2024

Asymmetric CuH-catalyzed Reductive Coupling of Allenamides with Carbonyl and Imine Electrophiles

Stephen Collins
Virginia Commonwealth University

Asymmetric CuH-catalyzed Reductive Coupling of Allenamides with Carbonyl and Imine Electrophiles

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University

by

Stephen Andrew Collins

Bachelor of Science, University of North Carolina at Charlotte, 2019

Advisor and Dissertation Director: Dr. Joshua D. Sieber, Assistant Professor, Department of Chemistry

Committee: Dr. Joshua Sieber, Dr. Julio Alvarez, Dr. Vladimir Sidorov, Dr. Thomas Roper

Virginia Commonwealth University

Richmond, Virginia

April 2024

ABSTRACT

Asymmetric CuH-catalyzed Reductive Coupling of Allenamides with Carbonyl and Imine Electrophiles

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

By Stephen A. Collins

Virginia Commonwealth University, 2024

Advisor: Dr. Joshua D. Sieber, Assistant Professor, Department of Chemistry

The carbon scaffold of many drugs and natural products contain multiple stereogenic centers bearing heteroatoms. As a result of this, chemists have long sought methods to efficiently install these multi-heteroatom functionalities. Reductive coupling reactions have been extensively studied over the past decades, and the allylation of carbonyls via the reductive coupling approach has been a key method for generating chiral allylic alcohols. This work utilizes inexpensive Cu for the asymmetric reductive coupling of allenamides with carbonyls or imines to simultaneously install two heteroatoms (either oxygen and nitrogen or nitrogen and nitrogen, respectively) onto the

product. These molecules have a polarity profile that makes them difficult to make using traditional methods. Herein, we report a method for the asymmetric reductive coupling reactions. Chapter 1 describes the development of a regio- and diastereoselective CuH-catalyzed reductive coupling of *N*-based allenes and imines, where stereoselectivity is controlled by a chiral auxiliary. This protocol provides access to branched products bearing the 1,2-diamine motif. Chemical transformations were performed on one of the branched products to furnish an aminopiperidine derivative that is a valuable intermediate to a major fragment of the potent NK-1 inhibitor compounds CP-99,994 and CP-122,721. Chapter 2 details the development of an asymmetric enantioselective aminoallylation of ketones, which builds on work previously published by our laboratory. This new protocol massively increases the enantiocontrol over this transformation by preventing an on-cycle carbamate migration that eroded enantioselectivity in the previous work and used allenamide protecting groups that were easier to cleave. This protocol provides an atom-economical approach for the synthesis of 1,2-aminoalcohols. Chapter 3 describes ongoing attempts to develop an asymmetric enantioselective aminoallylation of aldimines. This protocol would provide the same branched 1,2-diamine motif, as stated previously, but in a manner that would be more atom economical due to the chirality being provided by the catalyst instead of a chiral auxiliary.

This work is dedicated to:

Gretchen Fink

Michael Collins

Michael Woodliff

Skylar Woodliff

Jacob Woodliff

Caleigh Watkins

ACKNOWLEDGEMENTS

I would like to take the time to thank my advisor, Dr. Joshua Sieber, for his guidance and unparalleled knowledge. This would not have been possible without you, and I would not be anywhere near the quality of chemist that I am if not for you.

My fellow Sieber group members for their friendship, collaboration, and assistance in collecting data for various research projects.

My parents, Gretchen Fink and Michael Collins, and Brother, Michael Woodliff, for always believing in and supporting me, and for your constant love and guidance. I would not be the person I am today without you.

My friend, Jacob Lipovsky, for being one of the best friends I have had since starting my undergraduate degree. Since that time, you have always had my back through thick and thin. The experiences we've shared and will continue to share will be something that I will always remember.

To all of the friends that I have made in graduate school: Mike, Corey, Francisco, Jacob, Aidan, and Griffin. The experiences that I have shared with you all have been some of the most fun that I have ever had and hopefully there will be more to come.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF SCHEMES

LIST OF ABBREVIATIONS

Cy	cyclohexyl
DCM	dichloromethane
DIBAL	diisobutylaluminium hydride
DMF	dimethyl formamide
equiv	equivalence
Et	ethyl
EtOAc	ethyl acetate
FG	functional group
Hex.	hexane
IPr	Isopropyl
Me	methyl
MS	molecular sieves
MsCl	methanesulfonyl chloride
MTBE	methyl tertiary-butyl ether
Ph	phenyl
PhCF3	trifluorotoluene
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
t-Bu	tertiary-butyl
THF	tetrahydrofuran
TMS	Trimethylsilyl

Chapter 1 Development of Asymmetric CuH-Catalyzed Reductive Coupling of a Chiral Allenamide with Aldimine Electrophiles

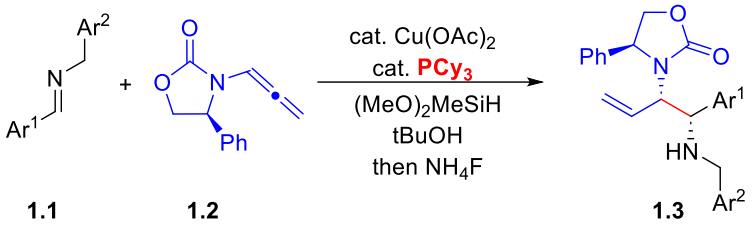
I. Introduction

Chiral molecules containing multi-heteroatom functional groups are ubiquitous in drugs and natural products.[1–3] These compounds, such as aminoalcohols[4] and diamines[5], have widespread applications in these areas and thus it has become necessary to develop synthetic methodologies to access these motifs in a high yielding and highly sterio- and enantioselective manner.

Depending on the substitution pattern these multi-heteroatom functional groups can range from simple to extremely challenging to synthesize. These methodologies are difficult to develop when the polar functional groups are arranged in configurations that result in a mismatch of the heteroatom induced polarization throughout the carbon framework of the molecule.[6] These particular substitution patterns need to be prepared through unconventional routes such as reversing the polarity of one of the reactants.[7] Perhaps one of the simplest ways to effect a transformation that would bring together two fragments containing electron-withdrawing groups would be through the use of reductive coupling.

This work advances the field of CuH-catalysis for organic synthesis by inverting the inherent polarity profiles of allenamide containing fragments to generate dissonant molecules that would otherwise be difficult to synthesize. This chapter discusses the development of a diastereoselective CuH-catalyzed reductive coupling of a chiral *N*-substituted allenamide derived from Evans' oxazolidinone and aldimine electrophiles (**Scheme 1.1**).

Scheme 1.1: *Method Development for CuH-Catalyzed Reductive Coupling of Allenamides and Imine Electrophiles*



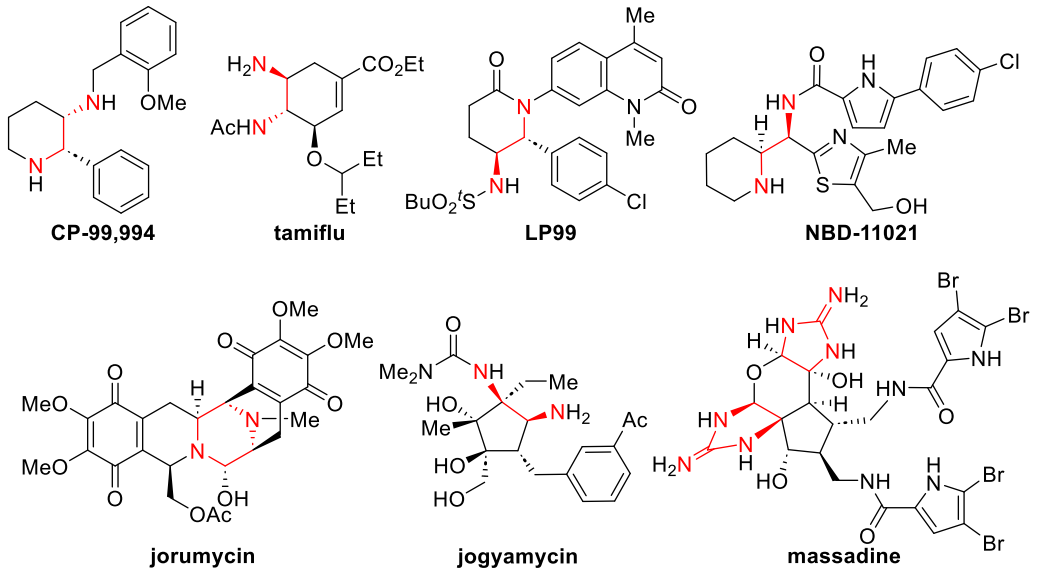
1.1 **1.2** **1.3**

II. Background

A. Multi-Heteroatom Containing Natural Products and Drugs

In both nature and the pharmaceutical industry many examples can be found of highly functionalized molecules.[8–11] These molecules (**Fig 1.1**) often contain multiple chiral heteroatoms, especially amines and alcohols, and can be challenging to synthesize. Consequently, unique methodologies must be developed to synthesize them in an enantioselective and high yielding manner.

Figure 1.1*: Multi-Heteroatom Containing Natural Products and Drugs*



CP-99,994 **tamiflu** **LP99** **NBD-11021**

jorumycin **jogyamycin** **massadine**

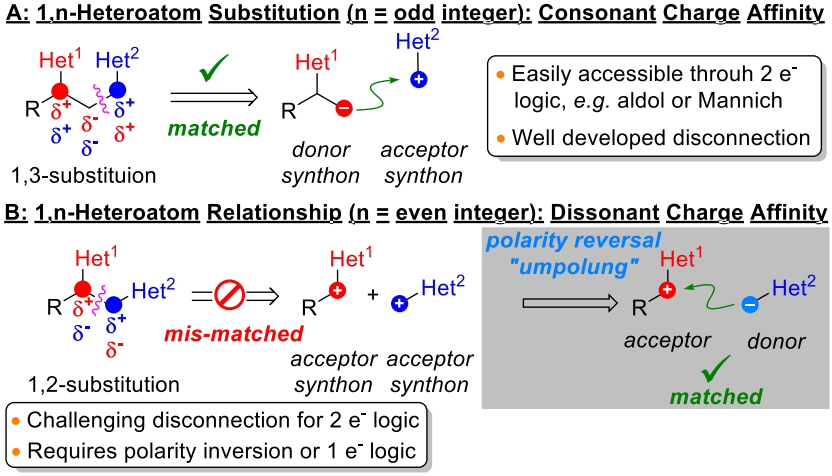
B. Methods of Introducing Chiral Amines and Alcohols

There are many possible methods of synthesizing chiral amines and alcohols. Enantioselective hydroamination[12] and hydroxylation[13] represent one potential method of accessing these motifs. Asymmetric transfer hydrogenation of carbonyl and imine containing compounds showcases another approach.[14] These methods all depict viable ways of accessing chiral amines or alcohols, but one potential issue with these reactions is that they are mainly only focused on introducing one chiral functional group into the molecule. There exists a plethora of examples, like the ones shown before, where molecules contain multiple chiral functional groups. Thus, it would be a great addition to the chemist's toolkit for reactions that introduce multiple chiral heteroatomic functional groups into a molecule in a single step.

C. Consonant/Dissonant Theory

When considering synthetic pathways to synthesize a compound containing multiple heteroatoms the difficulty is dependent on the congruence of the polarities induced by the heteroatoms. If the heteroatoms have a substitution pattern that results in a matching of the induced polarizations, termed "consonant charge affinity" (**Fig 1.2 A**), then the disconnection is easily achievable through two-electron logic.[15,16] However, if the substitution pattern is such that there is a mis-match in the induced polarizations, termed "dissonant charge affinity" (**Fig 1.2 B**), then common two-electron logic is not easily applicable. In these cases, either one-electron logic (radical chemistry) or polarity inversion (umpolung) is typically applied.[6,17,18]

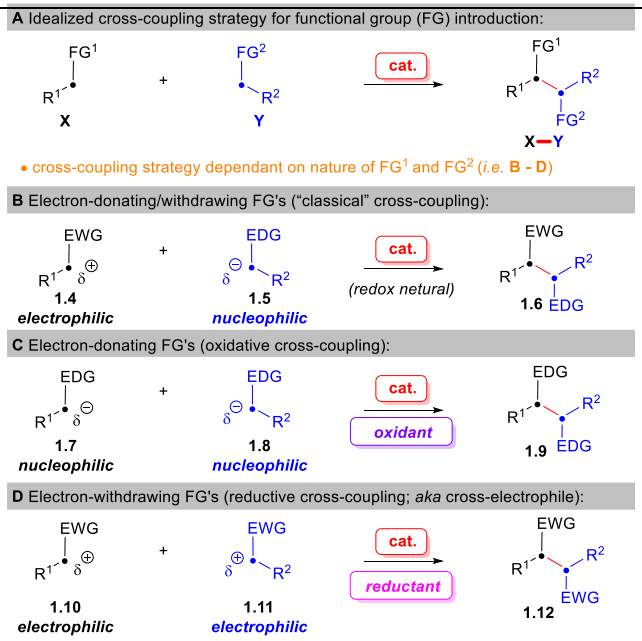
Figure 1.2: *Consonant and Dissonant Theory in 1,n-substituted molecular frameworks with electron-withdrawing heteroatom groups*[19]



D. Coupling Theory

The idealized strategy for forming molecules containing multiple functional groups would be using cross-coupling, wherein fragment **X** containing functional group 1 could be coupled to fragment **Y** containing functional group 2 using some catalyst to generate molecule **X-Y** (**Fig 1.3 A**).[20] However, reality is far from ideal, and the simplicity of this process is dependent on the nature of the functional groups in question. If one fragment has an electron-donating group and the other has an electron-withdrawing group, then classical, or redox neutral, cross-coupling can be employed (**Fig 1.3 B**).[21] However, if both fragments contain a functional group that is electron-donating, then oxidative cross-coupling must be utilized.[22] In this case, the catalyst must be accompanied by an external oxidant to accept excess electrons from the substrates (**Fig 1.3 C**). Lastly if both fragments contain electron-withdrawing groups, then reductive cross-coupling must be implemented, wherein the catalyst is accompanied by an external reductant to donate electrons to the substrates (**Fig 1.3 D**).[23]

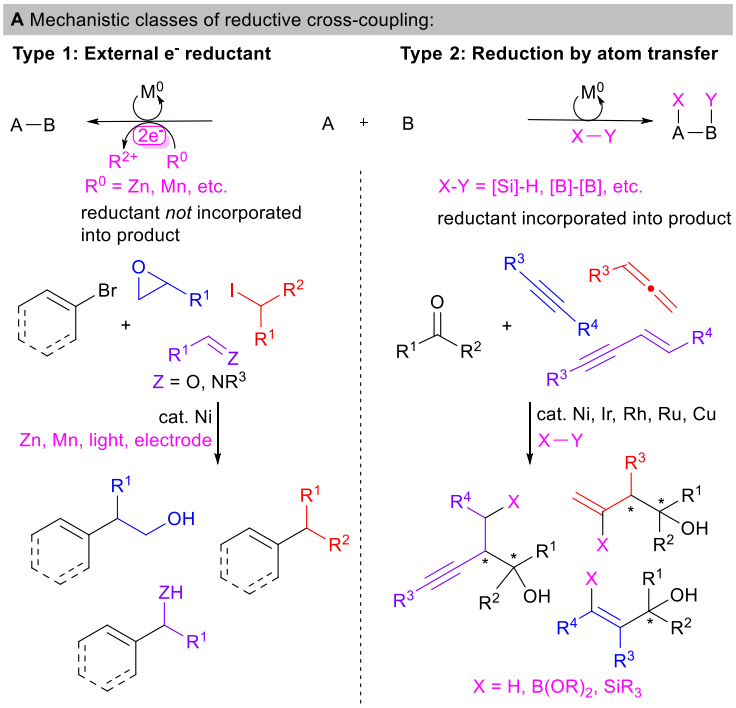
***Figure 1.3**: Examples of Different Types of Coupling*



E. Reductive Coupling

Due to the electron-withdrawing ability of both alcohols and amines, it would be necessary for reactions involving coupling fragments containing them to utilize reductive coupling. Catalytic reductive coupling processes are known to go through two types of mechanistic pathways based on the nature of the reducing agent (**Fig 1.4**).[20,24] One of these involves external electron reductants that provide the requisite electrons (Type 1 process) such as stoichiometric transition metal reductants (*e.g.* Zn or Mn)[25], photocatalysis[26], or electrochemically[27]. The other mechanistic pathway involves utilizing a terminal reductant (*e.g.* $HSiR_3$, ZnR2, $B_2(OR)_4$, etc)[24] to enable catalyst turnover through incorporation of atoms from the reductant into the final product (Type 2 process).

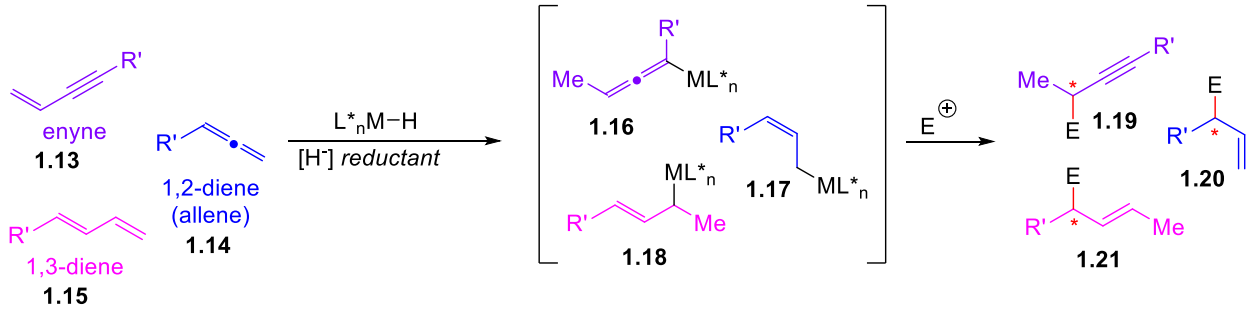
***Figure 1.4**: The Two Mechanistic Classes of Reductive Coupling*[20]



F. Catalytic Allylative Reductive Coupling

One form of reductive coupling that has attracted much interest over the past few decades is metal catalyzed allylative reductive coupling **(Scheme 1.2)**. Pioneered by Krische in the mid-2000s, these processes typically involve a pronucleophile such as enynes[28], 1,2-dienes[29], and 1,3-dienes[30] being converted into their nucleophilic forms by a metal hydride. These nucleophilic organometallic reagents proceed to react with electrophiles to generate the coupled products such as homoallylic alcohols when aldehydes are used as the electrophilic partner.[29]

***Scheme 1.2**: Examples of Catalytic Allylative Reductive Coupling*



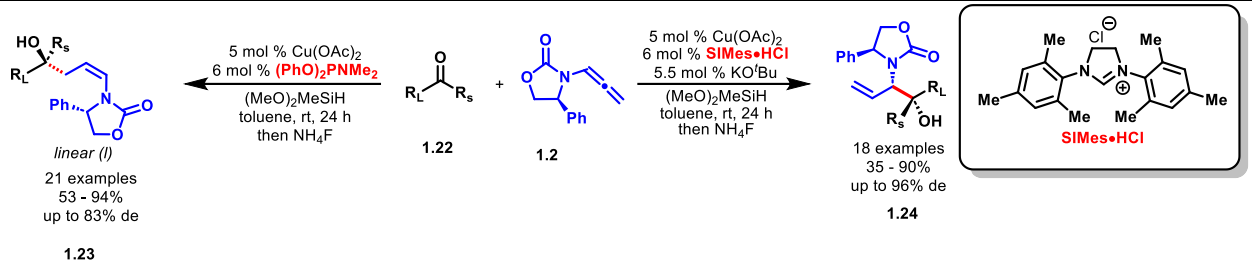
One disadvantage of the systems pioneered by Krische is that they all require expensive precious metals such as Ir[31], Rh[32], and Ru[30]. The extreme costs associated with these metals necessitated further research to expand the chemistry to more earth abundant metals. Research into the field by Buchwald showed that similar reactivities could be obtained by using copper as the catalytic system for enyne[33], 1,2-diene[34], and 1,3-diene[35] pronucleophiles. Pronucleophiles containing heteroatoms are also viable coupling partners with a copper catalytic system to furnish coupled products containing heteroatoms such as nitrogen.[36,37]

III. Research Design

A. Past Work

Prior studies in the Sieber lab revealed that chiral auxiliary containing allenamides can undergo hydrocupration to furnish an allylcopper intermediate which can then proceed to react with electrophiles in either a branched or linear selective manner (**Scheme 1.3**).[37,38] These works were able to showcase the utilization of catalytic reductive coupling to efficiently install both an alcohol and an amine synthon in a single step. They were also able to showcase effective deprotection sequences and functionalization into natural products.

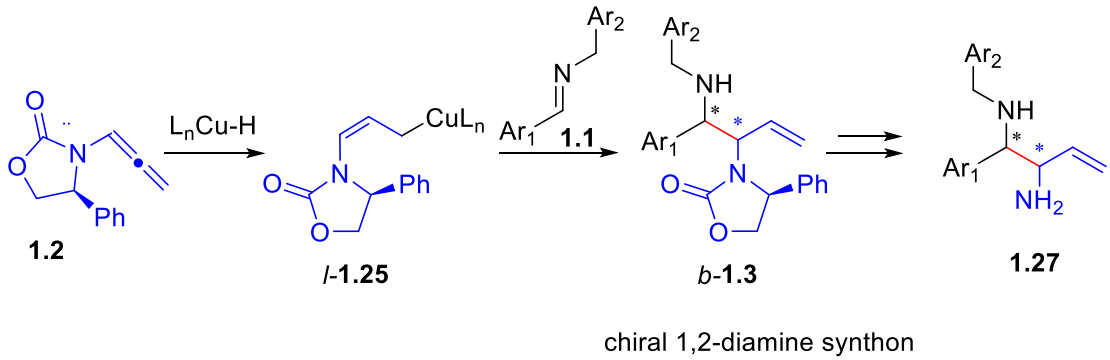
***Scheme 1.3**: Past Work From the Sieber Lab Involving Catalytic Reductive Coupling*



B. This Work

While the previous works were focused on using ketone electrophiles to access their desired products, it was believed that intermediate *l*-**1.25** could also react with aldimine electrophile **1.1** to produce chiral 1,2-diamine **1.27** upon cleavage of the auxiliary (**Scheme 1.4**). Ideally this would occur, similarly to the previous works, in a single step and with high yields and selectivity. These 1,2-diamines could then be functionalized into natural products that contain the aforementioned motif.

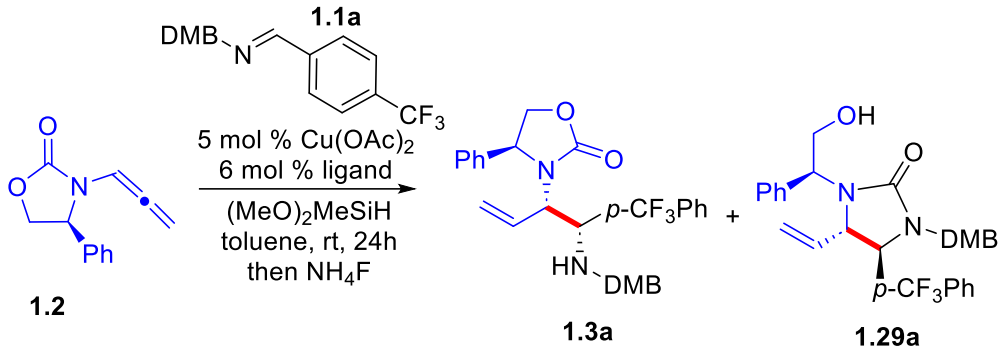
***Scheme 1.4**: Proposed Strategy Towards Accessing Chiral 1,2-Diamine Synthons*



IV. Aldimine Reductive Coupling Protocol Employing a Chiral Auxiliary

A. Reaction Development

Table 1.1: *Ligand Optimization for the Reductive Coupling Using 1.1a.*[a]



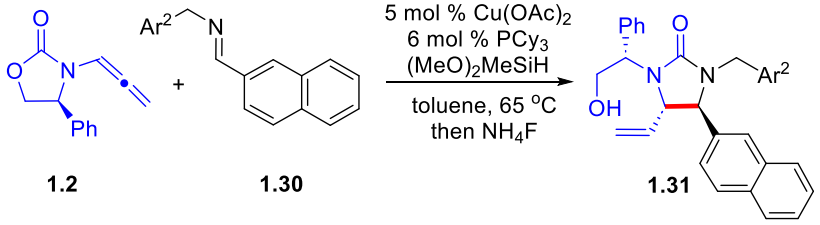
Entry	Ligand	%Yield 1.3a[b]	%Yield 1.29a[b]
1	dcpe	< 5	58
2	PCy3	< 5	86
3	$P(adam)_3$	< 5	28
4	XPhos	< 5	22
5	$P(NMe_2)_3$	< 5	66
6	$P(OEt)_3$	< 5	60
7	$(PhO)_2PNMe_2$	< 5	66
8	SIMes	< 5	8
9[c]	PCy3	< 5	51
10[d]	PCy3	< 5	54
11[e]	PCy3	< 5	52
12[f]	PCy3	< 5	31
13[g]	PCy3	90	< 5

[a]129 mg (0.400 mmol) **1.1a**, 96.6 mg (0.480 mmol) **1.2**, 5 mol % $Cu(OAc)_2$, 6 mol % ligand, and 1.0 mL of toluene. A single diastereomer of product was obtained in all cases by analysis of the unpurified reaction mixture by ^{1}HNMR spectroscopy.[b] Yield determined by ^{1}H NMR spectroscopy on the unpurified reaction mixture using dimethylfumarate as analytical standard. [c]Reaction performed in MTBE. [d]Reaction performed in dioxane. [e]Reaction performed in CH_2Cl_2. [f]Reaction performed in THF. [g]Performed using 2.0 equiv of *t*-BuOH as additive. DMB = 2,4-dimethoxybenzyl.

Similarly to the Sieber lab's previously published work, the investigation began by using an allenamide derived from the Evans' Oxazolidinone (**1.2, Table 1.1**).[39] The main reasons for selecting this auxiliary were because it is commercially available and reasonably priced and allenamide **1.2** can be easily synthesized from it.[40] We began the

studies by investigating the impact of various ligands on the system with other reaction conditions similar to those from previous publications of ours (**Table 1.1**).[38,41] These results were obtained in collaboration with Dr. Toolika Agrawal. A variety of mono- and bidentate ligands were tested and it was observed that, in all cases, cyclic urea product **1.29a** was produced exclusively with PCy_3 providing the highest yield. Changes of the solvent were also examined but it was observed that no solvent provided higher yields than the starting solvent of toluene. Diamine product **1.3a** could also be obtained exclusively with the addition of two equivalents of *tert*-butanol to the reaction mixture.

Table 1.2: *Effect of Imine N-Substitution on Reactivity*[a]



1.2 **1.30** **1.31**

Entry	Ar^2	% yield[b]
1	2,4-dimethoxyphenyl	17
2	4-methoxyphenyl	58
3	Phenyl	70
4	4-fluorophenyl	71
5	4-trifluoromethylphenyl	79

[a]Conditons: **1.30** (0.400 mmol), 106 mg (0.480 mmol) of **1.2**, 5 mol % $Cu(OAc)_2$, 6 mol % PCy_3, 99 µL (0.80 mmol) of $(MeO)_2MeSiH$, and 1.0 mL of toluene. A single diastereomer of product was obtained in all cases by analysis of the unpurified reaction mixture by ^1H NMR spectroscopy. [b]Yield determined by ^1H NMR spectroscopy on the unpurified reaction mixture using dimethylfumarate as analytical standard.

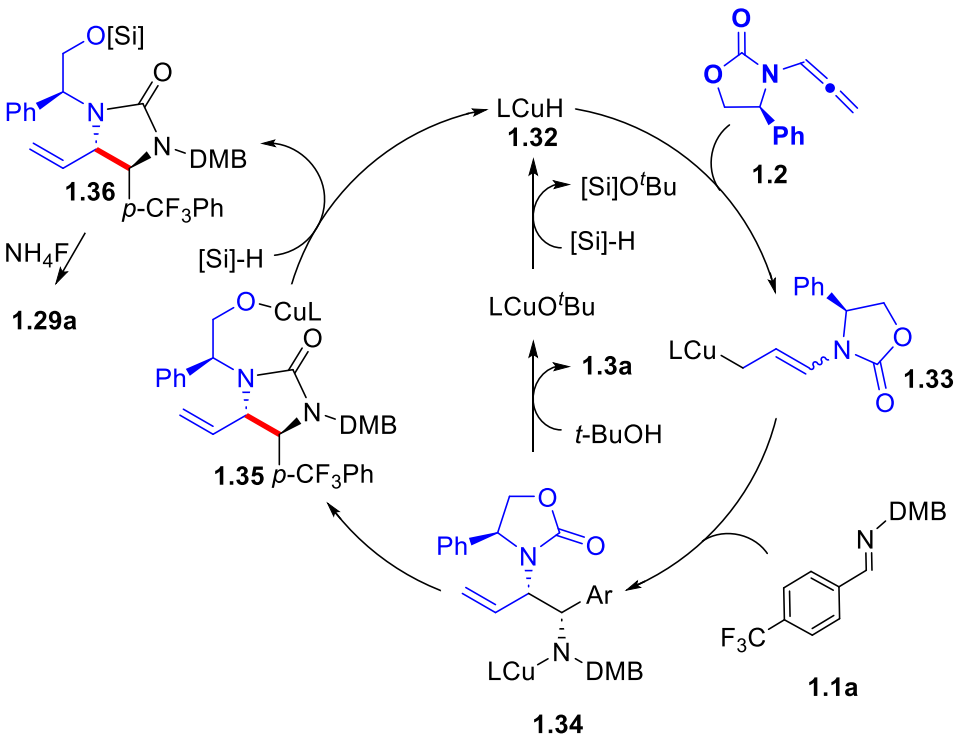
The nature of the aldimine protecting group was next examined (**Table 1.2**), and a clear trend of reactivity was observed. As the electron-withdrawing ability of the protecting group increases, the yield of the reductive coupling process increased. However, the drawback to using more electron-deficient protecting groups that promote higher reactivity is that they are more difficult to cleave, as evidenced by the fact that 2,4-dimethoxyphenyl is cleavable with acid while phenyl and 4-trifluoromethylphenyl require functional group incompatible conditions such as hydrogenation.[42,43] Due to the fact that the ability for further functionalization of the allyl moiety that is produced in this reaction was desired, it was decided that most of the substrates would be run with protecting groups with more mild deprotection conditions.

B. Catalytic Cycle

Similarly to our previous work and the work of Buchwald, the proposed catalytic cycle for this process begins with allenamide **1.2** undergoing hydrocupration to furnish allylcopper intermediate **1.33**.[36,37,44] This intermediate can then react with an electrophile, such as aldimine **1.1a**, to produce copper amide complex **1.34**. It is at this point that the divergence of products in the presence of an alcohol becomes apparent. Due to the high basicity of the nitrogen on complex **1.34**, the nitrogen can attack the carbonyl in the auxiliary and open up that ring while forming the cyclic urea product **1.29a** after silylation and aqueous fluoridic workup. However, in the presence of an alcohol, the copper amide complex **1.34** can be protonated to produce the diamine product **1.3a** along with a copper alkoxide intermediate that can be transmetalated back to the active catalyst with silane.[45] Further support for the catalytic cycle given in **Fig 1.5**

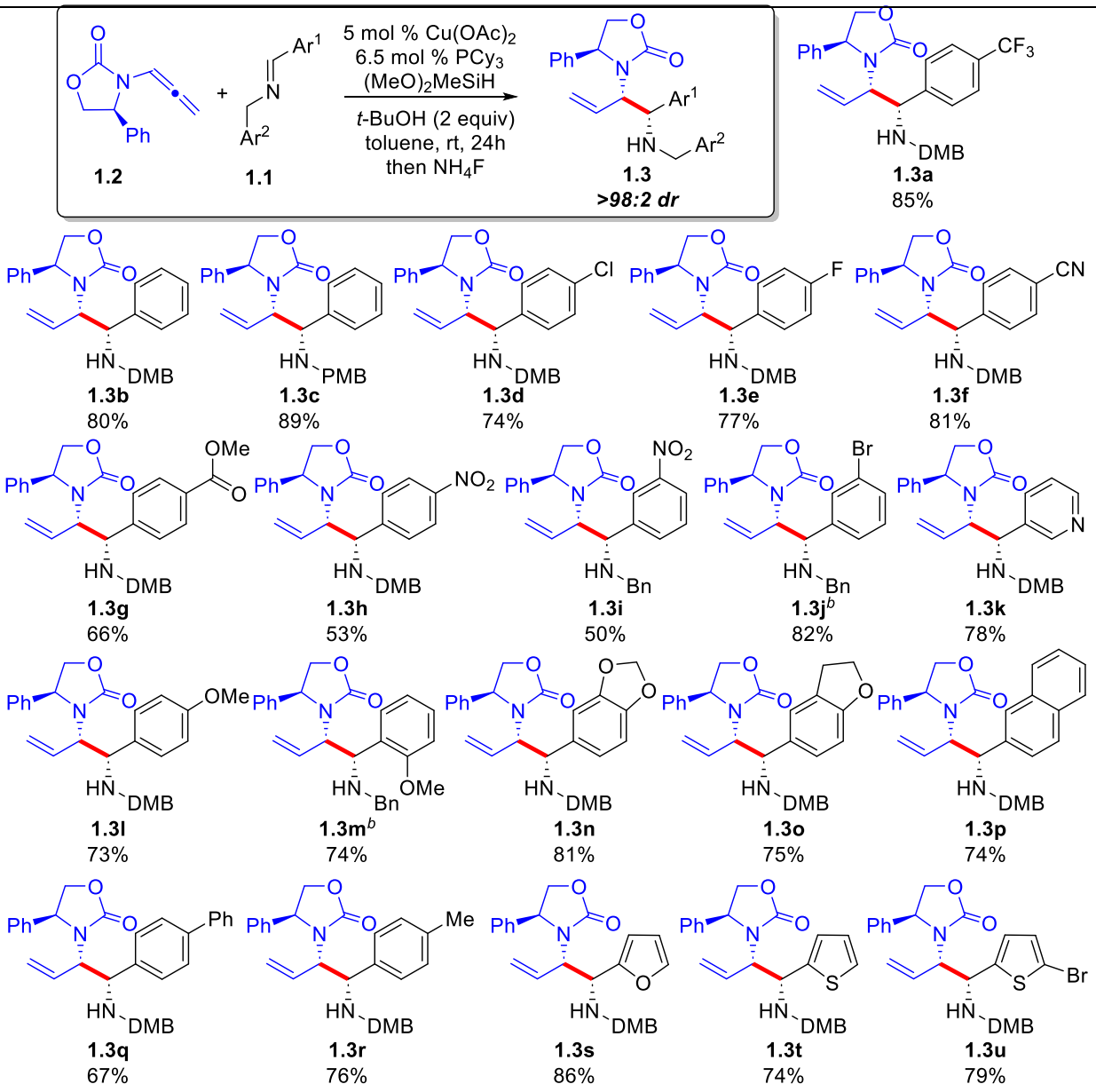
was obtained by DFT molecular orbital calculation performed by our collaborator Prof. Osvaldo Gutierrez.[46]

***Figure 1.5**: Catalytic Cycle For Allenamide-Imine Reductive Coupling*



C. Substrate Scope

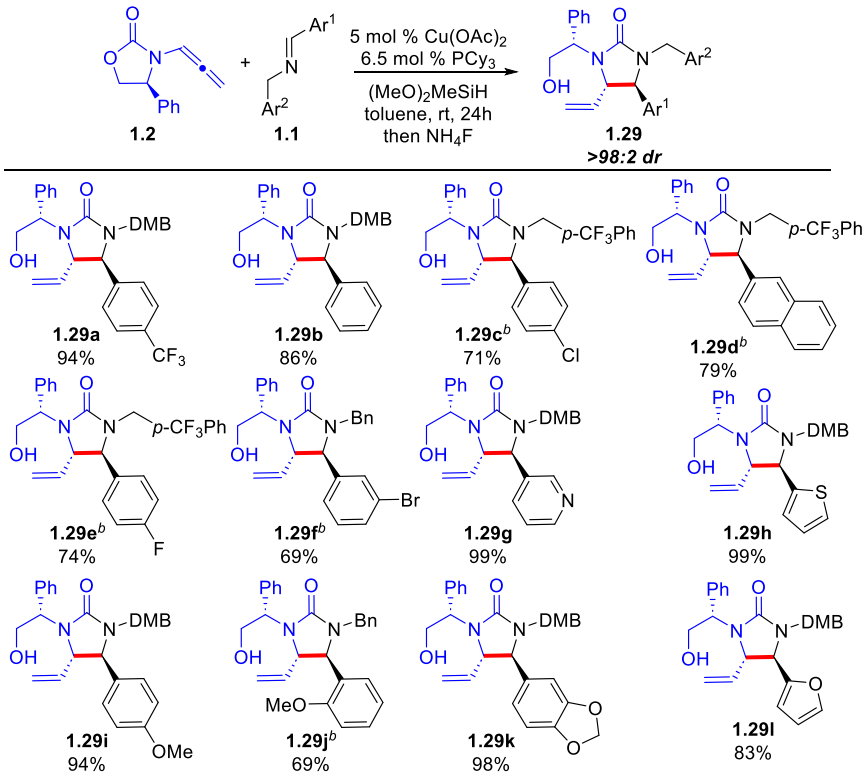
***Scheme 1.5**: Imine Generality in the Cu-Catalyzed Reductive Coupling to Access 1,2-Diamino Synthons.*[a]



[a]Conditions: **1.1a-u** (0.400 mmol), **1.2** (96.6 mg, 0.48 mmol), $Cu(OAc)_2$ (5 mol %), PCy_3 (6.5 mol %), *t*-BuOH (76 µL, 0.80 mmol), $Me(MeO)_2SiH$ (99 µL, 0.80 mmol), and 1.0 mL of toluene, rt 24 h followed by treatment with NH_4F/MeOH. A single diastereomer of product was obtained in all cases by analysis of the unpurified reaction mixture by ^1H NMR spectroscopy. Yields represent isolated yield. [b]Reaction performed at 65 °C.

With the optimal reaction conditions in hand, the scope of the reaction was investigated using a variety of sterically and electronically different aldimines (**Scheme 1.5**). These results were obtained in collaboration with Dr. Toolika Agrawal. Overall, this reaction provided a high degree of generality across a wide range of substrates with electron deficient (**1.3a, 1.3d-k**) and electron rich (**1.3l-o**) aromatic aldimines performing similarly well and providing single diastereomers of product. Interestingly, even ortho-substituted aromatic aldimines (**1.3m**) performed quite well. Aliphatic aldimines were unsuccessful in the transformation.

***Scheme 1.6**: Imine Generality in the Cu-Catalyzed Reductive Coupling to Access Chiral Ureas.*[a]

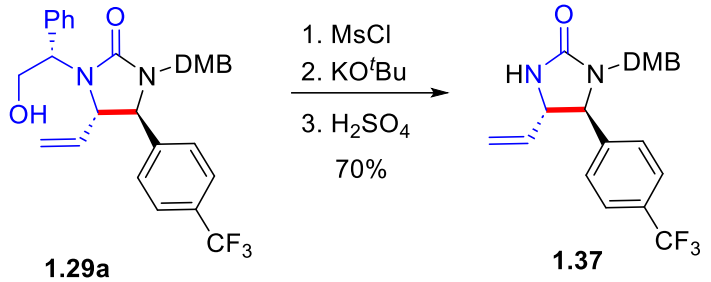


[a]Conditions: **1.29a-l** (0.40 mmol), **1.2** (96.6 mg, 0.48 mmol), $Cu(OAc)_2$ (5 mol %), PCy_3 (6.5 mol %), $Me(MeO)_2SiH$ (99 µL, 0.80 mmol), and 1.0 mL of toluene, rt 24 h followed by treatment with NH_4F/MeOH. See the supporting information for more details. A single diastereomer of product was obtained in all cases by analysis of the unpurified reaction mixture by ^1H NMR spectroscopy. Yields represent isolated yield. [b]Reaction performed at 65 °C.

The synthesis of cyclic ureas under reaction conditions lacking *tert*-butanol as an additive was also investigated (**Scheme 1.6**). Not surprisingly, similar generality to that of the process containing *tert*-butanol was obtained considering the pathway diverges after the stereodetermining step. Both electron rich (**1.29i-k**) and electron deficient (**1.29a,c,e,f**) aromatic aldimines performed comparably well to provide high yields of single diastereomers. Also, sterically demanding *meta*- (**1.29f**) and *ortho*-(**1.29j**) substitution patterns were well tolerated.

D. Synthetic Applications

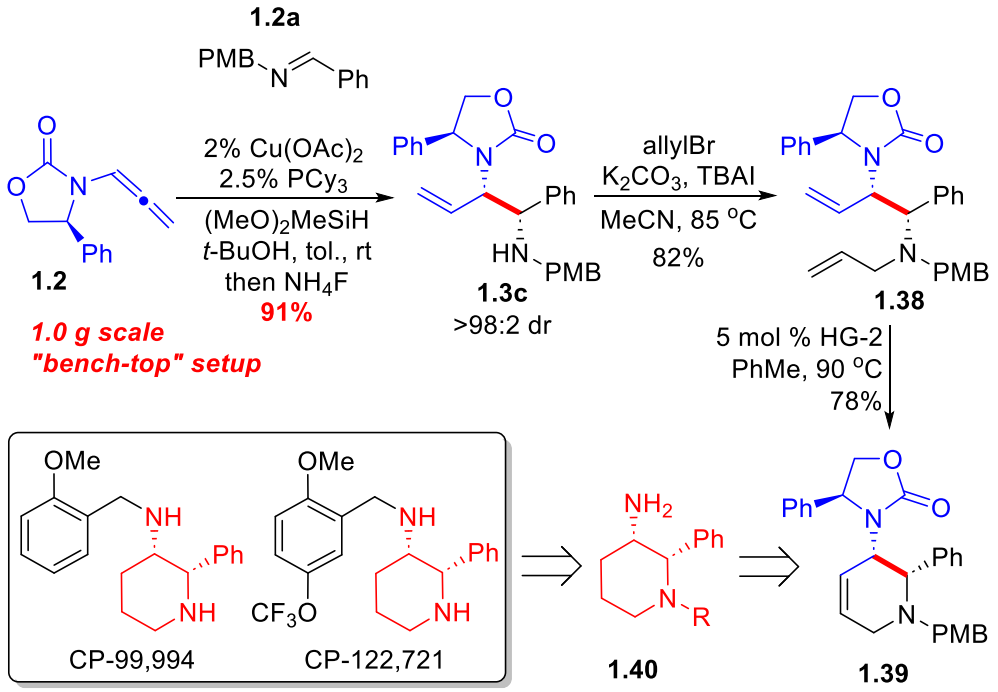
***Scheme 1.7**: Phenethanol Group Cleavage*



1.29a **1.37**

Cyclic urea product **1.29a** contains a phenethanol side chain that occurs due to the opening of the cyclic carbamate during the rearrangement process (**Scheme 1.7**). This phenethanol unit can be cleaved in a three-step telescoped process developed by Toolika Agrawal. This process involves alcohol activation by mesylation, followed by base mediated elimination with potassium tert-butoxide to generate the enamine intermediate, followed by an acidic hydrolysis to cleave off the enamine and produce the free urea product **1.37**. This urea can then undergo further substitution on the nitrogen as is desired for whatever chemistry needs to be accomplished.

***Scheme 1.8**: Application of Reductive Coupling Methodology Towards NK-1 Inhibitor Fragment*



The diamine selective reaction employing allenamide **1.2** and aldimine **1.2a** was successfully scaled up to a 1.0 gram scale without issue to generate branched product **1.3c** (**Scheme 1.8**). This product was then allylated with allylbromide and underwent ring closing metathesis with the Second Generation Hoveyda-Grubbs catalyst to produce cyclic amine **1.39**. This aminopiperidine derivative is a valuable intermediate to compound **1.40** which is a major fragment of the potent NK-1 inhibitor compounds CP-99,994 and CP-122,721.[11]

V. Conclusion

This strategy for the stereoselective reductive coupling of aldimines and chiral allenamides to selectively generate both cyclic ureas and 1,2-diamine synthons is an effective tool for accessing molecules with a dissonant charge affinity. The low costs associated with the

catalyst and the starting materials make this a process that lends itself well to applications in the industrial sector. This generally high yielding protocol generates branched products with high diastereoselectivity owing to the chiral auxiliary. Applications have been shown towards the removal of the phenethanol side chain on the urea to allow for further functionalization and towards the synthesis of drug fragments from the diamine reductive

VI. Experimental Methods

General. ^{1}H NMR spectra were recorded on Bruker 600 MHz spectrometers. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, h = hextet, hept = heptet, br = broad, m = multiplet), and coupling constants (Hz). ^{13}C NMR spectra were recorded on Bruker 600 MHz (151 MHz) instrument with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard (CDCl3: 77.0 ppm). Liquid chromatography was performed using forced flow (flash chromatography) on silica gel purchased from Silicycle. Thin layer chromatography (TLC) was performed on glass-backed 250 μm silica gel F_{254} plates purchased from Silicycle. Visualization was achieved by using UV light, a 10% solution of phosphomolybdic acid in EtOH or potassium permanganate in water followed by heating. HRMS was collected using a Jeol AccuTOF-DART^{TM} mass spectrometer using DART source ionization. All reactions were conducted in oven or flame dried glassware under an inert atmosphere of nitrogen or argon with magnetic stirring unless otherwise noted. Solvents were obtained from VWR as HPLC grade and transferred to septa sealed bottles, degassed by argon sparge, and analysed by Karl-Fischer titration to ensure water content was ≤ 600 ppm. $Me(MeO)_2SiH$ was purchased from Alfa Aesar and used as received. Allenamides **15** were prepared in one step as described in the literature.[26] Aldehydes were purchased from Sigma

Aldrich, Combi-Blocks, TCI America, Alfa Aesar or Oakwood Chemicals and used as received. Tricyclohexylphosphine and $Cu(OAc)_2$ were purchased from the Strem Chemical Company and used as received. All other materials were purchased from VWR, Sigma Aldrich, Combi-Blocks, or Alfa Aesar and used as received. Imines **1.1a**,[34] **1.1b**,[47] **1.1c**,[48] **1.1h**,[49] **1.1i**,[50] **1.1j**,[51] **1.1l**,[45] **1.1m**,[47] **1.1u**[45] were synthesized as described in the literature. Compounds' whose spectra are not shown below were synthesized by Dr. Toolika Agrawal.

General Procedure A for the synthesis of imines. A 25 ml round bottom flask equipped with a magnetic stirring bar was charged with aldehyde (6.0 mmol, 1.0 equiv) and dichloromethane (8 ml). Anhydrous magnesium sulfate was added to this solution while stirring followed by 2,4-dimethoxy benzylamine (6.0 mmol, 1.0 equiv) dropwise. The reaction mixture was stirred at room temperature for 12 h under a nitrogen atmosphere. After the reaction is complete the crude reaction mixture was filtered through celite to remove magnesium sulfate. The filtrate was concentrated *in vacuo* to yield the pure imine, which was stored under nitrogen in the fridge.

Characterization Data:

*(E)-1-(4-chlorophenyl)-N-(2,4-dimethoxybenzyl)methanimine (**1.3d**).* Following General Procedure A, 4-chloro benzaldehyde (0.84 g, 6.0 mmol), 2,4-dimethoxybenzylamine (1.0 g, 6.0 mmol) magnesium sulfate (2.0 g) and dichloromethane (8 ml) were used. The title compound was obtained as a pale-yellow solid (1.54 g, 89%). m.p. – 59.5-60.5 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.21 – 7.15 (m, 1H), 6.51 – 6.43 (m, 2H), 4.75 (s, 2H), 3.81 (s, 6H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 160.3, 160.2, 158.3, 136.4, 134.9, 130.2, 129.4, 128.8, 119.6, 104.1, 98.5, 58.9, 55.4. HRMS (DART) *m/z* calcd for $C_{16}H_{17}ClNO_2$ $[M + H]^+$: 290.0948; Found $[M + H]^+$: 290.0950.

*(E)-N-(2,4-dimethoxybenzyl)-1-(4-fluorophenyl)methanimine (**1.3e**).* Following General Procedure A, 4-fluorobenzaldehyde (0.742 g, 6.0 mmol), 2,4-dimethoxybenzylamine (1.0 g, 6.0 mmol) magnesium sulfate (2.0 g) and dichloromethane (8 ml) were used. The title compound was obtained as a yellow solid (1.36 g, 84 %). m.p. – 39.7-41.1 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.76 (dd, *J* = 8.5, 5.7 Hz, 2H), 7.23 – 7.16 (m, 1H), 7.08 (t, *J* = 8.6 Hz, 2H), 6.52 – 6.45 (m, 2H), 4.76 (s, 2H), 3.81 (s, 6H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 165.06 (C-F, 1J C-F = 250.66 Hz), 163.40 (C-F, 1J C-F = 250.66 Hz), 160.23, 160.21, 158.32, 132.80 (C-F, 3J C-F =3.02 Hz), 132.78 (C-F, 3J C-F = 3.02 Hz), 132.2, 130.15, 130.11, 130.06, 119.84, 115.66 (C-F, 2J C-F = 22.65 Hz), 115.51 (C-F, 2J C-F = 22.65 Hz), 104.1, 98.54, 58.85. ^{19}F NMR (565 MHz, $CDCl_3$) δ -109.87. HRMS (DART) *m/z* calcd for $C_{16}H_{17}FNO_2$ $[M + H]^+$: 274.1243; Found $[M + H]^+$: 274.1269.

*(E)-4-(2,4-dimethoxybenzyl iminomethyl)benzonitrile (**1.3f**).* Following General Procedure A, 4-formyl benzonitrile (0.784 g, 6.0 mmol), 2,4-dimethoxybenzylamine (1.0 g, 6.0 mmol) magnesium sulfate (2.0 g) and dichloromethane (8 ml) were used. The title compound was obtained as a yellow solid (1.59 g, 95 %). m.p. – 54.0-56.2 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.84 (d, *J* = 8.0 Hz, 2H), 7.67 (d, *J* = 8.1 Hz, 2H), 7.17 (d, *J* = 9.0 Hz, 1H), 6.51 – 6.44 (m, 2H), 4.80 (s, 2H), 3.80 (s, 6H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 160.4, 159.6, 158.4, 140.3, 132.3, 130.3, 128.6, 119.0, 118.6, 113.7, 104.2, 98.5, 59.1, 55.4. HRMS (DART) *m/z* calcd for $C_{17}H_{17}N_2O_2$ $[M + H]^+$: 281.1290; Found $[M + H]^+$: 281.1306.

*Methyl (E)-4-(2,4-dimethoxybenzyl iminomethyl)benzoate (**1.3g**).* Following General Procedure A, methyl-4-formyl benzoate (0.982 g, 6.0 mmol), 2,4-dimethoxybenzylamine (1.0 g, 6.0 mmol) magnesium sulfate (2.0 g) and dichloromethane (8 ml) were used. The title compound was obtained as a yellow solid (1.87 g, 100 %). m.p. – 54.5-56.3 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.06 (d, *J* = 8.0 Hz, 2H), 7.82 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 9.0 Hz, 1H), 6.48 (m, 2H), 4.79 (s, 2H), 3.91 (s, 3H), 3.79 (s, 6H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 166.7, 160.6, 160.2,

158.3, 140.3, 131.6, 130.2, 129.7, 128.0, 119.4, 104.1, 98.5, 59.1, 55.3, 55.3, 52.2. HRMS (DART) *m/z* calcd for $C_{18}H_{20}NO_4$ $[M + H]^+$: 314.1392; Found $[M + H]^+$: 314.1422.

*(E)-N-(2,4-dimethoxybenzyl)-1-(pyridin-3-yl)methanimine (**1.3k**).* Following General Procedure A, 3-pyridinecarboxaldehyde (0.64 g, 6.0 mmol), 2,4-dimethoxybenzylamine (1.0 g, 6.0 mmol) magnesium sulfate (2.0 g) and dichloromethane (8 ml) were used. The title compound was obtained as a pale-yellow oil (1.51 g, 99 %). ^{1}HNMR (600 MHz, $CDCl_3$)δ: 8.85 (s, 1H), 8.63 (d, *J* = 4.8 Hz, 1H), 8.34 (s, 1H), 8.14 (d, *J* = 7.9 Hz, 1H), 7.33-7.31 (dd, *J* = 7.9 Hz, 4.8 Hz, 1H), 7.19 (d, *J* = 8.9 Hz, 1H), 6.49-6.47 (m, 2H), 4.78 (s, 2H), 3.81 (s, 3H), 3.80 (s, 3H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 160.3, 158.7, 158.3, 151.3, 150.2, 134.5, 131.9, 130.3, 123.6, 119.2, 104.1, 98.5, 59.1, 55.3. HRMS (DART) *m/z* calcd for $C_{15}H_{17}N_2O_2$ $[M + H]^+$: 257.1290; Found $[M + H]^+$: 257.1297.

*(E)-1-(benzo[d][1,3]dioxol-5-yl)-N-(2,4-dimethoxybenzyl)methanimine (**1.3n**).* Following General Procedure A, piperonal (0.89 g, 6.0 mmol), 2,4-dimethoxybenzylamine (1.0 g, 6.0 mmol) magnesium sulfate (2.0 g) and dichloromethane (8 ml) were used. The title compound was obtained as a pale-yellow solid (1.77 g, 99 %). m.p. – 54.3-55.7 °C. ^{1}HNMR (600 MHz, $CDCl_3$)δ: 8.2 (s, 2H), 7.4 (s, 1H), 7.18 (d, J = 8.9 Hz, 1H), 7.12 (d, J = 7.9 Hz, 1H), 6.8 (d, J = 7.9 Hz, 1H), 6.47-6.46 (m, 2H), 5.9 (s, 2H), 4.71 (s, 2H), 3.808 (s, 3H), 3.802 (s, 3H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 160.8, 160.0, 158.2, 149.7, 148.2, 131.3, 130.0, 124.3, 120.1, 107.9, 106.7, 104.0, 101.4, 98.5, 58.6, 55.3. HRMS (DART) *m/z* calcd for $C_{17}H_{18}NO_4$ $[M + H]^+$: 300.1236; Found $[M + H]^+$: 300.1253.

*(E)-1-(2,3-dihydrobenzofuran-5-yl)-N-(2,4-dimethoxybenzyl)methanimine (**1.3o**).* Following General Procedure A, 2,3-dihydrobenzofuran-5-carbaldehyde (0.886 g, 6.0 mmol), 2,4-dimethoxybenzylamine (1.0 g, 6.0 mmol) magnesium sulfate (2.0 g) and dichloromethane (8 ml) were used. The title compound was obtained as a pale-yellow oil (1.94 g, 72 % purity, 78 % yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.73 (s, 1H), 7.44 (d, *J* = 12 Hz, 1H), 7.19 (d, *J* = 8.9

Hz, 1H), 6.78 (d, *J* = 8.2 Hz, 1H), 6.49 – 6.43 (m, 2H), 4.71 (s, 2H), 4.60 (t, *J* = 8.7 Hz, 2H), 3.80 (s, 6H), 3.20 (t, *J* = 8.7 Hz, 2H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 162.3, 161.3, 160.0, 158.2, 130.0, 129.8, 129.6, 127.7, 124.2, 120.3, 109.0, 104.0, 98.4, 71.7, 58.7, 55.3, 29.2. HRMS (DART) *m/z* calcd for $C_{18}H_{20}NO_3$ $[M + H]^+$: 298.1443; Found $[M + H]^+$: 298.1466.

*(E)-1-([1,1'-biphenyl]-4-yl)-N-(2,4-dimethoxybenzyl)methanimine (**1.3q**).* Following General Procedure A, 4-phenylbenzaldehyde (1.09 g, 6.0 mmol), 2,4-dimethoxybenzylamine (1.0 g, 6.0 mmol) magnesium sulfate (2.0 g) and dichloromethane (8 ml) were used. The title compound was obtained as a white solid (1.82 g, 94 % purity, 86 % yield). m.p. – 91.3-93.9 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.88 (d, *J* = 8.0 Hz, 2H), 7.70 – 7.63 (m, 4H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.40 (t, *J* = 6 Hz, 1H), 7.29 – 7.23 (m, 1H), 6.55 – 6.50 (m, 2H), 4.83 (s, 2H), 3.86 (s, 3H), 3.84 (s, 3H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 161.3, 160.1, 158.3, 143.2, 140.5, 135.4, 130.3, 130.1, 129.0, 128.8, 128.7, 128.5, 127.7, 127.4, 127.2, 127.1, 120.0, 104.1, 98.5, 59.0, 55.4. HRMS (DART) *m/z* calcd for $C_{22}H_{22}NO_2$ $[M + H]^+$: 332.1651; Found $[M + H]^+$: 332.1667.

*(E)-N-(2,4-dimethoxybenzyl)-1-(p-tolyl)methanimine (**1.3r**).* Following General Procedure A, *p*-tolualdehyde (0.72 g, 6.0 mmol), 2,4-dimethoxybenzylamine (1.0 g, 6.0 mmol) magnesium sulfate (2.0 g) and dichloromethane (8 ml) were used. The title compound was obtained as a pale-yellow oil (1.28 g, 80%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.72 (d, *J* = 7.8 Hz, 2H), 7.27 (d, *J* = 7.4 Hz, 3H), 6.55 – 6.51 (m, 2H), 4.81 (s, 2H), 3.86 (s, 6H), 2.38 s, 3H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 161.7, 160.1, 158.2, 140.7, 133.8, 130.0, 129.8, 129.7, 129.2, 128.2, 120.1, 104.0, 98.5, 58.9, 55.3, 21.5. HRMS (DART) *m/z* calcd for $C_{17}H_{20}NO_2$ $[M + H]^+$: 270.1494; Found $[M + H]^+$: 270.1495.

*(E)-N-(2,4-dimethoxybenzyl)-1-(furan-2-yl)methanimine (**1.3s**).* Following General Procedure A, furfural (0.57 g, 6.0 mmol), 2,4-dimethoxybenzylamine (1.0 g, 6.0 mmol) magnesium sulfate (2.0 g) and dichloromethane (8 ml) were used. The title compound was obtained as a brown oil (1.6 g, 91 % purity, 99 % yield). ^{1}HNMR (600 MHz, $CDCl_3$)δ: 8.08 (s, 1H), 7.49 (s, 1H), 7.18 (d, J =

8.1 Hz, 1H), 6.73 (d, J = 3.4 Hz, 1H), 6.47-6.45 (m, 3H), 4.73 (s, 2H), 3.80 (s, 3H), 3.79 (s, 3H). $^{13}C\{1H\}$ NMR (151 MHz, $CDCl_3$)δ: 160.28, 158.46, 151.96, 150.13, 144.51, 130.69, 119.30, 113.59, 111.53, 104.07, 98.47, 58.89, 55.40, 55.33. HRMS (DART) *m/z* calcd for $C_{14}H_{16}NO_3$ [M + H]$^+$: 246.1130; Found [M + H]$^+$: 246.1126.

*(E)-N-(2,4-dimethoxybenzyl)-1-(thiophen-2-yl)methanimine (**1.3t**).* Following General Procedure A, thiophene-2-carboxaldehyde (0.67 g, 6.0 mmol), 2,4-dimethoxybenzylamine (1.0 g, 6.0 mmol) magnesium sulfate (2.0 g) and dichloromethane (8 ml) were used. The title compound was obtained as a yellow solid (1.15 g, 74 %). m.p. – 47.4-50.2 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.37 (d, *J* = 6 Hz, 1H), 7.29 (d, *J* = 3.6 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 7.06 (t, *J* = 6 Hz, 1H), 6.50 – 6.46 (m, 2H), 4.74 (s, 2H), 3.80 (s, 6H). $^{13}C\{1H\}$ NMR (151 MHz, $CDCl_3$) δ 160.2, 158.3, 154.8, 142.9, 130.3, 130.2, 128.6, 127.2, 119.6, 104.1, 98.4, 58.2, 55.4, 55.3. HRMS (DART) *m/z* calcd for $C_{14}H_{16}NO_2S$ [M + H]$^+$: 262.0902; Found [M + H]$^+$: 262.0915.

General Procedure B for the synthesis of 1.3. To a 20 ml crimp cap vial with a stir bar in an Ar filled glove-box was charged $Cu(OAc)_2$ (3.6 mg, 20 µmol) and PCy_3 (7.3 mg, 26 µmol) followed by toluene (1.0 ml) and tert-butanol (76.5 µl, 2 eq). The mixture was stirred for 5 mins. Allenamide **1.2** (96.6 mg, 480 µmol) followed by imine (400 µmol) was then charged and the vial was sealed with a crimp-cap septum and removed from the glove box. Dimethoxymethylsilane (0.099 ml, 2 eq) was then charged to the reaction mixture *(caution: dimethoxymethylsilane should be handled in a well-ventilated fume hood because it is known to cause blindness. Syringes were quenched with 2M NaOH, gas evolution! prior to disposal)*. The mixture was then stirred at RT for 24 h. The reaction was quenched by addition of 200 mg of NH_4F and 2.5 ml of MeOH followed by agitation at RT for 30 mins. 10 ml of 5% $NaHCO_3$ was then added to the mixture followed by extraction with DCM (2X5 ml). The combined organics were dried with Na_2SO_4, filtered, and concentrated

in vacuo. Crude product was purified by flash chromatography on silica gel to afford the desired product.

Characterization Data:

*(S)-3-((1S,2S)-1-((2,4-dimethoxybenzyl)amino)-1-(4-(trifluoromethyl)phenyl)but-3-en-2-yl)-4-phenyloxazolidin-2-one (**1.3a**).* According to the general procedure B, the product was purified by silica gel chromatography (5 % E.A. in DCM) to provide 180 mg (85 %) of **1.3a** as a white foam as a single diastereomer. R_f = 0.43 (50 % EtOAC/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.0 Hz, 1H), 7.36 (dd, *J* = 5.1, 1.8 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.21 – 7.17 (m, 1H), 6.99 (d, *J* = 6 Hz, 1H), 6.49 (s, 1H), 6.47 (d, *J* = 8.3 Hz, 1H), 5.15 – 5.09 (dt, *J* = 18 Hz, 12 Hz, 1H), 4.73 (d, *J* = 12 Hz, 1H), 4.70 (d, *J* = 17.1 Hz, 1H), 4.61 (t, *J* = 8.2 Hz, 1H), 4.52 (t, *J* = 12 Hz, 1H), 4.17 (d, *J* = 6 Hz, 1H), 4.11 (t, *J* = 8.0 Hz, 1H), 3.93 (t, *J* = 9.6 Hz, 1H), 3.83 (s, 6H). 3.66 (d, *J* = 12 Hz, 1H), 3.36 (d, *J* = 18 Hz, 1H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 160.3, 158.8, 158.3, 145.2, 138.2, 132.6, 130.5, 129.94 (C-F, $^2J_{C\text{-}F}$ = 31.71 Hz), 129.73 (C-F, $^2J_{C\text{-}F}$ = 31.71 Hz), 129.51 (C-F, $^2J_{C\text{-}F}$ = 31.71 Hz), 129.29 (C-F, $^2J_{C\text{-}F}$ = 31.71 Hz), 129.17, 129.11, 128.8, 127.8, 126.90 (C-F, $^1J_{C\text{-}F}$ = 271.8 Hz), 125.12 (C-F, $^3J_{C\text{-}F}$ = 4.53 Hz), 125.09 (C-F, $^2J_{C\text{-}F}$ = 4.53 Hz), 123.29 (C-F, $^1J_{C\text{-}F}$ = 271.8 Hz), 121.49 (C-F, $^1J_{C\text{-}F}$ = 271.8 Hz), 120.5, 119.6, 103.6, 98.6, 70.2, 63.4, 61.2, 59.3, 55.4, 55.2, 46.0. ^{19}F NMR (565 MHz, $CDCl_3$) δ -62.36. HRMS (DART) *m/z* calcd for $C_{29}H_{30}F_3N_2O_4$ $[M + H]^+$: 527.2158; Found $[M + H]^+$: 527.2153.

*(S)-3-((1S,2S)-1-((2,4-dimethoxybenzyl)amino)-1-phenylbut-3-en-2-yl)-4-phenyloxazolidin-2-one (**1.3b**).* According to the general procedure B, the product was purified by silica gel chromatography (10 % E.A. in DCM) to provide 147 mg (80 %) of **1.3b** as a colourless foam as a single diastereomer. R_f = 0.35 (50 % EtOAc/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 4.5, 2.3 Hz, 3H), 7.25 – 7.22 (d, *J* = 6 Hz, 2H), 7.22 – 7.19 (d, *J* = 6 Hz, 1H), 7.18 – 7.16 (d, J

= 12 Hz, 2H), 7.15 – 7.14 (m, 2H), 7.03 (d, *J* = 8.0 Hz, 1H), 6.48 (s, 1H), 6.46 (d, *J* = 8.3 Hz, 1H), 5.05 – 4.97 (dt, J = 18 Hz, 12 Hz, 1H), 4.70 (d, *J* = 17.0 Hz, 1H), 4.64 (d, *J* = 10.2 Hz, 1H), 4.59 (t, *J* = 6 Hz, 1H), 4.46 (t, *J* = 8.6 Hz, 1H), 4.12 – 4.04 (dt, J = 18 Hz, 6 Hz, 2H), 3.99 (d, *J* = 10.0 Hz, 1H), 3.81 (s, 6H), 3.67 (d, *J* = 13.4 Hz, 1H), 3.34 (d, *J* = 13.4 Hz, 1H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 160.2, 158.8, 158.6, 140.6, 138.9, 133.3, 130.6, 128.98, 128.96, 128.4, 128.2, 127.8, 127.4, 120.9, 119.0, 103.6, 98.6, 70.2, 63.2, 61.5, 58.9, 55.4, 55.2, 45.8. HRMS (DART) *m/z* calcd for $C_{28}H_{31}N_2O_4$ $[M + H]^+$: 459.2284; Found $[M + H]^+$: 459.2300.

*(S)-3-((1S,2S)-1-((4-methoxybenzyl)amino)-1-phenylbut-3-en-2-yl)-4-phenyloxazolidin-2-one (**1.3c**).* According to the general procedure B, the product was purified by silica gel chromatography (10 % E.A. in DCM) to provide 153 mg (89 %) of **1.3c** as a white solid as a single diastereomer. M.p. 101 – 104°C. R_f = 0.41 (50 % EtOAc/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 – 7.33 (m, 3H), 7.31 (m, 2H), 7.27 (m, 3H), 7.20 (d, *J* = 6 Hz, 2H), 7.18 – 7.14 (m, 2H), 6.96 (d, *J* = 12 Hz, 2H), 5.10 (dt, *J* = 16.5, 9.6 Hz, 1H), 4.76 – 4.69 (m, 2H), 4.66 (t, *J* = 8.4 Hz, 1H), 4.60 (t, *J* = 12 Hz, 1H), 4.18 (t, *J* = 12 Hz, 1H), 4.12 (t, *J* = 12 Hz, 1H), 4.02 (d, *J* = 10.2 Hz, 1H), 3.86 (s, 3H), 3.64 (d, *J* = 13.0 Hz, 1H), 3.41 (d, *J* = 12.9 Hz, 1H), 1.91 (s, 1H). ^{13}C{1H} NMR (151 MHz, Chloroform-*d*) δ 159.1, 158.7, 140.5, 138.5, 133.2, 132.5, 129.8, 128.9, 128.9, 128.4, 128.2, 127.8, 127.5, 119.2, 113.7, 70.3, 63.2, 61.5, 60.4, 59.0, 55.3, 49.9, 21.0, 14.2. HRMS (DART) *m/z* calcd for $C_{27}H_{29}N_2O_3$ $[M + H]^+$: 429.2178; Found $[M + H]^+$: 429.2196.

*(S)-3-((1S,2S)-1-(4-chlorophenyl)-1-((2,4-dimethoxybenzyl)amino)but-3-en-2-yl)-4-phenyloxazolidin-2-one (**1.3d**).* According to the general procedure B, the product was purified by silica gel chromatography (5 % E.A. in DCM) to provide 146 mg (74 %) of **1.3d** as a colourless foam and a single diastereomer. R_f = 0.33 (50 % EtOAc/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 – 7.33 (m, 3H), 7.23 (d, *J* = 8.2 Hz, 2H), 7.20 – 7.16 (m, 2H), 7.12 (d, *J* = 8.1 Hz, 2H), 6.99 (d, *J* = 8.1 Hz, 1H), 6.49 (s, 1H), 6.47 (d, *J* = 8.2 Hz, 1H), 5.11 – 5.03 (dt, J = 18 Hz, 12 Hz, 1H),

4.72 (s, 1H), 4.69 (d, *J* = 7.9 Hz, 1H), 4.60 (t, *J* = 8.1 Hz, 1H), 4.49 (t, *J* = 8.6 Hz, 1H), 4.10 (t, *J* = 7.9 Hz, 1H), 4.05 (d, *J* = 10.1 Hz, 1H), 3.95 (t, *J* = 9.6 Hz, 1H), 3.83 (s, 6H), 3.66 (d, *J* = 13.4 Hz, 1H), 3.33 (d, *J* = 13.4 Hz, 1H), 2.08 (s, 1H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 160.3, 158.8, 158.4, 139.3, 138.4, 133.0, 132.8, 130.6, 129.8, 129.10, 129.07, 128.4, 127.8, 120.6, 119.4, 103.6, 98.6, 70.2, 63.4, 60.8, 59.2, 55.4, 55.2, 45.9.HRMS (DART) *m/z* calcd for $C_{28}H_{30}ClN_2O_4$ [M + H]$^+$: 493.1894; Found [M + H]$^+$: 493.1929.

*(S)-3-((1S,2S)-1-((2,4-dimethoxybenzyl)amino)-1-(4-fluorophenyl)but-3-en-2-yl)-4-phenyloxazolidin-2-one (**1.3e**).* According to the general procedure B, the product was purified by silica gel chromatography (5 % E.A. in DCM) to provide 147 mg (77 %) of **1.3e** as a colourless foam and a single diastereomer. R_f = 0.35 (50 % EtOAc/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 – 7.32 (m, 3H), 7.20 – 7.12 (m, 4H), 7.00 (d, *J* = 8.1 Hz, 1H), 6.94 (t, *J* = 8.6 Hz, 2H), 6.50 (s, 1H), 6.48 (d, *J* = 6 Hz, 1H), 5.06 (dt, *J* = 18.2, 9.5 Hz, 1H), 4.70 (d, *J* = 16.6 Hz, 2H), 4.60 (t, *J* = 8.1 Hz, 1H), 4.49 (t, *J* = 8.6 Hz, 1H), 4.10 (t, *J* = 7.9 Hz, 1H), 4.05 (d, *J* = 10.1 Hz, 1H), 3.96 (t, *J* = 9.6 Hz, 1H), 3.83 (s, 6H), 3.66 (d, *J* = 13.4 Hz, 1H), 3.34 (d, *J* = 13.5 Hz, 1H), 2.10 (s, 1H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 162.93 (C-F, 1J C-F = 244.62 Hz), 161.31 (C-F, 1J C-F = 244.62 Hz), 160.2 , 158.8, 158.4, 138.5, 136.4, 133.0, 130.5, 129.9, 129.8, 129.07 (C-F, 3J C-F = 4.53 Hz), 129.05 (C-F, 3J C-F = 4.53 Hz), 127.8, 120.7, 119.2, 115.13 (C-F, 2J C-F = 21.14 Hz), 114.99 (C-F, 2J C-F = 21.14 Hz), 103.6, 98.6, 70.2, 63.5, 60.7, 59.1, 55.4, 55.2, 45.9.^{19}F NMR (565 MHz, $CDCl_3$) δ -115.14. HRMS (DART) *m/z* calcd for $C_{28}H_{30}FN_2O_4$ [M + H]$^+$: 477.2190; Found [M + H]$^+$: 477.2204.

*4-((1S,2S)-1-((2,4-dimethoxybenzyl)amino)-2-((S)-2-oxo-4-phenyloxazolidin-3-yl)but-3-en-1-yl)benzonitrile (**1.3f**).* According to the general procedure B, the product was purified by silica gel chromatography (10 % E.A. in DCM) to provide 157 mg (81 %) of **1.3f** as a colourless foam and a single diastereomer. R_f = 0.36 (50 % EtOAc/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54 (d, *J*

= 7.9 Hz, 2H), 7.39 – 7.34 (m, 3H), 7.30 (d, *J* = 7.9 Hz, 2H), 7.22 – 7.18 (m, 2H), 6.95 (d, *J* = 8.1 Hz, 1H), 6.49 (s, 1H), 6.46 (d, *J* = 8.1 Hz, 1H), 5.14 (dt, *J* = 16.9, 9.8 Hz, 1H), 4.73 (d, *J* = 10.1 Hz, 1H), 4.66 (d, *J* = 17.0 Hz, 1H), 4.59 (t, *J* = 8.2 Hz, 1H), 4.51 (t, *J* = 8.6 Hz, 1H), 4.20 (d, *J* = 10.0 Hz, 1H), 4.12 (t, *J* = 8.1 Hz, 1H), 3.82 (s, 7H), 3.63 (d, *J* = 13.5 Hz, 1H), 3.32 (d, *J* = 13.5 Hz, 1H), 2.20 (s, 1H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 160.4, 158.7, 158.2, 146.8, 137.9, 132.0, 130.5, 129.3, 129.2, 129.1, 127.8, 120.3, 119.9, 118.8, 111.2, 103.7, 98.6, 70.2, 63.4, 61.3, 59.4, 55.4, 55.2, 46.2. HRMS (DART) *m/z* calcd for $C_{29}H_{30}N_3O_4$ $[M + H]^+$: 484.2236; Found $[M + H]^+$: 484.2255.

*(S)-3-((1S,2S)-1-([1,1'-biphenyl]-4-yl)-1-((2,4-dimethoxybenzyl)amino)but-3-en-2-yl)-4-phenyloxazolidin-2-one (**1.3q**).* According to the general procedure B, the product was purified by silica gel chromatography (5 % E.A. in DCM) to provide 144 mg (67 %) of **1.3q** as a colourless foam and a single diastereomer. R_f = 0.26 (50 % EtOAc/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.9 Hz, 2H), 7.51 (d, *J* = 7.9 Hz, 2H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.37 – 7.30 (m, 4H), 7.26 (d, *J* = 6.0 Hz, 3H), 7.21 – 7.16 (m, 2H), 7.08 (d, *J* = 8.0 Hz, 1H), 6.52 – 6.47 (m, 2H), 5.08 (dt, *J* = 18.1, 9.6 Hz, 1H), 4.76 (d, *J* = 17.0 Hz, 1H), 4.70 (d, *J* = 10.2 Hz, 1H), 4.63 (t, *J* = 8.0 Hz, 1H), 4.50 (t, *J* = 8.6 Hz, 1H), 4.17 – 4.05 (m, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.73 (d, *J* = 13.5 Hz, 1H), 3.42 (d, *J* = 13.4 Hz, 1H), 2.07 (s, 1H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 160.2, 158.8, 158.6, 140.7, 140.1, 139.8, 138.8, 133.2, 130.6, 129.0, 128.9, 128.8, 128.7, 127.8, 127.2, 126.9, 126.8, 121.0, 119.2, 103.6, 98.6, 70.3, 63.2, 61.3, 59.0, 55.4, 55.2, 45.9. HRMS (DART) *m/z* calcd for $C_{34}H_{35}N_2O_4$ $[M + H]^+$: 535.2597; Found $[M + H]^+$: 535.2631.

*(S)-3-((1S,2S)-1-((2,4-dimethoxybenzyl)amino)-1-(p-tolyl)but-3-en-2-yl)-4-phenyloxazolidin-2-one (**1.3r**).* According to the general procedure B, the product was purified by silica gel chromatography (5 % E.A. in DCM) to provide 143 mg (76 %) of **1.3r** as a colourless foam and a

single diastereomer. R_f = 0.29 (50 % EtOAc/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 4.6, 2.3 Hz, 3H), 7.18 – 7.14 (m, 2H), 7.08 (s, 4H), 7.05 (d, *J* = 8.1 Hz, 1H), 6.51 – 6.46 (m, 2H), 5.00 (dt, *J* = 18.1, 9.6 Hz, 1H), 4.74 (d, *J* = 17.0 Hz, 1H), 4.66 (d, *J* = 10.2 Hz, 1H), 4.61 (t, *J* = 7.9 Hz, 1H), 4.47 (t, *J* = 8.6 Hz, 1H), 4.13 (t, *J* = 9.6 Hz, 1H), 4.08 (t, *J* = 6 Hz, 1H), 3.95 (d, *J* = 9.9 Hz, 1H), 3.83 (s, 6H), 3.68 (d, *J* = 13.4 Hz, 1H), 3.35 (d, *J* = 13.3 Hz, 1H), 2.31 (s, 3H), 2.02 (s, 1H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 160.2, 158.8, 158.6, 139.0, 137.5, 137.0, 133.50, 130.6, 128.96, 128.94, 128.91, 128.3, 127.8, 121.0, 118.9, 103.6, 98.6, 70.3, 63.1, 61.2, 58.8, 55.4, 55.2, 45.7, 21.1. HRMS (DART) *m/z* calcd for $C_{29}H_{33}N_2O_4$ $[M + H]^+$: 473.2440; Found $[M + H]^+$: 473.2459.

*(S)-3-((1S,2S)-1-((2,4-dimethoxybenzyl)amino)-1-(thiophen-2-yl)but-3-en-2-yl)-4-phenyloxazolidin-2-one (**1.3t**).* According to the general procedure B, the product was purified by silica gel chromatography (5 % E.A. in DCM) to provide 137 mg (74 %) of **1.3t** as a pale-yellow foam and as a single diastereomer. R_f = 0.33 (50 % EtOAc/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 – 7.31 (m, 3H), 7.21 (d, *J* = 5.1 Hz, 1H), 7.18 – 7.13 (m, 2H), 7.07 (d, *J* = 8.1 Hz, 1H), 6.90 (ddd, *J* = 4.8, 3.5, 1.1 Hz, 1H), 6.85 (d, *J* = 3.4 Hz, 1H), 6.50 (s, 1H), 6.48 (d, *J* = 7.9 Hz, 1H), 5.15 (dt, *J* = 16.2, 9.6 Hz, 1H), 4.84 (d, *J* = 17.0 Hz, 1H), 4.77 (d, *J* = 10.2 Hz, 1H), 4.56 (dd, *J* = 8.6, 7.2 Hz, 1H), 4.47 (td, *J* = 8.6, 1.1 Hz, 1H), 4.39 (d, *J* = 9.6 Hz, 1H), 4.08 (ddd, *J* = 11.6, 6.7, 2.8 Hz, 2H), 3.82 (s, 3H), 3.83 (s, 3H), 3.80 (d, *J* = 13.4 Hz, 1H), 3.48 (d, *J* = 13.4 Hz, 1H), 2.11 (s, 1H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 160.3, 158.8, 158.3, 145.5, 138.6, 132.8, 130.8, 129.0, 127.7, 126.2, 126.0, 124.8, 120.6, 119.3, 103.6, 98.6, 70.3, 63.5, 60.4, 59.0, 57.2, 55.4, 55.2, 46.0. HRMS (DART) *m/z* calcd for $C_{26}H_{29}N_2O_4S$ $[M + H]^+$: 465.1848; Found $[M + H]^+$: 465.1852.

*(S)-3-((1S,2S)-1-(5-bromothiophen-2-yl)-1-((2,4-dimethoxybenzyl)amino)but-3-en-2-yl)-4-phenyloxazolidin-2-one (**1.3u**).* According to the general procedure B, the product was purified by silica gel chromatography (3 % E.A. in DCM) to provide 172 mg (79 %) of **1.3u** as a pale-yellow

foam as a single diastereomer and a 95:5 mixture of the branched to rearranged product. R_f = 0.38 (50 % EtOAc/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 4.2, 2.5 Hz, 3H), 7.17 (dd, *J* = 6.0, 2.6 Hz, 2H), 7.04 (d, *J* = 8.1 Hz, 1H), 6.84 (d, *J* = 6 Hz, 1H), 6.59 (d, *J* = 6 Hz, 1H), 6.50 (s, 1H), 6.48 (d, *J* = 12 Hz, 1H), 5.24 (dt, *J* = 16.7, 9.5 Hz, 1H), 4.89 – 4.83 (m, 2H), 4.54 (t, *J* = 8.0 Hz, 1H), 4.50 (t, *J* = 12 Hz, 1H), 4.39 (d, *J* = 9.6 Hz, 1H), 4.11 (t, *J* = 12 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.80 (d, *J* = 13.5 Hz, 1H), 3.51 (d, *J* = 13.4 Hz, 1H), 2.24 (s, 1H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 160.3, 158.8, 158.0, 147.7, 138.0, 132.2, 130.7, 129.2, 129.1, 129.1, 127.7, 126.4, 120.3, 119.8, 111.6, 103.6, 98.6, 70.2, 63.6, 59.4, 57.7, 55.4, 55.2, 46.1. HRMS (DART) *m/z* calcd for $C_{26}H_{28}BrN_2O_4S$ $[M + H]^+$: 543.0953; Found $[M + H]^+$: 543.0949.

General Procedure C for the synthesis of 1.29. To a 20 ml crimp cap vial with a stir bar in an Ar filled glove-box was charged $Cu(OAc)_2$ (3.6 mg, 20 µmol) and PCy_3 (7.3 mg, 26 µmol) followed by toluene (1.0 ml) and the mixture was stirred for 5 mins. Allenamide **15a** (96.6 mg, 480 µmol) followed by imine (400 µmol) was then charged and the vial was sealed with a crimp-cap septum and removed from the glove box. Dimethoxymethylsilane (0.099 ml, 2 eq) was then charged to the reaction mixture *(caution: dimethoxymethylsilane should be handled in a well-ventilated fume hood because it is known to cause blindness. Syringes were quenched with 2M NaOH, gas evolution! prior to disposal)*. The mixture was then stirred at RT for 24 h. The reaction was quenched by addition of 200 mg of NH_4F and 2.5 ml of MeOH followed by agitation at RT for 30 mins. 10 ml of 5% $NaHCO_3$ was then added to the mixture followed by extraction with DCM (2X5 ml). The combined organics were dried with Na_2SO_4, filtered, and concentrated in vacuo. Crude product was purified by flash chromatography on silica gel to afford the desired product **1.29**.

Characterization Data:

*(4S,5S)-1-(2,4-dimethoxybenzyl)-3-((S)-2-hydroxy-1-phenylethyl)-5-(4-(trifluoromethyl)phenyl)-4-vinylimidazolidin-2-one (**1.29a**).* According to the general procedure C, the product was purified by silica gel chromatography (5 % E.A. in DCM) to provide 198 mg (94 %) of **1.29a** as a colourless foam as a single diastereomer. R_f = 0.36 (50 % EtOAc/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.0 Hz, 2H), 7.35 – 7.30 (m, 2H), 7.26 (m, 4H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.03 (d, *J* = 8.2 Hz, 1H), 6.41 (d, *J* = 6.0 Hz, 1H), 6.35 (d, *J* = 2.4 Hz, 1H), 5.59 (ddd, *J* = 17.0, 9.3, 8.7, 1.0 Hz, 1H), 5.20 (d, *J* = 10.1 Hz, 1H), 4.90 (t, *J* = 7.0 Hz, 1H), 4.85 (d, *J* = 17.1 Hz, 1H), 4.78 (d, *J* = 14.7 Hz, 1H), 4.32 (m, 1H), 4.25 (dd, *J* = 7.9, 3.4 Hz, 1H), 4.06 – 4.03 (m, 1H), 4.01 (d, *J* = 7.9 Hz, 1H), 3.86 (d, *J* = 14.7 Hz, 1H), 3.79 (s, 3H), 3.59 (s, 3H), 3.39 (t, *J* = 8.3 Hz, 1H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 161.1, 160.7, 158.6, 143.0, 137.6, 134.8, 131.7, 130.55 (C-F, 2J C-F = 31.71 Hz), 130.39 (C-F, 2J C-F = 31.71 Hz), 130.18 (C-F, 2J C-F = 31.71 Hz),129.96 (C-F, 2J C-F = 31.71 Hz), 128.7, 127.8, 127.6, 127.4, 126.7 (C-F, 1J C-F = 271.8 Hz), 125.51 (C-F, 3J C-F = 3.02 Hz), 125.48 (C-F, 3J C-F = 3.02 Hz), 124.89 (C-F, 1J C-F = 271.8 Hz), 123.09 (C-F, 1J C-F = 271.8 Hz), 121.4, 121.29 (C-F, 2J C-F = 271.8 Hz), 116.2, 104.2, 98.1, 66.2, 64.9, 63.3, 61.9, 55.3, 54.9, 40.8. ^{19}F NMR (565 MHz, $CDCl_3$) δ -62.54. HRMS (DART) *m/z* calcd for $C_{29}H_{30}F_3N_2O_4$ $[M + H]^+$: 527.2158; Found $[M + H]^+$: 527.2173.

*(4S,5S)-1-benzyl-5-(3-bromophenyl)-3-((S)-2-hydroxy-1-phenylethyl)-4-vinylimidazolidin-2-one (**1.29j**).* Reaction was set up according to general procedure C and stirred at 65 °C for 24 h. The product was purified by silica gel chromatography (5 % E.A. in DCM) to provide 131 mg (69 %) of **1.29j** as a colourless foam as a single diastereomer. R_f = 0.46 (50 % EtOAc/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.1 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.34 – 7.24 (m, 8H), 7.17 (t, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 6.6 Hz, 2H), 7.01 (d, *J* = 7.6 Hz, 1H), 5.59 (ddd, *J* = 17.0, 10.0, 8.7 Hz, 1H), 5.21 (d, *J* = 10.1 Hz, 1H), 4.98 (d, *J* = 14.9 Hz, 1H), 4.91 (d, *J* = 17.0 Hz, 1H), 4.82 (t, *J* = 7.0 Hz, 1H), 4.38 – 4.27 (m, 2H), 4.08 – 4.05 (m, 1H), 3.94 (d, *J* = 7.5 Hz, 1H), 3.64 (d, *J* = 14.9 Hz, 1H), 3.48 (t, *J* = 8.1 Hz, 1H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 160.6, 140.3, 137.5, 135.9,

134.5, 131.6, 130.4, 130.2, 128.8, 128.7, 128.6, 127.9, 127.7, 127.6, 125.9, 123.0, 121.4, 66.2, 64.8, 62.8, 62.0, 45.7. HRMS (DART) *m/z* calcd for $C_{26}H_{26}BrN_2O_2$ $[M + H]^+$: 477.1178; Found $[M + H]^+$: 477.1207.

*(4S,5S)-1-(2,4-dimethoxybenzyl)-3-((S)-2-hydroxy-1-phenylethyl)-5-(pyridin-3-yl)-4-vinylimidazolidin-2-one (**1.29k**).* According to the general procedure C, the product was purified by silica gel chromatography (50 % E.A. in DCM) to provide 183 mg (99 %) of **1.29k** as a pale-yellow foam as a single diastereomer and as a 86:14 mixture of the rearranged **1.29k** to branched product **1.3k**. R_f = 0.10 (60 % EtOAc/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.26 (s, 1H), 7.44 (d, *J* = 6.0 Hz, 1H), 7.36 – 7.30 (m, 3H), 7.28 – 7.24 (m, 4H), 7.06 (d, *J* = 8.2 Hz, 1H), 6.40 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.35 (d, *J* = 2.4 Hz, 1H), 5.58 (ddd, *J* = 17.1, 10.0, 8.7 Hz, 1H), 5.20 (d, *J* = 10.1 Hz, 1H), 4.90 (t, *J* = 6.9 Hz, 1H), 4.85 (d, *J* = 17.1 Hz, 1H), 4.76 (d, *J* = 14.6 Hz, 1H), 4.34 – 4.29 (m, 1H), 4.26 (dd, *J* = 7.8, 3.3 Hz, 1H), 4.07 – 4.02 (m, 1H), 3.97 (d, *J* = 8.1 Hz, 1H), 3.86 (dd, *J* = 18.0 6.0 Hz 2H), 3.79 (s, 3H), 3.60 (s, 3H), 3.43 (t, *J* = 8.4 Hz, 1H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 161.1, 160.7, 158.6, 149.6, 149.1, 137.6, 134.5, 131.8, 129.1, 128.7, 127.85, 127.82, 127.6, 121.6, 116.1, 104.2, 98.1, 66.3, 64.8, 61.8, 61.5, 55.3, 55.0, 40.7. HRMS (DART) *m/z* calcd for $C_{27}H_{30}N_3O_4$ $[M + H]^+$: 460.2236; Found $[M + H]^+$: 460.2247.

*(4S,5S)-1-(2,4-dimethoxybenzyl)-3-((S)-2-hydroxy-1-phenylethyl)-5-(4-methoxyphenyl)-4-vinylimidazolidin-2-one (**1.29l**).* According to the general procedure C, the product was purified by silica gel chromatography (10 % E.A. in DCM) to provide 184 mg (94 %) of **1.29l** as a colourless foam as a single diastereomer. R_f = 0.29 (50 % EtOAc/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (t, *J* = 7.7 Hz, 2H), 7.31 – 7.25 (m, 3H), 7.02 (d, *J* = 8.0 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 6.0 Hz, 2H), 6.42 – 6.40 (m, 2H), 5.64 – 5.56 (ddd, J = 17.0, 9.3, 8.6 Hz, 1H), 5.18 (d, *J* = 10.3 Hz, 1H), 5.15 (t, *J* = 7.1 Hz, 1H), 4.87 (d, *J* = 17.0 Hz, 1H), 4.79 (d, *J* = 14.8 Hz, 1H), 4.35 – 4.24 (m, 2H), 4.07 – 4.04 (m, 1H), 3.94 (d, *J* = 7.8 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.67 (s, 3H), 3.46 (t, *J* = 8.2 Hz, 1H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 161.0, 160.5, 159.4, 158.7,

137.9, 135.3, 131.4, 130.6, 128.6, 128.4, 127.7, 127.6, 120.8, 116.7, 113.9, 104.0, 98.1, 66.6, 65.1, 63.1, 61.8, 55.3, 55.2, 55.1, 40.5. HRMS (DART) *m/z* calcd for $C_{29}H_{33}N_2O_5$ $[M + H]^+$: 489.2389; Found $[M + H]^+$: 489.2387.

*(4S,5S)-1-benzyl-3-((S)-2-hydroxy-1-phenylethyl)-5-(2-methoxyphenyl)-4-vinylimidazolidin-2-one (**1.29m**).* Reaction was set up according to general procedure C and stirred at 65 °C for 24 h. The product was purified by silica gel chromatography (10 % E.A. in DCM) to provide 118 mg (69 %) of **1.29m** as a colourless foam as a single diastereomer. R_f = 0.37 (50 % EtOAc/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26 (tdd, *J* = 14.3, 11.1, 7.6 Hz, 10H), 7.13 (d, *J* = 6.9 Hz, 3H), 6.94 (t, *J* = 7.5 Hz, 1H), 6.80 (d, *J* = 8.2 Hz, 1H), 5.68 (ddd, *J* = 16.8, 10.0, 8.3 Hz, 1H), 5.20 – 5.14 (m, 2H), 4.94 (dd, *J* = 16.1, 12.9 Hz, 2H), 4.50 (m, 1H), 4.33 – 4.27 (m, 2H), 4.06 – 4.00 (m, 1H), 3.70 (d, *J* = 15.0 Hz, 1H), 3.61 (s, 3H), 3.59 (m, 1H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 160.7, 157.5, 138.0, 136.8, 135.6, 129.3, 128.5, 128.4, 127.6, 127.5, 127.3, 120.6, 119.7, 110.9, 65.2, 61.9, 55.1, 45.6. HRMS (DART) *m/z* calcd for $C_{27}H_{29}N_2O_3$ $[M + H]^+$: 429.2178; Found $[M + H]^+$: 429.2195.

*(4S,5S)-4-(benzo[d][1,3]dioxol-5-yl)-3-(2,4-dimethoxybenzyl)-1-((S)-2-hydroxy-1-phenylethyl)-5-vinylimidazolidin-2-one (**1.29n**).* According to the general procedure C, the product was purified by silica gel chromatography (10 % E.A. in DCM) to provide 197 mg (98 %) of **1.29n** as a colourless foam as a single diastereomer. R_f = 0.26 (50 % EtOAc/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 – 7.32 (m, 2H), 7.29 – 7.25 (m, 4H), 7.03 (d, *J* = 8.1 Hz, 1H), 6.68 (d, *J* = 7.9 Hz, 1H), 6.57 (s, 1H), 6.49 (d, *J* = 7.9 Hz, 1H), 6.42 – 6.38 (m, 2H), 5.95 – 5.91 (m, 2H), 5.61 – 5.53 (ddd, *J* = 17.1, 9.3, 8.5 Hz, 1H), 5.18 (d, *J* = 10.1 Hz, 1H), 5.06 (d, *J* = 7.9 Hz, 1H), 4.88 (d, *J* = 17.0 Hz, 1H), 4.77 (d, *J* = 14.8 Hz, 1H), 4.33 – 4.22 (m, 2H), 4.03 (m, 1H), 3.89 (d, *J* = 7.7 Hz, 1H), 3.83 (d, *J* = 14.8 Hz, 1H), 3.80 (s, 3H), 3.68 (s, 3H), 3.42 (t, *J* = 8.2 Hz, 1H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 160.9, 160.5, 158.7, 147.4, 137.8, 135.2, 132.6, 131.4, 128.6, 127.6, 120.9,

120.8, 116.6, 108.0, 107.1, 104.0, 101.1, 98.1, 66.5, 65.1, 63.5, 61.8, 55.3, 55.1, 40.6. HRMS (DART) *m/z* calcd for $C_{29}H_{31}N_2O_6$ $[M + H]^+$: 503.2182; Found $[M + H]^+$: 503.2211.

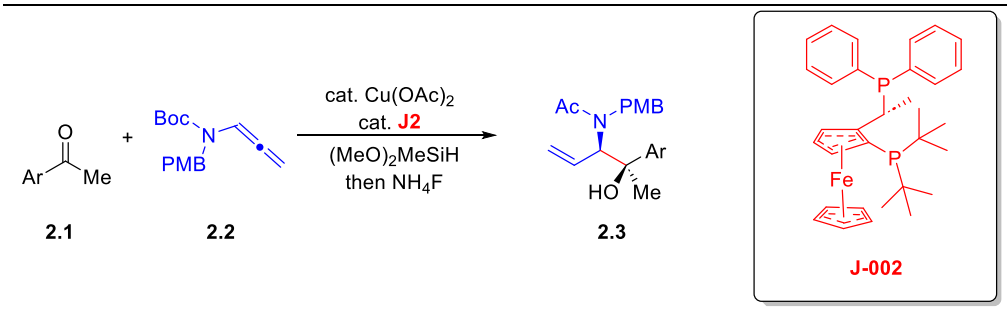
*(4S,5S)-1-(2,4-dimethoxybenzyl)-5-(furan-2-yl)-3-((S)-2-hydroxy-1-phenylethyl)-4-vinylimidazolidin-2-one (**1.29s**).* According to the general procedure C, the product was purified by silica gel chromatography (5 % E.A. in DCM) to provide 149 mg (83 %) of **1.29s** as a colourless foam as a single diastereomer. R_f = 0.28 (50 % EtOAc/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 3H), 7.27 – 7.21 (m, 4H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.41 – 6.37 (m, 2H), 6.26 – 6.23 (m, 1H), 6.08 (d, *J* = 3.2 Hz, 1H), 5.61 (ddd, J = 17.1, 10.1, 8.7 Hz, 1H), 5.16 (d, *J* = 10.1 Hz, 1H), 5.08 – 5.05 (m, 1H), 4.98 (d, *J* = 18.0 Hz, 1H), 4.71 (d, *J* = 15.0 Hz, 1H), 4.30 – 4.23 (m, 2H), 4.08 (d, *J* = 6.7 Hz, 1H), 3.98 – 3.94 (m, 1H), 3.85 (d, *J* = 15.0 Hz, 1H), 3.77 (s, 3H), 3.74 – 3.69 (m, 4H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 160.5, 160.2, 158.6, 151.0, 142.8, 137.7, 135.1, 131.0, 128.6, 127.6, 127.6, 120.6, 116.8, 110.2, 108.7, 104.0, 98.3, 65.2, 62.7, 62.0, 57.1, 55.3, 55.2, 40.7. HRMS (DART) *m/z* calcd for $C_{26}H_{29}N_2O_5$ $[M + H]^+$: 449.2076; Found $[M + H]^+$: 449.2066.

Chapter 2 Development of Asymmetric CuH-Catalyzed Reductive Coupling of an Achiral Allenamide with Ketone Electrophiles with Improved Enantiocontrol

I. Introduction

While methodologies based around the Evans oxazolidinone may be preferable from a cost viewpoint, they are not very atom economical. The atom efficiency could be greatly improved if the chiral induction could be carried out by a chiral Cu catalyst reacting with an achiral allenamide. A stereoselective protocol for the aminoallylation of ketones using achiral allenamides and chiral ligands has been previously developed by our group.[52] This protocol was innovative, owing to the fact that no previous enantioselective metal catalyzed ketone aminoallylation had been previously reported. However, this reaction suffered from low to moderate enantiocontrol that varied with the nature of the aryl ketone substrates employed. Our efforts towards improving the enantiocontrol of the aminoallylation using ketone electrophiles are discussed herein (**Scheme 2.1**).

Scheme 2.1: *Method Development for CuH-Catalyzed Reductive Coupling of Achiral Allenamides and Ketone Electrophiles*



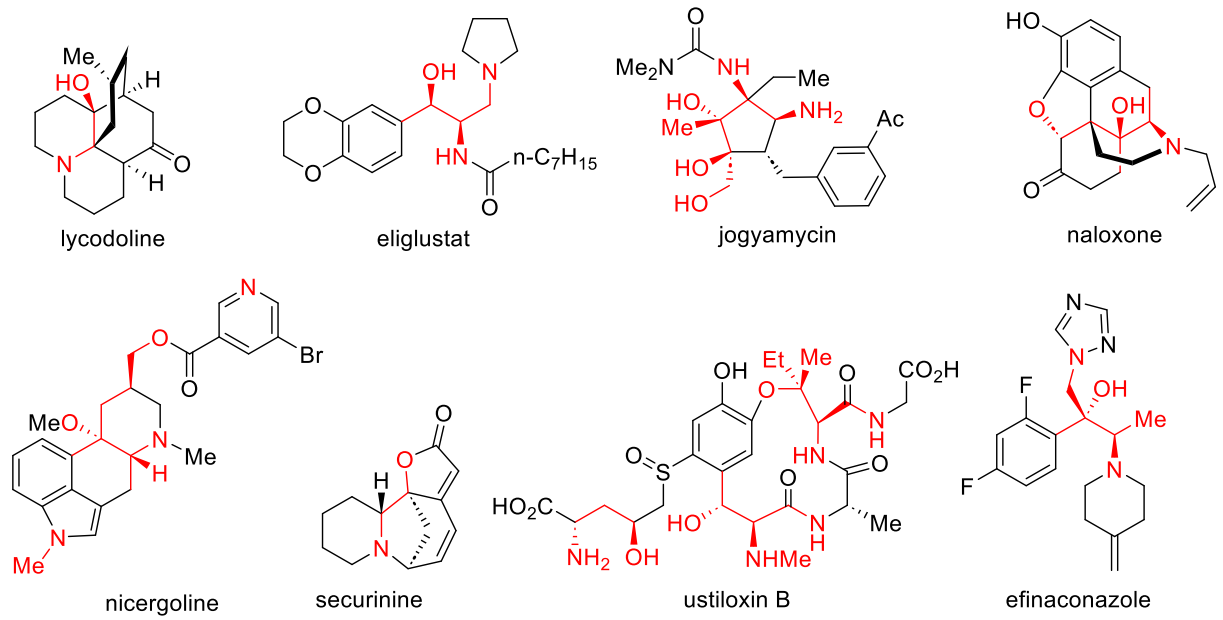
2.1 2.2 2.3

II. Background

A. Aminoalcohol Containing Natural Products and Drugs

There are countless examples of the 1,2-aminoalcohol motif in both pharmaceuticals and natural products (**Fig. 2.1**).[2,53–59] Similarly to the diamine motif, these aminoalcohols are also challenging to synthesize due to the dissonant charge affinity that is present across the carbon framework. This fact necessitates the design of methodologies that can easily synthesize these multi-heteroatom functional groups in a single step, while also being in an efficient and stereoselective manner.

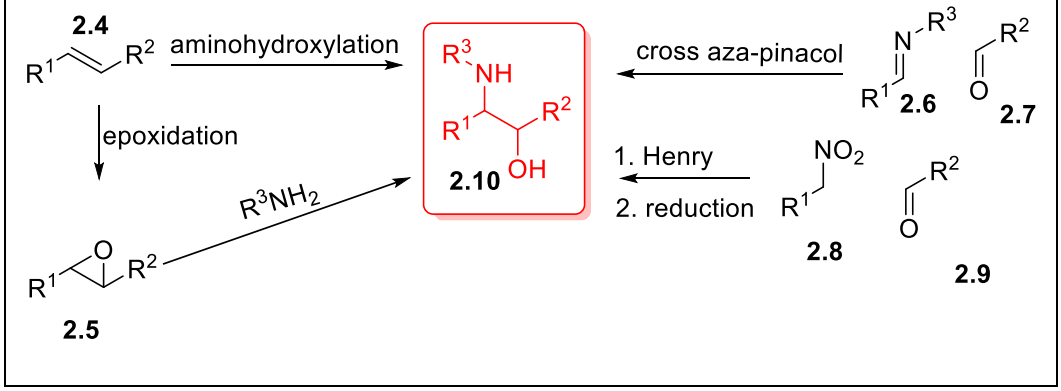
***Figure 2.1**: Aminoalcohol Containing Natural Products and Drugs*



B. Prior Art for Chiral Aminoalcohol Synthesis

There exist many possible strategies to access the 1,2-aminoalcohol motif in a chiral fashion (**Fig 2.2**). One common precursor to aminoalcohols are alkenic systems. From this precursor, aminohydroxylation[60] and enantioselective epoxidation[61] followed by ring-opening with an amine[62] represent attractive methodologies to synthesize this motif. The drawbacks to these are that the epoxidation – ring opening method requires two steps and the enantioselective aminohydroxylation can require extremely toxic metals such as osmium. The cross aza-pinacol reaction is another potential way to access this framework, this time through one-electron chemistry, with the coupling of an aldimine and an aldehyde.[63] However, as this reaction goes through a radical pathway there is the possibility of issues with dimerization. Another route to access this framework can come in the form of performing a Henry reaction[64] between a nitroalkane and an aldehyde followed by a reduction[65] of the nitro group. Even so, the difficulty of reducing nitroalkanes can limit the functional group compatibility of this process.[66] It would be advantageous if there existed a methodology for the chemist to use that would allow the synthesis of the 1,2-aminoalcohol motif in a way that was high yielding, highly functional group tolerant, and able to be performed in a minimum number of steps.

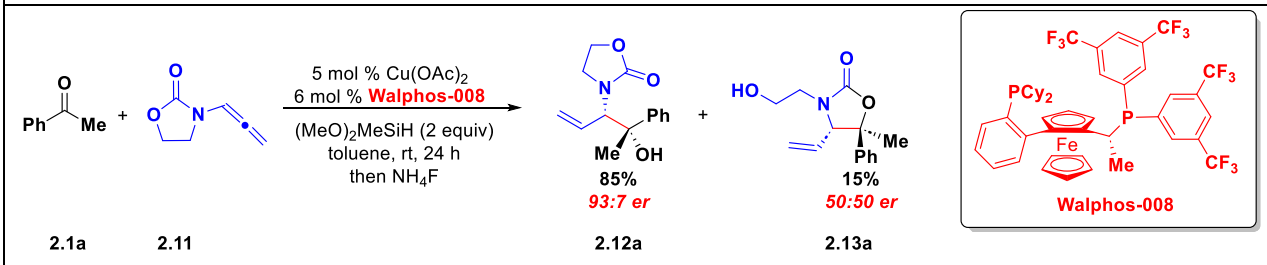
***Scheme 2.2**: Potential Routes to Access 1,2-aminoalcohols*



C. Prior Art for Enantioselective Allenamide – Ketone Reductive Coupling

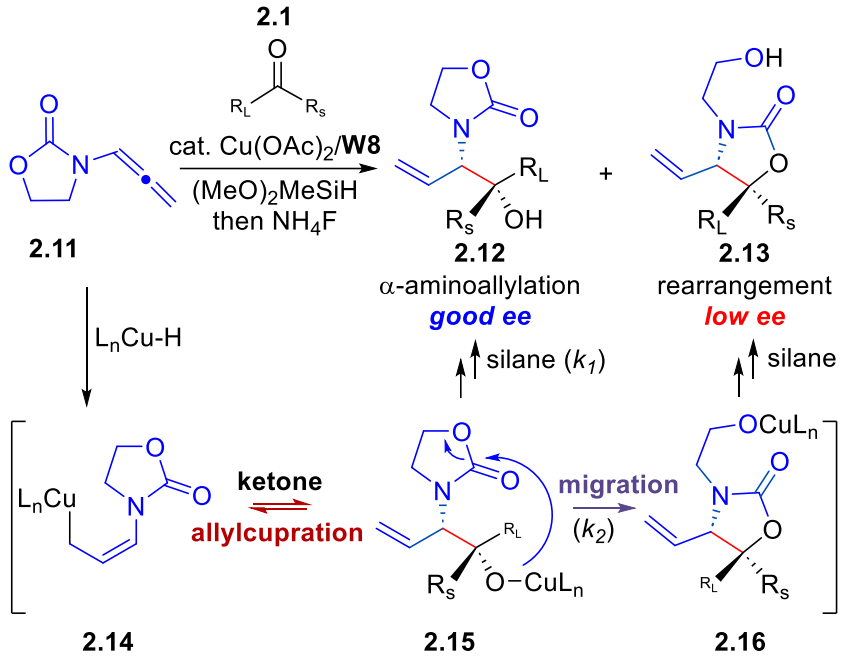
Our group has previously published work describing the enantioselective aminoallylation of aryl ketones with achiral allenamide **2.11** using the Walphos-008 ligand as the source of chirality **(Scheme 2.3)**.[52] This work did induce a moderate degree of enantioselectivity into the aminoalcohol synthon product but suffered from a competitive on-cycle carbamate migration. This would, in theory, not be an issue due to the fact that the aminoalcohol can be easily converted to the carbamate product in a single step.[37] This product can then be transformed into the free aminoalcohol in four steps. However, the issue with this process is that, when analyzing the products of the reaction, carbamate product **2.13a** has a vastly different enantiomeric ratio than aminoalcohol product **2.12a**.

***Scheme 2.3**: Prior Art for Enantioselective Allenamide – Ketone Reductive Coupling*



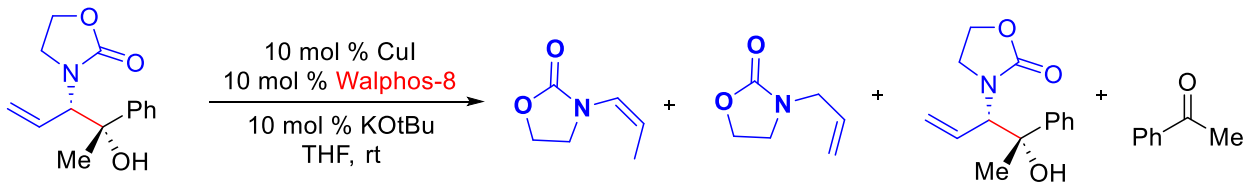
The difference in enantioselectivities was theorized to be due to a reversable allylcupration between allylcopper intermediate **2.14** and copper alkoxide **2.15** (**Scheme 2.4**). Reversible allylation at ambient conditions in metal catalyzed reductive coupling reactions had not been identified prior to this work. If the allylcupration step is reversible, then the enantiopurity of the product would be dependent on the rate of silylation (k_1) vs carbamate migration (k_2) of copper alkoxide **2.15**.

***Scheme 2.4**: Ketone Aminoallylation With Migration Mechanism*



Further evidence to support the idea of a reversible allylcupration was found by subjecting aminoalcohol synthon **2.12a** to catalytic amounts of copper and walphos-8 under basic conditions (**Scheme 2.5**).[52] The results of this experiment show that protonated forms of the potential isomers of allylcopper intermediate **2.14** in **Scheme 2.4**, ketone, and the allenamide in different enantiopurity, can be recovered from the reaction.

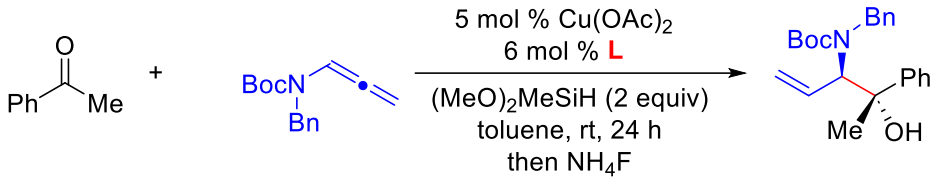
***Scheme 2.5**: Evidence For Reversible Allylcupration*



III. Research Design

Due to issues with enantiopurity loss from the on-cycle carbamate migration and a laborious deprotection sequence, further improvements to this methodology had to be developed.[52] The easiest way to accomplish both of these improvements was thought to be through changing the protecting groups on the nitrogen of the allenamide. If suitable protecting groups could be found that were both resistant to the rearrangement and offered facile deprotection then the methodology could be greatly improved. Initially the protecting groups that were chosen were the Boc and PMB protecting groups (**Scheme 2.6**).

Scheme 2.6: *Initial Design of the Aminoallylation Reaction*

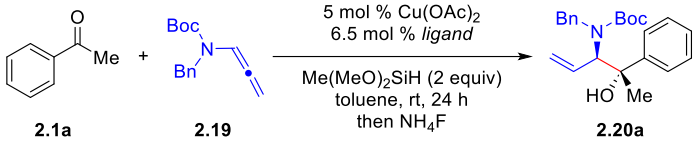


2.1a **2.19** **2.20a**

IV. Ketone Reductive Coupling Protocol Employing Chiral Ligands

A. Reaction Development

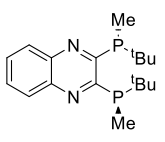
Table 2.1: *Ligand Optimization in the Cu-Catalyzed Reductive Coupling*[a]



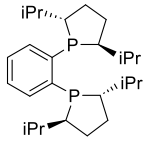
2.1a **2.19** (1.2 equiv) **2.20a**

Entry	Ligand	% yield **2.20a**[b]	Dr **2.20a**[c]	Er **2.20a**[d]
1	(*R*,*R*)-Ph-BPE	73	53:47	71:27
2	(*R*)-BINAP	84	52:48	78:22
3	(*R*)-SegPhos	82	56:44	78:22
4	(*R*)-DuanPhos	82	45:52	73:27
5	W8	10	100:0	63:37
6	(*R*)-DBTM-SegPhos	78	69:31	77:23
7	(*R*)-Xyl-BINAP	69	63:37	73:27
8	A-120	100	55:45	39:61
9	A-131	68	75:25	29:71
10	(*R*)-iPr-DuPhos	83	53:47	79:21
11	(*R*)-QuinoxP*	98	55:45	82:18
12	M3	12	100:0	60:40
13	J9	72	61:39	92:8
14	J7	100	50:50	88:12
15	J15	70	53:47	79:21
16	J2	76	51:49	97:3
17	J8	95	51:49	88:12
18	J11	62	52:48	82:18
19	J3	42	54:46	97:3
20	J5	49	39:61	89:11

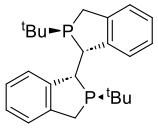
[a]Reaction performed according to the general procedure employing 0.200 mmol of ketone, 0.240 mmol of **2.19**, 0.40 mmol of $Me(OMe)_2SiH$ in 0.50 mL of toluene at rt for 24 h. [b]Yield of **2.20a** determined by quantitative ^{1}HNMR spectroscopy on the unpurified reaction mixture using dimethyl fumarate as the analytical standard. [c]The ratio was determined by ^{1}HNMR spectroscopic analysis on the unpurified reaction mixture. [d]Enantiomeric ratio for the major diastereomer was determined by HPLC analysis using a chiral stationary phase.



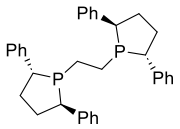
QuinoxP*



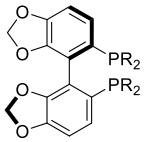
(*R,R*)-**iPr-DuPhos**



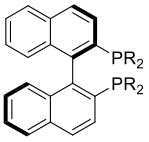
DuanPhos



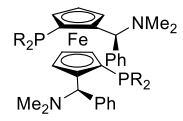
(*R,R*)-**Phenyl-BPE**



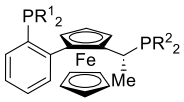
(*R*)-**SEGPHOS** R = Ph
(*R*)-**DTBM-SEGPHOS** R = 3,5-(^{t}Bu)$_2$-4-OMe-Ph



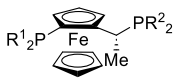
(*R*)-**BINAP** R = Ph
(*R*)-**DM-BINAP** R = 3,5-(Me)$_2$-Ph



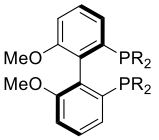
M3 R = 3,5-(CF$_3$)$_2$-Ph



W8 R^1 = 3,5-(CF$_3$)$_2$-Ph, R^2 = Cy



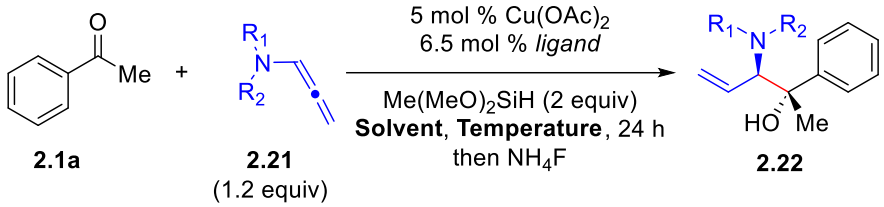
J2 R^1 = Ph, R^2 = ^{t}Bu
J3 R^1 = R^2 = Cy
J5 R^1 = Ph, R^2 = 3,5-(Me)$_2$-Ph
J7 R^1 = 3,5-(Me)$_2$-4-OMe-Ph, R^2 = Cy
J8 R^1 = 3,5-(CF$_3$)$_2$-Ph, R^2 = 3,5-(Me)$_2$-Ph
J9 R^1 = Cy, R^2 = ^{t}Bu
J11 R^1 = 4-CF$_3$-Ph, R^2 = ^{t}Bu
J15 R^1 = 3,5-(Me)$_2$-Ph, R^2 = 2-furyl



A-120 R = 3,5-(Me)$_2$-Ph
A-121 R = 3,5-(^{t}Bu)$_2$-Ph

This investigation began by analyzing the applicability of various chiral ligands towards the reductive coupling of achiral allenamide **2.19** and aryl ketone **2.1a** (**Table 2.1**). Moderate to excellent yields and enantioselectivities were obtained for the majority of ligands tested albeit with extremely poor diastereoselectivity for most cases. Since Josiphos-002 (**J2**, entry 16) offered the best combination of the yield and enantioselectivity it was used as the model ligand to test various other changes to the reaction conditions.

Table 2.2: *Solvent, Temperature, and Allenamide Survey in the Cu-Catalyzed Reductive Coupling*[a]



2.1a **2.21** (1.2 equiv) **2.22**

Entry	R_1, R_2	Solvent	Temperature	% yield **2.22**[b]	Dr **2.22**[c]	Er **2.22**[d]
1	Boc, Bn	Toluene	22 °C	76	53:47	97:3
2	Boc, Bn	THF	22 °C	81	54:46	96:4
3	Boc, Bn	MTBE	22 °C	78	50:50	98:2
4	Boc, Bn	1,4-Dioxane	22 °C	81	58:42	95:5
5	Boc, Bn	Me-THF	22 °C	85	52:48	95:5
6	Boc, Bn	CF_3-Toluene	0 °C	87	53:47	96:4
7	Boc, Bn	Toluene	0 °C	76	58:42	98:2
8	Boc, Bn	Dioxane	0 °C	61	59:41	98:2
9	Boc, Bn	Toluene	50 °C	86	56:44	94:6
10	Boc, Bn	Toluene/1,4-Dioxane	0 °C	81	58:42	98:2
11	Ac, PMB	Toluene/1,4-Dioxane	0 °C	87	90:10	97:3
12	CO*i*-Pr, PMB	Toluene/1,4-Dioxane	0 °C	68	79:21	87:13

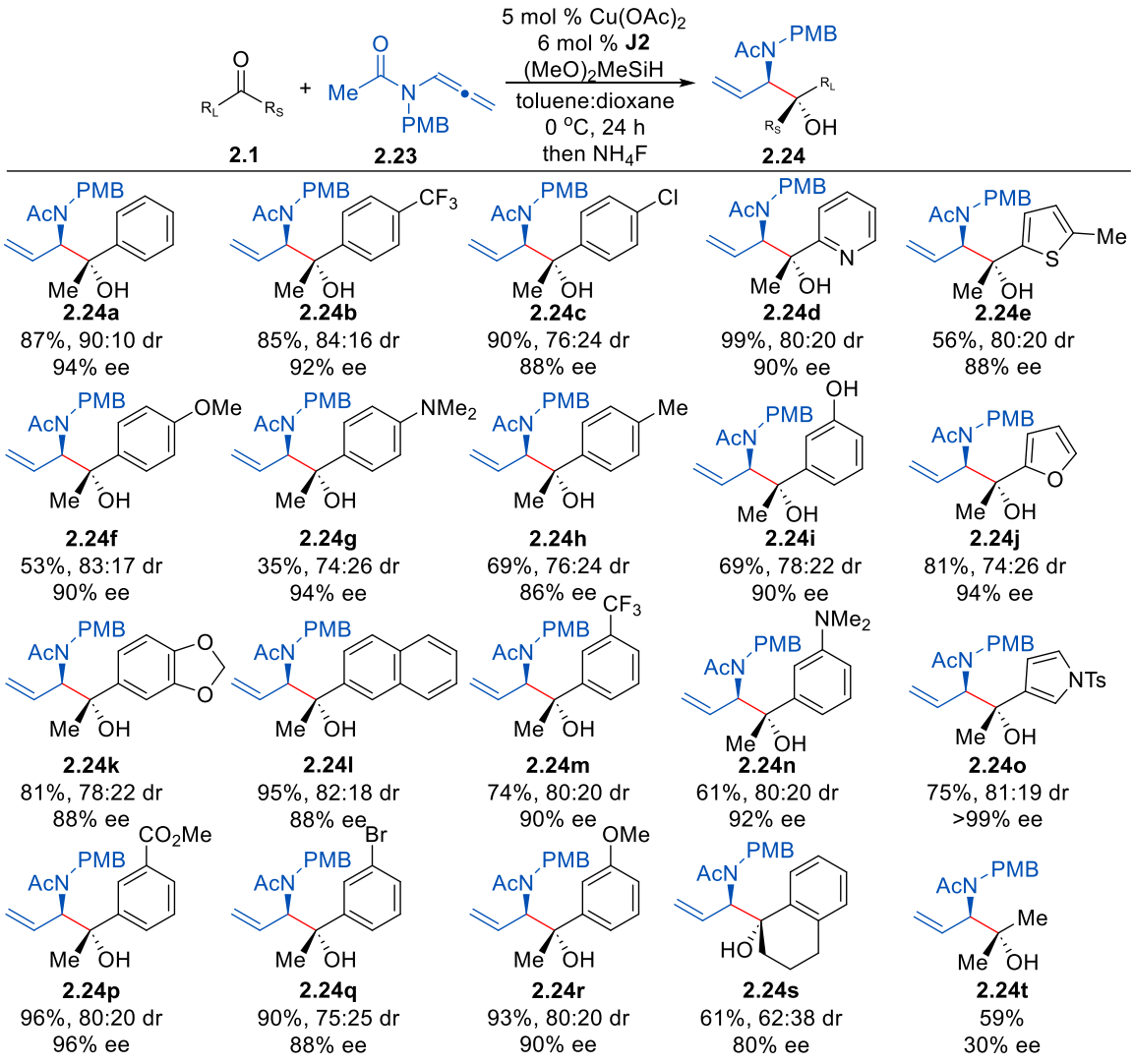
[a]Reaction performed according to the general procedure employing 0.200 mmol of **ketone**, 0.240 mmol of **2.21**, 0.40 mmol of $Me(Ome)_2SiH$ in 0.50 mL of solvent at the specified temperature for 24 h. [b]Yield of **2.22** determined by quantitative ^{1}HNMR spectroscopy on the unpurified reaction mixture using dimethyl fumarate as the analytical standard. [c]The ratio was determined by ^{1}HNMR spectroscopic analysis on the unpurified reaction mixture. [d]Enantiomeric ratios for the major diastereomer were determined by HPLC analysis using a chiral stationary phase.

A survey of solvent, temperature, and allenamide protecting group was then conducted (**Table 2.2**). It was observed that a 50/50 mixture of toluene and 1,4-dioxane run at 0 °C provided the optimal combination of yield and enantioselectivity, albeit still with poor diastereoselectivity (Entry 10). The only factors that seemed to impact the diastereoselectivity in a major way were the protecting groups on the allenamide (entries 10 – 12). When the acetyl

and *para*-methoxybenzyl protecting groups were used, an acceptable diastereoselectivity was finally obtained (Entry 11).

B. Substrate Scope

***Scheme 2.7**: Scope of the Ketone – Allenamide Reductive Coupling Reaction*



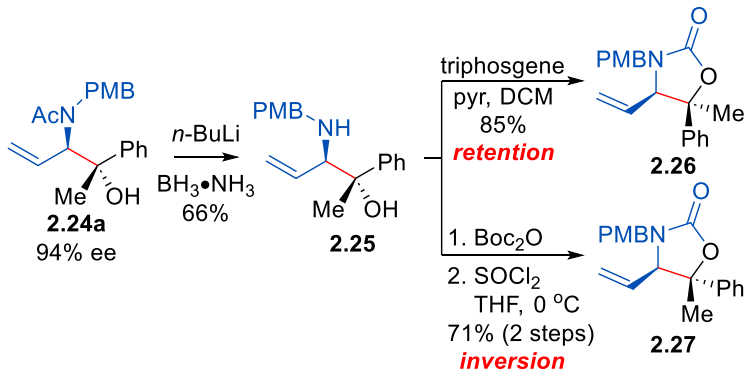
With the optimal reaction conditions in hand, the scope of the reaction was investigated using a variety of sterically and electronically different ketones (**Scheme 2.7**).[67] High yields, as well as diastereo- and enantioselectivities were observed for a number of electron deficient (**2.24b, 2.24m, and 2.24p)** and electron rich (**2.24f-i, 2.24k, 2.24n, and 2.24r)** aryl ketones. Of

exceptional note were certain hetereocyclic products such as those derived from 3-acetylpyridine (**2.24d**) and 1-tosyl-3-acetylpyrrole (**2.24o**) that had near perfect yield and enantiopurity respectively. Alkyl ketones (**2.24s-t)**) functioned poorly, with low yields and enantioselectivities.

C. Deprotection

The acetyl protecting group on aminoallylation product **2.24a** could be efficiently cleaved using LAB to furnish free secondary amine **2.25** (**Scheme 2.8**).[68] The stereocenter of the carbon bearing the alcohol substituent can be inverted through a process involving re-protection of the amine with Boc anhydride, activation of the alcohol with $SOCl_2$, and neighboring group participation of the Boc group to attack the activated alcohol.[69] This afforded inverted carbamate **2.27**, which was compared to the same compound prepared from authentic material to confirm the absolute and relative stereochemistry.[67] Conversion of deprotected amine **2.25** to carbamate **2.27** was also performed, expected to proceed through retention of stereochemistry, as a control. Notably, this divergent pathway allows for either diastereomer of the aminoalcohol synthon to be obtained, depending on what is desired by the chemist.

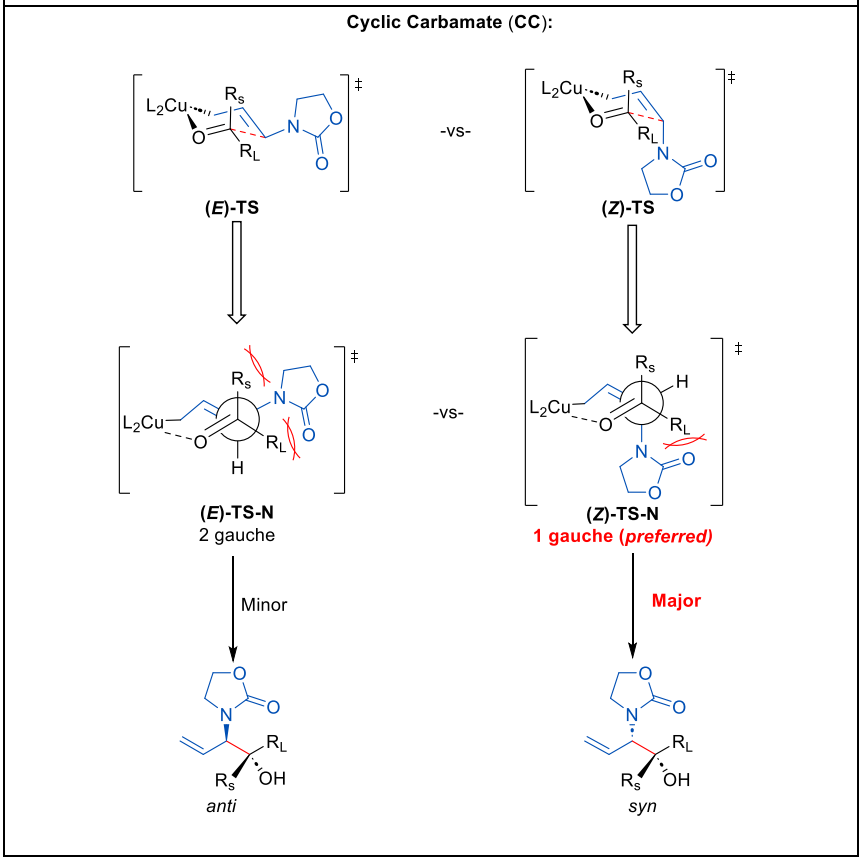
Scheme 2.8: *Deprotection and Stereocenter Inversion*



D. Stereochemical Rationalization

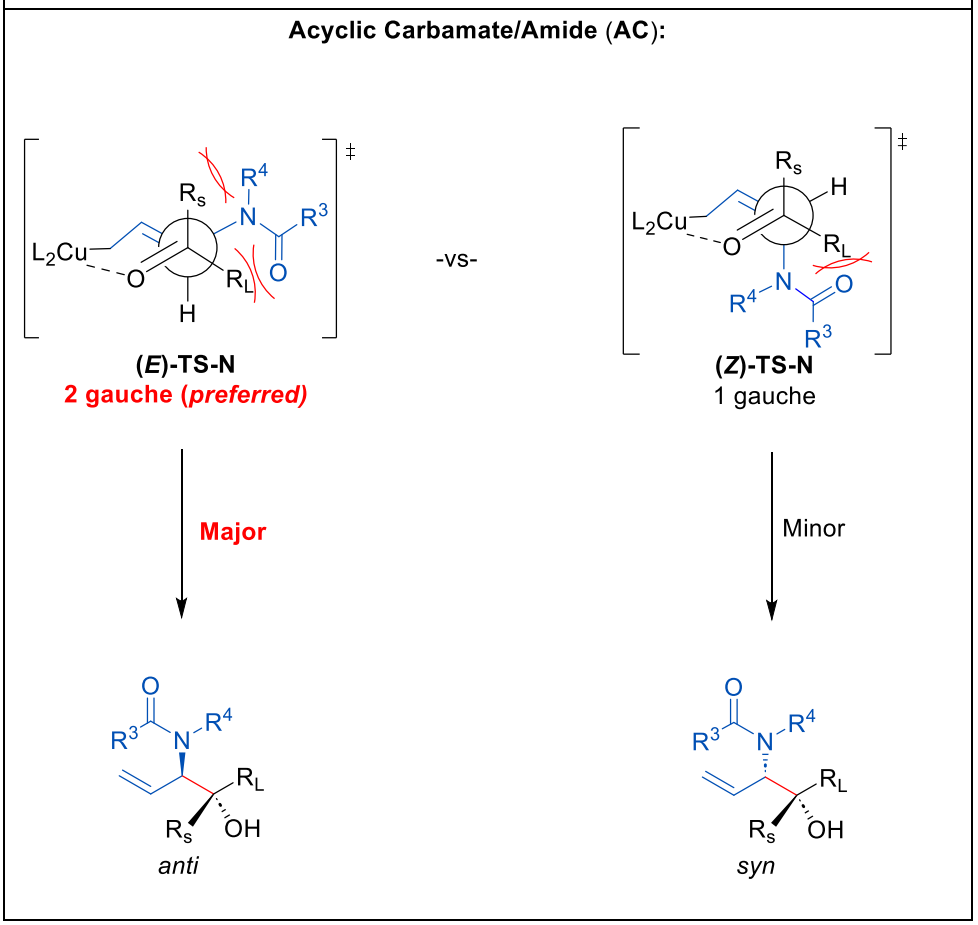
One realization of particular interest is that the major diastereomer that is produced from the reaction with acyclic allenamides is inverted compared to that of cyclic allenamides. To understand this result, one must examine the Newman projections of each transition state structure leading to each diastereomeric product. For the case involving cyclic carbamate (CC) derived allenamides, the major diastereomer is the one that is predicted by the Newman analysis (**Fig 2.2**). The transition state leading to the major *syn*-diastereomer (**Z-TS-N**) has one gauche interaction, while the transition state leading to the minor *anti*-diastereomer (**E-TS-N**) has two gauche interactions. The reduced strain from the number of gauche interactions observed correctly rationalizes the *syn*-product selectivity of the reaction.

***Figure 2.2**: Newman Analysis for Cyclic Carbamate (CC) Derived Allenamides*



Counterintuitively, the major diastereomer produced by the reaction employing acyclic amide derived allenamides is the opposite of the one predicted by an analogous Newman analysis (**Fig 2.3**). The transition state leading to the now major *anti*-diastereomer (**E-TS-N**) has two gauche interactions, while the transition state leading to the minor *syn*-diastereomer (**Z-TS-N**) only has one gauche interaction.

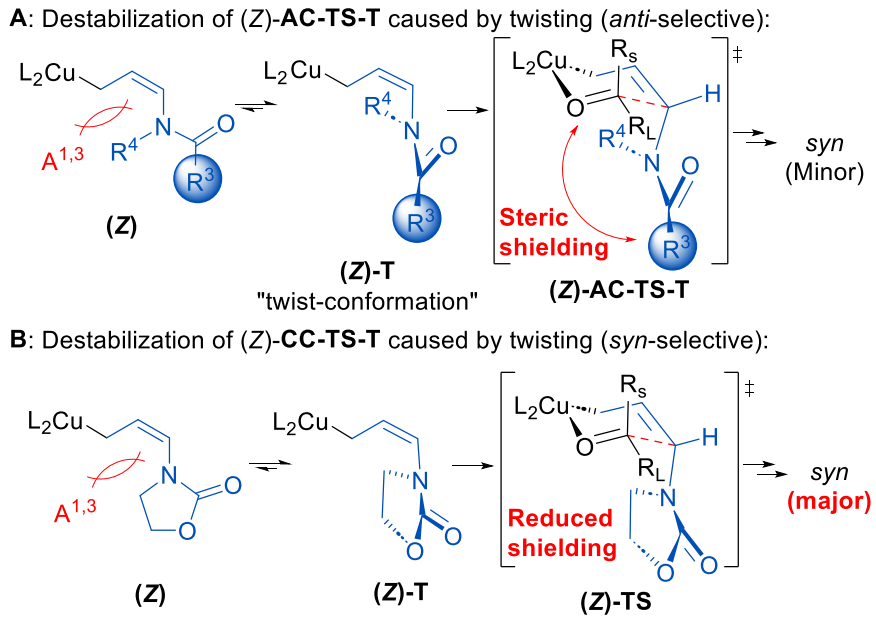
***Figure 2.3**: Newman Analysis for the Acyclic Carbamate/Amide*



This oddity can be rationalized by the fact that Newman analysis assumes a degree of planarity throughout the molecule being studied, which in many cases is not true. Previous studies of (*Z*)-substituted enamides have demonstrated that these structures are not planar and exist as

"twisted" amides due to the presence of $A^{1,3}$ strain.[70] This "twisting" serves to reduce the $A^{1,3}$ strain that is present, but also heavily shields the ketone approach vector that results in the *syn* diastereomer in the case of the acyclic amide derived allenamides (Fig **2.4, A**). The amide twist phenomenon is also present in the case of the cyclic carbamate (CC) derived allenamides, but the reduced steric bulk of the oxazolidinone moiety compared to the R^3 substituent of the acyclic amide derived allenamide results in a much lower ability to shield allylcopper intermediate **(Z)-T** from the ketone approach vector (**Fig 2.4, B**).

***Figure 2.4**: Amide Twist Depiction*



V. Conclusion

This strategy for the stereoselective reductive coupling of ketones and achiral allenamides to selectively generate 1,2-aminoalcohol synthons is an effective tool for accessing molecules with a dissonant charge affinity. This improves upon work previously published by our group by increasing enantiocontrol over the process through the modification of the

allenamide substituents to remove the carbamate migration step that was deleterious to the enantioselectivity of the products. This generally high yielding protocol generates branched products with high diastereo- and enantioselectivities, owing to the chiral ligand. The acetyl protecting group can be easily removed and the resulting *anti*-aminoalcohol can undergo boc-protection followed by anchimerically assisted cyclocarbamation with $SOCl_2$ to furnish the *syn*-aminoalcohol carbamate product.

VI. Experimental Methods

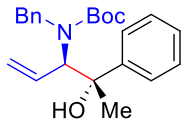
General. ^{1}H NMR spectra were recorded on Bruker 600 MHz spectrometers. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as an internal standard ($CDCl_3$: 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, h = hextet, hept = heptet, br = broad, m = multiplet), and coupling constants (Hz). ^{13}C NMR was recorded on a Bruker 600 MHz (151 MHz) instrument with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard ($CDCl_3$: 77.0 ppm). Chiral Column HPLC analyses were performed on a Shimadzu Prominence i-series LC-2030C using chiral Daicel columns purchased from Chiral Technologies, Inc. Liquid chromatography was performed using forced flow (flash chromatography) on silica gel purchased from Silicycle. Thin layer chromatography (TLC) was performed on glass-backed 250 μm silica gel F254 plates purchased from Silicycle. Visualization was achieved using UV light, a 10% solution of phosphomolybdic acid in EtOH, or potassium permanganate in water followed by heating. HRMS was collected using a Jeol AccuTOF-DART^{TM} mass spectrometer using DART source ionization. All reactions were conducted in oven or flame dried glassware under an inert atmosphere of nitrogen or argon with magnetic stirring unless otherwise noted. Solvents were obtained from VWR as HPLC grade and transferred to septa sealed bottles, degassed by Ar sparge, and analyzed by Karl-Fischer titration to ensure water content was $\leq$ 600 ppm. $Me(MeO)_2SiH$ was purchased from Gelest and used as received. Ketones were purchased from Sigma Aldrich, TCI America, Alfa Aesar, or Oakwood Chemicals and used as received. All other materials were purchased from VWR, Sigma Aldrich, Combi-Blocks, Alfa-Aesar, or Strem Chemical Company and used as received.

Method A: General procedure for Cu(J2) catalyzed reductive coupling with ketones.

To a 20 mL crimp-cap vial with stir-bar in an Ar-filled glove-box was charged 1.8 mg (0.0100 mmol, 0.05 equiv) of $Cu(OAc)_2$ and 7.1 mg (0.0130 mmol, 0.065 equiv) of **J-2**. Toluene (0.25 mL) and 1,4-dioxane (0.25 mL) was then added, and the mixture was allowed to stir for 30 min. Alleneamide **2.23** (0.240 mmol, 1.2 equiv) was then charged along with the ketone (0.200 mmol, 1 equiv, 0.4 M in solvent), and reaction vessel sealed with a crimp-cap septum and removed from the glove-box. The reaction was then cooled in an ice bath, and dimethoxymethylsilane (49 μL, 0.4 mmol, 2 equiv) was then charged by syringe (*caution: dimethoxymethylsilane should be handled in a well-ventilated fume hood because it is known to cause blindness. Syringes were quenched with 2M NaOH, gas evolution!, prior to disposal)* After 24 h at 0 ^{o}C, the reaction was then quenched by the addition of 95 mg of NH_4F and 3.0 mL of

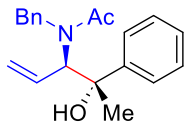
MeOH followed by agitation at rt for 30 min – 1 h. To the mixture was then charged 5 mL of 5% $NaHCO_3$ followed by extraction with CH_2Cl_2 (2x5mL). The combined organics were dried with Na_2SO_4 and concentrated *in vacuo*. An aliquot of the crude mixture was analyzed by ^{1}HNMR spectroscopy to determine dr. The crude residue was then purified by flash chromatography on silica gel to afford the desired product. Enantioselectivity was determined by chiral column HPLC analysis relative to authentic racemate prepared by the above procedure employing *rac*-BINAP as the ligand.

Characterization Data



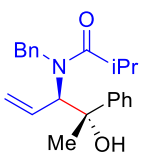
2.19

tert-butyl benzyl((3S,4R)-4-hydroxy-4-phenylpent-1-en-3-yl)carbamate (2.19): According to the general procedure A using allenamide **2.23a**, the product was purified by silica gel chromatography (2.5 % EtOAc in Hexanes) to provide 60 mg (81 %) of **2.19** as a white foam with a diastereomeric ratio of 58:42 with the major diastereomer having an enantiomeric ratio of 98:2. R_f =0.67 (50 % EtOAc/hexanes). The stereochemistry was assigned by analogy to **2.24a**. ^{1}HNMR ($CDCl_3$, 600 MHz) δ: 7.39 (d, *J* = 7.10 Hz, 2H, minor), 7.33 (d, *J* = 7.93 Hz, 2H, major), 7.29 (t, *J* = 7.57 Hz, 2H, minor), 7.28 (d, *J* = 7.74 Hz, 2H, major), 7.23 (d, *J* = 8.68 Hz, 2H, major), 7.22 (m, 4H, minor), 7.18 (t, *J* = 7.36 Hz, 1H, major), 6.96 – 7.00 (m, 2H), 6.90 (d, *J* = 8.49 Hz, 2H, major), 6.74 (br s, 1H, minor), 6.42 (ddd, *J* = 17.51 Hz, 9.77 Hz, 8.05 Hz, 1H, minor), 5.88 (ddd, *J* = 17.37 Hz, 8.68 Hz, 8.31 Hz, 1H, major), 5.18 (d, *J* = 10.36 Hz, 1H, minor), 4.95 (d, *J* = 10.82 Hz, 1H, major), 4.85 (d, *J* = 18.00 Hz, 1H, minor), 4.64 (t, *J* = 17.88 Hz, 2H, major), 4.18 (d, *J* = 17.00 Hz, 1H, major), 4.17 (d, *J* = 15.82 Hz, 1H, minor), 3.98 (br s, 1H, major), 3.67 (d, *J* = 8.18 Hz, 1H, minor), 3.51 (d, *J* = 15.27 Hz, 1H, minor), 1.48 – 1.57 (m, 12H, major), 1.32 (s, 12H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 157.2, 146.8, 138.1, 137.7, 132.5, 131.5, 128.5, 128.2, 128.0, 127.9, 127.8, 127.2, 126.5, 126.4, 125.5, 125.2, 119.1, 81.4, 81.0, 76.9, 73.5, 54.7, 28.5, 28.4, 28.3. HRMS (DART) *m/z* calcd for $C_{23}H_{28}NO_2$ $[M - OH]^+$: 350.2115; Found $[M - OH]^+$: 350.2145.



2.23b

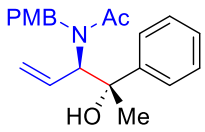
N-benzyl-N-((3R,4S)-4-hydroxy-4-phenylpent-1-en-3-yl)acetamide (2.2b): According to the general procedure A using allenamide **2.23b**, the product was purified by silica gel chromatography (10 - 20 % EtOAc in Hexanes) to provide 54 mg (87 %) of **13b** as a white foam with a diastereomeric ratio of 88:12 with the major diastereomer having an enantiomeric ratio of 96:4. R_f =0.37 (50 % EtOAc/hexanes). The stereochemistry was assigned by analogy to **2.24a**. ^{1}HNMR ($CDCl_3$, 600 MHz) δ: 7.22 – 7.40 (m, 9H), 7.19 (t, *J* = 7.38 Hz, 1H), 5.95 (ddd, *J* = 16.94 Hz, 9.12 Hz, 8.69 Hz, 1H), 4.99 (d, *J* = 10.86 Hz, 1H), 4.65 (d, *J* = 16.07 Hz, 1H), 4.58 (d, *J* = 16.51 Hz, 1H), 4.28 (d, *J* = 16.51 Hz, 1H), 2.27 (s, 3H), 1.38 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 173.5, 146.2, 136.2, 131.0, 128.8, 128.1, 127.9, 127.8, 127.78, 127.71, 126.6, 125.6, 76.2, 29.7, 29.6, 28.4, 23.2. HRMS (DART) *m/z* calcd for $C_{20}H_{22}NO$ $[M - OH]^+$: 292.1696; Found $[M - OH]^+$: 292.1672.



2.21c

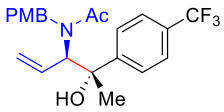
N-((3R,4S)-4-hydroxy-4-phenylpent-1-en-3-yl)-N-methylisobutyramide (2.21c). According to the general procedure A using allenamide **2.23c** and 0.250 mmol of acetophenone, a crude mixture of **2.21c** of 79:21 dr (^{1}HNMR spectroscopy) was obtained and purified by silica gel chromatography (eluent: 0 – 20% EtOAc in Hexanes) to provide 46 mg (68%) of **2.21c** as a diasteromeric mixture in 87:13 er.

The stereochemistry was assigned by analogy to **2.24a**. R_f = 0.10 (20 % EtOAc/hexanes). ^{1}HNMR ($CDCl_3$, 600 MHz) δ: 7.08 – 7.31 (m, 10H), 5.85 (m, 1H), 4.89 (d, J = 10.31 Hz, 1H), 4.43 – 4.74 (m, 2H), 4.14 – 4.31 (m, 2H), 2.70 – 2.84 (m, 1H), 1.33 (s, 3H), 1.13 (d, J = 6.66 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 180.0, 146.6, 132.5, 131.2, 128.7, 127.8, 127.1, 126.6, 125.7, 125.4, 120.1, 76.9, 31.9, 28.3, 19.8, 19.6, 18.4. HRMS (DART) *m/z* calcd for $C_{22}H_{26}NO$ [M - OH]$^+$: 320.2009; Found [M - OH]$^+$: 320.1997.



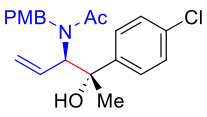
2.24a

N-((3S,4R)-4-hydroxy-4-phenylpent-1-en-3-yl)-N-(4-methoxybenzyl)acetamide (2.24a): According to the general procedure A using allenamide **2.23d**, the product was purified by silica gel chromatography (10 % to 20 % EtOAc in Hexanes) to provide 59 mg (87 %) of **2.24a** as a white foam with a diastereomeric ratio of 90:10 with the major diastereomer having an enantiomeric ratio of 97:3. Relative and absolute stereochemistry was assigned by conversion to authentic material, see pages S27-S29 R_f =0.30 (50 % EtOAc/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.15-7.22 (m, 6H), 6.92 (d, *J* = 8.80 Hz, 2H), 5.95 (ddd, *J* = 17.41 Hz, 8.97 Hz, 8.96 Hz, 1H), 4.98 (d, *J* = 10.61 Hz, 1H), 4.54-4.61 (m, 2H), 4.23 (d, *J* = 15.98 Hz, 1H), 3.83 (s, 3H), 2.30 (s, 3H), 1.29 (s, 3H) ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.2, 159.5, 146.4, 131.0, 129.2, 128.0, 127.8, 126.5, 125.6, 118.2, 114.2, 75.9, 55.4, 53.5, 28.5, 23.3. HRMS (DART) *m/z* calcd for $C_{21}H_{24}NO_2$ [M - OH]$^+$: 322.1802; Found [M - OH]$^+$: 322.1825.



2.24b

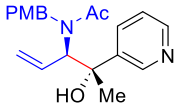
N-((3S,4R)-4-hydroxy-4-(4-(trifluoromethyl)phenyl)pent-1-en-3-yl)-N-(4-methoxybenzyl)acetamide (2.24b): According to the general procedure A using allenamide **2.23d**, the product was purified by silica gel chromatography (10 % - 30 % EtOAc in Hexane) to provide 69 mg (85 %) of **2.24b** as a glass with a diastereomeric ratio of 84:16 with the major diastereomer having an enantiomeric ratio of 96:4. The stereochemistry was assigned by analogy to **2.24a**. R_f = 0.47 (50 % EtOAC/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.35 Hz, 2H), 7.37 (d, *J* = 8.14 Hz,2H), 7.19 (d, *J* = 8.47 Hz, 2H), 6.93 (d, *J* = 8.63 Hz, 2H), 5.96 (ddd, *J* = 17.45 Hz, 8.95 Hz, 8.63 Hz, 1H), 4.97 (d, *J* = 10.54 Hz, 2H), 4.61 (d, *J* = 16.22 Hz, 1H), 4.54 (d, *J* = 17.35 Hz, 1H), 4.24 (d, *J* = 15.84 Hz, 1H), 3.84 (s, 3H), 2.33 (s, 3H), 1.30 (s, 3H) ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.2, 159.7, 150.7, 130.4, 129.5, 128.8 (q, *J* = 32.7 Hz), 127.6, 126.0, 124.8 (q, *J* = 4.3 Hz), 124.2 (J = 271.9 Hz), 118.6, 114.3, 75.6, 55.4, 54.7, 28.3, 23.3. ^{19}F NMR (565 MHz, $CDCl_3$) δ -62.33. HRMS (DART) *m/z* calcd for $C_{22}H_{23}F_3NO_2$ [M - OH]$^+$: 390.1675; Found [M - OH]$^+$: 390.1700.



2.24c

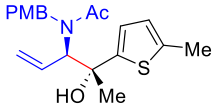
N-((3S,4R)-4-(4-chlorophenyl)-4-hydroxypent-1-en-3-yl)-N-(4-methoxybenzyl)acetamide (2.24c): According to the general procedure A using allenamide **2.23d**, the product was purified by silica gel chromatography (10 % - 30 % EtOAc in Hexane) to provide 67 mg (90 %) of **2.24c** as a glass with a diastereomeric ratio of 76:24 with the major diastereomer having an enantiomeric ratio of 98:2. The stereochemistry was assigned by analogy to **2.24a**. R_f = 0.40 (50 % EtOAC/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.15-7.22 (m, 6H), 6.92 (d, J= 8.80 Hz, 2H), 5.95 (ddd, *J* = 17.41 Hz, 8.97 Hz, 8.96 Hz, 1H), 4.98 (d, *J* = 10.61 Hz, 1H), 4.54-4.61 (m, 2H), 4.23 (d, *J* = 15.98 Hz, 1H), 3.83 (s, 3H), 2.30 (s, 3H), 1.29 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ

173.2, 150.6, 145.1, 132.3, 130.6, 129.4, 128.8, 127.9, 127.2, 118.6, 114.2, 75.6, 55.4, 55.3, 28.4, 23.3. HRMS (DART) *m/z* calcd for $C_{21}H_{23}ClNO_2$ [M - OH]$^+$: 356.1412; Found [M - OH]$^+$: 356.1433.



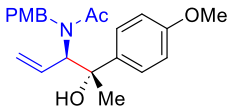
2.24d

N-((3S,4R)-4-hydroxy-4-(pyridin-3-yl)pent-1-en-3-yl)-N-(4-methoxybenzyl)acetamide (2.24d): According to the general procedure A using allenamide **2.23d**, the product was purified by silica gel chromatography (50 % - 100 % EtOAc in Hexane) to provide 71 mg (99 %) of **2.24d** as a glass with a diastereomeric ratio of 80:20 with the major diastereomer having an enantiomeric ratio of 95:5. The stereochemistry was assigned by analogy to **2.24a**. R_f = 0.08 (50 % EtOAC/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.41 (s, 2H), 7.71 (d, 7.74 Hz, 1H), 7.16 (d, 8.64 Hz, 3H), 6.90 (d, *J* = 8.64 Hz, 2H), 5.97 (ddd, *J* = 17.21 Hz, 8.99 Hz, 8.48 Hz, 1H), 4.96 (d, *J* = 10.8 Hz, 1H), 4.59 (d, *J* = 16.57, 1H), 4.52 (d, *J* = 17.21 Hz, 1H), 4.23 (d, *J* = 17.21 Hz, 1H), 3.80 (s, 3H), 2.30 (s, 3H), 1.30 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.1, 159.7, 147.8, 147.4, 133.8, 130.3, 129.4, 129.2, 128.7, 127.5, 119.1, 114.3, 74.7, 55.4, 43.3, 28.1, 23.3. HRMS (DART) *m/z* calcd for $C_{20}H_{23}N_2O_2$ [M - OH]$^+$: 323.1754; Found [M - OH]$^+$: 323.1782.



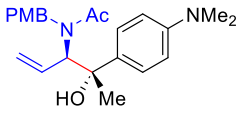
2.24e

N-((3S,4S)-4-hydroxy-4-(5-methylthiophen-2-yl)pent-1-en-3-yl)-N-(4-methoxybenzyl)acetamide (2.24e): According to the general procedure A using allenamide **2.23d**, the product was purified by silica gel chromatography (10 % - 40 % EtOAc in Hexane) to provide 40 mg (56 %) of **2.24e** as a glass with a diastereomeric ratio of 80:20 with the major diastereomer having an enantiomeric ratio of 94:6. The stereochemistry was assigned by analogy to **2.24a**. R_f = 0.39 (50 % EtOAC/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.12 (d, *J* = 8.53 Hz, 2H), 6.88 (d, 8.53 Hz, 2H), 6.55 (d, 3.59 Hz, 1H), 6.48 (d, 3.59 Hz, 1H), 6.03 (ddd, *J* = 17.29 Hz, 9.17 Hz, 8.65 Hz, 1H), 5.08 (d, 10.35 Hz, 1H), 4.86 (d, *J* = 17.16 Hz, 1H), 4.49 (d, 16.46 Hz, 1H), 4.16 (d, 16.46 Hz, 1H), 3.81 (s, 3H), 2.41 (s, 3H), 2.24 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.5, 159.4, 149.1, 138.3, 131.1, 130.1, 129.0, 128.1, 124.8, 122.2, 114.1, 76.0, 55.3, 53.8, 29.7, 23.1, 15.2. HRMS (DART) *m/z* calcd for $C_{20}H_{24}NO_2S$ [M - OH]$^+$: 342.1522; Found [M - OH]$^+$: 342.1548.



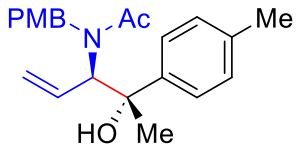
2.24f

N-((3S,4R)-4-hydroxy-4-(4-methoxyphenyl)pent-1-en-3-yl)-N-(4-methoxybenzyl)acetamide (2.24f): According to the general procedure A using allenamide **2.23d**, the product was purified by silica gel chromatography (10 % - 30 % EtOAc in Hexane) to provide 39 mg (53 %) of **2.24f** as a glass with a diastereomeric ratio of 83:17 with the major diastereomer having an enantiomeric ratio of 95:5. The stereochemistry was assigned by analogy to **2.24a**. R_f = 0.28 (50 % EtOAC/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.67 Hz, 2H) 7.15 (d, *J* = 8.17 Hz, 2H), 6.90 (d, *J* = 8.46 Hz, 2H), 6.79 (d, *J* = 8.88 Hz, 2H), 5.94 (ddd, *J* = 16.58 Hz, 8.39 Hz, 8.85 Hz, 1H), 4.99 (d, *J* = 10.41 Hz, 1H), 4.48-4.70 (m, 2H), 4.20 (d, *J* = 16.26 Hz, 1H), 3.82 (s, 3H), 3.77 (s, 3H), 2.27 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.2, 159.5, 158.2, 138.5, 132.4, 131.1, 129.7, 129.2, 126.8, 126.3, 114.2, 113.1, 76.6, 75.7, 55.4, 55.2, 28.6, 23.2. HRMS (DART) *m/z* calcd for $C_{22}H_{26}NO_3$ [M - OH]$^+$: 352.1907; Found [M - OH]$^+$: 352.1920 .



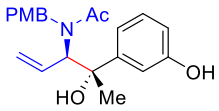
2.24g

N-((3S,4R)-4-(4-(dimethylamino)phenyl)-4-hydroxypent-1-en-3-yl)-N-(4-methoxybenzyl)acetamide (2.24g): According to the general procedure A using allenamide **2.23d**, the product was purified by silica gel chromatography (20 % - 60 % EtOAc in Hexane) to provide 27 mg (35 %) of **2.24g** as a glass with a diastereomeric ratio of 74:26 with the major diastereomer having an enantiomeric ratio of 96:4. The stereochemistry was assigned by analogy to **2.24a**. R_f = 0.21 (50 % EtOAC/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.11-7.19 (m, 4H), 6.89 (d, *J* = 8.44 Hz, 2H), 6.65 (d, *J* = 8.74 Hz, 2H), 5.93 (ddd, *J* = 17.03 Hz, 8.36 Hz, 8.25 Hz, 1H), 5.00 (d, *J* = 10.27 Hz, 2H), 4.71 (d, *J* = 12.31 Hz, 1H), 4.52 (d, *J* = 16.34 Hz, 1H), 4.20 (d, *J* = 16.23 Hz, 1H), 3.82 (s, 3H), 2.91 (s, 6H), 2.26 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.5, 170.9, 159.4, 149.2, 132.6, 131.4, 129.7, 126.3, 116.7, 114.1, 112.0, 76.6, 55.4, 49.7, 47.5, 40.7, 28.6, 23.3. HRMS (DART) *m/z* calcd for $C_{23}H_{29}N_2O_2$ [M - OH]$^+$: 365.2224; Found [M - OH]$^+$: 365.2226.



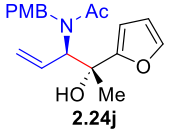
2.24h

N-((3S,4R)-4-hydroxy-4-(p-tolyl)pent-1-en-3-yl)-N-(4-methoxybenzyl)acetamide (2.24h): According to the general procedure A using allenamide **2.23d**, the product was purified by silica gel chromatography (20 % - 40 % EtOAc in Hexane) to provide 49 mg (69 %) of **2.24h** as a glass with a diastereomeric ratio of 76:24 with the major diastereomer having an enantiomeric ratio of 94:6. R_f = 0.33 (50 % EtOAC/hexanes). The stereochemistry was assigned by analogy to **2.24a**. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.14-7.7.19 (m, 4H), 7.07 (d, *J* = 8.01 Hz, 2H), 6.90 (d, *J* = 8.56 Hz, 2H), 5.94 (ddd, *J* = 16.54 Hz, 8.83 Hz, 7.98 Hz, 1H), 4.98 (d, *J* = 10.35 Hz, 1H), 4.51-4.69 (m, 2H), 4.23 (d, *J* = 16.09 Hz, 1H), 3.82 (s, 3H), 2.30 (s, 3H), 2.28 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.2, 159.4, 143.5, 136.0, 131.1, 130.1, 129.2, 128.6, 128.1, 125.5, 114.2, 75.9, 55.4, 29.8, 28.6, 23.3, 21.0. HRMS (DART) *m/z* calcd for $C_{22}H_{26}NO_2$ [M - OH]$^+$: 336.1958; Found [M - OH]$^+$: 336.1982.



2.24i

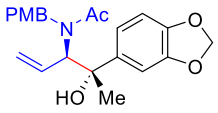
N-((3S,4R)-4-hydroxy-4-(3-hydroxyphenyl)pent-1-en-3-yl)-N-(4-methoxybenzyl)acetamide (2.24i): According to the general procedure A using allenamide **2.23d** and 3 equiv. of $(Meo)_2MeSiH$, the product was purified by silica gel chromatography (30 % - 60 % EtOAc in Hexane) to provide 49 mg (69 %) of **2.24i** as a glass with a diastereomeric ratio of 78:22 with the major diastereomer having an enantiomeric ratio of 95:5. The stereochemistry was assigned by analogy to **2.24a**. R_f = 0.24 (50 % EtOAC/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.05 – 7.19 (m, 4H), 6.88 (d, *J* = 7.69 Hz, 2H), 6.60 – 6.71 (m, 2H), 5.89 – 6.03 (m, 1H), 4.99 (d, *J* = 11.53 Hz, 1H), 4.70 (br s, 1H), 4.51 (d, *J* = 15.38 Hz, 1H), 4.26 (d, *J* = 16.92 Hz, 1H), 3.80 (s, 3H), 2.26 (s, 3H), 1.37 (s, 3H).^{13}C NMR (151 MHz, $CDCl_3$) δ 173.8, 159.3, 159.2, 156.2, 147.5, 130.8, 129.0, 128.0, 116.9, 114.3, 114.0, 113.8, 113.5, 70.2, 55.3, 28.2, 23.2, 22.7. HRMS (DART) *m/z* calcd for $C_{21}H_{24}NO_3$ [M - OH]$^+$: 338.1751; Found [M - OH]$^+$: 338.1769.



2.24j

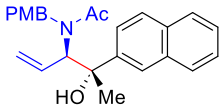
N-((3S,4S)-4-(furan-2-yl)-4-hydroxypent-1-en-3-yl)-N-(4-methoxybenzyl)acetamide (2.24j): According to the general procedure A using allenamide **2.23d**, the product was purified by silica gel chromatography (20 % - 60 % EtOAc in Hexane) to provide 53 mg (81 %) of **2.24j** as a glass with a diastereomeric ratio of 74:26 with the major diastereomer having an enantiomeric ratio of 97:3. The stereochemistry was assigned by analogy to **2.24a**. R_f = 0.44 (50 % EtOAC/hexanes). ^{1}H

NMR (600 MHz, $CDCl_3$) δ 7.19 (s, 1H), 7.04 (d, *J* = 8.58 Hz, 2H), 6.77 (d, *J* = 8.70 Hz, 2H), 6.17 – 6.20 (m, 2H), 5.95 (ddd, *J* = 17.28 Hz, 9.22 Hz, 8.35 Hz), 4.94 (d, *J* = 10.44 Hz, 1H), 4.66 (d, 17.13 Hz, 1H), 4.35 (d, *J* = 16.45 Hz, 1H), 4.16-4.26 (m, 2H), 3.70 (s, 3H), 2.12 (s, 3H), 1.28 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.6, 159.3, 158.1, 141.1, 131.3, 130.1, 128.6, 128.0, 119.0, 114.1, 110.4, 106.1, 74.8, 55.3, 54.1, 26.6, 23.0. HRMS (DART) *m/z* calcd for $C_{19}H_{22}NO_3$ [M - OH]$^+$: 312.1594; Found [M - OH]$^+$: 312.1610.



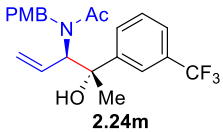
2.24k

N-((3S,4R)-4-(benzo[d][1,3]dioxol-5-yl)-4-hydroxypent-1-en-3-yl)-N-(4-methoxybenzyl)acetamide (2.24k): According to the general procedure A using allenamide **2.23d**, the product was purified by silica gel chromatography (10 % - 30 % EtOAc in Hexane) to provide 62 mg (81 %) of **2.24k** as a glass with a diastereomeric ratio of 78:22 with the major diastereomer having an enantiomeric ratio of 94:6. The stereochemistry was assigned by analogy to **2.24a**. R_f = 0.31 (50 % EtOAC/hexanes). ^1H NMR (600 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.63 Hz, 2H), 6.91 (d, *J* = 9.11 Hz, 2H), 6.80 (s, 1H), 6.75 (d, *J* = 8.07 Hz, 1H), 6.69 (d, *J* = 8.07 Hz, 1H), 5.92 - 6.00 (m, 1H), 5.91 (s, 2H), 5.00 (d, *J* = 10.44, 1H), 4.52 - 4.72 (m, 2H), 4.23 (d, *J* = 16.30, 1H), 3.82 (s, 3H), 2.28 (s, 3H), 1.29 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.2, 159.7, 147.3, 146.0, 140.6, 131.1, 129.7, 129.3, 128.0, 118.9, 114.2, 107.6, 106.7, 100.9, 75.8, 55.5, 28.8, 23.3, 14.2. HRMS (DART) *m/z* calcd for $C_{22}H_{24}NO_4$ [M - OH]$^+$: 366.1700; Found [M - OH]$^+$: 366.1725.



2.24l

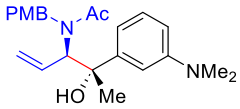
N-((3S,4R)-4-hydroxy-4-(naphthalen-2-yl)pent-1-en-3-yl)-N-(4-methoxybenzyl)acetamide (2.24l): According to the general procedure A using allenamide **2.23d**, the product was purified by silica gel chromatography (10 % - 30 % EtOAc in Hexane) to provide 74 mg (95 %) of **2.24l** as a glass with a diastereomeric ratio of 82:18 with the major diastereomer having an enantiomeric ratio of 94:6. The stereochemistry was assigned by analogy to **2.24a**. R_f = 0.33 (50 % EtOAC/hexanes). ^1H NMR (600 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.79 (dt, *J* = 8.49 Hz, 1.84 Hz, 2H), 7.73 (d, *J* = 8.95 Hz, 1H), 7.44 (m, 2H), 7.19 - 7.28 (m, 3H), 6.95 (d, *J* = 8.49 Hz, 2H), 6.00 (ddd, *J* = 16.99 Hz, 8.72 Hz, 8.70 Hz, 1H), 4.95 (d, *J* = 9.79 Hz, 1H), 4.52 - 4.67 (m, 2H), 4.27 (d, *J* = 15.77 Hz, 1H), 3.85 (s, 3H), 2.33 (s, 3H), 1.41 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.2, 159.7, 143.9, 133.1, 132.2, 130.8, 129.5, 128.4, 127.5, 127.4, 125.9, 125.7, 124.7, 123.8, 114.2, 76.0, 55.4, 29.9, 25.6, 23.3. HRMS (DART) *m/z* calcd for $C_{25}H_{26}NO_2$ [M - OH]$^+$: 372.1958; Found [M - OH]$^+$: 372.1965.



2.24m

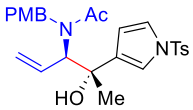
N-((3S,4R)-4-hydroxy-4-(3-(trifluoromethyl)phenyl)pent-1-en-3-yl)-N-(4-methoxybenzyl)acetamide (2.24m): According to the general procedure A using allenamide **2.23d**, the product was purified by silica gel chromatography (10 % - 40 % EtOAc in Hexane) to provide 60 mg (74 %) of **2.24m** as a glass with a diastereomeric ratio of 80:20 with the major diastereomer having an enantiomeric ratio of 95:5. The stereochemistry was assigned by analogy to **2.24a**. R_f = 0.44 (50 % EtOAC/hexanes). ^1H NMR (600 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.85 Hz, 1H), 7.43 (d, *J* = 7.83 Hz, 1H), 7.40 (s, 1H), 7.36 (t, *J* = 7.83 Hz, 1H), 7.20 (d, J= 8.47 Hz, 2H), 6.94 (d, *J* = 8.59 Hz, 2H), 5.94 (ddd, *J* = 17.16 Hz, 8.90 Hz, 8.23 Hz, 1H), 4.99 (d, *J* = 10.17 Hz, 1H), 4.64 (d, *J* = 15.85 Hz, 1H), 4.55 (d, *J* =

17.16 Hz, 1H), 4.17 (d, *J* = 15.57 Hz, 1H), 3.84 (s, 3H), 2.34 (s, 3H), 1.25 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.2, 160.0, 147.8, 130.3, 130.0, 129.8, 129.1, 128.2, 127.6, 124.4 (q, *J* = 274.8 Hz), 123.4 (q, *J* = 3.2 Hz), 122.5 (q, *J* = 4.5 Hz), 114.3, 75.5, 55.3, 54.6, 28.3, 23.4. ^{19}F NMR (565 MHz, $CDCl_3$) δ -62.37. HRMS (DART) *m/z* calcd for $C_{22}H_{23}F_3NO_2$ [M - OH]$^+$: 390.1675; Found [M - OH]$^+$: 390.1701.



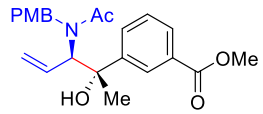
2.24n

N-((3S,4R)-4-(3-(dimethylamino)phenyl)-4-hydroxypent-1-en-3-yl)-N-(4-methoxybenzyl)acetamide (2.24n): According to the general procedure A using allenamide **2.23d**, the product was purified by silica gel chromatography (20 % - 40 % EtOAc in Hexane) to provide 47 mg (61 %) of **2.24n** as a glass with a diastereomeric ratio of 80:20 with the major diastereomer having an enantiomeric ratio of 96:4. The stereochemistry was assigned by analogy to **2.24a**. R_f = 0.29 (50 % EtOAC/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.06 Hz, 2H), 7.12 (t, *J* = 8.06 Hz, 1H), 6.88 – 6.93 (m, 2H), 6.77 (s, 1H), 6.57 (s, 2H), 5.93 (ddd, *J* = 15.36 Hz, 8.89 Hz, 8.24 Hz, 1H), 4.99 (d, *J* = 10.49 Hz, 1H), 4.52 – 4.75 (m, 2H), 4.20 (d, *J* = 15.73 Hz, 1H), 3.81 (s, 3H), 2.90 (s, 6H), 2.30 (s, 3H), 1.30 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.0, 159.5, 150.4, 150.3, 147.6, 147.4, 132.5, 131.1, 128.6, 128.5, 127.7, 119.9, 114.2, 77.2, 55.3, 40.8, 28.7, 23.4, 23.0. HRMS (DART) *m/z* calcd for $C_{23}H_{29}N_2O_2$ [M - OH]$^+$: 365.2244; Found [M - OH]$^+$: 365.2226.



2.24o

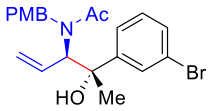
N-((3S,4R)-4-hydroxy-4-(1-tosyl-1H-pyrrol-3-yl)pent-1-en-3-yl)-N-(4-methoxybenzyl)acetamide (2.24o): According to the general procedure A using allenamide **2.23d**, the product was purified by silica gel chromatography (30 % - 70 % EtOAc in Hexane) to provide 72 mg (75 %) of **2.24o** as a glass with a diastereomeric ratio of 81:19 with the major diastereomer having an enantiomeric ratio of >99:1. The stereochemistry was assigned by analogy to **2.24a**. R_f = 0.19 (50 % EtOAC/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.55 Hz, 2H), 7.24 (d, *J* = 8.55 Hz, 2H), 7.08 (d, *J* = 8.19 Hz, 2H), 7.03 (d, *J* = 11.75 Hz, 2H), 6.87 (d, *J* = 8.90 Hz, 2H), 5.87 – 5.96 (m, 2H), 4.96 (d, *J* = 10.33 Hz, 1H), 4.65 (d, *J* = 17.45 Hz, 1H), 4.44 (d, *J* = 15.67 Hz, 1H), 4.12 (d, *J* = 16.03 Hz, 1H), 3.80 (s, 3H), 2.37 (s, 3H), 2.22 (s, 3H), 1.18 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.2, 159.4, 144.8, 136.2, 135.5, 130.9, 130.0, 129.9, 129.0, 127.9, 126.8, 120.9, 117.9, 114.1, 111.8, 73.6, 55.3, 53.9, 28.0, 23.1, 21.6. HRMS (DART) *m/z* calcd for $C_{26}H_{29}N_2O_4S$ [M - OH]$^+$: 465.1843; Found [M - OH]$^+$: 465.1864.



2.24p

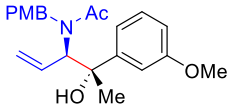
methyl-3-((2R,3S)-2-hydroxy-3-(N-(4-methoxybenzyl)acetamido)pent-4-en-2-yl)benzoate (2.24p): According to the general procedure A using allenamide **2.23d**, the product was purified by silica gel chromatography (20 % - 40 % EtOAc in Hexane) to provide 76 mg (96 %) of **2.24p** as a glass with a diastereomeric ratio of 80:20 with the major diastereomer having an enantiomeric ratio of 98:2. The stereochemistry was assigned by analogy to **2.24a**. R_f = 0.37 (50 % EtOAC/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85 - 7.90 (m, 2H), 7.58 (d, *J* = 8.01, 1H), 7.33 (t, *J* = 7.69 Hz, 1H), 7.19 (d, *J* = 8.09, 2H), 6.94 (d, *J* = 8.50 Hz, 2H), 5.97 (ddd, *J* = 16.19 Hz, 9.31 Hz, 8.50 Hz, 1H), 4.96 (d, *J* = 10.12 Hz, 1H), 4.51 - 4.63 (m, 2H), 4.24 (d, *J* = 16.19 Hz, 1H), 3.90 (s, 3H), 3.84 (s, 3H), 2.31 (s, 3H), 1.31 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.2, 167.2, 159.6, 147.1, 131.8, 130.6, 130.5, 129.8, 129.4, 128.7, 128.0, 127.9,

126.7, 114.3, 76.7, 75.8, 55.4, 52.1, 28.4, 23.4. HRMS (DART) *m/z* calcd for $C_{23}H_{26}NO_4$ [M - OH]$^+$: 380.1856; Found [M - OH]$^+$: 380.1870.



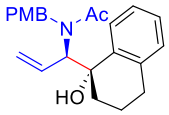
2.24q

N-((3S,4R)-4-(3-bromophenyl)-4-hydroxypent-1-en-3-yl)-N-(4-methoxybenzyl)acetamide (2.24q): According to the general procedure A using allenamide **2.23d**, the product was purified by silica gel chromatography (10 % - 40 % EtOAc in Hexane) to provide 75 mg (90 %) of **2.24q** as a glass with a diastereomeric ratio of 75:25 with the major diastereomer having an enantiomeric ratio of 94:6. The stereochemistry was assigned by analogy to **2.24a**. R_f = 0.22 (50 % EtOAC/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 (s, 1H), 7.30 (d, *J* = 7.98 Hz, 1H), 7.19 (d, *J* = 7.45 Hz, 3H), 7.11 (t, *J* = 7.98 Hz, 1H), 6.94 (d, *J* = 7.98 Hz, 2H), 5.94 (ddd, *J* = 16.50 Hz, 9.33 Hz, 9.05 Hz, 1H), 5.00 (d, *J* = 10.31 Hz, 1H), 4.61 (d, *J* = 15.23 Hz, 2H), 4.21 (d, *J* = 15.72 Hz, 1H), 3.84 (s, 3H), 2.31 (s, 3H), 1.25 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.1, 159.7, 149.2, 130.5, 130.1, 129.6, 129.5, 129.4, 129.0, 127.7, 124.3, 122.2, 114.3, 75.4, 60.5, 55.4, 28.4, 23.3. HRMS (DART) *m/z* calcd for $C_{21}H_{23}BrNO_2$ [M - OH]$^+$: 400.0907; Found [M - OH]$^+$: 400.0915.



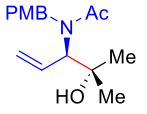
2.24r

N-((3S,4R)-4-hydroxy-4-(3-methoxyphenyl)pent-1-en-3-yl)-N-(4-methoxybenzyl)acetamide (2.24r): According to the general procedure A using allenamide **2.23d**, the product was purified by silica gel chromatography (10 % - 30 % EtOAc in Hexane) to provide 69 mg (93 %) of **2.24r** as a glass with a diastereomeric ratio of 80:20 with the major diastereomer having an enantiomeric ratio of 95:5. The stereochemistry was assigned by analogy to **2.24a**. R_f = 0.37 (50 % EtOAC/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.14 – 7.20 (m, 2H), 6.89 (m, 3H), 6.77 – 6.82 (m, 2H), 6.72 (dd, *J* = 8.09 Hz, 2.38 Hz, 1H), 5.95 (ddd, *J* = 17.33 Hz, 8.84 Hz, 8.50 Hz, 1H), 4.98 (d, *J* = 10.54 Hz, 1H), 4.53 – 4.68 (m, 2H), 4.23 (d, *J* = 15.63 Hz, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 2.29 (s, 3H), 1.31 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.1, 159.5, 159.3, 148.3, 132.2, 130.9, 129.3, 129.0, 128.8, 128.6, 128.0, 127.4, 120.1, 117.9, 114.2, 112.2, 111.4, 76.9, 75.9, 55.4, 55.2, 28.6, 23.3. HRMS (DART) *m/z* calcd for $C_{22}H_{26}NO_3$ [M - OH]$^+$: 352.1907; Found [M - OH]$^+$: 352.1930.



2.24s

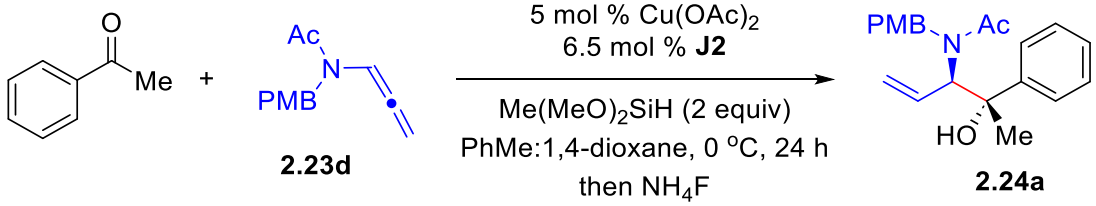
N-((S)-1-((S)-1-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)allyl)-N-(4-methoxybenzyl)acetamide (2.24s): According to the general procedure A using allenamide **2.23d**, the product was purified by silica gel chromatography (10 % - 30 % EtOAc in Hexane) to provide 45 mg (61 %) of **2.24s** as a glass with a diastereomeric ratio of 62:38 with the major diastereomer having an enantiomeric ratio of 90:10. The stereochemistry was assigned by analogy to **2.24a**. R_f = 0.39 (50 % EtOAC/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.55 Hz, 1H), 7.20 (t, *J* = 7.85 Hz, 1H), 7.04 – 7.14 (m, 3H), 6.80 – 6.86 (m, 3H), 6.32 – 6.45 (m, 1H), 5.20 (d, *J* = 10.24 Hz, 1H), 5.09 (d, *J* = 10.84 Hz, 1H), 4.49 – 4.69 (m, 3H), 3.79 (s, 3H), 2.58 – 2.87 (m, 3H), 2.22 (s, 3H), 1.69 – 1.88 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.5, 159.2, 140.5, 136.0, 132.3, 130.1, 128.7, 128.6, 128.2, 127.0, 124.8, 120.2, 114.0, 74.8, 55.3, 35.4, 33.4, 29.1, 23.5, 19.6. HRMS (DART) *m/z* calcd for $C_{23}H_{26}NO_2$ [M - OH]$^+$: 348.1958; Found [M - OH]$^+$: 348.1980.



2.24t

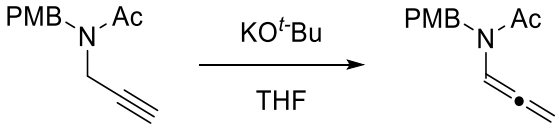
(S)-N-(4-hydroxy-4-methylpent-1-en-3-yl)-N-(4-methoxybenzyl)acetamide (2.24t): According to the general procedure A using allenamide **2.23d**, the product was purified by silica gel chromatography (40 % - 80 % EtOAc in Hexane) to provide 33 mg (59 %) of **2.24t** as a glass with an enantiomeric ratio of 65:35. The stereochemistry was assigned by analogy to **2.24a**. R_f = 0.13 (50 % EtOAC/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.14 (d, *J* = 8.37 Hz, 2H), 6.87 (d, *J* = 8.79 Hz, 2H), 6.25 (ddd, *J* = 16.95 Hz, 9.42 Hz, 8.58 Hz, 1H), 5.53 (br s, 1H), 5.20 (dd, *J* = 10.16 Hz, 1.39 Hz, 1H), 4.97 (d, *J* = 17.26 Hz, 1H), 4.46 (s, 2H), 3.80 (s, 3H), 3.57 (d, *J* = 9.11 Hz, 1H), 2.20 (s, 3H), 1.11 (s, 3H), 1.09 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.8, 159.4, 132.3, 128.8, 128.0, 119.4, 114.1, 73.0, 71.7, 55.3, 54.4, 28.3, 28.0, 23.2. HRMS (DART) *m/z* calcd for $C_{16}H_{22}NO_2$ [M - OH]$^+$: 260.1645; Found [M - OH]$^+$: 260.1661.

Reaction Performed on 1.0 mmol scale:



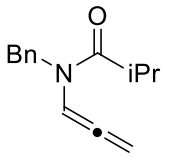
To a 20 mL crimp-cap vial with stir-bar in an Ar-filled glove-box was charged 9.1 mg (0.05 mmol) of $Cu(OAc)_2$ and 35.3 mg (0.0625 mmol) of **J2**. Toluene (1.25 mL) and 1,4-dioxane (1.25 mL) was then added, and the mixture was allowed to stir for 30 min. Alleneamide **2.23d** (261 mg, 1.2 mmol) was then charged along with the 120 mg (1 mmol) of acetophenone, sealed with a crimp-cap septum and removed from the glove-box. The reaction was then cooled in an ice bath, and dimethoxymethylsilane (247 µL, 2.0 mmol) was then charged by syringe (*caution: dimethoxymethylsilane should be handled in a well-ventilated fume hood because it is known to cause blindness. Syringes were quenched with 2M NaOH, gas evolution!, prior to disposal)* After 24 h at 0 °C, the reaction was quenched by the addition of 475 mg of NH_4F and 5.0 mL of MeOH followed by agitation at rt for 30 min – 1 h. To the mixture was then charged 20 mL of 5% NaHCO3 followed by extraction with CH_2Cl_2 (3x10mL). The combined organics were dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was then purified by flash chromatography on silica gel (gradient, 10 – 20% EtOAc in Hexane). The product spot (R_f = 0.20, 20% EtOAc in Hexane) was then collected and concentrated *in vacuo* to afford 295 mg (85%) of **2.24a** in a diastereomeric ratio of 88:12. Enantioselectivity was determined by chiral column HPLC analysis to be 97:3 er.

Allene Synthesis:



2.23d

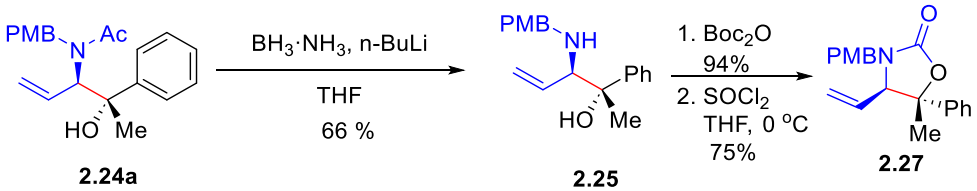
To a flame dried round bottom flask with 50 mL of THF was charged *N*-(4-methoxybenzyl)-N-(prop-2-yn-1-yl)acetamide (2.1 g, 9.7 mmol, 0.2 M in solvent) and then KO^{t}Bu (271 mg, 2.4 mmol, 0.25 equiv). The mixture was then stirred for 30 minutes and quenched with 50 mL of H_2O. The mixture was extracted with EtOAc (3 x 50 mL), dried with $MgSO_4$, decolorized with activated charcoal, filtered and concentrated *in vacuo.* The product was purified by silica gel chromatography (eluent: 10 – 20% EtOAc in Hexane) to provide 1.3 g (60%) of the desired product as a yellow oil in a 54:46 mixture of rotamers. R_f = 0.39 (50% EtOAc in Hexane). ^{1}HNMR ($CDCl_3$, 600 MHz) δ: 7.64 (t, *J* = 6.91 Hz, 1H, minor), 7.21 (d, *J* = 8.45 Hz, 1H), 7.09 (d, *J* = 8.33 Hz, 1H), 6.86 (d, *J* = 8.53 Hz, 1H), 6.81 (d, *J* = 8.72 Hz, 1H), 6.68 (t, *J* = 6.39 Hz, 1H, major), 5.31 (dd, *J* = 33.72 Hz, 6.66 Hz, 2H), 4.60 (d, *J* = 33.30 Hz, 2H), 3.79 (s, 3H, minor), 3.77 (s, 3H, major), 2.23 (s, 3H, major), 2.13 (s, 3H, minor). ^{13}C NMR (151 MHz, $CDCl_3$): δ 202.3 (minor), 201.4 (major), 169.3 (minor), 168.5 (major), 158.9 (minor), 158.7 (major), 129.8 (major), 128.8 (minor), 129.5 (major), 127.3 (minor), 114.2 (minor), 113.7 (major), 100.8 (major), 99.4 (minor), 87.4 (minor), 87.0 (major), 55.3 (minor), 55.2 (major), HRMS (DART) *m/z* calcd for $C_{13}H_{16}NO_2$ $[M]^+$: 218.1181; Found $[M + H]^+$: 218.1168.



2.21

N-benzyl-N-(propa-1,2-dien-1-yl)isobutyramide (2.21): According to the general procedure for allene synthesis, the product was purified by silica gel chromatography (0 % - 10 % EtOAc in Hexane) to provide 400 mg (39 %) of **2.21** as a yellow oil in a 57:43 mixture of rotamers. R_f = 0.35 (20 % EtOAC/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (t, J = 6.90 Hz, 1H, minor), 7.33 (t, J = 7.76 Hz, 1H), 7.20 – 7.30 (m, 3H), 7.15 (d, J = 7.76 Hz, 1H), 6.84 (t, J = 6.34 Hz, 1H, major), 5.30 (d, J = 6.11 Hz, 2H, major), 5.25 (d, J = 6.60, 2H, minor), 4.71 (d, J = 10.99 Hz, 2H), 2.92 – 3.00 (m, 1H, major), 2.71 – 2.79 (m, 1H, minor), 1.22 (d, J = 7.08 Hz, 6H, major), 1.09 (d, J = 6.84 Hz, 6H, minor). ^{13}C NMR (151 MHz, $CDCl_3$): δ
202.5 (minor), 201.6 (major), 176.1 (minor), 175.2 (major), 138.0 (major), 137.3 (minor), 128.8 (minor), 128.3 (major), 127.8 (major), 127.3 (minor), 126.9 (major), 125.8 (major), 100.2 (major), 99.6 (minor), 87.3 (minor), 86.8 (major), 49.0 (minor), 47.4 (major), 31.4 (minor), 30.8 (major), 19.7 (minor), 19.3 (major). HRMS (DART) *m/z* calcd for $C_{14}H_{18}NO$ $[M]^+$: 216.1388; Found $[M + H]^+$: 216.1369.

Absolute and relative stereochemistry determination for reaction products:



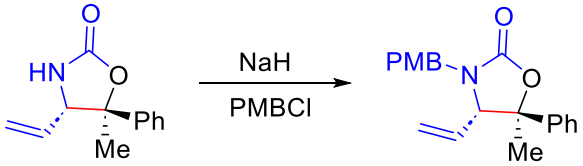
2.24a **2.25** **2.27**

Diastereo- and enantioenriched **2.24a** was obtained from careful chromatographic separation on silica gel and was converted to **2.27** by the given 3 step procedure.

To a solution of borane ammonia complex (17 mg, 0.47 mmol, 85%) in 0.3 mL THF at 0 °C in a flame dried 2-dram vial was charged *n*-BuLi (0.27 mL, 0.47 mmol, 1.75 M in hexanes). The resulting solution was stirred at 0 °C for 5 minutes and then 22 °C for 5 minutes. The solution was then cooled to 0 °C and a solution of aminoalcohol **2.24a** (41 mg, 0.12 mmol) in 0.2 mL THF was added dropwise and the resulting solution was allowed to stir overnight. The reaction mixture was then quenched with 2 M HCl (1 mL) and volatiles were removed *in-vacuo*. The aqueous layer was then washed with Et_2O (2 x 2 mL) and then basified with 2 M NaOH. The solution was then extracted with CH_2Cl_2 (3 x 5 mL), dried with Na_2SO_4, and concentrated *in vacuo* to afford 23 mg (66 %) of pure **2.27**. ^{1}HNMR ($CDCl_3$, 600 MHz) δ: 7.37 (dd, *J* = 8.52 Hz, 1.05 Hz, 2H), 7.31 (t, *J* = 7.92 Hz, 2H), 7.24 (dt, *J* = 7.32 Hz, 1.20 Hz, 1H), 7.21 (d, *J* = 8.67 Hz, 2H), 6.86 (d, *J* = 8.82 Hz, 2H), 5.27 – 5.37 (m, 2H), 5.18 (dd, *J* = 16.41 Hz, 2.54 Hz, 1H), 3.80 (s, 3H), 3.72 (d, *J* = 13.15 Hz, 1H), 3.48 (d, *J* = 12.57 Hz, 1H), 3.04 (d, *J* = 8.57 Hz, 1H), 1.57 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 158.9, 144.3, 136.5, 131.8, 129.5, 127.8, 126.7, 126.4, 125.5, 119.1, 113.9, 73.9, 70.4, 55.3, 50.2, 26.2. HRMS (DART) *m/z* calcd for $C_{19}H_{22}NO$ $[M\text{-}OH]^+$: 280.1696; Found $[M - OH]^+$: 280.1671

To a solution of the aminoalcohol **2.25** (22 mg, 0.074 mmol) in 0.10 mL of H_2O at 40 °C in a 2-dram vial was charged Boc_2O (0.02 mL, 0.081 mmol) and stirred for 4 h. The reaction mixture was then diluted with 2 mL H_2O, extracted with 2 x 5 mL CH_2Cl_2, dried with Na_2SO_4, and concentrated *in vacuo*. The crude material was used without further purification. The crude material was then dissolved in THF (0.30 mL) and $SOCl_2$ (0.051 mL, 0.69 mmol) was added. This was allowed to stir overnight before being quenched into NH_4OH (2 mL, 30%). This was extracted with 2 x 5 mL EtOAc, dried with Na_2SO_4, and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (eluent: 30% EtOAc in Hexane) to afford 17 mg (71%) of **2.27** as an oil in 97:3 er. R_f = 0.57 (50% EtOAc/hexane). ^{1}HNMR ($CDCl_3$, 600 MHz) δ: 7.27 – 7.34 (m, 5H), 7.02 (d, *J* = 8.72, 2H), 6.73 (d, *J* = 8.72 Hz, 2H), 5.85 (ddd, *J* = 17.01 Hz, 9.78 H, 8.51 Hz, 1H), 5.49 (d, *J* = 9.99 Hz, 1H), 5.27 (d, *J* = 17.01 Hz, 1H), 4.73 (d, *J* = 15.10 Hz, 1H), 3.91 (d, *J* = 12.42 Hz, 1H), 3.89 (d, *J* = 6.75, 1H), 3.75 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 159.1, 157.2, 144.3, 132.3, 129.5, 128.6, 127.8, 123.9, 122.9, 113.9, 82.9, 68.6, 55.2, 45.5, 24.0. HRMS (DART) *m/z* calcd for $C_{19}H_{20}NO_3$ $[M+H]^+$: 310.1443; Found $[M + H]^+$: 310.1449.

Preparation of authentic 2.27:

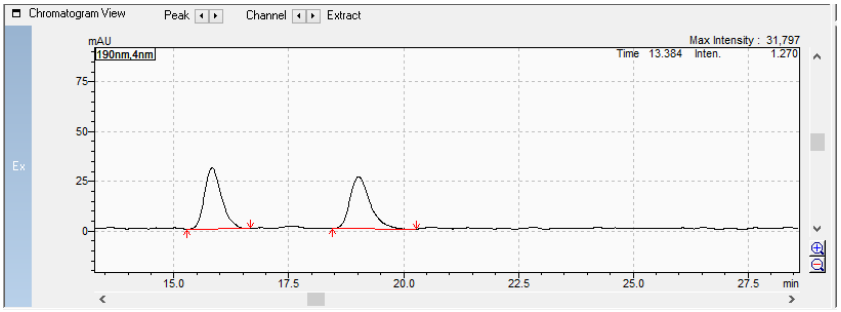


SI-1 *ent*-**2.27**

To **SI-1** of known stereochemical configuration (11.0 mg, 0.0541 mmol) in 0.20 mL of *N*-methylpyrrolidone was charged 2.8 mg (0.074 mmol) of NaH (60 wt% in oil) and the resultant mixture was allowed to stir at rt for 20 min. PMBCl (11 mg, 0.070 mmol) was then added and the mixture allowed to stir overnight. Water (1 mL) was then added, and the mixture was extracted with Et_2O (3x1mL). The combined organic layers were dried with anhydrous Na_2SO_4 and conentrated *in vacuo*. The crude residue was the purified on flash silica gel column chromatography (gradient, 0 – 20% EtOAc in hexanes) to afford 15.0 mg (86%) of *ent*-**2.27** with ^{1}HNMR spectral data that matched the material prepared above starting from **2.24a**.

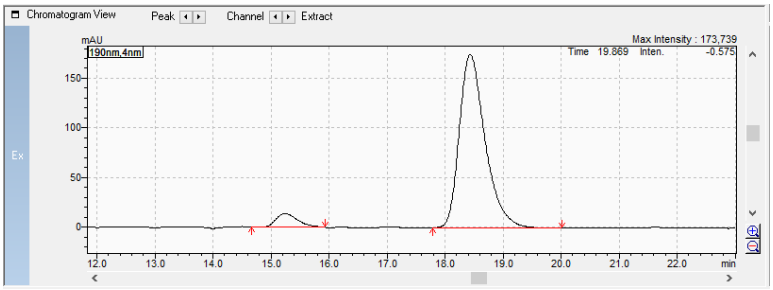
Chiral column HPLC analysis (Chiralcel AD-3 x 250 mm, 1.0 mL/min, 90:10 heptane:isopropanol, λ = 190 nm) t_R = 15.2 min (S,S-isomer), 18.4 min (R,R-isomer):

Racemic **2.27**:



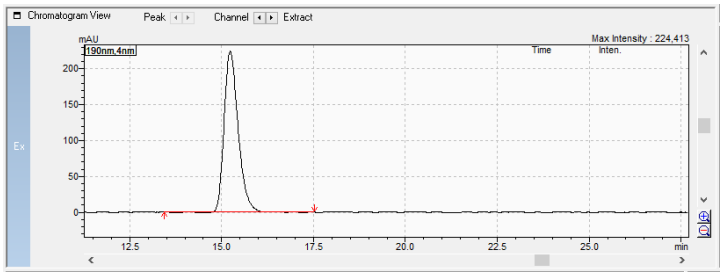
Ret. Time	Area%	Height	Conc.
15.829	50.166	30697	50.166
19.019	49.834	26143	49.834
	100.000	56840	100.000

Enantioenriched **2.27** prepared from **2.24a**:



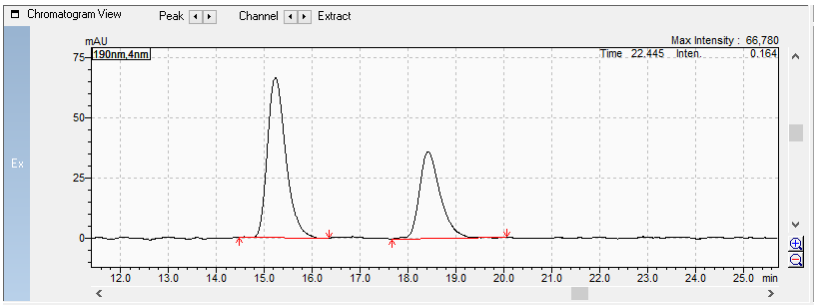
Ret. Time	Area%	Height	Conc.
15.247	3.139	9324	3.139
18.434	96.861	174265	96.861
	100.000	183589	100.000

Authentic **2.27:**



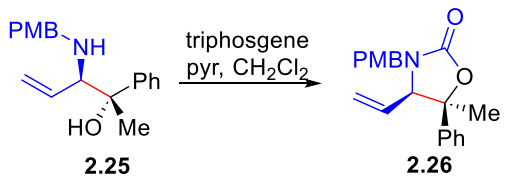
Ret. Time	Area%	Height	Conc.
15.232	100.000	224057	100.000
	100.000	224057	100.000

Enantioenriched **2.27** from **2.24a +** authentic spike:



Ret. Time	Area%	Height	Conc.
15.238	61.936	66273	61.936
18.428	38.064	35928	38.064
	100.000	102201	100.000

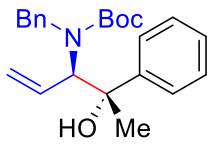
Carbamate formation by retention:



2.25 **2.26**

To a solution of **2.25** (10 mg, 0.034 mmol) and Pyridine (5.3 mg, 0.067 mmol) in CH_2Cl_2 (0.5 mL) was charged a solution of triphosgene (6.2 µL, 0.034 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C. The mixture was stirred for 24 h at room temperature and quenched with brine (5 mL) and extracted with CH_2Cl_2 (2 x 5 mL). The combined organics were dried with Na_2SO_4, filtered, and concentrated *in vacuo.* The product was purified by silica gel chromatography (eluent: 10 – 30% EtOAc in Hexane) to afford 9 mg (82%) of **2.26** as an oil. R_f = 0.52 (50% EtOAc/hexane). ^{1}HNMR ($CDCl_3$, 600 MHz) δ: 7.31 – 7.35 (m, 2H), 7.28 (d, J = 7.25 Hz, 1H), 7.24 (d, J = 7.81 Hz, 2H), 7.21 (d, J = 8.65 Hz, 2H), 6.88 (d, J = 8.93 Hz, 2H), 5.12 (d, J = 14.23 Hz, 1H), 5.09 (d, J = 21.20 Hz, 1H), 4.95 (dt, J = 17.02 Hz, 9.49 Hz, 1H), 4.82 (d, J = 14.79 Hz, 1H), 3.82 (s, 3H), 3.76 (d, J = 19.18 Hz, 1H), 1.69 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 159.3, 157.2, 139.7, 133.4, 129.8, 128.6, 128.2, 127.8, 125.7, 123.9, 121.0, 114.2, 83.4, 68.6, 55.3, 45.4, 29.7, 28.0. HRMS (DART) *m/z* calcd for $C_{19}H_{20}NO_3$ $[M+H]^+$: 310.1443; Found $[M + H]^+$: 310.1428.

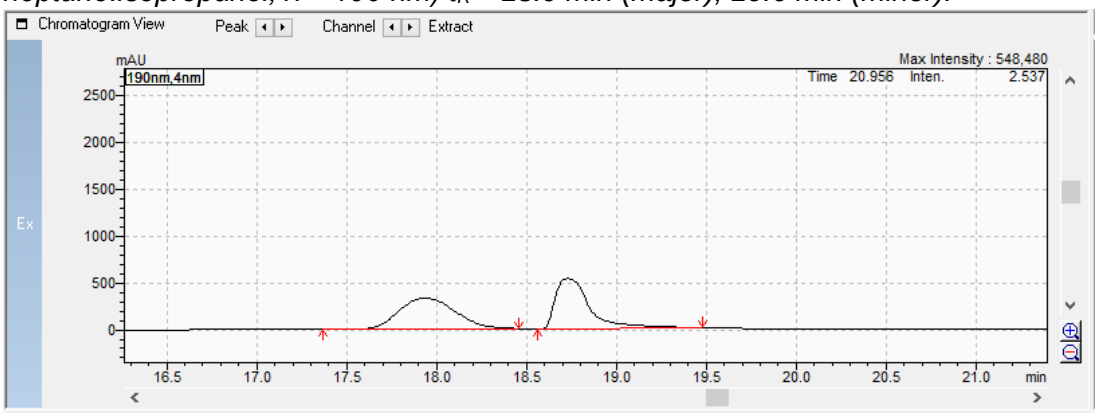
HPLC Chromatograms:



2.19

Racemic syn-2.19:

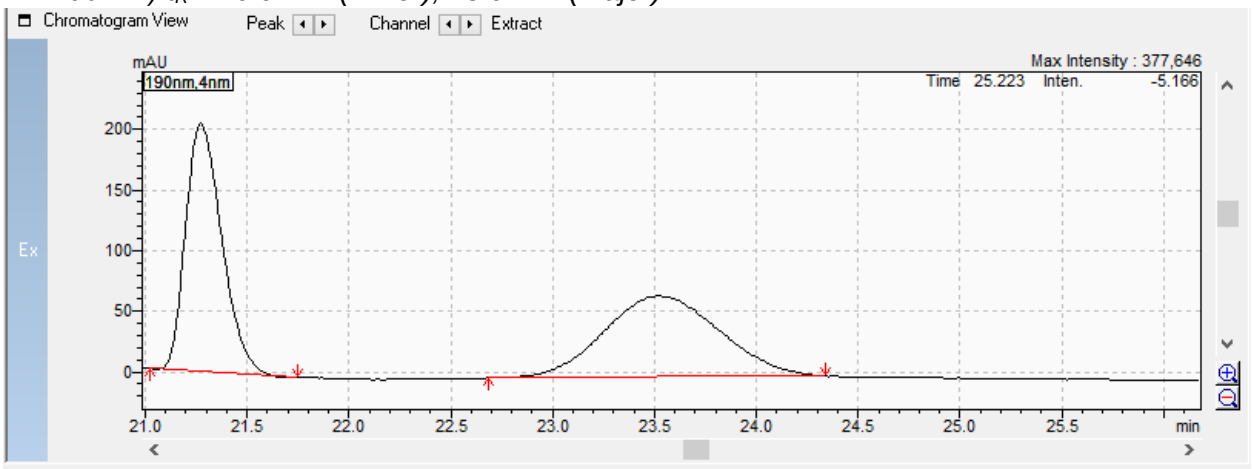
Chiral column HPLC analysis (Chiralcel OD-3 x 250 mm, 0.25 mL/min, 99:01 heptane:isopropanol, λ = 190 nm) t_R = 18.0 min (major), 19.6 min (minor):



Ret. Time	Area%	Height	Conc.
17.936	49.931	328316	49.931
18.731	50.069	536769	50.069
	100.000	865085	100.000

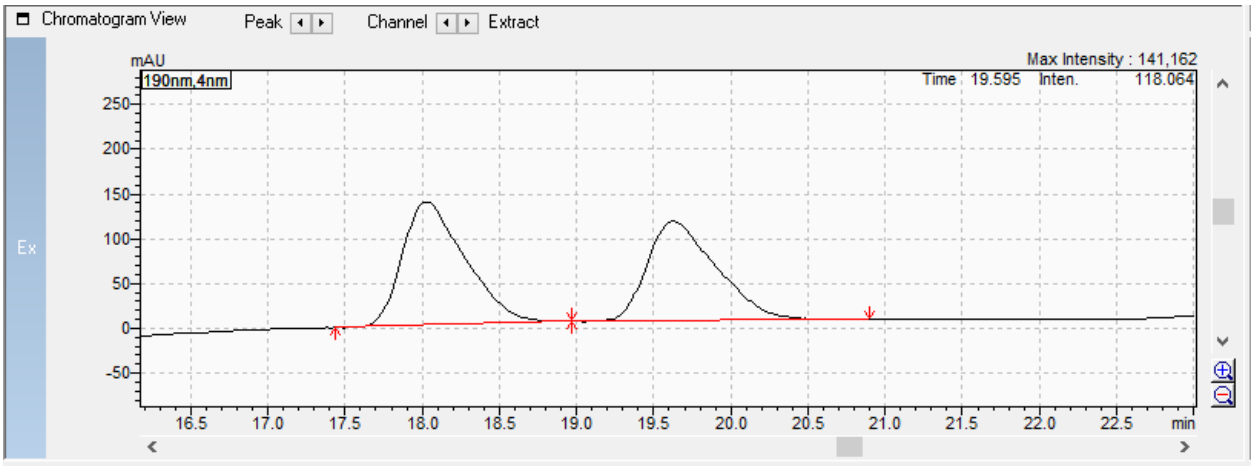
Racemic anti-2.19:

Chiral column HPLC analysis (Chiralcel OD-3 x 250 mm, 0.25 mL/min, 99:01heptane:isopropanol, λ = 190 nm) t_R = 20.9 min (minor), 23.0 min (major):



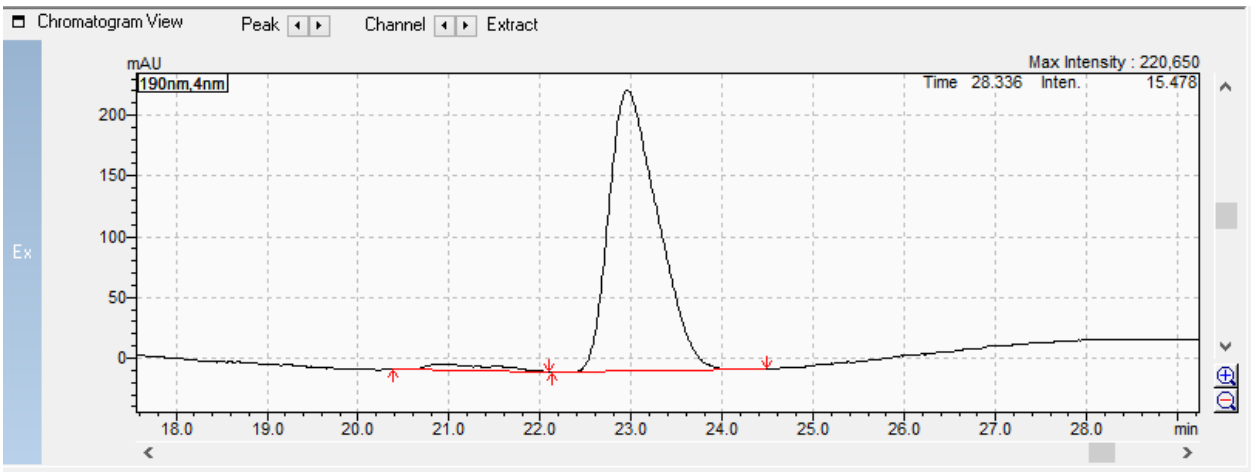
Ret. Time	Area%	Height	Conc.
21.274	49.157	204802	49.157
23.517	50.843	66755	50.843
	100.000	271557	100.000

syn-2.19 from $Cu(OAc)_2$/J2 reaction:

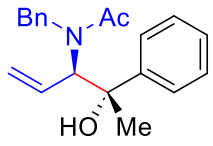


Ret. Time	Area%	Height	Conc.
18.025	53.327	137503	53.327
19.624	46.673	110749	46.673
	100.000	248252	100.000

anti-2.19 from $Cu(OAc)_2$/J2 reaction:



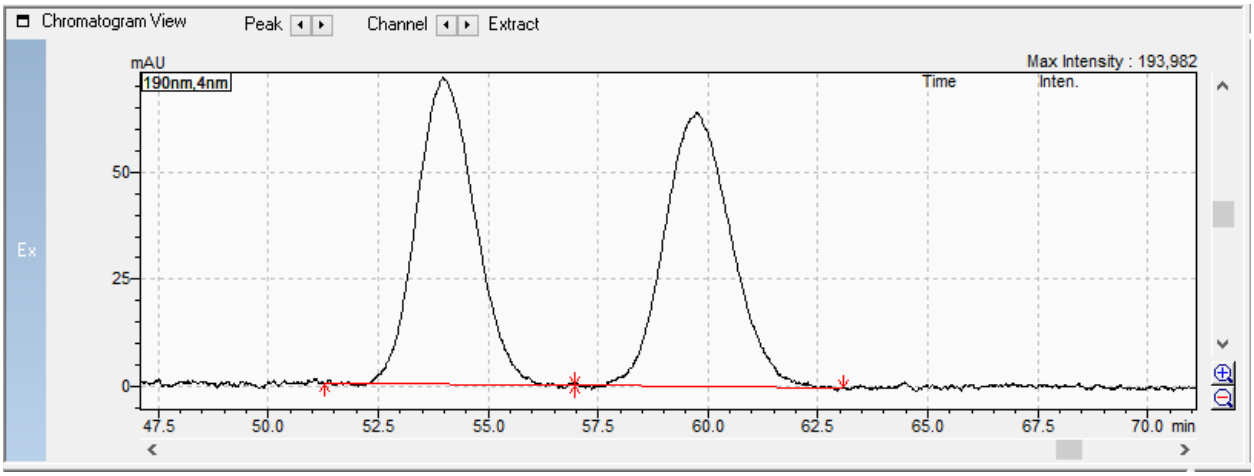
Ret. Time	Area%	Height	Conc.
20.907	3.086	5396	3.086
22.956	96.914	230818	96.914
	100.000	236214	100.000



2.23b

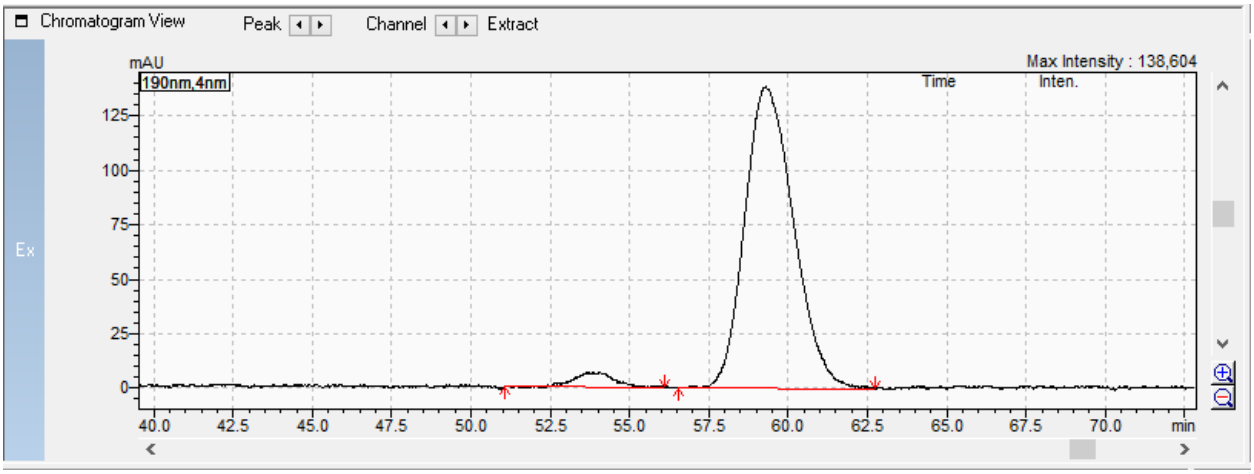
Chiral column HPLC analysis (Chiralcel IC-3 x 250 mm, 1.0 mL/min, 90:10 heptane:isopropanol, λ = 190 nm) t_R = 54.0 min (minor), 59.3 min (major):

Racemic 2.23b:

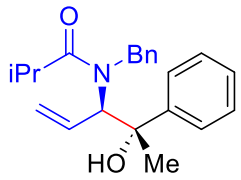


Ret. Time	Area%	Height	Conc.
53.963	49.579	71605	49.579
59.730	50.421	63812	50.421
	100.000	135417	100.000

2.23b from $Cu(OAc)_2$/J2 reaction:



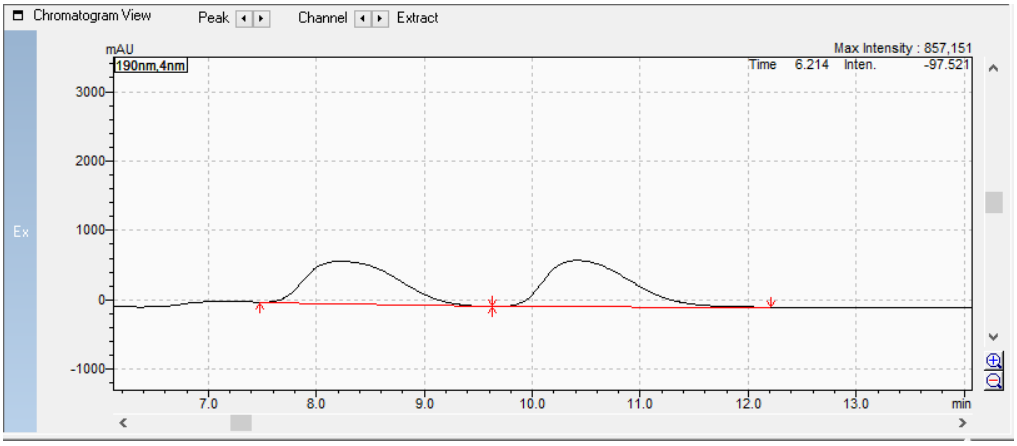
Ret. Time	Area%	Height	Conc.
54.045	3.876	6845	3.876
59.295	96.124	138495	96.124
	100.000	145340	100.000



2.21c

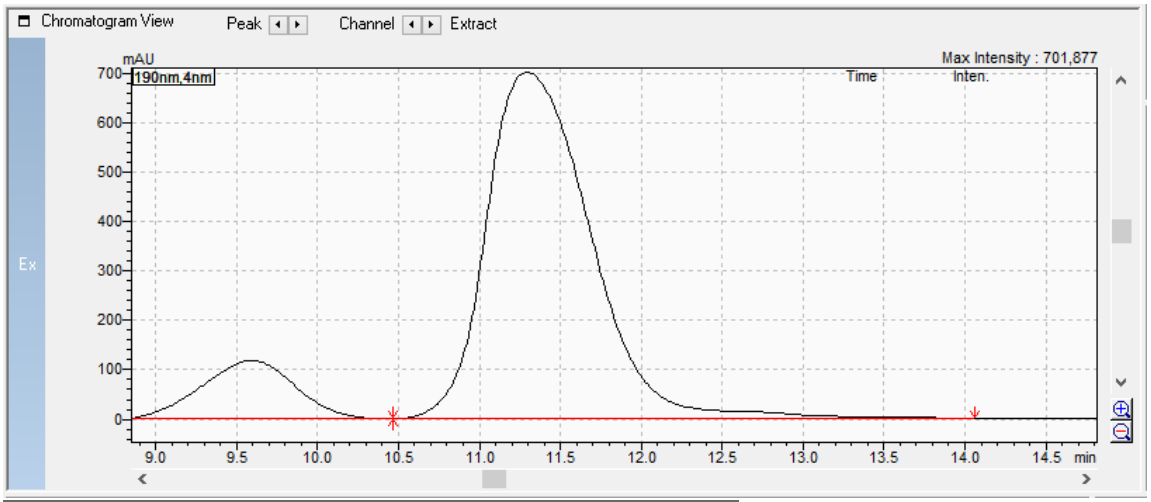
Chiral column HPLC analysis (Chiralcel OD-3 x 250 mm, 1.0 mL/min, 95:05 heptane:isopropanol, λ = 190 nm) t_R = 8.2 min (minor), 10.4 min (major):

Racemic 2.21c:

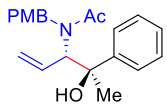


Ret. Time	Area%	Height	Conc.
8.226	49.482	609334	49.482
10.418	50.518	667206	50.518
	100.000	1276540	100.000

2.21c from $Cu(OAc)_2$/J2 reaction:



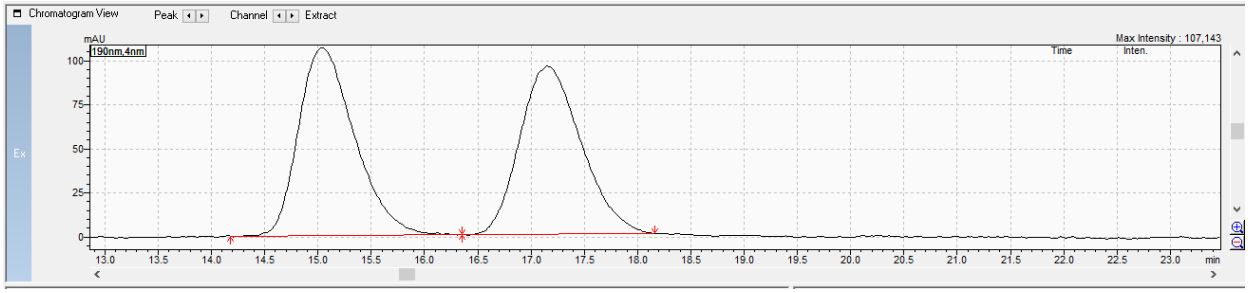
Ret. Time	Area%	Height	Conc.
9.592	12.910	117416	12.910
11.295	87.090	700794	87.090
	100.000	818210	100.000



2.24a

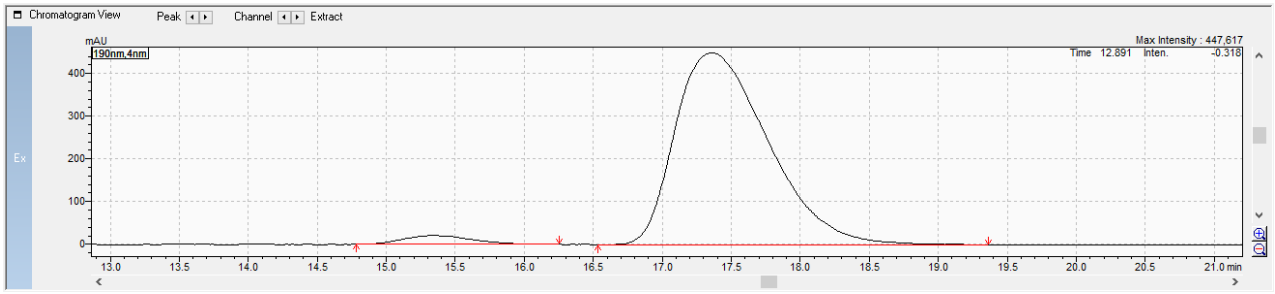
Chiral column HPLC analysis (Chiralcel AD-3 x 250 mm, 1.0 mL/min, 90:10 heptane:isopropanol, λ = 190 nm) t_R = 15.3 min (minor), 17.4 min (major):

Racemic 2.24a:

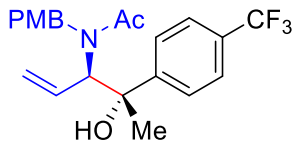


Ret. Time	Area%	Height	Conc.
15.046	50.444	106398	50.444
17.154	49.556	95544	49.556
	100.000	201942	100.000

2.24a from $Cu(OAc)_2$/J2 reaction:

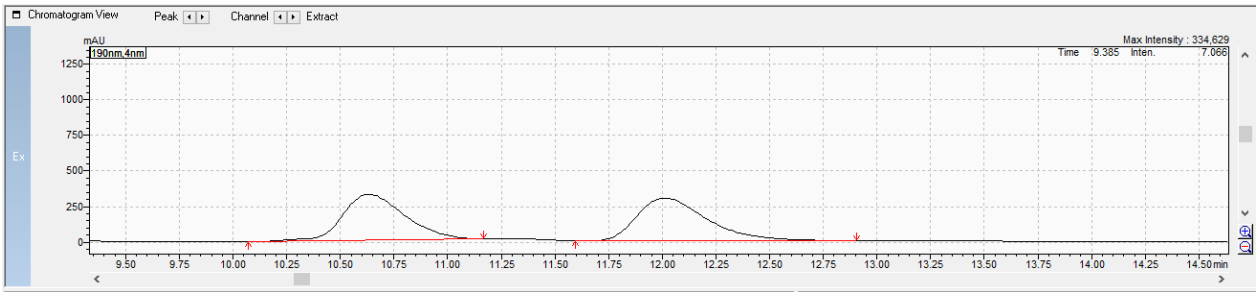


Ret. Time	Area%	Height	Conc.
15.332	3.272	20325	3.272
17.364	96.728	448551	96.728
	100.000	468876	100.000



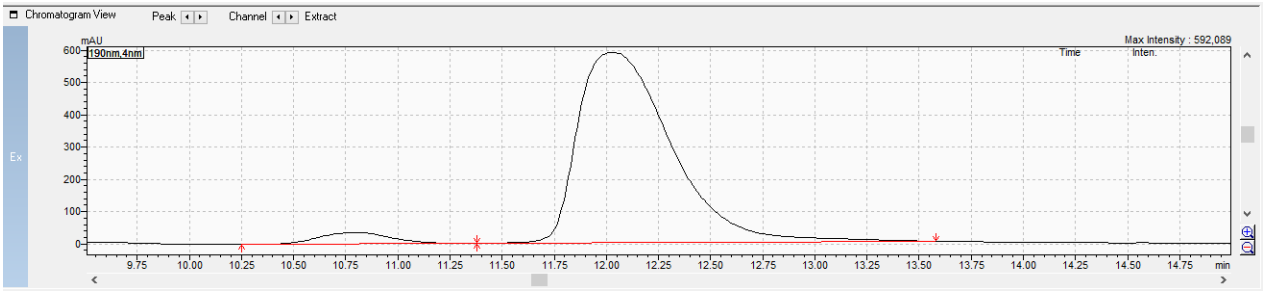
Chiral column HPLC analysis (Chiralcel AD-3 x 250 mm, 1.0 mL/min, 90:10 heptane:isopropanol, λ = 190 nm) t_R = 10.8 min (minor), 12.0 min (major):

Racemic 2.24b:

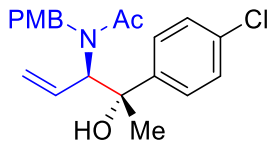


Ret. Time	Area%	Height	Conc.
10.632	49.514	323135	49.514
12.013	50.486	298740	50.486
	100.000	621875	100.000

2.24b from $Cu(OAc)_2$/J2 reaction:

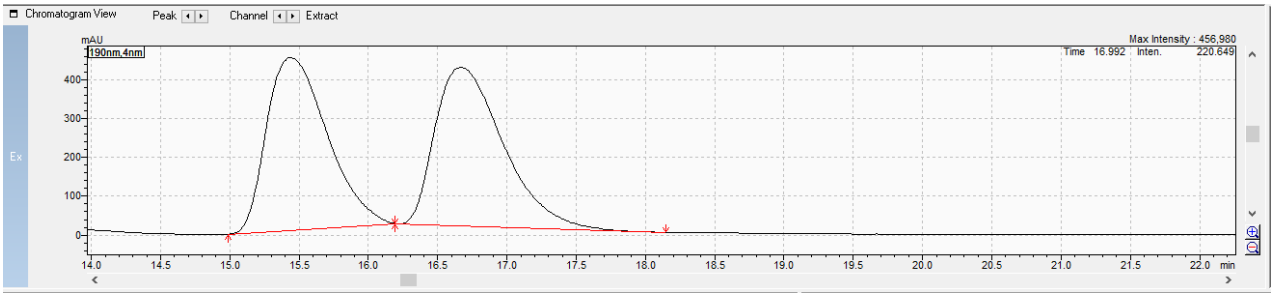


Ret. Time	Area%	Height	Conc.
10.796	4.160	34806	4.160
12.031	95.840	588205	95.840
	100.000	623011	100.000



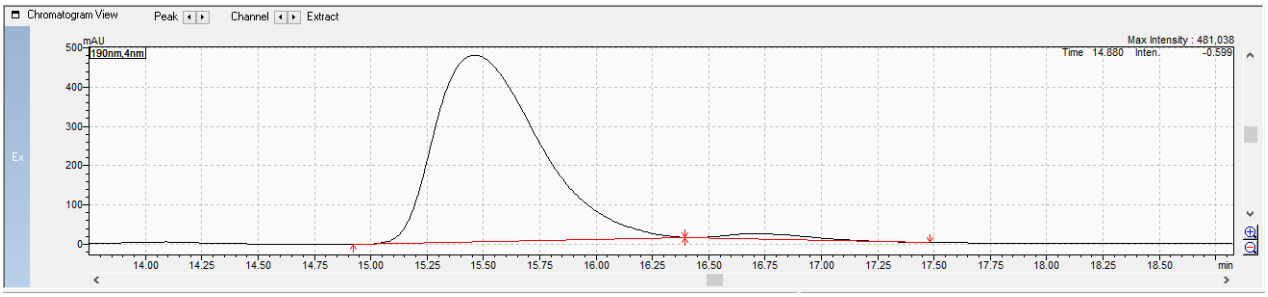
Chiral column HPLC analysis (Chiralcel AD-3 x 250 mm, 1.0 mL/min, 90:10 heptane:isopropanol, λ = 190 nm) t_R = 15.4 min (major), 16.7 min (minor):

Racemic 2.24c:

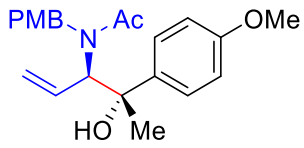


Ret. Time	Area%	Height	Conc.
15.440	49.258	444646	49.258
16.662	50.742	407347	50.742
	100.000	851994	100.000

2.24c from $Cu(OAc)_2$/J2 reaction:

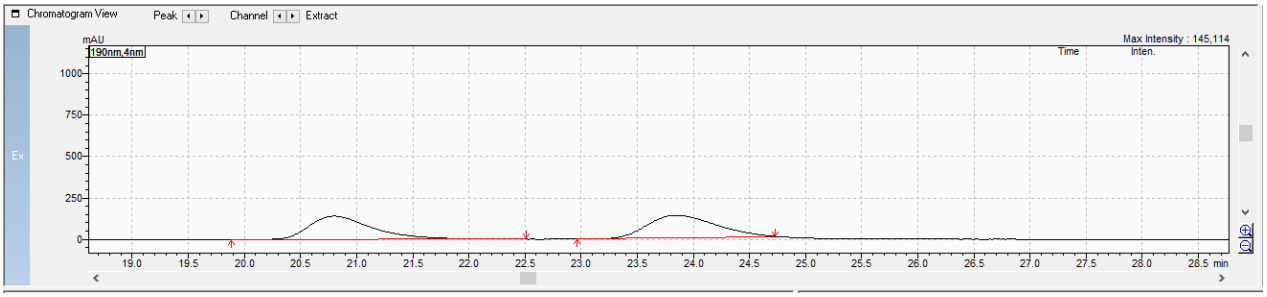


Ret. Time	Area%	Height	Conc.
15.466	97.962	474901	97.962
16.712	2.038	13575	2.038
	100.000	488477	100.000



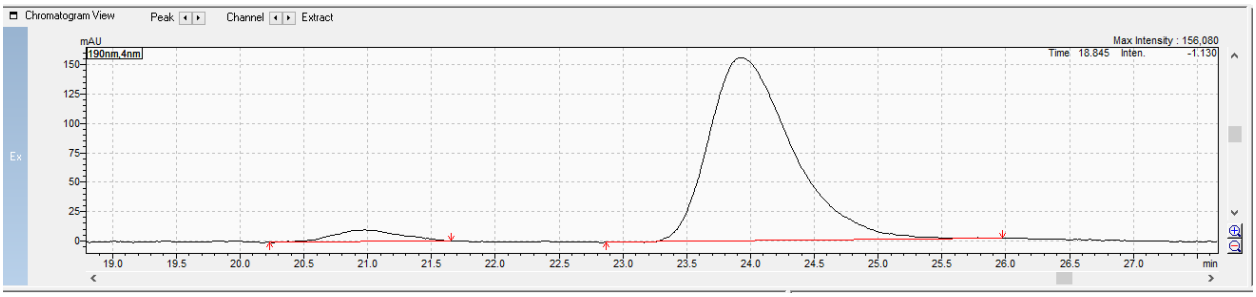
Chiral column HPLC analysis (Chiralcel AD-3 x 250 mm, 1.0 mL/min, 90:10 heptane:isopropanol, λ = 190 nm) t_R = 21.0 min (minor), 23.9 min (major):

Racemic 2.24d:

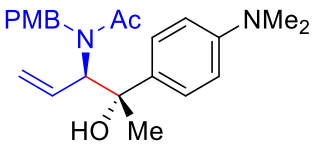


Ret. Time	Area%	Height	Conc.
20.794	49.177	140247	49.177
23.860	50.823	135152	50.823
	100.000	275399	100.000

2.24d from $Cu(OAc)_2$/J2 reaction:

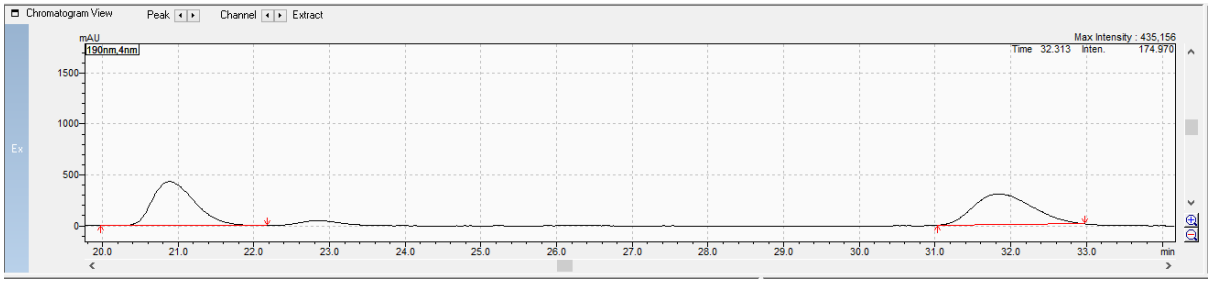


Ret. Time	Area%	Height	Conc.
20.974	4.897	10086	4.897
23.925	95.103	156116	95.103
	100.000	166202	100.000



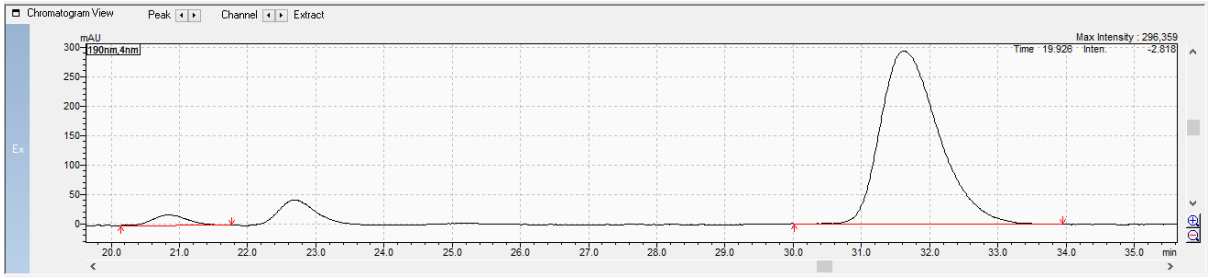
Chiral column HPLC analysis (Chiralcel AD-3 x 250 mm, 1.0 mL/min, 90:10 heptane:isopropanol, λ = 190 nm) t_R = 20.9 min (minor), 31.6 min (major):

Racemic 2.24g:

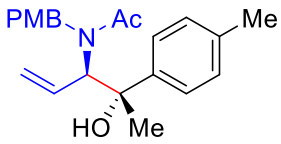


Ret. Time	Area%	Height	Conc.
20.889	50.455	432966	50.455
31.824	49.545	302248	49.545
	100.000	735214	100.000

2.24g from $Cu(OAc)_2$/J2 reaction:

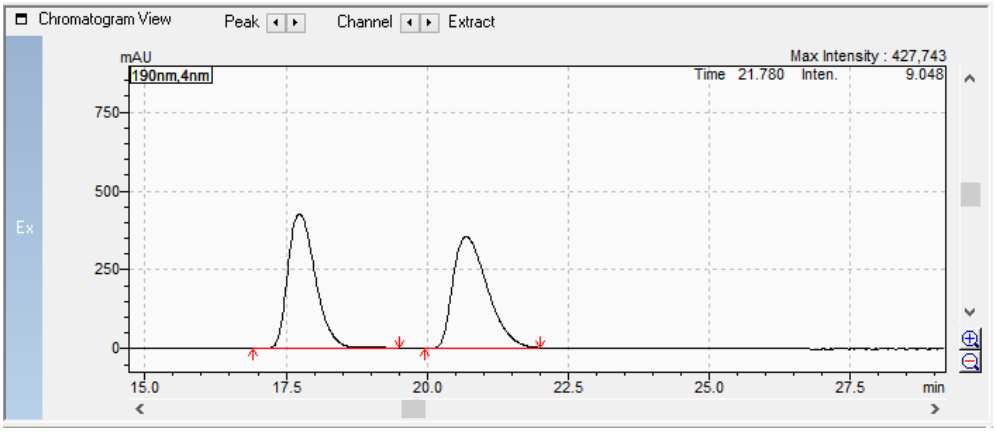


Ret. Time	Area%	Height	Conc.
20.870	3.519	17849	3.519
31.611	96.481	293838	96.481
	100.000	311687	100.000



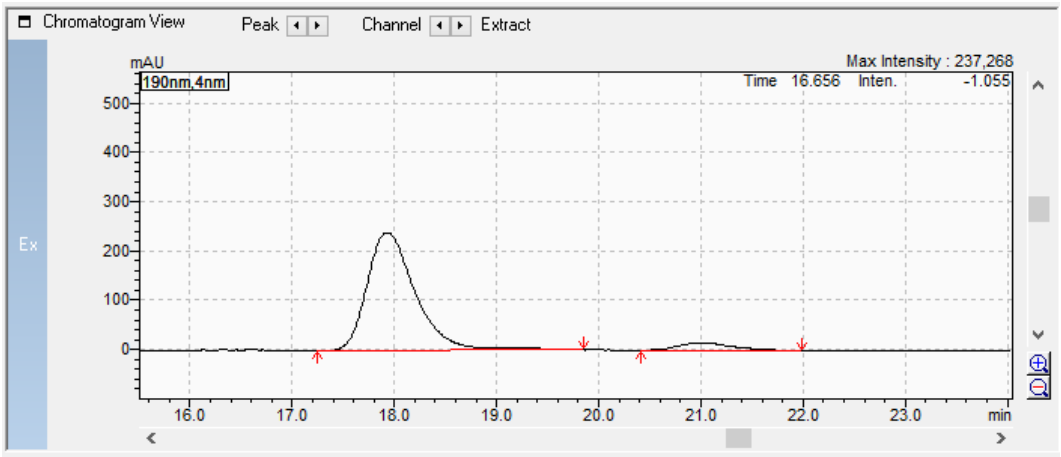
Chiral column HPLC analysis (Chiralcel AD-3 x 250 mm, 1.0 mL/min, 90:10 heptane:isopropanol, λ = 190 nm) t_R = 17.9 min (major), 21.0 min (minor):

Racemic 2.24h:

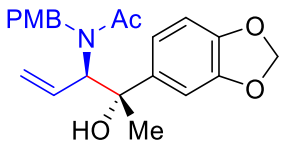


Ret. Time	Area%	Height	Conc.
17.736	49.270	426885	49.270
20.692	50.730	355030	50.730
	100.000	781914	100.000

2.24h from $Cu(OAc)_2$/J2 reaction:

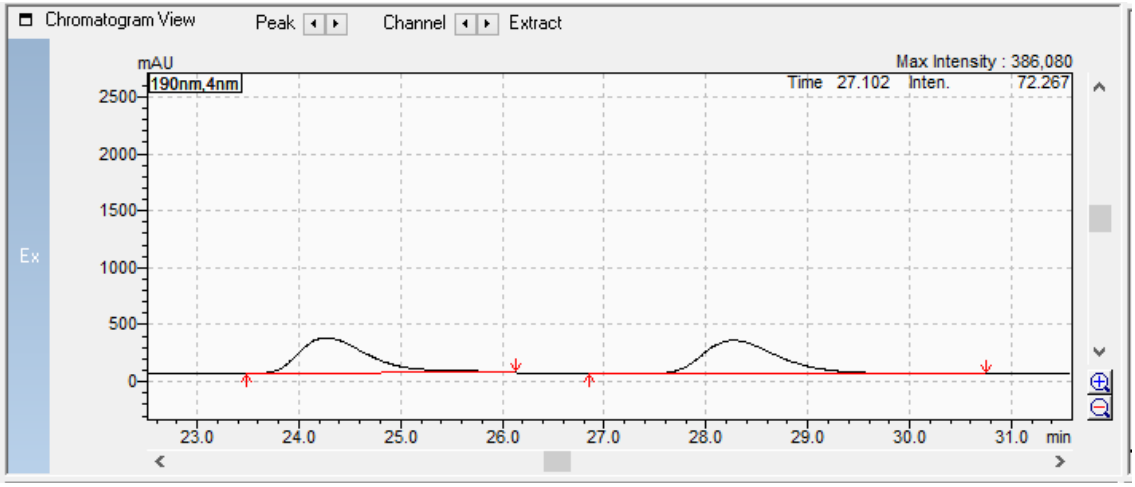


Ret. Time	Area%	Height	Conc.
17.928	93.541	239091	93.541
20.967	6.459	15234	6.459
	100.000	254325	100.000



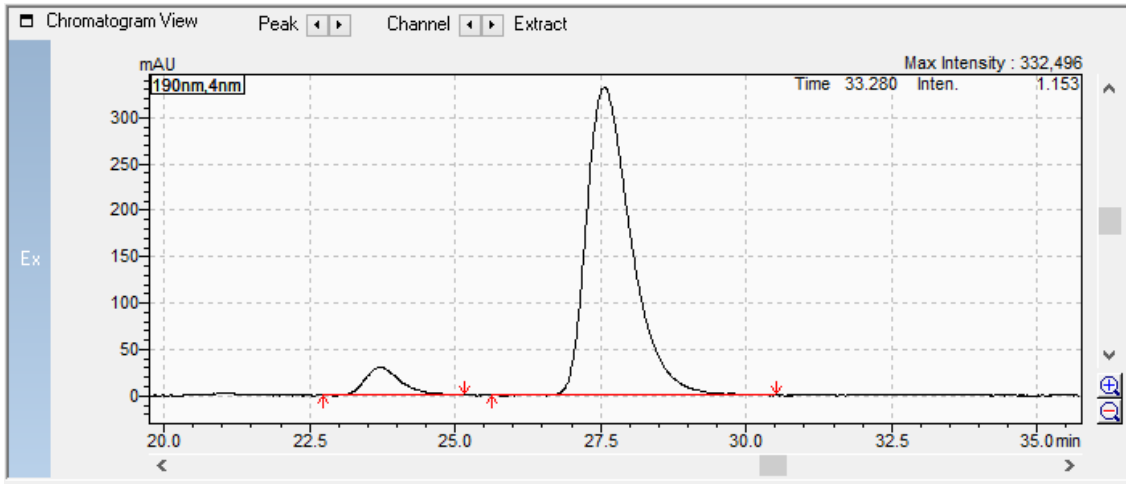
Chiral column HPLC analysis (Chiralcel AD-3 x 250 mm, 1.0 mL/min, 90:10 heptane:isopropanol, λ = 190 nm) t_R = 23.7 min (minor), 27.6 min (major):

Racemic 2.24k:

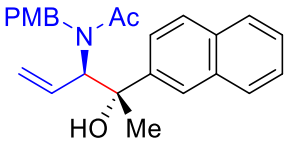


Ret. Time	Area%	Height	Conc.
24.272	50.508	312008	50.508
28.266	49.492	291305	49.492
	100.000	603313	100.000

2.24k from $Cu(OAc)_2$/J2 reaction:

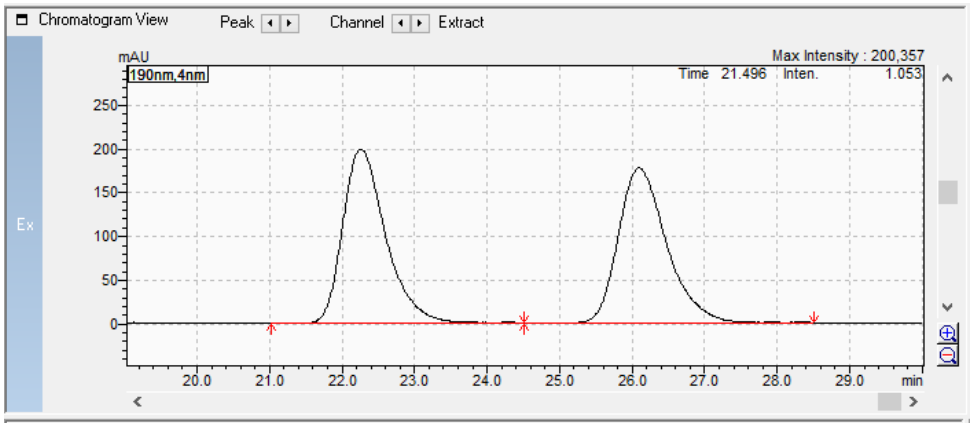


Ret. Time	Area%	Height	Conc.
23.715	6.832	29908	6.832
27.570	93.168	331588	93.168
	100.000	361496	100.000



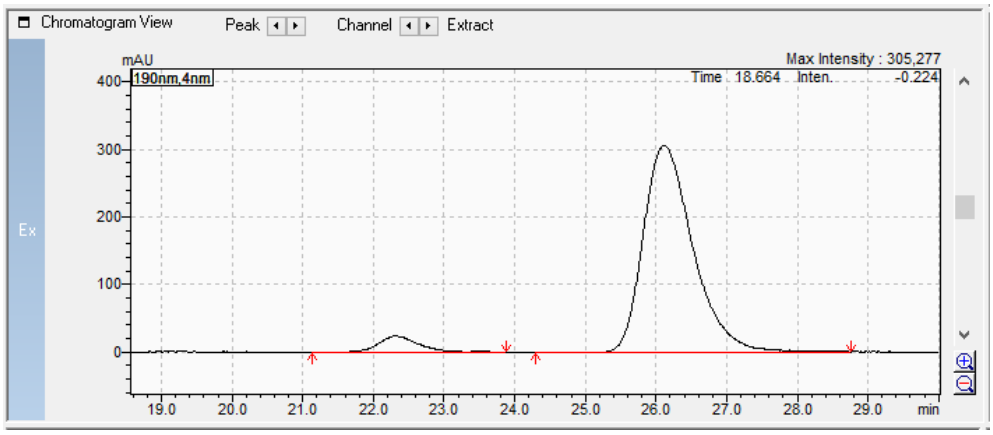
Chiral column HPLC analysis (Chiralcel AD-3 x 250 mm, 1.0 mL/min, 90:10 heptane:isopropanol, λ = 190 nm) t_R = 22.3 min (minor), 26.1 min (major):

Racemic 2.24l:

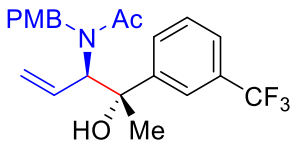


Ret. Time	Area%	Height	Conc.
22.258	49.802	199247	49.802
26.092	50.198	177406	50.198
	100.000	376653	100.000

2.24l from $Cu(OAc)_2$/J2 reaction:

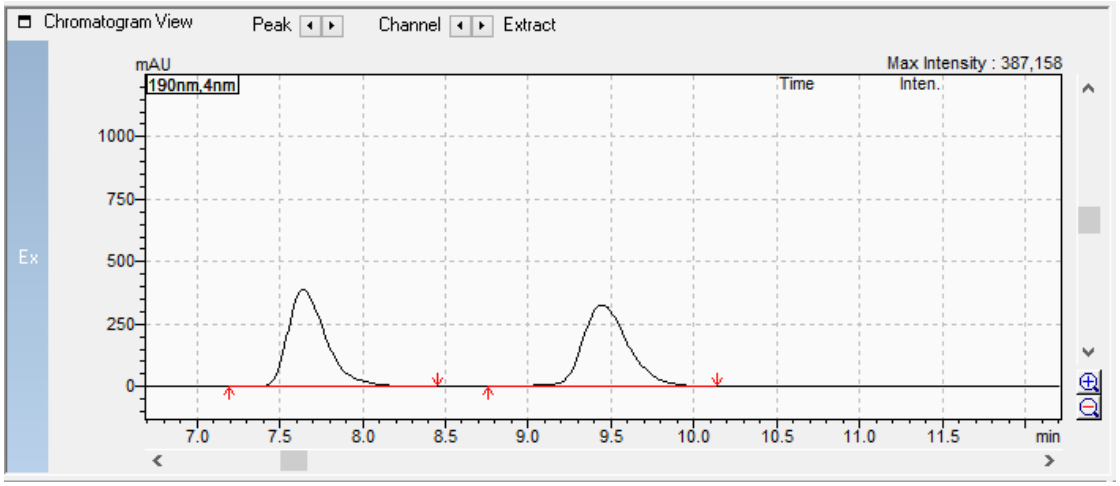


Ret. Time	Area%	Height	Conc.
22.313	6.013	24233	6.013
26.106	93.987	305764	93.987
	100.000	329997	100.000



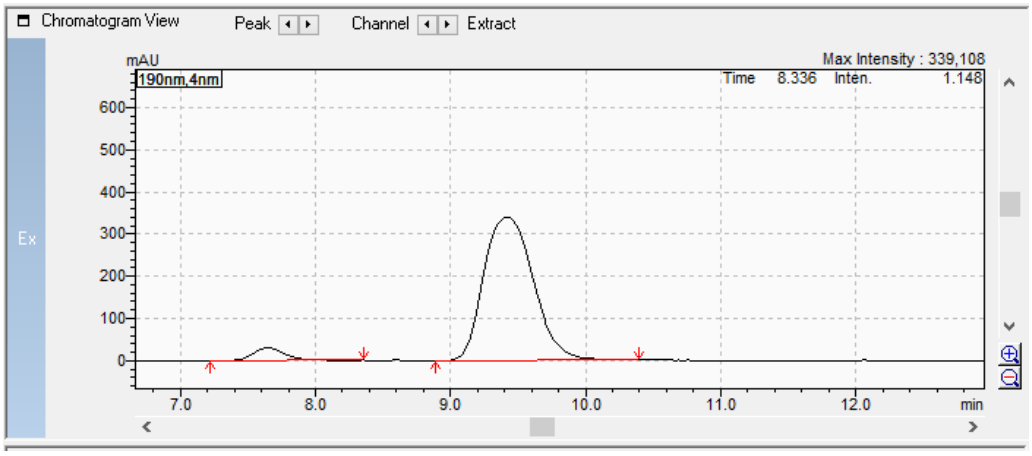
Chiral column HPLC analysis (Chiralcel AD-3 x 250 mm, 1.0 mL/min, 90:10 heptane:isopropanol, λ = 190 nm) t_R = 7.6 min (minor), 9.4 min (major):

Racemic 2.24m:

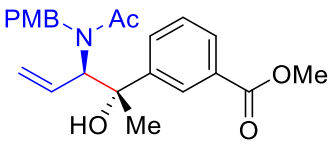


Ret. Time	Area%	Height	Conc.
7.644	49.751	386631	49.751
9.448	50.249	325833	50.249
	100.000	712464	100.000

2.24m from $Cu(OAc)_2$/J2 reaction:

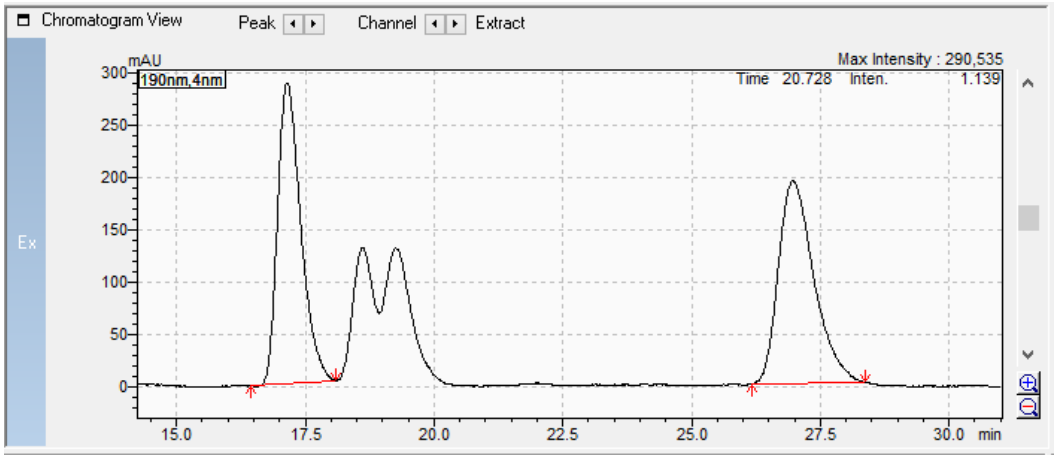


Ret. Time	Area%	Height	Conc.
7.649	5.253	30285	5.253
9.421	94.747	337909	94.747
	100.000	368193	100.000



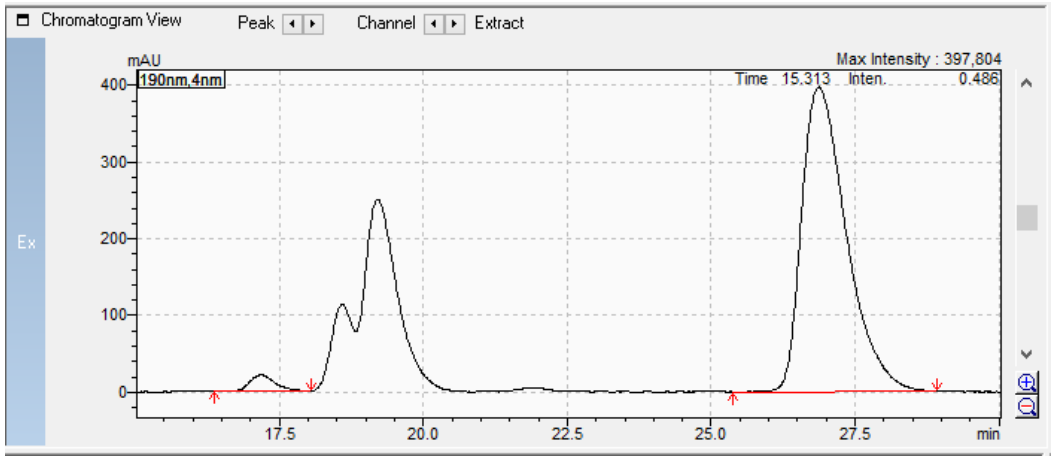
Chiral column HPLC analysis (Chiralcel AD-3 x 250 mm, 1.0 mL/min, 90:10 heptane:isopropanol, λ = 190 nm) t_R = 17.2 min (minor), 26.9 min (major):

Racemic 2.24p:

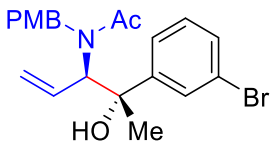


Ret. Time	Area%	Height	Conc.
17.151	49.178	287001	49.178
26.961	50.822	193215	50.822
	100.000	480215	100.000

2.24p from $Cu(OAc)_2$/J2 reaction:

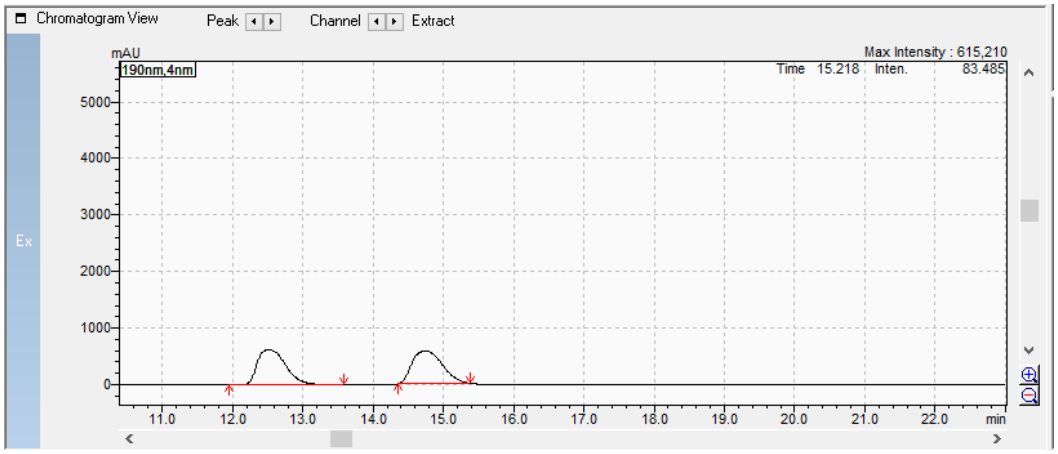


Ret. Time	Area%	Height	Conc.
17.175	2.927	20988	2.927
26.872	97.073	397082	97.073
	100.000	418069	100.000



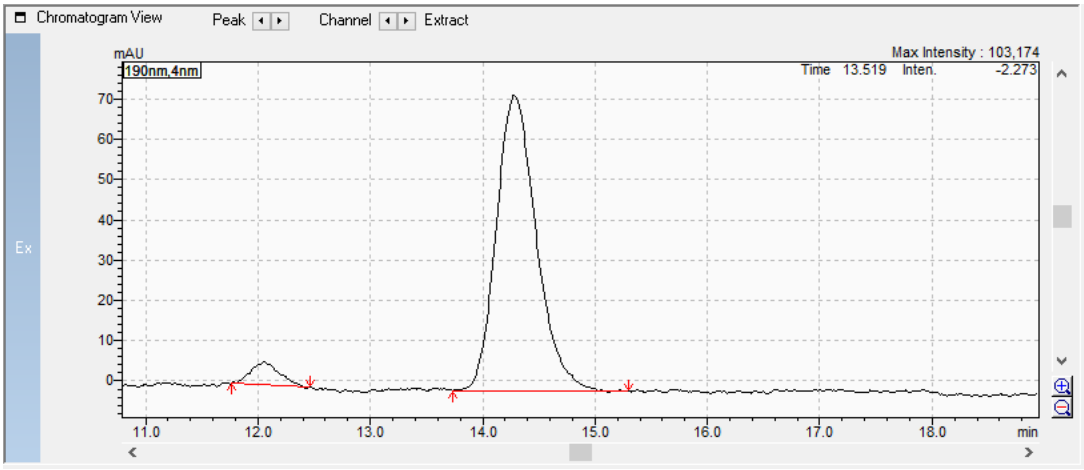
Chiral column HPLC analysis (Chiralcel AD-3 x 250 mm, 1.0 mL/min, 90:10 heptane:isopropanol, λ = 190 nm) t_R = 12.1 min (minor), 14.3 min (major):

Racemic 2.24q:

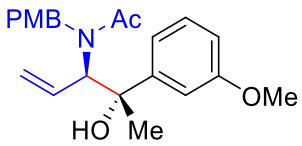


Ret. Time	Area%	Height	Conc.
12.516	49.719	615352	49.719
14.738	50.281	575156	50.281
	100.000	1190509	100.000

2.24q from $Cu(OAc)_2$/J2 reaction:

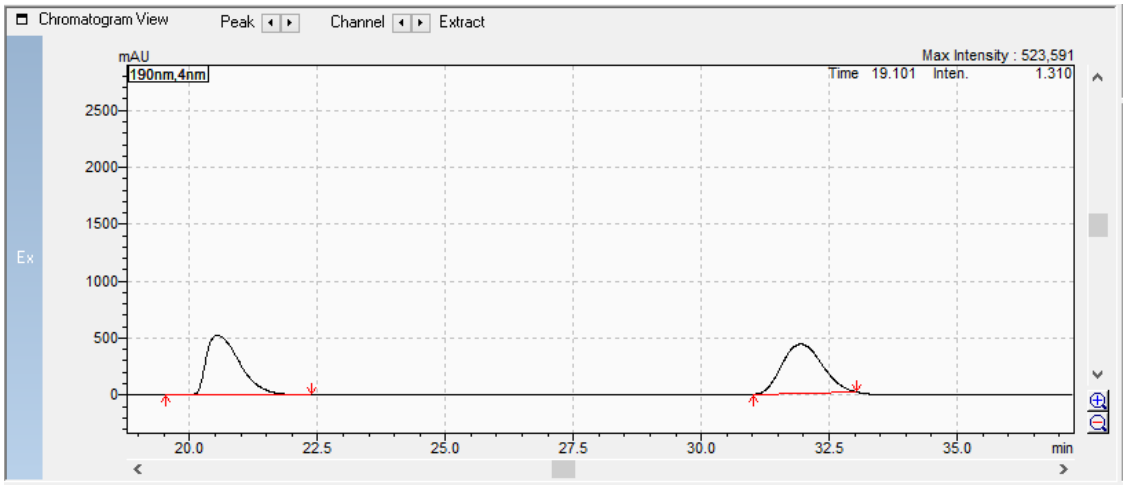


Ret. Time	Area%	Height	Conc.
12.056	5.310	5710	5.310
14.280	94.690	73415	94.690
	100.000	79124	100.000



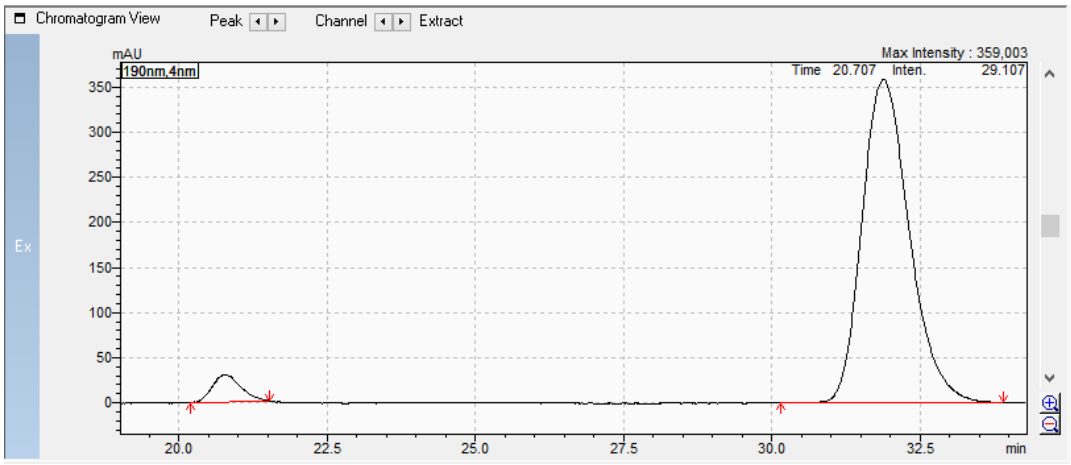
Chiral column HPLC analysis (Chiralcel AD-3 x 250 mm, 1.0 mL/min, 90:10 heptane:isopropanol, λ = 190 nm) t_R = 20.8 min (minor), 31.9 min (major):

Racemic 2.24r:

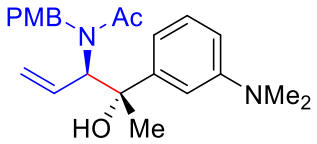


Ret. Time	Area%	Height	Conc.
20.542	50.003	521932	50.003
31.929	49.997	432677	49.997
	100.000	954609	100.000

2.24r from $Cu(OAc)_2$/J2 reaction:

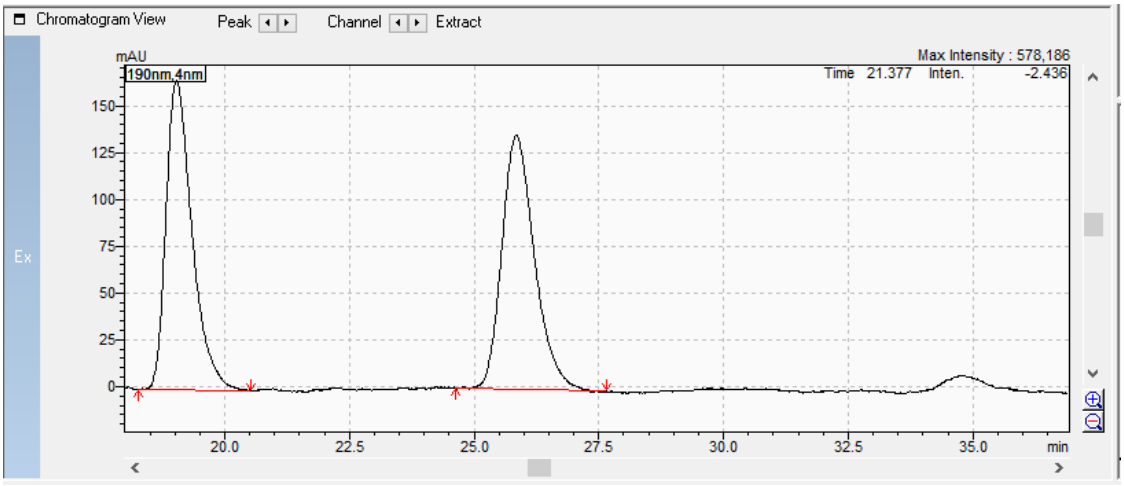


Ret. Time	Area%	Height	Conc.
20.775	4.785	29805	4.785
31.892	95.215	358805	95.215
	100.000	388610	100.000



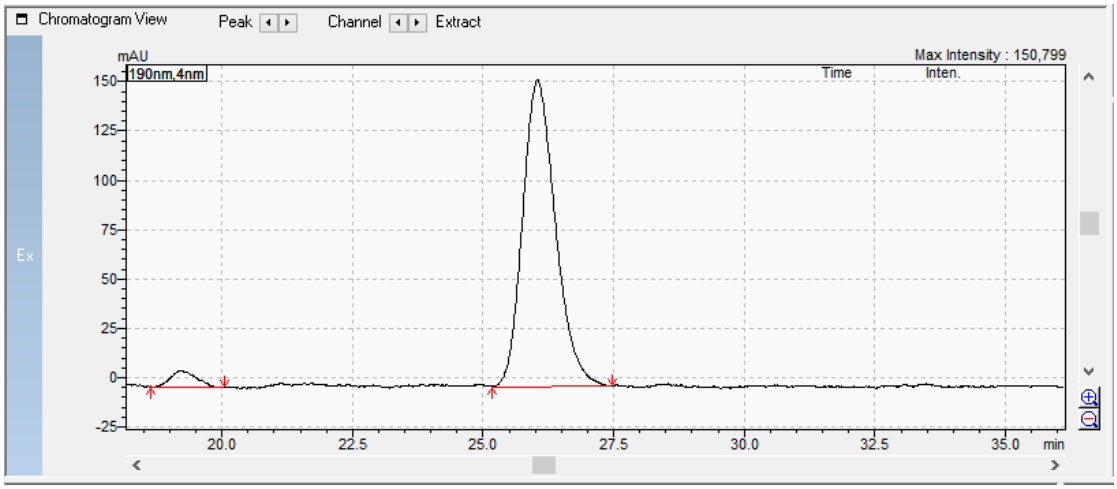
Chiral column HPLC analysis (Chiralcel AD-3 x 250 mm, 1.0 mL/min, 90:10 heptane:isopropanol, λ = 190 nm) t_R = 19.2 min (minor), 26.0 min (major):

Racemic 2.24n:

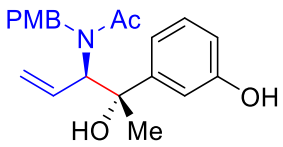


Ret. Time	Area%	Height	Conc.
19.030	49.411	165293	49.411
25.844	50.589	135554	50.589
	100.000	300847	100.000

2.24n from $Cu(OAc)_2$/J2 reaction:

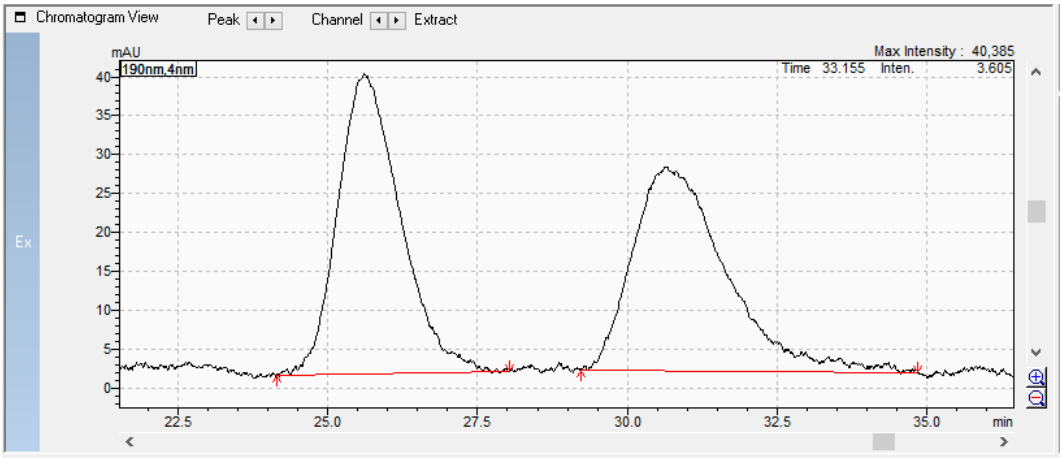


Ret. Time	Area%	Height	Conc.
19.221	3.885	8107	3.885
26.038	96.115	155152	96.115
	100.000	163259	100.000



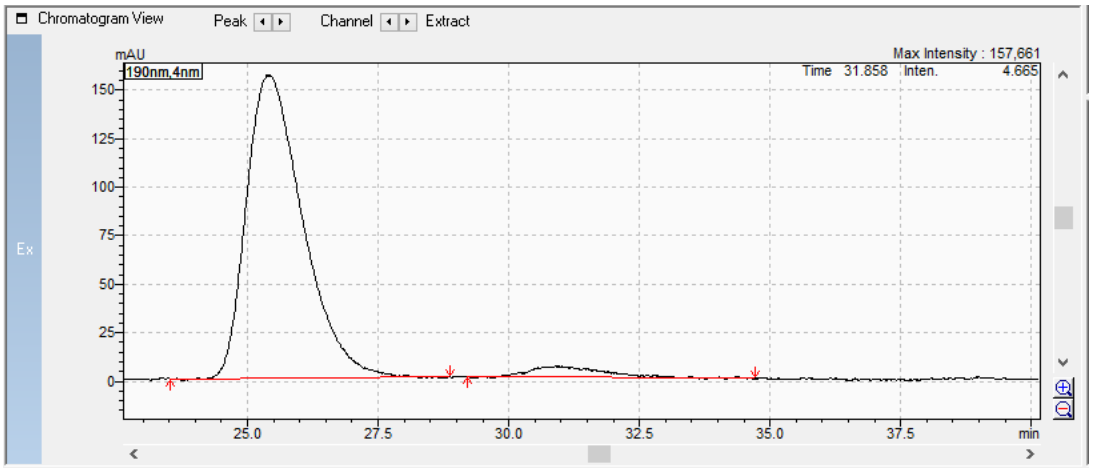
Chiral column HPLC analysis (Chiralcel AD-3 x 250 mm, 1.0 mL/min, 90:10 heptane:isopropanol, λ = 190 nm) t_R = 25.4 min (major), 30.9 min (minor):

Racemic 2.24i:

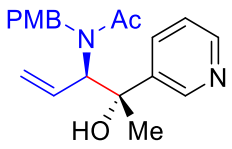


Ret. Time	Area%	Height	Conc.
25.609	49.646	38623	49.646
30.631	50.354	26294	50.354
	100.000	64916	100.000

2.24i from $Cu(OAc)_2$/J2 reaction:

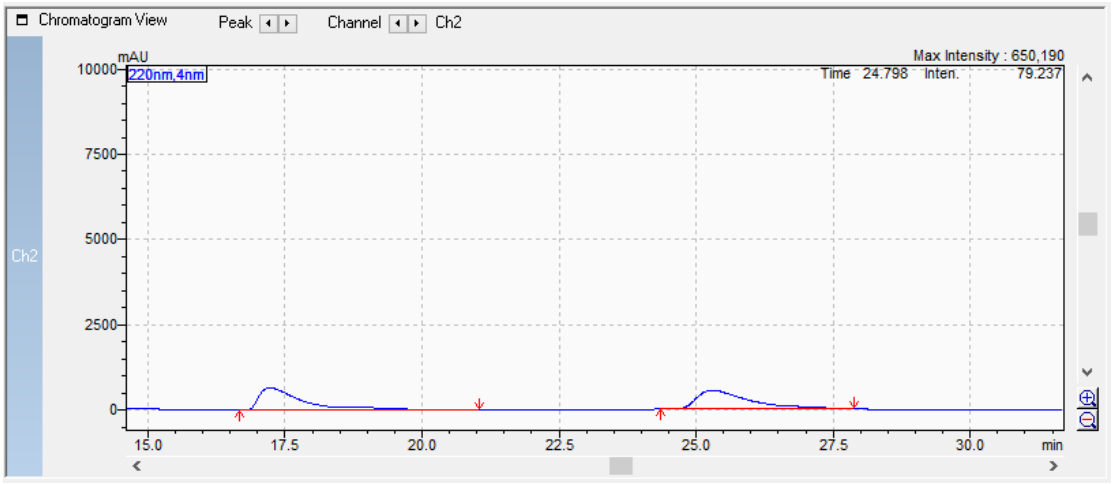


Ret. Time	Area%	Height	Conc.
25.374	95.286	156056	95.286
30.892	4.714	5863	4.714
	100.000	161919	100.000



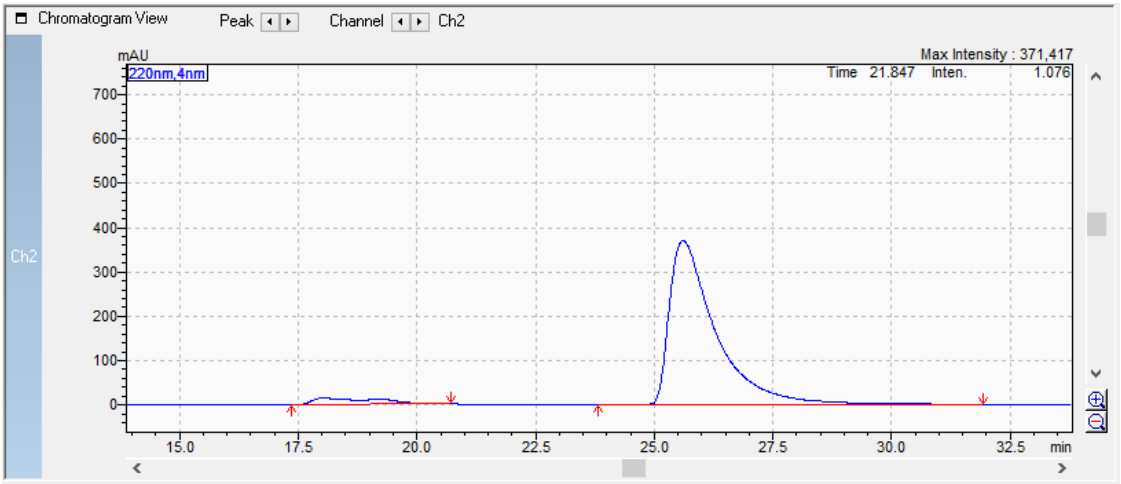
Chiral column HPLC analysis (Chiralcel AD-3 x 250 mm, 1.0 mL/min, 90:10 heptane:isopropanol, λ = 220 nm) t_R = 18.0 min (minor), 25.6 min (major):

Racemic 2.24d:

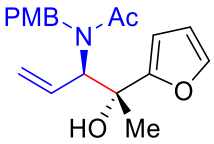


Ret. Time	Area%	Height	Conc.
17.225	49.300	644473	0.000
25.297	50.700	550842	0.000
	100.000	1195315	0.000

2.24d from $Cu(OAc)_2$/J2 reaction:

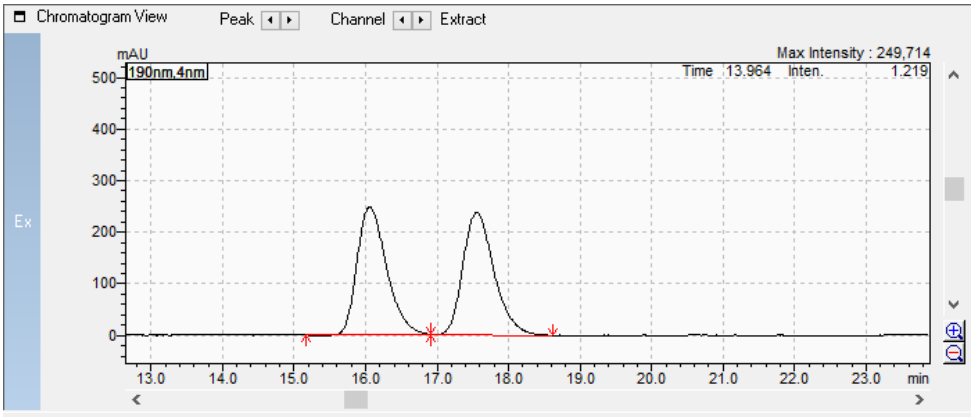


Ret. Time	Area%	Height	Conc.
18.020	5.396	14746	0.000
25.607	94.604	370632	0.000
	100.000	385378	0.000



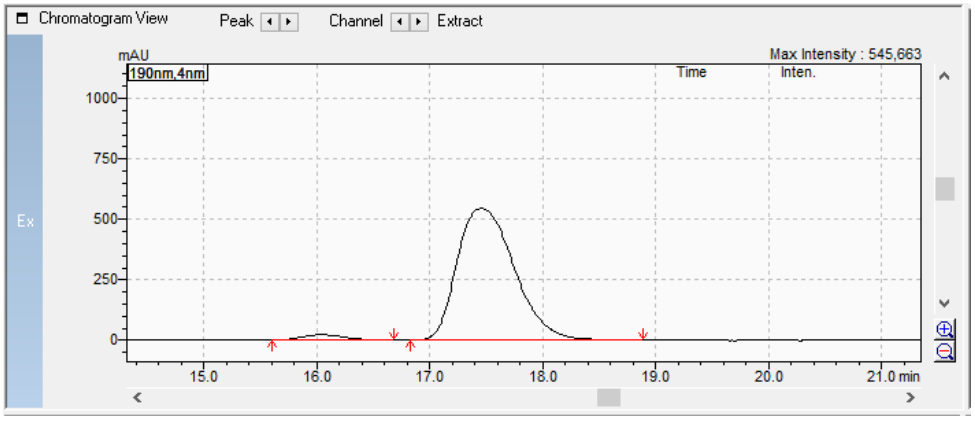
Chiral column HPLC analysis (Chiralcel AD-3 x 250 mm, 1.0 mL/min, 90:10 heptane:isopropanol, λ = 190 nm) t_R = 16.0 min (minor), 17.5 min (major):

Racemic 2.24j:

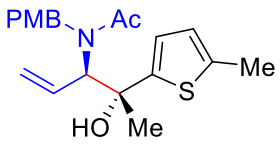


Ret. Time	Area%	Height	Conc.
16.057	49.703	248242	49.703
17.556	50.297	237796	50.297
	100.000	486038	100.000

2.24j from $Cu(OAc)_2$/J2 reaction:

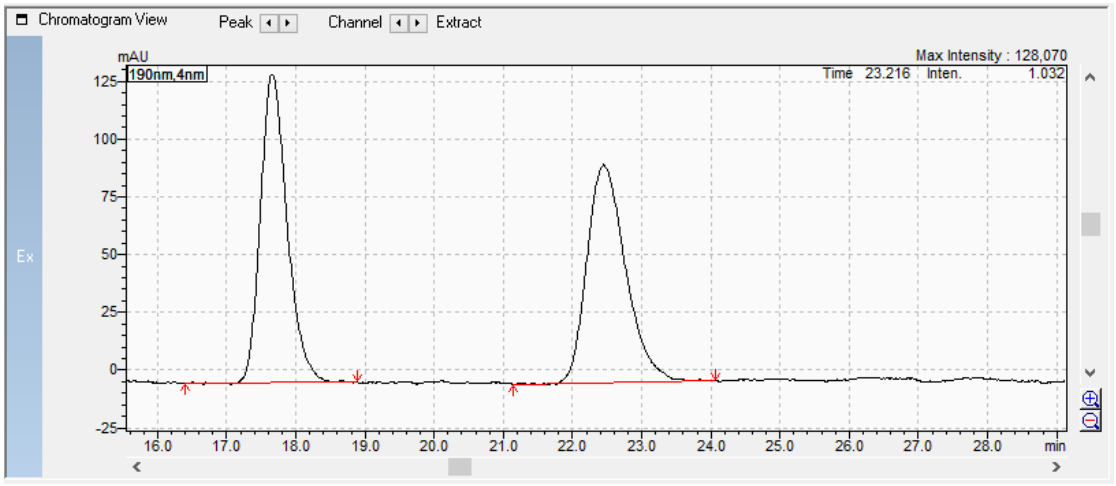


Ret. Time	Area%	Height	Conc.
16.036	3.093	22432	3.093
17.455	96.907	544630	96.907
	100.000	567062	100.000



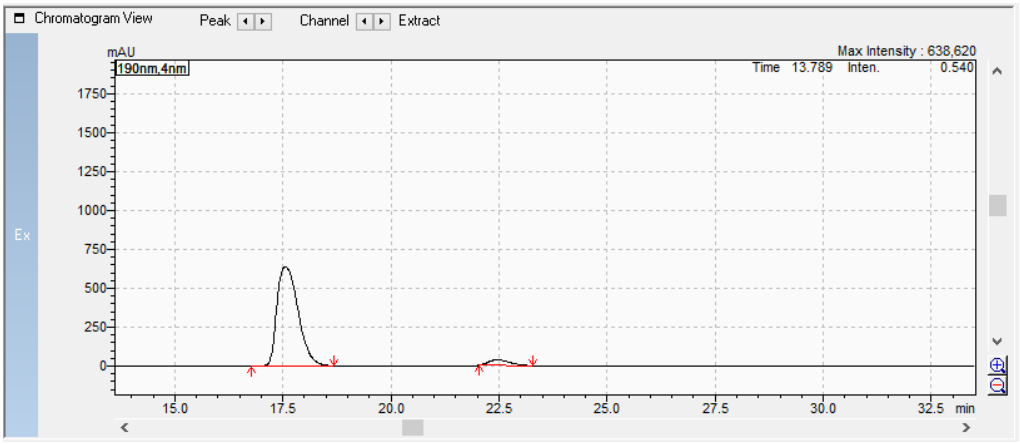
Chiral column HPLC analysis (Chiralcel AD-3 x 250 mm, 1.0 mL/min, 90:10 heptane:isopropanol, λ = 190 nm) t_R = 17.6 min (major), 22.5 min (minor):

Racemic 2.24e:

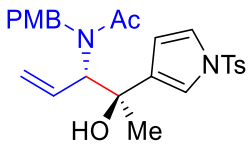


Ret. Time	Area%	Height	Conc.
17.656	49.130	133492	49.130
22.454	50.870	94631	50.870
	100.000	228123	100.000

2.24e from $Cu(OAc)_2$/J2 reaction:

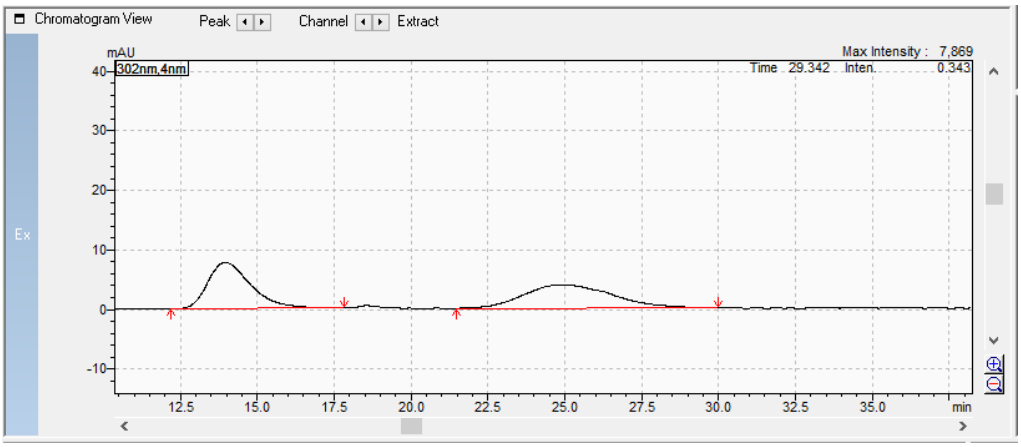


Ret. Time	Area%	Height	Conc.
17.556	94.786	636959	94.786
22.476	5.214	34883	5.214
	100.000	671842	100.000



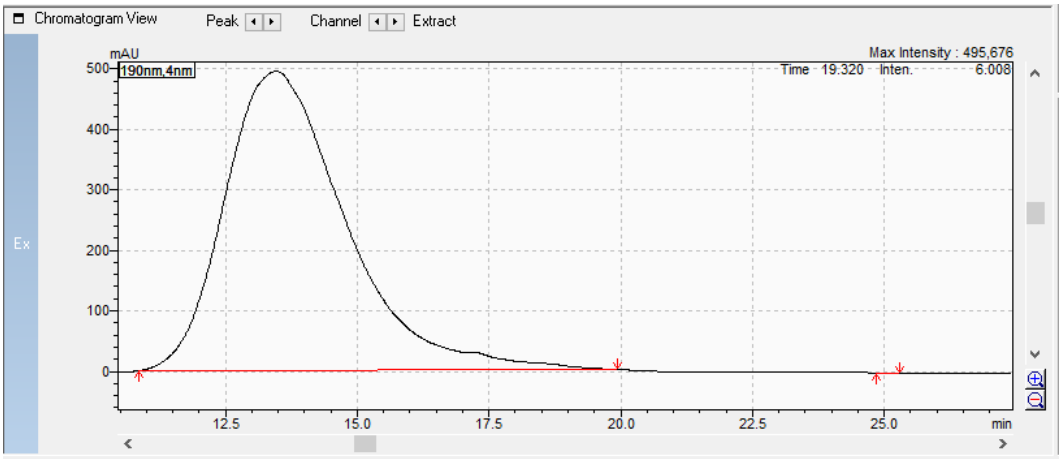
Chiral column HPLC analysis (Chiralcel AD-3 x 250 mm, 1.0 mL/min, 90:10 heptane:isopropanol, λ = 190 nm) t_R = 13.5 min (major), 24.9 min (minor):

Racemic 2.24o:

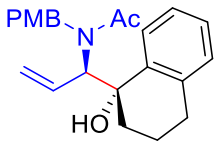


Ret. Time	Area%	Height	Conc.
13.969	49.020	7708	49.020
24.933	50.980	3951	50.980
	100.000	11659	100.000

2.24o from $Cu(OAc)_2$/J2 reaction:

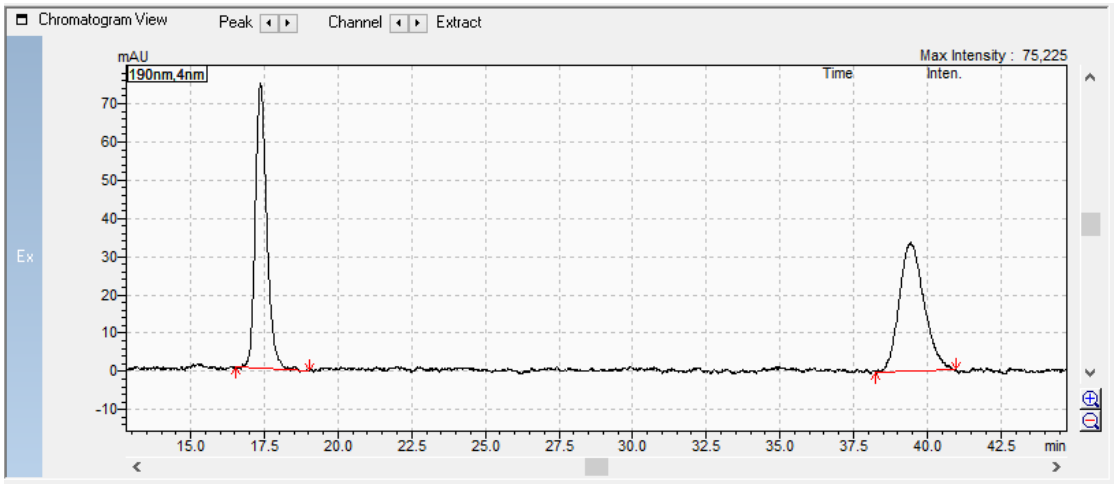


Ret. Time	Area%	Height	Conc.
13.454	99.988	494117	99.988
24.930	0.012	549	0.012
	100.000	494666	100.000



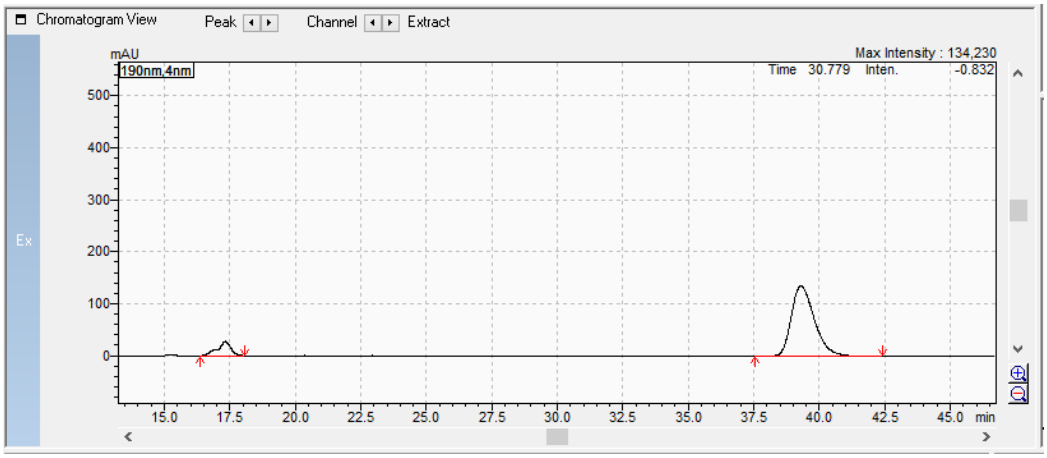
Chiral column HPLC analysis (Chiralcel AD-3 x 250 mm, 1.0 mL/min, 90:10 heptane:isopropanol, λ = 190 nm) t_R = 17.3 min (minor), 39.3 min (major):

Racemic 2.24s:

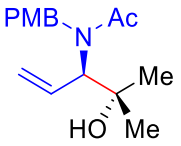


Ret. Time	Area%	Height	Conc.
17.368	50.315	74402	50.315
39.446	49.685	33878	49.685
	100.000	108279	100.000

2.24s from $Cu(OAc)_2$/J2 reaction:

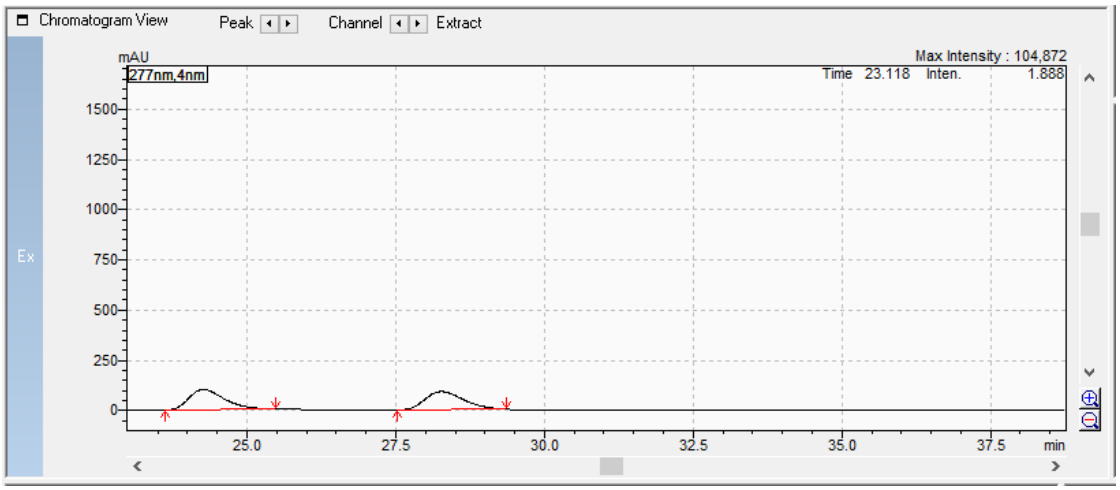


Ret. Time	Area%	Height	Conc.
17.330	10.329	27383	10.329
39.301	89.671	135509	89.671
	100.000	162892	100.000



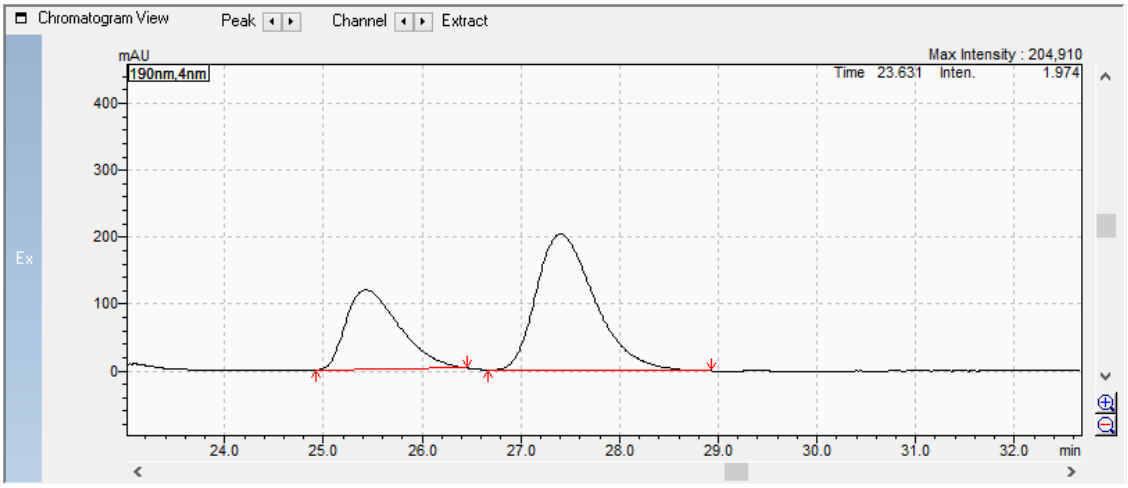
Chiral column HPLC analysis (Chiralcel AD-3 x 250 mm, 1.0 mL/min, 90:10 heptane:isopropanol, λ = 190 nm) t_R = 25.4 min (minor), 27.4 min (major):

Racemic 2.24t:



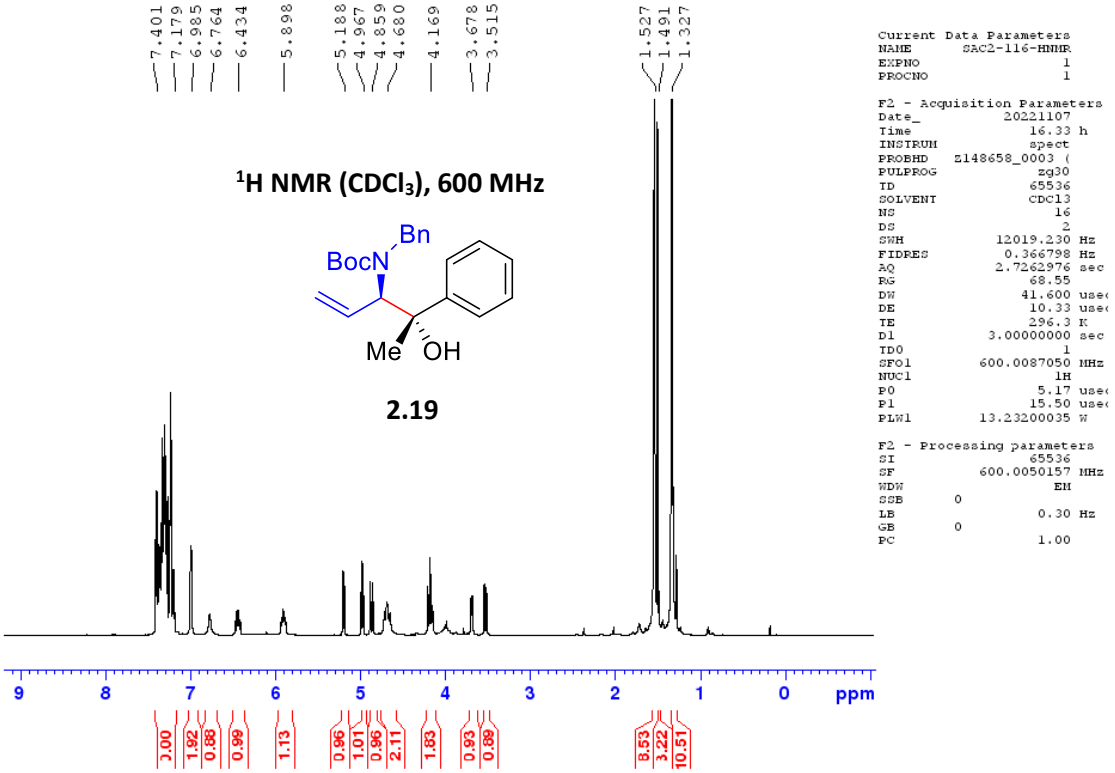
Ret. Time	Area%	Height	Conc.
24.869	50.588	28276	50.588
27.963	49.412	50873	49.412
	100.000	79149	100.000

2.24t from $Cu(OAc)_2$/J2 reaction:



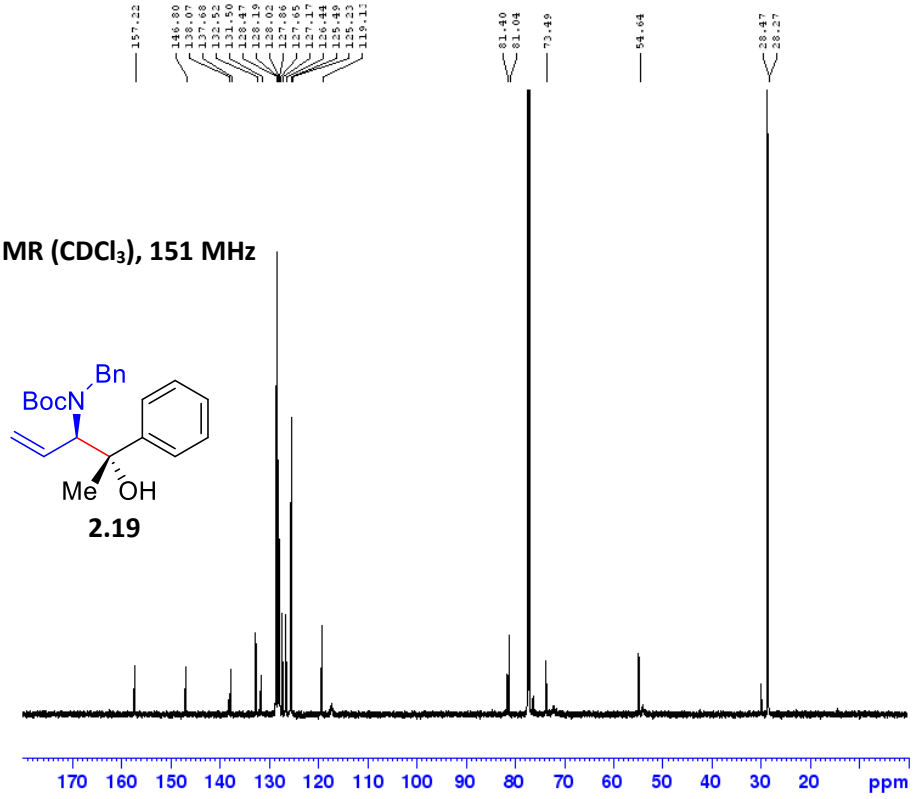
Ret. Time	Area%	Height	Conc.
25.430	34.810	118760	34.810
27.406	65.190	203646	65.190
	100.000	322405	100.000

NMR Data




```
Current Data Parameters
NAME        SAC2-116-HNMR
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20221107
Time              16.33 h
INSTRUM           spect
PROBHD    Z148658_0003 (
PULPROG           zg30
TD               65536
SOLVENT          CDCl3
NS                  16
DS                   2
SWH           12019.230 Hz
FIDRES         0.366798 Hz
AQ             2.7262976 sec
RG                68.55
DW               41.600 use
DE               10.33 use
TE               296.3 K
D1            3.00000000 sec
TD0                  1
SFO1        600.0087050 MHz
NUC1                 1H
P0                5.17 use
P1               15.50 use
PLW1         13.23200035 W

F2 - Processing parameters
SI               65536
SF          600.0050157 MHz
WDW                  EM
SSB       0
LB              0.30 Hz
GB        0
PC              1.00
```

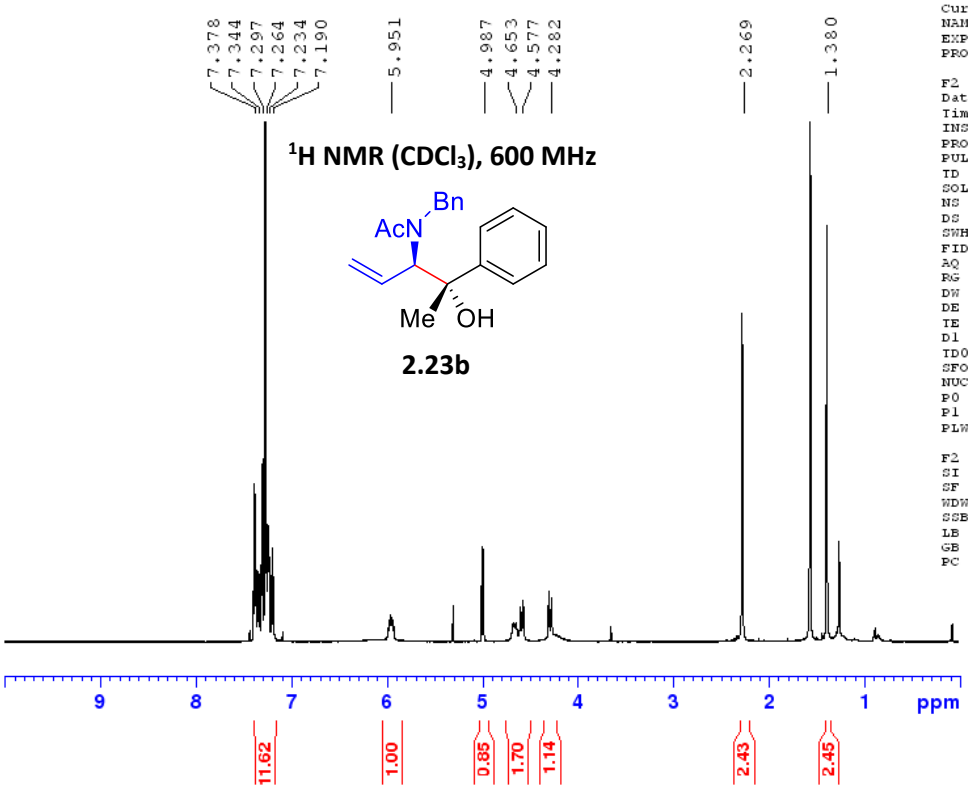
^{13}C NMR ($CDCl_3$), 151 MHz



2.19

```
Current Data Parameters
NAME       SAC2-116-CNMR
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_           20221107
Time              20.28 h
INSTRUM             spect
PROBHD    Z148658_0003 (
PULPROG           zgpg30
TD                65536
SOLVENT           CDCl3
NS                 1024
DS                    4
SWH           36231.883 Hz
FIDRES        1.105709 Hz
AQ            0.9043968 sec
RG               199.73
DW               13.800 use
DE                6.50 use
TE               297.9 K
D1            4.00000000 sec
D11           0.03000000 sec
TD0                   1
SFO1        150.8864644 MHz
NUC1                13C
P0                4.00 use
P1               12.00 use
PLW1         77.65699768 W
SFO2        600.0074000 MHz
NUC2                1H
CPDPRG[2         waltz65
PCPD2             70.00 use
PLW2         13.23200035 W
PLW12         0.64876997 W
PLW13         0.32633001 W

F2 - Processing parameters
SI                32768
SF          150.8713773 MHz
WDW                  EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```

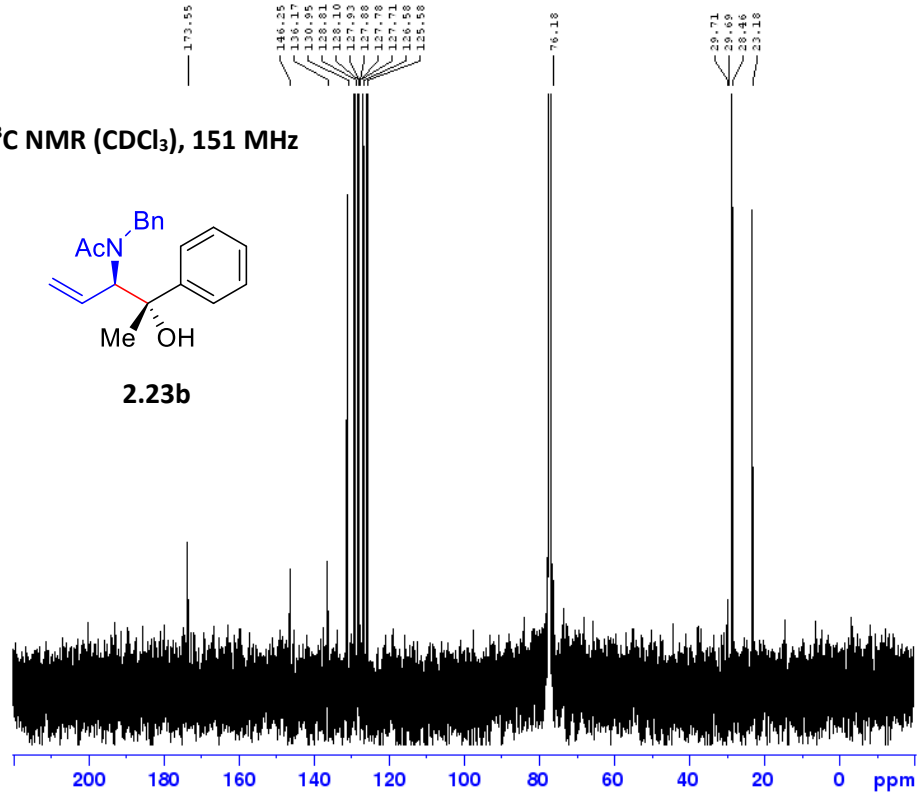
^{1}H NMR ($CDCl_3$), 600 MHz



2.23b

```
Current Data Parameters
NAME       SAC2-197-HNMR
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_           20221116
Time              11.07 h
INSTRUM             spect
PROBHD    Z148658_0003 (
PULPROG             zg30
TD                65536
SOLVENT           CDCl3
NS                   64
DS                    2
SWH           12019.230 Hz
FIDRES        0.366798 Hz
AQ            2.7262976 sec
RG               199.73
DW               41.600 use
DE               10.33 use
TE               296.3 K
D1            3.00000000 sec
TD0                   1
SFO1        600.0087050 MHz
NUC1                1H
P0                5.17 use
P1               15.50 use
PLW1         13.23200035 W

F2 - Processing parameters
SI                65536
SF          600.0050161 MHz
WDW                  EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```

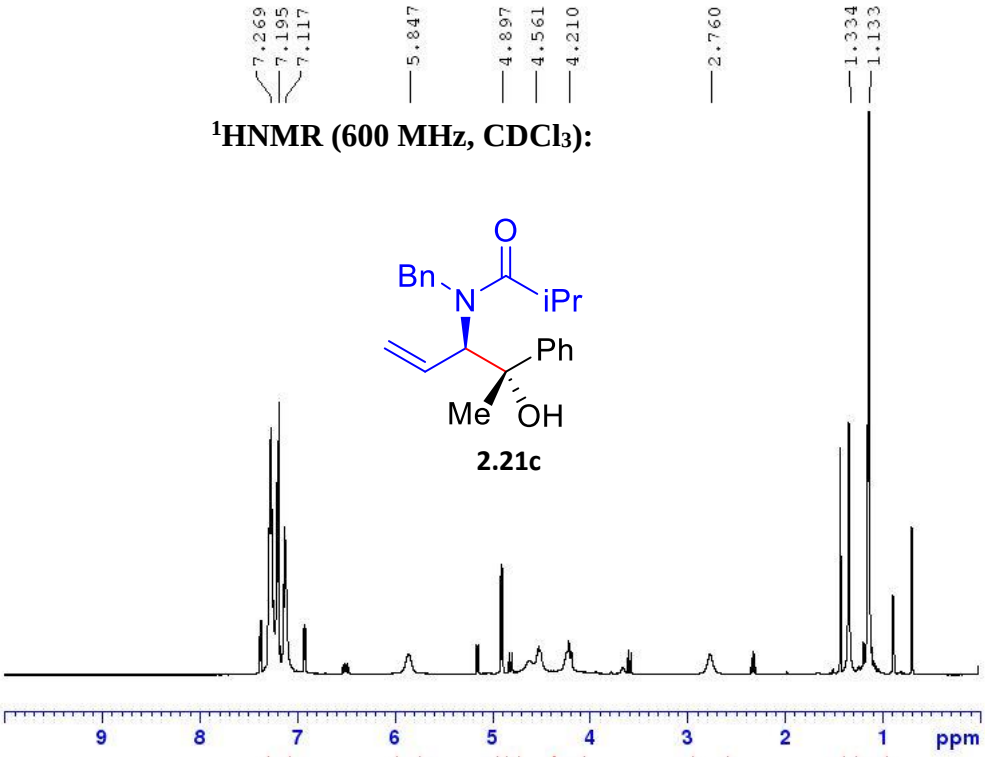
^{13}C NMR ($CDCl_3$), 151 MHz



2.23b

```
Current Data Parameters
NAME       SAC2-197-CNMR
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_           20221121
Time               5.31 h
INSTRUM            spect
PROBHD    Z148658_0003 (
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                 8192
DS                    4
SWH           36231.883 Hz
FIDRES         1.105709 Hz
AQ             0.9043968 sec
RG                199.73
DW                13.800 use
DE                 6.50 use
TE                298.1 K
D1            4.00000000 sec
D11           0.03000000 sec
TD0                   1
SFO1        150.8864644 MHz
NUC1                13C
P0                 4.00 use
P1                12.00 use
PLW1         77.65699768 W
SFO2        600.0074000 MHz
NUC2                1H
CPDPRG[2        waltz65
PCPD2             70.00 use
PLW2         13.23200035 W
PLW12         0.64876997 W
PLW13         0.32633001 W

F2 - Processing parameters
SI                32768
SF          150.8713773 MHz
WDW                  EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```

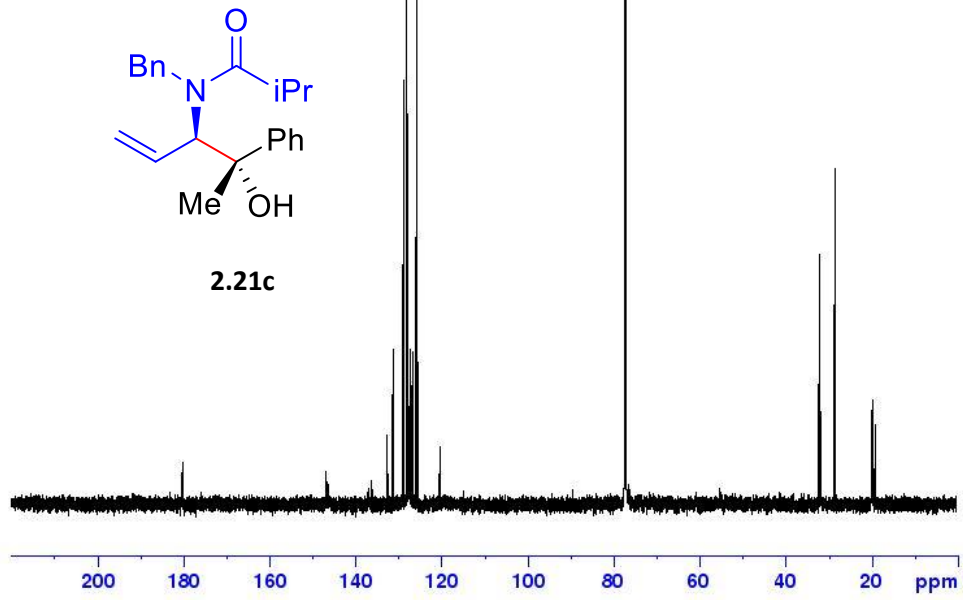
^{1}HNMR (600 MHz, $CDCl_3$):



2.21c

```
Current Data Parameters
NAME       SAC4-053-HNMR
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_           20230207
Time              10.35 h
INSTRUM            spect
PROBHD    Z148658_0003 (
PULPROG             zg30
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH           12019.230 Hz
FIDRES         0.366798 Hz
AQ             2.7262976 sec
RG                106.9
DW                41.600 use
DE                10.33 use
TE                296.6 K
D1            3.00000000 sec
TD0                   1
SFO1        600.0087050 MHz
NUC1                1H
P0                 5.17 use
P1                15.50 use
PLW1         13.23200035 W

F2 - Processing parameters
SI                65536
SF          600.0050630 MHz
WDW                  EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```

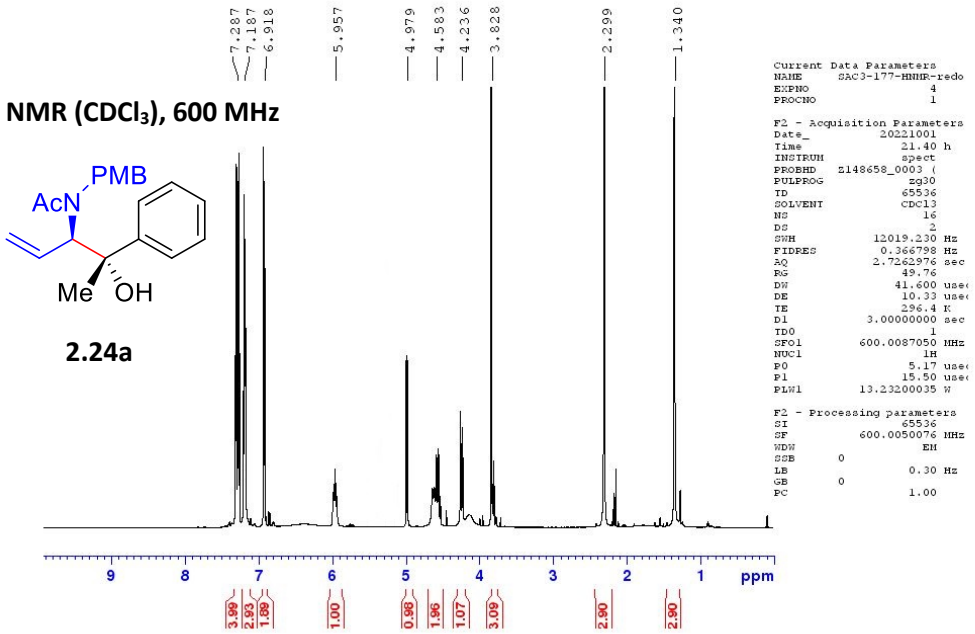
^{13}CNMR (151 MHz, $CDCl_3$):



2.21c

```
Current Data Parameters
NAME        SAC4-053-CNMR
EXPNO                  3
PROCNO                 1

F2 - Acquisition Parameters
Date_           20230207
Time              10.49 h
INSTRUM             spect
PROBHD    Z148658_0003 (
PULPROG           zgpg30
TD                65536
SOLVENT             CDCl3
NS                  256
DS                    4
SWH           36231.883 Hz
FIDRES         1.105709 Hz
AQ            0.9043968 sec
RG                199.73
DW                13.800 use
DE                 6.50 use
TE                298.0 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                   1
SFO1        150.8864644 MHz
NUC1                13C
P0                 4.00 use
P1                12.00 use
PLW1        77.65699768 W
SFO2        600.0074000 MHz
NUC2                1H
CPDPRG[2         waltz65
PCPD2             70.00 use
PLW2        13.23200035 W
PLW12        0.64876997 W
PLW13        0.32633001 W

F2 - Processing parameters
SI                32768
SF          150.8713773 MHz
WDW                 EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```

^{1}H NMR ($CDCl_3$), 600 MHz

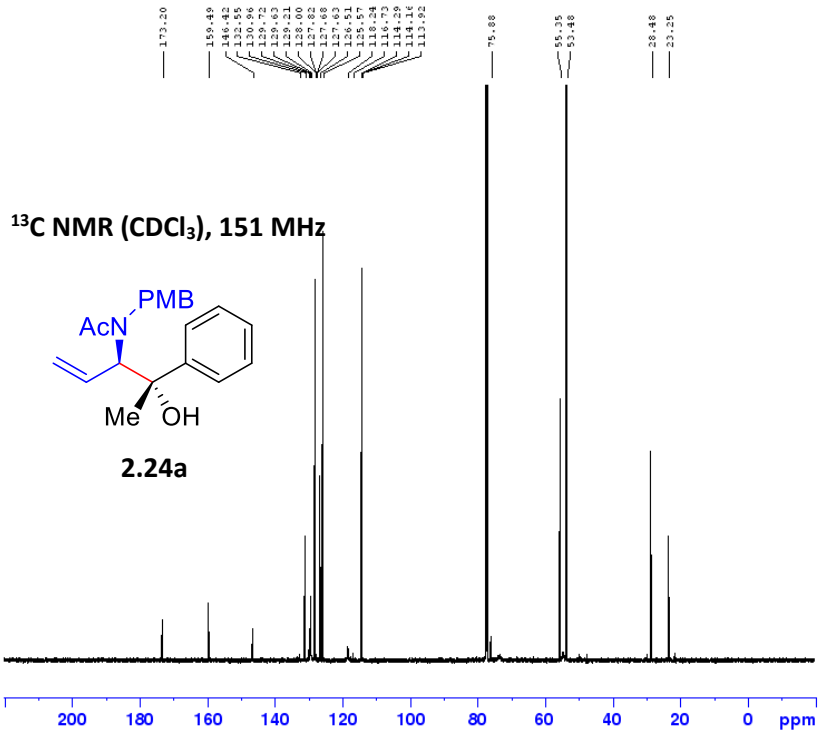


2.24a

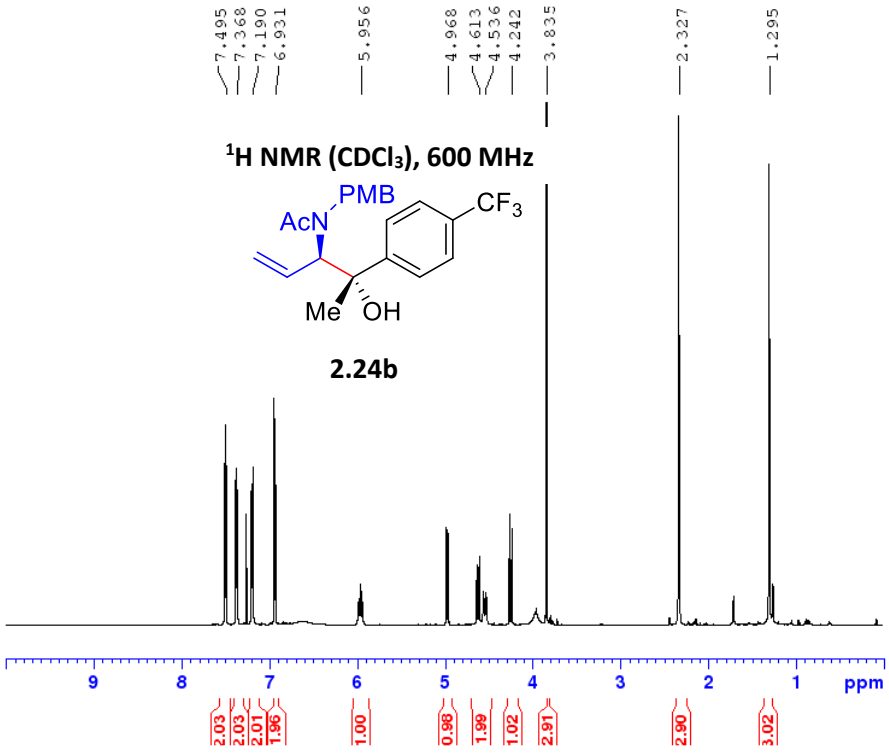
Current Data Parameters
NAME SAC3-177-HNMR-redo
EXPNO 4
PROCNO 1

F2 - Acquisition Parameters
Date_ 20221001
Time 21.40 h
INSTRUM spect
PROBHD Z148658_0003 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 2.7262976 sec
RG 49.76
DW 41.600 use
DE 10.33 use
TE 296.4 K
D1 3.00000000 sec
TD0 1
SFO1 600.0087050 MHz
NUC1 1H
P0 5.17 use
P1 15.50 use
PLW1 13.23200035 W

F2 - Processing parameters
SI 65536
SF 600.0050076 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

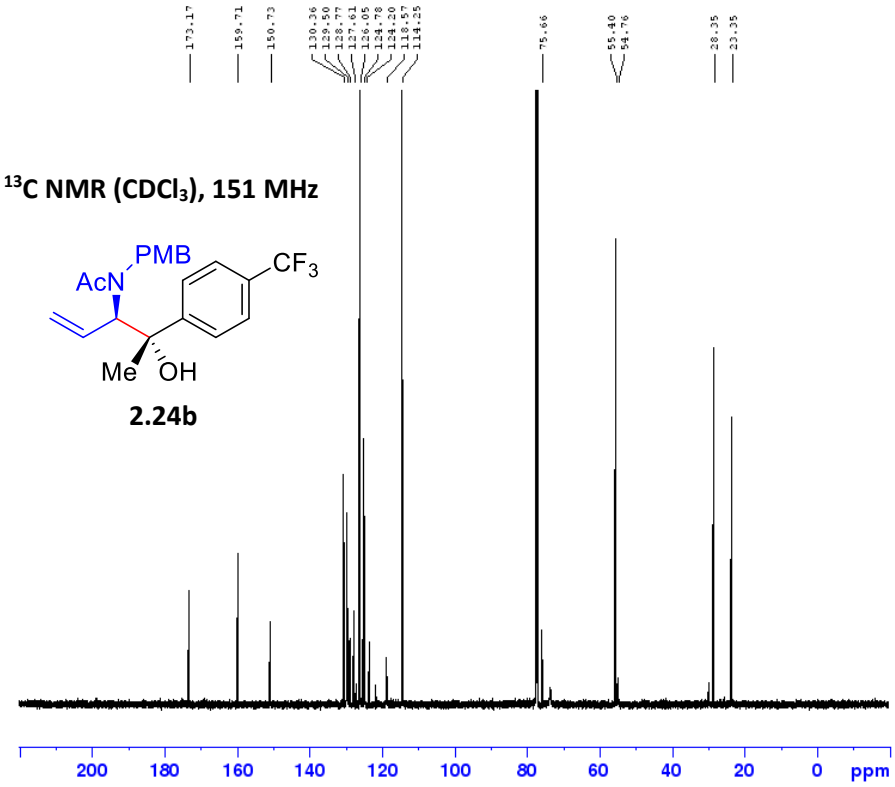



```
Current Data Parameters
NAME        SAC3-177-CNMR-redo
EXPNO                        5
PROCNO                       1

F2 - Acquisition Parameters
Date_                 20221002
Time                      3.46 h
INSTRUM                  spect
PROBHD    Z148658_0003 (
PULPROG                zgpg30
TD                      65536
SOLVENT                 CDCl3
NS                       1024
DS                          4
SWH                 36231.883 Hz
FIDRES              1.105709 Hz
AQ                  0.9043968 sec
RG                     199.73
DW                     13.800 use
DE                      6.50 use
TE                     298.1 K
D1                 4.00000000 sec
D11                0.03000000 sec
TD0                         1
SFO1               150.8864644 MHz
NUC1                       13C
P0                      4.00 use
P1                     12.00 use
PLW1               77.65699768 W
SFO2               600.0074000 MHz
NUC2                       1H
CPDPRG[2              waltz65
PCPD2                  70.00 use
PLW2               13.23200035 W
PLW12               0.64876997 W
PLW13               0.32633001 W

F2 - Processing parameters
SI                         32768
SF                 150.8713773 MHz
WDW                           EM
SSB          0
LB                      1.00 Hz
GB           0
PC                      1.40
```




```
Current Data Parameters
NAME        SAC3-009-HNMR-redo
EXPNO                        5
PROCNO                       1

F2 - Acquisition Parameters
Date_                 20221001
Time                     21.45 h
INSTRUM                  spect
PROBHD    Z148658_0003 (
PULPROG                  zg30
TD                      65536
SOLVENT                 CDCl3
NS                         16
DS                          2
SWH                12019.230 Hz
FIDRES              0.366798 Hz
AQ                  2.7262976 sec
RG                       99.5
DW                     41.600 use
DE                     10.33 use
TE                     296.4 K
D1                 3.00000000 sec
TD0                         1
SFO1               600.0087050 MHz
NUC1                       1H
P0                      5.17 use
P1                     15.50 use
PLW1               13.23200035 W

F2 - Processing parameters
SI                         65536
SF                 600.0050164 MHz
WDW                           EM
SSB          0
LB                      0.30 Hz
GB           0
PC                      1.00
```

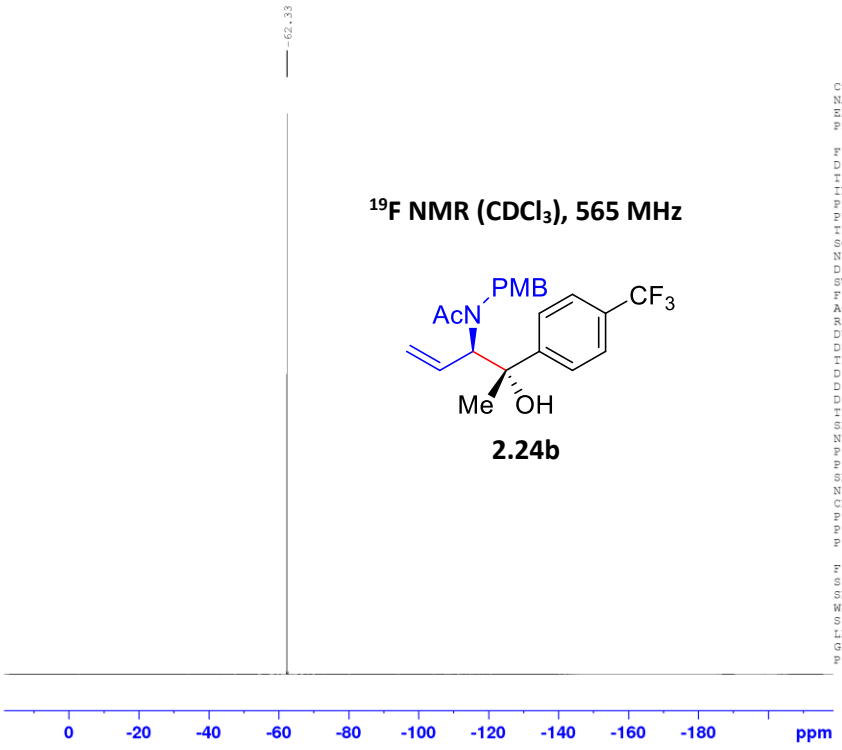
^{13}C NMR ($CDCl_3$), 151 MHz



2.24b

```
Current Data Parameters
NAME      SAC3-009-CNMR-redo
EXPNO                      7
PROCNO                     1

F2 - Acquisition Parameters
Date_            20221002
Time                2.17 h
INSTRUM            spect
PROBHD    Z148658_0003 (
PULPROG           zgpg30
TD                 65536
SOLVENT            CDCl3
NS                  1024
DS                     4
SWH            36231.883 Hz
FIDRES          1.105709 Hz
AQ              0.9043968 sec
RG                 199.73
DW                 13.800 use
DE                  6.50 use
TE                298.0 K
D1             4.00000000 sec
D11            0.03000000 sec
TD0                    1
SFO1         150.8864644 MHz
NUC1                13C
P0                 4.00 use
P1                12.00 use
PLW1         77.65699768 W
SFO2         600.0074000 MHz
NUC2                1H
CPDPRG[2         waltz65
PCPD2             70.00 use
PLW2         13.23200035 W
PLW12         0.64876997 W
PLW13         0.32633001 W

F2 - Processing parameters
SI                 32768
SF          150.8713773 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```

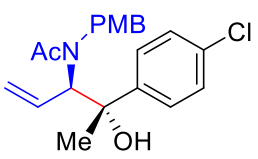
^{19}F NMR ($CDCl_3$), 565 MHz



2.24b

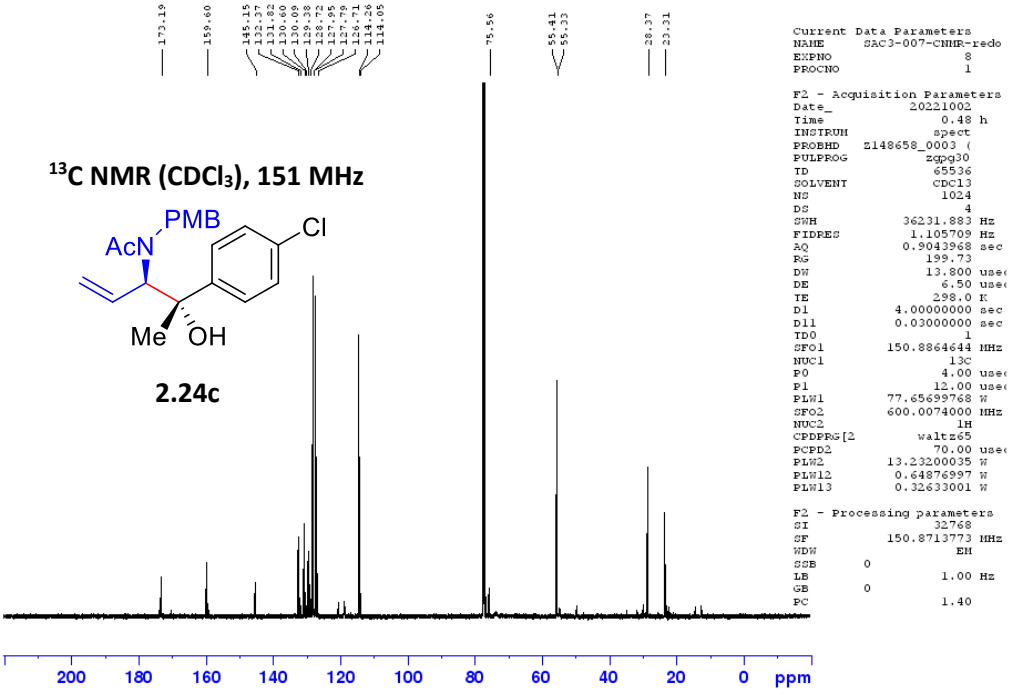
```
Current Data Parameters
NAME      SAC3-009-FNMR
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_            20221026
Time               10.50 h
INSTRUM            spect
PROBHD    Z148658_0003 (
PULPROG       zgfhigqn.2
TD                131072
SOLVENT            CDCl3
NS                    16
DS                     4
SWH           133928.578 Hz
FIDRES          2.043588 Hz
AQ              0.4893355 sec
RG                 199.73
DW                 3.733 usec
DE                  6.50 usec
TE                296.6 K
D1             1.00000000 sec
D11            0.03000000 sec
D12            0.00002000 sec
TD0                    1
SFO1          564.5123141 MHz
NUC1                19F
P1                15.00 usec
PLW1          26.76399994 W
SFO2          600.0074000 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2             70.00 usec
PLW2          13.23200035 W
PLW12          0.64876997 W

F2 - Processing parameters
SI                 65536
SF          564.5687710 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

^{1}H NMR ($CDCl_3$), 600 MHz



2.24c

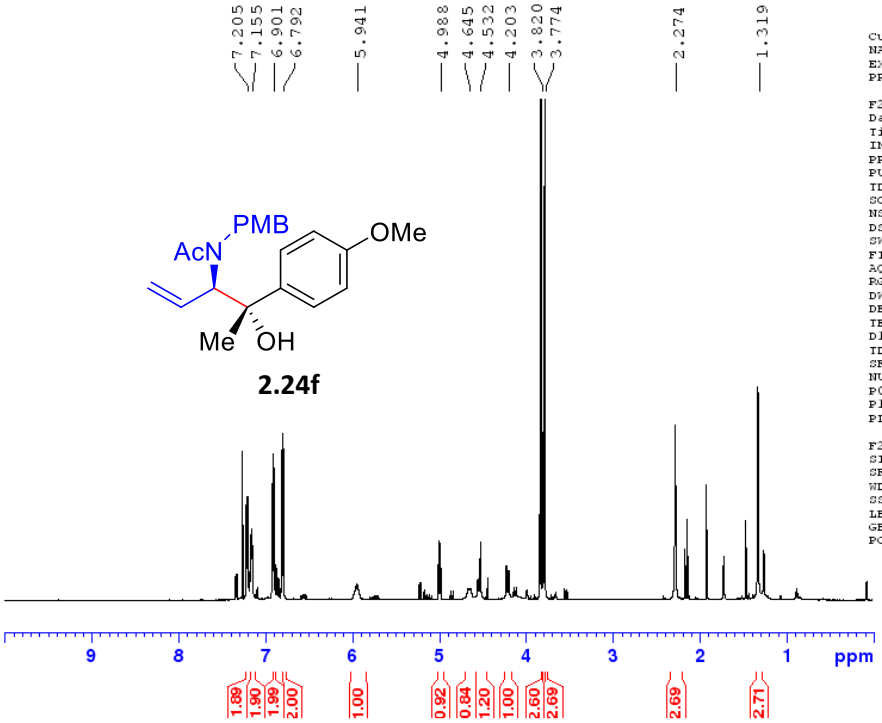

```
Current Data Parameters
NAME      SAC3-007-HNMR-redo
EXPNO                   10
PROCNO                   1

F2 - Acquisition Parameters
Date_              20221001
Time                 23.22 h
INSTRUM              spect
PROBHD    Z148658_0003 (
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH              12019.230 Hz
FIDRES           0.366798 Hz
AQ               2.7262976 sec
RG                    99.5
DW                  41.600 use
DE                  10.33 use
TE                  296.7 K
D1               3.00000000 sec
TD0                       1
SFO1          600.0087050 MHz
NUC1                   1H
P0                   5.17 use
P1                  15.50 use
PLW1          13.23200035 W

F2 - Processing parameters
SI                    65536
SF            600.0050158 MHz
WDW                     EM
SSB       0
LB                   0.30 Hz
GB        0
PC                   1.00
```



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

2.24c

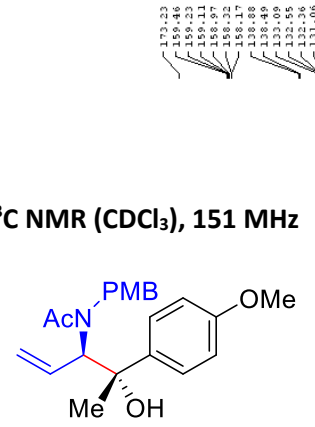
```
Current Data Parameters
NAME      SAC3-007-CNMR-redo
EXPNO                      8
PROCNO                     1

F2 - Acquisition Parameters
Date_              20221002
Time                   0.48 h
INSTRUH               spect
PROBHD    Z148658_0003 (
PULPROG              zgpg30
TD                    65536
SOLVENT               CDCl3
NS                     1024
DS                        4
SWH               36231.883 Hz
FIDRES             1.105709 Hz
AQ                 0.9043968 sec
RG                     199.73
DW                     13.800 use
DE                      6.50 use
TE                     298.0 K
D1                4.00000000 sec
D11               0.03000000 sec
TD0                        1
SFO1          150.8864644 MHz
NUC1                     13C
P0                      4.00 use
P1                     12.00 use
PLW1           77.65699768 W
SFO2          600.0074000 MHz
NUC2                     1H
CPDPRG[2              waltz65
PCPD2                  70.00 use
PLW2           13.23200035 W
PLW12           0.64876997 W
PLW13           0.32633001 W

F2 - Processing parameters
SI                     32768
SF            150.8713773 MHz
WDW                       EM
SSB          0
LB                      1.00 Hz
GB           0
PC                      1.40
```



2.24f

```
Current Data Parameters
NAME      SAC3-011-HNMR-redo
EXPNO                      7
PROCNO                     1

F2 - Acquisition Parameters
Date_              20221001
Time                  21.50 h
INSTRUH               spect
PROBHD    Z148658_0003 (
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH               12019.230 Hz
FIDRES             0.366798 Hz
AQ                 2.7262976 sec
RG                     106.9
DW                    41.600 use
DE                    10.33 use
TE                    296.4 K
D1                3.00000000 sec
TD0                        1
SFO1          600.0087050 MHz
NUC1                     1H
P0                     5.17 use
P1                    15.50 use
PLW1           13.23200035 W

F2 - Processing parameters
SI                     65536
SF            600.0050158 MHz
WDW                       EM
SSB          0
LB                      0.30 Hz
GB           0
PC                      1.00
```

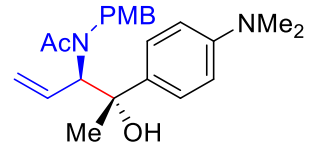
^{13}C NMR ($CDCl_3$), 151 MHz



2.24f

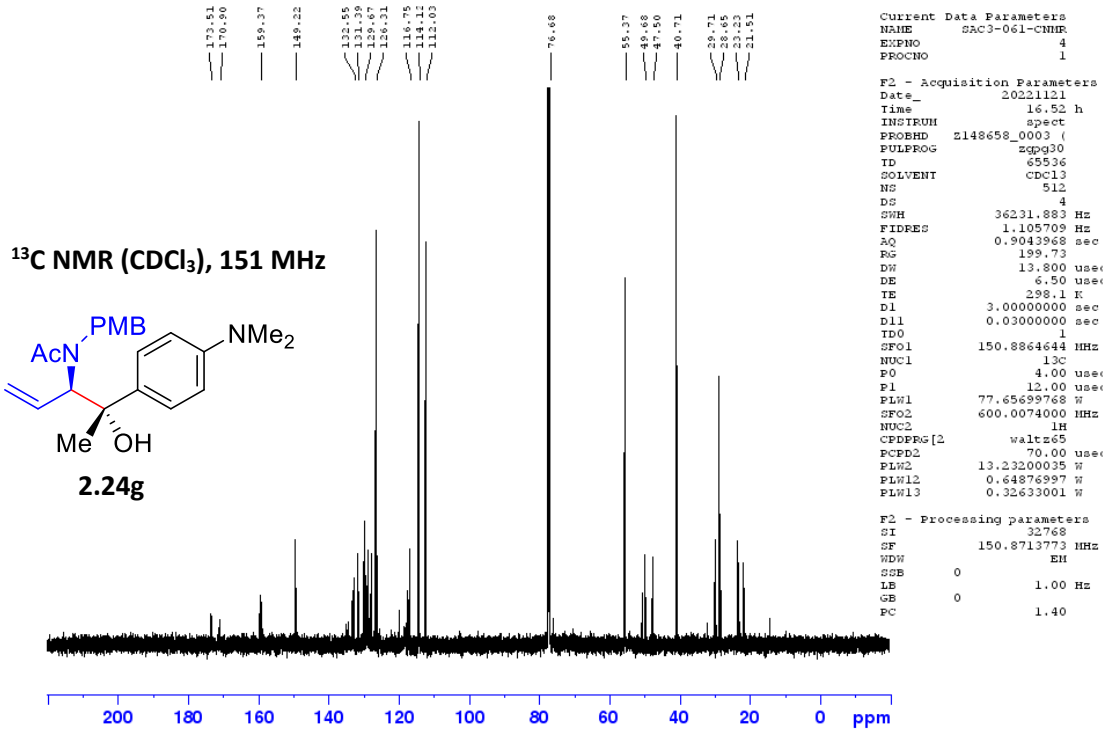

```
Current Data Parameters
NAME      SAC3-011-CNMR-redo
EXPNO                      1
PROCNO                     1

F2 - Acquisition Parameters
Date_              20221010
Time                   1.54 h
INSTRUM               spect
PROBHD    Z148658_0003 (
PULPROG              zgpg30
TD                    65536
SOLVENT               CDCl3
NS                     2048
DS                        4
SWH               36231.883 Hz
FIDRES             1.105709 Hz
AQ                 0.9043968 sec
RG                    199.73
DW                    13.800 use
DE                     6.50 use
TE                    298.5 K
D1                4.00000000 sec
D11               0.03000000 sec
TD0                       1
SFO1          150.8864644 MHz
NUC1                    13c
P0                     4.00 use
P1                    12.00 use
PLW1           77.65699768 W
SFO2          600.0074000 MHz
NUC2                    1H
CPDPRG[2            waltz65
PCPD2                 70.00 use
PLW2           13.23200035 W
PLW12           0.64876997 W
PLW13           0.32633001 W

F2 - Processing parameters
SI                    32768
SF            150.8713773 MHz
WDW                      EM
SSB          0
LB                     1.00 Hz
GB           0
PC                     1.40
```

^{1}H NMR ($CDCl_3$), 600 MHz



2.24g

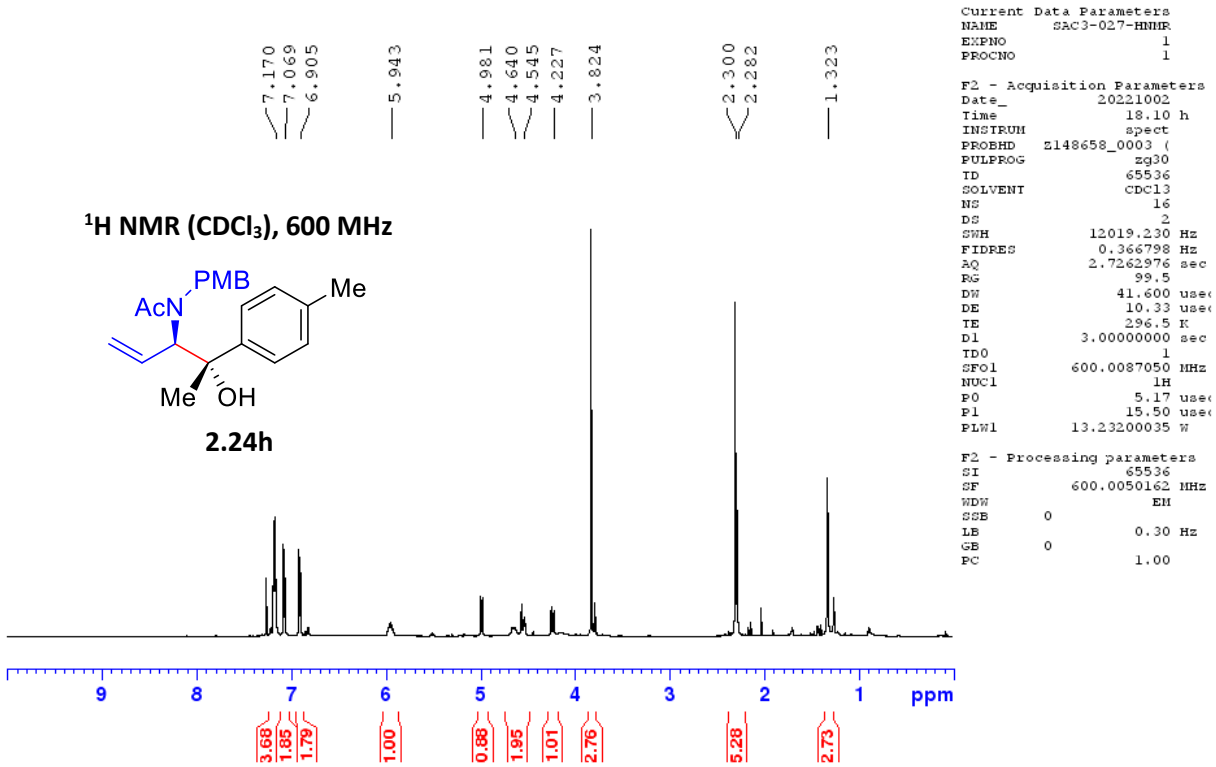

```
Current Data Parameters
NAME       SAC3-061-HNMR
EXPNO                  4
PROCNO                 1

F2 - Acquisition Parameters
Date_           20220501
Time               20.28 h
INSTRUM           spect
PROBHD    Z148658_0003 (
PULPROG             zg30
TD                 65536
SOLVENT           CDCl3
NS                    32
DS                     2
SWH           12019.230 Hz
FIDRES         0.366798 Hz
AQ             2.7262976 sec
RG                199.73
DW                41.600 use
DE                10.33 use
TE                296.2 K
D1             3.00000000 sec
TD0                    1
SFO1       600.0087050 MHz
NUC1                1H
P0                 5.17 use
P1                15.50 use
PLW1       13.23200035 W

F2 - Processing parameters
SI                 65536
SF         600.0050167 MHz
WDW                   EM
SSB          0
LB                 0.30 Hz
GB           0
PC                 1.00
```



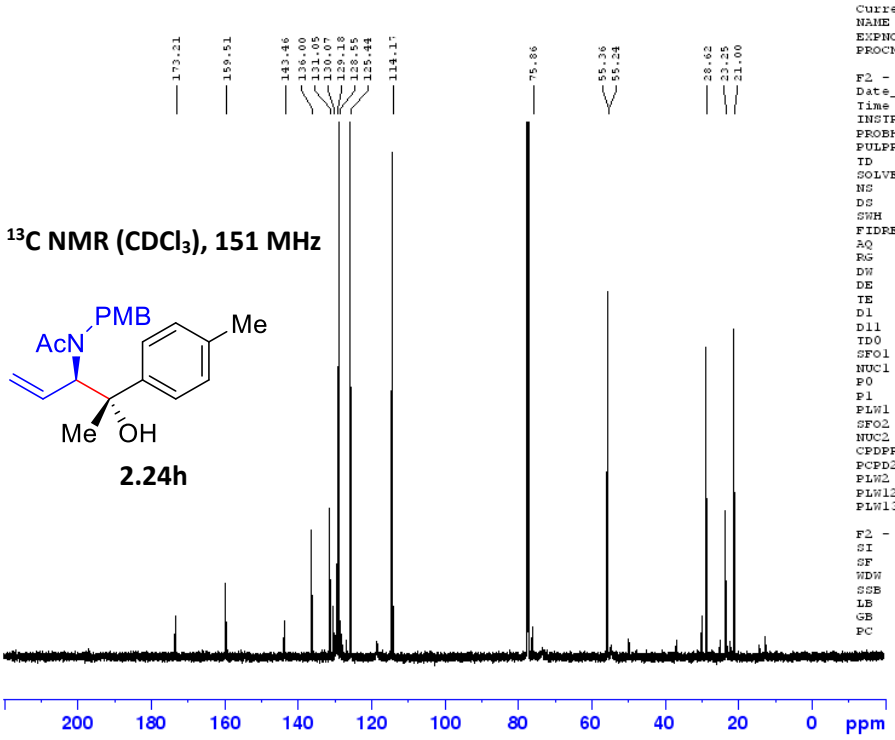
^{13}C NMR ($CDCl_3$), 151 MHz

2.24g

```
Current Data Parameters
NAME          SAC3-061-CNMR
EXPNO                    4
PROCNO                   1

F2 - Acquisition Parameters
Date_              20221121
Time                 16.52 h
INSTRUH              spect
PROBHD    Z148658_0003 (
PULPROG              zgpg30
TD                   65536
SOLVENT              CDCl3
NS                     512
DS                       4
SWH              36231.883 Hz
FIDRES            1.105709 Hz
AQ                0.9043968 sec
RG                   199.73
DW                   13.800 use
DE                    6.50 use
TE                  298.1 K
D1                3.00000000 sec
D11               0.03000000 sec
TD0                      1
SFO1           150.8864644 MHz
NUC1                   13C
P0                    4.00 use
P1                   12.00 use
PLW1           77.65699768 W
SFO2           600.0074000 MHz
NUC2                   1H
CPDPRG[2           waltz65
PCPD2                70.00 use
PLW2           13.23200035 W
PLW12           0.64876997 W
PLW13           0.32633001 W

F2 - Processing parameters
SI                   32768
SF             150.8713773 MHz
WDW                    EM
SSB          0
LB                    1.00 Hz
GB           0
PC                    1.40
```

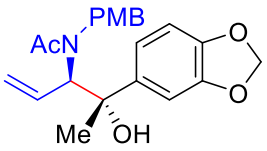



```
Current Data Parameters
NAME       SAC3-027-HNMR
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_           20221002
Time               18.10 h
INSTRUM             spect
PROBHD    Z148658_0003 (
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH            12019.230 Hz
FIDRES             0.366798 Hz
AQ                 2.7262976 sec
RG                    99.5
DW                   41.600 use
DE                   10.33 use
TE                   296.5 K
D1             3.00000000 sec
TD0                    1
SFO1           600.0087050 MHz
NUC1                  1H
P0                   5.17 use
P1                  15.50 use
PLW1           13.23200035 W

F2 - Processing parameters
SI                 65536
SF             600.0050162 MHz
WDW                   EM
SSB       0
LB                   0.30 Hz
GB        0
PC                   1.00
```




```
Current Data Parameters
NAME       SAC3-027-CNMR
EXPNO                   3
PROCNO                  1

F2 - Acquisition Parameters
Date_           20221002
Time               21.08 h
INSTRUM             spect
PROBHD    Z148658_0003 (
PULPROG           zgpg30
TD                 65536
SOLVENT            CDCl3
NS                  1024
DS                     4
SWH            36231.883 Hz
FIDRES             1.105709 Hz
AQ                 0.9043968 sec
RG                   199.73
DW                   13.800 use
DE                    6.50 use
TE                   298.2 K
D1             4.00000000 sec
D11            0.03000000 sec
TD0                    1
SFO1           150.8864644 MHz
NUC1                  13C
P0                   4.00 use
P1                  12.00 use
PLW1           77.65699768 W
SFO2           600.0074000 MHz
NUC2                  1H
CPDPRG[2          waltz65
PCPD2                70.00 use
PLW2           13.23200035 W
PLW12           0.64876997 W
PLW13           0.32633001 W

F2 - Processing parameters
SI                 32768
SF             150.8713773 MHz
WDW                   EM
SSB       0
LB                   1.00 Hz
GB        0
PC                   1.40
```

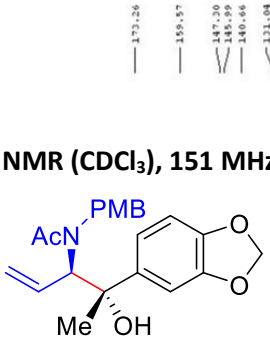
^{1}H NMR ($CDCl_3$), 600 MHz



2.24k


```
Current Data Parameters
NAME       SAC3-030-HNMR
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20221008
Time              20.29 h
INSTRUM           spect
PROBHD    Z148658_0003 (
PULPROG           zg30
TD               65536
SOLVENT          CDCl3
NS                  16
DS                   2
SWH           12019.230 Hz
FIDRES        0.366798 Hz
AQ            2.7262976 sec
RG                89.69
DW               41.600 usec
DE               10.33 usec
TE               296.4 K
D1            3.00000000 sec
TD0                  1
SFO1        600.0087050 MHz
NUC1                1H
P0                5.17 usec
P1               15.50 usec
PLW1         13.23200035 W

F2 - Processing parameters
SI               65536
SF          600.0050161 MHz
WDW                 EM
SSB       0
LB              0.30 Hz
GB        0
PC              1.00
```

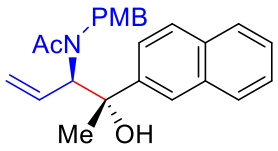
^{13}C NMR ($CDCl_3$), 151 MHz



2.24k

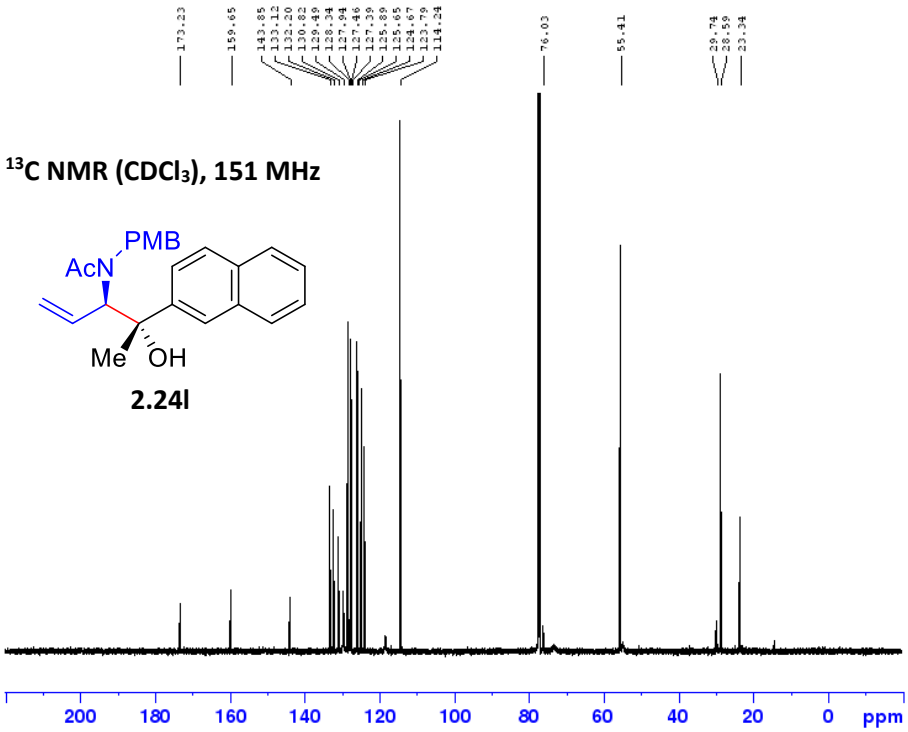

```
Current Data Parameters
NAME       SAC3-030-CHNMR
EXPNO                   3
PROCNO                  1

F2 - Acquisition Parameters
Date_            20221009
Time                5.01 h
INSTRUH              spect
PROBHD    Z148658_0003 (
PULPROG            zgpg30
TD                  65536
SOLVENT             CDCl3
NS                   1024
DS                      4
SWH             36231.883 Hz
FIDRES          1.105709 Hz
AQ              0.9043968 sec
RG                 199.73
DW                 13.800 use
DE                  6.50 use
TE                298.0 K
D1             4.00000000 sec
D11            0.03000000 sec
TD0                     1
SFO1          150.8864644 MHz
NUC1                  13C
P0                  4.00 use
P1                 12.00 use
PLW1          77.65699768 W
SFO2          600.0074000 MHz
NUC2                  1H
CPDPRG[2          waltz65
PCPD2              70.00 use
PLW2          13.23200035 W
PLW12          0.64876997 W
PLW13          0.32633001 W

F2 - Processing parameters
SI                  32768
SF            150.8713773 MHz
WDW                    EM
SSB                     0
LB                  1.00 Hz
GB                      0
PC                  1.40
```

^{1}H NMR ($CDCl_3$), 600 MHz

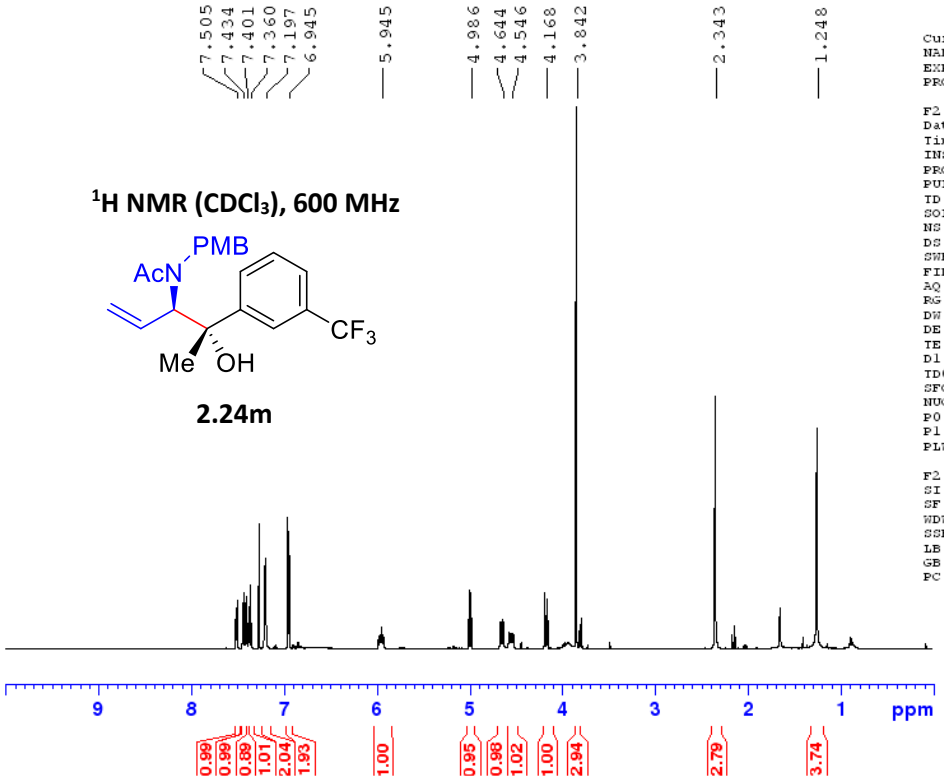


2.24l


```
Current Data Parameters
NAME       SAC3-034-HNMR
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20221008
Time               20.34 h
INSTRUH              spect
PROBHD    Z148658_0003 (
PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH             12019.230 Hz
FIDRES          0.366798 Hz
AQ              2.7262976 sec
RG                 68.55
DW                 41.600 use
DE                 10.33 use
TE                296.4 K
D1             3.00000000 sec
TD0                     1
SFO1          600.0087050 MHz
NUC1                  1H
P0                  5.17 use
P1                 15.50 use
PLW1          13.23200035 W

F2 - Processing parameters
SI                  65536
SF            600.0050156 MHz
WDW                    EM
SSB                     0
LB                  0.30 Hz
GB                      0
PC                  1.00
```



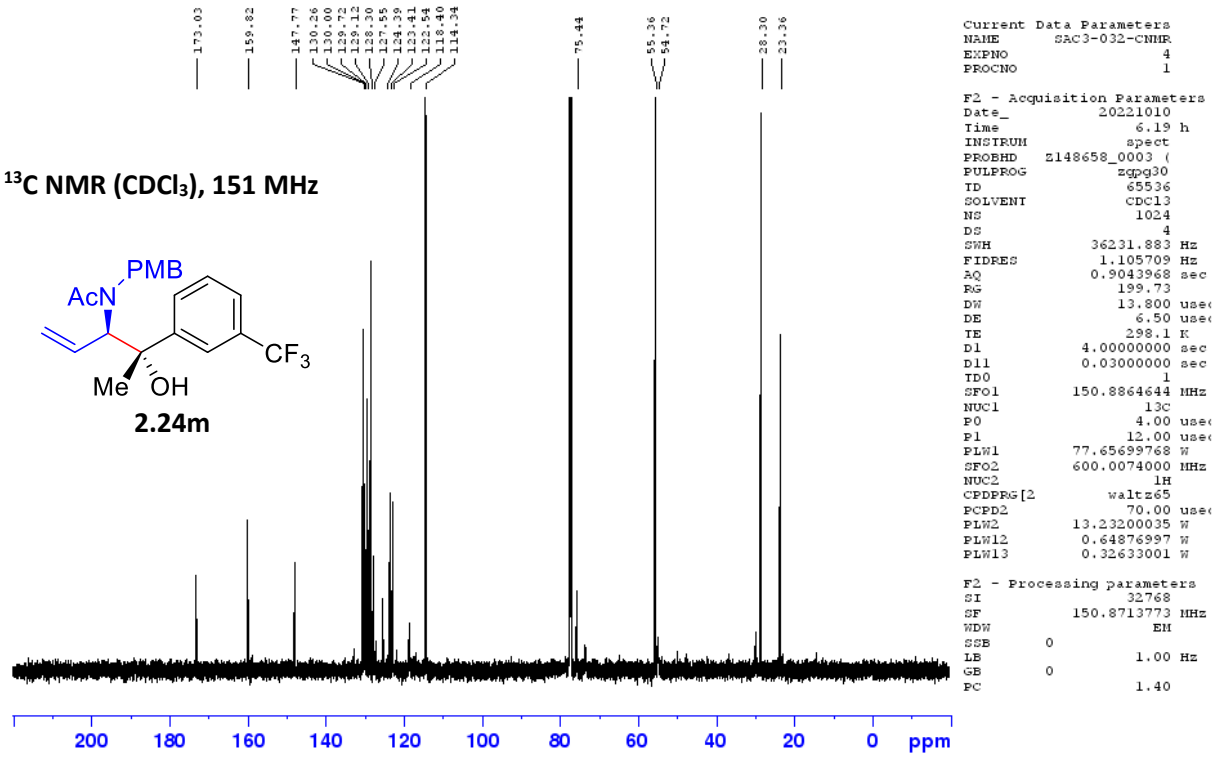

```
Current Data Parameters
NAME       SAC3-034-CNMR
EXPNO                 3
PROCNO                1

F2 - Acquisition Parameters
Date_           20221009
Time                6.29 h
INSTRUM            spect
PROBHD    Z148658_0003 (
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                 1024
DS                    4
SWH           36231.883 Hz
FIDRES         1.105709 Hz
AQ             0.9043968 sec
RG                199.73
DW                13.800 use
DE                 6.50 use
TE                298.0 K
D1             4.00000000 sec
D11            0.03000000 sec
TD0                   1
SFO1          150.8864644 MHz
NUC1                13C
P0                 4.00 use
P1                12.00 use
PLW1          77.65699768 W
SFO2          600.0074000 MHz
NUC2                1H
CPDPRG[2         waltz65
PCPD2             70.00 use
PLW2          13.23200035 W
PLW12          0.64876997 W
PLW13          0.32633001 W

F2 - Processing parameters
SI                32768
SF          150.8713773 MHz
WDW                  EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```



^{1}H NMR ($CDCl_3$), 600 MHz

2.24m

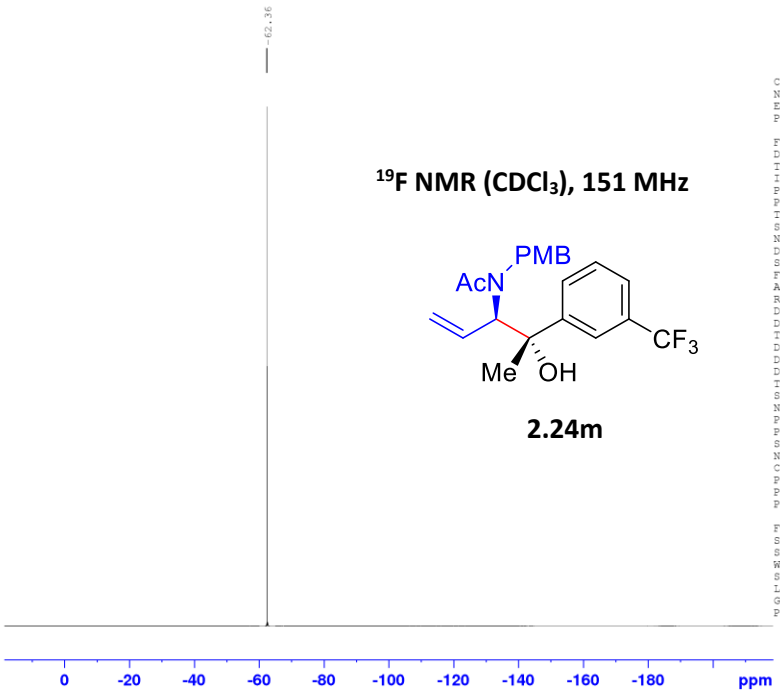
```
Current Data Parameters
NAME        SAC3-032-HNMR
EXPNO                  3
PROCNO                 1

F2 - Acquisition Parameters
Date_           20221010
Time               4.53 h
INSTRUM           spect
PROBHD    Z148658_0003 (
PULPROG           zg30
TD               65536
SOLVENT          CDCl3
NS                  16
DS                   2
SWH          12019.230 Hz
FIDRES        0.366798 Hz
AQ            2.7262976 sec
RG               135.67
DW                41.600 use
DE                10.33 use
TE               296.8 K
D1           3.00000000 sec
TD0                  1
SFO1        600.0087050 MHz
NUC1                1H
P0                5.17 use
P1               15.50 use
PLW1        13.23200035 W

F2 - Processing parameters
SI               65536
SF          600.0050150 MHz
WDW                 EM
SSB       0
LB             0.30 Hz
GB        0
PC             1.00
```



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

2.24m

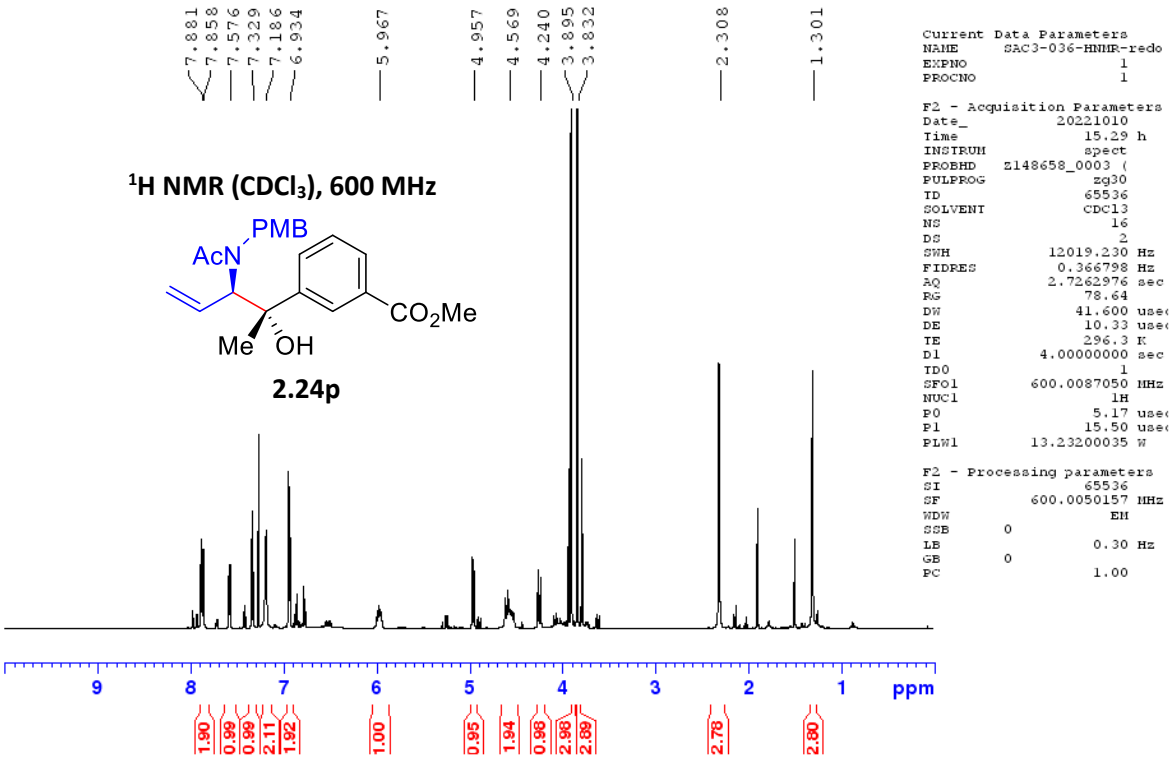
```
Current Data Parameters
NAME       SAC3-032-CNMR
EXPNO                 4
PROCNO                1

F2 - Acquisition Parameters
Date_          20221010
Time               6.19 h
INSTRUM           spect
PROBHD   Z148658_0003 (
PULPROG        zgpg30
TD              65536
SOLVENT         CDCl3
NS               1024
DS                  4
SWH         36231.883 Hz
FIDRES       1.105709 Hz
AQ           0.9043968 sec
RG              199.73
DW              13.800 use
DE               6.50 use
TE              298.1 K
D1          4.00000000 sec
D11         0.03000000 sec
TD0                 1
SFO1       150.8864644 MHz
NUC1              13C
P0               4.00 use
P1              12.00 use
PLW1       77.65699768 W
SFO2       600.0074000 MHz
NUC2              1H
CPDPRG[2       waltz65
PCPD2            70.00 use
PLW2       13.23200035 W
PLW12       0.64876997 W
PLW13       0.32633001 W

F2 - Processing parameters
SI                32768
SF         150.8713773 MHz
WDW                EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```



^{19}F NMR ($CDCl_3$), 151 MHz

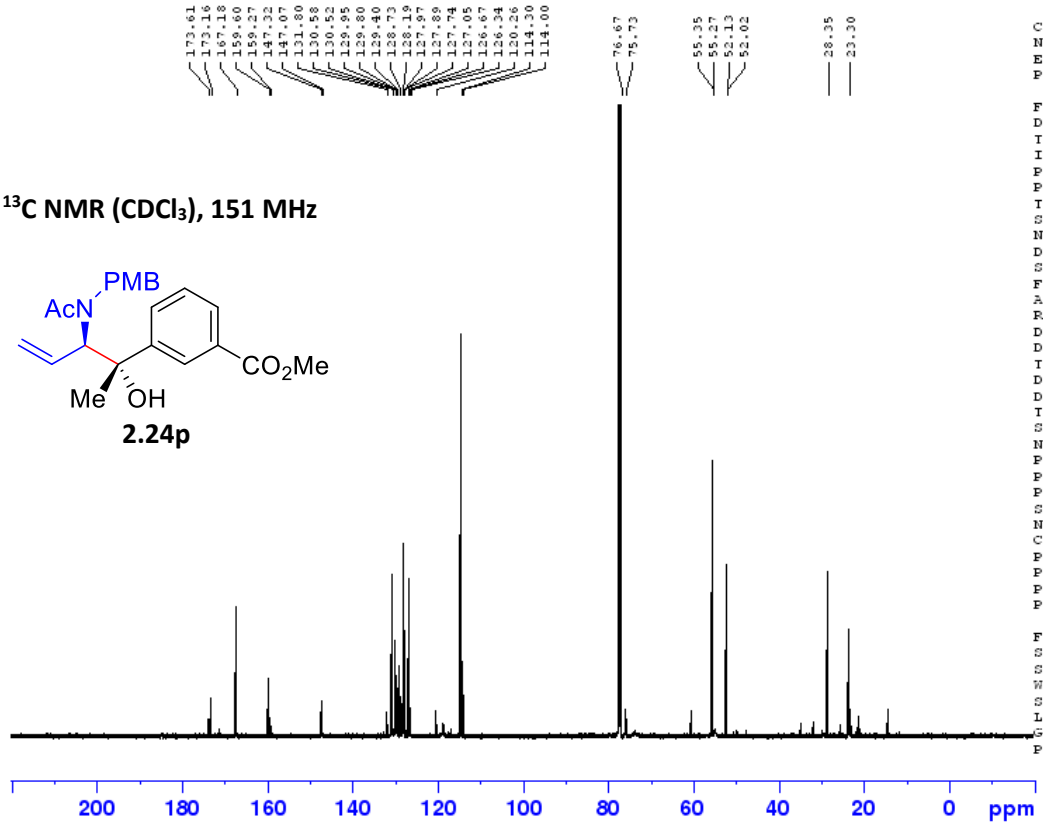
2.24m

```
Current Data Parameters
NAME       SAC3-032-FNMR
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_          20221113
Time              21.47 h
INSTRUM           spect
PROBHD   Z148658_0003 (
PULPROG       zgfhigqn.2
TD              131072
SOLVENT         CDCl3
NS                16
DS                 4
SWH         133928.578 Hz
FIDRES        2.043588 Hz
AQ           0.4893355 sec
RG              199.73
DW               3.733 usec
DE               6.50 usec
TE              296.5 K
D1          1.00000000 sec
D11         0.03000000 sec
D12         0.00002000 sec
TD0                 1
SFO1       564.5123141 MHz
NUC1              19F
P1              15.00 usec
PLW1       26.76399994 W
SFO2       600.0074000 MHz
NUC2              1H
CPDPRG[2       waltz16
PCPD2            70.00 usec
PLW2       13.23200035 W
PLW12       0.64876997 W

F2 - Processing parameters
SI              65536
SF         564.5687710 MHz
WDW                EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```



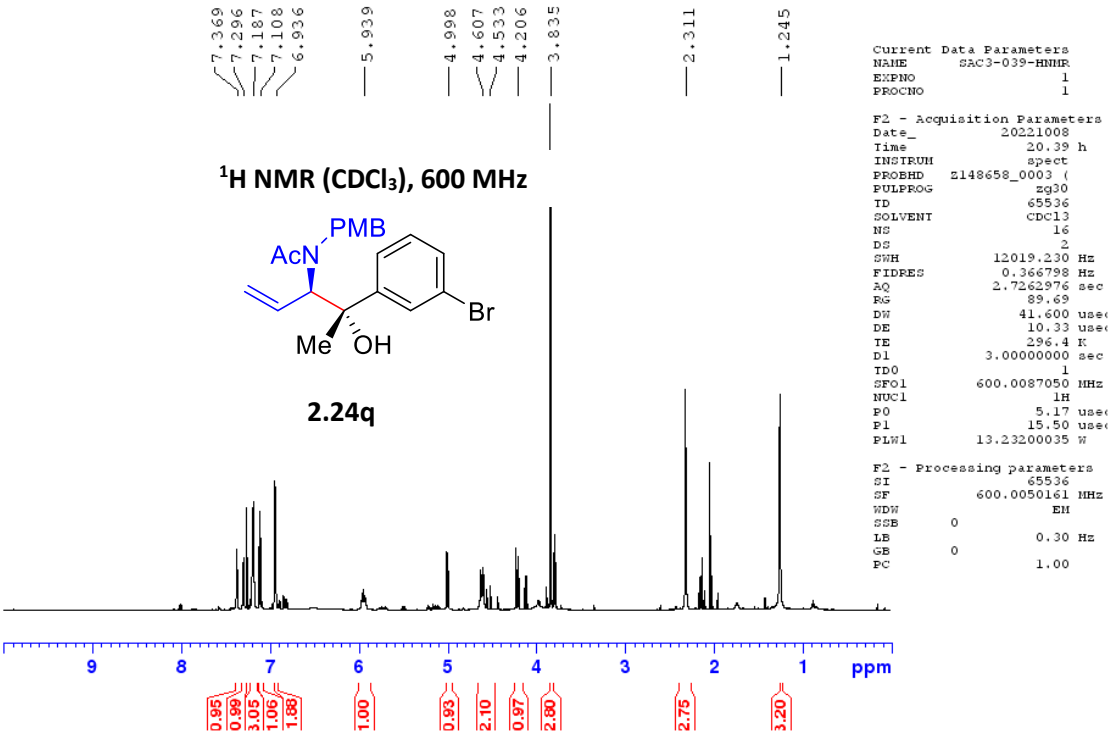

```
Current Data Parameters
NAME      SAC3-036-HNMR-redo
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_             20221010
Time                15.29 h
INSTRUM              spect
PROBHD    Z148658_0003 (
PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH             12019.230 Hz
FIDRES          0.366798 Hz
AQ              2.7262976 sec
RG                  78.64
DW                41.600 use
DE                10.33 use
TE                296.3 K
D1             4.00000000 sec
TD0                     1
SFO1          600.0087050 MHz
NUC1                   1H
P0                  5.17 use
P1                 15.50 use
PLW1          13.23200035 W

F2 - Processing parameters
SI                  65536
SF            600.0050157 MHz
WDW                    EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

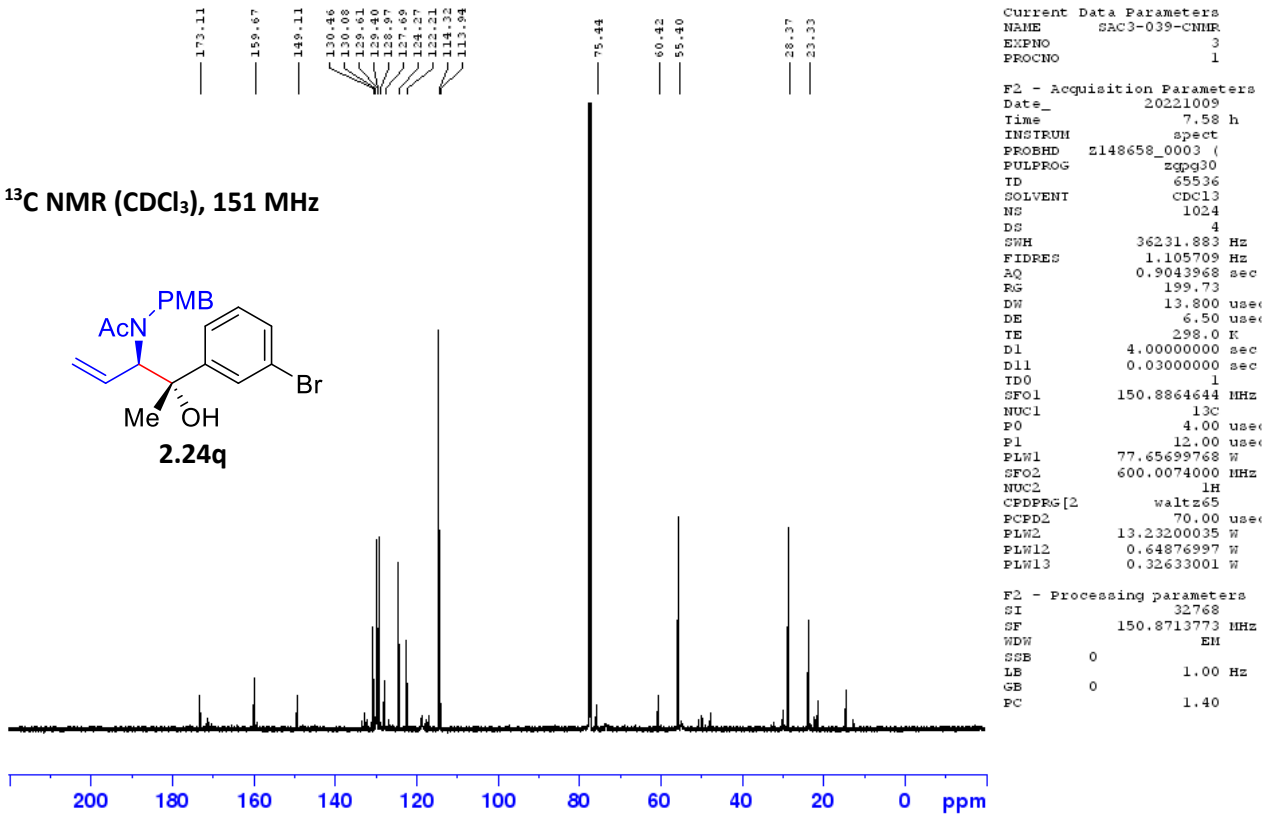
^{13}C NMR ($CDCl_3$), 151 MHz



2.24p

```
Current Data Parameters
NAME       SAC3-036-CNMR
EXPNO                 7
PROCNO                1

F2 - Acquisition Parameters
Date_           20221010
Time                7.50 h
INSTRUM            spect
PROBHD    Z148658_0003 (
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                 1024
DS                    4
SWH           36231.883 Hz
FIDRES         1.105709 Hz
AQ            0.9043968 sec
RG               199.73
DW               13.800 use
DE                6.50 use
TE               298.1 K
D1          4.00000000 sec
D11         0.03000000 sec
TD0                   1
SFO1        150.8864644 MHz
NUC1                13C
P0                 4.00 use
P1                12.00 use
PLW1        77.65699768 W
SFO2        600.0074000 MHz
NUC2                1H
CPDPRG[2        waltz65
PCPD2             70.00 use
PLW2        13.23200035 W
PLW12        0.64876997 W
PLW13        0.32633001 W

F2 - Processing parameters
SI                32768
SF          150.8713773 MHz
WDW                 EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```


7.369
7.296
7.187
7.108
6.936
5.939
4.998
4.607
4.533
4.206
3.835
2.311
1.245
¹H NMR (CDCl₃), 600 MHz
PMB
AcN
Br
Me
OH
2.24q
9
8
7
6
5
4
3
2
1
ppm
0.95
0.99
3.05
1.06
1.88
1.00
0.93
2.10
0.97
2.80
2.75
3.20
Current Data Parameters
NAME SAC3-039-HNMR
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20221008
Time 20.39 h
INSTRUM spect
PROBHD Z148658_0003 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 2.7262976 sec
RG 89.69
DW 41.600 use
DE 10.33 use
TE 296.4 K
D1 3.00000000 sec
TD0 1
SFO1 600.0087050 MHz
NUC1 1H
P0 5.17 use
P1 15.50 use
PLW1 13.23200035 W
F2 - Processing parameters
SI 65536
SF 600.0050161 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

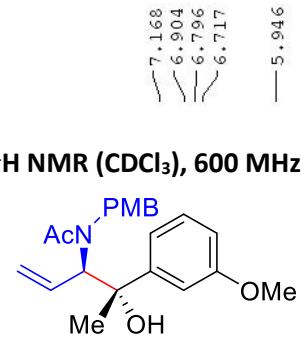


^{13}C NMR ($CDCl_3$), 151 MHz

2.24q

```
Current Data Parameters
NAME       SAC3-039-CNMR
EXPNO                 3
PROCNO                1

F2 - Acquisition Parameters
Date_          20221009
Time               7.58 h
INSTRUM           spect
PROBHD    Z148658_0003 (
PULPROG         zgpg30
TD                65536
SOLVENT           CDCl3
NS                 1024
DS                    4
SWH           36231.883 Hz
FIDRES         1.105709 Hz
AQ             0.9043968 sec
RG                199.73
DW                13.800 use
DE                 6.50 use
TE                298.0 K
D1           4.00000000 sec
D11          0.03000000 sec
TD0                   1
SFO1        150.8864644 MHz
NUC1               13C
P0                 4.00 use
P1                12.00 use
PLW1        77.65699768 W
SFO2        600.0074000 MHz
NUC2               1H
CPDPRG[2        waltz65
PCPD2             70.00 use
PLW2        13.23200035 W
PLW12        0.64876997 W
PLW13        0.32633001 W

F2 - Processing parameters
SI                32768
SF          150.8713773 MHz
WDW                EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```

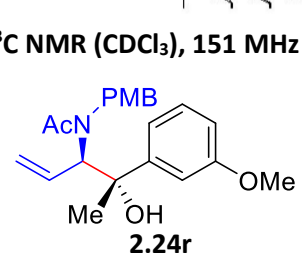
^{1}H NMR ($CDCl_3$), 600 MHz



2.24r


```
Current Data Parameters
NAME        SAC3-041-HNMR
EXPNO                   2
PROCNO                  1

F2 - Acquisition Parameters
Date_            20221008
Time                20.44 h
INSTRUM             spect
PROBHD    Z148658_0003 (
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             12019.230 Hz
FIDRES          0.366798 Hz
AQ              2.7262976 sec
RG                    61
DW                41.600 use
DE                10.33 use
TE                296.4 K
D1             3.00000000 sec
TD0                    1
SFO1          600.0087050 MHz
NUC1                  1H
P0                 5.17 use
P1                15.50 use
PLW1          13.23200035 W

F2 - Processing parameters
SI                 65536
SF            600.0050173 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

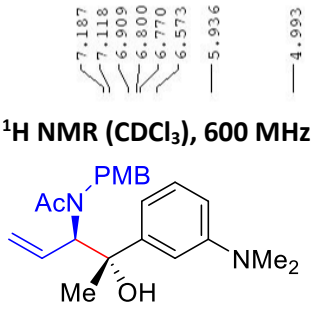
^{13}C NMR ($CDCl_3$), 151 MHz



2.24r


```
Current Data Parameters
NAME        SAC3-041-CNMR
EXPNO                  4
PROCNO                 1

F2 - Acquisition Parameters
Date_           20221009
Time               9.27 h
INSTRUM            spect
PROBHD    Z148658_0003 (
PULPROG         zgpg30
TD              65536
SOLVENT         CDCl3
NS                1024
DS                   4
SWH           36231.883 Hz
FIDRES         1.105709 Hz
AQ             0.9043968 sec
RG                199.73
DW                13.800 use
DE                 6.50 use
TE               298.2 K
D1           4.00000000 sec
D11          0.03000000 sec
TD0                  1
SFO1         150.8864644 MHz
NUC1                13C
P0                 4.00 use
P1                12.00 use
PLW1         77.65699768 W
SFO2         600.0074000 MHz
NUC2                1H
CPDPRG[2         waltz65
PCPD2             70.00 use
PLW2         13.23200035 W
PLW12         0.64876997 W
PLW13         0.32633001 W

F2 - Processing parameters
SI                 32768
SF           150.8713773 MHz
WDW                  EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```

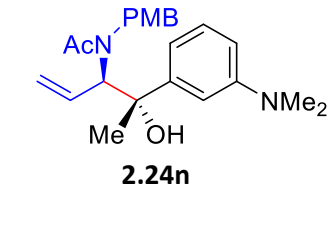
^{1}H NMR ($CDCl_3$), 600 MHz



2.24n


```
Current Data Parameters
NAME        SAC3-046-HNMR
EXPNO                   5
PROCNO                  1

F2 - Acquisition Parameters
Date_            20221107
Time                18.27 h
INSTRUM              spect
PROBHD    Z148658_0003 (
PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH             12019.230 Hz
FIDRES          0.366798 Hz
AQ              2.7262976 sec
RG                  68.55
DW                 41.600 usec
DE                 10.33 usec
TE                 296.5 K
D1              3.00000000 sec
TD0                     1
SFO1          600.0087050 MHz
NUC1                   1H
P0                  5.17 usec
P1                 15.50 usec
PLW1           13.23200035 W

F2 - Processing parameters
SI                  65536
SF            600.0050157 MHz
WDW                    EM
SSB         0
LB                  0.30 Hz
GB          0
PC                  1.00
```

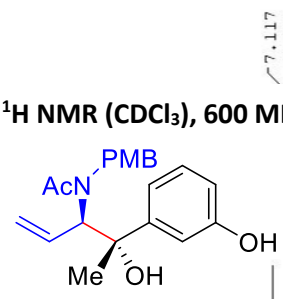
^{13}C NMR ($CDCl_3$), 151 MHz



2.24n

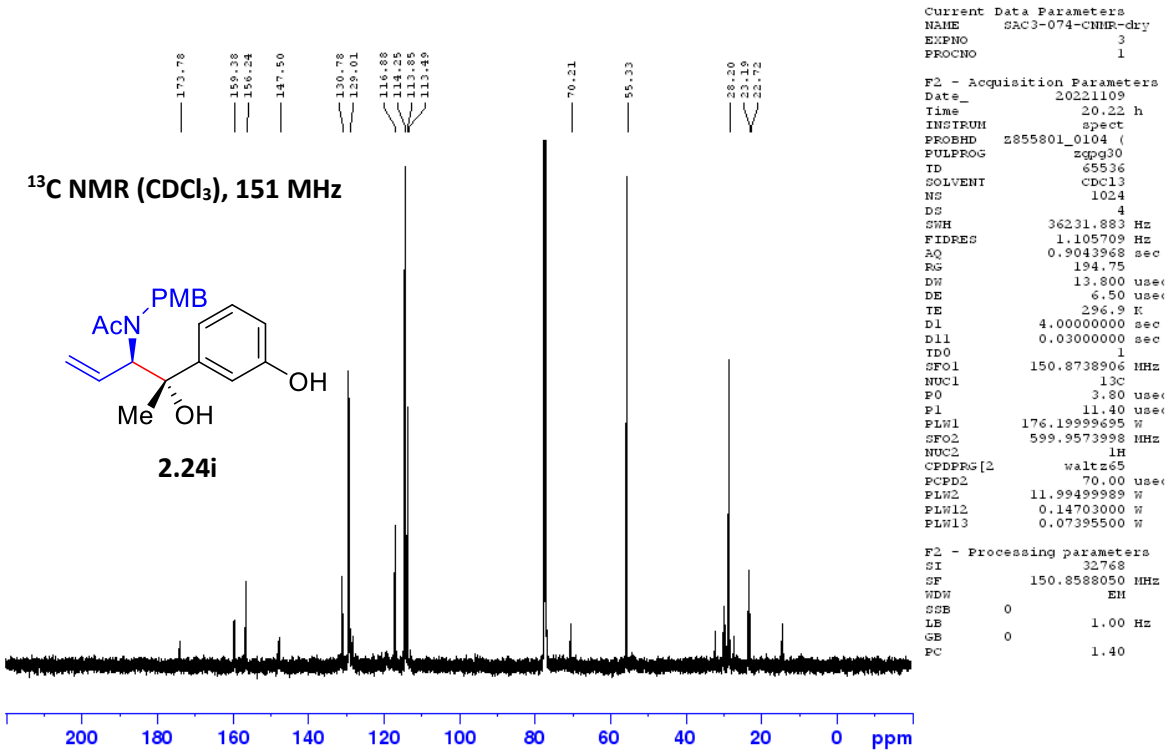

```
Current Data Parameters
NAME        SAC3-046-CNMR
EXPNO                   6
PROCNO                  1

F2 - Acquisition Parameters
Date_            20221107
Time                21.57 h
INSTRUM              spect
PROBHD    Z148658_0003 (
PULPROG            zgpg30
TD                  65536
SOLVENT             CDCl3
NS                   1024
DS                      4
SWH             36231.883 Hz
FIDRES          1.105709 Hz
AQ              0.9043968 sec
RG                 199.73
DW                 13.800 usec
DE                  6.50 usec
TE                 298.1 K
D1              4.00000000 sec
D11             0.03000000 sec
TD0                     1
SFO1          150.8864644 MHz
NUC1                   13C
P0                  4.00 usec
P1                 12.00 usec
PLW1           77.65699768 W
SFO2          600.0074000 MHz
NUC2                   1H
CPDPRG[2         waltz65
PCPD2              70.00 usec
PLW2           13.23200035 W
PLW12           0.64876997 W
PLW13           0.32633001 W

F2 - Processing parameters
SI                  32768
SF            150.8713773 MHz
WDW                    EM
SSB         0
LB                  1.00 Hz
GB          0
PC                  1.40
```

^{1}H NMR ($CDCl_3$), 600 MHz

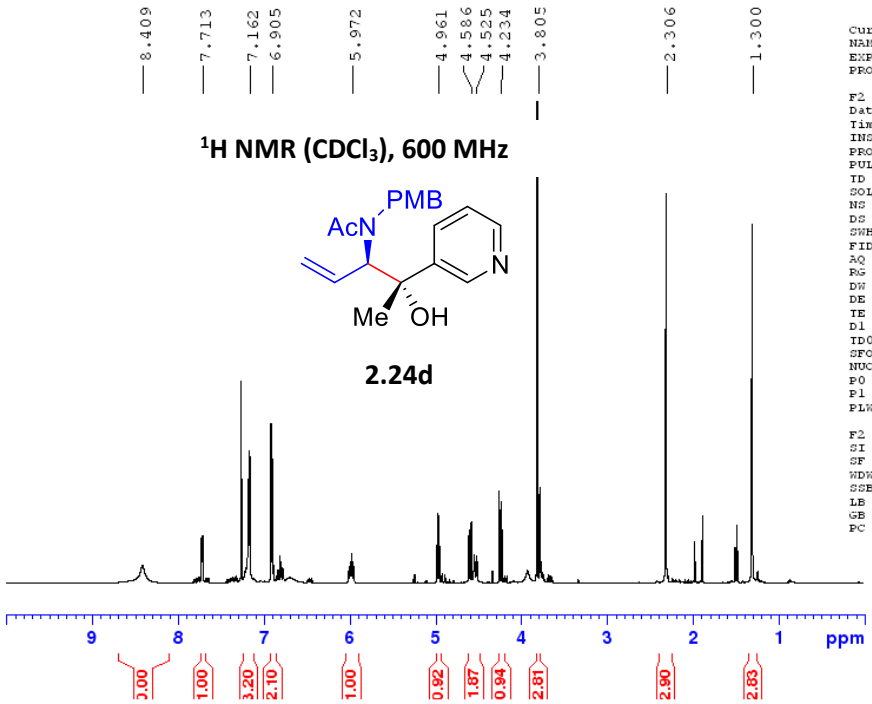


2.24i

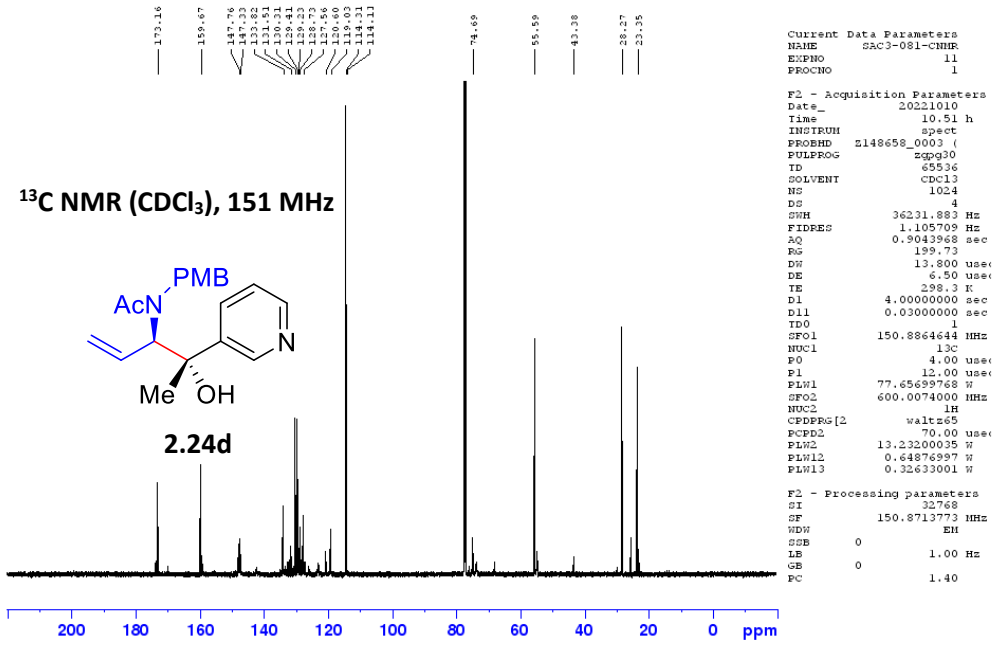

```
Current Data Parameters
NAME      SAC3-074-HNMR-dry
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20221109
Time                 18.55 h
INSTRUM              spect
PROBHD    Z855801_0104 (
PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH             12019.230 Hz
FIDRES          0.366798 Hz
AQ              2.7262976 sec
RG                  30.85
DW                 41.600 use
DE                 11.65 use
TE                 299.3 K
D1              3.00000000 sec
TD0                     1
SFO1         599.9587047 MHz
NUC1                   1H
P0                  2.58 use
P1                  7.75 use
PLW1         11.99499989 W

F2 - Processing parameters
SI                  65536
SF           599.9550158 MHz
WDW                    EM
SSB         0
LB                  0.30 Hz
GB          0
PC                  1.00
```



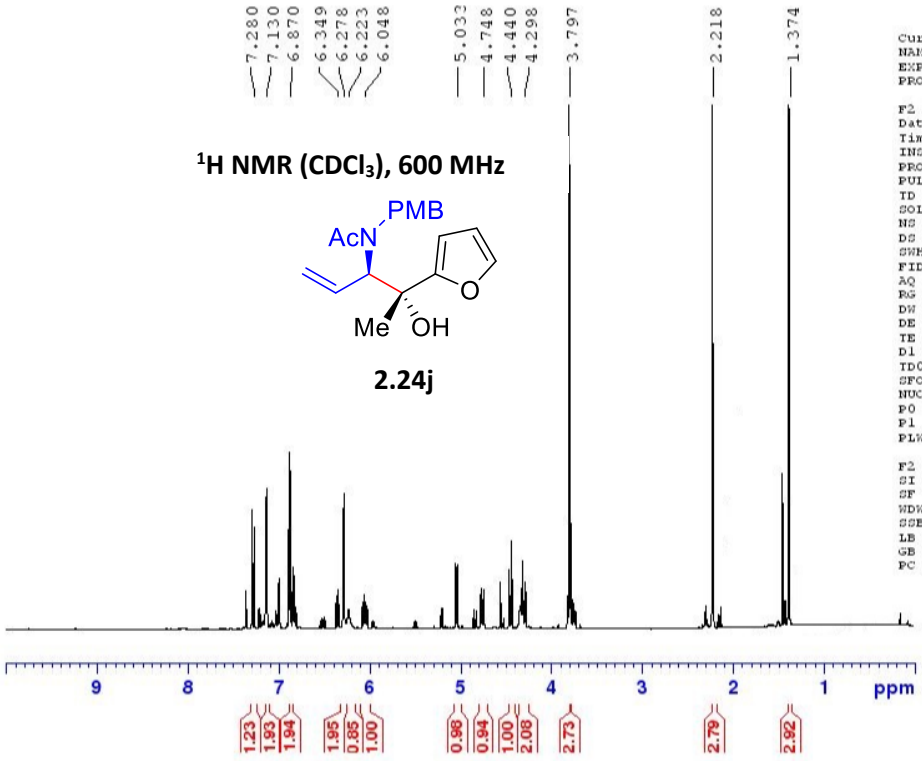

```
Current Data Parameters
NAME      SAC3-074-CNMR-dry
EXPNO                     3
PROCNO                    1

F2 - Acquisition Parameters
Date_            20221109
Time                20.22 h
INSTRUM              spect
PROBHD    Z855801_0104 (
PULPROG            zgpg30
TD                  65536
SOLVENT             CDCl3
NS                   1024
DS                      4
SWH             36231.883 Hz
FIDRES          1.105709 Hz
AQ              0.9043968 sec
RG                 194.75
DW                 13.800 use
DE                  6.50 use
TE                296.9 K
D1             4.00000000 sec
D11            0.03000000 sec
TD0                     1
SFO1          150.8738906 MHz
NUC1                  13C
P0                  3.80 use
P1                 11.40 use
PLW1         176.19999695 W
SFO2          599.9573998 MHz
NUC2                  1H
CPDPRG[2          waltz65
PCPD2              70.00 use
PLW2          11.99499989 W
PLW12          0.14703000 W
PLW13          0.07395500 W

F2 - Processing parameters
SI                    32768
SF            150.8588050 MHz
WDW                     EM
SSB       0
LB                  1.00 Hz
GB        0
PC                  1.40
```



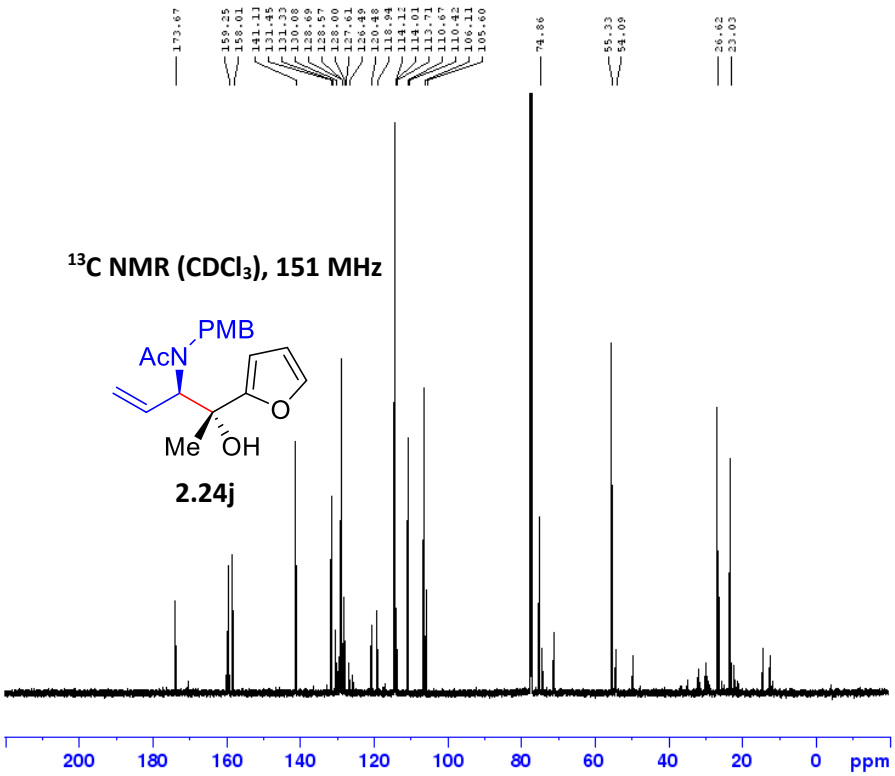

```
Current Data Parameters
NAME      SAC3-081-HNMR-redo
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_            20221009
Time                20.00 h
INSTRUM              spect
PROBHD    Z148658_0003 (
PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH             12019.230 Hz
FIDRES          0.366798 Hz
AQ              2.7262976 sec
RG                 68.55
DW                 41.600 use
DE                 10.33 use
TE                296.6 K
D1             3.00000000 sec
TD0                     1
SFO1          600.0087050 MHz
NUC1                  1H
P0                  5.17 use
P1                 15.50 use
PLW1          13.23200035 W

F2 - Processing parameters
SI                    65536
SF            600.0050160 MHz
WDW                     EM
SSB       0
LB                  0.30 Hz
GB        0
PC                  1.00
```



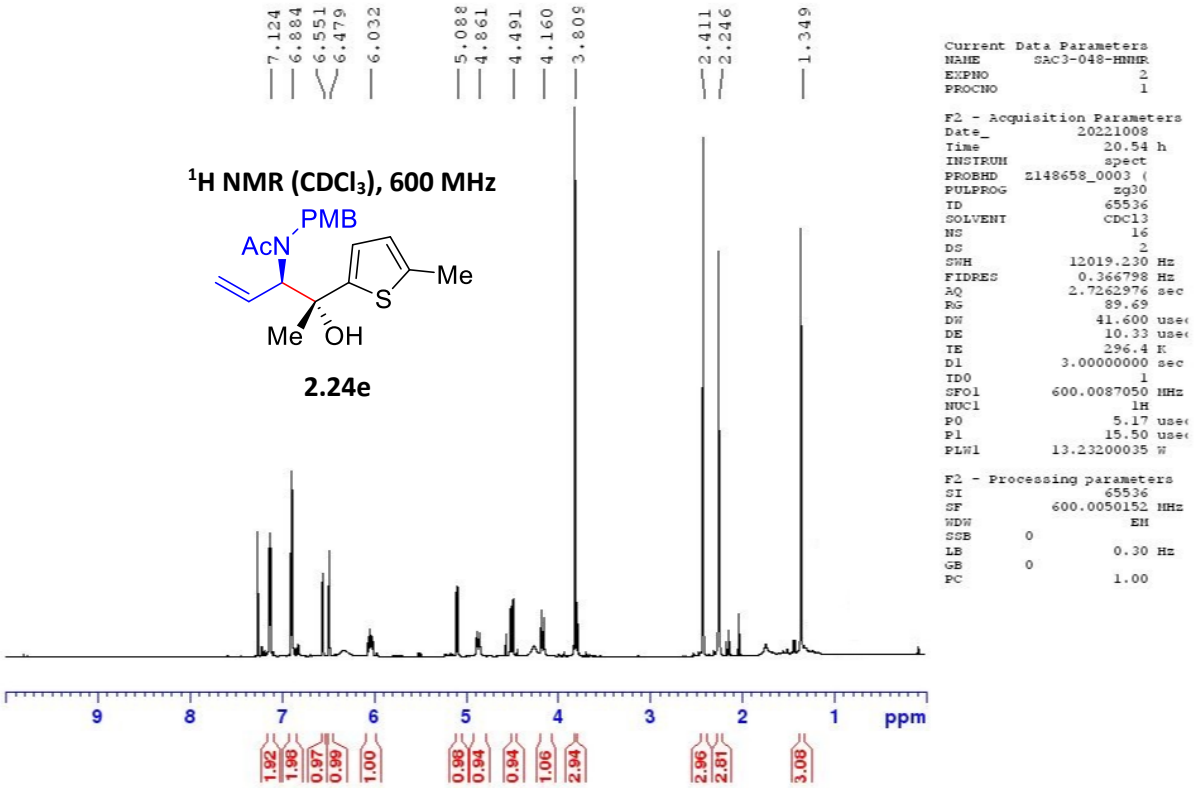

```
Current Data Parameters
NAME        SAC3-081-CNMR
EXPNO                  11
PROCNO                  1

F2 - Acquisition Parameters
Date_            20221010
Time                10.51 h
INSTRUM              spect
PROBHD    Z148658_0003 (
PULPROG           zgpg30
TD                 65536
SOLVENT            CDCl3
NS                  1024
DS                     4
SWH            36231.883 Hz
FIDRES         1.105709 Hz
AQ             0.9043968 sec
RG                199.73
DW                13.800 use
DE                 6.50 use
TE                298.3 K
D1            4.00000000 sec
D11           0.03000000 sec
TD0                    1
SFO1          150.8864644 MHz
NUC1                  13C
P0                 4.00 use
P1                12.00 use
PLW1          77.65699768 W
SFO2          600.0074000 MHz
NUC2                  1H
CPDPRG[2          waltz65
PCPD2             70.00 use
PLW2          13.23200035 W
PLW12          0.64876997 W
PLW13          0.32633001 W

F2 - Processing parameters
SI                 32768
SF            150.8713773 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```




```
Current Data Parameters
NAME        SAC3-026-HNMR
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_            20221002
Time                18.05 h
INSTRUM              spect
PROBHD    Z148658_0003 (
PULPROG              zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH            12019.230 Hz
FIDRES         0.366798 Hz
AQ             2.7262976 sec
RG                 68.55
DW                41.600 use
DE                10.33 use
TE                296.5 K
D1            3.00000000 sec
TD0                    1
SFO1          600.0087050 MHz
NUC1                  1H
P0                 5.17 use
P1                15.50 use
PLW1          13.23200035 W

F2 - Processing parameters
SI                 65536
SF            600.0050156 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```




```
Current Data Parameters
NAME       SAC3-026-CNMR
EXPNO                 3
PROCNO                1

F2 - Acquisition Parameters
Date_           20221002
Time              19.38 h
INSTRUM             spect
PROBHD   Z148658_0003 (
PULPROG           zgpg30
TD                65536
SOLVENT           CDCl3
NS                 1024
DS                    4
SWH           36231.883 Hz
FIDRES         1.105709 Hz
AQ             0.9043968 sec
RG                199.73
DW                13.800 use
DE                 6.50 use
TE                298.3 K
D1           4.00000000 sec
D11          0.03000000 sec
TD0                   1
SFO1        150.8864644 MHz
NUC1                13C
P0                 4.00 use
P1                12.00 use
PLW1        77.65699768 W
SFO2        600.0074000 MHz
NUC2                1H
CPDPRG[2        waltz65
PCPD2             70.00 use
PLW2        13.23200035 W
PLW12        0.64876997 W
PLW13        0.32633001 W

F2 - Processing parameters
SI                32768
SF          150.8713773 MHz
WDW                  EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```

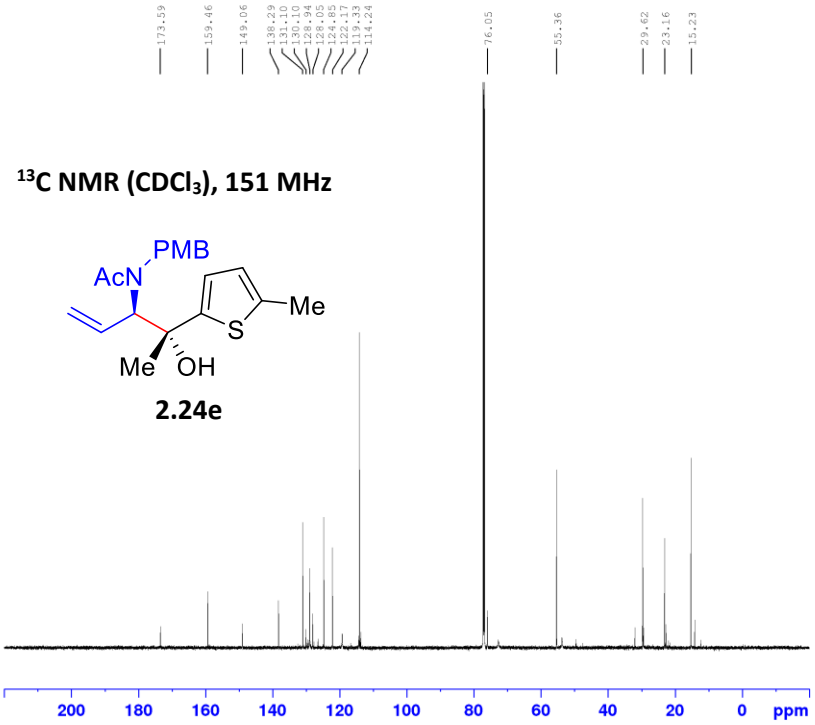


^{1}H NMR ($CDCl_3$), 600 MHz

2.24e

```
Current Data Parameters
NAME       SAC3-048-HNMR
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_          20221008
Time              20.54 h
INSTRUM           spect
PROBHD   Z148658_0003 (
PULPROG           zg30
TD               65536
SOLVENT          CDCl3
NS                  16
DS                   2
SWH           12019.230 Hz
FIDRES         0.366798 Hz
AQ             2.7262976 sec
RG                89.69
DW               41.600 use
DE               10.33 use
TE               296.4 K
D1            3.00000000 sec
TD0                  1
SFO1        600.0087050 MHz
NUC1                1H
P0                5.17 use
P1               15.50 use
PLW1        13.23200035 W

F2 - Processing parameters
SI               65536
SF          600.0050152 MHz
WDW                 EM
SSB       0
LB             0.30 Hz
GB        0
PC             1.00
```

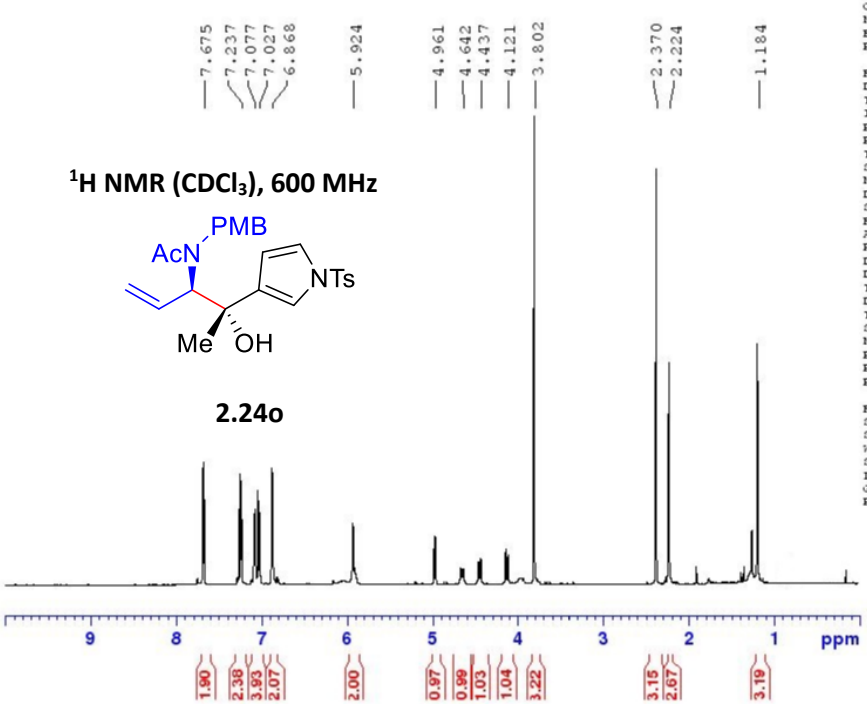
^{13}C NMR ($CDCl_3$), 151 MHz



2.24e

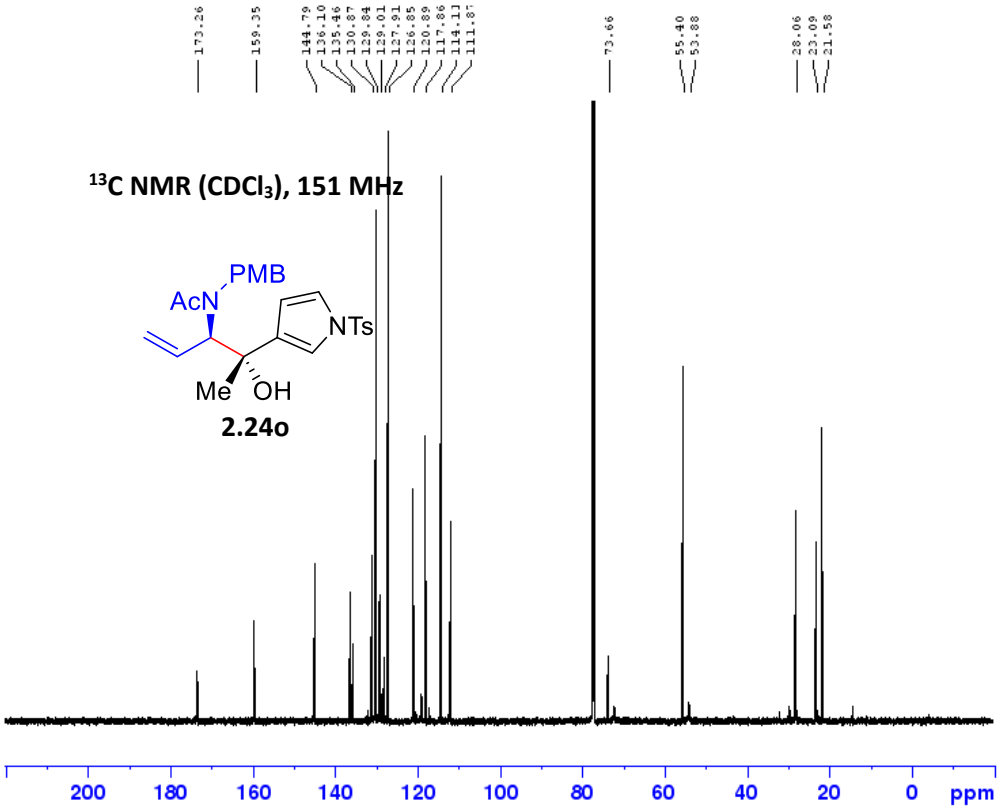
```
Current Data Parameters
NAME       SAC3-048-CNMR
EXPNO                 4
PROCNO                1

F2 - Acquisition Parameters
Date_           20221009
Time              12.25 h
INSTRUM             spect
PROBHD   Z148658_0003 (
PULPROG           zgpg30
TD                65536
SOLVENT           CDCl3
NS                 1024
DS                    4
SWH          36231.883 Hz
FIDRES        1.105709 Hz
AQ           0.9043968 sec
RG              199.73
DW             13.800 usec
DE              6.50 usec
TE              298.1 K
D1          4.00000000 sec
D11         0.03000000 sec
TD0                   1
SFO1        150.8864644 MHz
NUC1                13C
P0                 4.00 usec
P1                12.00 usec
PLW1        77.65699768 W
SFO2        600.0074000 MHz
NUC2                1H
CPDPRG[2         waltz65
PCPD2             70.00 usec
PLW2        13.23200035 W
PLW12        0.64876997 W
PLW13        0.32633001 W

F2 - Processing parameters
SI                32768
SF          150.8713773 MHz
WDW                  EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```

^{1}H NMR ($CDCl_3$), 600 MHz

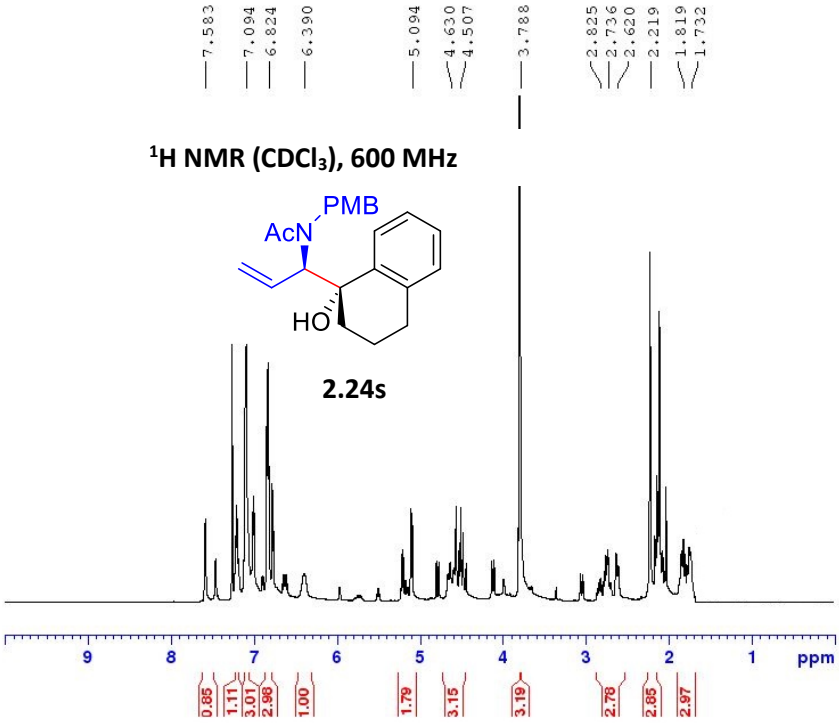


2.24o

```
Current Data Parameters
NAME      SAC3-052-HNMR-redo
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_           20221010
Time              15.15 h
INSTRUH             spect
PROBHD   Z148658_0003 (
PULPROG             zg30
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH          12019.230 Hz
FIDRES        0.366798 Hz
AQ           2.7262976 sec
RG                   61
DW             41.600 use
DE             10.33 use
TE              296.3 K
D1          4.00000000 sec
TD0                   1
SFO1        600.0087050 MHz
NUC1                1H
P0                 5.17 use
P1                15.50 use
PLW1        13.23200035 W

F2 - Processing parameters
SI                65536
SF          600.0050161 MHz
WDW                  EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```



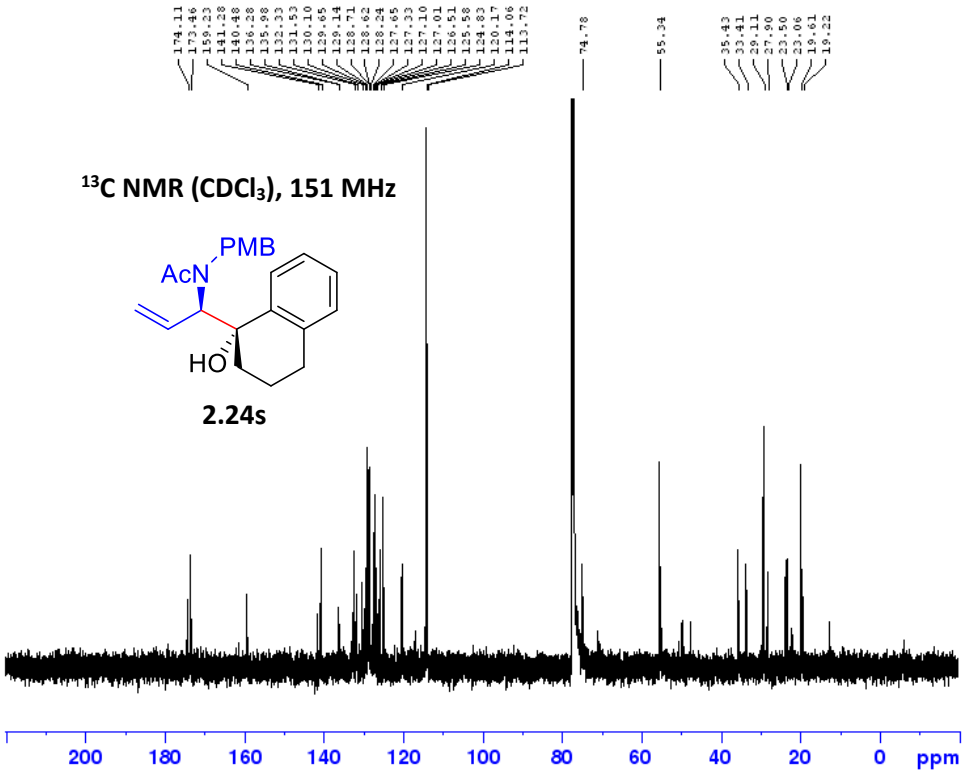

```
Current Data Parameters
NAME      SAC3-052-CNMR-new
EXPNO                    5
PROCNO                   1

F2 - Acquisition Parameters
Date_           20221103
Time               19.29 h
INSTRUM             spect
PROBHD    Z148658_0003 (
PULPROG           zgpg30
TD                65536
SOLVENT           CDCl3
NS                 1024
DS                    4
SWH           36231.883 Hz
FIDRES         1.105709 Hz
AQ             0.9043968 sec
RG                199.73
DW                13.800 use
DE                 6.50 use
TE                298.0 K
D1           4.00000000 sec
D11          0.03000000 sec
TD0                   1
SFO1         150.8864644 MHz
NUC1                 13C
P0                 4.00 use
P1                12.00 use
PLW1         77.65699768 W
SFO2         600.0074000 MHz
NUC2                 1H
CPDPRG[2         waltz65
PCPD2             70.00 use
PLW2         13.23200035 W
PLW12         0.64876997 W
PLW13         0.32633001 W

F2 - Processing parameters
SI                32768
SF           150.8713773 MHz
WDW                  EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```



^{1}H NMR ($CDCl_3$), 600 MHz

2.24s

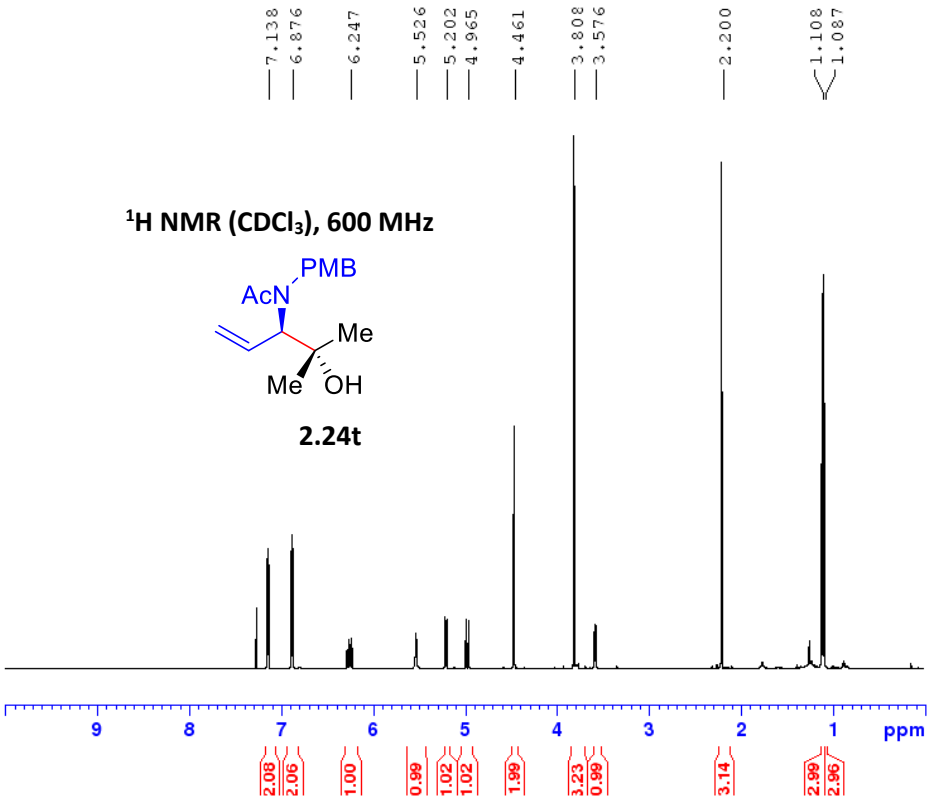
```
Current Data Parameters
NAME      SAC3-080-HNMR-new
EXPNO                9
PROCNO               1

F2 - Acquisition Parameters
Date_          20221103
Time              3.14 h
INSTRUM           spect
PROBHD   Z855801_0104 (
PULPROG           zg30
TD               65536
SOLVENT          CDCl3
NS                  16
DS                   2
SWH          12019.230 Hz
FIDRES        0.366798 Hz
AQ            2.7262976 sec
RG               89.24
DW              41.600 use
DE              11.65 use
TE              297.4 K
D1           3.00000000 sec
TD0                  1
SFO1         599.9587047 MHz
NUC1                 1H
P0                2.58 use
P1                7.75 use
PLW1         11.99499989 W

F2 - Processing parameters
SI               65536
SF           599.9550171 MHz
WDW                 EM
SSB       0
LB             0.30 Hz
GB        0
PC             1.00
```



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

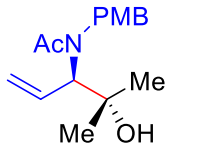
2.24s

```
Current Data Parameters
NAME      SAC3-080-HNMR-new
EXPNO               10
PROCNO               1

F2 - Acquisition Parameters
Date_          20221103
Time              6.07 h
INSTRUM           spect
PROBHD   Z855801_0104 (
PULPROG         zgpg30
TD               65536
SOLVENT          CDCl3
NS                2056
DS                   4
SWH          36231.883 Hz
FIDRES        1.105709 Hz
AQ            0.9043968 sec
RG               194.75
DW              13.800 use
DE               6.50 use
TE              297.6 K
D1           4.00000000 sec
D11          0.03000000 sec
TD0                  1
SFO1         150.8738906 MHz
NUC1                13C
P0                3.80 use
P1               11.40 use
PLW1        176.19999695 W
SFO2         599.9573998 MHz
NUC2                 1H
CPDPRG[2         waltz65
PCPD2             70.00 use
PLW2         11.99499989 W
PLW12         0.14703000 W
PLW13         0.07395500 W

F2 - Processing parameters
SI               32768
SF           150.8588050 MHz
WDW                 EM
SSB       0
LB             1.00 Hz
GB        0
PC             1.40
```



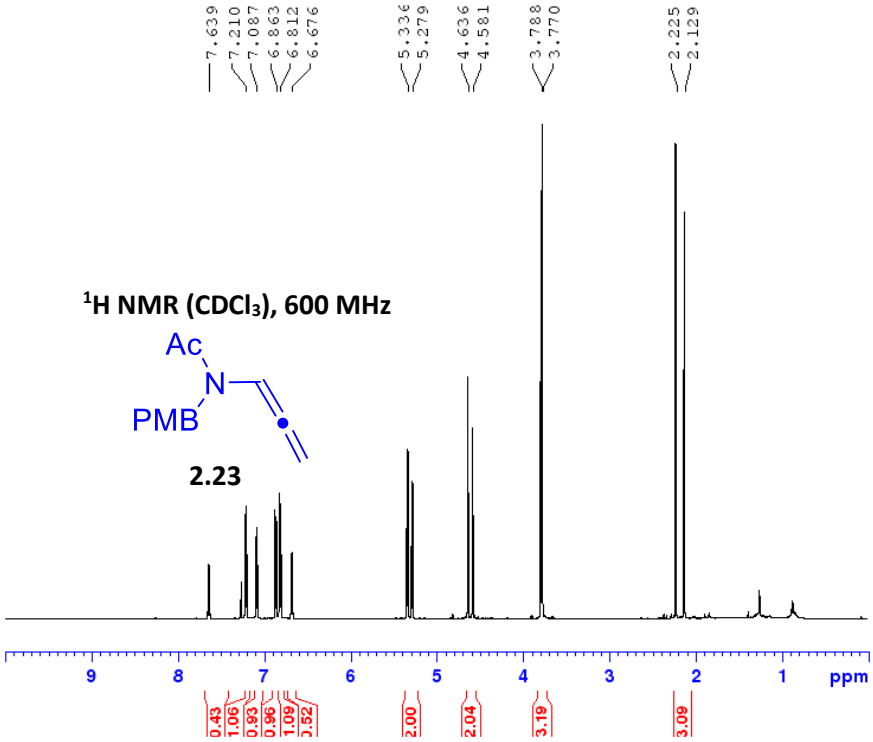

```
Current Data Parameters
NAME        SAC3-056-HNMR
EXPNO                   5
PROCNO                  1

F2 - Acquisition Parameters
Date_            20221107
Time                18.32 h
INSTRUM              spect
PROBHD    Z148658_0003 (
PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH             12019.230 Hz
FIDRES              0.366798 Hz
AQ               2.7262976 sec
RG                  106.9
DW                 41.600 use
DE                 10.33 use
TE                 296.4 K
D1              3.00000000 sec
TD0                     1
SFO1          600.0087050 MHz
NUC1                   1H
P0                  5.17 use
P1                 15.50 use
PLW1           13.23200035 W

F2 - Processing parameters
SI                  65536
SF            600.0050156 MHz
WDW                    EM
SSB         0
LB                  0.30 Hz
GB          0
PC                  1.00
```

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



2.24t

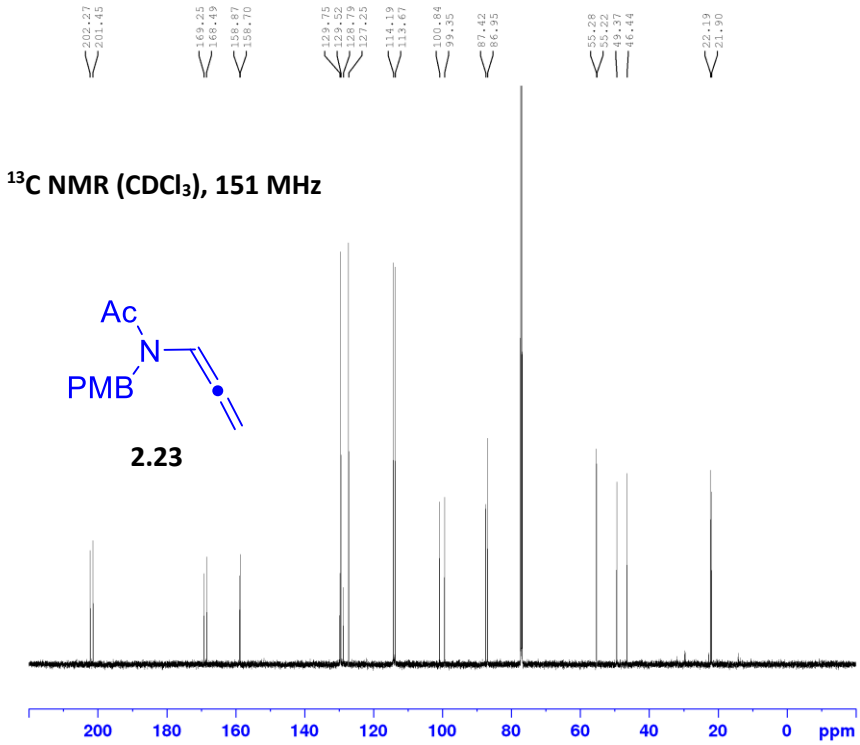

```
Current Data Parameters
NAME       SAC3-056-CNMR
EXPNO                 7
PROCNO                1

F2 - Acquisition Parameters
Date_          20221107
Time              23.26 h
INSTRUM           spect
PROBHD    Z148658_0003 (
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                 1024
DS                    4
SWH           36231.883 Hz
FIDRES         1.105709 Hz
AQ             0.9043968 sec
RG                199.73
DW                13.800 use
DE                 6.50 use
TE                298.1 K
D1            4.00000000 sec
D11           0.03000000 sec
TD0                   1
SFO1          150.8864644 MHz
NUC1                 13C
P0                 4.00 use
P1                12.00 use
PLW1          77.65699768 W
SFO2          600.0074000 MHz
NUC2                 1H
CPDPRG[2          waltz65
PCPD2             70.00 use
PLW2          13.23200035 W
PLW12          0.64876997 W
PLW13          0.32633001 W

F2 - Processing parameters
SI                32768
SF          150.8713773 MHz
WDW                  EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```



^{1}H NMR ($CDCl_3$), 600 MHz

2.23

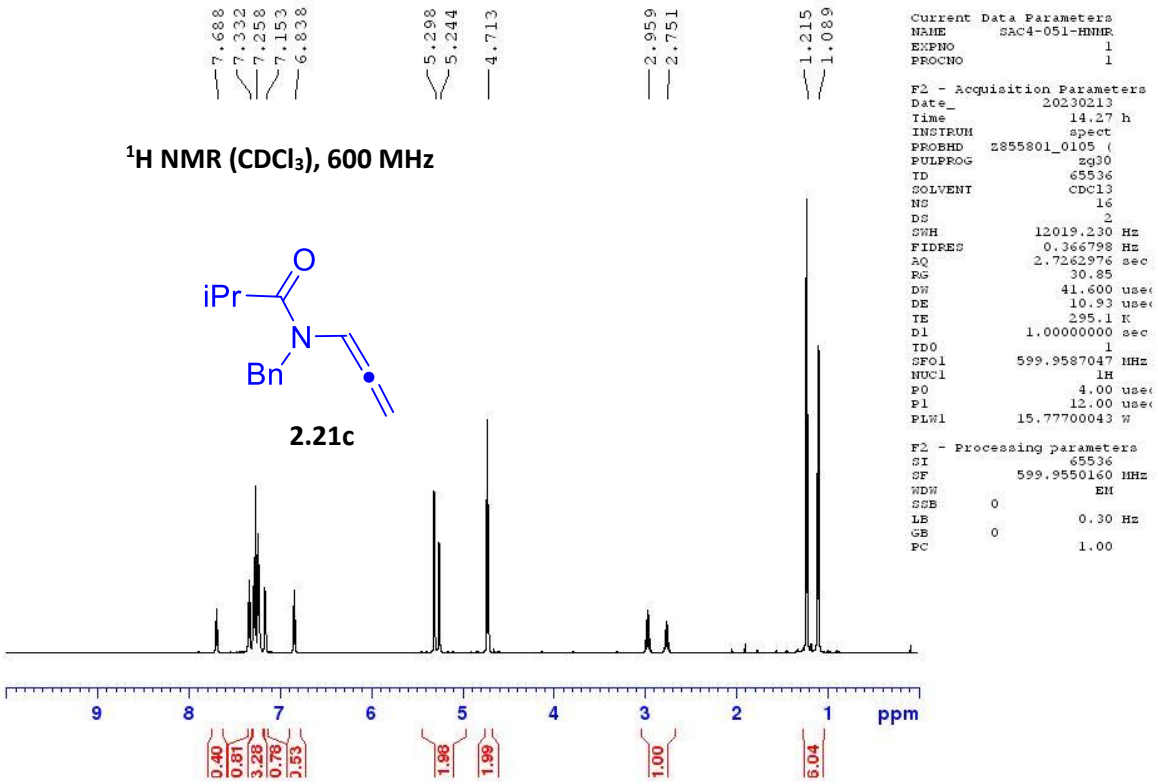
```
Current Data Parameters
NAME      Allene-HNMR-Dry
EXPNO                   3
PROCNO                  1

F2 - Acquisition Parameters
Date_              20221107
Time                 17.59 h
INSTRUM              spect
PROBHD    Z148658_0003 (
PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH             12019.230 Hz
FIDRES          0.366798 Hz
AQ              2.7262976 sec
RG                  68.55
DW                 41.600 usec
DE                 10.33 usec
TE                 296.3 K
D1              3.00000000 sec
TD0                     1
SFO1           600.0087050 MHz
NUC1                   1H
P0                  5.17 usec
P1                 15.50 usec
PLW1           13.23200035 W

F2 - Processing parameters
SI                  65536
SF             600.0050154 MHz
WDW                    EM
SSB         0
LB                  0.30 Hz
GB          0
PC                  1.00
```



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

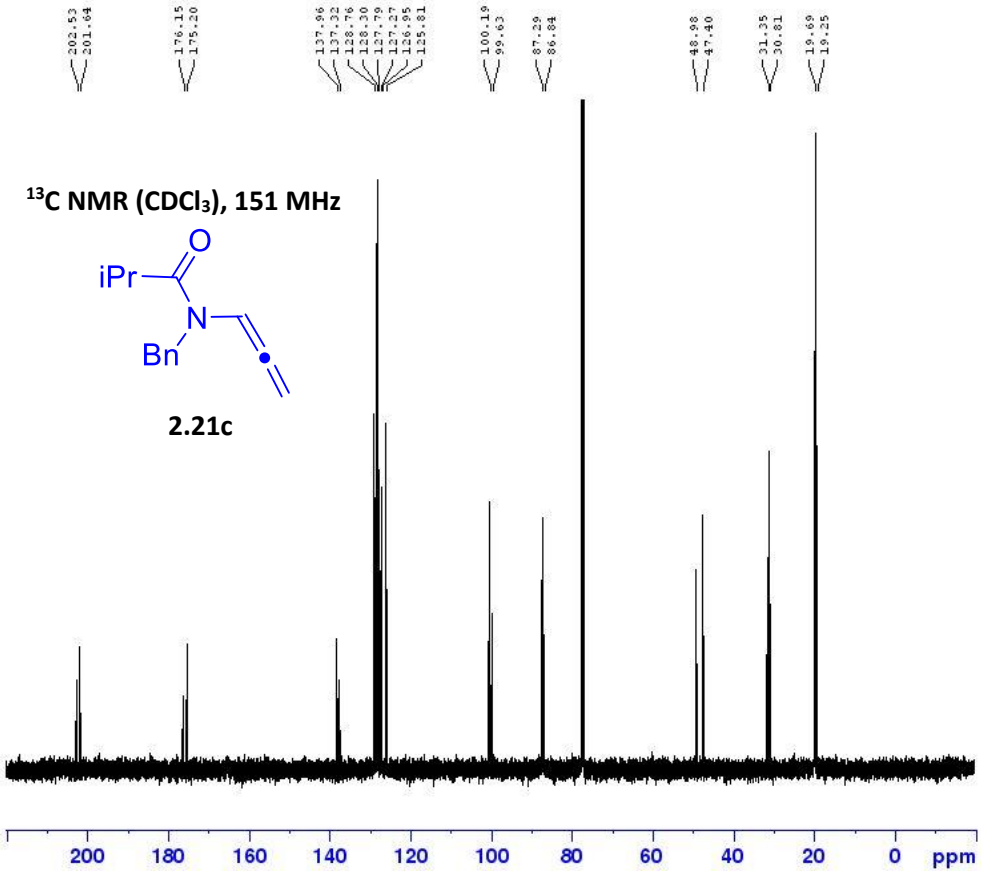
2.23

```
Current Data Parameters
NAME      Allene-CNMR-Dry
EXPNO                   4
PROCNO                  1

F2 - Acquisition Parameters
Date_              20221107
Time                 18.21 h
INSTRUM              spect
PROBHD    Z148658_0003 (
PULPROG            zgpg30
TD                  65536
SOLVENT             CDCl3
NS                    256
DS                      4
SWH            36231.883 Hz
FIDRES          1.105709 Hz
AQ              0.9043968 sec
RG                  199.73
DW                 13.800 usec
DE                  6.50 usec
TE                 297.8 K
D1              4.00000000 sec
D11             0.03000000 sec
TD0                     1
SFO1           150.8864644 MHz
NUC1                   13C
P0                  4.00 usec
P1                 12.00 usec
PLW1           77.65699768 W
SFO2           600.0074000 MHz
NUC2                   1H
CPDPRG[2            waltz65
PCPD2              70.00 usec
PLW2           13.23200035 W
PLW12           0.64876997 W
PLW13           0.32633001 W

F2 - Processing parameters
SI                  32768
SF             150.8713773 MHz
WDW                    EM
SSB         0
LB                  1.00 Hz
GB          0
PC                  1.40
```



^{1}H NMR ($CDCl_3$), 600 MHz

2.21c

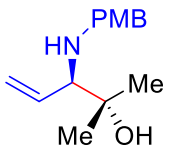


^{13}C NMR ($CDCl_3$), 151 MHz

2.21c

```
Current Data Parameters
NAME        SAC4-051-CNMR
EXPNO                   2
PROCNO                  1

F2 - Acquisition Parameters
Date_            20230213
Time               14.38 h
INSTRUH             spect
PROBHD    Z855801_0105 (
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                  197
DS                    4
SWH           36231.883 Hz
FIDRES         1.105709 Hz
AQ            0.9043968 sec
RG                194.75
DW                13.800 use
DE                 6.50 use
TE                297.0 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                   1
SFO1        150.8738906 MHz
NUC1                13C
P0                 3.67 use
P1                11.00 use
PLW1       178.30999756 W
SFO2       599.9573998 MHz
NUC2                1H
CPDPRG[2         waltz65
PCPD2             70.00 use
PLW2        15.77700043 W
PLW12        0.46366000 W
PLW13        0.23322000 W

F2 - Processing parameters
SI                32768
SF          150.8588050 MHz
WDW                 EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```

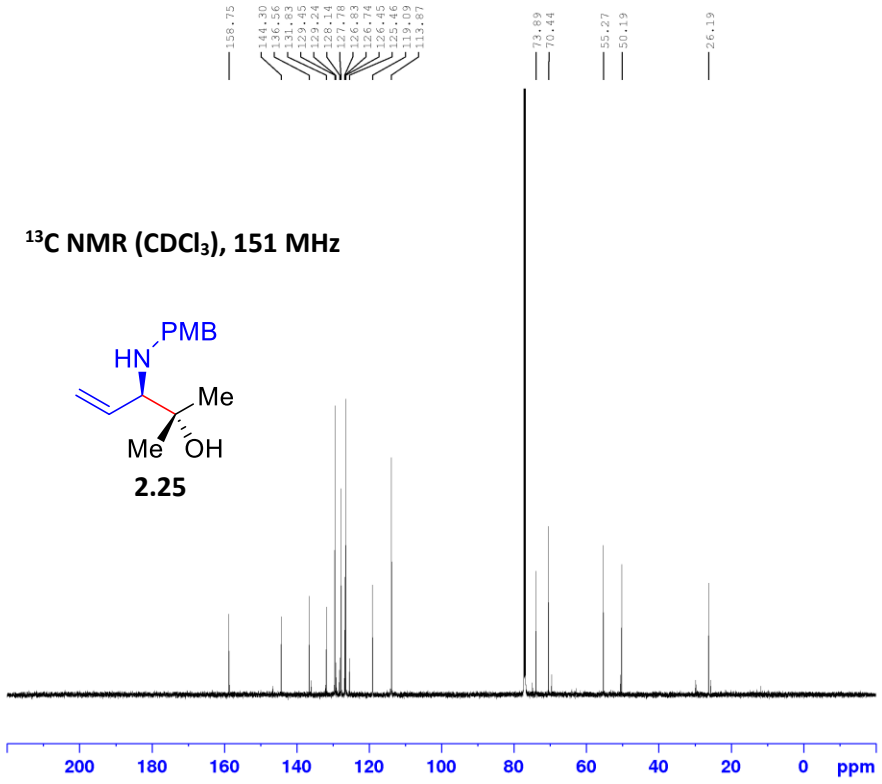
^{1}H NMR ($CDCl_3$), 600 MHz



2.25


```
Current Data Parameters
NAME       SAC3-196-HNMR
EXPNO                 3
PROCNO                1

F2 - Acquisition Parameters
Date_           20221107
Time              18.38 h
INSTRUM             spect
PROBHD    Z148658_0003 (
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH           12019.230 Hz
FIDRES        0.366798 Hz
AQ            2.7262976 sec
RG                157.38
DW                41.600 use
DE                10.33 use
TE                296.3 K
D1            3.00000000 sec
TD0                    1
SFO1        600.0087050 MHz
NUC1                  1H
P0                 5.17 use
P1                15.50 use
PLW1        13.23200035 W

F2 - Processing parameters
SI                 65536
SF          600.0050157 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

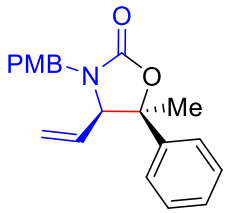
^{13}C NMR ($CDCl_3$), 151 MHz



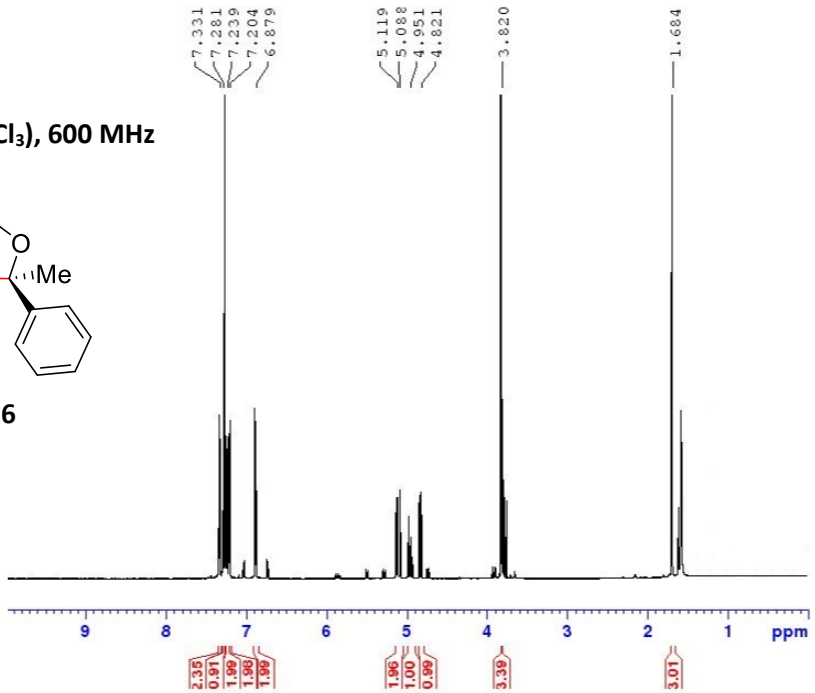
2.25


```
Current Data Parameters
NAME       SAC3-196-CNMR
EXPNO                 4
PROCNO                1

F2 - Acquisition Parameters
Date_           20221108
Time              0.54 h
INSTRUM             spect
PROBHD    Z148658_0003 (
PULPROG           zgpg30
TD                 65536
SOLVENT            CDCl3
NS                  1024
DS                     4
SWH           36231.883 Hz
FIDRES        1.105709 Hz
AQ            0.9043968 sec
RG                199.73
DW                13.800 usec
DE                 6.50 usec
TE                298.0 K
D1            4.00000000 sec
D11           0.03000000 sec
TD0                    1
SFO1        150.8864644 MHz
NUC1                  13C
P0                 4.00 usec
P1                12.00 usec
PLW1        77.65699768 W
SFO2        600.0074000 MHz
NUC2                  1H
CPDPRG[2          waltz65
PCPD2              70.00 usec
PLW2        13.23200035 W
PLW12        0.64876997 W
PLW13        0.32633001 W

F2 - Processing parameters
SI                 32768
SF          150.8713773 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```

^{1}H NMR ($CDCl_3$), 600 MHz

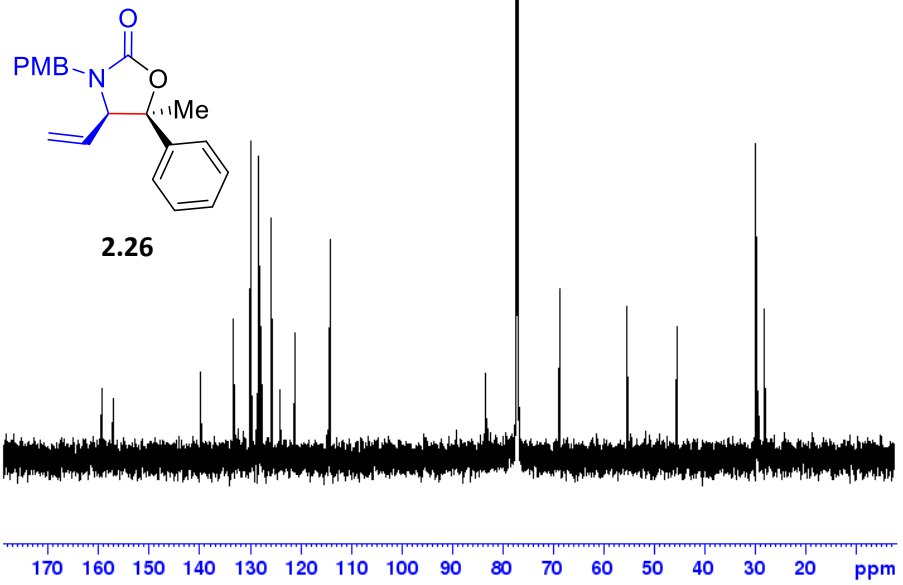


2.26




```
Current Data Parameters
NAME       SAC3-167-HNMR
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20221110
Time              11.09 h
INSTRUM           spect
PROBHD   Z148658_0003 (
PULPROG           zg30
TD               65536
SOLVENT          CDCl3
NS                  32
DS                   2
SWH           12019.230 Hz
FIDRES        0.366798 Hz
AQ            2.7262976 sec
RG               199.73
DW               41.600 use
DE               10.33 use
TE               296.5 K
D1            3.00000000 sec
TD0                  1
SFO1         600.0087050 MHz
NUC1                 1H
P0                5.17 use
P1               15.50 use
PLW1         13.23200035 W

F2 - Processing parameters
SI               65536
SF         600.0050157 MHz
WDW                 EM
SSB       0
LB              0.30 Hz
GB        0
PC              1.00
```

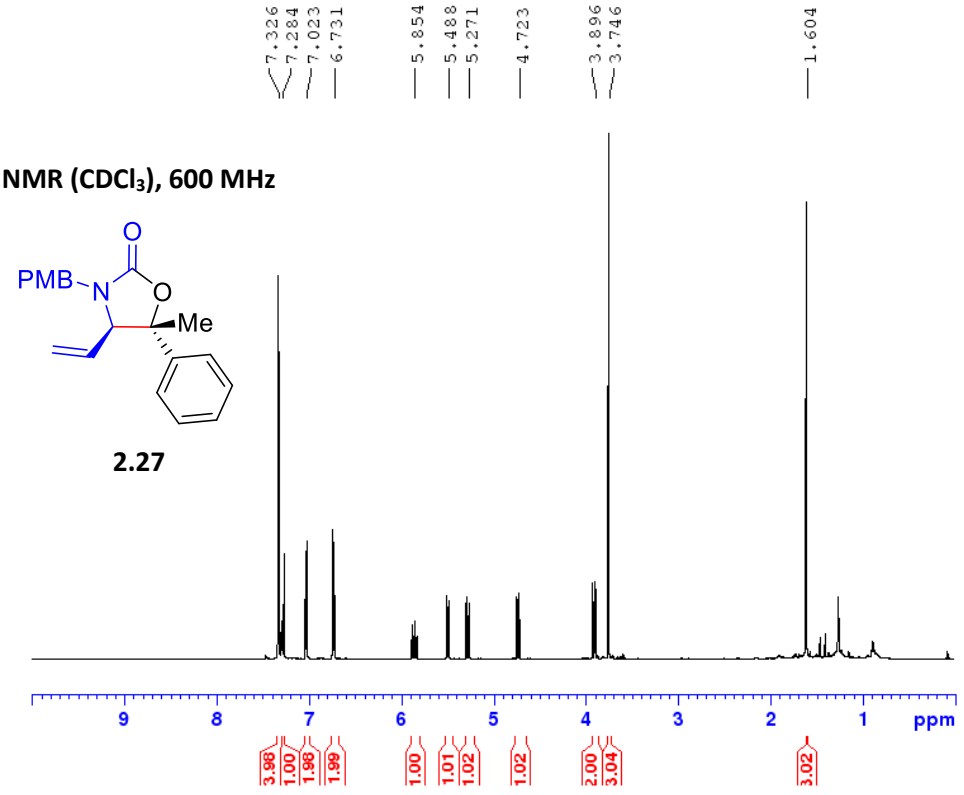
^{13}C NMR ($CDCl_3$), 151 MHz



2.26

```
Current Data Parameters
NAME       SAC3-167-CNMR
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_           20221115
Time              2.04 h
INSTRUM           spect
PROBHD    Z148658_0003 (
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                 2048
DS                    4
SWH           36231.883 Hz
FIDRES         1.105709 Hz
AQ            0.9043968 sec
RG               199.73
DW               13.800 use
DE                6.50 use
TE               297.9 K
D1           4.00000000 sec
D11          0.03000000 sec
TD0                   1
SFO1        150.8864644 MHz
NUC1                13C
P0                 4.00 use
P1                12.00 use
PLW1        77.65699768 W
SFO2       600.0074000 MHz
NUC2                1H
CPDPRG[2        waltz65
PCPD2             70.00 use
PLW2        13.23200035 W
PLW12        0.64876997 W
PLW13        0.32633001 W

F2 - Processing parameters
SI                32768
SF          150.8713773 MHz
WDW                  EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```

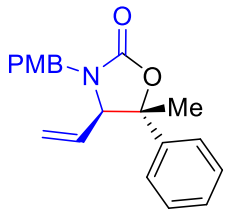
^{1}H NMR ($CDCl_3$), 600 MHz



2.27

```
Current Data Parameters
NAME       SAC4-003-HNMR
EXPNO                 3
PROCNO                1

F2 - Acquisition Parameters
Date_           20221105
Time              18.08 h
INSTRUM           spect
PROBHD    Z148658_0003 (
PULPROG             zg30
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH           12019.230 Hz
FIDRES         0.366798 Hz
AQ            2.7262976 sec
RG               176.24
DW               41.600 use
DE               10.33 use
TE               296.9 K
D1           3.00000000 sec
TD0                   1
SFO1        600.0087050 MHz
NUC1                1H
P0                5.17 use
P1               15.50 use
PLW1        13.23200035 W

F2 - Processing parameters
SI                65536
SF          600.0050158 MHz
WDW                  EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```

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



2.27

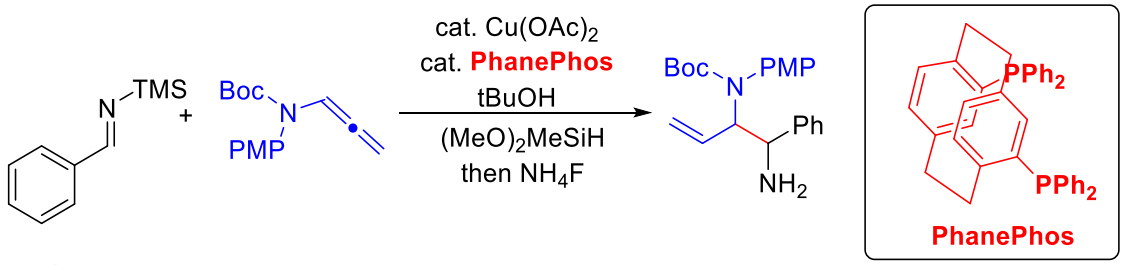

```
Current Data Parameters
NAME       SAC4-003-CNMR
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20221105
Time              18.05 h
INSTRUM           spect
PROBHD   Z148658_0003 (
PULPROG         zgpg30
TD               65536
SOLVENT          CDCl3
NS                1024
DS                   4
SWH          36231.883 Hz
FIDRES        1.105709 Hz
AQ           0.9043968 sec
RG              199.73
DW              13.800 usec
DE               6.50 usec
TE              298.1 K
D1           4.00000000 sec
D11          0.03000000 sec
TD0                  1
SFO1       150.8864644 MHz
NUC1              13C
P0               4.00 usec
P1              12.00 usec
PLW1       77.65699768 W
SFO2       600.0074000 MHz
NUC2              1H
CPDPRG[2       waltz65
PCPD2            70.00 usec
PLW2       13.23200035 W
PLW12       0.64876997 W
PLW13       0.32633001 W

F2 - Processing parameters
SI               32768
SF         150.8713773 MHz
WDW                 EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```

Chapter 3 Development of Asymmetric CuH-Catalyzed Reductive Coupling of an Achiral Allenamide with Aldimine Electrophiles

I. Introduction

A stereoselective protocol for the aminoallylation of aldimines using chiral allenamides has been previously developed by our group (see Chapter 1).[46] This reaction provided high selectivity towards the desired product but suffered from low atom economy and a 3-step deprotection sequence due to the use of a chiral auxiliary. Our efforts towards developing a methodology for the enantioselective aminoallylation of aldimine electrophiles are discussed herein (**Scheme 3.1**).

Scheme 3.1: *Model System for CuH-Catalyzed Reductive Coupling of Achiral Allenamides and Aldimine Electrophiles*



3.1 **3.2** **3.3**

II. Background

A. Chiral Auxiliary

Chiral auxiliaries are enantiopure molecules that are temporarily incorporated into organic compounds to bias the stereochemical outcomes of further reactions.[71] These compounds have been used in a variety of asymmetric syntheses targeting complex biologically

active compounds.[72] They also allow for the, otherwise impossible, separation of enantiomers by making the two compounds diastereomeric due to the incorporation of a new stereocenter from the auxiliary.[73] The benefits of chiral auxiliaries are counterbalanced by the fact that additional steps must be added to the synthetic process to both install and remove the auxiliary, which can be a laborious task that reduces the atom economy of the overall process.[74]

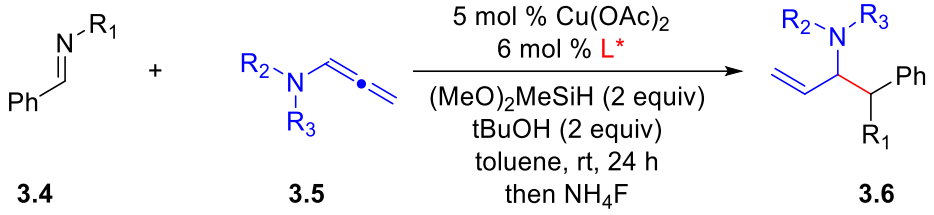
B. Chiral Catalysis

The other major method of imparting absolute stereochemistry in a reaction is through the utilization of chiral catalysis, and this can be either in the form of organocatalysis[75] or metal catalysis[76]. Catalytic amounts of chiral information are used in these methodologies to bias the stereochemical outcome of the reaction in question, often by complexation with achiral starting materials. Chiral catalysis offers benefits such as greatly improved atom economy compared to approaches using chiral auxiliaries.[77] However, this is counterbalanced by the large degree of optimization needed for many chiral catalytic reactions and the costs associated with some of the catalytic sources of chiral information.[78]

III. Research Design

Prior publications in the Sieber lab have demonstrated the enantioselective aminoallylation of ketones utilizing chiral ligands can be performed in a high yielding and stereoselective manner.[52,67] It was desired to extend this methodology to utilize aldimines instead of ketones in order to access chiral 1,2-diamine synthons instead of the 1,2-aminoalcohol variant. A similar system to that of the previous publication about 1,2-diamines was utilized wherein an aldimine and an achiral allenamide would be coupled together using asymmetric Cu catalyzed reductive coupling with *tert*-butanol being used as an additive (**Scheme 3.2**).

Scheme 3.2: *Method Development for CuH-Catalyzed Reductive Coupling of Achiral Allenamides and Aldimine Electrophiles*



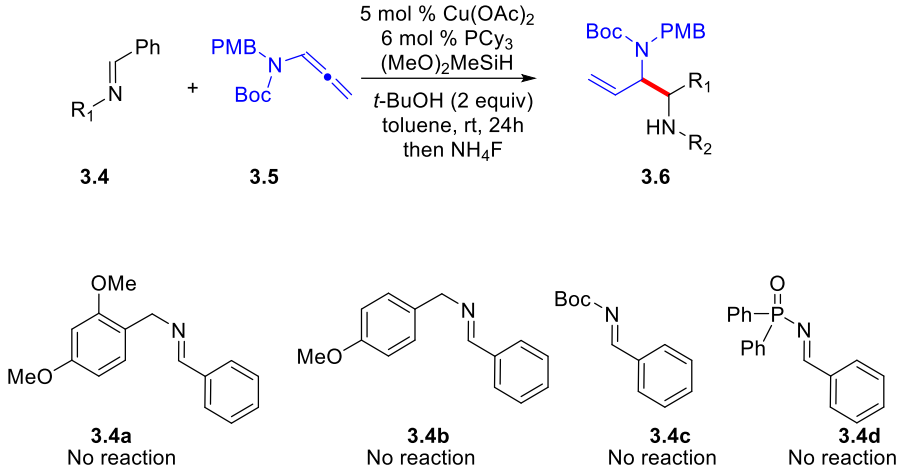
3.4 **3.5** **3.6**

IV. Development of the Asymmetric Reductive Coupling of Allenamides and Aldimines

A. Initial Studies

Initial studies towards developing an enantioselective copper catalyzed aldimine aminoallylation protocol began by reacting acyclic allenamide **3.5** with a variety of protected aldimines in a protocol similar to the one previously developed for chiral auxiliaries (**Scheme 3.3**).[46] None of the aldimines that were examined gave any appreciable amounts of the desired product. Based on previously published work, we knew that the Cu-H can efficiently add into the allenamide being studied.[52] This implied that all the aldimines that were tested were too unreactive towards the allylcopper nucleophile. Thus, further ideas had to be explored to increase the reactivity of the aldimine.

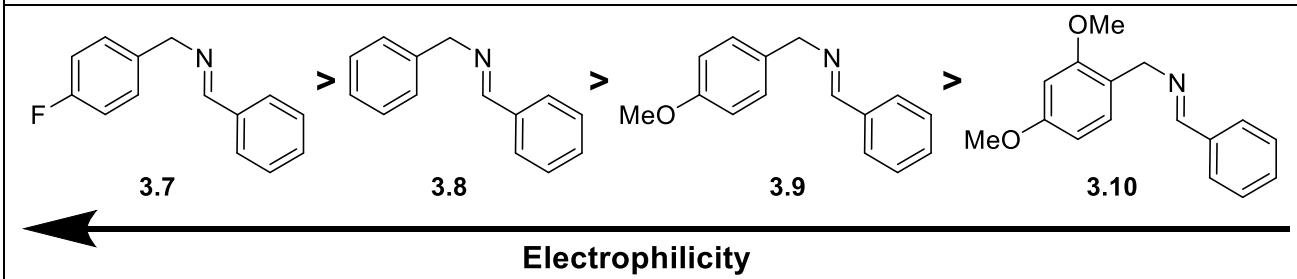
Scheme 3.3: *Initial Studies Towards Reductive Coupling Development*



B. Transition Towards Silyl Protected Aldimines

The nature of the *N*-substituent on an aldimine has a large impact on the electrophilicity of the molecule, with more electron-donating substituents resulting in lower electrophilicity (**Fig 3.1**).[46] From this fact, one would presume that the optimal substituent would be something with an electron-withdrawing nature such as 4-fluorobenzyl. However, the benefit of increased reactivity in this case is offset by the difficult nature of removing substituted benzyl protecting groups that are not electron-donating.[43]

Fig. 3.1: *Relative Electrophilicities of Aldimines*

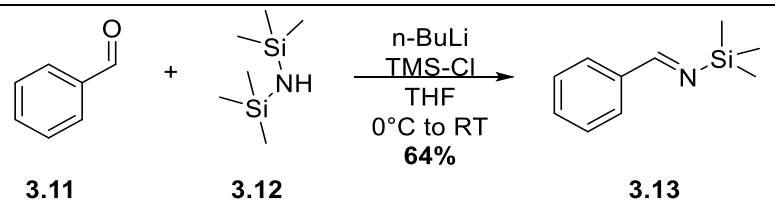


One theoretical strategy to address the reactivity issues that were being faced is to use a "unmasked" aldimine, in which the protecting group on the nitrogen is replaced with a hydrogen atom. This formal ammonia derived aldimine would serve to increase the reactivity of the electrophile by reducing the steric congestion around the aldimine. However, the issue with this approach is that free ammonia-derived aldimines are incredibly unstable and cannot be isolated, thus making it necessary for them to be created *in-situ*. One of the major precursors that can be used to create these *in-situ* are trimethylsilyl protected aldimines. This class of compound was first discovered in 1963[79] and has found a number of uses in reactions including cycloadditions to access β-lactams[80] and addition from chiral allylboranes to access chiral allylic amines[81].

It was not until the work by Brown in 1999 that the reactivity of the trimethylsilyl protected aldimines was well understood.[82] In this work, Brown attempted to repeat the Itsuno allylboration and, upon ^{11}B- and ^{1}H-NMR analysis, discovered that no reaction had taken place even after much longer reaction times than were reported by Itsuno.[81] However, it was discovered that upon aqueous workup an exothermic reaction took place that resulted in the desired product being obtained. Further studies were performed in which one equivalent of water was added to the reaction between the trimethylsilyl aldimine and chiral allylborane, which was theorized to cleave the extremely weak N-Si bond, and the desired chiral amine was obtained without an aqueous workup. This led Brown to believe that it was the free aldimine that was the active species in the reaction.

With this information in mind, we next set out to synthesize the trimethylsilyl protected derivative of benzaldehyde, in a procedure adapted from Colvin, (**Scheme 3.4**) to test in our reaction.[83]

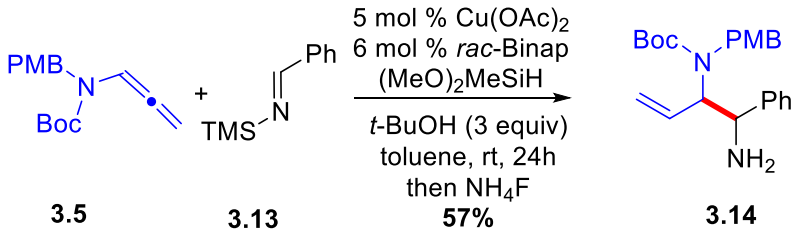
Scheme 3.4: *Synthesis of Trimethylsilyl Protected Aldimine*



3.11 **3.12** **3.13**

Gratifyingly, the desired product was obtained in moderate yield with racemic Binap as the ligand using conditions slightly modified from those used in testing the other aldimines (**Scheme 3.5**). An additional equivalent of *tert*-butanol was added to the reaction as the requisite proton source for the cleavage of the N-Si bond in the protected aldimine to release the free aldimine.

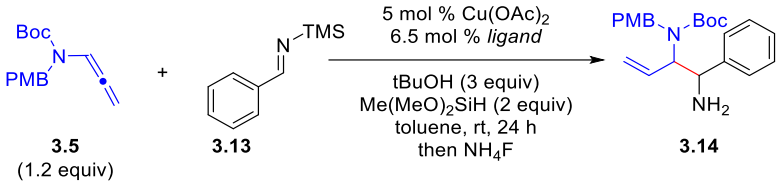
Scheme 3.5: *Initial Results for Trimethylsilyl Protected Aldimine*



3.5 **3.13** **3.14**
> 98:2 dr

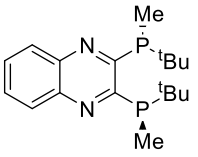
C. Ligand Survey

Table 3.1: *Ligand Survey in the Cu-Catalyzed Reductive Coupling of Allenamide 3.5 and Aldimine* ***3.13***[a]

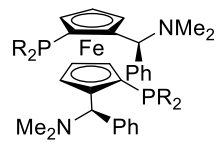


Entry	Ligand	% yield **3.14**[b]	Er **3.14**[c]
1	(*R*,*R*)-Ph-BPE	70	57:43
2	(*R*)-BINAP	57	53:47
3	(*R*)-SegPhos	45	55:45
4	(*R*)-DuanPhos	41	52:48
5	W3	72	50:50
6	W12	67	51:49
7	(*R*)-DBTM-SegPhos	34	56:44
8	(*R*)-Xyl-BINAP	17	61:39
9	(*R*)-QuinoxP*	53	51:49
10	A120	22	53:47
11	A121	20	55:45
12	M3	0	N/A
13	M9	85	68:32
14	NMDPP	0	N/A
15	MOP	0	N/A
16	DTBM-Garphos	41	52:48
17	J1	21	59:41
18	J2	59	54:46
19	J3	0	N/A
20	J7	56	53:47
21	J8	65	51:49
22	J9	0	N/A
23	J11	0	N/A
24	J15	17	51:49
25	PhanePhos	68	79:21

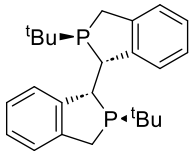
[a]Reaction performed according to the general procedure employing 0.200 mmol of aldimine, 0.240 mmol of **3.5**, 0.40 mmol of $Me(OMe)_2SiH$, and 0.6 mmol of tBuOH in 0.50 mL of toluene at rt for 24 h. A single diastereomer was observed in all cases. [b]Yield of **3.14** determined by quantitative ^{1}HNMR spectroscopy on the unpurified reaction mixture using trimethoxybenzene as the analytical standard. [c]Enantiomeric ratios were determined by HPLC analysis using a chiral stationary phase.



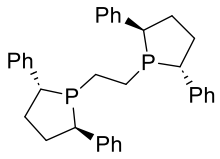
QuinoxP*



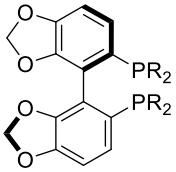
M3 R = 3,5-$(CF_3)_2$-Ph
M9 R = 3,5-$(Me)_2$-Ph



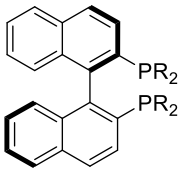
DuanPhos



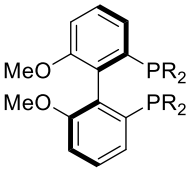
(*R*,*R*)-**Phenyl-BPE**



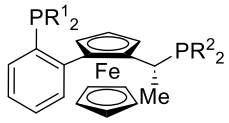
(*R*)-**SEGPHOS** R = Ph
(*R*)-**DTBM-SEGPHOS** R = 3,5-(^{t}Bu)$_2$-4-OMe-Ph



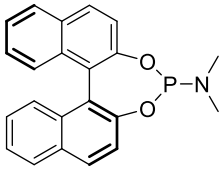
(*R*)-**BINAP** R = Ph
(*R*)-**DM-BINAP** R = 3,5-$(Me)_2$-Ph



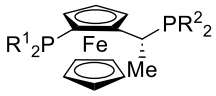
A-120 R = 3,5-$(Me)_2$-Ph
A-121 R = 3,5-(^{t}Bu)$_2$-Ph



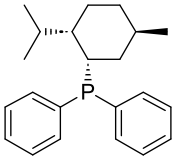
W3 R^1 = Ph, R^2 = Cy
W12 R^1 = Ph, R^2 = ^{t}Bu



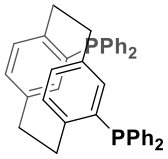
(S)-**MOP**



J1 R^1 = Ph, R^2 = Cy
J2 R^1 = Ph, R^2 = ^{t}Bu
J3 R^1 = R^2 = Cy
J7 R^1 = 3,5-$(Me)_2$-4-OMe-Ph, R^2 = Cy
J8 R^1 = 3,5-$(CF_3)_2$-Ph, R^2 = 3,5-$(Me)_2$-Ph
J9 R^1 = Cy, R^2 = ^{t}Bu
J11 R^1 = 4-CF_3-Ph, R^2 = ^{t}Bu
J15 R^1 = 3,5-$(Me)_2$-Ph, R^2 = 2-furyl



(S)-**NMDPP**



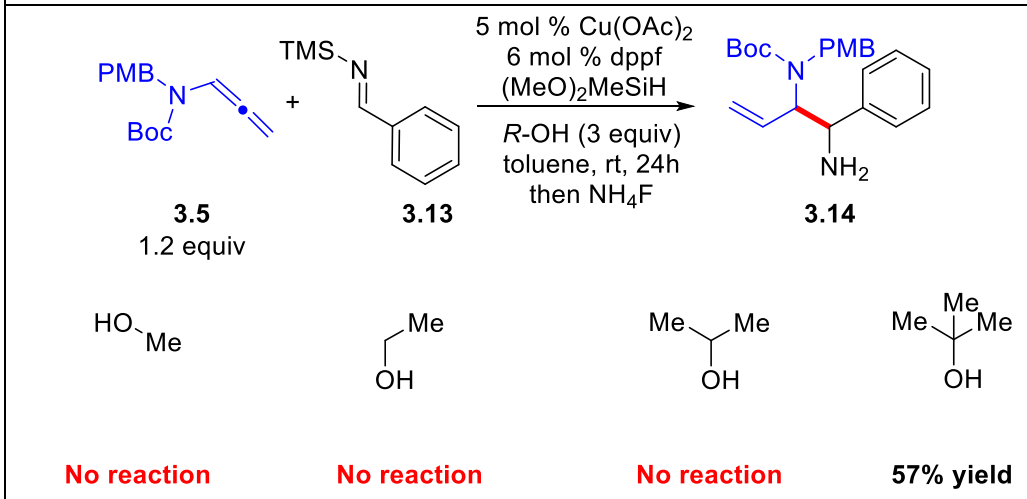
PhanePhos

This investigation began by testing aldimine **3.13** and allenamide **3.5** against a variety of mono- and bidentate ligands (**Table 3.1**). None of the monodentate ligands resulting in any appreciable amounts of product being obtained (entries 14 and 15). A wide range of yields were obtained when examining bidentate ligands, with Ph-BPE (entry 1), Walphos-003 (entry 5), and Mandyphos-009 (entry 13) providing the highest yields. However, in all these cases the enantioselectivity was exceptionally poor. It was not until the PhanePhos ligand was tested (entry 25) that any appreciable degree of enantioinduction was observed. Due to this result, this ligand was the one chosen for further examination in an attempt to increase the yield and enantioselectivity.

D. Additive Survey

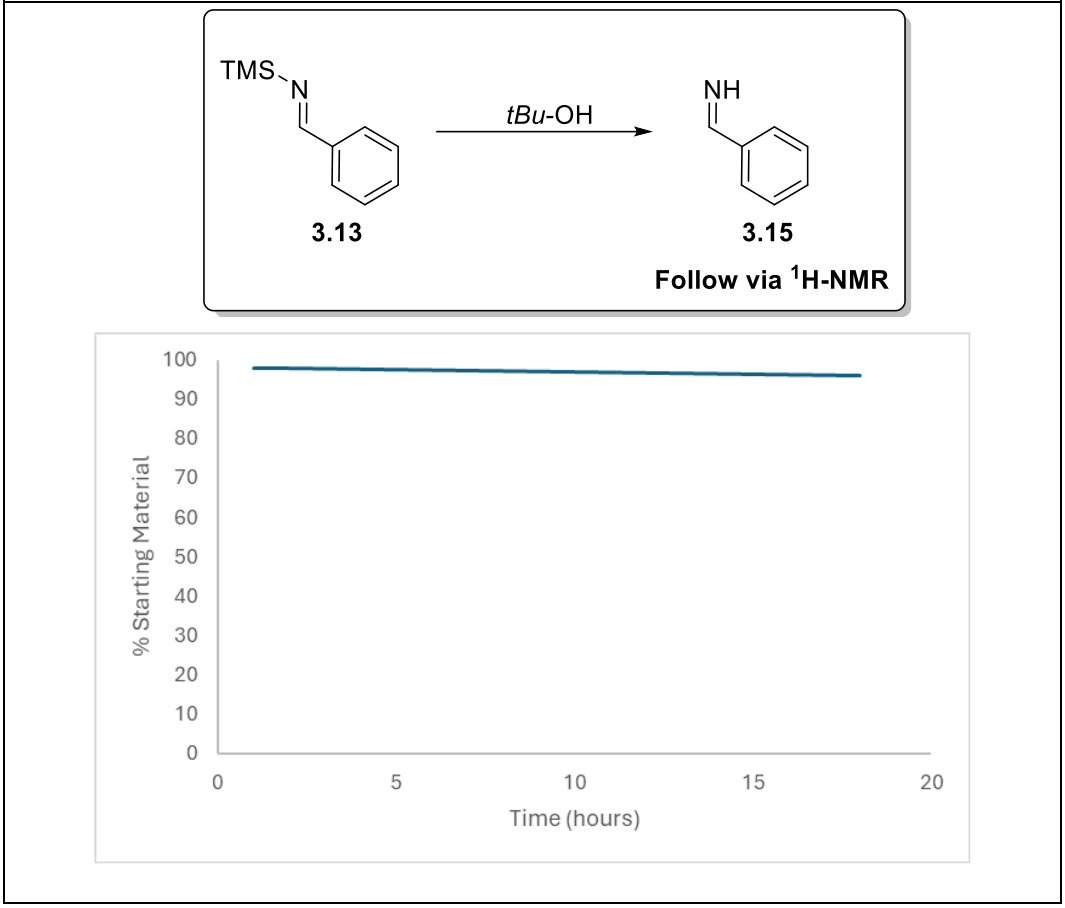
Next, different alcohols were surveyed to ascertain if less hindered ones would be beneficial to the yield (**Scheme 3.6**). It was found that any alcohol less hindered than *tert*-butanol was used then no amount of product would be obtained and starting materials would be recovered. Mixtures of alcohols were also tested and if any quantity of a less hindered alcohol was used then the reaction completely stopped.

Scheme 3.6: *Alcohol Additive Survey*



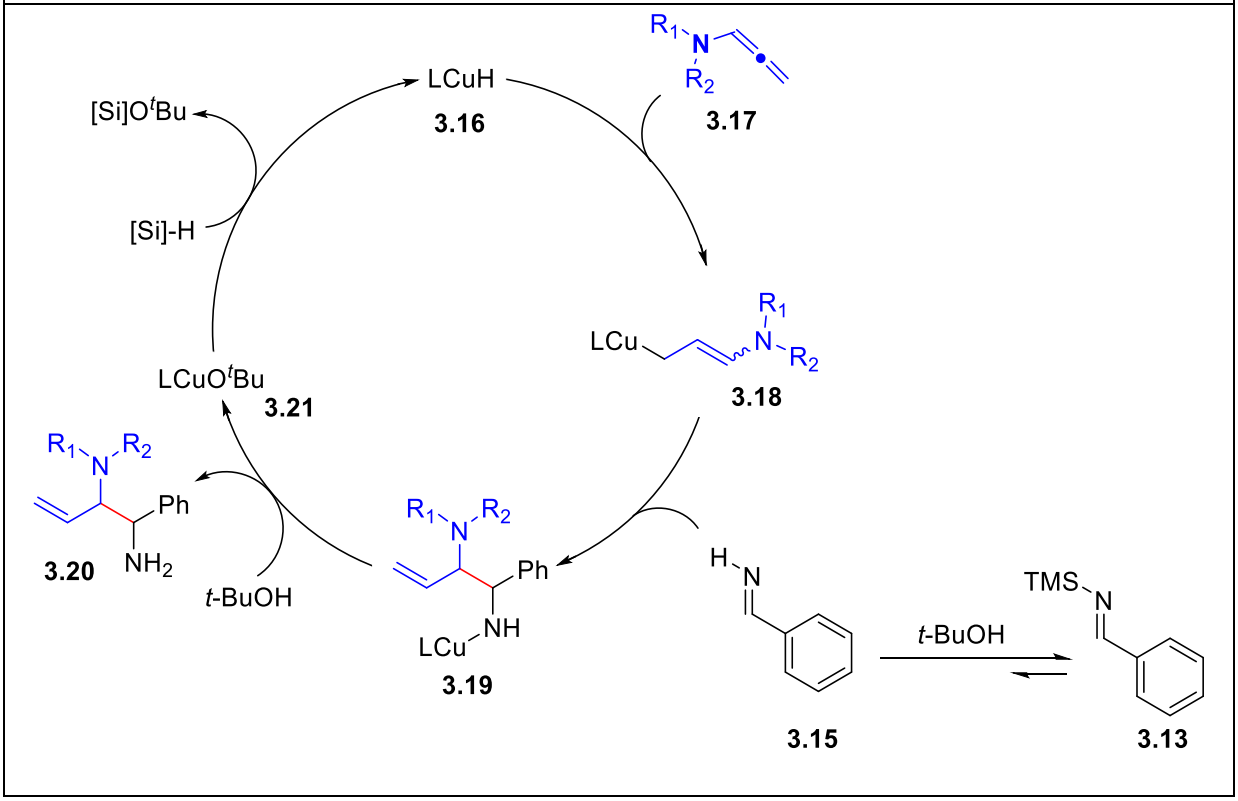
A kinetics study was then conducted to see if an explanation for this phenomenon could be observed, wherein the aldimine would be placed in a vial along with two equivalents of tert-butanol in toluene-d8 and ^{1}H-NMR spectra were obtained at various time points over a eighteen-hour period (**Fig 3.2**). It was observed that, even after eighteen hours, greater than ninety percent of the aldimine remained upon ^{1}H-NMR analysis. This would then imply that the cleavage of the N-Si bond by *tert*-butanol is in an equilibrium that is heavily biased towards the aldimine.

Figure 3.2: *NMR Study of Trimethylsilyl Group Cleavage*



Since prior literature has shown that reactions involving these aldimines can be extremely quick in the presence of a proton source[82], the logical explanation is that the step in the mechanism that consumes the free aldimine to generate the copper-amido complex (**Fig 3.3**) is slow enough that any less-hindered alcohol present has enough time to protonate either copper hydride **3.16** or allylcopper intermediate **3.18** and thus remove the active species from the system.

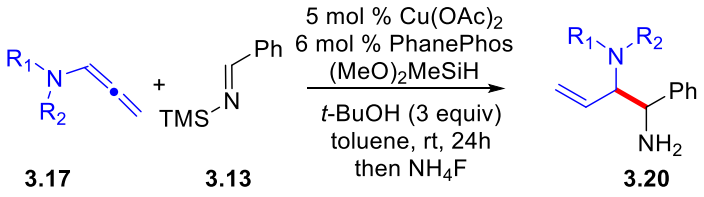
Figure 3.3: *Catalytic Cycle for Allenamide – Aldimine Reductive Coupling*



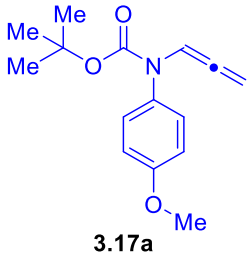
E. Allenamide Survey

Next, a variety of allenamides were examined to determine if an improvement in the enantioselectivity of the reaction could be achieved (**Scheme 3.7**). Initial studies began with allenamide **3.17a**, with the *N*-Boc and *para*-methoxyphenyl protecting groups, that was supplied by Dr. Sieber, which provided a large increase in yield and a small increase in enantioselectivity. Allenamides that followed (**3.17b-3.17e**) either resulted in a large decrease in yield or enantioselectivity, with **3.17f** showing no reactivity at all.

Scheme 3.7: *Allenamide Survey*

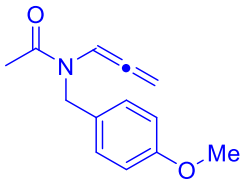


3.17 **3.13** **3.20**



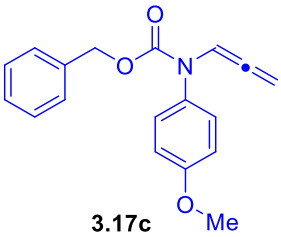
3.17a

Yield = 94%
ER = 82:18
> 98:2 dr



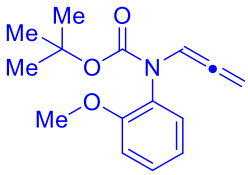
3.17b

Yield = 38%
ER = 75:25
DR = 65:35



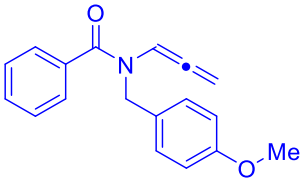
3.17c

Yield = 30%
ER = 86:14
> 98:2 dr



3.17d

Yield = 56%
ER = 76:24
> 98:2 dr



3.17e

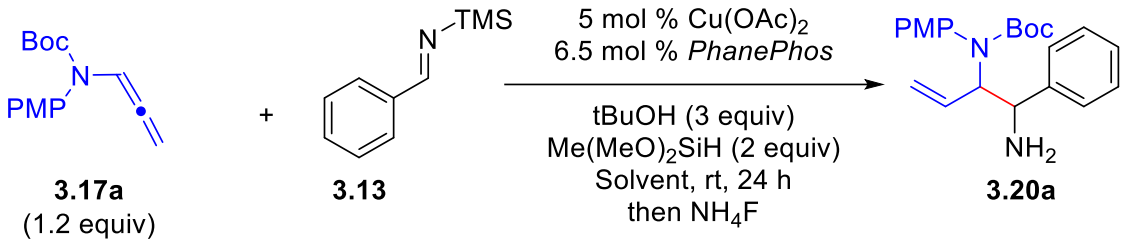
Yield = 62%
ER = 57:43
DR = 82:18

3.17f

Yield = 0%

F. Solvent Survey

Table 3.2: *Solvent Survey in the Cu-Catalyzed Reductive Coupling of Allenamide 3.17a and Aldimine 3.13*[a]



3.17a (1.2 equiv) + **3.13** → **3.20a**

Entry	Solvent	% yield **3.20a**[b]	Er **3.20a**[c]
1	Dioxane	90	82:18
2	CF_3-Toluene	0	N/A
3	Fluorobenzene	87	80:20
4	DCM	51	83:17
5	EtOAc	72	81:19
6	DME	0	N/A
7	Diglyme	68	81:19
8	THF	55	82:18
9	Toluene	94	82:18
10[d]	Toluene	43	88:12

[a]Reaction performed according to the general procedure employing 0.200 mmol of ketone, 0.240 mmol of **11a**, 0.40 mmol of $Me(OMe)_2SiH$ in 0.50 mL of toluene at rt for 24 h. [b]Yield of **3.20a** determined by quantitative ^{1}HNMR spectroscopy on the unpurified reaction mixture using trimethoxybenzene as the analytical standard. [c]Enantiomeric ratios were determined by chiral column HPLC analysis. [d]Reaction was performed at 0 °C

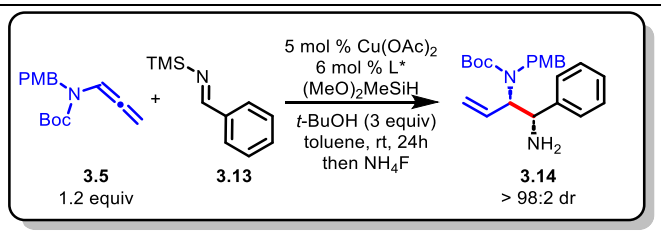
The effect of the solvent on the reaction was then surveyed (**Table 3.2**). No effect on the enantioselectivity could be observed with all solvents tested providing similar selectivity. The only exception to this was when the reaction was run in toluene at 0 °C, which resulted in a

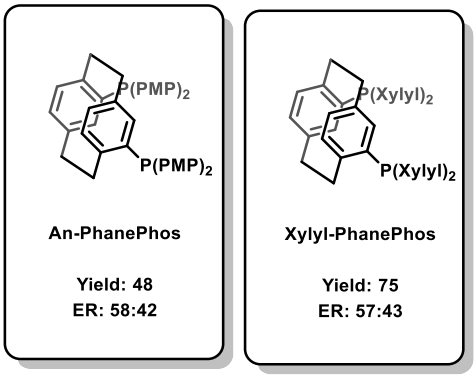
minor increase in enantioselectivity but a major decrease in the yield (entry 10). A negative effect on the yield was observed for most coordinating solvents (entries 6-8). CF_3-Toluene and DME (entries 2 and 6) resulted in no reaction being observed. It was noted that these two reactions remained heterogeneous for the entire reaction time, and it is likely that sufficient amount of catalyst needed to effect the transformation never dissolved.

V. Future Work

Further research needs to be performed to increase the enantiocontrol of this reaction. One avenue of research that is currently in progress is computational calculations to determine if ligands with substituents on the PhanePhos core can be discovered. Initial experimental studies have shown that substitution on the PhanePhos core can influence the enantioselectivity of the reaction, and ideally computational calculations can determine what substituents will have an optimal effect (**Scheme 3.8**).

***Scheme 3.8**: Initial Studies on the PhanePhos Class of Ligands*

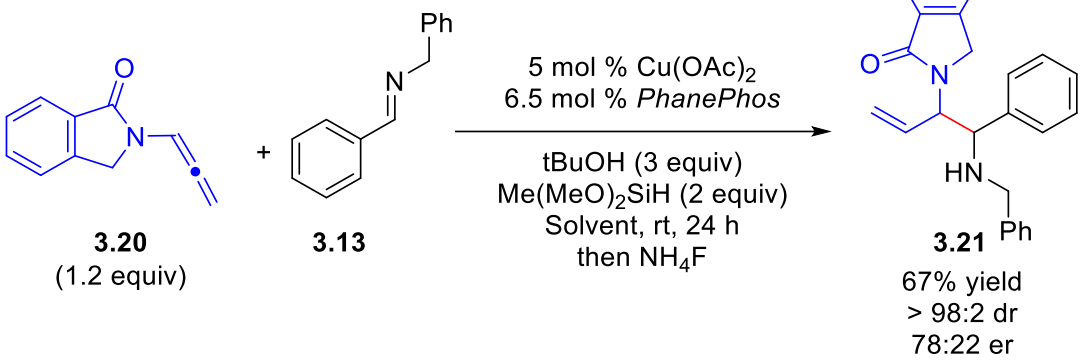




Other carbamate protecting groups will also be examined due to the fact that an increase in enantioselectivity can be observed between the reactions employing Cbz protected and Boc protected allenamides (**Scheme 3.7**).

Also, initial studies have shown that certain cyclic allenamides can also be employed in this methodology (**Scheme 3.9**). Adequate deprotection strategies for aminoallylation product **3.21** need to be ascertained before significant effort is put forth to find a ligand that provides optimal enantioselectivity. One potential deprotection strategy involves performing a visible-light-driven α-oxidation of the amide to produce the phthalimide moiety.[84] The new phthalimide unit should be easily cleavable based off of previous work from the Sieber lab.[85] Alternatively, hydride reduction of the lactam **3.21** to the cyclic dibenzylamine offers another strategy for deprotection.

Scheme 3.9: *Initial Studies with Cyclic Allenamides*



VI. Conclusion

This strategy for the stereoselective reductive coupling of aldimines and achiral allenamides to selectively generate 1,2-diamine synthons is yet to be completed but will be an effective tool for accessing molecules with a dissonant charge affinity when finished. This work will improve upon previously published work by our group by increasing the atom economy of

the process for synthesizing these synthons by removing the need for a chiral auxiliary. Current work is ongoing regarding changing the protecting groups on both the allenamide and aldimine to increase enantioselectivity.

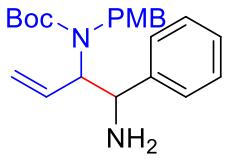
VII. Experimental Methods

General. ^{1}H NMR spectra were recorded on Bruker 600 MHz spectrometers. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as an internal standard ($CDCl_3$: 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, h = hextet, hept = heptet, br = broad, m = multiplet), and coupling constants (Hz). ^{13}C NMR was recorded on a Bruker 600 MHz (151 MHz) instrument with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard ($CDCl_3$: 77.0 ppm). Chiral Column HPLC analyses were performed on a Shimadzu Prominence i-series LC-2030C using chiral Daicel columns purchased from Chiral Technologies, Inc. Liquid chromatography was performed using forced flow (flash chromatography) on silica gel purchased from Silicycle. Thin layer chromatography (TLC) was performed on glass-backed 250 μm silica gel F254 plates purchased from Silicycle. Visualization was achieved using UV light, a 10% solution of phosphomolybdic acid in EtOH, or potassium permanganate in water followed by heating. HRMS was collected using a Jeol AccuTOF-DART™ mass spectrometer using DART source ionization. All reactions were conducted in oven or flame dried glassware under an inert atmosphere of nitrogen or argon with magnetic stirring unless otherwise noted. Solvents were obtained from VWR as HPLC grade and transferred to septa sealed bottles, degassed by Ar sparge, and analyzed by Karl-Fischer titration to ensure water content was $\leq$ 600 ppm. $Me(MeO)_2SiH$ was purchased from Gelest and used as received. All other materials were purchased from VWR, Sigma Aldrich, Combi-Blocks, Alfa-Aesar, or Strem Chemical Company and used as received.

Method A: General procedure for Cu catalyzed reductive coupling with aldimines. To a 20 mL crimp-cap vial with stir-bar in an Ar-filled glove-box was charged 1.8 mg (0.0100 mmol, 0.05 equiv) of $Cu(OAc)_2$ and 0.0120 mmol (0.06 equiv) of PhanePhos. Solvent (0.5 mL) was then added, and the mixture was allowed to stir for 15 min. Allenamide (0.240 mmol, 1.2 equiv) was then charged along with the aldimine (0.200 mmol, 1 equiv, 0.4 M in solvent). This was followed by the addition of *tert*-butanol (0.600 mmol, 3 equiv) and dimethoxymethylsilane (49 μL, 0.4 mmol, 2 equiv) by syringe (*caution: dimethoxymethylsilane should be handled in a well-ventilated fume hood because it is known to cause blindness. Syringes were quenched with 2M NaOH, gas evolution!, prior to disposal)*. The reaction vessel was then sealed with a crimp-cap septum and removed from the glove-box. After 24 h the reaction was then quenched by the addition of 95 mg of NH_4F and 3.0 mL of MeOH followed by agitation at rt for 30 min – 1 h. To the mixture was then charged 5 mL of 5% $NaHCO_3$ followed by extraction with CH_2Cl_2 (2x5mL). The combined organics were dried with Na_2SO_4 and concentrated *in vacuo*. An aliquot of the crude mixture was analyzed by ^{1}HNMR spectroscopy to determine dr. The crude residue was then purified by flash chromatography on silica gel to afford the desired product.

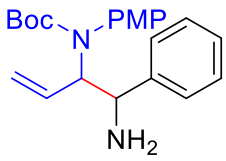
Enantioselectivity was determined by HPLC analysis using a chiral stationary phase relative to authentic racemate prepared by the above procedure employing dppf as the ligand.

Characterization Data:



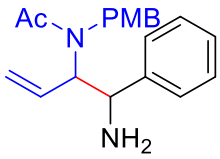
3.14

tert-butyl (1-amino-1-phenylbut-3-en-2-yl)(4-methoxybenzyl)carbamate (3.14): According to the general procedure A using allenamide **3.17**, the product was purified by silica gel chromatography (40 - 70 % EtOAc in Hexanes) to provide 52 mg (68 %) of **3.14** as a white foam with an enantiomeric ratio of 79:21. R_f =0.21 (50 % EtOAc/hexanes). ^{1}HNMR ($CDCl_3$, 55 °C, 600 MHz) δ: 7.06 – 7.17 (m, 5H), 6.89 (d, *J* = 7.55 Hz, 2H), 6.65 (d, J = 8.83 Hz, 2H), 5.56 (ddd, *J* = 16.76 Hz, 8.63 Hz, 8.53 Hz, 1H), 5.44 (br s, 1H), 5.07 (d, *J* = 10.44 Hz, 2H), 4.58 (br s, 1H), 3.63 (s, 3H), 3.52 (d, J = 13.07 Hz, 1H), 3.26 (d, J = 13.32 Hz, 1H), 3.19 (br s, 1H), 1.27 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 158.6, 155.7, 137.6, 132.2, 129.1, 128.5, 127.3, 126.7, 118.2, 114.8, 79.4, 64.5, 55.3, 50.3, 29.7, 28.4.



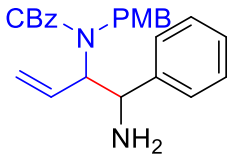
3.20a

tert-butyl (1-amino-1-phenylbut-3-en-2-yl)(4-methoxyphenyl)carbamate (3.20a): According to the general procedure A using allenamide **3.17a**, the product was purified by silica gel chromatography (40 - 70 % EtOAc in Hexanes) to provide 69 mg (94 %) of **3.20a** as a white foam with an enantiomeric ratio of 82:18. R_f =0.18 (50 % EtOAc/hexanes). ^{1}HNMR ($CDCl_3$, 55 °C, 600 MHz) δ: 7.13 – 7.28 (m, 8H), 6.84 (d, *J* = 8.47 Hz, 2H), 5.60 (ddd, *J* = 17.52 Hz, 10.22 Hz, 8.25 Hz, 1H), 4.91 (d, *J* = 10.47 Hz, 1H), 4.87 (d, *J* = 17.32 Hz, 1H), 4.55 (br s, 1H), 4.18 (br s, 1H), 3.80 (s, 3H), 3.78 (br s, 1H), 1.42 (s, 9H).



3.20b

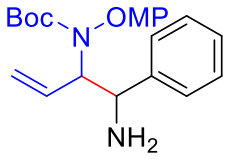
N-(1-amino-1-phenylbut-3-en-2-yl)-N-(4-methoxybenzyl)acetamide (3.20b): According to the general procedure A using allenamide **3.17b**, the product was purified by silica gel chromatography (40 - 70 % EtOAc in Hexanes) to provide 25 mg (38 %) of **3.20b** as a white foam with an enantiomeric ratio of 79:21. R_f =0.30 (50 % EtOAc/hexanes). ^{1}HNMR ($CDCl_3$, 55 °C, 600 MHz) δ: 7.71 (d, *J* = 6.74 Hz, 2H), 7.48 (d, *J* = 7.32 Hz, 2H), 7.35 (t, *J* = 4.53 Hz, 1H), 6.76 (d, *J* = 8.48 Hz, 2H), 6.64 (d, *J* = 8.60 Hz, 2H), 5.65 (ddd, *J* = 17.09 Hz, 8.60 Hz, 6.04 Hz, 1H), 5.03 (d, *J* = 10.33 Hz, 1H), 4.96 (d, *J* = 17.16 Hz, 1H), 4.26 (d, *J* = 9.54 Hz, 1H), 4.22 (d, *J* = 15.44 Hz, 1H), 3.67 (s, 3H), 2.33 (s, 3H).



3.20c

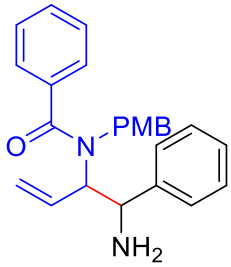
tert-butyl (1-amino-1-phenylbut-3-en-2-yl)(4-methoxyphenyl)carbamate (3.20c): According to the general procedure A using allenamide **3.17c**, the product was purified by silica gel chromatography (30 - 60 % EtOAc in Hexanes) to provide 26 mg (30 %) of **3.20c** as a white foam with an enantiomeric ratio of 79:21. R_f =0.36 (50 % EtOAc/hexanes). ^{1}HNMR ($CDCl_3$, 55 °C, 600 MHz) δ: 7.19 – 7.28 (m, 8H), 7.12 - 7.17 (m, 5H), 6.72 (d, *J* = 8.45 Hz, 2H), 6.65 (d, *J* = 8.90 Hz, 2H), 5.45 (ddd, *J* = 17.50 Hz, 9.34 Hz, 7.88 Hz,

1H), 5.03 (d, *J* = 8.85 Hz, 1H), 5.01 (br s, 1H), 4.86 (d, *J* = 5.55 Hz, 1H), 4.71 – 4.79 (m, 3H) 3.63 (s, 3H).



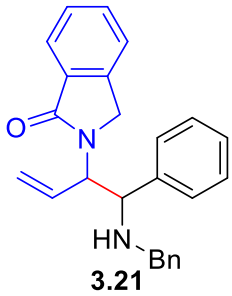
3.20d

tert-butyl (1-amino-1-phenylbut-3-en-2-yl)(4-methoxyphenyl)carbamate (3.20d): According to the general procedure A using allenamide **3.17d**, the product was purified by silica gel chromatography (40 - 70 % EtOAc in Hexanes) to provide 41 mg (56 %) of **3.20d** as a white foam with an enantiomeric ratio of 79:21. R_f =0.16 (50 % EtOAc/hexanes). ^{1}HNMR ($CDCl_3$, 55 °C, 600 MHz) δ: 7.36 (d, J = 7.75 Hz, 1H), 7.07 - 7.17 (m, 4H), 6.83 – 6.90 (m, 1H), 6.61 (t, J = 9.4 Hz, 1H), 6.00 (ddd, *J* = 13.19 Hz, 9.07 Hz, 8.90 Hz, 1H), 5.03 (d, *J* = 17.15 Hz, 1H), 4.83 – 4.93 (m, 2H), 3.39 (s, 3H), 1.45 (s, 9H).



3.20e

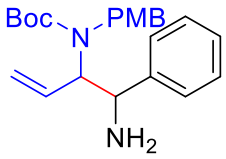
tert-butyl (1-amino-1-phenylbut-3-en-2-yl)(4-methoxyphenyl)carbamate (3.20e): According to the general procedure A using allenamide **3.17e**, the product was purified by silica gel chromatography (30 - 60 % EtOAc in Hexanes) to provide 48 mg (62 %) of **3.20e** as a white foam with an enantiomeric ratio of 79:21. R_f =0.25 (50 % EtOAc/hexanes). ^{1}HNMR ($CDCl_3$, 55 °C, 600 MHz) δ: 7.77 (d, J = 7.57 Hz, 1H), 7.46 (t, J = 7.30, 1H), 7.39 (t, J = 7.57 Hz, 1H), 7.31 (br s, 1H), 7.22 – 7.27 (m, 5H), 6.98 (d, J = 8.74 Hz, 2H), 6.74 (d, J = 8.74 Hz, 2H), 5.73 (ddd, *J* = 18.28 Hz, 9.28 Hz, 8.30 Hz, 1H), 5.10 – 5.23 (m, 3H), 3.73 (s, 3H).



3.21

tert-butyl (1-amino-1-phenylbut-3-en-2-yl)(4-methoxyphenyl)carbamate (3.21): According to the general procedure A using allenamide **3.17f**, the product was purified by silica gel chromatography (10 - 30 % EtOAc in Hexanes) to provide 50 mg (68 %) of **3.21** as a white foam with an enantiomeric ratio of 79:21. R_f =0.17 (20 % EtOAc/hexanes). ^{1}HNMR ($CDCl_3$, 55 °C, 600 MHz) δ: 7.82 (d, J = 6.97 Hz, 1H), 7.47 (t, J = 7.34 Hz, 1H), 7.40 Hz (t, J = 7.22 Hz, 1H), 7.27 – 7.32 (m, 4H), 7.21 (m, 1H), 7.11 (t, J = 3.67 Hz, 3H), 7.00 – 7.03 (m, 2H), 5.55 (ddd, *J* = 17.97 Hz, 8.79 Hz, 5.77 Hz, 1H), 5.06 (t, *J* = 8.00 Hz, 1H), 4.95 (d, J = 10.62 Hz, 1H), 4.89 (d, J = 17.58 Hz, 1H), 4.16 (d, J = 16.79 Hz, 1H), 3.91 (d, J = 16.40 Hz, 1H), 3.77 (d, J = 9.97 Hz, 1H), 3.58 (d, J = 13.64 Hz, 1H), 3.30 (d, J = 13.90 Hz, 1H).

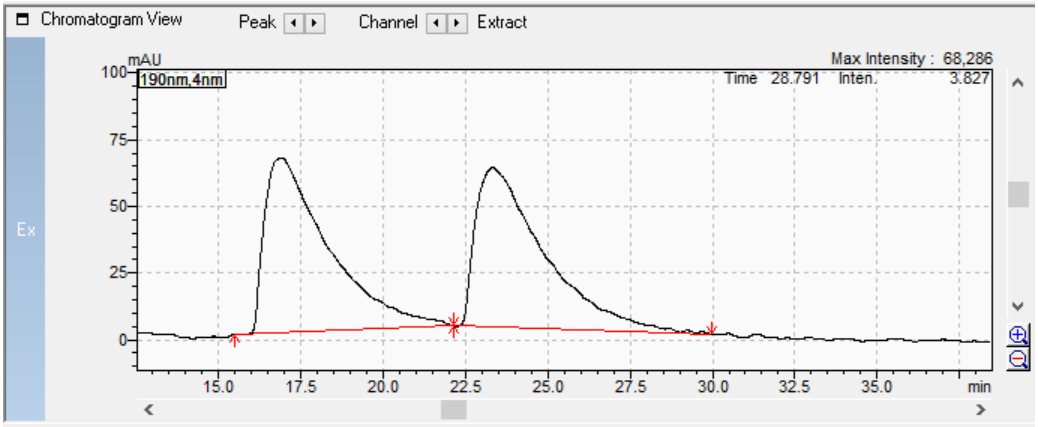
HPLC Chromatograms:



3.14

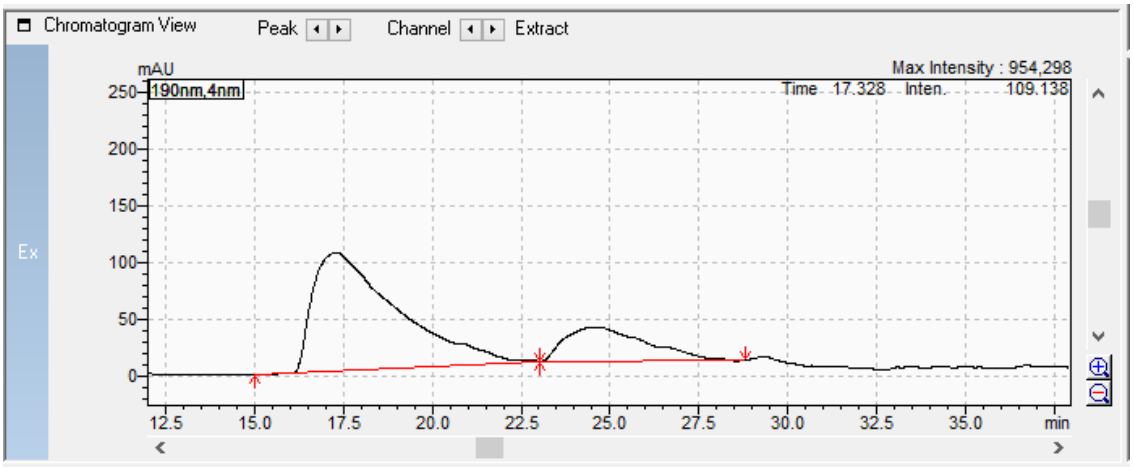
Chiral column HPLC analysis (Chiralcel OD-3 x 250 mm, 1.0 mL/min, 98:02 hexane:isopropanol, λ = 190 nm) t_R = 17.3 min (major), 24.6 min (minor):

Racemic 3.14:

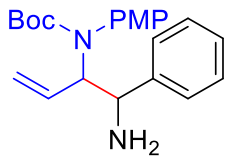


Ret. Time	Area%	Height	Area
16.936	50.610	65722	8853028
23.308	49.390	59727	8639788
	100.000	125448	17492817

3.14 from Cu(OAc)$_2$/PhanePhos reaction:



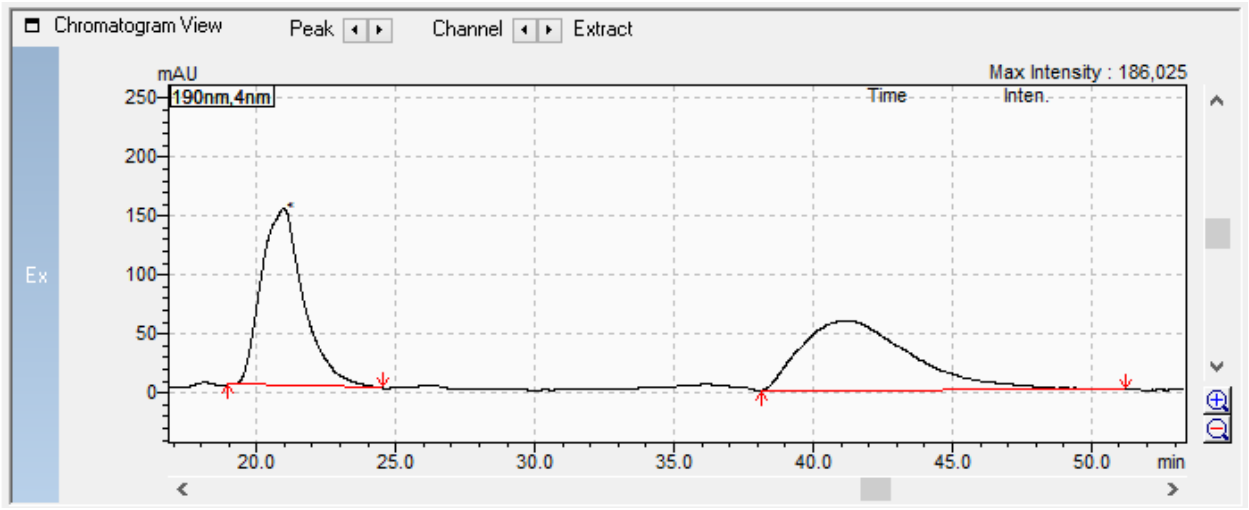
Ret. Time	Area%	Height	Area
17.321	78.367	103879	17024861
24.630	21.633	29729	4699707
	100.000	133608	21724567



3.20a

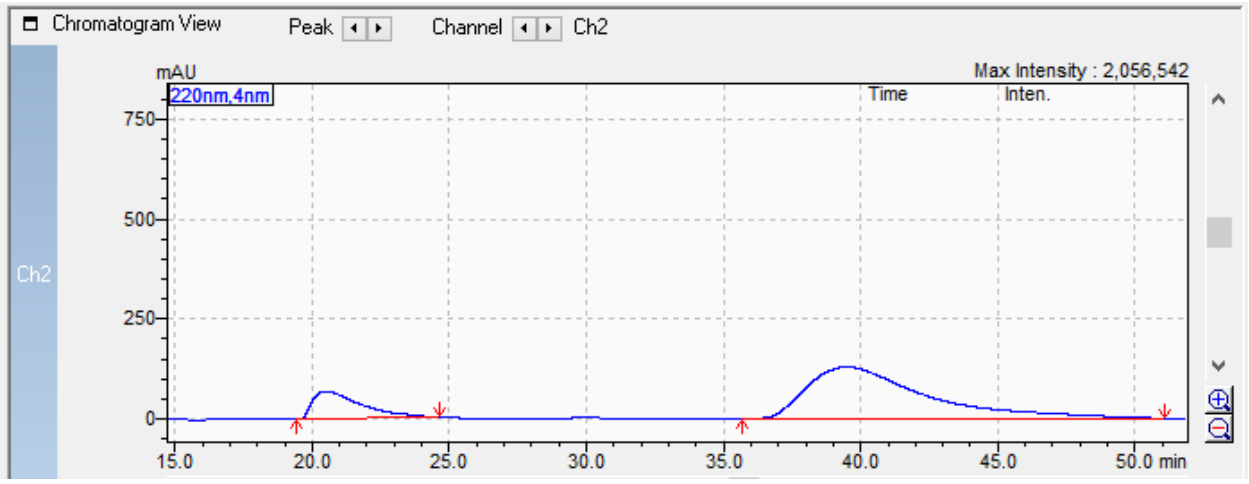
Chiral column HPLC analysis (Chiralcel AD-3 x 250 mm, 1.0 mL/min, 97:03 hexane:isopropanol, λ = 190 nm) t_R = 39.4 min (major), 20.5 min (minor):

Racemic 3.20a:

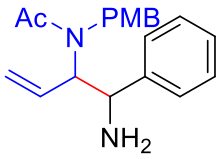


Ret. Time	Area%	Height	Area
20.973	49.971	149969	15927140
41.033	50.029	58334	15945709
	100.000	208302	31872849

3.20a from $Cu(OAc)_2$/PhanePhos reaction:



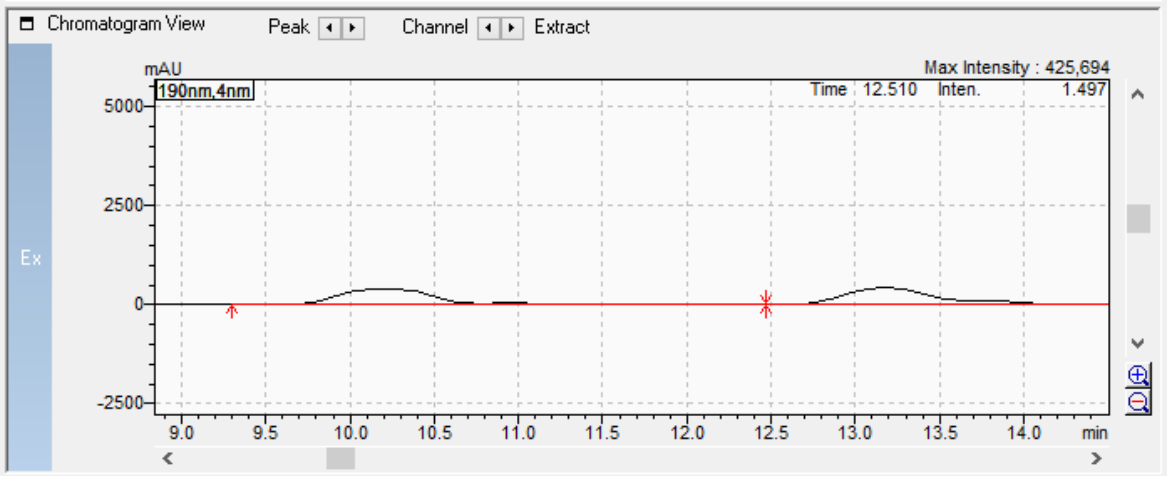
Ret. Time	Area%	Height	Area
20.538	17.889	69436	8526431
39.403	82.111	130694	39135920
	100.000	200131	47662351



3.20b

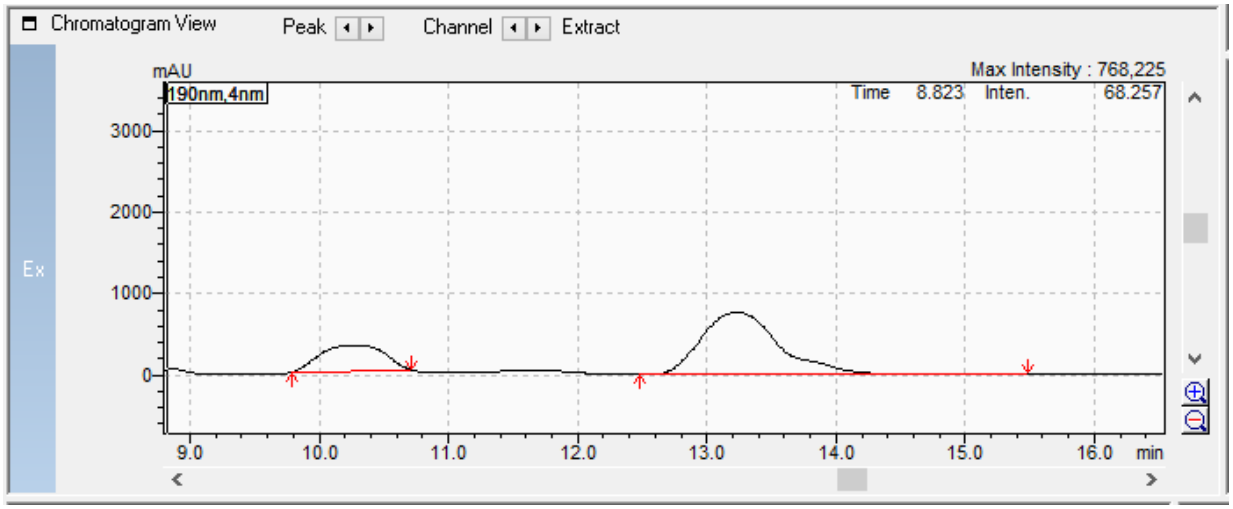
Chiral column HPLC analysis (Chiralcel AD-3 x 250 mm, 1.0 mL/min, 90:10 hexane:isopropanol, λ = 190 nm) t_R = 13.2 min (major), 10.3 min (minor):

Racemic 3.20b:

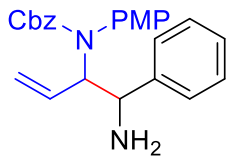


Ret. Time	Area%	Height	Area
10.198	49.538	389409	16765883
13.176	50.462	424582	17078659
	100.000	813991	33844543

3.20b from Cu(OAc)$_2$/PhanePhos reaction:



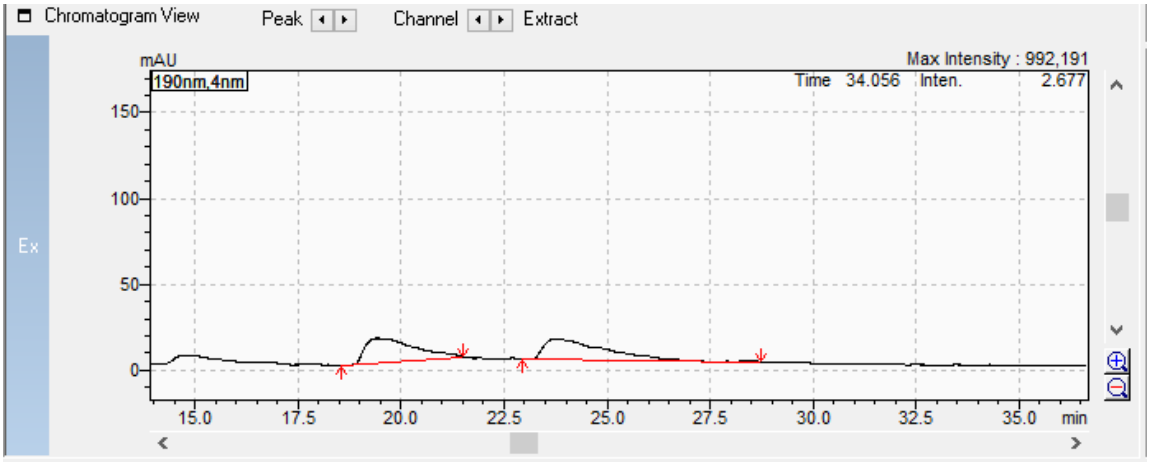
Ret. Time	Area%	Height	Area
10.271	25.164	309637	10789327
13.234	74.836	762832	32086304
	100.000	1072469	42875631



3.20c

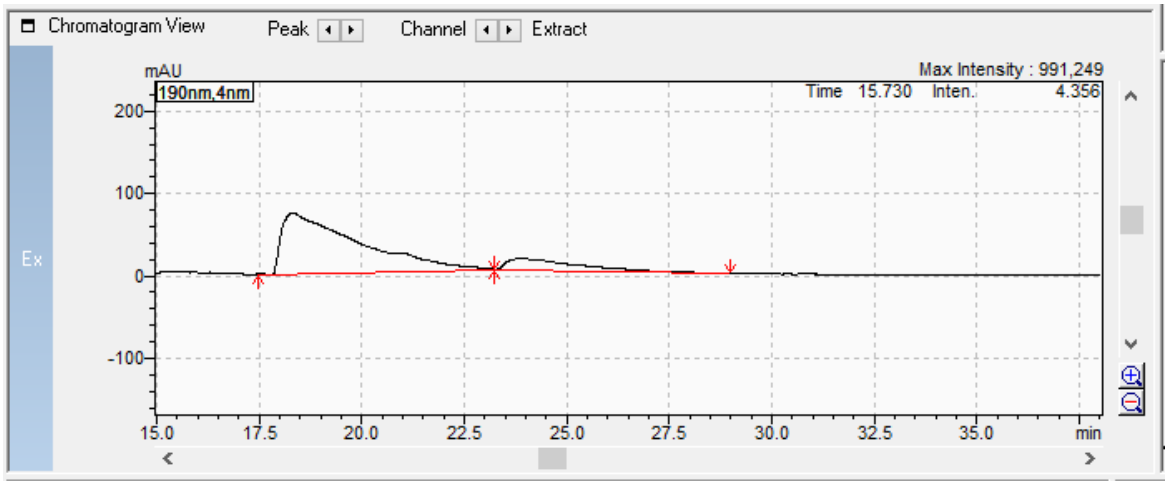
Chiral column HPLC analysis (Chiralcel AD-3 x 250 mm, 1.0 mL/min, 90:10 hexane:isopropanol, λ = 190 nm) t_R = 18.3 min (major), 23.9 min (minor):

Racemic 3.20c:

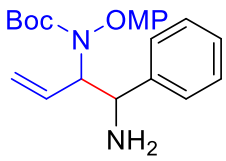


Ret. Time	Area%	Height	Area
19.395	49.912	14232	1168614
23.766	50.088	11682	1172752
	100.000	25914	2341366

3.20c from Cu(OAc)$_2$/PhanePhos reaction:



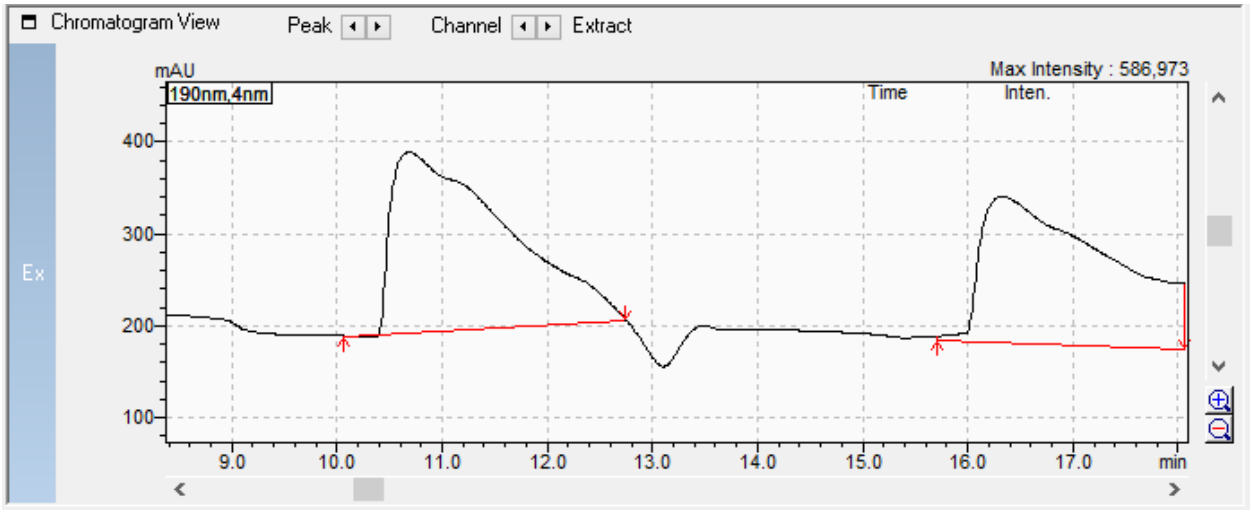
Ret. Time	Area%	Height	Area
18.326	85.624	73188	9485890
23.872	14.376	13304	1592604
	100.000	86492	11078493



3.20d

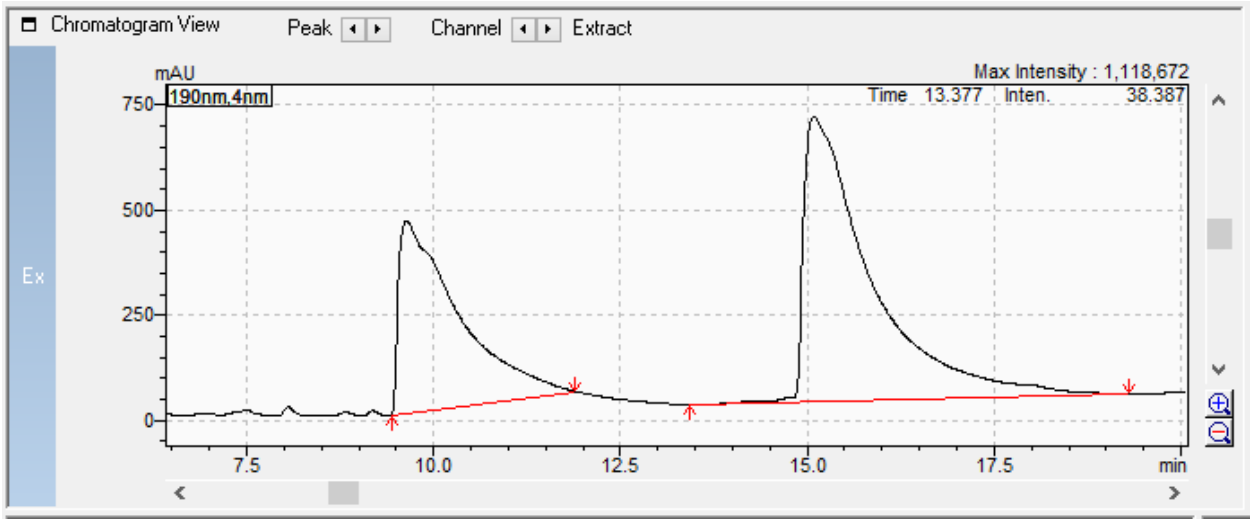
Chiral column HPLC analysis (Chiralcel AD-3 x 250 mm, 1.0 mL/min, 95:05 hexane:isopropanol, λ = 190 nm) t_R = 15.1 min (major), 9.6 min (minor):

Racemic 3.20d:

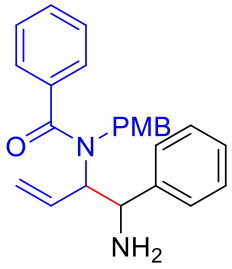


Ret. Time	Area%	Height	Area
10.685	50.617	193666	13239835
16.326	49.383	153892	12916927
	100.000	347557	26156762

3.20d from Cu(OAc)$_2$/PhanePhos reaction:



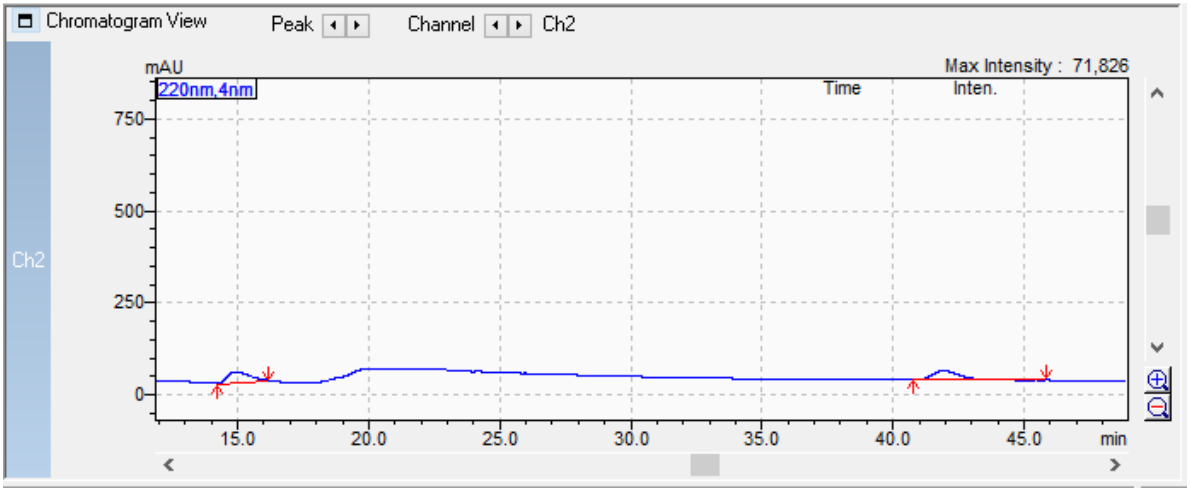
Ret. Time	Area%	Height	Area
9.634	37.484	457603	25367919
15.091	62.516	677456	42308651
	100.000	1135060	67676570



3.20e

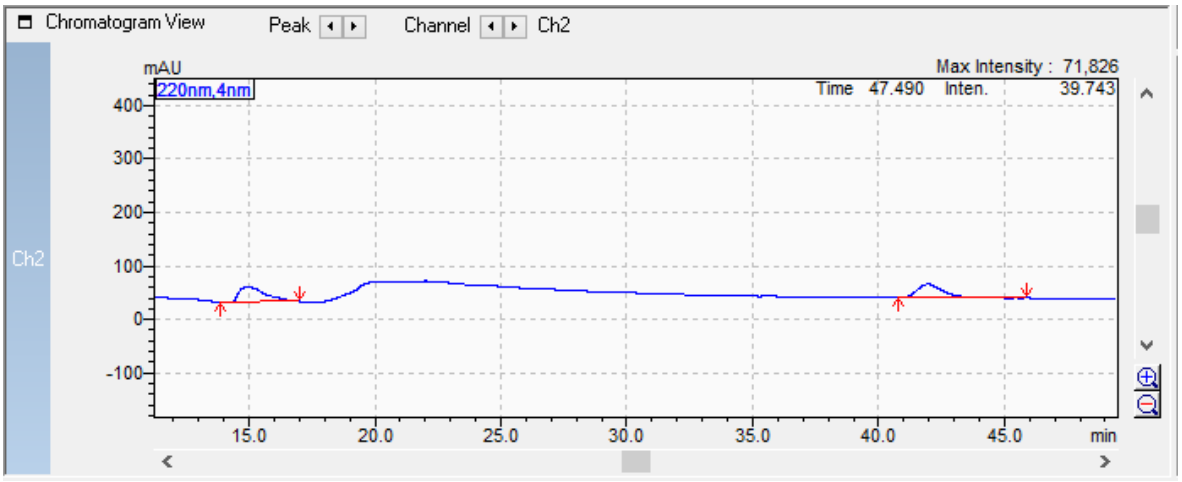
Chiral column HPLC analysis (Chiralcel AD-3 x 250 mm, 1.0 mL/min, 95:05 hexane:isopropanol, λ = 190 nm) t_R = 14.9 min (major), 42.0 min (minor):

Racemic 3.20e:

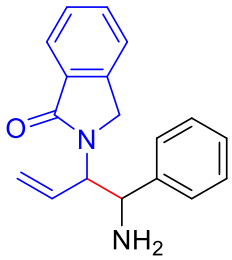


Ret. Time	Area%	Height	Area
15.280	53.442	28105	1405547
42.203	46.558	20399	1224477
	100.000	48504	2630024

3.20e from Cu(OAc)$_2$/PhanePhos reaction:



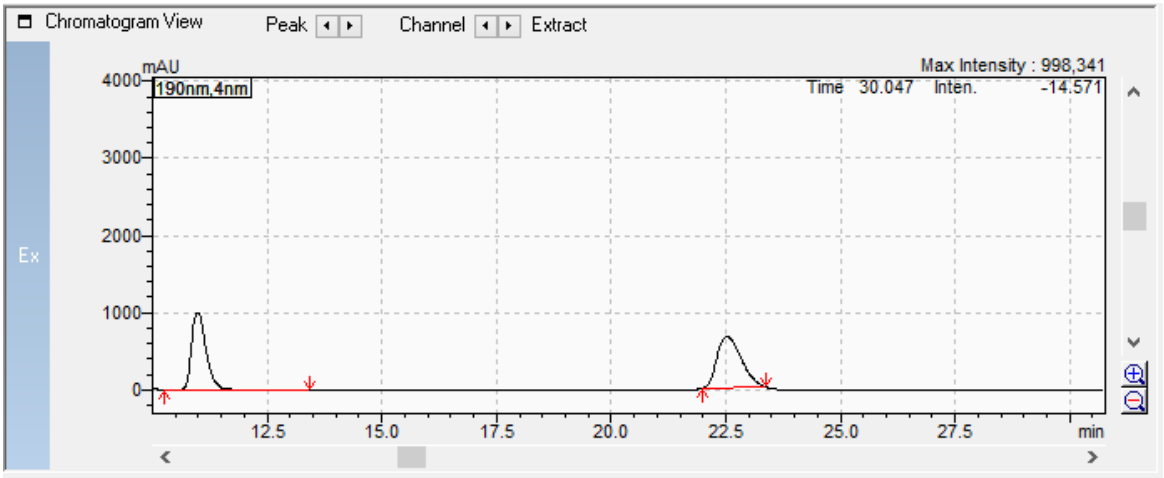
Ret. Time	Area%	Height	Area
14.897	53.957	28229	1970518
41.966	46.043	24709	1681471
	100.000	52939	3651989



3.21

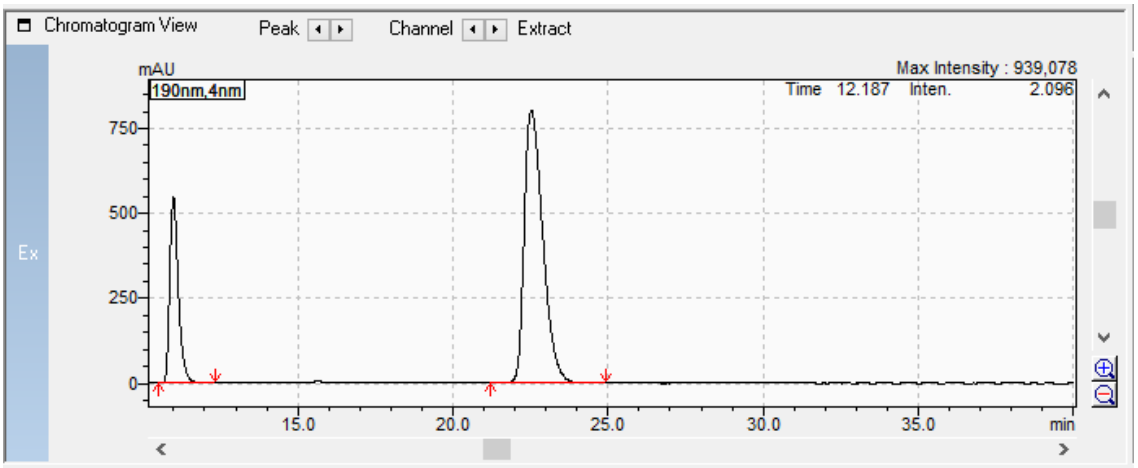
Chiral column HPLC analysis (Chiralcel AD-3 x 250 mm, 1.0 mL/min, 90:10 hexane:isopropanol, λ = 190 nm) t_R = 22.5 min (major), 11.0 min (minor):

Racemic 3.21:



Ret. Time	Area%	Height	Area
10.984	47.038	997369	21849238
22.523	52.962	662071	24601083
	100.000	1659440	46450321

3.21 from $Cu(OAc)_2$/PhanePhos reaction:



Ret. Time	Area%	Height	Area
10.992	23.815	545279	10432058
22.527	76.185	801171	33372540
	100.000	1346450	43804598

References

(1) Gupta, P.; Mahajan, N. Biocatalytic Approaches towards the Stereoselective Synthesis of Vicinal Amino Alcohols. *New Journal of Chemistry*. Royal Society of Chemistry 2018, pp 12296–12327. https://doi.org/10.1039/c8nj00485d.

(2) Iwatsuki, M.; Nishihara-Tsukashima, A.; Ishiyama, A.; Namatame, M.; Watanabe, Y.; Handasah, S.; Pranamuda, H.; Marwoto, B.; Matsumoto, A.; Takahashi, Y.; Otoguro, K.; Omura, S. Jogyamycin, a New Antiprotozoal Aminocyclopentitol Antibiotic, Produced by Streptomyces Sp. a-WM-JG-16.2. *Journal of Antibiotics* **2012**, *65* (3), 169–171. https://doi.org/10.1038/ja.2011.136.

(3) Sehl, T.; Maugeri, Z.; Rother, D. Multi-Step Synthesis Strategies towards 1,2-Amino Alcohols with Special Emphasis on Phenylpropanolamines. *J Mol Catal B Enzym* **2015**, *114*, 65–71. https://doi.org/10.1016/j.molcatb.2014.12.005.

(4) Bamou, F. Z.; Le, T. M.; Volford, B.; Szekeres, A.; Szakonyi, Z. Synthesis and Application of 1,2-Aminoalcohols with Neoisopulegol-Based Octahydrobenzofuran Core. *Molecules* **2020**, *25* (1). https://doi.org/10.3390/molecules25010021.

(5) Shao, X.; Li, K.; Malcolmson, S. J. Enantioselective Synthesis of Anti-1,2-Diamines by Cu-Catalyzed Reductive Couplings of Azadienes with Aldimines and Ketimines. *J Am Chem Soc* **2018**, *140* (23), 7083–7087. https://doi.org/10.1021/jacs.8b04750.

(6) Seebach, D. Methods of Reactivity Umpolung. *Angewandte Chemie International Edition in English* **1979**, *18* (4), 239–258. https://doi.org/10.1002/anie.197902393.

(7) Seebach, D. *ANGEWANDTE ©[X]~[DJD~ International Edition in English Methods of Reactivity U Mpolung*; 1979; Vol. 18.

(8) Welin, E. R.; Ngamnithiporn, A.; Klatte, M.; Lapointe, G.; Pototschnig, G. M.; Mcdermott, M. S. J.; Conklin, D.; Gilmore, C. D.; Tadross, P. M.; Haley, C. K.; Negoro, K.; Glibstrup, E.; Grünanger, C. U.; Allan, K. M.; Virgil, S. C.; Slamon, D. J.; Stoltz, B. M. *Concise Total Syntheses of (-)-Jorunnamycin A and (-)-Jorumycin Enabled by Asymmetric Catalysis*. https://www.science.org.

(9) Su, S.; Seiple, I. B.; Young, I. S.; Baran, P. S. Total Syntheses of (±)-Massadine and Massadine Chloride. *J Am Chem Soc* **2008**, *130* (49), 16490–16491. https://doi.org/10.1021/ja8074852.

(10) Sagandira, C. R.; Mathe, F. M.; Guyo, U.; Watts, P. The Evolution of Tamiflu Synthesis, 20 Years on: Advent of Enabling Technologies the Last Piece of the Puzzle? *Tetrahedron*. Elsevier Ltd September 11, 2020. https://doi.org/10.1016/j.tet.2020.131440.

(11) Clark, P. G. K.; Vieira, L. C. C.; Tallant, C.; Fedorov, O.; Singleton, D. C.; Rogers, C. M.; Monteiro, O. P.; Bennett, J. M.; Baronio, R.; Müller, S.; Daniels, D. L.; Méndez, J.; Knapp, S.; Brennan, P. E.; Dixon, D. J. LP99: Discovery and Synthesis of the First Selective BRD7/9 Bromodomain Inhibitor. *Angewandte Chemie* **2015**, *127* (21), 6315–6319. https://doi.org/10.1002/ange.201501394.

(12) Miao, H.; Guan, M.; Xiong, T.; Zhang, G.; Zhang, Q. Cobalt-Catalyzed Enantioselective Hydroamination of Arylalkenes with Secondary Amines. *Angewandte Chemie - International Edition* **2023**, *62* (2). https://doi.org/10.1002/anie.202213913.

(13) Dinér, P.; Nielsen, M.; Bertelsen, S.; Niess, B.; Jørgensen, K. A. Enantioselective Hydroxylation of Nitroalkenes: An Organocatalytic Approach. *Chemical Communications* **2007**, No. 35, 3646–3648. https://doi.org/10.1039/b707844g.

(14) Noyori, R.; And, †; Hashiguchi, S. *Asymmetric Transfer Hydrogenation Catalyzed by Chiral Ruthenium Complexes*; 1997. https://pubs.acs.org/sharingguidelines.

(15) Nazari, A.; Heravi, M. M.; Zadsirjan, V. Oxazolidinones as Chiral Auxiliaries in Asymmetric Aldol Reaction Applied to Natural Products Total Synthesis. *Journal of Organometallic Chemistry*. Elsevier B.V. January 15, 2021. https://doi.org/10.1016/j.jorganchem.2020.121629.

(16) Lisnyak, V. G.; Snyder, S. A. A Concise, Enantiospecific Total Synthesis of Chilocorine C Fueled by a Reductive Cyclization/Mannich Reaction Cascade. *J Am Chem Soc* **2020**, *142* (28), 12027–12033. https://doi.org/10.1021/jacs.0c04914.

(17) Jiang, Y.; Liu, D.; Rotella, M. E.; Deng, G.; Liu, Z.; Chen, W.; Zhang, H.; Kozlowski, M. C.; Walsh, P. J.; Yang, X. Net-1,2-Hydrogen Atom Transfer of Amidyl Radicals: Toward the Synthesis of 1,2-Diamine Derivatives. *J Am Chem Soc* **2023**, *145* (29), 16045–16057. https://doi.org/10.1021/jacs.3c04376.

(18) Smith, A. B.; Zhu, W.; Shirakami, S.; Sfouggatakis, C.; Doughty, V. A.; Bennett, C. S.; Sakamoto, Y. Total Synthesis of (+)-Spongistatin 1. An Effective Second-Generation Construction of an Advanced EF Wittig Salt, Fragment Union, and Final Elaboration. *Org Lett* **2003**, *5* (5), 761–764. https://doi.org/10.1021/ol034037a.

(19) Gargaro, S. L. *Asymmetric CuH-Catalyzed Reductive Coupling of Alleneamides with Carbonyl Electrophiles & Mechanistic Investigation into the Suzuki-Miyaura Cross-Coupling Reaction of Electron-Deficient Systems*; 2022.

(20) Collins, S.; Sieber, J. D. Development of Regiodivergent Asymmetric Reductive Coupling Reactions of Allenamides to Access Heteroatom-Rich Organic Compounds. *Chemical Communications* **2023**, *59* (67), 10087–10100. https://doi.org/10.1039/d3cc03013j.

(21) Farhang, M.; Akbarzadeh, A. R.; Rabbani, M.; Ghadiri, A. M. A Retrospective-Prospective Review of Suzuki–Miyaura Reaction: From Cross-Coupling Reaction to Pharmaceutical Industry Applications. *Polyhedron*. Elsevier Ltd November 15, 2022. https://doi.org/10.1016/j.poly.2022.116124.

(22) Funes-Ardoiz, I.; Maseras, F. Oxidative Coupling Mechanisms: Current State of Understanding. *ACS Catalysis*. American Chemical Society February 2, 2018, pp 1161–1172. https://doi.org/10.1021/acscatal.7b02974.

(23) Knappke, C. E. I.; Grupe, S.; Gärtner, D.; Corpet, M.; Gosmini, C.; Jacobi Von Wangelin, A. Reductive Cross-Coupling Reactions between Two Electrophiles. *Chemistry - A European Journal* **2014**, *20* (23), 6828–6842. https://doi.org/10.1002/chem.201402302.

(24) Agrawal, T.; Sieber, J. D. Recent Developments in C-C Bond Formation Using Catalytic Reductive Coupling Strategies. *Synthesis (Germany)*. Georg Thieme Verlag September 16, 2020, pp 2623–2638. https://doi.org/10.1055/s-0040-1707128.

(25) Richmond, E.; Moran, J. Recent Advances in Nickel Catalysis Enabled by Stoichiometric Metallic Reducing Agents. *Synthesis (Germany)* **2018**, *50* (3), 499–513. https://doi.org/10.1055/s-0036-1591853.

(26) Sakai, H. A.; Liu, W.; Le, C.; MacMillan, D. W. C. Cross-Electrophile Coupling of Unactivated Alkyl Chlorides. *J Am Chem Soc* **2020**, *142* (27), 11691–11697. https://doi.org/10.1021/jacs.0c04812.

(27) Jutand, A. Contribution of Electrochemistry to Organometallic Catalysis. *Chem Rev* **2008**, *108* (7), 2300–2347. https://doi.org/10.1021/cr068072h.

(28) Kong, J. R.; Ngai, M. Y.; Krísche, M. J. Highly Enantioselective Direct Reductive Coupling of Conjugated Alkynes and α-Ketoesters via Rhodium-Catalyzed Asymmetric Hydrogenation. *J Am Chem Soc* **2006**, *128* (3), 718–719. https://doi.org/10.1021/ja056474l.

(29) Han, S. B.; Kim, I. S.; Han, H.; Krische, M. J. Enantioselective Carbonyl Reverse Prenylation from the Alcohol or Aldehyde Oxidation Level Employing 1,1-Dimethylallene as the Prenyl Donor. *J Am Chem Soc* **2009**, *131* (20), 6916–6917. https://doi.org/10.1021/ja902437k.

(30) Shibahara, F.; Bower, J. F.; Krische, M. J. Ruthenium-Catalyzed C-C Bond Forming Transfer Hydrogenation: Carbonyl Allylation from the Alcohol or Aldehyde Oxidation Level Employing Acyclic 1,3-Dienes as Surrogates to Preformed Allyl Metal Reagents. *J Am Chem Soc* **2008**, *130* (20), 6338–6339. https://doi.org/10.1021/ja801213x.

(31) In, S. K.; Ngai, M. Y.; Krische, M. J. Enantioselective Iridium-Catalyzed Carbonyl Allylation from the Alcohol or Aldehyde Oxidation Level Using Allyl Acetate as an Allyl Metal Surrogate. *J Am Chem Soc* **2008**, *130* (20), 6340–6341. https://doi.org/10.1021/ja802001b.

(32) Komanduri, V.; Krische, M. J. Enantioselective Reductive Coupling of 1,3-Enynes to Heterocyclic Aromatic Aldehydes and Ketones via Rhodium-Catalyzed Asymmetric Hydrogenation: Mechanistic Insight into the Role of Brønsted Acid Additives. *J Am Chem Soc* **2006**, *128* (51), 16448–16449. https://doi.org/10.1021/ja0673027.

(33) Yang, Y.; Perry, I. B.; Lu, G.; Liu, P.; Buchwald, S. L. Copper-Catalyzed Asymmetric Addition of Olefin-Derived Nucleophiles to Ketones. *Science (1979)* **2016**, *353* (6295), 144–150. https://doi.org/10.1126/science.aaf7720.

(34) Liu, R. Y.; Yang, Y.; Buchwald, S. L. Regiodivergent and Diastereoselective CuH-Catalyzed Allylation of Imines with Terminal Allenes. *Angewandte Chemie* **2016**, *128* (45), 14283–14286. https://doi.org/10.1002/ange.201608446.

(35) Li, C.; Shin, K.; Liu, R. Y.; Buchwald, S. L. Engaging Aldehydes in CuH-Catalyzed Reductive Coupling Reactions: Stereoselective Allylation with Unactivated 1,3-Diene Pronucleophiles. *Angewandte Chemie* **2019**, *131* (47), 17230–17236. https://doi.org/10.1002/ange.201911008.

(36) Klake, R. K.; Gargaro, S. L.; Gentry, S. L.; Elele, S. O.; Sieber, J. D. Development of a Strategy for Linear-Selective Cu-Catalyzed Reductive Coupling of Ketones and Allenes for the Synthesis of Chiral γ-Hydroxyaldehyde Equivalents. *Org Lett* **2019**, *21* (19), 7992–7998. https://doi.org/10.1021/acs.orglett.9b02973.

(37) Gargaro, S. L.; Klake, R. K.; Burns, K. L.; Elele, S. O.; Gentry, S. L.; Sieber, J. D. Access to a Catalytically Generated Umpolung Reagent through the Use of Cu-Catalyzed Reductive Coupling of Ketones and Allenes for the Synthesis of Chiral Vicinal Aminoalcohol Synthons. *Org Lett* **2019**, *21* (23), 9753–9758. https://doi.org/10.1021/acs.orglett.9b03937.

(38) Klake, R. K.; Gargaro, S. L.; Gentry, S. L.; Elele, S. O.; Sieber, J. D. Development of a Strategy for Linear-Selective Cu-Catalyzed Reductive Coupling of Ketones and Allenes for the Synthesis of Chiral γ-Hydroxyaldehyde Equivalents. *Org Lett* **2019**, *21* (19), 7992–7998. https://doi.org/10.1021/acs.orglett.9b02973.

(39) Evans, D. A.; Bartroli, J.; Shih, T. L. Enantioselective Aldol Condensations. 2. Erythro-Selective Chiral Aldol Condensations via Boron Enolates. *J Am Chem Soc* **1981**, *103* (8), 2127–2129. https://doi.org/10.1021/ja00398a058.

(40) Wei, L.-L.; Mulder, J. A.; Xiong, H.; Zificsak, C. A.; Douglas, C. J.; Hsung, R. P. Efficient Preparations of Novel Ynamides and Allenamides. *Tetrahedron* **2001**, *57* (3), 459–466. https://doi.org/10.1016/S0040-4020(00)01014-0.

(41) Gargaro, S. L.; Klake, R. K.; Burns, K. L.; Elele, S. O.; Gentry, S. L.; Sieber, J. D. Access to a Catalytically Generated Umpolung Reagent through the Use of Cu-Catalyzed Reductive Coupling of Ketones and Allenes for the Synthesis of Chiral Vicinal Aminoalcohol Synthons. *Org Lett* **2019**, *21* (23), 9753–9758. https://doi.org/10.1021/acs.orglett.9b03937.

(42) Burgey, C. S.; Paone, D. V.; Shaw, A. W.; Deng, J. Z.; Nguyen, D. N.; Potteiger, C. M.; Graham, S. L.; Vacca, J. P.; Williams, T. M. Synthesis of the (3R,6S)-3-Amino-6-(2,3-Difluorophenyl)Azepan-2-One of Telcagepant (MK-0974), a Calcitonin Gene-Related Peptide Receptor Antagonist for the Treatment of Migraine Headache. *Org Lett* **2008**, *10* (15), 3235–3238. https://doi.org/10.1021/ol8011524.

(43) Kanai, M.; Yasumoto, M.; Kuriyama, Y.; Inomiya, K.; Katsuhara, Y.; Higashiyama, K.; Ishii, A. Highly Regioselective Hydrogenolysis of Bis(α-Methylbenzyl)Amine Derivatives Affected by the Trifluoromethyl Substituent on the Aromatic Ring. *Org Lett* **2003**, *5* (7), 1007–1010. https://doi.org/10.1021/ol034014w.

(44) Tsai, E. Y.; Liu, R. Y.; Yang, Y.; Buchwald, S. L. A Regio- and Enantioselective CuH-Catalyzed Ketone Allylation with Terminal Allenes. *J Am Chem Soc* **2018**, *140* (6), 2007–2011. https://doi.org/10.1021/jacs.7b12271.

(45) Hughes, G.; Kimura, M.; Buchwald, S. L. Catalytic Enantioselective Conjugate Reduction of Lactones and Lactams. *J Am Chem Soc* **2003**, *125* (37), 11253–11258. https://doi.org/10.1021/ja0351692.

(46) Agrawal, T.; Martin, R. T.; Collins, S.; Wilhelm, Z.; Edwards, M. D.; Gutierrez, O.; Sieber, J. D. Access to Chiral Diamine Derivatives through Stereoselective Cu-Catalyzed Reductive Coupling of Imines and Allenamides. *Journal of Organic Chemistry* **2021**, *86* (7), 5026–5046. https://doi.org/10.1021/acs.joc.0c02971.

(47) Xu, B.; Arndtsen, B. A. Palladium-Catalyzed Stille-Type Coupling of N -Acyl Iminium Ions with Distannanes: A Multicomponent Synthesis of α-Amidostannanes. *ACS Catal* **2014**, *4* (3), 843–846. https://doi.org/10.1021/cs401164z.

(48) Koch, V.; Lorion, M. M.; Barde, E.; Bräse, S.; Cossy, J. Cobalt-Catalyzed α-Arylation of Substituted α-Halogeno β-Lactams. *Org Lett* **2019**, *21* (16), 6241–6244. https://doi.org/10.1021/acs.orglett.9b02122.

(49) Grigg, R.; McMeekin, P.; Sridharan, V. X=Y-ZH Systems as Potential 1,3-Dipoles. Part 45.1,2 Proton Sponge Effects on the 1,2-Prototropic Formation of Azomethine Ylides from Arylidene Benzylamines. *Tetrahedron* **1995**, *51* (48), 13331–13346. https://doi.org/10.1016/0040-4020(95)00846-Z.

(50) Lee, B.; Lee, K. H.; Lim, B. W.; Cho, J.; Nam, W.; Hur, N. H. Direct Synthesis of Imines via Solid State Reactions of Carbamates with Aldehydes. *Adv Synth Catal* **2013**, *355* (2–3), 389–394. https://doi.org/10.1002/adsc.201200907.

(51) Achar, T. K.; Maiti, S.; Mal, P. IBX Works Efficiently under Solvent Free Conditions in Ball Milling. *RSC Adv* **2014**, *4* (25), 12834–12839. https://doi.org/10.1039/c4ra00415a.

(52) Klake, R. K.; Edwards, M. D.; Sieber, J. D. Synthesis of 1,2-Aminoalcohols through Enantioselective Aminoallylation of Ketones by Cu-Catalyzed Reductive Coupling. *Org Lett* **2021**, *23* (16), 6444–6449. https://doi.org/10.1021/acs.orglett.1c02258.

(53) Heathcock, C. H.; Kleinman, E. F.; Binkley, E. S. Total Synthesis of Lycopodium Alkaloids: (.+-.)-Lycopodine, (.+-.)-Lycodine, and (.+-.)-Lycodoline. *J Am Chem Soc* **1982**, *104* (4), 1054–1068. https://doi.org/10.1021/ja00368a024.

(54) Kong, Y.; Boggu, P. R.; Park, G. M.; Kim, Y. S.; An, S. H.; Kim, I. S.; Jung, Y. H. Total Synthesis of Eliglustat via Diastereoselective Amination of Chiral Para-Methoxycinnamyl Benzyl Ether. *Molecules* **2022**, *27* (8), 2603. https://doi.org/10.3390/molecules27082603.

(55) Endoma-Arias, M. A. A.; Cox, D. P.; Hudlicky, T. General Method of Synthesis for Naloxone, Naltrexone, Nalbuphone, and Nalbuphine by the Reaction of Grignard Reagents with an Oxazolidine Derived from Oxymorphone. *Adv Synth Catal* **2013**, *355* (9), 1869–1873. https://doi.org/10.1002/adsc.201300284.

(56) Moon, P. J.; Yin, S.; Lundgren, R. J. Ambient Decarboxylative Arylation of Malonate Half-Esters via Oxidative Catalysis. *J Am Chem Soc* **2016**, *138* (42), 13826–13829. https://doi.org/10.1021/jacs.6b08906.

(57) Dhudshia, B.; Cooper, B. F. T.; MacDonald, C. L. B.; Thadani, A. N. The Asymmetric Total Synthesis of (-)-Securinine. *Chemical Communications* **2009**, No. 4, 463–465. https://doi.org/10.1039/b816576a.

(58) Li, P.; Evans, C. D.; Wu, Y.; Cao, B.; Hamel, E.; Joullié, M. M. Evolution of the Total Syntheses of Ustiloxin Natural Products and Their Analogues. *J Am Chem Soc* **2008**, *130* (7), 2351–2364. https://doi.org/10.1021/ja710363p.

(59) Tamura, K.; Kumagai, N.; Shibasaki, M. An Enantioselective Synthesis of the Key Intermediate for Triazole Antifungal Agents; Application to the Catalytic Asymmetric Synthesis of Efinaconazole (Jublia). *Journal of Organic Chemistry* **2014**, *79* (7), 3272–3278. https://doi.org/10.1021/jo500369y.

(60) Bodkin, J. A.; McLeod, M. D. The Sharpless Asymmetric Aminohydroxylation. *Journal of the Chemical Society. Perkin Transactions 1*. December 21, 2002, pp 2733–2746. https://doi.org/10.1039/b111276g.

(61) He, Q.; Pu, M. P.; Jiang, Z.; Wang, H.; Feng, X.; Liu, X. Asymmetric Epoxidation of Alkenes Catalyzed by a Cobalt Complex. *J Am Chem Soc* **2023**, *145* (28), 15611–15618. https://doi.org/10.1021/jacs.3c05476.

(62) Tyagi, A.; Yadav, N.; Khan, J.; Mondal, S.; Hazra, C. K. Brønsted Acid-Catalysed Epoxide Ring-Opening Using Amine Nucleophiles: A Facile Access to β-Amino Alcohols. *Chem Asian J* **2022**, *17* (14). https://doi.org/10.1002/asia.202200379.

(63) Hu, H.; Wang, Z. Cr-Catalyzed Asymmetric Cross Aza-Pinacol Couplings for β-Amino Alcohol Synthesis. *J Am Chem Soc* **2023**, *145* (38), 20775–20781. https://doi.org/10.1021/jacs.3c08493.

(64) Jin, W.; Li, X.; Wan, B. A Highly Diastereo-and Enantioselective Copper(I)-Catalyzed Henry Reaction Using a Bis(Sulfonamide)-Diamine Ligand. *Journal of Organic Chemistry* **2011**, *76* (2), 484–491. https://doi.org/10.1021/jo101932a.

(65) Adams, J. P. Nitro and Related Groups. *Journal of the Chemical Society. Perkin Transactions 1*. September 16, 2002, pp 2586–2597. https://doi.org/10.1039/b009711j.

(66) Kende, A. S.; Mendoza, J. S. Controlled Reduction of Nitroalkanes to Alkyl Hydroxylamines or Amines by Samarium Diiodide. *Tetrahedron Lett* **1991**, *32* (14), 1699–1702. https://doi.org/10.1016/S0040-4039(00)74307-3.

(67) Collins, S.; Sieber, J. D. Studies Toward Improved Enantiocontrol in the Asymmetric Cu-Catalyzed Reductive Coupling of Ketones and Allenamides: 1,2-Aminoalcohol Synthesis. *Org Lett* **2023**, *25* (9), 1425–1430. https://doi.org/10.1021/acs.orglett.3c00157.

(68) Myers, A. G.; Yang, B. H.; Kopecky, D. J. *Lithium Amidotrihydroborate, a Powerful New Reductant. Transformation of Tertiary Amides to Primary Alcohols*; 1996; Vol. 37.

(69) Kano, S.; Yuasa, Y.; Yokomatsu, T.; Shibuya, S. Diastereoconversion of Threo 2-Amino Alcohols to Erythro Isomers Through a New Cyclocarbamation. *Heterocycles* **1988**, *27* (5), 1241. https://doi.org/10.3987/COM-88-4501.

(70) Clark, A. J.; Curran, D. P.; Fox, D. J.; Ghelfi, F.; Guy, C. S.; Hay, B.; James, N.; Phillips, J. M.; Roncaglia, F.; Sellars, P. B.; Wilson, P.; Zhang, H. Axially Chiral Enamides: Substituent Effects, Rotation Barriers, and Implications for Their Cyclization Reactions. *Journal of Organic Chemistry* **2016**, *81* (13), 5547–5565. https://doi.org/10.1021/acs.joc.6b00889.

(71) Evans, D. A.; Bartroli, J.; Shih, T. L. Enantioselective Aldol Condensations. 2. Erythro-Selective Chiral Aldol Condensations via Boron Enolates. *J Am Chem Soc* **1981**, *103* (8), 2127–2129. https://doi.org/10.1021/ja00398a058.

(72) Diaz-Muñoz, G.; Miranda, I. L.; Sartori, S. K.; de Rezende, D. C.; Alves Nogueira Diaz, M. Use of Chiral Auxiliaries in the Asymmetric Synthesis of Biologically Active Compounds: A Review. *Chirality*. John Wiley and Sons Inc. October 1, 2019, pp 776–812. https://doi.org/10.1002/chir.23103.

(73) Gnas, Y.; Glorius, F. Chiral Auxiliaries - Principles and Recent Applications. *Synthesis*. June 14, 2006, pp 1899–1930. https://doi.org/10.1055/s-2006-942399.

(74) Heravi, M. M.; Zadsirjan, V.; Farajpour, B. Applications of Oxazolidinones as Chiral Auxiliaries in the Asymmetric Alkylation Reaction Applied to Total Synthesis. *RSC Adv* **2016**, *6* (36), 30498–30551. https://doi.org/10.1039/C6RA00653A.

(75) Xiang, S. H.; Tan, B. Advances in Asymmetric Organocatalysis over the Last 10 Years. *Nature Communications*. Nature Research December 1, 2020. https://doi.org/10.1038/s41467-020-17580-z.

(76) Trost, B. M. *Asymmetric Catalysis: An Enabling Science*; 2004. https://www.pnas.org.

(77) Matsunaga, S.; Shibasaki, M. Recent Advances in Cooperative Bimetallic Asymmetric Catalysis: Dinuclear Schiff Base Complexes. *Chemical Communications* **2014**, *50* (9), 1044–1057. https://doi.org/10.1039/c3cc47587e.

(78) Sheldon, R. A. ReviewChirotechnology: Designing Economic Chiral Syntheses. *Journal of Chemical Technology & Biotechnology* **1996**, *67* (1), 1–14. https://doi.org/10.1002/(sici)1097-4660(199609)67:1<1::aid-jctb531>3.0.co;2-l.

(79) Kruger, C.; Rochow, E. G.; Wannagat, U. . *Chem Ber* **1963**, *96*, 2132.

(80) Panunzio, M.; Zarantonello, P. *Synthesis and Use of N-(Trimethylsilyl)Imines*; 1998. https://pubs.acs.org/sharingguidelines.

(81) Watanabe, K.; Ito, K.; Itsuno, S. *Enantioselective Addition of Chiraily Modified Allylboranes to N-(Trimethylsilyl)Benzaldehyde Imine*; 1995; Vol. 6.

(82) Chen, G. M.; Ramachandran, P. V.; Brown, H. C. The Critical Importance of Water in the Asymmetric Allylboration of N- Trimethylsilylbenzaldimines with B-Allyldiisopinocampheylborane. *Angewandte Chemie - International Edition* **1999**, *38* (6), 825–826. https://doi.org/10.1002/(SICI)1521-3773(19990315)38:6<825::AID-ANIE825>3.0.CO;2-V.

(83) Colvin, E. W.; McGarry, D.; Nugent, M. J. Silicon-Assisted Synthesis of β-Lactams. *Tetrahedron* **1988**, *44* (13), 4157–4172. https://doi.org/10.1016/S0040-4020(01)86663-1.

(84) Chang, H. H.; He, X. X.; Zang, Z. L.; Zhou, C. H.; Cai, G. X. Visible-Light-Driven α-Oxidation of Amide C(Sp3)−H Bonds to Imides via N-Bromosuccinimide and Water. *Asian J Org Chem* **2022**, *11* (12). https://doi.org/10.1002/ajoc.202200500.

(85) Gargaro, S. L.; Klake, R. K.; Sieber, J. D. Asymmetric Access to Boryl-Substituted Vicinal Aminoalcohols through Cu-Catalyzed Reductive Coupling. *Org Lett* **2023**, *25* (25), 4644–4649. https://doi.org/10.1021/acs.orglett.3c01459.