Synthesis of Quinoline Derivatives as Nucleoside Triphosphate Diphosphohydrolases Inhibitors and Development of Ruthenium and Boron Mediated Reaction Methodologies

A dissertation Submitted to the Department of Chemistry,

Quaid-i-Azam University, Islamabad, in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Philosophy

in

Organic Chemistry

by

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2023

“In the Name of Allah, the Most Gracious, the Most Merciful”

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Dedication

To my loving parents, brothers and sisters, of course

Acknowledgements

All praises and gratitude to **Almighty Allah**, the most compassionate, the most beneficent and ever merciful, for His countless blessings, courage and power to accomplish this work. This was not possible to complete this degree without the support of many people around me who always elevated my spirit and encouraged me through my hard times.

I would like to thank my research supervisor **Dr. Abbas Hassan,** Department of Chemistry, Quaid-i-Azam University, Islamabad, for his sincere cooperation, guidance and encouragement. His incomparable dedication and personal interest in this work always motivated me to complete it. I feel overwhelmed to thank **Prof. Dr. Aamer Saeed**, Chairman, Department of Chemistry, Quaid-i-Azam University, Islamabad, **Prof. Dr. Shahid Hameed**, Ex-Chairman, and Head of Organic Section, **Prof. Dr. Humaira Masood Siddiqi** for providing necessary research facilities. I am thankful to all faculty members of Chemistry Department for their expertise, and support.

I am thankful to **Prof.Varinder Kumar Aggarwal** at University of Bristol, England during my visit to his group as visiting research scholar. His guidance and knowledge played significant role in my learning and completion of PhD degree. I am also thankful to other group members Alexander Fawcett, Joe Bateman, Sheenagh Aiken, Rory Mykura, Steven Bennet and Nandakumar Meganathan.

I would like to extend my thanks to my friends Sadia Shahbaz, Sadia Baig, Shumaila Zubair and to my friend Rifhat Sikendar, this would have been much more difficult without you. I am thankful to my lab fellows Dr. Shaista Parveen, Tayyaba, Bisma, Komal, Maryam Ilyas, Sardaraz, Muhammad Ilyas, Haseen Ahmed, Dr. Ismatullah, Hafiz Asif Nazeer, Safdar Abbas and Gohar Zaman for their support.

My love goes to my family. I am forever grateful to my father who has been so supportive at every step of my life with his constant words of hope and encouragement, my loving mother, brothers and sisters who encouraged me,

prayed for my success and supported me morally and spiritually for the completion of the research work. Special thanks to my mother-in-law, no words can appreciate your affection and help at home. I would like to thank my husband who supported me morally and financially to complete this work. Last but not the least, all those who assisted and guided me in the completion of this study.

CONTENTS

List of Schemes

List of Figures

List of Tables

List of Abbreviations

α-	Alpha	Å	Angstrom
ABB	Azabicyclo[1.1.0]butane	ADP	Adenosine diphosphate
Ag	Silver	$AgBF_4$	Silver tetrafluoroborate
AMP	Adenosine monophosphate	aq	Aqueous
ATP	Adenosine triphosphate	Au	Gold
β-	Beta	BINOL	1,1′-Bi-2-naphthol
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl	Bn	Benzyl
Boc	tert-butoxycarbonyl	BOX	Bisoxazoline
Bpin	Pinacolboron	^{t}Bu	Tertiarybutyl
Bus	Butylthio	Bz	Benzoyl
Cbz	Benzyloxycarbonyl	COD	Cyclooctadiene
CuI	Copper iodide	Cy	Cyclohexyl
Co	Cobalt	DCM	Dichloromethane
dippf	1,1'-Bis(diphenylphosphino)ferrocene	DMSO	Dimethylsulfoxide
DMAP	4-Dimethylaminopyridine	EtOH	Ethanol

equiv	Equivalent	Fe	Iron
ICI	Iodine monochloride	IC_{50}	Half-maximal inhibitory concentration
In	Indium	LiTMP	Lithium 2,2,6,6-tetramethylpiperidide
MW	Microwave	MS	Molecular sieves
MTBE	2-Methoxy-2-methylpropane	NBS	*N*-Bromosuccinimide
NIS	*N*-Iodosuccinimide	Ni	Nickel
NME	*N*-Methylephedrine	OCb	Carbamate
OTIB	triisopropylbenzoate	$Pd(PPh_3)_2Cl_2$	Bis(triphenylphosphine)palladium (II) dichloride
Pd/C	Palladium charcol	PMB	*p*-Methoxybenzyl ether
^{i}Pr	isopropyl	*rac*	Racemic
SAR	Structure-activity relationship	Sn	Tin
sp	Sparteine	TBAF	Tetrabutylammonium fluoride
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy	TfOH	Trifluoromethanesulfonic acid
TFA	Trifluoroacetic acid	Ti	Titanium
TMS	Trimethylsilyl	TMEDA	Tetramethylethylenediamine
p-TsOH	*p*-Toluenesulfonic acid	Ts	*p*-Toluenesulfonyl

UDP	Uridine diphosphate	UTP	Uridine triphosphate
Zn	Zinc		

Abstract

Nucleoside triphosphate diphosphohydrolases (NTPDases) are the extracellular enzymes which catalyze the hydrolysis of extracellular nucleotides. However, over-expression of NTPDases is linked with various pathological diseases such as cancer. Therefore, inhibitors of NTPDases are required to treat the diseases caused by over-expression of these enzymes. In the present research study, a series of quinoline derivatives were synthesized by using molecular iodine as catalyst and their activity as NTPDase inhibitor was analyzed against four isoenzymes of *h*-NTPDases and IC_{50} were calculated. Among synthesized derivatives many showed promising activities against four isoenzymes of human nucleoside triphosphate diphosphohydrolases. These quinoline derivatives had IC_{50} (μM) values in the range of 0.20–1.75, 0.77–2.20, 0.36–5.50 and 0.90–1.82 for NTPDase1, NTPDase2, NTPDase3 and NTPDase8, respectively. Some derivatives were also selective towards these enzymes. Most active compounds were later analyzed for their mode of inhibition and binding interactions through molecular docking studies.

Different transition metals such as Zn, Cu, Ag, Au and Co has been reported to catalyze the enantioselective addition of alkynes to isatin. A new catalyst system based on $[Ru(COD)Cl_2]_n$ catalyst with chiral (*R*)-H_8-BINAP ligand was developed for the synthesis of chiral 3-alkynyl-3-hydroxyindolin-2-ones. Ruthenium acetylides synthesized *in situ* by C-H activation of terminal alkynes were added across different substituted isatins. The chiral 3-alkynyl-3-hydroxyindolin-2-one derivatives were obtained in good to excellent yields (up to 98%) with high enantioselectivities (up to 92%).

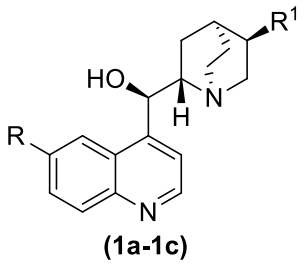
Azetidine is a very important four-membered nitrogen based heterocycle. The azetidine moiety is featured in several pharmaceuticals. Besides its immense medicinal importance, synthetic methodologies to synthesize this scaffold are rare. Employing lithiation-borylation methodology, synthesis of azetidine boronic esters was achieved. Ring strain of azabicyclo [1.1.0] butane was exploited for

synthesis of this four membered nitrogen heterocycle. Synthesized boronic esters were later transformed into different azetidine based compounds.

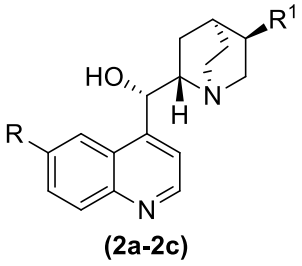
CHAPTER-1
INTRODUCTION

1.1 Quinoline

Quinoline is an aromatic nitrogen containing heterocycle also known as 1-azanaphthalene or benzo[*b*]pyridine. Quinoline is a weak tertiary base (*p*Ka = 4.85). It can form a salt with acids and undergoes reactions similar to those of pyridine and benzene. It exhibits both electrophilic and nucleophilic substitution reactions. Quinoline core persists in many natural products with remarkable pharmacological properties. The famous Cinchona alkaloids found in *Cinchona* bark have quinoline as the core structure. The prominent chemical constituents of *Cinchona* species are quinine, quinidine, cinchonine, cinchonidine, dihydroquinine and dihydroquinidine and quinine being the most famous among these six alkaloids has been used as antimalarial medicine for the long period of time.[1]



(1a-1c)



(2a-2c)

	R	R^1
Quinine **1a** =	$-OCH_3$	$-CH=CH_2$
Cinchonidine **1b** =	-H	$-CH=CH_2$
Dihydroquinine **1c** =	-H	$-CH_2-CH_3$

	R	R^1
Quinidine **2a** =	$-OCH_3$	$-CH=CH_2$
Cinchonine **2b** =	-H	$-CH=CH_2$
Dihydroquinidine **2c** =	-H	$-CH_2-CH_3$

Fig 1.1 Cinchona alkaloids

1.1.1 Biological Importance of Quinoline

Quinoline and its derivatives have emerged as useful drug candidates because of their enormous biological activities. Quinoline core is associated with diverse biological applications. Therefore, it is the part of many marketed drugs and the major prevalence is as antimalarial drugs. Chloroquine **3** as an antimalarial drug was the first drug discovered in 1934 by Hans Andersag and co-workers at the Bayer laboratories.[2] Later its analogue mefloquine **4** was discovered for treatment of malaria because of resistance to chloroquine was developed worldwide by malarial parasite. Several new quinoline compounds e.g., amodiaquine **5** and AQ-13 **6** have been reported as potent antimalarial drugs (Fig 1.2). These two are the promising leads for development of new drugs.[3]

Quinoline compounds constitute the drugs for other diseases as well. This includes antibiotic ciprofloxacin **7** and its analogues norfloxacin **8**, sparfloxacin **11**, levofloxacin **9**, moxifloxacin **10** and gatifloxacin **12**.[4] In the category of anticancer drugs, cabozantinib **13** was first approved in 2012 and is a non-specific tyrosine kinase inhibitor for the treatment of metastatic medullary thyroid cancer. Other drugs include lenvatinib **14** and irinotecan **15**.

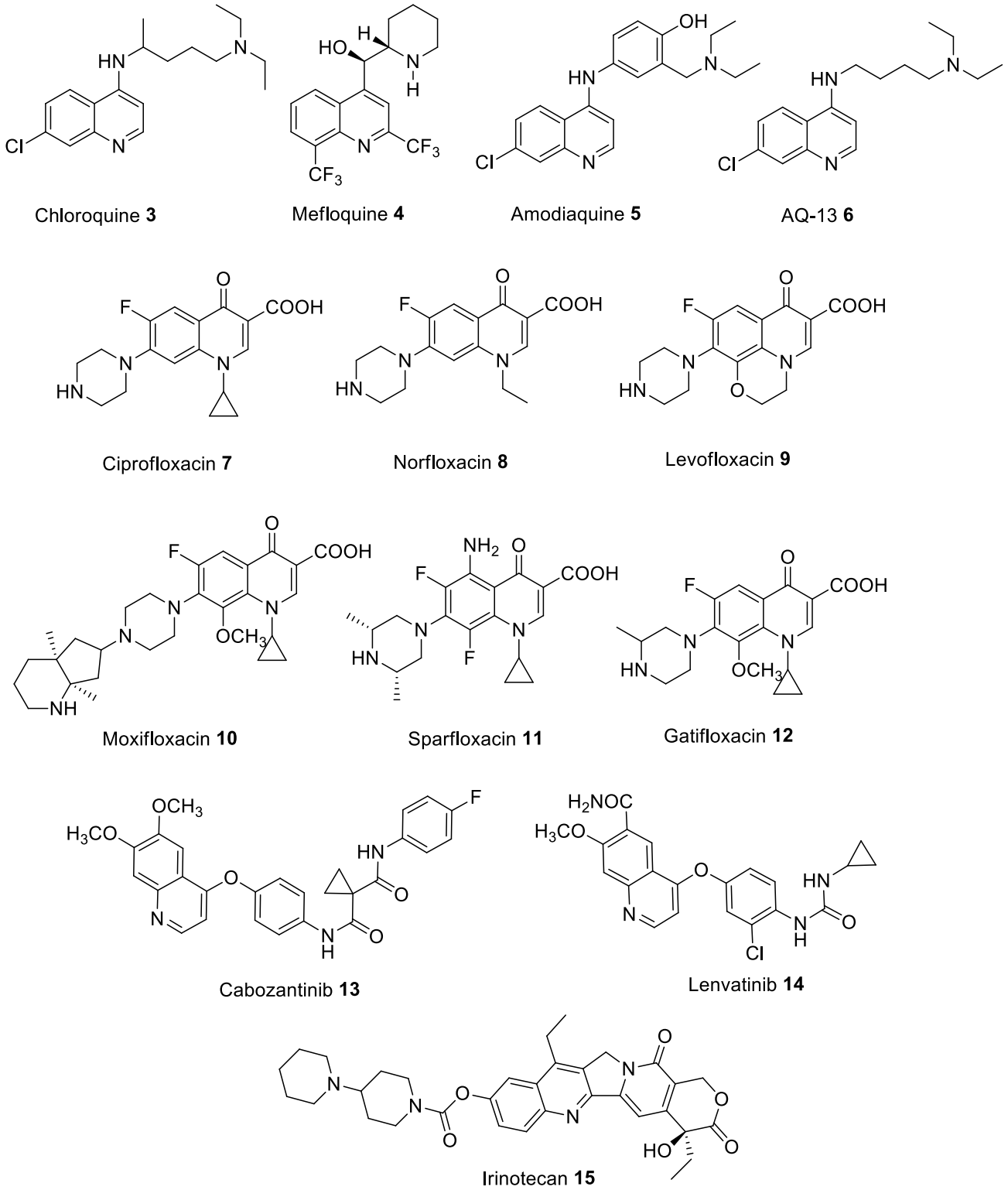


Fig 1.2 Quinoline based approved drugs

1.1.2 Recent Reports on Biological Importance of Quinoline Derivatives

Quinoline is privileged heterocyclic compound in the field of drug discovery and development. Its derivatives serve as antimalarial, antibacterial, antimicrobial, anticancer and antileishmanial agents.[1] Researchers have been attributing more attention to exploit quinoline scaffold and its derivatives in medicinal chemistry. Desai and coworkers[5] synthesized quinoline derivatives with pyrazole ketones **16** and screened them for their antibacterial and antifungal activities. Different derivatives showed potential as antibacterial, antifungal and antimicrobial agents. Pyrazole bearing quinoline derivatives **17** as antimicrobial agents were also synthesized by El Shehry[6] and coworkers. Majority of the compounds appeared as potent antibacterial and antifungal agents. Fu and coworkers[7] synthesized oxazino quinoline derivatives **18** and evaluated their antibacterial activities against Gram-positive (G^+) and Gram-negative (G^-) bacterial strains. Quinolone coupled hybrid derivative **19** exerted promising effect against these strains thereby showing antibacterial activities against broad spectrum of bacteria.

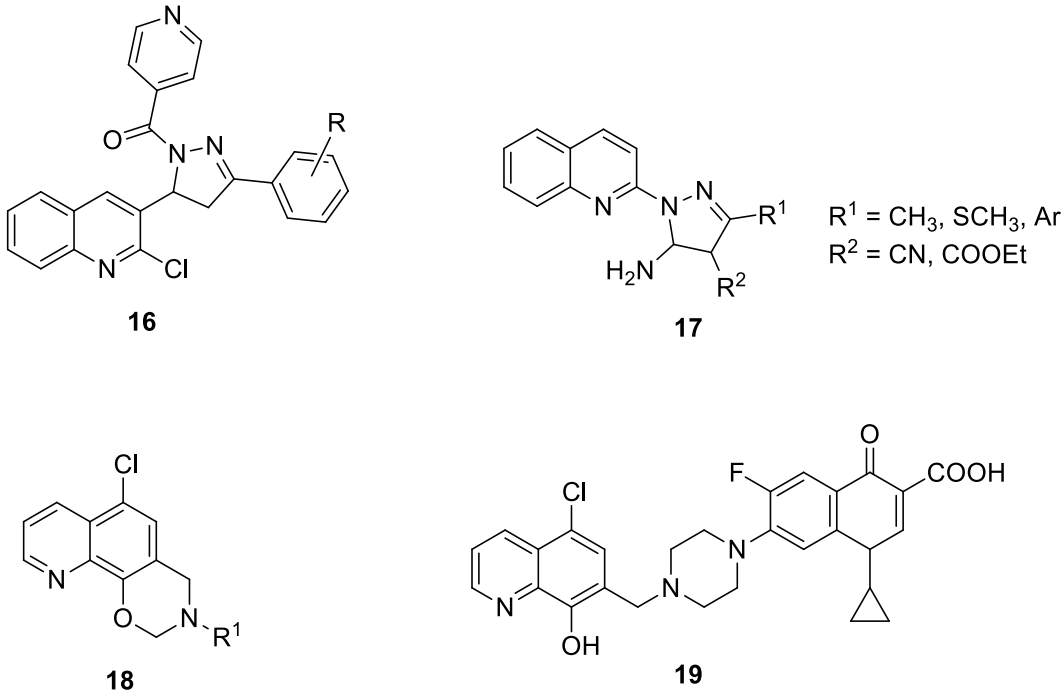


Fig 1.3 Quinoline derivatives with antibacterial activities

Katariya and coworkers[8] recently reported the synthesis of quinoline based hydrazone analogues **20**. These compounds were not only active anticancer agents but also possessed antimicrobial activity. Benzo- and tetrahydro benz[*h*]quinoline derivatives with flexible (dimethylamino)ethylcarboxamide side chain were designed and synthesized by Ghodsi and coworkers[9]. Structure of these derivatives resembles some known DNA intercalating antitumor agents. The cytotoxic activity of the synthesized compounds was evaluated against four human cancer cell lines. In general, tetrahydro benzo[*h*]quinoline derivatives **22** were better in activity than benzo[*h*]quinolines **21**.

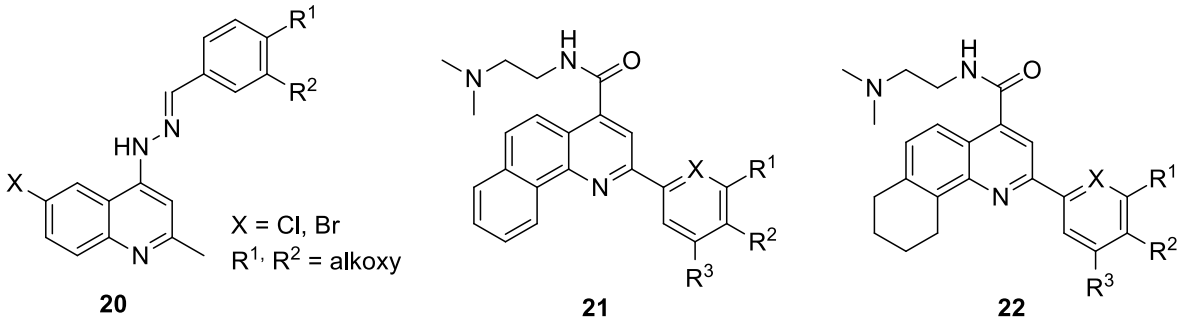


Fig 1.4 Quinoline derivatives with anticancer activities

Quinoline based thiadiazole analogues **23** were synthesized by Taha and coworkers[10] and these compounds depicted tremendous potential to be used as antileishmanial agents. Triazolyl 2-methyl-4-phenylquinoline-3-carboxylate derivatives **24** were also reported as antileishmanial agents.[11]

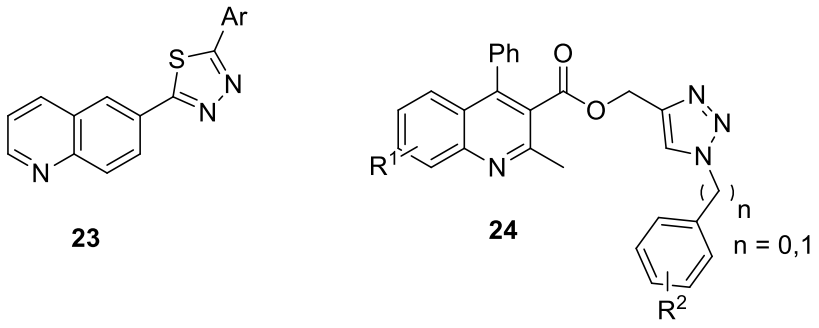
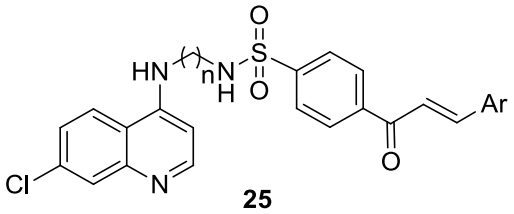


Fig 1.5 Quinoline derivatives with antileishmanial activities

Quinoline derivatives are the dominant class of antimalarial drugs. Most recently Vinindwa and coworkers[12] reported the hybrid molecules **25** as antimalarial agents. They comprises quinoline scaffold, coupled with chalcone through an appropriate linker. These molecular hybrids appeared as good antiplasmodial agents.



25

Fig 1.6 Quinoline derivatives with antimalarial activities

1.1.3 Nucleoside Triphosphate Diphosphohydrolases (NTPDases)

Ectonucleotidases are the extracellular enzymes that metabolize nucleosides and nucleotides outside the cell. Nucleosides and nucleotides derived from the purine (ADP and ATP) or pyrimidine moiety (UDP and UTP) are the important signaling molecules linked with the cell signaling mechanism. Metabolization or dephosphorylation of these nucleosides and nucleotides activates their respective receptors (P1 and P2) which are responsible for various physiological functions such as blood clotting, inflammation, immune responses, pain perception, smooth muscle contraction and cell proliferation.[13–15]

Ectonucleotidases are divided into four different families; nucleoside triphosphate diphosphohydrolases (NTPDases), ecto-5′-nucleotidase (ecto-5′-NT), nucleotide pyrophosphatase/phosphodiesterases (NPPs), and alkaline phosphatases (APs). All these enzymes are responsible for the hydrolysis of nucleotidases (Fig 1.7). Generally, these enzymes convert adenosine triphosphate (ATP), as well as diphosphate (ADP) and monophosphate (AMP), into adenosine. Nucleoside triphosphate diphosphohydrolases (NTPDases) also called ecto-apyrases or E-ATPases are metal dependant enzymes. They require Ca^{2+} or Mg^{2+} ions for their optimal functioning otherwise deactivate. NTPDases hydrolyze nucleoside di- and

triphosphates (ATP and ADP) but do not hydrolyze monophosphates. There are eight different NTPDases depending upon differences in cellular localization and substrate specificity. NTPDase-1, 2, 3 and 8 are membrane bound enzymes with extracellular active site. They are distributed in various systems where they have been reported to perform distinct biological functions. For example, NTPDase1 has been detected on the surface of endothelial cells and Treg cells where it has been reported to be involved in the regulation of vascular hemostasis and immune responses. Moreover, its presence in leukocytes and lymphocytes has been reported to modulate inflammatory responses and cytokine expression.[13,16] NTPDase2 is abundantly expressed in taste buds where it plays an important role in the modulation of taste bud functions.[17] In addition, NTPDase2, expressed on portal fibroblast, plays an important role in protecting against liver fibrosis caused by hepatocellular injury.[18] NTPDase3 is expressed in pancreatic islets where it has been suggested to regulate the insulin secretion. Although NTPDase8 has been detected in liver, its function is not clearly defined.[19] They are basically dominant ecto-nucleotidases and work in hydrolysis of nucleotidases. NTPDase4, 5, 6, and 7 enzymes are located in the intracellular domain.

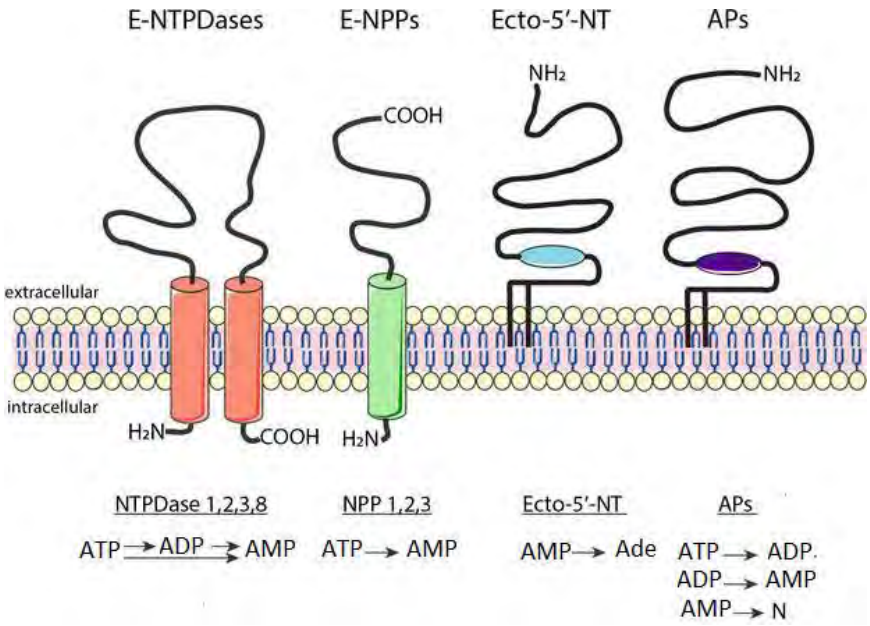


Fig 1.7 The nucleotide-hydrolysing pathway consisting of four ecto-enzymes[20]

1.1.4 NTPDase Inhibitors

Pathogens interfere with human immune response by disrupting the extracellular ATP levels in host thereby interrupting the purinergic signaling pathways which leads to unwanted physiological reactions. These extracellular ATP levels are strictly controlled by NTPDases (which are almost exclusively present in eukaryotes). Overexpression of NTPDases is linked with several diseases e.g. tumor development in certain areas. Therefore, inhibitors are required to control NTPDase activity and thus nucleotides level.

There is dire need to seek specific NTPDase inhibitors to investigate their role as therapeutic immunomodulatory agents for the possible treatment of cancer, cardiovascular, and central nervous system related disorders. NTPDase subtype selective inhibitors are rare and it is inferred in the literature that NTPDase inhibitors are usually ATP analogues which are physiologically and chemically less stable. ATP analogue ARL-67156[21] **26** is stable against E-NTPDases and ectoalkaline phosphatases but E-NPPs can hydrolyze it. 8-BuS-ATP derivatives[22] **27** are another class of nucleotide base inhibitors (Fig 1.8) reported as selective inhibitor for NTPDase1. PSB-6426[23] **28** which is nucleotide mimetic derived from uridine-5′-carboxamide was reported to be the potent inhibitor of NTPDase2.

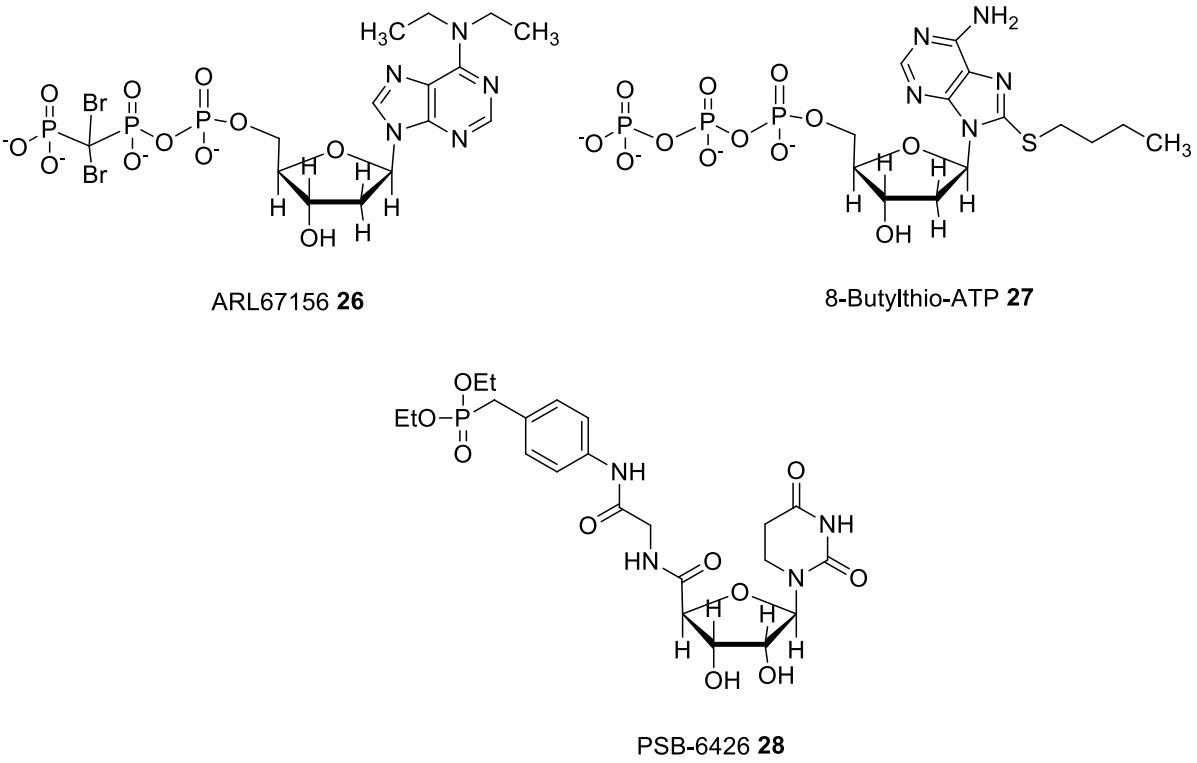


Fig 1.8 Nucleotide-derived E-NTPDase inhibitors

Some common non-nucleotide NTPDase inhibitors include dyes molecules with sulfonate group such as suramin **29**, pyridoxalphosphate-6-azophenyl-2',4'-disulfonic acid (PPADS) **30** and reactive blue 2 (RB2) [24] **31**. Shiff bases of tryptamin **32**,[25] polyoxometalates[26] **33** and anthraquinones[27] **34** have been reported as NTPDase inhibitors (Fig 1.9). All these compounds are non-selective in nature.

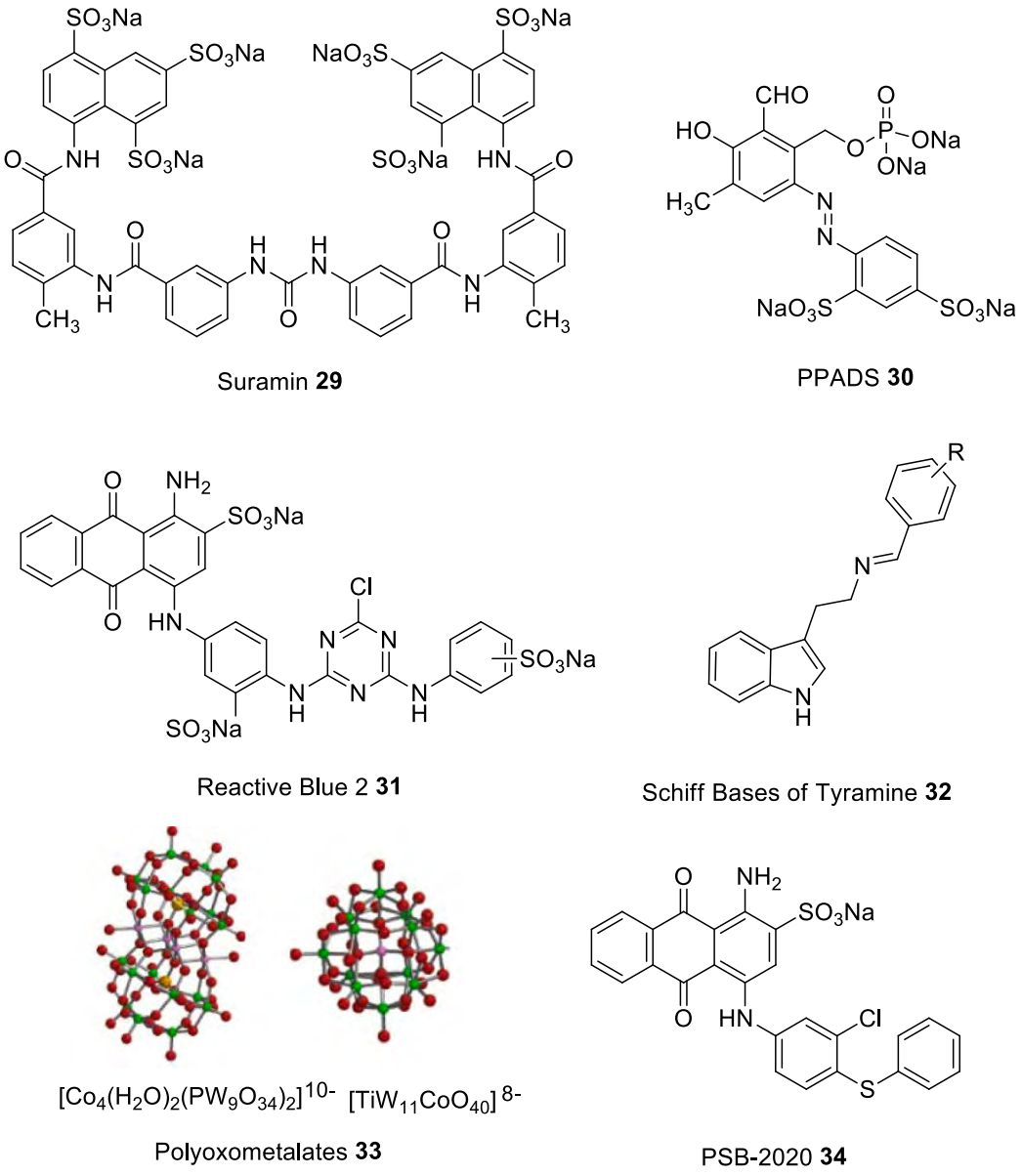


Fig 1.9 Non-nucleotide NTPDase inhibitors

1.1.5 Synthesis of Quinoline

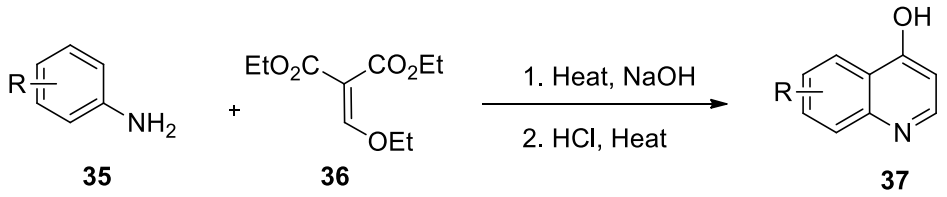
Quinoline is the most appreciated aromatic heterocycle because of its remarkable biological and industrial applications. Therefore, interest in the advancement of efficient methodologies for the quinoline synthesis is increasing. Different methods have been developed for the synthesis of quinoline derivatives that include Gould–Jacob reaction, Friedländer reaction, Skraup synthesis, Doebner–

von Miller reaction, and Conrad–Limpach reaction.[28] Other than these classical methods, transition metal catalyzed reactions and greener chemical reactions are emerging as more efficient methods of synthesis.

1.1.5.1 Conventional Approaches Towards the Quinoline Synthesis

1.1.5.1.1 Gould–Jacob Reaction

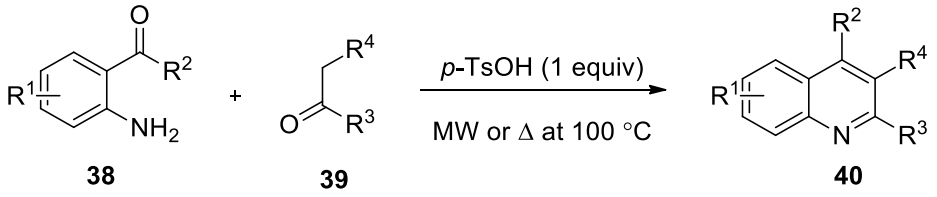
This reaction is mainly used for the synthesis of 4-hydoxyquinoline which usually exists as 4-quinolone. 4-Hydroxyquinoline core is the part of many commercial drugs and this methodology helps in the preparation of the well-known nonsteroidal anti-inflammatory drugs floctafenine and glafenine.[29] In this protocol, aniline is condensed with alkoxy methylenemalonic ester (Scheme 1.1) which undergoes series of reactions to yield 4-hydroxy quinoline **37**.[30]



Scheme 1.1 Gould-Jacob reaction for synthesis of quinoline

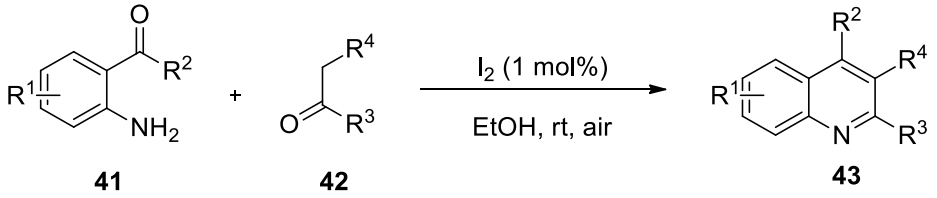
1.1.5.1.2 Friedländer Reaction

In this synthesis, *o*-aminoaryl aldehydes or ketones are condensed with a ketone having methylene group. The resulting intermediate undergoes cyclocondensation in the presence of acid or base to form quinoline skeleton.[31] In a modified procedure, polysubstituted quinolines **40** were synthesized using *p*-toluenesulfonic acid as catalyst (Scheme 1.2). Reaction works well under solvent-free conditions by conventional heating or microwave irradiation.[32]



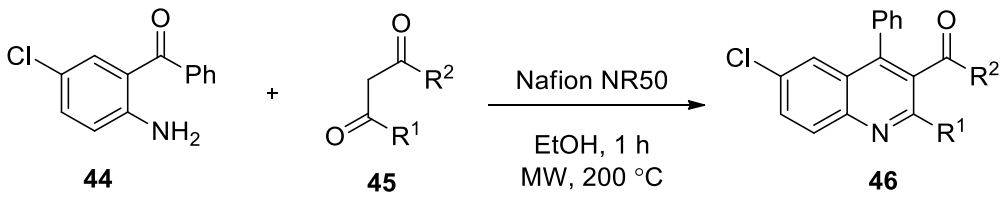
Scheme 1.2 Friedländer reaction for synthesis of polysubstituted quinoline

Molecular iodine was also reported as an efficient catalyst for Friedländer annulation.[33] Using iodine as catalyst avoids the use of harsh acids or bases. Various quinolines and polycyclic quinolines were synthesized under mild reaction conditions (Scheme 1.3).



Scheme 1.3 Iodine catalyzed Friedländer annulation reaction

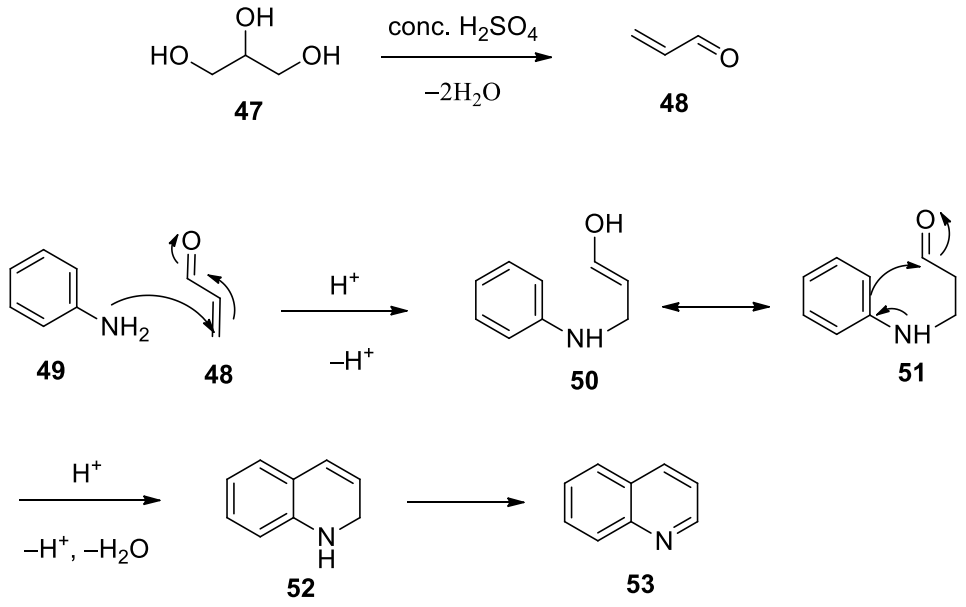
In a more recent approach sloid catalyst Nafion NR50 (Scheme 1.4) was used for Friedländer annulation which is environment-friendly and reusable catalyst. Reaction was assisted by microwave irradiations using ethanol solvent.[34]



Scheme 1.4 Nafion NR50 catalyzed Friedländer annulation reaction

1.1.5.1.3 Skraup Synthesis

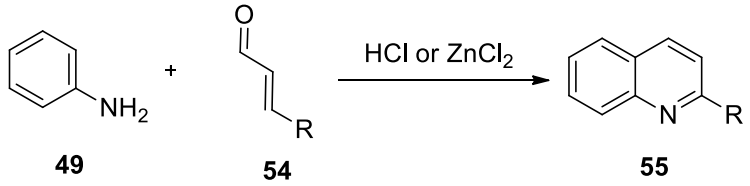
In Skraup synthesis aniline is heated with glycerol in the presence of sulfuric acid and an oxidizing agent.[35] It was first developed by Skraup and he used nitrobenzene as an oxidizing agent which was later replaced by arsenic pentoxide or iodine as better oxidizing agents. Crotonaldehyde intermediate **48** is generated by dehydration of glycerol that undergoes 1,4-nucleophilic addition by the attack of aniline (Scheme 1.5) to yield intermediate **50**, which tautomerizes followed by nucleophilic attack of benzene to aldehyde group resulting in the dihydroquinoline derivative **52**. It oxidizes to quinoline.



Scheme 1.5 Skraup synthesis

1.1.5.1.4 Doebner-Miller Synthesis

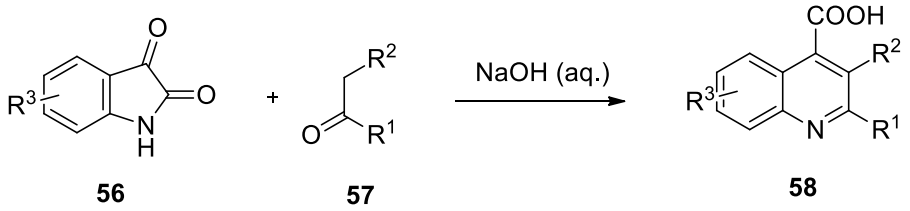
This reaction is the variation of Skraup reaction that involves heating of *α,β*-unsaturated carbonyl compounds with aniline under acidic conditions. Concentrated hydrochloric acid or zinc chloride is usually used without additional oxidizing agent (Scheme 1.6).[36]



Scheme 1.6 Doebner-Miller synthesis

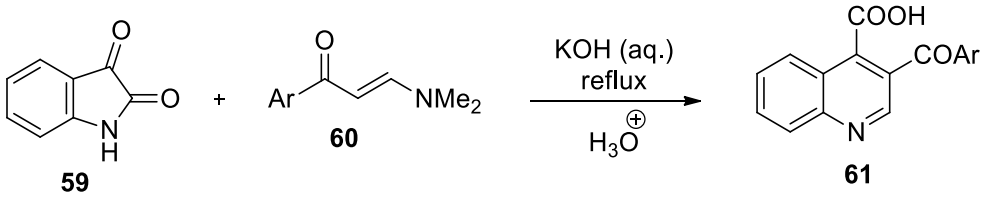
1.1.5.1.5 Pfitzinger Synthesis

This is also known as Pfitzinger–Borsche reaction that uses isatin or its derivatives and α-methylene carbonyl compound employing base in ethanol to synthesize quinoline 4-carboxylic acid (Scheme 1.7).[37]



Scheme 1.7 Pfitzinger synthesis

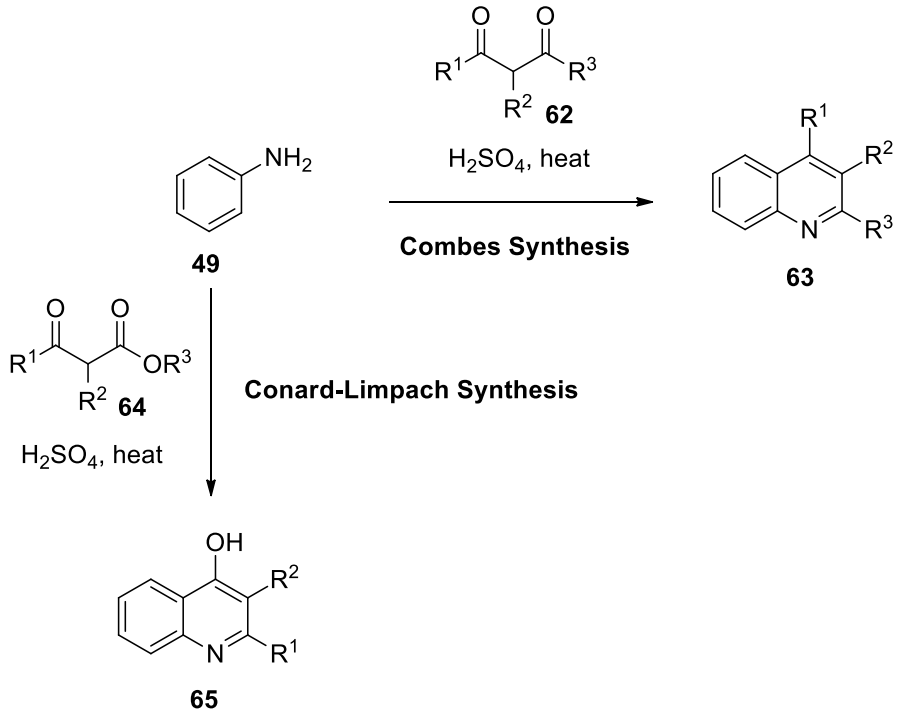
Elghamry and coworkers have reported the synthesis of quinoline-4-carboxylic acid **61** (Scheme 1.8) by reacting isatin with enaminones **60** under Pfitzinger reaction conditions.[38]



Scheme 1.8 Synthesis of quinoline derivative **61** through Pfitzinger reaction

1.1.5.1.6 Combes Synthesis

In this synthesis, unsubstituted anilines are condensed with β-diketones (Scheme 1.9).[36] Under acidic conditions, intermediate Schiff base cyclizes to quinoline. In the similar Conard–Limpach reaction, β-ketoesters are reacted with aryl amines to form 4-hydroxyquinolines **65**.[35]



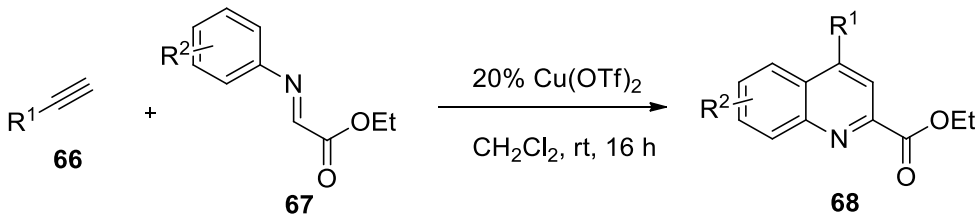
Scheme 1.9 General reaction scheme for Combes and Conard-Limpach reaction

1.1.5.2 Recent Progress in the Synthesis of Quinoline

1.1.5.2.1 Transition Metal Catalyzed Synthesis of Quinoline

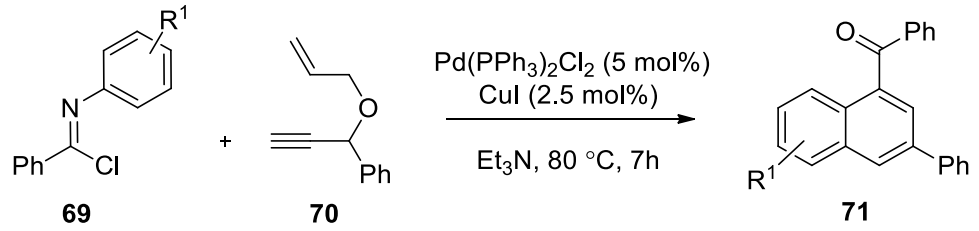
Transition-metal catalyzed synthetic methods are considered more efficient methods for the synthesis of complex molecules due to their appealing catalytic ability. Organic and medicinal chemists have relied more on these methods since past decades. Complex compound libraries can be generated from readily available starting materials using metal catalysts. Huang and coworkers reported

the synthesis of quinoline-2-carboxylate derivatives **68** employing ligand free copper catalyst (Scheme 1.10). Alkynes were added onto imines to afford quinoline skeleton through sequence of intramolecular addition reactions.[39]



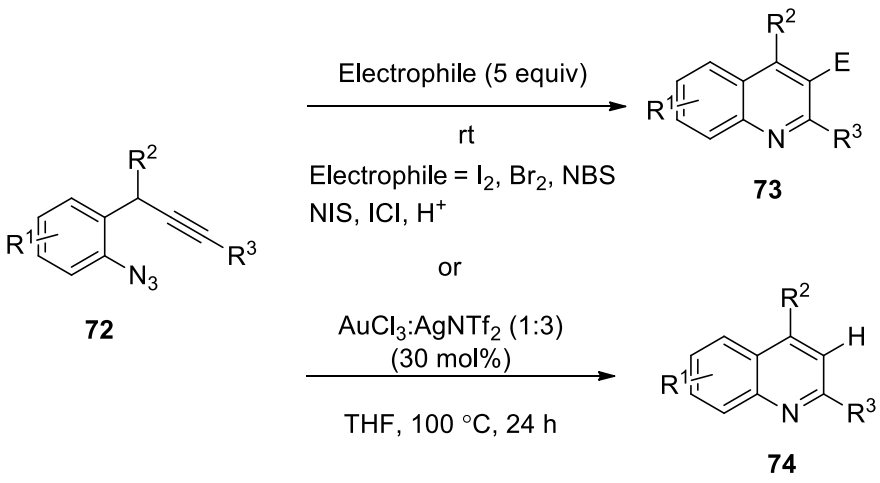
Scheme 1.10 Copper catalyzed synthesis of quinoline derivatives

Sonogashira coupling of benzimidoyl chlorides with 1,6-enynes catalyzed by palladium for the synthesis of quinoline derivatives was reported by Gao and coworkers (Scheme 1.11). The reaction is efficient with simple reaction conditions and furnishes quinoline products in moderate to good yields.[40]



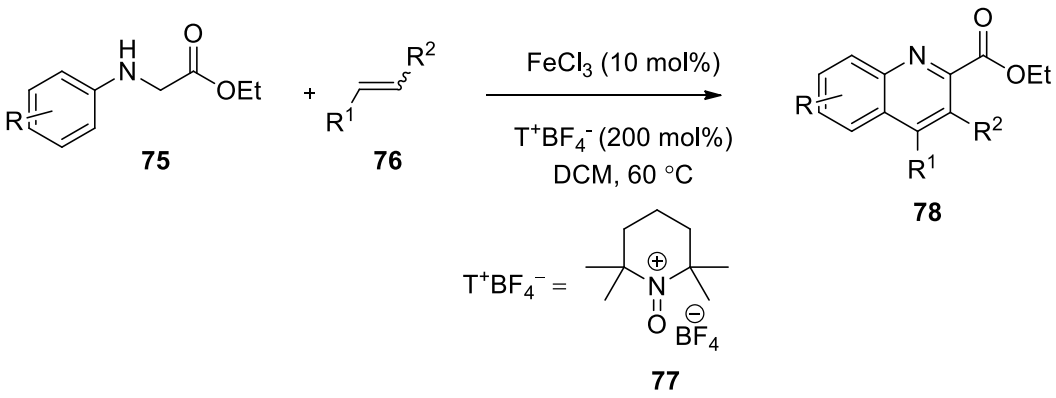
Scheme 1.11 Sonogashira coupling reaction for the synthesis of quinoline derivative

1-Azido-2-alkynylbenzene **72** can be cyclized intramolecularly to quinolines **73** in the presence of an electrophilic reagent (I_2, Br_2, NBS, NIS, ICI, H^+) or using catalytic amount of $AuCl_3/AgNTf_2$ catalytic system to afford quinoline derivatives **74** (Scheme 1.12).[41]



Scheme 1.12 Synthesis of substituted quinolines via electrophilic cyclization

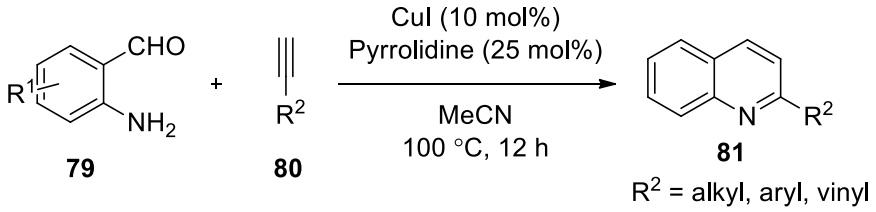
Synthesis of quinoline in one-pot dehydrogenative manner using a TEMPO oxoammonium salt as an oxidant in combination with $FeCl_3$ catalyst was reported (Scheme 1.13).[42] *N*-Alkyl anilines, such as ethyl glycines, were reacted with a variety of mono- and 1,2-disubstituted aryl and alkyl olefins. Reaction is efficient employing cheap catalyst and mild and non-toxic oxidant.



Scheme 1.13 TEMPO oxoammonium salt mediated synthesis of substituted quinolines

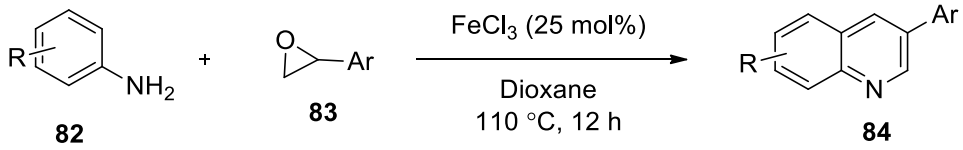
To access 2-substituted quinolines **81**, 2-aminobenzaldehyde was coupled with terminal alkynes using CuI iodide in combination with pyrrolidine as catalyst

Scheme 1.14).[43] This method of synthesis is applicable to naturally and pharmaceutically important compounds.



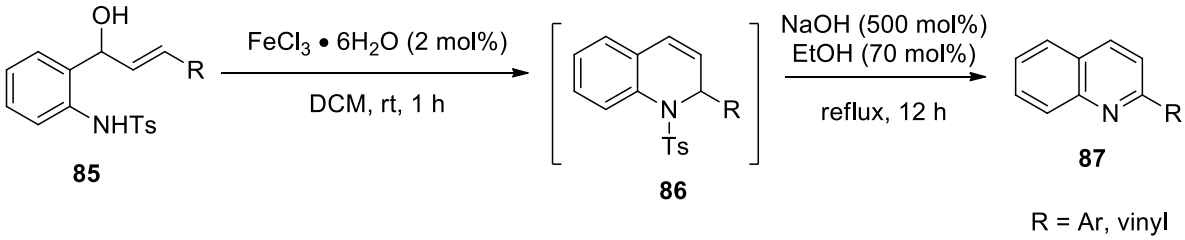
Scheme 1.14 Copper and pyrrolidine catalyzed synthesis of 2-substituted quinolines

Synthesis of 3-arylquinolines **84** was reported from aniline and styrene oxide using $FeCl_3$ catalyst (Scheme 1.15).[44] The reaction involves C-C cleavage and C-H activation with inexpensive iron catalyst.



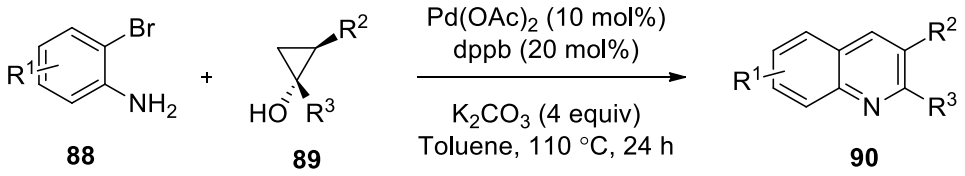
Scheme 1.15 Iron catalyzed synthesis of 3-arylquinoline

In another report $FeCl_3.6H_2O$ was used as catalyst for the synthesis of 2- or 4-substituted quinolines via intramolecular allylic amination of *N*-protected 2-aminophenyl-1-en-3-ols at room temperature (Scheme 1.16).[45]



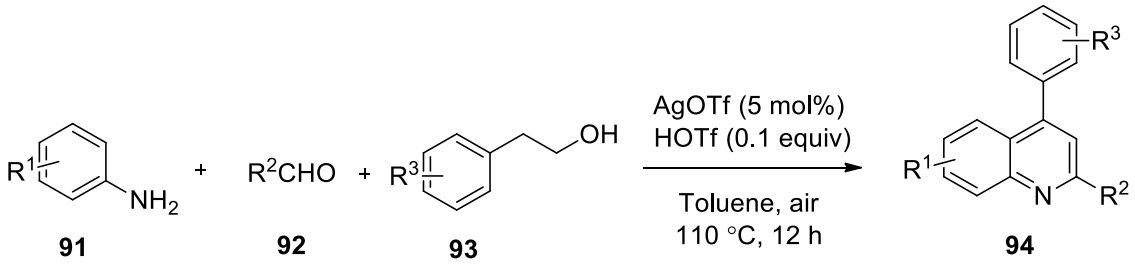
Scheme 1.16 Iron catalyzed synthesis of 2-substituted quinolines

Palladium catalyzed cross coupling of *ortho*-bromomaniline with cyclopropanols yields substituted quinolines in single step (Scheme 1.17).[46] Reaction involves intramolecular condensation and palladium-catalyzed oxidation sequence.



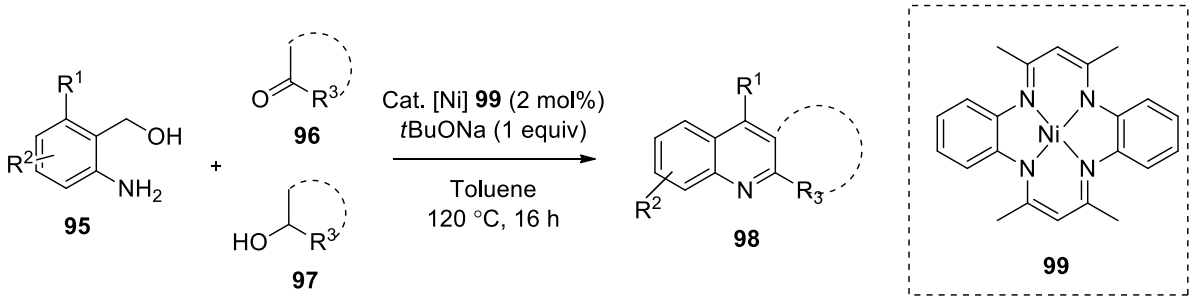
Scheme 1.17 Palladium catalyzed synthesis of substituted quinolines

Zhang and coworkers reported the synthesis of polysubstituted quinolines **94** from aniline, alcohol and aldehyde using silver catalyst (Scheme 1.18).[47]



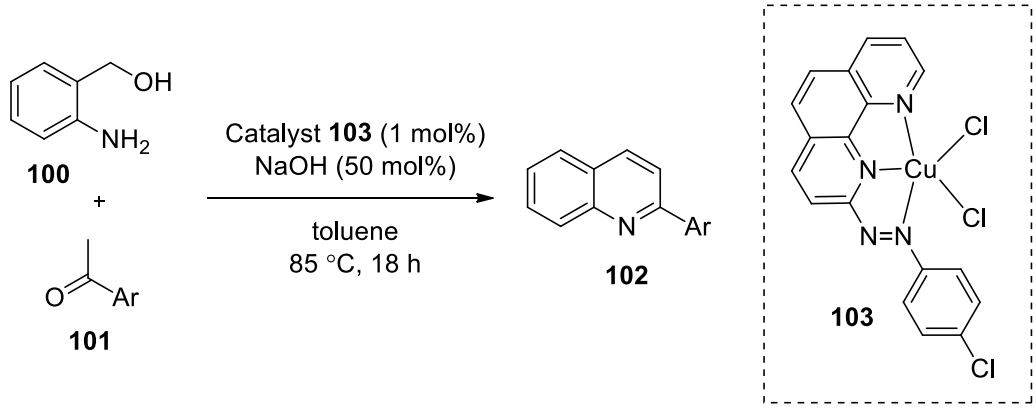
Scheme 1.18 Silver catalyzed synthesis of polysubstituted quinolines

Synthesis of polysubstituted quinoline was also reported by Das and coworkers where they reacted α-aminoaryl alcohol with ketone or secondary alcohol using cheap nickel catalyst (Scheme 1.19).[48] Reaction involves dehydrogenation and condensation sequence.



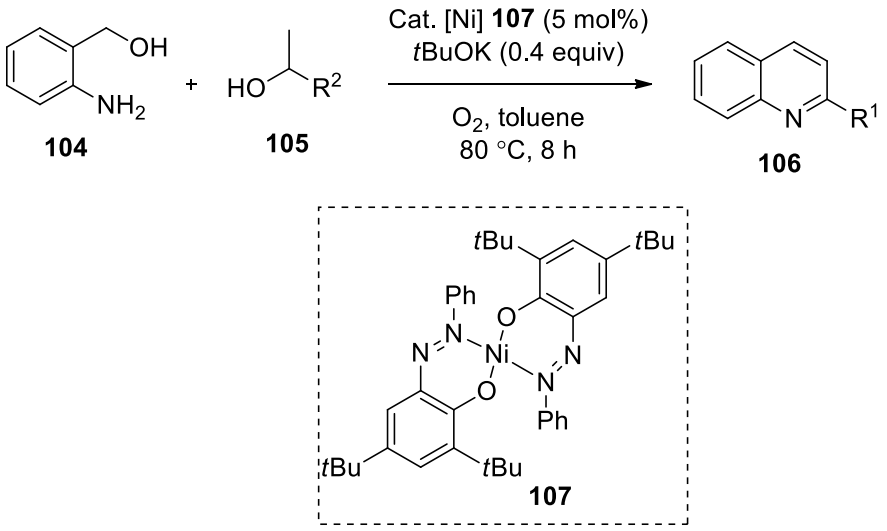
Scheme 1.19 Nickel catalyzed synthesis of polysubstituted quinolines

In a cooperative metal-ligand approach quinolines were synthesized from alcohols by dehydrogenative functionalization reported by Das and coworkers (Scheme 1.20).[49] Copper catalyst **103** was used in this transformation.



Scheme 1.20 Copper catalyzed dehydrogenative coupling of 2-aminobenzyl alcohol with acetophenones

In another similar dehydrogenative coupling approach nickel catalyst **107** was employed for the synthesis of quinolines from 2-aminobenzyl alcohol under aerobic conditions (Scheme 1.21).[50]



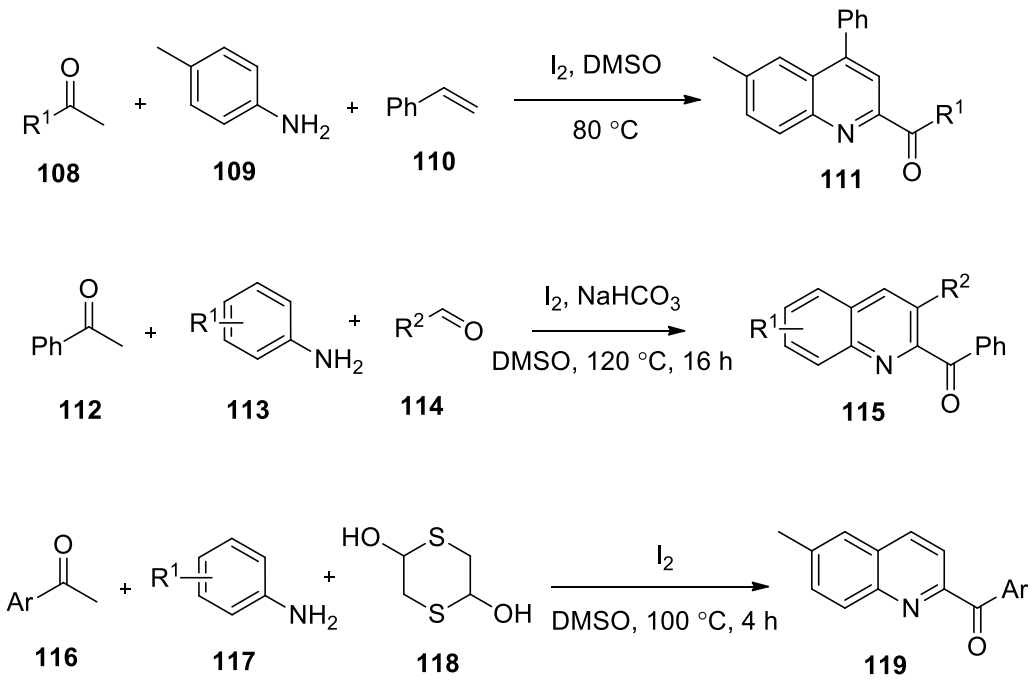
Scheme 1.21 Nickel catalyzed synthesis of 2-substituted quinolines

1.1.5.2.2 Metal Free Synthesis of Quinolines

Researchers are focusing on finding metal-free mediated protocols for the synthesis of quinoline. Such reactions use Lewis acids or bases, ionic liquids, iodine as catalyst or even catalyst free reactions which makes them eco-friendly and they also have high atom efficiency. These greener approaches are the part of run these days.

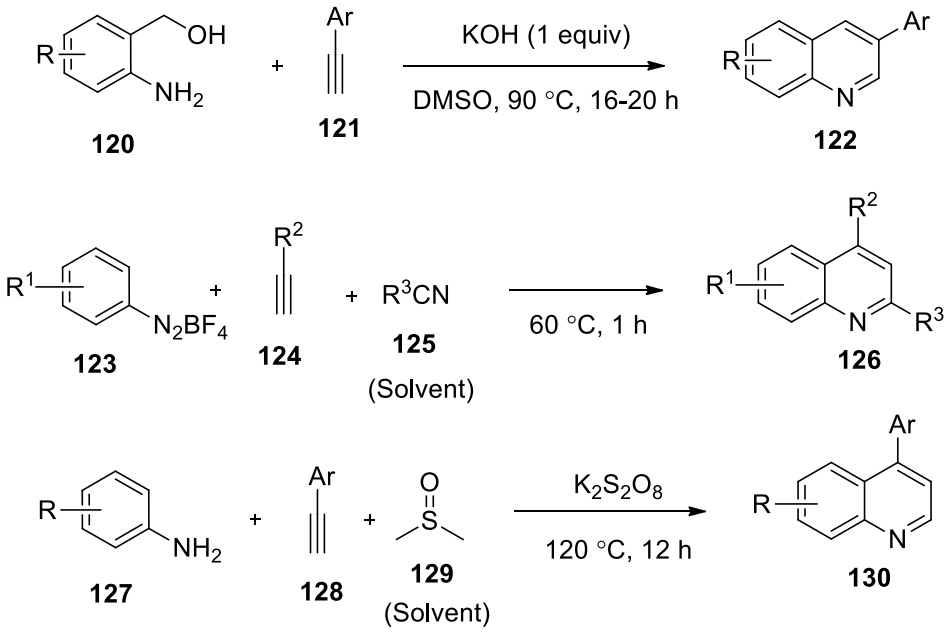
Gao and coworkers reported the synthesis of quinolines **111** from three components i.e, methyl ketones **108**, arylamines **109**, and styrenes **110** in [3+2+1] cycloaddition manner which is in principle a Povarov cyclization reaction. Molecular iodine assists this cyclization reaction.[51] Another Povarov type reaction was reported for the synthesis of 2-acyl-3-aryl(alkyl)quinolines **115** by [4+2] cycloaddition of methyl ketones, arylamines, and aryl or alkyl acetaldehydes which work as alkene surrogates. Reaction is promoted by iodine and aryl amine as well. Aryl amine helps in enamine formation and acts as reactant as well.[52] Wu and coworkers reported I_2-promoted formal [4+2] cycloaddition reaction for the synthesis of 2-acylquinolines **119** from methyl ketones and arylamines using 1,4-

dithane-2,5-diol **118** as an ethylene surrogate. Reaction involved iodination/Kornblum oxidation/Povarov/ aromatization sequence.[53]



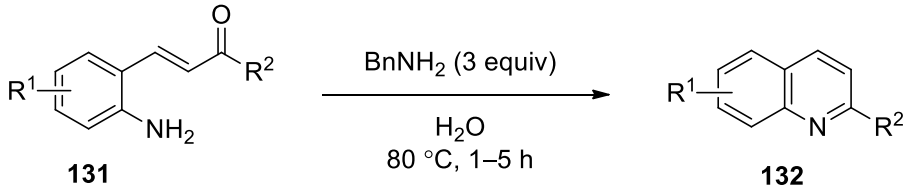
Scheme 1.22 I_2 mediated Povarov type cyclization reactions for quinoline synthesis

KOH promoted [4+2] cycloaddition of azadienes with terminal alkynes was reported for the synthesis of 3-substituted quinolines **122**. Azadienes were synthesized *in situ* from 2-aminobenzyl alcohol (Scheme 1.23).[54] In another approach, multisubstituted quinolines **126** were synthesized by three components coupling of aryl diazonium salts, nitriles, and alkynes without any catalyst or additive.[55] Acetonitrile used as the solvent, acts as one component in this reaction. Synthesis of 4-arylquinolines **130** was reported from readily accessible anilines and alkynes in the presence of potassium persulfate ($K_2S_2O_8$) and DMSO.[56] DMSO acts as one carbon source in addition to its use as solvent.



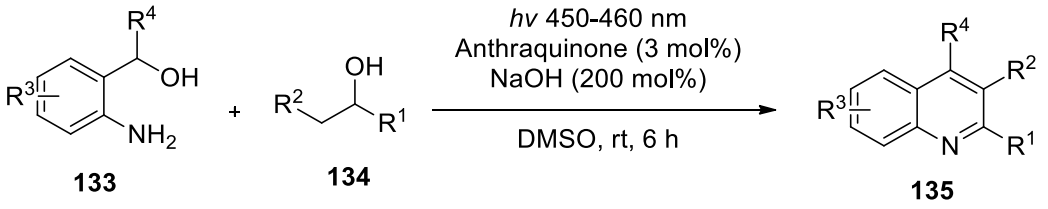
Scheme 1.23 Metal free synthesis of quinoline derivatives

Synthesis of 2-substituted quinolines was reported by 2-aminochalcone by Lee and coworkers using water as solvent.[57] Benzylamine acted as nucleophilic catalyst in this reaction.



Scheme 1.24 On-water synthesis of 2-substituted quinolines from 2-aminochalcones

Photocatalysis in organic synthesis has emerged as a powerful tool to direct novel organic transformations under mild reaction conditions.[58] Organic photocatalyst, the use of small organic molecules as catalyst offers advantages over transition metal catalysts in terms of simple work-up, low toxicity, and special reactivity.[59] More recently, anthraquinone catalyzed synthesis of quinolines was reported from 2-aminobenzyl alcohols and secondary alcohols at room temperature (Scheme 1.25).



Scheme 1.25 Visible light mediated synthesis of quinoline

1.2 Asymmetric Addition of Alkyne Nucleophiles to Carbonyl Compounds

Asymmetric addition of terminal alkynes to unsaturated carbon−carbon or carbon−heteroatom bonds provides not only atom-economic methods to prepare complex molecules with versatile alkyne functions but also an opportunity to construct chiral scaffolds. Enantioselective addition of terminal alkynes to carbonyl compounds give rise to propargylic alcohols which are valuable building blocks as they serve as precursors to different synthetic transformations (Fig 1.10).

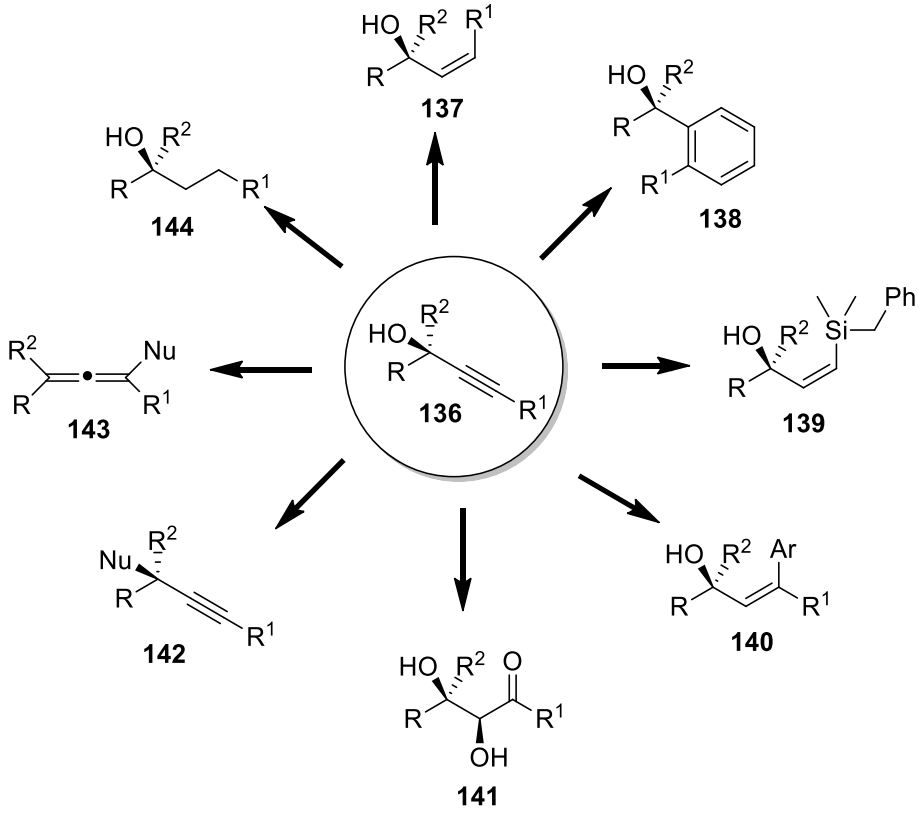
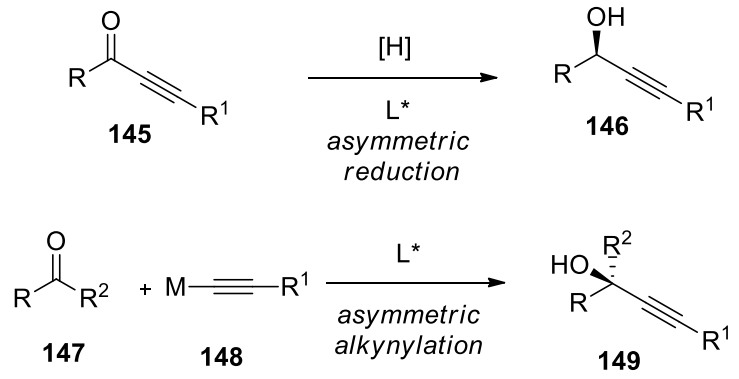


Fig 1.10 Propargylic alcohols as synthetic intermediates

Optically active propargylic alcohols can be synthesized either by asymmetric reduction of an ynone **145** or by asymmetric metal-catalyzed alkyne addition to carbonyl group (Scheme 1.26). Asymmetric reduction of ynone is less employed for the synthesis of propargylic alcohols because of instability of ynone starting material. It can decompose, isomerize or react with other compounds. Contrary to

ynones reduction, alkynes addition to carbonyl compounds is practical method to access propargylic alcohols. Any aldehyde or ketone can be attacked by alkynes.



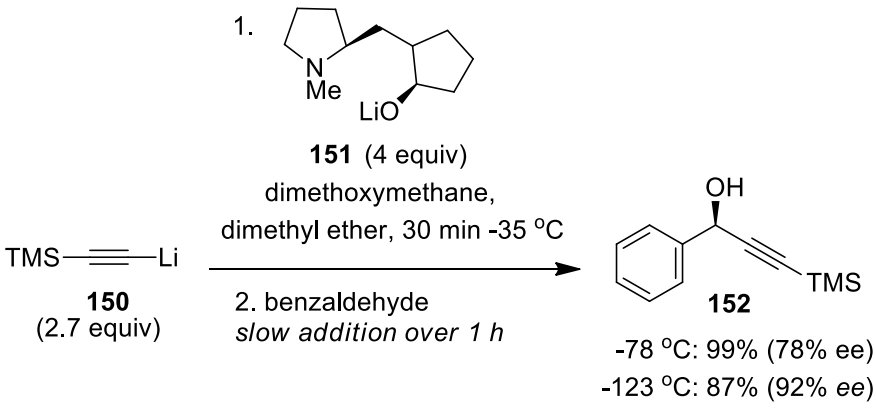
Scheme 1.26 General schemes for the synthesis of propargylic alcohols

1.2.1 Asymmetric Addition of Alkynes to Aldehydes

The asymmetric addition of alkynes to aldehydes is one of the most powerful methods of synthesis in organic synthetic chemistry, where the formation of one carbon-carbon bond and one chiral center of propargylic alcohol can be achieved in one step.[60] To date, several studies have been reported in this area.[61]

1.2.1.1 Addition of Lithium Acetylides to Aldehydes

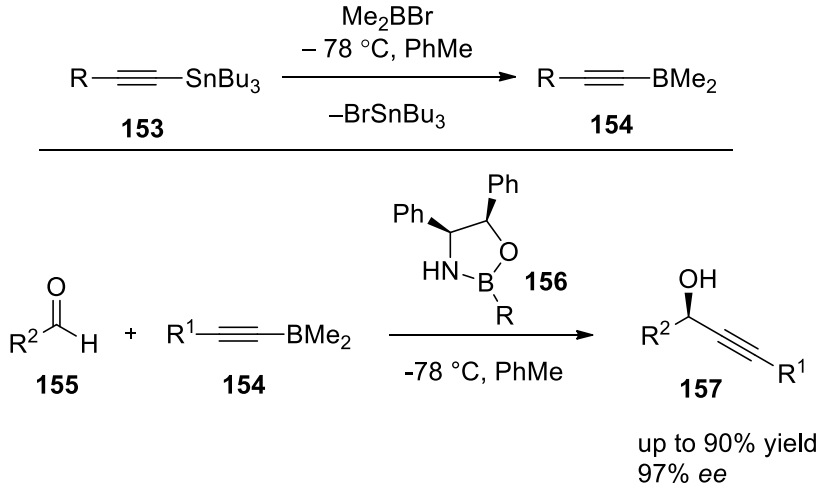
Mukiyama and coworkers provided the addition of lithium trimethylsilylacetylide **150** to aldehydes in the presence of (2*S*,2'*S*)-2-hydroxymethyl-1-[(1-methylpyrrolidin-2-methyl]pyrrolidine **151** as chiral ligand (Scheme 1.27). Enantiomeric excesses of up to 92% were obtained using superstoichiometric amounts of the ligand.[62]



Scheme 1.27 Addition of llithium trimethylsilylacetylide to aldehydes

1.2.1.2 Addition of Alkynylborane to Aldehydes

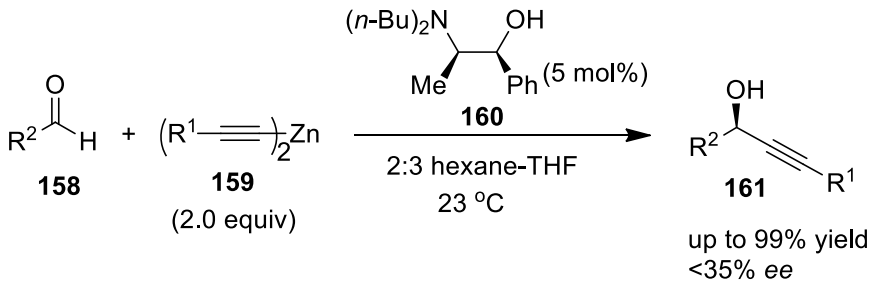
In 1994, Corey and coworkers reported the addition of alkynes to aldehyde using stoichiometric oxazaborolidine **156**. Bromodimethylborane was reacted with alkynylstannane **153** to generate *in situ* dimethyl-(alkynyl)borane **154**. Oxazaborolidine **156** was then added to the same pot followed by an aldehyde. Excellent yields and enantioselectivities were attained (Scheme 1.28).[63]



Scheme 1.28 Addition of alkynylboranes to aldehydes

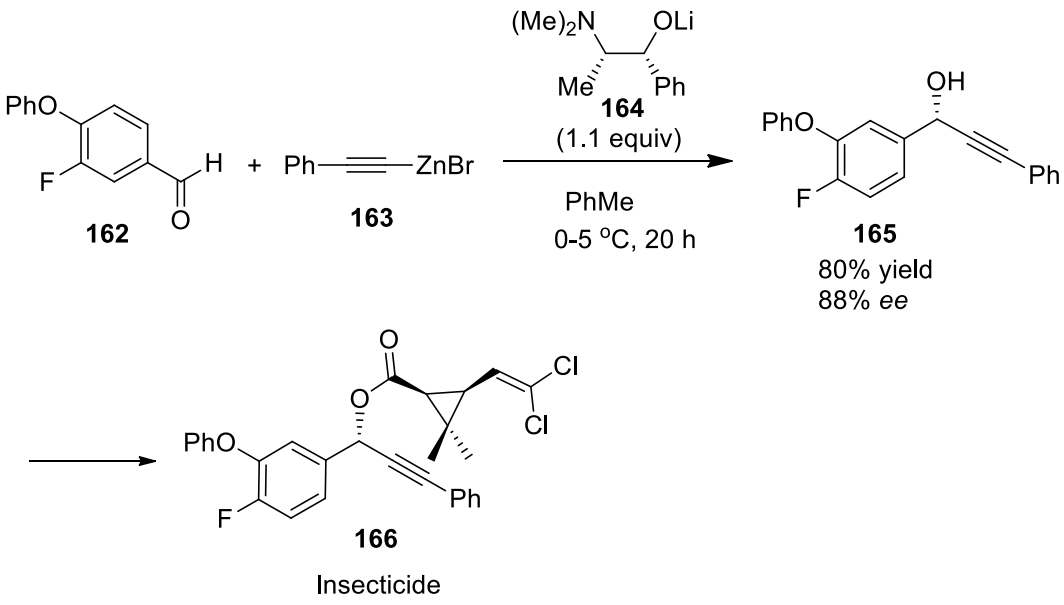
1.2.1.3 Alkyl Zinc Mediated Addition of Alkynes to Aldehydes

Soai and coworkers developed the methodology of using alkylzinc reagents for the addition of alkynes to aldehydes.[64] Alkyne was heated with diethylzinc in THF to form bis-alkynylzinc **159** followed by its treatment with amino alcohol ligand **160** and an aldehyde forming propargylic alcohol in excellent yields, but in lower enantioselectivities (Scheme 1.29).



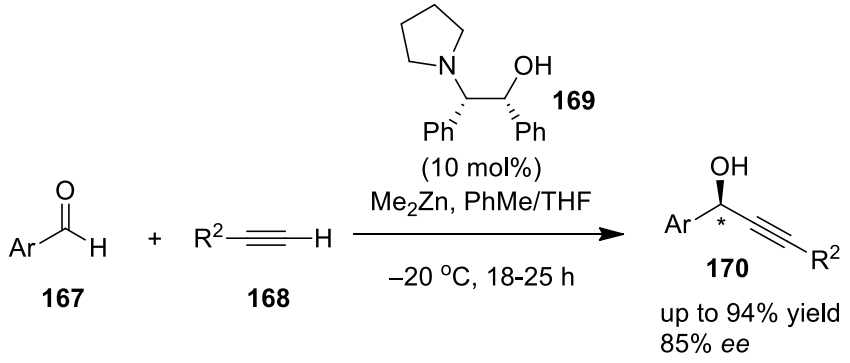
Scheme 1.29 Addition of bisalkynylzinc reagents to aldehydes

Moderate enantioselectivities of alkynols provided by Soai and coworkers were later overcome by researchers by exploring different aminoacohol ligands. In this regard Tombo and coworkers reported the use of *N*-methylephedrine ligand for alkynylation of aldehydes.[65] Moderate yield and enantioselectivity was observed when *N*-methylephedrine ligand was employed for the addition of ethyl-(2-phenylethynyl)zinc to aldehyde. When reaction was performed with lithium salt of *N*-methylephedrine **164** and reacting phenylacetylene with zinc bromide and adding it to aldehyde resulted in 80% yield and 88% ee (Scheme 1.30). Developed reaction was used for the synthesis of insecticide **166**.



Scheme 1.30 Addition of zinc-acetylides to aldehydes using lithium salt of *n*-methylephedrine as ligand

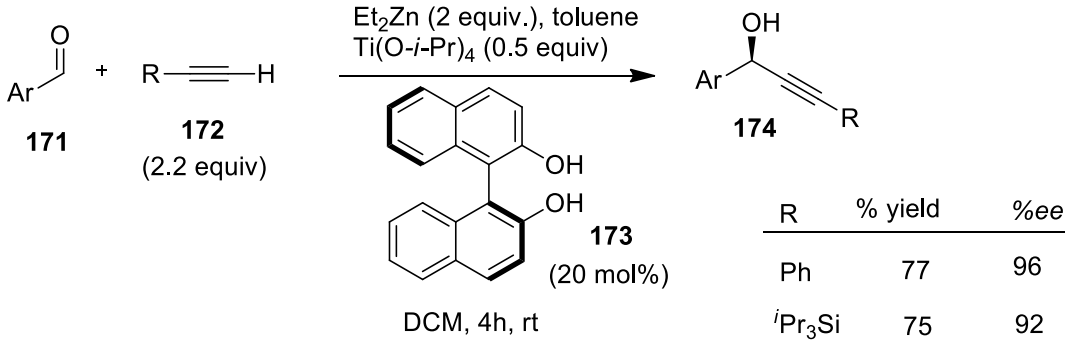
Use of 10 mol% of ephedrine derived ligand **169** for the addition of zinc alkynylides to aromatic aldehydes at -20°C was explored by researchers at Merck and good yields and enantioselectivities were reported (Scheme 1.31).[66]

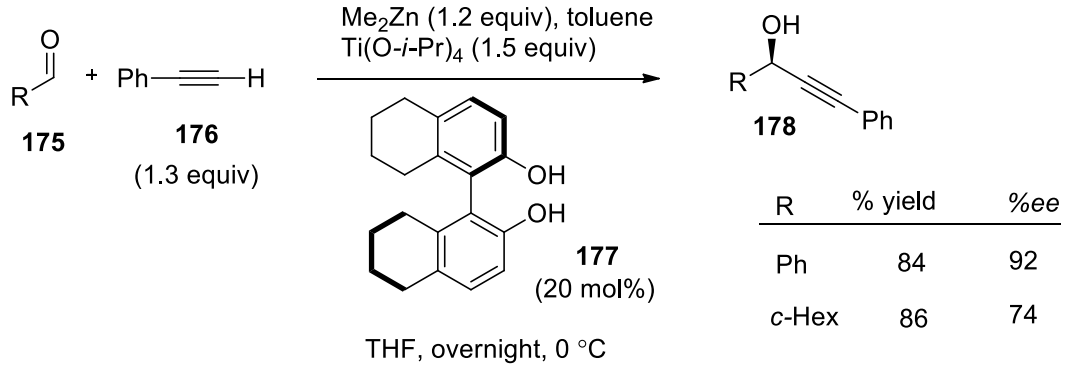


Scheme 1.31 Addition of zinc alkynylides to aromatic aldehydes catalyzed by ephedrine derived ligand

In further investigations, titanium was found beneficial in addition of zinc acetylide to aldehydes. Pu and Chan independently reported the enantioselective addition of alkynes to aldehydes using titanium-BINOL catalyst-ligand system.

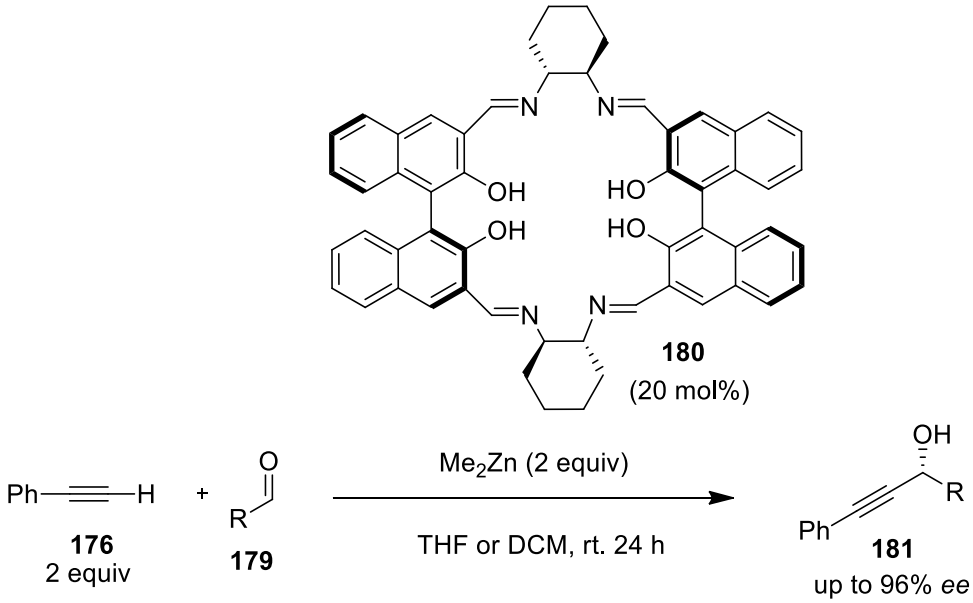
Pu and coworkers used the readily available (*S*)-BINOL **173** ligand with $Ti(O^iPr)_4$ for addition of phenylacetylene to different substituted aromatic aldehydes and reported *ee* upto 96% (Scheme 1.32).[67] Chan reported the similar method for the synthesis of chiral propargylic alcohols derived from aromatic aldehydes using $Ti(O^iPr)_4$ catalyst along with (*R*)-H_8-BINOL ligand **177** and zinc acetylides were prepared using dimethyl zinc.[68]





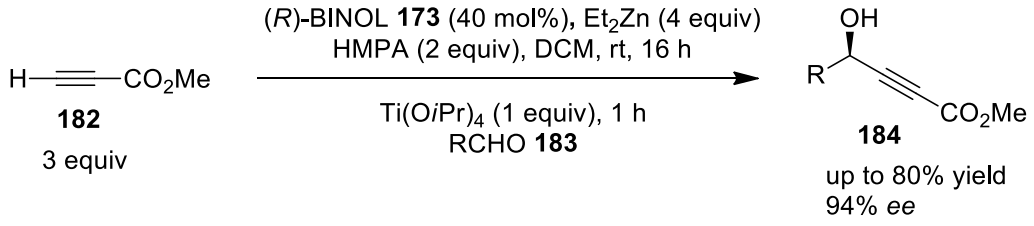
Scheme 1.32 Titanium-BINOL catalyzed enantioselective addition of alkynes to aldehydes

Pu and coworkers found that $Ti(O^iPr)_4$ and (*S*)-BINOL **173** can be utilized for asymmetric alkynylation of aliphatic aldehydes, aromatic aldehydes, and *α,β*-unsaturated aldehydes to generate chiral propargyl alcohols with 91−99% *ee* at room temperature just by increasing the catalyst-ligand loading.[69] Later a chiral macrocycle ligand **180** was introduced by the same researcher to facilitate the addition of phenyl acetylene to aliphatic and vinyl aldehydes (Scheme 1.33).[70]



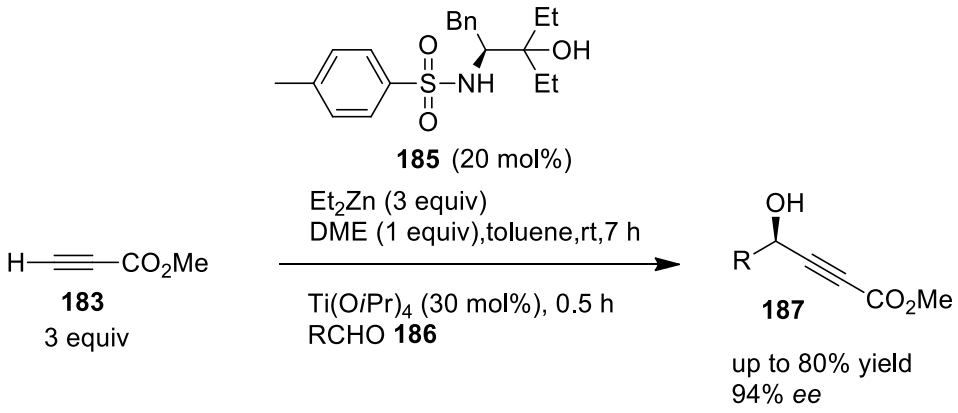
Scheme 1.33 Enantioselective addition of phenyl acetylene to aldehydes catalyzed by macrocycle ligand

Addition of additives was found beneficial for the formation zinc alkynylide by Pu and coworkers. They used hexamethylphosphoramide (HMPA) to synthesize zinc alkynylide under mild reaction conditions at ambient temperature. This strategy was utilized for enantioselective propiolate addition onto aldehyde (Scheme 1.34).[71]



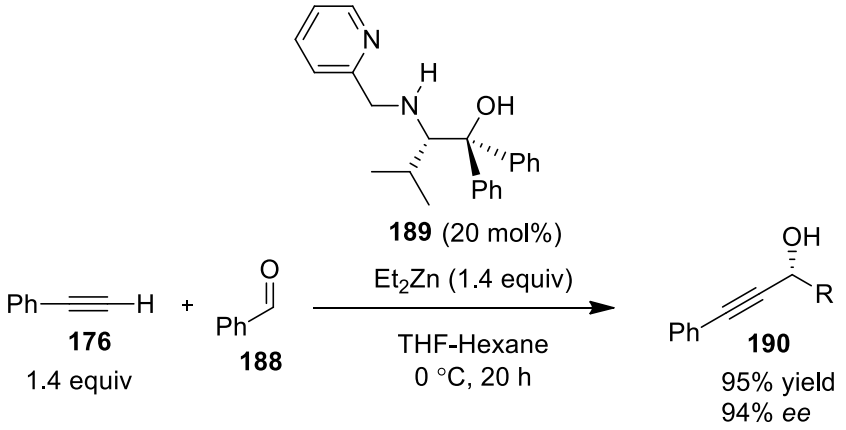
Scheme 1.34 Titanium-BINOL-HMPA catalyst for the zinc propiolate addition to aldehydes

Wang and coworkers prepared *β*-sulfonamide alcohols **185** [72] and used as ligands for enantioselective addition of propiolate to aldehydes (Scheme 1.35).[73]



Scheme 1.35 *β*-Sulfonamide alcohols catalyzed enantioselective addition of propiolate to aldehydes

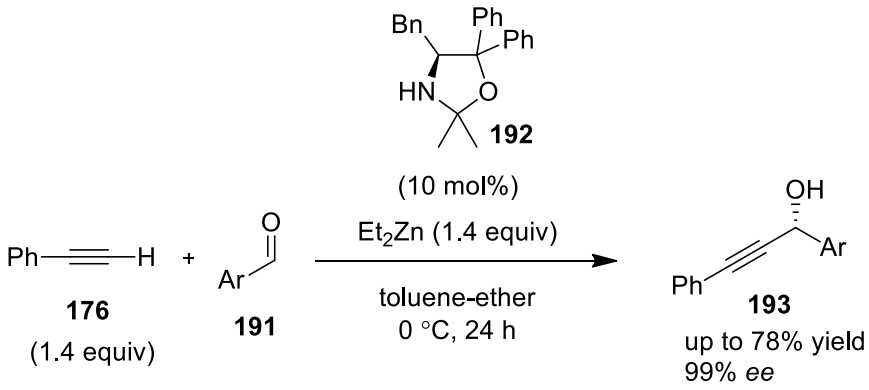
Furthermore, Wang and co-workers introduced bifunctional pyridine-containing amino alcohol ligand **189** for the addition of zinc alkynylide to aldehyde. High yields and enantioselectivities were acheived using only 20 mol% of the ligand (Scheme 1.36).[74]



Scheme 1.36 Bifunctional pyridyl amino alcohol ligand catalyzed addition of zinc alkynylide to benzaldehyde

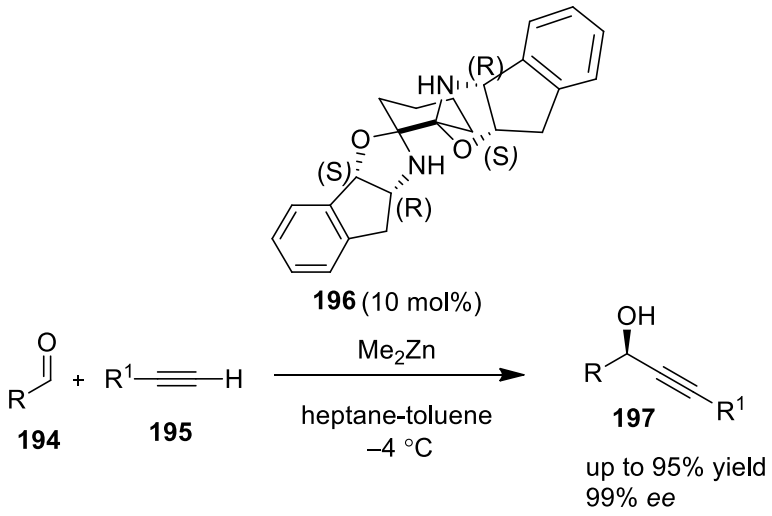
Mono-oxazolidine and bis-oxazolidine ligands have been successfully employed in the synthesis of chiral propargylic alcohols by asymmetric alkynylation of aldehydes. Wang and coworkers reported mono-oxazolidine ligand **192**

synthesized from amino acid and utilized it in addition of pheylacetylene to various aromatic aldehydes and achieved high enantioselectivities upto 99% (Scheme 1.37).[75]



Scheme 1.37 Mono-oxazolidine catalyzed addition of zinc-acetylide to aldehydes

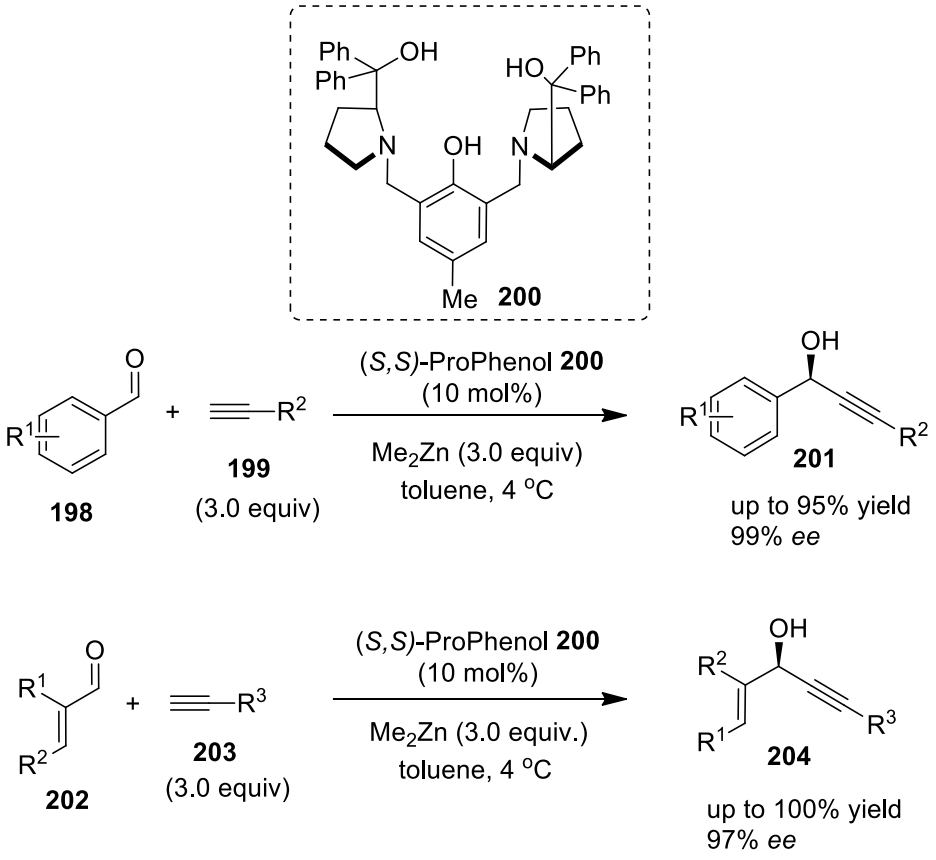
Wolf and coworkers reported the C_2-symmetric bisoxazolidine ligands synthesized from inexpensive amino indanol for asymmetric alkynylation of both aliphatic and aromatic aldehydes (Scheme 1.38).[76]



Scheme 1.38 C_2-symmetric bisoxazolidine ligands catalyzed addition of zinc-acetylide to aldehydes

Trost and coworkers reported the alkynylation of aromatic and α,β-unsaturated aldehydes using proline-derived dinuclear zinc catalyst system. High yields and enatioselectivities (upto 99%) were obtained for different aromatic aldehdes and

in case of *α,β*-unsaturated aldehydes, 100% yield and 97% ee was observed (Scheme 1.39).[77]

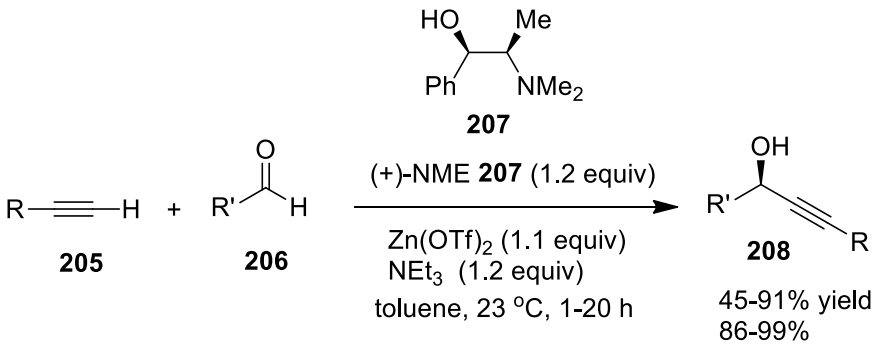


Scheme 1.39 Trost's prophenol ligand catalyzed addition of zinc acetylides to aldehydes

1.2.1.4 Zinc Salts Mediated Addition of Alkynes to Aldehydes

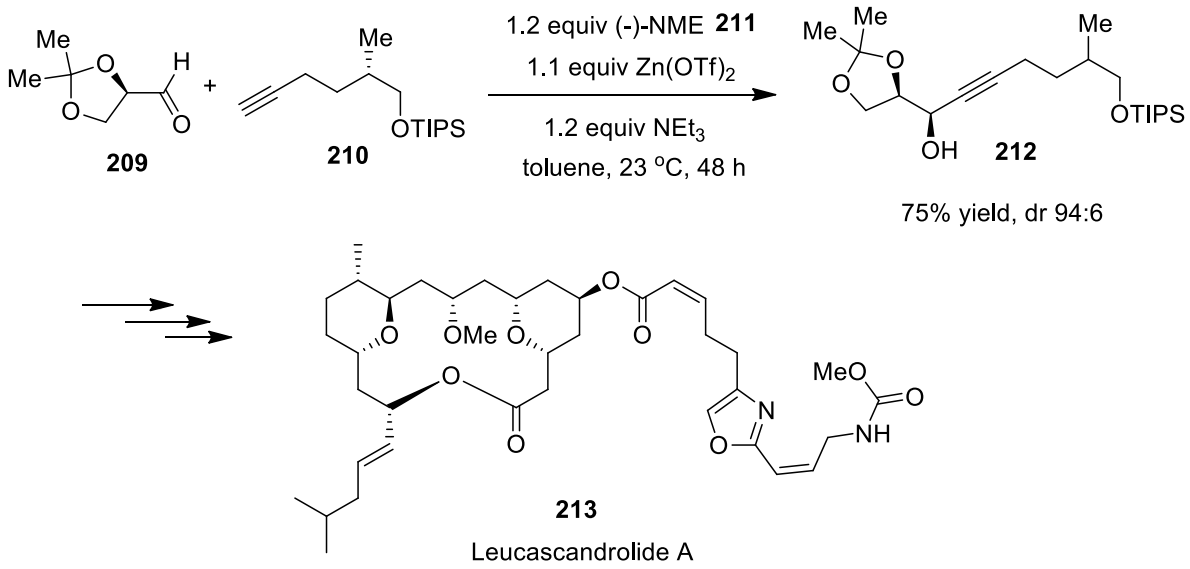
Laboratory processes that made use of inert atmosphere or rigorously dried and degassed solvent are sometimes difficult to accomplish. The development of processes that are easy to perform is an important goal in modern synthetic methodology. Use of zinc salts in place of alkyl zinc reagents was reported by different researchers.

Carriera and coworkers reported high enantioselectivities (up to 99%) of propargylic alcohols by using R_3N/Zn(II) catalyst system with chiral *N*-methylephedrine ((+)-NME) ligand **207**.[78] Alkynylzinc reagents generated *in situ* by the reaction of the terminal alkynes with $Zn(OTf)_2$ in the presence of the amine base, were added to aldehydes to get propargylic alcohols (Scheme 1.40).



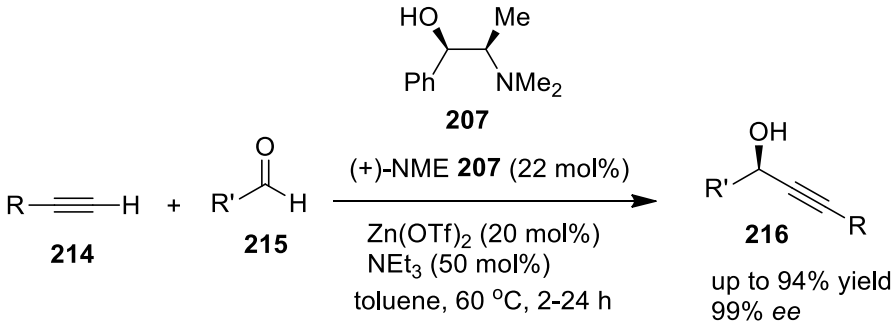
Scheme 1.40 (+)-NME-mediated enantioselective addition of $Zn(OTf)_2$ by carriera

Carriera used above reported conditions in synthesis of marine macrolide leucascandrolide **213**.[79]



Scheme 1.41 Synthesis of leucascandrolide A

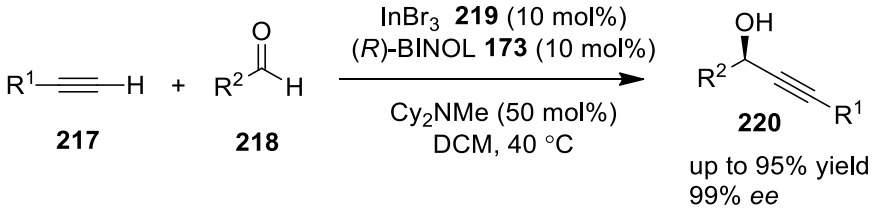
Carriera and coworkers used catalytic amounts of $Zn(OTf)_2$ salt and (+)-*N*-methyl ephedrine ligand **207** for addition of acetylenes across different aromatic and aliphatic aldehydes and achieved high level of enantioselectivities (upto 99%) (Scheme 1.42). [80] They also reported the utilization of reagent grade solvent thus following convenient reaction conditions for enantioselective addition reactions to aldehydes by terminal acetylenes and achieved promising results.[81]



Scheme 1.42 Catalytic and highly enantioselective addition of alkynes to aldehydes by Carriera

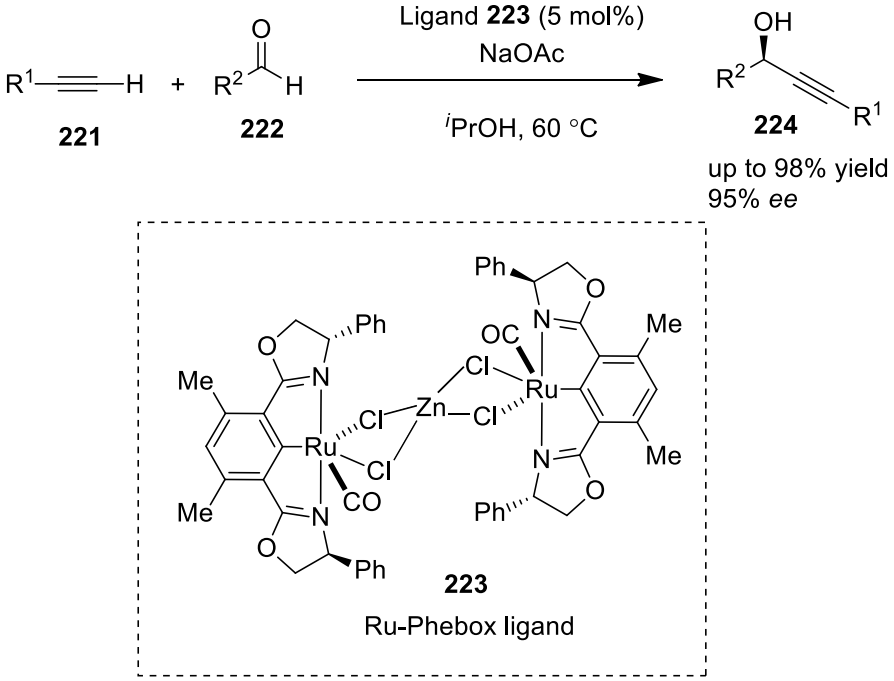
1.2.1.5 Addition of Alkynes to Aldehydes Catalyzed by Other Metal Salts

Alkynylation of aldehydes by soft metal catalysts is not limited to zinc only but it has been extended to different metal catalysts. Shibasaki and coworkers described a catalytic asymmetric alkynylation of both aromatic and aliphatic aldehydes promoted by a chiral In(III)/BINOL complex (Scheme 1.43). Indium plays bifunctional character as it acts as a lewis acid and an activator. It facilitates the reaction by activating alkynes and aldehydes. Low loading of catalyst and ligand worked for enantioselective addition of alkynes to aldehydes.



Scheme 1.43 In(III)/BINOL catalyzed addition of alkynes to aldehydes

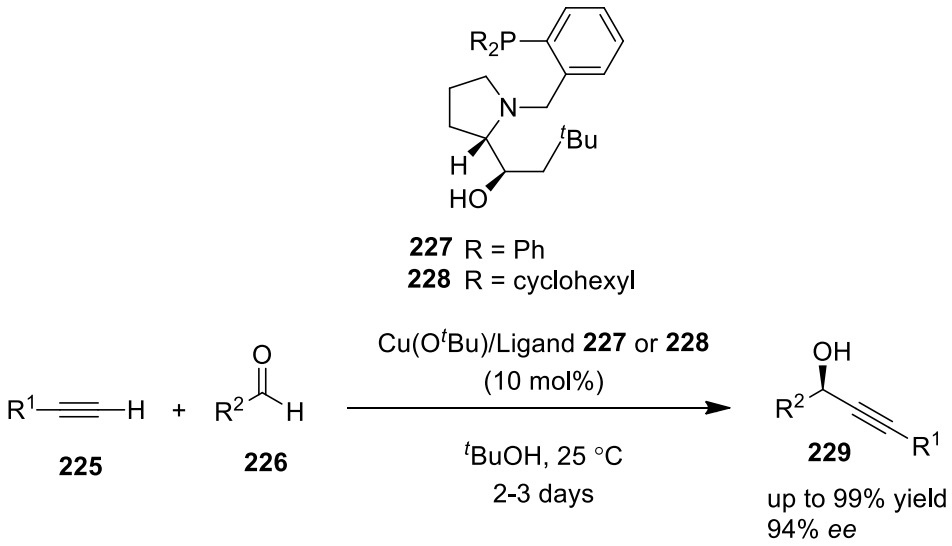
Asymmetric direct alkynylation of aldehydes was achieved using ruthenium phebox (bisoxazoline phenyl) ligand **223**.[82] High enantioselectivities were observed using 5 mol% Ru-phebox complex (Scheme 1.44).



Scheme 1.44 Addition of alkynes to aldehydes catalyzed by ruthenium phebox ligand

Copper catalyzed direct alkynylation of aldehydes was reported by Sawamura and coworkers. They used copper(I) catalyst and prolinol-based hydroxyl amino phosphane chiral ligands **227** and **228**.[83] This catalyst-ligand system is efficient

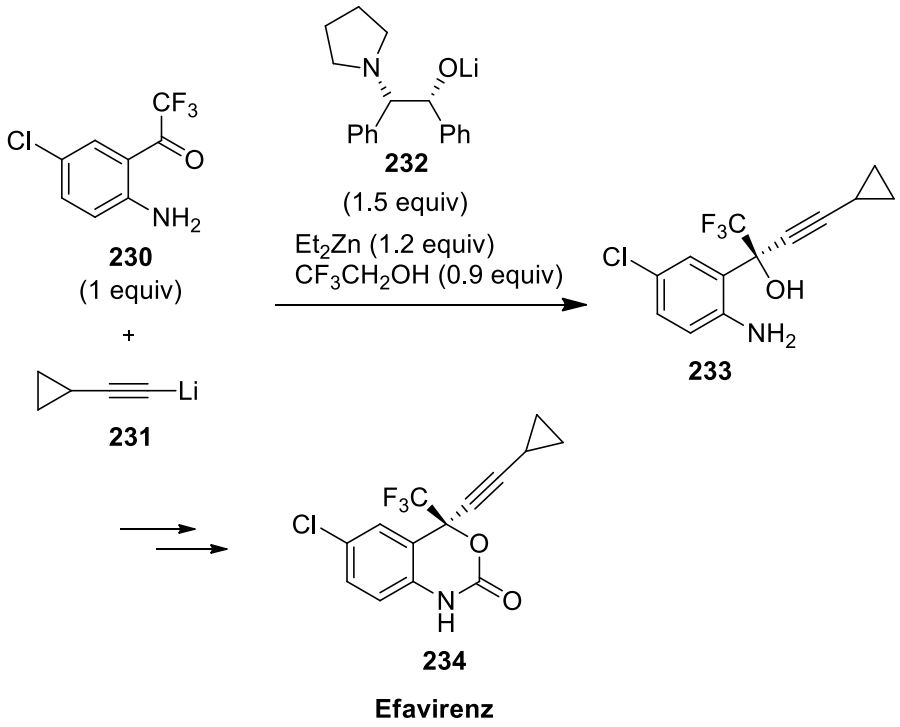
for the addition of different alkynes to both aliphatic and aromatic aldehydes to access enantioenriched propargylalcohols (Scheme 1.45).



Scheme 1.45 Copper catalyzed addition of alkynes to aldehydes

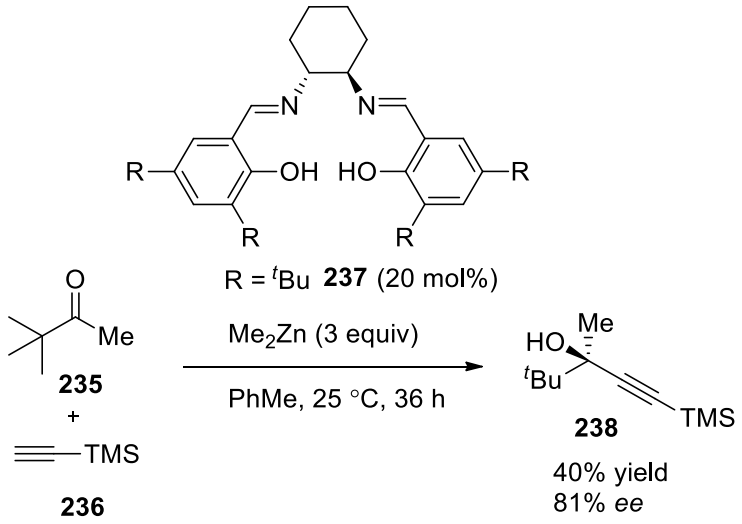
1.2.2 Asymmetric Alkynylation of Ketones

Addition of alkynes to ketones results in the formation of quaternary centered tertiary propargylic alcohols. Generation of quaternary stereocentres is still very challenging for organic chemists. In contrast to the significant progress made with asymmetric alkynylation of aldehydes, ketones as a substrate has received less attention which can be attributed to inertness or low reactivity of ketones.[84] In 1995, the first example of enantioselective alkynylation of a ketone was reported by Thompson and Corey working at Merck laboratories, for the synthesis of anti-AIDS drug efavirenz **234**.[85] Lithium cyclopropylacetylide **231** was added to trifluoromethyl ketone **230** in the presence of lithium based ephedrine alkoxide and 99% ee was achieved (Scheme 1.46).



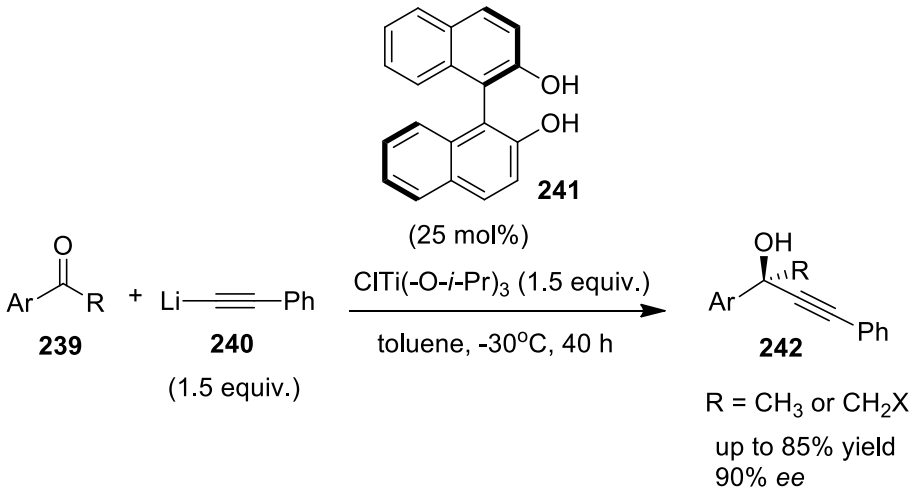
Scheme 1.46 Synthesis of anti-AIDS drug efavirenz

Cozzi and coworkers demonstrated the first catalytic example of alkynylation of ketones (Scheme 1.47). Addition of terminal alkynes to a various unactivated ketones was achieved in the presence of dimethylzinc and Jacobsen's chiral salen ligand **237**.[86] Salen ligand-metal complex has the bifunctional character, acting as Lewis acid and Lewis base at the same time thus activating ketone and alkyne. To improve the enantioselectivity of alkynes addition to ketone, a more sterically demanding salen ligand was reported later.[87]



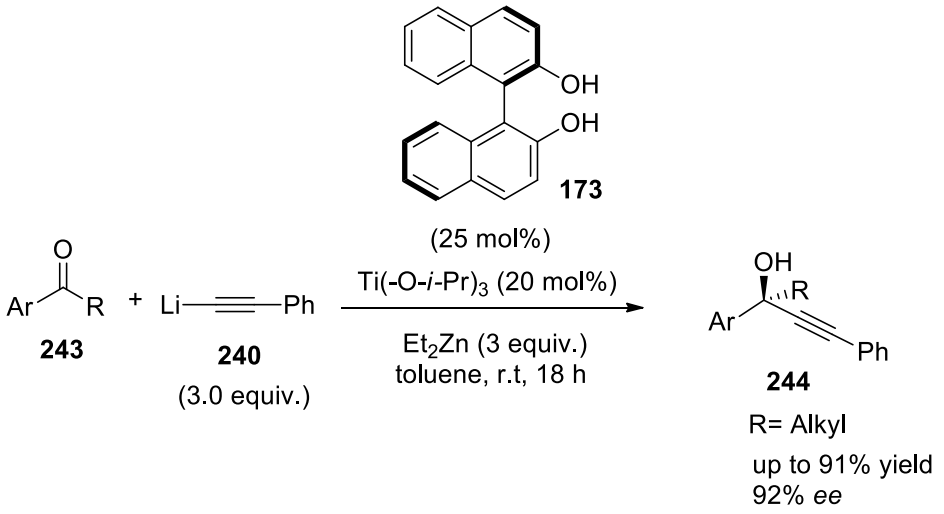
Scheme 1.47 Chiral salen ligand catalyzed addition of alkynes to ketones by Cozzi

A titanium-BINOL system was developed by Cozzi[88] and Wang[89] independently, to achieve alkynylation of ketones. Cozzi made use of titanium phenylacetylides in stoichiometric amount with BINOL as catalyst (Scheme 1.48).



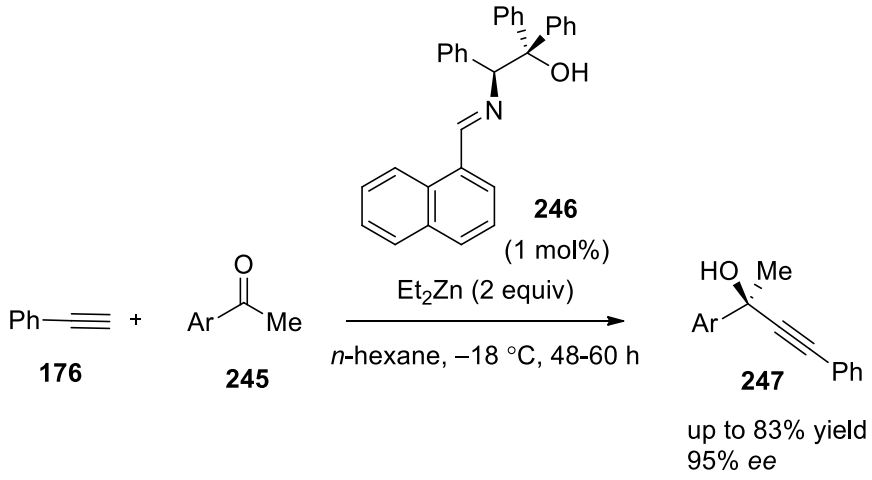
Scheme 1.48 Titanium-BINOL catalyzed addition of phenylacetylides to ketones by Cozzi

Wang employed preformed BINOL-titanium(IV) complex in catalytic amount to bring alkynylation of ketones (Scheme 1.49).



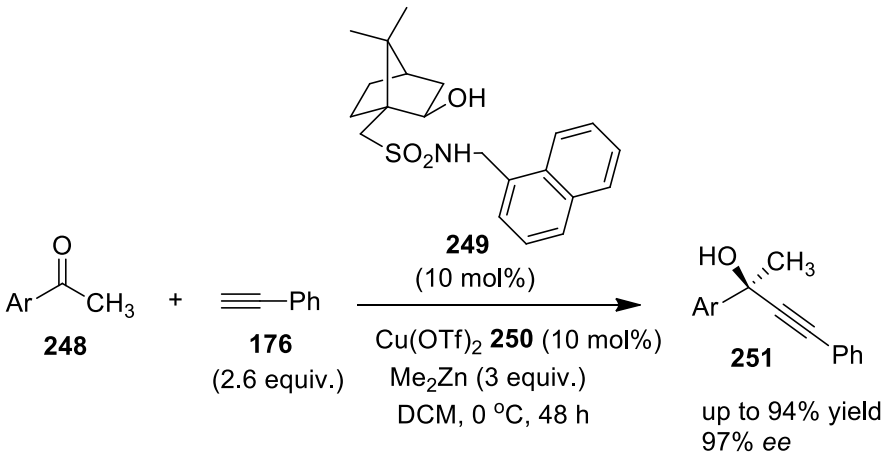
Scheme 1.49 Titanium-BINOL catalyzed addition of phenylacetylides to ketones by Wang

Wang and co-workers used Schiff base amino alcohol ligand **246** derived from L-phenylglycine for asymmetric addition of alkynes to ketone. They synthesized zinc phenylacetylide by the addition of phenylacetylene to dimethylzinc and subsequently added them to ketones. Only 1% ligand loading resulted in 95% ee (Scheme 1.50).[90]



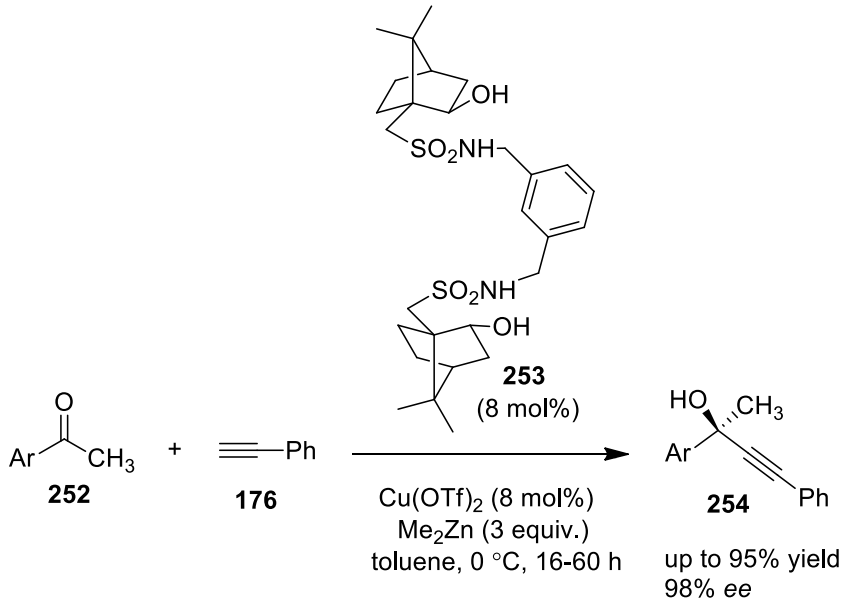
Scheme 1.50 Schiff base amino alcohol ligand catalyzed ketone alkynylation

Chan and coworkers in 2003 added alkynylzinc reagents to simple ketones using $Cu(OTf)_2$ in combination with camphorsulfonamide ligand **249**.[91] They used only 10 mol% of catalyst and ligand loading (Scheme 1.51).



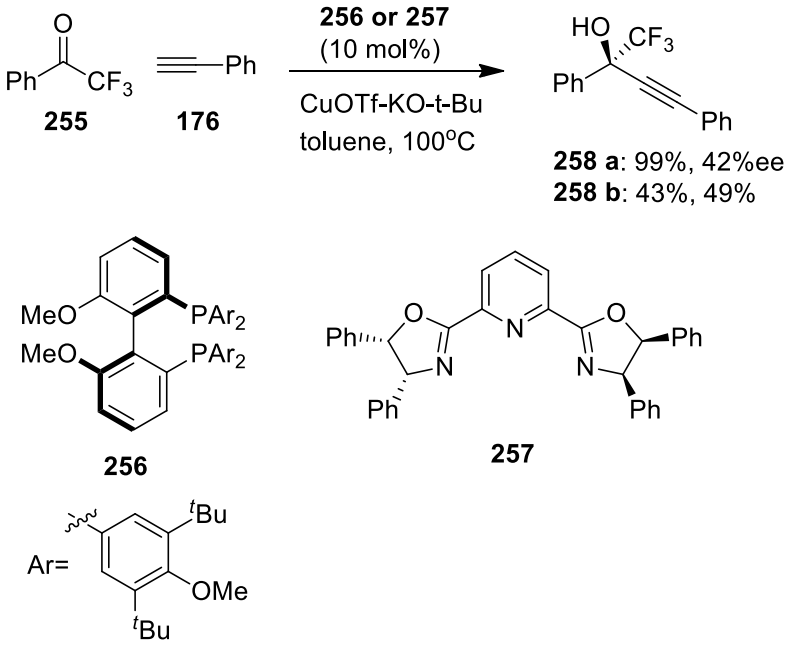
Scheme 1.51 $Cu(OTf)_2$-camphorsulfonamide ligand catalyzed ketone alkynylation

Wang and coworkers reported the use of 8 mol % of each $Cu(OTf)_2$ and bis(hydroxycamphorsulfonamide) chiral ligand **253** to catalyze the addition of zinc alkynylides to a variety of aromatic and aliphatic ketones (Scheme 1.52).[92]



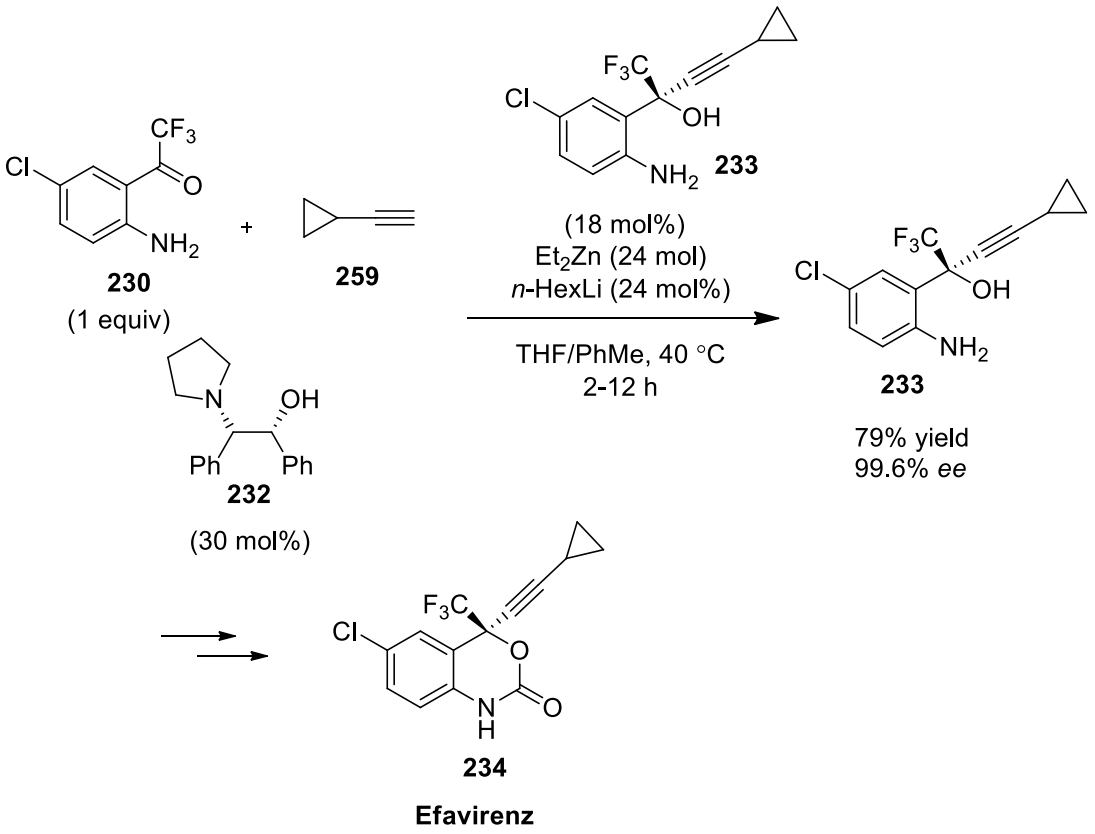
Scheme 1.52 $Cu(OTf)_2$-bis(hydroxycamphorsulfonamide) ligand catalyzed ketone alkylation

Shibasaki reported enantioselective alkynylation of activated trifluoromethyl ketones **255** employing chiral bidentate phosphine ligand **256** or pybox **257** and a catalytic copper salt as a base (Scheme 1.53).[93] This approach signifies the high atom-economic strategy for alkynylation of ketones as metal and ligand both are in catalytic amount.



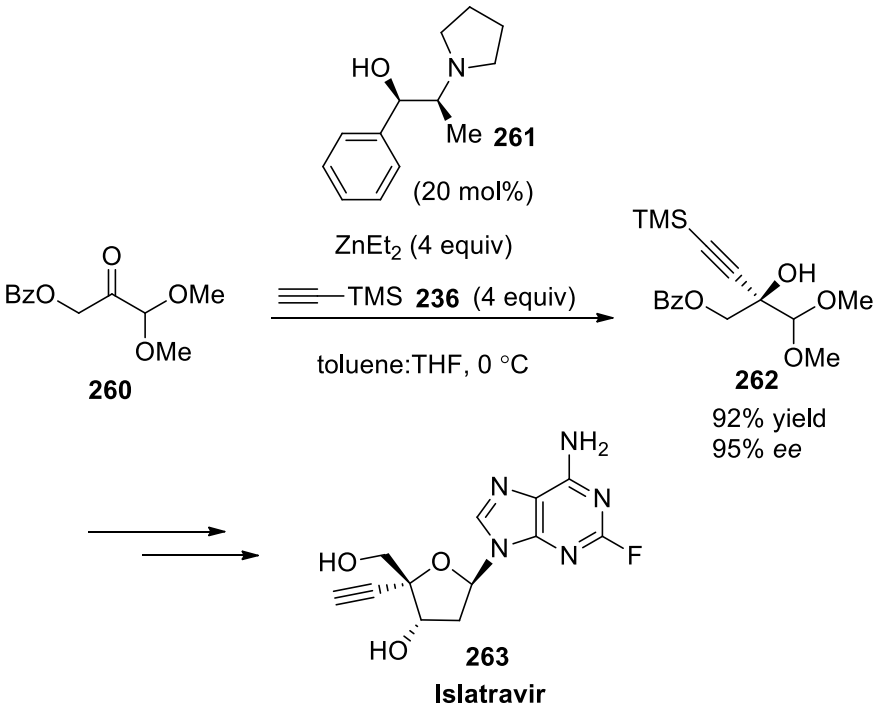
Scheme 1.53 Enantioselective alkynylation of trifluoromethyl ketones by Cu-Pybox ligand

In 2011, Carreira and coworkers have reported a catalytic enantioselective approach towards the synthesis of a key precursor to efavirenz (Scheme 1.54).[94] This is a novel autocatalytic approach where product has inherent catalytic ability that avoids the cost of external catalyst thus making process economical. Zn-acetylide addition to ketones takes place with 79% yield in 99.6% ee.



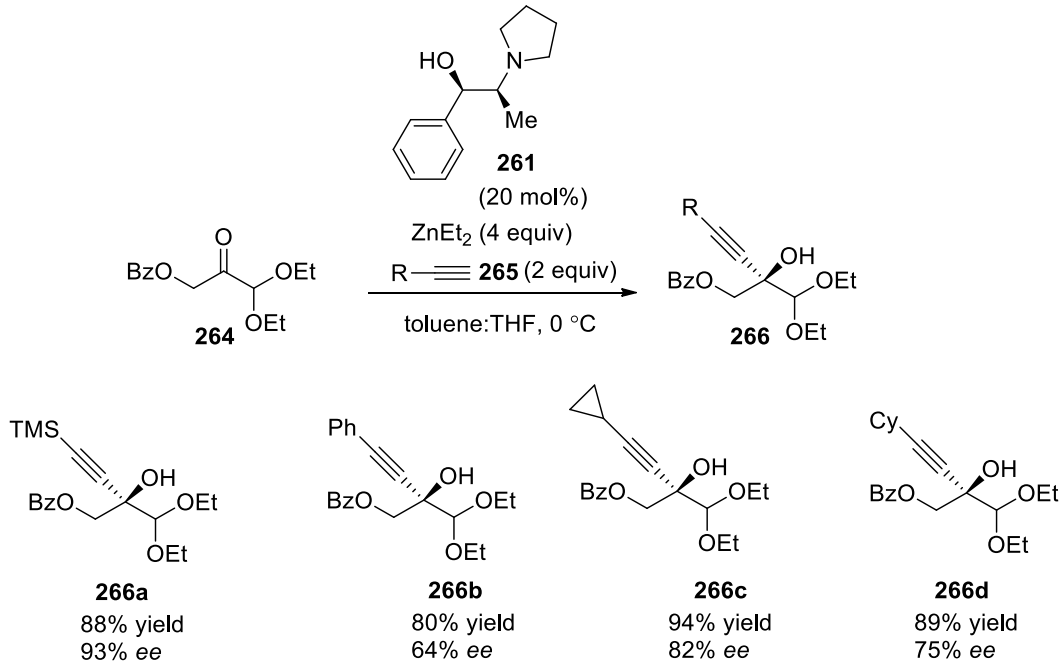
Scheme 1.54 Autocatalytic approach towards the synthesis of efavirenz by Carriera

More recently, synthesis of the anti-HIV drug candidate islatravir **263** was reported and it involved the intermediate that formed by asymmetric alkynylation of ketone.[95] Chiral *N*-pyrolidinyl ligand **261** was employed with Et_2Zn reagent and high yield and high enantioselectivity was achieved.



Scheme 1.55 Synthesis of the anti-HIV drug islatravir

This fragment was synthesized on 120 g scale. The scope of this enantioselective transformation with respect to the nucleophile was further evaluated on diethyl acetal and high yields and high enantioselectivities were observed (Scheme 1.56).

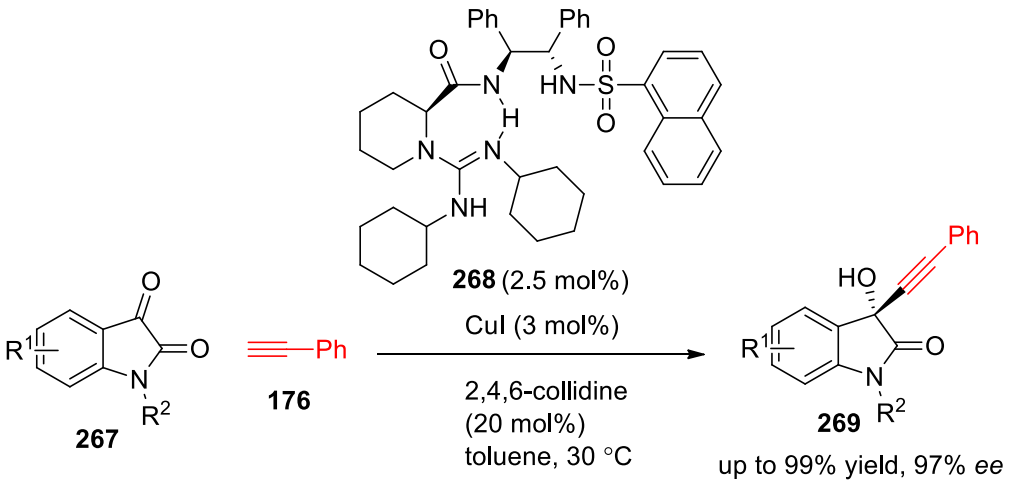


Scheme 1.56 Enantioselective alkynylation of ketone **264**

1.2.3 Asymmetric Alkynylation of Isatin

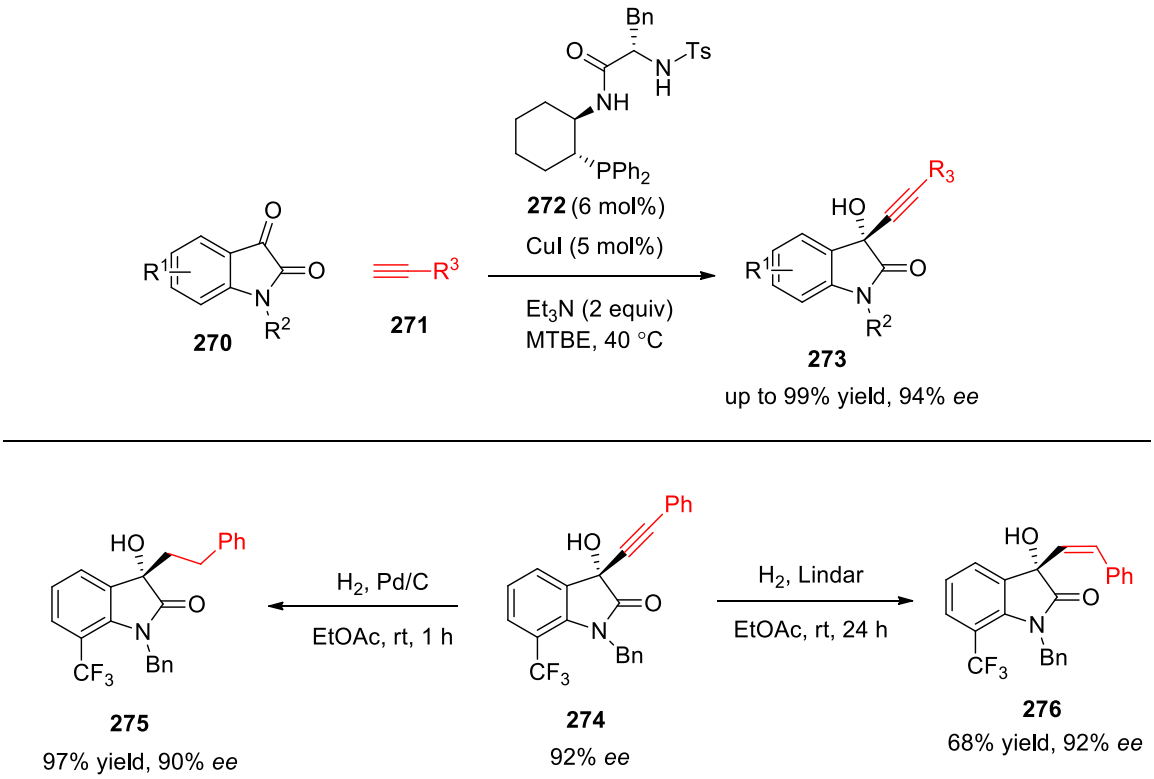
Addition of alkynes to isatin results in 3-alkynyl-3-hydroxy-2-oxindole compounds which have been found to possess important biological activities.[96,97] Moreover, 3-substituted oxindole scaffolds are widely distributed in majority of biologically important natural products and drug candidates.[96] 3-Alkynyl-3-hydroxy-2-oxindoles have been used as versatile synthons in a wide variety of synthetic applications to prepare biologically active spirooxindoles and heterocyclic compounds.[98,99]

The highly enantioselective addition of alkynes to isatin derivatives has been realized only recently. In 2016, Liu and coworkers[100] reported the use of chiral guanidine ligand **268** in combination with CuI for addition of alkynes to isatins employing mild reaction conditions (Scheme 1.57). Excellent yields and enatioselectivities up to 96% were reported.



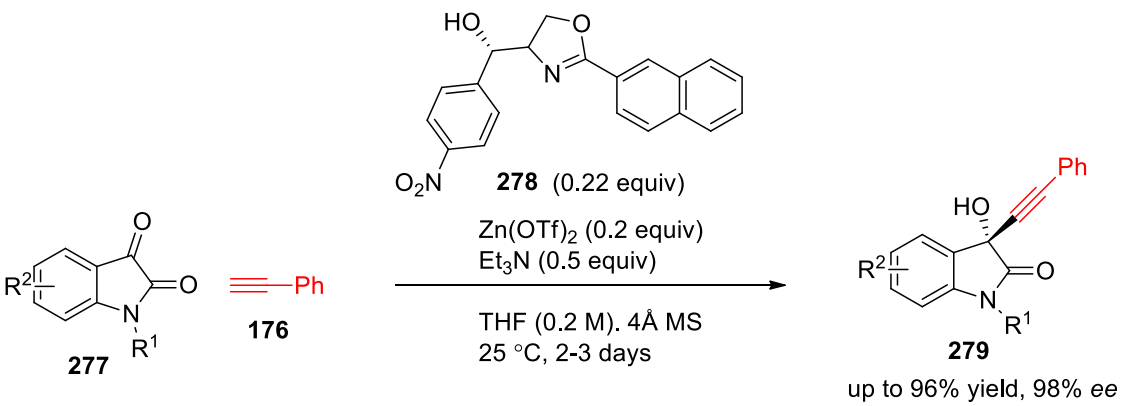
Scheme 1.57 Cu-guanidine catalyzed addition of phenylacetylene to isatin

Xu and coworkers reported the synthesis of chiral 3-alkynyl-3-hydroxyindolin-2-ones by using CuI in combination with chiral phosphine ligand **272**.[101] They demonstrated the broad reaction scope with different alkynes and isatins. Additionally, they showed the synthetic importance of chiral 3-alkynyl-3-hydroxyindolin-2-ones by performing partial and complete reduction (Scheme 1.58). For example, the reduction of product **274** with Pd/C provided corresponding product in 97% yield with 90% ee, while reduction with Lindlar catalyst afforded **276** in 68% yield with 92% ee.



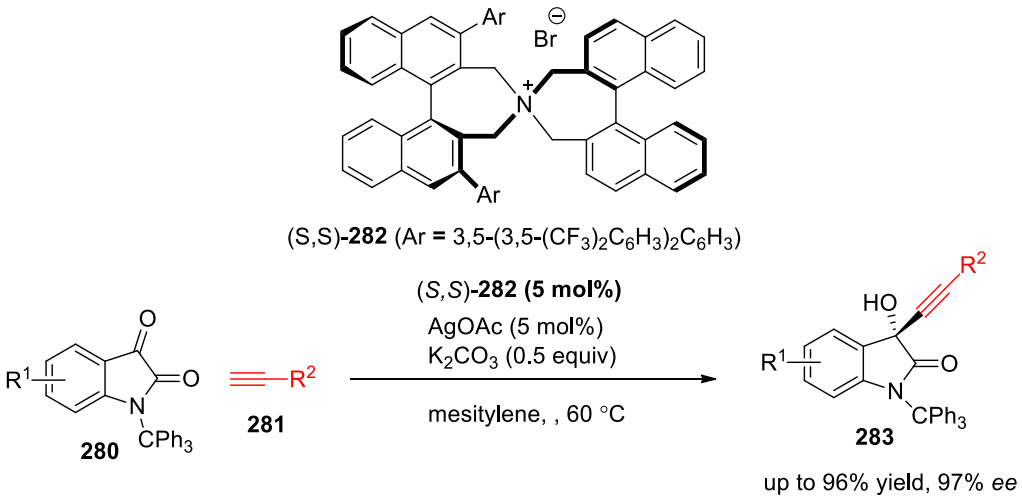
Scheme 1.58 CuI/phosphine ligand catalyzed addition of alkynes to isatin and reduction of the synthesized derivative **274**

In 2018, Chen and coworkers reported the use of chiral hydroxyl oxazoline ligand **278** with $Zn(OTf)_2$ for the addition of alkynes to isatin.[102] They demonstrated the good reaction scope for this transformation and achieved 98% ee (Scheme 1.59).



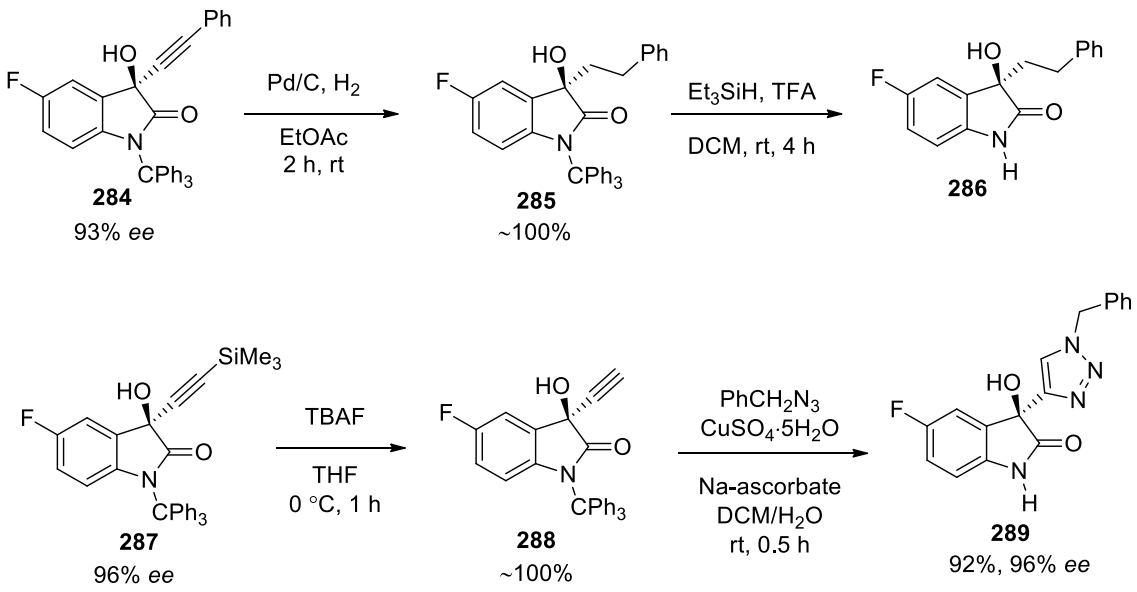
Scheme 1.59 Zn-oxazoline Catalyzed alkynylation of isatin

In 2019, Maruoka and coworkers developed hybrid catalytic process employing a chiral phase-transfer/transition-metal catalyst system for asymmetric alkynylation of trityl protected isatins with high yields and enantioselectivities (Scheme 1.60).[103]



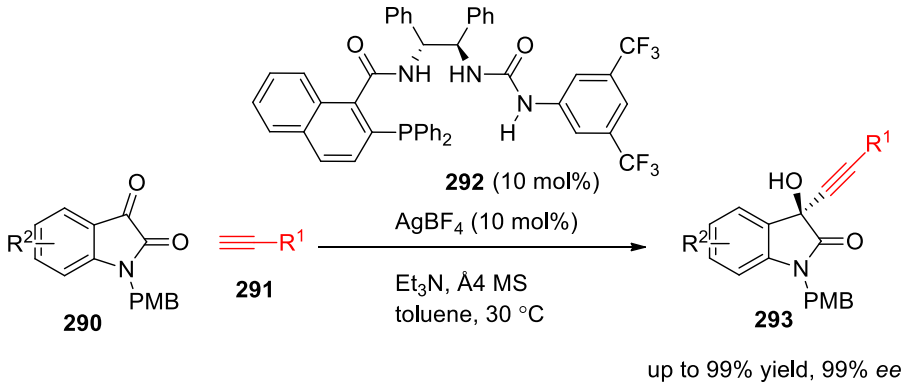
Scheme 1.60 Silver acetate and phase transfer catalyst mediated alkynylation of isatin

They further demonstrated the synthetic utility of the synthesized product by performing useful transformations (Scheme 1.61). The chiral tertiary alcohol **284** was reduced with Pd/C and H_2, followed by removal of the trityl group that furnished oxindole **286** in good yield as almost a single enantiomer. In another transformation, TMS group of **287** was deprotected with TBAF, followed by azide−alkyne cycloaddition afforded triazole **289** in high yield without any erosion of enantioselectivity.



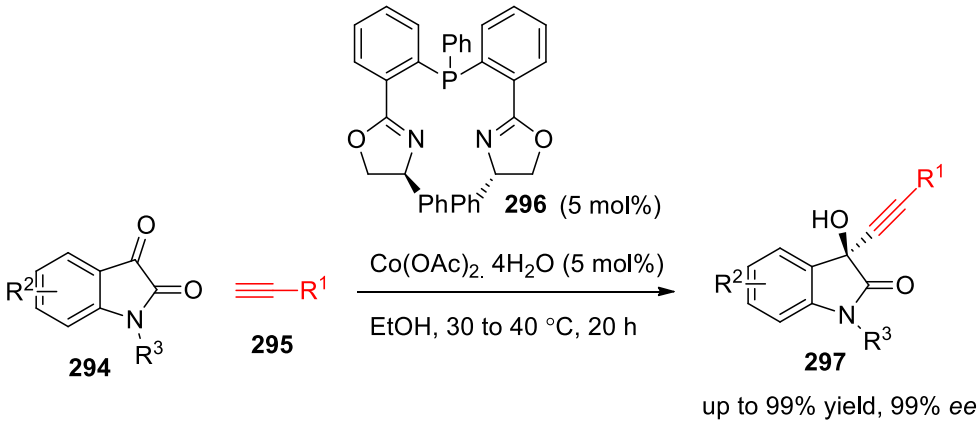
Scheme 1.61 Transformation of the synthesized alkynylation products

Zhang and coworkers demonstrated the combination of organocatalyst and metal catalyst using bifunctional amidophosphine–urea **292**/$AgBF_4$ complex as the catalyst for the asymmetric alkynylation of isatin (Scheme 1.62). Excellent enantioselectivities (up to 99% *ee*) and good yields were achieved.[104]



Scheme 1.62 Amidophosphine–urea/$AgBF_4$ catalyzed alkynylation of isatin

Recently, Li and coworkers demonstrated $Co(OAc)_2$ and chiral bisoxazolinephosphine ligand **296**, a tridentate ligand for the addition of different aromatic and aliphatic alkynes to isatin under neutral conditions (Scheme 1.63).[105]



Scheme 1.63 Cobalt acetate and chiral bisoxazolinephosphine ligand catalyzed alkynylation of isatin

1.3 Azetidine

Nitrogen containing heterocycles are the most encountered and fascinating heterocycles in medicinal chemistry. These are the valuable source of therapeutic agents[106] and 75% of FDA approved drugs and marketed drugs contain nitrogen based heterocycles as their structural part.[107] Among saturated nitrogen based heterocycles, nitrogen containing four membered heterocycle azetidine has not received much attention from synthetic chemist as compared to its higher analogues piperidine and pyrrolidine.[108,109] However, azetidines possess useful structural features; structural rigidity and satisfactory stability which makes it suitable core to be tuned as desired to impart useful pharmacological properties in the compound containing this structural motif. Azetidine is prevalent in many bioactive compounds[110–112] and natural products.[113] Additionally, many drugs contain this core as main structural unit.[106]

1.3.1 Azetidine Based Natural Products and Pharmaceuticals

L-Azetidine-2-carboxylic acid **298** was first azetidine based natural product isolated from *Convallaria majalis*. It is proline receptor antagonist. Penaresidin A **299** and penaresidin B **300** were obtained from an Okinawan aquatic sponge of Penares species. Mugineic acid **301**, β'-deoxymugineic acid **302**, and nicotianamine **303** are iron chelating agents, produced in plants to support the uptake of iron required for the biosynthesis of chlorophyll.[114,115] Fig 1.11 shows azetidine based natural products.

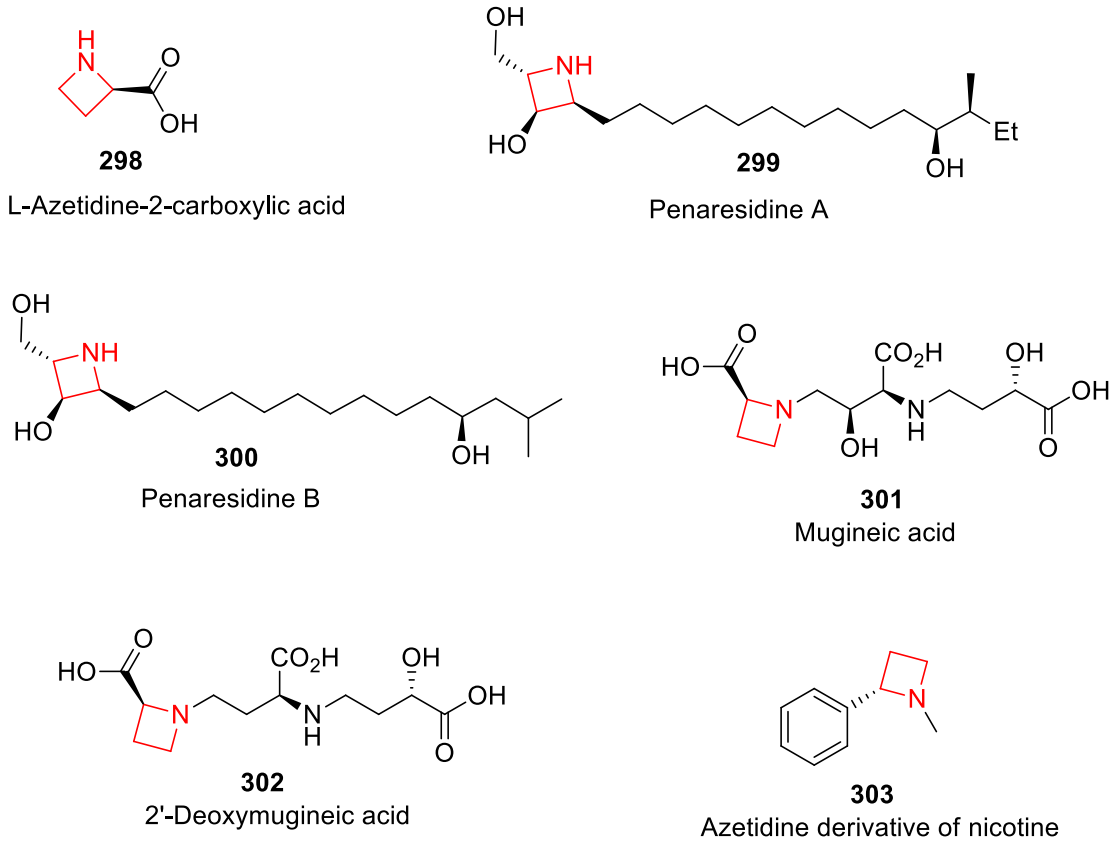
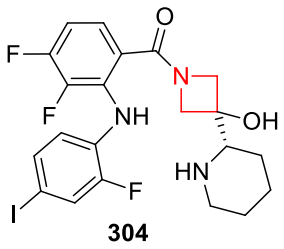


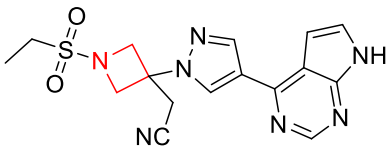
Fig 1.11 Azetidine based natural products

Azetidine derivatives have shown wide array of biological activities such as antibacterial, anticancer, antidiabetic, antiobesity, dopamine antagonist, analgesic and antioxidant activities, and they can be used for the treatment of central nervous system (CNS) disorders like Alzheimer's disease, depression, anxiety, schizophrenia, psychosis and so forth (Fig 1.12). These important biological activities make azetidine the part of many marketed drugs and bioactive drug lead compounds.[106]



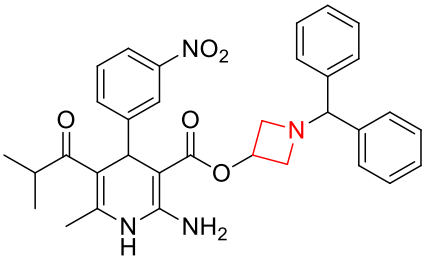
304

Cobimetinib: MEK inhibitor-treats melanoma



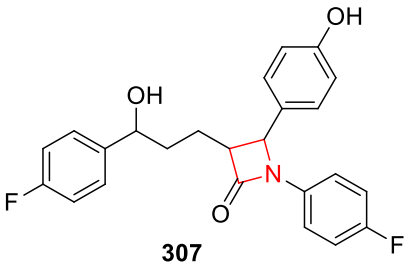
305

Baricitinib: Rheumatoid arthritis



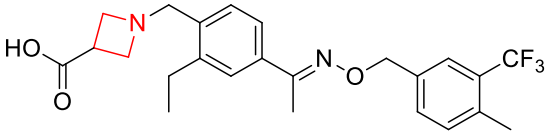
306

Azelnidipine: Ca^{2+}- channel blocker



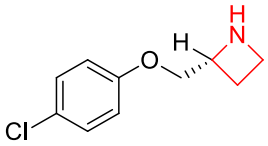
307

Ezetimibe: Reduces Plasma Cholesterol



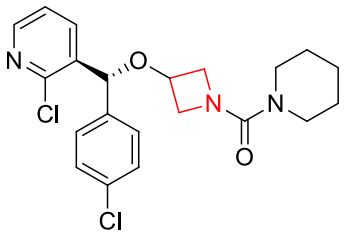
308

Siponimod (Multiple Sclerosis)



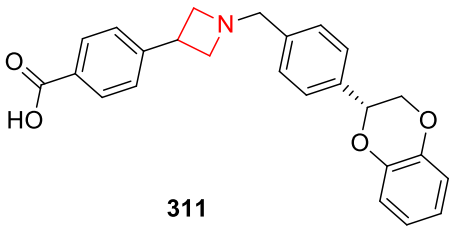
309

Tebanicline (non-opioid analgesic)



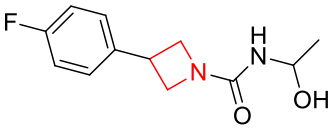
310

Anti-obesity (Vernalis patent)



311

Cardiovascular disease
(boehringer Ingelheim patent)



312

Active against CNS diseases
(Vernalis Patent)

Fig 1.12 Azetidine based bioactive compounds

1.3.2 Synthesis of Azetidines

In general, there is dearth of methods for the synthesis of azetidines. The common strategies used for the synthesis of azetidines are cyclization reactions via nucleophilic substitution, reduction of the *β*-lactam ring, [2+2] cycloaddition reaction (aza Paternò−Büchi reaction) between imines and alkenes and strain release (Fig 1.13).

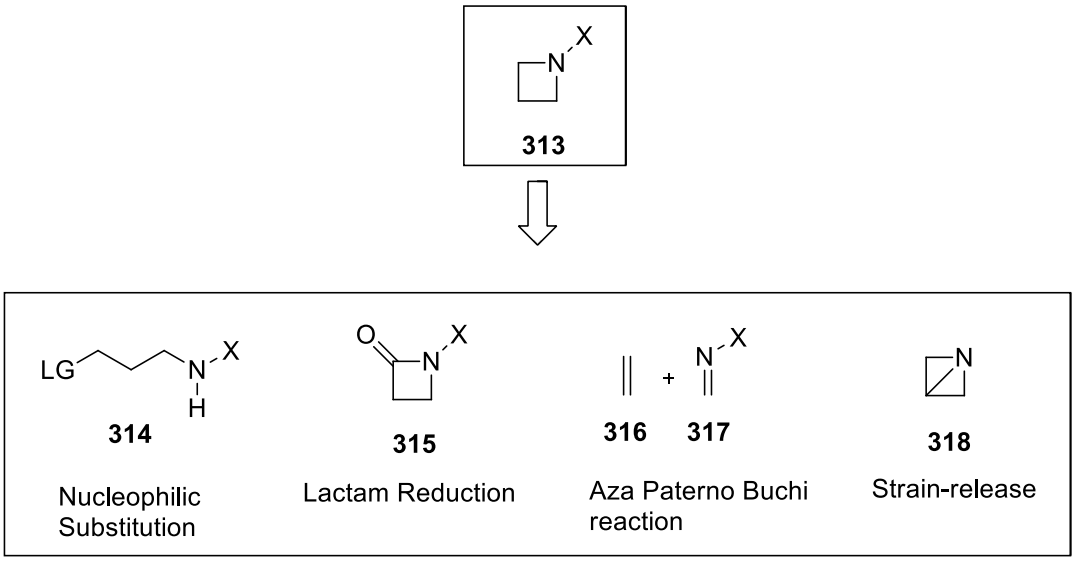
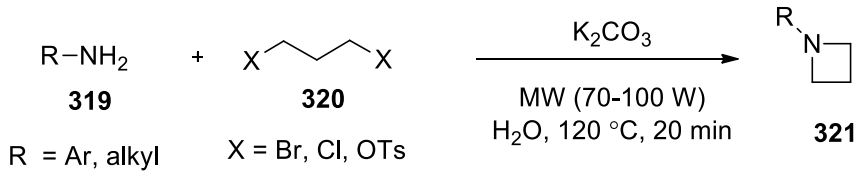


Fig 1.13 General methods for the synthesis of azetidine

1.3.2.1 Synthesis of Azetidine *via* Nucleophilic Substitution

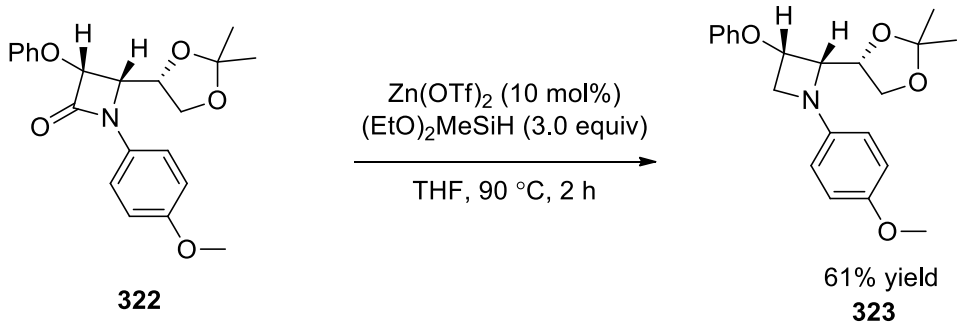
Intermolecular substitution reaction between 1,3-dihalides or ditosylates with primary amines like aniline for azetidine synthesis, Varma and coworkers reported a simple and efficient cyclocondensation between aniline and 1,3-dichloropropane in aqueous medium using K_2CO_3 as a base under microwave irradiation (Scheme 1.64).[116] This greener approach was utilized for the synthesis of different heterocycles including azetidine.



Scheme 1.64 Synthesis of azetidine by nucleophilic substitution

1.3.2.2 Synthesis of Azetidine by Reduction of the *β*-lactam Ring

Synthesis of azetidine by reduction of *β*-lactam ring is the straightforward and efficient method. Alcaide and coworkers reported the synthesis of azetidine derivatives by reducing *β*-lactams **322** using $Zn(OTf)_2$ and $(EtO)_2MeSiH$ (Scheme 1.65).[117]



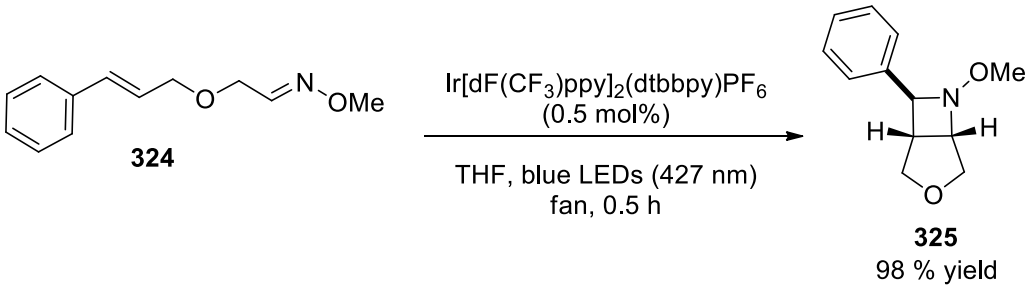
Scheme 1.65 Synthesis of azetidine by reduction of *β*-lactam ring

1.3.2.3 [2+2] Cycloaddition Reaction (Aza Patern. −Büchi reaction) for the Synthesis of Azetidine

Aza Paternò−Büchi reaction is the [2 + 2] photocycloaddition reaction between an imine and an alkene. It is one of the most efficient ways to synthesize small rings including functionalized azetidines in a single synthetic assembly. However, it suffers some limitations because of the side reactions that arise due to photo excitation of the substrates.

Becker and coworkers developed visible light-mediated aza Paternò–Büchi reaction between alkene and oxime moieties that results in the direct formation of

functionalized azetidines using Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ photocatalyst (Scheme 1.66).[118] This reported reaction overcame previous challenges associated with the excitation of functionalized imines by selectively exciting alkene and thus hindering undesired competing reaction paths.



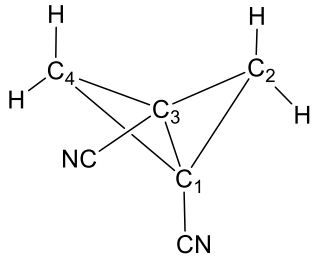
Scheme 1.66 Aza Paternò−Büchi reaction for the synthesis of azetidine

1.3.2.4 Synthesis of Azetidine by Strain Release of Azabicyclo[1.1.0]butane

1.3.2.4.1 Azabicyclo[1.1.0]butane: Chemistry and Synthesis

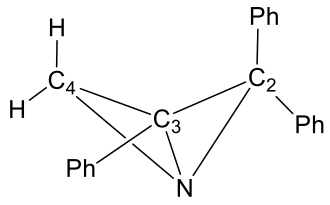
1-Azabicyclo[1.1.0]butane is a nitrogen analog of bicyclo[1.1.0]butane having a nitrogen atom at one of the bridgehead positions. Its structural features and reactivity resembles bicyclo[1.1.0]butane. 3-Phenyl-1-azabicyclio[1.1.0]butane was the first compound prepared and isolated by Hortmann and Robertson in 1967.[119] Funke in 1969[120] synthesized unsubstituted 1-azabicyclobutane. In 1993, crystal structural for 2,2,3-triphenyl-1-azabicyclo[1.1.0]butane **327** was developed and studied.[121] Crystal structure confirmed resemblance of azabicyclo[1.1.0]butane to bicyclo[1.1.0]butane[122] with comparable bond lengths, bond angles, the dihedral angle (angle between the plane of the both three-membered rings), and the N-C(3)-CR angle (Fig 1.14). In addition, molecular orbital analysis for 1-azabicyclo[1.1.0]butane recommended that the N-C3 bond has a strong *p*-character[123] because it forms by overlapping of non-hybridized orbitals of nitrogen and carbon. This makes C3-H bond more acidic because it has more *s*-charater and acidity of C3-H bond is presumably parallel to acetylenes.

However, strain energy and the p*K*a of the C(3)-H bond is undetermined because physical properties of 1- azabicyclo[1.1.0]butane have not been extensively explored.



1,3-Dicyanobicyclo[1.1.0]butane **326**

Bond Lengths (Å)	Bond Angles (°)
C_1-C_2 = C_1-C_4 = 1.48	C_1-C_2-C_3 = 60.9
C_2-C_3 = C_3-C_4 = 1.48	C_2-C_3-C_1 = 59.5
C_1-C_3 = 1.50	C_2-C_1-C_3 = 59.6
	C_1-C_4-C_3 = 60.9
	C_4-C_3-C_1 = 59.6
	C_3-C_1-C_4 = 59.5

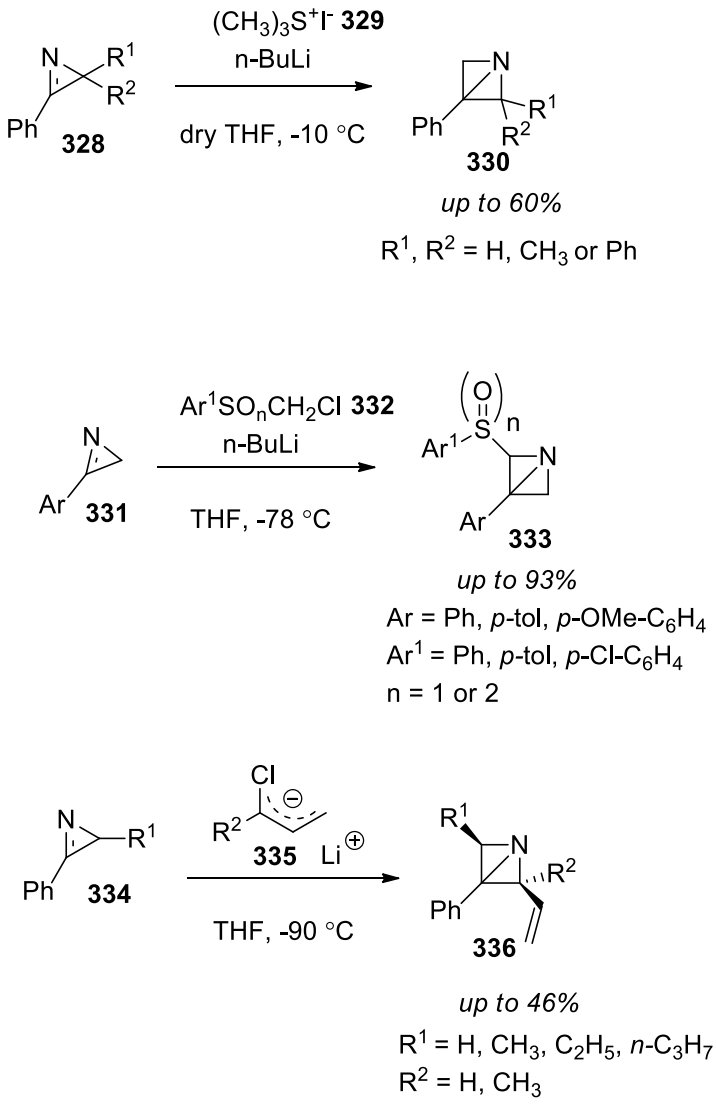


2,2,3-Triphenyl-1-azabicyclo[1.1.0]butane **327**

Bond Lengths (Å)	Bond Angles (°)
N-C_2 = N-C_4 = C_2-C_3 = 1.50	N-C_2-C_3 = 60.7
N-C_3 = 1.52	C_2-C_3-N = 59.7
C_3-C_4 = 1.47	C_2-N-C_3 = 59.6
	N-C_4-C_3 = 61.3
	C_4-C_3-N = 60.3
	C_3-N-C_4 = 58.4

Fig 1.14 Comparison of bond lengths and bond angles of bicyclo[1.1.0]butane to azabicyclo[1.1.0]butane

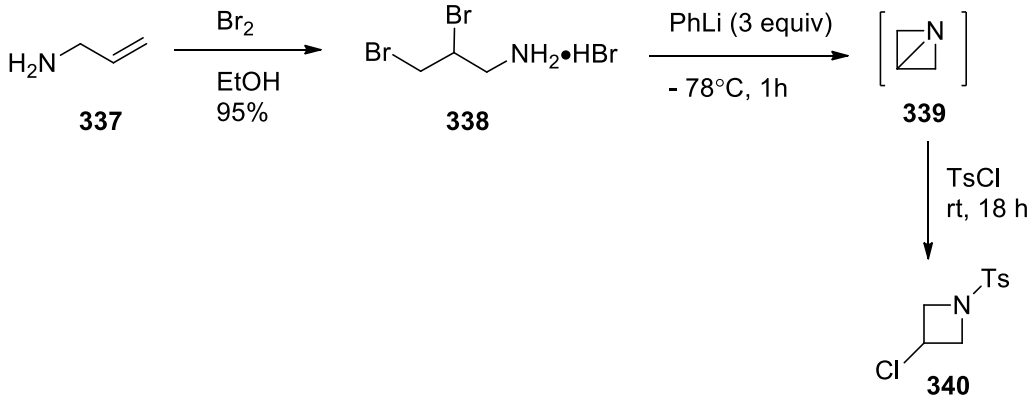
Regarding the synthesis of azabicyclo[1.1.0]butane, synthetic protocols are limited because of its unusual structure and absence in natural products and pharmaceuticals. The most widely encountered approaches include cyclopropanation of azirines and the cyclization of dibromopropylamines. Hortmann and coworkers presented the first synthesis of 3-phenyl-1-azabicyclo[1.1.0]butane **330**. They reacted 3-phenyl-2*H*-azirine **328** with sulfonium methylide **329** as CH_2 donor and broadened the scope to various 2,3-disubstituted azabicyclo[1.1.0]butanes by varying the substrate.[119,124] In a Similar approach, Calet and coworkers[125] efficiently synthesized functionalized azabyciclo[1.1.0]butanes **333** using sulfone or sulfoxide substituted halomethylcarbanion **332** and azirines. Azirines were also utilized for the synthesis of various 2-vinyl-3-phenylazabicyclo[1.1.0]butanes **336** by addition of lithiated allylchlorides (Scheme 1.67).



Scheme 1.67 Synthesis of azabicyclo[1.1.0]butane from aziridines

Cyclization of dibromopropylamines represents the most direct strategy with broad reaction scope for the synthesis of 1-azabicyclo[1.1.0]butanes. Funke and coworkers in 1969[120] synthesized various 3-alkyl azabicyclo[1.1.0]butanes from 1,3-dibromo-2-amminopropanes hydrobromides using hydroxyl base but 1-azabicyclo[1.1.0]butane was obtained in 7% yield only. In 1999 Nagao and coworkers[126] improved the Funke's protocol by reacting 2,3-dibromopropylamine hydrobromide **338** with organolithium bases (Scheme 1.68). The addition of 3 equivalents of *n*-butyllithium or phenyllithium in THF at -78°C *in situ* generated

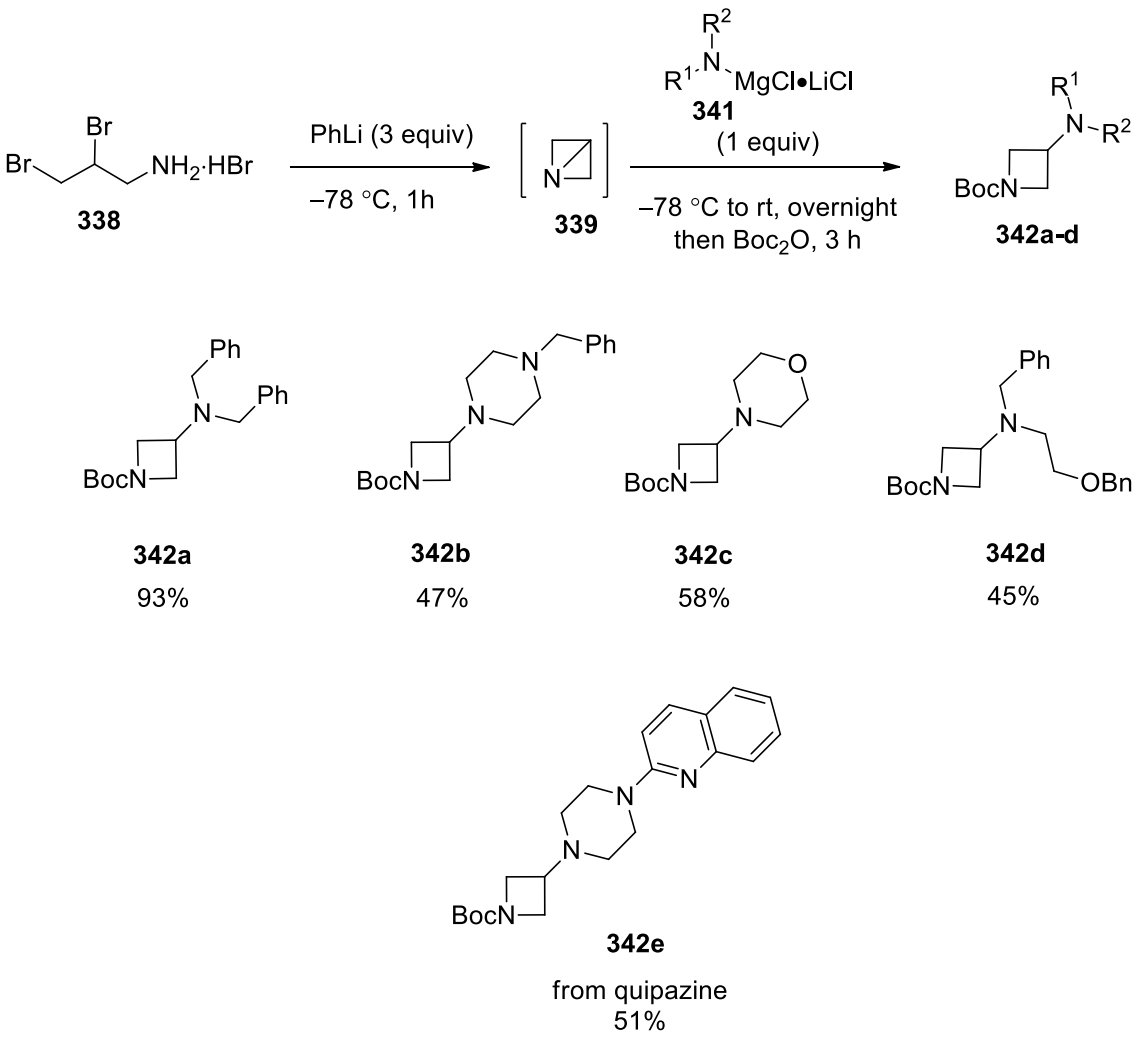
1-azabicyclobutane **339** that upon reaction with tosyl chloride, afforded 1-tosyl-3-chloroazetidine **340** in 87% yields.



Scheme 1.68 Synthesis of azabicyclo[1.1.0]butane from 2,3-dibromopropylamine hydrobromide

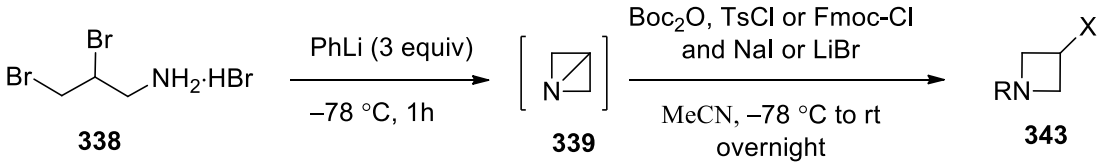
1.3.2.4.2 Azetidine Synthesis from Azabicyclo[1.1.0]butane

Azabicyclobutanes have been used as precursors for the synthesis of functionalized azetidines due to their unusual reactivity of the C3–N bond. Literature shows that different amines,[127,128] nitro and azide nucleophiles[129,130] have been added to azabicyclobutane to synthesize azetidines. Baran and coworkers[131] improved the addition of amine nucleophiles to azabicyclo[1.1.0]butane to form 3-amino azetidines. Basically, they generated *Turbo*-Hauser amides **341** by the deprotonation of amines with isopropylmagnesium chloride lithium chloride and later added them to the 3-position of azabicyclobutane. Reaction scope was extended from different heterocyclic amines to pharmaceutical compounds (Scheme 1.69).



Scheme 1.69 Synthesis of 3-amino azetidines

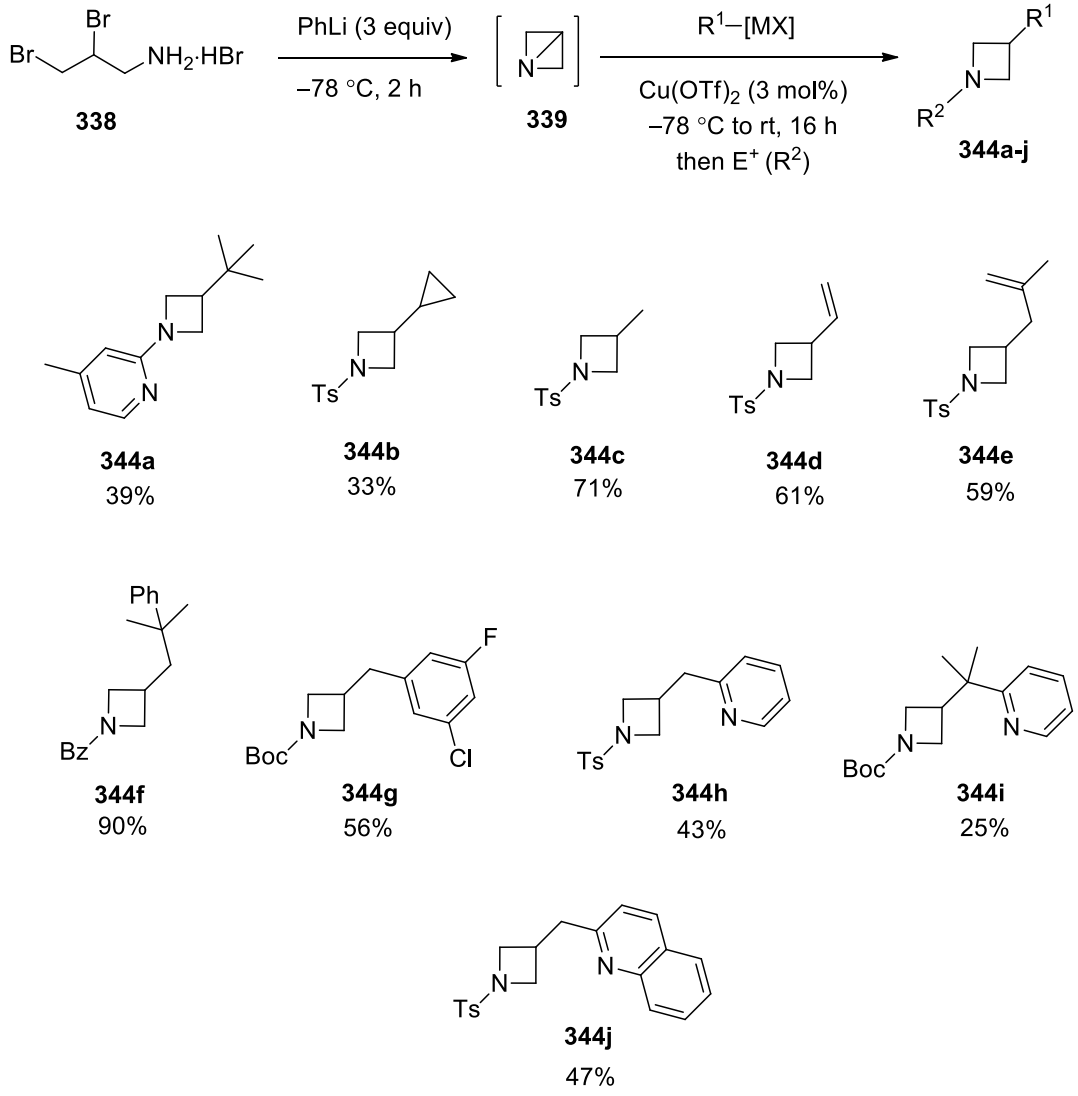
3-Halo and 3-carboxyl azetidine building blocks were prepared by Lopchuk and coworkers[132] by treating azabicyclobutane with sodium halide salt and either di-*tert*-butyl dicarbonate (Boc_2O) or *p*-toluenesulfonyl chloride (TsCl) to form the corresponding 3-halogenated azetidines (Scheme 1.70). Synthesized azetidines are highly valuable compounds to prepare medicinal agents.



X	R	%Yield
I	Boc	81
I	Ts	81
Br	Boc	79
Br	Fmoc	82

Scheme 1.70 Synthesis of 3-halo azetidines

Gianatassio and coworkers[133] reported the addition of organomagnesium and zinc reagents to azabicyclobutane catalyzed by copper(II) triflate (Scheme 1.71). Organometal reagent is added to 3-position of azabicyclobutane and nitrogen is subsequently trapped by variety of electrophiles to form bis-functionalized azetidines.



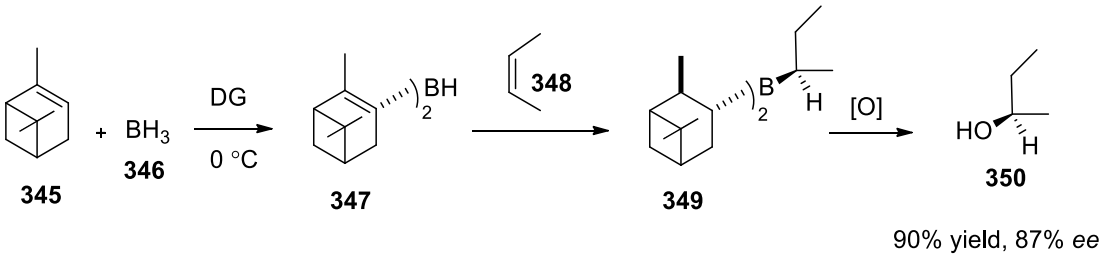
Scheme 1.71 Copper catalyzed synthesis of 3-substituted azetidines from azabicyclo[1.1.0]butane

1.3.3 Lithiation-Borylation

1.3.3.1 Organoborons in Asymmetric Synthesis

Synthetic chemistry has vast applications spanning from medicine to materials. For the advancement of synthetic chemistry there is always a need to develop new methods that could enable the synthesis of new and complex molecules with complete control of their 3-D shape.

Organoboranes are the compounds of considerable value in asymmetric synthesis. Enantioriched organoboron compounds can be transformed into variety of functional groups leading to broad array of diverse molecules with high enantioselectivity. H. C. Brown in 1961[134] provided the first non-enzymatic example of asymmetric hyroboration of alkenes using diisopinocampheylborane **347**, Ipc_2BH **347** reagent with high enantioselectivity (Scheme 1.72). In fact, this was the first asymmetric synthesis with high enantioselectivity. Later on, chemistry of alkylboranes was explored by transforming C-B bond to variety of functional groups (Fig 1.15).[135]



Scheme 1.72 Asymmetric hydroboration of alkenes by H.C Brown

cis,cis,cis,trans,trans,trans etc.

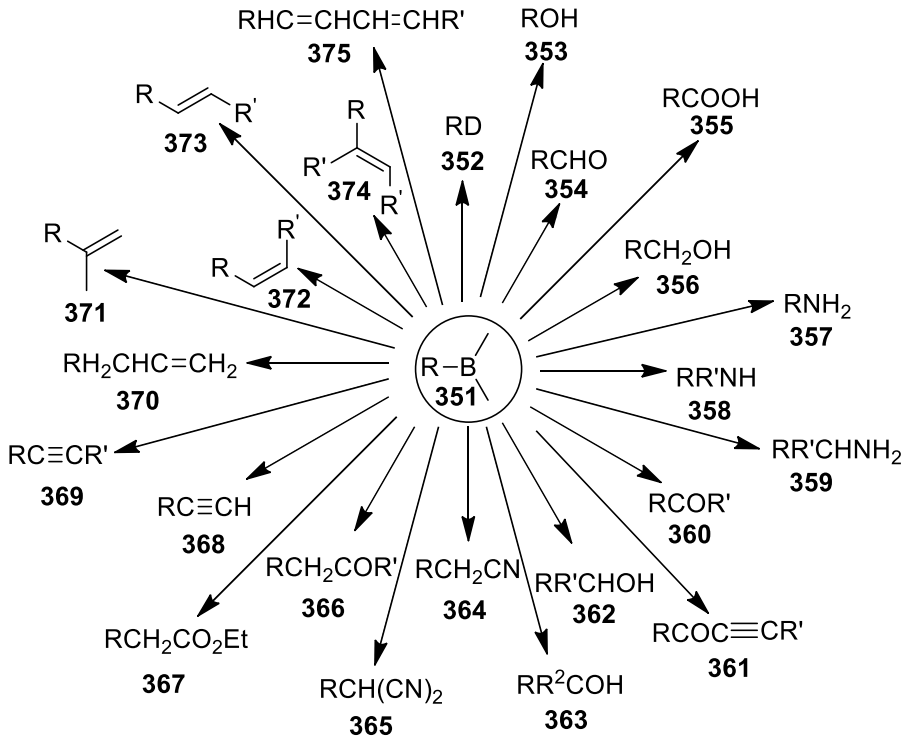


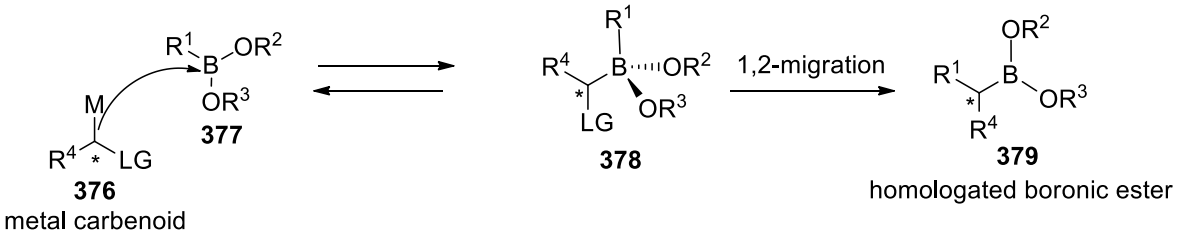
Fig 1.15 Transformation of C-B bond into different functional groups by H.C Brown

However, synthetic utility of alkylborons is hindered by their air and moisture sensitivity although they are central to many reactions.[136,137] Converting organoborane into a boronic ester (RB[OR']2) makes purification easy, especially in the case of boronic acid pinacol esters (RBpin). Enhanced reactivity, higher compatibility with many reagents and better solubility in organic solvents facilitates the use of boronic esters in synthesis and as a tool to create new C-C bonds as in the Suzuki-Miyaura coupling reaction.[138,139]

Chiral boronic esters have been appreciated as valuable building blocks in asymmetric synthesis. They can be prepared with high enantioselectivity. Moreover, they undergo a broad array of transformations that lead to the stereocontrolled formation of C−C and C−X (X = heteroatom) bonds.[140] They are also ideal building blocks for iterative molecular assembly.[141]

1.3.3.2 Homologation of Boronic Esters: Synthesis of Chiral Boronic Esters

Boronic esters undergo substrate or reagent directed homologations upon treatment with metal carbenoids in a stereocontrolled manner. In this homologation process (Scheme 1.73) boronate complex forms, and presence of a leaving group on the same carbon atom α to the boron atom leads to stereospecific 1,2-metallate rearrangement (1,2-migration).



Scheme 1.73 Synthesis of chiral boronic esters

The boronic ester group is retained in the resulting product and can be subjected to further transformation or homologations in an iterative manner. [140, 141] Continuous extension of the carbon chain is referred as 'assembly-line synthesis.

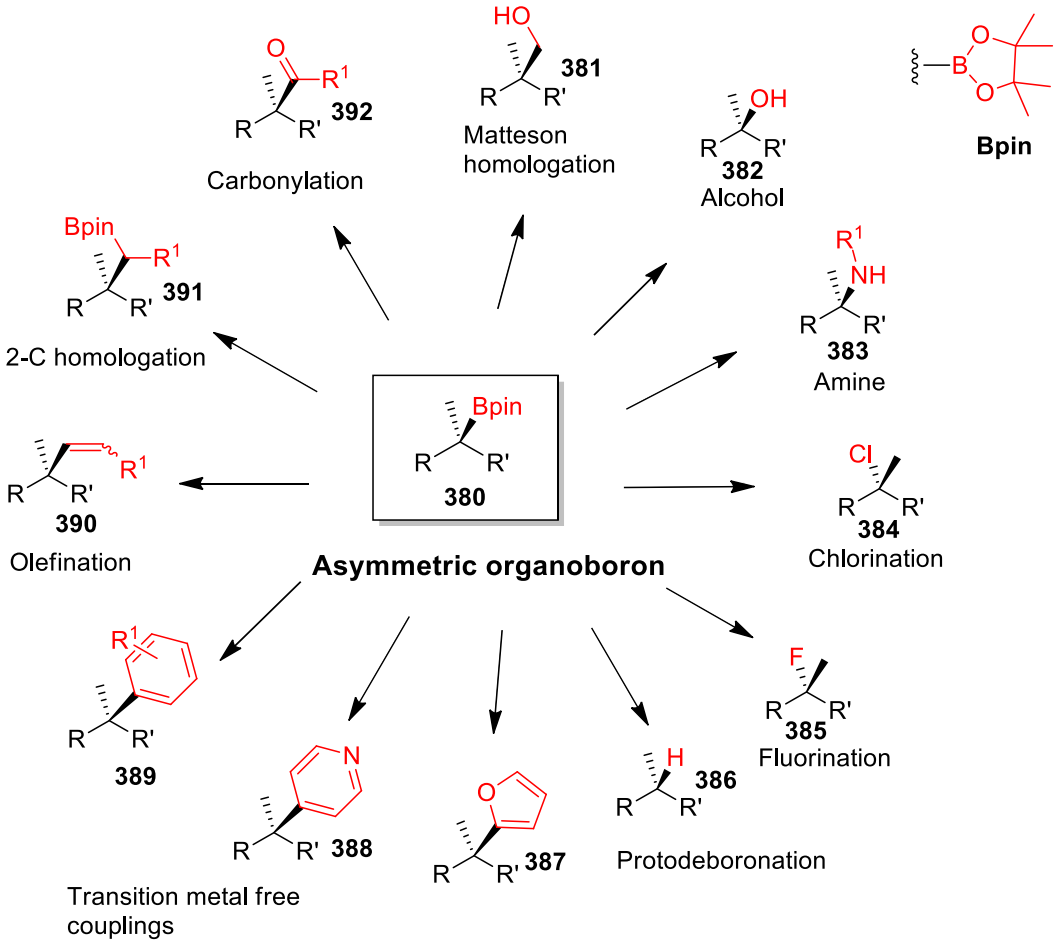
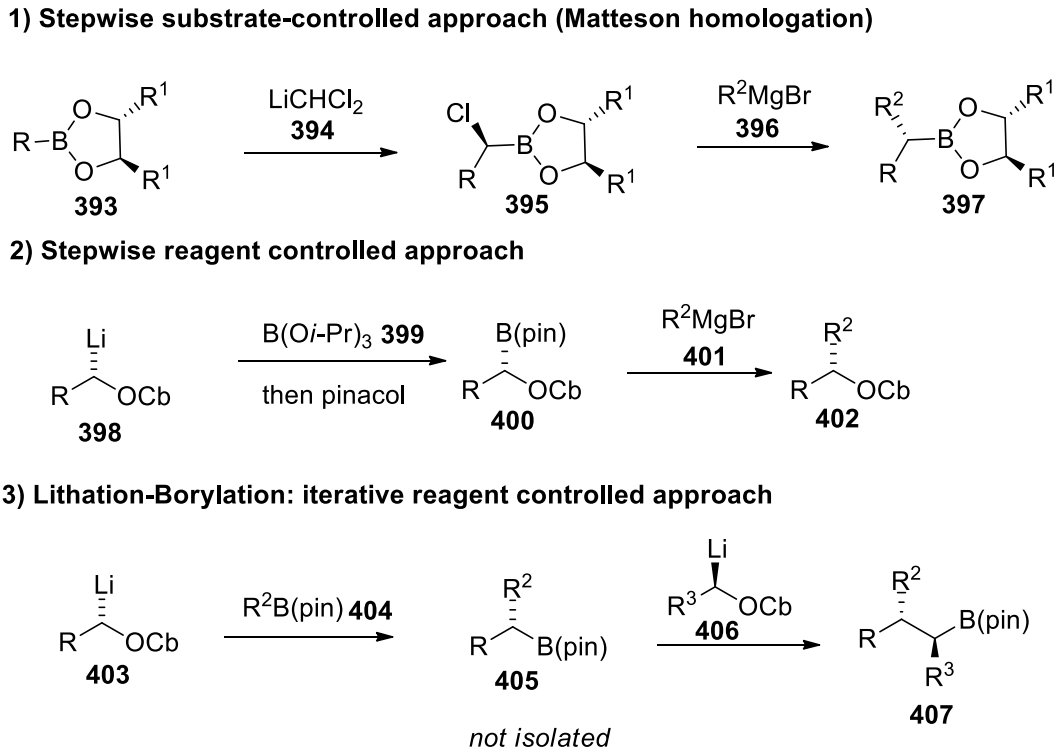


Fig 1.16 General sketch for transformation of Bpin into different functional groups

After the development of Asymmetric hydroboration by H.C Brown in 1961,[134] Matteson provided a complementary route to chiral boronic esters.[142,143] In his approach, substrate has the chirality embedded in the diol of the boronic ester which is carried out to the homologation product. So, this substrate controlled approach has two basic sequences; (i) addition of dichloromethyl lithium ($LiCHCl_2$) to the boronic ester to give a chiral α-chloro organoboron **395** followed by (ii) addition of an achiral Grignard reagent **396** (or other nucleophile) to deliver the homologation product **397** (Scheme 1.74).

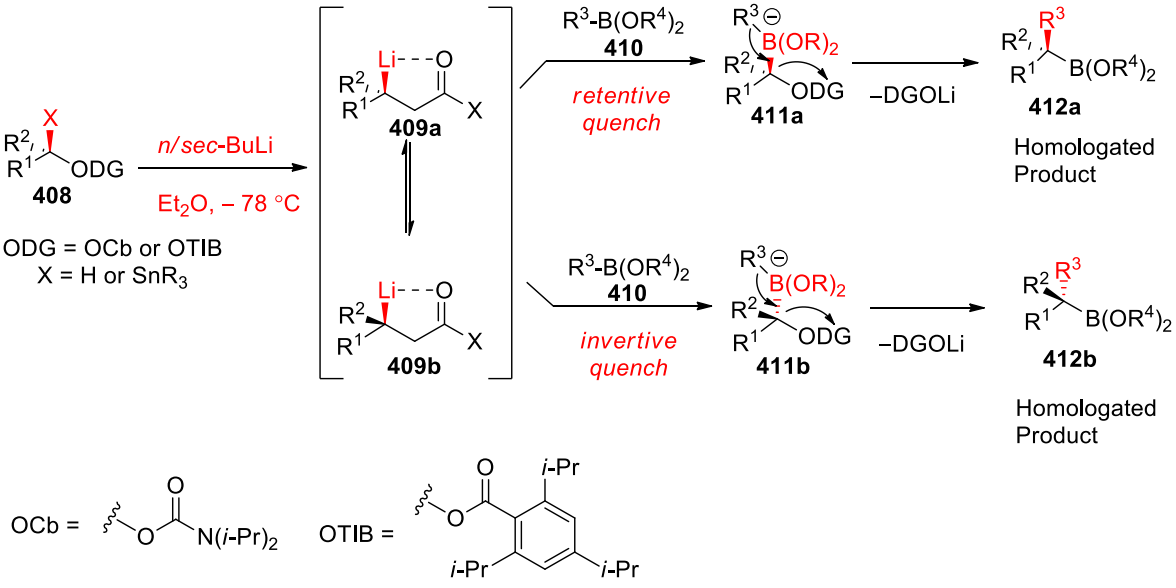


Scheme 1.74 Different approaches for the synthesis of chiral boronic esters

Matteson reaction is extremely powerful to control stereochemical outcome of the homologation product but suffers some limitations as well.[143] In order to get different stereoisomer of the product, chiral diol has to be change which is difficult sometime because of the problems associated with hydrolysis of boron ester. Reagent-controlled lithiation approach works well in that case. In this approach a chiral reagent **398** is used to construct a related chiral ate complex, which subsequently evolves into the chiral boronic ester **400** following 1,2-metalate rearrangement. Chiral reagent **398** behaves as a chiral carbanion and possesses a leaving group at the same carbon atom like Hoppe's lithiated carbamates[144] suitable for stereocontrolled homologation of boronic esters. Aggarwal[140,145] used the similar reagent controlled approach called Lithation-Borylation to synthesize chiral boronic esters **405** that can be homologated multiple times in a one-pot sequence.

1.3.3.3 Lithiation-Borylation Mechanism

Three steps are involved in a general prototypic lithiation-borylation (Scheme 1.75): (i) generation of lithium carbanion by α-lithiation of a carbamate (OCb) or a hindered benzoate (OTIB), (ii) electrophilic trapping of lithiated specie by addition of an organoboron reagent that leads to chiral "boronate" complex (iii) 1,2-metalate rearrangement transforms boronate complex into homologated organoboron product **412** which can be further utilized for another reaction sequence or for further transformations.

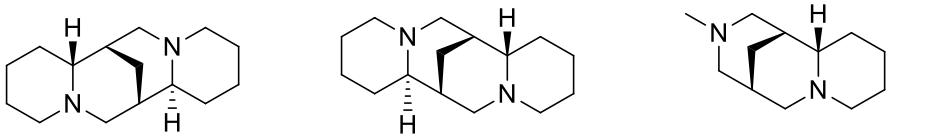


Scheme 1.75 Lithiation-borylation mechanism

1) Lithiation

The chiral lithium carbanion of primary carbamates or benzoates is generated by chiral ligand assisted asymmetric deprotonation using chiral diamine as ligands (Fig 1.17). Enantioenriched secondary carbamates or benzoates give lithium carbenoid by stereospecific deprotonation and α-Sn carbamates or benzoates undergo stereospecific tin−lithium exchange to generate lithiated carbanion **409a** or **409b**. Chiral organolithium needs to be both chemically and configurationally

stable under the reaction conditions to avoid detrimental decomposition and racemization.



413
(–)-sparteine
(–)-sp

414
(+)-sparteine
(+)-sp

415
(+)-sparteine surrogate
(+)-sps

Fig 1.17 Chiral diamine used in asymmetric deprotonation

2) Electrophilic Trapping

Addition of organoboron reagent (boron electrophile) **410** to lithium carbenoid results in boronate complex **411**. This electrophilic trapping should be faster than the following 1,2-metalate rearrangement. Electrophilic trapping of chiral organolithiums with organoborons should be stereospecific and generally occurs with retention of configuration, but invertive pathways have been observed in the case of secondary benzylic carbamates and boranes.

3) 1,2-Metallate Rearrangement

Once the boronate complex **411** has formed it undergoes 1,2-rearrangement. For stereospecific 1,2-metalate rearrangement migrating group on boron and the carbamate or benzoate leaving group should be antiperiplanar to each other and this step needs to proceed at temperatures higher than the borylation step to avoid undesired over-homologations.

1.3.3.4 Lithiation-Borylation in Synthesis of Natural Products

Lithiation–borylation is a powerful synthetic technique, allowing the construction of complex substrates through stereocontrolled homologation of boronic esters. A key feature of lithiation–borylation is the formation of homologated boronic ester

products, which are further homologated in an iterative manner with complete stereocontrol, referred to as assembly line synthesis. Diverse classes of natural products has been synthesized employing Lithiation and Borylation reaction sequence.[140,146] Fig 1.18 shows few examples of natural products synthesized through lithiation and borylation methodology.

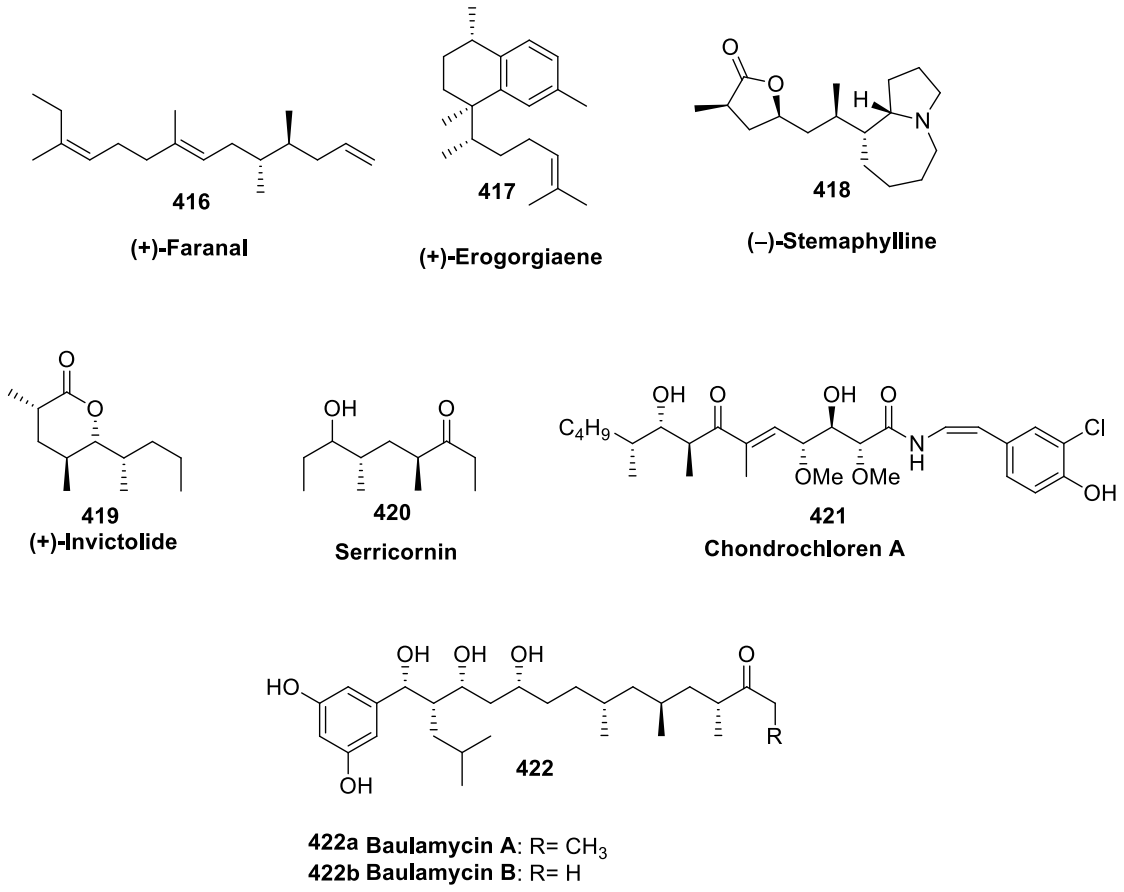
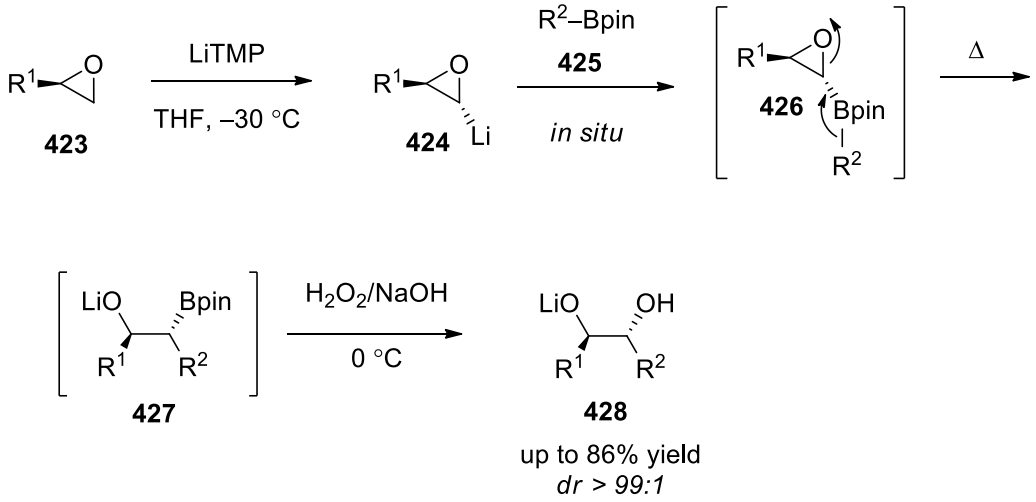


Fig 1.18 Lithiation-borylation in synthesis of natural products

1.3.3.5 Lithiation-Borylation in Strained Rings

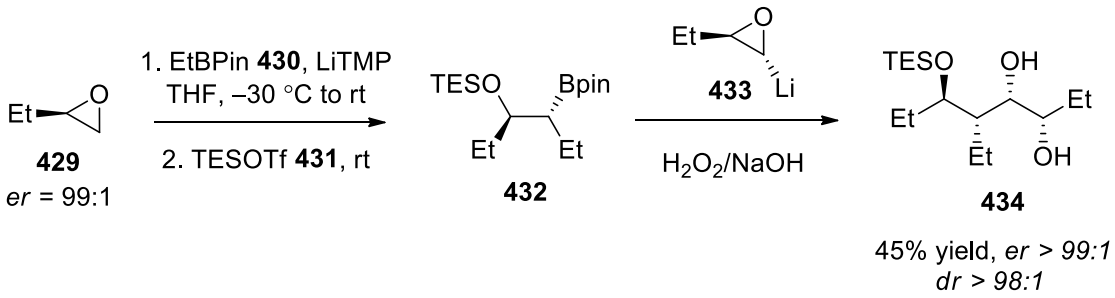
Strained rings like epoxides, aziridines and azetidines have been exploited in lithiation followed by borylation reaction yielding corresponding open chain analogues.[147] Release of strain energy is the driving force behind the ring opening of these small heterocyclic compounds.

Aggarwal group reported the homologation of boronic esters with lithiated epoxides (Scheme 1.76).[148] For lithiation of alkyl epoxides, lithium 2,2,6,6-tetramethylpiperidide-mediated deprotonation of terminal epoxide was employed given by Hodgson.[149] Lithiated epoxides **424** reacted with different boronic esters and boronate complexes were formed with retention of configuration, 1,2-metalate rearrangement occurred afterwards followed by oxidation which provided the resulting diols **428** with high distereoselectivities. Homologation of enantioriched epoxide with alkyl boronic ester proceeded with complete stereocontrolled product.



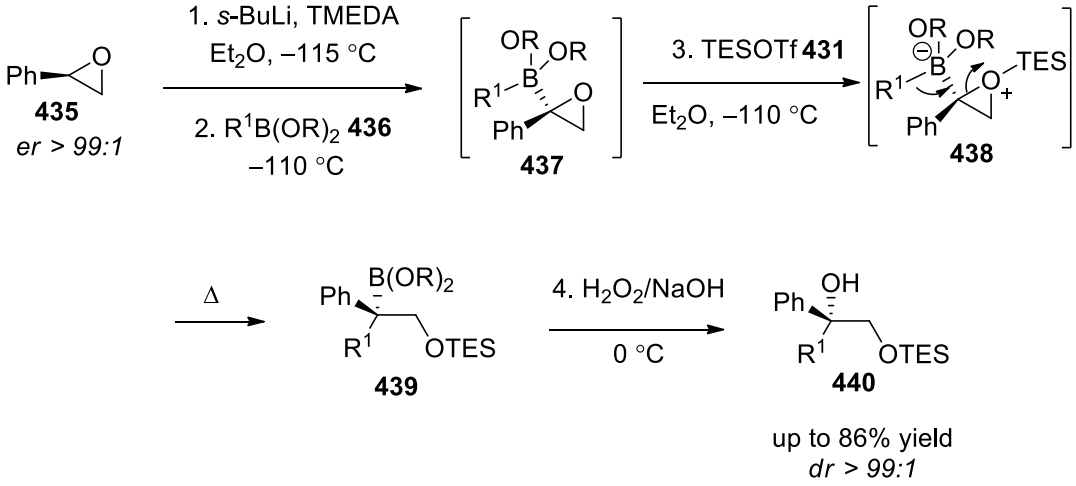
Scheme 1.76 Homologation of boronic esters with lithiated epoxide

Enantioenriched *β*-oxy-boronic esters were isolated as *β*-silyloxy-boronic ester **432** by the addition of triethylsilyl trifluoromethanesulfonate (TESOTf) aiding further potential. The boronic ester **432** was reacted with an enantioenriched lithiated epoxide **433** to give boronate ester which suffered 1,2-metalate rearrangement followed by oxidation to give the highly enantio- and diastereoenriched 1,2,4-triol **434** (Scheme 1.77).



Scheme 1.77 Homologation of enantioriched epoxide with *β*-oxy-boronic Ester

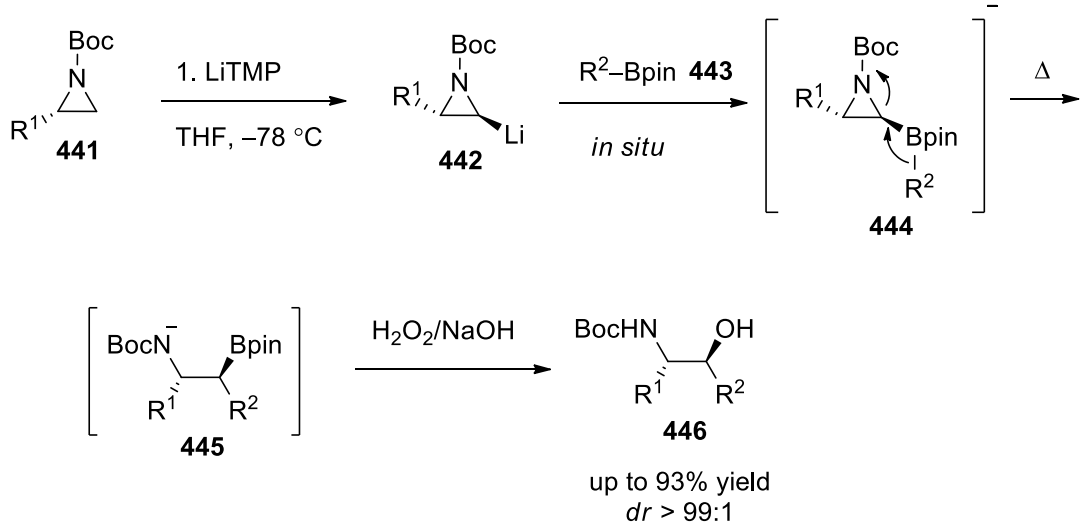
Styrene oxide **435** was also lithiated following the Florio's protocol (Scheme 1.78),[150] s-BuLi/TMEDA deprotonated adjacent to phenyl group. After the addition of boronic ester, reaction occurred with retention of configuration of the lithiated carbon center of the epoxide. *β*-Alkoxy boronate **437** was trapped with TESOTf to avoid its elimination. Oxidation gave the corresponding tertiary alcohols **440**. Primary, secondary, allyl, and aryl boronic esters were evaluated with good yield and enantioenrichment observed throughout. Notably, chirality transfer was observed strongly dependent on temperature.



Scheme 1.78 Lithiation/borylation of styrene oxide

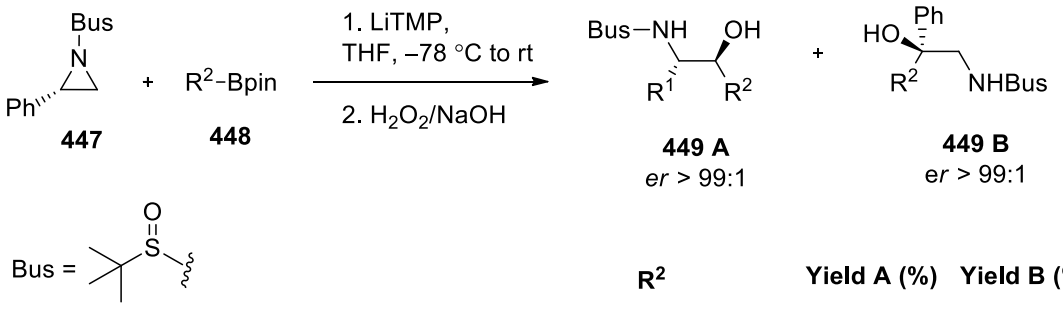
Hodgson and coworkers[151,152] reported the *trans*-selective lithiation of terminal *N*-Boc-protected alkyl aziridines with sterically demanding LTMP and subsequently

synthesized aziridinyl esters. Aggarwal and coworkers[153] used the same lithium carbenoid for homologation with boronic esters and synthesized *β*-aminoalcohol **446**. In case of enantioriched aziridines, complete transfer of chirality was observed.



Scheme 1.79 Lithiation/borylation of *N*-Boc protected alkyl aziridines

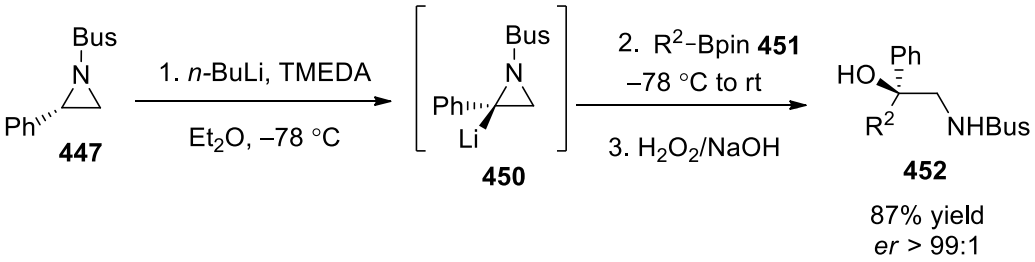
N-Bus protected aziridines **447** were also employed for the above lithiation-borylation reaction (Scheme 1.80) and it was observed that in case of aryl and viny boronic esters, reaction proceeded with good yield and high diastereoselectivity. Although using alkyl boronic ester, provided the mixture of secondary and tertiary alcohols depending upon the site of lithiation with complete chirality control.



R^2	Yield A (%)	Yield B (%)
Ethenyl	73	<5
Ph	83	<5
p-OMePh	87	<5
Allyl	60	23
Et	63	15
n-Bu	70	20
c-Hex	61	20

Scheme 1.80 Lithiation/borylation of *N*-Bus protected aziridine

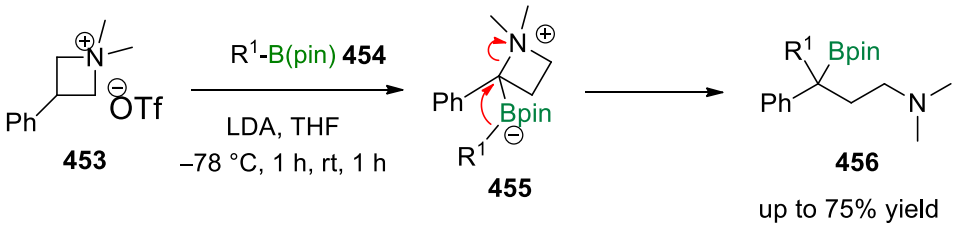
The use of *n*-BuLi/TMEDA instead of LiTMP for lithiation furnished the complete regioselective benzylic lithiated aziridine **450** and following the borylation with range of boronic esters gave the boronate complex which upon 1,2-metalate rearrangement and subsequent oxidation provided tertiary alcohols **452** in excellent yield and complete chirality transfer (Scheme 1.81).



Scheme 1.81 *n*-BuLi/TMEDA mediated lithiation/borylation of *N*-Bus protected aziridines

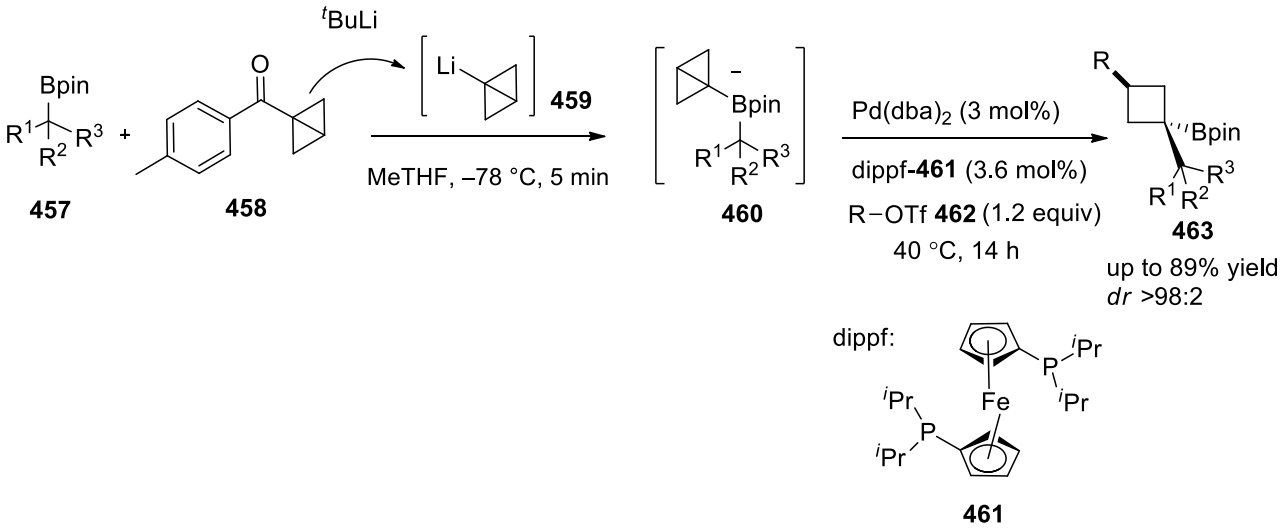
Aggarwal and coworkers[154] demonstrated the lithiation-borylation of phenyl substituted azetidinium ions **453** to synthesize 3-aryl-1-aminopropane derivatives **456** (Scheme 1.82). Initial investigation of the reaction was made following lithiation conditions established by Couty and David[155] using LiHMDS, reaction

suffered low yield of the ultimate γ-dimethylamino tertiary boronic ester product. Further investigation suggested that the use of LDA was beneficial. When 2-phenyl azetidinium ions **453** were deprotonated with LDA in the presence of boronic esters, the resulting azetidinium ylides **455** undergo ring opening carboboration to give γ-dimethylamino tertiary boronic esters **456** that can be later transformed.



Scheme 1.82 Lithiation-borylation of phenyl substituted azetidinium ions

Homologation of boronic esters by a cyclobutane unit using bicyclo[1.1.0]butyl lithium **459** was reported by Aggarwal and coworkers.[156] Reaction demonstrated that bicyclo[1.1.0]butyl lithium **459** could react with boronic esters to form highly strained bicyclo[1.1.0]butyl boronate complexes **460**, which then underwent 1,2-metalate rearrangement upon treatment with electrophilic palladium(II)−aryl complexes resulting in the formation of C–Pd bond and ultimately a range of diastereomerically pure borylated cyclobutanes (Scheme 1.83). The 1,2-metalate rearrangement is driven by relief of the high ring strain of the bicycle. The overall process couples readily available aryl triflates and organoboronic esters across a cyclobutane unit with total diastereocontrol.



Scheme 1.83 Homologation of boronic esters by cyclobutane

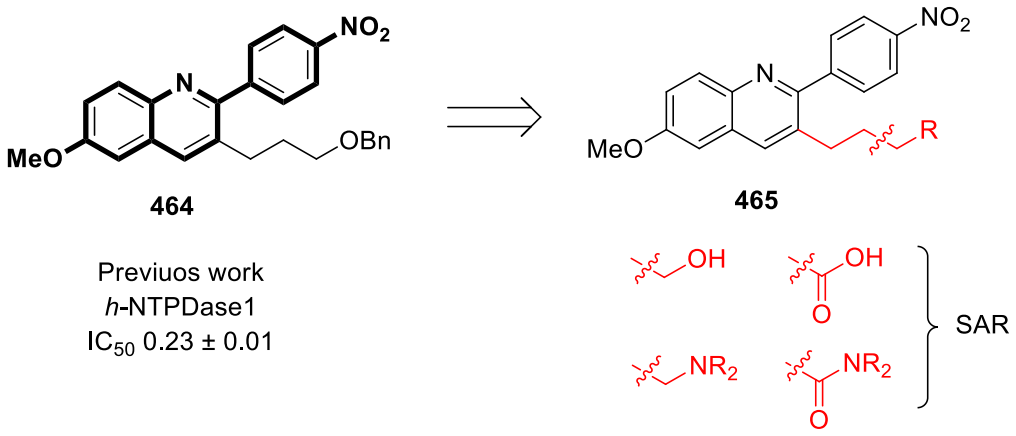
1.4 Plan of Work

Research work presented in this dissertation has been divided into three parts

Part A:

Synthesis of Quinoline Derivatives as Nucleoside Triphosphate Diphosphohydrolase Inhibitors

Quinoline is privileged heterocyclic compound in the field of drug discovery and development because of its enormous biological activities. It prevails in many bioactive compounds. Quinoline derivatives has emerged as antimalarial, antibacterial, antimicrobial, anticancer and antileishmanial agents.[1] Apart from these well-known biological activities quinoline derivatives were reported recently as nucleoside triphosphate diphosphohydrolases inhibitors (NTPDase inhibitors) by Abbas research group.[157] Research work presented in part A is further elaboration of quinoline derivatives as NTPDase inhibitors (Scheme 1.84).



Scheme 1.84 Synthesis of quinoline derivatives as NTPDase inhibitors

Quinoline derivative **464** has been reported as the most potent *h*-NTPDase1inhibitor. Molecular Docking Studies and experimental results showed that 6-methoxy-2-(4-nitrophenyl)quinoline core is the most suitable for potential activities. In the present study, position-3 of the quinoline derivative **464** will be further explored by introducing alkyl chains of different chain lengths and polar

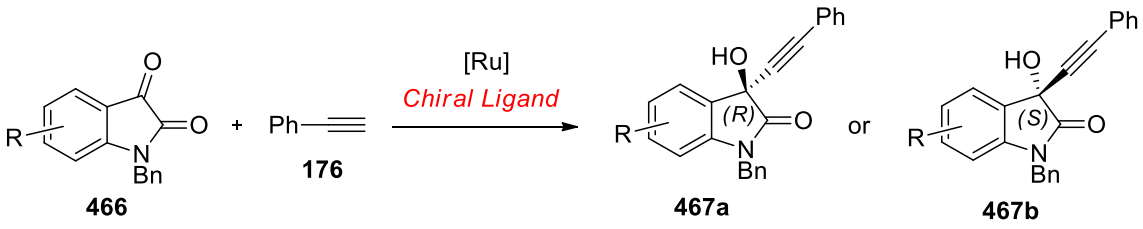
functional groups starting from unmasking the hydroxyl group and its conversion to amines and carboxylic acid and its derivatives. Inhibitory activity of all synthesized derivatives will be explored against four isoenzymes *h*-NTPDase1,2,3 and 8.

Part B:

Ruthenium Catalyzed Asymmetric Addition of Alkynes to Different Substituted Isatin

Asymmetric addition of alkynes to isatins has been realized recently and different transition metal like Cu, Zn, Co and Ag has been reported in this regard. Resulting 3-alkynyl-3-hydroxy-2-oxindole compounds have been found to possess important biological activities.[96,97] Additionally, 3-alkynyl-3-hydroxy-2-oxindoles have been used as versatile synthons in a wide variety of synthetic applications to prepare biologically active compounds.[98,99]

Research work presented in part B of this dissertation is about using ruthenium as transition metal with a chiral ligand to perform the enantioselective addition of alkynes to different isatins (Scheme 1.85). Different chiral ligands will be screened and reaction conditions will be optimized to get high yields and enantioselectivities.



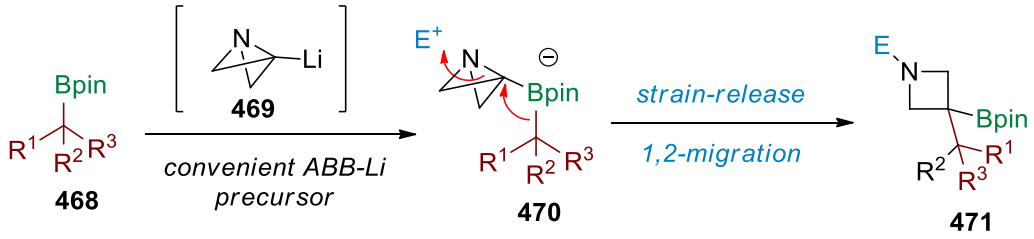
Scheme 1.85 Ruthenium catalyzed asymmetric addition of alkynes to isatins

Part C:

Synthesis of Azetidine Boronic Esters by Lithiation-Borylation Reaction Methodology

Azetidine, a four membered nitrogen containing heterocyle, has inspiring biological importance. It is the part of many marketed drugs and bioactive compounds. However, synthetic protocols for to access this heterocycle are limited. Lithiation followed by borylation is a powerful tool for homologation of boronic esters. Boronic ester can be transformed in to different functional groups.

This part of research work involves the homologation of boronic esters by azetidine unit which is in fact the synthesis of azetidines (Scheme 1.86). Azabicyclo[1.1.0]butane **339** will be used as precursor as it releases its strain by transforming to azetidine molecule. Research design involves the reaction of azabicyclo[1.1.0]butyl lithium **469** with boronic esters to form strained boronate complex **470.** Boronate complex **470** will undergo strain-release 1,2-migration and breaking of C-N bond to form azetidine boronic ester **471**. Nitrogen atom of azetidine will be trapped by an electrophile (H^+, Boc or Cbz).



Scheme 1.86 Synthesis of azetidine boronic esters

CHAPTER-2
EXPERIMENTAL

2.1 General Considerations

All the experiments in Part-A and B in this dissertation have been performed at the Department of Chemistry, Quaid-i-Azam University Islamabad, Pakistan in Dr. Abbas research group while Part-C was performed at the university of Bristol, England in Prof. VK Aggarwal research group.

Chemicals were purchased from Merck and Alfa-Aesar chemical companies and were used as such for most of the reactions. Cyclohexyl pinacol boronic ester was purified through flash column chromatography (SiO_2; 95:5 Pentane:Et_2O) prior its use. Lithium reagents e.g, phenyl lithium, *tert*-butyl lithium, *sec*-butyl lithium was regularly titrated after the first use. For ruthenium catalyzed coupling reactions, 13×100 mm high pressure sealed tubes were used and availability of freshly distilled solvents was made sure. Ruthenium catalysts $RuHCl(CO)(PPh_3)_3$,[158] $RuCl(OCOCF_3)(CO)(PPh_3)_2]$,[159] and $Ru(OCOCF_3)_2(CO)(PPh_3)_2]$[159] were synthesized in the lab following the literature procedures.

All reactions were monitored by thin layer chromatography (TLC) using the pre-coated silica gel-60 F_{254}. TLC plates were purchased from Merck (Germany). UV visible spots were inspected under UV light at 254 nm. Different staining reagents such as potassium permanganate, phosphomolybdic acid (PMA), anisaldehyde or ninhydrine solution were used where required. Flash column chromatography using silica gel (particle size 200-300 mesh) was used for purification.

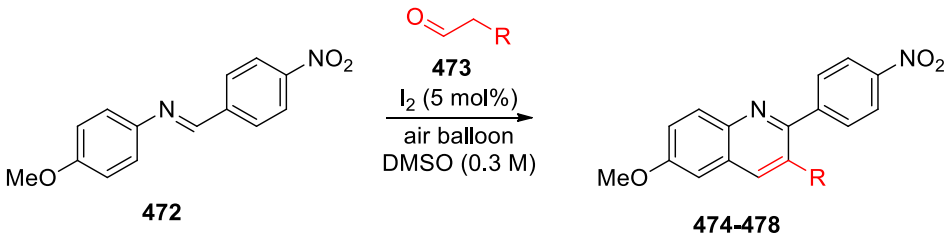
For part A and B in this dissertation, IR spectra were recorded on Schimadzu Fourier Transform Infra-Red Spectrophotometer model 270 using ATR (Attenuated total reflectance) facility. Mass spectrometric (HRMS)

experiments were carried out on Finnigan MAT-311A (Germany) mass spectrometer with (ESI) ionization techniques. NMR spectra were obtained using a Bruker 300 NMR MHz spectrometer in deuterated solvents using TMS as an internal reference, at 300 MHz (^{1}H NMR) and 75 MHz (^{13}C NMR). Chemical shifts are mentioned in delta (δ) units while coupling constants (*J*) values are in Hertz unit (Hz). For Chiral high-performance liquid chromatography (HPLC), Agilent 1100 Series HPLC instrument equipped with UV-vis. diode array detector was used.

For part C of this work, ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on Jeol ECS 400 MHz, Varian VNMR 400 MHz and Varian VNMR 500 MHz spectrometers. High resolution mass spectra (HRMS) were recorded on a Bruker Daltonics MicrOTOF II by Electrospray Ionisation (ESI). IR spectra were recorded on a Perkin Elmer Spectrum One FT-IR as a thin film. Melting points were recorded on Kofler hot-stage microscope apparatus and are represented in degrees Celsius (°C). Chiral HPLC was performed on an Agilent 1100 Series HPLC unit equipped with UV-vis. diode array detector. Optical rotation $[\propto]_D^T$ was measured on a Bellingham and Stanley Ltd. ADP220 polarimeter. Gas Chromatography (GC) was performed on an Agilent 7890A using an Agilent HP-5 column (15 m x 0.25 mm x 0.25 μm).

2.2 Part A: Synthesis of Quinoline Derivatives as Nucleoside Triphosphate Diphosphohydrolase (NTPDases) Inhibitors

2.2.1 General Procedure A: Molecular Iodine Catalyzed Synthesis of Various Quinoline Derivatives

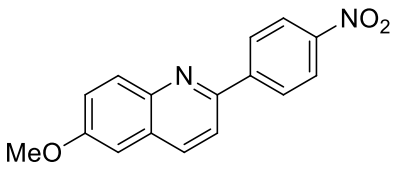


Scheme 2.1 General reaction for the synthesis of quinoline derivatives

To a 25 mL round bottom flask was added *N*-(4-methoxyphenyl)-1-(4-nitrophenyl)methanimine (140 mg, 0.5 mmol, 100 mol%), molecular iodine (6.35 mg, 0.025 mmol, 5 mol%) in DMSO (1.7 mL, 0.3 M) and aldehyde (0.6 mmol, 120 mol %). The flask was fitted with rubber septum and air balloon (the balloon was filled from air pump passing through dry magnesium sulfate). The reaction mixture was stirred at 70 °C overnight. Reaction progress was monitored by TLC. After reaction completion, water (20 mL) was added, and the reaction mixture was extracted with ethyl acetate (30 mL x 3). The combined organic layer was dried over anhydrous sodium sulphate, concentrated under reduced pressure and purified by flash column chromatography (ethyl acetate: n-hexane).

2.2.1.1 Characterization of Quinoline Derivatives Synthesized by Molecular Iodine Catalyzed Coupling of Aryl imine and Aliphatic Aldehydes

2.2.1.1 (a) 6-Methoxy-2-(4-nitrophenyl)quinolone



474

According to General Procedure A for quinoline synthesis, *N*-(4-methoxyphenyl)-1-(4-nitrophenyl)methanimine (140 mg, 0.5 mmol, 100 mol%) was reacted with acetaldehyde (0.03 ml, 0.6 mmol, 120 mol %) in DMSO (1.7 mL, 0.3 M) using

molecular iodine (6.35 mg, 0.025 mmol, 5 mol%) as catalyst. Flash chromatography (SiO_2; 7:3 hexane:EtOAc) was used to purify the crude residue to yield the compound as white solid (74 mg, 53%).

m.p. = 155-157 °C

TLC: R_f = 0.4 (ethyl acetate: *n*-hexane; 2:8)

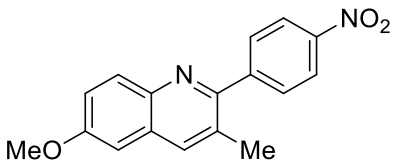
^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.37-8.29 (m, 4H), 8.17 (d, J = 8.4 Hz, 1H), 8.07 (d, J = 9.2 Hz, 1H), 7.87 (d, J = 8.7 Hz, 1H), 7.42 (dd, J = 9.2 Hz, 2.8 Hz, 1H), 7.11 (d, J = 2.8 Hz, 1H), 3.96 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.5, 152.1, 148.1, 145.7, 144.5, 136.0, 131.5, 128.8, 128.0, 124.1, 123.3, 119.2, 104.9, 55.8 ppm.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{16}H_{13}N_2O_3$, 281.0921; found: 281.0924.

FTIR (neat): $\bar{\upsilon}$ 3060, 3028, 2924, 2855, 1723, 1595, 1516, 1489, 1453, 1342, 1314 cm^{-1}

2.2.1.1 (b) 6-Methoxy-3-methyl-2-(4-nitrophenyl)quinoline



475

According to General Procedure A for quinoline synthesis, *N*-(4-methoxyphenyl)-1-(4-nitrophenyl)methanimine (140 mg, 0.5 mmol, 100 mol%) was reacted with propionaldehyde (0.04 ml, 0.6 mmol, 120 mol %) in DMSO (1.7 mL, 0.3 M) using molecular iodine (6.35 mg, 0.025 mmol, 5 mol%) as catalyst. Flash column chromatography (SiO_2; 7:3 hexane:EtOAc) was used to purify crude residue to yield the compound as white solid (90 mg, 61%).

m.p. = 162-164 °C

TLC: R_f = 0.4 (ethyl acetate: *n*-hexane; 2:8)

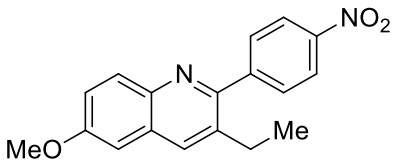
^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.34 (d, J = 8.8 Hz, 2H), 8.03-7.94 (m, 2H), 7.78 (d, J = 8.8 Hz, 2H), 7.35 (dd, J = 9.2 Hz, 2.8 Hz, 1H), 7.06 (d, J = 2.7 Hz, 1H), 3.96 (s, 3H), 2.45 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.4, 155.4, 147.7, 147.4, 142.9, 136.3, 130.9, 130.3, 129.0, 128.9, 123.6, 123.2, 104.3, 55.9, 20.1 ppm.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{17}H_{15}N_2O_3$, 295.1077; found: 295.1080.

FTIR (neat): $\bar{\upsilon}$ 3060, 3028, 2924, 2855, 1723, 1595, 1516, 1489, 1453, 1342, 1314 cm^{-1}

2.2.1.1 (c) 3-Ethyl-6-methoxy-2-(4-nitrophenyl)quinoline



476

According to General Procedure A for quinoline synthesis, *N*-(4-methoxyphenyl)-1-(4-nitrophenyl)methanimine (140 mg, 0.5 mmol, 100 mol%) was reacted with butanal (0.05 ml, 0.6 mmol, 120 mol %) in DMSO (1.7 mL, 0.3 M) using molecular iodine (6.35 mg, 0.025 mmol, 5 mol%) as catalyst. Flash column chromatography (SiO_2; 7:3 hexane:EtOAc) was used to purify the crude residue to yield the compound as white solid (119 mg, 77%).

m.p. = 170-172 °C

TLC: R_f = 0.45 (ethyl acetate: *n*-hexane; 2:8)

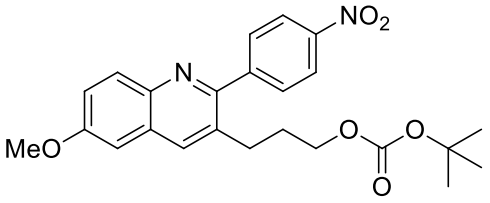
^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.21 (d, J = 8.6 Hz, 2H), 7.96 – 7.87 (m, 2H), 7.64 (d, J = 8.6 Hz, 2H), 7.26 (dd, J = 9.2, 2.7 Hz, 1H), 7.03 (d, J = 2.7 Hz, 1H), 3.86 (s, 3H), 2.69 (q, J = 7.5 Hz, 2H), 1.13 (t, J = 7.5 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.1, 155.2, 147.4, 147.3, 142.4, 134.6, 134.9, 130.5, 130.0, 129.1, 123.2, 122.2, 104.3, 55.5, 25.8, 14.7 ppm.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{18}H_{17}N_2O_3$, 309.1234; found: 309.1237.

FTIR (neat): $\bar{\upsilon}$ 3070, 3028, 2924, 2855, 1723, 1595, 1516, 1489, 1453, 1380, 1314, 1035 cm^{-1}

2.2.1.1 (d) *tert*-Butyl (3-(6-methoxy-2-(4-nitrophenyl)quinolin-3-yl)propyl) carbonate



477

According to General Procedure A for quinoline synthesis, *N*-(4-methoxyphenyl)-1-(4-nitrophenyl)methanimine (140 mg, 0.5 mmol, 100 mol%) was reacted with tert-butyl (5-oxopentyl) carbonate (121 mg, 0.6 mmol, 120 mol %) in DMSO (1.7 mL, 0.3 M) using molecular iodine (6.35 mg, 0.025 mmol, 5 mol%) as catalyst. Flash column chromatography (SiO_2; 7:3 hexane:EtOAc) was used to purify the crude residue to yield the compound (110 mg, 50%) as white solid.

m.p. = 210-212 °C

TLC: R_f: 0.4 (ethyl acetate: *n*-hexane; 2:8)

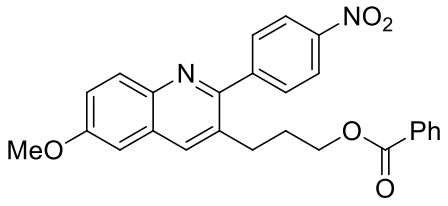
^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.35 (d, J = 8.8 Hz, 2H), 8.00-7.97 (m, 2H), 7.74 (d, J = 8.8 Hz, 2H), 7.36 (dd, J = 9.3 Hz, 2.8 Hz, 1H), 7.08 (d, J = 2.7 Hz, 1H), 3.99 (t, J = 6.4 Hz, 2H), 3.95 (s, 3H), 2.86 (t, J = 7.8 Hz, 2H), 1.94-1.84 (m, 2H), 1.44 (s, 9H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.5, 155.4, 153.5, 147.5, 147.3, 142.8, 135.4, 132.3, 130.2, 130.2, 129.0, 123.8, 122.7, 104.4, 82.3, 65.9, 55.7, 29.6, 29.1, 27.8 ppm.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{24}H_{27}N_2O_6$, 439.1864; found, 439.1866.

FTIR (neat): $\bar{\upsilon}$ 3070, 3028, 2924, 2855, 1760, 1723, 1595, 1516, 1489, 1453, 1380, 1314, 1170, 1035 cm^{-1}.

2.2.1.1 (e) 3-(6-Methoxy-2-(4-nitrophenyl)quinolin-3-yl)propyl benzoate



478

According to General Procedure A for quinoline synthesis, *N*-(4-methoxyphenyl)-1-(4-nitrophenyl)methanimine (140 mg, 0.5 mmol, 100 mol%) was reacted with 5-oxopentyl benzoate (124 mg, 0.6 mmol, 120 mol %) in DMSO (1.7 mL, 0.3 M) using molecular iodine (6.35 mg, 0.025 mmol, 5 mol%) as catalyst. Flash column chromatography (SiO_2; 7:3 hexane:EtOAc) was used to purify the crude residue to yield the compound (133 mg, 60%) as white solid.

m.p. = 250-254 °C

TLC: R_f = 0.5 (ethyl acetate: *n*-hexane; 3:7)

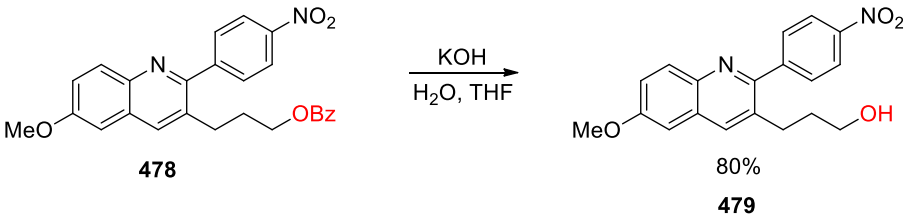
^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.25-8.22 (m, 2H), 8.04 (s, 1H), 8.00 (d, J = 9.2 Hz, 2H), 7.85-7.82 (m, 2H), 7.72-7.69 (m, 2H), 7.57-7.51 (m, 1H), 7.41-7.34 (m, 3H), 7.07 (d, J = 2.7 Hz, 1H), 4.24 (t, J = 6.0 Hz, 2H), 3.94 (s, 3H), 2.96 (t, J = 7.2 Hz, 2H), 2.03 (m, 2H) ppm

^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.4, 158.5, 155.3, 147.5, 147.2, 142.8, 135.6, 133.3, 132.3, 130.8, 130.2, 129.9, 129.4, 129.0, 128.4, 123.6, 122.8, 104.3, 63.8, 55.7, 30.0, 29.3 ppm

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{26}H_{23}N_2O_5$, 443.1601; found: 443.1604.

FTIR (neat): $\bar{\upsilon}$ 3070, 3028, 2924, 2855, 1740, 1723, 1595, 1516, 1489, 1453, 1380, 1314, 1170, 1035 cm^{-1}.

2.2.2 Synthesis of 3-(6-methoxy-2-(4-nitrophenyl)quinolin-3-yl)propan-1-ol



Scheme 2.2 Synthesis of quinoline alcohol derivative

In a 100 mL round bottom flask 3-(6-methoxy-2-(4-nitrophenyl)quinolin-3-yl)propyl benzoate (500 mg, 1.13 mmol, 100 mol%) was dissolved in THF (20 mL) and then aqueous solution of KOH (254 mg, 4.52 mmol, 400 mol% dissolved in water in equal volume as THF) was added. Reaction was left for stirring at room temperature until completion, as shown by TLC. After completion of reaction, water (30 mL) was added, and the reaction mixture was extracted with ethyl acetate (50 mL x 3). The combined organic layer was dried over anhydrous sodium sulphate, concentrated *in vacuo* and purified by flash column chromatography (SiO_2: ethyl acetate: *n*-hexane; 1:1) to afford the white solid (306 mg, 80%).

m.p. = 215-217°C

TLC: R_f = 0.4 (ethyl acetate: *n*-hexane; 1:1)

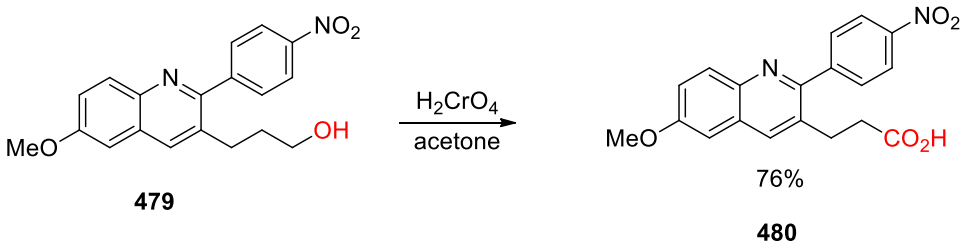
^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.27 (d, J = 8.7 Hz, 2H), 8.00 (d, J = 10.4 Hz, 2H), 7.69 (d, J = 8.7 Hz, 2H), 7.35 (dd, J = 9.1 Hz, 2.7 Hz, 1H), 7.08 (d, J = 2.7 Hz, 1H), 3.95 (s, 3H), 3.52 (t, J = 6.2 Hz, 2H), 2.82 (t, J = 7.8 Hz, 2H), 2.17 (br s, 1H), 1.79-1.70 (m, 2H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.5, 155.3, 147.6, 147.1, 142.4, 135.4, 133.0, 130.5, 130.1, 129.2, 123.7, 122.7, 104.4, 61.7, 55.7, 33.2, 29.0 ppm

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{18}H_{19}N_2O_4$, 339.1339; found: 339.1343.

FTIR (neat): $\bar{\upsilon}$ 3340, 3029, 2923, 2854, 1602, 1510, 1495, 1453, 1362, 1246, 1165, 1090 cm^{-1}

2.2.3 Synthesis of 3-(6-methoxy-2-(4-nitrophenyl)quinolin-3-yl)propanoic acid



479 **480**

Scheme 2.3 Synthesis of quinoline carboxylic acid derivative

3-(6-Methoxy-2-(4-nitrophenyl)quinolin-3-yl)propan-1-ol (500 mg, 1.48 mmol, 100 mol%) was dissolved in acetone and added dropwise to the chromic acid solution (1.18 mL, 1.48 mmol, 2.5 M), 2.96 mmol, 200 mol%) in a 50 ml round bottom flask kept in ice-bath. After addition of alcohol, ice-bath was removed, and reaction mixture was stirred at room temperature for 20 minutes. TLC showed complete consumption of alcohol. Then reaction was quenched with diethyl ether (10 mL) and filtered. In filtrate was added aqueous solution of saturated $NaHCO_3$ until *p*H reaches to 9-10. Ethyl acetate (15 mL) was added and organic layer was separated out. To aqueous layer was added HCl dropwise until *p*H reaches 3 and then extracted with ethyl acetate (30 mL x 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated *in vacuo* to get crude acid which was recrystallized with methanol-water (396 mg, 76%) as white solid.

m.p. = 260-262°C

TLC: R_f = 0.2 (methanol: chloroform; 5:95)

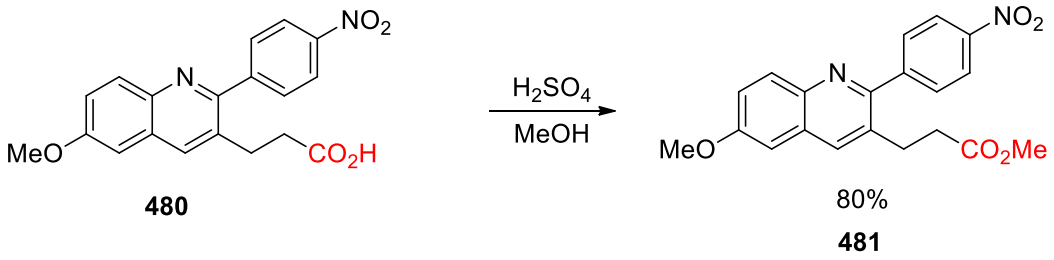
^{1}H NMR ($CDCl_3$, 300 MHz): δ 12.1 (br s, 1H), 8.35 (d, J = 7.5 Hz, 2H), 8.25 (s, 1H), 7.93-7.84 (m, 3H), 7.40-7.36 (m, 2H), 3.92 (s, 3H), 2.99 (t, J = 7.5 Hz, 2H), 2.54 (t, J = 7.5 Hz, 2H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.8, 158.0, 155.4, 147.4, 147.3, 142.3, 135.1, 132.4, 130.7, 130.5, 128.9, 123.7, 122.5, 105.0, 55.9, 33.9, 27.9 ppm

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{19}H_{17}N_2O_5$, 353.1132; found, 353.1136.

FTIR (neat): $\bar{\upsilon}$ 3490, 3029, 2923, 2854, 1760, 1732, 1602, 1510, 1495, 1453, 1362, 1246, 1165, 1090 cm^{-1}.

2.2.4 Synthesis of methyl 3-(6-methoxy-2-(4-nitrophenyl)quinolin-3-yl)propanoate



Scheme 2.4 Synthesis of quinoline derivative **481** through Fisher esterification

To a 25 mL round bottom flask was added 3-(6-methoxy-2-(4-nitrophenyl)quinolin-3-yl)propanoic acid (200 mg, 0.56 mmol, 100 mol%) and methanol (1.5 mL). Reaction mixture was placed in an ice-bath and conc.H_2SO_4 (1.5 μL, 0.03 mmol, 5 mol%) was added dropwise. Reaction mixture was heated under reflux for 12 hours. After completion (as shown on TLC), the the residue was partitioned between CH_2Cl_2 (10 ml) and H_2O (5 mL). The organic phase washed with saturated aqueous sodium bicarbonate solution (4 mL x 3). Combined organic layer was dried over Na_2SO_4, filtered, then the solvent was evaporated under reduced pressure. Flash column chromatography (SiO_2; ethyl acetate: n-hexane; 3:7) was used to purify the crude residue to give white solid (164 mg, 80%).

m.p. = 264-266 °C

TLC: R_f = 0.6 (ethyl acetate: *n*-hexane; 1:1)

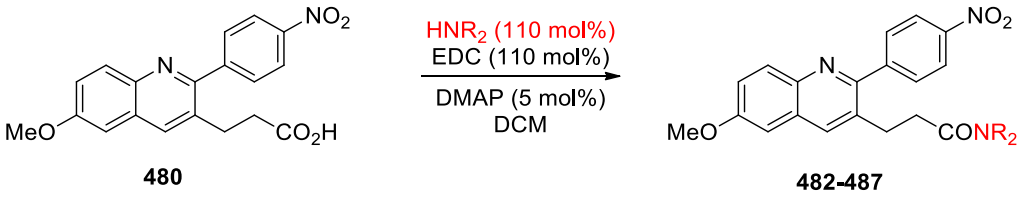
^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.35 (d, J = 8.7 Hz, 2H), 7.99 (d, J = 10.5 Hz, 2H), 7.74 (d, J = 8.4 Hz, 2H), 7.36 (dd, J = 9.3 Hz, 2.4 Hz, 1H), 7.08 (d, J = 2.4 Hz, 1H), 3.95 (s, 3H), 3.60 (s, 3H), 3.10 (t, J = 7.5 Hz, 2H), 2.53 (t, J = 7.8 Hz, 2H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.6, 158.5, 155.2, 147.7, 147.0, 142.7, 135.4, 133.5, 130.7, 130.2, 128.9, 123.8, 122.9, 104.4, 55.7, 51.9, 34.3, 27.8 ppm.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{20}H_{19}N_2O_5$, 367.1288; found: 367.1292.

FTIR (neat): $\bar{\upsilon}$ 3070, 3028, 2924, 2855, 1760, 1723, 1595, 1516, 1489, 1453, 1380, 1314, 1170, 1035 cm^{-1}.

2.2.5 General Procedure B: Synthesis of Amides from 3-(6-methoxy-2-(4-nitrophenyl)quinolin-3-yl)propanoic acid



480 482-487

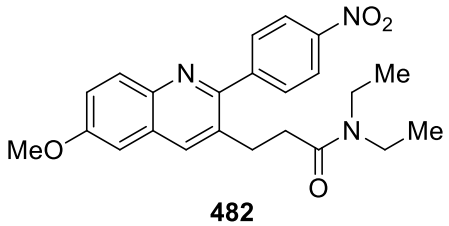
Scheme 2.5 General reaction for the synthesis of quinoline amide derivatives

A slightly modified reported method was followed for the synthesis of amide.[160] A 25 ml round bottom flask was charged with 3-(6-methoxy-2-(4-nitrophenyl)quinolin-3-yl)propanoic acid (200 mg, 0.56 mmol, 100 mol%), amine (0.61 mmol, 110 mol%) and DMAP (6.8 mg, 0.056mmol, 5 mol%). DCM (4 mL, 0.15 M) and DMF (0.4 mL) were added as solvents and reaction flask was purged with nitrogen and kept in ice-bath before the dropwise addition of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (100 μL, 0.56 mmol, 100 mol%). The resulting mixture was stirred overnight at room temperature. Aqueous solution of HCl (25 mL, 1 N) was added and extracted with DCM (25 mL x 3). Combined

organic layer was dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. Residue was purified by flash column chromatography (SiO_2).

2.2.5.1 Characterization of Quinoline Amide Derivatives

2.2.5.1 (a) *N, N*-Diethyl-3-(6-methoxy-2-(4-nitrophenyl)quinolin-3-yl)propanamide



482

According to General Procedure B, 3-(6-methoxy-2-(4-nitrophenyl)quinolin-3-yl)propanoic acid (200 mg, 0.56 mmol, 100 mol%) was reacted with *N,N*-diethyl amine (74 μL, 0.61 mmol, 110 mol%) using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (100 μL, 0.56 mmol, 100 mol%) as coupling reagent and flash chromatography (SiO_2; methanol: chloroform; 1:9) was used to purify the crude residue to yield white solid (160 mg, 70%).

m.p. = 255-257 °C

TLC: R_f = 0.4 (methanol: chloroform; 5:9.5)

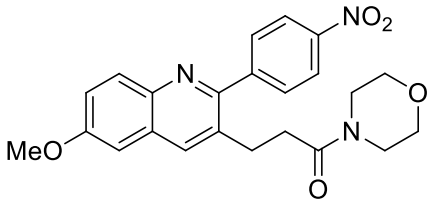
^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.30 (d, J = 5.7 Hz, 2H), 8.23 (s, 1H), 7.87-7.80 (m, 3H), 7.35-7.28 (m, 2H), 3.86 (s, 3H), 3.17-3.08 (m, 4H), 2.94 (t, J = 6.9 Hz, 2H), 2.50 (t, J = 7.0 Hz, 2H), 0.94-0.91 (m, 3H), 0.89-0.86 (m, 2H) ppm.

^{13}C NMR (DMSO-d_6, 75 MHz): δ 169.7, 157.7, 155.2, 147.1, 147.0, 141.9, 135.0, 132.8, 130.5, 130.2, 128.7, 123.3, 122.0, 104.9, 55.6, 41.2, 39.4, 32.9, 27.8, 14.2, 13.0 ppm.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{23}H_{26}N_3O_4$, 408.1918; found, 408.1921.

FTIR (neat): $\bar{\upsilon}$ 3029, 2923, 2854, 1732, 1680, 1602, 1510, 1495, 1453, 1362, 1246, 1165, 1090 cm^{-1}.

2.2.5.1 (b) 3-(6-Methoxy2-(4-nitrophenyl)quinolin-3-yl)-1-morpholinopropan-1-one



483

According to General Procedure B, 3-(6-methoxy-2-(4-nitrophenyl)quinolin-3-yl)propanoic acid (200 mg, 0.56 mmol, 100 mol%) was reacted with morpholine (52 μL, 0.61 mmol, 110 mol%) using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (100 μL, 0.56 mmol, 100 mol%) as coupling reagent and flash chromatography (SiO_2; methanol: chloroform; 1:9) was used to purify the crude residue to yield white solid (187 mg, 80%).

m.p. = 234-236 °C

TLC: R_f = 0.6 (methanol: chloroform; 5:9.5)

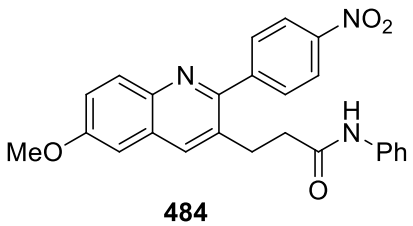
^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.16-8.13 (m, 3H), 7.74-7.66 (m, 3H), 7.20 (dd, J = 9.1 Hz, 2.6 Hz, 1H), 7.15 (d, J = 2.6 Hz, 1H), 3.71 (s, 3H), 3.27 (t, J = 4.2 Hz, 4H), 3.15 (t, J = 4.2 Hz, 4H), 2.76 (t, J = 7.2 Hz, 2H), 2.43 (t, J = 7.2 Hz, 2H) ppm.

^{13}C NMR (DMSO-d_6, 75 MHz): δ 172.3, 169.7, 169.6, 158.3, 153.7, 147.7, 132.5, 131.0, 130.8, 129.2, 129.2, 123.8, 123.5, 105.3, 63.2, 55.9, 51.5, 42.6, 33.3, 26.8 ppm.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{23}H_{24}N_3O_5$, 422.1710; found, 422.1242.

FTIR (neat): $\bar{\upsilon}$ 3330, 3029, 2960, 2923, 2854, 1732, 1680, 1602, 1510, 1495, 1453, 1362, 1246, 1165, 1090 cm^{-1}.

2.2.5.1 (c) 3-(6-Methoxy-2-(4-nitrophenyl)quinolin-3-yl)-*N*-phenylpropanamide



484

According to General Procedure B, 3-(6-methoxy-2-(4-nitrophenyl)quinolin-3-yl)propanoic acid (200 mg, 0.56 mmol, 100 mol%) was reacted with aniline (55 μL, 0.61 mmol, 110 mol%) using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (100 μL, 0.56 mmol, 100 mol%) as coupling reagent and flash chromatography (SiO_2; methanol: chloroform; 1:9) was used to purify the crude residue to yield white solid (153 mg, 64%).

m.p. = 296-298 °C

TLC: R_f = 0.5 (methanol: chloroform; 5:9.5)

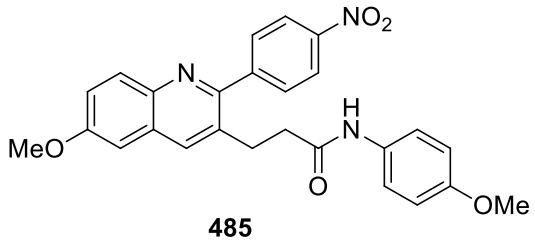
^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.84 (s, 1H), 8.27 (d, J = 8.1 Hz, 2H), 8.20 (s, 1H), 7.87-7.81 (m, 3H), 7.45 (d, J = 8.1 Hz, 2H), 7.34-7.30 (m, 2H), 7.22-7.17 (m, 2H), 6.96-6.91 (m, 1H), 3.85 (s, 3H), 3.04 (t, J = 7.2 Hz, 2H), 2.58 (t, J = 7.8 Hz, 2H) ppm.

^{13}C NMR (DMSO-d_6, 75 MHz): δ 169.9, 157.8, 155.1, 147.1, 147.0, 142.0, 139.1, 134.9, 132.5, 130.5, 130.1, 128.7, 128.6, 123.3, 123.1, 121.1, 119.1, 104.9, 56.0, 36.4, 27.6 ppm.

HRMS-ESI (m/z) $[M+H]^+$ calculated for $C_{25}H_{22}N_3O_4$, 428.1605; found, 428.1608.

FTIR (neat): $\bar{\upsilon}$ 3066, 3029, 2960, 2923, 2854, 1732, 1640, 1602, 1510, 1495, 1453, 1362, 1246, 1165, 1090 cm^{-1}.

2.2.5.1 (d) 3-(6-Methoxy-2-(4-nitrophenyl)quinolin-3-yl)-*N*-(4-methoxyphenyl)propanamide



485

According to General Procedure B, 3-(6-methoxy-2-(4-nitrophenyl)quinolin-3-yl)propanoic acid (200 mg, 0.56 mmol, 100 mol%) was reacted with *p*-anisidine (75 mg, 0.61 mmol, 110 mol%) using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (100 μL, 0.56 mmol, 100 mol%) as coupling reagent and flash chromatography (SiO_2; methanol: chloroform; 1:9) was used to purify the crude residue to yield white solid (160 mg, 67%).

m.p. = 305-307 °C

TLC; R_f = 0.55 (methanol: chloroform; 5:9.5)

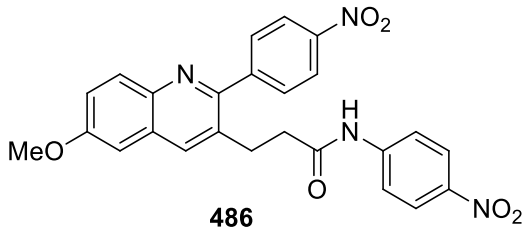
^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.74 (s, 1H), 8.33 (d, J = 8.4 Hz, 2H), 8.24 (s, 1H), 7.91-7.85 (m, 3H), 7.39-7.33 (m, 4H), 6.80 (d, J = 8.7 Hz, 2H), 3.89 (s, 3H), 3.66 (s, 3H), 3.06 (t, J = 7.5 Hz, 2H), 2.56 (t, J = 7.5 Hz, 2H) ppm.

^{13}C NMR (DMSO-d_6, 75 MHz): δ 169.3, 157.8, 155.1, 155.1, 147.1, 146.9, 141.9, 134.9, 132.5, 132.2, 130.5, 130.2, 128.6, 123.3, 122.2, 120.6, 113.8, 104.9, 55.6, 55.1, 36.3, 27.8 ppm.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{26}H_{24}N_3O_5$, 458.1710; found: 458.1713.

FTIR (neat): $\bar{\upsilon}$ 3360, 3029, 2960, 2923, 2854, 1732, 1602, 1510, 1560, 1495, 1453, 1362, 1320, 1246, 1165, 1090 cm^{-1}.

2.2.5.1 (e) 3-(6-Methoxy-2-(4-nitrophenyl)quinolin-3-yl)-*N*-(4-nitrophenyl)propanamide



486

According to General Procedure B, 3-(6-methoxy-2-(4-nitrophenyl)quinolin-3-yl)propanoic acid (200 mg, 0.56 mmol, 100 mol%) was reacted with 4-nitroaniline (84 mg, 0.61 mmol, 110 mol%) using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (100 μL, 0.56 mmol, 100 mol%) as coupling reagent and flash chromatography (SiO_2; methanol: chloroform; 1:9) was used to purify the crude residue to yield white solid (145 mg, 55%).

m.p. = 300-302 °C

TLC; R_f = 0.3 (methanol: chloroform; 5:9.5)

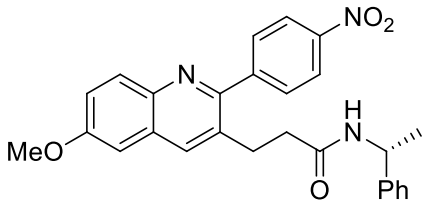
^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.74 (s, 1H), 8.33 (d, J = 8.4 Hz, 2H), 8.24 (s, 1H), 7.91-7.85 (m, 3H), 7.39-7.33 (m, 4H), 6.80 (d, J = 8.7 Hz, 2H), 3.89 (s, 3H), 3.06 (t, J = 7.5 Hz, 2H), 2.56 (t, J = 7.5 Hz, 2H) ppm.

^{13}C NMR (DMSO-d_6, 75 MHz): δ 173.8, 169.9, 165.1, 157.8, 147.1, 142.0, 139.1, 134.9, 132.5, 130.5, 130.1, 128.7, 128.6, 123.3, 123.1, 121.1, 119.1, 104.9, 56.0, 36.4, 27.6 ppm.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{25}H_{21}N_4O_6$, 473.1456; found: 473.1460.

FTIR (neat): $\bar{\upsilon}$ 3360, 3029, 2960, 2923, 2854, 1732, 1602, 1510, 1560, 1495, 1453, 1362, 1320, 1246, 1165, 1090 cm^{-1}.

2.2.5.1 (f) *(R)*-3-(6-Methoxy-2-(4-nitrophenyl)quinolin-3-yl)-*N*-(1-phenylethyl)propanamide



487

According to General Procedure B, 3-(6-methoxy-2-(4-nitrophenyl)quinolin-3-yl)propanoic acid (200 mg, 0.56 mmol, 100 mol%) was reacted with *(1R)*-1-phenylethanamine (74μL, 0.61 mmol, 110 mol%) using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (100 μL, 0.56 mmol, 100 mol%) as coupling reagent and flash chromatography (SiO_2; methanol: chloroform; 1:9) was used to purify the crude residue to yield white solid (217 mg, 85%).

m.p. = 302-304 °C

TLC; R_f = 0.5 (methanol: chloroform; 5:9.5),

$[\alpha]_D^{19.6}$ = + 33 (*c* = 1.0, CH_2Cl_2).

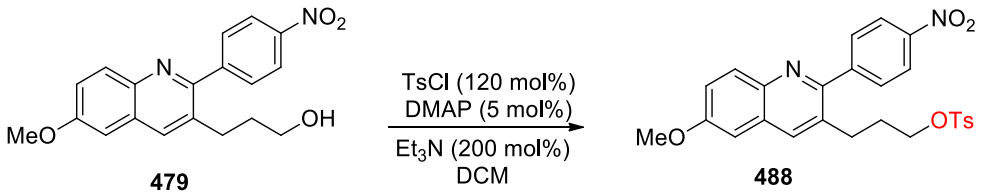
^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.32-8.21 (m, 3H), 8.13 (s, 1H), 7.87 (d, *J* = 9.2 Hz, 1H), 7.80 (d, *J* = 8.6 Hz, 2H), 7.35 (dd, *J* = 9.2 Hz, 2.7 Hz, 1H), 7.23 (d, *J* = 2.7 Hz, 1H), 7.14-7.06 (m, 4H), 4.80 (quin, *J* = 7.1 Hz, 1H), 3.87 (s, 3H), 2.94 (t, *J* = 7.2 Hz, 2H), 2.46-2.38 (m, 2H), 1.21 (d, *J* = 7.0 Hz, 3H) ppm.

^{13}C NMR (DMSO-d_6, 75 MHz): δ 169.9, 157.7, 155.1, 147.0, 146.9, 144.6, 141.9, 134.9, 132.3, 130.1, 130.2, 128.6, 128.1, 126.5, 125.8, 123.3, 122.1, 104.9, 55.6, 47.6, 35.4, 27.9, 22.4 ppm.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{27}H_{26}N_3O_4$, 456.1918; found, 456.1919.

FTIR (neat): $\bar{\upsilon}$ 3360, 3029, 2960, 2923, 2854, 1732, 1602, 1510, 1495, 1453, 1362, 1320, 1246, 1165, 1090 cm^{-1}.

2.2.6 Synthesis of 3-(6-methoxy-2-(4-nitrophenyl)quinolin-3-yl)propyl 4-methylbenzenesulfonate



Scheme 2.6 Tosylation of quinoline alcohol derivative **479**

To a 50 mL round bottom flask 3-(6-methoxy-2-(4-nitrophenyl)quinolin-3-yl)propan-1-ol (1 g, 2.96 mmol, 100 mol%) was dissolved in 10 mL of CH_2Cl_2. The resulting solution was stirred and cooled in an ice-bath followed by the addition of DMAP (18 mg, 0.15 mmol, 5 mol%), Et_3N (0.82 mL, 5.92 mmol, 200 mol%) and TsCl (676 mg, 3.55 mmol, 120 mol%). Reaction mixture was stirred at room temperature overnight. After completion, resulting mixture was diluted with DCM (10 mL) and water (30 mL) was added in it. Organic layer was separated. Aqueous layer was extracted two more times with DCM (20 mL). Combined organic layer was dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. Flash column chromatography (SiO_2; ethyl acetate: *n*-hexane; 3:7) was used to purify the crude residue to give yellow solid (0.87g, 60%)

m.p. = 280-282 °C

TLC: R_f = 0.5 (ethyl acetate: *n*-hexane; 3:7)

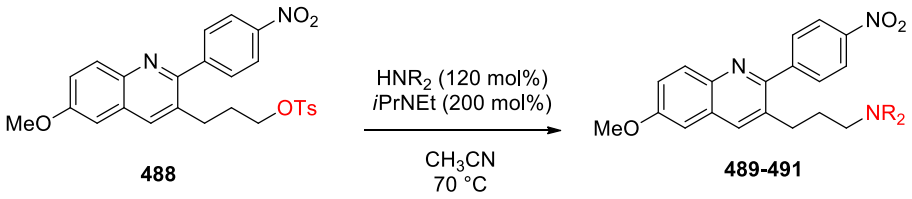
^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.29 (d, J = 8.7 Hz, 2H), 8.02-7.96 (m, 2H), 7.68 (dd, J = 8.5 Hz, 3.4 Hz, 4H), 7.37 (dd, J = 9.2 Hz, 2.7 Hz, 1H), 7.29 (d, J = 8.1 Hz, 2H), 7.07 (d, J = 2.7 Hz, 1H), 3.96 (s, 3H), 3.96-3.93 (m, 2H), 2.89 – 2.79 (m, 2H), 2.43 (s, 3H),1.89-1.80 (m, 2H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.5, 155.1, 147.7, 146.9, 145.1, 142.7, 135.7, 132.8, 131.5, 130.7, 130.1, 129.9, 128.9, 127.8, 123.8, 122.9, 104.4, 69.0, 55.7, 29.6, 28.7, 21.7 ppm.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{26}H_{25}N_2O_6S$, 493.1428; found: 493.1428.

FTIR (neat): $\bar{\upsilon}$ 3080, 3028, 2960, 2855, 1723, 1595, 1516, 1489, 1453, 1420, 1380, 1314, 1200, 1170, 1035 cm^{-1}.

2.2.7 General Procedure C: Nucleophilic Substitution of 3-(6-methoxy-2-(4-nitrophenyl)quinolin-3-yl)propyl 4-methylbenzenesulfonate

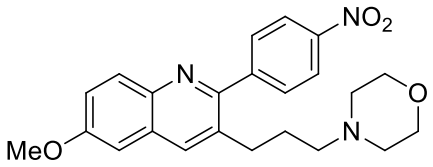


Scheme 2.7 General reaction for the synthesis of quinoline tertiary amine derivatives through nucleophilic substitution

A 25 ml round bottom flask was charged with 3-(6-methoxy-2-(4-nitrophenyl)quinolin-3-yl)propyl 4-methylbenzenesulfonate (150 mg, 0.30 mmol, 100 mol%), amine nucleophile (0.37 mmol, 120 mol%) and K_2CO_3 (84 mg, 0.61 mmol, 200 mol%) and CH_3CN (1.5 mL). Reaction mixture was refluxed overnight. TLC showed complete consumption of starting material. After completion of reaction, water was added (10 mL) to the mixture and extracted with ethyl acetate (15 mL x 3). Combined organic layer was dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. Flash column chromatography (DCM: ethyl acetate; 1:1) was used to purify the crude residue.

2.2.7.1 Characterization of Quinoline Tertiary Amine Derivatives Synthesized by Nucleophilic Substitution

2.2.7.1 (a) 4-(3-(6-Methoxy-2-(4-nitrophenyl)quinolin-3-yl)propyl)morphol



489

According to General Procedure C, 3-(6-methoxy-2-(4-nitrophenyl)quinolin-3-yl)propyl 4-methylbenzenesulfonate (150 mg, 0.30 mmol, 100 mol%) was refluxed with morpholine nucleophile (32 μL, 0.37 mmol, 120 mol%) in acetonitrile. Flash chromatography (SiO_2; ethyl acetate: DCM; 1:1) was used to purify the crude residue to afford white solid (74 mg, 61%).

m.p. = 260-264 °C

TLC: R_f = 0.45 (ethyl acetate: DCM; 1:1)

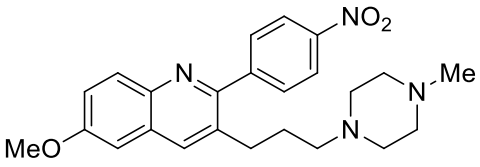
^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.32 (d, J = 8.8 Hz, 2H), 8.03-7.92 (m, 2H), 7.73 (d, J = 8.8 Hz, 2H), 7.34 (dd, J = 9.2 Hz, 2.8 Hz, 1H), 7.07 (d, J = 2.7 Hz, 1H), 3.94 (s, 3H), 3.66-3.63 (m, 4H), 2.34-2.26 (m, 6H),1.77-1.70 (m, 2H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.4, 155.4, 147.6, 147.5, 142.7, 135.3, 132.9, 130.8, 130.2, 129.0, 123.6, 122.5, 104.4, 66.7, 58.0, 55.6, 53.5, 30.4, 27.3 ppm.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{23}H_{26}N_3O_4$, 408.1918; found: 408.1919.

FTIR (neat): $\bar{\upsilon}$ 3330, 3029, 2960, 2923, 2854, 1732, 1602, 1510, 1495, 1453, 1362, 1246, 1165, 1090 cm^{-1}

2.2.7.1 (b) 6-Methoxy-3-(3-(4-methylpiperazin-1-yl)propyl)-2-(4-nitrophenyl)quinoline



490

According to General Procedure C, 3-(6-methoxy-2-(4-nitrophenyl)quinolin-3-yl)propyl 4-methylbenzenesulfonate (150 mg, 0.30 mmol, 100 mol%) was refluxed with *N*-methyl piperazine nucleophile (41 μL, 0.37 mmol, 120 mol%) in acetonitrile. Flash chromatography (SiO_2; ethyl acetate: DCM; 1:1) to purify the crude residue to afford gummy brown solid (100 mg, 61%).

m.p. = 244-246 °C

TLC: R_f = 0.6 (methanol: chloroform; 1:9)

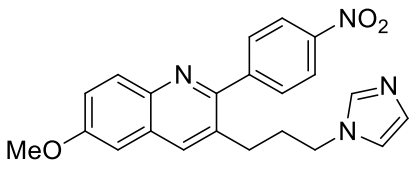
^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.33 (d, J = 8.7 Hz, 2H), 7.99-7.95 (m, 2H), 7.72 (d, J = 8.7 Hz, 2H), 7.35 (dd, J = 9.0 Hz, 3.0 Hz, 1H), 7.05 (d, J = 2.7 Hz, 1H), 3.94 (s, 3H), 2.80-2.74 (m, 2H), 2.60 (s,3H), 2.52-2.42 (m, 4H), 2.35-2.30 (m, 6H),1.77-1.67 (m, 2H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.5, 155.4, 147.6, 147.5, 142.7, 135.3, 132.9, 130.2, 129.0, 123.6, 122.6, 104.4, 57.4, 55.7, 54.2, 51.9, 45.2, 41.0, 30.5, 27.5 ppm.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{24}H_{29}N_4O_3$, 421.2234; found: 421.2237.

FTIR (neat): $\bar{\upsilon}$ 3040, 2923, 2856, 1730, 1602, 1510, 1495, 1453, 1362, 1250, 1165, 1090 cm^{-1}.

2.2.7.1 (c) 3-(3-(*1H*-Imidazol-1-yl)propyl)-6-methoxy-2-(4-nitrophenyl)quinoline



491

According to General Procedure C, 3-(6-methoxy-2-(4-nitrophenyl)quinolin-3-yl)propyl 4-methylbenzenesulfonate (150 mg, 0.30 mmol, 100 mol%) was refluxed with imidazole nucleophile (25 mg, 0.37 mmol, 120 mol%) in acetonitrile. Flash chromatography (SiO_2; ethyl acetate: DCM; 1:1) was used to purify the crude residue to afford gummy brown solid (86 mg, 60%).

m.p. = 276-278 °C;

TLC: R_f = 0.45 (methanol: chloroform; 1:9)

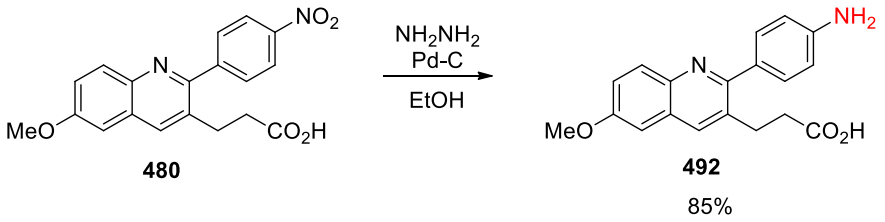
^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.32 (d, J = 8.4 Hz, 2H), 7.99-7.94 (m, 2H), 7.71-7.66 (m, 3H), 7.37 (dd, J = 9.0 Hz, 2.7 Hz, 1H), 7.08-7.05 (m, 2H), 6.78 (s, 1H), 3.94 (s, 3H) 3.92-3.90 (m, 2H), 2.77 (t, J = 7.5 Hz, 2H), 2.04-1.93 (m, 2H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.6, 155.1, 147.6, 147.5, 142.7, 135.4, 133.0, 132.5, 131.0, 130.8, 130.2, 129.9, 128.9, 123.6, 122.5, 104.4, 55.7, 53.5, 30.4, 27.8 ppm.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{22}H_{21}N_4O_3$, 389.1608; found: 389.1612.

FTIR (neat): $\bar{\upsilon}$ 3029, 2923, 2854, 1732, 1690, 1602, 1510, 1495, 1453, 1362, 1246, 1165, 1090 cm^{-1}.

2.2.8 Synthesis of 3-(2-(4-aminophenyl)-6-methoxyquinolin-3-yl)propanoic acid



Scheme 2.8 Pd/C Reduction of Quinoline Derivative **480**

3-(2-(4-Nitrophenyl)-6-methoxyquinolin-3-yl)propanoic acid (200 mg, 0.56 mmol, 100 mol%) was dissolved in ethanol (25 mL) in a 50 mL round bottom flask under nitrogen. Palladium charcoal (20 mg) was added and heated under reflux for 2 hours followed by the addition of hydrazine hydrate (0.8 ml). Reaction mixture was heated under reflux for 12 hours. After completion, Pd-Charcoal was filtered out from mixture and filtrate concentrated *in vacuo*. Residue was purified by recrystallization with ethyl acetate-methanol to yield yellow solid (153 mg, 85%).

m.p. = 260-264 °C

TLC: R_f = 0.35 (methanol: chloroform; 1:9)

^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.08 (s, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.33-7.25 (m, 4H), 6.66 (d, J = 8.4 Hz, 2H), 3.89 (s, 3H), 3.38 (bs, 2H), 3.04 (t, J = 7.5 Hz, 2H), 1.93-1.89 (m, 2H) ppm.

^{13}C NMR (DMSO-d_6, 75 MHz): δ 173.7, 157.7, 157.0, 148.7, 142.1, 134.3, 132.4, 129.9, 129.8, 127.8, 127.7, 121.3, 113.2, 104.9, 55.4, 33.8, 27.9 ppm.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{19}H_{19}N_2O_3$, 323.1390; found: 323.1394.

FTIR (neat): $\bar{\upsilon}$ 3510, 3410, 3300, 3029, 2960, 2923, 2854, 1760, 1650, 1602, 1510, 1560, 1495, 1453, 1362, 1320, 1246, 1165, 1090 cm^{-1}.

2.3 Part B: Ruthenium Catalyzed Asymmetric Addition of Alkynes to Isatins

2.3.1 Synthesis of Different Ruthenium Catalysts

2.3.1.1 Hydridochlorocarbonyltris-(triphenylphosphine) ruthenium(II) [$RuHCl(CO)(PPh_3)_3$]

[$RuHCl(CO)(PPh_3)_3$] was prepared according to reported procedure.[158] To the boiling solution of triphenylphosphine (15.8 g, 60 mmol) in 2-methoxyethanol (300 ml), a solution of $RuCl_3.3H_2O$ (2.61 g, 10 mmol) in 2-methoxyethanol (154 ml) and aqueous formaldehyde (200 ml; 40%, w/v) was added rapidly with continuous stirring. The nmixture was refluxed for 10 minutes then it was allowed to cool, precipitate formed were filtered and washed with ethanol and hexane and dried in vacuum to get a light brown colored solid in 88% yield.

Melting point: 208-210 ºC; Reported: 209-210 ºC[161]

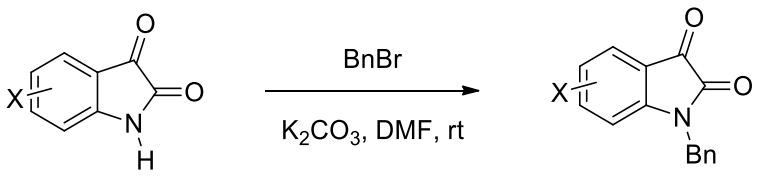
2.3.1.2 Carbonylchlorotrifluoroacetatobis(triphenylphosphine)ruthenium(II) trifluoroacetic acid adduct [$RuCl(OCOCF_3)(CO)(PPh_3)_2$]-$CF_3COOH$

[$RuCl(OCOCF_3)(CO)(PPh_3)_2$]-$CF_3COOH$ was prepared according to reported procedure.[159] Trifluoroacetic acid (0.5 ml) was added dropwise to a suspension of hydridochlorocarbonyltris-(triphenylphosphine) ruthenium(II) complex-[$RuHCl(CO)(PPh_3)_3$] (300 mg) in 2-methoxyethanol (5.0 ml). The mixture was refluxed for 10 min which turned to clear yellow liquid. 2-Methoxyethanol was evaporated under reduced pressure and product obtained was recrystallized from DCM-Hexane and dried in *vacuo* to obtain a yellow solid in 80% yield.

2.3.1.3 Bis(trifluoroacetato)carbonylbis(triphenylphosphine)ruthenium(II) methanol adduct $Ru(OCOCF_3)_2(CO)(PPh_3)_2$-MeOH

According to literature procedure[159], carbonyldihydridotris(tripheny1phosphine)-ruthenium (0.46 g) was dissolved in benzene (10 ml) followed by the addition of trifluoroacetic acid (1 ml). The resulting mixture was refluxed for an hour and solvent was evaporated under reduced pressure. The residue was crystallized from dichloromethane-methanol and the product filtered off, washed repeatedly in methanol, water, and methanol, then dried *in vacuo* as yellow crystals (77%).

2.3.2 General Procedure A: *N*-Benzylation of Different Isatins



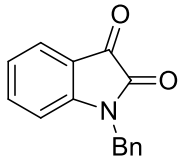
56 **493-497**

Scheme 2.9 General reaction for the *N*-alkylation of isatin

In 250 ml round bottom flask, isatin (1*H*-indole-2,3-dione) (13.6 mmol, 100 mol%) and K_2CO_3 (2.2 g, 16.3 mmol, 120 mol%) was stirred in DMF (10 ml) for 15-20 minutes at room temperature. Benzyl bromide (2.4 ml, 20.4 mmol, 150 mol%) was then added dropwise and reaction progress was monitored by TLC until completion. After completion of reaction, aqueous workup followed by extraction with DCM (15 ml x3) was performed. The combined organic layers were washed with brine, dried over anhydrous sodium sulphate and evaporated *in vacuo* to obtain solid product. This product was recrystallized with dichloromethane-hexane.

2.3.2.1 Substrate Synthesis

2.3.2.1 (a) 1-Benzylindoline-2,3-dione



493

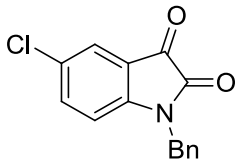
According to General Procedure A, isatin (1*H*-indole-2,3-dione) (2g, 13.6 mmol, 100 mol%) was benzylated with benzyl bromide (2.4 ml, 20.4 mmol, 150 mol%) in DMF. The crude residue after workup was recrystallized with DCM-hexane to afford orange red solid (2.6 g, 80%).

m.p. = 122-124 ºC,

TLC: R_f = 0.28 (Ethyl acetate: *n*-hexane; 2:8).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, J = 7.8 Hz, 1H), 7.49 (t, J = 7.9 Hz, 1H), 7.23-7.36 (m, 5H), 7.15 (t, J = 7.5 Hz, 1H), 6.75 (d, J = 7.8 Hz, 1H), 4.98 (s, 2H) ppm.

2.3.2.1 (b) 1-Benzyl-5-chloroindoline-2,3-dione



494

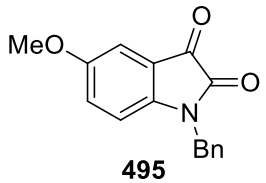
According to General Procedure A, 5-chloroindoline-2,3-dione (2.5 g, 13.6 mmol, 100 mol%) was benzylated with benzyl bromide (2.4 ml, 20.4 mmol, 150 mol%) in DMF. The crude residue after workup was recrystallized with DCM-hexane to afford orange solid (3 g, 81%).

m.p. = 130-133 ºC

TLC: R_f = 0.36 (Ethyl acetate: *n*-hexane; 2:8)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (d, J = 2.1 Hz, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.23-7.36 (m, 5H), 6.65 (d, J = 7.8 Hz, 1H), 4.99 (s, 2H) ppm.

2.3.2.1 (c) 1-Benzyl-5-methoxyindoline-2,3-dione



495

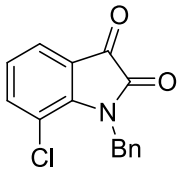
According to General Procedure A, 5-methoxyindoline-2,3-dione (2.4 g, 13.6 mmol, 100 mol%) was benzylated with benzyl bromide (2.4 ml, 20.4 mmol, 150 mol%) in DMF. The crude residue after workup was recrystallized with DCM-hexane to afford dark brown solid (3 g, 82%).

m.p. = 123-126 ºC

TLC: R_f = 0.22 (Ethyl acetate: *n*-hexane; 2:8)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23-7.32 (m, 5H), 7.06 (d, J = 2.1 Hz, 1H), 6.78 (dd, J = 8.4 Hz, J = 2.1 Hz, 1H), 6.63 (d, J = 8.4 Hz, 1H), 4.99 (s, 2H), 3.80 (s, 3H) ppm.

2.3.2.1 (d) 1-Benzyl-7-chloroindoline-2,3-dione



496

According to General Procedure A, 7-chloroindoline-2,3-dione (2.5 g, 13.6 mmol, 100 mol%) was benzylated with benzyl bromide (2.4 ml, 20.4 mmol, 150 mol%)

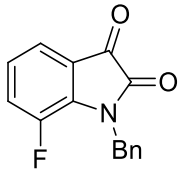
in DMF. The crude residue after workup was recrystallized with DCM-hexane to afford orange solid (3.1 g, 84%).

m.p. = 153-155 ºC

TLC: R_f = 0.36 (Ethyl acetate: *n*-hexane; 2:8)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62-7.54 (m, 2H), 7.36-7.26 (m, 4H), 7.26-7.23 (m, 1H), 7.08-7.02 (d, J = 8.1 Hz, 1H), 5.36 (s, 2H) ppm.

2.3.2.1 (e) 1-Benzyl-7-fluoroindoline-2,3-dione



497

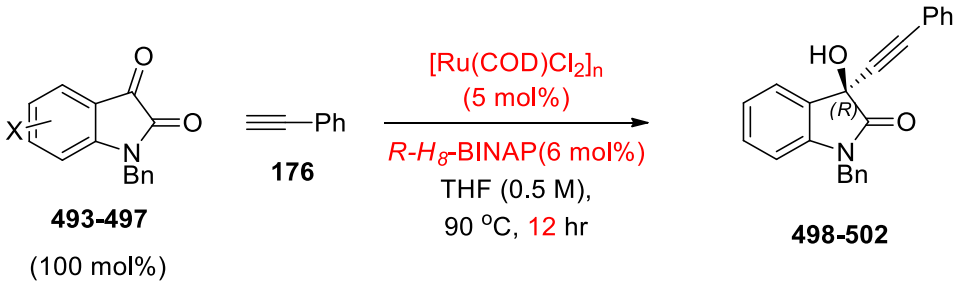
According to General Procedure A, 7-fluoroindoline-2,3-dione (2.2 g, 13.6 mmol, 100 mol%) was benzylated with benzyl bromide (2.4 ml, 20.4 mmol, 150 mol%) in DMF. The crude residue after workup was recrystallized with DCM-hexane to afford red solid (2.8 g, 82%).

m.p. = 143-145 ºC,

TLC: R_f = 0.38 (Ethyl acetate: *n*-hexane; 2:8)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78-7.64 (m, 2H), 7.54-7.32 (m, 4H), 7.26-7.23 (m, 1H), 7.17-6.91 (m, 1H), 4.96 (s, 2H) ppm.

2.3.3 General Procedure B: Asymmetric Addition of Phenylacetylene to Different Substituted Isatins



Scheme 2.10 General reaction for ruthenium catalyzed asymmetric addition of phenylacetylene to different isatins

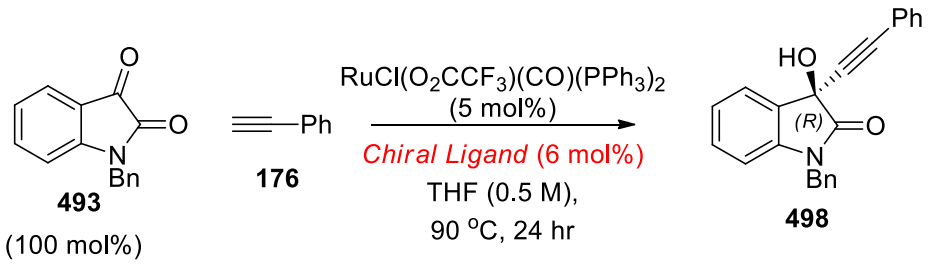
To an oven dried sealed tube (100×13 mm) equipped with magnetic bar was added different substituted *N*-benzylisatins (0.2 mmol, 100 mol%), $[Ru(COD)Cl)_2]_n$ (2.8 mg, 0.01 mmol, 5 mol%), (*R*)-H_8-BINAP (7.6 mg, 0.012 mmol, 6 mol%) and phenylacetylene (44 μL, 0.4 mmol, 200 mol%). Then it was purged with nitrogen before adding freshly dry distilled THF (0.4 ml, 0.5 M) as solvent and purged again. The reaction mixture was stirred at 90°C for 12 h. After 12 h, reaction mixture was allowed to cool to room temperature. Solvent was evaporated under reduced pressure and flash column chromatography (SiO_2) was used for purification of crude residue.

2.3.3.1 Reaction Optimization for Asymmetric Addition of Phenylacetylene to 1-benzylindoline-2,3-dione

2.3.3.1.1 Ligand Screening:

All reactions shown in the table below have been performed according to General Procedure B, 1-benzylindoline-2,3-dione (47 mg, 0.2 mmol, 100 mol%), $RuCl(OCOCF_3)(CO)(PPh_3)_2$ (8 mg, 0.01 mmol, 5 mol%), chiral ligand (0.012 mmol, 6 mol%) and phenylacetylene (44 µL, 0.4 mmol, 200 mol%) have been reacted together in THF (0.4 ml, 0.5 M) at 90°C for 24 h.

Table 2.1 Ligand Screening for Asymmetric Addition of Phenylacetylene to 1-benzylindoline-2,3-dione

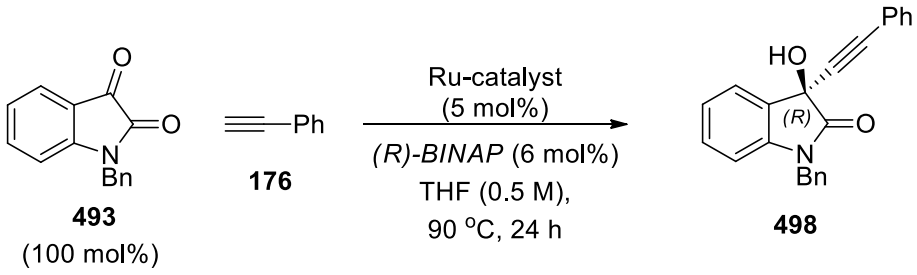


S.No	Chiral Ligand	Yield%	ee%
1	(*R*)-BINAP	66	69
2	(*R*)-Tol-BINAP	87	78
3	(*R*)-DM-BINAP	77	78
4	(*R*)-H_8-BINAP	78	86
5	(*R*)-Segphos	88	48
6	(*R, R*)-DIOP	36	0

2.3.3.1.2 Catalyst Screening

All reactions shown in the table below have been performed according to General Procedure B, 1-benzylindoline-2,3-dione (47 mg, 0.2 mmol, 100 mol%), Ru-catalyst (0.01 mmol, 5 mol%), (*R*)- BINAP (7 mg, 0.012 mmol, 6 mol%) and phenylacetylene (44 μL, 0.4 mmol, 200 mol%) have been reacted together in THF (0.4 ml, 0.5 M) at 90°C for 24 h.

Table 2.2 Ruthenium Catalyst Screening for Asymmetric Addition of Phenylacetylene to 1-benzylindoline-2,3-dione

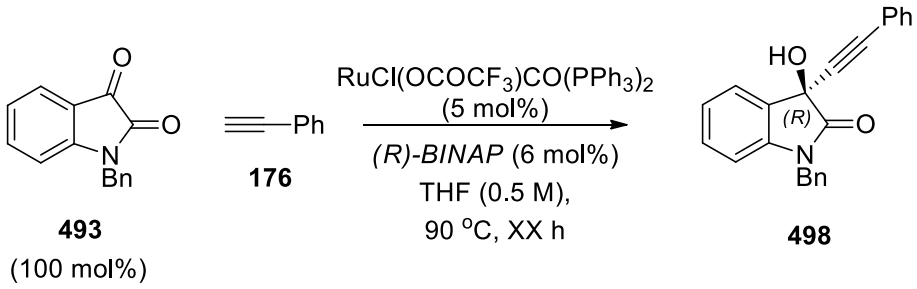


S. No	Ru-Catalyst	Yield%	ee%
1	$RuCl(OCOCF_3)CO(PPh_3)_2$	66	69
2	$Ru(OCOCF_3)_2CO(PPh_3)_2$	68	60
3	$[RuCl_2(p\text{-cymene})_2]$	47	68
4	$[Ru(COD)Cl_2]_n$	80	72

2.3.3.1.3 Reaction Time Screening

All reactions shown in the table below have been performed according to General Procedure B, 1-benzylindoline-2,3-dione (47 mg, 0.2 mmol, 100 mol%), $RuCl(OCOCF_3)(CO)(PPh_3)_2$ (8 mg, 0.01 mmol, 5 mol%), (*R*)- BINAP (7 mg, 0.012 mmol, 6 mol%) and phenylacetylene (44 μL, 0.4 mmol, 200 mol%) have been reacted together in THF (0.4 ml, 0.5 M) at 90°C for different time hours.

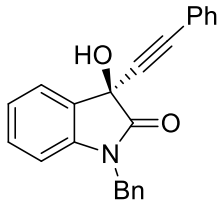
Table 2.3 Reaction Time Screening for Asymmetric Addition of Phenylacetylene to 1-benzylindoline-2,3-dione



S. No	Time (h)	Yield%	ee%
1	24	66	69
2	12	98	82
3	8	91	80

2.3.3.2 Scope of Ruthenium Catalyzed Addition of Alkynes to Isatin

2.2.3.2 (a) (*R*)-1-Benzyl-3-hydroxy-3-(2-phenylethynyl)indolin-2-one



498

According to General Procedure B, 1-benzylindoline-2,3-dione (47 mg, 0.2 mmol, 100 mol%) was treated with phenylacetylene (44 μL, 0.4 mmol, 200 mol%) using [Ru(COD)Cl$_2$]n catalyst (2.8 mg, 0.01 mmol, 5 mol%), and (*R*)-H$_8$-BINAP (7.6 mg, 0.012 mmol, 6 mol%) in THF at 90ºC for 12 hours. Flash column chromatography (SiO$_2$: *n*-hexane: ethylacetate 2.5:7.5) was performed to get white solid (55 mg, 81%, 92 % ee (*R*)) as pure product.

m.p. = 160-162 °C

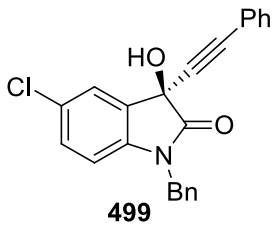
TLC; R_f = 0.25 (Ethyl acetate: *n*-hexane; 2:8).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, J = 7.8 Hz, 1H), 7.47 (dd, J = 8.1, 1.2 Hz, 2H), 7.23-7.39 (m, 9H), 7.15 (t, J = 7.5 Hz, 1H), 6.75 (d, J = 7.8 Hz, 1H), 4.95 (s, 2H), 4.02 (s, 1H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 174.3, 149.2, 146.0, 136.3, 132.2, 129.2, 128.8, 128.3, 127.8, 127.4, 124.7, 121.5, 120.8, 118.7, 118.4, 87.0, 85.1, 69.7, 45.8 ppm.

Chiral HPLC: The ee was measured by HPLC (Chiralcel AD-H column, λ = 254 nm, eluent: *n*-hexane/*i*-PrOH = 90/10, flow rate: 0.9 mL/min, t_1 = 15.16 min (*R*), t_2 = 22.12 min (*S*). Absolute stereochemistry was assigned by comparing the retention time with the literature.[101]

2.2.3.2 (b) (*R*)-1-Benzyl-5-chloro-3-hydroxy-3-(2-phenylethynyl)indolin-2-one



499

According to General Procedure B, 1-benzyl-5-chlorolindoline-2,3-dione (54 mg, 0.2 mmol, 100 mol%) was treated with phenylacetylene (44 μL, 0.4 mmol, 200 mol%) using [Ru(COD)Cl$_2$]n catalyst (2.8 mg, 0.01 mmol, 5 mol%), and (*R*)-H$_8$-BINAP (7.6 mg, 0.012 mmol, 6 mol%) in THF at 90^{o}C for 12 hours. Flash column chromatography (SiO_2: *n*-hexane: ethylacetate 2:8) was performed to get white solid (73 mg, 98%, 90% ee) as pure product.

m.p. = 157-159 °C,

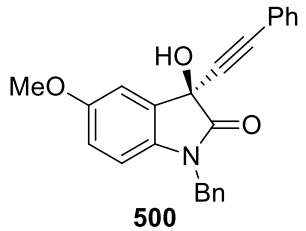
TLC; R_f = 0.31 (Ethyl acetate: *n*-hexane; 2:8)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (d, *J* = 2.1 Hz, 1H), 7.49-7.46 (m, 2H), 7.34-7.32 (m,1H), 7.32-7.29 (m, 6H),7.28-7.26 (m,1H), 6.65 (d, *J* = 8.4 Hz, 1H), 4.93 (s, 2H), 4.59 (s, 1H) ppm..

^{13}C NMR (75 MHz, $CDCl_3$): δ 174.0, 140.6, 134.6, 132.2, 130.5, 130.4, 129.3, 129.1, 128.6, 128.4, 128.1, 127.2, 125.5, 121.4, 111.1, 87.2, 84.8, 69.6, 44.3 ppm.

Chiral HPLC: The ee was measured by HPLC (Chiralcel AD-H column, λ = 254 nm, eluent: *n*-hexane/*i*-PrOH = 70/30, flow rate: 0.9 mL/min, t_1 = 14.69 min (*R*), t_2 = 15.89 min (*S*))

2.2.3.2 (c) (*R*)-1-Benzyl-5-methoxy-3-hydroxy-3-(2-phenylethynyl)indolin-2-one



500

According to General Procedure B, 1-benzyl-5-methoxylindoline-2,3-dione (53 mg, 0.2 mmol, 100 mol%) was treated with phenylacetylene (44 μL, 0.4 mmol, 200 mol%) using $[Ru(COD)Cl_2]n$ catalyst (2.8 mg, 0.01 mmol, 5 mol%) and (*R*)-H_8-BINAP (7.6 mg, 0.012 mmol, 6 mol%) in THF at 90°C for 12 hours. Flash column chromatography (SiO_2: *n*-hexane: ethylacetate 3:7) was used to get light brown solid (60 mg, 81%, 71% ee) as pure product.

m.p. = 158-160 °C

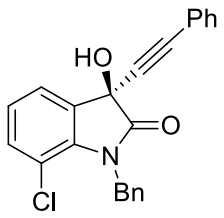
TLC: R_f = 0.17 (Ethyl acetate: *n*-hexane; 2:8).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49-7.46 (m, 2H), 7.34-7.29 (m, 6H), 7.29-7.26 (m, 3H), 6.78 (dd, *J* = 8.7, 2.1 Hz, 2H), 6.63 (d, *J* = 8.7, 1H) 4.92 (s, 2H), 3.80 (s, 3H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 174.2, 156.8, 135.4, 135.1, 132.2, 130.1, 129.1, 128.9, 128.3, 127.8, 127.3, 121.7, 115.5, 111.5, 110.7, 86.7, 85.6, 70.1, 55.9, 44.3 ppm.

Chiral HPLC: The ee was measured by HPLC (Chiralcel AD-H column, λ = 254 nm, eluent: *n*-hexane/*i*-PrOH = 70/30, flow rate: 0.9 mL/min, t_1 = 19.23 min (*R*), t_2 = 28.05 min (*S*))

2.2.3.2 (d) (*R*)-1-Benzyl-7-chloro-3-hydroxy-3-(2-phenylethynyl)indolin-2-one



501

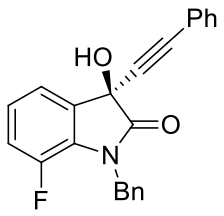
According to General Procedure B, 1-benzyl-7-chlorolindoline-2,3-dione (54 mg, 0.2 mmol, 100 mol%) was treated with phenylacetylene (44 μL, 0.4 mmol, 200 mol using $[Ru(COD)Cl)_2]n$ catalyst (2.8 mg, 0.01 mmol, 5 mol%) and (*R*)-H_8-BINAP (7.6 mg, 0.012 mmol, 6 mol%) in THF at 90°C for 12 hours. Flash column chromatography (SiO_2: *n*-hexane: ethylacetate 3:7) to get light brown solid (74 mg, 98%, 92% ee) as pure product.

m.p. = 151–153 °C

TLC: R_f = 0.32 (Ethyl acetate: *n*- hexane; 2:8).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49 (dd, J = 7.3, 1.2 Hz, 1H), 7.38-7.34 (m, 2H), 7.24 – 7.22 (m, 2H), 7.22 – 7.18 (m, 5H), 7.17-7.13 (m, 2H), 5.27 (s, 2H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$): δ 175.0, 138.3, 136.8, 132.9, 132.2, 131.8, 129.3, 128.8, 128.4, 127.5, 126.4, 124.9, 123.7, 121.5, 116.2, 87.1, 85.1, 69.2, 45.3 ppm.
Chiral HPLC: The ee was measured by HPLC (Chiralcel AD-H column, λ = 254 nm, eluent: *n*-hexane/*i*-PrOH = 90/10, flow rate: 0.9 mL/min, t_1 = 9.85 min (*R*), t_2 = 14.02 min (*S*))

2.2.3.2 (e) (*R*)-1-Benzyl-3-hydroxy-7-fluoro-3-(2-phenylethynyl)indolin-2-one



502

According to General Procedure B, 1-benzyl-7-fluorolindoline-2,3-dione (51 mg, 0.2 mmol, 100 mol%) wastreated with phenylacetylene (44 μL, 0.4 mmol, 200 mol%) using [Ru(COD)Cl)$_2$]n catalyst (2.8 mg, 0.01 mmol, 5 mol%) and (*R*)-H$_8$-BINAP (7.6 mg, 0.012 mmol, 6 mol%) in THF at 90^{o}C for 12 hours. Flash column chromatography (SiO$_2$: *n*-hexane: ethylacetate 2:8) to get white solid (70 mg, 98%, 92% ee) as pure product.

m.p. = 118–120 ^{o}C

TLC: R_f = 0.34 (Ethyl acetate: *n*-hexane; 2:8)

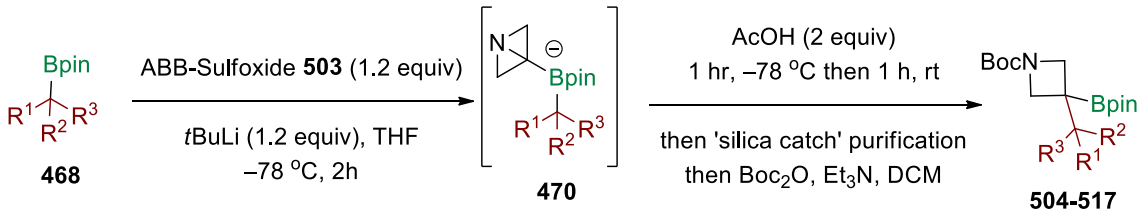
^{1}H NMR (300 MHz, CDCl$_3$): δ 7.40–7.35 (m, 6H), 7.30-7.28 (m, 2H), 7.25-7.21 (m, 3H), 7.17-7.06 (m, 2H), 5.02 – 4.98 (m, 2H) ppm.

^{13}C NMR (75 MHz, CDCl$_3$): δ 173.2, 148.3, 145.1, 136.7, 133.2, 131.6, 129.4, 128.8 (d, J = 9.8Hz), 127.5, 126.5, 124.6 (d, J = 6.3 Hz), 120.9, 120.6, 118.2, 117.9, 86.9, 85.0, 68.8 (d, J = 2.8 Hz), 44.7 (d, J = .4.7 Hz) ppm.

Chiral HPLC: The ee was measured by HPLC (Chiralcel AD-H column, λ = 254 nm, eluent: *n*-hexane/*i*-PrOH = 90/10, flow rate: 0.9 mL/min, t_1 = 9.74 min (*R*), t_2 = 12.89 min (*S*))

2.4 Part C: Synthesis of Azetidine Boronic Esters

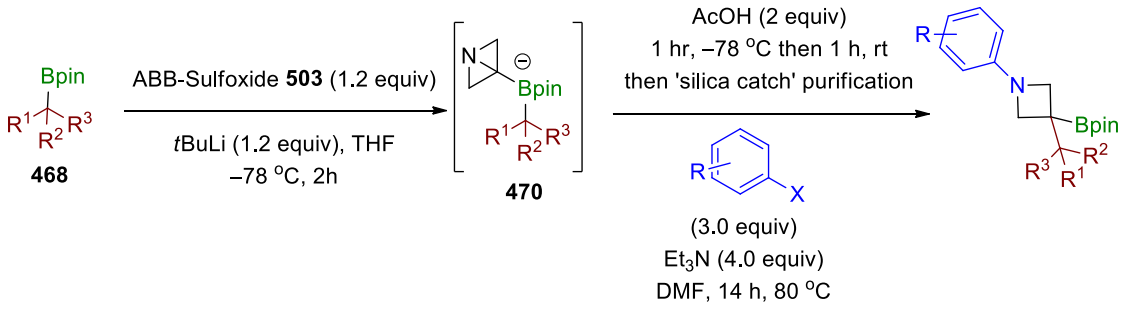
2.4.1 General Procedure A: Homologation of Boronic Esters with Azetidine



Scheme 2.11 General reaction for azetidine homologation of boronic esters

General Procedure A: In an oven dried, flame dried schlenk tube was added ABB-sulfoxide **503** (55 mg, 0.28 mmol, 1.2 equiv) and the boronic ester (0.24 mmol, 1.0 equiv) in anhydrous THF (2 mL) at –78 °C (dry ice/acetone) under nitrogen. *tert*-Butyl lithium (in pentane, 0.28 mmol, 1.2 equiv)was then added slowly dropwise. Resulting mixture was allowed to stir for 2 h at –78 °C. Acetic acid (0.03 mL, 0.48 mmol, 2.0 equiv) was then added and the mixture was stirred for 1 h at –78 °C again and eventually brought to room temperature and stirred for additional 1 h. Short column was packed with silica gel (10 mL silica, 2.5 cm diameter) and the crude reaction mixture was then directly added onto the top of a silica. The solvent (EtOAc) was then eluted through the silica plug and washed multiple times with EtOAc (ca. 30 mL total). The top layer of the silica (ca. 0.5 cm) was cautiously removed and added into a small round bottom flask. DCM (10 mL) was then added, di-*tert*-butyl dicarbonate (Boc_2O) (0.1 mL, ca. 0.48 mmol, ca. 2 equiv) followed by triethylamine (0.14 mL, 0.96 mmol, 4.0 equiv), and the resulting mixture was stirred overnight. The reaction mixture was then filtered through a plug of cotton wool and sand and then concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2) to yield the desired azetidines.

2.4.2 General Procedure B: S_NAr Reactions

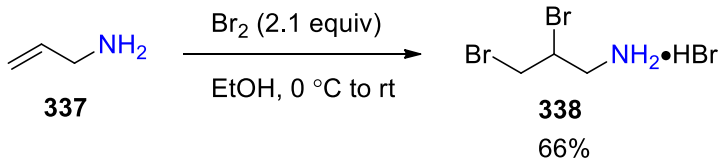


Scheme 2.12 General reaction for the synthesis of different protecting groups on nitrogen of azetidine

General Procedure B: According to General Procedure A, a boronic ester (0.24 mmol, 1.0 equiv) was homologated by an azetidine unit but with an alternative nitrogen reaction: To a flask containing the azetidine intermediate on silica was added DMF (5.0 mL), followed by the arene (0.72 mmol, 3.0 equiv) and triethylamine (0.14 mL, 0.96 mmol, 4.0 equiv), and the resulting mixture was left stirring overnight at 80 °C in an oil bath. The mixture was cooled and filtered through a plug of sand and cotton wool, using EtOAc (15 mL) as eluent. The solution was washed with water (20 mL), and the aqueous phase was extracted with EtOAc (3× 15 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude reside was purified by flash column chromatography (SiO_2) to afford the corresponding azetidines.

2.4.3 Synthesis of ABB-Sulfoxide

2.4.3.1 Synthesis of 2,3-Dibromopropan-1-ammonium bromide



Scheme 2.13 Synthesis of 2,3-dibromopropan-1-ammonium bromide

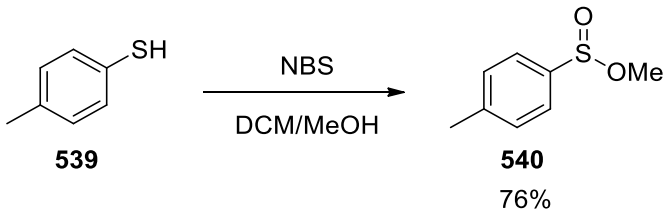
2,3-Dibromopropan-1-ammonium bromide was synthesized according to a literature procedure.[162] A flask containing ethanol (25 mL) at 0 °C was set to vigorous stirring then Br_2 (10 mL, 0.196 mol, 2.1 equiv) was added very slowly dropwise to ethanol. After the addition was complete, allylamine (7 mL, 0.09 mol, 1.0 equiv) was added very slowly dropwise under vigorous stirring at 0 °C. The mixture was warmed to room temperature and stirred for 16 h. Precipitate formed were collected *via* suction filtration and washed with small portions of ice-cold Et_2O. The crude material was then dissolved in the minimum amount of methanol and then a small amount of Et_2O was added until a white precipitate formed. After complete precipitation, the desired ammonium salt (18 g, 66%) was collected as a colorless solid via suction filtration and then thoroughly dried under high vacuum.

m.p.: 162 – 164 °C (MeOH/Et_2O)

^{1}H NMR (400 MHz, MeOD): δ 4.56 (dddd, J = 9.5, 8.6, 4.6, 3.2 Hz, 1H), 4.05 (dd, J = 11.0, 4.7 Hz, 1H), 3.90 (dd, J = 11.0, 8.6 Hz, 1H), 3.75 (dd, J = 14.0, 3.2 Hz, 1H), 3.39 (dd, J = 14.1, 9.6 Hz, 1H) ppm.

^{13}C NMR (101 MHz, MeOD): δ 47.9, 45.6, 34.0 ppm.

2.4.3.2 Methyl 4-methylbenzenesulfinate



539 **540**
76%

Scheme 2.14 Synthesis of Methyl 4-methylbenzenesulfinate

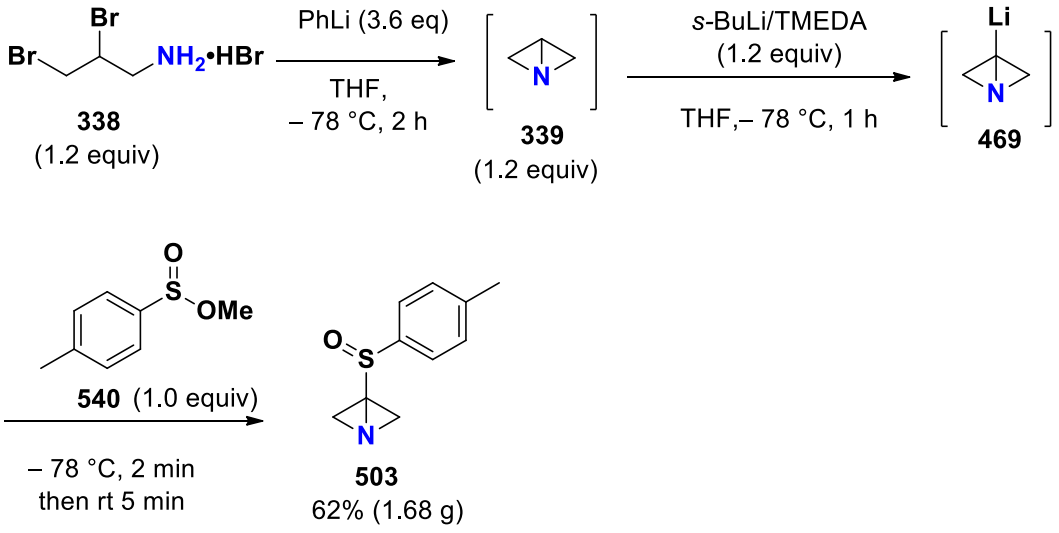
In a round bottom flask, 4-methylbenzenethiol (10 g, 80.4 mmol, 1.0 equiv) was dissolved in equal volume (100 mL each) of DCM and methanol at 0 °C. Resulting solution was stirred vigorously before adding *N*-bromosuccinimide (28.6 g, 161 mmol, 2.0 equiv) in one portion. The resulting solution was stirred at 0 °C for 1 h and the warmed to room temperature and stirred for further 1 h. This mixture was poured into saturated aqueous solution of $NaHCO_3$ (200 mL) at 0 °C and shaken until discoloration occured. The organic layer was separated and collected and the aqueous layer was extracted with DCM (2× 100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography (SiO_2; 67:30:3 pentane:DCM:EtOAc) was performed to purify the crude residue and sulfinate was obtained as a colorless oil (10.5 g, 76%).

TLC: R_f= 0.24 (pentane:DCM:EtOAc; 67:30:3)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 – 7.57 (m, 2H), 7.35 – 7.33 (m, 2H), 3.46 (s, 3H), 2.43 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 143.0, 141.1, 129.9, 125.5, 49.5, 21.6 ppm.

2.4.3.3 3-(p-Tolylsulfinyl)-1-azabicyclo[1.1.0]butane (ABB-sulfoxide)



Scheme 2.15 Synthesis of ABB-sulfoxide **503**

Azabicyclobutane was synthesized according to a literature procedure[1]. Phenyl lithium (in Bu_2O, 50.4 mmol, 3.6 equiv) was added dropwise using a syringe pump at a rate of 0.5 mL/min to a suspension of 2,3-dibromopropan-1-ammonium bromide salt (5.0 g, 16.8 mmol, 1.2 equiv) in anhydrous tetrahydrofuran (51 mL) at −78 °C (dry ice/acetone). After complete addition, the resulting solution was stirred for a further 2 h at −78 °C. TMEDA (2.5 mL, 16.8 mmol, 1.2 equiv) and *sec*-butyl lithium (in hexane, 16.8 mmol, 1.2 equiv) were then added dropwise using a syringe pump at a rate of 0.5 mL/min and the resulting solution was stirred for another 1 h at −78 °C. Methyl 4-methylbenzenesulfinate (2.1 mL, 14 mmol, 1.0 equiv) was then added dropwise and the resulting solution was stirred for 2 min and then cooling bath was removed and mixture was brought to the room temperature. Water (100 mL) was then added to quench the reaction, and the mixture was extracted with EtOAc (3× 75 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2; 50:50 hexane:EtOAc) to give the desired sulfoxide (1.68 g, 62%) as a pale yellow solid.

TLC: R_f = 0.13 (*n*-hexane:EtOAc; 70:30)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 – 7.56 (m, 2H), 7.36 – 7.33 (m, 2H), 2.94 (dd, J = 6.2, 2.4 Hz, 1H), 2.57 (dd, J = 6.2, 2.2 Hz, 1H), 2.42 (s, 3H), 1.67 – 1.65 (m, 2H) ppm.

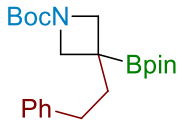
^{13}C NMR (101 MHz, $CDCl_3$): δ 142.5, 138.0, 130.1, 125.0, 56.3, 55.5, 44.3, 21.6 ppm.

HRMS (m/z): (ESI) calculated for $C_{10}H_{11}NNaOS$ $[M+Na]^+$: 216.0454, found: 216.0454.

2.4.4 Substrate Scope

2.4.4.1 Primary Boronic Esters

2.4.4.1 (a) *tert*-Butyl 3-phenethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidine-1- carboxylate



504

According to **General Procedure A**, phenethyl pinacol boronic ester[163] (56 mg, 0.24 mmol, 1.0 equiv) was reacted with ABB-sulfoxide **503** and Boc_2O to give a crude reside. Flash column chromatography (SiO_2; 85:15 pentane:EtOAc) provided the pure azetidine (39 mg, 42%) as a colorless oil.

TLC: R_f = 0.24 (pentane:EtOAc; 85:15)

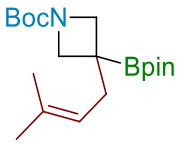
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 – 7.26 (m, 2H), 7.20 – 7.16 (m, 3H), 4.01 (d, J = 8.2 Hz, 2H), 3.57 (d, J = 8.2 Hz, 2H), 2.56 – 2.52 (m, 2H), 2.03 – 1.99 (m, 2H), 1.44 (s, 9H), 1.29 (s, 12H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.6, 142.2, 128.5, 128.4, 126.0, 84.0, 79.3, 39.5, 33.2, 28.6, 24.9 ppm.

HRMS (*m/z*): (ESI) calculated for $C_{22}H_{34}BNNaO_4$ $[M+Na]^+$: 410.2477, found: 410.2494

IR (thin film) ν_{max}: 2977, 2931, 1702, 1380, 1323, 1141 and 853 cm^{-1}

2.4.4.1 (b) *tert*-Butyl 3-(3-methylbut-2-en-1-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2- yl)azetidine-1-carboxylate



505

According to **General Procedure A**, 3-methylbut-2-en-1-yl pinacol boronic ester[164] (47 mg, 0.24 mmol, 1.0 equiv) was reacted with ABB-sulfoxide **503** and Boc_2O to give a crude reside. Flash column chromatography (SiO_2; 90:10 pentane:EtOAc) provided the pure azetidine (42 mg, 50%) as a colorless oil.

TLC: R_f = 0.21 (pentane:EtOAc; 90:10)

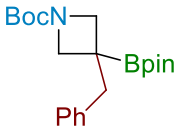
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.04 – 5.00 (m, 1H), 3.95 (d, J = 8.1 Hz, 2H), 3.56 (d, J = 8.1 Hz, 2H), 2.37 (d, J = 6.9 Hz, 2H), 1.67 (s, 3H), 1.64 (s, 3H), 1.43 (s, 9H), 1.23 (s, 12H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.7, 133.8, 120.8, 83.9, 79.1, 35.5, 28.6, 26.1, 24.8, 18.3 ppm.

HRMS (*m/z*): (ESI) calculated for $C_{19}H_{35}BNO_4$ $[M+H]^+$: 352.2657, found: 352.2648

IR (thin film) ν_{max}: 2976, 2930, 2872, 1701, 1372, 1321, 1167, 1138, 1064 and 852 cm^{-1}

2.4.4.1 (c) *tert*-Butyl 3-benzyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidine-1- carboxylate



506

According to General Procedure A, benzyl pinacol boronic ester (51 mg, 0.24 mmol, 1.0 equiv) was reacted with ABB-sulfoxide **503** and Boc_2O to give a crude reside. Flash column chromatography (SiO_2; 80:20 pentane:EtOAc) provided the pure azetidine (59 mg, 68%) as a colorless oil.

TLC: R_f = 0.31 (pentane:EtOAc; 80:20)

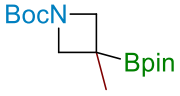
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 – 7.22 (m, 2H), 7.19 – 7.15 (m, 3H), 4.01 (d, J = 8.3 Hz, 2H), 3.73 (d, J = 8.3 Hz), 3.05 (s, 2H), 1.44 (s, 9H), 1.17 (s, 12H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.7, 139.6, 129.0, 128.4, 126.4, 84.1, 79.3, 42.6, 28.6, 24.8 ppm.

HRMS (m/z): (ESI) calculated for $C_{21}H_{32}BNaNO_4$ $[M+Na]^+$: 396.2320, found: 396.2321

IR (thin film) ν_{max}: 2977, 1699, 1364, 1322, 1137, 849 and 701 cm^{-1}

2.4.4.1 (a)d*tert*-Butyl 3-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidine-1- carboxylate



507

According to **General Procedure A**, methyl pinacol boronic ester[165] (34 mg, 0.24 mmol, 1.0 equiv) was reacted with ABB-sulfoxide **503** and Boc_2O to give a crude

reside. Flash column chromatography (SiO_2; 85:15 pentane:EtOAc) provided the pure azetidine (26 mg, 37%) as a colorless oil.

TLC: R_f = 0.27 (pentane:EtOAc; 85:15)

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.01 (d, J = 8.0 Hz, 2H), 3.48 (d, J = 8.0 Hz), 1.43 (s, 9H), 1.29 (s, 3H), 1.25 (s, 12H) ppm.

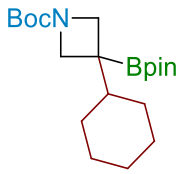
^{13}C NMR (101 MHz, $CDCl_3$): δ 156.7, 83.9, 79.2, 28.6, 24.8, 22.7 ppm.

HRMS (*m/z*): (ESI) calculated for $C_{15}H_{28}BNaNO_4$ $[M+Na]^+$: 320.2006, found: 320.2020

IR (thin film) ν_{max}: 2976, 2872, 1700, 1364, 1321, 1140, 1093 and 850 cm^{-1}

2.4.4.2 Secondary Boronic Esters

2.4.4.2 (a) *tert*-Butyl 3-cyclohexyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidine-1- carboxylate



508

According to **General Procedure A**, cyclohexyl pinacol boronic ester (50 mg, 0.24 mmol, 1.0 equiv) was reacted with ABB-sulfoxide **503** and Boc_2O to give a crude reside. Flash column chromatography (SiO_2; 90:10 pentane:EtOAc) provided the pure azetidine (66 mg, 76%) as a white solid.

m.p.: 119 – 121 °C (pentane)

TLC: R_f = 0.24 (pentane:EtOAc; 90:10)

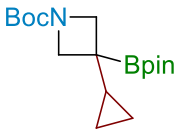
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.92 (d, J = 8.2 Hz, 2H), 3.64 (d, J = 8.2 Hz, 2H), 1.76 – 1.63 (m, 6H), 1.55 – 1.48 (m, 1), 1.43 (s, 9H), 1.25 (s, 12H), 1.22 – 0.94 (m, 4H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.6, 83.8, 79.1, 45.4, 29.1, 28.6, 26.7, 24.9 ppm.

HRMS (*m/z*): (ESI) calc'd for $C_{20}H_{36}BNNaO_4$ $[M+Na]^+$: 388.2633, found: 388.2648

IR (solid state) ν_{max}: 2925, 1694, 1374, 1360, 1320, 1139 and 858 cm^{-1}

2.4.4.2 (b) *tert*-Butyl 3-cyclopropyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidine-1- carboxylate



509

According to **General Procedure A**, cyclopropyl pinacol boronic ester (0.04 mL, 0.24 mmol, 1.0 equiv) was reacted with ABB-sulfoxide **503** and Boc_2O to give crude reside. Flash column chromatography (SiO_2; 90:10 pentane:EtOAc) provided the pure azetidine (46 mg, 61%) as a colorless oil.

TLC: R_f = 0.15 (pentane:EtOAc; 90:10)

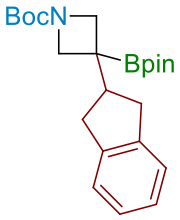
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.91 (d, J = 8.2 Hz, 2H), 3.51 (d, J = 8.2 Hz, 2H), 1.42 (s, 9H), 1.25 (s, 12H), 1.10 – 1.03 (m, 1H), 0.46 – 0.42 (m, 2H), 0.31 – 0.27 (m, 2H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.6, 83.9, 79.2, 28.6, 24.9, 15.6, 1.4 ppm.

HRMS (*m/z*): (ESI) calculated for $C_{17}H_{30}BNNaO_4$ $[M+Na]^+$: 346.2163, found: 346.2180

IR (thin film) ν_{max}: 2977, 2878, 1700, 1378, 1319, 1138, 1110 and 860 cm^{-1}

2.4.4.2 (c) *tert*-Butyl 3-(2,3-dihydro-1*H*-inden-2-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2- yl)azetidine-1-carboxylate



510

According to **General Procedure A**, 2-(2,3-dihydro-1*H*-inden-2-yl) pinacol boronic ester[166] (58 mg, 0.24 mmol, 1.0 equiv) was reacted with ABB-sulfoxide **503** and Boc_2O to give a crude reside. Flash column chromatography (SiO_2; 85:15 pentane:EtOAc) afforded the pure azetidine (59 mg, 62%) as a white solid.

m.p.: 128 – 132 °C (pentane)

TLC: R_f = 0.29 (pentane:EtOAc; 85:15)

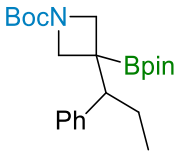
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 – 7.15 (m, 2H), 7.13 – 7.09 (m, 2H), 4.01 (d, J = 8.4 Hz, 2H), 3.70 (d, J = 8.4 Hz, 2H), 3.04 (dd, J = 15.2, 8.0 Hz, 2H), 2.88 (app p, J = 7.6 Hz, 1H), 2.77 (dd, J = 15.2, 6.9 Hz, 2H), 1.44 (s, 9H), 1.13 (s, 12H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.6, 143.0, 126.4, 124.7, 83.9, 79.3, 44.8, 35.6, 28.6, 24.8 ppm.

HRMS (*m/z*): (ESI) calculated for $C_{23}H_{34}BNNaO_4$ $[M+Na]^+$: 422.2477, found: 422.2475

IR (thin film) ν_{max}: 2976, 1699, 1365, 1321 and 1139 cm^{-1}

2.4.4.2 (d) *tert*-Butyl 3-(1-phenylpropyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidine-1- carboxylate



511

According to **General Procedure A**, 1-phenylpropyl pinacol boronic ester[167] (59 mg, 0.24 mmol, 1.0 equiv) was reacted with ABB-sulfoxide **503** and Boc_2O to give a crude reside. Flash column chromatography (SiO_2; 90:10 pentane:EtOAc) afforded the pure azetidine (66 mg, 69%) as a colorless oil.

TLC: R_f = 0.20 (pentane:EtOAc; 90:10)

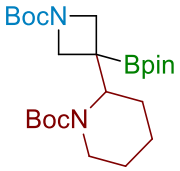
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 – 7.16 (m, 5H), 3.98 (d, J = 8.3 Hz, 1H), 3.85 – 3.81 (m, 2H), 3.74 – 3.59 (br m, 1H), 2.68 – 2.64 (m, 1H), 1.84 – 1.78 (m, 2H), 1.42 (s, 9H), 1.18 (s, 12H), 0.76 (t, J = 7.3 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$:) δ 156.6, 142.8, 128.8, 128.3, 126.6, 83.8, 77.5, 28.6, 24.9, 24.8, 12.8 ppm. *$N(CH_2)_2$ was not observed.*

HRMS (*m/z*): (ESI) calculated for $C_{23}H_{37}BNO_4$ $[M+H]^+$: 402.2814, found: 402.2809

IR (thin film) ν_{max}: 2975, 1699, 1364, 1318, 1137, 855 and 701 cm^{-1}

2.4.4.2 (e) *tert*-Butyl 2-(1-(*tert*-butoxycarbonyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2- yl)azetidin-3-yl)piperidine-1-carboxylate



512

According to **General Procedure A**, tert-butyl 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2- yl)piperidine-1-carboxylate[168] (75 mg, 0.24 mmol, 1.0 equiv was reacted with ABB-sulfoxide **503** and Boc_2O to give a crude reside. Flash column chromatography (SiO_2; 75:25 pentane:EtOAc) afforded the pure azetidine (60 mg, 54%) as a colorless oil that solidified slowly upon standing.

m.p.: 110 – 114 °C (DCM)

TLC: R_f = 0.19 (pentane:EtOAc; 75:25)

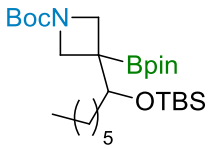
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.99 (d, J = 8.1 Hz, 1H)), 3.88 (d, J = 8.1 Hz, 1H), 3.74 – 3.54 (br m, 3H), 1.79 – 1.65 (br m, 8H), 1.44 (s, 9H), 1.42 (s, 9H), 1.23 (s, 12H) ppm.

^{13}C NMR (101 MHz, $CDCl_{3:}$) δ 155.7 (C=O), 80.7, 79.0, 28.6, 25.3 ppm.

HRMS (*m/z*): (ESI) calculated for $C_{24}H_{43}BN_2NaO_6$ $[M+Na]^+$: 489.3111, found: 489.3119

IR (thin film) ν_{max}: 2975, 2931, 1698, 1365, 1141 and 1027 cm^{-1}

2.4.4.2 (f) *tert*-Butyl 3-(1-((*tert*-butyldimethylsilyl)oxy)heptyl)-3-(4,4,5,5-tetramethyl-1,3,2- dioxaborolan-2-yl)azetidine-1-carboxylate



513

According to **General Procedure A**, *tert*-butyldimethyl((1-(4,4,5,5-tetramethyl-1,3,2- dioxaborolan-2-yl)heptyl)oxy)silane[169] (86 mg, 0.24 mmol, 1.0 equiv) was reacted with ABB-sulfoxide **503** and Boc_2O to give a crude reside. Flash column chromatography (SiO2; 93:7 to 90:10 pentane:EtOAc) to afford the corresponding azetidine (73 mg, 59%) as a colorless oil.

TLC: R_f = 0.12 (pentane:EtOAc; 93:7)

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.96 (d, J = 7.5 Hz, 1H), 3.90 (d, J = 7.5 Hz, 1H), 3.83 (t, J = 4.4 Hz, 1H), 3.80 (d, J = 8.1 Hz, 1H), 3.70 (d, J = 8.1 Hz, 1H), 1.41 (s, 9H), 1.29 – 1.23 (m, 22H, Bpin), 0.90 (s, 9H), 0.88 (t, J = 7.0 Hz, 3H), 0.08 (s, 3H), 0.07 (s, 3H) ppm.

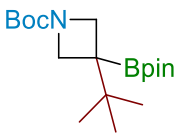
^{13}C NMR (101 MHz, $CDCl_3$): δ 156.4, 83.8, 78.9, 74.0, 36.5, 31.8, 29.9, 28.6, 26.1, 24.9, 24.8, 22.7, 18.4, 14.2, −3.6, −4.3 ppm. *$N(CH_2)_2$ was not observed.*

HRMS (*m/z*): (ESI) calc'd for $C_{27}H_{55}BNO_5Si$ $[M+H]^+$: 512.3942, found: 512.3938

IR (thin film) ν_{max}: 2929, 2857, 1703, 1365, 1320, 1254, 1141, 1065, 833 and 772 cm^{-1}

2.4.4.3 Tertiary Boronic Esters

2.4.4.3 (a) *tert*-Butyl 3-(*tert*-butyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidine-1- carboxylate



514

According to **General Procedure A**, *tert*-butyl pinacol boronic ester (44 mg, 0.24 mmol, 1.0 equiv) was reacted with ABB-sulfoxide **503** and Boc_2O to give a crude reside. Flash column chromatography (SiO_2; 90:10 pentane:EtOAc) afforded the pure azetidine (51 mg, 63%) as a colorless oil.

TLC: R_f = 0.24 (pentane:EtOAc; 90:10)

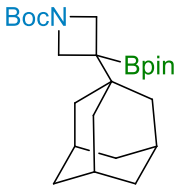
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.87 (d, J = 8.8 Hz, 2H), 3.72 (d, J = 8.8 Hz, 2H), 1.42 (s, 9H), 1.25 (s, 12H), 0.93 (s, 9H) ppm.

^{13}C NMR (101 MHz, CDCl3): δ 156.5, 83.8, 79.1, 53.2, 51.8, 32.7, 28.6, 26.0, 24.9 ppm.

HRMS (*m/z*): (ESI) calculated for $C_{18}H_{34}BNNaO_4$ $[M+Na]^+$: 362.2476, found: 362.2487

IR (thin film) ν_{max}: 2977, 1693, 1350, 1311, 1166, 1134, 1104, 919, 852 and 731 cm^{-1}

2.4.4.3 (b) *tert*-Butyl 3-(adamantan-1-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidine- 1-carboxylate



515

According to **General Procedure A**, adamantyl pinacol boronic ester[166] (63 mg, 0.24 mmol, 1.0 equiv) was reacted with ABB-sulfoxide **503** and Boc_2O to give a crude reside. Flash column chromatography (SiO2; 90:10 pentane:EtOAc) afforded the pure azetidine (86 mg, 86%) as a white solid.

m.p.: 107 – 110 °C (DCM)

TLC: R_f = 0.23 (pentane:EtOAc; 90:10)

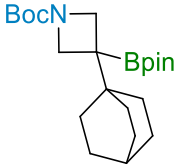
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.85 – 3.79 (m, 4H), 1.98 (br s, 3H), 1.72 – 1.58 (m, 12H), 1.42 (s, 9H), 1.26 (s, 12H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.5, 83.8, 79.1, 37.6, 37.2, 34.2, 28.6, 28.5, 24.9 ppm. *$N(CH_2)_2$ was not observed.*

HRMS (*m/z*): (ESI) calculated for $C_{24}H_{41}BNO_4$ $[M+H]^+$: 418.3128, found: 418.3136

IR (solid state) ν_{max}: 2976, 2901, 2849, 1698, 1351, 1141, 1073 and 855 cm^{-1}

2.4.4.3 (c) *tert*-Butyl 3-(4-pentylbicyclo[2.2.2]octan-1-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan- 2-yl)azetidine-1-carboxylate



516

According to **General Procedure A**, 4-pentylbicyclo[2.2.2]octan-1-yl pinacol boronic ester[166] (72 mg, 0.24 mmol, 1.0 equiv) was reacted with ABB-sulfoxide **503** and Boc_2O to give a crude reside. Flash column chromatography (SiO2; 90:10 pentane:EtOAc) provided the pure azetidine (75 mg, 69%) as a colorless oil.

TLC: R_f = 0.25 (pentane:EtOAc; 90:10)

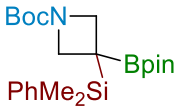
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.81 – 3.76 (m, 4H), 1.47 – 1.01 (m, 20H), 1.42 (s, 9H), 1.25 (s, 12H), 0.86 (t, J = 7.2 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.5, 83.7, 79.0, 41.8, 33.3, 33.0, 31.1, 30.7, 28.6, 27.0, 24.9, 23.5, 22.9, 14.2 ppm.

HRMS (*m/z*): (ESI) calculated for $C_{27}H_{48}BNNaO_4$ $[M+Na]^+$: 484.3573, found: 484.3562

IR (thin film) ν_{max}: 2928, 2857, 1702, 1352 and 1142 cm^{-1}

2.4.4.3 (d) *tert*-Butyl 3-(dimethyl(phenyl)silyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2- yl)azetidine-1-carboxylate



517

According to **General Procedure A**, (dimethylphenylsilyl) pinacol boronic ester (0.07 mL, 0.24 mmol, 1.0 equiv) was reacted with ABB-sulfoxide **503** and Boc_2O to give a crude reside. Flash column chromatography (SiO_2; 90:10 pentane:EtOAc) afforded the pure azetidine (71 mg, 71%) as a colorless oil.

TLC: R_f = 0.21 (pentane:EtOAc; 90:10)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 – 7.50 (m, 2H), 7.37 – 7.30 (m, 3H), 4.11 (d, J = 7.6 Hz, 2H), 3.95 (br s, 2H), 1.38 (s, 9H), 1.15 (s, 12H), 0.37 (s, 6H) ppm.

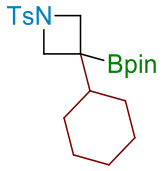
^{13}C NMR (101 MHz, $CDCl_3$): δ 156.1, 136.7, 134.2, 129.5, 127.9, 83.7, 79.2, 28.5, 24.9, −5.1 ppm. *$N(CH_2)_2$ was not observed.*

HRMS (*m/z*): (ESI) calculated for $C_{22}H_{37}BNO_4Si$ $[M+H]^+$: 418.2584, found: 418.2581

IR (solid state) ν_{max}: 2977, 2874, 1700, 1335, 1251, 1128, 834, 813, 774 and 700 cm^{-1}

2.4.5 Alternative Protecting Groups and Nitrogen Reactions

2.4.5 (a) 3-Cyclohexyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosylazetidine



518

According to **General Procedure A**, cyclohexyl pinacol boronic ester (50 mg, 0.24 mmol, 1.0 equiv) was homologated by an azetidine unit but with an alternative nitrogen protection: Dichloromethane (10 mL) is added to a flask containing the intermediate on silica, followed by triethylamine (0.14 mL, 0.96 mmol, 4.0 equiv) and tosyl chloride (92 mg, 0.48 mmol, 2.0 equiv), and the resulting mixture is stirred overnight. The crude reside was purified by flash column chromatography (SiO_2; 90:10 pentane:EtOAc) to afford the corresponding azetidine (64 mg, 64%) as a white solid.

m.p.: 160 – 164 °C (pentane)

TLC: R_f = 0.35 (pentane:EtOAc; 90:10)

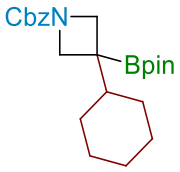
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 – 7.71 (m, 2H), 7.37 – 7.35 (m, 2H), 3.75 (d, J = 7.7 Hz, 2H), 3.54 (d, J = 7.7 Hz, 2H), 2.44 (s, 3H), 1.69 – 1.50 (m, 6H), 1.31 – 0.96 (m, 3H), 1.12 (s, 12H), 0.88 – 0.78 (m, 2H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 143.7, 131.6, 129.7, 128.7, 83.9, 56.6, 44.5, 29.0, 26.5, 24.7, 21.7 ppm.

HRMS (*m/z*): (ESI) calculated for $C_{22}H_{34}BNNaO_4S$ $[M+Na]^+$: 442.2198, found: 442.2199

IR (solid state) ν_{max}: 2925, 2850, 1340, 1358, 1162, 1142, 1093, 854, 817, 674, 619 and 547 cm^{-1}

2.4.5 (b) Benzyl 3-cyclohexyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidine-1-carboxylate



519

According to **General Procedure A**, cyclohexyl pinacol boronic ester (50 mg, 0.24 mmol, 1.0 equiv) was homologated by an azetidine unit but with an alternative nitrogen protection: Dichloromethane (10 mL) is added to a flask containing the intermediate on silica, followed by triethylamine (0.14 mL, 0.96 mmol, 4.0 equiv) and benzyl chloroformate (0.07 mL, 0.48 mmol, 2.0 equiv), and the resulting mixture is stirred overnight. The crude reside was purified by flash column chromatography (SiO_2; 90:10 pentane:EtOAc) to afford the corresponding azetidine (60 mg, 63%) as a white solid.

m.p.: 114 – 116 °C (pentane)

TLC: R_f = 0.54 (pentane:EtOAc; 80:20)

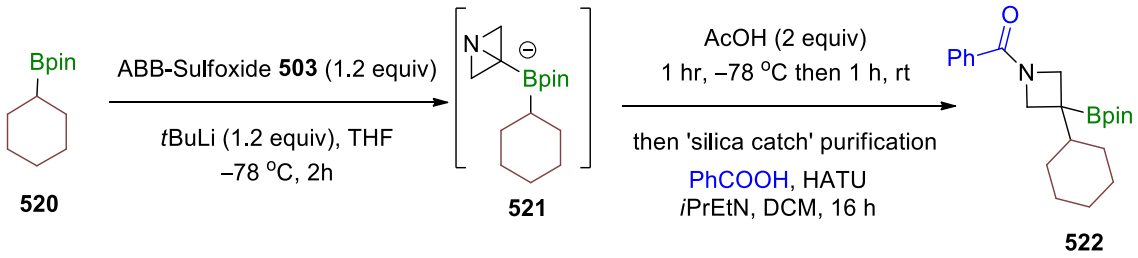
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.27 (m, 5H), 5.08 (s, 2H), 4.02 (d, J = 8.3 Hz, 2H), 3.73 (d, J = 8.3 Hz, 2H), 1.76 – 1.62 (m, 4H), 1.56 – 1.49 (m,1H)), 1.25 (s, 12H), 1.22 – 0.95 (m, 6H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.6, 137.1, 128.5, 128.0, 83.8, 66.5, 45.3, 29.0, 26.7, 24.9 ppm.

HRMS (*m/z*): (ESI) calculated for $C_{23}H_{34}BNNaO_4$ $[M+Na]^+$: 422.2477, found: 422.2463

IR (solid state) ν_{max}: 2924, 2850, 1705, 1390, 1358, 1320, 1162, 1142, 1114, 699, 674 and 547cm^{-1}

2.4.5 (c) (3-Cyclohexyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidin-1-yl)(phenyl) methanone



Scheme 2.16 Amide coupling of azetidine N-H intermediate

According to **General Procedure A**, cyclohexyl pinacol boronic ester **520** (50 mg, 0.24 mmol, 1.0 equiv) was homologated by an azetidine unit but with an alternative nitrogen protection: the gathered silica layer containing the intermediate was added to a flask containing *N*,*N*-diisopropylethylamine (0.17 mL, 0.96 mmol, 4.0 equiv), HATU (128 mg, 0.34 mmol, 1.4 equiv) and benzoic acid (35 mg, 0.28 mmol, 1.2 equiv) in dichloromethane (10 mL) (pre-stirred for 20 min), and the resulting mixture was stirred overnight. The crude reside was purified by flash column chromatography (SiO_2; 40:60 hexane:EtOAc) to afford the corresponding azetidine **522** (62 mg, 70%) as a white solid.

m.p.: 90 – 92 °C (pentane)

TLC: R_f = 0.24 (*n*-hexane:EtOAc; 30:70)

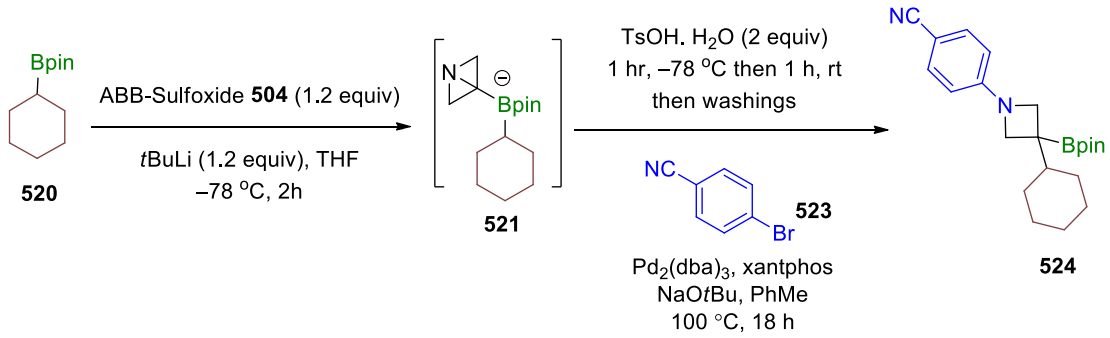
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 – 7.64 (m, 2H), 7.46 – 7.37 (m, 3H), 4.34 (d, J = 8.4 Hz, 1H), 4.17 (d, J = 9.9 Hz, 1H), 3.97 – 3.94 (m, 2H), 1.77 – 1.52 (m, 6H), 1.26 (s, 9H), 1.24 – 0.93 (m, 5H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.2, 133.7, 130.8, 128.4, 128.1, 84.0, 59.5, 54.6, 45.4, 29.1, 29.0, 26.6, 24.9 ppm.

HRMS (*m/z*): (ESI) calculated for $C_{22}H_{32}BNNaO_3$ $[M+Na]^+$: 392.2385, found: 392.2371

IR (solid state) ν_{max}: 2925, 2850, 1629, 1379, 1358, 1318, 1167, 1142, 1236, 964, 850, 712 and 701 cm^{-1}

2.4.5 (d) 4-(3-Cyclohexyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidin-1-yl) benzonitrile



Scheme 2.17 Buchwald-Hartwig coupling of azetidine N-H intermediate

ABB-sulfoxide (55 mg, 0.28 mmol, 1.2 equiv) and cyclohexyl boronic ester (50 mg, 0.24 mmol, 1.0 equiv) were added in anhydrous THF (2 mL) at –78 °C (dry ice/acetone) followed by dropwise addition of *tert*-butyl lithium (in pentane, 0.28 mmol, 1.2 equiv) and the resulting mixture was allowed to stir for 2 h. *p*-Toluenesulfonic acid monohydrate (138 mg, 0.72 mmol, 3.0 equiv) was then added and the mixture was stirred for 1 h at –78 °C (dry ice/acetone) then warmed to ambient temperature and stirred for a further 1 h. Pentane (4 mL) was then added and then the precipitate was allowed to settle. The solvent was carefully removed using a syringe. This pentane wash and solvent removal was then repeated twice. 4-Bromobenzonitrile (44 mg, 0.24 mmol, 1.0 equiv), tris(dibenzylideneacetone)dipalladium(0) (6.6 mg, 7 µmol, 3 mol%), Xantphos (8.3 mg, 14 µmol, 6 mol%), sodium *tert*-butoxide (69 mg, 0.72 mmol, 3 equiv) and toluene (2.4 mL) were then added, and the mixture was stirred at 100 °C for 18 h (oil bath). The reaction mixture was allowed to cool to ambient temperature and then filtered through a short pad of silica and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2; 90:10 pentane:EtOAc) to afford the corresponding azetidine **524** (63 mg, 71%) as a white solid.

m.p.: 196 – 198 °C (Et_2O)

TLC: R_f = 0.54 (hexane:EtOAc; 80:20)

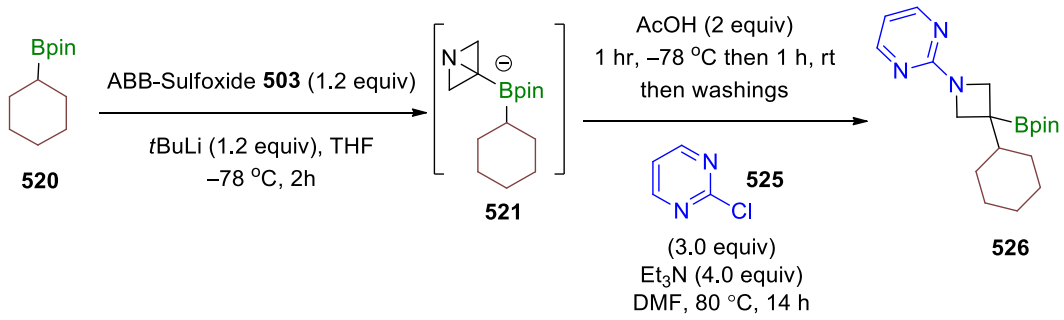
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.39 (m, 2H), 6.33 – 6.29 (m, 2H), 3.99 (d, J = 7.4 Hz, 2H), 3.66 (d, J = 7.4 Hz, 2H), 1.78 – 1.54 (m, 5H), 1.30 – 0.99 (m, 5H), 1.27 (s, 12H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 153.6, 133.4, 121.0, 110.3, 97.7, 84.0, 57.4, 45.6, 29.2, 26.7, 24.9 ppm.

HRMS (*m/z*): (MALDI) calculated for $C_{22}H_{31}BN_2NaO_2$ $[M+Na]^+$: 389.2384, found: 389.2374

IR (solid state) ν_{max}: 2977, 2924, 2848, 2215, 1604, 1519, 1479, 1372, 1360, 1324, 1137, 1171, 963, 857, 829, 687, 549, 481, 423 and 409 cm^{-1}

2.4.5 (e) 2-(3-Cyclohexyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidin-1-yl)pyrimidine



Scheme 2.18 S_NAr reaction of azetidine N-H intermediate

According to **General Procedure B**, cyclohexyl pinacol boronic ester (50 mg, 0.24 mmol, 1.0 equiv) was homologated by an azetidine unit and the azetidine nitrogen atom arylated using 2-chloropyrimidine (82 mg, 0.71 mmol, 3.0 equiv) to give a crude residue, which was purified by flash column chromatography (SiO_2; 60:40 pentane:EtOAc) to afford the corresponding arylated azetidine **526** (53 mg, 65%) as a white solid.

m.p.: 148 – 151 °C (Et_2O)

TLC: R_f = 0.26 (pentane:EtOAc; 60:40)

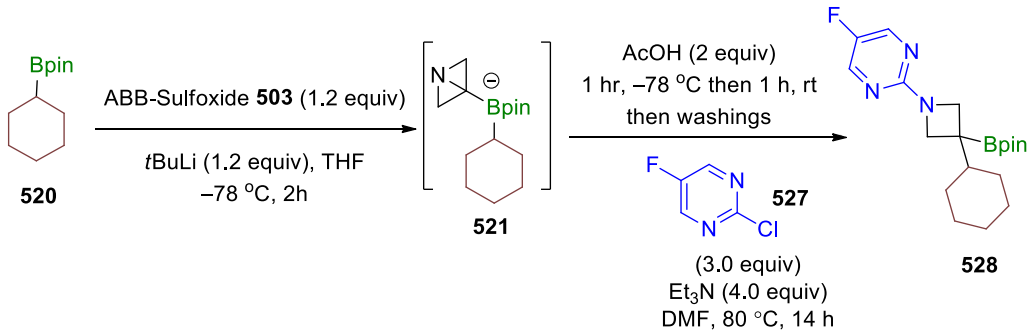
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, J = 4.8 Hz, 2H), 6.46 (t, J = 4.8 Hz, 1H), 4.15 (d, J = 8.4 Hz, 2H), 3.86 (d, J = 8.4 Hz, 2H), 1.76 – 1.57 (m, 6H), 1.25 (s, 12H), 1.22 – 1.01 (m, 5H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 162.7, 158.0, 109.7, 83.7, 55.8, 45.4, 29.1, 26.7, 24.9 ppm.

HRMS (*m/z*): (ESI) calculated for $C_{19}H_{30}BN_3NaO_2$ $[M+Na]^+$: 366.2327, found: 366.2330

IR (solid state) ν_{max}: 2924, 2851, 1581, 1549, 1506, 1387 and 1140 cm^{-1}

2.4.5 (f) 2-(3-Cyclohexyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidin-1-yl)-5- fluoropyrimidine



Scheme 2.19 S_NAr reaction of azetidine N-H intermediate

According to **General Procedure B**, cyclohexyl pinacol boronic ester (50 mg, 0.24 mmol, 1.0 equiv) was homologated by an azetidine unit and the azetidine nitrogen atom arylated using 2-chloro-5-fluoropyrimidine (133 mg, 0.71 mmol, 3.0 equiv) to give a crude residue, which was purified by flash column chromatography (SiO_2; 90:10 pentane:EtOAc) to afford the corresponding arylated azetidine **528** (47 mg, 55%) as a colorless solid.

m.p.: 131 – 133 °C (Et_2O)

TLC: R_f = 0.23 (pentane:EtOAc; 90:10)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (s, 2H), 4.12 (d, J = 8.3 Hz, 2H), 3.83 (d, J = 8.3 Hz), 1.77 – 1.56 (m, 6H), 1.25 (s, 12H), 1.22 – 1.00 (m, 5H) ppm.

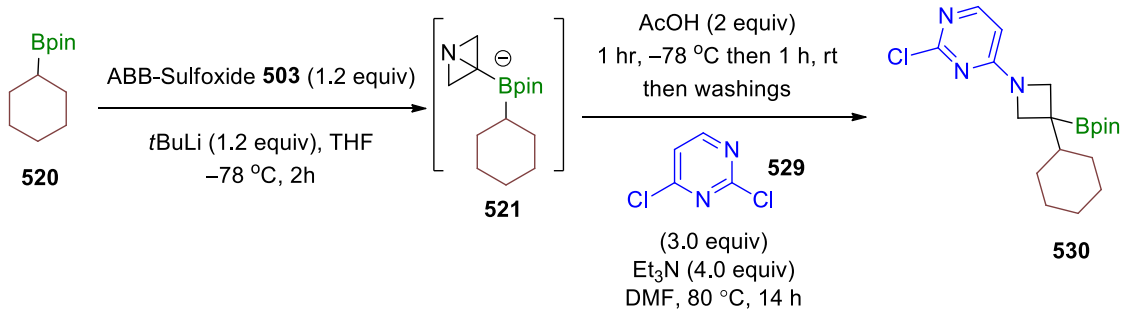
^{13}C NMR (101 MHz, $CDCl_3$): δ 160.3, 152.0, 145.5, 83.8, 56.4, 45.4, 29.1, 26.7, 24.9 ppm.

^{19}F NMR (377 MHz, $CDCl_3$) δ −157.3 ppm

HRMS (*m/z*): (ESI) calculated for $C_{19}H_{30}BFN_3O_2$ $[M+H]^+$: 362.2413, found: 362.2402

IR (solid state) ν_{max}: 2925, 2853, 1601, 1510, 1479, 1389, 1316, 1235 and 1142 cm^{-1}

2.4.5 (g) 2-Chloro-4-(3-cyclohexyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidin-1- yl)pyrimidine



Scheme 2.20 S_NAr reaction of azetidine N-H intermediate

According to **General Procedure B**, cyclohexyl pinacol boronic ester (50 mg, 0.24 mmol, 1.0 equiv) was homologated by an azetidine unit and the azetidine nitrogen atom arylated using 2,4-dichloropyrimidine (106 mg, 0.71 mmol, 3.0 equiv) to give a crude residue, which was purified by flash column chromatography (SiO_2; 70:30 pentane:EtOAc) to afford the corresponding arylated azetidine **530** (55 mg, 61%) as a colorless solid.

m.p.: 167 – 170 °C (DCM)

TLC: R_f = 0.28 (pentane:EtOAc; 70:30)

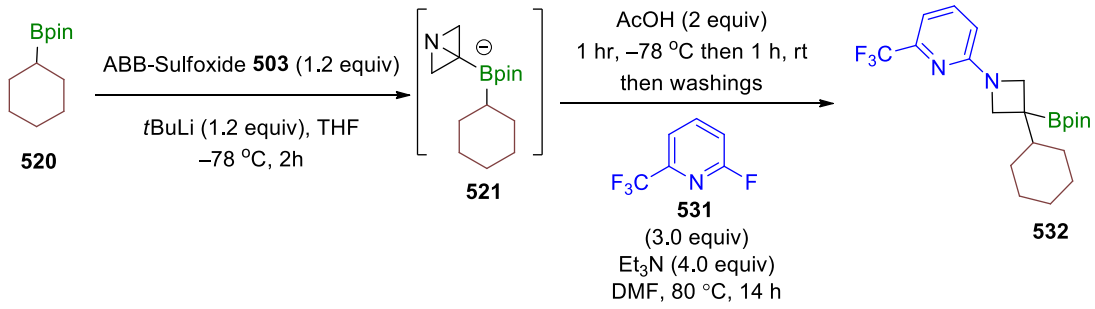
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, J = 5.9 Hz, 1H), 6.01 (d, J = 5.9 Hz, 1H), 4.13 – 3.72 (br m, 4H), 1.78 – 1.67 (m, 5H), 1.59 – 1.53 (m, 1H), 1.25 (s, 12H), 1.22 – 1.03 (m, 5H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 163.3, 161.0, 156.0, 100.4, 84.1, 55.8, 45.4, 29.0, 26.6, 24.9 ppm.

HRMS (*m/z*): (ESI) calculated for $C_{19}H_{30}BClN_3O_2$ $[M+H]^+$: 378.2118, found: 378.2107

IR (solid state) ν_{max}: 2924, 2852, 1584, 1355, 1137 and 967 cm^{-1}

2.4.5 (h) 2-(3-Cyclohexyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidin-1-yl)-6- (trifluoromethyl)pyridine



Scheme 2.21 S_NAr reaction of azetidine N-H intermediate

According to **General Procedure B**, cyclohexyl pinacol boronic ester (50 mg, 0.24 mmol, 1.0 equiv) was homologated by an azetidine unit and the azetidine nitrogen atom arylated using 2-fluoro-6-(trifluoromethyl)pyridine (118 mg, 0.71 mmol, 3.0 equiv) to give a crude residue, which was purified by flash column chromatography (SiO_2; 95:5 pentane:EtOAc) to afford the corresponding arylated azetidine **532** (57 mg, 58%) as a colorless solid.

m.p.: 148 – 152 °C (Et_2O)

TLC: R_f = 0.29 (pentane:EtOAc; 95:5)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (t, J = 7.9 Hz, 1H), 6.87 (d, J = 7.9 Hz, 1H), 6.35 (d, J = 7.9 Hz, 1H), 4.09 (d, J = 7.8 Hz, 2H), 3.78 (d, J = 7.8 Hz, 2H), 1.77 – 1.57 (m, 6H), 1.26 (s, 12H), 1.23 – 1.01 (m, 5H) ppm.

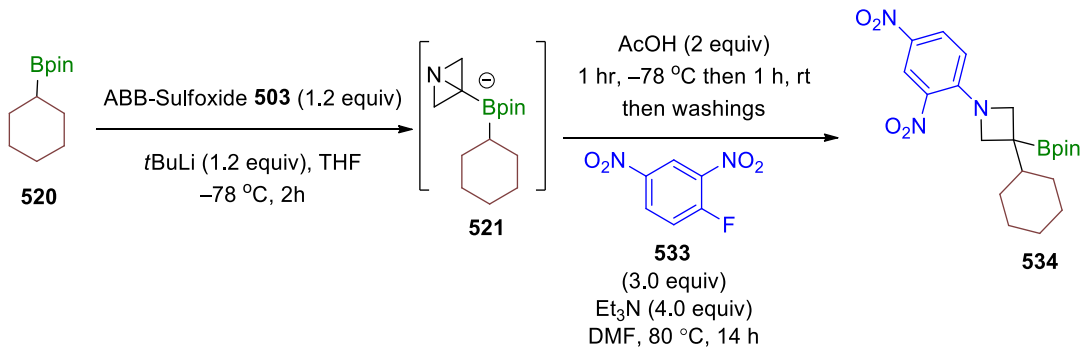
^{13}C NMR (101 MHz, $CDCl_3$): δ 160.4, 146.8, 137.4, 121.9, 108.2, 83.8, 56.7, 45.8, 29.2, 26.7, 25.0 ppm.

^{19}F NMR (377 MHz, $CDCl_3$): δ −68.7 ppm.

HRMS (*m/z*): (ESI) calculated for $C_{21}H_{30}BF3N_2NaO_2$ $[M+Na]^+$: 433.2248, found: 433.2253

IR (solid state) ν_{max}: 2924, 2854, 1607, 1477, 1383, 1135, 1104 and 800 cm^{-1}.

2.4.5 (i) 3-Cyclohexyl-1-(2,4-dinitrophenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2- yl)azetidine



Scheme 2.22 S_NAr reaction of azetidine N-H intermediate

According to **General Procedure B**, cyclohexyl pinacol boronic ester (50 mg, 0.24 mmol, 1.0 equiv) was homologated by an azetidine unit and the azetidine nitrogen atom arylated using 1-fluoro-2,5-dinitrobenzene (0.09 mL, 0.71 mmol, 3.0 equiv) to give a crude residue, which was purified by flash column chromatography (SiO_2; 90:10 hexane:EtOAc) to afford the corresponding arylated azetidine **534** (53 mg, 51%) as a yellow solid.

m.p.: 162 – 164 °C (Et_2O)

TLC: R_f = 0.56 (hexane:EtOAc; 80:20)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 (d, J = 2.6 Hz, 1H), 8.15 (dd, J = 9.4, 2.6 Hz, 1H), 6.53 (d, J = 9.4 Hz, 1H), 4.11 (d, J = 9.8 Hz, 2H), 3.88 (d, J = 9.8 Hz, 2H), 1.79 – 1.56 (m, 6H), 1.26 (s, 12H), 1.22 – 1.01 (m, 5H) ppm.

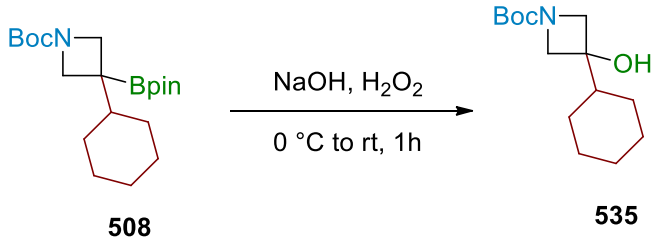
^{13}C NMR (101 MHz, $CDCl_3$): δ 147.6, 135.8, 133.1, 127.9, 124.1, 114.8, 84.3, 60.0, 45.4, 29.0, 26.6, 26.5, 24.9 ppm.

HRMS (*m/z*): (MALDI) calculated for $C_{23}H_{34}BNNaO_4$ [M+Na]+: 454.2124, found: 454.2135

IR (solid state) ν_{max}: 2926, 1604, 1577, 1524, 1496, 1465, 1374, 1333, 1302, 1267, 1255, 1140, 1124, 1073, 1055, 961, 914, 854, 830, 740 and 693 cm^{-1}.

2.4.6 Boronic Ester Functionalization

2.4.6 (a) *tert*-Butyl 3-cyclohexyl-3-hydroxyazetidine-1-carboxylate



508 **535**

Scheme 2.23 Oxidation of Bpin

Boronic ester **508** (100 mg, 0.27 mmol, 1.0 equiv) was dissolved in THF (3 mL) and cooled to 0 °C (ice/water). A mixture of NaOH and H_2O_2 (v/v 2:1) at 0 °C (ice/water) was prepared by mixing 2 mL of NaOH (3 M aqueous solution) and 1 mL of H_2O_2 (30% aqueous solution) and degassing by gently bubbling N_2 through the solution for 1 min. Addition of this aqueous solution was carried out to vigorously stirring boronic ester solution, and resulting mixture was warmed to room temperature and allowed to stir for 1 h. After which NH_4Cl (saturated aqueous solution, 5 mL) was added carefully, and extracted was performed with EtOAc (3× 10 mL). All organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2; 70:30 pentane:EtOAc) yielded the alcohol **535** (61 mg, 87%) as a colorless oil that slowly crystallised upon standing.

m.p.: 99 – 102 °C (Et_2O)

TLC: R_f = 0.27 (pentane:EtOAc; 70:30)

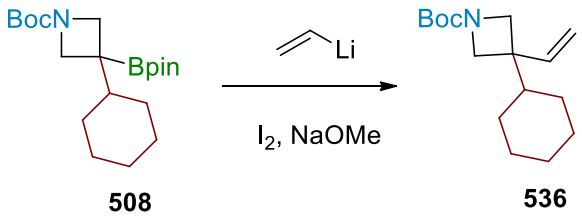
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.90 (d, J = 9.9 Hz, 2H), 3.71 (d, J = 9.9 Hz, 2H), 1.84 – 1.80 (m, 6H), 1.56 – 1.49 (m, 1H), 1.44 (s, 9H), 1.30 – 1.03 (m, 4H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.6, 79.7, 73.2, 60.7, 45.0, 28.5, 26.3, 26.2, 25.8 ppm.

HRMS (*m/z*): (ESI) calculated for $C_{14}H_{25}NNaO_3$ $[M+ Na]^+$: 278.1727, found: 278.1739

IR (thin film) ν_{max}**:** 3406, 2926, 2853, 1672, 1420, 1366, 1162, 1135, 1056 and 769 cm^{-1}

2.4.6 (b) *tert*-Butyl 3-cyclohexyl-3-vinylazetidine-1-carboxylate



508 **536**

Scheme 2.24 Olefination of boronic ester

Following a literature procedure[170], addition of *n*-butyl lithium (in hexanes, 0.19 mL, 0.30 mmol, 1.1 equiv) was carried out in a manner to neat tetravinyltin (0.11 mL, 0.60 mmol, 2.2 equiv) with stirring at room temperature. The resulting solution was stirred at room temperature for 30 min. A white precipitate (vinyl lithium) appeared during stirring. THF (1.3 mL) was added to the precipitate. Addition of this solution to a stirred mixture of boronic ester **508** (100 mg, 0.27 mmol, 1.0 equiv) in THF (1.4 mL) at −78 °C (dry ice/acetone) was carried out slowly dropwise. The mixture was stirred at −78 °C for 15 min and then warmed to 0 °C (ice/water) and stirred for 15 min. The reaction mixture was recooled to −78 °C and a suspension of NaOMe (44 mg, 0.82 mmol, 3.0 equiv) in MeOH (0.50 mL) was added in a single portion followed by dropwise addition of a solution of iodine (83 mg, 0.33 mmol, 1.2 equiv) in MeOH (0.7 mL). The resulting mixture was warmed to 0 °C (ice/water) and stirred for 30 min. After this time, saturated aqueous sodium thiosulfate (5 mL) and dichloromethane (5 mL) were added. The organic layer was separatef and then the aqueous phase was extracted with dichloromethane (3× 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2; 95:5 pentane: EtOAc) resulted in pure alkene **536** (38 mg, 52%) as a colorless oil.

TLC: R_f= 0.28 (95:5 pentane:EtOAc)

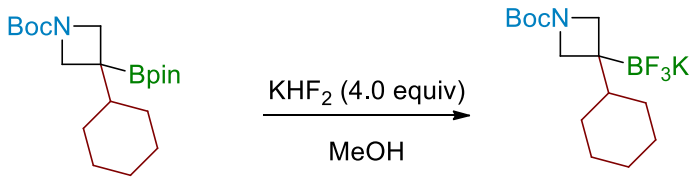
^{1}H NMR (400 MHz, $CDCl_3$):: δ 5.85 (dd, J = 17.4, 10.8 Hz, 1H), 5.22 (dd, J = 10.8, 1.0 Hz, 1H), 5.07 (dd, J = 17.4, 1.0 Hz, 1H), 3.78 (d, J = 8.3 Hz, 2H), 3.71 (d, J = 8.3 Hz, 2H), 1.78 – 1.51 (m, 6H), 1.43 (s, 9H), 1.27 – 1.03 (m, 3H), 0.96 – 0.86 (m, 2H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.7, 139.4, 115.0, 79.4, 46.0, 43.5, 28.6, 27.1, 26.6, 26.5 ppm. *$N(CH_2)_2$ was not observed.*

HRMS (*m/z*): (ESI) calculated for $C_{16}H_{27}NNaO_2$ $[M+Na]^+$: 288.1934, found: 288.1938

IR (thin film) ν_{max}: 2925, 2853, 1702, 1392, 1365, 1166 and 1130 cm^{-1}

2.4.6 (c) Potassium (1-(*tert*-butoxycarbonyl)-3-cyclohexylazetidin-3-yl)trifluoroborate



508 **537**

Scheme 2.25 Synthesis of trifluoroborate from boronic ester

According to a literature procedure[171], boronic ester **508** (100 mg, 0.27 mmol, 1.0 equiv) was dissolved in methanol (4.5 mL) in a vial then KHF_2 (4.5 M aqueous solution, 0.35 mL) was added dropwise and the resulting mixture was stirred at room temperature for 30 min. Mixture was concentrated by removing all volatiles under reduced pressure and methanol (6 mL) and water (4 mL) were added again to the vial containing the crude residue, before concentrating again under reduced pressure. All pinacol was removed by repeating this cycle again and again (10×). The residue was triturated with Et_2O (3× 5 mL) and all liquid phases were concentrated under reduced pressure to yield the desired trifluoroborate salt **537** (85 mg, 90%) as a white solid.

^{1}H NMR (400 MHz, CD_3CN): δ 3.71 – 3.58 (br m, 2H), 3.36 – 3.23 (br m, 2H), 1.76 – 1.55 (br m, 5H), 1.38 (s, 9H), 1.33 – 1.11 (br m, 6H) ppm.

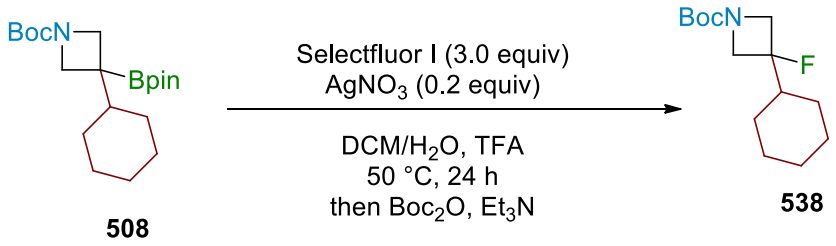
^{13}C NMR (101 MHz, CD_3CN): δ 157.4, 78.3, 48.0, 29.6, 28.8, 28.3, 27.9 ppm.

^{19}F NMR (377 MHz, CD_3CN): δ −145.6 ppm.

HRMS (*m/z*): (ESI) calculated for $C_{14}H_{24}BF_3NO_2$ $[M–K^+]^–$: 306.1860, found: 306.1861

IR (solid state) ν_{max}: 2926, 1679, 1416, 1155 and 1131 cm^{-1}.

2.4.6 (d) *tert*-Butyl 3-cyclohexyl-3-fluoroazetidine-1-carboxylate



508 **538**

Scheme 2.26 Fluorination of boronic ester

According to a literature procedure,[172] boronic ester **508** (100 mg, 0.27 mmol, 1.0 equiv), $AgNO_3$ (9.3 mg, 0.05 mmol, 0.2 equiv) and Selectfluor I (291 mg, 0.82 mmol, 3.0 equiv) were added to a vial, followed by DCM (1.3 mL), water (1.3 mL) and trifluoroacetic acid (0.08 mL, 1.09 mmol, 4.0 equiv). The vial was then sealed, and mixture heated for 24 h at 50 °C. Then, it was cooled to room temperature and triethylamine (0.31 mL, 2.16 mmol, 8.0 equiv) and di-*tert*-butyl dicarbonate (0.15 mL, approx. 0.54 mmol, 2.0 equiv) were added and the mixture was stirred for 16 h. Extraction was performed with Et_2O (3× 5 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and solvent removed under reduced pressure. Flash column chromatography (SiO_2; 95:5 pentane:EtOAc) was used to purify crude residue to give the desired alkyl fluoride **538** (21 mg, 30%) as a colorless oil.

TLC: R_f = 0.21 (95:5 pentane:EtOAc)

^{1}H NMR (400 MHz, $CDCl_3$:) δ 3.96 (s, 2H), 3.91 (s, 2H), 1.82 – 1.54 (m, 6H), 1.43 (s, 9H), 1.17 – 1.06 (m, 5H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.4, 94.3, 80.0, 58.3, 43.1, 28.5, 26.1, 25.9, 25.4 ppm.

^{19}F NMR (377 MHz, $CDCl_3$): δ −159.7 ppm.

HRMS (*m/z*): (ESI) calc'd for $C_{14}H_{24}FNNaO_2$ $[M+Na]^+$: 280.1683, found: 280.1681

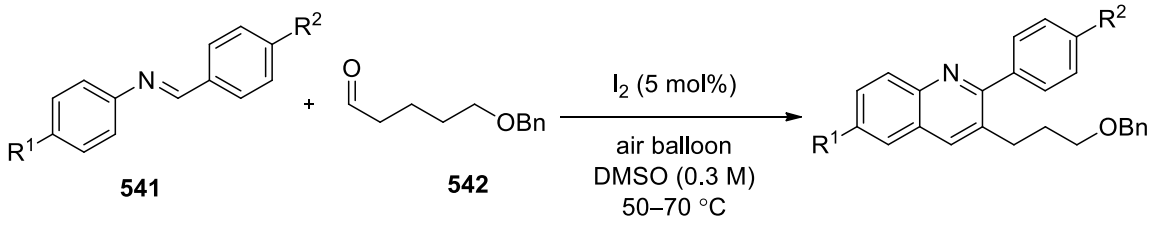
IR (thin film) ν_{max}: 2929, 2856, 1704, 1394, 1366, 1165, 1131 and 1052 cm^{-1}

CHAPTER-3
RESULTS AND DISCUSSION

3.1 Part A: Synthesis of Quinoline Derivatives as Nucleoside Triphosphate Diphosphohydrolase (NTPDases) Inhibitors

Quinoline scaffold, one of the most privileged nitrogen containing heterocycles, is known for numerous interesting biological activities[1] for example antimalarial,[12] anti-cancer[173], antimicrobial[174] and antibacterial activities.[4] Quinoline structure is the integral part of many FDA approved drugs and drug candidates under clinical trials.[1] There have been great progress in the synthesis of the quinoline scaffold and its functionalization for biological and pharmaceutical applications.[28]

Abbas research group at Quaid-i-Azam University, Islamabad, Pakistan[157] previously synthesized 3-benzyloxypropyl substituted highly functionalized 2-arylquinoline derivatives and evaluated their NTPDase inhibitory potential. Synthesis of these derivatives was carried out using mild and greener molecular iodine catalyst.



Scheme 3.1 Synthesis of quinoline derivatives through iodine catalysis by Abbas and coworkers

Among the synthesized derivatives, compound **543**, **544**, **545**, **546** were found the most potent inhibitors of *h*-NTPDase1, 2, 3 and 8 respectively (Fig 3.1). Compound **543** is the most powerful inhibitor (IC_{50}=0.23 ± 0.01 μM).

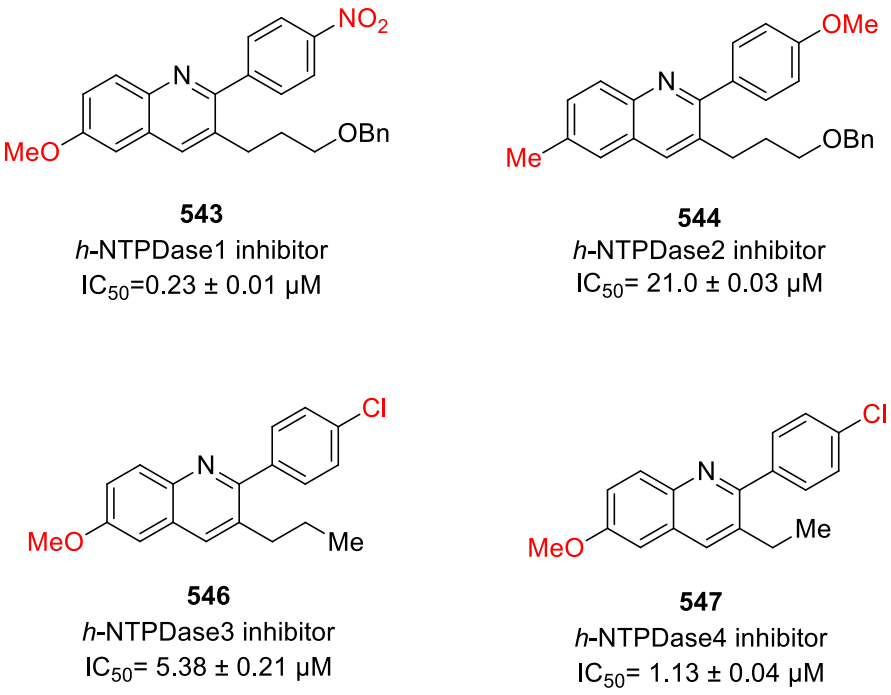


Fig 3.1 Inhibitors of *h*-NTPDase1, 2, 3 and 8

In the present study, the most active compound **543** was further explored by keeping the substitution on core structure intact and bringing variations at the side chain in terms of different chain lengths and bringing different functional groups at the end of the chain (Fig 3.2). Later on, inhibitory potential of the synthesized compounds was studied and structure-activity relationship was established.

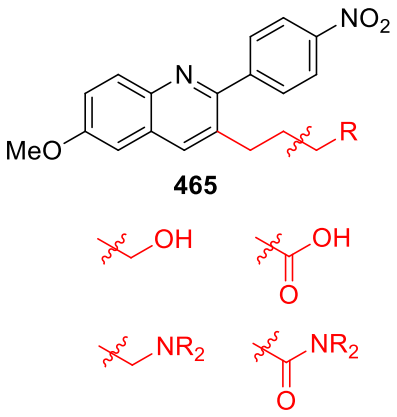
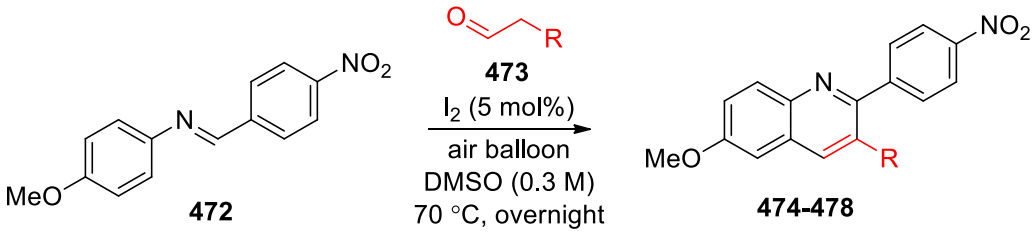


Fig 3.2 Exploration of quinoline derivatives from the previous study[157]

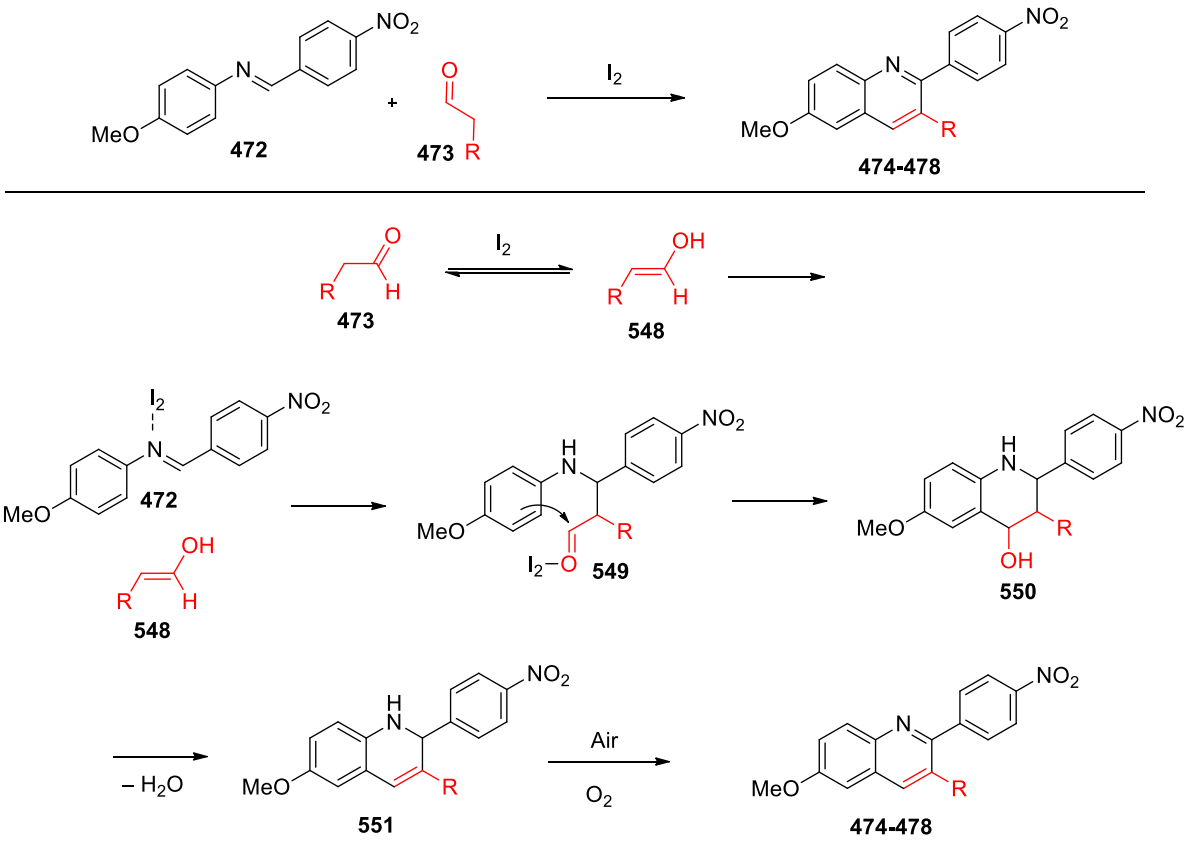
3.1.1 Molecular Iodine Catalyzed Synthesis of Quinoline Derivatives

Synthetic protocol involves the cyclization of an imine with an aldehyde using molecular iodine as catalyst[175]. Imine **472** was reacted with different aldehydes in a one pot reaction manner using 5 mol% iodine catalyst in DMSO at 70 ℃ under air atmosphere (Scheme 3.2).



Scheme 3.2 Molecular iodine catalyzed synthesis of quinoline derivatives

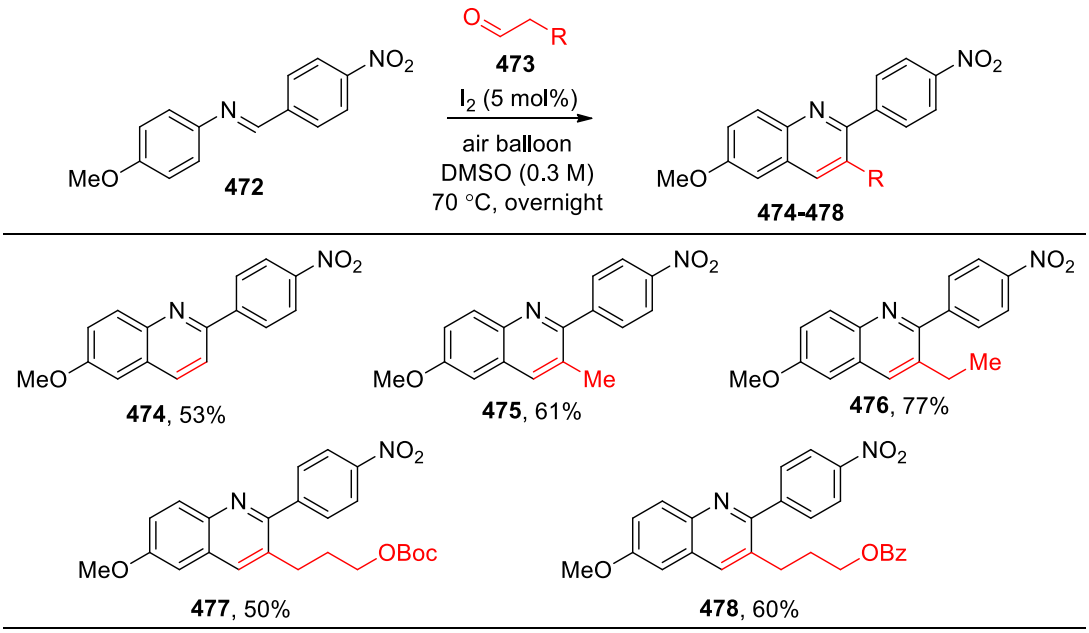
Iodine catalyzes the reaction acting as mild Lewis acid. It facilitates the conversion of aldehyde to enol form in the beginning of the reaction and activates the imine as well. *In situ* generated enol **548** reacts with activated imine to form aldehyde intermediate **549**. Intramolecular Friedel–Crafts cyclization followed by dehydration results in dihydroquinoline **551** which is oxidized by air to form quinoline.



Scheme 3.3 Mechanism of molecular catalyzed synthesis of quinoline derivatives from aryl imine and aldehyde

3.1.2 Synthesis of Quinoline Derivatives with Different Aliphatic Aldehydes

The synthesis was started by reacting 4-methoxy-*N*-(4-nitrobenzylidene)aniline with different aliphatic aldehydes under iodine catalysis .

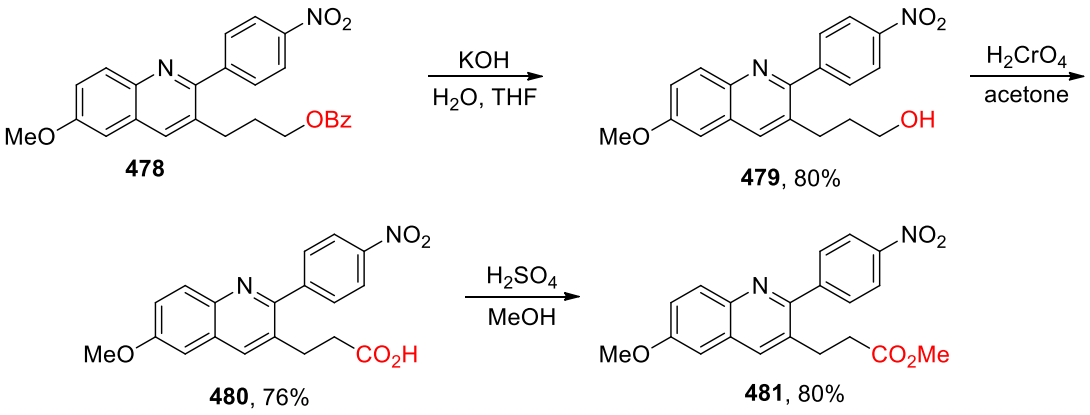


Scheme 3.4 Synthesis of quinoline derivatives with different aliphatic aldehydes

Preliminary reaction of imine **472** with acetaldehyde resulted in 53% quinoline product **474**. Similarly, propionaldehyde reacted with aryl imine and afforded product **475** having methyl substituent at position-3 in 61% yield. Reaction furnished the higher yield than the initial reaction. Butyraldehyde gave homologous products **476** in 77% yield with ethyl substituents at position-3 of quinoline formed. Increase in the yield with butyraldehyde can be attributed to its greater solubility than propionaldehyde and acetaldehyde. To broaden the scope of aliphatic aldehydes in terms of biological activities and diversification of quinoline derivatives the reaction *tert*-butoxycarbonyloxy and benzoyloxy substituted aldehyde were also reacted with imine. Reaction with *tert*-butoxycarbonyloxy aldehyde being bulky and sterically hindered aldehyde produced **477** in 50% yield and reaction with benzoyloxy substituted aldehyde produced **478** product in 60% yield.

3.1.3 Synthesis of Quinoline Derivatives Through Functional Group Interconversion

Quinoline derivatives **477** and **478** with *tert*-butoxycarbonyloxy and benzoyloxy groups respectively can be deprotected by hydrolysis to alcohol derivative. *tert*-Butoxycarbonyloxy (Boc) group can be easily deprotected using trifluoroacetic acid (TFA) but practically it resulted in low yield of the product. Therefore, benzoyloxy substituted quinoline derivative **478** was converted to alcohol derivative **479** when subjected to basic hydrolysis using potassium hydroxide base. This basic hydrolysis reaction was very efficient giving out 80% yield of the product.



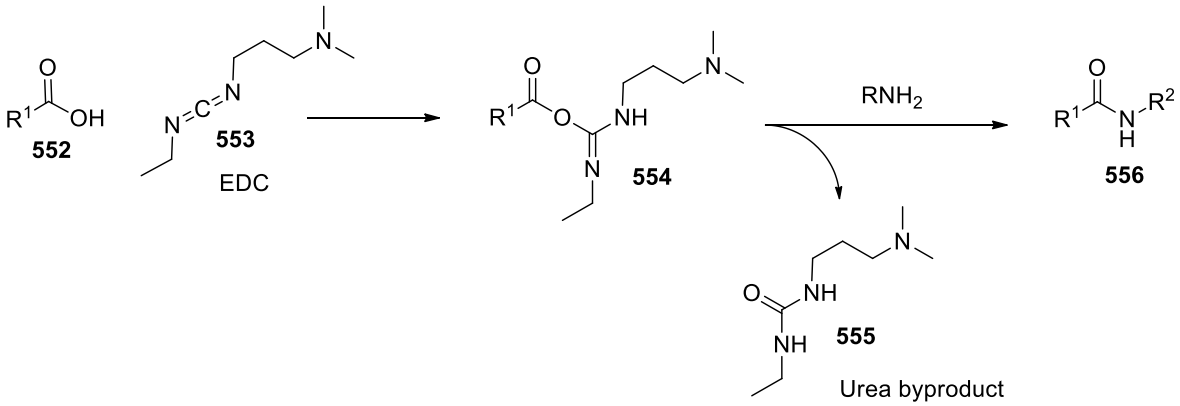
Scheme 3.5 Synthesis of quinoline derivatives through functional group interconversion

Quinoline derivative **479** can be transformed further to different functional groups and thus it provides diversification for biological screening. Free hydroxyl group in **479** can be oxidized to carboxylic acid. Hence, Jones oxidation was employed for converting **479** to carboxylic acid derivative **480** in 76% yield of the reaction. This quinoline derivative **480** with carboxylic acid end group can be utilized further in synthesizing different functional group derivatives e.g. esters and amides. Methyl ester **481** of carboxylic acid derivative **480** was synthesized using

Fischer esterification reaction conditions and reaction furnished excellent yield (80%) of the product.

3.1.4 Synthesis of Quinoline Amide Derivatives from Carboxylic Acid

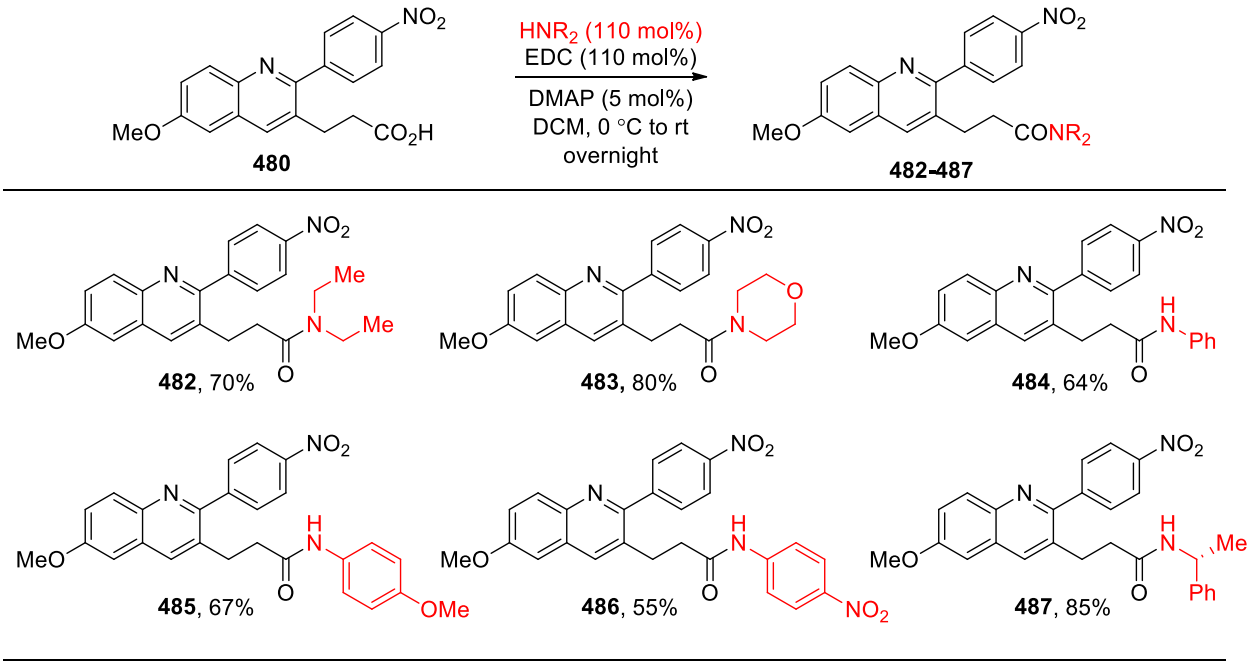
Different methods have been reported for the synthesis of amides from carboxylic acid. In the present research work, quinoline amide derivatives were synthesized using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) coupling reagent[160]. Advantage of using EDC over other carbodiimides like dicyclohexylcarbodiimide (DCC) or diisopropylcarbodiimide (DIC) is that the urea by-product formed in the reaction is water soluble and can be removed easily through aqueous workup which is difficult to separate from amide product otherwise.



Scheme 3.6 Synthesis of Amides from carboxylic acids and amines using EDC coupling reagent

Reaction of carboxylic acid **480** with *N,N*-diethylamine afforded amide product **482** in 70% yield and similarly morpholine being more nucleophilic amine gave **483** derivative in 80% yield. Aromatic amines were also employed for synthesis of amide derivatives to elaborate the structure-activity relationship on biological activity. Aromatic amines although less nucleophilic than aliphatic amines upon reaction with quinoline carboxylic acid derivative **480** gave appreciable amount of products. Aniline resulted in the amides **484** in 64% yield and and *p*-anisidine which is relatively more nucleophilic than aniline gave amide product in 67%

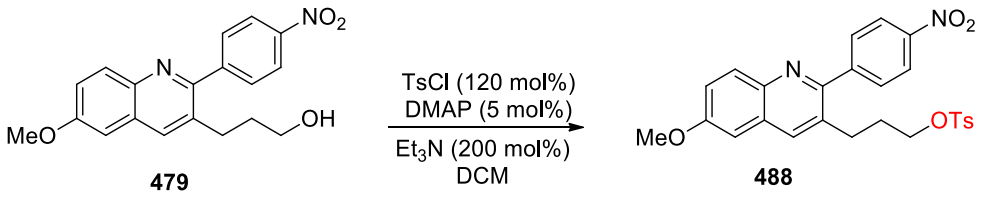
isolated yield. 4-Nitroaniline being less nucleophilic than aniline because of electron withdrawing nitro group resulted in low yield of the amide product. Amide **486** was obtained in 55% yield. Finally (*S*)-α-methylbenzylamine furnished amide **487** in 85% yield. The wide range of amide derivatives gave a quick broad scope screening of different substitutions and functional group that will offer a comprehensive assay for the enzyme inhibition.



Scheme 3.7 Synthesis of quinoline amide derivatives through EDC coupling of carboxylic acids and amines

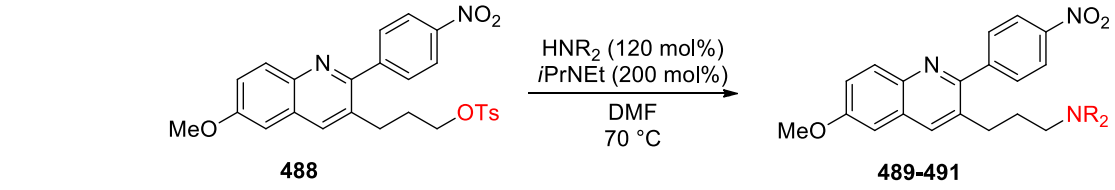
3.1.5 Synthesis of Amine Derivatives by Nucleophilic Substitution

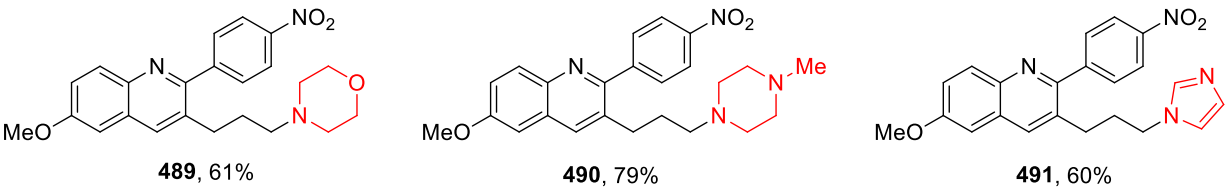
Quinoline alcohol derivative **479** was utilized further for synthesizing tertiary amine derivatives through nucleophilic substitution reaction. Alcohol was first tosylated to make hydroxyl a good leaving group and reacted with amines afterwards. For tosylation, quinoline alcohol was treated with tosyl chloride using DMAP as the catalyst under standard reported conditions[176] and obtained tosylated alcohol product **488** in 60% yield.



Scheme 3.8 Tosylation of quinoline alcohol derivative

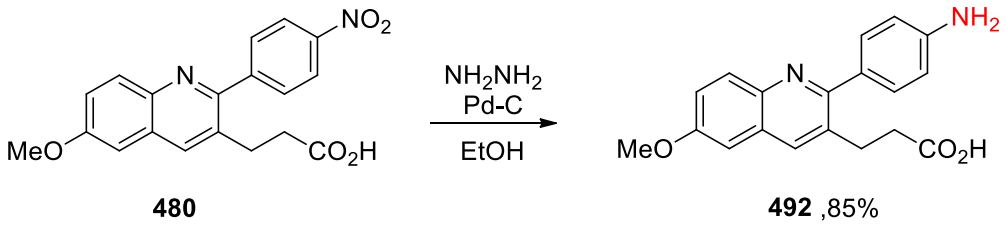
Quinoline tosylate **488** was subjected to nucleophilic substitution reaction. Initial reaction was carried out with morpholine, a heterocyclic amine with useful biological applications. Amine derivative **489** was obtained in 61% yield. *N*-methylpiperazine was used further in nucleophilic substitution reaction and reaction occured smoothly furnishing product **490** in 79% yield. Higher yield of **490** is because *N*-methylpiperazine is more nucleophilic than morpholine because of more electron donating nitrogen atom in the ring than oxygen in the morpholine. Eventually, aromatic amine imidazole was employed in nucleophilic substitution reaction because of immense incorporation of imidazole in biologically active compounds. Reaction with imidazole resulted in *N*-substituted imidazole derivative **491** in 60% yield.





Scheme 3.9 Synthesis of quinoline derivatives through nucleophilic substitution

Finally, nitro group on the basic core structure in compound **480** was reduced using Pd/hydrazine reduction method to furnish the amine **492** in excellent yield. The purpose of reducing nitro group was to observe the importance of nitro substituent in terms of inhibitory activity.



480 **492** ,85%

Scheme 3.10 Pd/hydrazine reduction of nitro group

3.1.6 Biological Screening of Synthesized Quinoline Derivatives

Synthesized quinoline derivatives were evaluated for their inhibitory activity against four isoenzymes (NTPDase1, NTPDase2, NTPDase3 and NTPDase8) of human nucleoside triphosphate diphosphohydrolases (*h*-NTPDases) using suramin as a standard inhibitor. The compounds which showed >50% inhibition of any isoform of *h*-NTPDase were further tested at different concentrations to calculate their IC_{50} values. Biological screening results have been summarized in the table 3.1.

Table 3.1 Inhibitory Activity of All Synthesized Quinoline Derivatives Against *h*-NTPDase1,2,3 and 8**.**

Sr. No.	Compound	*h*-NTPDase1	*h*-NTPDase2	*h*-NTPDase3	*h*-NTPDase8
1	**474**	32%[b]	38%[b]	33%[b]	46%[b]
2	**475**	1.30 ± 0.15[a]	48%[b]	3.01 ± 0.30[a]	36%[b]
3	**476**	1.20 ± 0.13[a]	45%[b]	0.86 ± 0.06[a]	0.90 ± 0.08[a]
4	**477**	33%[b]	38%[b]	32%[b]	45%[b]

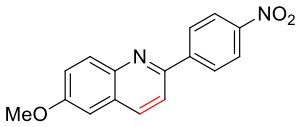
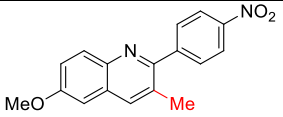
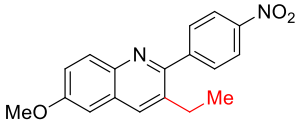
5	**478**	1.06 ± 0.08[a]	2.20 ± 0.11[a]	40%[b]	38%[b]
6	**479**	0.73 ± 0.08[a]	46%[b]	3.50 ± 0.17[a]	42%[b]
7	**480**	30%[b]	42%[b]	42%[b]	46%[b]
8	**481**	1.34 ± 0.05[a]	1.70 ± 0.10[a]	0.36 ± 0.01[a]	1.82± 0.07[a]
9	**482**	30%[b]	39%[b]	41%[b]	38%[b]
10	**483**	0.50 ± 0.03[a]	0.77 ± 0.06[a]	48%[b]	47%[b]
11	**484**	37%[b]	47%[b]	33%[b]	45%[b]
12	**485**	32%[b]	2.64 ± 0.13[a]	1.01 ± 0.09[a]	41%[b]
13	**486**	1.75 ± 0.12[a]	1.81 ± 0.05[a]	2.90 ± 0.07[a]	37%[b]
14	**487**	0.20 ± 0.02[a]	45%[b]	5.50 ± 0.51[a]	36%[b]
15	**488**	1.40 ± 0.18[a]	7.40 ± 0.19[a]	0.51 ± 0.04[a]	48%[b]
16	**489**	45%[b]	46%[b]	32%[b]	46%[b]
17	**490**	33%[b]	35%[b]	44%[b]	33%[b]
18	**491**	42%[b]	40%[b]	42%[b]	0.65 ± 0.05[b]
19	**492**	43%[b]	35%[b]	35%[b]	46%[b]
20	**Suramin**	16.1 ± 1.02[a]	24.1 ± 3.01[a]	4.31 ± 0.41[a]	>100[a]

[a] IC_{50} values are presented as means ± standard error of mean (S.E.M) of three separate experiments. [b] Percent inhibition determined at 100 μM.

3.1.6.1 NTPDase Inhibitor Activity

Most of the compounds have shown activity against *h*-NTPDase1, *h*-NTPDase2 and *h*-NTPDase3 whereas only three compounds were active against *h*-NTPDase8.

Table 3.2 Inhibitory Activity of Quinoline Derivatives with Different Aliphatic Chain at Position-3 Against *h*-NTPDase1,2,3 and 8.

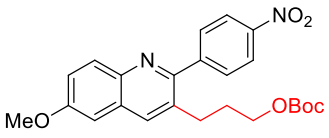
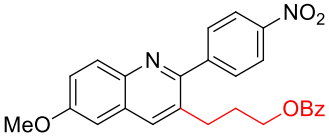
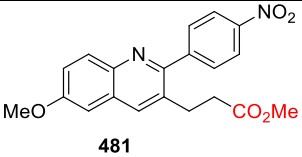
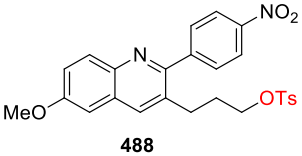
Compounds	*h*-NTPDase1	*h*-NTPDase2	*h*-NTPDase3	*h*-NTPDase8
 **474**	32%[b]	38%[b]	33%[b]	46%[b]
 **475**	1.30 ± 0.15[a] (71%)	48%[b]	3.01 ± 0.30[a] (55%)	36%[b]
 **476**	1.20 ± 0.13[a] (64%)	45%[b]	0.86 ± 0.06[a] (74%)	0.90 ± 0.08[a] (70%)
Suramin	16.1 ± 1.02[a]	24.1 ± 3.01[a]	4.31 ± 0.41[a]	>100[a]

[a] IC_{50} values are presented as means ± standard error of mean (S.E.M) of three separate experiments. [b] Percent inhibition determined at 100 μM.

The lead compound **474** with no substitution at position 3 of quinoline ring showed minor inhibitory effect (<50% inhibition) against all the four isoforms, however, activity was altered when different substituents were introduced at C3-position of quinoline ring. The compound **475** and **476**, substituted with a methyl and ethyl alkyl group respectively, were found to be non-selective inhibitors of *h*-NTPDases. The compound **475** was observed a dual inhibitor of *h*-NTPDase1 (IC_{50} = 1.30 ± 0.15 μM) and *h*-NTPDase3 (3.01 ± 0.30 μM). In contrast, compound **476** with an ethyl chain showed the best inhibitory activity against *h*-NTPDase3 (IC_{50} = 0.86 ± 0.06 μM) followed by *h*-NTPDase8 (IC_{50} = 0.90 ± 0.08 μM) and *h*-NTPDase1 (IC_{50} = 1.20 ± 0.13 μM). By comparing the IC_{50} of these

compounds, it can be suggested substitution is important at the C3. Ethyl group is more promising as compared to methyl group although later brought slight selectivity.

Table 3.3 Inhibitory Activity of the Quinoline Derivatives with Ester End Group Against *h*-NTPDase1,2,3 and 8.

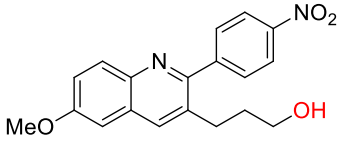
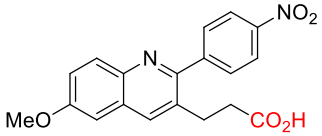
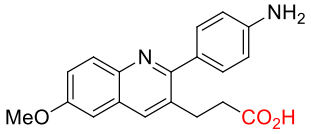
Compounds	*h*-NTPDase1	*h*-NTPDase2	*h*-NTPDase3	*h*-NTPDase8
 **477**	33%[b]	38%[b]	32%[b]	45%[b]
 **478**	1.06 ± 0.08[a] (62%)	2.20 ± 0.11[a] (53%)	40%[b]	38%[b]
 **481**	1.34 ± 0.05[a] (75%)	1.70 ± 0.10[a] (78%)	0.36 ± 0.01[a] (87%)	1.82± 0.07[a] (68%)
 **488**	1.40 ± 0.18[a] (61%)	7.40 ± 0.19[a] (51%)	± 0.04[a] (76%)	48%[b]
Suramin	16.1 ± 1.02[a]	24.1 ± 3.01[a]	4.31 ± 0.41[a]	100[a]

[a] IC_{50} values are presented as means ± standard error of mean (S.E.M) of three separate experiments. [b] Percent inhibition determined at 100 μM.

The compounds **477**, **478**, **481** and **488** were substituted with different ester groups exhibited variable activity. The compound **477** with Boc (butyloxycarbonyloxy) end group showed <50% inhibition of all the isoforms. On the other hand, compound **481** which has methyl ester at the chain end was active

against all the *h*-NTPDases. This compound **481** exhibited the best inhibitory potential against *h*-NTPDase3 (IC_{50} = 0.36 ± 0.01 μM). In addition, it also demonstrated good activity against *h*-NTPDase1 (IC_{50} = 1.34 ± 0.05 μM), *h*-NTPDase2 (IC_{50} = 1.70 ± 0.10 μM) and *h*-NTPDasse8 (IC_{50} = 1.82 ± 0.07 μM). Similarly, the tosylate ester **488** was non-selective inhibitor of *h*-NTPDase1 (IC_{50} = 1.40 ± 0.18 μM), *h*-NTPDase2 (IC_{50} = 7.40 ± 0.19 μM) and *h*-NTPDase3 (IC_{50} = 0.51 ± 0.04 μM). The benzoate ester **478** showed dual inhibition against *h*-NTPDase1 (IC_{50} = 1.06 ± 0.08 μM) and *h*-NTPDase2 (IC_{50} = 2.20 ± 0.11 μM). Comparison of inhibitory activity of these ester compounds indicates that the presence of small ester groups such as methyl propanoate is preferred over bulky group like Boc.

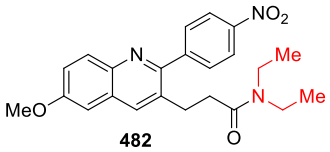
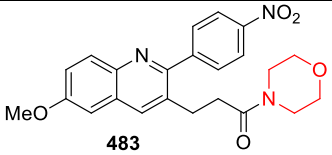
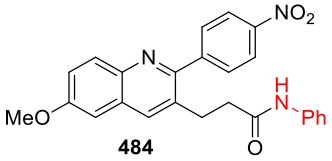
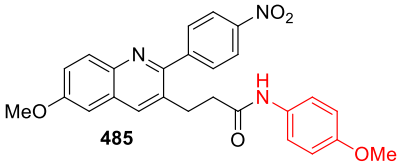
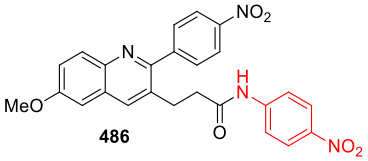
Table 3.4 Inhibitory Activity of the Quinoline Derivatives Synthesized Through Functional Group Interconversion Against *h*-NTPDase1,2,3 and 8.

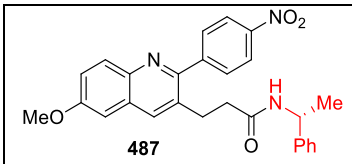
Compounds	*h*-NTPDase1	*h*-NTPDase2	*h*-NTPDase3	*h*-NTPDase8
 **479**	0.73 ± 0.08[a] (84%)	46%[b]	3.50 ± 0.17[a] (58%)	42%[b]
 **480**	30%[b]	42%[b]	42%[b]	46%[b]
 **492**	43%[b]	35%[b]	35%[b]	46%[b]
Suramin	16.1 ± 1.02[a]	24.1 ± 3.01[a]	4.31 ± 0.41[a]	>100[a]

[a] IC_{50} values are presented as means ± standard error of mean (S.E.M) of three separate experiments. [b] Percent inhibition determined at 100 μM.

The compound **479** bears free hydroxyl group at the end of propyl chain at C3. It was recognized as dual inhibitor of *h*-NTPDase1 (IC_{50} = 0.73 ± 0.08 µM) and *h*-NTPDase3 (IC_{50} = 3.50 ± 0.17 μM), being slightly selective for *h*-NTPDase1. The compound **480** with a propionic acid group at C3-position of quinoline ring showed limited inhibitory activity i.e., <50% inhibition against all the four *h*-NTPDases. This behavior is same for the compound **492** which is nitro reduced form of **480** and basically an amino acid.

Table 3.5 Inhibitory Activity of the Quinoline Amide Derivatives Against *h*-NTPDase1,2,3 and 8.

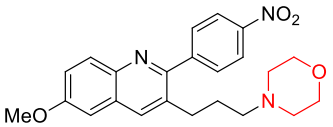
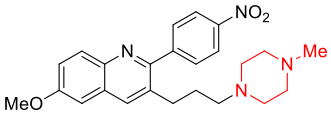
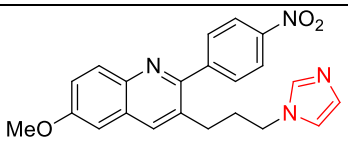
Compounds	*h*-NTPDase1	*h*-NTPDase2	*h*-NTPDase3	*h*-NTPDase8
 **482**	30%[b]	39%[b]	41%[b]	38%[b]
 **483**	0.50 ± 0.03[a] (79%)	0.77 ± 0.06[a] (71%)	48%[b]	47%[b]
 **484**	37%[b]	47%[b]	33%[b]	45%[b]
 **485**	32%[b]	2.64 ± 0.13[a] (57%)	1.01 ± 0.09[a] (63%)	41%[b]
 **486**	1.75 ± 0.12[a] (63%)	1.81 ± 0.05[a] (62%)	2.90 ± 0.07[a] (55%)	37%[b]

 487	0.20 ± 0.02[a] (82%)	45%[b]	5.50 ± 0.51[a] (54%)	36%[b]
Suramin	16.1 ± 1.02[a]	24.1 ± 3.01[a]	4.31 ± 0.41[a]	100[a]

[a] IC_{50} values are presented as means ± standard error of mean (S.E.M) of three separate experiments. [b] Percent inhibition determined at 100 μM.

Quinoline amide derivatives (**482-487**), the compound **482** and **484** are not the potential inhibitors because these compounds showed overall reduced activity against all the isoforms of *h*-NTPDase whereas compound **482** is dual inhibitor of *h*-NTPDase1 (IC_{50} = 0.50 ± 0.03 μM) and *h*-NTPDase2 (IC_{50} = 0.77 ± 0.06 μM) being the most active *h*-NTPDase2 inhibitor of all the compounds. Compound **485** was found to be a dual inhibitor of *h*-NTPDase2 (IC_{50} = 2.64 ± 0.13 μM) and *h*-NTPDase3 (IC_{50} = 1.01 ± 0.09 μM). In contrast, compound **486** showed a non-selective behavior and inhibited the *h*-NTPDase1, -2 and -3, with an IC_{50} value of 1.75 ± 0.12 μM, 1.81 ± 0.05 μM and 2.90 ± 0.07 μM, respectively. Similarly, the compound **487** was also identified as a dual inhibitor of *h*-NTPDase1 and -3, being the most active *h*-NTPDase1 inhibitor of this series with an IC_{50} value of 0.20 ± 0.02 μM. Moreover, this compound also showed selectivity towards *h*-NTPDase1 over *h*-NTPDase3. A structural comparison of these compounds revealed that compounds bearing a substituted phenyl ring like *p*-anisidine **485**, *p*-nitro phenyl **486** and 2-phenylethyl **487** were superior to those having an unsubstituted phenyl ring **484** or an alkyl chain **482**. Thus, it can be proposed that presence of substituted phenyl ring was contributing towards the activity of these compounds **485-486** since the introduction of an unsubstituted phenyl ring **483** or an alkyl chain **482** was detrimental and resulted in reduced activity.

Table 3.6 Inhibitory Activity of the Quinoline Tertiary Amine Derivatives Against *h*-NTPDase1,2,3 and 8.

Compounds	*h*-NTPDase1	*h*-NTPDase2	*h*-NTPDase3	*h*-NTPDase8
 **489**	45%[b]	46%[b]	32%[b]	46%[b]
 **490**	33%[b]	35%[b]	44%[b]	33%[b]
 **491**	42%[b]	40%[b]	42%[b]	0.65 ± 0.05[b] (72%)
Suramin	16.1 ± 1.02[a]	24.1 ± 3.01[a]	4.31 ± 0.41[a]	>100[a]

[a] IC_{50} values are presented as means ± standard error of mean (S.E.M) of three separate experiments. [b] Percent inhibition determined at 100 μM.

The compound **489-491** incorporated different heterocyclic rings including morpholine, imidazole and *N*-methyl piperazine. Except **491**, all the compounds were inactive against *h*-NTPDases. Interestingly the compound **491** was involved in the selective inhibition of *h*-NTPdase8 and its activity against other isoforms was less than 50%.

3.1.6.2 Molecular Docking Studies

Molecular docking studies were performed using homology models as protein data bank does not contain the crystal structures of human NTPDases. BioSolveIT's LeadIT software was used for docking studies.

The compounds **483**, **481** and **476** which are the most active inhibitors of *h*-NTPDase2, *h*-NTPDase3 and *h*-NTPDase8 respectively were subjected to molecular docking studies. Compound **483**, most active inhibitor of *h*-NTPDase2, was forming hydrogen bond with Try436, Ala437 and Arg392. The quinoline ring was interacting through pi-pi stacking with His50 and Try350 whereas, a T-shaped pi-pi interaction was observed between nitrophenyl ring and Ph354. Moreover, nitrogen atom of nitro group was forming a pi-cation interaction with Asp45 and Trp436 while pi-anion interaction was observed between Phe54 and one of the oxygen atoms of nitro group.

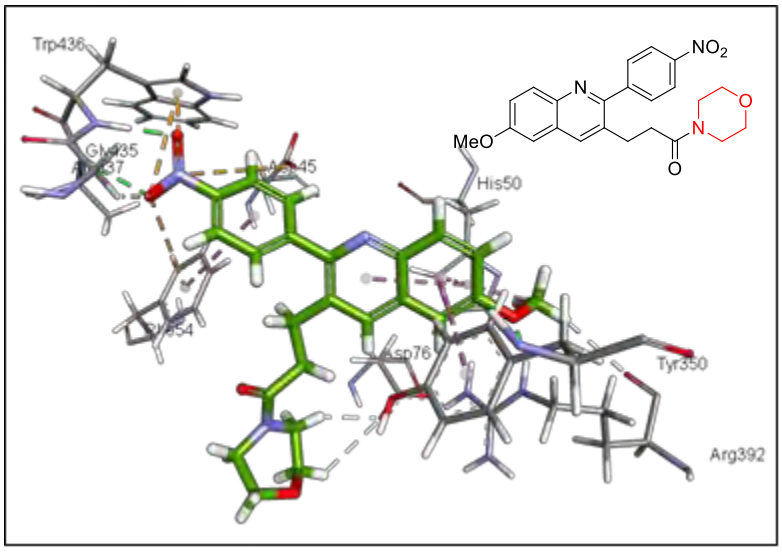


Fig 3.3 3D representation of the plausible docked conformation of compound **483** inside the active site of modeled *h*-NTPDase2

The compound **481**, the most active *h*-NTPDase3 inhibitor, formed multiple hydrogen bonds with the surrounding amino acids. For example, oxygen atom of ester group was forming hydrogen bonds with Ala223, Ser224 and Gly222. Similarly, another oxygen atom of ester group was making hydrogen bond with Thr139. Oxygen atom of the methoxy group was forming another hydrogen bond with Trp459. The amino acid Ala140 was interacting with CH_3 group via alkyl interaction, whereas a pi-alkyl interaction was observed betweenTrp459 and CH_3 of methoxy group.

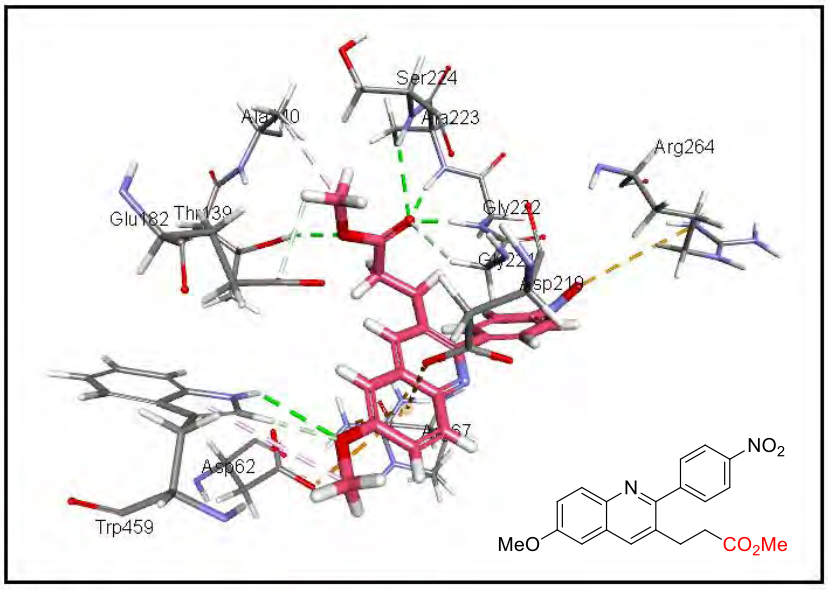


Fig 3.4 3D representation of the plausible docked conformation of compound **481** inside the active site of modeled *h*-NTPDase3

Docking studies of the compound **476** (*h*-NTPDase8 inhibitor) revealed that oxygen atom of OCH_3 group was interacting through hydrogen bonds with amino acids Tyr59 and Gln74. Similarly, one of the oxygen atom of nitro group was interacting with Meth206 via hydrogen bond formation while the other oxygen atom was observed to have a pi-anion interaction with Mg^{+2}. The quinoline ring was involved in a pi-pi stacked interaction with Phe57 whereas, Leu442 and Val436 exhibited an alkyl interaction with CH_3 of methoxy group.

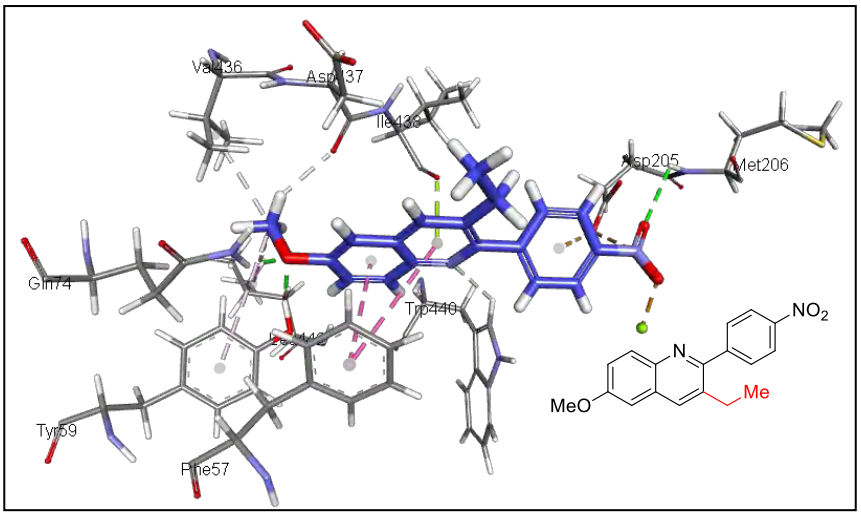
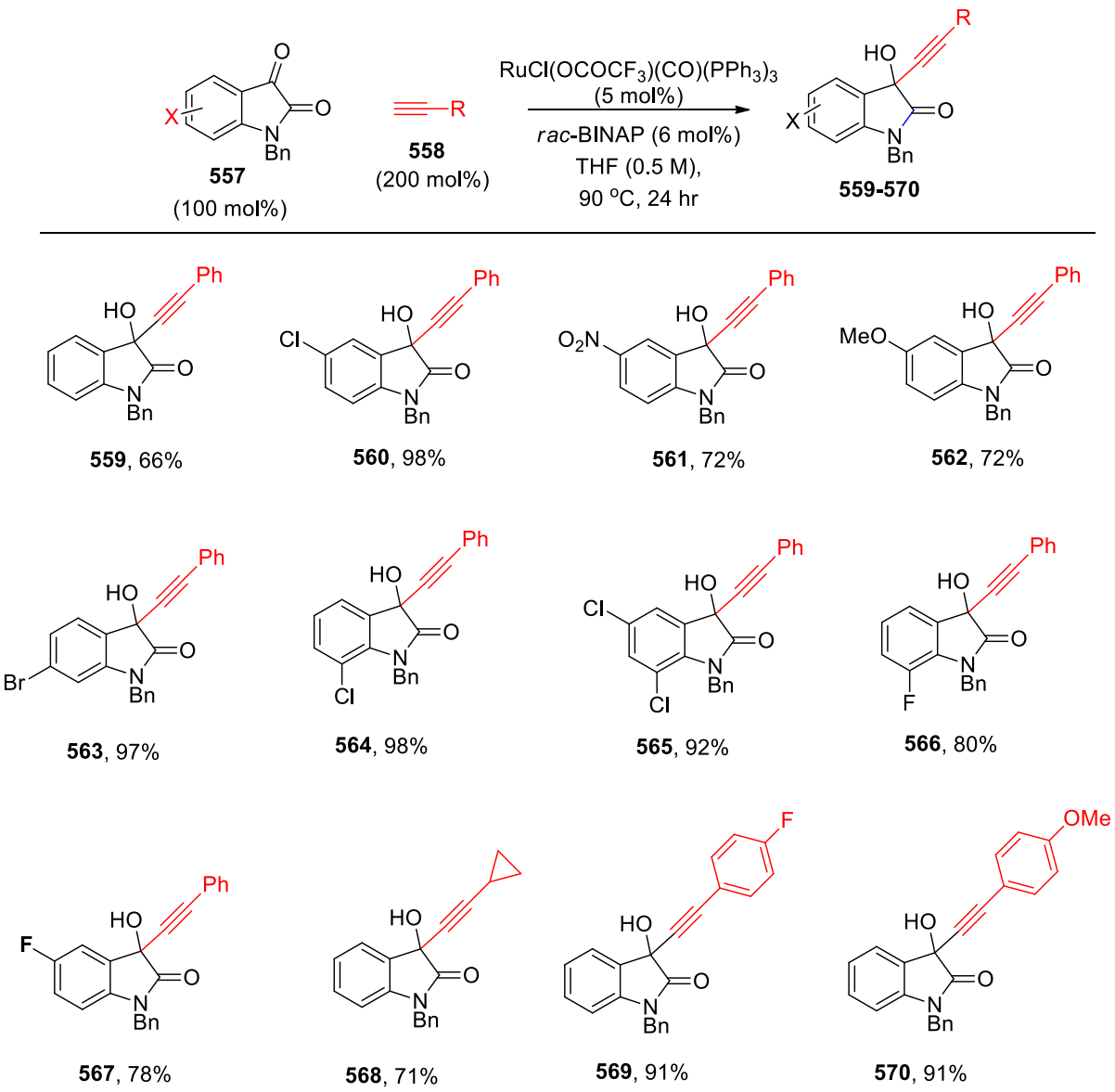


Figure 3.5 3D representation of the plausible docked conformation of compound **476** inside the active site of modeled *h*-NTPDase8

3.2 Part B: Ruthenium Catalyzed Asymmetric Addition of Alkynes to Isatins

Asymmetric alkynylation of unsaturated carbon-carbon or carbon-heteroatom bond provides atom-economic method to construct chiral scaffolds.[177] Addition of alkynes to isatins results in 3-alkynyl-3-hydroxy-2-oxindole compounds which have been found to possess important biological activities.[94,96,97] 3-Alkynyl-3-hydroxy-2-oxindoles have been used as versatile synthons in a wide variety of synthetic applications to prepare biologically active spirooxindoles and heterocyclic compounds.[98] Transition metal catalysis furnishes efficient methods for asymmetric addition of alkynes to isatins. Different metal catalysts and ligands have been reported to achieve asymmetric alkynylation of isatins.[100,102,104]

Abbas research group at Quaid-i-Azam University, Islamabad, Pakistan had previously developed an achiral approach for the synthesis of 3-substituted 3-hydroxyindolin-2-ones using ruthenium catalyst. Ruthenium acetylides were synthesized *in situ* by employing ($RuCl(OCOCF_3)(CO)(PPh_3)_3$) catalyst and were added across different substituted *N*-benzyl isatins under optimized reaction conditions and reaction furnished propargylic alcohol products in good to excellent yield (Scheme 3.11).

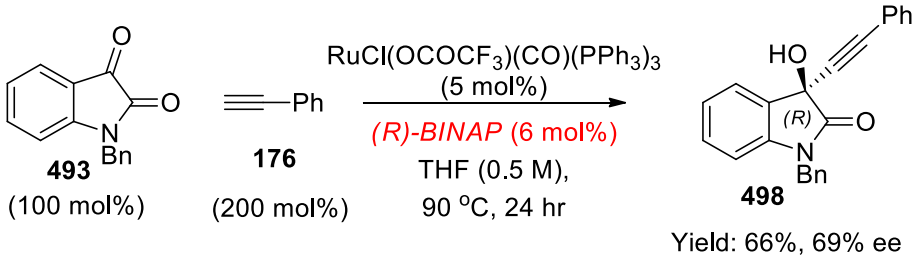


Scheme 3.11 Achiral approach for the ruthenium catalyzed addition of alkynes to isatins by Abbas research group (*M.Phil dissertation by Amna Murtaza*)

3.2.1 Asymmetric Addition of Alkynes to Isatins

Chiral 3-substituted 3-hydroxyindolin-2-ones were also synthesized by addition of alkynes to isatins using ruthenium catalyst with chiral ligand. Initial reaction was performed employing the optimized reaction conditions from achiral approach with the change of racemic ligand. Phenylacetylene (200 mol%) was reacted with

N-benzylisatin (100 mol%) using ($RuCl(OCOCF_3)(CO)(PPh_3)_3$) catalyst (5 mol%), (*R*)-BINAP (6 mol%) in THF (0.5 M) at 90 °C for 24 hour. Reaction afforded the product in 66% yield and 68% enantioselectivity measured by HPLC and it was found that enantiomer *R* is in excess over *S* enantiomer by comparing the retention times with the reported values.[101]



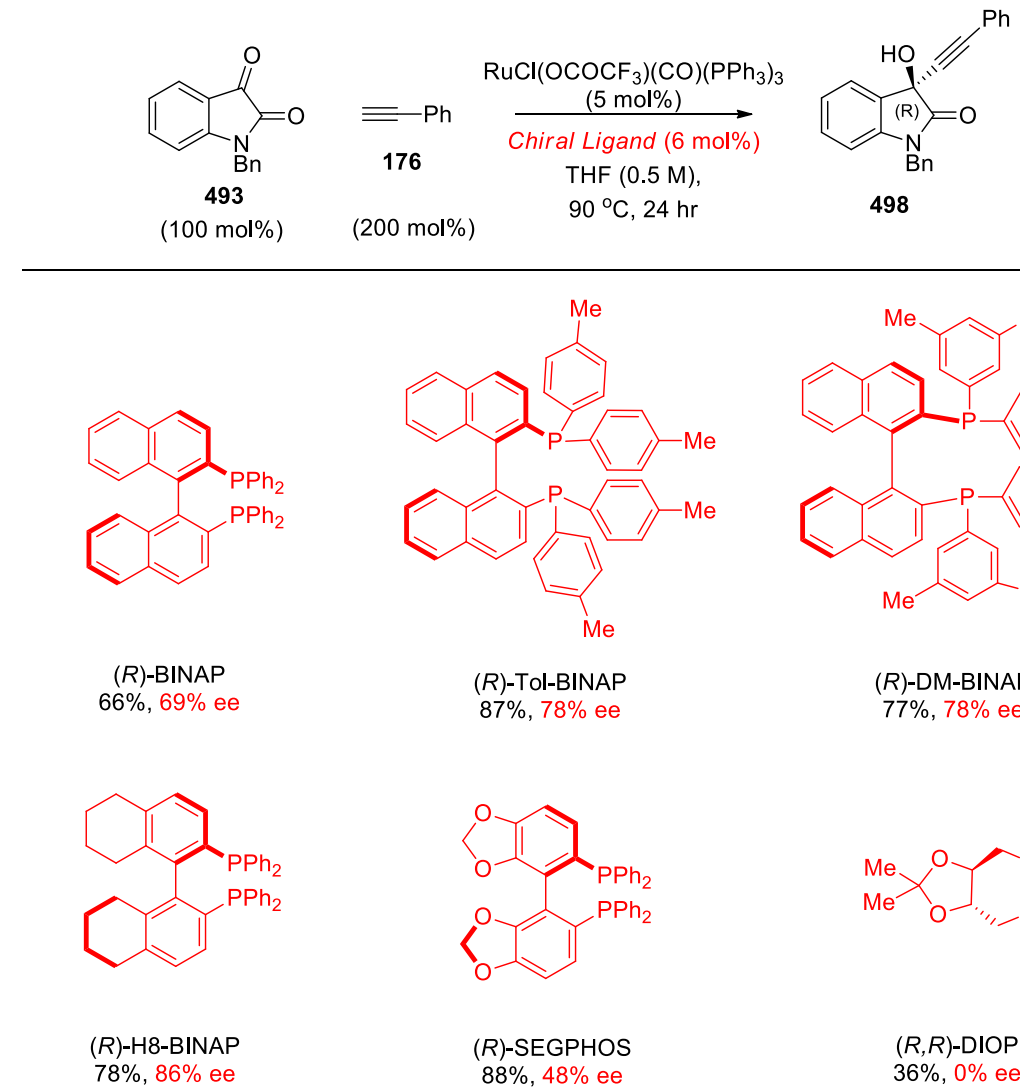
Scheme 3.12 Ruthenium catalyzed asymmetric addition of phenylacetylene to *N*-Benzyl isatin

3.2.1.1 Optimization of Reaction Conditions

Initial reaction required optimization to increase the yield and enantioselectivity of the product. Ligand, reaction time and reaction temperature were screened in this regard to find out the optimum conditions.

3.2.1.1.1 Ligand Screening

To improve the yield and enantioselectivity of the reaction, different chiral ligands were screened using $RuCl(OCOCF_3)(CO)(PPh_3)_3$ (5 mol%) catalyst, chiral ligand (6 mol%), THF (0.5 M) solvent at the temperature of 90 °C for 24 hour.



Chiral HPLC: AD-H column; 30% *i*-PrOH:*n*-hex, 0.9 ml/min

Scheme 3.13 Ligand screening for asymmetric addition of phenylacetylene to *N*-benzyl isatin

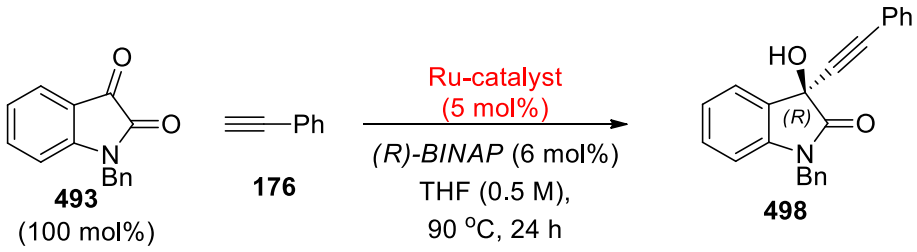
Initial reaction that involved the addition of phenylacetylene to *N*-benzylisatin using $RuCl(OCOCF_3)(CO)(PPh_3)_3$ catalyst and (*R*)-BINAP ligand afforded 66% desired product with 68% enantioselectivity. When the same reaction was performed with (*R*)-Tol-BINAP which is sterically more hindered than (*R*)-BINAP, yield and enantioselectivity improved to 87% and 78% respectively. The more sterically hindered (*R*)-DM-BINAP ligand gave product in 77% yield and

78% enantioselectivity which is better than using (*R)*-BINAP. Using (*R*)-H_8-BINAP which is hydrogenated form of BINAP and has the flexible backbone, enantioselectivity of the desired 3-substituted 3-hydroxyindolin-2-one product improved to 86% and yield was 78%. When reaction was performed with more electron rich ligands i.e., (*R*)-SEGPHOS and (*R,R*)-DIOP, enantioselectivity dropped but yield was better with the former one. From these results it can be inferred that (*R*)-H_8-BINAP is the best ligand to increase the reaction yield and enantioselectivity.

3.2.1.1.2 Ruthenium Catalyst Screening

After finding out the most effective ligand, reaction was screened for different ruthenium catalysts. Ligand (*R*)-BINAP was used for screening reactions instead of (*R*)-H_8-BINAP because of the cost of the later. Phenylacetylene was added to *N*-benzylisatin using Ru-catalyst (5 mol%), (*R*)-BINAP (6 mol%), THF (0.5 M) as solvent at the temperature of 90 °C for 24 hours.

Table 3.7 Ruthenium Catalyst Screening for Asymmetric Addition of Phenylacetylene to *N*-Benzyl Isatin



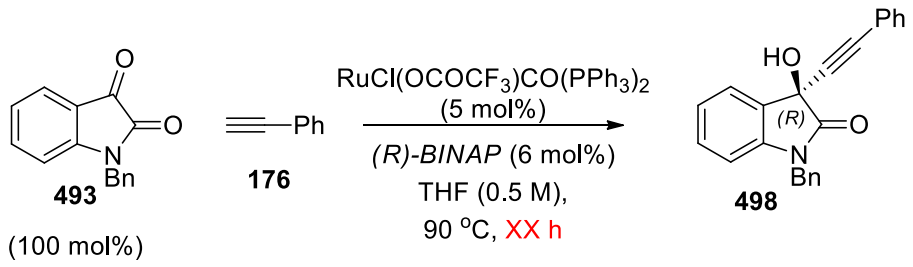
S. No	Ru-Catalyst	Yield%	ee%
1	$RuCl(OCOCF_3)CO(PPh_3)_2$	66	69
2	$Ru(OCOCF_3)_2CO(PPh_3)_2$	68	60
3	$[RuCl_2(p\text{-cymene})_2]$	47	68
4	$[Ru(COD)Cl_2]_n$	80	72

Initial investigation with $RuCl(OCOCF_3)CO(PPh_3)_2$/(R)-BINAP catalyst-ligand combination afforded 66% yield and 69% enantioselectivity (entry 1). When catalyst was changed to $Ru(OCOCF_3)_2CO(PPh_3)_2$ (entry 2) there is slight increase in the yield of the reaction (68%) but enantioselectivity had decreased to 60%. Using (*p*-cymene)ruthenium(II) chloride dimer (entry 3) gave the desired product in low yield i.e., 40% and enantioselectivity is same as initial reaction (entry 1). Finally, Dichloro(1,5-cyclooctadiene)ruthenium(II) polymer catalyst $[Ru(COD)Cl_2]_n$ (entry 4) gave enhanced yield (80%) and enantioselectivity (72%) of the reaction.

3.2.1.1.3 Reaction Time Screening

Initial investigation of asymmetric addition of phenylacetylene to *N*-benzylisatin was also screened for different time intervals. In this optimization study, phenylacetylene (200 mol%) was added to *N*-benzylisatin (100 mol%) using $RuCl(OCOCF_3)CO(PPh_3)_2$ (5 mol%), (*R*)-BINAP (6 mol%), THF (0.5 M) as solvent at the temperature of 90 ^oC for different reaction hours.

Table 3.8 Reaction Time Screening for Asymmetric Addition of Phenylacetylene to *N*-Benzyl Isatin



S. No	Time (h)	Yield%	ee%
1	24	66	69
2	12	98	82
3	8	91	80

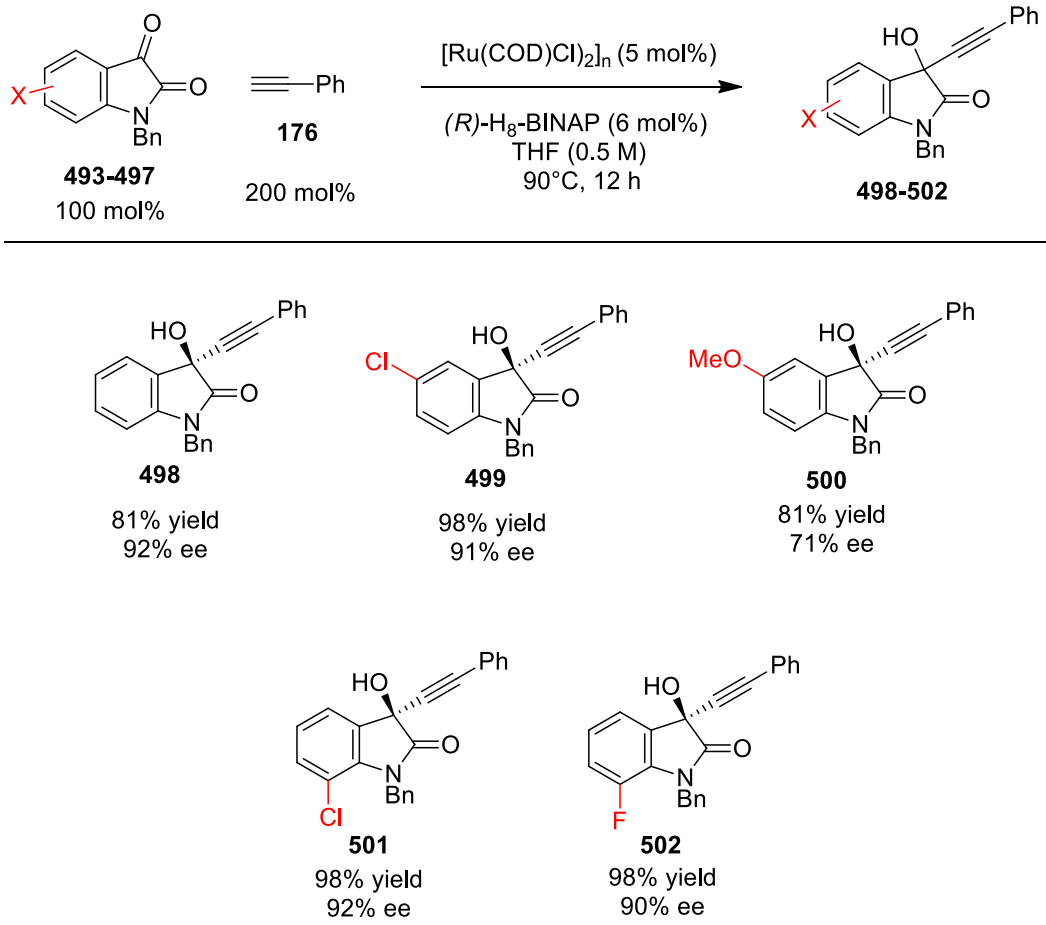
It was noticed that reducing reaction time to half from the initial reaction time (24 hours) pleasingly increased the yield and enantioselectivity of the reaction. For 12 hours reaction (entry 2) yield and enantioselectivity was 98% and 82% respectively. When reaction time was further reduced to 8 hours (entry 3) there was drop in the reaction yield and enantioselectivity. From these findings it can be inferred that reaction might be reversible. Therefore, increase reaction time (24 hours) makes reaction less selective and less productive because of reversibility of the reaction and reactants remain unreacted at the end of the reaction.

Concluding the reaction optimization study, it was found that asymmetric addition of phenylacetylene to *N*-benzylisatin was improved in yield and enantioselectivity with $[Ru(COD)Cl_2]_n$/(*R*)-H_8-BINAP catalyst-ligand combination in THF as solvent at the temperature of 90 ºC for 12 hours.

3.2.2 Scope of Asymmetric Addition of Alkynes to Isatin

The generality and efficacy of the reaction was illustrated by developing its scope by varying substrates. Different substituted *N*-benzylisatins were used in this case. Phenylacetylene (200 mol%) was added to different substituted *N*-benzylisatins (100 mol%) using $[Ru(COD)Cl_2]_n$ catalyst (5 mol%), (*R*)-H_8-BINAP ligand (6 mol%) in THF (0.5M) as solvent at the temperature of 90 ºC for 12 hours.

Initial reaction of phenylacetylene with unsubstituted *N*-benzylisatin under optimized reaction conditions afforded desired product in 81% yield and 92% enantioselectivity. Reaction with 5-methoxy *N*-benzylisatin gave product in 81% yield but enantioselectivity dropped to 71%. 5-Chloro and 7-chloro *N*-benzylisatin afforded the similar yield and enantioselectivity of the product which is 98% and 92% respectively. 7-Fluoro *N*-benzylisatin produced propargylic alcohol product in 98% yield and 91% enantioselectivity. From these findings, it can be inferred that electron withdrawing group on isatin substrate is responsible for enhanced enantioselectivity while methoxy group being less electronegative and more electron donating than halogen group has resulted in decreased enantioselectivity of the product.

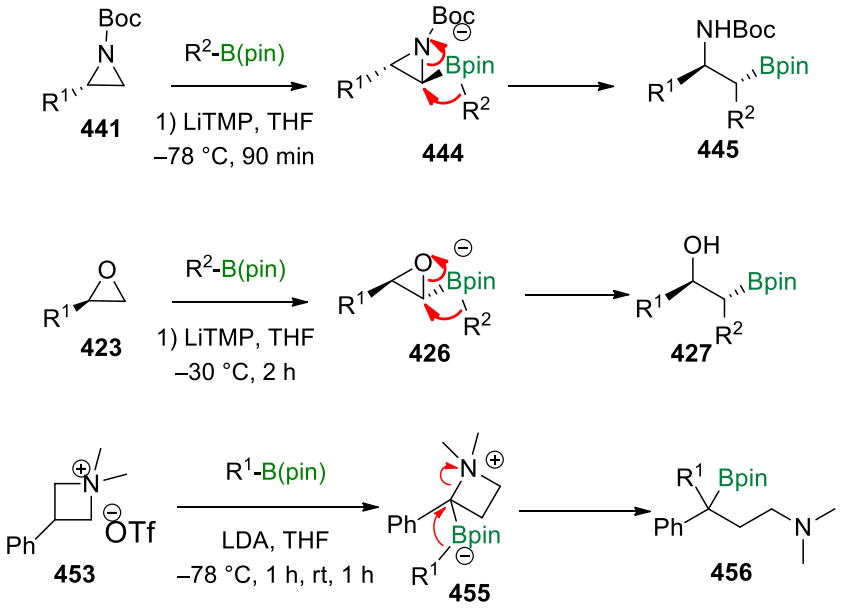


Scheme 3.14 Substrate scope for ruthenium catalyzed asymmetric addition of phenylacetylene to *N*-benzyl isatin

3.3 Part C: Strain-Release Driven Synthesis of Azetidine Boronic Esters

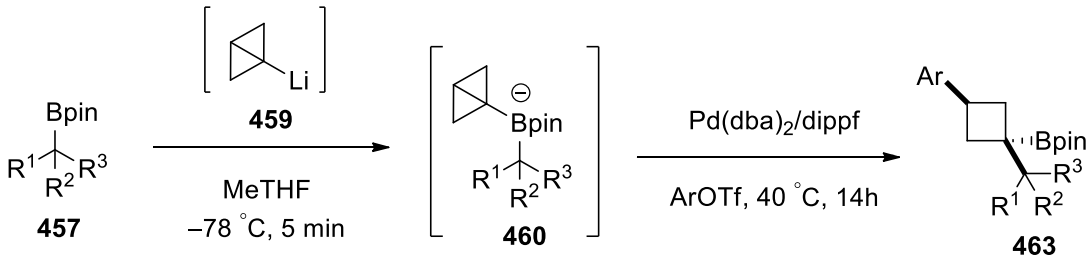
Azetidine is an important structural motif in medicinal chemistry. It prevails in many bioactive compounds and natural products. In addition to this, many marketed drugs have this core structure. From synthetic point of view, azetidine has received less attention than its higher analogues like piperidine and pyrrolidine.[109] Some common methods of synthesis of azetidines include inter- and intramolecular alkylation of amine nucleophiles, reduction of *β*-lactams, and the aza Paternò−Büchi reaction.[178] Therefore, new methodologies for the efficient synthesis of azetidine are highly appreciated.

Lithiation-borylation is an important technique for the construction of complex structures through homologation of boronic esters. Boronic esters can be later transformed into different functional group compounds.[156]Aggarwal group at University of Bristol, England has previously reported the lithiation followed by borylation in strained rings which includes epoxides, aziridines and azetidinium ions. These strained compounds undergo lithiation followed by borylation to form boron-ate complexes which suffer 1,2-metalate rearrangement to convert in to their corresponding open chain analogues by release of ring strain.



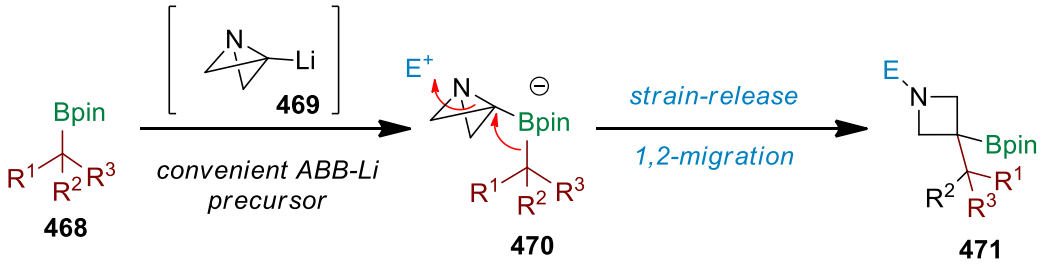
Scheme 3.15 Lithiation-borylation in strained rings

Recently, bicyclo[1.1.0]butyl lithium was utilized for homologation of boronic ester by cyclobutane unit reported by Aggarwal group. Bicyclo[1.1.0]butyl lithium was reacted with different boronic esters to form highly strained bicyclo[1.1.0]butyl boronate complexes. These anionic complexes then underwent 1,2-metalate rearrangement when treated with electrophilic palladium(II)−aryl complexes to ultimately form a range of diastereomerically pure borylated cyclobutanes.



Scheme 3.16 Homologation of boronic esters by cyclobutane

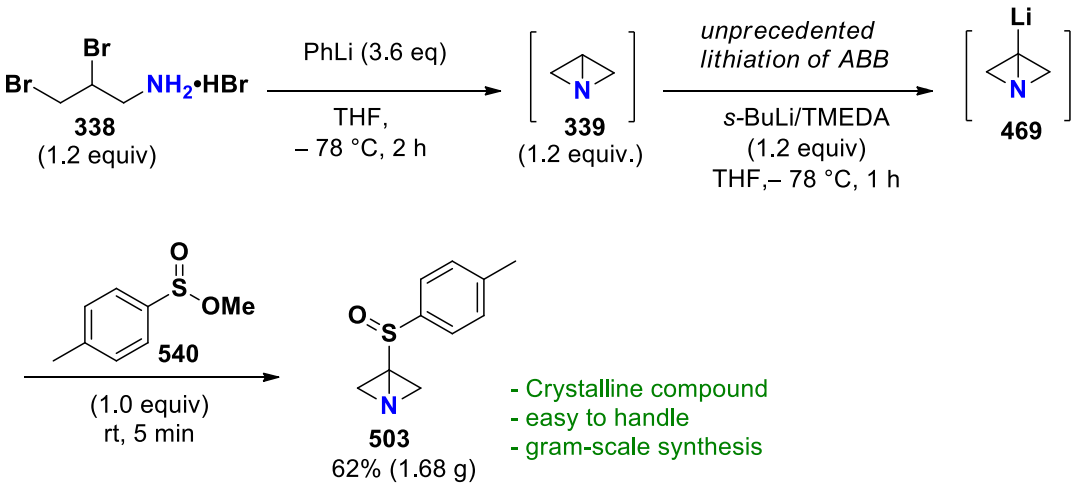
1-Azabicyclo[1.1.0]butane is a nitrogen analog of bicyclo[1.1.0]butane. Structural features and reactivity of 1-azabicyclo[1.1.0]butane resembles bicyclo[1.10]butane. Azabicyclobutanes have been utilized in the synthesis of functionalized azetidines exploiting the unusual reactivity of C3-N bond. In the present research, azabicyclo[1.1.0]butane was lithiated at position-3 and resulting azabicyclo[1.1.0]butyl lithium **469** was reacted with different boronic esters. Azabicyclo[1.1.0]butyl lithium upon reaction with boronic esters forms highly strained boronate complex which undergoes 1,2-metalate rearrangement in the presence of an electrophile to form azetidinyl boronic esters. These azetidinyl boronic esters can be later transformed into functionalized azetidine.



Scheme 3.17 Homologation of boronic esters by azetidine unit

3.3.1 Lithiation of Azabicyclo[1.1.0]butane

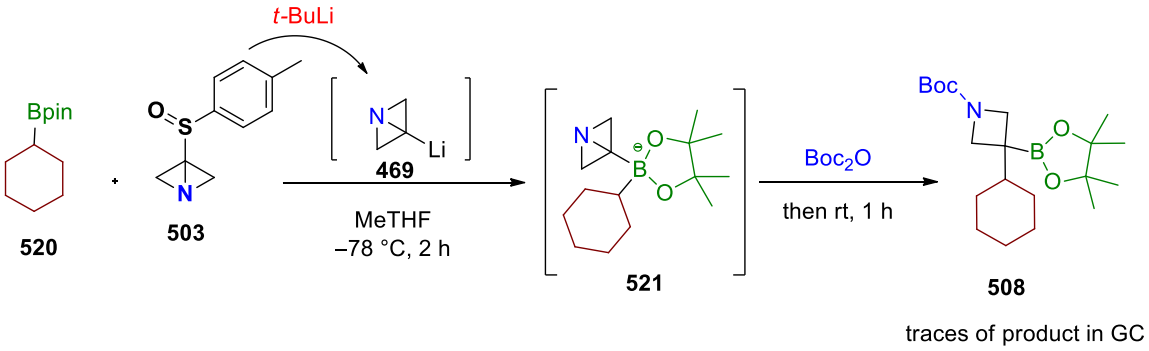
Lithiation of azabicyclo[1.1.0] butane **339** is not reported before. In order to lithiate azabicyclo[1.1.0]butane **339**, hydrogen at C-3 which is bridgehead carbon is considered most acidic because of more s-character. For lithiation of **339**, different protocols for lithiation of strained rings from literature were employed. After several attempts using different lithium reagents it was found that using *sec*-butyl lithium/TMEDA[179], azabicyclo[1.1.0]butane **339** can be lithiated at position-3. Azabicyclo[1.1.0]butane **339** is synthesized *in situ* from ammonium salt using phenyl lithium at −78 °C.[162] After lithiation of **339** the generated specie **469** which is lithium carbenoid is very reactive and it can react with its own precursor **339** *in situ* to form polymerized product.[123] So, as soon as lithium anion **469** is generated it should be trapped. Therefore, azabicyclo[1.1.0]butyl lithium **469** was trapped with methyl 4-methylbenzenesulfinate **555** to form sulfoxide. In this way, the resulting sulfoxide can be considered as convenient azabicyclobutyl lithium precursor and used further for reaction with boronic esters. Sulfoxide **504** was obtained in 62% yield. 3-(*p*-Tolylsulfinyl)-1-azabicyclo[1.1.0]butane **504** was presumed as solid and stable reagent that can be utilized to regenerate lithiated specie **469** through lithium-sulfoxide exchange.[156] Lithiation is fast step occurring at low temperature that hampers polymerization reaction. Sulfoxide **503** emerged as stable and easy-to-handle crystalline solid.



Scheme 3.18 Lithiation of azabicyclo[1.1.0]butane and synthesis of azabicyclobutane sulfoxide (ABB-S)

3.3.2 Trapping of ABB-Li with Boronic Ester

Azabicyclo[1.1.0]butyl sulfoxide **503** was used to generate azabicyclo[1.1.0]butyl lithium **469** and then it was trapped with cyclohexyl pinacol boronic ester **520**. In the initial investigation boronic ester **520** was mixed with ABB-sulfoxide (1.3 equiv) in 2-methyl tetrahydrofuran at −78 °C and reacted with tertbutyl lithium[10] (1.3 equiv) and then reaction mixture was stirred for 2 h. It resulted in complete boronate complex formation, as evidenced by a single peak at ca. 6 ppm in the ^{11}B NMR spectrum of the reaction mixture. To facilitate 1,2-metalate rearrangement Boc_2O (2 equiv) was added in the mixture and stirred for an hour at room temperature. Only traces of the product were observed in GC.

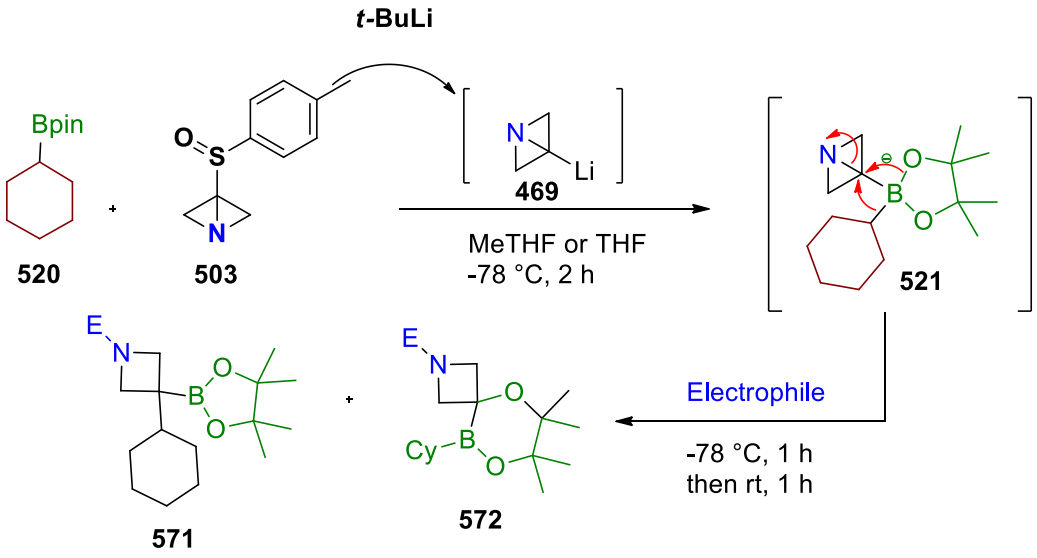


Scheme 3.19 Azabicyclobutyl lithium reaction with cyclohexyl pinacol boronic ester followed by trapping with Boc_2O

3.3.3 Reaction Optimization

Initial study revealed that boronate complex **533** did not undergo spontaneous 1,2-metalate rearrangement although it has the high strain energy which should be released upon ring opening. Therefore, to facilitate the 1,2-metalate rearrangement there should be a better leaving group on amine.[180] In this regard, different activating reagents were explored with variation in the reaction conditions.

Table 3.9 Reaction Optimization for the Reaction of Azabicyclobutyl Lithium with Cyclohexyl pinacol boronic ester



Entry	*t*-BuLi (equiv)	Solvent	Electrophile	571/%[a]	572/%[a]
1	1.30	MeTHF	CbzCl	55	37
2	1.30	MeTHF	PhCOCl	49	19
3	1.30	MeTHF	AcOH[b]	78	No
4	1.20	THF	AcOH[b]	80[c,d]	No
5	1.20	THF	TsOH[b]	80	No

[a]NMR yield. [b]Followed by Boc protection. [c]Isolated yield. [d]Gramscale (4.76 mmol)

When benzyl chloroformate was added after the formation of boronate complex **521** and afterwards stirring reaction at −78 °C for an hour and then warming it for another hour, it gave the inseparable mixture of boronic and borinic ester **571** and **572** resulting from C- and O-migration, respectively, in a 1.5:1.0 ratio and a combined 92% NMR yield (entry 1). It is clear from the reaction yield that boronate complex **521** formation is almost complete, but it is converting into two products. ^{11}B NMR showed two peaks one at 32.9 ppm for boronic ester (the desired product) and other at 47.0 ppm, which corresponds to a borinic ester. The

^{1}H NMR spectrum of the purified product contains two sets of peaks, most clearly in the azetidine region (~4.50 – 3.50 ppm).

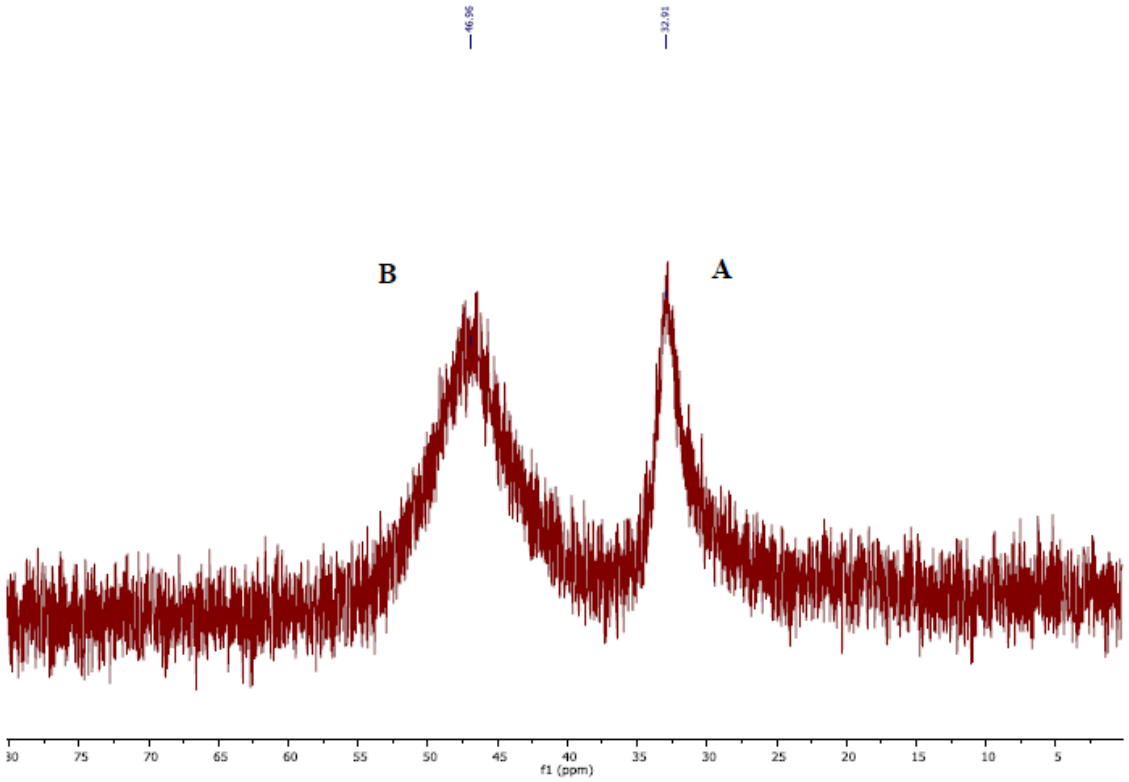


Fig 3.6 Presence of boronic ester **571** and borinic acid **572** product in ^{11}B NMR

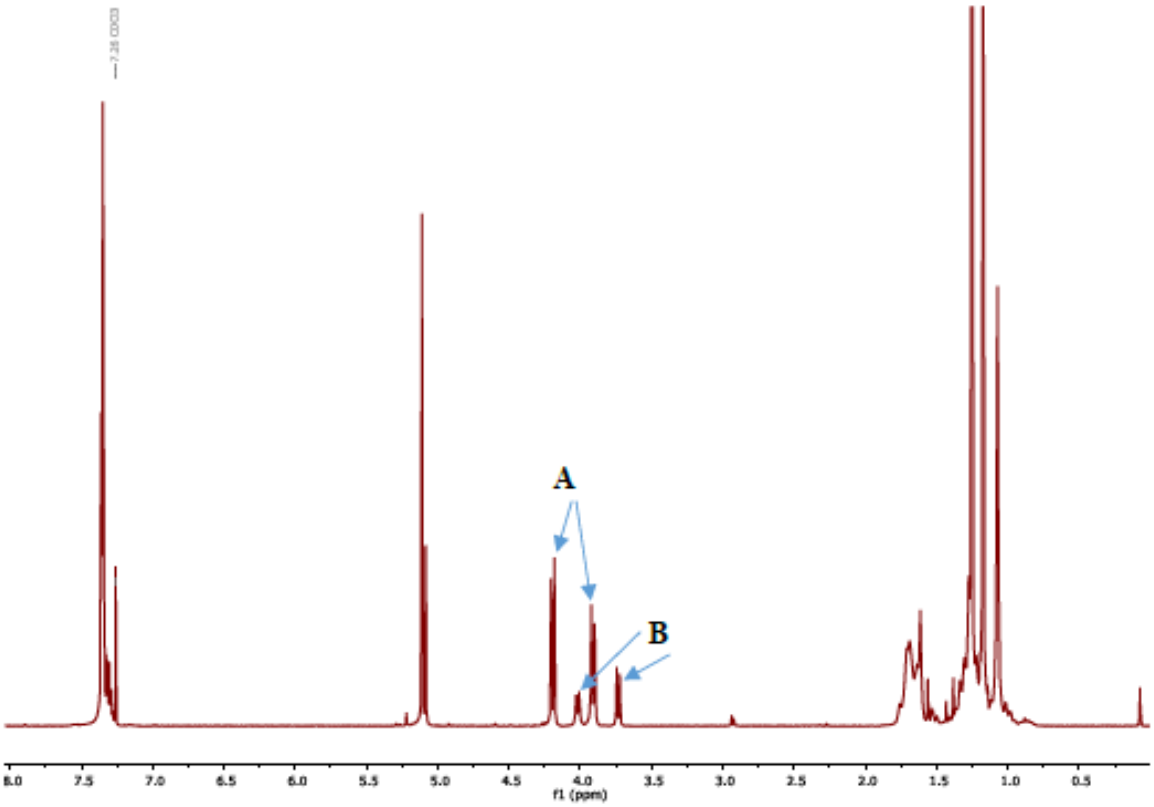


Fig 3.7 Presence of boronic ester **571** and borinic acid **572** product in ^{1}H NMR

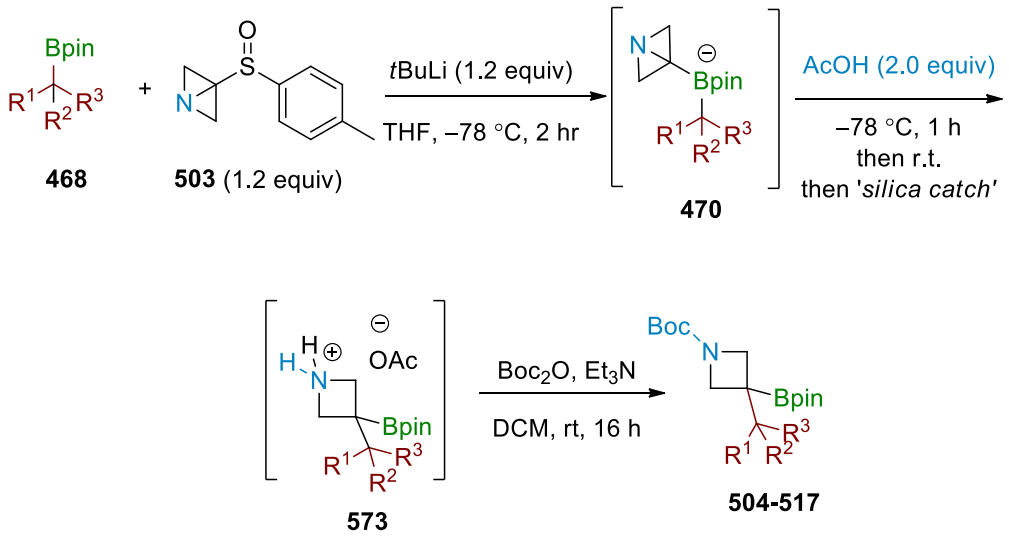
When benzoyl chloride was added in the reaction it behaved similarly giving both the products **571** and **572** but in relatively low NMR yield (entry 2). When boronate complex **521** was treated with acetic acid as an alternative it resulted in exclusive C-migration product and following protection with Boc group, azetidine **571** was found in 78% NMR yield (entry 3). Unprotected N−H azetidine is generated as an intermediate in this approach which is additional benefit of this reaction because N−H azetidine can be reacted in any desired manner. Furthermore, changing the solvent from MeTHF to THF and slightly modifying the stoichiometry (entry 4) improved the reaction yield.

For purification of N−H azetidine products 'silica catch' method was introduced. Following this method, N−H azetidine products were easily separated from the sulfoxide byproduct by filtering through a plug of silica gel: the azetidine acetic

acid salt was retained on the silica, and all other compounds eluted. The top layer of the silica gel plug was then collected and protected with Boc, giving pure **571** in 80% isolated yield (1.39 g, 3.81 mmol, entry 4). It was investigated further that the reaction could be triggered using TsOH which enabled purification of the azetidine by precipitation of the tosylate salt without using the "silica catch" purification (entry 5).

3.3.4 Scope of the Reaction

The optimized reaction sequence for azetidine boronic ester synthesis is as under:

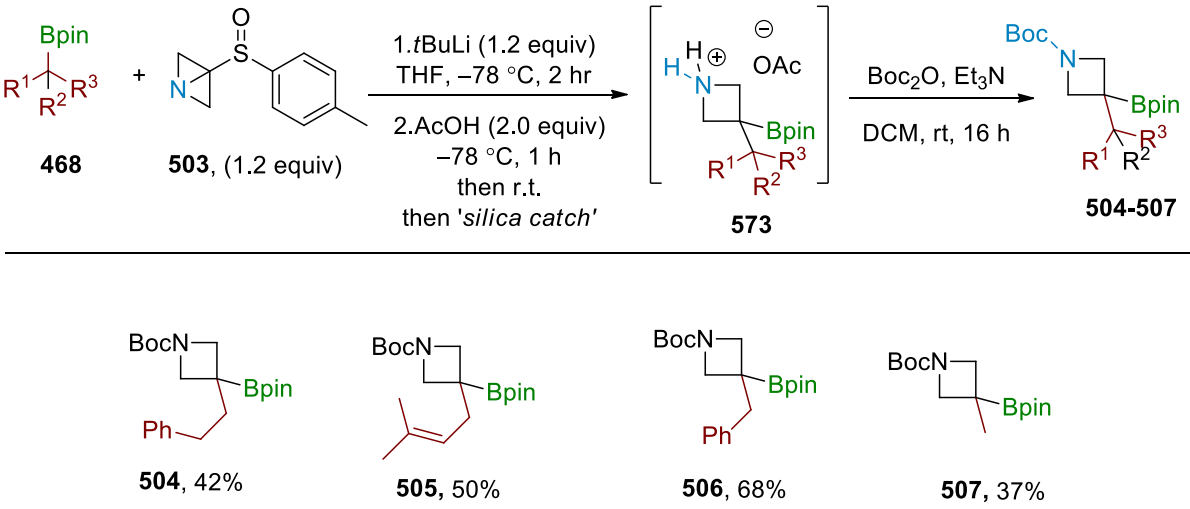


Scheme 3.20 Optimized reaction conditions for synthesis of azetidine boronic ester

3.3.5 Boronic Ester Scope

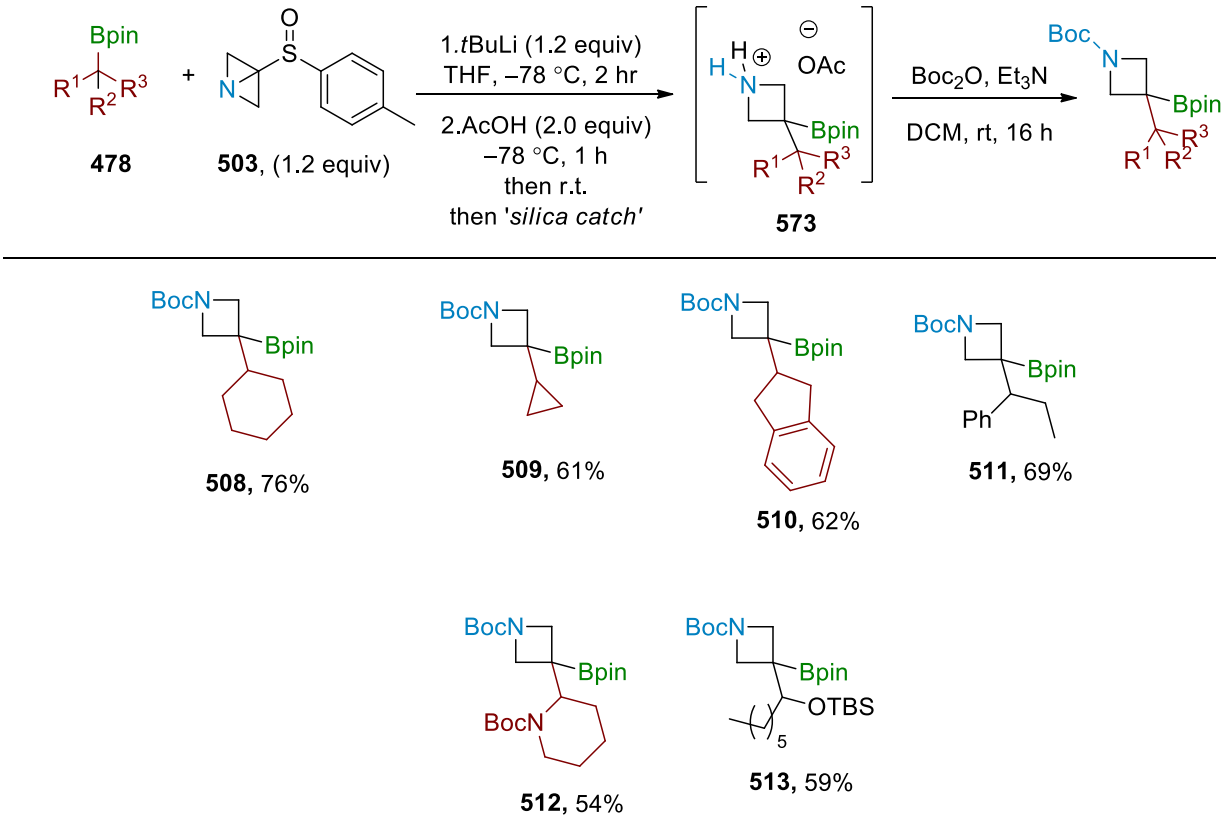
Different primary, secondary and tertiary boronic esters were treated under optimized reaction conditions to illustrate the scope and strength of the reaction. The range of primary boronic esters included *n*-alkyl **504**, allylic **505**, benzylic **506** and methyl **507**. Methyl group is useful substituent in medicinal chemistry,[181,182] but it is considered a poor migrating group.[183,184] So, there were chances for O-migration product as observed when benzyl chloroformate was

used as an activator. However, exclusive C-migration was observed when acetic acid was used with this challenging substrate to give product in modest yield.



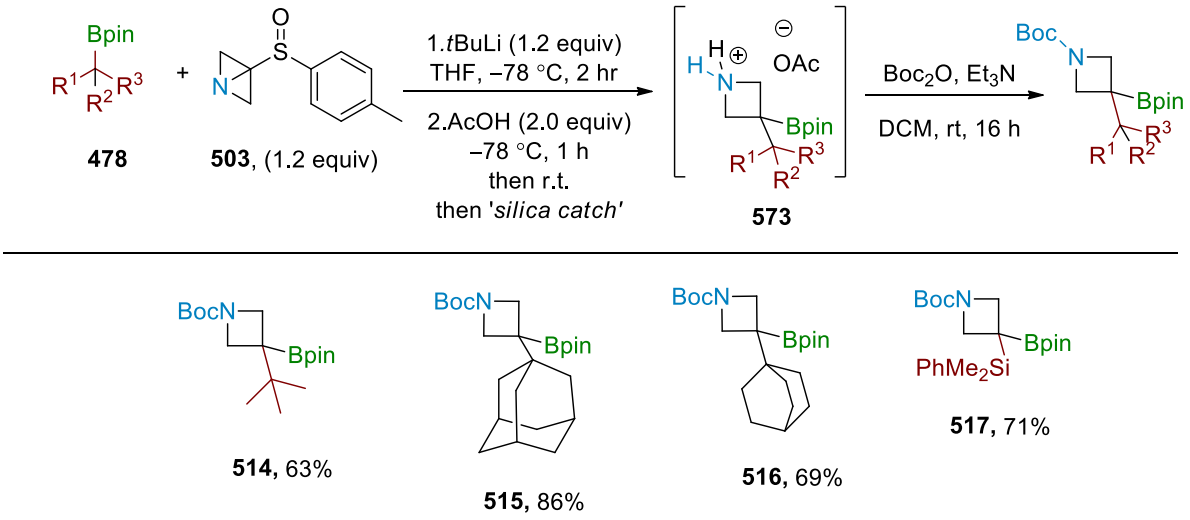
Scheme 3.21 Scope of primary boronic esters for homologation

In the category of secondary boronic esters, prominent candidates included an α-amino boronic ester[168] which gave piperidine bearing azetidine product **512** in 54% yield, and α-alkoxy boronic ester which gave **513** in 59% yield, both these products are part of previously reported azetidine encompassing pharmaceuticals.[110,185].



Scheme 3.22 Scope of secondary boronic esters for homologation

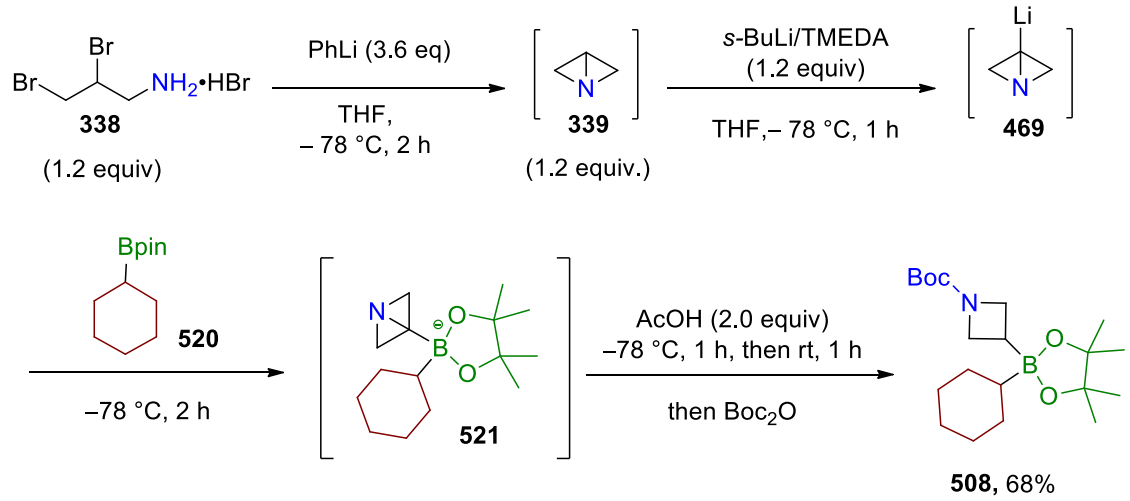
The tertiary boronic ester included *tert*-butyl **514**, adamantyl **515**, bicyclo[2.2.2]octyl[166] **516**, and dimethyl phenyl silyl **517** giving the azetidine products in good to excellent yields.



Scheme 3.23 Scope of tertiary boronic esters for homologation

Aryl and vinyl boronic esters were also employed, giving the desired azetidines in good yields but isolation of the resulting products was unsuccessful because of instability of N−H azetidine intermediates and the final *N*-tert-butyloxycarbonyl protected azetidine products on silica gel. Therefore, these products were not isolated rather quantified with ^{1}HNMR using internal standard method.

Finally, direct reaction from the ammonium salt **338** was explored thereby avoiding sulfoxide intermediate **503**, which could be more appropriate when a single azetidine product is required. Thus, ammonium salt **338** was treated with phenyl lithium, followed by *sec*-butyl lithium/TMEDA, cyclohexyl pinacol boronic ester **520**, acetic acid, and finally Boc protection, gave the homologated azetidine boronic ester product **508** in 68% yield.

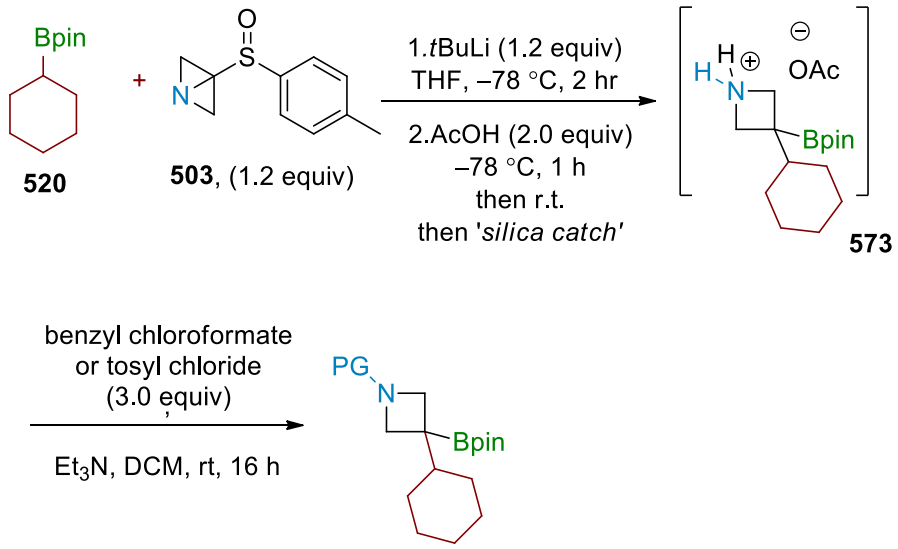


Scheme 3.24 Synthesis of azetidine boronic esters directly from the 2,3-dibromopropan-1-ammonium bromide

3.3.6 Nitrogen Reactions Scope

3.3.6.1 Scope of Different Protecting Groups on Nitrogen

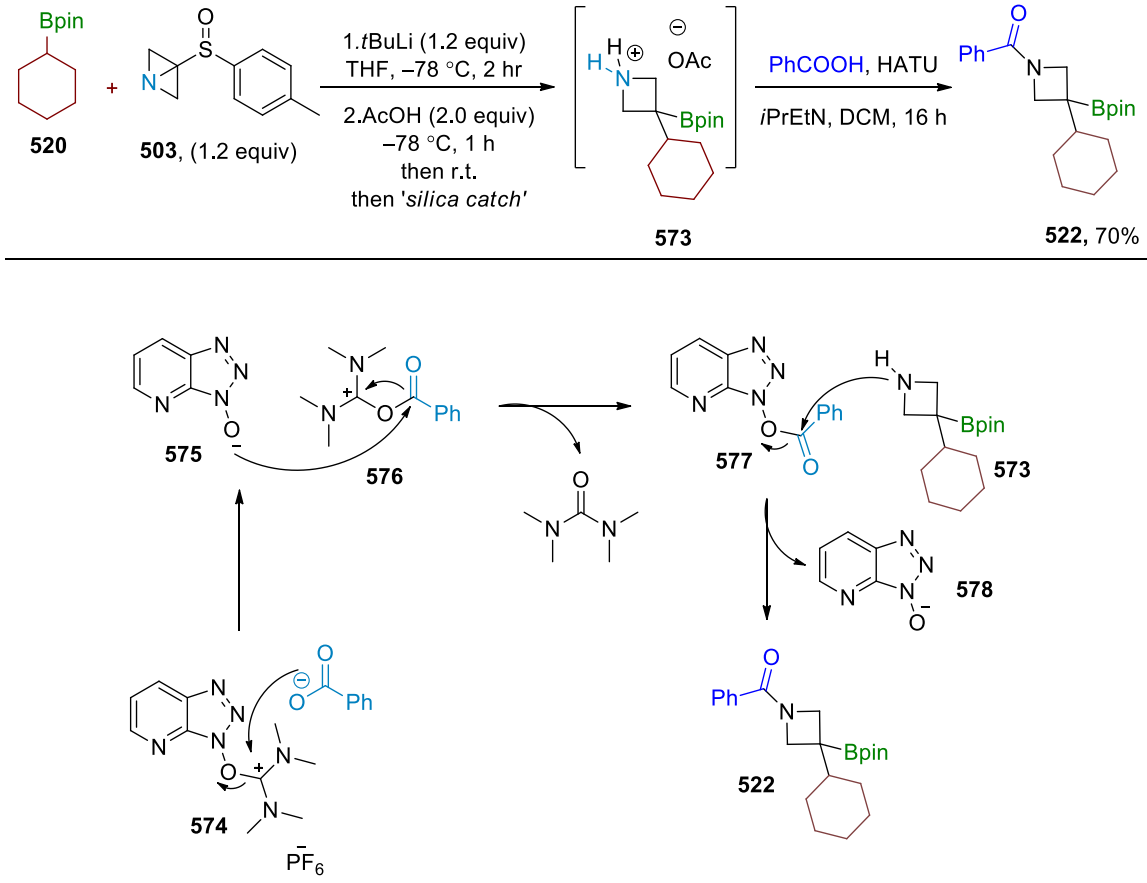
Different transformations of nitrogen of the intermediate N−H azetidines were carried out to demonstrate the reaction utility further. Apart from Boc protecting group, benzyloxycarbonyl (Cbz) and tosyl (Ts) groups were placed on nitrogen.



Scheme 3.25 Scope of the nitrogen reactions of borylated azetidines

3.3.6.2 Amide Coupling of N-H Azetidine Intermediate

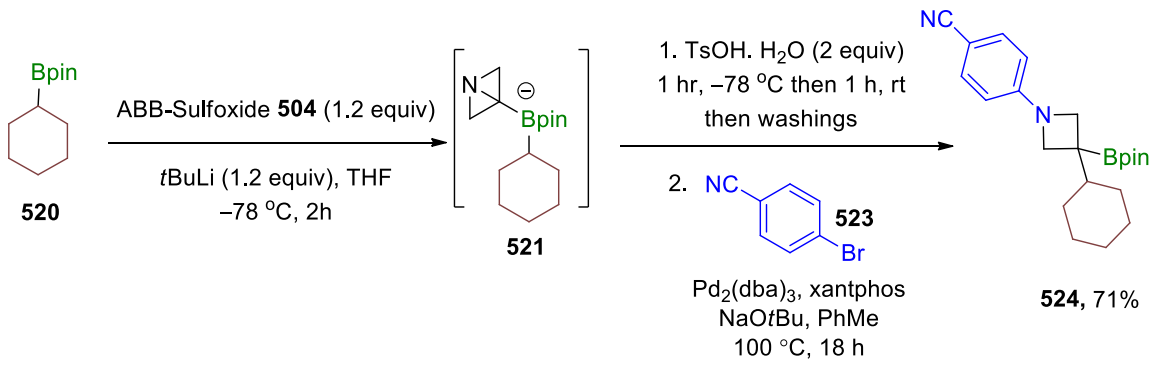
Intermediate N−H azetidine was also employed in amide coupling reaction using HATU (Hexafluorophosphate Azabenzotriazole Tetramethyl Uronium) as coupling reagent with benzoic acid. Reaction afforded product in 70% yield. Base deprotonates benzoic acid and resulting benzoate anion attacks on electron deficient carbon of HATU to form unstable O-acyl(tetramethyl)isouronium (OAt) salt. The OAt anion **575** attacks the isouronium salt **576**, affording the OAt-active ester **577** and releasing tetramethylurea. N-H azetidine intermediate reacts with OAt-active ester and results in acylation product **522**.



Scheme 3.26 Amide coupling of N-H azetidine intermediate using HATU as coupling reagent

3.3.6.3 Buchwald-Hartwing Coupling of N-H Azetidine

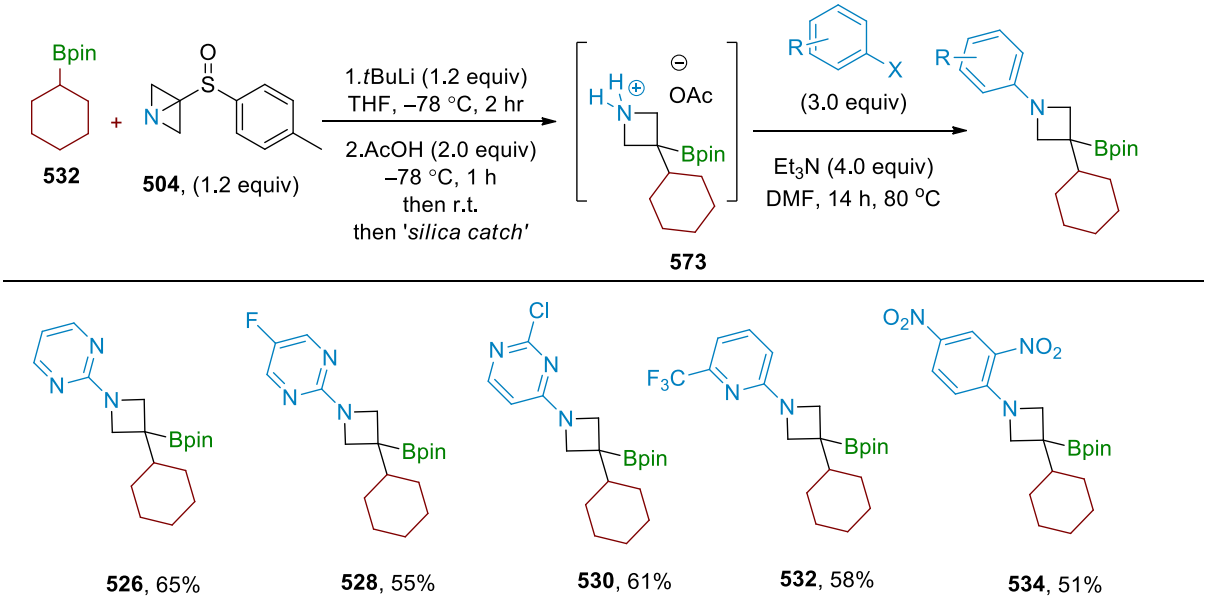
N−H azetidine intermediate could also be the amine candidate for Buchwald−Hartwig cross-coupling.[186] In an attempt N-H azetidine tosylate salt was coupled with 4-bromobenzonitrile using Pd_2dba_3/xantphos catalyst-ligand system giving 71% product. N-H azetidine acetic acid salt was not active in this reaction.



Scheme 3.27 Buchwald-Hartwig coupling of N-H azetidine intermediate

3.3.6.4 SNAr Reactions Scope of N-H Azetidine

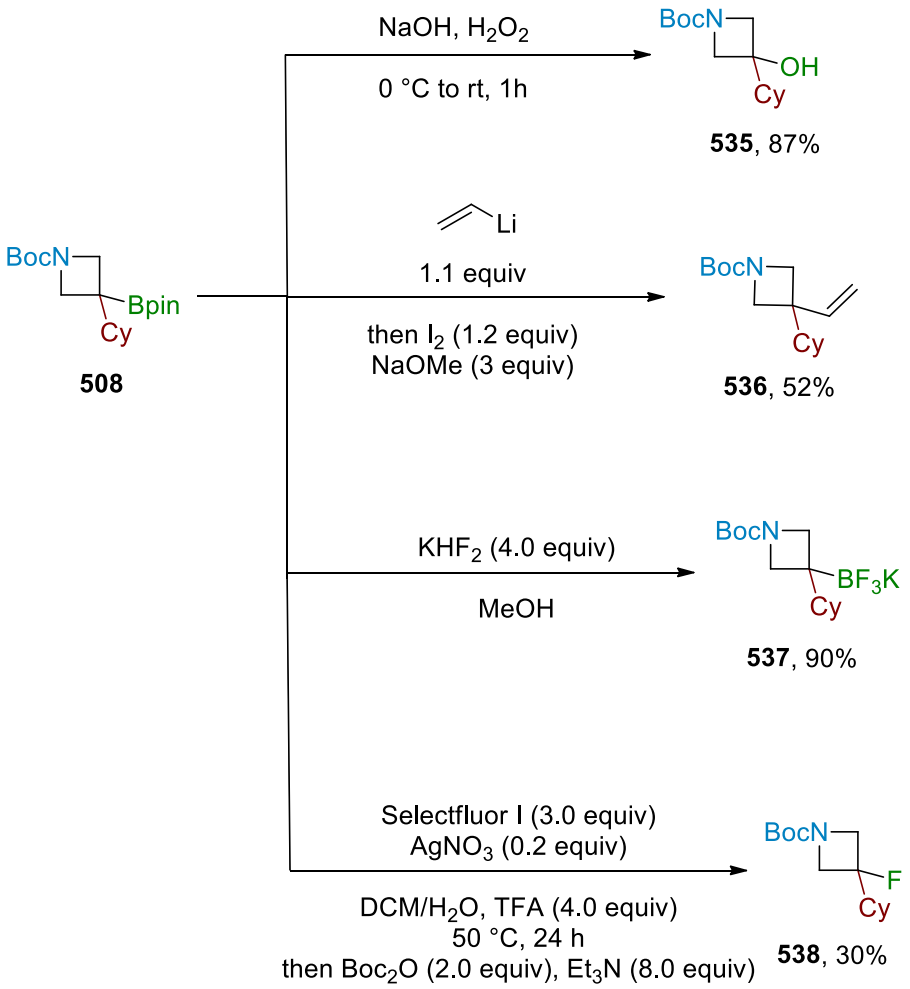
SNAr reactions were performed utilizing azetidine intermediate and range of (hetero)aryl halides to give substituted products in good yields. These reaction classes are among the most used reactions within the field of medicinal chemistry.[187]



Scheme 3.28 SNAr reactions scope of N-H azetidine

3.3.7 Transformation of Boronic Ester

To highlight the synthetic utility of borylated azetidine products, azetidinyl boronic ester was exposed to various boronic ester transformations. Initially, azetidinyl boronic ester **508** was treated with basic hydrogen peroxide to synthesize corresponding alcohol **535**. In another transformation, boronic ester **508** was converted to olefination product **536** when treated with vinyl lithium (derived from vinyl bromide through halogen-lithium exchange) employing Zweifel olefination conditions[170] (I_2/NaOMe). Trifluoroborate salt[171] **537** was also prepared by reacting boronic ester with KHF_2/MeOH. All these transformations afforded good to excellent yield of the azetidine product. Finally, fluorinated azetidine **538** was prepared through deboronative fluorination.[172] Reaction gave product in moderate yield. Fluorinated amines are significant motifs since the fluorine atom can tune physical and chemical properties of the molecule, including the *p*Ka of the amine.[188]



Scheme 3.29 Different transformations of boronic ester

Conclusions

Research work presented in this dissertation comprises three parts. Part A is the synthesis of quinoline derivatives as nucleoside triphosphate diphosphohydrolases inhibitors, Part B is Ruthenium catalyzed asymmetric addition of alkynes to different substituted isatins and Part C is synthesis of azetidine boronic esters by lithiation-borylation of azabicyclo[1.1.0]butane.

Quinoline derivatives were synthesized by reacting 4-methoxy-*N*-(4-nitrobenzylidene)aniline with different aldehydes using molecular iodine as catalyst. Inhibitory activity of synthesized derivatives was measured against four isoenzymes of human nucleoside triphosphate diphosphohydrolases *h*-NTPDase1,-2,-3 and -8 using suramin as the standard inhibitor. Almost all compounds showed promising results. Compounds **476**, **481**, **483** and **487** exhibited the excellent activities against NTPDase1,-2,-3 and -8, respectively and their IC_{50} values were in lower micro-molar range. Molecular docking studies were used to analyze the interaction of these derivatives with the enzymes. Molecular docking study revealed that these compounds inhibited the respective enzyme by interacting *via* hydrogen bond, pi-anion and pi-cation interactions. These derivatives can serve as the interesting scaffolds to be explored further for enhanced activity as well as selectivity against *h*-NTPDases.

Inspiring from the recent reports on the synthesis of chiral 3-alkynyl-3-hydroxy-2-oxindole compounds by employing different transition metal catalysts, ruthenium catalyzed enantioselective addition of alkynes to different substituted isatins was achieved. Reaction conditions were optimized by screening different catalysts, chiral ligands, temperature and time. $[Ru(COD)Cl)_2]_n$ in combination with chiral (*R*)-H_8-BINAP ligand catalyzed this reaction giving out the high yields and enantioselectivities. Excellent yields (up to 98%) and enantioselectivities (up to 92%) of 3-alkynyl-3-hydroxy-2-oxindole derivatives were obtained.

Azetidine has inspiring range of biological activities which makes it part of many marketed drugs and drug leading compounds. In this part of study, azetidines were synthesized by the homologation of boronic esters with an azetidine unit.

Azabicyclo[1.1.0]butane was lithiated at position-3 and azabicyclo[1.1.0]butyllithium **469** was reacted with different boronic esters to synthesize borylated azetidines. Boronic ester group of synthesized azetidine was later transformed into useful azetidine derivatives.

List of Publiations

1. Murtaza, A.; Afzal, S.; Zaman, G.; Saeed, A.; Pelletier, J.; Sévigny, J.; Iqbal, J.; Hassan, A. Divergent Synthesis and Elaboration of Structure Activity Relationship for Quinoline Derivatives as Highly Selective NTPDase Inhibitor. *Bioorg. Chem.* **2021**, *115* (June). https://doi.org/10.1016/j.bioorg.2021.105240.
2. Fawcett, A.; Murtaza, A.; Gregson, C. H. U.; Aggarwal, V. K. Strain-Release-Driven Homologation of Boronic Esters: Application to the Modular Synthesis of Azetidines. *J. Am. Chem. Soc.* **2019**, *141*, 4573–4578. https://doi.org/10.1021/jacs.9b01513.
3. Hayat, K.; Afzal, S.; Saeed, A.; Murtaza, A.; Ur Rahman, S.; Khan, K. M.; Saeed, A.; Zaib, S.; Lecka, J.; Sévigny, J.; Iqbal, J.; Hassan, A. Investigation of New Quinoline Derivatives as Promising Inhibitors of NTPDases: Synthesis, SAR Analysis and Molecular Docking Studies. *Bioorg. Chem.* **2019**, *87* (March), 218–226. https://doi.org/10.1016/j.bioorg.2019.03.019.

Bioorganic Chemistry 115 (2021) 105240

Contents lists available at ScienceDirect

Bioorganic Chemistry

journal homepage: www.elsevier.com/locate/bioorg

Divergent synthesis and elaboration of structure activity relationship for quinoline derivatives as highly selective NTPDase inhibitor

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ARTICLE INFO

Keywords:
Quinoline derivatives
Iodine catalysis
Human nucleoside triphosphate diphosphohydrolases (h-NTPDases)
Structure activity relationship
Molecular docking studies

ABSTRACT

Quinoline derivatives have interesting biological profile. In continuation for the comprehensive evaluations of substituted quinoline derivatives against human nucleoside triphosphate diphosphohydrolases (*h*-NTPDases) a series of substituted quinoline derivatives (**2a-g**, **3a-f**, **4**, **5a-c**, **6**) was synthesized. The inhibitory activities of the synthesized compounds were evaluated against four isoenzymes of human nucleoside triphosphate diphosphohydrolases (*h*-NTPDases). These quinoline derivatives had IC_{50} (μM) values in the range of 0.20–1.75, 0.77–2.20, 0.36–5.50 and 0.90–1.82 for NTPDase1, NTPDase2, NTPDase3 and NTPDase8, respectively. The derivative **3f** was the most active compound against NTPDase1 (IC_{50}, 0.20 ± 0.02 μM) that also possessed selectivity towards NTPDase1. Similarly, derivative **3b** (IC_{50}, 0.77 ± 0.06), **2h** (IC_{50}, 0.36 ± 0.01) and **2c** (IC_{50}, 0.90 ± 0.08) displayed excellent activity corresponding to NTPDase2, NTPDase3 and NTPdase8. The compound **5c** emerged as a selective inhibitor of NTPDase8. The most active compounds were then investigated to determine their mode of inhibition and finally binding interactions of the active compounds were analyzed through molecular docking studies. The obtained results strongly support the quinoline scaffold's potential as potent and selective NTPDase inhibitor.

1. Introduction

Ectonucleotidases represent an integrated network of metalloenzymes that are responsible for maintaining the extracellular concentration of nucleotides by catalysing the hydrolysis of nucleoside triphosphates, diphosphates and monophosphates to their corresponding nucleosides. There are four subfamilies of ectonucleotidases, including ecto-nucleoside triphosphate diphosphohydrolases (NTPDases), ecto-nucleotide pyrophosphatases/phosphodiesterases (NPPs), alkaline phosphatases (APs/ALPs) and ecto-5′-nucleotidase (ecto-5′-NT) [1–5]. These ectonucleotidases work in a coordinated fashion to hydrolyze the extracellular nucleotides. For example, adenosine triphosphate (ATP) is hydrolyzed to adenosine monophosphate (AMP) by NTPDases, and NPPs whereas, the resulting AMP is dephosphorylated to adenosine by ecto-5′-NT. However, APs act on a variety of substrates such as nucleoside triphosphates, nucleoside diphosphates, nucleoside monophosphates as well as phosphoric esters. All the nucleosides and nucleotides act as ligands for P1 and P2 receptors, respectively and modulate the various biological functions [6–8].

The NTPDases constitute an important family of ectonucleotidases that catalyze the hydrolysis of nucleoside triphosphate and diphosphate to nucleoside monophosphate, in the presence of divalent ions such as Ca^{+2} and Mg^{+2} [9,10]. Their presence has been detected in mammals and higher eukaryotes, although, some members of NTPDase family have also been discovered in parasites such as bacteria and fungi. In mammals, eight isoforms of NTPDase have been described, each encoded by a distinct gene [11,12]. They are known as NTPDase1-8 and all of them possess highly conserved domains, known as "apyrase conserved regions" [13,14]. Four members of this family are membrane bound proteins, including NTPDase1, −2, −3 and −8. These four members are also known as E-NTPDases since their catalytic site is oriented towards extracellular space. NTPDase4 and −7 are intracellular members of NTPDase family which are located inside the organelles and their catalytic site is positioned towards the cytoplasmic space. Although

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https://doi.org/10.1016/j.bioorg.2021.105240
Received 24 April 2021; Received in revised form 25 June 2021; Accepted 2 August 2021
Available online 4 August 2021

JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Cite This: J. Am. Chem. Soc. 2019, 141, 4573−4578
Communication
pubs.acs.org/JACS

Strain-Release-Driven Homologation of Boronic Esters: Application to the Modular Synthesis of Azetidines

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Supporting Information

ABSTRACT: Azetidines are important motifs in medicinal chemistry, but there are a limited number of methods for their synthesis. Herein, we present a new method for their modular construction by exploiting the high ring strain associated with azabicyclo[1.1.0]butane. Generation of azabicyclo[1.1.0]butyl lithium followed by its trapping with a boronic ester gives an intermediate boronate complex which, upon *N*-protonation with acetic acid, undergoes 1,2-migration with cleavage of the central C−N bond to relieve ring strain. The methodology is applicable to primary, secondary, tertiary, aryl, and alkenyl boronic esters and occurs with complete stereospecificity. The homologated azetidinyl boronic esters can be further functionalized through reaction of the N−H azetidine, and through transformation of the boronic ester. The methodology was applied to a short, stereoselective synthesis of the azetidine-containing pharmaceutical, cobimetinib.

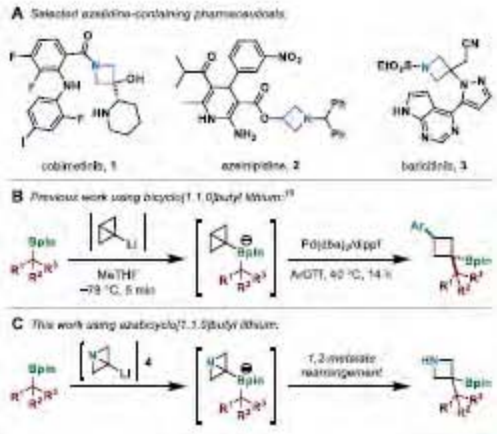


Figure 1. (A) Selected azetidine-containing pharmaceuticals. (B) Strain-release 1,2-metalate rearrangement of bicyclo[1.1.0]butyl boronate complexes. (C) This work: strain-release 1,2-metalate rearrangement of azabicyclo[1.1.0]butyl boronate complexes.

Nitrogen-containing heterocycles are the most prevalent and important heterocycles in medicinal chemistry, as evidenced by their presence in approximately 60% of U.S. FDA approved small-molecule drugs.[1] Among this class of compounds, the saturated heterocycles piperidine and pyrrolidine are some of the most commonly encountered. However, their four-membered ring analogue, azetidine,[2] is much less prevalent, despite possessing a range of desirable characteristics; its small, strained ring structure confers structural rigidity and fewer rotatable bonds, which has been shown to correlate with increased bioavailability,[3] and they have been demonstrated to exhibit greater metabolic stability and improved physicochemical properties relative to their larger ring analogues.[4] Indeed, the azetidine moiety is featured in several pharmaceuticals, including cobimetinib (**1**),[5] azelnipidine (**2**),[6] and baricitinib (**3**)[7] (Figure 1A), as well as in biologically active natural products.[8] However, despite these attractive features, there is a dearth of methods available to prepare azetidines.[2,9] Some current methods include inter- and intramolecular alkylation of amine nucleophiles, reduction of β-lactams,[2] and the aza Paternò−Büchi reaction.[10] Therefore, the development of new methodologies that facilitate the modular synthesis of azetidines from common building blocks would be highly attractive, particularly in advancing medicinal chemistry programs.[11] Herein, we describe a method to homologate readily available boronic esters with azabicyclo[1.1.0]butyl lithium (a novel species) to form versatile borylated azetidines, which can then be diversified through transformation of the amine and boronic ester functional groups.[12]

We recently reported the homologation of boronic esters by a cyclobutane unit by using bicyclo[1.1.0]butyl lithium (Figure 1B).[13] It was shown that bicyclo[1.1.0]butyl lithium could react with boronic esters to form highly strained bicyclo[1.1.0]butyl boronate complexes, which then underwent 1,2-metalate rearrangement upon treatment with electrophilic palladium(II)−aryl complexes to ultimately form a range of diastereomerically pure borylated cyclobutanes. The 1,2-metalate rearrangement is driven by relief of the high ring strain of the bicycle. We reasoned that the power inherent in the relief of ring strain could be harnessed to drive 1,2-metalate rearrangements in other related ring systems.[14] In particular, we were interested in the use of nitrogen-containing analogues of bicyclo[1.1.0]butyl lithium, such as azabicyclo[1.1.0]butyl lithium (**4**), since this would potentially enable the homologation of boronic esters to give synthetically and pharmaceutically important azetidines bearing a versatile boronic ester moiety (Figure 1C). However, such a

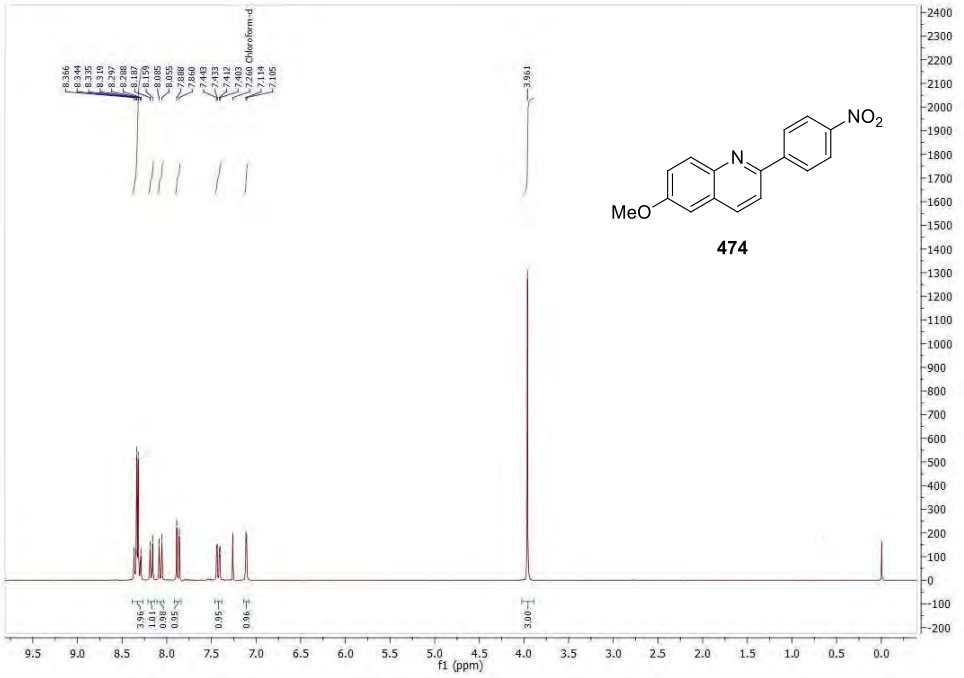
Received: February 8, 2019
Published: March 5, 2019

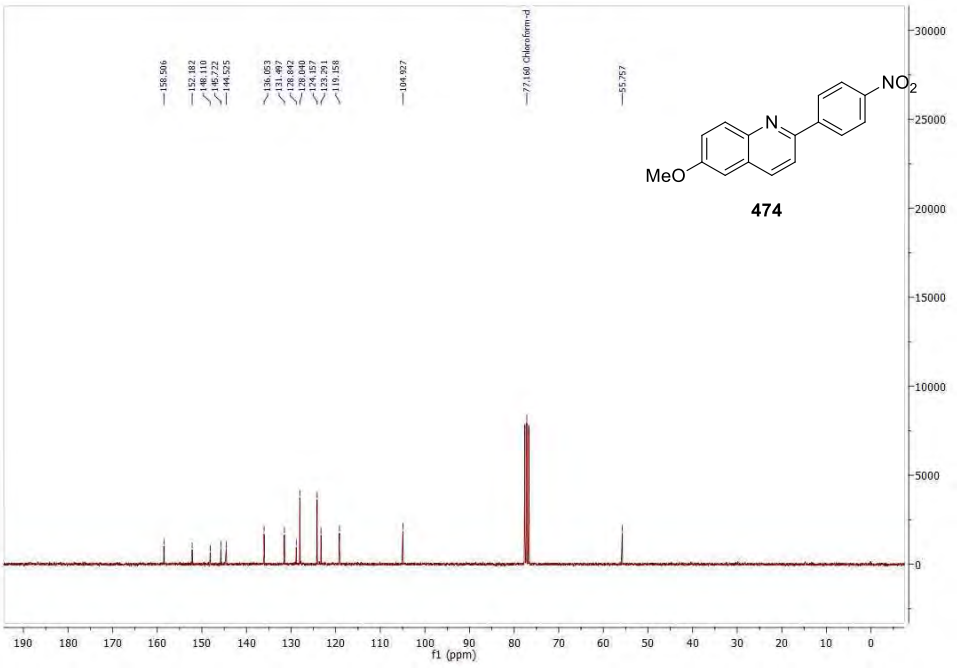
DOI: 10.1021/jacs.9b01573
J. Am. Chem. Soc. 2019, 141, 4573−4578

Appendix I: NMR Spectra of the Compounds

Part A: Synthesis of Quinoline Derivatives

6-Methoxy-2-(4-nitrophenyl)quinoline





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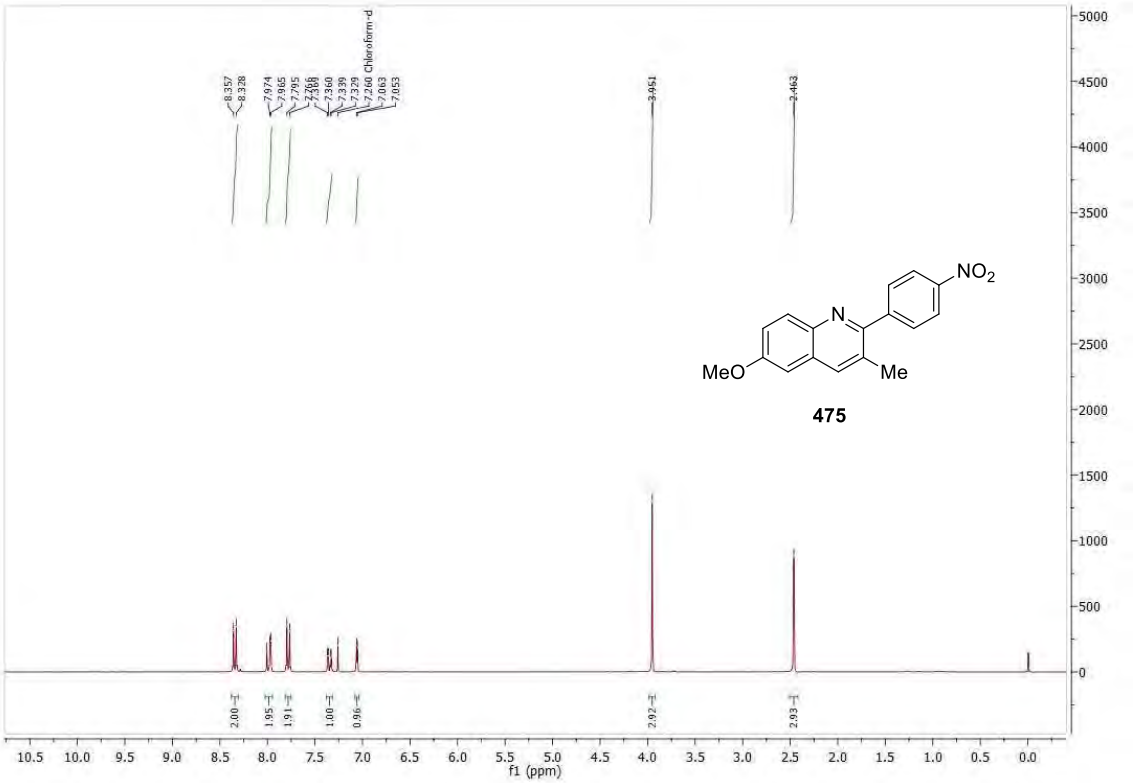
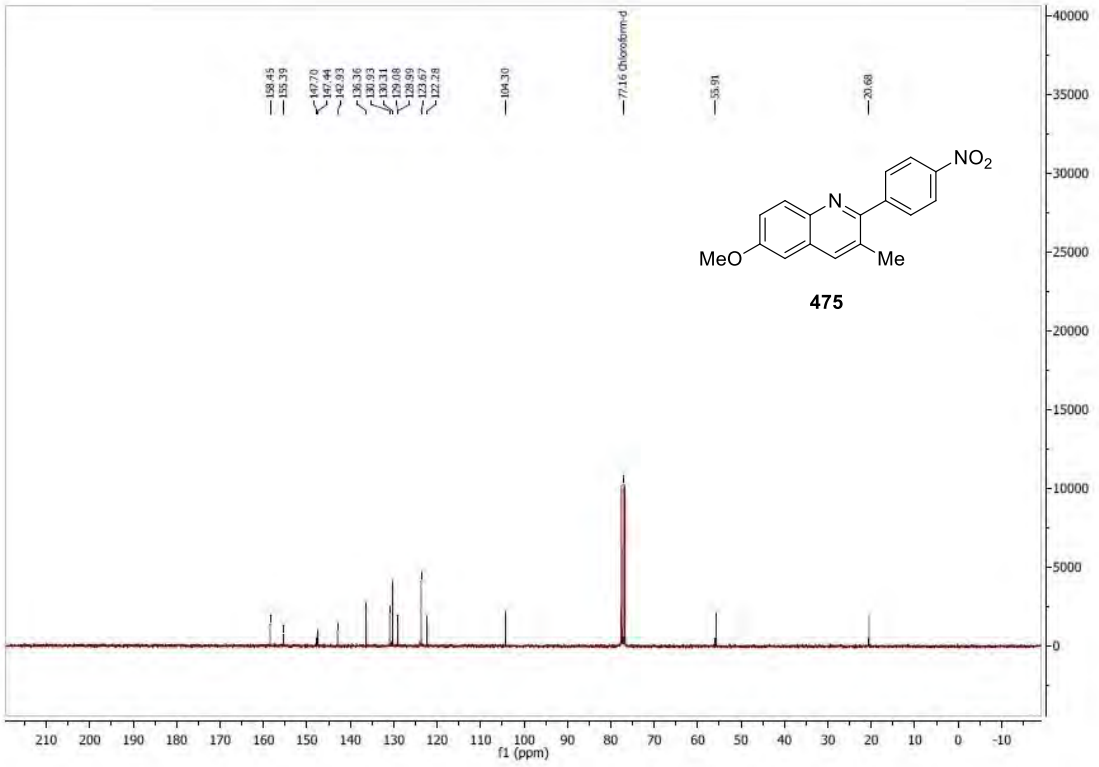
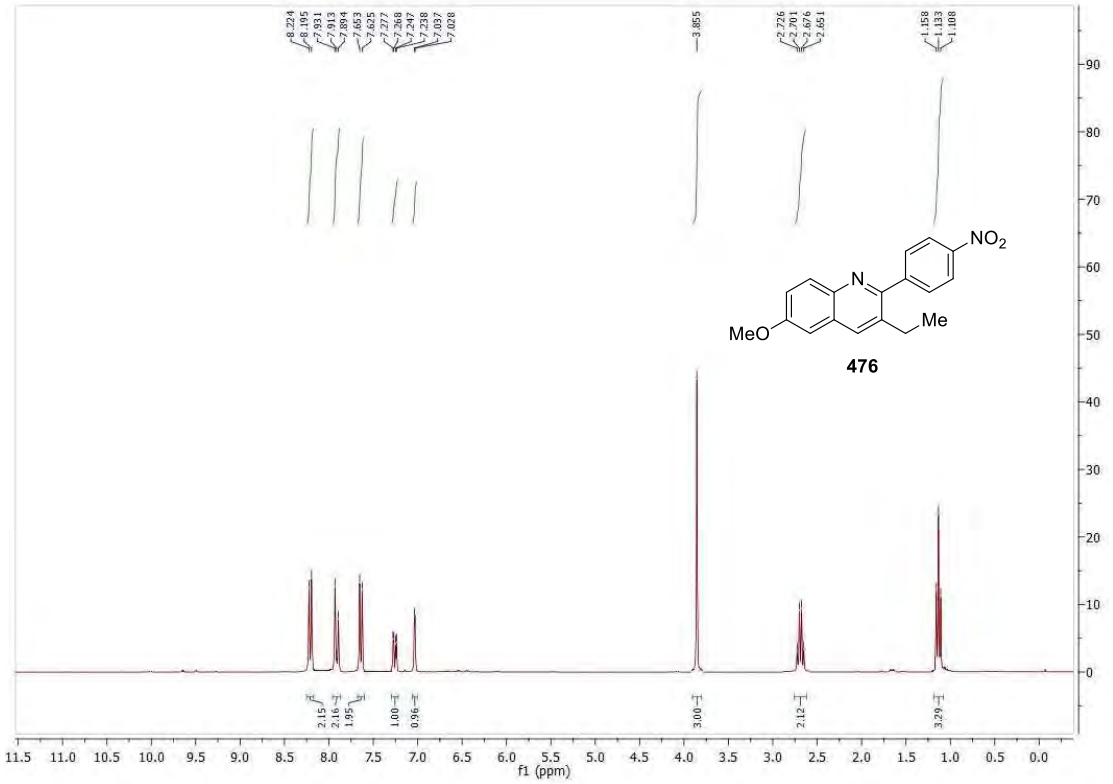
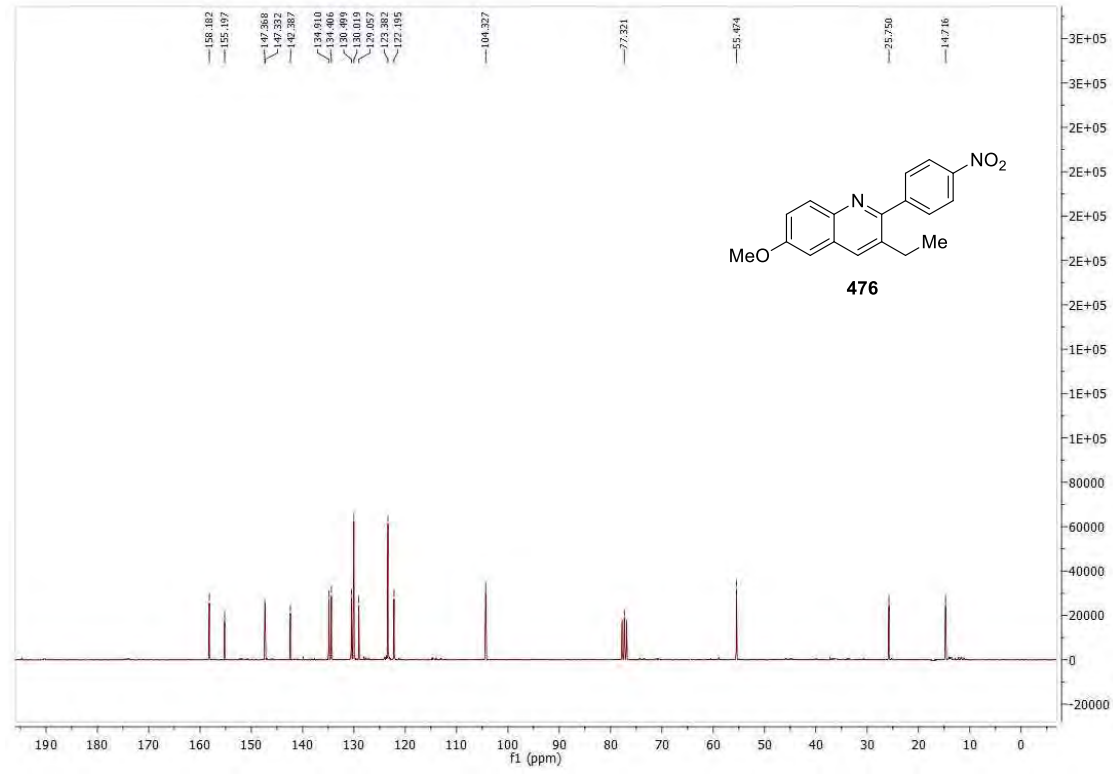


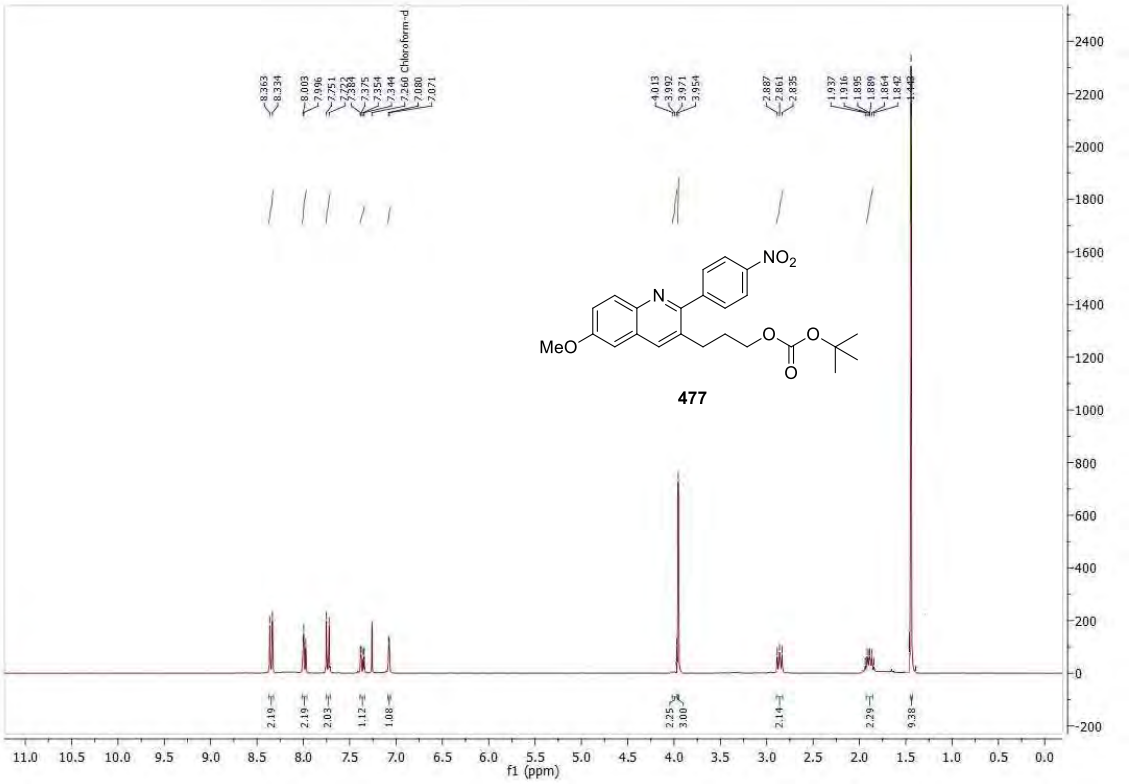


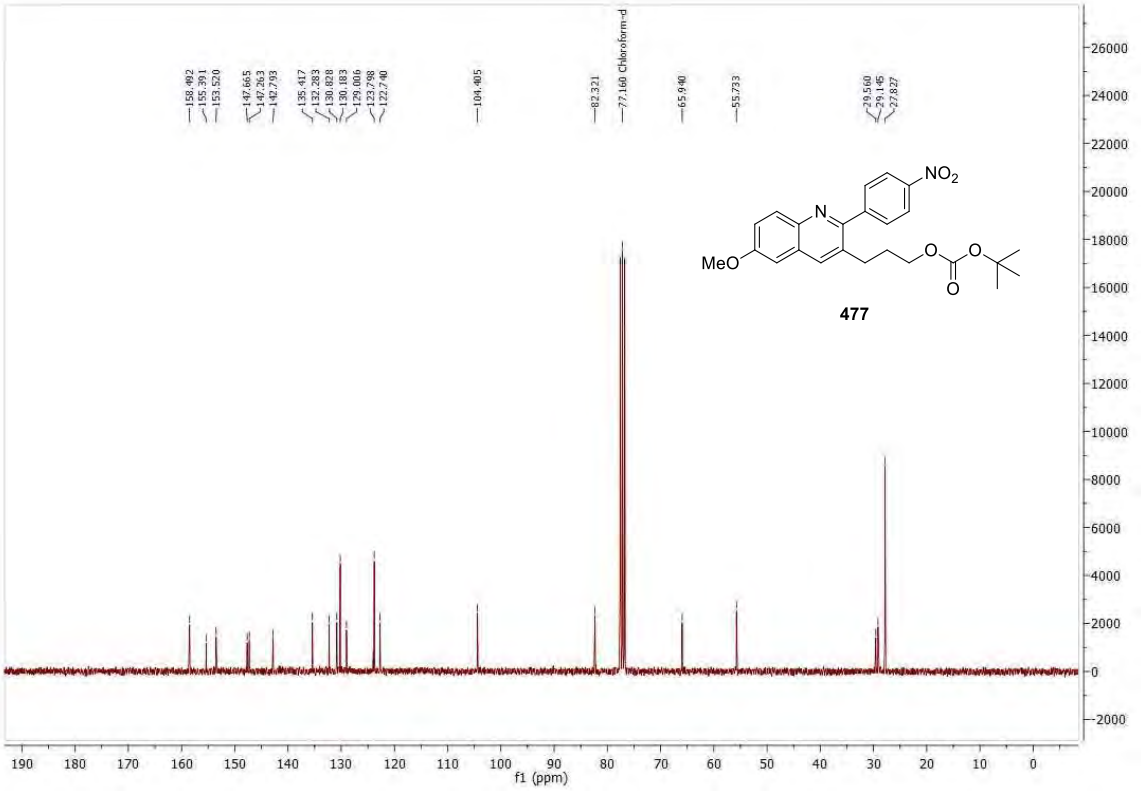
3-Ethyl-6-methoxy-2-(4-nitrophenyl)quinoline



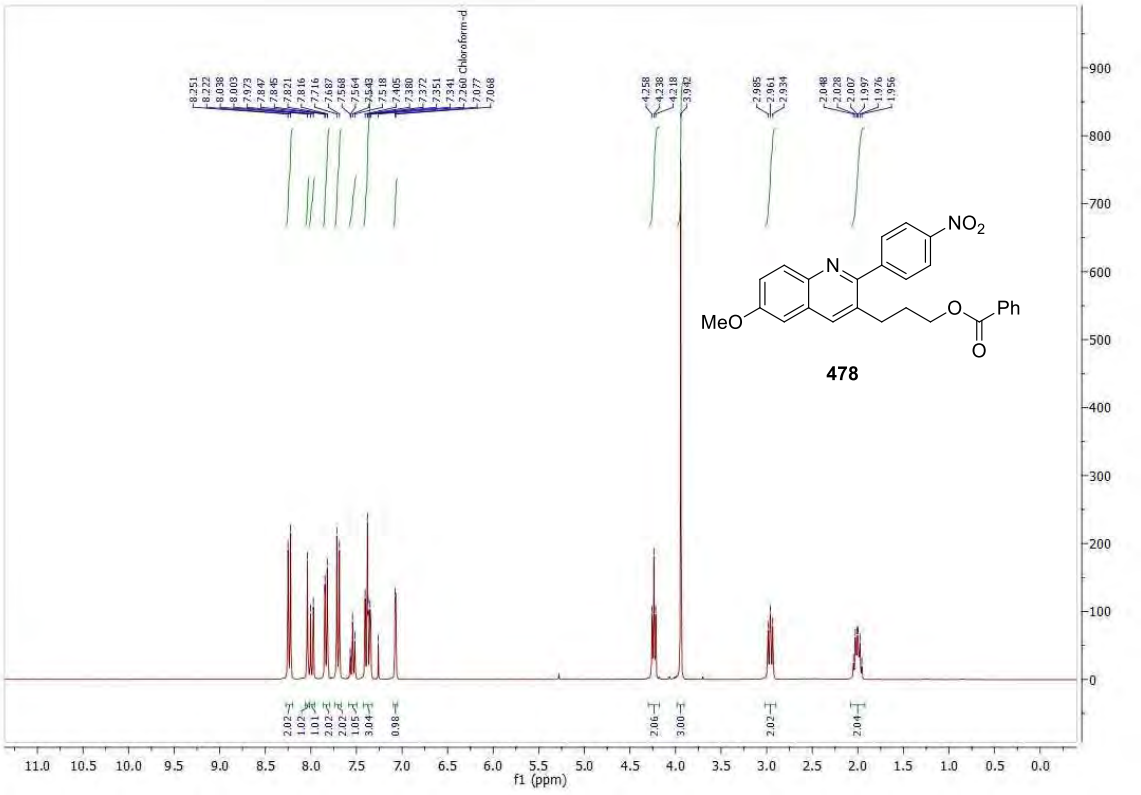


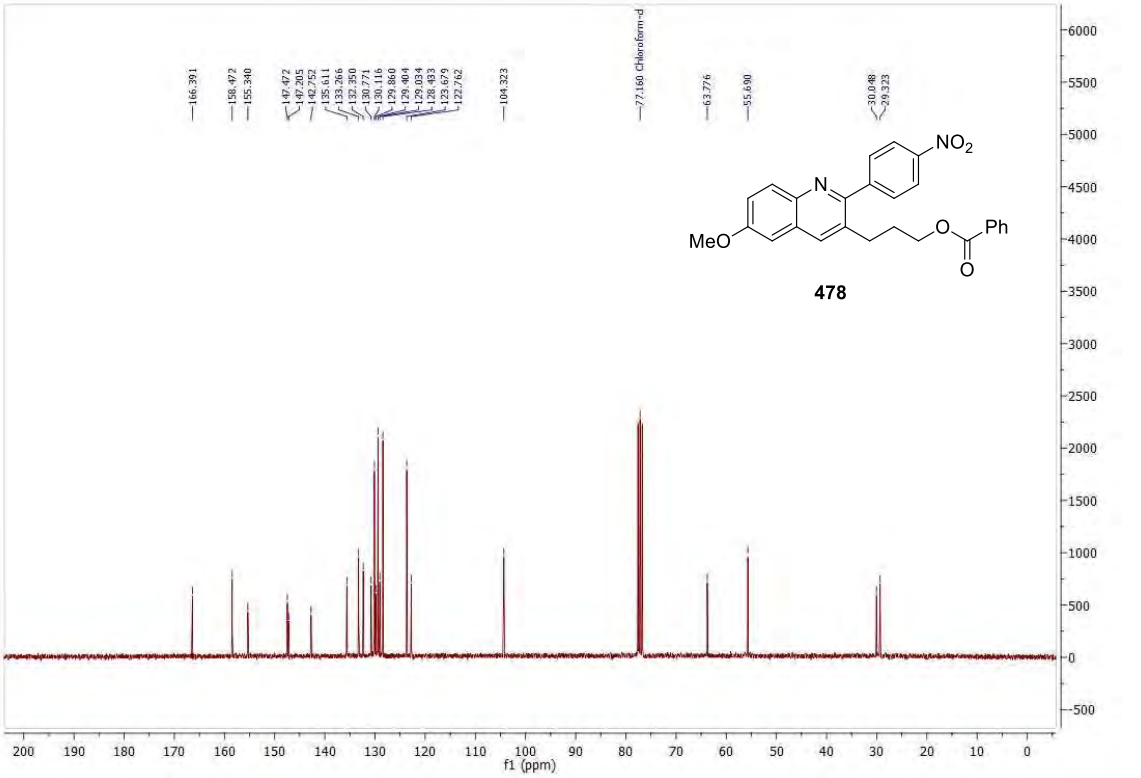
tert-Butyl (3-(6-methoxy-2-(4-nitrophenyl)quinolin-3-yl)propyl) carbonate



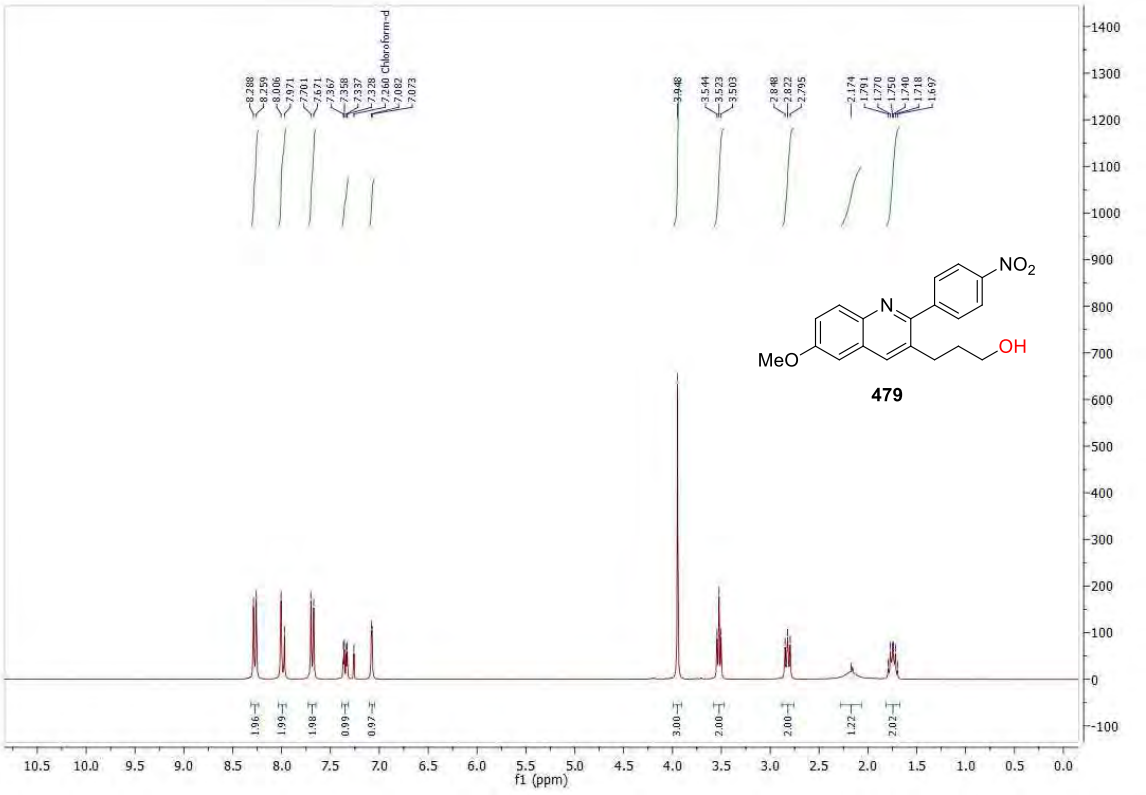


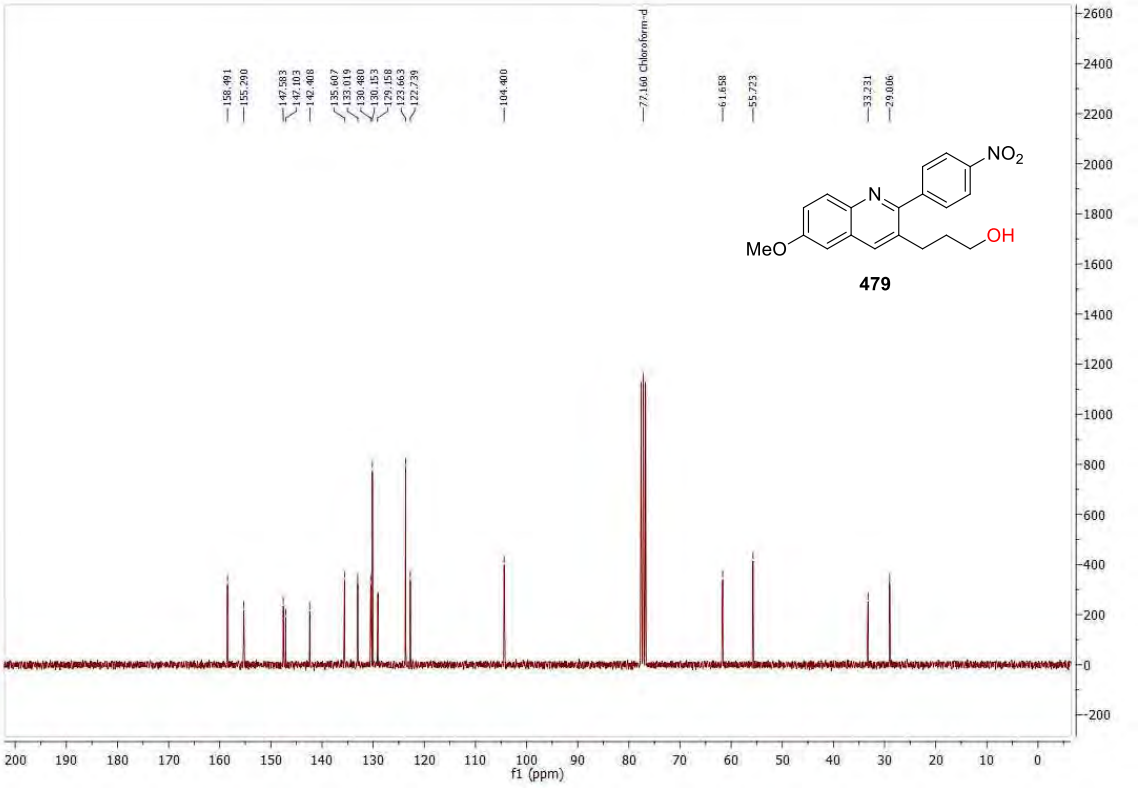
3-(6-Methoxy-2-(4-nitrophenyl)quinolin-3-yl)propyl benzoate



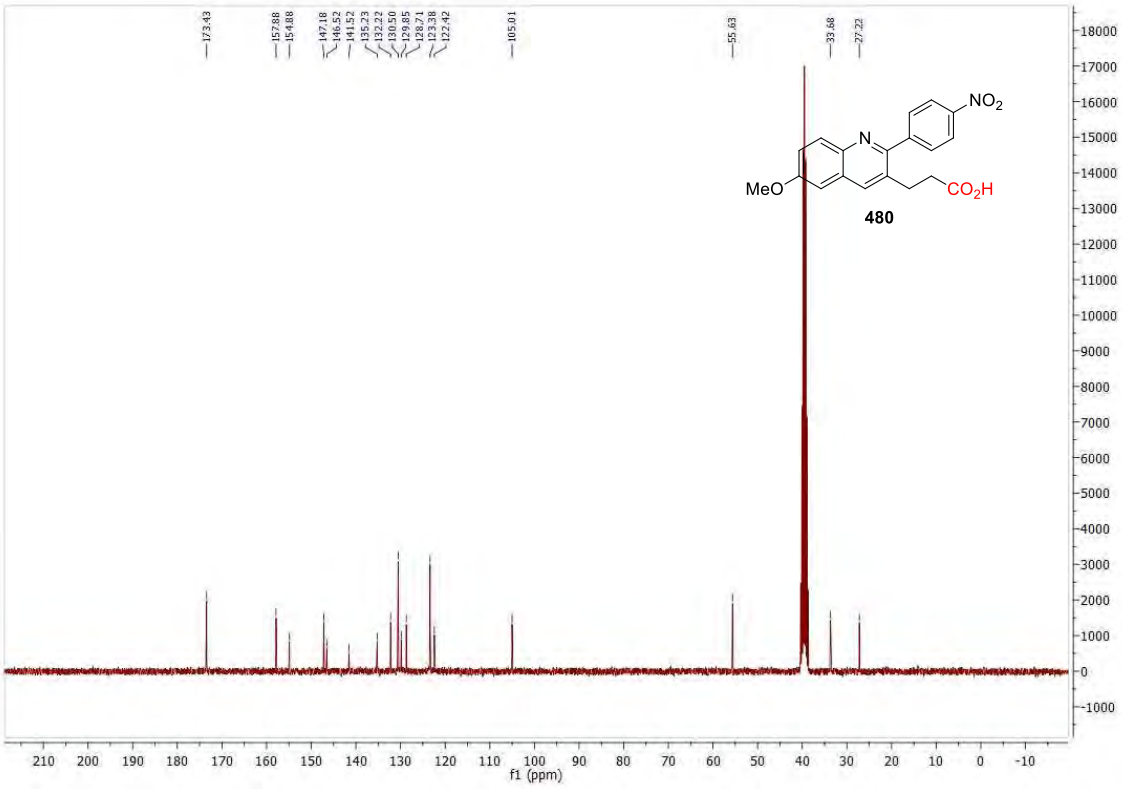


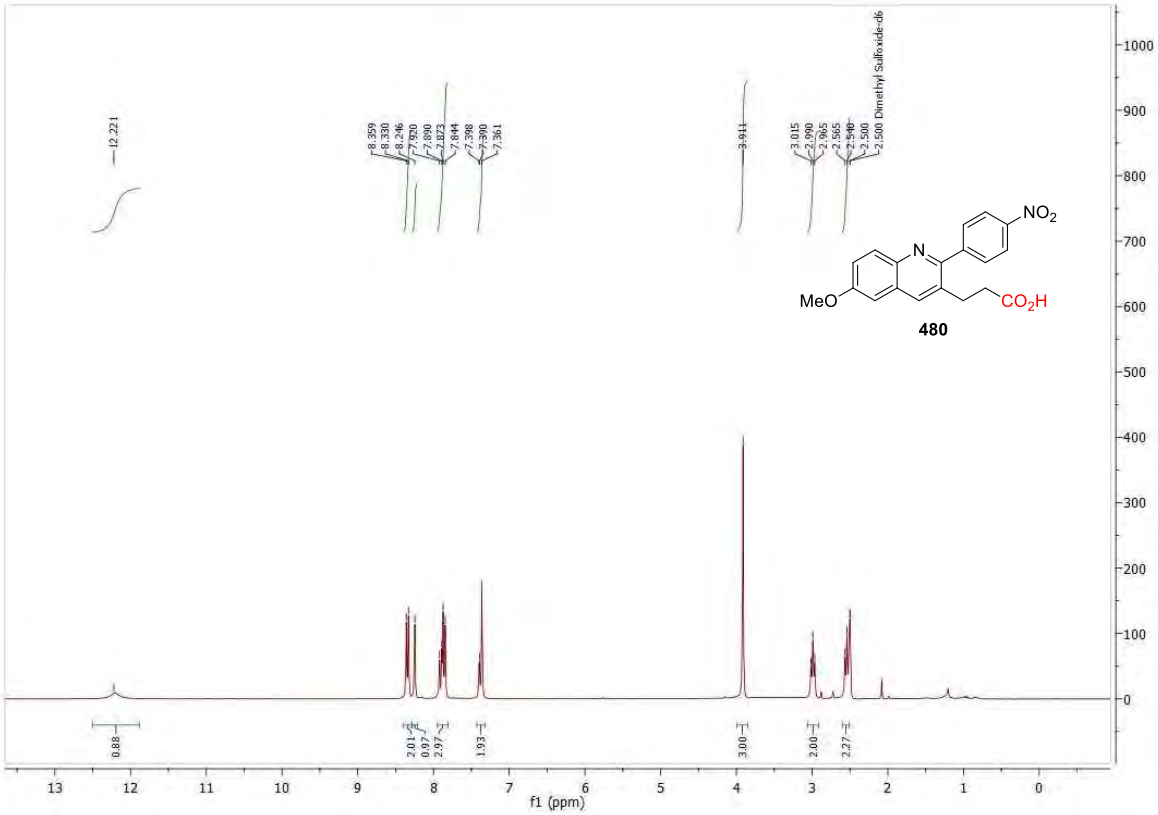
3-(6-methoxy-2-(4-nitrophenyl)quinolin-3-yl)propan-1-ol



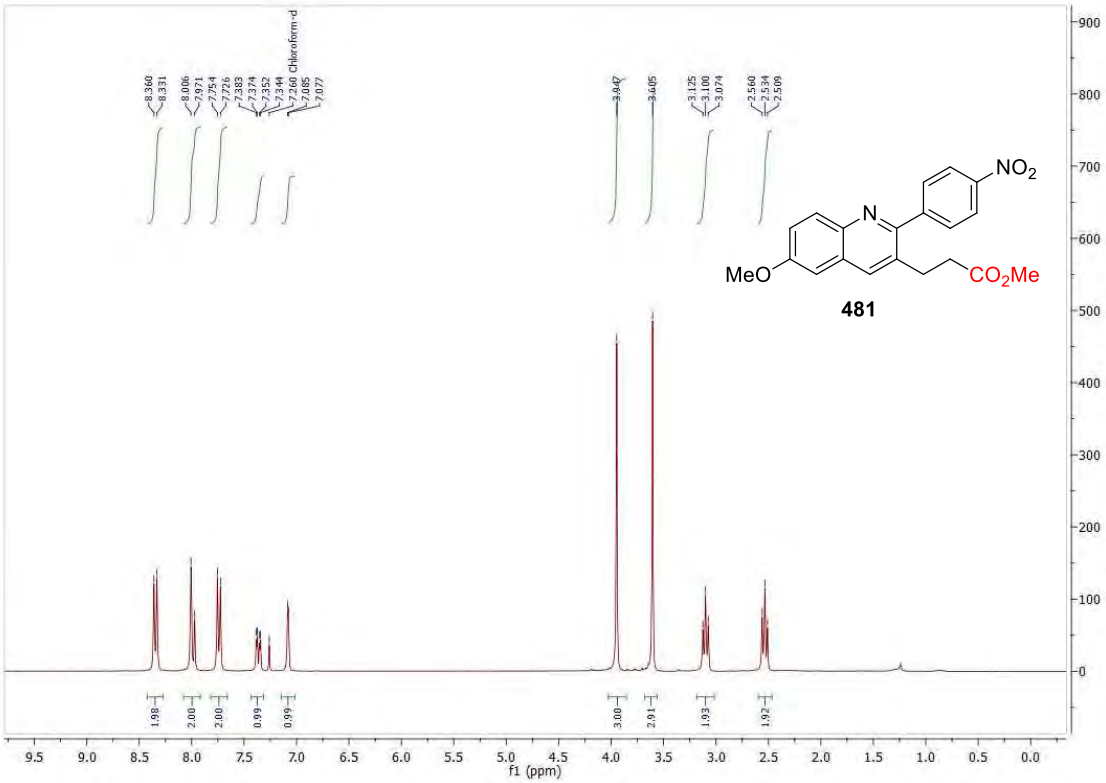


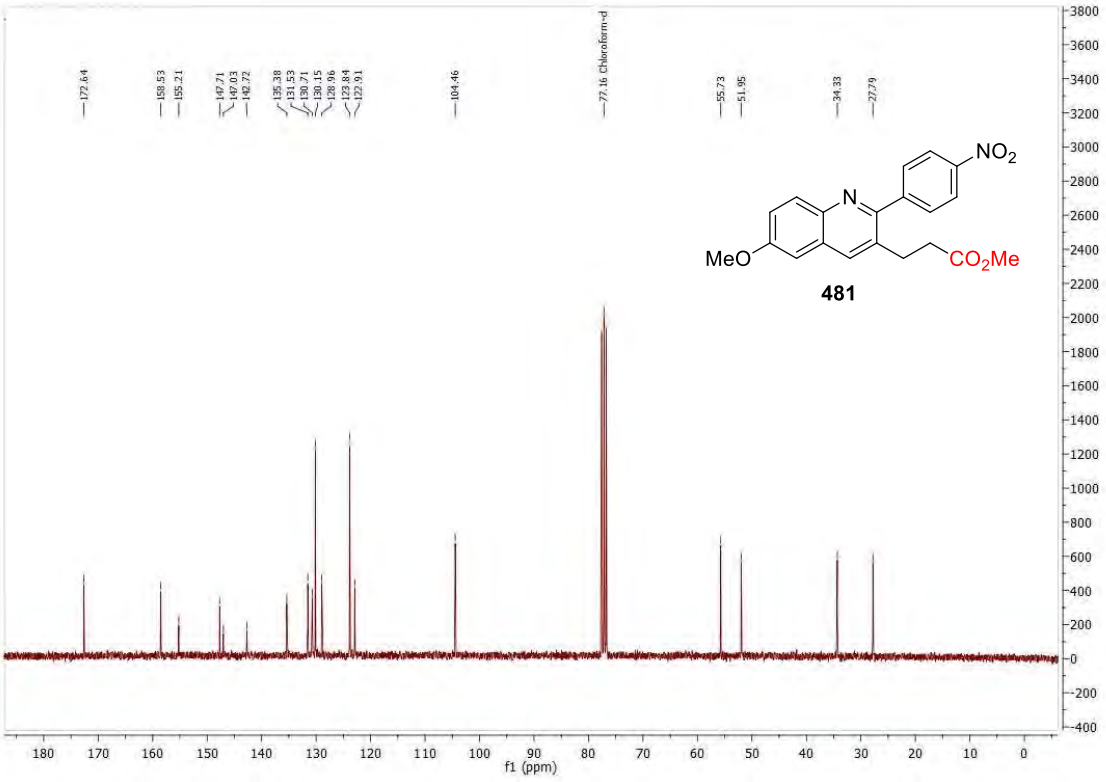
3-(6-methoxy-2-(4-nitrophenyl)quinolin-3-yl)propanoic acid



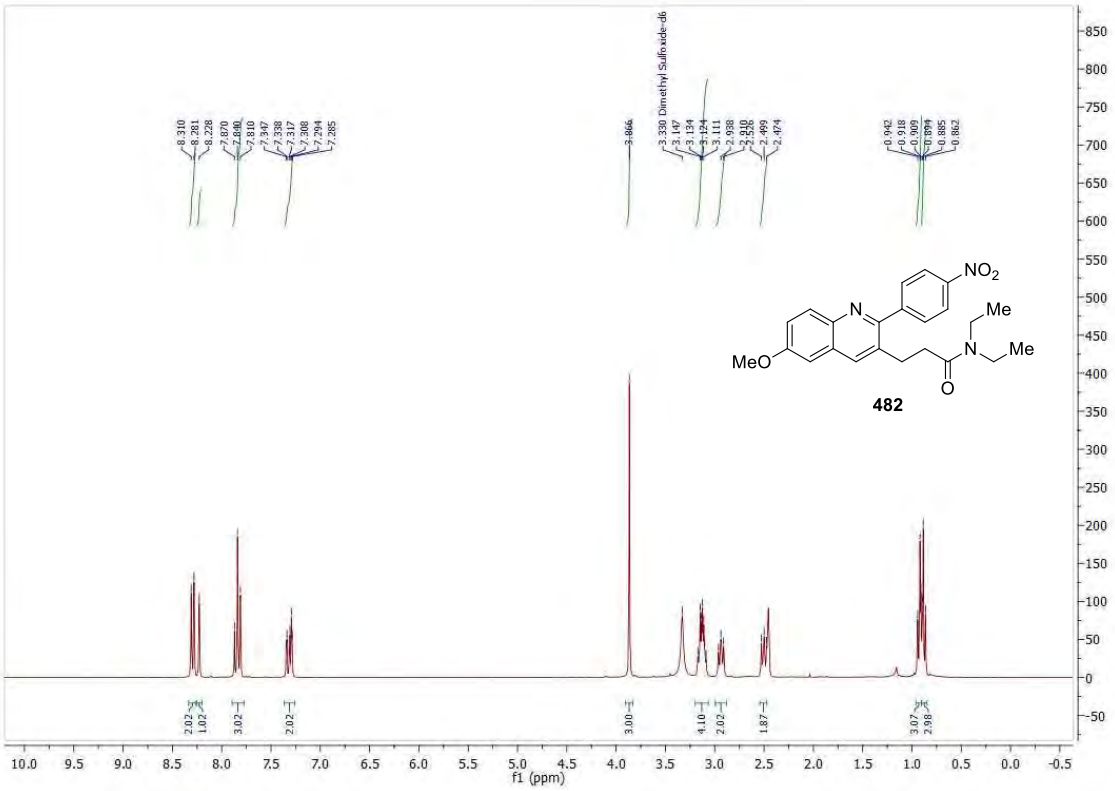


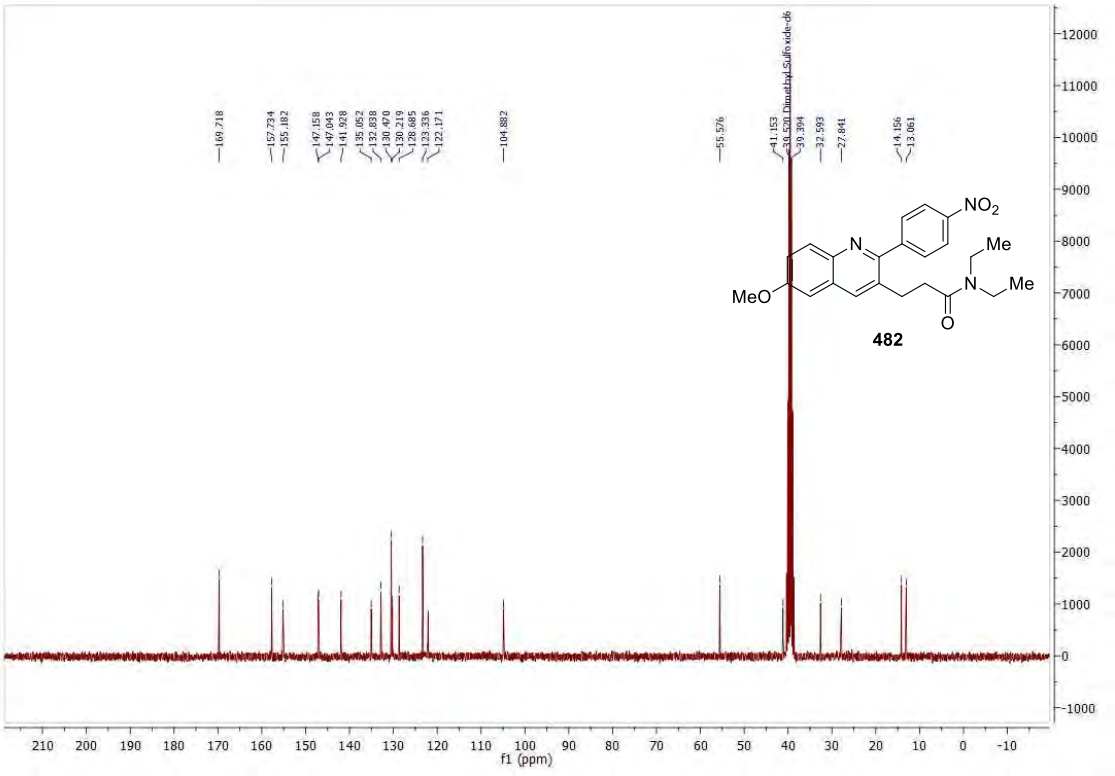
Methyl 3-(6-methoxy-2-(4-nitrophenyl)quinolin-3-yl)propanoate





N, N-Diethyl-3-(6-methoxy-2-(4-nitrophenyl)quinolin-3-yl)propenamide





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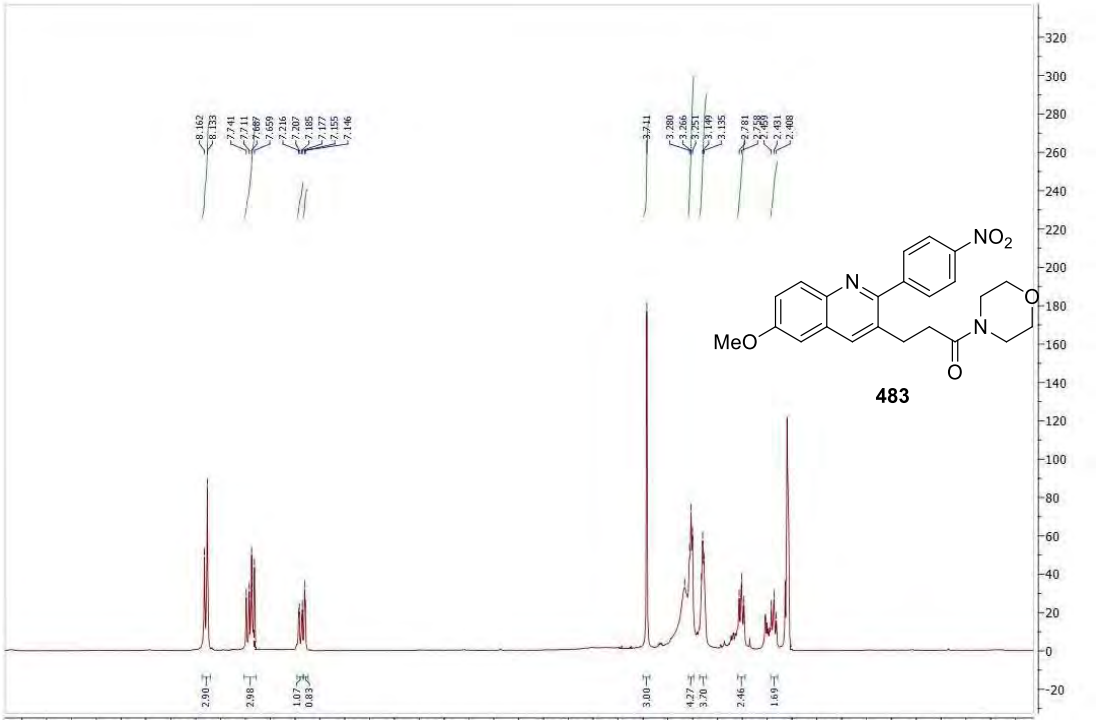
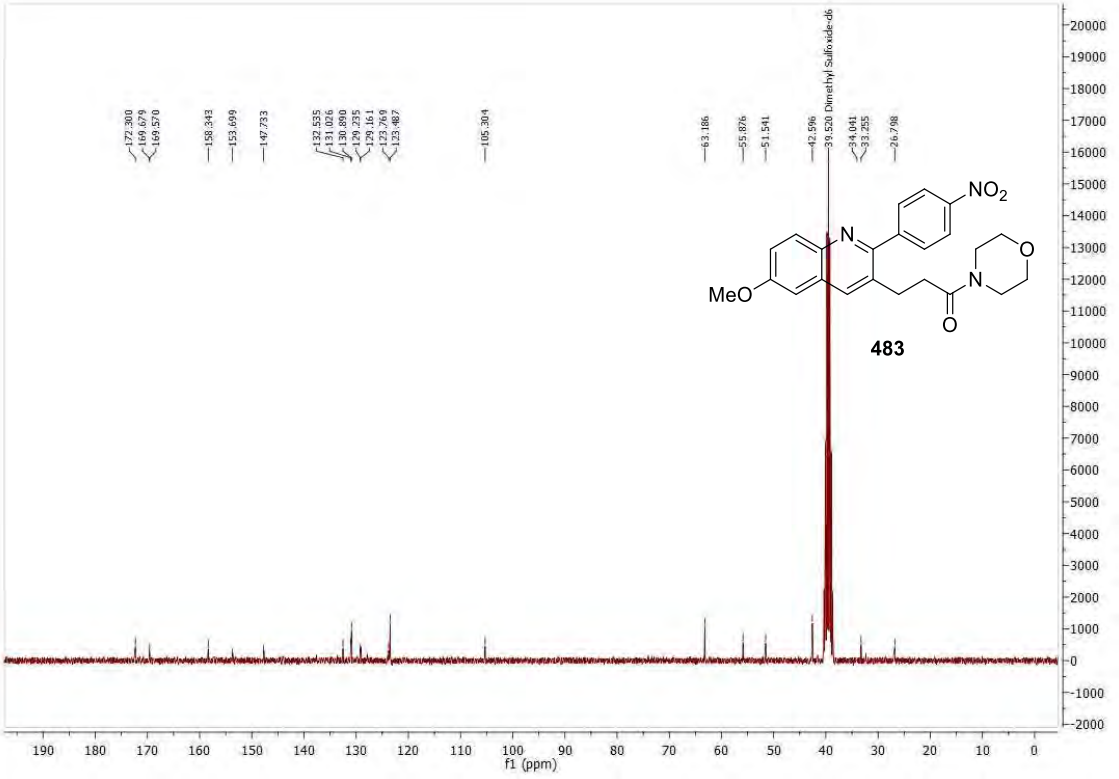
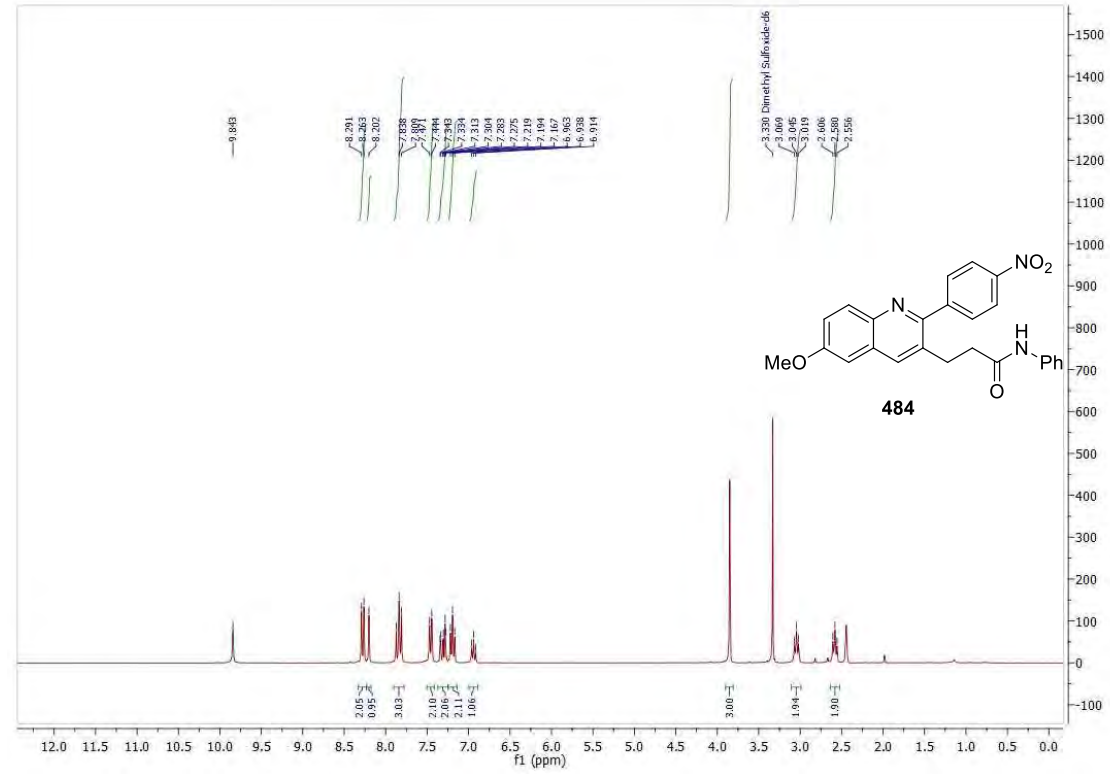
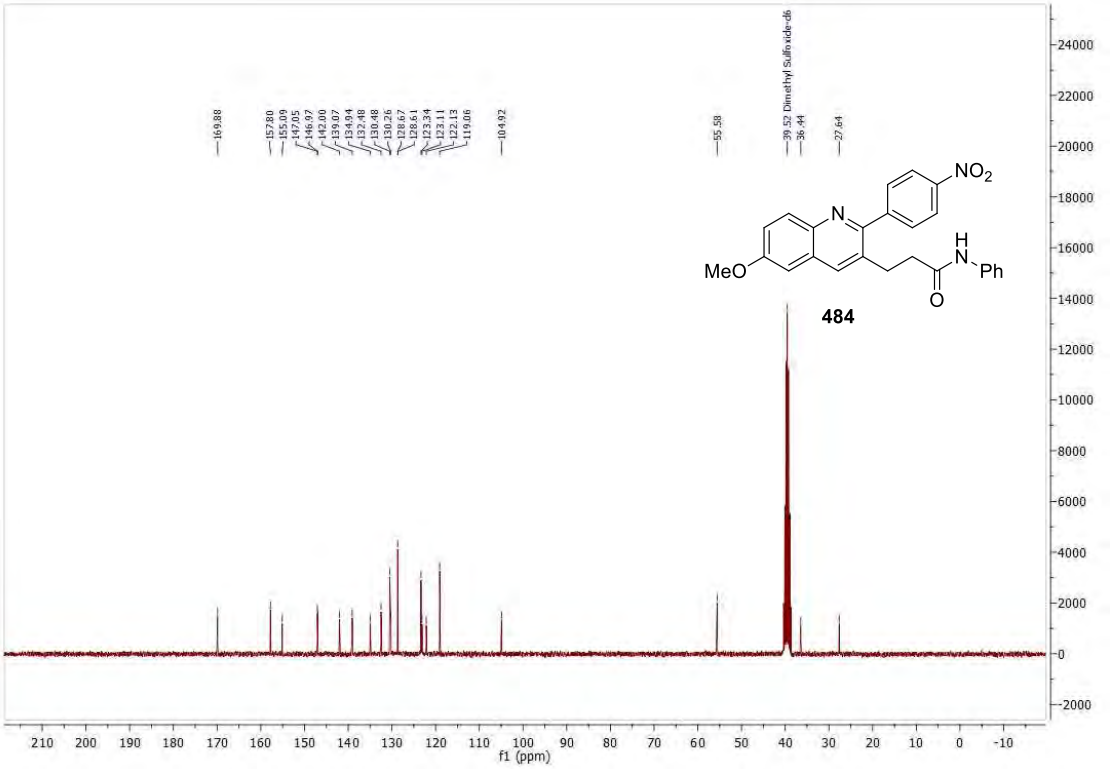




3-(6-Methoxy-2-(4-nitrophenyl)quinolin-3-yl)-*N*-phenylpropanamide





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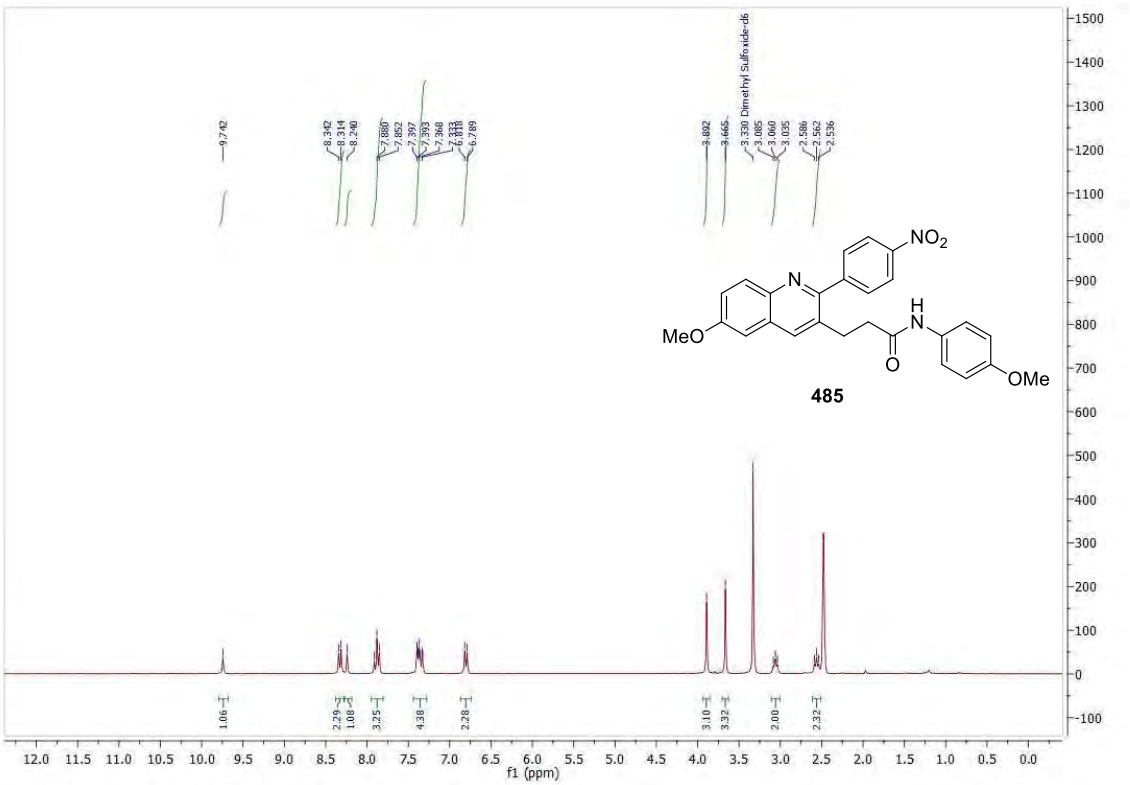
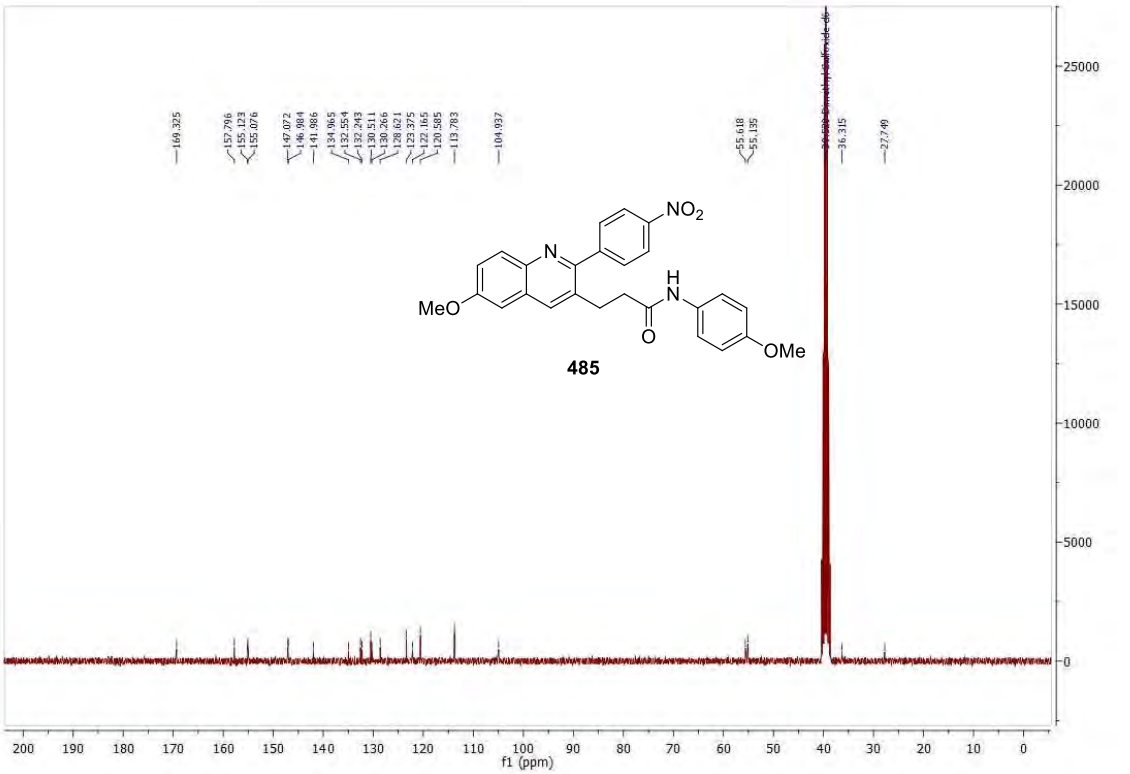
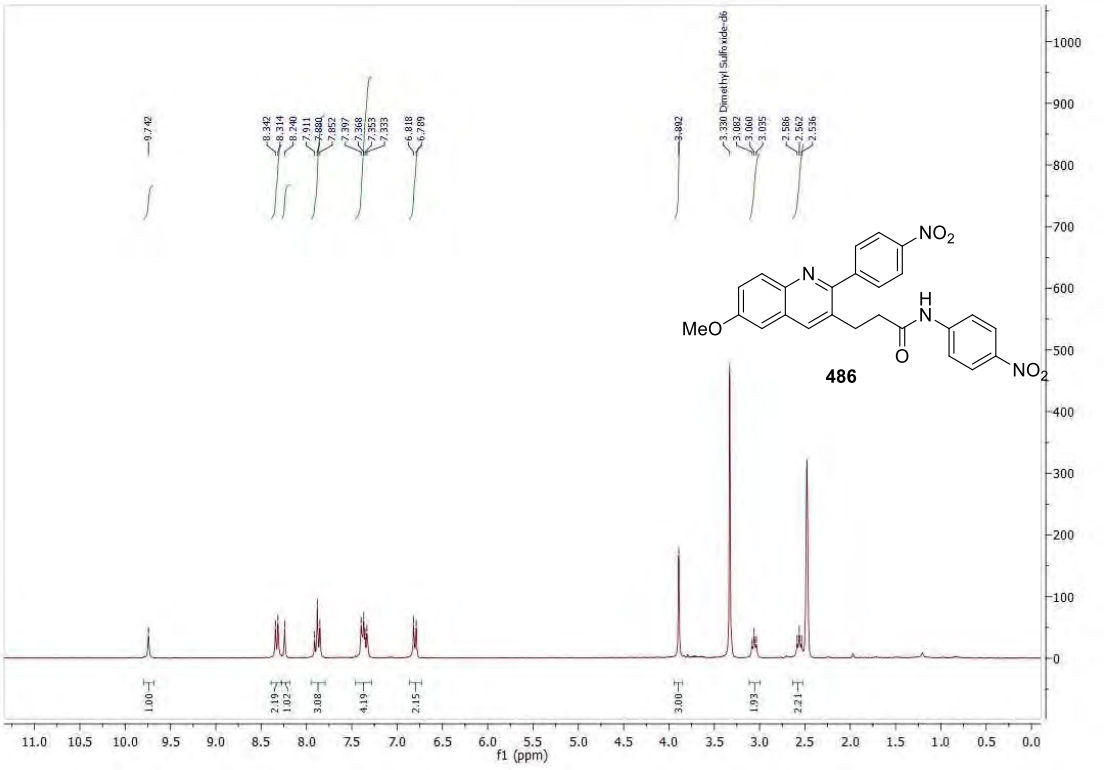
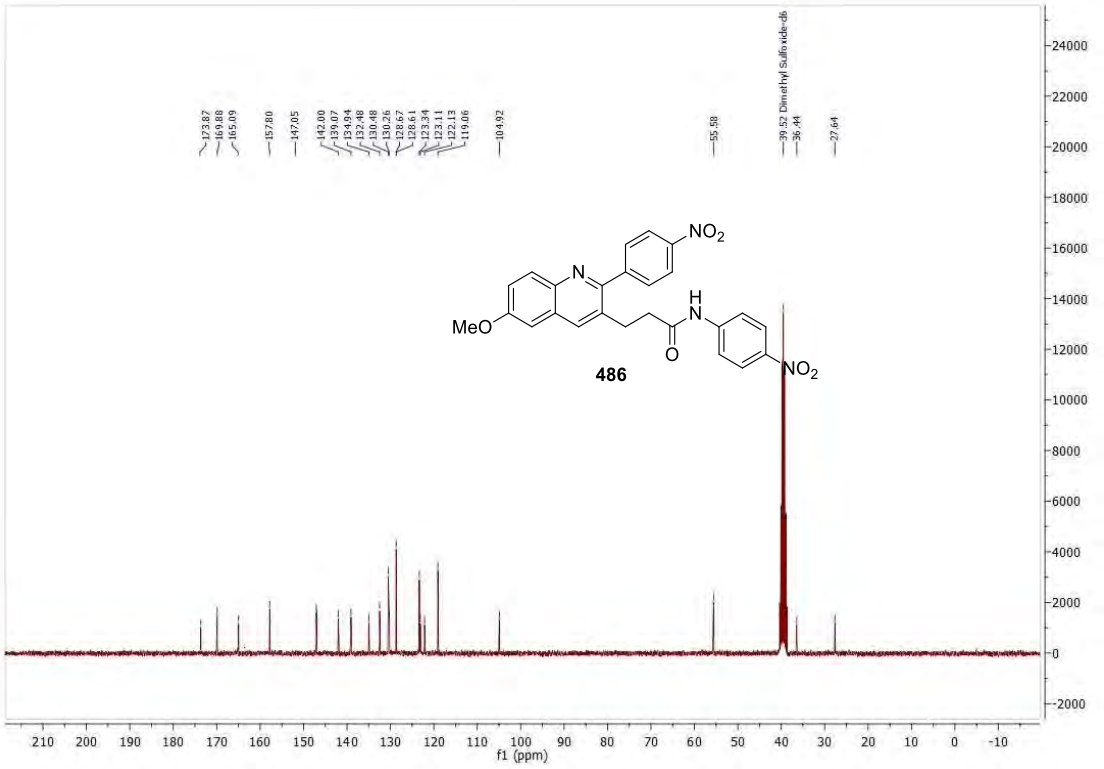




3-(6-Methoxy-2-(4-nitrophenyl)quinolin-3-yl)-*N*-(4-nitrophenyl)propenamide





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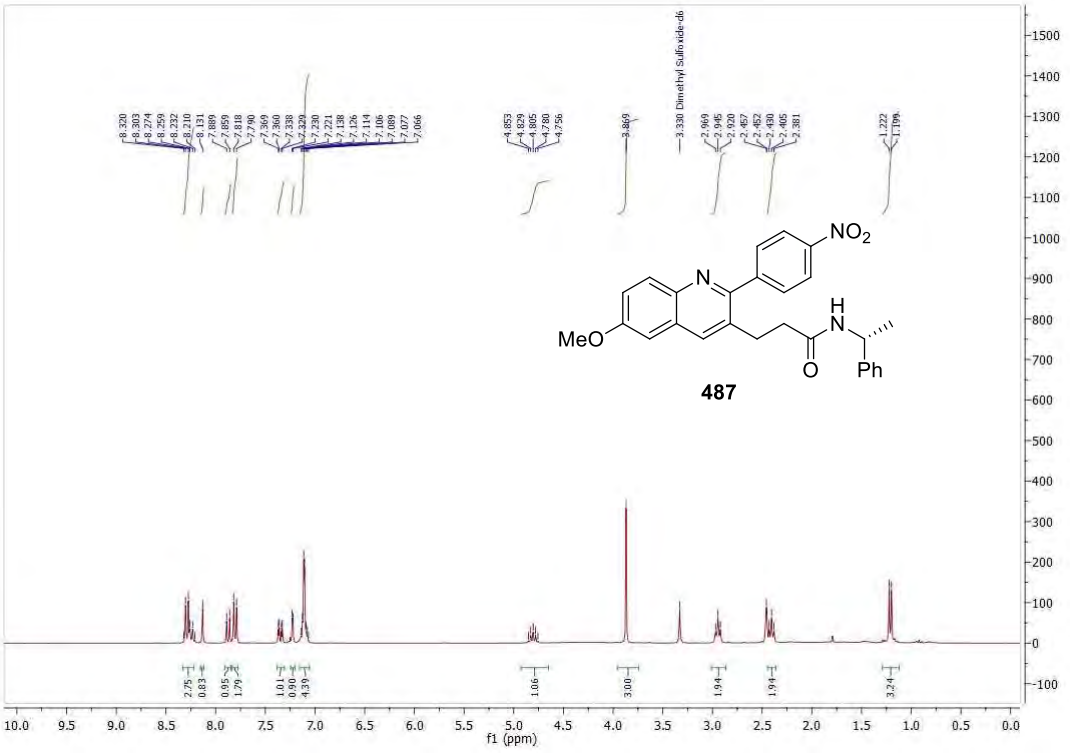
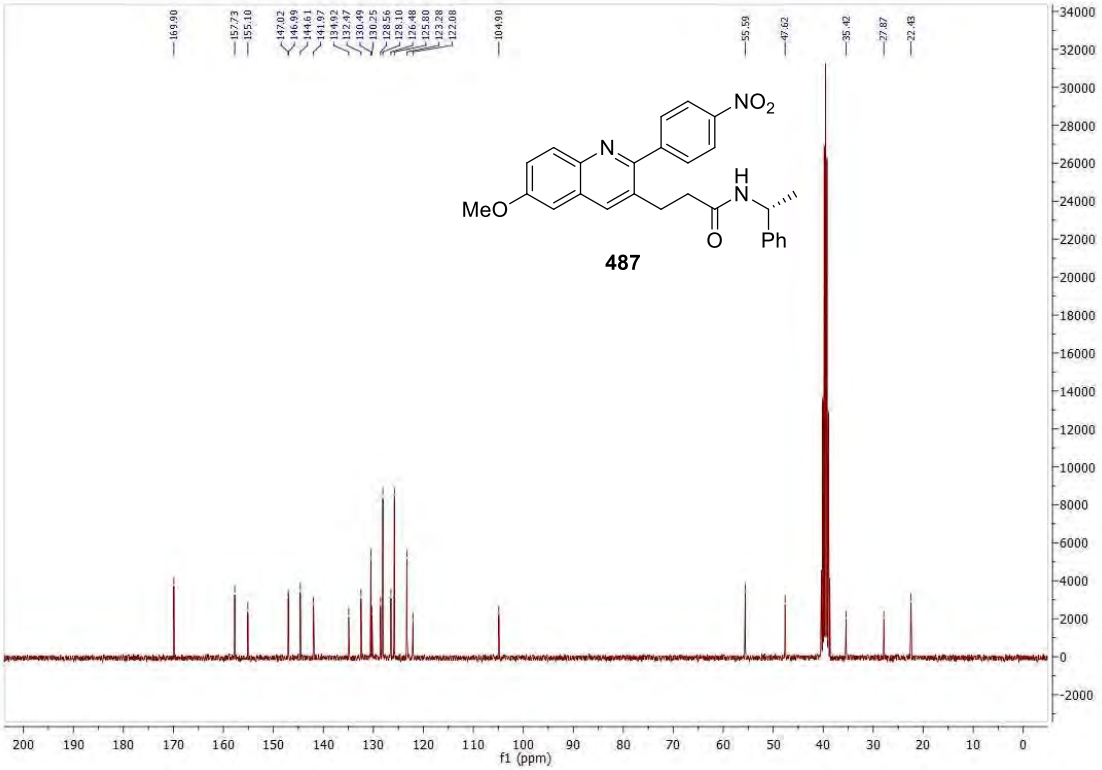
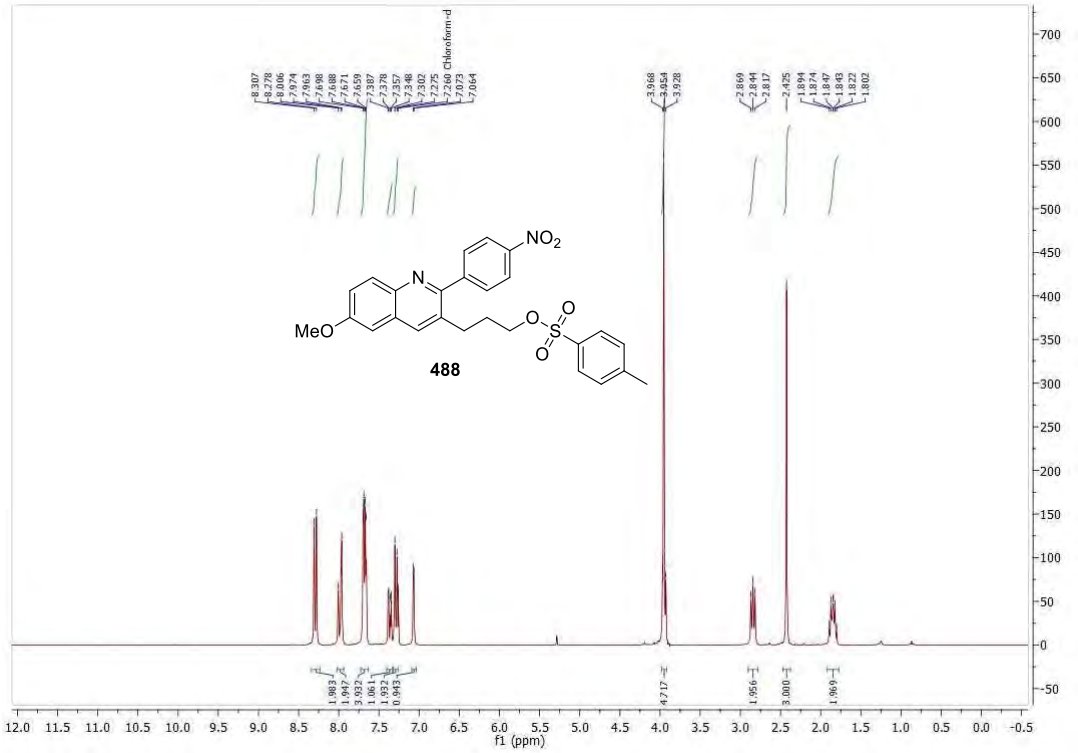
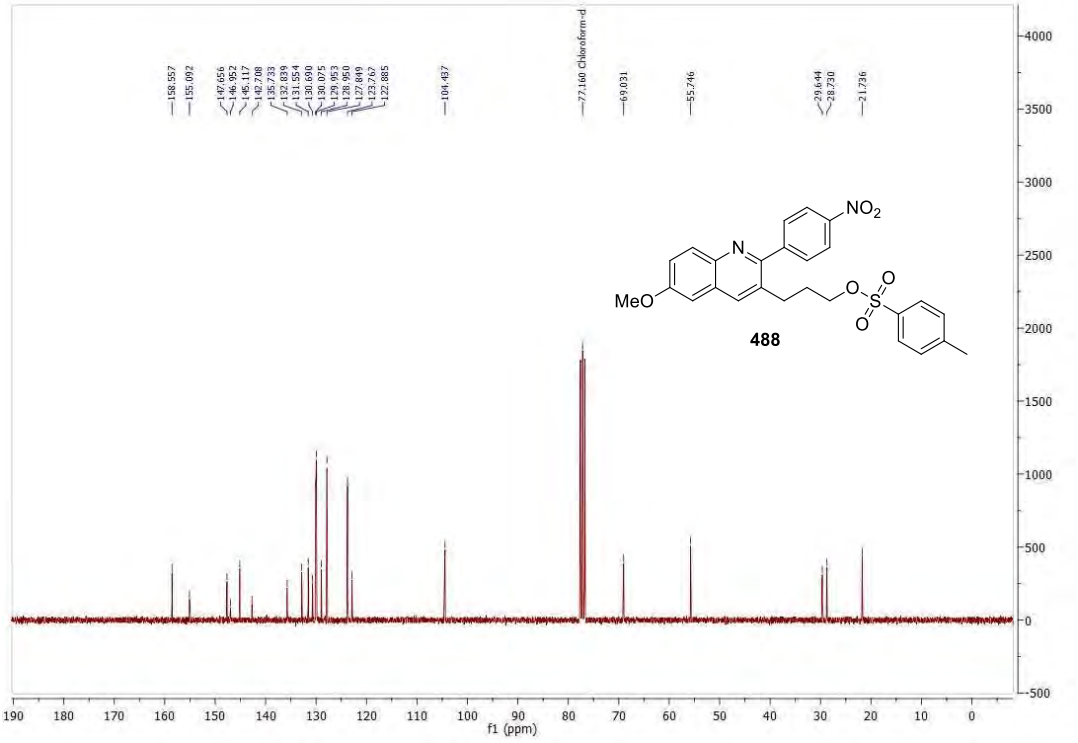




3-(6-methoxy-2-(4-nitrophenyl)quinolin-3-yl)propyl 4-methylbenzenesulfonate





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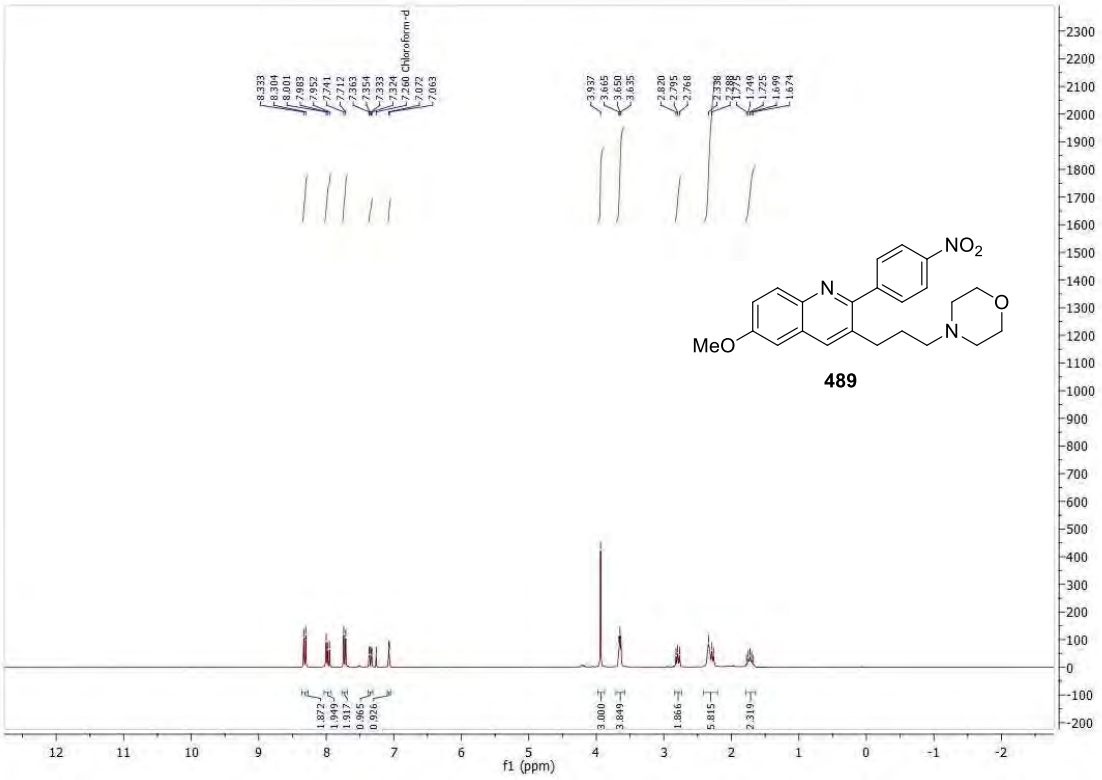

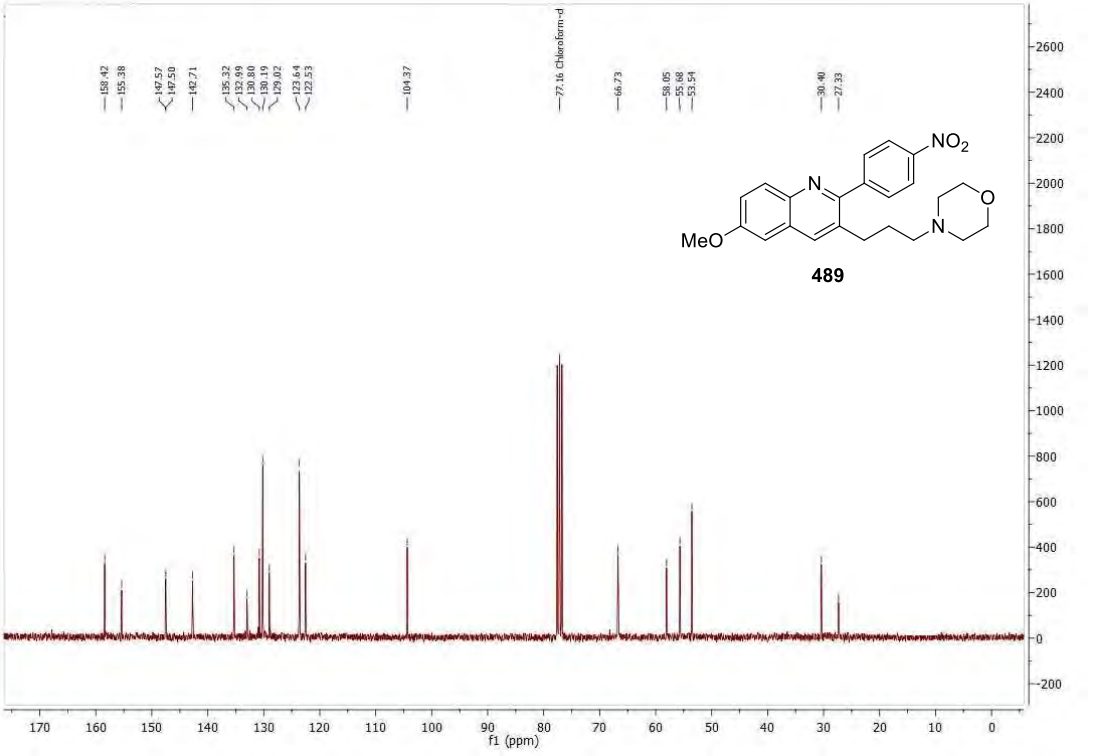

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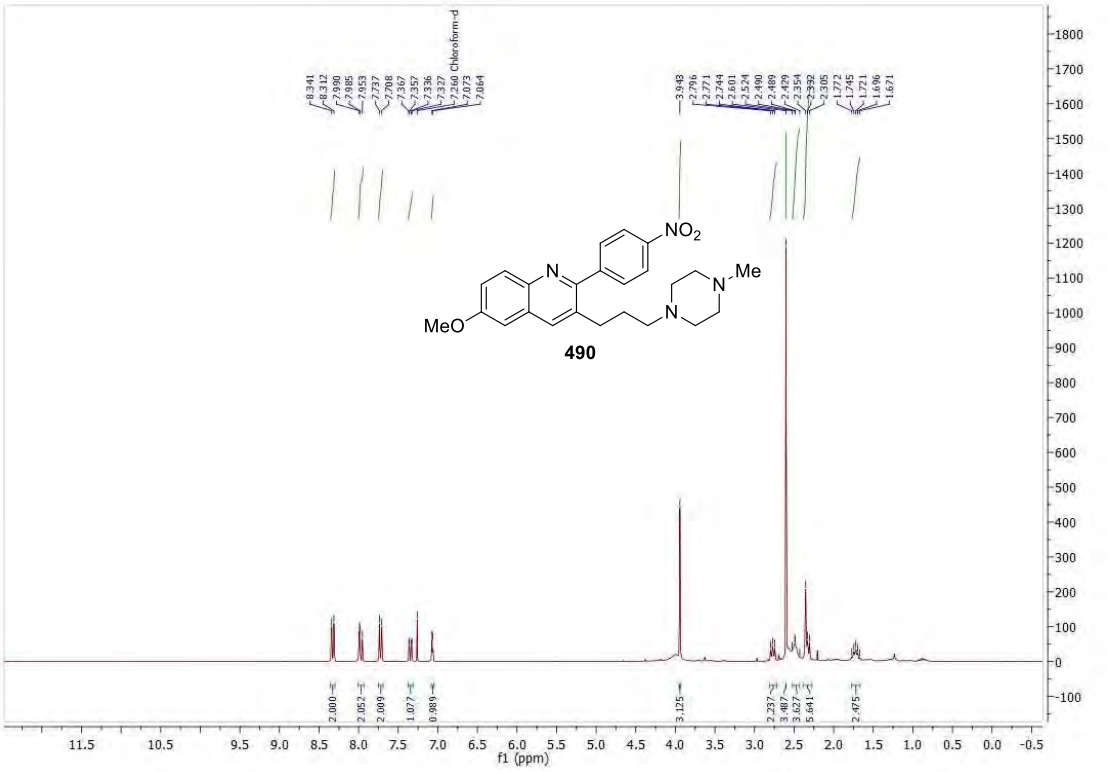
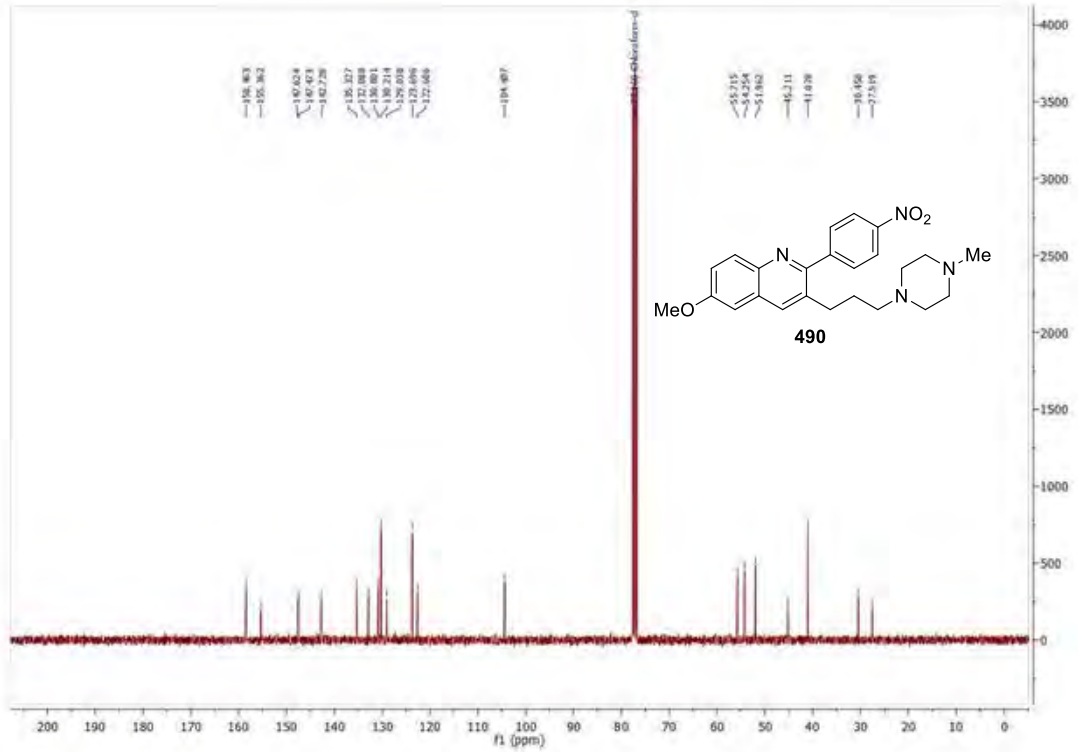
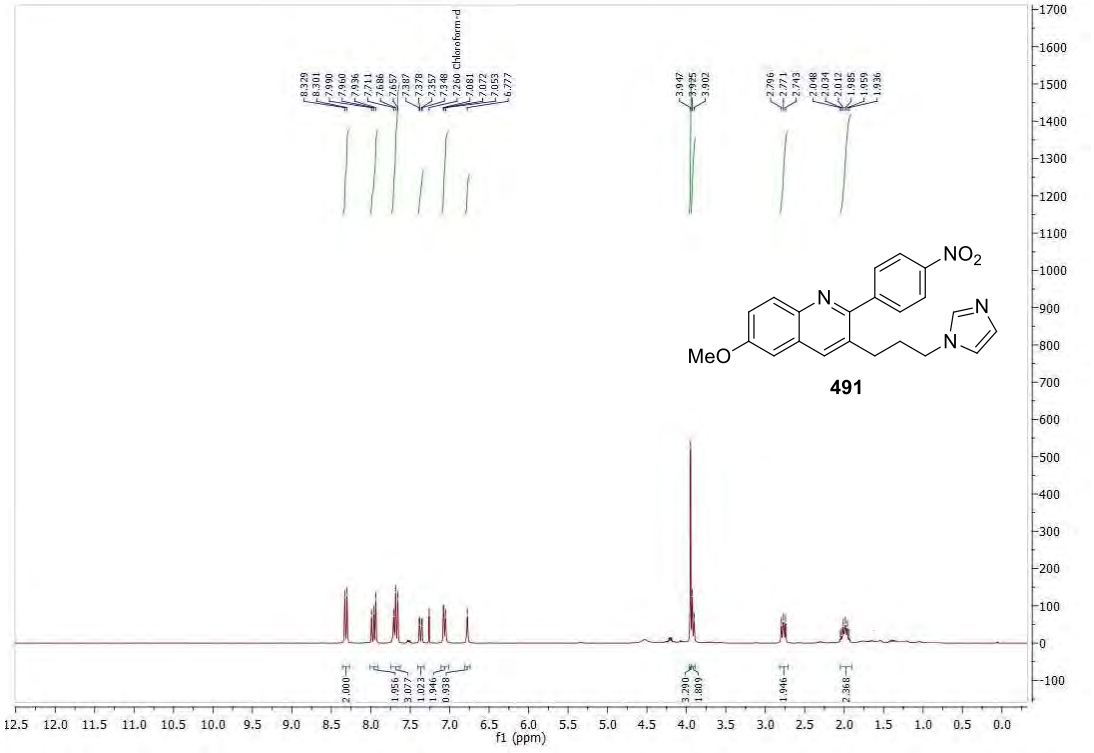
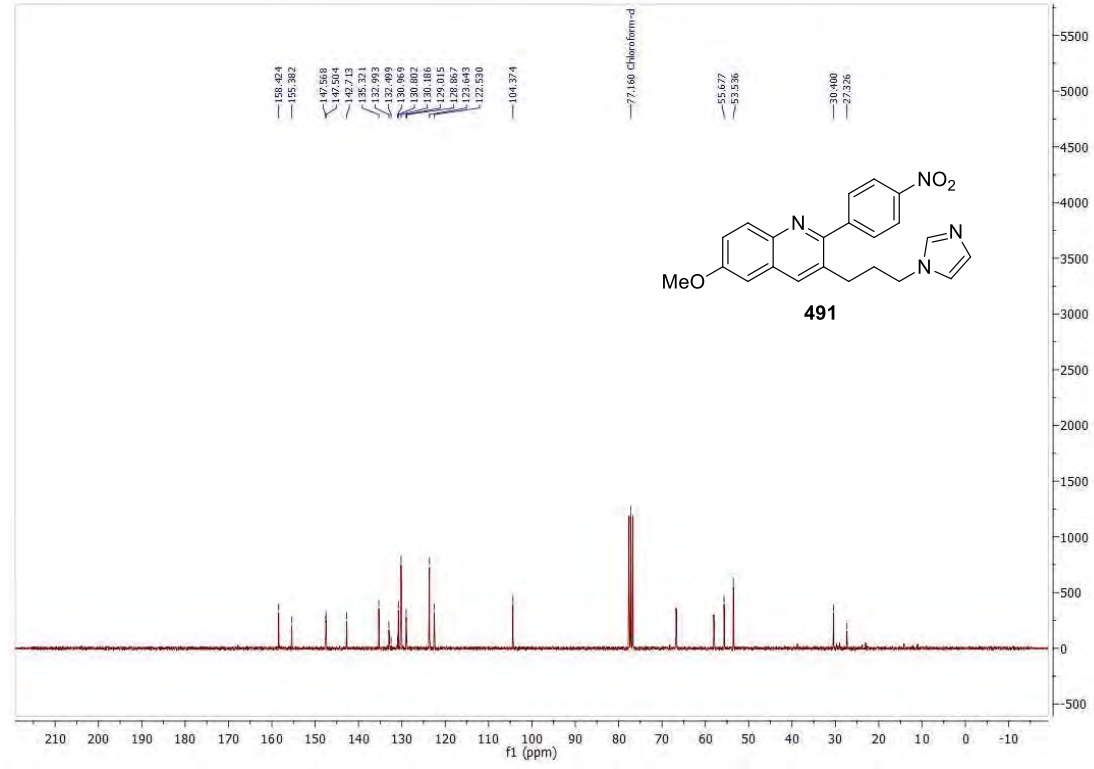


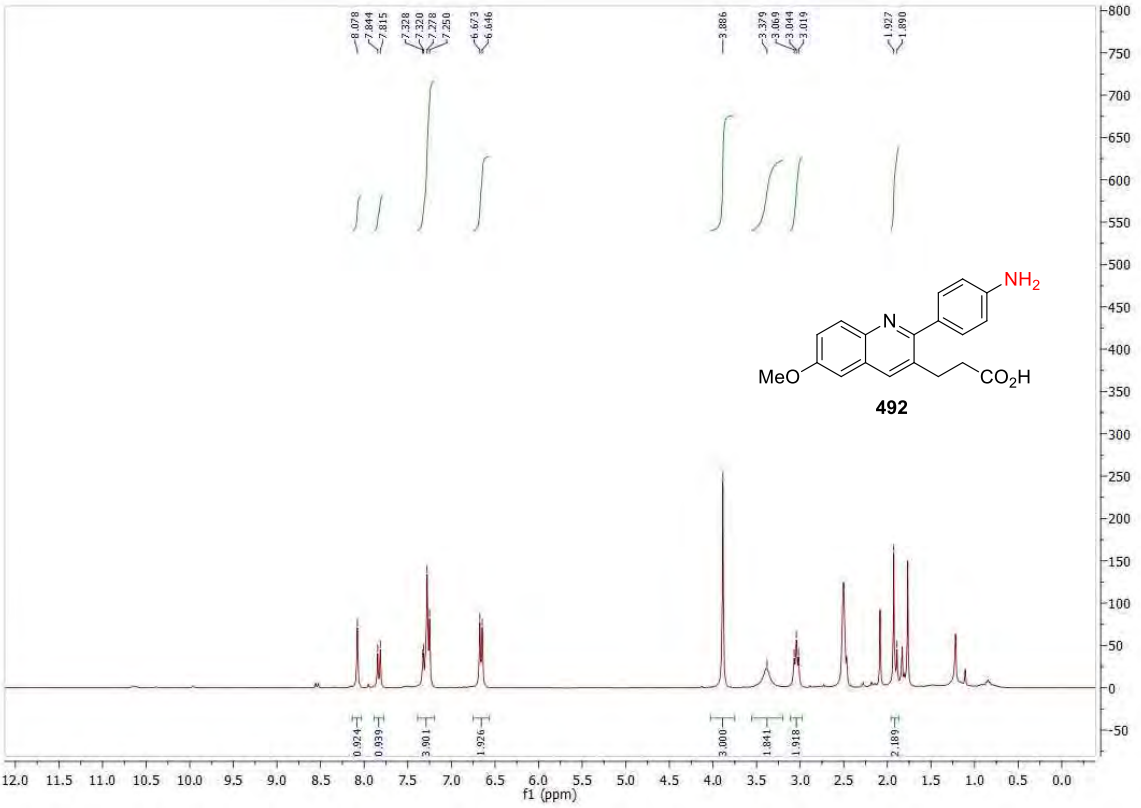


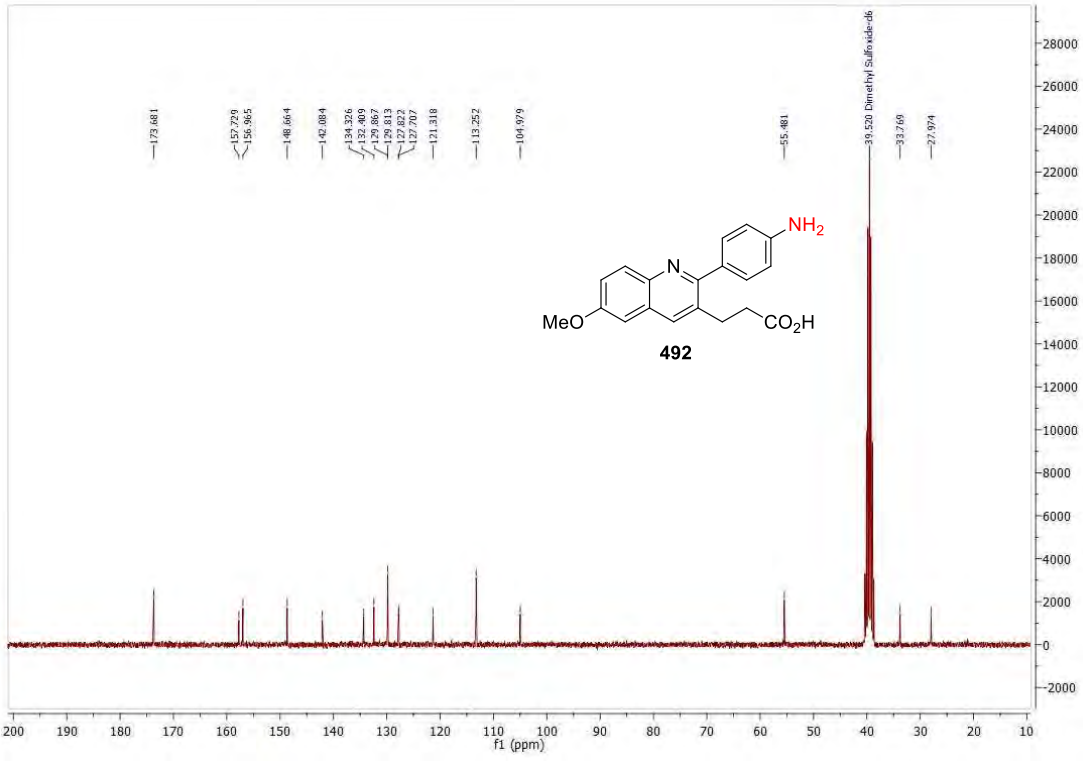
3-(3-(*1H*-Imidazol-1-yl)propyl)-6-methoxy-2-(4-nitrophenyl)quinoline



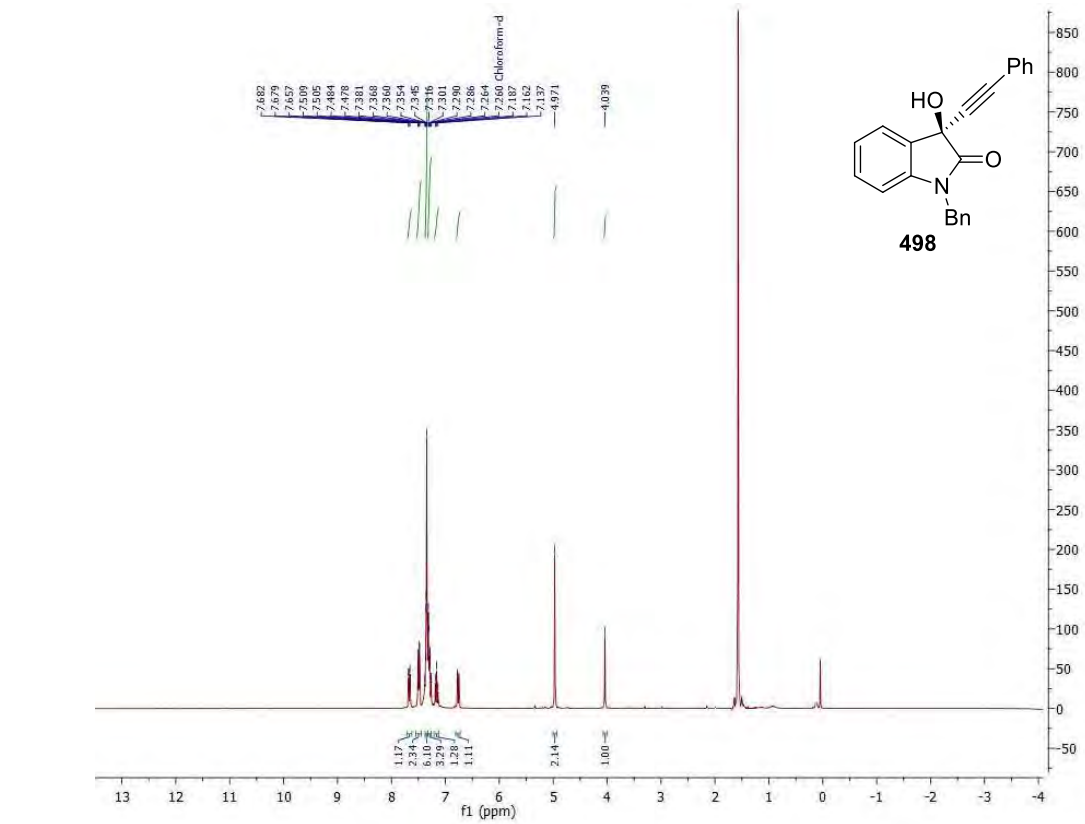


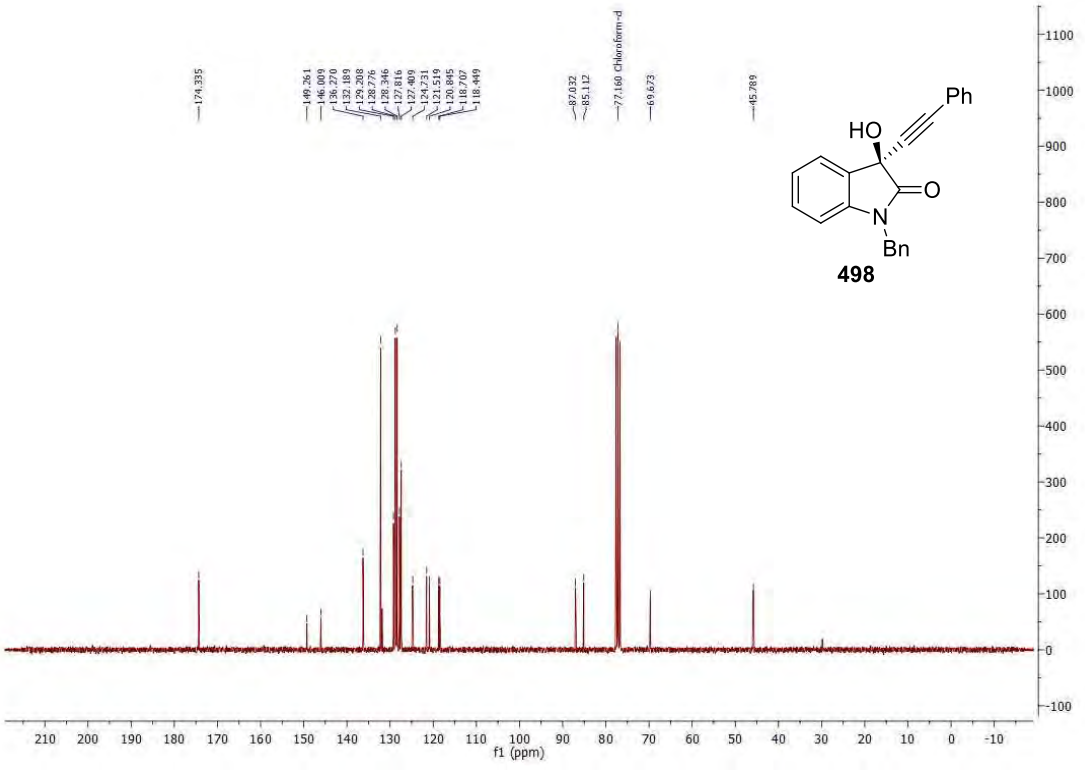
3-(2-(4-aminophenyl)-6-methoxyquinolin-3-yl)propanoic acid



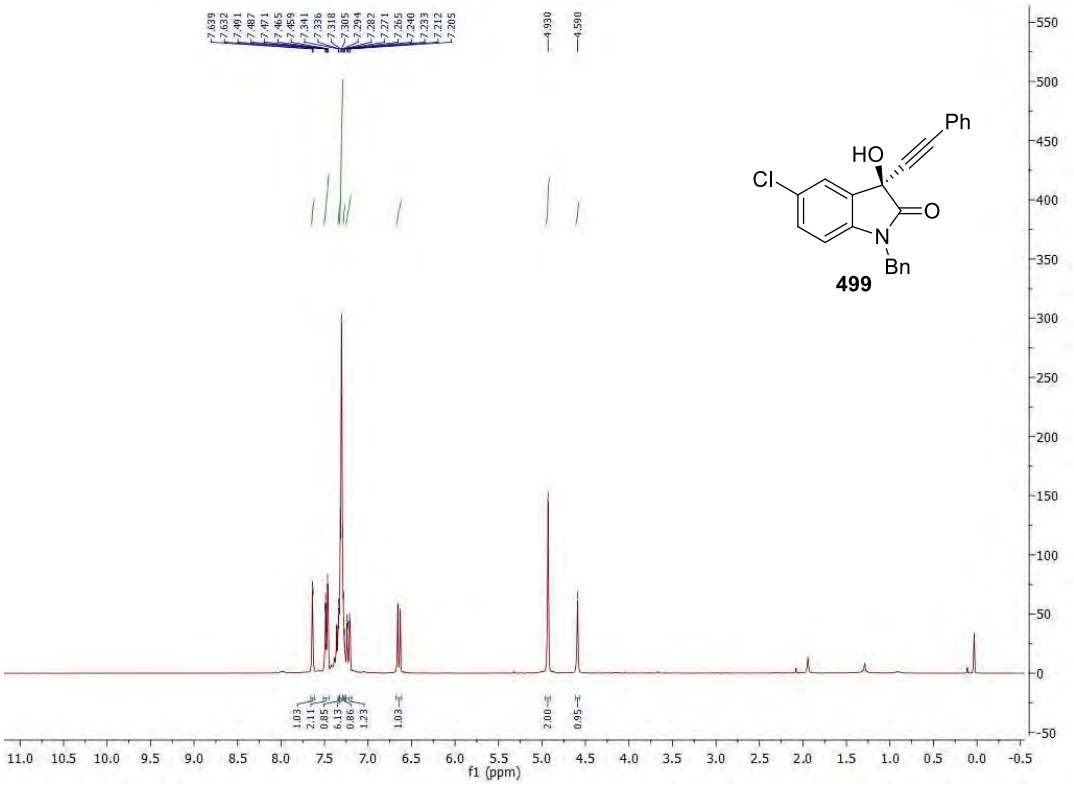


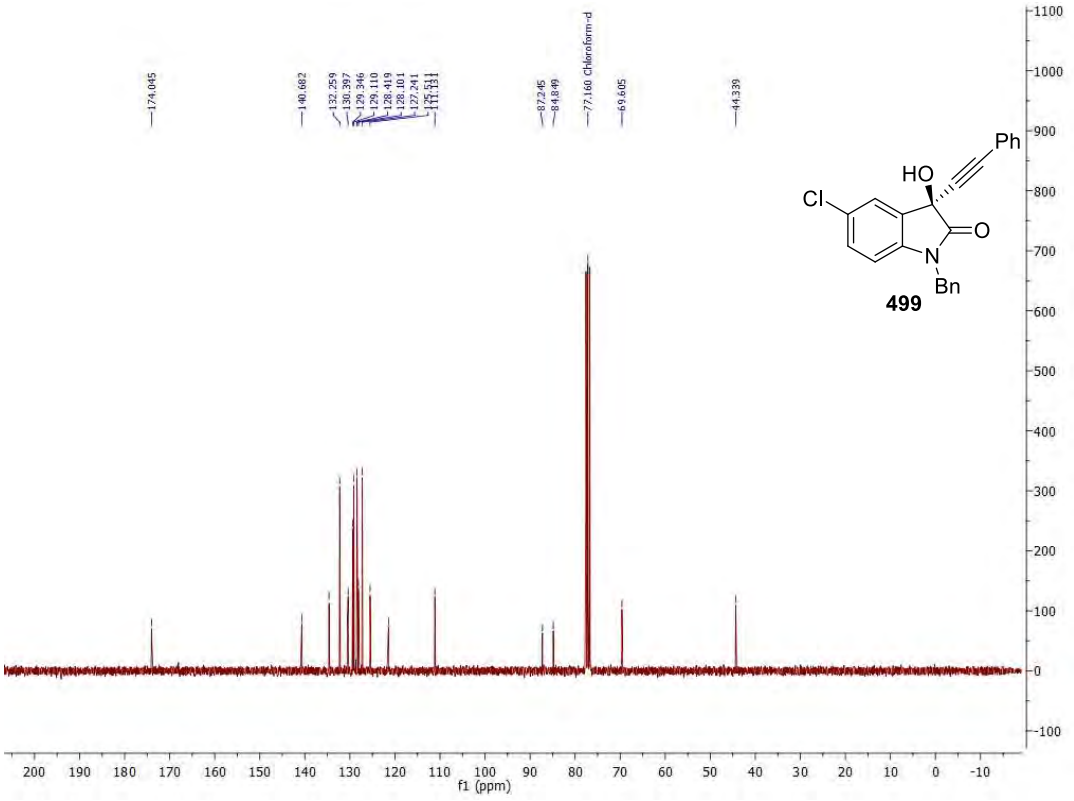
(*R*)-1-Benzyl-3-hydroxy-3-(2-phenylethynyl)indolin-2-one



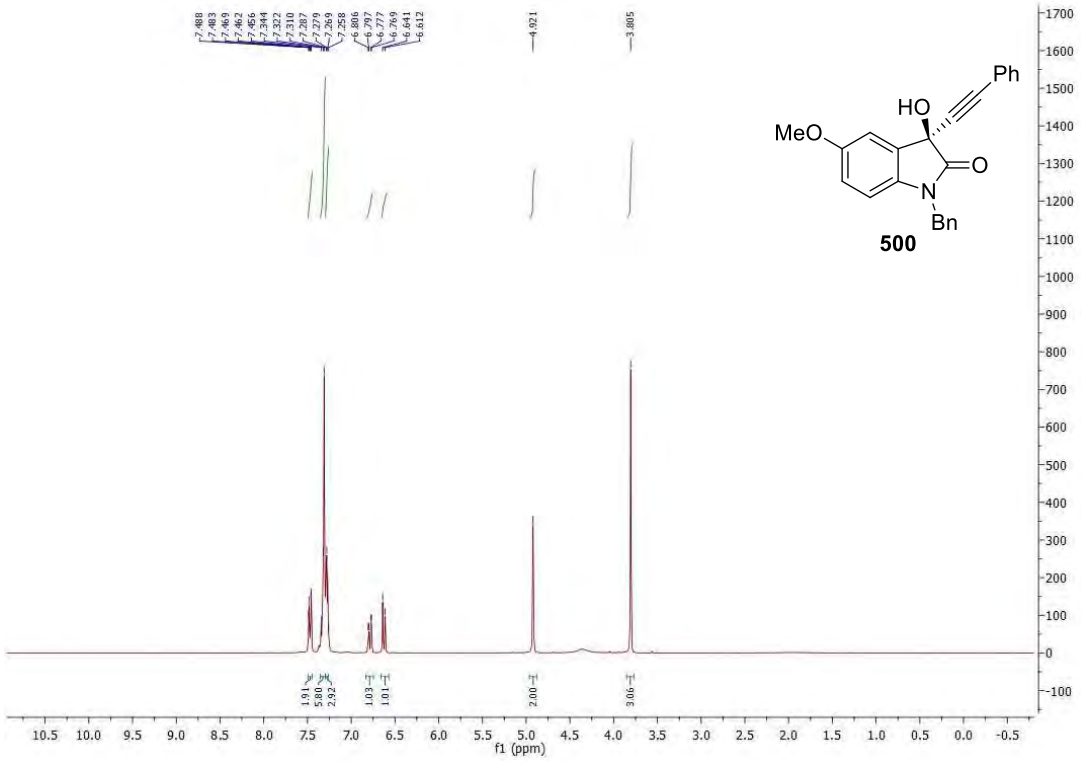


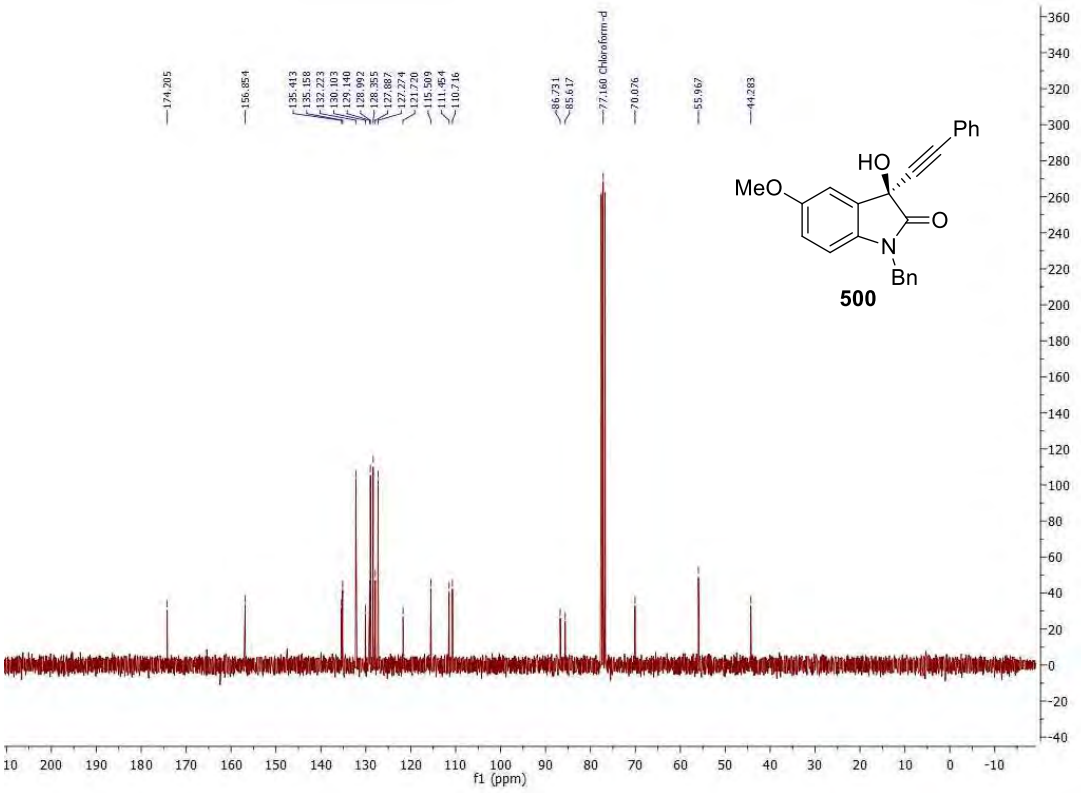
(*R*)-1-Benzyl-5-chloro-3-hydroxy-3-(2-phenylethynyl)indolin-2-one





(*R*)-1-Benzyl-5-methoxy-3-hydroxy-3-(2-phenylethynyl)indolin-2-one





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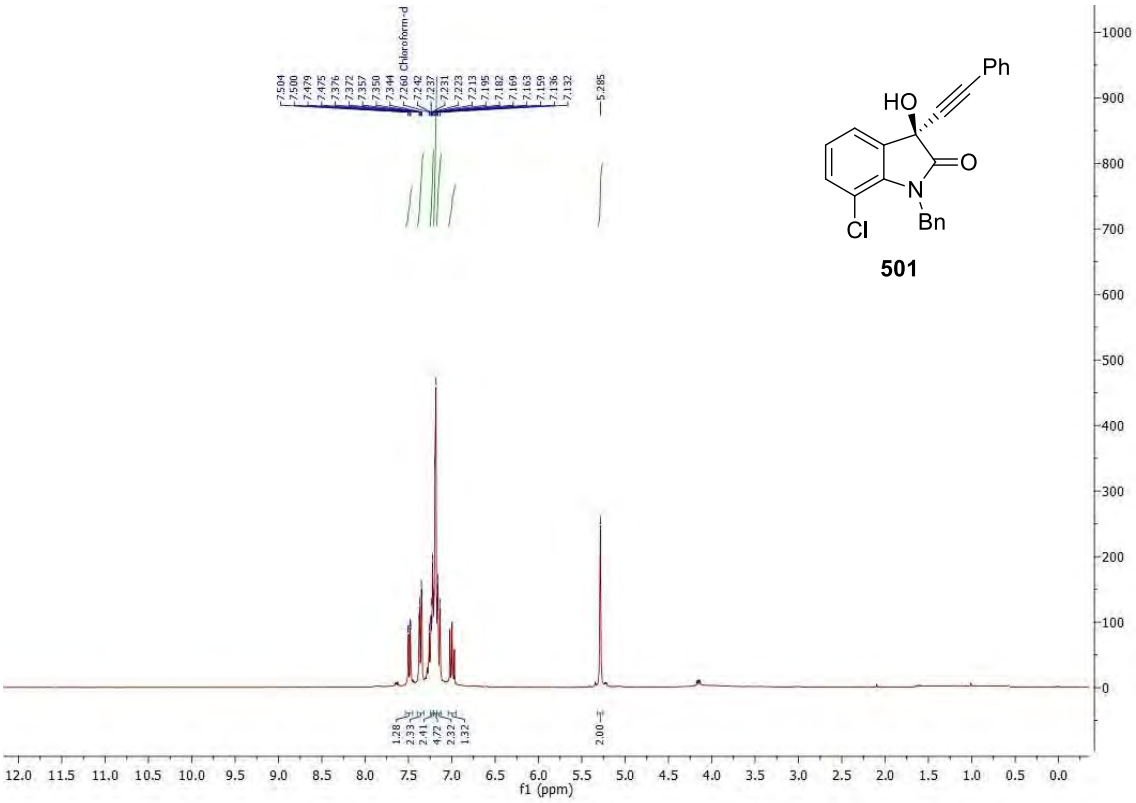
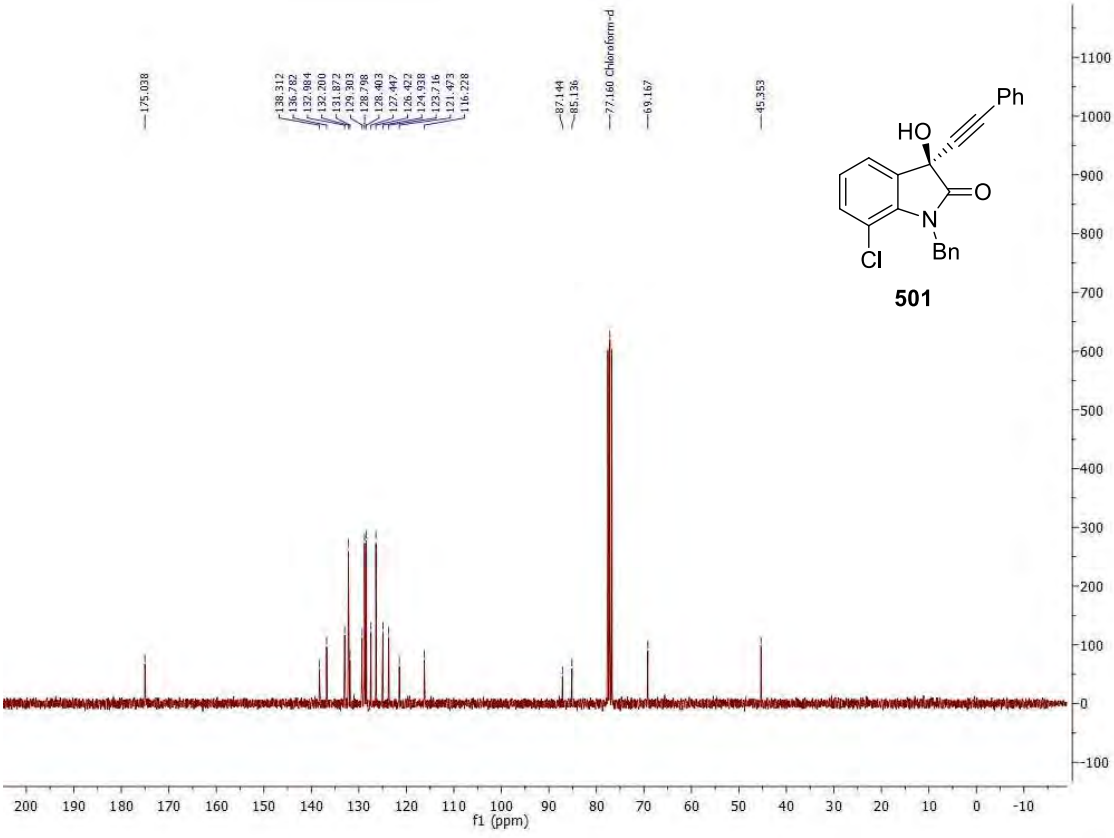
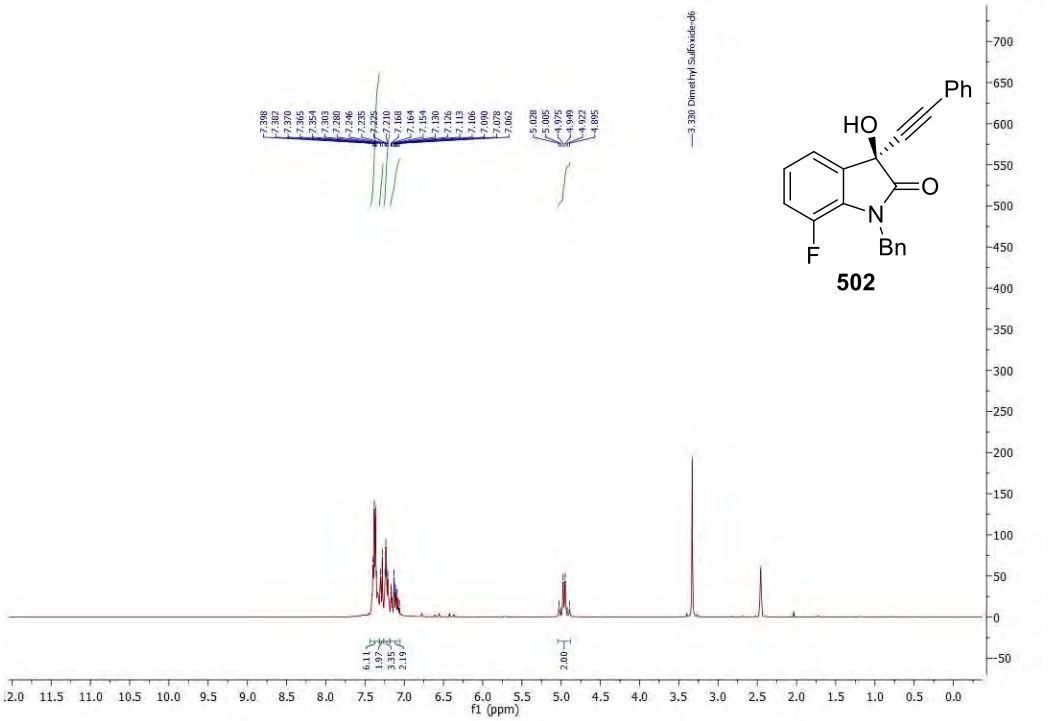
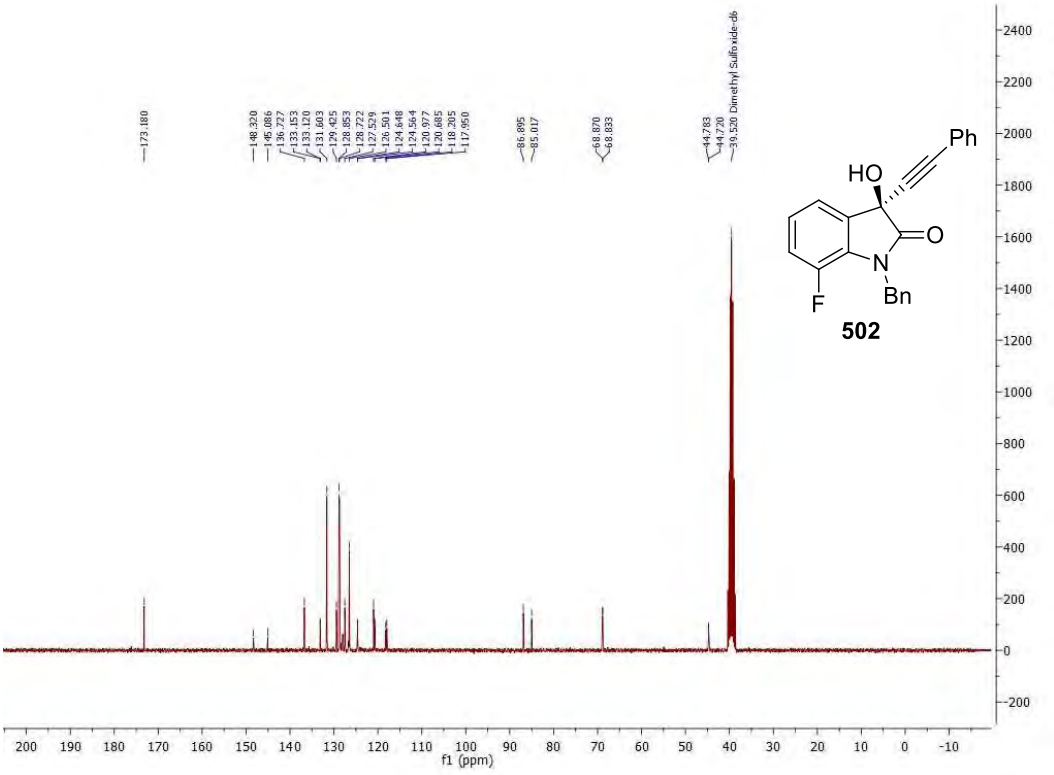




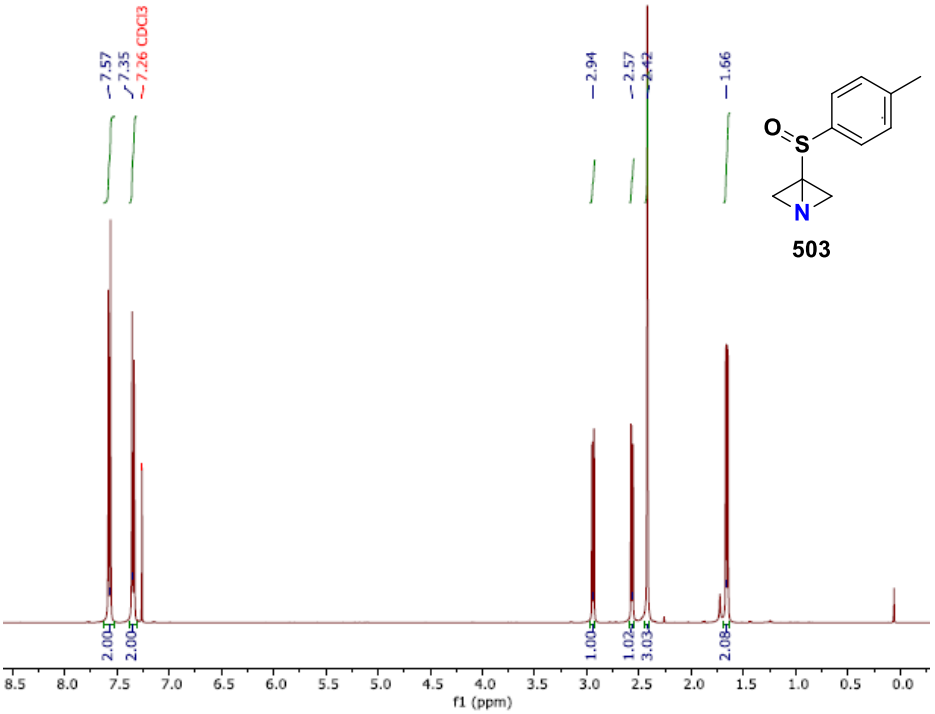
(*R*)-1-Benzyl-3-hydroxy-7-fluoro-3-(2-phenylethynyl)indolin-2-one

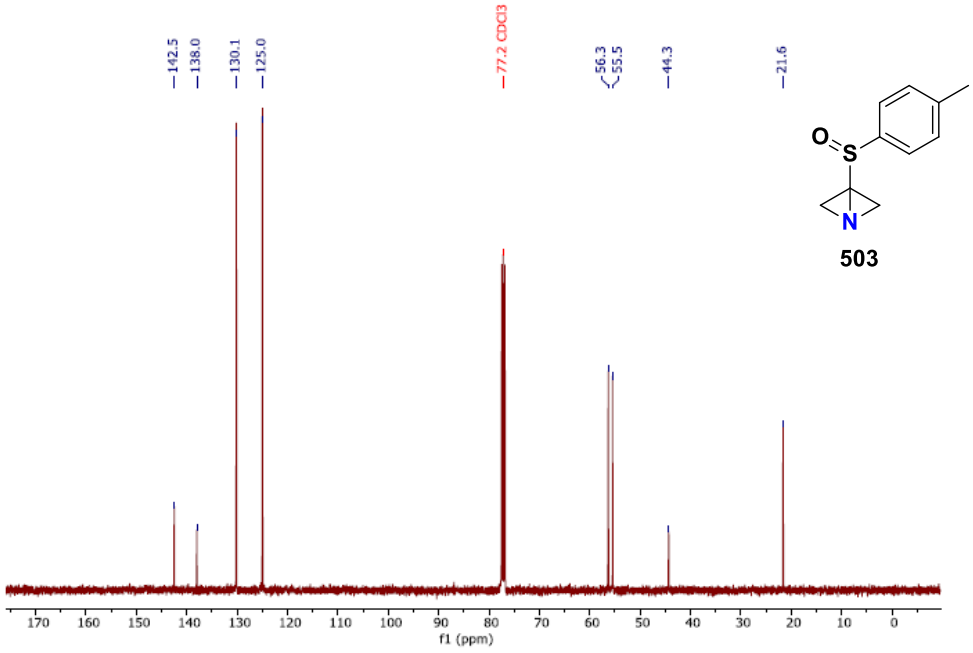




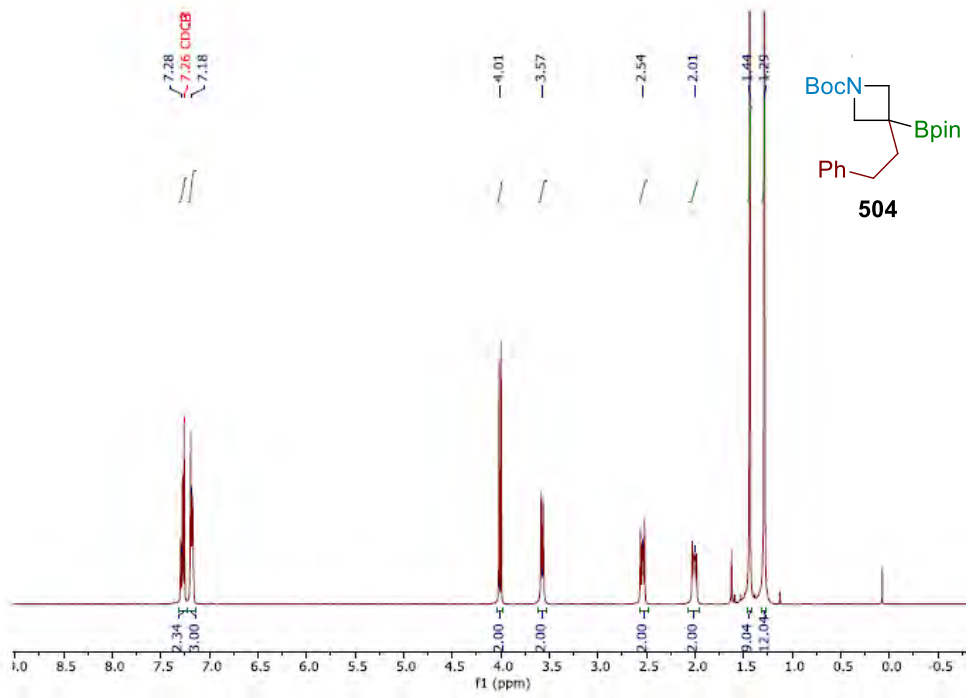
Part C: Synthesis of Azetidine Boronic Esters

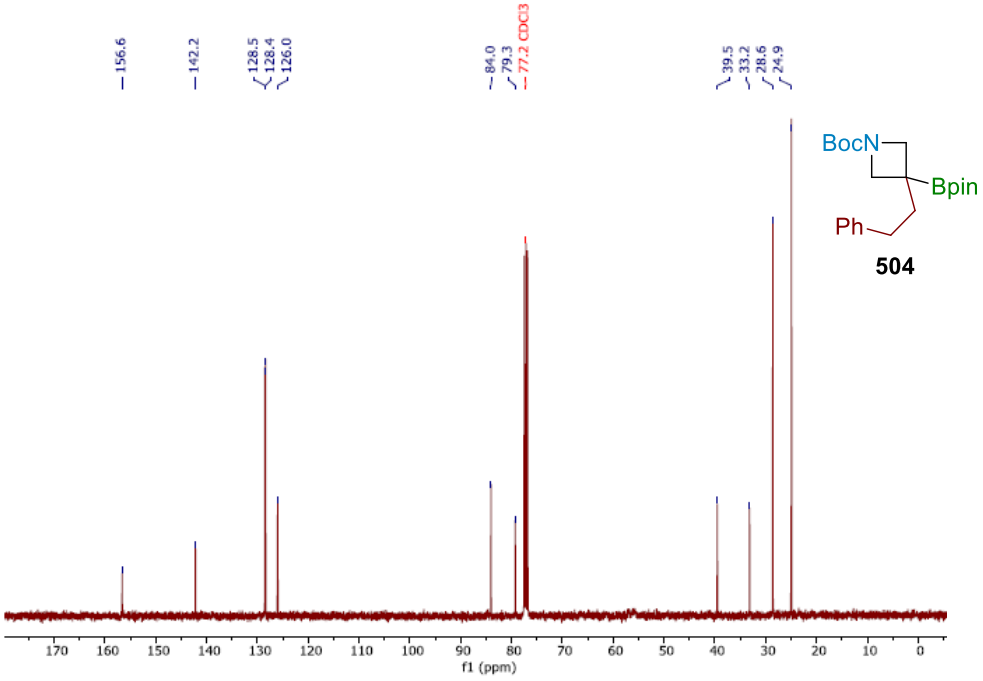
3-(*p*-Tolylsulfinyl)-1-azabicyclo[1.1.0]butane



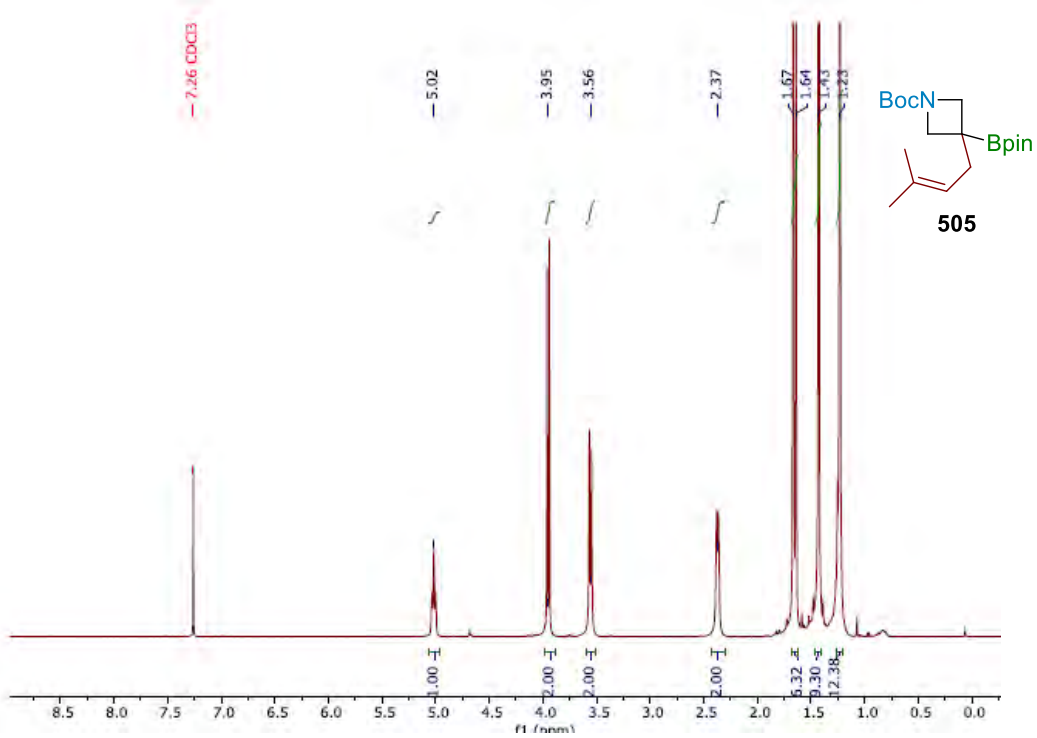


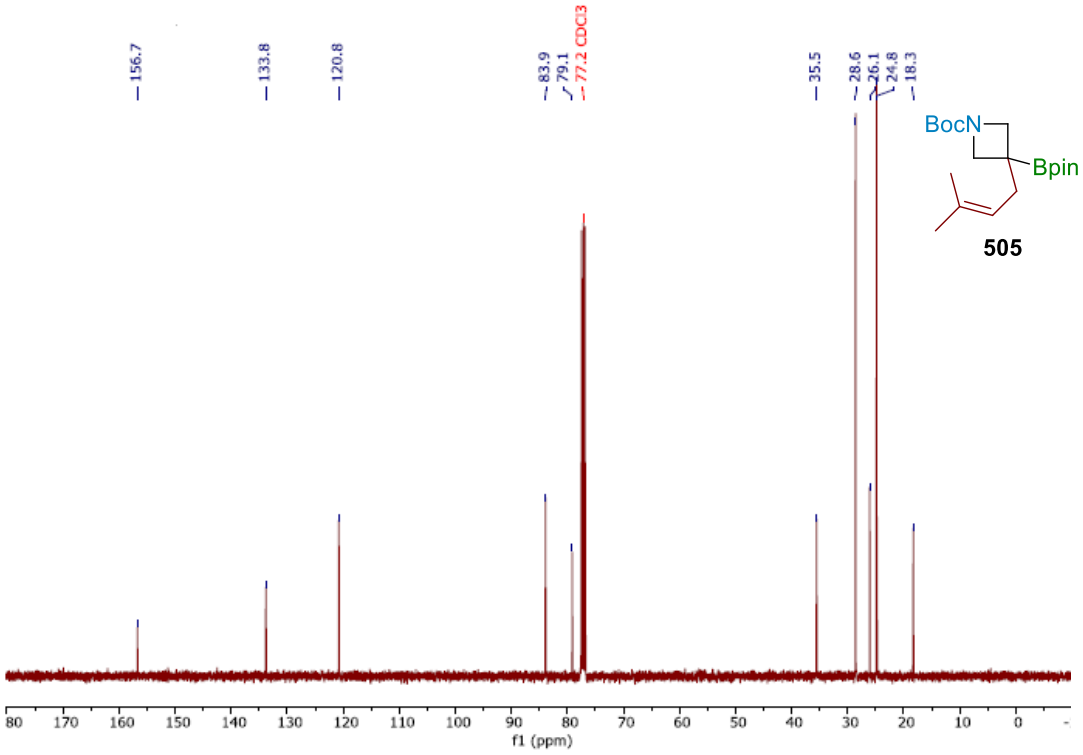
***tert*-Butyl 3-phenethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidine-1-carboxylate**



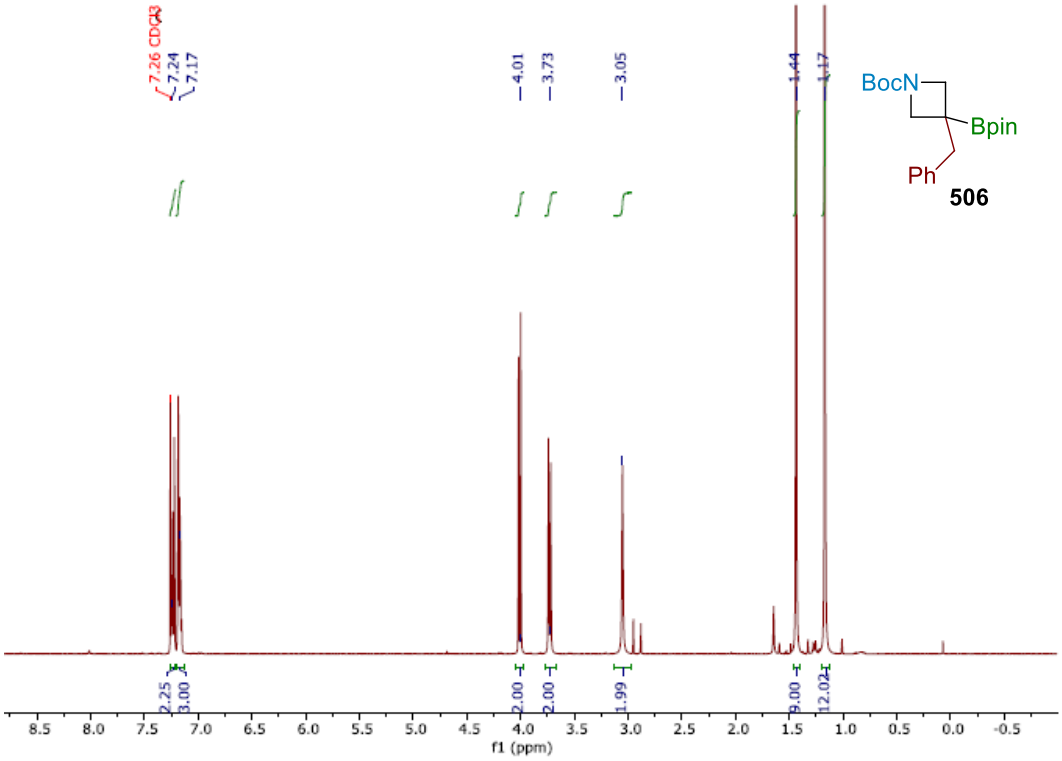


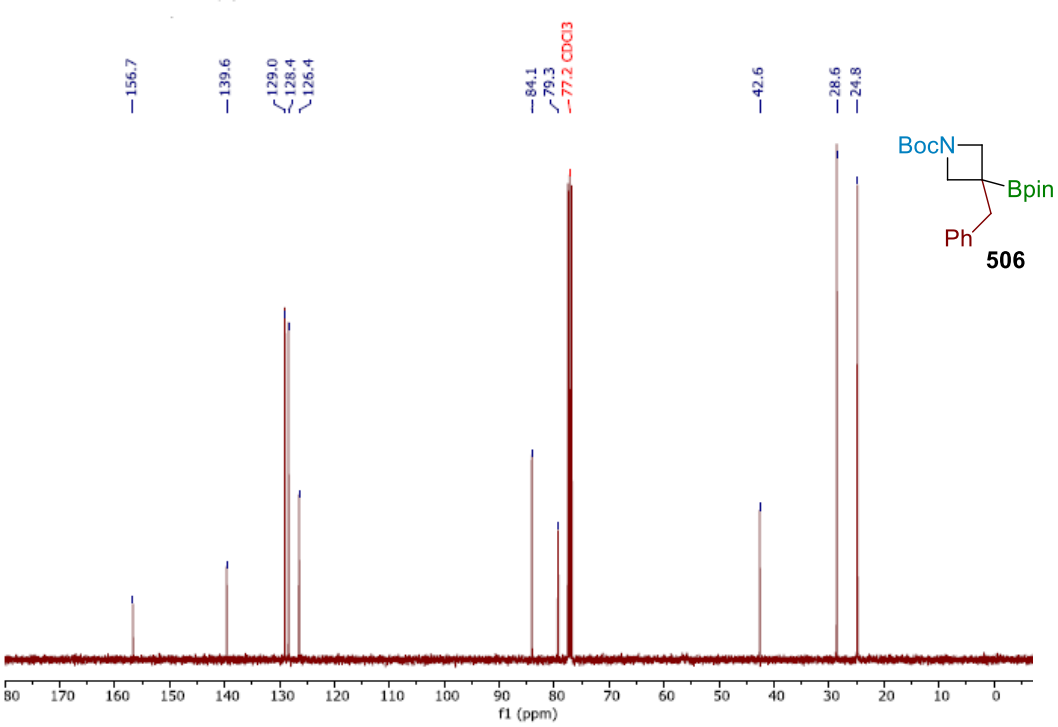
***tert*-Butyl 3-(3-methylbut-2-en-1-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidine-1-carboxylate**



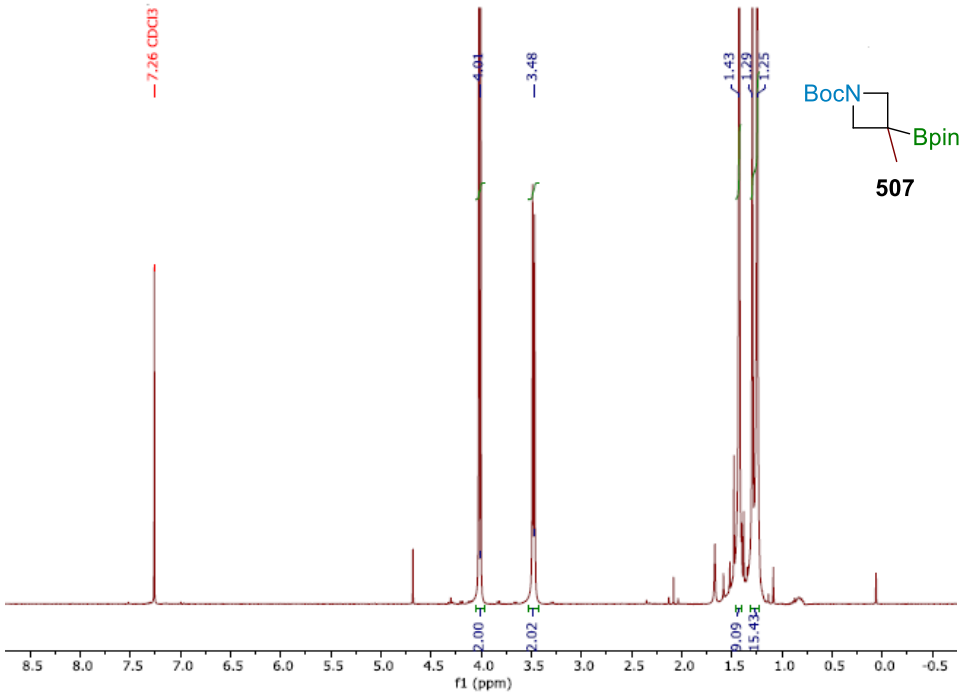


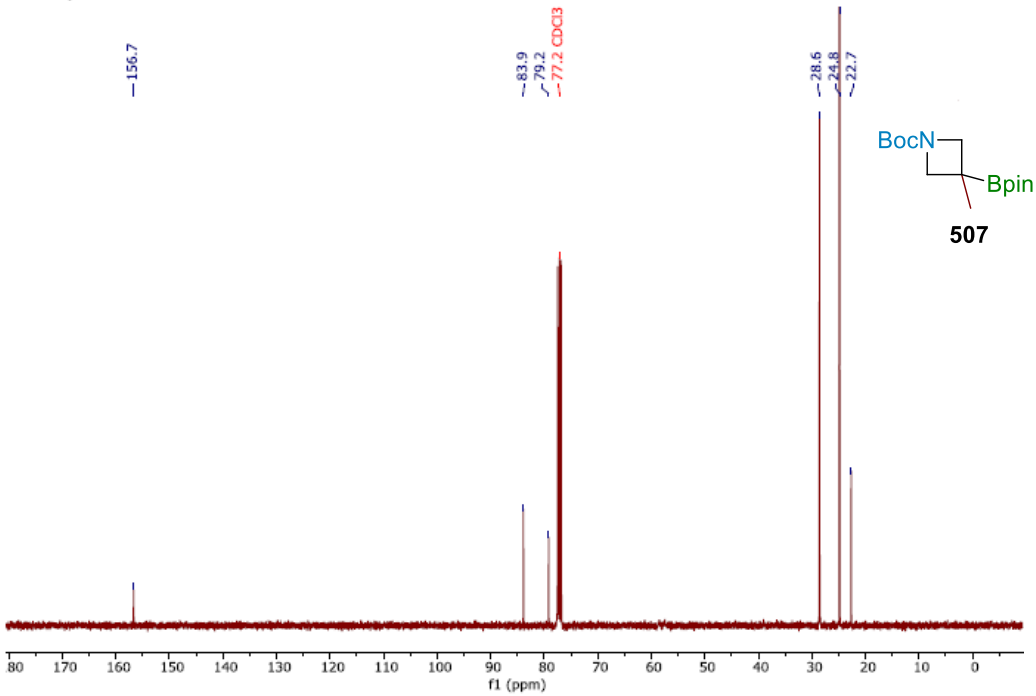
***tert*-Butyl 3-benzyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidine-1-carboxylate**



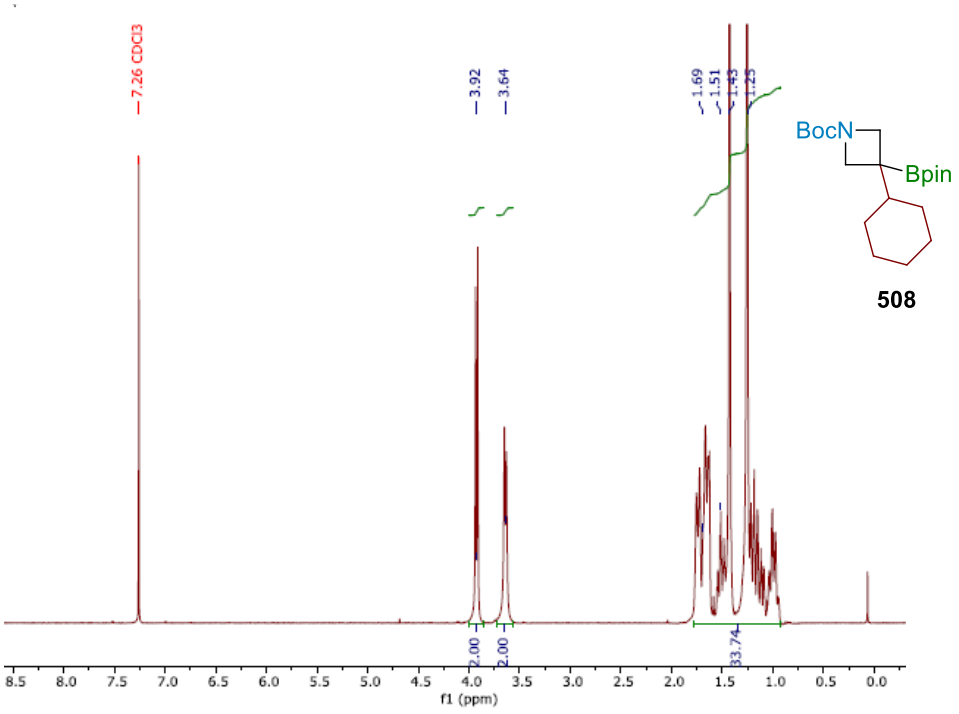


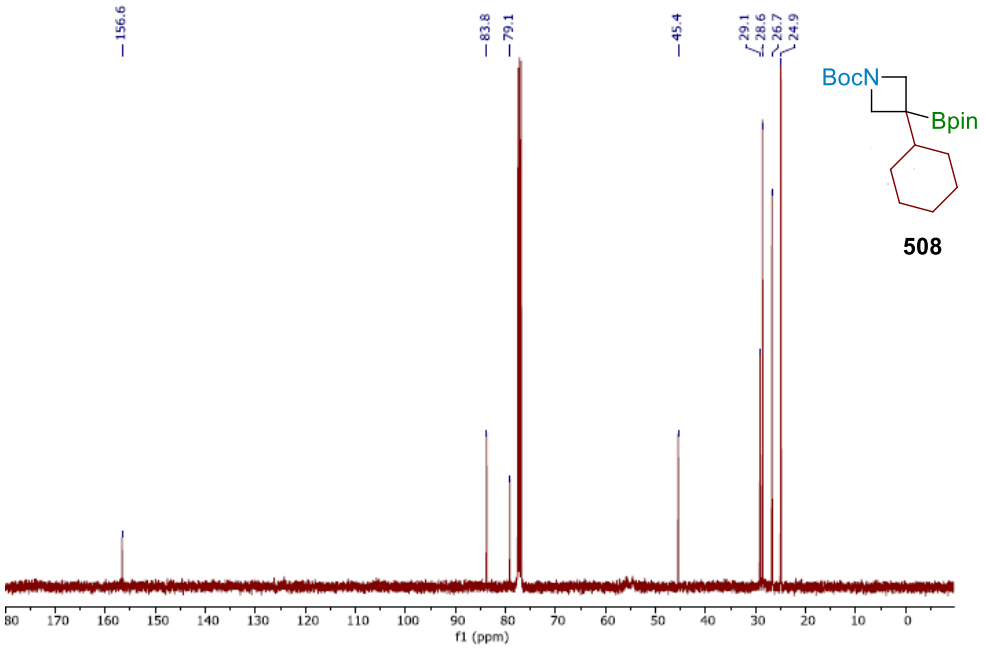
***tert*-Butyl 3-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidine-1-carboxylate**



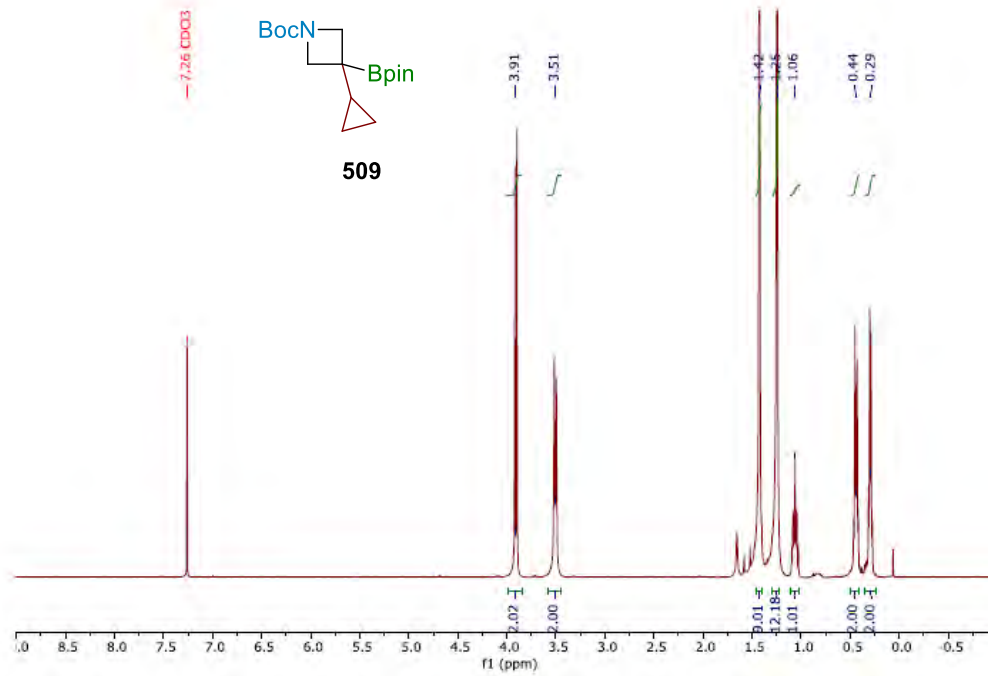


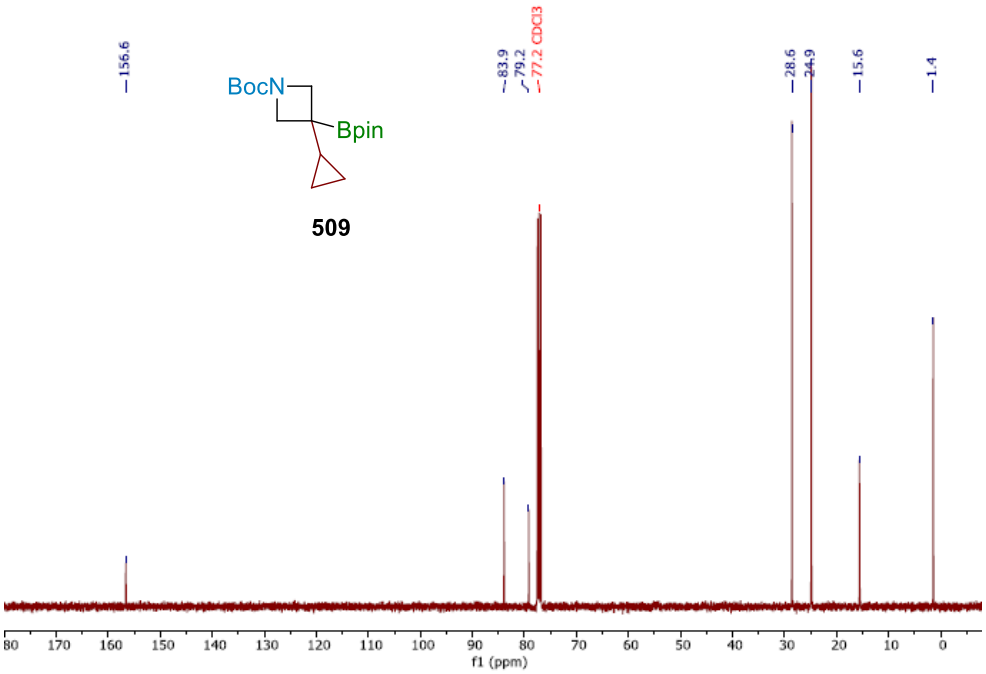
***tert*-Butyl 3-cyclohexyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidine-1-carboxylate**



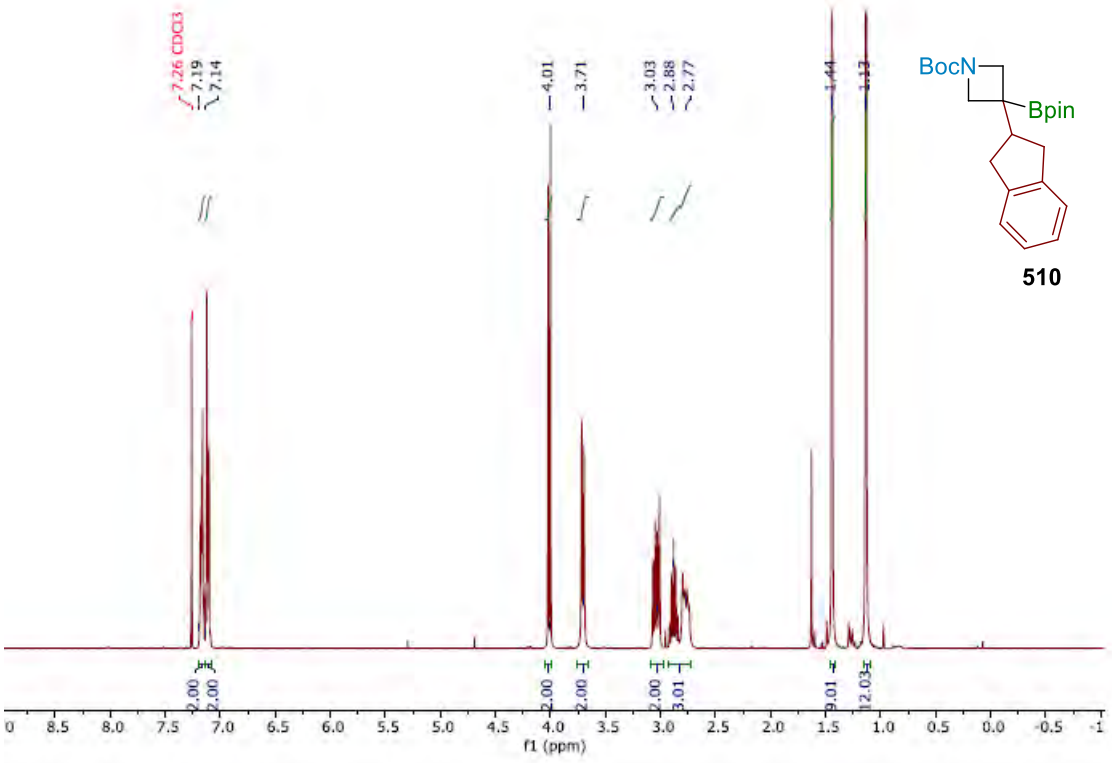


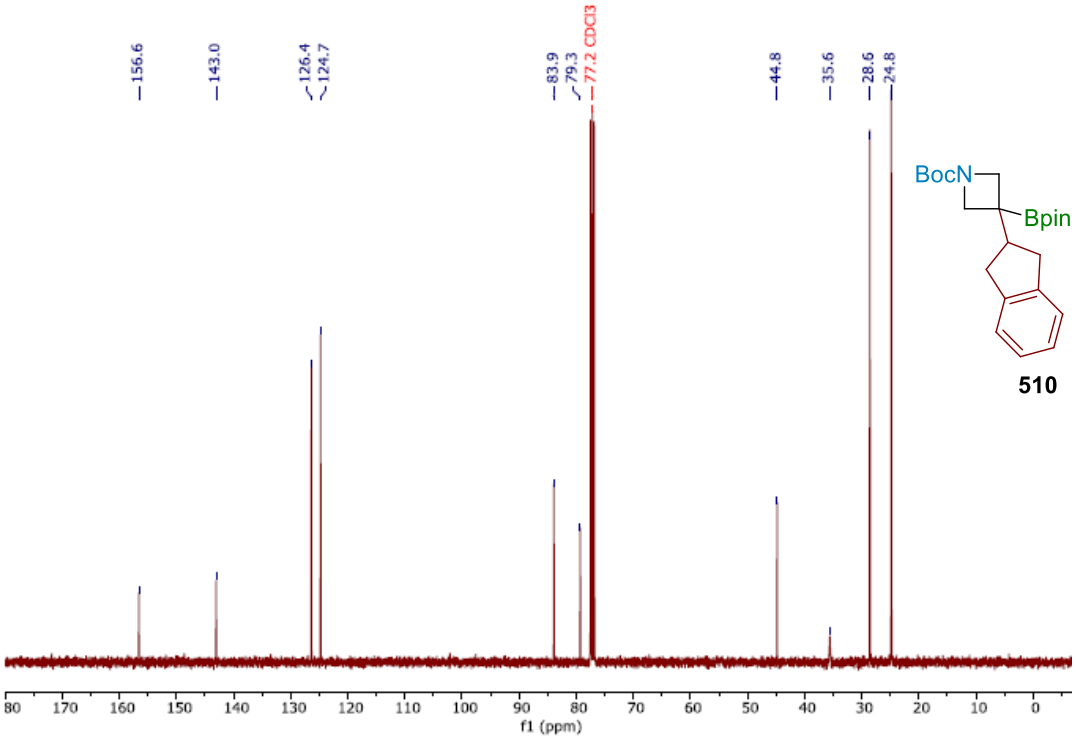
***tert*-Butyl 3-cyclopropyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidine-1-carboxylate**



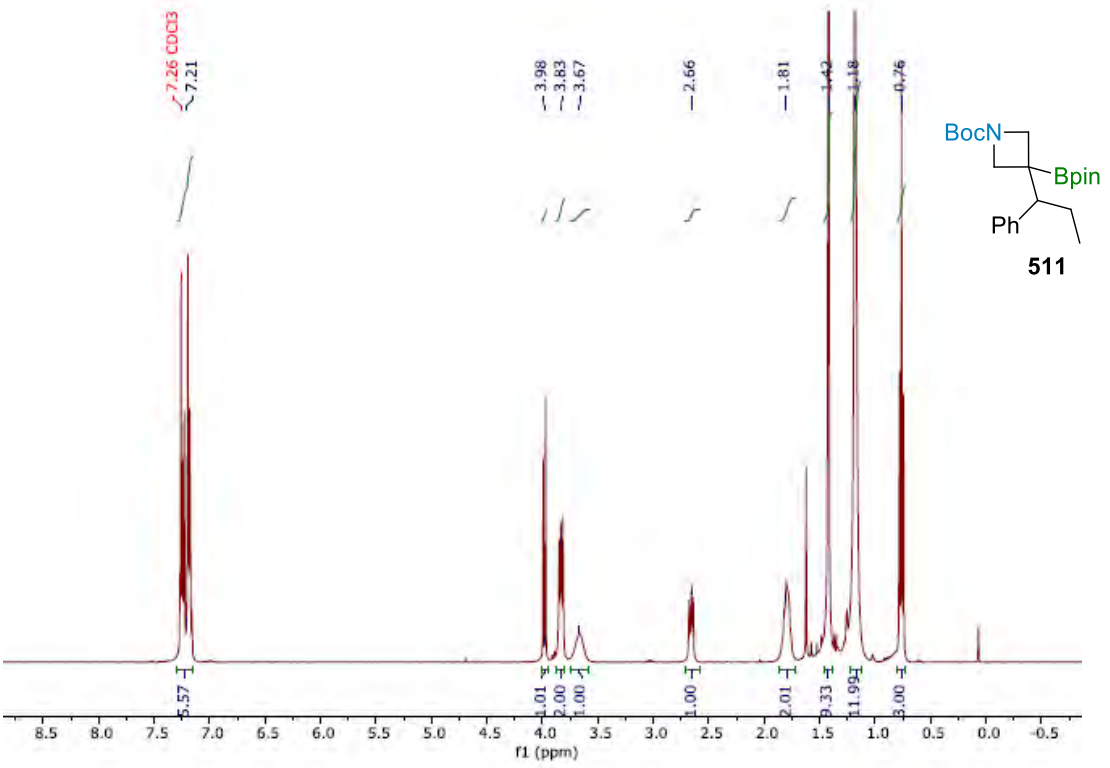


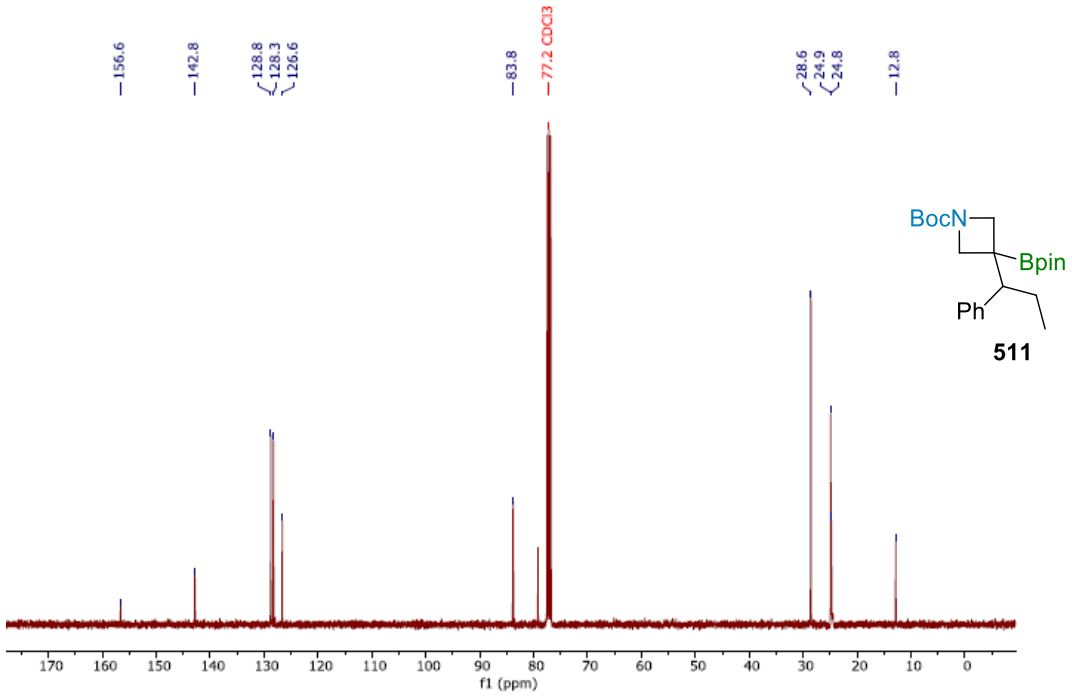
***tert*-Butyl 3-(2,3-dihydro-1*H*-inden-2-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2- yl)azetidine-1-carboxylate**



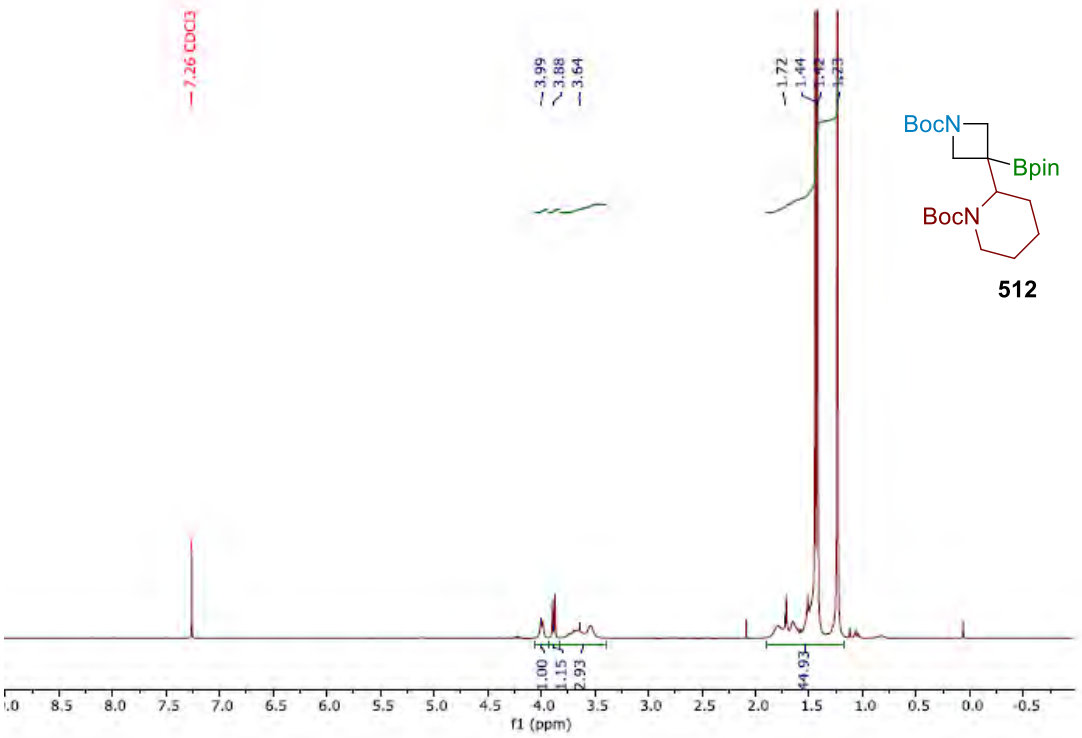


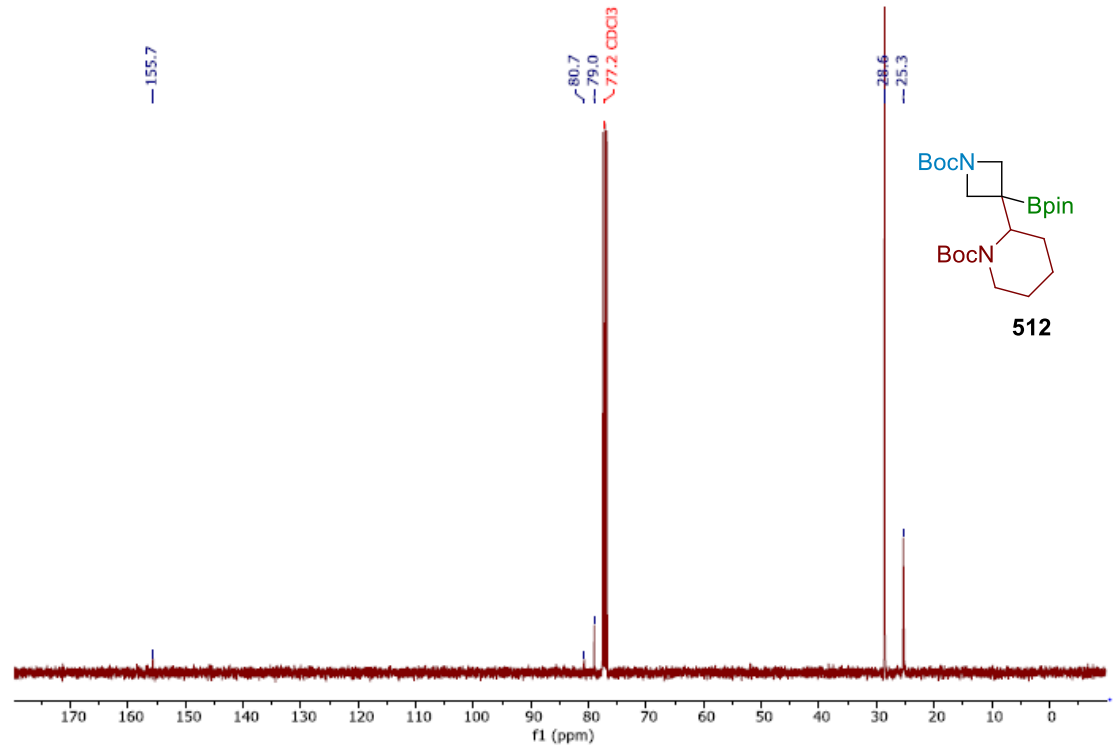
***tert*-Butyl 3-(1-phenylpropyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidine-1- carboxylate**



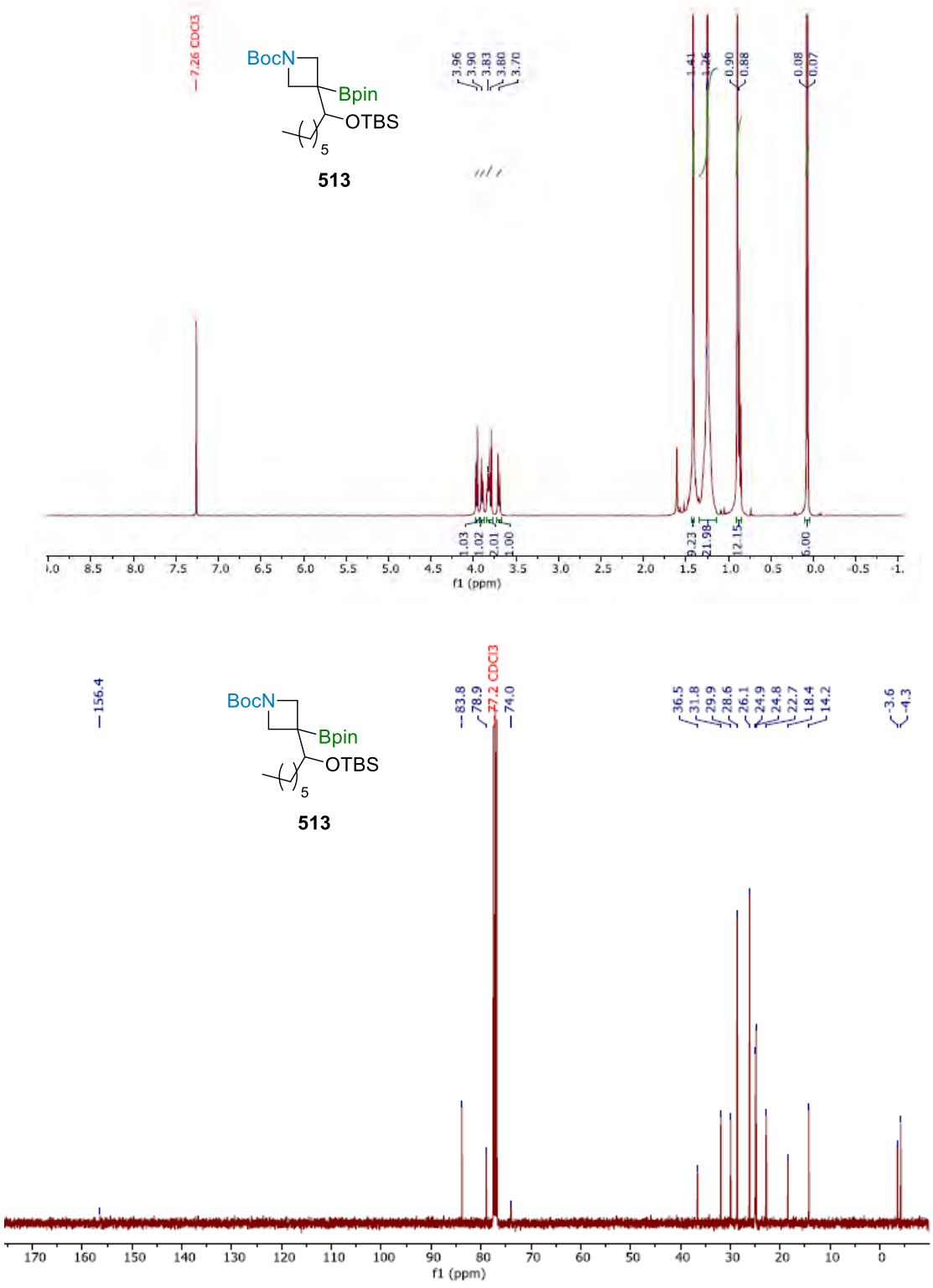


***tert*-Butyl 2-(1-(*tert*-butoxycarbonyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidin-3-yl)piperidine-1-carboxylate**

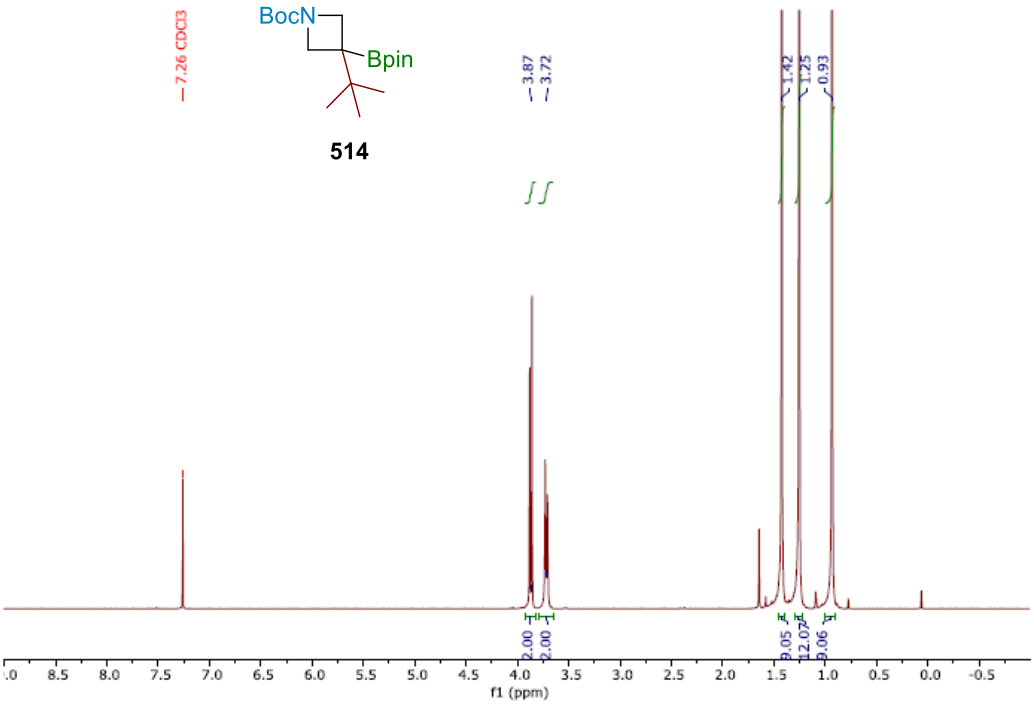


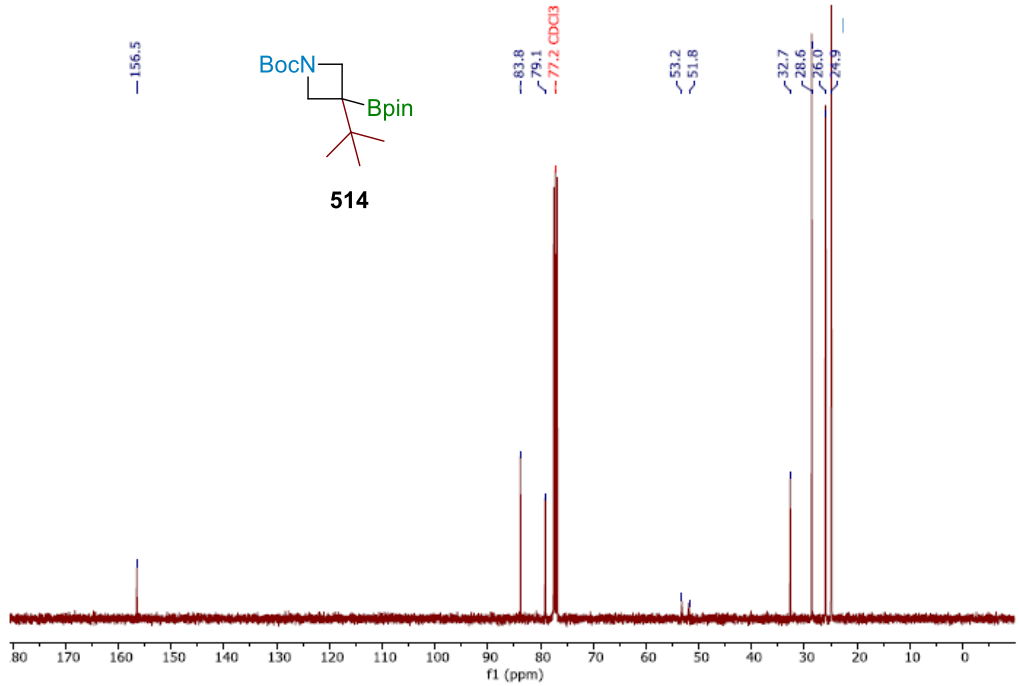


***tert*-Butyl 3-(1-((*tert*-butyldimethylsilyl)oxy)heptyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidine-1-carboxylate**



***tert*-Butyl 3-(*tert*-butyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidine-1-carboxylate**





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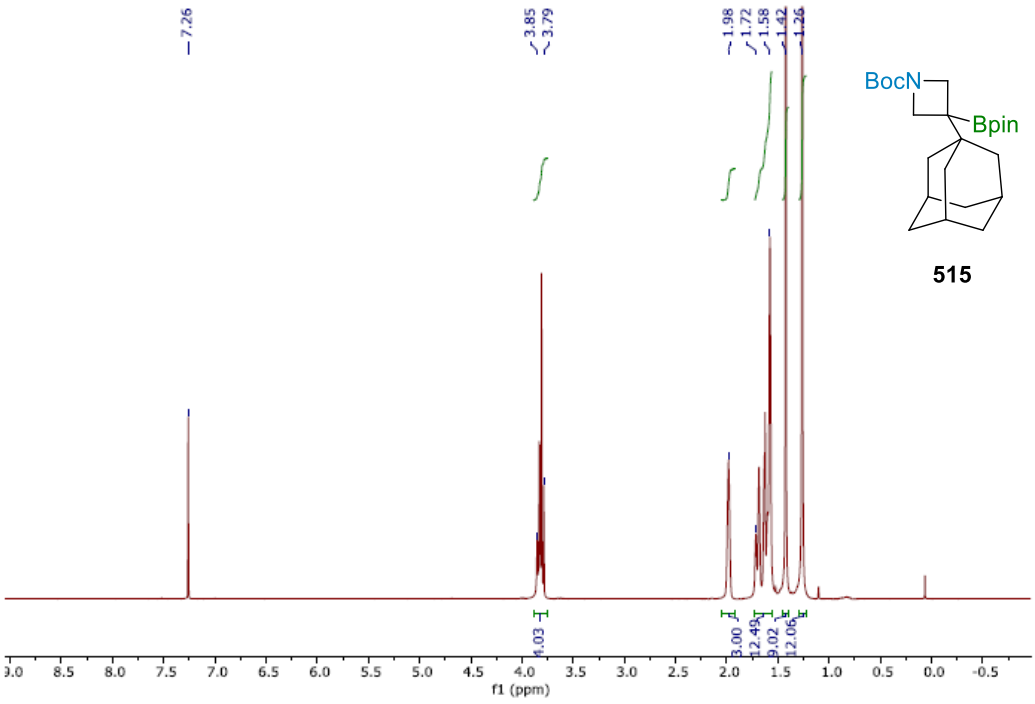
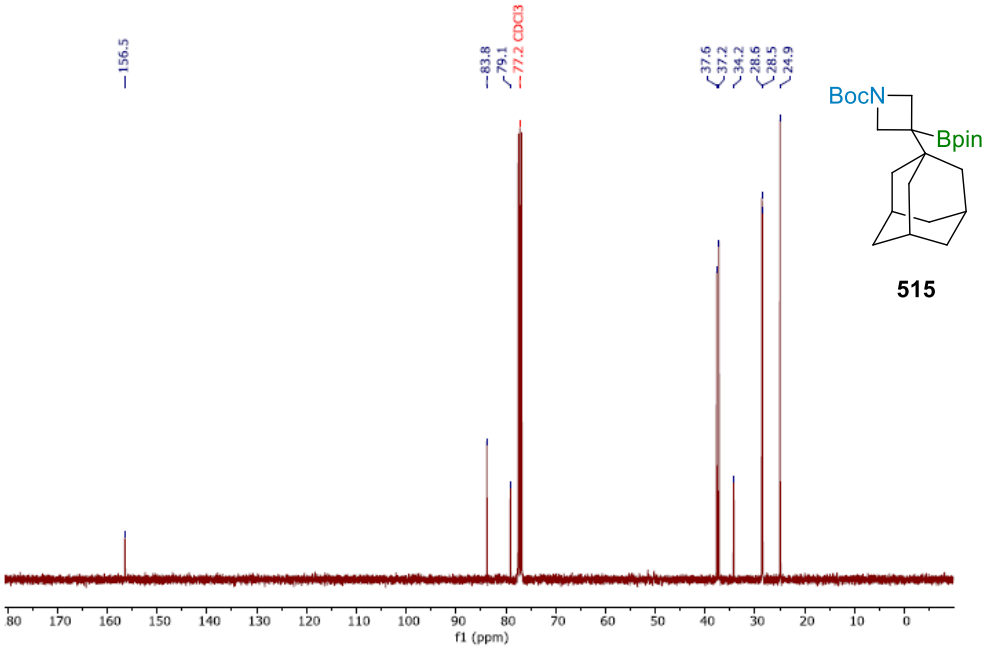
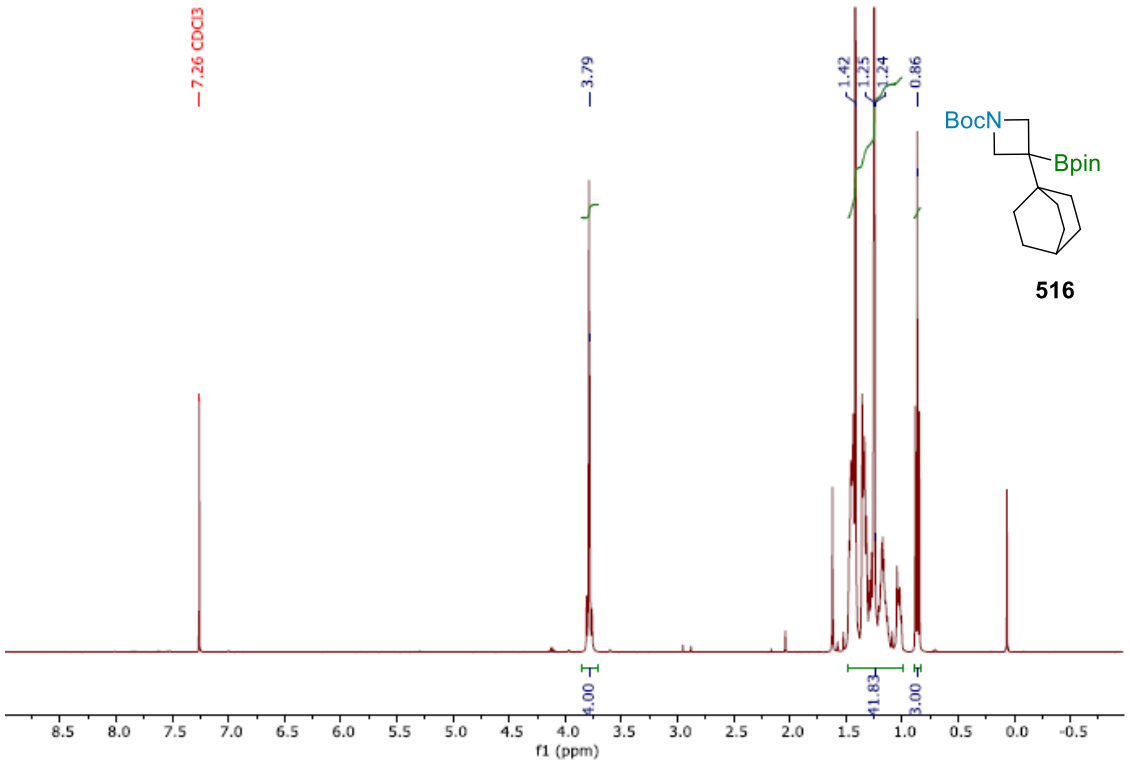




***tert*-Butyl 3-(4-pentylbicyclo[2.2.2]octan-1-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan- 2-yl)azetidine-1-carboxylate**



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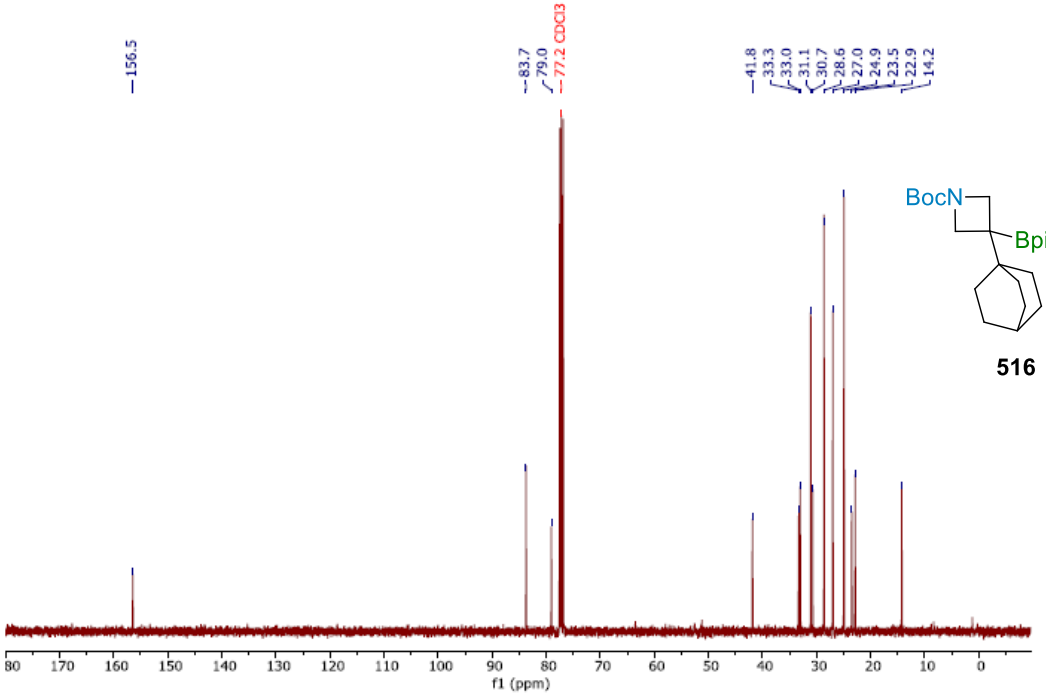

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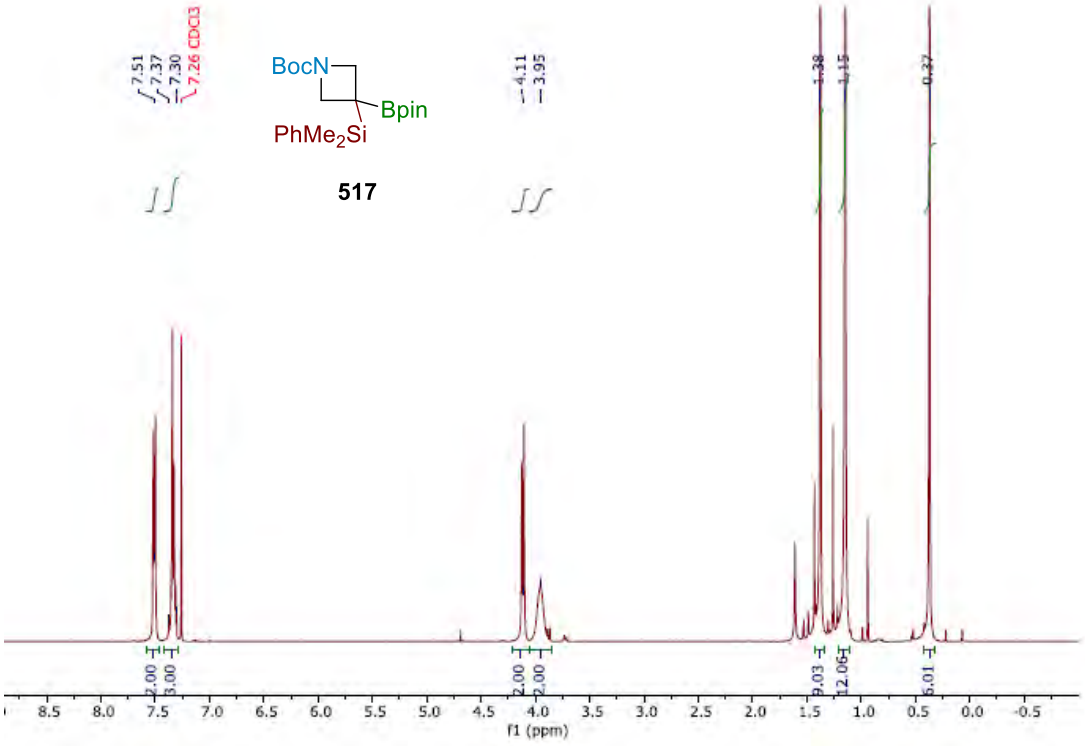
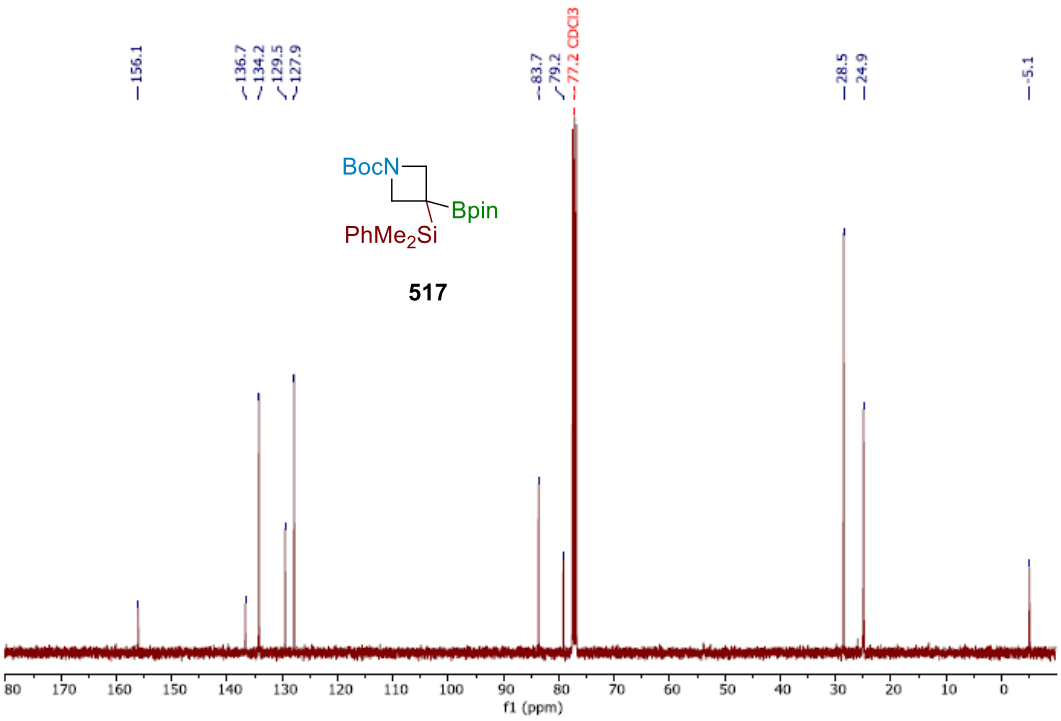
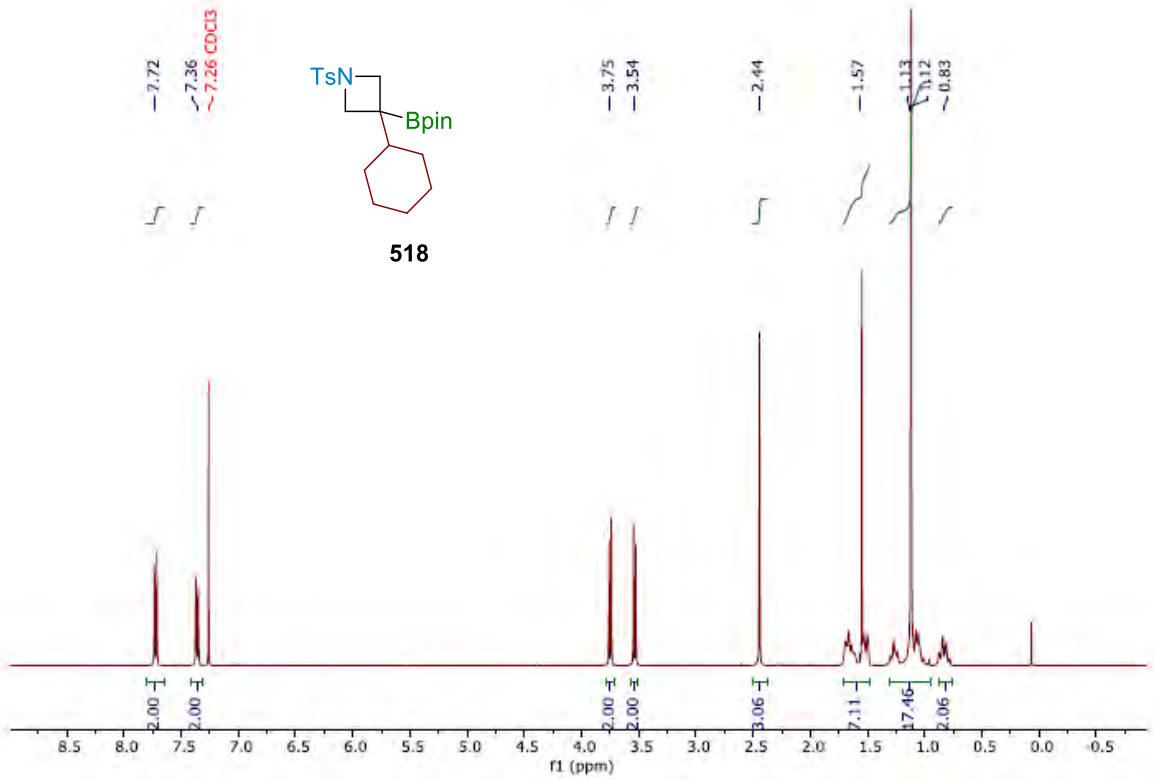
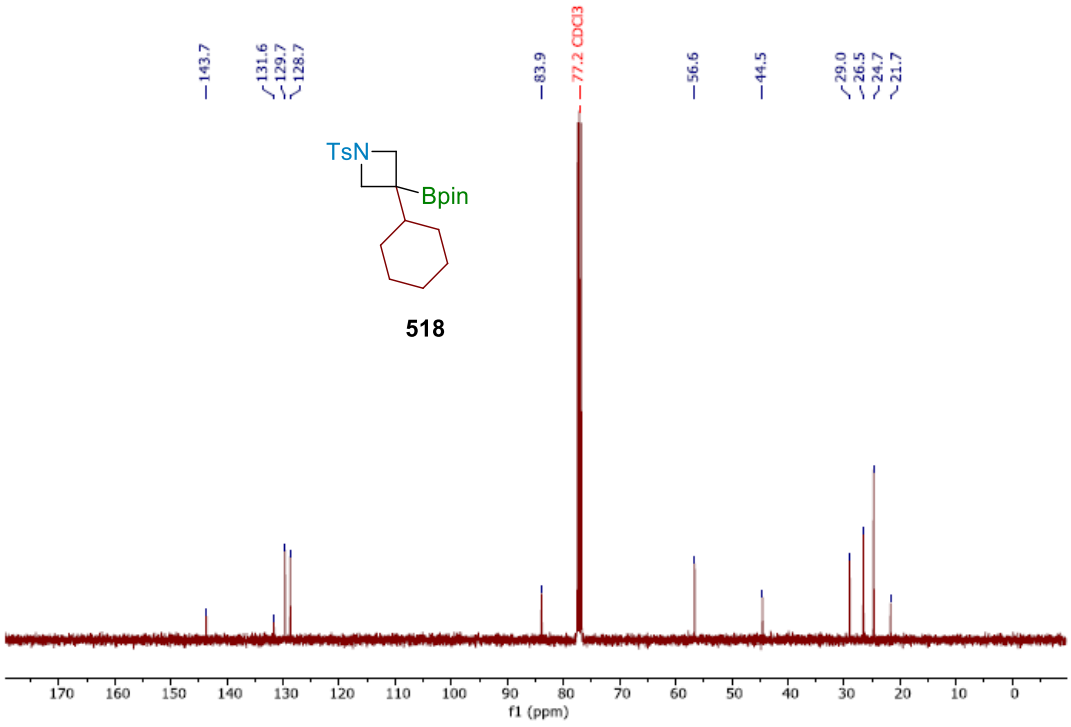


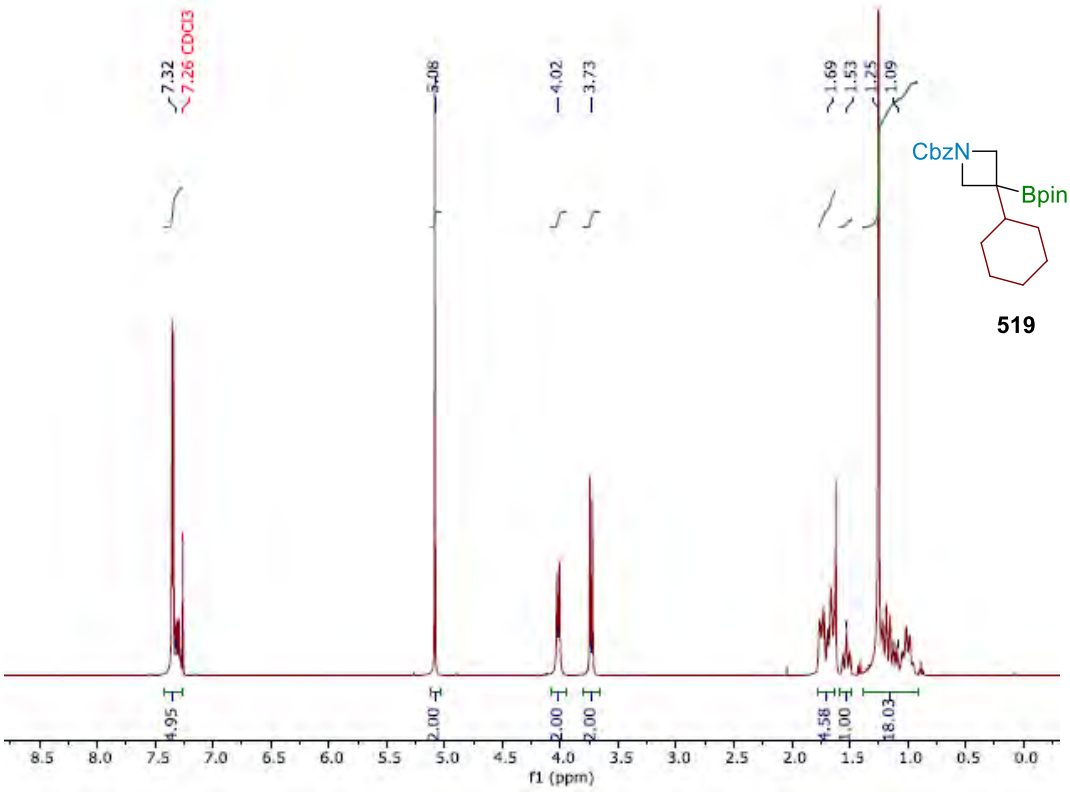


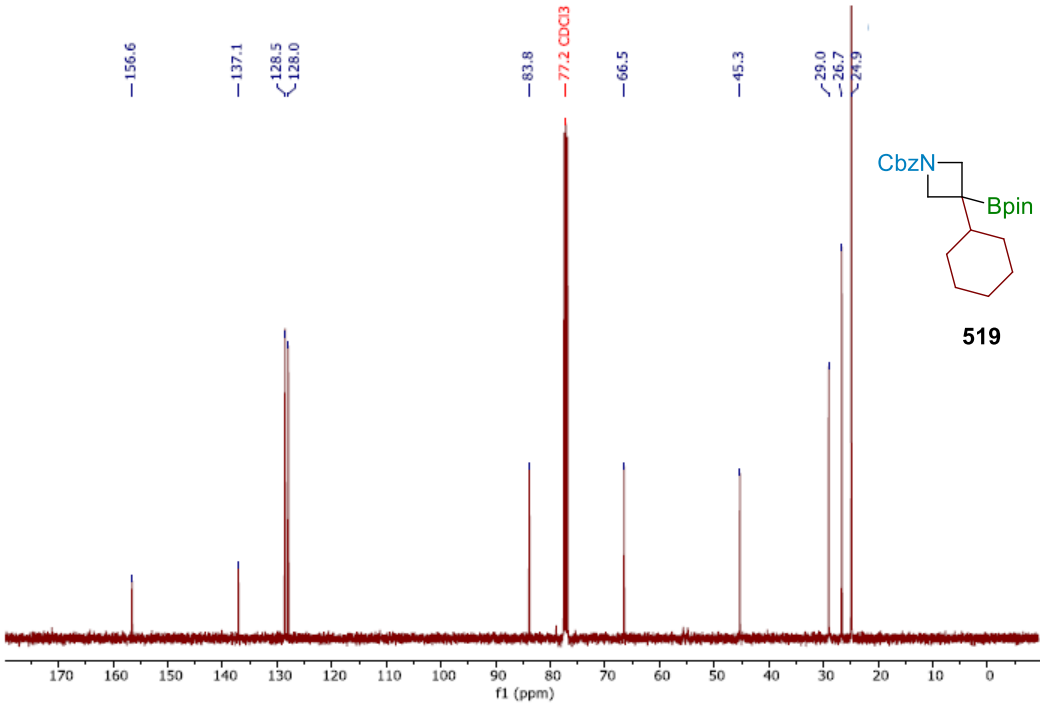
3-Cyclohexyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosylazetidine



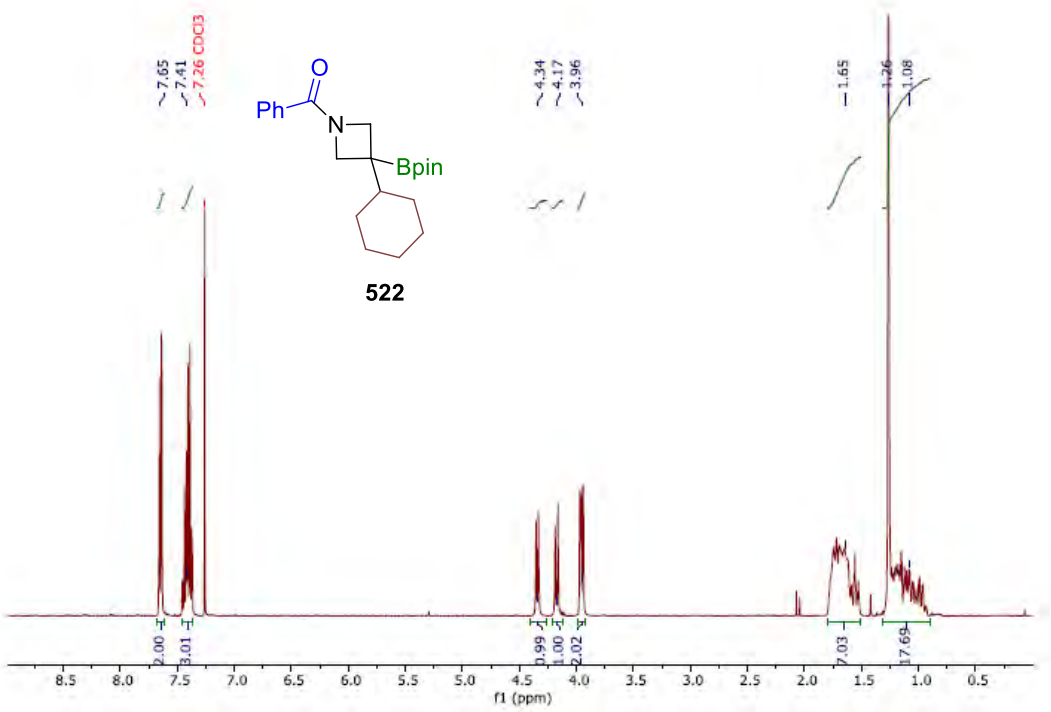


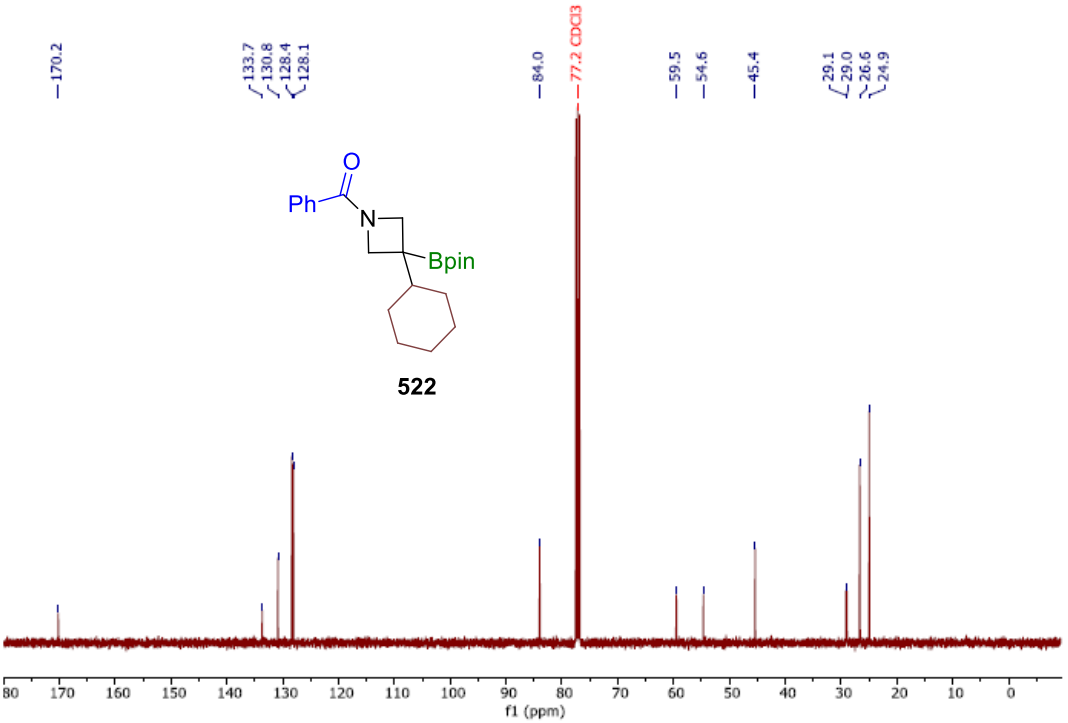
Benzyl 3-cyclohexyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidine-1-carboxylate



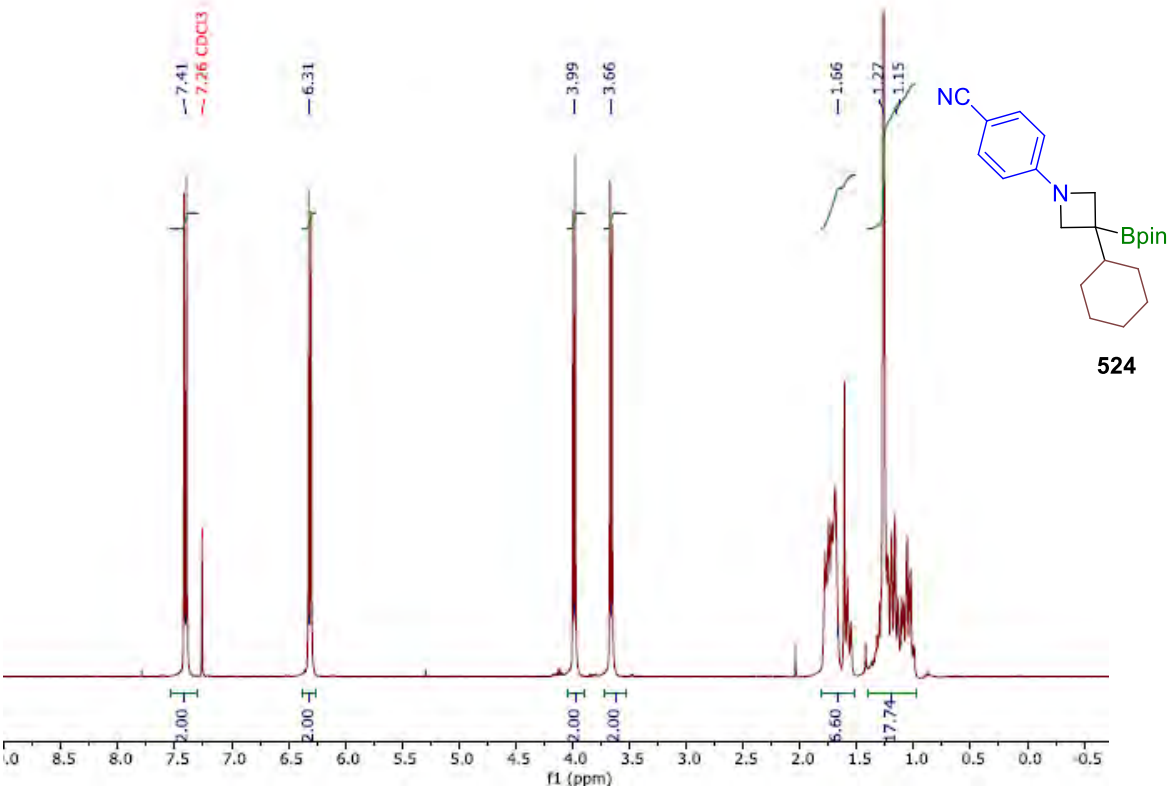


(3-Cyclohexyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidin-1-yl)(phenyl) methanone





4-(3-Cyclohexyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidin-1-yl) benzonitrile



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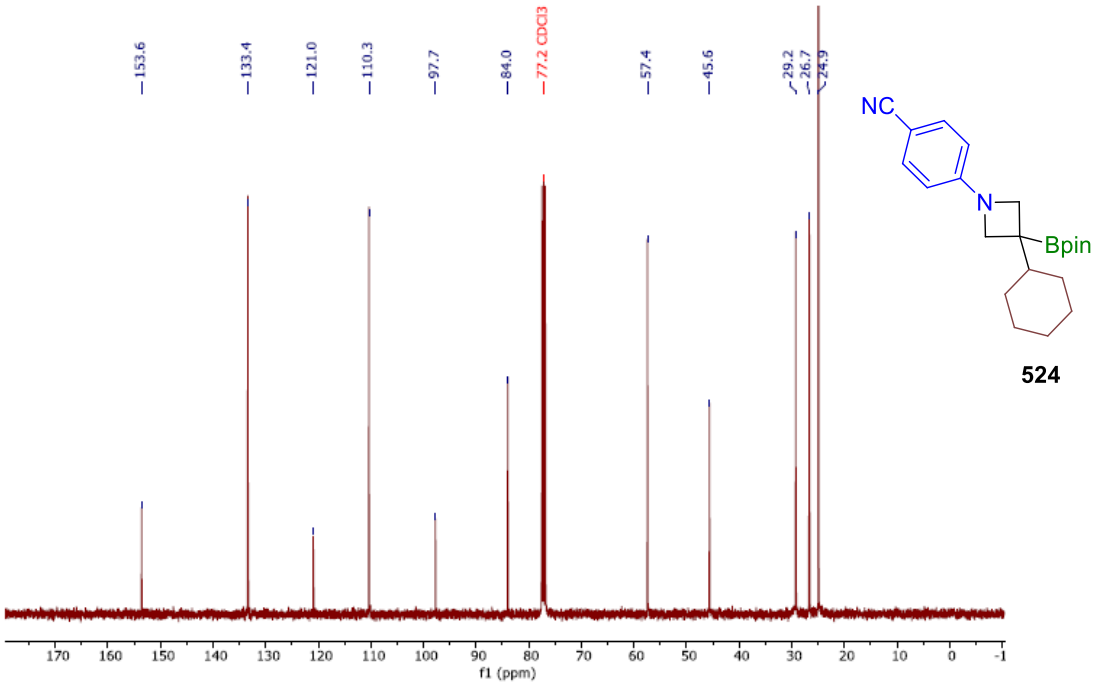

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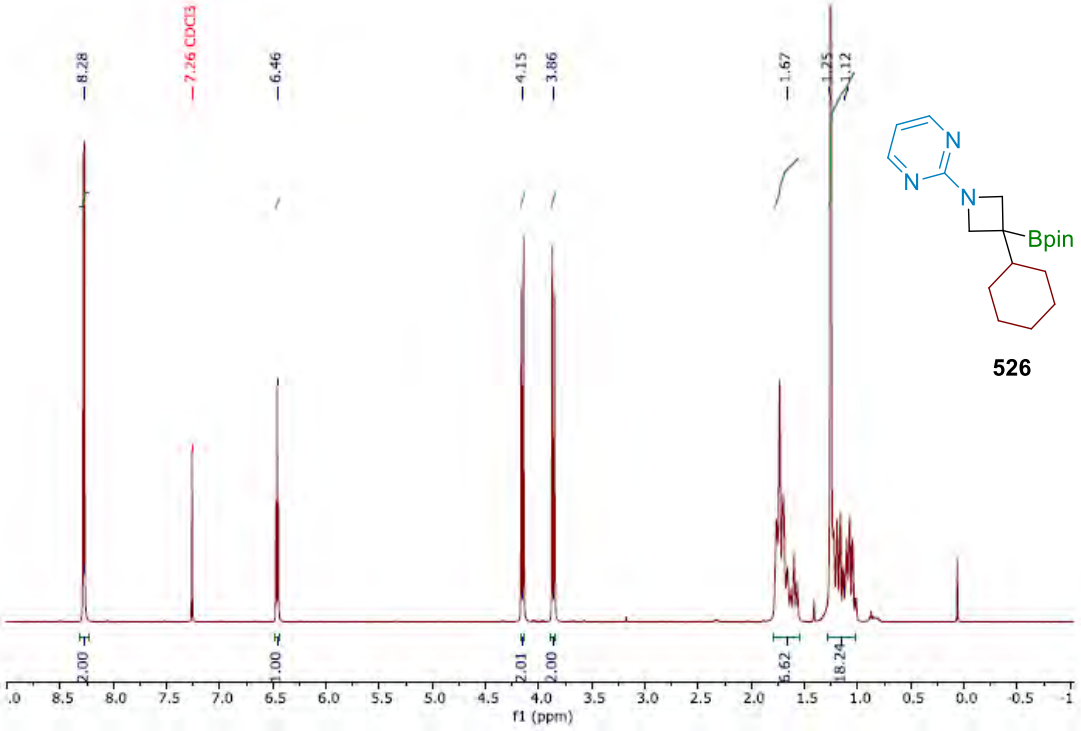
2-(3-Cyclohexyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidin-1-yl)pyrimidine



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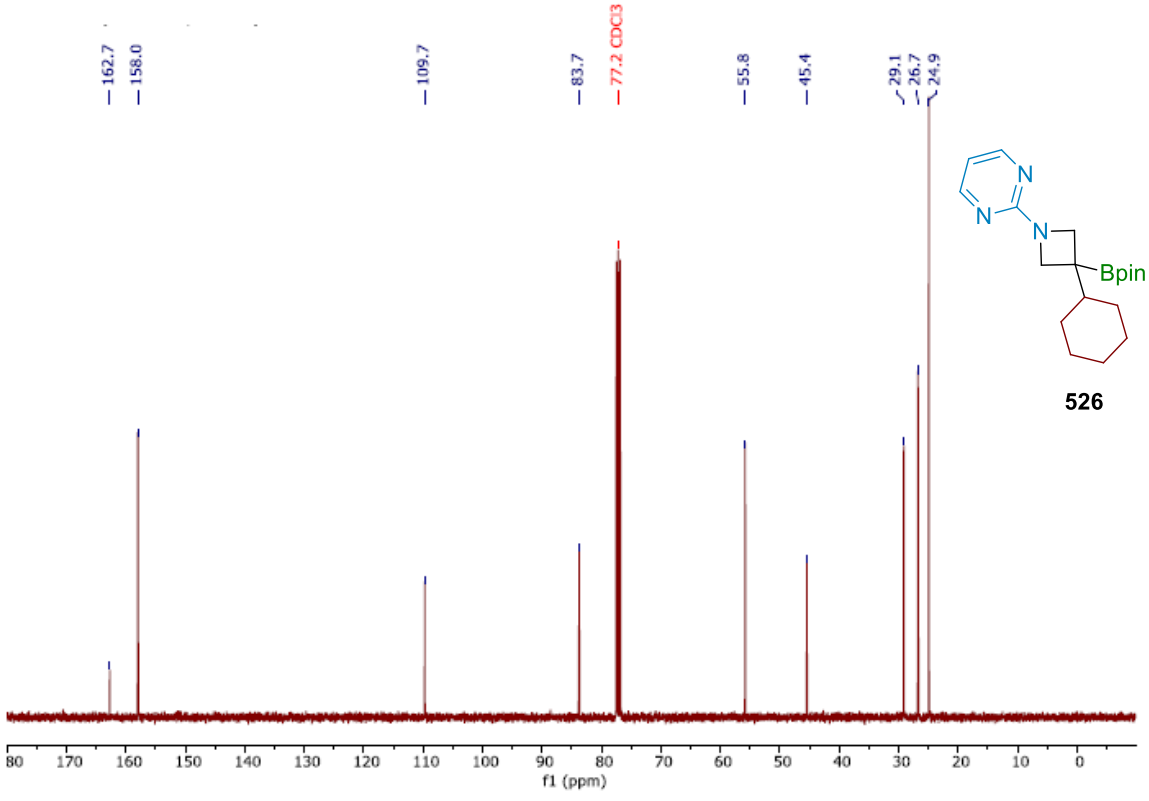

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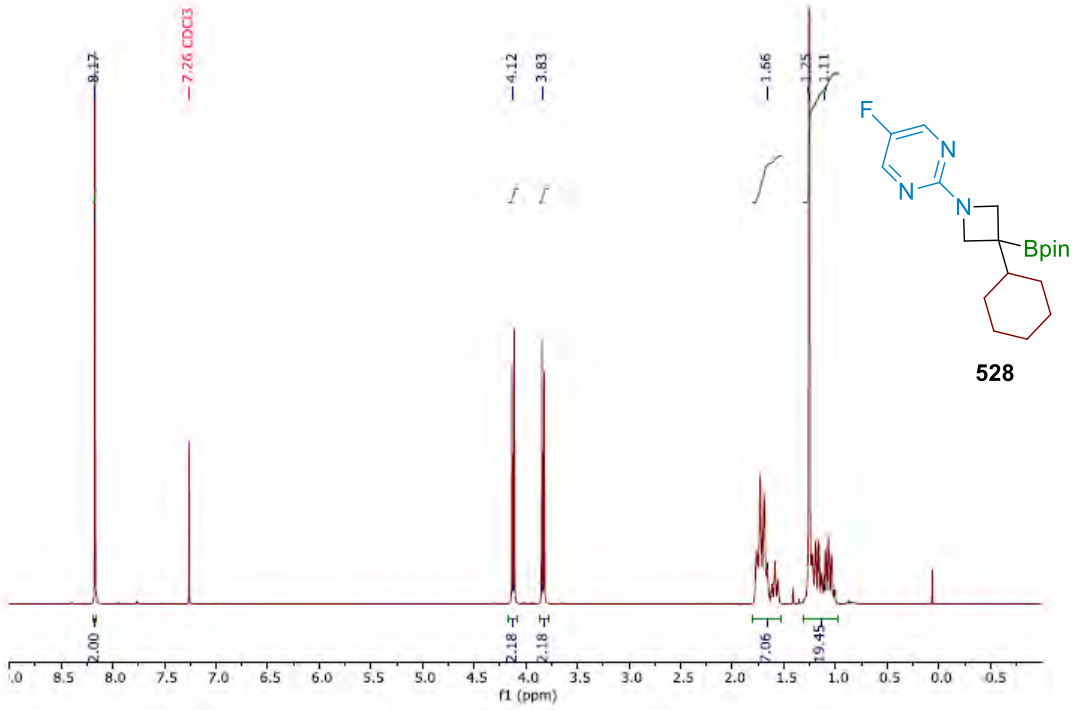
2-(3-Cyclohexyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidin-1-yl)-5-fluoropyrimidine



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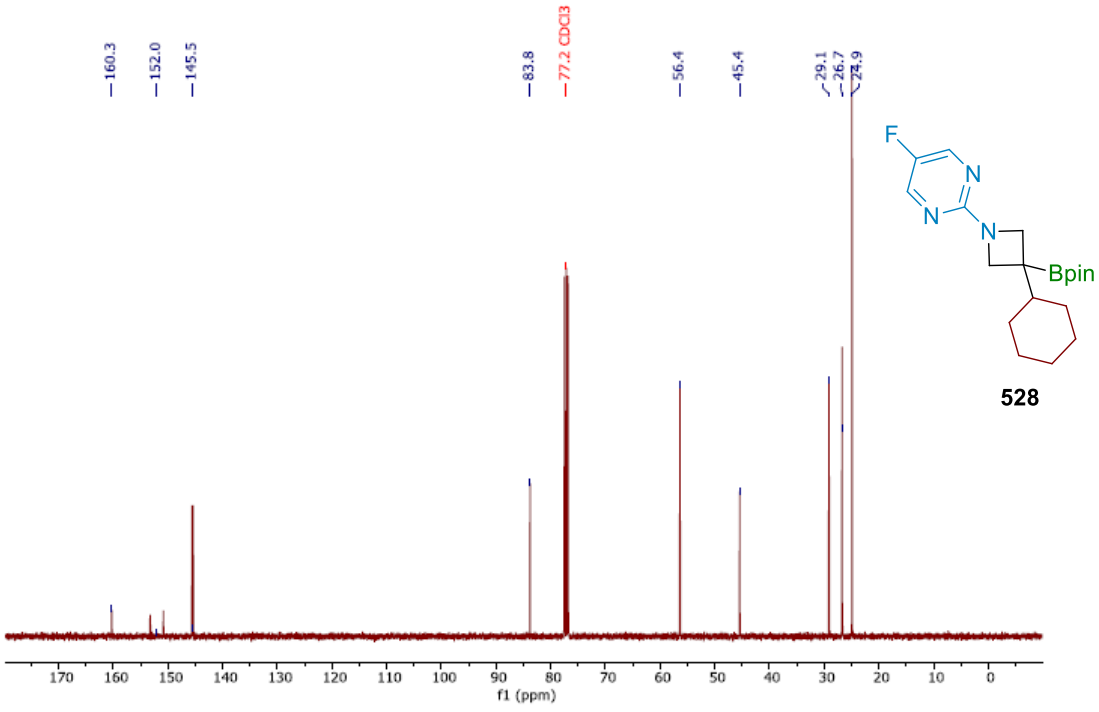

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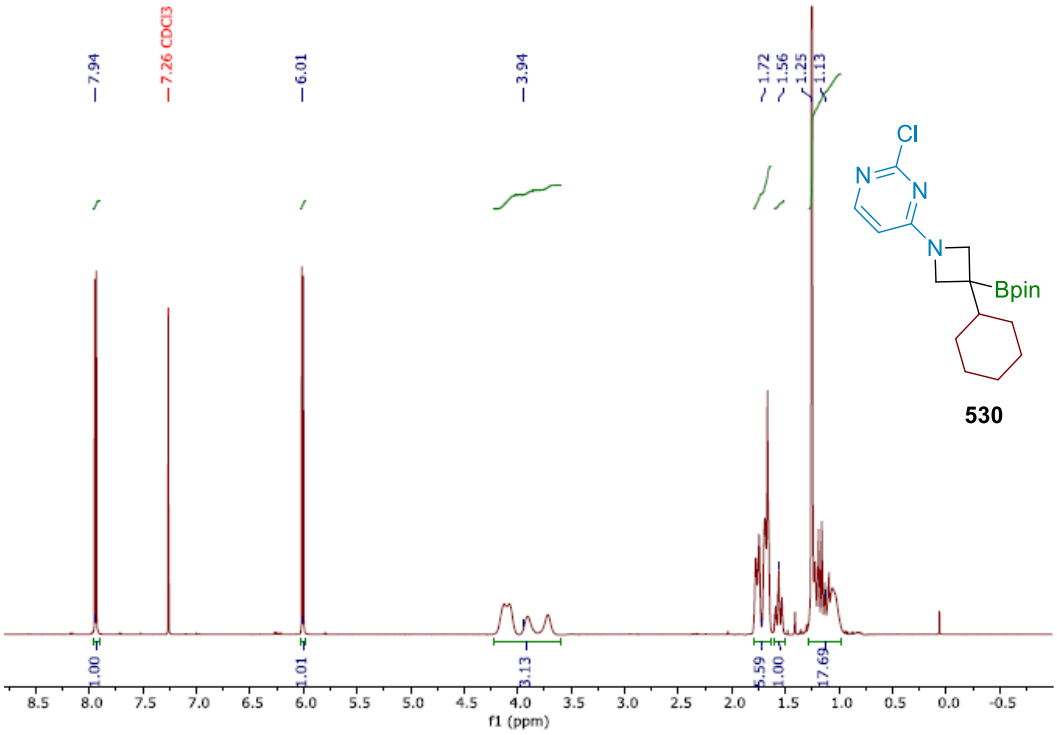
2-Chloro-4-(3-cyclohexyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidin-1-yl)pyrimidine



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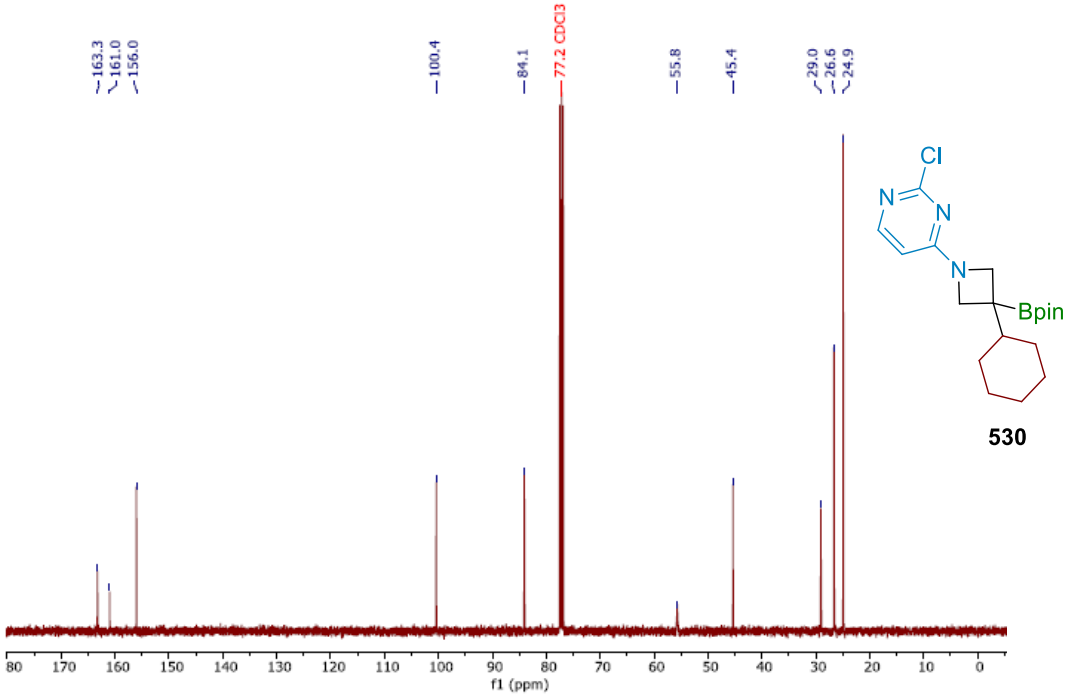

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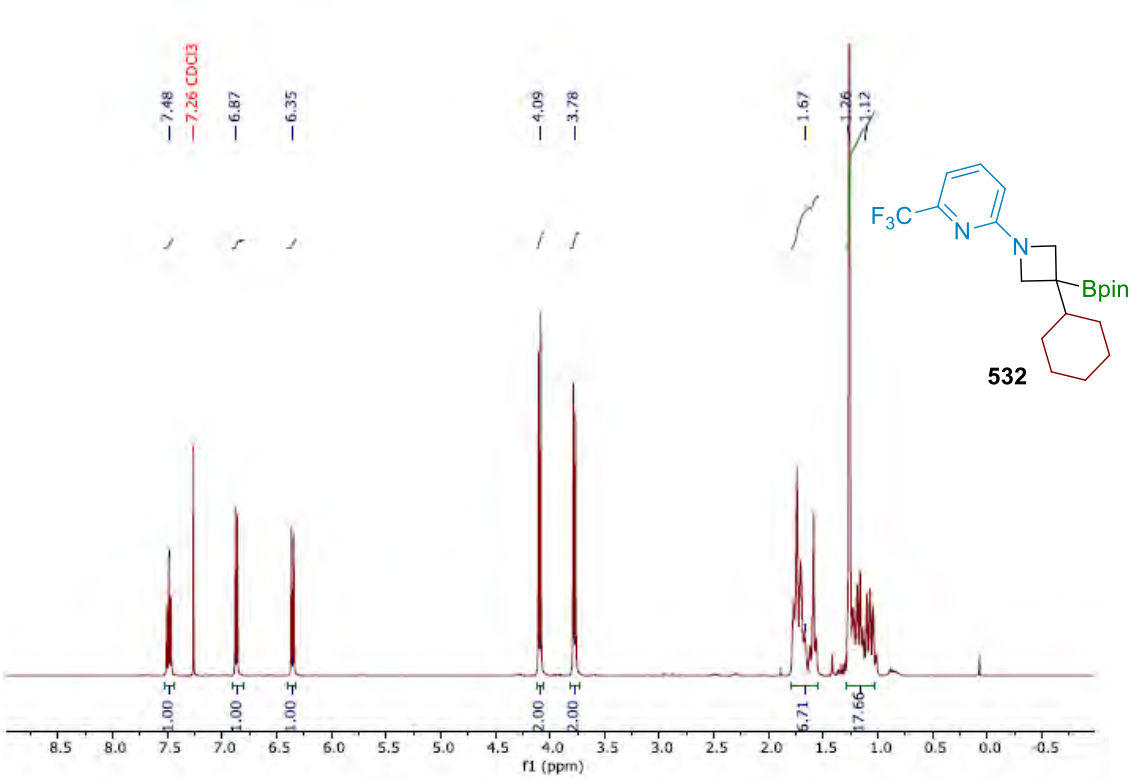
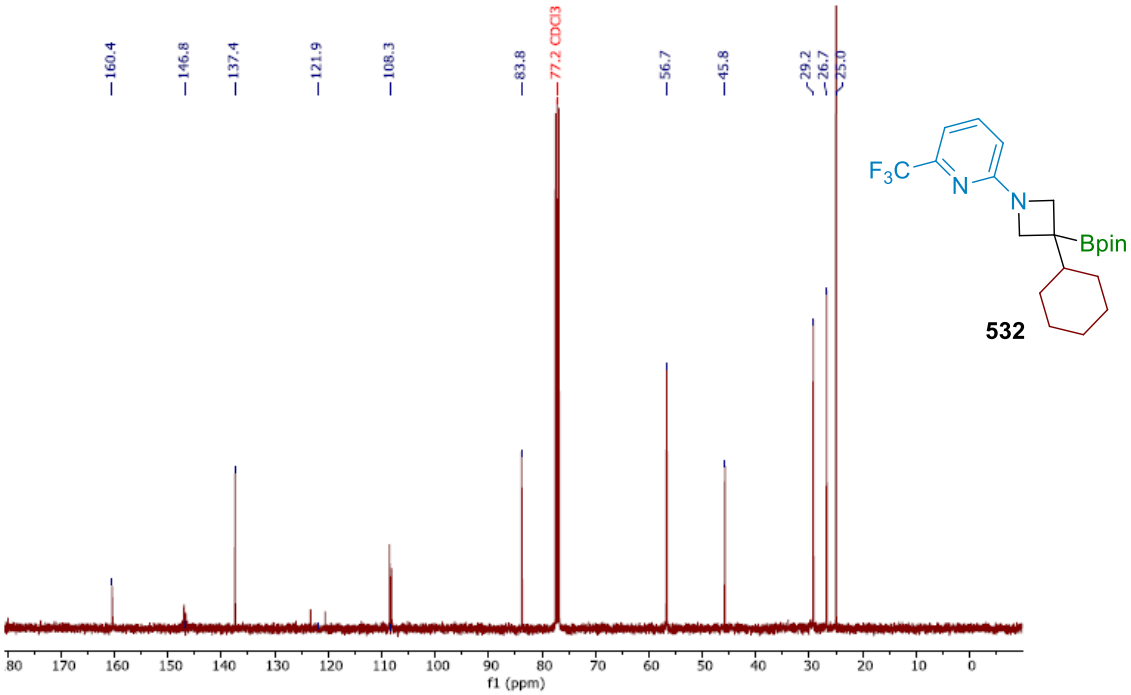
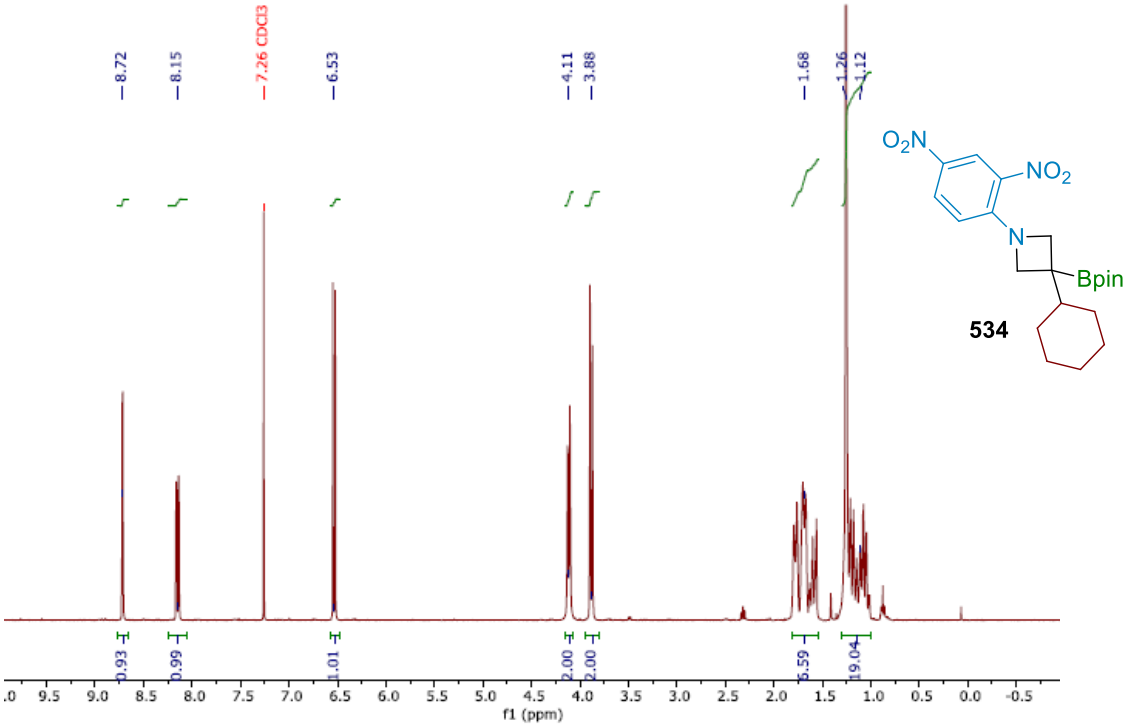
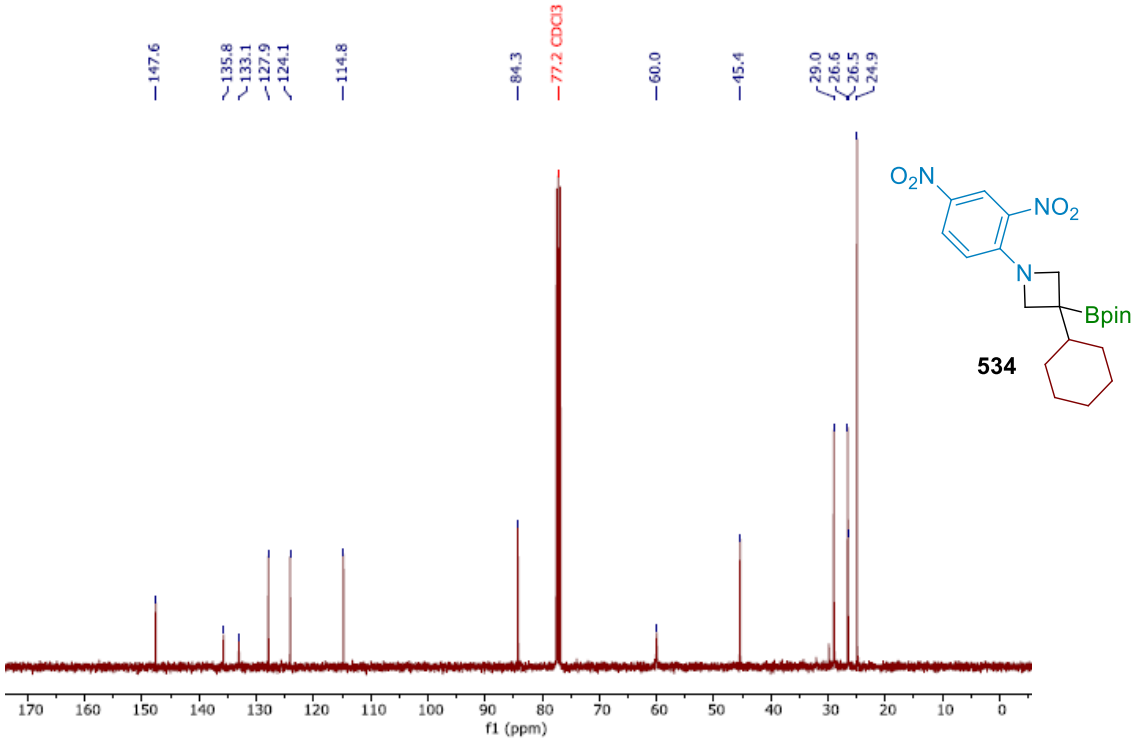
2-(3-Cyclohexyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidin-1-yl)-6-(trifluoromethyl)pyridine



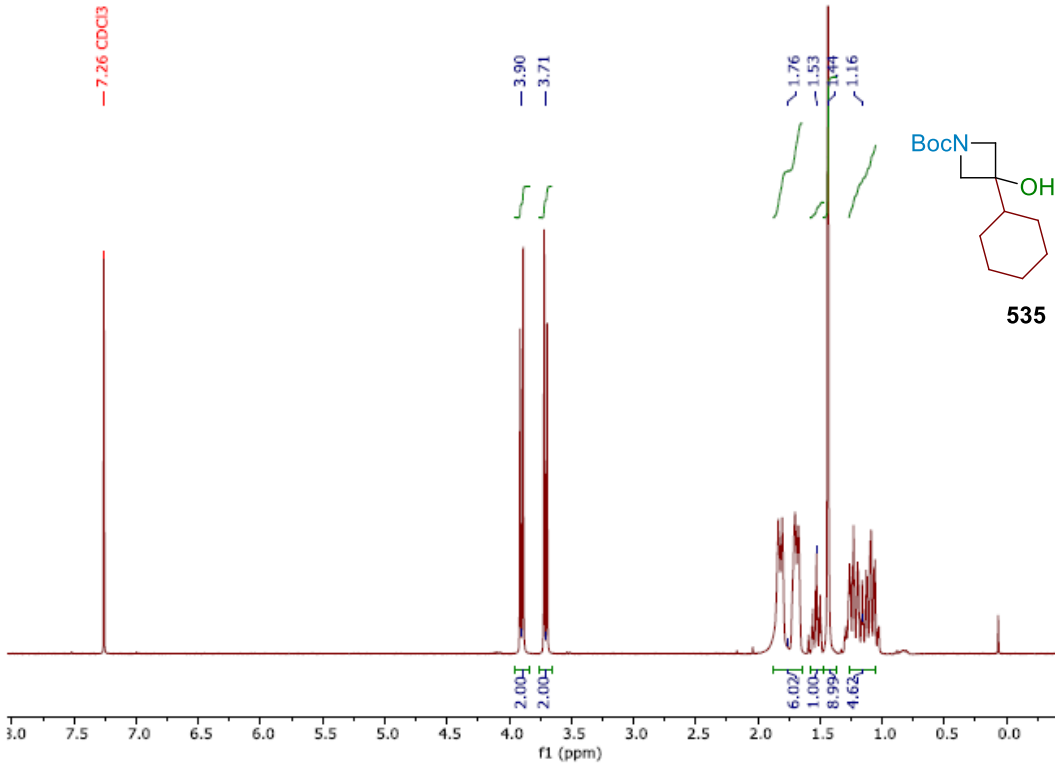


3-Cyclohexyl-1-(2,4-dinitrophenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidine





***tert*-Butyl 3-cyclohexyl-3-hydroxyazetidine-1-carboxylate**



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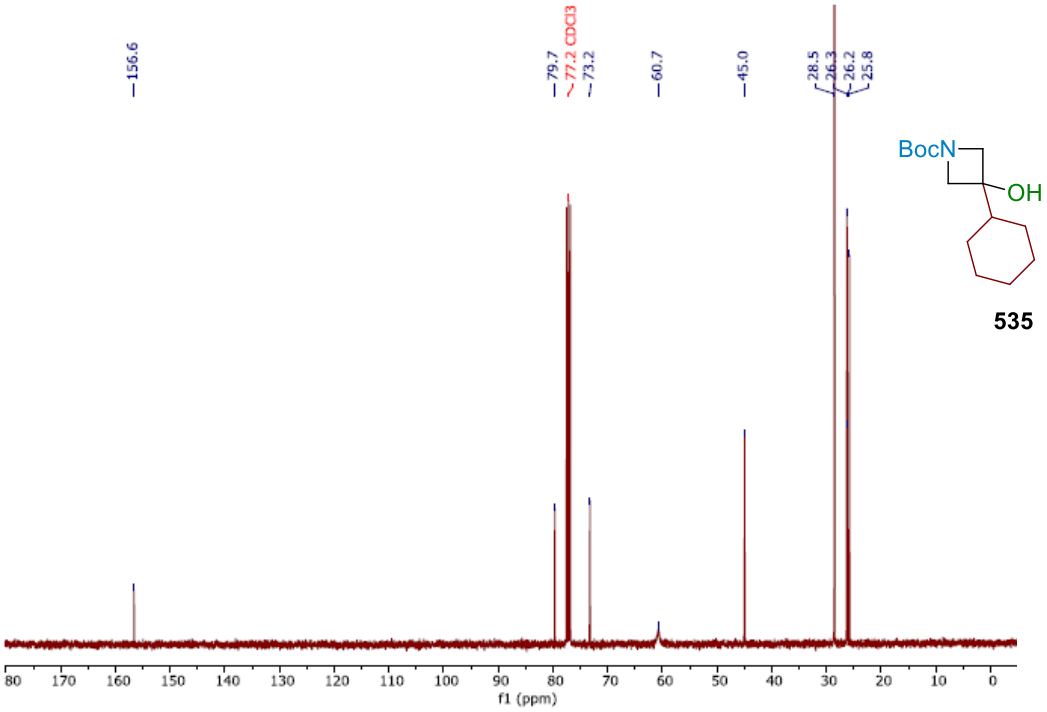

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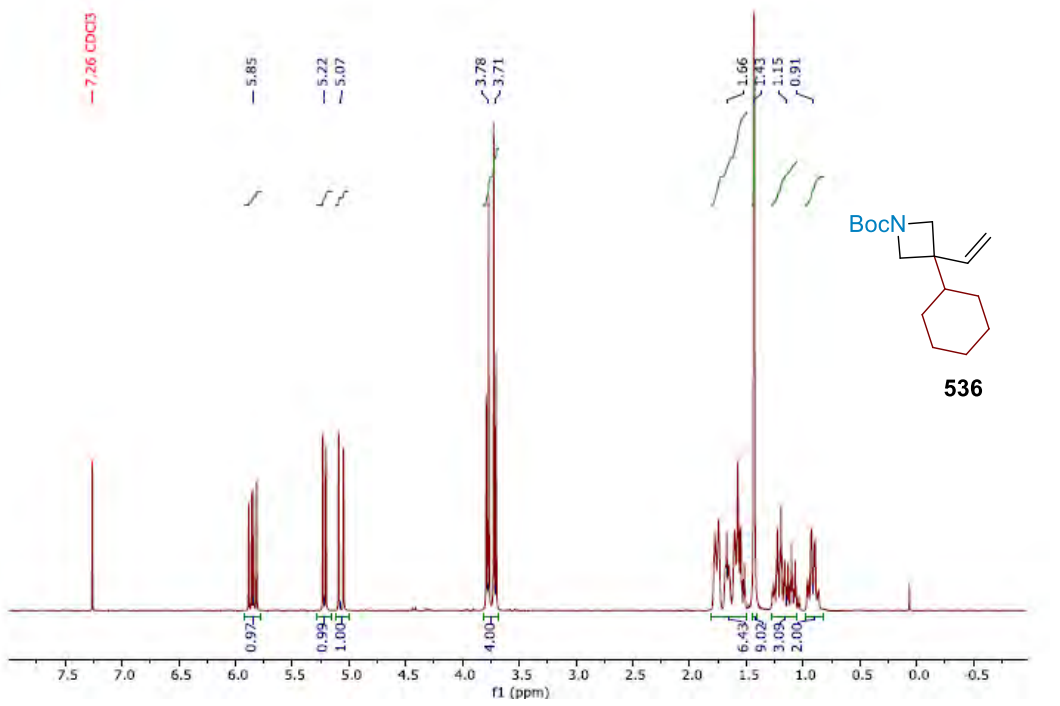
***tert*-Butyl 3-cyclohexyl-3-vinylazetidine-1-carboxylate**



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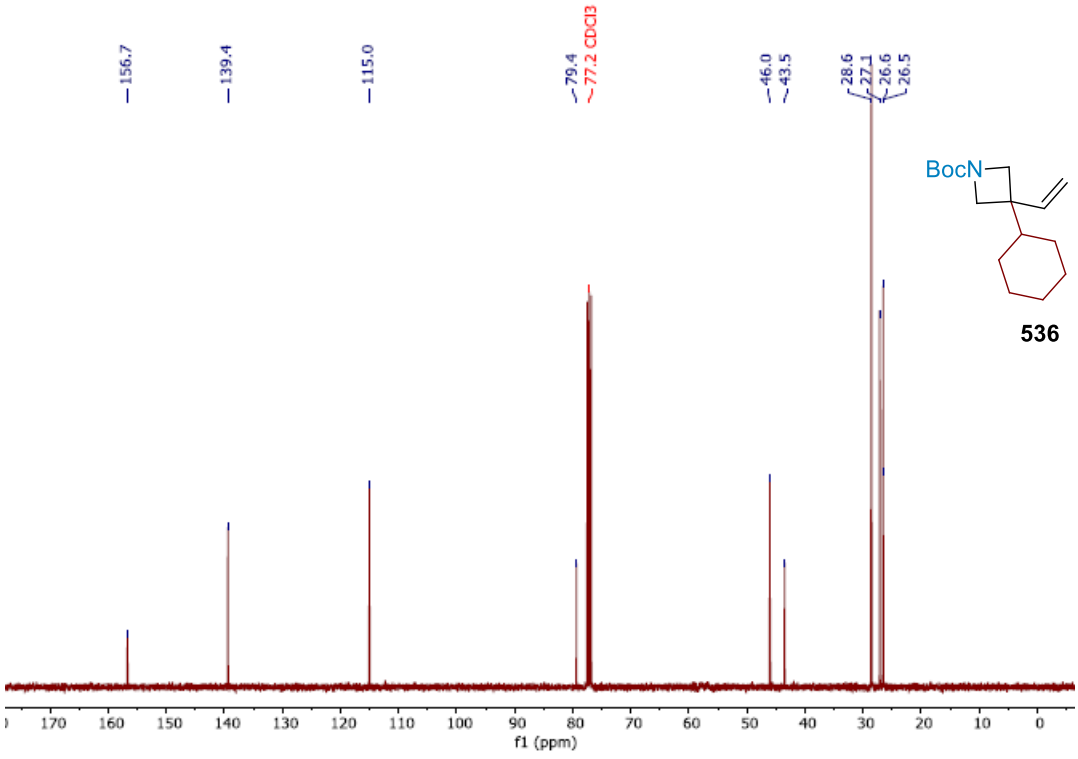
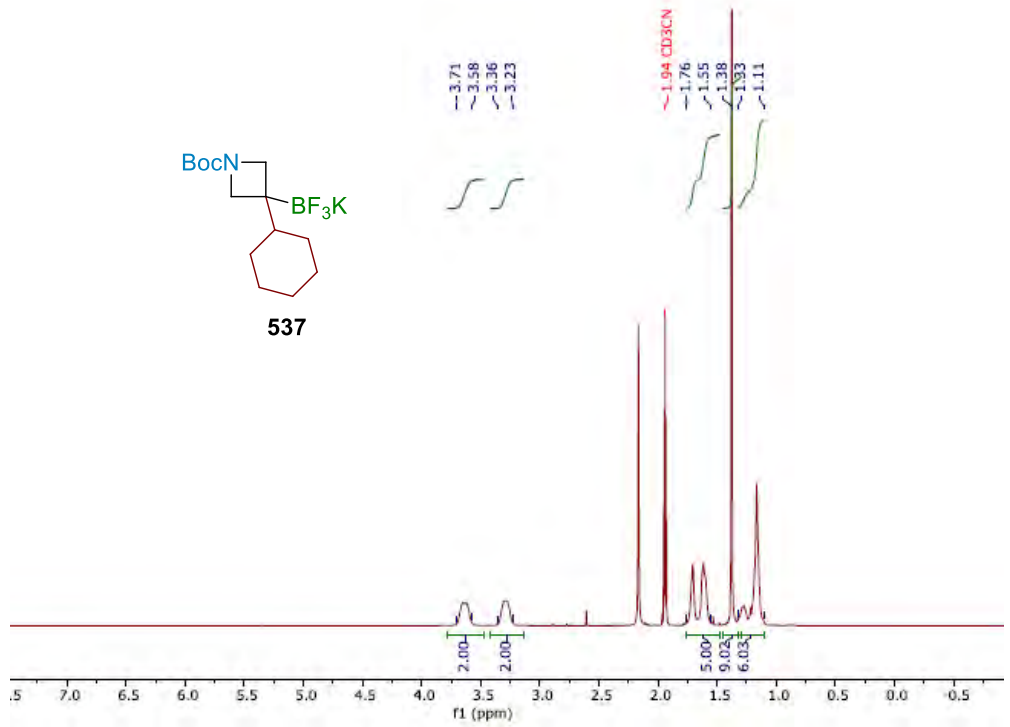
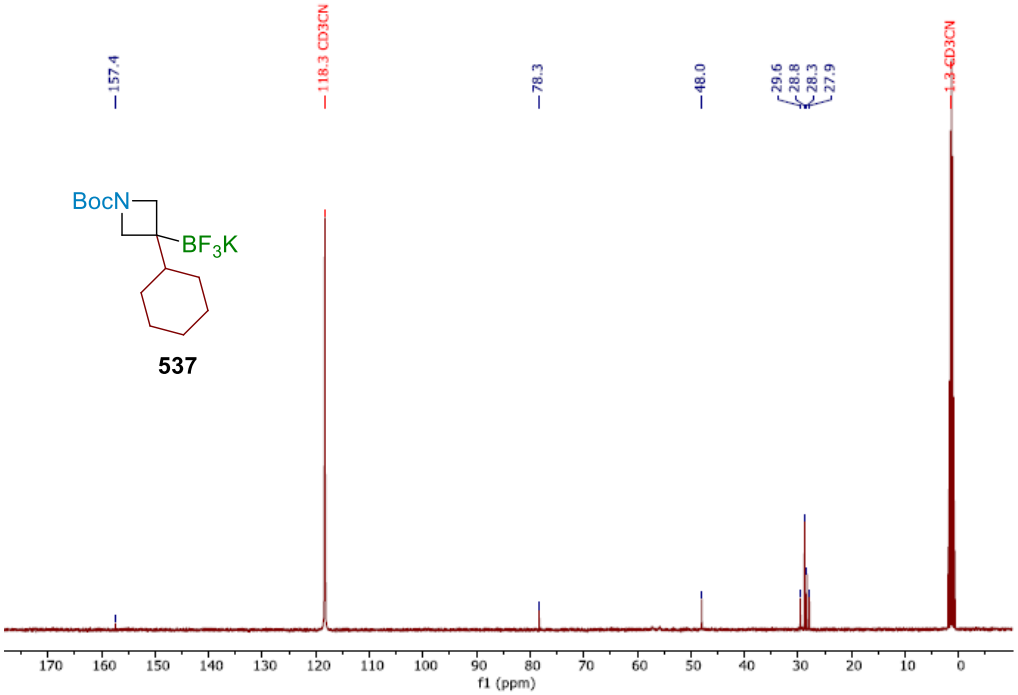


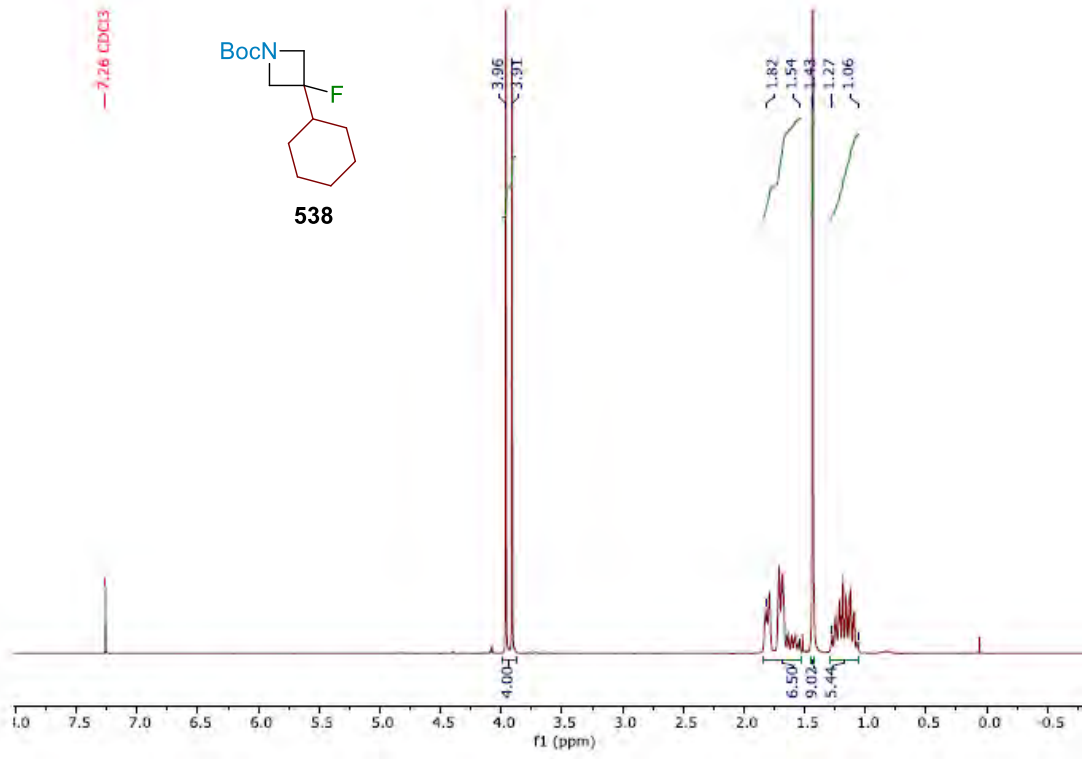
536

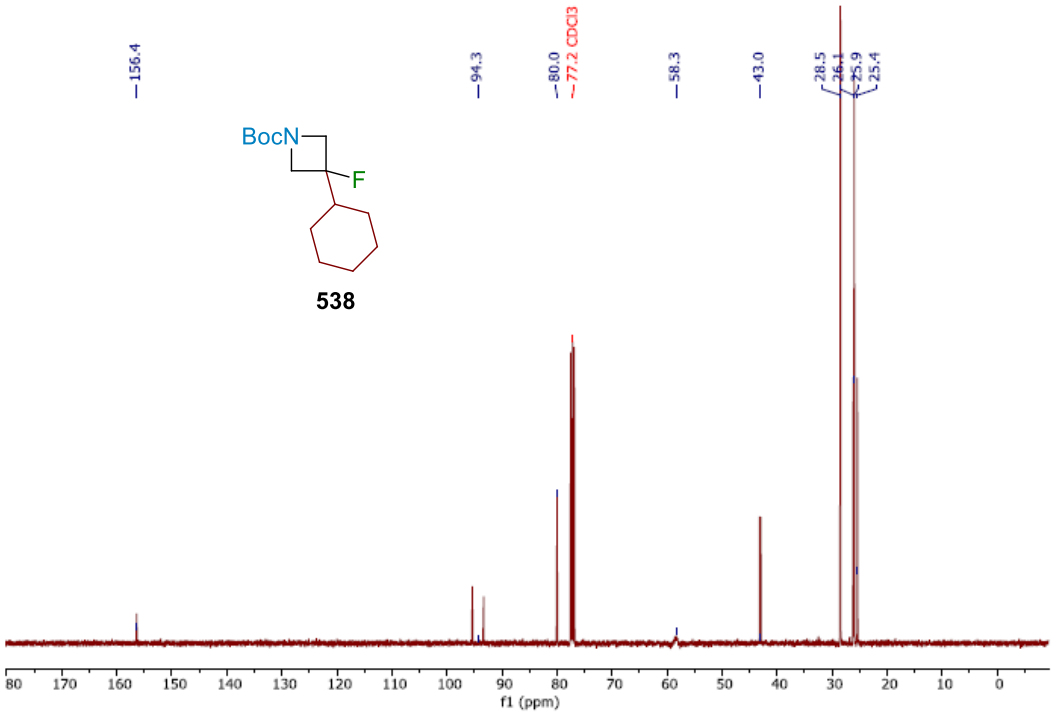
Potassium (1-(*tert*-butoxycarbonyl)-3-cyclohexylazetidin-3-yl)trifluoroborate





***tert*-Butyl 3-cyclohexyl-3-fluoroazetidine-1-carboxylate**





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