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Exploration of Carbon-oxygen and Carbon-nitrogen Bond Formation Utilizing Trichloroacetimidates and Investigations of New Reactions Mediated By Oxoammonium Salts

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Abstract:

Mono-O-alkylated 1,1′-bi-2-naphthols (BINOLs) are often used as the source of chirality for catalysts or ligand systems that are employed in asymmetric organic transformations. However, these BINOLs can be hard to synthesize. The *O*-alkylation of BINOL can be accomplished with primary and secondary alkyl halides or under Mitsunobu conditions, the yields of these alkylations with tertiary halides or alcohols are very low. A new protocol was developed utilizing trichloroacetamide electrophiles to install bulky groups onto one of the phenolic oxygens.

Trichloroacetimidates are also shown to be useful reactions for the synthesis of esters. These reagents proceeded through a symbiotic activation pathway. Under these conditions sensitive substrates did not decompose, which often is observed with other conditions using Lewis or Brønsted acids. These reactions have been broadened to benzyl esters without electron donating groups on the benzylic ring. The trichloroacetimidates therefore provide inexpensive and convenient methods that should find use in the formation of esters in complex substrates.

Benzylic amines are important structural features in pharmaceuticals, food additives, and insecticides. Many methods to synthesize benzylic amines have been developed but many of these protocols generate significant waste by-products. Additionally, the benzylic amines are often protected as amides or carbamates in a second step, which requires further resources and produces more waste. Alternatively, the rearrangement of benzylic trichloroacetimidates to acetamides may provide direct access to protected benzylic amine containing systems in a single step. The activity of palladium catalysts in the rearrangement of benzylic trichloroacetimidates to acetamides was explored. Using tris(dibenzylideneacetone)dipalladium(0) gave promising results. The exploration of chiral ligands to access enantioenriched products from this reaction has been investigated.

N-Alkylated pyrazoles and benzotriazoles are present in a number of natural products and pharmaceuticals. However, methods of synthesizing pyrazoles and benzotriazoles generally use hydrazine derivatives and limited regioselectivity. *N*-Alkylated pyrazole utilizing trichloroacetimidate electrophiles under Bronsted acid catalyzed conditions has been developed. Both primary and secondary imidates provided good yields. Benzylic primary imidates provided significantly better yields than phthalimidomethyl imidate. Structurally different pyrazoles were also studied in this transformation. Changing the halogen was tolerated, however, iodine provided the lowest yield. When adding methyl groups at the 3 and 5 position on the pyrazole, product was isolated in moderate yield. Interestingly, when using benzotriazole, a single product was isolated in good yield. This was the dearomatized alkylated product. Further substrate scope investigations and mechanism studies need to be performed to better understand these results.

Oxoammonium salts are commonly used to oxidize alcohols to aldehydes or ketones, but these reagents may also be used in a number of other oxidative transformations which are useful in organic chemistry. Taking advantage of these reagents, a new tandem elimination-oxidation process of tertiary alcohols has been discovered, synthesizing a protected allylic alcohol. Data suggests that the transformation first proceeds through elimination of the alcohol mediated by the oxoammonium salt. Then the allylic oxidation proceeds through an ene type mechanism. Additionally, the tetramethylpiperidine derived from the oxoammonium salt also serves as a protecting group for the newly generated allylic alcohol, resulting in a process with high atom economy. The optimization and scope of the reaction has been investigated.

N-Oxoammonium salts are also shown to be useful reagents for the metal free 1,2-difunctionalizations of alkenes with heteroatom nucleophiles. While many transformations for the 1,2-addition of heteroatoms to alkenes have been developed, most are dependent on transition

metals. Rarer are alkene difunctionalizations that utilize nonmetallic reagents, with most of these reactions relying on photochemical or radical conditions. Investigating these *N*-oxoammonium salt mediated additions provides a new method for the elaboration of alkenes into molecules with significantly greater complexity. The determination of the stereochemistry of the products of an amino-oxidation with *N*-oxoammonium salts was also accomplished. Attempts to improve the diastereoselectivity of this process were explored. Investigations have also been initiated to perform these alkene difunctionalizations in an enantioselective manner utilizing anionic phase transfer catalysis. Expansion of the *N*-oxoammonium salt mediated additions of alkenes with primary alcohols, water, and isatin was also initiated.

Exploration of Carbon-Oxygen and Carbon-Nitrogen Bond Formation Utilizing Trichloroacetimidates

and

Investigations of New Reactions Mediated by Oxoammonium Salts

By

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Thank you to my dad, Roy Meador, for supporting me through all my years of school.

Cheers to (finally) finishing my PhD!

"Success is stumbling from failure to failure with no loss of enthusiasm." – Winston Churchill

"If it doesn't challenge you, it won't change you." – Fred DeVito

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List of Abbreviations/Symbols

[α]	specific rotation
Å	angstrom(s)
Ac	acetyl
ACT	4-acetamido-2,2,6,6-tetramethylpiperidinyl
acac	acetylacetonate
AIBN	2,2-azobisisobutyronitrile
Anal.	combustion elemental analysis
anhyd	anhydrous
AO	atomic orbital
aq	aqueous
Ar	aryl
atm	atmosphere(s)
av	average
AZADO	2-azaadamantande N-oxyl
BINOL	1,1-bi-2-naphthol
Bn	benzyl
Boc	*tert*-butoxycarbonyl
bp	boiling point
bpy	2,2,2-bipyridyl
br	broad (spectral)
Bu	butyl
s-Bu	*sec*-butyl
t-Bu	*tert*-butyl
Bz	benzoyl
°C	degrees Celsius
calcd	calculated
CAN	ceric ammonium nitrate
cat	catalytic
Cbz	benzyloxycarbonyl
CIF	Crystallographic Information Framework
cm	centimeter(s)
cm^{-1}	wavenumber(s)
compd	compound
concd	concentrated
concn	concentration
COSY	correlation spectroscopy
Cp	cyclopentadienyl
m-CPBA	*meta*-chloroperoxybenzoic acid
Cy	cyclohexyl
δ	chemical shift in parts per million
DABCO	1,4-diazabicyclo[2.2.2]octane
	dansyl 5-(dimethylamino)-1-naphthalenesulfonyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene

DCC	*N*,*N*–2-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DEPT	distortionless enhancement by polarization transfer
DIBALH	diisobutylaluminum hydride
DMA	dimethylacetamide
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMDO	dimethyldioxirane
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
dr	diastereomer ratio
E1	unimolecular elimination
E2	bimolecular elimination
EA	ethyl acetate
ED50	dose effective in 50% of test subjects
EDTA	ethylenediaminetetraacetic acid
EI	electron impact
eq	equation
equiv	equivalent
er	enantiomer ratio
ESI	electrospray ionization
Et	ethyl
Fmoc	9-fluorenylmethoxycarbonyl
FT	Fourier transform
g	gram(s)
GC	gas chromatography
h	hour(s)
HMBC	heteronuclear multiple bond correlation
HMPA	hexamethylphosphoric triamide
HMQC	heteronuclear multiple quantum correlation
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
HSQC	heteronuclear single quantum correlation
Hz	hertz
IR	infrared
k	kilo
K	kelvin(s)
L	liter(s)
LAH	lithium aluminum hydride
LD50	dose that is lethal in 50% of test subjects
LDA	lithium diisopropylamide

LHMDS	lithium hexamethyldisilazane
lit.	literature value
LUMO	lowest unoccupied molecular orbital
μ	micro
m	multiplet (spectral); milli
M	molar (moles per liter)
M+	parent molecular ion
Me	methyl
MHz	megahertz
min	minute(s)
mM	millimolar (millimoles per liter)
MO	molecular orbital
mol	mole(s)
MOM	methoxymethyl
mp	melting point
Ms	methylsulfonyl (mesyl)
MS	mass spectrometry
MTBE	methyl *tert*-butyl ether
MW	molecular weight
m/*z*	mass-to-charge ratio
N	normal (equivalents per liter)
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
nm	nanometer(s)
NMO	*N*-methylmorpholine-*N*-oxide
NMP	*N*-methylpyrrolidone
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Nu	nucleophile
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PE	petroleum ether
Ph	phenyl
piv	pivaloyl
PMB	*p*-methoxybenzyl
PPA	poly(phosphoric acid)
ppm	part(s) per million
Pr	propyl
*i*Pr	isopropyl
PTC	phase-transfer catalysis
py	pyridine
q	quartet (spectral)
RCM	ring-closure metathesis
redox	reduction–oxidation

rel	relative
Rf	retention factor (in chromatography)
ROESY	rotating frame Overhauser effect spectroscopy
ROMP	ring-opening metathesis polymerization
rt	room temperature
s	singlet (spectral); second(s)
SET	single electron transfer
S_N1	unimolecular nucleophilic substitution
S_N2	bimolecular nucleophilic substitution
t	triplet (spectral)
TBS	*tert*-butyldimethylsilyl
TBHP	*tert*-butyl hydroperoxide
temp	temperature
TEMPO	2,2,6,6-tetramethylpiperidin-1-oxyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMS	trimethylsilyl; tetramethylsilane
TON	turnover number
*t*R	retention time (in chromatography)
Ts	*para*-toluenesulfonyl (tosyl)
TS	transition state
UV	ultraviolet
vis	visible
vol	volume
v/v	volume per unit volume
wt	weight
w/w	weight per unit weight

Chapter 1 – Trichloroacetimidates: A Versatile Tool in Organic Synthesis

Abstract:

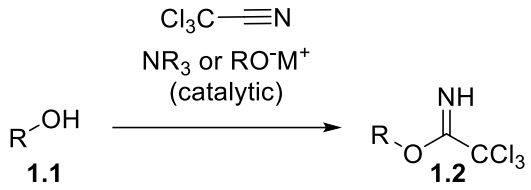
Trichloroacetimidates are often used as electrophiles when activated by a catalytic amount of a Brønsted or Lewis acid. Theses mild conditions allow for their application in multistep synthesis of complex polyfunctional molecules. Schmidt utilized this reagent in glycosidic bond formation in carbohydrate chemistry. Trichloroacetimidates have also been used as protecting groups for alcohols and carboxylic acids. Expanding on that chemistry, trichloroacetimidates were employed to synthesize substituted anilines and sulfonamides. Additionally, theses reagents have been used in Friedel-Crafts reactions forming new C-C bonds. Overman's rearrangement of allylic trichloroacetimidates to trichloroacetamides under thermal, acid, or transition metal catalyzed have been explored to a great extent, since this rearrangement provides easy access to protect amines. The use of chiral catalysts renders enantioselective conditions. This chapter provides an overview of the most common applications of trichloroacetimidates and summarizes recent developments.

Introduction:

Trichloroacetimidates, generally referred to as imidates, are a type of functional group that are characterized by an imine with a trichloromethyl and ether as R groups at the imine carbon (**1.2**, Scheme 1.1). These functional groups are typically synthesized with inexpensive trichloroacetonitrile, readily available alcohols, and a base. Steinkopf and Malinowski first reported synthesis of trichloroacetimidates utilizing trichloroacetonitrile, an alcohol, and an alkoxide as base (Scheme 1.1).[1, 2] Later, Cramer expanded the use of this functional group using benzylic trichloroacetimidates.[3] Cramer synthesized the benzylic imidates with catalytic amounts of metal hydride used as the base.[4] However, Bernet found the use of a milder bases, such as DBU,

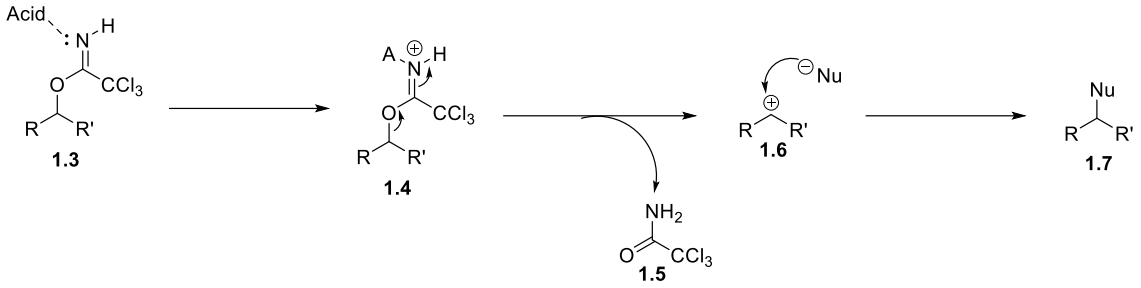
could be used instead of metal alkoxide and hydrides.[5] Unfortunately the preparation of tertiary imidates from less reactive tertiary alcohols still requires a strong metal hydride base.[4]

Scheme 1.1. Synthesis of Trichloroacetimidates



Imidates provide a good alternative to other electrophilic sources in displacement reactions. Since trichloroacetimidates have a basic nitrogen (part of the imine), they can be activated by an acid catalyst. Once activated, either by a Lewis or Brønsted acid catalyst, the imidate can serve as an electrophile or cation precursor (Scheme 1.2). This provides mild conditions for substitution reactions. Additionally, the trichloroacetamide **1.5** that is formed as a side product, is less acidic than strong acid byproducts produced in alkyl halide substitution reactions (Scheme 1.2).[6] This reactivity is enhanced by the trichloroacetimidates in these reactions, as after the substitution the imidate isomerizes to the corresponding amide. This isomerization is thermodynamically favored by ~14 kcal/mol, due to the stronger carbon oxygen double bond.[7, 8] Trichloroacetimidates have been utilized for C-O, C-S, and C-N bond formation in reactions such as glycosidic bond formation,[9-13] formation of protecting groups of alcohols,[14-17] carboxylic acids,[15, 18-21] thiols,[6] sulfonamides,[22] and anilines,[23] and synthesis of allylic amines.[24-27] Additionally, trichloroacetimidates have been used for the formation of C-C bonds in Friedel-Crafts alkylations,[28-32] and functionalization of pyrroloindolines.[33] In the following sections, the common uses for trichloroacetimidates in organic synthesis will be highlighted.

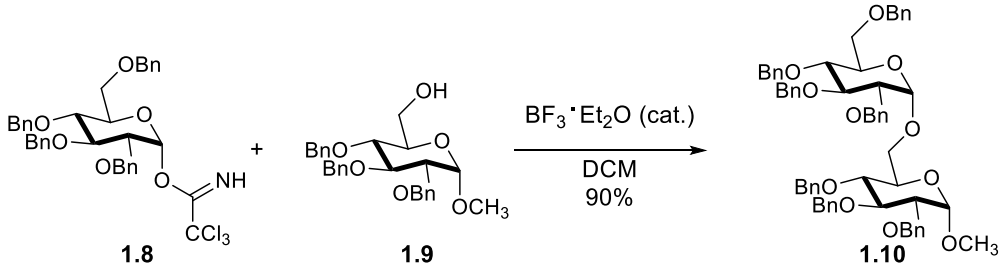
Scheme 1.2. Substitution of Trichloroacetimidate via Acid Catalyzed Activation



Glycosidic Bond formation with Trichloroacetimidates

Schmidt and co-workers in the 1980's first demonstrated the use of trichloroacetimidates as alkylating reagents for glycosidic bond formation.[11-13] Easy conversion of glucopyranose to the corresponding imidate is accomplished with base and trichloroacetonitrile addition to the anomeric hydroxyl group. The imidate can be displaced under Lewis acid catalyzed conditions with another glucopyranose to form the glycosidic bond (Scheme 1.3). Schmidt showed that both alpha and beta glycosyl imidates can be prepared from benzyl or acetyl protected glucopyranose.[12, 13]

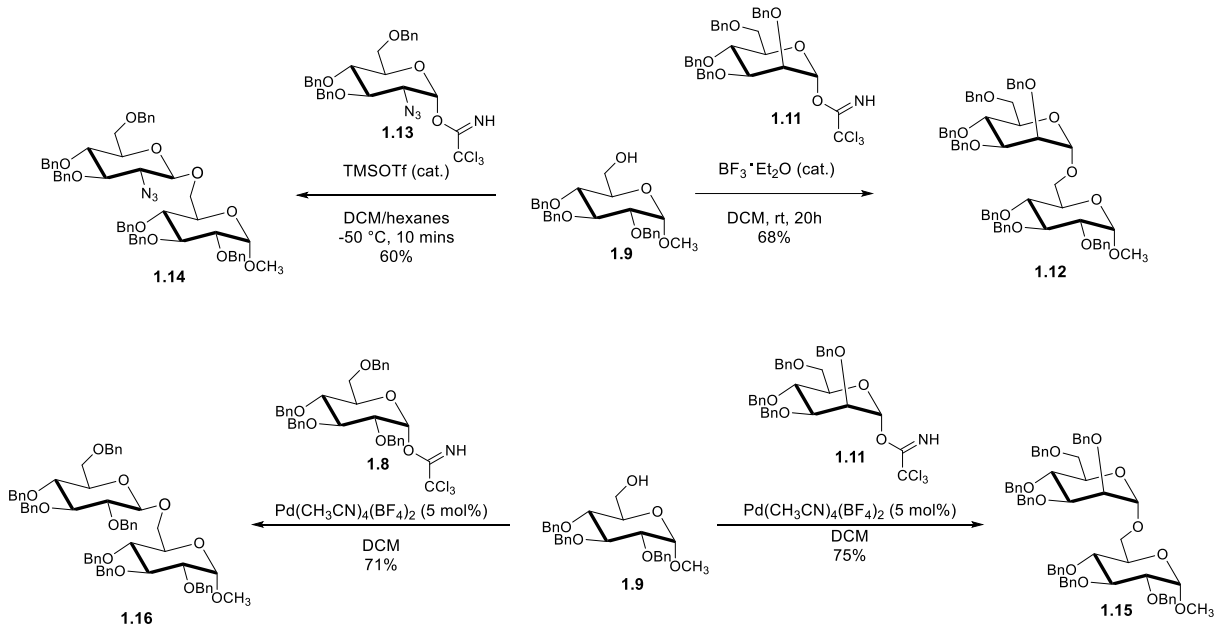
Scheme 1.3. Glycosidic Bond Formation with Trichloroacetimidates



This methodology provides advantages over other glycosidic bond formation reactions, which typically involve the displacement of halides with stoichiometric amounts of base or heavy metals.[34] The use of stoichiometric amounts of base or metals is not amenable to sensitive substrates, limiting their application. However, since trichloroacetimidates can be displaced under catalytic conditions, this methodology can be applied to more sensitive substrates. Additionally, the anomeric stereochemistry can be controlled. When the trichloroacetimidate is installed,

depending on which base is used, conditions have been established to produce either the α-anomer or the β-anomer. Strong bases, such as sodium hydride, provide the α-anomer. While weak bases, such as potassium carbonate, prove the β-anomer.[35] Since it is the displacement of the trichloroacetimidate that forms the glycosidic bond, it is important to be able to control the stereochemistry. Additionally the stereochemistry of the glycosidic bond formation is determined by steric effects,[36] neighboring groups,[37] and solvent effects[38] (Scheme 1.4). Nguyen developed conditions for stereoselectivity utilizing catalytic amounts of $Pd(CH_3CN)(BF_4)_2$ as the Lewis acid.[37] This palladium complex is air and moisture stable unlike other many other Lewis acids.

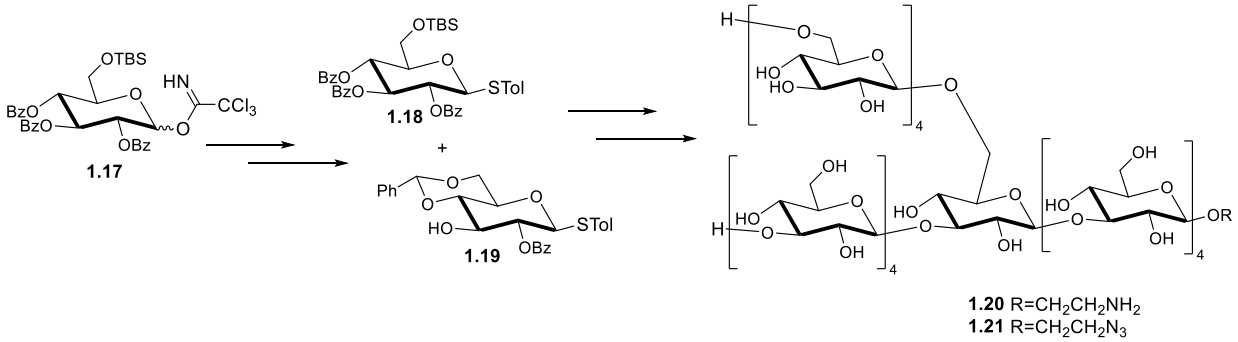
Scheme 1.4. Stereocontrol Glycosidic Bond Formation



Since the trichloroacetimidate can be selectively displaced under mild conditions, it has been applied to the synthesis of glycolipids, glycolyl amino acids, and other complex bioactive molecules.[39] Recently, Li and co-workers used this glycosylation for the convergent synthesis of β-glucan tridecasaccharides (Scheme 1.5) in 2021. These substates have been shown to have

biological activity such as anti-inflammatory and anti-microbial activities, which can be applied for cancer treatment or mycotic treatment.[40]

Scheme 1.5. Synthesis of β-glucan Tridecasaccharides



Trichloroacetimidates for Protecting Group Formation

Since Schmidt's research into glycosidic bond formation by using trichloroacetimidates, this led others to similar research in the formation of other C-O bonds using trichloroacetimidates. This research has been especially important for protecting groups in complex organic molecules which do not tolerate strong base needed to install protecting groups under Schotten-Bauman type conditions (NaOH, DCM/H_2O). Trichloroacetimidates have been used to install protecting groups to form a variety of bonds, such as C-O bonds to afford ethers and esters, and C-S bonds to afford thioethers. The most recent and well know conditions for these transformations are highlighted below.

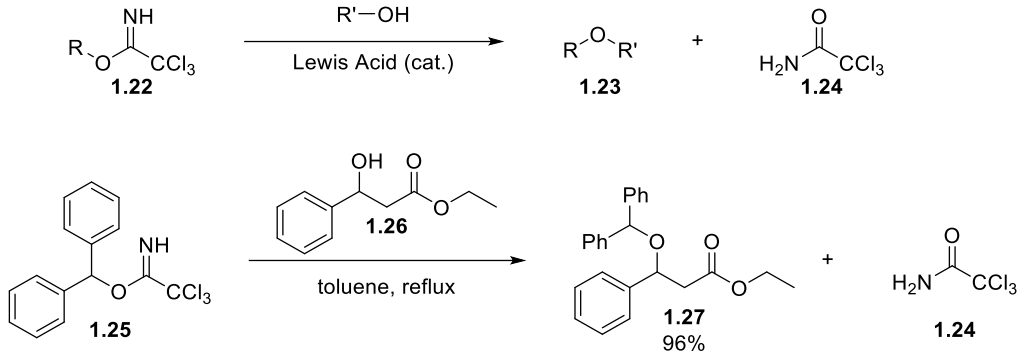
Trichloroacetimidates in C-O Bond Formation

Ethers can act as a protecting group of sensitive alcohols, which is valuable in organic synthesis.[41, 42] Mild conditions are desired to both protect and deprotect alcohol substrates in order to limit the molecules degradation in a multistep synthesis. The most commonly used methods for the etherification of alcohols are the Williamson ether synthesis, dehydration under strong acidic

conditions, and the use of transition metal catalysts such as tungsten[43] or palladium.[44-46] The Williamson ether synthesis uses strongly basic conditions to form an alkoxide, which then displaces an alkyl halide. Due to the strongly basic conditions, this method's application is limited to robust substrates. Sensitive substrates like beta-hydroxy esters (which undergoes retroaldol reactions under basic conditions) cannot be protected under Williamson conditions. Alternatively acid-catalyzed condensations have been established as a way to synthesize a symmetrical ether. However, when utilizing this method for secondary or tertiary alcohols substrates, elimination products are usually favored rather than the desired ether.[47] Additionally, this method can be problematic in the presence of acid sensitive bonds, such as silyl ethers and acetals, which can be cleaved by the acid. Metal catalysts have also been employed for ether synthesis, including Ullmann[48-50] and Buchwald-Hartwig[51-56] reactions; while these reactions provide milder conditions, they usually employ expensive catalysts and ligands.

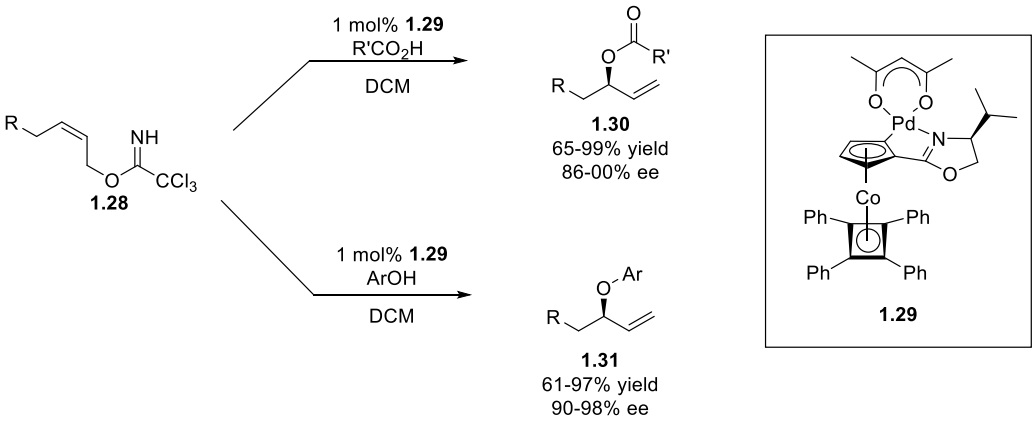
Due to these limitations, milder conditions for alcohol protection in complex molecules is an ongoing area of research. Recently trichloroacetimidates have been used to form ethers in the presence of a Brønsted or Lewis acid. Free alcohols, including secondary alcohols, have been protected with *t*-butyl, *p*-methoxybenzyl, and diphenylmethyl trichloroacetimidates.[15, 57, 58] These conditions have been proven to be mild and only side product being the trichloroacetamide. More recently it was shown that diphenylmethyl ethers can be formed under thermal conditions by refluxing the alcohol with diphenylmethyl trichloroacetimidate without the need for an acid catalyst (Scheme 1.6).[14] Recently similar trifluoroacetimidates,[59] phosphinimidates,[60] and pyridinium salts[61, 62] have been used to protect alcohols.

Scheme 1.6. Etherification utilizing Trichloroacetimidates



The synthesis of ethers utilizing trichloroacetimidates has also be employed for asymmetric reactions. Overman has shown ethers can be synthesized enantioselectively from *Z*-allylic trichloroacetimidates, an alcohol with a chiral cobalt oxazoline palladacyclic complex **1.29** (Scheme 1.7).[63-65] This catalyst could also be used for esterification by displacing z-allylic trichloroacetimidate with a carboxylic acid.

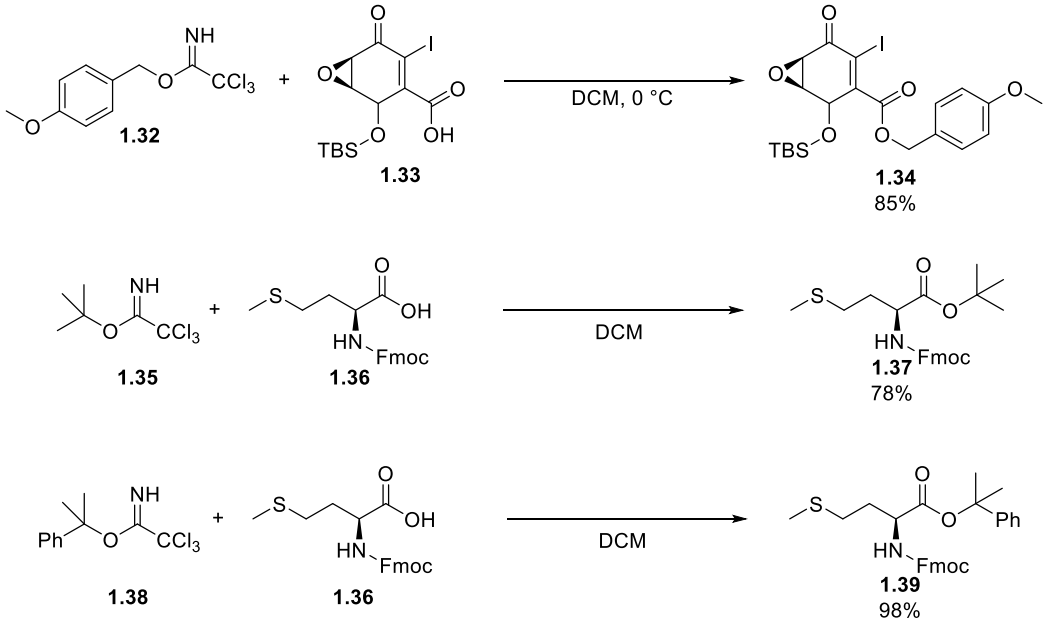
Scheme 1.7. Enantioselective Etherification and Esterification of *Z*-allylic Trichloroacetimidates



Typically, carboxylic acids also need to be protected as the corresponding ester during complex molecule synthesis. Commonly, esters are synthesized by alkylations of carboxylic acids with alkyl halides under basic conditions or by dehydration under acidic conditions. Both methods have limitations with sensitive substrates. Alternatively, carboxylic acids may be protected as

ethers using diazomethane derivatives; however, these reagents are typically unstable and toxic.[66, 67] Carboxylic acids have also been protected by trichloroacetimidates. Facile esterification utilizing allyl trichloroacetimidate,[21] glycosyl trichloroacetimidate,[13] benzyl trichloroacetimidate,[21] *p*-methoxybenzyl trichloroacetimidate,[68, 69] 2-phenylisopropyl trichloroacetimidates,[70, 71] and *tert*-butyl trichloroacetimidates have been reported. In most of these cases no additional acid is required, as the carboxylic acid itself is acidic enough to promote the esterification.

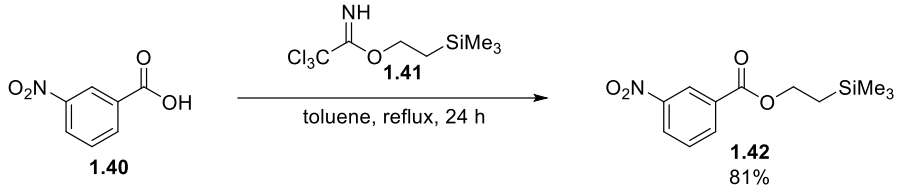
Scheme 1.8. Esterification using Trichloroacetimidates



Recently the Chisholm group utilized carboxylic acids and trichloroacetimidates for esterification.[19, 20, 72] First, in 2014 the Chisholm group found diphenylmethyl[20] and *p*-methoxybenzyl esters[73] can be synthesized utilizing the corresponding imidate without the need of an acid catalyst. This is synthetically useful since both PMB and DPM groups can be removed via hydrogenation or acidic conditions. Later in 2021 trichloroacetimidate **1.41** was used for

trimethylsilylethyl (TMSE) ester synthesis. Again, this was accomplished under thermal conditions without the need of a Lewis or Brønsted acid catalyst.[19] Trimethylsilylethyl esters have become popular for complex molecule synthesis since they can be cleaved with acid,[74] base,[75] or fluoride[76] without degrading other functionality in the molecule.

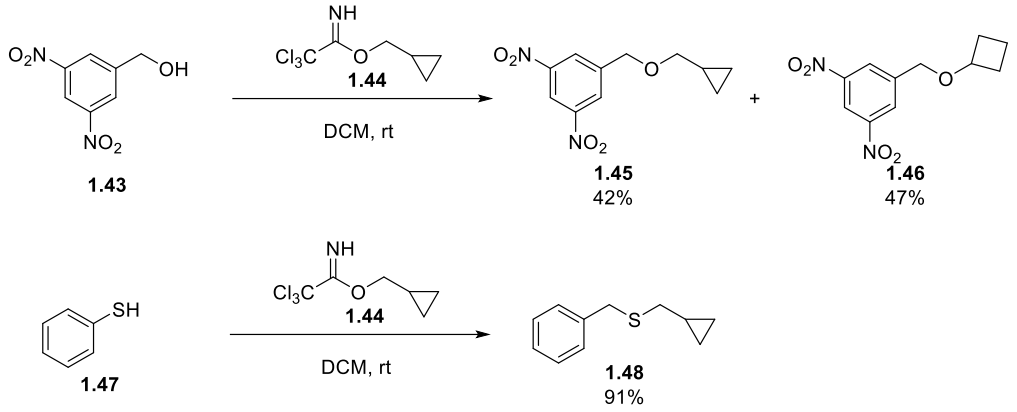
Scheme 1.9. Esterification with 2-(Trimethylsilyl)ethyl 2,2,2-Trichloroacetimidate



Trichloroacetimidates in C-S Bond Formation

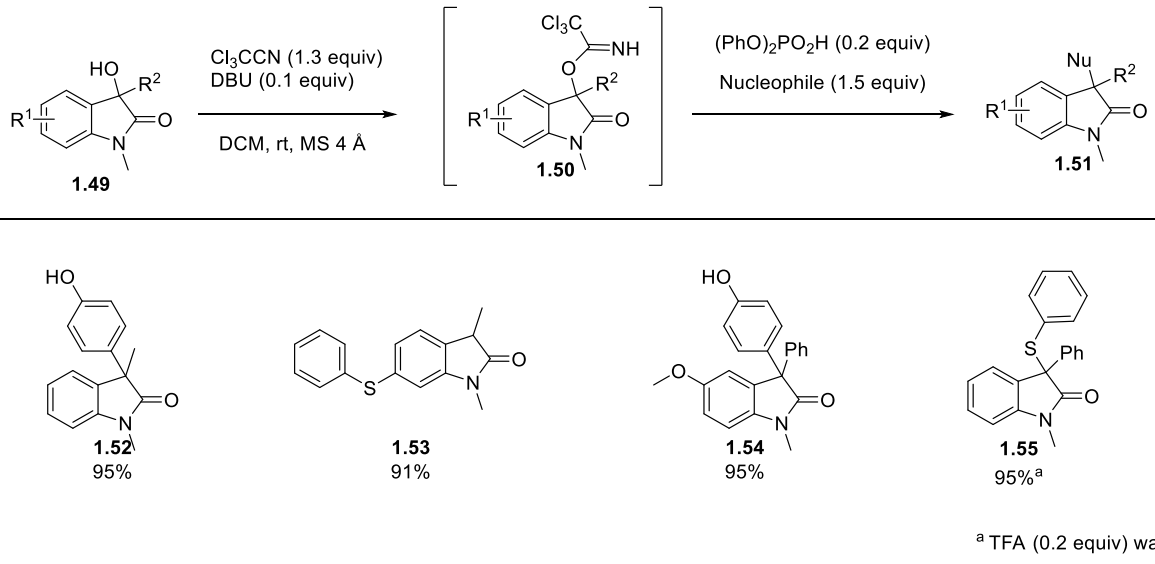
Sulfides have been used in many pharmaceuticals. However, there are only a few of examples of mild conditions to install these bonds outside of carbohydrate chemistry. One of the first reports of synthesizing sulfides utilizing trichloroacetimidates and thiols was with Schmidt and co-workers in 2012.[77] The O-cyclopropylmethyl trichloroacetimidate **1.44** was used. This substrate can be problematic as it can form the desired cyclopropylmethyl , or cyclobutyl products. These structures can occur from the rearrangement and trapping of the carbocation intermediate. Therefore, the product formation is dictated by nucleophilicity and sterics of the nucleophile attacking the imidate. Schmidt found that with alcohol **1.43** as the nucleophile a mixture of products formed; but when thiol **1.47** was used, only the desired product **1.48** was isolated (Scheme 1.10). This result was explained by the enhanced reactivity of the thiol resulting in more efficient trapping of the carbocation prior to rearrangement.

Scheme 1.10. Examples of Alkylation with O-cyclopropylmethyl Trichloroacetimidate



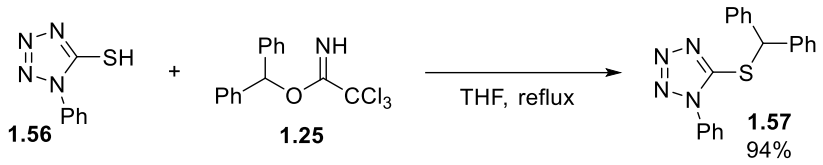
Later Zhu and co-workers discovered that hydroxyindole imidate **1.50**, formed in situ, could be displaced which provided a useful method for substituting oxindoles at the C-3 position.[78] Alcohols, phenol, amines, anilines, indoles, pyrroles, allyltin, and enol ethers were shown to be effective nucleophiles. When thiophenol was utilized, Friedel-Crafts (**1.53**) and direct substitution (**1.55**) products were isolated, which did not occur when other nucleophiles were employed. (Scheme 1.11) This was attributed to the increased nucleophilicity of sulfur.

Scheme 1.11. Substitution of 3-hydoxyindoles



Recently the Chisholm group developed a methodology to alkylate thiols under thermal conditions without acidic, basic, or metal catalysts utilizing trichloroacetimidates as the electrophile (Scheme 1.12). This reaction was shown to tolerate a variety of substrates including alkyl, allylic, propargylic, and benzylic trichloroacetimidates (including substrates with electron-donating and electron-withdrawing groups). Aromatic thiols tended to provide better yields, however alkyl substrates still delivered sulfide product. Conditions were also developed to generate the sulfide product from the corresponding alcohol in a single flask by generating the imidate *in situ*.[6]

Scheme 1.12. Alkylation of Thiols with Trichloroacetimidates Under Thermal Conditions

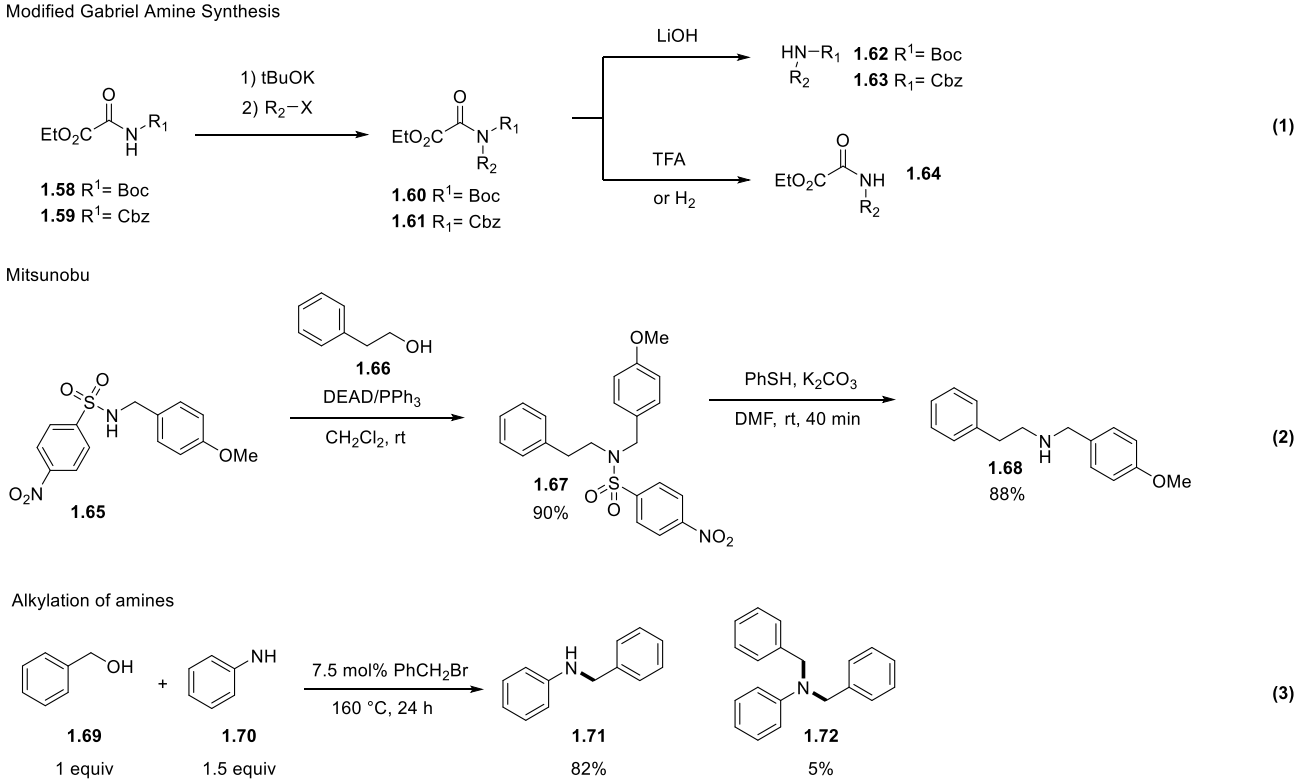


Rearrangement of Trichloroacetimidates for the Synthesis of Amines

Amines are widely seen in pharmaceuticals, natural products, and bioactive molecules.[79] Due to this, the development to new methods to form C-N bonds in organic scaffolds is of great interest. Given their importance, a number of different methods to synthesize amines have been developed from the corresponding alcohol as a starting material, such as Gabriel amine synthesis[80-83] and the Mitsunobu reaction. However, the harsh conditions of the Gabriel amine synthesis produce phthalhydrazide as a waste product and are only amenable to the synthesis of primary amines. A modified Gabriel amine synthesis has been developed using *N*-Boc **1.58** or *N*-Cbz ethyl oxamate **1.59**, which can be alkylated under basic conditions.[82] The free amine is formed by treating *N*-Boc **1.60** or *N*-Cbz ethyl oxamate **1.61** with lithium hydroxide. Trifluoroacetic acid can be used to remove the Boc group, or hydrogenation can be done to remove the Cbz group and provide amide **1.64** (Scheme 1.13, eq 1). The Mitsunobu reaction, while the stereochemistry can

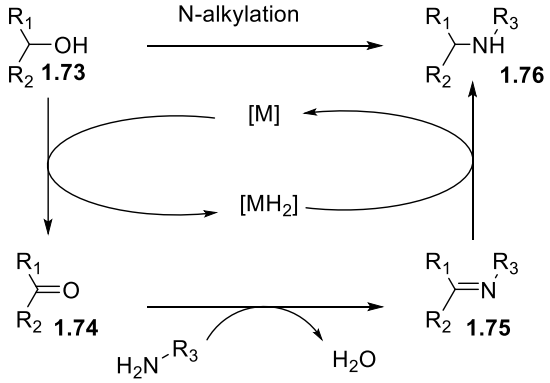
be controlled since the reaction proceeds through an S_N2 mechanism, the two major side products – a phosphine oxide and a hydrazinedicarboxylate – can be difficult to separate from the desired amine.[84-86] Additionally, harsh deprotection conditions are usually needed to synthesize the free amine (Scheme 1.13, eq 2). Amines may also be directly alkylated with alkyl halides; however, polyalkylation can occur, leading to undesired quaternary amine side products and limiting yields (Scheme 1.13, eq 3).[80-87] Reductive methods may also be employed to produce amines via the amides or imines.[88-92] Ketones and aldehydes can be transformed to amines through reductive amination using sodium cyanoborohydride or sodium borohydride and catalytic amounts of acid. This avoids the problem of over alkylation of amines; however, both the sodium cyanoborohydride and its byproducts from the reaction are highly toxic.[88] A more recent method of reductive amination uses a less toxic reagent, sodium triacetoxyborohydride.[90]

Scheme 1.13. Synthesis of Amines via Alkylations



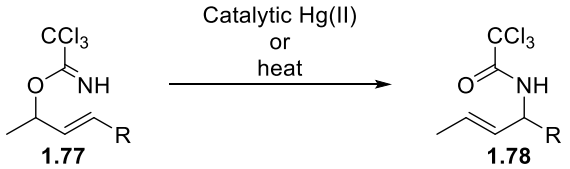
More recently amines have been synthesized directly from alcohols using "borrowing hydrogen" methods. These methods use transition metal catalysts and stoichiometric strong bases (Scheme 1.14).[92-94] Mechanistically, the transformation occurs by oxidation of the alcohol to the carbonyl, followed by imine formation the consequent reduction using the same hydrogen atoms from the starting alcohol to produce the substituted amine and water. As the same hydrogens which are removed from the starting material reappear in the product, the process is often referred to as "borrowing hydrogen".

Scheme 1.14. General Synthesis of Amines via the Borrowing Hydrogen Technique



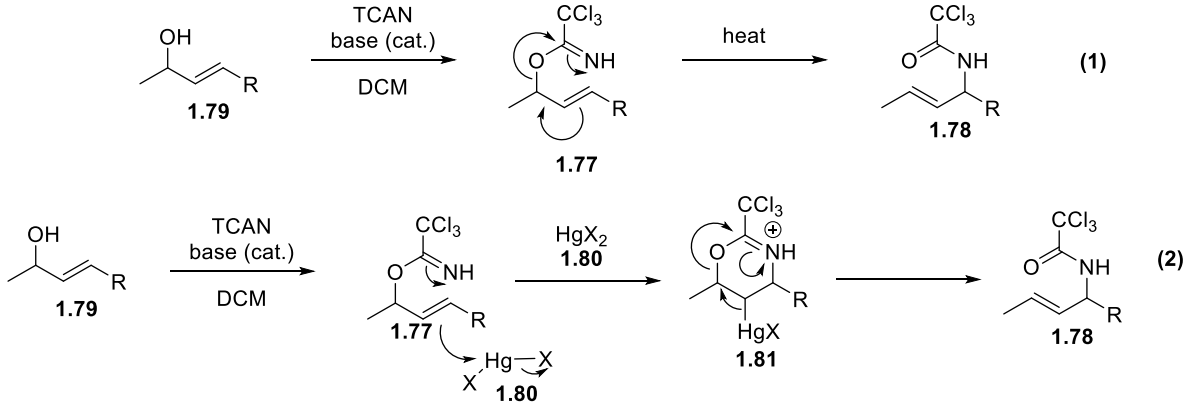
The aza-Claisen rearrangement (also known as the Overman Rearrangement) of allylic trichloroacetimidates, such as **1.77**, to provide allylic trichloroacetamides **1.78**, a protected amine, has also been used for synthesizing complex amines (Scheme 1.15).[24, 25] This occurs through a [3,3]-sigmatropic rearrangement of the trichloroacetimidate, which can be easily synthesized from the alcohol precursor, catalytic amount of base, and trichloroacetonitrile. Typically 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) is utilized as a base for primary or secondary alcohols. However, more hindered alcohols require hydride, such as KH, in order to synthesize the trichloroacetimidate.[65]

Scheme 1.15. Overman Rearrangement



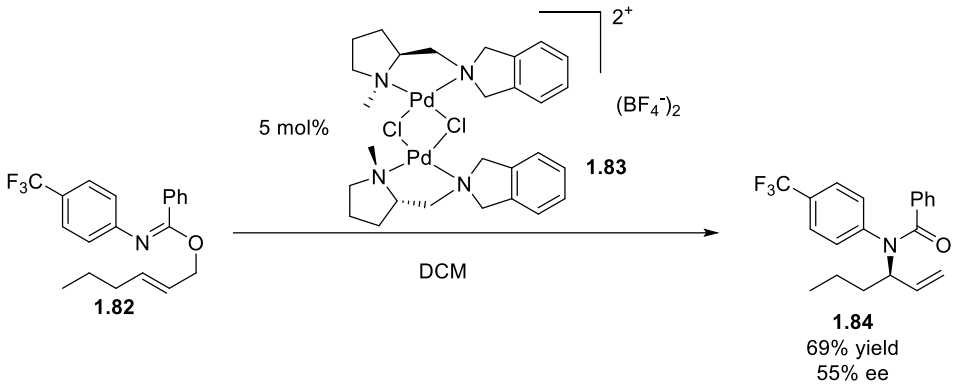
Overman and co-workers found that the trichloroacetimidate, when refluxed in *m*-xylene, a high boiling solvent (~140 °C), underwent rearrangement to provide the trichloroacetamide.[25] Alternatively, Overman also found when treated with catalytic amounts for mercury (II) trifluoroacetate the trichloroacetimidate also underwent rearrangement to the trichloroacetamide, even at room temperature (Scheme 1.16).[24, 26] This product can be transformed to the corresponding amine by treating the trichloroacetamide with aqueous sodium hydroxide. Mechanistically there are two possible pathways. When the rearrangement occurs thermally, the reaction is thought to occur through a concerted sigmatropic pathway (Scheme 1.16, eq 1). However, with the addition of catalytic mercuric trifluoroacetate a two-step reaction is proposed. First, the mercury adds across the alkene to form mercurinium ion **1.81**. Second, this intermediate **1.81** collapses to provide the product, trichloroacetamide **1.78**. This reaction is favored by a thermodynamic driving force since the amide is more stable than the imidate.

Scheme 1.16. Mechanisms of the Overman Rearrangement



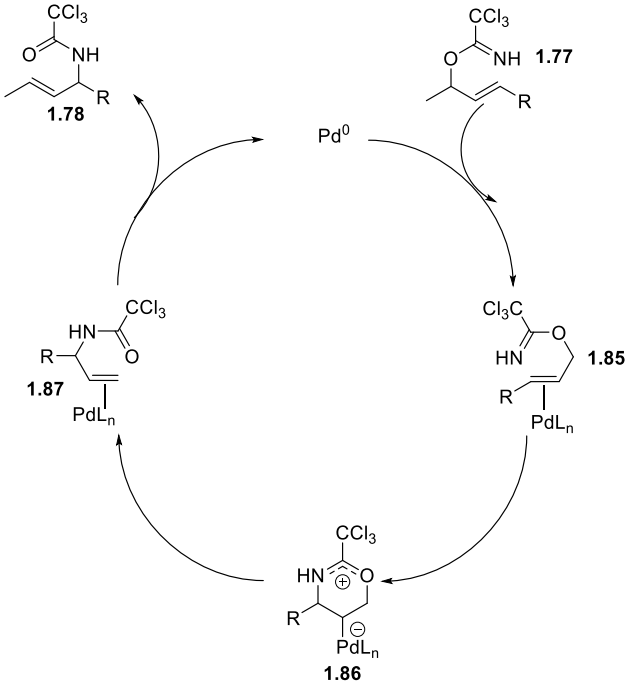
Later, Overman and co-workers investigated the use of palladium catalysts in these reactions. The use of palladium has several advantages compared to mercury. First, palladium is significantly less toxic than mercury. Additionally, chiral palladium complexes may be used to create asymmetric conditions. For these reasons, palladium has become a common catalyst for Overman rearrangements. For example, palladium complex **79** was used in enantioselective rearrangement of imidate **78** to amine **80** (Scheme 1.17).[95]

Scheme 1.17. Asymmetric Rearrangement of N-phenylbenzimidate with Chiral Pd Catalyst



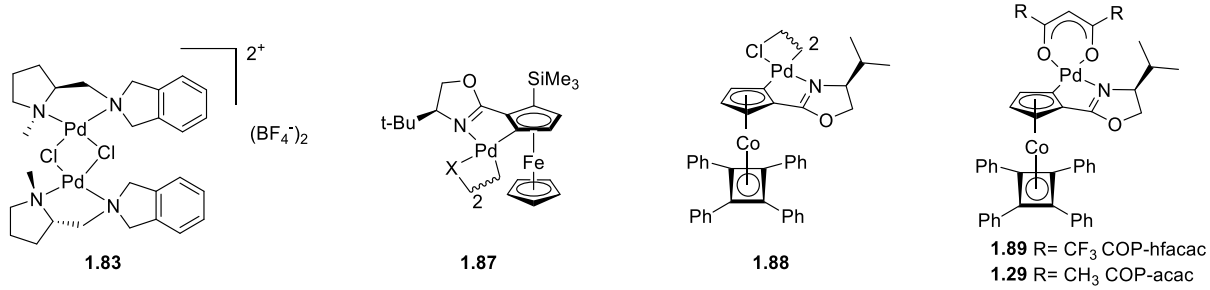
The palladium-catalyzed rearrangement is proposed to occur in a cyclization-induced rearrangement (CIR) mechanism, shown in Figure 1.1.[7] First the pi-allyl complex **1.85** is formed when a ligand is displaced by the allyl trichloroacetimidate **1.77** coordinated the palladium to the alkene. The cyclic intermediate **1.86** is formed by an intramolecular addition of the imidate nitrogen. The cyclized intermediate collapses to the rearranged intermediate **1.87**. This intermediate is displaced by a ligand, regenerating the catalyst and forming the final product **1.78**.

Figure 1.1 Cyclization Induced Rearrangement Mechanism

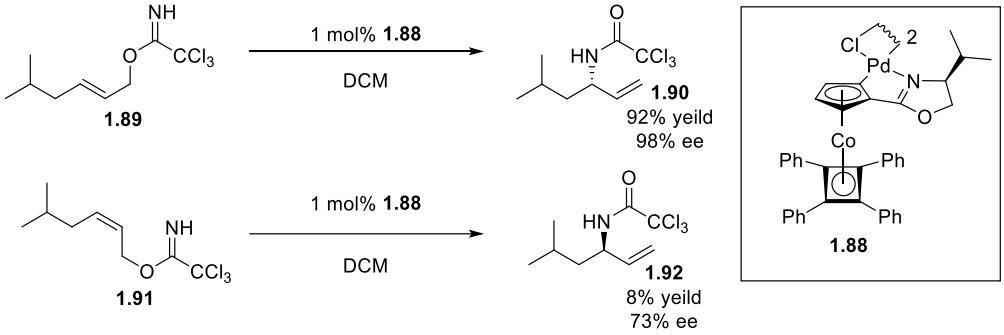


Enantioselectivity was first achieved with the palladium diamine complex 1.82. However, the diamine ligand only provided low enantioselectivity. This prompted for further investigation of ligands such as the palladium catalyst containing ferrocenyl-oxaoline[95] and cobalt oxazoline (COP-Cl), as shown in Figure 1.2. Overman found that with the COP-Cl catalyst the rearrangement of allylic trichloroacetimidates could be performed in high yields with excellent enantioselectivity (Scheme 1.18). Additionally, the trichloroacetyl group can be removed under, acidic, basic, or reducing conditions.[24, 25] However, these COP catalysts only provided high yields with *E*-allylic trichloracetaminidates.[63, 64] Although the *Z*-allylic trichloroacetimidates did not work well in the rearrangement, it was discovered that *Z*-allylic trichloroacetimidates underwent substitution reactions with phenols and carboxylic acids with a COP catalyst.[63, 64] Later the COP-Cl catalysts **85** were found to have limited solubility in organic solvents, leading to the development of other COP catalysts with improved solubility including the COP-acac catalyst **1.29**.[64, 96]

Figure 1.2. Overman's Chiral Palladium Complexes Used in Rearrangements

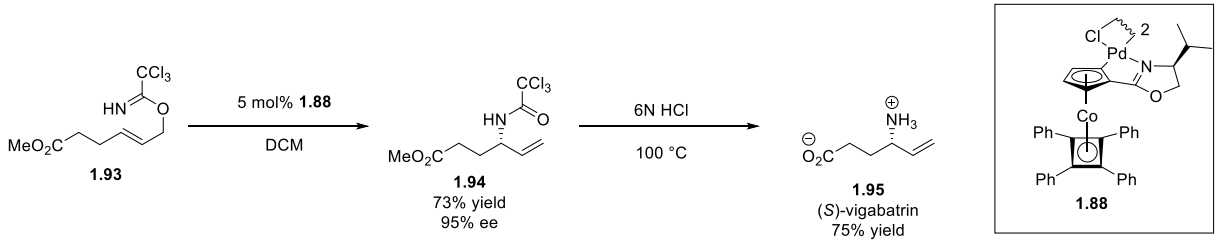


Scheme 1.18. Asymmetric Rearrangement Using COP Catalyst with Allylic Imidates



The enantioselective rearrangement of an imidate was employed for the synthesis of (*S*)-vigabatrin **1.92**, an GABA aminotransaminase inhibitor.[97] The COP catalyst **1.88** was used in this transformation and provided the corresponding trichloroacetamide **1.94** in good yield and high enantioselectivity. Once the trichloroacetamide was synthesized, the acid deprotection of the trichloroacetyl group provided the free amine **1.95** (Scheme 1.19).

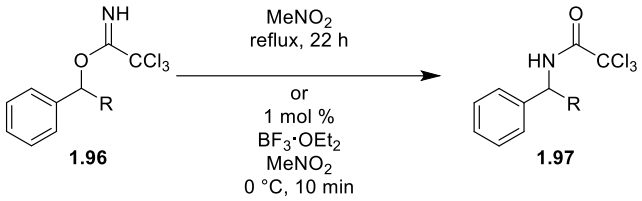
Scheme 1.19. Synthesis of (*S*)-Vigabatrin



Recently, the Chisholm group has become interested in the rearrangement of benzylic trichloroacetimidates to the acetamides, which may provide access to benzylic amine containing systems. While the rearrangement of allylic trichloroacetimidates is known, the benzylic

trichloroacetimidate rearrangement was not explored in detail before our work.[98] This rearrangement of benzylic imidates provides quick access to protected benzylic amines and analogues. In 1961, the rearrangement of benzylic trichloroacetimidates to the corresponding acetamide using a Lewis acid was first reported by Cramer.[99] Later, Schmidt and others found glycosidic trichloroacetimidates could be converted to the acetamide with Lewis acids.[100] More recently we developed both thermal and Lewis acid catalyzed conditions (Scheme 1.20) to promote the rearrangement.[27]

Scheme 1.20. Thermal and Acid Catalyzed Conditions of Imidate Rearrangement



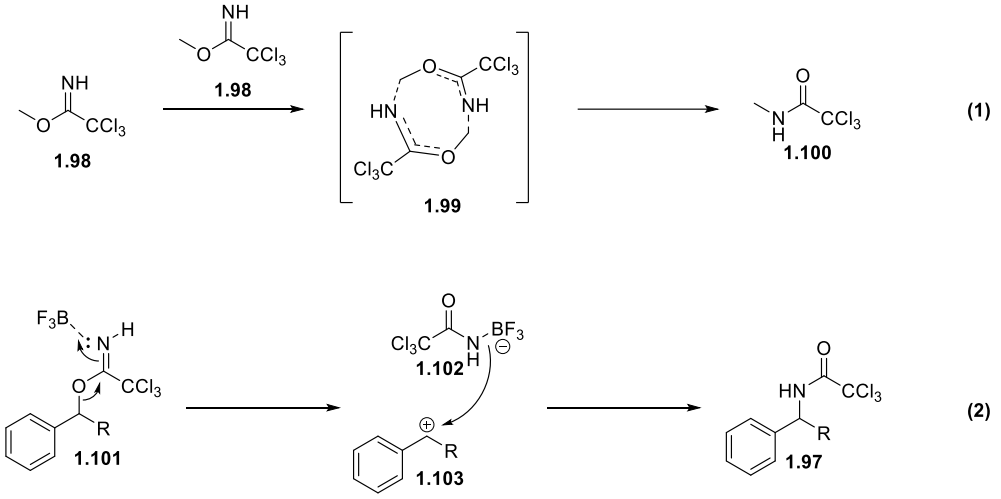
However, these conditions are not enantioselective. When performed with the imidate derived from enantiopure 1-phenethyl alcohol, both the thermal and acid catalyzed product gave product that exhibited less than 10% enantiomeric excess. This racemization was attributed to a carbocation intermediate in the rearrangement.

Alternative Trichloroacetimidate-Based Formation of C-N Bonds

While the Overman rearrangement is an established method for forming C-N bonds, there are some drawbacks, such as the use of an expensive transition metal catalyst, and few alternative methods available. Cramer reported the rearrangement of benzylic trichloroacetimidates to the corresponding acetamide using a Lewis acid.[99] This reaction was shown to tolerate a number of imidates, including more highly substituted benzyl imidates. For these substrates, formation of a

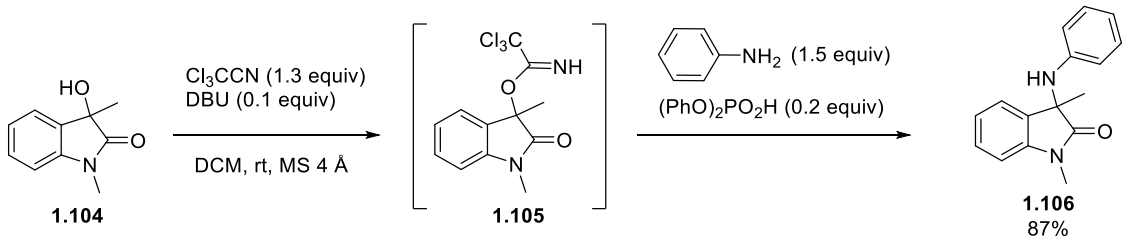
carbocation intermediate **1.103** enables the rearrangement (Scheme 1.21, eq 2). While methyl imidate **1.98** is thought to rearrange to the corresponding trichloroacetamide through a concerted mechanism, through intermediate **1.99** (Scheme 1.21, eq 1).

Scheme 1.21. General Imidate Rearrangement Mechanisms



A small number of direct alkylations to form C-N bonds utilizing trichloroacetimidates as electrophiles have been reported. For example, tert-butyl trichloroacetamide has been used to form C-N bonds with anilines but requires $BF_3{\cdot}OEt_2$.[101] Later, Zhu and co-workers developed discovered certain nitrogen nucleophiles, such as aniline, can be alkylated with hydroxyoxindoles by generating the imidate *in situ* (Scheme 1.22).

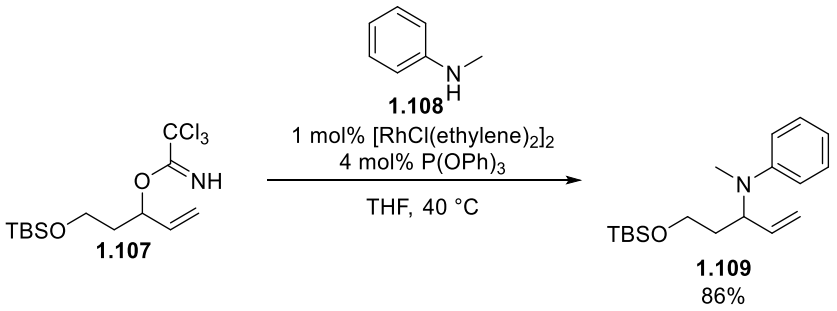
Scheme 1.22. Substitution of 3-hydoxyindoles with Aniline Nucleophile



There are a few examples reported of transition metal catalysts used to perform these transformations. Rhodium catalyzed alkylations of *N*-methyl anilines with allylic

trichloroacetimidates has been reported (Scheme 1.23).[102, 103] Nguyen and co-workers have also found asymmetric conditions for this reaction.[102] Notably, these reactions occurs favoring the branched *N*-arylamine, not the liner product and without the use of a Lewis acid catalyst. Investigations into expanding this chemistry has been done including the use of tertiary trichloroaceitmidates,[104] asymmetric aminations of tertiary trichloroacetimidates,[102] and enantioselective synthesis of seven-membered nitrogen heterocycles.[65] Other than rhodium catalysts, palladium has been used to synthesize pseudodisaccharides using trichloroactetimides.[105]

Scheme 1.23. Rhodium Catalyzed Alkylation of *N*-methyl Anilines

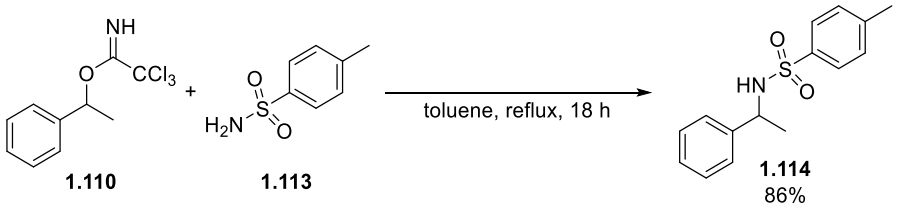


The Chisholm lab has displaced trichloroacetimidates to form C-N bonds with anilines and sulfonamides.[23, 106] For the monoalkylation of anilines using trichloroacetimidates as electrophiles, this was accomplished under Brønsted acid catalyzed conditions. While most anilines reacted well, electron-rich anilines competed in Friedel-Crafts reactions and more basic anilines formed the amine salt. This method was compatible with benzylic, allylic, and tertiary implying a carbocation intermediate. Additionally, a one-step protocol was developed for this method, where the imidate is generated in situ. This protocol was used in the synthesis a lipoxygenase inhibitor, onosmin B (Scheme 1.24).

Scheme 1.24. Brønsted Acid Monoalkylation of Anilines

The alkylation of sulfonamides with trichloroacetimidates was performed under thermal conditions (refluxing toluene); therefore, it does not require the use of acid, base, or transition metal catalyst. Several sulfonamides were utilized in this reaction where the least sterically hindered sulfonamides provided the best yields. Also, a number of trichloroacetimidates were employed in the reaction and it was determined that only trichloroacetimidates that would provide a stable carbocation precursor would react under these conditions, implying an S_N1 mechanism. This methodology was used to synthesize a ketoprofen analog in high yield (Scheme 1.25).[106]

Scheme 1.25. Alkylations of Sulfonamides under Thermal Conditions

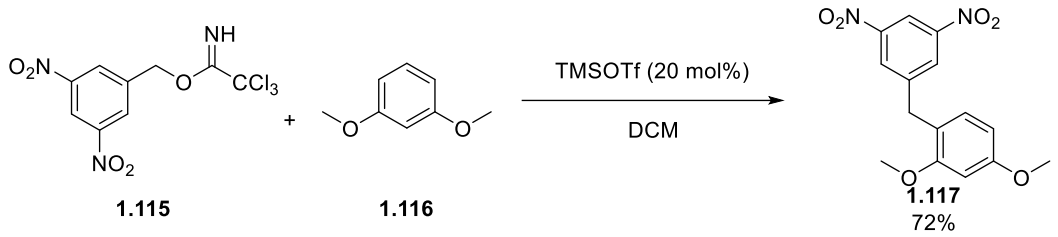


Trichloroacetimidates in Friedel-Crafts Alkylations and C-C Bond Forming Reactions

A common carbon-carbon forming reaction is the Friedel-Crafts alkylation. This reaction utilizes alkyl or acetal halide as a leaving group with a stoichiometric amounts of Lewis acid, such as aluminum trichloride. While carbon-carbon bond formation reactions are synthetically important, a significant draw back to this reaction is the stoichiometric amounts of metal salts as a byproduct. Additionally, the substrate scope for Friedel-Crafts is limited to only stable carbocation

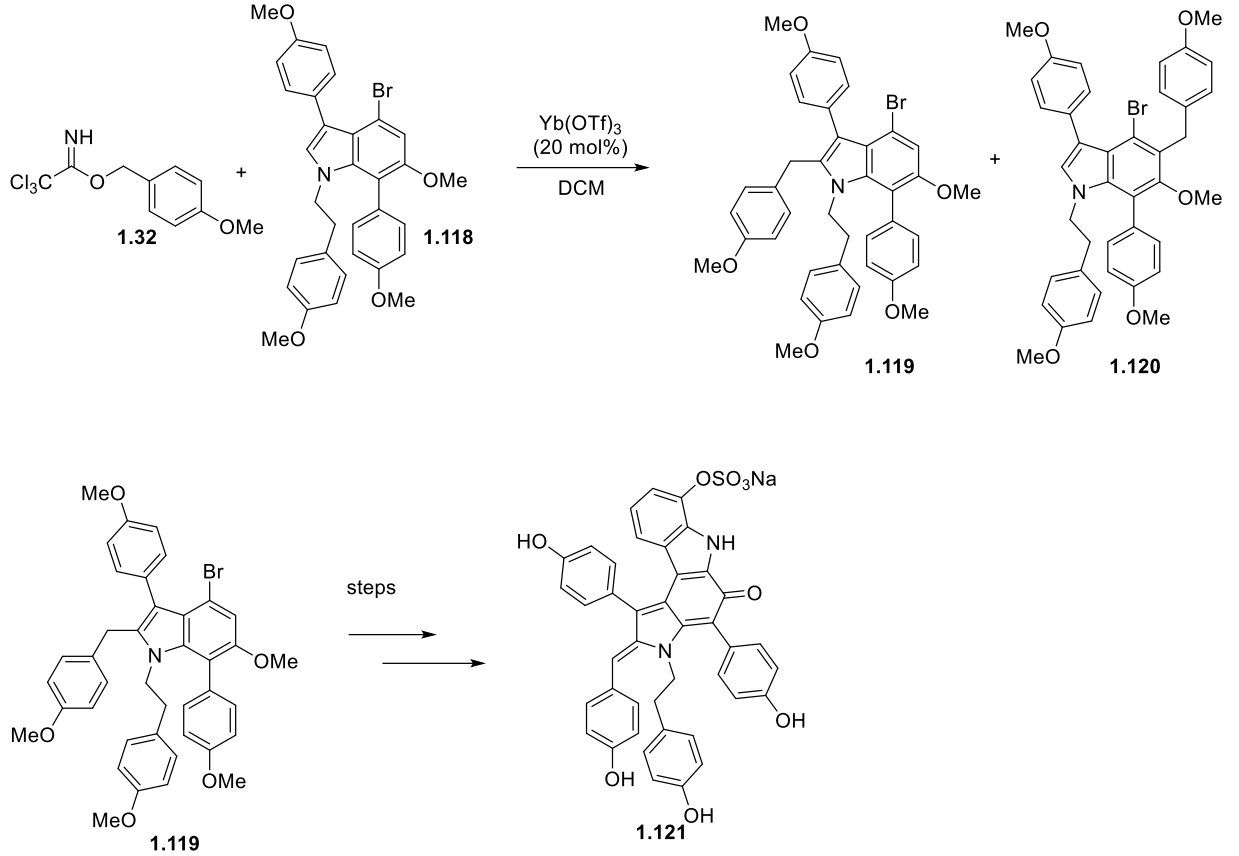
precursors as electrophiles and only electron rich aromatic rings. Due to these drawbacks, research has been done to ascertain more general and environmentally friendly reaction conditions. Schmidt showed trichloroacetimidates are suitable in Friedel-Crafts alkylations under acid catalytic conditions and using electron poor trichloroacetimidates (Scheme 1.26).[31] This reactivity may be due to thermodynamic driving force for the alkylation by forming acetamide byproduct.

Scheme 1.26. Friedel-Crafts Alkylations using Trichloroacetimidates



Trichloroacetimidates have been used to synthesize more complex molecules utilizing Friedel-Crafts chemistry. Since Schmidt has established trichloroacetimidates for glycosidic bond formation, predictably this methodology was employed in the synthesis of aryl-C glycoside visnagin[107] and flavone-C glycosides vitexin, isovitexin, isoembigenin.[108] Later, Fukuyama utilized this chemistry for the synthesis of dictyodendrins (Scheme 1.27). These compounds were isolated from a Japanese marine sponge *Dictyodendrilla verongiformis* and have inhibitory activity against telomerase, a target for cancer chemotherapy.[109] When Fukuyama and co-workers were synthesizing indole **1.119**, PMB-Cl was initially used, however, this route did not form any product. When using the PMB-imidate **1.32** and Lewis acid $Yb(OTf)_3$, indole **1.119** and 5-benzylated product **1.120** were isolated, demonstrating the advantage of trichloroacetimidates as electrophiles compared to halides. Additionally, these examples demonstrate the wide application of trichloroacetimidates to sensitive and complex substrates.

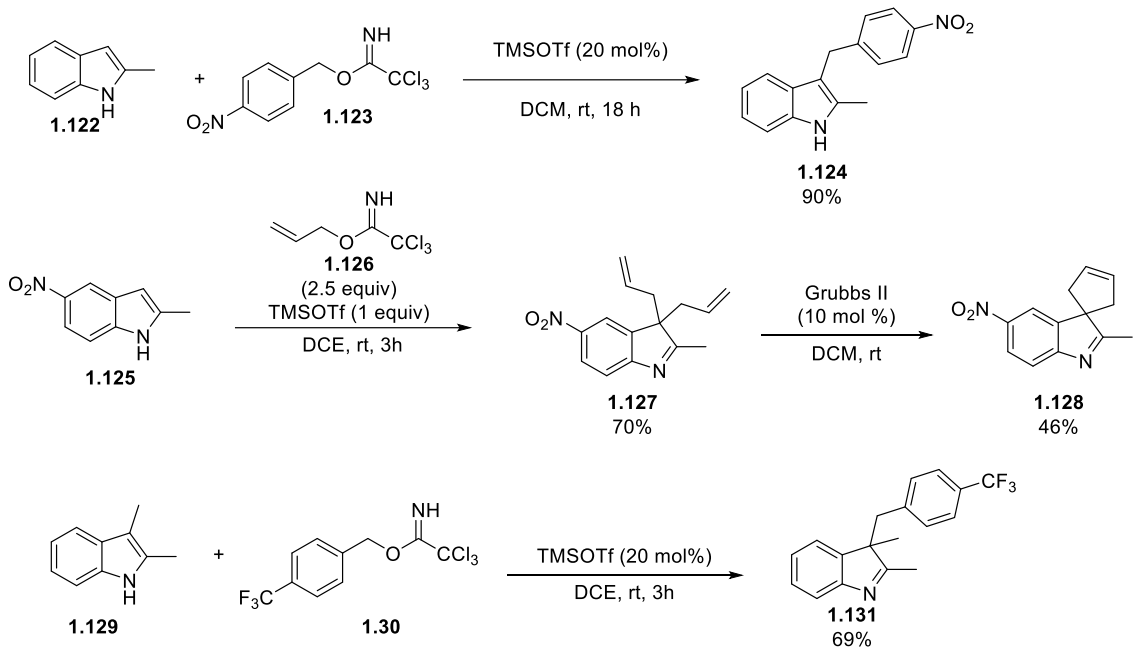
Scheme 1.27. Synthesis of Dictyodendrin E utilizing PMB-Trichloroacetimidate **1.32**



Recently, the Chisholm lab has utilized trichloroacetimidates to alkylate indoles.[28-30] It was shown to regioselectively monoalkylate indoles at the C3 position (Scheme 1.28). The best reaction conditions were when excess indole is used to avoid over alkylated products.[30] Dialkylation products were also optimized utilizing trichloroacetimidates and Lewis acid catalyst to provide indolenines. These indolenines are synthetic precursors for spirocyclic structures, such as **1.128**.[28] The synthesis of 3,3'-disubstiuted indolines was also accomplished by the alkylation of 2,3-disubstituted indoles with trichloroacetimides.[29] This reaction occurs with TMSOTf as an acid catalyst, which is an alternative to base or transition metal catalyzed reactions to access similar indolenines.[110-112] Allyl trichloroacetimidate **1.126** provided product in high yields for a number of substituted indoles. Benzyl trichloroacetimidates were investigated as well. The benzyl

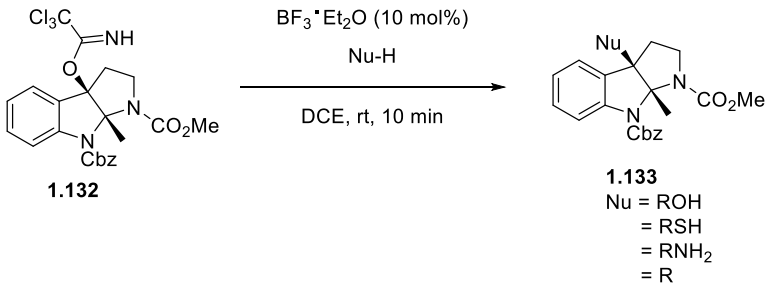
trichloroacetimidates with electron-withdrawing groups, such as imidate **1.123** exhibited significantly higher yield due to the benzylic trichloroacetimidates containing electron-donating groups competing with a Friedel-Crafts side product.

Scheme 1.28. Friedel-Crafts Alkylations of Indoles



Other carbon-carbon bond formation reactions with trichloroacetimidates have also been reported. The Chisholm lab has used the displacement of trichloroacetimidates to functionalize pyrroloindolines (Scheme 1.29).[33] The trichloroacetimidate intermediate **1.132** can be displaced by anilines, alcohols, thiols, and other carbon nucleophiles at the C3a position. [33]

Scheme 1.29. Displacement of Trichloroacetimidates to Functionalize Pyrroloindolines

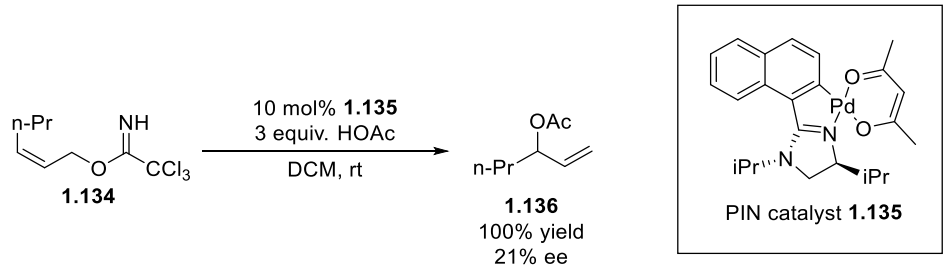


Trichloroacetimidates in Asymmetric Reactions

Since trichloroacetimidates have been established to provide efficient C-O, C-N, and C-C bonds, a number of asymmetric conditions for these transformations have been developed. Typically, these transformations utilize a chiral catalyst to achieve enantioselectivity. The most recent and well know asymmetric conditions are highlighted below.

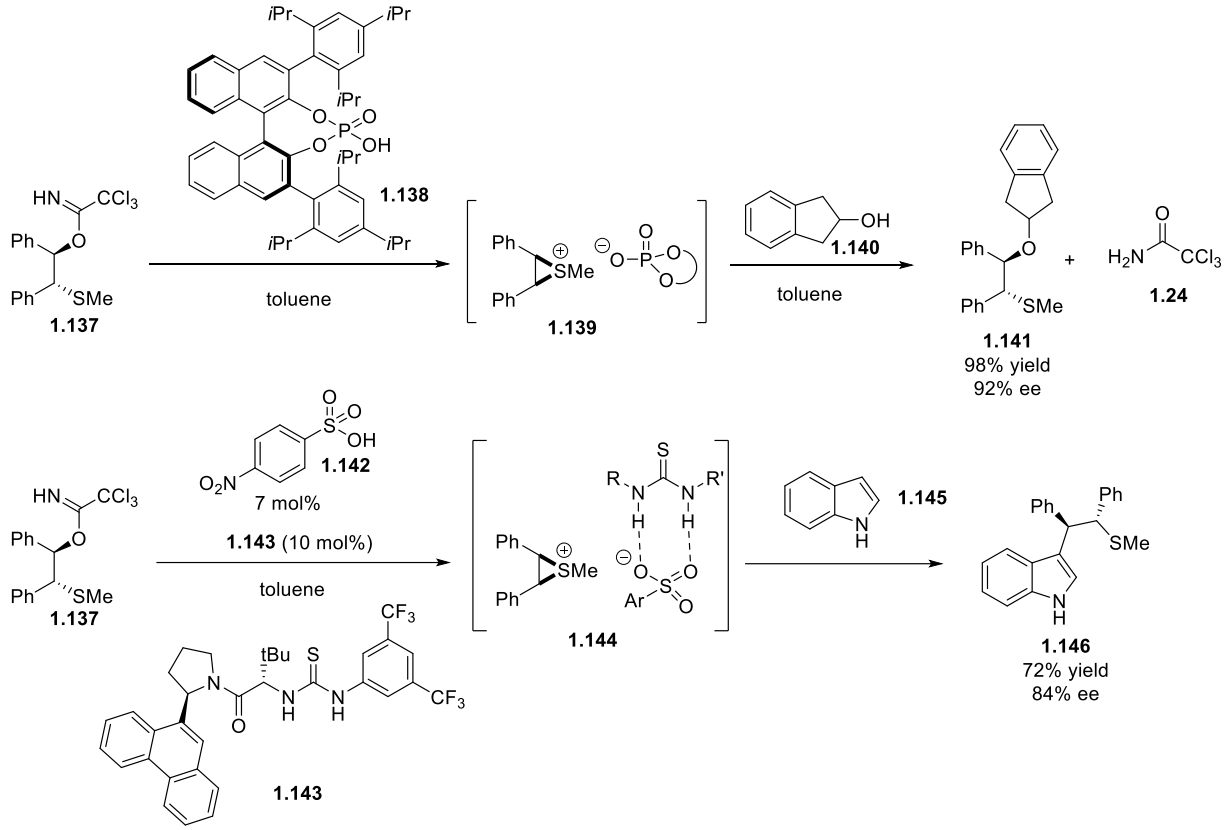
Overman's group developed several chiral catalysts for the rearrangement of trichloroacetimidates to trichloroacetamides. However, it was also discovered that the chiral COP catalyst was also useful for enantioselective esterification and etherification of allylic trichloraceimidates.[64, 113, 114] These COP catalysts only provided high yields with *E*-allylic trichloroacetimidates in the rearrangement to trichloroacetamides.[63, 64] Although the *Z*-allyl trichloroacetimidates did not work well in the rearrangement, it was discovered they underwent substitution reactions with phenols and carboxylic acids with a COP catalyst.[63, 64] This occurred in high yields and enantioselectivity (Scheme 1.7). Later Overman also developed a new group of catalyst, palladacyclic imidazoline-naphthalene complexes (PIN-acac **1.131**) that are air and moisture stable.[96] These PIN-acac catalysts were also utilized in the allylic substitution of allylic trichloroacetimidates. This was done with carboxylic acids in high yield but low enantioselectivity (Scheme 1.30).

Scheme 1.30. Asymmetric Substitutions of *Z*-allyl Trichloroacetimidates using PIN Catalyst **1.135**



Other transition metal free catalysts have been used for asymmetric transformations utilizing trichloroacetimidates as a starting material, such as Brønsted acid and thiourea catalysts (Scheme 1.31). For example, Toste and co-workers used a benzylic trichloroacetimidate **1.137** and BINOL phosphoric acid catalyst **1.138** for asymmetrically open an episulfonium ring. The imidate acts as a good leaving group after being protonated by the BINOL catalyst **1.138** and closes the ring, providing the episulfonium ion **1.139**. This forms ion pair with the BINOL catalysts. Additions to the meso-ion pair **1.139** with an alcohol nucleophile **1.140** occurs asymmetrically. The acid creates a chiral pocket for the nucleophilic addition to occur, resulting in enantioselectivity of the product formation. Similar additions have also been explored by Jacobsen's group utilizing a chiral urea catalyst **1.143** and indole nucleophile. In this case, the imidate **1.137** is protonated by a sulfonic acid **1.142**, leaves and forms the episulfonium ion **1.144**. This forms an ion pair with the acid and chiral thiourea complex **1.144**. From there, indole **1.145** nucleophile attacks the episulfonium ring and the thiourea complex controls the addition. The indole is rearomatized by the acid deprotonating the indole nitrogen, forming the product **1.146** and regenerating the catalyst **1.143**.

Scheme 1.31. Asymmetric Ring Opening of Episulfonium Ions using Thiourea and BINOL Catalysts



Summary:

Trichloroacetimidates have been used for C-O, C-N, C-S, and C-C bond formation in organic synthesis. Since these reagents can be activated with catalytic amounts of Lewis or Brønsted acid, providing mild conditions for etherification, esterification, and thioesterification. Schmidt utilized this reagent in glycosidic bond formation in carbohydrate chemistry. Trichloroacetimidates have also been employed as alkylating agents for indoles and pyrroloindolines. The Overman rearrangement has been widely used to form allylic amines form allylic alcohols. More investigations into the sigmatropic rearrangement have found conditions for benzylic trichloroacetimidates and asymmetric transformations. Recently trichloroacetimidates were used in asymmetric transformations using thiourea and BINOL based phosphoric acid

catalysts. We hypothesize benzylic trichloroacetimidates could be rearranged to the trichloroacetamide enantioselectively in the presence of a palladium catalyst and phosphine ligand. The reactivity of trichloroacetimidates led to the hypothesis that other imidates could be alkylating agents for other C-N bond formations such as isatins and pyrazoles. It is also hypothesized that other imidates could undergo promoter-free conditions for esterification. Additionally, trichloroacetimidates could be used to protect chiral alcohols useful for catalyst synthesis, such as BINOL derivatives.

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Chapter 2 – Carbon-Oxygen Bond Formation Under Mild Conditions Utilizing Trichloroacetimidates

Abstract:

Mono-O-alkylated 1,1′-bi-2-naphthols (BINOLs) are often used as the source of chirality for catalysts or ligand systems that are employed in asymmetric organic transformations. However, these BINOLs can be arduous to synthesize. While the O-alkylation of BINOL can be accomplished with primary and secondary alkyl halides or under Mitsunobu conditions, the yields of these alkylations with tertiary halides or alcohols are very low. A new protocol was developed utilizing trichloroacetamide electrophiles to install bulky groups onto one of the phenolic oxygens. Additionally, removal of the trichloroacetamide byproduct can be easily accomplished via flash chromatography. These conditions provide improved access to monoalkylated BINOL systems which may be employed in the development of new chiral catalysts.

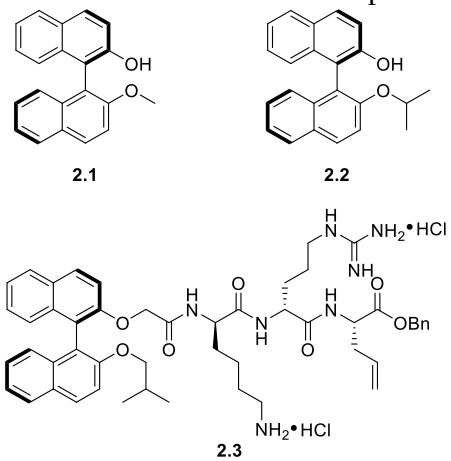
Trichloroacetimidates are also shown to be useful reagents for the synthesis of esters. These reagents did not require an exogenous promoter, and instead proceeded through a symbiotic activation pathway. Under these conditions sensitive substrates did not decompose, which often is observed with alternative conditions employing Lewis or Brønsted acids. Also the trichloroacetamide can be removed via chromatography. These reactions have been extended to benzyl esters without electron donating groups on the benzylic ring. The trichloroacetimidates therefore provide inexpensive and convenient methods that should find use in the formation of esters in complex substrates.

Introduction:

Aromatic systems with axial chirality are often utilized in the development of new catalysts for asymmetric transformations, however the de novo synthesis of these systems remains a

challange.[1] An alternative approach is to begin with an available compound with axial chirality and modify it to access useful scaffolds. As either enantiomer of chiral 1,1′-bi-2-naphthol (BINOL) are now available and inexpensive, mono-*O*-alkylated 1,1′-bi-2-naphthols (BINOLs) have become a common source of chirality for these systems (Figure 2.1).[2, 3] Scaffolds like these are typically accessed by the modification of one or both of the BINOL oxygens with alkyl groups, creating a chiral environment around the remining phenolic oxygens which then can be used as ligands for metals. These BINOL systems have been used for the development of new chiral Lewis acids,[4-6] a proton source for enantioselective protonation,[7-9] and new chiral Brønsted acids.[10] For example, phosphoramidites based on this scaffold have been applied to asymmetric hydroformylations,[11] hydroalkoxylations[12] and hydrovinylation reactions.[12] BINOLs such as **2.1** and **2.2**, have also been used as resolving agents, which have been useful in the separation of the enantiomers of racemic cyclopropanes[13] including the chrysanthemic acids.[14] Other uses for mono-*O*-alkylated 1,1′-bi-2-naphthols have also been described, including a report of their use as a conformational constraint in the development of peptoids with antibacterial properties, like **2.3**.[15-17]

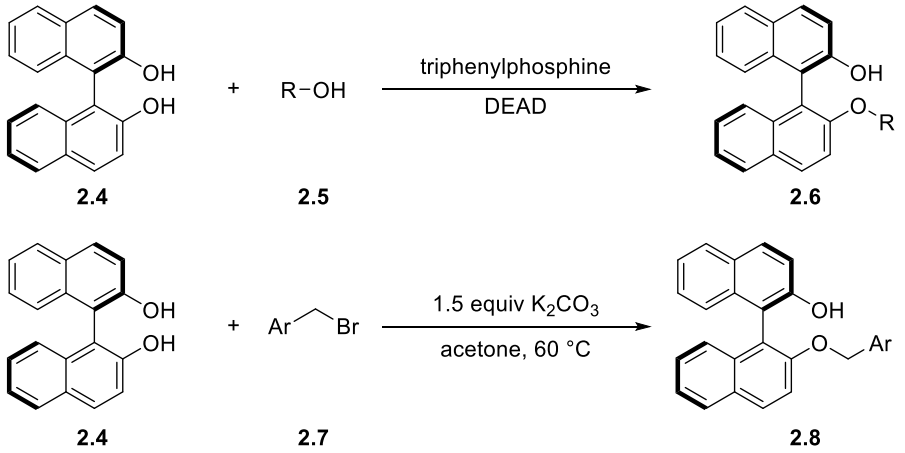
Figure 2.1. Mono-O-Alkylated BINOLs and their Incorporation in Antibacterials like **2.3**



Given the wide implementation of these structures, there has been surprisingly little development into new methods for their synthesis. The most common method for the

monoalkylation of BINOL is the Mitsunobu procedure advanced by Ogasawara.[18] This method works well for most primary and secondary alcohols to access the corresponding ether, forming a C-O bond. Unfortunately, tertiary alcohols are poor substrates in the Mitsunobu reaction,[19, 20] and usually provide only 10-15% yield with these methods (Scheme 2.1). Monoalkylation with primary[21] or benzylic[22] alkyl halides and potassium carbonate in acetone also provides good yields of the monoprotected BINOLs, but these etherifications proceed through an S_N2 mechanism which is not applicable to more hindered alkyl halides. Additionally, the Mitsunobu protocols generate large amounts of toxic waste since DEAD or similar azo reagents are typically employed, and triphenylphosphine oxide is generated as a stoichiometric side product. Given our previous work with the alkylation of more acidic oxygen,[23-25] sulfur,[26] nitrogen,[27] and some carbon[28] nucleophiles without the addition of an exogenous acid catalyst using trichloroacetimidates, it was hypothesized that a similar method could also be developed for the alkylation of BINOLs with hindered electrophiles for chiral scaffold synthesis.

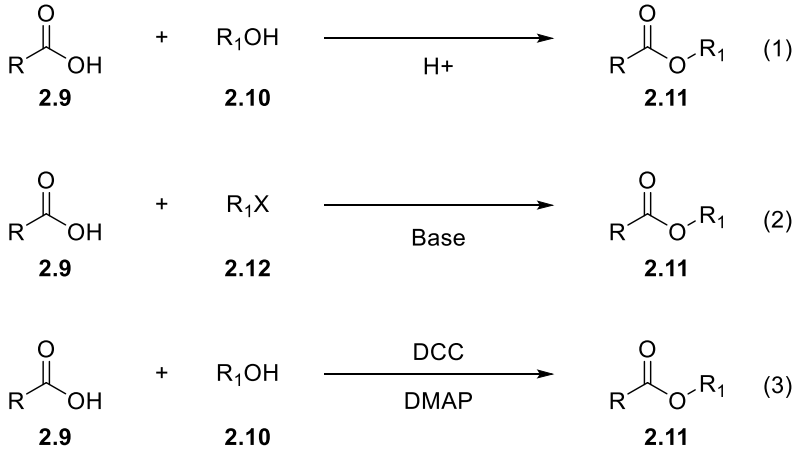
Scheme 2.1. BINOL Monoalkylation Methods



The reactions of some other oxygen nucleophiles with trichloroacetimidates were also investigated, in these cases carboxylic acids were utilized as the alkylation partner to access esters. Esters are commonly used as protecting groups for carboxylic acids, however traditional methods

to form esters require harsh reaction conditions. For example, one of the most common methods for esterification is the Fischer esterification (Scheme 2.2, eq 1),[29] which involves the dehydration of a carboxylic acid and alcohol with a strong acid. Another method is alkylation of carboxylic acids with alkyl halides under basic conditions (Scheme 2.2, eq 2).[30-33] However, each method require the use of strong acid or base, which limits their application with sensitive substrates. Alternatives to using harsh acid or base include using coupling agents such as DCC and DMAP[34] or methyl imidazole carbamate (Scheme 2.2, eq 3).[35] Unfortunately when coupling agents were used with *N*-protected amino acids, racemization was reported.[35] However, a uranium based coupling agent has been developed to avoid the racemization issue.[36]

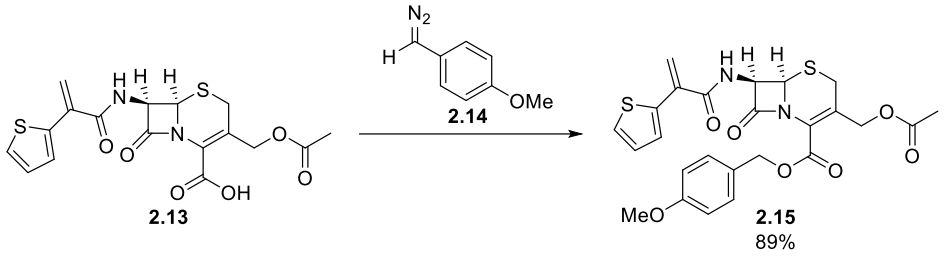
Scheme 2.2. Common Esterification Methods



Recently several alternative esterification methods have been developed to avoid the use of strong acid and bases, allowing for the protection of more sensitive carboxylic acids by activating both the carboxylic acid and the esterification reagent under the reaction conditions, termed symbiotic activation (Scheme 2.3). This is accomplished by the esterification reagent being basic enough to deprotonate the carboxylic acid, and the corresponding cationic salt being electrophilic enough to react with the newly formed carboxylate anion. One example of this type of reactivity is the reaction of carboxylic acids with diazoalkanes, such as **2.14** shown in Scheme 2.3. These

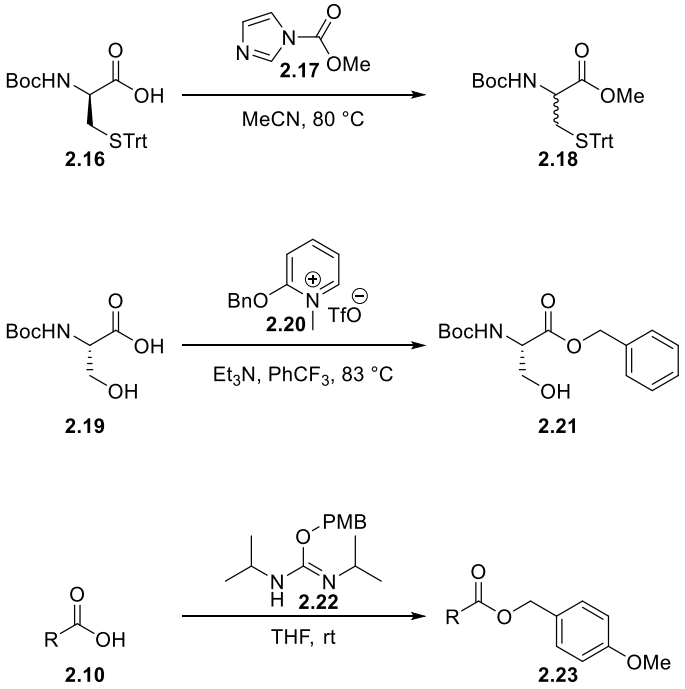
reactions have been reported to follow a pathway through a tight ion pair intermediate[37] formed after proton transfer from the carboxylic acid, and generate nitrogen gas as a side product. This is beneficial since the nitrogen gas as a side product would be unreactive to any functionality in the substrate. However, many diazoalkanes have been reported to be toxic and energetic, making them unattractive reagents and dampening enthusiasm for these methods.[38-41]

Scheme 2.3. Esterification Using Diazoalkane **2.14**



Several other groups have developed reagents that can affect esterifications under mild conditions (Scheme 2.4). The Sarpong group used methyl imidazole carbamate to protect carboxylic acids but observed racemization of *N*-protected amino acid **2.16**. Dudley and co-workers developed a pyridinium reagent **2.20** to synthesize benzyl esters that did not racemize the chiral center of an *N*-protected amino acid **2.19**.[42-44] Another example of reagents for esterification under mild conditions is the isourea based reagent **2.22**. However the urea side product typically needs to be removed via chromatography.[45]

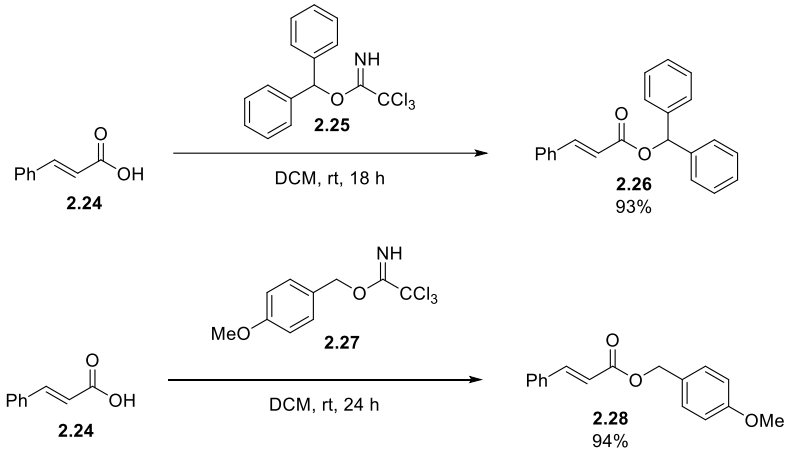
Scheme 2.4. Examples of Mild Esterifications



There have been reports of carboxylic acids reacting with trichloroacetimidates to form esters in the presence of a Brønsted or Lewis acid catalyst. These reactions have been reported with allyl trichloroacetimidate[46] and benzyl trichloroacetimidate.[46] Less well known are reactions that proceed without the addition of an exogenous acid, which occur through a symbiotic activation manifold. These types of reactions were first reported for glycosyl trichloroacetimidate,[47] and 2-phenylisopropyl trichloroacetimidates,[48, 49] while later the Chisholm group showed that these reactions also proceeded with *p*-methoxybenzyl trichloroacetimidate,[50, 51] 2-(trimethylsilyl)ethyl trichloroacetimidate,[52] and diphenylmethyl trichloroacetimidate.[53] The displacement of the imidate allows for the rearrangement of the imidate to the corresponding acetamide, which is a thermodynamic driving force, often leading to higher yields under mild conditions. Therefore, it is hypothesized that trichloroacetimidates would be effective esterification reagents under near neutral conditions, without the need of an acid catalyst. Initial studies in the Chisholm group showed that both diphenylmethyl (DPM) (**2.25**) and 4-methoxybenzyl (PMB) (**2.27**) imidates

could form esters at room temperature without the need for a promoter, as shown in Scheme 2.5.[53, 54] Additionally spontaneous esterification with glycosyl imidates has been reported.[47, 55] These promoter-free esterifications were shown to function well with sensitive carboxylic acids which decompose under more standard esterification conditions.[53, 56] These esterifications are notable as imidates are simple to prepare from inexpensive precursors, formed at room temperature from the alcohol and trichloroacetonitrile with a catalytic amount of DBU.[57] In addition, the trichloroacetamide side product may be removed by washing with aqueous NaOH solution, since the pKa of this acetamide is similar to a phenol (pKa of approximately 11). This is an advantage over isourea-based esterification reagents, which require chromatography to remove the side product. Given the utility and availability of trichloroacetimidates, the scope of these transformations was explored further.

Scheme 2.5 Esterification Reactions with Imidates Under Promoter Free Conditions

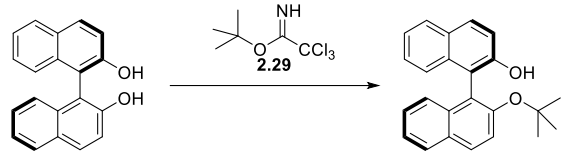


Results and Discussion Part 1: BINOL alkylations using trichloroacetimidates

In order to evaluate the direct, promoter free alkylation of BINOL with trichloroacetimidates, initial experiments were performed with BINOL **2.4** and *tert*-butyl 2,2,2-trichloroacetimidate **2.10** (Table 2.1 and Table 2.2) or diphenylmethyl 2,2,2-trichloroacetimidate

2.25 (Table 2.3). Previously our group has had some success with the alkylation of more acidic oxygen,[23-25, 58] sulfur,[26] nitrogen,[27] and some carbon[28] nucleophiles without the addition of an exogenous acid catalyst. *tert*-Butyl 2,2,2-trichloroacetimidate **2.28** was used to model the addition of a bulky group, and because this reagent is readily available from commercial sources. First a solvent screen was performed (Table 2.1, Entries 1-4). Non-polar solvents were used as the rearrangement of the imidate to the corresponding trichloroacetamide was slower in these solvents. 1,2-Dichloroethane (DCE) was found to be the optimal solvent, providing the highest yield (33%) after refluxing for 18 hours. This a significant improvement from the current values in literature (10-15%).[59] Additionally, removal of the trichloroacetamide byproduct can be easily accomplished via flash chromatography. A number of promoters were employed at room temperature to improve the yield further (Table 2.1, Entries 5-7), unfortunately, none of these reactions afforded desired product, but instead a mixture of Friedel-Crafts C-alkylation products was formed.

Table. 2.1. Etherification Reaction Conditions



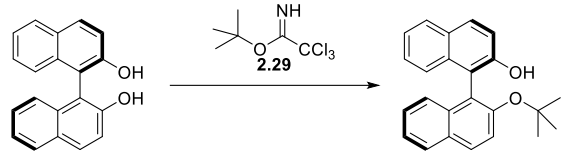
2.4 2.30

Entry[a]	Solvent	Imidate (equiv)	Catalyst	Temp. (°C)	Isolated yield (%)
1	toluene	2	-	reflux (111 °C)	17
2	xylene	2	-	reflux (138 °C)	0[b]
3	$MeNO_2$	2	-	reflux (101 °C)	16
4	***DCE***	***2***	**-**	***reflux (85 °C)***	***33***
5	DCE	2	20 mol % CSA	rt	0
6	DCE	2	20 mol % TMSOTf	rt	0
7	DCE	2	20 mol % BF_3•OEt_2	rt	0

[a] reactions were run for 18 h. [b] complex mixture of side products

The effects of changing the amounts of imidate **2.10** and the reaction concentration was then explored. Reducing the number of equivalents of imidate **2.10** reduced the yield (Table 2.2 Entry 1). It was previously found in the Chisholm lab that increasing the concentration of in alkylation of diols using trichloroacetimidates improved the yield.[60] With this in mind, the reaction was tested at a number of different concentrations. This trend held true in this system as well, the more concentrated the reaction the higher the yield, as seen in Table 2.3 Entries 6-9. The yield was improved significantly to 65% when using 4 equivalents of imidate and keeping the BINOL concentration at 1.0 M (Table 2.3, Entry 9). It is known that heating BINOL for long periods of time can racemize the BINOL.[61, 62] However, this did not occur during this reaction. This was determined via chiral HPLC analysis of the BINOL product **2.30** as compared to a sample prepared from racemic BINOL. Therefore, this methodology could be used to make chiral BINOL-based catalysts or ligands without racemization.

Table 2.2. Concentration and Imidate Equivalents Screening Reactions



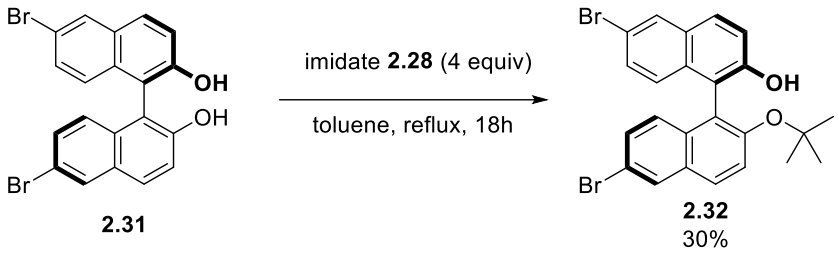
2.4 2.30

Entry	Solvent	Concentration	Imidate (equiv)	Temp. (°C)	Yield (%)
1	DCE	0.3	1	85	9
2	DCE	0.3	2	85	33
3	DCE	0.3	3	85	23
4	DCE	0.3	4	85	33
5	DCE	0.3	5	85	12
6	DCE	0.5	4	85	34
7	***DCE***	***1.0***	***4***	***85***	***65***
8	DCE	0.1	4	85	25
9	DCE	0.05	4	85	13

This methodology was then tested on the brominated BINOL derivative **2.31** (Scheme 2.6). The reaction proceeded with moderate yield under the optimized conditions. While the yield

decreased from optimized conditions, the electron withdrawing groups on BINOL **2.31** could slow the reaction down. It is possible that this phenoxide is a weaker nucleophile and is not trapping the cation efficiently from the imidate. Even though the rate determining step typically is cation formation, if the nucleophilic attack is slow, it is possible the t-butyl cation is undergoing elimination before the phenoxide attacks to form the product. Further exploration into the substrate scope is needed to determine the reason for the difference in yield.

Scheme 2.6. BINOL-**2.31** Alkylation

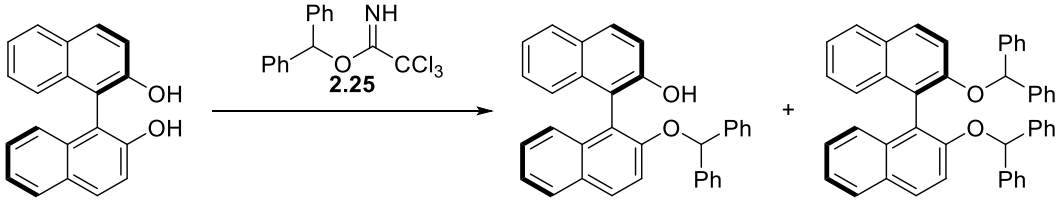


2.31

2.32
30%

When applying these reaction conditions to secondary imidates such as diphenylmethyl imidate **2.25**, we hypothesized that this addition would occur under similar conditions to the *t*-butyl imidate. However, when using excess of the diphenylmethyl imidate **2.25**, the dialkylation product **2.34** was observed in high yield (table 2.3, entry 1). Varying the equivalents showed that monoalkylation could be achieved in moderate yield when using one equivalent of imidate. When using 1.2 equivalents of imidate the yield of monoalkylated product **2.33** improved to 81% (compare Table 2.3, Entries 2 and 5).

Table 2.3 Etherification Conditions using DPM imidate **2.25**

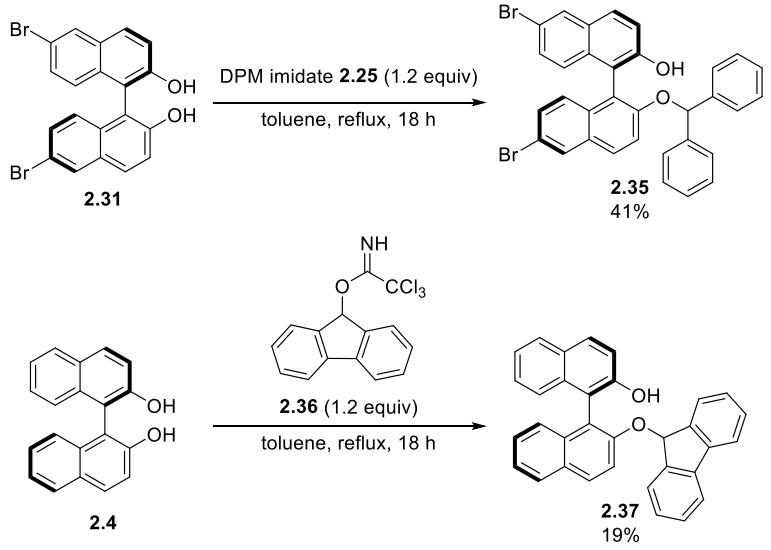


2.4 2.33 2.34

Entry	Solvent	Imidate	Temp. (°C)	Time	Yield (2.33)	Yield (2.34)
1	toluene	4	111	18 h	0	98
2	toluene	1	111	18 h	57	7
3	toluene	2	111	18 h	23	67
4	toluene	3	111	18 h	9	90
5	toluene	1.2	111	18 h	81	12
6	toluene	1.5	111	18 h	24	23

A couple of other examples of these O-alkylations were attempted in similar systems (Scheme 2.7). First a different BINOL was used, **2.31**, and 42% of the monoalkylated DPM ether product was isolated. It is possible having electron withdrawing groups on the aromatic rings deactivates the phenoxide, and the weaker nucleophile is not trapping the cation from the imidate efficiently, leading to C-alkylation side products. Then, a different secondary imidate **2.36**, was employed. This also resulted in a lower yield (19%), perhaps due to the highly reactive nature of the imidate. In the future a number of other imidates and BINOLs will be explored to determine if these reactions can be executed with a general protocol or whether different conditions are necessary for each imidate and BINOL.

Scheme 2.7. Initial Substrate Scope using Secondary Imidates

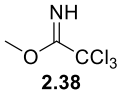
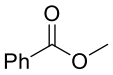
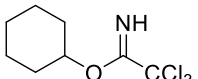
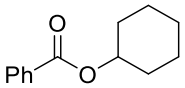
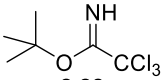
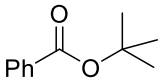
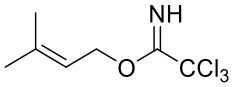
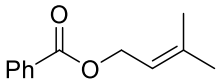
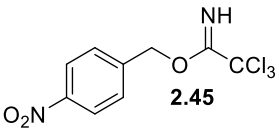
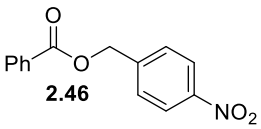


Results and Discussion Part 2: Promoter Free Esterifications with Trichloroacetimidates

Prompted by the need for mild esterification reagents, we began to further explore trichloroacetimidate esterifications, focusing on reaction conditions that do not need an acid promotor. Initially, the esterifications were studied with a number of different trichloroacetimidates to determine the scope with regard to trichloroacetimidate electrophile using benzoic acid as the nucleophile (Table 2.4). Simple alkyl trichloroacetimidates did not undergo esterification at room temperature or in refluxing toluene (Entries 1-2) with the exception being the *tert*-butyl trichloroacetimidate **2.28** (Entry 3). Curiously, the esterification with imidate **2.28** and benzoic acid gave a higher yield at room temperature in DCM than in refluxing toluene. This may be due to the tendency of imidate **2.28** to undergo elimination at elevated temperatures, decomposing to isoprene and trichloroacetamide. This has been reported to be a limitation in the formation of *tert*-butyl amines when using this imidate.[63] The prenyl trichloroacetimidate **2.43** gave a useful 73% yield of product at room temperature (Entry 4). While nearly all of the product was the prenyl ester **2.44**, a trace amount of the *tert*-prenyl isomer was detected in the ^{1}H NMR.

Benzylic trichloroacetimidates are of special interest, as these are some of the most common esters utilized in organic synthesis.[64, 65] However, benzylic imidates with electron-withdrawing substituents were unreactive under these promoter-free conditions, as shown by the lack of ester formation with the 4-nitrobenzyl trichloroacetimidate **2.45** (Entry 5).

Table 2.4 Esterification with Different Imidates

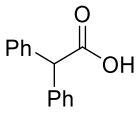
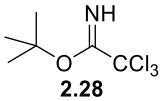
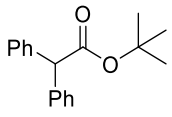
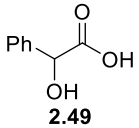
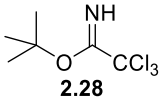
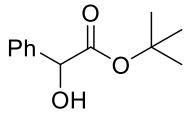
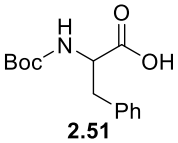
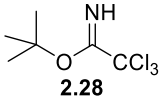
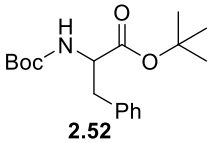
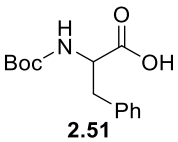
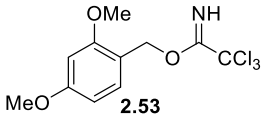
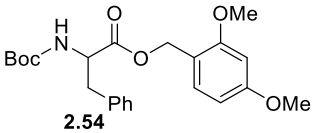
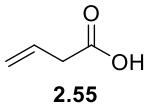
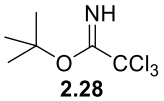
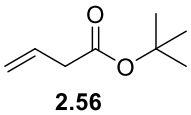
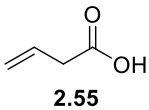
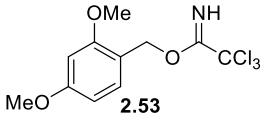
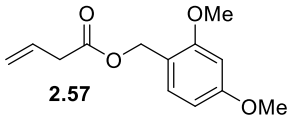
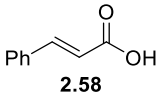
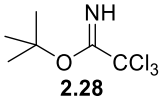
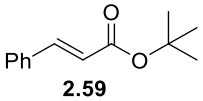
Entry	Imidate	Ester	Yield (%)[a]	Yield (%)[b]
1	 **2.38**	 **2.39**	0 (48h)	0 (18h)
2	 **2.40**	 **2.41**	0 (48h)	0 (18h)
3	 **2.28**	 **2.42**	84 (48h)	17 (18h)
4	 **2.43**	 **2.44**	73[c] (16h)	-
5	 **2.45**	 **2.46**	-	0 (48h)

[a]Isolated yield (DCM, rt). [b]Isolated yield (toluene, reflux). [c]Trace of the *tert*-prenyl isomer detected in the ^{1}H NMR.

A brief selection of carboxylic acids were esterified with *t*-butyl imidate **2.28** and (2,4-dimethoxyphenyl)methyl-2,2,2-trichloroacetimidate **2.53** to determine the effects of the carboxylic acid structure on the esterification reaction (Table 2.5). Initially the effects of the steric environment near the carboxylic acid were examined. Use of diphenylacetic acid **2.47** provided high yield of the corresponding ester (Table 2.5, Entry 1). The ability to form esters in the presence of other protic functionality was also investigated. Mandelic acid **2.49** was esterified under these conditions, demonstrating that the presence of an alcohol was well tolerated, providing a moderate

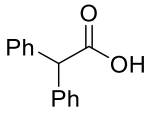
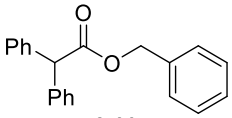
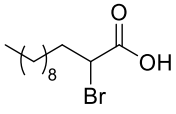
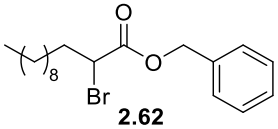
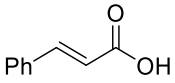
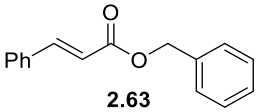
yield with *tert*-butyl imidate (Table 2.5, Entry 2). The protected amino acid (±)-Boc-phenylalanine **2.51** was also esterified under these conditions (Entries 3 and 4). The propensity of alkene isomerization under these reaction conditions was also explored. Vinyl acetic acid **2.55** was esterified in good yield under with DMB imidate **2.53** without any observed isomerization of the alkene. However, the *tert*-butyl ester of vinyl acetic acid **2.55** proved to be quite volatile and therefore was difficult to obtain a high isolated yield. Cinnamic acid **2.59** also proved to be a good substrate, providing the corresponding ester in good yield.

Table 2.5. Carboxylic Acid Scope with *t*-butyl Or Dimethoxybenzyl Imidate

Entry	Acid	Imidate	Product	Time (h)	Yield (%)
1	 **2.47**	 **2.28**	 **2.48**	48	81
2	 **2.49**	 **2.28**	 **2.50**	48	59
3	 **2.51**	 **2.28**	 **2.52**	48	62
4	 **2.51**	 **2.53**	 **2.54**	24	80
5	 **2.55**	 **2.28**	 **2.56**	48	30
6	 **2.55**	 **2.53**	 **2.57**	0.5	73
7	 **2.58**	 **2.28**	 **2.59**	48	60

The scope of the esterification reaction in refluxing toluene with benzyl trichloroacetimidate **2.66** was also explored (Table 2.6), as benzyl groups are common carboxylate protecting groups. The series of carboxylic acids underwent esterification in good yields. Additionally, no elimination products from the α-bromoacid **2.61** were observed, and the less reactive carboxylic acid **2.58** was also esterified under these conditions in good yield.

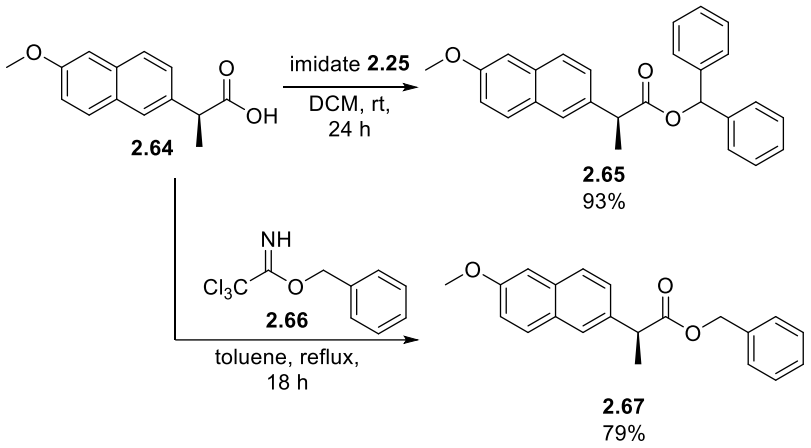
Table 2.6. Esterification of Benzyl Trichloroacetimidate in Refluxing Toluene

Entry	Carboxylic acid	Product	Yield (%)
1	 **2.47**	 **2.60**	78
2	 **2.61**	 **2.62**	80
3	 **2.58**	 **2.63**	77

The effects of these esterification reactions on a substrate with a chirality center next to the carboxylate were also investigated (Scheme 2.8). Chiral naproxen **2.64** was utilized for this study, since this substrate can racemize quickly as the chirality center is both benzylic and next to the electron-withdrawing carboxylate. Treatment of chiral naproxen with imidate **2.25** at room temperature in DCM gave the desired ester products in high yields. Evaluation of the enantiopurity of these samples by chiral HPLC analysis showed that virtually no racemization had occurred. While these results ensured that there was no racemization under these conditions, it did not provide information about the possibility of racemization with less reactive benzylic imidates which required refluxing toluene to affect the esterification. To address this, naproxen was heated

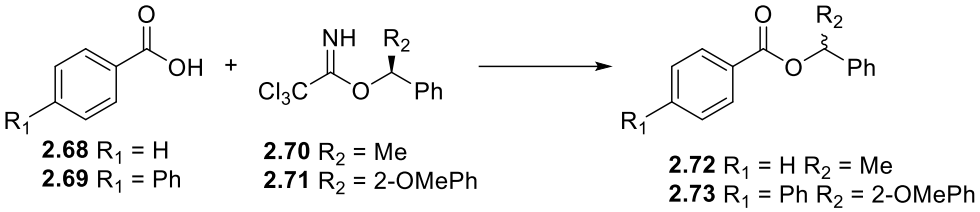
in refluxing toluene with benzyl trichloroacetimidate **2.66** to provide a 79% yield of benzyl ester **2.67**. Chiral HPLC analysis of **2.67** showed that virtually no racemization had occurred with this substrate compared to a racemic sample (racemic samples of **2.65** and **2.67** were prepared by heating the chiral esters with DBU in toluene).

Scheme 2.8. Esterification of Naproxen without Racemization



The mechanism of the esterification was briefly investigated by the use of two chiral imidate substrates in the esterification reaction. Chiral phenethyl trichloroacetimidate **2.70** has already been reported,[66, 67] and was therefore employed in the esterification reaction. In addition, the imidate of (S)-(2-methoxyphenyl)phenylmethanol[68] (imidate **2.71**) was also prepared. During the course of the esterification with chiral **2.70** substantial racemization was observed, with a completely racemic mixture being observed in refluxing toluene. Additionally, a 71:29 mixture of enantiomers was observed in DCM at room temperature (Table 2.7). Similar results were observed with imidate **2.71**, with a nearly racemic mixture being isolated in refluxing toluene and a scalemic 67:33 mixture being isolated from the esterification in DCM at room temperature.

Table 2.7 Esterification with Enantioenriched Imidates



2.68 R_1 = H
2.69 R_1 = Ph

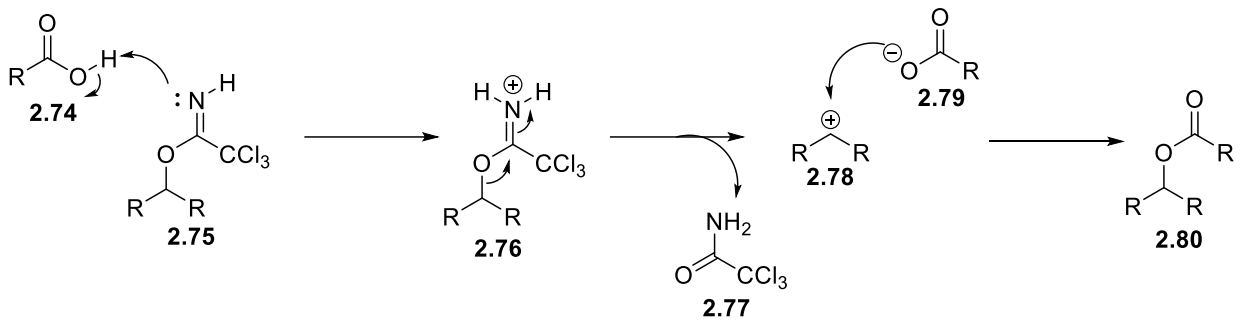
2.70 R_2 = Me
2.71 R_2 = 2-OMePh

2.72 R_1 = H R_2 = Me
2.73 R_1 = Ph R_2 = 2-OMePh

Entry	Imidate	Conditions	Yield (%)	e.r.
1	2.69	toluene, Δ, 24 h	95	50:50
2	2.69	DCM, rt, 24 h	35	71:29
3	2.70	toluene, Δ, 24 h	73	55:45
4	2.70	DCM, rt, 24 h	60	67:33

Since there was significant racemization observed with chiral imidates, an S_N2 type substitution mechanism was ruled out, as an S_N2 mechanism proceeds with inversion. This left either a radical or a cationic mechanism as possibilities for the formation of the esters. Given that a radical substitution reaction should proceed well with an electron poor imidate (like **2.45**), it seemed unlikely that a radical intermediate was involved. The available evidence seems to indicate a cationic mechanism, as shown in Figure 2.2. First, symbiotic activation of the imidate with the proton from carboxylic acid forms intermediate **2.76**. Loss of trichloroacetamide **2.77** then provides the carbocation **2.78**, which is trapped by the carboxylate anion **2.79** to give the ester product **2.80**. Further supporting this mechanism, is that the addition of triethylamine to esterifications with paramethoxyimidate[54] and diphenylmethyl imidate **2.25**[53] effectively poisoned the reaction and halted the esterification, as reported in literature. The more basic amine likely deprotonates the carboxylic acid, stopping the activation of the imidate and interrupting the esterification. While carbocation formation is predicted to provide a racemic mixture, scalemic mixtures can occur from cationic processes due to ion pairing.[69]

Figure 2.2. Ester formation via Symbiotic Activation of the Trichloroacetimidate



Conclusions and Future Work:

Mono-O-alkylated 1,1′-bi-2-naphthols (BINOLs) are commonly used as a source of chirality for a number of reagents and catalysts in asymmetric transformations. While the alkylation of BINOL can be achieved with primary and secondary alkyl halides or under Mitsunobu conditions, the yields of these alkylations with tertiary alkyl halides or alcohols are very low. Typically, bulky groups help achieve enantioselectivity. In order to access BINOLs with bulky groups on one of the phenolic oxygens, a new method was developed using trichloroacetimidates as electrophiles. This was accomplished under thermal conditions in DCE without the use of a Lewis or Bronsted acid promoter. The monoalkylation using t-butyl-2,2,2-trichloroacetimidate was achieved in moderate yield (65%), which is a significant improvement to current literature procedures (10-15%). Additionally, even under the thermal conditions, virtually no racemization occurred. Therefore, these conditions could facilitate access to the chiral products for new catalyst development. When applying this methodology to secondary imidates, moderate yields were achieved. However, this protocol utilizes mild conditions and avoids the use of any exogenous acid or base and minimizes byproduct formation. Further studies into the substrate scope will need to be performed to fully assess the utility of the reaction.

Trichloroacetimidates electrophiles were also employed in the synthesis of esters under mild conditions. Imidates that are precursors to stabilized carbocations were reliable esterification

reagents under promoter free conditions. These esterifications were accomplished at room temperature in DCM, or simple heating in refluxing toluene. Under these conditions, no alkene isomerization or alkylation of other protic functional groups occurred. This provides a useful methodology for complex systems or natural product synthesis. The mechanism of the reaction was briefly studied with chiral imidates. During the course of the reaction, racemization was observed, which combined with other observed results appears to implicate a cationic mechanism.

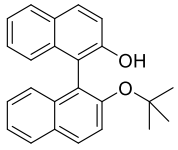
Experimental:

General Experimental Information

All anhydrous reactions were run under a positive pressure of argon. DCM (DCM) was dried by passage through an alumina column.[171] 1,2-Dichloroethane (DCE) was freshly distilled from calcium hydride before use. Silica gel column chromatography was performed using 60 Å silica gel (230−400 mesh). The methyl-2,2,2-trichloroacetimidate **10**, *t*-butyl-2,2,2-trichloroacetimidate **13**, and benzyl-2,2,2-trichloroacetimidate **17** used in these studies were purchased from commercial sources. Cyclohexyl-2,2,2-trichloroacetimidate **12**,[172] prenyl-2,2,2-trichloroacetimidate **15**,[173] (4-nitrophenyl)methyl-2,2,2-trichloroacetimidate **23**,[174] 1-phenethyl-2,2,2-trichloroacetimidate **25**,[22, 168] diphenylmethyl-2,2,2-trichloroacetimidate **26**[17, 20] and (2-methoxyphenyl)phenylmethyl-2,2,2-trichloroacetimidate **29**[27] were synthesized as previously reported.

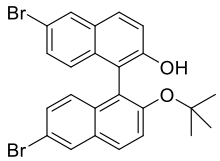
General Procedure for the alkylation of BINOL using tertiary trichloroacetimidates:

A round bottom flask was charged with (*R*)-BINOL (1 equiv) and *t*-butyl trichloroacetimidate (4 equiv) and put under an atmosphere of argon. Dry DCE was added to form a 1.0 M solution and the flask was heated to reflux (85 °C). The reaction was left to stir at reflux for 18h. After 18h, the reaction was cooled to room temperature and purified by dry loading silica gel flash column chromatography. Some BINOL products show additional carbon peaks in the NMR. After the monoalkylation more sigma bonds are hindered and reduces the symmetry.



2.30

Ether 2.30 : $[\alpha]^{20}_{D}$ -183.1 (*c* 0.49, DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91-7.81 (m, 4H), 7.46 (d, *J*= 8.7 Hz, 1H), 7.39-7.34 (m, 2H), 7.29-7.18 (m, 4H), 7.07 (d, *J*= 8.4 Hz, 1H), 5.62 (s, 1H), 1.06 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ; 152.6, 151.7, 133.9, 133.8, 130.8, 129.8, 129.7, 129.0, 128.0, 126.7, 126.4, 126.0, 125.8, 124.7, 123.8, 123.1, 118.5, 116.9, 81.0, 29.2; enantiomeric ratio was determined by HPLC using a chiral column (OJ-H), n-hexane:i-PrOH = 20:1, 1 mL/min; compared to a racemic sample which showed two peaks t_R = 7.4 and 9.3 min.



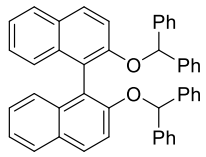
2.32

Ether 2.32: mp: 75-78 °C; TLC R_f = 0.46 (20% ethylacetate/80% hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, *J*= 19.2, 1.7 Hz, 2H), 7.81 (dd, *J*= 17.4, 9.0 Hz, 2H), 7.49 (d, *J*= 9.0 Hz, 1H), 7.36 (d, J= 8.8 Hz, 1H), 7.31-7.24 (m, 2H), 6.99 (d, *J*= 9.0 Hz, 1H), 6.88 (d, J= 9.0 Hz, 1H), 5.64 (s, 1H), 1.08 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ; 152.6, 151.7, 133.9, 133.8, 130.8, 129.8, 129.7, 129.0, 128.0, 126.7, 126.4, 126.0, 125.8, 124.7, 123.8, 123.1, 118.5, 116.9, 81.0, 29.2; Anal. Calcd for $C_{24}H_{20}Br_2O_2$: C, 57.63; H, 4.03; Found: C, 57.58; H, 4.00.

General Procedure for the alkylation of BINOL using secondary trichloroacetimidates:

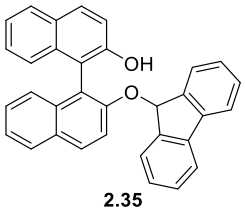
A round bottom flask was charged with (*R*)-BINOL (1 equiv) and diphenylmethyl-2,2,2-trichloroacetimidate (1.2 equiv) and put under an atmosphere of argon. Dry toluene was added to form a 1.0 M solution and the flask was heated to reflux (111 °C). The reaction was left to stir at

reflux for 18h. After 18h, the reaction was cooled to room temperature and purified by dry loading silica gel flash column chromatography. Some BINOL products show additional carbon peaks in the NMR. After the monoalkylation more sigma bonds are hindered and reduces the symmetry.



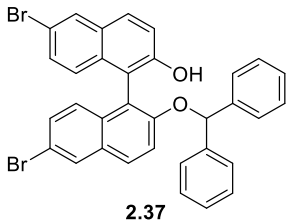
2.34

Ether 2.34: IR:3059, 3027, 1713, 1493, 693; mp: 50-53 °C; TLC in 5% ethylacetate/90% hexanes R_f = 0.43; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, *J*= 8.1, 15.4 Hz, 4H), 7.39-7.35 (m, 3H), 7.33-7.29 (m, 3H), 7.26-7.20 (m, 8H), 7.08-6.99 (m, 9H), 6.95-6.92 (m, 5H), 6.03 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 153.7, 142.0, 141.9, 139.8, 134.3, 130.1, 129.6, 129.4, 129.0, 128.9, 128.3, 128.2, 128.1, 128.0, 127.8, 127.3, 127.2, 127.0, 126.7, 126.2, 126.1, 125.8, 123.7, 121.5, 116.9, 82.5; Anal. Calcd for $C_{46}H_{34}O_2$: C, 89.29; H, 5.54; Found: C, 89.04; H, 5.64



2.35

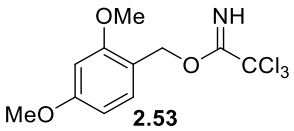
Ether 2.35: IR: 3504, 3055, 2979, 1584, 732 mp: 90-94 °C TLC R_f: 0.35 10% ethylacetate/90% hexanes NMR: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94-7.75 (m, 4H), 7.59-7.52 (m, 2H), 7.44-7.39 (m, 1H), 7.34-7.02 (m, 13H), 5.77 (s, 1H), 5.10 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 154.6, 151.5, 142.6, 142.5, 140.3, 140.2, 134.1, 133.8, 130.5, 130.3, 129.2, 129.1, 129.0, 128.2, 128.1, 127.7, 127.5, 127.2, 126.6, 125.5, 125.4, 125.1, 124.8, 123.4, 120.1, 120.0, 119.9, 118.6, 117.7, 115.1, 81.5; Anal. Calcd for $C_{33}H_{22}O_2$: C, 87.89; H, 4.92; Found: C, 87.62; H, 5.21.



2.37

Ether 2.37: IR: 3510, 3060, 1581, 1491, 696; mp: 75-79 °C; TLC in 10% ethylacetate/90% hexanes R_f = 0.32; NMR: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (dd, *J*= 1.6, 15.6 Hz, 2H), 7.74 (dd, *J*= 9.1, 15.6 Hz, 2H), 7.36 (d, *J*= 9.4 Hz, 1H), 7.29 (d, *J*= 8.8 Hz, 1H), 7.25 (dd, *J*= 1.6, 8.7 Hz, 1H), 7.18-7.08 (m, 4H), 7.04-6.94 (m, 6H), 6.82 (d, *J*= 7.0 Hz, 2H), 6.76 (d, *J*= 9.1 Hz, 1H), 6.16 (s, 1H), 4.85 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 154.3, 151.8, 140.9, 140.7, 132.5, 132.3, 130.7, 130.5, 130.3, 130.1, 130.0, 129.9, 129.7, 129.2, 128.5, 128.3, 127.7, 127.6, 126.8, 126.7, 126.6, 126.4, 126.3, 126.3, 118.8, 118.5, 117.8, 117.2, 117.1, 114.9, 82.5; Anal. Calcd for $C_{33}H_{22}Br_2O_2$: C, 64.94; H, 3.63; found: C, 64.91; H, 3.61

General Procedure for the synthesis of trichloroacetimidates from the corresponding alcohol: A flame dried 25 mL round bottom flask was charged with the alcohol starting material (1 equiv) under argon. Dry DCM was then added to form a 0.5 M solution, and the flask was cooled to 0 °C. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 0.2 equiv) was added to the solution, followed by trichloroacetonitrile (1.5 equiv). The reaction was monitored by TLC. After completion of the reaction, reaction mixture was concentrated, and silica gel column chromatography was performed to provide the desired trichloroacetimidates.

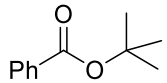


2.53

(2,4-Dimethoxyphenyl)methyl-2,2,2-trichloroacetimidate 2.53. Yellow oil (7.40 g, 99%), purified by silica gel chromatography (30% ethyl acetate/ 69% hexanes/ 1% triethylamine). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 6.49 (t, *J* = 2.4 Hz, 2H), 5.30 (s, 2H), 3.81 (s, 3H), 3.81 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 162.9, 161.3, 158.8, 130.6, 116.4, 104.0, 98.6, 98.4, 91.7, 66.6, 55.4; Anal. Calcd for $C_{11}H_{12}Cl_3NO_3$: C, 42.27; H, 3.87; N, 4.48. Found: C, 42.28; H, 3.56; N, 4.57.

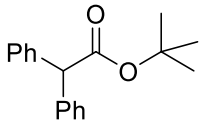
General procedure for esterification by method A: In a flame dried flask, the trichloroacetimidate (2 equiv) was dissolved in dichloromethane (0.25 M) under argon. The carboxylic acid (1 equiv) was then added and the mixture was stirred at room temperature. The reaction progress was monitored by thin layer chromatography. After completion the reaction mixture was poured into 2N NaOH and extracted with DCM (3x). The combined organic extracts were then dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography to give the ester product.

General procedure for esterification by method B: The carboxylic acid (1 equiv) and trichloroacetimidate (2 equiv) were placed in a flame dried round bottom flask under argon. Anhydrous toluene (0.25 M) was then added and the reaction was heated to reflux. The reaction progress was monitored by thin layer chromatography. After disappearance of the carboxylic acid the mixture was allowed to cool to rt, poured into 2N NaOH and extracted with DCM (3x). The combined organic extracts were then dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography to give the ester product.



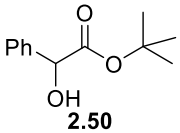
2.42

tert-Butyl benzoate 2.42. Clear oil (0.097 g, 84%), purified by silica gel chromatography (1% ethyl acetate/99% hexane). TLC R_f = 0.53 (10% ethyl acetate/ 90% hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01-7.91 (m, 2H), 7.55-7.49 (m, 1H), 7.41 (t, *J* = 7.6 Hz, 2H), 1.60 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 165.8, 132.4, 132.0, 129.4, 128.2, 81.0, 28.2.



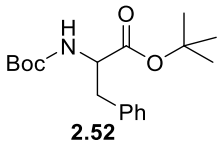
2.48

tert-Butyl 2,2-diphenylacetate 2.48.[175] White solid (0.064 g, 91%), purified by silica gel chromatography (2% ethyl acetate/98% hexanes). TLC R_f = 0.68 (10% ethyl acetate/90% hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.23 (m, 10 H), 4.91 (s, 1H), 1.44 (s, 9H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 171.7, 139.2, 128.6, 128.5, 127.0, 81.3, 58.0, 28.0.



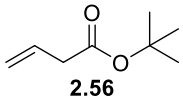
2.50

(±)-tert-Butyl-2-hydroxy-2-phenylacetate 2.50.[176] White solid (0.079 g, 59%), purified by silica gel chromatography (5% ethyl acetate/95% hexanes). TLC R_f = 0.65 (50% ethyl acetate/50% hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.30 (m, 5H), 5.03 (d, J = 6.0 Hz, 1H), 3.53 (d, J = 6.0 Hz, 1H), 1.40 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 172.9, 139.0, 128.4, 128.1, 126.4, 83.1, 73.0, 27.8.



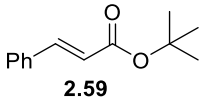
2.52

(±)-(tert-Butyl-2-[(tert-butoxycarbonyl)amino]phenylpropionate 2.52.[177] Clear oil (0.90 g, 90%), purified by silica gel chromatography (4% ethyl acetate/96% hexanes). TLC R_f = 0.75 (10% ethyl acetate/90% hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.16 (m, 5H), 5.00 (brs, 1H), 4.45-4.44 (m, 1H), 3.05 (d, J = 5.8 Hz, 2H), 1.42 (s, 9H), 1.40 (s, 9H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 171.0, 155.1, 136.4, 129.6, 128.3, 126.8, 82.0, 79.6, 54.9, 38.6, 28.3, 27.9.



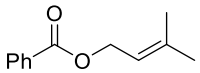
2.56

2,2-Dimethylpropyl but-3-enoate 2.56.[178] Clear colorless oil (70 mg, 35% yield), purified by silica gel column chromatography (10% diethyl ether, 90% pentane). TLC R_f = 0.76 (10% ethyl acetate/ 90% hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88-5.78 (ddt, *J*= 13.9, 9.8, 7.0 Hz, 1H), 5.06 (m, 2H), 2.93 (d, J = 6.9 Hz, 2H) 1.38 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz $CDCl_3$) δ 170.8, 130.9, 117.9, 80.5, 40.4, 28.0.



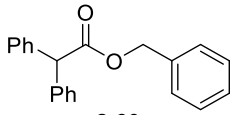
2.59

(E)-tert-Butyl cinnamate 2.59[179] Clear oil (0.052 g, 60%), purified by silica gel chromatography (1-4% ethyl acetate/hexanes). TLC R_f = 0.71 (10% ethyl acetate/90% hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 16.0 Hz, 1H), 7.50-7.49 (m, 2H), 7.36-7.36 (m, 3H), 6.37 (d, J = 16.0 Hz, 1H), 1.54 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 166.3, 143.5, 134.7, 129.9, 128.8, 128.0, 120.2, 80.5, 28.2.



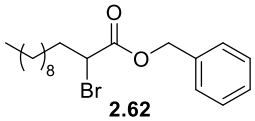
2.44

3-Methylbut-2-en-1-yl benzoate 2.44.[180] Clear colorless oil (0.126 g, 63% yield), purified by silica gel column chromatography (10% ethyl acetate, 90% hexanes). TLC R_f = 0.60 (10% ethyl acetate/ 90% hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08- 8.06 (m, 2H), 7.58-7.53 (m, 1H), 7.44 (t, J = 7.8 Hz, 2H) 5.52-5.48 (m, 1H), 4.85 (d, J= 7.2 Hz, 2H), 1.80 (d, J = 6.3 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz $CDCl_3$) δ 166.6, 139.1, 132.8, 130.5, 129.6, 128.3, 118.8, 61.9, 25.8, 18.1.



2.60

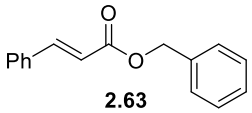
(Phenyl)methyl 2,2-diphenylacetate 2.60.[181] White solid (0.079 g, 88%), purified by silica gel chromatography (2% ethyl acetate/98% hexanes). TLC R_f = 0.60 (10% ethyl acetate/90% hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.25 (m, 15H), 5.17 (s, 2H), 5.07 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 172.4, 138.7, 135.8, 128.73, 128.68, 128.24, 128.21, 127.36, 127.33, 68.0, 57.1.



2.62

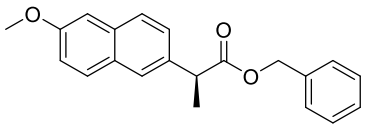
(Phenyl)methyl 2-bromododecanoate 2.62. Clear oil (0.193 g, 80%), purified by silica gel chromatography (3% ethyl acetate/97% hexane). TLC R_f = 0.68 (10% ethyl acetate/90% hexanes); IR (film, cm^{-1}) υ_{max} 3054, 2928, 2305, 1740, 1422, 1265, 738; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.35 (m, 5H), 5.20 (s, 2H), 4.25 (t, *J* = 7.3 Hz, 1H), 2.06-1.95 (m, 2H), 1.35-1.21 (m, 16H), 0.88 (t, *J* = 6.6 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.7, 135.2, 128.8, 128.6, 128.5, 128.3, 128.2, 70.7, 67.5, 46.0, 34.9, 31.9, 29.5, 29.5, 29.3, 28.8, 27.2, 22.7, 14.1. Anal. Calcd for

$C_{19}H_{29}BrO_2$: C, 61.79; H, 7.91. Found: C, 61.69; H, 8.01.



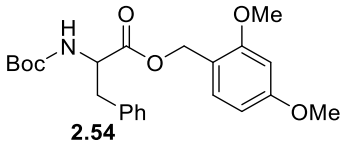
2.63

(Phenyl)methyl cinnamate 2.63.[182] Viscous oil (0.120 g, 77%), purified by silica gel chromatography (2% ethyl acetate/98% hexanes). TLC R_f = 0.63 (10% ethyl acetate/90% hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, J = 15.9 Hz, 1H), 7.47-7.44 (m, 2H), 7.36-7.27 (m, 8H), 6.42 (d, J = 16.2 Hz, 1H), 5.18 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.8, 145.2, 136.1, 134.4, 130.4, 128.9, 128.6, 128.3, 128.3, 128.1, 117.9, 66.4.



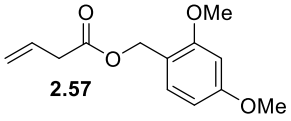
2.67

(S)-(Phenyl)methyl-2-(6-methoxynaphthalen-2-yl)propanoate 2.67. Yellow solid (0.110 g, 79%), purified by silica gel chromatography (2% ethyl acetate/98% hexanes). $[\alpha]_D^{23}$ -3.7 (*c* 0.35, DCM); mp = 72-73 °C; TLC R_f = 0.48 (10% ethyl acetate/90% hexanes); IR (film, cm^{-1}) υ_{max} 3055, 2982, 1733, 1634, 1265, 738; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70-7.65 (m, 3H), 7.41 (d, J = 1.6 Hz, 1H), 7.28-7.25 (m, 5H), 7.14-7.11 (m, 2H), 5.11 (q, J = 12.4 Hz, 2H), 3.93-3.88 (m, 4H), 1.59 (d, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 174.5, 157.6, 136.0, 135.6, 133.7, 129.3, 128.9, 128.5, 128.1, 127.9, 127.1, 126.3, 126.0, 119.0, 105.6, 66.5, 55.3, 45.5, 18.5. Anal. Calcd for $C_{21}H_{20}O_3$: C, 76.10; H, 6.01. Found: C, 76.35; H, 5.64. The er was determined by chiral HPLC (OD-H), n-hexane:*i*-PrOH = 99:1, 1 mL/min; t_1 = 10.1; t_2 = 12.2 min.



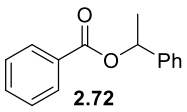
2.54

(±)-(2,4-Dimethoxyphenyl)methyl-2-[(tert-butoxycarbonyl)amino]phenylpropionate 2.54. Clear oil (0.101 g, 80%), purified by silica gel chromatography (15 % ethyl acetate/ 85% hexanes). TLC R_f = 0.37 (40% ethyl acetate/ 60% hexanes); IR (film, cm^{-1}) υ_{max} 3054, 2985, 1709, 1421, 1261, 739; ^1H NMR (300 MHz, CD_3OD) δ 7.26-7.16 (m, 6H), 6.56 (d, *J* = 2.2 Hz, 1H), 6.50 (dd, *J* = 8.3, 2.3 Hz, 1H), 5.11 (q, *J* = 12.1 Hz, 2H), 4.38 (q, *J* = 6.0 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.10 (dd, *J* = 13.9, 5.6 Hz, 1H), 2.91 (dd, *J* = 13.7, 8.6 Hz, 1H), 1.39 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, CD_3OD) δ 172.3, 161.7, 159.0, 156.4, 136.9, 131.2, 128.9, 128.0, 126.4, 116.0, 104.1, 97.9, 79.2, 62.1, 55.2, 54.6, 54.4, 37.3, 27.3. Anal Calcd for $C_{23}H_{29}N$: C, 66.49; H, 7.04; N, 3.37. Found: C, 66.20; H, 6.93; N, 3.76.



2.57

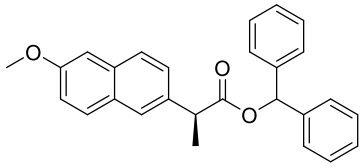
(2,4-Dimethoxyphenyl)methyl but-3-enoate 2.57. Clear oil (0.163 g, 73%), purified by silica gel chromatography (15% ethyl acetate/85% hexanes). TLC R_f = 0.40 (15% ethyl acetate/85% hexanes); IR (film, cm^{-1}) υ_{max} 2963, 2838, 2616, 1464, 1371, 1209, 739; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.9 Hz, 1H), 6.46 (m, 2H), 6.00-5.87 (ddt, *J*= 14.1, 9.9, 7.2 Hz, 1H), 5.18-5.11 (m, 4H), 3.81 (s, 3H), 3.80 (s, 3H), 3.11 (dt, *J* = 6.9, 1.4 Hz, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 171.6, 161.3, 159.0, 131.4, 130.5, 118.4, 116.7, 104.1, 98.6, 61.9, 55.5, 55.4, 39.2. Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 65.91; H, 6.47.



2.72

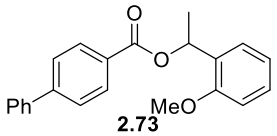
1-Phenethyl benzoate 2.72.[182] Clear oil (0.140 g, 95%), purified by silica gel chromatography

(2% ethyl acetate/98% hexane). TLC R_f = 0.23 (10% ethyl acetate/ 90% hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10-8.06 (m, 2H), 7.55-7.22 (m, 8H), 6.14 (q, J = 6.6 Hz, 1H), 1.66 (d, J = 6.6 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.8, 141.9, 133.0, 130.6, 129.7, 128.6, 128.4, 127.9, 126.1, 73.0, 22.5.



2.65

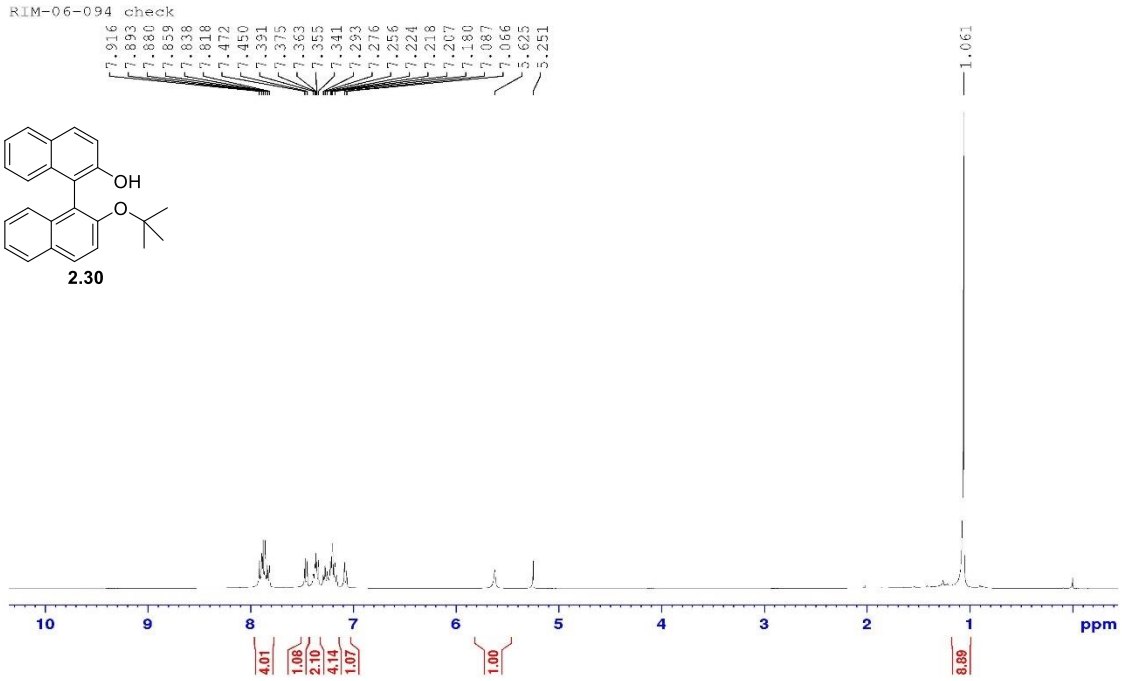
(S)-Diphenylmethyl 2-(2-methoxynaphthalen-6-yl)propanoate (+)-2.65. White solid (1.38 g, 89%), purified by silica gel chromatography (20% ethyl acetate/ 80% hexanes). mp = 132-134 °C; $[\alpha]^{20}_D$ +55.7 (*c* 1.1, $CHCl_3$); TLC R_f = 0.42 (20% ethyl acetate/ 80% hexanes); IR (KBr, cm^{-1}) υ_{max} 3059, 3000, 2942, 2359, 1723, 1604, 1162, 705; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70-7.60 (m, 3H), 7.37 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.29-7.04 (m, 12H), 6.84 (s, 1H), 4.01-3.93 (m, 4H), 1.59 (d, *J* = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 173.7, 157.8, 140.4, 140.3, 135.7, 133.9, 129.5, 129.1, 128.7, 128.5, 128.1, 127.9, 127.4, 127.3 126.9, 126.7, 126.3, 119.2, 105.8, 77.4, 55.5, 45.9, 18.6. Anal. Calcd for $C_{27}H_{24}O_3$: C, 81.79; H, 6.10. Found: C, 81.54; H, 6.11. The enantiomeric ratio was determined by HPLC using a chiral column (OD-H), n-hexane:i-PrOH = 99:1, 1 mL/min; compared to a racemic sample which showed two peaks t_R = 9.7 and 11.4 min.



2.73

(2-Methoxyphenyl)(phenyl)methyl [1,1'-biphenyl]-4-carboxylate 2.73. White solid (73 mg, 73% yield), purified by silica gel column chromatography (10% ethyl acetate, 90% hexanes). mp = 136-137 °C; TLC R_f = 0.35 (10% ethyl acetate/ 90% hexanes); IR (film, cm^{-1}) υ_{max} 3064, 2938,

1715, 1604, 1491, 1278, 1100, 857; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.2 Hz, 2H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.54-7.52 (m, 2H), 7.44-7.36 (m, 5H), 7.32-7.15 (m, 6H), 6.91-6.80 (m, 2H), 3.75 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz $CDCl_3$) δ 165.4, 156.5, 145.8, 140.3, 140.1, 130.3, 129.2, 129.1, 129.0, 128.9, 128.3, 128.2, 127.7, 127.3, 127.2, 127.1, 127.0, 120.7, 110.9, 72.2, 55.6. Anal Calcd for $C_{22}H_{20}O_3$: C, 82.21; H, 5.62. Found: C, 82.28; H, 5.67. The enantiomeric ratio was determined by HPLC using a chiral column (AD), n-hexane:i-PrOH = 95:5, 1 mL/min; compared to a racemic sample which showed two peaks t_R = 14.8 and 16.9 min.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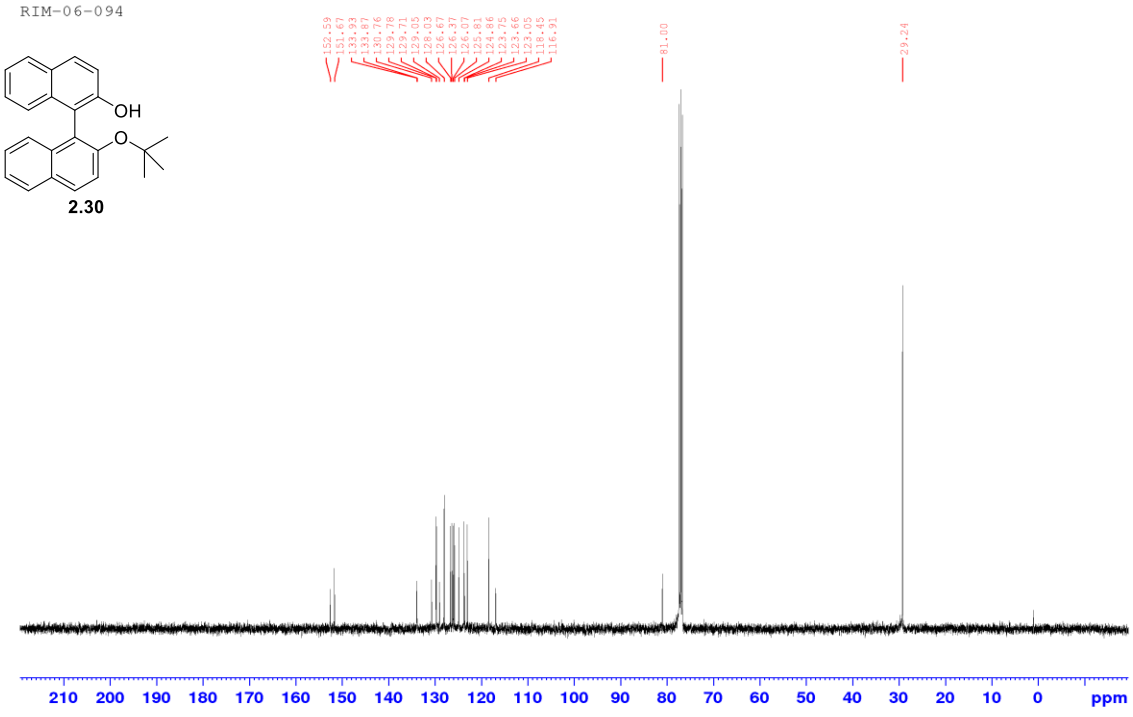
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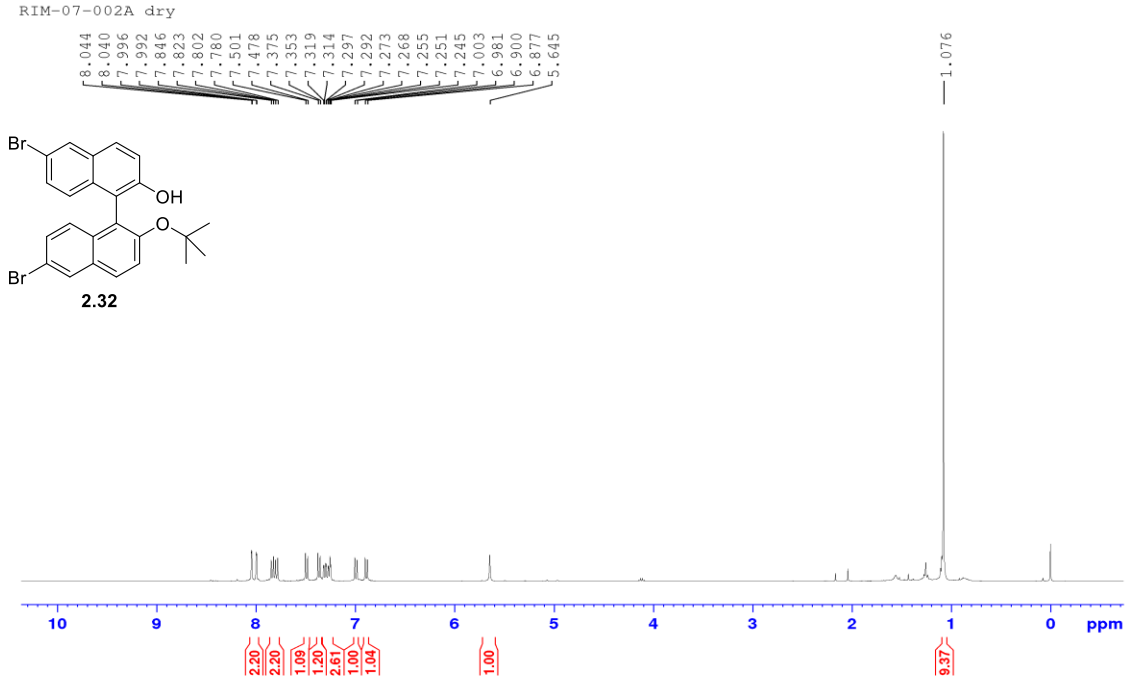
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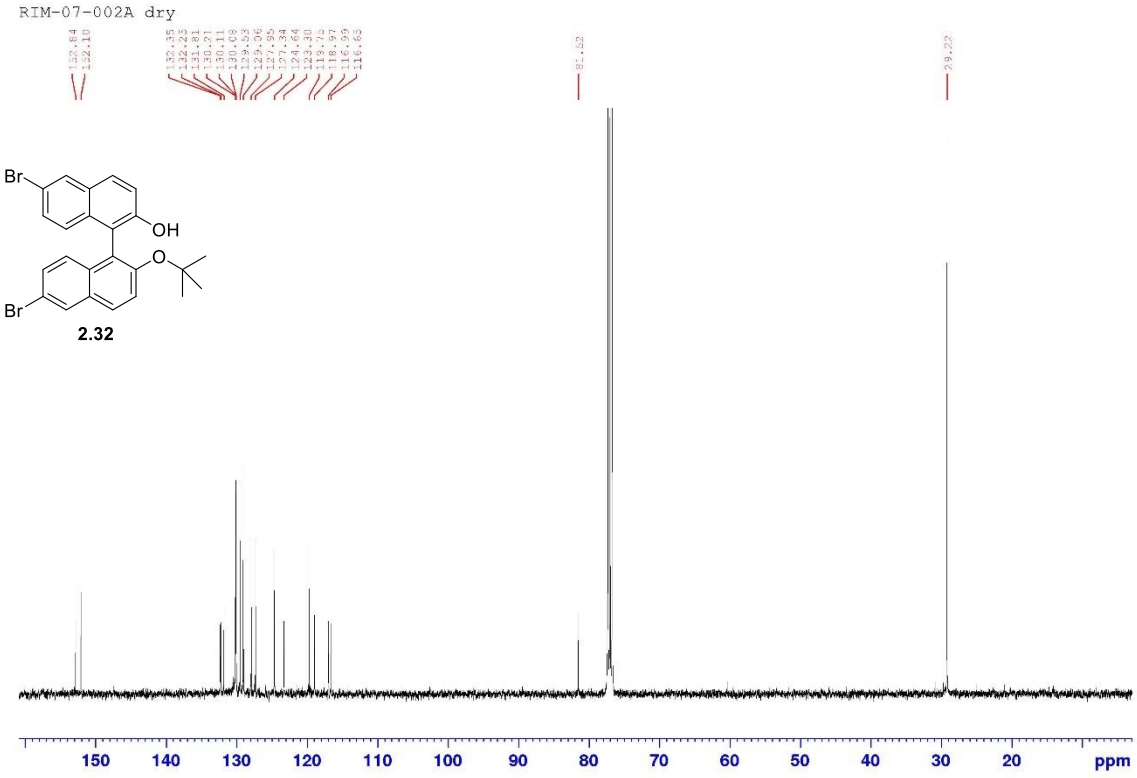
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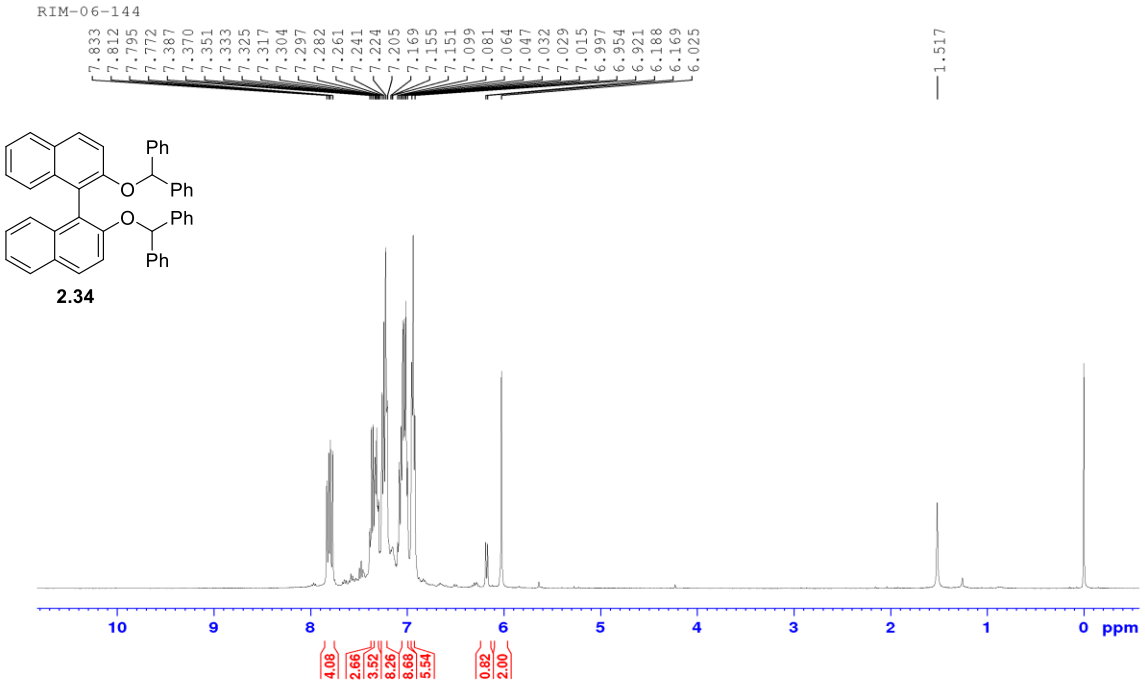
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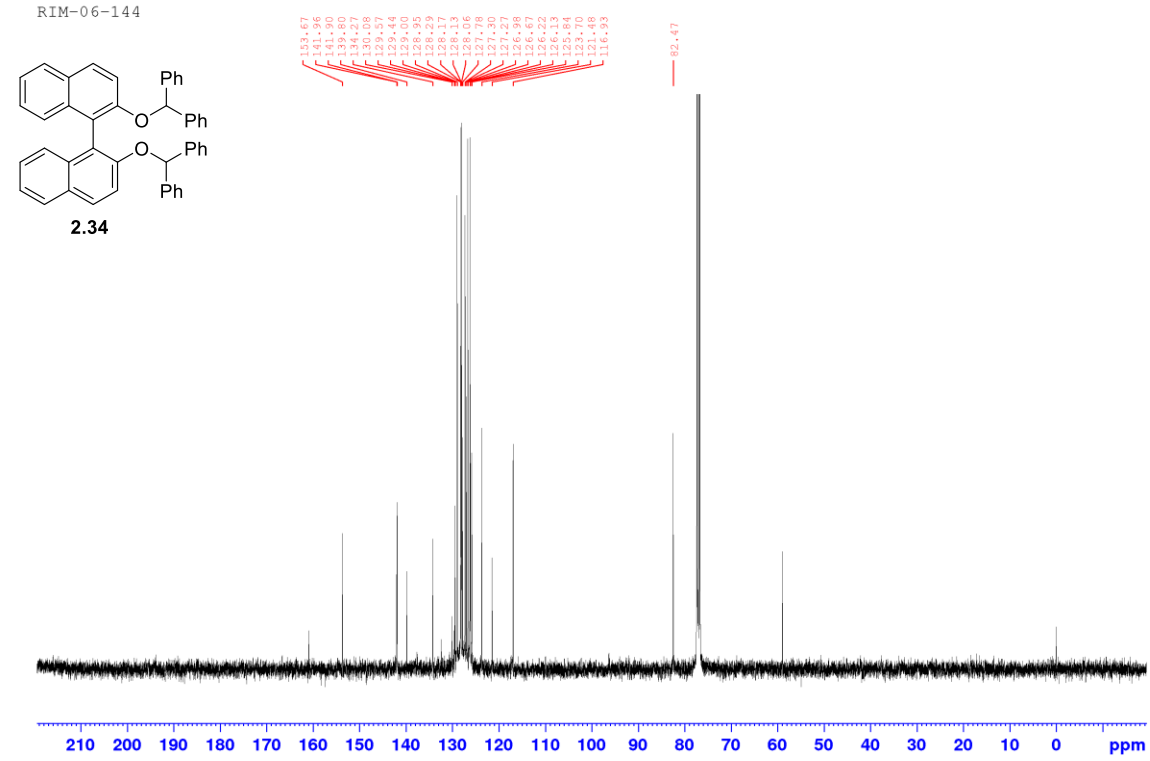
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Ph
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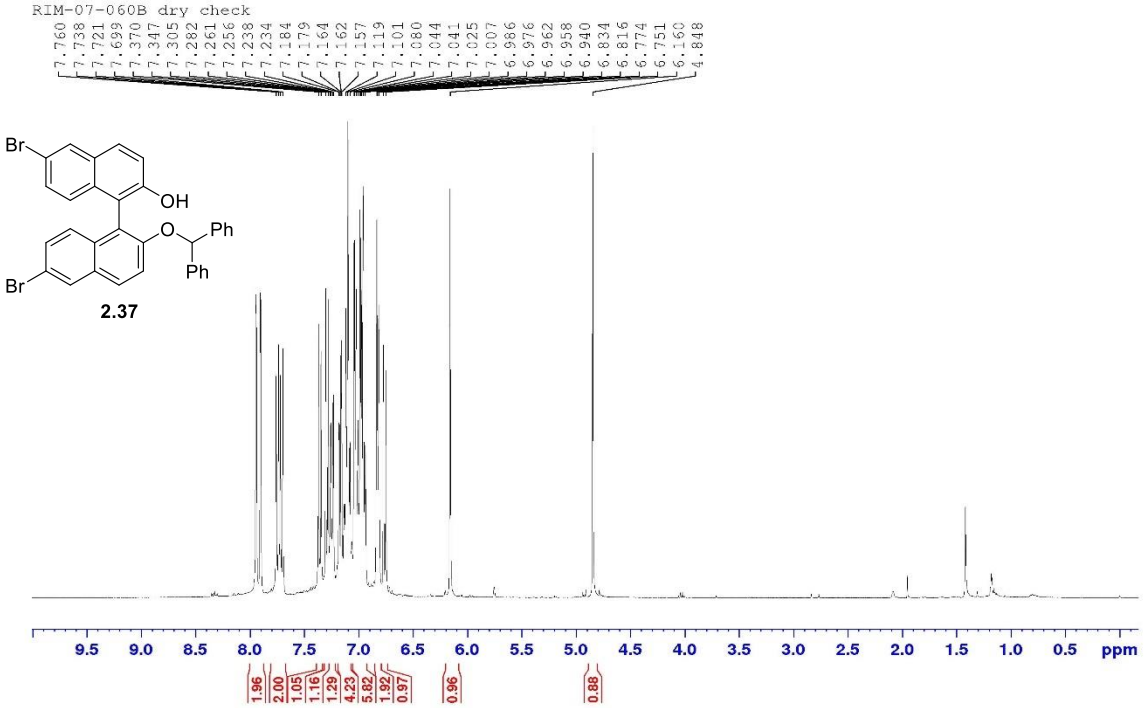
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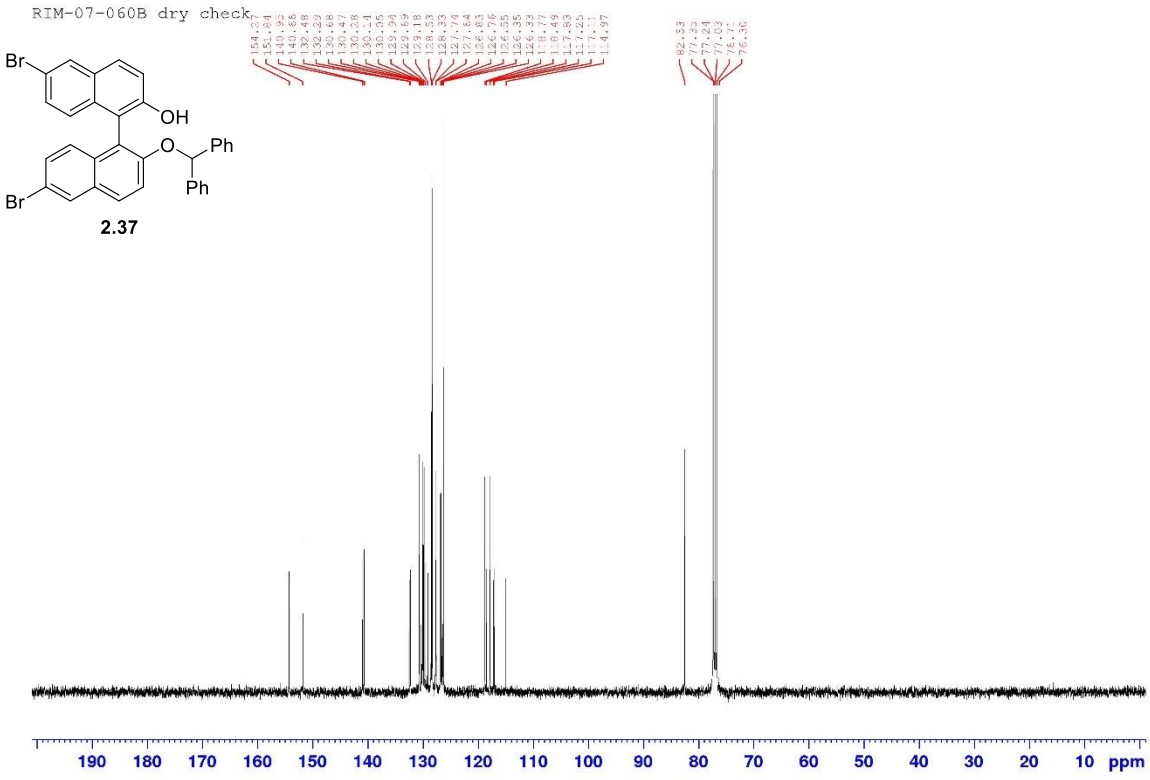
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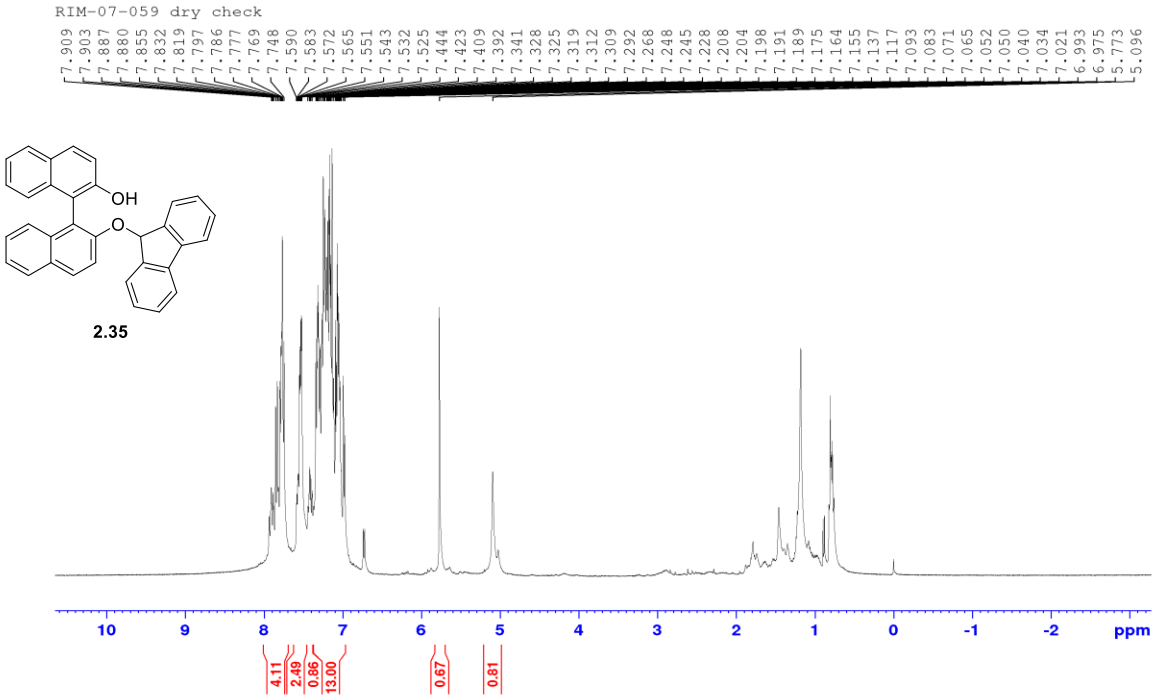
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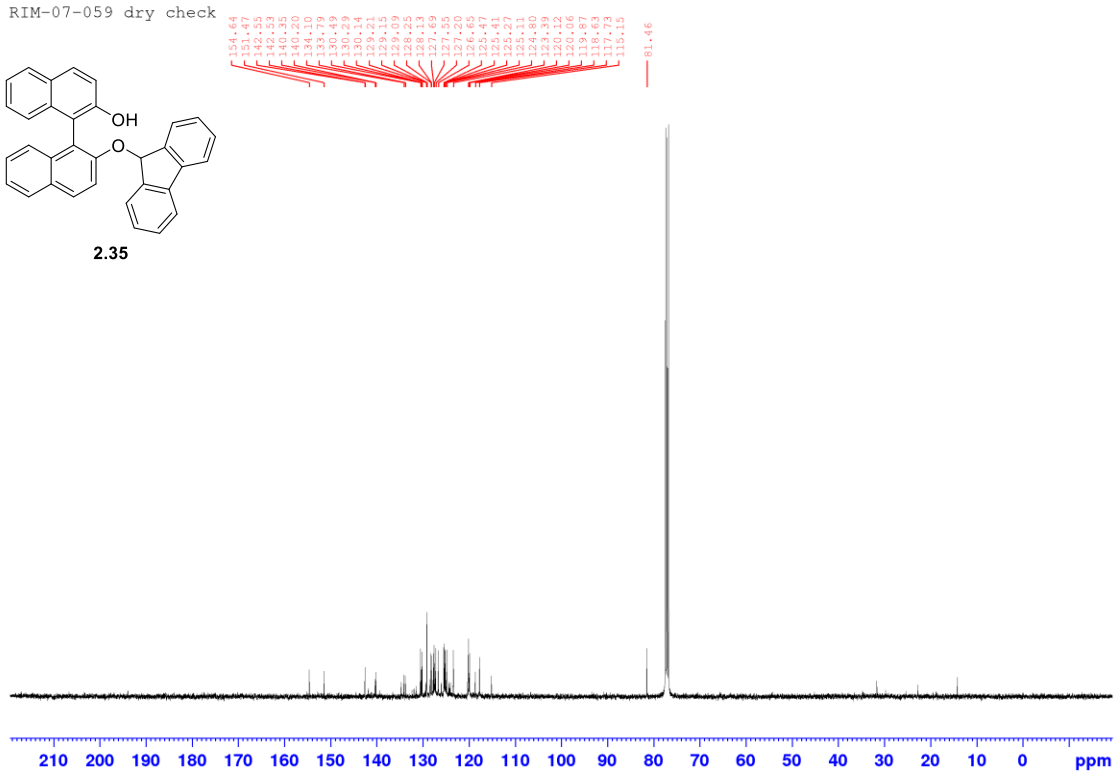
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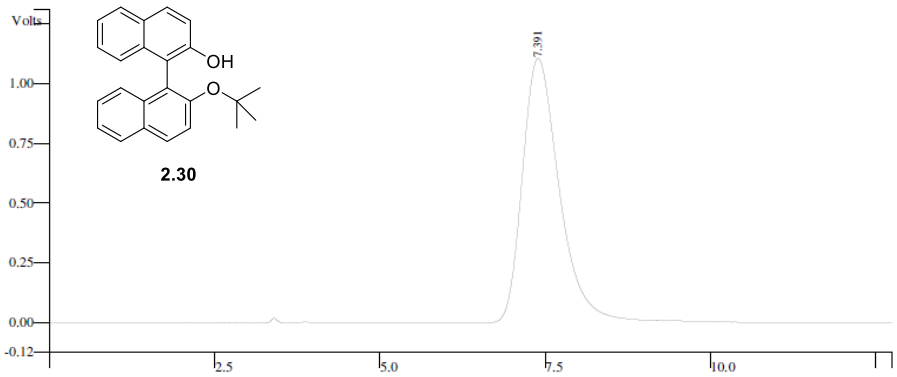

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settings\lab-admin\desktop\rim\rim-06-103b 5 ipa 1mlmin
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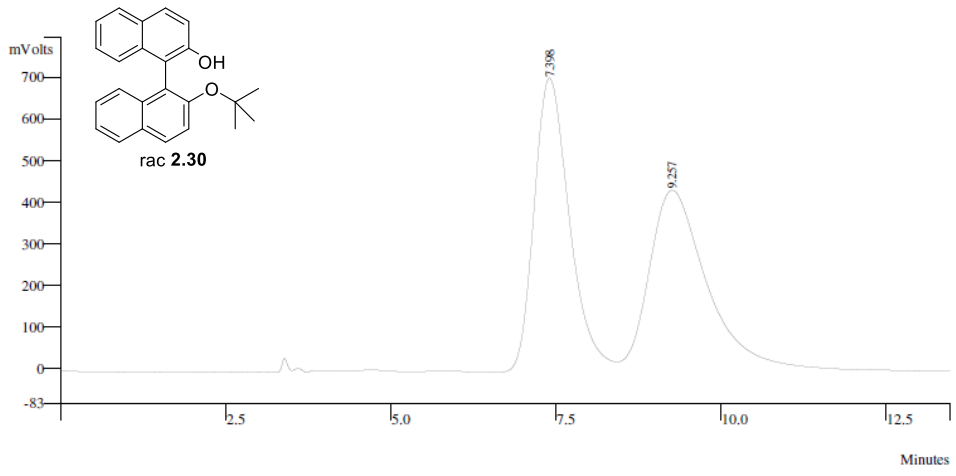

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Reaction conditions: rac BINOL used

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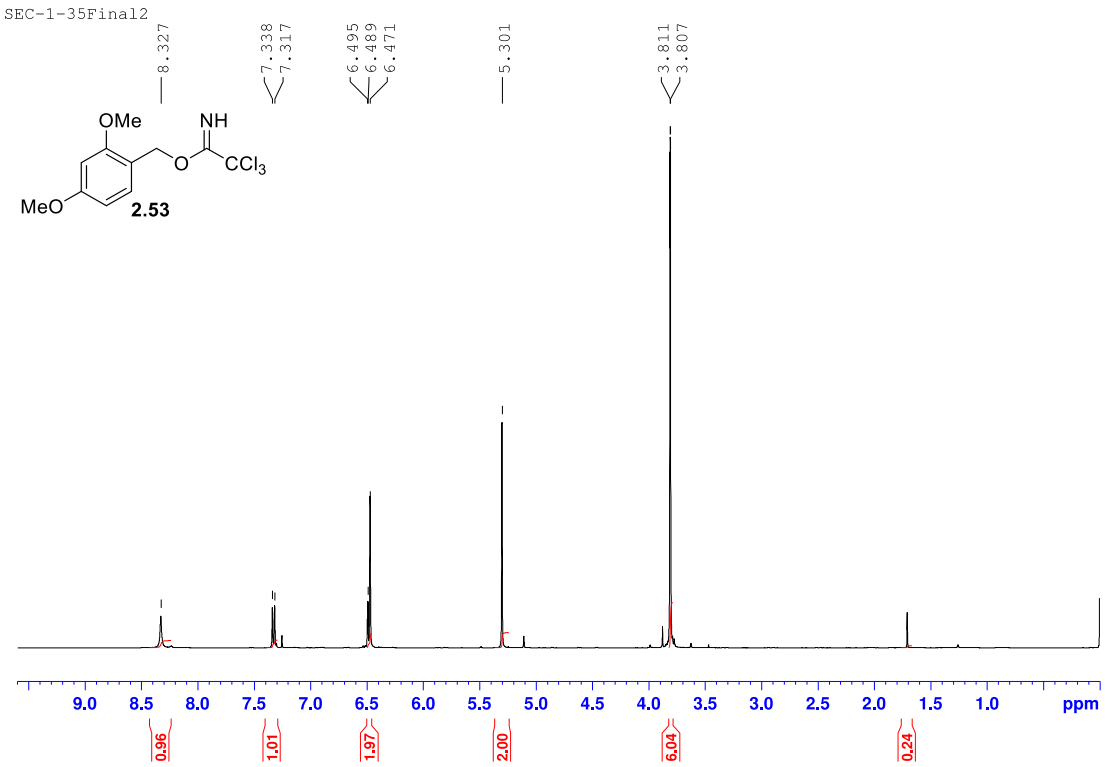
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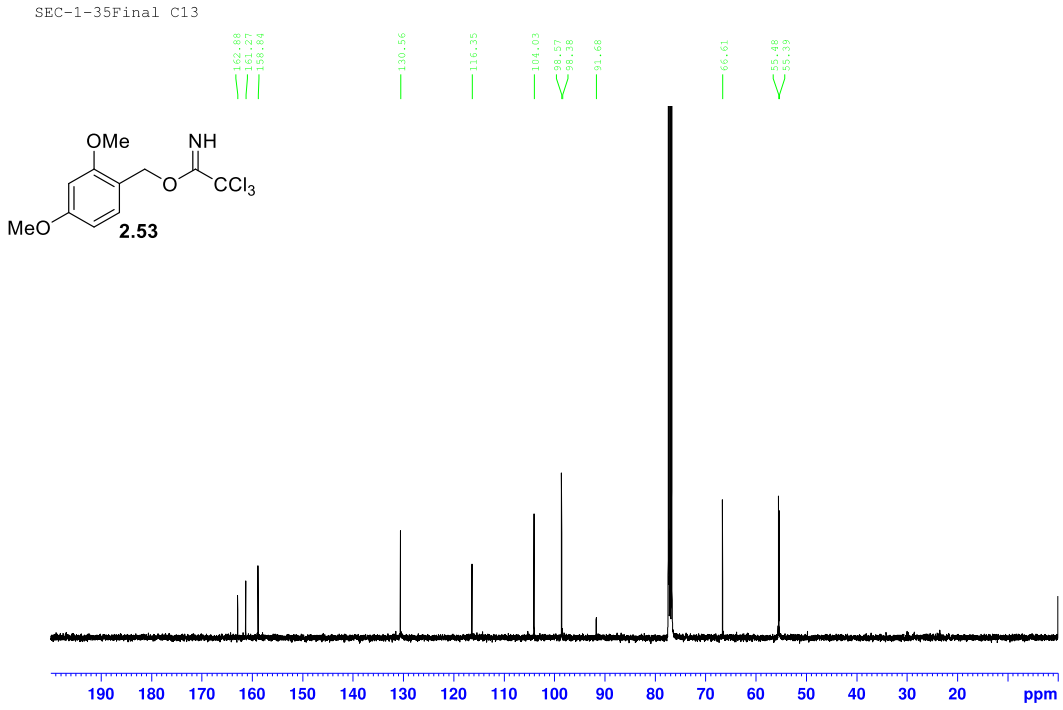
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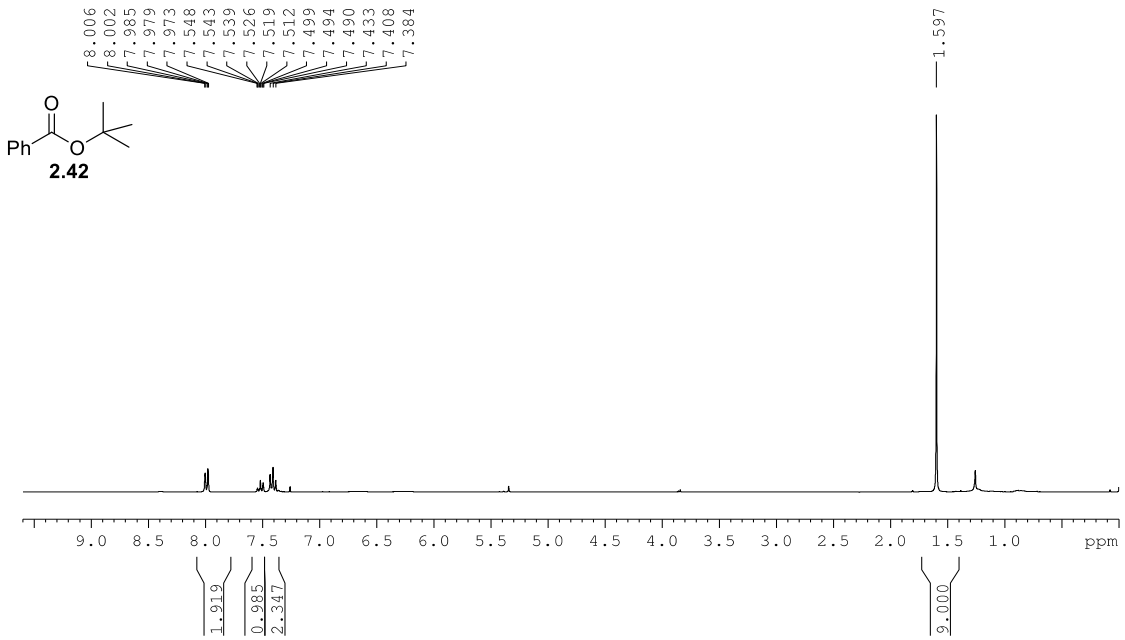
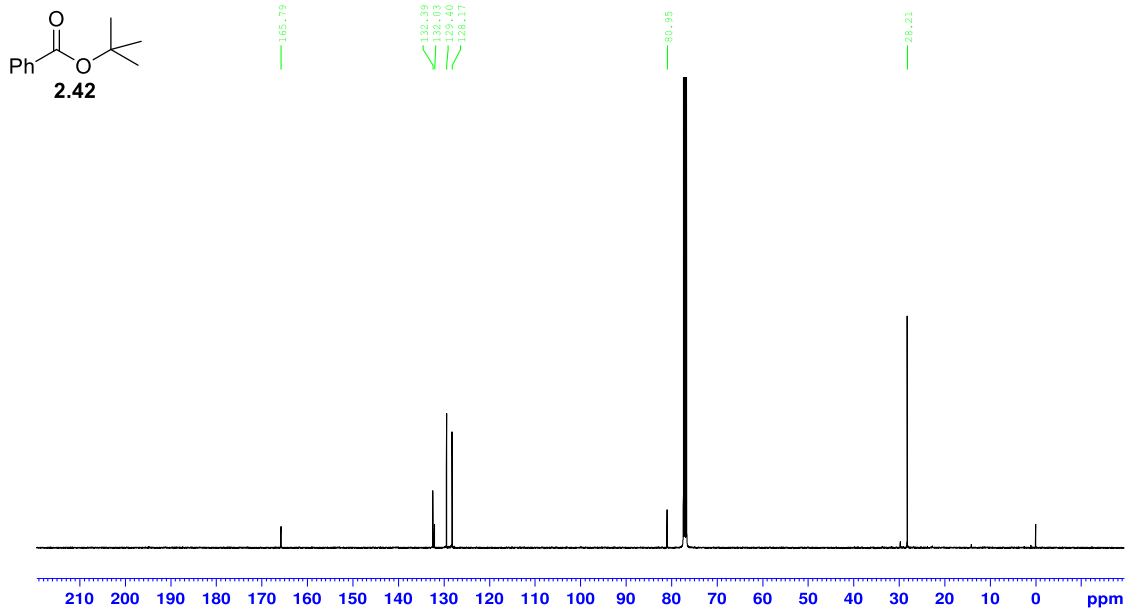
ppm

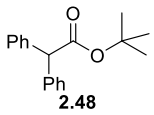
TJS-2-42Final



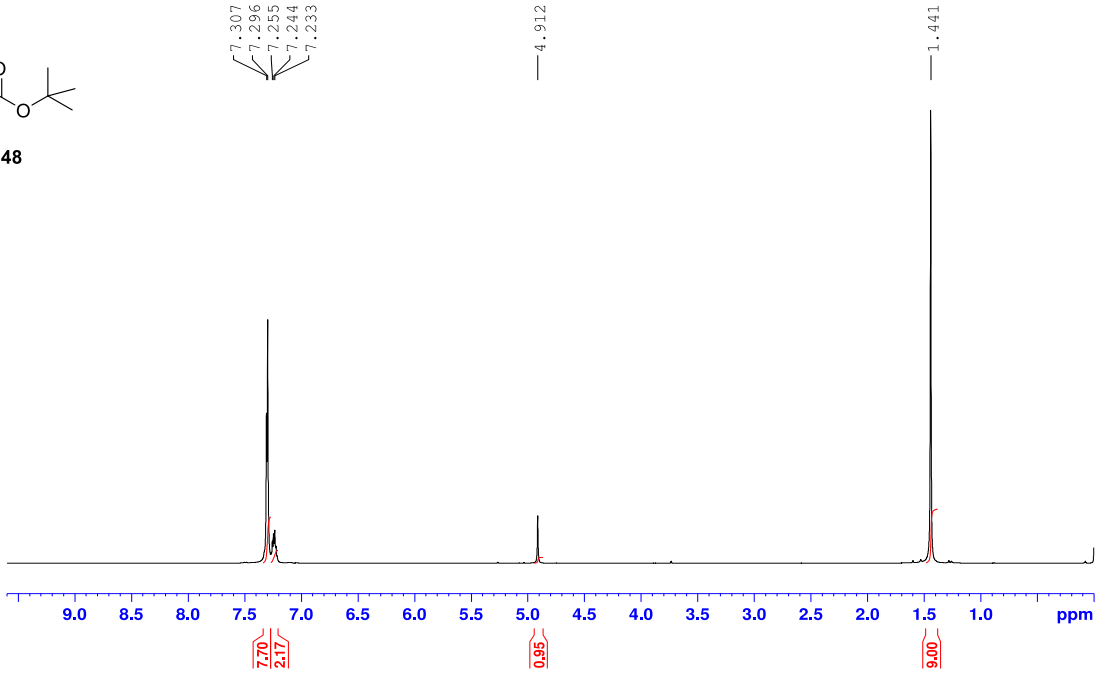
TJS-2-42FinalC13



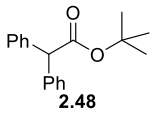
NSM-7-54Final



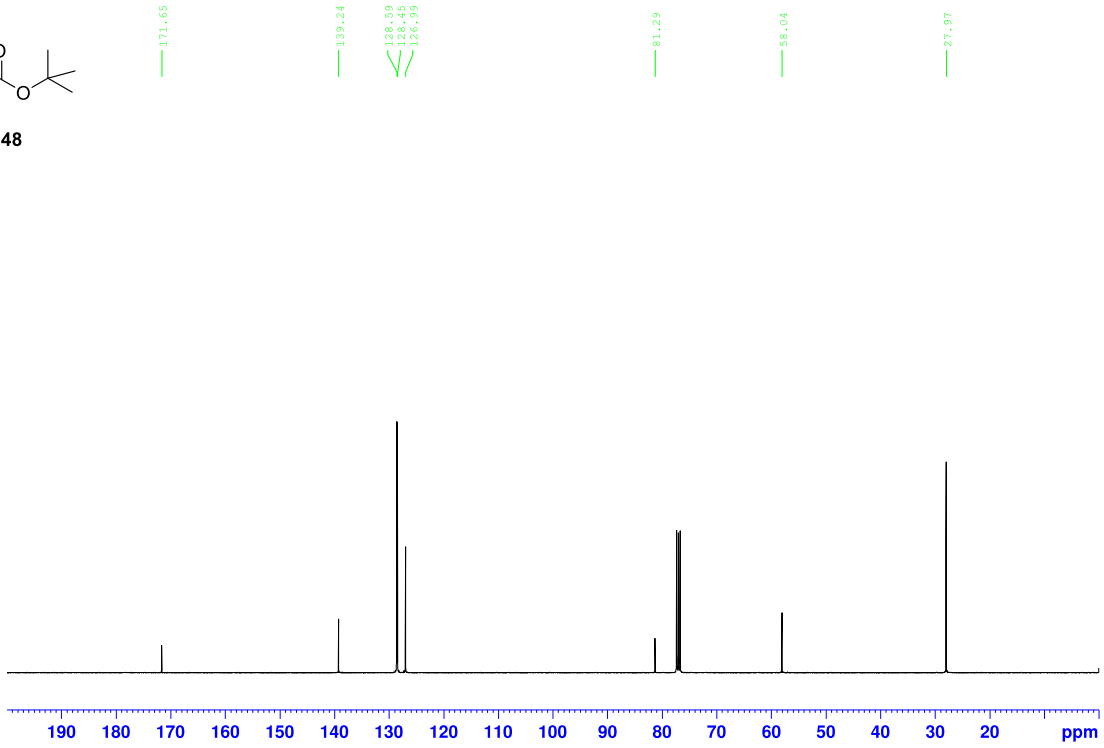
2.48



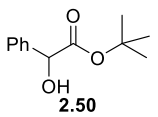
NSM-7-54FinalC13

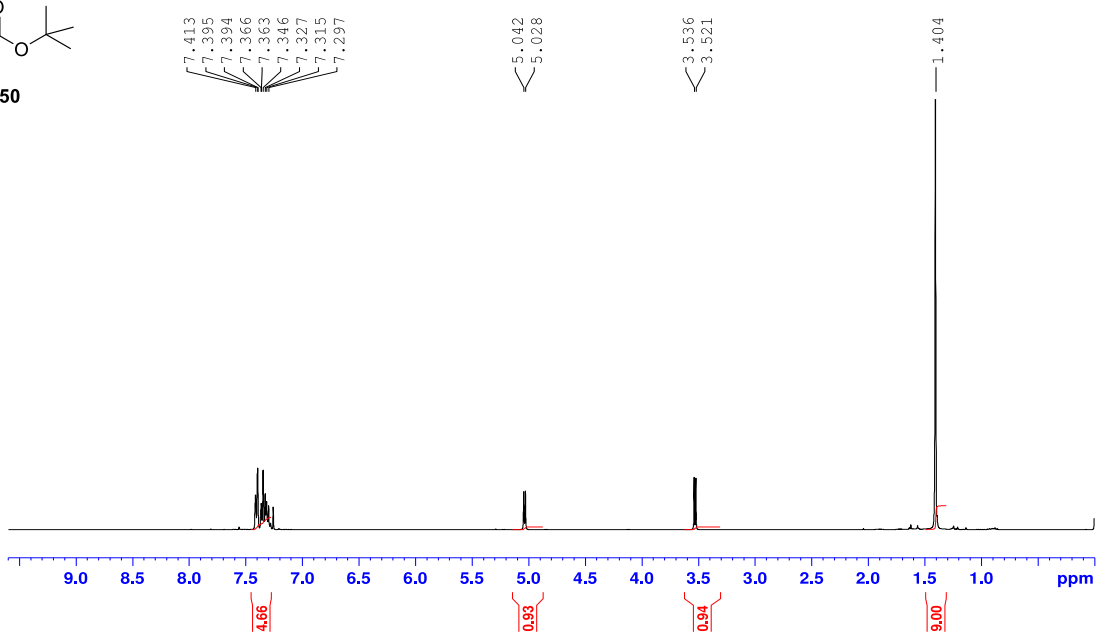


2.48

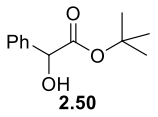


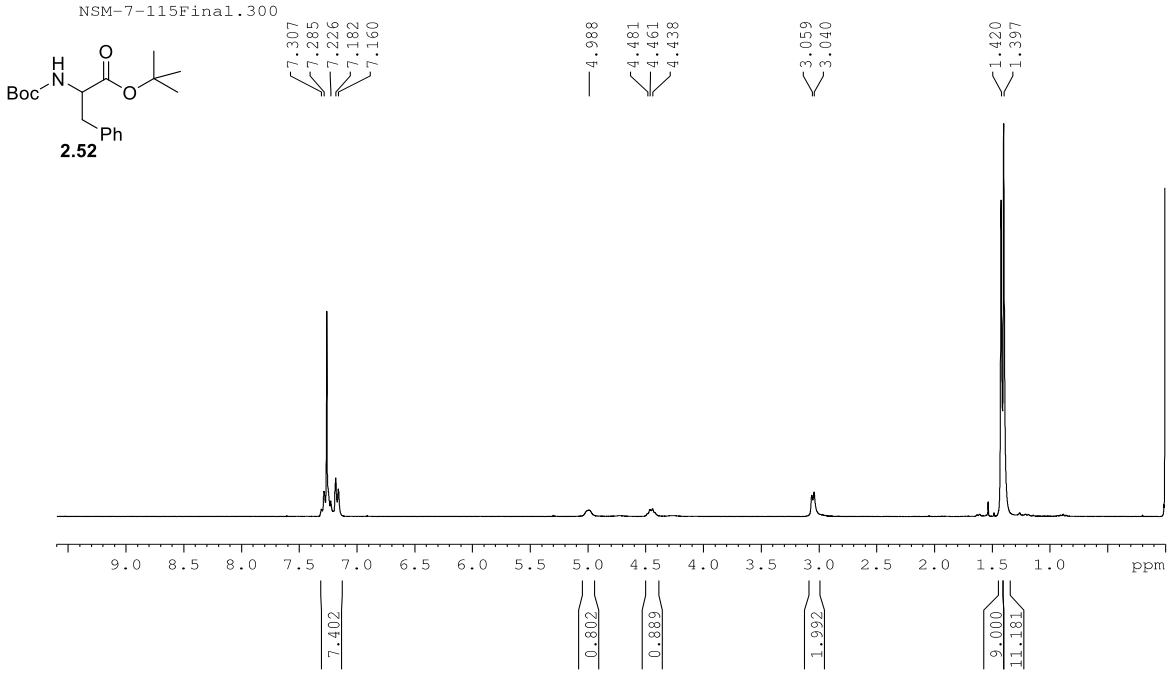
NSM-7-124B

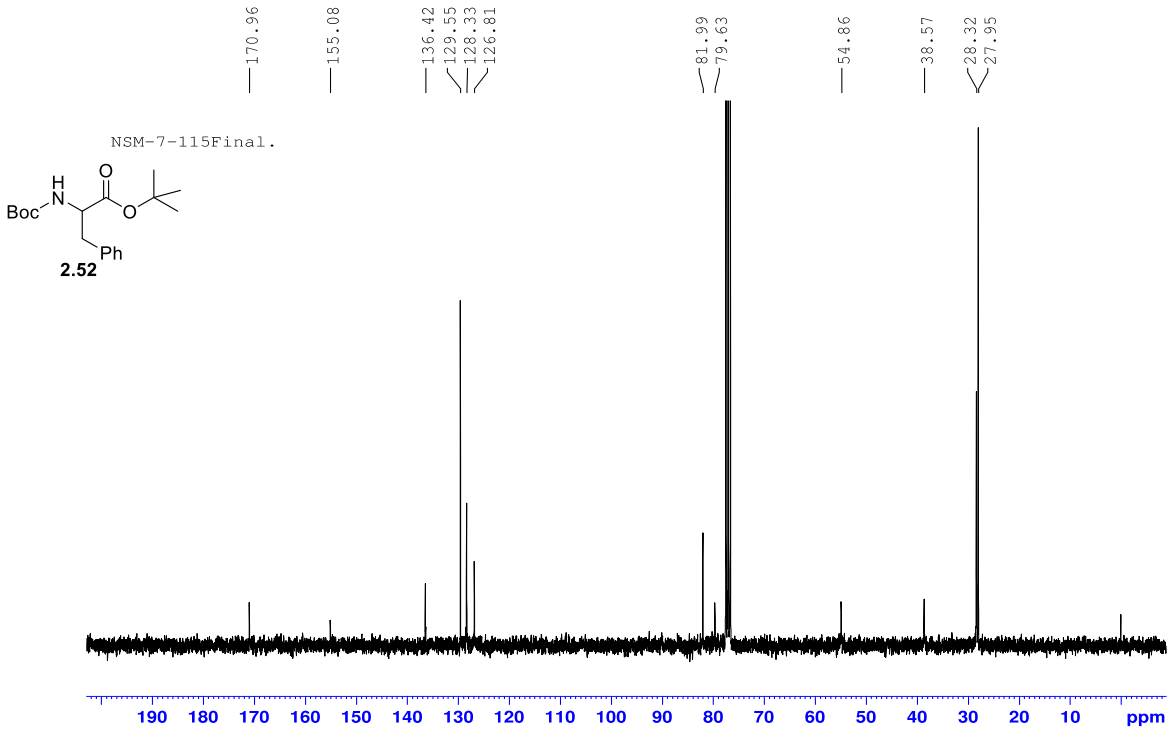


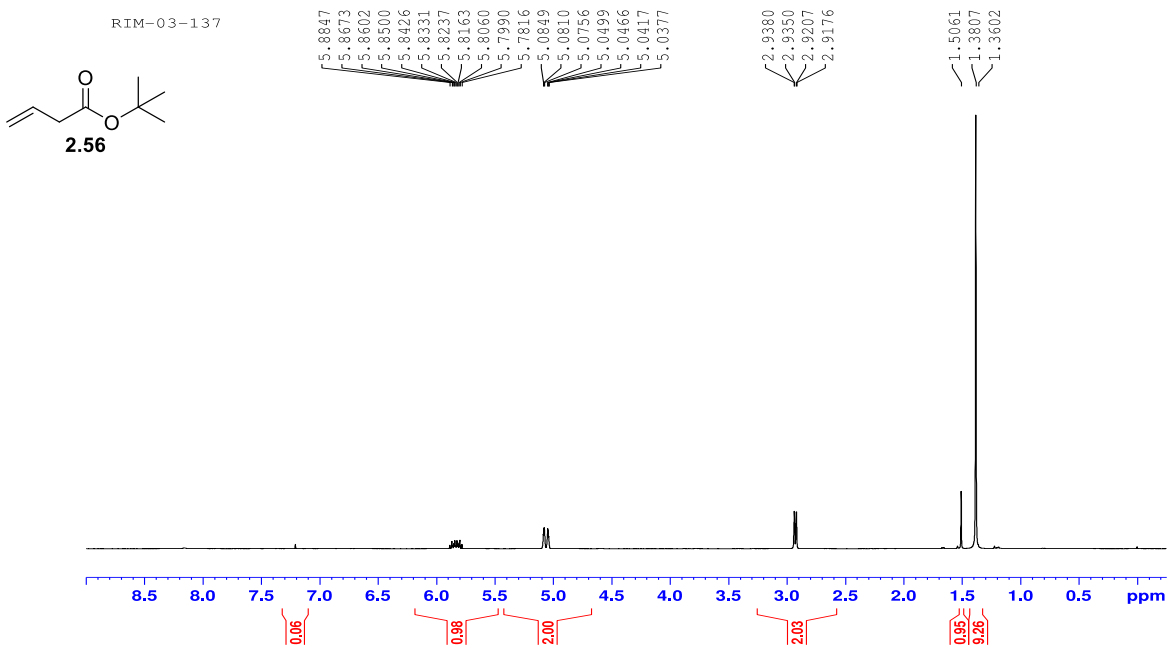


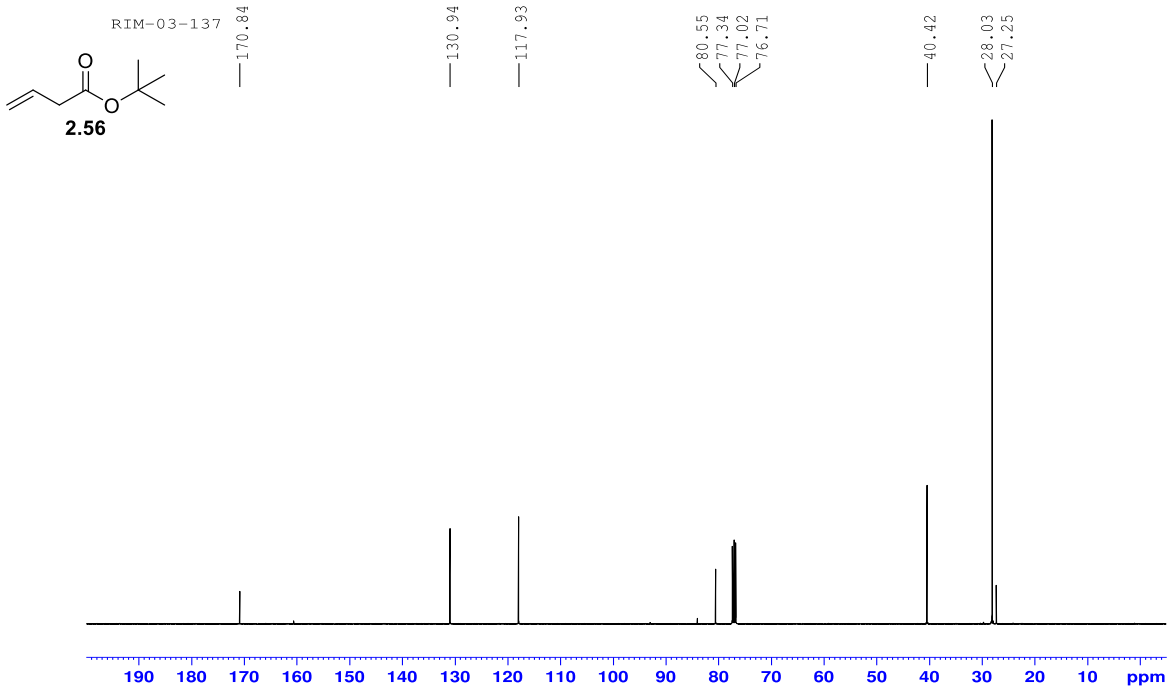
NSM-7-124inalC13



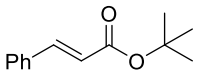

NSM-7-115Final.300
Boc
H
N
O
O
Ph
2.52
7.307
7.285
7.226
7.182
7.160
4.988
4.481
4.461
4.438
3.059
3.040
1.420
1.397
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
7.402
0.802
0.889
1.992
9.000
11.181


NSM-7-115Final.
Boc
H
N
O
O
Ph
2.52
170.96
155.08
136.42
129.55
128.33
126.81
81.99
79.63
54.86
38.57
28.32
27.95
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

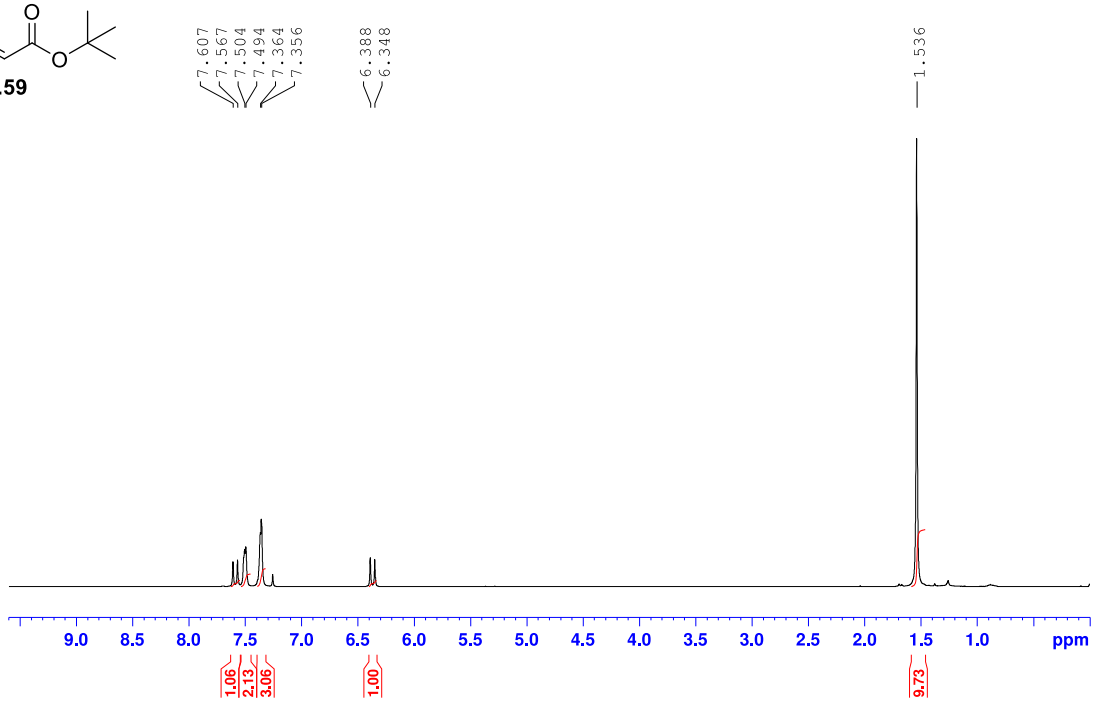

RIM-03-137
2.56
5.8847
5.8673
5.8602
5.8500
5.8426
5.8331
5.8237
5.8163
5.8060
5.7990
5.7816
5.0849
5.0810
5.0756
5.0499
5.0466
5.0417
5.0377
2.9380
2.9350
2.9207
2.9176
1.5061
1.3807
1.3602
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.06
0.98
2.00
2.03
0.95
9.26


RIM-03-137
2.56
170.84
130.94
117.93
80.55
77.34
77.02
76.71
40.42
28.03
27.25
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

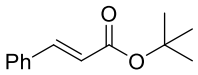
NSM-7-116A



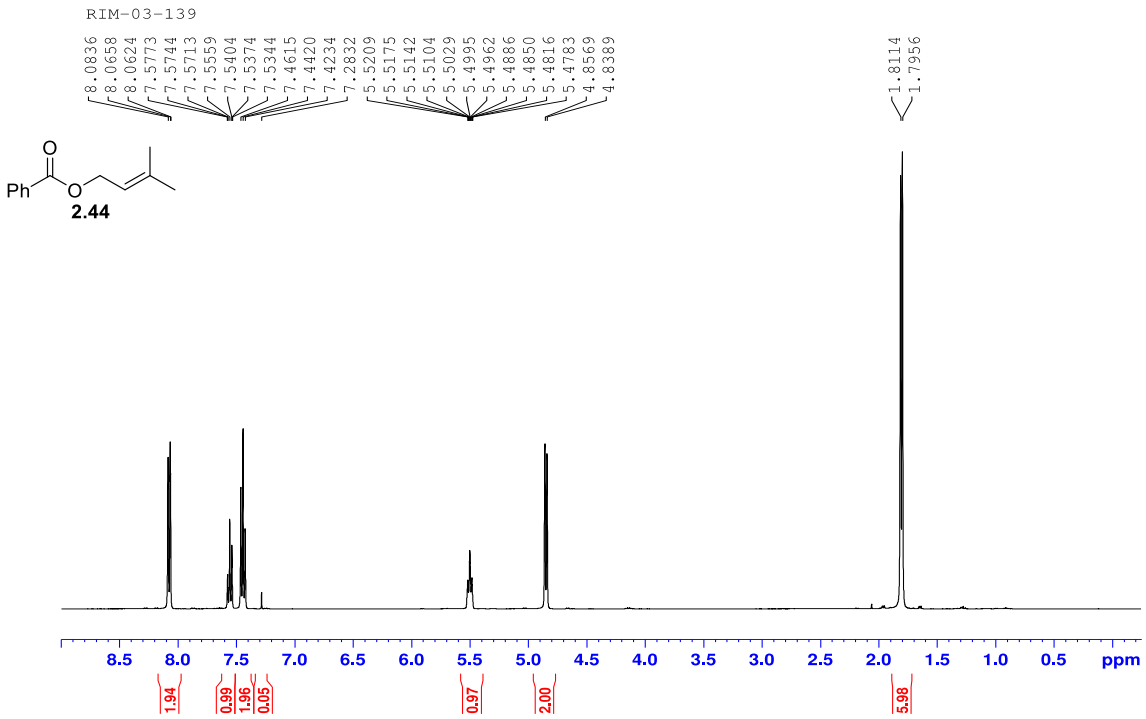
2.59

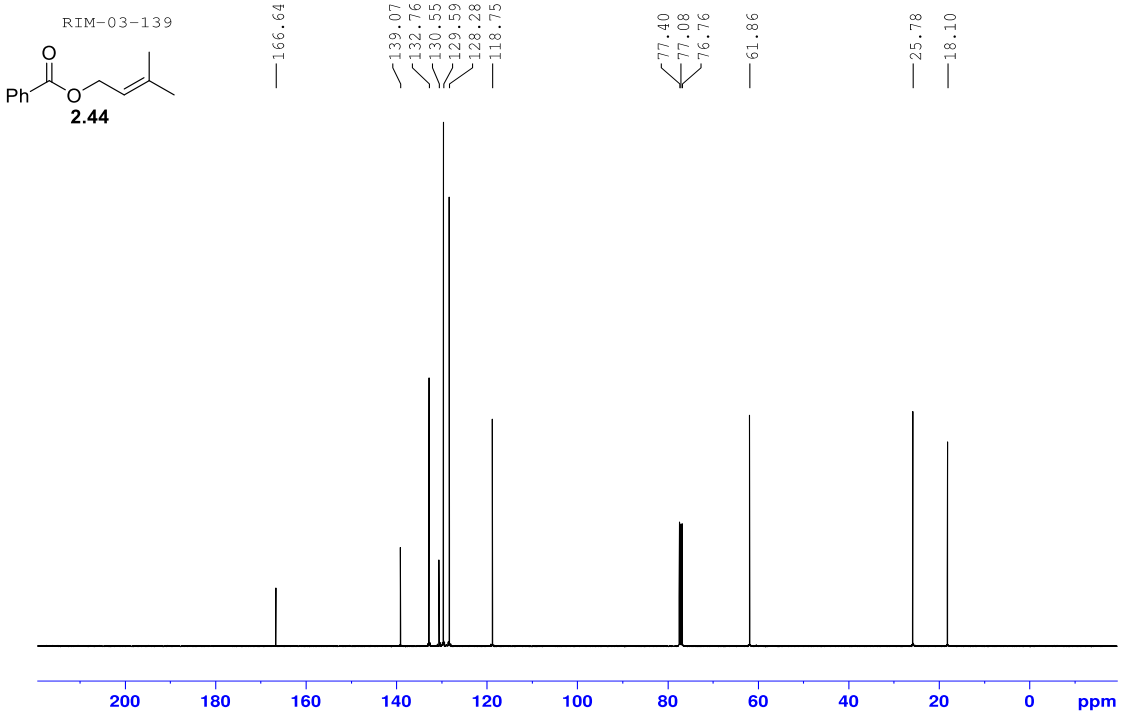


NSM-7-116FinalC13

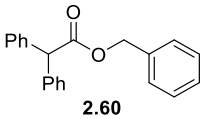


2.59

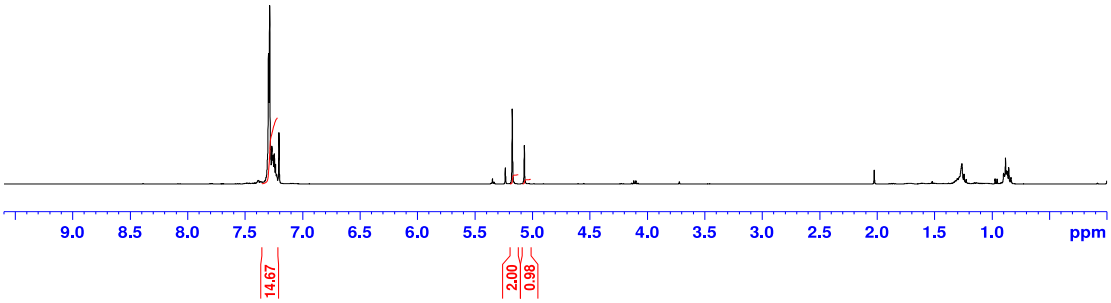

RIM-03-139
8.0836
8.0658
8.0624
7.5773
7.5744
7.5713
7.5559
7.5404
7.5374
7.5344
7.4615
7.4420
7.4234
7.2832
5.5209
5.5175
5.5142
5.5104
5.5029
5.4995
5.4962
5.4886
5.4850
5.4816
5.4783
4.8569
4.8389
1.8114
1.7956
Ph
O
O
2.44
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.94
0.99
1.96
0.05
0.97
2.00
5.98


RIM-03-139
166.64
139.07
132.76
130.55
129.59
128.28
118.75
77.40
77.08
76.76
61.86
25.78
18.10
Ph
O
O
2.44
200
180
160
140
120
100
80
60
40
20
0
ppm

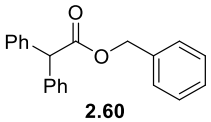
NSM-7-120.1



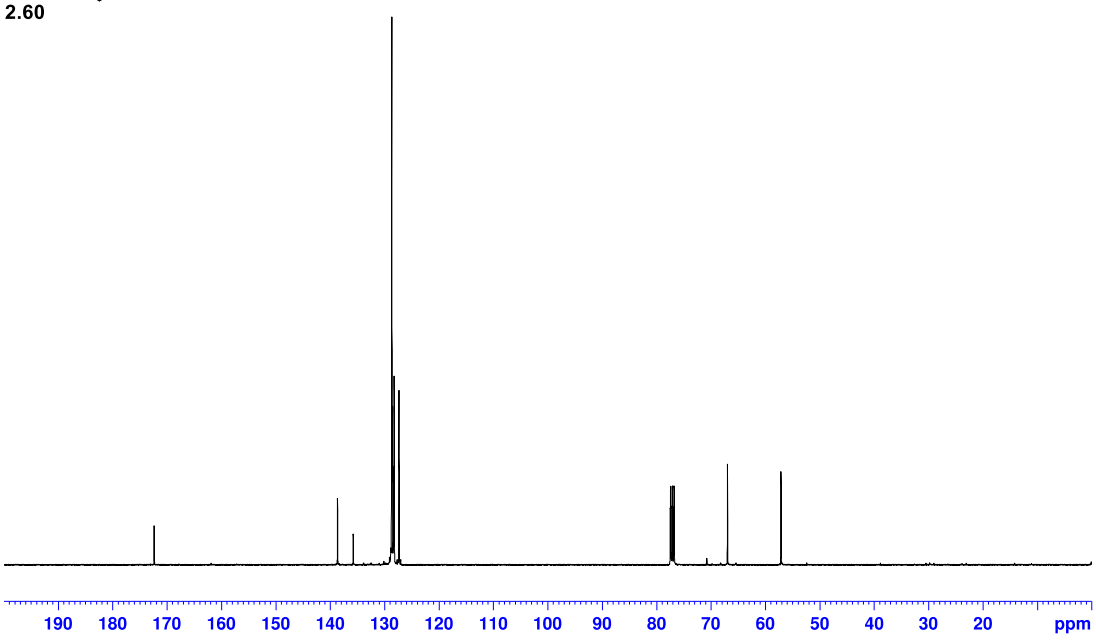
2.60

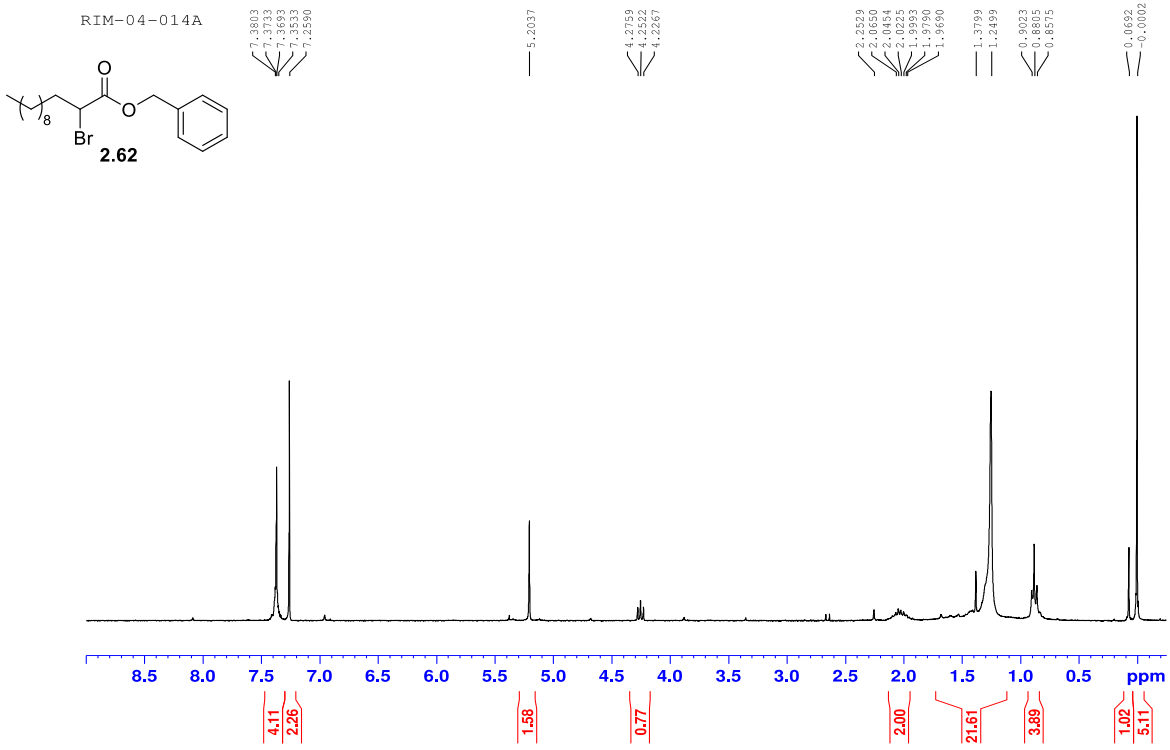


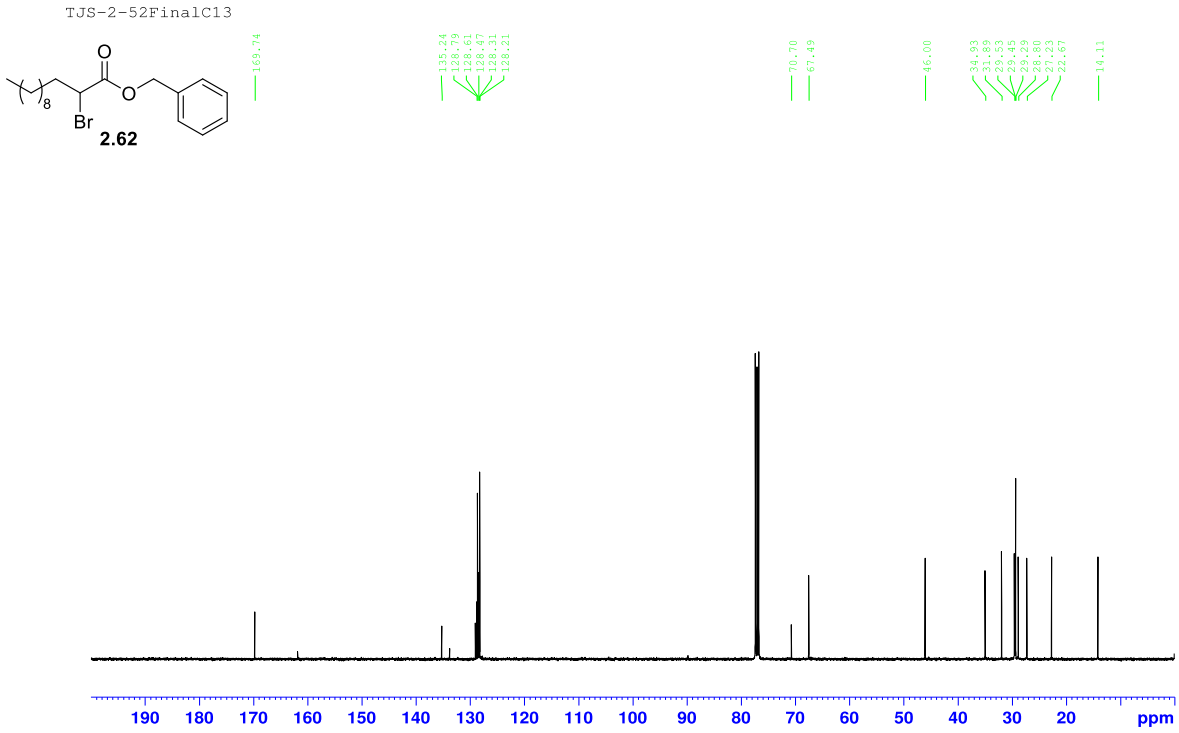
NSM-7-120FinalC13.R



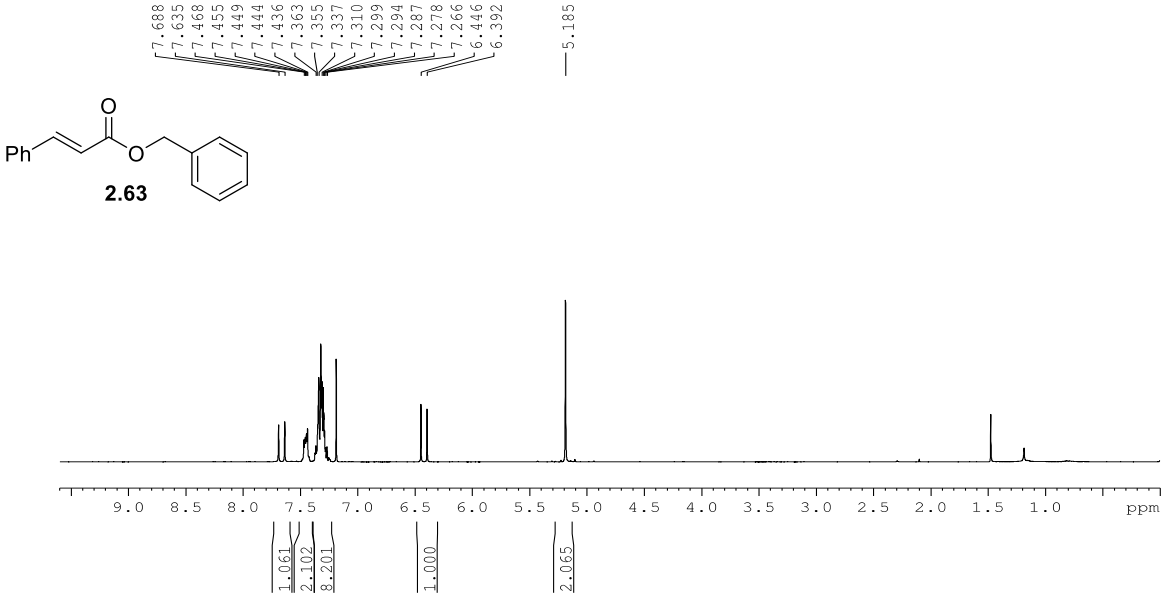
2.60



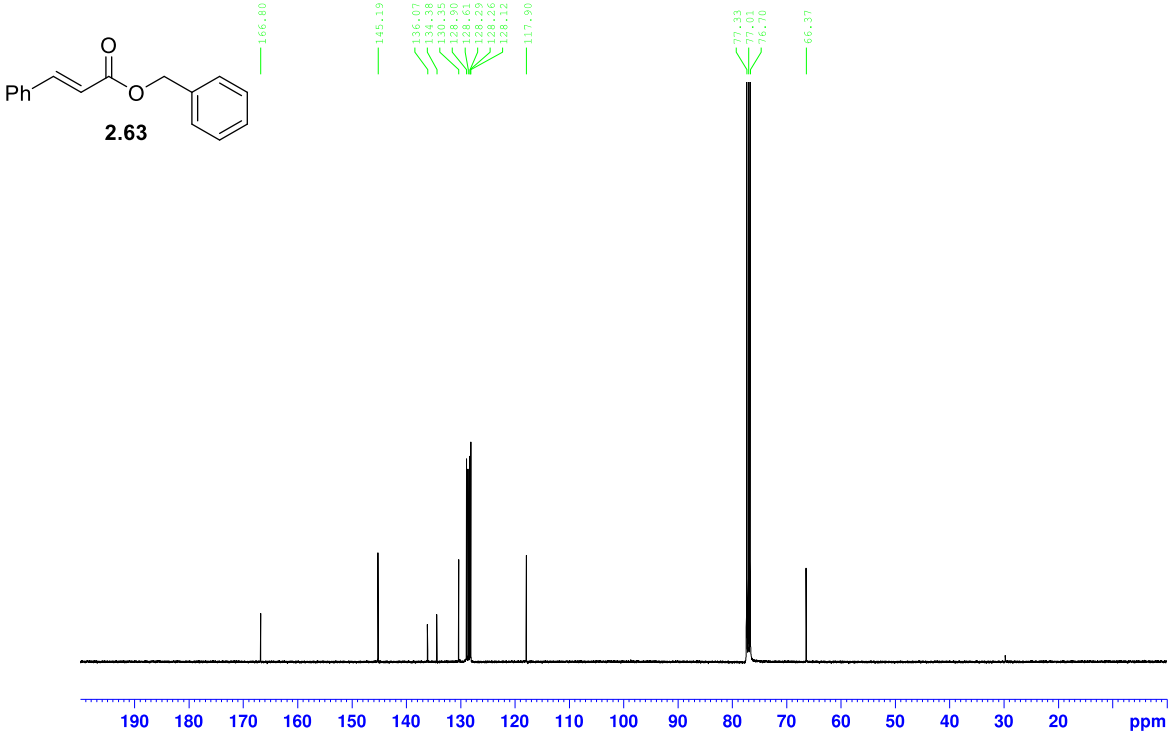

RIM-04-014A
2.62
7.3803
7.3733
7.3693
7.3533
7.2590
5.2037
4.2759
4.2522
4.2267
2.2529
2.0650
2.0454
2.0225
1.9993
1.9790
1.9690
1.3799
1.2499
0.9023
0.8805
0.8575
0.0692
-0.0002
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
4.11
2.26
1.58
0.77
2.00
21.61
3.89
1.02
5.11

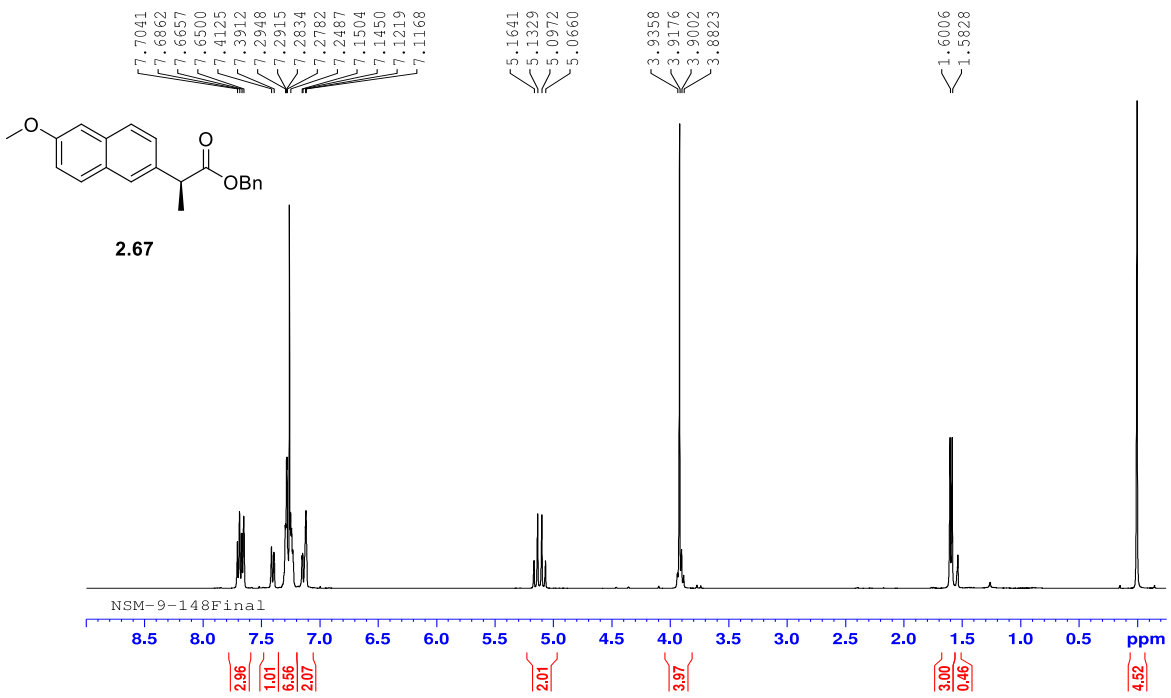

TJS-2-52FinalC13
2.62
169.74
135.24
128.79
128.61
128.47
128.31
128.21
70.70
67.49
46.00
34.93
31.89
29.53
29.45
29.29
28.80
27.23
22.67
14.11
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

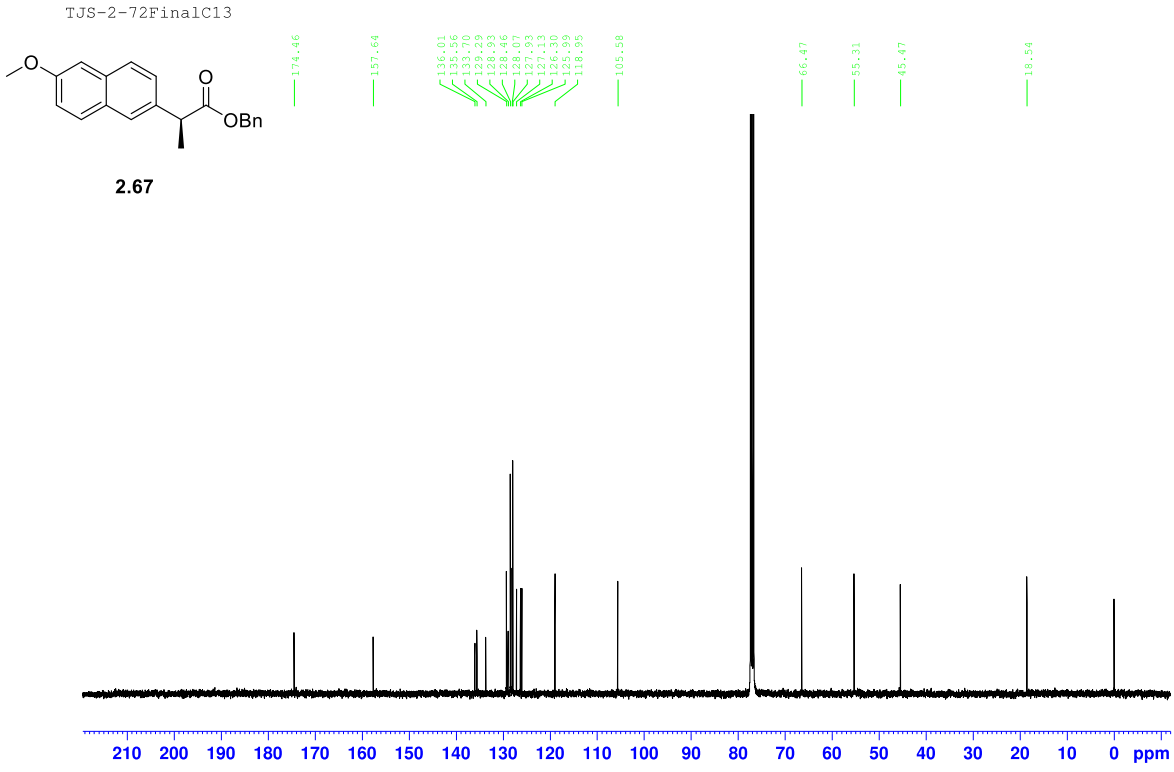
TJS-1-53.A.3

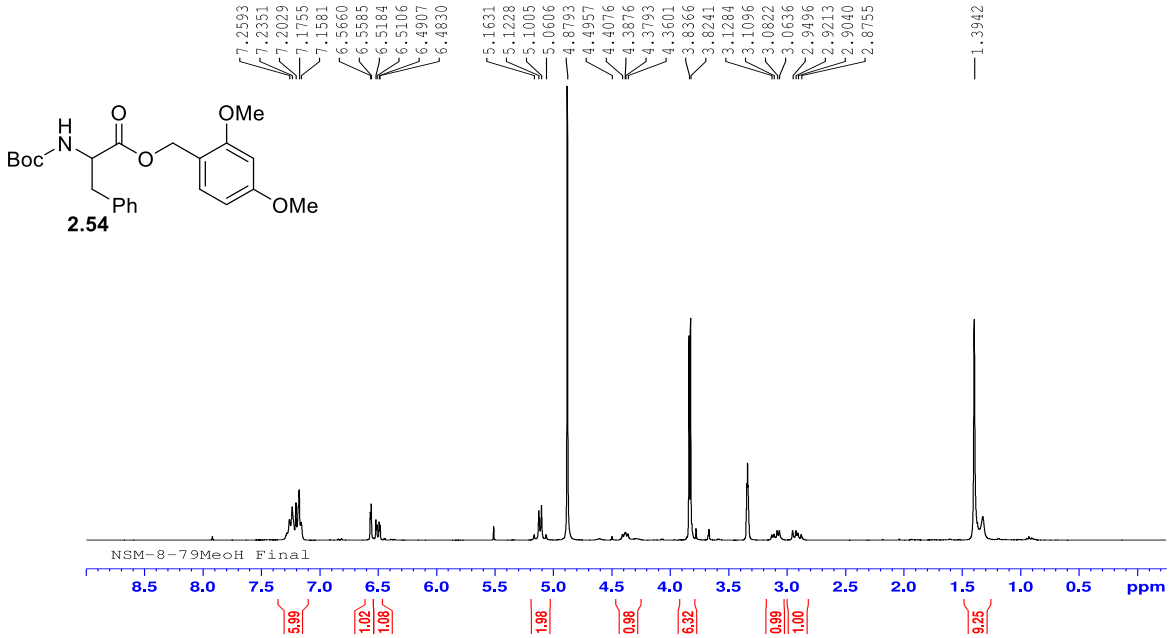


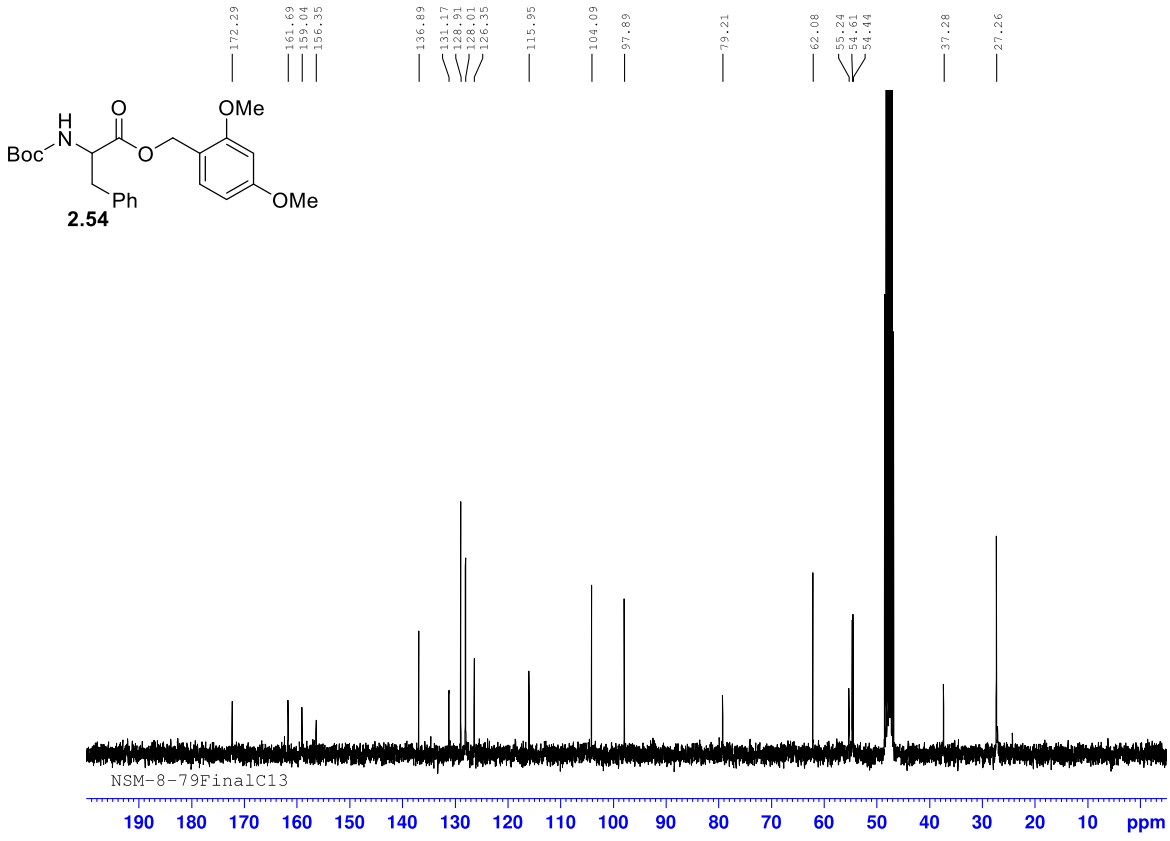
LIMS Container ID NSM-7-53Final C13



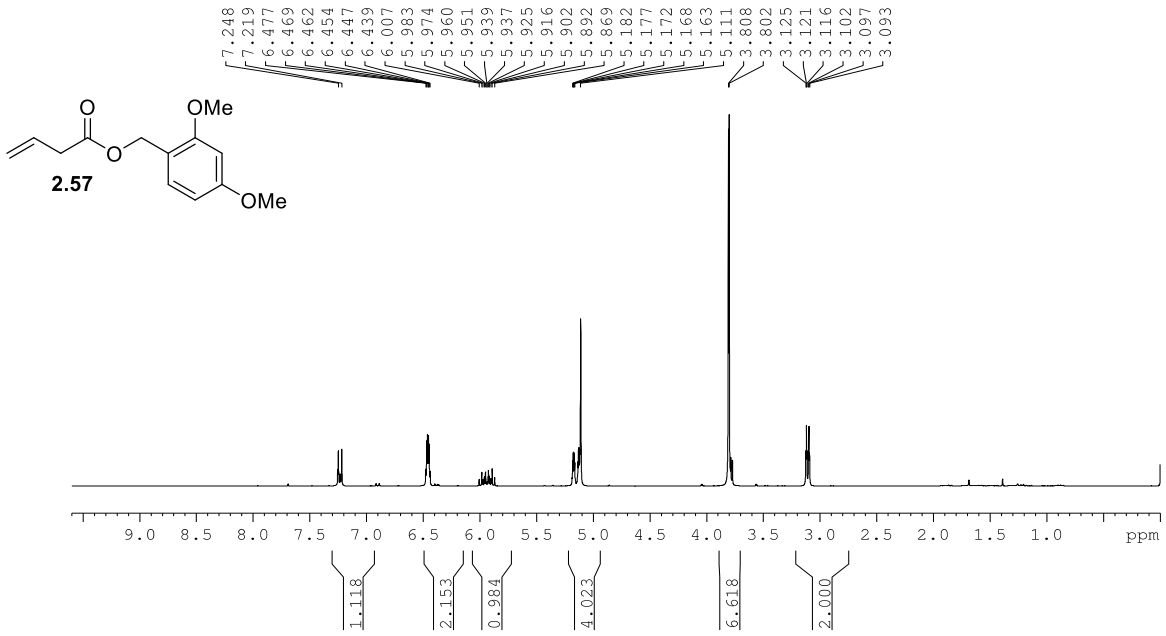

7.7041
7.6862
7.6657
7.6500
7.4125
7.3912
7.2948
7.2915
7.2834
7.2782
7.2487
7.1504
7.1450
7.1219
7.1168
5.1641
5.1329
5.0972
5.0660
3.9358
3.9176
3.9002
3.8823
1.6006
1.5828
O
O
OBn
2.67
NSM-9-148Final
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.96
1.01
6.56
2.07
2.01
3.97
3.00
0.46
4.52


TJS-2-72FinalC13
174.46
157.64
136.01
135.56
133.70
129.29
128.93
128.46
128.07
127.93
127.13
126.30
125.99
118.95
105.58
66.47
55.31
45.47
18.54
O
O
OBn
2.67
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

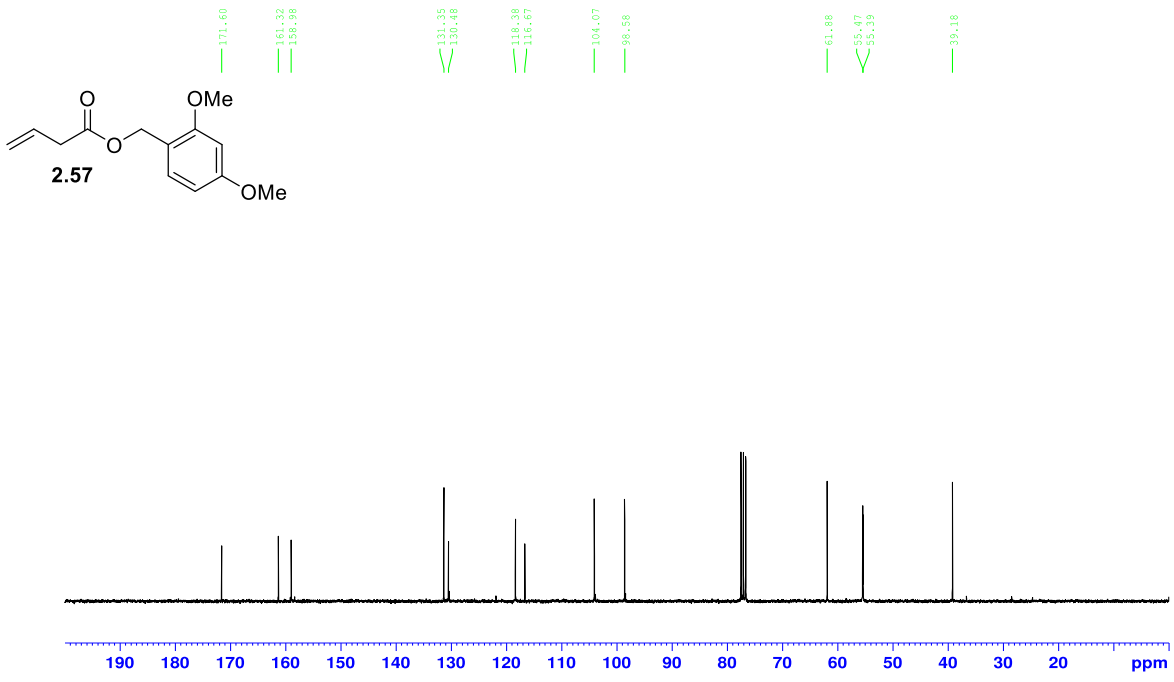

7.2593
7.2351
7.2029
7.1755
7.1581
6.5660
6.5585
6.5184
6.5106
6.4907
6.4830
5.1631
5.1228
5.1005
5.0606
4.8793
4.4957
4.4076
4.3876
4.3793
4.3601
3.8366
3.8241
3.1284
3.1096
3.0822
3.0636
2.9496
2.9213
2.9040
2.8755
1.3942
H
N
O
O
OMe
OMe
Boc
Ph
2.54
NSM-8-79MeoH Final
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
5.99
1.02
1.08
1.98
0.98
6.32
0.99
1.00
9.25

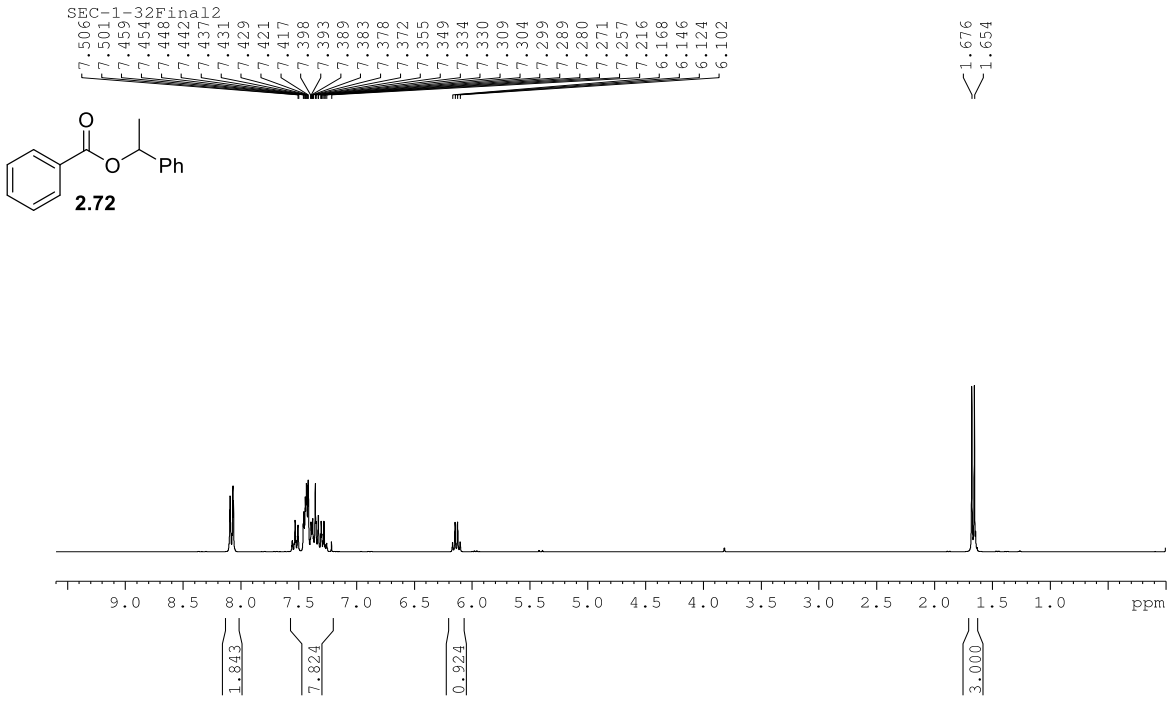

172.29
161.69
159.04
156.35
136.89
131.17
128.91
128.01
126.35
115.95
104.09
97.89
79.21
62.08
55.24
54.61
54.44
37.28
27.26
H
N
O
O
OMe
OMe
Boc
Ph
2.54
NSM-8-79FinalC13
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

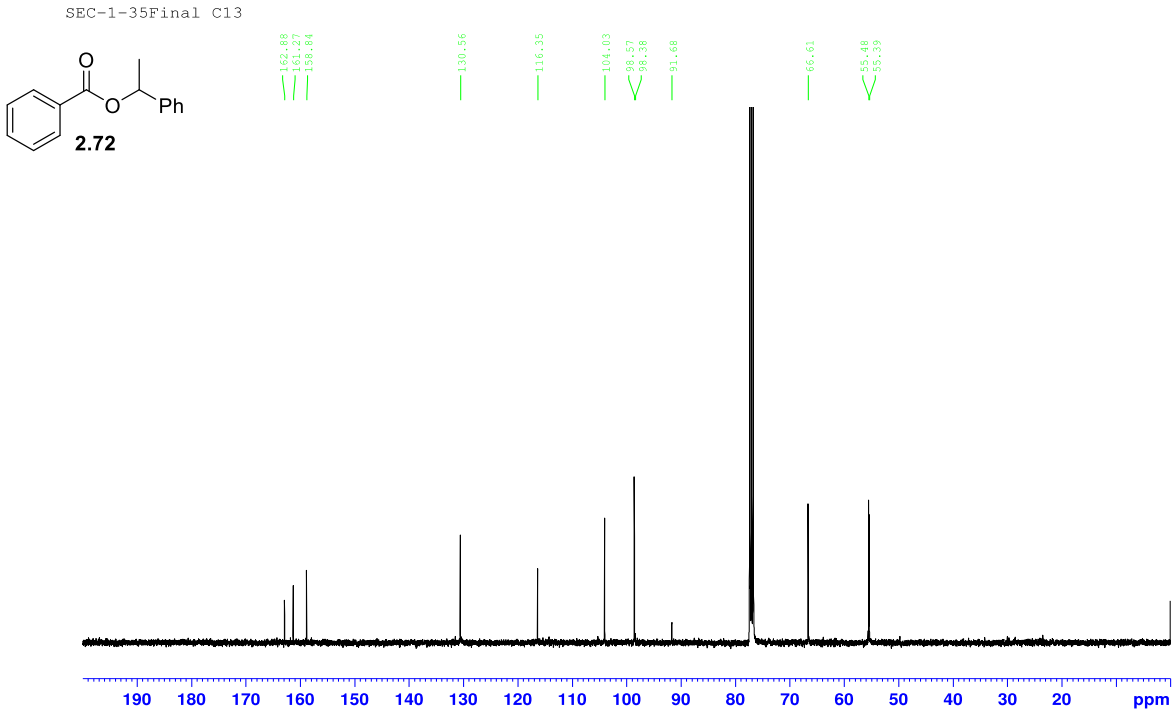
NSM-8-97Final.300

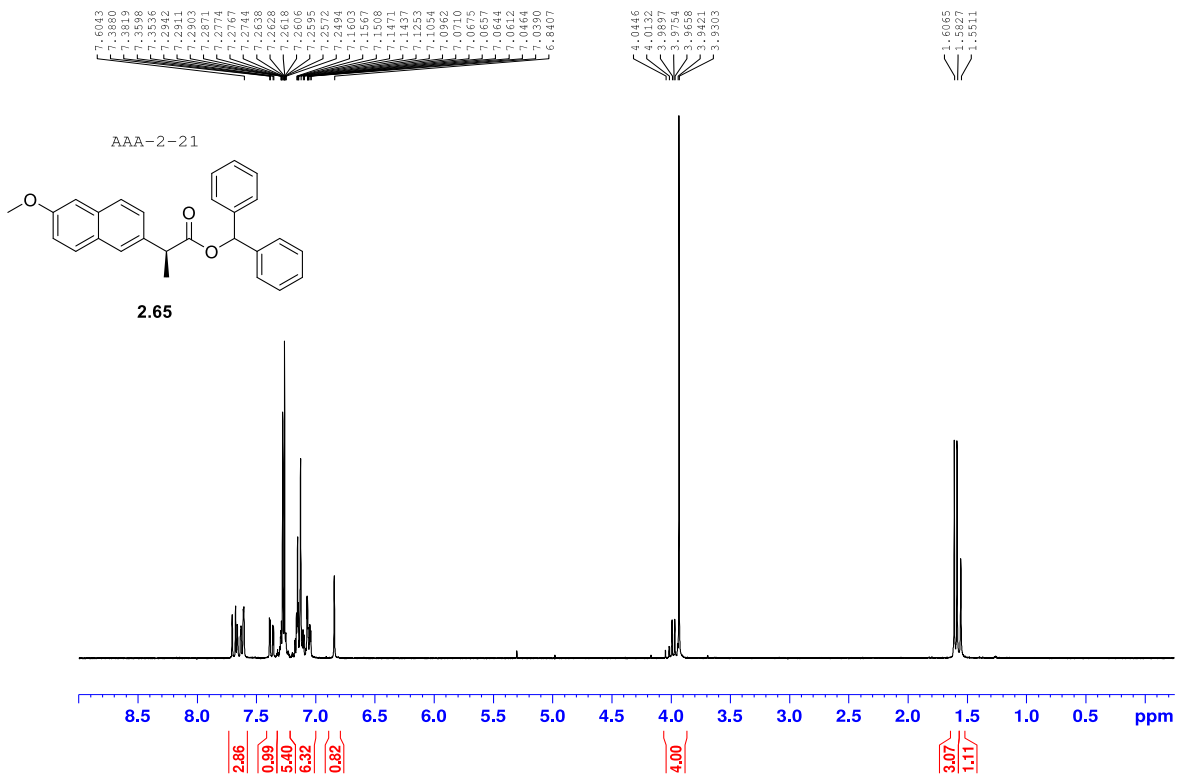


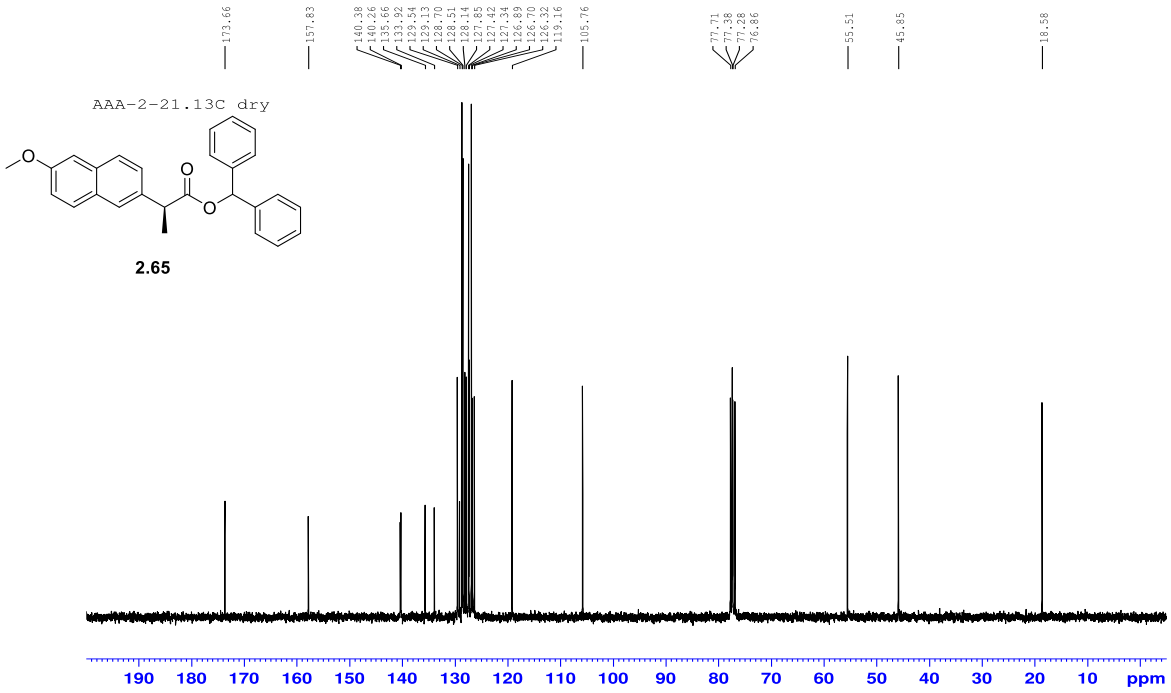
NSM-8-97FinalC13




SEC-1-32Final2
7.506
7.501
7.459
7.454
7.448
7.442
7.437
7.431
7.429
7.421
7.417
7.398
7.393
7.389
7.383
7.378
7.372
7.355
7.349
7.334
7.330
7.309
7.304
7.299
7.289
7.280
7.271
7.257
7.216
6.168
6.146
6.124
6.102
1.676
1.654
O
O
Ph
2.72
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.843
7.824
0.924
3.000


SEC-1-35Final C13
162.88
161.27
158.84
130.56
116.35
104.03
98.57
98.38
91.68
66.61
55.48
55.39
O
O
Ph
2.72
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


AAA-2-21
2.65
ppm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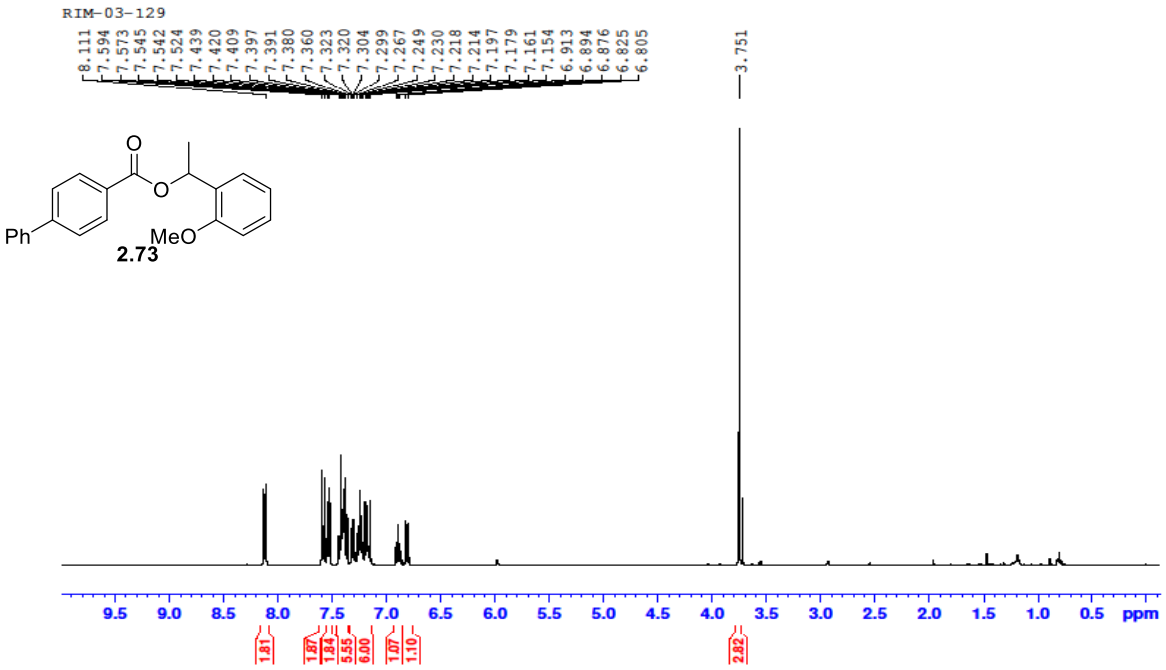
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7.420
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7.380
7.360
7.323
7.320
7.304
7.299
7.267
7.249
7.230
7.218
7.214
7.197
7.179
7.161
7.154
6.913
6.894
6.876
6.825
6.805
3.751
O
O
Ph
MeO
2.73
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
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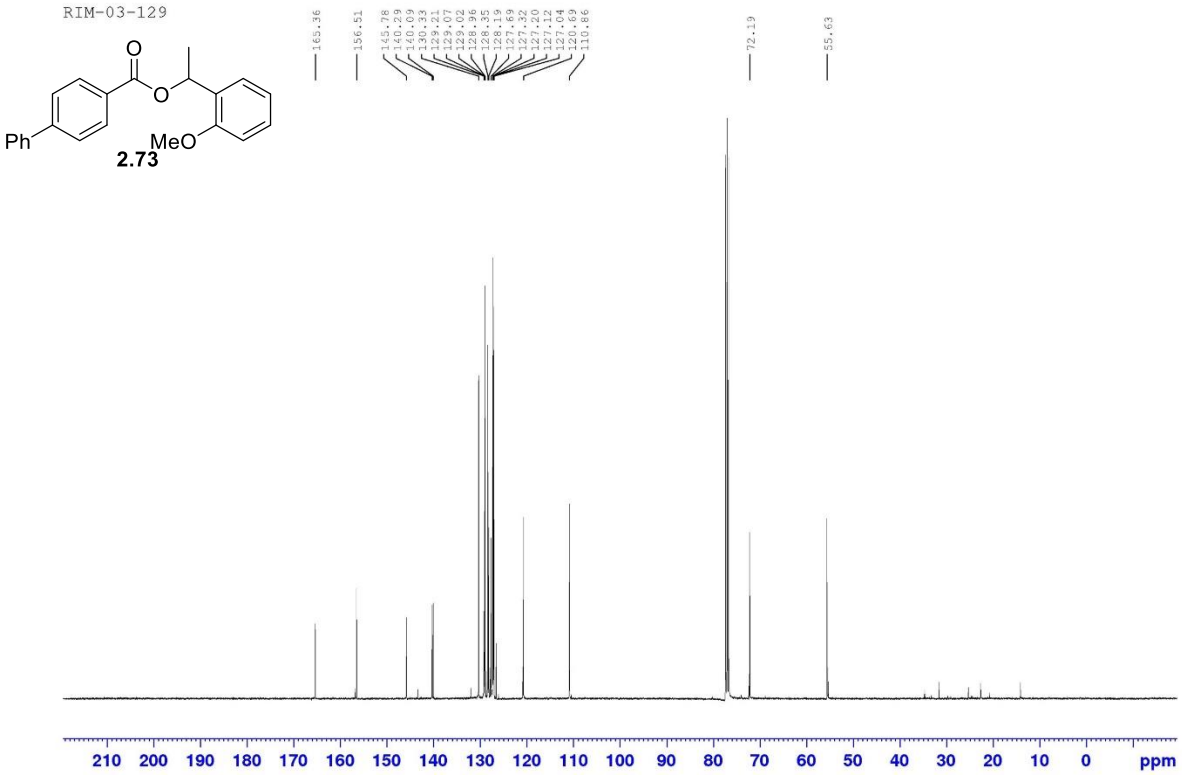
1.84
5.55
6.00
1.07
1.10
2.82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128.35
128.19
127.69
127.32
127.10
127.12
127.04
120.69
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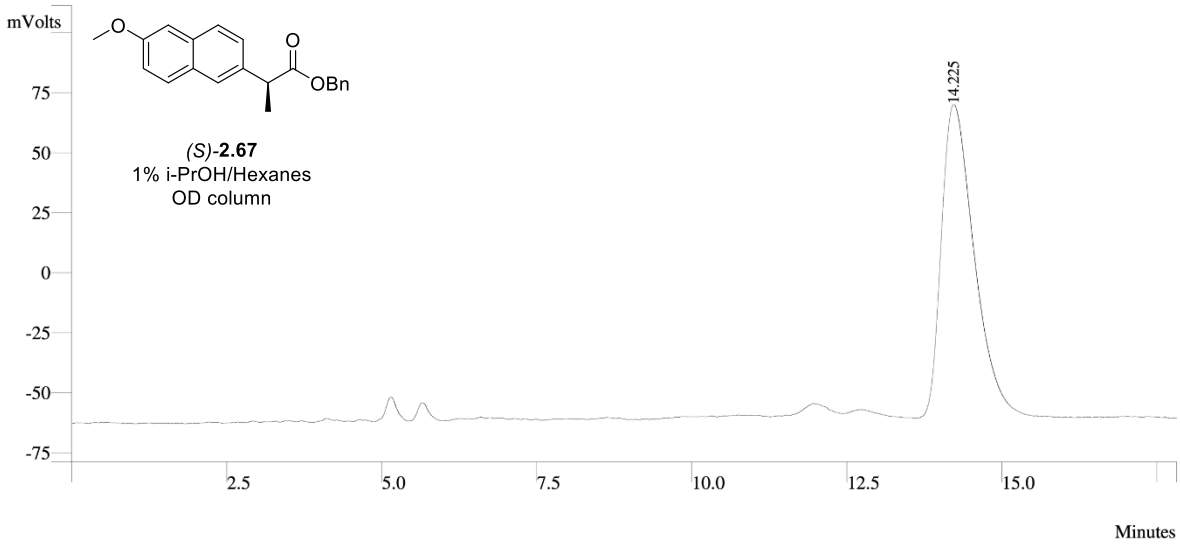
O
Ph
MeO
2.73
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



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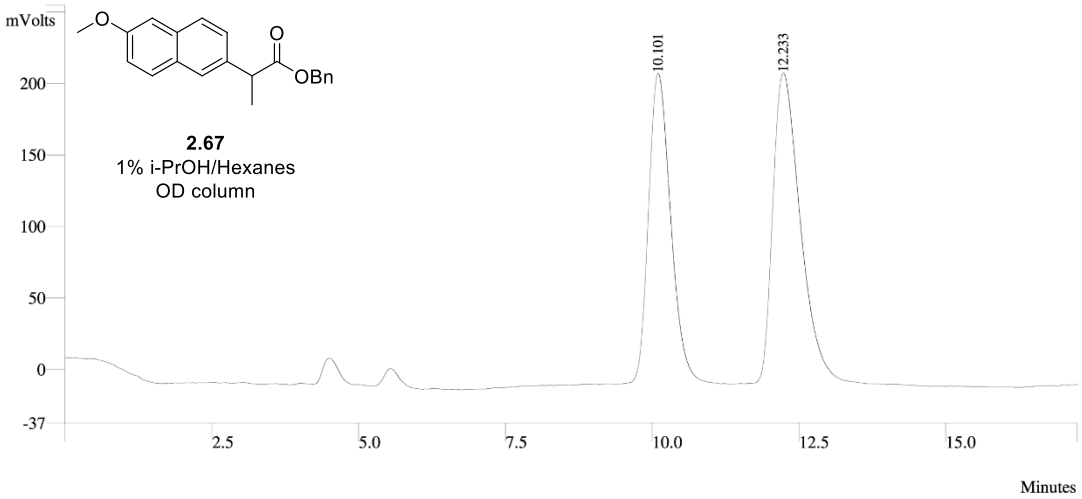

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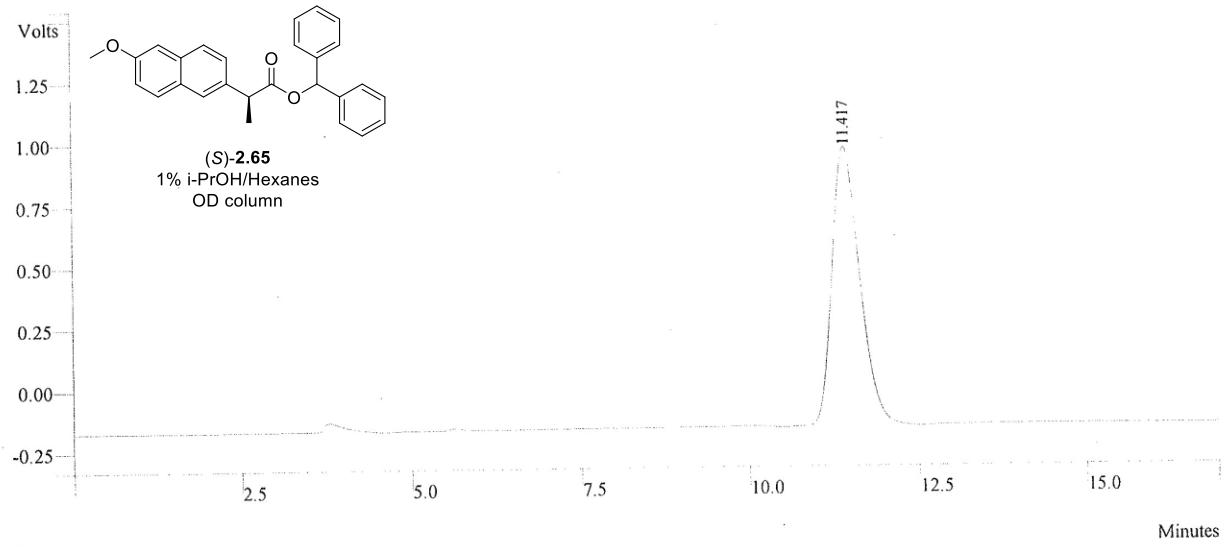
2		55.4306	12.233	0.000	7051221	0.00	BB	29.8		0
	Totals	**100.0000**		**0.000**	**12720814**					



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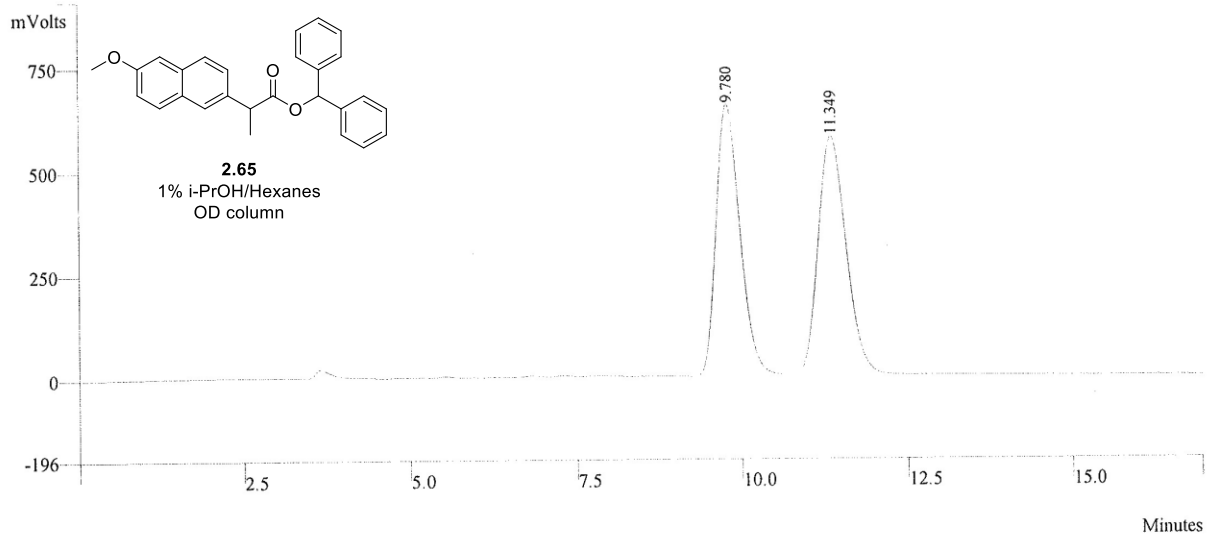
1		100.0000	11.417	0.000	32247062	0.00	BB	26.2		0
	Totals	**100.0000**		**0.000**	**32247062**					



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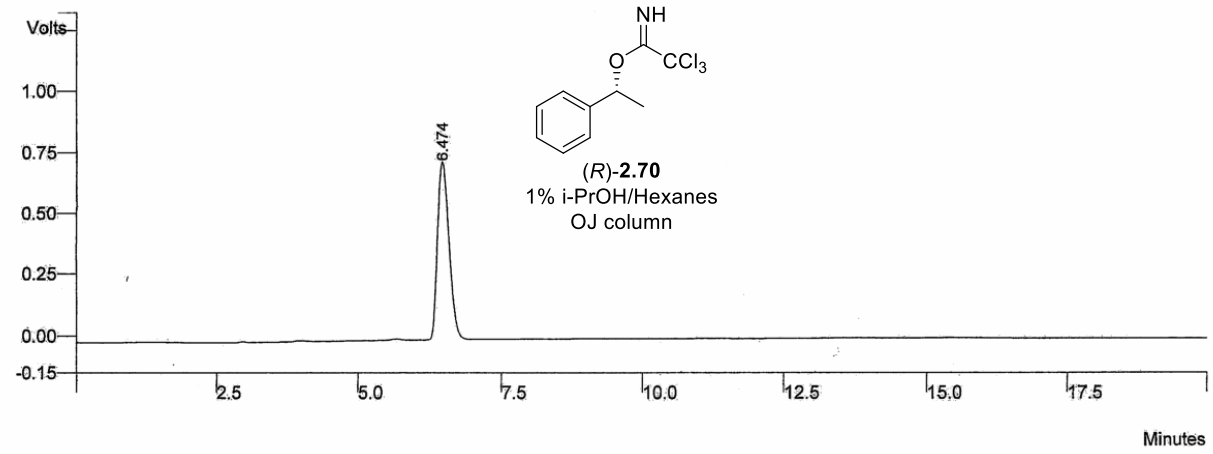
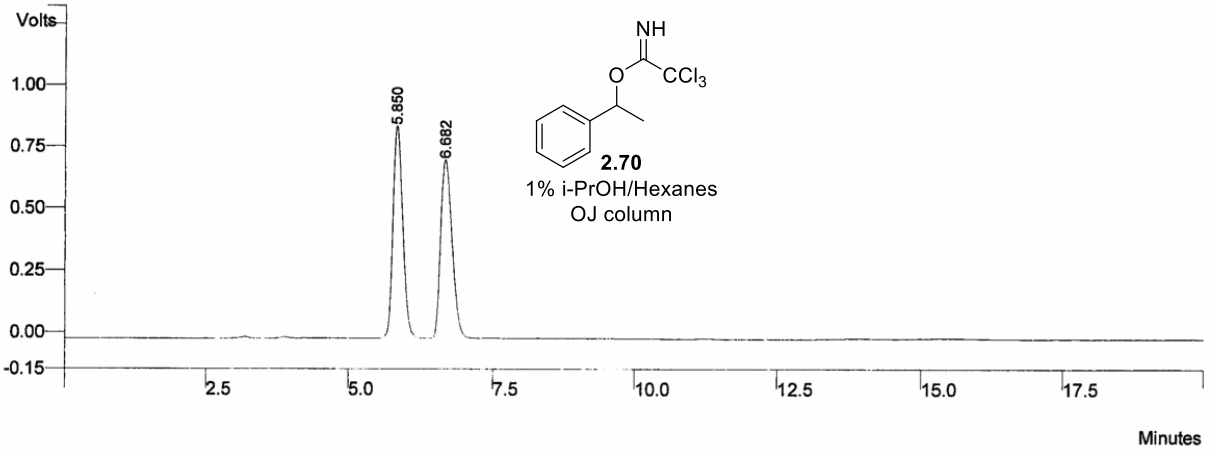
1		49.6425	9.780	0.000	16506846	0.00	BV	23.2		0
2		50.3575	11.349	0.000	16744576	0.00	VB	27.0		0
	Totals	**100.0000**		**0.000**	**33251422**					



Peak No	Ret. Time (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Result (Area%)
1	6.474	10175439	BB	13.3	100.0000
		10175439			**100.0000**



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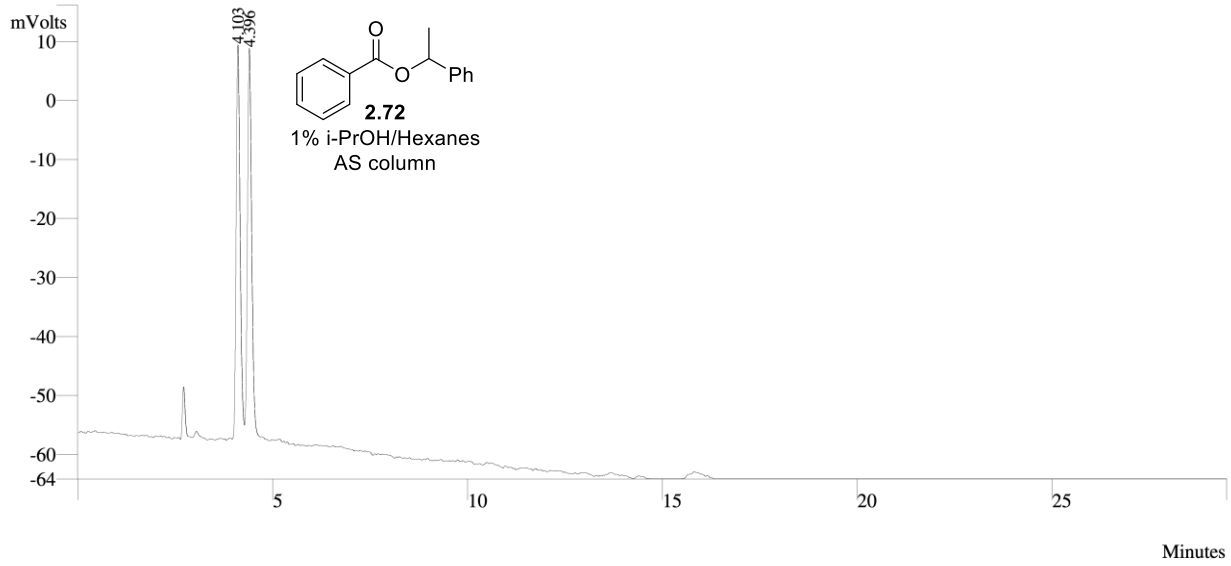
1	5.850	10219994	BV	11.1	50.4678
2	6.682	10030534	VB	13.1	49.5322
		20250528			**100.0000**



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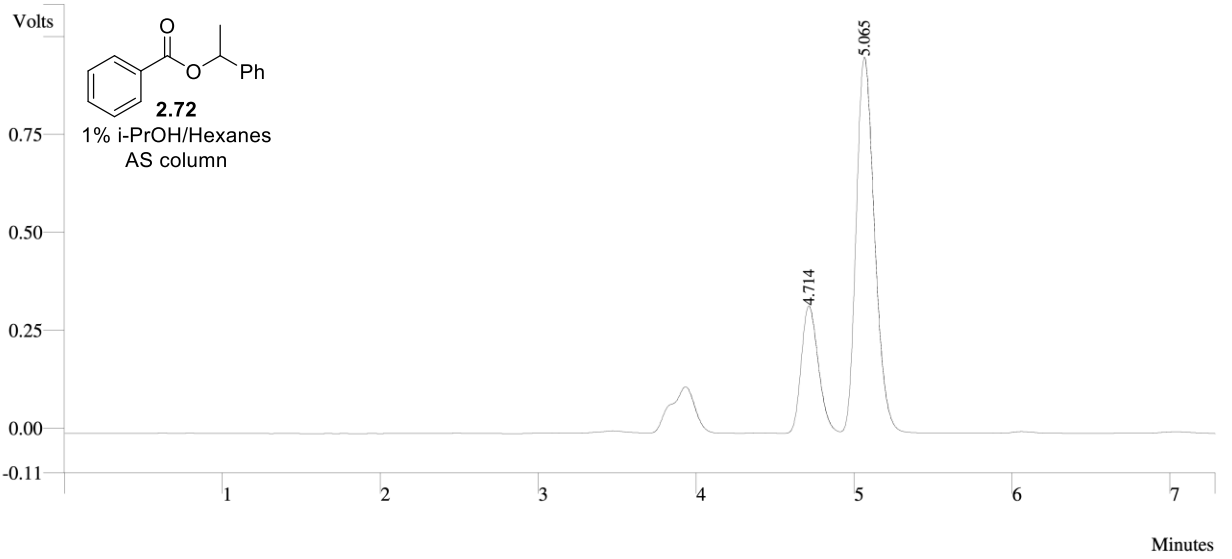
1		48.5749	4.103	0.000	475001	0.00	PV	6.6		0
2		51.4251	4.396	0.000	502874	0.00	VB	6.9		0
	Totals	**100.0000**		**0.000**	**977875**					



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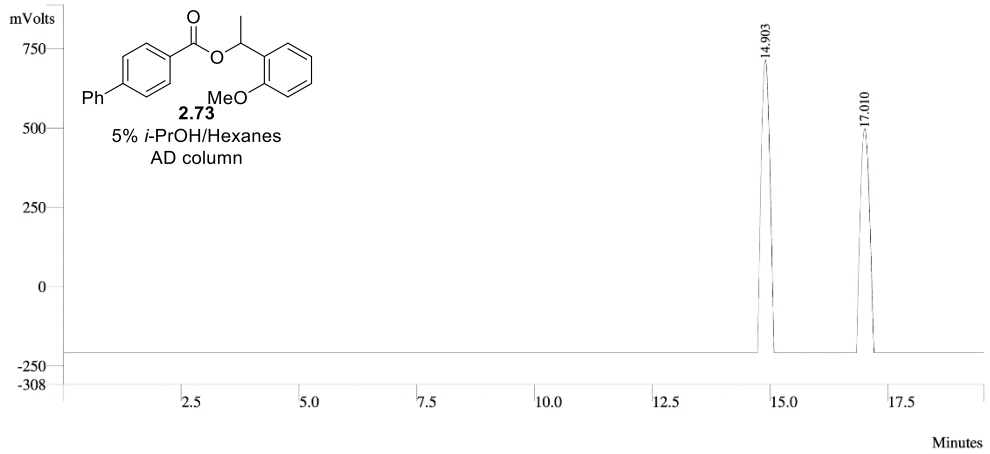
1		24.0312	4.714	0.000	2451316	0.00	BV	7.0		0
2		75.9688	5.065	0.000	7749253	0.00	VB	7.5		0
	Totals	**100.0000**		**0.000**	**10200569**					



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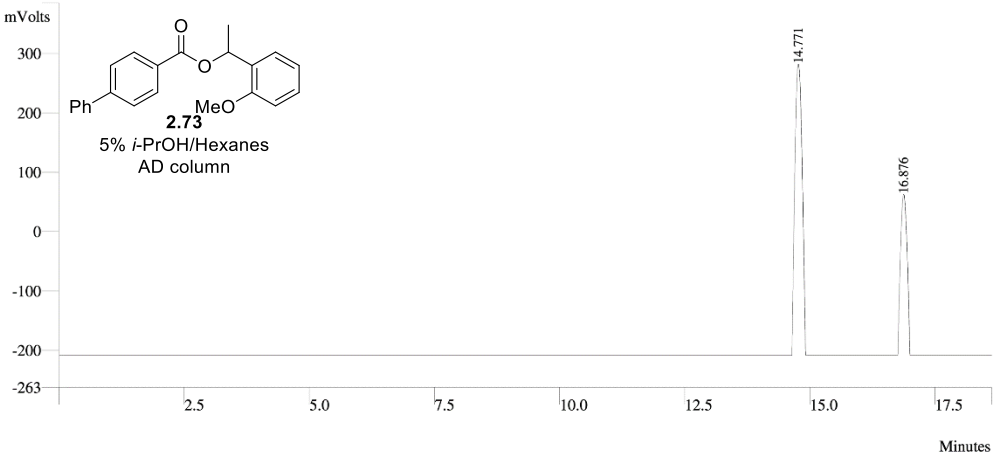
1		55.1168	14.903	0.000	11902913	0.00	BB	13.4		0
2		44.8832	17.010	0.000	9692872	0.00	BB	14.2		0
	Totals	**100.0000**		**0.000**	**21595784**					

HLPC:
loaded on with 1:1 hexanes:ipa

reaction conditions:
refluxing toluene overnight



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1		66.8169	14.771	0.000	5025223	0.00	BB	10.7		0
2		33.1831	16.876	0.000	2495666	0.00	BB	9.7		0
	Totals	**100.0000**		**0.000**	**7520889**					

HLPC:
loaded on with 1:1 hexanes:ipa

Reaction conditions:
DCM, rt, overnight

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Chapter 3 – Carbon-Nitrogen Bond Formation Utilizing Trichloroacetimidates in Rearrangements and Alkylations

Abstract:

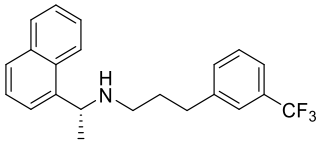
Benzylic amines are key structural features in pharmaceuticals, food additives, and insecticides. A large number of methods to synthesize benzylic amines have been developed but many of these protocols generate significant waste by-products. In addition, the benzylic amines are often protected as amides or carbamates in a second step, which requires additional resources and produces more waste. Alternatively, the rearrangement of benzylic trichloroacetimidates to acetamides may provide direct access to protected benzylic amine containing systems in a single step. The activity of palladium catalysts in the rearrangement of benzylic trichloroacetimidates to acetamides was explored. A catalytic system using tris(dibenzylideneacetone)dipalladium(0) gave promising results. The exploration of chiral ligands to access enantioenriched products from this reaction is now being investigated.

N-Alkylated pyrazoles and benzotriazoles are present in a number of natural products and pharmaceuticals. However current methods of synthesizing pyrazoles and benzotriazoles generally use hydrazine derivatives and exhibit limited regioselectivity. *N*-Alkylation of pyrazoles utilizing trichloroacetimidates electrophiles under Bronsted acid catalyzed conditions has been developed. Both primary and secondary imidates provided good yields. Benzylic primary imidates provided significantly better yields than phthalimidomethyl imidate. Structurally different pyrazoles were also studied in this transformation. Interestingly, when a similar alkylation was studied with benzotriazole, a single product was isolated in good yield. This was the dearomatized N^2-alkylated product. Further substrate scope investigations and mechanism studies need to be performed to better understand these results.

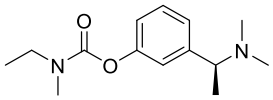
Introduction:

Benzylic amines are key structural features often found in pharmaceuticals, food additives, and insecticides.[1] Some examples from pharma include Cinacalcet, a drug used to treat chronic kidney disease (Figure 3.1).[2, 3] Amgen has made 357 million dollars in profit from this drug since its approval for sale.[4] Additionally the Novartis product Rivastigmine also features a benzylic amine, and is used to treat dementia (Figure 3.1).[5-7]

Figure 3.1. Structures of Cinacalcet and Rivastigmine[2-7]



3.1
Cinacalcet
Amgen
$357 million

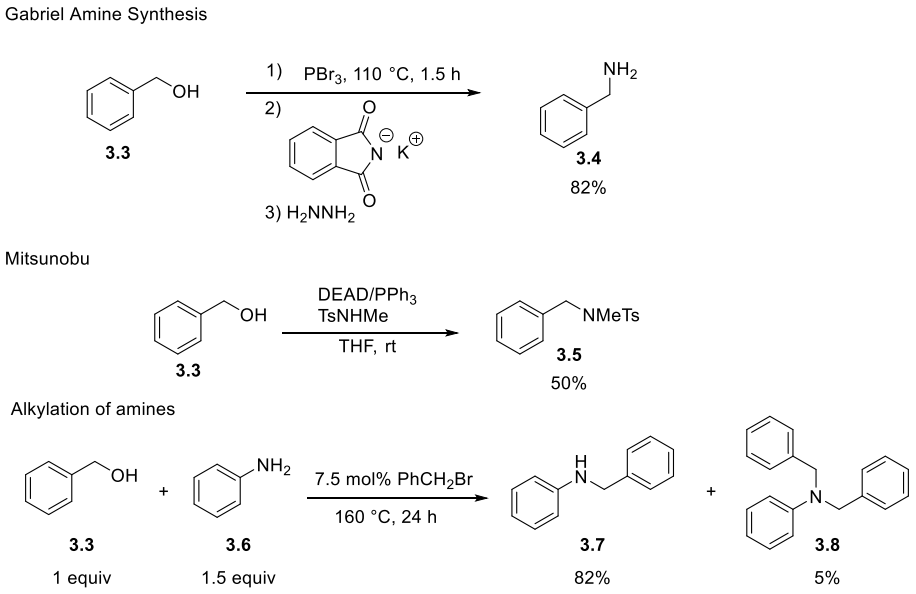


3.2
Rivastigmine
Novartis
$ 444 million

Given their importance, a number of different methods to synthesize benzylic amines have been developed from a variety of starting materials. Alkylations are one method to synthesize benzylic amines from simpler substrates. Benzylic alcohols can be converted to a leaving group (such as a bromide or sulfonate) which is then displaced with phthalimide. Removal of the phthalimide with hydrazine and heat provides the amine, with the entire process being referred to as the Gabriel amine synthesis. However, the harsh conditions which produce phthalhydrazide as a waste product are only amenable to the synthesis of primary amines.[8-11] Another method to synthesize amines from alcohols is the Mitsunobu reaction. While in this case the stereochemistry can be controlled, as the reaction proceeds through an S_N2 mechanism, two major side products – a phosphine oxide and a hydrazinedicarboxylate – are produced which can be difficult to separate from the desired amine.[12-14] Amines may also be directly alkylated with alkyl halides; however,

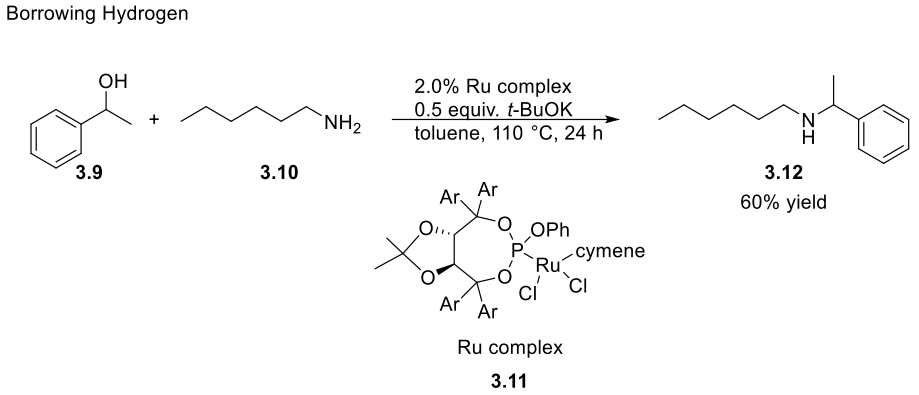
polyalkylation can occur, leading to undesired quaternary amine side products and limiting yields (Scheme 3.1).[8-15]

Scheme 3.1. Synthesis of Amines via Alkylations[8-15]



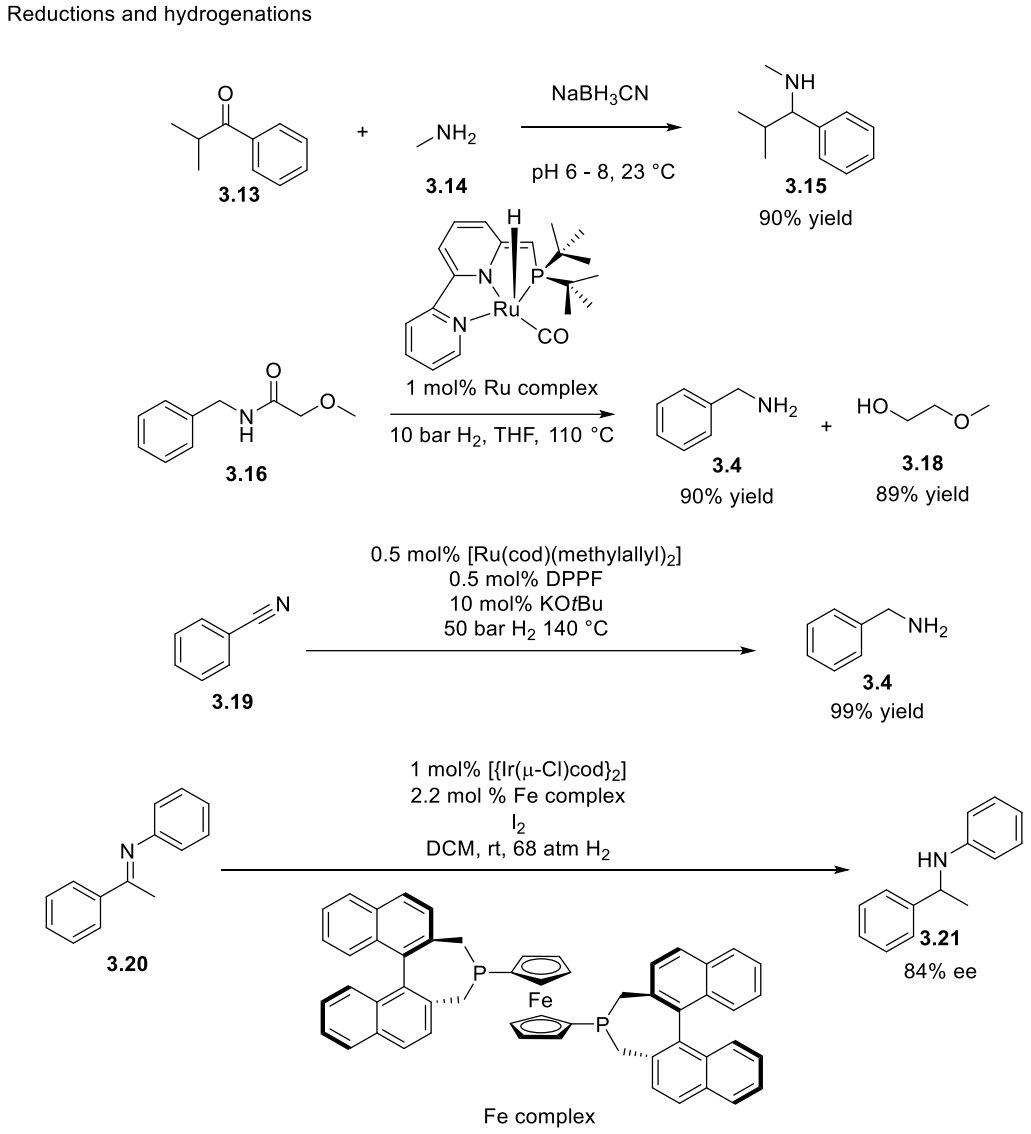
More recently amines have been synthesized directly from alcohols using "borrowing hydrogen" methods. These methods use transition metal catalysts and stoichiometric strong bases (Scheme 3.2).[16] Mechanistically, the transformation occurs by oxidation of the alcohol to the carbonyl, followed by imine formation with subsequent reduction using the same hydrogen atoms from the starting alcohol to produce the substituted amine and water. As the same hydrogens which are removed from the starting material reappear in the product, the process is often referred to as "borrowing hydrogen". While these methods are very atom economical, the reactions require high temperatures and strong bases, and in many cases the yields are only moderate.

Scheme 3.2. Synthesis of Amines via the Borrowing Hydrogen Technique[16]



Reductive methods may also be employed to produce benzylic amines via the amides or imines (Scheme 3.3).[16-20] Ketones and aldehydes can be transformed to amines through reductive amination using a hydride reducing agent and catalytic amounts of acid. This avoids the problem of over alkylation of amines; however, both the commonly used sodium cyanoborohydride and its byproducts are highly toxic.[17] A more recent protocol of reductive amination uses a less toxic reagent, sodium triacetoxyborohydride.[19] Nitriles can also be reduced to primary amines using lithium aluminum hydride. Unfortunately, lithium aluminum hydride is highly flammable.[18] Nitriles can also be hydrogenated to primary amines with a transition metal catalyst, a strong base, and hydrogen (Scheme 3.3).[19] Amides can be reduced as well with lithium aluminum hydride to synthesize primary, secondary or tertiary amines; however, these reactions still use a highly flammable reagent. Hydrogenation of amides with transition metals under high pressure of hydrogen gas may also be employed; however, these reactions produce an alcohol and a primary amine (Scheme 3.3).[20] Therefore, only one of the main products of the reaction is the desired product. The hydrogenation of imines can be performed with high enantioselectivity by using transition metals, chiral ligands, and high pressures of hydrogen (Scheme 3.3).[21] The high pressures of hydrogen are, unfortunately, not ideal for many applications.

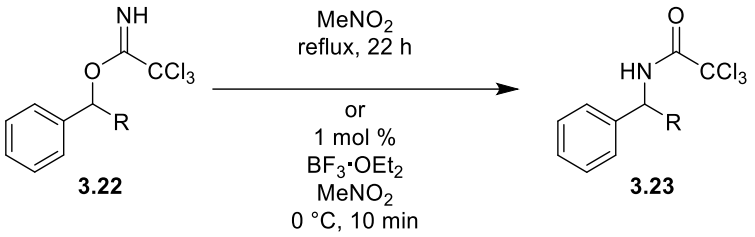
Scheme 3.3. Synthesis of Amines from Reductions and Hydrogenations[16-21]



Recently, our group has become interested in the rearrangement of benzylic trichloroacetimidates to the acetamides, which may provide access to benzylic amine containing systems. While the rearrangement of allylic trichloroacetimidates is known, the benzylic trichloroacetimidate rearrangement was not explored in detail before our work.[22] This rearrangement of benzylic imidates provides quick access to protected benzylic amines and analogues. In 1961, the rearrangement of benzylic trichloroacetimidates to the corresponding acetamide using a Lewis acid was first reported by Cramer.[23] Later, Schmidt and others found

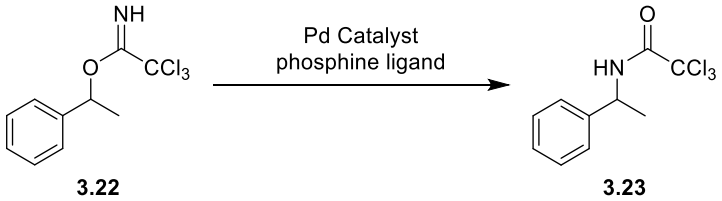
glycosidic trichloroacetimidates could be converted to the acetamide with Lewis acids.[24] More recently we developed both thermal and Lewis acid catalyzed conditions (Scheme 3.4) to promote the rearrangement. However, these conditions are not enantioselective. When performed with the imidate derived from enantiopure 1-phenethyl alcohol, both the thermal and acid catalyzed product gave product that exhibited less than 10% enantiomeric excess. This racemization was attributed to a carbocation intermediate in the rearrangement.

Scheme 3.4. Thermal and Acid Catalyzed Conditions of Imidate Rearrangement[22]



Investigations have now been initiated to develop an enantioselective rearrangement. An exploration of reaction conditions using palladium catalysts and phosphine ligands was performed using the system shown below (Scheme 3.5). While these conditions do employ a transition metal catalyst, they do not require a high pressure of hydrogen since it is not a hydrogenation reaction. These conditions are also atom economical since all the atoms in the substrate are in the product, with no stoichiometric waste by-products being produced.

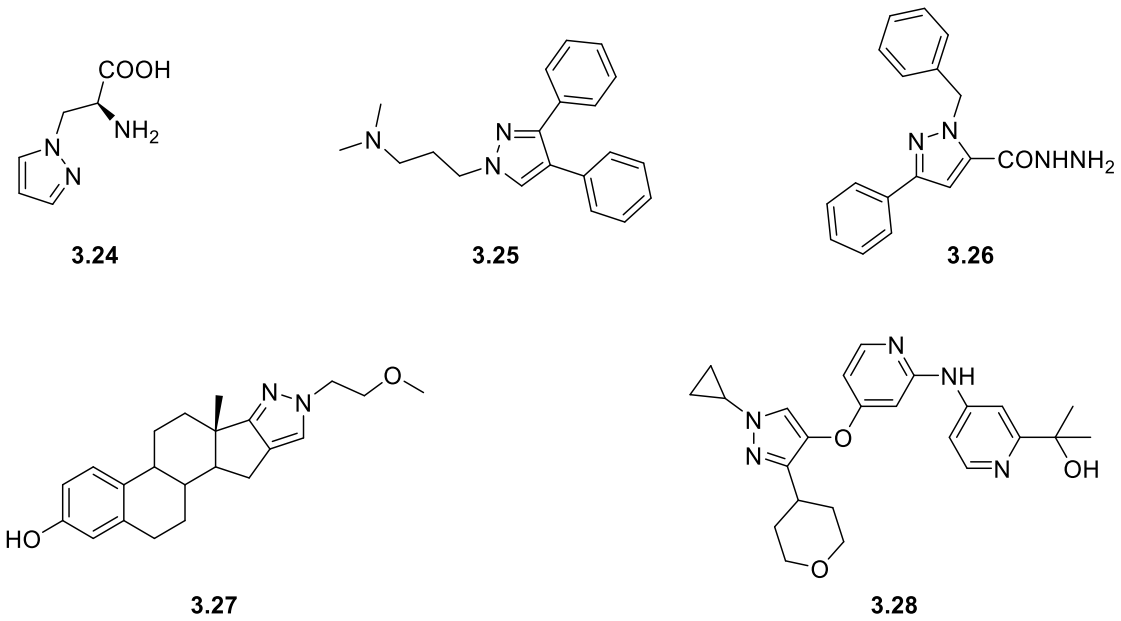
Scheme 3.5. Reaction for Screening Rearrangement Conditions



Trichloroactmidates were also investigared as alkyating agents for the *N*-alkylation nitrogen containing heterocycles, specifically pyrazoles and benzotriazoles. Pyrazole motifs are

present in a variety of natural products and pharmaceuticals (Figure 3.2).[25, 26] For example, amino acid **3.24** was isolated from *Citrullus vulgaris* and showed activity in some anti-diabetic assays.[27] Fezolamine **3.25** was used in clinical trials as an antidepressant. Hydrazine **3.26** was investigated as a possible lung cancer therapeutic.[28] Modified steroid **3.27** was found to be a potent inhibitor of 17β-HSD type 1, which could be used to treat hormone dependent breast cancer.[29] Eli Lilly and company currently has *N*-alkylated pyrazole **3.28** in clinical trials as a TβR-1 kinase inhibitor to prevent pro-tumorigenic cellular activity.[30]

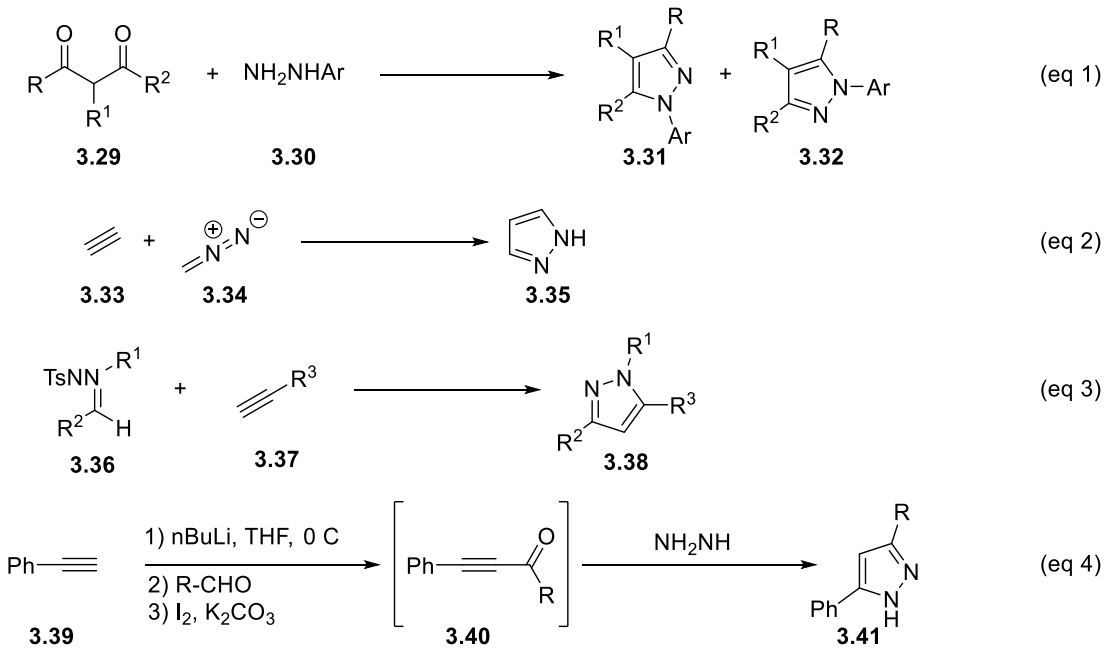
Figure 3.2. Examples of Pyrazole-based Biologically Active Compounds



The first synthesis of pyrazoles was reported by Knorr in 1883 (Scheme 3.6, eq 1). Current methods to synthesize pyrazoles include cyclocondensation of hydrazine and 1,3-dicarbonyl systems, dipolar cycloadditions, and multicomponent reactions.[31] While the cyclocondensation of 1,3-dicarbonyl compounds with hydrazine is a simple and rapid approach, it often provides two regioisomers, pyrazoles **3.31** and **3.32**. Also, hydrazine is a strong reducing agent that is toxic and explosive.[32] After the initial Knorr method, a cycloaddition approach to pyrazoles using acetylene

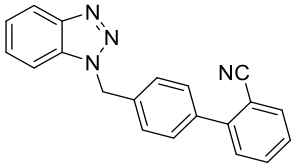
and diazomethane was reported by Pechmann in 1898 (Scheme 3.6, eq 2).[33] Again, high regioselectivity for substituted pyrazoles was difficult to achieve with this method. More recently, hydrazones were used as an *in situ* source of diazo compounds that can react with alkene or alkynes (Scheme 3.6, eq 3) to form pyrazoles. Under these conditions significant regioselectivity has been reported under basic[25] or acidic conditions.[34] Multicomponent one-pot synthesis of pyrazoles have been reported using terminal alkynes, aldehydes, and hydrazine (Scheme 3.6 eq 4).[35]

Scheme 3.6. Common Examples of Pyrazole Synthesis

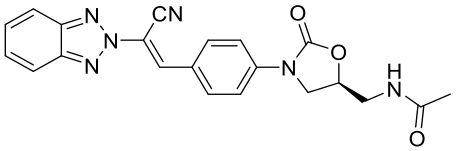


The structurally related benzotriazoles have also shown significant biological activity. Benzotriazole **3.42** is an antimicrobial and benzotriazole **3.43** is an antibacterial (Figure 3.3). [36, 37] Some biological active products are N^1 alkylated, and some products are N^2 alkylated. This has spurred investigations into the selective alkylation of the benzotriazole core, as the biological activity of the two alkylated isomers is quite distinct.

Figure 3.3. Examples of Biologically Active Benzotriazole-based Compounds



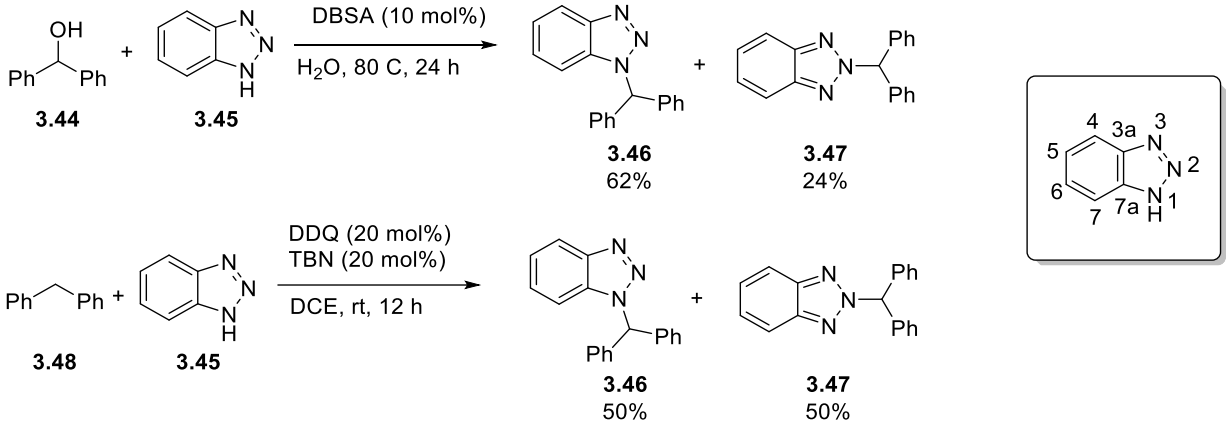
3.42



3.43

However, selectively alkylating N^1 or N^2 of a benzotriazole has proven synthetically challenging, typically resulting in mixtures (scheme 3.7).[38, 39] Since the isomers are so similar, separating the N^1 from N^2 alkylated products can be difficult. Therefore, research into selective alkylation conditions would be synthetically useful to access these products.

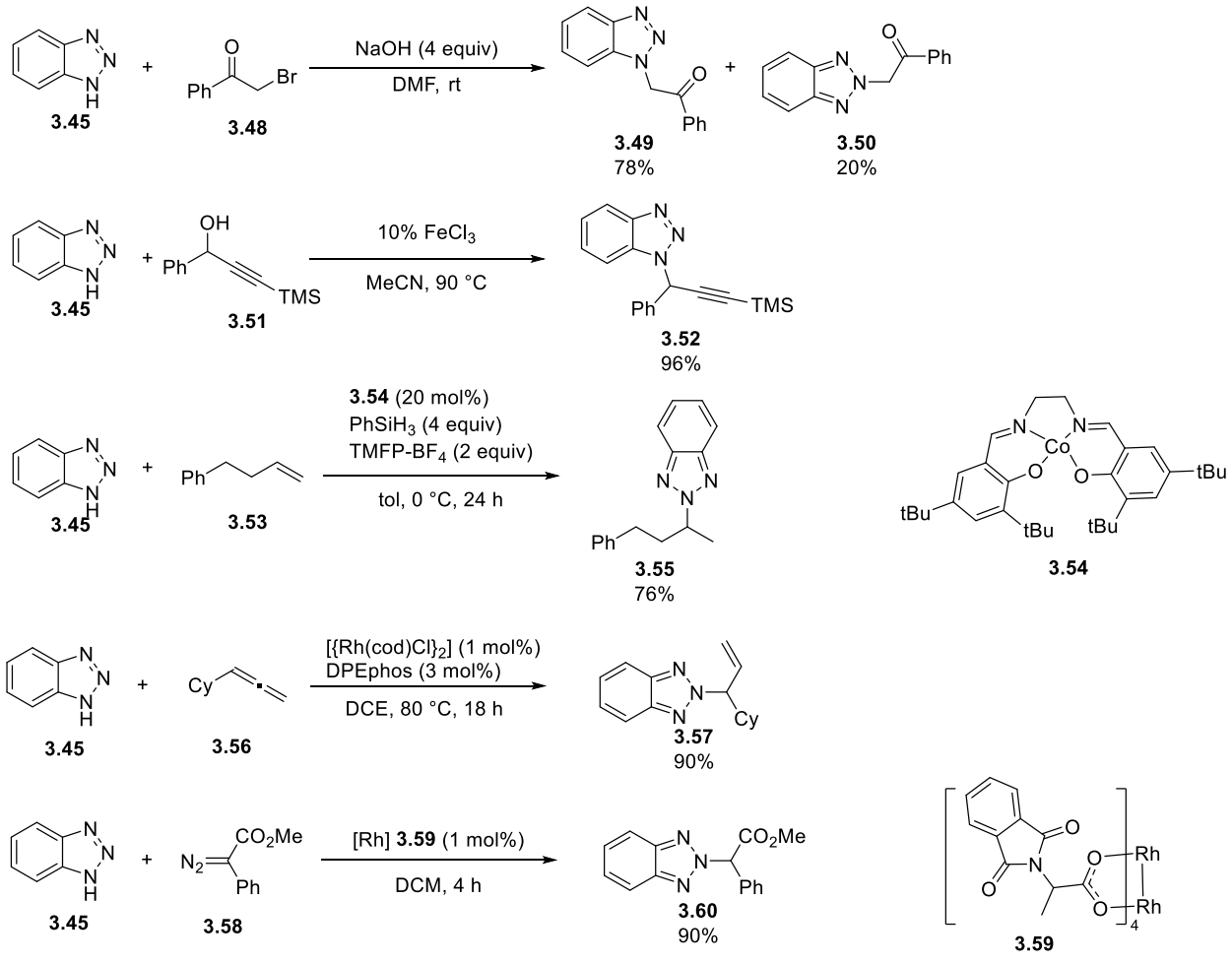
Scheme 3.7. Methods for *N*-Alkylation of Benzotriazole



In 1991, Greenhill and co-workers used excess hydroxide in DMF to alkylate benzotriazoles and 1,2,4-triazole.[40] While their findings were an improvement to using alkoxides[41] or hydrides[42] in respect to yield, these conditions typically provided a 1:1 mixture of N^1 and N^2 alkylation. However, when 2-bromoacetophenone **3.48** was used N^1 alkylation was favored (4:1, Scheme 3.8). Later different transition metal catalysts were employed in selective alkylations of triazoles. For example, Shi and co-workers found that utilizing an iron chloride in acetonitrile could provide selective N^1 alkylation of benzotriazole and secondary propargyl alcohols (Scheme

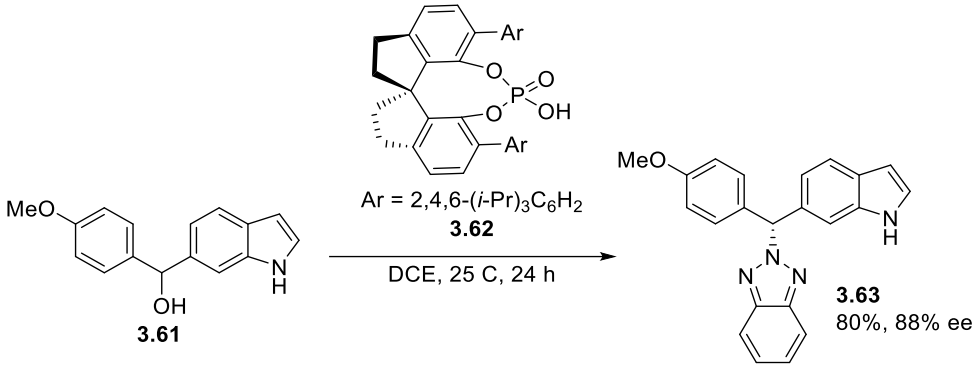
3.8).[43] Akai and co-workers reported a cobalt-catalyzed Markovnikov-selective hydroamination to provide selective N2 alkylation of benzotriazoles (scheme 3.8).[44] In 2014, Breit and co-workers developed the first N2 selectively alkylation benzotriazoles with allenes by using a rhodium and DPEphos catalytic system.[45] Later, a rhodium-catalyzed cross-coupling reaction with benzotriazoles and diazo or eynones was developed for regioselective N^2 alkylation by Sun and co-workers (Scheme 3.8).[46] This utilized a metal carbene to selectively alkylate N2 through 1,3 hydride shift.

Scheme 3.8. Examples of Benzotriazole Alkylations



These methods were not enantioselective; however, in 2020 an enantioselective N^2 alkylation using chiral phosphoric acid was developed via a 1,8-conjugate addition to 6-methylene-6H-indoles.[47] While this method is metal-free, it utilizes an expensive chiral phosphoric acid **3.62**, and takes several steps to synthesize, and is limited to alcohols that form very stable carbocations.

Scheme 3.9. Enantioselective N^2 Alkylation of Benzotriazole

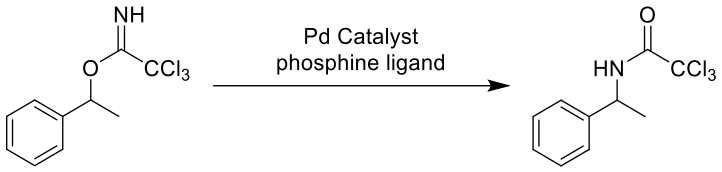


Given our recent studies on promotor free or acid catalyzed heteroatom substitution with trichloroacetimidate electrophiles,[48, 49] we hypothesized that trichloroacetimidates could be used as effective and regioselective tools for the *N*-alkylation of pyrazoles and triazoles.

Results and Discussion Part 1: Palladium Catalyzed Rearrangement of Benzylic Trichloroacetimidates to Trichloroacetamide

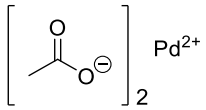
Palladium complexes were investigated to determine if they could catalyze the benzylic trichloroacetimidate rearrangement, as they are well known to catalyze the rearrangement of allylic trichloroactimidates.[50-58] An initial set of experiments were performed in methylene chloride at room temperature for the imidate rearrangement shown in Table 3.1. These reactions were carried out using 1-phenethyl imidate **3.22** (0.1M), 3 mol % of Pd, and 9 mol% of a phosphine ligand. However, these conditions did not promote the rearrangement of imidate **3.22** to the trichloroacetamide **3.23**. These results prompted the investigation of more vigorous conditions to execute the rearrangement.

Table 3.1. Initial Reaction Screening with Phenethyl Imidate **3.22**

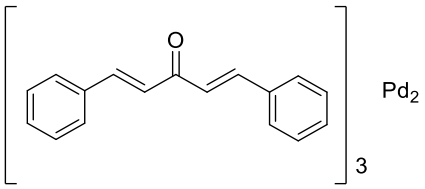


3.22 **3.23**

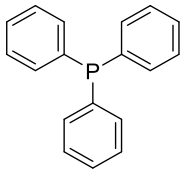
Entry[a]	Pd Catalyst	Ligand	Solvent	Temp. (° C)	Conversion*
1	3% $Pd(OAc)_2$	-	DCM	Rt	0
2	1.5 % $Pd_2(dba)_3 \cdot CHCl_3$	-	DCM	Rt	0
3	-	9% PPh_3	DCM	Rt	0
4	-	9% BINAP	DCM	Rt	0
5	3% $Pd(OAc)_2$	9% PPh_3	DCM	Rt	0
6	3% $Pd(OAc)_2$	9% BINAP	DCM	Rt	0
7	1.5% $Pd_2(dba)_3 \cdot CHCl_3$	9% PPh_3	DCM	Rt	0
8	1.5% $Pd_2(dba)_3 \cdot CHCl_3$	9% BINAP	DCM	Rt	0



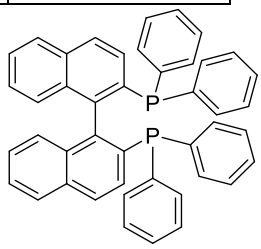
$Pd(OAc)_2$



$Pd_2(dba)_3 \cdot CHCl_3$



triphenylphosphine



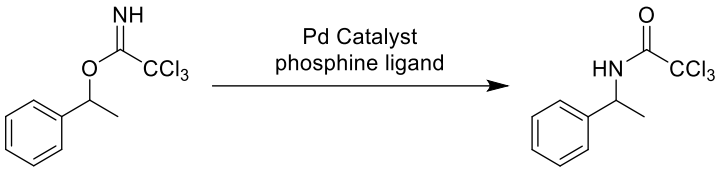
2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene (BINAP)

[a]reactions ran for 18h, *% conversion determined by ^{1}H NMR

A new set of screening reactions was then performed; this time with a higher catalyst loading (5 mol% of Pd) and a range of different solvents and temperatures (Table 3.2). The ^{1}H NMR spectrum of each crude reaction was analyzed to determine conversions (sample calculations in the experimental section). Previous results indicated that this rearrangement occurs best in polar aprotic solvents.[22] However, using more polar solvents did not increase conversion in the palladium catalyzed reaction. Instead, toluene at reflux showed the highest conversion.

Additionally, as shown by table 2 entry 15, no rearrangement occurs without the palladium catalyst. The $Pd(OAc)_2$ catalyst showed poor conversions (Table 3.2 entries 1, 2, 5, 6, 9, 10); however, $Pd_2(dba)_3 \cdot CHCl_3$ exhibited the good conversions to trichloroacetamide **3.23** with PPh_3. This suggests that Pd (0) complexes are preferred in this reaction. Using toluene at reflux with Pd_2dba_3 and triphenylphosphine gave the highest conversion of 86%, however there was a trace amount of styrene (the competing elimination product) observed. Across the board, the use of BINAP as a ligand was not favorable for this reaction, showing little or no rearrangement. The lower conversion with BINAP demonstrated that the reaction conversion could be modulated by choice of phosphine ligands, which was promising for an enantioselective rearrangement.

Table 3.2. Solvent and Temperature Screening



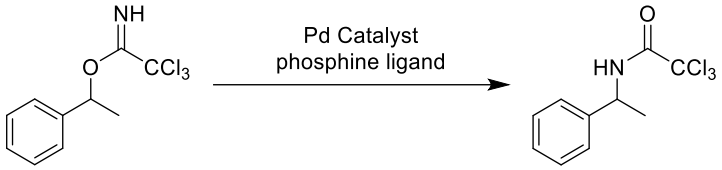
3.22 **3.23**

Entry[a]	Pd Catalyst	Ligand	Solvent	Temp. (° C)	Conversion*
1	5% $Pd(OAc)_2$	9% PPh_3	toluene	110	Trace
2	5% $Pd(OAc)_2$	9% BINAP	toluene	110	0
3	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	9% PPh_3	toluene	110	86[b]
4	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	9% BINAP	toluene	110	9[b]
5	5% $Pd(OAc)_2$	9% PPh_3	THF	60	12
6	5% $Pd(OAc)_2$	9% BINAP	THF	60	-
7	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	9% PPh_3	THF	60	49[b]
8	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	9% BINAP	THF	60	0
9	5% $Pd(OAc)_2$	9% PPh_3	acetonitrile	75	32
10	5% $Pd(OAc)_2$	9% BINAP	acetonitrile	75	0
11	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	9% PPh_3	acetonitrile	75	10
12	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	9% BINAP	acetonitrile	75	5
13	5% $Pd(OAc)_2$	9% PPh_3	DMF	150	0
14	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	9% PPh_3	DMF	150	0
15	-	-	toluene	110	0

[a]reactions ran for 18h, *% conversion determined by ^1H NMR, [b] trace amounts of styrene

With the optimum solvent being determined as toluene, a screening of the proper amount of ligand was undertaken (Table 3.3). Controls were performed for the rearrangement using only Pd complex in refluxing toluene and using only triphenylphosphine. Interestingly, performing the reaction with only the $Pd_2(dba)_3$ complex gave a 95% conversion. Some trace amounts of dibenzylideneacetone (dba) ligand were observed in the ^1H NMR as well. Later, isolated yields were obtained, however, these yields were low despite the reactions showing high conversion. This may be due to the formation of styrene as a byproduct which is removed by a silica plug before the conversion is calculated by ^1H NMR.

Table 3.3. Ligand Screening Reactions



3.22 3.23

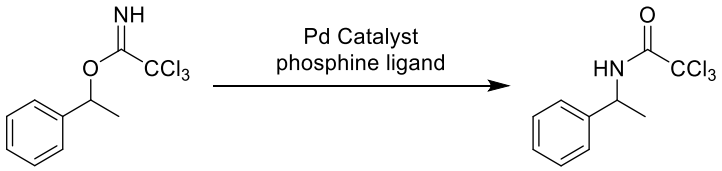
Entry[a]	Pd Catalyst	Ligand	Solvent	Temp. (° C)	Conversion*	Isolated Yield (%)[c]
1	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5% PPh_3	toluene	110	>99[b]	
2	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	10% PPh_3	toluene	110	>99	
3	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	15% PPh_3	toluene	110	98[b]	
4	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	20% PPh_3	toluene	110	>99[b]	16
5	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	-	toluene	110	95	40
6	-	15% PPh_3	toluene	110	3	

[a]reactions ran for 18h, *% conversion determined by ^1H NMR, [b]trace amounts of styrene, [c]trace amounts of dba

The temperature of the reaction was also investigated, as lower temperatures may have a better chance of providing enantioselective conditions and minimize the formation of elimination

side-products. Another set of experiments in toluene at lower temperatures were investigated, which are shown in Table 3.4. However, no conversion to the acetamide **3.23** was observed except in refluxing toluene, therefore refluxing toluene was utilized in the future investigations.

Table 3.4. Reactions in Toluene at Different Temperatures



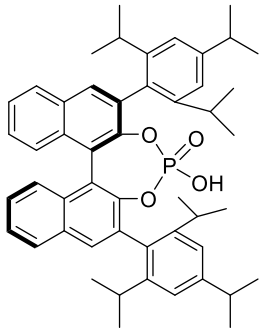
3.22 **3.23**

Entry	Pd Catalyst	Ligand	Solvent	Temp. (° C)	Conversion*
1	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	15% PPh_3	toluene	60	2
2	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	-	toluene	60	0[b]
3	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	15% PPh_3	toluene	rt	0
4	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	-	toluene	rt	0
5	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	15% PPh_3	toluene	rt[a]	0
6	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	-	toluene	rt[a]	0

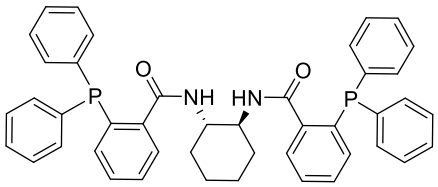
*% conversion determined by ^{1}H NMR, [a] reactions ran for 2 days at this temperature, [b] trace amounts of styrene

While these low isolated yields may be problematic, they may also be ligand dependent, so the use of chiral ligands to control the enantioselectivity of the transformation was also investigated. The chiral ligands that were utilized in this study are shown below in Figure 3.4. Ligand **3.65** was especially interesting, as it has been used to control enantioselectivity in other π-allyl systems and therefore may be able to control enantioselectivity in this rearrangement, if it is proceeding through a similar pathway.[59] Shown below in Table 3.5 are the initial studies of the rearrangement with chiral ligands.

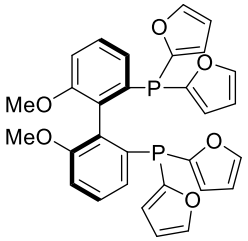
Figure 3.4. Chiral Ligands Evaluated in the Imidate Rearrangement



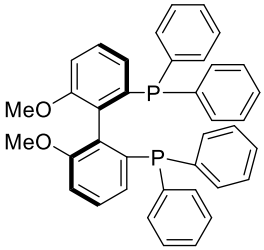
3.64



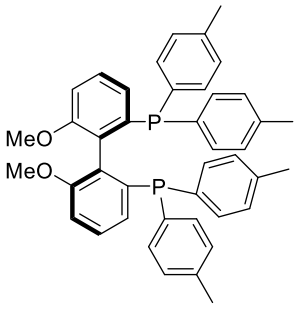
3.65



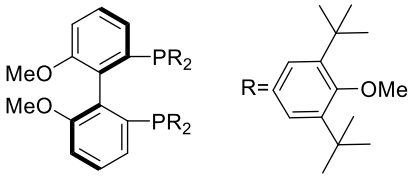
3.66



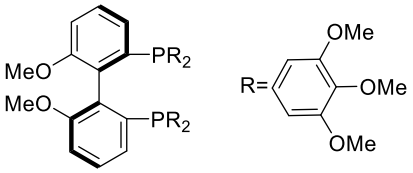
3.67



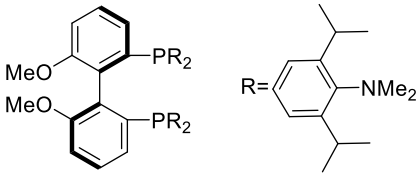
3.68



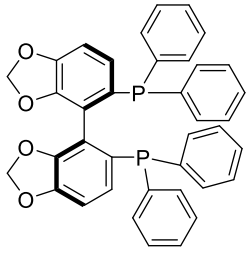
3.69



3.70

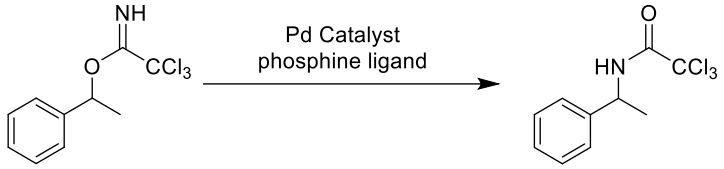


3.71



3.72

Table 3.5. Chiral Ligand Screening Reactions



22 23

Entry[a]	Pd Catalyst	% Pd	Ligand	Conversion[b]	Isolated yield (%)[c]
1	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5	5% **3.64**	88[d]	40
2	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5	10% **3.65**	68 [d]	14
3	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5	10% **3.66**	7	nd
4	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5	10% **3.67**	34	nd
5	-	0	5% **3.64**	0 [d]	0
6	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5	10% **3.68**	12	nd
7	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5	10% **3.69**	7	nd
8	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5	10% **3.70**	84 [d]	nd
9	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5	10% **3.71**	>99 [d]	nd

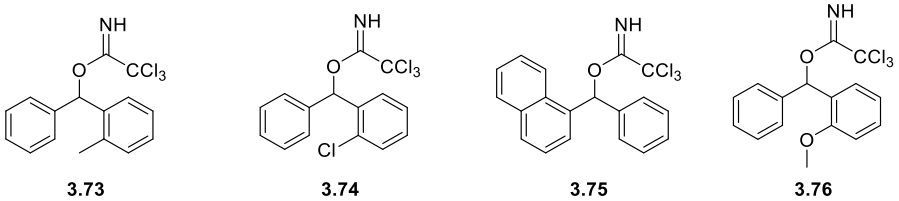
[a]all reactions were run in refluxing toluene for 18 h, [b]% conversion determined by ^{1}H NMR, [c]trace amounts of dba, [d]trace amounts of styrene, nd – not determined

The results in Table 3.5 show that the reaction conversion depends significantly on which phosphine is used, as shown by high conversions in entries 1, 8, and 9, and by poor conversions in entries 3, 6, and 7. Some isolated yields were obtained, but these were still significantly lower than the measured conversions. Again, this was attributed to loss of substrate through elimination. Trace amounts of dba ligand were present the isolated reaction product, causing problems with determining accurate isolated yields. Even though the dba ligand was found in trace amounts, it interfered with HPLC analysis of the reaction products. Since dba has a large UV extension coefficient compared to the acetamide,[60] even small amounts the dba signal may drown out the

acetamide peaks on the HPLC, as a UV detector was being used. Therefore, an accurate account of the enantioselectivity of these transformations from the HPLC proved impossible. The dba may have also degraded to multiple products causing additional noise in the HPLC experiments.

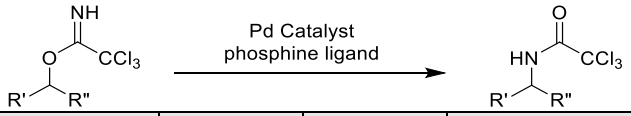
In order to simplify the system and avoid elimination, a series of diarylmethyltrichloroacetimidates were synthesized (Figure 3.5). These substrates should not be prone to competing elimination reactions and should also have different mobility on the chiral HPLC which may facilitate the evaluation of the enantioselectivity of the rearrangement. The diarylmethyltrichloroacetimidate reactivity in this reaction was explored (Table 3.6).

Figure 3.5. Diarylmethyltrichloroacetimidates Substrates



3.73 **3.74** **3.75** **3.76**

Table 3.6. Diarylmethyl Substrate Screening Reactions



Entry[a]	Pd Catalyst	% Pd	Imidate	Ligand	Solvent	yield (%)
1	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5	**3.73**	-	toluene	70
2	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5	**3.73**	10% PPh_3	toluene	77
3	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5	**3.74**	-	toluene	40
4	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5	**3.74**	10% PPh_3	toluene	83
5	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5	**3.75**	-	toluene	70
6	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5	**3.75**	20% PPh_3	toluene	20
7	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5	**3.76**	-	toluene	61
8	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5	**3.76**	10% PPh_3	toluene	43

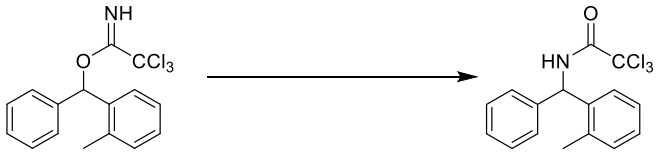
[a]all reactions were run in refluxing toluene for 18 h

The results from Table 3.6 show the diarylmethyl substrates provide higher yields in these reactions, as they cannot undergo elimination. Additionally, these products can be separated from

the dba ligand of the palladium catalyst, as seen in the isolated yields, which do not have trace amounts of dba in them.

Chiral ligands shown in Figure 3.2 were also utilized with imidate **3.73**. Shown below in Table 3.7 are the initial studies of the rearrangement with the chiral ligands. The results in Table 3.7 shows that the phosphine affects the reaction yields, which is consistent with previous screening reactions with different phosphines. This is seen with moderate isolated yields (Table 3.7 Entries 2, 6, and 7) and low isolated yields (Table 3.7 Entries 4 and 5). The chiral HPLC analysis of these products did not show any enantioselectivity.

Table 3.7. Chiral Ligand Screening Reactions with Diarylmethyl Substrates



3.73 **3.77**

Entry[a]	Pd Catalyst	% Pd	Imidate	Ligand	Solvent	Temp. (° C)	Isolated yield (%)[b]
1	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5	**3.73**	10% **3.64**	toluene	110	30
2	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5	**3.73**	5% **3.65**	toluene	110	35
3	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5	**3.73**	5% **3.66**	toluene	110	30
4	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5	**3.73**	5% **3.67**	toluene	110	23
5	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5	**3.73**	5% **3.68**	toluene	110	18
6	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5	**3.73**	5% **3.69**	toluene	110	34
7	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5	**3.73**	5% **3.70**	toluene	110	58
8	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5	**3.73**	5% **3.71**	toluene	110	30

[a]all reactions were run in refluxing toluene for 18 h, [b]isolated racemic material

To enhance enantioselectivity, a set of reactions with imidate **3.73** were run at lower temperatures and longer reaction times in toluene (Table 3.8).

Table 3.8. Temperature Screening Reactions with Diarylmethyl Substrates

3.73 **3.77**

Entry	Pd Catalyst	% Pd	Imidate	Ligand	Solvent	Temp. (° C)	Reaction time	Isolated yield (%)
1	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5	**3.73**	10% PPh_3	toluene	60	24 h	0
2	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5	**3.73**	10% PPh_3	toluene	60	48 h	21
3	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5	**3.73**	10% PPh_3	toluene	60	72 h	77
4	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5	**3.73**	10% PPh_3	toluene	rt	72 h	0
5	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5	**3.73**	10% PPh_3	toluene	45	72 h	0

As shown in Table 3.8, only entries 2 and 3 yielded any product, using toluene at 60 °C for 48 and 72 hours respectively. Since the reaction showed an improved yield after 72 hours, another set of screening reactions with chiral phosphines was performed in toluene at 60 °C or 100 °C for 72 hours (Table 3.9). In the literature, some additives were explored such as N,O-bis(trimethylsilyl)acetamide (BSA) or triethyl borane. These systems may improve yield and enantioselectivity by activating the leaving group, facilitating the formation of a π-allylpalladium species.[61, 62] Using imidate **3.73** and ligand **3.57**, these additives were tested in the reaction to determine if the yield or enantioselectivity would improve (Table 3.9 entries 8-11).

Table 3.9. Chiral Ligand Screening Reactions with Diarylmethyl Substrates

3.73 **3.77**

Entry[a]	Pd Catalyst	% Pd	Imidate	Ligand	Additive	Temp. (° C)	Isolated yield (%)	ee[b] (%)
1	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5	**3.73**	5% **3.67**	-	60	23	68
2	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5	**3.73**	5% **3.67**	-	100	28	82
3	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5	**3.73**	5% **3.68**	-	60	56	30
4	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5	**3.73**	5% **3.68**	-	100	51	42
5	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5	**3.73**	5% **3.69**	-	60	31	40
6	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5	**3.73**	5% **3.70**	-	100	85	72
7	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5	**3.73**	5% **3.72**	-	100	56	82
8	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5	**3.73**	5% **3.72**	BSA	100	23	80
9	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5	**3.73**	5% **3.72**	BSA, BEt_3	100	50	72
10	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5	**3.73**	5% **3.72**	BEt_3	100	12	78
11	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5	**3.73**	5% **3.72**	DPPF	100	12	30

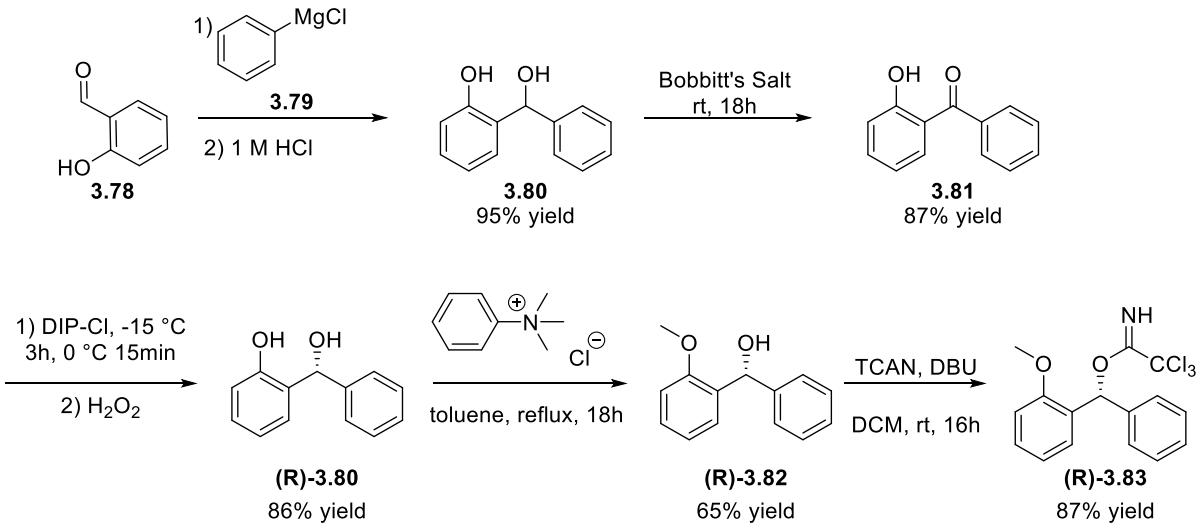
[a]all reactions were run in toluene for 72h. [b]ee= enantiomeric excess. Determined by chiral HPLC.

Interestingly, the ee (enantiomeric excess) was typically higher when the reaction was run at higher temperatures (Table 3.9). It is possible that the π-sigma-π transitions is slower at lower temperatures, resulting in lower ee. High isolated yields were achieved with good ee (table 3.9

entries 6 and 7) when the reaction was run at higher temperature with ligands **3.70** and **3.72**. Unfortunately, none of the additives increased the yield nor the enantiomeric excess (ee).

At this point we wanted to ensure that we were forming a π-allyl intermediate that would readily allow the formation of both enantiomers. Therefore, the chiral (*R*)-imidate **3.83** was synthesized (Scheme 3.8). Most steps were high yielding, including the asymmetric reduction of benzophenone **3.83** to alcohol **3.80** using DIP-Cl at low temperature, following a procedure from Carlson and co-workers.[63] To confirm that the asymmetric reduction did yield an enantiopure product, a sample was separated on the chiral HLPC (OD 80% hexanes/20% isopropanol 1 mL/min 13 min, 14 min) and the enantiomeric excess (ee) was calculated to be 98%. After each subsequent step, both HLPC and optical rotation were used to confirm the sample did not racemize. We hoped that this intermediate would provide racemic product, indicating that the reaction was proceeding through an intermediate that could be converted to either enantiomer of the product (either a free cation or a pi-allyl complex).

Scheme 3.10. Synthesis of (R)-imidate **3.83**.[22, 63-65]

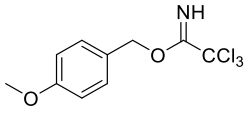


The (R)-imidate **3.83** was subjected to the rearrangement conditions with an achiral phosphine ligand, triphenyl phosphine, and the $Pd_2(dba)_3$ complex. The enantiomeric excess was

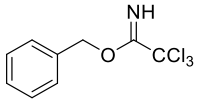
measured via HPLC and showed that the trichloroacetamide product was racemic, indicating that it should be possible to favor one enantiomer with the correct ligand system.

Some additional benzyl imidates were also tested (Table 3.11) under the Pd-catalyzed rearrangement conditions, as these substrates did not provide high yields of product under other conditions. However, these results were no better than previous work in the lab using Lewis acids or thermal conditions.[22]

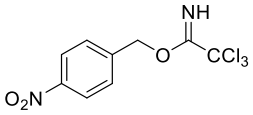
Table 3.10. Screening Reaction with Benzylic Imidates



3.84



3.85



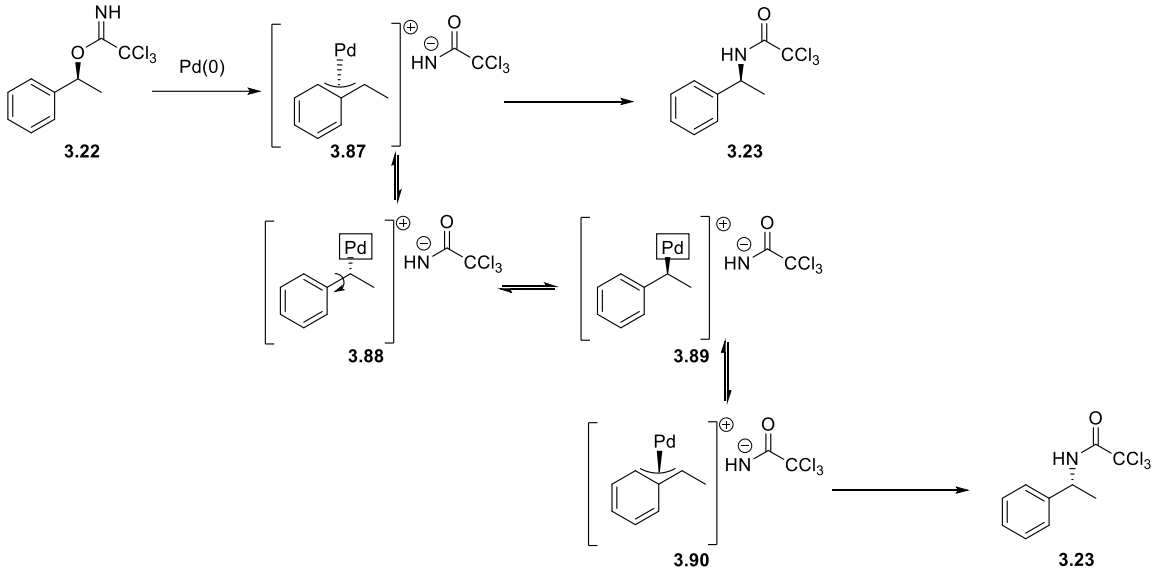
3.86

Entry	Pd Catalyst	% Pd	Imidate	Ligand	Solvent	Temp. (° C)	Reaction Time	Isolated Yield (%)
1	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5	**3.84**	5% **3.72**	toluene	100	18 h	13
2	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5	**3.85**	5% **3.72**	toluene	100	18 h	10
3	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	5	**3.86**	5% **3.72**	toluene	100	18 h	0

A proposed mechanism of the envisioned transition metal catalyzed rearrangement is shown below (Scheme 3.9), where the transformation goes through π-allyl mechanism. First the palladium displaces the imidate, forming the π-allyl complex **3.72** Then the trichloroacetamide anion can attack from the opposite face of the palladium to form acetamide **3.23**. However, the palladium complex can isomerize through a π-sigma-π mechanism to produce the other enantiomer of the π-allyl complex.[66] This proceeds by the palladium forming a sigma bond to the benzylic carbon, bond rotation and then reformation of the enantiomeric π-allyl complex. Since the ligands are attached to the metal during the π-sigma-π transitions, one confirmation of the palladium

complex (**3.72** or **3.75**) will be more energetically favorable with a chiral ligand present on the metal. This may provide a preference to which enantiomer over the other is formed as the main product, leading to an enantioselective transformation.

Scheme 3.11. Proposed Mechanism for Palladium Catalyzed Rearrangement



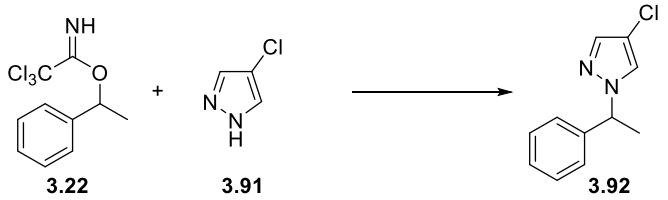
A catalytic system using tris(dibenzylideneacetone)dipalladium(0) gave good results in the rearrangement of some benzylic trichloroacetimidates. Elimination was found to be a problem in phenethyl systems. Diarylmethyl trichloroacetimidates gave more promising results, and the use of chiral ligands is now being explored. Further studies into the mechanism is needed. These studies may provide a new route to highly functionalized benzylic amines and related compounds.

Results and Discussion Part 2: *N*-Alkylations of Pyrazoles using Trichloroacetimidates

We recently began to investigate the use of trichloroacetimidates for pyrazole *N*-alkylations. Research into this transformation began by optimizing conditions for the alkylation of 4-chloropyrazole **3.91** with 1-phenethyltrichloroacetimidate **3.22**. Imidate **3.22** was used since it is easily prepared from 1-phenethylalcohol. First a number of different solvents were tested in the reaction with camphorsulfonic acid (CSA) as a Bronsted acid promotor. This Bronsted acid was

chosen since it has been shown to alkylate anilines under catalytic conditions.[49] When the reaction was performed in dichloroethane, the yield was the highest (Table 3.12, Entry 4). A number of different acid promotors were tested at room temperature with DCE as the solvent (Table 3.12, Entries 7-9). However, none of these catalysts provided a higher yield than CSA. Increasing the amount of catalyst lowered the yield, therefore only 20 mol percent was used. No product was formed without CSA (Table 3.12, Entry 5).

Table 3.11. Initial Optimization

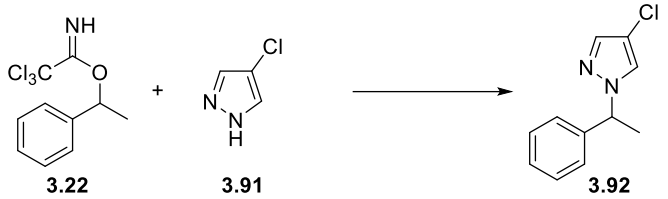


3.22 3.91 3.92

Entry	Solvent	Catalyst	Temp. (°C)	Time (h)	Yield (%)
1	Tol	20 mol % CSA	rt	24	69
2	MeCN	20 mol % CSA	rt	24	29
3	DCM	20 mol % CSA	rt	24	70
4	*DCE*	*20 mol % CSA*	*rt*	*24*	*76*
5	DCE	-	rt	24	0
6	DCE	50 mol % CSA	rt	24	54
7	DCE	20 mol % TMSOTf	rt	24	61
8	DCE	20 mol % BF_3•OEt_2	rt	24	68
9	DCE	10% BF_3•OEt_2, 10% TMSOTf	rt	24	55

From there, different times and temperatures were tested. It was concluded that the reaction needed at least 4 hours to go to completion. Less than 4 hours proved to lower the yield significantly (Table 3.13, Entry 1). However, there was only a 6% increase in yield when running the reaction for longer periods of time (Table 3.13, Entries 2-5). The effects of temperature were also briefly explored but heating the reaction mixture gave a similar yield while cooling was shown to be detrimental (Table 3.13, Entries 6-7).

Table 3.12. Time and Temperature Screening Reactions

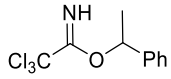
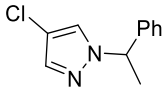
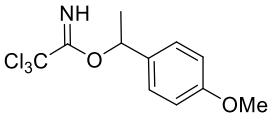
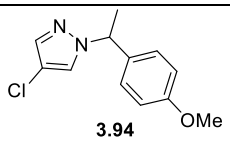
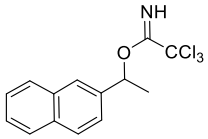
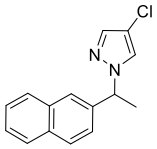
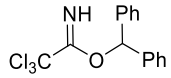
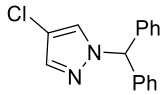
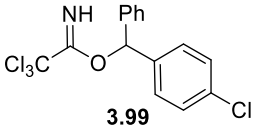
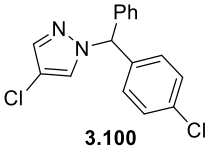
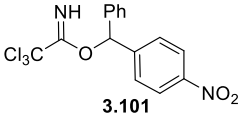
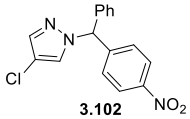
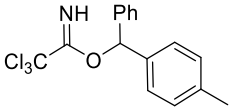
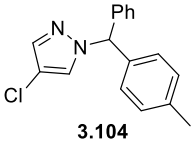
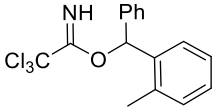
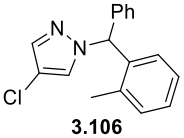
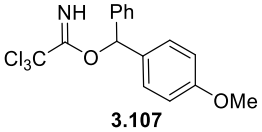
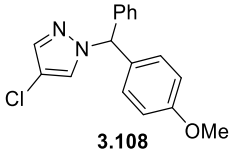
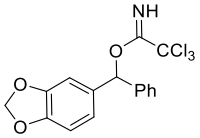
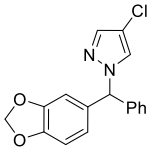


3.22 3.91 3.92

Entry	Solvent	Catalyst	Temp. (ºC)	Time (h)	Yield (%)
1	DCE	20 mol % CSA	rt	2	45
2	DCE	20 mol % CSA	rt	4	71
3	DCE	20 mol % CSA	rt	6	70
4	DCE	20 mol % CSA	rt	8	75
5	DCE	20 mol % CSA	rt	18	77
6	DCE	20 mol % CSA	reflux	4	71
7	DCE	20 mol % CSA	0 °C	4	16

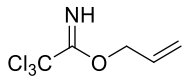
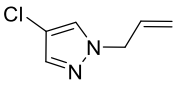
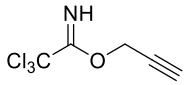
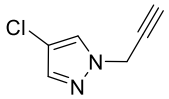
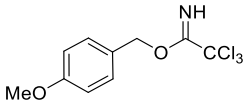
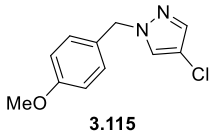
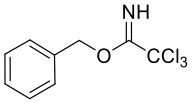
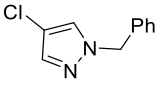
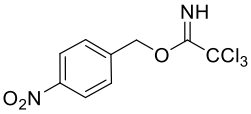
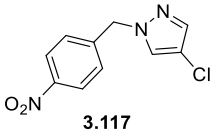
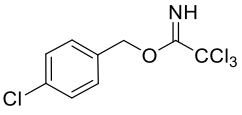
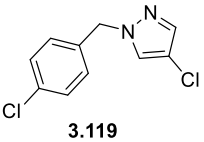
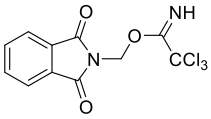
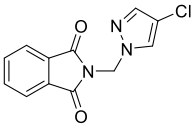
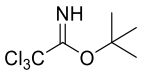
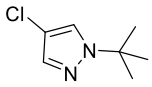
With optimized conditions in hand, we began evaluating the scope of the reaction with respect to the imidate (Table 3.14 and Table 3.15). First a number of different secondary imidates were evaluated. Adding an electron donating group to the aromatic ring increased the yield significantly to 97% (Table 3.14, Entry 2). Diarylmethyl systems also performed well, except when a strongly deactivating electron withdrawing group was added (Table 3.14, Entries 4-10). Again, the addition of electron donating groups on one of the aromatic rings of the imidate improved the yield of the reaction (Table 3.14, Entries 8-9). Employing imidate **3.93** which is decorated with multiple electron donating groups gave an excellent yield of 98%. The effect of sterics also influenced the reactivity as can be seen in the difference in yield when employing imidates **3.58** and **3.88** (Table 3.14, Entries 7-8). The lower reactivity imidate **3.58** is consistent with the addition of a substituent near the reacting position slowing the reaction due to steric hindrance.

Table 3.13. Secondary Imidates with 4-Chloropyrazole **3.91**

Entry	Imidate	Product	Isolated yield (%)
1	 **3.22**	 **3.92**	77
2	 **3.93**	 **3.94**	97
3	 **3.95**	 **3.96**	67
4	 **3.97**	 **3.98**	59
5	 **3.99**	 **3.100**	76
6	 **3.101**	 **3.102**	0
7	 **3.103**	 **3.104**	98
8	 **3.105**	 **3.106**	85
9	 **3.107**	 **3.108**	71
10	 **3.109**	 **3.110**	98

Since secondary imidates participated well in the alkylation, a number of primary imidates were evaluated in the reaction (Table 3.15). It was found that benzyl imidates worked the best, with imidate **3.84** providing a 92% yield. Consistent with the secondary imidates, the addition of electron withdrawing groups was detrimental to the reaction (Table 3.15, Entry 5). Allyl and propargyl imidates provided no product, possibly due to decomposition. However, phthalimidomethyl imidate **3.104** gave a moderate yield of 62% and could be used as a mild way to protect pyrazoles, as the phthalimidyl methyl group has been employed as a protecting group in other systems.[67]

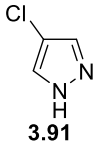
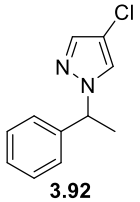
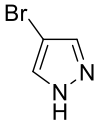
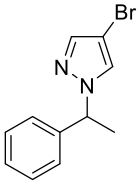
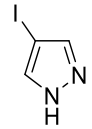
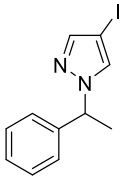
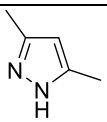
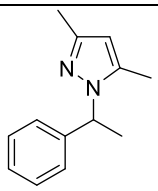
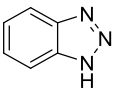
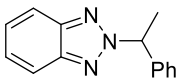
Table 3.14. Primary Imidates with 4-Chloropyrazole **3.91**

Entry	Imidate	Product	Isolated yield (%)
1	 **3.111**	 **3.112**	0
2	 **3.113**	 **3.114**	0
3	 **3.84**	 **3.115**	92
4	 **3.85**	 **3.116**	73
5	 **3.86**	 **3.117**	0
6	 **3.118**	 **3.119**	37
7	 **3.120**	 **3.121**	62
8	 **3.122**	 **3.123**	0

With the scope of the reaction with regard to the trichloroacetimidate determined, a brief exploration of the reaction with respect to the pyrazoles was done using imidate **3.22** (Table 3.16). Changing the halogen was tolerated, however the larger groups such as iodine lowered the yield to a more moderate 59%. Adding multiple groups to the pyrazole was tolerated, however, steric effects may have contributed to the decreased yield in some cases (Table 3.16, Entry 4).

Interestingly, when benzotriazole was utilized, a single product was isolated, even though there are two possible alkylation sites. This product was the dearomatized benzotriazole product **3.114**.

Table 3.15. Pyrazole Substrate Scope

Entry	Pyrazole	Product	Isolated yield (%)
1	 **3.91**	 **3.92**	77
2	 **3.124**	 **3.125**	70
3	 **3.126**	 **3.127**	59
4	 **3.128**	 **3.129**	50
5	 **3.45**	 **3.130**	56

Conclusions and Future Work:

The activity of palladium catalysts in the rearrangement of benzylic trichloroacetimidates to acetamides was explored. A catalytic system using tris(dibenzylideneacetone)dipalladium(0) gave good results. Additionally, these reactions with imidate **3.23** must be carried out at 110 °C in

toluene to achieve higher conversions, but isolated yields were significantly lower likely due to competing elimination. Trace amounts of styrene and dba were found in the reaction products. The styrene is the elimination product. The activity of the palladium catalyst in the rearrangement of diarylmethyltrichloroacetimidates to diarylmethylacetamides was explored as well, since these substrates cannot eliminate. While these reactions achieved high yields in refluxing toluene, no enantioselectivity was seen based on HPLC data. Carrying these reactions out at 60 ℃ or 100 ℃ in toluene for 72 h exhibited moderate yields. The moderate enantioselectivity for diarylmethylacetamides was achieved (82% ee). The exploration to use this reaction to access inverted amides, starting from a chiral trichloroacetimidate, is currently being investigated. These studies may provide a new route to highly functionalized benzylic amines and related compounds. However, further exploration into the mechanism and reaction substrate scope is needed.

Additionally, the *N*-alkylations of pyrazoles utilizing trichloroacetimidates electrophiles under Bronsted acid catalyzed conditions has been described. 4-chlorpyrazole was alkylated with CSA, in DCE at reflux for 4 hours. A variety of trichloroacetimidates were employed and proved to be compatible in this reaction. Both primary and secondary imidates provided good yields. Benzylic primary imidates provided significantly better yields than phthalimidomethyl imidate. It was found that electron donating groups improved the yield, while electron donating groups provided no product. Structurally different pyrazoles were also studied in this transformation. Changing the halogen was tolerated, however, the larger halogen, iodine, provided the lowest yield. When adding methyl groups at the 3 and 5 position to the pyrazole, product was isolated in moderate yield. Interestingly, when using benzotriazole, a single product was isolated in good yield. This was the dearomatized alkylated product. Further substrate scope investigations and mechanism studies are ongoing.

Experimental:

General:

Compounds were used as received from the manufacturer without modification. All reactions were run under a positive pressure of argon. All solvents were dried with the Grubbs method by passage through an alumina column.[68] Thin-layer Chromatography was done on silica at ambient temperature. Silica gel 60 was used as the stationary phase for flash chromatography. All ^{1}H NMR were taken using a Bruker Advance 400 MHz Fourier Transform Nuclear Magnetic Resonance Spectrometer. Abbreviations for spectra: s = singlet, bs = broad singlet d = doublet, t = triplet, q = quartet, quin = quintet, dd = doublet of doublets, td = triplet of doublets, m = multiplet.

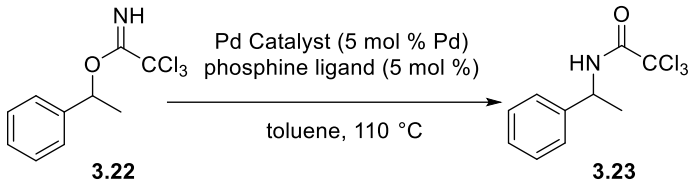
Screening reactions:

General:

A test tube was charged with a palladium catalyst (0.050 equiv) and a phosphine (0.050 equiv). The test tube was placed under an argon atmosphere. 1-Phenethyl imidate (**3.22**) (1 equiv) was dissolved in dry toluene and was injected into the test tube. The reaction was diluted with dry toluene to make the final concentration of the imidate **3.22** 0.1M. The test tube was placed in an oil bath at 110 °C and allowed to stir overnight. The next day, the reaction was removed from the heat and allowed to cool to room temperature. The reaction mixture was run through a plug of silica and eluted with 90% hexanes and 10% ethyl acetate, and one fraction was collected. The solvent was removed by rotary evaporation. A ^{1}H NMR spectrum was taken of the crude product. The conversion was then calculated by the following equation:

$$\frac{integration\ 1H\ of\ product}{integration\ 1\ H\ of\ starting\ material + integration\ of\ 1\ H\ of\ product} \times 100 = Conversion\ \%$$

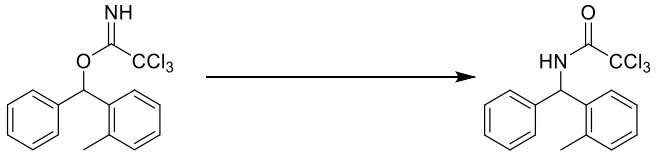
Example screening reaction of imidate rearrangement:



3.22 **3.23**

A test tube was charged with 8.6 mg (0.0188 mmol) of $Pd_2(dba)_3 \cdot CHCl_3$ and 8.8 mg (0.0338 mmol) of triphenylphosphine. The tube was put under an argon atmosphere. A solution of 100 mg (0.375 mmol) of **3.22** in 0.5 mL anhydrous toluene was injected into the tube. The reaction was diluted with anhydrous toluene to a final volume of 3.75 mL. The tube was placed in an oil bath at 110 °C and allowed to stir for overnight. The next day, the reaction was removed from heat and allowed to cool to room temperature. The reaction mixture was run through a silica column and eluted with 90% hexanes and 10% ethyl acetate and one fraction was collected. The solvent was removed via reduced pressure and a ^{1}H NMR spectrum was taken in $CDCl_3$. The conversion was calculated to be 86%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.40 (m, 8H), 5.99 (q, *J* = 6.5 Hz, 1H), 5.07 (q, *J* = 6.8 Hz, 1H), 1.82 (d, *J* = 6.8 Hz), 1.63 (d, *J* = 6.5 Hz, 1H).

$$\frac{1.0}{1.0 + 0.16} \times 100 = 86\ \%$$

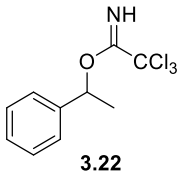


3.73 **3.77**

A test tube was charged with 10.0 mg (0.0219 mmol) of $Pd_2(dba)_3 \cdot CHCl_3$**,** 11.0 mg (0.044 mmol) of triphenylphosphine, and 0.150 g of imidate **3.58**. The tube was put under an argon atmosphere. The reaction was diluted with anhydrous toluene to a final volume of 4.4 mL. The tube was placed

in an oil bath at 110 °C and allowed to stir for overnight. The next day the reaction was removed from heat and allowed to cool to room temperature. The reaction mixture was run through a silica column and eluted with a gradient from 0% ethyl acetate to 10% ethyl acetate in hexanes. Fractions containing product were combined and the solvent was removed via reduced pressure to provide 0.116 g of acetamide **3.62** as a white solid. Yield: 77%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.385-7.102 (m, 10H), 6.337 (d, *J*= 7.77, 1H), 2.328 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 139.3, 137.8, 136.5, 131.1, 128.9, 128.1, 128.0, 127.3, 126.6, 126.5, 92.6, 56.1, 19.36; FT-IT (KBr pellet) 3286.5, 3025.9, 1707.8, 1688.2, 1601.8, 1526.1, 1492.9, 1268.6, 1055.1, 847.5, 820.6, 730.8, 655.3; Anal Calculated for $C_{16}H_{14}Cl_3NO$: C, 56.09; H, 4.12; N, 4.09. Found: C, 55.99; H, 4.10; N, 4.00

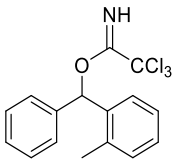
General Procedure for the synthesis of trichloroacetimidates from the corresponding alcohol: A flame dried 25 mL round bottom flask was charged with the alcohol starting material (1 equiv) under argon. Dry DCM was then added to form a 0.5 M solution, and the flask was cooled to 0 °C. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 0.2 equiv) was added to the solution, followed by trichloroacetonitrile (1.5 equiv). The reaction was monitored by TLC. After completion of the reaction, reaction mixture was concentrated, and silica gel column chromatography was performed to provide the desired trichloroacetimidates.



3.22

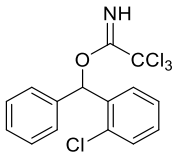
Trichloroacetimidate 3.22.[69] The residue was purified by a silica flash column chromatography (5% ethyl acetate/90% hexanes/5% triethylamine) to provide 1.74 g of **3.22** as a colorless oil.

Yield: 65%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.44-7.26 (m, 5H), 6.00 (q, *J* = 6.4 Hz, 1H) 1.66 (d, *J* = 6.4 Hz, 3H).[22, 70]



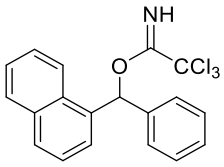
3.73

Trichloroacetimidate 3.73.[71] The residue was purified by a silica flash column chromatography (5% ethyl acetate/90% hexanes/5% triethylamine) to provide 0.825 g of **3.73** as a yellow oil. Yield: 96%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.61-7.12 (m, 10H), 2.37 (s, 3H).[71]



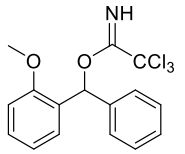
3.74

Trichloroacetimidate 3.74. The residue was purified by a silica flash column chromatography (10% ethyl acetate/85% hexanes/5% triethylamine) to provide 0.825 g of **3.74** as a yellow oil. Yield: 98%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.60-7.25 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 138.2, 137.5, 133.0, 129.7, 129.3, 128.5, 128.2, 128.0, 127.3, 127.2, 91.4; Anal Calculated for $C_{15}H_{11}Cl_4NO$: C, 49.62; H, 3.05; N, 3.86. Found: C, 49.74; H, 3.09; N, 4.05.



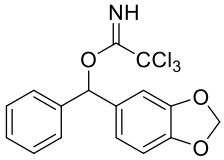
3.75

Trichloroacetimidate 3.75.[72] The residue was purified by a silica flash column chromatography (5% ethyl acetate /90% hexanes/5% triethylamine) to provide 0.502 g of **3.75** as a yellow oil. Yield: 76%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.88 -7.25 (m, 13H).



3.76

Trichloroacetimidate 3.76.[69] The residue was purified by silica gel chromatography (5% ethyl acetate/90% hexanes/5% triethylamine) to give the 0.278 g of **3.76** as a white solid. Yield: 76%.; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.42−7.38 (m, 3H), 7.26−7.15 (m, 5H), 6.89 (t, J = 7.5, Hz, 1H), 6.80 (d, J = 8.2 Hz, 1H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 156.4, 139.7, 129.1, 128.5, 128.3, 127.8, 127.0, 126.8, 120.7, 110.7, 91.7, 76.2, 55.6.[22]

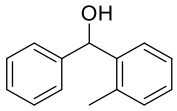


3.109

Trichloroacetimidate 3.109. The residue was purified by silica gel chromatography (10% ethyl acetate/85% hexanes/5% triethylamine) to give the 0.278 g as a white solid. Yield 67%; mp: 67-70 °C; R_f = 0.55 (10% EtOAc/90% hexanes); IR (film): 3336, 3030, 2889, 1662, 1487, 1237, 1065, 786 cm^{-1}; ^{1}H NMR (400 MHz, CDCl3) δ 8.32 (s, 1H), 7.35 (m, 2H), 7.28-24 (m, 2H), 7.22-7.20 (m, 1H), 6.82-6.78 (m, 3H), 6.69-6.67 (m, 1H), 5.85 (d, J= 1.0 Hz, 2H); ^{13}C{1H} NMR (100 MHz, CDCl3) δ 161.3, 147.8, 147.5, 139.8, 128.7, 128.5, 127.9,127.3, 127.2, 126.7, 121.1, 108.1, 107.7, 101.2, 81.2; Anal Calcd for $C_{16}H_{12}Cl_3NO_3$: C,51.57; H, 3.25; N, 3.76; Found: C,51.56; H, 3.21; N, 3.57.

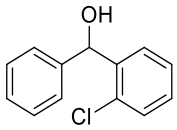
General Procedure for Synthesis of Alcohols:

The Grignard was synthesized by adding Mg turnings (1.5 equiv) and a small amount of dibromoethane, under argon, to an oven-dried round bottom flask and suspended in dry THF or dry ether. The reaction was refluxed for about 1 hour. After 1 hour the reaction was cooled to 0 °C and a solution of carbonyl (1 equiv) in dry THF or dry diethyl ether (0.3 M) was added dropwise. The solution was slowly warmed to room temperature, monitored by TLC, and allowed to stir overnight. The reaction was cooled to 0 °C and quenched with sat. NH_4Cl. The aqueous layer was extracted with ether, combined, dried over Na_2SO_4, filtered, and concentrated.



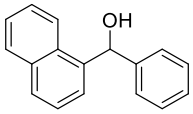
3.131

Alcohol 3.131.[73] The organic layer was dried over sodium sulfate and the solvent was evaporated off with a rotary evaporator. This provided 1.99 g of **3.131** as a white solid. Yield: 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.492 (d, *J*=27.3 Hz, 1H), 7.25-7.13 (m, 8H), 5.97 (s, 1H), 2.34 (s, 1H), 2.23 (s, 3H).



3.132

Alcohol 3.132.[64] The organic layer was dried over sodium sulfate and the solvent was evaporated off with a rotary evaporator. This provided 1.80 g of **3.132** as a yellow solid. Yield: 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.600 (dd, *J*=1.44, 7.52 Hz, 1H), 7.41-7.23 (m, 8H), 6.241 (d, *J*=2 Hz, 1H), 2.306 (s, 1H).



3.133

Alcohol 3.133.[74] The organic layer was dried over sodium sulfate and the solvent was evaporated off with a rotary evaporator. This provided 1.80 g of **3.133** as a yellow oil. Yield: 70%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J*=8.02 Hz, 1H), 7.87-7.80 (m, 2H), 7.63 (d, *J*=7.12 Hz, 1H), 7.45-7.24 (m, 8H), 6.52 (d, *J* = 4.0 Hz, 1H), 2.37 (d, *J* = 4.0 Hz, 1H).

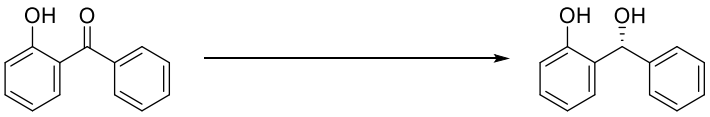
Chiral Alcohol Synthesis:

3.79 **3.78** **3.80**

Alcohol 3.80.[64] Phenyl magnesium chloride 2.0 M solution in THF (**3.79**, 4.10 g, 30.0 mmol) was added dropwise to a cooled solution of 1.22 g (10.0 mmol) of salicylaldehyde **3.78** in 1 mL THF. The reaction was warmed to room temperature and to stir overnight. It was quenched with aqueous NH_4Cl and water, extracted with ethyl acetate, and the organic layer was washed with brine. The organic layer was dried over sodium sulfate and the solvent was evaporated off with a rotary evaporator. This provided 1.90 g of **3.80** as a yellow solid. Yield: 95%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.37-7.29 (m, 5H), 7.18-7.14 (m, 1H), 6.88-6.77 (m, 3H), 5.96 (s, 1H), 3.11 (s, 1H). [64, 75]

3.80 **3.81**

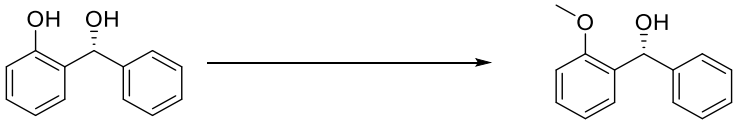
Benzophenone 3.81.[76] An oven dried flask was charged with 1.00 g (5.00 mmol) of alcohol **3.80**, dissolved in 16.7 mL of anhydrous acetonitrile, and put under an atmosphere of argon. Then 1.65 g (5.50 mmol) of Bobbitt's salt was added. The flask was purged with argon. The reaction was left to stir overnight at room temperature. The reaction was quenched with saturated sodium bicarbonate aqueous solution. The aqueous layer was extracted 3x16 mL DCM. The organic layers were combined and washed with brine. The organic layer was dried over sodium sulfate and concentrated via rotary evaporation. The residue was purified by silica gel chromatography, (10% ethyl acetate/90% hexanes) This provided 0.861 g of **3.81** as a yellow oil. Yield: 60%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.08 (s, 1H), 7.71-7.69 (m, 2H), 7.63-7.59 (m 2H), 7.53 (tt, *J*= 1.56, 7.84 Hz, 3H), 7.10 (dd, *J*=0.96 8.4 Hz, 1H), 6.90 (td, *J*= 1.12, 7.22 Hz, 1H).



3.81 **(R)-3.80**

Alcohol (*R*)- 3.80.[77] To an oven dried test tube, 0.100 g (0.504 mmol) of benzophenone **3.81** was added and dissolved in 1.7 mL THF. The test tube was put under argon and cooled to -15 °C in a salted ice bath. A solution of (-)-DIP-chloride in hexanes, was added dropwise to the reaction. The reaction stirred at -15 °C for 3 hours. The reaction was warmed to 0 °C and stirred for 15 minutes. To the reaction mixture at 0 °C a solution of 0.04 g of H_2O_2 (30 w%) in 1.5 mL DI water was added dropwise. The mixture was extracted 3x1 mL ethyl acetate, washed with NaHSO3, DI water, and brine. The organic layers were combined, dried over sodium sulfate, and concentrated. The residue was purified by silica column chromatography (3% ethyl acetate, 97% hexanes). This

provided 1.80 g of **(*R*)- 3.80** as a yellow oil. Yield: 86%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.37-7.29 (m, 5H), 7.18-7.14 (m, 1H), 6.88-6.77 (m, 3H), 5.96 (s, 1H), 3.06 (s, 1H). Chiral HPLC analysis: Chiralcel OD (hexanes/isopropanol = 80/20, 1 mL/min, 254 nm, 25 °C): t_1= 13 min, t_2= 14 min. [α]= -22.0 (c: 2.84, DCM)[63]



(R)-3.80 **(*R*)-3.82**

Alcohol (*R*)- 3.82 [65]:To a round bottom flask, 0.300 g (1.50 mmol) of **(*R*)- 3.80**, 0.386 g (2.25 mmol) of phenyltrimethylammonium chloride, and 0.292 g of Cs_2CO_3 (0.90 mmol). The flask was put under an atmosphere of argon. Then everything was dissolved in 3 mL of anhydrous toluene. The reaction was heated to reflux and left to stir overnight. The reaction was cooled to room temperature and quenched 1 M HCl. The organic layer was washed with water, dried over sodium sulfate, and concentrated. This provided 0.209 g of **(*R*)- 3.82** as a white solid. Yield: 65%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.26 (m, 7H), 7.00-6.92 (m, 2H), 6.10 (s, 1H), 3.84 (s, 3H). Chiral HPLC analysis: Chiralcel AD (hexanes/isopropanol = 95/5, 1 mL/min, 254 nm, 25 °C): t_1= 4 min, t_2= 5 min. [α]= -8.35 (c: 0.15, DCM)

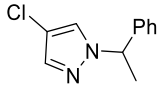
(*R*)-3.82 **(*R*)-3.83**

(*R*)-Trichloroacetimidate 3.68.[69] (*R*)-2-methoxyphenyl(phenyl)methanol **3.82** (0.190 g, 0.887 mmol) was added to a flame-dried round bottom flask under argon atmosphere. Dry methylene chloride (3.5 mL) was added, followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (0.013 g, 0.089

mmol). The reaction stirred at room temperature for 5 minutes. The reaction was cooled to 0 °C in an ice bath and trichloroacetonitrile (0.166 g, 1.15 mmol) was added via syringe. The reaction was warmed to room temperature and stirred overnight. The solvent was removed under vacuum. The residue was purified by a silica column and flash chromatography with the eluent of 95% hexanes, 5% ethyl acetate plus 5% triethylamine to provide 0.278 g of **(*R*)- 3.83** as a white solid. Yield: 87%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.42−7.38 (m, 3H), 7.26−7.15 (m, 5H), 6.89 (t, J = 7.5, Hz, 1H), 6.80 (d, J = 8.2 Hz, 1H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 156.4, 139.7, 129.1, 128.5, 128.3, 127.8, 127.0, 126.8, 120.7, 110.7, 91.7, 76.2, 55.6. [α]= -4.59 (c: 0.494, DCM) .[22]

General Procedure for pyrazole alkylation:

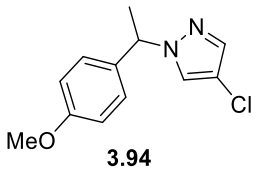
A round bottom flask was charged with imidate (1 equiv), pyrazole (1 equiv), and CSA (0.2 equiv) and put under an atmosphere of argon. Dry DCE was added to form a 0.25 M solution and the flask was heated to reflux (85 °C). The reaction was left to stir at reflux for 4h. After 4h, the reaction was cooled to room temperature and purified by dry loading silica gel flash column chromatography.



3.92

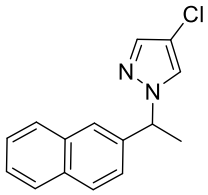
Pyrazole 3.92. Yield 77%; R_f = 0.37 (5% EtOAc/95% hexanes); IR (film):3129, 3030, 2936, 1493, 1310, 960, 696, 617 cm^{-1}; ^{1}H NMR (400 MHz, CDCl3) δ 7.50 (s, 1H), 7.39-7.30 (m, 4H), 7.24 (d, J= 7.6 Hz, 2H), 5.48 (q, J= 7.0 Hz, 1H), 1.89 (d, J= 7.0 Hz, 3H); ^{13}C{1H} NMR (100

MHz, CDCl3) δ 141.1, 137.5, 128.9, 128.2, 126.4, 126.0, 109.9, 61.9, 21.1; Anal Calcd for $C_{11}H_{11}ClN_2$: C, 63.93; H, 5.36; N, 13.55; Found: C, 63.86; H, 5.00; N, 13.57.



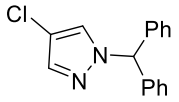
3.94

Pyrazole 3.94.[38] Yield 97%; R_f = 0.26 (5% EtOAc/95% hexanes); ^{1}H NMR (400 MHz, CDCl3) δ 7.33 (s, 1H), 7.20 (s, 1H), 7.05 (d, J= 8.4 Hz), 6.75 (d, J= 8.4 Hz, 2H), 5.27 (q, J= 7.4 Hz, 1H), 3.65 (s, 3H), 1.71 (d, J= 7.4 Hz, 3H); ^{13}C{1H} NMR (100 MHz, CDCl3) δ 159.4, 137.3, 133.0, 127.8, 125.8, 114.2, 109.7, 61.4, 55.3, 21.1



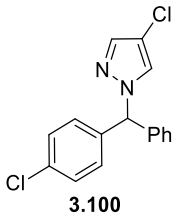
3.96

Pyrazole 3.96. Yield 67%; mp: 92-94 °C; R_f = 0.28 (5% EtOAc/95% hexanes); IR (film): 3112, 3047, 2991, 2952, 1388, 1313, 838, 747 cm^{-1}; ^{1}H NMR (400 MHz, CDCl3) δ 7.69 (d, J= 7.2 Hz, 3H), 7.56 (s, 1H), 7.38-7.35 (m, 3H), 7.26 (s, 1H), 7.19 (d, J= 8.2 Hz, 1H), 5.48 (q, J= 7.2 Hz, 1H), 1.83 (d, J= 7.2 Hz, 3H); ^{13}C{1H} NMR (100 MHz, CDCl3) δ 138.3, 137.6, 133.2, 133.0, 128.8, 128.1, 127.7, 126.5, 126.4, 126.1, 125.3, 124.3, 110.0, 62.0, 21.1; Anal Calcd for $C_{17}H_{13}ClN_2O_2$: C,70.18; H, 5.10; N, 10.91; Found: C,70.14; H, 5.05; N, 10.87.



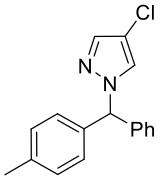
3.98

Pyrazole 3.98. Yield 59%; mp: 100-103 °C; R_f = 0.35 (5% EtOAc/95% hexanes); IR (film): 3108, 3027, 2927, 1520, 726, 694 cm^{-1}; ^1H NMR (400 MHz, CDCl3) δ 7.42 (s,1H), 7.26-7.22 (m, 6H), 7.13 (s, 1H), 7.00-6.99 (m, 4H), 6.61 (s, 1H); $^{13}C\{1H\}$ NMR (100 MHz, CDCl3) δ 138.8, 138.2. 128.8, 128.4, 128.2, 127.6, 110.0, 70.3; Anal Calcd for $C_{16}H_{13}ClN_2$: C, 71.51; H, 4.88; N, 10.42; Found: C, 71.58; H, 4.82; N, 10.19.



3.100

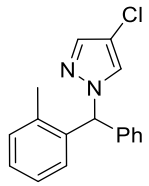
Pyrazole 3.100. Yield 76%; R_f = 0.46 (5% EtOAc/95% hexanes IR (film): 3133, 3096, 1490, 967, 735 cm^{-1}; ^1H NMR (400 MHz, CDCl3) δ 7.42 (s, 1H), 7.27-7.21 (m, 5H), 7.14 (s, 1H), 7.01-6.99 (m, 2H), 6.92 (d, J= 8.8 Hz, 2H), 6.56 (s, 1H); $^{13}C\{1H\}$ NMR (75 MHz, CDCl3) δ 138.5, 138.3, 137.5, 134.3, 129.5, 129.0, 128.9, 128.7, 128.3, 127.6, 110.6, 69.6; Anal Calcd for $C_{16}H_{12}ClN_2$: C, 63.39; H, 3.99; N, 9.24; Found: C, 63.19; H, 3.94; N, 9.59.



3.104

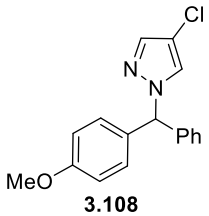
Pyrazole 3.104. Yield 98%; mp: 70-72 °C; R_f = 0.35 (5% EtOAc/95% hexanes); IR (film): 3129, 3055, 2919, 1512, 1293, 990, 735 cm^{-1}; ^1H NMR (400 MHz, CDCl3) δ 7.41 (s, 1H), 7.24-7.22 (m, 3H), 7.13 (s, 1H), 7.06 (d, J= 7.6 Hz, 2H), 6.98 (d, J= 6.9 Hz, 2H), 6.91 (d, J= 7.6 Hz, 2H), 6.57 (s, 1H), 2.25 (s, 3H); $^{13}C\{1H\}$ NMR (100 MHz, CDCl3) δ 13.1, 138.3, 138.2, 135.8, 129.5, 128.8,

128.3, 128.2, 128.0,127.5, 109.9, 70.1, 21.2; Anal Calcd for $C_{17}H_{15}ClN_2$: C,72.21; H, 5.35; N, 9.91; Found: C,71.20; H,5.20; N,9.74.



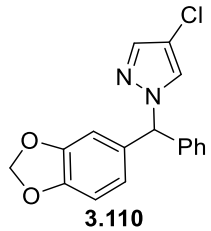
3.106

Pyrazole 3.106. Yield 85%; mp: 89-92 °C; R_f = 0.36 (5% EtOAc/95% hexanes); IR (film): 3099, 3029, 2920, 1488, 1299, 964, 708 cm^{-1}; ^1H NMR (400 MHz, CDCl3) δ 7.55 (s, 1H), 7.39-7.37 (m, 3H), 7.30-7.16 (m, 4H), 7.09-7.07 (m, 2H), 6.90 (s, 1H), 6.72 (d, J= 7.39 Hz, 1H), 2.23 (s, 3H); $^{13}C\{1H\}$ NMR (100 MHz, CDCl3) δ 138.3, 138.2, 137.2, 136.6, 130.9, 128.9, 128.4, 128.3, 128.1, 127.7, 126.4, 109.9, 67.6, 29.7, 19.2; Anal Calcd for $C_{17}H_{15}ClN_2$: C,72.21; H, 5.35; N, 9.91; Found: C,71.94; H,5.44; N,9.81.



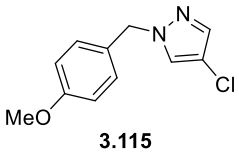
3.108

Pyrazole 3.108. Yield 71%; R_f = 0.30 (5% EtOAc/95% hexanes); IR (film): 3132, 3030, 2835, 1610, 1510, 1247, 730 cm^{-1}; ^1H NMR (400 MHz, CDCl3) δ 7.41 (s, 1H), 7.24-7.22 (m, 3H), 7.13 (s, 1H), 6.97-6.95 (m, 4H), 6.79-6.77 (m, 2H), 6.55 (s, 1H), 3.69 (s, 3H); $^{13}C\{1H\}$ NMR (100 MHz, CDCl3) δ 159.6, 139.4, 138.2, 130.8, 129.7, 128.8, 128.2, 127.8, 127.5, 114.2, 109.9, 69.8, 55.3; Anal Calcd for $C_{17}H_{15}ClN_2O$: C,68.34; H, 5.06; N, 9.38; Found: C, 68.39; H, 4.97; N, 9.41.



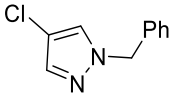
3.110

Pyrazole 3.110. Yield 98%; R_f = 0.30 (5% EtOAc/95% hexanes); ^{1}H NMR (400 MHz, CDCl3) δ 7.42 (s, 1H), 7.25-7.23 (m, 3H), 7.16 (s, 1H), 6.98 (d, J= 6.6 Hz, 2H), 6.67 (d, J= 7.7 Hz, 1H), 6.49 (m, 3H), 5.86 (s, 2H); ^{13}C{1H} NMR (100 MHz, CDCl3) δ 148.1, 147.7, 139.0, 138.3, 132.6, 128.8, 128.3, 127.9, 127.5, 122.1, 109.9, 108.8, 108.4, 101.4, 69.9; Anal Calcd for $C_{17}H_{13}ClN_2O_2$: C,65.29; H, 4.19; N, 8.96; Found: C,65.27; H, 4.14; N, 8.63.



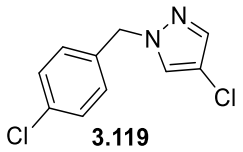
3.115

Pyrazole 3.115. Yield: 92%; R_f = 0.32 (10% EtOAc/90% hexanes); IR (film): 3124, 2999, 2933, 2834, 1612, 1511, 1244 cm^{-1}; ^{1}H NMR (400 MHz, CDCl3) δ 7.46 (s, 1H), 7.32 (s, 1H), 7.20 (d, J= 8.6 Hz, 2H), 6.90 (d, J= 8.6 Hz, 2H), 5.19 (s, 2H), 3.82 (s, 3H); ^{13}C{1H} NMR (100 MHz, CDCl3) δ 159.7, 137.7, 129.5, 127.6, 126.9, 114.3, 110.2, 56.3, 56.3; Anal Calcd for $C_{11}H_{11}ClN_2O$: C, 59.33; H, 4.98; N, 12.58; found: C, 59.44;H, 4.92; N, 12.83.



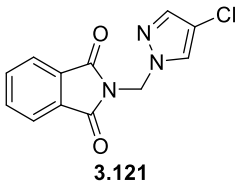
3.116

Pyrazole 3.116.[78] Yield 73%; R_f = 0.31 (10% EtOAc/90% hexanes); ^{1}H NMR (400 MHz, CDCl3) δ 7.49 (s, 1H), 7.37-7.33 (m, 4H), 7.24-7.22 (m, 2H), 5.23 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 137.9, 135.8, 130.0, 128.4, 127.9, 127.3, 110.3, 56.7.



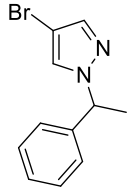
3.119

Pyrazole 3.119. Yield 37%; 52-55 °C; R_f = 0.27 (5% EtOAc/95% hexanes); IR (film): 3129, 3045, 2943, 1492, 970, 755 cm^{-1}; ^1H NMR (400 MHz, CDCl3) δ 7.37 (s, 1H), 7.25-7.22 (m, 4H), 7.05 (d, J= 8.3 Hz, 2H), 5.11 (s, 2H); $^{13}C\{1H\}$ NMR (100 MHz, CDCl3) δ 138.2, 134.4, 134.3, 129.1, 128.9, 127.2, 110.6, 55.9; Anal Calcd for $C_{10}H_8Cl_2N_2$: C,52.89; H, 3.55; N, 12.34; found: C, 52.81; H, 3.54; N, 12.17.



3.121

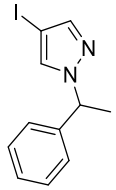
Pyrazole 3.121. Yield 62%; mp: 164-168 °C; R_f = 0.3 (30% EtOAc/70% hexanes); ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.13 (s, 1H), 7.95-7.88 (m, 4H), 7.58 (s, 1H), 5.85 (s, 2H); $^{13}C\{1H\}$ NMR (100 MHz, $(CD_3)_2SO$) δ 167.2, 138.7, 135.5, 131.6, 129.5, 124.1, 109.2, 52.8; Anal Calcd for $C_{12}H_8ClN_3O_2$: C,55.08; H, 3.08; N, 16.06; Found: C,54.73; H, 2.88; N, 16.40.



3.125

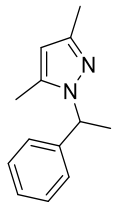
Pyrazole 3.125. Purified by silica chromatography 5% EtOAc/Hexanes to give product as colorless oil. Yield: 70%. IR (film): cm^{-1}; R_f 0.37 (5% EtOAc/95% hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ7.38 (s, 1H), 7.25-7.17 (m, 4H), 7.10 (d, J= 6.7 Hz, 2H), 5.35 (q, J= 7.0 Hz, 1H), 1.75 (d,

J= 7.0 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 141.1, 139.6, 128.9, 128.2, 128.1, 126.4, 93.1, 61.9, 21.2; Anal Calcd for $C_{11}H_{11}BrN_2$: C, 52.61; H, 4.42; N, 11.16; Found: C, 52.51; H, 4.46; N, 11.28.



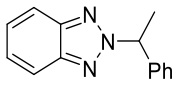
3.127

Pyrazole 3.127. Purified by silica chromatography 5% EtOAc/Hexanes to give product as colorless oil. Yield: 70%. IR (film): 3109, 2978, 1493, 960, 696 cm^{-1}; R_f 0.37 (5% EtOAc/95% hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.44 (s, 1H), 7.39-7.23 (m, 5H), 5.53 (q, J= 7.0 Hz, 1H), 1.90 (d, J= 6.9 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 144.2, 141.1, 132.4, 128.9, 128.2, 126.4, 61.7, 56.2, 21.3; Anal Calcd for $C_{11}H_{11}IN_2$: C, 44.32; H, 3.72; N, 9.40; Found: C, 44.02; H, 3.44; N, 9.03



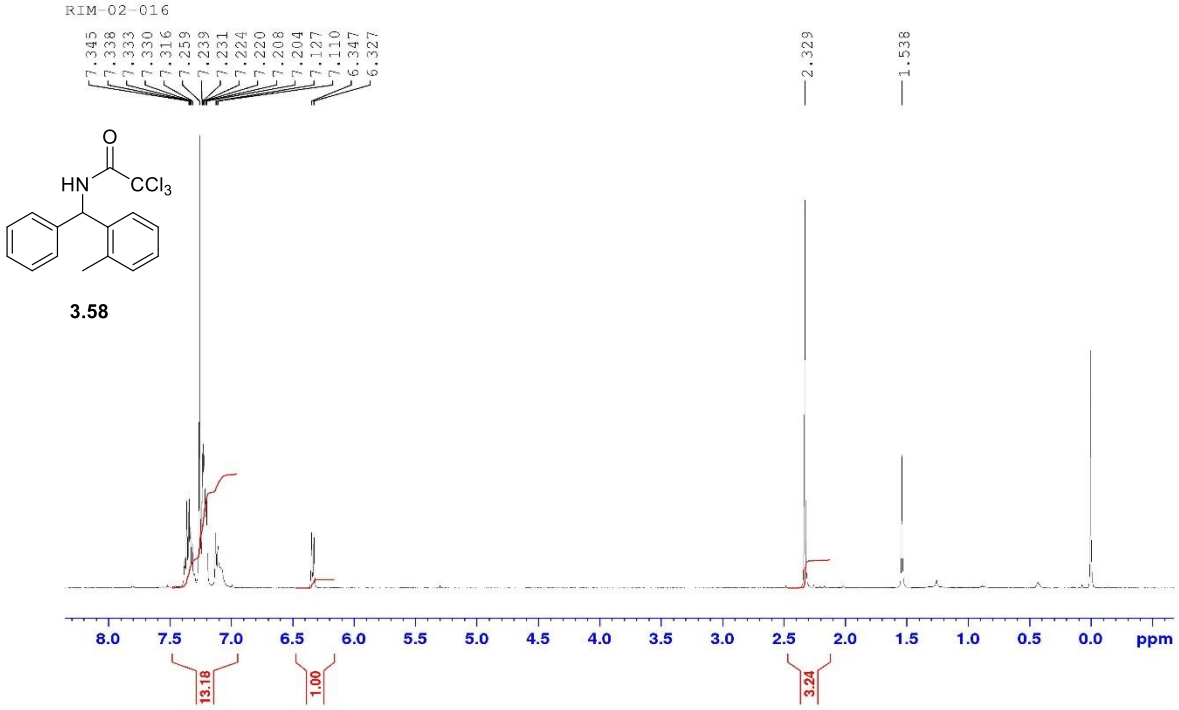
3.129

Pyrazole 3.129.[79] Purified by silica chromatography 5% EtOAc/Hexanes to give product as colorless oil. Yield: 52%. R_f 0.22 (5% EtOAc/95% hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-15 (m, 2H), 7.13-7.09 (m 1H), 6.99 (d, *J*= 7.4Hz, 2H), 5.73 (s, 1H), 5.24 (q, *J*= 7.0 Hz, 1H), 2.18 (s, 3H), 1.99 (s, 3H), 1.81 (d, *J*= 7.0 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 146.9, 143.0, 138.9, 138.6, 127.2, 125.9, 105.6, 57.3, 21.8, 13.8, 11.2



3.130

Benzotriazole 3.130.[38] Yield 56%; Purified by silica chromatography 5% EtOAc/Hexanes to give product as colorless oil. Yield: 56%. R_f 0.25 (5% EtOAc/95% hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94-7.91 (m, 2H), 7.46-39 (m, 2H), 7.38-7.31 (m, 5H), 6.20 (q, *J*= 7.1 Hz, 1H), 2.18 (d, *J*= 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 144.2, 140.3, 128.8, 128.3, 126.6, 126.2, 118.2, 66.2, 21.4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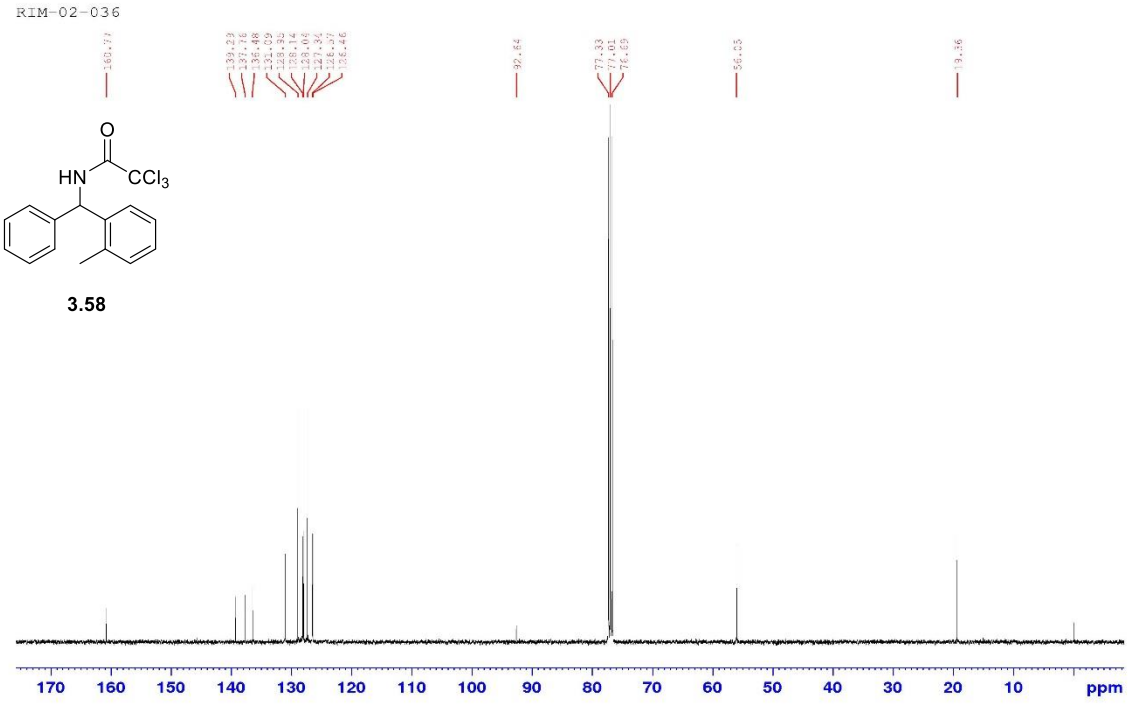
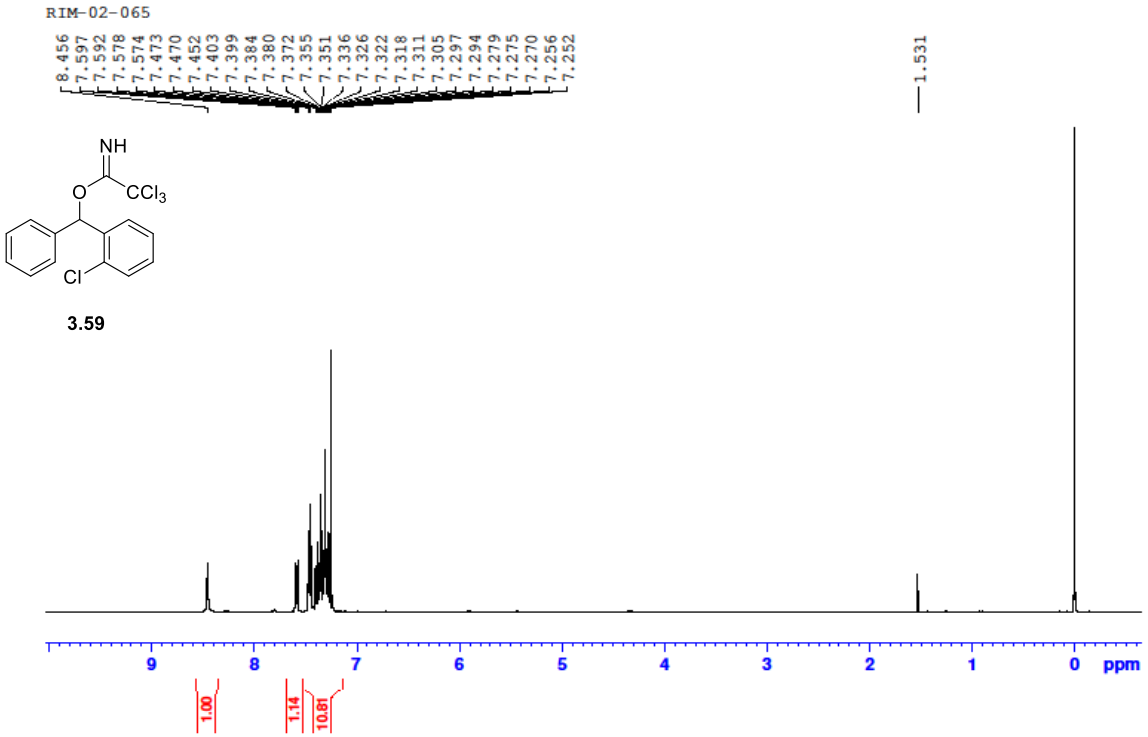
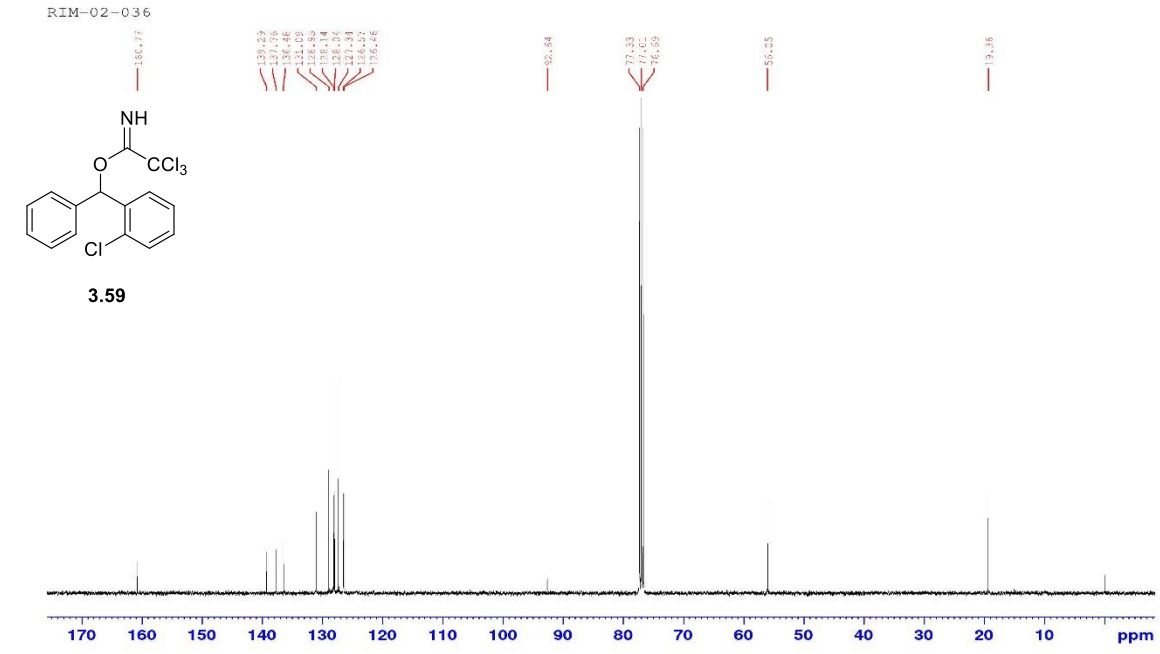
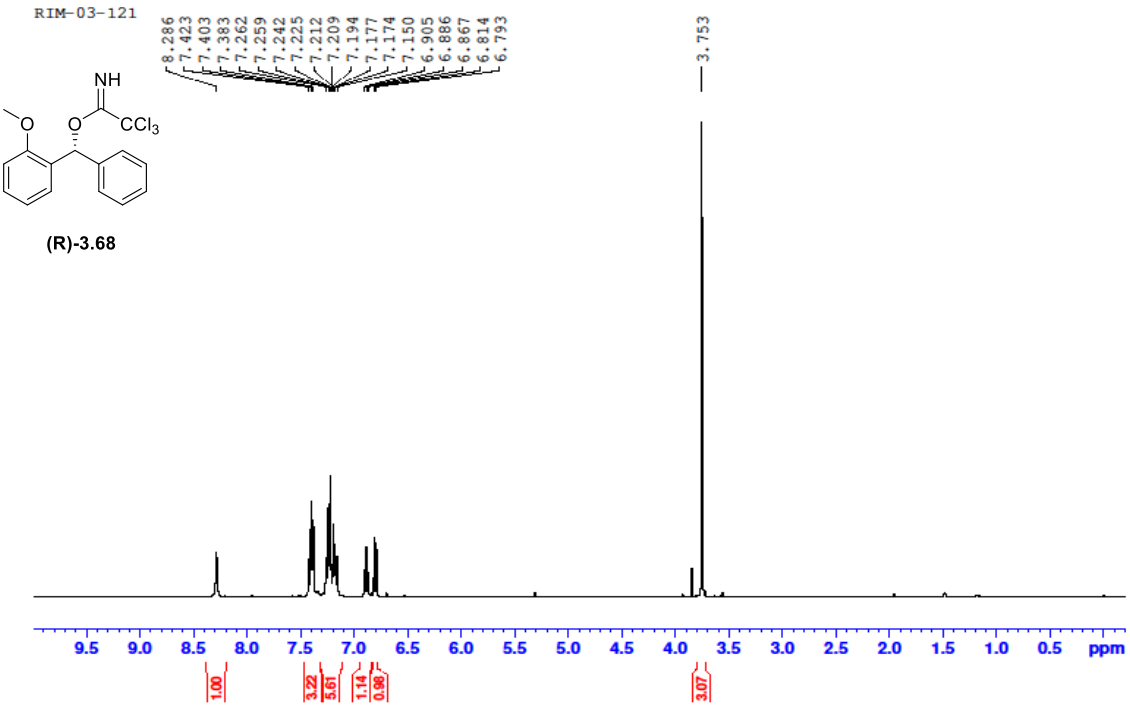
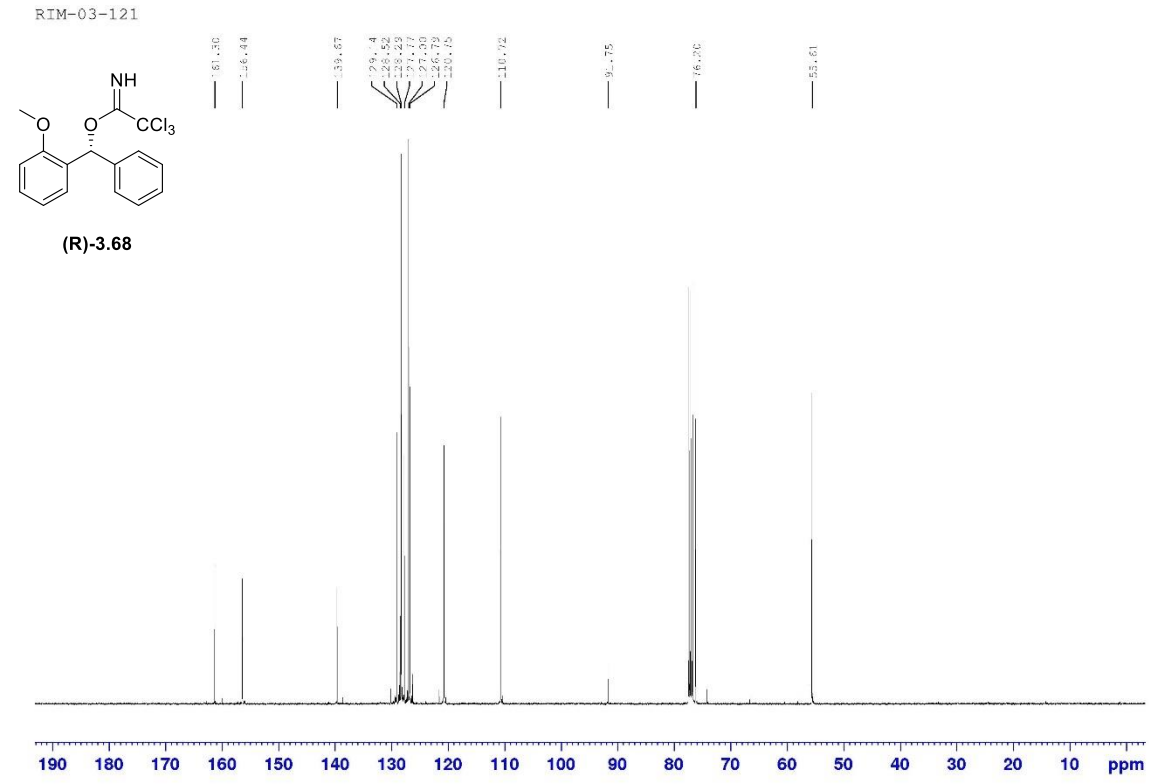
3.24


RIM-02-036
160.77
139.23
137.76
136.48
130.09
128.92
128.54
128.06
127.36
126.37
126.46
92.64
77.33
77.01
76.69
56.05
19.36
HN
CCl3
3.58
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

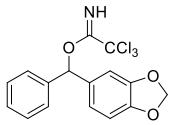

RIM-02-065
8.456
7.597
7.592
7.578
7.574
7.473
7.470
7.452
7.403
7.399
7.384
7.380
7.372
7.355
7.351
7.336
7.326
7.322
7.318
7.311
7.305
7.297
7.294
7.279
7.275
7.270
7.256
7.252
1.531
NH
O
CCl3
Cl
3.59
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.14
10.81


RIM-02-036
NH
O
CCl3
Cl
3.59
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


RIM-03-121
8.286
7.423
7.403
7.383
7.262
7.259
7.242
7.225
7.212
7.209
7.194
7.177
7.174
7.150
6.905
6.886
6.867
6.814
6.793
3.753
NH
O
O
CCl3
(R)-3.68
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
3.22
5.61
1.14
0.96
3.07

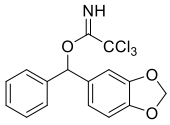

RIM-03-121
161.30
156.44
139.67
129.4
128.52
128.23
127.37
127.10
126.79
120.75
110.72
91.75
76.20
53.61
NH
O
O
CCl3
(R)-3.68
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

RIM-08-147 check



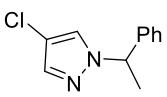
3.93

RIM-08-147 check



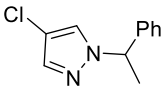
3.93

RIM-08-064

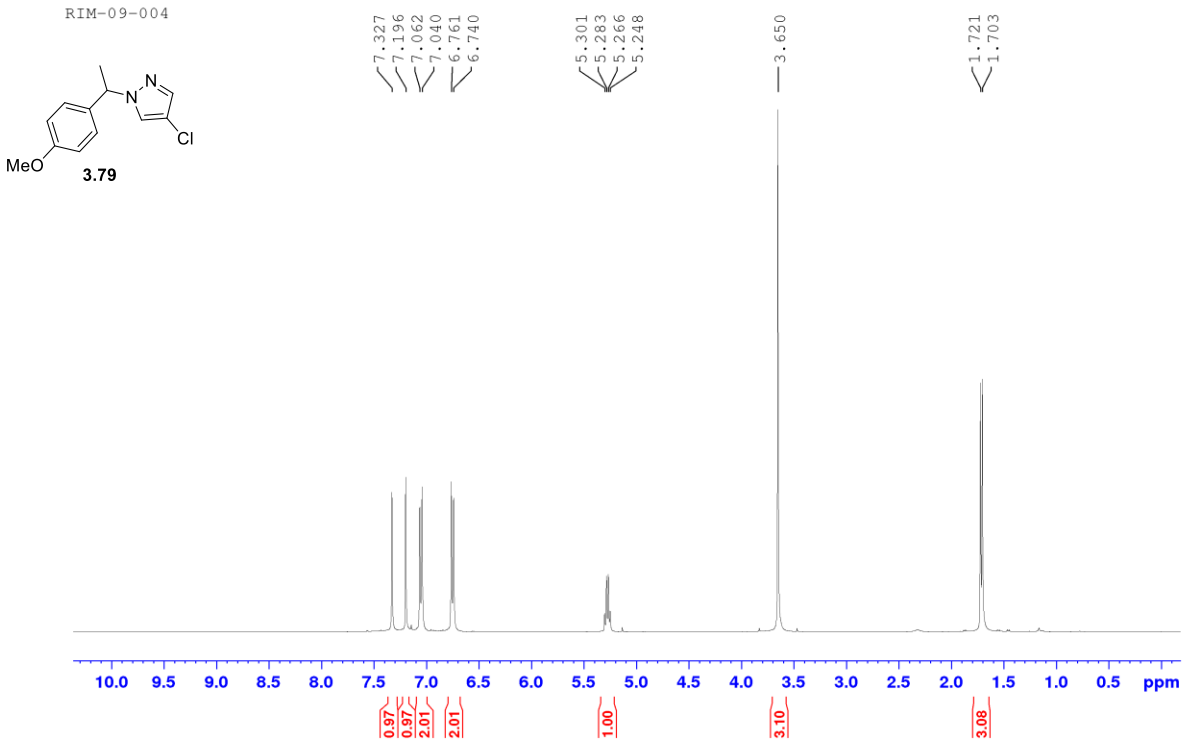


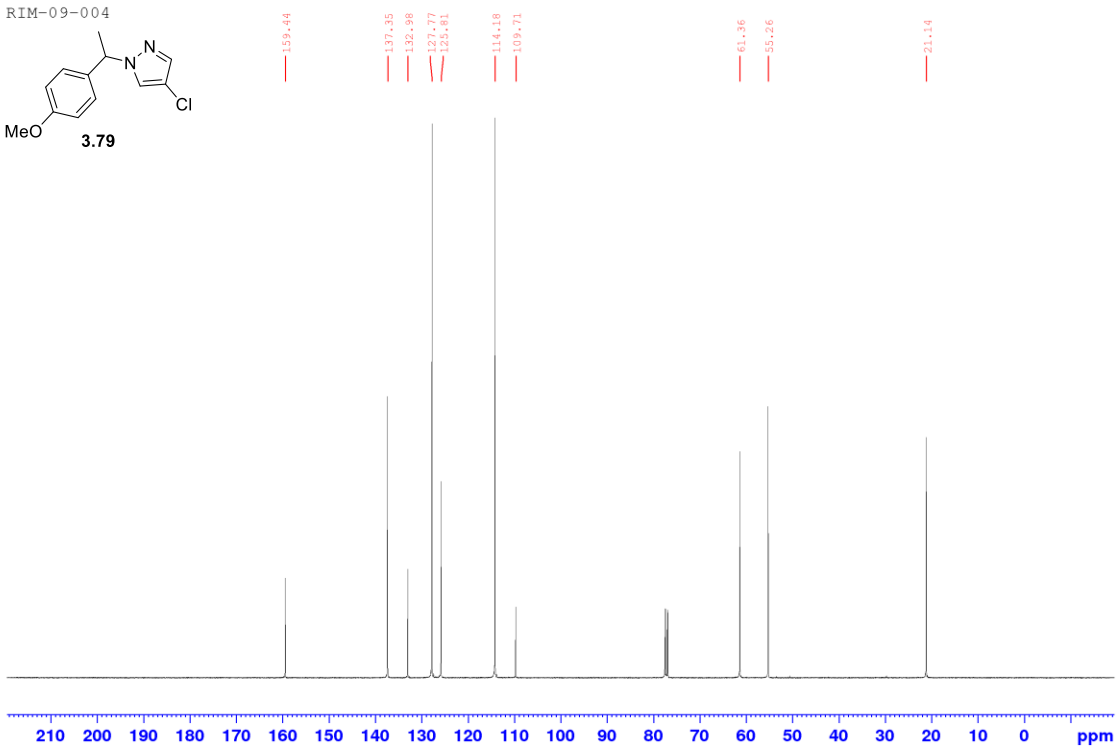
3.77

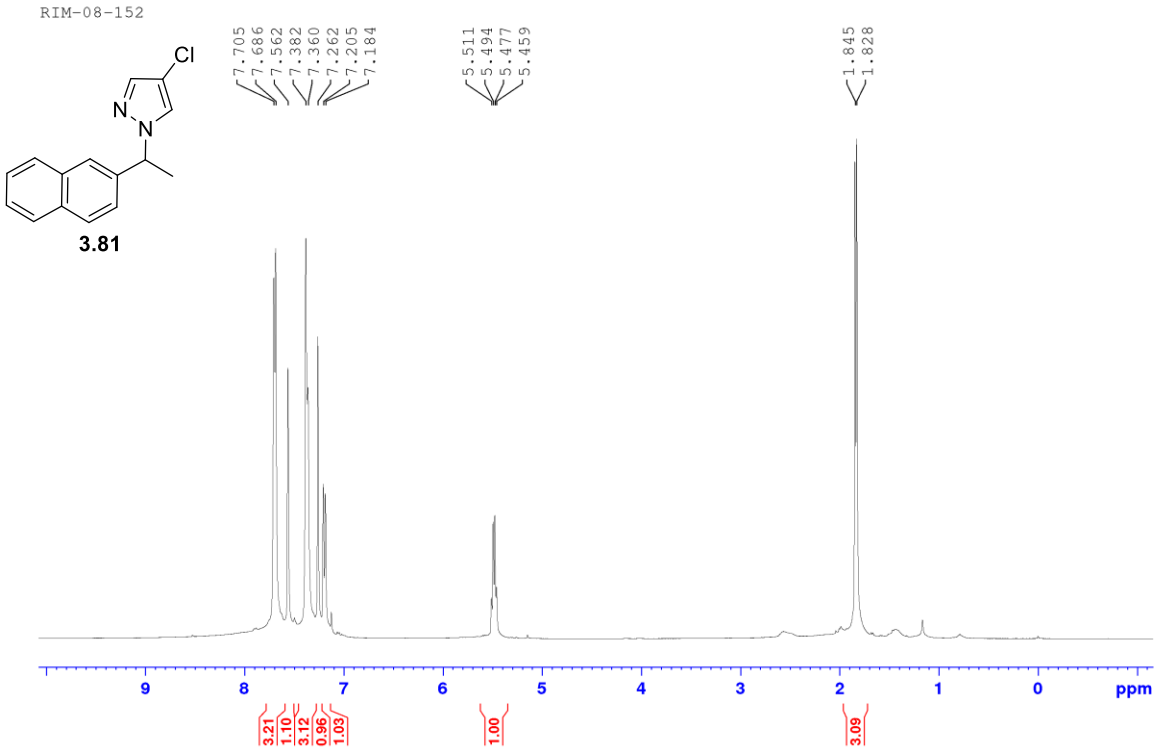
RIM-08-052

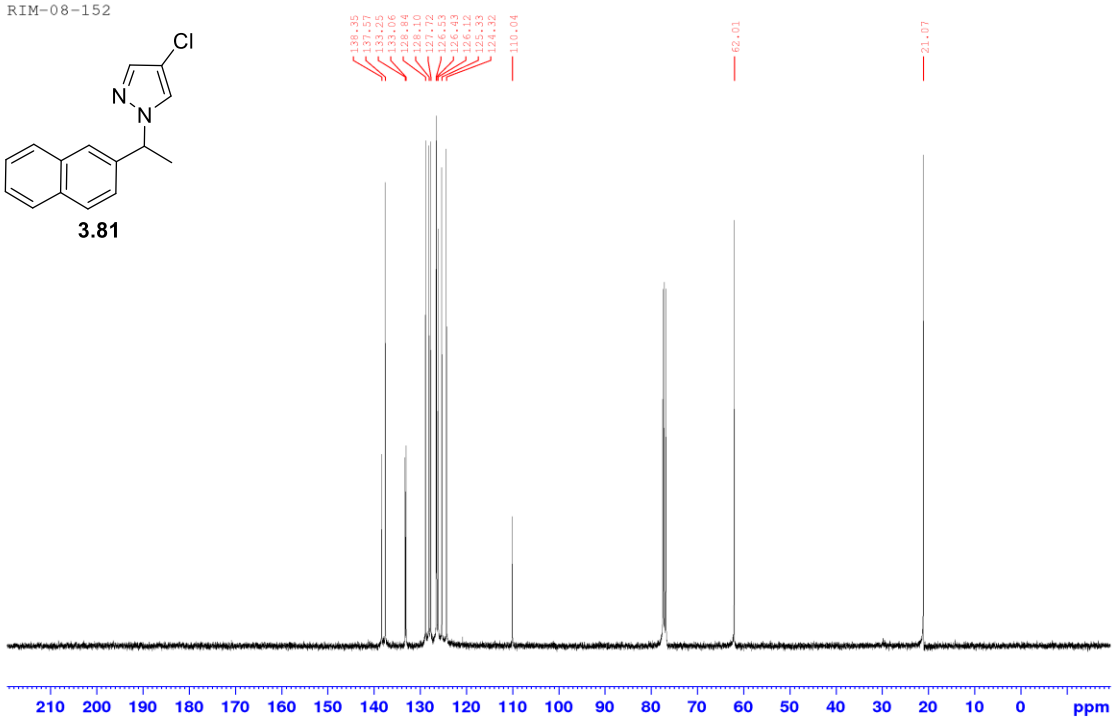


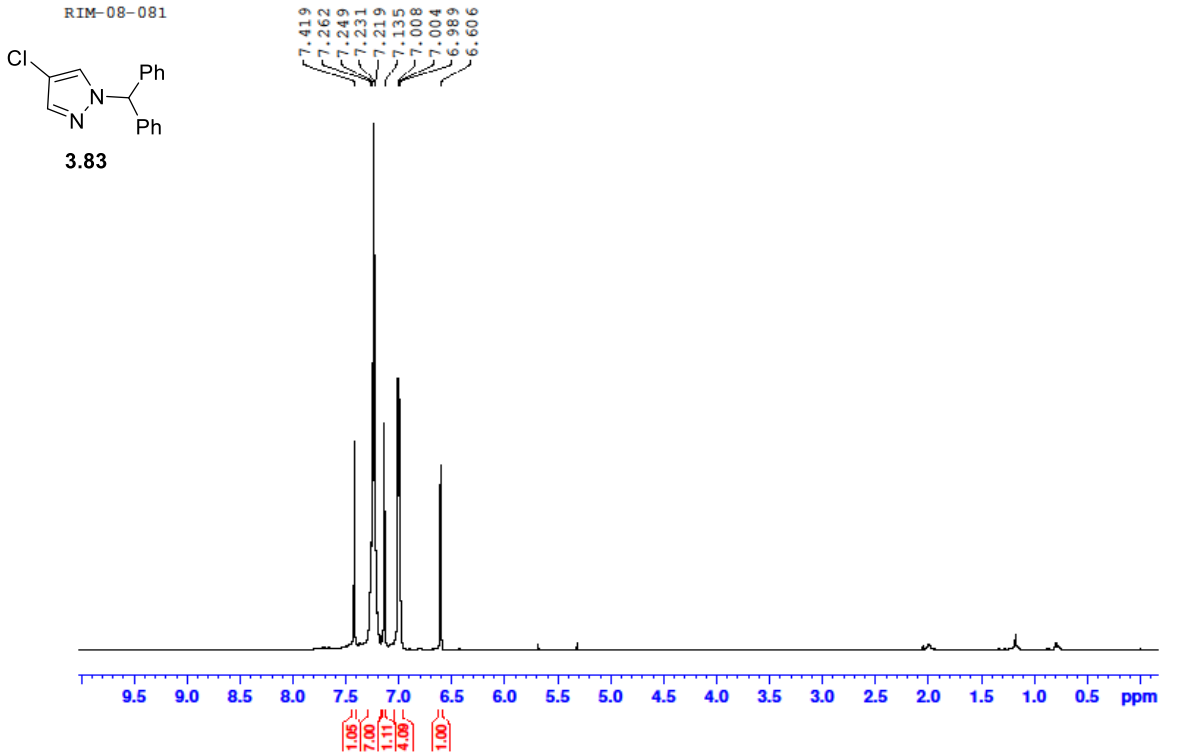
3.77

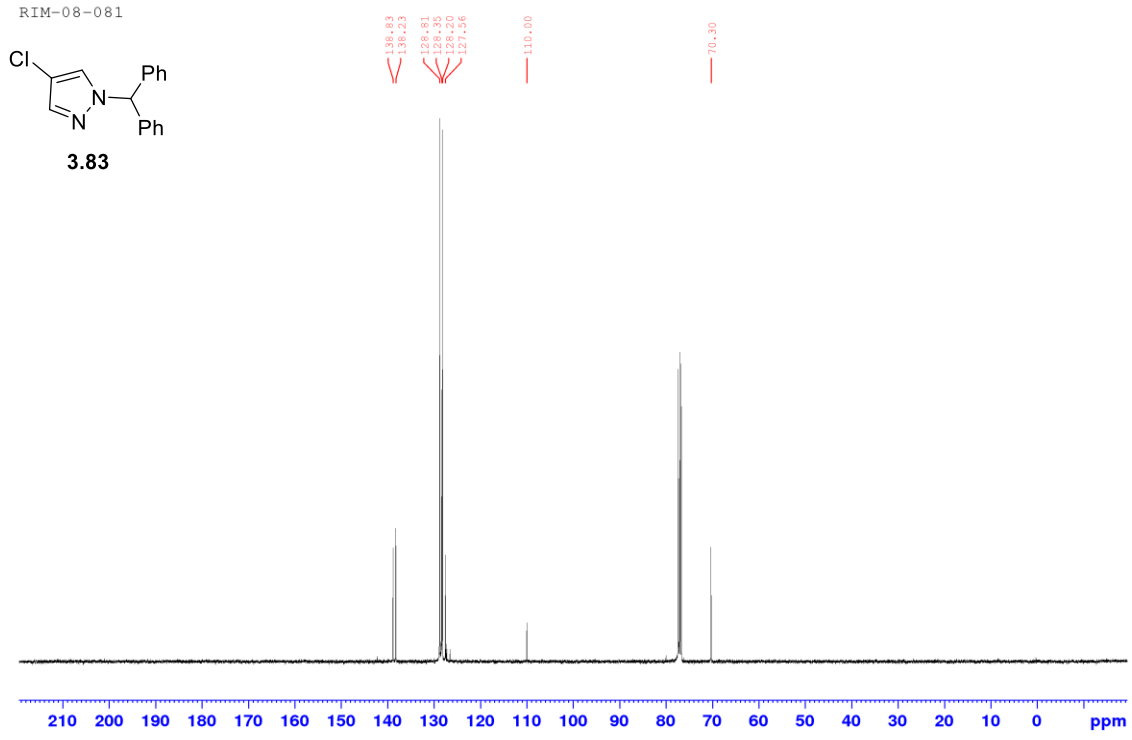

RIM-09-004
MeO
Cl
3.79
7.327
7.196
7.062
7.040
6.761
6.740
5.301
5.283
5.266
5.248
3.650
1.721
1.703
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.97
0.97
2.01
2.01
1.00
3.10
3.08

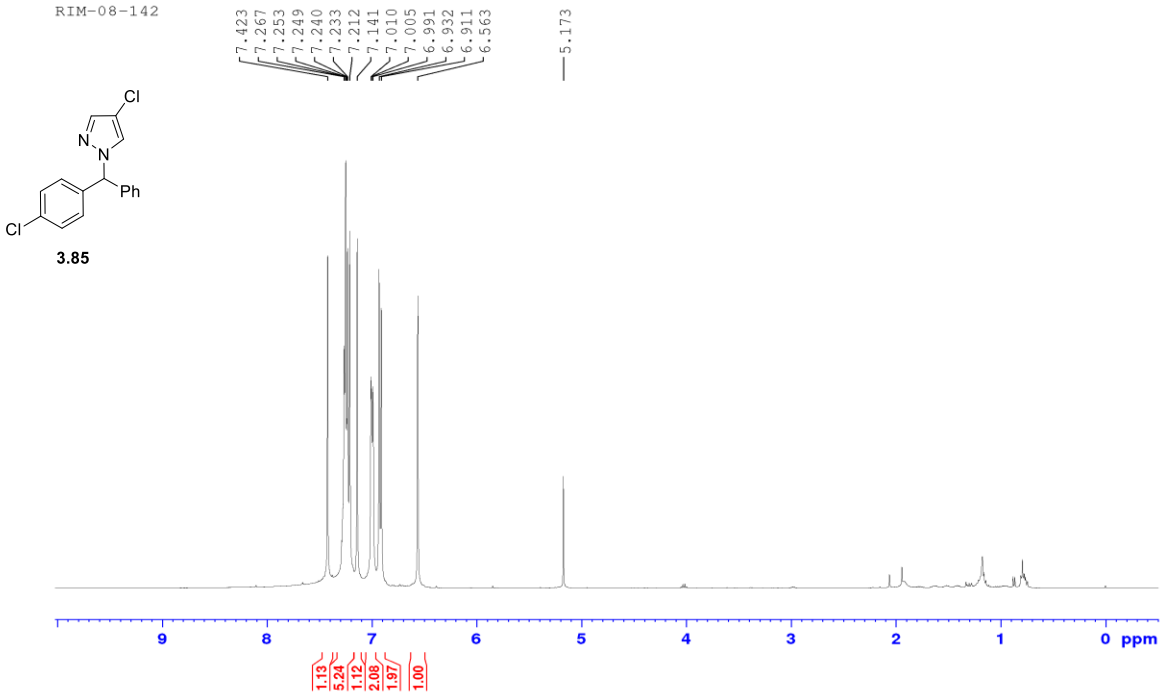

RIM-09-004
MeO
Cl
3.79
159.44
137.35
132.98
127.77
125.81
114.18
109.71
61.36
55.26
21.14
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

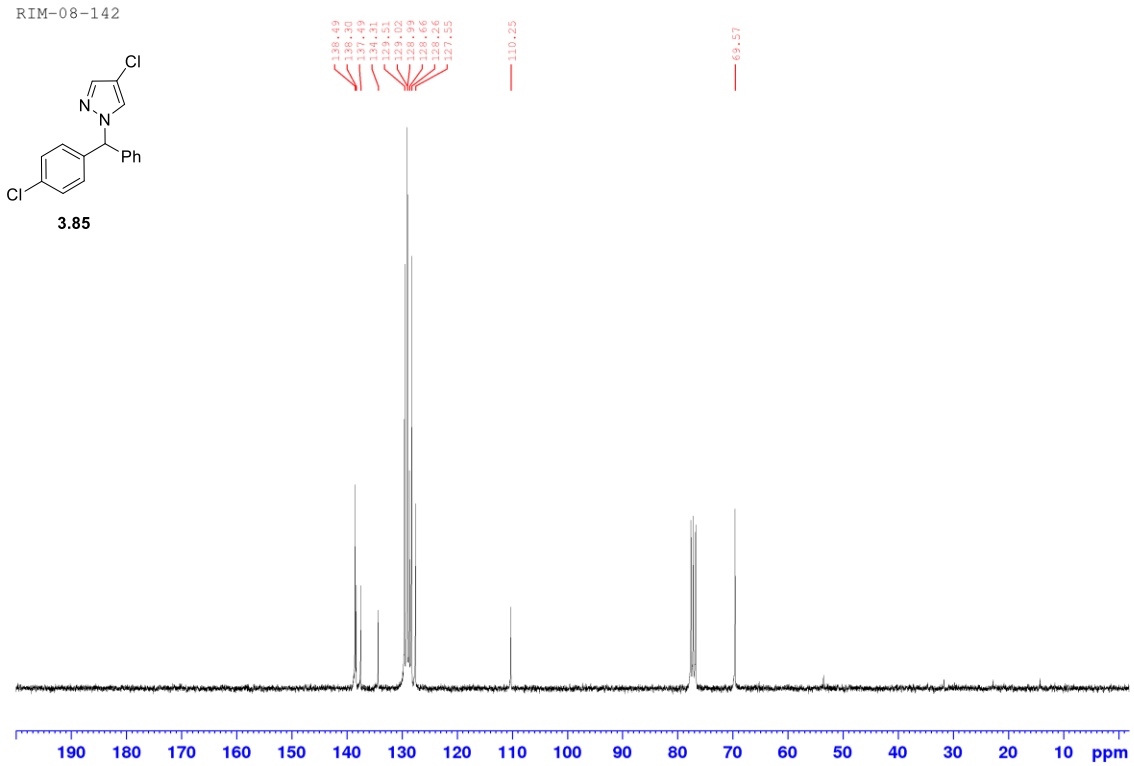

RIM-08-152
Cl
N
N
3.81
7.705
7.686
7.562
7.382
7.360
7.262
7.205
7.184
5.511
5.494
5.477
5.459
1.845
1.828
9
8
7
6
5
4
3
2
1
0
ppm
3.21
1.10
3.12
0.96
1.03
1.00
3.09

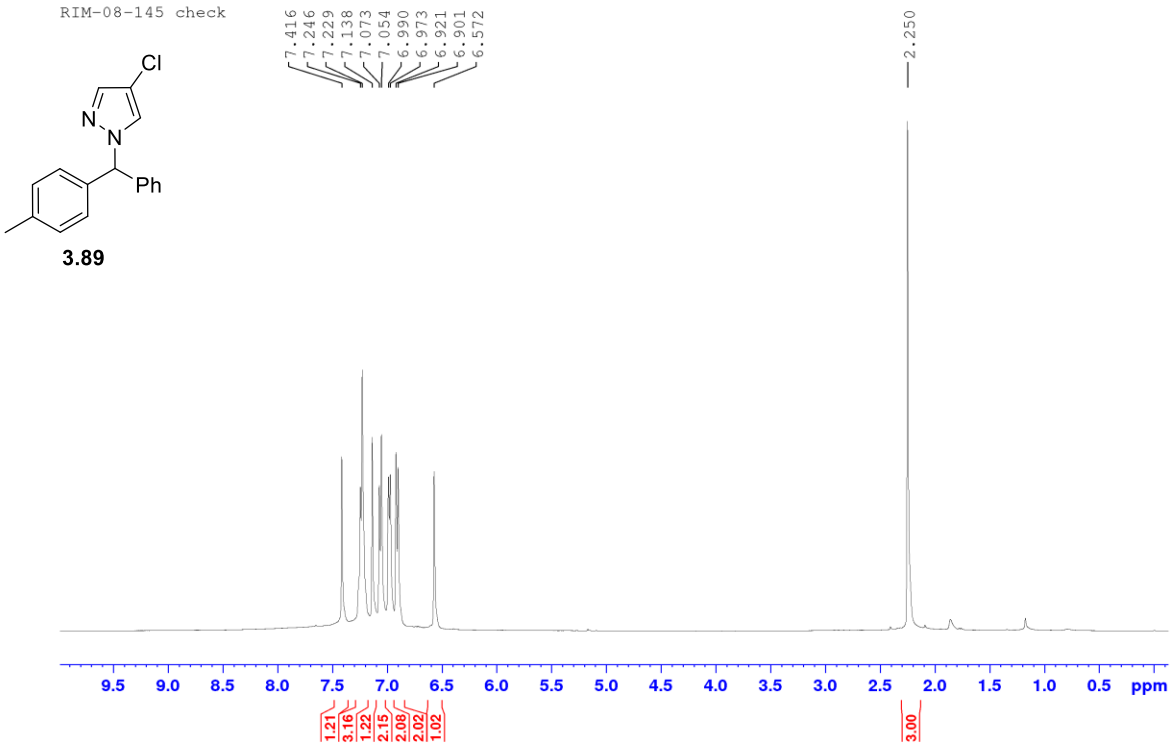

RIM-08-152
Cl
N
N
3.81
138.35
137.57
133.25
133.06
128.84
128.10
127.72
126.53
126.43
126.12
125.83
124.32
110.04
62.01
21.07
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

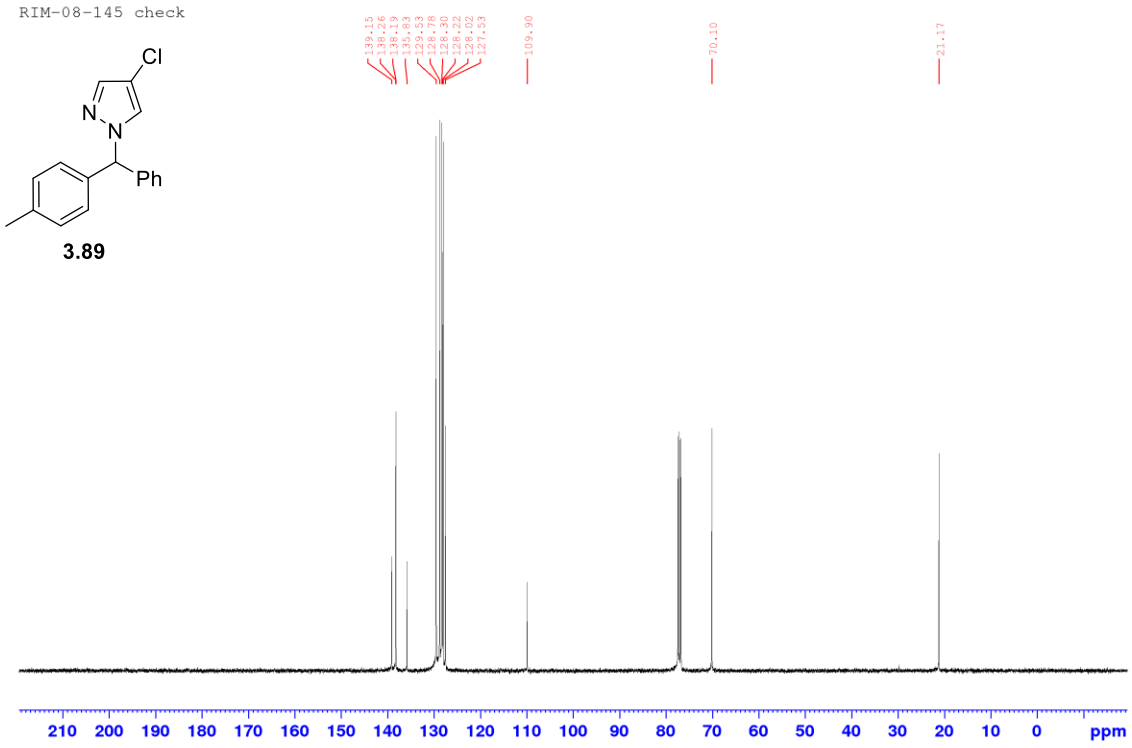

RIM-08-081
Cl
N
N
Ph
Ph
3.83
7.419
7.262
7.249
7.231
7.219
7.135
7.008
7.004
6.989
6.606
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.05
7.00
1.11
4.08
1.00

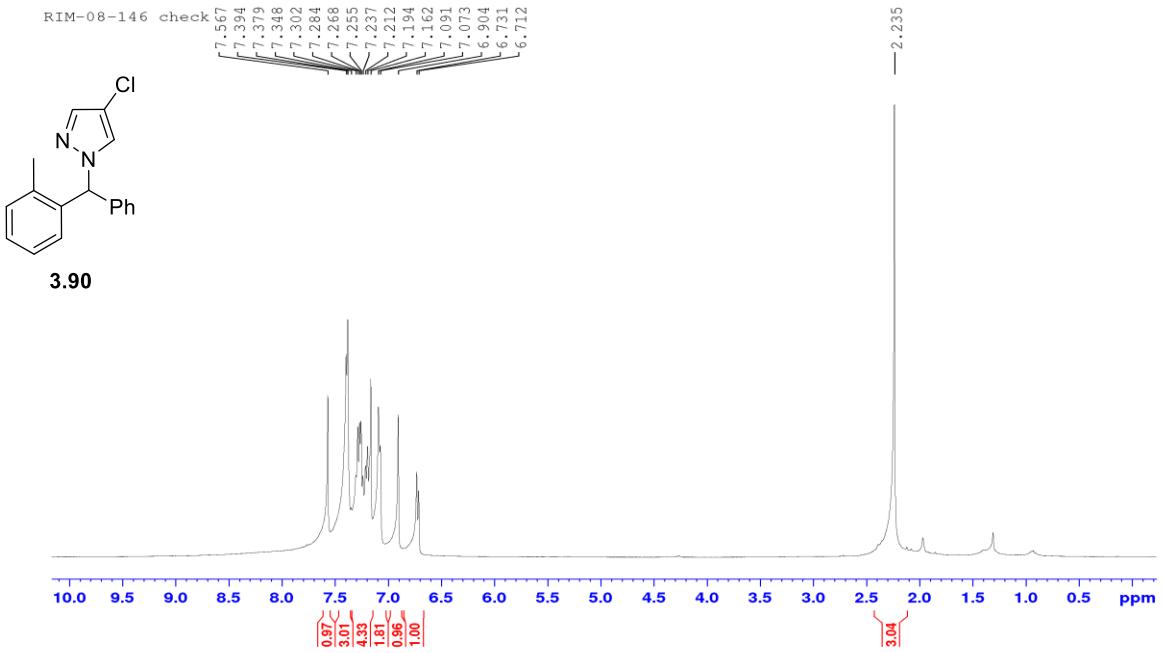

RIM-08-081
Cl
N
N
Ph
Ph
3.83
138.83
136.23
128.81
128.35
128.20
127.56
110.00
70.30
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

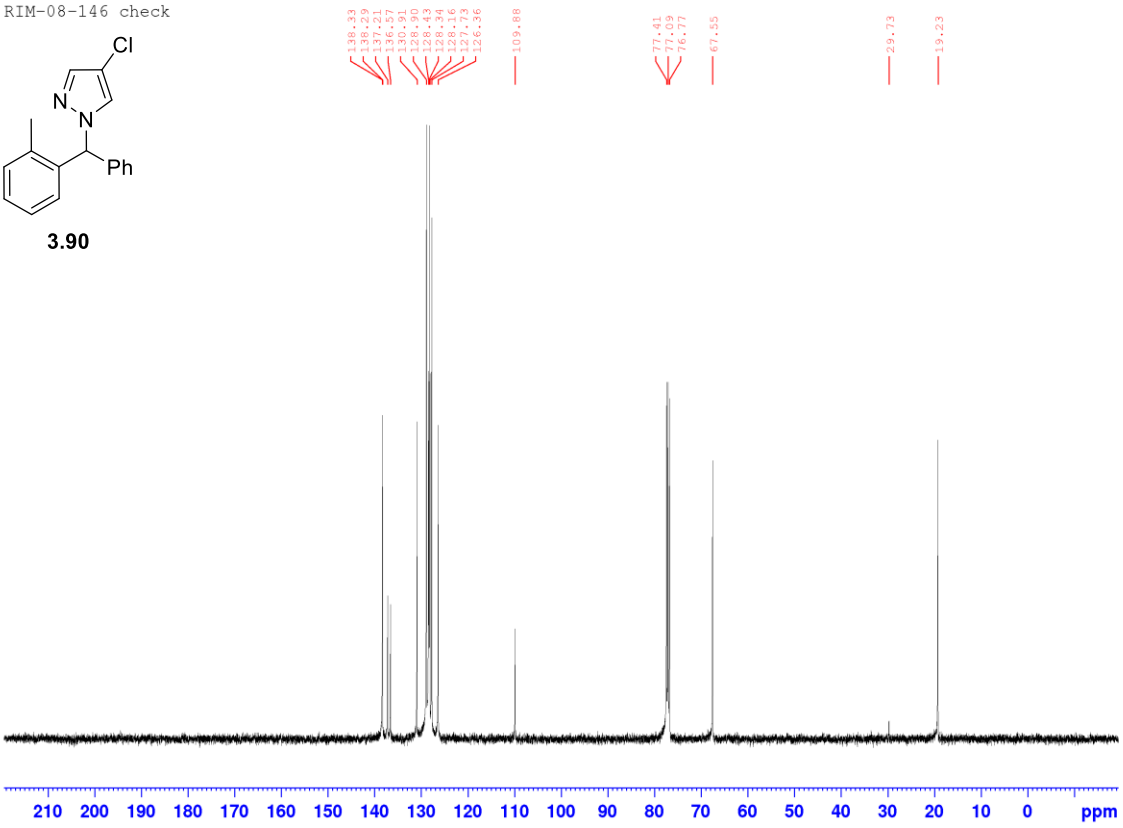

RIM-08-142
7.423
7.267
7.253
7.249
7.240
7.233
7.212
7.141
7.010
7.005
6.991
6.932
6.911
6.563
5.173
Cl
N
N
Ph
Cl
3.85
9
8
7
6
5
4
3
2
1
0 ppm
1.13
5.24
1.12
2.08
1.97
1.00

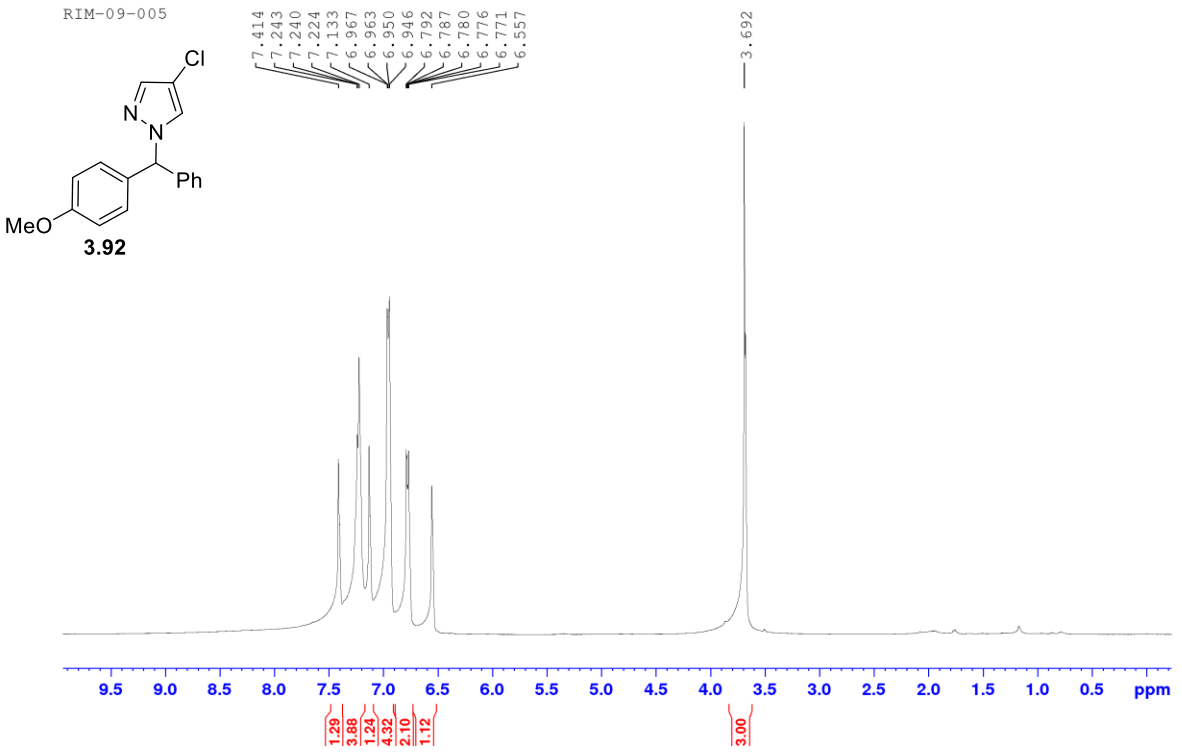

RIM-08-142
138.49
138.03
137.49
134.31
129.51
129.02
128.99
128.66
128.26
127.55
110.25
69.57
Cl
N
N
Ph
Cl
3.85
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

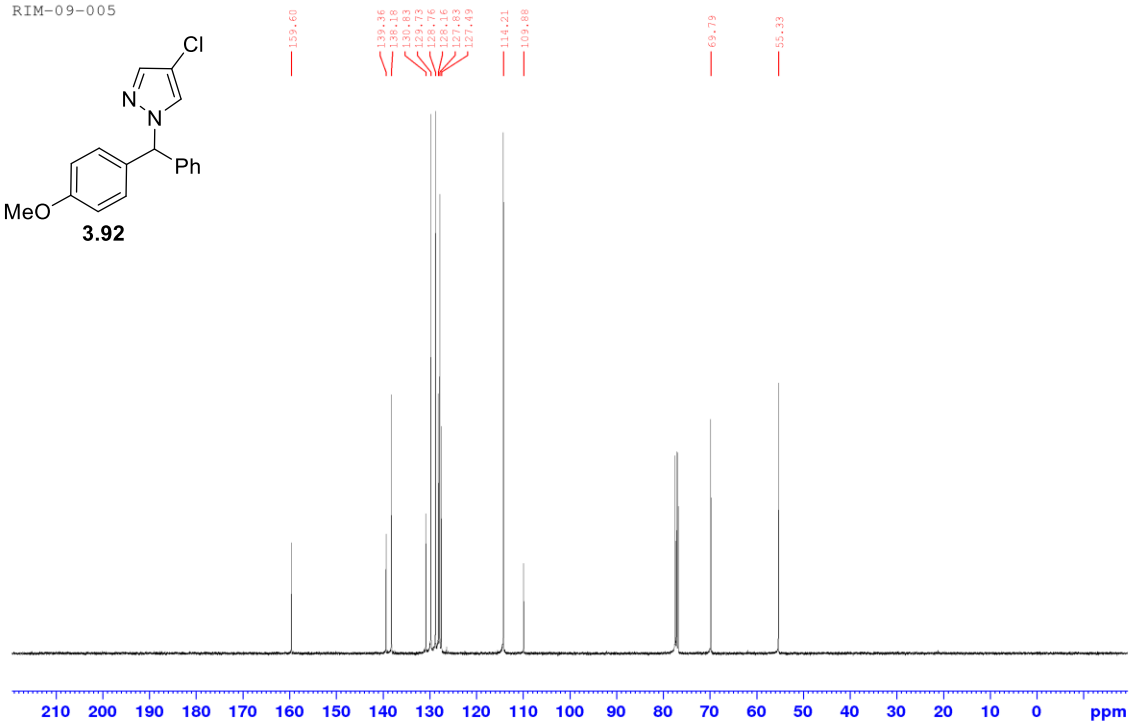

RIM-08-145 check
7.416
7.246
7.229
7.138
7.073
7.054
6.990
6.973
6.921
6.901
6.572
2.250
Cl
N
N
Ph
3.89
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.21
3.16
1.22
2.15
2.08
2.02
1.02
3.00

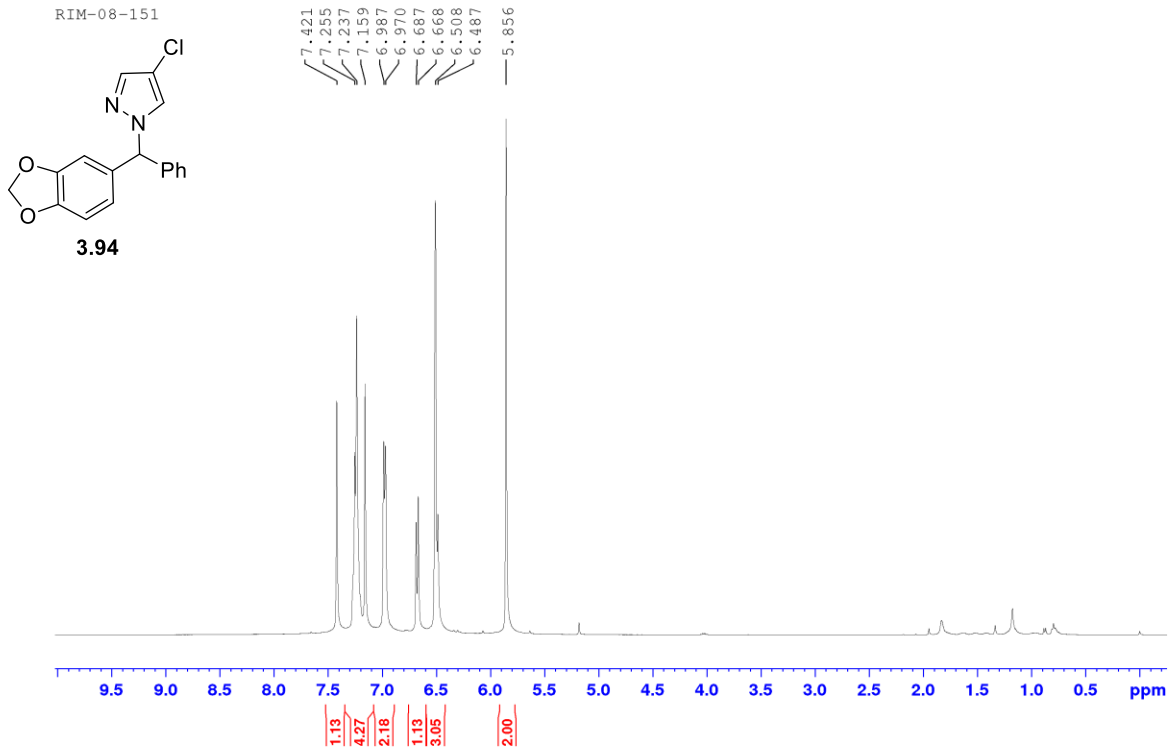

RIM-08-145 check
139.15
138.26
138.19
136.13
129.53
128.78
128.30
128.22
128.02
127.53
109.90
70.10
21.17
Cl
N
N
Ph
3.89
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

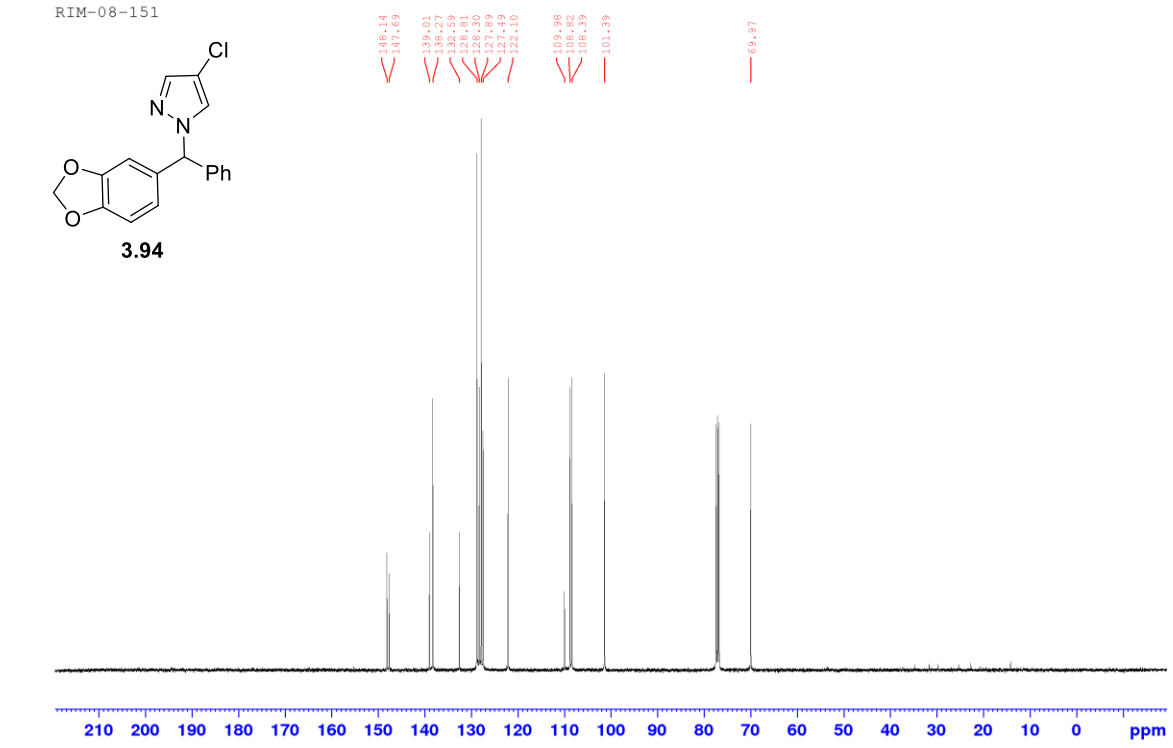

RIM-08-146 check
7.567
7.394
7.379
7.348
7.302
7.284
7.268
7.255
7.237
7.212
7.194
7.162
7.091
7.073
6.904
6.731
6.712
2.235
Cl
N
N
Ph
3.90
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.97
3.01
4.33
1.81
0.96
1.00
3.04

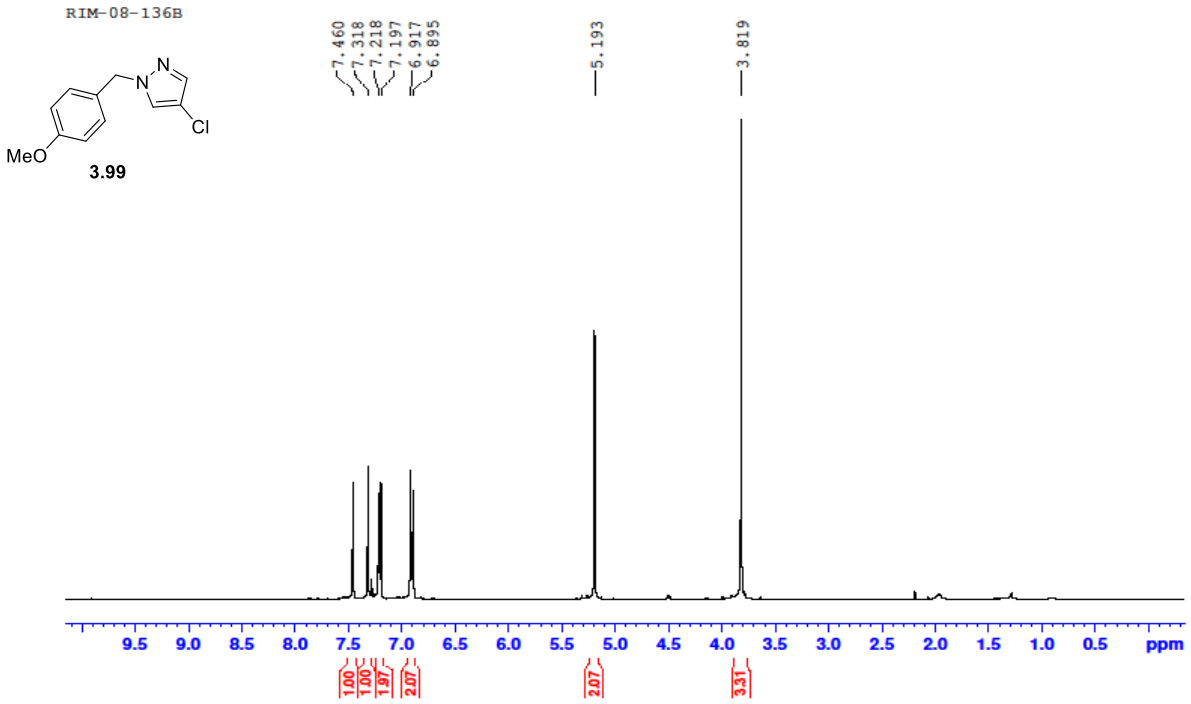

RIM-08-146 check
138.33
138.29
137.21
136.57
130.91
128.90
128.43
128.34
128.16
127.73
126.36
109.88
77.41
77.09
76.77
67.55
29.73
19.23
Cl
N
N
Ph
3.90
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

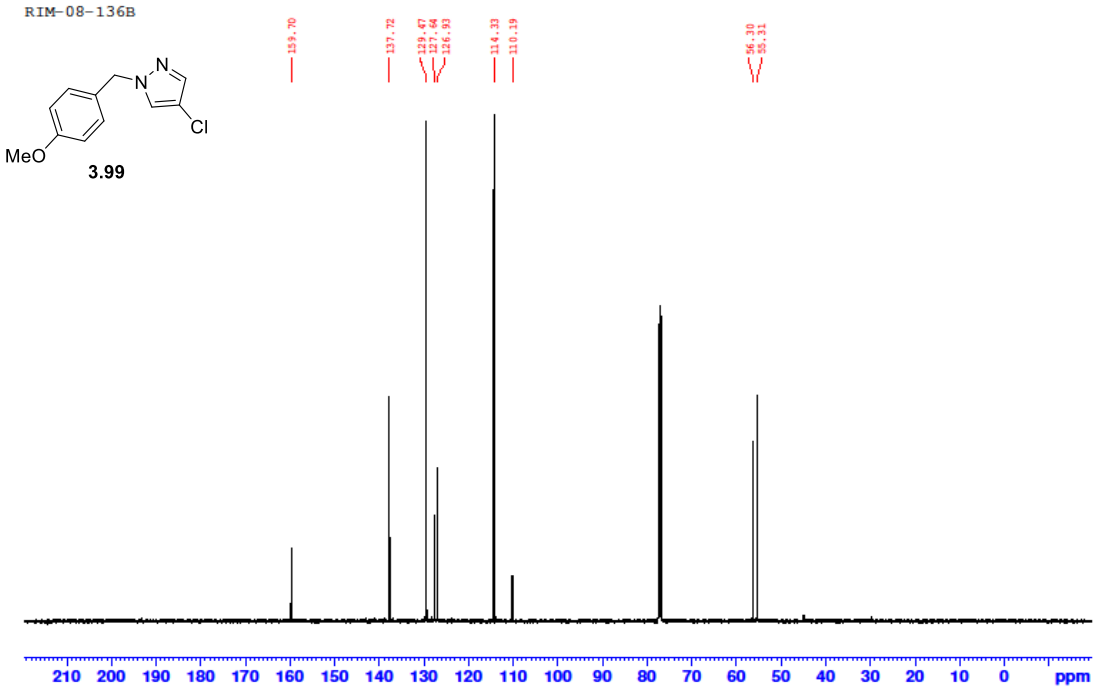

RIM-09-005
7.414
7.243
7.240
7.224
7.133
6.967
6.963
6.950
6.946
6.792
6.787
6.780
6.776
6.771
6.557
3.692
Cl
N
N
Ph
MeO
3.92
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.29
3.88
1.24
4.32
2.10
1.12
3.00

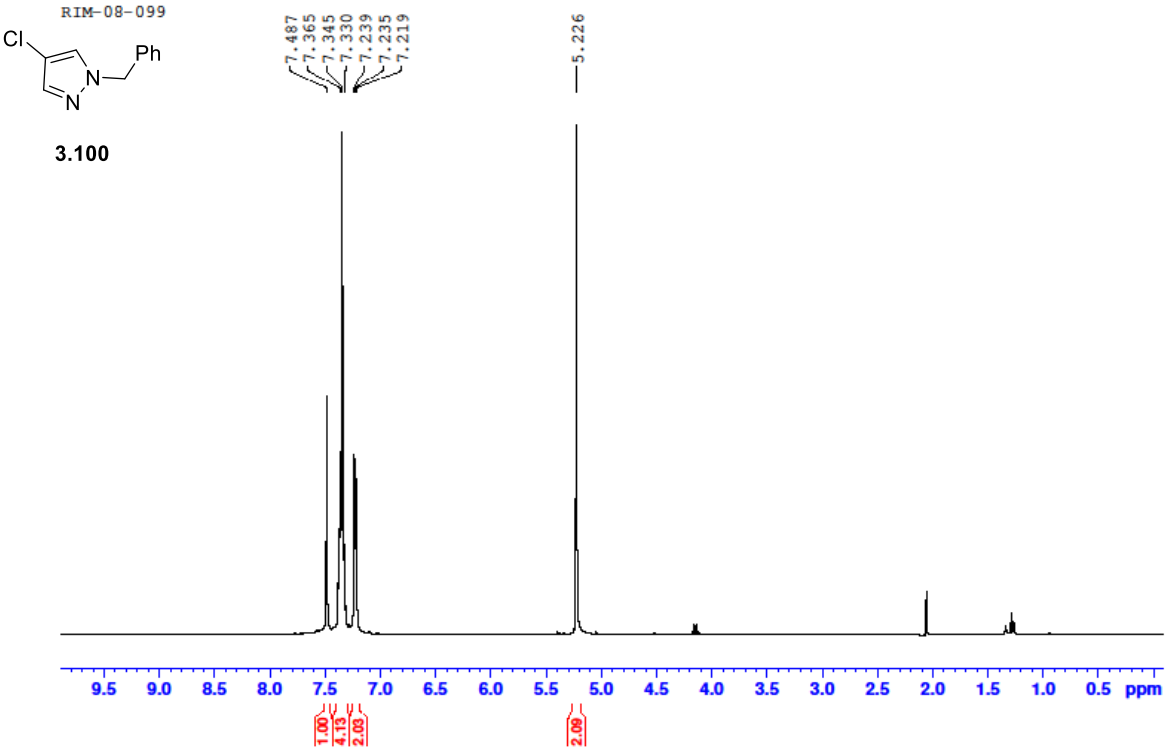

RIM-09-005
159.60
139.36
138.18
130.83
129.73
128.76
128.16
127.83
127.49
114.21
109.88
69.79
55.33
Cl
N
N
Ph
MeO
3.92
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

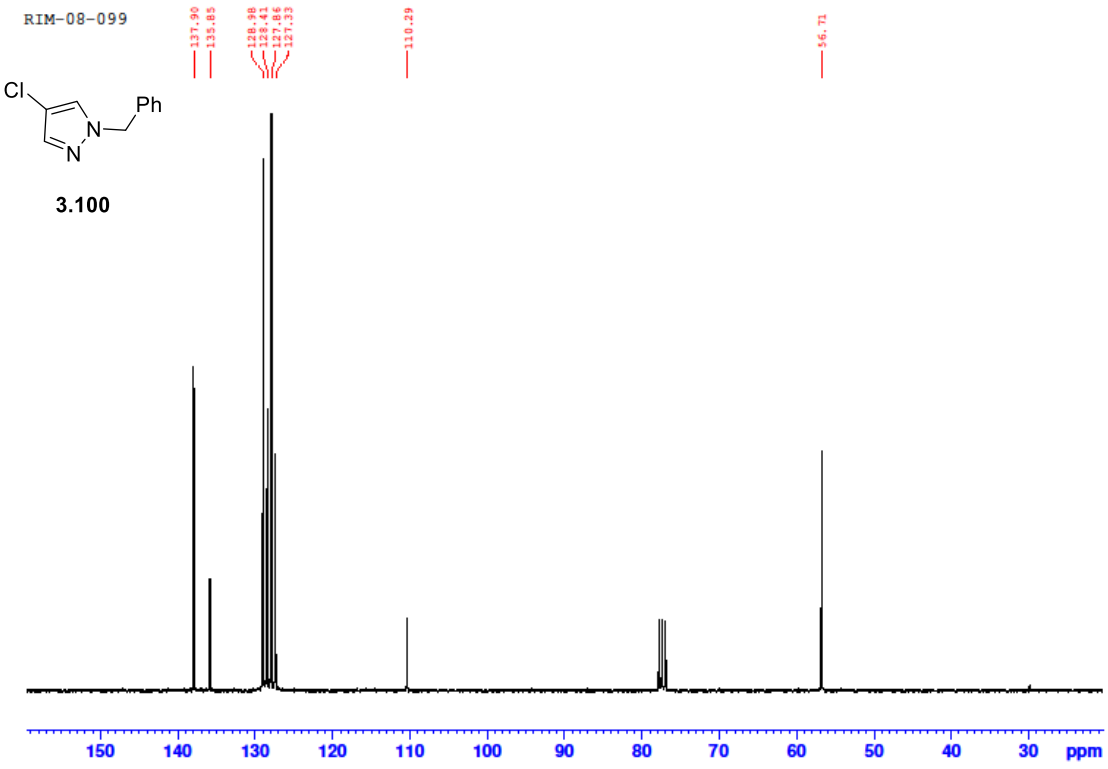

RIM-08-151
Cl
N
N
Ph
O
O
3.94
7.421
7.255
7.237
7.159
6.987
6.970
6.687
6.668
6.508
6.487
5.856
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.13
4.27
2.18
1.13
3.05
2.00

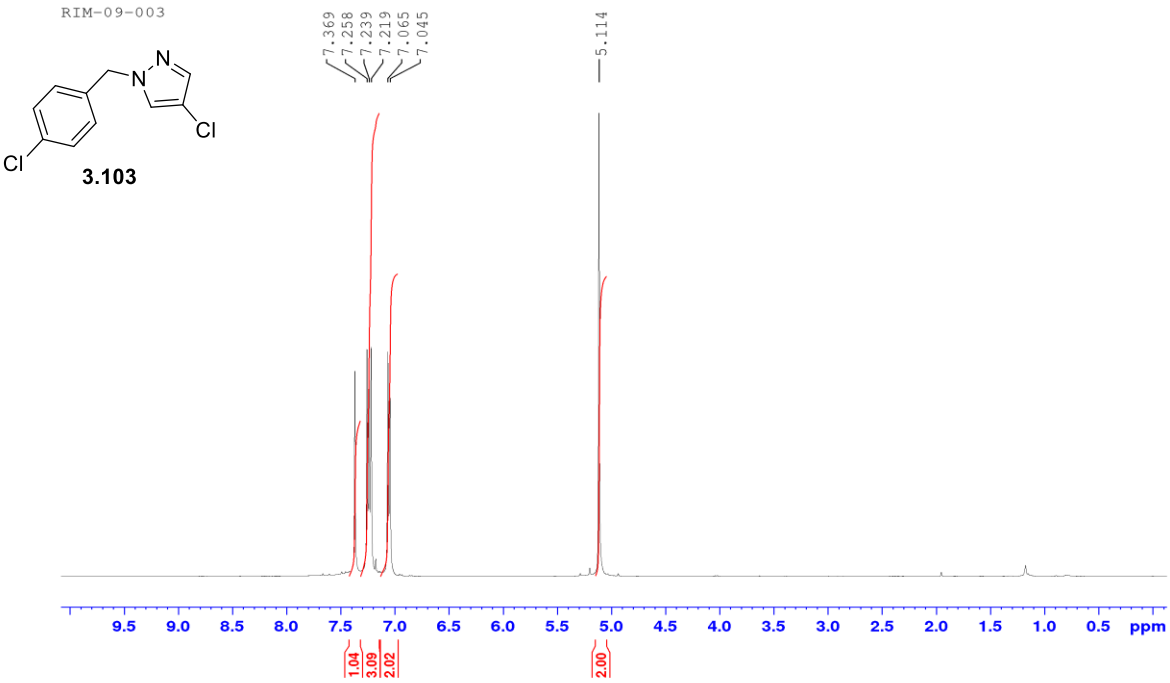

RIM-08-151
Cl
N
N
Ph
O
O
3.94
146.14
147.69
139.01
136.27
132.59
128.81
128.30
127.89
127.49
122.10
109.98
108.32
108.39
101.39
69.97
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

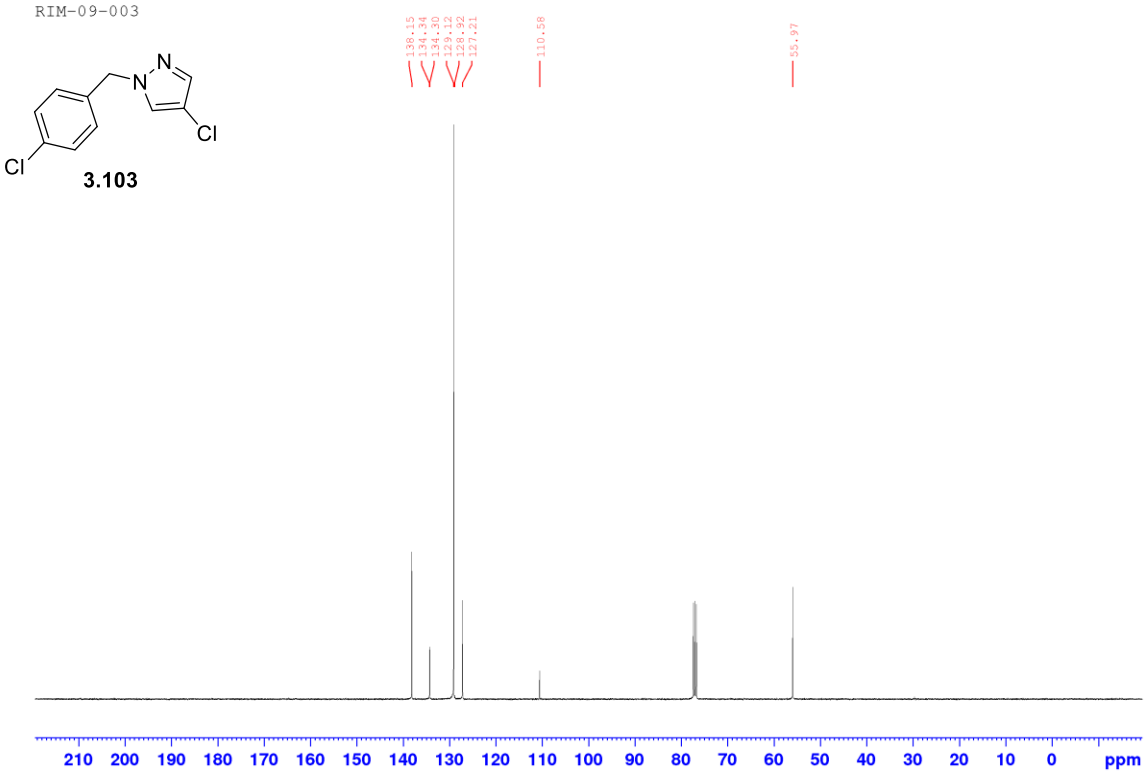

RIM-08-136B
7.460
7.318
7.218
7.197
6.917
6.895
5.193
3.819
N
N
Cl
MeO
3.99
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
1.00
1.97
2.07
2.07
3.31

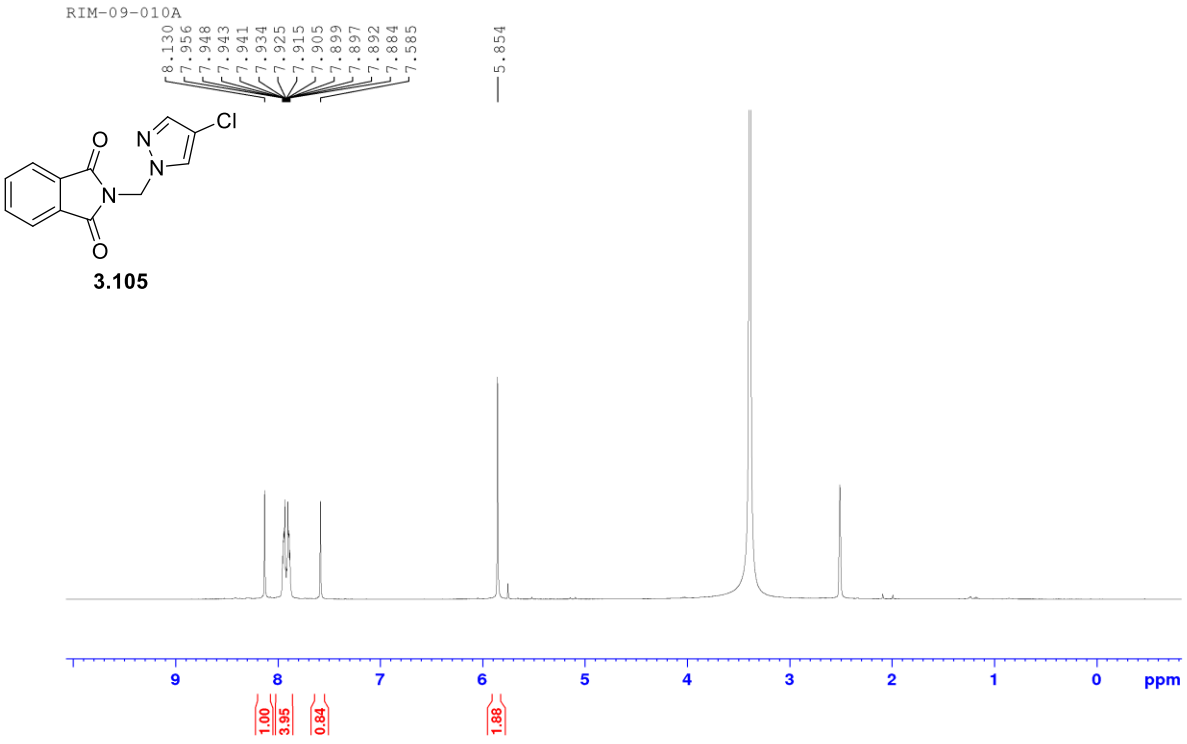

RIM-08-136B
159.70
137.72
129.47
127.64
126.93
114.33
110.19
56.30
55.31
N
N
Cl
MeO
3.99
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

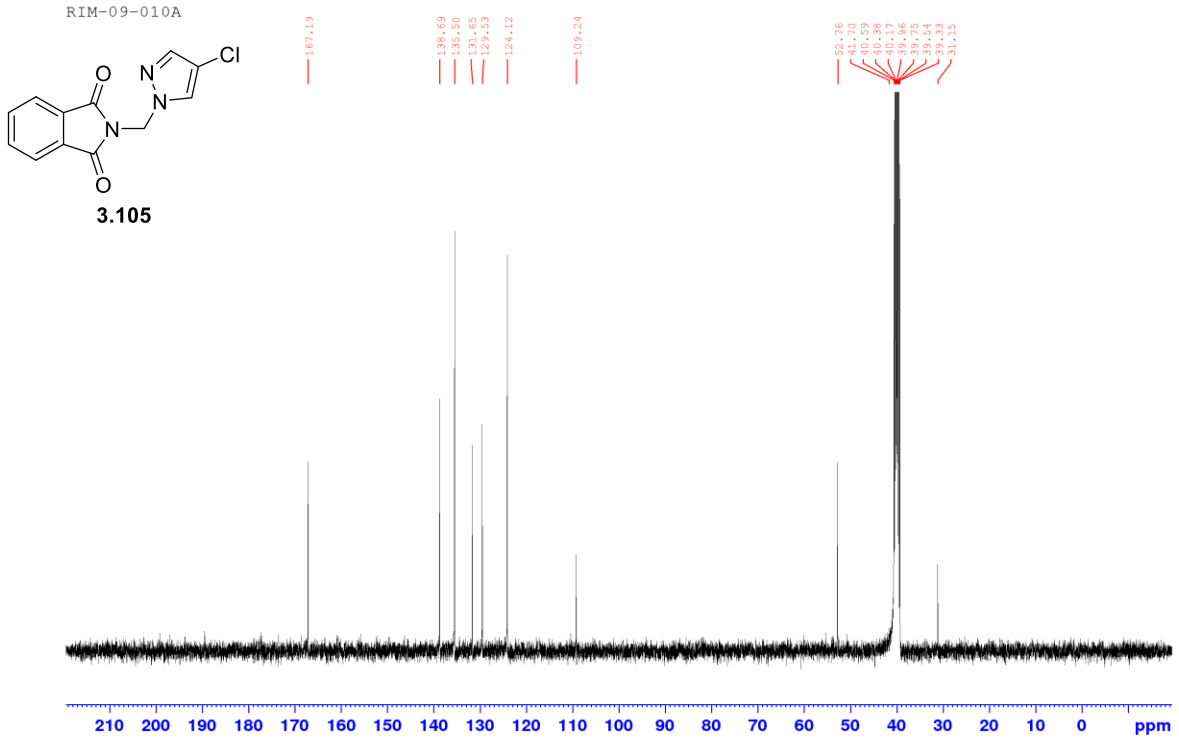

RIM-08-099
Cl
Ph
N
N
3.100
7.487
7.365
7.345
7.330
7.239
7.235
7.219
5.226
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
4.13
2.03
2.00

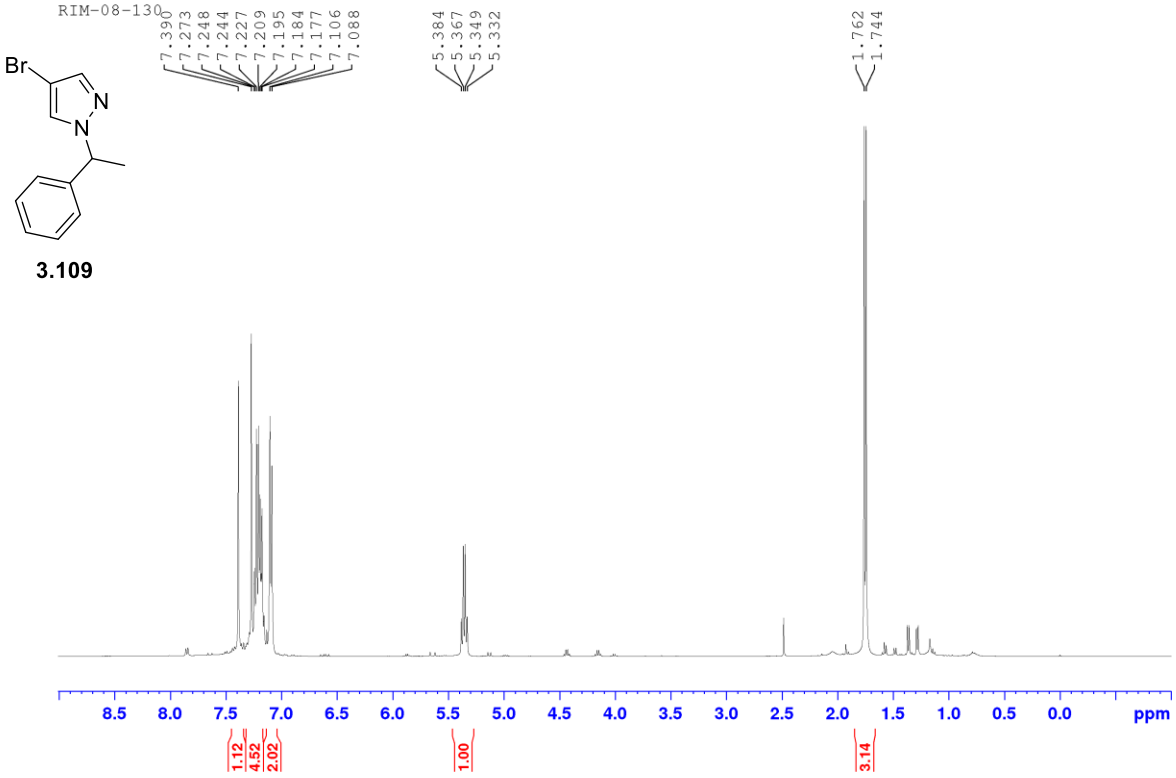

RIM-08-099
137.90
135.85
128.98
128.41
127.86
127.33
110.29
56.71
Cl
Ph
N
N
3.100
150 140 130 120 110 100 90 80 70 60 50 40 30 ppm

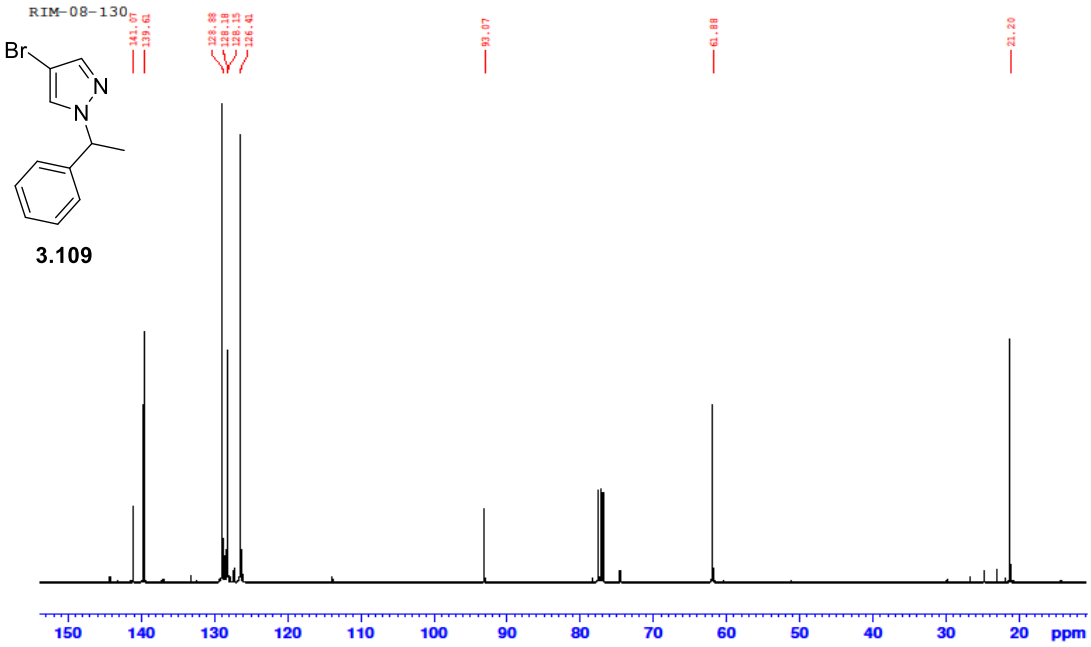

RIM-09-003
7.369
7.258
7.239
7.219
7.065
7.045
5.114
Cl
Cl
3.103
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.04
3.09
2.02
2.00

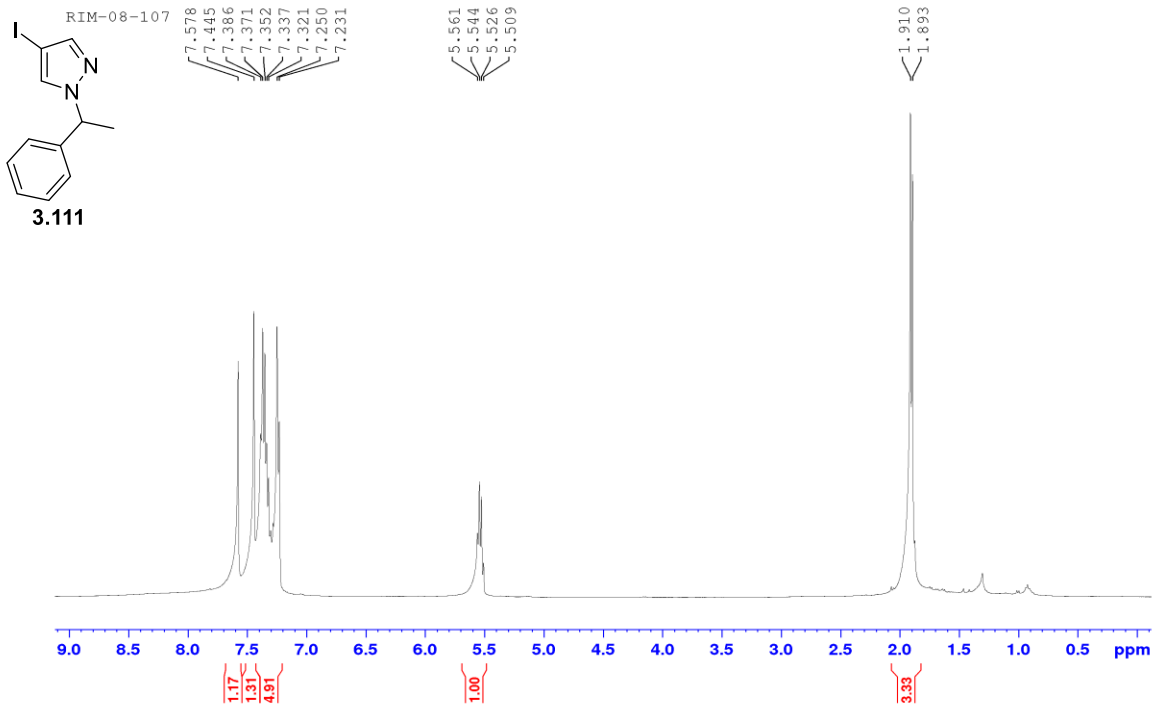

RIM-09-003
138.15
134.34
134.30
129.12
128.92
127.21
110.58
55.97
Cl
Cl
3.103
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

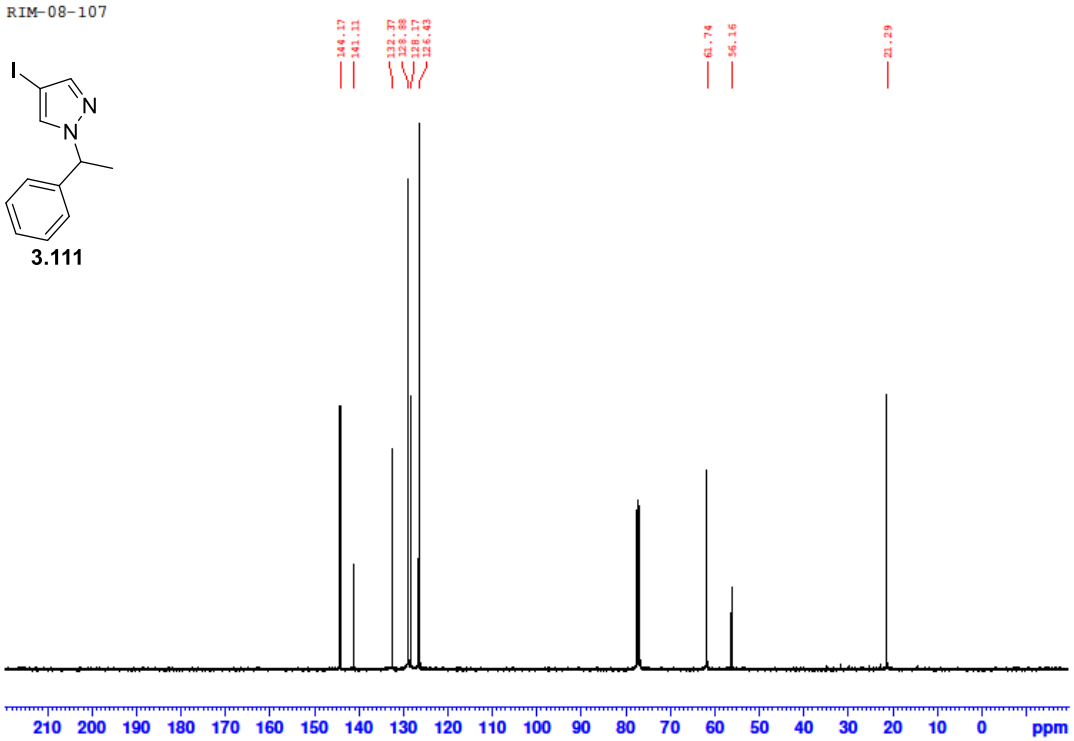

RIM-09-010A
8.130
7.956
7.948
7.943
7.941
7.934
7.925
7.915
7.905
7.899
7.897
7.892
7.884
7.585
5.854
Cl
O
N
N
O
N
O
3.105
9
8
7
6
5
4
3
2
1
0
ppm
1.00
3.95
0.84
1.88

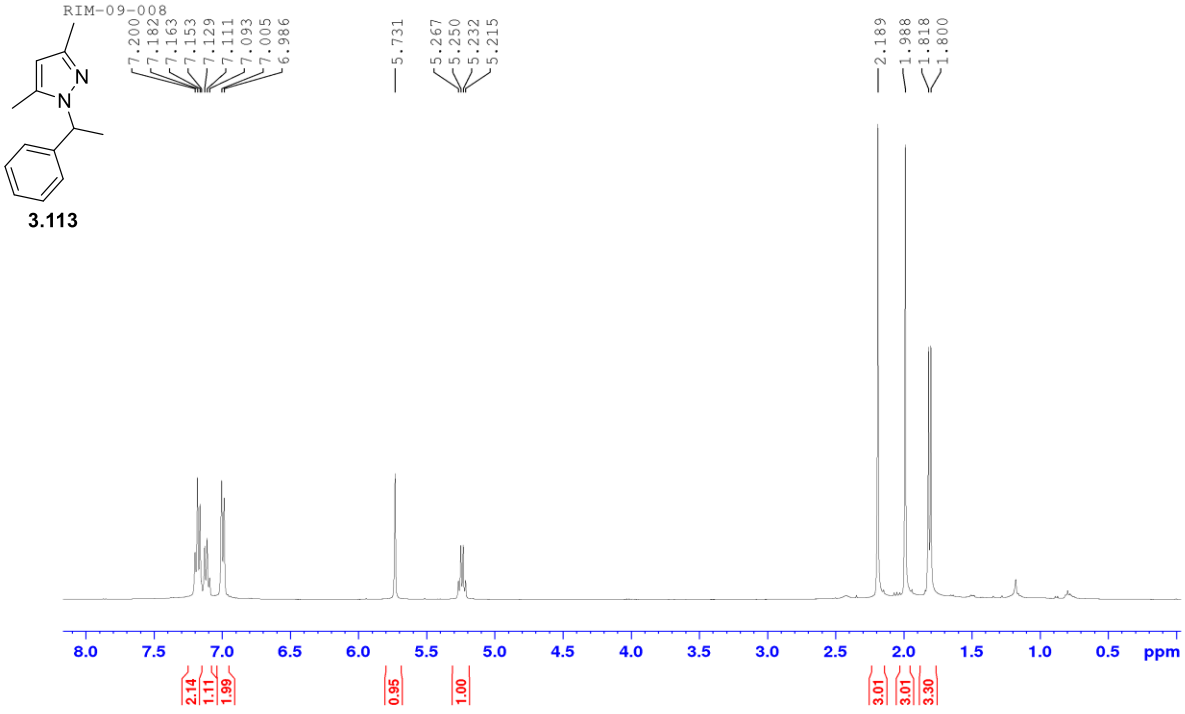

RIM-09-010A
167.19
138.69
135.50
131.65
129.53
124.12
109.24
52.76
41.70
40.59
40.38
40.17
39.96
39.75
39.54
39.33
31.15
Cl
O
N
N
O
N
O
3.105
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

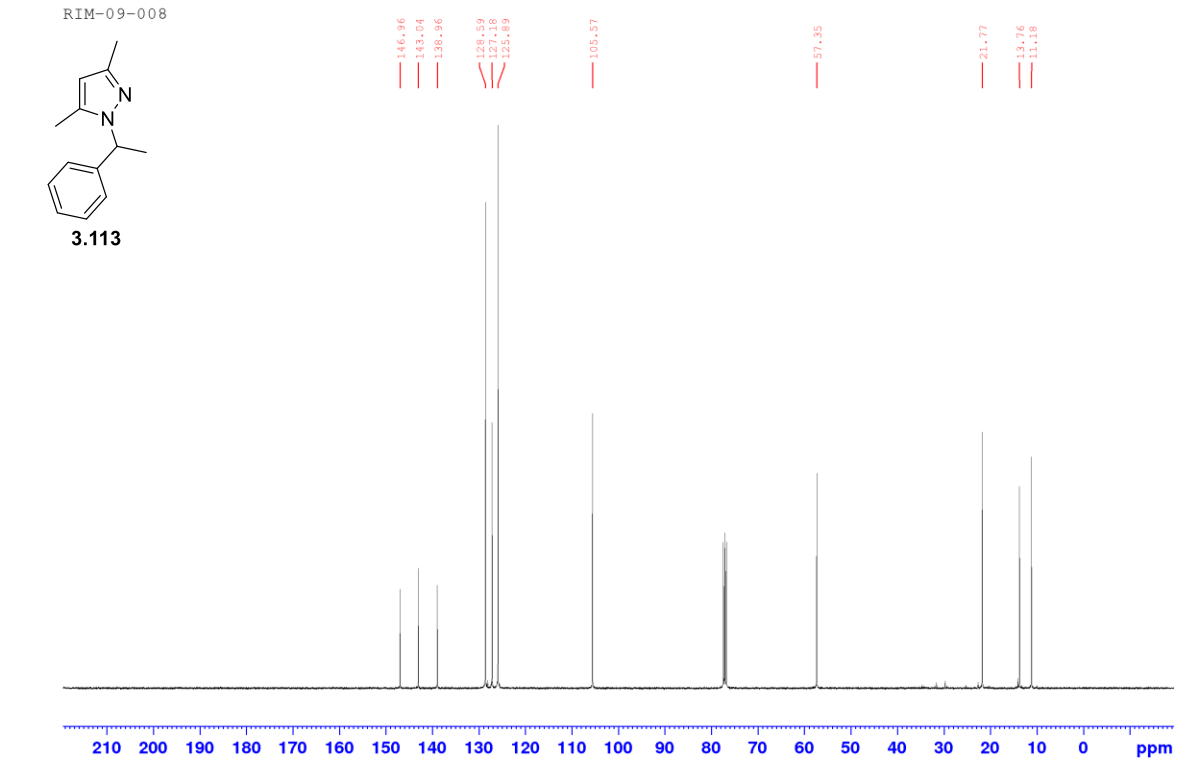

RIM-08-130
7.390
7.273
7.248
7.244
7.227
7.209
7.195
7.184
7.177
7.106
7.088
5.384
5.367
5.349
5.332
1.762
1.744
Br
N
N
3.109
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.12
4.52
2.02
1.00
3.14

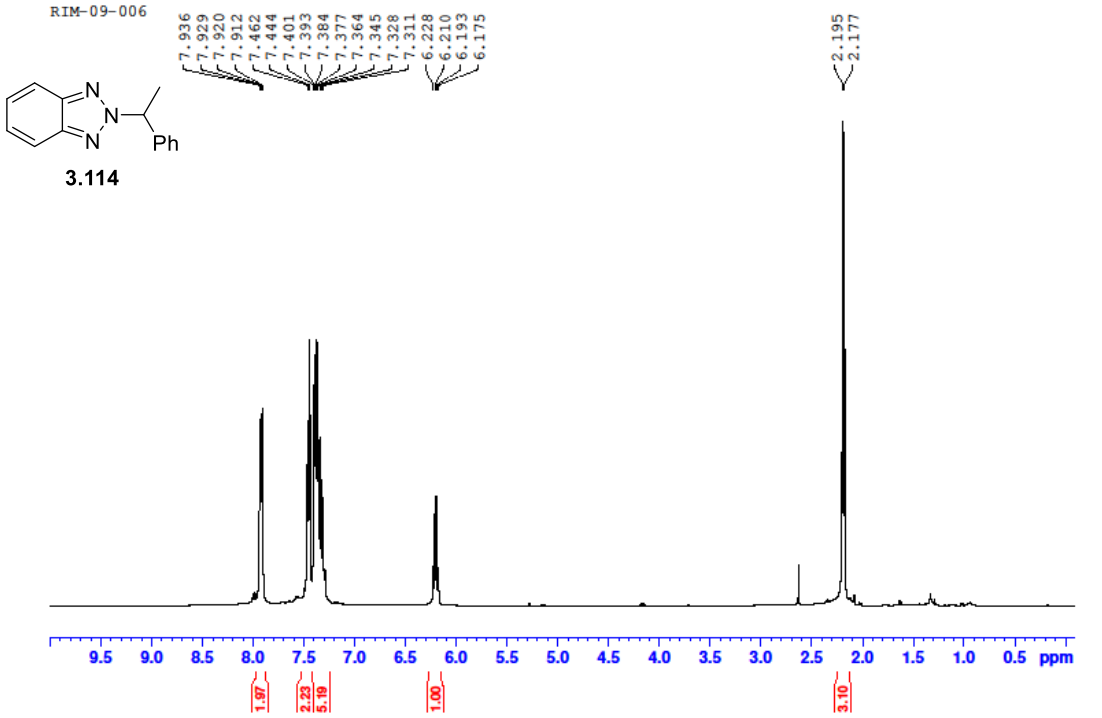

RIM-08-130
141.07
139.61
128.88
128.18
128.15
126.41
93.07
61.88
21.20
Br
N
N
3.109
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

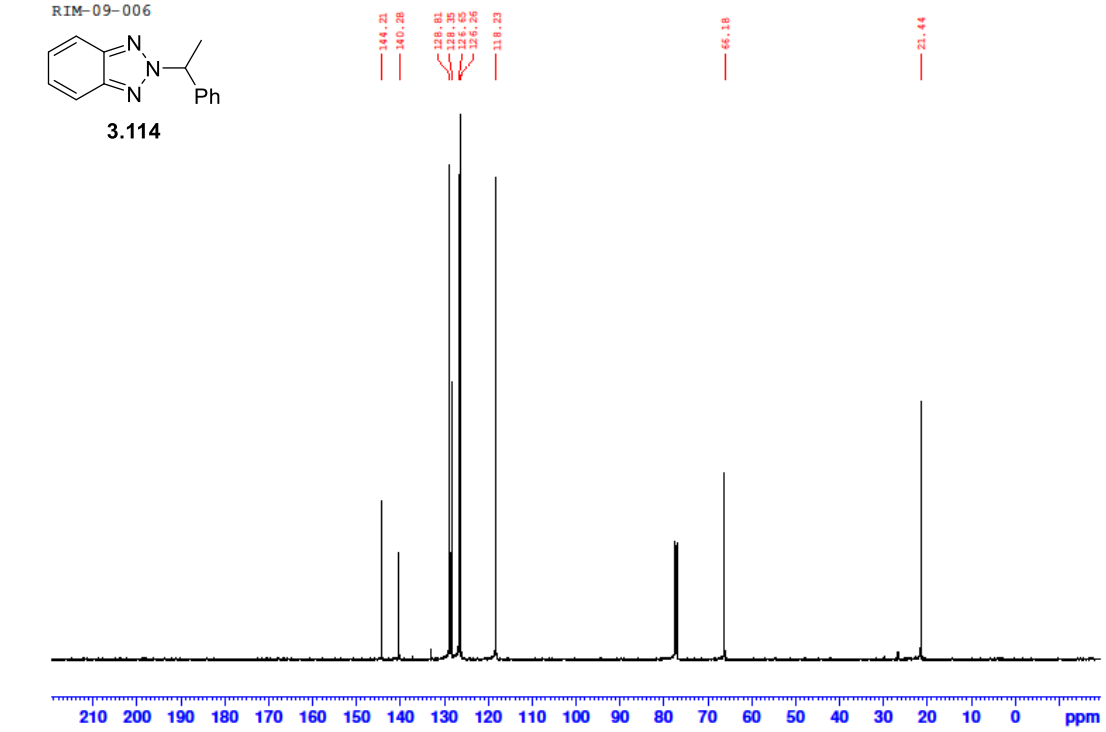

RIM-08-107
7.578
7.445
7.386
7.371
7.352
7.337
7.321
7.250
7.231
5.561
5.544
5.526
5.509
1.910
1.893
3.111
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.17
1.31
4.91
1.00
3.33


RIM-08-107
144.17
141.11
132.37
128.88
128.17
126.43
61.74
56.16
21.29
3.111
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


RIM-09-008
7.200
7.182
7.163
7.153
7.129
7.111
7.093
7.005
6.986
5.731
5.267
5.250
5.232
5.215
2.189
1.988
1.818
1.800
3.113
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.14
1.11
1.99
0.95
1.00
3.01
3.01
3.30


RIM-09-008
146.96
143.04
138.96
128.59
127.18
125.89
105.57
57.35
21.77
13.76
11.18
3.113
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


RIM-09-006
7.936
7.929
7.920
7.912
7.462
7.444
7.401
7.393
7.384
7.377
7.364
7.345
7.328
7.311
6.228
6.210
6.193
6.175
2.195
2.177
N
N
N
Ph
3.114
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.97
2.23
5.19
1.00
3.10


RIM-09-006
144.21
140.28
128.81
128.35
126.65
126.26
118.23
66.18
21.44
N
N
N
Ph
3.114
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

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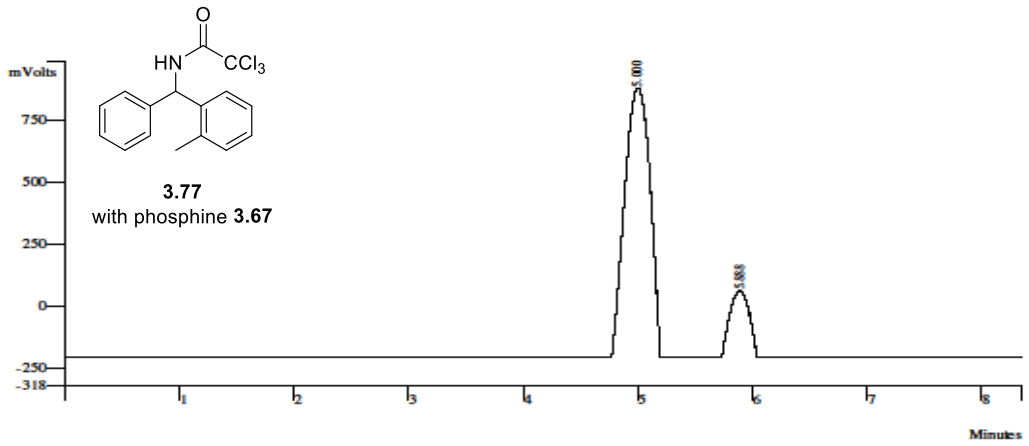

3.77
with phosphine **3.67**

Peak No	Peak Name	Result ()	Ret Time (min)	Time Offset (min)	Peak Area (counts)	Rel Ret Time	Sep. Code	Width 1/2 (sec)	Status Codes	Group
1		83.8524	5.000	0.000	16703406	0.00	BB	15.7		0
2		16.1476	5.888	0.000	3216602	0.00	BB	12.6		0
	Totals	**100.0000**		**0.000**	**19920008**					

c:\documents and settings\lab-admin\desktop\rim\rim_02_048_0.8ipa_1.5mlmi
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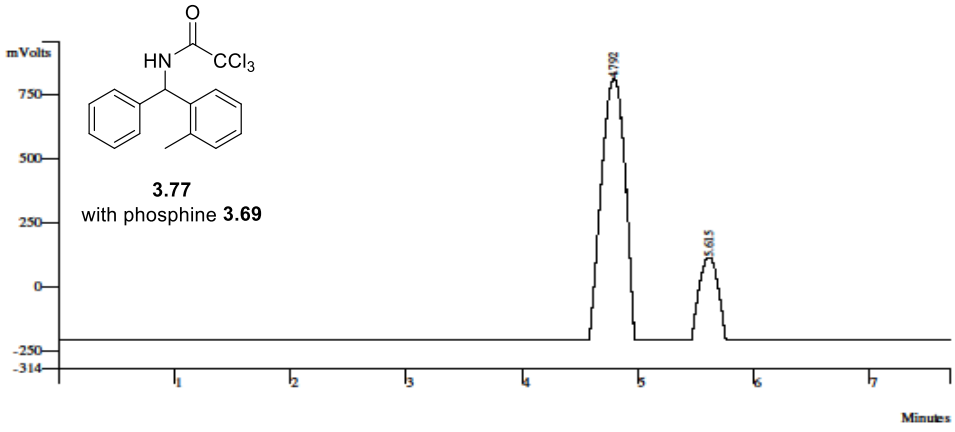
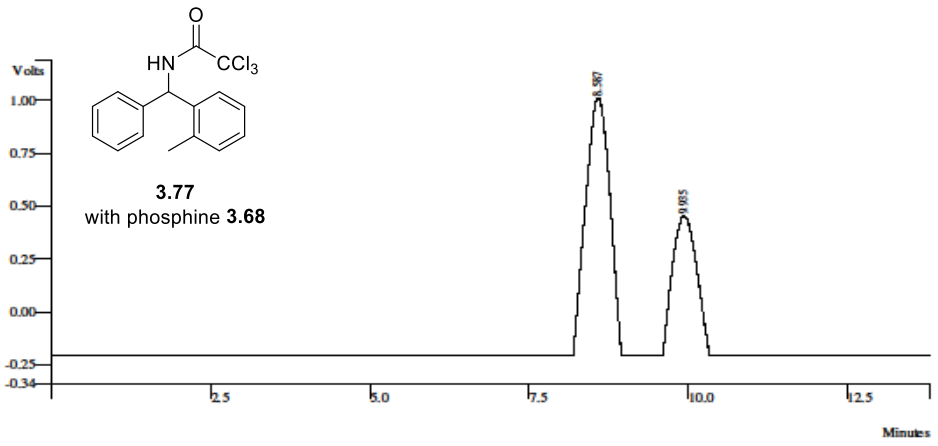


3.77
with phosphine **3.69**

Peak No	Peak Name	Result ()	Ret Time (min)	Time Offset (min)	Peak Area (counts)	Rel Ret Time	Sep. Code	Width 1/2 (sec)	Status Codes	Group
1		79.7238	4.792	0.000	14434164	0.00	BB	14.5		0
2		20.2762	5.615	0.000	3671057	0.00	BB	11.9		0
	Totals	**100.0000**		**0.000**	**18105220**					

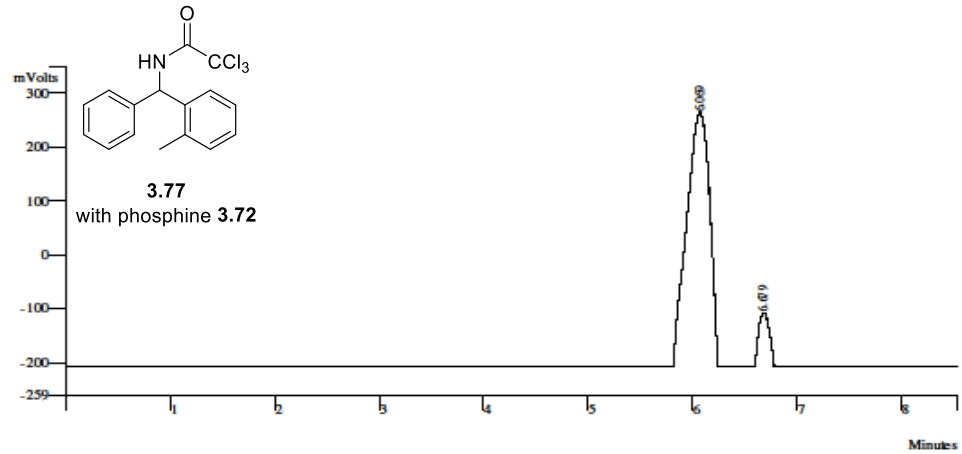
c:\documents and settings\lab-admin\desktop\rim\rim_02_075_0.8ipa_1.0mlmi
1 = Detector RESULTS



3.77
with phosphine **3.68**

Peak No	Peak Name	Result ()	Ret Time (min)	Time Offset (min)	Peak Area (counts)	Rel Ret Time	Sep. Code	Width 1/2 (sec)	Status Codes	Group
1		64.5810	8.587	0.000	32240670	0.00	BB	26.5		0
2		35.4190	9.935	0.000	17682190	0.00	BB	27.7		0
	Totals	**100.0000**		**0.000**	**49922860**					

c:\documents and settings\lab-admin\desktop\rim\rim_02_091_0.8ipa_1.5mlmi
1 = Detector RESULTS



3.77
with phosphine **3.72**

Peak No	Peak Name	Result ()	Ret Time (min)	Time Offset (min)	Peak Area (counts)	Rel Ret Time	Sep. Code	Width 1/2 (sec)	Status Codes	Group
1		90.7601	6.069	0.000	7200899	0.00	BV	15.4		0
2		9.2399	6.679	0.000	733094	0.00	VB	7.6		0
	Totals	**100.0000**		**0.000**	**7933993**					

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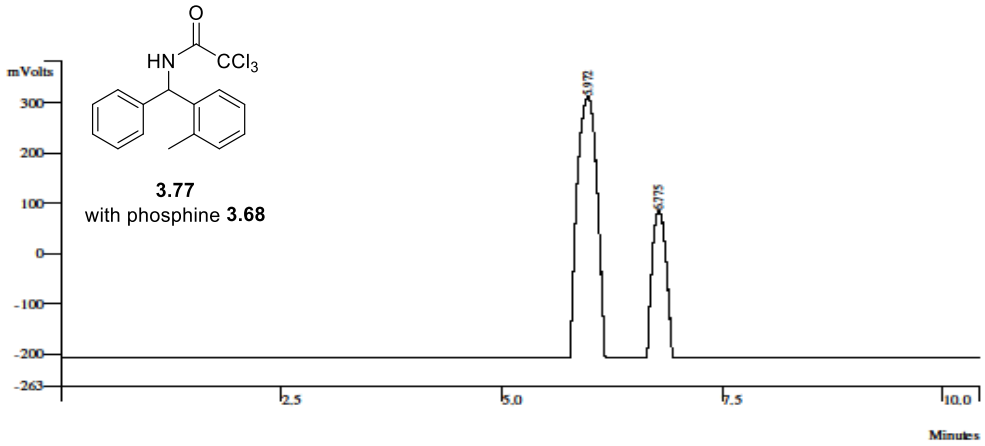
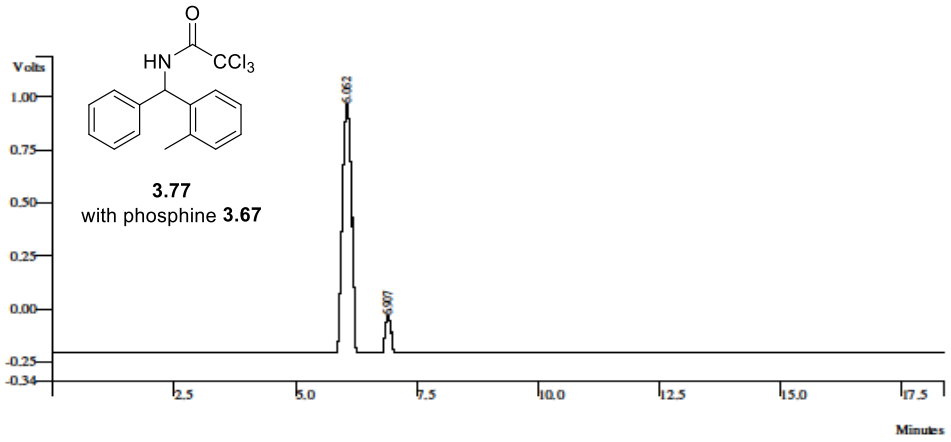


3.77
with phosphine **3.68**

Peak No	Peak Name	Result ()	Ret Time (min)	Time Offset (min)	Peak Area (counts)	Rel Ret Time	Sep. Code	Width 1/2 (sec)	Status Codes	Group
1		71.2854	5.972	0.000	8133438	0.00	BB	16.4		0
2		28.7146	6.775	0.000	3276247	0.00	BB	11.6		0
	Totals	**100.0000**		**0.000**	**11409685**					

c:\documents and settings\lab-admin\desktop\rim\rim_02_093_0.8ipa_1.5mlmi
1 = Detector RESULTS



3.77
with phosphine **3.67**

Peak No	Peak Name	Result ()	Ret Time (min)	Time Offset (min)	Peak Area (counts)	Rel Ret Time	Sep. Code	Width 1/2 (sec)	Status Codes	Group
1		91.3712	6.062	0.000	15518418	0.00	BB	13.4		0
2		8.6288	6.907	0.000	1465516	0.00	BB	9.0		0
	Totals	**100.0000**		**0.000**	**16983934**					

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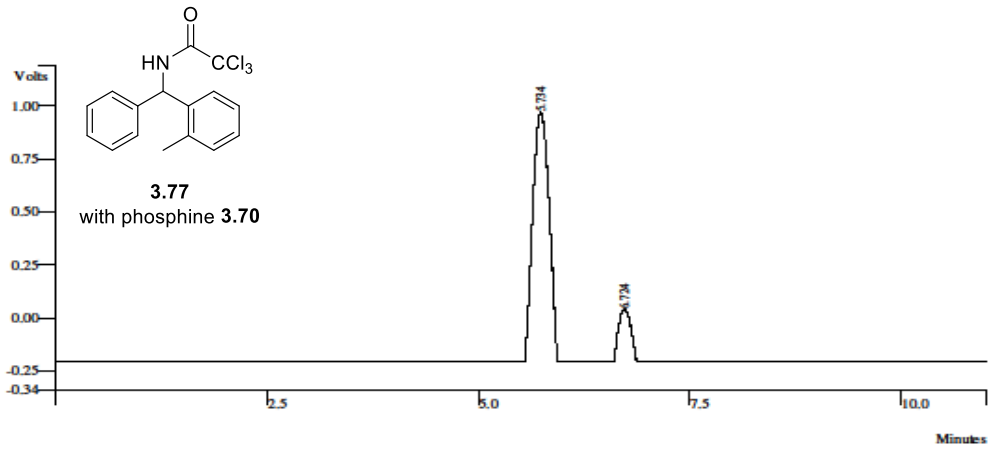
1 = Detector RESULTS



3.77
with phosphine **3.70**

Peak No	Peak Name	Result ()	Ret Time (min)	Time Offset (min)	Peak Area (counts)	Rel Ret Time	Sep. Code	Width 1/2 (sec)	Status Codes	Group
1		86.0627	5.734	0.000	15841895	0.00	BB	13.8		0
2		13.9373	6.724	0.000	2565495	0.00	BB	10.8		0
	Totals	**100.0000**		**0.000**	**18407390**					

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Chapter 4 – New Reactions Mediated by Oxoammonium Salts

Abstract:

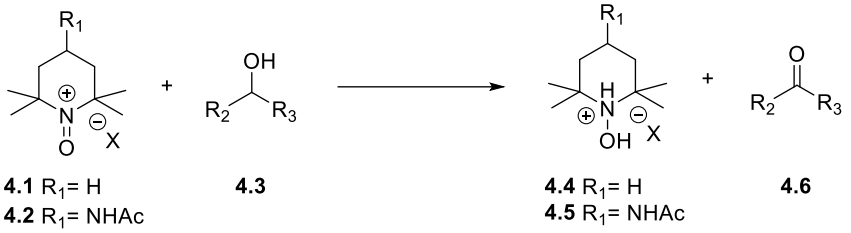
Oxoammonium salts are commonly used to oxidize alcohols to aldehydes or ketones, but these reagents may also be used in a number of other oxidative transformations which are useful in organic chemistry. Taking advantage of these reagents, a new tandem elimination-oxidation process of tertiary alcohols has been discovered, synthesizing a protected allylic alcohol. Data suggests that the transformation first proceeds through elimination of the alcohol mediated by the oxoammonium salt. Then the allylic oxidation proceeds through an ene type mechanism. Additionally, the tetramethylpiperidine derived from the oxoammonium salt also serves as a protecting group for the newly generated allylic alcohol, resulting in a process with high atom economy. The optimization and scope of the reaction has been investigated.

N-Oxoammonium salts are also shown to be useful reagents for the metal free 1,2-difunctionalizations of alkenes with heteroatom nucleophiles. While many transformations for the 1,2-addition of heteroatoms to alkenes have been developed, most are dependent on transition metals. Rarer are alkene difunctionalizations that utilize nonmetallic reagents, with most of these reactions relying on photochemical or radical conditions. Investigating these *N*-oxoammonium salt mediated additions provides a new method for the elaboration of alkenes into molecules with significantly greater complexity. The determination of the stereochemistry of the products of an amino-oxidation with *N*-oxoammonium salts was also accomplished. Attempts to improve the diastereoselectivity of this process were explored. Investigations have also been initiated to perform these alkene difunctionalizations in an enantioselective manner utilizing anionic phase transfer catalysis. Expansion of the *N*-oxoammonium salt mediated additions of alkenes with primary alcohols, water, and isatin was also initiated.

Introduction:

The oxidation of alcohols to the corresponding aldehyde and ketones using an oxoammonium salt was first reported by Golubev.[1] These *N*-oxoammonium salts were attractive reagents for these oxidations because they are environmentally benign and recyclable, unlike established chromium-based reagents or other toxic reagents based on heavy metals.[2, 3] These oxoammonium reagents have been shown to oxidize alcohols either stoichiometrically or catalytically (Scheme 4.1).[4] These oxidations can be performed under near neutral conditions in dichloromethane with silica gel,[3] or under basic conditions typically with pyridine bases.[5] Typically, these stoichiometric oxidations are colorimetric reactions, changing color from red to yellow as the oxidation proceeds. A variety of alcohols oxidized to the corresponding aldehyde or ketone using these methods, including allyl, benzyl, primary, and secondary alcohols. However, primary aliphatic alcohols react slowly, requiring long reaction times (often greater than 24 h). In fact, other functionally present in the molecule would often react before oxidation of the primary alcohol would occur, resulting in lower yields. Additionally, the presence of a β-oxygen or β-nitrogen group is usually not tolerated.[3] For example, a *t*-butyldimethylsilyl group on the alcohol is often lost during the reaction, causing a mixture of products. A β-Oxygen or β-nitrogen may coordinate to the nitrogen of the oxoammonium salt, hindering the reaction.[6] When oxidizing alcohols in the presence of pyridine bases, unless there is substitution in the 2- and 6-positions on the pyridine base, the ester of the two alcohols will form, not the desired aldehyde or ketone.[5] These optimized conditions utilizing 2,6-lutidine and oxoammonium salt **4.2** were useful in oxidizing α-trifluoromethyl alcohols to the corresponding ketone.[7]

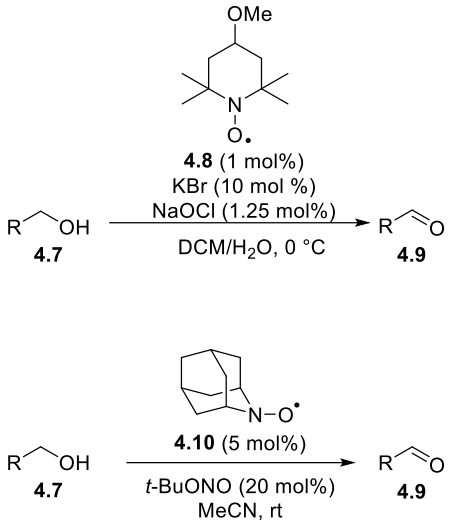
Scheme 4.1. Stoichiometric Oxidations with Oxoammonium Salts



4.1 R_1= H
4.2 R_1= NHAc
4.3
4.4 R_1= H
4.5 R_1= NHAc
4.6

Some drawbacks of using stoichiometric amounts of oxoammonium salts include the salts can be possibly hygroscopic and unstable, generating unwanted reactivity, the nitroxides are not always commercially available, and the oxidation efficiency often varies based on the counter ion. For example, chloride salts oxidize primary alcohols faster than perbromides, nitrates and tetrafluoroborates.[3] A number of catalytic conditions have been developed, typically generating the oxoammonium cation in situ from the nitroxide. This is done by adding another oxidant such as sodium hypochlorite (NaOCl, commercial bleach) to generate the oxoammonium cation.[8] More recently AZADO salts have be synthesized and utilized in alcohol oxidations.[9] Using the AZADO salts under aerobic conditions with *t*-butyl nitrite as a co-catalyst, primary alcohols were readily oxidized to the corresponding aldehyde. Additionally, this method is tolerant of many protecting groups. This may be due to an enhanced catalytic efficiency that has been reported for AZADO nitroxyl radicals attributed to the tricyclic structure.[10]

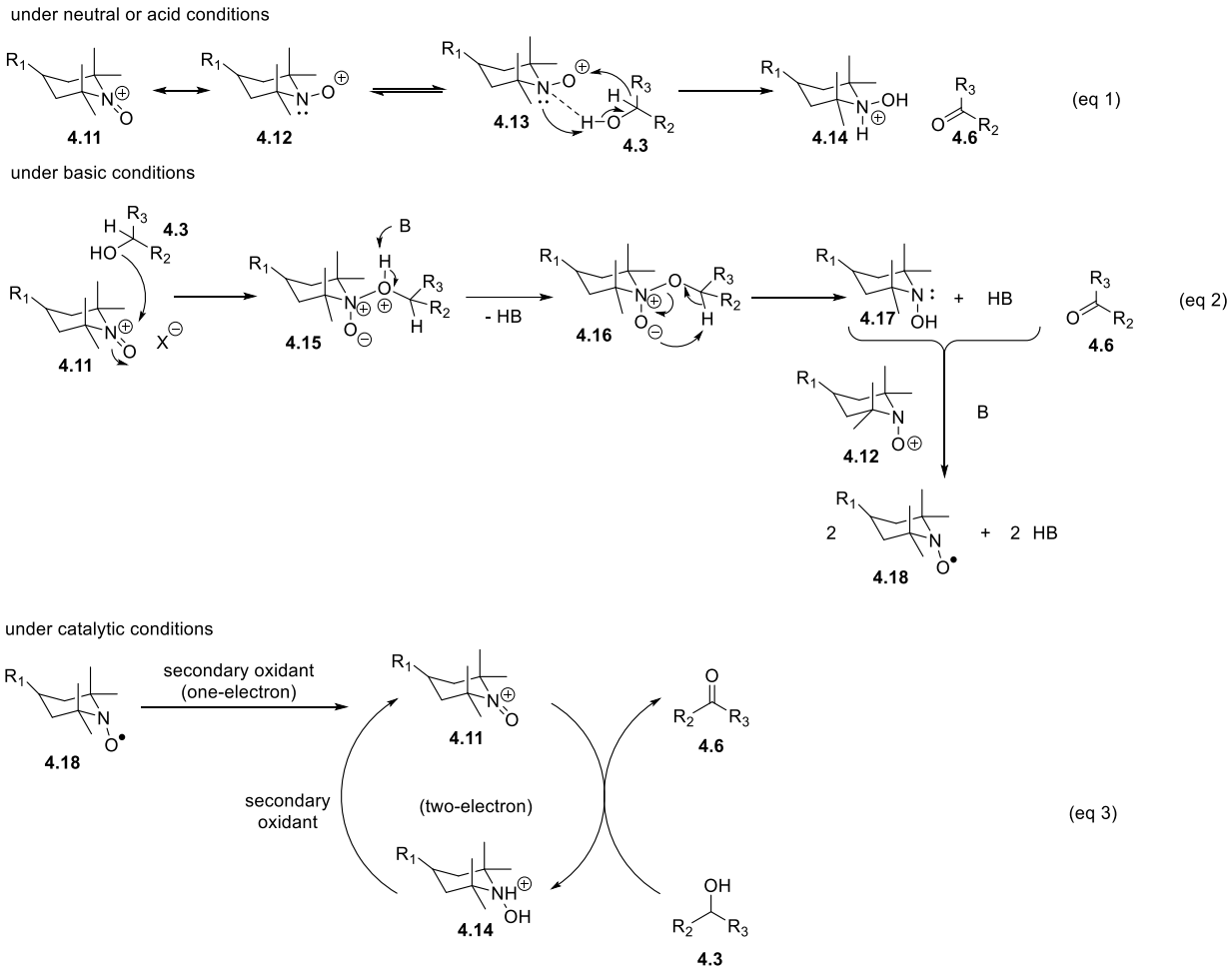
Scheme 4.2. Catalytic Oxidations with Oxoammonium Salts



The mechanism of the oxidations of primary and secondary alcohols with oxoammonium salts has been investigated.[8, 11] It was found that the reaction pathway and reaction rates change depending on the pH of the reaction medium. Under neutral or acidic conditions, the oxidation is thought to occur through a cyclic intermediate formed by a hydrogen bond between the nitrogen of the oxoammonium and the hydrogen of the alcohol (Scheme 4.3, eq 1). It was also found that the counter ions of the oxoammonium salt effect the reaction rates. For example, the chloride ion reacts faster than the perchlorate or tetrafluoroborate ions. However, the reaction rates using the perchlorate and tetrafluoroborate ions are increased when silica gel is used as a catalyst.[3] Additionally, this mechanism supports the lack of reactivity with alcohols that have β-oxygens (ethers or esters), since the β-oxygen could interfere with the initial hydrogen bonding to the alcohol. Under basic conditions, an alkoxide intermediate attacks the nitrogen of the oxoammonium salt. From there a hydride is abstracted generating the desired carbonyl and the hydroxylamine (Scheme 4.3, eq 2). However, since the base would neutralize the hydroxylamine, an excess of base and oxoammonium salt is needed. The hydroxylamine is then reoxidized by a terminal oxidant such as NaOCl. Typically, sodium bromide is added as a co-catalyst to form

hypobromite and reduce chlorination side products (Scheme 4.3, eq 3).[12, 13] It is possible to get the carboxylic acid under catalytic conditions in aqueous medium as well.[11]

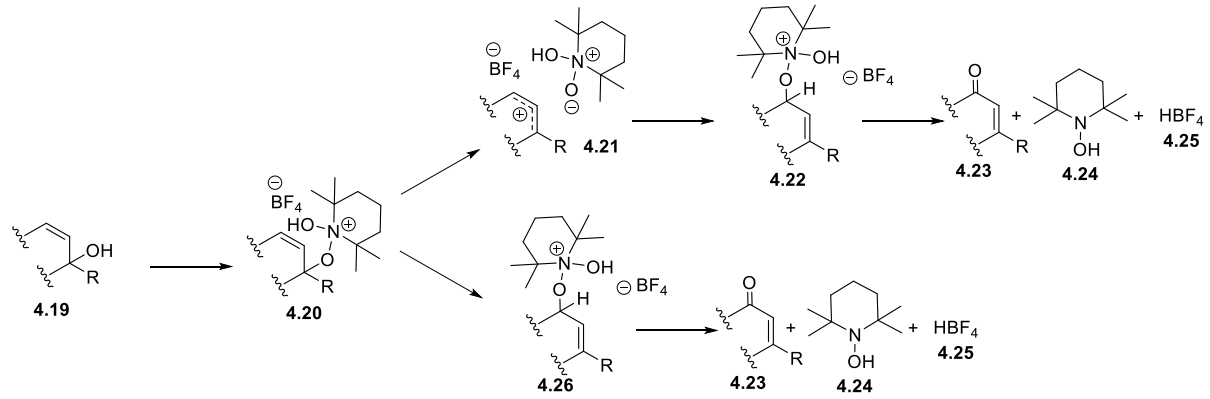
Scheme 4.3. Mechanisms of 1° and 2° Alcohol Oxidations With Oxoammonium Salts



Tertiary alcohols have also been reported to react with oxoammonium salts. For example, several groups have reported an oxidative rearrangement of tertiary allylic alcohols to β-substituted α-β-unsaturated ketones using oxoammonium salts.[14-16] This method is attractive because it accesses synthetically useful α-β-unsaturated ketones without the use of metal-based reagents. This rearrangement has also been reported utilizing hypervalent iodine reagents, such as IBX, either as a catalyst or co-catalyst to provide the α-β-unsaturated ketones.[14, 16] This oxoammonium mediated rearrangement occurs more rapidly when bulkier and poorly nucleophilic anions, such as BF_4^- or

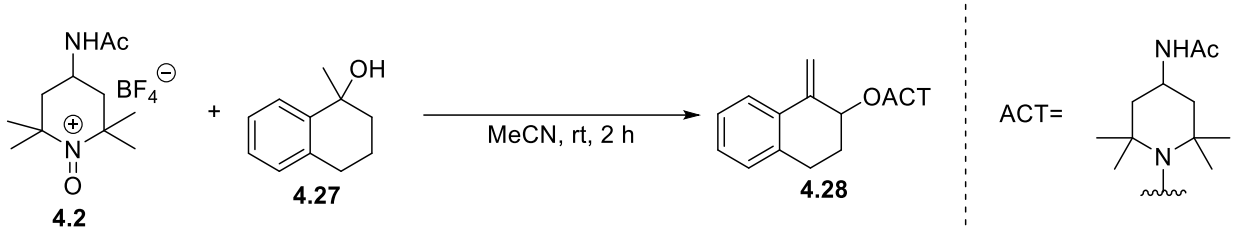
SbF_6^-, are used (95% yield in 3 minutes at room temperature).[15] When IBX is used as a co-catalyst it is thought to form IO_4^- as a counterion which enhances the reaction, consistent with previous findings. The mechanism for this rearrangement was investigated and a possible reaction mechanism proposed by Iwabuchi and co-workers is shown below (Scheme 4.4). The authors propose that the oxoammonium salt with a bulkier counterion would be more electrophilic,[16] allowing the nucleophilic attack on the nitrogen of the oxoammonium salt forming intermediate **4.20**. Once this intermediate is formed there are two possible pathways to give the product, either via an allylic cation (intermediate **4.21**) or a concerted intramolecular rearrangement that proceeds from **4.20** to intermediate **4.26**.

Scheme 4.4. Tertiary Alcohol Oxidation Mechanism



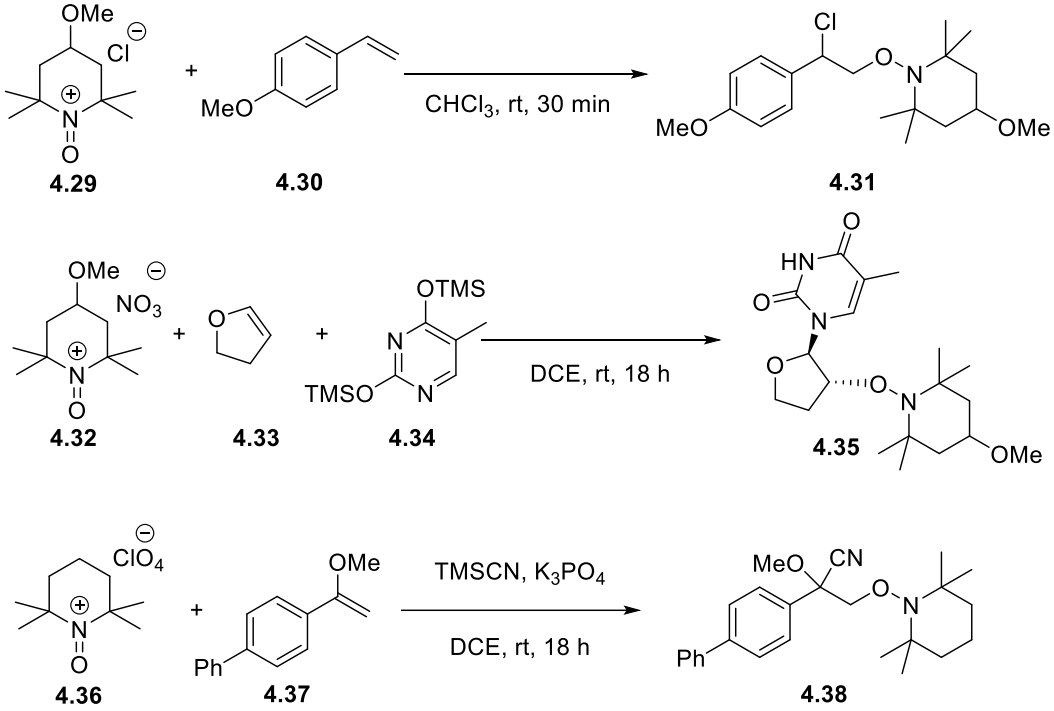
Recently we started to evaluate the reactivity of tertiary benzylic alcohols with oxoammonium salts (Scheme 4.5). It was found these substrates rapidly provided allylic ethers like **4.28** in a single step. This ether can later be cleaved under reductive conditions to provide the corresponding allylic alcohol. In earlier work, the rearrangement going from a tetralin to a protected allylic alcohol, such as **4.28**, usually involves multiple steps including a Wittig olefination, oxidation with selenium, and then protection of the alcohol.[17, 18] Since this new method with the oxoammonium salt was more efficient and atom economical, this transformation was further investigated.

Scheme 4.5. Tertiary Benzylic Alcohol Oxidations using An Oxoammonium Salt



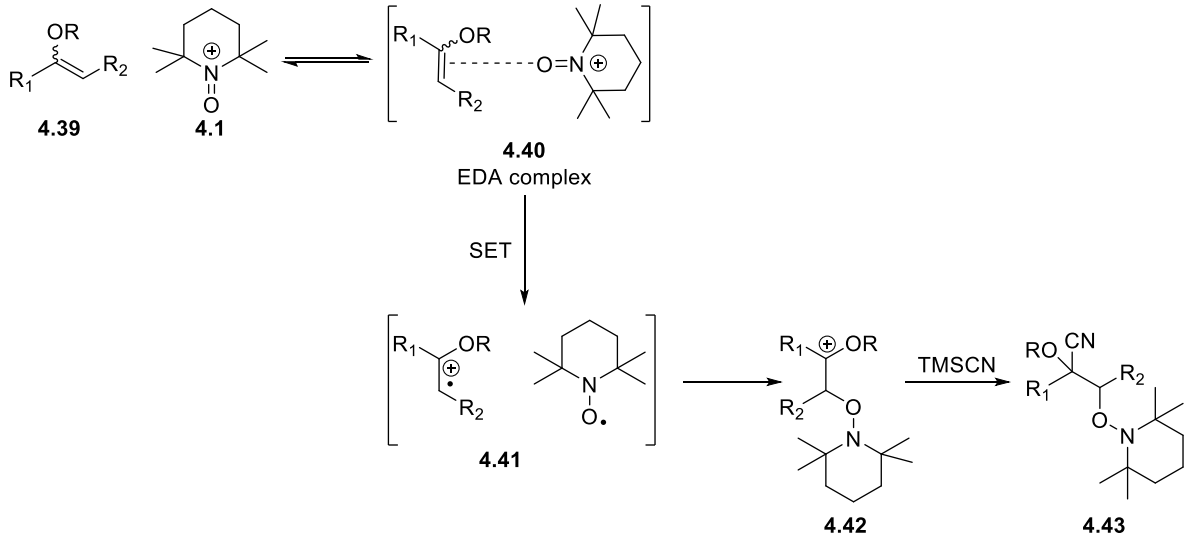
N-oxoammonium salts are also known to activate alkenes, providing a method for transforming the alkene to a more complex substrate. These reactions include allylic oxidation reagents[19], C-H activation,[20, 21] and the addition of nucleophiles to the alkene.[22] For example, a number of 1,2-difunctionalization reactions of alkenes mediated by oxoammonium salts are shown in Scheme 4.6. The first reported activation of alkenes for nucleophilic attack was by Endo and co-workers, who found that oxoammonium salt **4.29** gave chloro-oxidation product **4.31** when exposed to 4-methoxystyrene **4.30**.[23] Later the electrophilic addition of the nitrate salt **4.32** and silylated heterocycles (**4.34**) to enol ethers (**4.33**) was reported by Brower and co-workers.[24] It was noted that reactions with nitrate salt **4.35** had limited scope which included only enamides and enol ethers, styrenes were unreactive to these conditions. For example, reaction with 4-methoxystyrene **4.30** gave no addition products when using nitrogen nucleophiles.[24] Liu and co-workers recently used the perchlorate salt **4.36** and TMSCN in a carboetherification of enol ethers[25] and vinyl azides.[26]

Scheme 4.6. Recent *N*-Oxoammonium Salt Mediated Additions to Alkenes



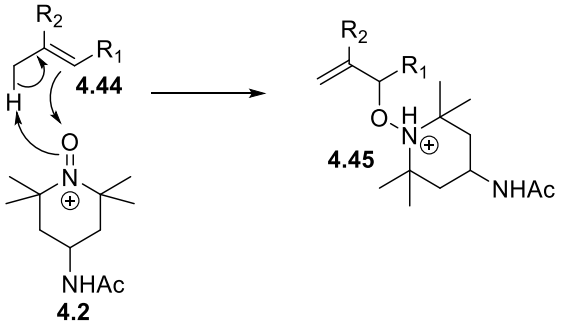
A proposed mechanism by Liu and co-workers is shown below in Scheme 4.7 for the oxycyanation of vinyl ethers. Initially, the oxoammonium salt and the alkene form an electron donor-acceptor (EDA) complex like **4.40**. After formation of EDA complex **4.40**, a single electron transfer pathway leads to radical cation **4.41**. Subsequently, a radical-radical recombination forms a C-O bond and cation **4.42**. A nucleophilic cyanation then provides desired product, alkoxynitrile **4.43**.

Scheme 4.7. Proposed Mechanism of Addition to Alkenes



The oxoammonium salt has also been shown to be a source of electrophilic oxygen. Given this reactivity, it is perhaps unsurprising that the salt reacts with an electron-rich alkene to give 1,2 addition products via a carbocation intermediate. The literature has also reported alternative reactivity of oxoammonium salts and alkenes, where the alkene reacts in an ene-like fashion with trisubstituted alkenes to provide allylic alkoxyamines, such as **4.45**. In this case the alkene attacks the electrophilic oxygen of the oxoammonium and π-bond of the oxoammonium abstracts the allylic proton, resulting in the transposition of the π-bond.

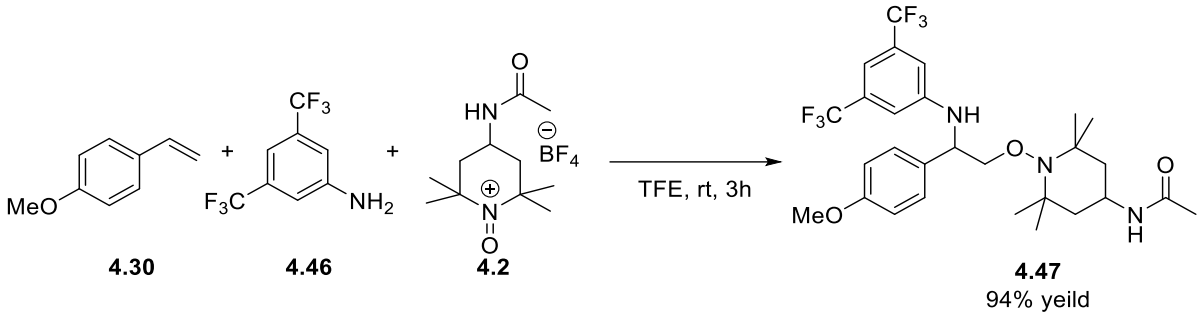
Scheme 4.8. Ene-like Addition to Trisubstituted Alkenes



Recently, our group has started exploring the reactivity of *N*-Oxoammonium salt **4.2** in additions to 4-methoxystyrene **4.30** with aniline **4.46** (Scheme 4.9). While similar products can be synthesized using copper catalysts,[27] these transformations typically require high temperatures and

long reaction times. The oxoammonium salt mediated reactions occur under mild conditions without the use of high heat or light, which minimizes the need for special equipment or complex protocols. Oxoammonium salt **4.2** (4-(acetylamino)-2,2,6,6-tetramethyl-1-oxo-piperidinium tetrafluoroborate)[28-30] was chosen as the oxoammonium salt of choice because this reagent is stable and can be synthesized on large scale from inexpensive starting materials.

Scheme 4.9. Alkene Amino-Oxidations Mediated by *N*-Oxoammonium Salts

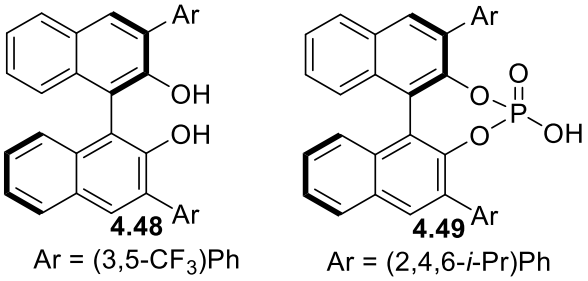


4.30 **4.46** **4.2** **4.47**
94% yeild

Additionally, we have started investigating an enantioselective variant of this alkene difuctionalization utilizing anionic phase transfer catalysts, such as **4.48** shown in Figure 4.1.[31, 32] Typically, phosphoric acid catalysts are utilized in asymmetric anionic phase transfer reactions, but the best catalysts are difficult to synthesize. This is due to the coupling reaction to install the bulky aromatic groups at the 3,3' positions of the BINOL, which tends to be low yielding due to sterics.[33] For this system, the BINOL was also evaluated as a phase transfer catalyst. In this scenario, the phenols will act as the phase transfer catalyst by becoming deprotonated and acting as the solubilizing counterion for the oxoammonium salt. By removing the phosphate group and interacting directly with the diol the ion pair should be seated deeper in the chiral pocket, therefore, we predict that smaller groups at the 3,3'-positions will result in similar enantioinduction. Normally, BINOL is not acidic enough to be deprotonated by a weak insoluble base like sodium carbonate (pKa of ~11 in DMSO), with unfunctionalized BINOL having a pKa of ~13 in DMSO. However, the addition of electron withdrawing phenyl groups at the 3,3'-positions significantly

lowers the pKa. For example, the 3,3'-bis(3,5-bis(trifluoromethyl)phenyl)BINOL **4.48** (Figure 4.1) recently was shown as having a pKa of 9.7 in DMSO.[34] To evaluate the possibility of using chiral anionic phase transfer catalysts to influence the stereochemical outcome of the alkene difunctionalization, preliminary experiments were done with the chiral phosphoric acid catalyst (*R*)-TRIP **4.49**. This catalyst has been previously shown to function well in asymmetric anionic phase transfer transformations with oxoammonium salts.[20, 32, 35-37]

Figure 4.1. Anionic Phase Transfer Catalysts



In addition to the work on the elimination/oxidation of benzylic alcohols, our group has also explored the reactivity of oxoammonium salt **4.2** in additions to electron-rich alkenes with electron-poor anilines (Scheme 4.9). An investigation of other nucleophiles with oxoammonium salt **4.2** has now been initiated using alcohols, water, and isatin, and this will be reported in the second part of the chapter.

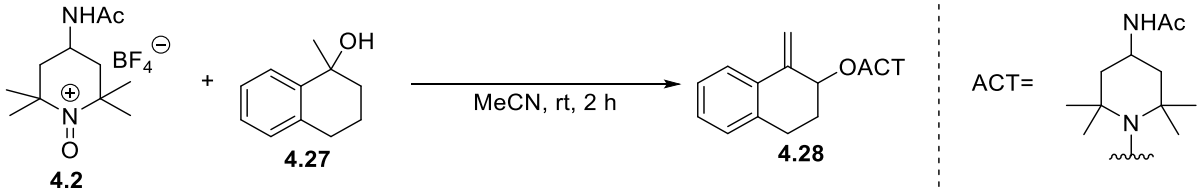
Results and Discussion

Part 1: Exploring a New Elimination-Oxidation of Tertiary Alcohols With Oxoammonium Salts

Initially the reaction of alcohol **4.27** and oxoammonium salt **4.2**[30, 38] was evaluated (Scheme 4.10). Combining one equivalent of the alcohol with the oxoammonium salt **4.2** in acetonitrile provided quick conversion to a new compound, alkene **4.28**. This structure was assigned based on

the ^{1}H, ^{13}C, and DEPT-135 NMR spectra, which showed the presence of three methylenes, and one of the methylenes was part of an alkene, as well as the incorporation of the 4-acetamido-2,2,6,6-tetramethylpiperidinyl (ACT) group into the structure. This transformation was notable as in other cases a similar rearrangement of functionality (going from tetralin to a protected allylic alcohol like **4.28**) requires multiple synthetic operations. These typically include a Wittig reaction on the ketone, oxidation with selenium (or another reagent), and then the protection of the allylic alcohol.[39, 40] Since this transformation occurred in a single step, making it highly atom economical,[41] the reaction was explored further.

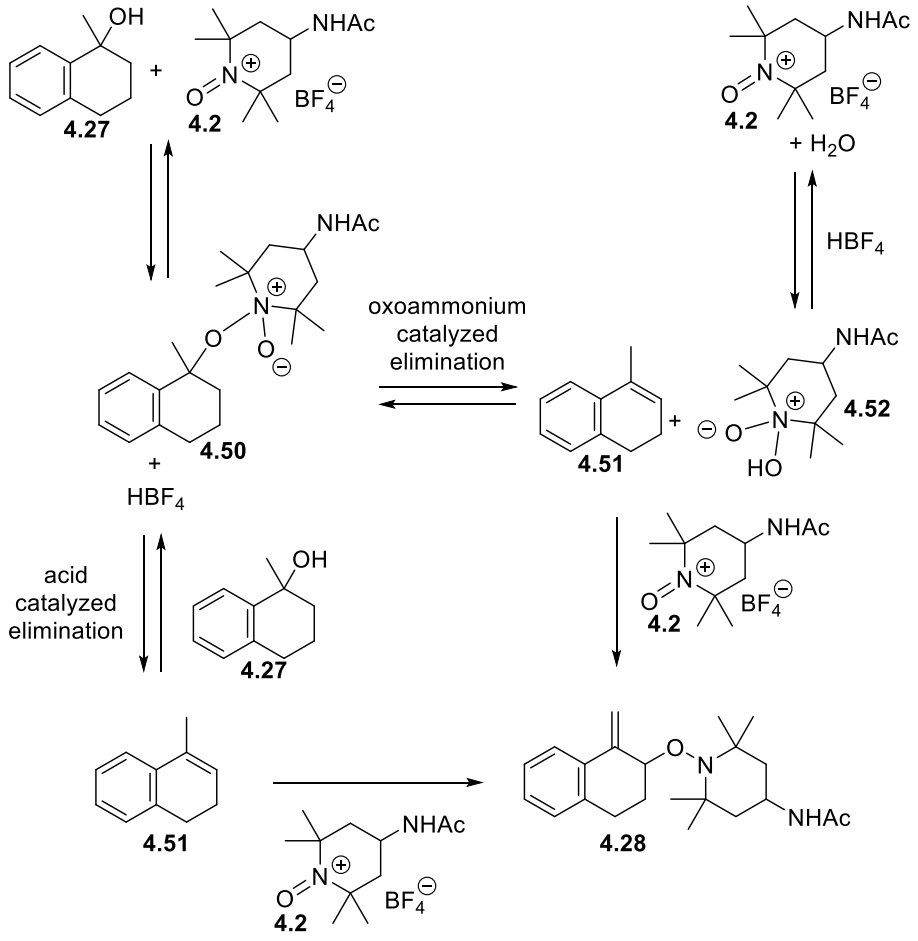
Scheme 4.10. Reaction of tertiary alcohol and oxoammonium salt



The formation of the allylic ether product **4.28** can be explained from the mechanistic rationale shown in Scheme 4.11. As the allylic oxidation of electron rich alkenes utilizing oxoammonium salts has been established, and was shown to proceed through an ene type process by Bailey and co-workers,[42] it was assumed that the trisubstituted alkene **4.51** was an intermediate in the reaction. To confirm that the alkene **4.51** was indeed an intermediate in this transformation, the alkene was synthesized via the known route[43] and subsequently subjected to oxoammonium salt **4.2** in acetonitrile. This gave the allylic ether product **4.28** in good yield of 67%. It is possible that the elimination reaction leading to alkene **4.51** may be an acid catalyzed by HBF_4 being formed from the addition of the tertiary alcohol to the oxoammonium salt, generating intermediate **4.50**. On the other hand, the oxoammonium salt is also known to react with primary and secondary alcohols to form *N*-oxides similar to **4.50**. These *N*-oxides then go on provide the corresponding aldehyde or ketone as the product. It is envisioned that the *N*-oxide intermediate **4.50** may form via reaction

with the tertiary alcohol, and direct elimination could occur removing the necessary hydrogen. A similar mechanistic step was proposed by Bobbitt in allylic oxidations of indole derivatives with oxoammonium salt **4.2**.[44] The hydrate of the oxoammonium salt (**4.52**) may regenerate the oxoammonium salt by dissociating water, the regenerated oxoammonium salt can proceed with the allylic oxidation. Intermediates similar to **4.50** have been proposed in TEMPO catalyzed allylic rearrangements of tertiary allylic alcohols to α,β-unsaturated ketones.[45] The final work up of the reaction is a wash with sodium bicarbonate, which would provide the final product **4.28** by deprotonating the ammonium salt.

Scheme 4.11. Proposed Mechanisms for the Elimination-Oxidation Reaction



The tandem elimination/oxidation process was optimized, and the mechanism of the reaction interrogated by changing the reaction conditions. Initial attempts focused on optimizing the yield

of the reaction. First, a solvent screen was completed (Table 4.1). Several polar solvents were examined, and acetonitrile gave the best yield. The effects of temperature were also explored. However, cooling the reaction mixture gave a similar yield, while heating the reaction mixture was unfavorable, leading to the formation of unidentifiable side products. Then the amount of oxoammonium salt was evaluated, with 1.2 equivalents seeming to give a slightly better yield. However, the use of a larger excess of the oxoammonium **4.2** provided lower yields, apparently from decomposition of the product. When desiccants were added to the reaction mixture there was a significant increase in yield. The desiccants were added to the mixture to remove the water produced from the elimination. Silica gel, sodium sulfate, and magnesium sulfate all gave considerable improvements to yield (Table 4.1, entries 13-15). The best yield was achieved with activated powdered 4 Å molecular sieves, that provided an 80% isolated yield of the allylic ether product **4.28**. Water may be damaging to the transformation since it may lead to forming of the hydrate **4.52**. This hydrate **4.52** cannot undergo the ene-type mechanism necessary to give the allylic ether product.

Table 4.1. Reaction Optimization

Entry	equiv 1	Solvent	Additive[a]	Temp	Time (h)	Yield
1	1	MeCN		rt	2	61
2	1	HFIP		rt	2	39
3	1	DMF		rt	2	trace
4	1	DCM		rt	2	30
5	1	MeCN		0 °C	2	60
6	1	MeCN		82 °C	2	43
7	1	MeCN		rt	4	61
8	1	MeCN		rt	6	63
9	1	MeCN		rt	8	52
10	1.2	MeCN		rt	6	64
11	1.5	MeCN		rt	6	60
12	2	MeCN		rt	6	54
13	1.2	MeCN	silica gel	rt	6	65
14	1.2	MeCN	Na_2SO_4	rt	6	70
15	1.2	MeCN	$MgSO_4$	rt	6	72
16	***1.2***	***MeCN***	***4 Å mol sieves***	***rt***	***6***	***80***
17	1.2	MeCN	TEA	rt	6	4
18	1.2	MeCN	DIPA	rt	6	60
19	1.2	MeCN	K_2CO_3	rt	6	41
20	1.2	MeCN	TsOH	rt	6	60
21	1.2	MeCN	TfOH	rt	6	22

[a]1.2 Equiv of the additive was added, for silica gel and 4 Å mol sieves the same weight as salt **1** was added.

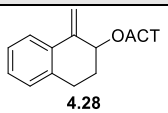
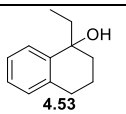
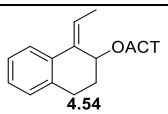
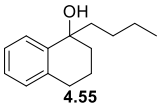
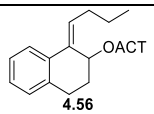
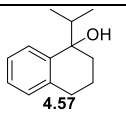
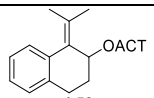
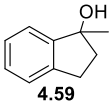
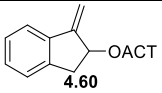
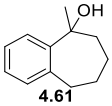
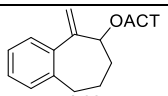
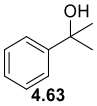
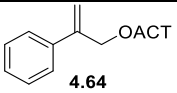
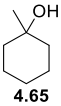
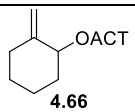
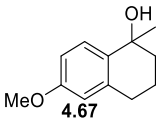
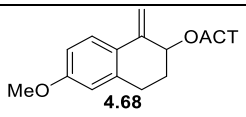
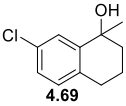
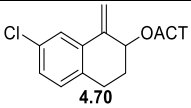
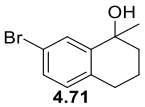
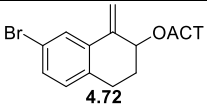
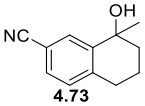
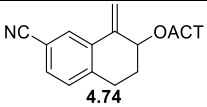
In order to gain understanding into the mechanism of the transformation, other additives were evaluated. The addition of triethylamine significantly lowered the yield of allylic ether **4.28**, which initially could indicate HBF_4 as catalyst for the elimination. However, it has been previously observed that unhindered tertiary amines, like triethylamine, form electron donor-acceptor (EDA) complexes with oxoammonium salts.[46] These complexes have been shown to severely reduce the reactivity of the oxoammonium salts in other transformations.[47] However, the use of a more hindered amine, such as diisopropylamine (Table 4.1, entry 18), did not have the same effect in the reaction. Instead, this gave an almost identical yield of 60% (compare entries 8 and 18 in Table

4.1). The more hindered amine may form a less stable EDA complex, retaining the reactivity of the oxoammonium salt, and therefore allows the oxidative transposition to still take place. The addition of solid K_2CO_3 to the reaction gave 41% yield. This may be from the formation of KBF_4 and the carbonate salt of the oxoammonium salt, which may be a less reactive oxidant (the counterion has been shown to significantly affect the reactivity of the oxoammonium salt[48]). Some protic acids were also evaluated as additives since, if the elimination is acid catalyzed, these may improve the yield of the reaction. However, no change was observed when *p*-toluenesulfonic acid was added (Table 4.1, entry 20), and the addition of trifluoromethanesulfonic acid actually gave a lower yield (Table 4.1, entry 21), possibly due to decomposition caused by the strong acid. These results indicate that the oxoammonium salt is the reagent responsible for the elimination, since significant amounts of product are still isolated even in the presence of hindered amine base.

A number of tertiary alcohols were evaluated in the transformation (Table 4.2) to determine the scope of this tandem reaction. It was found that increasing the length of the carbon chain off the tertiary alcohol still led to good yields (Table 4.2, entries 2 and 3). However, branched alkyl groups were not tolerated in the reaction, with alcohol **4.57** provided a complex mixture of products. This was attributed to steric effects preventing the oxoammonium cation from interacting with the tertiary alcohol. Changing the size of the aliphatic ring (Table 4.2, entries 5 and 6) also provided good yields. However, it was discovered that the tertiary alcohol did have to be benzylic and part of an alkane ring, since mostly starting alcohol was isolated for alcohols **4.63** and **4.65**. The lack of reactivity seemed to be caused by slow elimination for these substrates, as demonstrated by a control experiment with α-methylstyrene and oxoammonium salt **4.2** was performed and provided the allylic ether **4.64** in 45% yield. Substitution on the benzene ring was also explored (Table 4.2, entries 9-12). Adding an electron donating group onto the aromatic ring

(Table 4.2, entry 9) only yielded trace amounts of product in the crude ^{1}H NMR. This may be from polymerization due to carbocation formation. However, electron withdrawing groups were much better tolerated and the allylic ether products **4.70**, **4.72**, and **4.74** were isolated in moderate yields (Table 2, entries 10-12). Additionally, increasing the scale of the reaction to 6 mmols gave a similar 60% yield of allylic ether **4.28**.

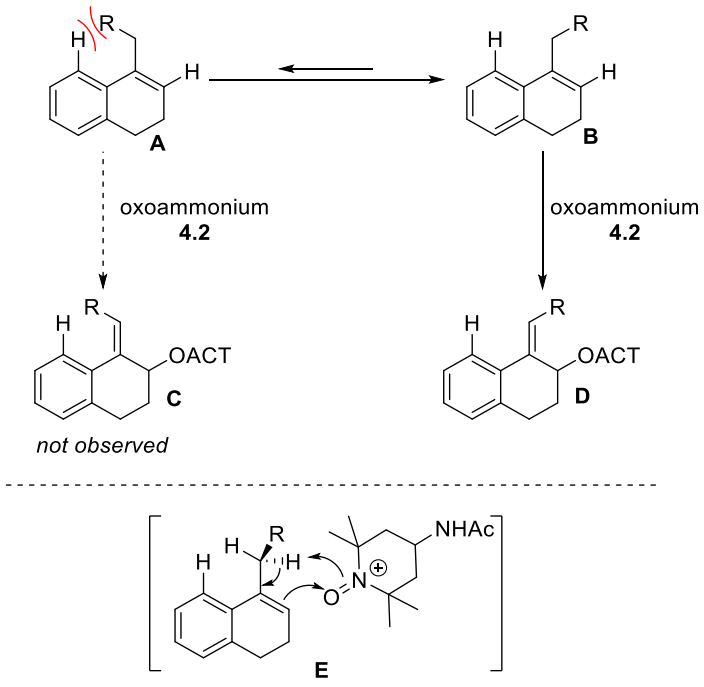
Table 4.2. Scope of the Tandem Elimination-Oxidation Reaction

Entry	Alcohol	Product	Yield
1	 4.27	 4.28	80 (60[a])
2	 4.53	 4.54	59
3	 4.55	 4.56	65
4	 4.57	 4.58	0[b]
5	 4.59	 4.60	51
6	 4.61	 4.62	67
7	 4.63	 4.64	0[c]
8	 4.65	 4.66	0[d]
9	 4.67	 4.68	trace[e]
10	 4.69	 4.70	41
11	 4.71	 4.72	36
12	 4.73	 4.74	43

[a]Reaction performed on a 6 mmol (2.20 g scale). [b]A complex mixture resulted.
[c]Starting material (89%) was recovered. [d]Starting material (60%) was recovered.
[e]trace amount of product detected via ^{1}H NMR.

A single alkene isomer was isolated from alcohols **4.53** and **4.55**. To determine which isomer, a NOESY experiment on allylic ether **4.54** was performed. This determined that the *Z* isomer was isolated exclusively, since a strong energy transfer was observed between the vinyl proton and one of the protons on the aromatic ring. The stereochemistry of allylic ether **4.56** was assigned by the same analogy. This selectivity can be rationalized by a conformational preference of the alkyl chain to rest on the same side as the methylene (conformation **B**, Scheme 4.12) to avoid steric interactions with the benzene hydrogen. Since the allylic oxidation is known to occur through an ene-like transition state (**E** in Scheme 4.12), then this preference leads to the formation of the *Z* alkene.

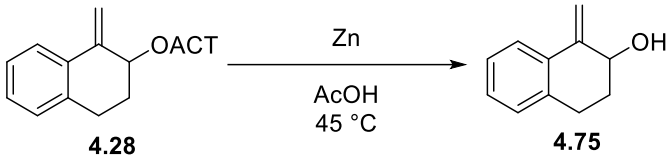
Scheme 4.12. Rational of Stereoselectivity of alkyl side chain



Removing the OACT group was also explored. Cleavage of this group was readily accomplished with activated zinc metal[49] in acetic acid (Scheme 4.13) to provide the allylic alcohol product **4.75**. The NMR spectra of alcohol **4.75** matched the reported values from the literature.[50]

Therefore, the ACT group can be considered to have similar reactivity as a TEMPO ether, which can be cleaved to the alcohol[49, 51] under similar conditions, in this system.

Scheme 4.13. Cleavage of ACT Ether



4.28 **4.75** 49%

In summary, an elimination-oxidation process with an oxoammonium salt has been explored. Available evidence indicates that the reaction occurs in two discrete steps: an elimination that occurs via the oxoammonium salt followed by an allylic oxidation. The scope of the reaction includes a number of tertiary alcohols. Alternative pathways to similar products require multistep procedures to perform the same modification of functionality.

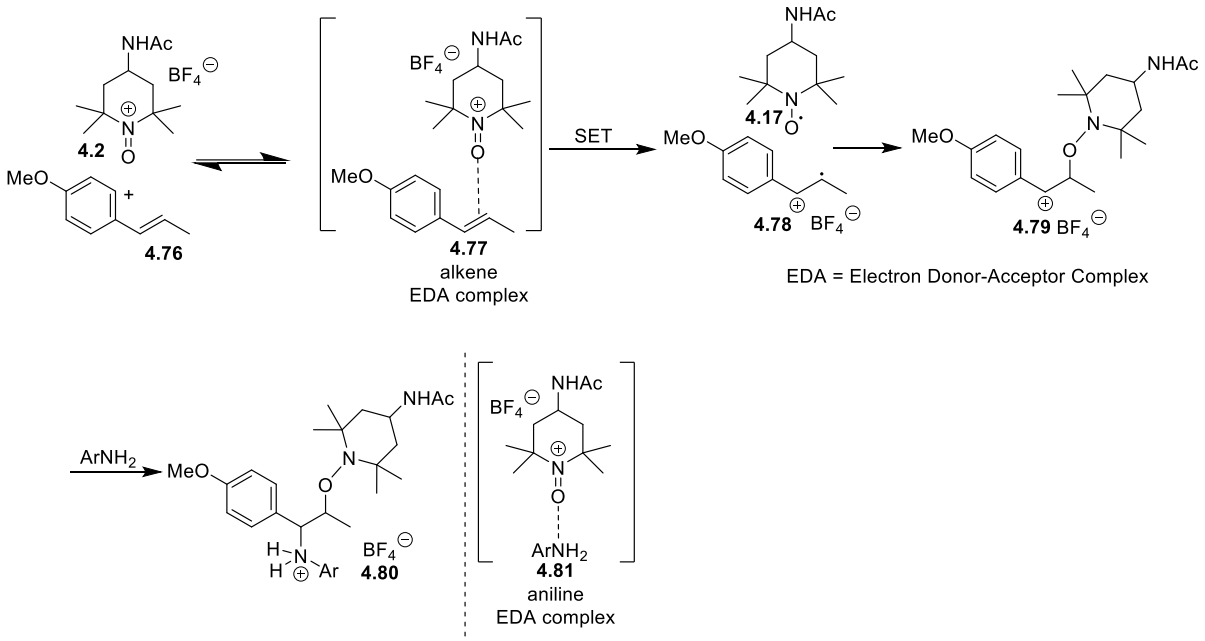
Results and Discussion

Part 2: New 1,2-Difunctionalizations of Alkenes with Oxoammonium Salts

Oxoammonium salt **4.2** was also used to investigate a single step amino-oxidation of electron rich alkenes. Initially, electron poor anilines were used as the nitrogen source, since these systems have been shown to behave like alcohols when alkylated with trichloroactimidates.[52] Additionally, some electron poor anilines (such as 2,4-dinitroanilines) can be converted to the corresponding amines by treatment with hydroxide to reveal the corresponding amine.[53, 54] This reaction was optimized by another member of the Chisholm group using 3,5-bis-trifluoromethylaniline **4.46**, 4-methoxystyrene **4.30**, and oxoammonium salt **4.2** as reactants for this metal free amino-oxidation. Yields as high as 98% could be obtained when 2,2,2-trifluoroethanol was used as the solvent. Oxidation reactions with oxoammonium salts like **4.2** are often facilitated by the addition of an amine base,[55, 56] so the addition of exogenous base was evaluated. However, the addition of strong

amine bases like DBU and TMG provided no product. The inhibition of the reaction with added DBU was attributed to the formation of an EDA complex between the amine and the *N*-oxoammonium salt (complex **4.81**, Scheme 4.14). This amine EDA complex is hypothesized to compete with the alkene, slowing formation of an EDA complex with the alkene (complex **4.77**, Scheme 4.14), which is required for the reaction to proceed as described in the proposed reaction mechanism (Scheme 4.14).

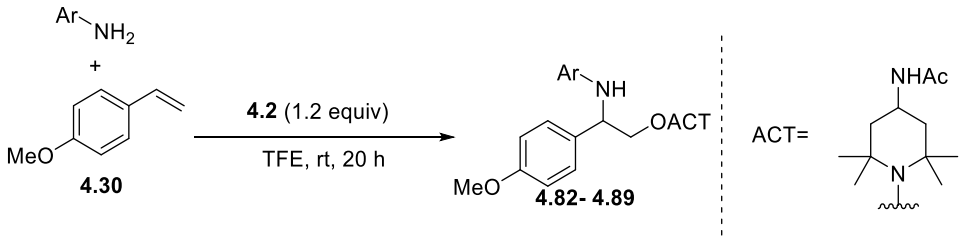
Scheme 4.14. Proposed Mechanism of the Alkene Difunctionalizations



A number of styrenes and anilines were evaluated in this reaction (Table 4.3 and Table 4.4). First the generality of the reaction with respect to the nitrogen nucleophile was investigated (Table 4.3). More electron poor anilines provided higher yields. This trend can be explained by the complexation of the more basic anilines to the *N*-oxoammonium salt, which competes with binding of the alkene, leading to reduced yields. This is consistent with the observation that the addition of DBU or TMG inhibited the amino-oxidation. The aniline *N*-oxoammonium salt EDA complex appears to be very sensitive to substituents on the aniline. Anilines with similar basicity

often perform quite differently in these transformations. For example, 2-iodoaniline (Table 4.3 entry 5) provided a 63% yield, while aniline (Table 4.3, entry 9) provided no discernable addition product. Additionally, the use of alkyl groups on the aniline nitrogen were explored using *N*-methyl-2-nitroaniline (Table 4.3, entry 8). While an addition product was formed from N-methyl-2-nitroaniline, the *N*-methyl group was lost during the transformation, and the addition product **4.88** was instead isolated, indicating an oxidative demethylation of the *N*-methyl addition product. Oxidative demethylation of nitroanilines has been reported with *m*-CPBA,[57] $KMnO_4$[58] and CrO_3[59] previously, evidently the oxoammonium salt also can also effect this transformation.

Table 4.3. Scope of the Amine in the Oxoammonium Salt Amino-oxidation

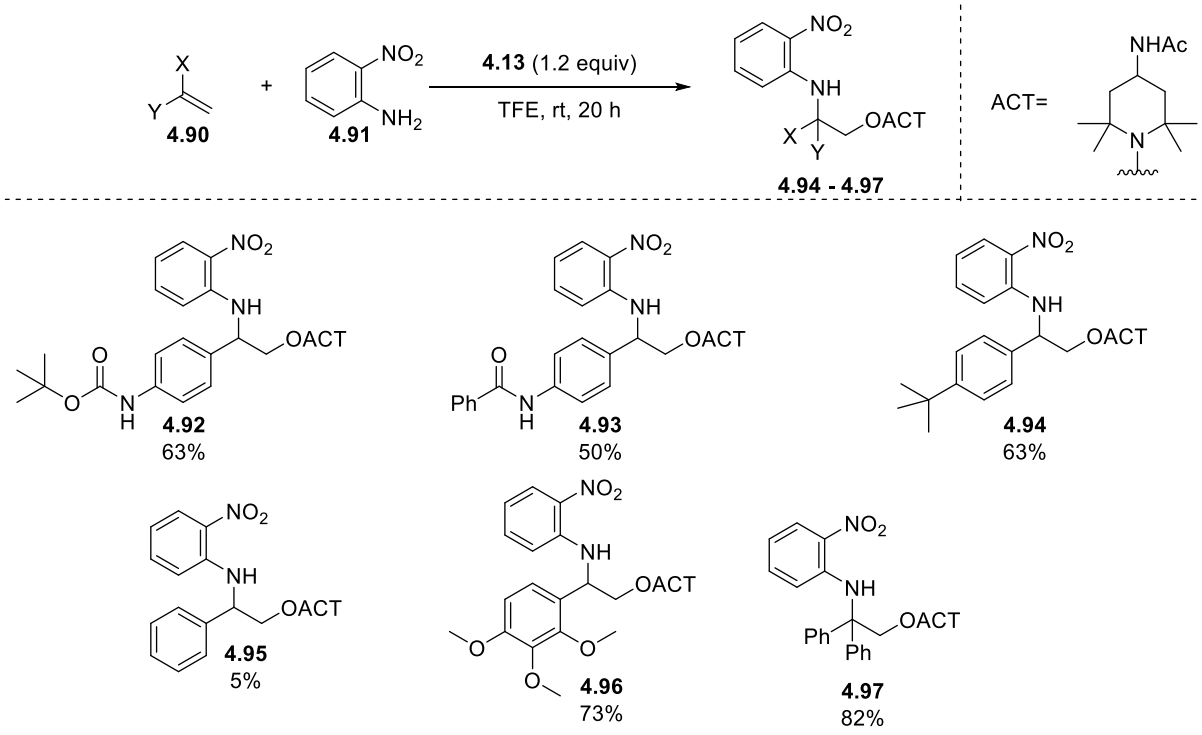


Entry	Amine	Product Yield (%)
1	3,5-bis(trifluoromethyl)aniline	94 (**4.82**)
2	2-chloro-5-trifluoromethylaniline	98 (4.83)
3	2,6-dichloroaniline	69 (**4.84**)
4[a]	2-bromoaniline	61 (4.85)
5[a]	2-iodoaniline	55 (4.86)
6	methyl 3-amino-4-chlorobenzoate	83 (**4.87**)
7	2-nitroaniline	93 (4.88)
8	*N*-methyl-2-nitroaniline	54 (**4.88**[b])
9	aniline	0 (4.89)

[a] reaction was performed for 2h [b] yield is for the addition product without the *N*-methyl group

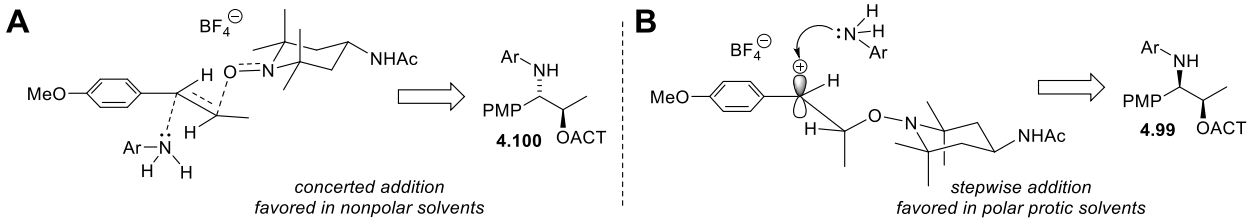
Next a number of styrenes were evaluated in the amino-oxidation reaction using 2-nitroaniline as the amine (Table 4.4). Generally, electron rich styrenes were required for good yields in the reaction. Protected 4-aminostyrenes participated in the addition in good yields (**4.92** and **4.93**, Table 4.4). 4-*tert*-Butyl styrene gave a 63% yield of the addition product **4.94**. However, only trace amounts of the addition product were obtained from styrene itself. This could be due to competing polymerization. The addition of multiple electron donating groups on the styrene was explored, with adduct **4.96** providing good yield (73%) in the amino-oxidation. 1,1-Disubstituted alkenes were also successfully utilized, with 1,1-diphenylethyene providing an 82% yield of the amino-oxidation product **4.97**. However, simple alkyl substituted alkenes, such as 1-octene did not participate in the addition reaction and returned only unreacted starting material. Therefore, it appears that extended conjugation is necessary for the addition to occur.

Table 4.4. Scope of the Styrene in the Oxoammonium Salt Amino-oxidation



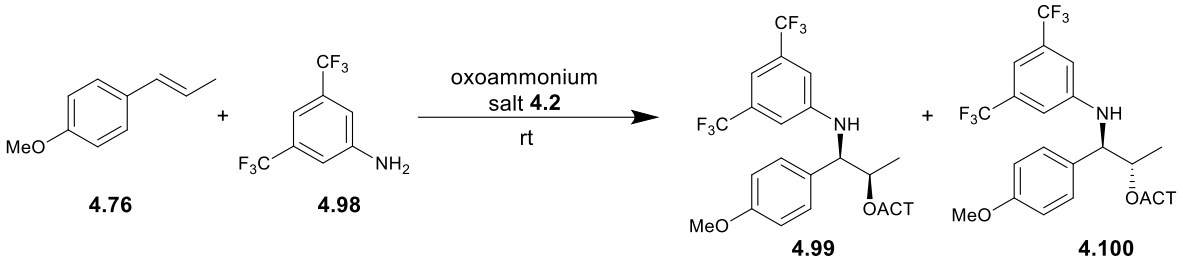
The mechanistic hypothesis for this amino-oxidation was further explored using *trans*-anethole **4.76**. This should provide predominantly the syn product from the stepwise addition as shown in Scheme 4.15B, while the anti-product should be preferred from the concerted transition state shown in Scheme 4.15A. The anti-product is favored in nonpolar solvents, while the syn product is favored in polar protic solvents which is consistent with these transition states (see below). Kinetic studies may also be rewarding in this system. In the cationic mechanism the rate determining step should be cation formation, so the concentration of the aniline should not influence the reaction rate. Alternatively, in a concerted addition, the aniline concentration should significantly influence the reaction rate. Getting insight to the mechanism will help continue to improve the selectivity of the alkene difunctionalizations. The role of temperature is also being explored, as greater selectivity may be accessible by lowering the reaction temperature.

Scheme 4.15. Solvent Effects in the Alkene Difunctionalizations



Using *trans*-anethole **4.76** the diastereoselectivity was evaluated (Table 4.5). Both the syn and the anti-addition products could be accessed with significant selectivity. A trend in dielectric constant (ε) of the solvent was found, with polar protic solvents (HFIP) favoring the formation of the syn diastereomer **4.99** while the less polar THF favored the formation of the anti-product **4.100**.

Table 4.5. Diastereoselectivity in the Oxoammonium Salt Mediated Amino-Oxidation



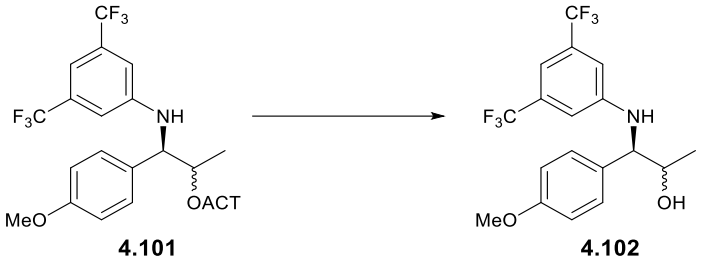
4.76 **4.98** **4.99** **4.100**

Entry	Solvent	ε	Yield (%)	Ratio (99:100)[a]
1	HFIP	17.8	76	74:26
2	DCM	8.9	60	60:40
3	TFE	8.5	80	48:52
4	THF	7.5	52	21:79

[a]determined by ^{1}H NMR in CD_3CN

The removal of the OACT group in these systems has proven to be difficult. Several conditions have been evaluated (Table 4.6). While the removal of similar unfunctionalized TEMPO ethers has been reported to be removed with zinc and acetic acid[60-62], these conditions did not perform well on these substrates (Table 4.6, entries 1-4). Under those conditions, impurities were formed that were difficult to separate from the amino-alcohol **4.102**. A number of ways reported to cleave N-O bonds or to reduce a nitro group were evaluated to remove the OACT group.[63-68] When utilizing anhydrous nickel chloride and lithium aluminum hydride at – 78 °C to room temperature, the OACT group was removed and product was purified by column chromatography with an 43% yield (Table 4.6, entry 12).

Table 4.6. Conditions Used to Cleave the N-O Bond



4.101 **4.102**

Entry	Reagent(s)	Solvent	Temp (° C)	Time (h)	Yield (%)
1	Zn, AcOH	H_2O	60	16	48[a]
2	Zn, AcOH	H_2O/THF	67	4	50[a]
3	Zn, AcOH	H_2O/THF	67	72	60[a]
4	Zn, TMSCl, AcOH	H_2O/THF	34-60	6	>100[a]
5	$RuCl_3$*$3H_2O$, Zn	EtOH	100	16	0
6	$Mo(CO)_6$, $NaBH_4$	MeCN/H_2O	90	16	0
7	$Mo(CO)_6$, Et_3N	MeCN/H_2O	80	16	0
8	$Mo(CO)_6$	EtOH	reflux	16	0
9	SmI_2	THF/MeOH	0	7	0
10	$NiCl_2$*H_2O/$NaBH_4$	MeOH	reflux	16	0
11	$CoCl_2$ /$NaBH_4$	MeOH	reflux	16	0
12	***$NiCl_2$/$LiAlH_4$***	***THF***	***-78 to 0***	***16***	***43***
13	Na(Hg), Na_2HPO_4	EtOH/THF	0 to rt	16	0
14	Pd/C, CSA, H_2	EtOAc/MeOH	60	16	0
15	AIBN, $(Bu)_3SnH$	toluene	reflux	24	0

[a] impurities present

The stereochemistry of the addition was verified by an x-ray diffraction experiment on a cyclized piperidine derivative **4.108** once the OACT group was removed. Since the diastereomers **4.103** and **4.104** could not be separated, a modified system was explored (Scheme 4.10). The alcohols **4.106** and **4.107** were difficult to separate as well, so they were cyclized to the corresponding oxazolidinone **4.108** using CDI. The major diastereomer cyclized more quickly and was separated (the remaining starting material was still a mixture of diastereomers). This diastereomer was characterized as the trans-derivative **4.108** via x-ray crystallography, shown in Figure 4.2, providing explicit assignment of the stereochemistry of the major stereoisomer of the amino-oxidation. While the OACT group could be removed under oxidative conditions to directly

provide ketone **4.105** with *m*-CPBA,[60] this made proof of the major diastereomer impossible (Scheme 4.16).

Scheme 4.16. Functionalization of OACT Group and Proof of Stereochemistry

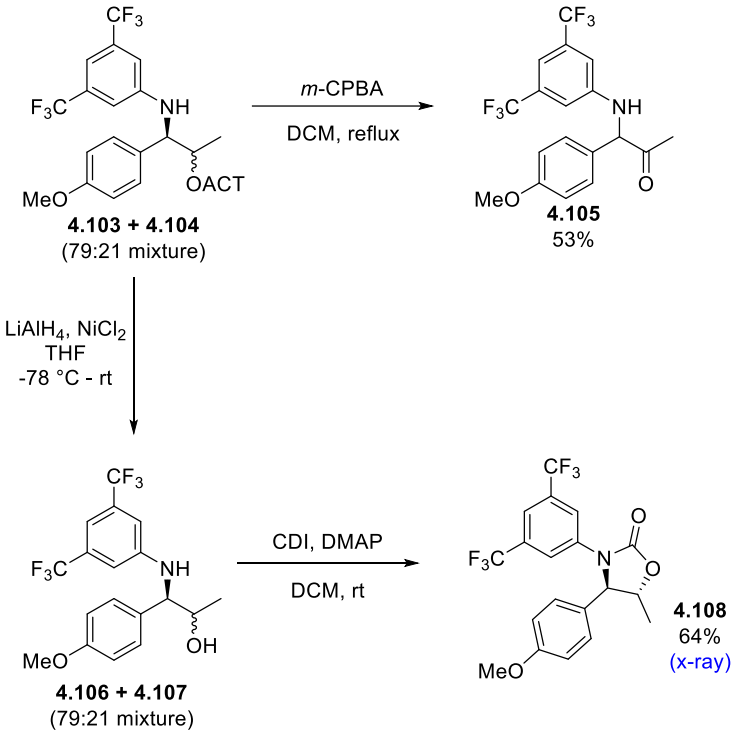
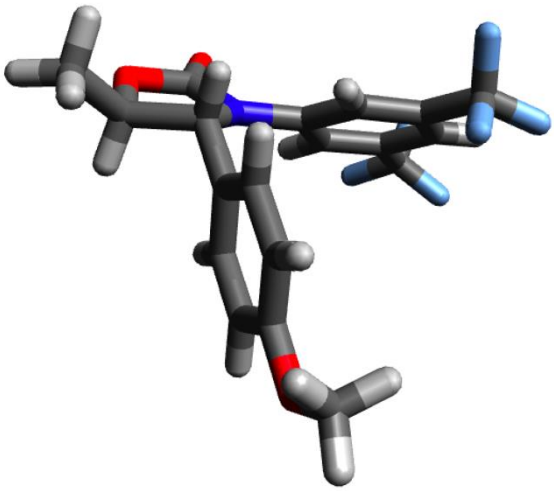
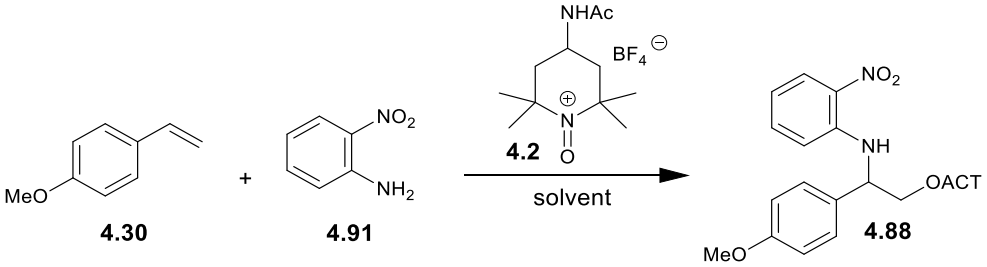


Figure 4.2. X-ray Structure of Oxazolidinone **4.108**



Another pressing question was if this reaction could be performed in an enantioselective manner. To investigate this possibility, the use of chiral anionic phase transfer catalysts was evaluated. An initial solvent screen was performed to ascertain if the reaction could occur in other solvents, including non-polar solvents, as the ion pairing interactions necessary for high enantioinduction with chiral anionic phase transfer catalysts perform best in nonpolar solvents. As shown below in Table 4.7, the most polar solvent provided the best yield (Table 4.7, entry 1). More nonpolar solvents, such as hexanes, gave a much lower yield. Increasing the time of the reaction did increase the yield for the more nonpolar solvents (Table 4.7, entry 4).

Table 4.7. Solvent Screening for Amino-Oxidation Mediated by Oxoammonium Salt

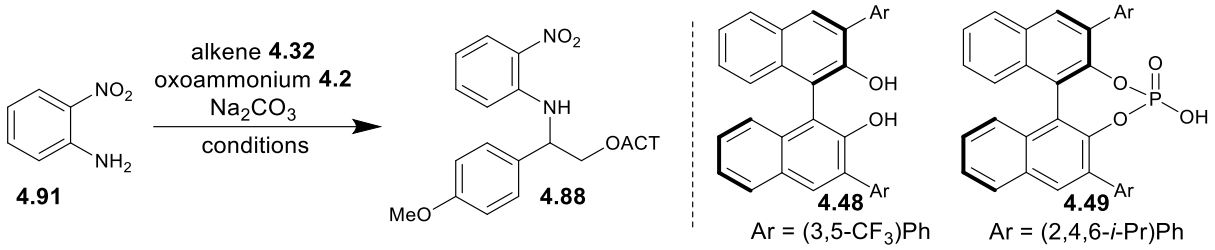


Entry	Solvent	Temp. (° C)	Time (h)	Yield (%)
1	DCM	rt	5	62
2	THF	rt	5	9
3	toluene	rt	5	7
4	toluene	rt	16	23
5	hexanes	rt	16	0
6	α,α,α-trifluorotoluene	rt	20	26
7	fluorobenzene	rt	20	10

Some preliminary experiments were undertaken with the chiral phosphoric acid catalyst (*R*)-TRIP **4.49**. This catalyst has been previously shown to function well in asymmetric anionic phase transfer transformations with oxoammonium salts.[32, 35-37] Since previous work indicated the insoluble base Na_2CO_3 appeared compatible with the reaction conditions, an alkene difunctionalization with aniline **4.91** in DCM with Na_2CO_3 and catalyst **4.49** was evaluated (Table 4.8). This provided a 33% yield of product which showed 32% ee. Changing the solvent to the less

polar toluene improved the ee significantly to 54%, which supports the anionic phase transfer pathway (the less polar solvent should lead to a more highly associated ion pair, giving increased enantioselectivity, shown in Scheme 4.17). The diol (*R*)-**4.48** was also evaluated as a catalyst, with significant enantioselectivity being achieved. The lower yields are due to the limited solubility of the 2-nitroaniline in nonpolar solvents, other anilines that are more soluble are now being evaluated in these asymmetric alkene difunctionalizations to improve yields.

Table 4.8. Initial Results with Chiral Anionic Phase Transfer Catalyst

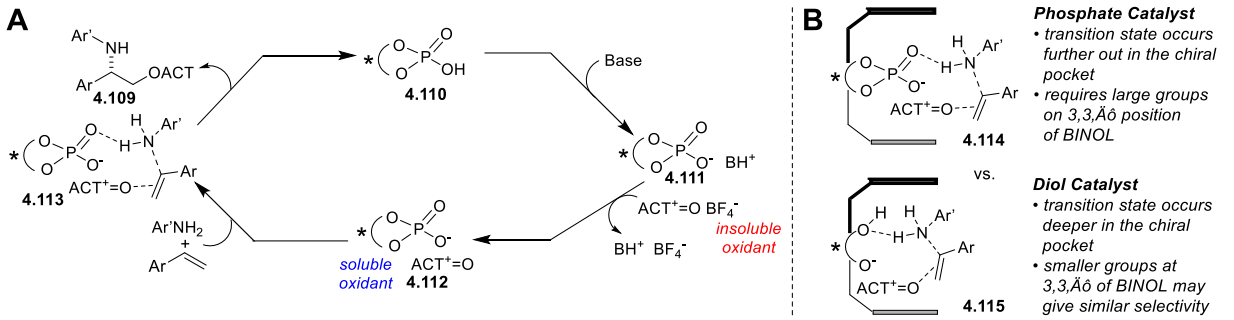


Entry	Solvent	Catalyst	Temp (° C)	Time (h)	Yield (%)	ee (%)
1	DCM	10 mol% (*R*)-**49**	rt	18	33	32
2	toluene	10 mol% (*R*)-**49**	rt	20	10	54
3	toluene	6 mol% (*R*)-**48**	rt	20	21	20
4	DCM	10 mol% (*R*)-**48**	rt	20	23	10
5	DCM/toluene (1:9)	10 mol% (*R*)-**48**	rt	20	20	20

A proposed mechanism is shown below in Scheme 4.17. In this reaction the oxoammonium salt **4.2** was used in a nonpolar solvent where it was sparingly soluble, such as toluene and DCM.[69] The chiral protic acid (either a phosphate **4.49** or a diol **4.48**) was added and subsequently deprotonated by Na_2CO_3, forming anion **4.111**. Since anion **4.111** would be hydrophobic, it would be soluble in the nonpolar reaction medium. Ion pair **4.111** can then undergo salt metathesis with the oxoammonium salt **4.2**, forming the soluble version of the oxoammonium salt (**4.112**). Then, the alkene addition can occur, but since the anion of the ion pair **4.112** is chiral, and is in close

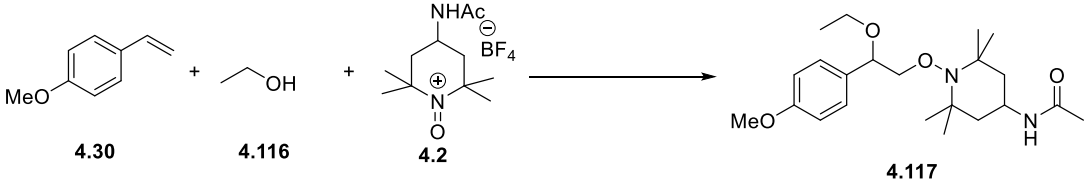
proximity to the oxoammonium salt, the alkene difunctionalization would occur in a chiral environment to provide enantioenriched product.

Scheme 4.17. Enantioselective Alkene Difuctionalization with Anionic Phase Transfer Catalysts



Oxoammonium salt **4.2** was also used to investigate the *N*-oxoammonium salt mediated addition of primary alcohols to alkenes. Initially it was thought that primary alcohols would be poor substrates, since oxoammonium salt **4.2** is known to oxidize alcohols to aldehydes.[2, 70] However, the relative rates of oxidation of electron poor primary aliphatic alcohols are significantly slower than other alcohols.[69] An initial set of experiments using ethanol **4.116**, oxoammonium salt **4.2**, 4-methoxystrene **4.30**, and varying amounts of base was performed (Table 4.9). All of these reactions were allowed to proceed for 18 hours.

Table 4.9. Additions to 4-Methoxystrene using Ethanol and Oxoammonium Salt **4.2**



4.30 **4.116** **4.2** **4.117**

Entry[a]	Alcohol 4.116 equiv	Base	Solvent	Temp. (°C)	Isolated yield (%)
1	70	-	-	rt	19
2	6	-	THF	rt	25
3	2	-	acetonitrile	rt	62
4	2	-	DCM	rt	33
5	2	-	TFE	rt	50
6	70	-	HFIP	rt	27
7	2	DBU (1 equiv)	acetonitrile	rt	48
8	2	DBU (1 equiv)	TFE	rt	38
9	2	-	acetonitrile	80	52
10	2	-	acetonitrile	-15	30
11	2	-	EtOAc	rt	43

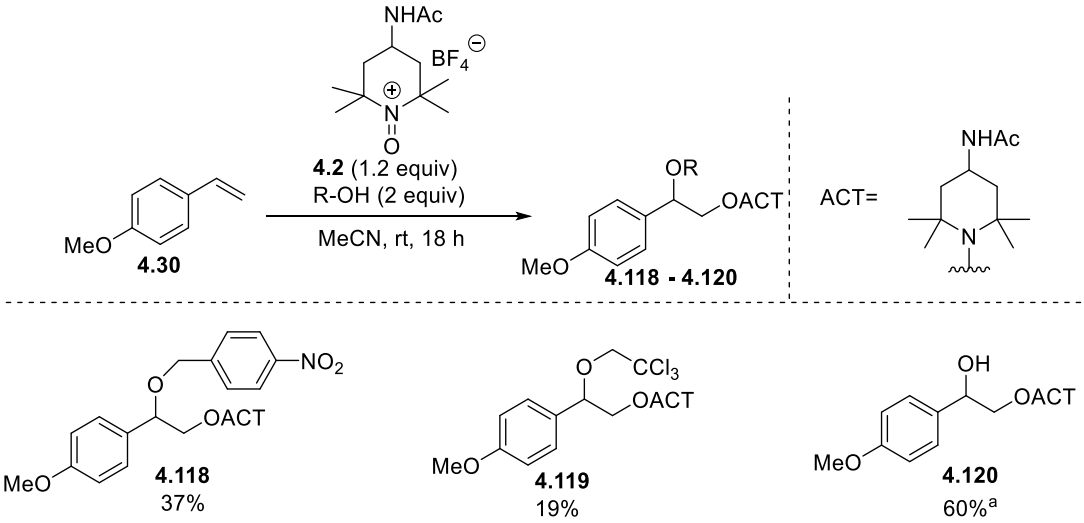
[a]all reactions utilized 1.0 equiv of **4.30** (0.25 M) and 1.5 equiv of **4.2** for 18 h

The use of a large excess of ethanol resulted in low yield (Table 4.9 entries 1 and 2). Since there is so much ethanol in the reaction, the oxoammonium salt **4.2** could just be oxidizing the alcohol before it has a chance to react with 4-methoxystryene **4.30**. A variety of solvents were screened in this reaction (Table 4.9, entries 2-6). The reactions using acetonitrile and TFE were high yielding (Table 4.9, entries 3 and 5), while the reactions using THF, DCM, and HFIP were low yielding (Table 4.9. entries 2, 4, 6). The addition of 1 equivalent of DBU lowered the yield (Table 4.9, entries 7 and 8). The base could be reacting with the oxoammonium salt **4.2** instead of the ethanol. Lastly, a variety of temperature in acetonitrile was tried (Table 4.9, entries 3, 9, 10). The reaction at room temperature showed to be the best conditions.

Other alcohols were tested in this reaction (Table 4.10). Electron poor alcohols are known to be slow to oxidize with oxoammonium salts,[71] 4-Nitrobenzyl alcohol was initially evaluated and gave a 37% unoptimized yield of **4.118**. Addition of water provided a 60% yield of the

monoprotected diol product **4.120** under these conditions. Further studies on optimizing the alkene difunctionalization with alcohols and water will be undertaken. This will include a full solvent screen, the effects of concentration and temperature as well as the reaction time on the yield.

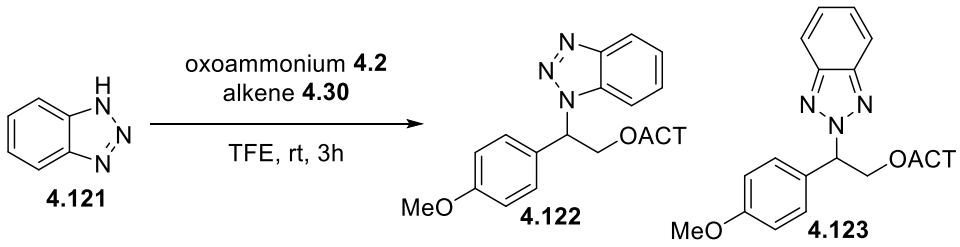
Table 4.10. Addition to 4-Methoxystrene Using Alcohols and Oxoammonium salt **4.2**



[a]used 20 equiv of water and in EtOAc as solvent.

Previously, our group investigated the nitrogen heterocycle benzotriazole **4.121**, in this reaction. This provided a 2:1 mixture of **4.122** and **4.123** as products (Scheme 4.18), which were not separable. However, this showed benzotriazole acted as an efficient nucleophile in the transformation.

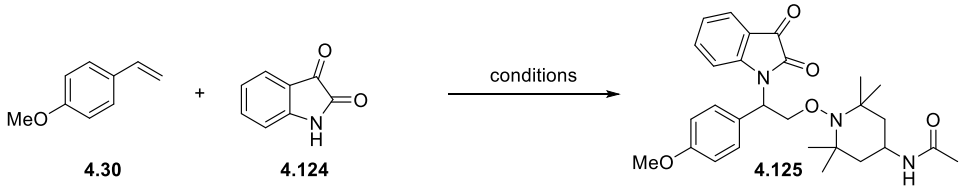
Scheme 4.18. Alkene Difuctionalization Reaction with Benzotriazole



Since there was some success utilizing benzotriazole, exploration into other nitrogen heterocycles was performed using isatin (Table 4.11). A solvent scree was performed using

acetonitrile, DCE, and THF (Table 4.11 entries 1, 2, and 3) with acetonitrile providing the best yield of 25%. It was determined that the reaction did not need to be heated, as running the reaction in acetonitrile at room temperature provided the same yield (25%, Table 4.11 entry 12). Next a variety of bases were evaluated. When a soluble organic base, DBU, was utilized, the yield dropped significantly to 3% (Table 4.11, entry 7). Using a larger excess of inorganic bases hindered the reaction, as shown in Table 4.11, entries 8-10, impacted the reaction. The excess base could be reacting with the oxoammonium salt **4.2** instead of the isatin. However, when a slight excess of potassium carbonate was used, the yield improved to 44% (Table 4.11, entry 4). Additionally, isatin was difficult to solubilize in most solvents leading to heterogeneous reaction mixtures, making it difficult to probe how to further optimize the reaction. Further studies with different heterocycles will be investigated in the future to optimize the alkene difunctionalization.

Table 4.11. Addition to 4-Methoxystrene Using Isatin and Oxoammonium Salt **4.2**



4.30 4.124 4.125

Entry[a]	Solvent	Temp (° C)	Base	Yield (%)
1	MeCN	reflux	-	25
2	DCE	reflux	-	20
3	THF	83	-	7
4	MeCN	rt	K_2CO_3 (1.2 equiv)	44
5	MeCN	rt	Cs_2CO_3 (1.2 equiv)	23
6	MeCN	rt	Na_2CO_3 (1.2 equiv)	20
7	MeCN	rt	DBU (1.2 equiv)	3
8	MeCN	rt	K_2CO_3 (2.4 equiv)	23
9	MeCN	rt	Cs_2CO_3 (2.4 equiv)	6
10	MeCN	rt	Na_2CO_3 (2.4 equiv)	19
11	TFE	rt	-	4
12	MeCN	rt	-	25

[a]All reactions were run at 0.3 M of styrene **4.30**, 1.2 equiv of oxoammonium salt **4.2** for 18 h.

Conclusions and Future Work:

In summary, an elimination-oxidation process mediated by an oxoammonium salt has been discovered. Evidence appeared to suggest that this transformation first proceeds through an elimination via the oxoammonium salt, since the addition of hindered base does not significantly inhibit the reaction. Then an allylic oxidation occurs through an ene type mechanism, previously reported by Bailey. The scope of the reaction consists of tertiary alcohols derived from tetralones. Other pathways require multistep routes to achieve the same rearrangement of functionality. Additionally, the oxoammonium salt also serves as a protecting group for the newly generated allylic alcohol, resulting in a process with high atom economy.

Additionally, *N*-oxoammonium salt mediated additions as metal free alternatives for alkene difunctionalizations have been investigated.[23] These *N*-oxoammonium salt mediated additions may provide new methods for the elaboration of alkenes into molecules with significantly greater complexity. Using *trans*-anethole the diastereoselectivity was evaluated. Both the syn and the anti-addition products could be accessed with significant selectivity, following a trend in dielectric constant (ε) of the solvent. Polar solvents (HFIP) favored the formation of the syn diastereomer, while the less polar THF favored the formation of the anti-product. The removal of the OACT group has proven to be difficult; utilizing anhydrous nickel chloride and lithium aluminum hydride at – 78 °C to room temperature, providing an 43% yield of the amino-alcohol product. Other reagents mentioned gave less than 15%. The stereochemistry of the addition was verified by x-ray diffraction on a cyclized piperidine derivative. The cyclized oxazolidinone derivative was synthesized via an intramolecular CDI coupling in high yield of 96%. Studies to evaluate if this reaction could be done enantioselectivity were initiated using chiral anionic phase transfer catalyst. Some preliminary experiments were undertaken with the chiral phosphoric acid catalyst (*R*)-TRIP,

known to work in asymmetric anionic phase transfer transformations with oxoammonium salts.[32, 35-37] The alkene difunctionalization with 2-nitroaniline, Na_2CO_3, (*R*)-TRIP in toluene provided a significant ee of 54%. A chiral diol catalyst was also employed, with significant enantioselectivity being achieved, however with lower yields. Anilines that are more soluble will be evaluated in these asymmetric alkene difunctionalizations to improve yields.

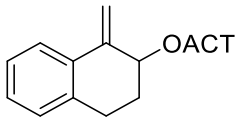
An investigation of the *N*-Oxoammonium salt mediated additions to alkenes with primary alcohols, water, and isatin. The use of a large excess of ethanol resulted in low yield. The reactions using acetonitrile and TFE were high yielding while the reactions using THF, DCM, and HFIP were low yielding. The addition of DBU also lowered the yield. Lastly, a variety of temperature in acetonitrile was tried and the reaction at room temperature showed to be the best conditions. Addition of water provided a 60% yield of the monoprotected diol product using ethyl acetate as the solvent. Further studies on optimizing the alkene difunctionalization with other nucleophiles will be evaluated.

Experimental:

General Experimental Information

All anhydrous reactions were run under a positive pressure of argon. DCM (DCM) was dried by passage through an alumina column.[171] 1,2-Dichloroethane (DCE) was freshly distilled from calcium hydride before use. Silica gel column chromatography was performed using 60 Å silica gel (230−400 mesh). Melting points are uncorrected. The benzylic alcohols used in the study were prepared as reported in the literature.[303]

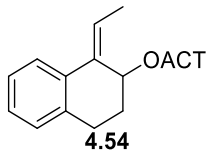
General procedure for allylic oxidation: To a solution of 0.33 mmol of alkene (1 equiv) in acetonitrile (0.33 M), 4 Å molecular sieves was added. The flask was put under an atmosphere of argon. Then 0.40 mmol of *N*-oxoammonium salt (1.2 equiv) was added in one portion. The flask was purged with argon. The reaction mixture was left to stir at room temperature for 6 hours. The reaction was quenched with saturated aqueous bicarbonate solution, extracted with ethyl acetate (3x), and washed with brine (3x). The organic layers were combined, dried over sodium sulfate, and concentrated. The residue was purified by silica chromatography to give the product.



4.28

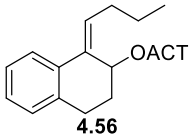
***N*-{2,2,6,6-Tetramethyl-1-[(1-methylidene-3,4-dihydro-2H-naphthalen-2-yl)oxy]piperidin-4-yl} acetamide (4.28).** Followed general procedure. Purified by silica chromatography using a solvent gradient of 50-70%. EA/hexanes to give product as an off-white solid. When scaled up to 6 mmol obtained 1.32 g of product. Yield: 60%. IR (film): 3246, 3073, 2969, 1633, 1363, 777 cm^{-1}; TLC R_f = 0.30 (70% EA/30% hexanes); mp = 143-145 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48-7.46 (m, 1H), 7.11-7.01 (m, 3H), 5.44 (s, 1H), 5.25 (bs, 2H), 4.43 (t, *J* = 4.63 Hz, 1H), 4.06- 4.02

(m, 1H), 3.08-3.00 (m, 1H), 2.69 (dt, *J* = 16.7, 5.4, 1H), 2.07-2.03 (m, 2H), 1.86 (s, 3H), 1.75-1.72 (m, 1H), 1.63 (dt, *J* =12.3, 3.6 Hz, 1H), 1.30-1.24 (m, 1H), 1.19-1.17 (m, 7H), 0.97 (s, 3H), 0.87 (s, 3H); $^{13}C^{226}$ NMR (100 MHz, $CDCl_3$) δ 169.3, 144.5, 136.4, 134.3, 128.7, 127.5, 126.0, 125.0, 110.6, 82.0, 60.3, 59.8, 46.3, 46.1, 41.7, 34.4, 34.2, 29.4, 26.2, 23.6, 21.2, 21.0; Anal Calcd for $C_{22}H_{32}N_2O_2$: C, 74.12; H, 9.05; N, 7.86; Found: C, 73.56; H, 9.01; N, 7.75.



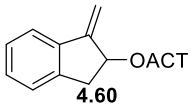
4.54

***N*-(1-{[(1*Z*)-1-Ethylidene-3,4-dihydro-2H-naphthalen-2-yl]oxy}-2,2,6,6-tetramethylpiperidin-4-yl) acetamide (4.54).** Followed general procedure. Purified by silica chromatography using a solvent gradient of 50-70%. EA/hexanes to give 0.070 g product as a white solid. Yield: 57%. IR (film) 3254, 3091, 2921, 1637, 1374, 952, 769 cm^{-1}; TLC R_f = 0.31 (70% EA/30% hexanes); mp = 141-143 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36-7.34 (m, 1H), 7.06-7.00 (m, 3H), 5.96 (q, *J* = 6.7 Hz, 1H), 5.09 (d, *J* = 6.7 Hz, 1H), 4.91 (bs, 1H), 4.03-3.95 (m, 1H), 3.12-3.04 (m, 1H), 2.63 (dd, *J* = 16.5, 5.4 Hz, 1H), 2.28-2.25 (m, 1H), 1.87-1.86 (m, 3H), 1.85 (s, 3H), 1.75-1.59 (m, 5H), 1.26 (s, 3H), 1.15 (s, 3H), 0.80 (s, 3H), 0.78 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.2, 137.6, 136.1, 135.5, 128.5, 126.4, 125.9, 124.6, 121.7, 74.8, 60.6, 59.1, 46.4, 46.1, 41.2, 33.8, 33.6, 28.8, 24.8, 23.6, 20.9, 20.7, 14.5; Anal Calcd for $C_{23}H_{34}N_2O_2$: C, 74.55; H, 9.25; N, 7.56; Found: C, 74.34; H, 9.30; N, 7.25. Alkene geometry was determined to be Z via NOESY NMR.



4.56

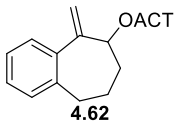
***N*-(1-{[(1Z)-1-Butylidene-3,4-dihydro-2H-naphthalen-2-yl]oxy}-2,2,6,6-tetramethylpiperidin-4-yl) acetamide (4.56).** Followed general procedure. Purified by silica chromatography using a solvent gradient of 50-70%. EA/hexanes to give 0.075 g product as an oil. Yield: 56%. IR (film) 3272, 2925, 2868, 1640, 1550, 1373, 1362, 777 cm^{-1}; TLC R_f = 0.32 (70% EA/30% hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.54-7.42 (m, 1H), 7.13-7.07 (m, 3H), 5.93 (t, *J*= 7.4 Hz, 1H), 5.33 (d, *J*= 7.2 Hz, 1H), 4.94 (s, 1H), 4.14-4.01 (m, 1H), 3.19-3.11 (m, 1H), 2.69 (dd, *J*= 5.6, 16.4 Hz, 1H), 2.46-2.39 (m, 1H), 2.27-2.25 (m, 2H), 1.91 (s, 3H), 1.81-1.72 (m, 3H), 1.67-1.64 (m, 1H), 1.58-1.42 (m, 3H), 1.31 (s, 3H), 1.22 (s, 3H), 0.96 (t, *J*= 7.2 Hz, 3H), 0.87 (s, 3H), 0.83 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.2, 136.8, 136.2, 135.7, 128.5, 127.8, 126.4, 125.9, 124.8, 75.1, 60.6, 59.1, 46.4, 46.1, 41.2, 33.9, 33.7, 30.8, 28.9, 24.8, 23.6, 23.0, 20.9, 20.7, 14.1; Anal Calcd for $C_{25}H_{38}N_2O_2$: C, 75.33; H, 9.61; N, 7.03; Found: C, 75.31; H, 9.50; N, 6.87. Alkene geometry was determined to be Z via NOESY NMR



4.60

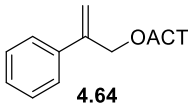
***N*-{2,2,6,6-Tetramethyl-1-[(1-methylidene-2,3-dihydroinden-2-yl)oxy]piperidin-4-yl}acetamide (4.60).** Followed general procedure. Purified by silica chromatography using a solvent gradient of 50-70%. EA/hexanes to give 0.061 g product as a solid. Yield: 53%. IR (film) 3267, 2924, 1637, 1362, 732 cm^{-1}; TLC R_f = 0.23 (70% EA/30% hexanes); mp = 150-153 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.43 (m, 1H), 7.21 (s, 3H), 5.55 (d, *J*=1.7 Hz, 1H), 5.42 (s, 1H), 5.22 (d, *J*= 6.9 Hz, 1H), 5.11 (t, *J*= 6.9 Hz, 1H), 4.21-4.12 (m, 1H), 3.22 (dd, *J*= 7.5, 15.5 Hz, 1H), 3.06 (dd, *J* = 6.8, 15.5 Hz, 1H), 1.95 (s, 3H), 1.83-1.81 (m, 2H), 1.38-1.34 (m, 5H), 1.27-1.23 (m,

9H);$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 169.2, 149.7, 142.1, 139.1, 128.7, 126.9, 125.2, 120.8, 105.9, 87.1, 61.0, 59.5, 46.4, 46.3, 41.1, 38.7, 34.5, 33.0, 23.6, 21.2, 21.0; Anal Calcd for $C_{21}H_{30}N_2O_2$: C, 73.65; H, 8.83; N, 8.18; Found: C, 73.62; H, 8.55; N, 7.80.



4.62

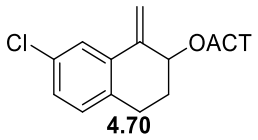
***N*-[2,2,6,6-Tetramethyl-1-({5-methylidene-6,7,8,9-tetrahydrobenzo[7]annulen-6-yl}oxy)piperidin-4-yl] acetamide (4.62).** Followed general procedure. Purified by silica chromatography using a solvent gradient of 50-70%. EA/hexanes to give 0.058 g product as an oil. Yield: 47%. IR (film) 3267, 3081, 2971, 1636, 1550, 1362, 778 cm^{-1}; TLC R_f = 0.23 (70% EA/30% hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.13 (m, 3H), 7.07-7.06 (m, 1H), 5.31 (s,1H), 5.18 (d, *J* = 3.8 Hz, 1H), 5.07 (s, 1H), 4.31 (bs, 1H), 4.14-4.07 (m, 2H), 2.79-2.69 (m, 2H), 2.21 (bs, 1H), 2.13-2.03 (m, 2H), 1.92 (s, 4H), 1.79-1.68 (m, 3H), 1.29-1.23 (m, 2H), 1.20 (s, 4H), 1.16 (s, 2H), 1.12 (s, 2H), 1.09 (s, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 169.3, 153.6, 140.1, 129.0, 128.7, 128.6, 127.2, 127.0, 126.0, 112.8, 86.2, 60.5, 59.4, 46.3, 41.1, 37.5, 35.9, 34.8, 33.8, 23.6, 21.0, 20.9, 14.2; Anal Calcd for $C_{23}H_{34}N_2O_2$: C, 74.55; H, 9.25; N, 7.56; Found: C, 74.34; H, 9.30; N, 7.25.



4.64

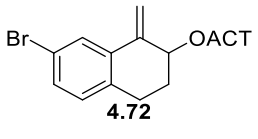
***N*-{2,2,6,6-Tetramethyl-1-[(2-phenylprop-2-en-1-yl)oxy]piperidin-4-yl}acetamide (4.64).** Followed general procedure. Purified by silica chromatography using a solvent gradient of 50-70% EA/hexanes to give product as colorless oil. Yield: 45%. IR (film) 3273, 3081, 2973, 1633, 1550, 705 cm^{-1}; TLC R_f = 0.26 (70% EA/30% hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.12

(m, 5H), 5.38 (s, 1H), 5.33 (s, 1H), 5.19 (bs, 1H), 4.57 (s, 1H), 4.09-4.04 (m, 1H), 1.88-1.71 (m, 5H), 1.29-1.23 (m, 3H), 1.16-1.15 (m, 12H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 169.3, 144.2, 139.4, 128.3, 127.6, 126.0, 112.7, 78.4, 60.13, 45.8, 41.1, 32.9, 23.6, 20.9; Anal Calcd for $C_{20}H_{30}N_2O_2$: C, 72.69; H, 9.15; N, 8.48; Found: C, 72.48; H, 8.79; N, 8.46.



4.70

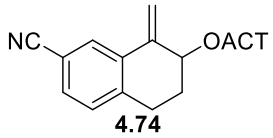
***N*-{1-[(7-Chloro-1-methylidene-3,4-dihydro-2H-naphthalen-2-yl)oxy]-2,2,6,6-tetramethylpiperidin-4-yl}acetamide (4.70).** Followed general procedure. Purified by silica chromatography using a solvent gradient of 50-70%. EA/hexanes to give 0.062 g product as a white solid. Yield: 48%. IR (film) 3255, 2970, 1634, 1362 cm^{-1}; TLC R_f = 0.25 (70% EA/30% hexanes); mp = 102-105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 2.1 Hz, 1H), 7.13 (dd, *J* = 2.1, 8.2 Hz, 1H), 7.04 (d, *J* = 8.2 Hz, 1H), 5.51 (s, 1H), 5.28 (s, 1H), 5.14 (d, *J* = 6.9 Hz, 1H), 4.49 (d, *J* = 3.5 Hz, 1H), 4.15-4.07 (m, 1H), 3.11-3.03 (m, 1H), 2.75-2.68 (m, 1H), 2.17- 2.14 (m,1H), 2.07-2.03 (m, 1H), 1.93 (s, 3H), 1.89- 1.69 (m, 4H), 1.24 (m, 6H), 1.03 (s, 3H), 0.91 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 169.3, 143.4, 135.9, 134.8, 131.7, 130.1, 127.5, 124.8, 112.1, 81.6, 60.5, 59.8, 46.2, 46.1, 41.1, 34.5, 34.2, 29.1, 25.5, 23.6, 21.2, 20.9; Anal calcd for $C_{22}H_{31}ClN_2O_2$: C, 67.59; H, 7.99; N, 7.17; Found: C, 67.26; H, 8.02; N, 7.33.



4.72

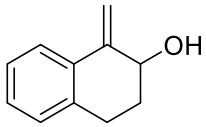
***N*-{1-[(7-Bromo-1-methylidene-3,4-dihydro-2H-naphthalen-2-yl)oxy]-2,2,6,6-tetramethylpiperidin-4-yl} acetamide (4.72).** Followed general procedure. Purified by silica chromatography using a solvent gradient of 50-70%. EA/hexanes to give 0.065 g product as a yellow solid. Yield: 45%. IR (film) 3270, 2928, 1640, 1555, 731 cm^{-1}; TLC R_f = 0.22 (70%

EA/30% hexanes); mp = 140-144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* =1.8 Hz, 1H), 7.27 (d, *J* = 10.0 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 5.50 (s, 1H), 5.28 (s, 1H), 5.17 (bs, 1H), 4.49 (bs,1H), 4.11 (bs, 1H), 3.09-3.01 (m, 1H), 2.72-2.68 (m, 1H), 2.15-2.13 (m, 1H), 2.07-2.03 (m, 1H). 1.93 (s, 3H), 1.81 (d, *J*= 11.6 Hz, 1H), 1.71 (d, *J*= 11.9 Hz, 1H), 1.25-1.23 (m, 8H), 1.03 (s, 3H), 0.91 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.3, 143.3, 136.3, 135.3, 130.4, 128.6, 127.8, 119.7, 112.2, 81.6, 60.5, 59.8, 46.2, 41.1, 34.5, 34.1, 29.7, 29.0, 25.6, 23.6, 21.2, 20.9; Anal calcd for $C_{22}H_{31}BrN_2O_2$: C, 60.69; H, 7.18; N, 6.43; Found: C, 60.53; H, 6.93; N, 6.14.



4.74

***N*-{1-[(7-Cyano-1-methylidene-3,4-dihydro-2H-naphthalen-2-yl)oxy]-2,2,6,6-tetramethylpiperidin-4-yl} acetamide (4.74).** Followed general procedure. Purified by silica chromatography using a solvent gradient of 50-70%. EA/hexanes to give 0.051 g product as a tan solid. Yield: 40%. IR (film) 3291, 2974, 2932, 1661, 1516, 902, 723 cm^{-1}; TLC R_f = 0.20 (70% EA/30% hexanes); mp = 153-157 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.35 (d, *J*= 7.7 Hz, 1H), 7.13 (d, *J*= 7.7 Hz, 1H), 5.48 (s, 1H), 5.27 (s, 1H), 5.12 (d, *J*= 5.9 Hz, 1H), 4.45 (d, *J*= 3.0 Hz, 1H), 4.06-4.02 (m, 1H), 3.14-3.06 (m, 1H), 2.77-2.70 (m, 1H), 2.18-2.14 (m,1H), 1.97-1.95 (m, 1H), 1.87 (s, 3H), 1.76-1.61 (m, 3H), 1.31-1.23 (m, 1H), 1.19 (s, 3H), 1.16 (s, 3H), 0.91 (s, 3H), 0.79 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.3, 142.7, 141.9, 135.5, 130.3, 129.6, 129.2, 119.2, 113.4, 110.0, 81.4, 60.6, 59.7, 46.1, 46.0, 41.1, 34.6, 34.1, 28.6, 26.1, 23.6, 21.1, 20.1; Anal calcd for $C_{23}H_{31}N_3O_2$: C, 72.41; H, 8.19; N, 11.01; Found: C, 72.49; H, 8.16; N, 10.67.



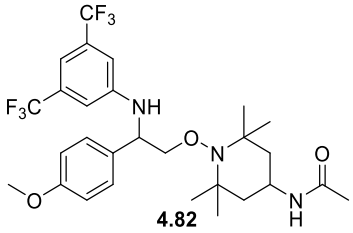
4.75

1-Methylene-3,4-dihydro-2(2H)-naphthalene (4.75). In an oven dried round-bottom flask, 0.734 g (11.2 mmol, 10 equiv) of zinc powder was added and suspended in 18 mL ether (0.62 M). The zinc powder was activated with 0.099 g (0.896 mmol, 0.8 equiv) TMSCl. The reaction was refluxed for 30 minutes. After 30 minutes, the zinc suspension was cooled to room temperature and the ether was evaporated. A solution of 0.400 g (1.12 mmol) allylic ether **4.30** was dissolved in 14.4 mL 1:1 AcOH:H_2O (0.08 M) and added drop wise to the activated zinc. The reaction was heated to 45 °C and left to stir for 2 h. After 2 h the reaction was cooled to room temperature, diluted with water and extracted with ether (3x). The organic layers were combined, dried over magnesium sulfate, and concentrated. The residue was purified by silica chromatography (30%. ether/pentanes) to give 0.088 g product as an oil. Yield: 49%. TLC R_f = 0.32 (30% ether/70% pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.55 (m, 1H), 7.18-7.04 (m, 3H), 5.54 (s, 1H), 5.23 (s, 1H), 4.45 (dd, *J* = 3.2, 7.6 Hz, 1H), 3.00 (dt, *J* = 6.4, 16.2 Hz, 1H), 2.80 (dt, *J*= 6.4, 16.9 Hz, 1H), 2.04-1.87 (m, 2H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 146.2, 136.2, 132.8, 128.9, 128.0, 126.2, 124.9, 108.5, 70.9, 31.4, 26.3. This compound has been previously reported.[281]

General Procedure for the Amino-Oxidation

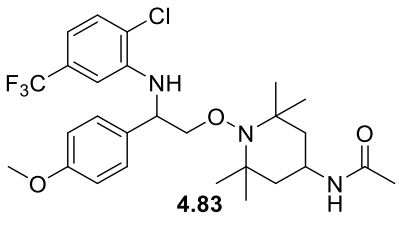
In an oven-dried round bottom flask, 0.25 mmol of alkene (1 equiv) and 0.25 mmol of aniline (1 equiv) was dissolved in trifluoroethanol (0.25 M). The flask was put under an atmosphere of argon. Then 0.30 mmol of oxammonium salt **4.2** (1.2 equiv) was added in one portion to the reaction mixture. The flask was purged with argon. The reaction mixture was left to stir at room temperature for 16 hours. The reaction mixture was quenched with sat. aq. sodium bicarbonate solution and

extracted with EA (3x). The combined organic extracts were then washed with brine (3x). The organic layer was dried over sodium sulfate and concentrated. The residue was purified by silica gel chromatography using the system noted under TLC to give the product.



4.82

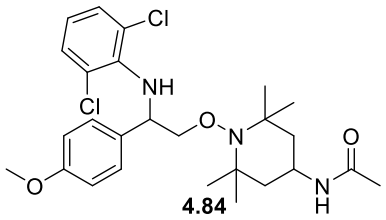
1-(1-{2-[3,5-Bis(trifluoromethyl)phenylamino]-2-(*p*-methoxyphenyl)ethoxy}-2,2,6,6-tetramethyl-4-piperidylamino)-1-ethanone (4.82). Followed general procedure. mp = 95-97 °C; TLC R_f = 0.56 (100% EA); IR (neat) 3290, 2974, 1656, 1511, 1274, 1123, 1035 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 7.7 Hz, 2H), 7.11 (s, 1H), 6.90-6.87 (m, 3H), 6.86 (s, 1H), 5.19 (d, *J* = 7.7 Hz, 1H), 4.91 (d, *J* = 4.5 Hz, 1H), 4.55-4.47 (m, 1H), 4.13-4.01 (m, 2H), 3.98-3.92 (m, 1H), 3.79 (s, 3H), 1.92 (s, 3H), 1.81-1.71 (m, 2H), 1.33-1.24 (m, 2H), 1.21 (s, 3H), 1.17 (s, 3H), 1.15 (s, 3H), 1.05 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.4, 159.3, 148.2, 132.2 (q, *J* = 33 Hz), 131.1, 127.8, 123.5 (q, *J* = 271 Hz), 114.2, 113.0, 110.6, 80.3, 60.4, 60.3, 57.5, 55.3, 45.8, 45.7, 40.9, 33.1, 32.9, 23.5, 20.8 (2C). Anal calcd for $C_{28}H_{35}F_6N_3O_3$: C, 58.43; H, 6.13; N, 7.30. Found: C, 58.27; H, 6.09; N, 7.30.



4.83

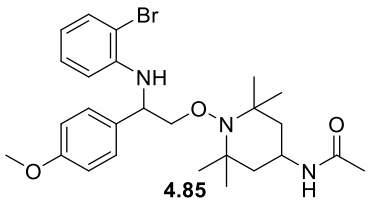
1-(1-{2-[2-Chloro-5-(trifluoromethyl)phenylamino]-2-(*p*-methoxyphenyl)ethoxy}-2,2,6,6-tetramethyl-4-piperidylamino)-1-ethanone (4.83). Followed general procedure. mp = 152-155 °C; TLC R_f = 0.42 (100% EA); IR (neat) 3416, 3289, 2931, 1629, 1510, 1249, 1126, 1056 cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.1 Hz, 1H), 7.27 (d, *J* = 9.2 Hz, 2H), 6.86 (d, 2H), 6.85-6.79 (m, 1H), 6.61 (d, *J* = 1.4 Hz, 1H), 5.51 (d, *J* = 4.9 Hz, 1H), 5.24 (bs, 1H), 4.54-4.48 (m, 1H), 4.18-4.04 (m, 2H), 4.01-3.92 (m, 1H), 3.78 (s, 3H), 1.92 (s, 3H), 1.82-1.70 (m, 3H), 1.35-1.27 (m, 1H), 1.24 (s, 3H), 1.21 (s, 3H), 1.16 (s, 3H), 1.03 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.3, 159.2, 143.6, 131.3, 130.0 (q, *J* = 32.3 Hz), 129.3, 127.8, 122.8, 114.1, 113.9 (q, *J* = 3.7 Hz), 109.0 (q, *J* = 3.7 Hz), 80.1, 60.5, 60.4, 57.1, 55.3, 45.9, 45.8, 41.0, 33.1, 32.9, 23.6, 20.9, 20.8; Anal calcd for $C_{27}H_{35}ClF_3N_3O_3$: C, 59.83; H, 6.51; N, 7.75. Found: C, 59.73; H, 6.44; N, 7.38



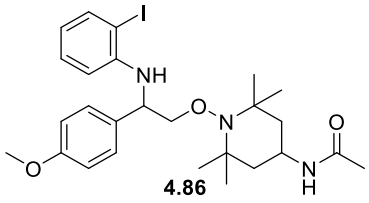
4.84

1-{1-[2-(2,6-Dichlorophenylamino)-2-(*p*-methoxyphenyl)ethoxy]-2,2,6,6-tetramethyl-4-piperidylamino}-1-ethanone (4.84). mp = 67-70 °C; TLC R_f = 0.40 (100% EA); IR (neat) 3273, 2930, 1648, 1510, 1244, 1174, 1034 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.6 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 6.78 (d, *J* = 8.7 Hz, 2H), 6.64 (t, *J* = 8.0 Hz, 1H), 5.22 (s, 1H), 5.17-5.11 (m, 1H), 4.24 (d, *J* = 7.3 Hz, 1H), 4.15-4.04 (m, 1H), 3.95 (d, *J* = 7.8 Hz, 1H), 3.75 (s, 3H), 1.92 (s, 3H), 1.80-1.66 (m, 3H), 1.31-1.24 (m, 2H), 1.22 (s, 3H), 1.21 (s, 3H), 1.09 (s, 3H), 0.82 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.4, 158.8, 141.4, 133.2, 129.1, 128.7, 125.2, 121.0, 113.6, 80.4, 60.5, 60.4, 59.1, 55.5, 55.4, 55.3, 46.0, 41.1, 33.2, 32.5, 29.9, 23.7, 21.0, 20.9; Anal calcd for $C_{26}H_{35}Cl_2N_3O_3$: C, 61.42; H, 6.94; N, 8.26. Found: C, 61.35; H, 6.98; N, 8.57.



4.85

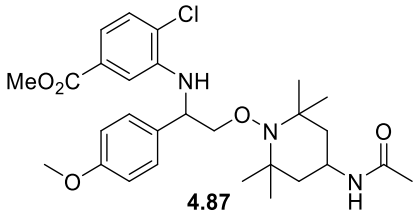
1-{1-[2-(*o*-Bromophenylamino)-2-(*p*-methoxyphenyl)ethoxy]-2,2,6,6-tetramethyl-4-piperidylamino}-1-ethanone (4.85). Followed general procedure. mp = 78-82 °C; TLC R_f = 0.43 (100% EA); IR (neat) 3273, 2929, 1649, 1508, 1243, 1173, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.28 (d, *J* = 3.8 Hz, 2H), 6.97 (t, *J* = 7.7 Hz, 1H), 6.85 (d, *J* = 8.6 Hz, 2H), 6.51 (t, *J* = 7.6 Hz, 1H), 6.34 (d, *J* = 8.1 Hz, 1H), 5.39 (d, *J* = 4.4 Hz, 1H), 5.25 (bs, 1H), 4.51-4.45 (m, 1H), 4.18-4.05 (m, 2H), 3.95 (t, *J* = 6.8 Hz, 1H), 3.78 (s, 3H), 1.93 (s, 3H), 1.84-1.70 (m, 2H), 1.33-1.27 (m, 2H), 1.26 (s, 3H), 1.23 (s, 3H), 1.17 (s, 3H), 1.02 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.4, 159.0, 144.4, 132.3, 132.2, 128.3, 127.9, 118.1, 114.0, 112.9, 110.4, 80.4, 60.5, 60.4, 57.4, 55.4, 45.9, 45.8, 41.0, 33.2, 32.9, 23.7, 21.0, 20.9; Anal calcd for $C_{26}H_{36}BrN_3O_3$: C, 60.23; H, 7.00; N, 8.10. Found: C, 60.16; H, 6.82; N, 8.20.



4.86

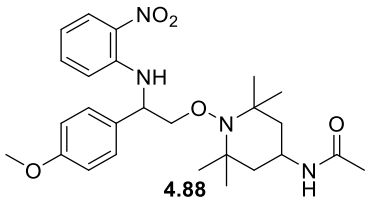
1-{1-[2-(*o*-Iodophenylamino)-2-(*p*-methoxyphenyl)ethoxy]-2,2,6,6-tetramethyl-4-piperidylamino}-1-ethanone (4.86). Followed general procedure. mp = 85-90 °C; TLC R_f = 0.41 (100% EA); IR (neat) 3274, 2928, 1648, 1508, 1243, 1172, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.26 (d, *J* = 8.7 Hz, 2H), 7.00 (t, *J* = 7.7 Hz, 1H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.38 (t, *J* = 7.5 Hz, 1H), 6.27 (d, *J* = 8.2 Hz, 1H), 5.23 (d, *J* = 4.6 Hz, 1H), 5.19-5.10 (m, 1H), 4.52-4.45 (m, 1H), 4.17-4.03 (m, 2H), 4.00-3.90 (m, 1H), 3.77 (s, 3H), 1.92 (s, 3H), 1.82-1.60 (m, 4H), 1.28 (s, 3H), 1.25 (s, 3H), 1.18 (s, 3H), 1.01 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz,

$CDCl_3$) δ 169.4, 159.1, 146.6, 139.1, 132.1, 129.3, 128.0, 119.0, 114.1, 112.3, 86.1, 80.5, 60.6, 60.5, 57.8, 55.4, 46.0, 45.9, 41.1, 33.3, 33.0, 23.7, 21.1 (2C); Anal calcd for $C_{26}H_{36}IN_3O_3$: C, 55.22; H, 6.42; N, 7.43. Found: C, 54.89; H, 6.11; N, 7.17.



4.87

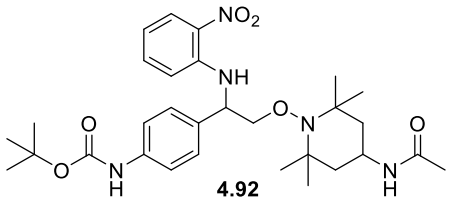
Methyl 3-[2-(4-acetylamino-2,2,6,6-tetramethyl-1-piperidyloxy)-1-(*p*-methoxyphenyl)ethylamino]-4-chlorobenzoate (4.87). Followed general procedure. mp = 83-87 °C; TLC R_f = 0.33 (100% EA); IR (neat) 3277, 2933, 1720, 1650, 1509, 1244, 1173, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 7.9 Hz, 2H), 7.27-7.22 (m, 1H), 7.21-7.05 (m, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 5.44 (d, *J* = 5.1 Hz, 1H), 5.40-5.23 (m, 1H), 4.62-4.52 (m 1H), 4.16-4.01 (m, 2H), 4.0-3.93 (m, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 1.92 (s, 3H), 1.80-1.65 (m, 2H), 1.33-1.24 (m, 2H), 1.24 (s, 3H), 1.20 (s, 3H), 1.15 (s, 3H), 1.01 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.3, 166.8, 159.0, 143.2, 131.7, 129.5, 128.9, 127.9, 124.3, 118.5, 114.0, 113.2, 80.1, 60.4, 60.3, 57.0, 55.3, 55.2, 52.1, 45.7, 40.9, 33.1, 32.8, 23.5, 20.8, 20.7; Anal calcd for $C_{28}H_{38}ClN_3O_5$: C, 63.21; H, 7.20; N, 7.90. Found: C, 63.22; H, 7.48; N, 7.62.



4.88

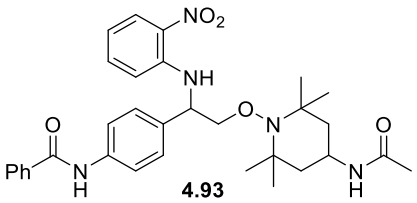
1-{1-[2-(*p*-Methoxyphenyl)-2-(*o*-nitrophenylamino)ethoxy]-2,2,6,6-tetramethyl-4-piperidylamino}-1-ethanone (4.88). Followed general procedure. mp = 93-96 °C; TLC R_f = 0.38

(100% EA); IR (neat) 3376, 3275, 2931, 1652, 1615, 1507, 1242, 1034 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (d, *J* = 5.6 Hz, 1H), 8.18 (dd, *J* = 8.9, 1.6 Hz, 1H), 7.27 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.63-6.57 (m, 2H), 5.23-5.17 (m, 1H), 4.67-4.62 (m, 1H), 4.18-4.10 (m, 2H), 3.79 (s, 3H), 1.93 (s, 3H), 1.82-1.70 (m, 2H), 1.56 (s, 2H), 1.30 (s, 3H),1.28-1.24 (m, 2H), 1.23 (s, 3H), 1.13 (s, 3H), 0.95 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 169.4, 159.3, 144.8, 136.1, 132.5, 131.4, 128.0, 126.9, 115.8, 115.3, 114.2, 79.9, 60.6, 60.5, 56.9, 55.4, 46.0, 45.9, 41.1, 33.2, 32.7, 23.7, 20.9 (2C); Anal calcd for $C_{26}H_{36}N_4O_5$: C, 64.44; H, 7.49; N, 11.56. Found: C, 64.48; H, 7.20; N, 11.78.



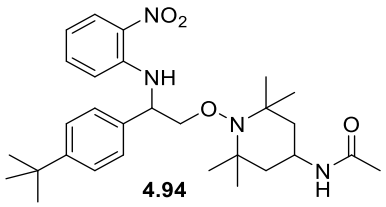
4.92

4-Acetylamino-2,2,6,6-tetramethyl-1-{2-(*o*-nitrophenylamino)-2-[*p*-(*tert*-butoxycarbonylamino)phenyl] ethoxy}piperidine (4.92). Followed general procedure. mp = 139-143 °C; TLC R_f = 0.37 (100% EA); IR (neat) 3374, 3261, 2976, 2931, 1707, 1652, 1616, 1506, 1243, 1152, 1073, 740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (d, *J* = 5.6 Hz, 1H), 8.18 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.35-7.21 (m, 4H), 6.64-6.55 (m, 2H), 6.46 (bs, 1H), 5.10-5.00 (m, 1H), 4.67-4.61 (m, 1H), 4.18-4.08 (m, 2H), 4.05-3.96 (m, 1H), 1.93 (s, 3H), 1.81-1.70 (m, 2H), 1.54-1.51 (m, 1H), 1.50 (s, 9H), 1.30 (s, 3H), 1.29-1.22 (m, 2H), 1.23 (s, 3H), 1.12 (s, 3H), 0.94 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 169.4, 152.9, 144.7, 138.1, 136.1, 133.9, 132.6, 127.6, 126.9, 118.8, 115.9, 115.3, 80.8, 79.8, 60.7, 60.6, 56.9, 46.0, 41.1, 33.2, 32.8, 29.9, 28.5, 23.7, 20.9 (2C); Anal calcd for $C_{30}H_{43}N_5O_6$: C, 63.25; H, 7.61; N, 12.29. Found: C, 63.00; H, 7.57; N, 12.34.



4.93

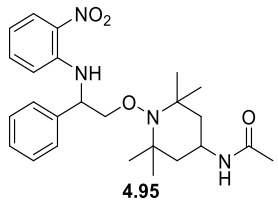
1-(1-{2-[*p*-(Benzoylamino)phenyl]-2-(*o*-nitrophenylamino)ethoxy}-2,2,6,6-tetramethyl-4-piperidylamino)-1-ethanone (4.93). Followed general procedure. mp = 137-140 °C; TLC R_f = 0.34 (100% EA); IR (neat): 3290, 2972, 1652, 1615, 1506, 1411, 1239, 1073, 741, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.92 (d, *J* = 5.7 Hz, 1H), 8.43 (s, 1H), 8.16 (dd, *J* = 8.5, 1.3 Hz, 1H), 7.86 (d, *J* = 7.3 Hz, 2H), 7.69 (d, *J* = 8.3 Hz, 2H), 7.50 (t, *J* = 7.3 Hz, 1H), 7.46-7.40 (m, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 6.63-6.56 (m, 2H), 5.48-5.40 (m, 1H), 4.70-4.64 (m, 1H), 4.20-4.14 (m, 1H), 4.12-4.00 (m, 2H), 1.88 (s, 3H), 1.76-1.63 (m, 2H), 1.26 (s, 3H), 1.22 (s, 3H), 1.06 (s, 3H), 0.89 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.6, 166.1, 144.6, 137.9, 136.2, 135.4, 135.0, 132.5, 132.0, 128.8, 127.5, 127.3, 126.9, 120.6, 116.0, 115.3, 79.6, 60.6, 60.5, 56.9, 45.8, 41.0, 33.2, 32.7, 32.0, 23.6, 20.9 (2C); Anal calcd for $C_{32}H_{39}N_5O_5$: C, 67.00; H, 6.85; N, 12.21. Found: C, 67.08; H, 7.09; N, 12.29.



4.94

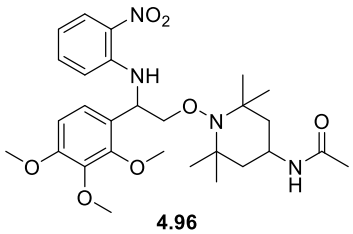
1-(2,2,6,6-Tetramethyl-1-{2-(*o*-nitrophenylamino)-2-[*p*-(*tert*-butyl)phenyl]ethoxy}-4-piperidylamino)-1-ethanone (4.94). Followed general procedure. mp = 91-94 °C; TLC R_f = 0.34 (100% EA); IR (neat) 3375, 3277, 2964, 1652, 1507, 1267, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.82 (d, *J* = 5.5 Hz, 1H), 8.11 (d, *J* = 8.5 Hz, 1H), 7.31-7.25 (m, 2H), 7.22-7.15 (m, 3H), 6.57 (d, *J* = 8.1 Hz, 1H), 6.53 (d, *J* = 7.4 Hz, 1H), 5.07 (bs, 1H), 4.64-4.60 (m, 1H), 4.09-4.01 (m, 2H), 3.97-3.92 (m, 1H), 1.85 (s, 3H), 1.73-1.70 (m, 2H), 1.66-1.62 (m, 2H), 1.22 (s, 9H), 1.15 (s, 6H),

1.04 (s, 3H), 0.86 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 169.2, 150.8, 144.7, 135.9, 132.4, 127.8, 126.8, 126.3, 125.5, 115.6, 115.2, 79.9, 60.42, 60.36, 56.9, 45.8, 40.9, 34.5, 33.0, 32.5, 31.3, 23.5, 20.8, 20.7, 20.6; Anal calcd for $C_{29}H_{42}N_4O_4$: C, 68.21; H, 8.64; N, 10.97; Found: C, 68.46; H, 8.64; N, 10.89.



4.95

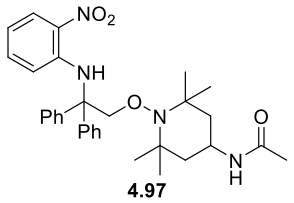
1-{2,2,6,6-Tetramethyl-1-[2-(*o*-nitrophenylamino)-2-phenylethoxy]-4-piperidylamino}-1-ethanone (4.95). Followed general procedure. Yellow oil. TLC R_f = 0.41 (70% EA/30% hexanes); IR (film) 3287, 3054, 2928, 1653, 1264, 733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (bs, 1H), 8.15 (d, *J* = 8.6 Hz, 1H), 7.40-7.31 (m, 5H), 6.74 (d, *J* = 8.6 Hz, 1H), 6.62 (t, *J* = 7.8 Hz, 1H), 5.17-5.12 (m, 1H), 4.19-4.14 (m, 2H), 3.83-3.70 (m, 2H), 3.63-3.58 (m, 1H), 1.93 (s, 3H), 1.83-1.79 (m, 1H), 1.76-1.73 (m, 1H), 1.54 (t, *J* = 12 Hz, 1H), 1.41(t, *J* = 12.0 Hz, 1H), 1.31 (s, 6H), 1.20 (s, 3H), 1.03 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 169.4, 145.0, 140.2, 136.2, 132.0, 128.5, 128.1, 126.9, 126.8, 115.3, 113.6, 83.2, 61.3, 60.4, 49.3, 45.9, 45.8, 41.0, 34.1, 32.9, 23.6, 21.2, 21.0. Anal. Calcd for $C_{25}H_{34}N_4O_2$: C, 66.06; H, 7.54; N, 12.33; Found: C, 66.06; H, 7.26; N, 11.94.



4.96

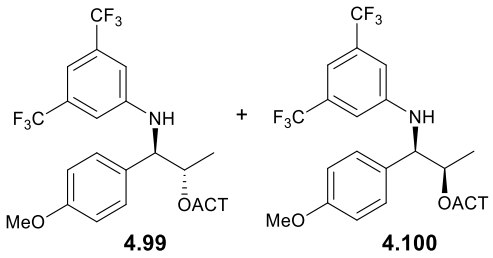
1-{2,2,6,6-Tetramethyl-1-[2-(*o*-nitrophenylamino)-2-(2,3,4-trimethoxyphenyl)ethoxy]-4-piperidylamino}-1-ethanone (4.96). Followed general procedure. mp = 87-90 °C; TLC R_f = 0.40 (100% EA); IR (neat) 3376, 2934, 1652, 1616, 1493, 1250, 1092, 742 cm^{-1}; ^{1}H NMR (400 MHz,

$CDCl_3$) δ 8.88 (d, *J* = 6.2 Hz, 1H), 8.17 (dd, *J* = 8.6, 1.4 Hz, 1H), 6.96 (d, *J* = 8.7 Hz, 1H), 6.65-6.56 (m, 3H), 5.11 (d, *J* = 7.5 Hz, 1H), 5.07-5.01 (m, 1H), 4.19-4.07 (m, 2H), 4.01 (s, 3H), 3.86 (s, 3H), 3.82 (s, 3H), 1.93 (s, 3H), 1.82-1.69 (m, 2H), 1.62 (s, 1H), 1.30 (s, 3H), 1.25 (s, 3H), 1.23-1.11 (m, 3H), 1.09 (s, 3H), 0.95 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.4, 153.5, 151.2, 144.9, 142.0, 136.2, 132.5, 127.0, 124.4, 122.2, 115.7, 115.0, 107.2, 78.7, 61.3, 61.0, 60.6, 60.5, 56.1, 51.3, 46.0 (2C), 41.1, 33.2, 32.7, 23.8, 20.9 (2C); Anal calcd for $C_{28}H_{40}N_4O_7$: C, 61.75; H, 7.40; N, 10.29. Found: C, 61.69; H, 7.36; N, 10.25.



4.97

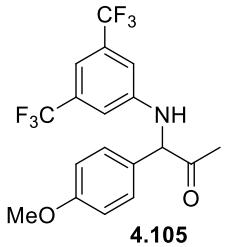
1-{2,2,6,6-Tetramethyl-1-[2-(*o*-nitrophenylamino)-2,2-diphenylethoxy]-4-piperidylamino}-1-ethanone (4.97). Followed general procedure. mp = 110-113 °C; TLC R_f = 0.41 (100% EA); IR (neat) 3279, 2928, 1652, 1614, 1497, 1238, 739, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.53 (s, 1H), 8.18 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.54 (d, *J* = 7.4 Hz, 4H), 7.38-7.29 (m, 5H), 6.92 (t, *J* = 7.3 Hz, 1H), 6.53 (t, *J* = 7.4 Hz, 1H), 6.28 (d, *J* = 8.8 Hz, 1H), 5.04 (d, *J* = 7.8 Hz, 1H), 4.43 (s, 2H), 4.10-4.00 (m, 1H), 1.90 (s, 3H), 1.72-1.66 (m, 2H), 1.27-1.17 (m, 3H), 1.04 (s, 6H), 0.94 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.4, 144.1, 140.3, 134.6, 133.3, 128.5, 127.8, 126.9, 118.4, 116.0, 83.2, 66.9, 60.7 (2C), 46.3 (2C), 41.0 (2C), 32.7 (2C), 23.7, 20.9 (2C); Anal calcd for $C_{31}H_{38}N_4O_4$: C, 70.16; H, 7.22; N, 10.56. Found: C, 70.03; H, 7.29; N, 10.95.



4.99 **4.100**

~ 1:1 mixture

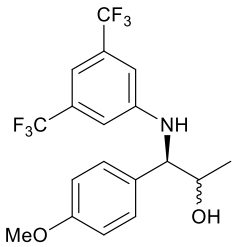
Syn and anti 1-(1-{2-[3,5-Bis(trifluoromethyl)phenylamino]-1-methyl-2-phenylethoxy}-2,2,6,6-tetramethyl-4-piperidylamino)-1-ethanone (4.99 and 4.100). To an oven dried test tube *trans*-anethole (**4.76**, 0.037 g, 0.250 mmol) and 3,5-bistrifluoromethylaniline (**4.98**, 0.020 g, 0.444 mmol) were added. The test tube was put under an atmosphere of argon and 1 mL of TFE was added. The reaction was stirred for 5 minutes, then oxoammonium salt **4.2** (0.09 g, 0.300 mmol) was added. The reaction was stirred at room temperature for 16 hours. The reaction was quenched with saturated aqueous sodium bicarbonate solution, extracted with DCM, and washed with brine. The organic layers were combined, dried over sodium sulfate and concentrated. The residue was purified by silica column chromatography (40- 80% ethyl acetate/ hexanes) to provide 0.117 g **4.99** and **4.100** as white solid. Yield: 80%. White solid. mp = 104-107 °C. TLC R_f = 0.30 (70% ethyl acetate/ 30% hexanes); ^{1}H NMR (400 MHz, CD_3CN) δ 7.39-7.32 (m, 4H), 7.10 (d, *J*=6.7 Hz, 6H), 6.92-6.89 (m, 4H) 6.23 (bs, 1H), 5.83-5.79 (m, 2H), 4.73 (dd, *J*= 6.8, 4.0 Hz, 1H), 4.55 (dd, *J*= 7.1, 4.8 Hz, 1.09 H), 4.40-4.24 (m, 2H), 4.05-3.95 (m, 2H), 3.77 (s, 6H), 2.00 (s, 6H), 1.99-1.95 (m, 1H), 1.83 (s, 6H), 1.79-1.58 (m, 4H) 1.37-1.29 (m, 6H), 1.26 (s, 3H), 1.23 (s, 4H), 1.21 (s, 3H), 1.15 (s, 5H), 1.07 (s, 2H), 1.02 (s, 3H). Anal Calcd for $C_{29}H_{37}F_6N_3O_3$: C, 59.07; H, 6.33; N, 7.13. Found: C, 58.96; H, 6.39; N, 6.83. Raito of **4.99**:**4.100** was determined by looking the ratio of peaks at δ 4.7 and 4.5 in CD_3CN.



4.105

1-[3,5-Bis(trifluoromethyl)phenylamino]-1-phenyl-2-propanone (4.105). An oven dried round bottom flask was charged with 0.050 g (0.085 mmol, 1 equiv) of amines **4.103** and **4.104** (~50:50 mixture) and 0.018 g (0.102 mmol, 1.2 equiv) of *m*-CPBA. The flask was put under an atmosphere of argon and 0.8 mL DCM was added. The reaction mixture was then heated to 40 °C. After 16 h the reaction was cooled to room temperature, quenched with 1 mL of sat. aq. $Na_2S_2O_3$, and let stir for 1 h. Then the organic layer was then washed 3 x 1 mL of sat. aq. $NaHCO_3$, dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica column chromatography (20% ethyl acetate/ 80% hexanes) to provide 17 mg ketone **4.105** as a yellow oil (53% yield).

4.105. TLC R_f = 0.50 (20% EA/ 80% hexanes). IR (film) 3383, 3076, 2918, 1718, 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J*= 8.8 Hz, 2H), 7.09 (s, 1H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.89 (s, 2H), 5.94 (d, *J* = 6.4 Hz, 1H), 4.97 (d, *J* =4.0 Hz, 1H), 3.80 (s, 3H), 2.14 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 202.7, 160.0, 146.4, 132.8, 132.2 (q, *J* = 33.1 Hz), 128.8, 123.4 (q, *J* = 270.9 Hz), 115.0, 114.2, 110.5 (q, *J* = 3.8 Hz), 66.6, 55.6, 26.5; Anal Calcd for $C_{18}H_{15}F_6NO_2$: C, 55.25; H, 3.86; N, 3.58; Found: C, 55.12; H, 3.92; N, 3.67.

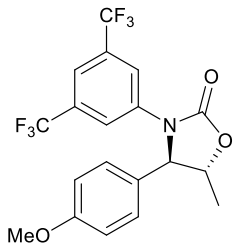


4.106 + 4.107

Syn and anti 1-[3,5-Bis(trifluoromethyl)phenylamino]-1-phenyl-2-propanol (4.106 and 4.107) An oven dried round bottom flask was charged with 0.050 g (0.085 mmol, 1 equiv) amines **4.103** and **4.104** (~1:1 mixture), 0.033 g (0.255 mmol, 3 equiv) anhydrous $NiCl_2$, 0.6 mL THF, and put under an atmosphere of argon. The reaction was cooled to -78 °C. Once cooled, 0.25 mL of $LiAlH_4$ (0.1 M in THF, 0.255 mmol, 3 equiv) was added dropwise. The reaction was warmed to room temperature and let stir for 16 h. Then, the reaction was cooled to 0 °C in an ice bath. Once cooled the reaction was diluted with ether (1 mL). Then 0.01 mL water, 0.01 mL 15% NaOH, and 0.03 mL water was added slowly. The reaction was warmed to room temperature and let stir for 15 minutes. After 15 minutes magnesium sulfate was added and let stir at room temperature for an addition 15 minutes. The reaction mixture was filtered and concentrated. The residue was purified by silica column (0 to 5% MeOH/ 100 to 95% DCM) to provide 15 mg of the alcohols **4.106** and **4.107** as a yellow oil (45 % yield).

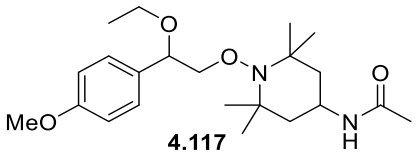
4.106 and 4.107 (~1:1 mixture). Yellow oil. TLC R_f = 0.71 (5% methanol/ 95% DCM); IR (film) 3390, 2973, 1612, 1510, 1274, 683 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.18-7.15 (m, 5H), 7.02 (d, *J* = 13.6 Hz, 2H), 6.85-6.80 (m, 9H), 4.22 (d, *J* = 3.2 Hz, 1H) 4.13-4.09 (m, 2H), 3.98 (p, *J* = 5.6 Hz, 1H) 3.72-3.71 (m, 6H), 1.22 (d, *J* = 6.3 Hz, 3H) 1.07 (d, *J* = 6.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.5, 159.4, 147.6, 132.4, 132.3, 132.1, 132.0, 130.4, 128.8, 128.6, 127.9, 124.8, 122.1, 114.5, 114.3, 114.2, 113.8, 113.2, 112.8, 110.9, 71.1, 70.3, 63.6, 62.2, 55.3, 55.3,

50.1, 20.3, 20.0. Anal Calcd for $C_{18}H_{17}F_6NO_2$: C, 54.97; H, 4.36; N, 3.56; Found: C, 55.10; H, 4.69; N, 3.30



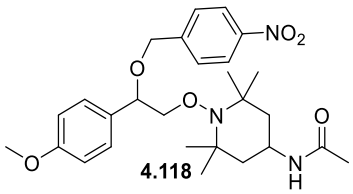
4.110

***trans*-3-[3,5-Bis(trifluoromethyl)phenyl]-5-methyl-4-phenyl-1,3-oxazolidin-2-one (4.108)** To an oven-dried round bottom flask carbonyldiimidazole (0.062 g, 0.381 mmol) and DMAP (0.015 g, 0.127 mmol) were added. The flask was put under an atmosphere of argon a solution of amino-alcohols **4.106** and **4.107** (0.100 g, 0.254 mmol) in 7.0 mL anhydrous DMF was added via syringe. The reaction mixture was stirred at room temperature for 72 hours. After 72 hours, the reaction was diluted with ethyl acetate, washed with water, and dried over sodium sulfate. The residue was purified by silica column chromatography (dry loaded, 5-25% ethyl acetate/hexanes) to provide 76 mg of product as a white solid. The diastereomers were purified by HPLC (3% isopropanol/97% hexanes, normal phase preparative silica gel column, t_R = 10 min) to provide pure oxazolidinone **4.108**. Yield: 72%. White solid. mp = 162-164 °C. TLC R_f = 0.46 (20% EA/ 80% hexanes); IR (film) 3071, 2939, 2844, 1753, 1515, 1395, 1105, 698 cm^{-1}; ^1H NMR (400 MHz, CD_3CN) δ 7.97 (s, 2H), 7.68 (s, 1H), 7.40-7.38 (m, 2H), 6.94-6.92 (m, 2H), 5.21 (d, J = 7.0 Hz, 1H), 4.55 (p, J = 7.0 Hz, 1H), 3.76 (s, 3H), 1.55 (d, J = 6.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.4, 154.8, 138.8, 132.1 (q, J= 34.2 Hz), 127.7, 127.6, 122.9 (q, J = 271.6 Hz), 120.2, 117.6, 115.1, 79.1, 67.3, 55.3, 19.2. Anal Calcd for $C_{19}H_{15}F_6NO_3$: C, 54.42; H, 3.61; N, 3.34; Found: C, 54.42; H, 3.52; N, 3.27.



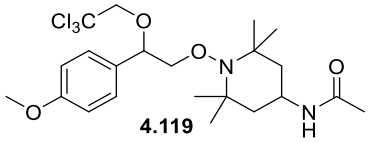
4.117

Ether 4.117. To an oven dried test tube 4-methoxystyrene (**4.30**, 0.030 g, 0.222 mmol) and ethanol (**4.116**, 0.020 g, 0.444 mmol) were added. The test tube was put under an atmosphere of argon and 1 mL of anhydrous acetonitrile was added. The reaction was stirred for 5 min, then oxoammonium salt **4.2** (0.10 g, 0.333 mmol) was added. The reaction was stirred at room temperature for 16 h. The reaction was quenched with saturated aqueous sodium bicarbonate solution and extracted with DCM. The organic layers were combined, dried over sodium sulfate, and concentrated. The residue was purified by silica column chromatography to provide 0.057 g **4.117** as a solid. Yield: 62%. mp = 45-47 °C; TLC R_f = 0.48 (100% EA); IR (film) 3269, 3070, 2929, 16.53, 1509, 1243 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, *J*=8.8 Hz, 2H), 6.79 (d, *J*= 8.8 Hz, 2H), 5.17 (d, *J*= 7.3 Hz, 1H), 4.38 (t, *J*= 6.0 Hz, 1H), 4.13-4.07 (m, 1H), 3.99 (dd, *J*= 7.4, 9.0 Hz, 1H), 3.89-3.75 (m, 4H), 3.46 (qd, *J*= 2.3, 7.0 Hz, 2H), 1.93 (s, 3H), 1.75-1.70 (m, 3H), 1.28-1.24 (m, 3H), 1.21 (s, 3H), 1.19-1.18 (m, 4H), 1.10 (s, 3H), 1.00 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.3, 159.0, 127.9, 127.5, 113.8, 113.7, 113.6, 81.4, 79.7, 72.4, 64.6, 55.3, 55.2, 45.7, 41.0, 40.9, 33.0, 32.7, 23.5, 20.8, 20.7, 15.4; Anal calcd for $C_{22}H_{36}N_2O_4$: C, 67.32; H, 9.24; N, 7.14. Found: C, 67.58; H, 9.08; N, 7.14.



4.118

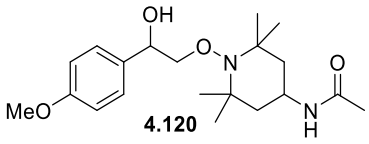
Ether 4.118. To an oven dried test tube 4-methoxystyrene (**4.30**, 0.037 g, 0.222 mmol) and 2-nitrobenzyl alcohol (0.068 g, 0.444 mmol) were added. The test tube was put under an atmosphere of argon and 1 mL of anhydrous acetonitrile was added. The reaction was stirred for 5 minutes, then oxoammonium salt **4.2** (0.10 g, 0.333 mmol) was added. The reaction was stirred at room temperature for 16 hours. The reaction was quenched with saturated aqueous sodium bicarbonate solution and extracted with DCM. The organic layers were combined, dried over sodium sulfate, and concentrated. The residue was purified by silica column chromatography to provide 0.041 g **4.118** as an oil. Yield: 37%; TLC R_f = 0.42 (100% EA); IR (neat) 3281, 3075, 2971, 2932, 1651, 1510, 1243 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J*=8.6 Hz, 2H), 7.54 (d, *J*= 8.6 Hz, 2H), 7.30 (d, *J*= 8.3, 2H), 6.87 (d, *J*=8.3, 2H), 5.19 (s, 1H), 4.87 (dd, *J*= 8.3, 4.0 Hz, 1H), 4.13-4.07 (m, 2H), 3.89-3.81 (m, 3H), 3.80 (s, 3H), 1.93 (s, 3H), 1.79-1.75 (m, 4H), 1.21 (s, 3H), 1.16 (s, 6H), 1.07 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.3. 159.2, 132.6, 130.3, 128.9, 128.2, 127.8, 127.5, 127.4, 123.6, 113.9, 113.7, 81.9, 81.4, 72.4, 69.3, 55.3, 45.7, 40.9, 32.8, 23.6, 20.8, 20.7; Anal calcd for $C_{27}H_{37}N_3O_6$: C, 64.91; H, 7.47; N, 8.41. Found: C, 64.83; H, 7.47; N, 8.01.



4.119

Ether 4.119. To an oven dried test tube 4-methoxystyrene (**4.30**, 0.030 g, 0.222 mmol) and 2,2,2-trichloroethanol (0.020 g, 0.444 mmol) were added. The test tube was put under an atmosphere of argon and 1 mL of anhydrous acetonitrile was added. The reaction was stirred for 5 minutes, then

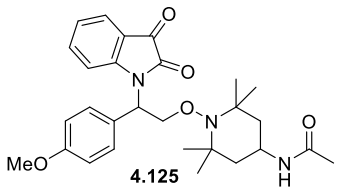
oxoammonium salt **4.2** (0.10 g, 0.333 mmol) was added. The reaction was stirred at room temperature for 16 hours. The reaction was quenched with saturated aqueous sodium bicarbonate solution and extracted with DCM. The organic layers were combined, dried over sodium sulfate, and concentrated. The residue was purified by silica column chromatography to provide 0.057 g **4.119** as a solid. Yield: 19%. Mp= 80-82 °C; TLC R_f = 0.43 (100% EA); IR (film) 3279, 2923, 1648, 1510, 1243 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J*=8.7 Hz, 2H), 6.87 (d, *J*= 8.7 Hz, 2H), 5.17 (bs, 1H), 4.87 (dd, *J*= 8.8, 3.5 Hz, 1H), 4.15-4.07 (m, 2H), 3.91-3.82 (m, 4H), 3.80 (s, 3H), 1.94 (s, 3H), 1.87-1.76 (m, 6H), 1.22 (s, 6H), 1.16 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.4, 159.2, 132.6, 130.3, 128.9, 127.5, 113.8, 113.7, 113.6, 81.9, 72.4, 55.5, 55.3, 55.2, 45.7, 40.9, 32.9, 29.7, 23.5, 20.8, 20.7; Anal calcd for $C_{22}H_{33}Cl_3N_2O_4$: C, 53.29; H, 6.71; N, 5.65. Found: C, 53.60; H, 6.86; N, 5.57.



4.120

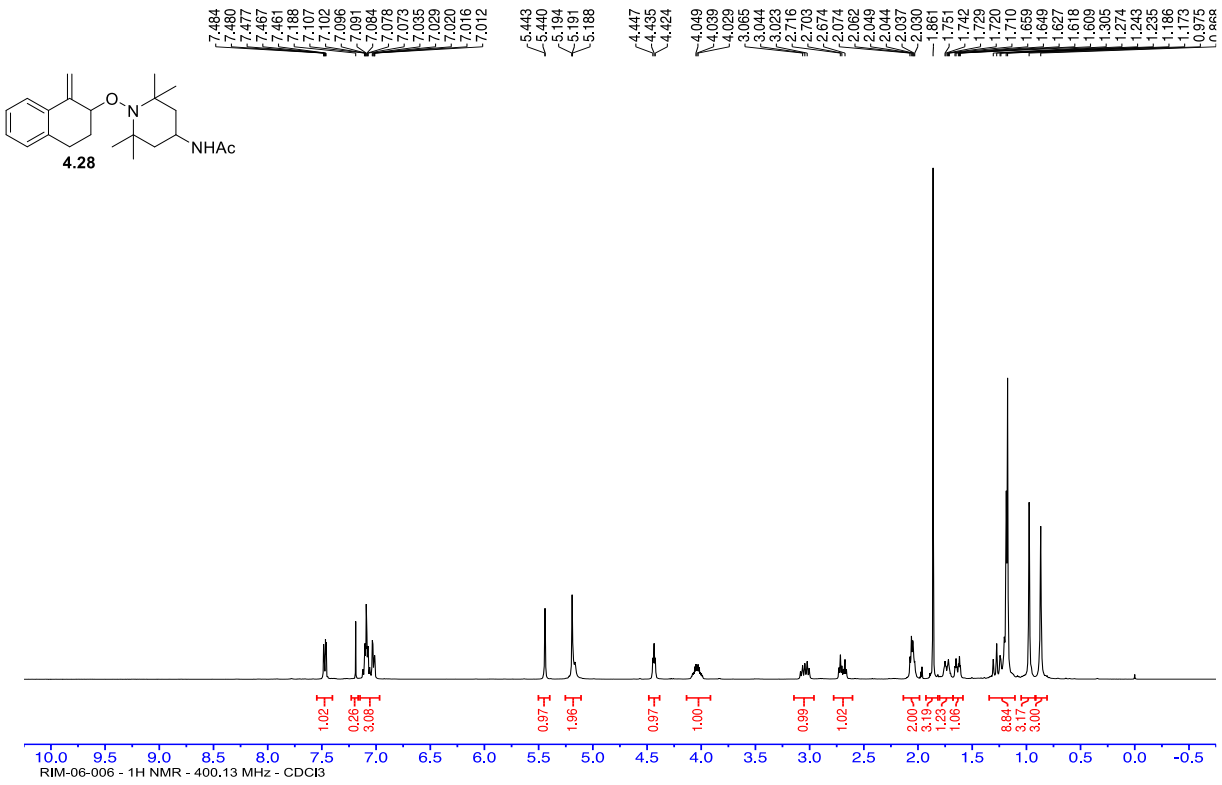
Alcohol 4.120. To an oven dried test tube 4-methoxystyrene (**4.30**, 0.037 g, 0.333 mmol) and water (0.120 g, 6.66 mmol) were added. The test tube was put under an atmosphere of argon and 3.3 mL of ethyl acetate was added. The reaction was stirred for 5 minutes, then oxoammonium salt **4.2** (0.10 g, 0.333 mmol) was added. The reaction was stirred at room temperature for 16 hours. The reaction was quenched with saturated aqueous sodium bicarbonate solution and extracted with DCM. The organic layers were combined, dried over sodium sulfate, and concentrated. The residue was purified by silica column chromatography to provide 0.073 g **4.120** as an oil. Yield: 60%. TLC R_f = 0.40 (10% EtOAc/90% hexanes); IR (neat) 3278, 3078, 2925, 1648, 1511, 1243 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J*=8.6 Hz, 2H), 6.87 (d, *J*= 8.6 Hz, 2H), 5.40 (bs, 1H), 4.86

(dd, *J*= 8.1, 3.3 Hz, 1H), 4.14-4.09 (m, 3H), 3.91-3.81 (m, 3H), 3.79 (s, 3H), 2.81 (bs, 1H), 1.93 (s, 3H), 1.77-1.70 (m, 2H), 1.32-1.29 (m, 2H), 1.20 (s, 6H), 1.15 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 169.3, 159.2, 132.6, 129.1, 127.5, 126.9, 113.7, 81.9, 72.3, 60.3, 55.3, 45.7, 40.9, 32.9, 29.7, 23.5, 20.8, 20.7; Anal calcd for $C_{20}H_{32}N_2O_4$: C, 65.41; H, 8.85; N, 7.69. Found: C, 65.53; H, 8.76; N, 7.63.



4.125

Isatin 4.125. To an oven dried test tube 4-methoxystyrene (**4.30**, 0.037 g, 0.278 mmol), isatin (0.040 g, 0.278 mmol), and potassium carbonate (0.046 g, 0.333 mmol) were added. The test tube was put under an atmosphere of argon and 1 mL of anhydrous acetonitrile was added. The reaction was stirred for 5 minutes, then oxoammonium salt **4.2** (0.10 g, 0.333 mmol) was added. The reaction was stirred at room temperature for 18 hours. The reaction was quenched with saturated aqueous sodium bicarbonate solution and extracted with DCM. The organic layers were combined, dried over sodium sulfate, and concentrated. The residue was purified by silica column chromatography to provide 0.063 g **4.125** as a yellow solid. Yield: 44%. mp = 77-80 °C; TLC R_f = 0.36 (100% EA); IR (neat) 3279, 3077, 2971, 2931, 1651, 1611, 1510, 1243 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.27 (m, 3H), 7.21-7.16 (m, 1H), 6.92-6.79 (m, 4H), 5.48 (bs, 1H), 4.86 (dd, *J*= 8.4, 3.6 Hz, 1H) 4.14-4.09 (m, 2H), 3.91-3.80 (m, 4H), 3.79 (s, 3H) 1.92 (s, 3H), 1.25 (s, 3H), 1.21 (s, 3H), 1.20 (s, 6H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 169.3, 159.2, 132.6, 130.4, 129.11,128.9, 127.5, 126.9, 113.8, 113.7, 81.9, 72.4, 60.3, 55.5, 55.3, 45.7, 40.9, 32.9, 23.6, 20.8, 20.7; Anal calcd for $C_{28}H_{35}N_3O_5$: C, 68.13; H, 7.15; N, 8.51. Found: C, 68.03; H, 7.20; N, 8.56.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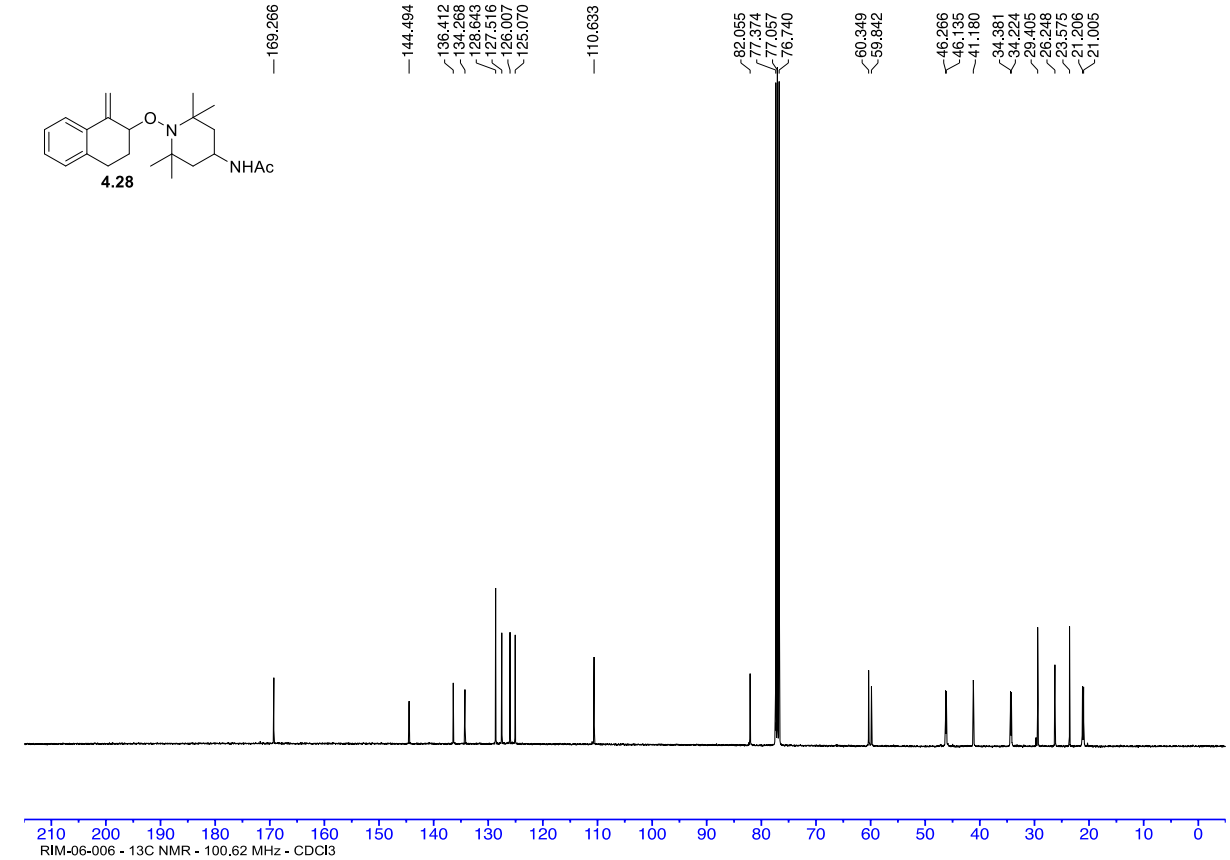
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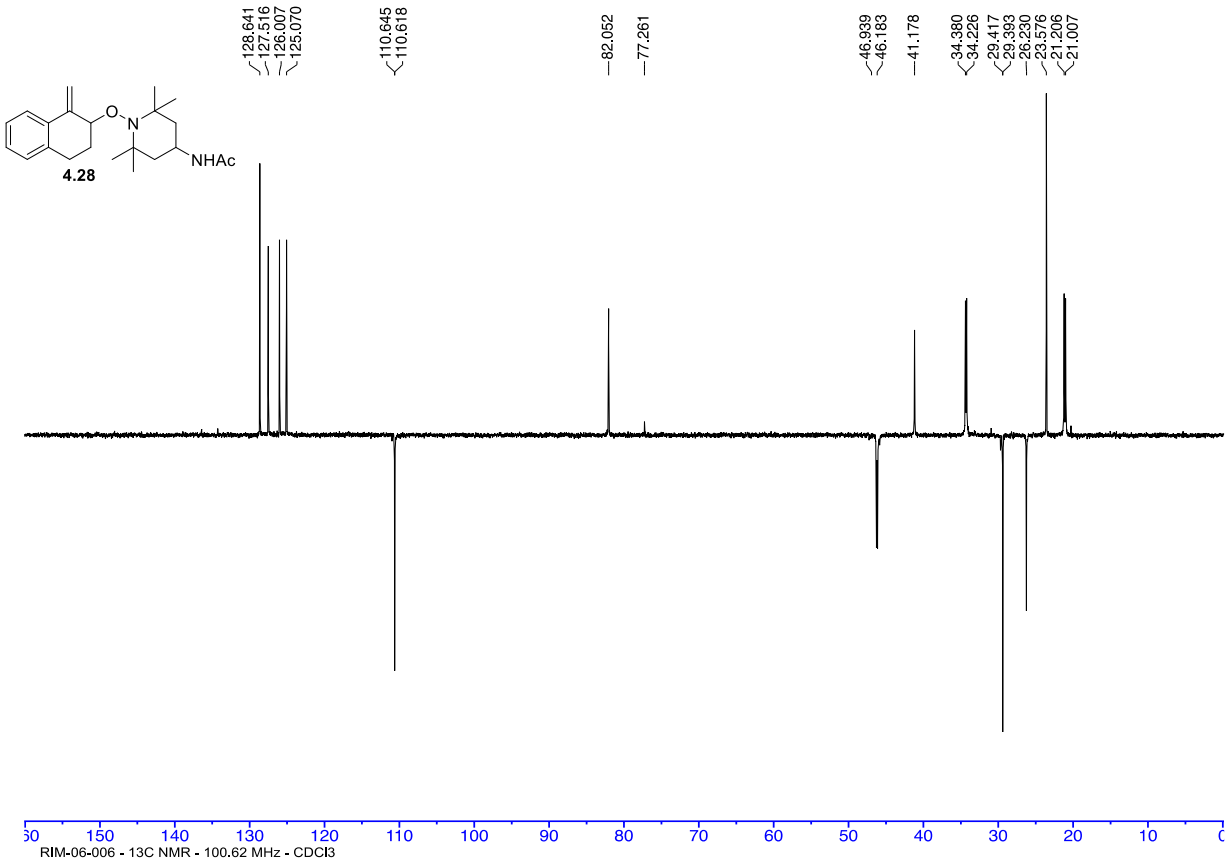
82.055
77.374
77.057
76.740
60.349
59.842
46.266
46.135
41.180
34.381
34.224
29.405
26.248
23.575
21.206
21.005
O
N
NHAc
4.28
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
RIM-06-006 - 13C NMR - 100.62 MHz - CDCl3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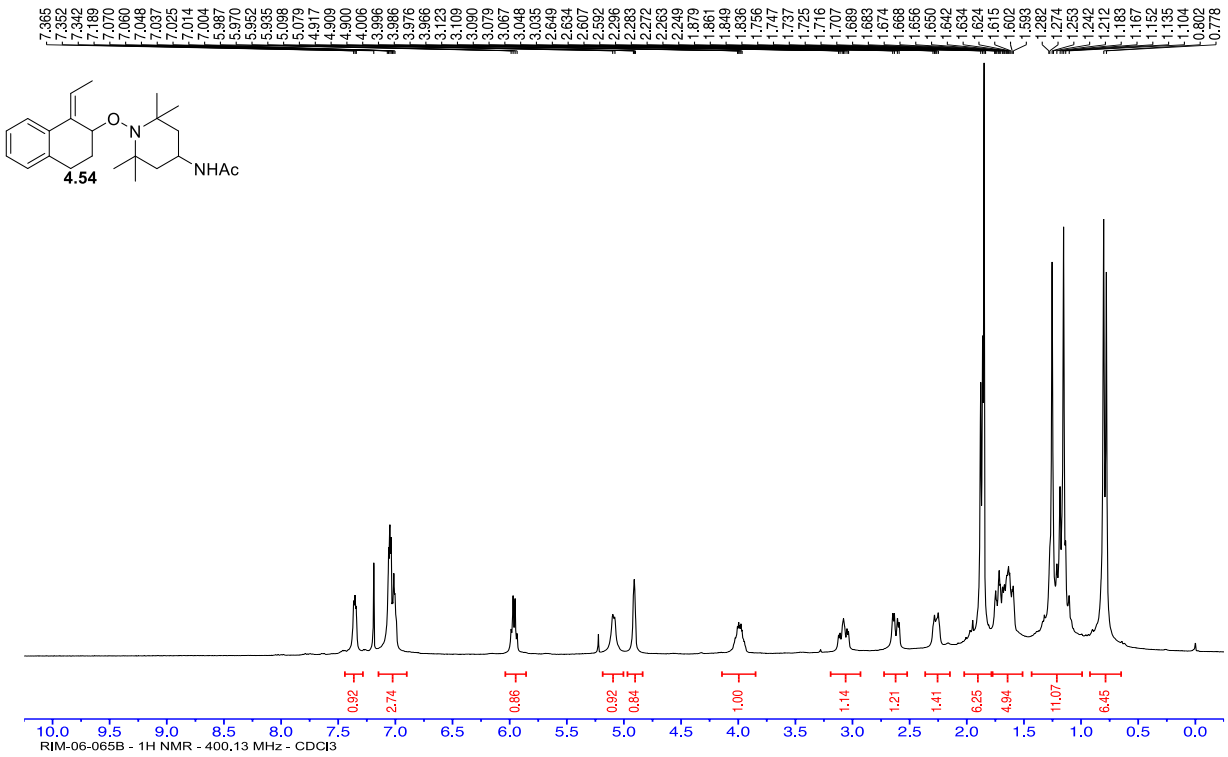
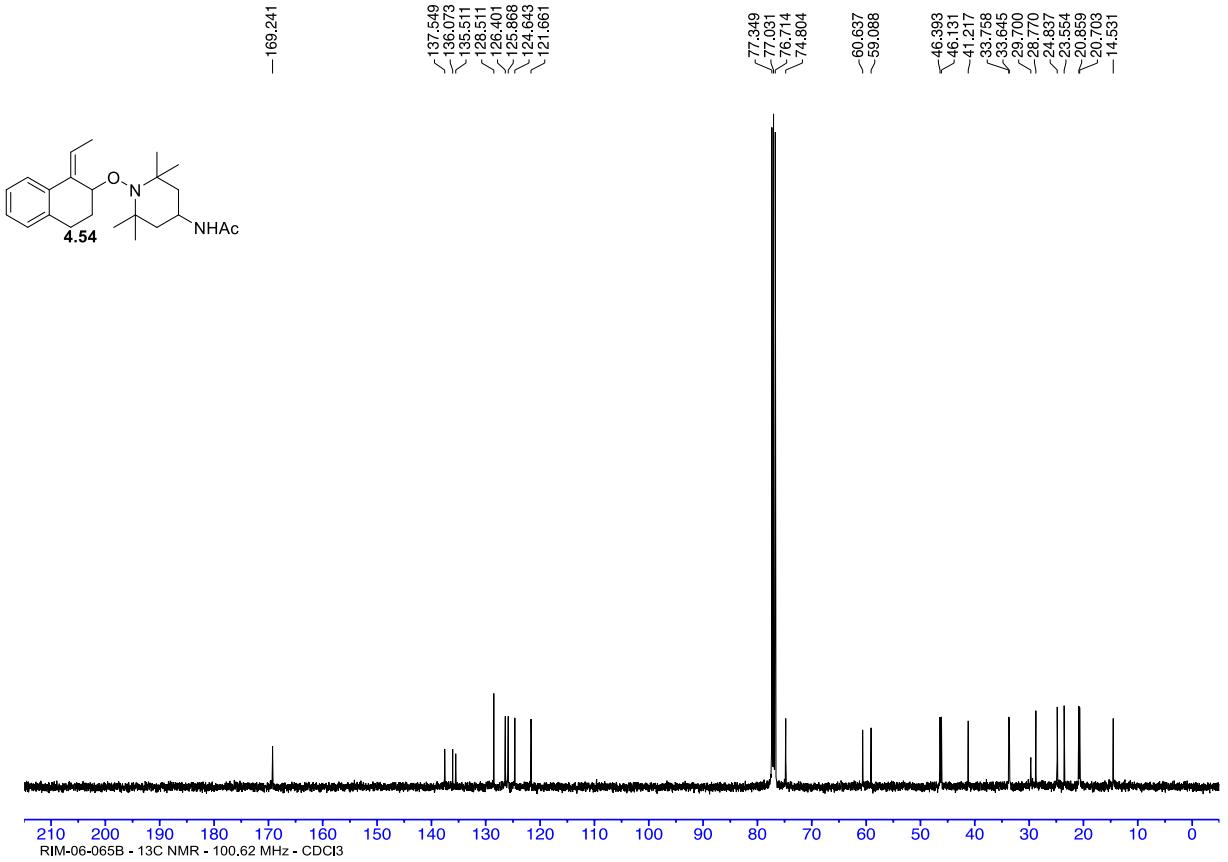
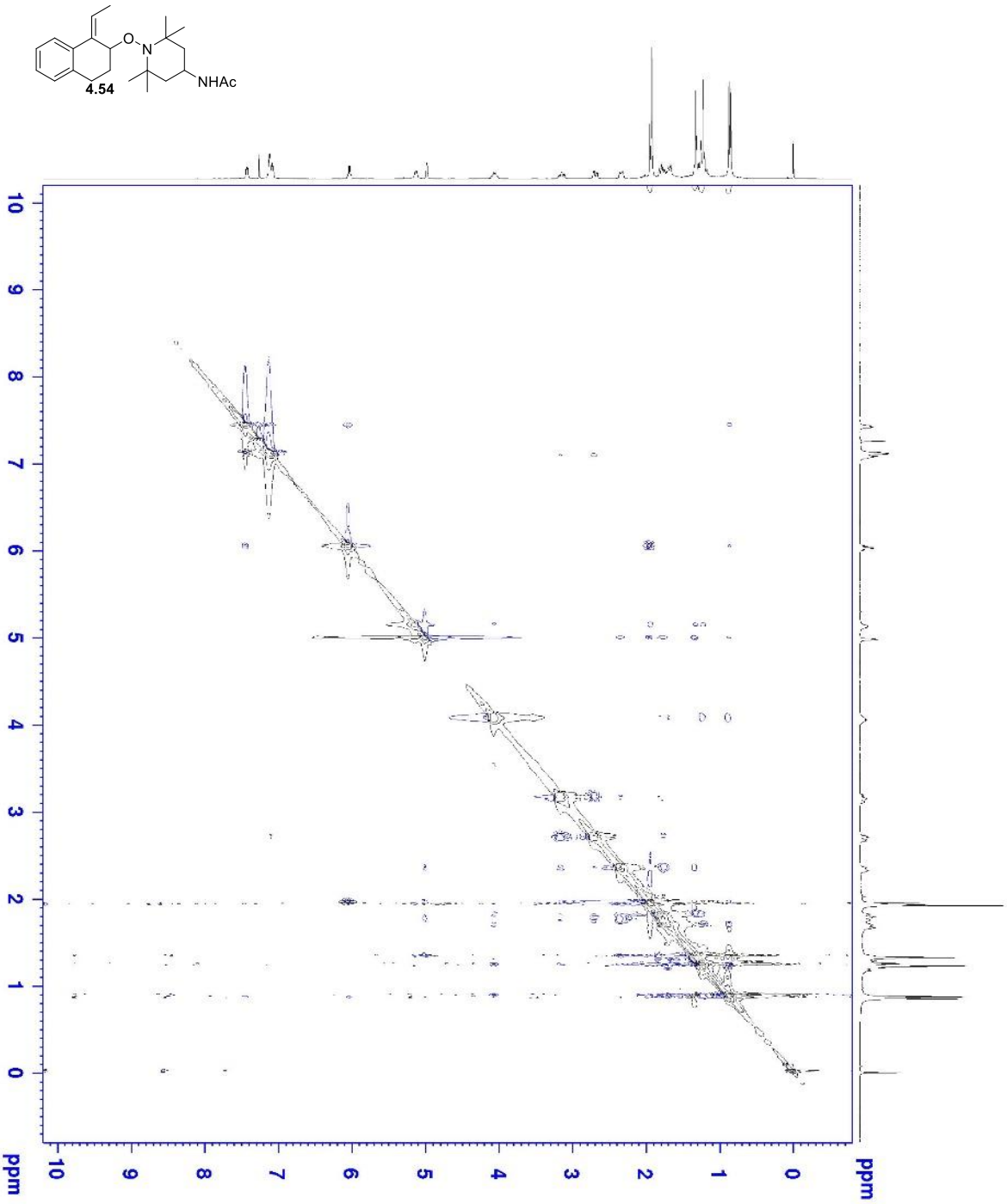
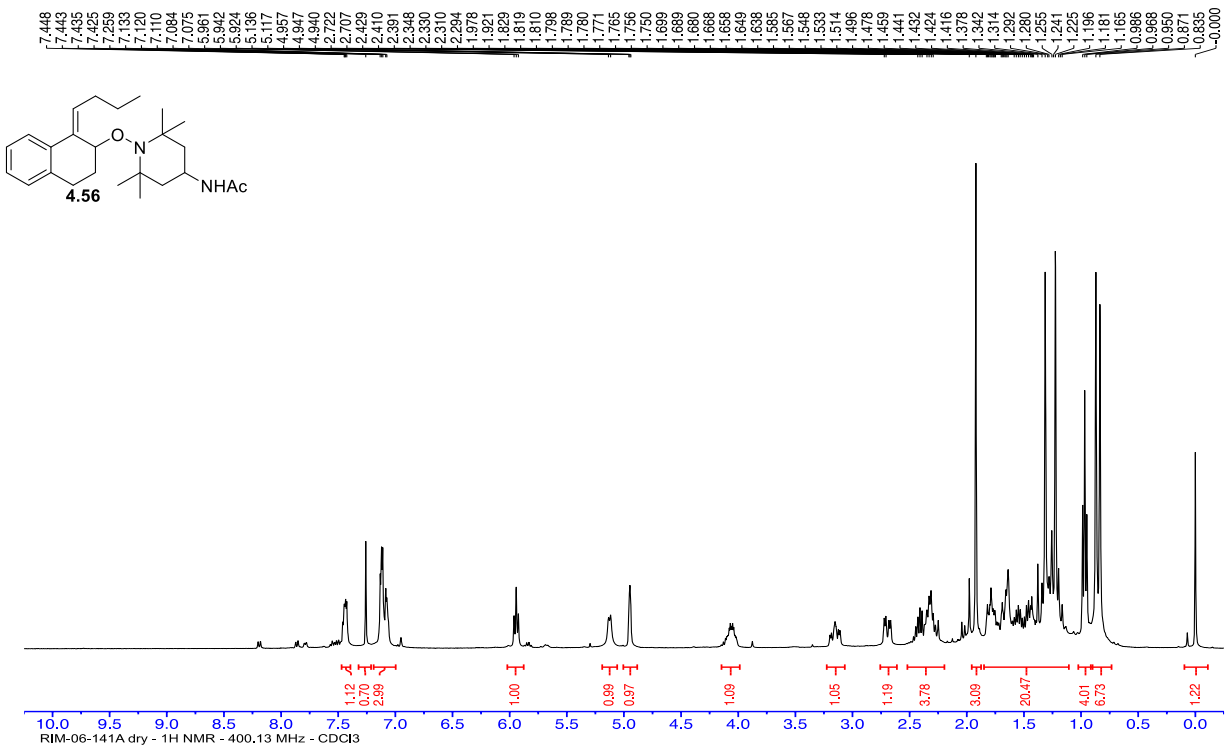
127.516
126.007
125.070
110.645
110.618
82.052
77.261
46.939
46.183
41.178
34.380
34.226
29.417
29.393
26.230
23.576
21.206
21.007
O
N
NHAc
4.28
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
RIM-06-006 - 13C NMR - 100.62 MHz - CDCl3


7.365
7.352
7.342
7.189
7.070
7.060
7.048
7.037
7.025
7.014
7.004
5.987
5.970
5.952
5.935
5.098
5.079
4.917
4.909
4.900
4.006
3.996
3.986
3.976
3.966
3.123
3.109
3.090
3.079
3.067
3.048
3.035
2.649
2.634
2.607
2.592
2.296
2.283
2.272
2.263
2.249
1.879
1.861
1.849
1.836
1.756
1.747
1.737
1.725
1.716
1.707
1.689
1.683
1.674
1.668
1.656
1.650
1.642
1.634
1.624
1.615
1.602
1.593
1.282
1.274
1.253
1.242
1.212
1.183
1.167
1.152
1.135
1.104
0.802
0.778
O
N
NHAc
4.54
0.92
2.74
0.86
0.92
0.84
1.00
1.14
1.21
1.41
6.25
4.94
11.07
6.45
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
RIM-06-065B - 1H NMR - 400.13 MHz - CDCl3


169.241
137.549
136.073
135.511
128.511
126.401
125.868
124.643
121.661
77.349
77.031
76.714
74.804
60.637
59.088
46.393
46.131
41.217
33.758
33.645
29.700
28.770
24.837
23.554
20.859
20.703
14.531
O
N
NHAc
4.54
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
RIM-06-065B - 13C NMR - 100.62 MHz - CDCl3

NOESY spectra of Allylic Ether **4.56**

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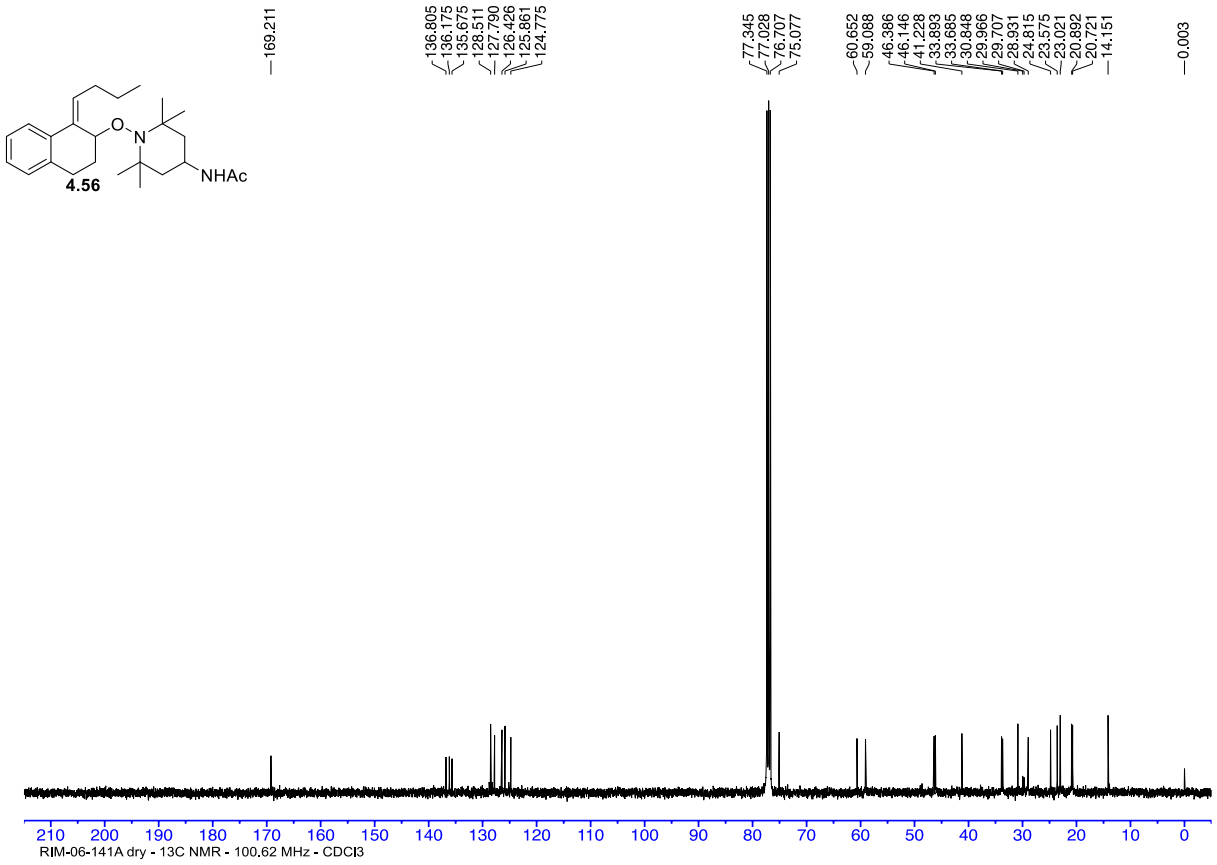
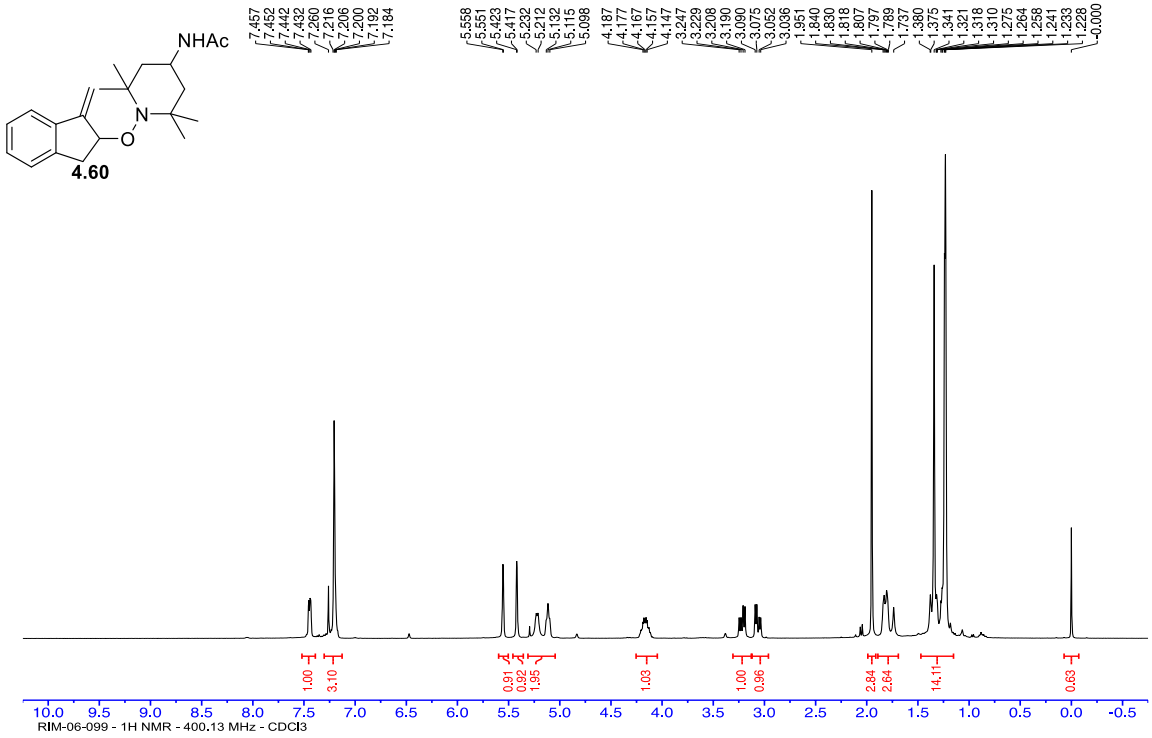
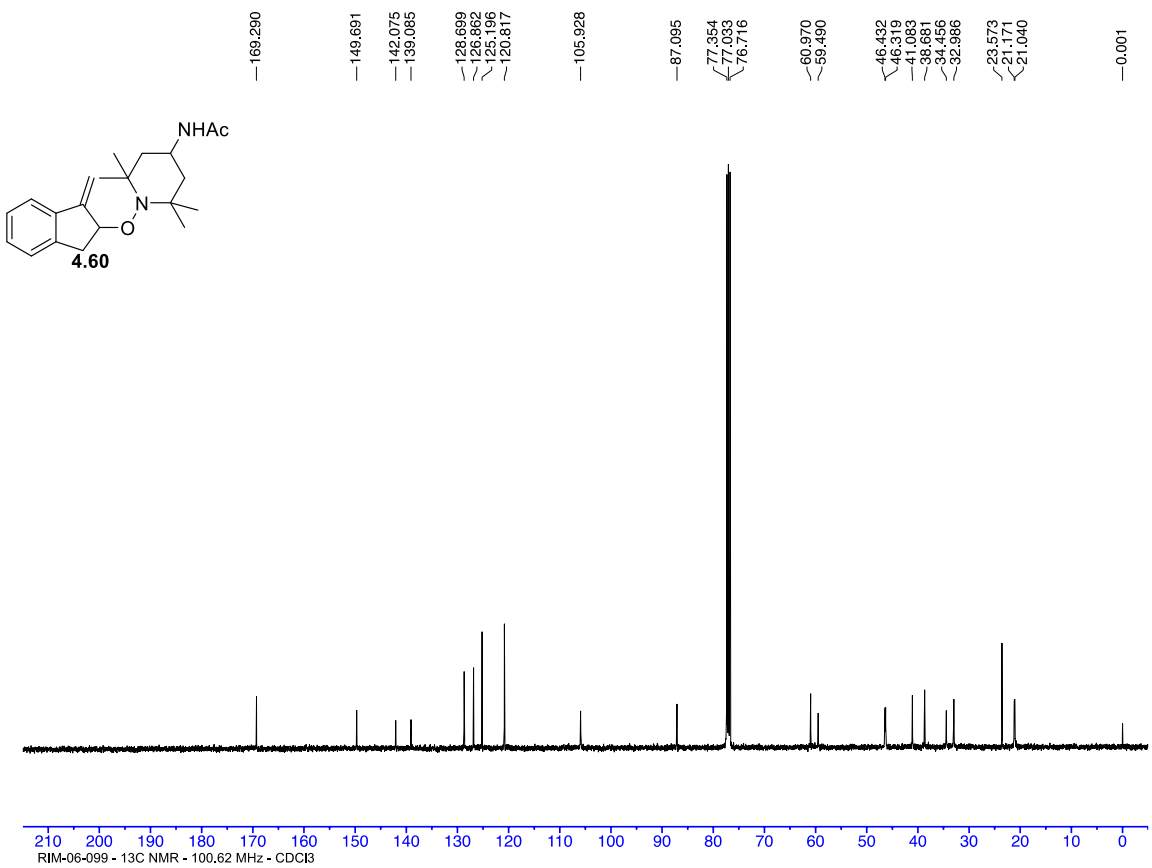
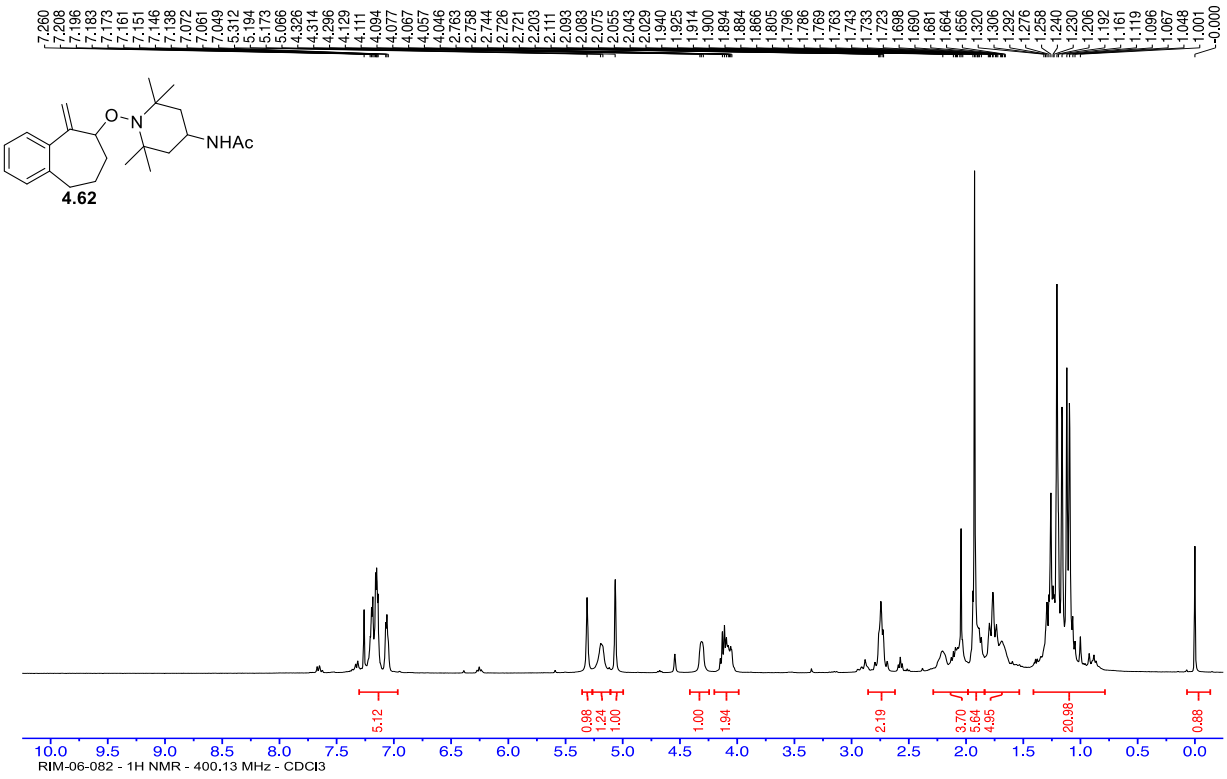
7.443
7.435
7.425
7.259
7.133
7.120
7.110
7.084
7.075
5.961
5.942
5.924
5.136
5.117
4.957
4.947
4.940
2.722
2.707
2.429
2.410
2.391
2.348
2.330
2.310
2.294
1.978
1.921
1.829
1.819
1.810
1.798
1.789
1.780
1.771
1.765
1.756
1.750
1.699
1.689
1.680
1.668
1.658
1.649
1.638
1.585
1.567
1.548
1.533
1.514
1.496
1.478
1.459
1.441
1.432
1.424
1.416
1.378
1.342
1.314
1.292
1.280
1.255
1.241
1.225
1.196
1.181
1.165
0.986
0.968
0.950
0.871
0.835
0.000
4.56
NHAc
1.12
0.70
2.99
1.00
0.99
0.97
1.09
1.05
1.19
3.78
3.09
20.47
4.01
6.73
1.22
RIM-06-141A dry - 1H NMR - 400.13 MHz - CDCl3

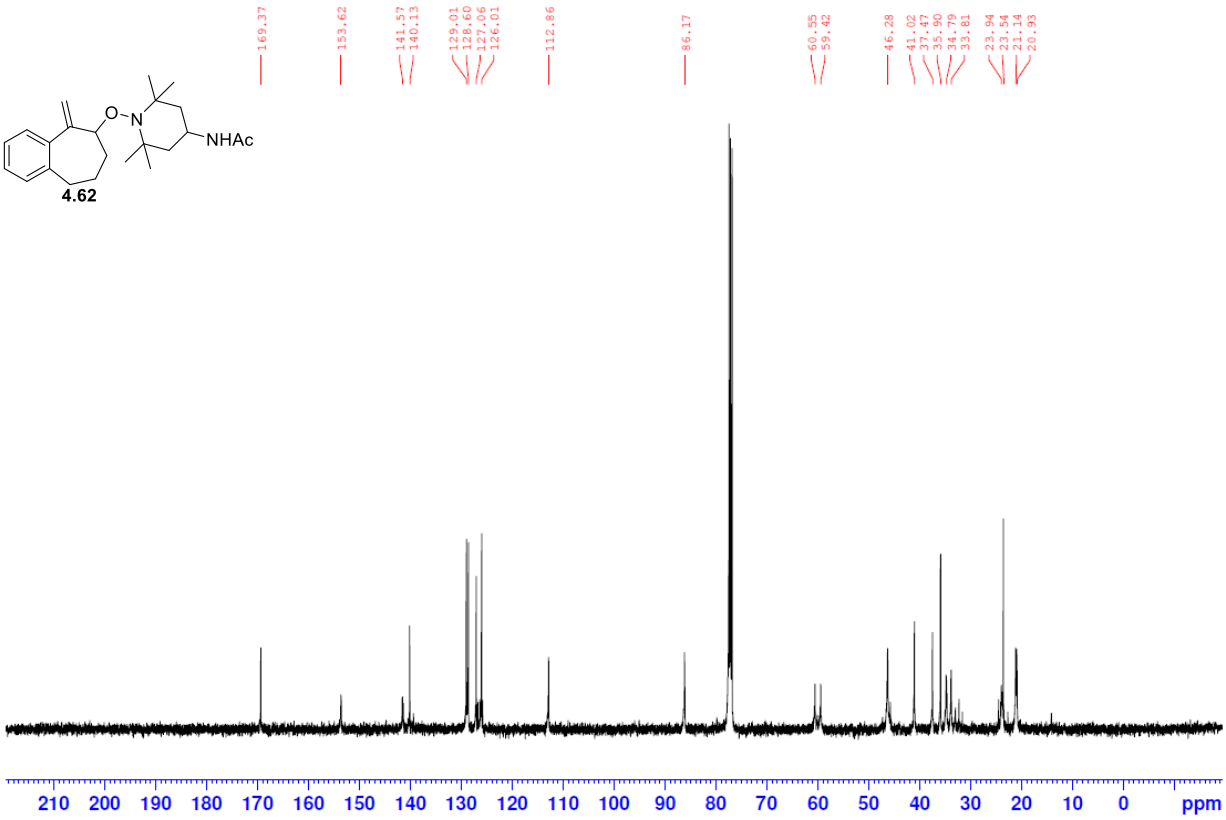

169.211
136.805
136.175
135.675
128.511
127.790
126.426
125.861
124.775
77.345
77.028
76.707
75.077
60.652
59.088
46.386
46.146
41.228
33.893
33.685
30.848
29.966
29.707
28.931
24.815
23.575
23.021
20.892
20.721
14.151
0.003
4.56
NHAc
RIM-06-141A dry - 13C NMR - 100.62 MHz - CDCl3

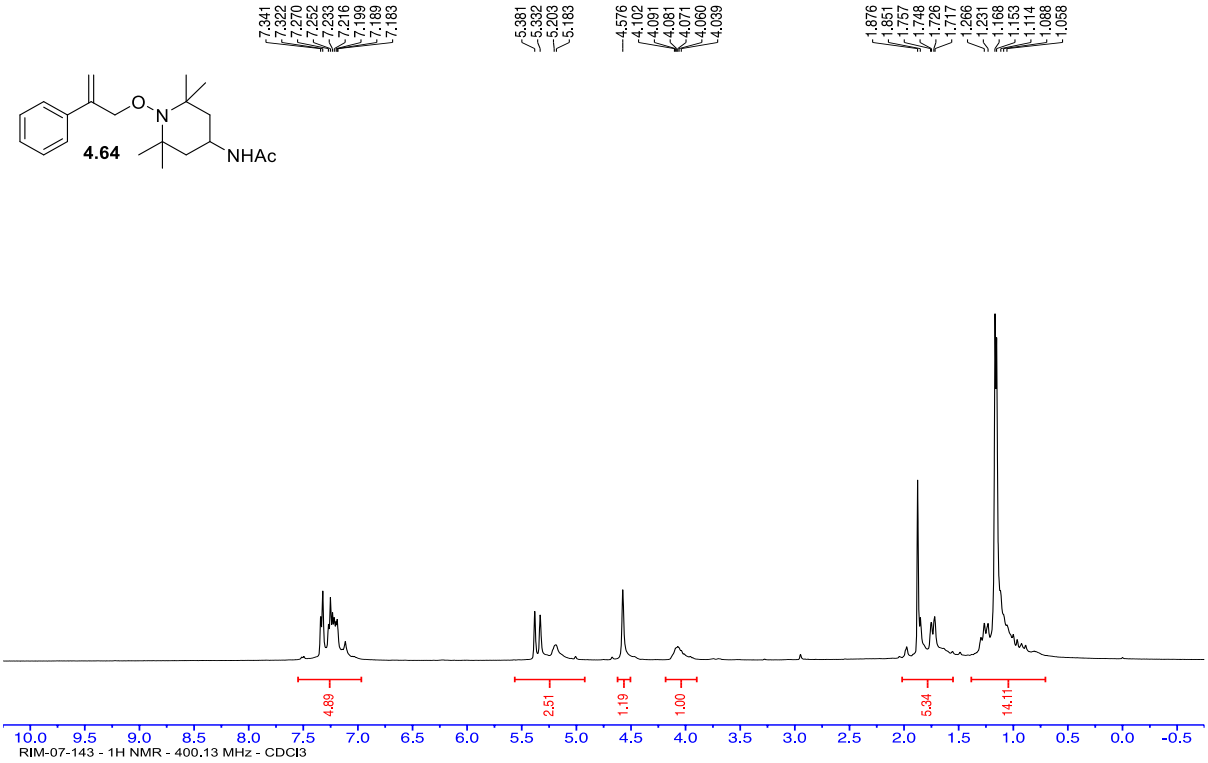

NHAc
N
O
4.60
7.457
7.452
7.442
7.432
7.260
7.216
7.206
7.200
7.192
7.184
5.558
5.551
5.423
5.417
5.232
5.212
5.132
5.115
5.098
4.187
4.177
4.167
4.157
4.147
3.247
3.229
3.208
3.190
3.090
3.075
3.052
3.036
1.951
1.840
1.830
1.818
1.807
1.797
1.789
1.737
1.380
1.375
1.341
1.321
1.318
1.310
1.275
1.264
1.258
1.241
1.233
1.228
-0.000
1.00
3.10
0.91
0.82
1.95
1.03
1.00
0.96
2.84
2.64
14.11
0.63
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
RIM-06-099 - 1H NMR - 400.13 MHz - CDCl3

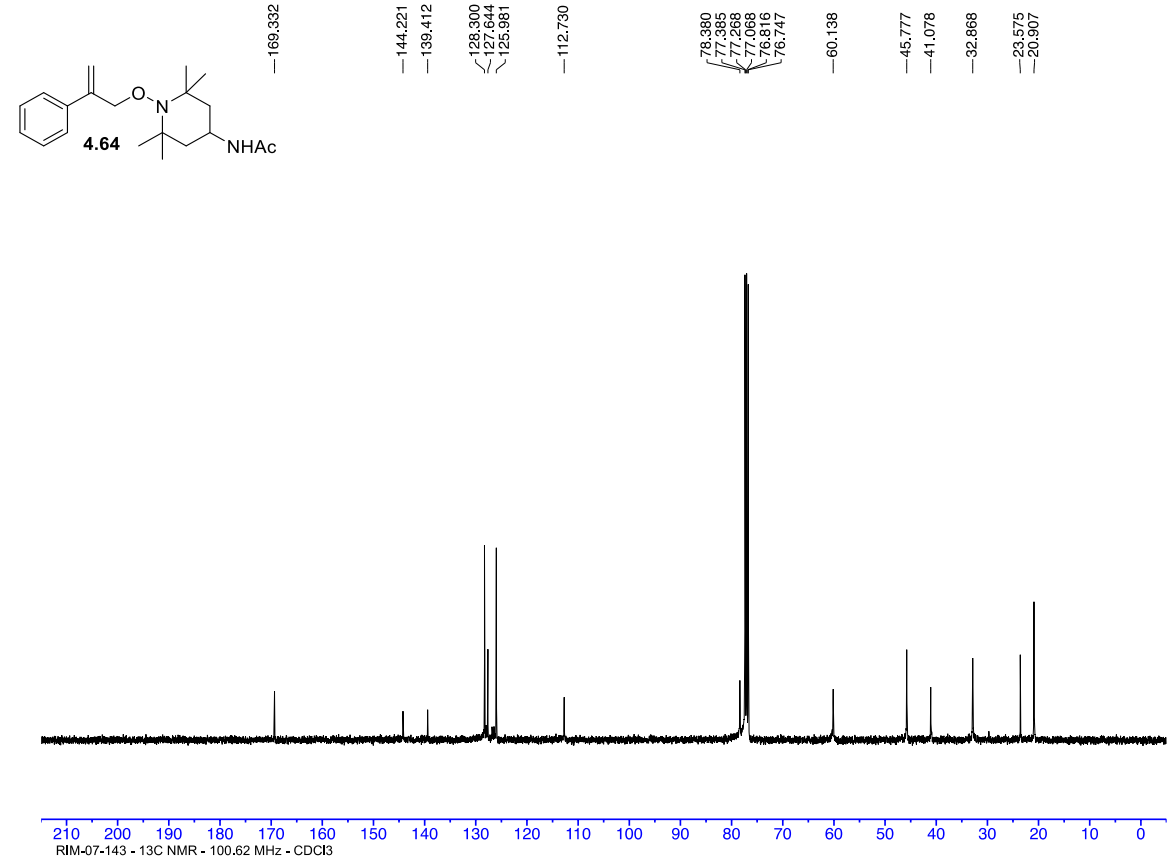

169.290
149.691
142.075
139.085
128.699
126.862
125.196
120.817
105.928
87.095
77.354
77.033
76.716
60.970
59.490
46.432
46.319
41.083
38.681
34.456
32.986
23.573
21.171
21.040
0.001
NHAc
N
O
4.60
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
RIM-06-099 - 13C NMR - 100.62 MHz - CDCl3

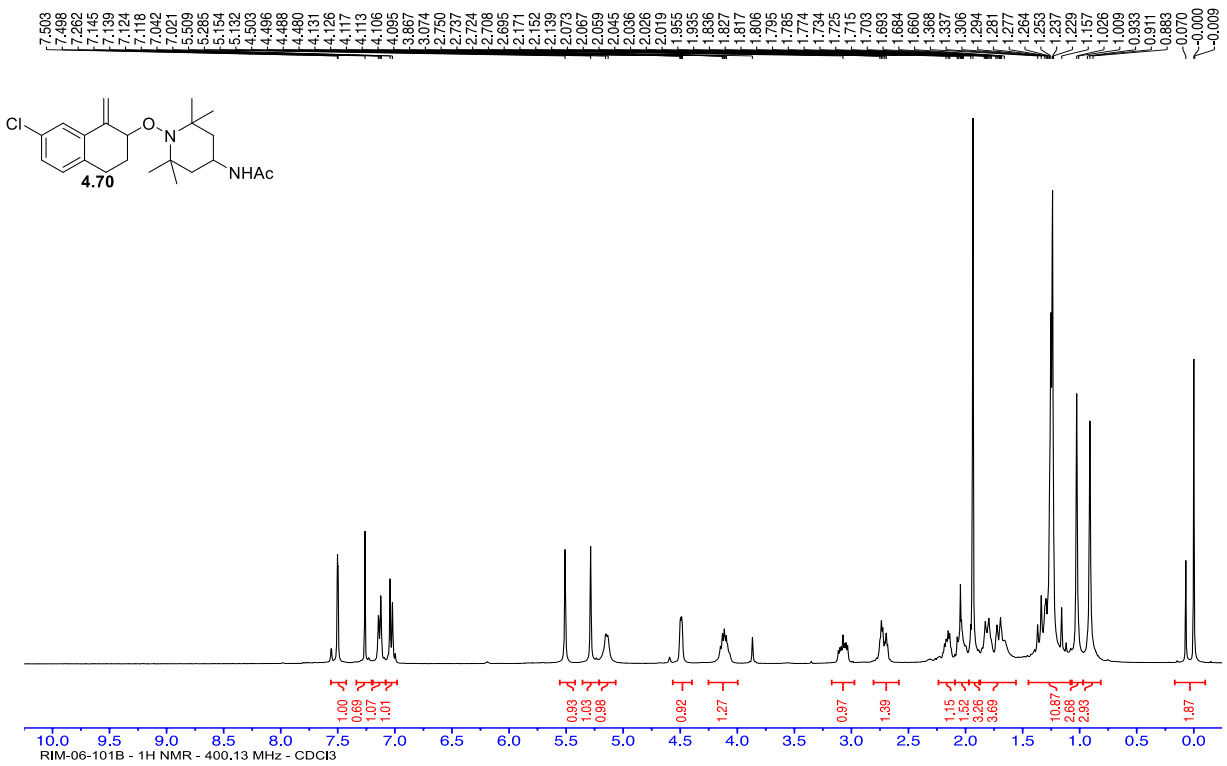


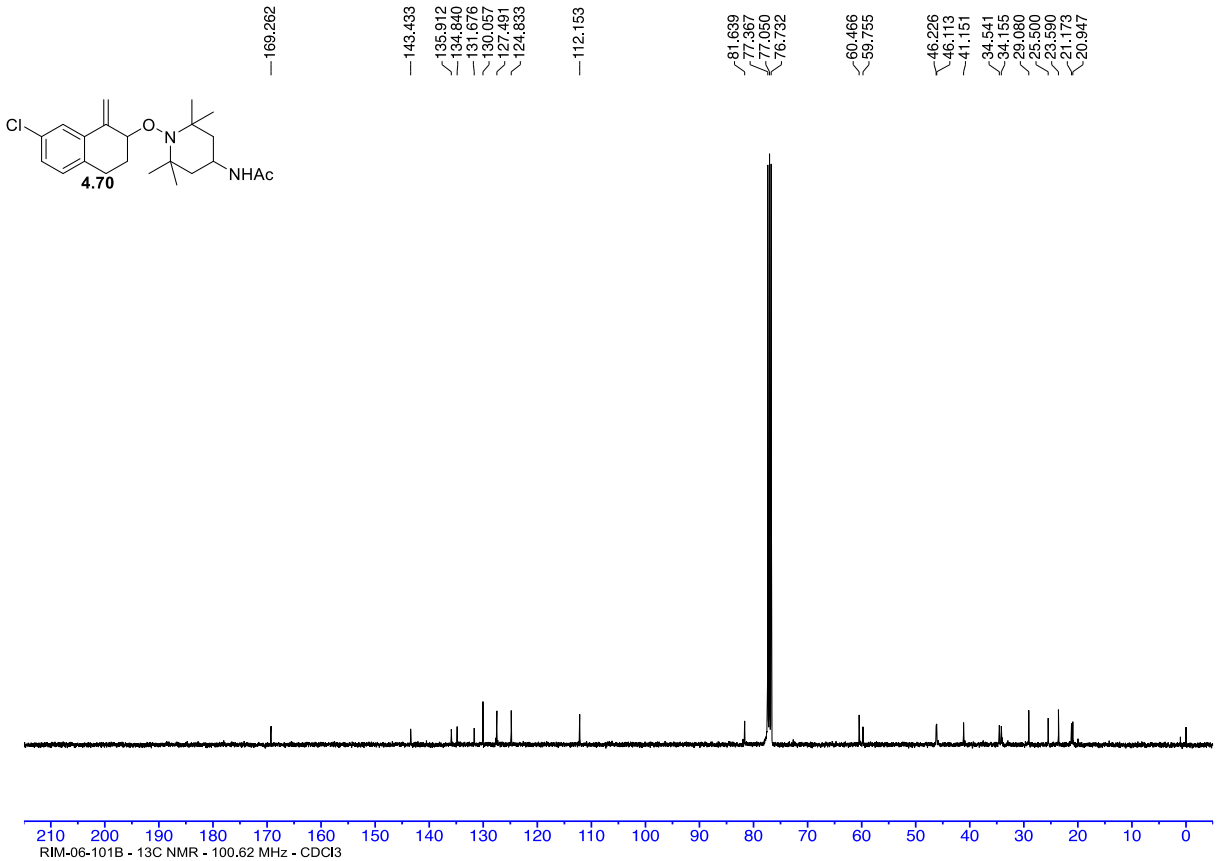
RA-2-115 recrystallized trial 2_7

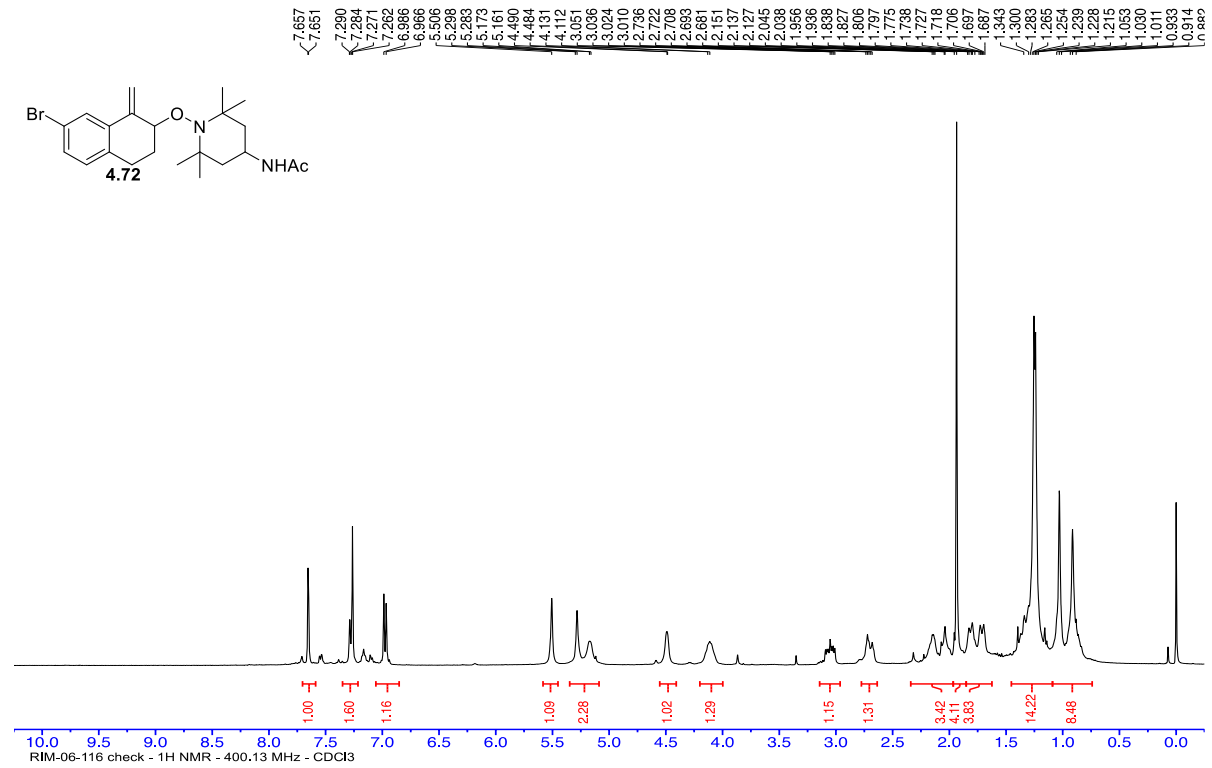



7.341
7.322
7.270
7.252
7.233
7.216
7.199
7.189
7.183
5.381
5.332
5.203
5.183
4.576
4.102
4.091
4.081
4.071
4.060
4.039
1.876
1.851
1.757
1.748
1.726
1.717
1.266
1.231
1.168
1.153
1.114
1.088
1.058
O
N
4.64
NHAc
4.89
2.51
1.19
1.00
5.34
14.11
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
RIM-07-143 - 1H NMR - 400.13 MHz - CDCl3


169.332
144.221
139.412
128.300
127.644
125.981
112.730
78.380
77.385
77.268
77.068
76.816
76.747
60.138
45.777
41.078
32.868
23.575
20.907
O
N
4.64
NHAc
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
RIM-07-143 - 13C NMR - 100.62 MHz - CDCl3


7.503
7.498
7.262
7.145
7.139
7.124
7.118
7.042
7.021
5.509
5.285
5.154
5.132
4.503
4.496
4.488
4.480
4.131
4.126
4.117
4.113
4.106
4.095
3.867
3.074
2.750
2.737
2.724
2.708
2.695
2.171
2.152
2.139
2.073
2.067
2.059
2.045
2.036
2.026
2.019
1.955
1.935
1.836
1.827
1.817
1.806
1.795
1.785
1.774
1.734
1.725
1.715
1.703
1.693
1.684
1.660
1.368
1.337
1.306
1.294
1.281
1.277
1.264
1.253
1.237
1.229
1.157
1.026
1.009
0.933
0.911
0.883
0.070
-0.000
-0.009
Cl
O
N
NHAc
4.70
1.00
0.69
1.07
1.01
0.93
1.03
0.98
0.92
1.27
0.97
1.39
1.15
1.52
3.26
3.69
10.87
2.68
2.93
1.87
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
RIM-06-101B - 1H NMR - 400.13 MHz - CDCl3


169.262
143.433
135.912
134.840
131.676
130.057
127.491
124.833
112.153
81.639
77.367
77.050
76.732
60.466
59.755
46.226
46.113
41.151
34.541
34.155
29.080
25.500
23.590
21.173
20.947
Cl
O
N
NHAc
4.70
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
RIM-06-101B - 13C NMR - 100.62 MHz - CDCl3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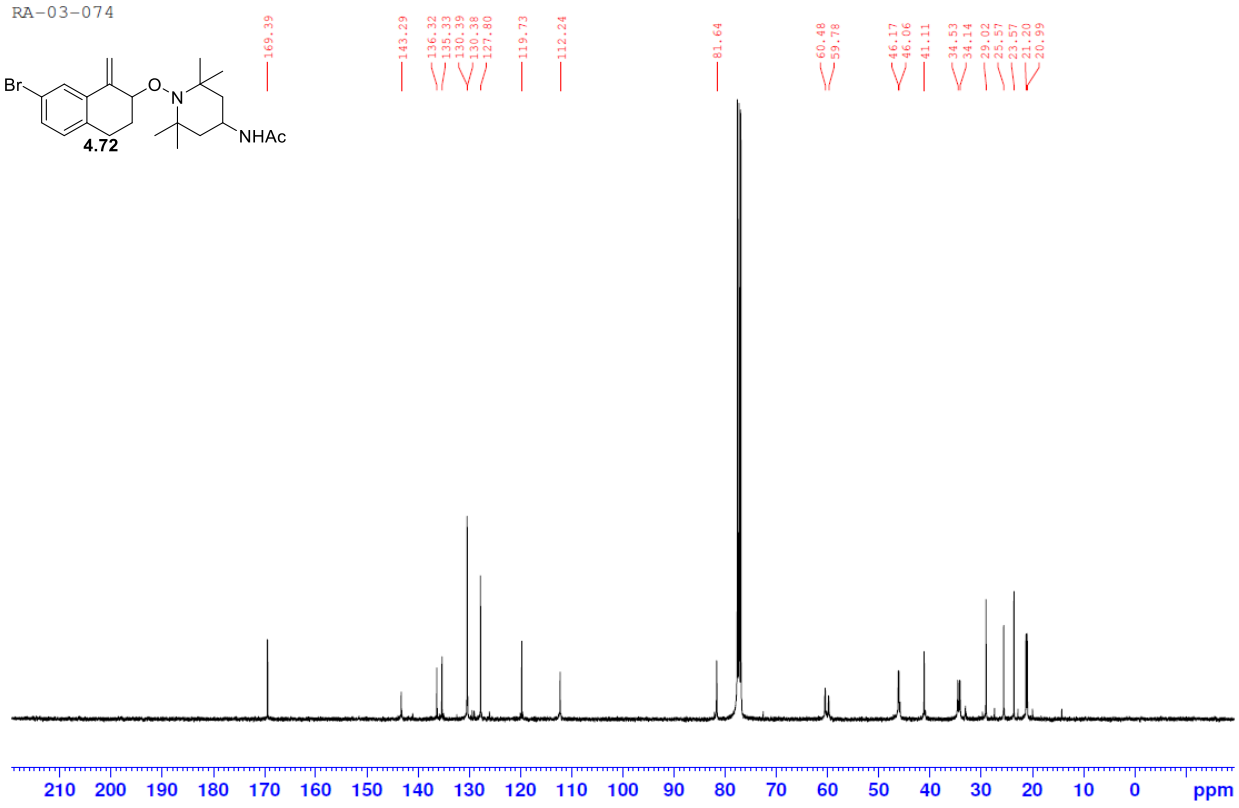
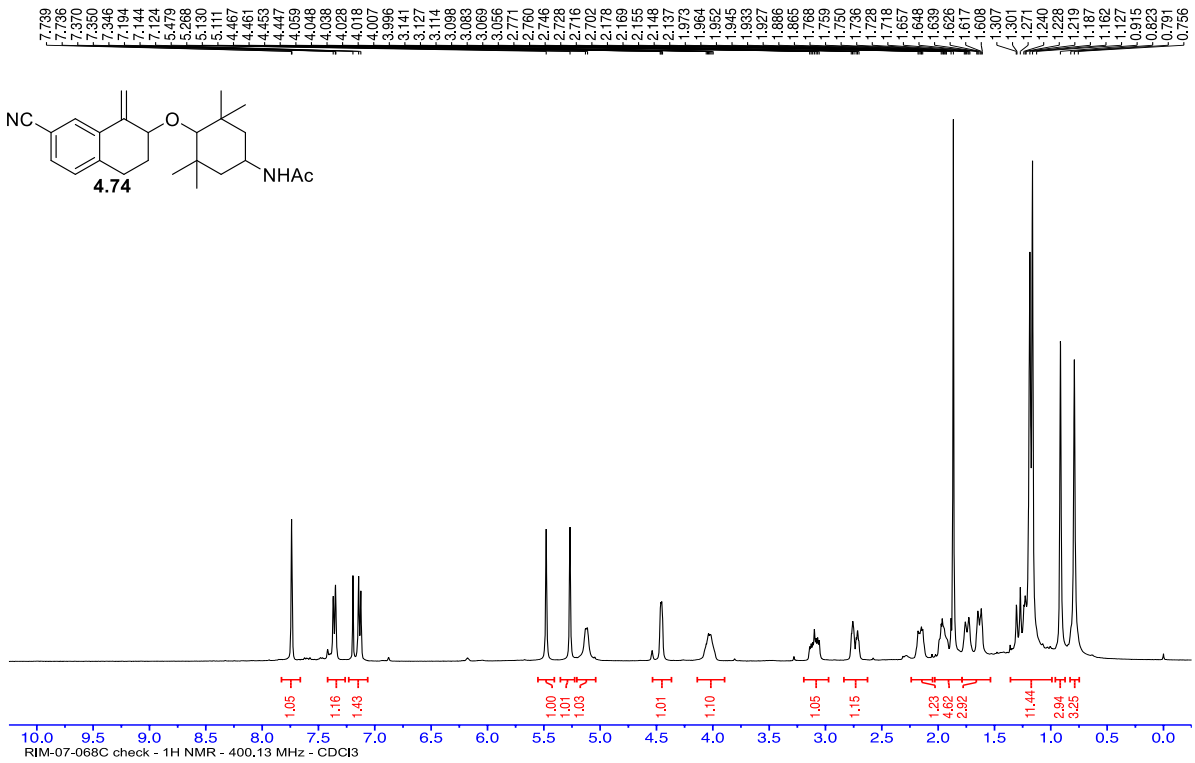
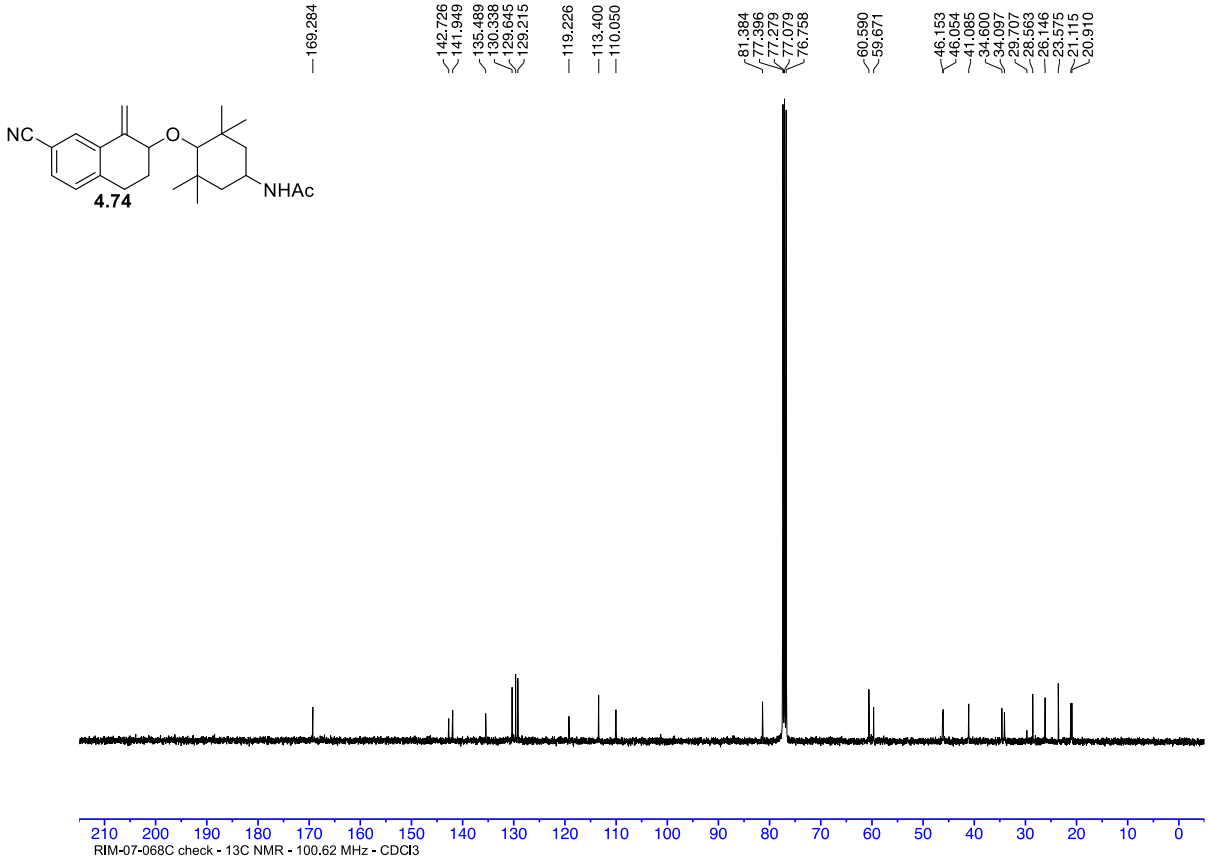
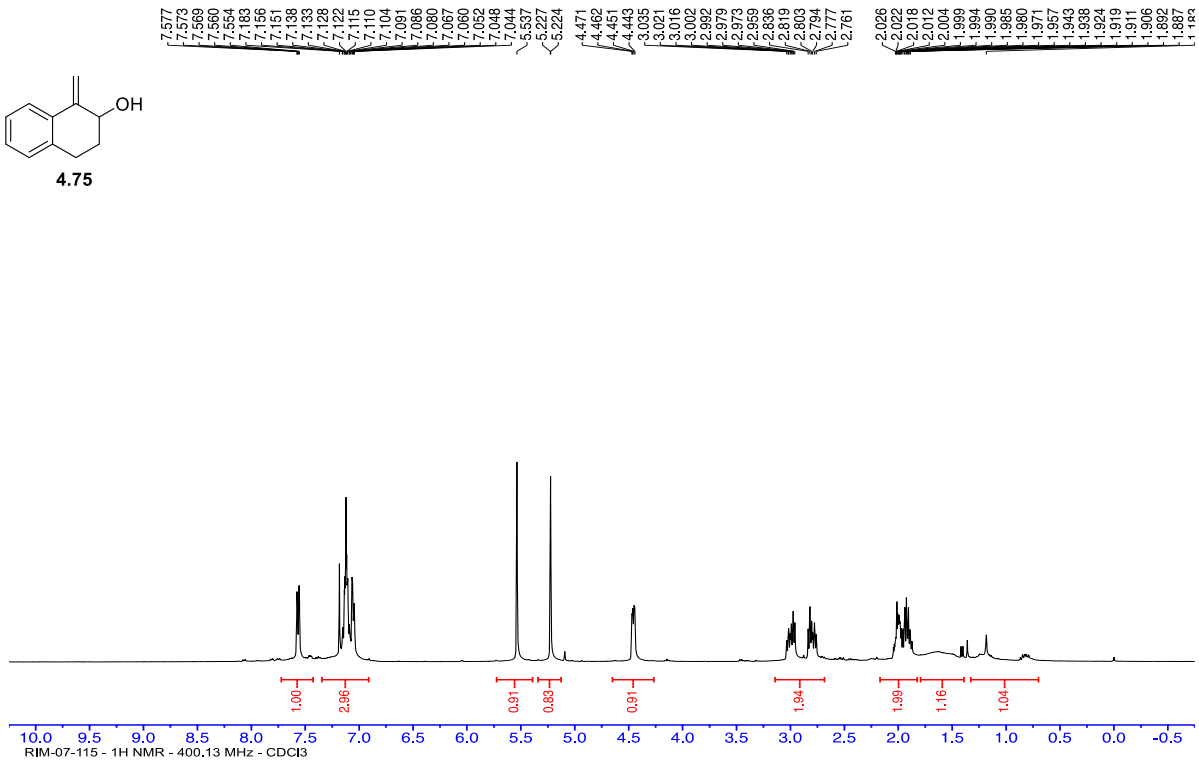
7.651
7.290
7.284
7.271
7.262
6.986
6.966
5.506
5.298
5.283
5.173
5.161
4.490
4.484
4.131
4.112
3.051
3.036
3.024
3.010
2.736
2.722
2.708
2.693
2.681
2.151
2.137
2.127
2.045
2.038
1.956
1.936
1.838
1.827
1.806
1.797
1.775
1.738
1.727
1.718
1.706
1.697
1.687
1.343
1.300
1.283
1.265
1.254
1.239
1.228
1.215
1.053
1.030
1.011
0.933
0.914
Br
O
N
NHAc
4.72
1.00
1.60
1.16
1.09
2.28
1.02
1.29
1.15
1.31
3.42
4.11
3.83
14.22
8.48
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
RIM-06-116 check - 1H NMR - 400.13 MHz - CDCl3


RA-03-074
169.39
143.29
136.32
135.33
130.39
130.38
127.80
119.73
112.24
81.64
60.48
59.78
46.17
46.06
41.11
34.53
34.14
29.02
25.57
23.57
21.20
20.99
Br
O
N
NHAc
4.72
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


NC
O
NHAc
4.74
RIM-07-068C check - 1H NMR - 400.13 MHz - CDCl3


NC
O
NHAc
4.74
RIM-07-068C check - 13C NMR - 100.62 MHz - CDCl3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7.560
7.554
7.183
7.156
7.151
7.138
7.133
7.128
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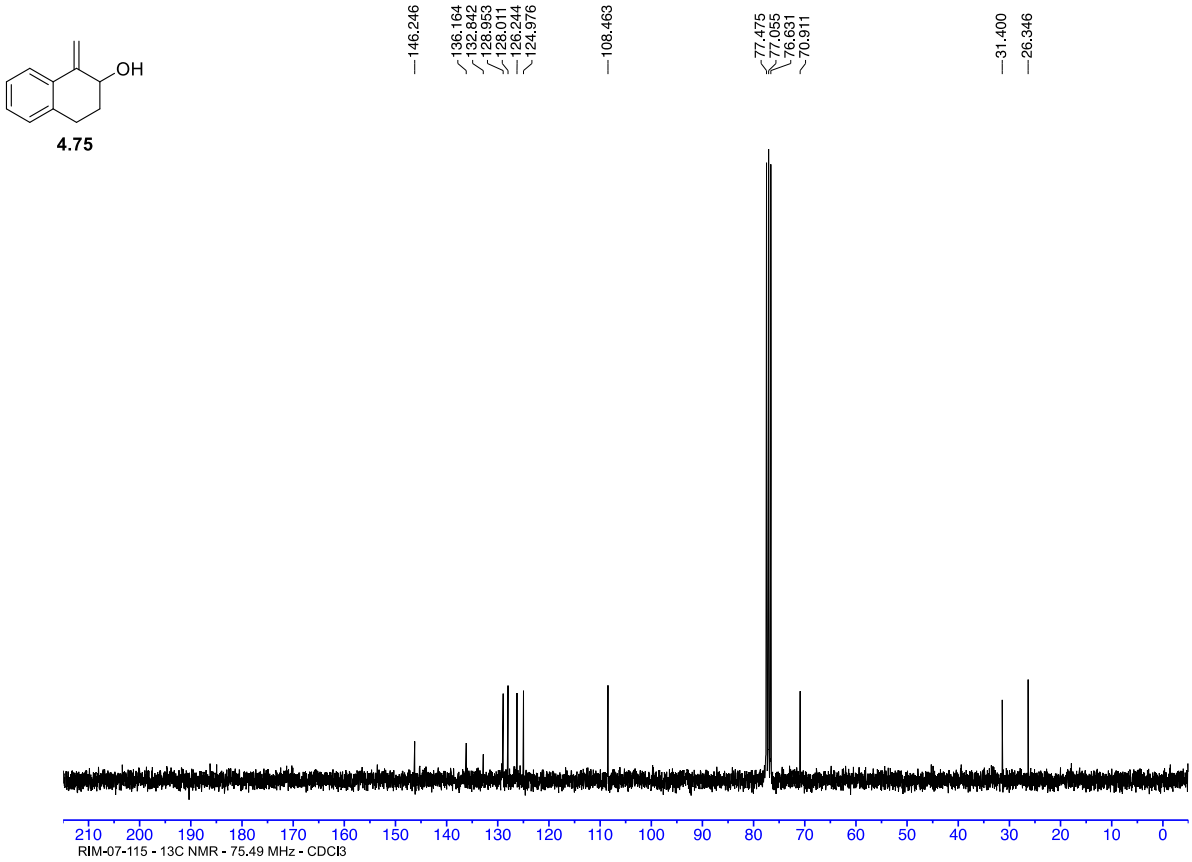
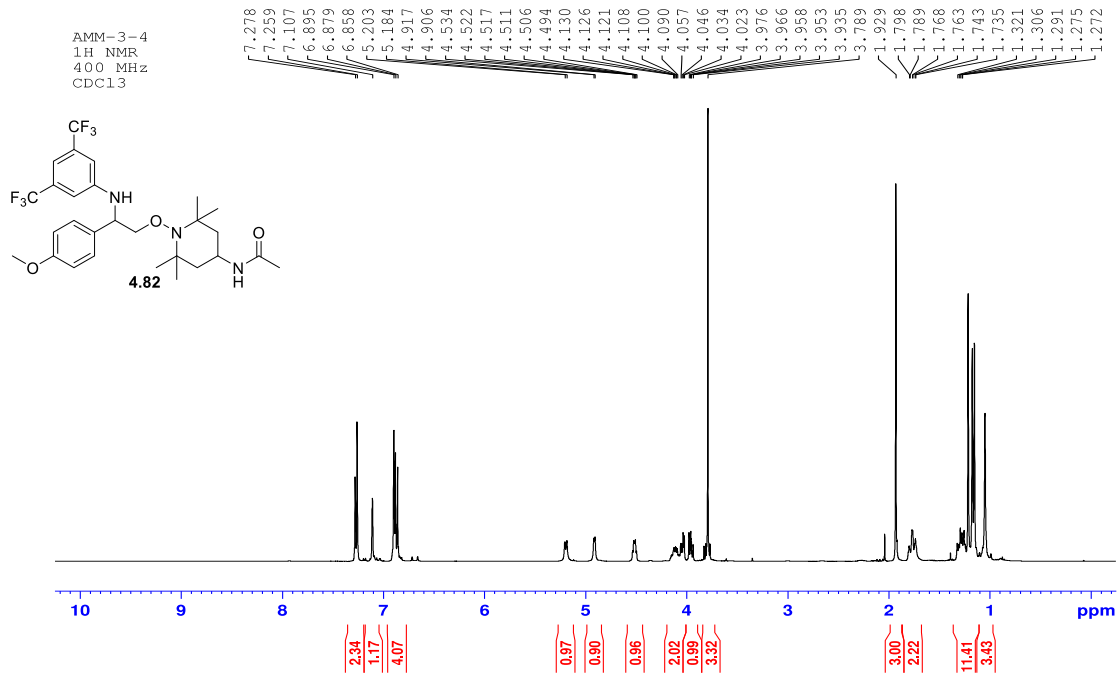
7.115
7.110
7.104
7.091
7.086
7.080
7.067
7.060
7.052
7.048
7.044
5.537
5.227
5.224
4.471
4.462
4.451
4.443
3.035
3.021
3.016
3.002
2.992
2.979
2.973
2.959
2.836
2.819
2.803
2.794
2.777
2.761
2.026
2.022
2.018
2.012
2.004
1.999
1.994
1.990
1.985
1.980
1.971
1.957
1.943
1.938
1.924
1.919
1.911
1.906
1.892
1.887
OH
4.75
1.00
2.96
0.91
0.83
0.91
1.94
1.99
1.16
1.04
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
RIM-07-115 - 1H NMR - 400.13 MHz - CDCl3


146.246
136.164
132.842
128.953
128.011
126.244
124.976
108.463
77.475
77.055
76.631
70.911
31.400
26.346
OH
4.75
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
RIM-07-115 - 13C NMR - 75.49 MHz - CDCl3


AMM-3-4
1H NMR
400 MHz
CDCl3
7.278
7.259
7.107
6.895
6.879
6.858
5.203
5.184
4.917
4.906
4.534
4.522
4.517
4.511
4.506
4.494
4.130
4.126
4.121
4.108
4.100
4.090
4.057
4.046
4.034
4.023
3.976
3.966
3.958
3.953
3.935
3.789
1.929
1.798
1.789
1.768
1.763
1.743
1.735
1.321
1.306
1.291
1.275
1.272
CF3
F3C
NH
O
N
O
N
H
O
4.82
10
9
8
7
6
5
4
3
2
1
ppm
2.34
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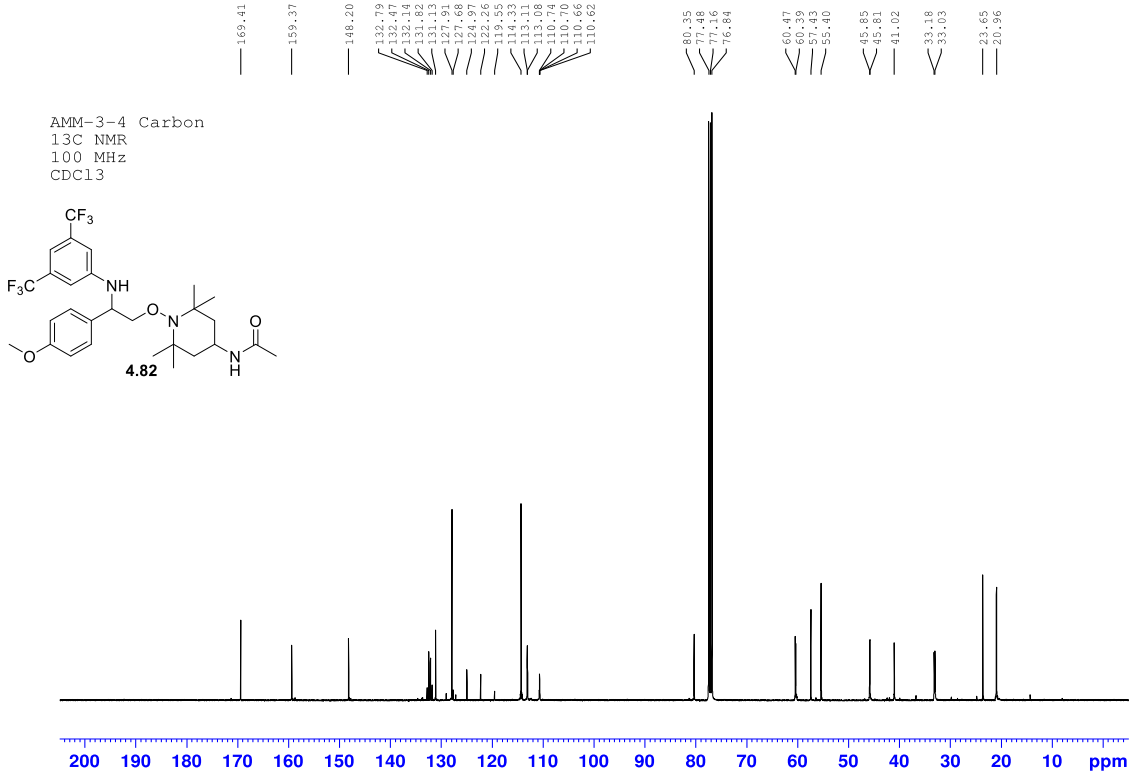
0.90
0.96
2.02
0.99
3.32
3.00
2.22
11.41
3.43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159.37
148.20
132.79
132.47
132.14
131.82
131.13
127.91
127.68
124.97
122.26
119.55
114.33
113.11
113.08
110.74
110.70
110.66
110.62
80.35
77.48
77.16
76.84
60.47
60.39
57.43
55.40
45.85
45.81
41.02
33.18
33.03
23.65
20.96
AMM-3-4 Carbon
13C NMR
100 MHz
CDCl3
CF3
F3C
NH
O
N
O
N
H
O
4.82
200
190
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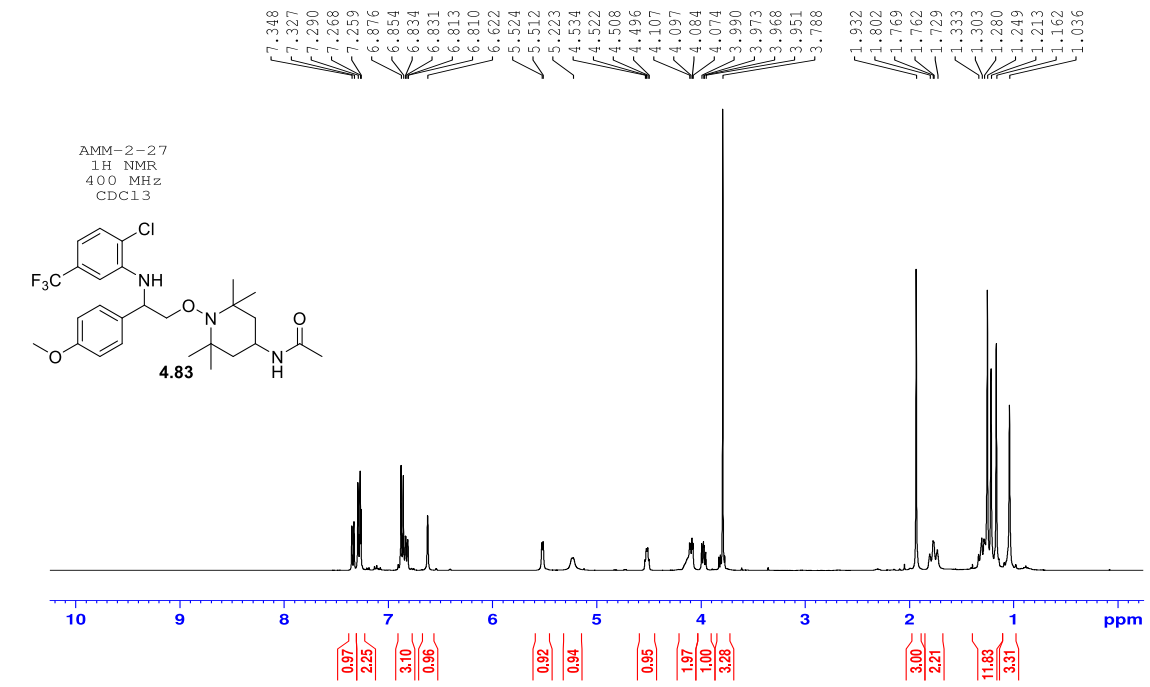
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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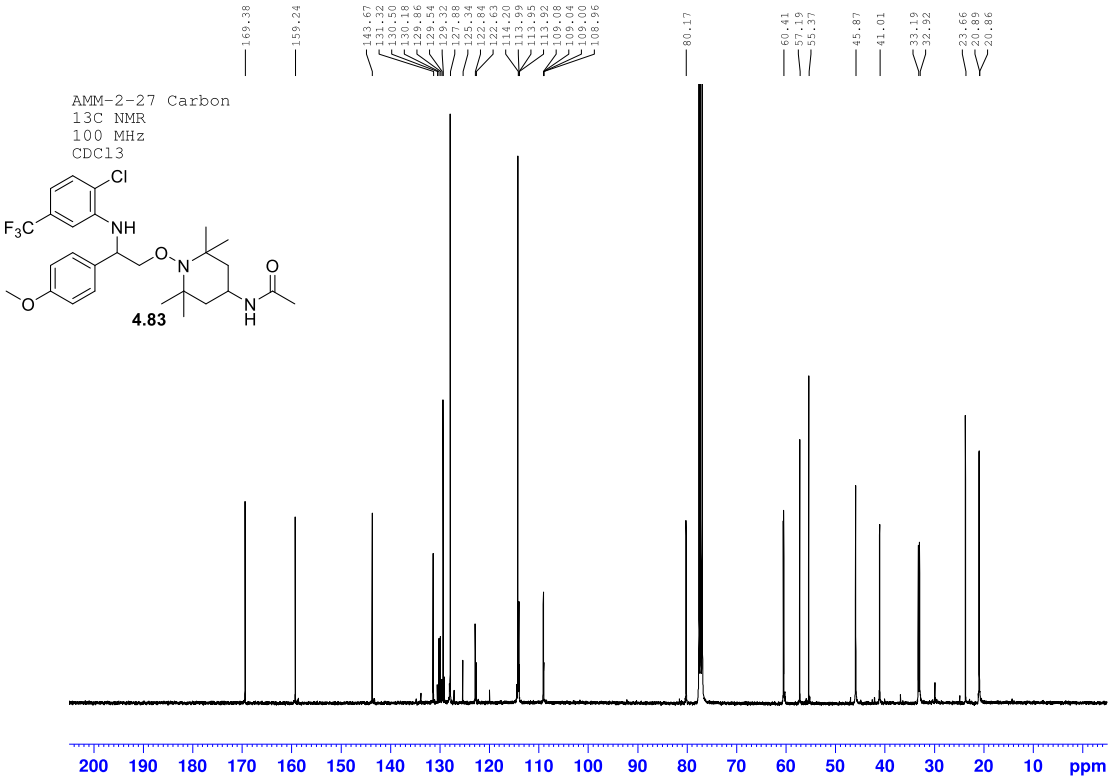
7.327
7.290
7.268
7.259
6.876
6.854
6.834
6.831
6.813
6.810
6.622
5.524
5.512
5.223
4.534
4.522
4.508
4.496
4.107
4.097
4.084
4.074
3.990
3.973
3.968
3.951
3.788
1.932
1.802
1.769
1.762
1.729
1.333
1.303
1.280
1.249
1.213
1.162
1.036
AMM-2-27
1H NMR
400 MHz
CDCl3
Cl
F3C
NH
O
N
O
N
H
O
4.83
10
9
8
7
6
5
4
3
2
1
ppm
0.97
2.25
3.10
0.96
0.92
0.94
0.95
1.97
1.00
3.28
3.00
2.21
11.83
3.31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159.24
143.67
131.32
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130.18
129.86
129.54
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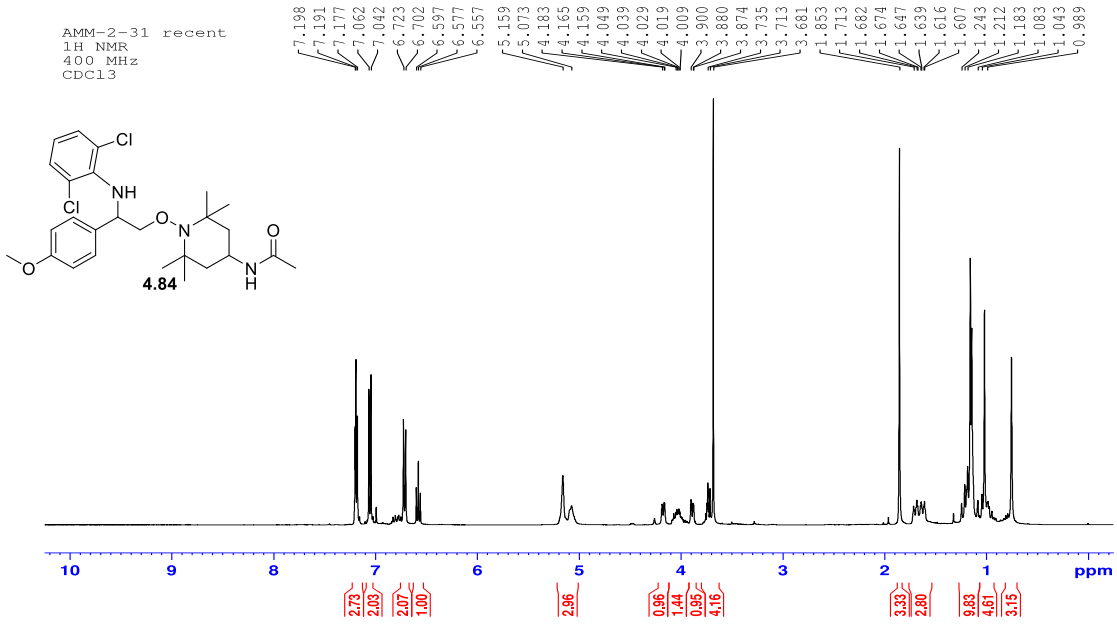
127.88
125.34
122.84
122.63
114.20
113.99
113.95
113.92
109.08
109.04
109.00
108.96
80.17
60.41
57.19
55.37
45.87
41.01
33.19
32.92
23.66
20.89
20.86
AMM-2-27 Carbon
13C NMR
100 MHz
CDCl3
Cl
F3C
NH
O
N
O
N
H
O
4.83
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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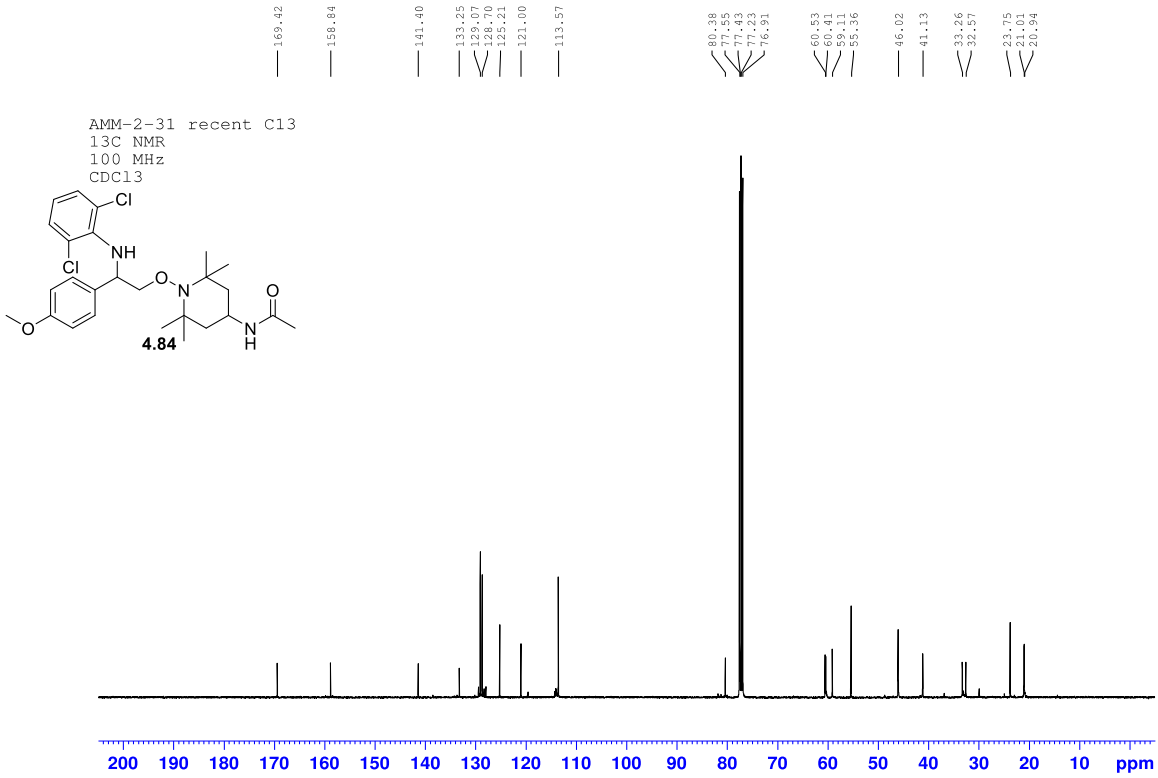
1H NMR
400 MHz
CDCl3
7.198
7.191
7.177
7.062
7.042
6.723
6.702
6.597
6.577
6.557
5.159
5.073
4.183
4.165
4.159
4.049
4.039
4.029
4.019
4.009
3.900
3.880
3.874
3.735
3.713
3.681
1.853
1.713
1.682
1.674
1.647
1.639
1.616
1.607
1.243
1.212
1.183
1.083
1.043
0.989
Cl
NH
Cl
O
O
N
N
H
O
4.84
10
9
8
7
6
5
4
3
2
1
ppm
2.73
2.03
2.07
1.00
2.96
0.96
1.44
0.95
4.16
3.33
2.80
9.83
4.61
3.15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141.40
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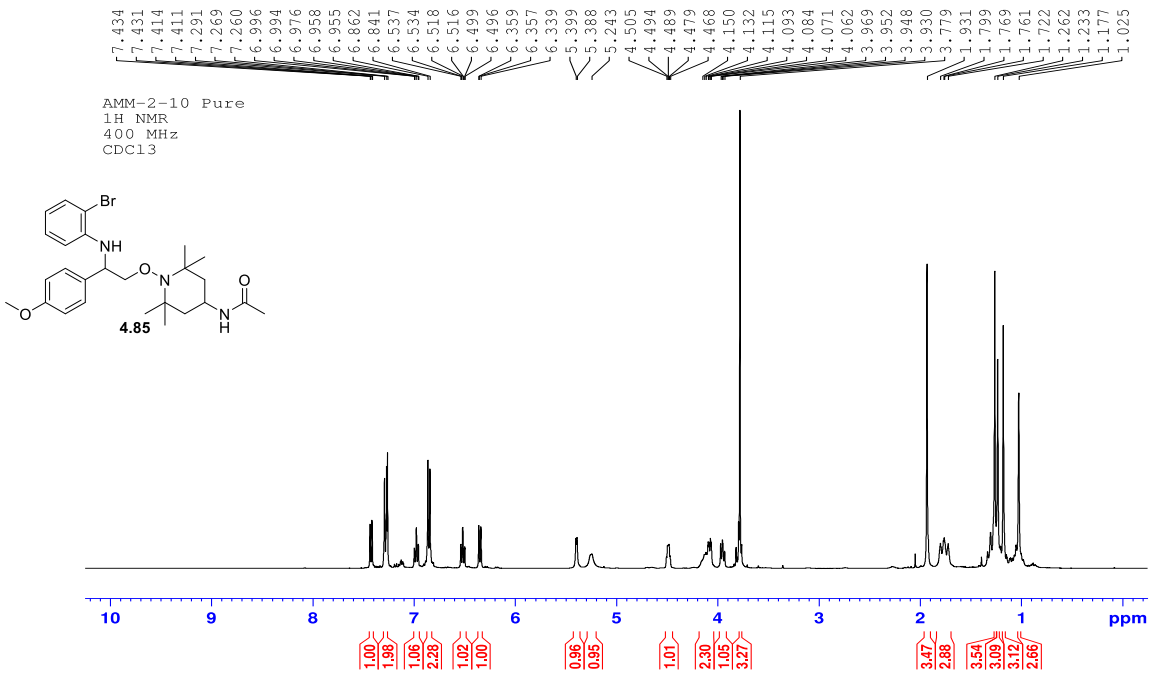
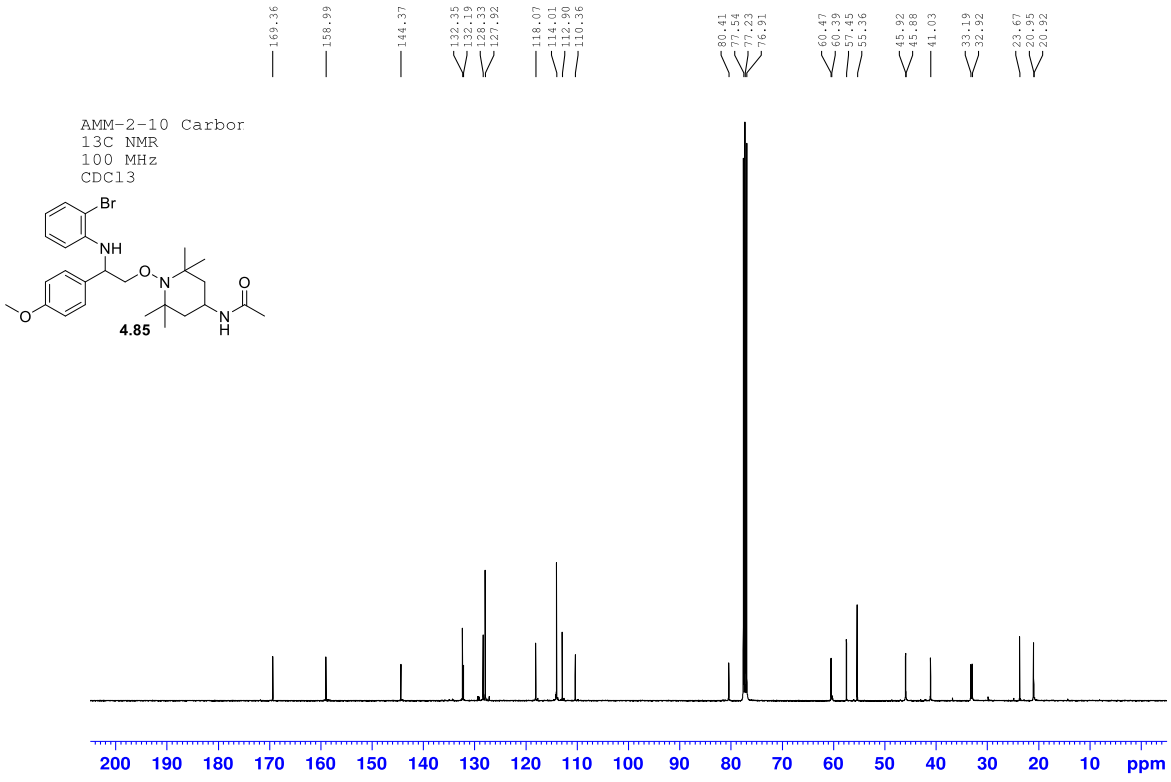
129.07
128.70
125.21
121.00
113.57
80.38
77.55
77.43
77.23
76.91
60.53
60.41
59.11
55.36
46.02
41.13
33.26
32.57
23.75
21.01
20.94
AMM-2-31 recent C13
13C NMR
100 MHz
CDCl3
Cl
NH
Cl
O
O
N
N
H
O
4.84
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


7.434
7.431
7.414
7.411
7.291
7.269
7.260
6.996
6.994
6.976
6.958
6.955
6.862
6.841
6.537
6.534
6.518
6.516
6.499
6.496
6.359
6.357
6.339
5.399
5.388
5.243
4.505
4.494
4.489
4.479
4.468
4.150
4.132
4.115
4.093
4.084
4.071
4.062
3.969
3.952
3.948
3.930
3.779
1.931
1.799
1.769
1.761
1.722
1.262
1.233
1.177
1.025
AMM-2-10 Pure
1H NMR
400 MHz
CDCl3
Br
NH
O
N
O
N
H
O
4.85
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.98
1.06
2.28
1.02
1.00
0.96
0.95
1.01
2.30
1.05
3.27
3.47
2.88
3.54
3.09
3.12
2.66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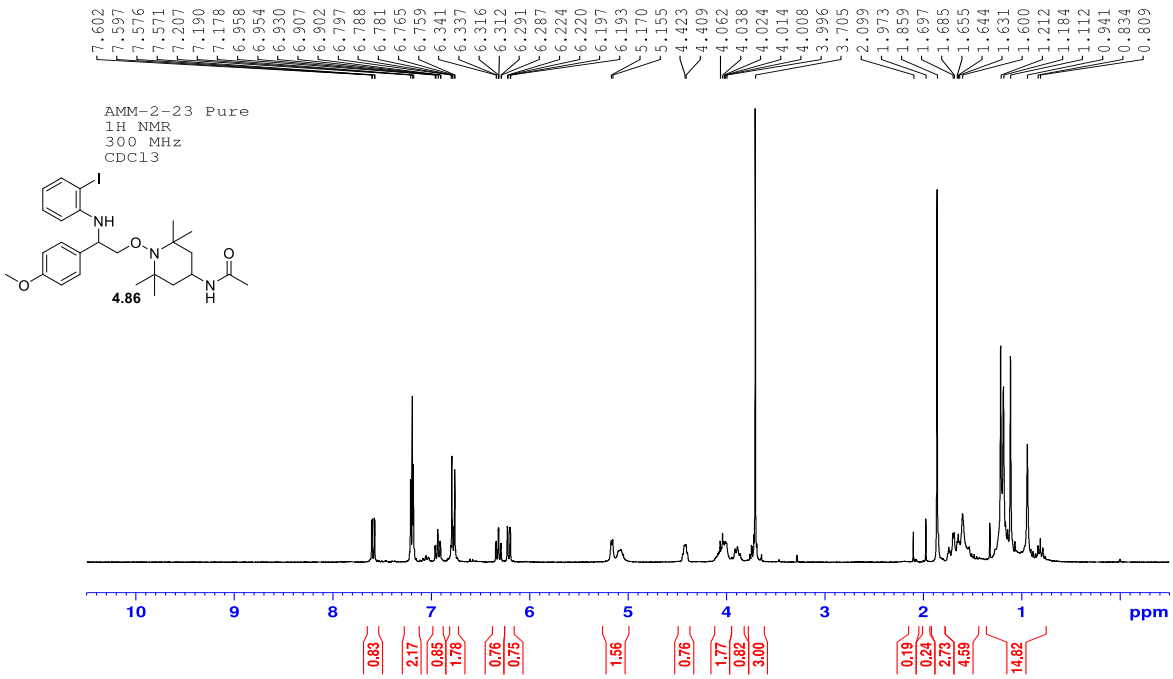
158.99
144.37
132.35
132.19
128.13
127.92
118.07
114.01
112.90
110.36
80.41
77.54
77.33
76.91
60.47
60.39
57.45
55.36
45.92
45.88
41.03
33.19
32.92
23.67
20.95
20.92
AMM-2-10 Carbor
13C NMR
100 MHz
CDCl3
Br
NH
O
N
O
N
H
O
4.85
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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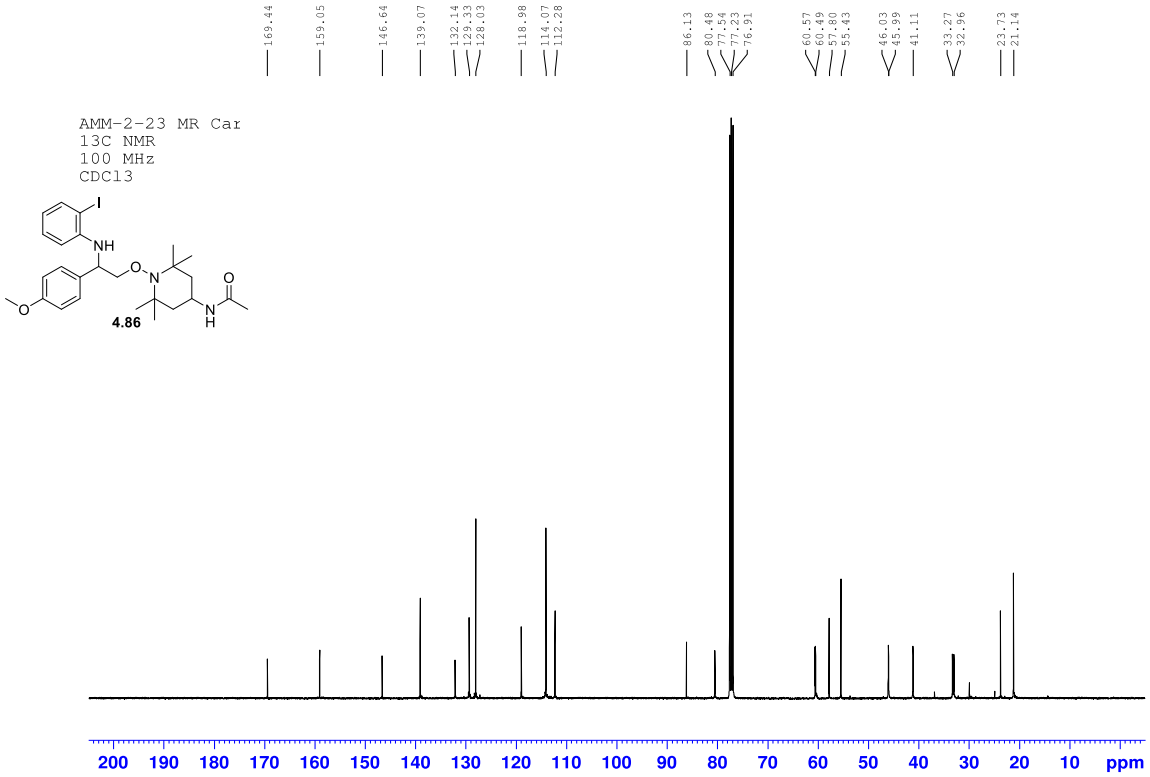
7.597
7.576
7.571
7.207
7.190
7.178
6.958
6.954
6.930
6.907
6.902
6.797
6.788
6.781
6.765
6.759
6.341
6.337
6.316
6.312
6.291
6.287
6.224
6.220
6.197
6.193
5.170
5.155
4.423
4.409
4.062
4.038
4.024
4.014
4.008
3.996
3.705
2.099
1.973
1.859
1.697
1.685
1.655
1.644
1.631
1.600
1.212
1.184
1.112
0.941
0.834
0.809
AMM-2-23 Pure
1H NMR
300 MHz
CDCl3
4.86
10
9
8
7
6
5
4
3
2
1
ppm
0.83
2.17
0.85
1.78
0.76
0.75
1.56
0.76
1.77
0.82
3.00
0.19
0.24
2.73
4.59
14.82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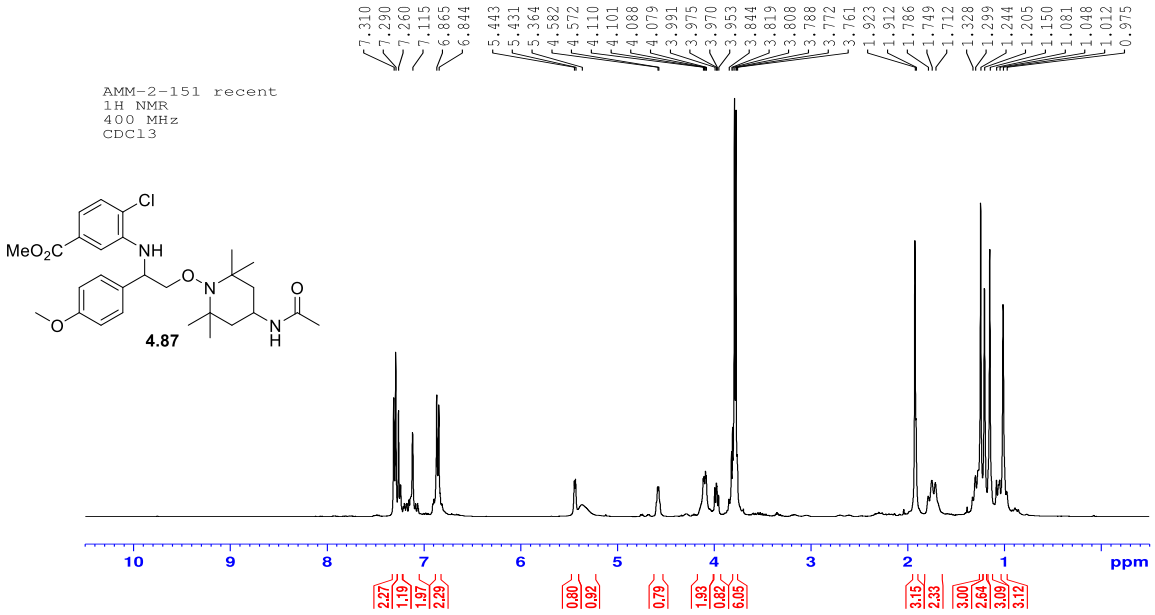
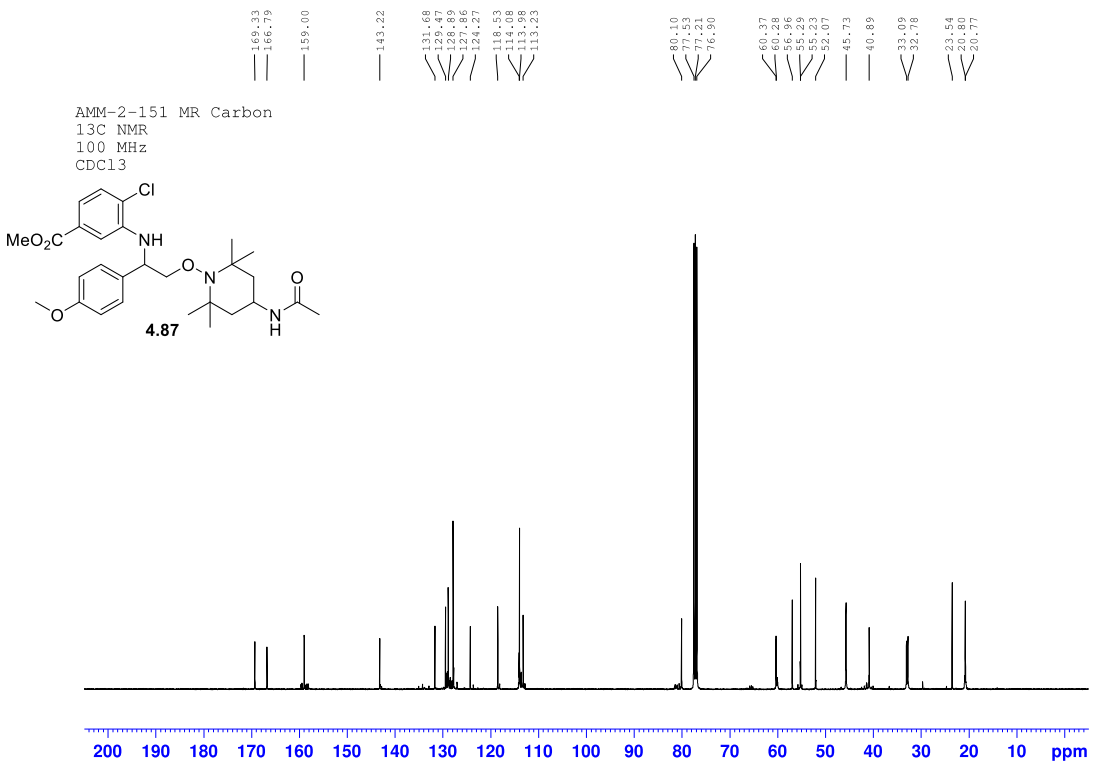
159.05
146.64
139.07
132.14
129.33
128.03
118.98
114.07
112.28
86.13
80.48
77.54
77.23
76.91
60.57
60.49
57.80
55.43
46.03
45.99
41.11
33.27
32.96
23.73
21.14
AMM-2-23 MR Car
13C NMR
100 MHz
CDCl3
4.86
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


7.310
7.290
7.260
7.115
6.865
6.844
5.443
5.431
5.364
4.582
4.572
4.110
4.101
4.088
4.079
3.991
3.975
3.970
3.953
3.844
3.819
3.808
3.788
3.772
3.761
1.923
1.912
1.786
1.749
1.712
1.328
1.299
1.244
1.205
1.150
1.081
1.048
1.012
0.975
AMM-2-151 recent
1H NMR
400 MHz
CDCl3
Cl
MeO2C
NH
O
N
O
N
H
O
4.87
10
9
8
7
6
5
4
3
2
1
ppm
2.27
1.19
1.97
2.29
0.80
0.92
0.79
1.93
0.82
6.05
3.15
2.33
3.00
2.64
3.09
3.12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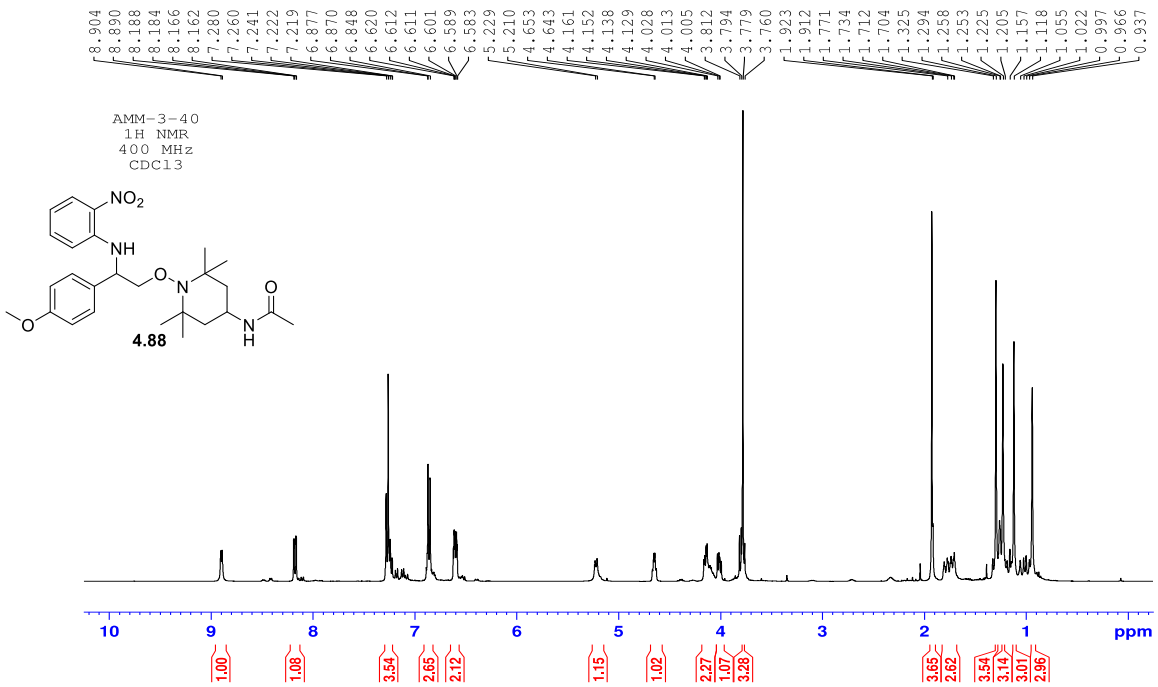
131.68
129.47
128.89
127.86
124.27
118.53
113.88
113.58
113.23
80.10
77.53
77.21
76.90
60.37
56.28
56.96
55.29
55.23
52.07
45.73
40.89
33.09
32.78
23.54
20.80
20.77
AMM-2-151 MR Carbon
13C NMR
100 MHz
CDCl3
Cl
MeO2C
NH
O
N
O
N
H
O
4.87
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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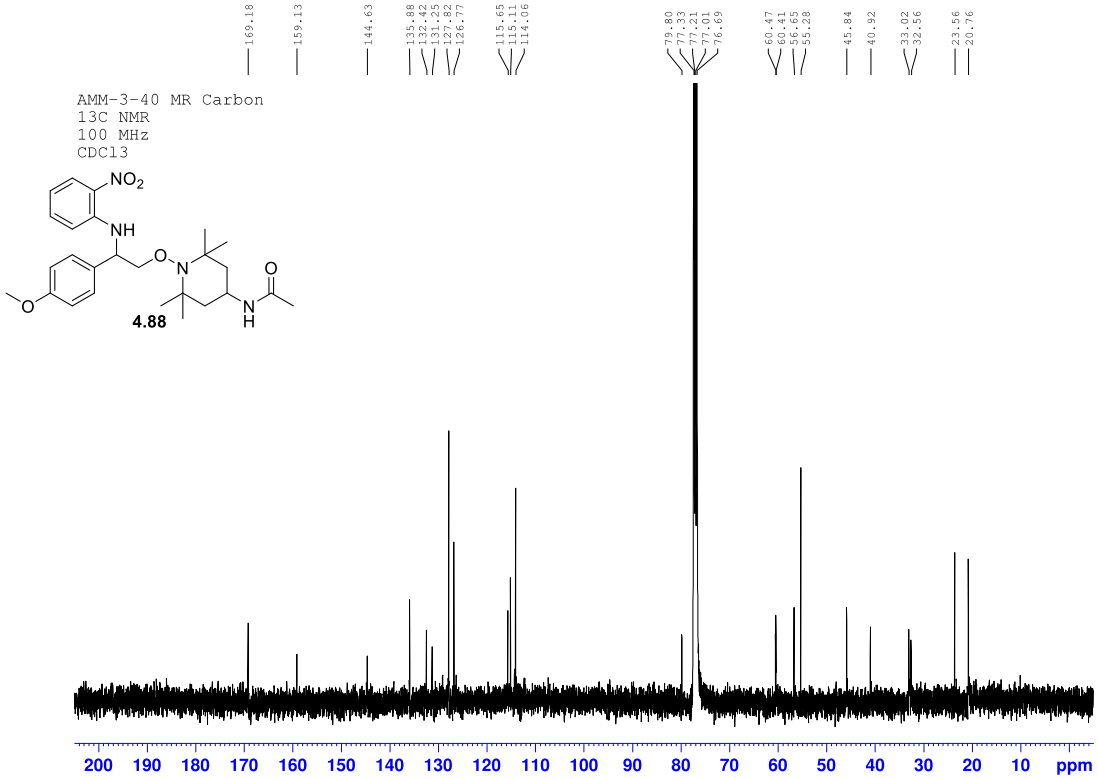
8.890
8.188
8.184
8.166
8.162
7.280
7.260
7.241
7.222
7.219
6.877
6.870
6.848
6.620
6.612
6.611
6.601
6.589
6.583
5.229
5.210
4.653
4.643
4.161
4.152
4.138
4.129
4.028
4.013
4.005
3.812
3.794
3.779
3.760
1.923
1.912
1.771
1.734
1.712
1.704
1.325
1.294
1.258
1.253
1.225
1.205
1.157
1.118
1.055
1.022
0.997
0.966
0.937
AMM-3-40
1H NMR
400 MHz
CDCl3
NO2
NH
O
N
O
N
H
O
4.88
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.08
3.54
2.65
2.12
1.15
1.02
2.27
1.07
3.28
3.65
2.62
3.54
3.14
3.01
2.96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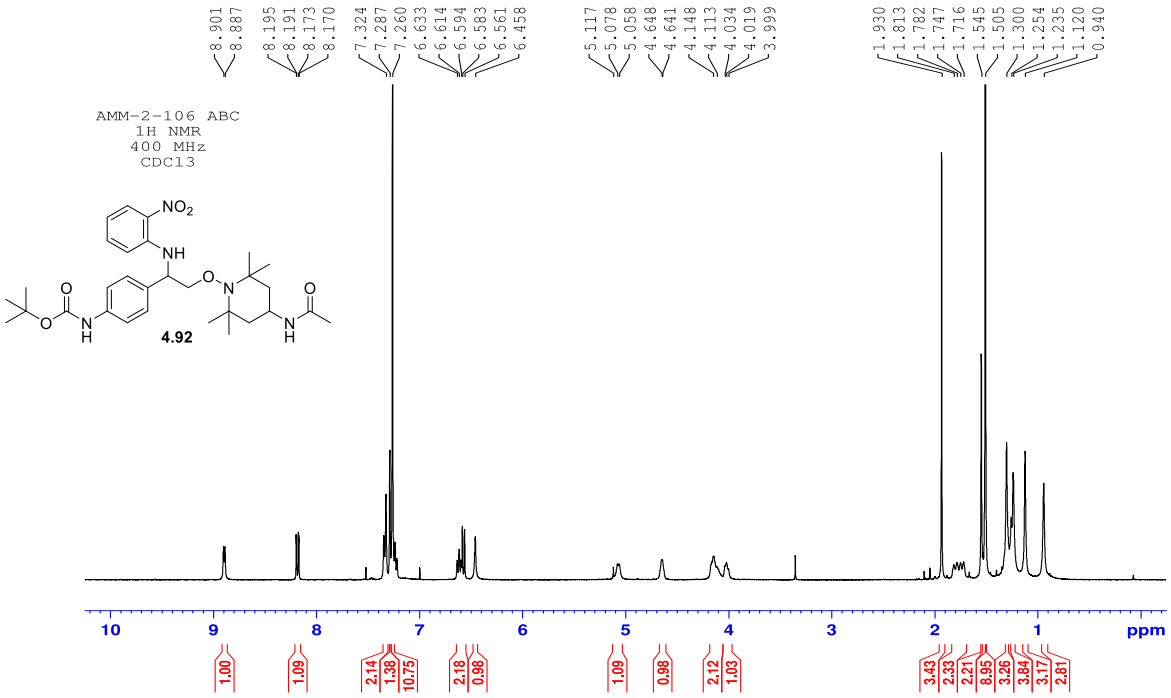
144.63
135.88
132.42
131.25
127.82
126.77
115.65
115.11
114.06
79.80
77.33
77.21
77.01
76.69
60.47
60.41
56.65
55.28
45.84
40.92
33.02
32.56
23.56
20.76
AMM-3-40 MR Carbon
13C NMR
100 MHz
CDCl3
NO2
NH
O
N
O
N
H
O
4.88
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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1H NMR
400 MHz
CDCl3
4.92
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8.887
8.195
8.191
8.173
8.170
7.324
7.287
7.260
6.633
6.614
6.594
6.583
6.561
6.458
5.117
5.078
5.058
4.648
4.641
4.148
4.113
4.034
4.019
3.999
1.930
1.813
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1.747
1.716
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1.300
1.254
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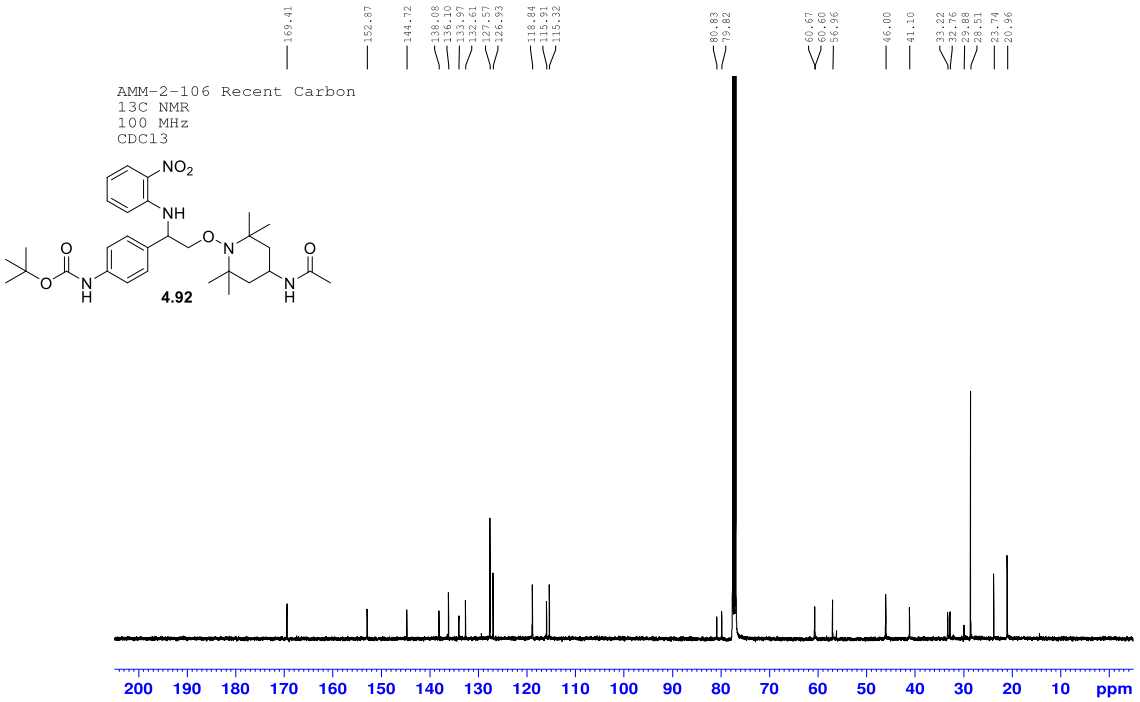
1.120
0.940
ppm


AMM-2-106 Recent Carbon
13C NMR
100 MHz
CDCl3
4.92
169.41
152.87
144.72
138.08
136.10
133.97
132.61
127.57
126.93
118.84
115.91
115.32
80.83
79.82
60.67
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56.96
46.00
41.10
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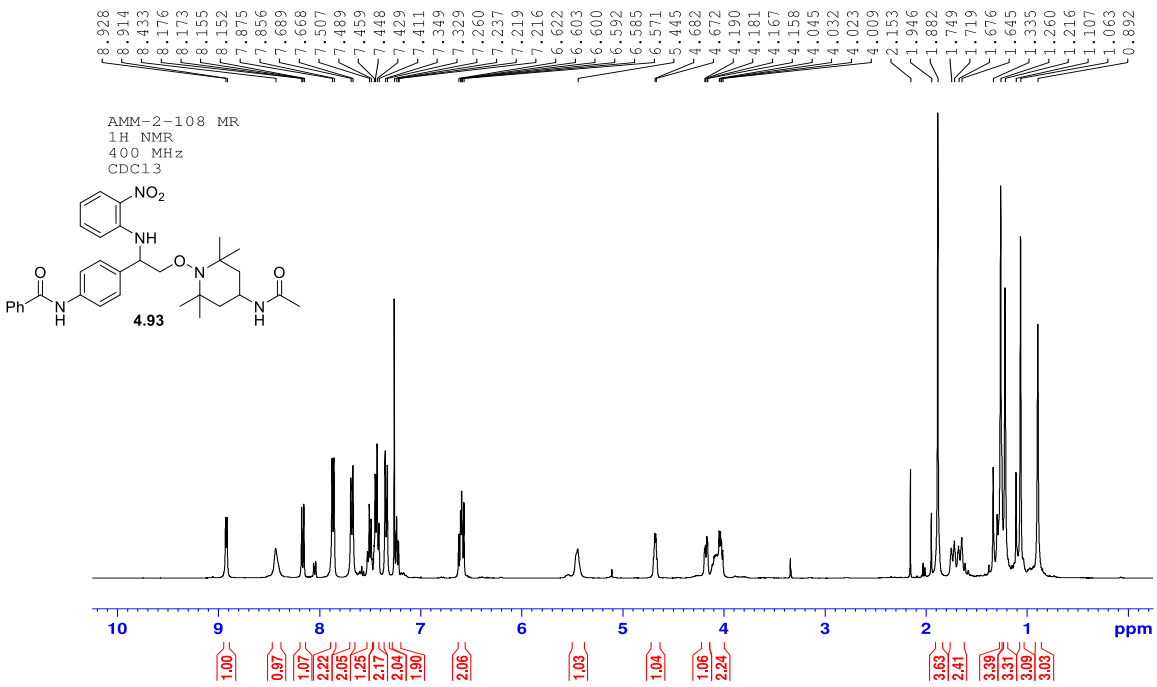
32.76
29.88
28.51
23.74
20.96
ppm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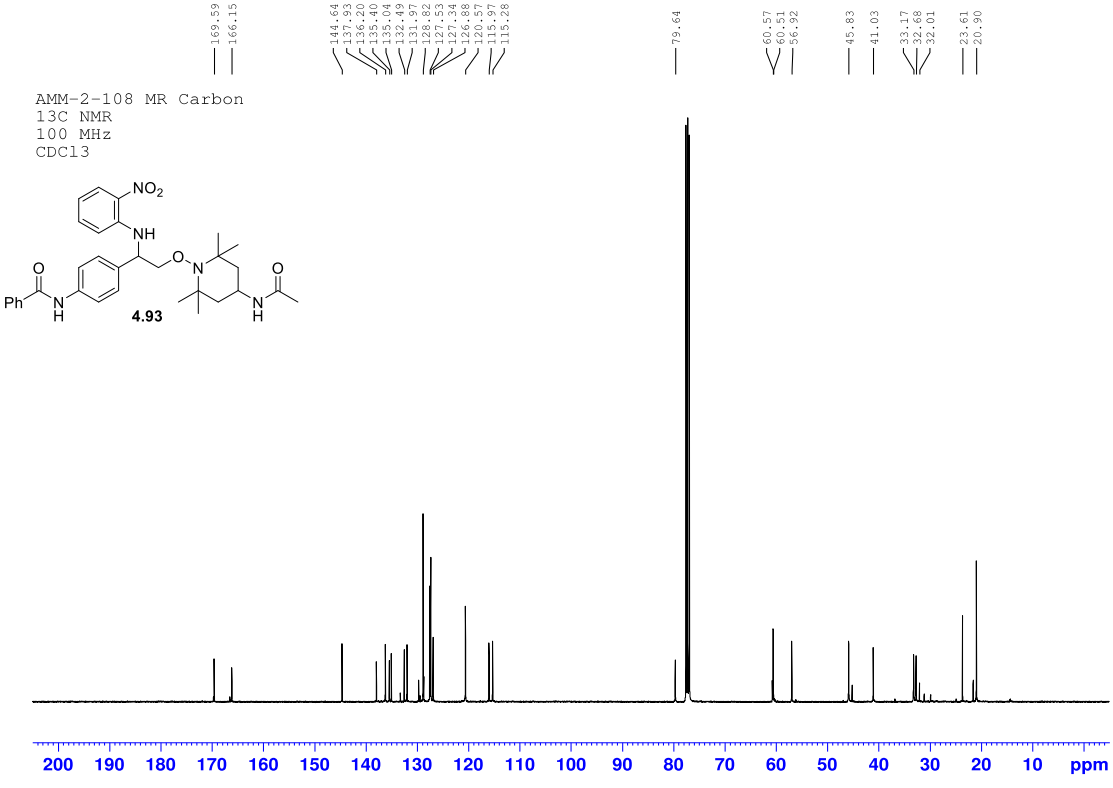
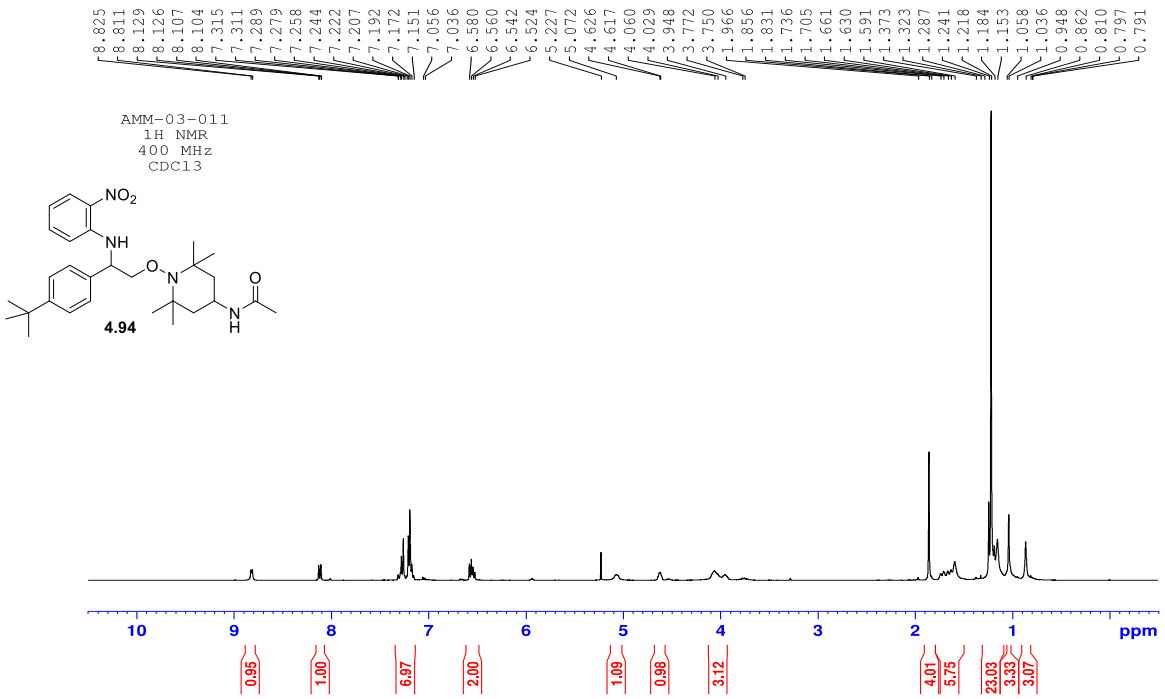
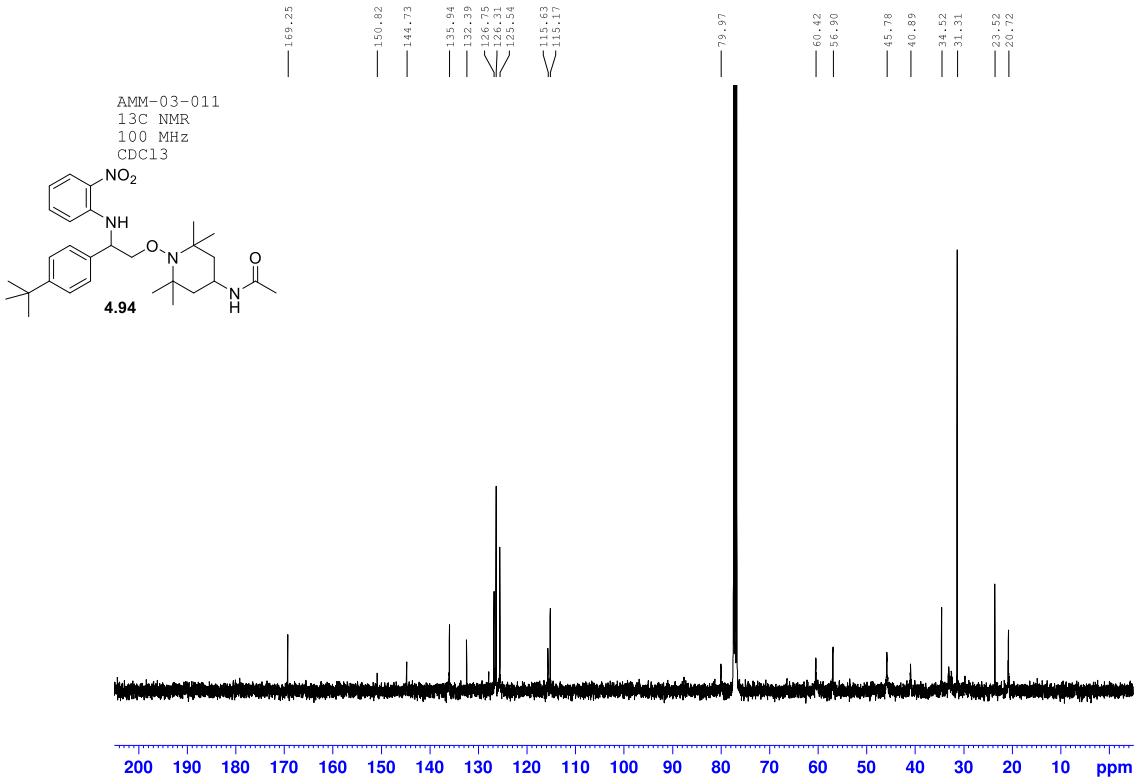
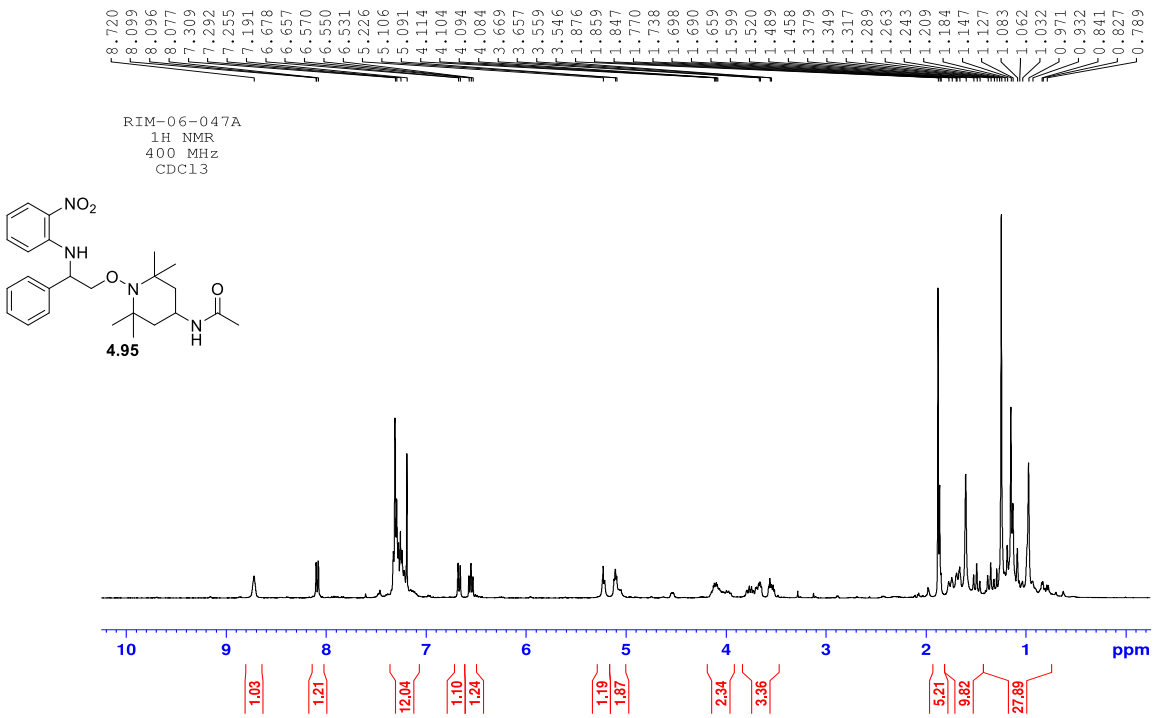
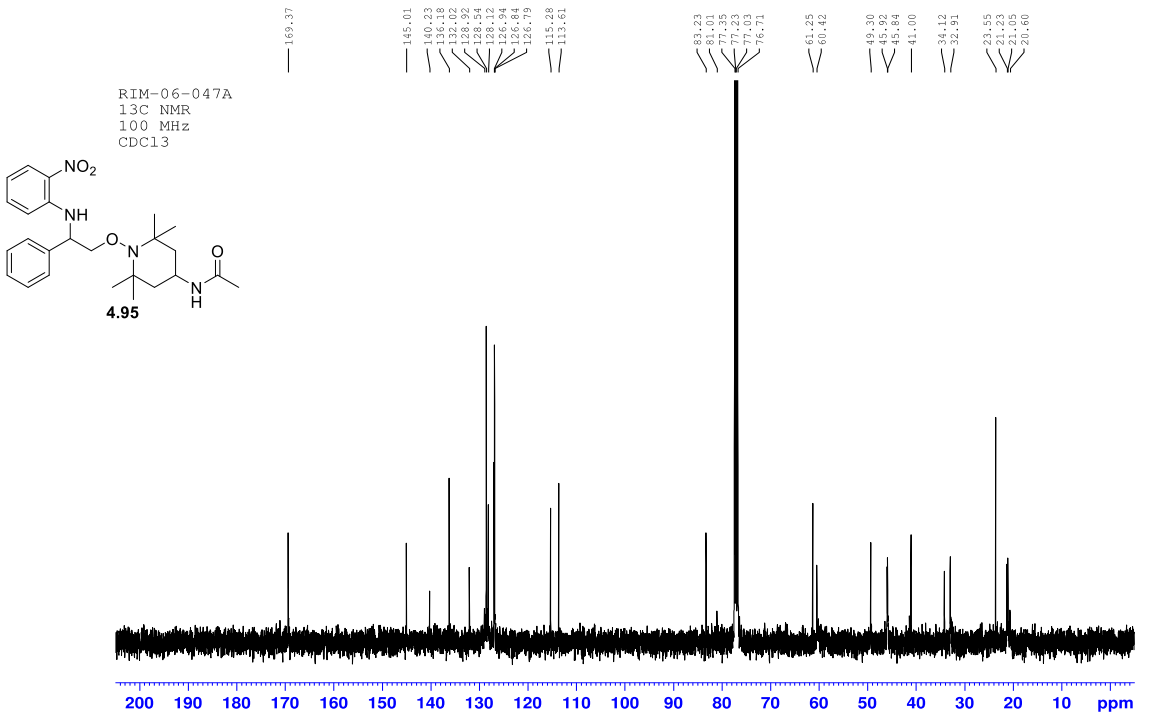
8.914
8.433
8.176
8.173
8.155
8.152
7.875
7.856
7.689
7.668
7.507
7.489
7.459
7.448
7.429
7.411
7.349
7.329
7.260
7.237
7.219
7.216
6.622
6.603
6.600
6.592
6.585
6.571
5.445
4.682
4.672
4.190
4.181
4.167
4.158
4.045
4.032
4.023
4.009
2.153
1.946
1.882
1.749
1.719
1.676
1.645
1.335
1.260
1.216
1.107
1.063
0.892
AMM-2-108 MR
1H NMR
400 MHz
CDCl3
NO2
NH
O
N
O
Ph
N
H
O
N
H
4.93
10
9
8
7
6
5
4
3
2
1
ppm
1.00
0.97
1.07
2.22
2.05
1.25
2.17
2.04
1.90
2.06
1.03
1.04
1.06
2.24
3.63
2.41
3.39
3.31
3.09
3.03

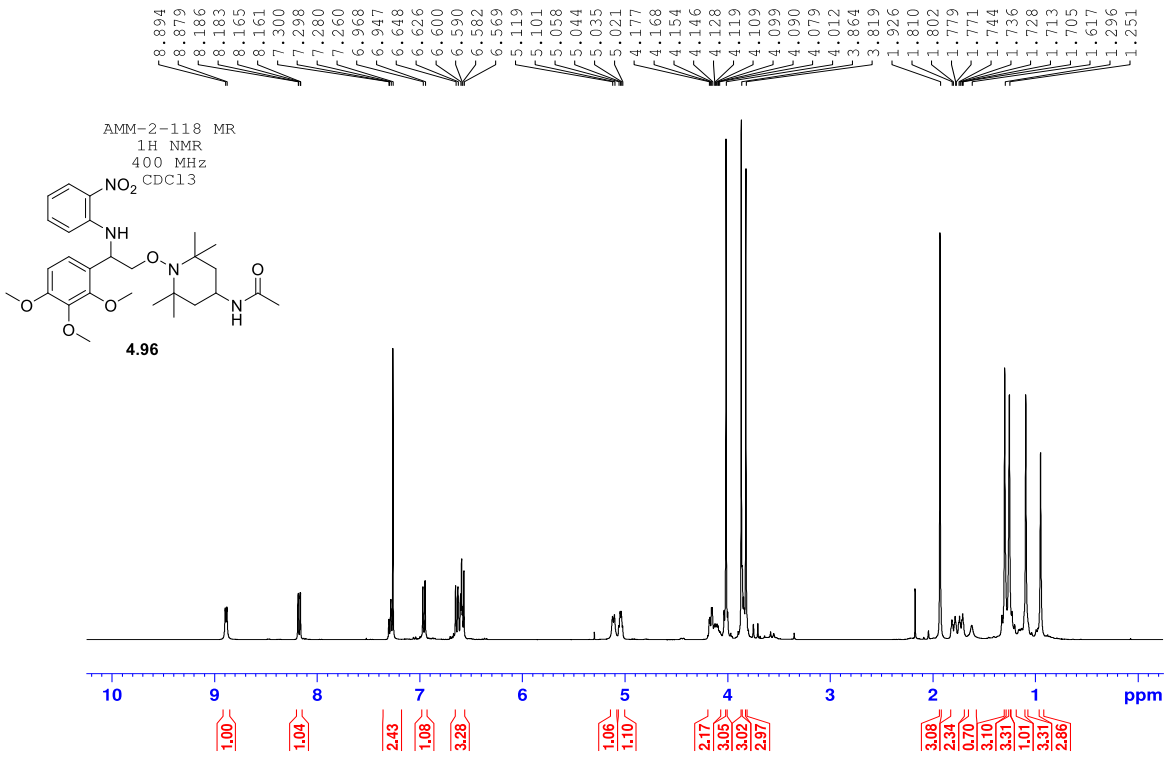

169.59
166.15
144.64
137.93
136.20
135.40
133.04
132.49
131.97
128.82
127.53
127.34
126.88
120.57
115.97
115.28
79.64
60.57
60.51
56.92
45.83
41.03
33.17
32.68
32.01
23.61
20.90
AMM-2-108 MR Carbon
13C NMR
100 MHz
CDCl3
NO2
NH
O
N
O
Ph
N
H
O
N
H
4.93
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

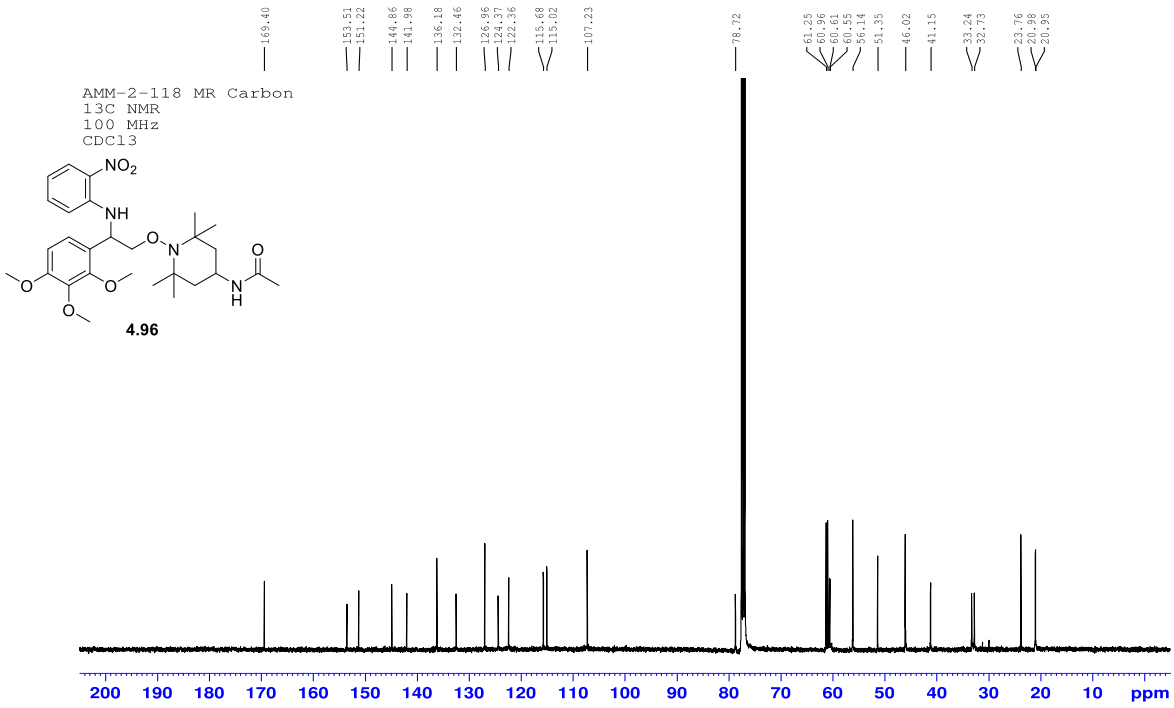

8.825
8.811
8.129
8.126
8.107
8.104
7.315
7.311
7.289
7.279
7.258
7.244
7.222
7.207
7.192
7.172
7.151
7.056
7.036
6.580
6.560
6.542
6.524
5.227
5.072
4.626
4.617
4.060
4.029
3.948
3.772
3.750
1.966
1.856
1.831
1.736
1.705
1.661
1.630
1.591
1.373
1.323
1.287
1.241
1.218
1.184
1.153
1.058
1.036
0.948
0.862
0.810
0.797
0.791
AMM-03-011
1H NMR
400 MHz
CDCl3
NO2
NH
O
N
O
N
H
4.94
10
9
8
7
6
5
4
3
2
1
ppm
0.95
1.00
6.97
2.00
1.09
0.98
3.12
4.01
5.75
23.03
3.33
3.07

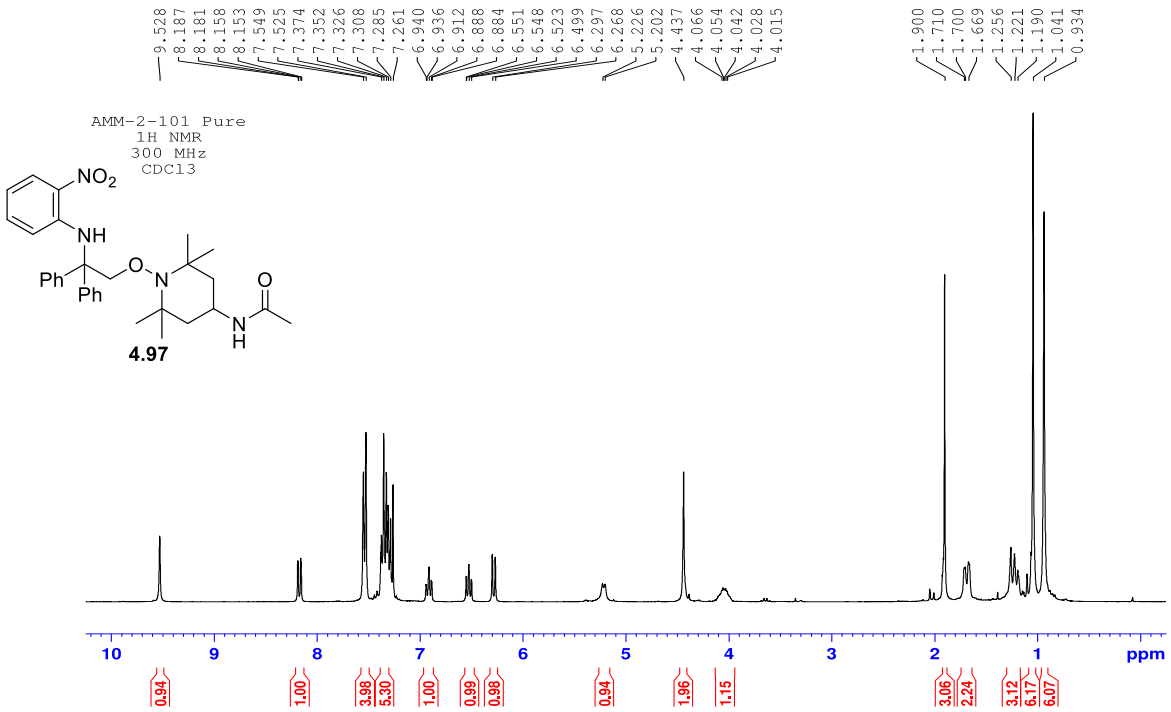

169.25
150.82
144.73
135.94
132.39
126.75
126.31
125.54
115.63
115.17
79.97
60.42
56.90
45.78
40.89
34.52
31.31
23.52
20.72
AMM-03-011
13C NMR
100 MHz
CDCl3
NO2
NH
O
N
O
N
H
4.94
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

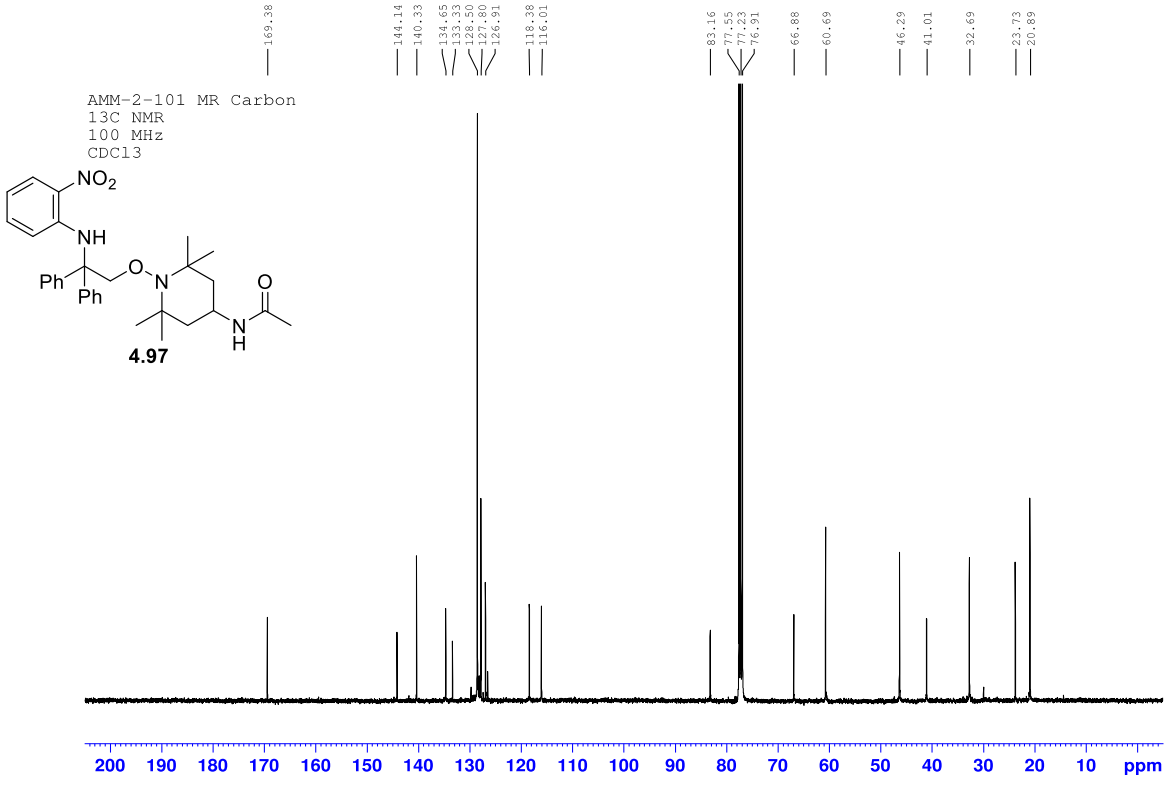

8.720
8.099
8.096
8.077
7.309
7.292
7.255
7.191
6.678
6.657
6.570
6.550
6.531
5.226
5.106
5.091
4.114
4.104
4.094
4.084
3.669
3.657
3.559
3.546
1.876
1.859
1.847
1.770
1.738
1.698
1.690
1.659
1.599
1.520
1.489
1.458
1.379
1.349
1.317
1.289
1.263
1.243
1.209
1.184
1.147
1.127
1.083
1.062
1.032
0.971
0.932
0.841
0.827
0.789
RIM-06-047A
1H NMR
400 MHz
CDCl3
NO2
NH
O
N
O
N
H
4.95
10
9
8
7
6
5
4
3
2
1
ppm
1.03
1.21
12.04
1.10
1.24
1.19
1.87
2.34
3.36
5.21
9.82
27.89

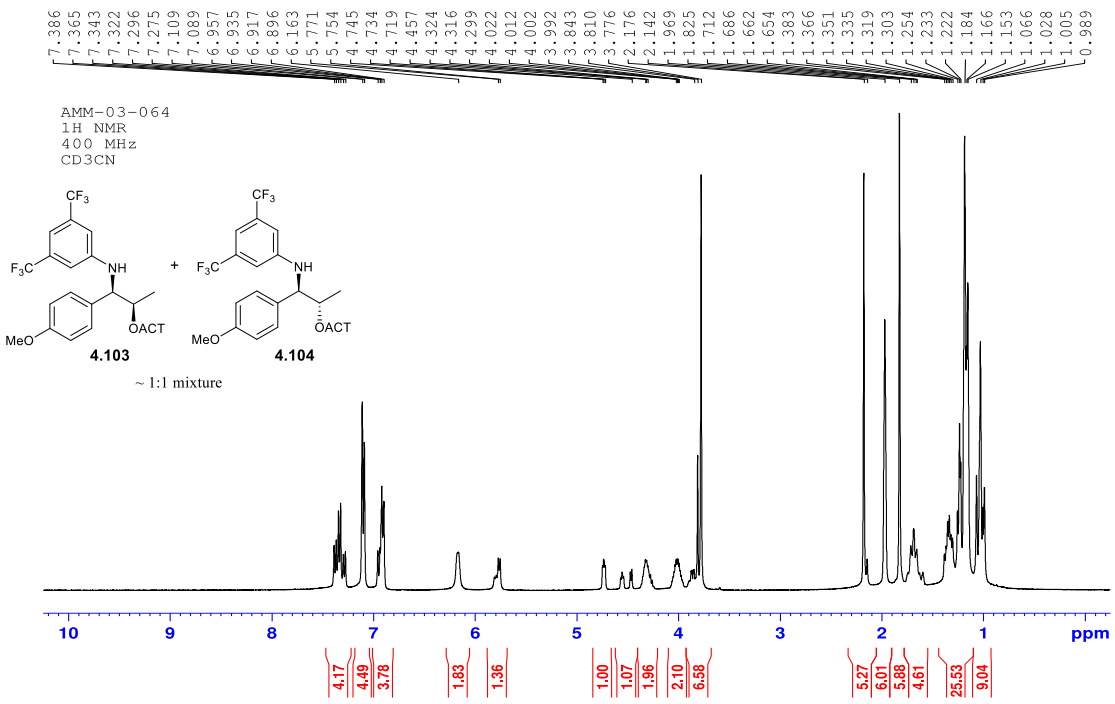

169.37
145.01
140.23
136.18
132.02
128.92
128.54
128.12
126.94
126.84
126.79
115.28
113.61
83.23
81.01
77.35
77.03
76.71
61.25
60.42
49.30
45.92
45.84
41.00
34.12
32.91
23.55
23.23
21.05
20.60
RIM-06-047A
13C NMR
100 MHz
CDCl3
NO2
NH
O
N
O
N
H
4.95
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

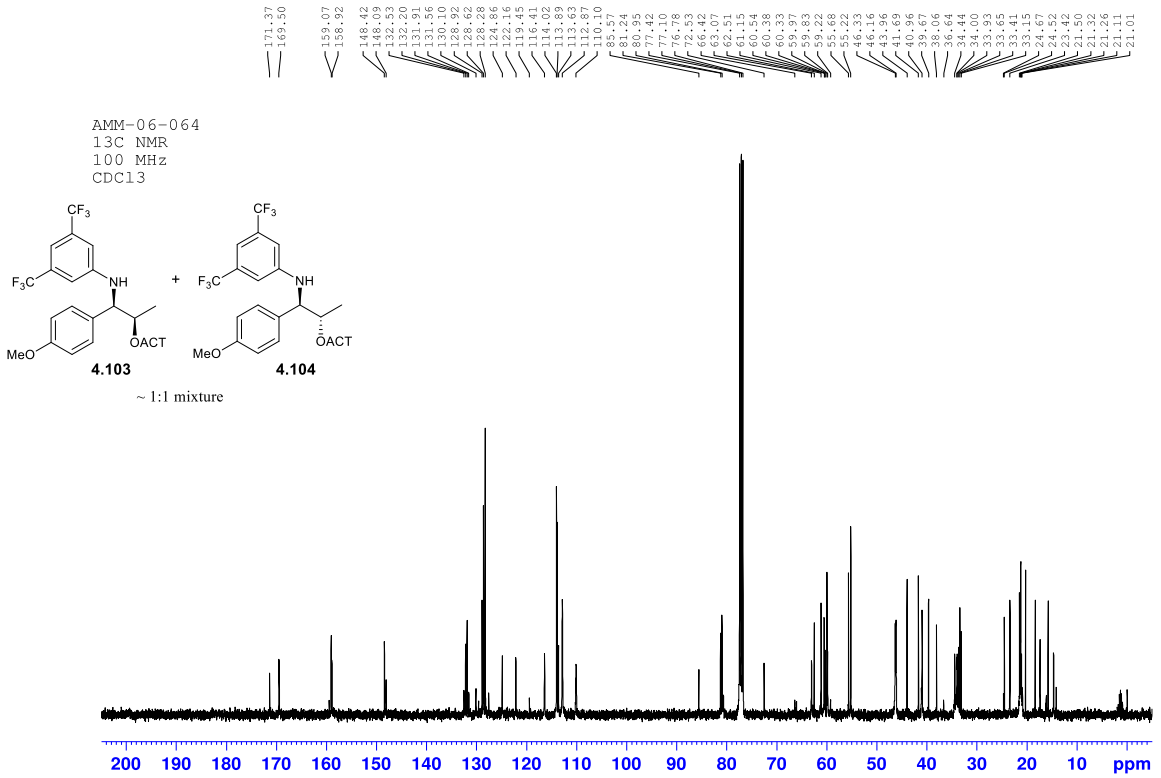

8.894
8.879
8.186
8.183
8.165
8.161
7.300
7.298
7.280
7.260
6.968
6.947
6.648
6.626
6.600
6.590
6.582
6.569
5.119
5.101
5.058
5.044
5.035
5.021
4.177
4.168
4.154
4.146
4.128
4.119
4.109
4.099
4.090
4.079
4.012
3.864
3.819
1.926
1.810
1.802
1.779
1.771
1.744
1.736
1.728
1.713
1.705
1.617
1.296
1.251
AMM-2-118 MR
1H NMR
400 MHz
CDCl3
4.96
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.04
2.43
1.08
3.28
1.06
1.10
2.17
3.05
3.02
2.97
3.08
2.34
0.70
3.10
3.31
1.01
3.31
2.86

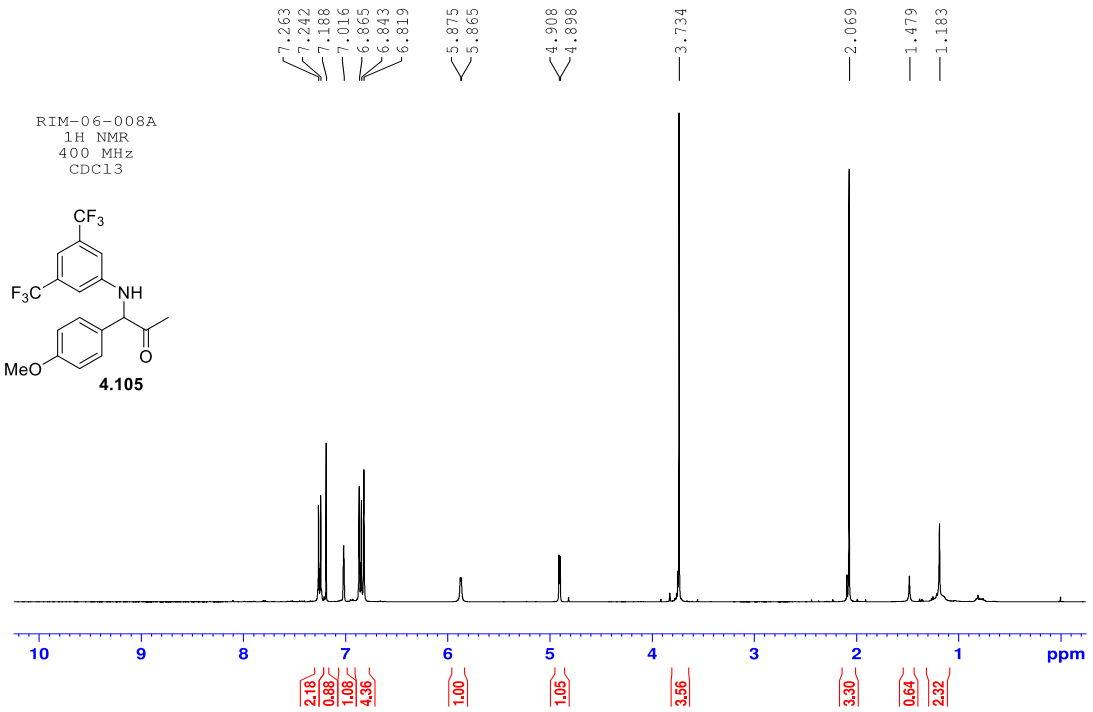

169.40
153.51
151.22
144.86
141.98
136.18
132.46
126.96
124.37
122.36
115.68
115.02
107.23
78.72
61.25
60.96
60.61
60.55
56.14
51.35
46.02
41.15
33.24
32.73
23.76
20.98
20.95
AMM-2-118 MR Carbon
13C NMR
100 MHz
CDCl3
4.96
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

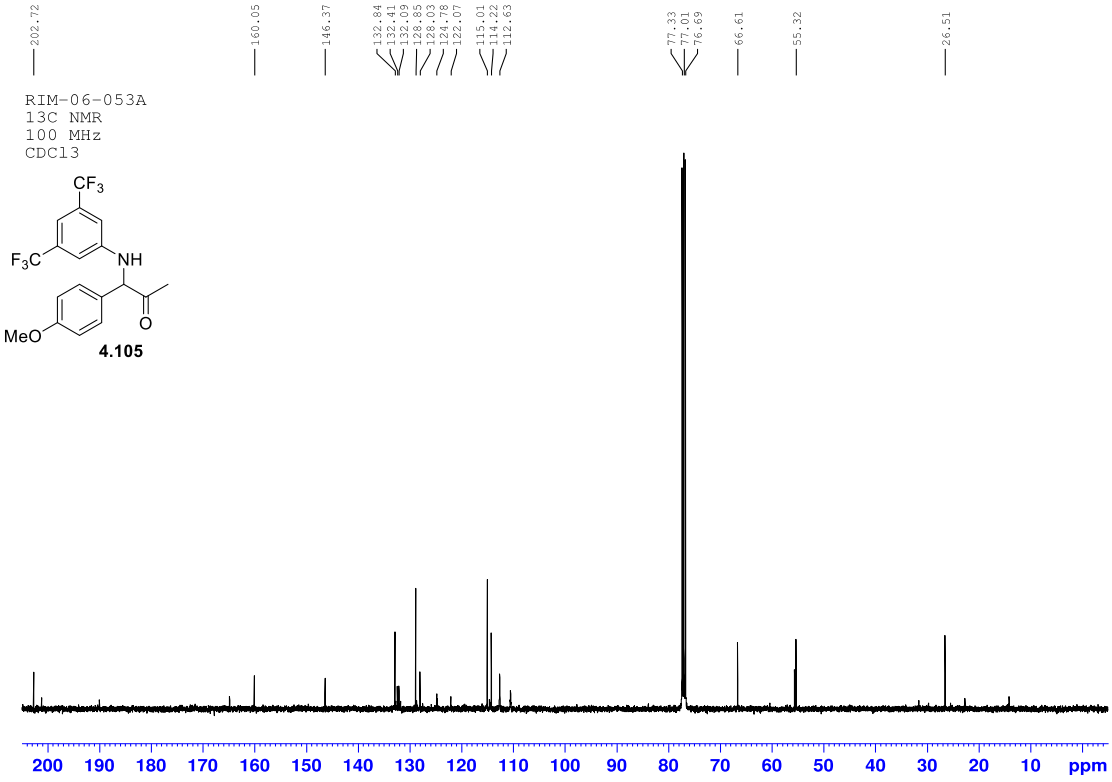

9.528
8.187
8.181
8.158
8.153
7.549
7.525
7.374
7.352
7.326
7.308
7.285
7.261
6.940
6.936
6.912
6.888
6.884
6.551
6.548
6.523
6.499
6.297
6.268
5.226
5.202
4.437
4.066
4.054
4.042
4.028
4.015
1.900
1.710
1.700
1.669
1.256
1.221
1.190
1.041
0.934
AMM-2-101 Pure
1H NMR
300 MHz
CDCl3
NO2
NH
Ph
Ph
O
N
O
N
H
4.97
10
9
8
7
6
5
4
3
2
1
ppm
0.94
1.00
3.98
5.30
1.00
0.99
0.98
0.94
1.96
1.15
3.06
2.24
3.12
6.17
6.07

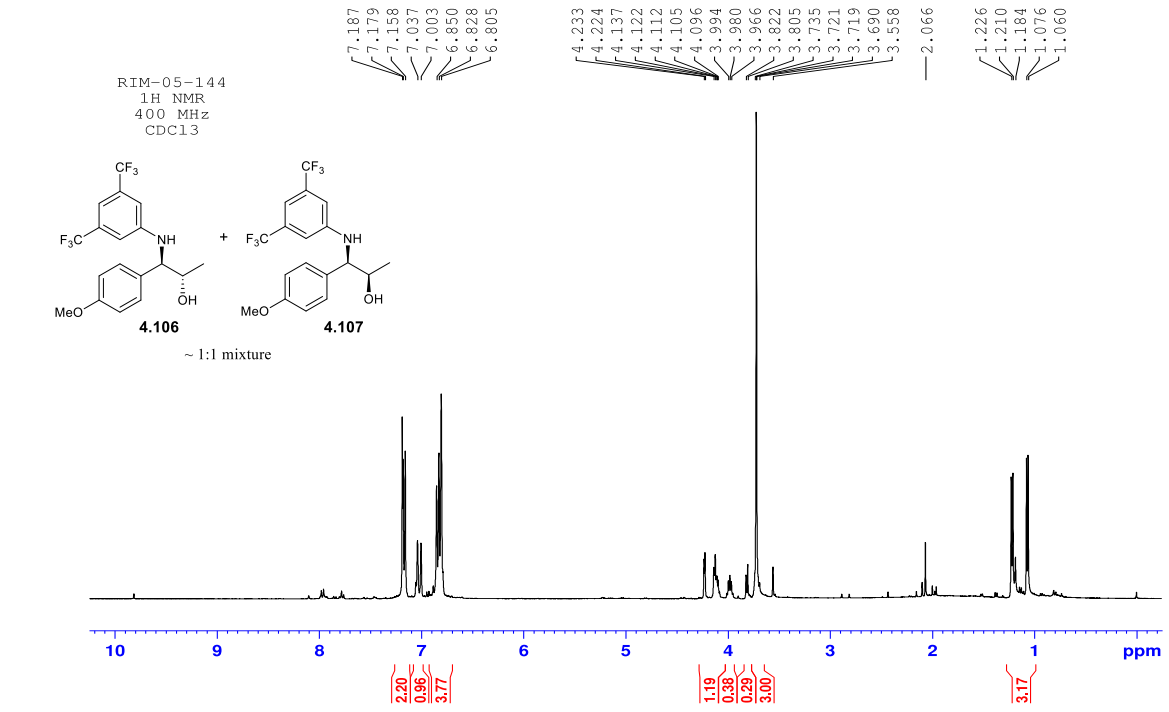

169.38
144.14
140.33
134.65
133.33
128.50
127.80
126.91
118.38
116.01
83.16
77.55
77.23
76.91
66.88
60.69
46.29
41.01
32.69
23.73
20.89
AMM-2-101 MR Carbon
13C NMR
100 MHz
CDCl3
NO2
NH
Ph
Ph
O
N
O
N
H
4.97
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

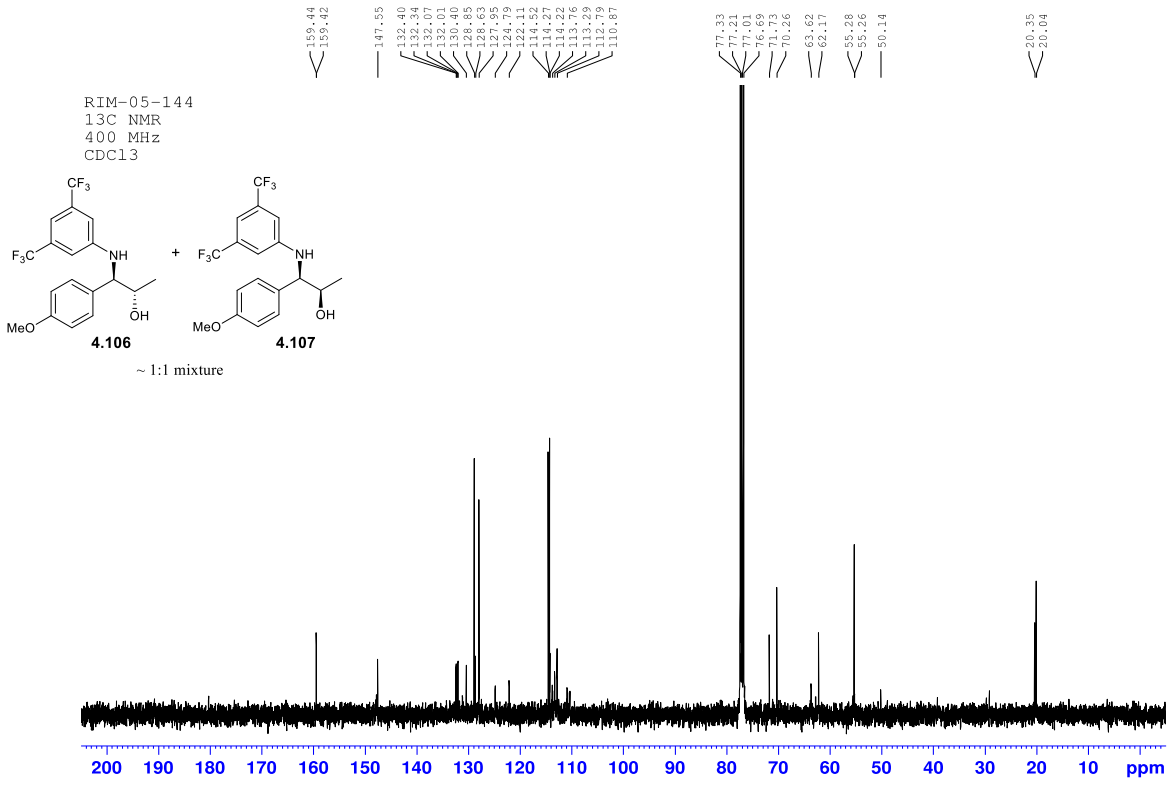

AMM-03-064
1H NMR
400 MHz
CD3CN
4.103
4.104
~ 1:1 mixture
ppm

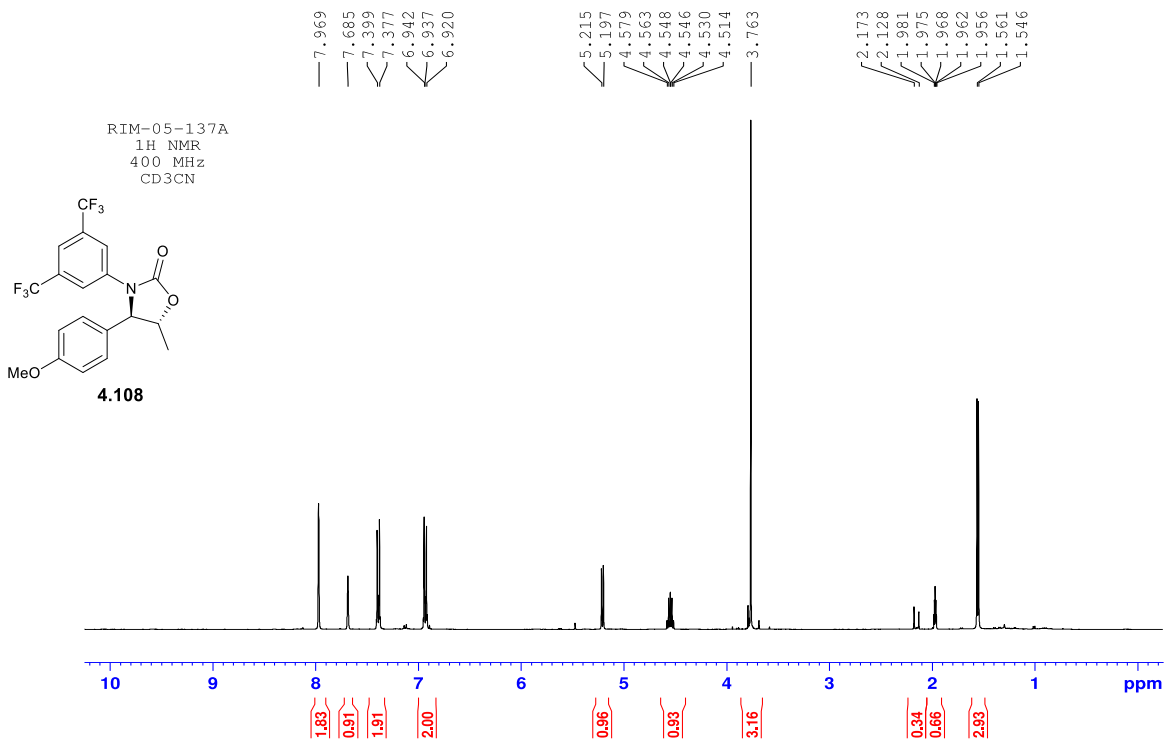

AMM-06-064
13C NMR
100 MHz
CDCl3
4.103
4.104
~ 1:1 mixture
ppm

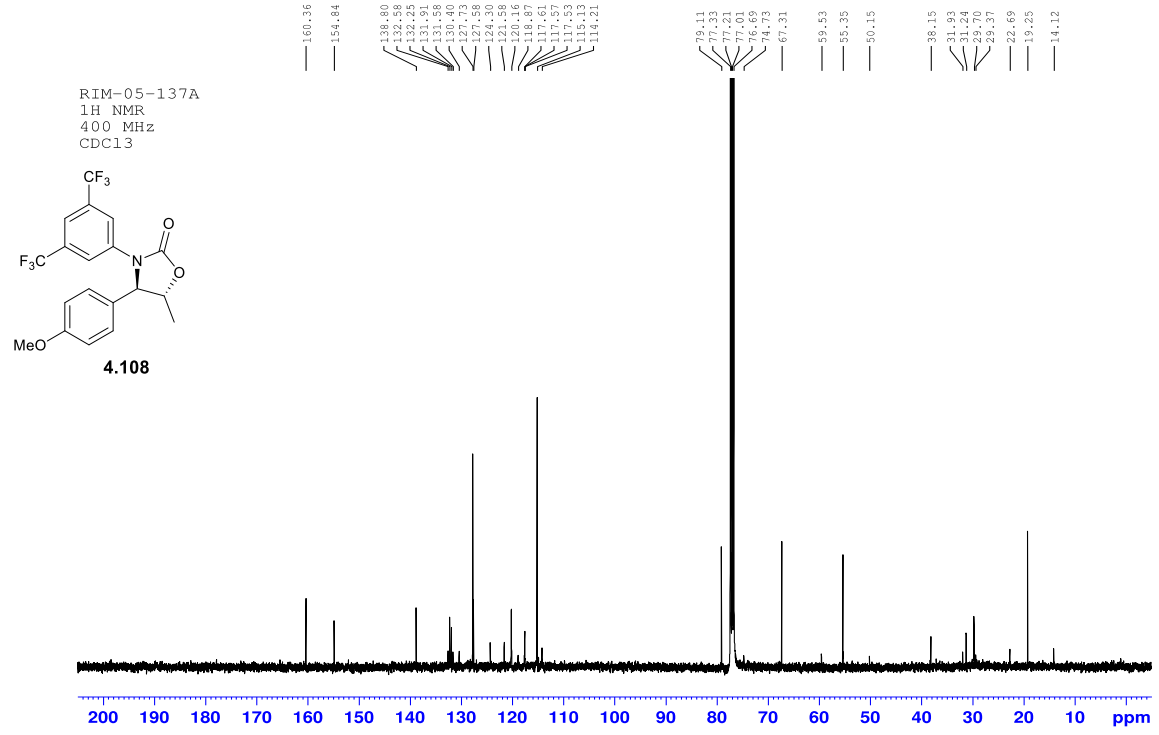

7.263
7.242
7.188
7.016
6.865
6.843
6.819
5.875
5.865
4.908
4.898
3.734
2.069
1.479
1.183
RIM-06-008A
1H NMR
400 MHz
CDCl3
CF3
F3C
NH
MeO
O
4.105
10
9
8
7
6
5
4
3
2
1
ppm
2.18
0.88
1.08
4.36
1.00
1.05
3.56
3.30
0.64
2.32

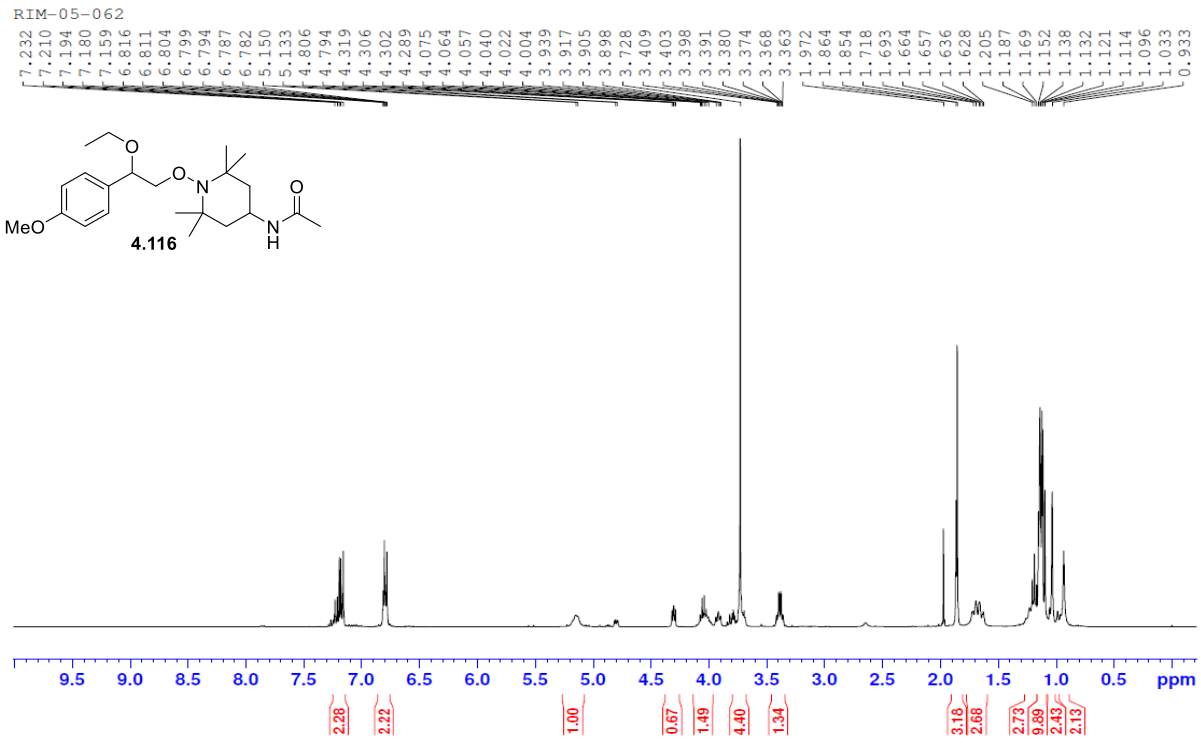

202.72
160.05
146.37
132.84
132.41
132.09
128.85
128.03
124.78
122.07
115.01
114.22
112.63
77.33
77.01
76.69
66.61
55.32
26.51
RIM-06-053A
13C NMR
100 MHz
CDCl3
CF3
F3C
NH
MeO
O
4.105
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

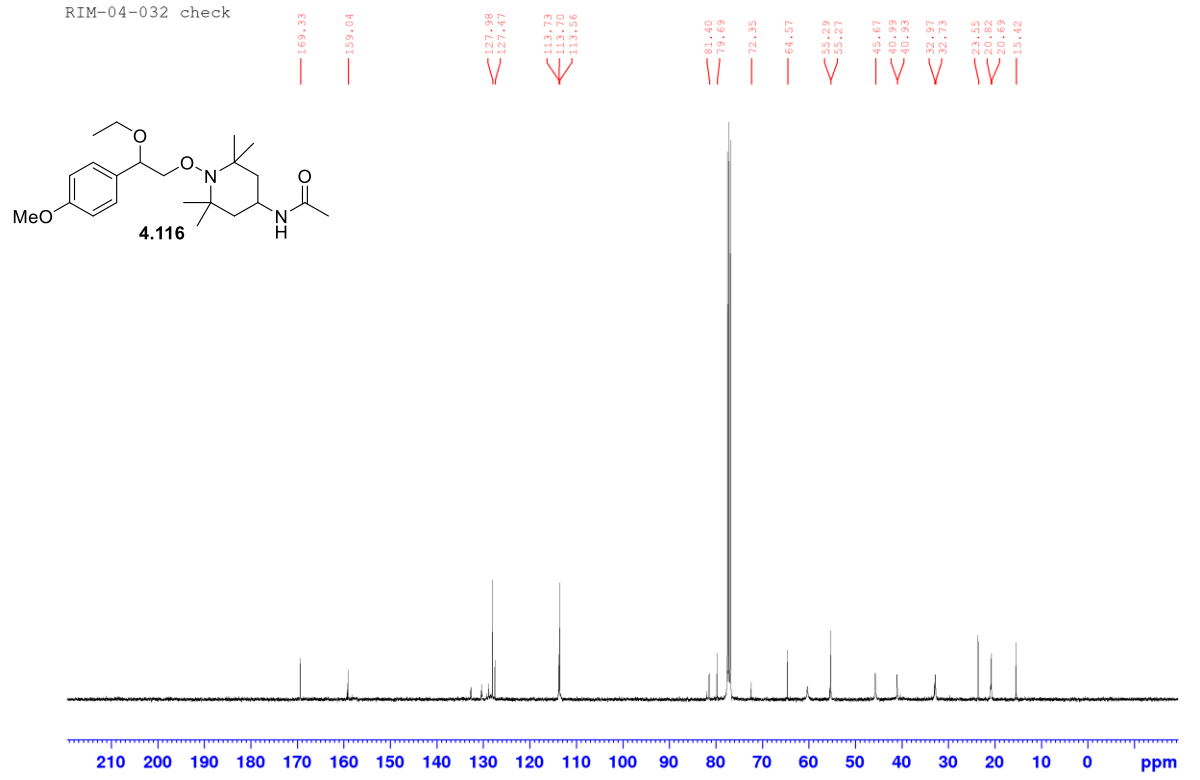

RIM-05-144
1H NMR
400 MHz
CDCl3
4.106
4.107
~ 1:1 mixture
7.187
7.179
7.158
7.037
7.003
6.850
6.828
6.805
4.233
4.224
4.137
4.122
4.112
4.105
4.096
3.994
3.980
3.966
3.822
3.805
3.735
3.721
3.719
3.690
3.558
2.066
1.226
1.210
1.184
1.076
1.060
10
9
8
7
6
5
4
3
2
1
ppm
2.20
0.96
3.77
1.19
0.38
0.29
3.00
3.17

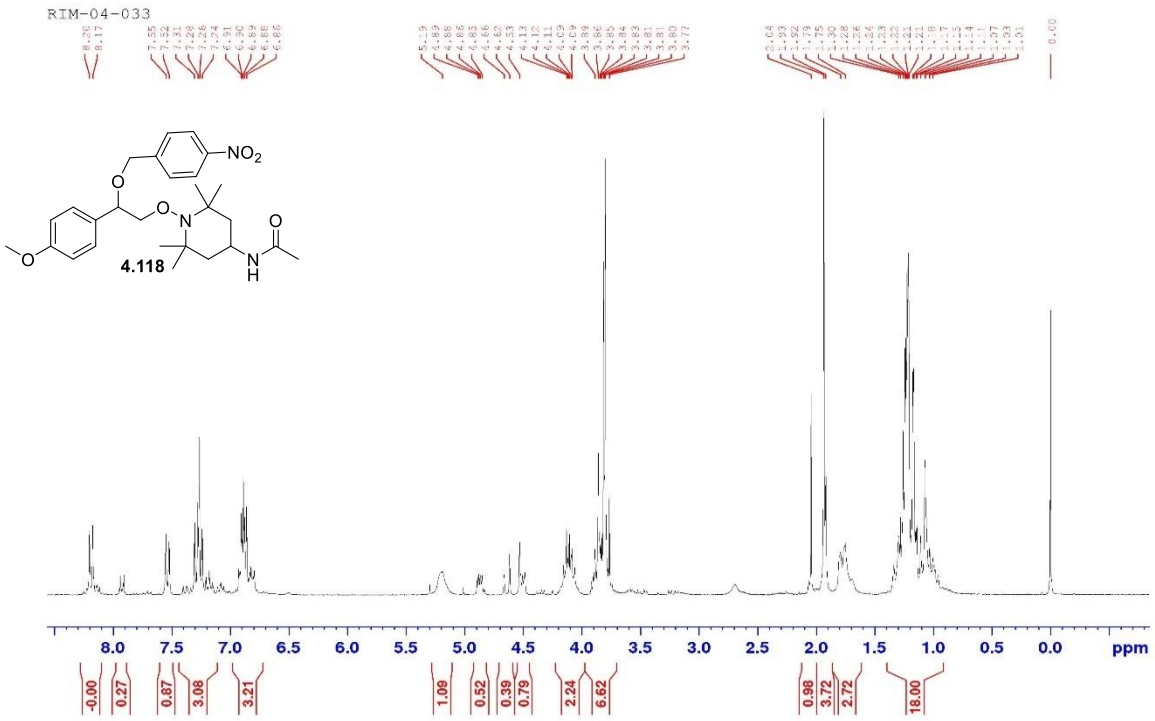

RIM-05-144
13C NMR
400 MHz
CDCl3
4.106
4.107
~ 1:1 mixture
159.44
159.42
147.55
132.40
132.34
132.07
132.01
130.40
128.63
127.95
124.79
122.11
114.52
114.27
114.22
113.76
113.29
112.79
110.87
77.33
77.21
77.01
76.69
71.73
70.26
63.62
62.17
55.28
55.26
50.14
20.35
20.04
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

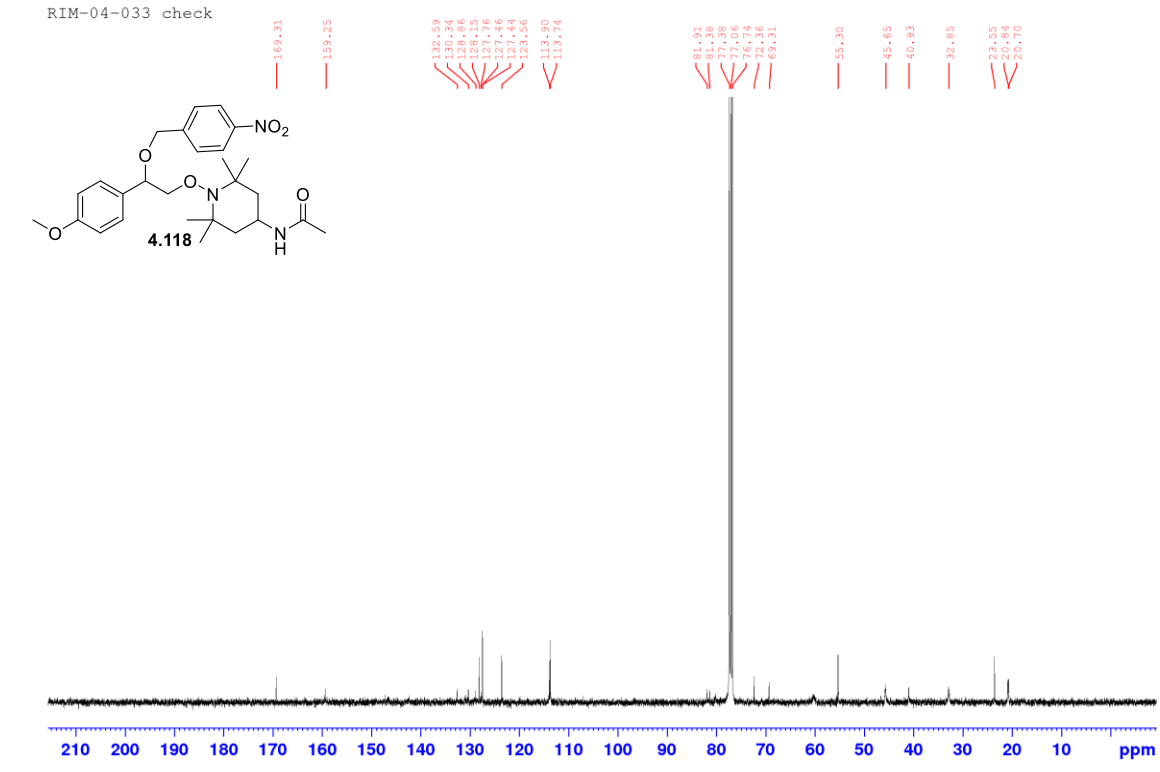

7.969
7.685
7.399
7.377
6.942
6.937
6.920
5.215
5.197
4.579
4.563
4.548
4.546
4.530
4.514
3.763
2.173
2.128
1.981
1.975
1.968
1.962
1.956
1.561
1.546
RIM-05-137A
1H NMR
400 MHz
CD3CN
CF3
F3C
N
O
O
MeO
4.108
10
9
8
7
6
5
4
3
2
1
ppm
1.83
0.91
1.91
2.00
0.96
0.93
3.16
0.34
0.66
2.93

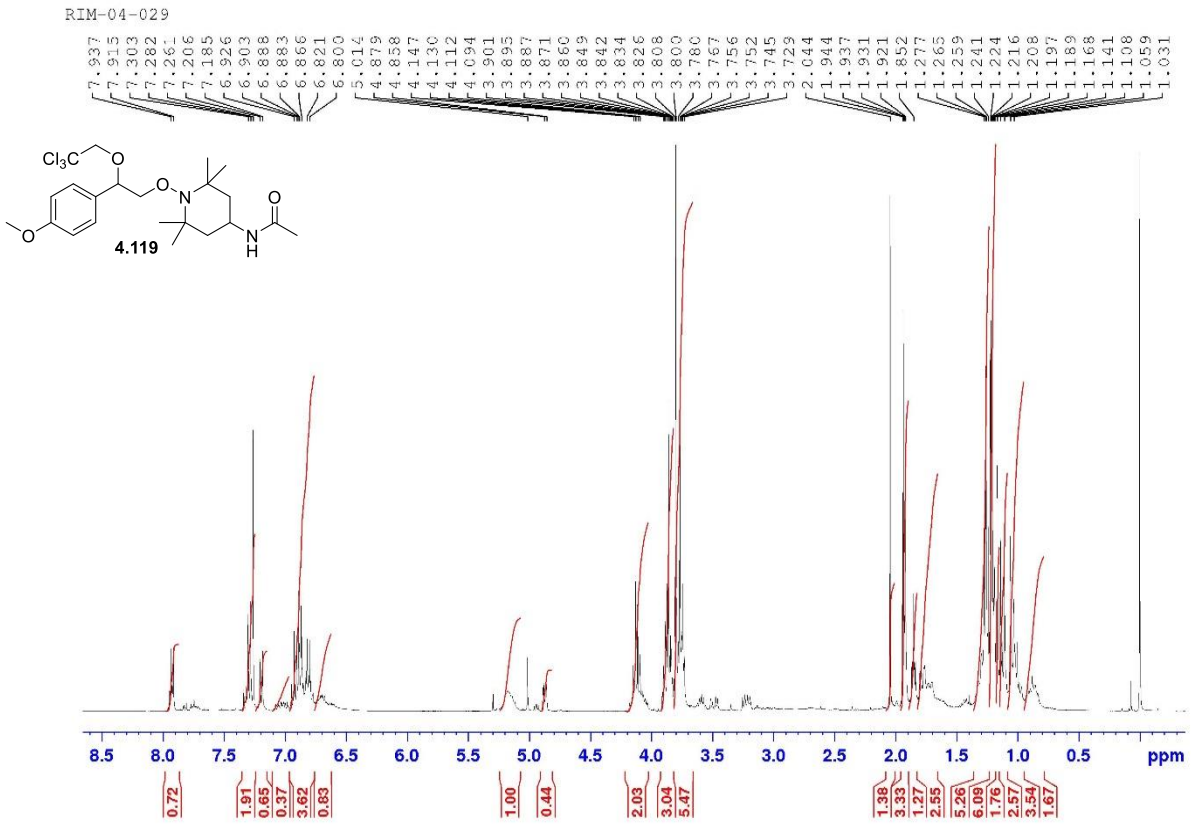

160.36
154.84
138.80
132.58
132.25
131.91
131.58
130.40
127.73
127.58
124.30
123.58
120.16
118.87
117.61
117.57
117.53
115.13
114.21
79.11
77.33
77.21
77.01
76.69
74.73
67.31
59.53
55.35
50.15
38.15
31.93
31.24
29.70
29.37
22.69
19.25
14.12
RIM-05-137A
1H NMR
400 MHz
CDCl3
CF3
F3C
N
O
O
MeO
4.108
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

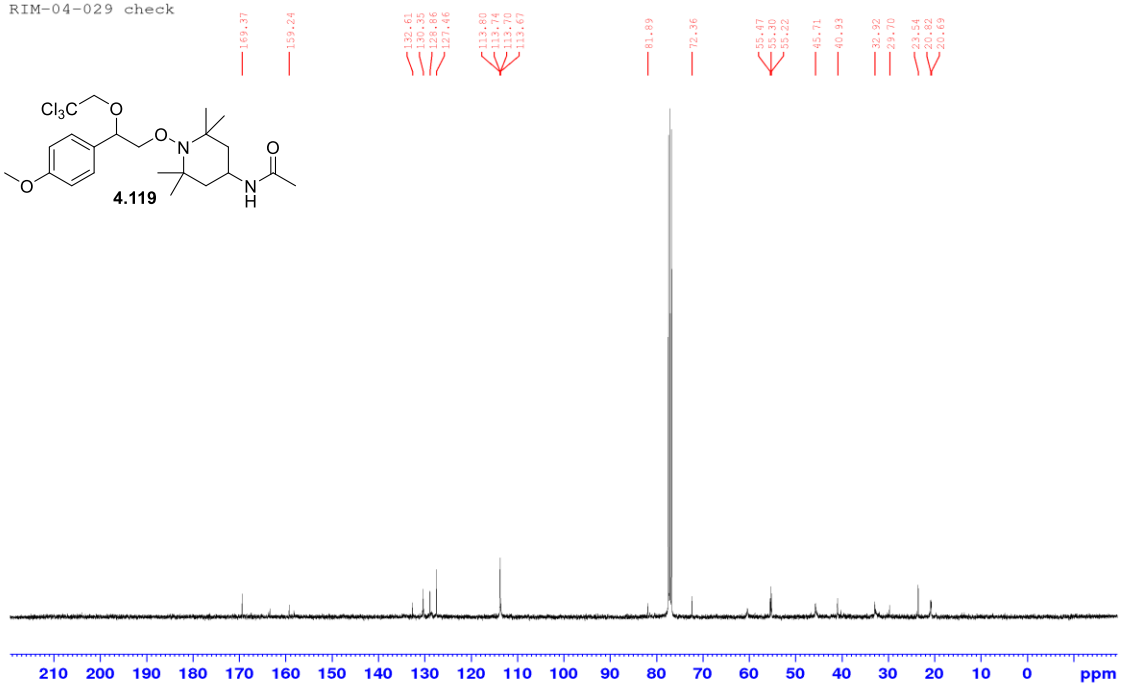

RIM-05-062
7.232
7.210
7.194
7.180
7.159
6.816
6.811
6.804
6.799
6.794
6.787
6.782
5.150
5.133
4.806
4.794
4.319
4.306
4.302
4.289
4.075
4.064
4.057
4.040
4.022
4.004
3.939
3.917
3.905
3.898
3.728
3.409
3.403
3.398
3.391
3.380
3.374
3.368
3.363
1.972
1.864
1.854
1.718
1.693
1.664
1.657
1.636
1.628
1.205
1.187
1.169
1.152
1.138
1.132
1.121
1.114
1.096
1.033
0.933
MeO
O
N
O
N
H
O
4.116
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.28
2.22
1.00
0.67
1.49
4.40
1.34
3.18
2.68
2.73
9.89
2.43
2.13


RIM-04-032 check
169.33
159.04
127.98
127.47
113.73
113.70
113.56
81.40
79.69
72.35
64.57
55.29
55.27
45.67
40.99
40.93
32.97
32.73
23.55
20.82
20.69
15.42
MeO
O
N
O
N
H
O
4.116
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


RIM-04-033
NO2
O
O
N
O
N
H
O
O
4.118
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
0.00
0.27
0.87
3.08
3.21
1.09
0.52
0.39
0.79
2.24
6.62
0.98
3.72
2.72
18.00


RIM-04-033 check
NO2
O
O
N
O
N
H
O
O
4.118
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


RIM-04-029
4.119
ppm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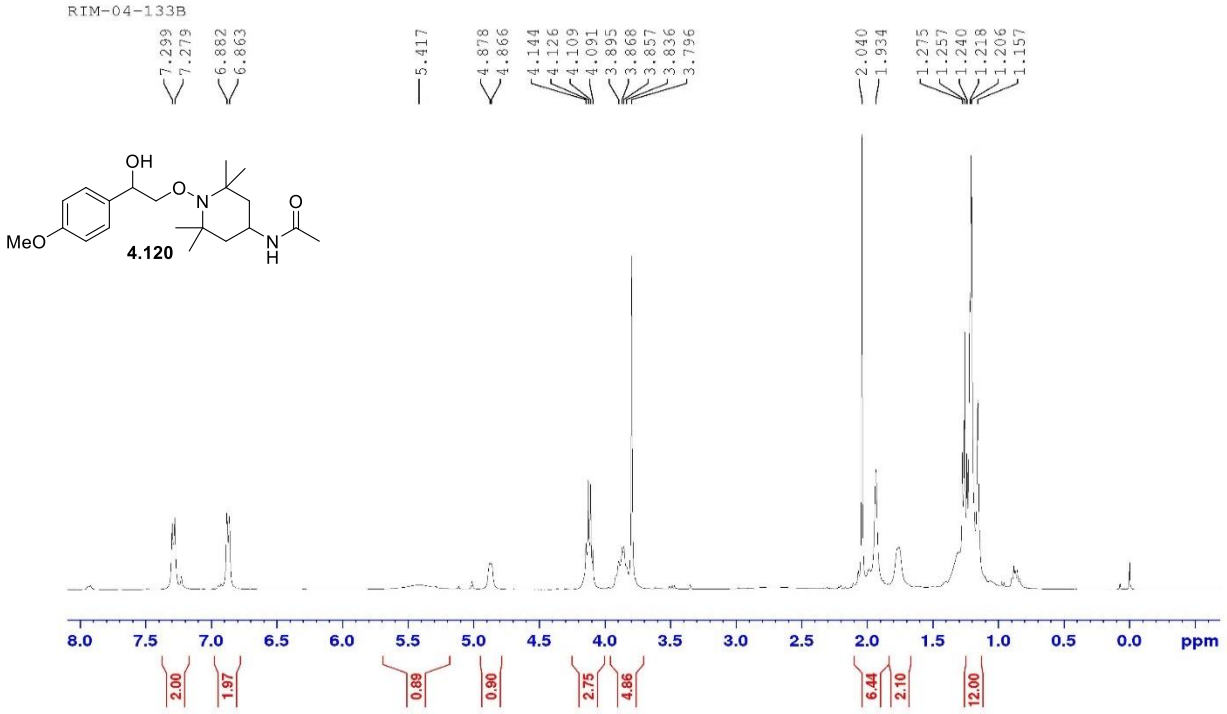
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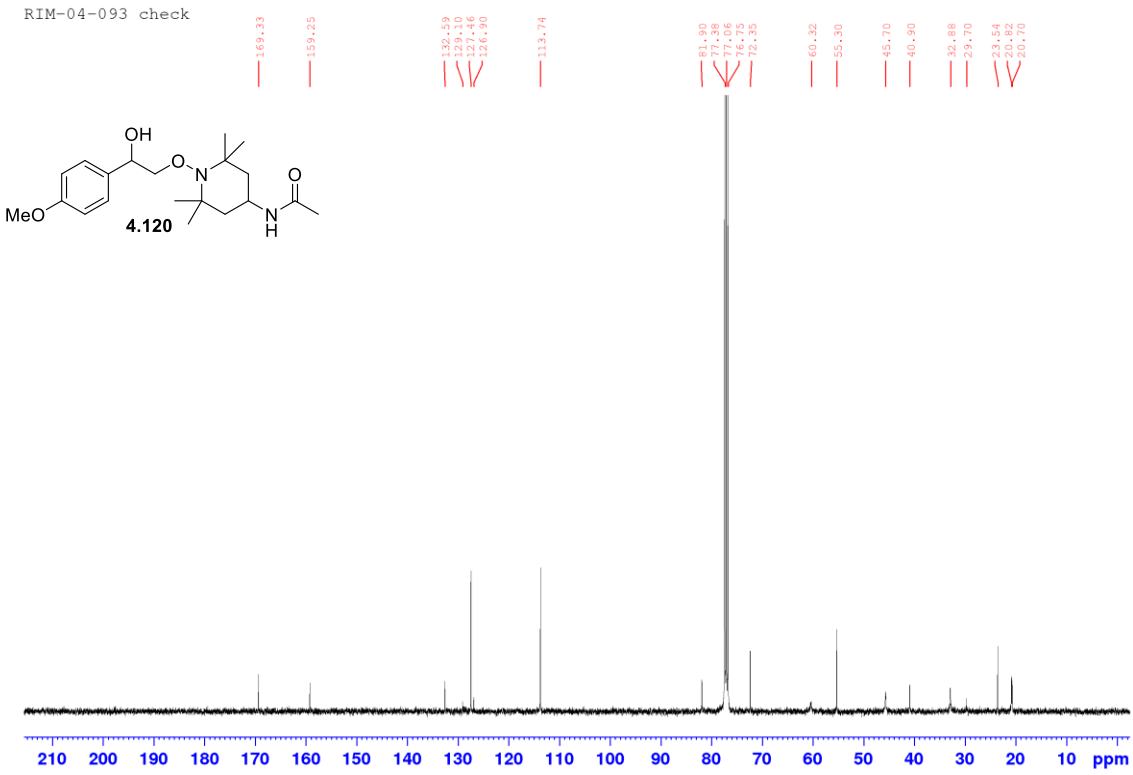
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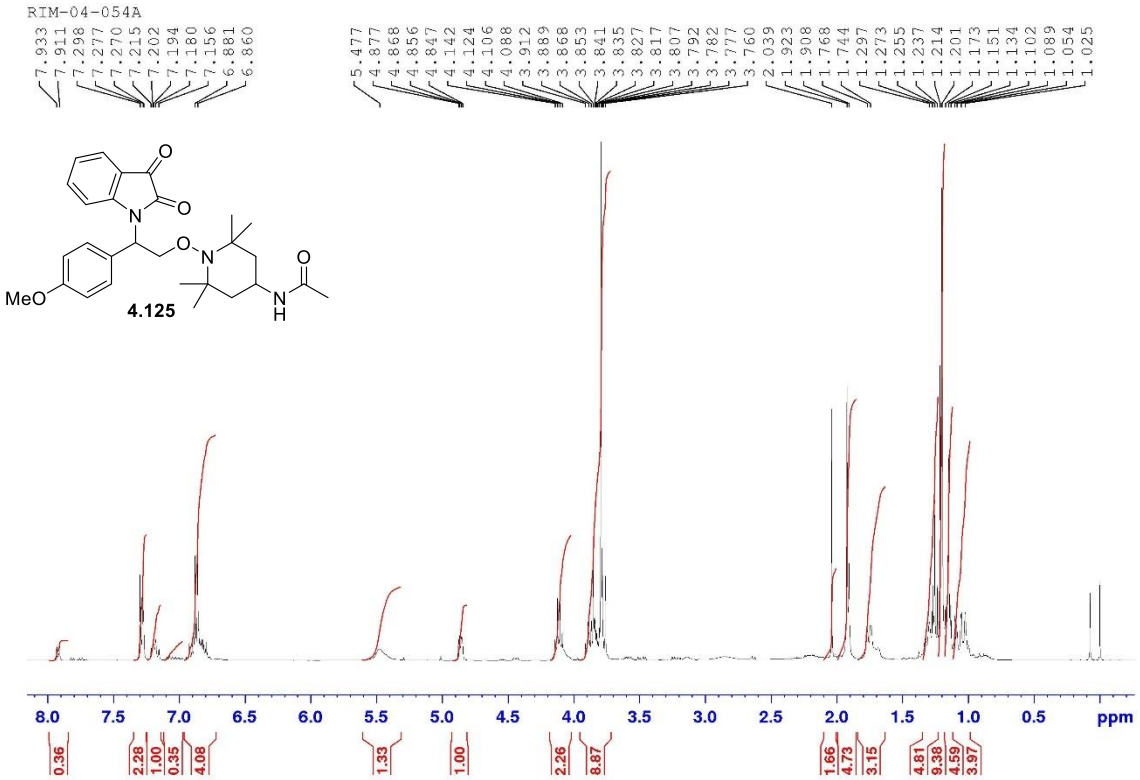
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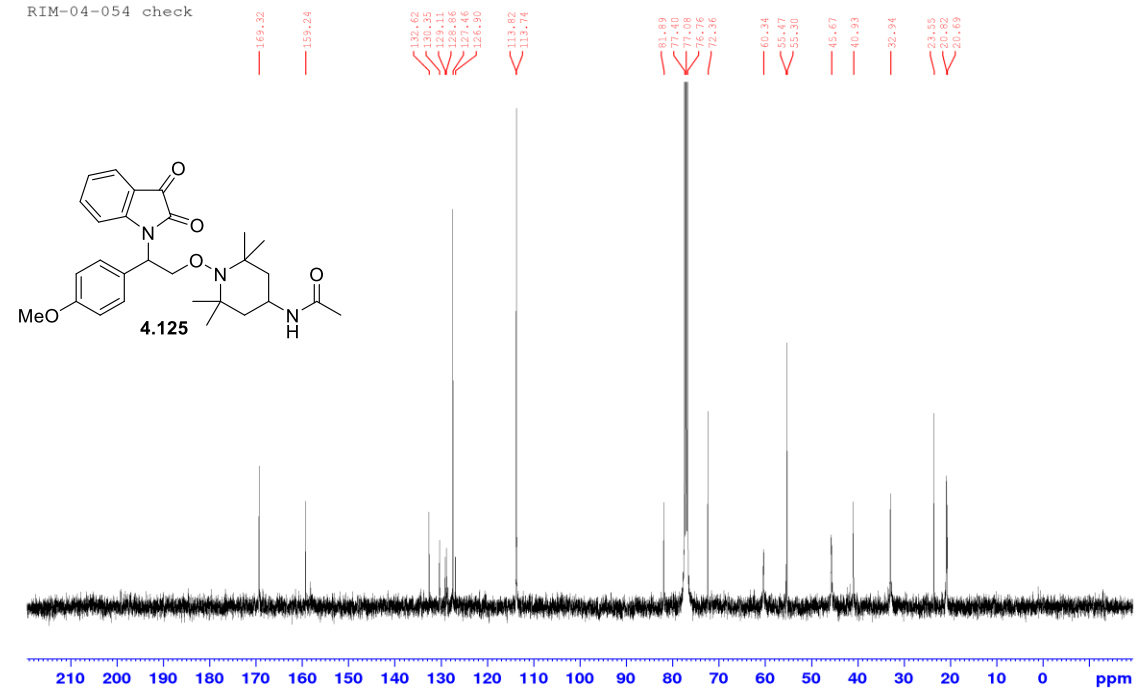
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60.34
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20.82
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Rowan Meador

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EDUCATION

Syracuse University – Syracuse, NY, **August 2016 – October 2021**
PhD in Chemistry

Syracuse University – Syracuse, NY **Spring 2018**
Masters of Philosophy in Chemistry
Gettysburg College – Gettysburg, PA, **Jan 2013- May 2016**
Bachelor of Science in Chemistry, Minor in Mathematics
Lancaster University – Lancaster, UK, Fall 2014
University of New England – Biddeford, ME, Fall 2012

AWARDS and HONORS

- GAAN Fellowship from Syracuse University Aug. 2017 – Aug. 2018
- J. B. Zinn Research Award from Gettysburg College, May 2016

RESEARCH EXPERIENCE

Department of Chemistry, Syracuse University, Syracuse, NY
Doctoral Research **2016 – present**
Research Advisor: Dr. John D. Chisholm

- Palladium catalyzed rearrangement of benzylic trichloroacetimidates to trichloroacetamides
- Exploration of enantioselective reactions
- Investigation of new *N*-oxoammonium salts additions of alkenes
- Synthesis of *N*-oxoammonium salts and DDQ derivatives
- Investigation of Oxoammonium Salt Mediated oxidations

Department of Chemistry, Gettysburg College, Gettysburg, PA
Undergraduate Research **2015-2016**
Research Advisor: Dr. Timothy W. Funk

- Exploring Oxidative Cyclizations of Diols to Lactones Using Iron Catalysts

Undergraduate Summer Research **2014-2015**
Research Advisor: Dr. Timothy W. Funk

- Multi-step synthesis of strained alkyne
- Oxidative cyclizations of diols to lactones using iron catalysts

TEACHING EXPERIENCE

Syracuse University **Fall 2016 – Fall 2020**
Teaching Assistant

- General Chemistry Lab (Fall 2016)
- Organic Chemistry Recitation (Spring 2017, Fall 2018, Spring 2019, Spring 2020, Fall 2020)

Future Professoriate Program **Fall 2016 – Spring 2021**

- SCI 544 – Teaching of College Science

- Course description: Analysis of teaching techniques and focus on more active learning methods. Supervised teaching experiences to help improve as a college teacher.
- Attend seminars on current research in the field

Mentoring and training **Fall 2017 – Spring 2021**

- Mentored and trained undergraduate and graduate students in good lab practice.
- Trained students how to use equipment, analyze data, problem solve in an organic research lab.
- Taught organic mechanisms relevant to project.

Gettysburg College **2013 – 2016**

Teaching Assistant

- General Chemistry Lab
- General Chemistry Recitation
- Organic Chemistry Lab

Peer Science Mentor

- Tutor students with general chemistry lecture topics, hold review sessions. Certified peer mentor.

PUBLICATIONS

Meador, R. I. L.; Anderson, R. E.; Chisholm, J. D. "Tandem Elimination-Oxidation of Tertiary Benzylic Alcohols with an Oxoammonium Salt" *Org. Biomol. Chem.* **2021**, *19*, 6233-6236. DOI: 10.1039/D1OB00965F

Millimaci, A. M.; **Meador, R. I.L.**; Dampf, S. J.; Chisholm, J. D. "Metal Free Amino-Oxidation of Electron Rich Alkenes Mediated by an Oxoammonium Salt." *Isr. J. Chem.* **2021**, *61*, 322-326. DOI: 10.1002/ijch.202000080. *ChemRxiv* DOI:10.26434/chemrxiv.12988682.v1.

Tang, Y.; **Meador, R. I. L**.; Malinchak, C. T.; Harrison, E. E.; McCaskey, K. A.; Hempel, M. C.; Funk, T. W., (Cyclopentadienone)iron-Catalyzed Transfer Dehydrogenation of Symmetrical and Unsymmetrical Diols to Lactones. *J. Org. Chem.* **2020,** *85*, 1823-1834. DOI: 10.1021/acs.joc.9b01884

Mahajani, N. S.; **Meador, R. I. L.**; Smith, T. J.; Canarelli, S. E.; Adhikari, A. A.; Shah, J. P.; Russo, C. M.; Wallach, D. R.; Howard, K. T.; Millimaci, A. M.; Chisholm, J. D. "Ester Formation via Symbiotic Activation Utilizing Trichloroacetimidate Electrophiles" *J. Org. Chem.* **2019**, *84*, 7871-7882. DOI: 10.1021/acs.joc.9b00745

PRESENTATIONS

"Exploring Oxidative Cyclizations of Diols to Lactones Using Iron Catalysts," Gettysburg College Celebration, Gettysburg College, Gettysburg, PA, May 2016, Poster Presentation

"Exploring Oxidative Cyclizations of Diols to Lactones Using Iron Catalysts," Intercollegiate Student Chemists Convention, Ursinus College, Collegeville, PA, April 2016, PowerPoint Presentation

"Exploring Oxidative Cyclizations of Diols to Lactones Using Iron Catalysts," American Chemical Society National Meeting, San Diego, March 2016, Poster Presentation

"Exploring Oxidative Cyclizations of Diols to Lactones Using Iron Catalysts," Gettysburg College Chemistry Seminar, Gettysburg College, Gettysburg, PA, Fall 2015, Power Point Presentation

"Synthesis of a Photo-cleavable Linker for GlcNAc-ligated Protein Purification," Gettysburg College Celebration Gettysburg College, Gettysburg, PA, May 2015, Poster Presentation

"Synthesis of a Photo-cleavable Linker for Protein Purification," Gettysburg College Chemistry Seminar, Spring 2015, PowerPoint Presentation

TECHNICAL SKILLS

- Multi-step synthesis of organic compounds
- Calibration curves for GC analysis, HPLC analysis, and UV-Vis analysis
- Characterization of organic compound by ^{1}H NMR, ^{13}C NMR, 2D NMR, elemental analysis, and HPLC
- Determination of reaction conversions by ^{1}H NMR,
- Strong knowledge of HyperChem, ChemDraw, LaText, R, MatLab, Microsoft Word, Excel, Powerpoint, and Prezi.
- Strong verbal and written communication

RELATED EXPERIENCE

Museum of Science and Technology (MOST) Volunteer **Spring 2019 – Present**
Syracuse, NY

- Work with MOST educators to teach children about different areas of science.

President of Sceptical Chymist Club **Aug. 2015 – May 2016**
Gettysburg College, Gettysburg, PA

- Organize guest lecturers to speak at Gettysburg College, plan dinners with visiting speakers, construct experiments for social events.

Camp Invention Leadership Intern **Summers 2011 - 2013, 2015**
Pottstown, PA

- Construct games related to science modules, instruct about 10 children (ages 8-10) in science module group activities, liaison to parents throughout the camp experience.

University of New England Neuroscience Club **Fall 2012**
Biddeford, ME

- Work with Neuroscience department to promote the field, teach children of all ages about the brain, train in several modules to teach the children, travel to surrounding area schools.