of magnesium, this mechanism is commonly believed to occur through a radical SET (single electron transfer) mechanism [11]. Nevertheless, new quantum-chemical calculations have indicated the significance of other processes, including a nucleophilic pathway [12].

To enhance the reaction progress, it is necessary to activate the typically oxidized magnesium turnings or powder. This can be achieved by using substances such as iodine or 1,2-dibromoethane [13, 14]. Various methods have been listed for the synthesis of organometallic compounds:

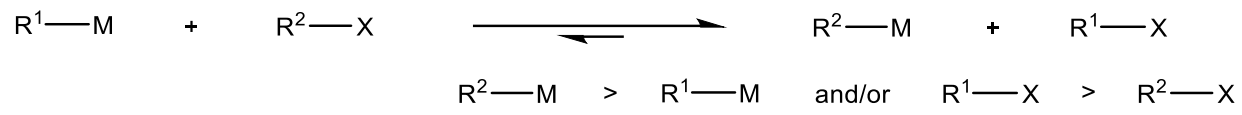
Firstly, the oxidative addition is a crucial reaction step that results in a formal change in the oxidation state of the metal Mg to Mg^{+2}, through the transfer of two electrons from the metal to two newly coordinating ligands [15] as shown in Scheme 1.



Scheme 1. Mechanism for the oxidative addition of magnesium into carbon-halogen bonds.

1.2 Halogen-Metal Exchange Reactions

The halogen-metal exchange is a highly convenient and fast method for synthesizing organometallic compounds. Since Prevost's discovery in 1931 [16] of bromine-magnesium exchange reactions, it has been found that various other metals, including transition metals and lanthanides, can also participate in metal-exchange processes [17, 18]. A halogen-metal exchange refers to a process in which an organometallic species and an organic halide are in equilibrium (Scheme 2). The equilibrium direction is shifted based on the relative stability of the carbon-metal bonds, promoting the production of the most stable organometallic reagent [19].



Scheme 2. A typical halogen-metal exchange reaction.

The stability of the produced organometallic compound is primarily determined by the hybridization of the carbon atom, as well as extra stabilizing inductive and mesomeric effects. The order of stability, from highest to lowest, is as follows: sp > sp^2_{vinyl} > sp^2_{aryl} > sp^3_{prim} > sp^3_{sec} > sp^3_{tert} [8]. The direction of the exchange is primarily determined by the organic component, whereas the rate of the exchange is heavily influenced by the electronegativity of the metal. As a result, a halogen-lithium exchange occurs more rapidly than a halogen-magnesium exchange [20].

1.3 Transmetalation

Transmetalation emerged as a convenient alternative to create organometallic compounds that cannot be synthesized using oxidative insertion, halogen-metal exchange processes, or directed metalation. The transmetalation of an organometallic reagent to another organometallic compound can be achieved by treating it with a metal salt, provided that the cation in the salt has greater electronegativity than the metal in the original organometallic reagent [21, 22], (Scheme 3).

Scheme 3. The general transmetalation reaction.

Transmetalations serve two primary objectives: Initially, organometallic compounds that are otherwise unstable can be converted into more stable, functional group tolerant species with modified reactivity [23]. Transmetalation results in the formation of organometallic species, capable of facilitating certain reactions, such as copper-catalyzed allylations or Negishi cross-coupling reactions [24, 25], in which transmetalation reactions also have a significant impact on the catalytic cycle. Furthermore, the process of rapidly generating organomagnesium or organolithium compounds and then transmetalation is typically faster than alternative methods used to synthesize more covalent organometallic species, such as organo-boron, -tin or -

silicon compounds. This approach is also widely favored in the field of organolanthanide chemistry [26-29].

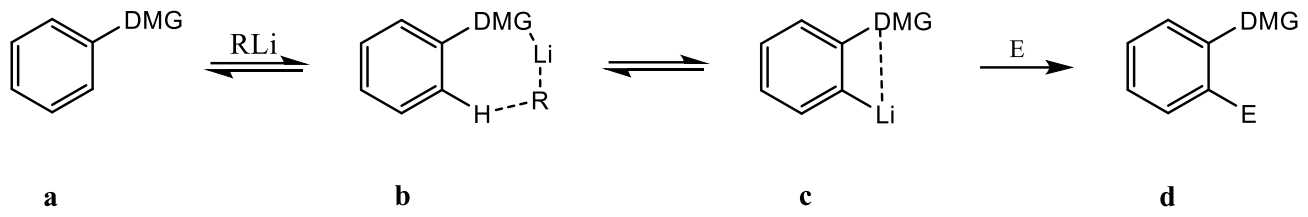
1.4 Deprotonation of Alkynes

Alkynes, characterized by C–H bonds derived from sp orbitals, have the highest acidity among hydrocarbons, with pK_as about equal to 25. They can undergo deprotonation by more basic organometallic compounds such as ethylmagnesium bromide or butyllithium (Scheme 4). Alkynes possess enough acidity to undergo deprotonation even by nitrogen bases. Another commonly employed method for deprotonating alkynes involves the use of $NaNH_2$ (sodium amide), which is generated by reacting sodium with liquid ammonia.

Scheme 4. The general reaction for the deprotonation of alkyne [30].

1.5 Deprotonation of aromatic ring (Ortholithiation)

Butyllithium can abstract a proton under specific conditions from sp^2 hybridized carbon atom of aromatic ring, resulting in the formation of an aryllithium compound. The reason it works is that the protons attached to sp^2 carbons are more acidic than the protons attached to sp^3 carbons, although they are significantly less acidic than alkyne protons. However, there is another factor included, for a proton to be eliminated, there must be a functional group adjacent to it called directing metalating group (DMG) that contains oxygen or sometimes nitrogen **(a)**. The functional group facilitates the attack of butyllithium to neighboring protons. This is achieved by creating a complex with the lithium atom (Lewis acid), **(b)**. This is like how ether solvents dissolve Grignard reagents by building complexes with their Lewis acidic metal ions. The ortholithiation reaction involves the removal of protons located ortho to the functional group **(c)** after that various electrophiles (E) can be substituted **(d)** as shown in Scheme 5.

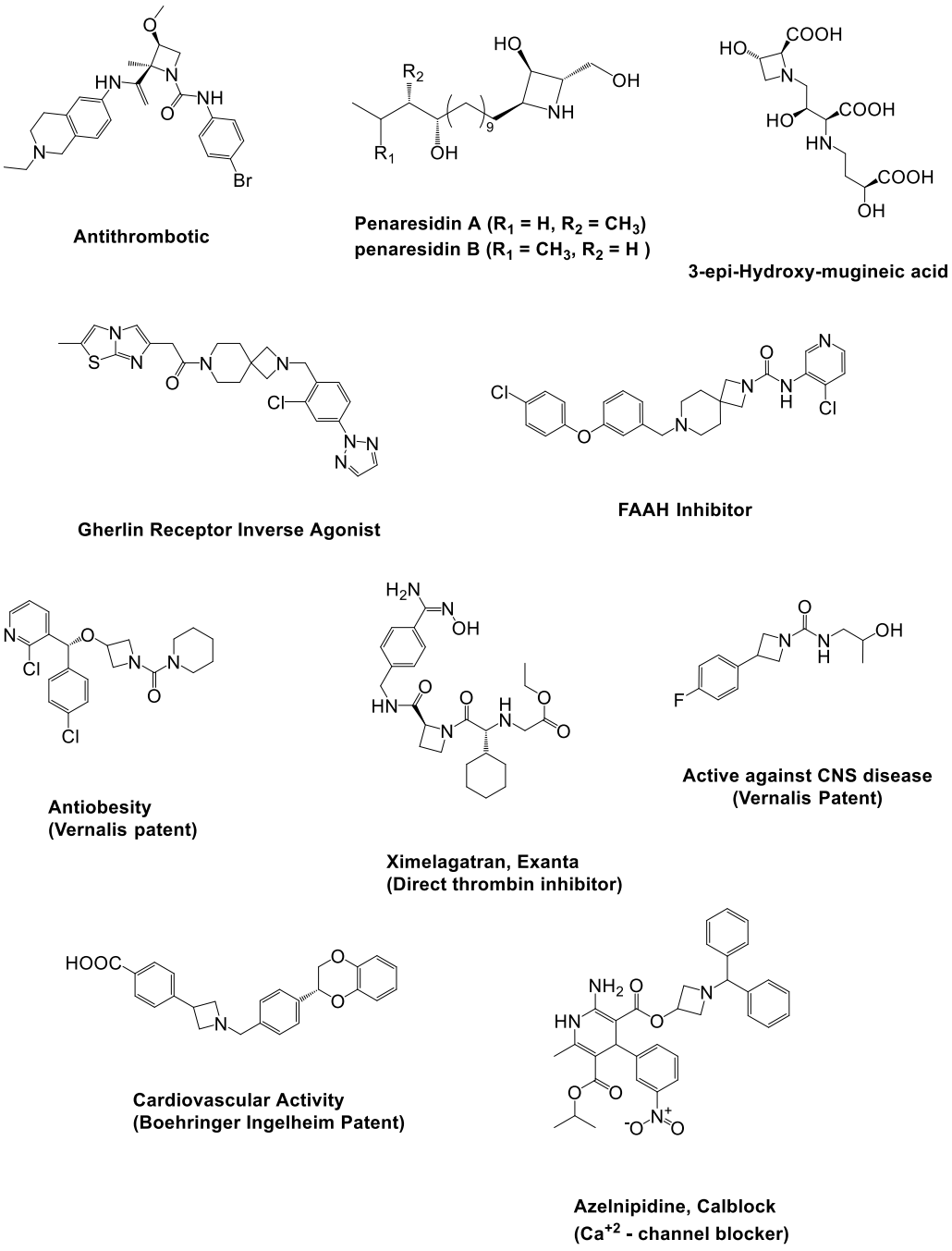


Scheme 5. Reaction for the ortholithiation of aromatic ring [31].

Ortholithiation is advantageous since the starting material does not require the use of a halogen atom. However, it is less general compared to the other methods we have mentioned for producing organolithium compounds, as there are strict restrictions on the types of groups that the aromatic ring must possess.

2 Azetidines

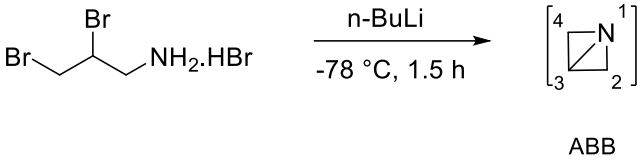
Synthetic chemical research continues to focus heavily on the synthesis and elaboration of saturated nitrogen-containing heterocycles, which are among the most valuable structural motifs found in natural products, commercialized drugs, and bioactive compounds [32, 33]. The increasing demand for drug candidates with improved degrees of saturation and three-dimensionality has made effective access to substituted heterocycle derivatives even more important in recent years [34].
Azetidines, a class of under explored saturated N-bearing heterocycles [35], are particularly intriguing because they possess a good balance between strong molecular rigidity and satisfactory stability, which enables effective modification of the pharmacological properties exhibited by molecules containing this moiety [36-38]. Several commercial applications attest to the fact that synthetic chemists have historically paid far greater attention to the chemistry of higher and lower homologues with respect to this four-membered aza-heterocycle [39-42]. Despite this, due to its presence in several natural compounds and drugs, the azetidine core is becoming increasingly attractive to the pharmaceutical and agrochemical sectors [37, 43-45].
Azetidines have also been used in certain applications as chiral auxiliaries and ligands in metal-catalyzed transformations [46]. Among the many useful applications of the azetidine ring, the most notable examples are probably associated with drugs like Ximelagatran (Exanta®) and Azelnipidine (Calblock®), or with a wide range of 3- and 2-substituted azetidines exhibiting various pharmacological properties [47-50], (Scheme. 6).



Scheme 6. Examples of biologically active drugs and natural substances including azetidine.

2.1 Synthesis of azetidines

Azetidine can be synthesized from the easily obtainable 1-azabicyclo[1.1.0]butane (ABB), which has a significant strain in the C-N-C dihedral angles (Scheme 7). Consequently, ABB is regarded as a highly reactive entity that rapidly reacts with various nucleophiles and then electrophiles, resulting in the formation of a variety of functionalized azetidines [51].

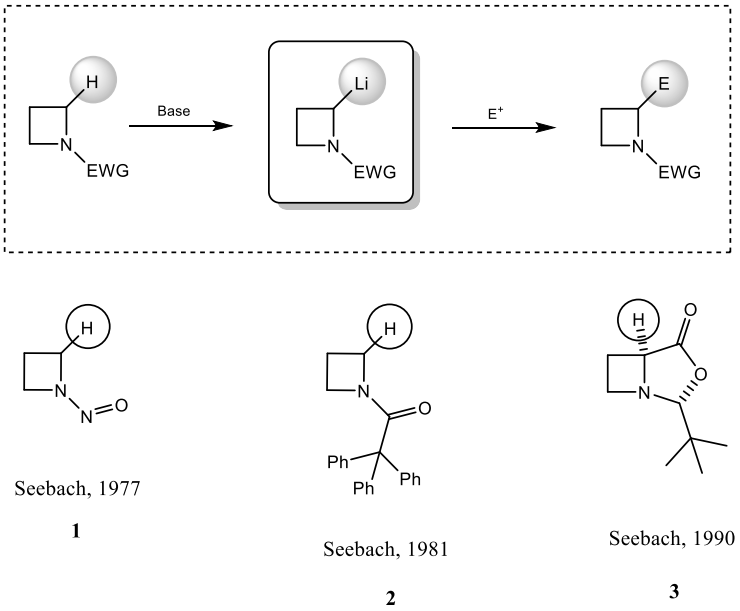


Scheme 7. Strain-released driven synthesis of azetidines using ABB.

Several methods have been reported for the synthesis of functionalized azetidines, due to their high reactivity. Also, high ring strain in azetidines, makes it thermodynamically anticipated that these monomers would undergo ring opening and polymerization reactions, resulting in the formation of high molecular-weight polymers [52]. Hence, there exist some potential methods for producing functionalized azetidines, including cyclization, cycloaddition, β-lactam reduction and ring expansion or contraction [53]. The creation of reliable synthetic techniques to obtain azetidines is undoubtedly highly valuable. Nonetheless, several azetidine preparation techniques have been documented throughout the last several decades [54].

2.2 α-Lithiation of azetidines

During the 1970s and 1980s, Seebach et al. conducted significant research in this area by working with azetidines that had electron-withdrawing groups (EWG) on both the nitrogen atom and the C_2, hence activating α-C-H bond by enhancing its acidity [55-57], (Scheme 8).



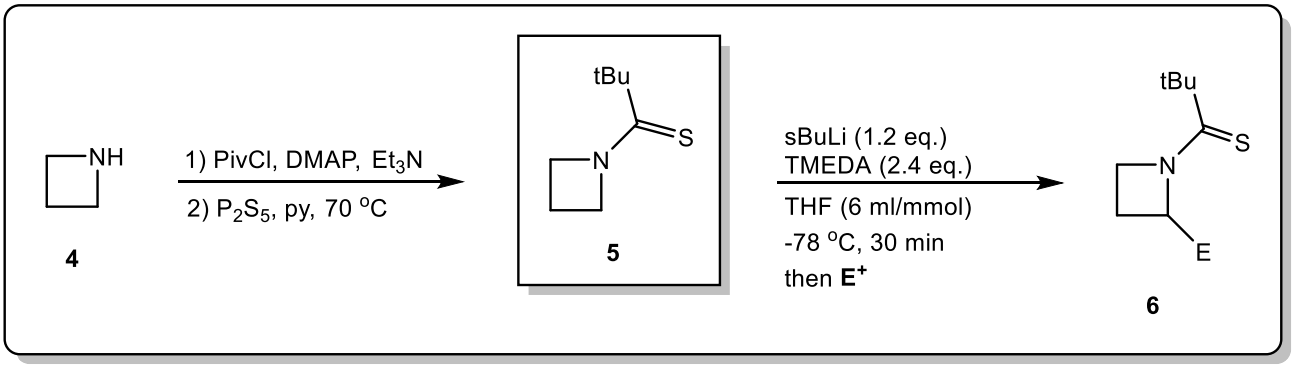
Scheme 8. First reported examples of α-lithiated azetidines.

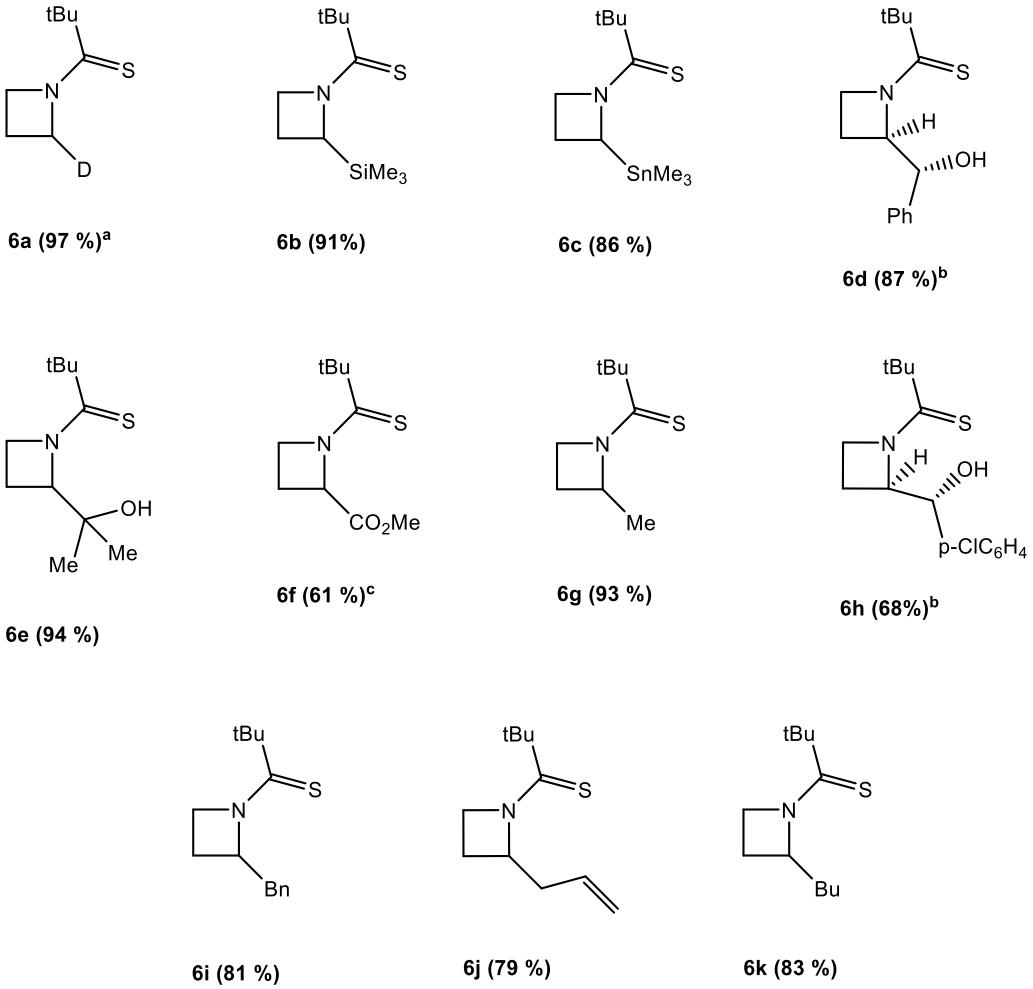
These protocols have a number of disadvantages, though, such as the carcinogenicity linked to the lithiation of N-nitrosoazetidine **1** using LDA (THF, -78 °C) [57] and the poor prospects for the development of an asymmetric application because of t-BuLi to attain the metallation of N-(triphenylacetyl)azetidine **2** (THF, - 40 °C), [56, 58]. Furthermore, a carbamoyl 1-3 shift was noticed after competitive ortho-lithiation at the triphenylacetyl protecting group. Moreover, at that time no beneficial synthetic applications were reported [56].

More systematic investigations on the α-lithiation of N-protected azetidines have just recently been conducted, allowing for a greater awareness of their reactivity, and providing mechanistic insights that may help overcome the knowledge gap.

2.3 Activation/Electrophilic substitution of azetidines

Hodgson published a successful α-lithiation–trapping sequence in 2010 at the 2-position of azetidines containing the unique Seebach's [59] N-thiopivaloyl activating group [60]. The thioamide **5** can be made by simply N-protecting azetidine **4** with pivaloyl chloride and then treating with P_2S_5. Excellent yields of 2-substituted azetidines **6a–k** were obtained by lithiation with s-BuLi/TMEDA in THF at −78 °C followed by trapping with several electrophiles for 30 minutes (Scheme 9).





6a (97 %)[a] **6b (91%)** **6c (86 %)** **6d (87 %)**[b] **6e (94 %)** **6f (61 %)**[c] **6g (93 %)** **6h (68%)**[b] **6i (81 %)** **6j (79 %)** **6k (83 %)**

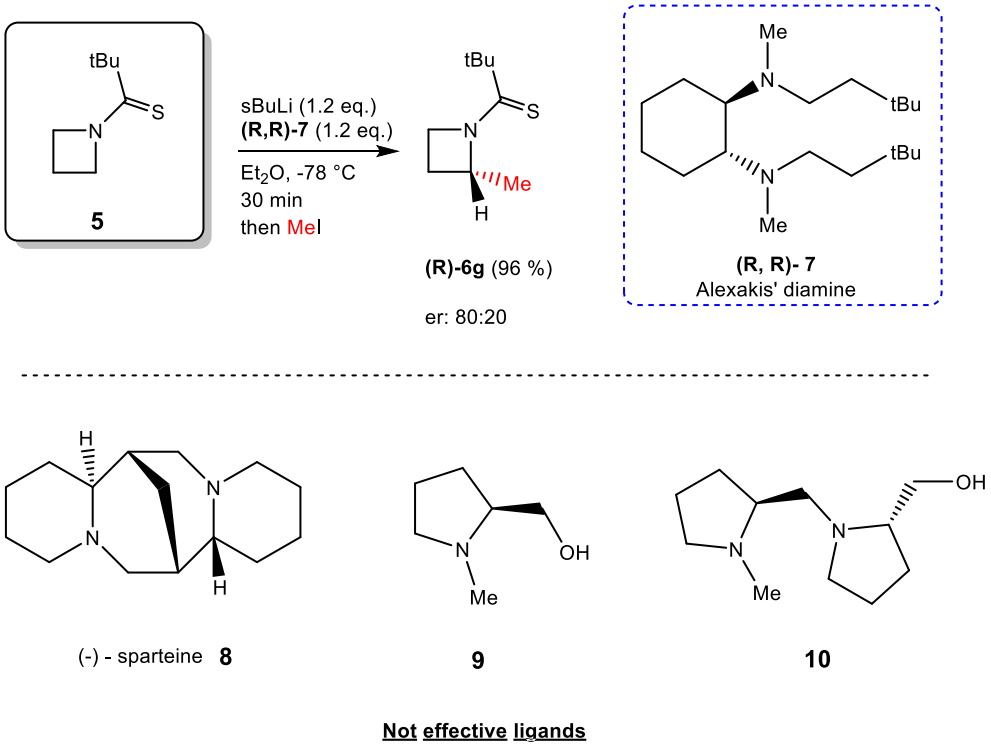
Scheme 9. Presents preparation, lithiation, and electrophilic trapping of N-thiopivalamide **5**. The yields provided are specifically for the product that has been separated. [a]100% D, determined by ^{1}H NMR and GC-MS. [b]Main diastereomers. [c]Isolated as methyl ester after reacting with $TMSCHN_2$. DMAP = 4-dimethylaminopyridine, py = pyridine, and Piv = pivaloyl.

Numerous distinct electrophiles were supported by this technique, including alkyl halides, carbonyl derivatives (such as enolizable ones like acetone), and silyl- and stannyl chlorides. Prochiral aldehydes were used in the reactions, which produced products **6d** and **6h** as the primary diastereomers.

Unlike the comparable aziridines, it was found that different EWG containing nitrogen atom, such as Boc, t-$BuSO_2$, t-BuSO and $PO(OEt)_2$, were not suited for successful α-lithiation/trapping on unsubstituted azetidines [61].

The N-thiopivaloyl group was unquestionably crucial to the success of this transformation, since when the corresponding pivalamide derivative was metalated at α-position,

only the attack of s-BuLi at the carbonyl group was detected, whereas the use of LTMP resulted in only unreacted starting material. However, the authors propose that it can be found in the combination of α-position activation and a decreased or even non-existent susceptibility of the lithium base to attack the thiocarbonyl group. It is important to emphasize that this procedure also enabled an efficient asymmetric variation by substituting TMEDA with various chiral ligands [60]. The process of lithiation of N-thiopivaloyl azetidine **5** using Alexakis' trans-cyclohexane diamine (R,R)-**7** [62] in Et_2O resulted in the formation of α-methyl azetidine **(R)-6g** with a high yield of 96% and an enantiomeric ratio of 80:20 (Scheme 10), after being trapped with MeI.

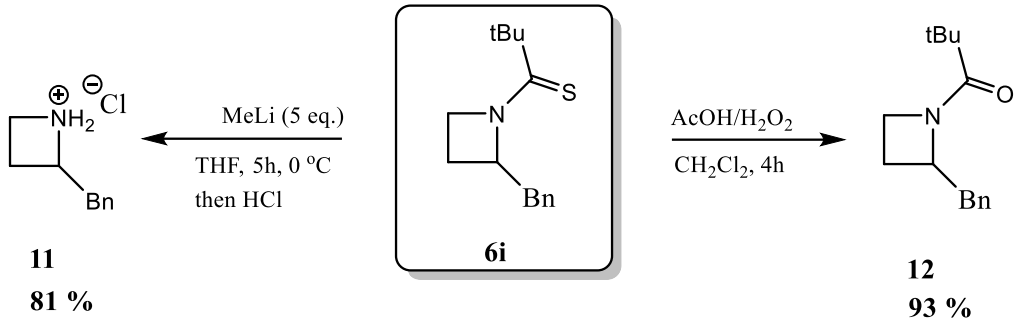


Scheme 10. N-thiopivaloyl azetidine **5** undergoes an asymmetric lithiation-methylation sequence.

Nevertheless, the use of various chiral ligands, such as (−)-sparteine **8** or proline-based ligands **9** and **10**, along with different solvents (both ethereal and non-ethereal), led to decreased enantiomeric ratios. The stereo selectivity of the reaction was different from that observed previously utilizing N-Boc pyrrolidine and N-Boc piperidine, along with s-BuLi and (−)-sparteine **8** or **(R,R)-7** [63-66].

2.4 Removal of N-thiopivaloyl group

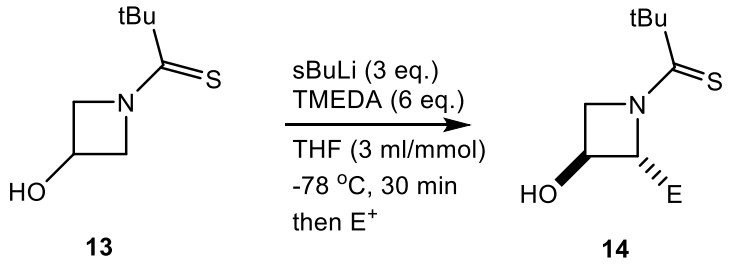
The N-thiopivaloyl protecting group was successfully removed from azetidine **6i** using MeLi. Furthermore, conversion into the equivalent pivalamide **12** was also performed by employing CH_3CO_3H (Scheme 11), [60].

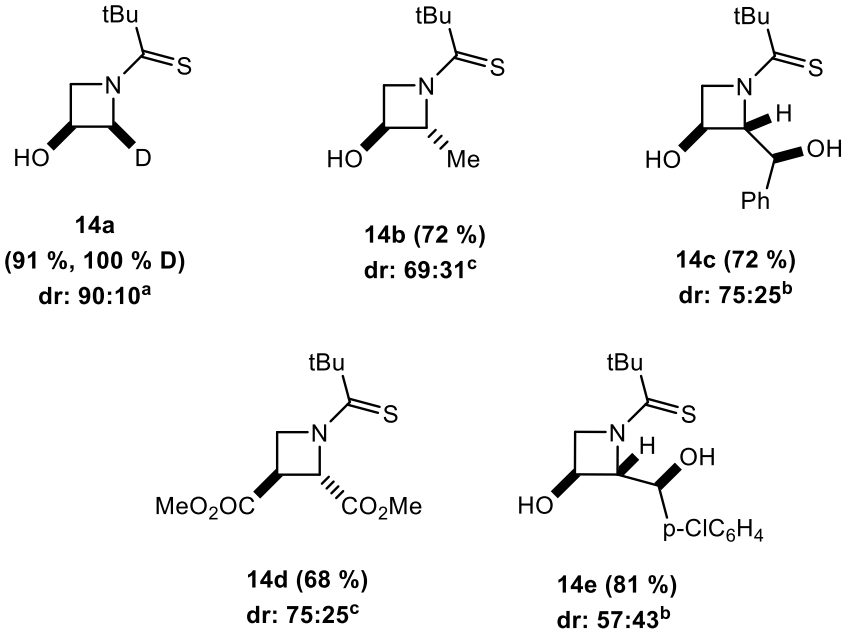


Scheme 11. Removal and transformation of the N-thiopivaloyl group.

2.5 Alpha-Lithiation/Electrophilic substitution of N-thiopivaloylazetidin-3-ol

After some time, the author applied the same lithiation method to N-thiopivaloylazetidin-3-ol **13**, which enabled the synthesis of a variety of 2-substituted 3-hydroxyazetidines **14a–e** with good diastereoselectivity, (Scheme 12). Interestingly, the cis-isomer was the predominant product only when deuteration was involved [67].



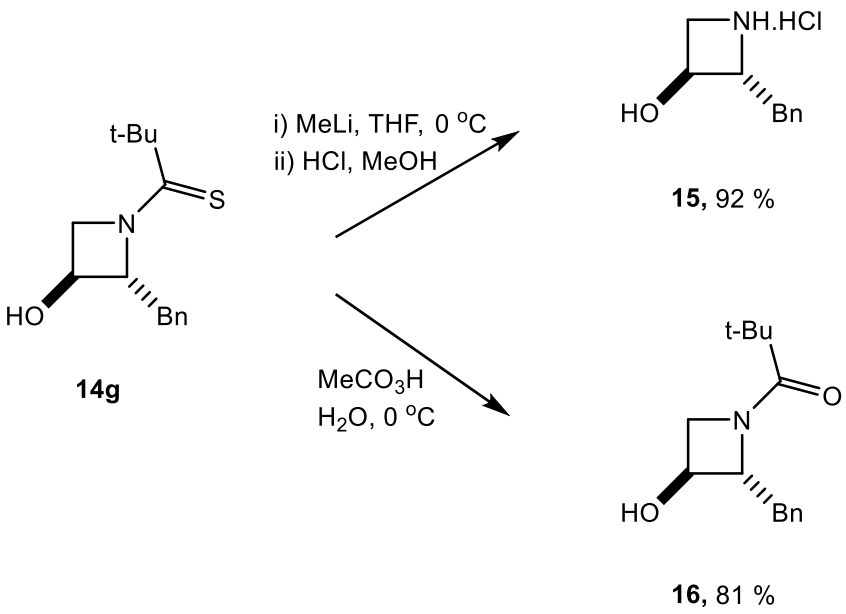


Scheme 12. Electrophilic incorporation into N-thiopivaloylazetidin-3-ol **13**. The yields mentioned are specifically for the product that has been separated. [a]Ratio of cis/trans isomers is indicated, with the dominant diastereoisomer being depicted. The major diastereoisomer displayed has a cis/trans ratio[c]. [b]Mixture of epimers at the side chain carbinol, with the major diastereoisomer being depicted.

For the reaction to achieve the best result, it was necessary to utilize 3 equivalents of s-BuLi due to the existence of the free hydroxyl substituent, and higher concentration needed compared to the case of unsubstituted N-thiopivaloyl azetidine **5**. The optimal thermal condition was found to be -78 °C, while higher temperatures resulted in decreased diastereomeric ratios, and no substantial improvement was detected at lower temperatures either. Furthermore, the presence of TMEDA in THF was also determined to be essential for achieving good yields. The use of Mander's reagent (methyl cyanoformate) resulted in the formation of C- and O-methoxycarbonylated azetidine **14d**, found attractive, due to the chance of obtaining azetidine-based amino acids.

2.6 Deprotection of 2-Substituted N-thiopivaloylazetidin-3-ol

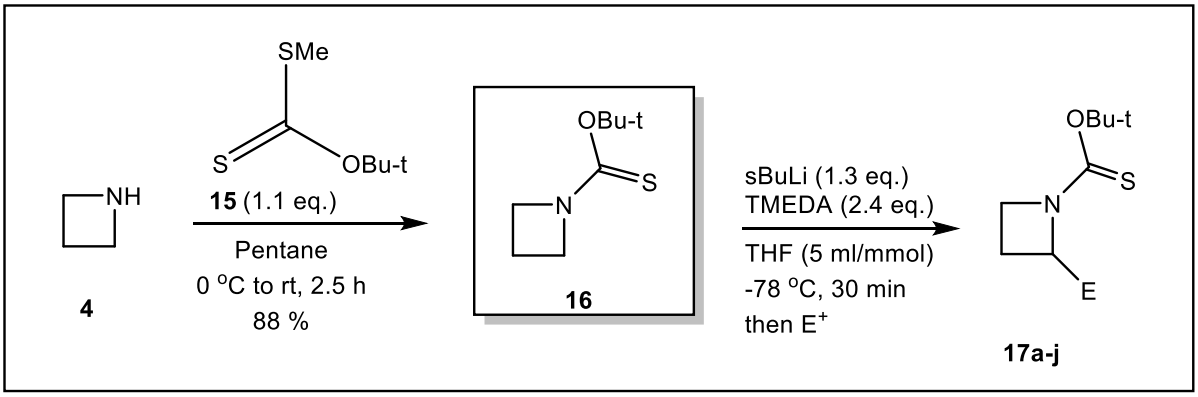
The α-substituted azetidinol **14** can be efficiently deprotected by employing MeLi in THF with TMEDA at 0 °C. This method yields a 92% conversion from **14g** and the product is separated as the hydrochloride salt **15**, as shown in Scheme 13. The conversion of **14g** to pivalamide **16** was achieved with a yield of 81% using $MeCO_3H$ as a facilitator.

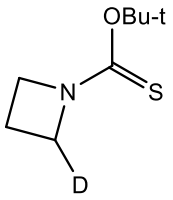


Scheme 13. Removal and conversion of the thioamide to amide conversion.

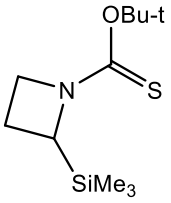
2.7 Electrophilic trapping/Deprotection of N-Botc azetidine

In 2015, Hodgson and coworkers also reported on the efficacy of the tert-butoxythiocarbonyl group (Botc) in facilitating azetidine α-lithiation, allowing deprotection under mild conditions simultaneously [68]. The compound N-Botc-azetidine **16** was produced with a high yield of 88% by reacting the easily accessible dithiocarbonic acid O-tert-butyl ester **15** with azetidine **4**, as shown in Scheme 13. No evidence of the formation of the dithiocarbamate, as described in the reaction of tertiary alkyl xanthate esters with amines [69], was found. N-Botc-azetidine **15** can be lithiated effectively and then reacted with various electrophiles to produce 2-substituted N-Boc-azetidines **17 a-j,** (Scheme 13).

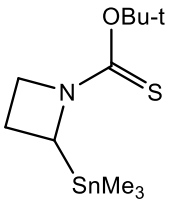




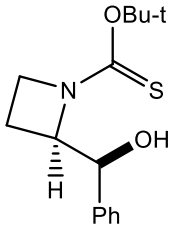
17a (90 %)[a]



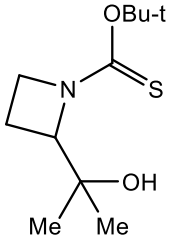
17b (76 %)



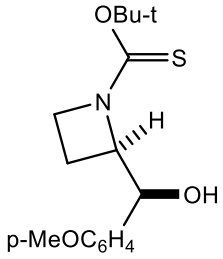
17c (75 %)



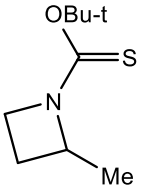
17d (74 %)[b,c]



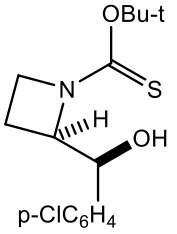
17e (65 %)



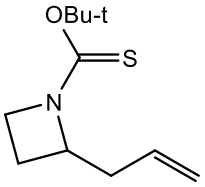
17f (57 %)[b,c]



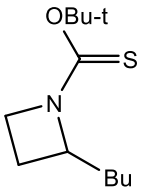
17g (79 %)



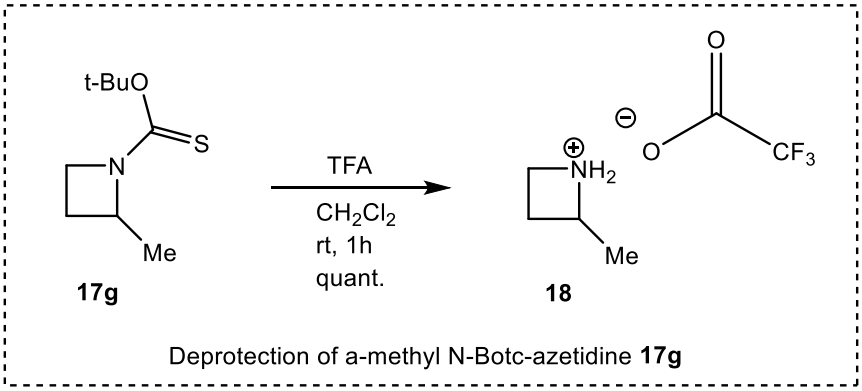
17h (69 %)[b,c]



17i (53 %)



17j (77 %)

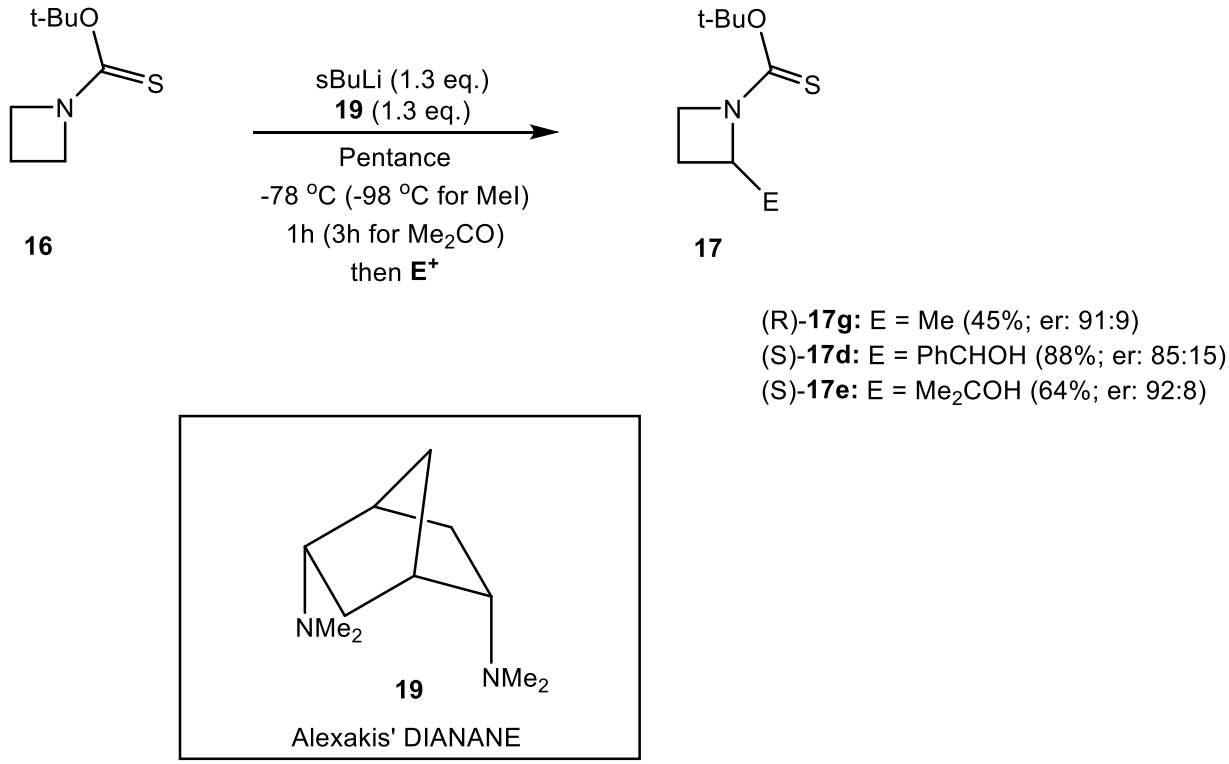


Scheme 13. Preparation, lithiation, and electrophilic trapping N-Botc azetidine **16**. **17g** is deprotected using TFA. The yields mentioned are specifically for the product that has been separated. [a]95 % D, determined by mass spectrometry. [b]dr (70:30), and the dominant diastereomer is displayed. [c]1.0 equivalent of s-BuLi was used.

Remarkably, the processes of silylation, stannylation, alkylation, and reaction with carbonyl compounds proceeded without difficulty. However, there was a modest decrease in the yields when dealing with electrophiles that were more electron-rich, such as p-anisaldehyde. As previously stated, N-Botc-azetidines were successfully deprotected under mild acidic conditions without any ring opening detected. This was proved with α-methyl N-Botc-azetidine **17 h**, which was transformed into α-methyl-azetidine **18** using TFA.

2.8 Enantioselective α-electrophilic substitution of N-Botc-azetidine

Alexakis' DIANANE **19** (N,N,N′,N′-endo,endo-tetramethyl-2,5-diaminonorbornane) [70] was found to be the most effective chiral ligand for the N-Botc-azetidine enantioselective α-electrophilic substitution **16** .When compared to (−)-sparteine 8 and trans-cyclohexane diamine **(R,R)-7**, exhibits high levels of asymmetric induction, with an enantiomeric ratio of up to 92:8, as stated in Scheme 14.

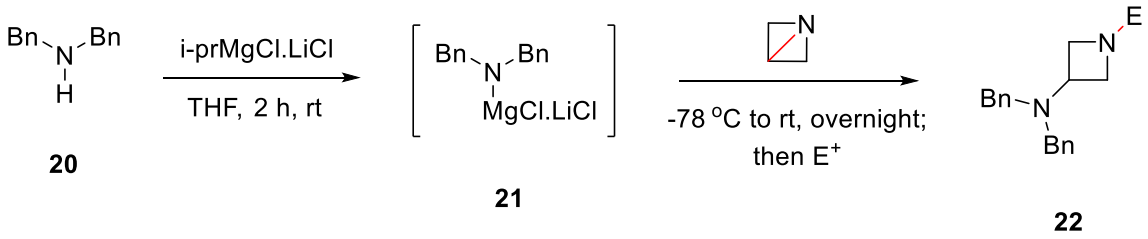


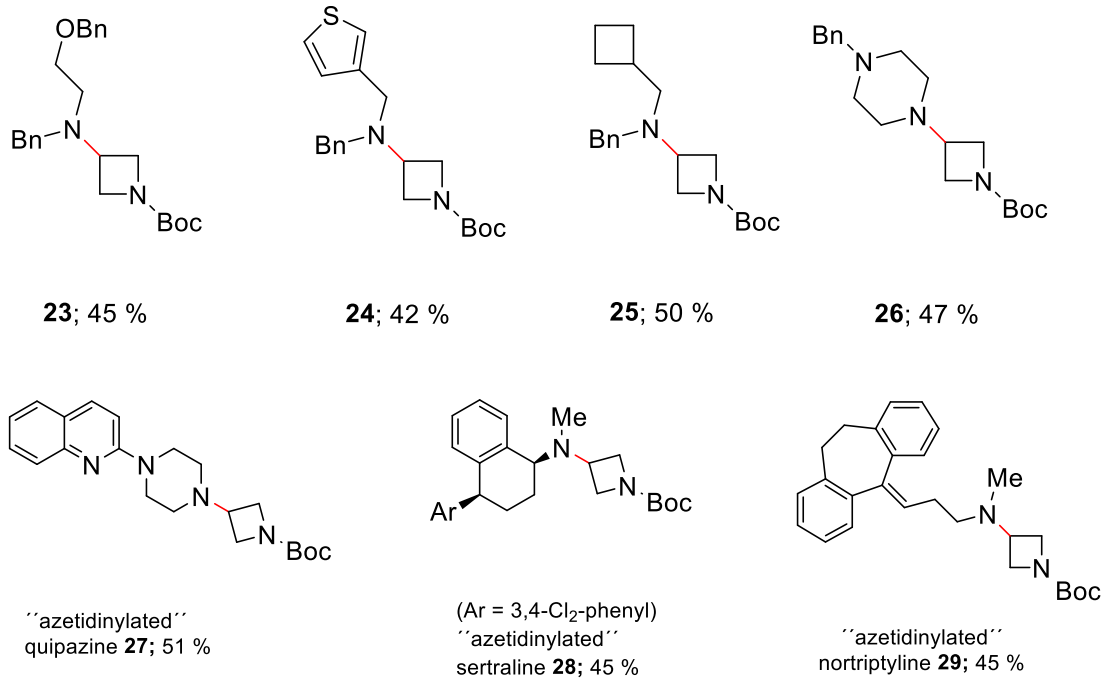
Scheme 14. The lithiated N-Botc-azetidine **16** undergoes enantioselective α-electrophilic substitution.

The enantioselectivity of the reaction seems to be solely dependent on experimental conditions, such as the reaction temperature and lithiation time. Asymmetric methylation proceeded well at a temperature of -98 °C with a lithiation time of 1 hour, using DIANANE **19** in pentane. Similarly, lithiation and subsequent reaction with benzaldehyde resulted in high enantiomeric ratios at a temperature of -78 °C, with a lithiation time of 1 hour. In the instance of acetone, asymmetric trapping required a longer lithiation time of 3 hours and a low temperature of -78 °C.

2.9 2, 3-disubstituted azetidines

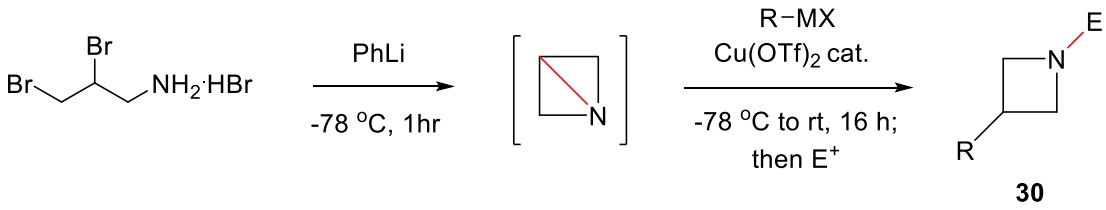
Azabicyclo[1.1.0]butanes (ABBs) are significant synthetic agents used to create functionalized azetidines. Azabicyclo[1.1.0]butanes typically undergo transformations that entail breaking the connection between carbon atom 3 and nitrogen atom, enabling the modification of the azacycles at positions 1 and 3. Significant progress in the subject has recently resulted in the development of new strained compounds derived from ABBs. The discovery of a fast effective method for synthesizing azetidines was expected to result in a greater utilization of these compounds in biomedical research. Research has demonstrated that 1-azabicyclo[1.1.0]butanes can be used as highly effective intermediates for the rapid synthesis of bis-functionalized azetidines [71-75].
Nagao and other researchers have demonstrated that ABB can be seized by different nucleophiles to synthesize functionalized azetidines [76-89]. Baran has recently demonstrated that ABB can undergo amination using "turbo amides" in a one-pot way [90, 91], Scheme 15.



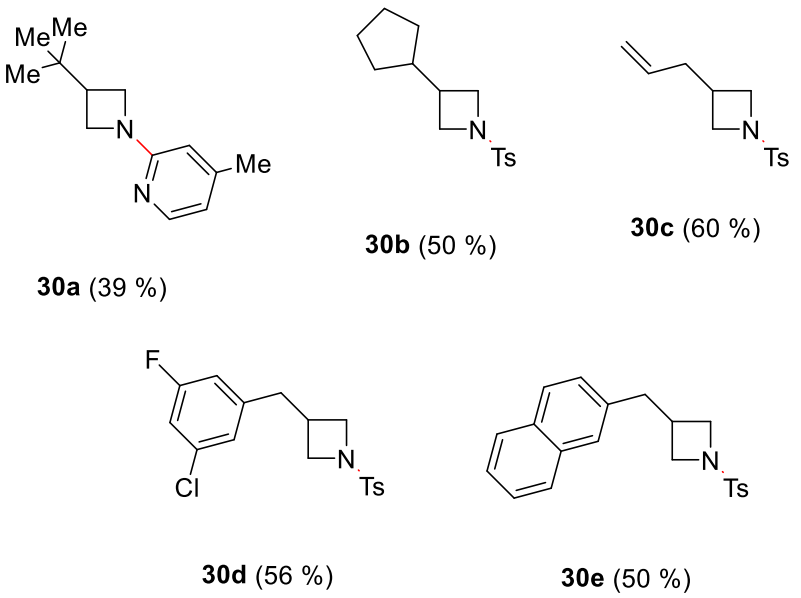


Scheme 15. Strian-release azetidinylation of amine-containing substrates.

Gianatassio et.al in 2019, presented a general technique for the direct alkylation of 1-azabicyclo[1.1.0]butane (ABB). The bis-functionalized azetidines can be readily prepared by reacting organometal reagents with $Cu(OTf)_2$, Scheme 16. This technique enables the synthesis of azetidines containing allyl, alkyl, benzyl, and vinyl substituents. The catalyst system was further expanded to aziridines and spirocycles. A multitude of building blocks and drug-like molecules were efficiently synthesized with high yield [92].



- R = 1°, 2°, 3° alkyl, vinyl, allyl, benzyl
- Compatable with RMgX, RMgX.LiCl, and RZnBr reagents
- Variety of electrophiles tolerated



30a (39 %) **30b** (50 %) **30c** (60 %)

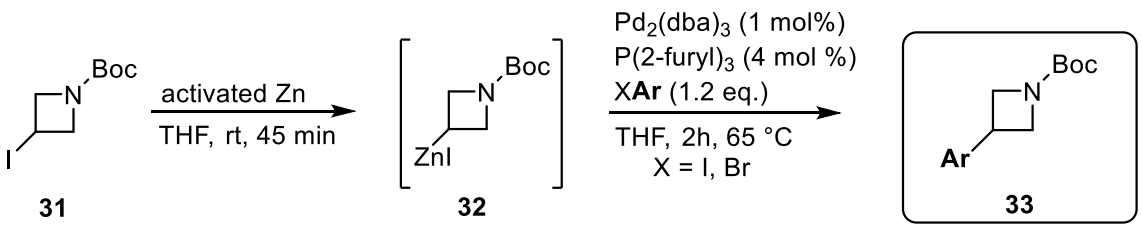
30d (56 %) **30e** (50 %)

Scheme 16. Direct alkylation at 3 position of azetidines.

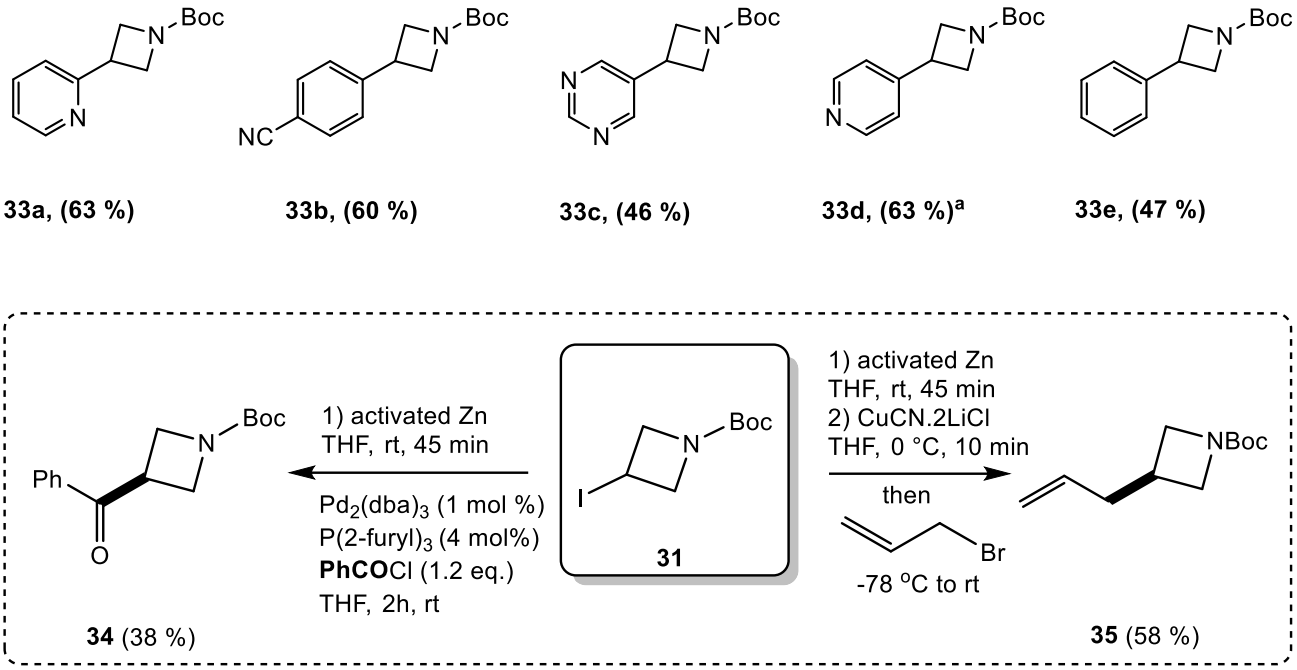
It is important to mention that Boc can be used as an electrophile. In comparison to piperidines which are common ring systems and are widespread in marketed drugs, azetidines are rarely used as a core scaffold [93-95]. The lack of azetidines as a commonly used structure can be attributed to their limited ease of synthesis [95].

2.10 Carbon-Carbon bond formation of azetidines

A common approach for synthesizing 3-substituted azetidines involves cross-coupling reactions using palladium catalysts and phosphine ligands. This method utilizes the appropriate 3-iodo azetidine as a starting material and proceeds through the formation of organometallic intermediates [96]. In this procedure, an azetidine-zinc complex must be formed prior to the following reaction with an appropriate aryl halide or benzyl chloride (Scheme 15).



31 **32** **33**

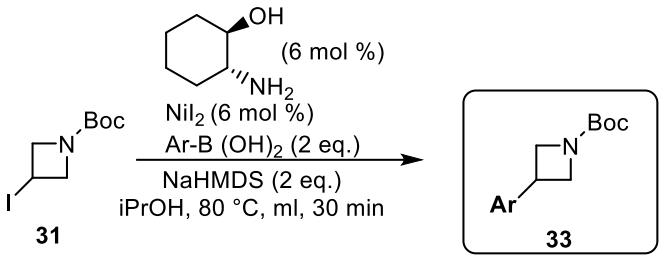


Scheme 15. The reaction involves the use of Pd(0) to facilitate cross coupling and transmetalation with CuCN·2LiCl of organozinc species **31** generated from azetidine. [a]Reaction is conducted at room temperature. The organozinc species **32** can easily undergo transmetalation with CuCN·2LiCl in THF. Upon reaction with allyl bromide, it produces azetidine **35** with a moderate yield.

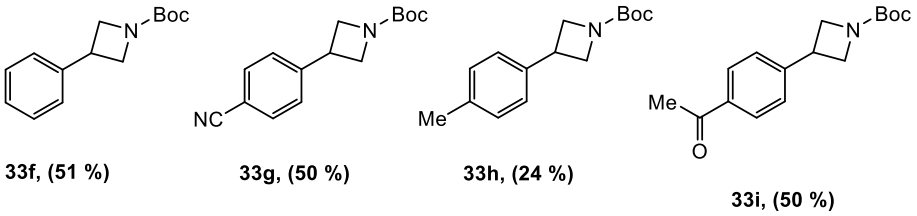
In addition, there have been reports of nickel catalyzed processes using a ligand, which have allowed the synthesis of 3-functionalised azetidines. However, the success of these procedures has been restricted [97, 98], (Scheme 16).

In 2008, Duncton published a noteworthy microwave-assisted Suzuki coupling to introduce functional groups at the C-3 position of 3-iodo-azetidine **31** [97]. The reaction involving various aryl boronic acids occurred in the presence of catalytic quantities of nickel (II) iodide and trans-2-aminocyclohexanol as a ligand (Scheme 16, a).

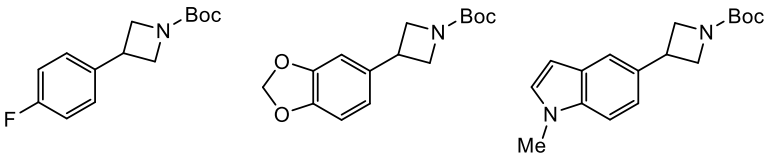
Molander demonstrated the feasibility of conducting a reductive cross coupling reaction by employing air-stable Ni (II) sources along with a diamine ligand, an inorganic salt as an additive, and a reducing metal. The objective was to introduce (hetero) aryl halides at the C-3 position of the azetidine ring [98]. This reaction pathway is depicted in Scheme 16, b.



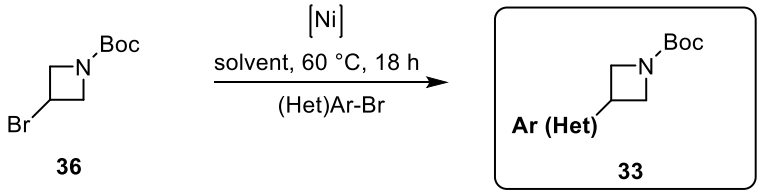
a: Alkyl-Aryl Suzuki coupling



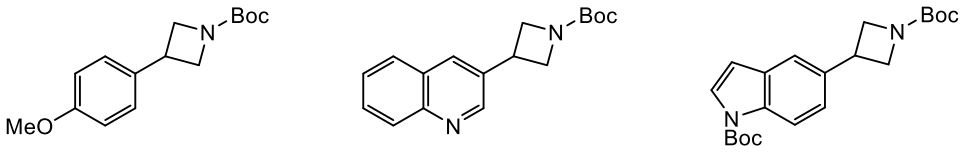
33f, (51 %) **33g, (50 %)** **33h, (24 %)** **33i, (50 %)**



33j, (57 %) **33k, (45 %)** **33l, (25 %)**



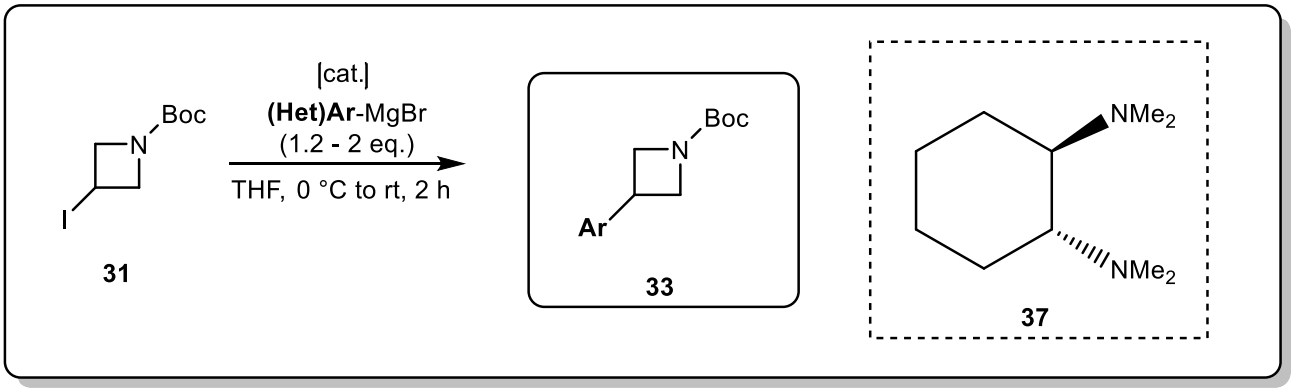
b: Reductive cross-coupling

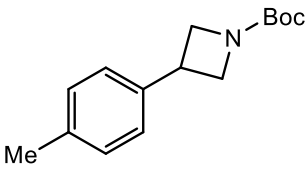


33m, (48 %)[a] **33n, (30 %)[b]** **33o, (36 %)[b]**

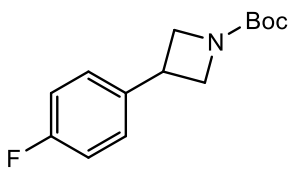
Scheme 16. Methods utilizing nickel to produce 3-aryl azetidines. [a]$NiCl_2$.glyme(10 mol%), 4-ethylpirydine (50 mol%), phenanthroline (20 mol%), MeOH (0.2 M). [b]NiI_2 (10 mol%), $NaBF_4$ (50 mol%), Mn (2 eq.), di-tBu-bipyridine (10 mol%), DMA (0.2 M), 4-ethylpyridine (1 eq.), Mn (2 eq.), and $MgCl_2$ (1 eq.).

Reports have described effective techniques for the coupling of azetidine **31** using inexpensive cobalt or iron catalysts and easily accessible organomagnesium chemicals, without the need for any extra phosphine ligands [47, 99]. Cossy and coworkers revealed that both $CoCl_2$ and $FeCl_2$ catalysts facilitate the efficient reaction between azetidine **31** and a wide range of (hetero)aryl Grignard reagents, generally with similar performances [99], (Scheme 17).

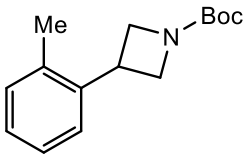




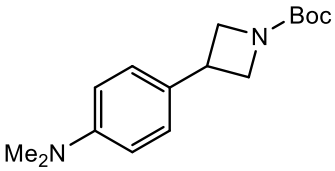
33p, 81 %[a] ; 84 %[b]



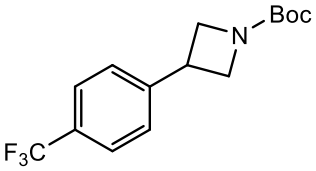
33q, 68 %[a] ; 74 %[b]



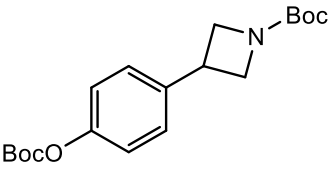
33r, 79 %[a] ; 83 %[b]



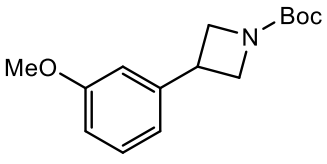
33s, 79 %[a] ; 74 %[b]



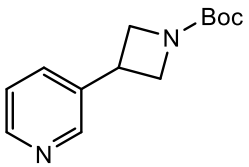
33t, 95 %[a] ; 81 %[b]



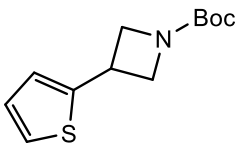
33u, 84 %[a]



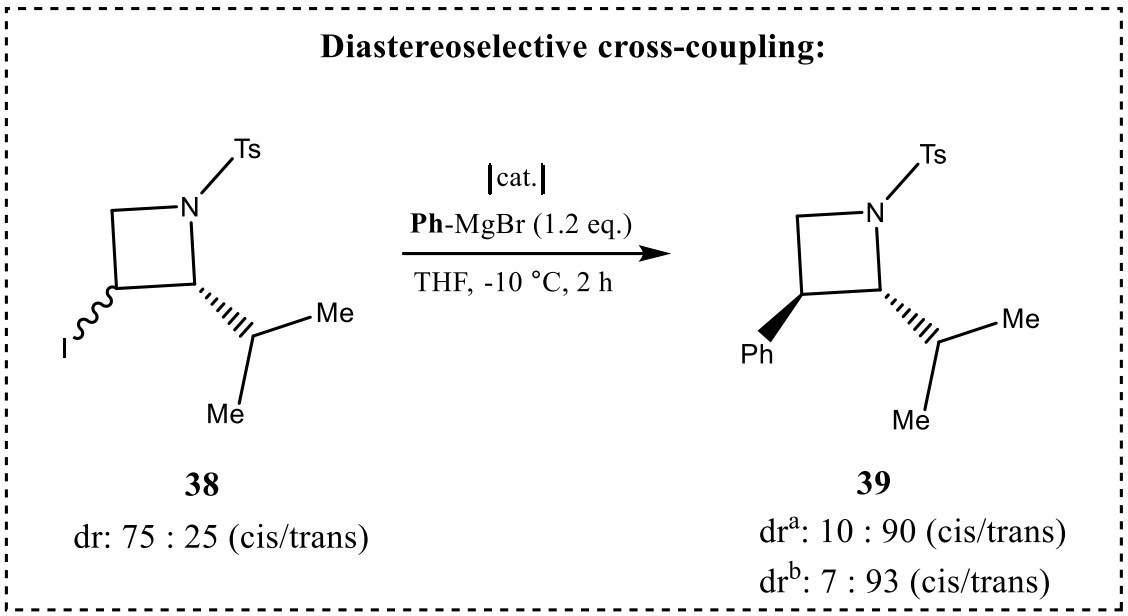
33v, 92 %[a] ; 86 %[b]



33w, 90 %[a] ; 90 %[b]



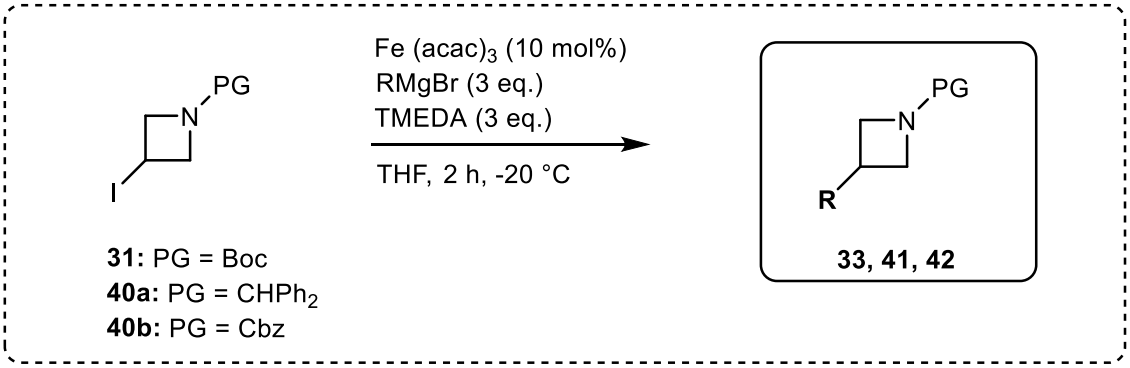
33w, 91 %[a]

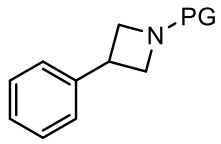


Scheme 17. Iron- and cobalt-facilitated arylation of azetidines. [a][cat.] = $CoCl_2$ (5 mol%). [b][cat.] = $FeCl_2$ (10 mol%). Ts = Tosyl.

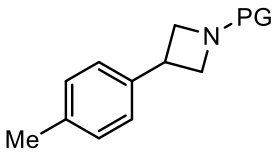
The products were obtained in significant quantities, and the technique demonstrated a high tolerance for a wide range of functional groups. However, it was necessary to employ ligand **37** ((R,R)-tetramethyl cyclohexan-1,2-diamine). Surprisingly, when 2,3-disubstituted iodo-azetidine **38** (dr: 75:25 cis/trans) was reacted with PhMgBr in the presence of both catalytic systems, the intended product **39** was successfully produced with a favorable trans diastereoselectivity (Scheme 17). The authors predicted that the change in stereochemistry could be attributed to the formation of a radical intermediate at carbon-3.

In addition, Rueping published an approach that uses $Fe(acac)_3$ as the catalyst. Furthermore, this approach proved efficient and chemoselective selectivity, and it was able to withstand a wide range of (hetero)aryl, alkyl, and vinyl Grignard reagents. It also accommodated various protective groups on the nitrogen atom [47], as shown in Scheme 18.

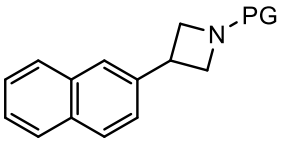




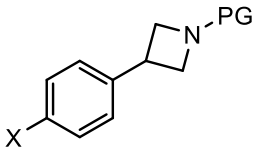
33x: PG = Boc **(60 %)**
41a: PG = $CHPh_2$ **(67 %)**
1 mmol scale: **(66 %)**
42a: PG = Cbz **(64 %)**



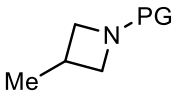
33y: PG = Boc **(66 %)**
41b: PG = $CHPh_2$ **(60 %)**
42b: PG = Cbz **(66 %)**



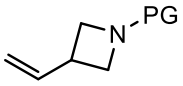
33z: PG = Boc **(69 %)**
41c: PG = $CHPh_2$ **(64 %)**



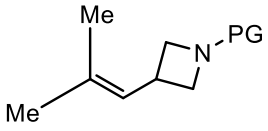
PG = $CHPh_2$
41d: X = tBu **(56 %)**
41e: X = Ph **(32 %)**
41f: X = F **(61 %)**



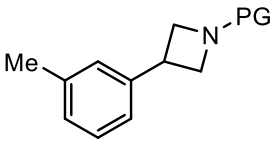
PG = $CHPh_2$
41g (62 %)



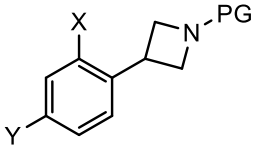
PG = $CHPh_2$
41h (74 %)



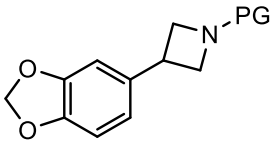
PG = $CHPh_2$
41i (37 %)



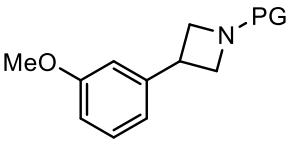
PG = $CHPh_2$
41j (40 %)



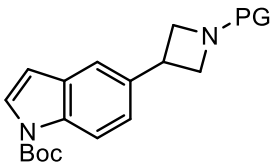
PG = $CHPh_2$
41k: X = iPr, X = H **(96 %)**
41l: X = Y = Me **(69 %)**



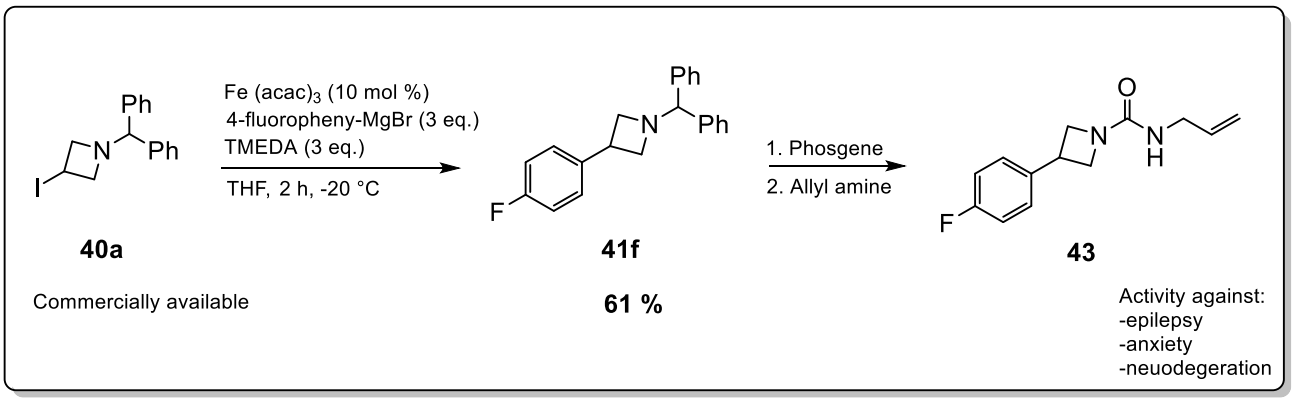
PG = $CHPh_2$
41m (85 %)



PG = $CHPh_2$
41n (65 %)



PG = $CHPh_2$
41o (54 %)



Scheme 18. Involves Rueping's azetidine cross-coupling using Grignard reagents and synthetic application of pharmaceutical importance.

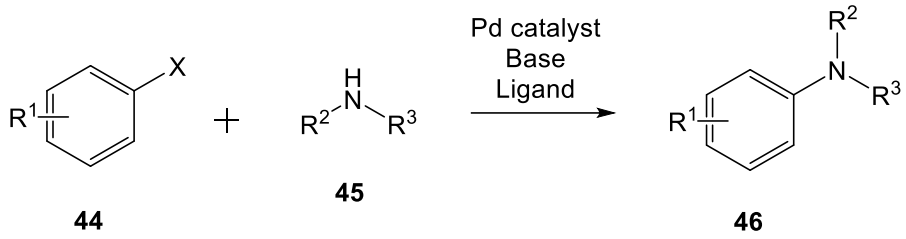
The synthetic capabilities of this pathway can be highlighted in view of its effective use in the concise formal synthesis of the complex molecule **42**, which has pharmacological action against

central nervous system illnesses [47] (Scheme 18). The patented method for preparing this molecule (and similar compounds) involves three steps, two days of effort, and two chromatographic separations. This process yields intermediate **41f** with an overall cumulative yield of 42% [47]. Remarkably, through the utilization of the advanced iron-catalyzed cross-coupling method directly on the commercially available iodide **40a**, Rueping and coworkers were able to obtain compound **88f** with a yield of 61%. The latter can be readily transformed into the required molecule **42** via a documented protecting group exchange procedure [47].

2.11 Carbon-Nitrogen bond formation

The carbon–nitrogen cross-coupling reaction is a crucial and necessary conversion in organic synthesis because arylamines, one of its products, are essential building blocks of many medicines, natural products, and other biologically active substances. Buchwald and Hartwig presented a wide range of ligands in addition to the typical Cu and Pd catalysts that were crucial in the development of this significant C–N coupling process. In organic chemistry, a cross-coupling reaction is the joining of two fragments together with the help of a metal catalyst. Pd-catalyzed cross-coupling reactions have been identified as being particularly significant in the field of organic synthesis [100, 101]. Using a range of commercially available Pd complexes and ligands, a variety of commonly used Pd catalyzed cross-coupling reactions can now be carried out in water under ambient and mild conditions. Among the most often utilized C–C bond producing reactions are these coupling bond transformations, which include Sonogashira, Heck, Negishi, Suzuki, and Stille. However, the C-N bond's creation is important because it creates a pathway for the amine linkages to be introduced into organic compounds [102-105]. A lot of functional groups and materials, including medicines, agrochemicals, flavors, dyes, perfumes, etc., contain C–N bonds [106, 107]. Pd catalysts have also been widely used for the purpose of cross-coupling reactions [108, 109]. In 1983, Migita et al. stated the achievement of a Pd-catalyzed C–N coupling process [110]. But Buchwald and Hartwig earned all the credit and honor for their consecutive articles from 1994 until the late 2000s that demonstrated and validated the extent of this evolution. The limitations of conventional techniques (nucleophilic substitution, reductive amination, etc.) for the synthesis of aromatic C–N bonds are the main cause of the reaction's synthetic applicability. Most of these strategies struggled with a narrow range of substrates and lacked the tolerance of various functional groups. Many reactions carried out and documented over time, following a methodology first created by Buchwald and Hartwig, today make it possible to synthesize aryl amines more easily and efficiently.

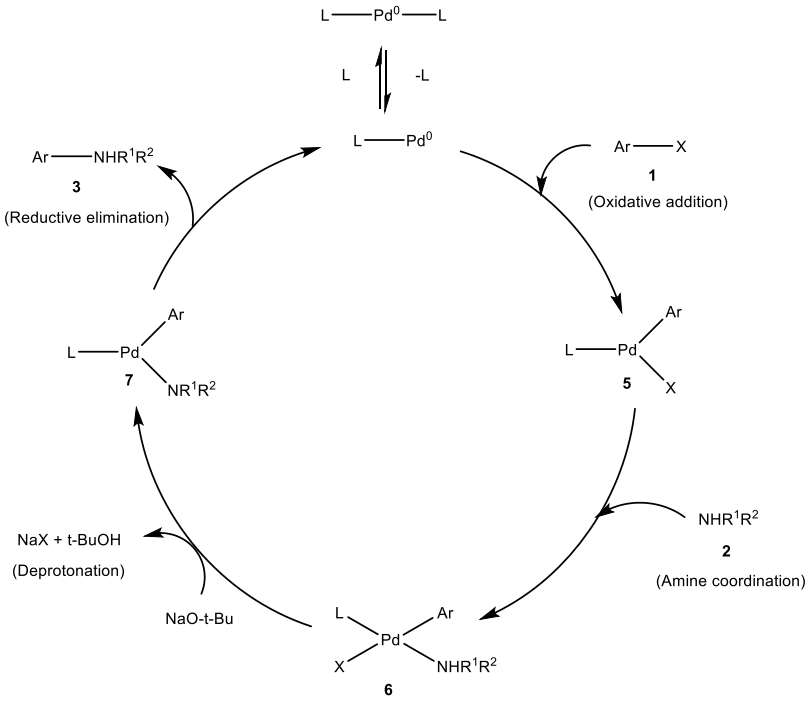
The more harsh processes (such as the Goldberg reaction [111, 112], nucleophilic aromatic substitution, etc.) have been improved by it; as a result, the list of potential C–N bond formations is expanding [113], (Scheme 19).



R^1: Electron-donating and -withdrawing groups.
R^2: Alkyl, Aryl, H.
R^3: Alkyl, Aryl.
X: I, Br, Cl, OTf.

Scheme 19. General reaction for the formation of Pd catalyzed C-N bond.

Important structural motifs found in substances with biological activity and organic electronic materials are arylamines 46 [114-118]. Through the Pd-catalyzed coupling reactions of amines with aryl halides, the Buchwald-Hartwig (BH) amination is a chemical reaction used in organic chemistry to create C–N bonds. Since it has been widely and successfully used in both industry and academia, it is currently regarded as one of the most potent synthetic methodologies in organic chemistry [119]. For the cross-coupling processes that result in the production of C–N bonds, a variety of affordable homogenous and heterogeneous Pd catalysts have been employed over time [120]. Pd [121, 122], Ni [123], and Cu [124] species have all been successfully employed as catalysts in coupling processes for the production of C–N and C–O via nucleophilic aromatic substitution with aryl halides. Pd has been proven to be superior in most circumstances, but it has several drawbacks, including toxicity, which is costly and damaging to the environment. As a result, it is not economical to use Pd in large-scale production, Scheme 20.

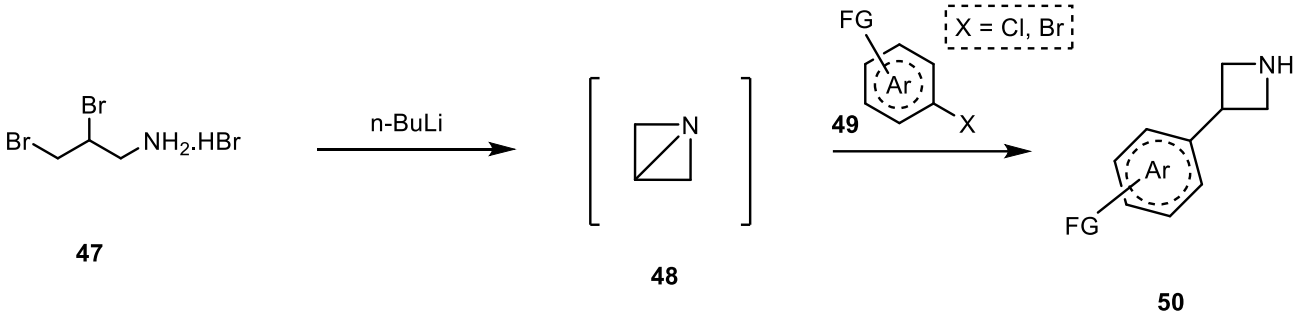


Scheme 20. Sketch of the Buchwald-Hartwig amination catalytic cycle.

Nowadays, highly active and recyclable heterogeneous Pd nanoparticles are developed and widely employed to get beyond these drawbacks [125]. The BH reaction is frequently employed in the synthesis of novel compounds and the production of various materials, particularly in drug research, and it exhibits a very flexible catalytic technique to create aryl C–N bonds [126]. Since the reaction's discovery, research and development have concentrated on designing advantageous and appropriate ligands and pre-catalysts to locate a broad range of compatible substrates [127-131]. Using palladium(II) acetate as a catalyst and a large, electron-rich ligand, the amination process proceeds rapidly [132].

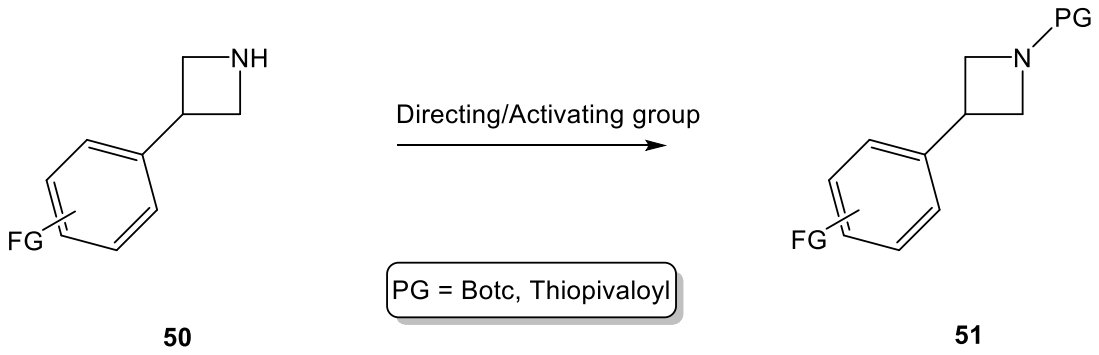
3 Objectives

The aim of the first project is to develop the stereoselective synthesis of 3-arylated-2-substituted azetidine compounds using various Grignard reagents and electrophiles. There has been an increasing interest in strained ring structures in recent years, particularly because they are being used in drug discovery programs. The facile modulation of their structure enables access to a broad platform of functionalized substrates. Therefore, initial focus is to prepare various Grignard reagents and further complementary approaches for the formation of 3-arylated azetidines by means of strained1-azabicyclo[1.1.0]butane system **48** as shown in Scheme 21.



Scheme 21. Formation of 3-arylated azetidines using Grignard reagents.

Use of protecting/activating groups may lead to the formation of 3-arylated N-protected azetidines that directs the substitution of various electrophiles at the alpha position of azetidines (Scheme 22).



Scheme 22. Substitution of protecting groups on 3-arylated azetidines.

The R^1 group attached to scaffold **52** causes a steric hindrance on one of the two diastereotopic faces of the azetidine as shown in Figure 1. Consequently, we anticipate that the metalation process will be more favorable on the side with less hindrance (opposite to R^1).

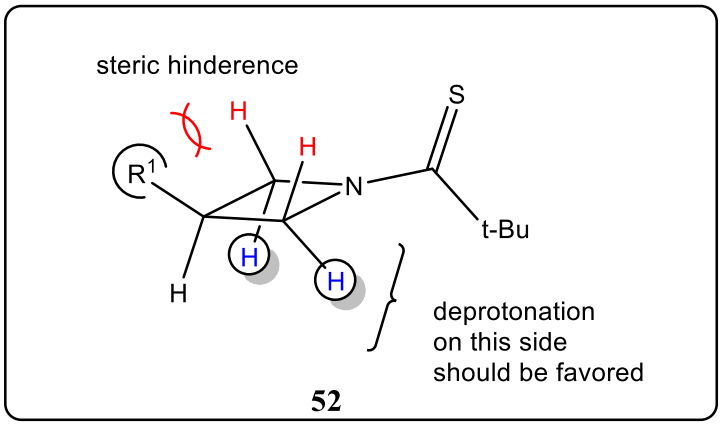
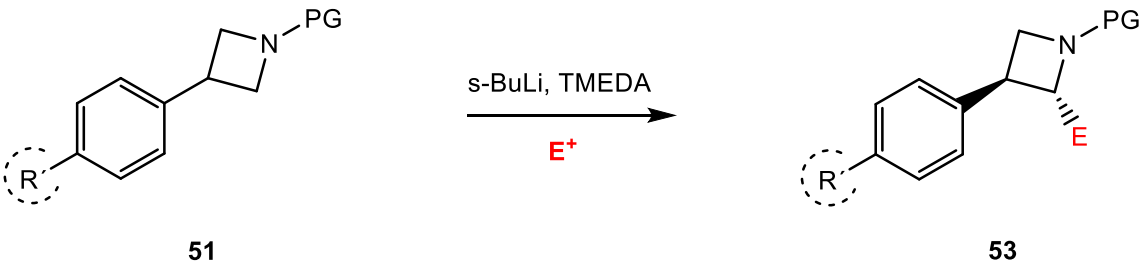


Figure 1. Displays the favourable deprotonation side opposite to R^1 group due to steric hindrance.

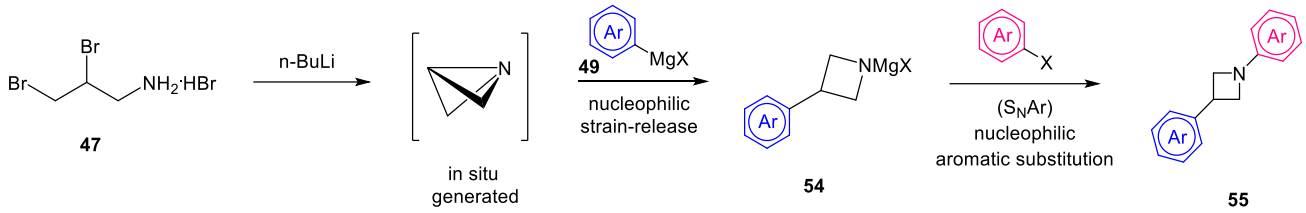
The main work would be α-lithiation and then electrophile trapping of 3-arylated N-protected azetidine by employing various conditions and electrophiles to control the yield of the desired product. At last, evaluation of the diastereoselectivity is going to check at the α-position of 3-arylated N-protected azetidines (Scheme 23). As stated, the product 3-arylated azetidines-2-carboxylic acid can be further used to form peptide chains [133].



Scheme 23. α-lithiation/electrophilic substitution 3-arylated N-protected azetidines using various conditions and electrophiles.

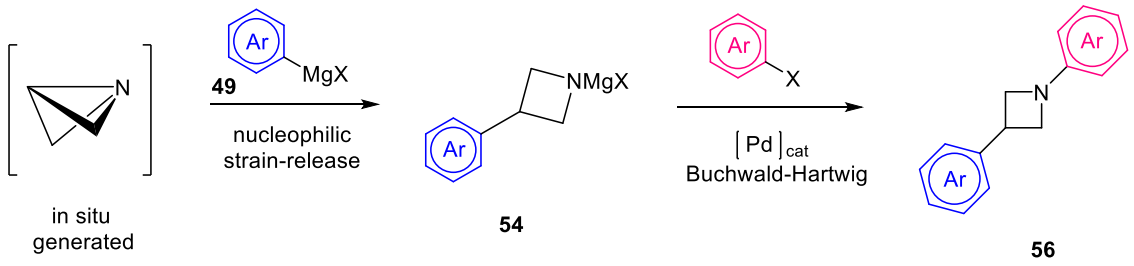
In the second project our goal is to introduce ex-situ generated nucleophilic organometallic species onto azabicyclobutanes that are formed in the reaction mixture to selectively create 3-arylated azetidine intermediates by the release of strain. Moreover, creation of a highly effective method for the 1,3-bis-arylation of azetidines firstly through S_NAr approach, Scheme 24. A novel arylation at

position 3 will be carried out using arylmagnesium reagents, by modifying the solvent system to prevent the formation of unwanted products. These experiments are expected to accommodate various functional groups.



Scheme 24. Nucleophilic aromatic substitutions (S_NAr) of 3-arylated azetidines.

Furthermore, subsequent advancements in the development of single pot techniques for the N-arylation of azetidines will be carried out by using Buchwald-Hartwig couplings, Scheme 25. Efficient and flexible methods for creating C-N bonds will be used, enabling the synthesis of a wide range of chemical building blocks. These building blocks include analogues of drug compounds, which is a significant advancement towards incorporating rigid sp^3-rich structures in drug discovery programs.



Scheme 25. C-N bond formation of 3-arylazetidines via Buchwald–Hartwig coupling.

B. Results and Discussion

1 Stereoselective approach for the electrophilic α-substitution of 3-arylated azetidines

1.1 Introduction

To enhance the effectiveness of potential drugs, present medicinal chemists are progressively applying an unconventional structural patterns such as small and strained ring structures. The ease of operation, mild reaction conditions, low-cost preparation, and stereoselectivity demonstrated by strain-release reagents like cyclobutanes, bicyclo[1.1.1]pentanes or 1-azabicyclo[1.1.0]butane expedite their widespread use [91]. In comparison, azetidines present a bit flexibility and more acceptance to functional groups hence, adaption to various drug compounds makes it notable, Figure 2. In this study, we have developed a method, to utilize the stored potential energy and harnessing the inherent reactivity of the highly strained C-N bond of azetidines by treating with significant nucleophiles and further utilization in protein chemistry. On a broader scale, a wide range of reagents can be envisioned using this method.

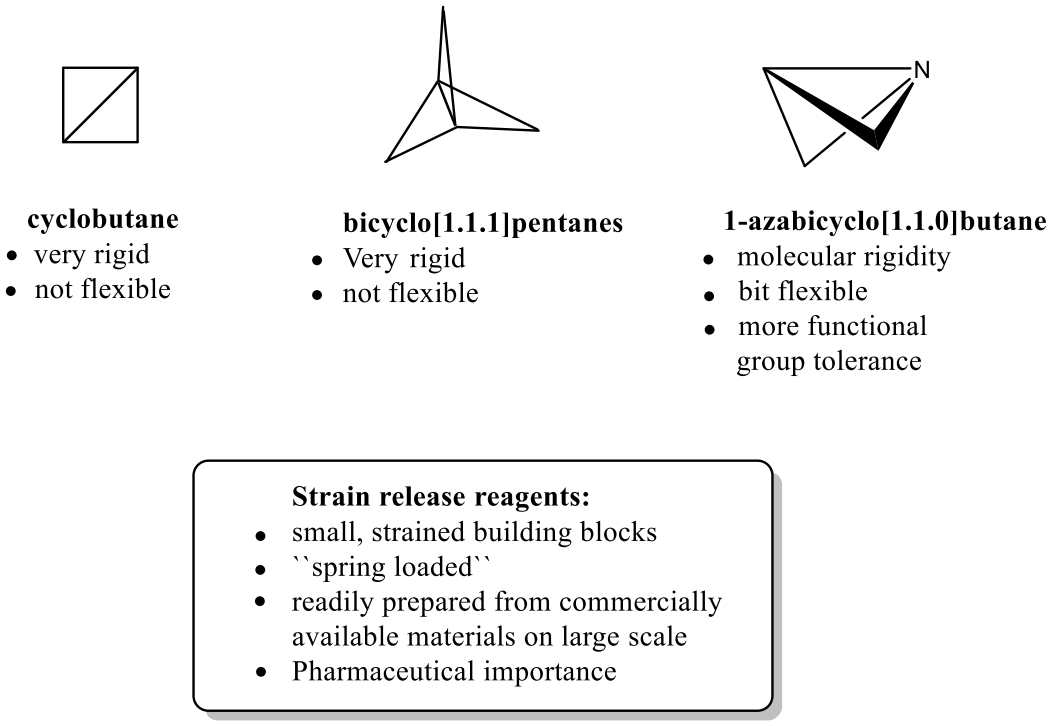


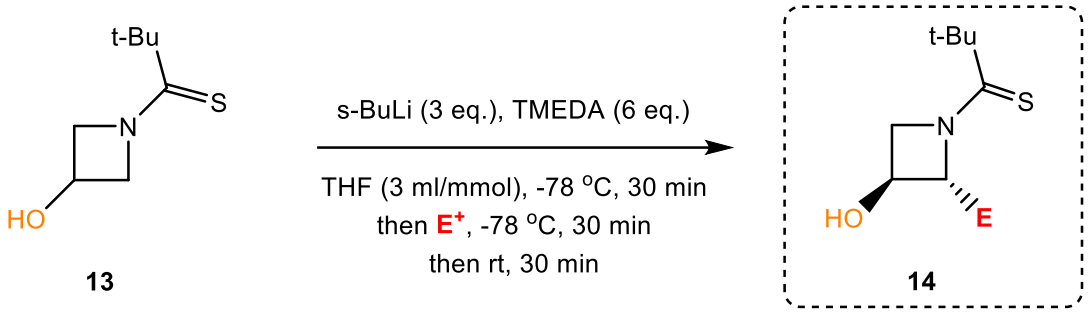
Figure 2. Strain-release reagents use for medicinal discovery.

As substituted azetidines pose difficulties in their synthesis but are of great importance and currently attract attention as bioactive compounds. Additionally, they have been employed as ligands in metal-catalyzed reactions and as chiral auxiliaries [37, 95, 134]. The initial instance of a successful α-lithiation–trapping process was presented by Hodgson in 2010, [60]. This process involved the addition of a lithium atom at the 2-position of azetidines that had the distinctive Seebach's [59] N-thiopivaloyl activating group. Highly favorable results were achieved by employing lithiation with s-BuLi/TMEDA in THF at −78 °C, followed by capturing with various electrophiles for a duration of 30 minutes, resulting in the production of 2-substituted azetidines [60]. Furthermore, electrophilic substitution on azetidine was investigated using chiral ligands resulting high enantioselectivity [60]. Later, the author employed the lithiation approach on N-thiopivaloylazetidin-3-ol, resulting in the synthesis of a range of 2-substituted 3-hydroxyazetidines **14** (Scheme 26). The process consistently achieved a high level of trans-diastereoselectivity [67]. As studied, 3-hydroxy- or 3-alkoxyazetidine motif can be found in a number drug candidates [45, 135] as well as in natural compounds [136, 137].

Recently, the same author stated that the compound tert-Butoxythiocarbonyl (Botc), allows for α-lithiation and the addition of electrophiles to N-Botc-azetidine. Easy deprotection of N-Botc compound, can be carried out using TFA (EtOH, reflux, 12 h) [138]. Alternatively, the removal of the N-thiopivaloyl group demands the use of severe conditions, such as MeLi (5 equivalents), THF, at 0 °C for a duration of 5 hours [67].

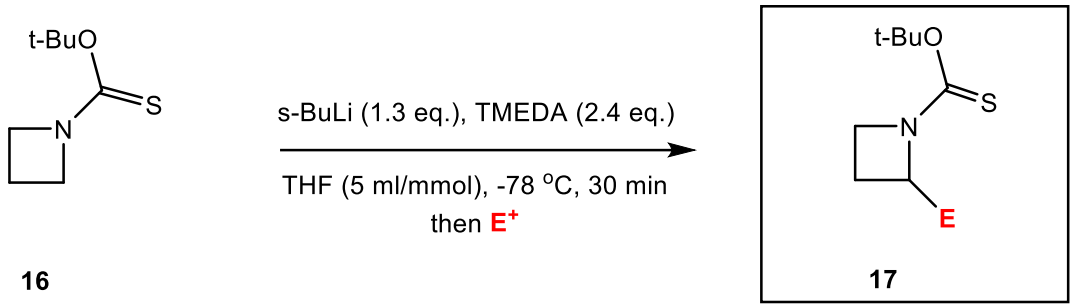
To the best of our knowledge, we were the first to perform the diastereoselective synthesis of 3-arylated-2-substituted azetidine compounds using various functionalized aromatic Grignard reagents and a variety of electrophiles (Scheme 26). Both the protecting groups (N-Botc and N-tPiv) enabled us to impart various electrophiles at the alpha position of azetidines with high selectivity.

a) previous work – Stereoselective synthesis of 2-Substituted 3-Hydroxyazetidines



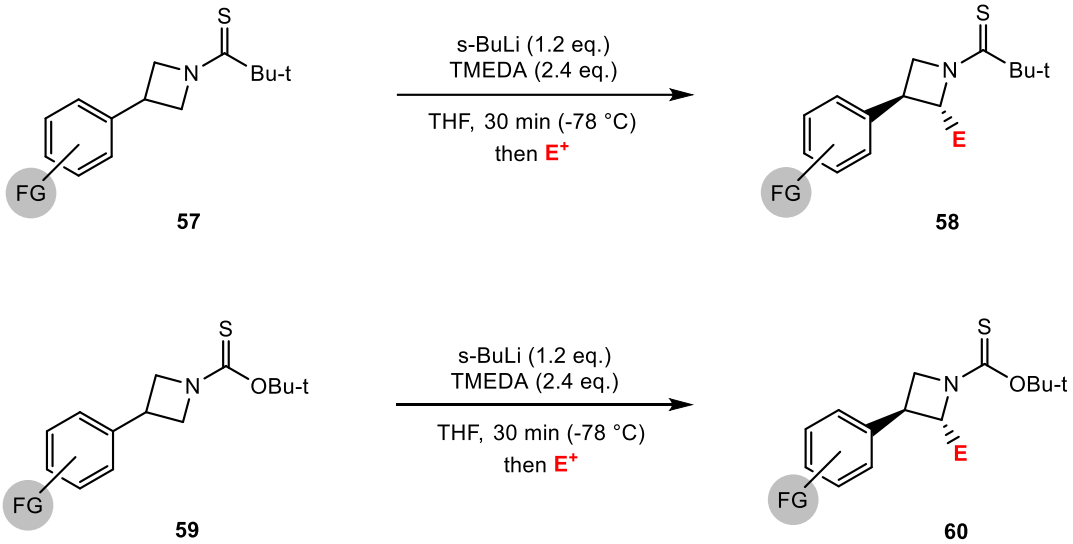
---

b) recent work – Lithiation-Electrophilic substitution of N-tert-Butoxythiocarbonylazetidines



---

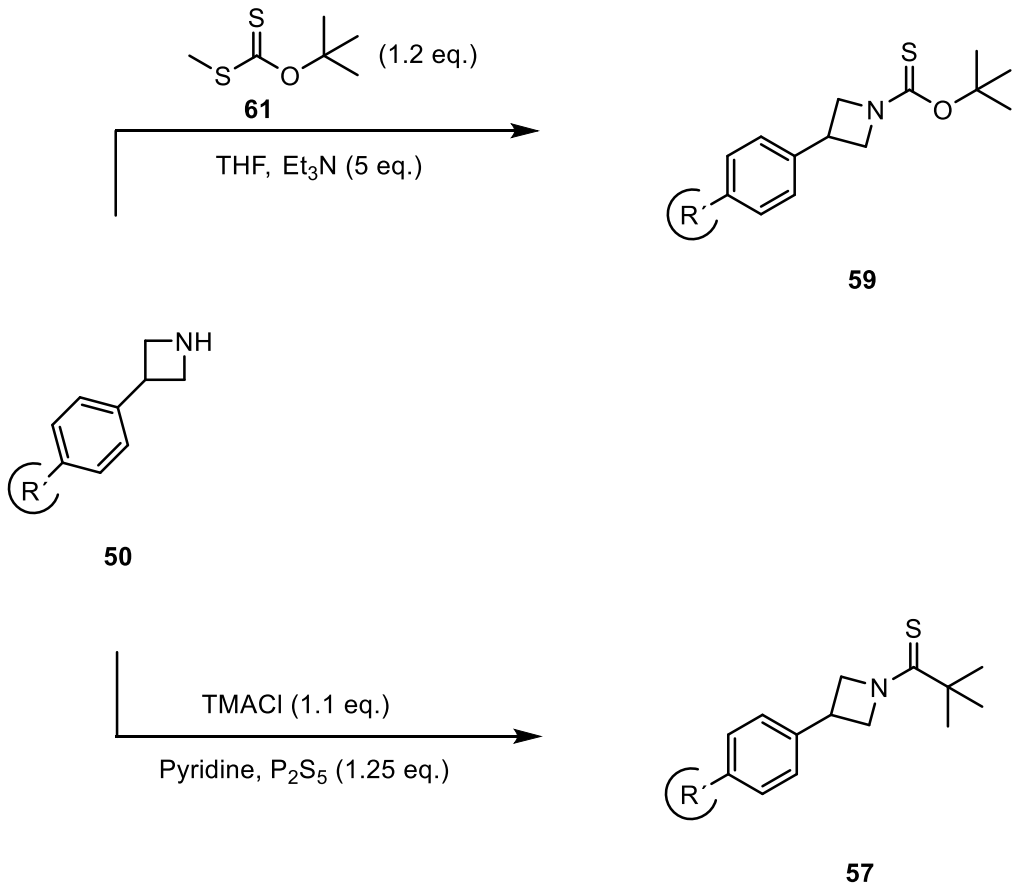
a) this work - Stereoselective electrophilic substitution of 3-arylated-N-protected azetidines

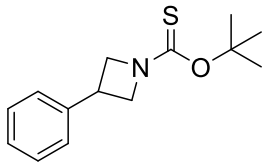


Scheme 26. Comparison among previous and current work for α-lithiation/electrophilic substitution of azetidines.

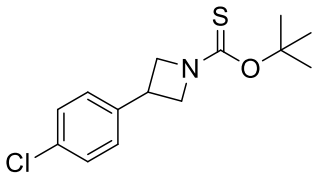
1.2 Optimization and Scope of the lithiation/electrophilic trapping of azetidines

At first, we have successfully synthesized the starting materials by employing strain release approach. For this, various functionalized aromatic Grignard reagents were introduced onto azetidine scaffold then directing groups (tPiv and Botc) were imparted further to achieve 3-substituted N-protected azetidines **59, 57** (Scheme 27). N-Botc protected 3-substituted azetidines **(59a - 59c)** were successfully synthesized but the synthesis of **59d** and **59e** did not work possibly due to the nature of substituents attached with the aromatic ring system. Furthermore, N-tPiv protected 3-substituted azetidines **(57a – 57f)** were successfully synthesized but again the synthesis from **(57g** – **57i)** did not work possibly because of the same reason as discussed (Scheme 27).

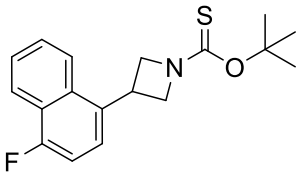




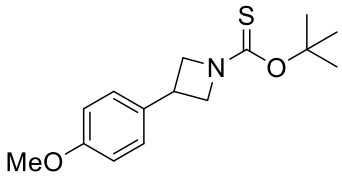
59a (35 %)



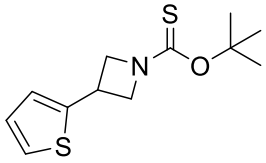
59b (31 %)



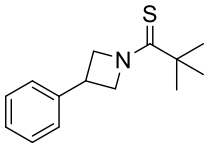
59c (29 %)



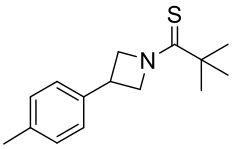
59d (Not Formed)



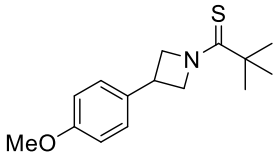
59e (Not Formed)



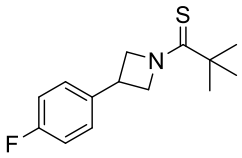
57a (77 %)



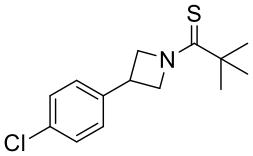
57b (39 %)



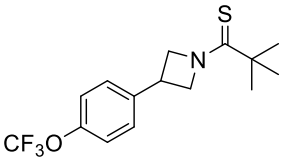
57c (72 %)



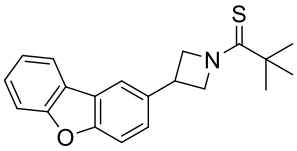
57d (32 %)



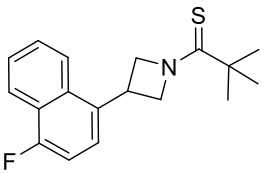
57e (22 %)



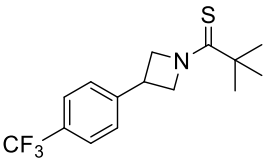
57f (37 %)



57g (Not Formed)



57h (Not Formed)



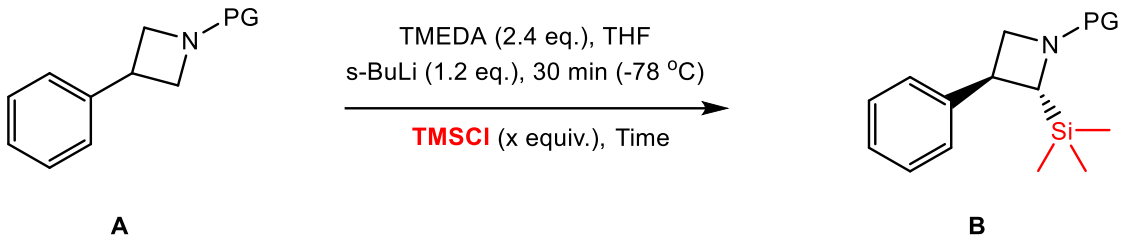
57i (Not formed)

Scheme 27. Synthesis of N-protected 3-subsituted azetidines using Botc and tPiv groups.

This work shows in-depth study of the N-protecting/activating groups (Botc, tPiv) that are not often employed for deprotonation at the alpha position to the nitrogen atom [42, 67, 139], **Table 1**. In the conversion of compound **A** to **B,** N-Boc-azetidine exhibited inertness towards lithium amides (LDA

or LTMP, LTMP=lithium 2,2,6,6-tetramethylpiperidide) also the use of n-BuLi, s-BuLi, t-BuLi/TMEDA was ineffective as shown in entry 1 (Table 1). The remarkable diastereoselectivity achieved for N-Botc (> 98% D) entry 2, as it is not typically observed for aziridines [61], N-Boc-pyrrolidine, or N-Boc-piperidines [140]. As well, the N-thiopivaloyl group which has not been much investigated before [59, 141] also plays a crucial role, entry 3. Further the reaction was examined using different equivalents of electrophiles and by changing reaction time. The optimum yield is measured for both directing groups when 2 eq. of Trimethylsilyl chloride (E^+) was added in the reaction mixture at -78 ^oC for 30 min and stirred reaction further for 30 min from -78 ^oC to rt, entry 2, 3. The use of reduced amount of TMEDA resulted in low yields and the product does not form without it. The experiments conducted in Et_2O and toluene was not significant, which can be attributed to the limited solubility of the deprotonated species.

Table 1. Optimization of α-lithiation/electrophilic substitution at 3-arylated N-protected azetidines.

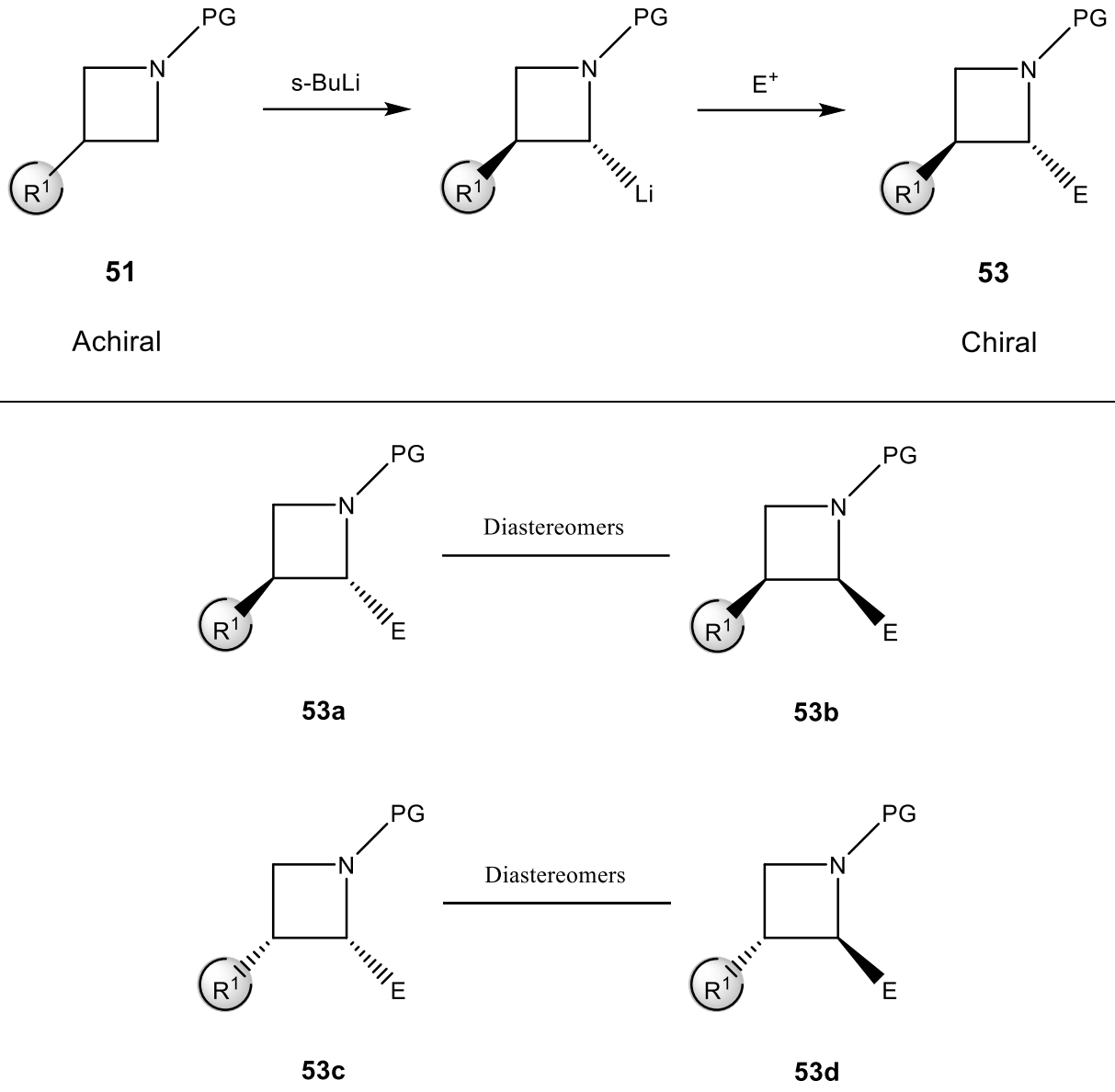


A B

Entry	PG	Time	E^+ (eq.)	Yield (%)	dr
1	Boc[a]	30 min	2	*None*	-
2	**Botc[b]**	**30 min**	**2**	**63**	**81:1**
3	t-Piv[b]	30 min	2	41	17:1
4	Botc	1 h	2	61	80:1
5	t-Piv	1 h	2	40	17:1
6	t-Piv	30 min	3	38	16:1
7	Botc	30 min	3	61	80:1
8	Botc	1 h	3	57	78:1
9	t-Piv	1 h	3	37	15:1

[a]Reactions performed with n-Buli, s-Buli, t-Buli/TMEDA, lithium amides (LDA, LTMP) under THF, diethyl ether and toluene as a solvent. [b]Reactions performed in THF using TMEDA (2.4 eq.), s-BuLi (1.2 eq.) at -78 °C (30 min) and then E^+ (2 eq.), rt (30 min). Diastereoselective ratio (dr) is estimated using ^1H NMR spectrum.

The starting material **51** is Achiral as it does not have any stereocenter. On the other hand, the electrophilic substitution product **53** has two stereocentres, Scheme 28.



Scheme 28. Possible stereoisomers of N-protected 2,3-disubsituted azetidine.

Remarkably, Botc protection demonstrated compatibility with α-lithiation−electrophile trapping under same conditions as those used for N-thiopivaloyl 3-arylated azetidines, resulting generally in good yields and significant diastereoselectivity. This effort produces high level of trans-diastereoselectivity due to the steric hindrance caused by the bulky group at position 3 as evidenced by X-ray diffraction (Figure 3).

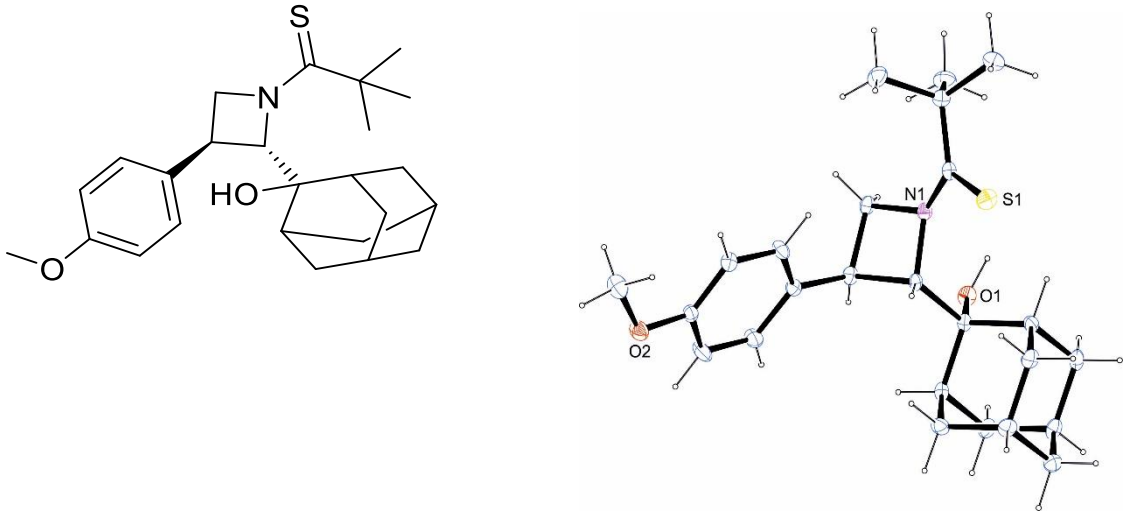


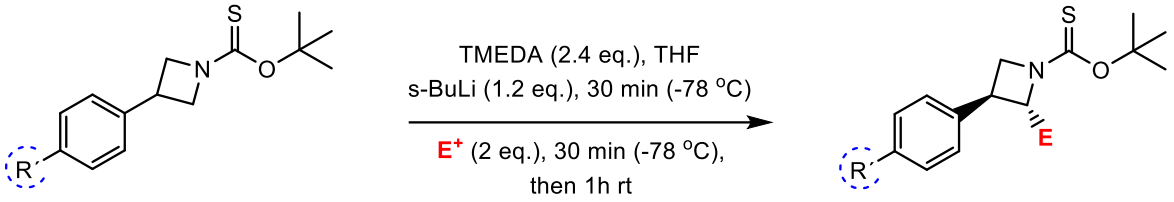
Figure 3. Major trans-diastereomer observed for 2,3-disubstituted azetidine as revealed by X-ray diffraction technique.

This demonstrates that the electrophile scope of these groups extends beyond the previously described approaches. This also suggests that there are more opportunities to generate diversity in azetidine using these methods.

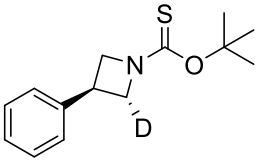
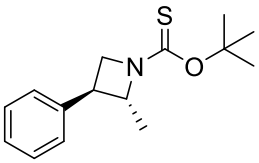
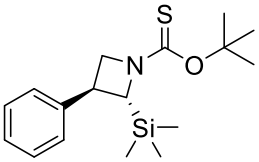
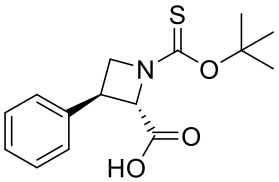
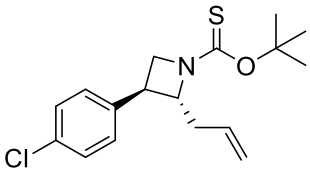
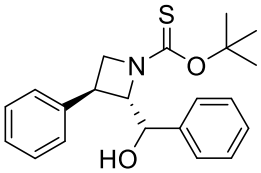
1.3 Stereoselectivity of 3-arylated azetidines upon electrophilic incorporation

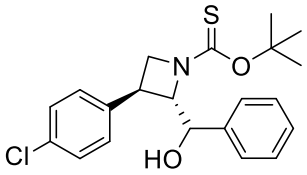
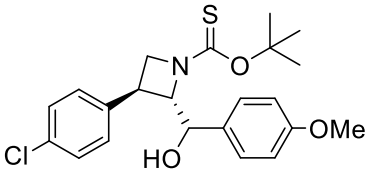
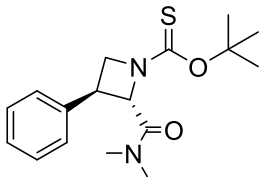
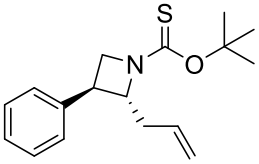
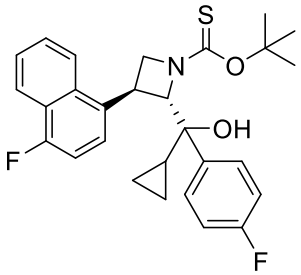
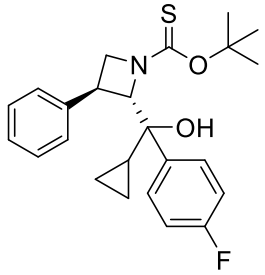
The process of α-lithiation of 3-substituted N-Botc protected azetidines followed by electrophile trapping allows for the synthesis of a variety of 2,3-disubstituted azetidines, Table 2. In this method electrophiles exhibited a significant level of trans-diastereoselectivity upon incorporation **(60a – 60e)** with a yields ranging from 19 to 97%. The highest yield of 97 % was obtained **(60a)** when employing Deuterium oxide (D_2O) is employed as an electrophile, entry 1. Furthermore, optimum dr (81:1) observed **(60c)** with TMSCl (E^+); major trans diastereomer (> 98% D) due to steric hindrance at 3-position of azetidine, entry 3. Additionally, certain products from reactions involving different electrophiles either weren't formed at all or were in the form of a complicated mixture that was challenging to isolate **(60f - 60l)**.

Table 2. Scope of Electrophilic Incorporation into 3-Arylated N-Botc azetidines



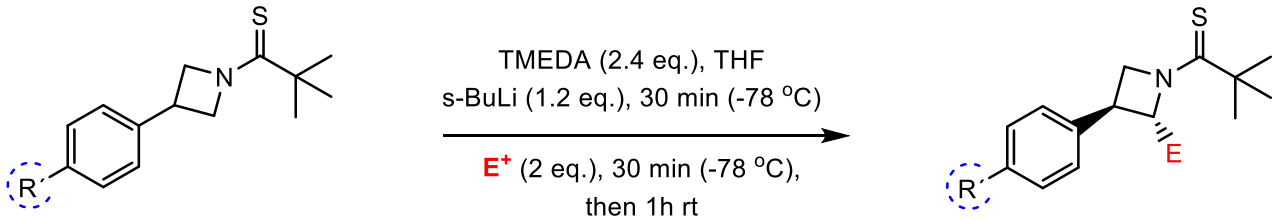
59 **60**

Entry	Compound	2, 3-disubstituted azetidine 9	Yield (%)	dr
1	**60*a***		97[a]	20: 1
2	**60*b***		68	3: 1
3	**60*c***		63	81: 1
4	**60*d***		19	2: 1
5	**60*e***		38	14: 1
6	**60*f***		Not formed[b]	–

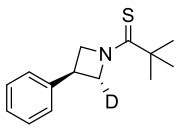
7	**60*g***		-	–
8	**60*h***		-	–
9	**60*i***		-	–
10	**60*j***		-	–
11	**60*k***		-	–
12	**60*l***		-	–

[a]Optimum dr obtained using TMSCl as an electrophile; major trans diastereomer (> 98% D) due to steric hindrance at 3 position of azetidines. [b]Reactions tried using various electrophiles some products were not formed and others were in the form of complex mixture could not isolate. Diastereoselectivity is estimated via ^{1}H NMR spectrum.

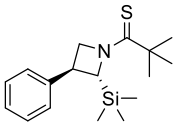
Moreover, the process of α-lithiation of 3-substituted N-tPiv protected azetidines followed by electrophile trapping allows for the synthesis of a variety of 2,3-disubstituted azetidines, Scheme 29. Likewise, electrophiles exhibited a significant level of trans-diastereoselectivity upon incorporation (**58a – 58p)** with a yield ranging from 31 to 87%. Deuterium oxide **58a** gives a good yield of 81%. When TMSCl is employed as an electrophile **58b** and **58c** are obtained in 41% and 37% yield, respectively. Methyl substitution at position 2 gives 36% of **58d**. Allyl bromide gives **58e** in 39% Various challenging electrophiles such as cyclopropyl(4-fluorophenyl)methanone (**58g – 58j)** and adamantan-2-one **(58k – 58l)** gives outstanding yields mostly above 80 % except **58g** and **58l**. Electron donating group on **58h** gives high yield of 85% in comparison with **58g** (43%). On the other hand, electron withdrawing group showed slight decrease in yield **58i** (83%). Noticeable decrease in yield observed with EWG on **58l** (32%) compared with **58k** (82%). Optimum yield up to 87 % obtained for **58n** when carbon dioxide gas (CO_2) is bubbled in the reaction mixture. Furthermore, optimum dr (94:1) seen with cyclobutanone **(58f)**; major trans diastereomer (> 98% D) due to steric hindrance at 3-position of azetidine. Also, reactions tried using various electrophiles some products were not formed or in the form of complex mixture difficult to isolate (**58aa – 58ss)**.



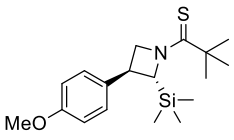
57 **58**



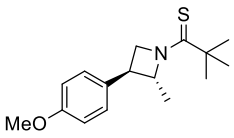
58a (81 %)
dr: 6:1



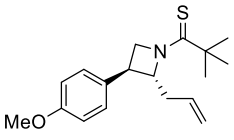
58b (41 %)
dr: 17:1



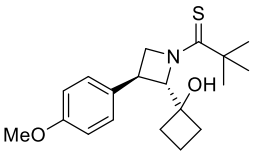
58c (37 %)
dr: 4:1



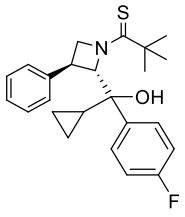
58d (36 %)
dr: 8:1



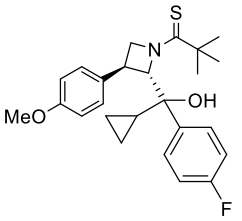
58e (39 %)
dr: 13:1



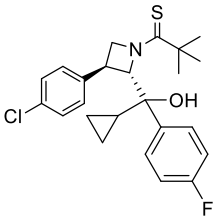
58f (31 %)
dr: 94:1



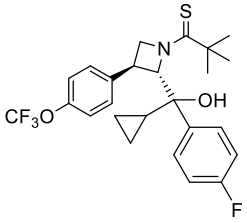
58g (43 %)
dr: 58:1



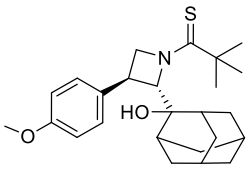
58h (85 %)
dr: 5:1



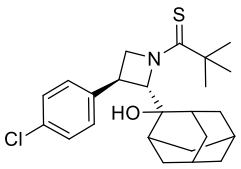
58i (83 %)
dr: 20:1



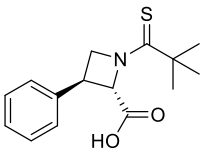
58j (81 %)
dr: 7:1



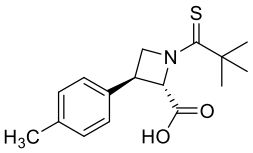
58k (82 %)
dr: 47:1



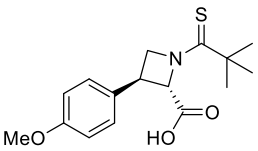
58l (32 %)
dr: 17:1



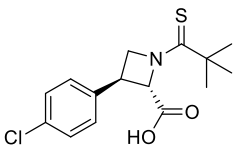
58m (69 %)
dr: 6:1



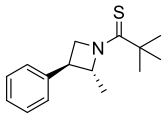
58n (87 %)
dr: 5:1



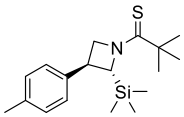
58o (81 %)
dr: 16:1



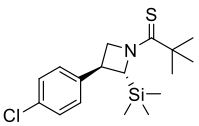
58p (51 %)
dr: 20:1



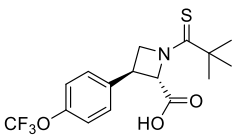
58aa (Not formed)



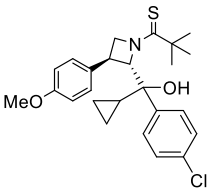
58bb (Not formed)



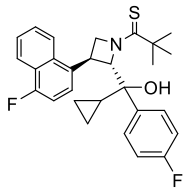
58cc (Not formed)



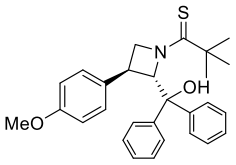
58dd (Not formed)



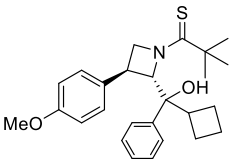
58ee (Not formed)



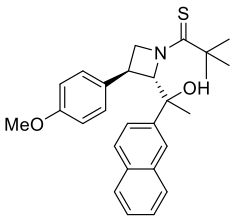
58ff (Not formed)



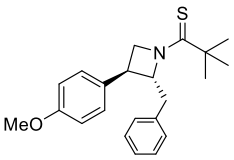
58gg (Not formed)



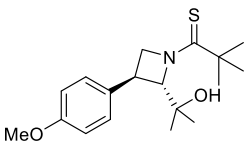
58hh (Not formed)



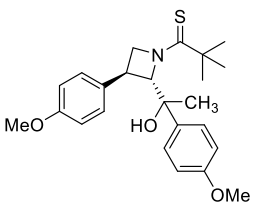
58ii (Not formed)



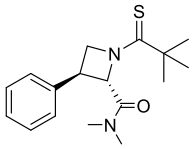
58jj (Not formed)



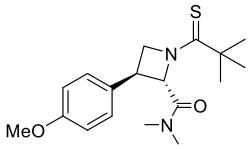
58kk (Not formed)



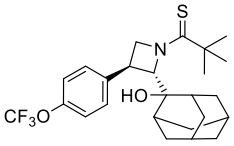
58ll (Not formed)



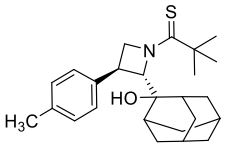
58mm (Not formed)



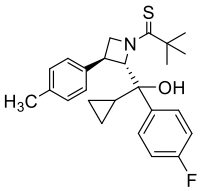
58nn (Not formed)



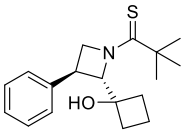
58oo (Not formed)



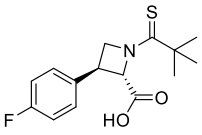
58pp (Not formed)



58qq (Not formed)



58rr (Not formed)

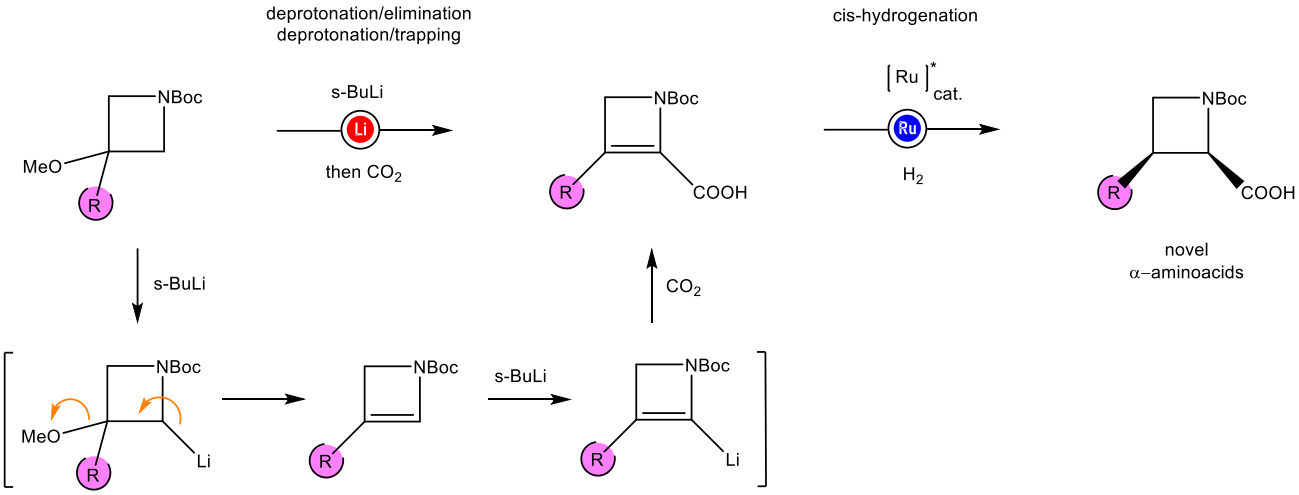


58ss (Not formed)

Scheme 29. α-lithiation/electrophilic trapping of 3-arylated N-tPiv protected azetidines using various electrophiles.

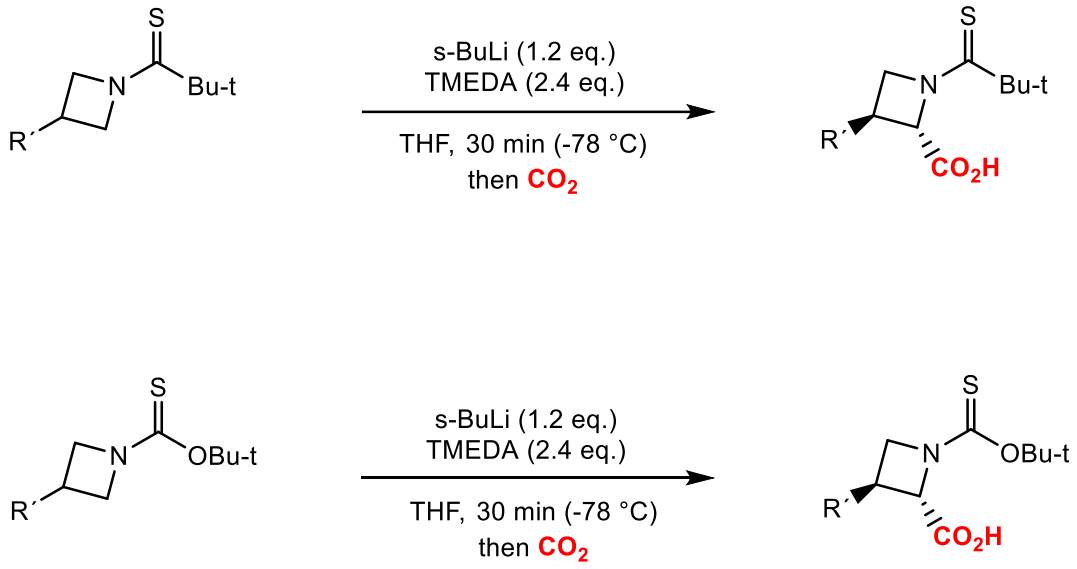
1.4 Competition between stereochemistry of electrophilic substituted azetidines

α-Amino acids are fundamental components that form the structural framework of proteins. Azetidine-based amino acids that are not naturally occurring have notable characteristics in the field of protein engineering as it enables the exploration of novel characteristics. In light of our progress in synthesizing four-membered carbo- and heterocycles [142-152] a simple organometallic pathway for the synthesis of unsaturated carboxylic acid precursors is demonstrated recently by our group, following metal-catalyzed asymmetric reduction, a diastereospecific synthesis (dr > 99:1) of functionalized 2-azetidinecarboxylic acid was performed [153]. This technique produced the targeted creation of cis-isomers, (Scheme 30) [154, 155].



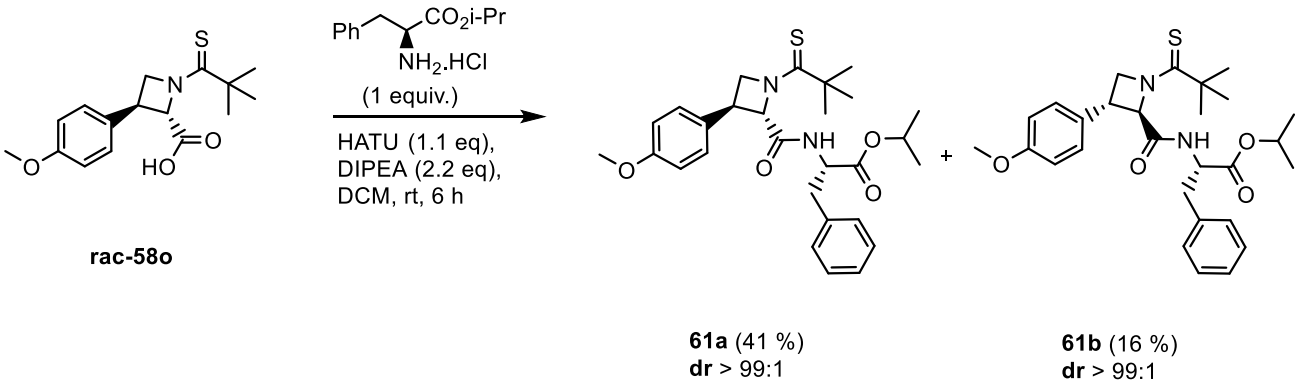
Scheme 30. Metal-catalyzed asymmetric reduction for the diastereoselective synthesis of novel α-amino acids [153].

In this work further studies were performed to examine the formation of azetidine-based amino acids selectively using N-tPiv and N-Botc protected azetidines. For this, carboxylic acid substituted azetidines were firstly generated by introducing carbon dioxide (CO_2) gas into the reaction mixture. The study then proceeded to analyze the tolerance of various functional groups by adding different substituents on the aryl part of the substrate. It is important to mention that the method of adding lithium to saturated cyclic systems resulted in trans-isomers (Scheme 31), providing an effective and distinct alternative to existing methods [56, 153].



Scheme 31. Diastereoselective synthesis of novel α-aminoacids using tPiv, **58m-58p** (51 to 87 %) and Botc, **60d** (19 %), respectively.

Employing a diverse collection of α-amino acid building blocks, our objective was to integrate them into short peptide chains. Compound-**58o** was selected for amidification with stereodefined L-phenylalanine isopropyl ester using HATU as a peptide coupling agent [156]. The two diastereoisomers, namely **61a** and **61b**, could be effectively separated using column chromatography and obtained yields of 42 % and 16 % respectively, resulting in a total yield of 58% (Scheme 32). In the future, we anticipate that these effective designs will be highly valuable for protein engineering and the investigation of secondary structures including azetidines.



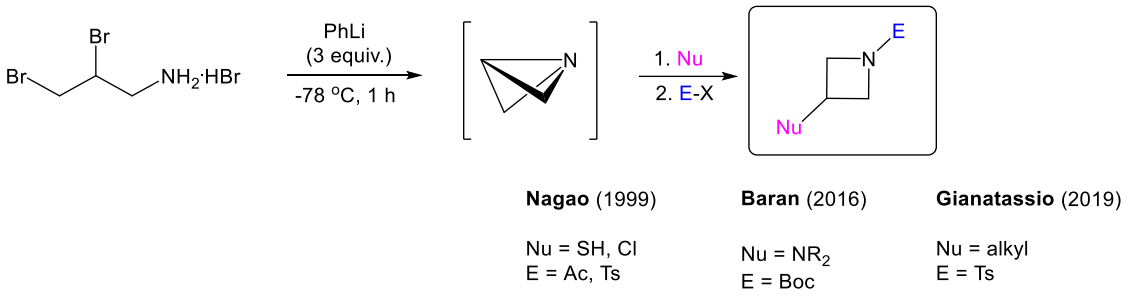
Scheme 32. Synthesis of peptide chains via functionalized 2-azetidinecarboxylic acid.

2 Bis-arylation of azetidines by means of strain release approach

2.1 Introduction

Over the past few years, strained sp^3-rich heterocycles have become significant frameworks in medicinal chemistry, they are valuable in adjusting pharmacokinetic characteristics [39, 157-160]. Azetidines have gathered noteworthy attention among those. They have been employed in various occasions to rigidify amine structures or as phenyl isosteres [161, 162]. Various approaches enable the creation of substituted azetidines, such as [2+2]-cycloadditions [163, 164], ring expansions [165-167], ring contractions [168-171] and ring closures [172]. Furthermore, we have made new contributions to this field by manipulating unsaturated analogues, specifically 2H-azetines, using Diels-Alder cycloadditions or hydrogenation reactions [148, 151, 153]. 1-Aza-bicyclo[1.1.0]-butanes (ABB) have a unique reactivity towards nucleophiles due to their ring strain. This makes them a promising substrate for further functionalization's. Due to the significant strain in C–N–C dihedral angles, aza-bicyclobutanes exhibit strong nucleophilic properties and are expected to readily undergo reactions with electrophilic species. Inspired by Funke's [173] groundbreaking research, Nagao's team further explored the concept of strain-release using nucleophiles such as thiols and halogens. They conducted their experiments in the presence of N-trapping reagents such as tosyl- and acyl chlorides [81]. Later, Baran created a highly effective strain release amination approach based on the use of turbo-amides (primary and secondary) as a nucleophile for the modification of drug-like compounds [91]. In 2019, Gianatassio and his colleagues have demonstrated the nucleophilic addition of Grignard reagents in the synthesis of 3-alkylazetidines. They achieved this by employing TsCl, acyl chlorides or Boc_2O as electrophiles, (Scheme 33) [92]. Also, the substitution of azetidines at position 3 can be efficiently achieved via 1,2-boronate rearrangements [174]. In this work we introduced nucleophilic organometallic species onto azabicyclobutanes that are formed in situ and selectively created 3-arylated azetidine intermediates by the release of strain. Subsequent advancements were made in the development of single pot techniques for the N-arylation of azetidines by using either Buchwald-Hartwig couplings or S_NAr reactions. A highly effective method is introduced for 1,3-bis-arylation of azetidines, arylmagnesium reagents were used to conduct an unprecedented arylation at position 3. The solvent system has been modified to prevent undesirable products and showcasing the method's strong tolerance for functional groups. By using straightforward and adaptable C-N bond formation techniques, a large library of building blocks, including drug compound analogues could be designed moving closer to the difficult task of implementing rigid sp^3-rich scaffolds in drug-discovery programs.

a) literature – Strain release / electrophilic trapping of azetidines



Nagao (1999)

Nu = SH, Cl
E = Ac, Ts

Baran (2016)

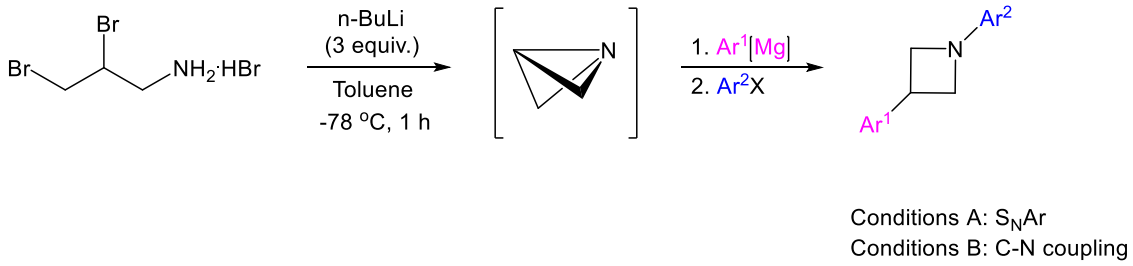
Nu = NR_2
E = Boc

Gianatassio (2019)

Nu = alkyl
E = Ts

---

b) this work – Strain - release bis-arylation of azetidines



Conditions A: S_NAr
Conditions B: C-N coupling

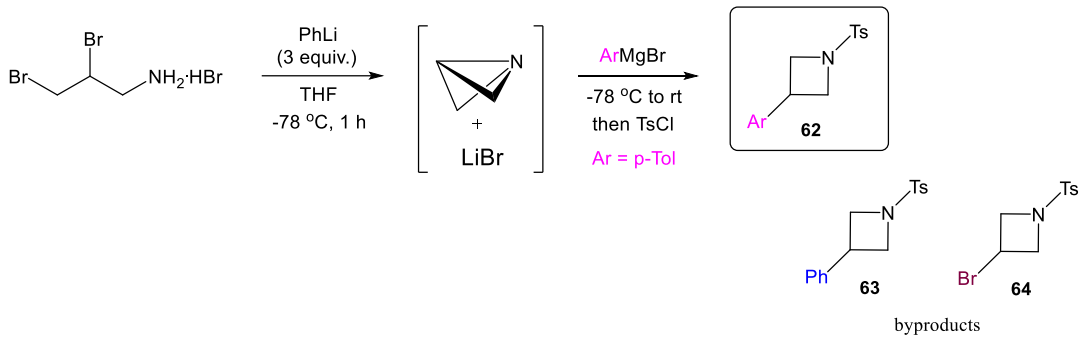
Scheme 33. Synthetic approach to 1,3-bisfunctionalized azetidines.

Surprisingly, there is a lack of literature on compounds as uncomplicated as 1,3-bisarylated azetidines, primarily due to the challenging nature of efficient and selective formation of their structure. Although the attempts have been made, the process of introducing aryl groups at position 3 of aza-bicyclobutanes through strain-release has not been revealed. Driven by a broad fascination with 4-membered carbo- and heterocycles and their applicability in drug development [175], we set out to develop a reliable method for creating these functionalized azetidine structures.

2.2 Optimization and scope for the strain release bis-arylation of azetidines

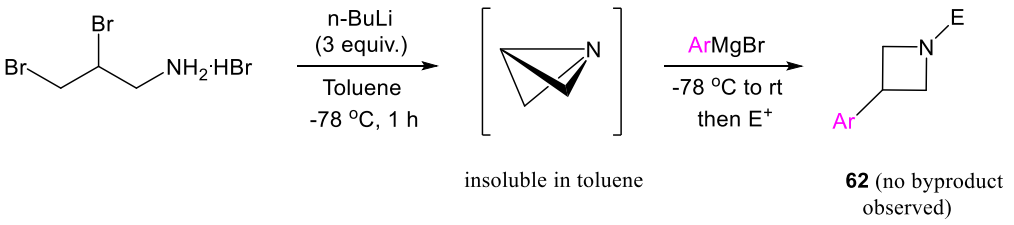
We initiated our investigations by examining the ring-opening reactions using aryl-Grignard reagents that were synthesized ex situ. Previously, AAB were formed in THF by a process of double cyclization, using an excessive amount of phenyl lithium as a base to remove protons. The initial experiments were conducted at the specified circumstances (PhLi, THF), but many by-products were observed, Scheme 34. The desired product **62**, which is formed through the nucleophilic addition of ArMgBr (p-Tol), was only obtained in small quantities and could not be separated from the

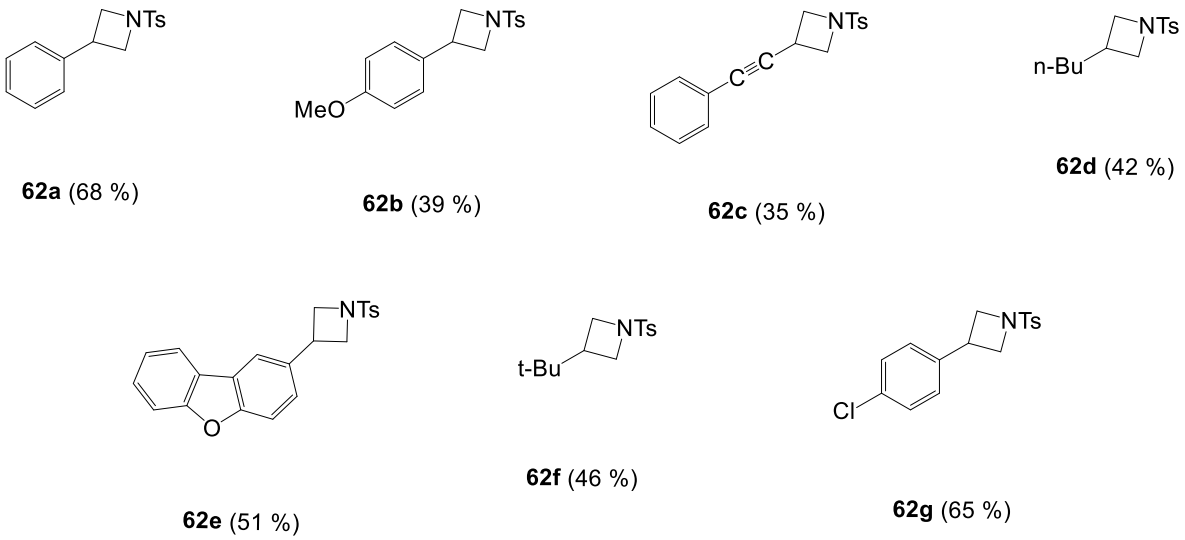
byproducts **63** and **64**. These byproducts were formed due to the nucleophilic additions of residual PhLi and THF-soluble LiBr, individually.



Scheme 34. Issues related with the reported conditions for the bis-functionalization of azetidines.

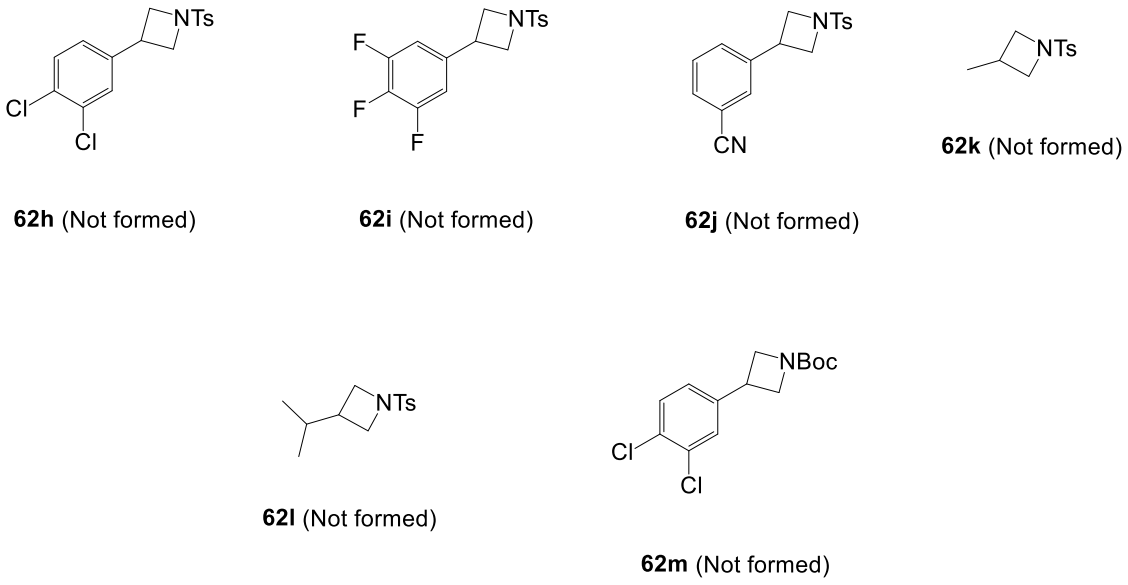
We envisioned that n-BuLi which is more basic, less nucleophilic than PhLi could serve as a substitute for PhLi, thereby preventing the production of molecule **63**, which is difficult to separate. n-BuLi is more alkaline, but less nucleophilic, compared to PhLi. The prevention of the creation of **64** was accomplished by using toluene as the solvent to cause the precipitation of LiBr produced during the cyclization process, therefore, hinders the unwanted reactivity between LiBr and ABB, Scheme 35. With new conditions, products **62a-g** were separated without any byproducts in yields ranging from 35% to 68% [51] upon the introduction of TsCl as an electrophiles. Optimum yield of 68% is obtained for **62a** with phenyl magnesium bromide as a nucleophile. The aryl-Grignard reagents exhibited a unique nucleophilic addition onto aza-bicyclobutanes, resulting in an efficient and smooth incorporation of aryl groups at position 3. Electron donating group on **62b** gives 39% yield in comparison with EWG on **62g** which gives a yield of 65%. Products **62h - 62m** tried with various Grignard reagents and electrophiles but was not successful.





62a (68 %) **62b** (39 %) **62c** (35 %) **62d** (42 %)

62e (51 %) **62f** (46 %) **62g** (65 %)



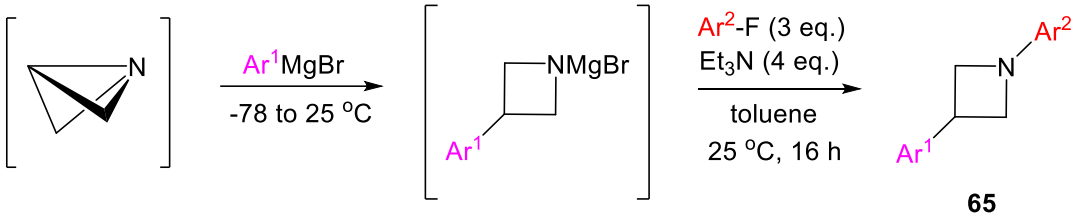
62h (Not formed) **62i** (Not formed) **62j** (Not formed) **62k** (Not formed)

62l (Not formed) **62m** (Not formed)

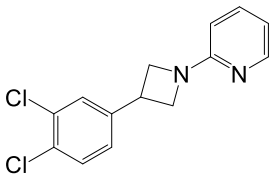
Scheme 35. Establishing conditions for the strain-release reaction with aryl-magnesium reagents**.**

We anticipated that the intermediate magnesium amide**,** which is formed through a ring opening reaction, may be directly utilized in a subsequent nucleophilic aromatic substitution onto electron-deficient aromatics, providing a first way for the synthesis of bis-arylated structures, Scheme 36. 2-Fluorinated pyridines were selected as suitable substrates for this reaction due to their electron-deficient properties. Following the successful formation of the N-azetidinylmagnesium species in the reaction mixture using PhMgBr, additional S_NAr (nucleophilic aromatic substitution) was carried out in the presence of triethylamine and an excess of the electrophilic 2-fluoropyridine. This resulted in the production of compound **65a-e** with a yield ranging from 27 to 65%. Optimum yield obtained for

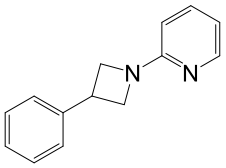
65b (65%). Further, by altering the substitution pattern of 2-fluoropyridines, we obtained halogenated compounds **65c** (43%). Aryl-Grignard reagents with electron-withdrawing substituents (Cl) were also observed in this reaction, producing compounds **65a** and **65e** with yields 27% and 47%, respectively. The compounds **65f** and **65g** were unfortunately not obtained.



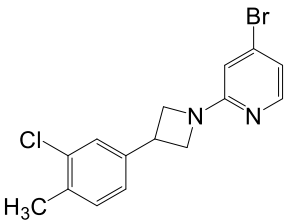
65



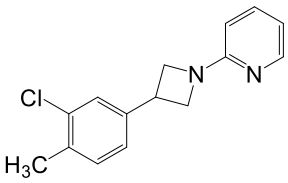
65a (27 %)



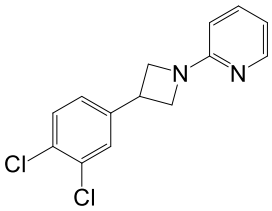
65b (65%)



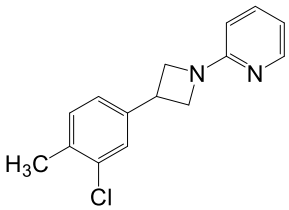
65c (43 %)



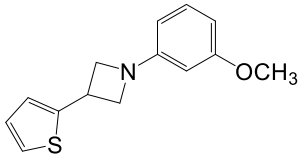
65d (35 %)



65e (47 %)



65f (Not formed)



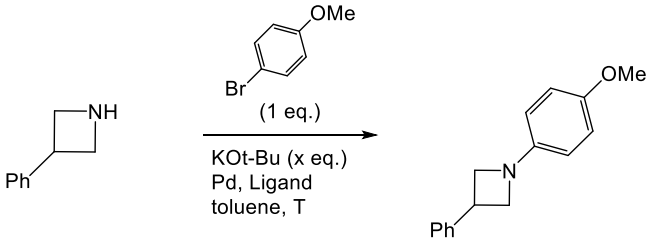
65g (Not formed)

Scheme 36. Nucleophilic aromatic substitutions (S_NAr) of 3-arylated azetidines.

While this approach shown effectiveness, it is limited to the replacement of fluorides on electrophiles that resemble pyridine. Other electron deficient aryl compounds containing nitro, cyano, or ester groups were unable to produce the intended N-arylated azetidines, thus restricting the range of the reaction. Consequently, we sought an alternative method that would expand the options for creating C–N bonds and focused our attention on Pd-catalyzed conversions. The Buchwald-Hartwig coupling reactions have experienced significant advancements since the groundbreaking studies conducted by the researchers who are credited with the discovery of this transformation [176, 177]. Several instances of drug discovery programs have been documented on the coupling of 2^{o} amines, including some azetidines also [174, 178].

Phenyl azetidine **A´** coupled with p-bromoanisole was examined for the purpose of enhancing the reaction process, table 3. While $Pd_2(dba)_3$/BINAP or $Pd(OAc)_2$/Xantphos catalytic systems (entries 1-3) produced the coupling product **B´** in a yields of 27 to 60% (using either KOt-Bu or NaOt-Bu as the base). The optimum yield (82%) obtained when azetidine is combined with the xPhosPdG3/Brettphos catalytic system (entry 5). While reducing the catalyst loading to 1 mol% did not have any detrimental effect on the effectiveness of the coupling, lower temperatures did lead to reduced yields.

Table 3. Optimization of conditions for Buchwald–Hartwig couplings of azetidines

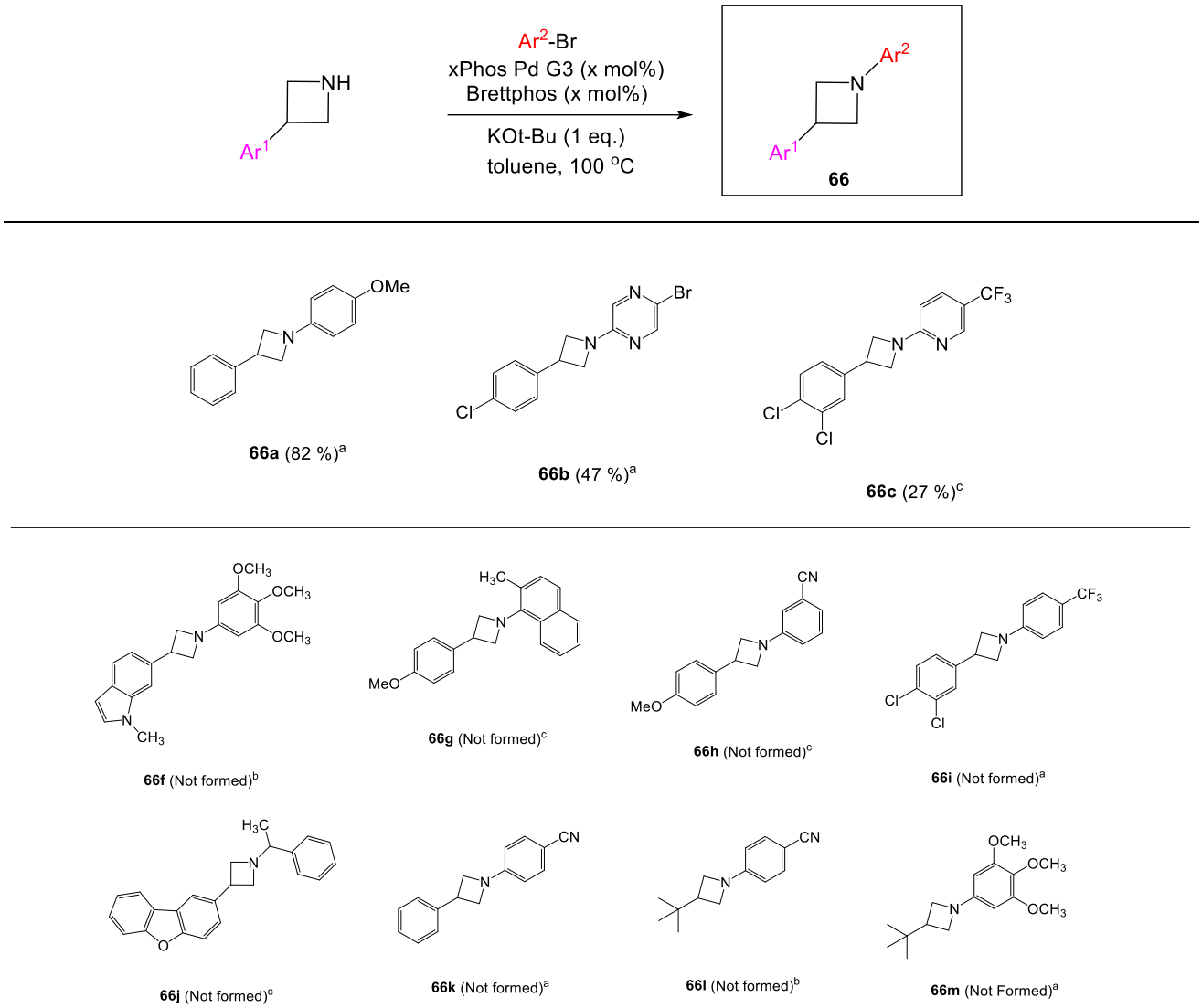


Entry	[Pd]/Ligand	T (°C)	Yield (%)
1	$Pd_2(dba)_3$/BINAP[a]	100	60
2	$Pd_2(dba)_3$/BINAP[a]	100	58[b]
3	$Pd(OAc)_2$/Xantphos[a]	100	27
4	RuPhosPdG3/RuPhos[c]	100	79
5	xPhosPdG3/Brettphos[c]	100	82
6	xPhosPdG3/Brettphos[c]	80	73

[a] Reactions performed with 3 mol% [Pd], [Pd]/Ligand = 1.5 : 1, 3.0 eq. KOt-Bu. [b] NaOt-Bu instead of KOt-Bu. [c] Reactions performed with 1 mol% [Pd], [Pd]/Ligand = 1 : 1, 1.4 eq. KOt-Bu.

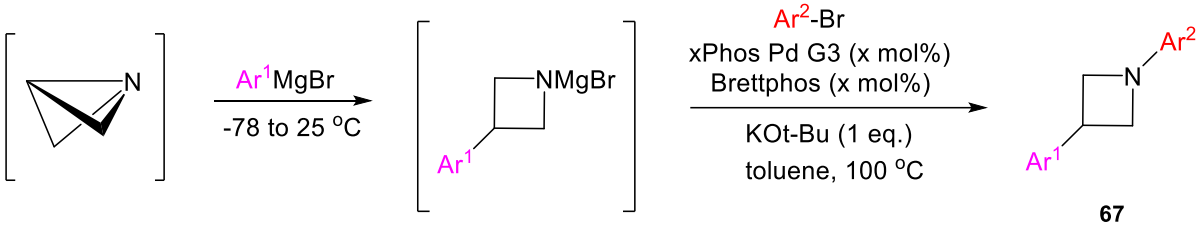
By employing optimal conditions, the potential of Buchwald–Hartwig coupling on 3-arylazetidines produced ex situ was assessed under favorable conditions, using variously substituted aryl and heteroaryl bromides. 3-Phenylazetidine combined with both electron-rich and electron-poor aryl bromides, resulting in the formation of 1,3-bis-arylated azetidines **66a–c** with significant yields ranging from 27% to 82%.

It is important to mention that a higher amount of product was produced using Buchwald-Hartwig coupling on 4-bromoanisole (**66a,** 82%**)** compared to S_NAr conditions (**65a-e,** 27 to 65%). By introducing an electron-deficient Grignard reagent, a 27% yield of **66c** was obtained. The reaction shown a good level of tolerance towards functional groups. Despite, the formation of compounds from **66f – 66m** was not successful, (Scheme 37).

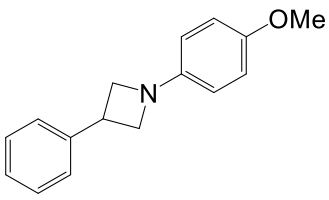


Scheme 37. Buchwald–Hartwig coupling of 3-arylazetidines. [a] x = 1 mol%, [b] x = 2 mol%, [c] x = 3 mol%.

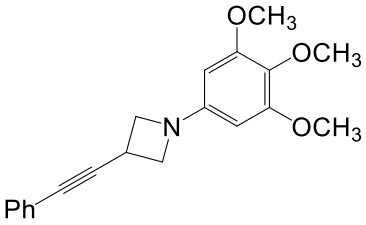
The coupling techniques used for the azetidine bis-arylation process, led to a variety of various functionalized molecules. Our next objective was to improve the efficiency of the process by eliminating the need to purify the free azetidine at an intermediate stage. A one-pot procedure was designed to facilitate the bis-arylation of azetidines. This method combines the stages of strain release and Buchwald-Hartwig coupling in the same solvent system. The formation of aza-bicyclobutane occurred in situ then arylation at position 3 is performed via strain release using aryl magnesium species and finally coupling reaction is carried out under Pd-catalyzed conditions, (Scheme 38). By altering the compositions, various functionalized compounds **67a-c** were synthesized with moderate to high yields (36 to 72%) by Buchwald-Hartwig C-N coupling reactions. Compound **67a** was obtained with a bit reduced yield (72%) compared to the two-step process **66a** (82%).



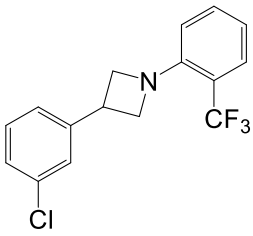
67



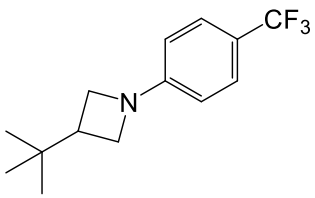
67a (72 %)[a]



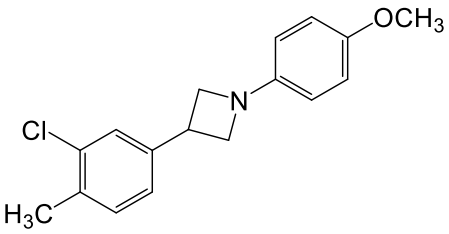
67b (35 %)[c]



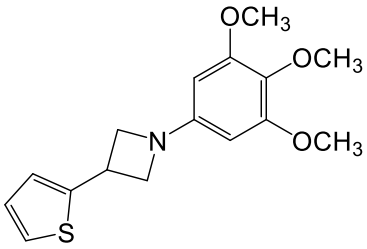
67c (36 %)[b]



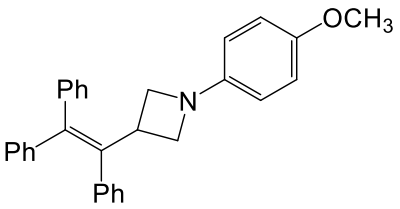
67d (Not Formed)[c]



67e (Not Formed)[a]



67g (Not Formed)[a]

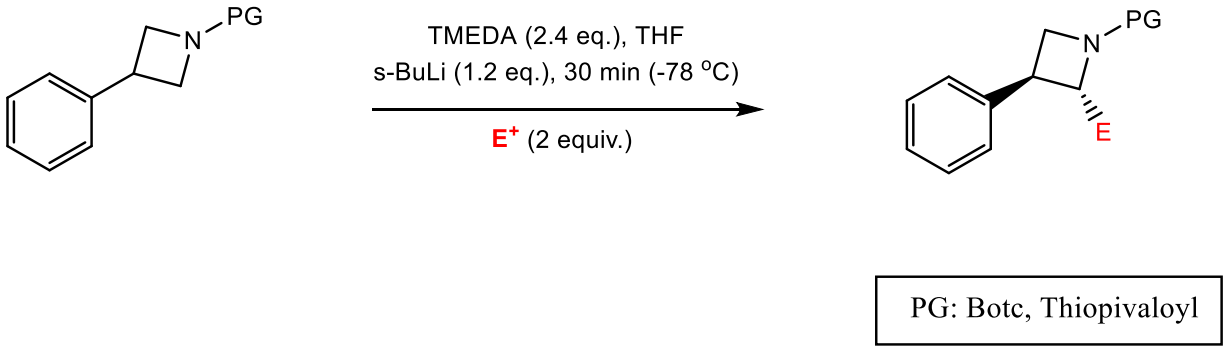


67f (Not Formed)[b]

Scheme 38. One-pot ring-opening/Buchwald–Hartwig coupling sequence of 3-arylated azetidines. [a] x = 3 mol%, [b] x = 4 mol%, [c] x = 5 mol%.

3 Conclusion

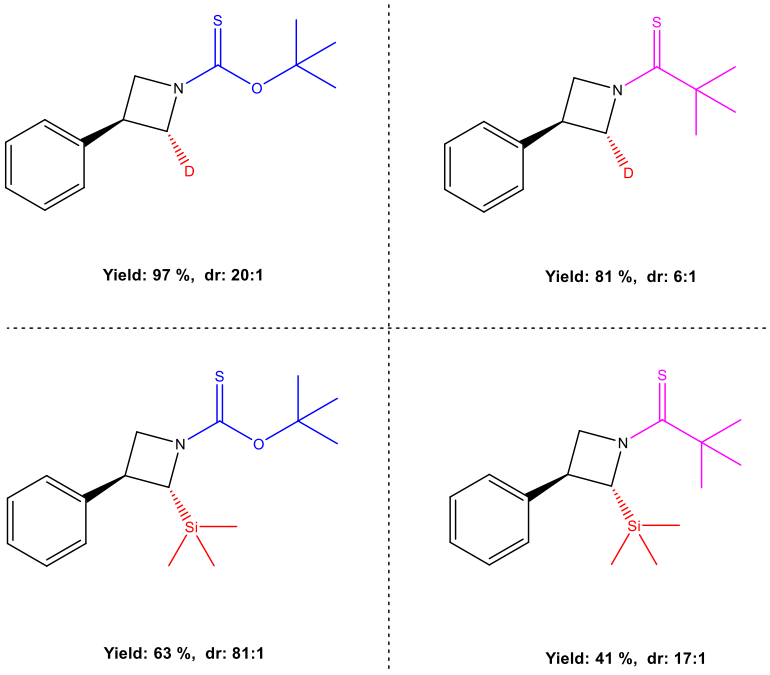
This study demonstrated different strategies for the synthesis of functionalized azetidine compounds, which are widely recognized and acknowledged methodologies due to their selectivity. Many Grignard reagents were synthesized at the start and utilized further for the synthesis of 3-arylated azetidines. Moreover, protecting groups were employed for the formation of 3-arylated N-protected azetidines. Hence, α-lithiation and subsequent electrophile trapping of 3-arylated N-protected azetidine have been successfully performed using different reaction conditions to get optimum yield of the final products, Scheme 39.



Scheme 39. Electrophilic trapping at 2 position of N-protected functionalized azetidines.

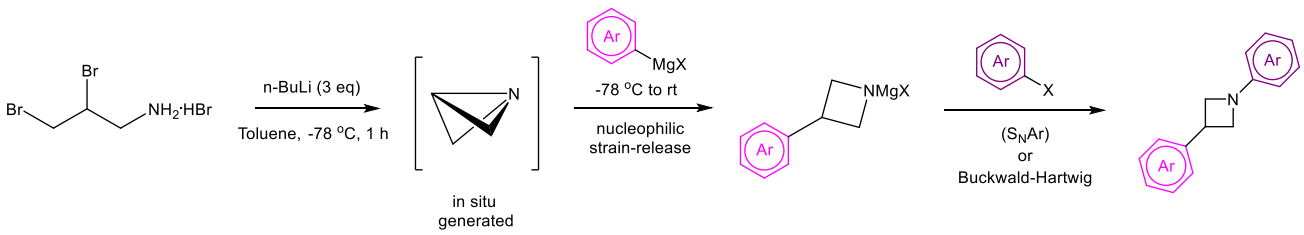
Ultimately, the diastereoselectivity have been measured at the α-position of 3-arylated N-protected azetidines. O-tert-butyl carbothioate protecting group showed good yield and diastereoselective ratio (dr) when compared to thiopivaloyl group, also deprotection of this group does not require harsh conditions. The comparison has been made for the diastereomeric ratio among 3-arylated azetidines protected with O-tert-butyl carbothioate group and thiopivaloyl group containing different electrophiles (Deuterium oxide and TMSCl), Botc showed greater yield with good diastereoselectivity in comparison (Scheme 40).

Also, reactions tried using various electrophiles some products were not formed or in the form of complex mixture difficult to isolate depending on the nature of substituent at position 3 of azetidine and attacking electrophile.



Scheme 40. Comparison of the yield and diastereomeric ratio among 3-arylated N protected azetidines containing electrophiles (Deuterium oxide and TMSCl).

For the second project, we have created a highly effective method for the 1,3-bis-arylation of azetidines by employing reactive strained aza-bicyclobutanes, generated in situ. A novel arylation at position 3 was carried out using arylmagnesium reagents, by modifying the solvent system to prevent the formation of unwanted products, Scheme 41. These experiments showcased the method's exceptional ability to accommodate various functional groups. Efficient and flexible methods for creating C-N bonds were used in a single pot reaction, enabling the synthesis of a wide range of chemical building blocks. These building blocks include analogues of drug compounds, which is a significant advancement towards incorporating rigid sp^3-rich structures in drug discovery programs.



Scheme 41. Strain release approach for the bis-arylation of azetidines.

C. Experimental Section

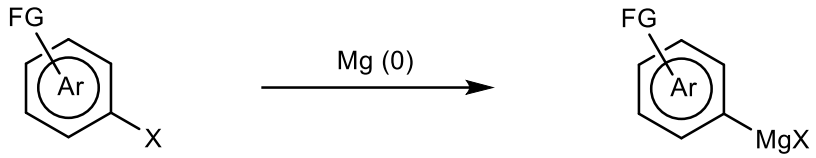
3 General Considerations

Starting materials used were commercially available without any further purification except otherwise stated. All the reactions were performed using flame-dried glassware under N_2 atmosphere. Syringes were purged with nitrogen three times before use to transfer reagents or anhydrous solvents. THF 99.5 % pure and toluene 99.85 % pure was bought from Acros Organics. Solution of n-BuLi in hexane was purchased from Rockwood Lithium and the concentration was measured via titration using 1,10-phenanthroline in THF with iPrOH. s-BuLi as a solution in cyclohexane was purchased from Albemarle. Phenyl magnesium chloride solution in THF was purchased from Rockwood Lithium and the concentration was determined by titration using iodine in THF. Aryl Grignard reagents were titrated using iodine in THF at rt. Chromatography purifications were carried out using silica gel (SiO_2, 0.040-0.063 mm, 230- 400 mesh ASTM) from Merck. The spots were seen under UV (254 nm) or by staining the TLC plate with the solution of $KMnO_4$ (K_2CO_3, 10 g – $KMnO_4$, 1.5 g – H_2O, 150 ml – NaOH 10% in H_2O, 1.25 ml). NMR and GC analysis were used to estimate % age purity of final products. The ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on VARIAN VXR 400 S and BRUKER at 400, 599, 151, 101 and 377 MHz instruments. Chemical shift (δ) values were reported in ppm relative to the residual solvent peak (^{1}H-NMR, ^{13}C-NMR) in deuterated chloroform ($CDCl_3$: δ 7.26 ppm for ^{1}H-NMR and δ 77.16 ppm for ^{13}C-NMR). Signal coupling abbreviations are as follows: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet) and br (broad). Reactions were monitored via GC to check the endpoints using n-undecane as an internal standard. Gas Chromatography was performed using instruments of Agilent Technologies 7890, having a column type HP 5 (Agilent 5% phenylmethylpolysiloxane; length: 15 m; diameter: 0.25 mm; film thickness: 0.25 μm) or Hewlett-Packard 6890 or 5890 series II, using a column of type HP 5 (Hewlett-Packard, 5% phenylmethylpolysiloxane; length: 15 m; diameter: 0.25 mm; film thickness: 0.25 μm). High resolution mass spectra (HRMS) and low-resolution mass spectra (LRMS) were recorded on Finnigan MAT 95Q, Finnigan MAT 90 instrument or JEOL JMS-700. Infrared spectra were recorded on a Perkin 281 IR spectrometer and samples were measured neat (ATR, Smiths Detection DuraSample IR II Diamond ATR). The absorption bands were reported in wave numbers (cm^{-1}) and abbreviations used for intensity are as follows: vs (very strong; maximum intensity), s (strong; above 75% of max. intensity), m (medium;

from 50% to 75% of max. intensity), w (weak; below 50% of max. intensity) and br (broad). Melting points were measured on a Büchi B-540 apparatus.

4 General Procedures

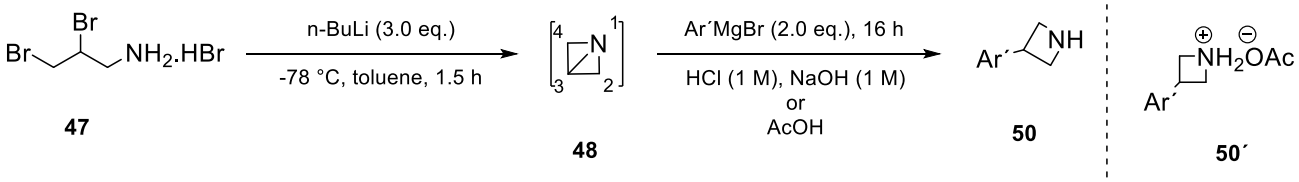
4.1 Synthesis of Aryl Grignard Reagents



FG = functional group; X = Br, Cl

Schlenk flask dried by heat gun (600 °C, 2 x 5 min) was charged with magnesium turnings (972.2 mg, 40 mmol, 2 eq.). THF (5.0 mL) and iodine (1 grain) were added, and the mixture was heated to reflux using heat gun to activate the magnesium. Aryl bromide (20 mmol, 1.0 equiv.) dissolved in THF was added dropwise to the activated magnesium suspension. After that the mixture was stirred for 1 h at room temperature to get a THF-solution of aryl magnesium reagents. The concentration of the prepared Grignard reagent was determined by titrating with I_2.

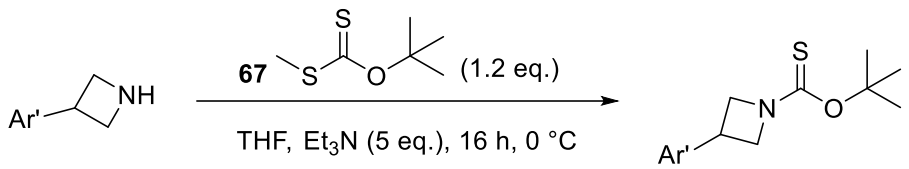
4.2 Synthesis of 3-substituted azetidines



2,3-dibromopropan-1-amine (1 eq.) was suspended in toluene (extra dry) in a dried round bottom flask. The suspension was cooled down to -78° C the n-BuLi (3 equiv.) was added dropwise, and the reaction was stirred for 1.5 h. Afterwards the Grignard reagent (2 equiv.) was added dropwise to the solution, and the reaction was left stirring for one hour at -78°C and then at rt for 16 h under N_2 atmosphere. The reaction was quenched with HCl (1 M) until (pH ~ 1), and then washed with Et_2O (3x). The aqueous layer was basified with NaOH solution to (pH ~ 10-12) and extracted with EtOAc (3x). The combined organic layer was dried over $MgSO_4$ and concentrated in vacuo. The product **50**

was then used for other preparations without further purification. Alternatively, the reaction can be quenched using AcOH. The excess AcOH was removed with toluene in vacuo (3 x) to get the solid product **50´**.

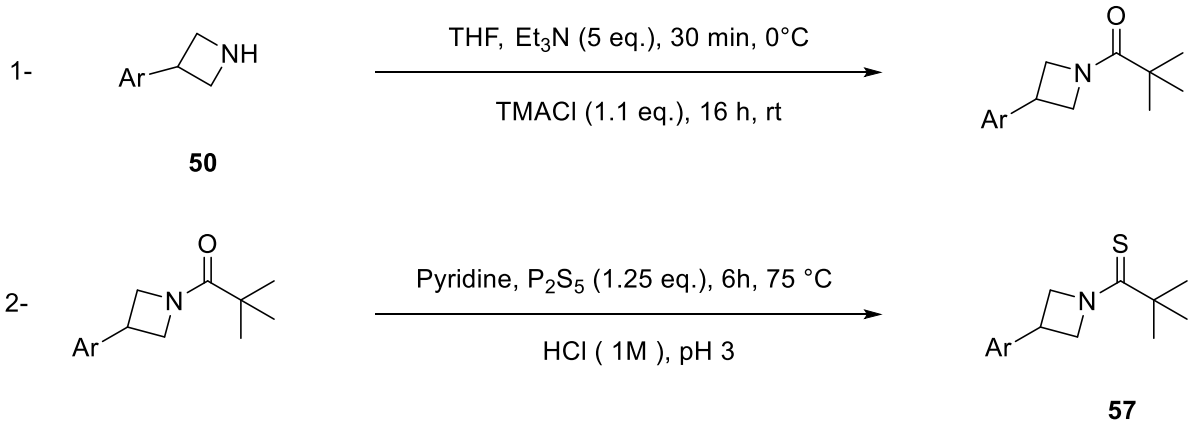
4.3 Preparation of O-(tert-butyl) 3-pheylazetidine-1-carbothioate



50 **59**

3-Arylated azetidine (1 eq.) was suspended in THF (6 ml) under nitrogen. Triethylamine (5 eq.) was added then the mixture was stirred for 10 mins at 0 ℃. S-methyl O-t-butyl dithiocarbonate (1.2 eq.) was added and the reaction was stirred for 16 hrs. After that the mixture was quenched with saturated solution of NH_4Cl and extracted with ether (3x) then the ether was removed in vacuum. Purification was done via column chromatography to obtain a desired product.

4.4 Preparation of N-thiopivaloyl 3-arylated azetidines

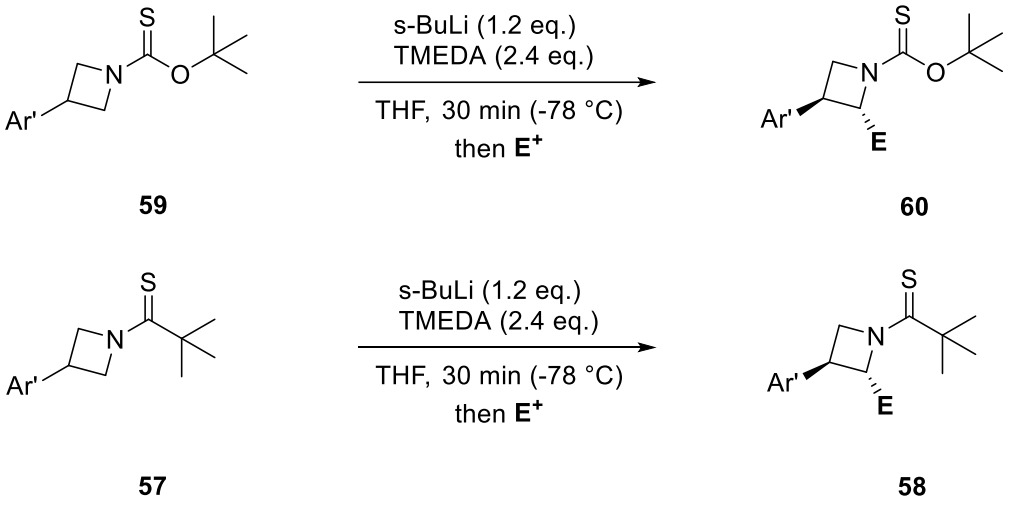


50 **57**

3-arylazetidine (1 eq.) was mixed with 10 ml THF (extra dry) in a flame dried round bottom flask. Triethylamine (5 eq.) was added dropwise via a syringe to the mixture at 0 ℃, and the reaction was stirred for 30 min. Afterwards trimethyl acetyl chloride (1.1 eq.) was added dropwise, and the resulting solution was allowed to attain rt and stirred for 16 h under N_2 atmosphere. The reaction was then quenched with 1 M HCl (5 ml) and aqueous layer was extracted with DCM (3 x 30 ml). The

combined organic layer was dried over $MgSO_4$ and concentrated in vacuo to give the crude N-pivaloyl azetidine. The crude residue was then mixed with pyridine (15 ml) and phosphorus pentasulfide P_2S_5 (1.25 eq.) was added to the reaction and stirred at 75 ℃ for 6 hours. The solution was cooled to rt and then 1 M HCl (aq) (15 mL) was added into it to reach pH 3. The resulting solution was stirred at rt for 2 h and then extracted with DCM (3 × 30 mL). The combined organic extracts were washed with 1 M HCl (aq) (10 mL), water (10 mL) and brine (10 mL), dried with $MgSO_4$ and evaporated under reduced pressure to give the crude product. Purification via flash column chromatography on silica with 9:1 Hexane-Et_2O as an eluent gave desired product in 77 % yield.

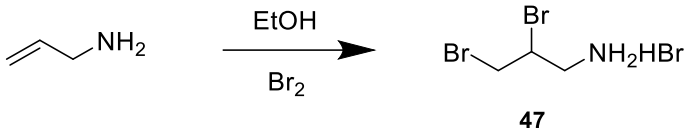
4.5 Lithiation-electrophilic substitution



N-protected-3-arylated azetidine (1 eq.) was dissolved in THF (extra dry) 2-3 ml and charged into a nitrogen flushed, flame dried flask, and cooled to -78 ℃. TMEDA (2.4 eq) and s-BuLi (1.2 eq) were added to the reaction mixture and left stirring for 30 min at -78 ℃. After that trimethylsilyl chloride (2 eq) in 0.5 ml THF was added dropwise and then stirred for 30 min at -78°C and for additional one hour at rt. The mixture was then quenched with sat. NH_4Cl solution (3 ml) and the extracted with EtOAc (3 x 15 mL). The combined organic layer was dried over $MgSO_4$ and removed in vacuo. The crude product was purified via column chromatography to afford final product.

5 Preparation and Characterization of compounds

2,3-Dibromopropan-1-amine hydrobromide



47

The compound was prepared using a modified literature procedure [179]. Bromine liquid (40 ml, 0.785 mol, 2.1eq.) was added dropwise to ethanol 100 ml in a reaction flask at 0 °C. After that, allylamine (28 mL, 0.374 mol, 1 eq.) was added slowly to the solution and allowed to warm to room temperature. After 4 h of stirring the precipitate was filtered and the crude product was washed with ice cold Et_2O (3 × 15 mL). The solid was recrystallized three times using methanol (30 mL) to obtain title compound (87.85 g, 0.295 mol, 79 % overall yield) as a colorless crystal.

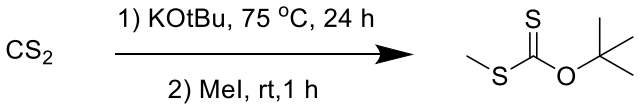
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.02 (dddd, *J* = 9.7, 8.2, 4.7, 3.3 Hz, 1H), 2.47 (dd, *J* = 11.0, 4.7 Hz, 1H), 2.34 (dd, *J* = 11.0, 8.4 Hz, 1H), 2.18 (dd, *J* = 14.0, 3.2 Hz, 1H), 1.85 – 1.75 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 49.64, 49.43, 49.21, 49.00, 48.79, 48.58, 48.36, 48.02, 45.56, 34.19.

HRMS (ESI) m/z: $[M\text{-}Br]^+$ calculated for $C_3H_8Br_2N^+$: 217.8998; found: 217.8996.

IR (Diamond-ATR, neat) $\tilde{\nu}max$: 2998,54, 2943,65, 2857,74, 2787,57, 2639,15, 2561,34, 2433,76, 1974,12, 1588,73, 1472,66, 1441,50, 1428,10, 1393,68, 1324,59, 1223,75, 1168,39, 1111,55, 1091,68, 1052,43, 1018,15, 961, 42, 882,03, 823,96.

Synthesis of S-Methyl O-t-Butyl Dithiocarbonate



67

Following the procedure described in the literature [180]. S-Methyl O-t-Butyl Dithiocarbonate was synthesized on a 110 mmol scale. KOtBu (11.89 g, 0.1 mol, 1eq.) was suspended in toluene 250 ml and heated to 75 °C for 24 hr then CS_2 (6.6 ml, 0.11 mol, 1.1eq.) was added slowly for 15 mins. The yellow solid was filtered off, washed extensively with hexane, and then dried under vacuo. After that

the solid was suspended in ether and iodomethane (9.9 ml, 0.16 mol, 1.5 eq.) was added dropwise. After stirring the reaction for 1 h the mixture was filtered, and the solvent was removed in vacuum. The product was obtained (11 g, 67 mmol) as a yellow oil with a yield of 67 %. The S-methyl o-t-butyl dithiocarbonate was then used for further reactions without further purification.

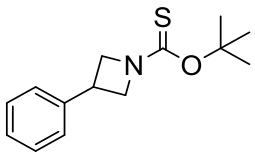
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 2.46 (s, 3H), 1.70 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 213.31, 110.48, 90.91, 77.35, 77.03, 76.71, 28.01, 24.13, 20.18, 19.19, 1.03.

HRMS (EI) m/z: $[M-H]^+$ calculated for $C_6H_{11}OS_2^+$: 163.0246; found: 163.0541.

IR (Diamond-ATR, neat) $\tilde{\nu}max$: 2925,95, 2855,38, 1740,65, 1458,17, 1369,79, 1220,28, 1166,17, 1100,25, 1045,43, 1023,44, 959,31.

O-(tert-butyl) 3-phenylazetidine-1-carbothioate (59a)



3-phenylazetidine (379.6 mg, 2.85 mmole, 1 eq.) was suspended in THF 6 ml under nitrogen. Triethylamine (1.97 ml, 14.25 mmole, 5 eq.) was added and the mixture was stirred for 10 mins at 0 °C. S-methyl O-t-butyl dithiocarbonate (561 mg, 3.42 mmole, 1.2 eq.) was added and the reaction was stirred for 16 hrs. After that the mixture was quenched with saturated solution of NH_4Cl and extracted with ether (3x) then the ether was removed in vacuum. Purification was done via column chromatography (99:1 – Hexane: Ether) to obtain a final product (249.3 mg, 1 mmole) as a yellow oil with 35 % yield.

R_f = 0.26

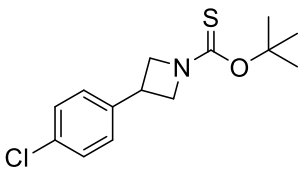
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.35 – 7.26 (m, 2H), 7.26 – 7.20 (m, 3H), 4.47 (ddd, *J* = 10.2, 8.8, 1.3 Hz, 1H), 4.36 (ddd, *J* = 10.2, 8.9, 1.3 Hz, 1H), 4.18 – 4.12 (m, 1H), 4.01 – 3.95 (m, 1H), 3.68 (tt, *J* = 8.8, 6.0 Hz, 1H), 1.62 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 185.47, 141.49, 128.82, 127.21, 126.81, 85.12, 77.37, 77.05, 76.74, 58.84, 58.08, 32.11, 28.44, 1.04.

HRMS (EI) m/z: $[M-C_4H_9]^+$ calculated for $C_{10}H_{10}NOS^+$: 193.0517; found: 193.0554.

IR (Diamond-ATR, neat) $\tilde{\nu}max$: 2966,70, 1699,00, 1457,64, 1435,56, 1394,51, 1361,89, 1286,90, 1257,45, 1228,62, 1199,60, 1148,34, 1085,54, 1013,56, 916,07, 756,38, 697,93.

O-(tert-butyl) 3-(4-chlorophenyl)azetidine-1-carbothioate (59b)



3-(4-chlorophenyl)azetidine (553.1 mg, 3.3 mmole, 1 eq.) was suspended in THF 6 ml under nitrogen. Triethylamine (2.28 ml, 16.5 mmole, 5 eq.) was added and the mixture was stirred for 10 mins at 0 ℃. S-methyl O-t-butyl dithiocarbonate (650.5 mg, 3.96 mmole, 1.2 eq.) was added and the reaction was stirred for 16 hrs. After that the mixture was quenched with saturated solution of NH_4Cl and extracted with ether (3x) then the ether was removed in vacuum. Purification was done via column chromatography (99: 1 – Hexane: Ether) to obtain a final product (292.3 mg, 1.03 mmole) as a yellow oil with 31% yield.

R_f = 0.23

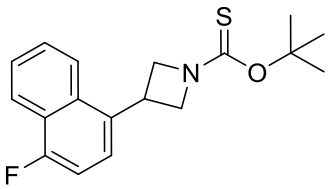
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.35 – 7.29 (m, 2H), 7.25 – 7.20 (m, 2H), 4.50 (ddd, *J* = 10.2, 8.8, 1.2 Hz, 1H), 4.40 (ddd, *J* = 10.1, 8.8, 1.2 Hz, 1H), 4.14 (dd, *J* = 10.5, 6.0 Hz, 1H), 3.97 (dd, *J* = 10.3, 6.0 Hz, 1H), 3.69 (tt, *J* = 8.8, 6.0 Hz, 1H), 1.66 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 185.57, 139.94, 132.99, 128.93, 128.17, 85.25, 77.30, 76.98, 76.66, 58.71, 57.93, 31.57, 28.37, 0.99.

HRMS (EI) m/z: $[M]^+$ calculated for $C_{14}H_{18}ClNOS$: 283.0798; found: 283.0796.

IR (Diamond-ATR, neat) $\tilde{\nu}max$: 2973,35, 2880,35, 1484,31, 1462,25, 1443,97, 1412,94, 1390,33, 1364,94, 1274,17, 1238,72, 1140,29, 1092,23, 1055,11, 1014,04, 949,54, 894,94, 819,37, 761,86, 734,76, 713,80.

O-(tert-butyl) 3-(4-fluoronaphthalen-1-yl)azetidine-1-carbothioate (59c)



3-(4-fluoronaphthalen-2-yl)azetidine (400 mg, 1.98 mmole, 1 eq.) was suspended in THF 7 ml under nitrogen. Triethylamine (1.4 ml, 9.9 mmole, 5 eq.) was added and the mixture was stirred for 10

mins at 0 ℃. S-methyl O-t-butyl dithiocarbonate (390 mg, 2.37 mmole, 1.2 eq.) was added and the reaction was stirred for 16 hrs. After that the mixture was quenched with saturated solution of NH_4Cl and extracted with ether (3x) then the ether was removed in vacuum. Purification was done via column chromatography (9: 1 – Hexane : Ethyl acetate) to obtain a final product (18 mg, 0.057 mmole) as a yellow oil with 29% yield.

R_f = 0.37

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.20 – 8.14 (m, 1H), 7.73 – 7.67 (m, 1H), 7.63 – 7.55 (m, 2H), 7.37 (ddd, *J* = 8.0, 5.2, 1.0 Hz, 1H), 7.14 (dd, *J* = 10.1, 8.0 Hz, 1H), 4.63 (dddd, *J* = 31.8, 9.8, 8.5, 0.9 Hz, 2H), 4.43 – 4.32 (m, 2H), 4.20 – 4.13 (m, 1H), 1.66 (s, 9H).

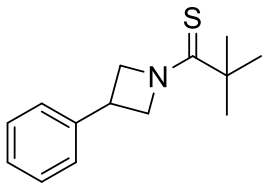
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 185.50, 159.41, 156.91, 132.51, 132.47, 132.05, 132.01, 127.42, 126.32, 126.30, 124.22, 124.06, 123.10, 123.07, 122.86, 122.78, 121.69, 121.63, 108.80, 108.60, 85.27, 77.36, 77.04, 76.72, 56.64, 56.28, 29.10, 28.43, 11.74, 1.05.

^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) = -123.93 – -124.06 (m).

HRMS (EI) m/z: $[M]^+$ calculated for $C_{18}H_{20}FNOS$: 317.1250; found: 317.1243.

IR (Diamond-ATR, neat) $\tilde{\nu}max$: 2964,21, 2925,75, 1603,66, 1513,06, 1486,17, 1460,58, 1446,85, 1390,85, 1365,03, 1277,72, 1262,33, 1241,47, 1140,51, 1069,52, 1041,01, 1008,79, 929,22, 884,62.

2,2-dimethyl-1-(3-phenylazetidin-1-yl)propane-1-thione (57a)



3-phenylazetidine (492.8 mg, 3.7 mmole, 1 eq.) was mixed with 10 ml THF (extra dry) in a flame dried round bottom flask. Triethylamine (2.56 ml, 18.5 mmole, 5 eq.) was added dropwise via a syringe to the mixture at 0 ℃, and the reaction was stirred for 30 min. Afterwards trimethylacetyl chloride (0.5 ml, 4.07 mmole, 1.1 eq.) was added dropwise, and the resulting solution was allowed to attain rt and stirred for 16 h under N_2 atmosphere. The reaction was then quenched with 1 M HCl (5 ml) and aqueous layer was extracted with DCM (3 x 30 ml). The combined organic layer was dried over $MgSO_4$ and concentrated in vacuo to give the crude N-pivaloyl azetidine. The crude residue was then mixed with pyridine (15 ml) and phosphorus pentasulfide P_2S_5 (1 g, 4.6 mmole, 1.25 eq.) was added to the reaction and stirred at 75 ℃ for 6 hours. The solution was cooled to rt and then 1 M HCl(aq) (15 mL) was added into it to reach pH 3. The resulting solution was stirred at rt for 2 h and

then extracted with DCM (3 × 30 mL). The combined organic extracts were washed with 1 M HCl(aq) (10 mL), water (10 mL) and brine (10 mL), dried with $MgSO_4$ and evaporated under reduced pressure to give the crude product. Purification via flash column chromatography on silica with (9: 1 – Hexane : Ether) as an eluent gave desired product (665 mg, 2.85 mmole) in 77 % yield as a brown oil.

$R_{f\,=}$ 0.31

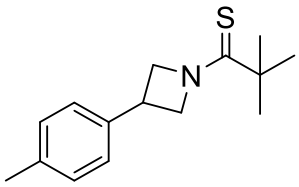
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.42 – 7.27 (m, 5H), 4.92 (ddd, *J* = 10.6, 8.9, 1.8 Hz, 1H), 4.68 (ddd, *J* = 12.4, 9.0, 1.8 Hz, 1H), 4.48 (ddd, *J* = 10.5, 6.1, 1.8 Hz, 1H), 4.37 (ddd, *J* = 12.4, 6.0, 1.8 Hz, 1H), 3.81 (tt, *J* = 9.0, 6.1 Hz, 1H), 1.40 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 210.17, 141.27, 129.00, 127.42, 126.68, 77.36, 77.04, 76.72, 64.31, 62.77, 43.26, 32.76, 29.74.

HRMS (EI) m/z: $[M]^+$ calculated for $C_{14}H_{19}NS$: 233.1238; found: 233.1232.

IR (Diamond-ATR, neat) $\tilde{\nu}max$: 2966,70, 1699,00, 1457,64, 1435,56, 1394,51, 1361,89, 1286,90, 1257,45, 1228,62, 1199,60, 1148,34, 1085,54, 1013,56, 916,07, 756,38, 697,93.

2,2-dimethyl-1-(3-(p-tolyl)azetidin-1-yl)propane-1-thione (57b)



3-(p-tolyl)azetidine (1.1689 g, 7.9 mmole, 1 eq.) was mixed with 10 ml toluene (extra dry) in a flame dried round bottom flask. Triethylamine (5.4 ml, 39.5 mmole, 5 eq.) was added dropwise via a syringe to the mixture at 0 ℃, and the reaction was stirred for 30 min. Afterwards trimethylacetyl chloride (1.0 ml, 8.69 mmole, 1.1 eq.) was added dropwise, and the resulting solution was allowed to attain rt and stirred for 16 h under N_2 atmosphere. The reaction was then quenched with 1 M HCl (5 ml) and aqueous layer was extracted with DCM (3 x 30 ml). The combined organic layer was dried over $MgSO_4$ and concentrated in vacuo to give the crude N-pivaloyl azetidine. The crude residue was then mixed with pyridine (15 ml) and phosphorus pentasulfide P_2S_5 (2.1 g, 9.8 mmole, 1.25 eq.) was added to the reaction and stirred at 75 ℃ for 6 hours. The solution was cooled to rt and then 1 M HCl(aq) (15 mL) was added into it to reach pH 3. The resulting solution was stirred at rt for 2 h and then extracted with DCM (3 × 30 mL). The combined organic extracts were washed with 1 M HCl(aq) (10 mL), water (10 mL) and brine (10 mL), dried with $MgSO_4$ and evaporated under

reduced pressure to give the crude product. Purification via flash column chromatography on silica with (9: 1 – Hexane : Ether) as an eluent gave desired product (445 mg, 1.8 mmole) in 39 % yield as a brown oil.

R_f = 0.34

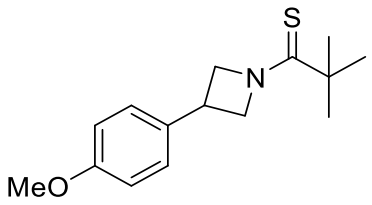
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.18 (s, 4H), 4.90 (ddd, *J* = 10.6, 8.9, 1.9 Hz, 1H), 4.65 (ddd, *J* = 12.4, 9.0, 1.9 Hz, 1H), 4.44 (dddd, *J* = 10.5, 6.1, 2.0, 0.6 Hz, 1H), 4.34 (dddd, *J* = 12.4, 6.1, 1.9, 0.6 Hz, 1H), 3.77 (tt, *J* = 8.9, 6.1 Hz, 1H), 2.35 (s, 3H), 1.39 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 209.03, 137.19, 136.10, 128.60, 125.53, 76.32, 76.00, 75.68, 63.41, 61.85, 42.21, 31.39, 28.70, 20.05, 0.01.

HRMS (EI) m/z: $[M]^+$ calculated for $C_{15}H_{21}NS$: 247.1395; found: 247.1388.

IR (Diamond-ATR, neat) $\tilde{\nu}max$: 2964,92, 2360,15, 1702,60, 1625,94, 1516,45, 1473,11, 1450,52, 1394,46, 1363,14, 1286,81, 1257,86, 1149,94, 1116,61, 1017,48, 938,36, 812,82, 717,85, 657,03.

1-(3-(4-methoxyphenyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione (57c)



3-(4-methoxyphenyl)azetidine (1.79 g, 10.99 mmole, 1 eq.) was mixed with 10 ml THF (extra dry) in a flame dried round bottom flask. Triethylamine (7.6 ml, 54.95 mmole, 5 eq.) was added dropwise via a syringe to the mixture at 0 ℃, and the reaction was stirred for 30 min. Afterwards trimethylacetyl chloride (1.48 ml, 12.089 mmole, 1.1 eq.) was added dropwise, and the resulting solution was allowed to attain rt and stirred for 16 h under N_2 atmosphere. The reaction was then quenched with 1 M HCl (5 ml) and aqueous layer was extracted with DCM (3 x 30 ml). The combined organic layer was dried over $MgSO_4$ and concentrated in vacuo to give the crude N-pivaloyl azetidine. The crude residue was then mixed with pyridine (15 ml) and phosphorus pentasulfide P_2S_5 (3 g, 13.7 mmole, 1.25 eq.) was added to the reaction and stirred at 75 ℃ for 6 hours. The solution was cooled to rt and then 1 M HCl(aq) (15 mL) was added into it to reach pH 3. The resulting solution was stirred at rt for 2 h and then extracted with DCM (3 × 30 mL). The combined organic extracts were washed with 1 M HCl(aq) (10 mL), water (10 mL) and brine (10 mL), dried with $MgSO_4$ and evaporated under reduced pressure to give the crude product.

Purification via flash column chromatography on silica with (8: 2 – Hexane : Ether) as an eluent gave desired product (2.08 g, 7.896 mmole) in 72 % yield as a brown oil.

R_f = 0.21

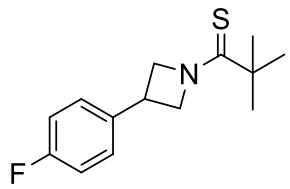
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.24 – 7.18 (m, 2H), 6.93 – 6.88 (m, 2H), 4.89 (ddd, *J* = 10.6, 8.9, 1.8 Hz, 1H), 4.65 (ddd, *J* = 12.4, 9.0, 1.9 Hz, 1H), 4.42 (ddd, *J* = 10.6, 6.1, 1.8 Hz, 1H), 4.32 (ddd, *J* = 12.4, 6.1, 1.8 Hz, 1H), 3.81 (s, 3H), 3.78 – 3.71 (m, 1H), 1.39 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 210.08, 158.86, 133.28, 127.76, 114.34, 77.36, 77.04, 76.72, 64.60, 63.08, 55.37, 43.25, 32.13, 29.74, 1.05.

HRMS (EI) m/z: $[M]^+$ calculated for $C_{15}H_{21}NOS$: 263.1344; found: 263.1346.

IR (Diamond-ATR, neat) $\tilde{\nu}max$: 2969,88, 2833,47, 1878,26, 1699,04, 1609,20, 1582,67, 1513,97, 1474,67, 1451,01, 1418,43, 1393,51, 1362,78, 1300,10, 1281,99, 1244,58, 1177,46, 1144,02, 1113,90, 1023,39, 951,85, 912,37, 869,17, 858,71, 824,28, 802,59, 784,62, 723,17, 667,33, 655,66.

1-(3-(4-fluorophenyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione (57d)



3-(4-fluorophenyl)azetidine (340.3 mg, 2.2 mmole, 1 eq.) was mixed with 10 ml THF (extra dry) in a flame dried round bottom flask. Triethylamine (1.5 ml, 11 mmole, 5 eq.) was added dropwise via a syringe to the mixture at 0 ℃, and the reaction was stirred for 30 min. Afterwards trimethyl acetyl chloride (0.29 ml, 2.42 mmole, 1.1 eq.) was added dropwise, and the resulting solution was allowed to attain rt and stirred for 16 h under N_2 atmosphere. The reaction was then quenched with 1 M HCl (5 ml) and aqueous layer was extracted with DCM (3 x 30 ml). The combined organic layer was dried over $MgSO_4$ and concentrated in vacuo to give the crude N-pivaloyl azetidine. The crude residue was then mixed with pyridine (15 ml) and phosphorus pentasulfide P_2S_5 (0.6 g, 2.75 mmole, 1.25 eq.) was added to the reaction and stirred at 75 ℃ for 6 hours. The solution was cooled to rt and then 1 M HCl(aq) (15 mL) was added into it to reach pH 3. The resulting solution was stirred at rt for 2 h and then extracted with DCM (3 × 30 mL). The combined organic extracts were washed with 1 M HCl(aq) (10 mL), water (10 mL) and brine (10 mL), dried with $MgSO_4$ and evaporated under reduced pressure to give the crude product. Purification via flash column chromatography on silica

with (8: 2 – Hexane : Ether) as an eluent gave desired product (175.9 mg, 0.7 mmole) in 32 % yield as a clear oil.

R_f = 0.25

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.29 – 7.22 (m, 2H), 7.10 – 7.01 (m, 2H), 4.91 (ddd, *J* = 10.6, 8.9, 1.8 Hz, 1H), 4.66 (ddd, *J* = 12.4, 9.0, 1.8 Hz, 1H), 4.42 (ddd, *J* = 10.5, 6.0, 1.8 Hz, 1H), 4.31 (ddd, *J* = 12.4, 6.1, 1.8 Hz, 1H), 3.79 (tt, *J* = 8.9, 6.1 Hz, 1H), 1.39 (s, 9H).

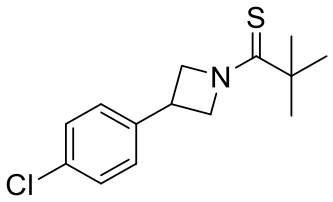
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 209.32, 162.19, 159.75, 135.99, 135.96, 127.27, 127.19, 114.95, 114.74, 76.33, 76.01, 75.69, 63.34, 61.82, 42.25, 31.14, 28.70, 0.01.

^{19}F NMR (377 MHz, $CDCl_3$): δ -123.94 – -124.07 (m).

HRMS (EI) m/z: $[M]^+$ calculated for $C_{14}H_{18}FNS$: 251.1144; found: 251.1136.

IR (Diamond-ATR, neat) $\tilde{\nu}max$: 2964,07, 2916,23, 2362,36, 1606,14, 1511,67, 1471,25, 1451,07, 1418,40, 1393,93, 1362,61, 1257,49, 1225,10, 1147,65, 1047,58, 1014,10, 830,69, 815,78, 790,86, 741,80, 720,23, 701,08 690,78, 683,97, 678,39, 670,17, 667,40, 653,32.

1-(3-(4-chlorophenyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione (57e)



3-(4-chlorophenyl)azetidine (934 mg, 5.5 mmole, 1 eq.) was mixed with 10 ml THF (extra dry) in a flame dried round bottom flask. Triethylamine (3.8 ml, 27.5 mmole, 5 eq.) was added dropwise via syringe to the mixture at 0 ℃, and the reaction was stirred for 30 min. Afterwards trimethyl acetyl chloride (0.74 ml, 6.05 mmole, 1.1 eq.) was added dropwise, and the resulting solution was allowed to attain rt and stirred for 16 h under N_2 atmosphere. The reaction was then quenched with 1 M HCl (5 ml) and aqueous layer was extracted with DCM (3 x 30 ml). The combined organic layer was dried over $MgSO_4$ and concentrated in vacuo to give the crude N-pivaloyl azetidine. The crude residue was then mixed with pyridine (15 ml) and phosphorus pentasulfide P_2S_5 (1.5 g, 6.8 mmole, 1.25 eq.) was added to the reaction and stirred at 75 ℃ for 6 hours. The solution was cooled to rt and then 1 M HCl(aq) (15 mL) was added into it to reach pH 3. The resulting solution was stirred at rt for 2 h and then extracted with DCM (3 × 30 mL). The combined organic extracts were washed with 1 M HCl(aq) (10 mL), water (10 mL) and brine (10 mL), dried with $MgSO_4$ and evaporated under

reduced pressure to give the crude product. Purification via flash column chromatography on silica with (9: 1 – Hexane : Ethyl acetate) as an eluent gave desired product (321.3 mg, 1.2 mmole) as a yellow oil in 22 % yield.

R_f = 0.33

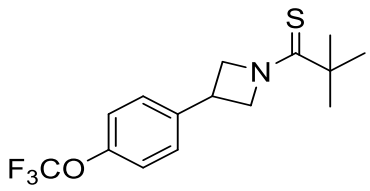
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.39 – 7.32 (m, 2H), 7.25 – 7.20 (m, 2H), 4.99 – 4.87 (m, 1H), 4.66 (ddd, *J* = 12.4, 9.0, 1.8 Hz, 1H), 4.42 (ddd, *J* = 10.6, 6.0, 1.8 Hz, 1H), 4.36 – 4.28 (m, 1H), 3.78 (tt, *J* = 8.9, 6.0 Hz, 1H), 1.39 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 210.37, 139.71, 133.22, 129.13, 128.07, 110.00, 77.24, 77.03, 76.82, 64.17, 62.60, 43.27, 38.42, 32.25, 29.71, 27.02.

HRMS (EI) m/z: $[M]^+$ calculated for $C_{14}H_{18}ClNS$: 267.0848; found: 267.0841.

IR (Diamond-ATR, neat) $\tilde{\nu}max$: 2965,78, 2934,49, 1699,98, 1466,68, 1454,77, 1436,05, 1411,17, 1396,36, 1369,25, 1360,22, 1338,35, 1288,40, 1255,21, 1230,06, 1199,61, 1150,21, 1107,72, 1092,90, 1043,06, 1011,41, 934,53, 916,02, 849,88, 827,37, 818,42, 790,33, 756,57, 714,94, 661,39.

2,2-dimethyl-1-(3-(4-(trifluoromethoxy)phenyl)azetidin-1-yl)propane-1-thione (57f)



3-(4-(trifluoromethoxy)phenyl)azetidine (750 mg, 3.4 mmole, 1 eq.) was mixed with 10 ml toluene (extra dry) in a flame dried round bottom flask. Triethylamine (2.3 ml, 17.2 mmole, 5 eq.) was added dropwise via a syringe to the mixture at 0 ℃, and the reaction was stirred for 30 min. Afterwards trimethyl acetyl chloride (0.45 ml, 3.7 mmole, 1.1 eq.) was added dropwise, and the resulting solution was allowed to attain rt and stirred for 16 h under N_2 atmosphere. The reaction was then quenched with 1 M HCl (5 ml) and aqueous layer was extracted with DCM (3 x 30 ml). The combined organic layer was dried over $MgSO_4$ and concentrated in vacuo to give the crude N-pivaloyl azetidine. The crude residue was then mixed with pyridine (15 ml) and phosphorus pentasulfide P_2S_5 (0.9 g, 4.25 mmole, 1.25 eq.) was added to the reaction and stirred at 75 ℃ for 6 hours. The solution was cooled to rt and then 1 M HCl(aq) (15 mL) was added into it to reach pH 3. The resulting solution was stirred at rt for 2 h and then extracted with DCM (3 × 30 mL). The combined organic extracts were washed with 1 M HCl(aq) (10 mL), water (10 mL) and brine (10 mL), dried with $MgSO_4$ and evaporated under reduced pressure to give the crude product.

Purification via flash column chromatography on silica with (9 : 1 – Hexane : Ethyl acetate)) as an eluent gave desired product (25.4 mg, 0.08 mmole) as a brown oil in 37 % yield.

R_f = 0.29

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.35 – 7.29 (m, 2H), 7.25 – 7.20 (m, 2H), 4.93 (ddd, *J* = 10.6, 8.9, 1.8 Hz, 1H), 4.68 (ddd, *J* = 12.4, 9.0, 1.8 Hz, 1H), 4.44 (ddd, *J* = 10.6, 6.0, 1.8 Hz, 1H), 4.34 (ddd, *J* = 12.5, 6.0, 1.8 Hz, 1H), 3.82 (tt, *J* = 8.9, 6.0 Hz, 1H), 1.39 (s, 9H).

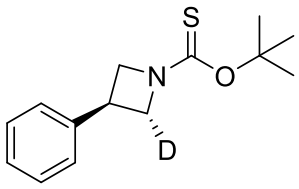
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 210.51, 148.42, 148.40, 140.00, 128.13, 121.72, 121.57, 119.16, 77.35, 77.04, 76.72, 64.17, 62.59, 43.31, 32.24, 29.74.

^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) = -57.93.

HRMS (EI) m/z: $[M]^+$ calculated for $C_{15}H_{18}F_3NOS$: 317.1061; found: 317.1055.

IR (Diamond-ATR, neat) $\tilde{\nu}max$: 2969,57, 2928,71, 1619,29, 1511,46, 1479,76, 1448,86, 1421,15, 1394,84, 1362,58, 1257,80, 1217,26, 1195,84, 1149,35, 1105,93, 1056,17, 1014,40, 918,54, 878,43, 842,39, 805,19, 667,59.

O-(tert-butyl) (2R,3S)-3-phenylazetidine-1-carbothioate-2-d (60a)



O-(tert-butyl) 3-phenylazetidine-1-carbothioate (101.7 mg, 0.40 mmol, 1 eq.) was dissolved in THF (extra dry) 2-3 ml and charged into a nitrogen flushed, flame dried flask and cooled to -78 ℃. TMEDA (0.14 mL, 0.96 mmol, 2.4 eq) and s-BuLi (0.34 mL, 0.48 mmol, 1.31 M, 1.2 eq) were added to the reaction mixture and left stirring for 30 min at -78 ℃. After that deuterium oxide (0.01 ml, 0.72 mmole, 2 eq) in 0.5 ml THF was added dropwise and then stirred for 30 min at -78°C and for additional one hour at rt. The mixture was then quenched with sat. NH_4Cl solution (3 ml) and the extracted with EtOAc (3 x 15 mL). The combined organic layer was dried over $MgSO_4$ and removed in vacuo. The crude product was purified via column chromatography (99 : 1 – Hexane : Ether) to afford final product (97 mg, 0.389 mmol, 97 %) as a clear oil.

R_f = 0.26 and **dr:** 20:1

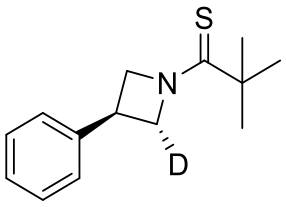
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.34 – 7.20 (m, 5H), 4.41 (dt, *J* = 41.3, 9.5 Hz, 1H), 4.15 (dd, *J* = 10.5, 6.1 Hz, 1H), 3.98 (dd, *J* = 10.2, 6.2 Hz, 1H), 3.72 – 3.64 (m, 1H), 1.62 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 185.50, 185.47, 141.49, 128.82, 127.20, 126.81, 85.12, 77.35, 77.04, 76.72, 58.84, 58.53, 58.30, 58.08, 57.78, 32.11, 31.99, 28.44, 1.03.

HRMS (EI) m/z: $[M\text{-}C_5H_9S]^+$ calculated for $C_9H_9DN^+$: 133.0876; found: 133.0867.

IR (Diamond-ATR, neat) $\tilde{\nu}max$: 2967,68, 2927,70, 1725,96, 1479,51, 1462,55, 1442,89, 1390,37, 1364,86, 1272,33, 1139,57, 1083,71, 1044,26, 1000,22, 949,15, 926,72, 897,66, 823,68, 753,98, 697,14.

2,2-dimethyl-1-((2R,3S)-3-phenylazetidin-1-yl-2-d)propane-1-thione (58a)



2,2-dimethyl-1-(3-phenylazetidin-1-yl)propane-1-thione (84.2 mg, 0.36 mmol, 1 eq.) was dissolved in THF (extra dry) 2-3 ml and charged into a nitrogen flushed, flame dried flask and cooled to -78 °C. TMEDA (0.13 mL, 0.864 mmol, 2.4 eq) and s-BuLi (0.33 mL, 0.432 mmol, 1.31 M, 1.2 eq) were added to the reaction mixture and left stirring for 30 min at -78 °C. After that deuterium oxide (0.01 ml, 0.72 mmole, 2 eq) in 0.5 ml THF was added dropwise and then stirred for 30 min at -78°C and for additional one hour at rt. The mixture was then quenched with sat. NH_4Cl solution (3 ml) and the extracted with EtOAc (3 x 15 mL). The combined organic layer was dried over $MgSO_4$ and removed in vacuo. The crude product was purified via column chromatography (9: 1 – Hexane : Ether) to afford final product (68.4 mg, 0.292 mmol, 81 %) as a clear oil.

R_f = 0.26 and **dr:** 6:1

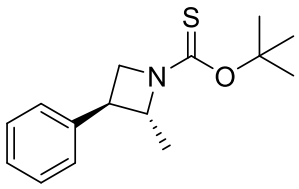
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.42 – 7.37 (m, 2H), 7.34 – 7.28 (m, 3H), 5.22 (dd, *J* = 5.1, 1.7 Hz, 1H), 5.00 (ddd, *J* = 10.5, 8.9, 1.7 Hz, 1H), 4.55 (dd, *J* = 10.2, 5.4 Hz, 1H), 4.04 (dt, *J* = 9.8, 5.2 Hz, 1H), 1.42 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 185.50, 185.47, 141.49, 128.82, 127.20, 126.81, 85.12, 77.35, 77.04, 76.72, 58.84, 58.08, 32.11, 31.99, 28.44, 1.03.

HRMS (EI) m/z: $[M]^+$ calculated for $C_{14}H_{18}DNS$: 234.1301; found: 234. 1296.

IR (Diamond-ATR, neat) $\tilde{\nu}max$: 2967,68, 2927,70, 1725,96, 1479,51, 1462,55, 1442,89, 1390,37, 1364,86, 1272,33, 1139,57, 1083,71, 1044,26, 1000,22, 949,15, 926,72, 897,66, 823,68, 753,98, 697,14.

O-(tert-butyl) (2R,3S)-2-methyl-3-phenylazetidine-1-carbothioate (60b)



O-(tert-butyl) 3-phenylazetidine-1-carbothioate (69.5 mg, 0.275 mmol, 1 eq.) was dissolved in THF (extra dry) 2-3 ml and charged into a nitrogen flushed, flame dried flask, and cooled to -78 ℃. TMEDA (0.09 mL, 0.66 mmol, 2.4 eq) and s-BuLi (0.24 mL, 0.33 mmol, 1.31 M, 1.2 eq) were added to the reaction mixture and left stirring for 30 min at -78 ℃. After that methyl iodide (0.05 ml, 0.825 mmole, 2 eq) in 0.5 ml THF was added dropwise and then stirred for 30 min at -78°C and for additional one hour at rt. The mixture was then quenched with sat. NH_4Cl solution (3 ml) and the extracted with EtOAc (3 x 15 mL). The combined organic layer was dried over $MgSO_4$ and removed in vacuo. The crude product was purified via column chromatography (98: 2 – Hexane: Ether) to afford final product (49 mg, 0.1860 mmol, 68%) as a clear oil.

R_f = 0.28 and **dr:** 3:1

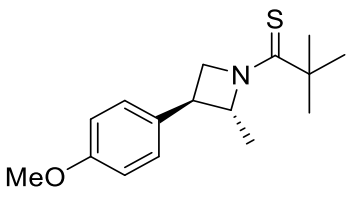
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.38 – 7.32 (m, 2H), 7.29 – 7.26 (m, 2H), 7.25 (d, *J* = 5.0 Hz, 1H), 4.46 – 4.36 (m, 1H), 4.30 (p, *J* = 6.2 Hz, 1H), 4.11 (dd, *J* = 10.6, 6.5 Hz, 1H), 3.24 (dt, *J* = 8.9, 6.1 Hz, 1H), 1.67 (s, 9H), 1.54 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 186.03, 140.81, 128.79, 127.21, 127.17, 126.91, 126.82, 85.13, 77.35, 77.04, 76.72, 68.62, 68.00, 56.40, 55.82, 53.46, 41.65, 41.19, 28.55, 28.52, 20.35, 19.80.

HRMS (EI) m/z: $[M]^+$ calculated for $C_{15}H_{21}NOS$: 263.1344; found: 263.1344.

IR (Diamond-ATR, neat) $\tilde{\nu}max$: 2957,96, 2925,98, 1676,88, 1475,06, 1459,37, 1442,59, 1389,71, 1268,85, 1248,12, 1232,43, 1138,93, 1080,24, 996,80, 942,54, 932,94, 909,77, 838,02, 821,22, 781,78, 756,13 698,23.

1-((2R,3S)-3-(4-methoxyphenyl)-2-methylazetidin-1-yl)-2,2-dimethylpropane-1-thione (58d)



1-(3-(4-methoxyphenyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione (200 mg, 0.75 mmol, 1 eq.) was dissolved in THF (extra dry) 2-3 ml and charged into a nitrogen flushed, flame dried flask and cooled to -78 ℃. TMEDA (0.26 mL, 1.8 mmol, 2.4 eq) and s-BuLi (0.68 mL, 0.9 mmol, 1.31 M, 1.2 eq) were added to the reaction mixture and left stirring for 30 min at -78 ℃. After that methyl iodide (0.09 ml, 1.5 mmole, 2 eq) in 0.5 ml THF was added dropwise and then stirred for 30 min at -78°C and for additional one hour at rt. The mixture was then quenched with sat. NH_4Cl solution (3 ml) and the extracted with EtOAc (3 x 15 mL). The combined organic layer was dried over $MgSO_4$ and removed in vacuo. The crude product was purified via column chromatography (9.5: 0.5 – Hexane : Ether) to afford final product (75 mg, 0.27 mmol, 36 %) as a yellow oil.

R_f = 0.31 and **dr:** 8:1

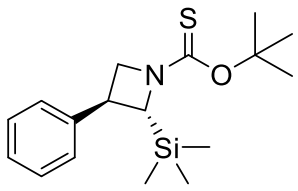
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.19 – 7.15 (m, 2H), 6.91 – 6.87 (m, 2H), 4.94 (ddd, *J* = 10.5, 8.8, 1.7 Hz, 1H), 4.83 (tt, *J* = 6.3, 5.4 Hz, 1H), 4.33 (dd, *J* = 10.5, 5.3 Hz, 1H), 3.80 (s, 3H), 3.23 (dt, *J* = 9.4, 5.0 Hz, 1H), 1.70 (d, *J* = 6.3 Hz, 3H), 1.38 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 210.76, 158.84, 133.48, 127.67, 114.35, 77.34, 77.03, 76.71, 72.47, 63.24, 55.36, 43.45, 41.27, 29.65, 18.52, 1.03.

HRMS (EI) m/z: $[M + H]^+$ calculated for $C_{16}H_{24}NOS^+$: 278.15; found: 278.1485.

IR (Diamond-ATR, neat) $\tilde{\nu}max$: 2959,69, 2924,86, 1725,56, 1612,16, 1513,82, 1431,17, 1418,69, 1363,21, 1305,68, 1289,91, 1246,11, 1178,21, 1147,48, 1115,19, 1032,86, 1011,86, 984,09, 884,71, 829,42, 802,51.

O-(tert-butyl) (2R,3S)-3-phenyl-2-(trimethylsilyl)azetidine-1-carbothioate (60c)



O-(tert-butyl) 3-phenylazetidine-1-carbothioate (69.5 mg, 0.275 mmol, 1 eq.) was dissolved in THF (extra dry) 2-3 ml and charged into a nitrogen flushed, flame dried flask, and cooled to -78 ℃. TMEDA (0.09 mL, 0.66 mmol, 2.4 eq) and s-BuLi (0.24 mL, 0.33 mmol, 1.31 M, 1.2 eq) were added to the reaction mixture and left stirring for 30 min at -78 ℃. After that trimethylsilyl chloride (0.1 ml, 0.825 mmole, 2 eq) in 0.5 ml THF was added dropwise and then stirred for 30 min at -78°C and for additional one hour at rt. The mixture was then quenched with sat. NH_4Cl solution (3 ml) and the extracted with EtOAc (3 x 15 mL). The combined organic layer was dried over $MgSO_4$ and

removed in vacuo. The crude product was purified via column chromatography (9.8: 0.2 – Hexane : Ethyl acetate) to afford final product (56 mg, 0.174 mmol, 63 %) as a clear oil.

R_f = 0.17 and **dr:** 81:1

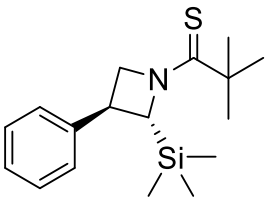
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.35 – 7.27 (m, 3H), 7.25 – 7.20 (m, 2H), 4.46 – 4.35 (m, 1H), 4.32 – 4.23 (m, 1H), 4.06 – 3.97 (m, 1H), 3.39 (dt, *J* = 8.4, 5.8 Hz, 1H), 1.67 (s, 9H), 0.15 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 186.30, 186.27, 146.70, 145.05, 144.89, 130.87, 130.78, 130.14, 129.06, 129.04, 128.85, 128.65, 127.73, 126.94, 87.58, 87.39, 86.95, 86.21, 79.36, 79.04, 78.72, 68.84, 68.58, 68.32, 67.70, 62.01, 61.49, 60.91, 60.56, 37.04, 36.93, 32.67, 31.69, 30.75, 30.52, 30.40, 0.00, -0.69, -0.95, -1.21, -3.01.

HRMS (EI) m/z: $[M\text{-}C_4H_9]^+$ calculated for $C_{13}H_{18}NOSSi^+$: 264.0878; found: 264.0862.

IR (Diamond-ATR, neat) $\tilde{\nu}max$: 2957,96, 2925,98, 1475,06, 1459,37, 1442,59, 1389,71, 1364,07, 1268,85, 1248,12, 1232,43, 1138,93, 1080,24, 1021,39, 996,80, 942,54, 932,94, 909,77, 838,02, 821,22, 781,78, 756,13, 743,91, 698,23.

2,2-dimethyl-1-((2R,3S)-3-phenyl-2-(trimethylsilyl)azetidin-1-yl)propane-1-thione (58b)

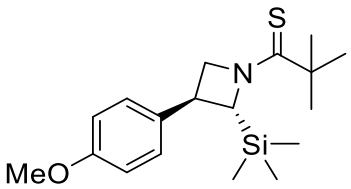


2,2-dimethyl-1-(3-phenylazetidin-1-yl)propane-1-thione (100 mg, 0.42 mmol, 1 eq.) was dissolved in THF (extra dry) 2-3 ml and charged into a nitrogen flushed, flame dried flask and cooled to -78 ℃. TMEDA (0.16 mL, 1 mmol, 2.4 eq) and s-BuLi (0.38 mL, 0.5 mmol, 1.31 M, 1.2 eq) were added to the reaction mixture and left stirring for 30 min at -78 ℃. After that trimethylsilyl chloride (0.1 ml, 0.84 mmole, 2 eq) in 0.5 ml THF was added dropwise and then stirred for 30 min at -78°C and for additional one hour at rt. The mixture was then quenched with sat. NH_4Cl solution (3 ml) and the extracted with EtOAc (3 x 15 mL). The combined organic layer was dried over $MgSO_4$ and removed in vacuo. The crude product was purified via column chromatography (9.5: 0.5 – Hexane: Ether) to afford final product (53 mg, 0.174 mmol, 41%) as a clear oil.

R_f = 0.37 and **dr:** 17:1

^{1}H NMR (599 MHz,$CDCl_3$): δ (ppm) = 7.35 – 7.30 (m, 2H), 7.26 – 7.21 (m, 3H), 4.82 (ddd, *J* = 10.9, 8.7, 2.2 Hz, 1H), 4.60 (dd, *J* = 6.4, 2.1 Hz, 1H), 4.43 (dd, *J* = 10.8, 5.1 Hz, 1H), 3.49 (ddd, *J* = 8.7, 6.3, 5.2 Hz, 1H), 1.36 (s, 9H), 0.19 (s, 9H).
^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 209.34, 206.77, 143.06, 140.68, 129.33, 129.21, 129.18, 129.00, 128.40, 128.06, 127.98, 127.34, 127.24, 127.05, 126.66, 126.44, 126.39, 125.53, 110.00, 84.25, 82.51, 77.25, 77.03, 76.82, 71.02, 70.84, 70.67, 64.32, 63.17, 51.63, 42.96, 42.82, 42.73, 41.14, 38.95, 35.98, 35.54, 31.23, 31.05, 30.31, 30.15, 29.82, 29.64, 29.44, 27.46, 27.37, 3.98, 1.04, -1.07, -1.24, -1.42, -1.88.
HRMS (EI) m/z: $[M]^+$ calculated for $C_{17}H_{27}NSSi$: 305.1633; found: 305.1628.
IR (Diamond-ATR, neat) $\tilde{\nu}max$: 2959,66, 1458,59, 1437,04, 1362,51, 1245,76, 1144,26, 1077,69, 1012,21, 925,68, 873,16, 838,88, 755,04, 698,10.

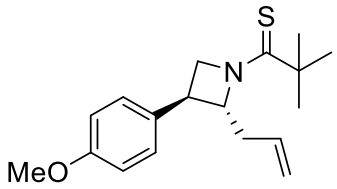
1-((2R,3S)-3-(4-methoxyphenyl)-2-(trimethylsilyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione (58c)



1-(3-(4-methoxyphenyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione (200 mg, 0.75 mmol, 1 eq) was dissolved in THF (extra dry) 2-3 ml and charged into a nitrogen flushed, flame dried flask and cooled to -78 ℃. TMEDA (0.26 mL, 1.8 mmol, 2.4 eq) and s-BuLi (0.68 mL, 0.9 mmol, 1.31 M, 1.2 eq) were added to the reaction mixture and left stirring for 30 min at -78 ℃. After that trimethylsilyl chloride (0.19 ml, 1.5 mmole, 2 eq) in 0.5 ml THF was added dropwise and then stirred for 30 min at -78°C and for additional one hour at rt. The mixture was then quenched with sat. NH_4Cl solution (3 ml) and the extracted with EtOAc (3 x 15 mL). The combined organic layer was dried over $MgSO_4$ and removed in vacuo. The crude product was purified via column chromatography (9.5: 0.5 – Hexane : Ethyl acetate) to afford final product (94 mg, 0.28 mmol, 37 %) as a pink oil.
R_f = 0.19 and **dr:** 4:1
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.22 – 7.17 (m, 2H), 6.92 – 6.85 (m, 2H), 4.82 (ddd, *J* = 10.8, 8.7, 2.2 Hz, 1H), 4.58 (dd, *J* = 6.4, 2.1 Hz, 1H), 4.39 (ddd, *J* = 10.1, 6.7, 4.8 Hz, 1H), 3.80 (s, 3H), 3.46 (dt, *J* = 8.6, 5.7 Hz, 1H), 1.38 (s, 9H), 0.21 (s, 9H).

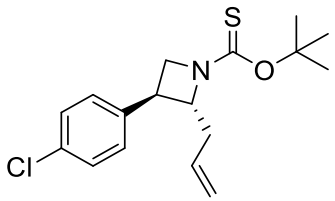
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 208.04, 160.02, 136.33, 129.44, 128.99, 115.78, 115.61, 78.61, 78.29, 77.97, 72.33, 65.88, 56.62, 44.09, 36.16, 31.43, 31.11, 30.93, 2.31, 0.01.
HRMS (EI) m/z: $[M]^+$ calculated for $C_{18}H_{29}NOSSi$: 335.1739; found: 335.1731.
IR (Diamond-ATR, neat) $\tilde{\nu}max$: 2955,81, 2920,09, 2851,09, 1612,33, 1514,03, 1463,69, 1450,20, 1394,05, 1363,44, 1290,56, 1246,31, 1177,90, 1144,28, 1034,30, 873,73, 829,58, 770,17, 688,34, 668,02.

1-((2R,3S)-2-allyl-3-(4-methoxyphenyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione (58e)



1-(3-(4-methoxyphenyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione (60 mg, 0.22 mmol, 1 eq.) was dissolved in THF (extra dry) 2-3 ml and charged into a nitrogen flushed, flame dried flask and cooled to -78 ℃. TMEDA (0.08 mL, 0.54 mmol, 2.4 eq) and s-BuLi (0.19 mL, 0.26 mmol, 1.31 M, 1.2 eq) were added to the reaction mixture and left stirring for 30 min at -78 ℃. After that Allyl bromide (0.05 ml, 0.66 mmole, 2 eq) in 0.5 ml THF was added dropwise and then stirred for 30 min at -78°C and for additional one hour at rt. The mixture was then quenched with sat. NH_4Cl solution (3 ml) and the extracted with EtOAc (3 x 15 mL). The combined organic layer was dried over $MgSO_4$ and removed in vacuo. The crude product was purified via column chromatography (9: 1 – Hexane : Ether) to afford final product (26 mg, 0.0856 mmol, 39 %) as a yellow oil.
R_f = 0.22 and **dr:** 13:1
^{1}H NMR (599 MHz, $CDCl_3$): δ (ppm) = 7.17 – 7.15 (m, 2H), 6.89 – 6.87 (m, 2H), 5.79 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1H), 5.21 – 5.15 (m, 2H), 4.86 – 4.78 (m, 2H), 4.32 (dd, *J* = 10.4, 5.0 Hz, 1H), 3.80 (s, 3H), 3.37 (dt, *J* = 9.3, 4.9 Hz, 1H), 3.00 – 2.89 (m, 2H), 1.37 (s, 9H).
^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 210.81, 158.74, 133.63, 132.25, 128.03, 127.79, 118.95, 114.31, 110.00, 77.23, 77.02, 76.81, 74.88, 63.47, 55.33, 43.48, 37.94, 34.66, 29.77, 29.73, 29.65, 29.60, 26.59.
HRMS (EI) m/z: $[M]^+$ calculated for $C_{18}H_{25}NOS$: 303.1657; found: 303.1653.
IR (Diamond-ATR, neat) $\tilde{\nu}max$: 2959,69, 2925,88, 1612,53, 1513,83, 1432,96, 1362,87, 1290,98, 1246,20, 1178,13, 1145,87, 1034,03, 1003,13, 918,62, 826,50, 807,87.

O-(tert-butyl) (2R,3S)-2-allyl-3-(4-chlorophenyl)azetidine-1-carbothioate (60e)



O-(tert-butyl) 3-(4-chlorophenyl)azetidine-1-carbothioate (61.8 mg, 0.21 mmol, 1 eq.) was dissolved in THF (extra dry) 2-3 ml and charged into a nitrogen flushed, flame dried flask and cooled to -78 °C. TMEDA (0.075 mL, 0.5 mmol, 2.4 eq) and s-BuLi (0.17 mL, 0.24 mmol, 1.31 M, 1.2 eq) were added to the reaction mixture and left stirring for 30 min at -78 °C. After that allyl bromide (0.036 ml, 0.42 mmole, 2 eq) in 0.5 ml THF was added dropwise and then stirred for 30 min at -78°C and for additional one hour at rt. The mixture was then quenched with sat. NH_4Cl solution (3 ml) and the extracted with EtOAc (3 x 15 mL). The combined organic layer was dried over $MgSO_4$ and removed in vacuo. The crude product was purified via column chromatography (99: 1 – Hexane: Ether) to afford final product (26 mg, 0.08 mmol, 38%) as clear oil.

R_f = 0.19 and **dr:** 14:1

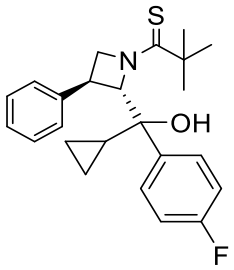
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.32 – 7.29 (m, 2H), 7.20 – 7.16 (m, 2H), 5.74 (ddt, *J* = 16.8, 9.6, 6.9 Hz, 1H), 5.19 – 5.13 (m, 2H), 4.38 – 4.23 (m, 2H), 4.05 (dd, *J* = 10.6, 6.1 Hz, 1H), 3.34 (dt, *J* = 8.8, 5.7 Hz, 1H), 2.80 – 2.56 (m, 2H), 1.67 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 186.00, 139.54, 132.94, 132.05, 128.92, 128.47, 119.20, 85.53, 77.35, 77.03, 76.72, 70.68, 56.02, 37.88, 37.53, 28.51, 1.05.

HRMS (EI) m/z: $[M]^+$ calculated for $C_{17}H_{22}ClNOS$: 323.1111; found: 323.1104.

IR (Diamond-ATR, neat) $\tilde{\nu}max$: 2916,36, 2833, 20, 1611,02, 1582,42, 1514,18, 1475,76, 1443,85, 1420,44, 1291,29, 1244,42, 1178,00, 1160,01, 1114,45, 1032,02, 1006,23, 955,90, 866,73, 825,55, 792,48, 723,33.

1-((2S,3S)-2-(cyclopropyl(4-fluorophenyl)(hydroxy)methyl)-3-phenylazetidin-1-yl)-2,2-dimethylpropane-1-thione (58g)



2,2-dimethyl-1-(3-phenylazetidin-1-yl)propane-1-thione (124.2 mg, 0.53 mmol, 1 eq) was dissolved in THF (extra dry) 2-3 ml and charged into a nitrogen flushed, flame dried flask and cooled to -78 °C. TMEDA (0.19 mL, 1.27 mmol, 2.4 eq) and s-BuLi (0.48 mL, 0.636 mmol, 1.31 M, 1.2 eq) were added to the reaction mixture and left stirring for 30 min at -78 °C. After that cyclopropyl(4-fluorophenyl)methanone (170 mg, 1.06 mmole, 2 eq) in 0.5 ml THF was added dropwise and then stirred for 30 min at -78°C and for additional one hour at rt. The mixture was then quenched with sat. NH_4Cl solution (3 ml) and the extracted with EtOAc (3 x 15 mL). The combined organic layer was dried over $MgSO_4$ and removed in vacuo. The crude product was purified via column chromatography (9: 1 – Hexane : Ethyl acetate) to afford final product (90 mg, 0.226 mmol, 43 %) as a colorless oil.

R_f = 0.45 and **dr:** 58:1

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.71 – 7.65 (m, 2H), 7.40 – 7.35 (m, 2H), 7.32 – 7.27 (m, 1H), 7.25 – 7.24 (m, 1H), 7.13 – 7.07 (m, 2H), 6.56 (d, *J* = 0.9 Hz, 1H), 5.28 (dd, *J* = 4.7, 1.7 Hz, 1H), 4.08 (dd, *J* = 10.3, 4.3 Hz, 1H), 3.76 (d, *J* = 1.6 Hz, 1H), 3.35 (dt, *J* = 8.9, 4.5 Hz, 1H), 1.28 (s, 9H), 0.81 (d, *J* = 5.3 Hz, 1H), 0.55 – 0.41 (m, 3H), 0.33 – 0.26 (m, 1H).

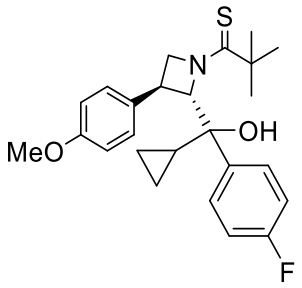
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 212.09, 162.60, 160.15, 139.99, 138.36, 138.33, 128.32, 128.23, 128.15, 126.70, 125.74, 113.80, 113.60, 83.80, 76.47, 76.15, 75.83, 62.40, 42.73, 36.51, 28.68, 13.98, 0.16, -0.01, -0.97.

^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) = -115.46 (tt, *J* = 8.6, 5.4 Hz).

HRMS (EI) m/z: $[M]^+$ calculated for $C_{24}H_{28}FNOS$: 397.1876; found: 397.1870.

IR (Diamond-ATR, neat) $\tilde{\nu}max$: 3222,61, 2970,47, 1668,85, 1600,55, 1508,13, 1456,79, 1430,80, 1396,90, 1382,70, 1365,11, 1298,49, 1222,70, 1156,23, 1144,35,1097,98, 1031,18, 993,71, 869,32, 835,66, 817,64, 752,74, 734,41, 698,91, 684,45, 661,02.

1-((2S,3S)-2-(cyclopropyl(4-fluorophenyl)(hydroxy)methyl)-3-(4-methoxyphenyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione (58h)



1-(3-(4-methoxyphenyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione (60 mg, 0.22 mmol, 1 eq.) was dissolved in THF (extra dry) 2-3 ml and charged into a nitrogen flushed, flame dried flask and cooled to -78 ℃. TMEDA (0.08 mL, 0.54 mmol, 2.4 eq) and s-BuLi (0.19 mL, 0.26 mmol, 1.31 M, 1.2 eq) were added to the reaction mixture and left stirring for 30 min at -78 ℃. After that cyclopropyl(4-fluorophenyl)methanone (70 mg, 0.44 mmole, 2 eq) in 0.5 ml THF was added dropwise and then stirred for 30 min at -78°C and for additional one hour at rt. The mixture was then quenched with sat. NH_4Cl solution (3 ml) and the extracted with EtOAc (3 x 15 mL). The combined organic layer was dried over $MgSO_4$ and removed in vacuo. The crude product was purified via column chromatography (9: 1 – Hexane : Ethyl acetate) to afford final product (80 mg, 0.187 mmol, 85 %) as a yellow oil.

R_f = 0.37 and **dr:** 5:1

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.70 – 7.64 (m, 2H), 7.19 – 7.15 (m, 2H), 7.12 – 7.06 (m, 2H), 6.92 – 6.88 (m, 2H), 5.23 (dd, *J* = 4.7, 1.7 Hz, 1H), 4.03 (dd, *J* = 10.3, 4.3 Hz, 1H), 3.81 (s, 3H), 3.73 (ddd, *J* = 10.5, 8.9, 1.7 Hz, 1H), 3.29 (dt, *J* = 8.9, 4.4 Hz, 1H), 1.27 (s, 9H), 0.80 (dtd, *J* = 9.4, 5.5, 4.0 Hz, 1H), 0.59 – 0.33 (m, 3H), 0.29 (dddd, *J* = 9.1, 8.0, 6.0, 3.9 Hz, 1H).

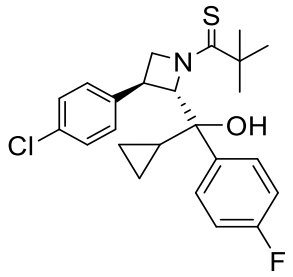
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 212.95, 163.47, 161.02, 158.93, 139.29, 139.26, 132.92, 130.29, 129.10, 129.02, 127.68, 114.64, 114.53, 114.44, 113.89, 113.29, 84.96, 77.34, 77.03, 76.71, 63.56, 55.35, 55.32, 43.89, 43.60, 37.64, 36.71, 29.81, 29.72, 29.57, 15.30, 14.86, 0.85, 0.72, 0.26, -0.12.

^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) = -115.46 (tt, *J* = 8.6, 5.4 Hz).

HRMS (ESI) m/z: $[M\text{-}OH]^+$ calculated for $C_{25}H_{29}FNOS^+$: 410.1948; found: 410.1955.

IR (Diamond-ATR, neat) $\tilde{\nu}max$: 3216,63, 2966,67, 1669,61, 1601,28, 1509,02, 1460,91, 1435,22, 1396,83, 1365,11, 1289,54, 1247,47, 1222,96, 1179,13, 1144,30, 1112,85, 1032,12, 1003,62, 869,26, 830,86, 816.09, 746,37, 679,49, 659,92.

1-((2S,3S)-3-(4-chlorophenyl)-2-(cyclopropyl(4-fluorophenyl)(hydroxy)methyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione (58i)



O-(tert-butyl) 3-(4-chlorophenyl)azetidine-1-carbothioate (74.7 mg, 0.27 mmol, 1 eq.) was dissolved in THF (extra dry) 2-3 ml and charged into a nitrogen flushed, flame dried flask and cooled to -78 °C. TMEDA (0.09 mL, 0.648 mmol, 2.4 eq.) and s-BuLi (0.24 mL, 0.324 mmol, 1.31 M, 1.2 eq) were added to the reaction mixture and left stirring for 30 min at -78 °C. After that cyclopropyl(4-fluorophenyl)methanone (88.6 mg, 0.54 mmole, 2 eq.) in 0.5 ml THF was added dropwise and then stirred for 30 min at -78°C and for additional one hour at rt. The mixture was then quenched with sat. NH_4Cl solution (3 ml) and the extracted with EtOAc (3 x 15 mL). The combined organic layer was dried over $MgSO_4$ and removed in vacuo. The crude product was purified via column chromatography (9: 1 – Hexane : Ethyl acetate) to afford final product (97 mg, 0.2245 mmol, 83 %) as a white solid.

Melting point: 196 °C

R_f = 0.31 and **dr:** 20:1

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.69 – 7.63 (m, 2H), 7.37 – 7.33 (m, 2H), 7.21 – 7.16 (m, 2H), 7.13 – 7.06 (m, 2H), 5.23 (dd, *J* = 4.7, 1.7 Hz, 1H), 4.02 (dd, *J* = 10.4, 4.3 Hz, 1H), 3.76 (ddd, *J* = 10.5, 8.9, 1.7 Hz, 1H), 3.32 (dt, *J* = 8.9, 4.4 Hz, 1H), 1.27 (s, 9H), 0.91 – 0.76 (m, 2H), 0.52 (d, *J* = 5.6 Hz, 2H), 0.33 – 0.25 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 7213.23, 139.37, 139.01, 133.46, 129.38, 129.05, 128.97, 127.99, 114.75, 114.54, 84.57, 77.35, 77.03, 76.72, 63.14, 43.64, 36.92, 29.55, 14.85, 1.05, 0.83, -0.07.

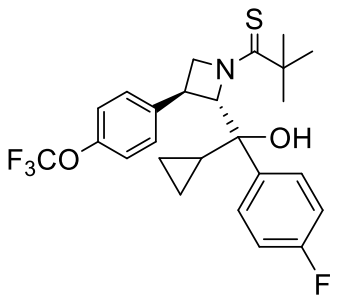
^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) = 7 -115.20 (tt, *J* = 8.6, 5.3 Hz).

HRMS (ESI) m/z: $[M\text{-}OH]^+$ calculated for $C_{24}H_{26}ClFNS^+$: 414.1453; found: 414.1460.

IR (Diamond-ATR, neat) $\tilde{\nu}max$: 3181,18, 2959,80, 2920,67, 1603,97, 1508,72, 1493,30, 1463,26, 1445,65, 1415,42, 1396,03, 1364,56, 1295,64, 1258,66, 1223,55, 1210,86, 1183,24, 1161,74,

1145,14, 1133,65, 1108,04, 1094,11, 1023,94, 1014,11, 1003,99, 855,38, 838,80, 827,51, 801,49, 815,10, 653,75.

1-((2S,3S)-2-(cyclopropyl(4-fluorophenyl)(hydroxy)methyl)-3-(4-(trifluoromethoxy)phenyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione (58j)



2,2-dimethyl-1-(3-(4-(trifluoromethoxy)phenyl)azetidin-1-yl)propane-1-thione (88 mg, 0.28 mmol, 1 eq) was dissolved in THF (extra dry) 2-3 ml and charged into a nitrogen flushed, flame dried flask and cooled to -78 °C. TMEDA (0.1 mL, 0.672 mmol, 2.4 eq) and s-BuLi (0.25 mL, 0.336 mmol, 1.31 M, 1.2 eq) were added to the reaction mixture and left stirring for 30 min at -78 °C. After that cyclopropyl(4-fluorophenyl)methanone (90 mg, 0.56 mmole, 2 eq) in 0.5 ml THF was added dropwise and then stirred for 30 min at -78°C and for additional one hour at rt. The mixture was then quenched with sat. NH_4Cl solution (3 ml) and the extracted with EtOAc (3 x 15 mL). The combined organic layer was dried over $MgSO_4$ and removed in vacuo. The crude product was purified via column chromatography ((9: 1 – Hexane : Ethyl acetate) to afford final product (110 mg, 0.228 mmol, 81%) as a yellow oil.

R_f = 0.48 and **dr:** 7:1

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.70 – 7.63 (m, 2H), 7.28 (d, *J* = 8.8 Hz, 2H), 7.25 – 7.20 (m, 2H), 7.14 – 7.07 (m, 2H), 5.26 (dd, *J* = 4.6, 1.7 Hz, 1H), 4.05 (dd, *J* = 10.3, 4.2 Hz, 1H), 3.77 (ddd, *J* = 10.5, 8.9, 1.7 Hz, 1H), 3.36 (dt, *J* = 8.8, 4.4 Hz, 1H), 1.27 (s, 9H), 0.86 – 0.78 (m, 2H), 0.58 – 0.42 (m, 2H), 0.35 – 0.26 (m, 1H).

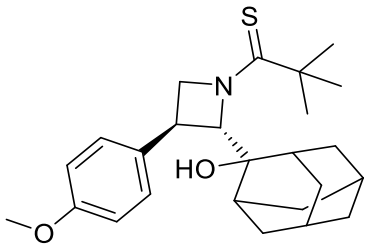
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 212.95, 163.47, 161.02, 158.93, 139.29, 139.26, 132.92, 130.29, 129.10, 129.02, 127.68, 114.64, 114.53, 114.44, 113.89, 113.29, 84.96, 77.34, 77.03, 76.71, 63.56, 55.35, 55.32, 43.89, 43.60, 37.64, 36.71, 29.81, 29.72, 29.57, 15.30, 14.86, 0.85, 0.72, 0.26, -0.12.

^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) = -57.90, -115.16 (tt, *J* = 8.6, 5.4 Hz).

HRMS (EI) m/z: $[M\text{-}OH]^+$ calculated for $C_{25}H_{26}F_4NOS^+$: 464.1666; found: 464.1590.

IR (Diamond-ATR, neat) $\tilde{\nu}max$: 2962,63, 2927,15, 1508,43, 1458,44, 1259,91, 1220,60, 1162,52, 1091,96, 1017,92, 797,95, 668,65.

1-((2S,3S)-2-(2-hydroxyadamantan-2-yl)-3-(4-methoxyphenyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione (58k)



1-(3-(4-methoxyphenyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione (97.4 mg, 0.36 mmol, 1 eq.) was dissolved in THF (extra dry) 2-3 ml and charged into a nitrogen flushed, flame dried flask and cooled to -78 °C. TMEDA (0.13 mL, 0.864 mmol, 2.4 eq) and s-BuLi (0.32 mL, 0.432 mmol, 1.31 M, 1.2 eq.) were added to the reaction mixture and left stirring for 30 min at -78 °C. After that adamantane-2-one (110 mg, 0.72 mmol, 2 eq.) in 0.5 ml THF was added dropwise and then stirred for 30 min at -78°C and for additional one hour at rt. The mixture was then quenched with sat. NH_4Cl solution (3 ml) and the extracted with EtOAc (3 x 15 mL). The combined organic layer was dried over $MgSO_4$ and removed in vacuo. The crude product was purified via column chromatography (9 : 1 – Hexane: Ethyl Acetate) to afford final product (126 mg, 0.295 mmol, 82%) as a yellow solid.

R_f = 0.18 and **dr:** 47:1

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.18 – 7.14 (m, 2H), 6.89 – 6.85 (m, 2H), 5.52 – 5.48 (m, 1H), 4.88 (ddd, *J* = 9.7, 8.7, 1.2 Hz, 1H), 4.11 (dd, *J* = 9.3, 4.0 Hz, 1H), 3.79 (s, 3H), 3.57 (dt, *J* = 8.4, 4.0 Hz, 1H), 2.79 – 2.72 (m, 1H), 2.25 (d, *J* = 12.5 Hz, 1H), 2.17 – 2.10 (m, 1H), 2.06 – 1.99 (m, 2H), 1.82 – 1.74 (m, 3H), 1.65 (tq, *J* = 5.7, 2.8 Hz, 3H), 1.60 – 1.57 (m, 1H), 1.53 (t, *J* = 2.6 Hz, 1H), 1.41 (s, 9H), 1.39 – 1.34 (m, 1H).

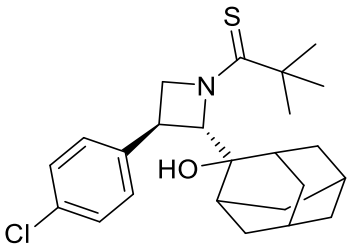
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 216.93, 158.63, 134.56, 127.82, 114.45, 80.94, 78.55, 77.35, 77.04, 76.72, 66.39, 55.30, 44.69, 38.04, 36.77, 35.89, 34.90, 33.68, 33.32, 33.21, 33.07, 30.44, 27.12, 26.71.

HRMS (EI) m/z: $[M]^+$ calculated for $C_{25}H_{35}NO_2S$: 413.2389; found: 413.2327.

IR (Diamond-ATR, neat) $\tilde{\nu}max$: 3567,79, 2906,70, 2858,33, 1705,23, 1612,36, 1584,35, 1513,92, 1457,81, 1442,01, 1426,45, 1399,43, 1389,38, 1360,33, 1299,58, 1287,68, 1246,84, 1179,32,

1148,47, 1128,36, 1102,44, 1063,67, 1037,79, 1005,48, 982,86, 930,84, 872,47, 825,78, 810,42, 785,60, 767,57, 724,47, 676,19, 661,75.
Melting point: 179 °C

1-((2S,3S)-3-(4-chlorophenyl)-2-(2-hydroxyadamantan-2-yl)azetidin-1-yl)-2,2-dimethylpropane-1-thione (58l)

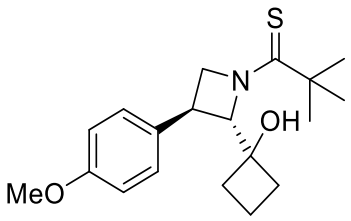


1-(3-(4-chlorophenyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione (82.3 mg, 0.30 mmol, 1 eq.) was dissolved in THF (extra dry) 2-3 ml and charged into a nitrogen flushed, flame dried flask and cooled to -78 °C. TMEDA (0.1 mL, 0.72 mmol, 2.4 eq.) and s-BuLi (0.27 mL, 0.36 mmol, 1.31 M, 1.2 eq.) were added to the reaction mixture and left stirring for 30 min at -78 °C. After that adamantane-2-one (90 mg, 0.6 mmol, 2 eq.) in 0.5 ml THF was added dropwise and then stirred for 30 min at -78°C and for additional one hour at rt. The mixture was then quenched with sat. NH_4Cl solution (3 ml) and the extracted with EtOAc (3 x 15 mL). The combined organic layer was dried over $MgSO_4$ and removed in vacuo. The crude product was purified via column chromatography (9: 1 – Hexane: Ethyl Acetate) to afford final product (41 mg, 0.095 mmol, 32 %) as a yellow solid.
R_f = 0.34 and **dr:** 17:1
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.33 – 7.29 (m, 2H), 7.19 – 7.15 (m, 2H), 5.50 (d, *J* = 3.9 Hz, 1H), 4.90 (ddd, *J* = 9.6, 8.6, 1.2 Hz, 1H), 4.09 (dd, *J* = 9.3, 3.9 Hz, 1H), 3.60 (dt, *J* = 8.3, 4.0 Hz, 1H), 2.75 (d, *J* = 13.3 Hz, 1H), 2.27 – 2.22 (m, 1H), 2.15 – 2.10 (m, 1H), 2.03 – 1.95 (m, 2H), 1.79 (dt, *J* = 16.3, 3.1 Hz, 3H), 1.66 (ddq, *J* = 10.2, 5.7, 2.9 Hz, 3H), 1.41 (s, 9H), 1.28 – 1.24 (m, 3H).
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 217.08, 141.01, 132.94, 129.28, 129.11, 128.17, 80.54, 78.55, 77.35, 77.04, 76.72, 65.93, 44.73, 37.97, 36.66, 36.19, 34.88, 33.67, 33.36, 33.17, 33.03, 32.46, 30.43, 29.73, 27.54, 27.07, 26.66, 1.05.
HRMS (EI) m/z: $[M]^+$ calculated for $C_{24}H_{32}ClNOS$: 417.1893; found: 417.1890.
IR (Diamond-ATR, neat) $\tilde{\nu}max$: 3563,36, 2907,87, 2857,20, 1641,03, 1494,35, 1478,46, 1457,64, 1413,90, 1398,94, 1389,18, 1359,33, 1312,85, 1283,46, 1245,59, 1209,83, 1147,79, 1130,23,

1093,28, 1063,28, 1025,65, 1006, 78, 1041,11, 931,31, 872,97, 823,14, 796,96, 786,41, 758,52, 711,30, 677,41, 665,45.

Melting point: 172 °C

1-((2S,3S)-2-(1-hydroxycyclobutyl)-3-(4-methoxyphenyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione (58f)



1-(3-(4-methoxyphenyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione (92.3 mg, 0.7 mmol, 1 eq.) was dissolved in THF (extra dry) 2-3 ml and charged into a nitrogen flushed, flame dried flask and cooled to -78 °C. TMEDA (0.125 mL, 1.68 mmol, 2.4 eq.) and s-BuLi (0.32 mL, 0.84 mmol, 1.31 M, 1.2 eq.) were added to the reaction mixture and left stirring for 30 min at -78 °C. After that cyclobutanone (0.1 ml, 1.4 mmol, 2 eq) in 0.5 ml THF was added dropwise and then stirred for 30 min at -78°C and for additional one hour at rt. The mixture was then quenched with sat. NH_4Cl solution (3 ml) and the extracted with EtOAc (3 x 15 mL). The combined organic layer was dried over $MgSO_4$ and removed in vacuo. The crude product was purified via column chromatography (9: 1 – Hexane : Ethyl Acetate) to afford final product (73 mg, 0.22 mmol, 31 %) as a clear oil.

R_f = 0.28 and **dr:** 94:1

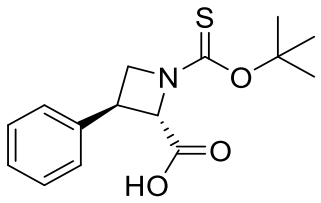
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.24 – 7.18 (m, 2H), 6.93 – 6.88 (m, 2H), 4.94 (dd, *J* = 6.0, 1.7 Hz, 1H), 4.86 (ddd, *J* = 10.8, 9.3, 1.8 Hz, 1H), 4.32 (dd, *J* = 10.4, 5.7 Hz, 1H), 3.81 (s, 3H), 3.60 (dt, *J* = 9.3, 5.8 Hz, 1H), 2.44 (ddt, *J* = 14.3, 8.1, 3.2 Hz, 1H), 2.34 – 2.23 (m, 1H), 2.20 – 2.00 (m, 3H), 1.76 – 1.65 (m, 1H), 1.40 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 213.06, 158.97, 133.08, 127.97, 114.51, 83.38, 77.36, 77.04, 76.73, 63.98, 55.38, 43.84, 36.04, 34.32, 31.33, 29.78, 13.91.

HRMS (ESI) m/z: $[M]^+$ calculated for $C_{19}H_{27}NO_2S$: 333.1762; found: 333.1727.

IR (Diamond-ATR, neat) $\tilde{\nu}max$: 2960,44, 1730,99, 1612,86, 1514,67, 1433,57, 1364,30, 1290,54, 1246,00, 1178,07, 1136,49, 1108,98, 1032,73, 1005,88, 929,06, 828,35, 810,07, 701,09, 658,74.

(2S,3S)-1-(tert-butoxycarbonothioyl)-3-phenylazetidine-2-carboxylic acid (60d)



O-(tert-butyl) 3-phenylazetidine-1-carbothioate (58.75 mg, 0.23 mmol, 1 eq.) was dissolved in THF (extra dry) 2-3 ml and charged into a nitrogen flushed, flame dried flask, and cooled to -78 ℃. TMEDA (0.08 mL, 0.552 mmol, 2.4 eq.) and s-BuLi (0.20 mL, 0.276 mmol, 1.31 M, 1.2 eq.) were added to the reaction mixture and left stirring for 30 min at -78 ℃. The reaction mixture was then bubbled with CO_2 gas for 5 min and stirred for 4 hours at -78°C and for additional one hour at rt. The mixture was then quenched with sat. NH_4Cl solution (3 ml) and the extracted with EtOAc (3 x 15 mL). The combined organic layer was dried over $MgSO_4$ and removed in vacuo. The crude product was purified via column chromatography (99:1, DCM: AcOH) to afford final product (13 mg, 0.045 mmol, 19 %) as a yellow oil.

R_f = 0.27 and **dr:** 2:1

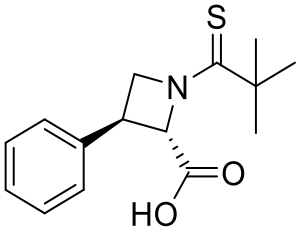
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.38 (t, *J* = 7.4 Hz, 2H), 7.33 – 7.27 (m, 3H), 4.97 (d, *J* = 6.0 Hz, 1H), 4.43 – 4.34 (m, 1H), 4.12 (q, *J* = 6.6, 5.9 Hz, 2H), 1.67 (s, 9H).

^{13}C NMR (101 MHz, DMSO): δ (ppm) = 207.00, 198.34, 186.13, 185.31, 170.91, 170.62, 154.36, 140.72, 129.26, 129.19, 128.90, 127.82, 127.75, 127.49, 127.42, 127.26, 127.05, 124.64, 85.43, 85.18, 70.43, 69.76, 56.95, 56.61, 45.72, 40.64, 40.59, 40.43, 40.38, 40.22, 40.17, 39.97, 39.76, 39.55, 39.34, 37.10, 36.92, 32.02, 31.17, 28.36, 28.25, 28.08, 27.54, 20.61, 9.18.

HRMS (EI) m/z: $[M]^+$ calculated for $C_{15}H_{19}NO_3S$: 293.1086; found: 293.1080.

IR (Diamond-ATR, neat) $\tilde{\nu}max$: 3398,75, 2925,38, 1723,63, 1646,35, 1462,24, 1444,24, 1392,05, 1366,37, 1284,80, 1223,51, 1144,43, 1048,34, 1023,92, 995,75, 879,35, 824,48, 760,04, 699,87.

(2S,3S)-1-(2,2-dimethylpropanethioyl)-3-phenylazetidine-2-carboxylic acid (58m)



2,2-dimethyl-1-(3-phenylazetidin-1-yl)propane-1-thione (125 mg, 0.54 mmol, 1 eq.) was dissolved in THF (extra dry) 2-3 ml and charged into a nitrogen flushed, flame dried flask and cooled to -78 ℃. TMEDA (0.19 mL, 1.29 mmol, 2.4 eq.) and s-BuLi (0.5 mL, 0.65 mmol, 1.31 M, 1.2 eq.) were added to the reaction mixture and left stirring for 30 min at -78 ℃. The reaction mixture was then bubbled with CO_2 gas for 5 min and stirred for 4 hours at -78°C and for additional one hour at rt. The mixture was then quenched with sat. NH_4Cl solution (3 ml) and the extracted with EtOAc (3 x 15 mL). The combined organic layer was dried over $MgSO_4$ and removed in vacuo. The crude product was purified via column chromatography (99:1, DCM: AcOH) to afford final product (100 mg, 0.375 mmol, 69 %) as a yellow oil.

R_f = 0.23 and **dr:** 6:1

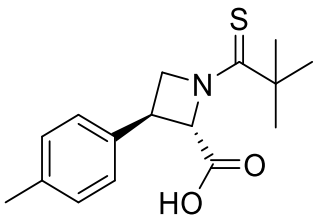
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.42 – 7.37 (m, 2H), 7.34 – 7.28 (m, 3H), 5.22 (dd, *J* = 5.1, 1.7 Hz, 1H), 5.00 (ddd, *J* = 10.5, 8.9, 1.7 Hz, 1H), 4.55 (dd, *J* = 10.2, 5.4 Hz, 1H), 4.04 (dt, *J* = 9.8, 5.2 Hz, 1H), 1.42 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 213.25, 170.31, 139.38, 129.24, 127.99, 126.60, 77.35, 77.03, 76.72, 74.09, 63.75, 43.60, 36.72, 30.98, 29.73, 29.64, 29.56.

HRMS (ESI) m/z: $[M-H]^+$ calculated for $C_{15}H_{18}NO_2S^+$: 276.1053; found: 276.1064.

IR (Diamond-ATR, neat) $\tilde{\nu}max$: 2960,30, 2923,54, 1714,16, 1456,44, 1427,81, 1363,82, 1283,16, 1252,71, 1225,67, 1161,20, 1081,72, 1049,58, 1018,27, 910,46, 804,40, 757,11, 731,46, 697,56.

(2S,3S)-1-(2,2-dimethylpropanethioyl)-3-(p-tolyl)azetidine-2-carboxylic acid (58n)



2,2-dimethyl-1-(3-(p-tolyl)azetidin-1-yl)propane-1-thione (75.2 mg, 0.30 mmol, 1 eq.) was dissolved in THF (extra dry) 2-3 ml and charged into a nitrogen flushed, flame dried flask and cooled to -78 ℃. TMEDA (0.10 mL, 0.72 mmol, 2.4 eq.) and s-BuLi (0.27 mL, 0.36 mmol, 1.31 M, 1.2 eq.) were added to the reaction mixture and left stirring for 30 min at -78 ℃. The reaction mixture was then bubbled with CO_2 gas for 5 min and stirred for 4 hours at -78°C and for additional one hour at rt. The mixture was then quenched with sat. NH_4Cl solution (3 ml) and the extracted with EtOAc (3 x 15 mL). The combined organic layer was dried over $MgSO_4$ and removed in vacuo. The crude product

was purified via column chromatography (99:1, DCM: AcOH) to afford final product (76 mg, 0.261 mmol, 87 %) as a yellow oil.

R_f = 0.31 and **dr:** 5:1

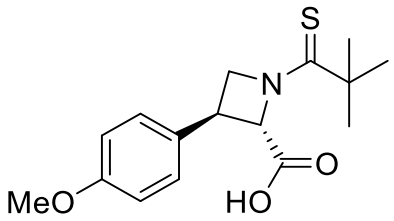
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.21 – 7.15 (m, 4H), 5.15 (dd, *J* = 5.1, 1.6 Hz, 1H), 4.98 (ddd, *J* = 10.3, 9.0, 1.7 Hz, 1H), 4.50 (dd, *J* = 10.1, 5.3 Hz, 1H), 3.93 (dt, *J* = 8.9, 5.3 Hz, 1H), 2.35 (s, 3H), 1.41 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 212.99, 171.59, 137.79, 136.36, 129.84, 129.38, 127.74, 126.50, 77.35, 77.04, 76.72, 73.84, 63.67, 60.16, 43.49, 36.48, 29.63, 29.55, 21.16, 21.12, 20.58.

HRMS (EI) m/z: $[M]^+$ calculated for $C_{16}H_{21}NO_2S$: 291.1293; found: 291.1286.

IR (Diamond-ATR, neat) $\tilde{\nu}max$: 2963,73, 2925,39, 1722,83, 1642,66, 1516,58, 1431,75, 1385,56, 1363,90, 1281,12, 1252,77, 1217,05, 1161,51, 1103,32, 1049,05, 1020,59, 853,88, 812,08, 720,53, 670,86.

(2S,3S)-1-(2,2-dimethylpropanethioyl)-3-(4-methoxyphenyl)azetidine-2-carboxylic acid (58o)



1-(3-(4-methoxyphenyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione (238.8 mg, 0.90 mmol, 1 eq.) was dissolved in THF (extra dry) 2-3 ml and charged into a nitrogen flushed, flame dried flask and cooled to -78 °C. TMEDA (0.32 mL, 2.16 mmol, 2.4 eq.) and s-BuLi (0.82 mL, 1.08 mmol, 1.31 M, 1.2 eq.) were added to the reaction mixture and left stirring for 30 min at -78 °C. The reaction mixture was then bubbled with CO_2 gas for 5 min and stirred for 4 hours at -78°C and for additional one hour at rt. The mixture was then quenched with sat. NH_4Cl solution (3 ml) and the extracted with EtOAc (3 x 15 mL). The combined organic layer was dried over $MgSO_4$ and removed in vacuo. The crude product was purified via column chromatography (99:1, DCM: AcOH) to afford final product (187.5 mg, 0.61 mmol, 68%) as a yellow oil.

R_f = 0.25 and **dr:** 16:1

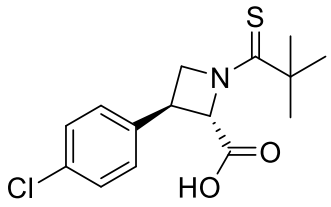
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.24 – 7.19 (m, 2H), 6.94 – 6.89 (m, 2H), 5.09 (dd, *J* = 5.0, 1.5 Hz, 1H), 4.99 (ddd, *J* = 10.4, 8.9, 1.7 Hz, 1H), 4.48 (dd, *J* = 10.0, 5.4 Hz, 1H), 3.85 (dt, *J* = 8.9, 5.2 Hz, 1H), 3.81 (s, 3H), 1.41 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 212.83, 177.15, 172.75, 159.26, 131.39, 129.09, 127.80, 114.54, 114.07, 77.36, 77.05, 76.73, 73.70, 63.62, 55.40, 55.32, 43.41, 43.28, 36.28, 29.62, 29.56, 20.75.

HRMS (ESI) m/z: $[M-H]^+$ calculated for $C_{16}H_{20}NO_3S^+$: 306.1158; found: 306.11718.

IR (Diamond-ATR, neat) $\tilde{\nu}max$: 2963,50, 1709,09, 1612,76, 1515,34, 1431,96, 1364,12, 1288,63, 1247,56, 1178,42, 1162,78, 1113,15, 1030,25, 914,38, 827,58, 726,67, 691,96.

(2S,3S)-3-(4-chlorophenyl)-1-(2,2-dimethylpropanethioyl)azetidine-2-carboxylic acid (58p)



1-(3-(4-chlorophenyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione (144.2 mg, 0.53 mmol, 1 eq.) was dissolved in THF (extra dry) 2-3 ml and charged into a nitrogen flushed, flame dried flask and cooled to -78 °C. TMEDA (0.19 mL, 1.272 mmol, 2.4 eq.) and s-BuLi (0.48 mL, 0.636 mmol, 1.31 M, 1.2 eq.) were added to the reaction mixture and left stirring for 30 min at -78 °C. The reaction mixture was then bubbled with CO_2 gas for 5 min and stirred for 4 hours at -78°C and for additional one hour at rt. The mixture was then quenched with sat. NH_4Cl solution (3 ml) and the extracted with EtOAc (3 x 15 mL). The combined organic layer was dried over $MgSO_4$ and removed in vacuo. The crude product was purified via column chromatography (99:1, DCM: AcOH) to afford final product (84 mg, 0.27 mmol, 51 %) as a yellow oil.

R_f = 0.27 and **dr:** 20:1

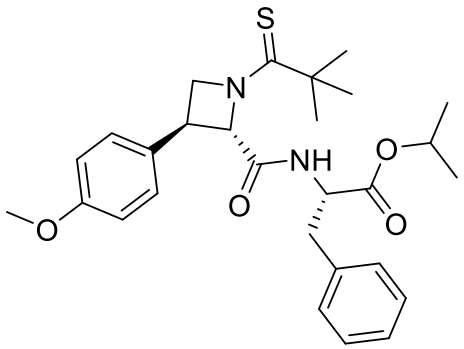
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.40 – 7.34 (m, 2H), 7.25 – 7.21 (m, 2H), 5.15 (dd, *J* = 5.1, 1.6 Hz, 1H), 5.00 (ddd, *J* = 10.4, 8.9, 1.7 Hz, 1H), 4.49 (dd, *J* = 10.2, 5.4 Hz, 1H), 3.98 (dt, *J* = 8.9, 5.2 Hz, 1H), 1.41 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 213.39, 170.90, 137.77, 133.93, 129.41, 128.02, 77.35, 77.04, 76.72, 73.62, 63.41, 43.59, 36.24, 29.56.

HRMS (ESI) m/z: $[M-H]^+$ calculated for $C_{15}H_{17}ClNO_2S^+$: 310.0663; found: 310.0675.

IR (Diamond-ATR, neat) $\tilde{\nu}max$: 3351,06, 1706,77, 1633,35, 1394,86, 1229,54, 1161,04, 1092,36, 1049,86, 1013,77, 819,40.

Isopropyl ((2S,3S)-1-(2,2-dimethylpropanethioyl)-3-(4-methoxyphenyl)azetidine-2-carbonyl)-L-phenylalaninate (61a)



A flask was charged with the (2S,3S)-1-(2,2-dimethylpropanethioyl)-3-(4-methoxyphenyl)azetidine-2-carboxylic acid (226 mg, 0.7 mmol, 1.0 equiv.), HATU (290 mg, 0.77 mmol, 1.1 eq.), DIPEA (0.26 ml, 1.54 mmol, 2.2 eq.) and L-Phenylalanin-iso-propylester-hydrochloride (170 mg, 0.7 mmol, 1.0 eq.) as well as extra dry DCM (6 mL). The mixture was allowed to stirrer at room temperature for 6 h and then quenched with saturated aqueous solution of NH_4Cl and extracted with DCM (3 × 20 ml). The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo. The crude product was purified by column chromatography on silica gel (8: 2 – Hexane: Ethyl Acetate) to give the corresponding peptide (144 mg, 0.29 mmol, 41 %) as a yellow oil.

R_f = 0.27 and **dr** > 99:1

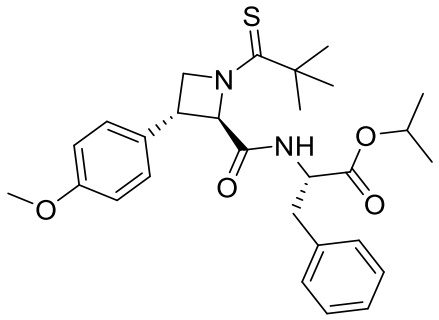
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.34 – 7.27 (m, 2H), 7.19 (tt, *J* = 7.5, 3.0 Hz, 4H), 6.96 – 6.88 (m, 3H), 5.09 – 4.86 (m, 4H), 4.42 (dt, *J* = 9.8, 4.9 Hz, 1H), 3.84 (s, 3H), 3.82 – 3.75 (m, 1H), 3.25 – 3.09 (m, 2H), 1.42 (s, 9H), 1.24 (dd, *J* = 11.3, 5.6 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 213.02, 212.59, 170.48, 167.82, 167.77, 159.07, 135.96, 135.89, 132.32, 132.24, 129.68, 129.60, 129.35, 128.47, 128.42, 127.81, 127.79, 127.01, 114.46, 114.43, 114.25, 77.37, 77.06, 76.74, 75.56, 75.39, 69.39, 69.33, 63.96, 63.78, 55.39, 55.37, 53.51, 53.38, 43.51, 43.46, 37.97, 37.89, 36.92, 36.63, 30.57, 29.68, 27.09, 21.82, 21.80, 21.74.

HRMS (EI) m/z: $[M]^+$ calculated for $C_{28}H_{36}N_2O_4S$: 496.2396; found: 496.2395.

IR (Diamond-ATR, neat) $\tilde{\nu}max$: 2981,12, 1732,81, 1670,76, 1613,26, 1514,82, 1435,20, 1364,77, 1284,89, 1249,00, 1211,94, 1179,60, 1105,77, 1032,02, 829,69, 740,48, 701,08.

Isopropyl ((2R,3R)-1-(2,2-dimethylpropanethioyl)-3-(4-methoxyphenyl)azetidine-2-carbonyl)-L-phenylalaninate (61b)



A flask was charged with the (2S,3S)-1-(2,2-dimethylpropanethioyl)-3-(4-methoxyphenyl)azetidine-2-carboxylic acid (226 mg, 0.7 mmol, 1.0 equiv.), HATU (290 mg, 0.77 mmol, 1.1 eq.), DIPEA (0.26 ml, 1.54 mmol, 2.2 equiv.) and L-Phenylalanin-iso-propylester-hydrochloride (170 mg, 0.7 mmol, 1.0 eq.) as well as extra dry DCM (6 mL). The mixture was allowed to stirrer at room temperature for 6 h and then quenched with saturated aqueous solution of NH_4Cl and extracted with DCM (3 × 20 ml). The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo. The crude product was purified by column chromatography on silica gel (8: 2 – Hexane: Ethyl Acetate) to give the corresponding peptide (54 mg, 0.11 mmol, 16 %) as a yellow oil.

R_f = 0.25 and **dr** > 99:1

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.19 (ddd, *J* = 8.0, 4.0, 1.7 Hz, 6H), 6.90 – 6.85 (m, 3H), 5.00 (pd, *J* = 6.2, 4.6 Hz, 1H), 4.83 – 4.71 (m, 3H), 4.26 (ddd, *J* = 10.4, 8.4, 6.2 Hz, 1H), 3.79 (s, 3H), 3.20 (dd, *J* = 14.0, 5.4 Hz, 1H), 3.09 (dt, *J* = 13.9, 6.5 Hz, 1H), 3.01 (dd, *J* = 13.9, 7.6 Hz, 1H), 1.21 (s, 9H), 1.20 – 1.17 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 180.18, 170.63, 170.54, 170.26, 170.04, 158.81, 136.46, 136.17, 132.59, 132.57, 129.49, 129.43, 128.44, 128.34, 127.84, 126.90, 126.85, 114.24, 77.35, 77.04, 76.72, 69.09, 69.01, 55.35, 53.62, 38.80, 38.72, 38.09, 37.93, 27.09, 27.03, 21.80, 21.76, 21.71.

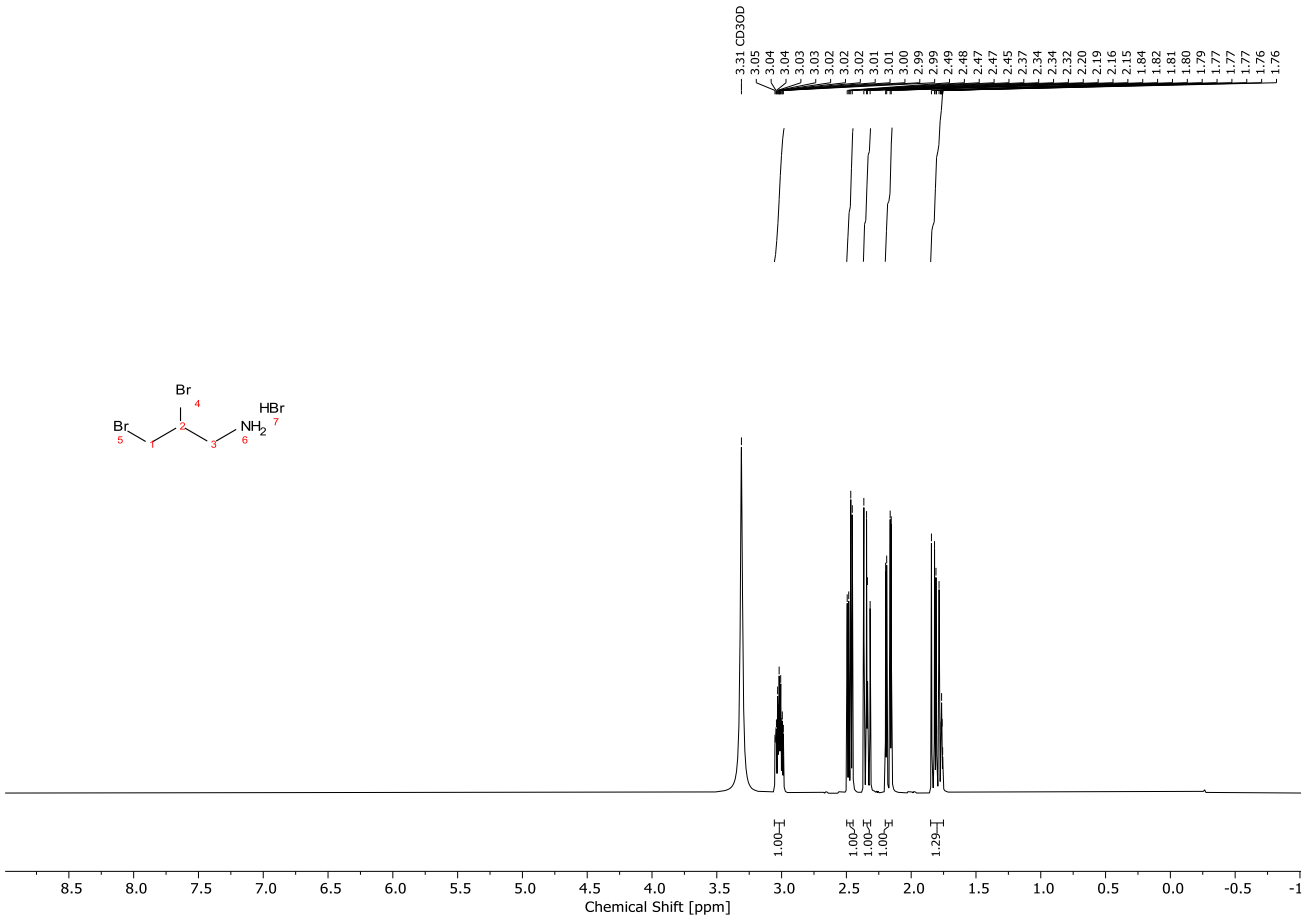
HRMS (EI) m/z: $[M]^+$ calculated for $C_{28}H_{36}N_2O_4S$: 496.2396; found: 496.2395.

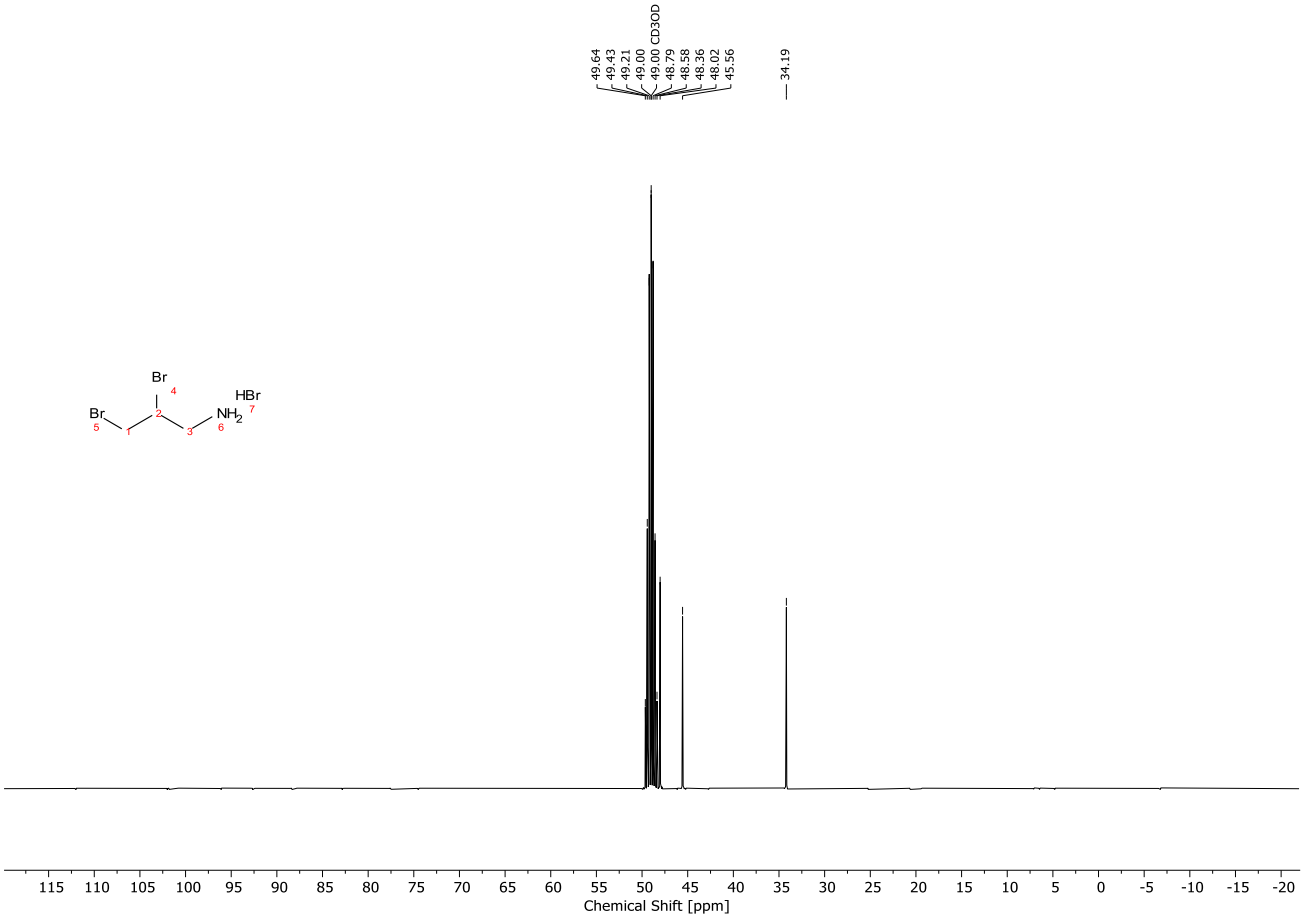
IR (Diamond-ATR, neat) $\tilde{\nu}max$: 2981,12, 1732,81, 1670,76, 1613,26, 1514,82, 1435,20, 1364,77, 1284,89, 1249,00, 1211,94, 1179,60, 1105,77, 1032,02, 829,69, 740,48, 701,08.

6 NMR Spectra

2,3-Dibromopropan-1-amine hydrobromide

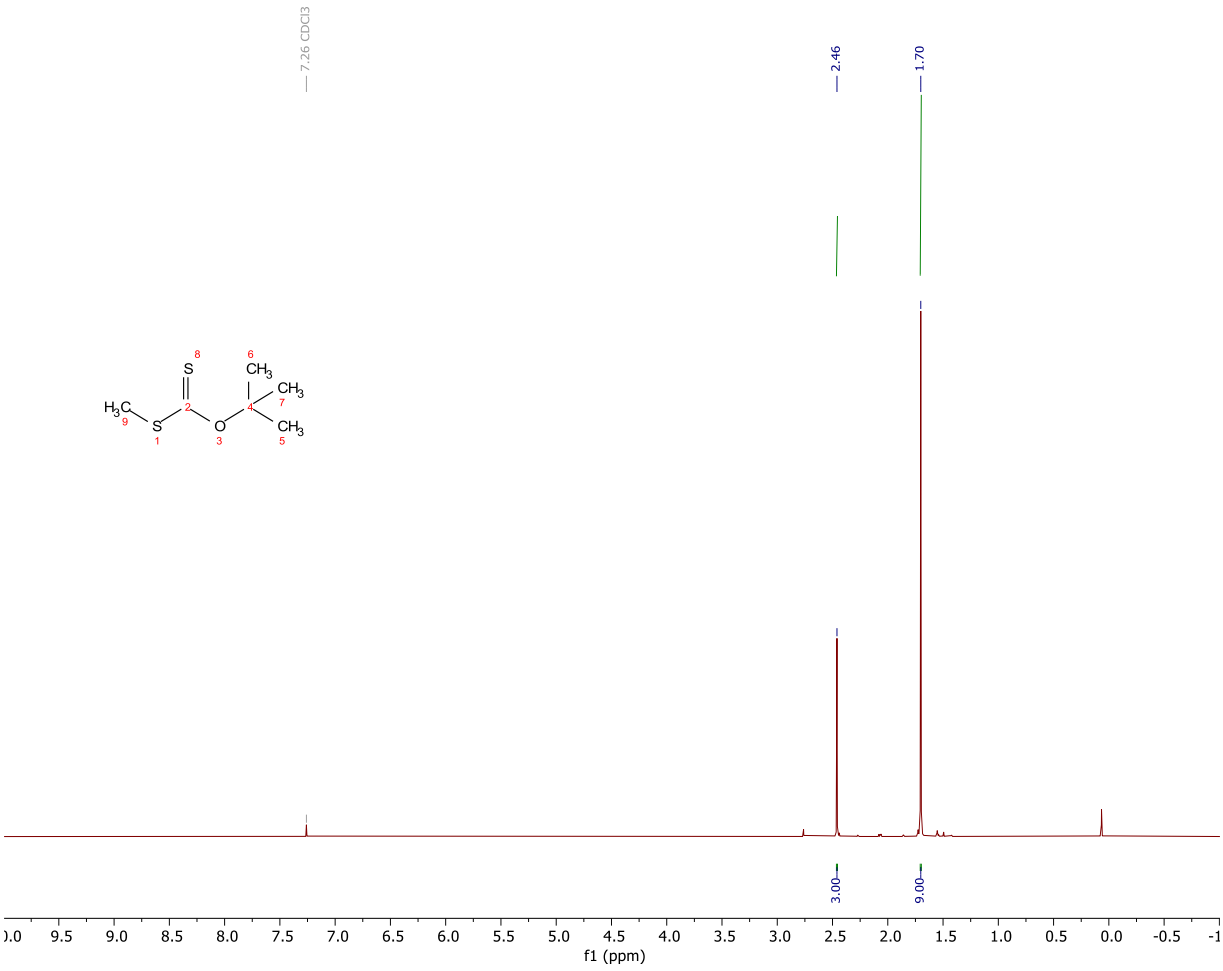
^{1}H NMR (400 MHz, $CDCl_3$) and **^{13}C NMR** (101 MHz, $CDCl_3$)

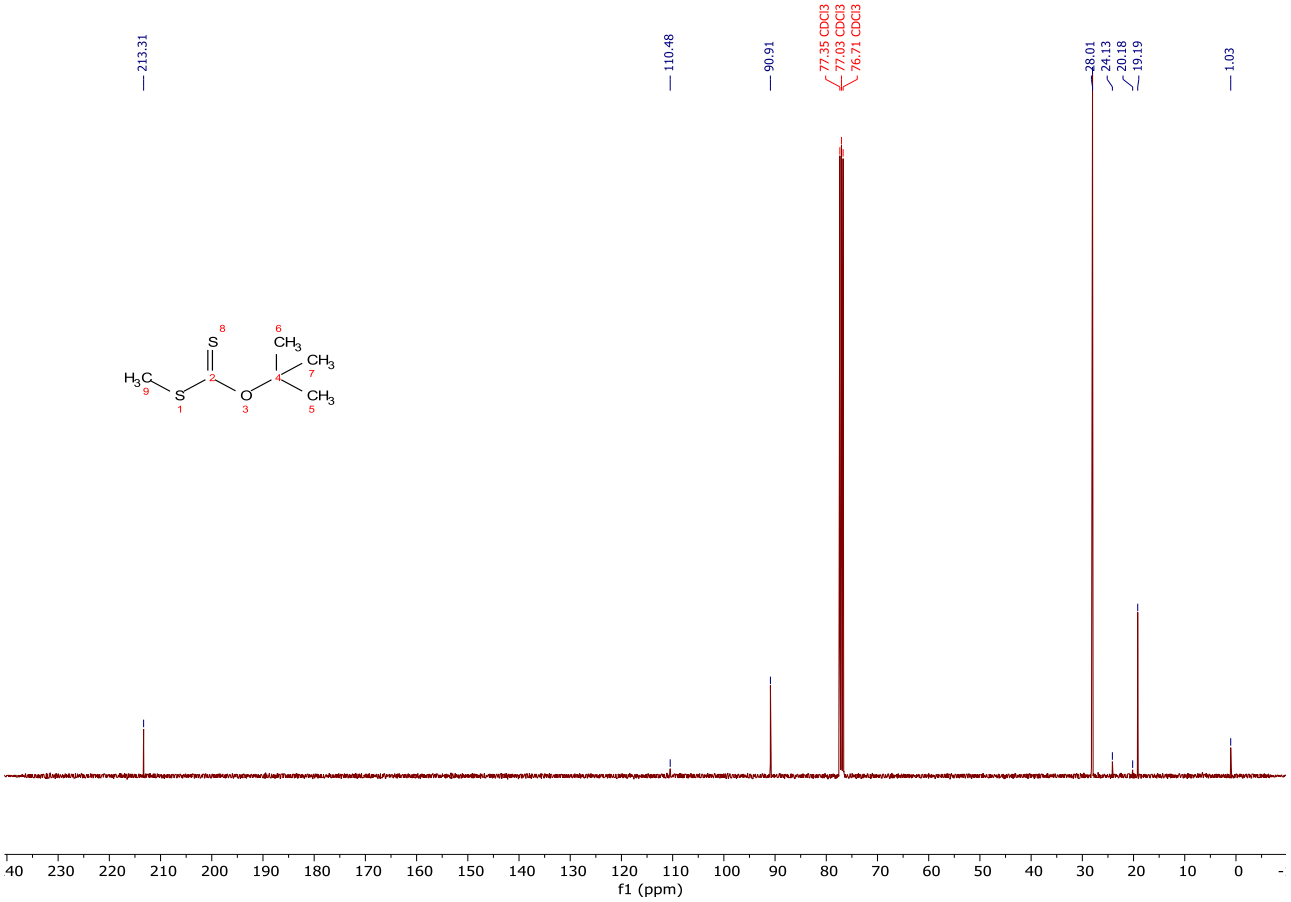



49.64
49.43
49.21
49.00
49.00 CD3OD
48.79
48.58
48.36
48.02
45.56
34.19
Br
4
HBr
7
Br
5
2
NH2
6
1
3
115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 -5 -10 -15 -20
Chemical Shift [ppm]

S-Methyl O-t-Butyl Dithiocarbonate

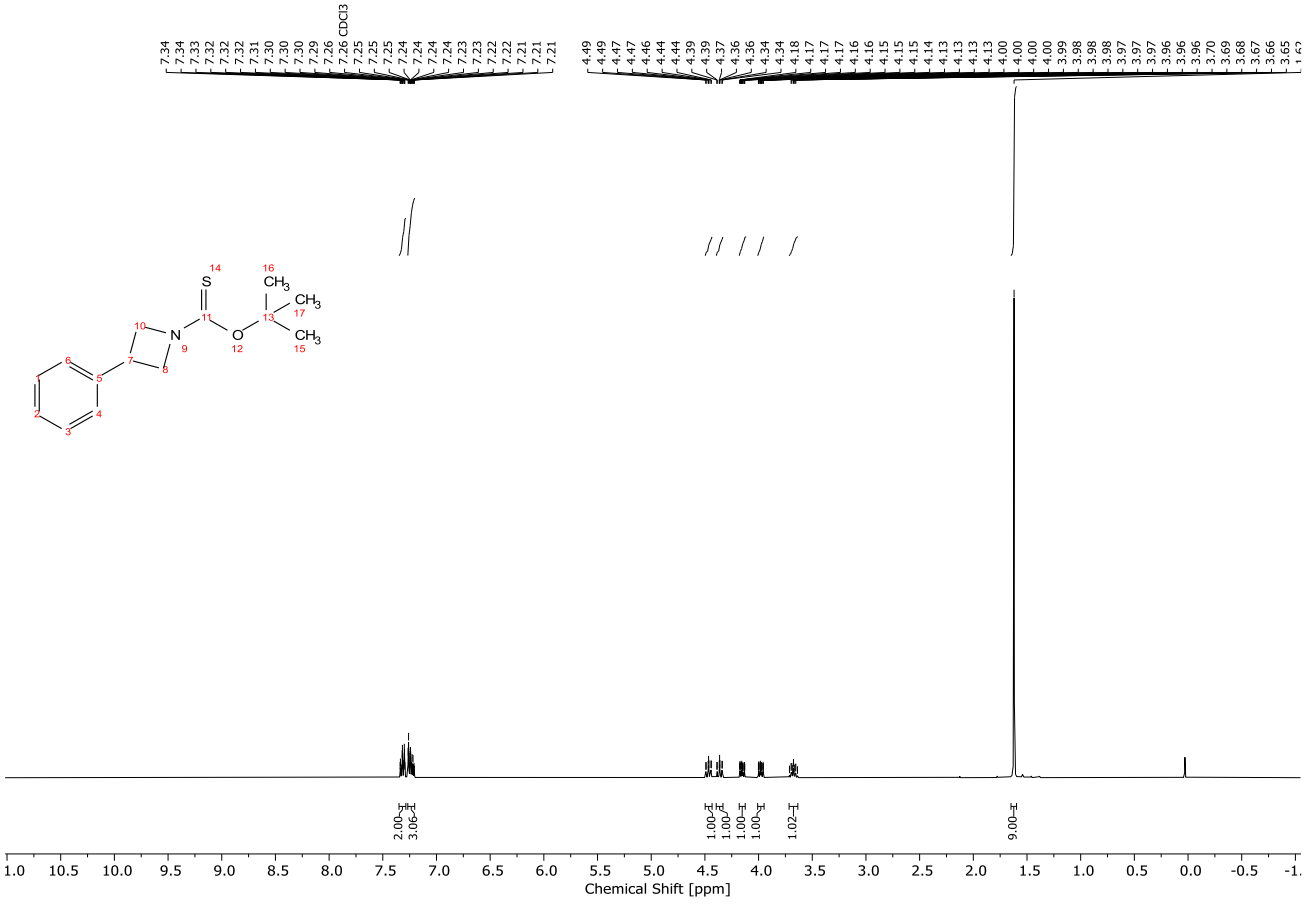
^{1}H NMR (400 MHz, $CDCl_3$) and **^{13}C NMR** (101 MHz, $CDCl_3$)

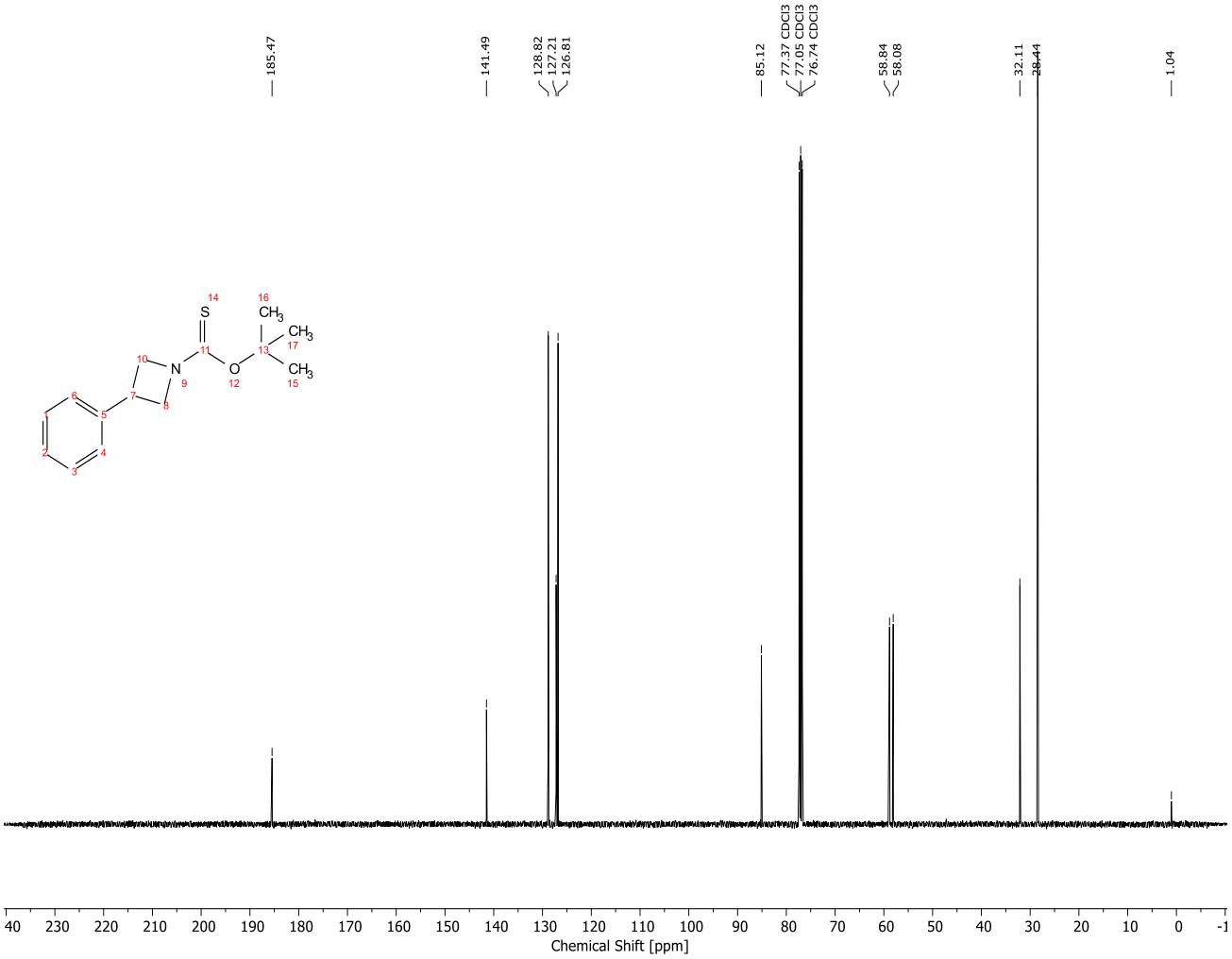



213.31
110.48
90.91
77.35 CDCl3
77.03 CDCl3
76.71 CDCl3
28.01
24.13
20.18
19.19
1.03
f1 (ppm)

O-(tert-butyl) 3-phenylazetidine-1-carbothioate

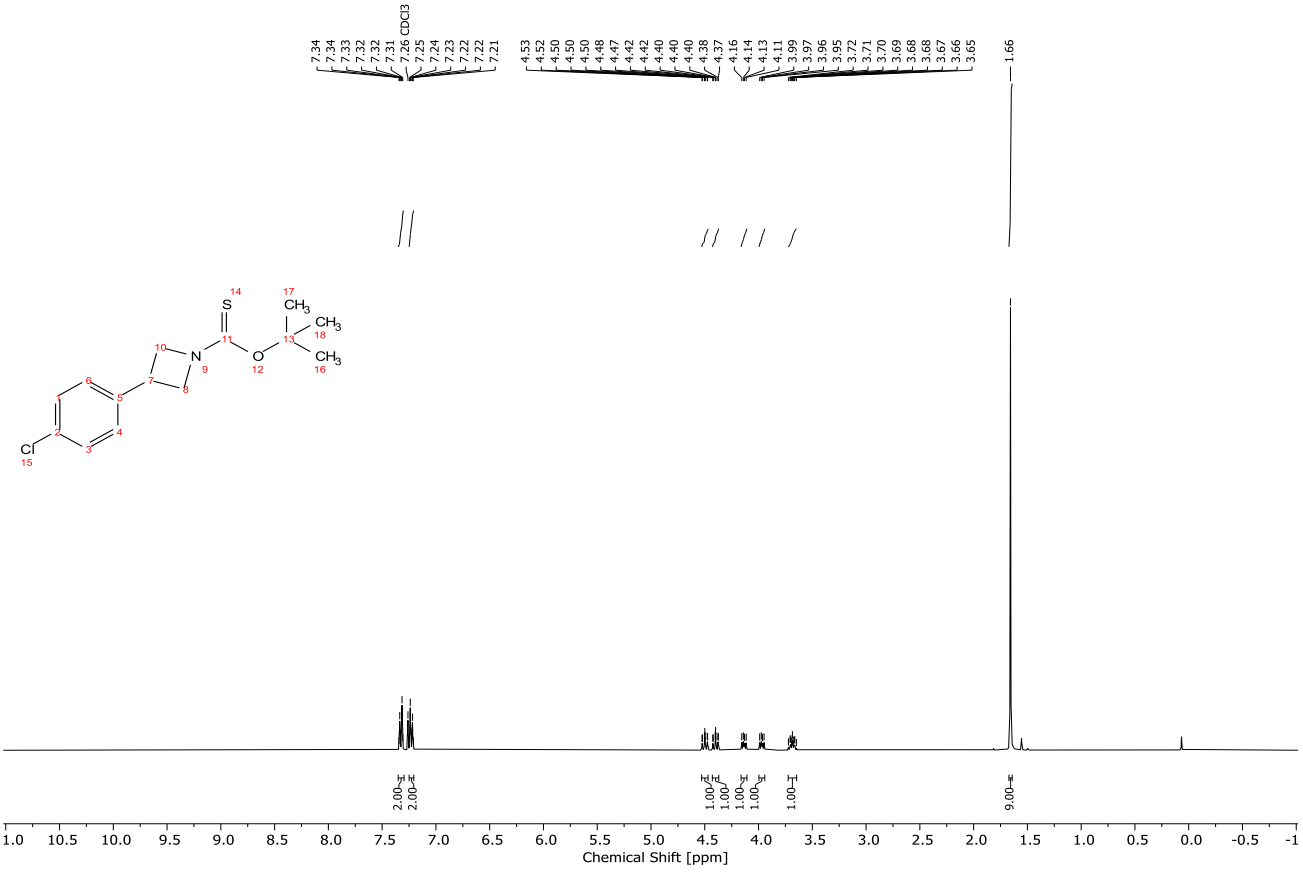
^{1}H NMR (400 MHz, $CDCl_3$) and **^{13}C NMR** (101 MHz, $CDCl_3$)

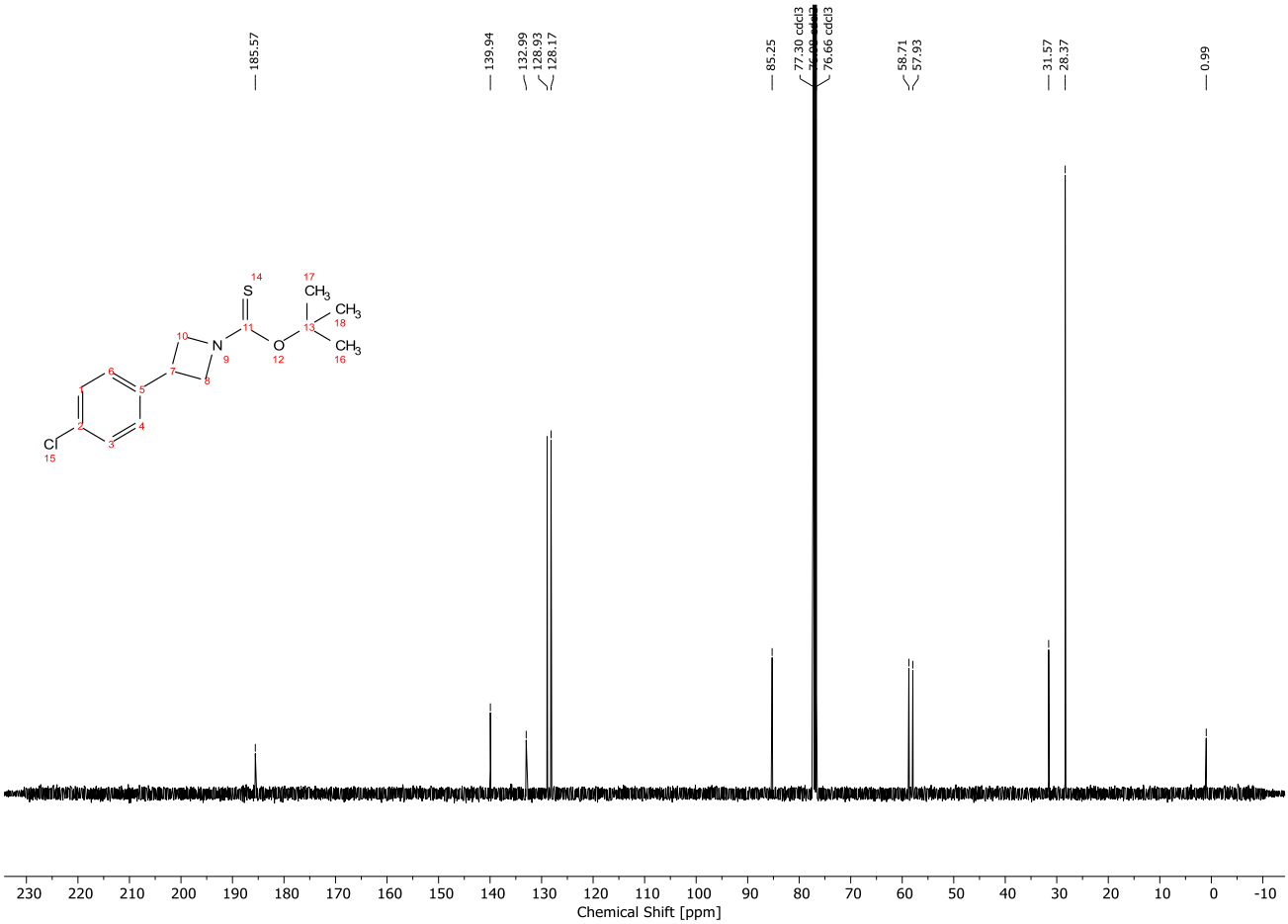



185.47
141.49
128.82
127.21
126.81
85.12
77.37 CDCl3
77.05 CDCl3
76.74 CDCl3
58.84
58.08
32.11
28.44
1.04
S
CH3
CH3
CH3
N
O
Chemical Shift [ppm]

O-(tert-butyl) 3-(4-chlorophenyl)azetidine-1-carbothioate

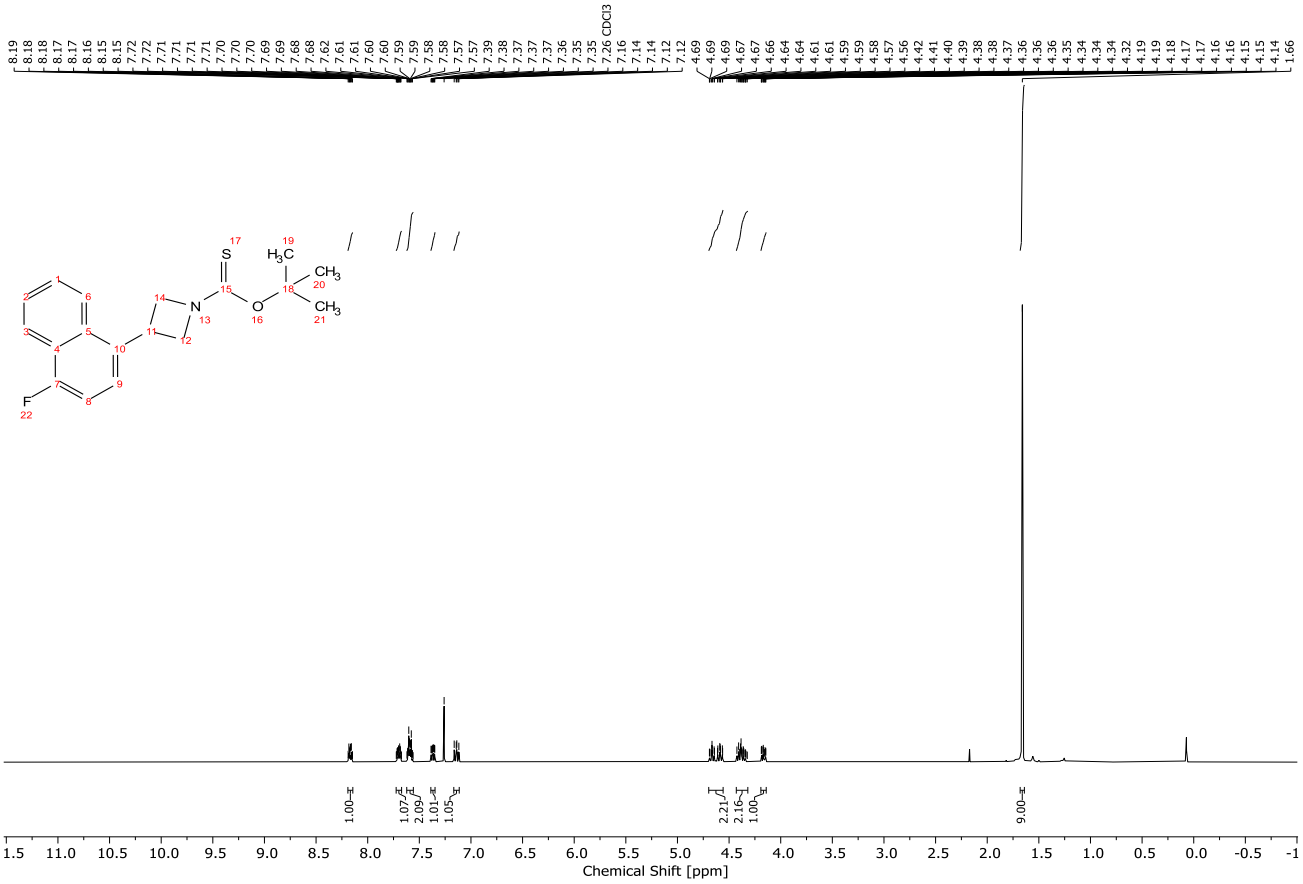
^{1}H NMR (400 MHz, $CDCl_3$) and **^{13}C NMR** (101 MHz, $CDCl_3$)

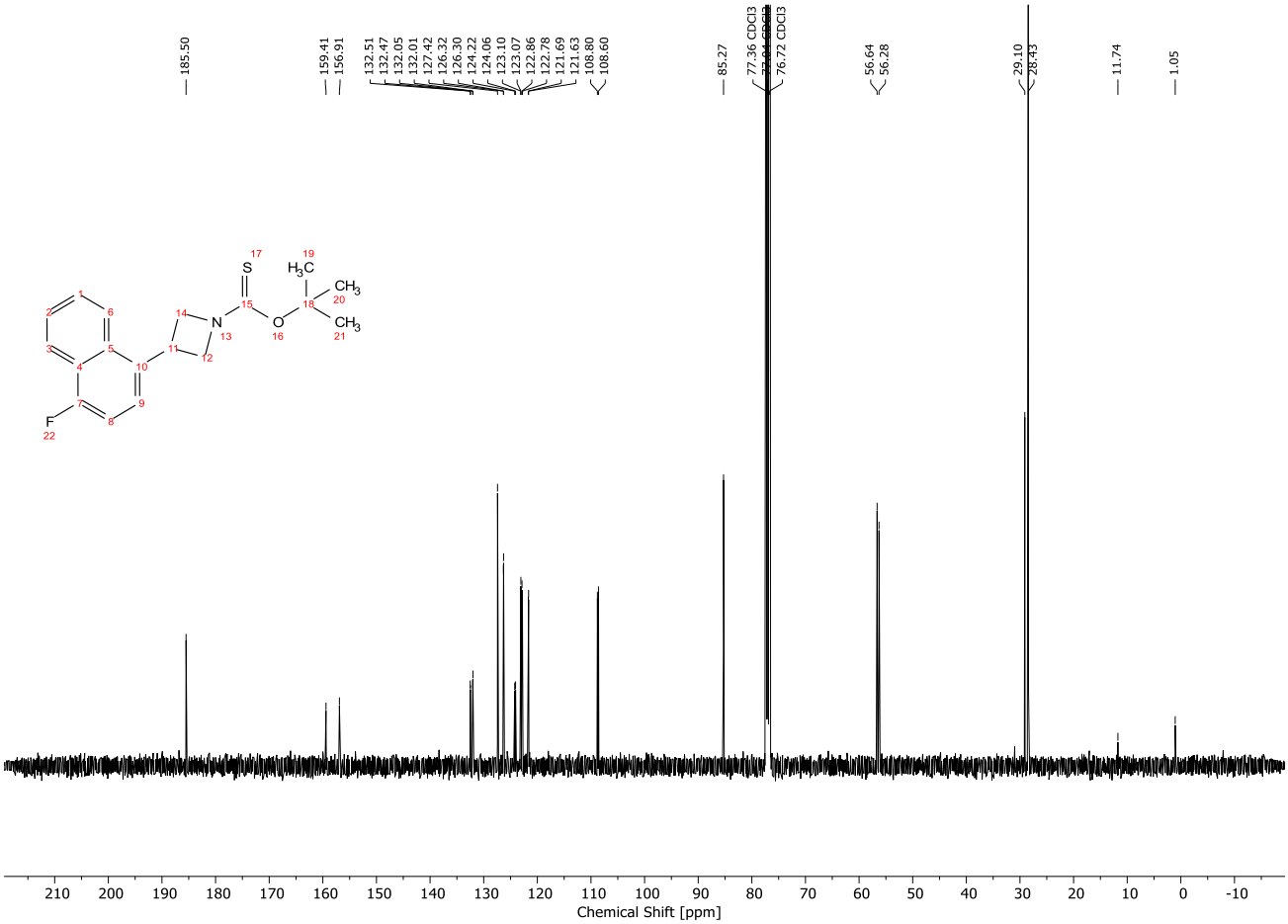


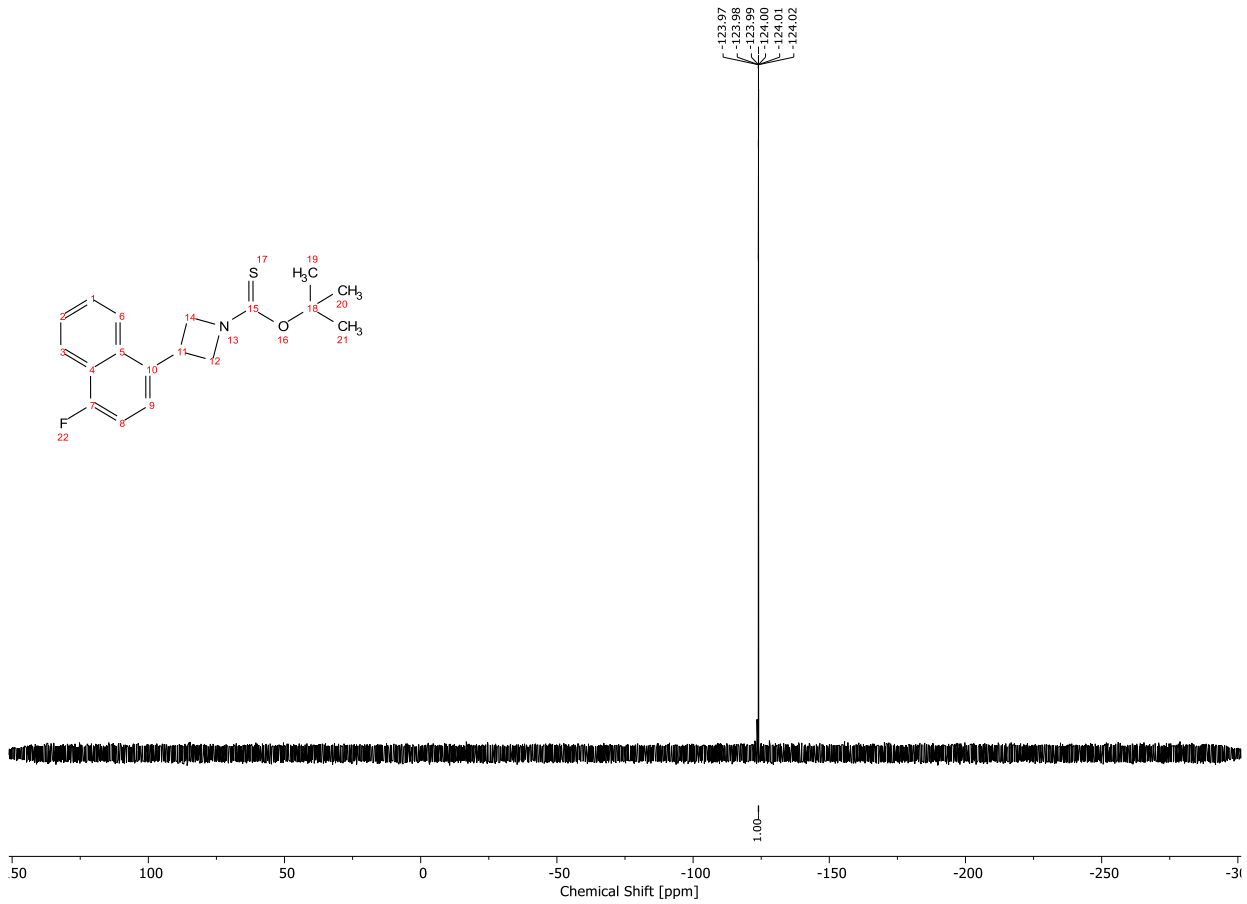

185.57
139.94
132.99
128.93
128.17
85.25
77.30 cdcl3
76.66 cdcl3
58.71
57.93
31.57
28.37
0.99
S
CH3
CH3
CH3
N
O
Cl
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift [ppm]

O-(tert-butyl) 3-(4-fluoronaphthalen-1-yl)azetidine-1-carbothioate

^{1}H NMR (400 MHz, $CDCl_3$), **^{13}C NMR** (101 MHz, $CDCl_3$) and **^{19}F NMR** (377 MHz, $CDCl_3$)

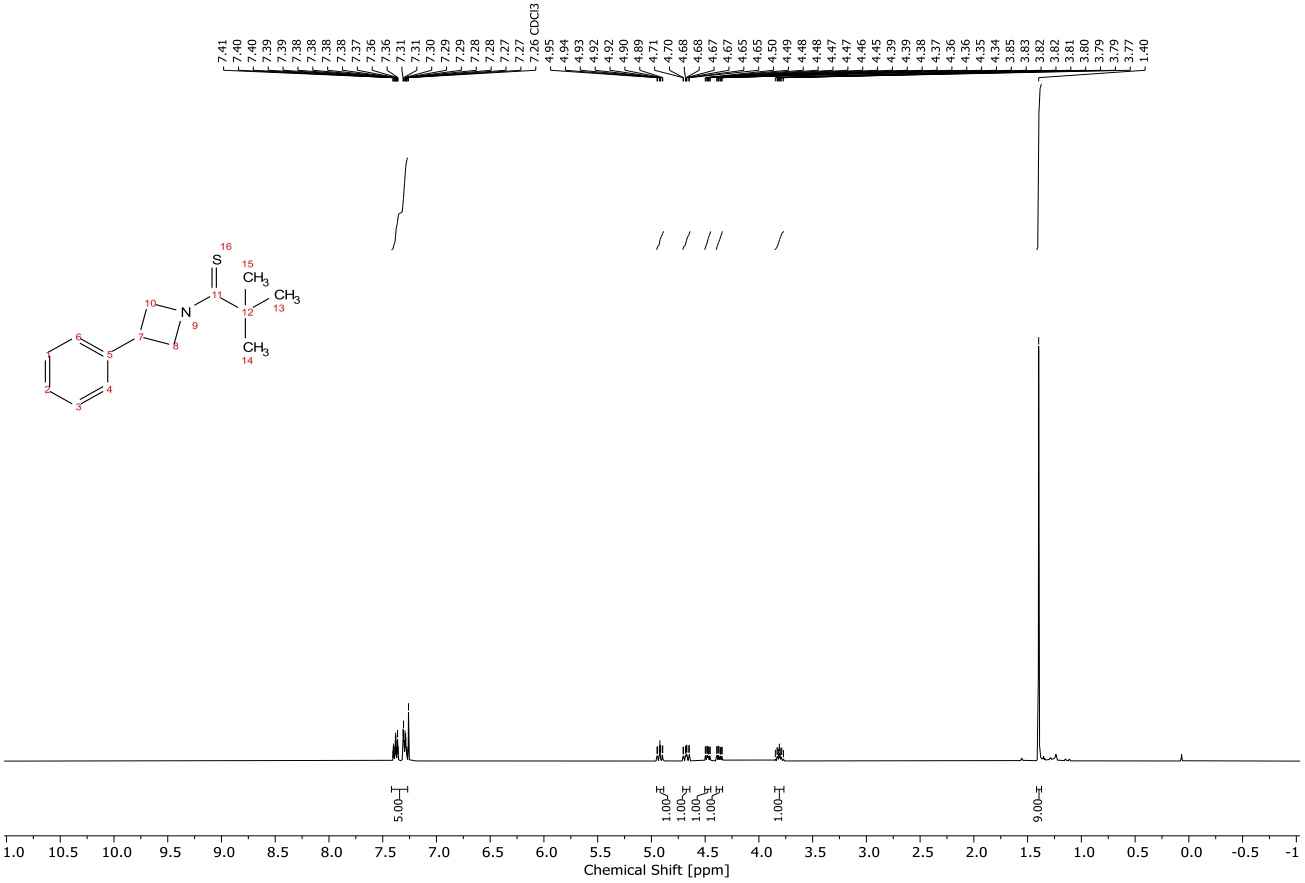


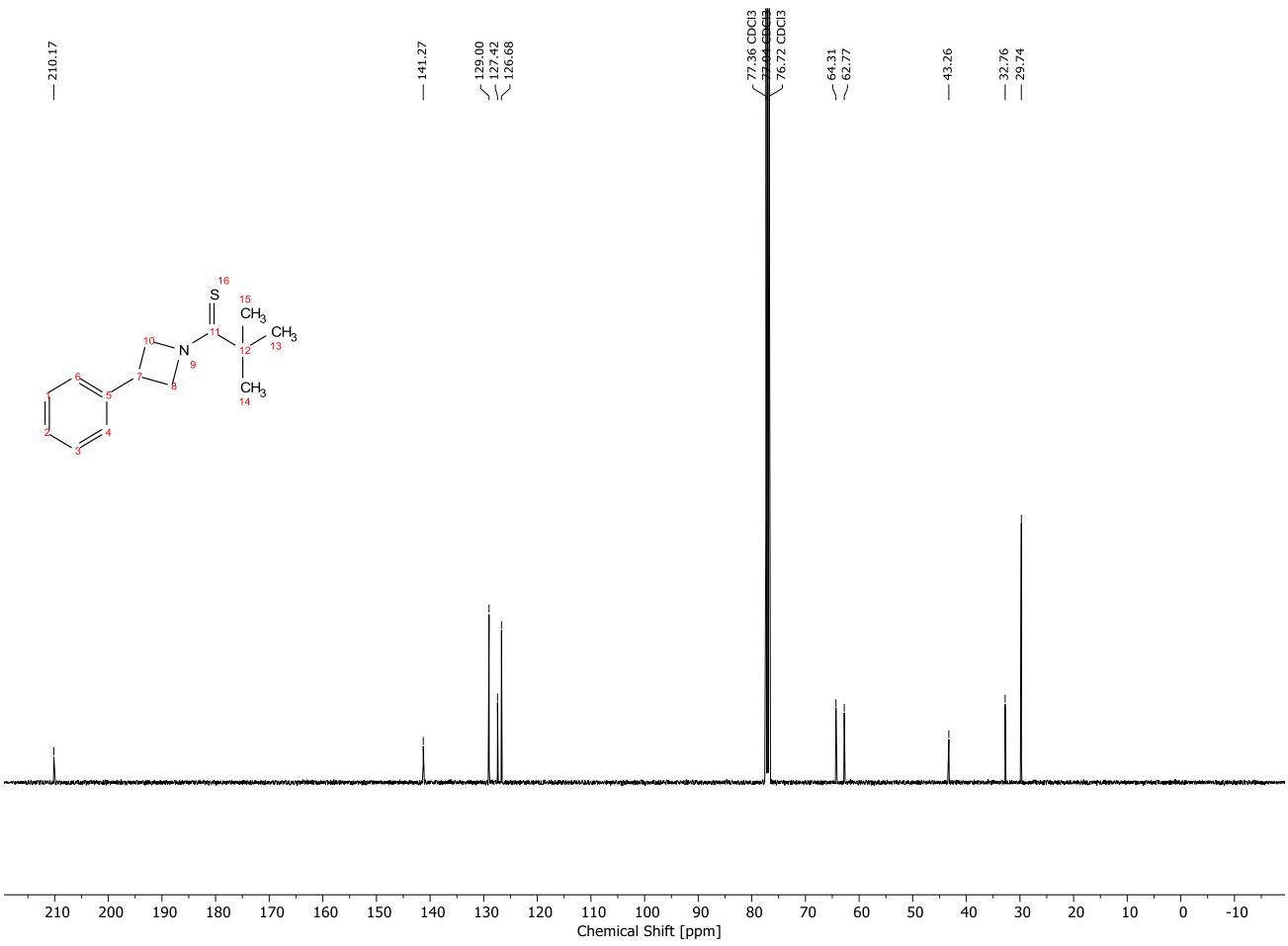

185.50
159.41
156.91
132.51
132.47
132.05
132.01
127.42
126.32
126.30
124.22
124.06
123.10
123.07
122.86
122.78
121.69
121.63
108.80
108.60
85.27
77.36 CDCl3
76.72 CDCl3
56.64
56.28
29.10
28.43
11.74
1.05
Chemical Shift [ppm]


-123.97
-123.98
-123.99
-124.00
-124.01
-124.02
1.00
Chemical Shift [ppm]

2,2-dimethyl-1-(3-phenylazetidin-1-yl)propane-1-thione

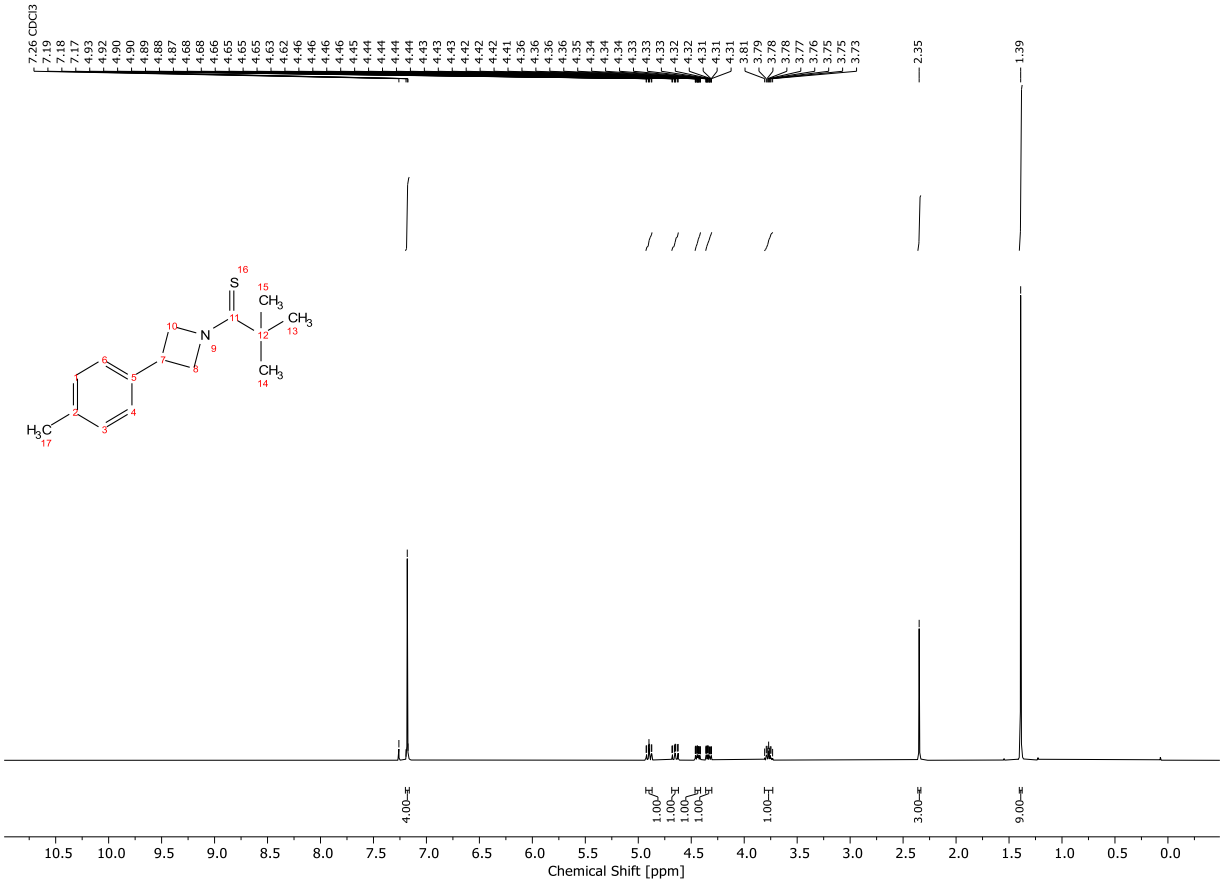
^{1}H NMR (400 MHz, $CDCl_3$) and **^{13}C NMR** (101 MHz, $CDCl_3$)

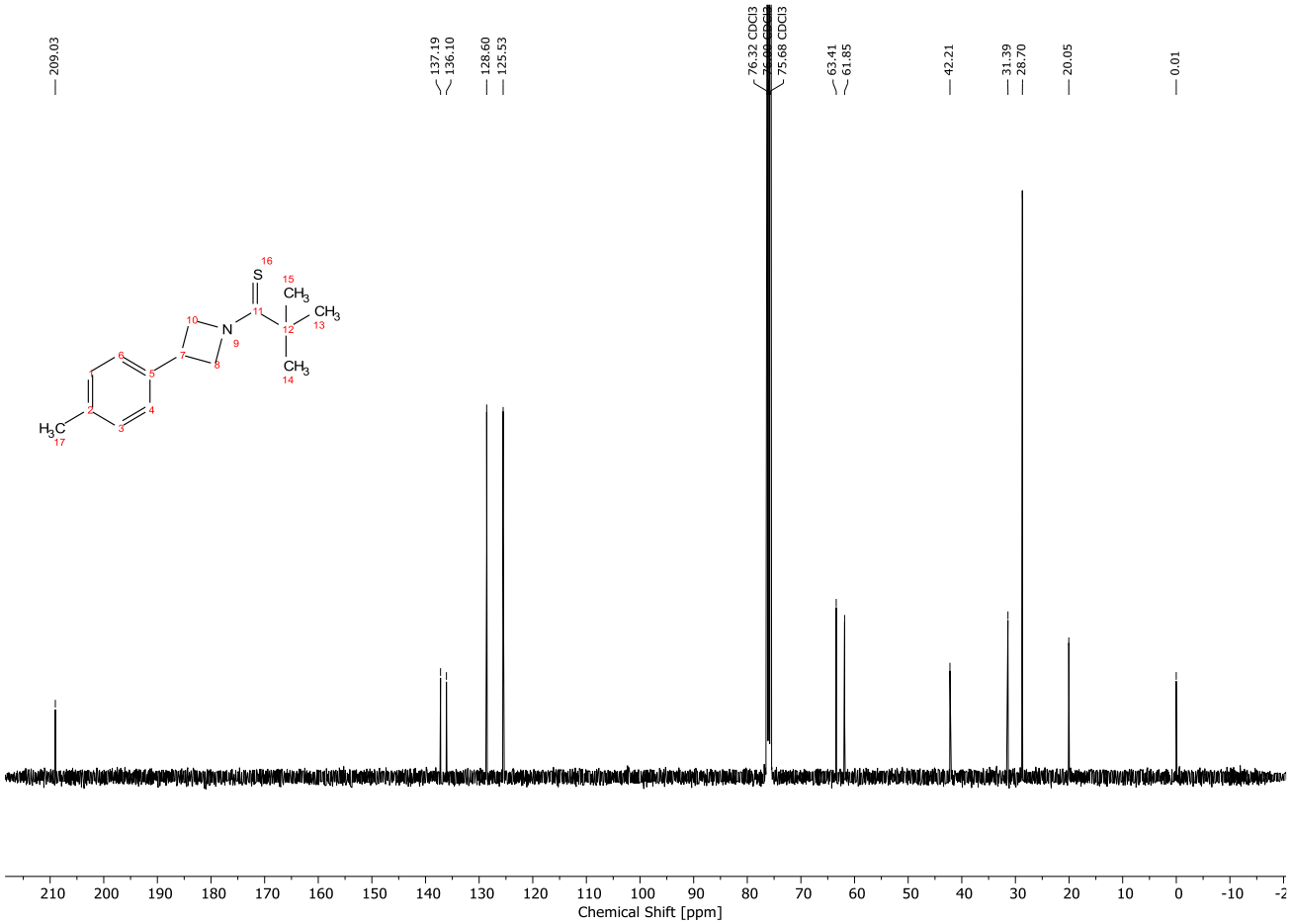



210.17
141.27
129.00
127.42
126.68
77.36 CDCl3
77.04 CDCl3
76.72 CDCl3
64.31
62.77
43.26
32.76
29.74
S
CH3
CH3
CH3
N
Chemical Shift [ppm]

2,2-dimethyl-1-(3-(p-tolyl)azetidin-1-yl)propane-1-thione

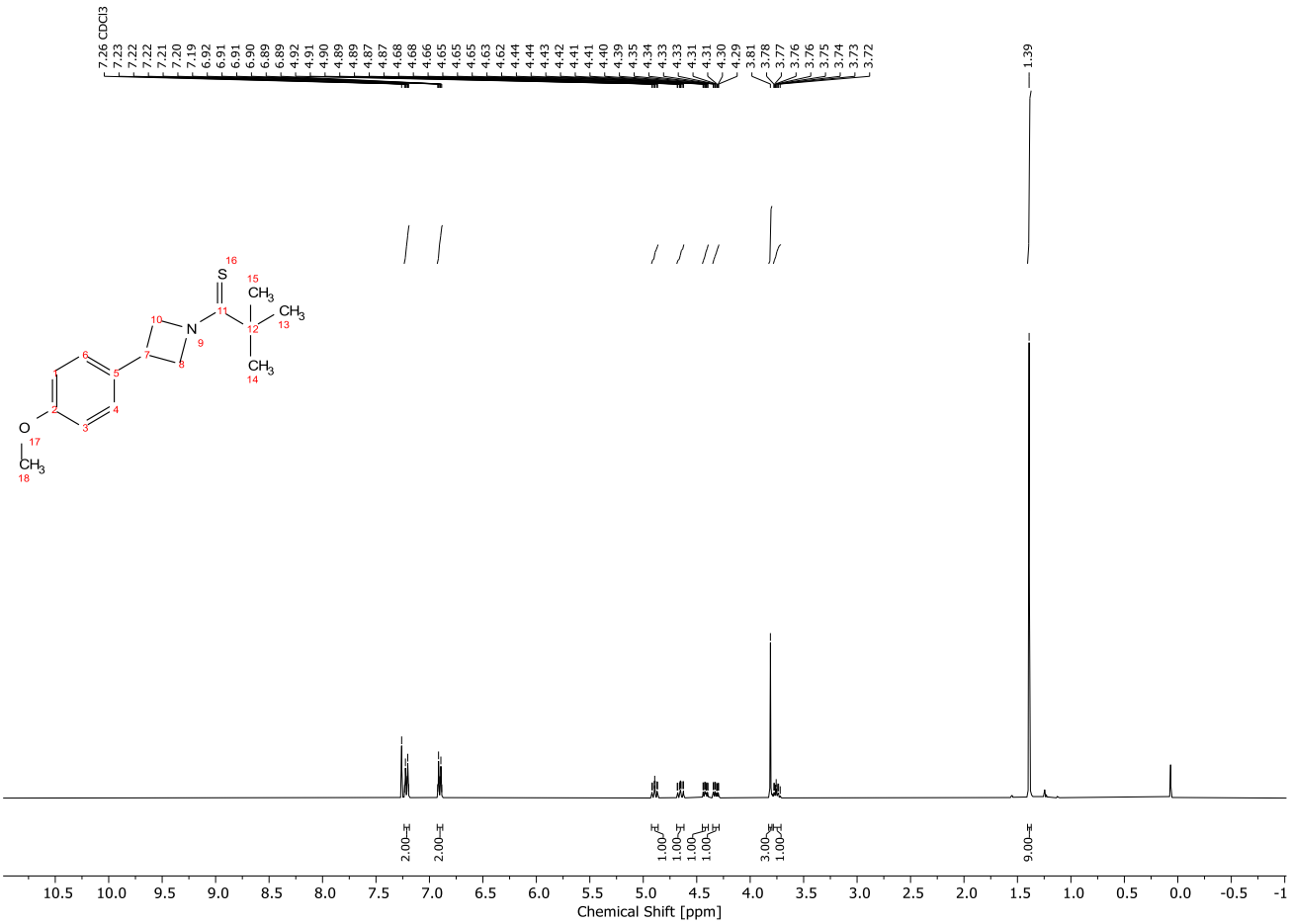
^{1}H NMR (400 MHz, $CDCl_3$) and **^{13}C NMR** (101 MHz, $CDCl_3$)

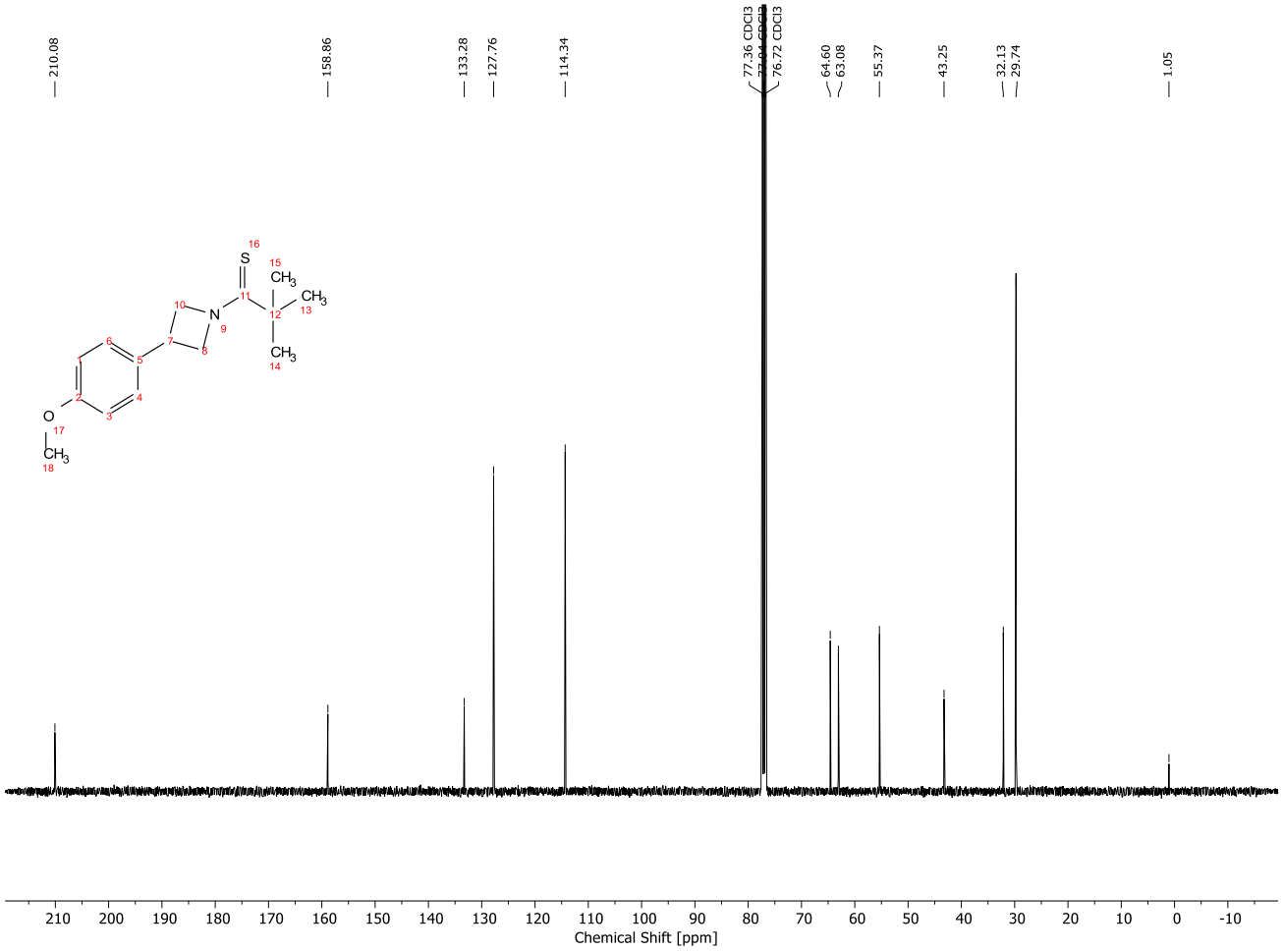



209.03
137.19
136.10
128.60
125.53
76.32 CDCl3
76.68 CDCl3
75.68 CDCl3
63.41
61.85
42.21
31.39
28.70
20.05
0.01
S
16
15
CH3
CH3
13
N
10
9
11
12
CH3
14
7
8
6
5
1
2
3
4
H3C
17
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift [ppm]

1-(3-(4-methoxyphenyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione

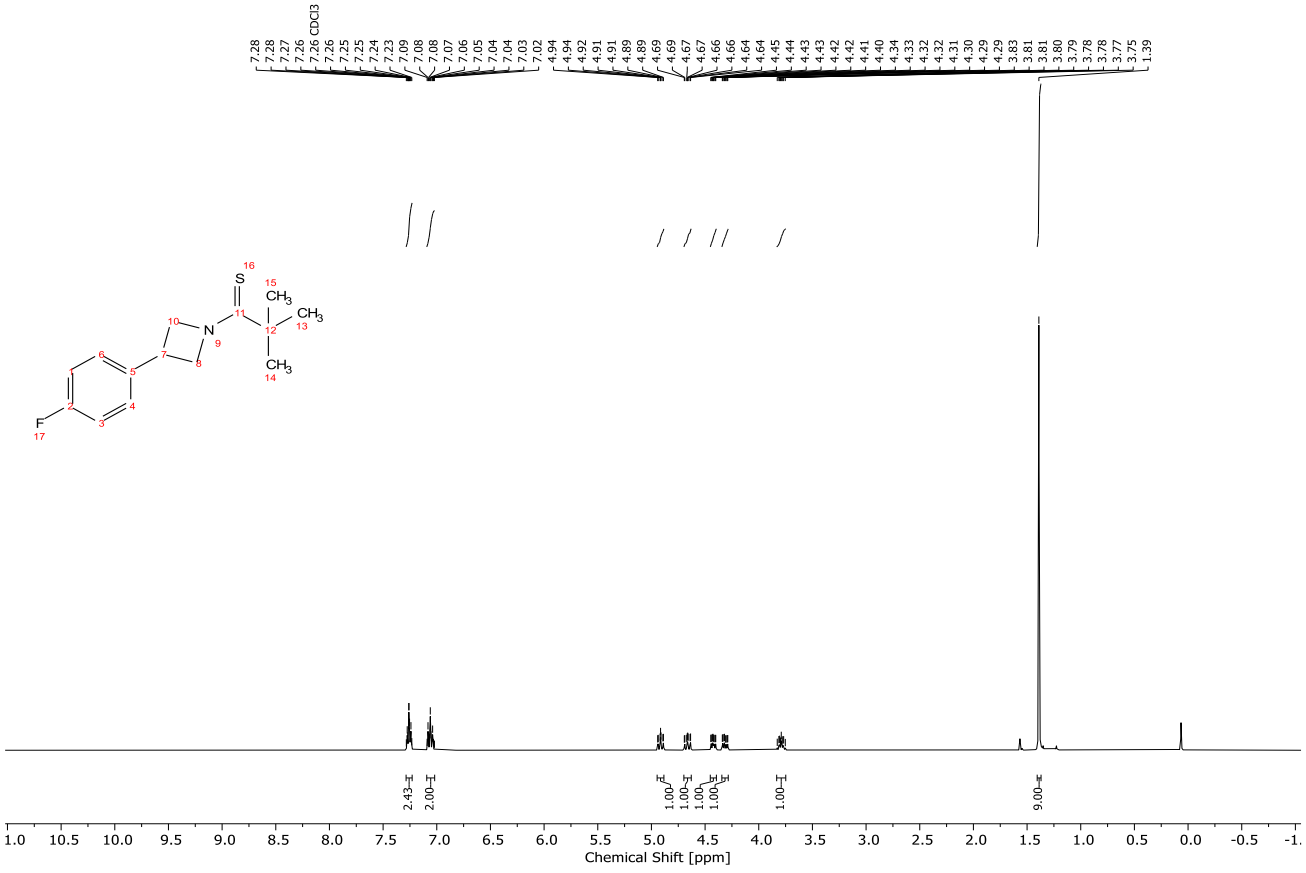
^{1}H NMR (400 MHz, $CDCl_3$) and **^{13}C NMR** (101 MHz, $CDCl_3$)

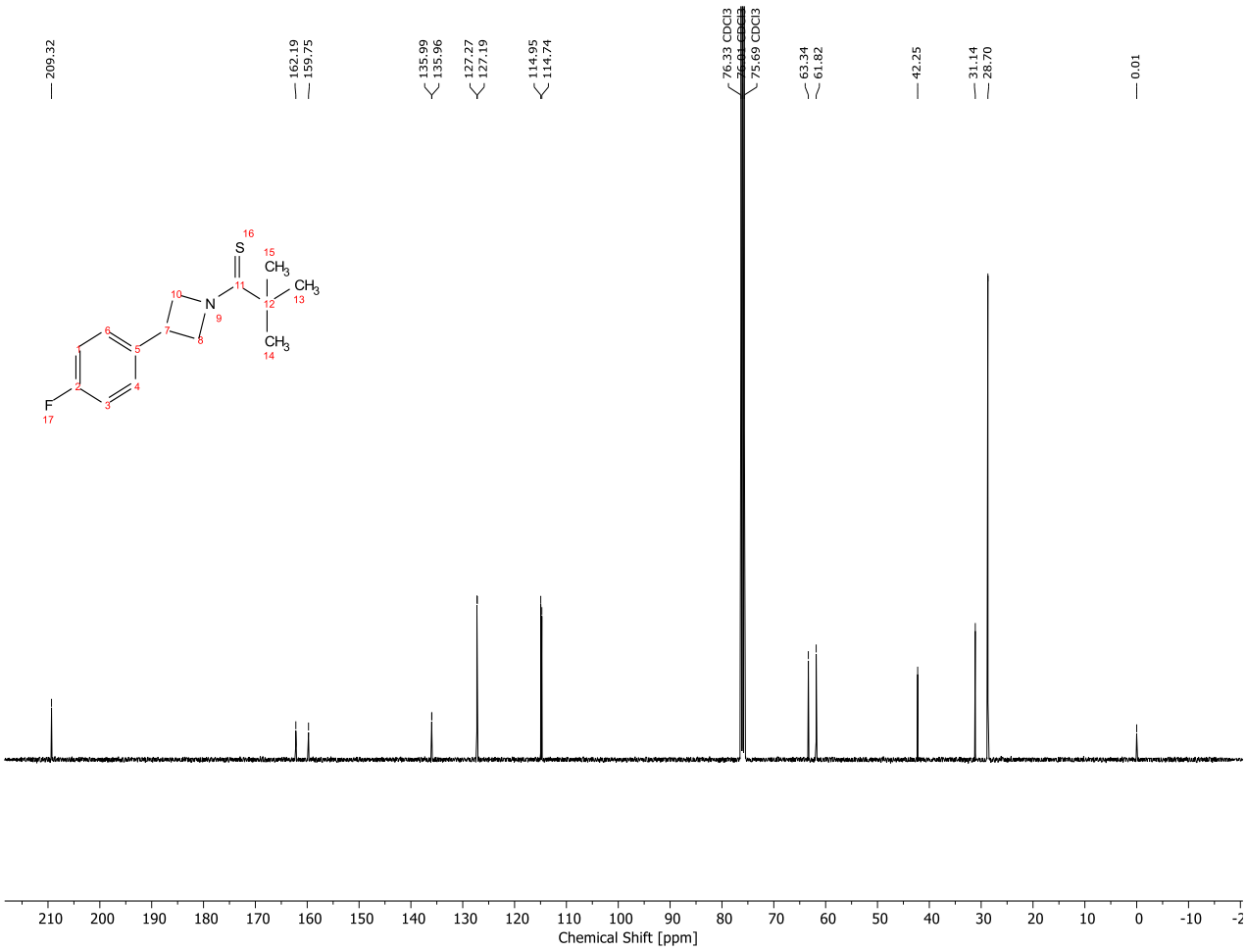


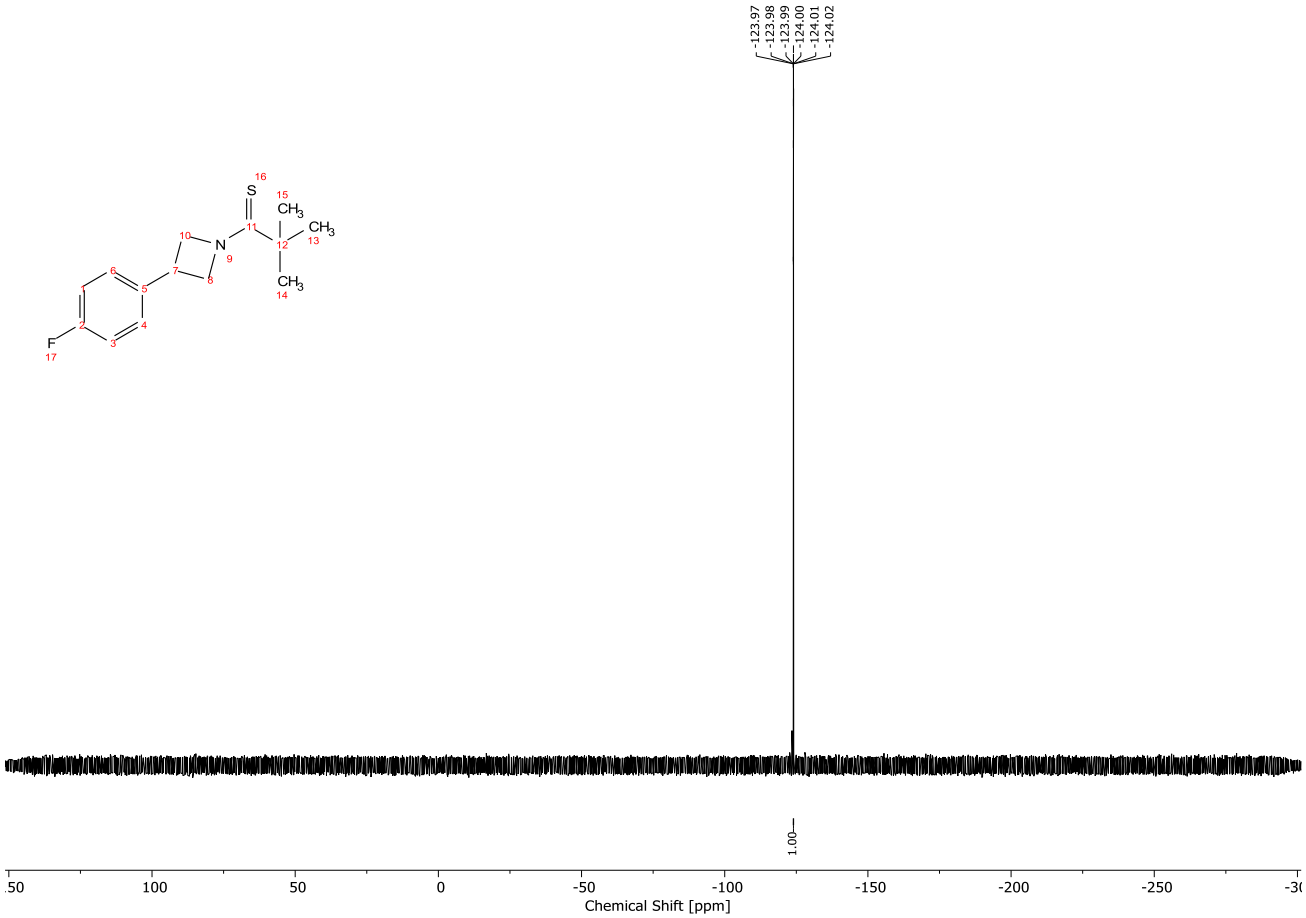

210.08
158.86
133.28
127.76
114.34
77.36 CDCl3
77.04 CDCl3
76.72 CDCl3
64.60
63.08
55.37
43.25
32.13
29.74
1.05
Chemical Shift [ppm]

1-(3-(4-fluorophenyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione

^{1}H NMR (400 MHz, $CDCl_3$), **^{13}C NMR** (101 MHz, $CDCl_3$) and **^{19}F NMR** (377 MHz, $CDCl_3$)

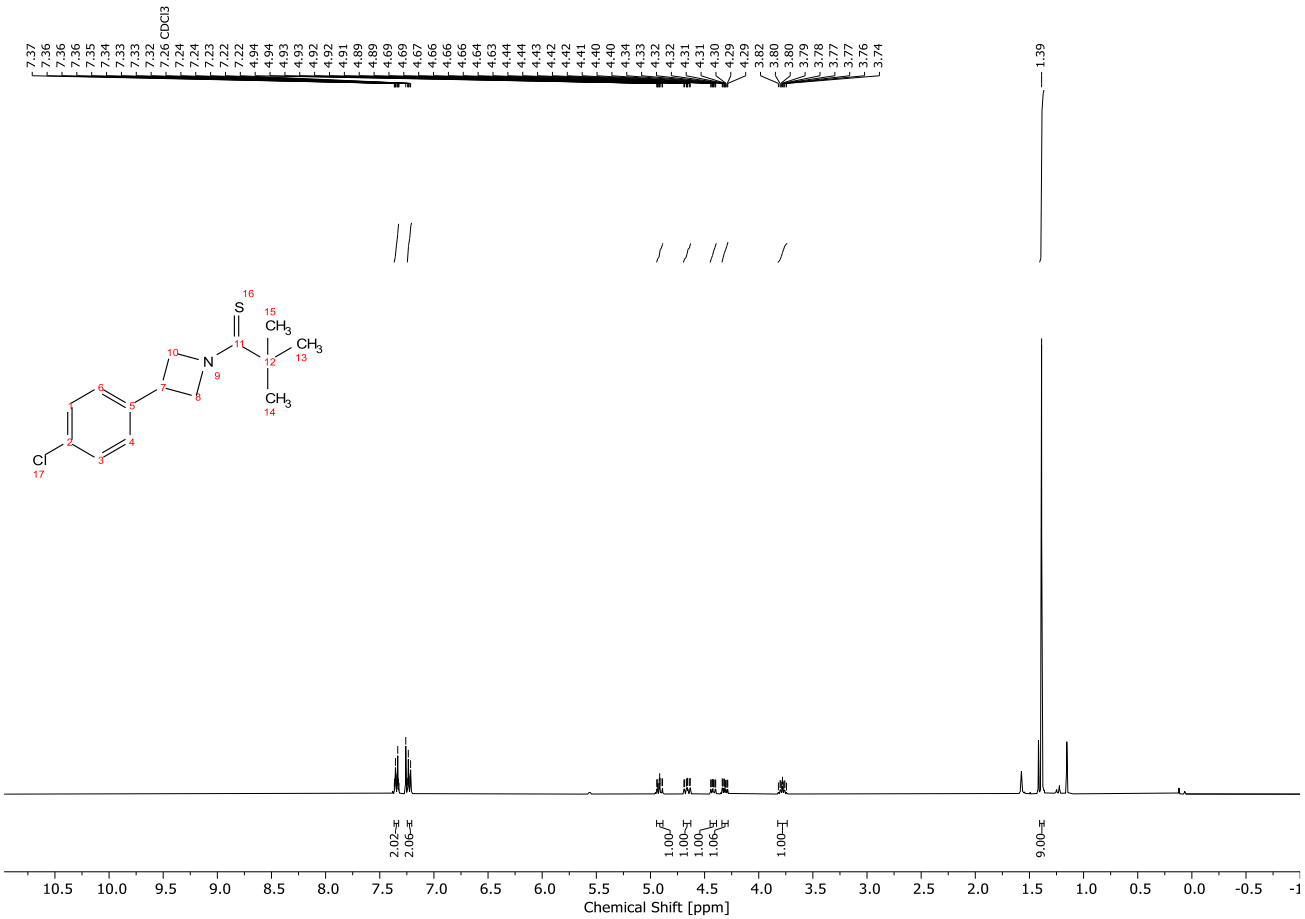


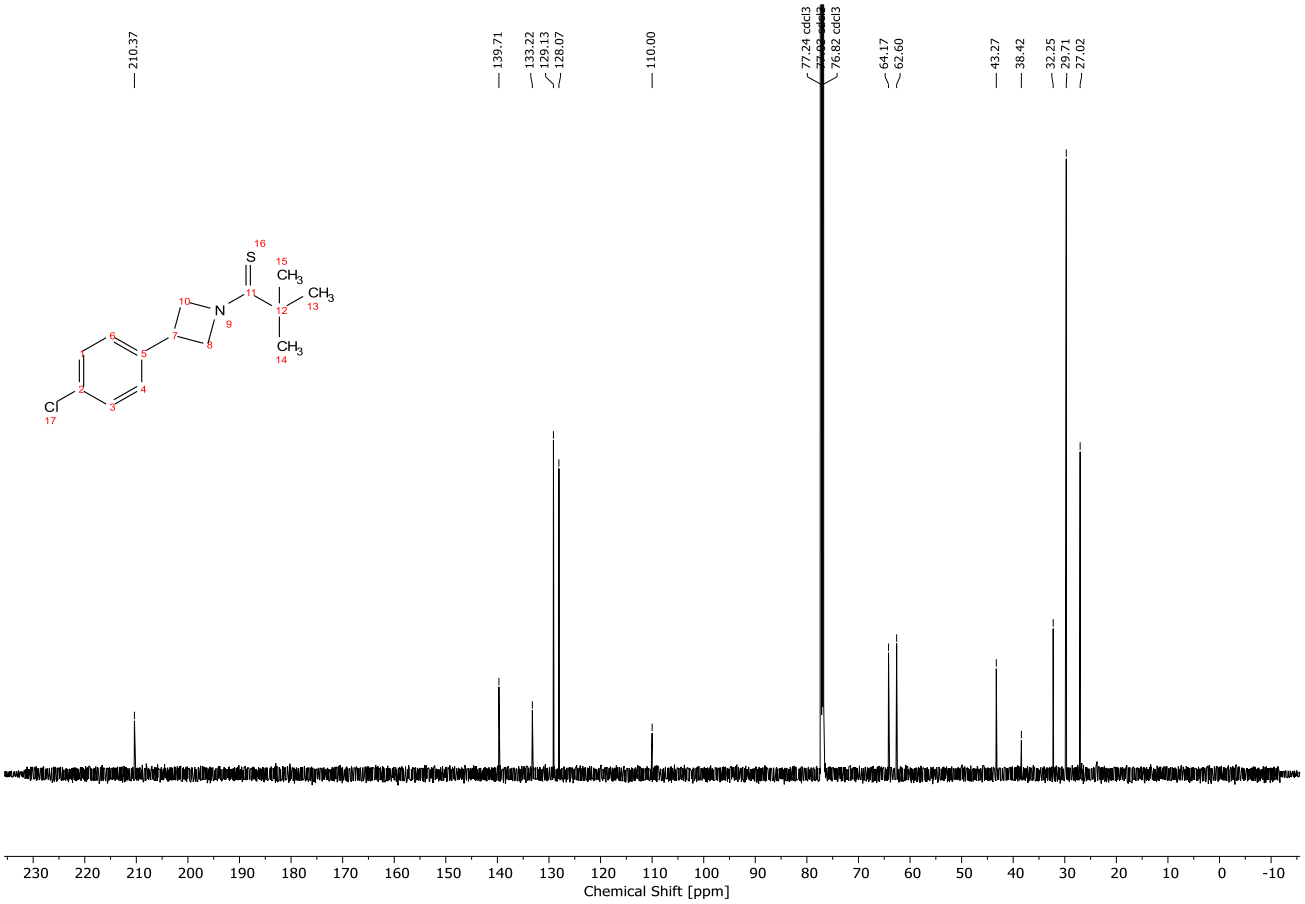

209.32
162.19
159.75
135.99
135.96
127.27
127.19
114.95
114.74
76.33 CDCl3
75.69 CDCl3
63.34
61.82
42.25
31.14
28.70
0.01
S
16
15
CH3
CH3
13
10
N
9
11
12
CH3
14
7
8
6
5
1
2
4
3
F
17
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift [ppm]


-123.97
-123.98
-123.99
-124.00
-124.01
-124.02
S
16
15
CH3
CH3
13
10
N
9
11
12
CH3
14
6
7
5
8
1
2
4
3
F
17
1.00
50
100
50
0
-50
-100
-150
-200
-250
Chemical Shift [ppm]

1-(3-(4-chlorophenyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione

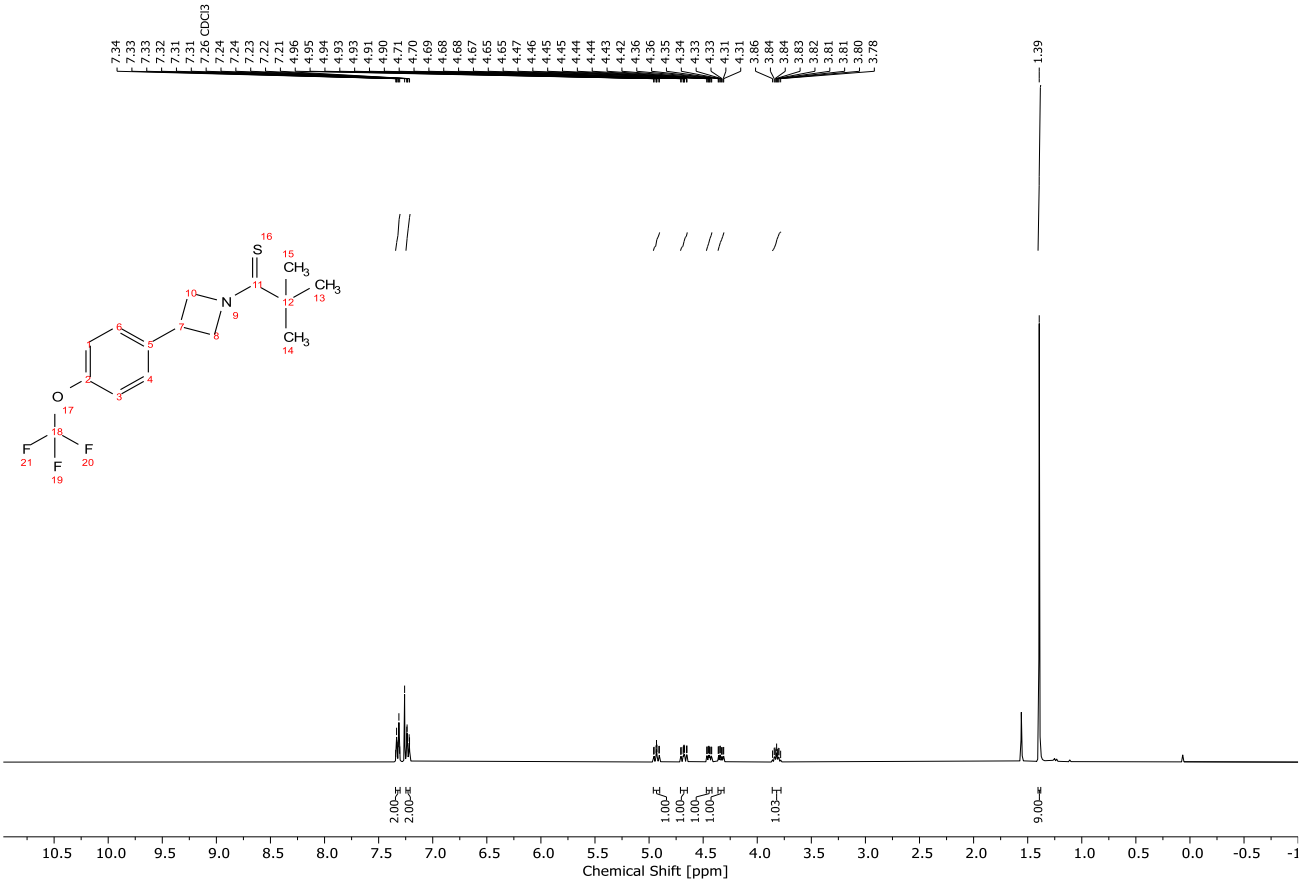
^{1}H NMR (400 MHz, $CDCl_3$) and **^{13}C NMR** (151 MHz, $CDCl_3$)

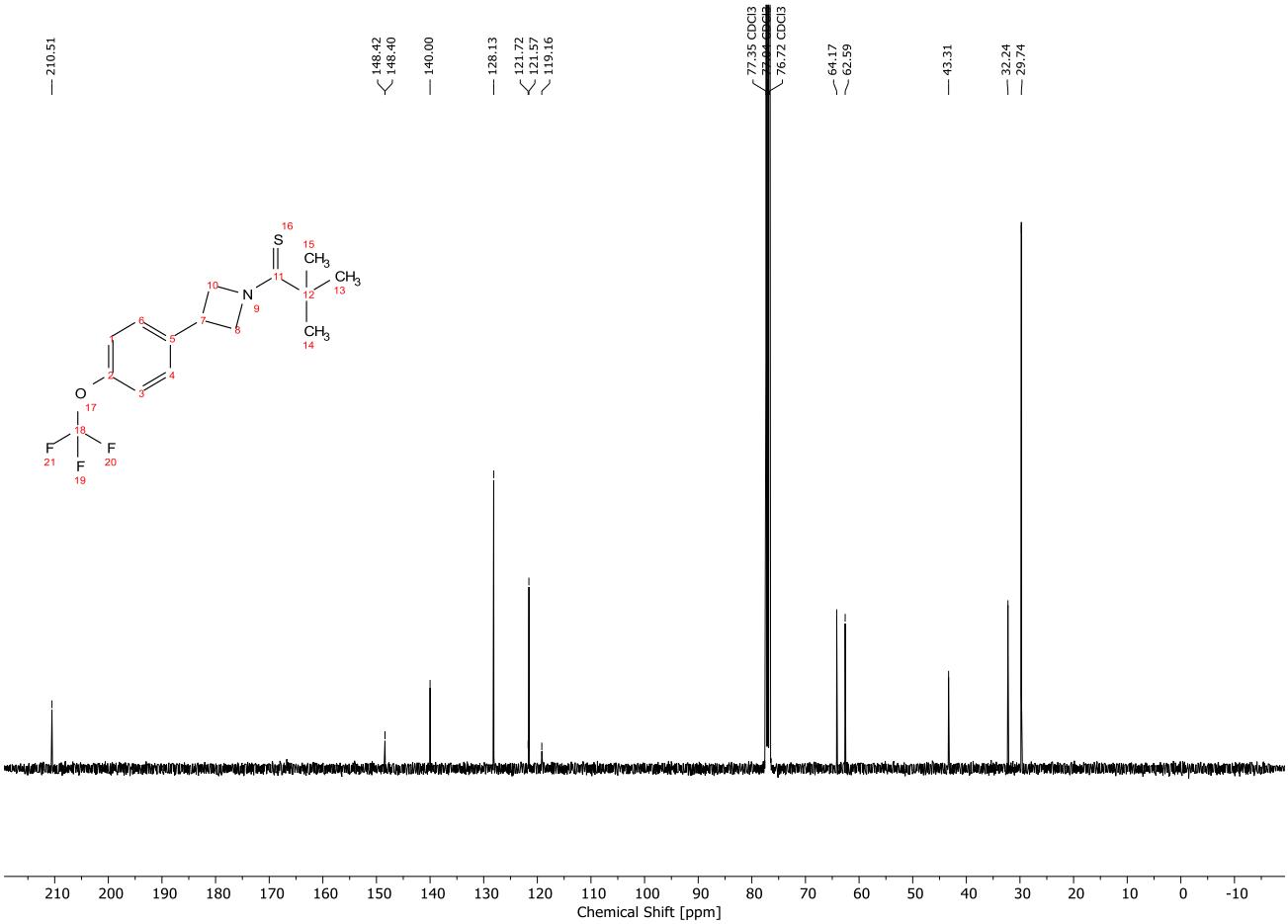


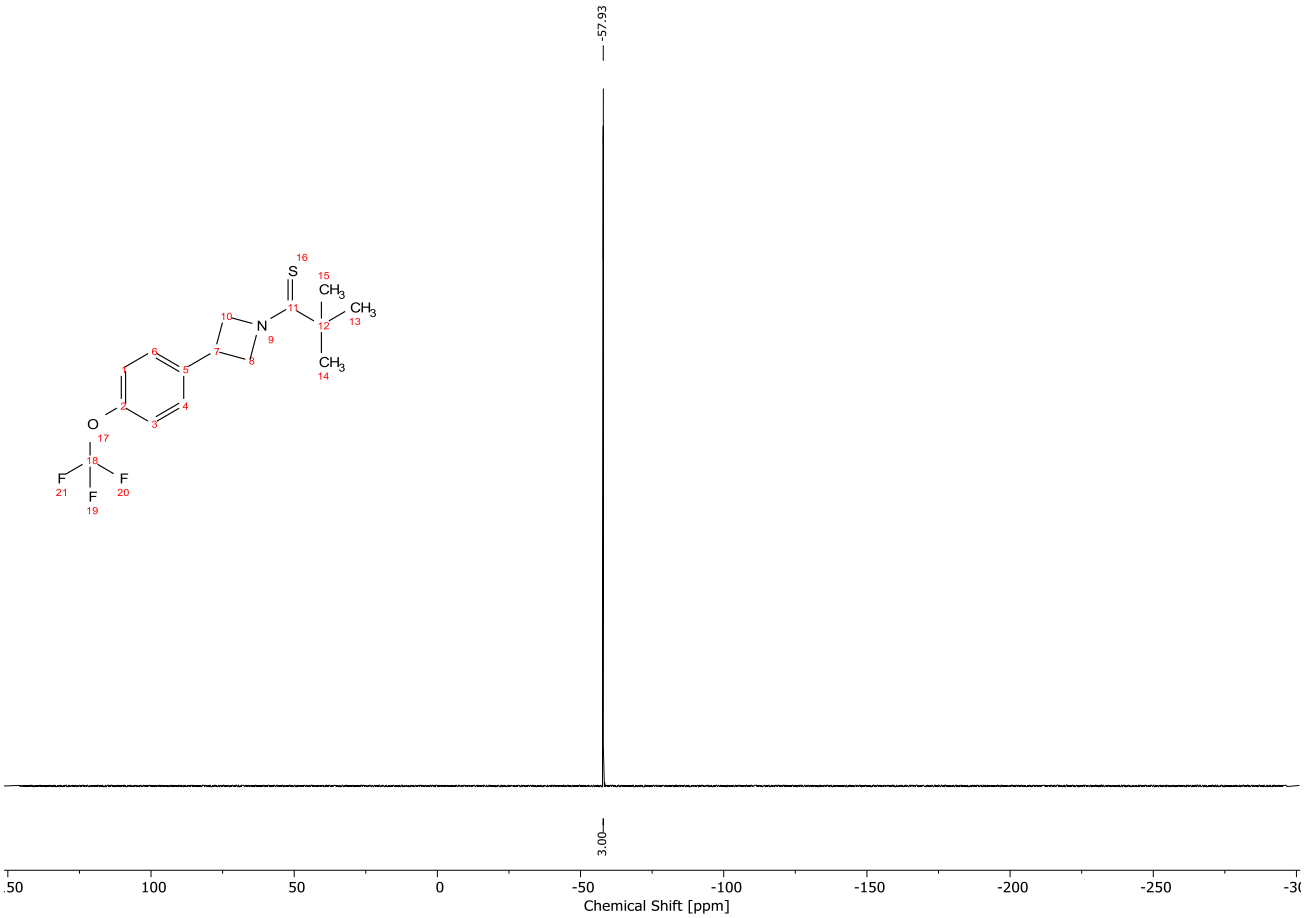

210.37
139.71
133.22
129.13
128.07
110.00
77.24 cdcl3
76.82 cdcl3
64.17
62.60
43.27
38.42
32.25
29.71
27.02
S
CH3
CH3
CH3
N
Cl
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift [ppm]

2,2-dimethyl-1-(3-(4-(trifluoromethoxy)phenyl)azetidin-1-yl)propane-1-thione

^{1}H NMR (400 MHz, $CDCl_3$), **^{13}C NMR** (101 MHz, $CDCl_3$) and **^{19}F NMR** (377 MHz, $CDCl_3$)

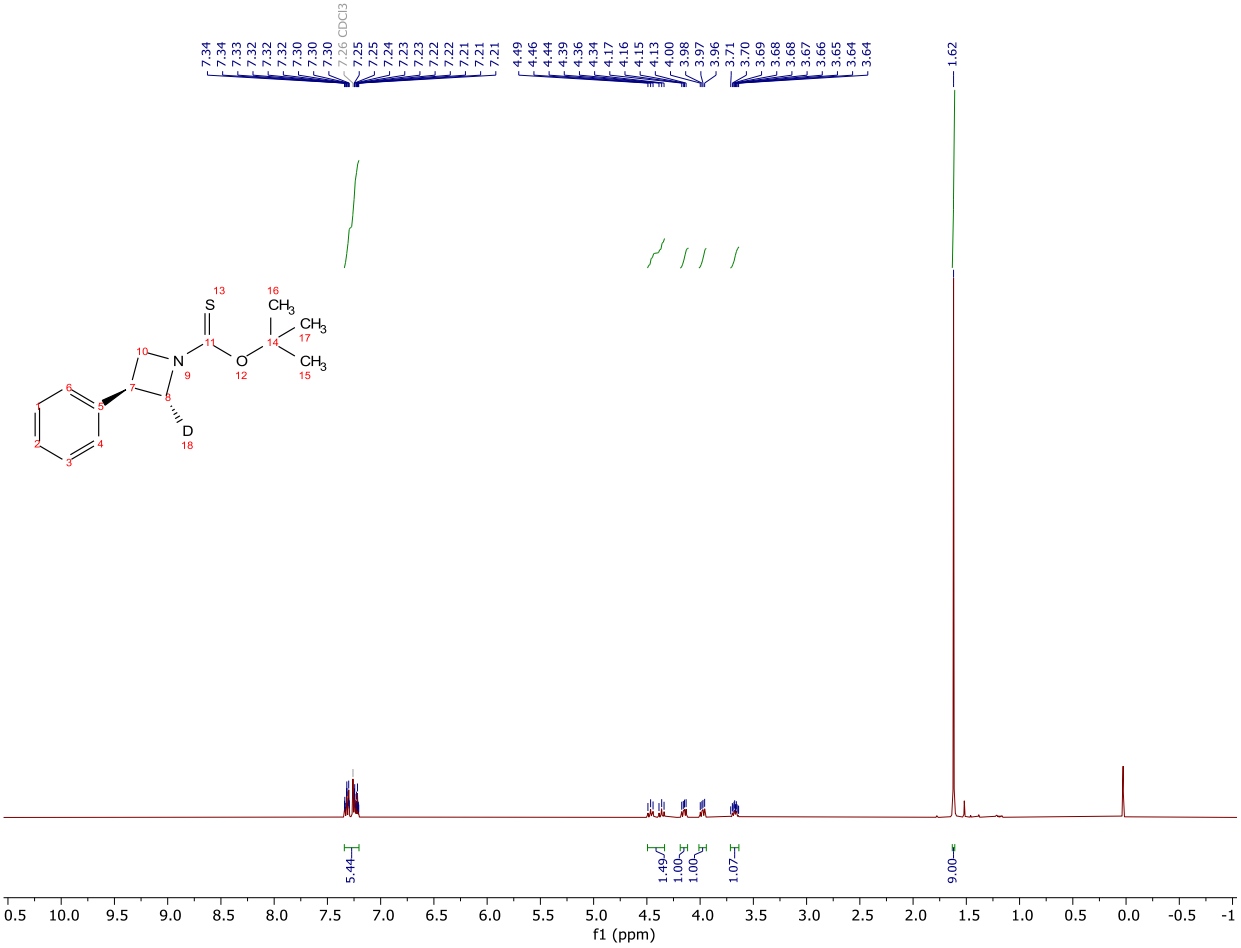


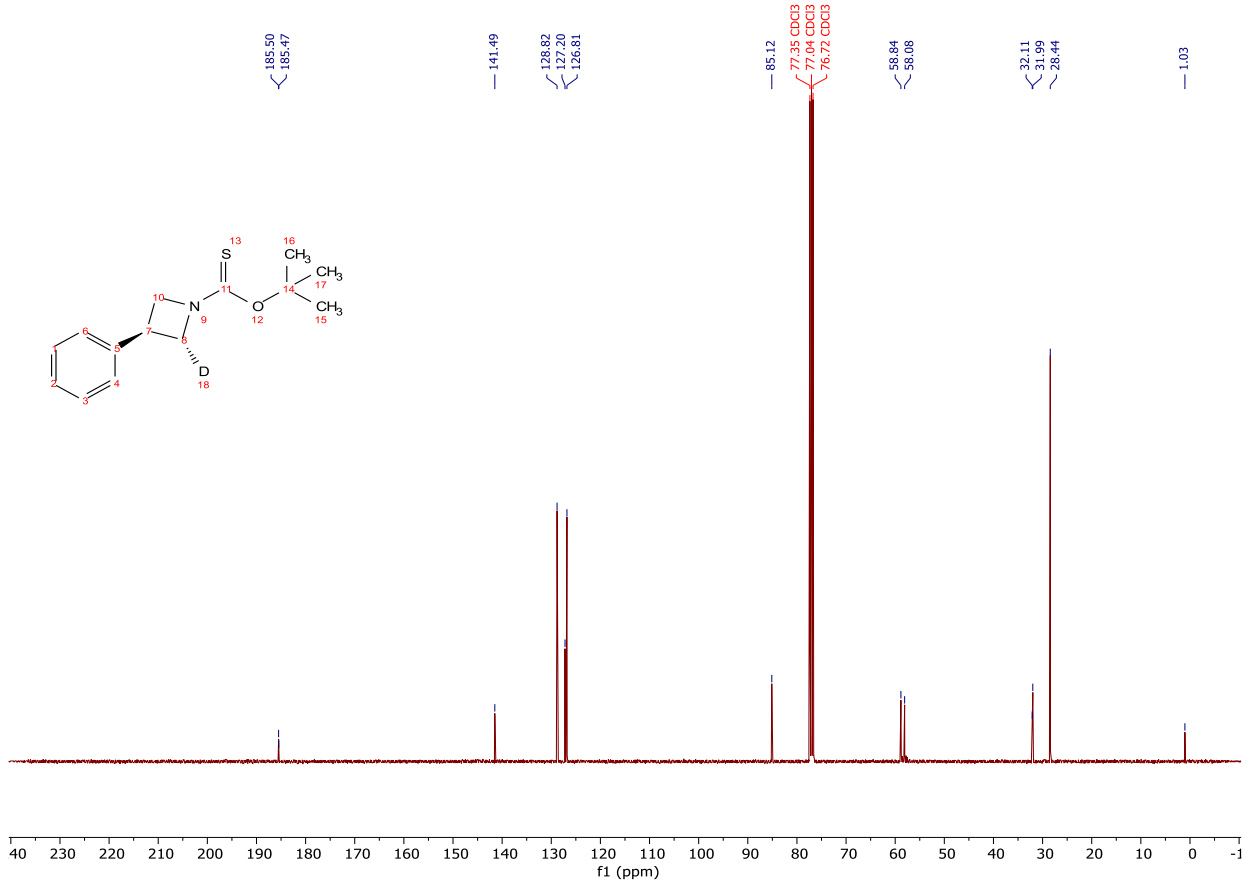

210.51
148.42
148.40
140.00
128.13
121.72
121.57
119.16
77.35 CDCl3
77.04 CDCl3
76.72 CDCl3
64.17
62.59
43.31
32.24
29.74
Chemical Shift [ppm]


-57.93
3.00
Chemical Shift [ppm]

(O-(tert-butyl) (2R,3S)-3-phenylazetidine-1-carbothioate-2-d)

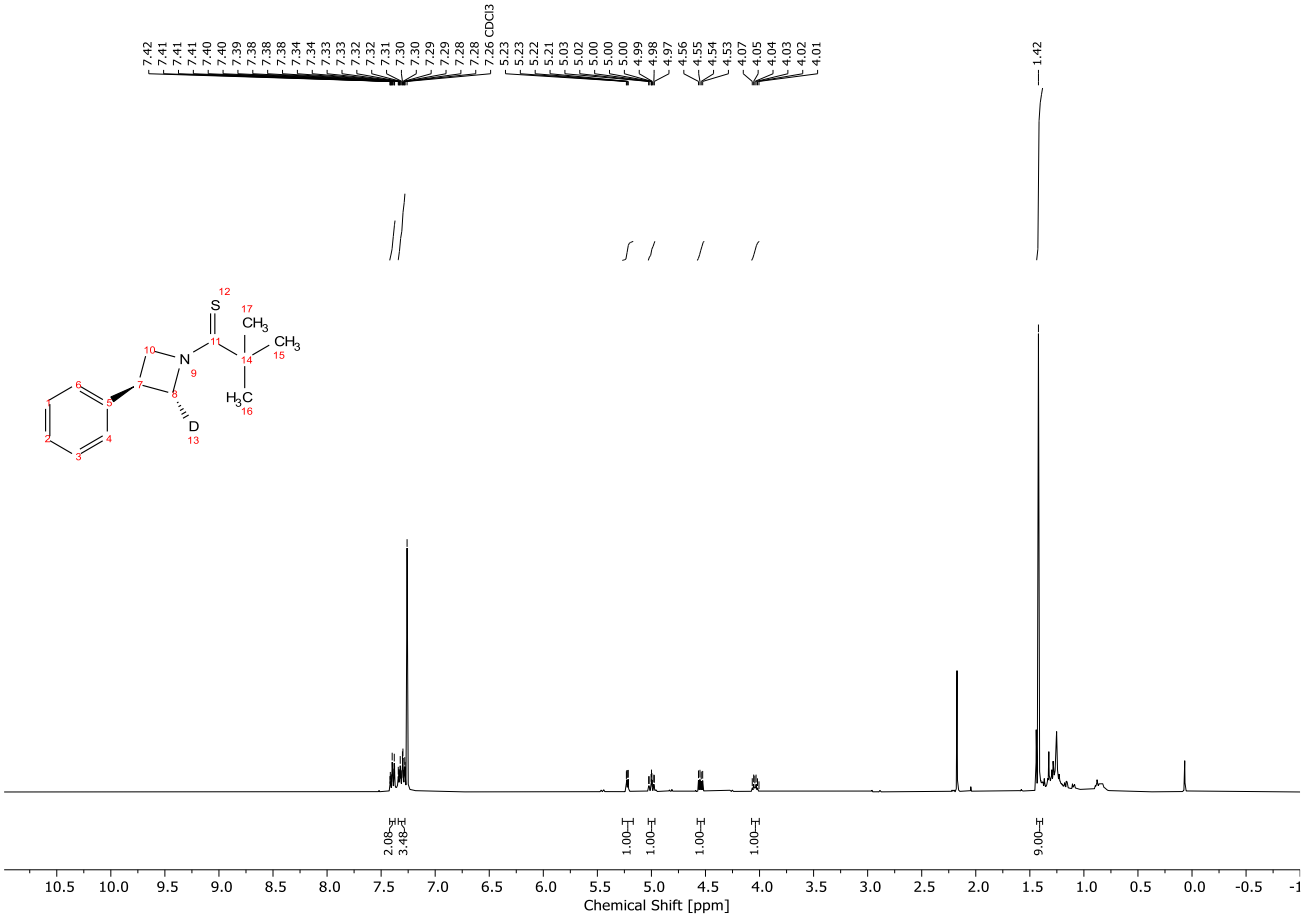
^{1}H NMR (400 MHz, $CDCl_3$) and **^{13}C NMR** (101 MHz, $CDCl_3$)

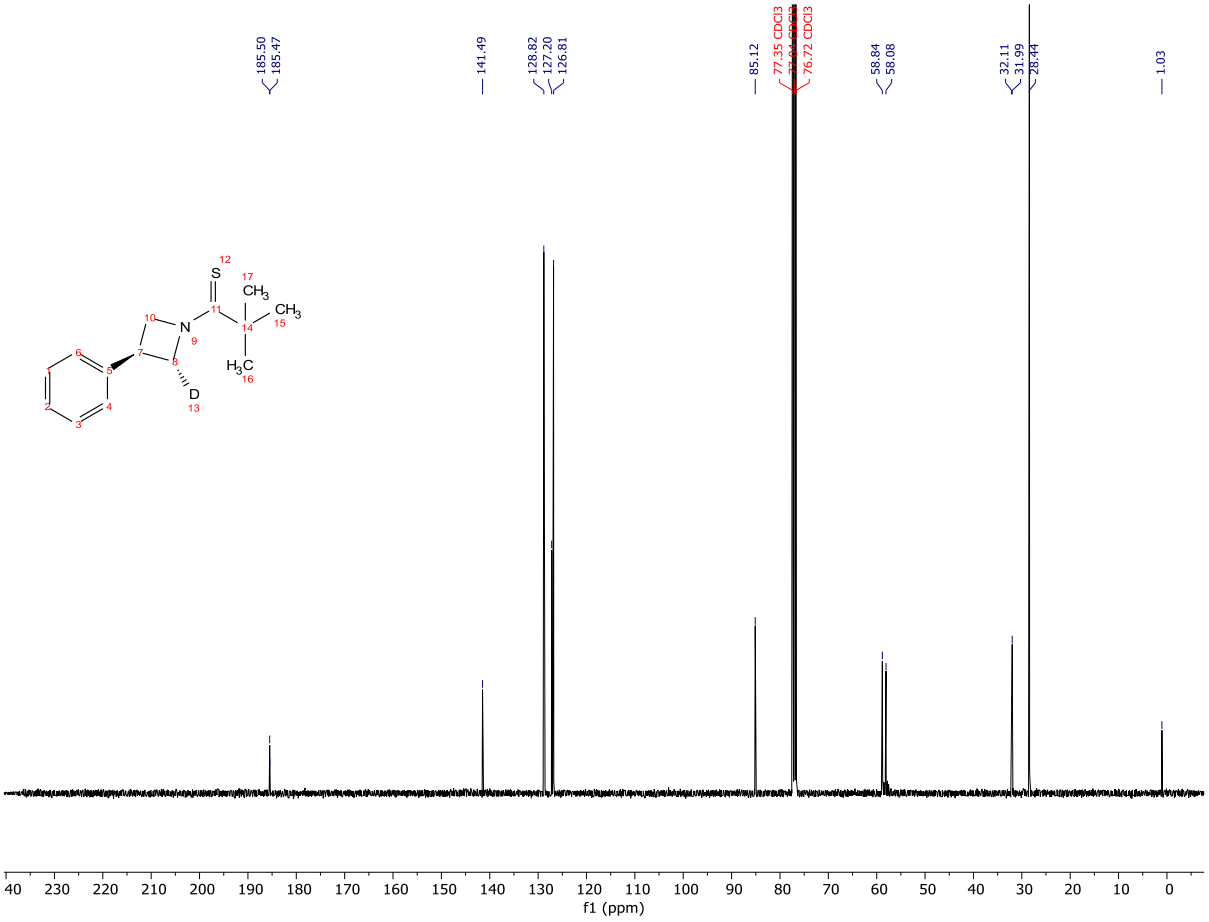



185.50
185.47
141.49
128.82
127.20
126.81
85.12
77.35 CDCl3
77.04 CDCl3
76.72 CDCl3
58.84
58.08
32.11
31.99
28.44
1.03
S
CH3
CH3
CH3
N
O
D
f1 (ppm)

2,2-dimethyl-1-((2R,3S)-3-phenylazetidin-1-yl-2-d)propane-1-thione

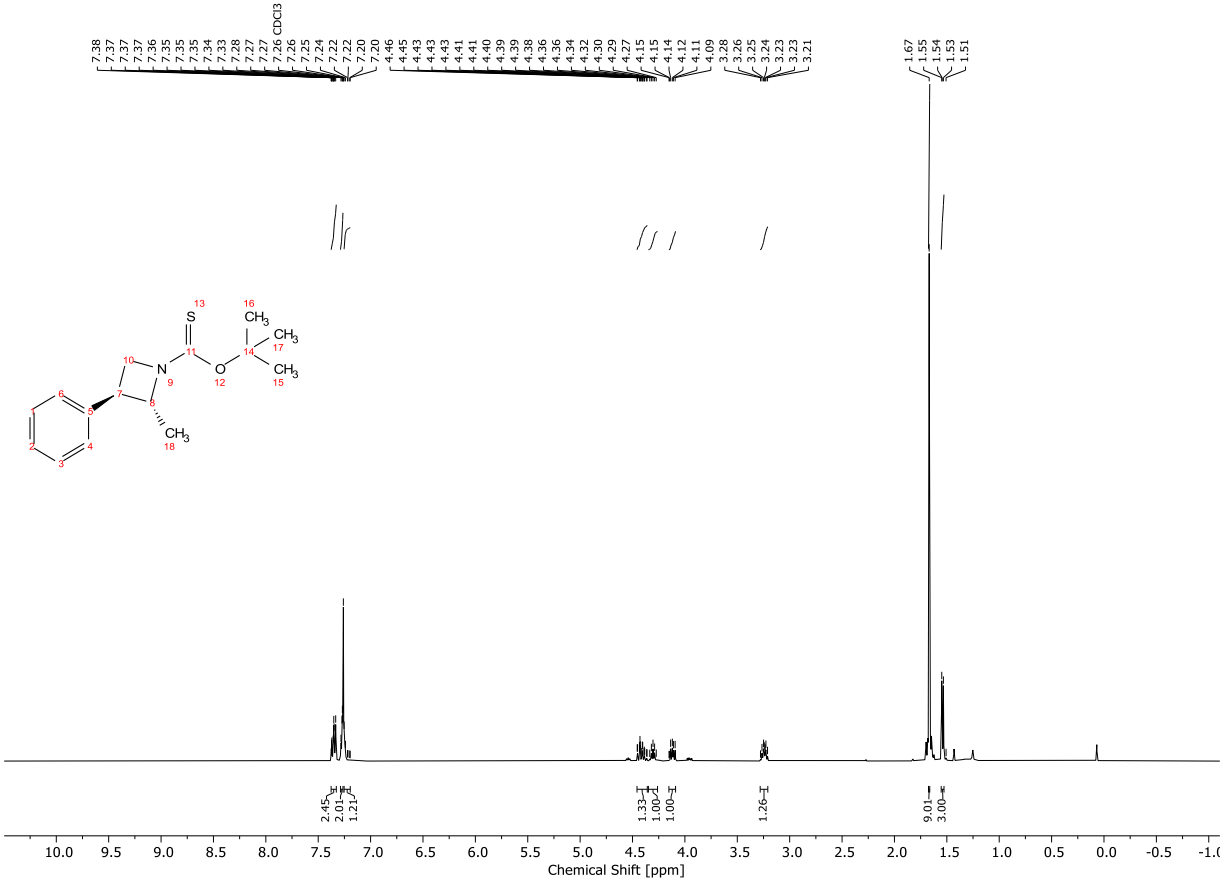
^{1}H NMR (400 MHz, $CDCl_3$) and **^{13}C NMR** (101 MHz, $CDCl_3$)

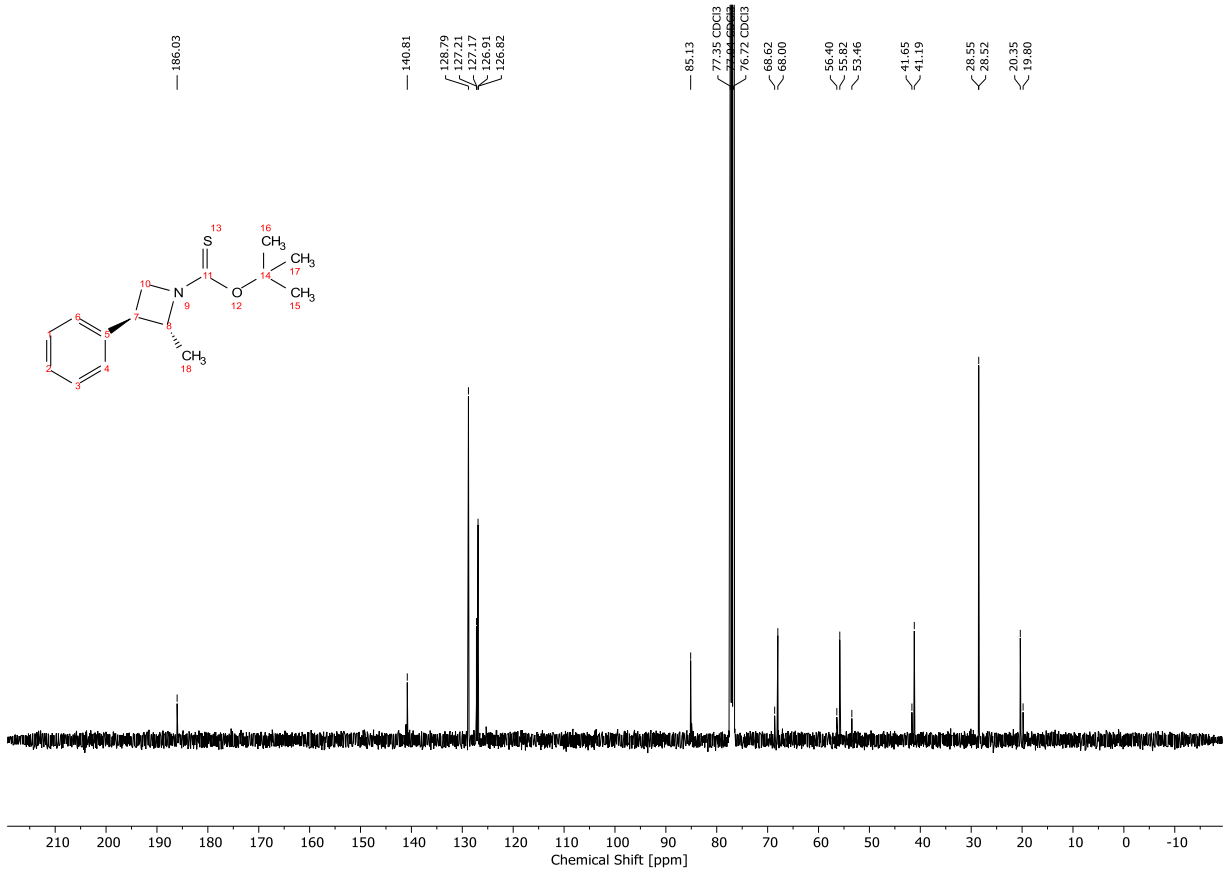



185.50
185.47
141.49
128.82
127.20
126.81
85.12
77.35 CDCl3
77.04 CDCl3
76.72 CDCl3
58.84
58.08
32.11
31.99
28.44
1.03
S
12
CH3
17
CH3
15
N
9
10
11
14
7
8
5
6
1
2
3
4
H3C
16
D
13
40 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

(O-(tert-butyl) (2R,3S)-2-methyl-3-phenylazetidine-1-carbothioate)

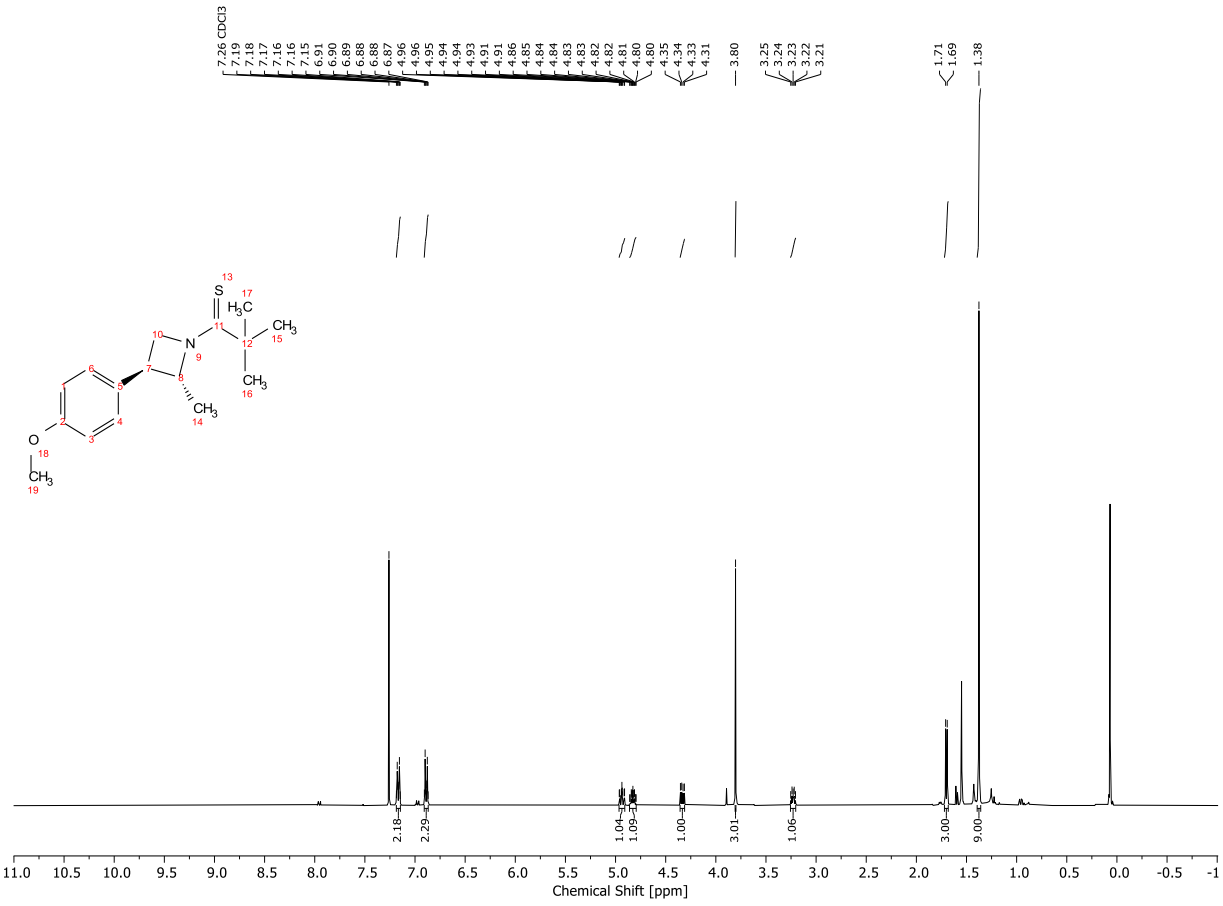
^{1}H NMR (400 MHz, $CDCl_3$) and **^{13}C NMR** (101 MHz, $CDCl_3$)

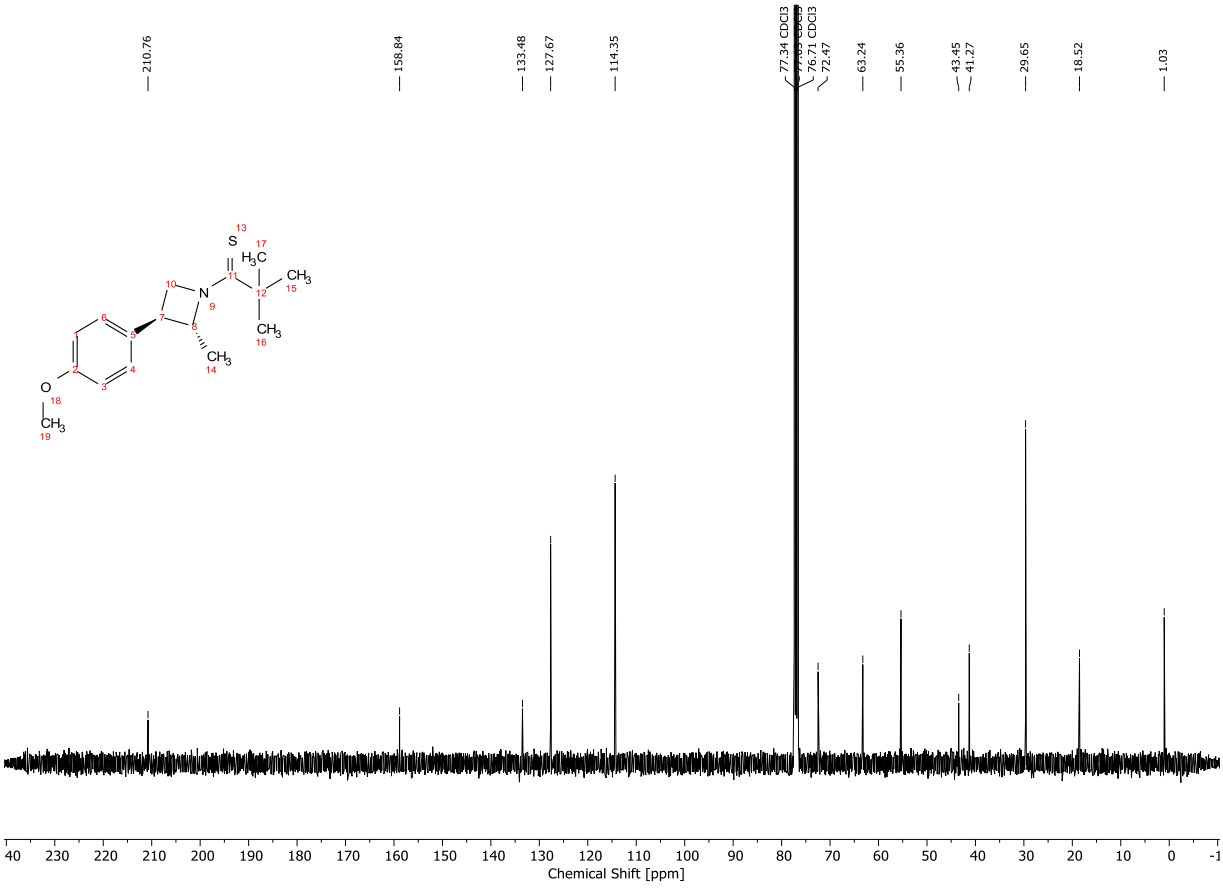



186.03
140.81
128.79
127.21
127.17
126.91
126.82
85.13
77.35 CDCl3
77.04 CDCl3
76.72 CDCl3
68.62
68.00
56.40
55.82
53.46
41.65
41.19
28.55
28.52
20.35
19.80
Chemical Shift [ppm]

1-((2R,3S)-3-(4-methoxyphenyl)-2-methylazetidin-1-yl)-2,2-dimethylpropane-1-thione

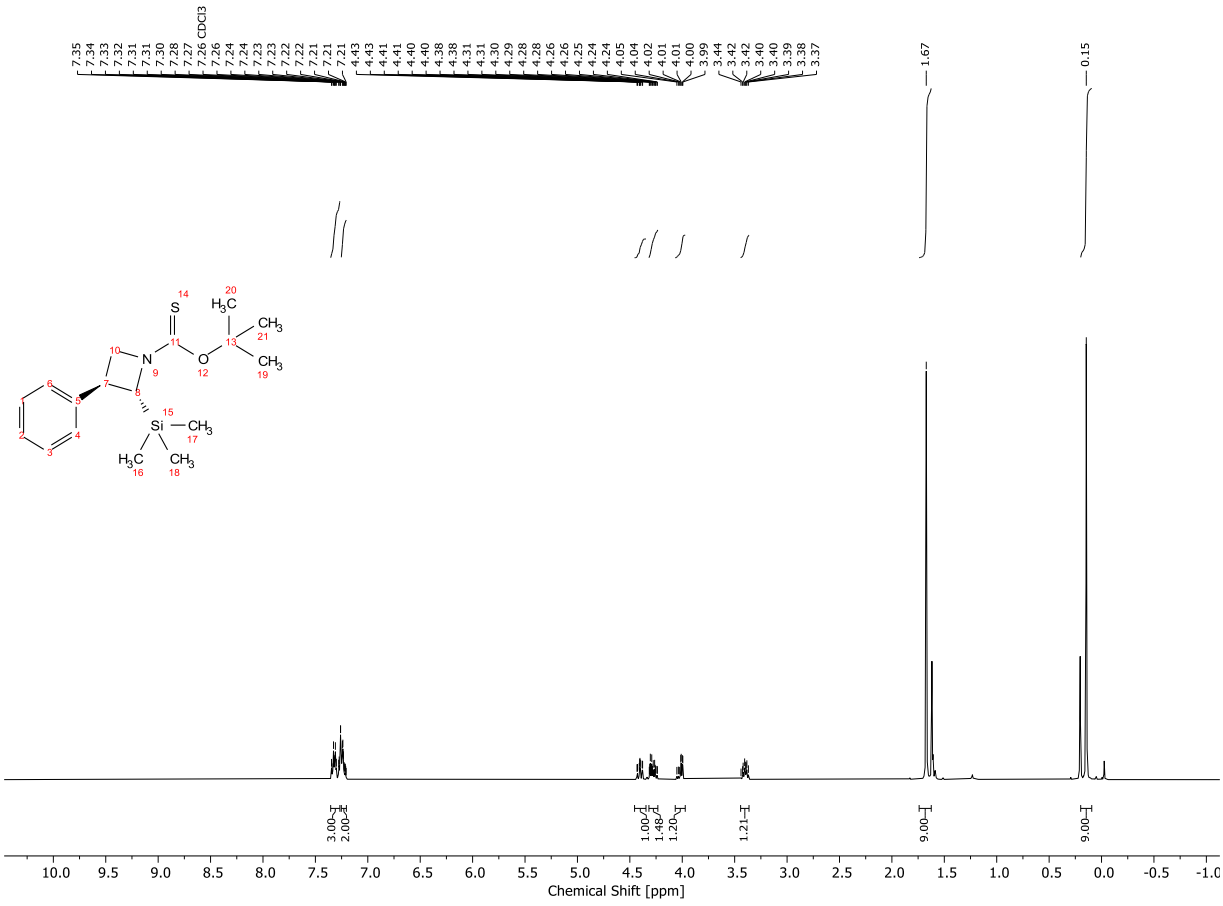
^{1}H NMR (400 MHz, $CDCl_3$) and **^{13}C NMR** (101 MHz, $CDCl_3$)

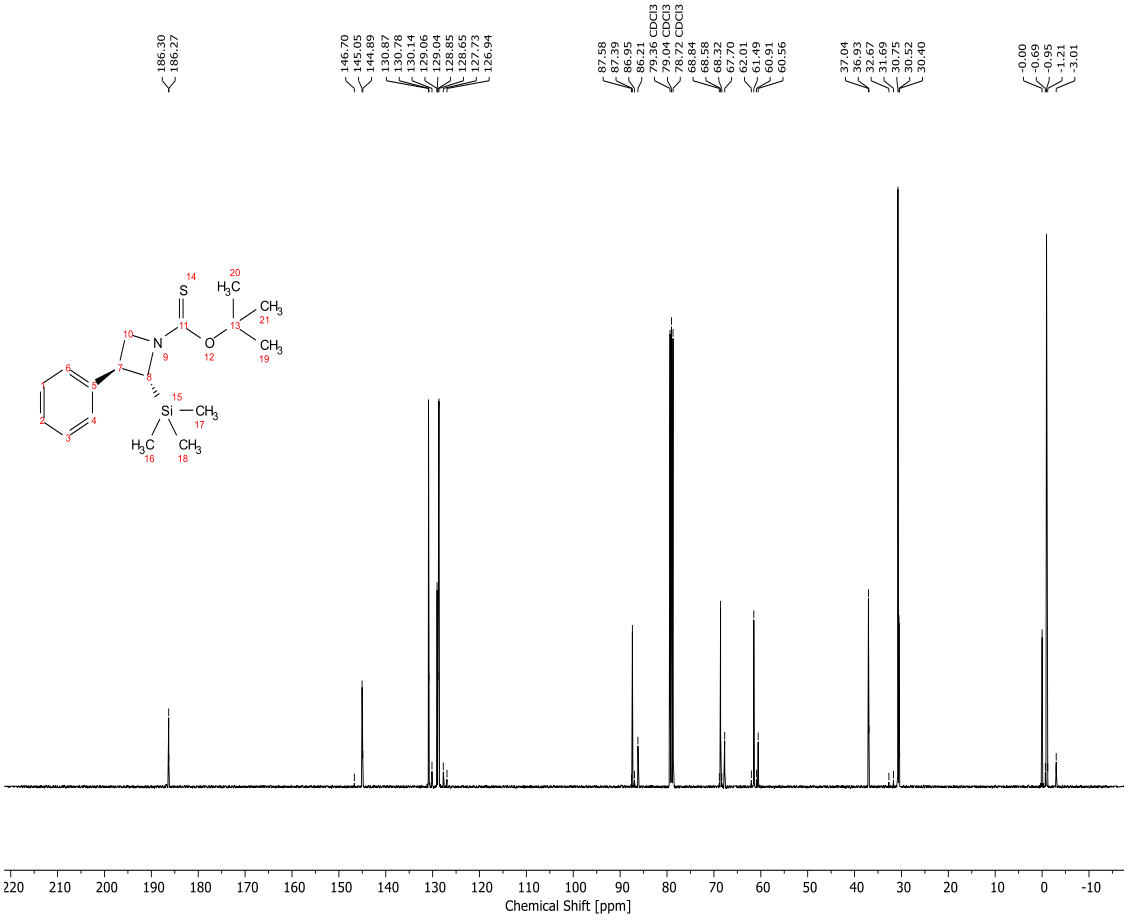



210.76
158.84
133.48
127.67
114.35
77.34 CDCl3
76.71 CDCl3
72.47
63.24
55.36
43.45
41.27
29.65
18.52
1.03
Chemical Shift [ppm]

(O-(tert-butyl) (2R,3S)-3-phenyl-2-(trimethylsilyl)azetidine-1-carbothioate)

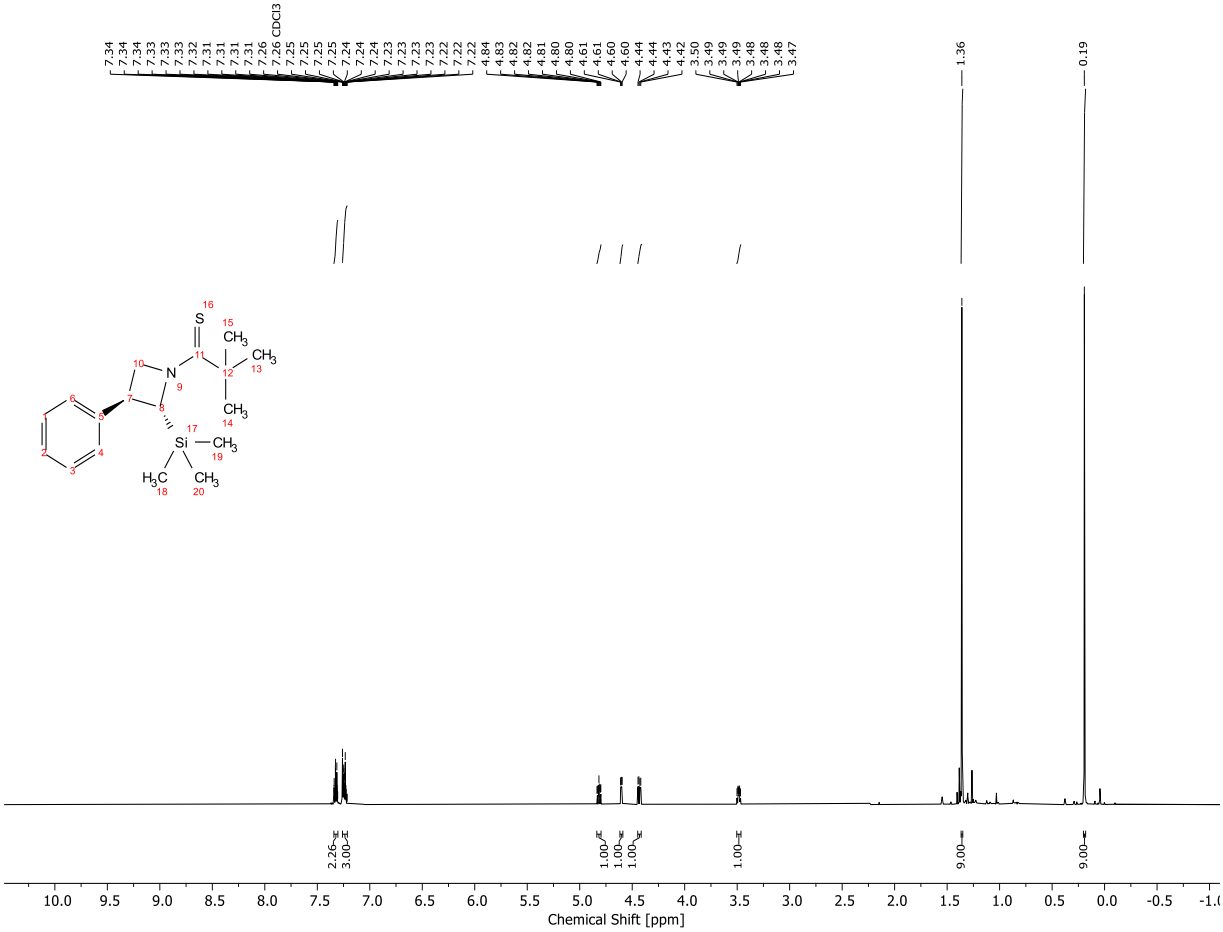
^{1}H NMR (400 MHz, $CDCl_3$) and **^{13}C NMR** (101 MHz, $CDCl_3$)

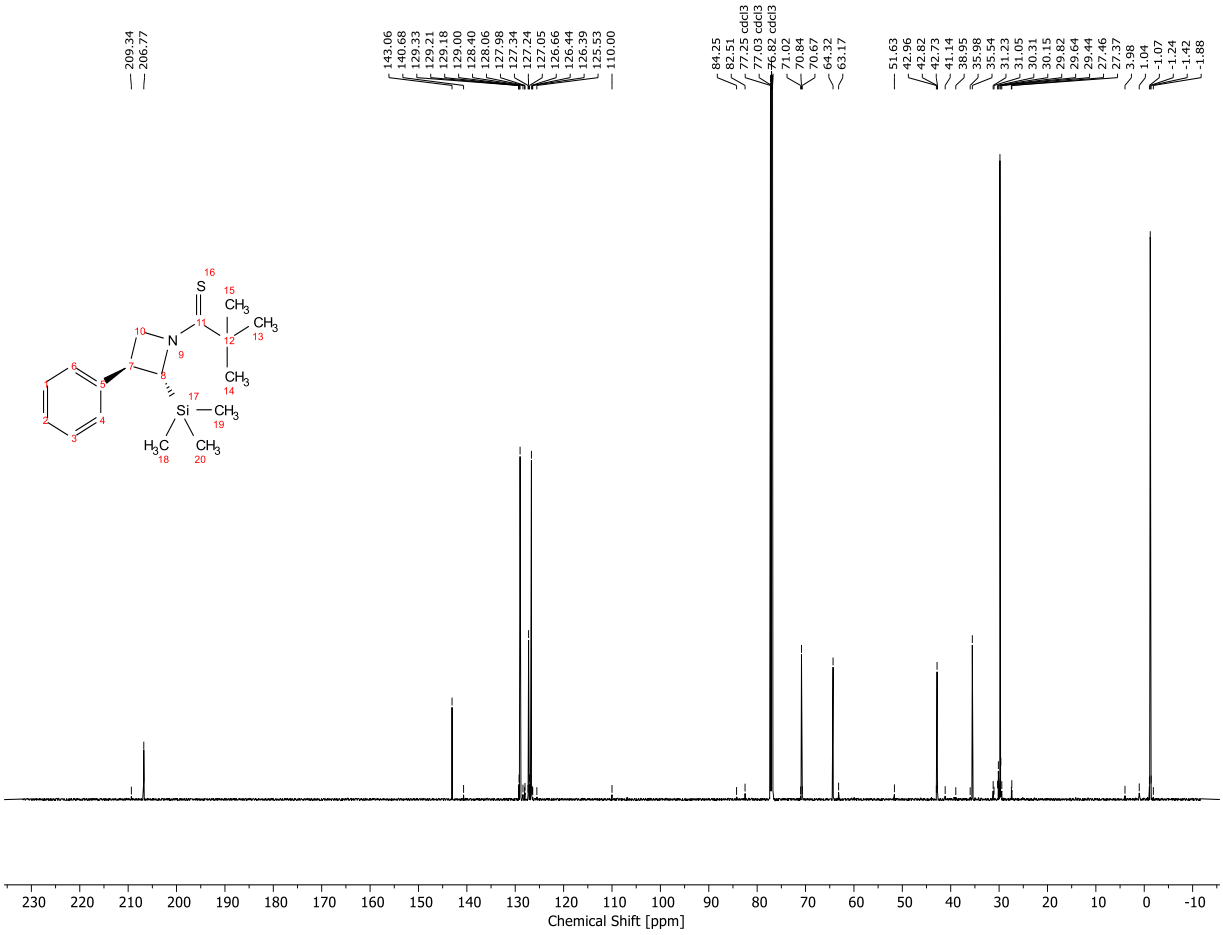



186.30
186.27
146.70
145.05
144.89
130.87
130.78
130.14
129.06
129.04
128.85
128.65
127.73
126.94
87.58
87.39
86.95
86.21
79.36 CDCl3
79.04 CDCl3
78.72 CDCl3
68.84
68.58
68.32
67.70
62.01
61.49
60.91
60.56
37.04
36.93
32.67
31.69
30.75
30.52
30.40
-0.00
-0.69
-0.95
-1.21
-3.01
S
14
H3C
20
CH3
21
N
10
9
O
12
11
13
CH3
19
6
7
8
5
2
4
3
Si
15
CH3
17
H3C
16
CH3
18
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift [ppm]

(2,2-dimethyl-1-((2R,3S)-3-phenyl-2-(trimethylsilyl)azetidin-1-yl)propane-1-thione)

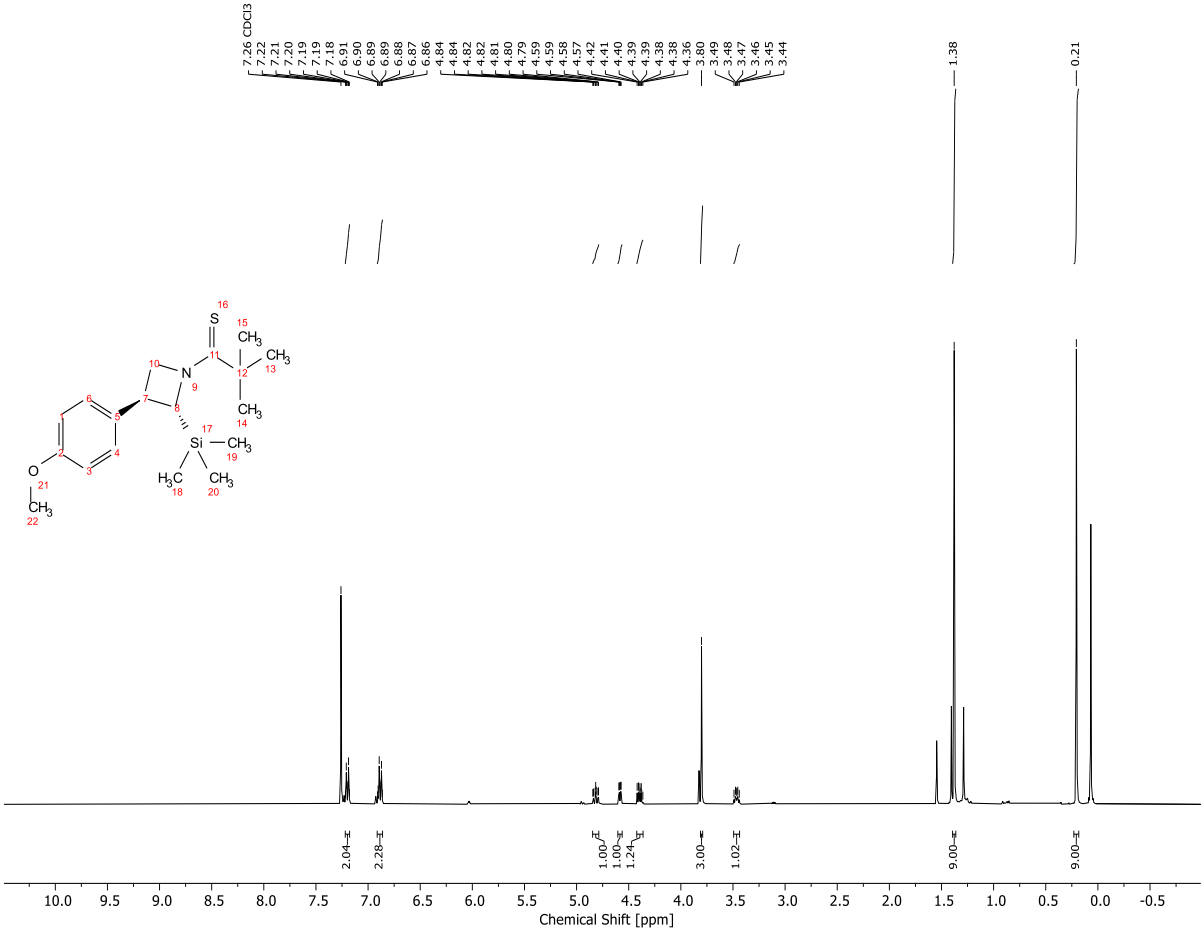
^{1}H NMR (599 MHz, $CDCl_3$) and **^{13}C NMR** (151 MHz, $CDCl_3$)

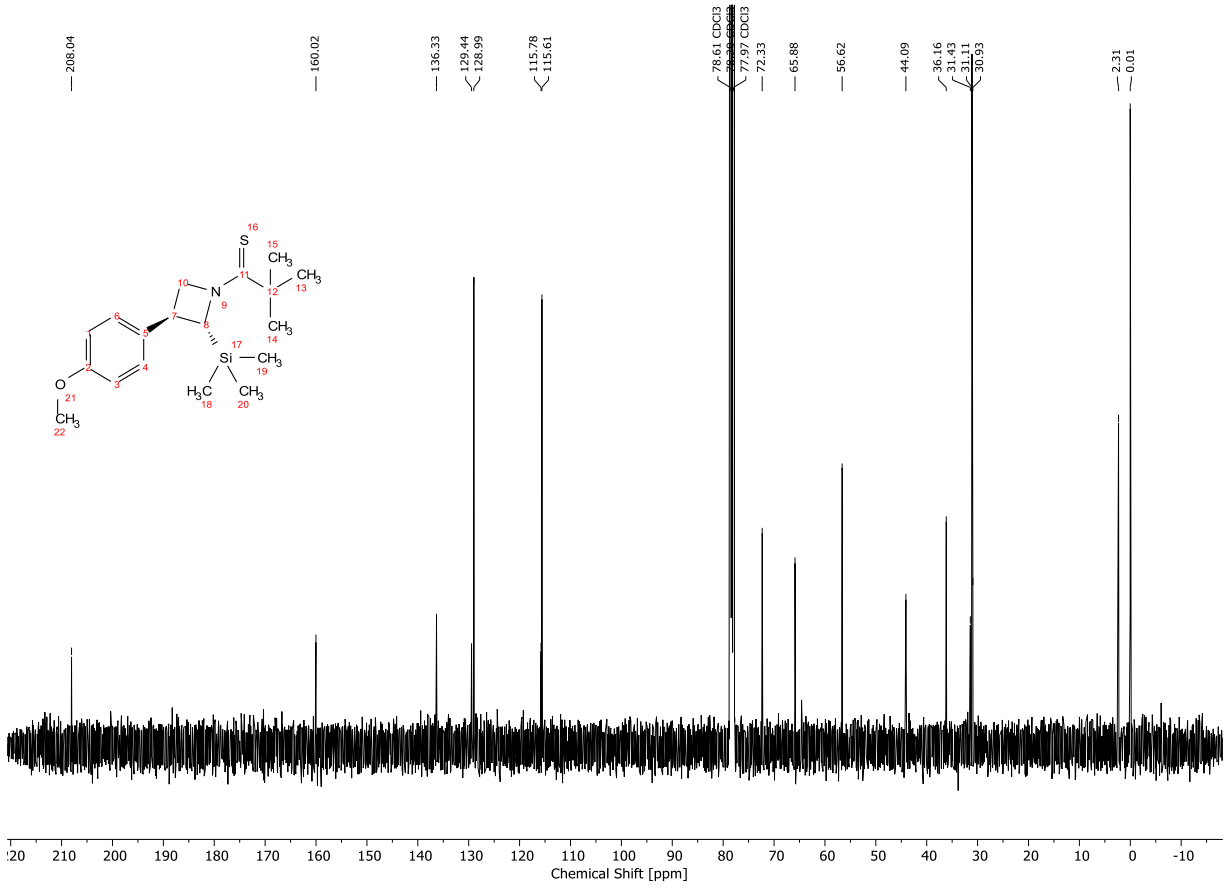



209.34
206.77
143.06
140.68
129.33
129.21
129.18
129.00
128.40
128.06
127.98
127.34
127.24
127.05
126.66
126.44
126.39
125.53
110.00
84.25
82.51
77.25 cdcl3
77.03 cdcl3
76.82 cdcl3
71.02
70.84
70.67
64.32
63.17
51.63
42.96
42.82
42.73
41.14
38.95
35.98
35.54
31.23
31.05
30.31
30.15
29.82
29.64
29.44
27.46
27.37
3.98
1.04
-1.07
-1.24
-1.42
-1.88
S
CH3
CH3
CH3
N
Si
CH3
H3C
CH3
16
15
13
14
10
11
12
9
7
8
17
19
18
20
6
5
1
2
4
3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift [ppm]

(1-((2R,3S)-3-(4-methoxyphenyl)-2-(trimethylsilyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione)

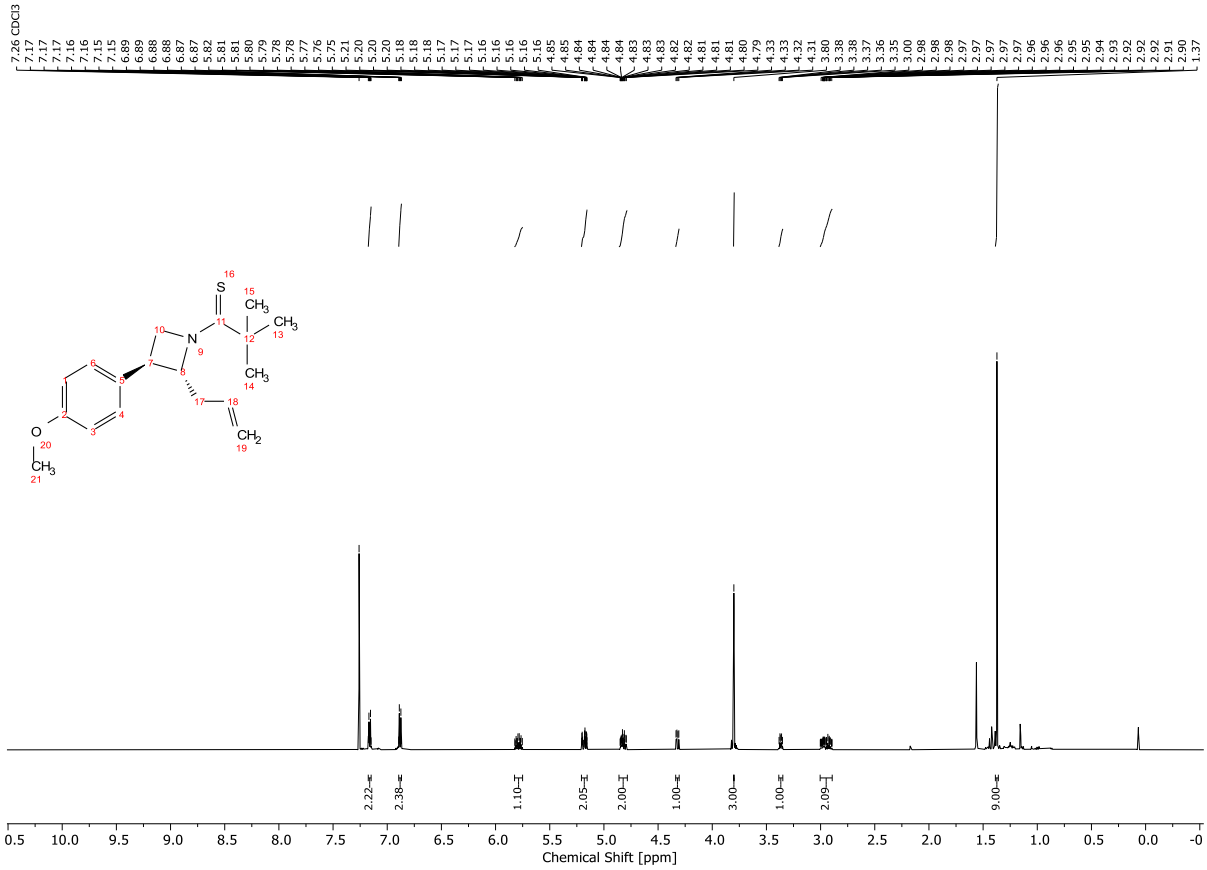
^{1}H NMR (400 MHz, $CDCl_3$) and **^{13}C NMR** (101 MHz, $CDCl_3$)

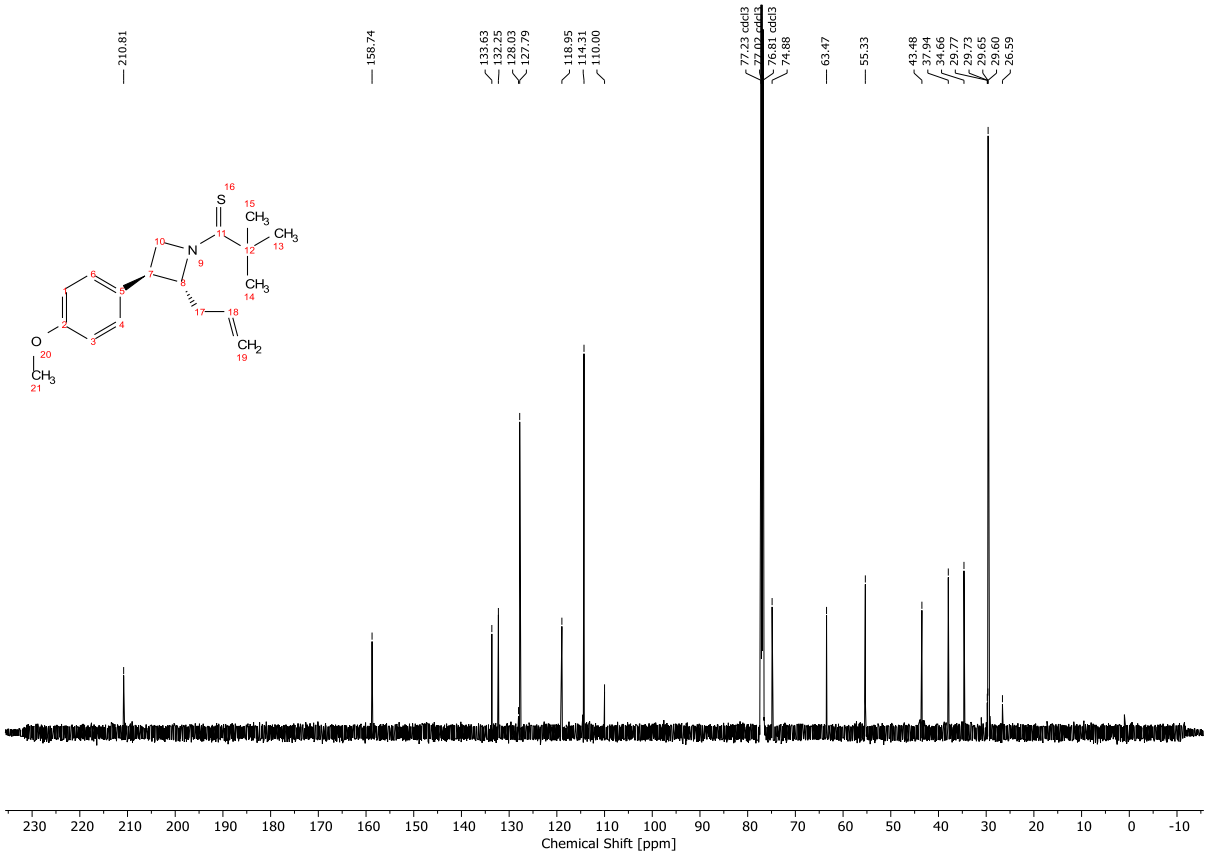



208.04
160.02
136.33
129.44
128.99
115.78
115.61
78.61 CDCl3
77.97 CDCl3
72.33
65.88
56.62
44.09
36.16
31.43
31.11
30.93
2.31
0.01
Chemical Shift [ppm]

(1-((2R,3S)-2-allyl-3-(4-methoxyphenyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione)

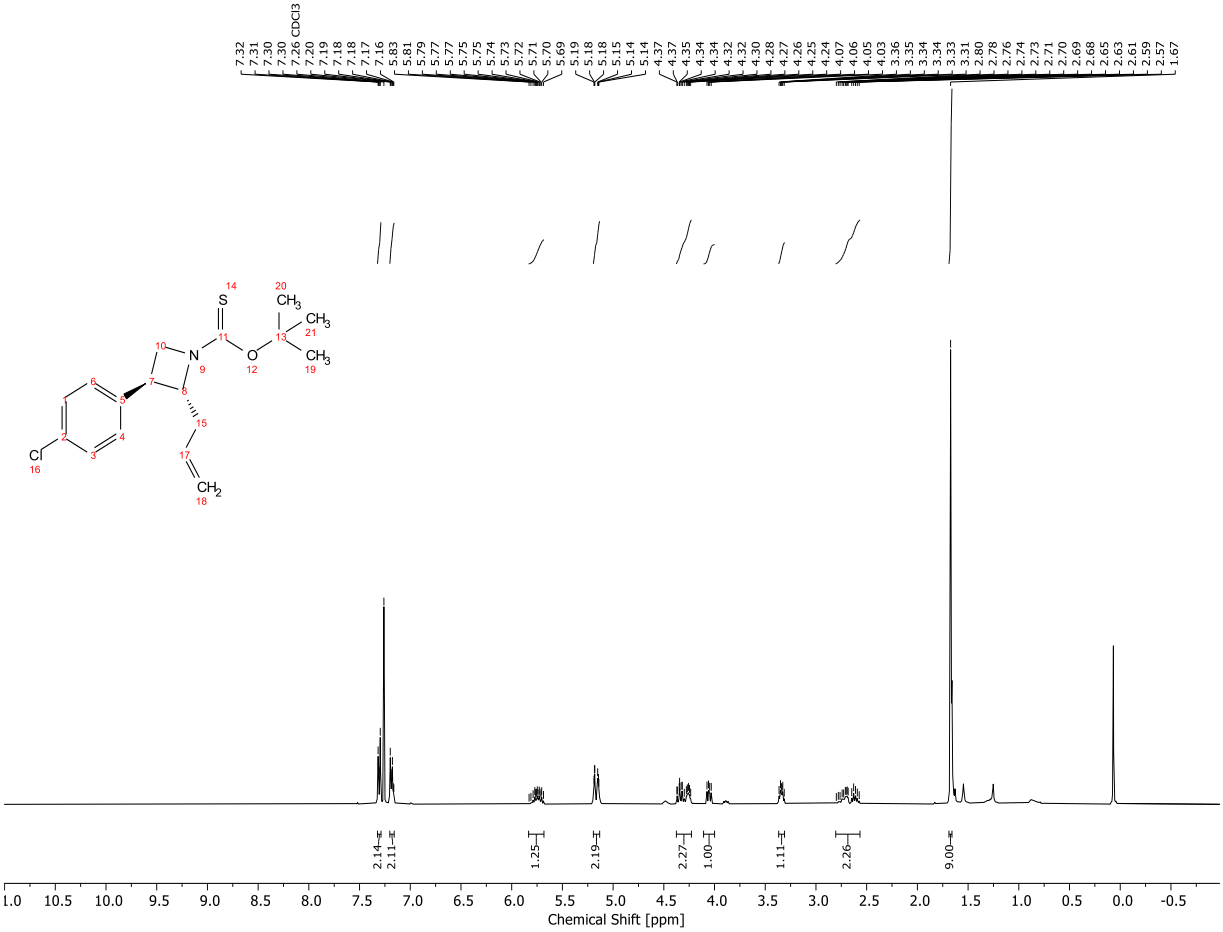
^{1}H NMR (599 MHz, $CDCl_3$) and **^{13}C NMR** (151 MHz, $CDCl_3$)

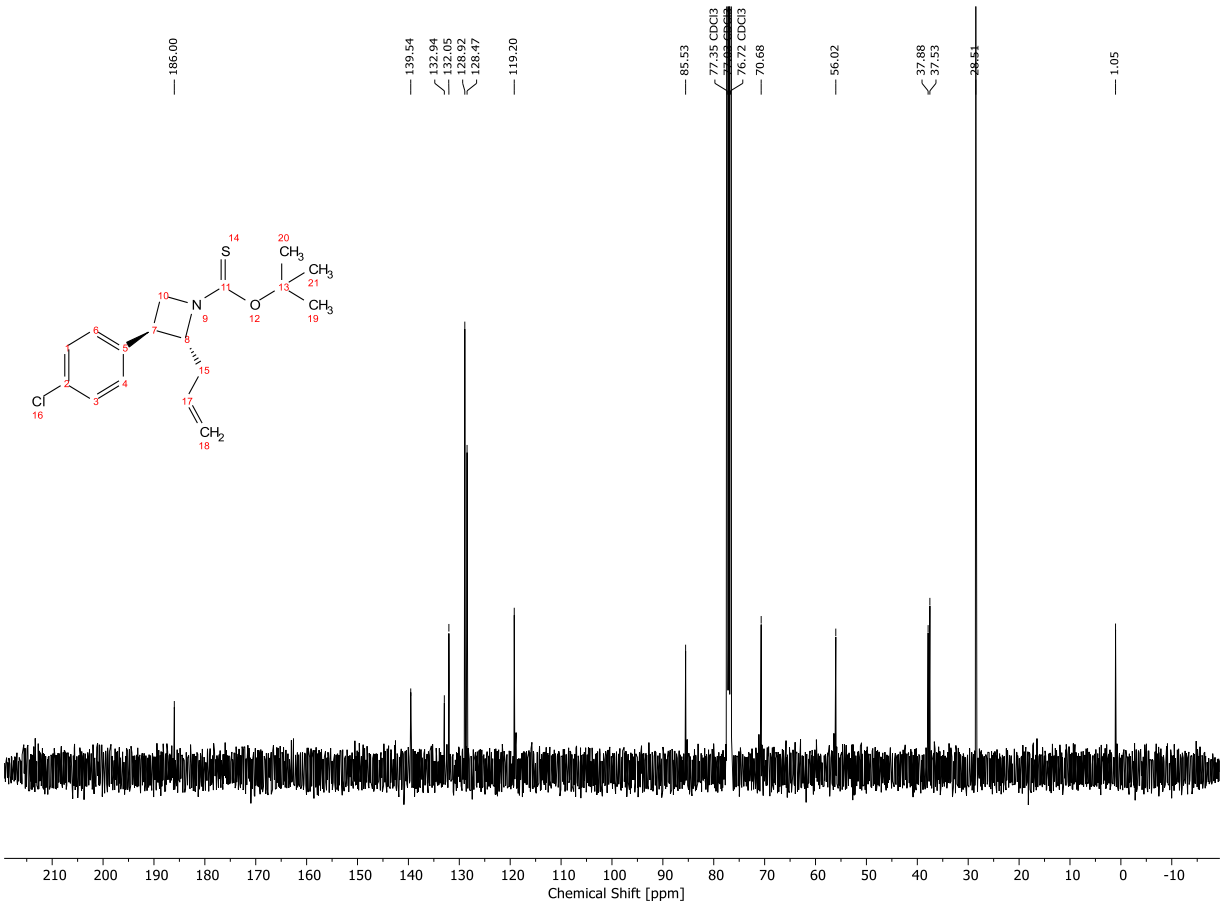



210.81
158.74
133.63
132.25
128.03
127.79
118.95
114.31
110.00
77.23 cdcl3
77.02 cdcl3
76.81 cdcl3
74.88
63.47
55.33
43.48
37.94
34.66
29.77
29.73
29.65
29.60
26.59
Chemical Shift [ppm]

(O-(tert-butyl) (2R,3S)-2-allyl-3-(4-chlorophenyl)azetidine-1-carbothioate)

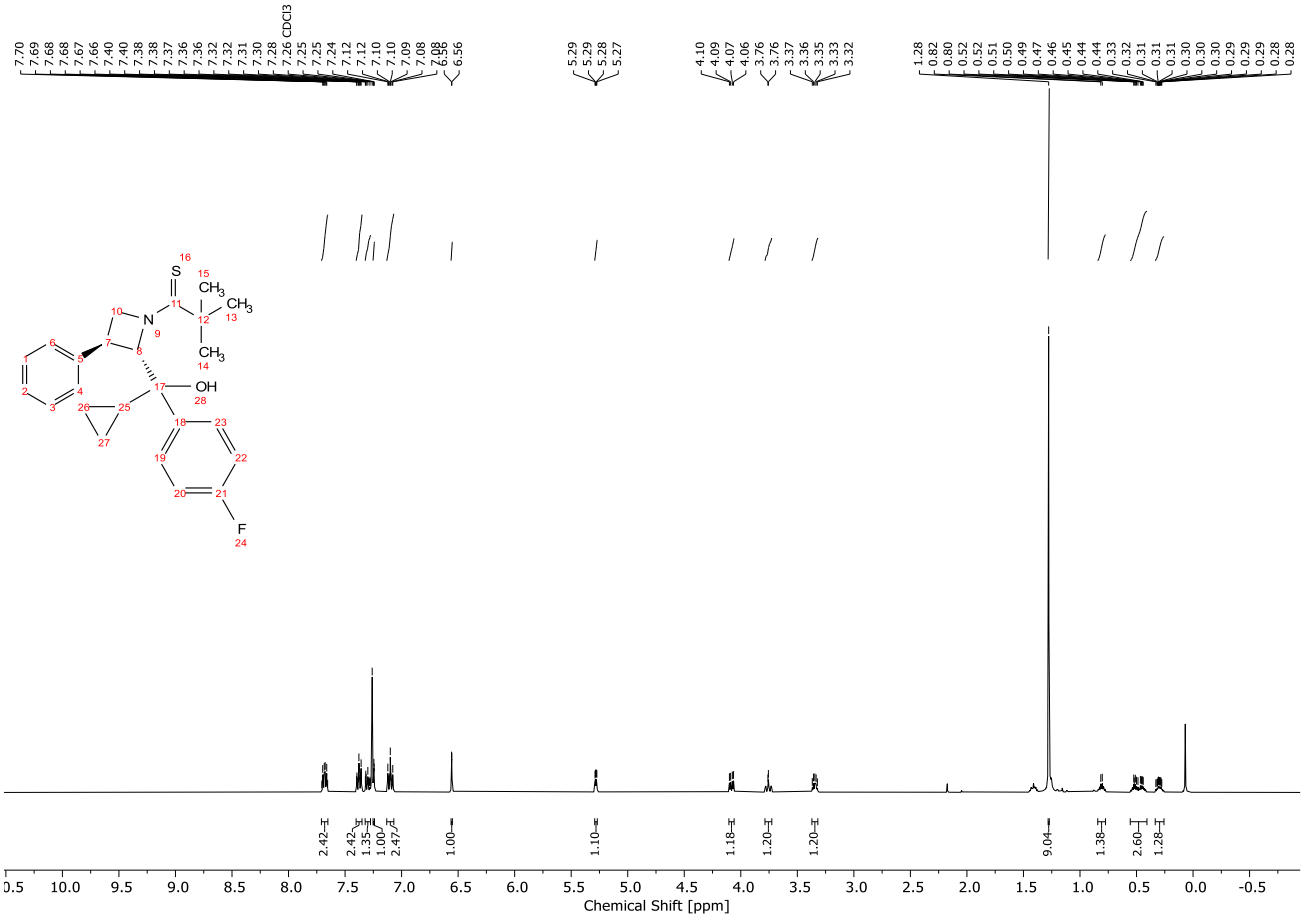
^{1}H NMR (400 MHz, $CDCl_3$) and **^{13}C NMR** (101 MHz, $CDCl_3$)

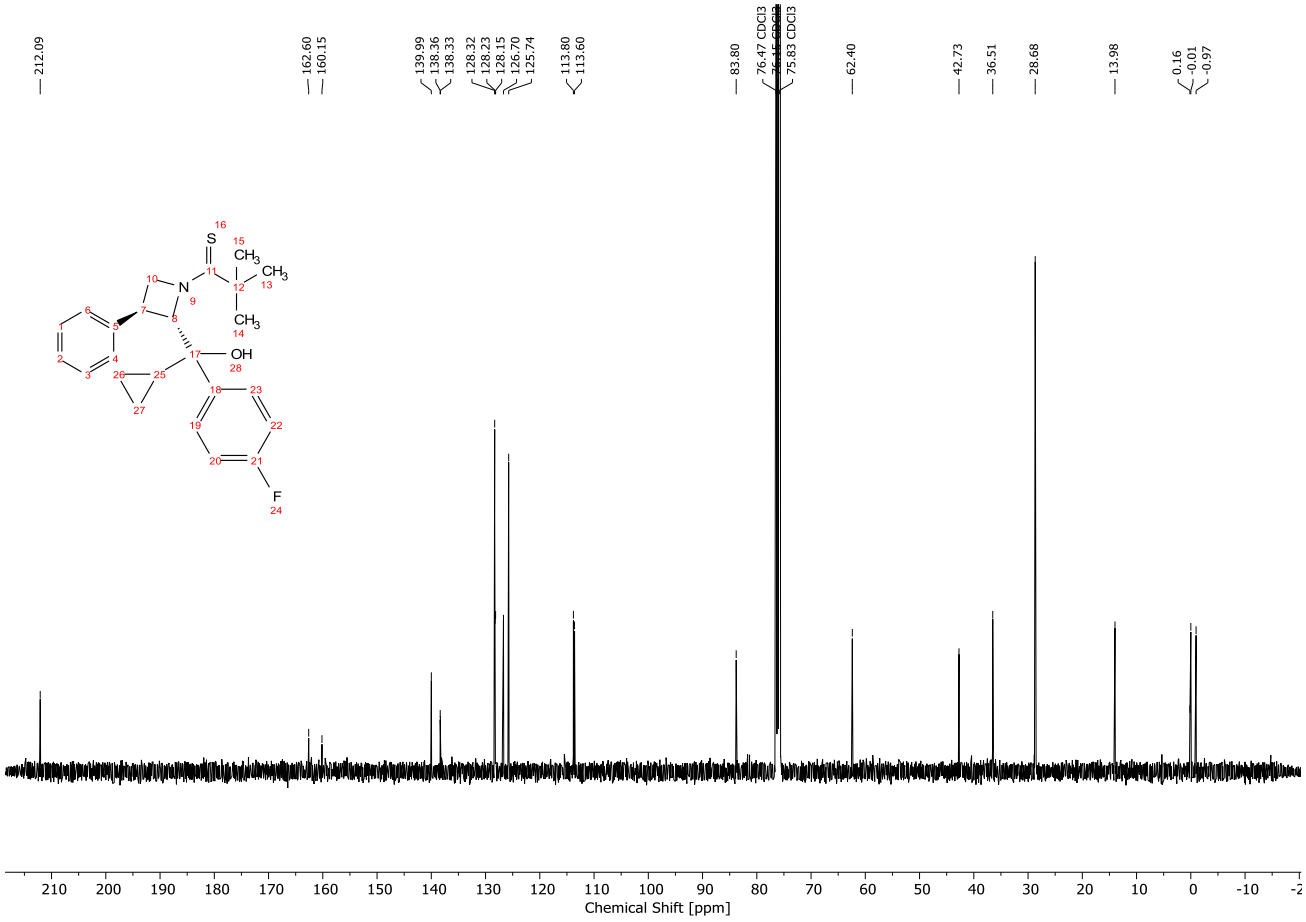


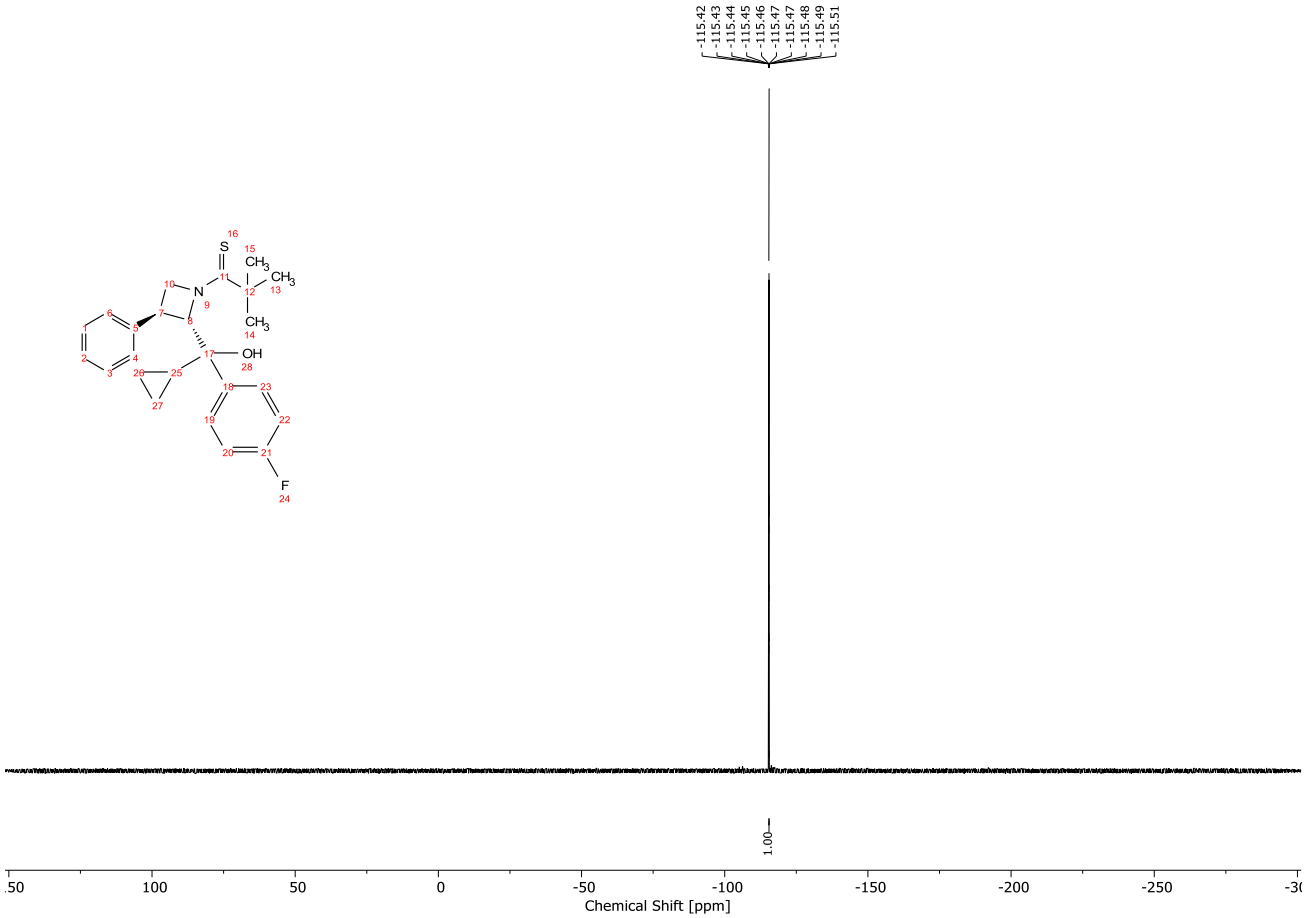

186.00
139.54
132.94
132.05
128.92
128.47
119.20
85.53
77.35 CDCl3
76.72 CDCl3
70.68
56.02
37.88
37.53
28.51
1.05
Chemical Shift [ppm]

(1-((2S,3S)-2-(cyclopropyl(4-fluorophenyl)(hydroxy)methyl)-3-phenylazetidin-1-yl)-2,2-dimethylpropane-1-thione)

^{1}H NMR (400 MHz, $CDCl_3$), **^{13}C NMR** (101 MHz, $CDCl_3$) and **^{19}F NMR** (377 MHz, $CDCl_3$)

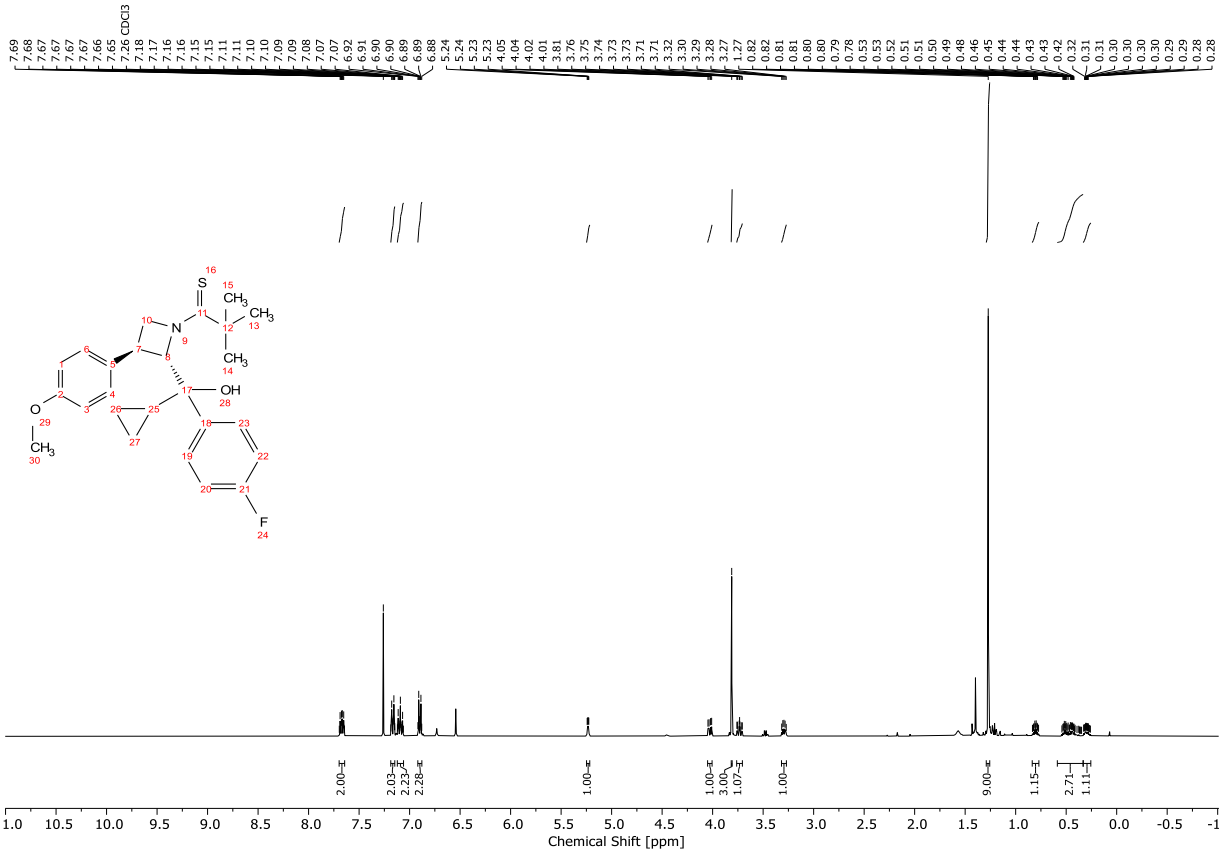


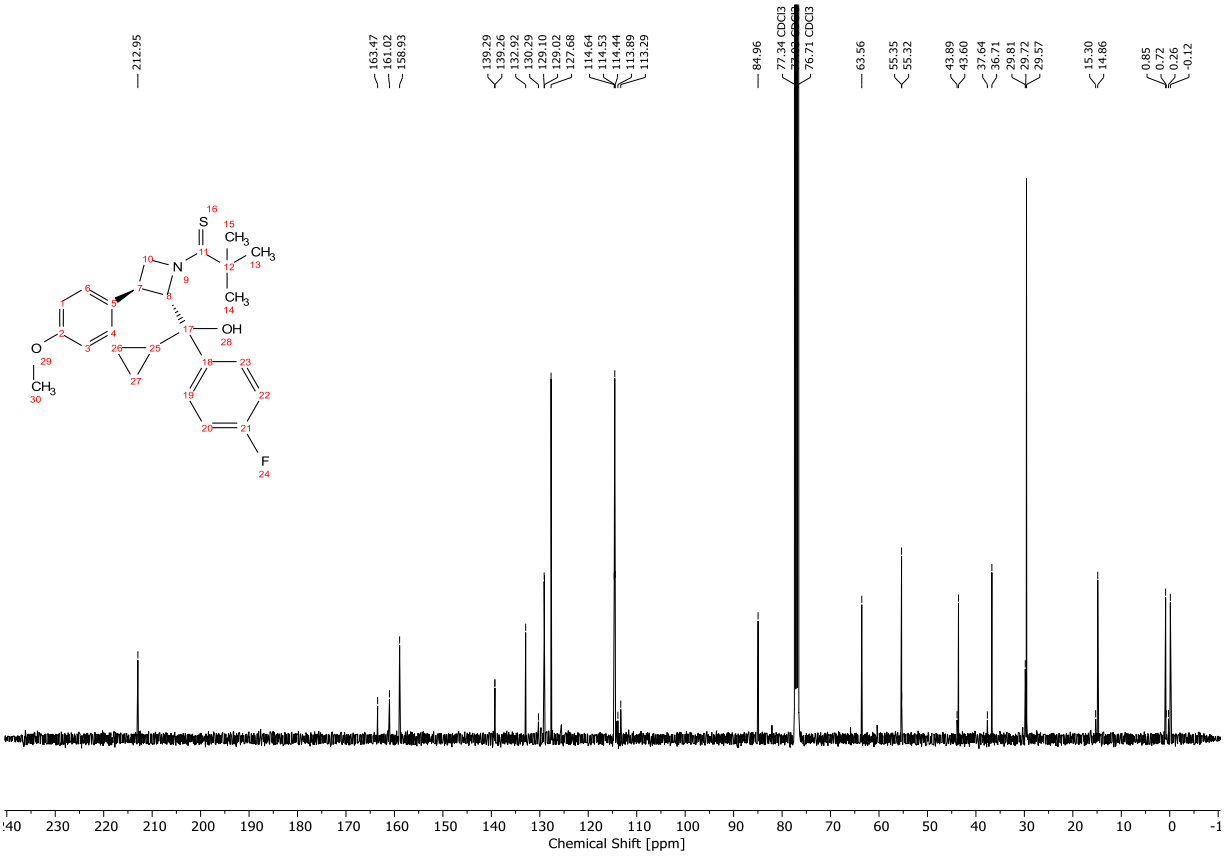

212.09
162.60
160.15
139.99
138.36
138.33
128.32
128.23
128.15
126.70
125.74
113.80
113.60
83.80
76.47 CDCl3
76.15 CDCl3
75.83 CDCl3
62.40
42.73
36.51
28.68
13.98
0.16
-0.01
-0.97
Chemical Shift [ppm]

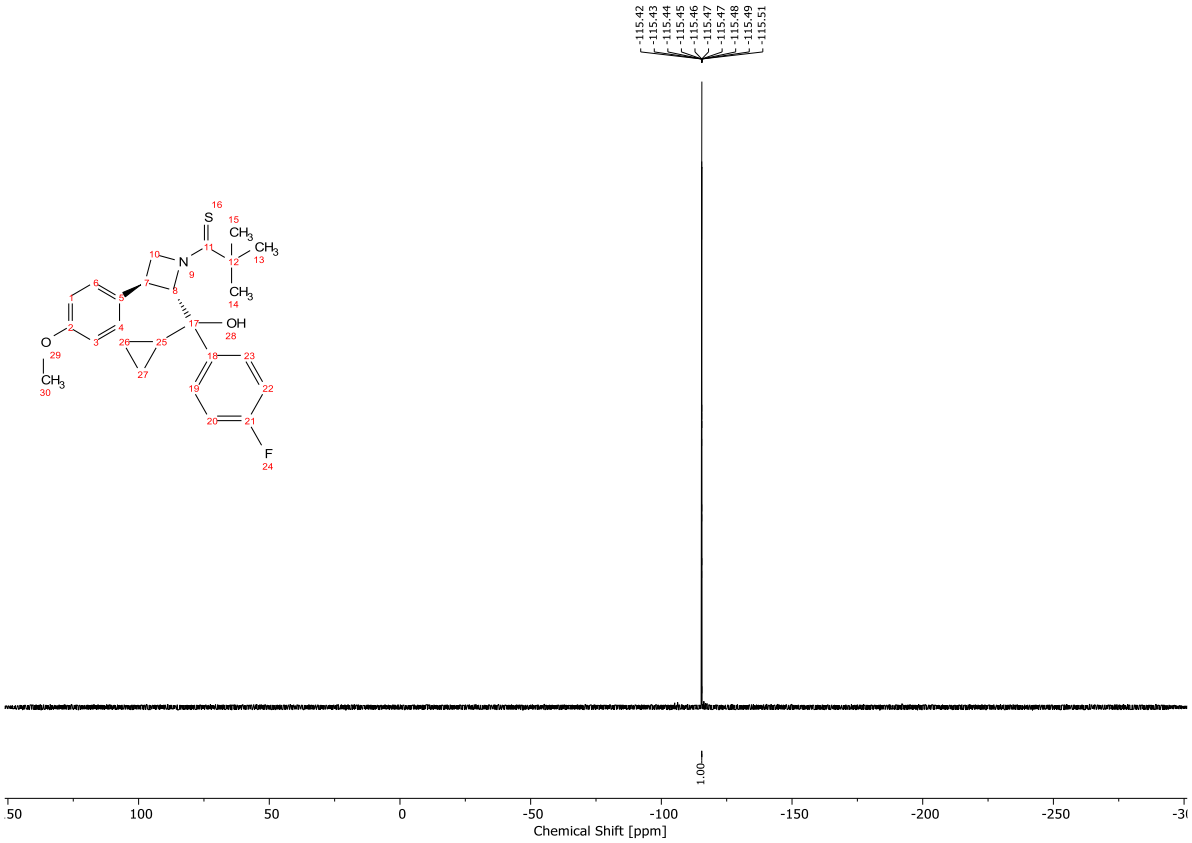

-115.42
-115.43
-115.44
-115.45
-115.46
-115.47
-115.47
-115.48
-115.49
-115.51
1.00
100
50
0
-50
-100
-150
-200
-250
Chemical Shift [ppm]

(1-((2S,3S)-2-(cyclopropyl(4-fluorophenyl)(hydroxy)methyl)-3-(4-methoxyphenyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione)

^{1}H NMR (400 MHz, $CDCl_3$), **^{13}C NMR** (101 MHz, $CDCl_3$) and **^{19}F NMR** (377 MHz, $CDCl_3$)

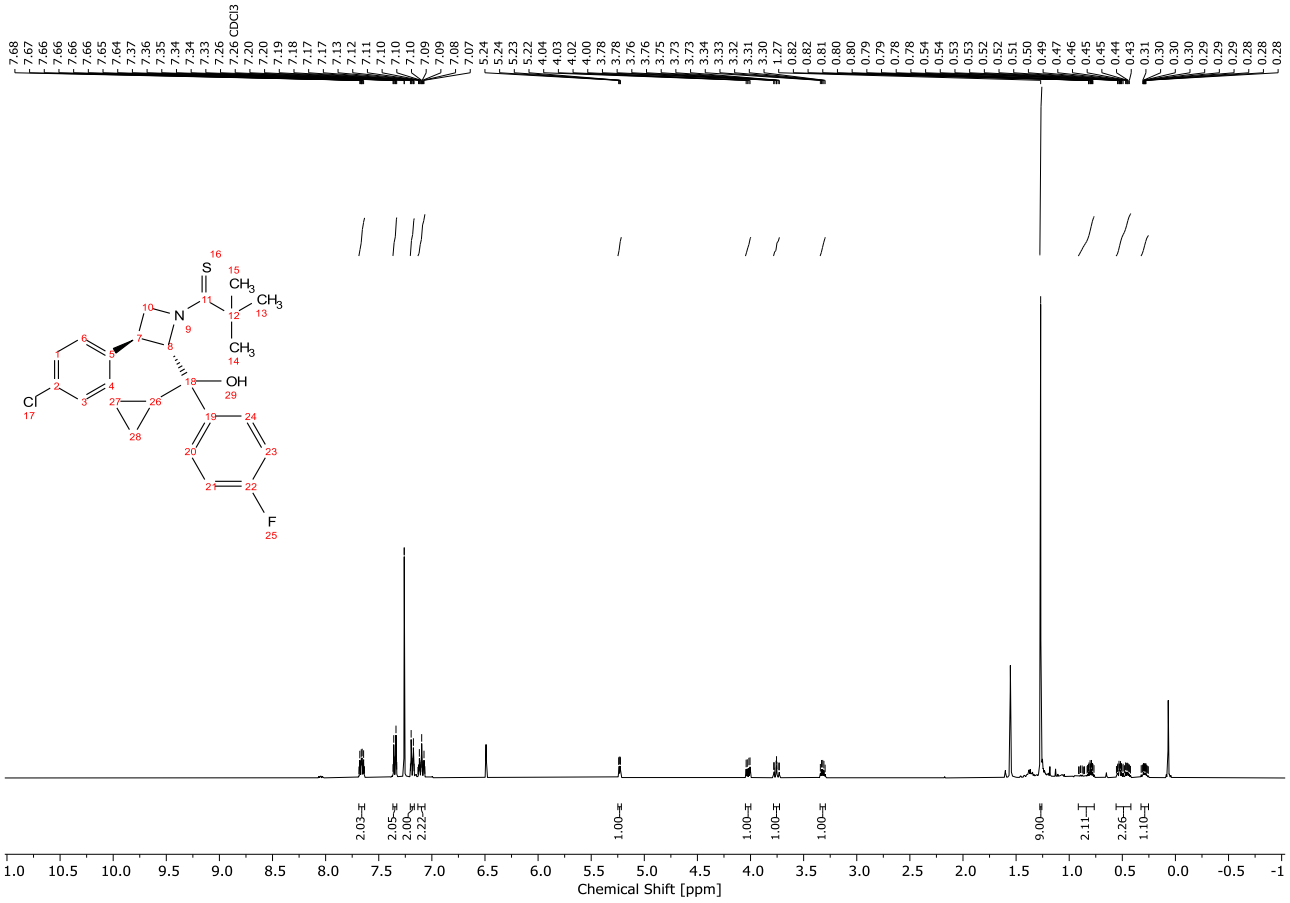


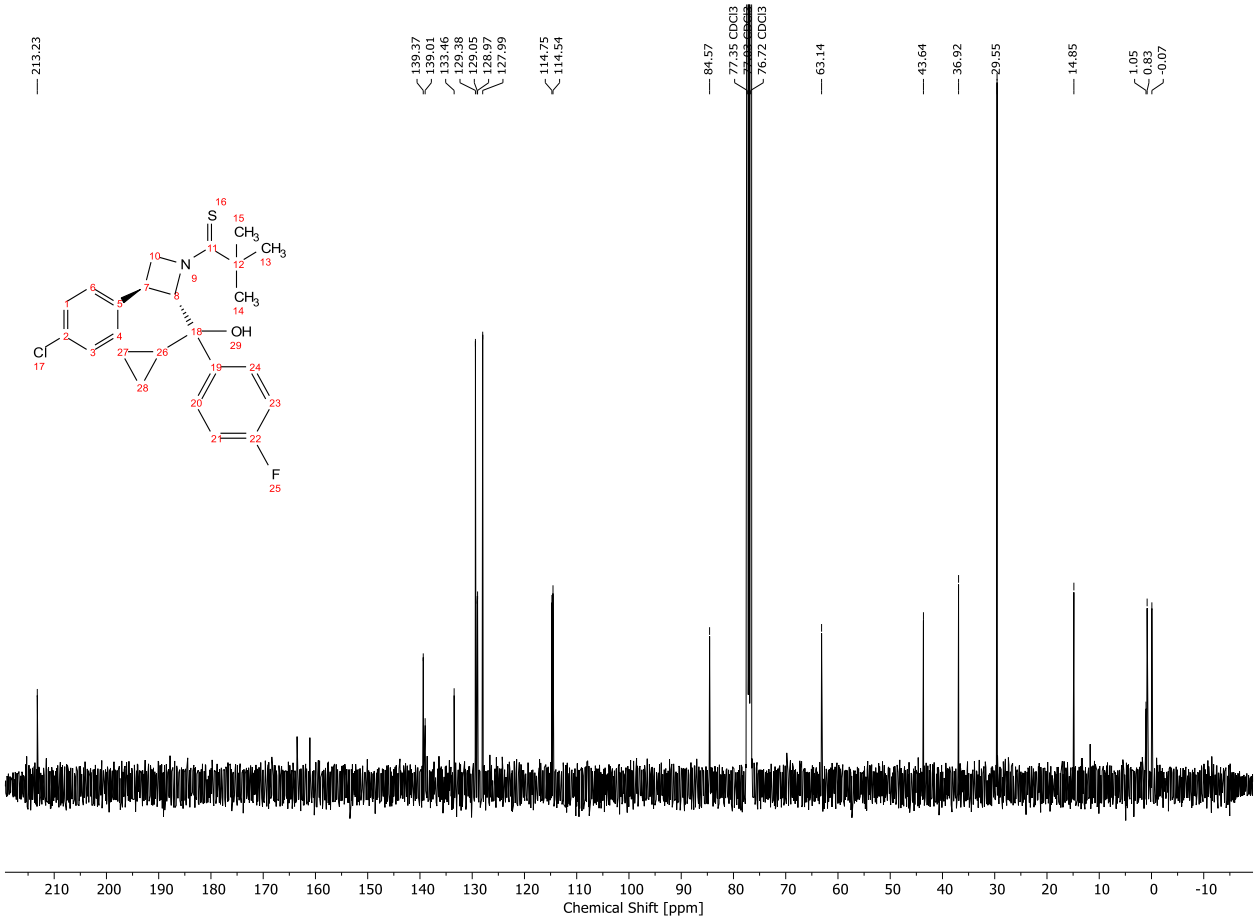

212.95
163.47
161.02
158.93
139.29
139.26
132.92
130.29
129.10
129.02
127.68
114.64
114.53
114.44
113.89
113.29
84.96
77.34 CDCl3
76.71 CDCl3
63.56
55.35
55.32
43.89
43.60
37.64
36.71
29.81
29.72
29.57
15.30
14.86
0.85
0.72
0.26
-0.12
Chemical Shift [ppm]

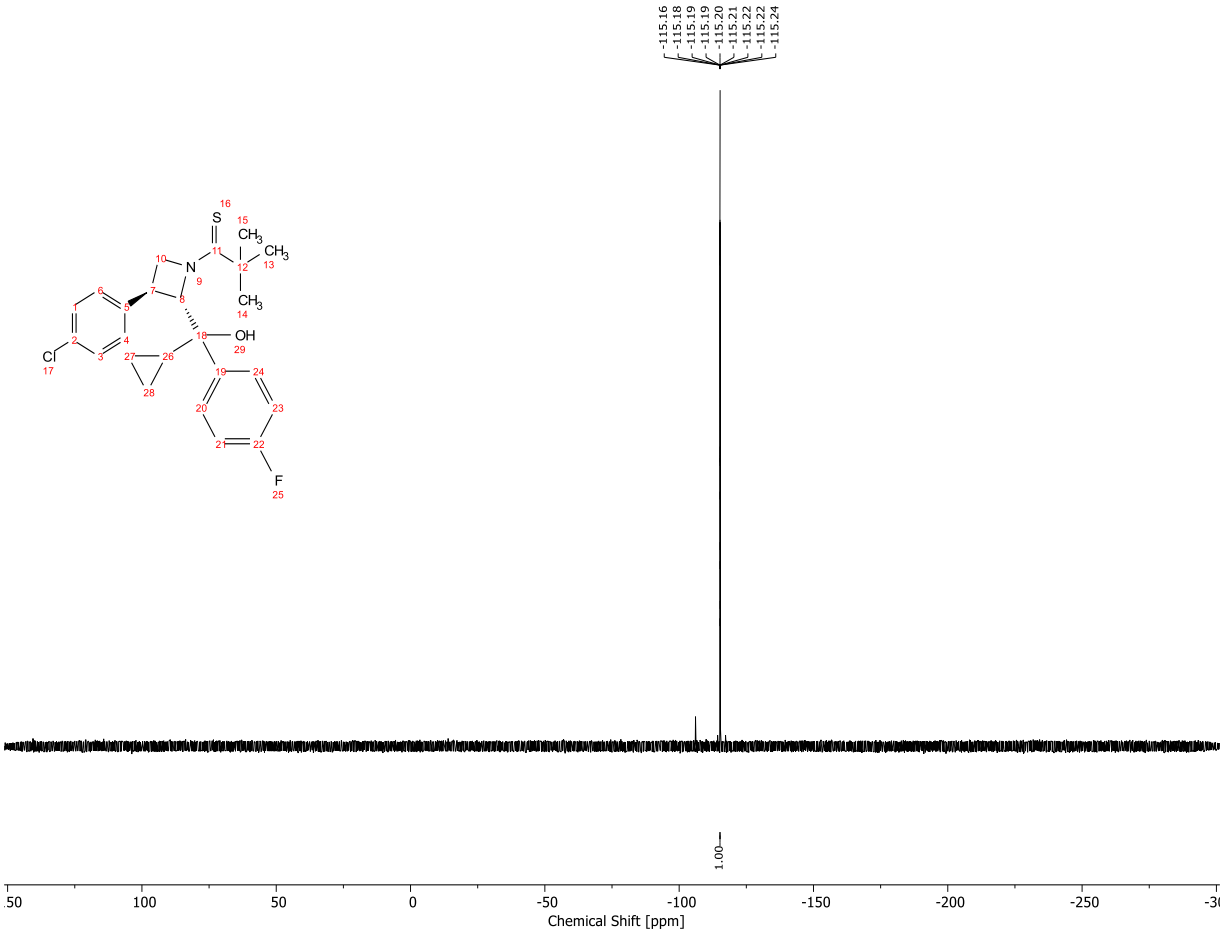

-115.42
-115.43
-115.44
-115.45
-115.46
-115.47
-115.47
-115.47
-115.48
-115.49
-115.51
1.00
50
100
50
0
-50
-100
-150
-200
-250
Chemical Shift [ppm]

(1-((2S,3S)-3-(4-chlorophenyl)-2-(cyclopropyl(4-fluorophenyl)(hydroxy)methyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione)

^{1}H NMR (400 MHz, $CDCl_3$), **^{13}C NMR** (101 MHz, $CDCl_3$) and **^{19}F NMR** (377 MHz, $CDCl_3$)

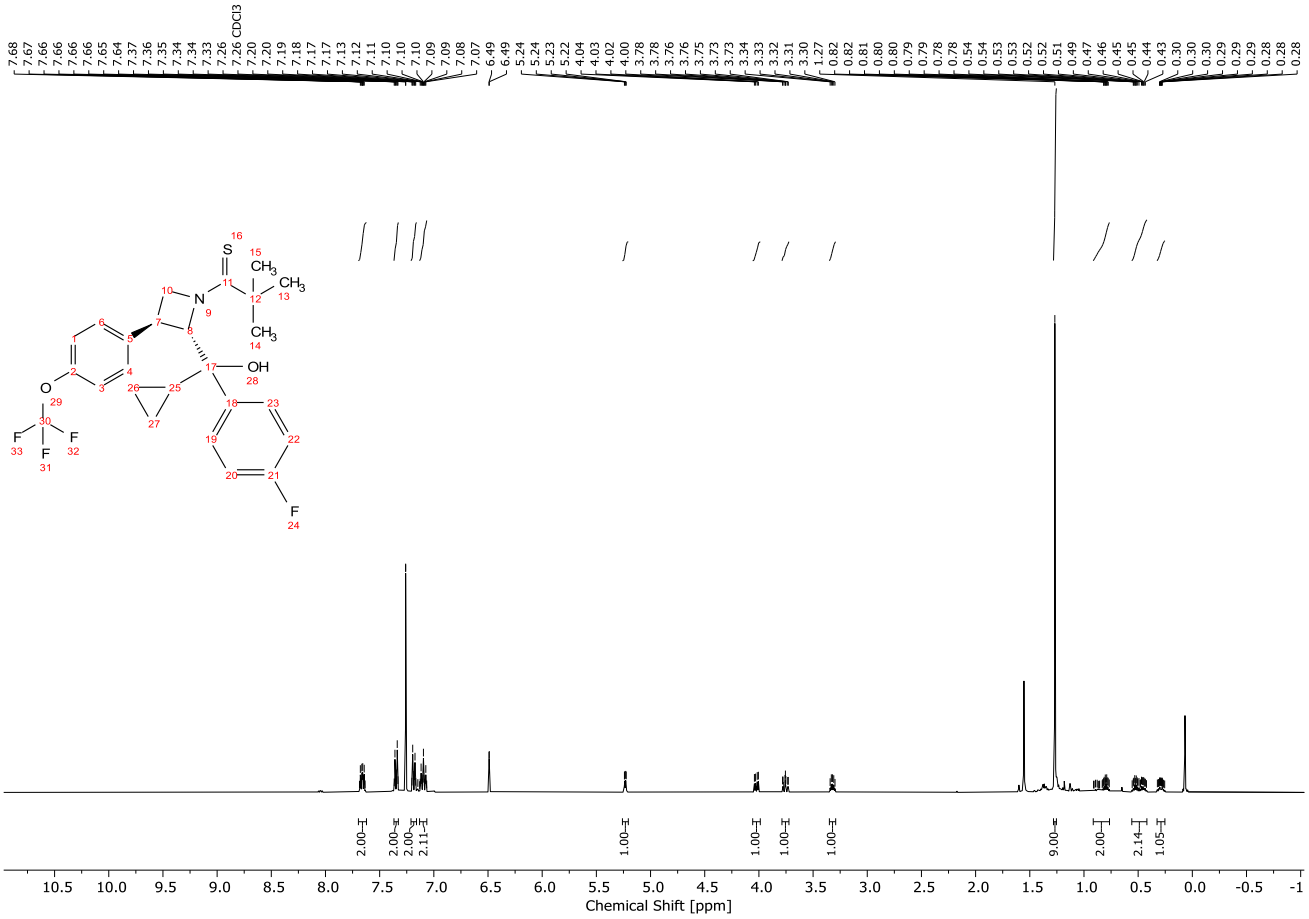


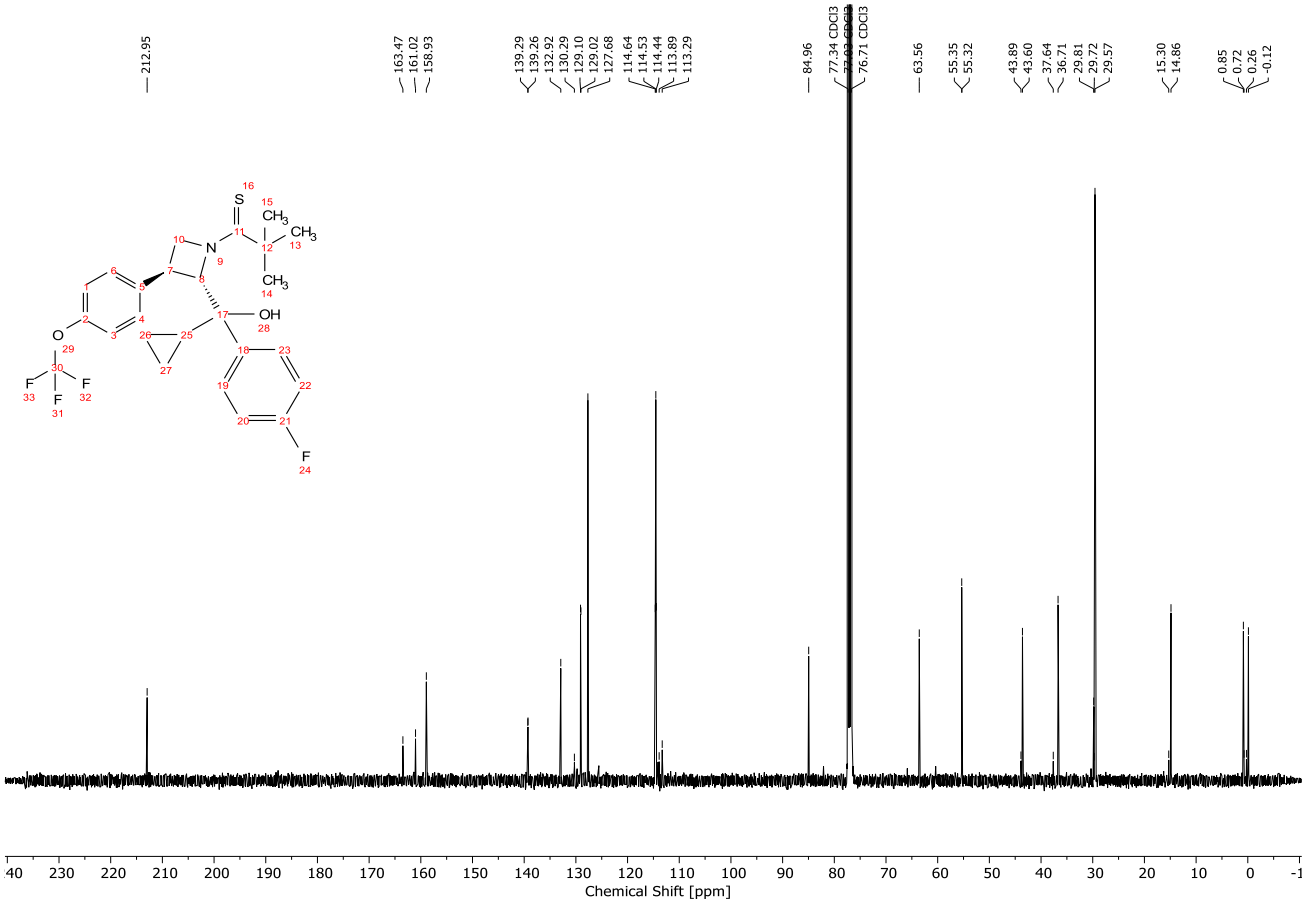

213.23
139.37
139.01
133.46
129.38
129.05
128.97
127.99
114.75
114.54
84.57
77.35 CDCl3
76.72 CDCl3
63.14
43.64
36.92
29.55
14.85
1.05
0.83
-0.07
S
CH3
CH3
CH3
N
OH
Cl
F
Chemical Shift [ppm]

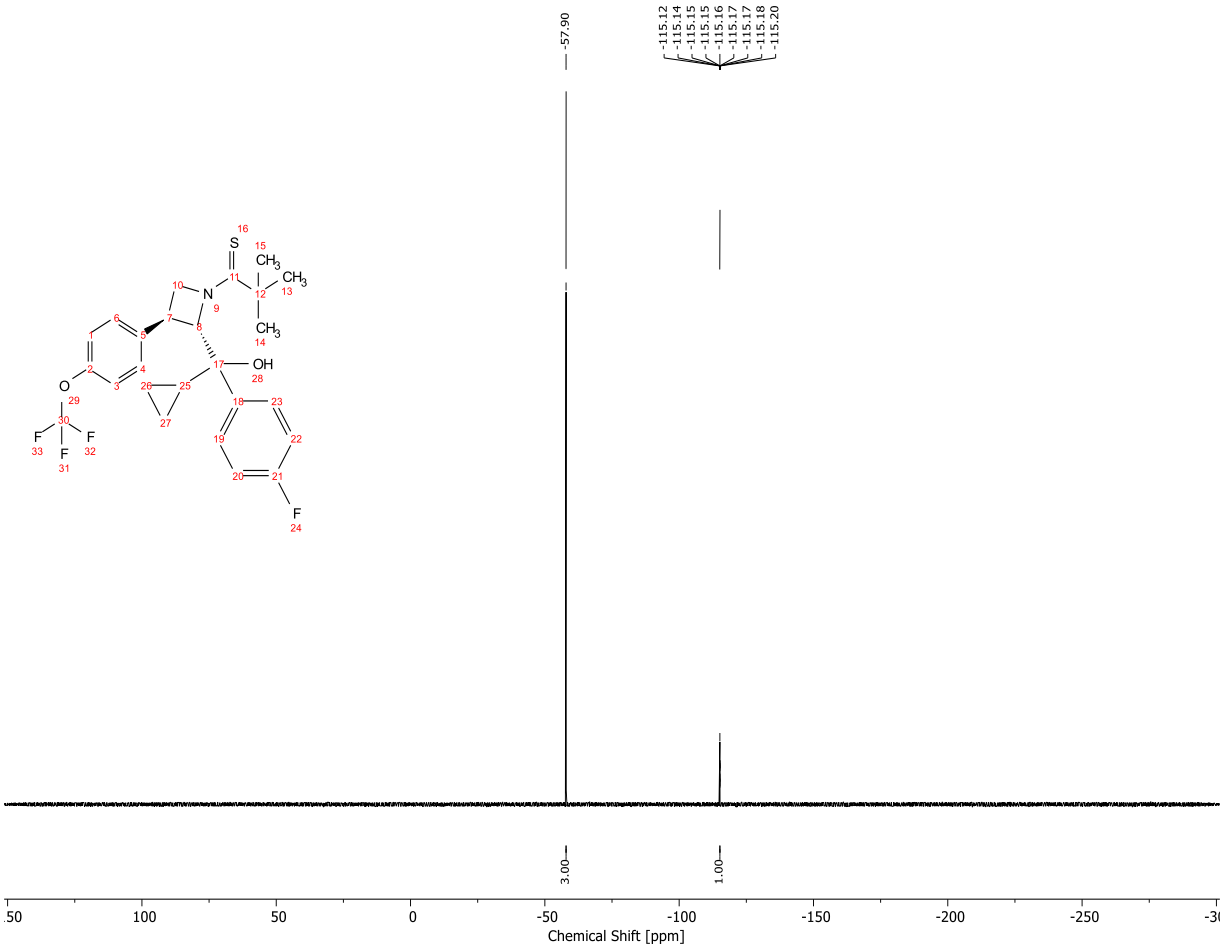

-115.16
-115.18
-115.19
-115.19
-115.20
-115.21
-115.22
-115.22
-115.24
1.00
50
100
50
0
-50
-100
-150
-200
-250
Chemical Shift [ppm]

(1-((2S,3S)-2-(cyclopropyl(4-fluorophenyl)(hydroxy)methyl)-3-(4-(trifluoromethoxy)phenyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione)

^{1}H NMR (400 MHz, $CDCl_3$), **^{13}C NMR** (101 MHz, $CDCl_3$) and **^{19}F NMR** (377 MHz, $CDCl_3$)

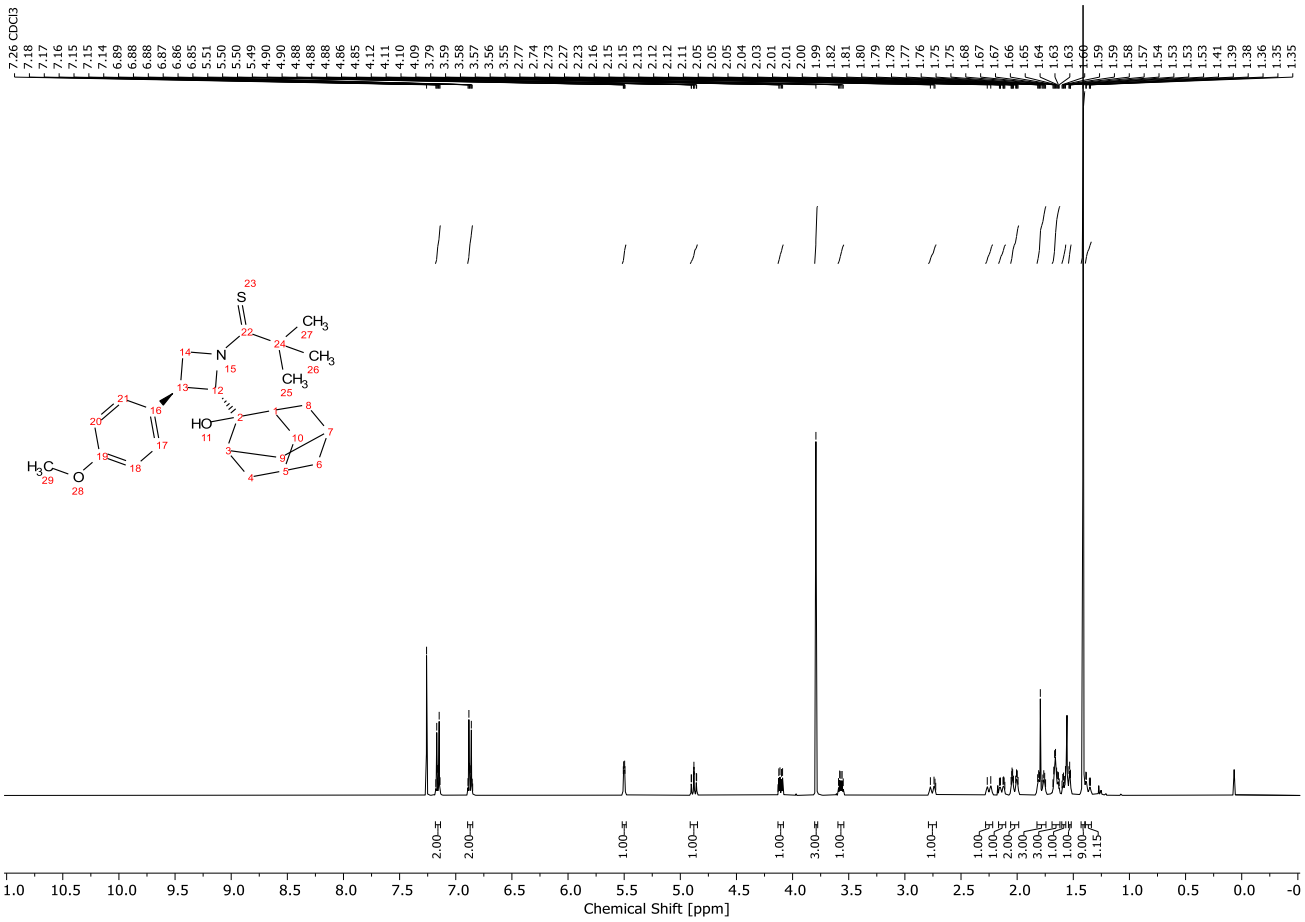


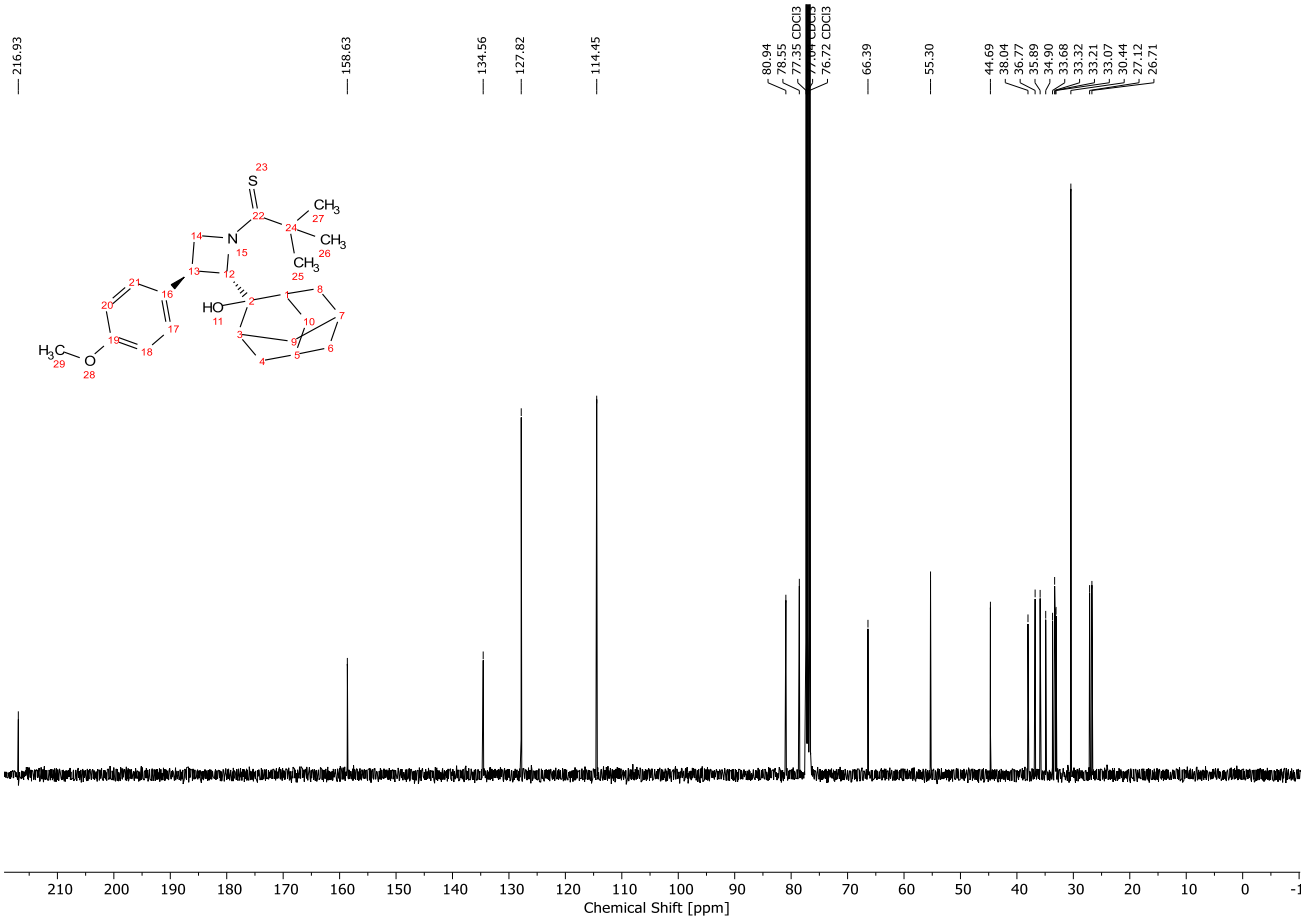

212.95
163.47
161.02
158.93
139.29
139.26
132.92
130.29
129.10
129.02
127.68
114.64
114.53
114.44
113.89
113.29
84.96
77.34 CDCl3
76.71 CDCl3
63.56
55.35
55.32
43.89
43.60
37.64
36.71
29.81
29.72
29.57
15.30
14.86
0.85
0.72
0.26
-0.12
Chemical Shift [ppm]


-57.90
-115.12
-115.14
-115.15
-115.15
-115.16
-115.17
-115.17
-115.18
-115.20
3.00
1.00
100
50
0
-50
-100
-150
-200
-250
Chemical Shift [ppm]

1-((2S,3S)-2-(2-hydroxyadamantan-2-yl)-3-(4-methoxyphenyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione

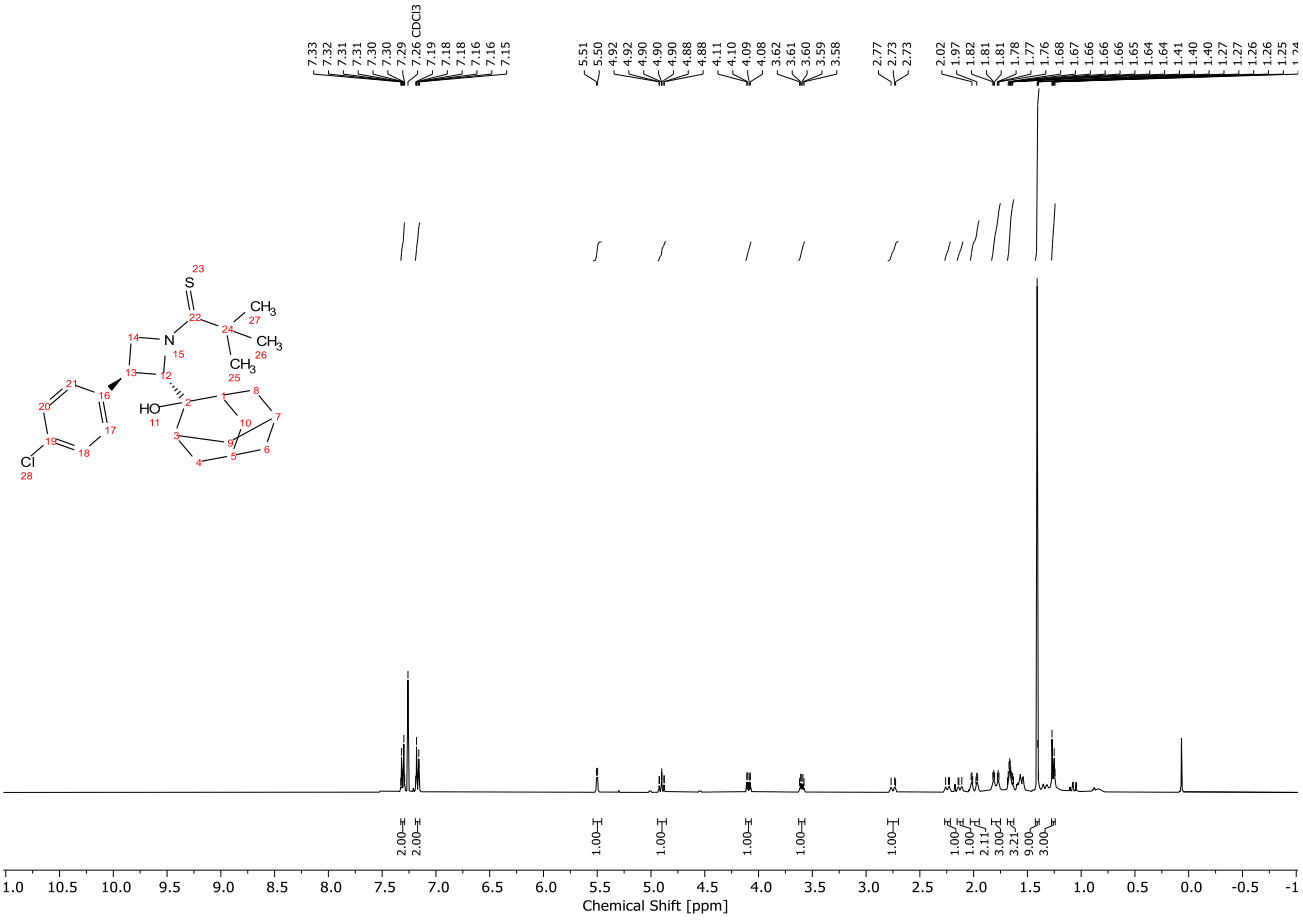
^{1}H NMR (400 MHz, $CDCl_3$) and **^{13}C NMR** (101 MHz, $CDCl_3$)

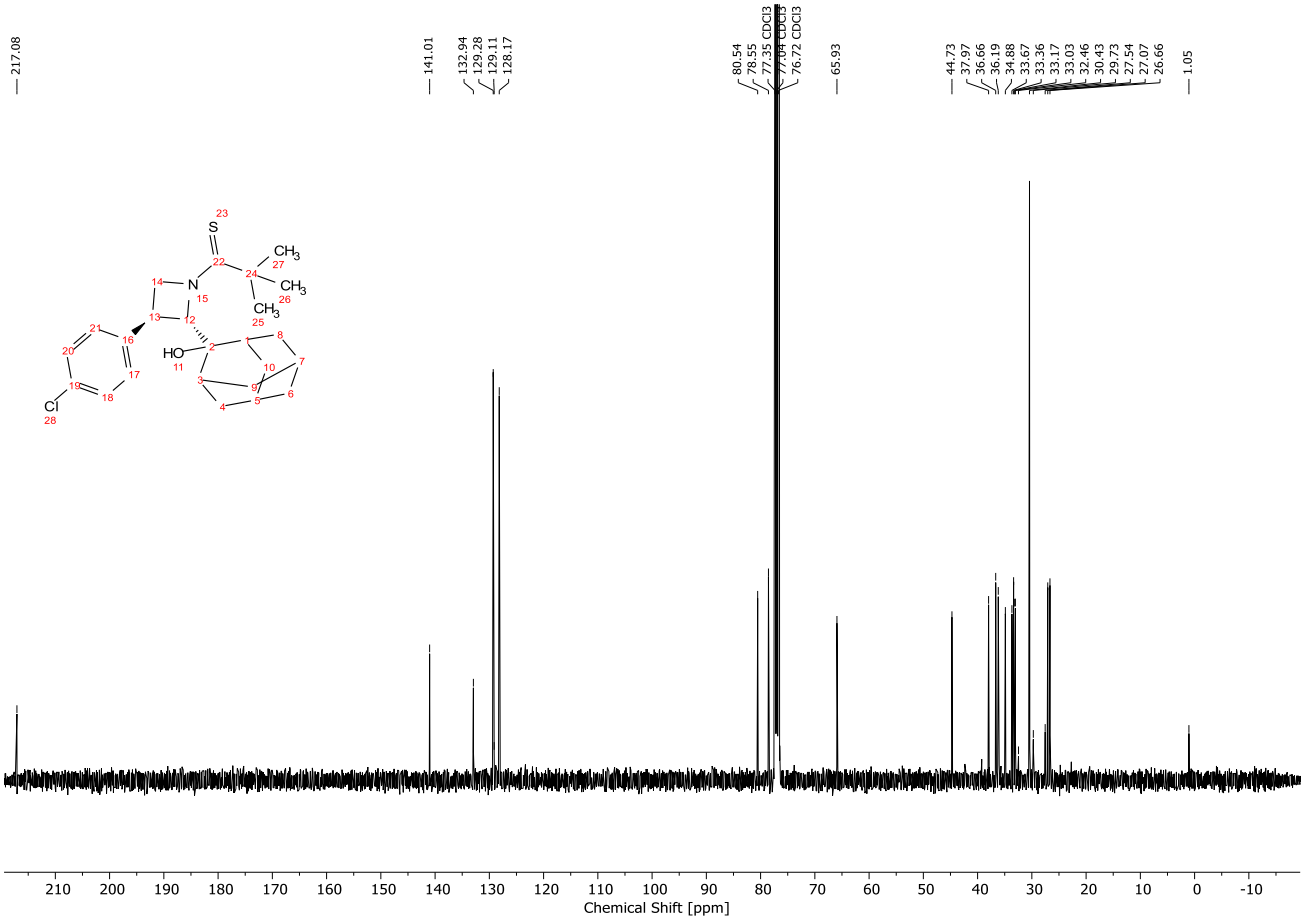



216.93
158.63
134.56
127.82
114.45
80.94
78.55
77.35 CDCl3
77.04 CDCl3
76.72 CDCl3
66.39
55.30
44.69
38.04
36.77
35.89
34.90
33.68
33.32
33.21
33.07
30.44
27.12
26.71
Chemical Shift [ppm]

1-((2S,3S)-3-(4-chlorophenyl)-2-(2-hydroxyadamantan-2-yl)azetidin-1-yl)-2,2-dimethylpropane-1-thione

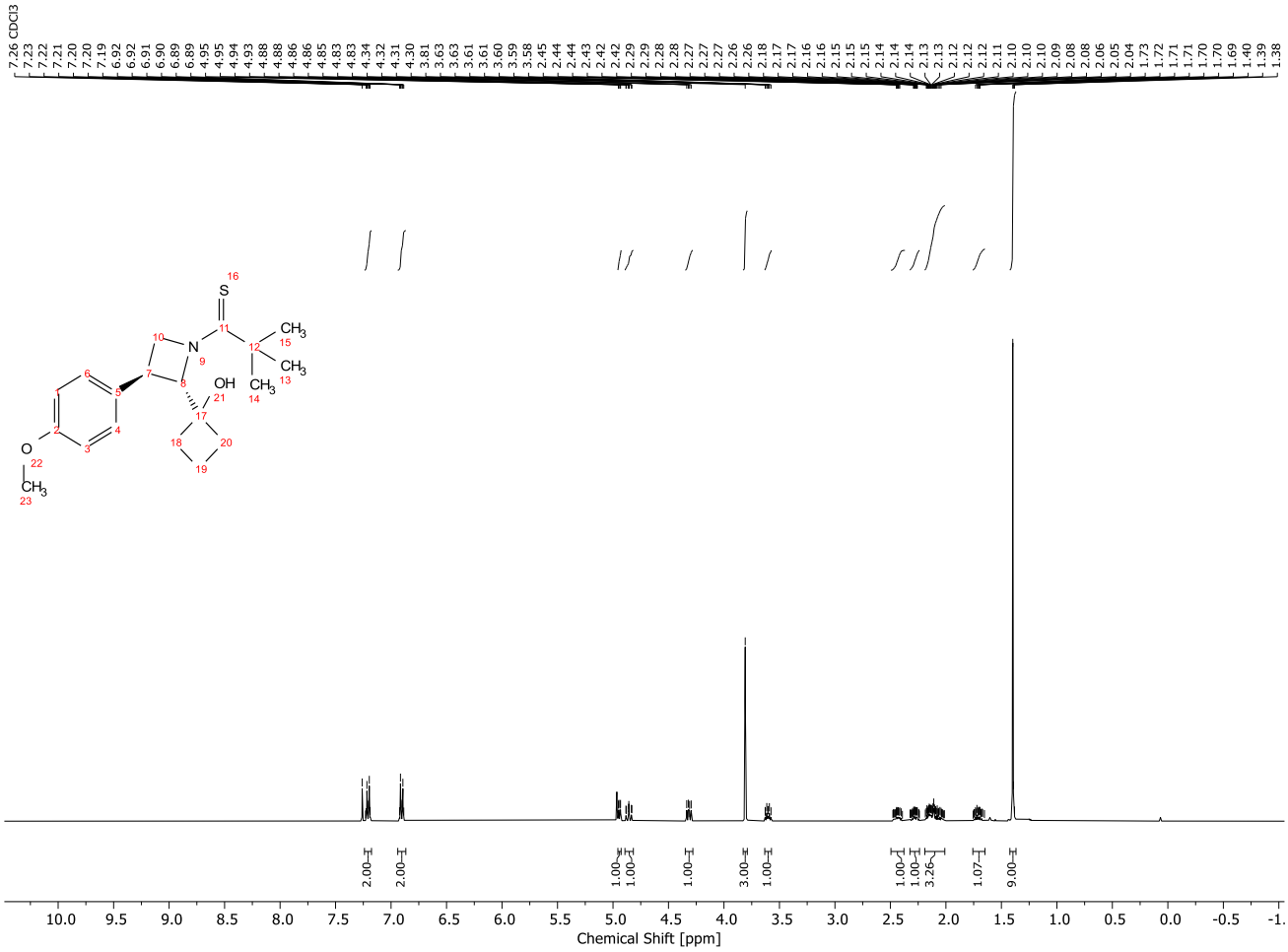
^{1}H NMR (400 MHz, $CDCl_3$) and **^{13}C NMR** (101 MHz, $CDCl_3$)

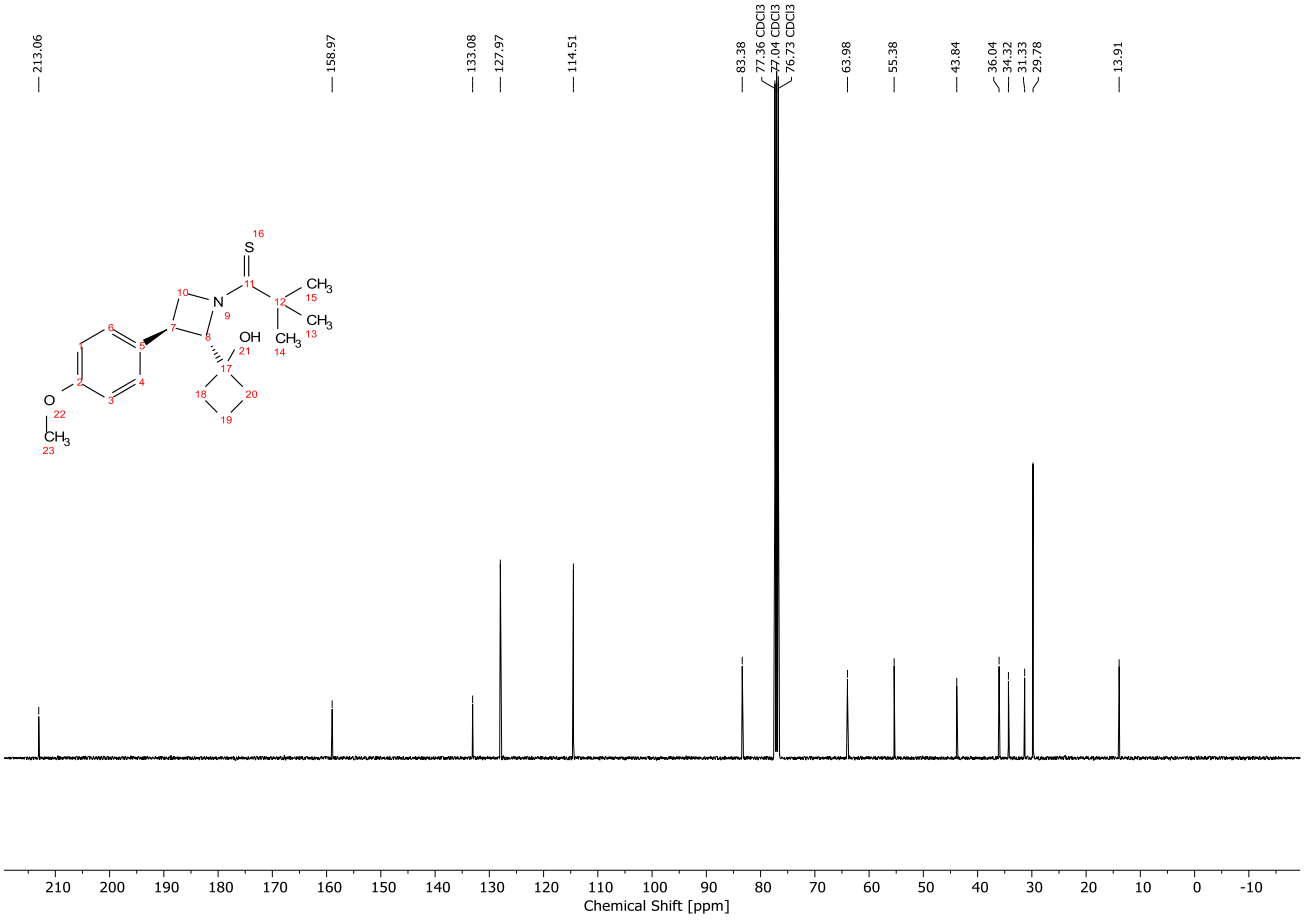



217.08
141.01
132.94
129.28
129.11
128.17
80.54
78.55
77.35 CDCl3
77.04 CDCl3
76.72 CDCl3
65.93
44.73
37.97
36.66
36.19
34.88
33.67
33.36
33.17
33.03
32.46
30.43
29.73
27.54
27.07
26.66
1.05
S
23
CH3
27
22
24
CH3
26
N
15
14
CH3
25
13
12
21
16
20
HO
11
2
1
8
10
7
17
3
9
19
18
6
4
5
Cl
28
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift [ppm]

1-((2S,3S)-2-(1-hydroxycyclobutyl)-3-(4-methoxyphenyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione

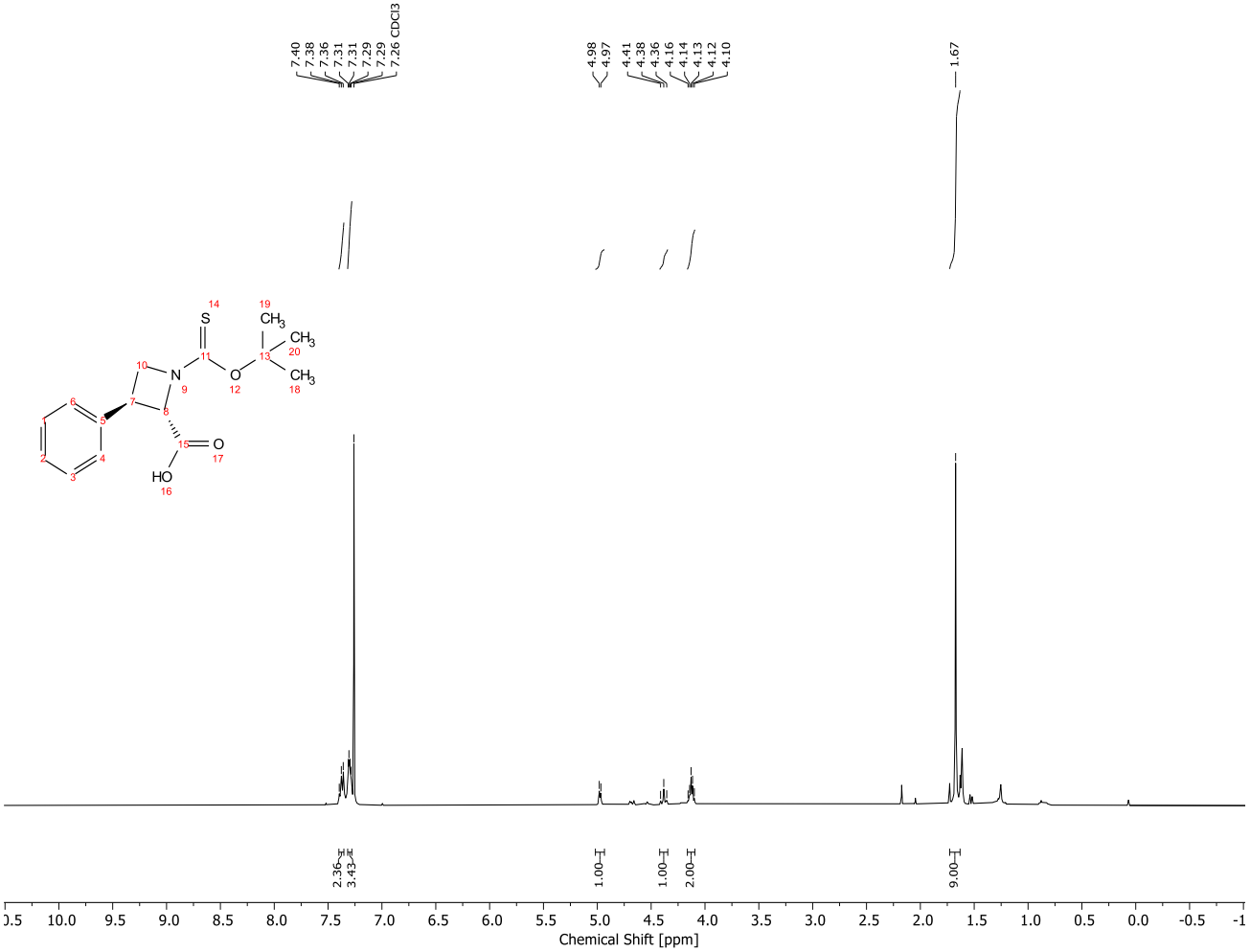
^{1}H NMR (400 MHz, $CDCl_3$) and **^{13}C NMR** (101 MHz, $CDCl_3$)

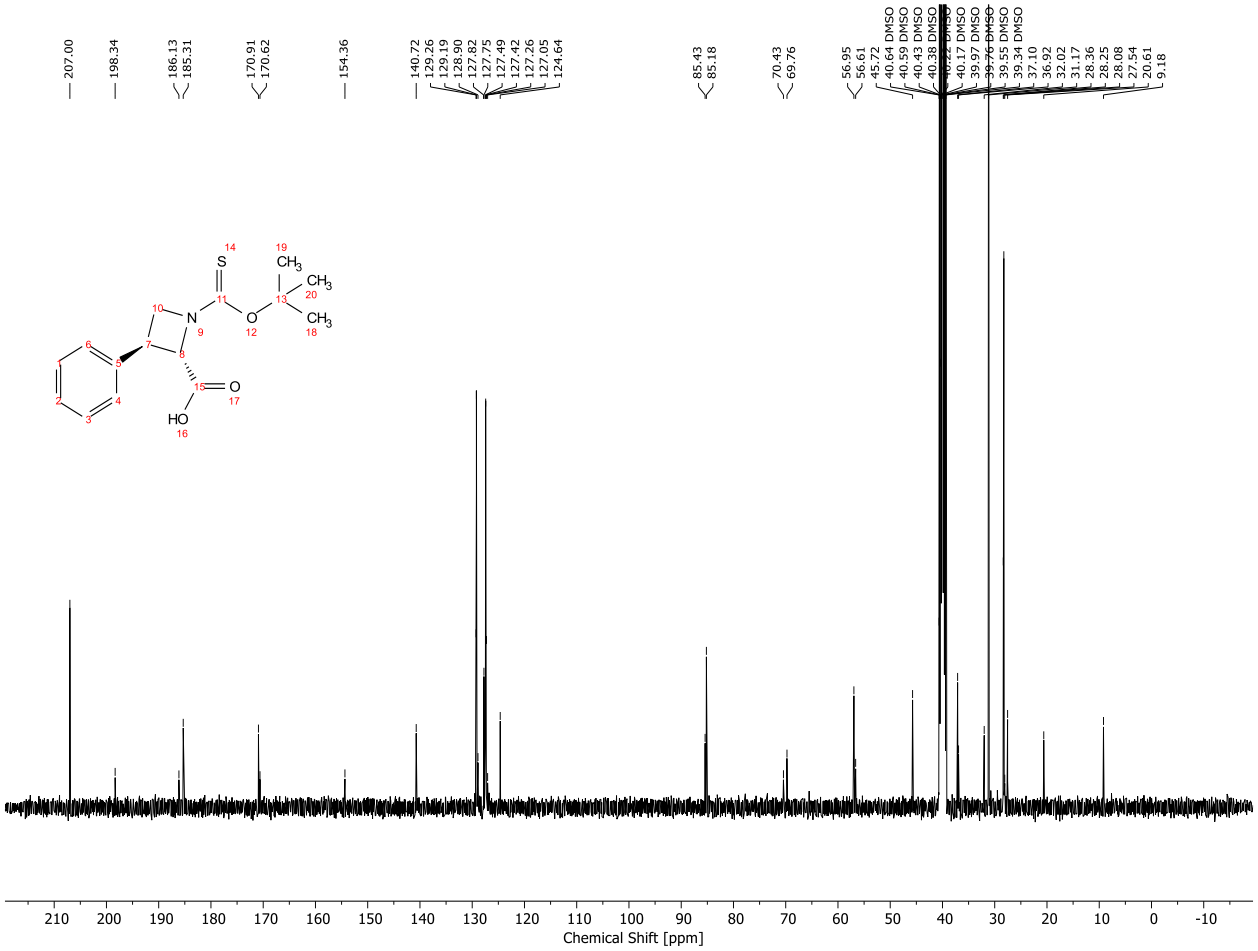



213.06
158.97
133.08
127.97
114.51
83.38
77.36 CDCl3
77.04 CDCl3
76.73 CDCl3
63.98
55.38
43.84
36.04
34.32
31.33
29.78
13.91
S
N
OH
O
CH3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift [ppm]

((2S,3S)-1-(tert-butoxycarbonothioyl)-3-phenylazetidine-2-carboxylic acid)

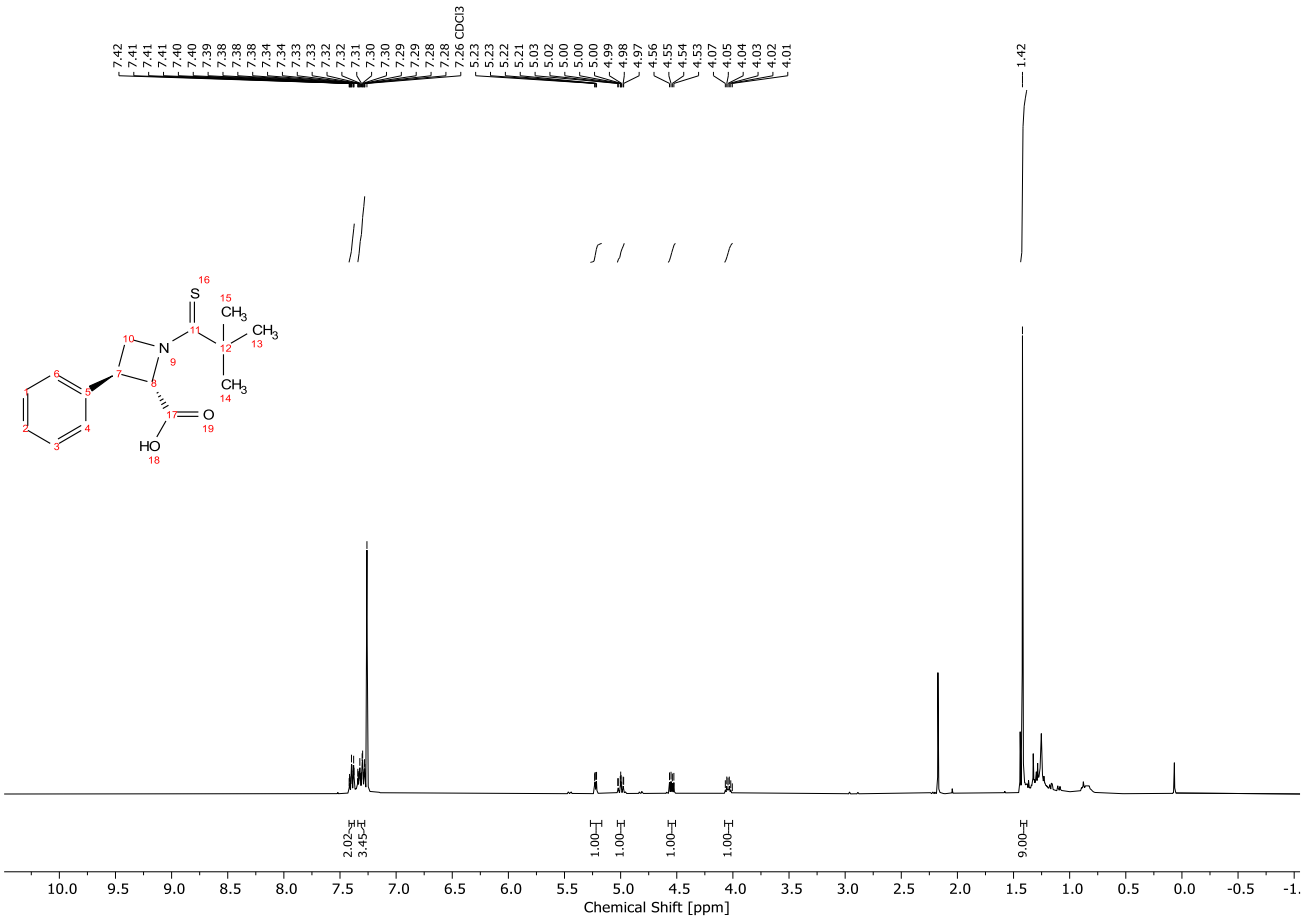
^{1}H NMR (400 MHz, $CDCl_3$) and **^{13}C NMR** (101 MHz, DMSO)

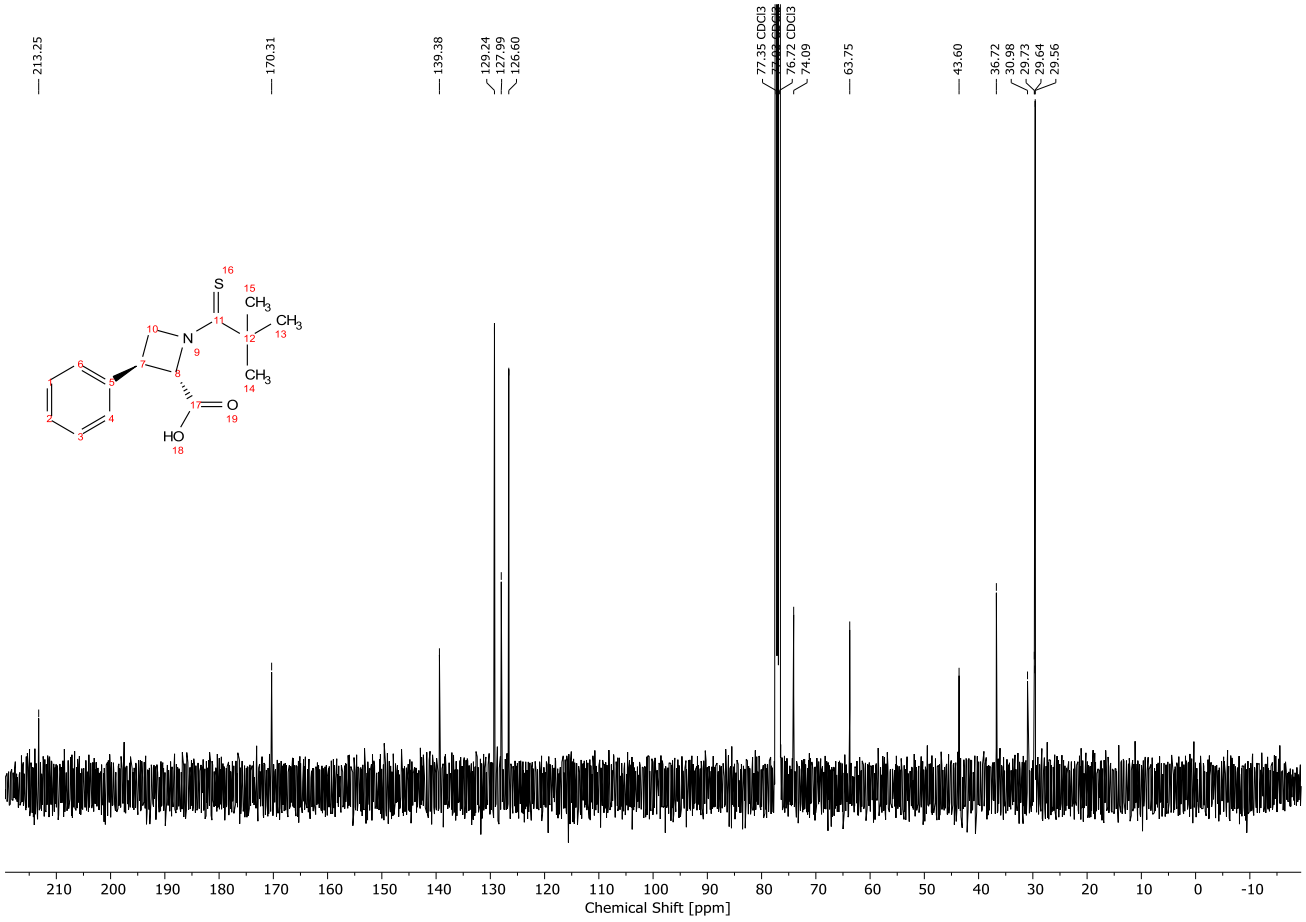



207.00
198.34
186.13
185.31
170.91
170.62
154.36
140.72
129.26
129.19
128.90
127.82
127.75
127.49
127.42
127.26
127.05
124.64
85.43
85.18
70.43
69.76
56.95
56.61
45.72
40.64 DMSO
40.59 DMSO
40.43 DMSO
40.38 DMSO
40.17 DMSO
39.97 DMSO
39.76 DMSO
39.55 DMSO
39.34 DMSO
37.10
36.92
32.02
31.17
28.36
28.25
28.08
27.54
20.61
9.18
S
CH3
CH3
CH3
N
O
O
HO
Chemical Shift [ppm]

((2S,3S)-1-(2,2-dimethylpropanethioyl)-3-phenylazetidine-2-carboxylic acid)

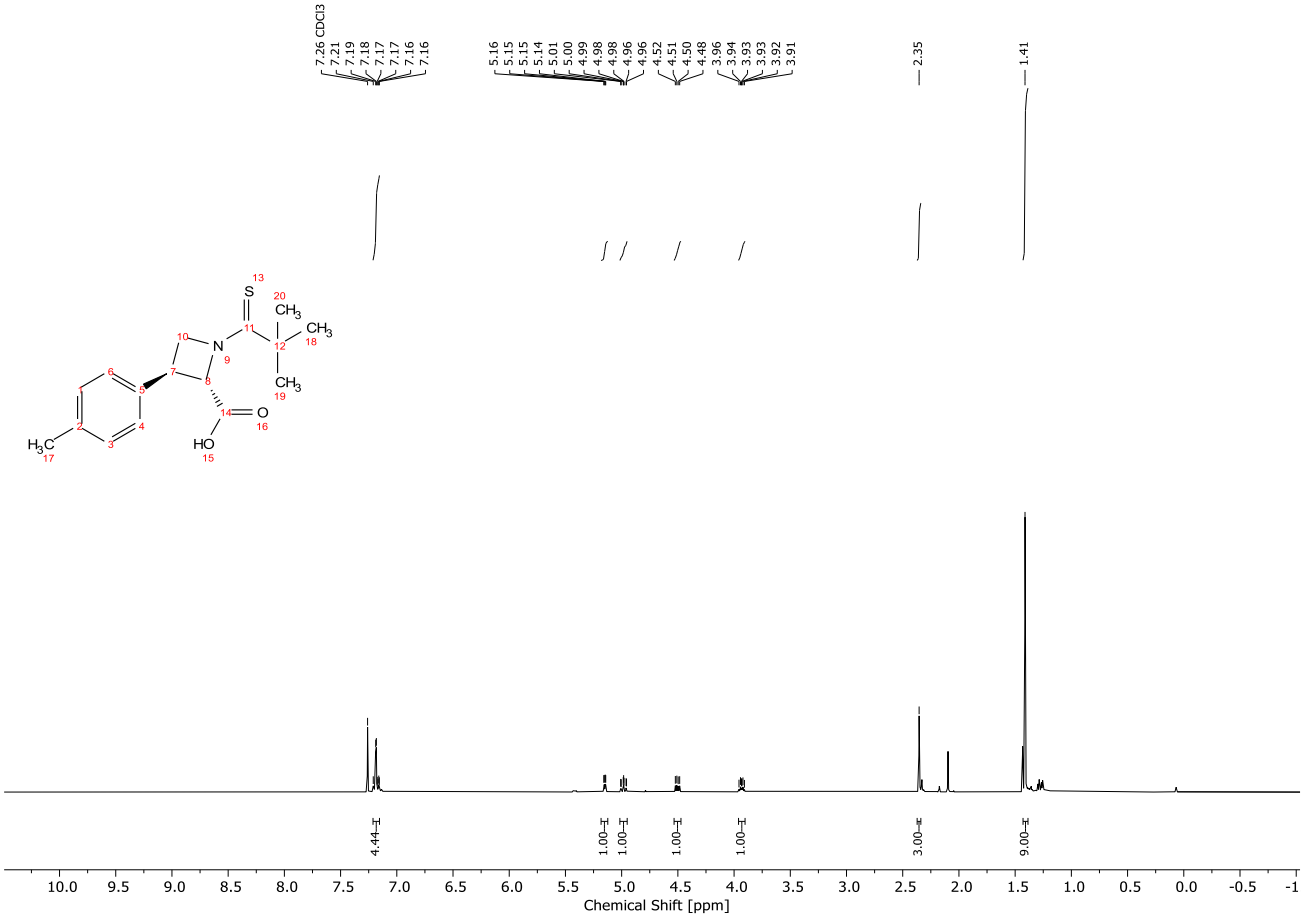
^{1}H NMR (400 MHz, $CDCl_3$) and **^{13}C NMR** (101 MHz, $CDCl_3$)

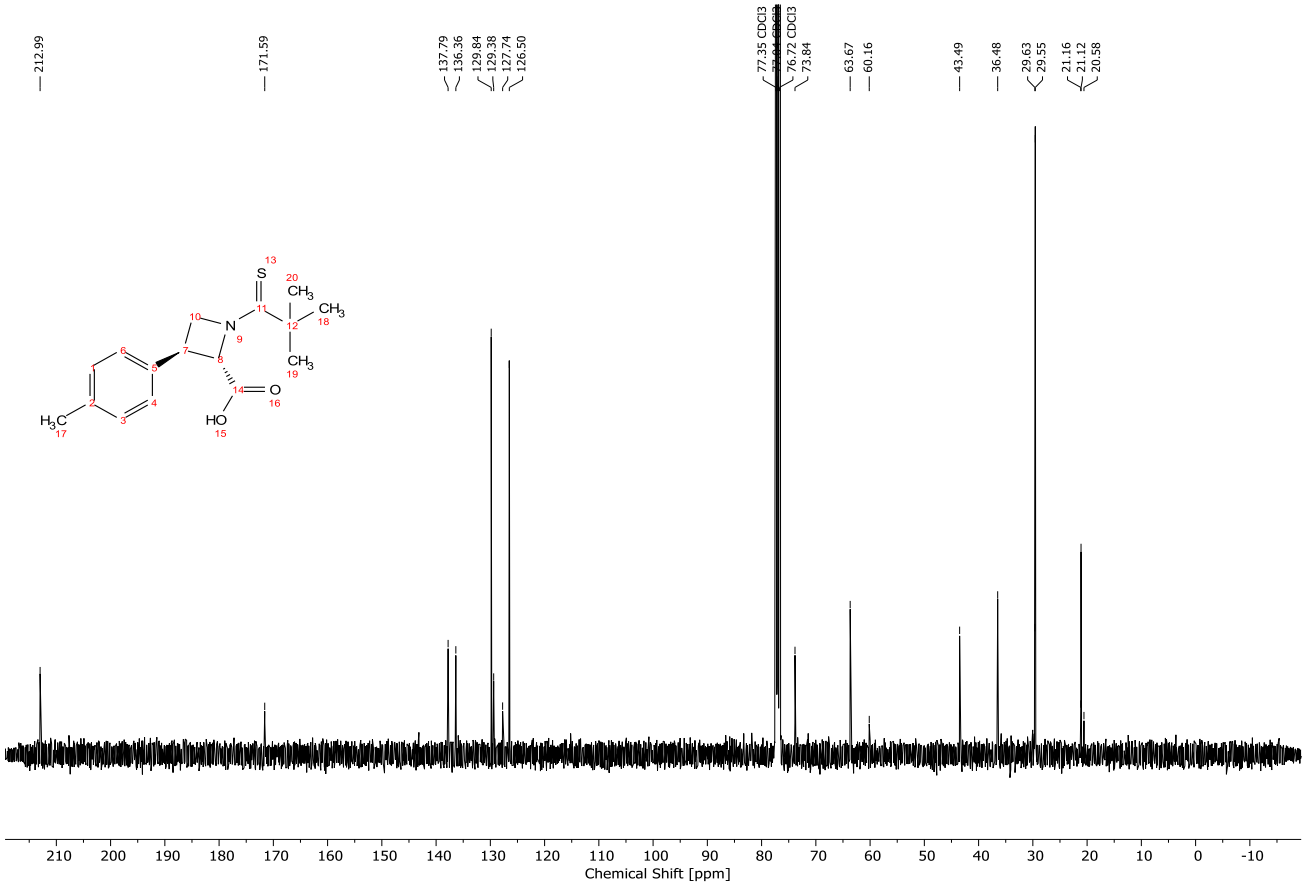



213.25
170.31
139.38
129.24
127.99
126.60
77.35 CDCl3
77.03 CDCl3
76.72 CDCl3
74.09
63.75
43.60
36.72
30.98
29.73
29.64
29.56
S
CH3
CH3
CH3
N
HO
O
Chemical Shift [ppm]

(2S,3S)-1-(2,2-dimethylpropanethioyl)-3-(p-tolyl)azetidine-2-carboxylic acid

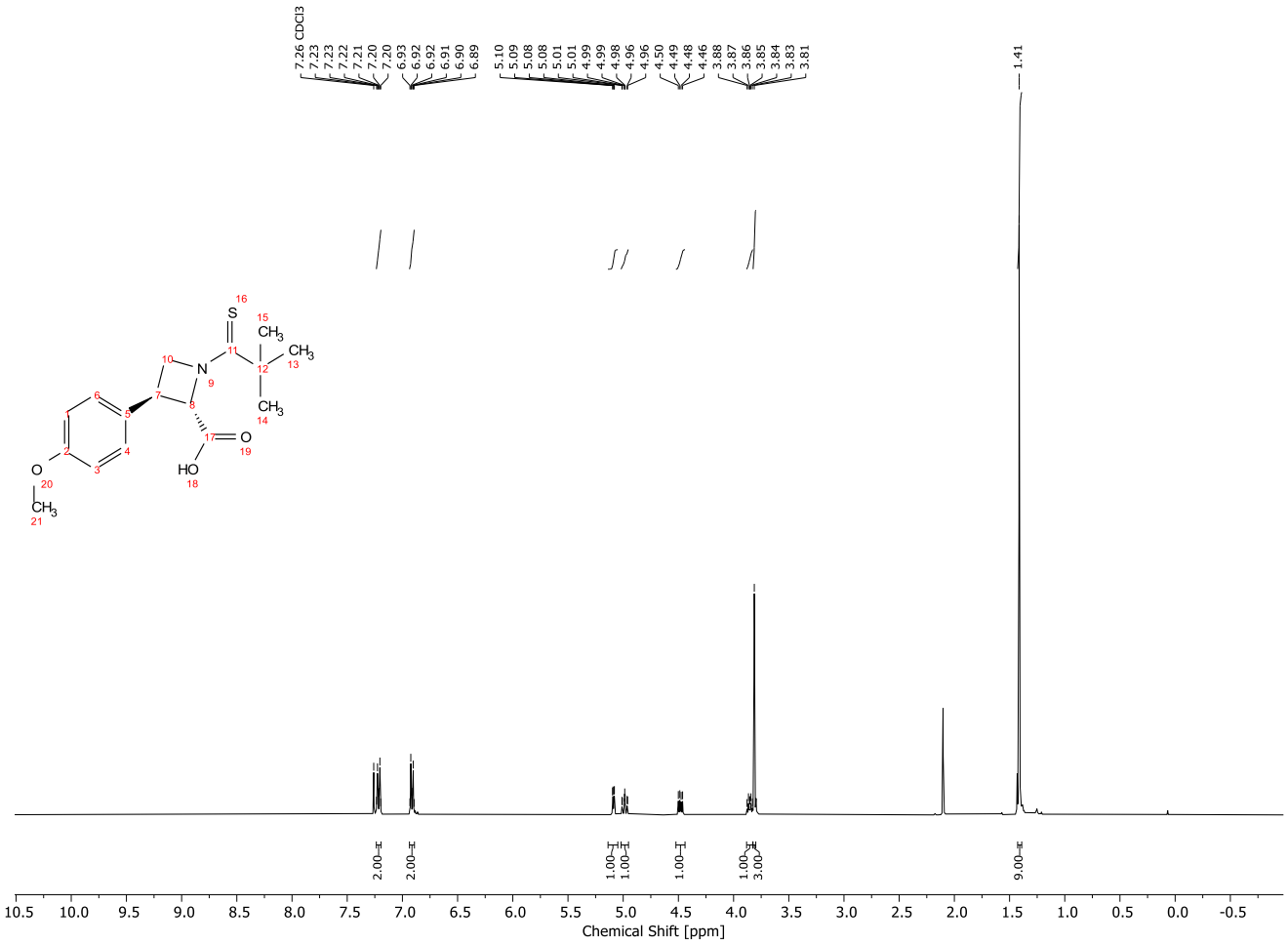
^{1}H NMR (400 MHz, $CDCl_3$) and **^{13}C NMR** (101 MHz, $CDCl_3$)

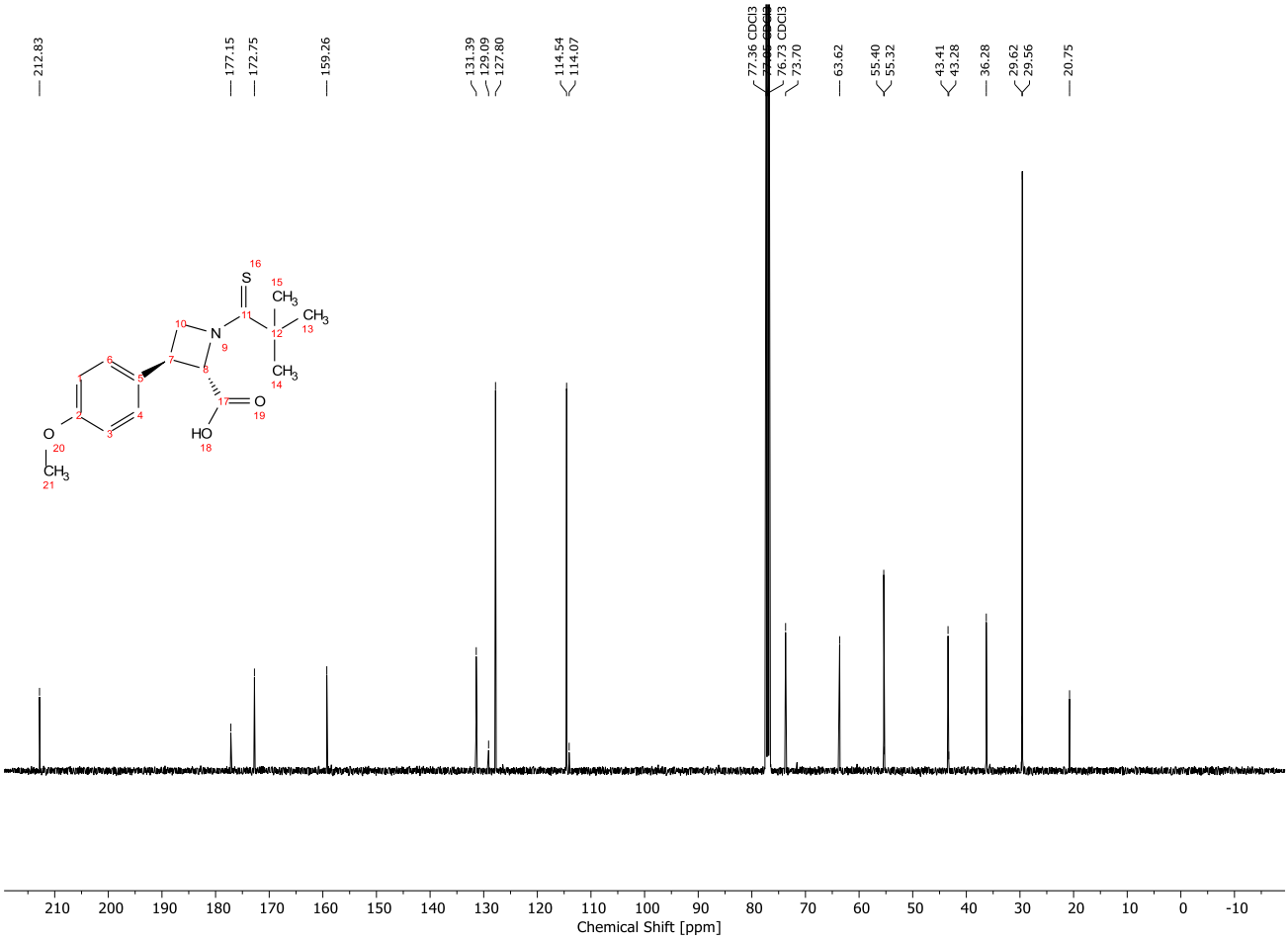



212.99
171.59
137.79
136.36
129.84
129.38
127.74
126.50
77.35 CDCl3
76.72 CDCl3
73.84
63.67
60.16
43.49
36.48
29.63
29.55
21.16
21.12
20.58
Chemical Shift [ppm]

((2S,3S)-1-(2,2-dimethylpropanethioyl)-3-(4-methoxyphenyl)azetidine-2-carboxylic acid)

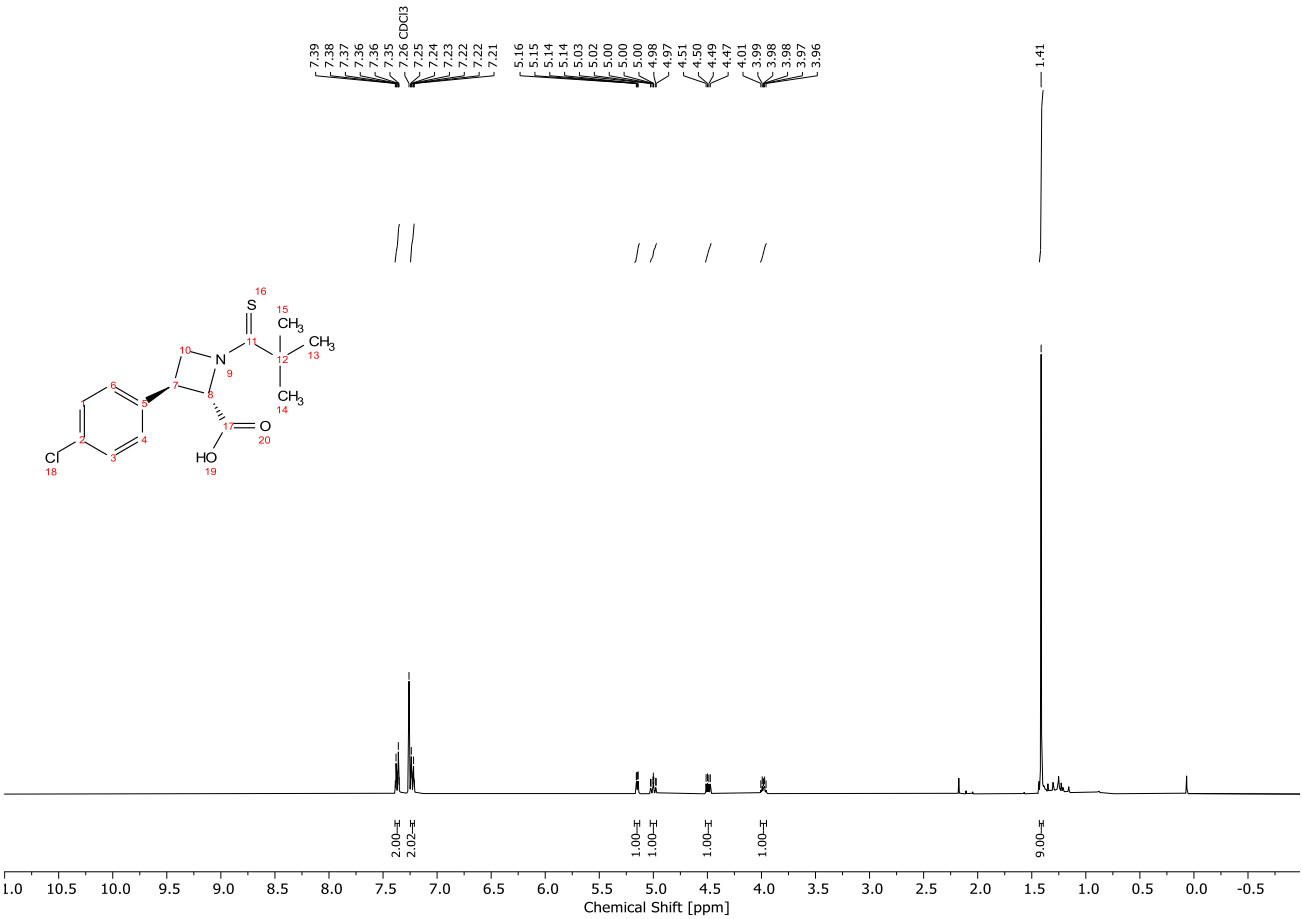
^{1}H NMR (400 MHz, $CDCl_3$) and **^{13}C NMR** (101 MHz, $CDCl_3$)

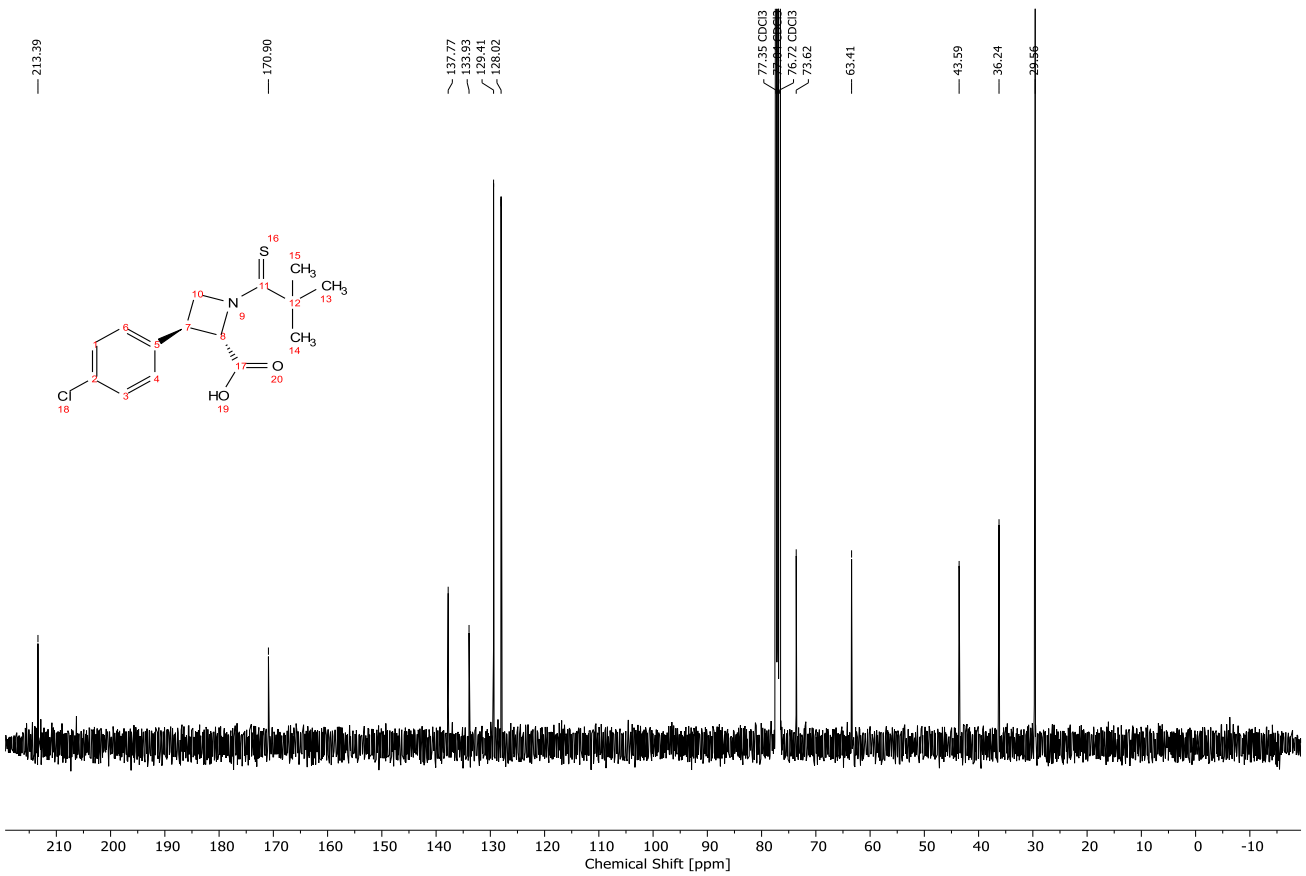



212.83
177.15
172.75
159.26
131.39
129.09
127.80
114.54
114.07
77.36 CDCl3
76.73 CDCl3
73.70
63.62
55.40
55.32
43.41
43.28
36.28
29.62
29.56
20.75
Chemical Shift [ppm]

(2S,3S)-3-(4-chlorophenyl)-1-(2,2-dimethylpropanethioyl)azetidine-2-carboxylic acid

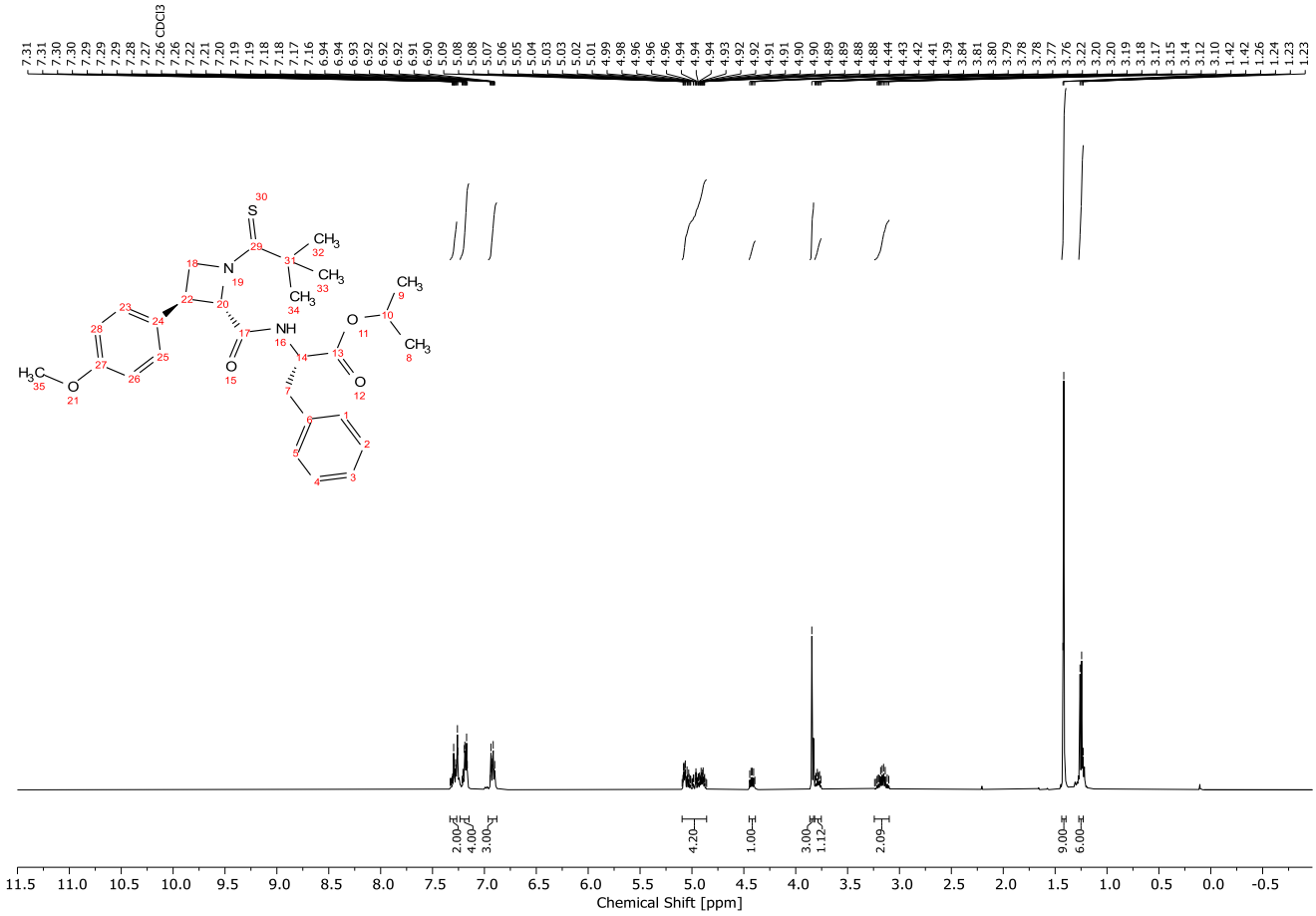
^{1}H NMR (400 MHz, $CDCl_3$) and **^{13}C NMR** (101 MHz, $CDCl_3$)

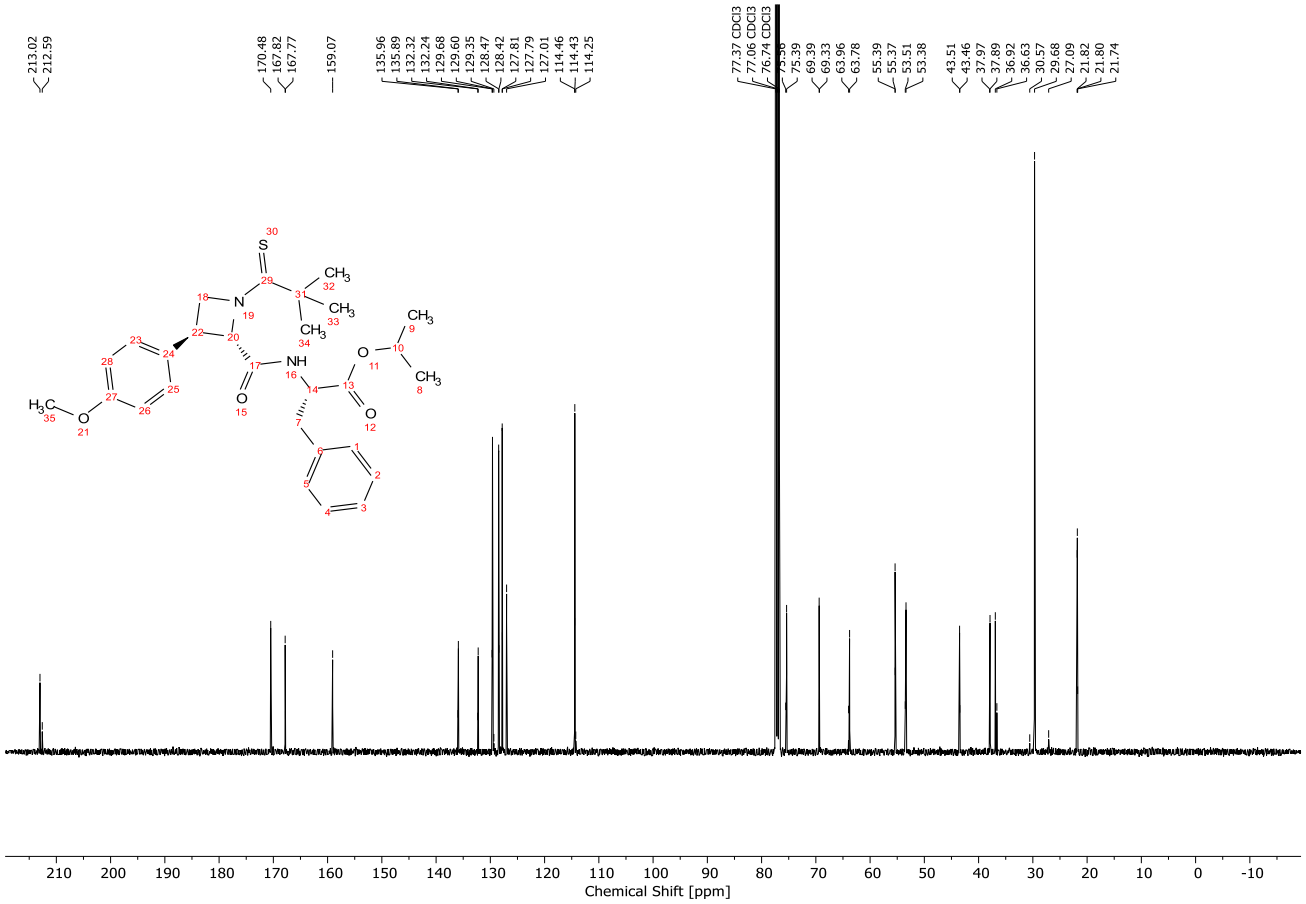


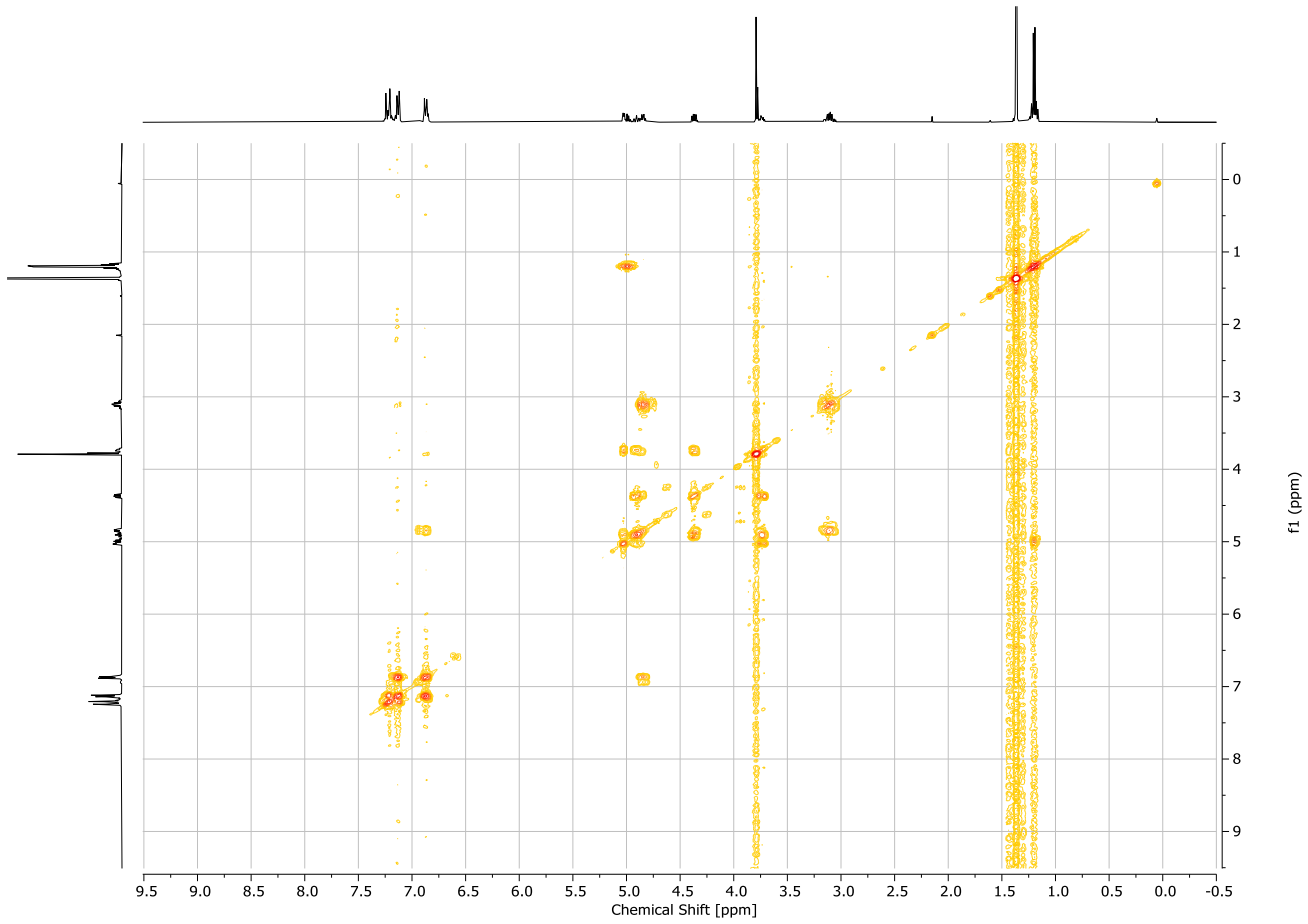

213.39
170.90
137.77
133.93
129.41
128.02
77.35 CDCl3
76.72 CDCl3
73.62
63.41
43.59
36.24
29.56
Chemical Shift [ppm]

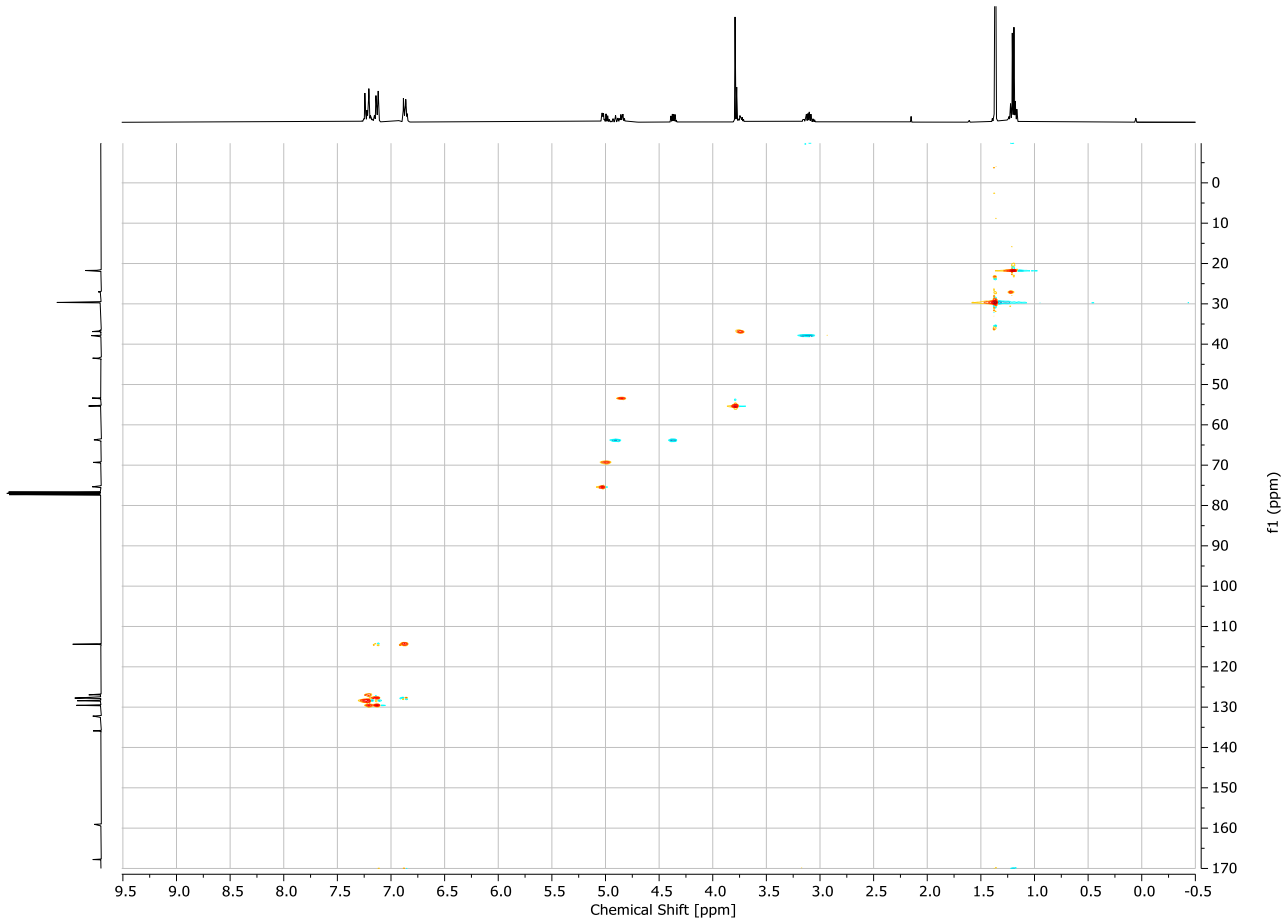
Isopropyl ((2S,3S)-1-(2,2-dimethylpropanethioyl)-3-(4-methoxyphenyl)azetidine-2-carbonyl)-L-phenylalaninate

^{1}H NMR (400 MHz, $CDCl_3$) and **^{13}C NMR** (101 MHz, $CDCl_3$)



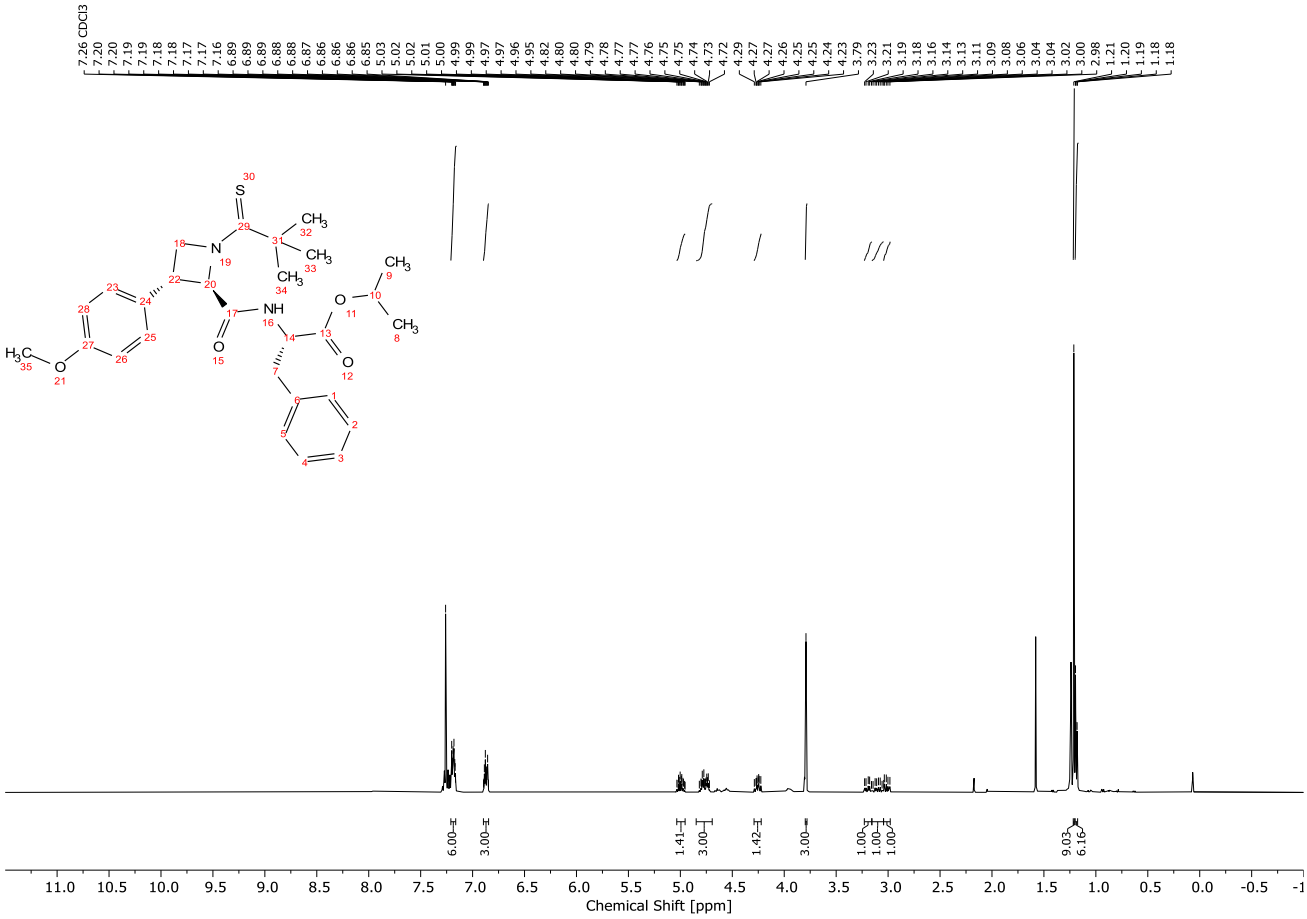

213.02
212.59
170.48
167.82
167.77
159.07
135.96
135.89
132.32
132.24
129.68
129.60
129.35
128.47
128.42
127.81
127.79
127.01
114.46
114.43
114.25
77.37 CDCl3
77.06 CDCl3
76.74 CDCl3
75.39
69.39
69.33
63.96
63.78
55.39
55.37
53.51
53.38
43.51
43.46
37.97
37.89
36.92
36.63
30.57
29.68
27.09
21.82
21.80
21.74
Chemical Shift [ppm]

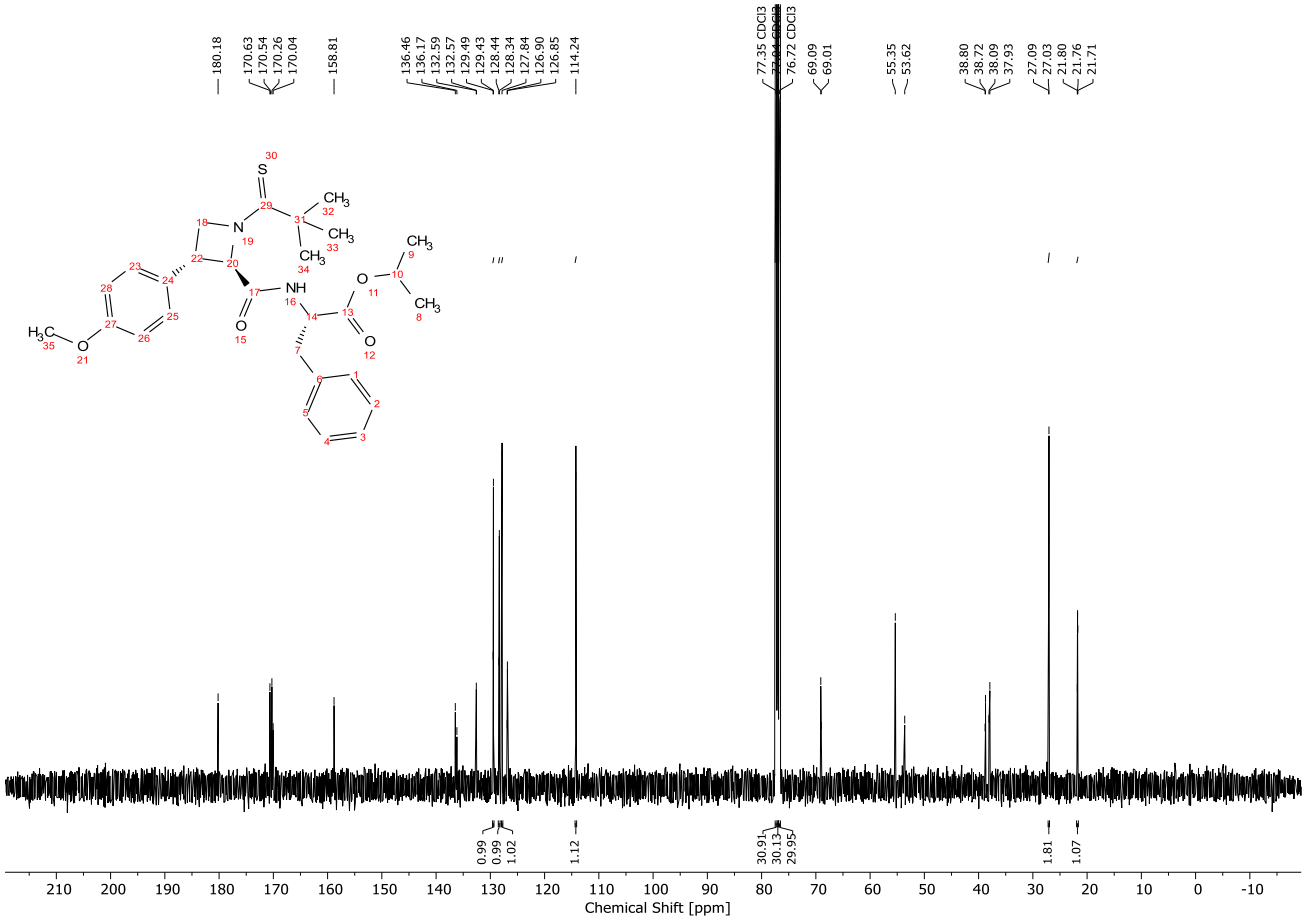

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
Chemical Shift [ppm]
0 1 2 3 4 5 6 7 8 9
f1 (ppm)

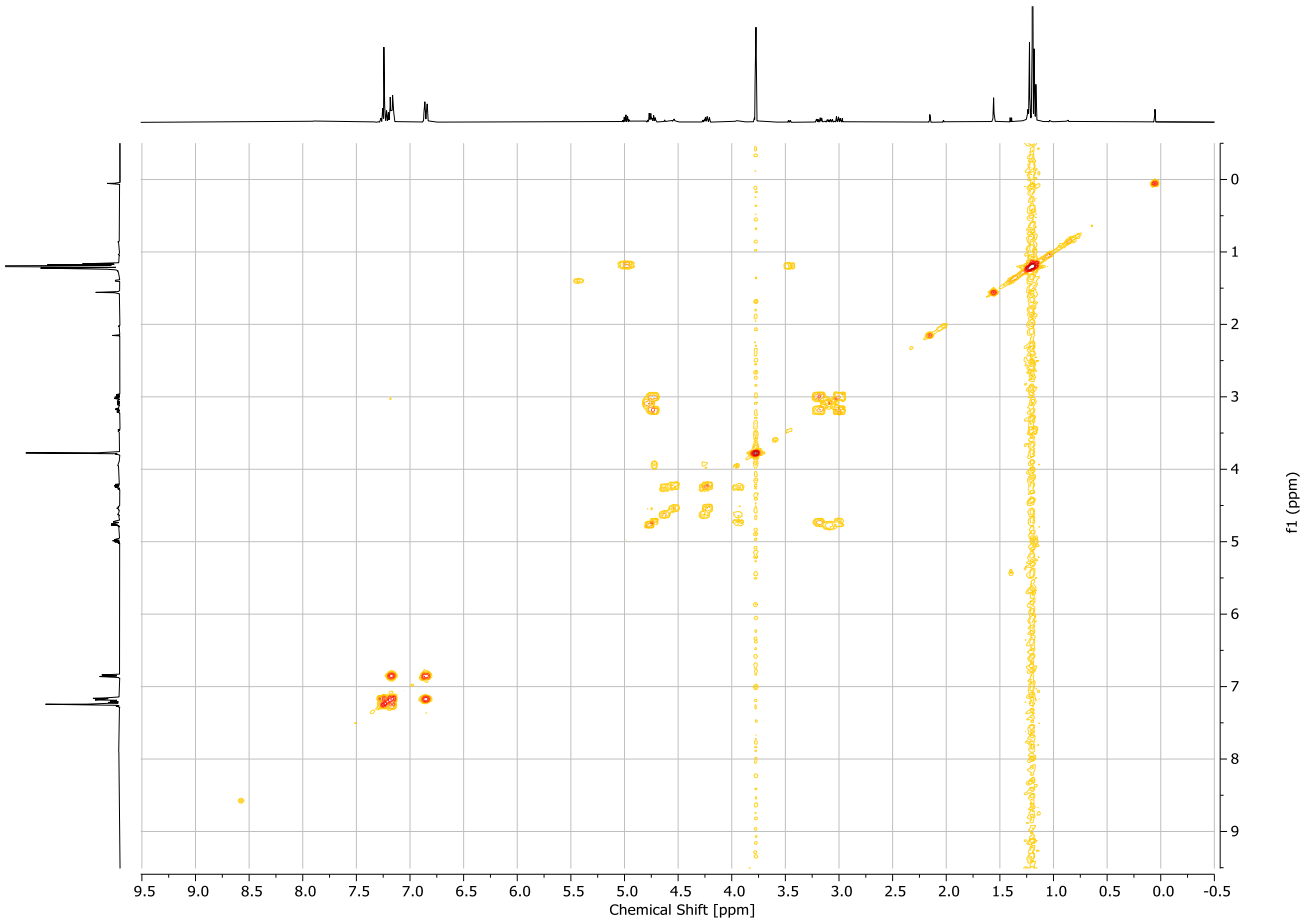

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
Chemical Shift [ppm]
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170
f1 (ppm)

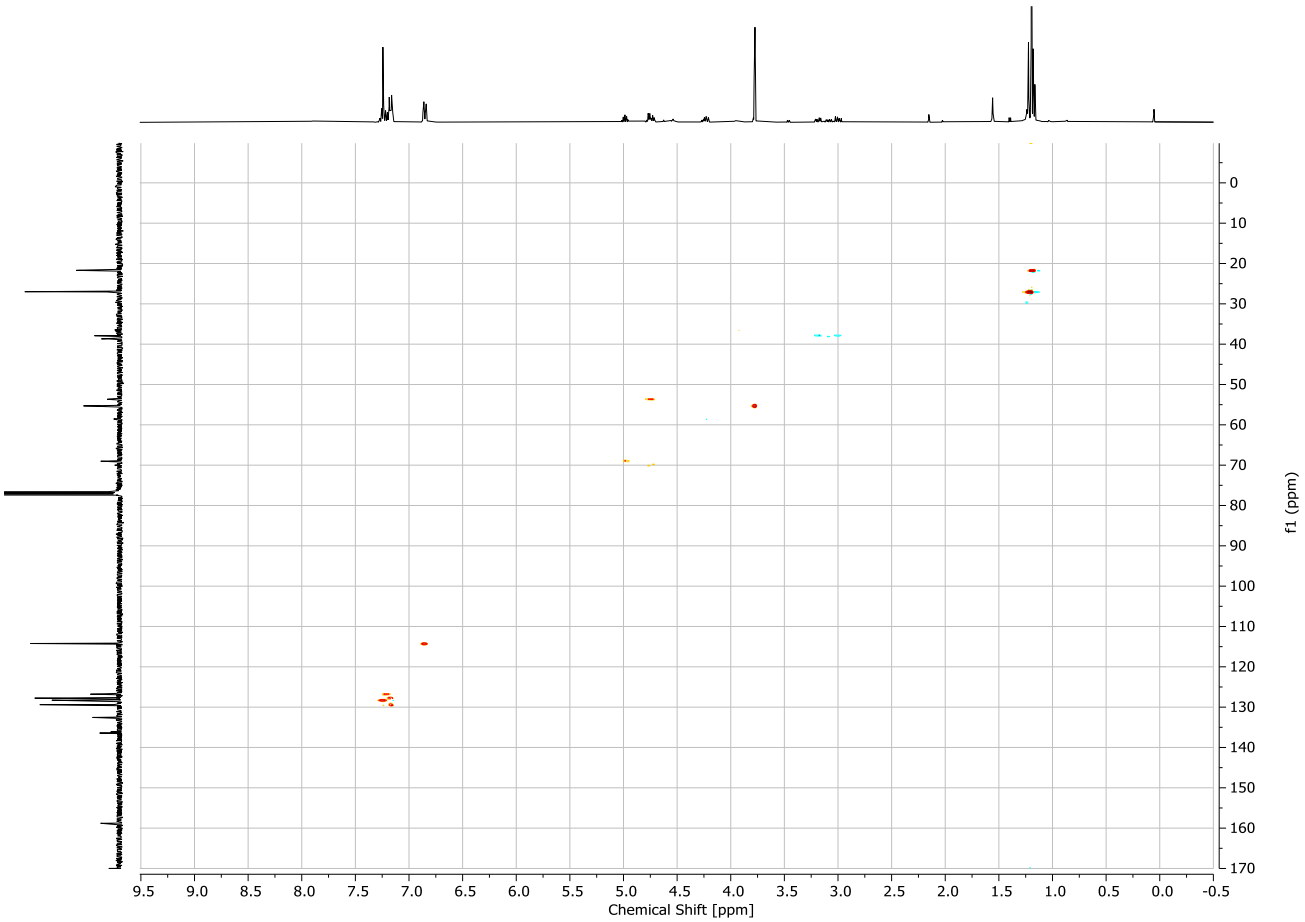
Isopropyl ((2R,3R)-1-(2,2-dimethylpropanethioyl)-3-(4-methoxyphenyl)azetidine-2-carbonyl)-L-phenylalaninate

^{1}H NMR (400 MHz, $CDCl_3$) and **^{13}C NMR** (101 MHz, $CDCl_3$)




180.18
170.63
170.54
170.26
170.04
158.81
136.46
136.17
132.59
132.57
129.49
129.43
128.44
128.34
127.84
126.90
126.85
114.24
77.35 CDCl3
77.04 CDCl3
76.72 CDCl3
69.09
69.01
55.35
53.62
38.80
38.72
38.09
37.93
27.09
27.03
21.80
21.76
21.71
0.99
0.99
1.02
1.12
30.91
30.13
29.95
1.81
1.07
Chemical Shift [ppm]


9.5 9.0 8.5 8.0 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 0.0 -0.5
Chemical Shift [ppm]
0 1 2 3 4 5 6 7 8 9
f1 (ppm)


0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
f1 (ppm)
9.5
9.0
8.5
8.0
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
0.0
-0.5
Chemical Shift [ppm]

7 Single Crystal X-Ray Diffraction

Experimental details

The X-ray intensity data of av498 were measured on a Bruker D8 Venture TXS system equipped with a multilayer mirror monochromator and a Mo Kα rotating anode X-ray tube (λ = 0.71073 Å). The frames were integrated with the Bruker SAINT software package [1]. Data were corrected for absorption effects using the Multi-Scan method (SADABS) [2]. The structure was solved and refined using the Bruker SHELXTL Software Package [3]. All C-bound hydrogen atoms have been calculated in ideal geometry riding on their parent atoms, the O-bound hydrogen atoms have been refined freely. The figures have been drawn at the 25% ellipsoid probability level [4]. The asymmetric unit contains two formula units one of which has been depicted above.

References:

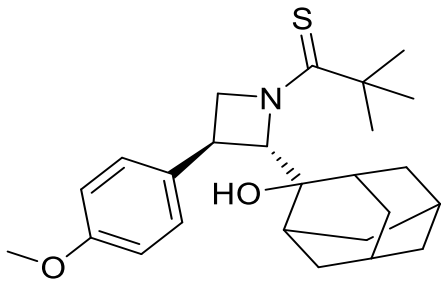
[1] Bruker (2012). SAINT. Bruker AXS Inc., Madison, Wisconsin, USA.

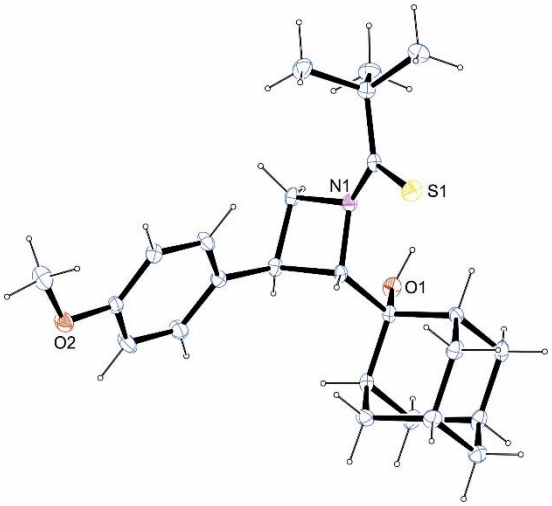
[2] Sheldrick, G. M. (1996). SADABS. University of Göttingen, Germany.

[3] Sheldrick, G. M. (2015). Acta Cryst. A71, 3-8.

[4] Farrugia, L. J. (2012). J. Appl. Cryst. 45, 849-854.

Crystallographic Data of 1-(2-(2-hydroxyadamantan-2-yl)-3-(4-methoxyphenyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione.

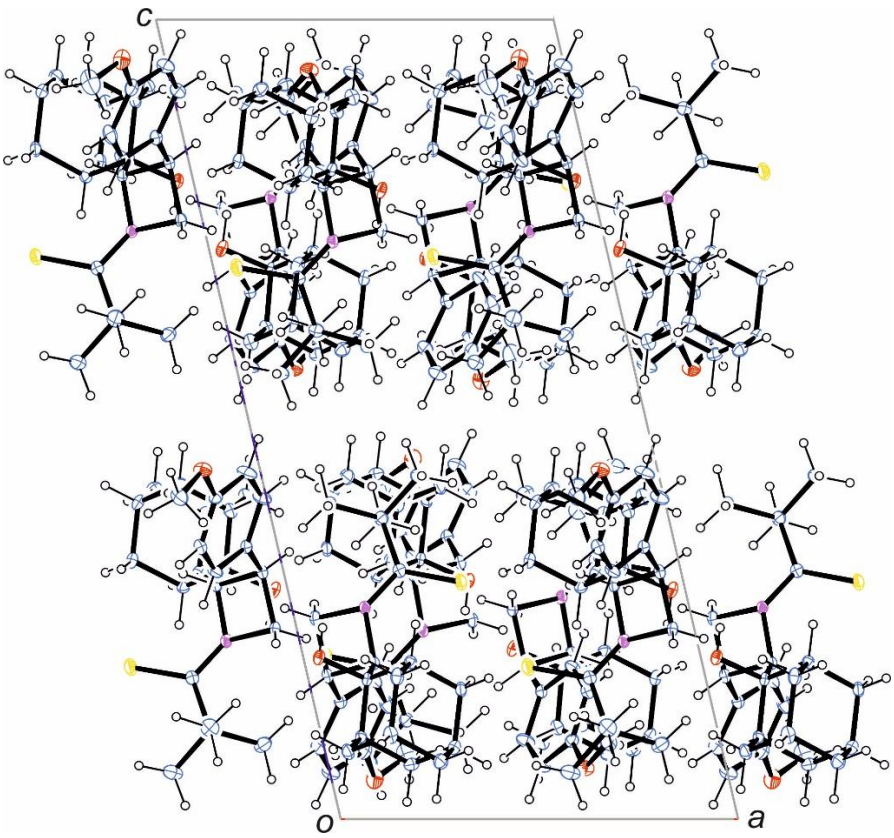




net formula	$C_{25}H_{35}NO_2S$
M_r/g mol^{-1}	413.60
crystal size/mm	0.120 × 0.080 × 0.060
T/K	173.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	monoclinic
space group	'P 1 21/n 1'
a/Å	10.4054(7)
b/Å	20.4549(15)
c/Å	21.4505(15)
α/°	90
β/°	103.022(2)
γ/°	90
V/Å^3	4448.1(5)
Z	8
calc. density/g cm^{-3}	1.235

μ/mm^{-1}	0.167
absorption correction	Multi-Scan
transmission factor range	0.93–0.99
refls. measured	70397
R_{int}	0.0712
mean $\sigma(I)/I$	0.0403
θ range	2.787–25.350
observed refls.	6470
x, *y* (weighting scheme)	0.0283, 9.3305
hydrogen refinement	mixed
Flack parameter	?
refls in refinement	8131
parameters	539
restraints	0
$R(F_{obs})$	0.0681
$R_w(F^2)$	0.1518
S	1.122
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.347
min electron density/e Å^{-3}	−0.343

Cell:



D. References

[1] K. Meyer and H. Braunschweig, "Organometallic chemistry in Europe," vol. 37, ed: ACS Publications, 2018, pp. 625-627.

[2] K. Nicolaou, D. Vourloumis, N. Winssinger, and P. S. Baran, "The art and science of total synthesis at the dawn of the twenty-first century," *Angewandte Chemie International Edition,* vol. 39, no. 1, pp. 44-122, 2000.

[3] A. Boudier, L. O. Bromm, M. Lotz, and P. Knochel, "New applications of polyfunctional organometallic compounds in organic synthesis," *Angewandte Chemie International Edition,* vol. 39, no. 24, pp. 4414-4435, 2000.

[4] K. Nicolaou, P. G. Bulger, and D. Sarlah, "Palladium-catalyzed cross-coupling reactions in total synthesis," *Angewandte Chemie International Edition,* vol. 44, no. 29, pp. 4442-4489, 2005. [Online]. Available: https://onlinelibrary.wiley.com/doi/10.1002/anie.200500368.

[5] S. D. Robertson, M. Uzelac, and R. E. Mulvey, "Alkali-metal-mediated synergistic effects in polar main group organometallic chemistry," *Chemical reviews,* vol. 119, no. 14, pp. 8332-8405, 2019. [Online]. Available: https://pubs.acs.org/doi/10.1021/acs.chemrev.9b00047.

[6] P. Stanetty and M. D. Mihovilovic, "Half-lives of organolithium reagents in common ethereal solvents," *Journal of organic chemistry,* vol. 62, no. 5, pp. 1514-1515, 1997.

[7] D. Seyferth, "The grignard reagents," vol. 28, ed: ACS Publications, 2009, pp. 1598-1605.

[8] D. Hauk, S. Lang, and A. Murso, "Minimization of side reactions in bromine magnesium exchanges with i-PrMgCl/LiCl and s-BuMgCl/LiCl mixtures," *Organic process research & development,* vol. 10, no. 4, pp. 733-738, 2006.

[9] E. von Frankland, "Ueber die Isolirung der organischen Radicale," *Justus Liebigs Annalen der Chemie,* vol. 71, no. 2, pp. 171-213, 1849.

[10] M. Schlosser, "Organoalkali chemistry," *Organometallics in Synthesis: A Manual,* vol. 2, 2002.

[11] H. R. Rogers, C. L. Hill, Y. Fujiwara, R. J. Rogers, H. L. Mitchell, and G. M. Whitesides, "Mechanism of formation of Grignard reagents. Kinetics of reaction of alkyl halides in diethyl ether with magnesium," *Journal of the American Chemical Society,* vol. 102, no. 1, pp. 217-226, 1980.

[12] R. M. Peltzer, J. r. Gauss, O. Eisenstein, and M. Cascella, "The Grignard reaction–unraveling a chemical puzzle," *Journal of the American Chemical Society,* vol. 142, no. 6, pp. 2984-2994, 2020. [Online]. Available: https://pubs.acs.org/doi/pdf/10.1021/jacs.9b11829.

[13] D. Pearson, D. Cowan, and J. Beckler, "A study of the entrainment method for making Grignard reagents," *The Journal of Organic Chemistry,* vol. 24, no. 4, pp. 504-509, 1959.

[14] U. Tilstam and H. Weinmann, "Activation of Mg metal for safe formation of Grignard reagents on plant scale," *Organic process research & development,* vol. 6, no. 6, pp. 906-910, 2002.

[15] F. G. A. Stone, R. West, M. J. Fink, A. F. Hill, and P. J. Pérez, "Advances in organometallic chemistry," *(No Title)*.

[16] C. Prévost, "The action of alpha-ethylenic bromides on organomagnesium bromides-collected results," *Bull. Soc. Chim. Fr,* vol. 49, p. 1372, 1931.

[17] M. Ganiek, "Metalation and Halogen-Lithium exchange of sensitive substrates and mild ester homologation in continuous flow," lmu, 2018.

[18] A. Music, C. Hoarau, N. Hilgert, F. Zischka, and D. Didier, "Catalyst-Free Enantiospecific Olefination with In Situ Generated Organocerium Species," *Angewandte Chemie International Edition,* vol. 58, no. 4, pp. 1188-1192, 2019.

[19] H. J. Winkler and H. Winkler, "Mechanism of Halogen-Metal Interconversion between Aryl Bromides and Aryllithium Compounds. I. Equilibria," *Journal of the American Chemical Society,* vol. 88, no. 5, pp. 964-969, 1966.

[20] L. Anthore-Dalion, A. D. Benischke, B. Wei, G. Berionni, and P. Knochel, "The Halogen–Samarium Exchange Reaction: Synthetic Applications and Kinetics," *Angewandte Chemie International Edition,* vol. 58, no. 12, pp. 4046-4050, 2019. [Online]. Available: https://onlinelibrary.wiley.com/doi/10.1002/anie.201814373.
[21] S. C. Rasmussen, "Transmetalation: a fundamental organometallic reaction critical to synthesis and catalysis," *ChemTexts,* vol. 7, no. 1, p. 1, 2020.
[22] C. Elschenbroich, "Organometallchemie, Teubner, Wiesbaden, 6," ed: Auflage, 2008.
[23] H. Kurosawa and A. Yamamoto, *Fundamentals of molecular catalysis*. Elsevier, 2003.
[24] A. Metzger, F. M. Piller, and P. Knochel, "Polyfunctional benzylic zinc chlorides by the direct insertion of magnesium into benzylic chlorides in the presence of LiCl and ZnCl 2," *Chemical communications,* no. 44, pp. 5824-5826, 2008.
[25] F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, and P. Knochel, "Preparation of polyfunctional arylmagnesium, arylzinc, and benzylic zinc reagents by using magnesium in the presence of LiCl," *Chemistry–A European Journal,* vol. 15, no. 29, pp. 7192-7202, 2009. [Online]. Available: https://chemistry-europe.onlinelibrary.wiley.com/doi/10.1002/chem.200900575.
[26] T. Imamoto, T. Kusumoto, and M. Yokoyama, "Generation and reactivities of organocerium reagents," *Journal of the Chemical Society, Chemical Communications,* no. 18, pp. 1042-1044, 1982.
[27] T. Imamoto and Y. Sugiura, "Selective 1, 2-addition of organocerium (III) reagents to α, β-unsaturated carbonyl compounds," *Journal of Physical Organic Chemistry,* vol. 2, no. 2, pp. 93-102, 1989.
[28] G. A. Molander, "Application of lanthanide reagents in organic synthesis," *Chemical reviews,* vol. 92, no. 1, pp. 29-68, 1992.
[29] V. Alexander, "Design and synthesis of macrocyclic ligands and their complexes of lanthanides and actinides," *Chemical reviews,* vol. 95, no. 2, pp. 273-342, 1995.
[30] N. Krause and A. Hoffmann-Röder, "Synthesis of allenes with organometallic reagents," *Tetrahedron,* vol. 60, no. 51, pp. 11671-11694, 2004.
[31] M. Alshammari, "Use of organometallic intermediates in organic synthesis," Cardiff University, 2012.
[32] E. A. Mitchell, A. Peschiulli, N. Lefevre, L. Meerpoel, and B. U. Maes, "Direct α-functionalization of saturated cyclic amines," *Chemistry–A European Journal,* vol. 18, no. 33, pp. 10092-10142, 2012. [Online]. Available: https://chemistry-europe.onlinelibrary.wiley.com/doi/10.1002/chem.201201539.
[33] V. Capriati, S. Florio, and R. Luisi, "Complexation Phenomena and Dynamics at Work in the Lithiation Reactions of Small-Ring Heterocycles: Regio-and Stereoselectivity," *European Journal of Organic Chemistry,* vol. 2014, no. 25, pp. 5397-5417, 2014.
[34] F. Lovering, J. Bikker, and C. Humblet, "Escape from flatland: increasing saturation as an approach to improving clinical success," *Journal of medicinal chemistry,* vol. 52, no. 21, pp. 6752-6756, 2009. [Online]. Available: https://pubs.acs.org/doi/10.1021/jm901241e.
[35] J. Parrick and L. Mehta, "Four-membered ring systems," in *Progress in Heterocyclic Chemistry*, vol. 10: Elsevier, 1998, pp. 70-86.
[36] N. H. Cromwell and B. Phillips, "The azetidines. Recent synthetic developments," *Chemical Reviews,* vol. 79, no. 4, pp. 331-358, 1979.
[37] A. Brandi, S. Cicchi, and F. M. Cordero, "Novel syntheses of azetidines and azetidinones," *Chemical Reviews,* vol. 108, no. 9, pp. 3988-4035, 2008. [Online]. Available: https://pubs.acs.org/doi/10.1021/cr800325e.
[38] F. Couty and G. Evano, "Azetidines: new tools for the synthesis of nitrogen heterocycles," *Synlett,* vol. 2009, no. 19, pp. 3053-3064, 2009.
[39] E. M. Carreira and T. C. Fessard, "Four-membered ring-containing spirocycles: synthetic strategies and opportunities," *Chemical reviews,* vol. 114, no. 16, pp. 8257-8322, 2014. [Online]. Available: https://pubs.acs.org/doi/10.1021/cr500127b.

[40] B. H. Rotstein, S. Zaretsky, V. Rai, and A. K. Yudin, "Small heterocycles in multicomponent reactions," *Chemical reviews,* vol. 114, no. 16, pp. 8323-8359, 2014. [Online]. Available: https://pubs.acs.org/doi/10.1021/cr400615v.

[41] M. Han, C. Song, N. Jeong, and H.-G. Hahn, "Exploration of 3-Aminoazetidines as triple reuptake inhibitors by bioisosteric modification of 3-α-Oxyazetidine," *ACS Medicinal Chemistry Letters,* vol. 5, no. 9, pp. 999-1004, 2014. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4160755/pdf/ml500187a.pdf.

[42] J. Royer, "Asymmetric Synthesis of Nitrogen Heterocycles."

[43] Y. Han, M. Han, D. Shin, C. Song, and H.-G. Hahn, "Exploration of novel 3-substituted azetidine derivatives as triple reuptake inhibitors," *Journal of Medicinal Chemistry,* vol. 55, no. 18, pp. 8188-8192, 2012. [Online]. Available: https://pubs.acs.org/doi/10.1021/jm3008294.

[44] H. Bräuner-Osborne *et al.*, "Azetidinic amino acids: stereocontrolled synthesis and pharmacological characterization as ligands for glutamate receptors and transporters," *Organic & biomolecular chemistry,* vol. 3, no. 21, pp. 3926-3936, 2005.

[45] T. Hart *et al.*, "Fatty acid amide hydrolase inhibitors. Surprising selectivity of chiral azetidine ureas," *Bioorganic & medicinal chemistry letters,* vol. 19, no. 15, pp. 4241-4244, 2009.

[46] J. Alvarez-Builla, J. J. Vaquero, and J. Barluenga, *Modern heterocyclic chemistry*. Wiley Online Library, 2011.

[47] D. Parmar, L. Henkel, J. Dib, and M. Rueping, "Iron catalysed cross-couplings of azetidines–application to the formal synthesis of a pharmacologically active molecule," *Chemical communications,* vol. 51, no. 11, pp. 2111-2113, 2015. [Online]. Available: https://pubs.rsc.org/en/content/articlelanding/2015/cc/c4cc09337b.

[48] D. W. Kung *et al.*, "Identification of spirocyclic piperidine-azetidine inverse agonists of the ghrelin receptor," *Bioorganic & medicinal chemistry letters,* vol. 22, no. 13, pp. 4281-4287, 2012.

[49] J. M. Keith *et al.*, "Heteroarylureas with spirocyclic diamine cores as inhibitors of fatty acid amide hydrolase," *Bioorganic & medicinal chemistry letters,* vol. 24, no. 3, pp. 737-741, 2014.

[50] M. D. Palkowitz, B. Tan, H. Hu, K. Roth, and R. A. Bauer, "Synthesis of diverse N-acryloyl azetidines and evaluation of their enhanced thiol reactivities," *Organic letters,* vol. 19, no. 9, pp. 2270-2273, 2017. [Online]. Available: https://pubs.acs.org/doi/10.1021/acs.orglett.7b00788.

[51] F. Trauner *et al.*, "Strain-release arylations for the bis-functionalization of azetidines," *Chemical Communications,* vol. 58, no. 15, pp. 2564-2567, 2022.

[52] E. Goethals, E. Schacht, Y. Bogaert, S. Ali, and Y. Tezuka, "The polymerization of azetidines and azetidine derivatives," *Polymer Journal,* vol. 12, no. 9, pp. 571-581, 1980.

[53] J. Barluenga and J. Alvarez-Builla, *Modern Heterocyclic Chemistry*. Wiley-VCH, 2011.

[54] T. Shono, Y. Matsumura, K. Uchida, and F. Nakatani, "A Facile Syntehsis of 2-Substituted Azetidines," *Bulletin of the Chemical Society of Japan,* vol. 61, no. 8, pp. 3029-3031, 1988.

[55] Z. Sajjadi Hashemi, "Substituted azetidine-2 carboxylic acid synthesis," 2006.

[56] W. Wykypiel, J. J. Lohmann, and D. Seebach, "Lithiierung in α-Stellung zum N-Atom von Triphenylacetamiden aus cyclischen sekundären Aminen. Umlagerung metallierter Triphenylacetamide unter 1, 3-Verschiebung der Carbamoylgruppe," *Helvetica Chimica Acta,* vol. 64, no. 5, pp. 1337-1346, 1981.

[57] D. Seebach, D. Enders, and B. Renger, "Lithiierung und elektrophile Substitution an α-Methylengruppen von Nitrosaminen Umpolung der Reaktivität sekundärer Amine," *Chemische Berichte,* vol. 110, no. 5, pp. 1852-1865, 1977.

[58] D. M. Hodgson, *Organolithiums in enantioselective synthesis*. Springer Science & Business Media, 2003.

[59] W. Lubosch and D. Seebach, "Nucleophile Aminoalkylierung mit Thiopivalamiden," *Helvetica Chimica Acta,* vol. 63, no. 1, pp. 102-116, 1980.

[60] D. Hodgson and J. Kloesges, "Lithiation-electrophilic substitution of N-thiopivaloylazetidine," *Angewandte Chemie (International ed. in English),* vol. 49, no. 16, pp. 2900-2903, 2010. [Online]. Available: https://onlinelibrary.wiley.com/doi/10.1002/anie.201000058.

[61] D. M. Hodgson, S. P. Hughes, A. L. Thompson, and T. D. Heightman, "Terminal aziridines by α-deprotonation/electrophile trapping of N-protected aziridine," *Organic letters,* vol. 10, no. 16, pp. 3453-3456, 2008. [Online]. Available: https://pubs.acs.org/doi/10.1021/ol801224g.

[62] J.-C. Kizirian, J.-C. Caille, and A. Alexakis, "Conceptually new chiral tertiary C2 symmetric diamines in asymmetric synthesis," *Tetrahedron letters,* vol. 44, no. 49, pp. 8893-8895, 2003.

[63] P. Beak, S. T. Kerrick, S. Wu, and J. Chu, "Complex induced proximity effects: enantioselective syntheses based on asymmetric deprotonations of N-Boc-pyrrolidines," *Journal of the American Chemical Society,* vol. 116, no. 8, pp. 3231-3239, 1994.

[64] W. F. Bailey, P. Beak, S. T. Kerrick, S. Ma, and K. B. Wiberg, "An experimental and computational investigation of the enantioselective deprotonation of Boc-piperidine," *Journal of the American Chemical Society,* vol. 124, no. 9, pp. 1889-1896, 2002.

[65] D. Stead, P. O'Brien, and A. Sanderson, "A new sparteine surrogate for asymmetric deprotonation of N-Boc pyrrolidine," *Organic Letters,* vol. 10, no. 7, pp. 1409-1412, 2008.

[66] I. Coldham *et al.*, "Asymmetric deprotonation of N-Boc-piperidines," *Tetrahedron: Asymmetry,* vol. 18, no. 17, pp. 2113-2119, 2007.

[67] D. M. Hodgson, C. I. Pearson, and A. L. Thompson, "α-Lithiation–Electrophile Trapping of N-Thiopivaloylazetidin-3-ol: Stereoselective Synthesis of 2-Substituted 3-Hydroxyazetidines," *The Journal of Organic Chemistry,* vol. 78, no. 3, pp. 1098-1106, 2013. [Online]. Available: https://pubs.acs.org/doi/10.1021/jo3025225.

[68] D. M. Hodgson, C. L. Mortimer, and J. M. McKenna, "Amine Protection/α-Activation with the tert-Butoxythiocarbonyl Group: Application to Azetidine Lithiation–Electrophilic Substitution," *Organic letters,* vol. 17, no. 2, pp. 330-333, 2015. [Online]. Available: https://pubs.acs.org/doi/pdf/10.1021/ol503441d.

[69] G. Barrett and C. Martins, "Aminolysis of tertiary alkyl xanthates: a new route to dithiourethanes," *Journal of the Chemical Society, Chemical Communications,* no. 11, pp. 638-639, 1972.

[70] J. Praz, L. Guenee, S. Aziz, A. Berkessel, and A. Alexakis, "Evaluation of the Chiral DIANANE Backbone as Ligand for Organolithium Reagents," *Advanced Synthesis & Catalysis,* vol. 354, no. 9, pp. 1780-1790, 2012.

[71] P. R. Dave, "Acylative Dealkylation of N-tert-Butyl-3-substituted Azetidines: Facile Access to [1.1. 0] Azabicyclobutane, 3-Hydroxyazetidinium Hydrochloride, and 3-Azetidinones," *The Journal of Organic Chemistry,* vol. 61, no. 16, pp. 5453-5455, 1996.

[72] A. P. Marchand, D. Rajagopal, S. G. Bott, and T. G. Archibald, "A novel approach to the synthesis of 1, 3, 3-trinitroazetidine," *The Journal of Organic Chemistry,* vol. 60, no. 15, pp. 4943-4946, 1995.

[73] R. Bartnik, D. Cal, A. P. Marchand, S. Alihodzic, and A. Devasagayaraj, "New Method for the Generation and Trapping of 1-Azabicyclo [1.1. 0] butane. Application to the Synthesis of 1, 3-Dinitroazetidine," *Synthetic communications,* vol. 28, no. 21, pp. 3949-3954, 1998.

[74] M. Woznicka, K. Urbaniak, G. Mloston, and H. Heimgartner, "Strained 1-azabicyclo [1.1. 0] butanes in the synthesis of azetidinethiocarboxylate derivatives," *Heterocycles,* vol. 69, pp. 351-364, 2006.

[75] G. Mlostoń, M. Celeda, A. Linden, and H. Heimgartner, "Two-and Three-Component Reactions Leading to New Enamines Derived from 2, 3-Dicyanobut-2-enoates," *Helvetica Chimica Acta,* vol. 92, no. 8, pp. 1520-1537, 2009.

[76] K. Hayashi, E. Kujime, H. Katayama, S. Sano, and Y. Nagao, "Reaction of 1-azabicyclo [1.1. 0] butane with activated amides," *Heterocycles,* vol. 78, no. 7, pp. 1777-1786, 2009.

[77] K. Hayashi, S. Hiki, T. Kumagai, and Y. Nagao, "Synthesis of Azetidine Derivatives Using 1-Azabicyclo (1.1. 0) butane," *Heterocycles-Sendai Institute of Heterocyclic Chemistry,* vol. 56, no. 1-2, pp. 433-442, 2002.

[78] K. Hayashi, Y. Ikee, S. Goto, M. Shiro, and Y. Nagao, "Mechanistic considerations for the consecutive cyclization of 2, 3-dibromopropylamine hydrobromide giving a strained molecule, 1-azabicyclo [1.1. 0] butane," *Chemical and pharmaceutical bulletin,* vol. 52, no. 1, pp. 89-94, 2004. [Online]. Available: https://www.jstage.jst.go.jp/article/cpb/52/1/52_1_89/_pdf.

[79] Y. Ikee *et al.*, "Synthesis of new quinolone antibiotics utilizing azetidine derivatives obtained from 1-azabicyclo [1.1. 0] butane," *Chemical and Pharmaceutical Bulletin,* vol. 56, no. 3, pp. 346-356, 2008. [Online]. Available: https://www.jstage.jst.go.jp/article/cpb/56/3/56_3_346/_pdf.

[80] K. Hayashi, T. Kumagai, and Y. Nagao, "Improved Synthesis of an Energetic Material, 1, 3, 3-Trinitroazetidine Exploiting 1-Azabicyclo (1.1. 0) butane," *Heterocycles-Sendai Institute of Heterocyclic Chemistry,* vol. 53, no. 2, pp. 447-452, 2000.

[81] K. Hayashi *et al.*, "Novel efficient synthesis of 1-azabicyclo [1.1. 0] butane and its application to the synthesis of 1-(1, 3-thiazolin-2-yl) azetidine-3-thiol useful for the pendant moiety of an oral 1β-methylcarbapenem antibiotic L-084," *Tetrahedron letters,* vol. 40, no. 19, pp. 3761-3764, 1999.

[82] Y. Ikee *et al.*, "Synthesis and antibacterial activities of new quinolone derivatives utilizing 1-azabicyclo [1.1. 0] butane," *Bioorganic & medicinal chemistry letters,* vol. 17, no. 4, pp. 942-945, 2007.

[83] R. Bartnik and G. Mlostoń, "Alan P. Marchand* and Sulejman Alihodžić Department of Chemistry, University of North Texas, Denton, Texas 76203-5070," *HETEROCYCLES,* vol. 50, no. 1, p. 131, 1999.

[84] G. Mlostoń, A. Galindo, R. Bartnik, A. R. Marchand, and D. Rajagopal, "Ring-opening reactions of 3-substituted 1-azabicyclo [1.1. 0] butane with dichlorocarbene," *Journal of heterocyclic chemistry,* vol. 33, no. 1, pp. 93-96, 1996.

[85] G. Mlostoń and H. Heimgartner, "Three-Component Reactions with 3-Phenyl 1-azabicyclo [1.1. 0] butane, Dimethyl Dicyanofumarate, and Primary Aromatic Amines," *Heterocycles,* vol. 80, no. 2, pp. 1091-1102, 2010.

[86] G. Mlostoń and M. Celeda, "Ring Opening of 1-Azabicyclo [1.1. 0] butanes with Hydrazoic Acid–a Facile Access to N-Unsubstituted Azetidin-3-Amines," *Helvetica chimica acta,* vol. 88, no. 7, pp. 1658-1663, 2005.

[87] Y. Ji, L. Wojtas, and J. M. Lopchuk, "An improved, gram-scale synthesis of protected 3-haloazetidines: rapid diversified synthesis of azetidine-3-carboxylic acids," *Arkivoc,* vol. 2018, pp. 195-214, 2018.

[88] G. Alvernhe, A. Laurent, K. Touhami, R. Bartnik, and G. Mloston, "Synthese de fluoro-3 azacyclanes: action de l'acide fluorhydriqiue sur les aza-1 bicyclo [n. 1.0] alcanes," *Journal of fluorine chemistry,* vol. 29, no. 4, pp. 363-384, 1985.

[89] G. Mlostoń, M. Woźnicka, J. Drabowicz, A. Linden, and H. Heimgartner, "Addition Reactions of Sulfenyl and Sulfinyl Chlorides with 3-Phenyl-1-azabicyclo [1.1. 0] butane," *Helvetica Chimica Acta,* vol. 91, no. 8, pp. 1419-1429, 2008.

[90] J. M. Lopchuk *et al.*, "Strain-release heteroatom functionalization: development, scope, and stereospecificity," *Journal of the American Chemical Society,* vol. 139, no. 8, pp. 3209-3226, 2017. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5334783/pdf/ja6b13229.pdf.

[91] R. Gianatassio *et al.*, "Strain-release amination," *Science,* vol. 351, no. 6270, pp. 241-246, 2016. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4730898/pdf/nihms743538.pdf.

[92] R. Gianatassio and D. Kadish, "Direct alkylation of 1-azabicyclo [1.1. 0] butanes," *Organic letters,* vol. 21, no. 7, pp. 2060-2063, 2019. [Online]. Available: https://pubs.acs.org/doi/10.1021/acs.orglett.9b00321.

[93] N. A. McGrath, M. Brichacek, and J. T. Njardarson, "A graphical journey of innovative organic architectures that have improved our lives," *Journal of chemical education,* vol. 87, no. 12, pp. 1348-1349, 2010.

[94] K. Wellington and L. J. Scott, "Azelnidipine," *Drugs,* vol. 63, pp. 2613-2621, 2003.

[95] D. Antermite, L. Degennaro, and R. Luisi, "Recent advances in the chemistry of metallated azetidines," *Organic & Biomolecular Chemistry,* vol. 15, no. 1, pp. 34-50, 2017.

[96] S. Billotte, "Synthesis of C-substituted cyclic amines using azacycloalkyl organozinc reagents," *Synlett,* vol. 1998, no. 04, pp. 379-380, 1998.

[97] M. A. Duncton *et al.*, "Preparation of aryloxetanes and arylazetidines by use of an alkyl− aryl Suzuki coupling," *Organic Letters,* vol. 10, no. 15, pp. 3259-3262, 2008. [Online]. Available: https://pubs.acs.org/doi/10.1021/ol8011327.

[98] G. A. Molander, K. M. Traister, and B. T. O'Neill, "Reductive cross-coupling of nonaromatic, heterocyclic bromides with aryl and heteroaryl bromides," *The Journal of organic chemistry,* vol. 79, no. 12, pp. 5771-5780, 2014. [Online]. Available: https://pubs.acs.org/doi/10.1021/jo500905m.
[99] B. Barre *et al.*, "Iron-and cobalt-catalyzed arylation of azetidines, pyrrolidines, and piperidines with Grignard reagents," *Organic letters,* vol. 16, no. 23, pp. 6160-6163, 2014.
[100] R. Jana, T. P. Pathak, and M. S. Sigman, "Advances in transition metal (Pd, Ni, Fe)-catalyzed cross-coupling reactions using alkyl-organometallics as reaction partners," *Chemical reviews,* vol. 111, no. 3, pp. 1417-1492, 2011.
[101] Á. Molnár, "Efficient, selective, and recyclable palladium catalysts in carbon− carbon coupling reactions," *Chemical reviews,* vol. 111, no. 3, pp. 2251-2320, 2011.
[102] C. Fischer and B. Koenig, "Palladium-and copper-mediated N-aryl bond formation reactions for the synthesis of biological active compounds," *Beilstein journal of organic chemistry,* vol. 7, no. 1, pp. 59-74, 2011.
[103] J. Lindley, "Tetrahedron report number 163: Copper assisted nucleophilic substitution of aryl halogen," *Tetrahedron,* vol. 40, no. 9, pp. 1433-1456, 1984.
[104] H.-J. Federsel, M. Hedberg, F. R. Qvarnström, M. P. Sjögren, and W. Tian, "Construction of a chiral central nervous system (CNS)-active aminotetralin drug compound based on a synthesis strategy using multitasking properties of (S)-1-phenylethylamine," *Accounts of chemical research,* vol. 40, no. 12, pp. 1377-1384, 2007.
[105] J. Ji *et al.*, "Discovery of fused azetidines as novel selective α4β2 neuronal nicotinic receptor (NNR) agonists," *Pure and applied chemistry,* vol. 77, no. 12, pp. 2041-2045, 2005.
[106] J. F. Hartwig, "Evolution of a fourth generation catalyst for the amination and thioetherification of aryl halides," *Accounts of chemical research,* vol. 41, no. 11, pp. 1534-1544, 2008.
[107] D. S. Surry and S. L. Buchwald, "Biaryl phosphane ligands in palladium-catalyzed amination," *Angewandte Chemie International Edition,* vol. 47, no. 34, pp. 6338-6361, 2008.
[108] C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot, and V. Snieckus, "Palladium-catalyzed cross-coupling: a historical contextual perspective to the 2010 Nobel Prize," *Angewandte Chemie International Edition,* vol. 51, no. 21, pp. 5062-5085, 2012.
[109] P. G. Gildner and T. J. Colacot, "Reactions of the 21st century: two decades of innovative catalyst design for palladium-catalyzed cross-couplings," *Organometallics,* vol. 34, no. 23, pp. 5497-5508, 2015.
[110] M. Kosugi, M. Kameyama, and T. Migita, "Palladium-catalyzed aromatic amination of aryl bromides with N, N-di-ethylamino-tributyltin," *Chemistry Letters,* vol. 12, no. 6, pp. 927-928, 1983.
[111] F. Ullmann, "Ueber eine neue Bildungsweise von Diphenylaminderivaten," *Berichte der deutschen chemischen Gesellschaft,* vol. 36, no. 2, pp. 2382-2384, 1903.
[112] I. Goldberg, "Ueber phenylirungen bei gegenwart von kupfer als katalysator," *Berichte der deutschen chemischen Gesellschaft,* vol. 39, no. 2, pp. 1691-1692, 1906.
[113] S. Rohrbach *et al.*, "Concerted nucleophilic aromatic substitution reactions," *Angewandte Chemie International Edition,* vol. 58, no. 46, pp. 16368-16388, 2019.
[114] Y. Shirota and H. Kageyama, "Charge carrier transporting molecular materials and their applications in devices," *Chemical reviews,* vol. 107, no. 4, pp. 953-1010, 2007.
[115] J. Wang, K. Liu, L. Ma, and X. Zhan, "Triarylamine: versatile platform for organic, dye-sensitized, and perovskite solar cells," *Chemical reviews,* vol. 116, no. 23, pp. 14675-14725, 2016.
[116] F. Leroux, P. Jeschke, and M. Schlosser, "α-Fluorinated ethers, thioethers, and amines: anomerically biased species," *Chemical reviews,* vol. 105, no. 3, pp. 827-856, 2005.
[117] S. Tasler, J. Mies, and M. Lang, "Applicability aspects of transition metal-catalyzed aromatic amination protocols in medicinal chemistry," *Advanced Synthesis & Catalysis,* vol. 349, no. 14-15, pp. 2286-2300, 2007.
[118] J. A. Bikker, N. Brooijmans, A. Wissner, and T. S. Mansour, "Kinase domain mutations in cancer: implications for small molecule drug design strategies," *Journal of medicinal chemistry,* vol. 52, no. 6, pp. 1493-1509, 2009.

[119] P. A. Forero-Cortés and A. M. Haydl, "The 25th anniversary of the Buchwald–Hartwig amination: development, applications, and outlook," *Organic Process Research & Development,* vol. 23, no. 8, pp. 1478-1483, 2019.
[120] G. C. Fortman and S. P. Nolan, "N-Heterocyclic carbene (NHC) ligands and palladium in homogeneous cross-coupling catalysis: a perfect union," *Chemical Society Reviews,* vol. 40, no. 10, pp. 5151-5169, 2011.
[121] R. Ghorbani-Vaghei, S. Hemmati, M. Hamelian, and H. Veisi, "An efficient, mild and selective Ullmann-type N-arylation of indoles catalysed by Pd immobilized on amidoxime-functionalized mesoporous SBA-15 as heterogeneous and recyclable nanocatalyst," *Applied Organometallic Chemistry,* vol. 29, no. 4, pp. 195-199, 2015.
[122] H. Veisi, M. R. Poor Heravi, and M. Hamelian, "SBA-15-functionalized melamine–pyridine group-supported palladium (0) as an efficient heterogeneous and recyclable nanocatalyst for N-arylation of indoles through Ullmann-type coupling reactions," *Applied Organometallic Chemistry,* vol. 29, no. 5, pp. 334-337, 2015.
[123] J. Arnt and T. Skarsfeldt, "Do novel antipsychotics have similar pharmacological characteristics? A review of the evidence," *Neuropsychopharmacology,* vol. 18, no. 2, pp. 63-101, 1998.
[124] M. G. Boswell, F. G. Yeung, and C. Wolf, "Copper-catalyzed C–N bond formation with N-heterocycles and aryl halides," *Synlett,* vol. 2012, no. 08, pp. 1240-1244, 2012.
[125] L. Yin and J. Liebscher, "Carbon− carbon coupling reactions catalyzed by heterogeneous palladium catalysts," *Chemical Reviews,* vol. 107, no. 1, pp. 133-173, 2007.
[126] C. Valente, M. Pompeo, M. Sayah, and M. G. Organ, "Carbon–Heteroatom Coupling Using Pd-PEPPSI Complexes," *Organic Process Research & Development,* vol. 18, no. 1, pp. 180-190, 2014.
[127] C. Valente, S. Çalimsiz, K. H. Hoi, D. Mallik, M. Sayah, and M. G. Organ, "The development of bulky palladium NHC complexes for the most-challenging cross-coupling reactions," *Angewandte Chemie International Edition,* vol. 51, no. 14, pp. 3314-3332, 2012.
[128] J. Nasielski *et al.*, "Structure–Activity Relationship Analysis of Pd–PEPPSI Complexes in Cross-Couplings: A Close Inspection of the Catalytic Cycle and the Precatalyst Activation Model," *Chemistry–A European Journal,* vol. 16, no. 35, pp. 10844-10853, 2010.
[129] E. A. B. Kantchev, C. J. O'Brien, and M. G. Organ, "Palladium complexes of N-heterocyclic carbenes as catalysts for cross-coupling reactions—A synthetic chemist's perspective," *Angewandte Chemie International Edition,* vol. 46, no. 16, pp. 2768-2813, 2007.
[130] S. Diez-Gonzalez, N. Marion, and S. P. Nolan, "N-heterocyclic carbenes in late transition metal catalysis," *Chemical Reviews,* vol. 109, no. 8, pp. 3612-3676, 2009.
[131] C. J. O'Brien *et al.*, "Towards the rational design of palladium-N-heterocyclic carbene catalysts by a combined experimental and computational approach," *Tetrahedron,* vol. 61, no. 41, pp. 9723-9735, 2005.
[132] T. Yamamoto, M. Nishiyama, and Y. Koie, "Palladium-catalyzed synthesis of triarylamines from aryl halides and diarylamines," *Tetrahedron Letters,* vol. 39, no. 16, pp. 2367-2370, 1998.
[133] F. Reiners, E. Joseph, B. Nissl, and D. Didier, "Stereoselective Access to Azetidine-Based alpha-Amino Acids and Applications to Small Peptide Synthesis," *Org Lett,* vol. 22, no. 21, pp. 8533-8537, Nov 6 2020, doi: 10.1021/acs.orglett.0c03131.
[134] G. Singh, M. D'hooghe, and N. De Kimpe, "Comprehensive heterocyclic chemistry III," *Katritzky, A. Ramsden, C. AAA, E., Taylor, R., editors,* vol. 2, pp. 1-110, 2008.
[135] K. Gerlach, H. Priepke, W. Wienen, A. Schuler-Metz, and H. Nar, "Substituted azetidines, manufacturing and use thereof as medicaments," *International Patent,* vol. 2008135525, p. A2, 2008.
[136] F. Matsuura, Y. Hamada, and T. Shioiri, "Total syntheses of phytosiderophores, 3-epi-hydroxymugineic acid, distichonic acid A, and 2'-hydroxynicotianamine," *Tetrahedron,* vol. 50, no. 1, pp. 265-274, 1994.

[137] S. Raghavan and V. Krishnaiah, "An efficient stereoselective synthesis of penaresidin A from (E)-2-protected amino-3, 4-unsaturated sulfoxide," *The Journal of Organic Chemistry,* vol. 75, no. 3, pp. 748-761, 2010. [Online]. Available: https://pubs.acs.org/doi/10.1021/jo9022638.

[138] M. S. Newman and F. W. Hetzel, "Preparation of olefins by pyrolysis of O-alkyldimethythiocarbamates," *The Journal of Organic Chemistry,* vol. 34, no. 11, pp. 3604-3606, 1969.

[139] P. Beak, W. J. Zajdel, and D. B. Reitz, "Metalation and electrophilic substitution of amine derivatives adjacent to nitrogen:. alpha.-metallo amine synthetic equivalents," *Chemical Reviews,* vol. 84, no. 5, pp. 471-523, 1984.

[140] P. Beak and W. K. Lee, ". alpha.-Lithioamine synthetic equivalents: syntheses of diastereoisomers from Boc derivatives of cyclic amines," *The Journal of Organic Chemistry,* vol. 58, no. 5, pp. 1109-1117, 1993.

[141] D. Seebach and W. Lubosch, "Nucleophile Aminoalkylierung. Lithiiertes N, N-Dimethyl-thiopivalamid," *Angewandte Chemie,* vol. 88, no. 10, pp. 339-340, 1976.

[142] M. Eisold and D. Didier, "Highly Diastereoselective Synthesis of Methylenecyclobutanes by Merging Boron-Homologation and Boron-Allylation Strategies," *Angewandte Chemie International Edition,* vol. 54, no. 52, pp. 15884-15887, 2015. [Online]. Available: https://onlinelibrary.wiley.com/doi/10.1002/anie.201507444.

[143] M. Eisold, G. M. Kiefl, and D. Didier, "Single-pot asymmetric approach toward enantioenriched quaternary stereocenter-containing alkylidenecyclobutanes," *Organic letters,* vol. 18, no. 12, pp. 3022-3025, 2016. [Online]. Available: https://pubs.acs.org/doi/10.1021/acs.orglett.6b01432.

[144] M. Eisold, A. N. Baumann, G. M. Kiefl, S. T. Emmerling, and D. Didier, "Unsaturated Four-Membered Rings: Efficient Strategies for the Construction of Cyclobutenes and Alkylidenecyclobutanes," *Chemistry–A European Journal,* vol. 23, no. 7, pp. 1634-1644, 2017. [Online]. Available: https://chemistry-europe.onlinelibrary.wiley.com/doi/10.1002/chem.201604585.

[145] A. N. Baumann, M. Eisold, and D. Didier, "Stereoselective Sequence toward Biologically Active Fused Alkylidenecyclobutanes," *Organic letters,* vol. 19, no. 8, pp. 2114-2117, 2017.

[146] M. Eisold and D. Didier, "Stereoselective access to alkylidenecyclobutanes through γ-selective cross-coupling strategies," *Organic letters,* vol. 19, no. 15, pp. 4046-4049, 2017. [Online]. Available: https://pubs.acs.org/doi/10.1021/acs.orglett.7b01803.

[147] A. N. Baumann, M. Eisold, A. Music, G. Haas, Y. M. Kiw, and D. Didier, "Methods for the synthesis of substituted azetines," *Organic letters,* vol. 19, no. 20, pp. 5681-5684, 2017.

[148] A. Music, A. N. Baumann, M. Eisold, and D. Didier, "Regiodivergent stereoselective access to fused alkylideneazetidines," *The Journal of Organic Chemistry,* vol. 83, no. 2, pp. 783-792, 2018. [Online]. Available: https://pubs.acs.org/doi/10.1021/acs.joc.7b02786.

[149] A. N. Baumann, M. Eisold, A. Music, and D. Didier, "One-Pot Preparation of Stable Organoboronate Reagents for the Functionalization of Unsaturated Four-and Five-Membered Carbo-and Heterocycles," *Synthesis,* vol. 50, no. 16, pp. 3149-3160, 2018.

[150] M. Eisold, A. Müller-Deku, F. Reiners, and D. Didier, "Parallel approaches for the functionalization of thietes: α-metalation versus C–H activation," *Organic letters,* vol. 20, no. 15, pp. 4654-4658, 2018. [Online]. Available: https://pubs.acs.org/doi/10.1021/acs.orglett.8b01961.

[151] A. N. Baumann, F. Reiners, T. Juli, and D. Didier, "Chemodivergent and stereoselective access to fused isoxazoline azetidines and thietanes through [3+ 2]-cycloadditions," *Organic letters,* vol. 20, no. 21, pp. 6736-6740, 2018.

[152] A. N. Baumann, F. Reiners, A. F. Siegle, P. Mayer, O. Trapp, and D. Didier, "Thiete Dioxides as Templates Towards Twisted Scaffolds and Macrocyclic Structures," *Chemistry–A European Journal,* vol. 26, no. 27, pp. 6029-6035, 2020. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7318563/pdf/CHEM-26-6029.pdf.

[153] F. Reiners, E. Joseph, B. Nißl, and D. Didier, "Stereoselective access to azetidine-based α-amino acids and applications to small peptide synthesis," *Organic Letters,* vol. 22, no. 21, pp. 8533-8537, 2020. [Online]. Available: https://pubs.acs.org/doi/10.1021/acs.orglett.0c03131.

[154] M. Maetani *et al.*, "Synthesis of a bicyclic azetidine with in vivo antimalarial activity enabled by stereospecific, directed C (sp3)–H arylation," *Journal of the American Chemical Society,* vol. 139, no. 32, pp. 11300-11306, 2017. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5561537/pdf/ja7b06994.pdf.

[155] M. Shang *et al.*, "Modular, stereocontrolled Cβ–H/Cα–C activation of alkyl carboxylic acids," *Proceedings of the National Academy of Sciences,* vol. 116, no. 18, pp. 8721-8727, 2019.

[156] L. A. Carpino *et al.*, "The uronium/guanidinium peptide coupling reagents: Finally the true uronium salts," *Angewandte Chemie International Edition,* vol. 41, no. 3, pp. 441-445, 2002. [Online]. Available: https://onlinelibrary.wiley.com/doi/10.1002/1521-3773(20020201)41:3%3C441::AID-ANIE441%3E3.0.CO;2-N.

[157] D. Wang and S. Gao, "Sonogashira coupling in natural product synthesis," *Organic Chemistry Frontiers,* vol. 1, no. 5, pp. 556-566, 2014.

[158] C. Lamberth, "Alkyne chemistry in crop protection," *Bioorganic & medicinal chemistry,* vol. 17, no. 12, pp. 4047-4063, 2009.

[159] A. K. Simlandy, M.-Y. Lyu, and M. K. Brown, "Catalytic arylboration of spirocyclic cyclobutenes: rapid access to highly substituted spiro [3. n] alkanes," *ACS catalysis,* vol. 11, no. 20, pp. 12815-12820, 2021.

[160] T. W. Reidl and L. L. Anderson, "Divergent functionalizations of azetidines and unsaturated azetidines," *Asian Journal of Organic Chemistry,* vol. 8, no. 7, pp. 931-945, 2019.

[161] H. Mughal and M. Szostak, "Recent advances in the synthesis and reactivity of azetidines: strain-driven character of the four-membered heterocycle," *Organic & Biomolecular Chemistry,* vol. 19, no. 15, pp. 3274-3286, 2021.

[162] N. A. Meanwell, "Synopsis of some recent tactical application of bioisosteres in drug design," *Journal of medicinal chemistry,* vol. 54, no. 8, pp. 2529-2591, 2011. [Online]. Available: https://pubs.acs.org/doi/10.1021/jm1013693.

[163] J. B. Denis, G. Masson, P. Retailleau, and J. Zhu, "Cinchona alkaloid amide catalyzed enantioselective formal [2+ 2] cycloadditions of allenoates and imines: Synthesis of 2, 4-disubstituted azetidines," *Angewandte Chemie,* vol. 23, no. 123, pp. 5468-5472, 2011.

[164] T. Nishimura, Y. Yasuhara, and T. Hayashi, "Highly selective 1, 6-addition of aryl boronic acids to α, β, γ, δ-unsaturated carbonyl compounds catalyzed by an iridium complex," *Angew. Chem., Int. Ed,* vol. 45, pp. 5164-5166, 2006.

[165] J.-Q. Han, H.-H. Zhang, P.-F. Xu, and Y.-C. Luo, "Lewis acid and (hypo) iodite relay catalysis allows a strategy for the synthesis of polysubstituted azetidines and tetrahydroquinolines," *Organic letters,* vol. 18, no. 20, pp. 5212-5215, 2016. [Online]. Available: https://pubs.acs.org/doi/10.1021/acs.orglett.6b02430.

[166] S. C. Schmid, I. A. Guzei, and J. M. Schomaker, "A stereoselective [3+ 1] ring expansion for the synthesis of highly substituted methylene azetidines," *Angewandte Chemie International Edition,* vol. 56, no. 40, pp. 12229-12233, 2017. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5693379/pdf/nihms915255.pdf.

[167] S. Malik and U. K. Nadir, "A facile synthesis of 1-arenesulfonylazetidines through reaction of 1-arenesulfonylaziridines with dimethylsulfoxonium methylide generated under microwave irradiation," *Synlett,* vol. 2008, no. 01, pp. 108-110, 2008.

[168] P. Quinodoz, B. Drouillat, K. Wright, J. Marrot, and F. Couty, "N-Arylazetidines: Preparation through anionic ring closure," *The Journal of Organic Chemistry,* vol. 81, no. 7, pp. 2899-2910, 2016. [Online]. Available: https://pubs.acs.org/doi/10.1021/acs.joc.6b00169.

[169] R. M. de Figueiredo, R. Fröhlich, and M. Christmann, "N, N ‘-Carbonyldiimidazole-mediated cyclization of amino alcohols to substituted azetidines and other N-heterocycles," *The Journal of organic chemistry,* vol. 71, no. 11, pp. 4147-4154, 2006. [Online]. Available: https://pubs.acs.org/doi/10.1021/jo060130b.

[170] S. P. Fritz, J. F. Moya, M. G. Unthank, E. M. McGarrigle, and V. K. Aggarwal, "An efficient synthesis of azetidines with (2-bromoethyl) sulfonium triflate," *Synthesis,* vol. 44, no. 10, pp. 1584-1590, 2012.

[171] P. Sulmon, N. De Kimpe, N. Schamp, B. Tinant, and J.-P. Declercq, "Synthesis of azetidines from β-chloro imines," *Tetrahedron,* vol. 44, no. 12, pp. 3653-3670, 1988.
[172] N. Kern, A.-S. Felten, J.-M. Weibel, P. Pale, and A. Blanc, "Robust synthesis of N-sulfonylazetidine building blocks via ring contraction of α-bromo N-sulfonylpyrrolidinones," *Organic letters,* vol. 16, no. 23, pp. 6104-6107, 2014. [Online]. Available: https://pubs.acs.org/doi/10.1021/ol5029496.
[173] W. Funke, "Synthesis and properties of 1-azabicyclo [1.1. 0] butanes," *Angewandte Chemie International Edition in English,* vol. 8, no. 1, pp. 70-71, 1969.
[174] A. Fawcett, A. Murtaza, C. H. Gregson, and V. K. Aggarwal, "Strain-release-driven homologation of boronic esters: application to the modular synthesis of azetidines," *Journal of the American Chemical Society,* vol. 141, no. 11, pp. 4573-4578, 2019. [Online]. Available: https://pubs.acs.org/doi/10.1021/jacs.9b01513.
[175] D. Didier and F. Reiners, "Uncommon Four-Membered Building Blocks–Cyclobutenes, Azetines and Thietes," *The Chemical Record,* vol. 21, no. 5, pp. 1144-1160, 2021. [Online]. Available: https://onlinelibrary.wiley.com/doi/pdfdirect/10.1002/tcr.202100011?download=true.
[176] J. Louie and J. F. Hartwig, "Palladium-catalyzed synthesis of arylamines from aryl halides. Mechanistic studies lead to coupling in the absence of tin reagents," *Tetrahedron Letters,* vol. 36, no. 21, pp. 3609-3612, 1995.
[177] A. S. Guram, R. A. Rennels, and S. L. Buchwald, "A simple catalytic method for the conversion of aryl bromides to arylamines," *Angewandte Chemie International Edition in English,* vol. 34, no. 12, pp. 1348-1350, 1995.
[178] J. A. Burkhard, B. Wagner, H. Fischer, F. Schuler, K. Müller, and E. M. Carreira, "Synthesis of azaspirocycles and their evaluation in drug discovery," *Angewandte Chemie International Edition,* vol. 20, no. 49, pp. 3524-3527, 2010.
[179] J. L. Tyler, A. Noble, and V. K. Aggarwal, "Strain-Release Driven Spirocyclization of Azabicyclo [1.1. 0] butyl Ketones," *Angewandte Chemie,* vol. 133, no. 21, pp. 11930-11935, 2021.
[180] A. W. Mott and G. Barany, "Synthesis and characterisation of bis [(methylthio) carbonyl] polysulphanes," *Journal of the Chemical Society, Perkin Transactions 1,* pp. 2615-2621, 1984.