NORTHWESTERN UNIVERSITY

I. Lewis Base-Promoted Additions of Trialkoxysilylalkynes
II. Multi-component Homoenolate Reactions Using Acylsilanes

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ABSTRACT

I. Lewis Base-Promoted Additions of Trialkoxysilylalkynes
II. Multi-component Homoenolate Reactions Using Acylsilanes

Robert Bryant Lettan II

Two new methods have been developed employing silicon-containing molecules in novel organic transformations. The first strategy utilizes Lewis base-activation of triethoxysilylalkynes to deliver mild acetylide nucleophile equivalents. The second approach involves the use of enolate additions to acylsilanes to generate β-silyloxy homoenolate intermediates.

Lewis base-catalyzed activation of triethoxysilylalkynes promotes the addition of alkynyl units to aldehydes and ketones. The resulting propargyl alcohols are isolated in high yields. The use of Lewis base catalysis in this reaction allows for the mild acetylide generation. This facet allows for the addition of alkynyl units to base-sensitive functionality (e.g. aliphatic aldehydes and ketones) and for the selective addition to aldehydes and ketones in the presence of other carbonyl functionality (e.g. esters). Mechanistic studies indicate that the reaction is proceeding by an auto-catalytic cycle. Additionally, the Lewis base-activated pentavalent intermediate can be visualized by low temperature ^{29}Si NMR spectroscopy. Furthermore, the developed reaction has been applied to the diastereoselective Lewis base-promoted addition of alkynes to *N-tert-*

butanesulfonyl imines, affording chiral propargyl amines in exceptional yield and selectivity.

Amide enolate additions to acylsilanes generate stable β-silyloxy homoenolate intermediates. These homoenolates have been shown to undergo addition to a variety of electrophiles, including alkyl halides, aldehydes, ketones, and imines in good yields. Intramolecular cyclization of the β-silyloxy homoenolate intermediate onto the amide carbonyl is not observed. Additionally, the addition to imines leads to the formation of γ-amino-β-hydroxy amides with excellent diastereoselectivities. Importantly, these products can be efficiently cyclized under microwave-assisted conditions to form biologically valuable highly substituted γ-lactams. The use of chiral amide auxiliary control in the process permits the stereoselective formation of the homoenolate addition products, through a mechanistically investigated thermodynamic equilibration pathway.

Thesis Advisor: Professor Karl A. Scheidt

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List of Abbreviations

18-c-6 = 18-crown-6 ether

Ac = acetyl

Ar = aryl

ax. = axial

BINOL = 1,1'-bi(2-naphthol)

Bn = benzyl

Boc = *tert*-butyloxycarbonyl

BP = boiling point

Bu = butyl

cAMP = cyclic adenosine monophosphate

conc. = concentrated

Cy = cyclohexyl

DABCO = 1,4-diazabicyclo[2.2.2]octane

DMAP = 4-(dimethylamino)pyridine

DMF = *N*,*N*-dimethylformamide

DMPU = *N*,*N′*-dimethyl-*N*,*N′*-propylene urea

DMSO = dimethylsulfoxide

dr = diastereomeric ratio

E = electrophile

ED_{50} = effective dose, 50% (amount of drug that produces a therapeutic response in 50% of the people taking it)

ee = enantiomeric excess

EI = electron impact

eq. = equatorial

equiv. = equivalents

Et = ethyl

EWG = electron withdrawing group

FT = Fourier transform

GC = gas chromatography

GCMS = gas chromatography mass spectrometry

HIV = human immunodeficiency virus

HMPA = hexamethylphosphorictriamide

HOMO = highest occupied molecular orbital

HPLC = high pressure liquid chromatography

IC_{50} = half maximal inhibitory concentration (concentration of inhibitor that is required for 50% inhibition of its target)

IPA = isopropanol

IR = infrared

K_i = binding affinity

LA = Lewis acid

LB = Lewis base

LDA = lithium diisopropylamine

Lindlar's catalyst = 5% $Pd/CaCO_3$ + $Pb(OCOCH_3)$ + quinoline

LUMO = lowest unoccupied molecular orbital

Me = methyl

mes = mesityl (2,4,6-trimethylphenyl)

mp = melting point

N = nucleophile

NMP = *N*-methylpyrrolidine

NMR = nuclear magnetic resonance

NOE = nuclear Overhauser enhancement

ORTEP = Oak Ridge thermal ellipsoid plot

Ph = phenyl

PPTS = pyridinium *p*-toluenesulfonate

Pr = propyl

R_f = response factor

$\Delta S^{\ddagger}$ = entropy of activation

TBAF = tetrabutylammonium fluoride

TBAT = tetrabutylammonium triphenyldifluorosilicate

TBC = tetrabutylammonium cyanide

TBDPS = *tert*-butyldiphenylsilyl

TFA = trifluoroacetic acid

THF = tetrahydrofuran

TIPS = triisopropylsilyl

TLC = thin layer chromatography

TMEDA = *N*, *N*, *N′*,*N′*-tetramethylethylenediamine

TOPO = trioctylphosphine oxide

UV = ultra-violet

Dedication

This work is dedicated to my wife Janna and my two buddies, Doc and Charlie. They are the reason I get up every morning and have a smile on my face every night I go home.

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Lewis Base-Promoted Additions of Trialkoxysilylalkynes

Portions of this chapter appear in the following publication:

Lettan, R. B., II; Scheidt, K. A. "Lewis Base-Catalyzed Additions of Alkynes Using Triethoxysilylalkynes." *Org. Lett.* **2005**, *7*, 3227-3230.

Chapter 1 Lewis Base-Promoted Additions of Trialkoxysilylalkynes

1.1 Lewis Base-Activation as a Method for Synthesis

Chemical reactions catalyzed by nucleophilic species (Lewis bases) possess significant potential for new bond-forming strategies. The success of this approach is dictated by the ability of the nucleophilic Lewis base to increase the energy of the highest occupied molecular orbital (HOMO) of the nucleophilic species (Figure 1-1), creating a more favorable reaction.[1] Conversely, the more commonly employed Lewis acid counter-approach utilizes an electrophilic Lewis acid to decrease the energy of the lowest unoccupied molecular orbital (LUMO) of the electrophilic moiety of a reaction. In addition to the mode of activation illustrated in Figure 1-1, nucleophilic addition of a Lewis base to an electrophile can also occur, decreasing the LUMO of the electrophile in the reaction process (see section 1.2.3).[2,3]

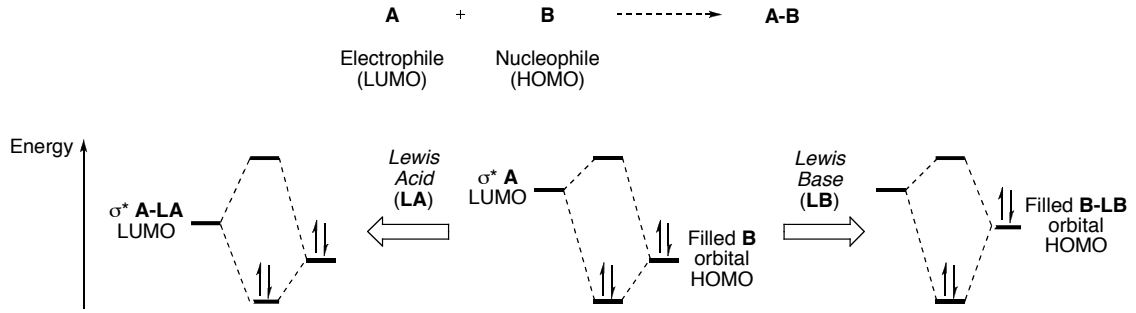


Figure 1-1. Lewis acid/base activation

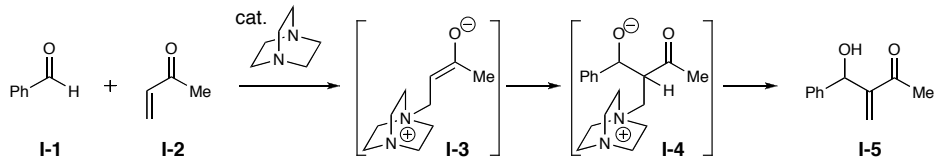
Although many advances in Lewis base-catalyzed processes have been realized over the past decade, they have not been explored nearly to the same extent as Lewis acid or transition metal-promoted processes. Consequently, these organocatalytic nucleophilic manifolds possess considerable promise in new carbon-carbon bond-forming reactions.

1.2 Lewis Base-Activated Processes

1.2.1 Morita-Baylis-Hillman and Rauhut-Currier Reactions

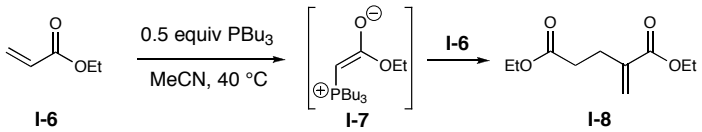
At approximately the same time, Morita and coworkers,[4] and Baylis and Hillman,[5] reported the carbon-carbon bond-formation of an electron poor alkene with a carbon nucleophile (Scheme 1-1). In the presence of methyl vinyl ketone (**I-2**), a catalytic amount of the tertiary amine Lewis base 1,4-diazabicyclo[2.2.2]octane (DABCO) undergoes a conjugate addition to give enolate **I-3**. Aldol addition of enolate **I-3** to benzaldehyde gives alkoxide **I-4**, which upon elimination of DABCO proceeds to yield vinyl ketone **I-5**.

Scheme 1-1. Morita-Baylis-Hillman reaction



Tertiary phosphines have also been shown to be effective Lewis base promoters for this reaction manifold. In fact, the Rauhut and Currier process pre-dated the Morita-Baylis-Hilman reaction with a similar transformation utilizing tributylphosphine addition in the dimerization of ethyl acrylate (**I-6**, Scheme 1-2).[6] Michael addition of enolate **I-7** to another equivalent of ethyl acrylate affords vinyl ketone **I-8**.

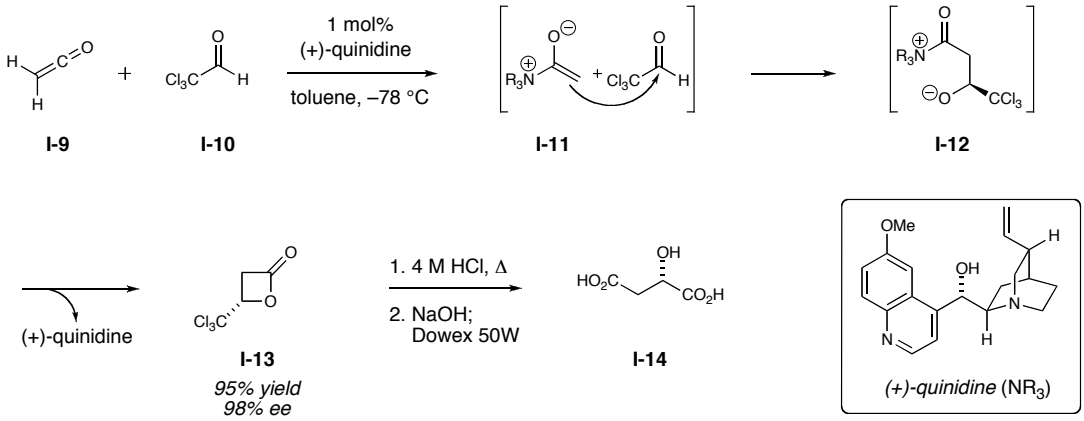
Scheme 1-2. Rauhut-Currier reaction



1.2.2 Enantioselective Synthesis of β-Lactones and β-Lactams

In 1982, Wynberg and Staring reported a Lewis base-catalyzed approach toward the asymmetric synthesis of β-lactones (Scheme 1-3).[7] With this method, ketene (**I-9**) undergoes nucleophilic attack from (+)-quinidine to afford zwitterionic intermediate **I-11**. Subsequent diastereoselective addition of intermediate **I-11** to chloral (**I-10**), followed by intramolecular cyclization, affords (*S*)-β-lactone **I-13**, which can be readily converted to *(S)*-malic acid (**I-14**). Twenty years after Wynberg and Stering's report, Lectka and coworkers published a similar protocol for the enantioselective synthesis of β-lactams, substituting *N*-tosyl-α-imino esters for chloral.[8]

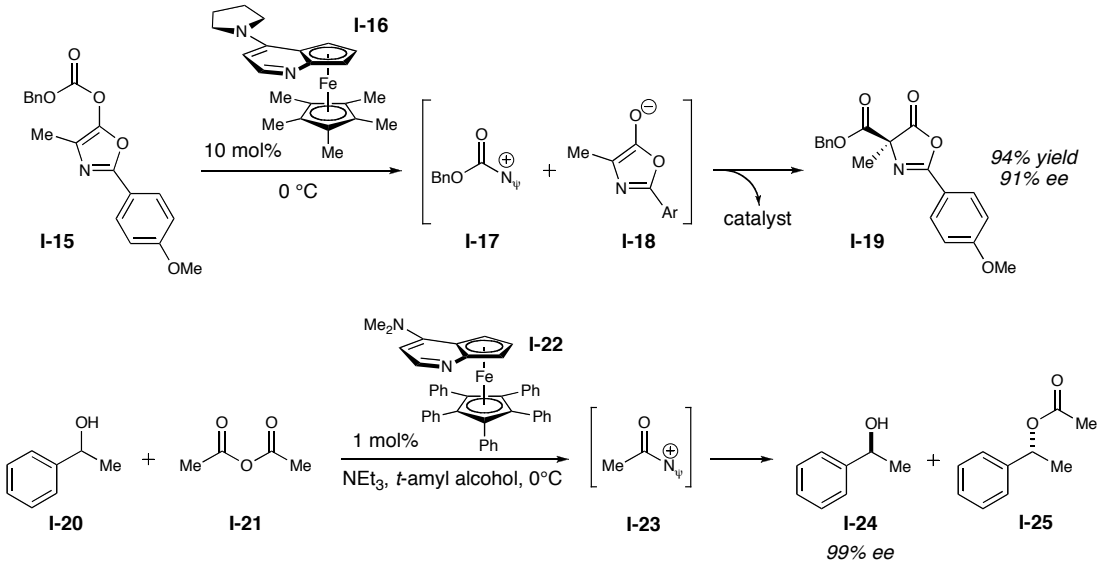
Scheme 1-3. Asymmetric synthesis of *(S)*-malic acid from ketene and chloral



1.2.3 Lewis Base-Catalyzed Activation of Anhydrides

The acylation of alcohols by anhydrides, catalyzed by 4-(dimethylamino)pyridine (DMAP) is perhaps the most frequently encountered example of nucleophilic Lewis base catalysis.[2,3,9] Expanding upon this concept, Fu has utilized planar-chiral pyrroles to facilitate asymmetric reactions with anhydrides (Scheme 1-4).[2] In one application, planar-chiral azaferrocene **I-16** catalyzes the enantioselective rearrangement of *O*-acylated azalactone **I-15** to generate α-substituted α-amino acid derivative **I-19**. In another example, planar-chiral DMAP derivative **I-22** catalyzes the kinetic resolution of *sec*-phenethyl alcohol (**I-20** to **I-24** and **I-25**). In both reactions, the Lewis basic catalyst adds to the anhydride to produce a chiral acylating agent (**I-17** and **I-23**).

Scheme 1-4. Lewis base activation of anhydrides



1.2.4 Silicon as a Lewis Base Acceptor

As a group IVA element located directly beneath carbon on the periodic table, silicon has very similar properties to that of carbon. However, unlike carbon, silicon contains *d*-orbitals, which allow for unique reactivity. Tetravalent silicon can undergo reversible attack by an activating Lewis base catalyst (LB) to afford a pentavalent intermediate (Figure 1-2).[10-21] This silicate is susceptible to further addition of a second Lewis base, or in this illustration, addition of a lone pair from an electrophile (**:E**, e.g. a carbonyl), to form a hexacoordinate transition state. Following coordination of the electrophile, nucleophilic addition (**N**) to the electrophile occurs to generate the desired carbon-carbon bond formation (**N-E**), along with a new tetravalent species.

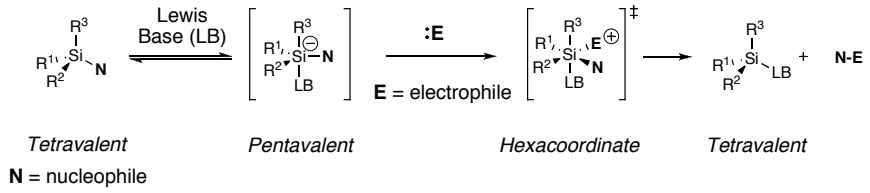


Figure 1-2. Hypervalent silicon

Rate determination of Lewis base-initiated silicon reactions yields large negative values for $\Delta S^{\ddagger}$, which is consistent with a highly organized transition state (e.g. hexacoordinate transition state), supporting the above mechanistic pathway.[12,13] The ability of silicon to form pentavalent intermediates was confirmed by Rudman, Hamilton, Novick, and Goldfarb by single crystal X-ray diffraction of dimethylsilylamine ($Me_2NSiH_3^-$).[21] Schomburg later isolated pentavalent tetrapropylammonium tetrafluorophenylsilane by single crystal X-ray diffraction (Figure 1-3).[20]

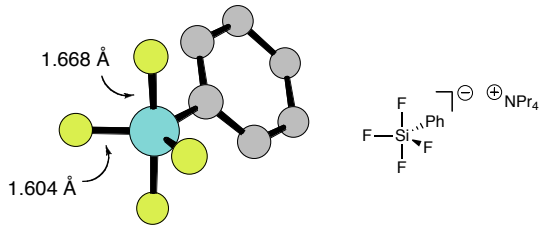


Figure 1-3. Representation of the crystal structure of tetrapropylammonium tetrafluorophenylsilane

The electronic propensity for silicon to accept increased substitution to afford hypervalent conformations is explained by the spillover effect (Figure 1-4).[19] As one or two additional ligands (X) are added to silicon, the net overall charge increases to –1 (pentavalent) and –2 (hexacoordinate) respectively. Interestingly, the charge distribution is divided entirely between the substituents, giving the silicon a formal charge of zero, regardless of the net charge. This counter-intuitive rationale can be examined even further through *ab initio* calculations, in which the silicon is predicted to become more electron deficient as more ligands are added. Conversely, the ligands attached to silicon become more electron rich, taking on more of the electronic charge. Silicon species with highly electronegative substituents (e.g. fluoride) have a large positive charge and are very susceptible to nucleophilic attack due to σ-electron withdrawing effects of the substituents.

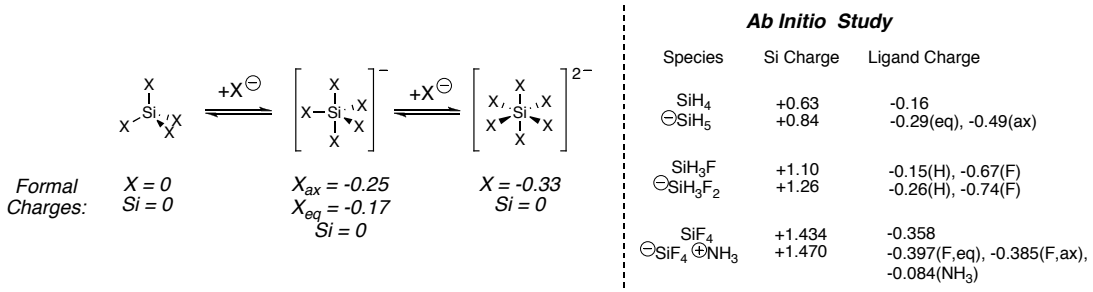
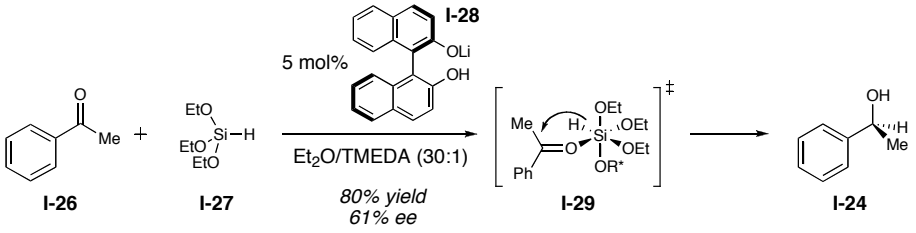


Figure 1-4. Spillover effect

1.2.4.1 Reduction of Ketones with Hypervalent Silicates

Several researchers have utilized hypervalent silicates for organic transformations. One area that has been extensively investigated is Lewis base promoted carbonyl reductions using silanes.[22-29] For example, Kagan and Schiffers employed catalytic amounts of the mono-lithium salt of (*R*)-BINOL (**I-28**) towards the asymmetric reduction of acetophenone (**I-26**, Scheme 1-5).[28] The addition of alkoxide **I-28** to triethoxysilane (**I-27**), followed by coordination of acetophenone, provides transition state **I-29**. A hydride transfer from the silane to acetophenone then occurs to yield (*S*)-*sec*-phenethyl alcohol (**I-24**) in high yield and moderate selectivity.

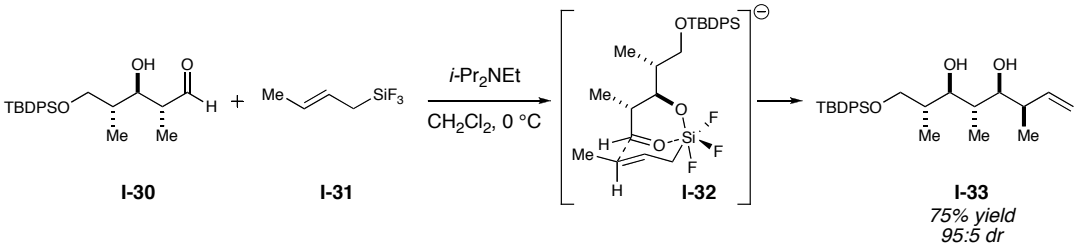
Scheme 1-5. Catalytic asymmetric reduction of ketones



1.2.4.2 Allyl- and Crotylation with Hypervalent Silicates

Asymmetric allyl and crotyl additions are another area in which hypervalent silicates have been employed.[25,30-42] Chemler and Roush developed a method for the diastereoselective addition of allyl and crotyl groups to β-hydroxy-α-methyl aldehydes using allyltrifluorosilanes (Scheme 1-6).[30,31,42] In this reaction, the β-hydroxyl functionality of aldehyde **I-30** acts as the Lewis base in the presence of *N,N*-diisopropylethylamine, undergoing an addition to crotyltrifluorosilane **I-31**. Subsequent coordination of the aldehyde to the silane sets the stage for addition through an energy-minimized Zimmerman-Traxler transition state (**I-32**), generating the 4,5-*anti*-dipropionate steroid (**I-33**) with excellent diastereoselectivity (95:5).

Scheme 1-6. Diastereoselective crotylation of aldehydes



I-30 **I-31** **I-32** **I-33**

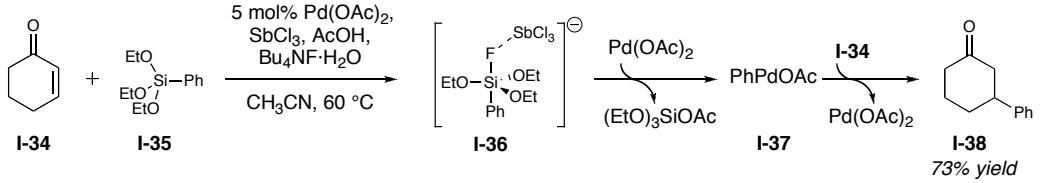
75% yield
95:5 dr

1.2.4.3 Metal-Catalyzed Transformations with Hypervalent Silicates

Hypervalent silicates have been utilized in 1,4-conjugate additions[43-45] and cross-coupling reactions[46,47] in the presence of transition metal catalysts. Denmark and Amishiro demonstrated the conjugate addition of triethoxyphenylsilanes to a series of α,β-unsaturated carbonyls in the presence of catalytic amounts of palladium (Scheme 1-7).[43] In this process, fluoride addition (from tetrabutylammonium fluoride) to

triethoxyphenylsilane (**I-35**) affords pentavalent silicate **I-36**. The activated intermediate **I-36** undergoes transmetallation with palladium(II) acetate, generating a tetraalkoxysilane and the nucleophilic phenyl palladium species (**I-37**). Conjugate addition of phenyl palladium(II) acetate (**I-37**) to cyclohexenone (**I-34**) yields 3-phenyl cylohexanone (**I-38**) in good yield. The addition of antimony (III) chloride ($SbCl_3$) to the reaction mixture is critical for this process. This additive is believed to play a role as a fluoride scavenger, thereby prohibiting the reduction of Pd(II) to Pd(0) by the fluoride. The coordination of $SbCl_3$ to fluoride is notably mild enough to still permit fluoride activation of triethoxyphenylsilane (**I-35**).[48]

Scheme 1-7. Palladium-catalyzed conjugate addition of triethoxyphenylsilane

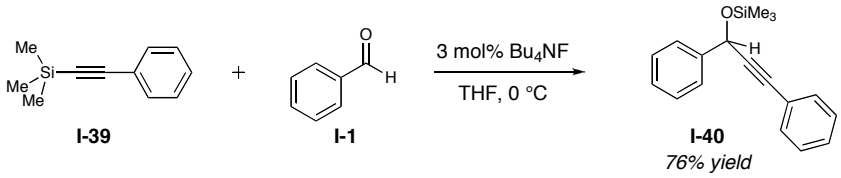


1.2.4.4 Alkyne Additions with Hypervalent Silicates

Silylalkynes have been investigated as acetylide equivalents in the presence of Lewis base.[49-54] During initial investigations conducted by Nakamura and Kuwajima, the tetrabutylammonium fluoride catalyzed addition of 1-phenyl-2-trimethylsilylacetylene (**I-39**) to benzaldehyde (**I-1**) to afford propargyl silyl ether **I-40** in good yield.[54] In this example and subsequent reported processes, 1-phenyl-2-trimethylsilylacetylene (**I-39**) has been shown to add to various aldehydes and ketones in the presence of catalytic (tetrabutylammonium fluoride or tetrabutylammonium triphenyldifluorosilicate)[53-55] or

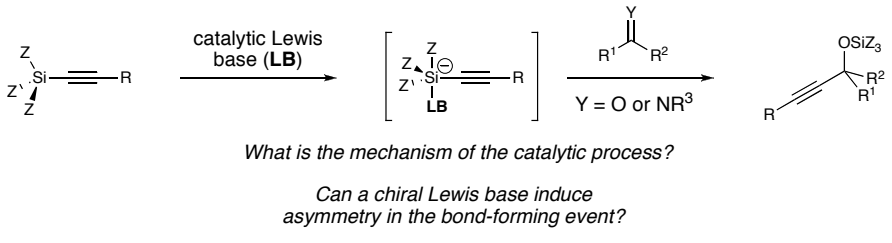
stoichiometric (CsF/CsOH)[50] quantities of fluoride Lewis base. In these separate investigations, **I-39** was the only silylacetylene explored, and it was applied only to a small range of aldehydes, ketones, and alkyl halides.

Scheme 1-8. Catalytic addition of phenyltrimethylsilylacetylene to benzaldehyde



Due to the limited reported utilization of Lewis base-activated silylalkynes as acetylide equivalents, we were interested in investigating this transformation (Scheme 1-9). Specifically, our areas of interest included defining a broader substrate scope and exploring alternative substitution on silicon (in addition to methyl). Furthermore, we were interested in exploring asymmetric variants of this process, by use of chiral Lewis bases or chiral electrophiles. Understanding the mechanism of this reaction was also an important goal, so that we might gain a further understanding of the reactivity of silicon reagents in Lewis base-catalyzed transformations.

Scheme 1-9. Proposed investigation of silylalkynes as acetylide equivalents



What is the mechanism of the catalytic process?

Can a chiral Lewis base induce asymmetry in the bond-forming event?

1.3 Lewis Base Activation of Trialkoxysilylalkynes

1.3.1 Preparation of Triethoxysilylalkynes

To commence with our reaction studies, we decided to investigate the use of electron-deficient trialkoxysilylalkynes. The alkoxy substituents on the silicon were chosen to promote hypervalency in the presence of a Lewis base catalyst, while maintaining ease of synthetic accessibility (Figure 1-5). The electronegative alkoxy substituents provide σ-withdrawing effects that promote distribution of electron charge away from the electrophilic silicon center. These electronics make the silicon more susceptible to initial nucleophilic attack of the Lewis base. Furthermore, the resultant pentavalent silicate intermediate is even more electrophilic in accordance to the previous explained spillover effect (section 1.2.4), facilitating the requisite hexacoordinate transition state for eventual alkyne transfer to the aldehyde. This increased silicon electrophilicity could have significant reactivity differences than the corresponding previously utilized trimethylsilylalkynes. Additionally, these silanes were selected for the possibility of future asymmetric control with chiral Lewis bases.[28,56]

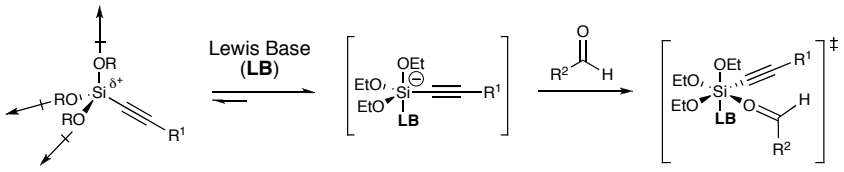
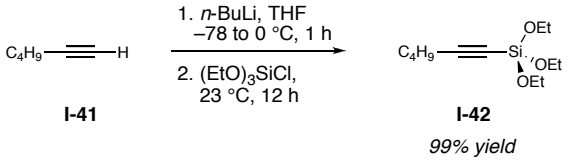


Figure 1-5. Electron withdrawing alkoxy substitution on silicon increases reactivity

Triethoxysilylalkynes were initially prepared according to the reported procedure by Jun and Crabtree (Scheme 1-10).[57] The addition of the lithium acetylide of hexyne (**I-41**) to triethoxysilylchloride gave triethoxysilylhexyne (**I-42**) in 99% yield.

Scheme 1-10. Triethoxysilylhexyne from triethoxysilylchloride

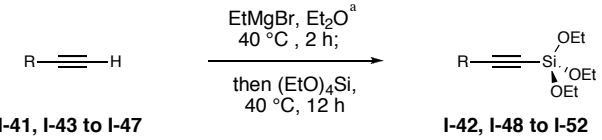


I-41 **I-42**

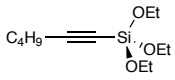
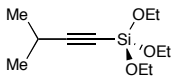
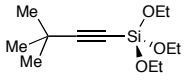
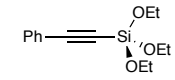
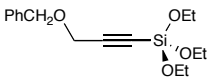
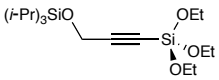
99% yield

Despite excellent reaction efficiency in accessing triethoxysilylalkynes, triethoxysilylchloride is a fairly expensive starting reagent ($68/25 g, Sigma-Aldrich, Inc.). Alternatively, the addition of the alkynyl Grignard reagent of hexyne to tetraethyl orthosilicate ($37/1 L, Sigma-Aldrich, Inc.) provides triethoxysilylhexyne in excellent yield (entry 1, Table 1-1).[58] This reaction is applicable to the range of alkynes surveyed (**I-42** to **I-47**), providing the triethoxysilylalkynes in high yields (entries 2-6).

Table 1-1. Triethoxysilylalkynes from tetraethyl orthosilicate



I-41, I-43 to I-47 **I-42, I-48 to I-52**

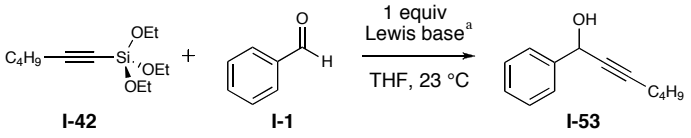
entry	R		product		yield (%)
1	C_4H_9	**I-41**		**I-42**	83
2	*i*-Pr	**I-43**		**I-48**	81
3	*t*-Bu	**I-44**		**I-49**	91
4	Ph	**I-45**		**I-50**	86
5	CH_2OCH_2Ph	**I-46**		**I-51**	79
6	$CH_2OSi(i\text{-}Pr)_3$	**I-47**		**I-52**	79

a. Tetraethyl orthosilicate added to a 1 M solution of the alkynyl Grignard reagent in Et_2O at 23 °C, then heated to reflux.

1.3.2 Initial Reactivity Studies

To probe the viability of the addition of triethoxysilylalkynes to aldehydes, several Lewis bases were surveyed for reactivity (Table 1-2). In the presence of tetrabutylammonium triphenyldifluorosilicate (TBAT),[55] the addition of triethoxysilylhexyne (**I-42**) to benzaldehyde (**I-1**) proceeded to afford propargyl alcohol **I-53** in moderate yield (entry 1). Surprisingly, conducting the reaction with TBAF instead of TBAT, was unsuccessful in generating the desired bond-formation (entry 2). Other Lewis bases initially surveyed, also proved ineffective for this transformation (entries 3-5).

Table 1-2. Survey of Lewis bases for initial reactivity



I-42 **I-1** **I-53**

entry	Lewis base		time (h)	yield (%)
1	TBAT	$Bu_4N^{\oplus}$ $^{\ominus}F_2Si(Ph)_3$	19	45
2	TBAF	$Bu_4N^{\oplus}$ $^{\ominus}F$	24	0[b]
3	CsF		24	0[b]
4	TBC	$Bu_4N^{\oplus}$ $^{\ominus}CN$	24	0[b]
5	TOPO	$O^{\ominus}$, $P^{\oplus}(C_8H_{17})_3$	24	0[b]

a. A 0.25M solution of **I-42** in THF was added to the Lewis base, and stirred for 1 h prior to the addition of **I-1**. b. No reaction.

The initial success of the TBAT-promoted reaction process warranted further investigation. Solvent optimization was attempted, monitoring the product yields over time by gas chromatography (Figure 1-6). Regardless of solvent choice, product degradation was observed over time under the reaction conditions. At this point, it appeared that some key issues would have to be overcome to reach the goal of achieving catalytic reactivity. The necessity of stoichiometric quantities of TBAT to provide the desired product after long reaction times at room temperature, would make a catalytic variant of this process difficult to achieve. Even if the reaction did proceed to completion with substoichiometric amounts of TBAT, the probable increased reaction times would have significant impact on the yield based on the trend observed in Figure 1-6. Additionally, the secondary goal of promoting asymmetry in these reactions would more than likely necessitate lower reaction temperatures, which could considerably decrease the rate even further. In view of these potential obstacles, it was decided that other Lewis bases should be surveyed for potential rate enhancement.

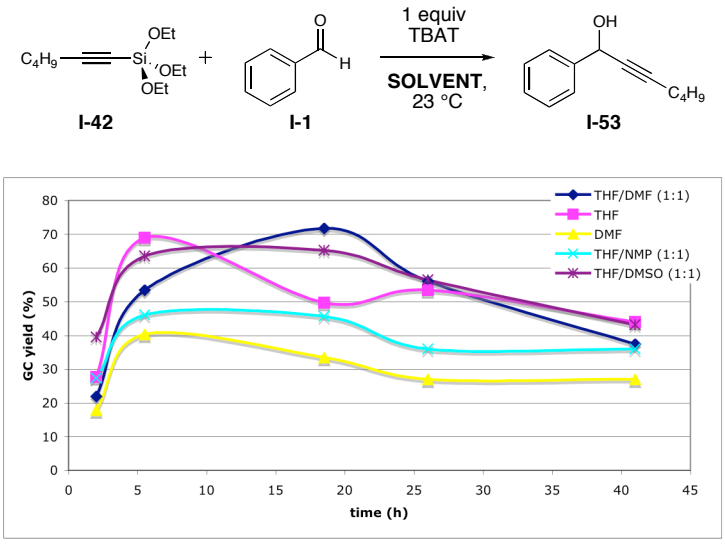
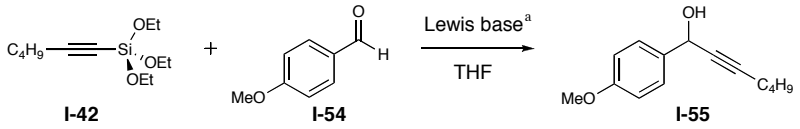


Figure 1-6. Product degradation over time for the TBAT promoted reaction

Prompted by the strong Si-O bond strength (110 kcal/mol), we examined simple alkoxides with various counterions (Table 1-3). Interestingly, while LiOMe afforded no product (entry 2), the use of alkoxides with more electropositive counterions (Na^+ and K^+) cleanly provided the desired propargyl alcohol **I-55**, with KOEt affording significant rate enhancement over NaOMe (entries 3 and 4). Gratifyingly, catalytic reaction conditions with only 10 mol% of KOEt at 0 °C generated alcohol **I-55** in high yield (entry 5). In addition, sterically hindered tertiary and secondary alkoxides can also be employed as catalysts (entries 6 and 7). The control experiment with 1-hexyne, KOEt, and *p*-anisaldehyde (**I-55**) does not produce desired alcohol **I-55** under the reaction conditions. The addition of tetraethyl orthosilicate, $Si(OEt)_3$, in this system yields no product either.

Table 1-3. Alkoxide-Lewis base survey for reactivity



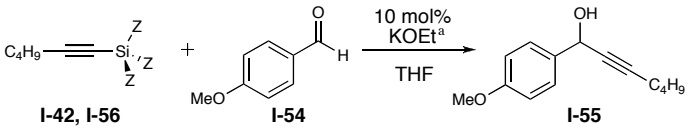
entry	Lewis base	mol %	time (h)	Temp. (°C)	yield (%)
1	*n*-$Bu_4N{\cdot}F_2SiPh_3$	100	16	23	50
2	LiOMe	100	24	23	0[b]
3	NaOMe	100	19	23	50
4	KOEt	100	1	23	57
5	KOEt	10	2	0	84
6	KO*t*-Bu	20	2	0	75
7	(±)-$KOCH(CH_3)Ph$	20	2	0	75

a. A 0.25M solution of **I-42** in THF was added to the Lewis base, and stirred for 1 h prior to the addition of **I-54**. b. No reaction.

1.3.3 Trimethylsilylalkynes

Before proceeding to examine the scope of the KOEt-catalyzed reaction process, the corresponding trimethylsilylalkyne was investigated for reactivity (Table 1-4). When trimethylsilylhexyne (**I-56**) is subjected to the developed reaction conditions at ambient temperature, propargyl alcohol **I-55** is acquired in comparable yield to that obtained with triethoxysilylhexyne (entries 1 and 2). However, at lower temperatures, the trimethylsilylhexyne was unreactive, whereas the corresponding triethoxysilylhexyne gave alcohol **I-55** in high yield (entries 3 and 4). To note, Mukaiyama and coworkers published a report after our initial commnunication using catalytic amounts of tetrabutylammonium phenoxide to carry out low temperature reactions with trimethylsilylalkynes.[51] Interestingly, this process proceeded in high yields (up to 99%) for aromatic substituted alkynes (e.g. 1-phenyl-2-trimethylsilylacetylene) but was low yielding with unsubstituted alkynes (trimethylsilylethyne) and unreactive with alkyl-substituted alkynes (trimethylsilylhexyne). This result is further evidence of the increased reactivity attained through the use of trialkoxy substitution.

Table 1-4. Triethoxysilylhexyne versus trimethylsilylhexyne



I-42, I-56 **I-54** **I-55**

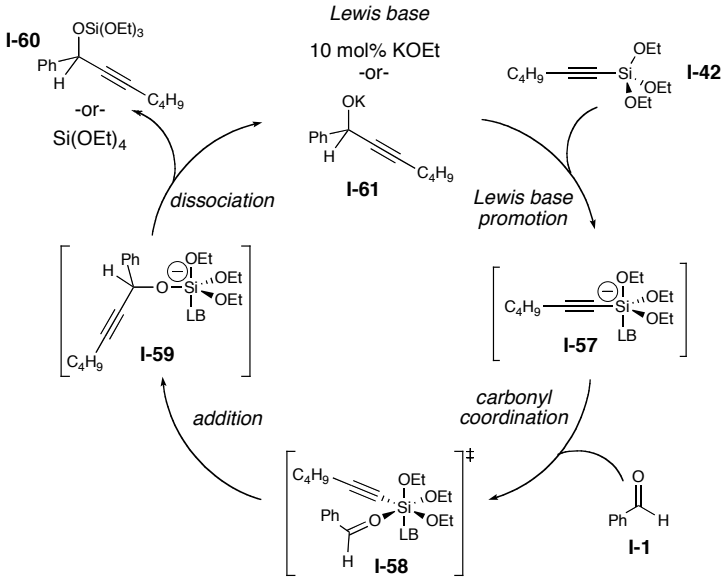
entry	Z	time (h)	Temp. (°C)	yield (%)
1	OEt	1	23	75
2	Me	2	23	72
3	OEt	2	0	84
4	Me	24	0	0[b]

a. A 0.25M solution of **I-42** or **I-56** in THF was added to the Lewis base, and stirred for 1 h prior to the addition of **I-54**. b. No reaction.

1.4 Proposed Reaction Mechanism and Investigation

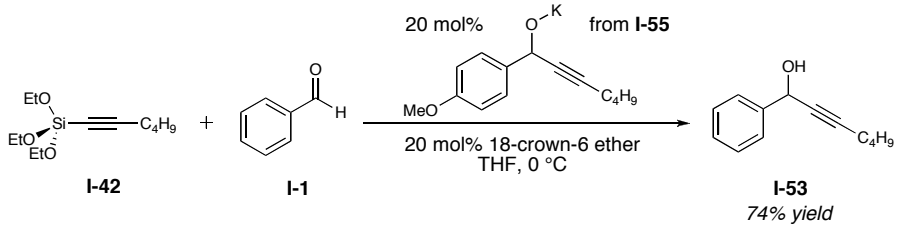
Our preliminary investigations of this process have provided important clues about the potential reaction mechanism. The proposed mechanistic pathway involves Lewis base initiation of an auto-catalytic cycle (Scheme 1-11). The initial addition of a Lewis base such as KOEt to triethoxysilylalkyne **I-42** leads to the formation of a pentavalent silicon intermediate **I-57**, which can mediate the transfer of an alkynyl nucleophile via hexacoordinate transition state **I-58**. The resulting pentavalent silylated alkyne-addition product (**I-59**) dissociates, leading to generation of alkoxide base **I-61**. This newly generated propargyl alkoxide is proposed to act as a Lewis base, adding to another molecule of silylalkyne **I-42** to perpetuate the reaction cycle. Following addition this time, pentavalent intermediate **I-59** dissociates to form propargyl silyl ether **I-60** and another molecule of propargyl alkoxide **I-61**.

Scheme 1-11. General mechanistic proposal



An intriguing aspect of the reaction is that the propargyl product is initially an alkoxide and may well activate the trialkoxysilylalkyne in a manner similar to KOEt (auto-catalysis). To probe this product-activation possibility, the potassium salt of propargyl alcohol **I-55** was added (20 mol%) to silylalkyne **I-42** and benzaldehyde (Scheme 1-12). Interestingly, propargyl alcohol **I-53** was isolated in good yield after acidic work up.

Scheme 1-12. Confirming the possibility of a product alkoxide promoted reaction



In the proposed reaction mechanism (Scheme 1-11), the active alkynyl nucleophile is a hypervalent silicate intermediate resulting from reversible addition of alkoxide to the triethoxysilylalkyne. Evidence for a pentavalent intermediate (**I-57**) was obtained by the low temperature ^{29}Si NMR experimentation (Figure 1-7). Analysis of a mixture of trialkoxysilylalkyne **I-42**, 1.0 equiv of KOEt, and 1.0 equiv of 18-crown-6, produced a new and distinct signal at –126 ppm, corresponding to pentavalent intermediate **I-57**. This observed shift is similar to the findings reported by Holmes and coworkers.[14] At temperatures less than –30 °C, they found ^{29}Si NMR shifts of –58 ppm for $PhSi(OEt)_3$ and a corresponding shift of –117 ppm for pentavalent $K{\cdot}PhSi(OEt)_4$. Similarly, they reported ^{29}Si NMR shifts of –60 ppm for $(vinyl)Si(OEt)_3$ with a shift of –117 ppm for pentavalent $K{\cdot}(vinyl)Si(OEt)_4$. In agreement to our experimentation, they

likewise observed ^{29}Si NMR shifts of –82 ppm for $Si(OEt)_4$ and a shift of –131 ppm for pentavalent $K{\cdot}Si(OEt)_5$. The formation of $Si(OEt)_4$ and $K{\cdot}Si(OEt)_5$ would indicate the generation of some potassium acetylide, which could be the active nucleophile in the reaction. Our ^{29}Si NMR study is with stoichiometric amounts of KOEt though, possibly leading to the formation of these byproducts as a result. In comparison, potassium acetylides have had much different effects on particular substrates in comparison to the Lewis base-promoted additions with triethoxysilylalkynes. These results will be discussed in the proceeding sections.

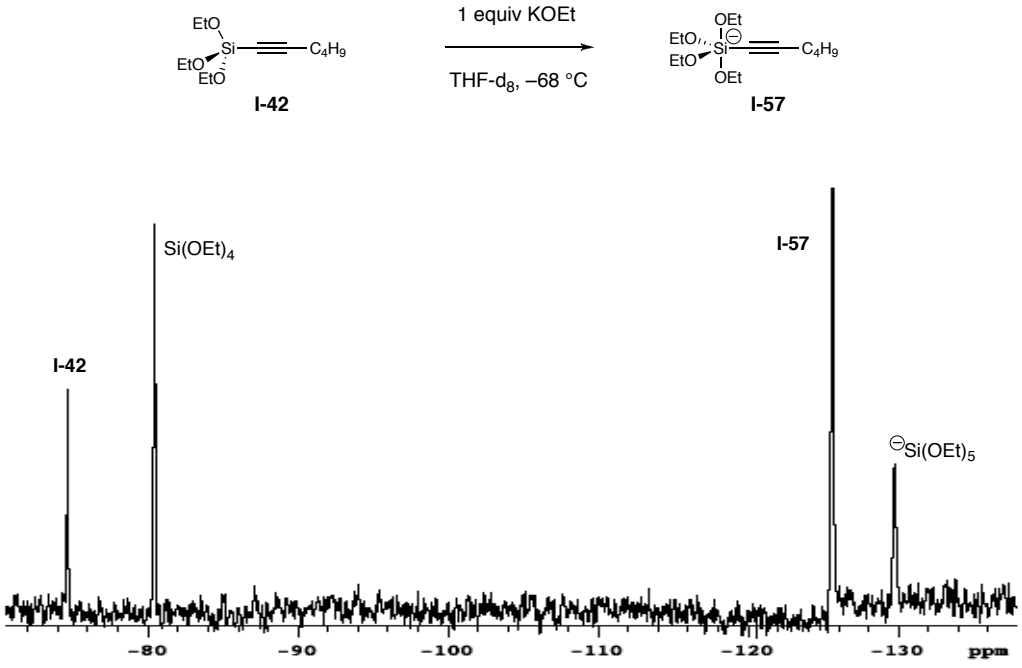


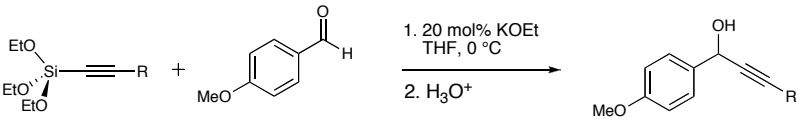
Figure 1-7. Observance of pentavalent silicate intermediate **I-57** by ^{29}Si NMR spectroscopy.

1.5 Lewis Base-Catalyzed Addition of Silylalkynes to Aldehydes and Ketones

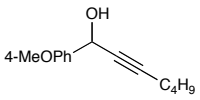
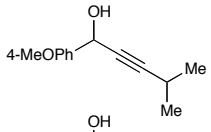
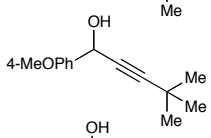
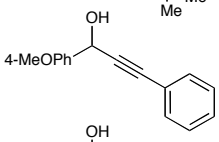
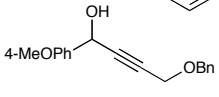
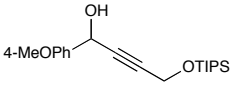
1.5.1 Scope of the Addition of Silylalkynes to Aldehydes and Ketones

With conditions identified for the Lewis base-catalyzed addition of triethoxysilylhexyne to *p*-anisaldehyde, the structure of the alkyne nucleophile was varied (Table 1-5). The reaction is facile at 0 °C, and the alkyne can accommodate linear or branched alkyl groups (entries 1-3) as well as aryl substitution (entry 4). Propargyl systems employing benzyl and triisopropylsilyl protecting groups smoothly afford the desired carbinols in good yields (entries 5 and 6). Removal of these protecting groups allows access to primary propargyl alcohols, that can be further functionalized.

Table 1-5. Scope of alkyne addition



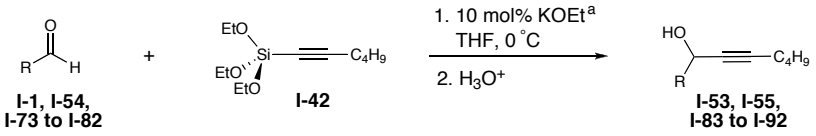
I-42, I-63 to I-67 **I-54** **I-55, I-68 to I-72**

entry	Alkyne	R	product		yield (%)
1	**I-42**	*n*-butyl		**I-55**	84
2	**I-63**	*i*-Pr		**I-68**	75
3	**I-64**	*t*-Bu		**I-69**	73
4	**I-65**	Ph		**I-70**	77
5	**I-66**	CH_2OBn		**I-71**	76
6	**I-67**	CH_2OTIPS		**I-72**	76

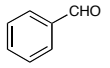
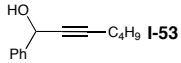
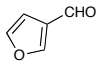
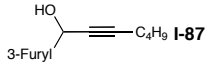
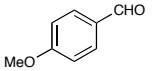
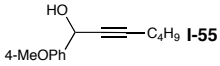
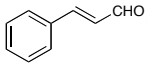
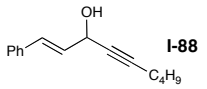
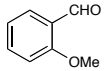
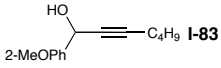
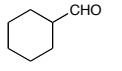
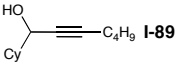
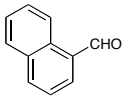
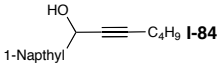
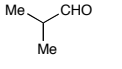
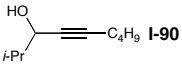
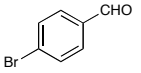
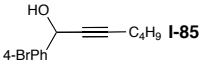
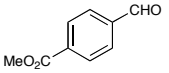
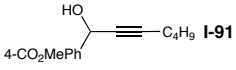
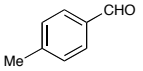
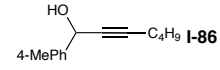
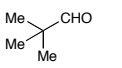
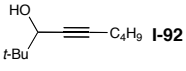
a. A 0.25M solution of acylsilane in THF was added to the Lewis base, and stirred for 1 h prior to the addition of **I-54**.

Under Lewis base-catalyzed conditions (10 mol% KOEt), triethoxysilylalkyne **I-42** undergoes facile addition to various aldehydes in good yields (Table 1-6). The reaction is high yielding with electron rich (entries 2-4 and 7) and electron deficient (entry 5) aromatic aldehydes, and is mild enough to accommodate enolizable aldehydes (entries 9-10). Notably, this process affords selective additions in the presence of esters (entry 11). In contrast, the lithium and potassium acetylide addition to methyl 4-formylbenzoate (**I-81**) affords complex mixtures from the addition to both carbonyl compounds. This result is evidence that a potassium acetylide is not necessarily the active species for this reaction, and thereby supporting the proposed hypervalent silicate mediated mechanism.

Table 1-6. Triethoxysilylhexyne (**I-42**) additions to aldehydes



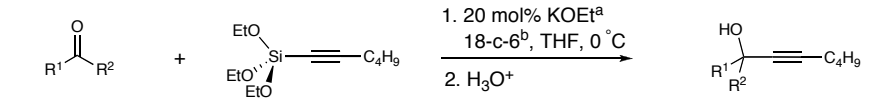
I-1, I-54, I-73 to I-82 + **I-42** → **I-53, I-55, I-83 to I-92**

entry	RCHO		product		yield (%)	entry	RCHO		product		yield (%)
1		**I-1**		**I-53**	74	7		**I-77**		**I-87**	85
2		**I-54**		**I-55**	84	8[b]		**I-78**		**I-88**	59
3		**I-73**		**I-83**	82	9		**I-79**		**I-89**	56
4		**I-74**		**I-84**	76	10		**I-80**		**I-90**	58
5		**I-75**		**I-85**	76	11		**I-81**		**I-91**	78
6		**I-76**		**I-86**	80	12		**I-82**		**I-92**	93

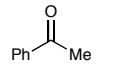
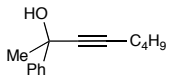
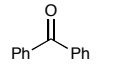
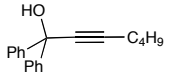
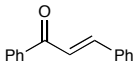
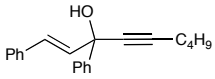
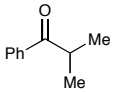
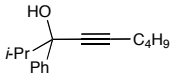
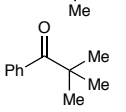
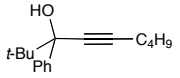
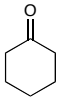
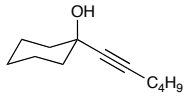
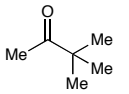
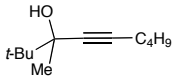
a. A 0.25M solution of **I-42** in THF was added to the Lewis base, and stirred for 1 h prior to the addition of aldehyde. b. >95% (*E*)-cinnamaldehyde.

A distinctive and important attribute of this process is the capability of this new alkynyl nucleophilic reagent to undergo addition to ketones (Table 1-7). The conditions that afford the best yields employ a higher catalyst loading (20 mol%) and a crown ether (18-crown-6). The mechanism involving self-promotion is supported by the necessity of crown ether for catalytic turnover in the addition to ketones, where a more sterically congested tertiary propargyl alkoxide (**I-114**) is generated. The function of 18-crown-6 presumably is to coordinate with potassium, thus generating a more nucleophilic propargyl alkoxide for addition to the triethoxysilylalkyne. The crown ether is unnecessary for the additions of trialkoxysilylalkynes to aldehydes due to the decreased steric magnitude of the corresponding secondary propargyl potassium alkoxide. By utilizing these Lewis basic conditions, undesired aldol products are not observed with enolizable ketones as substrates, indicating that the basicity of these new reagents is attenuated relative to standard organometallic acetylides.

Table 1-7. Triethoxysilylhexyne (**I-42**) additions to ketones



I-26, I-93 to I-98 **I-42** **I-99 to I-105**

entry	Ketone		product		yield (%)
1		**I-26**		**I-99**	54
2		**I-93**		**I-100**	73
3		**I-94**[c]		**I-101**	54[d]
4		**I-95**		**I-102**	71
5		**I-96**		**I-103**	85
6		**I-97**		**I-104**	64
7		**I-98**		**I-105**	73

a. A 0.25M solution of **I-42** in THF was added to a mixture of the KOEt and 18-crown-6, and stirred for 1 h prior to the addition of the ketone. b. 20 mol% 18-crown-6. c. >95% *(E)*-chalcone. d. Only 1,2-addition product observed.

1.5.2 Investigation of Asymmetric Induction by Chiral Lewis Bases

Following exploration into the substrate scope of this Lewis base-catalyzed process, investigation to render the reaction asymmetric through the use of chiral Lewis base activation were proposed (Figure 1-8). Following pre-complexation of the Lewis base to triethoxysilylhexyne (**I-42**), *p*-anisaldehyde was added, and the reaction was monitored for the formation of propargyl alcohol (**I-55***). A wide range of lithium and potassium alkoxides were surveyed for asymmetric induction with a number of the potassium alkoxides examined leading to the formation of propargyl alcohol (**I-55***). Unfortunately, no enantioselectivity was observed with any of the investigated chiral

Lewis bases. All potassium alkoxides for these experiments were formed from the corresponding alcohol by the addition of potassium hydride and a crown ether. As a control, it was demonstrated that potassium hydride and 18-crown-6 alone do not promote the reaction. This observation indicates that the pre-formed chiral alkoxides were the reactive Lewis bases for these reactions, and produced no asymmetry.

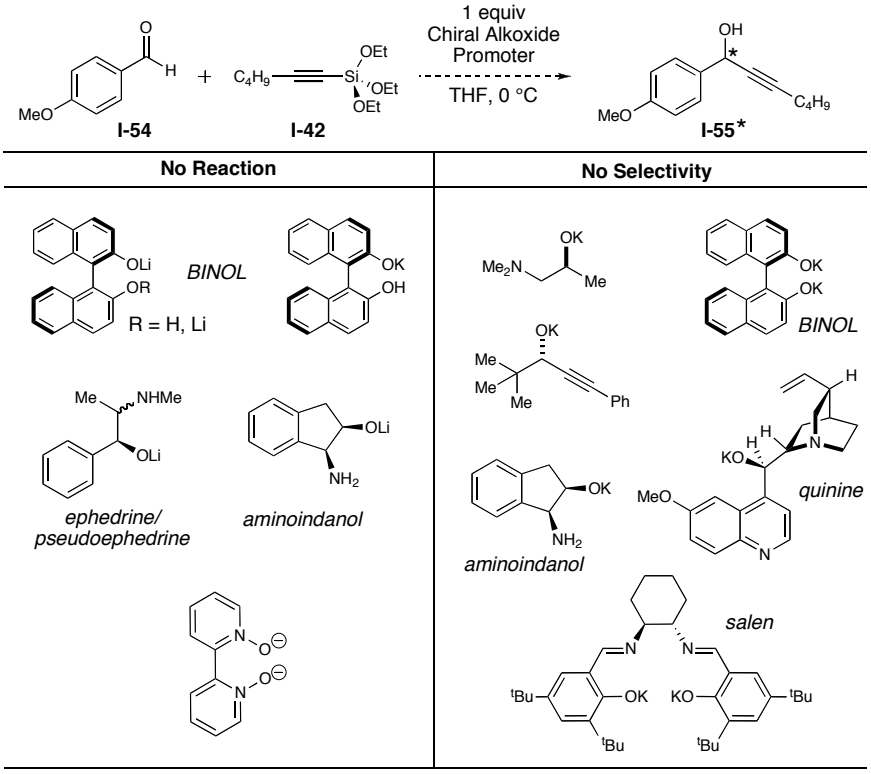
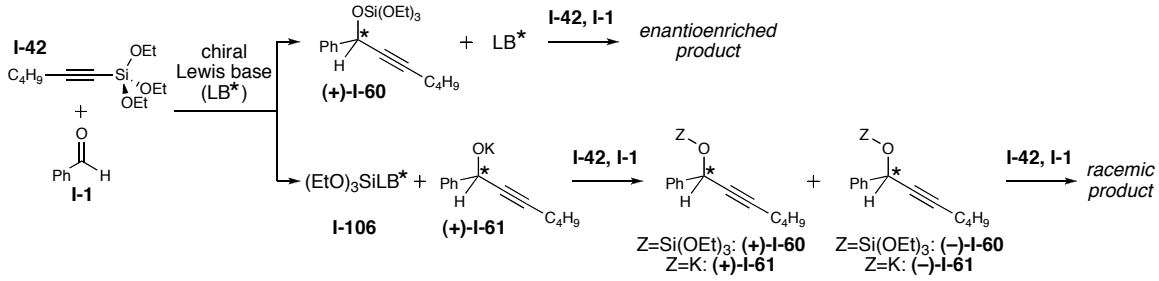


Figure 1-8. Chiral Lewis base activation

The proposed mechanistic pathway (Scheme 1-11) can account for the lack of enantioselectivity observed for the chiral Lewis base-activated reactions. Chiral Lewis base promotion of the developed reaction sequence would generate one enantiomer of the silylated propargyl ether product ((**+)-I-60**), with dissociation of the chiral Lewis base to

further propagate the reaction (Scheme 1-13). With the proposed auto-catalytic pathway, triethoxysilyl-Lewis base moiety (**I-106**) would be formed instead, along with a chiral propargyl alkoxide ((**+)-I-61**). Ideally, this alkoxide would proceed catalytically as a chiral Lewis base to continue the reaction, generating exclusively one enantiomer of the desired product ((**+)-I-60**/(**+)-I-61**). Alternatively, alkoxide **(+)-I-61** could generate the opposing enantiomer of product ((**–)-I-60**/(**–)-I-61**). This "scrambling" effect would lead to a racemic mixture of product. In yet another potential scenario, the initially formed alkoxide ((**+)-I-61**) might promote the reaction without relaying any stereochemical information, again leading to low/no selectivity overall.

Scheme 1-13. Addition of a chiral Lewis base to promote asymmetry



1.6 Diastereoselective Addition of Silylalkynes to Imines

1.6.1 N-Sulfinyl Imines in Synthesis

Amines are prevalent in many biologically active molecules, and considerable efforts into synthetic methods for the formation of chiral amines have been investigated.[59-61] One reliable route towards the synthesis of chiral amines is nucleophilic addition to chiral *N*-sulfinyl imines. This powerful tactic was initially investigated with *N-p*-toluenesulfinyl imines by Davis and coworkers,[62,63] then later further enhanced by the use of *N-tert*-butanesulfinyl imines by Ellman and coworkers (Figure 1-9).[64]

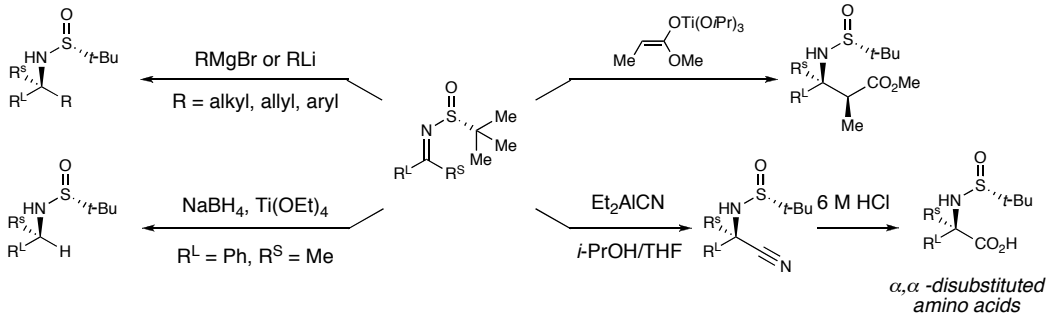
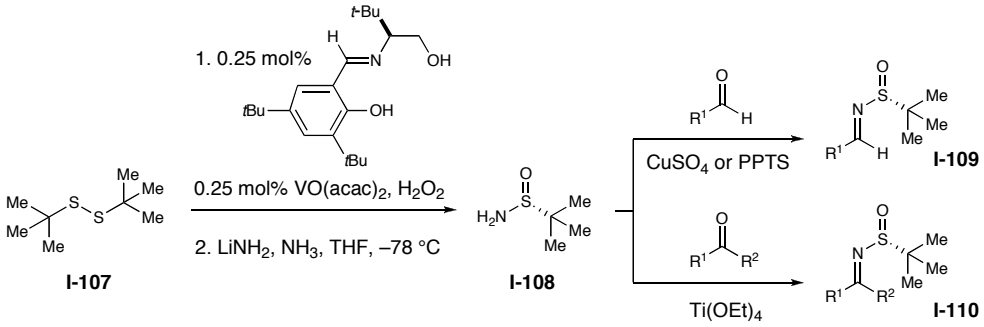


Figure 1-9. *N-tert*-Butanesulfinyl imines in synthesis

1.6.2 Preparation of N-Sulfinyl Imines

N-tert-Butanesulfinyl imines (**I-109** and **I-110**) are readily prepared from the condensation of commercially available *tert*-butanesulfinamide (**I-108**) with the corresponding carbonyl compound under Lewis acid-promoted conditions (Scheme 1-14).[65,66] Additionally, *tert*-butanesulfinamide (**I-108**) can be prepared in large quantities from the asymmetric oxidation of *tert*-butyl disulfide (**I-107**) followed by reaction of the resulting *tert*-butanethiosulfinate with lithium amide.[67]

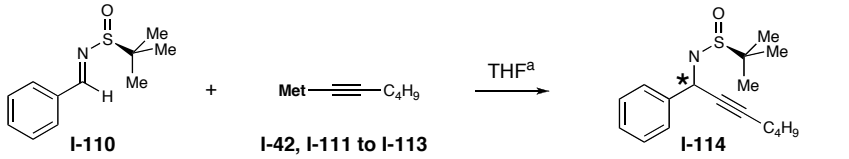
Scheme 1-14. Synthesis of *N-tert*-butanesulfinyl imines



1.6.3 Diastereoselective Addition of Silylalkynes to N-Sulfinyl Imines

The unique properties and synthetic potential of the Lewis base-catalyzed activation of trialkoxysilylalkynes can be utilized to form secondary propargyl amines (Table 1-8). The KOEt-promoted addition of triethoxysilylalkyne (**I-42**) to *N-tert*-butylsulfinyl imine **I-110** affords amine **I-114** in high yield with excellent selectivity favoring the (S_S,*R*) diastereomer at 0 °C (entry 1). Prior to this study, the addition of metal acetylides to *N-tert*-butylsulfinyl imines had not been reported. Surprisingly, alternative alkynyl organometallic nucleophiles are either less selective (Met = K) or prefer the *opposite* stereoisomer (Met = Li or MgBr).[68] Gratifyingly, lowering the temperature to –78 °C gave amine **I-114** in exceptional yield and selectivity. To note, other electron deficient imines were surveyed including *N*-phosphinoyl imines[69] and *N*-toluenesulfonyl imines,[70] but surprisingly no reactivity was observed with these imines.

Table 1-8. Acetylide additions to *N-tert*-butanesulfinyl imine **I-110**



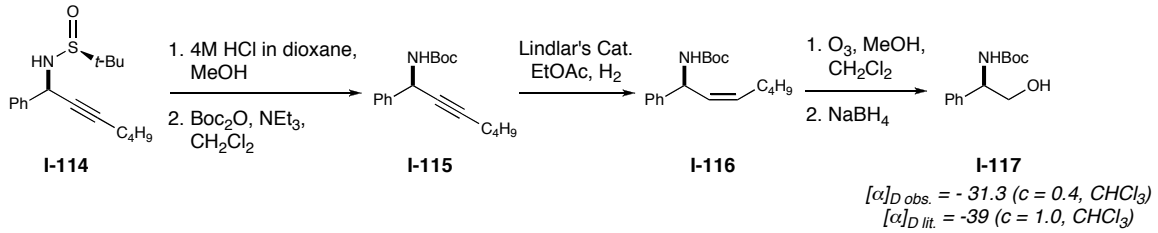
I-110 + **I-42, I-111 to I-113** → **I-114**

entry	Met		time (h)	temp. (°C)	yield (%)	diastereomeric ratio (*R*:*S*)[b]
1	$Si(OEt)_3$	**I-42**	2	0	88	10:1
2	Li	**I-111**	2	0	99	1:7
3	MgBr	**I-112**	16	0	74	1:3
4	K	**I-113**	16	0	30	2:1
5	$Si(OEt)_3$	**I-42**	5	–78	95	20:1
6	Li	**I-111**	12	–78	0[d]	–
7	MgBr	**I-112**	12	–78	0[d]	–
8	K	**I-113**	12	–78	0[d]	–

a. To a 0.25 M solution of the acetylide in THF was added a solution of **I-110** in THF. b. Determined by ^{1}H NMR spectroscopy. c. 1.0 equiv. KOEt and 18-crown-6. d. No reaction.

Determination of the absolute stereochemistry of propargyl amine **I-114** was accomplished by derivatizing the product over a five-step sequence to form the previously synthesized and characterized amino alcohol **I-117** (Scheme 1-15).[71-73] Acid-promoted removal of the *tert*-butanesulfinyl group,[74] followed by *tert*-butyl carboxylate protection of the resultant free amine[75] gave propargyl amine **I-115**. Reduction of alkyne **I-115** to olefin **I-116**[76] and subsequent reductive ozonolysis[77] afforded amino alcohol **I-117**. Comparison of the optical rotation of the amino alcohol (**I-117**) derived from propargyl amine **I-114** to know literature values[71,72] defined the absolute configuration of **I-114**, while simultaneously identifying the configuration of the propargyl amine product resulting from the corresponding metal-acetylide addition processes through analogy.

Scheme 1-15. Determination of the absolute stereochemistry of amine **I-114**



1.6.4 Mechanism for the Diastereoselective Addition of Triethoxysilylalkynes to Imines

Lewis base promoted addition of triethoxysilylalkyne **I-42** leads to the diastereoselective addition of an acetylide unit to *N-tert*-butanesulfonyl imine **I-110**, affording enantioenriched propargyl amine **I-114** (Figure 1-10). The invoked stereoinduction model for nucleophilic addition to *N-tert*-butanesulfonyl imines involves a six-membered Zimmerman-Traxler transition state.[64] When applied to this system, the six-membered transition state model gives the minor diastereomer. This corresponds to the observed major diastereomer for the addition of organometallic acetylides (Li and MgBr). Alternatively, an open transition state can also be employed, wherein the alkyne would approach from the least-sterically hindered side of the imine.[79] This pathway would lead to the observed major diastereomer.

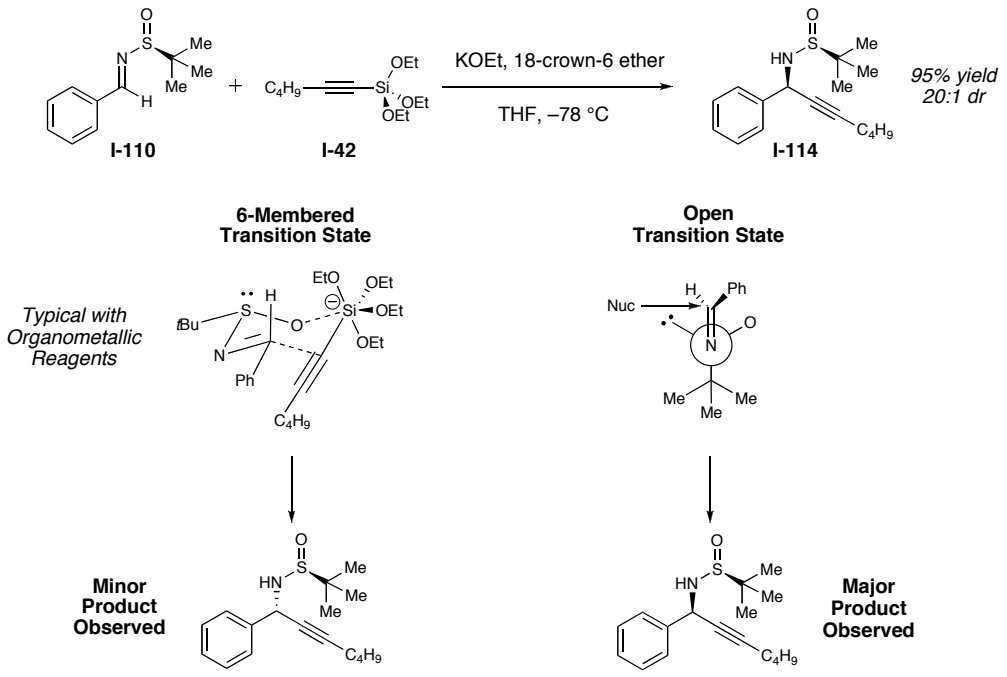


Figure 1-10. Possible transition state models for diastereoselective amine formation

1.7 1,4-Conjugate Addition Reactions

Several 1,4-conjugate acceptors were surveyed for reactivity with the Lewis base-promoted triethoxysilylalkyne addition process (Figure 1-11). It was rationalized that a possible six-membered transition state (**I-119**) might facilitate this transformation. Unfortunately, of the conjugate acceptors surveyed, the desired 1,4-addition product (**I-120**) was not observed.

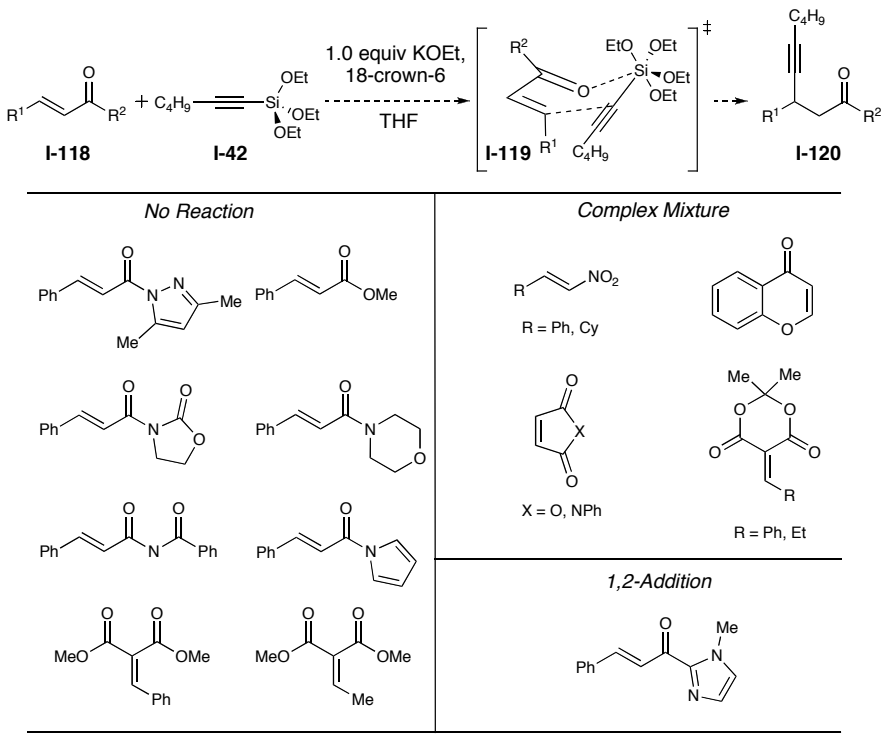


Figure 1-11. 1,4-Conjugate addition attempts

1.8 Summary

This chapter summarizes the development of an efficient nucleophile-catalyzed addition reaction of alkynes. This new strategy utilizes trialkoxysilylalkynes as stable nucleophile precursors with preliminary mechanistic data implicating a hypervalent organosilane as the active reagent. The new alkynyl species accessed by the addition of a Lewis base undergoes smooth, and in some cases, highly selective additions to aldehydes, ketones and imines. Mechanistic investigations of this Lewis base-catalyzed strategy based on trialkoxy-organosilane activation support an auto-catalytic reaction pathway. Overall, this study was successful in providing a method to access mild acetylide equivalents while identifying key mechanistic insights, and is a noteable addition to the area of Lewis base activation in synthetic organic chemistry.

1.9 Experimental

General Information. All reactions were carried out under a nitrogen atmosphere in flame-dried glassware with magnetic stirring. THF was purified by passage through a bed of activated alumina.[80] Reagents were purified prior to use unless otherwise stated following the guidelines of Perrin and Armarego.[81] Purification of reaction products was carried out by flash chromatography using EM Reagent silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and ceric ammonium nitrate stain or potassium permangenate stain followed by heating. Infrared spectra were recorded on a Perkin Elmer 1600 series FT-IR spectrometer. ^{1}H-NMR spectra were recorded on a Varian Inova 500 (500 MHz) or Mercury 400 (400 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data are reported as (ap = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad; coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C-NMR spectra were recorded on a Varian Inova 500 (125 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.0 ppm). GCMS experiments were carried out on a computer-interfaced Hewlett-Packard 6890 gas chromatograph equipped with a 5973 network mass selective detector. The column used was a 30 m HP-SMS capillary column with a 0.25 mm inner diameter and a 0.25 mL film thickness.

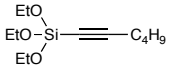
1.9.1 Preparation of Triethoxysilylalkynes

Initially, triethoxysilylhexyne (**I-42**) was prepared according to a modified procedure of that reported by Jun and Crabtree.[57] The method of preparation was then changed to a modified procedure of that reported by Voronkov and Yarosh.[58] Benzyl propargylether was prepared according to the procedure of Sugimoto, Ishihara, and Murai.[82] Triisopropylsilyl propargylether was prepared according to the procedure of Stüdemann, Ibrahim-Ouali, and Knochel.[83]

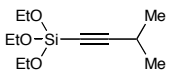
1.9.1.1 Representative Procedure for the Synthesis of Triethoxysilylalkynes

To a round-bottom flask equipped with a magnetic stir bar was charged the 1-hexyne (107.60 mmol), diethyl ether (80 mL), and ethyl magnesium bromide (3.0 M in Et_2O, 89.67 mmol). A condenser was attached, and the solution was heated at reflux for 2 hours. The reaction mixture was cooled to room temperature, and tetraethyl orthosilicate (161.4 mmol) was added. The reaction was again heated at reflux for 12 hours. The resulting mixture was filtered, and the distillate was concentrated by evaporation. The product was purified by fractional distillation under reduced pressure yield **I-42** (70.4 mmol) as a colorless liquid.

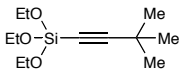
1.9.1.2 Characterization of Triethoxysilylalkynes I-42 and I-48 to I-52



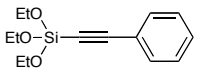
Triethoxy (hex-1-ynyl)silane (I-42): Purified by vacuum distillation, yielding 83% of **I-42** as a colorless liquid. BP = 50-55 °C (0.4 torr); IR (film) 2972, 2931, 2887, 2183, 1389, 1167, 1101, 1081, 961, 790, 717 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.87 (q, J = 7.0 Hz, 6H); 2.26 (t, J = 7.0 Hz, 2H); 1.54-1.51 (m, 2H); 1.45-1.42 (m, 2H); 1.25 (t, J = 6.5 Hz, 9H); 0.91 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 107.64, 76.02, 59.1, 30.4, 22.1, 19.5, 18.2, 13.7; GCMS (EI): Mass calculated for $C_{12}H_{24}O_3Si$, 244.4. Found 229 [M-CH_3], 199 [M-OCH_2CH_3]. All spectral data are similar to that acquired by Takaki and coworkers.[84]



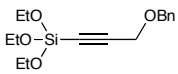
Triethoxy (3-methyl but-1-ynyl)silane (I-48): Purified by vacuum distillation, yielding 81% of **I-48** as a colorless liquid. BP = 75-80 °C (0.4 torr); IR (film) 2975, 2930, 2888, 2180, 1445, 1391, 1314, 1167, 1099, 1080, 970, 834, 791 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.86 (q, J = 7.0 Hz, 6H); 2.64-2.57 (m, 1H); 1.25 (t, J = 7.0 Hz, 9H); 1.19 (d, J = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 113.0, 74.8, 59.1, 22.7, 21.5, 18.2; GCMS (EI): Mass calculated for $C_{11}H_{22}O_3Si$, 230.4. Found 215 [M-CH_3], 187 [M-OCH_2CH_3].



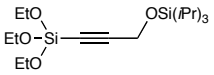
Triethoxy (3,3-dimethylbut-1-ynyl)silane (I-49): Purified by vacuum distillation, yielding 91% of **I-49** as a colorless liquid. BP = 90-97 °C (0.4 torr); IR (film) 2975, 2929, 2895, 2165, 1445, 1393, 1365, 1297, 1254, 1165, 1079, 966, 789 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.86 (q, J = 7.0 Hz, 6H); 1.26-1.24 (m, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 115.9, 73.8, 59.1, 30.8 (x2), 18.2; GCMS (EI): Mass Calculated for $C_{12}H_{24}O_3Si$, 244.4. Found 229 [M-CH_3], 199 [M-OCH_2CH_3].



Triethoxy (2-phenylethynyl)silane (I-50): Purified by vacuum distillation, yielding 86% of **I-50** as a colorless liquid. BP = 35-40 °C (0.4 torr); IR (film) 2974, 2928, 2888, 2166, 1487, 1443, 1391, 1164, 1099, 1082, 965, 841, 791, 758 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52-7.50 (m, 2H), 7.35-7.29 (m, 3H), 3.94 (q, J = 7.0 Hz, 6H), 1.29 (t, J = 7.0 Hz, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.6, 129.6, 128.5, 122.2, 104.35, 85.29, 59.3, 18.3; GCMS (EI): Mass calculated for $C_{14}H_{20}O_3Si$, 264.4. Found 264.



(3-(Benzyloxy)prop-1-ynyl) triethoxysilane (I-51): Purified by vacuum distillation, yielding 79% of **I-51** as a yellow liquid. BP = 105-112 °C (0.4 torr); IR (film) 2977, 2928, 2890, 2184, 1450, 1391, 1353, 1167, 1080, 1001, 969, 792, 726 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.35 (m, 5H) 4.62 (s, 2H), 4.21 (s, 2H), 3.90 (q, J = 7.0 Hz, 6H), 1.27 (t, J = 7.0 Hz, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.4, 128.7, 128.4, 128.2, 101.1, 83.3, 71.9, 59.3, 57.8, 18.3; GCMS (EI): Mass calculated for $C_{15}H_{24}O_4Si$, 308.4. Found 202 [M-OBn].



(3-(Triisopropylsilyl)prop-1-ynyl) triethoxysilane (I-52): Collected without purification, yielding 93% of **I-52** as a colorless liquid; IR (film) 2970, 2940, 2868, 2189, 1465, 1389, 1167, 1101, 1009, 966, 883, 791 cm^{-1}; ^{1}H NMR (500Mhz, $CDCl_3$) δ 4.40 (s, 2H), 3.86 (q, J = 7.0 Hz, 6H), 1.23 (t, J = 7.0 Hz, 9H), 1.12-1.06 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 104.2, 81.7, 59.2, 52.6, 18.2, 18.1, 12.2; GCMS (EI): Mass calculated for $C_{18}H_{38}O_4Si_2$, 374.7. Found 331 [M-OCH_2CH_3], 287 [M-2(OCH_2CH_3)], 245 [M-3(OCH_2CH_3)].

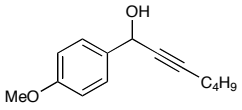
1.9.2 Preparation of Propargyl Alcohols

1.9.2.1 Representative Procedure for the Synthesis of Propargyl Alcohols I-53, I-55, I-68 to I-72, I-83 to I-92, and I-99 to I-105

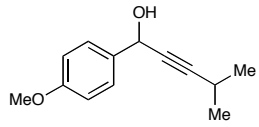
A screw-capped tube was charged with potassium ethoxide (0.12 mmol) and 18-crown-6 ether (0.0637 mmol) in a nitrogen-filled dry-box (18-crown-6 was used only to synthesize products **I-99** to **I-105**). The reaction tube was removed from the box and placed under a positive pressure of nitrogen. A solution of the triethoxysilylalkyne (0.637 mmol) in THF (2.5 mL) was added by cannulation to the tube and stirred for one hour. The reaction mixture was cooled to 0 °C, after which the aldehyde (0.531 mmol) was added by syringe. The reaction was allowed to stir at 0 °C for 2-5 hours. Upon completed consumption of the electrophile (aldehyde/ketone) as judged by GC analysis, the reaction was quenched by the addition of 0.6 M HCl, and then warmed to room temperature. After stirring at room temperature for one hour, the reaction was poured over saturated aqueous sodium bicarbonate. The aqueous layer was washed with ethyl

acetate (3x) and the combined organic extracts were dried over sodium sulfate, filtered, and concentrated by evaporation. The resulting residue was purified by flash column chromatography on silica gel.

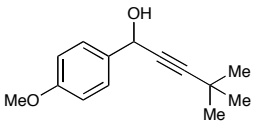
1.9.2.2 Characterization of Propargyl Alcohols I-53, I-55, I-68 to I-72, I-83 to I-92, and I-99 to I-105



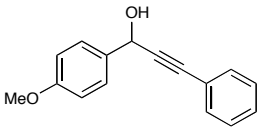
1-(4′-methoxyphenyl)hept-2-yn-1-ol (I-55): Purified with 10% ethyl acetate/hexanes, yielding 84 mg (84%) of **I-55** as a yellow oil. R_f = 0.20 (10:90 ethyl acetate/hexanes); IR (film) 3441, 2958, 2933, 2868, 2361, 2336, 1611, 1511, 1462, 1300, 1249, 1173, 1032, 834 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46 (m, 2H), 6.89 (m, 2H), 5.39 (s, 1H), 3.80 (s, 3H), 2.27 (q, J = 7.0 Hz, 2H), 1.55-1.52 (m, 2H), 1.45-1.41 (m, 2H), 0.92 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 133.9, 128.3, 114.1, 87.7, 80.4, 64.6, 55.6, 30.9, 22.2, 18.8, 13.9; GCMS (EI): Mass calculated for $C_{14}H_{18}O_2$ 218.3. Found 218.



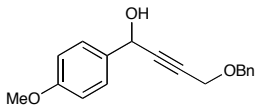
1-(4′-methoxyphenyl)-4-methylpent-2-yn-1-ol (I-68): Purified with 10% ethyl acetate/hexanes, yielding 75 mg (75%) of **I-68** as a yellow oil. R_f = 0.5 (30:70 ethyl acetate/hexanes); IR (film) 3397, 2968, 2934, 2873, 2247, 1609, 1510, 1462, 1303, 1248, 1173, 1035, 991, 834 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47 (m, 2H), 6.89 (m, 2H), 5.40 (s, 1H), 3.81 (s, 3H), 2.66-2.63 (m, 1H), 1.20 (d, J = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 133.9, 128.3, 114.1, 93.0, 79.5, 64.6, 55.6, 23.2, 20.8; GCMS (EI): Mass calculated for $C_{13}H_{16}O_2$ 204.3. Found 204.



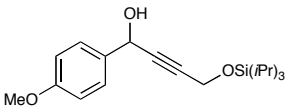
1-(4′-methoxyphenyl)-4,4-dimethylpent-2-yn-1-ol (I-69): Purified with 10% ethyl acetate/hexanes, yielding 73 mg (73%) of **I-69** as a yellow oil. R_f = 0.5 (30:70 ethyl acetate/hexanes); IR (film) 3399, 2965, 2928, 2866, 2234, 1611, 1511, 1459, 1300, 1248, 1173, 1067, 1035, 989, 833 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47 (m, 2H), 6.89 (m, 2H), 5.39 (s, 1H), 3.81 (s, 3H), 1.26 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.0, 134.1, 128.4, 114.1, 96.1, 79.2, 64.5, 55.6, 31.2, 21.0, 14.3; GCMS (EI): Mass calculated for $C_{14}H_{18}O_2$ 218.3. Found 218.



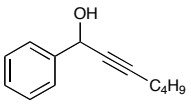
1-(4′-methoxyphenyl)-3-phenylprop2-yn-1-ol (I-70): Purified with 10% ethyl acetate/hexanes, yielding 77 mg (77%) of **I-70** as an orange oil. R_f = 0.3 (20:80 ethyl acetate/hexanes); IR (film) 3428, 3059, 2958, 2932, 2838, 2200, 2162, 1599, 1510, 1458, 1443, 1302, 1252, 1173, 1032, 963, 834, 758, 692 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.55 (m, 2H), 7.48-7.47 (m, 2H), 7.33-7.32 (m, 3H), 6.94-6.93 (m, 2H), 5.65 (s, 1H), 3.83 (s, 3H), 2.31 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.3, 132.0, 129.9, 128.8, 128.6, 128.4, 127.9, 122.8, 114.3, 89.2, 86.7, 65.0, 55.6; GCMS (EI): Mass calculated for $C_{16}H_{14}O_2$ 238.3. Found 238.



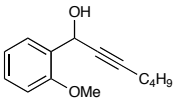
4-(benzyloxy)-1-(4′-methoxyphenyl)but-2-yn-1-ol (I-71): Purified with 10% ethyl acetate/hexanes, yielding 76 mg (76%) of **I-71** as a yellow oil. R_f = 0.4 (30:70 ethyl acetate/hexanes); IR (film) 3411, 3032, 2932, 2855, 1609, 1510, 1455, 1355, 1302, 1251, 1174, 1109, 1070, 1030, 837, 744, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.48-7.46 (m, 3H), 7.36-7.33 (m, 4H), 6.92-6.90 (m, 2H), 5.47 (s, 1H), 4.61 (s, 2H), 4.27 (s, 2H), 3.81 (s, 3H), 2.55 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 137.6, 133.1, 128.7, 128.3, 128.2, 114.2, 86.9, 82.7, 72.0, 64.4, 57.7, 55.6; GCMS (EI): Mass calculated for $C_{18}H_{18}O_3$ 282.3. Found 174 [M-OBn].



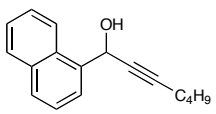
4-(Triisopropylsiloxy)-1-(4′-methoxyphenyl)but-2-yn-1-ol (I-72): Purified with 10% ethyl acetate/hexanes, yielding 76 mg (76%) of **I-72** as a yellow oil. R_f = 0.8 (30:70 ethyl acetate/hexanes); IR (film) 3422, 2943, 2866, 1601, 1510, 1464, 1251, 1173, 1126, 883, 685 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46 (m, 2H), 6.89 (m, 2H), 5.45 (s, 1H), 4.47 (s, 2H), 3.81 (s, 3H), 1.15-1.04 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.5, 132.7, 128.3, 114.1, 85.8, 84.6, 64.5, 55.6, 52.3, 18.2, 12.2; GCMS (EI): Mass calculated for $C_{20}H_{32}O_3Si$ 348.6. Found 349.



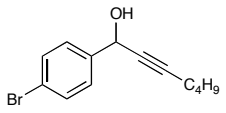
1-Phenylhept-2-yn-1-ol (I-53): Purified with 10% ethyl acetate/hexanes, yielding 74 mg (74%) of **I-53** as a yellow oil. R_f = 0.3 (10:90 ethyl acetate/hexanes); IR (film) 3447, 2959, 2933, 2868, 2235, 2202, 1643, 1450, 1314, 1266, 1175, 997, 912, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.56-7.54 (m, 2H), 7.40-7.37 (m, 2H), 7.34-7.32 (m, 1H), 5.45 (s, 1H), 2.28 (t, J = 7.0 Hz, 2H), 1.55-1.51 (m, 2H), 1.46-1.41 (m, 2H), .93 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.5, 128.8, 128.4, 126.9, 87.9, 65.1, 30.9, 22.2, 18.8, 13.9; GCMS (EI): Mass calculated for $C_{13}H_{16}O$ 188.3. Found 188.



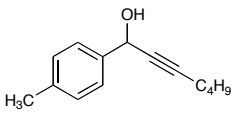
1-(2′-methoxyphenyl)hept-2-yn-1-ol (I-83): Purified with 10% ethyl acetate/hexanes, yielding 82 mg (82%) of **I-83** as a yellow oil. R_f = 0.2 (10:90 ethyl acetate/hexanes); IR (film) 3430, 2958, 2933, 2868, 1597, 1492, 1462, 1285, 1245, 1106, 1026, 754 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.62-7.60 (m, 1H), 7.31-7.29 (m, 1H), 7.01-6.98 (m, 1H), 6.92-6.90 (m, 1H), 5.73 (s, 1H), 3.89 (s, 1H), 2.98 (bs, 1H), 2.30 (t, J = 7.0 Hz, 2H), 1.56-1.52 (m, 2H), 1.47-1.42 (m, 2H), 0.93 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.0, 129.7, 129.6, 128.2, 121.0, 111.0, 87.4, 79.4, 61.4, 55.8, 31.0, 22.2, 18.8, 13.9; GCMS (EI): Mass calculated for $C_{14}H_{18}O_2$ 218.3. Found 218.



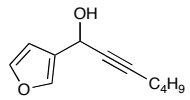
1-(napthalen-1-yl)hept-2-yn-1-ol (I-84): Purified with 10% ethyl acetate/hexanes, yielding 76 mg (76%) of **I-84** as a yellow oil. R_f = 0.2 (10:90 ethyl acetate/hexanes); IR (film) 3368, 3050, 2957, 2932, 2866, 1597, 1510, 1459, 1379, 1260, 1164, 1134, 988, 781 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.33-8.32 (m, 1H), 7.89-7.83 (m, 3H), 7.56-7.46 (m, 3H), 6.12 (s, 1H), 2.37 (bs, 1H), 2.30 (t, J = 7.0 Hz, 2H), 1.57-1.52 (m, 2H), 1.46-1.42 (m, 2H), 0.93 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.5, 134.3, 130.8, 129.4, 128.9, 126.5, 126.1, 125.5, 124.7, 124.3, 88.6, 79.9, 63.3, 30.9, 22.3, 18.9, 13.9; GCMS (EI): Mass calculated for $C_{17}H_{18}O$ 238.3. Found 238.



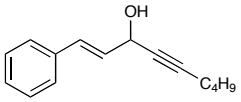
1-(4′-Bromophenyl)hept-2-yn-1-ol (I-85): Purified with 10% ethyl acetate/hexanes, yielding 76 mg (76%) of **I-85** as a yellow oil. R_f = 0.2 (10:90 ethyl acetate/hexanes); IR (film) 3382, 2958, 2932, 2868, 2234, 2202, 1643, 1587, 1483, 1398, 1264, 1134, 1070, 1007, 844, 774, 741 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.50-7.48 (m, 2H), 7.41-7.40 (m, 2H), 5.40 (s, 1H), 2.64 (t, J = 6.5 Hz, 2H), 1.53-1.49 (m, 2H), 1.44-1.39 (m, 2H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.5, 131.8, 128.6, 122.4, 88.3, 79.7, 64.4, 30.8, 22.2, 18.7, 13.8; GCMS (EI): Mass calculated for $C_{13}H_{15}OBr$ 267.2. Found 185 [M-Br].



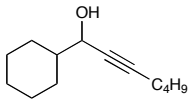
1-*p*-Tolylhept-2-yn-1-ol (I-86): Purified with 10% ethyl acetate/hexanes, yielding 80 mg (80%) of **I-86** as a yellow oil. R_f = 0.2 (10:90 ethyl acetate/hexanes); IR (film) 3368, 2958, 2930, 2863, 1513, 1458, 1429, 1379, 1179, 1132, 999, 820, 758 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (m, 2H), 7.19 (m, 2H), 5.42 (s, 1H), 2.37 (s, 3H), 2.28 (t, J = 7.0 Hz, 2H), 1.56-1.53 (m, 2H), 1.46-1.42 (m, 2H), 0.93 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 138.2, 129.5, 126.9, 87.6, 80.4, 64.9, 30.9, 22.3, 21.4, 18.8, 13.9; GCMS (EI): Mass calculated for $C_{14}H_{18}O$ 202.3. Found 202. All spectral data are similar to that acquired by Sheldon and coworkers.[85]



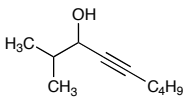
1-(furan-3-yl)hept-2-yn-1-ol (I-87): Purified with 10% ethyl acetate/hexanes, yielding 85 mg (85%) of **I-87** as a red oil. R_f = 0.2 (10:90 ethyl acetate/hexanes); IR (film) 3408, 2959, 2933, 2868, 1636, 1501, 1462, 1304, 1134, 1007, 932, 817, 739 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (m, 1H), 6.42 (m, 1H), 6.34 (m, 1H), 5.44 (s, 1H), 2.47 (bs, 1H), 2.27 (t, J = 7.0 Hz, 2H), 1.56-1.50 (m, 2H), 1.47-1.41 (m, 2H), 0.92 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9, 143.1, 110.6, 107.7, 87.1, 77.7, 58.5, 30.7, 22.2, 18.7, 13.8; GCMS (EI): Mass calculated for $C_{11}H_{14}O_2$ 178.2. Found 178.



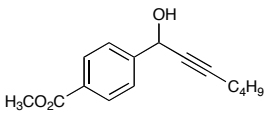
(*E*)-1-phenylnon-1-en-4-yn-3-ol (I-88): Purified with 10% ethyl acetate/hexanes, yielding 59 mg (59%) of **I-88** as a yellow oil. R_f = 0.3 (10:90 ethyl acetate/hexanes); IR (film) 3389, 3028, 2958, 2932, 2868, 2213, 1628, 1493, 1450, 1325, 1203, 1068, 966, 749, 694 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43-7.41 (m, 2H), 7.35-7.32 (m, 2H), 7.29-7.26 (m, 1H), 6.77 (d, J = 16.0 Hz, 1H), 6.32 (dd, J = 10.0 Hz, 5.0 Hz, 1H), 5.06 (d, J = 5.5 Hz, 1H), 2.29 (t, J = 7.0 Hz, 2H), 2.08 (bs, 1H), 1.58-1.52 (m, 2H), 1.49-1.42 (m, 2H), 0.94 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.5, 131.7, 129.1, 128.8, 128.2, 127.0, 87.8, 79.4, 63.5, 30.9, 22.2, 18.7, 13.9; GCMS (EI): Mass calculated for $C_{15}H_{18}O$ 214.3. Found 213.



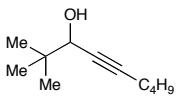
1-cyclohexylhept-2-yn-1-ol (I-89): Purified with 5% ethyl acetate/hexanes, yielding 56 mg (56%) of **I-89** as a colorless oil. R_f = 0.5 (30:70 ethyl acetate/hexanes); IR (film) 3368, 2927, 2853, 1451, 1379, 1328, 1140, 1080, 1011, 893 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.13 (d, J = 5.5 Hz, 1H), 1.84-1.82 (m, 2H), 1.77-1.72 (m, 3H), 1.52-1.46 (m, 3H), 1.44-1.38 (m, 2H), 1.28-1.20 (m, 3H), 1.18-1.10 (m, 2H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 86.5, 80.4, 67.7, 44.6, 31.1, 28.8, 28.3, 26.7, 26.2, 26.2, 22.2, 18.6, 13.8; GCMS (EI): Mass calculated for $C_{18}H_{22}O$ 194.3. Found 111 [M-C_6H_{11}].



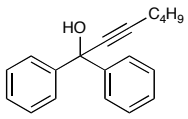
2-methylnon-4-yn-3-ol (I-90): Purified with 5% ethyl acetate/hexanes, yielding 58 mg (58%) of **I-90** as a colorless oil. R_f = 0.45 (30:70 ethyl acetate/hexanes); IR (film) 3364, 2960, 2933, 2872, 1464, 1381, 1325, 1149, 959, 930, 735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.14 (d, J = 5.5 Hz, 1H), 2.21 (t, J = 7.0 Hz, 2H), 1.81 (m, 2H) 1.48 (m, 2H), 1.40 (m, 2H), 0.97 (d, J = 10.0 Hz, 3H), 0.96 (d, J = 10.0, 3H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 86.4, 80.0, 68.4, 34.9, 31.0, 22.2, 18.6, 18.3, 17.6, 13.8; GCMS (EI): Mass calculated for $C_{10}H_{18}O$ 154.1. Found 111 [M-$CH(CH_3)_2$].



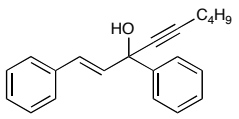
Methyl 4-(1-hydroxyhept-2-ynyl)benzoate (I-91): Purified with 10% ethyl acetate/hexanes, yielding 78 mg (78%) of **I-91** as a yellow oil. R_f = 0.4 (30:70 ethyl acetate/hexanes); IR (film) 3438, 2957, 2932, 2868, 1722, 1611, 1436, 1412, 1280, 1190, 1109, 1016, 868, 806, 751, 707 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.05-8.03 (m, 2H), 7.62-7.60 (m, 2H), 5.50 (s, 1H), 3.92 (s, 3H), 2.27 (t, J = 7.0 Hz, 2H), 1.54-1.51 (m, 2H), 1.44-1.39 (m, 2H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 146.3, 130.1, 130.0, 126.7, 88.5. 79.6, 64.6, 52.4, 30.8, 22.2, 18.7, 13.8; GCMS (EI): Mass calculated for $C_{15}H_{18}O_3$ 246.3. Found 187 [M-CO_2CH_3].



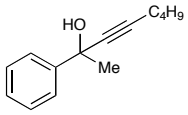
2,2-Dimethylnon-4-yn-3-ol (I-92): Collected without purification, yielding 93 mg (93%) of **I-92** as a yellow oil. R_f = 0.7 (20:80 ethyl acetate/hexanes); IR (film) 3420, 2958, 2934, 2871, 1462, 1363, 1137, 1038, 1003 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.97 (s, 1H), 2.21 (t, J = 6.5 Hz, 2H), 1.50-1.47 (m, 2H), 1.42-1.39 (m, 2H), 0.96 (s, 9H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 86.4, 80.0, 71.8, 36.0, 31.0, 25.5, 22.1, 18.6, 13.8; GCMS (EI): Mass calculated for $C_{11}H_{20}O$ 168.3. Found 111 [M-$C(CH_3)_3$].



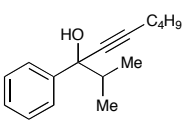
1,1-diphenylhept-2-yn-1-ol (I-99): Purified with 10% ethyl acetate/hexanes, yielding 73 mg (73%) of **I-99** as a yellow oil. R_f = 0.4 (10:90 ethyl acetate/hexanes); IR (film) 3458, 3061, 3028, 2958, 2932, 2862, 1597, 1489, 1450, 1329, 1204, 1141, 1004, 889, 754, 699, 643 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.66-7.64 (m, 4H), 7.37-7.34 (m, 4H), 7.30-7.27 (m, 2H), 2.79 (s, 1H), 2.38 (t, J = 7.0 Hz, 2H), 1.63-1.59 (m, 2H), 1.52-1.48 (m, 2H), 0.98 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.8, 128.4, 127.7, 126.3, 88.6, 83.3, 74.7, 31.0, 22.3, 18.9, 13.9; GCMS (EI): Mass calculated for $C_{19}H_{20}O$ 264.4. Found 264.



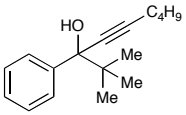
(*E*)-1,3-Diphenylnon-1-en-4-yn-3-ol (I-100): Purified with 5% ethyl acetate/hexanes, yielding 54 mg (54%) of **I-100** as a yellow oil. R_f = 0.5 (20:80 ethyl acetate/hexanes); IR (film) 3426, 3060, 3027, 2958, 2931, 2861, 1560, 1492, 1448, 1329, 1179, 1030, 965, 908, 747, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.71-7.70 (m, 2H), 7.43-7.38 (m, 4H), 7.34-7.31 (m, 3H), 7.28-7.25 (m, 1H), 6.96 (d, J = 16.0 Hz, 1H), 6.40 (d, J = 16.0 Hz, 1H), 2.55 (bs, 1H), 2.39 (t, J = 7.0 Hz, 2H), 1.66-1.60 (m, 2H), 1.55-1.48 (m, 2H), 0.98 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.2, 136.6, 133.8, 129.0, 128.6, 128.1, 128.0, 127.1, 126.1, 88.9, 81.4, 73.3, 31.0, 22.3, 18.8, 13.9; GCMS (EI): Mass calculated for $C_{21}H_{22}O$ 290.4. Found 290.



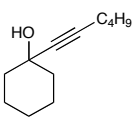
2-Phenyloct-3-yn-2-ol (I-101): Purified with 10% ethyl acetate/hexanes, yielding 54 mg (54%) of **I-101** as a yellow oil. R_f = 0.4 (20:80 ethyl acetate/hexanes); IR (film) 3401, 2958, 2931, 2861, 2241, 1448, 1365, 1327, 1233, 1177, 1095, 1065, 918, 763, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67-7.65 (m, 2H), 7.37-7.34 (m, 2H), 7.30-7.27 (m, 1H), 2.28 (t, J = 7.0 Hz, 2H), 1.75 (s, 3H), 1.57-1.52 (m, 2H), 1.46-1.42 (m, 2H), 0.93 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.5, 128.4, 127.7, 125.2, 86.0, 84.0, 70.3, 33.8, 31.0, 22.2, 18.7, 13.9; GCMS (EI): Mass calculated for $C_{14}H_{18}O$ 202.3. Found 187 [M-CH_3].



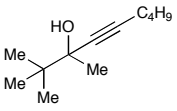
2-Methyl-3-phenylnon-4-yn-3-ol (I-102): Purified with 5% ethyl acetate/hexanes, yielding 71 mg (71%) of **I-102** as a yellow oil. $R_f = 0.5$ (20:80 ethyl acetate/hexanes); IR (film) 3456, 3061, 3027, 2961, 2932, 2870, 1448, 1377, 1331, 1217, 1169, 1007, 758, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.63-7.62 (m, 2H), 7.36-7.33 (m, 2H), 7.30-7.27 (m, 1H), 2.34 (t, J = 7.0 Hz, 2H), 2.09-2.05 (m, 1H), 1.61-1.56 (m, 2H), 1.51-1.47 (m, 2H), 1.08(d, J = 6.5 Hz, 3H), 0.96 (t, J = 7.0 Hz, 3H), 0.81 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.8, 128.0, 127.6, 126.5, 87.8, 81.4, 40.6, 31.1, 22.3, 18.7, 18.3, 17.8, 13.9; GCMS (EI): Mass calculated for $C_{16}H_{22}O$ 230.4. Found 187 [M-$CH(CH_3)_2$].



2,2-Dimethyl-3-phenylnon-4-yn-3-ol (I-103): Purified with 10% ethyl acetate/hexanes, yielding 85 mg (85%) of **I-103** as a yellow oil. $R_f = 0.6$ (10:90 ethyl acetate/hexanes); IR (film) 3479, 3060, 3026, 2958, 2932, 2870, 1677, 1599, 1483, 1447, 1387, 1362, 1325, 1218, 1180, 1040, 993, 903, 748, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65-7.64 (m, 2H), 7.35-7.32 (m, 2H), 7.30-7.28 (m, 1H), 2.33 (t, J = 7.0 Hz, 2H), 2.27 (bs, 1H), 1.62-1.56 (m, 2H), 1.54-1.48 (m, 2H), 1.04 (s, 9H), 0.98 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.8, 128.0, 127.4, 127.2, 86.6, 83.5, 39.7, 31.1, 25.8, 22.3, 18.7, 13.9; GCMS (EI): Mass calculated for $C_{17}H_{24}O$ 244.4. Found 187 [M-$C(CH_3)_3$].



1-(Hex-1-ynyl)cyclohexanol (I-104): Purified with 5% ethyl acetate/hexanes, yielding 64 mg (64%) of **I-104** as a colorless oil. R_f = 0.4 (20:80 ethyl acetate/hexanes); IR (film) 3392, 2932, 2858, 1449, 1330, 1179, 1063, 963 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.21 (t, J = 7.0 Hz, 2H), 1.87-1.85 (m, 2H), 1.67-1.65 (m, 2H), 1.57-1.46 (m, 8H), 1.43-1.39 (m, 2H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.7, 131.1, 43.8, 32.0, 31.0, 30.0, 28.9, 28.5, 26.8, 25.8; GCMS (EI): Mass calculated for $C_{12}H_{20}O$ 180.3. Found 180.



2,2,3-Trimethylnon-4-yn-3-ol (I-105): Purified with 10% ethyl acetate/hexanes, yielding 73 mg (73%) of **I-105** as a colorless oil. R_f = 0.6 (10:90 ethyl acetate/hexanes); IR (film) 3474, 2960, 2935, 2872, 1459, 1368, 1325, 1179, 1087, 1002, 910 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.19 (t, J = 7.0 Hz, 2H), 1.81 (bs, 1H), 1.49-1.45 (m, 2H), 1.42-1.38 (m, 5H), 1.02 (s, 9H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 84.4, 84.0, 74.2, 38.5, 31.1, 25.4, 25.3, 22.2, 18.5, 13.8; GCMS (EI): Mass calculated for $C_{12}H_{22}O$ 182.3. Found 125 [M-$C(CH_3)_3$].

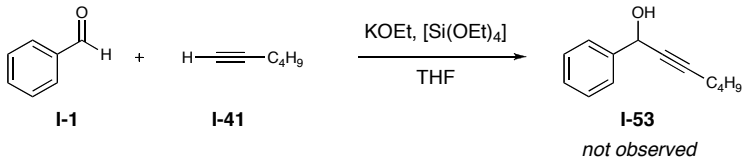
1.9.2.3 Representative Procedure In Situ-Generated Potassium Alkoxide-Promoted Reactions

A screw-capped reaction tube was charged with potassium hydride (0.125 mmol) and 18-crown-6 (0.125 mmol) in a nitrogen-filled drybox. The reaction tube was removed from the box and placed under a positive pressure of nitrogen. To the tube was added THF (0.6 mL), and cooled to 0 °C. A solution of *sec*-phenethyl alcohol (0.125 mmol) in THF (0.2 M) was added by cannulation to the test tube and let stir for one hour at 0 °C. A solution of **I-42** (1.20 equiv) in THF (0.2 M) was added by cannulation to the test tube and let stir for one hour at 0 °C. To the reaction was added the aldehyde by syringe and was allowed to stir at 0 °C for 2 hours. Upon completion by GC analysis, to the reaction was added 0.6 M HCl, and warmed to room temperature. After stirring at room temperature for one hour, the reaction was poured over saturated aqueous sodium bicarbonate. The aqueous layer was washed with ethyl acetate (3x) and the combined the organic extracts were dried over sodium sulfate, filtered, and concentrated by evaporation. The resulting residue was purified by flash column chromatography on silica gel.

1.9.2.4 Control Experiments

To assess the necessity of the triethoxysilylalkyne system, two control experiments were conducted (Scheme 1-16). The only difference between the two control experiments was the addition or absence of tetraethyl orthosilicate ($Si(OEt)_3$): A screw-capped tube was charged with potassium ethoxide (0.49 mmol) in a nitrogen-filled drybox. The reaction tube was removed from the box and placed under a positive pressure of nitrogen. To the tube was added THF (2.5 mL), 1-hexyne (0.49 mmol), tetraethyl orthosilicate (0.49 mmol, if necessary), and benzaldehyde (0.49 mmol), each by syringe. The reaction was stirred for 5 hours at ambient temperature and then quenched by the addition of 0.6 M HCl. After stirring for 30 minutes, the reaction was poured over saturated aqueous sodium bicarbonate. The aqueous layer was washed with ethyl acetate (3x) and the combined organic extracts were dried over sodium sulfate, filtered, and concentrated by evaporation. Neither ^1H NMR (500 MHz) spectroscopy or GC analysis of the unpurified reaction mixtures showed any traces of desired propargyl alcohol **I-53**.

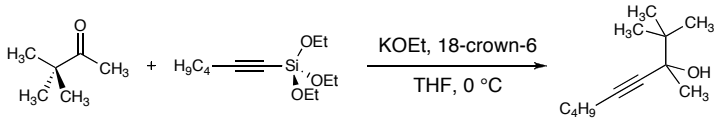
Scheme 1-16. Control Experiment



1.9.2.5 Determination of the Role of 18-Crown-6 in Tertiary Propargyl Alcohol Formation

Through initial studies it was apparent that 18-crown-6 was necessary as an additive along with potassium ethoxide to promote complete conversion of ketone starting materials in the addition of **I-42**. To delineate the role of 18-crown-6 in these reactions, experiments were conducted to accurately measure the level of conversion as a function of amount of crown ether present. Gas chromatographic analysis using dodecane as an internal standard permitted the calculation of pinacolone conversion.

Table 1-9. Role of 18-crown-6 ether



I-98 **I-42** **I-105**

entry	mol% KOEt	mol% 18-crown-6	% conversion
1	20	0	15
2	20	20	100
3	100	0	85

a. A 0.25M solution of **I-42** in THF was added to the KOEt/18-crown-6, and stirred for 1 h prior to the addition of **I-98**.

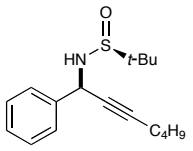
The data clearly indicates that the reaction proceeds to 85% with 100 mol% potassium ethoxide. More importantly, the use of only 20 mol% KOEt affords very low levels of conversion (15%). However, the addition of 20 mol% 18-crown-6 to 20 mol% KOEt afford 100% conversion. One explanation to account for this data is that if the product tertiary propargyl potassium alkoxide (**I-105**) is responsible for catalytic turnover (e.g. undergoing addition to **I-42** to form the reactive silicate).

1.9.3 Preparation of Propargyl Imine I-114

1.9.3.1 Procedure for the Synthesis of Propargyl Imine I-114

A screw-capped reaction tube was charged with potassium ethoxide (0.628 mmol) and 18-crown-6 (0.628 mmol) in a nitrogen-filled drybox. The reaction tube was removed from the box and placed under a positive pressure of nitrogen. To the tube was added THF by syringe (0.5 mL), and the whole reaction mixture was cooled to 0 °C. To the mixture was added a cooled to 0 °C solution of **I-42** (0.628 mmol) in THF (1 mL) by cannulation and let stir for 30 minutes. The reaction mixture was cooled to –78 °C after which a cooled to –78 °C solution of (*R*)-(benzylidene)-*tert*-butanesulfinamide (**I-110**, 0.418 mmol)[65] in THF (0.5 mL) was added by cannulation. The reaction was allowed to stir at –78 °C for 5 hours. To the reaction was added saturated aqueous sodium bicarbonate, and warmed to room temperature. After stirring at room temperature for one hour, the reaction was extracted with ethyl acetate (3x). The combined the organic extracts were dried over sodium sulfate, filtered, and concentrated by evaporation. The resulting residue was purified by flash column chromatography on silica gel to yield propargyl amine **I-114**.

1.9.3.2 Characterization of Propargyl Imine I-114



(S_s,*R*)-2-Methylpropane-2-sulfinic Acid (1-Phenylhept-2-ynyl) amide (I-114): Purified with 10% ethyl acetate/hexanes yielding 95% of **I-114** as a yellow oil; $R_{f(major)}$= 0.25 (30:70 ethyl acetate/hexanes); $R_{f(minor)}$= 0.35 (30:70 ethyl acetate/hexanes); IR (film) 3187, 3063, 3031, 2957, 2932, 2871, 2362, 2337, 1494, 1456, 1363, 1064, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.52-7.51 (m, 2H), 7.38-7.31 (m, 3H), 5.26 (s, 1H), 3.40 (s, 1H), 2.25 (t, J = 6.0 Hz, 2H), 1.53-1.49 (m, 2H), 1.45-1.40 (m, 2H), 1.22 (s, 9H), 0.91 (t, J = 7.0, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.2, 129.0, 128.8, 128.6, 127.9, 87.9, 78.4, 56.0, 51.5, 30.9, 22.8, 22.1, 18.7, 13.8; GCMS (EI): Mass calculated for $C_{17}H_{25}NOS$ 291.2. Found 291.

1.9.3.3 General Method for Metal-Acetylide Additions to N-tert-Butanesulfinyl Imine I-110

Preparation of the lithium acetylide of 1-hexyne (**I-111**): To a nitrogen-filled flask under a positive pressure of nitrogen was added THF (0.5 M) and 1-hexyne (1.0 equiv) by syringe, and cooled to –78 °C. To the flask was added *n*-butyl lithium (1.5 M in THF, 1.0 equiv) slowly by syringe. The reaction was warmed to 0 °C, and let stir for 2 hours. The resulting solution was used in the general alkoxide promoted addition reaction procedure as written below.

Preparation of the Grignard reagent of 1-hexyne (**I-112**): To a nitrogen-filled flask under a positive pressure of nitrogen was added THF (0.5 M), 1-hexyne (1.0 equiv), and ethyl magnesium bromide (3.0 M in Et_2O, 1.0 equiv) by syringe. A condenser was attached, and the solution was heated at reflux for 2 hours, and cooled to ambient temperature. The resulting solution was used in the general alkoxide promoted addition reaction procedure as written below.

Preparation of the potassium acetylide of 1-hexyne (**I-113**): To a flask was charged potassium hydride (1.0 equiv) and 18-crown-6 ether (1.0 equiv) in a nitrogen filled glove box. The flask was removed from the box and placed under a positive pressure of nitrogen. To the flask was added THF (0.5 M) by syringe, and cooled to 0 °C. To the flask was added 1-hexyne by syringe, and let stir at 0 °C for 1 hour. The resulting solution was used in the general alkoxide promoted addition reaction procedure as written below.

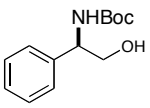
*General addition metal-acetylenes to **I-110***: A solution of M-hexyne (M = Li, K, MgBr) in THF was cooled to 0 °C. To the solution was added a cooled to 0 °C solution of **I-110** in THF, and let stir at 0 °C until completion. Reaction was quenched with saturated aqueous sodium bicarbonate, and warmed to room temperature. After stirring at room temperature for one hour, the reaction was extracted with ethyl acetate (3x). The combined the organic extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to yield **I-114** as an unpurified mixture. Diastereomeric ratios were determined via ^{1}H NMR analysis of the unpurified products. Purification was done per above to determine yield.

1.9.3.4 Determination of the New Propargyl Stereocenter of I-110

Desulfination[74] and Boc-protection[75]: To a flask containing **I-114** (0.351 mmol) was added MeOH (2 mL) and cooled to 0 °C. To the solution was added HCl (4 M in 1,4-dioxane, 1.40 mmol) slowly by syringe, and let stir at 0 °C for 20 minutes. The reaction was warmed to ambient temperature and concentrated *in vacuo* to yield 1-phenylhept-2-yn-1-amine as a white solid. To the flask was added CH_2Cl_2 (1.0 mL) and triethylamine (0.527 mmol) by syringe, and cooled to 0 °C. To the reaction was added di-*tert*-butyl dicarbonate (0.421 mmol) and let stir 3 hours. The reaction was quenched with 0.6 M HCl (1mL), and partitioned. The organic layer was washed with 0.6 M HCl (x2) and brine (x2), dried over magnesium sulfate, and concentrated by evaporation to yield *tert*-butyl 1-phenylhept-2-ynylcarbamate (**I-115**) as a white solid.

Alkyne reduction[76]: To a flask was charged Lindlar's catalyst (50 mg) and purged first with N_2, then with H_2. To the flask was added ethyl acetate (1.0 mL) by syringe, and let stir under H_2 for 1 hour. To the mixture was added a solution of *tert*-butyl 1-phenylhept-2-ynylcarbamate (0.351 mmol) in ethyl acetate (1.0 mL) by syringe and let stir for 3 hours. To the reaction was added more Lindlar's catalyst (50 mg), purged with H_2, and let stir under H_2 for 12 hours. The reaction mixture was filtered over a thin layer of celite, and concentrated by evaporation. The product was purified by flash chromatography (5:95 EtOAc/Hexanes, $R_f = 0.25$) to yield *tert*-butyl (*Z*)-1-phenylhept-2-enylcarbamate (**I-116**) as yellow oil.

Ozonolysis[77]: To a flask containing *tert*-butyl (*Z*)-1-phenylhept-2-enylcarbamate (0.180 mmol) was added MeOH (2 mL) and CH_2Cl_2 (0.5 mL), cooled to -78 °C, and bubbled with ozone for 1 hour. The resulting solution was purged with N_2. To the purged reaction was added $NaBH_4$ (0.359 mmol), and stirred at –78 °C for 1 hour. The reaction was let warm slowly to ambient temperature while stirring for 8 hours. The solvent was removed *in vacuo*. The remaining residue was partitioned with 0.6 M HCl and $CHCl_3$ and the aqueous layer was extracted with $CHCl_3$ (3x). The combined organic layers were dried over sodium sulfate, and concentrated by evaporation. The product was purified by flash chromatography (50:50 EtOAc/Hexanes) to yield *tert*-butyl (*R*)-2-hydroxy-1-phenylethylcarbamate (**I-117**) as a white solid. Optical rotation data is in agreement with Cox and Harwood[71] and O'Brien and coworkers.[72] All NMR spectroscopic data corresponds to that acquired by Dondoni, Perrone, and Semola.[73]

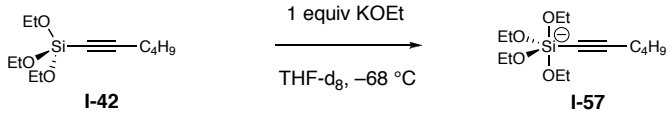


***tert*-Butyl (*R*)-2-hydroxy-1-phenylethylcarbamate (I-117):** Purified with 50% diethyl ether/ hexanes, yielding 73 mg (73%) of **I-117** as a colorless oil; $[\alpha]_D = -31.3$ (c = 0.3, $CHCl_3$); R_f = 0.16 (50:50 diethyl ether/ hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 9H), 3.85-3.86 (m, 2H), 4.78 (m, 1H), 5.21 (d, J = 7.0 Hz, 1H) 7.29-7.38 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 139.9, 129.0, 128.0, 126.8, 80.2, 67.3, 57.1, 28.5.

1.9.4 Pentavalent Silicon Studies Using ^{29}Si NMR Spectroscopy

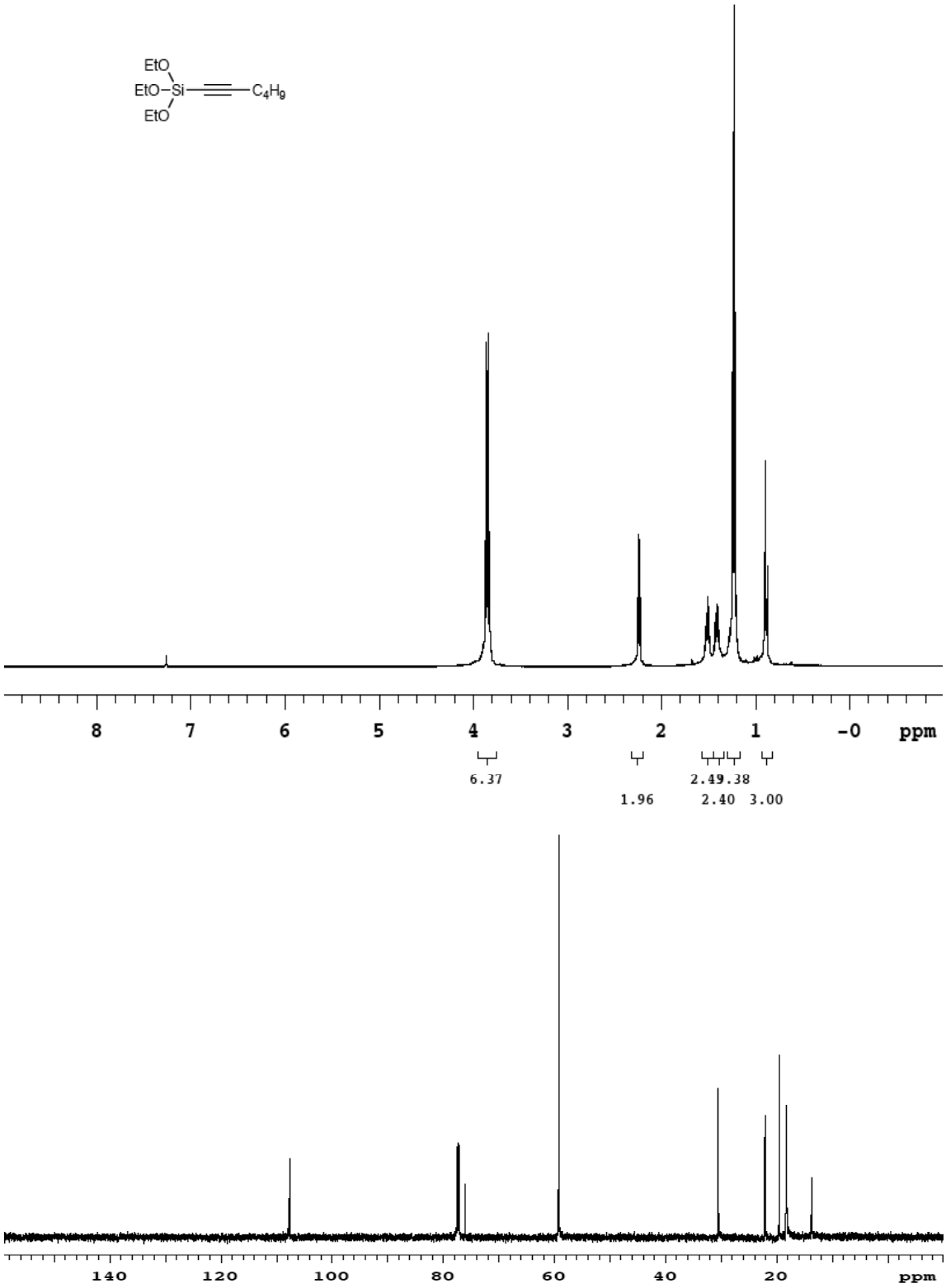
Low temperature ^{29}Si NMR spectroscopy studies were conducted to identify the predicted pentavalent silicon intermediate (**I-110**) in the reaction process (Table 1-10). To a valved NMR tube was charged potassium ethoxide (1.0 equiv) and 18-crown-6 ether (1.0 equiv). To the tube was added tetrahydrofuran-d_8 and cooled to –78 °C. To the tube was added a –78 °C solution of either tetraethyl orthosilicate or **I-42** (1 equiv) in tetrahydrofuran-d_8 by syringe. The reaction was then analyzed by ^{29}Si NMR spectroscopy at –68 °C. Spectral data are similar to that acquired by Holmes and coworkers.[14]

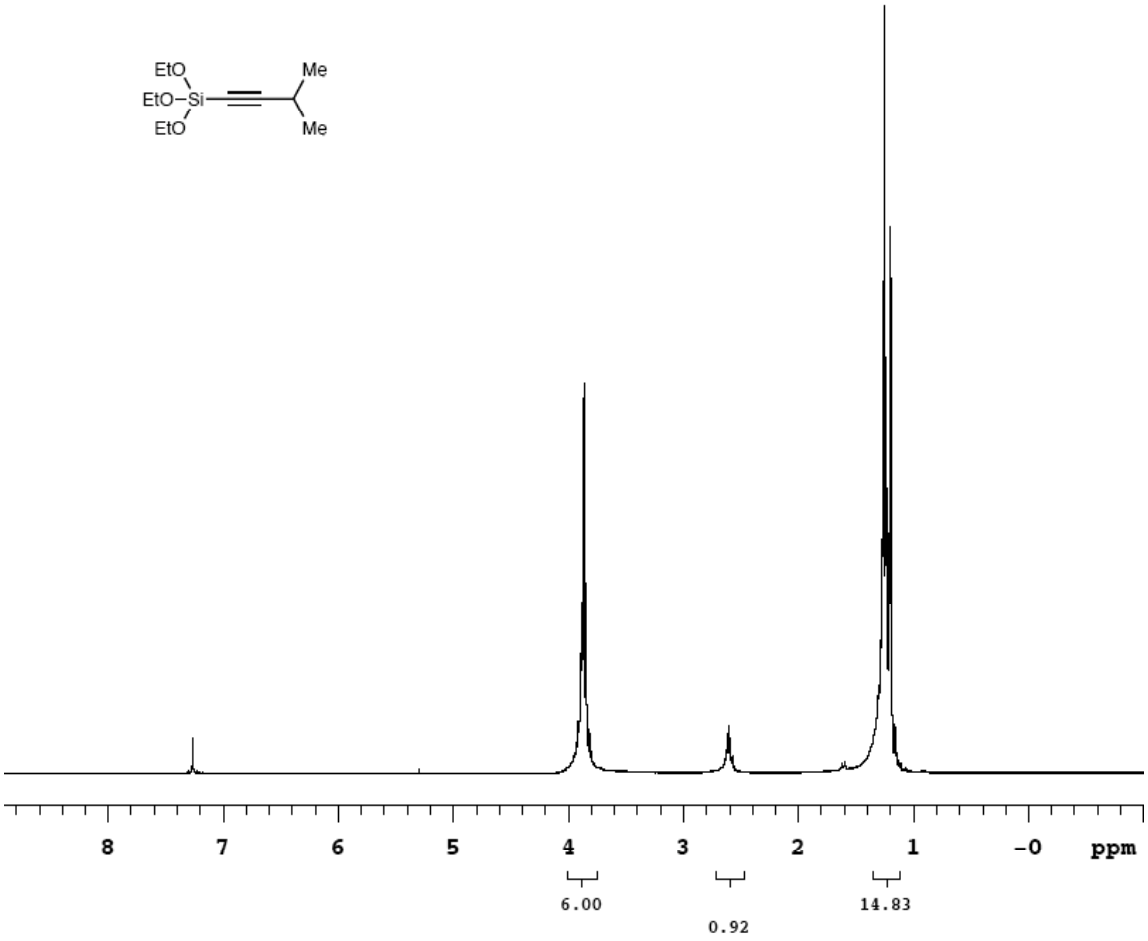
Table 1-10. ^{29}Si NMR spectroscopy studies



Silane	^{29}Si NMR lit. (δ)	^{29}Si NMR (δ)
$Si(OEt)_4$	- 82.4	- 80.6
$Si(OEt)_5$	-131.1	-130.0
$PhSi(OEt)_3$	- 58.0	-
$PhSi(OEt)_4$	- 117.3	-
$(vinyl)Si(OEt)_3$	- 59.9	-
$(vinyl)Si(OEt)_4$	- 117.2	-
H_9C_4—≡—$Si(OEt)_3$	-	- 74.6
H_9C_4—≡—$Si(OEt)_4$	-	- 125.6

1.9.5 Selected NMR Spectra

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4
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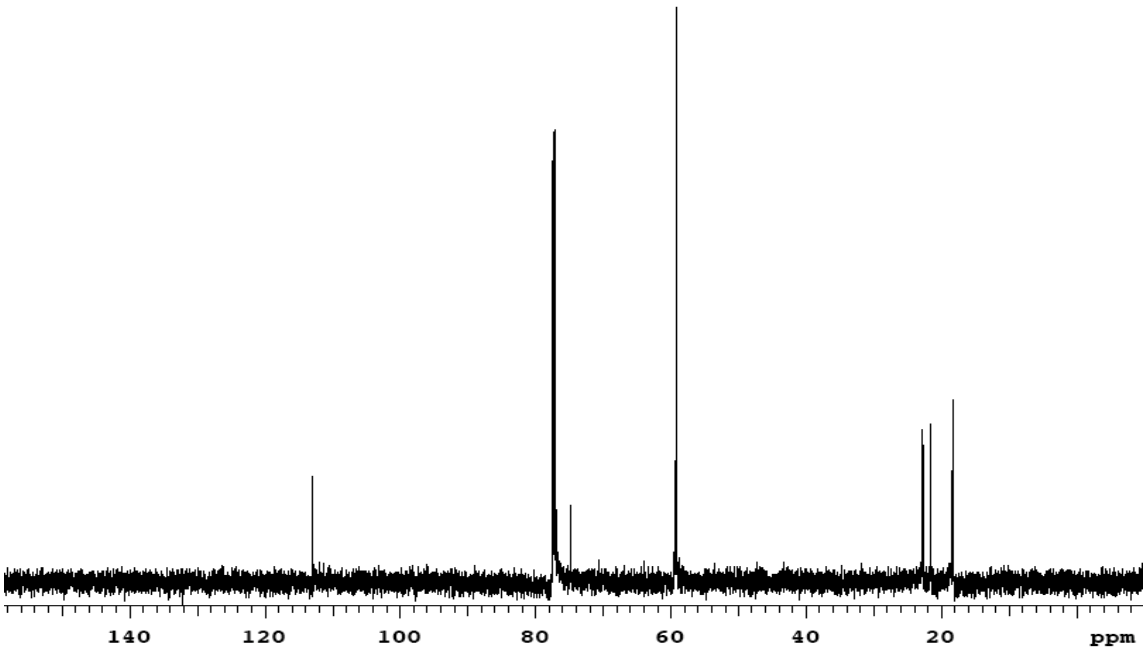
14.83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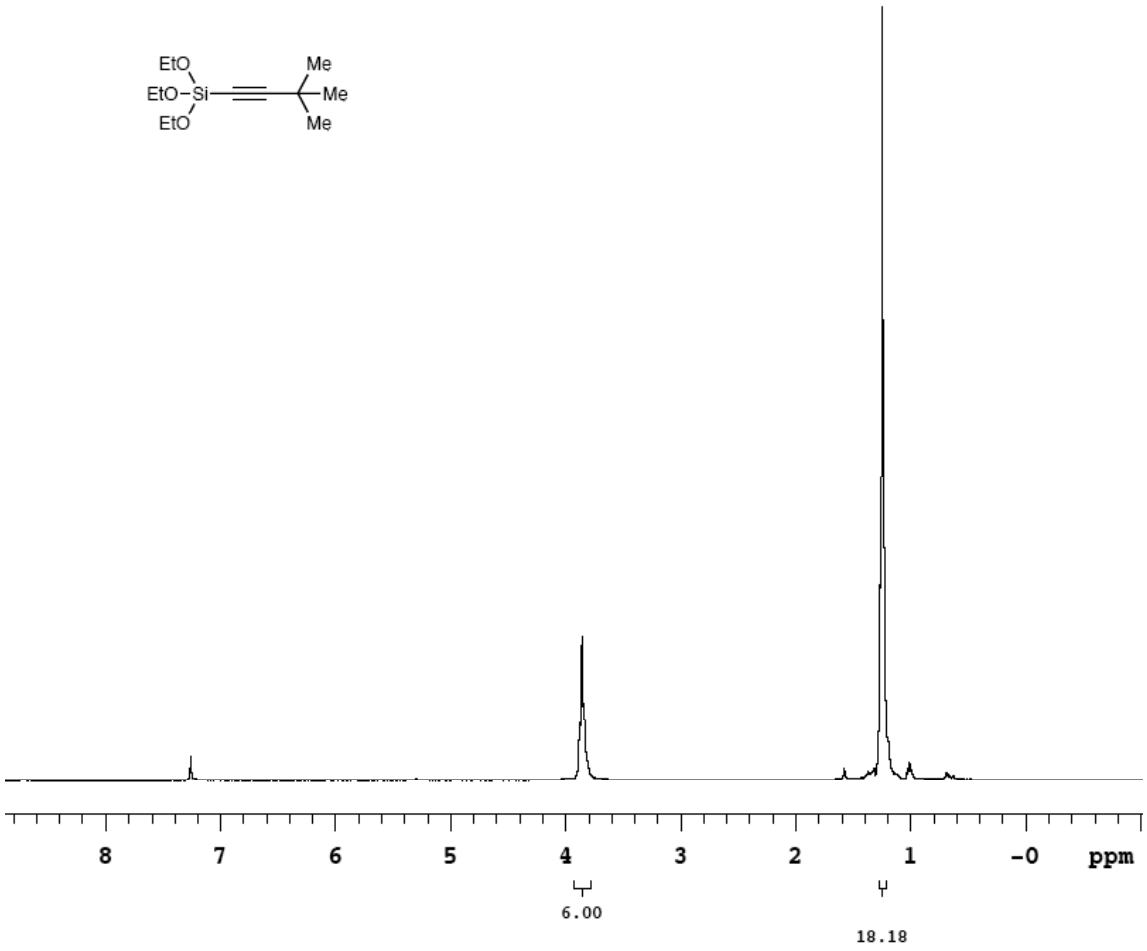
80
60
40
20
ppm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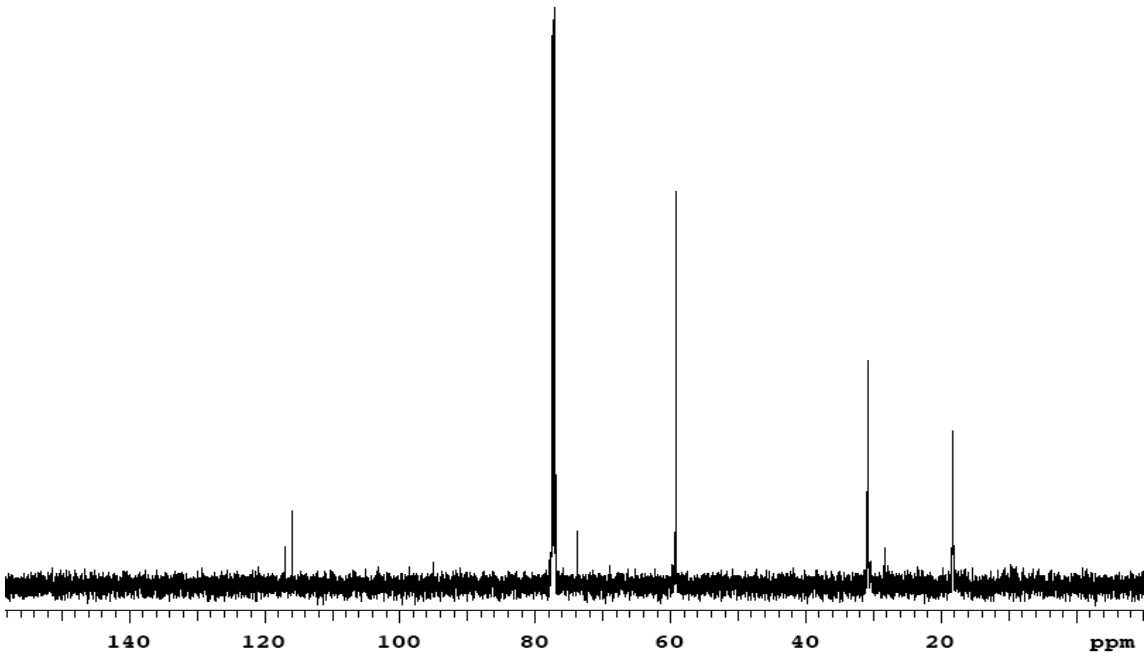
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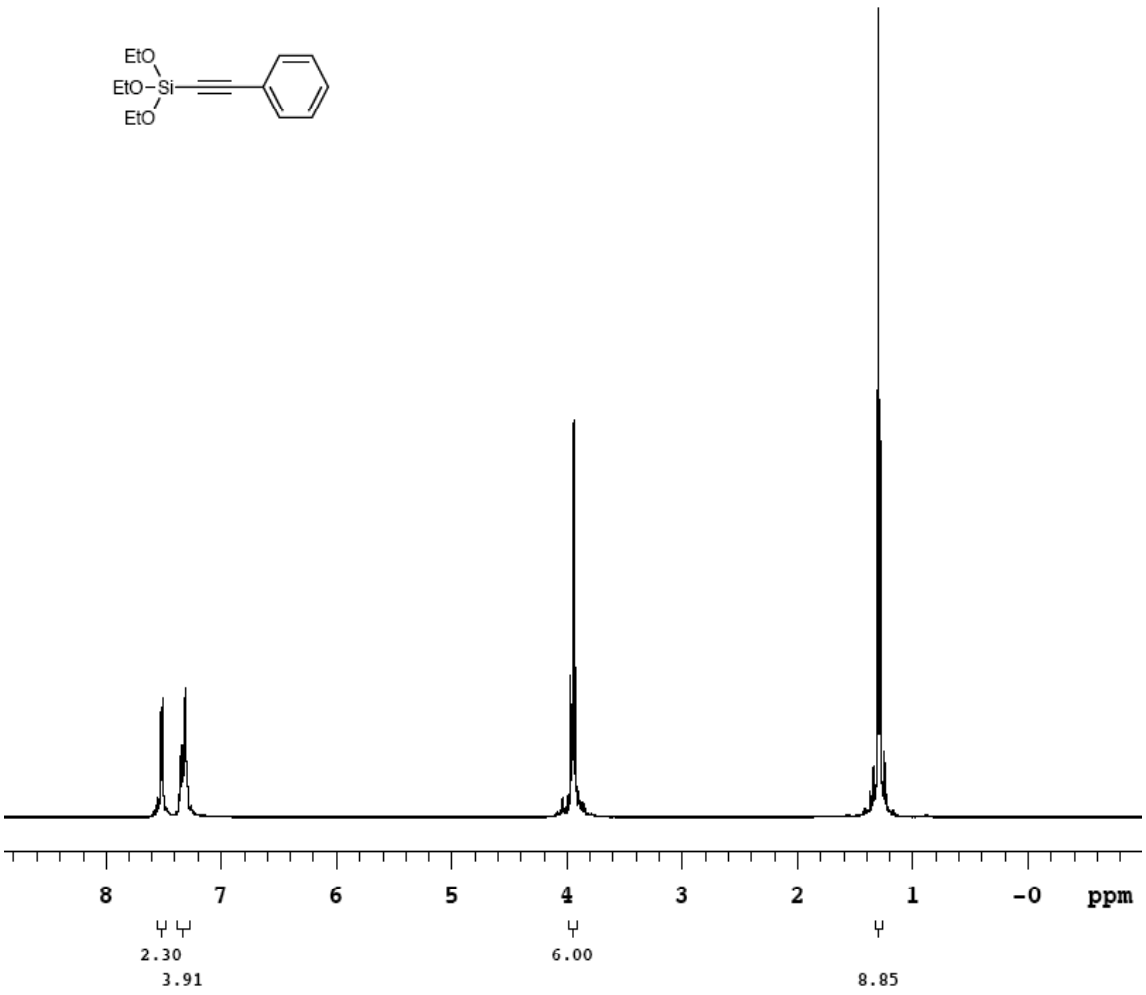
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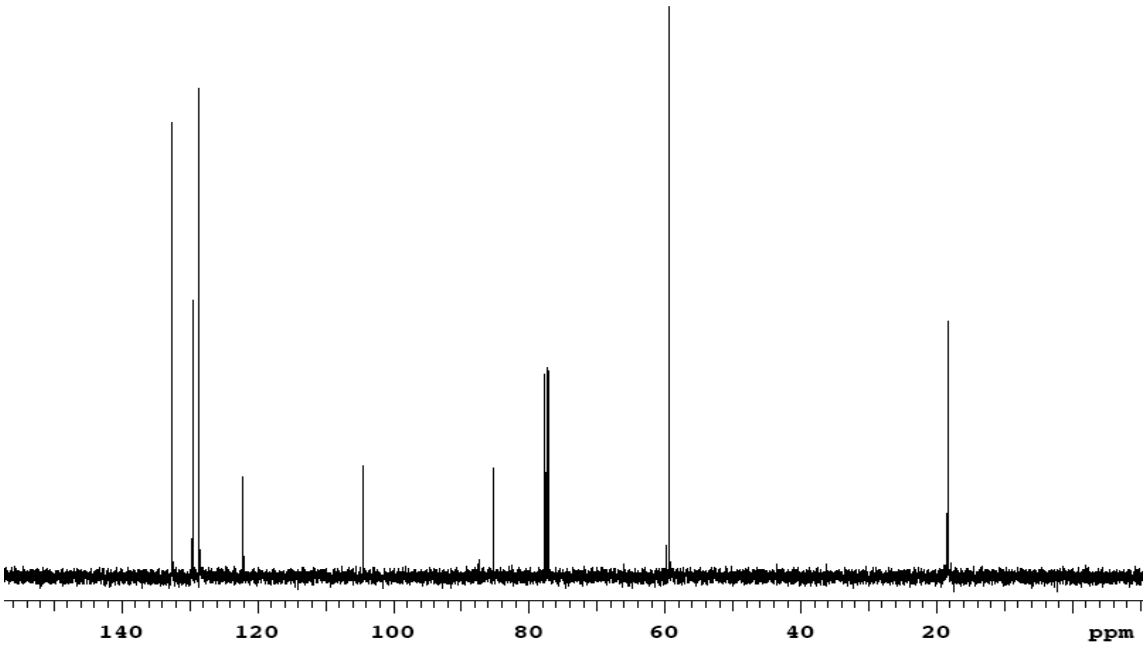
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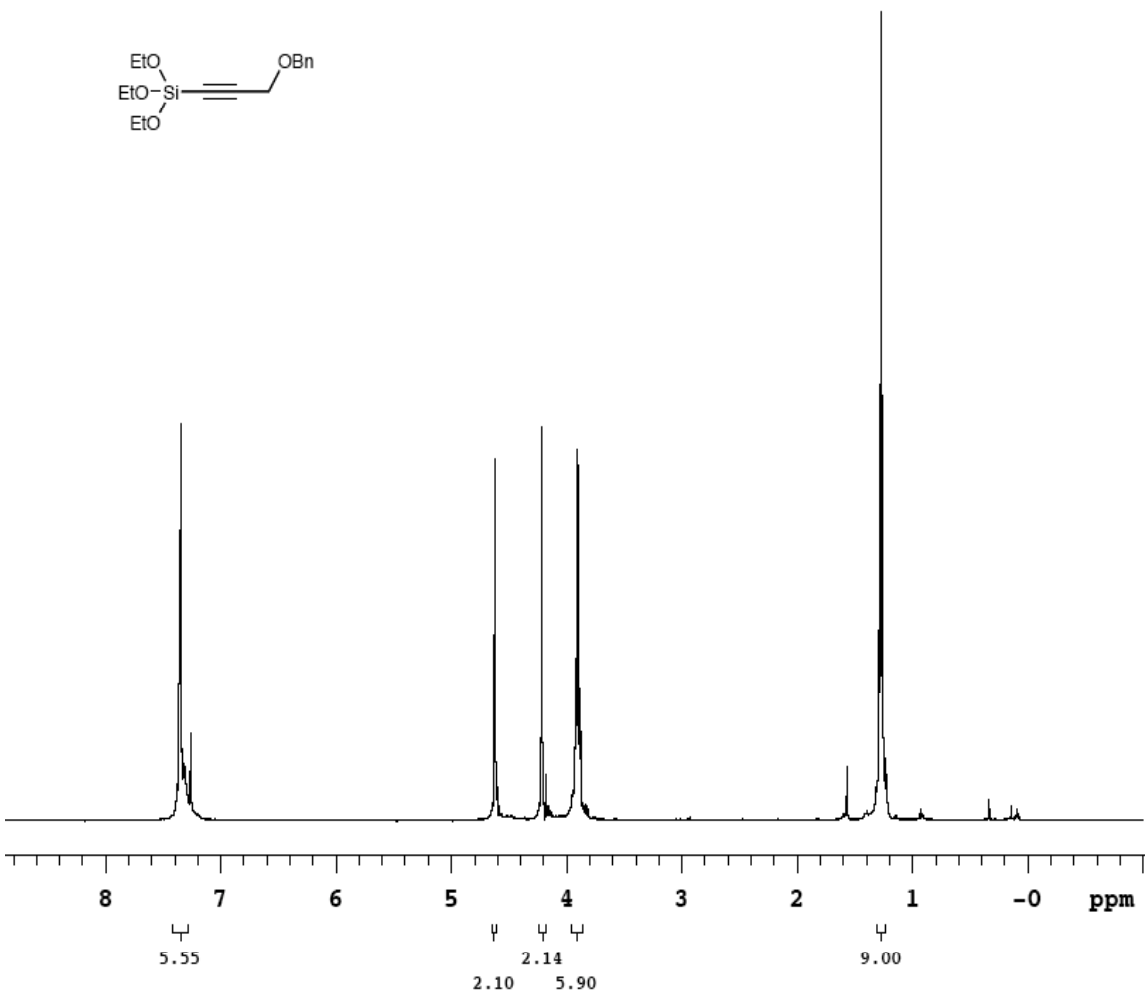
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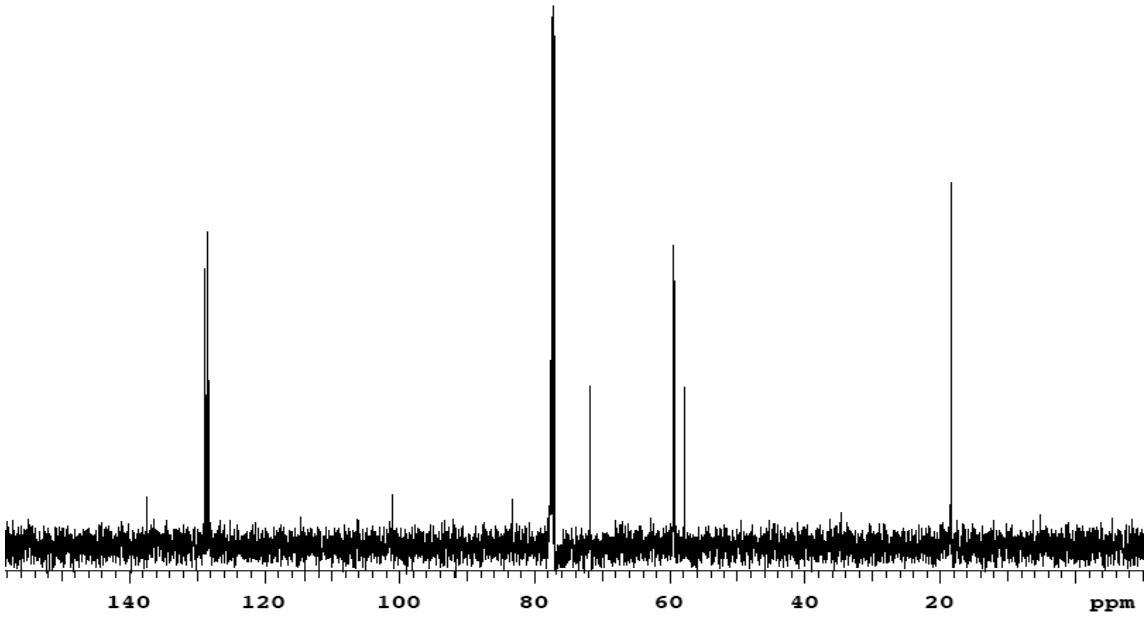
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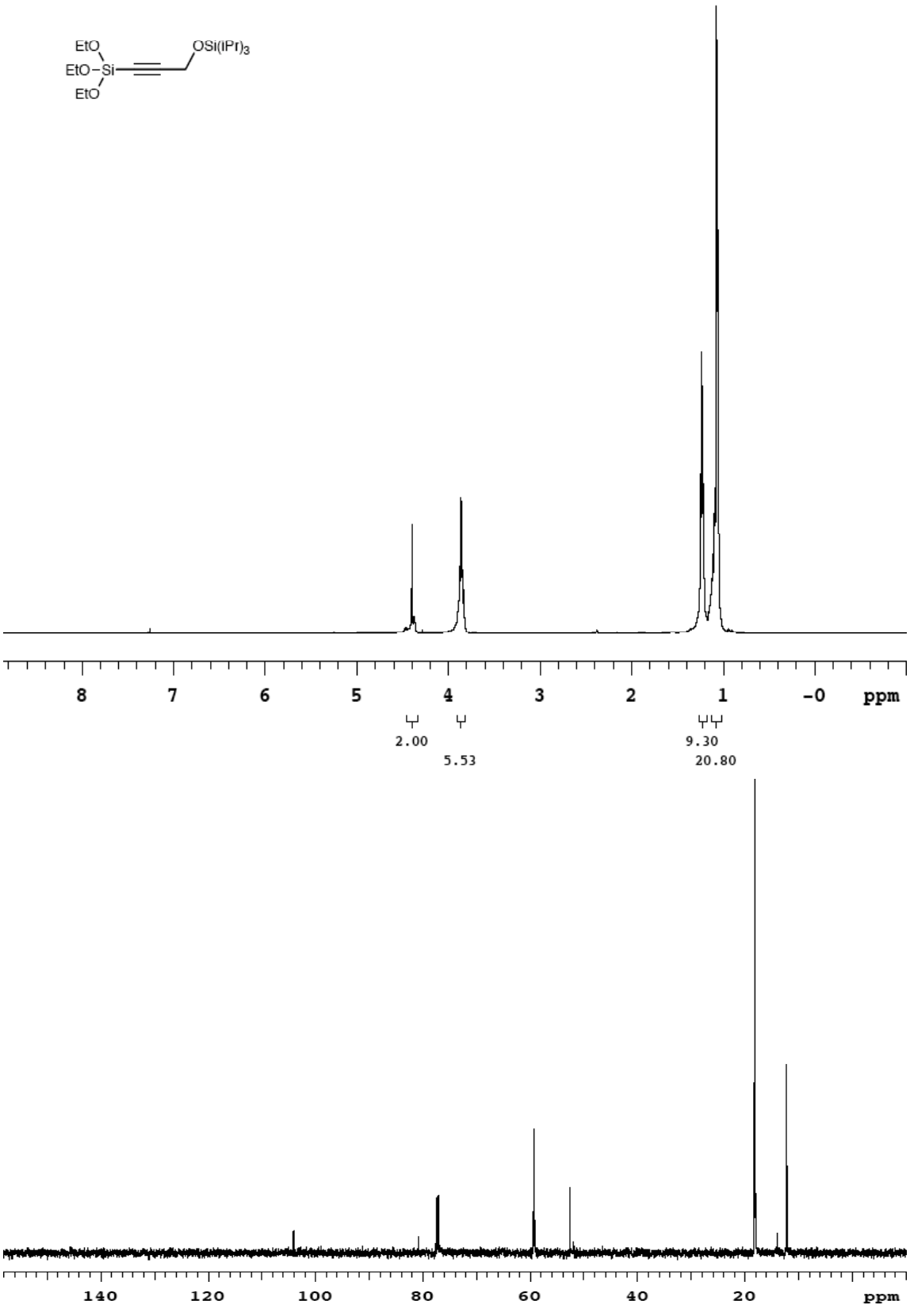
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EtO–Si
EtO
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6
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4
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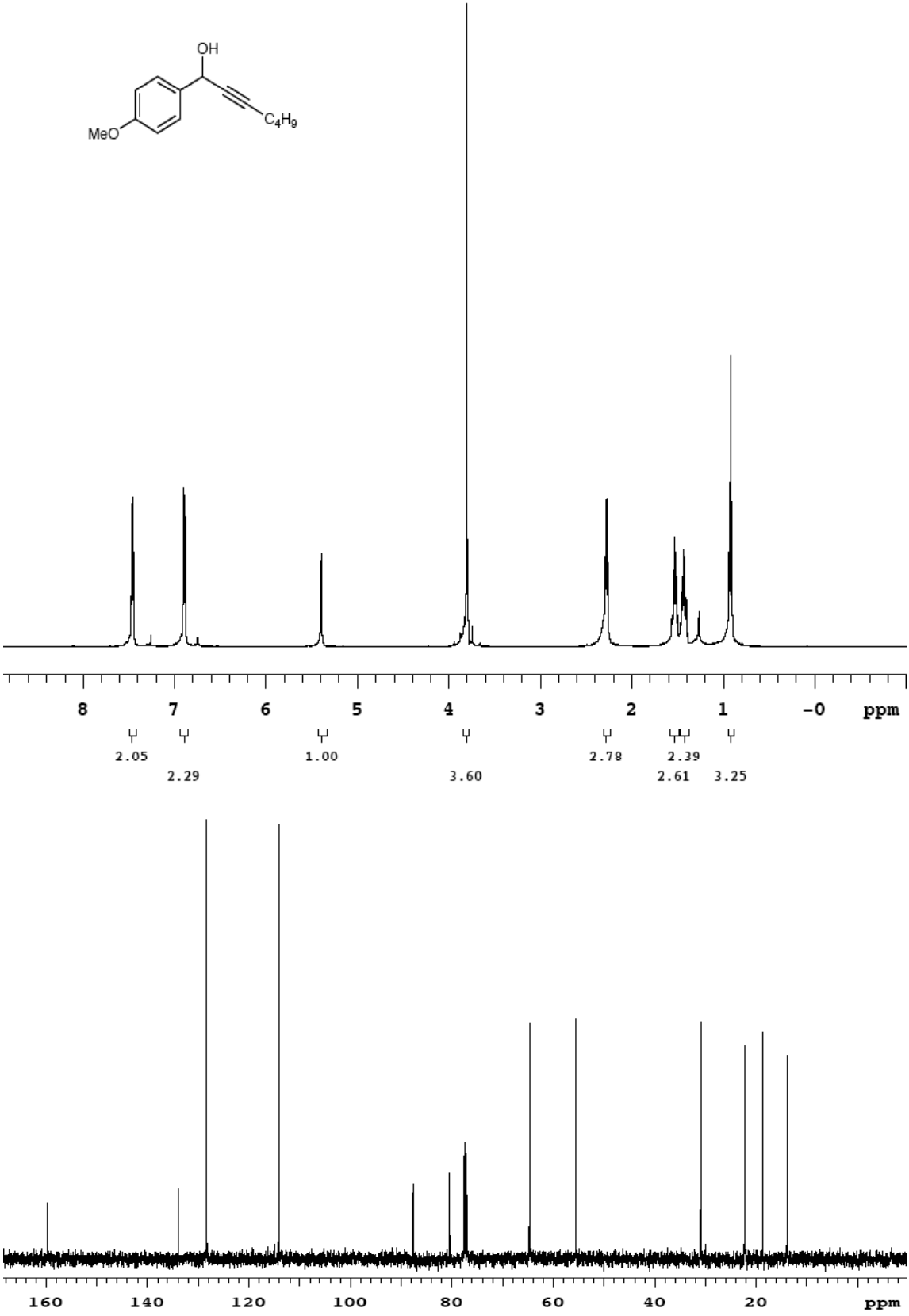
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6
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4
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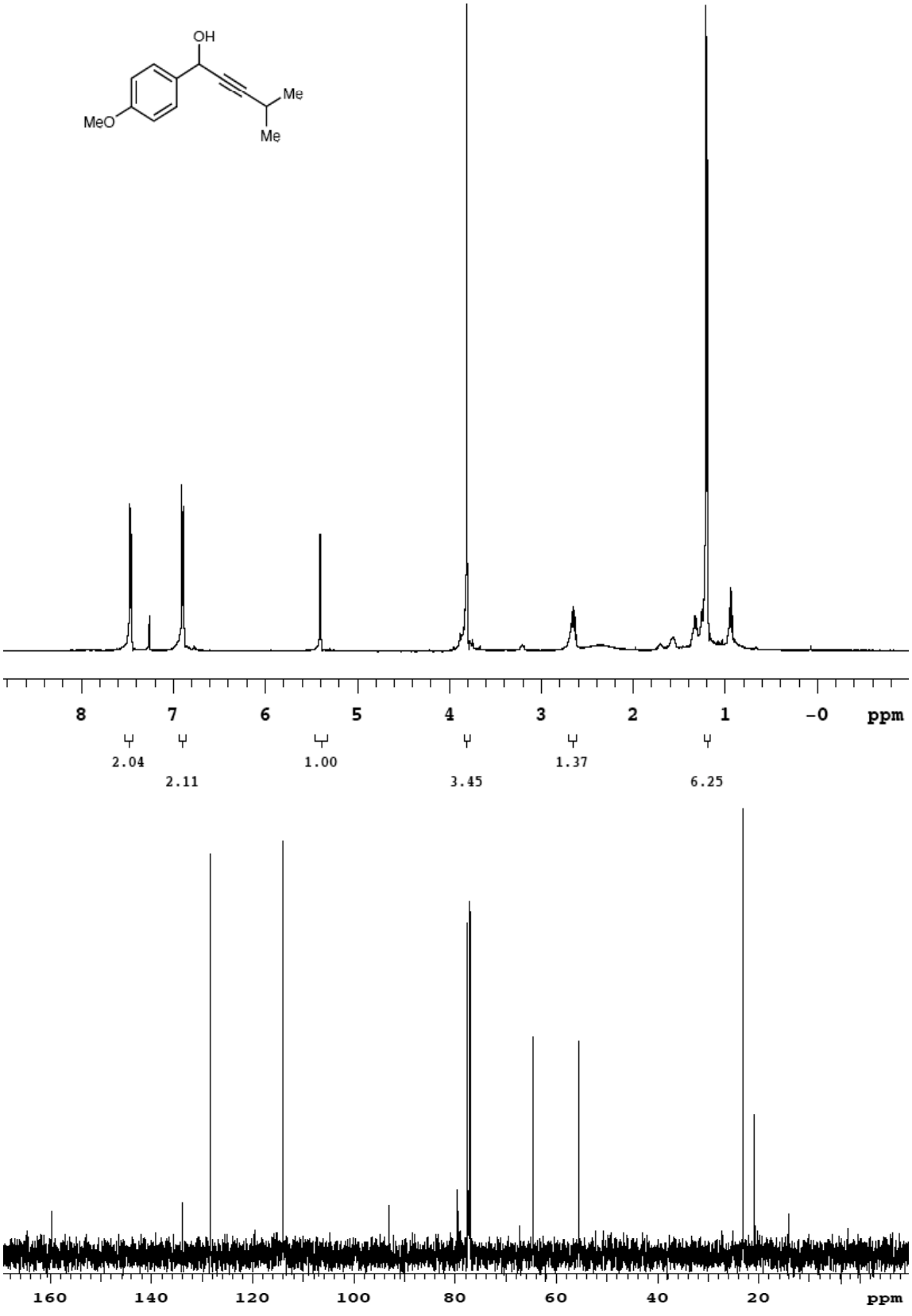
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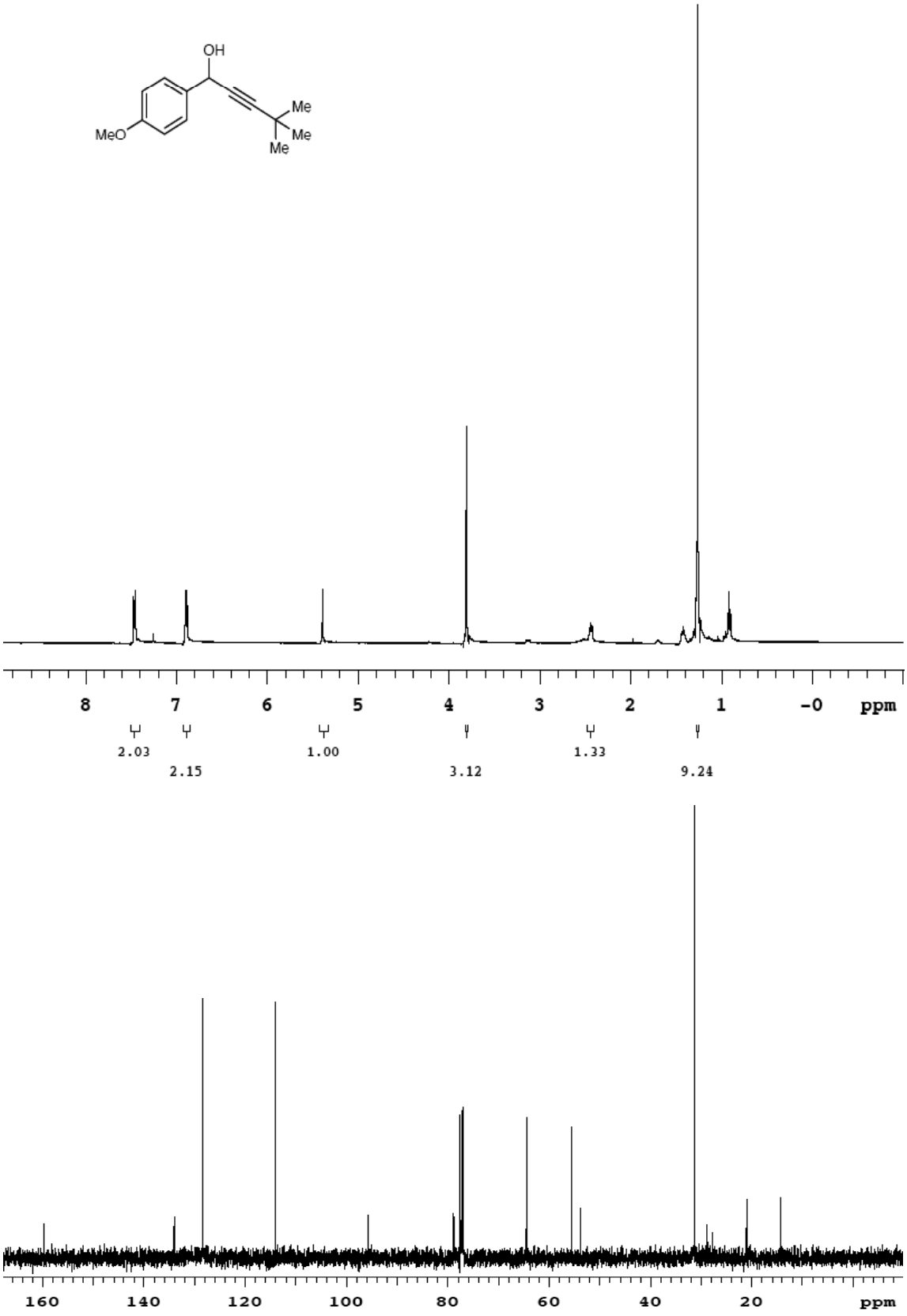
ppm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1.33
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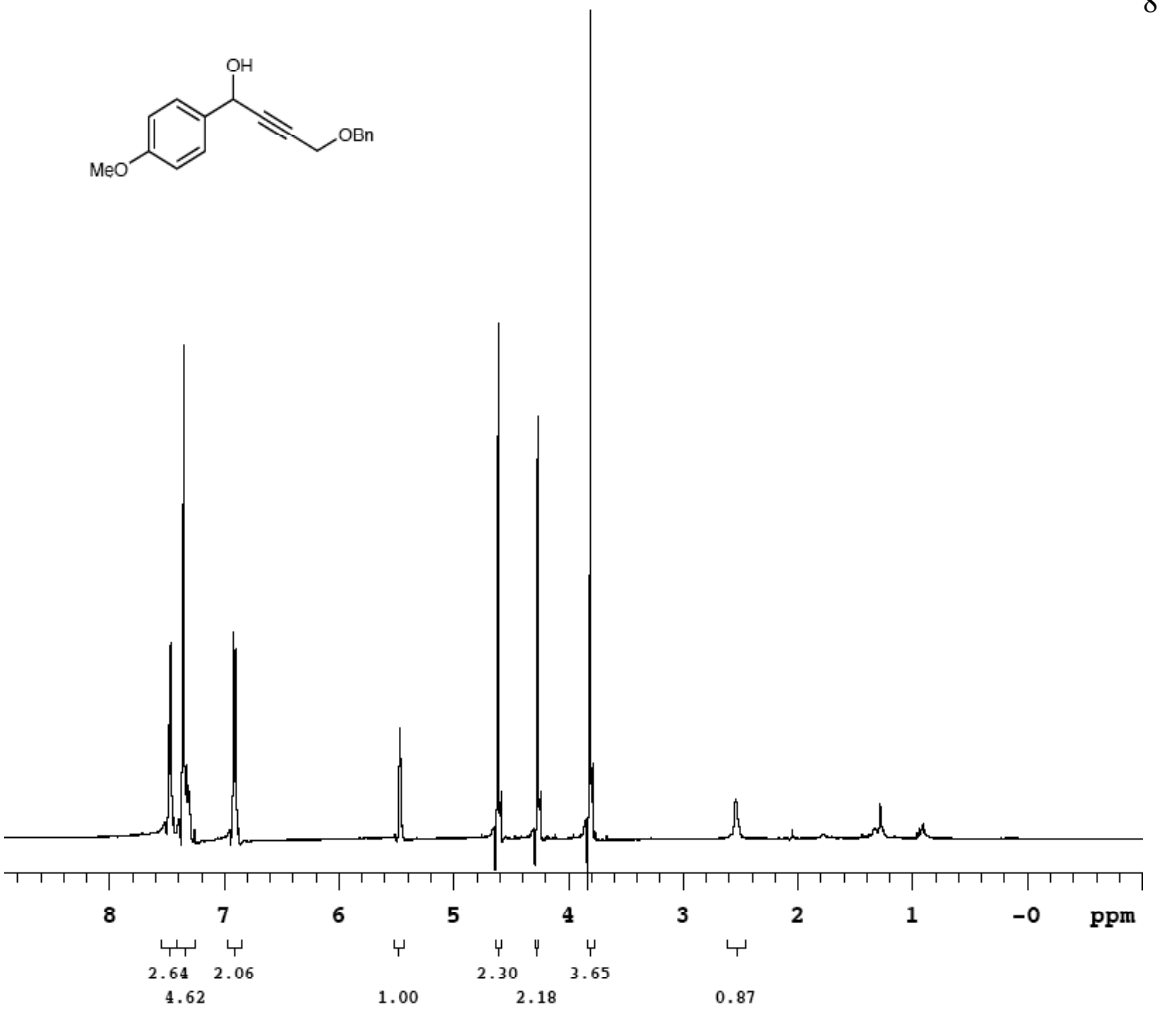
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MeO
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ppm
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1.00
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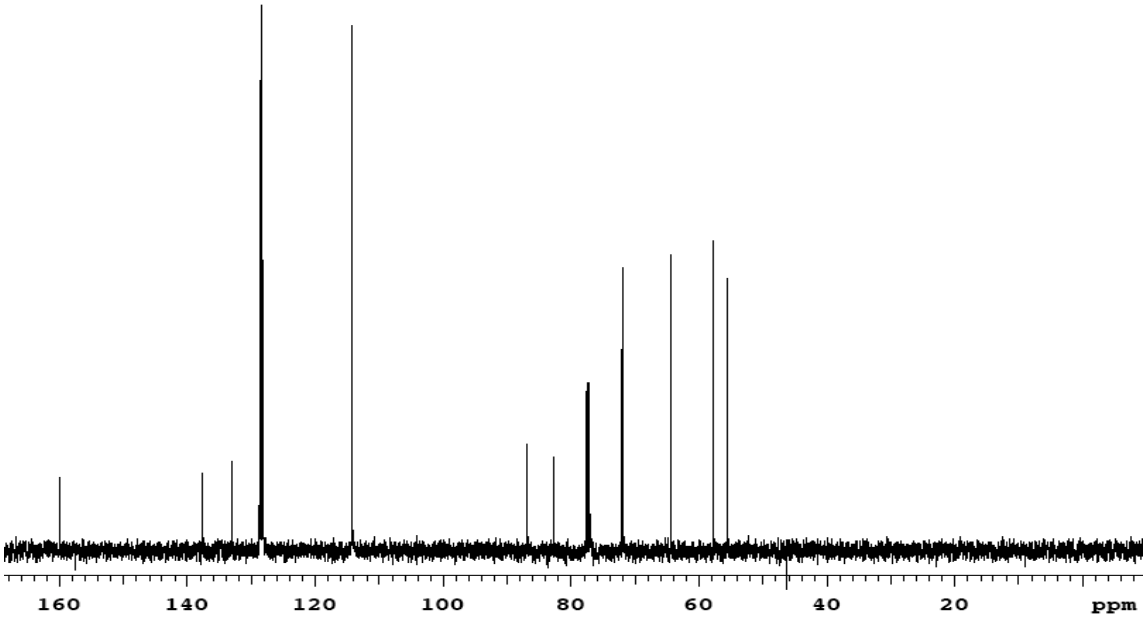
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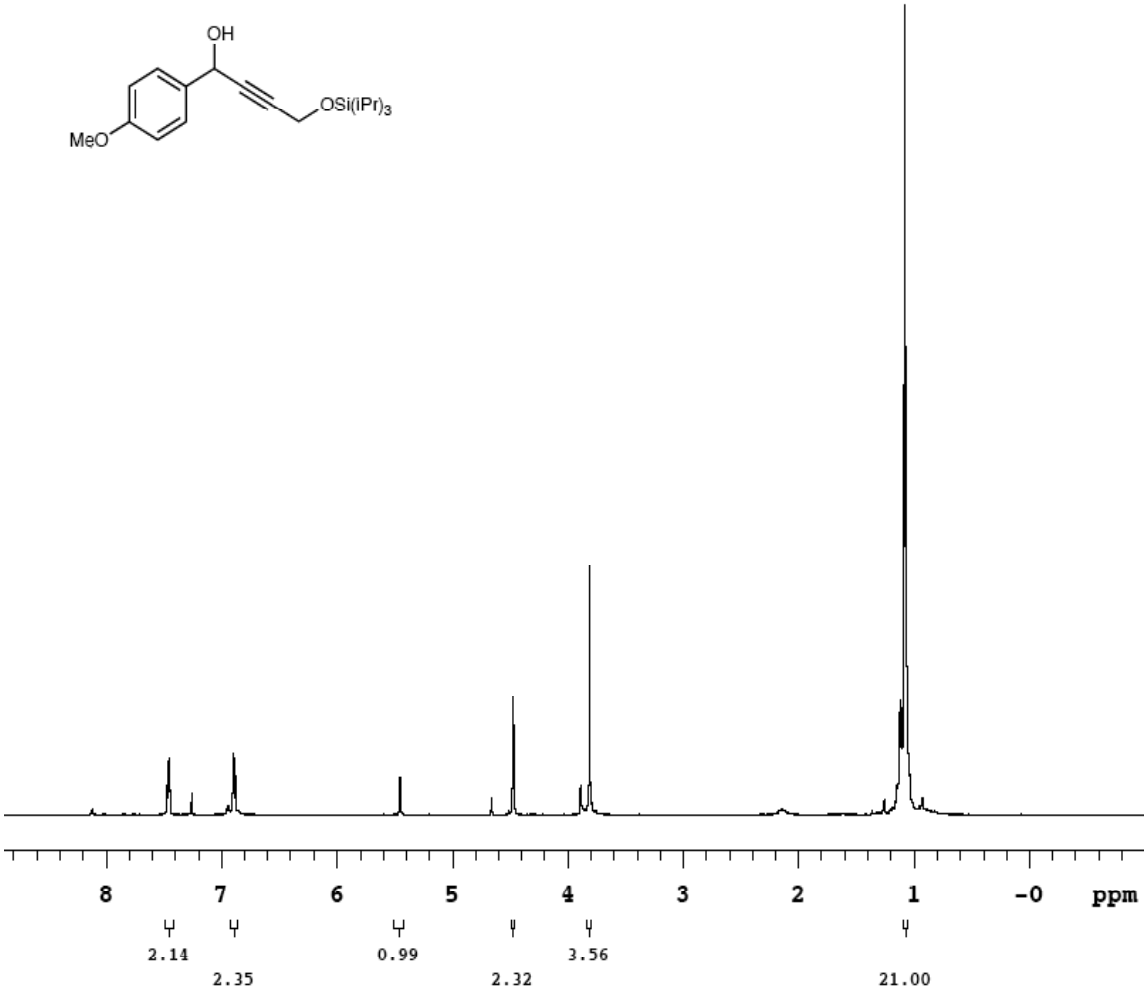
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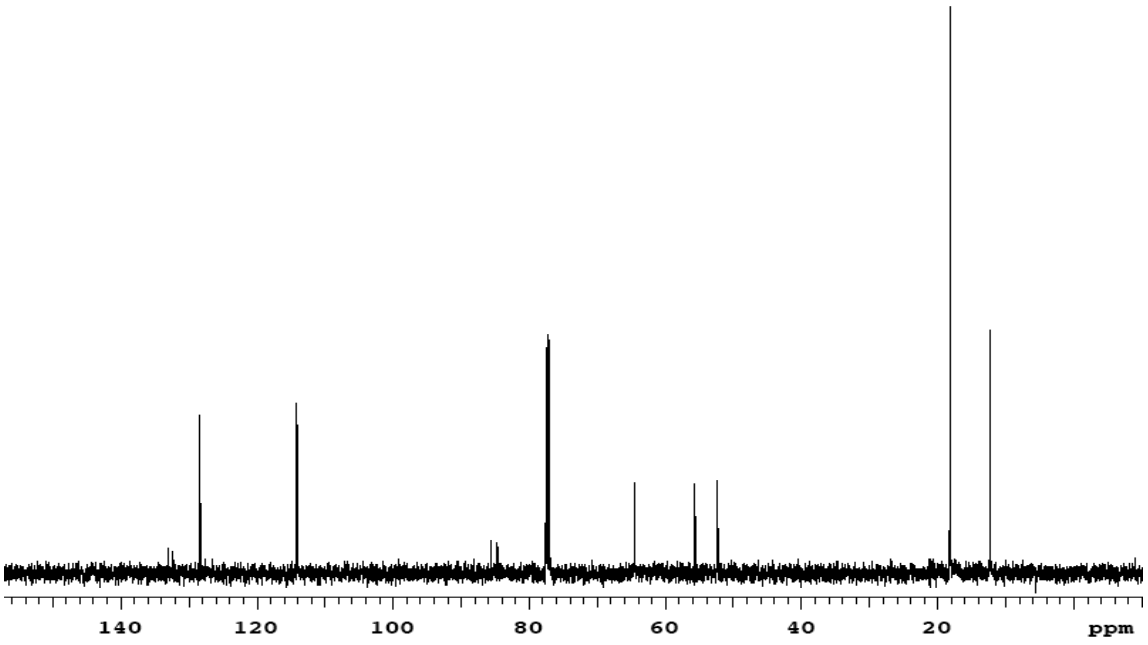
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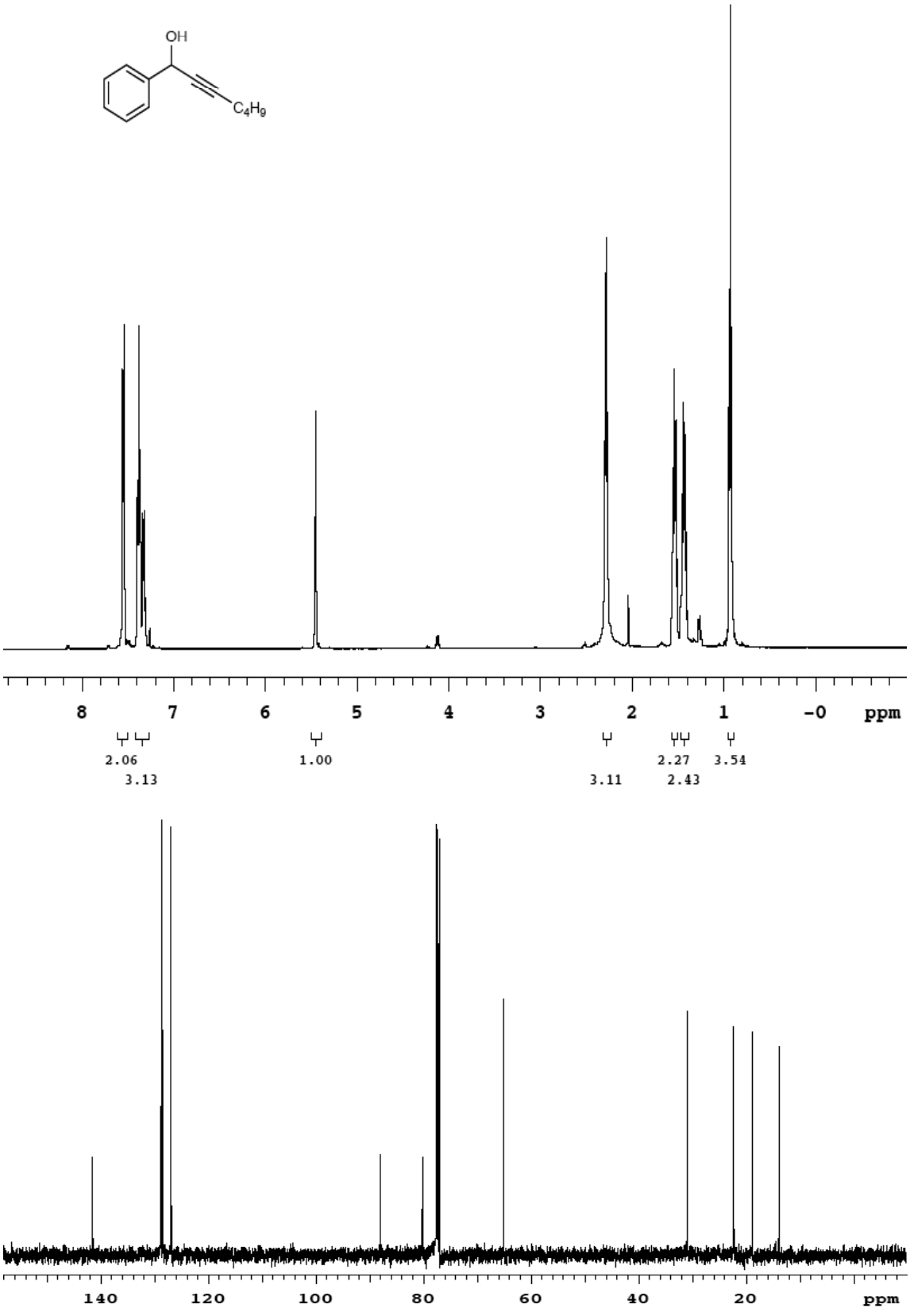
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7
6
5
4
3
2
1
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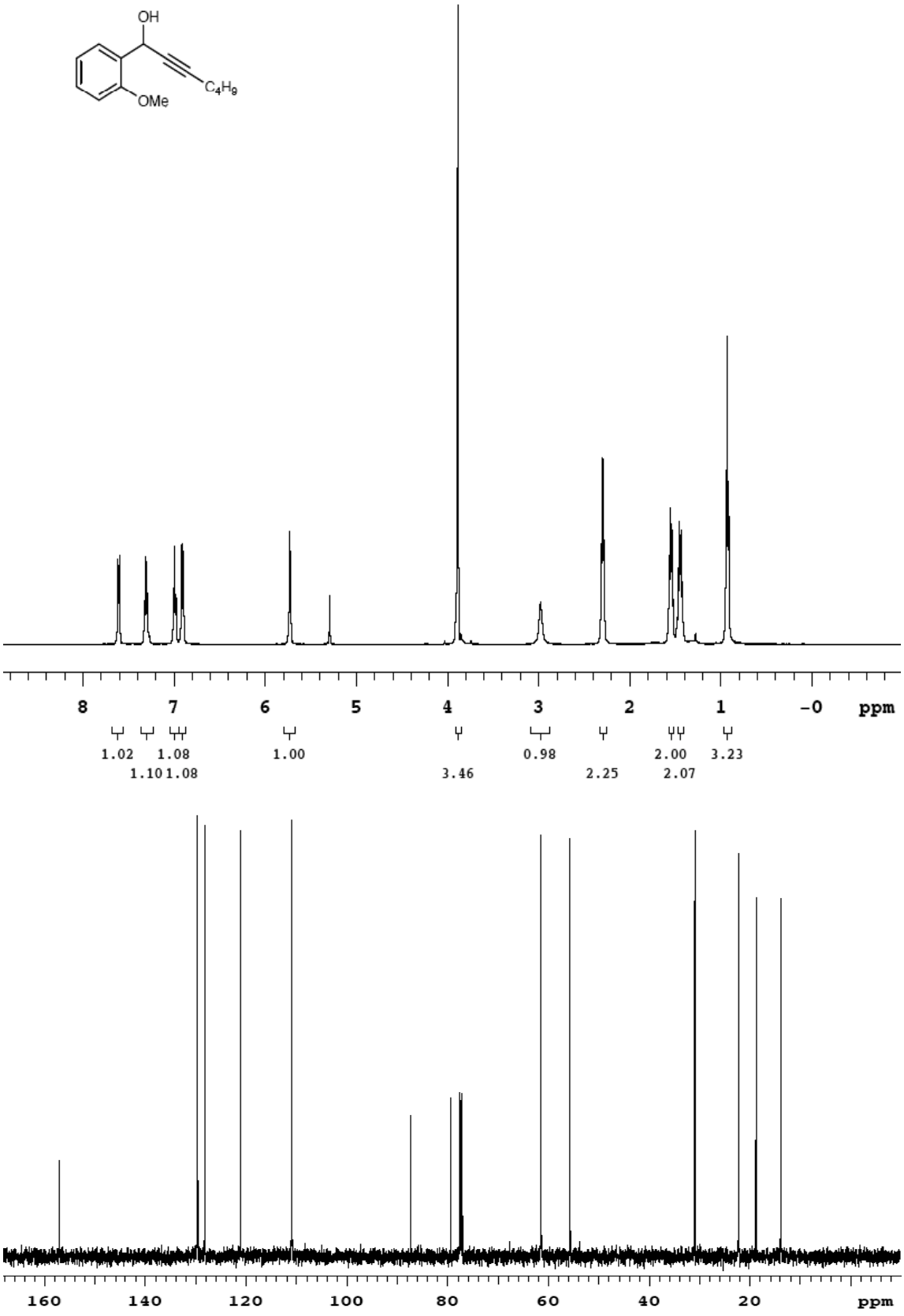
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7
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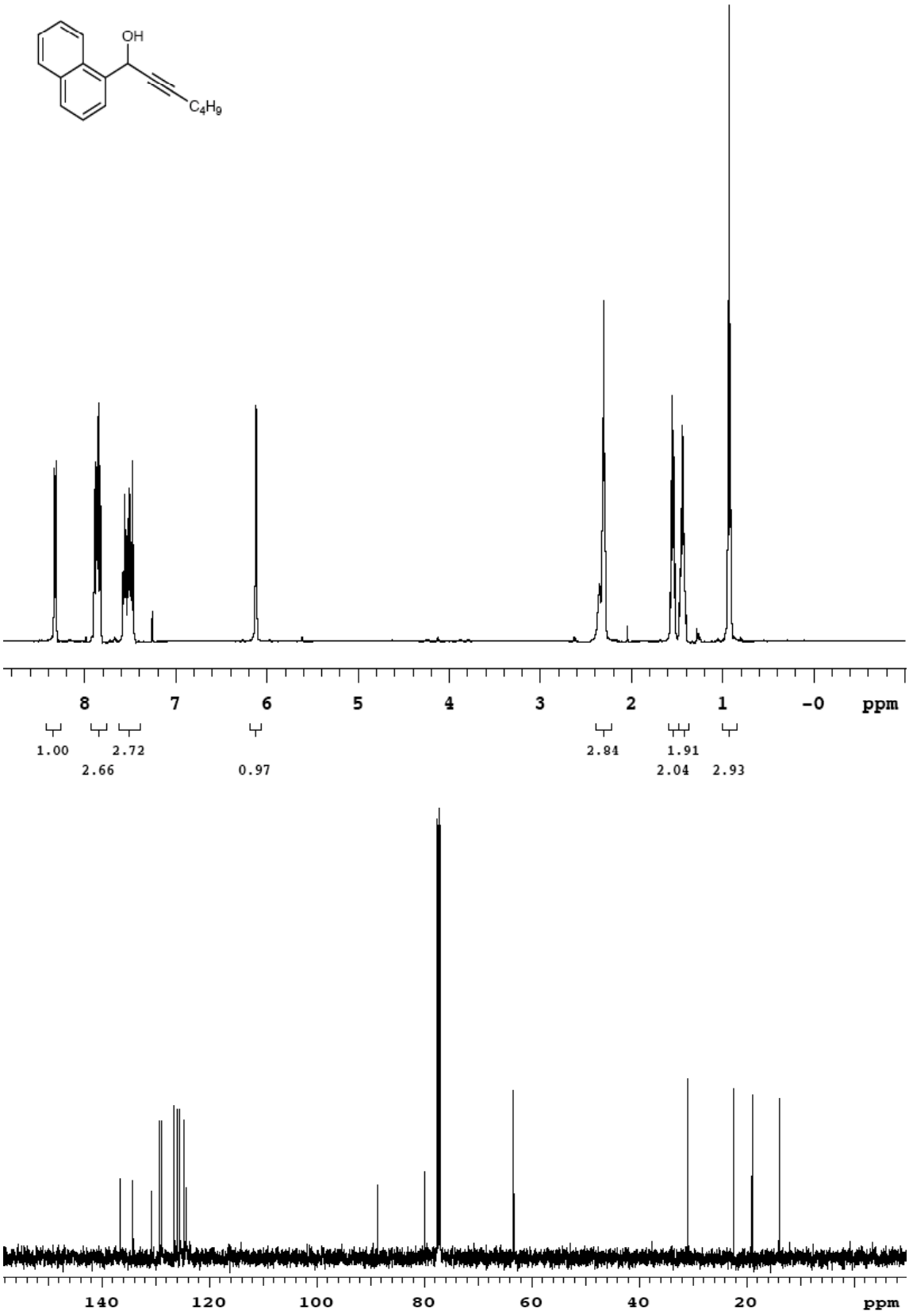
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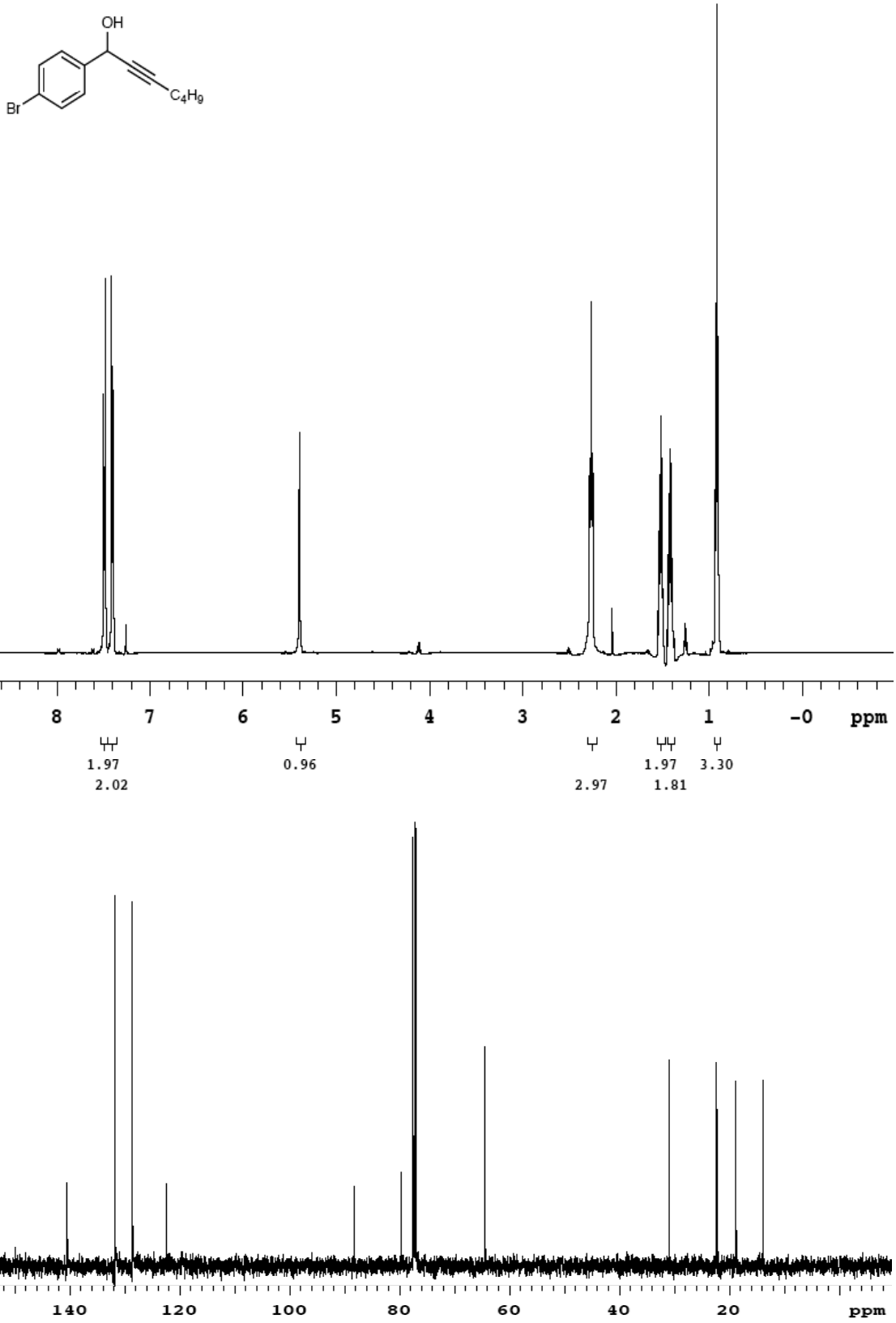
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C_4H_9
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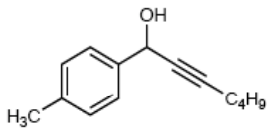
ppm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C4H9

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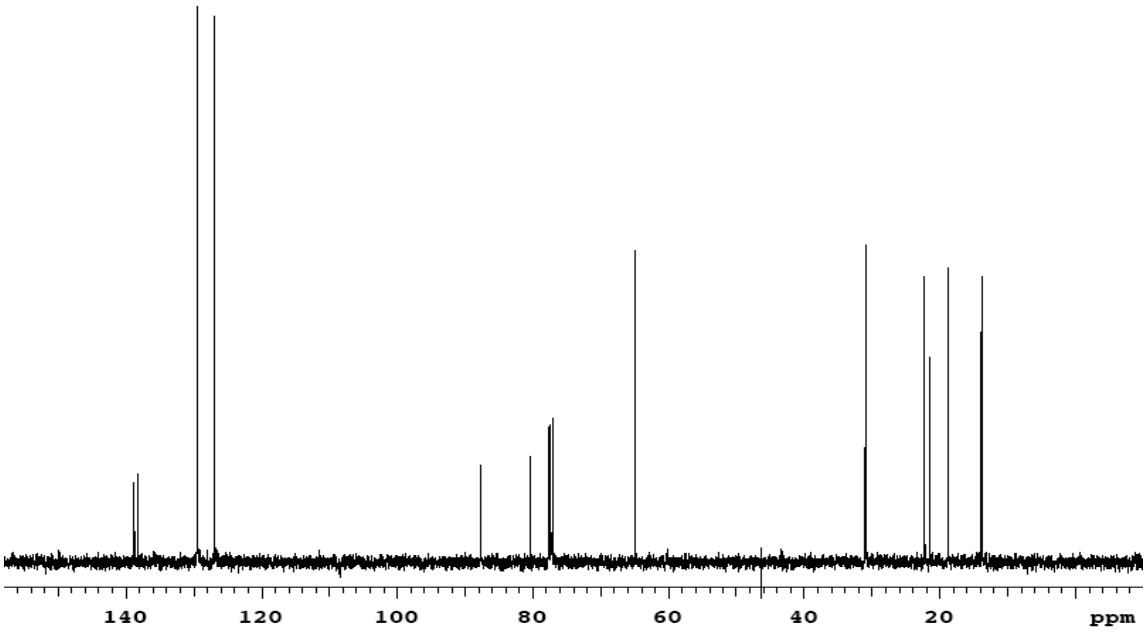
3.23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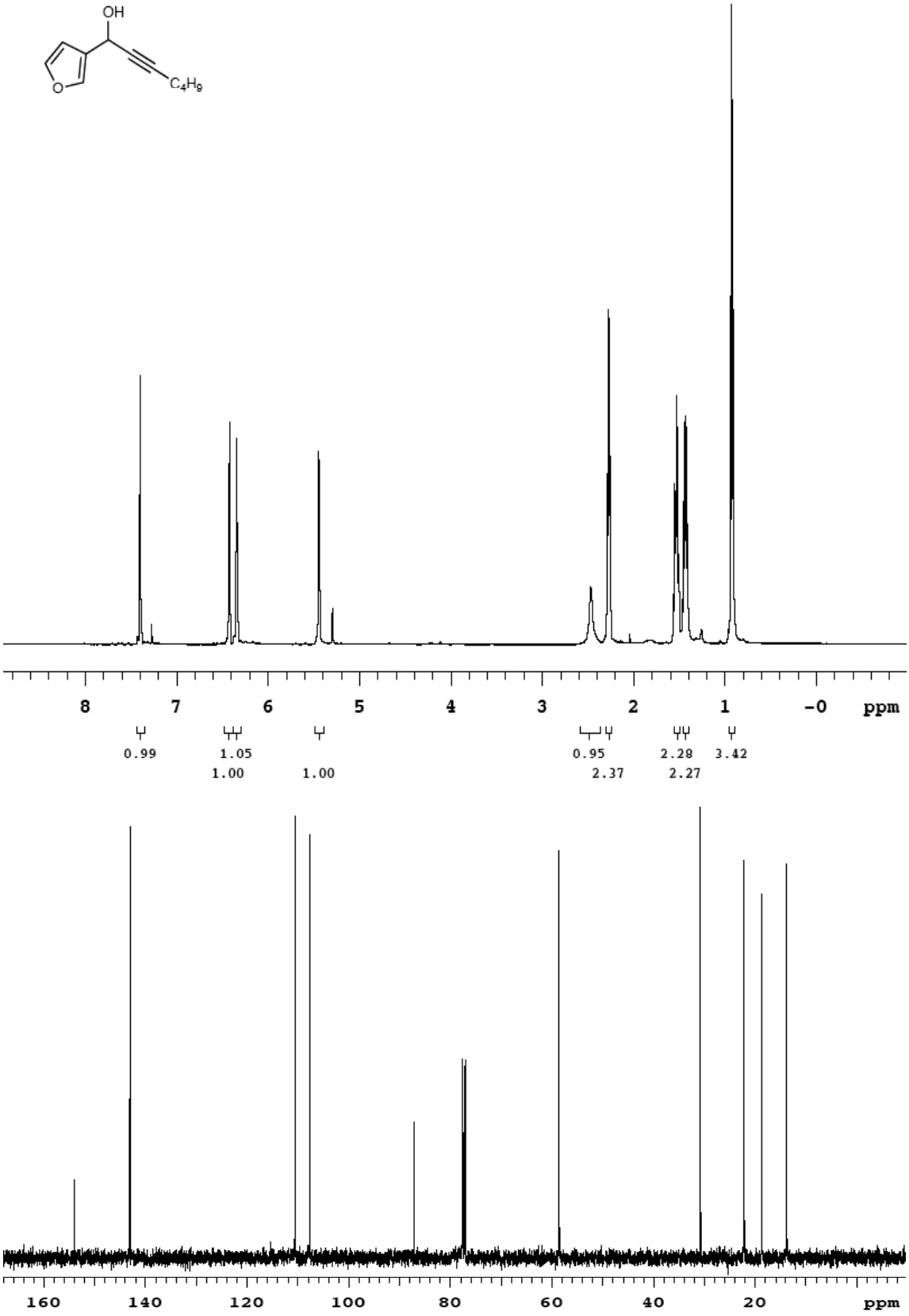
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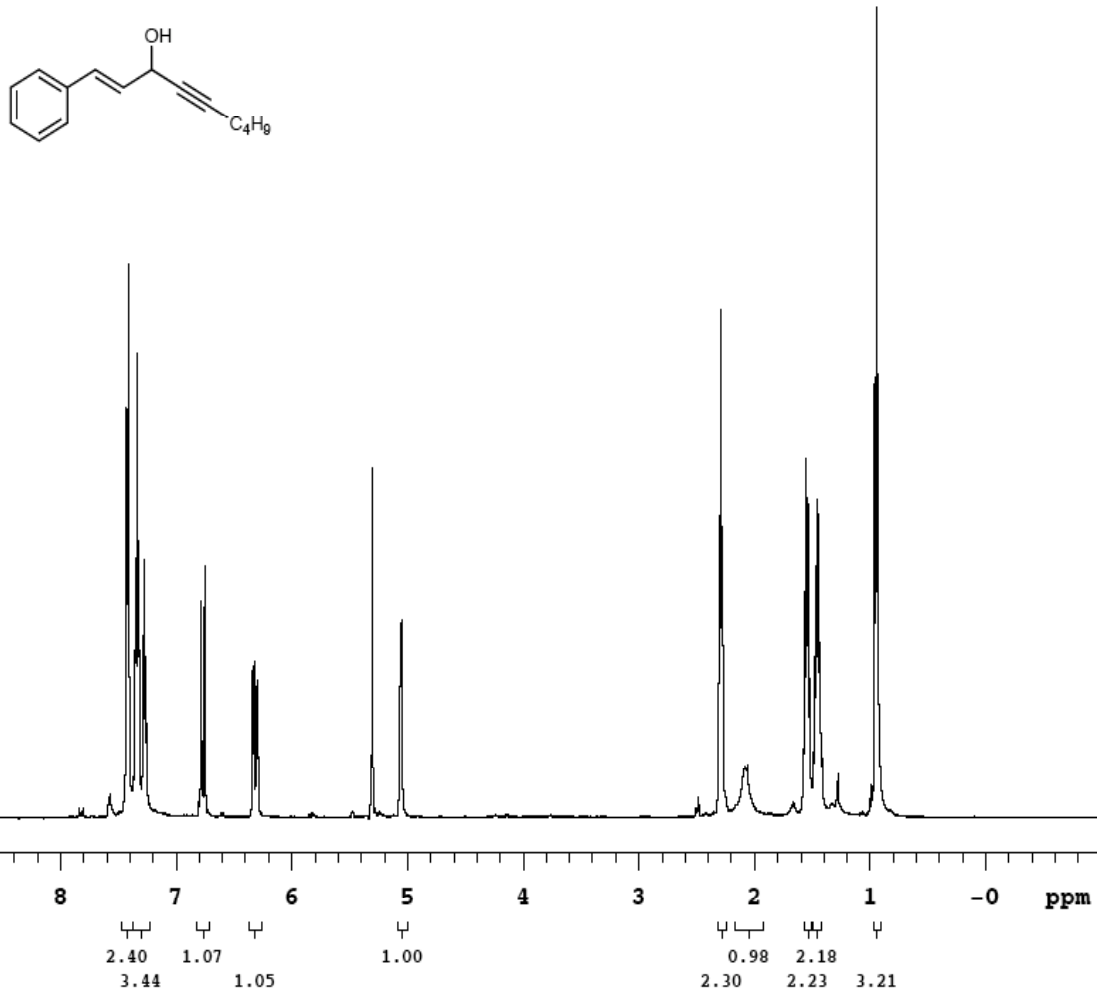
ppm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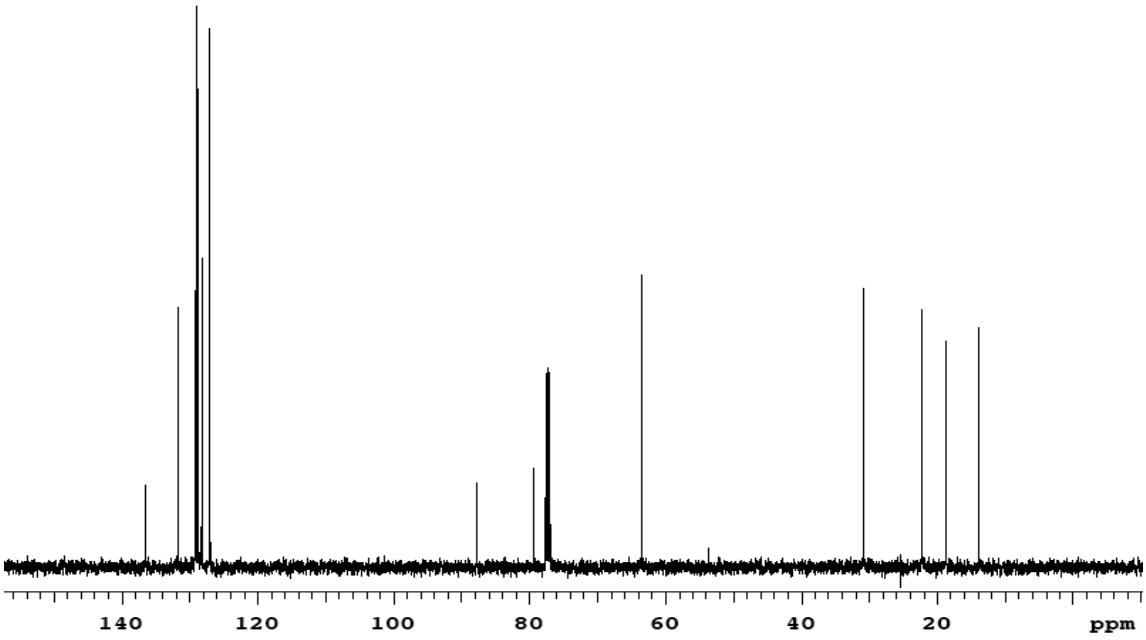
3.21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60
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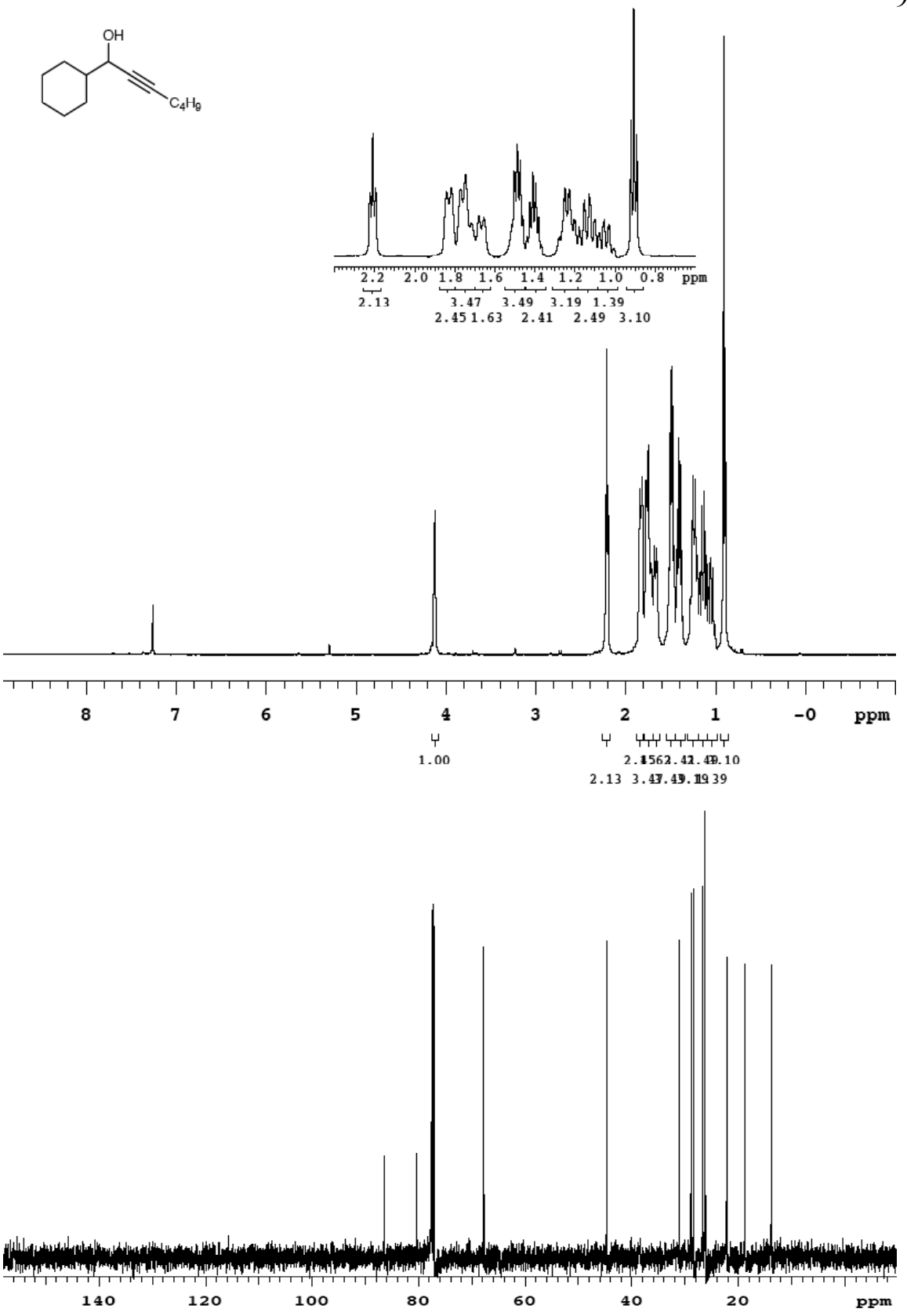
20
ppm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C_4H_9
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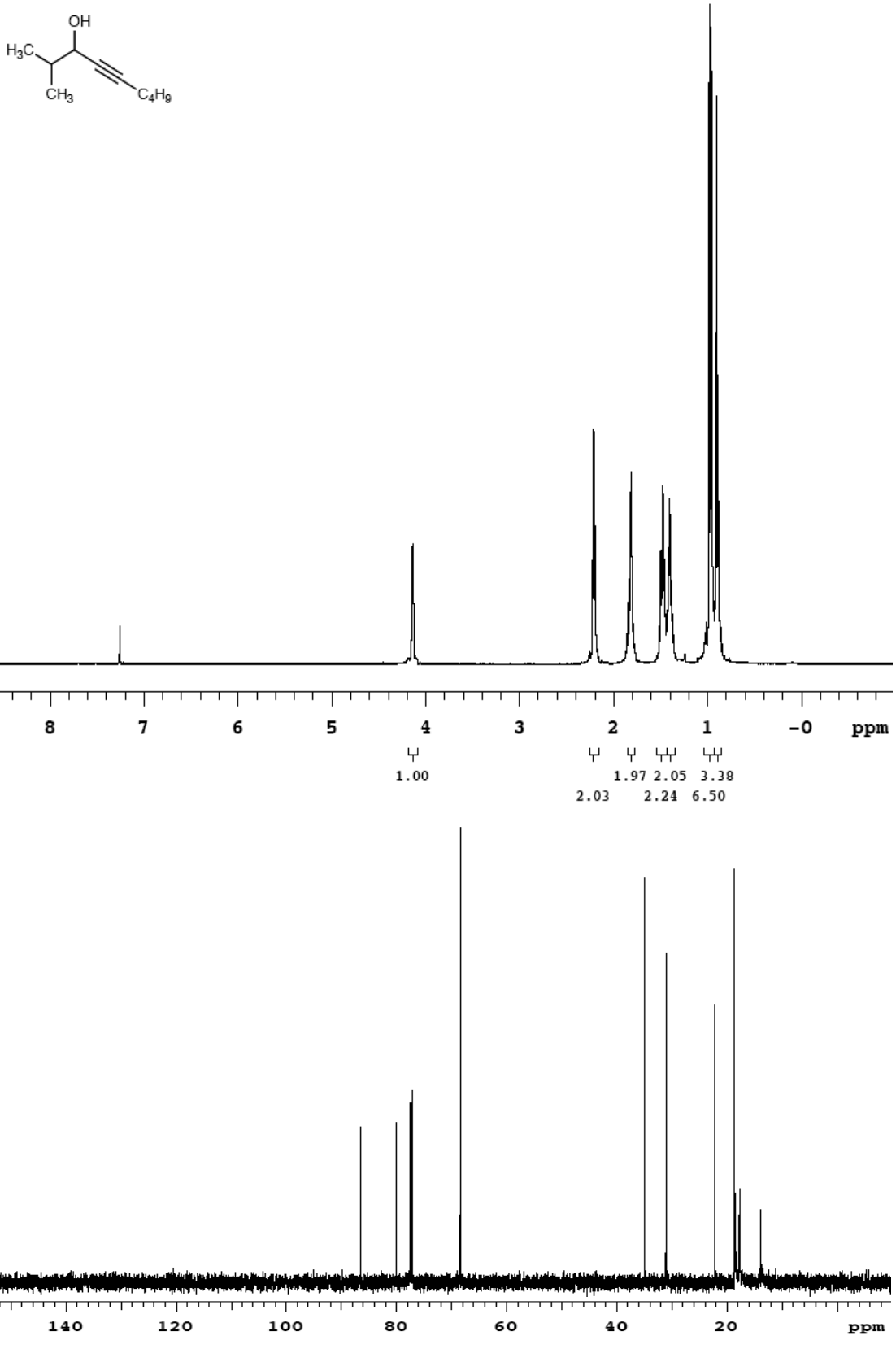
2.13 3.47 3.49 3.19 1.39
2.45 1.63 2.41 2.49 3.10
8 7 6 5 4 3 2 1 -0 ppm
1.00
2.13
140 120 100 80 60 40 20 ppm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C4H9
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7
6
5
4
3
2
1
-0
ppm
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2.24
2.05
6.50
3.38
140
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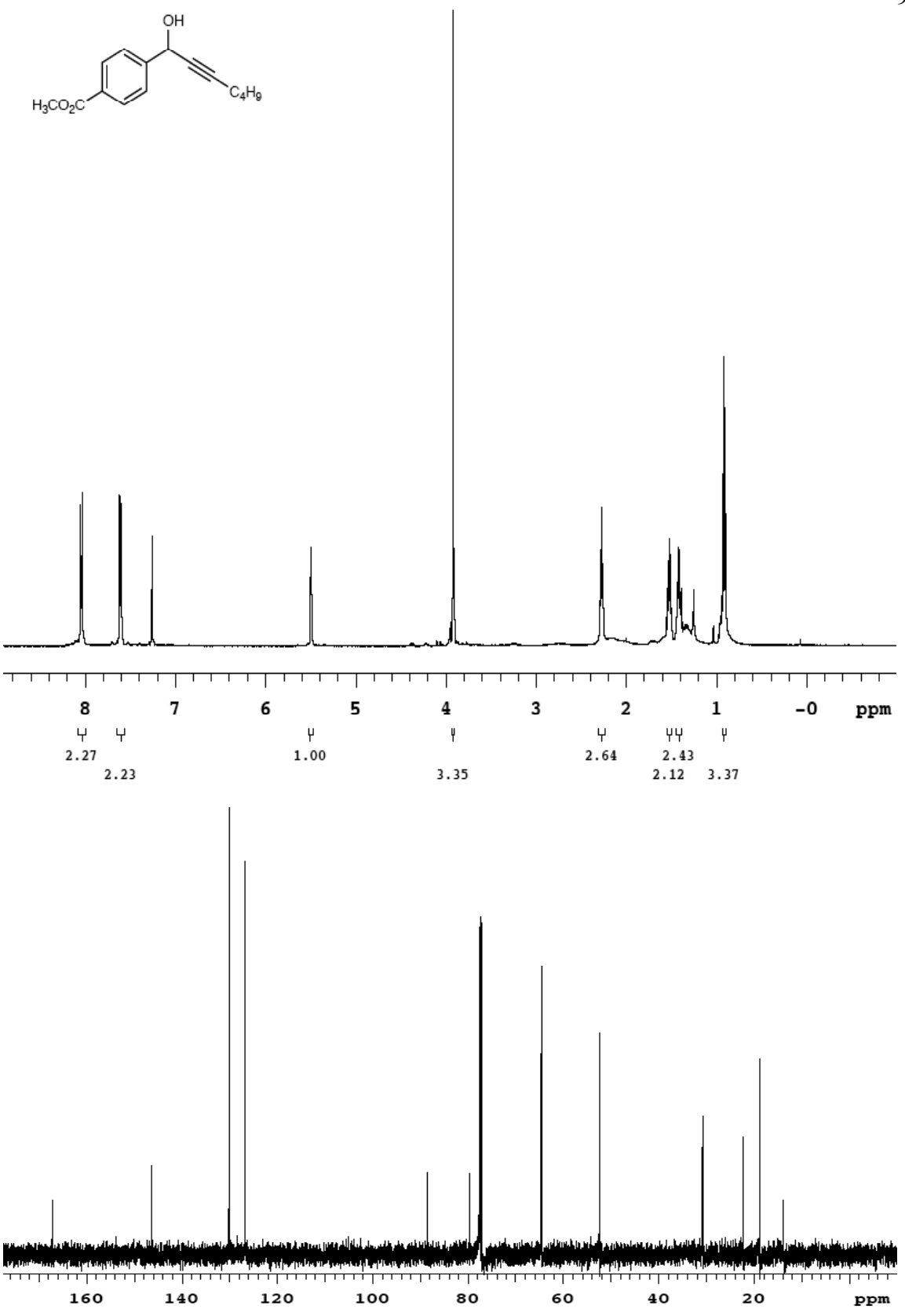
80
60
40
20
ppm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C4H9
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6
5
4
3
2
1
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ppm
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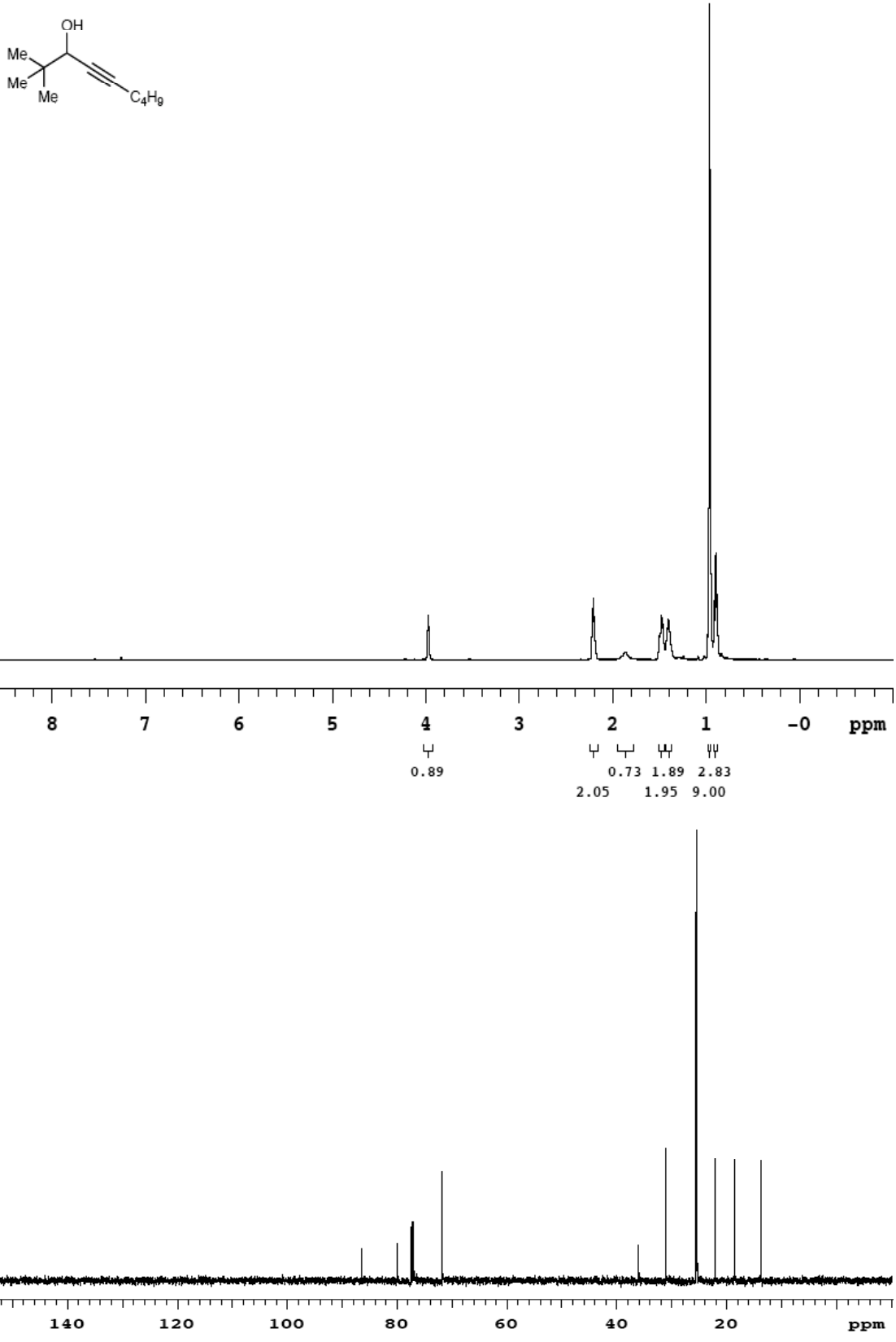
80
60
40
20
ppm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Me
Me
C4H9
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5
4
3
2
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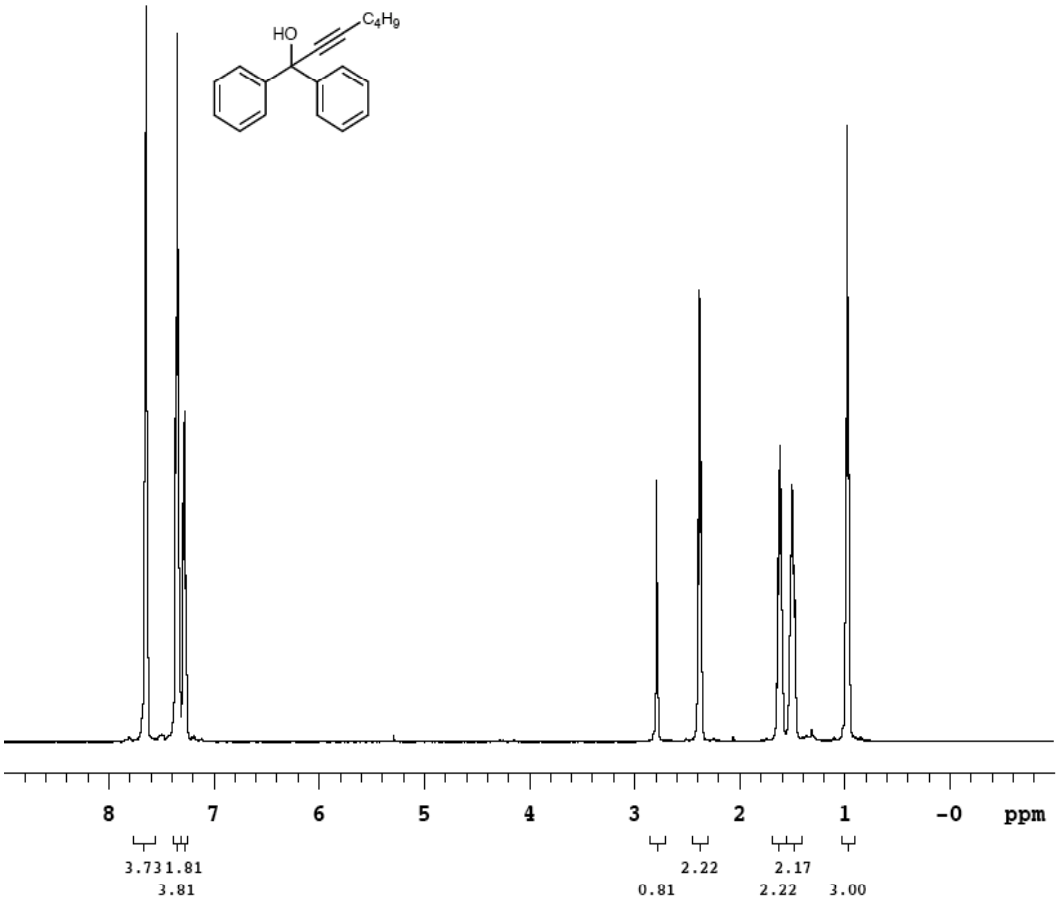
60
40
20
ppm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C4H9
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7
6
5
4
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-0
ppm
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0.81
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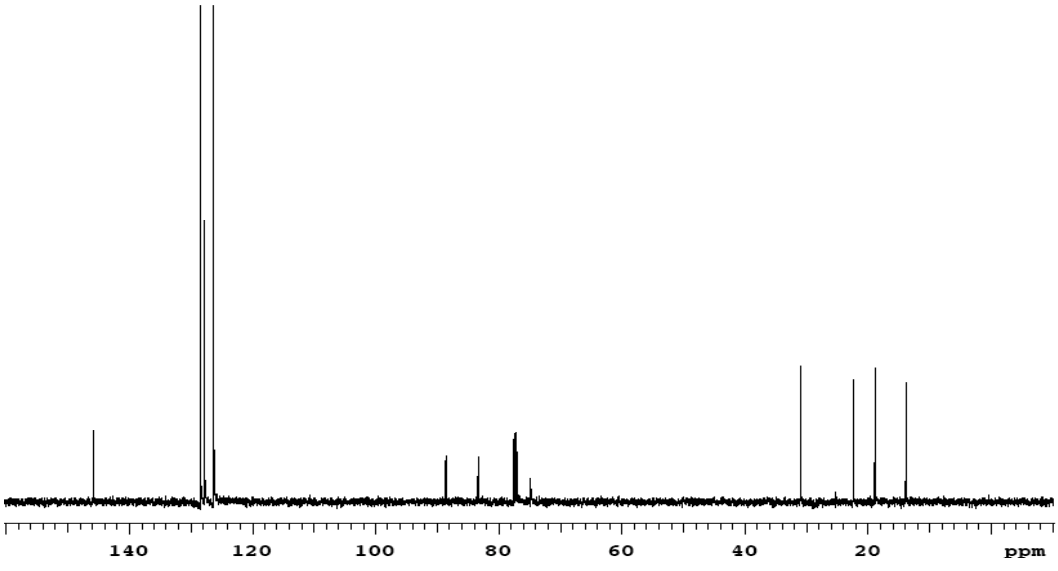
2.17
2.22
3.00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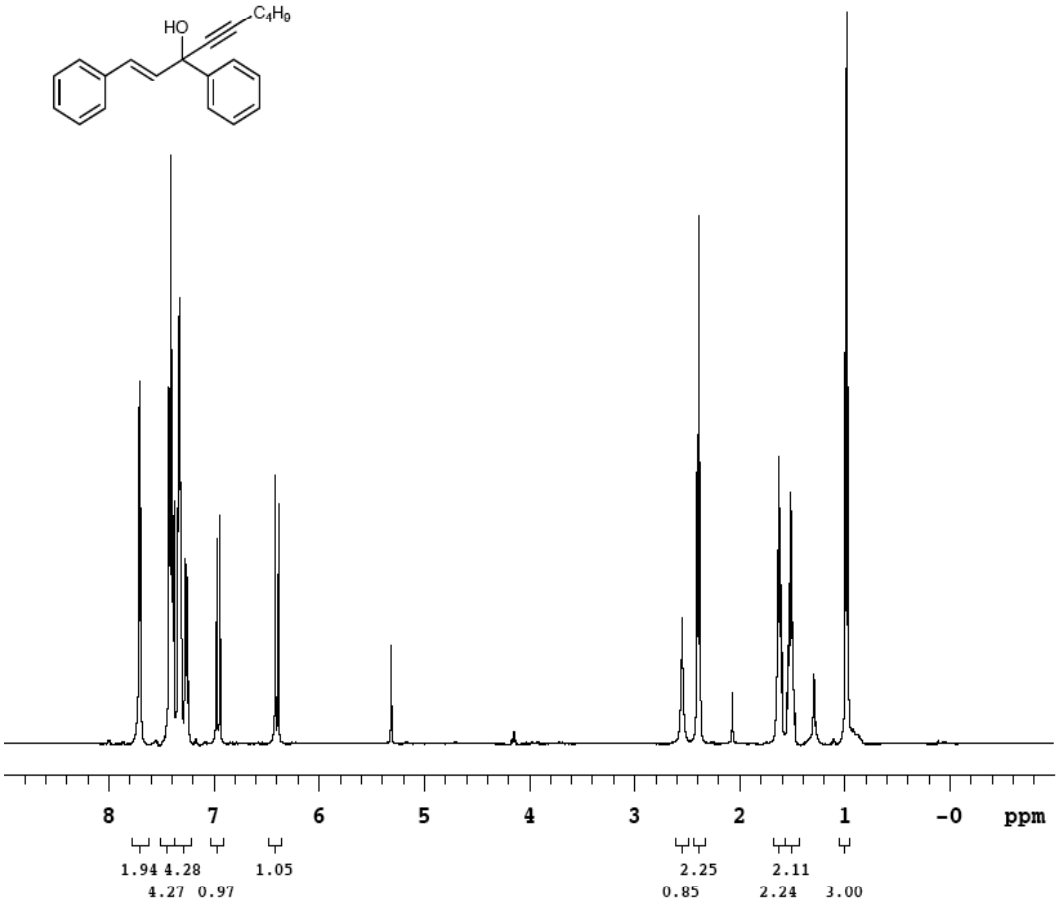
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6
5
4
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1
-0
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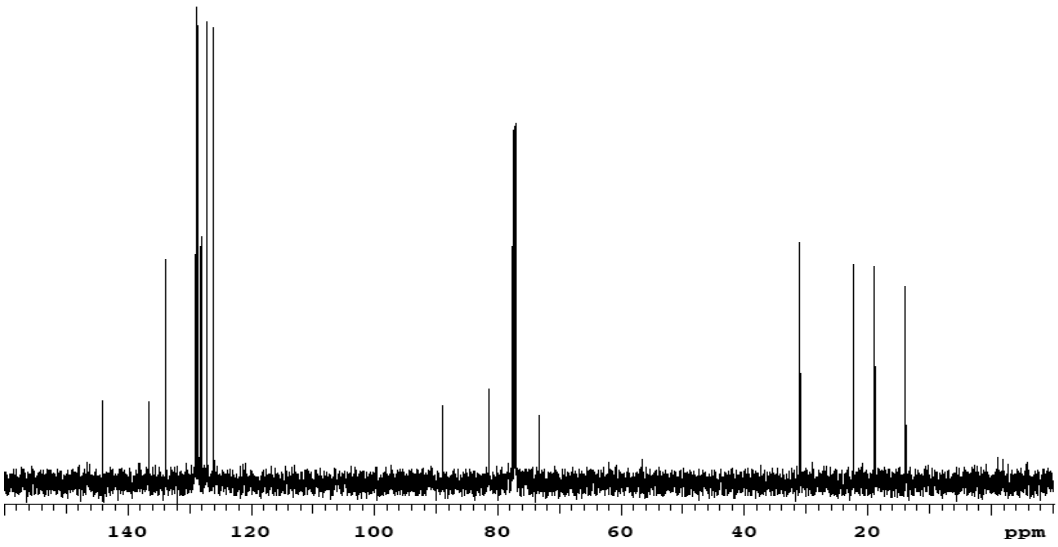
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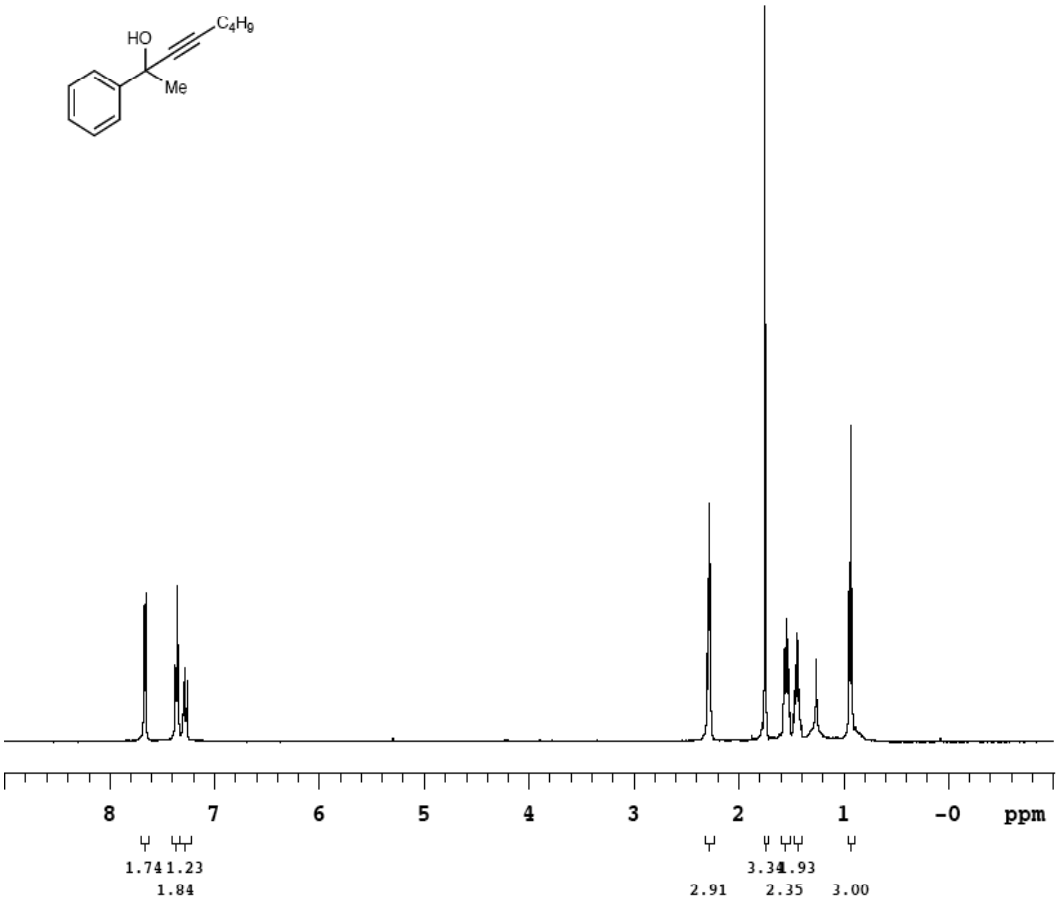
120
100
80
60
40
20
ppm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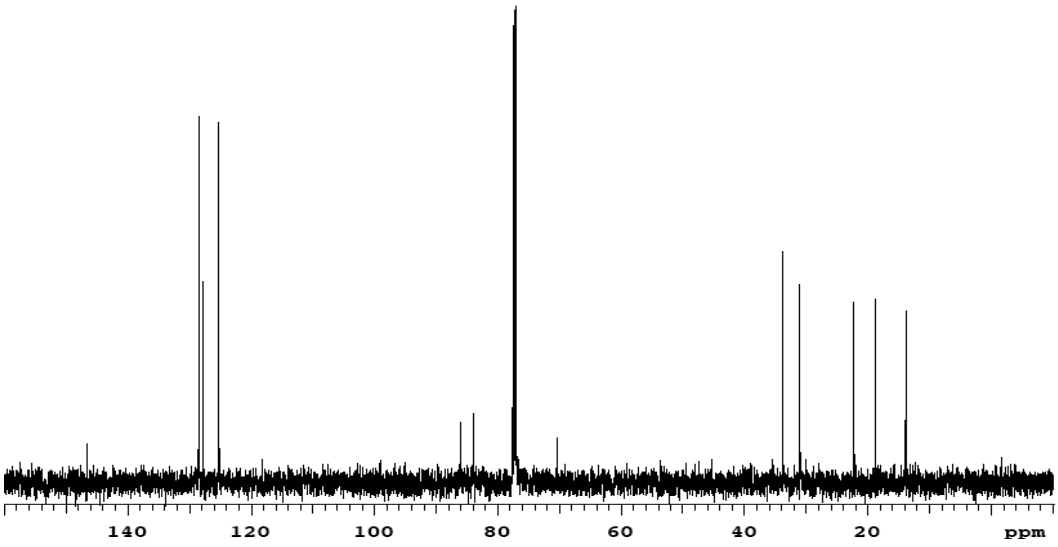
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20
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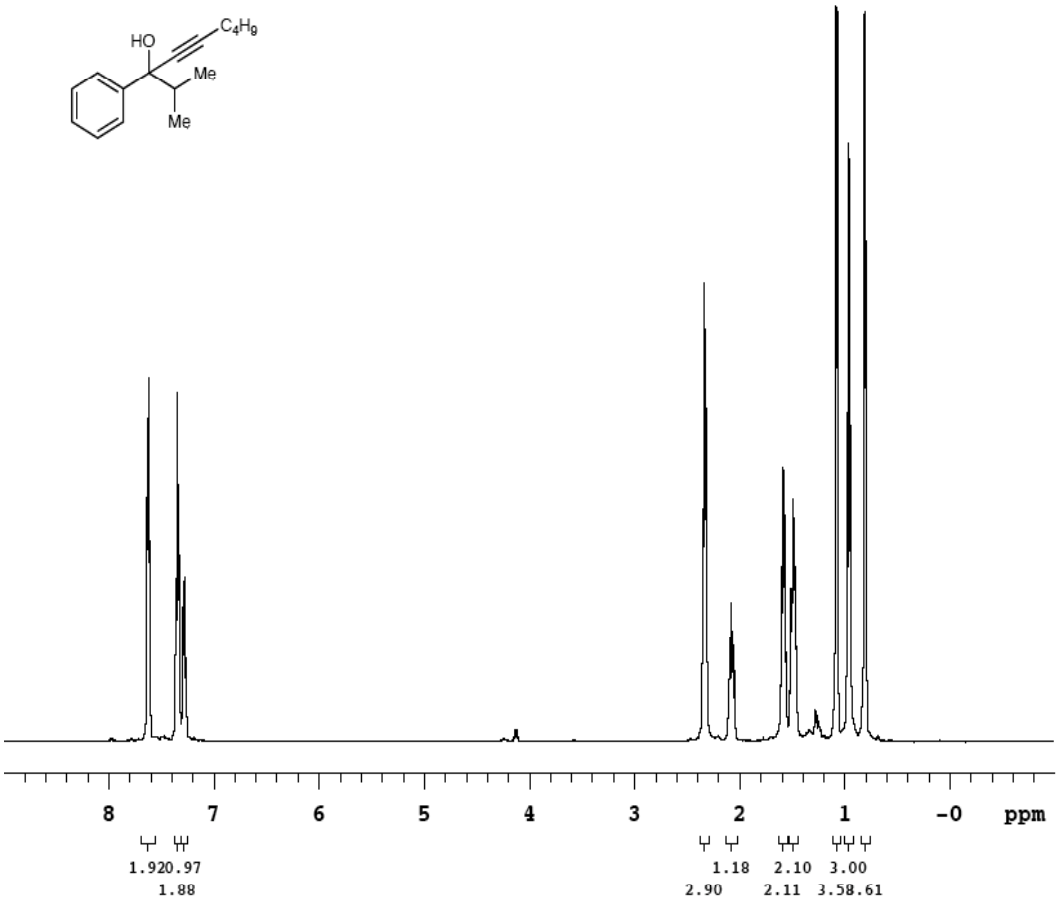
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Me
Me
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7
6
5
4
3
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1
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3.00
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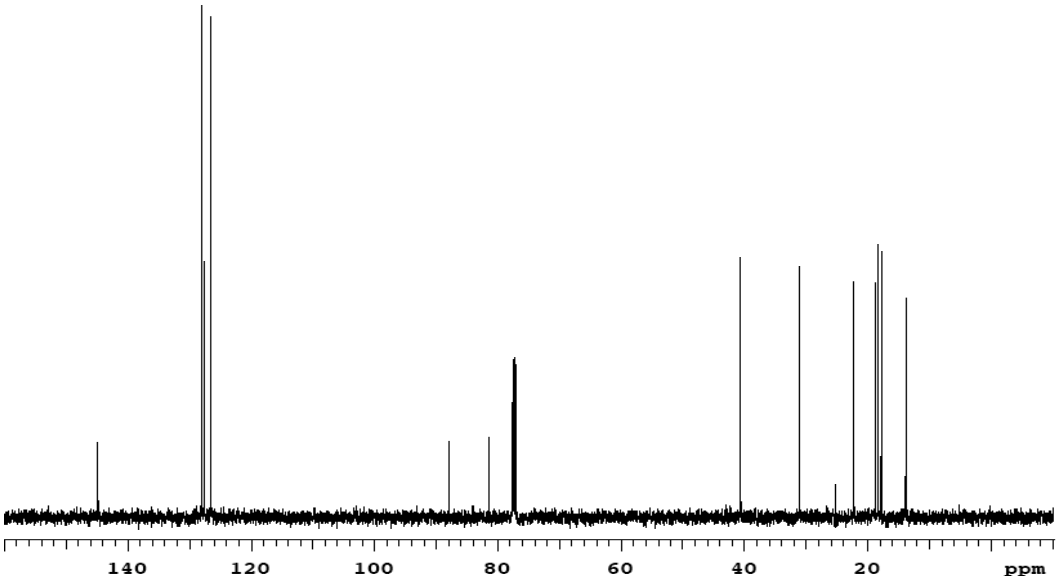
.61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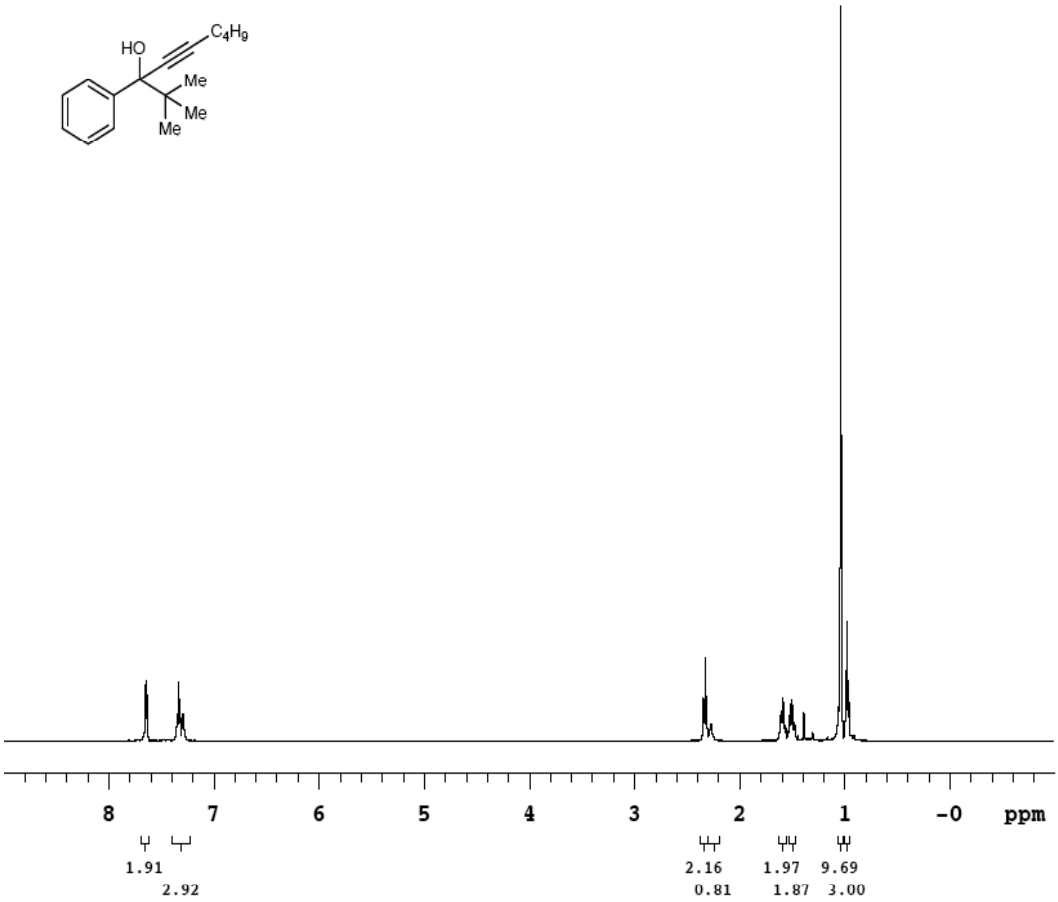
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C_4H_9
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Me
Me
8
7
6
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4
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ppm
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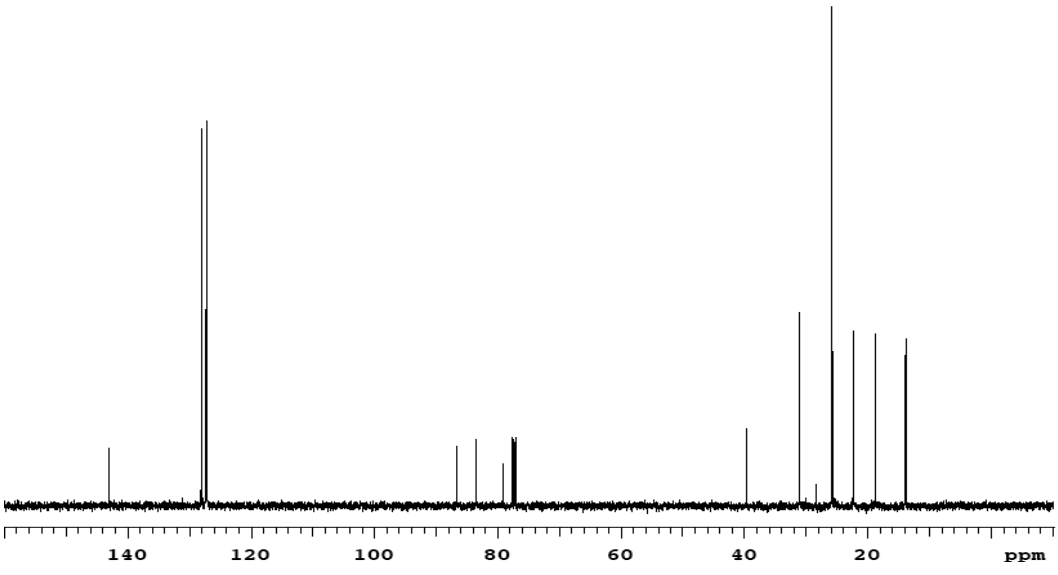
3.00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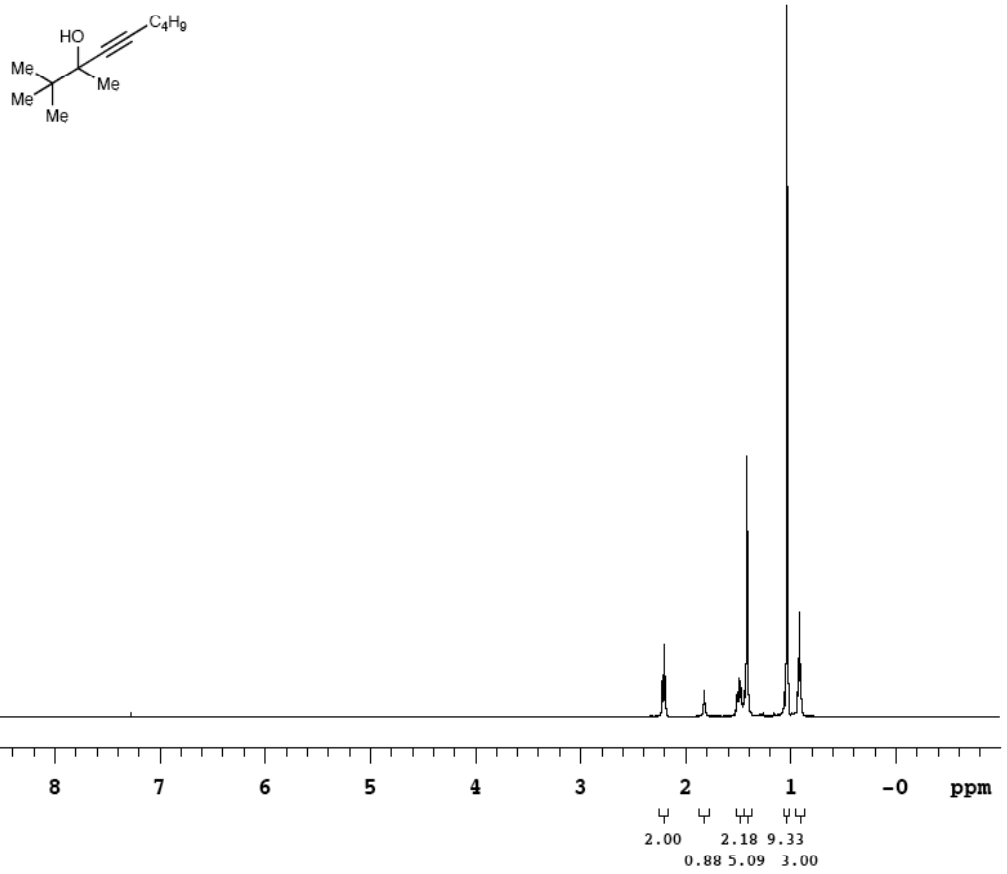
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C_4H_9
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Me
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4
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2.18
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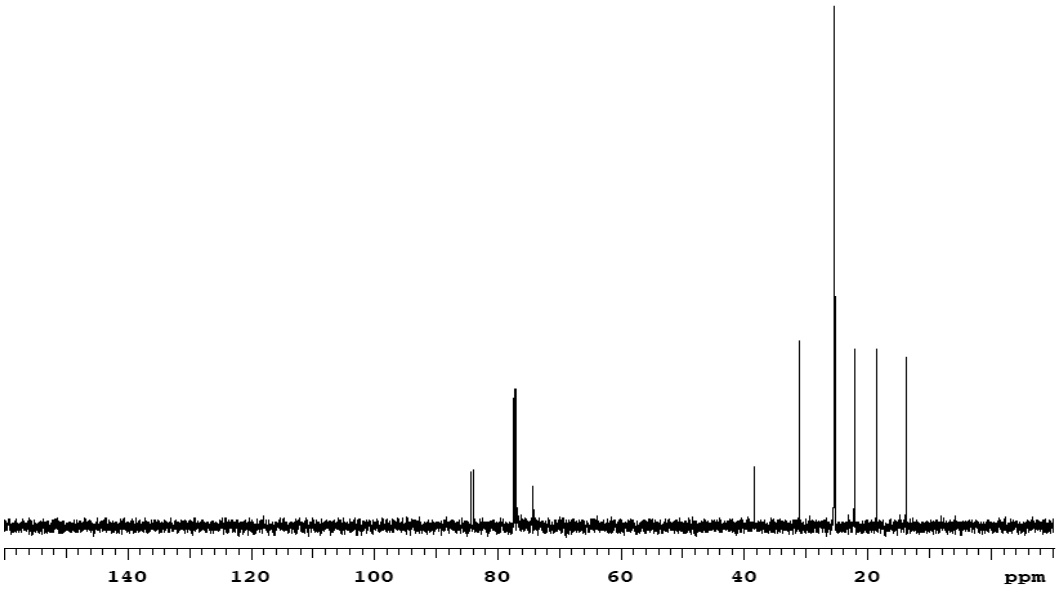
5.09
3.00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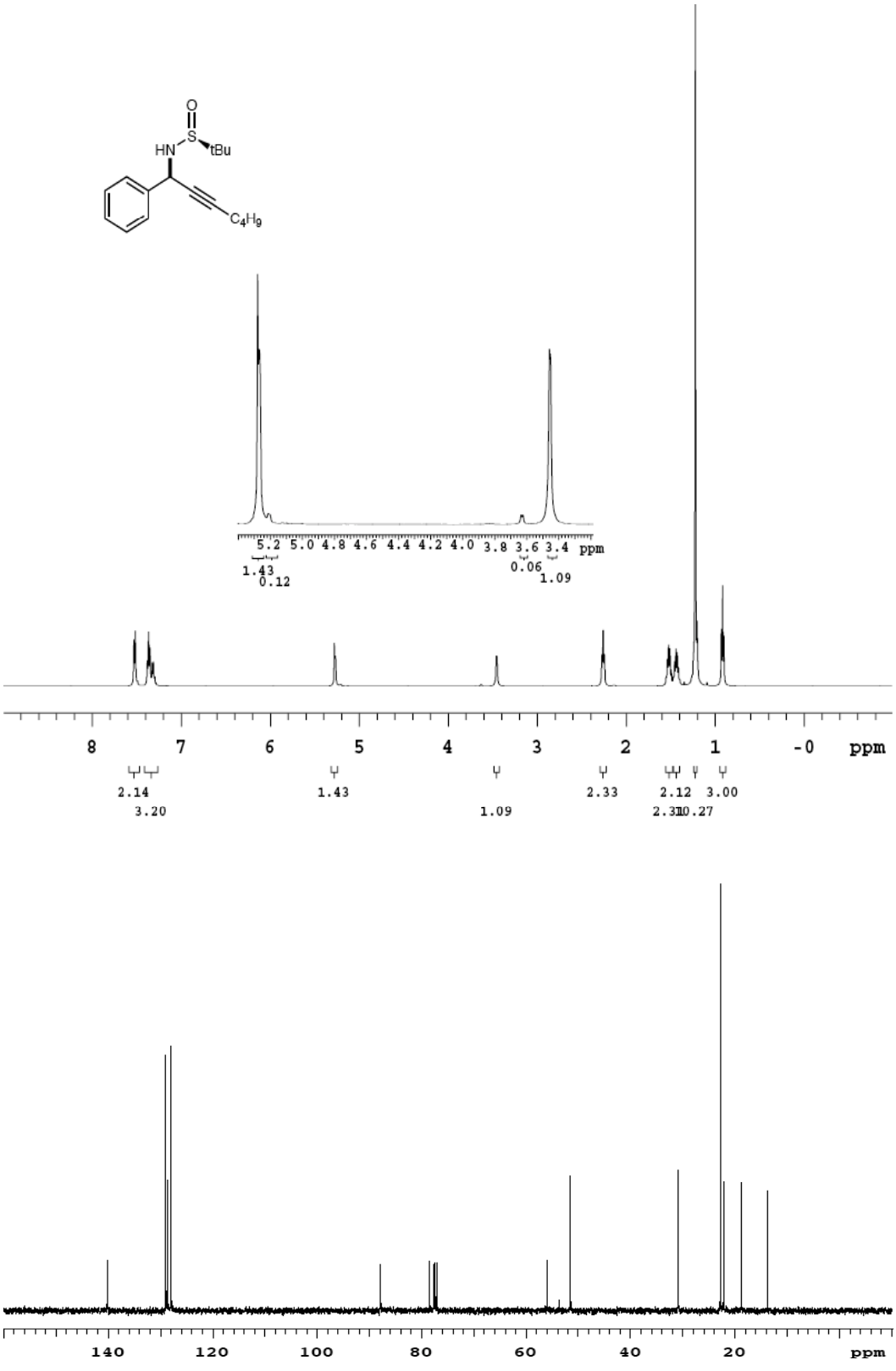
120
100
80
60
40
20
ppm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HN
S
tBu
C4H9
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1.43
0.12
0.06
1.09
8 7 6 5 4 3 2 1 -0 ppm
2.14
3.20
1.43
1.09
2.33
2.12
3.00
2.31
0.27
140 120 100 80 60 40 20 ppm

Chapter 2

Multi-Component Homoenolate Reactions Using Acylsilanes

Portions of this chapter appear in the following publications:

Lettan, R. B., II; Reynolds, T. E.; Galliford, C. V.; Scheidt, K. A. "Multicomponent Reaction of Acylsilanes, Enolates, and Alkyl Halides: Stereoselective Synthesis of Tertiary-β-hydroxy Amides." *J. Am. Chem. Soc.* **2006**, *128*, 15566-15567.

Lettan, R. B., II; Woodward, C. C.; Reynolds, T. E.; Scheidt, K. A. "Stereoselective Synthesis of Highly Substituted γ-Lactams From Acylsilanes." *J. Am. Chem. Soc.* **2007**, in preparation.

Lettan, R. B., II; Galliford, C. V.; Woodward, C. C.; Scheidt, K. A. "Synthetic Applications of Enolate Additions to Acylsilanes as Homoenolate Equivalents." *J. Am. Chem. Soc.* **2007**, in preparation.

Chapter 2 Multi-Component Homoenolate Reactions Using Acylsilanes

2.1 Umpolung Reactivity as a Tactic for Synthetic Transformations

The formation of carbon-carbon bonds through new strategies is vital in handling the challenges of escalating molecular complexity in target-based synthesis. Examination of tactics that employ novel and unusual reactivity are necessary to pursue previously unattainable structural motifs. Methods involving the inversion of polarity, or *Umpolung*,[1] have expanded the scope of bond-forming techniques to access organic target molecules. The homoenolate anion represents a model in the concept of *Umpolung* reactivity (Figure 2-1).[2]

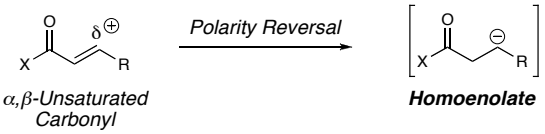
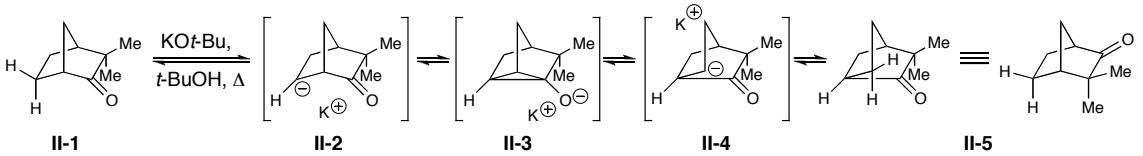


Figure 2-1. Homoenolate generation by the polarity reversal of α,β-unsaturated carbonyl compounds

In 1962, Lambert and and co-workers reported the first examples of homoenolate anion formation (Scheme 2-1).[3] Optically active camphenilone (**II-1**), which has no enolizable protons by classical reactivity standards, underwent racemization at elevated temperatures in the presence of potassium *tert*-butoxide. This loss of optical purity can best be attributed to formation of an active homoenolate intermediate (**II-2**). In spite of this notable observation being almost half a century ago, many researchers have been challenged in finding controllable and useful homoenolate equivalents for organic transformations.

Scheme 2-1. First observation of homoenolate reactivity

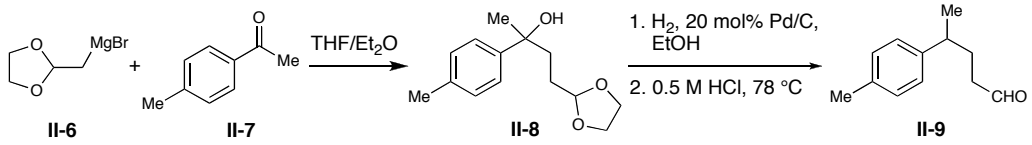


2.2 Homoenolates as Umpolung Reagents

2.2.1 Acetal-Masked Homoenolate Equivalents

Following Lambert's initial observance of homoenolate formation, synthetically useful methods for the generation and utilization of these reactive intermediates involved the use of acetal-masked Grignard reagents.[4] These homoenolate equivalents (**II-6**) have been used in 1,2-addition reactions to carbonyl compounds (Scheme 2-2),[5] acylations,[5,6] and conjugate additions.[4,7,8] The utility of these reactions has also been demonstrated in a number of natural product syntheses.[5,9,10]

Scheme 2-2. 1,2-Addition of an acetal-masked Grignard reagent to a ketone

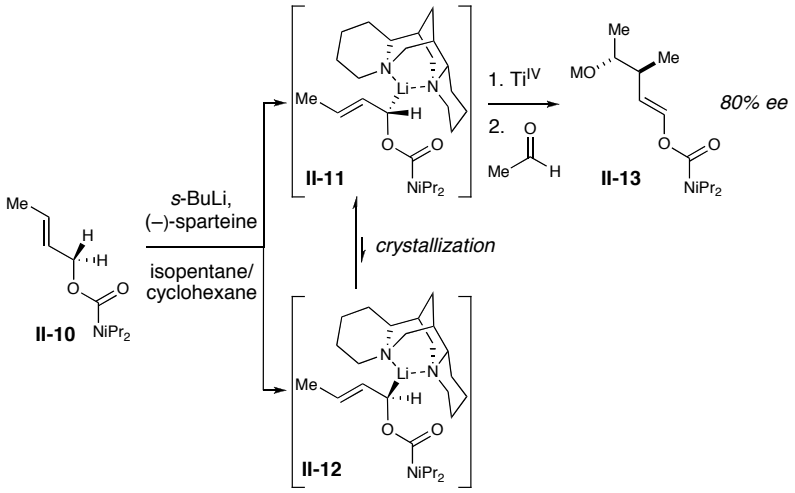


2.2.2 Lithiated Allyl Carbamates and Enantioselective Homoaldol Reactions

Approximately twenty years after Lambert's initial discovery of homoenolate reactivity, Hoppe tactfully employed novel sparteine-carbanion complexes of deprotonated 2-butenyl carbamates (**II-10**) for application in enantioselective homoaldol reactions (Scheme 2-3).[11,12] The observed 1,3-chirality transfer in this process can be

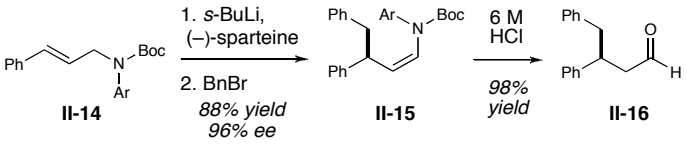
attributed to dynamic kinetic racemate resolution that occurs during the crystallization of the sparteine-carbanion intermediates (**II-11** and **II-12**).

Scheme 2-3. (–)-Sparteine-induced enantioselective homoaldol reaction



Beak later reported a similar transformation employing *N*-allyl carbamates (**II-14**) as homoenolate equivalents (Scheme 2-4).[13] The enamine product generated (**II-15**) can be readily hydrolyzed to the corresponding β-substituted aldehyde (**II-16**) in excellent yield.[14]

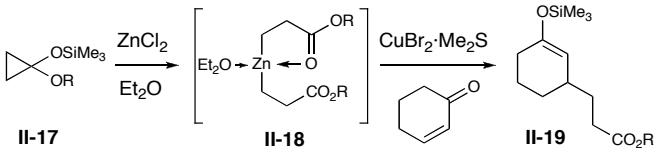
Scheme 2-4. Enantioselective homoaldol reaction with *N*-allyl carbamates



2.2.3 Zinc Homoenolates of Esters from Silyloxycyclopropanes

Nakamura and Kuwajima developed an alternative approach to homoenolate anion reactivity using silyloxycyclopropanes (**II-17**) as synthons (Scheme 2-5).[15] In the presence of zinc (II) chloride, the ring opening of silyloxycyclopropane **II-17** occurs readily to provide a stabilized etherate intermediate (**II-18**). This zinc homoenolate reacts with a variety of electrophiles to undergo synthetically useful carbon-carbon bond-forming reactions, while simultaneously avoiding undesired intramolecular cyclopropanation.

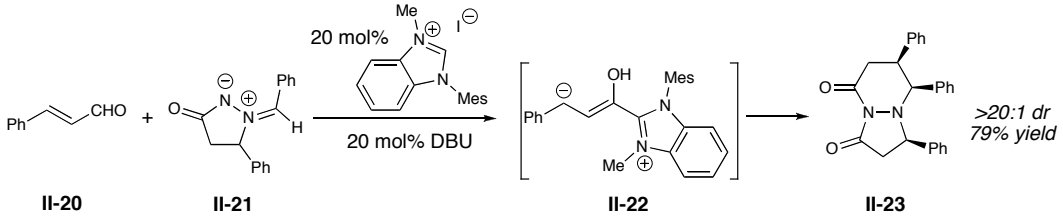
Scheme 2-5. Silyloxycyclopropanes as homoenolate equivalents



2.2.4 N-Heterocyclic Carbene-Catalyzed Homoenolate Equivalents

Recently, a new approach to homoenolate generation involving nucleophilic *N*-heterocyclic carbene (NHC)-catalyzed processes has been independently investigated by several researchers, including Glorius,[16,17] Bode,[18,19] Nair,[20,21] Zeitler,[22] and Scheidt.[23,24] For example, Chan and Scheidt recently reported the highly stereoselective formal [3+3] cycloaddition of enals (**II-20**) and azomethine imines (**II-21**) catalyzed by a benzimidazolium salt derived carbene (Scheme 2-6).[24]

Scheme 2-6. NHC-catalyzed stereoselective formal [3+3] cycloaddition



2.3 Acylsilanes and the Brook Rearrangement

2.3.1 Nucleophilic Additions to Acylsilanes

The addition of organometallic nucleophiles to acylsilanes typically induces a reversible 1,2-silyl group migration from carbon to oxygen (1,2-Brook rearrangement, Figure 2-2).[25] In this process, nucleophilic (M-R^2) addition to the acylsilane yields a silyl alkoxide intermediate, which is proposed to undergo reversible, stereospecific rearrangement via a silyl epoxide transition state (or intermediate, not clearly distinguished) to generate a silyloxy carbanion. The proposed highly-ordered cyclic silyl epoxide transition-state is supported by very large and negative entropies of activation ($\Delta S^{\ddagger}$ = –35 to –45 cal/K).[25] Overall, the unique reactivity of acylsilanes enable them to act sequentially as an electrophilic/nucleophilic element at the same carbon position. The additions of alkynyl lithium reagents or alkenyl Grignard reagents to acylsilanes have been shown to trigger this rearrangement to access useful silyloxy carbanions.[26-29]

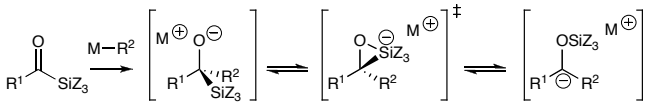
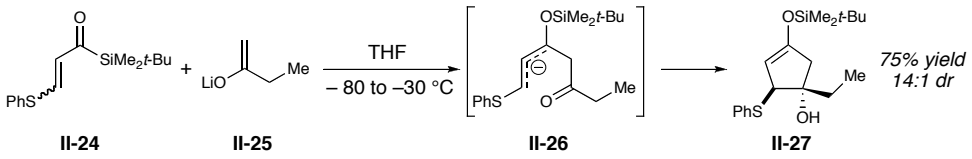


Figure 2-2. 1,2-Silyl migration following nucleophilic addition of an organometallic nucleophile (M-R^2)

2.3.2 Enolate Additions to Acylsilanes

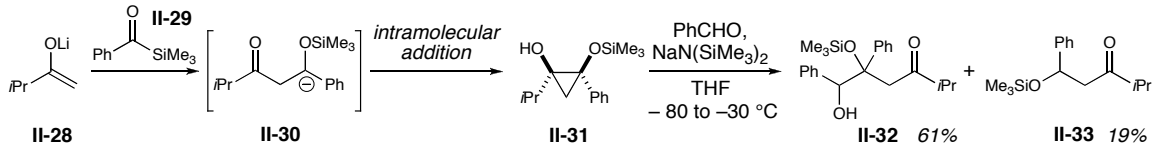
Interestingly, the addition of enolates to acylsilanes has seen much less development in comparison to other organometallic nucleophiles.[30,31] Takeda has reported on the addition of ketone enolates to acylsilanes in intramolecular annulation reactions (Scheme 2-7).[32-35] The addition of lithium enolate **II-25** to α,β-unsaturated acylsilane **II-24** yields electron delocalized allylic anion **II-26**. This intermediate then proceeds through an intramolecular homoaldol addition pathway to provide cyclized silylenolether **II-27**.

Scheme 2-7. [3+2] Annulation based on the Brook rearrangement



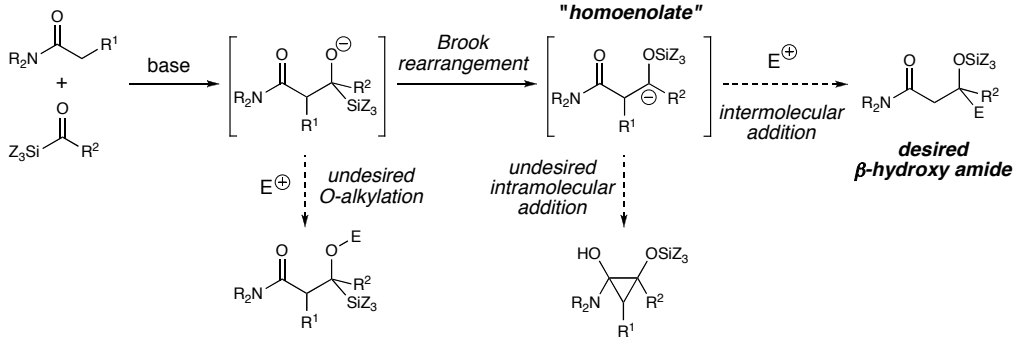
When the acylsilane lacks α,β-unsaturation, Takeda reports that the major product following *ketone enolate* addition to an acylsilane is the hydroxy cyclopropane (**II-31**, Scheme 2-8). This product arises from the intramolecular addition of the *in situ*-generated β-silyloxy homoenolate **II-30** onto the ketone carbonyl. Brief investigations were reported involving the use of hydroxy cyclopropane **II-31** as a homoenolate precursor in the presence of excess amounts of strong base, although γ-hydroxy ketone **II-32** was only observed in moderate yield for the addition to benzaldehyde. The ring-opened product (**II-33**) was observed as the major byproduct for this reaction. The only other reported electrophile, hexanal, gave primarily β-silyloxy ketone **II-33**, with no observance of the desired γ-hydroxy ketone.

Scheme 2-8. Cyclopropanation from the reaction of ketone enolates with acylsilanes



As is evident from previous publications in this field (*vide supra*), standard intermolecular addition methods for the homoenolate carbanion resulting from enolate addition to an acylsilane had not been realized prior to our investigation. We chose to explore the combination of alternative enolates and acylsilanes to access stable homoenolates, that could then proceed through the desired intermolecular addition pathway (Scheme 2-9). The success of this single-flask process depended on controlling the intermediates in the reaction to favor intermolecular reactivity via the β-silyloxy homoenolate (*C*-alkylation). Due to their decreased electrophilicity in comparison to ketones, we chose amide enolates (X = NR_2) to potentially disfavor the generation of the hydroxy cyclopropane, and promote intermolecular addition for the generation of tertiary β-hydroxy amides.

Scheme 2-9. Proposed amide enolate addition to acylsilanes as homoenolate equivalents

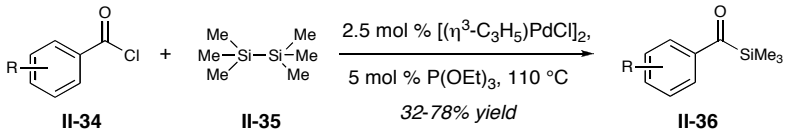


2.4 Synthesis of Tertiary β-Hydroxy Amides by Enolate Additions to Acylsilanes

2.4.1 Preparation of Acylsilanes

In order to begin our investigations, we examined methods to efficiently access acylsilanes. Aryl acylsilanes (**II-36**) were prepared according to the procedure of Yamamoto and coworkers (Scheme 2-10).[36] Heating a mixture of the allyl palladium chloride dimer, triethylphosphite, hexamethyldisilane, and an aryl acid chloride provides the corresponding aryl acylsilane (**II-36**) in moderate yields (32-78%). Unreacted acid chloride can be easily separated by silica chromatography (20:80 dichloromethane/hexanes). This product can be further purified by Kugelrohr distillation to yield pure acylsilane starting material.

Scheme 2-10. Preparation of aromatic acylsilanes

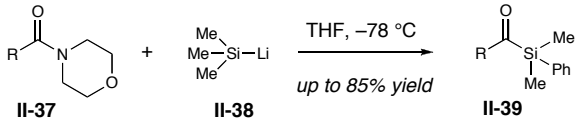


II-34 **II-35** **II-36**

Dimethylphenyl acylsilanes (**II-39**) were prepared according to the procedure from the Scheidt laboratory (Scheme 2-11).[37,38] The addition of dimethylphenyl silyllithium (**II-38**) to aliphatic morpholine amides (**II-37**) cleanly affords the corresponding acylsilanes in good yields after purification. The addition of anionic silyl nucleophiles to acid chlorides is typically the most direct method for the synthesis of acylsilanes, but this method requires at least two equivalents of the silyllithium reagent and suffers largely from the need for a stoichiometric amount of copper(I) cyanide required for the reaction to proceed in high yield.[39,40] Unfortunately, this process

becomes prohibitive on a preparative scale. Because the direct addition of organometallic reagents to morpholine amides without over-addition is possible,[41,42] and more economical than the corresponding Weinreb amides, a direct and efficient synthesis of acylsilanes from amides could be developed. The use of the morpholine amide minimizes over-addition of the silyl nucleophile and also provides the highest yields of the amides surveyed.

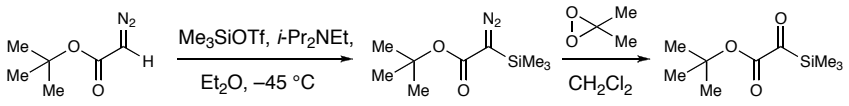
Scheme 2-11. Preparation of aliphatic acylsilanes



II-37 R = alkyl **II-38** **II-39**

The synthesis of *tert*-butyl trimethylsilylglyoxylate (**II-42**) was accomplished in two-steps from *tert*-butyl diazoacetate (**II-40**) according to a procedure reported by Nicewicz and Johnson (Scheme 2-12).[43] The intermediate *tert*-butyl trimethylsilyl diazoacetate (**II-41**) can be carried on to the oxidation step without purification, to afford *tert*-butyl trimethylsilylglyoxylate in a moderate yield (55%, 2 steps). Dimethyldioxirane (DMDO) is used directly without purification after preparation from the remaining sodium bicarbonate, water, and acetone.

Scheme 2-12. Preparation of *tert*-Butyl trimethylsilylglyoxylate

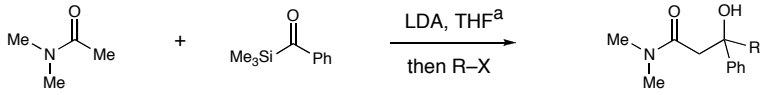


II-40 **II-41** **II-42**

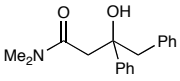
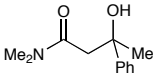
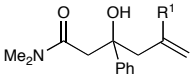
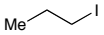
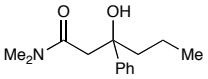
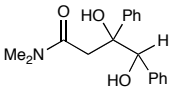
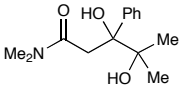
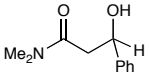
2.4.2 Reaction Development

Our investigations into the use of enolate additions to acylsilanes as homoenolate equivalents began by utilizing reactive and readily available/preparable starting materials. The initial reaction was conducted with dimethylacetamide and benzoyltrimethylsilane,[37,38] with benzyl bromide as the electrophile (Table 2-1, entry 1). Amide enolate formation with lithium diisopropylamine (LDA) in THF was followed by the addition of benzyl bromide. After 15 min at −78 °C (disappearance of acylsilane as observed by TLC), the alkyl halide was added. To our delight, this three-component reaction provided β-hydroxy amide **II-45** in 86% yield after desilylation. Notably, the corresponding hydroxy cyclopropane and *O*-alkylation compound were not observed. The absence of hydroxy cyclopropanes confirmed our hypothesis that the reduced electrophilicity of the amide carbonyl favors intermolecular reactivity. Encouraged by these results, a range of electrophiles was surveyed (Table 2-1). Primary, allylic and benzylic halides all afford the corresponding tertiary alcohols **II-45** to **II-49** in good yields (entries 1-5). The β-silyloxy homoenolate intermediate also undergoes addition to aldehydes and ketones (entries 6 and 7). In cases where elimination (entry 5) or deprotonation (entry 7) is a possibility, the reaction proceeds without complication. Furthermore, secondary β-hydroxy amide **II-52** can be generated by treating the homoenolate intermediate with acidic methanol (entry 8).

Table 2-1. Multi-component reaction with electrophiles



II-43 **II-44** **II-45 to II-52**

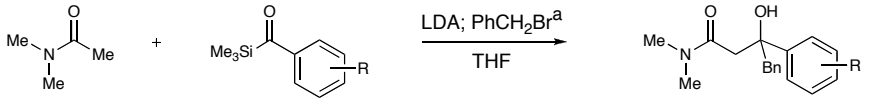
entry	R–X	product		yield (%)
1			**II-45**	86
2			**II-46**	77
3			**II-47** (R^1= H)	68
4			**II-48** (R^1= Me)	77
5			**II-49**	69
6			**II-50**	81[b]
7			**II-51**	78
8	AcOH/MeOH		**II-52**	80

a. Acylsilane and electrophile sequentially added to a 0.2 M enolate solution in THF at -78 °C. Initial silyl ether products treated with *n*-Bu_4NF in THF prior to purification. b. 1:1 mixture of diastereomers.

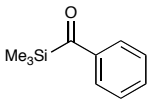
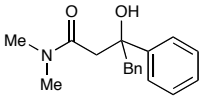
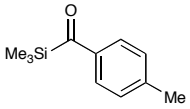
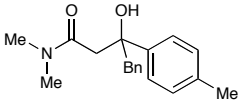
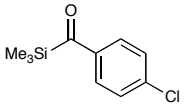
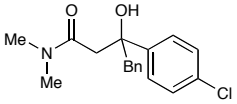
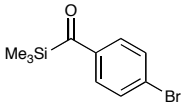
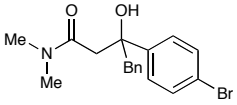
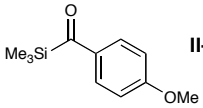
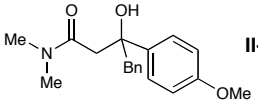
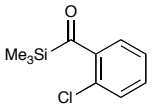
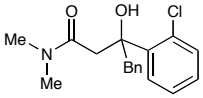
2.4.3 Examination of Acylsilanes in the Multi-Component Homoenolate Reaction

We proceeded to examine the acylsilane scope of the reaction (Table 2-2). The optimized reaction proceeds in good yields in the presence of both electron deficient (entries 3, 4 and 6) and electron rich (entry 5) aromatic systems.

Table 2-2. Multi-component reaction with aromatic acylsilanes



II-43 **II-44, II-53 to II-57** **II-45, II-58 to II-62**

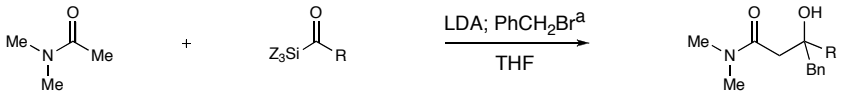
entry	acylsilane		product		yield (%)
1		**II-44**		**II-45**	86
2		**II-53**		**II-58**	73
3		**II-54**		**II-59**	73
4		**II-55**		**II-60**	69
5		**II-56**		**II-61**	75
6		**II-57**		**II-62**	67

a. Acylsilane and electrophile sequentially added to a 0.2 M enolate solution in THF at -78 °C. Initial silyl ether products treated with *n*-Bu_4NF in THF prior to purification.

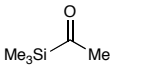
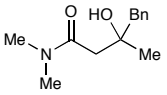
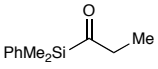
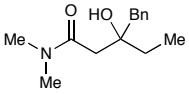
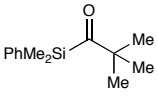
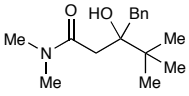
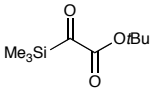
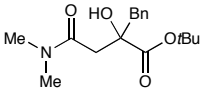
The success of the multi-component homoenolate reaction with aromatic acylsilanes led us to investigate aliphatic acylsilanes for this process (Table 2-3). When acetyltrimethylsilane (**II-63**) is employed, a complex mixture primarily containing *O*-alkylation product (no Brook rearrangement occurs) is recovered (entry 1). This observation is not surprising since aromatic substitution stabilizes the β-silyloxy homoenolate intermediate, promoting the Brook rearrangement in the previous examples (Table 2-2). Additionally, the deprotonation of an enolizable acylsilane by the enolate is a potentially competitive process that can interfere with the normal reaction pathway.

Aliphatic dimethylphenyl acylsilanes have been shown to be effective Brook rearrangement precursors due to the increased stabilization of pentavalent silyloxycyclopropane intermediate (see Figure 2-1) from the aromatic substituents.[44-52] Unfortunately, the β-hydroxy amide was not observed when using dimethylphenyl acylsilanes (entries 2 and 3). As an alternative to aliphatic acylsilanes, *tert*-butyl trimethylsilylglyoxylate (**II-66**)[43] did prove to be effective for this transformation, providing γ-carboxy-β-hydroxy amide **II-70** in moderate yield (entry 4). Installation of the *tert*-butyl ester provides a synthetic handle that can be further functionalized to access a variety of functional groups.[53]

Table 2-3. Multi-component reaction with aliphatic acylsilanes



II-43 **II-63 to II-66** **II-67 to II-70**

entry	acylsilane		product		yield (%)
1		**II-63**		**II-67**	0[b,c]
2		**II-64**		**II-68**	0[c]
3		**II-65**		**II-69**	0[c]
4		**II-66**		**II-70**	49

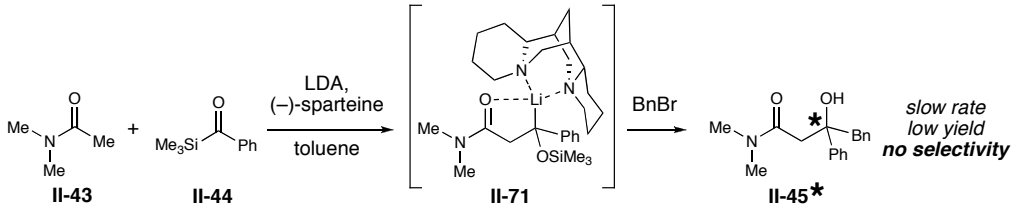
a. See Table 1 for reaction details b. Minor amounts of *O*-alkylation product observed. c. Complex mixture.

2.4.4 Asymmetric Homoenolate Additions

2.4.4.1 Enantioselective Lithium/Sparteine-Carbanion Pairs

Following the development of the multi-component homoenolate addition, investigation was directed toward the development of a stereoselective variant of this process. Drawing inspiration from the work of Hoppe[11,12] and Beak,[13,14] attempts were made to utilize lithium/sparteine-carbanion pairs to induce enantioselectivity (Scheme 2-13). Unfortunately, these experiments were unsuccessful in controlling asymmetry for this homoenolate reaction process. One limitation was the necessity of a non-coordinating solvent (e.g. toluene) to promote sparteine complexation. Under these conditions, the reaction rate and yield were greatly diminished, and no enantioselectivity was observed.

Scheme 2-13. Lithium/sparteine carbanion induced stereocontrol

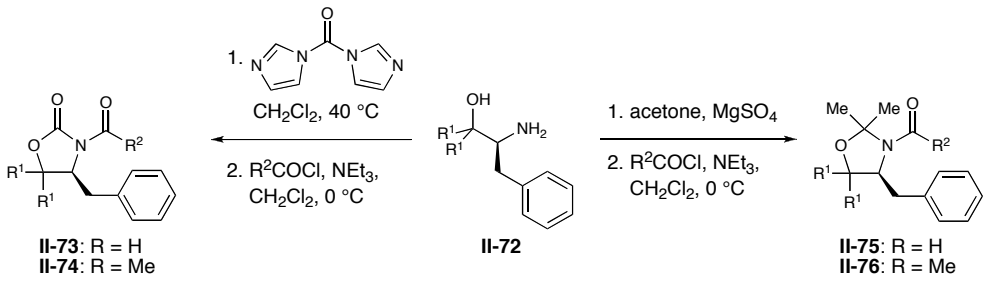


2.4.4.2 Preparation of Chiral Acetamides

An alternative method to asymmetric induction involved auxiliary control by the substitution of dimethylacetamide with a chiral acetamide. Cyclic chiral acetamide auxiliaries were primarily considered based on their rigidity and proven ability as asymmetric control elements. To this end, *N*-acyl oxazolidinones **II-73** and **II-74** were

synthesized according to procedures by Evans[54] and Davies,[55] respectively. *N*-Acyl oxazolidines **II-75** and **II-76** were synthesized according to a procedure by Kanemasa.[56,57]

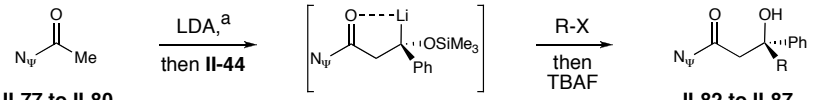
Scheme 2-14. Preparation of chiral acetamides



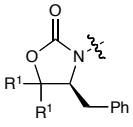
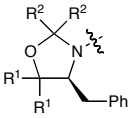
2.4.4.3 Auxiliary Controlled Diastereoselective Homoenolate Additions

Initial attempts to control the stereochemical outcome of the reaction with chiral oxazolidinone auxiliaries (**II-77** and **II-78**) gave complete decomposition of starting materials (Table 2-4). This is most likely due to nucleophilic addition of the intermediate carbanion (**II-81**) to the relatively electrophilic carbamate carbonyl of the oxazolidinone. However, the addition of the enantiopure lithium enolate of **II-79** or **II-80** to acylsilane **II-44**, followed by addition of benzyl bromide, affords the desired carbinols (**II-84** and **II-85**, after desilylation) with moderate diastereoselectivity under the established kinetically-controlled reaction conditions (–78 °C, entries 3 and 4). Suprisingly, when this sequence is conducted at 0 °C, the selectivities improve to >10:1. This inverse temperature to selectivity relationship suggests that the reaction is under thermodynamic control (entries 5-7).

Table 2-4. Diastereoselective Enolate/Acylsilane Reactions



II-77 to II-80 **II-81** **II-82 to II-87**

entry	N_Ψ		R–X	T (°C)	yield (%)	dr[b]	product
1		**II-77**: R^1=H	BnBr	−78	0[c]	–	**II-82**
2		**II-78**: R^1=Me	BnBr	−78	0[c]	–	**II-83**
3		**II-79**: R^1=H; R^2=Me	BnBr	−78	77	2:1	**II-84**
4		**II-80**: R^1=Me	BnBr	−78	80	3:1	**II-85**
5		**II-80**	BnBr	0	79	10:1	**II-85**
6		**II-80**	AllylBr	0	76	10:1	**II-86**
7		**II-80**	MeI	0	78	15:1	**II-87**

a. Acylsilane and electrophile sequentially added to a 0.2 M enolate solution in THF. Silyl ether products treated with *n*-Bu_4NF in THF prior to purification. b. Determined by ^{1}H NMR spectroscopy. c. Decomposition.

The absolute stereochemistry of β-hydroxy amide **II-85** was determined by single-crystal X-ray diffraction (Figure 2-3). The absolute stereochemistry of β-hydroxy amides **II-86** and **II-87** was assigned by analogy.

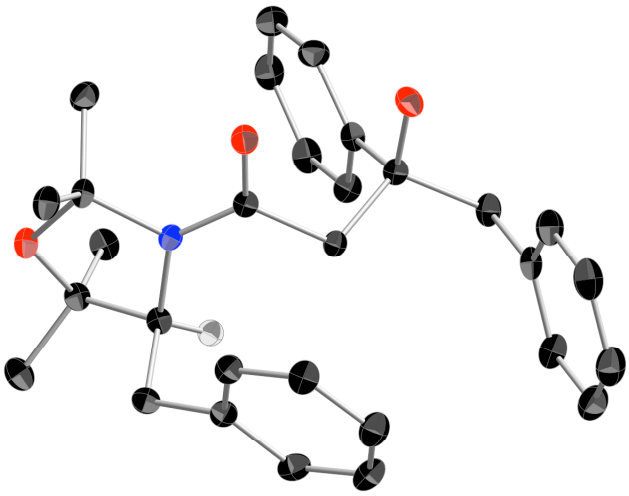


Figure 2-3. ORTEP representation of the crystal structure of β-hydroxy amide **II-85**. Thermal ellipsoids are drawn at 50% probability. Hydrogen atoms, other than the one on the oxazolidine ring, have been omitted for clarity.

2.5 Homoenolate Addition to Imines and the Synthesis of γ-Lactams

Based on the observed addition of the generated homoenolate to carbonyl electrophiles (benzaldehyde and acetone, Table 2-1, entries 6 and 7), an intriguing variant involved the addition of an imine as the electrophile (Figure 2-4). Utilization of an appropriate electron-withdrawing activating group (EWG), should permit access to highly substituted γ-amino-β-hydroxy amides. Importantly, cyclization of the amide to the corresponding γ-lactam was envisioned to be accomplished directly upon removal of the activating group on the imine nitrogen.

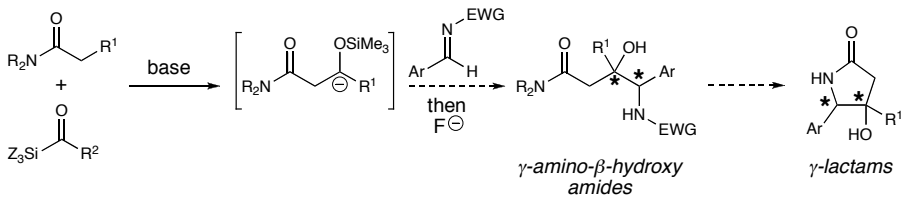


Figure 2-4. Homoenolate addition to imines and subsequent γ-lactam formation

The synthesis of γ-lactams[58-62] is an important goal due to their application in the drug-discovery process as key intermediates in the preparation of biologically and pharmaceutically relevant molecules (Figure 2-5).[63] Compounds containing these heterocycles have seen direct applications in the treatment of cancer,[64,65] fungal infections,[65] epilepsy,[66,67] HIV,[68,69] neurodegenerative diseases[70] and depression.[71]

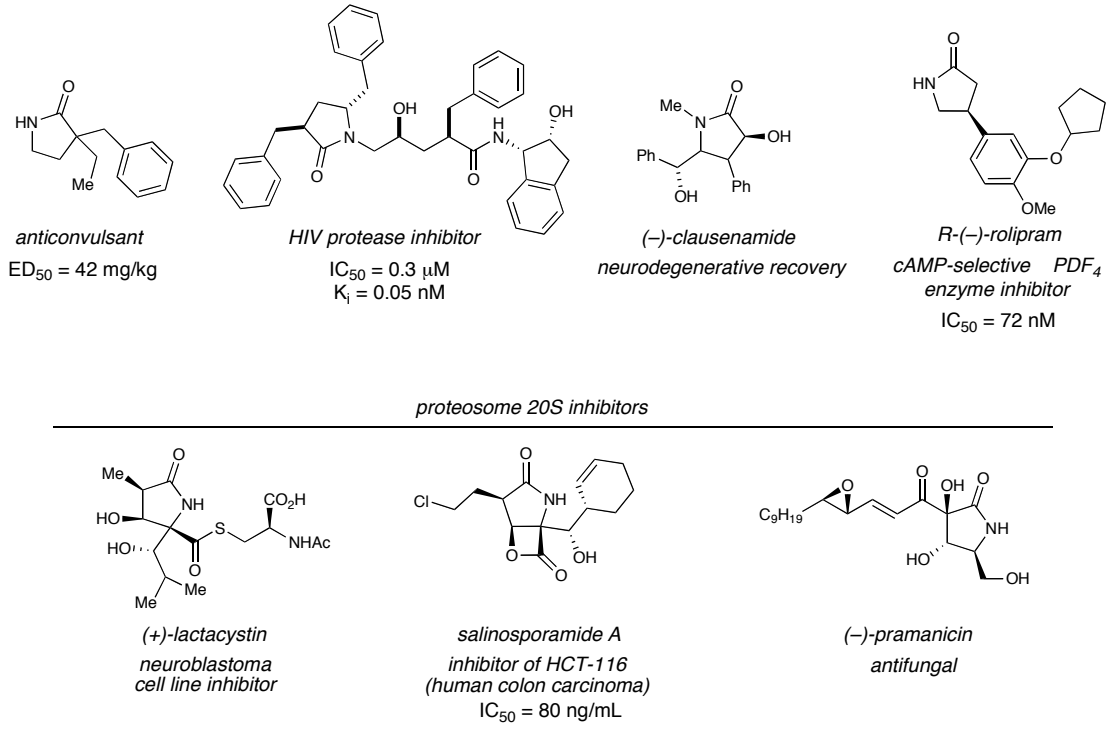


Figure 2-5. Examples of natural and synthetic γ-lactam derivatives

2.5.1 Preparation of Imines

Various *N*-substituted imines were considered for investigation of potential activity in the homoenolate addition process (Figure 2-6). For our purposes, diphenylphosphoryl functionality (**II-88**) was chosen because of a) its electron withdrawing capacity,[72] b) the steric magnitude associated with this functionality might provide non-bonding interactions during the addition event that could influence diastereoselection, and (c) the ease of removal of this group under acidic conditions could potentially facilitate cyclization to the γ-lactam. *N*-phosphinoyl imines have been used extensively as electrophiles in asymmetric reductions,[73-77] vinyl zinc additions,[78] acylanion additions,[79] and nucleophilic additions of arylboronic acids.[80]

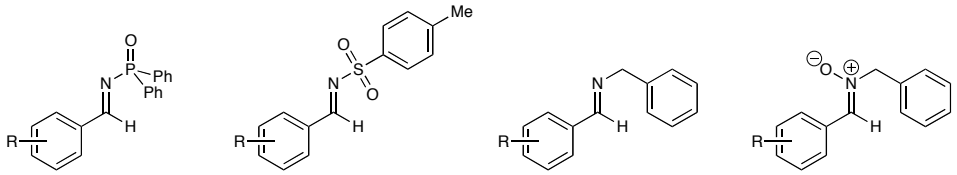
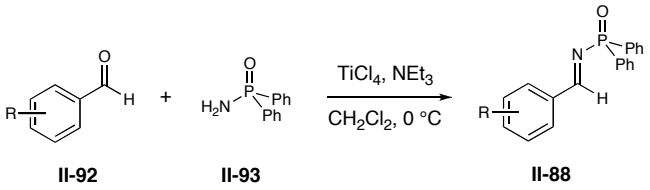


Figure 2-6. Examples of *N*-substituted imines

Three methods exist for the synthesis of *N*-phosphinoyl imines. A conventional procedure is the titanium(IV) chloride catalyzed condensation of diphenylphosphinic amide with an aldehyde or ketone, reported by Jennings and Lovely (Scheme 2-15).[81] This method is less than ideal due to consistent incomplete conversion in our laboratory. This lack of conversion can be attributed to possible irreversible complexation between the nitrogen of the diphenylphosphinic amide (**II-93**) or triethylamine to titanium(IV) chloride. In addition, insufficient reactivity also leads to purification difficulties.

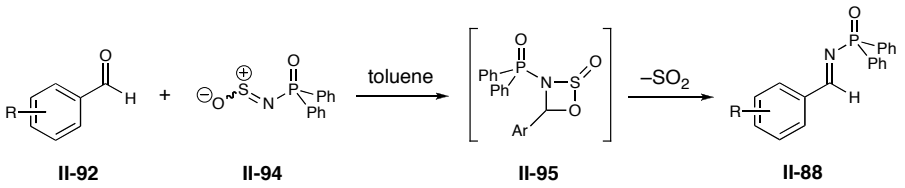
Scheme 2-15. Titanium (IV) chloride-catalyzed preparation of *N*-phosphinoyl imines



II-92 **II-93** **II-88**

Another approach to synthesize *N*-phosphinoyl imines was reported by Lauzon, Desrosiers, and Charette, and involves the use of the Kresze reaction (Scheme 2-16). Addition of *P*,*P*-diphenyl-*N*-sulfinylphosphoramidate (**II-94**) to an aromatic aldehyde (**II-92**) gives the *N*-phosphinoyl imine (**II-88**) upon extrusion of sulfur dioxide. This procedure is reported to have poor yields over multiple steps, and involves stoichiometric generation of sulfur dioxide, which has a very unpleasant odor. The synthesis of *N*-phosphinoyl imines by this method was not conducted.

Scheme 2-16. Preparation of *N*-phosphinoyl imines using the Kresze reaction

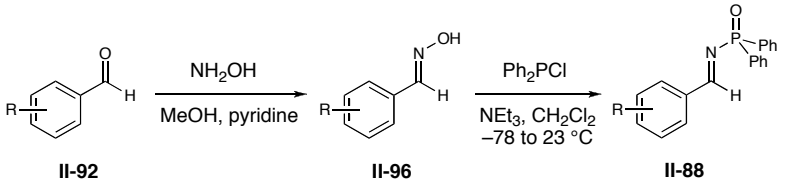


II-92 **II-94** **II-95** **II-88**

The method utilized for the synthesis of *N*-phosphinoyl imines was the procedure reported by Boyd, Jennings, and coworkers (Scheme 2-17).[82] Condensation of aldehyde **II-92** with hydroxylamine hydrochloride proceeds efficiently to provide hydroxylamine **II-96** in near quantitative yields. Nucleophilic addition of the hydroxylamine to chlorodiphenylphosphine, followed by a radical rearrangement generates the

corresponding *N*-phosphinoyl imine (**II-88**) in good yield (65-88%). The resulting product is easily purified by silica gel chromatography. Due to the reactivity of *N*-phosphinoyl imines to hydrolysis, they should be stored in a dessicator at lower temperatures (≤ 0 °C). Occasionally, an insoluble solid (in heated THF) will remain, which can be filtered for increased purity prior to further use. This solid was not identified.

Scheme 2-17. Preparation of *N*-phosphinoyl imines from oximes

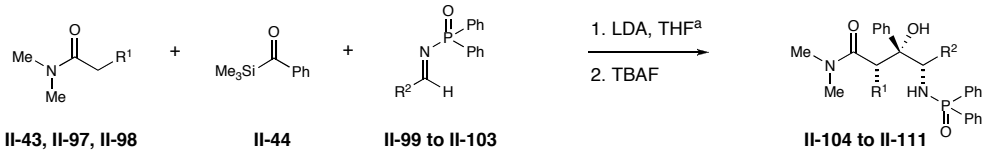


II-92 **II-96** **II-88**

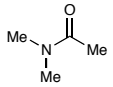
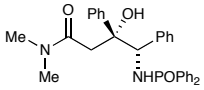
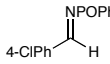
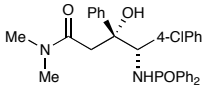
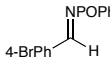
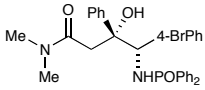
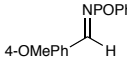
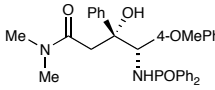
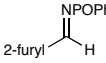
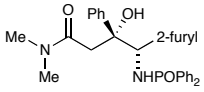
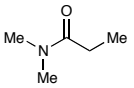
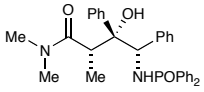
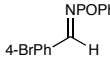
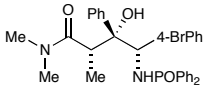
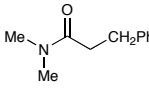
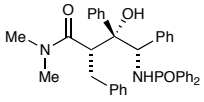
2.5.2 Multi-Component Homoenolate Additions to N-Phosphinoyl Imines

To evaluate the homoenolate addition to *N*-phosphinoyl imines, the developed muti-component reaction was conducted with dimethylacetamide (**II-43**) and benzoyltrimethylsilane (**II-44**), using the diphenylphosphoryl-benzylimine (**II-99**) as the electrophile (Table 2-5). Gratifyingly, this three-component reaction provided γ-amino-β-hydroxy amide **II-104** in 74% yield and ≥ 20:1 diastereomeric ratio after desilylation. An examination of the imine scope demonstrates that the reaction proceeds in good yields in the presence of both electron deficient (entries 2 and 3) and electron rich (entries 4 and 5) aromatic systems. We have also incorporated a third substituent with the use of α-substituted amides (**II-97** and **II-98**), isolating the α-substituted γ-amino-β-hydroxy amides with excellent levels of diastereoselection (entries 6-8).

Table 2-5. Diastereoselective homoenolate additions to *N*-phosphinoyl imines



II-43, II-97, II-98 **II-44** **II-99 to II-103** **II-104 to II-111**

entry	amide		imine		product		yield (%)	dr[b]
1		**II-43**		**II-99**		**II-104**	74	>20:1
2		**II-43**		**II-100**		**II-105**	71	>20:1
3		**II-43**		**II-101**		**II-106**	70	>20:1
4		**II-43**		**II-102**		**II-107**	71	>20:1
5		**II-43**		**II-103**		**II-108**	80	>20:1
6		**II-97**		**II-99**		**II-109**	84	>20:1
7		**II-97**		**II-101**		**II-110**	78	>20:1
8		**II-98**		**II-99**		**II-111**	75	>20:1

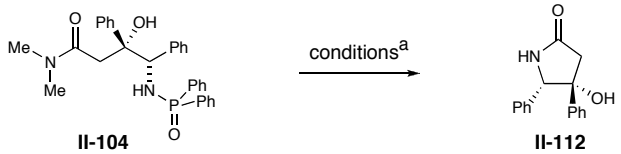
a. Acylsilane and electrophile added to a 0.1 M enolate solution in THF at -78 °C. Silyl ether products treated with *n*-Bu_4NF in THF prior to purification. b. Determined by ^1H NMR spectroscopy.

2.5.3 Synthesis of γ-Lactams

The diastereoselective multi-component addition reaction with imines provided the impetus to develop a general γ-lactam synthesis. Initial attempts to afford simultaneous deprotection and cyclization of γ-amino-β-hydroxy amide **II-104** to the corresponding γ-lactam under Lewis acidic conditions were uneventful, even at refluxing temperatures (Table 2-6, entries 1-4). Given the precedence for

diphenylphosphorylamine deprotection under Brønsted acid conditions,[79] we attempted the cyclization employing hydrochloric acid. Prior to conducting this experiment, there was some concern that elimination of water might occur to give either the α,β- or β,γ-unsaturated γ-lactams due to the potential aromatic stabilized carbocation at the β-position. Surprisingly, no elimination was observed, and desired γ-lactam **II-112** was recovered in excellent yield at ambient temperatures (entry 5). Unfortunately the formation of γ-lactam **II-112** under these conditions required long reaction times (2 days) and the necessity of large amounts of concentrated hydrochloric acid. Conducting the reaction at reflux provided notable rate enhancement, with no product decomposition or elimination of the β-hydroxyl group (entry 6). Gratifyingly, the use of microwave irradiation promoted the concomitant deprotection and lactam formation in only 5 minutes. Furthermore, the concentration of acid could be reduced to 3 M without loss of reactivity.

Table 2-6. γ-Lactam formation



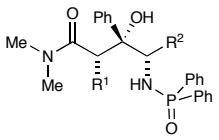
II-104 **II-112**

entry	conditions	temp. (°C)	time	yield (%)	dr
1	$BF_3{\cdot}OEt_2/CH_2Cl_2$	23	24 h	0[b]	—
2	$Sc(OTf)_2$/toluene[c]	115	24 h	0[b]	—
3	$Zn(OTf)_2$/toluene[c]	115	24 h	0[b]	—
4	$Cu(OTf)_2$/toluene[c]	115	24 h	0[b]	—
5	conc. HCl/THF	23	48 h	92	>20:1[d]
6	conc. HCl/THF	70[e]	17 h	96	>20:1[d]
7	conc. HCl/THF	150[f]	5 min	98	>20:1[d]
8	3 M HCl/THF	150[f]	5 min	98	>20:1[d]
9	2 M HCl/THF	150[f]	30 min	73[g]	>20:1[d]

a. A 0.1 M to 0.5 M solution of the amide in solvent. b. No reaction. c. Reaction also conducted in CH_2Cl_2: no reaction d. Determined by ^1H NMR spectroscopy. e. Reflux. f. Microwave irradiation. g. Incomplete conversion.

The optimized conditions developed permit the hydrolysis of the diphenylphosphoryl amide and resulting cyclization of the amines to form the β-hydroxy-γ-lactams in a single efficient operation (Table 2-6). Various dimethylacetamide derived γ-amino-β-hydroxy amides (R = H) cyclize in 5 minutes at 150 °C (condition A) to afford the corresponding γ-substituted β-hydroxy-γ-lactams in excellent yields, with retention of stereochemistry (entries 1-4). By decreasing the reaction temperature (condition B), the cyclization of 2-furyl amide **II-108** can be obtained without decomposition (entries 5 and 6). The α-methyl substituted γ-amino-β-hydroxy amide **II-109** provides the desired α-methyl-γ-lactam in high yield with the higher temperature conditions (A), but with inversion of stereochemistry at the α-position (entry 7). Fortunately, the lower temperature of condition B provides the corresponding α-substituted β-hydroxy-γ-lactams in excellent yield with stereochemical retention (entries 8-10).

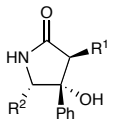
Table 2-7. γ-Lactam formationscope



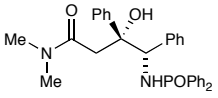
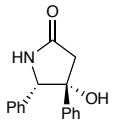
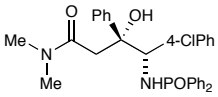
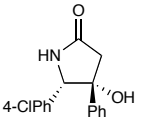
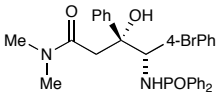
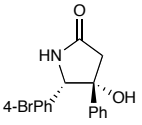
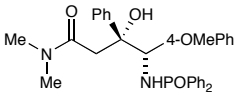
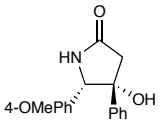
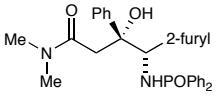
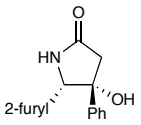
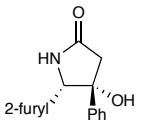
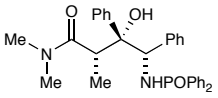
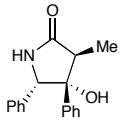
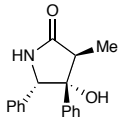
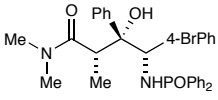
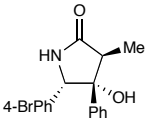
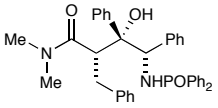
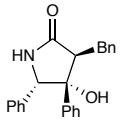
II-104 to II-111

3 M HCl/THF[a]

microwave irradiation



II-112 to II-119

entry	amide		conditions	product		yield (%)	dr[b]
1		**II-104**	**A**: 150 °C 1:1 3 M HCl/THF		**II-112**	98	>20:1
2		**II-105**	**A**		**II-113**	97	>20:1
3		**II-106**	**A**		**II-114**	93	>20:1
4		**II-107**	**A**		**II-115**	94	>20:1
5		**II-108**	**A**		**II-116**	0[c]	–
6		**II-108**	**B**: 70 °C 2:1 3 M HCl/THF		**II-116**	97	>20:1
7		**II-109**	**A**		**II-117**	92	1:4
8		**II-109**	**B**		**II-117**	96	>20:1
9		**II-110**	**B**		**II-118**	98	>20:1
10		**II-111**	**B**		**II-119**[d]	90	>20:1

a. A 0.1 M solution of the amide in THF/3M aqueous HCl was heated utilizing microwave irradiation. b. Determined by ^{1}H NMR spectroscopy. c. Decomposition. d. Bn = CH_2Ph

The relative stereochemistry of β-hydroxy-γ-lactam **II-114** was determined by single-crystal X-ray diffraction (Figure 2-7), and β-hydroxy-γ-lactams **II-112**, **II-113**, **II-15**, and **II-16** were assigned by analogy.

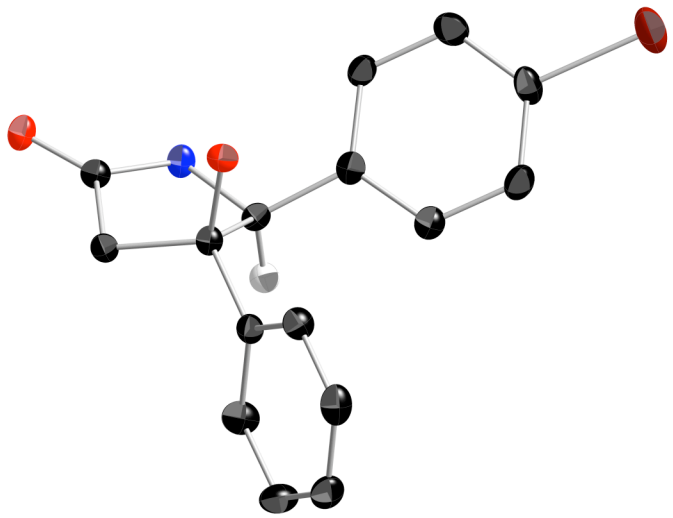


Figure 2-7. ORTEP representation of the crystal structure of β-hydroxy amide **II-114**. Thermal ellipsoids are drawn at 50% probability. Hydrogen atoms have been omitted for clarity.

The relative stereochemistry of α-methyl-β-hydroxy-γ-lactam **II-118** was determined by ^{1}H NOE (nuclear Overhauser enhancement) NMR spectroscopy (Figure 2-8). The relative stereochemistry of β-hydroxy-γ-lactams **II-117** and **II-119** were assigned by analogy.

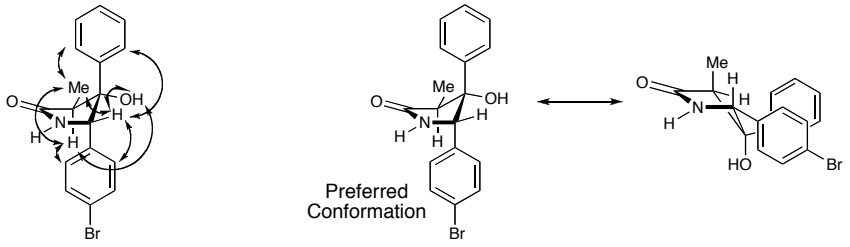


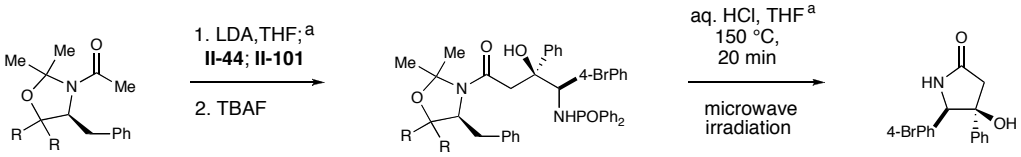
Figure 2-8. ^{1}H NOE NMR spectroscopy to assign the relative stereochemistry of α-methyl-β-hydroxy-γ-lactam **II-118**

2.5.4 Auxiliary Controlled Homoenolate Additions to Imines

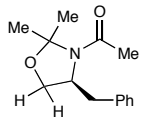
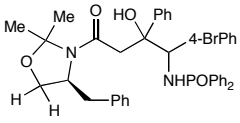
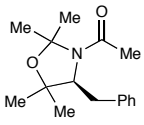
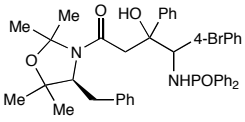
We investigated combining our previously discovered diastereoselective auxiliary controlled process (Section 2.4.4.3) with the aforementioned diastereoselective synthesis of highly substituted β-hydroxy-γ-lactams in an effort to control the absolute stereochemistry of the latter process (Table 2-8). Towards this end, the use of chiral acetamide **II-79** in the reaction described above with diphenylphosophoryl imine **II-101** as the electrophile, provides γ-lactam **II-114**, albeit with no absolute stereochemical control (entry 1). γ-Amino-β-hydroxy amide intermediate **II-119/II-120** was not isolated for these initial studies to ensure that the enantioselectivity of γ-lactam **II-114** was not modified due to inexact recovery of both diastereomers of **II-119/II-120** during the purification process. Conducting the experiment again with amide **II-79**, this time with an "equilibration" at 0 °C prior to addition of imine **II-101**, gives a moderate selectivity for the formation of **II-114** (entry 2). Further studies and mechanistic explanation of this reaction modification are described in further detail below. Continuing with our optimization survey of this homoenolate process, a similar trend was observed with amide **II-80** (entries 3 and 4), ultimately providing γ-lactam **II-114** with high

enantiomeric access (87% ee, entry 4). The γ-amino-β-hydroxy amide intermediate (**II-120**) was also isolated in good yield and high diastereoselectivity. Cyclization of isolated amide **II-120** generated optically active γ-lactam **II-114** in 92% yield and 87% ee. The enantioselectivity was determined by HPLC analyis on a chiracel OD-H column. Interestingly, typical hydrolysis of this sterically-hindered oxazolidine auxiliary requires forcing conditions (refluxing 6M H_2SO_4 in AcOH). With our products, hydrolysis of the oxazolidine under these conditions has led to elimination of the β-hydroxy functionality. The microwave irradiation protocol presented represents a more mild (3M HCl in THF) and efficient removal of this auxiliary.

Table 2-8. Enantioenriched β-hydroxy-γ-lactams



II-79, II-80 **II-119, II-120** **II-114**

entry	acetamide		temperature	γ-amino-β-hydroxy amide		yield (%)	dr[b]	**II-114** yield (%)	ee[c]
1		**II-79**	–78 °C		**II-119**	–	–	–	0
2		**II-79**	0 °C[d]		**II-119**	–	–	–	34
3		**II-80**	–78 °C		**II-120**	–	–	–	23
4		**II-80**	0 °C[d]		**II-120**	68	14:1	92 (63)[e]	87

a. See tables 6 and 5 for reaction details. b. Determined by ^{1}H NMR spectroscopy. c. Determined by HPLC analysis. d. Brief equilibration time at 0°C following consumption of **II-44**. e. 92% yield from **II-119**, 63% from **II-80**.

The absolute stereochemistry of enantioenriched β-hydroxy-γ-lactam **II-114** was determined by single-crystal X-ray diffraction of the corresponding 4-bromobenzoyl imide derived from **II-114** (**II-121**, Figure 2-9).

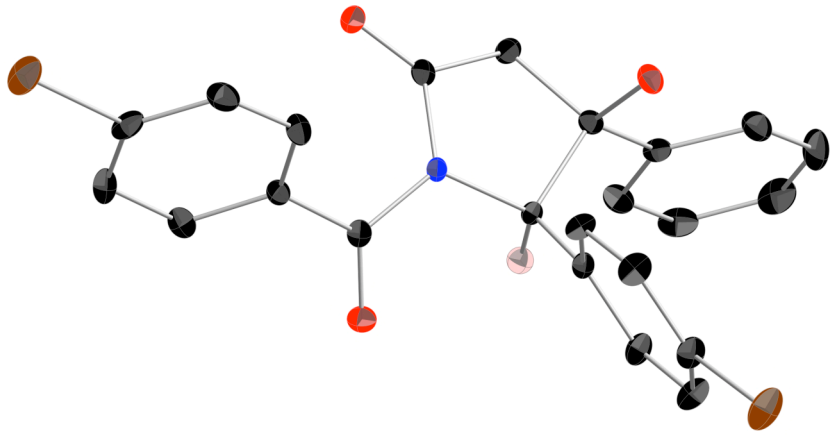


Figure 2-9. ORTEP representation of the crystal structure of the 4-bromobenzoyl imide of β-hydroxy amide **II-114** (**II-121**). Thermal ellipsoids are drawn at 50% probability. Hydrogen atoms have been omitted for clarity.

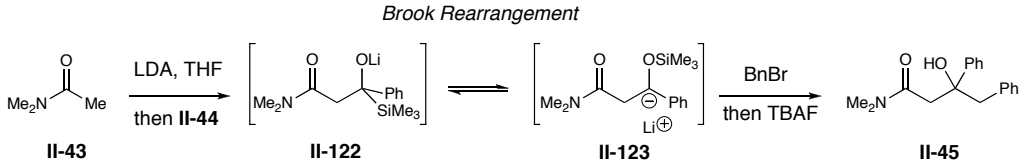
2.6 Proposed Reaction Mechanism

2.6.1 General Reaction Mechanism

As discussed, the proposed mechanism for the enolate addition to acylsilanes proceeds through a Brook rearrangement mediated pathway (Scheme 2-18). Enolate formation of the acetamide with LDA followed by addition to the acylsilane provides lithium-alkoxide intermediate **II-122**. This intermediate then undergoes a 1,2-silyl migration (Brook rearrangement) to provide active carbanion intermediate **II-123**. Suitable electron stabilizing functionality (aryl, carboxylate) is needed adjacent to this

carbanion to perturb the equilibrium to favor carbanion **II-123**. In this example, addition of carbanion **II-123** to benzylbromide proceeds to give β-hydroxy amide **II-45**, following desilylation.

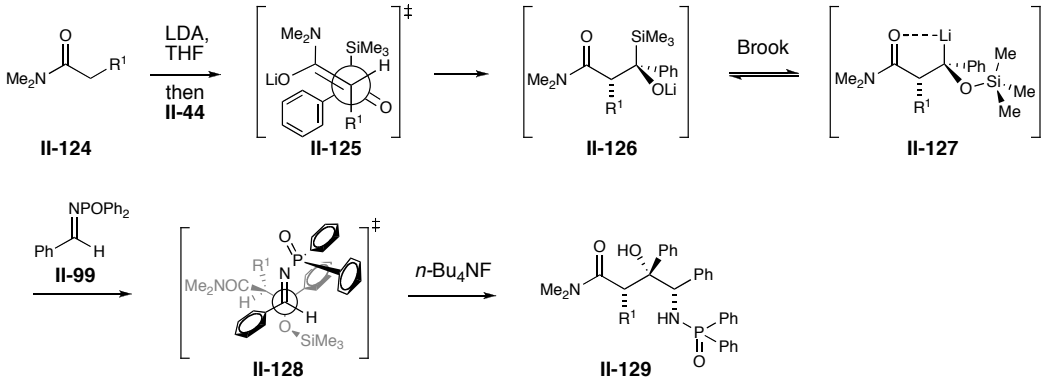
Scheme 2-18. General mechanism



2.6.2 Diastereoselective Homoenolate Additions to Imines

The general mechanism can be applied to explain the diastereoselective homoenolate additions to imines (Scheme 2-19). The current model involves the diastereoselective addition of the *Z*-enolate of amide **II-124** to acylsilane **II-44** and subsequent stereospecific 1,2-Brook rearrangement to give internally coordinated carbanion intermediate **II-127**. Subsequent electrophilic approach of imine **II-99** occurs by open transition-state **II-128** to alleviate the non-bonding interactions between the diphenylphosphoryl group of the imine and the silyloxy group of the homoenolate to yield γ-amino-β-hydroxy amide **II-129**. The overall process generates up to three contiguous stereogenic centers in a single operation with a high degree of control.

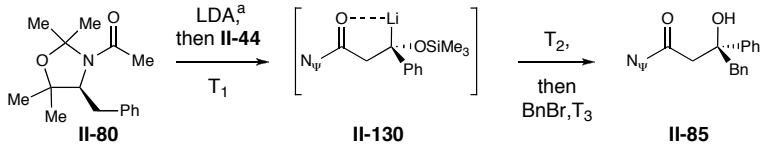
Scheme 2-19. Diastereoselective homoenolate addition to imines



2.6.3 Auxiliary Controlled Reactions

As noted earlier, drastic differences in diastereoselectivity are observed under kinetic and thermodynamic reaction conditions when chiral amides are used. Further analysis of the effects of temperature on the observed diastereoselectivity of this reaction was investigated (Table 2-9). When the entire reaction procedure is carried out at –78 °C, the observed diastereoselectivity for the addition process to benzyl bromide is 3:1 (entry 1). Conversely, when the entire reaction is conducted at 0 °C, an increase in diastereoselectivity to 10:1 is observed (entry 2). Importantly, high levels of stereoselectivity are also observed when only initial homoenolate intermediate **II-130** is warmed to 0 °C for 15 minutes, indicating the need for an equilibration process to generate the most stable carbanion intermediate.

Table 2-9. Effect of temperature on diastereoselectivity



II-80 **II-130** **II-85**

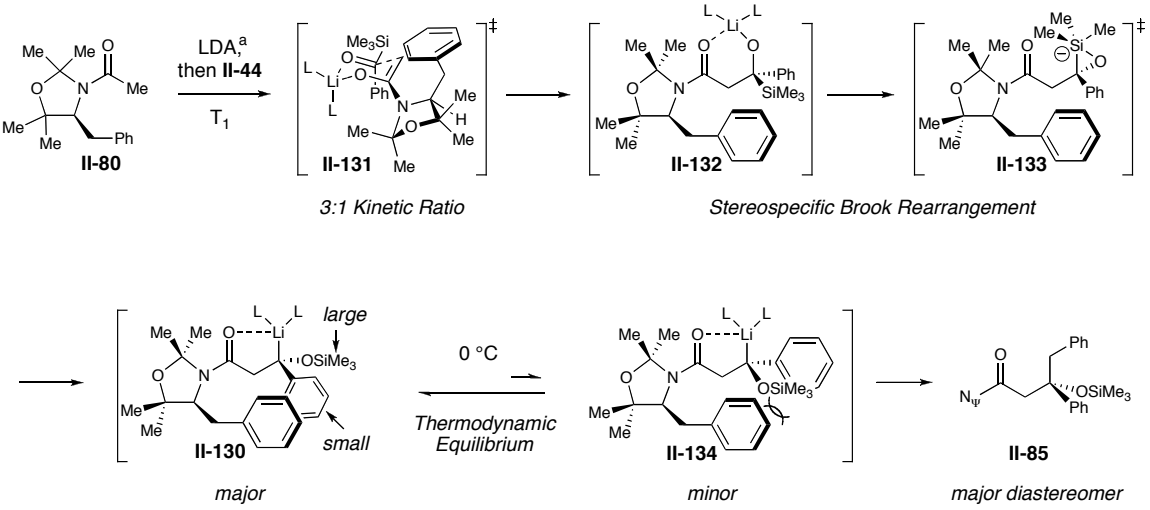
entry	T_1(°C)	T_2(°C)[b]	T_3(°C)	yield (%)	dr[c]
1	−78	−78	−78	80	3:1
2	0	0	0	79	10:1
3	−78	0	−78	79	10:1

a. Acylsilane and electrophile sequentially added to a 0.2 M enolate solution in THF. Silyl ether products treated with n-Bu_4NF in THF prior to purification. b. Reaction temp. after consumption of **II-44** and before the addition of R-X. c. Determined by ^{1}H NMR spectroscopy.

Based on the unusual temperature to diastereoselectivity relationship and the current understanding of 1,2-silyl migrations, we have proposed a mechanism that accounts for the observed stereochemistry (Scheme 2-20). The current model for diastereoselection involves enolate addition to acylsilane **II-44** through Zimmerman-Traxler transition state **II-131**, minimizing non-bonding interactions between the trimethylsilyl group and the auxiliary. This initial enolate addition lends way to the observed 3:1 ratio of products under kinetic conditions (–78 °C). Subsequent Brook rearrangement with stereochemical retention[83] occurs to give internally coordinated diastereomers **II-130** (major) and **II-134** (minor). Strongly coordinating additives (e.g. DMPU, HMPA) reduce the diastereoselectivity and yield of the reactions, supporting the proposed internal coordination of the amide carbonyl to the β-organolithium. Furthermore, *O*-alkylation is not observed when the reactions are conducted at –78 or 0 °C, suggesting that the Brook rearrangement occurs rapidly to generate carbanions **II-130/II-134**. The unusual inverse relationship of selectivity on temperature suggests that performing the reaction under thermodynamically-controlled conditions (0 °C) facilitates interconversion of **II-130/II-134** prior to alkylation. Since carbanion **II-134** is

destabilized by non-bonded interactions between the trimethylsilylether and benzyl group of the auxiliary, the reaction preferentially proceeds via intermediate **II-130** to give the β-hydroxy amide, following desilylation. Additionally, further stabilization of intermediate **II-130** might occur through possible π-stacking interactions between the phenyl substituent at the β-position and the phenyl ring of the oxazolidine auxiliary.

Scheme 2-20. Mechanism for the diastereoselective homoenolate addition to imines



2.7 Summary

A new strategy has been developed for the synthesis of tertiary β-hydroxy amides using β-silyloxy homoenolates accessed from amide enolates and acylsilanes. These unconventional nucleophilic species undergo addition to alkyl halides, aldehydes, ketones, and imines. Importantly, amide enolates strongly favor *C*-alkylation of the homoenolate over *O*-alkylation and avoid the formation of alkoxy cyclopropanes. Homoenolate addition to imines provides the γ-amino-β-hydroxy amides in a single flask operation with good yields and excellent selectivity for each newly formed stereocenter.

The use of microwave irradiation under acidic conditions promotes hydrolysis and cyclization to form the corresponding γ-lactams in excellent yields with retention of stereochemistry. Furthermore, the utilization of chiral acetamides allows for absolute stereochemical control of the tertiary alcohol and subsequent γ-lactam products. This new method, using acylsilanes and the power of the 1,2-Brook rearrangement to access synthetically useful homoenolate reactivity, is a noteworthy addition to *Umpolung* strategies.

2.8 Experimental

General Information. All reactions were carried out under a nitrogen atmosphere in flame-dried glassware with magnetic stirring. THF was purified by passage through a bed of activated alumina.[84] Reagents were purified prior to use unless otherwise stated following the guidelines of Perrin and Armarego.[85] Microwave reactions were carried out using a Biotage Initiator, SW version 1.2. Purification of reaction products was carried out by flash chromatography using EM Reagent silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and/or ceric ammonium nitrate stain followed by heating. Infrared spectra were recorded on a Perkin Elmer 1600 series FT-IR spectrometer. ^{1}H-NMR spectra were recorded on a Varian Inova 500 (500 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data are reported as (ap = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad; coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C-NMR spectra were recorded on a Varian Inova 500 (125 MHz)

spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.0 ppm). Mass spectra data were obtained on a Varian 1200 Quadrupole Mass Spectrometer and Micromass Quadro II Spectrometer.

2.8.1 Preparation of Acylsilanes

Aryl acylsilanes (**II-44**, **II-53** to **II-57**) were prepared according to the procedure of Yamamoto and coworkers.[36] Acetyltrimethylsilane (**II-63**) was purchased from Sigma-Aldrich, and purified by distillation prior to use. Alkyl acylsilanes (**II-64** and **II-65**) were prepared using the procedure developed in the Scheidt laboratory.[37,38] *tert*-Butyl silylglyoxylate (**II-66**) was preprared using the procedure of Nicewicz and Johnson.[43]

2.8.1.1 Representative Procedure for the Synthesis of Aryl Acylsilanes

To an oven-dried 50 mL round-bottom flask equipped with a magnetic stirring bar was charged allyl palladium chloride dimer (1.37 mmol, bright yellow solid), triethylphosphite (8.17 mmol), and hexamethyldisilane (56.7 mmol). A rubber septum was added, and the bright yellow mixture was stirred for 5 minutes under a positive pressure of nitrogen. To the reaction mixture was added distilled benzoyl chloride (54.3 mmol). The flask was fitted with a condensor and the reaction mixture was heated to 110 °C for 24 hours. The resulting mixture was cooled to ambient temperature, diluted with 20% dichloromethane in hexanes, and directly subjected to flash column chromatography (R_f = 0.35; 20% dichloromethane in hexanes; 7 cm diameter column, 400 mL silica gel, 30 mL fractions). The product is a bright yellow oil, that can be distilled to further purification by Kugelrohr distillation.

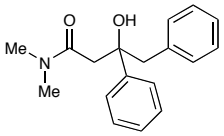
2.8.2 Homoenolate Additions to Alkyl Halides, Aldehydes, and Ketones

2.8.2.1 Representative Procedure for the Synthesis of β-Hydroxy Amides II-45 to II-52, II-58 to II-62 and II-66

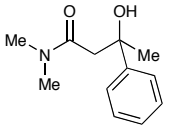
To a flame-dried, round bottom flask equipped with a magnetic stirring bar and purged with nitrogen was added THF (2 mL) and diisopropylamine (0.79 mmol). The solution was cooled to –78 °C and *n*-butyllithium (1.5 M in hexanes, 0.73 mmol) was added by syringe. The reaction was warmed to 0 °C, stirred for 30 minutes, then recooled to –78 °C. Dimethylacetamide (0.84 mmol) was added dropwise to the LDA solution and the reaction was warmed to 0 °C. After stirring at 0 °C for one hour, the reaction was cooled to –78 °C and a –78 °C solution of the acylsilane (0.56 mmol) in THF (0.5 mL) was added via cannula. The acylsilane delivery flask was rinsed with an additional portion of THF (0.5 mL) and this rinse was transferred to the reaction flask. The resulting homogeneous solution was stirred for 30 minutes after which time a solution of the electrophile (1.68 mmol) in THF (0.5 mL) was added via cannula, again rinsing the delivery flask with an additional portion of THF (0.5 mL). The reaction was warmed slowly to ambient temperature over six hours, and then stirred for an additional 6 hours at the same temperature. The reaction was quenched by the addition of saturated aqueous ammonium chloride and extracted with ethyl acetate (x3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The unpurified silyl ether product was dissolved in THF (2 mL). To this solution was added tetrabutylammonium fluoride (1.0 M in THF, 1.68 mmol) and the mixture was stirred at room temperature for 30 minutes. The reaction was quenched by the addition of water, extracted with ethyl acetate (x3), dried over anhydrous magnesium sulfate,

filtered, and concentrated by evaporation. The resulting residue was purified by flash column chromatography on silica gel.

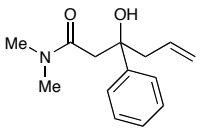
2.8.2.2 Characterization of β-Hydroxy Amides II-45 to II-52, II-58 to II-62 and II-66



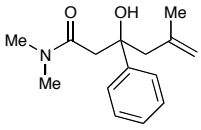
3-Hydroxy-*N*,*N*-dimethyl-3,4-diphenylbutanamide (II-45): Purified with 30% ethyl acetate/hexanes, yielding 136 mg (86%) of **II-45** as a white solid. R_f = 0.42 (50:50 ethyl acetate/hexanes); mp = 114-115 °C; IR (film) 3291, 3055, 3028, 2922, 1612, 1489, 1423, 1149, 694 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38-7.20 (m, 8H), 7.04-7.02 (m, 2H), 6.21 (s, 1H), 3.15-3.05 (m, 3H), 2.96 (s, 3H), 2.83 (s, 3H), 2.65 (d, 1H, *J* = 16.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 146.6, 137.2, 131.0, 128.2, 127.9, 126.8, 126.6, 125.5, 75.8, 50.1, 40.8, 37.6, 35.4; LRMS (ESI): Mass calculated for $C_{18}H_{21}NO_2$ $[M+H]^+$, 284.2. Found $[M+H]^+$, 284.4, $[M+Na]^+$, 306.6.



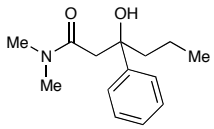
3-Hydroxy-*N*,*N*-dimethyl-3-phenylbutanamide (II-46): Purified with 20% acetone/hexanes, yielding 90 mg (77%) of **II-46** as a white solid. R_f = 0.51 (40:60 acetone/hexanes); mp = 85-87 °C; IR (film) 3338, 2975, 2931, 1618, 1495, 1398, 1161, 1065, 767, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46-7.45 (m, 2H), 7.34-7.31 (m, 2H), 7.23-7.20 (m, 1H), 6.12 (bs, 1H), 2.98 (d, 2H, *J* = 15.5 Hz), 2.93 (s, 3H), 2.85 (s, 3H), 2.65 (d, 2H, *J* = 16.0 Hz), 1.56 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 148.1, 128.4, 126.8, 124.7, 73.1, 43.7, 37.6, 35.4, 30.9; LRMS (ESI): Mass calculated for $C_{12}H_{17}NO_2$ $[M+H]^+$, 208.1. Found $[M+H]^+$, 208.4, $[M+Na]^+$, 230.6.



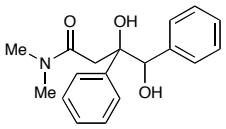
3-Hydroxy-*N*,*N*-dimethyl-3-phenylhex-5-enamide (II-47): Purified with 20% ethyl acetate/hexanes, yielding 90 mg (68%) of **II-47** as a white solid. R_f = 0.42 (30:70 ethyl acetate/hexanes); mp = 53-54 °C; IR (film) 3330, 3067, 3021, 2932, 1623, 1495, 1400, 1158, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42-7.41 (m, 2H), 7.33-7.30 (m, 2H), 7.22-7.21 (m, 1H), 6.15 (s, 1H), 5.75-5.68 (m, 1H), 5.05-5.01 (m, 2H), 2.97 (d, 1H, *J* = 16.0 Hz), 2.94 (s, 3H), 2.82 (s, 3H), 2.68 (d, 1H, *J* = 16.0 Hz), 2.59-2.56 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 146.6, 134.1, 128.3, 126.8, 125.2, 118.2, 75.0, 48.1, 41.5, 37.6, 35.4; LRMS (ESI): Mass calculated for $C_{14}H_{19}NO_2$ $[M+H]^+$, 234.1. Found $[M+H]^+$, 234.4, $[M+Na]^+$, 256.6.



3-Hydroxy-*N*,*N*,5-trimethyl-3-phenylhex-5-enamide (II-48): Purified with 30% ethyl acetate/hexanes, yielding 107 mg (77%) of **II-48** as a white solid. R_f = 0.32 (30:70 ethyl acetate/hexanes); mp = 83-85 °C; IR (film) 3289, 2917, 2849, 1614, 1444, 1396, 1313, 1256, 1154, 1110, 880, 770, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44-7.42 (m, 2H), 7.32-7.29 (m, 2H), 7.22-7.19 (m, 1H), 6.13 (s, 1H), 4.79 (s, 1H), 4.63 (s, 1H), 3.00 (d, 1H, *J* = 15.5 Hz), 2.94 (s, 3H), 2.81, (s, 3H), 2.72 (d, 1H, *J* = 16.0 Hz), 2.55 (d, 2H, *J* = 4.0 Hz), 1.62 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 147.0, 142.8, 128.2, 126.7, 125.3, 115.1, 75.5, 51.4, 41.8, 37.6, 35.4, 24.5; LRMS (ESI): Mass calculated for $C_{15}H_{21}NO_2$ $[M+]^+$, 248.2. Found $[M+H]^+$, 248.5, $[M+Na]^+$, 270.5.

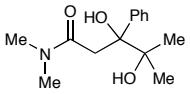


3-Hydroxy-*N*,*N*-dimethyl-3-phenylhexanamide (II-49): Purified with 40% ethyl acetate/hexanes, yielding 91 mg (69%) of **II-49** as a white solid. R_f = 0.68 (50:50 ethyl acetate/hexanes); mp = 73-75 °C; IR (film) 3338, 2957, 2932, 1621, 1495, 1448, 1399, 1161, 767, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42-7.41 (m, 2H), 7.34-7.31 (m, 2H), 7.22-7.20 (m, 1H), 6.08 (s, 1H), 2.98 (d, 1H, *J* = 15.5 Hz), 2.95 (s, 3H), 2.82 (s, 3H), 2.65 (d, 1H, *J* = 15.5 Hz), 1.87-1.81 (m, 1H), 1.78-1.72 (m, 1H), 1.43-1.37 (m, 1H), 1.07-1.02 (m, 1H), 0.83 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 146.8, 128.3, 126.6, 125.3, 75.4, 45.7, 42.8, 37.6, 35.4, 16.9, 14.6; LRMS (ESI): Mass calculated for $C_{14}H_{21}NO_2$ $[M+H]^+$ 236.2. Found $[M+H]^+$, 236.3, $[M+Na]^+$, 258.5

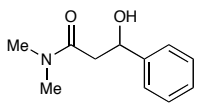


3,5-Dihydroxy-*N*,*N*-dimethyl-3,4-diphenylbutanamide (II-50): Purified with 50% ethyl acetate/hexanes, yielding 67 mg (40%) of one diastereomer of **II-50** as a white solid, and yielding 69 mg (41 %) of the second diastereomer of **II-50** as a white solid. R_f = 0.50, 0.29 (75:25 ethyl acetate/hexanes); diastereomer 1 mp = 164-166 °C, diastereomer 2 mp = 163-165 °C; IR (film) diasteromer 1: 3391, 3060, 3031, 2927, 1623, 1496, 1152, 1056 cm^{-1}; diastereomer 2: 3448, 3059, 3028, 2917, 1611, 1491, 1420, 1400, 1152, 1072; ^1H NMR (500 MHz, $CDCl_3$) diastereomer 1: δ 7.28-7.15 (m, 8H), 6.93-6.92 (m, 2H), 6.79 (s, 1H), 4.75 (s, 1H) 3.65 (s, 1H) 2.99 (s, 3H), 2.95 (d, 2H, *J* = 4.5 Hz), 2.83 (s, 3H); diastereomer 2: δ 7.40-7.12 (m, 8H), 7.04-7.02 (m, 2H), 6.52 (bs, 1H) 4.76 (s, 1H), 3.36 (bs, 1H), 3.19 (d, 1H, *J* = 16.5 Hz), 3.02-2.97 (m, 4H), 2.83 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) diastereomer 1: δ 173.1, 143.3, 138.2, 128.1(x2), 127.9, 127.6, 126.6, 81.3, 78.7, 37.6, 35.5, 34.0;

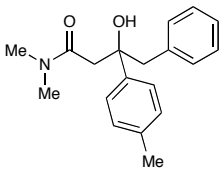
diastereomer 2: 173.0, 143.2, 139.5, 128.1, 128.0, 127.6, 127.2, 126.1, 80.4, 78.4, 38.5, 37.7, 35.6; LRMS (ESI): Mass calculated for $C_{18}H_{21}NO_3$ $[M+H]^+$, 300.2. Found for diastereomer 1 $[M+H]^+$, 300.6, $[M+Na]^+$, 322.7; diastereomer 2 $[M+H]^+$, 300.5, $[M+Na]^+$, 322.6.



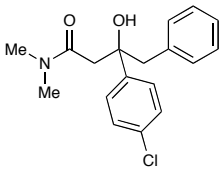
3,4-dihydroxy-*N*,*N*,4-trimethyl-3-phenylpentanamide (II-51): Purified with 50% ethyl acetate/hexanes, yielding 110 mg (78%) of **II-51** as a pale yellow solid. R_f = 0.36 (50:50 ethyl acetate/hexanes); IR (film) 3446, 2977, 2932, 1696, 1622, 1559, 1496, 1418, 1398, 1261, 1142, 1065, 1022, 946, 762, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.51-7.49 (m, 2H), 7.33-7.30 (m, 2H), 7.25-7.24 (m, 1H), 6.68 (s, 1H), 3.38 (d, 1H, *J* = 16.0 Hz), 3.09 (s, 3H), 2.96 (d, 1H, *J* = 16.0 Hz), 2.91 (s, 1H), 2.81 (s, 3H), 1.20 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 143.9, 127.9, 127.0, 126.7, 80.0, 75.1, 37.7, 35.5, 35.4, 25.0, 23.9; LRMS (ESI): Mass calculated for $C_{14}H_{21}NO_3$ $[M+H]^+$, 252.2. Found $[M+H]^+$, 252.5, $[M+Na]^+$, 274.6.



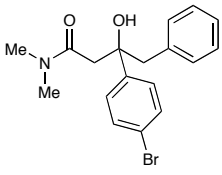
3-hydroxy-*N*,*N*-dimethyl-3-phenylpropanamide (II-52): Purified with 50% ethyl acetate/hexanes, yielding 87 mg (80%) of **II-52** as a yellow oil. R_f = 0.21 (50:50 ethyl acetate/hexanes); IR (film) 3397, 3029, 2928, 1626, 1496, 1453, 1419, 1399, 1262, 1144, 1061, 1022, 758 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40-7.39 (m, 2H), 7.36-7.33 (m, 2H), 7.31-7.26 (m, 1H), 5.13 (d, 1H, *J* = 9.0 Hz), 4.86 (s, 1H), 2.97 (s, 3H), 2.92 (s, 3H), 2.70-2.58 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 143.3, 128.7, 127.7, 126.0, 70.6, 42.2, 37.3, 35.5; LRMS (ESI): Mass calculated for $C_{11}H_{15}NO_2$ $[M+H]^+$, 194.1. Found $[M+H]^+$, 194.3, $[M+Na]^+$, 216.6.



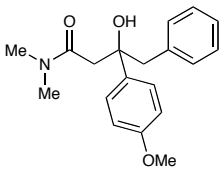
3-Hydroxy-*N*,*N*-dimethyl-4-phenyl-3-*p*-tolylbutanamide (II-58): Purified with 30% ethyl acetate/hexanes, yielding 122 mg (73%) of **II-58** as a white solid. R_f = 0.50 (50:50 ethyl acetate/hexanes); mp = 163-165 °C; IR (film) 3311, 3027, 2922, 1619, 1495, 1399, 1146, 694 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30-7.19 (m, 5H), 7.13-7.11 (m, 2H), 7.06-7.04 (m, 2H), 6.16 (s, 3H), 3.12 (d, 1H, *J* = 13.0 Hz), 3.07-3.02 (m, 2H), 2.95 (s, 3H), 2.83 (s, 3H), 2.62 (d, 1H, *J* = 16.0 Hz), 2.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 143.7, 137.4, 136.3, 131.1, 128.9, 127.9, 126.5, 125.3, 75.7, 50.2, 40.8, 37.6, 35.4, 21.3; LRMS (ESI): Mass calculated for $C_{19}H_{23}NO_2$ $[M+H]^+$, 298.2. Found $[M+H]^+$, 298.4, $[M+Na]^+$, 320.6.



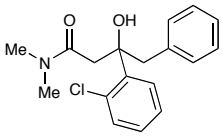
3-(4-Chlorophenyl)-3-hydroxy-*N*,*N*-dimethyl-4-phenylbutanamide) (II-59): Purified with 30% ethyl acetate/hexanes, yielding 122 mg (73%) of **II-59** as a white solid. R_f = 0.35 (50:50 ethyl acetate/hexanes); mp = 164-165 °C; IR (film) 3310, 3055, 3028, 2918, 1612, 1490, 1400, 1150, 1089, 1011, 880, 832, 694, 621 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.20-7.19 (m, 2H), 7.00-6.99 (m, 2H), 6.22 (s, 1H), 3.09-3.01 (m, 3H), 2.97(s, 3H), 2.83 (s, 3H), 2.65 (d, 1H, *J* = 16.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 145.3, 136.8, 132.6, 131.0, 128.3, 128.0, 127.0, 126.7, 75.5, 50.0, 40.8, 37.6, 35.5 ; LRMS (ESI): Mass calculated for $C_{18}H_{20}ClNO_2$ $[M+H]^+$, 318.1. Found $[M+H]^+$, 318.4.



3-(4-Bromophenyl)-3-hydroxy-*N*,*N*-dimethyl-4-phenylbutanamide (II-60): Purified with 30% ethyl acetate/hexanes, yielding 140 mg (69%) of **II-60** as a yellow oil. R_f = 0.39 (50:50 ethyl acetate/hexanes); mp = 170-171 °C; IR (film) 3026, 2923, 2361, 2337, 1734, 1700, 1653, 1623, 1559, 1507, 1457, 1419, 1147, 700, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42-7.40 (m, 2H), 7.22-7.20 (m, 5H), 7.01-6.99 (m, 2H), 6.21 (s, 1H), 3.09-3.01 (m, 3H), 2.97 (s, 3H), 2.83 (s, 3H), 2.64 (d, 1H, *J* = 16.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 145.8, 136.7, 131.2, 131.0, 128.0, 127.4, 126.7, 120.8, 75.6, 50.0, 40.7, 37.6, 35.5; LRMS (ESI): Mass calculated for $C_{18}H_{20}BrNO_2$ $[M+H]^+$, 362.1. Found $[M+H]^+$, 362.3.



3-Hydroxy-3-(4-methoxyphenyl)-*N*,*N*-dimethyl-4-phenylbutanamide (II-61): Purified with 30% ethyl acetate/hexanes, yielding 152 mg (75%) of **II-61** as a white solid. R_f = 0.29 (40:60 ethyl acetate/hexanes); mp = 151-152 °C; IR (film) 3303, 3028, 2931, 1617, 1511, 1399, 1248, 1178, 1147, 1032 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26-7.24 (m, 2H), 7.20-7.19 (m, 3H), 7.02-7.00 (m, 2H), 6.84-6.82 (m, 2H), 6.17 (s, 1H), 3.80 (s, 3H), 3.12-3.00 (s, 3H), 2.95 (s, 3H), 2.83 (s, 3H), 2.62 (d, 1H, *J* = 16.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 158.4, 138.7, 137.3, 131.0, 127.9, 126.6, 126.5, 113.5, 75.5, 55.4, 50.3, 40.8, 37.6, 35.5; LRMS (ESI): Mass calculated for $C_{19}H_{23}NO_3$ $[M+H]^+$, 314.2. Found $[M+H]^+$, 314.3, $[M+Na]^+$, 336.6.



3-(2-Chlorophenyl)-3-hydroxy-*N*,*N*-dimethyl-4-phenylbutanamide (II-62): Purified with 30% ethyl acetate/hexanes, yielding 120 mg (67%) of **II-62** as a white solid. R_f = 0.58 (40:60 ethyl acetate/hexanes); mp = 56-59 °C; IR (film) 3280, 3062, 3029, 2926, 1623, 1495, 1454, 1340, 1149, 1033, 762, 727, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.77-7.75 (m, 1H), 7.33-7.31 (m, 1H), 7.19-7.12 (m, 7H), 6.64 (s, 1H), 3.84 (d, 1H, *J* = 16.5 Hz), 3.42 (d, 1H, *J* = 14.0 Hz), 3.33 (d, 1H, *J* = 13.5 Hz), 3.00 (s, 3H), 2.78 (s, 3H), 2.67 (d, 1H, *J* = 16.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 142.7, 137.3, 131.0 (x2), 130.3, 129.9, 128.7, 127.9, 127.3, 126.5, 76.2, 45.2, 38.8, 37.7, 35.5; LRMS (ESI): Mass calculated for $C_{18}H_{20}ClNO_2$ $[M+H]^+$, 318.1. Found $[M+H]^+$, 318.5, $[M+Na]^+$, 340.6.

2.8.3 Preparation of Chiral Acetamides

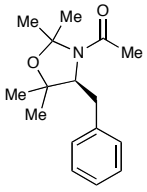
N-acyl oxazolidinone **II-77** was prepared according to the procedure of Gage and Evans.[54] *N*-acyl oxazolidinone **II-78** was prepared according to the procedure of Davies, Sanganee, and Szolcsanyi.[55] *N*-acyl oxazolidines **II-79** and **II-80** were prepared according to the procedure of Kanemasa and Onimura.[56,57]

2.8.3.1 Preparation of N-Acyl Oxazolidine II-80

A round bottom flask equipped with a stirbar was charged with (*S*)-3-amino-2-methyl-4-phenylbutan-2-ol (16.7 mmol), acetone (50 mL), and magnesium sulfate (5 g). The resulting mixture was stirred for 30 minutes. The solution was filtered and concentrated by evaporation. The unpurified heterocycle was dissolved in methylene chloride (60 mL) and cooled to 0 °C in an ice/water bath. To this solution was added

triethylamine (33.4 mmol), followed by dropwise addition of acetyl chloride (33.4 mmol). The reaction was stirred for 30 minutes and quenched by the addition of saturated aqueous ammonium chloride (20 mL). The organic layer was separated, and the aqueous layer was extracted with methylene chloride (2 x 20 mL). The organic layers were combined, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel.

2.8.3.2 Characterization of N-Acyl Oxazolidine II-80



1-((*S*)-4-benzyl-2,2,5,5-tetramethyloxazolidin-3-yl)ethanone (II-80): Purified with 30% ethyl acetate/hexanes, yielding 4.4 g (95%) of **II-80** as a pale yellow solid; $[\alpha]_D$ = -177.5 (*c* = 1.0, $CHCl_3$) (*t* = 23 °C); R_f = 0.25 (30:70 ethyl acetate/hexanes); mp = 55-57 °C; IR (film) 2980, 2938, 1647, 1400, 1371, 1264, 1203, 1150, 1203, 1150, 999, 951, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31-7.16 (m, 5H), 3.78 (dd, 1H, *J* = 8.5, 6.0 Hz), 2.99 (dd, 1H, *J* = 14.0, 6.0 Hz), 2.84 (dd; ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 138.2, 129.7, 129.2, 127.1, 94.5, 80.5, 68.0, 38.7, 29.4, 29.2, 28.2, 24.3, 23.3; LRMS (ESI): Mass calculated for $C_{22}H_{23}NO_3$ $[M+H]^+$, 334.2. Found $[M+H]^+$, 334.4, $[M+Na]^+$, 356.6.

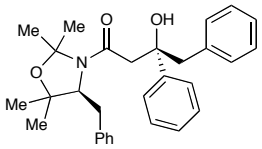
2.8.4 Asymmetric Homoenolate Additions to Alkyl Halides, Aldehydes, and Ketones

2.8.4.1 Representative Procedure for the Synthesis of β-Hydroxy Amides II-85 to II-87

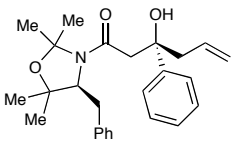
A screw-capped test tube equipped with septum and a stirbar was charged with calcium sulfate (100 mg). Calcium sulfate (Drierite, W. A. Hammond Drierite Company) was finely ground with a mortar and pestle, and heated in a beaker at 160 °C for at least 48 hours prior to use. The reaction tube and its contents were flame-dried, purged with nitrogen, and allowed to cool to ambient temperature. To this vessel was added THF (0.5 mL) and diisopropylamine (0.37 mmol). The resulting solution was cooled to –78 °C and *n*-butyllithium (1.6 M in hexanes, 0.37 mmol) was added dropwise by syringe. The reaction was warmed to 0 °C, stirred for 30 minutes, then cooled to –78 °C. To this solution of LDA was added a –78 °C solution of **II-80** (0.37 mmol) in THF (0.8 mL + 0.2 mL rinse) via cannula. The resulting reaction was warmed to 0 °C and stirred for 1 hour. To the reaction was added a cooled to 0 °C solution of **II-44** (0.280 mmol) in THF (0.3 mL) in one portion by cannula, again rinsing the delivery flask with an additional portion of THF (0.2 mL). The resulting reaction mixture was stirred at 0 °C for 15 minutes, monitoring for consumption of **II-44** by TLC (R_f = 0.67 (10:90 ethyl acetate/hexanes)). The electrophile (0.84 mmol) was added in one portion by syringe and the reaction mixture was warmed slowly to ambient temperature over 8 hours followed by stirring for an additional 4 hours at ambient temperature. The reaction was quenched by the addition of saturated aqueous ammonium chloride (2 mL) and extracted with ethyl acetate (x3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The unpurified silyl ether product was dissolved in THF (2 mL) and tetrabutylammonium fluoride (1.0 M in THF, 0.84 mmol) was added. After 30 min,

the desilylation reaction was quenched by the addition of water, extracted with ethyl acetate (x3), dried over anhydrous magnesium sulfate, filtered, and concentrated by evaporation. The resulting residue was purified by flash column chromatography on silica gel.

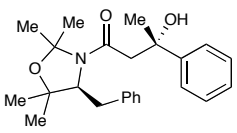
2.8.4.2 Characterization of β-Hydroxy Amides II-85 to II-87



(*S*)-1-((*S*)-4-benzyl-2,2,5,5-tetramethyloxazolidin-3-yl)-3-hydroxy-3,4-diphenylbutan-1-one (II-85): Purified with 10% ethyl acetate/hexanes, yielding 101 mg (79%) of **II-85** as a white solid; R_f(major) = 0.48, R_f(minor) = 0.47 (20:80 ethyl acetate/hexanes); mp = 144-154 °C; IR (film) 3321, 3027, 2937, 1608, 1496, 1407, 1372, 1261, 1203, 1002, 749, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36-7.33 (m, 2H), 7.27-7.16 (m, 13 H), 6.95-6.93 (m, 2H), 6.09 (s, 1H), 3.68 (dd, 1H, *J* = 10.0, 4.5 Hz), 2.94 (dd, 1H, *J* = 14.0, 4.5 Hz), 2.85-2.72 (m, 3H), 2.30 (d, 1H, *J* = 14.5 Hz), 1.66 (s, 3H), 1.27 (s, 3H), 1.19 (s, 3H), 1.11 (d, 1H, *J* = 14.5 Hz), 0.90 (s, 3H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 146.5, 137.6, 136.9, 131.2, 130.0, 129.4, 128.2, 127.8, 127.5, 126.9, 126.5, 125.6, 95.0, 80.4, 76.0, 67.6, 49.7, 42.9, 38.8, 28.8 (x2), 27.8, 24.3; LRMS (ESI): Mass calculated for $C_{30}H_{35}NO_3$ $[M+H]^+$, 458.3. Found $[M+H]^+$, 458.6, $[M+Na]^+$, 480.6.



(*S*)-1-((*S*)-4-benzyl-2,2,5,5-tetramethyloxazolidin-3-yl)-3-hydroxy-3-phenylhex-5-en-1-one (II-86): Purified with 10% ethyl acetate/hexanes, yielding 87 mg (76%) of **II-86** as a white solid; R_f (major) = 0.47, R_f (minor) = 0.46 (20:80 ethyl acetate/hexanes); mp = 124-131 °C; IR (film) 3290, 2980, 2917, 2849, 1772, 1734, 1700, 1653, 1617, 1559, 1539, 1457, 1419, 1409, 1374, 1262, 1241, 1203, 1000, 700, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42-7.33 (m, 3H), 7.30-7.22 (m, 4H), 7.19-7.16 (m, 3H), 6.06 (s, 1H), 5.61-5.55 (m, 1H), 4.99-4.91 (m, 2H), 3.67 (dd, 1H, *J* = 10.0, 4.0 Hz), 2.95 (dd, 1H, *J* = 13.5, 4.0 Hz), 2.75 (t, 1H, *J* = 11.5 Hz), 2.29-2.25 (m, 2H), 2.17 (d, 1H, *J* = 15.0 Hz), 1.68 (s, 3H), 1.28 (s, 3H), 1.21 (s, 3H), 1.08 (d, 1H, *J* = 15.0 Hz), 0.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 146.4, 137.6, 133.8, 130.2, 129.5, 128.3, 127.5, 126.8, 125.3, 118.1, 94.9, 80.3, 75.2, 67.7, 47.8, 43.4, 38.8, 28.9, 28.7, 27.9, 24.3; LRMS (ESI): Mass calculated for $C_{26}H_{33}NO_3$ $[M+H]^+$, 408.3. Found $[M+H]^+$, 408.6, $[M+Na]^+$, 430.6.



(*S*)-1-((*S*)-4-benzyl-2,2,5,5-tetramethyloxazolidin-3-yl)-3-hydroxy-3-phenylbutan-1-one (II-87): Purified with 10% ethyl acetate/hexanes, yielding 83 mg (78%) of **II-87** as a white solid; R_f(major) = 0.40, R_f (minor) = 0.40 (20:80 ethyl acetate/hexanes); mp = 134-136 °C; IR (film) 3363, 2979, 2917, 2849, 1610, 1496, 1408, 1373, 1263, 1202, 1190, 1147, 1129, 1066, 1001, 954, 940, 749, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41-7.33 (m, 3H), 7.31-7.25 (m, 4H), 7.20-7.15 (m, 3H), 6.10 (s, 1H), 3.65 (dd, 1H, *J* = 10.5, 4.0 Hz), 2.95 (dd, 1H, *J* = 14.0, 4.0 Hz), 2.76 (dd, 1H, *J* = 14.0, 10.5 Hz), 2.23 (d, 1H, *J* = 15.0 Hz), 1.69 (s, 3H), 1.26 (s, 3H), 1.07 (d, 1H, *J* = 15.0 Hz), 0.85 (s, 3H); δ 171.3, 147.6, 137.7, 130.2, 129.4, 128.3, 127.5, 126.7, 124.9, 94.9, 80.3, 73.3, 67.5, 45.4, 38.7, 30.8, 28.9, 28.7, 27.9, 24.3; LRMS (ESI): Mass calculated for $C_{24}H_{31}NO_3$ $[M+H]^+$, 382.2. Found $[M+H]^+$, 382.5, $[M+Na]^+$, 404.6.

2.8.5 Preparation of N-Phosphinoyl Imines

N-phosphinoyl imines **II-99** to **II-103** were prepared from the corresponding oxime, according to the procedure of Boyd, Jennings, and coworkers.[82]

2.8.5.1 Representative Procedure for the Synthesis of N-Phosphinoyl Imines II-99 to II-103

To a 100 mL round-bottom flask containing the dry oxime (10.0 mmol)[86] and a magnetic stirring bar, sealed with a rubber septum, and purged with nitrogen, was added CH_2Cl_2 (50 mL) and triethylamine (20.0 mmol). The resulting solution was cooled to –78 °C. To the reaction flask was added a solution of chlorodiphenylphosphine (12.0

mmol) in CH_2Cl_2 (25 mL) dropwise by cannulation over 40 minutes. The resulting reaction mixture was allowed to warm slowly to room temperature over approximately 12 hours. The reaction was transferred to a separatory funnel, washed with ice-cold water (x2), dried over Na_2SO_4, and concentrated by evaporation. The resulting residue was purified by flash column chromatography on silica gel, and stored in a dessicator at low temperatures (≤ 0 °C).

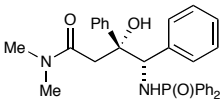
2.8.6 Diastereoselective Homoenolate Additions to N-Phosphinoyl Imines

2.8.6.1 Representative Procedure for the Synthesis of γ-Amino-β-Hydroxy Imines II-104 to II-111

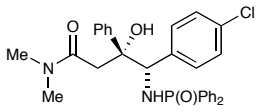
To a flame-dried, round-bottom flask equipped with a magnetic stirring bar and purged with nitrogen was added THF (2 mL) and diisopropylamine (0.54 mmol). The solution was cooled to –78 °C and *n*-butyllithium (1.6 M in hexanes, 0.54 mmol) was added by syringe. The reaction was warmed to 0 °C and stirred for 30 minutes. Dimethylacetamide (0.54 mmol) was added to the LDA solution and the reaction was stirred for one hour. The reaction was cooled to –78 °C, and a –78 °C solution of benzoyltrimethylsilane **(**0.59 mmol) in THF (0.5 mL) was added by cannula. The acylsilane delivery flask was rinsed with an additional portion of THF (0.5 mL), cooled to –78 °C and transferred to the reaction flask. The resulting homogeneous solution was stirred for 20 minutes after which a solution of the diphenylphosphonyl imine (0.65 mmol) in THF (2.0 mL) was added by cannula, again rinsing the delivery flask with an additional portion of THF (0.4 mL). The resulting reaction mixture was stirred at –78 °C for 15 hours. The reaction was quenched by the addition of saturated aqueous

ammonium chloride (2 mL), warmed to ambient temperature, stirred for 30 minutes, and extracted with ethyl acetate (x3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated by evaporation. The unpurified silyl ether product was dissolved in THF (2 mL). To this solution was added tetrabutylammonium fluoride (1.0 M in THF, 1.1 mmol) and the mixture was stirred at room temperature for 30 minutes. The reaction was quenched by the addition of water, extracted with methylene chloride (x3), dried over anhydrous magnesium sulfate, filtered, and concentrated by evaporation. The resulting residue was purified by flash column chromatography on silica gel.

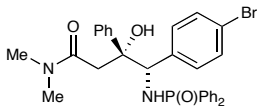
2.8.6.2 Characterization of γ-Amino-β-Hydroxy Imines II-104 to II-111



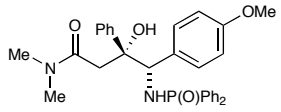
4-(diphenylphosphinamide)-3-hydroxy-*N*,*N*-dimethyl-3,4-diphenylbutanamide (II-104): Purified with 20-40% acetone/dichloromethane, yielding 192 mg (74%) of **II-104** as a white solid. R_f = 0.31 (30:70 acetone/dichloromethane); mp = 170 °C dec; IR (film) 3236, 3058, 2927, 1616, 1489, 1438, 1194, 1119, 721, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.85 (dd, 2H), 7.55-7.43 (m, 4H), 7.33 (t, 1H), 7.17-7.12 (m, 4H), 7.07-6.95 (m, 6H), 6.89 (s, 1H), 6.79 (d, 2H), 4.66 (t, 1H, *J* = 6.0 Hz), 4.24 (t, 1H, *J* = 6.5 Hz), 3.66 (d, 1H, *J* = 16.5 Hz), 3.36 (d, 1H, *J* = 16.5 Hz), 3.07 (s, 3H), 2.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 144.2, 140.3, 133.2, 133.1, 131.6, 131.5, 128.9, 128.8, 128.7, 128.3, 128.1, 127.8, 127.2, 126.6(x2), 125.6, 78.7, 63.2, 40.4, 37.8, 35.4; LRMS (ESI): Mass calculated for $C_{30}H_{31}N_2O_3P$ $[M+H]^+$, 499.6. Found $[M+H]^+$, 499.7, $[M+Na]^+$, 521.6.



4-(diphenylphosphinamide)-4-(4-chlorophenyl)-3-hydroxy-*N*,*N*-dimethyl-3-phenylbutanamide (II-105): Purified with 20-40% acetone/dichloromethane, yielding 197 mg (71%) of **II-105** as a white solid. R_f = 0.33 (30:70 acetone/dichloromethane); mp = 165 °C dec; IR (film) 3231, 3057, 2959, 1621, 1487, 1438, 1196, 1119, 723, 699, 530 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.82 (dd, 2H), 7.53-7.42 (m, 5H), 7.34 (t, 1H), 7.19-6.90 (m, 9H), 6.72 (d, 2H), 4.64 (t, 1H, *J* = 11.0 Hz), 4.22 (t, 1H, *J* = 11.0 Hz), 3.99 (d, 1H, *J* = 11.0 Hz), 3.03 (s, 3H), 2.73 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 143.9, 139.1, 133.1, 133.0, 132.3, 131.6, 131.5, 130.0, 128.9, 128.4, 128.2, 128.0, 127.4, 126.8, 125.5, 78.6, 62.5, 40.2, 37.8, 35.4; LRMS (ESI): Mass calculated for $C_{30}H_{30}ClN_2O_3P$ $[M+H]^+$, 534.0. Found $[M+H]^+$, 533.7.

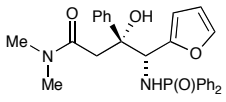


4-(diphenylphosphinamide)-4-(4-bromophenyl)-3-hydroxy-*N*,*N*-dimethyl-3-phenylbutanamide (II-106): Purified with 20-40% acetone/dichloromethane, yielding 211 mg (70%) of **II-106** as a white solid. R_f = 0.38 (30:70 acetone/dichloromethane); mp = 171 °C dec; IR (film) 3269, 3056, 2932, 1615, 1511, 1438, 1190, 1122, 725, 698, 521 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.90-7.80 (m, 2H), 7.53-7.32 (m, 6H), 7.18-6.96 (m, 9H), 6.67 (d, 2H), 4.65 (t, 1H, *J* = 11.0 Hz), 4.21 (t, 1H, *J* = 11.0 Hz), 3.58 (d, 1H, *J* = 16.5 Hz), 3.46 (s, 1H), 3.31 (d, 1H, *J* = 16.5 Hz), 3.01 (s, 3H), 2.71 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 143.8, 139.6, 133.1, 132.3, 131.6, 131.5, 130.4, 130.3, 128.9, 128.8, 128.4, 128.3, 128.0, 126.9, 125.5, 120.6, 78.5, 62.6, 40.2, 37.8, 35.3 LRMS (ESI): Mass calculated for $C_{30}H_{30}BrN_2O_3P$ $[M]^+$, 577.5. Found $[M]^+$, 577.6.

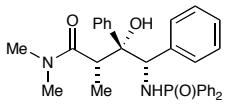


4-(diphenylphosphinamide)-3-hydroxy-4-(4-methoxyphenyl)-*N*,*N*-dimethyl-3-phenylbutanamide (II-107):

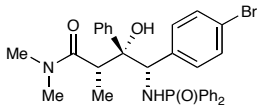
Purified with 20-40% acetone/dichloromethane, yielding 195 mg (71%) of **II-107** as a white solid. R_f = 0.33 (30:70 acetone/dichloromethane); mp = 175 °C dec; IR (film) 3231, 3056, 2929, 1616, 1495, 1435, 1192, 1119, 721, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.85-7.81 (m, 2H), 7.56-7.42 (m, 5H), 7.19-6.98 (m, 7H), 6.86 (s, 1H), 6.71 (m, 2H), 6.50 (m, 2H), 4.59 (t, 1H, *J* = 11.0 Hz), 4.22 (t, 1H, *J* = 11.0 Hz), 3.69 (s, 3H), 3.61 (d, 1H, *J* = 16.5 Hz), 3.33 (d, 1H, *J* = 16.0 Hz), 3.03 (s, 3H), 2.74 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 158.2, 144.3, 133.2, 133.1, 132.1, 131.6, 131.5, 129.7, 128.9, 128.7, 128.3, 128.2, 127.8, 126.6, 125.6, 112.6, 78.8, 62.6, 55.2, 40.5, 37.8, 35.3; LRMS (ESI): Mass calculated for $C_{31}H_{33}N_2O_4P$ $[M+H]^+$, 529.6. Found $[M+H]^+$, 529.6.



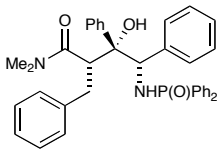
4-(diphenylphosphinamide)-4-(furan-3-yl)-3-hydroxy-*N*,*N*-dimethyl-3-phenylbutanamide (II-108): Purified with 20-40% acetone/dichloromethane, yielding 203 mg (80%) of **II-108** as a white solid. R_f = 0.31 (30:70 acetone/dichloromethane); mp = 180 °C dec; IR (film) 3254, 3057, 2932, 1617, 1489, 1438, 1200, 1119, 721, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.84-7.80 (m, 2H), 7.65-7.61 (m, 2H), 7.53-7.50 (m, 1H), 7.46-7.39 (m, 3H), 7.36-7.25 (m, 4H), 7.18-7.08 (m, 3H), 7.02 (bs, 1H), 5.97 (dd, 1H, *J* = 2.0, 1.0 Hz), 5.48 (d, 1H, *J* = 3.0 Hz), 4.51-4.48 (m, 2H), 3.53 (d, 1H, *J* = 16.5 Hz), 3.26 (d, 1H, *J* = 16.0 Hz), 3.00 (s, 3H), 2.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 144.1, 137.9, 133.1, 133.0, 132.2, 132.1(x2), 132.0, 131.7, 131.6, 128.9, 128.8(x2), 128.7, 128.1, 127.9, 125.5, 78.9, 63.4, 40.5, 37.8, 35.4; LRMS (ESI): Mass calculated for $C_{28}H_{29}N_2O_4P$ $[M+Na]^+$, 511.5. Found $[M+Na]^+$, 511.6.



4-(diphenylphosphinamide)-3-hydroxy-*N*,*N*,2-trimethyl-3,4-diphenylbutanamide (II-109): Purified with 20-40% acetone/dichloromethane, yielding 224 mg (84%) of **II-109** as a white solid. R_f = 0.40 (30:70 acetone/dichloromethane); mp = 170 °C dec; IR (film) 3258, 3050, 2926, 1615, 1491, 1436, 1387, 1202, 1123, 727, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.87-7.83 (m, 2H), 7.57-7.41 (m, 5H), 7.30-7.28 (m, 2H), 7.16-6.89 (m, 8H), 6.74 (m, 2H), 6.38 (s, 1H), 4.68 (t, 1H, *J* = 9.5 Hz), 4.27 (t, 1H, *J* = 10.0 Hz), 3.53 (q, 1H, *J* = 6.5 Hz), 2.84 (s, 3H), 2.56 (s, 3H), 1.69 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.3, 143.9, 141.0, 132.8, 132.7, 132.0, 131.9 (x2), 131.3, 128.9, 128.7, 128.6, 128.1, 128.0, 127.3, 126.9, 126.8, 79.5, 60.7, 42.3, 37.5, 35.3, 13.7; LRMS (ESI): Mass calculated for $C_{31}H_{33}N_2O_3P$ $[M+H]^+$, 513.6. Found $[M+H]^+$, 513.5.



4-(diphenylphosphinamide)-4-(4-bromophenyl)-3-hydroxy-*N*,*N*,2-trimethyl-3-phenylbutanamide (II-110): Purified with 10-30% acetone/dichloromethane, yielding 241 mg (78%) of **II-110** as a white solid. R_f = 0.44 (30:70 acetone/dichloromethane); mp = 183-185 °C; IR (film) 3249, 3055, 2932, 1613, 1493, 1438, 1196, 1119, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.94-7.81 (m, 2H), 7.52-7.42 (m, 6H), 7.34-7.28 (m, 1H), 7.18-7.14 (m, 2H), 7.07-6.96 (m, 6H), 6.62 (d, 2H), 6.54 (s, 1H), 4.66 (t, 1H, *J* = 9.0 Hz), 3.40 (dd, 1H, *J* = 12.0, 9.0 Hz), 3.53 (q, 1H, *J* = 7.0 Hz), 2.84 (s, 3H), 2.57 (s, 3H), 1.71 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 177.2, 143.9, 140.4, 132.6, 132.5, 132.1, 131.8, 131.7, 131.4, 130.6, 130.3, 128.8, 128.7, 128.1, 128.0, 127.0, 120.6, 79.3, 60.2, 42.7, 37.5, 35.3, 13.9; LRMS (ESI): Mass calculated for $C_{31}H_{32}BrN_2O_3P$ $[M]^+$, 591.5. Found $[M]^+$, 591.7.



4-(diphenylphosphinamide)-2-benzyl-3-hydroxy-*N*,*N*-dimethyl-3,4-diphenylbutanamide (II-111): Purified with 5-10% acetone/dichloromethane, yielding 231 mg (75%) of **II-111** as a white solid. R_f = 0.73 (30:70 acetone/dichloromethane); mp = 175 °C dec; IR (film) 3273, 2926, 2856, 1698, 1493, 1412, 1205, 1090, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.83-7.79 (m, 2H), 7.57-7.53 (m, 2H), 7.46-7.09 (m, 13H), 7.01-6.91 (m, 6H), 6.85 (d, 2H), 6.59 (s, 1H), 4.89 (t, 1H, *J* = 9.5 Hz), 4.34 (t, 1H, *J* = 10.5 Hz), 4.21 (dd, 1H *J* = 12.0, 3.5 Hz), 3.67 (dd, 1H, *J* = 11.0, 3.5 Hz), 3.28 (d, 1H, *J* = 12.5 Hz), 2.25 (s, 3H), 1.94 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 175.3, 143.9, 141.4, 139.6, 132.9, 132.8, 132.0, 131.8, 131.7, 131.4, 129.8, 129.0, 128.8, 128.7, 128.4, 128.1, 127.9, 127.4, 126.9, 126.8, 126.7, 79.9, 61.1, 51.2, 36.7, 34.8, 34.7; LRMS (ESI): Mass calculated for $C_{37}H_{37}N_2O_3P$ $[M+H]^+$, 589.7. Found $[M+H]^+$, 589.7.

2.8.7 Synthesis of β-Hydroxy-γ-Lactams

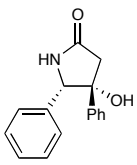
2.8.7.1 Representative Procedure for the Synthesis of β-Hydroxy-γ-Lactams II-112 to II-119

Condition A: A 0.5-2.0 mL Biotage microwave flask equipped with a stirbar was charged with the γ-amino-β-hydroxy amide (0.20 mmol), tetrahydrofuran (1.0 mL), and 3 M aqueous HCl (1.0 mL). The resulting mixture was stirred for 2 minutes, heated to 150 °C in the microwave, and stirred at this temperature for an additional 5 minutes. The resulting mixture was cooled to ambient temperature, slowly neutralized with solid sodium bicarbonate (evolution of gas ceases) and extracted with dichloromethane (x3). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and

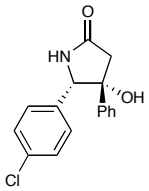
concentrated by evaporation. The resulting residue was purified by flash column chromatography on silica gel.

Condition B: A 0.5-2.0 mL Biotage microwave flask equipped with a stirbar was charged with the γ-amino-β-hydroxy amide (0.20 mmol), tetrahydrofuran (1.0 mL), and 3 M aqueous HCl (1.0 mL). The resulting mixture was stirred for 2 minutes, heated to 70 °C in the microwave, and stirred at this temperature for an additional 10 minutes. The resulting mixture was cooled to ambient temperature, slowly neutralized with solid sodium bicarbonate (evolution of gas ceases) and extracted with dichloromethane (x3). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated by evaporation. The resulting residue was purified by flash column chromatography on silica gel.

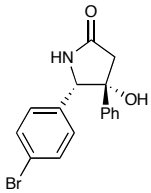
2.8.7.2 Characterization of β-Hydroxy-γ-Lactams II-112 to II-119



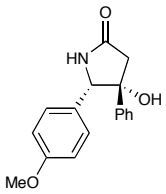
4-hydroxy-4,5-diphenylpyrrolidin-2-one (II-112): Purified with 10-30% acetone/dichloromethane, yielding 50 mg (98%) of **II-112** as a white solid. R_f = 0.19 (20:80 acetone/dichloromethane); mp = 198-200 °C; IR (film) 3303, 3188, 1701, 1668, 1443, 1337, 1214, 1071, 1031, 732, 691 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42-7.35 (m, 8H), 7.10 (d, 2H), 6.07 (s, 1H), 5.19 (s, 1H), 3.06 (d, 1H, *J* = 21.5 Hz), 2.83 (d, 1H, *J* = 21.5 Hz), 1.78 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5, 142.5, 133.7, 129.4, 128.8, 128.0, 127.4, 125.4, 79.6, 69.4, 47.6; LRMS (ESI): Mass calculated for $C_{16}H_{15}NO_2$ $[M+H]^+$, 254.3. Found $[M+H]^+$, 254.5.



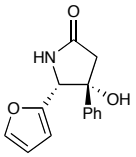
5-(4-chlorophenyl)-4-hydroxy-4-phenylpyrrolidin-2-one (II-113): Purified with 20-40% acetone/dichloromethane, yielding 56 mg (97%) of **II-113** as a white solid. R_f = 0.42 (30:70 acetone/dichloromethane); mp = 173-175 °C; IR (film) 3283, 2924, 1693, 1489, 1409, 1332, 1204, 1065, 1011, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41-7.29 (m, 7H), 7.02 (d, 2H), 6.48 (s, 1H), 5.13 (s, 1H), 3.08 (d, 1H, *J* = 17.5 Hz), 2.81 (d, 1H, *J* = 17.0 Hz), 1.95 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7, 142.1, 135.1, 132.4, 129.2, 128.9 (x2), 128.2, 125.4, 79.7, 69.0, 47.6; LRMS (ESI): Mass calculated for $C_{16}H_{14}ClNO_2$ $[M+H]^+$, 288.7. Found $[M+H]^+$, 288.4.



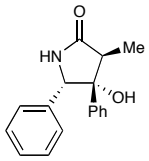
5-(4-bromophenyl)-4-hydroxy-4-phenylpyrrolidin-2-one (II-114): Purified with 20-40% acetone/dichloromethane, yielding 62 mg (93%) of **II-114** as a white solid. R_f = 0.40 (30:70 acetone/dichloromethane); mp = 144-146 °C; IR (film) 3283, 2924, 1693, 1489, 1409, 1332, 1204, 1065, 1011, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45-7.34 (m, 7H), 6.95 (d, 2H), 6.78 (s, 1H), 5.10 (s, 1H), 3.07 (d, 1H, *J* = 17.0 Hz), 2.79 (d, 1H, *J* = 17.5 Hz), 1.55 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.6, 142.0, 132.9, 132.2, 129.2, 128.9, 128.2, 125.4, 123.3, 79.6, 69.0, 47.6 LRMS (ESI): Mass calculated for $C_{16}H_{14}BrNO_2$ $[M+H]^+$, 333.2. Found $[M+H]^+$, 333.0.



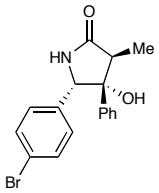
4-hydroxy-5-(4-methoxyphenyl)-4-phenylpyrrolidin-2-one (II-115): Purified with 10-30% acetone/dichloromethane, yielding 53 mg (94%) of **II-115** as a white solid. R_f = 0.21 (20:80 acetone/dichloromethane); mp = 169-171 °C; IR (film) 3323, 2927, 2833, 1697, 1611, 1517, 1423, 1251, 1178, 1034, 732, 704 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42-7.28 (m, 2H), 6.99 (d, 2H), 6.84 (d, 2H), 6.74 (s, 1H), 5.13 (s, 1H), 3.78 (s, 3H), 3.03 (d, 1H, *J* = 17.0 Hz), 2.80 (d, 1H, *J* = 17.0 Hz), 1.99 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.1, 160.3, 142.7, 128.7 (x2), 127.9, 125.5, 125.3, 114.5, 79.5, 69.2, 55.5, 47.6; LRMS (ESI): Mass calculated for $C_{17}H_{17}NO_3$ $[M+H]^+$, 284.3. Found $[M+H]^+$, 284.5.



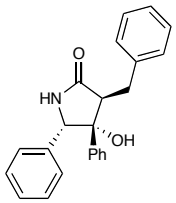
5-(furan-3-yl)-4-hydroxy-4-phenylpyrrolidin-2-one (II-116): Purified with 10-30% acetone/dichloromethane, yielding 47 mg (97%) of **II-116** as a white solid. R_f = 0.28 (20:80 acetone/dichloromethane); mp = 206-208 °C; IR (film) 3291, 3054, 2919, 1697, 1509, 1447, 1312, 1206, 1060, 810, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.84-7.72 (m, 3H), 7.53-7.51 (m, 1H), 7.46-7.35 (m, 3H), 7.01 (d, 1H), 6.08 (s, 1H), 5.35 (s, 1H), 3.11 (d, 1H, *J* = 17.5 Hz), 2.88 (d, 1H, *J* = 17.5 Hz), 1.82 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5, 142.6, 133.2, 128.8, 128.1, 128.0, 127.0, 125.4, 79.7, 69.6, 47.6; LRMS (ESI): Mass calculated for $C_{14}H_{13}NO_3$ $[M+H]^+$, 244.3. Found $[M+H]^+$, 244.4.



4-hydroxy-3-methyl-4,5-diphenylpyrrolidin-2-one (II-117): Purified with 10-30% acetone/dichloromethane, yielding 51 mg (96%) of **II-117** as a white solid. R_f = 0.55 (30:70 acetone/dichloromethane); mp = 144-146 °C; IR (film) 3263, 3060, 2926, 1699, 1491, 1446, 1337, 1119, 1019, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.59-7.57 (d, 2H), 7.42-7.31 (m, 8H), 6.46 (s, 1H), 5.37 (s, 1H), 2.70 (q, 1H, *J* = 7.5 Hz), 1.85 (s, 1H), 0.91 (d, 3H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.8, 141.1, 135.2, 129.3, 129.2, 128.7, 128.2, 128.0, 126.3, 100.0, 82.2, 64.6, 49.6, 12.9; LRMS (ESI): Mass calculated for $C_{17}H_{17}NO_2$ $[M+H]^+$, 268.3. Found $[M+H]^+$, 268.6.



5-(4-bromophenyl)-4-hydroxy-3-methyl-4-phenylpyrrolidin-2-one (II-118): Purified with 2-30% acetone/dichloromethane, yielding 68 mg (98%) of **II-118** as a white solid. R_f = 0.29 (10:90 acetone/dichloromethane); mp = 181-183 °C; IR (film) 3344, 2919, 1701, 1492, 1456, 1071, 1014, 761, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, 2H), 7.47-7.33 (m, 5H), 7.18 (d, 2H), 6.99 (s, 1H), 5.34 (s, 1H), 2.66 (q, 1H, *J* = 7.5 Hz), 1.85 (s, 1H), 0.89 (d, 3H, *J* = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.9, 140.6, 134.2, 132.3, 129.6, 128.8, 128.4, 126.2, 125.7, 82.2, 64.1, 49.6, 30.5; LRMS (ESI): Mass calculated for $C_{17}H_{16}BrNO_2$ $[M]^+$, 346.2. Found $[M]^+$, 346.4.



3-benzyl-4-hydroxy-4,5-diphenylpyrrolidin-2-one (II-119): Purified with 5-20% acetone/dichloromethane, yielding 62 mg (90%) of **II-119** as a white solid. R_f = 0.51 (10:90 acetone/dichloromethane); mp = 56-58 °C; IR (film) 3270, 3029, 2915, 1693, 1492, 1451, 1333, 1063, 907, 728, 695 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, 2H), 7.42-7.29 (m, 7H), 7.19-7.08 (m, 3H), 7.00 (s, 1H), 6.91 (d, 2H), 6.44 (s, 1H), 5.06 (s, 1H), 3.07 (dd, 1H, *J* = 8.0, 6.0 Hz), 2.97 (dd, 1H, *J* = 15.0, 6.0 Hz), 2.51 (dd, 1H, *J* = 15.0, 8.0 Hz), 1.61 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.3, 142.4, 139.2, 136.0, 129.2, 129.1, 128.8, 128.4, 128.3, 128.0, 126.3, 126.0, 81.7, 66.2, 54.6, 32.6; LRMS (ESI): Mass calculated for $C_{23}H_{21}NO_2$ $[M+H]^+$, 344.4. Found $[M+H]^+$, 344.6.

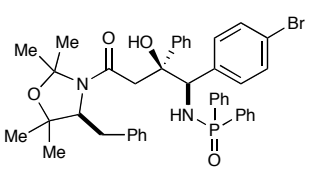
2.8.8 Synthesis of Enantioenriched β-Hydroxy-γ-Lactams

2.8.8.1 Representative Procedure for the Synthesis of Enantioenriched γ-Amino-β-Hydroxy Amide II-120

To a flame-dried, round-bottom flask equipped with a magnetic stir bar and purged with nitrogen was added THF (2.0 mL) and diisopropylamine (0.62 mmol). The resulting solution was cooled to –78 °C and *n*-butyllithium (1.6 M in hexanes, 0.62 mmol) was added dropwise by syringe. The reaction was warmed to 0 °C, stirred for 30 minutes, then cooled to –78 °C. To this solution of LDA was added a –78 °C solution of chiral amide **II-80** (0.62 mmol) in THF (0.7 mL + 0.3 mL rinse) by cannulation. The resulting reaction was warmed to 0 °C, stirred for 1 hour, then recooled to –78 °C. To the reaction was added a cooled to –78 °C solution of benzoyltrimethylsilane (**II-44**, 0.56 mmol) in THF (0.7 mL) in one portion by cannula, again rinsing the delivery flask with

an additional portion of THF (0.3 mL). The resulting reaction mixture was stirred at –78 °C for 30 minutes, monitoring for consumption of benzoyltrimethylsilane (**II-44**) by TLC (R_f = 0.67 (10:90 ethyl acetate/hexanes)). Following consumption of benzoyltrimethylsilane (**II-44**), the reaction was warmed to 0 °C, stirred for 30 minutes, and recooled to –78 °C. *This equilibration period at 0 °C is necessary for the increased diastereoselectivity*. A solution of the *N*-phosphinoyl imine (**II-101**, 0.67 mmol) in THF (1.3 mL) was added in one portion by by cannula, again rinsing the delivery flask with an additional portion of THF (0.3 mL). Following addition of the imine, the reaction mixture was stirred at –78 °C for 15 hours. The reaction was quenched by the addition of saturated aqueous ammonium chloride (2 mL), warmed to ambient temperature, stirred for 30 minutes, and extracted with ethyl acetate (x3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated by evaporation. The unpurified silyl ether product was dissolved in THF (2 mL) and tetrabutylammonium fluoride (1.0 M in THF, 0.84 mmol) was added. After 30 min, the desilylation reaction was quenched by the addition of water, extracted with methylene chloride (x3), dried over anhydrous sodium sulfate, filtered, and concentrated by evaporation. The resulting residue was purified by flash column chromatography on silica gel.

2.8.8.2 Characterization of Enantioenriched γ-Amino-β-Hydroxy Amide II-120



***N*-((1*R*,2*S*)-4-((*S*)-4-benzyl-2,2,5,5-tetramethyloxazolidin-3-yl)-1-(4-bromophenyl)-2-hydroxy-4-oxo-2-phenylbutyl)-*P*,*P*-diphenylphosphinic amide (II-120)**: Purified with 5-20% acetone/dichloromethane, yielding 286 mg (68%) of **II-120** as a pale yellow solid. R_f = 0.41 (10:90 acetone/dichloromethane); mp = 99-102 °C; IR (film) 3273, 2978, 1607, 1436, 1415, 1201, 1123, 1010, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.83-7.74 (m, 2H), 7.56-7.28 (m, 10H), 7.25-6.91 (m, 10H), 6.66 (d, 2H), 6.60 (s, 1H), 4.29-4.26 (m, 2H), 3.87 (t, 1H, *J* = 7.0 Hz), 2.98 (dd, 1H, *J* = 6.0, 14.0 Hz), 2.85-2.62 (m, 2H), 2.31 (d, 1H, *J* = 15.0 Hz), 1.63 (s, 3H), 1.19 (s, 3H), 1.08 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 143.5, 139.4, 137.4, 132.7, 132.6, 131.8, 131.7, 130.7, 130.3, 130.2, 129.5, 128.9, 128.8, 128.2, 128.1 (x2), 127.2, 127.1, 120.6, 94.8, 80.6, 79.0 (x2), 67.2, 61.8, 42.9, 39.0, 31.2, 28.7, 17.5; LRMS (ESI): Mass calculated for $C_{42}H_{44}BrN_2O_4P$ $[M+H]^+$, 751.2. Found $[M+H]^+$, 751.2.

2.8.8.3 Representative Procedure for the Synthesis of Enantioenriched β-Hydroxy-γ-Amino Amide II-114

γ-Amino-β-hydroxy amide **II-120** (0.38 mmol) was transferred to a 2.0-5.0 mL Biotage microwave flask equipped with a stirbar. The solid was dissolved in THF (1.5 mL) and 3M aqueous HCl (3.0 mL). The reaction mixture was stirred for 2 minutes, heated to 150 °C in the microwave, and stirred at this temperature for 20 minutes. The resulting mixture was cooled to ambient temperature and slowly neutralized with solid sodium bicarbonate (evolution of gas ceases) and extracted with dichloromethane (x3).

The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated by evaporation. The resulting residue was purified by flash column chromatography on silica gel (2-30% acetone/dichloromethane), yielding 77 mg (63%) of (4*S*,5*R*)-5-(4-bromophenyl)-4-hydroxy-4-phenylpyrrolidin-2-one (**II-114)** as a white solid. ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy, mass spectrometry, and melting point data are equivalent to that observed for racemic b-hydroxy lactam **II-114**. Chiral HPLC analysis (see page 10) indicates an 87% ee, corresponding to approximately a 14:1 diastereoselectivity in relation to the chiral auxiliary for the addition event. Enantioenriched β-hydroxy lactam **II-114** was also recovered without purification and isolation of γ-amino-β-hydroxy amide **II-120** (63% yield overall, 87% ee). This experiment was conducted to insure that the observed selectivity was not being unintentionally augmented during the purification of intermediate **II-120**.

2.8.8.4 Determination of Enantioselectivity of Enantioenriched γ-Amino-β-Hydroxy Amide II-114

The enantioselectivity of enantioenriched γ-amino-β-hydroxy amide **II-114** was determined by HPLC analysis using an OD-h chiralcel column (10:90 isopropanol/hexanes, 1.0 mL/min).

(±)-5-(4-bromophenyl)-4-hydroxy-4-phenylpyrrolidin-2-one (**II-114**):

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Ad-H column, 10%IPA/hex

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                                                  Inj Volume : 5 µl
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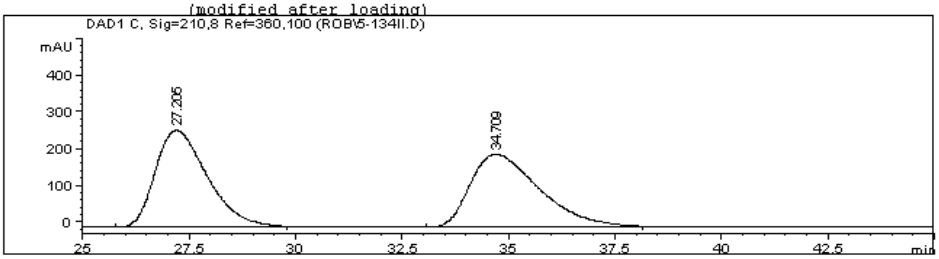


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Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 C, Sig=210,8 Ref=360,100

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   2  34.709 BB    1.5671 2.20895e4   197.46222  49.9660

Totals :                  4.42091e4   460.10712

 Results obtained with enhanced integrator!
==========================================================================
                          *** End of Report ***
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(4*S*,5*R*)-5-(4-bromophenyl)-4-hydroxy-4-phenylpyrrolidin-2-one (**II-114**):

Data File C:\HPCHEM\2\DATA\ROB\5-1765B1.D Sample Name: RBL5-176VB

ODH, 10% IPA/Hex

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                                               Inj Volume : 5 µl
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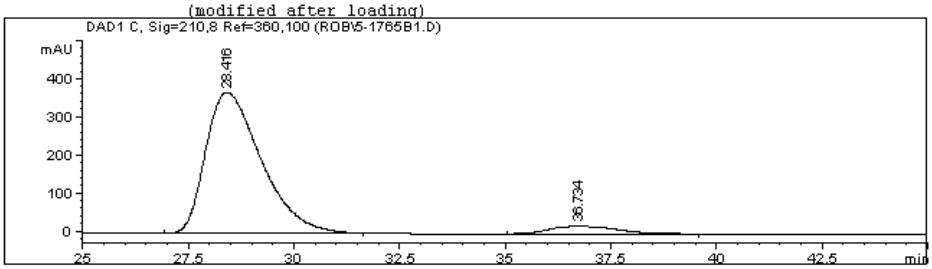


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Totals :                  3.63320e4   391.11694

 Results obtained with enhanced integrator!
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                        *** End of Report ***
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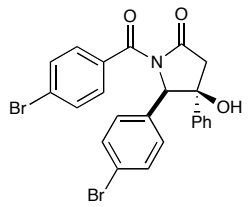
2.8.8.5 Determination of the Absolute Stereochemistry of Enantioenriched β-Hydroxy Lactam II-114

The absolute configuration of enantioenriched β-hydroxy lactam **II-114** was determined by single-crystal X-ray diffraction of (4*S*,5*R*)-5-(4-bromophenyl)-1-(4-bromophenylcarbonyl)-4-hydroxy-4-phenylpyrrolidin-2-one (**II-121**), which was prepared from enantioenriched **II-114** as follows:

To a round-bottom flask equipped with a magnetic stir bar and purged with nitrogen was dissolved enantioenriched lactam **II-114** (0.069 mmol) in THF (350 mL), and cooled in an ice-water bath. To the cooled solution was added NaH (0.152 mmol, 60% in mineral oil) in one portion, and stirred at 0 °C for 15 minutes. To the reaction was added 4-bromobenzoyl chloride in one portion, and stirred at 0 °C for 5 hours. The reaction was quenched by dropwise addition of saturated aqueous NH_4Cl, extracted with CH_2Cl_2 (x3), dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by flash column chromatography on silica gel.



(4*S*,5*R*)-5-(4-bromophenyl)-1-(4-bromophenylcarbonyl)-4-hydroxy-4-phenylpyrrolidin-2-one (II-121): Purified with 80% dichloromethane/hexanes, yielding 21 mg (59%) of **II-121** as a pale yellow solid. R_f = 0.41 (80:20 dichloromethane/hexanes); mp = 268-271 °C; IR (film) 2919, 1748, 1689, 1658, 1587, 1484, 1447, 1273, 1232, 1176, 1070, 1032, 1010, 963, 896, 841, 806, 779, 765, 745, 715, 701, 597 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.74-7.73 (m, 2H), 7.63-7.61 (m, 2H), 7.44-7.38 (m, 7H), 6.92-6.90 (m, 2H), 5.69 (s, 1H), 3.21 (d, 1H, *J* = 18.5 Hz), 3.06 (d, 1H, *J* = 18.0 Hz), 1.41 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 170.0, 140.9, 132.8, 132.3, 131.9 (x2), 131.8, 129.1, 128.8, 128.7, 128.6, 125.3, 123.2, 76.0, 71.6, 48.6; LRMS (ESI): Molecular weight calculated for C23H17Br2NO3 $[M+H]^+$, 516.2. Mass found $[M+H]^+$, 516.1.

2.8.9 Temperature Control Studies for the Synthesis of β-Hydroxy Amide II-85

In an effort to better understand the mechanistic origin of diastereoselectivity for this reaction, the temperature was varied in different steps throughout the procedure as described below, and the diastereoselectivities were observed:

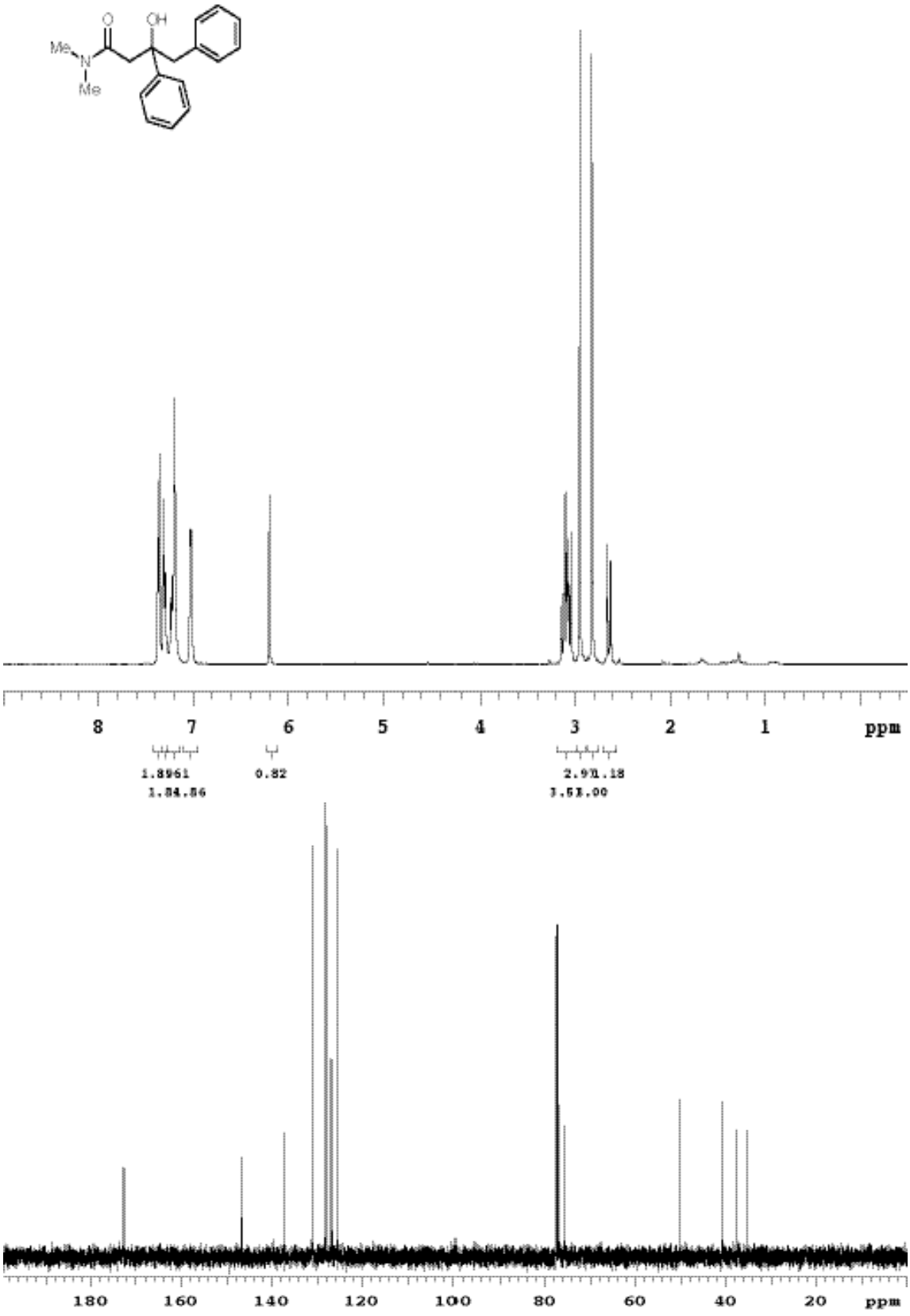
A: The general procedure was followed as described above for the synthesis of β-hydroxy amides **II-85** to **II-87** (**2.8.4**). Following formation of the Li-acetamide, the reaction was cooled to –78 °C. The solution of the acylsilane in THF at –78 °C was added to the reaction via cannulation, with rinse, and stirred for 15 min at –78 °C. The solution of benzylbromide in THF at –78 °C was added to the reaction by cannulation, and stirred at –78 °C for 12 h. A standard aqueous work-up and desilylation were

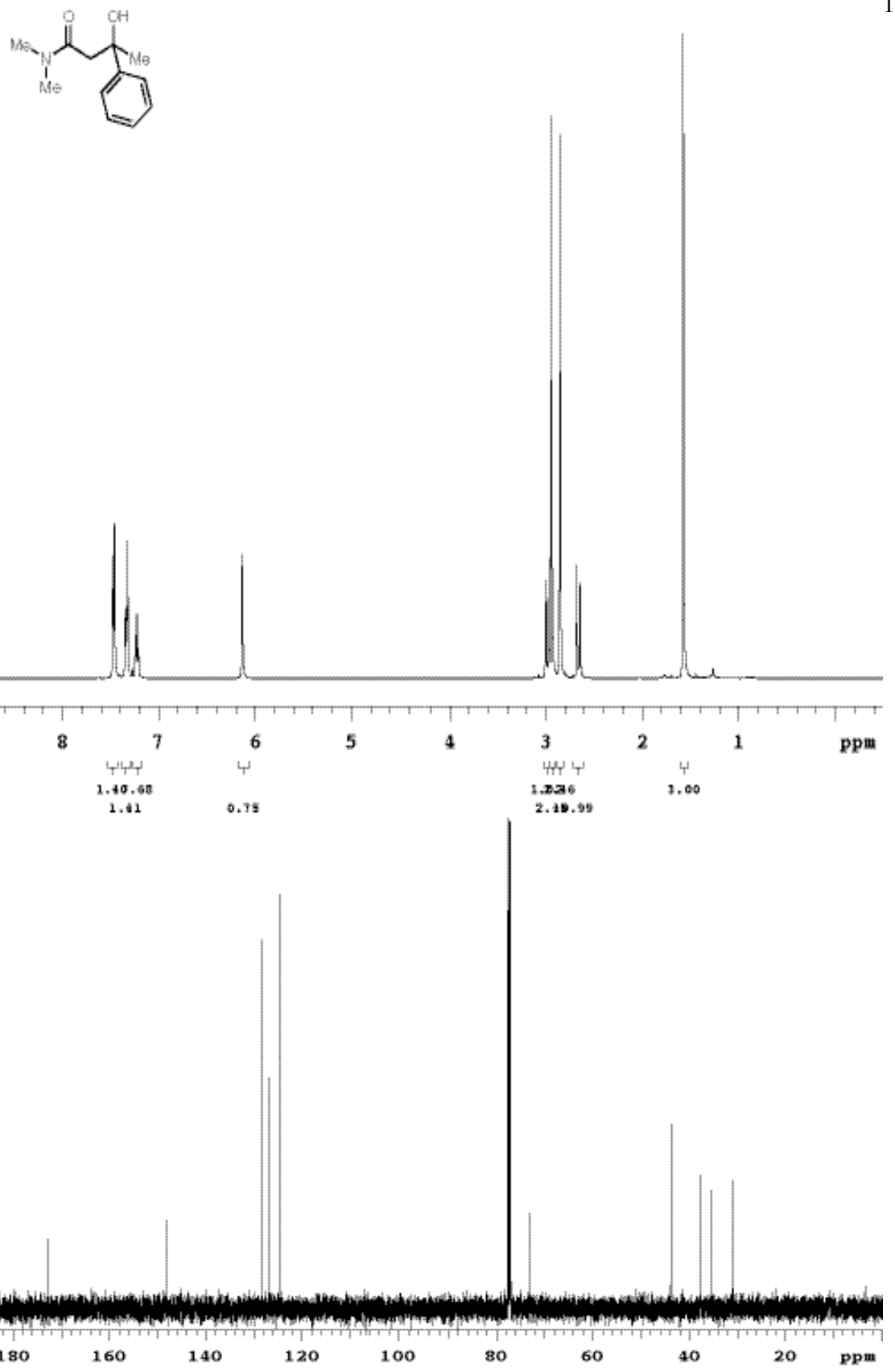
conducted after completion of the reaction. The resulting diastereomeric ratio was 3:1 as determined by 500 MHz ^{1}H NMR of the unpurified reaction mixture.

B: The general procedure was followed as described for the synthesis of β-hydroxy amides **II-85** to **II-87** (**2.8.4**). Following consumption of the acylsilane at 0 °C, the reaction was cooled to –78 °C. To the reaction was added the solution of benzylbromide in THF at –78 °C by cannulation, and stirred at –78 °C for A standard aqueous work-up and desilylation were conducted after completion of the reaction. The resulting diastereomeric ratio was 10:1 as determined by 500 MHz ^{1}H NMR of the unpurified reaction mixture.

C: The general procedure was followed as described above for the synthesis of β-hydroxy amides **II-85** to **II-87** (**2.8.4**). Following formation of the Li-acetamide, the reaction was cooled to –78 °C. The solution of the acylsilane in THF at –78 °C was added to the reaction via cannulation, with rinse, and stirred for 15 min at –78 °C. The reaction was warmed to 0 °C, stirred for 15 min, and recooled to –78 °C. The solution of benzylbromide in THF at –78 °C was added to the reaction by cannulation, and stirred at –78 °C for 12 h. A standard aqueous work-up and desilylation were conducted after completion of the reaction. The resulting diastereomeric ratio was 10:1 as determined by 500 MHz ^{1}H NMR of the unpurified reaction mixture.

2.8.10 Selected NMR Spectra

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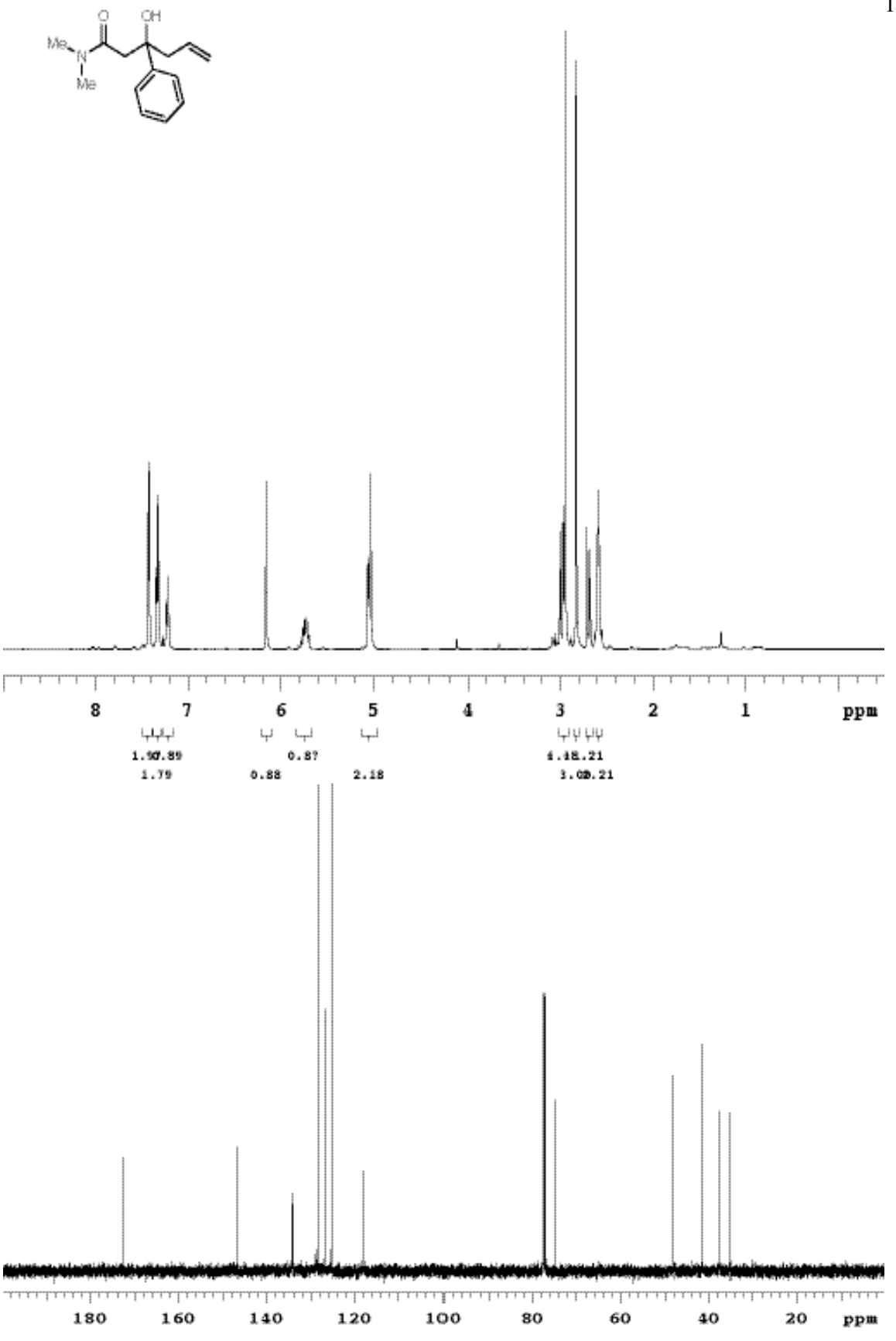
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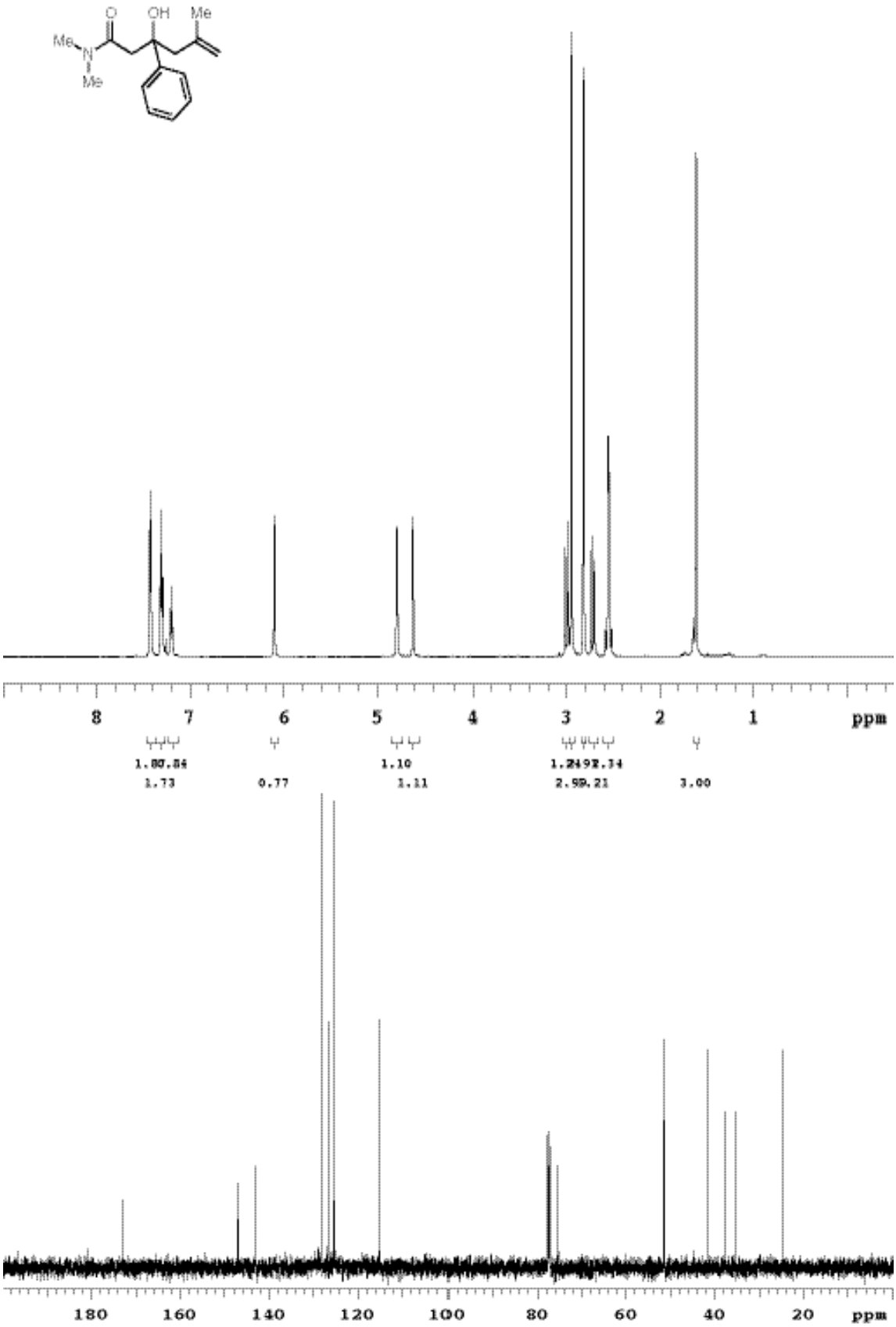
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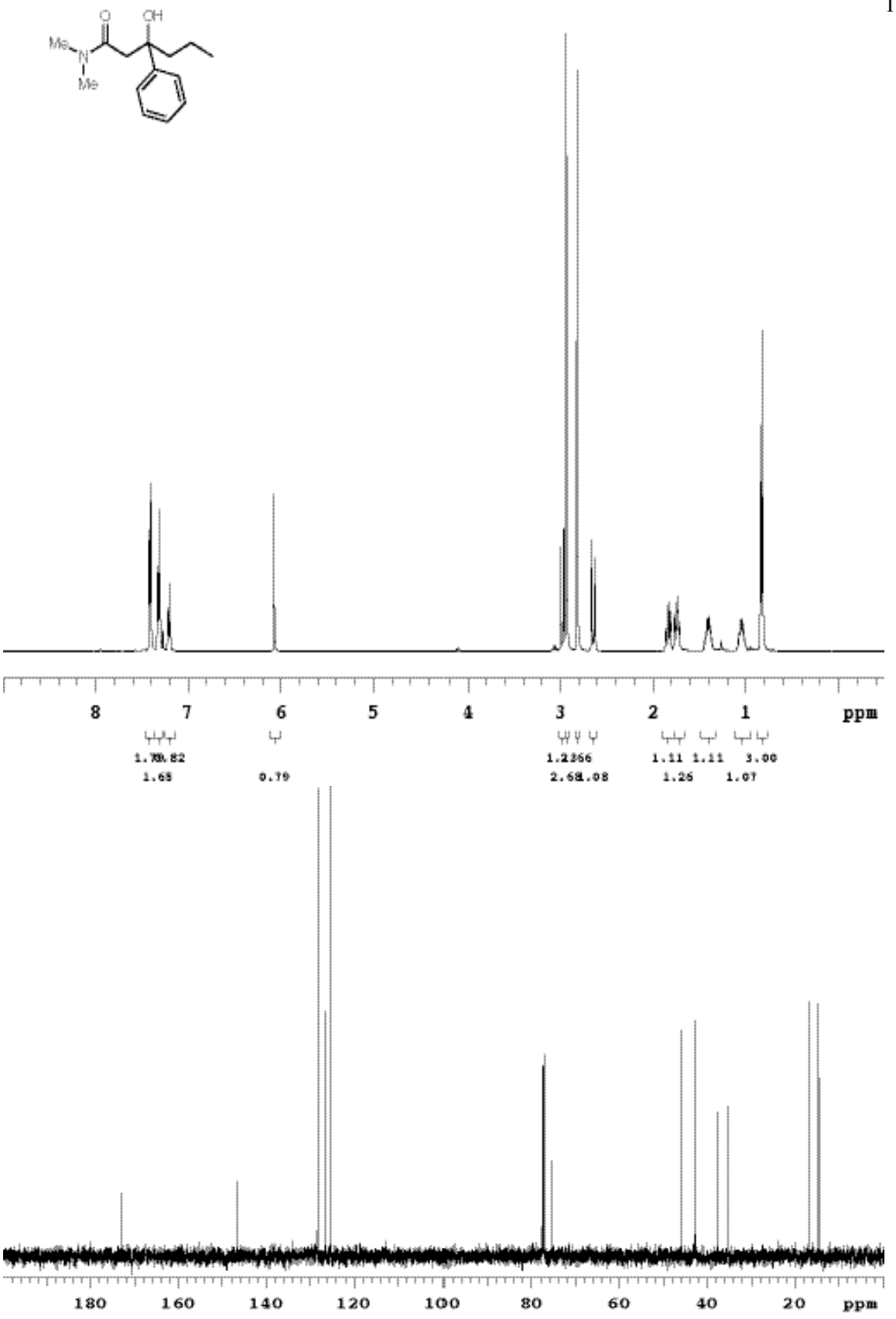
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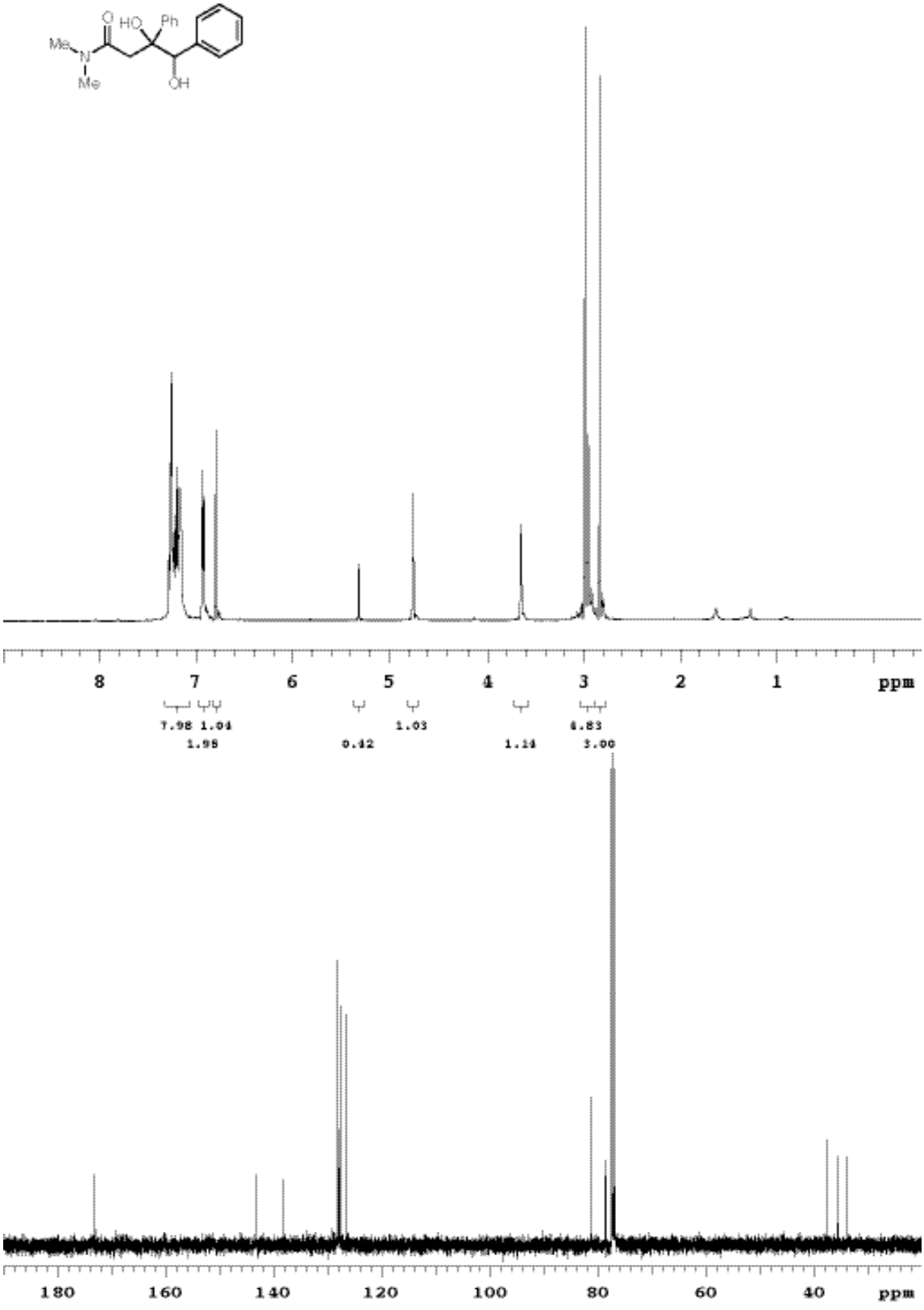

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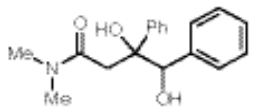

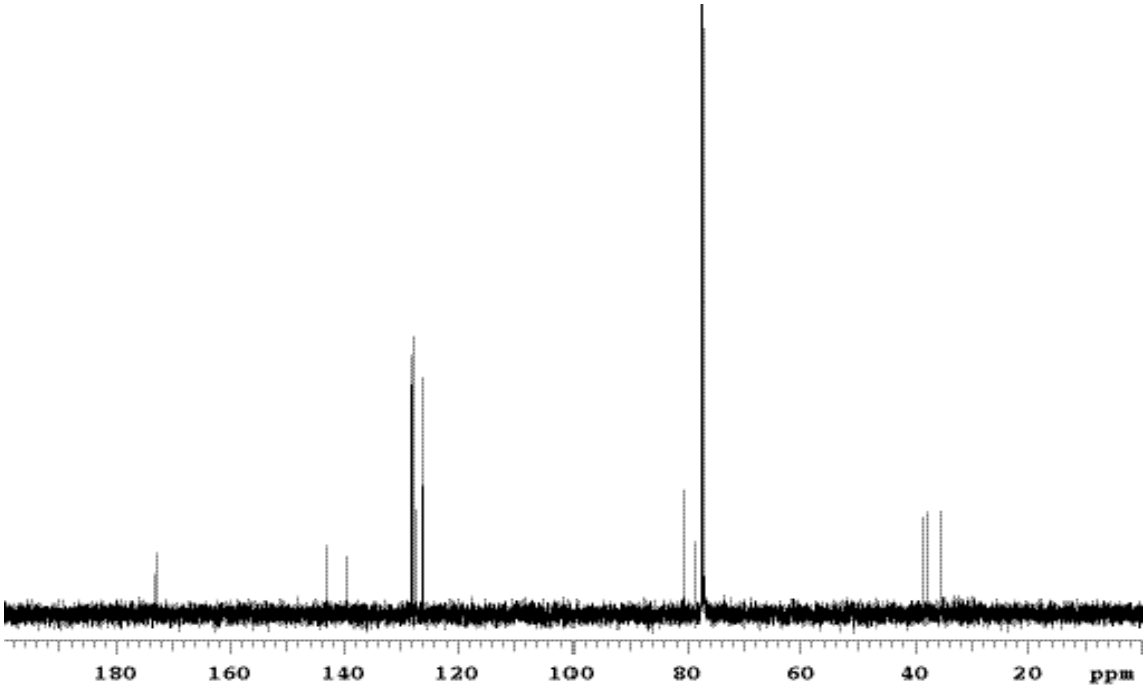

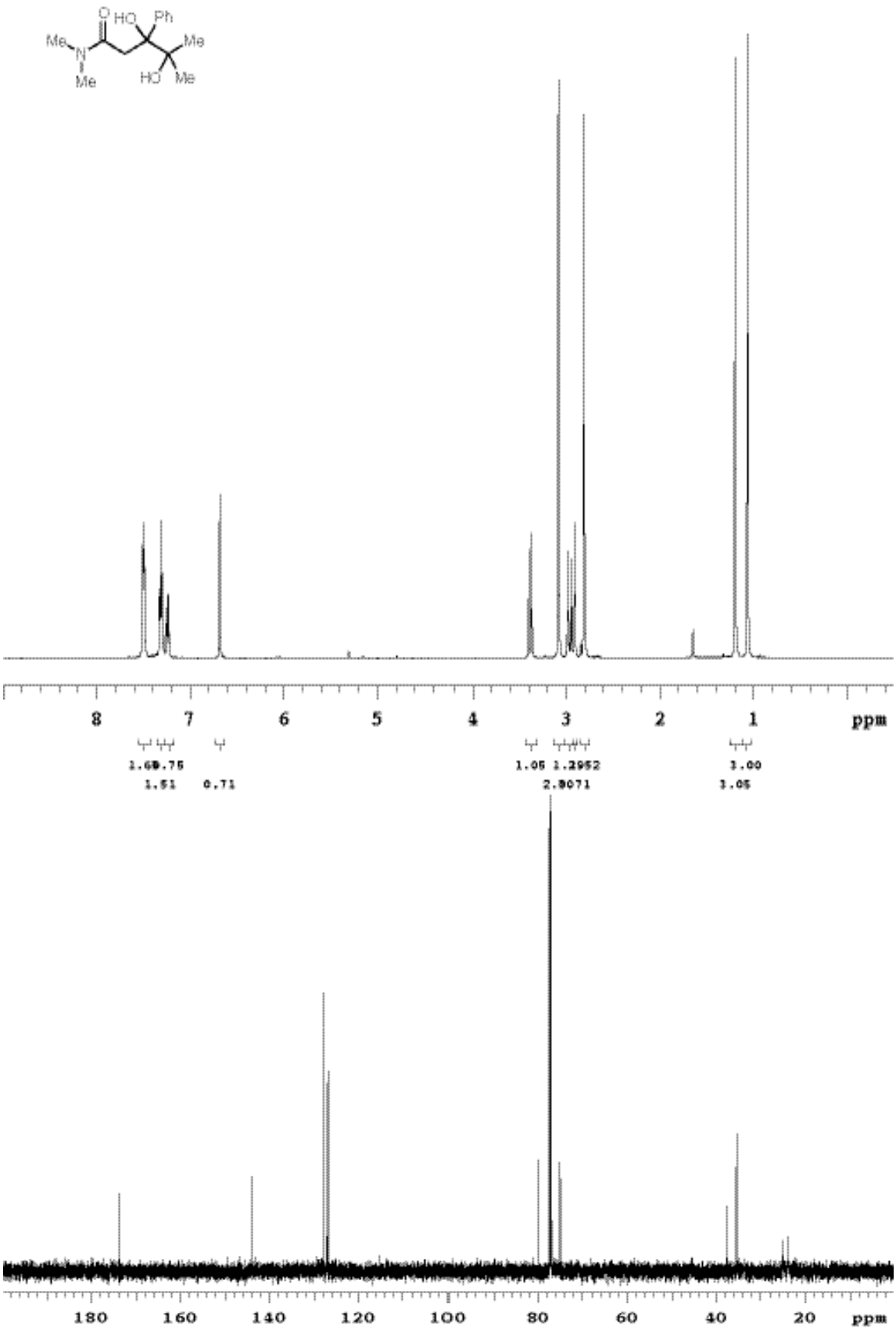
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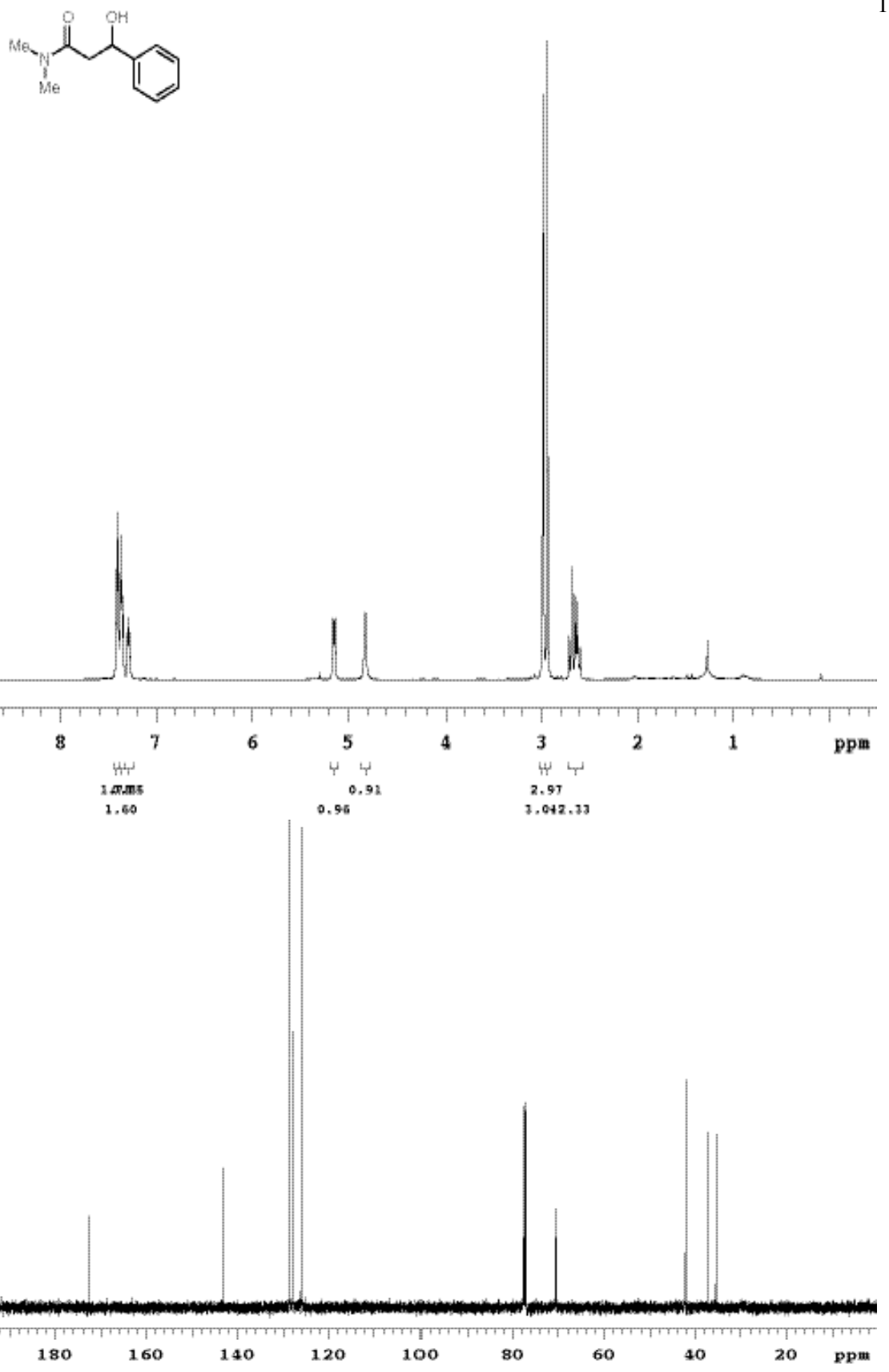
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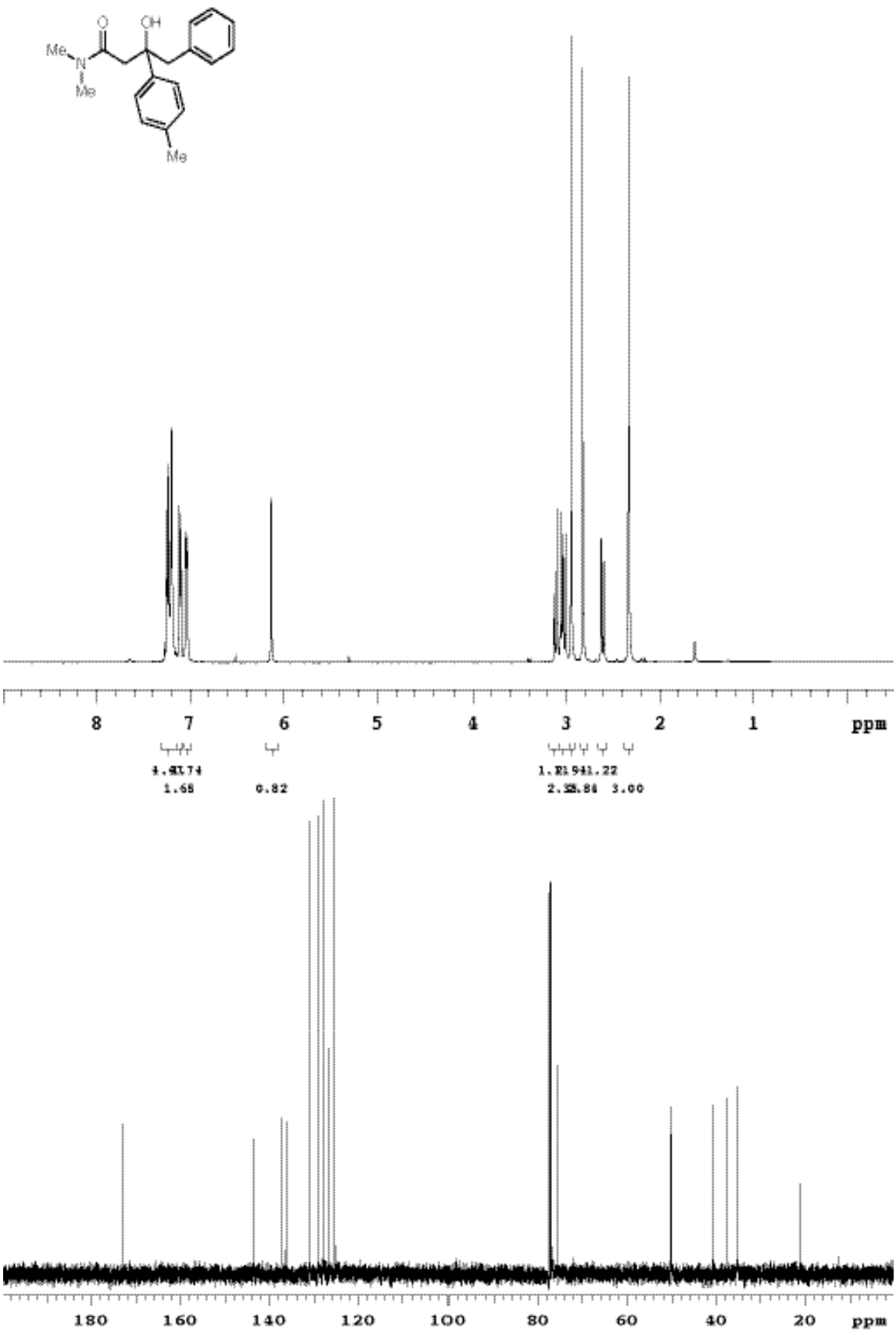
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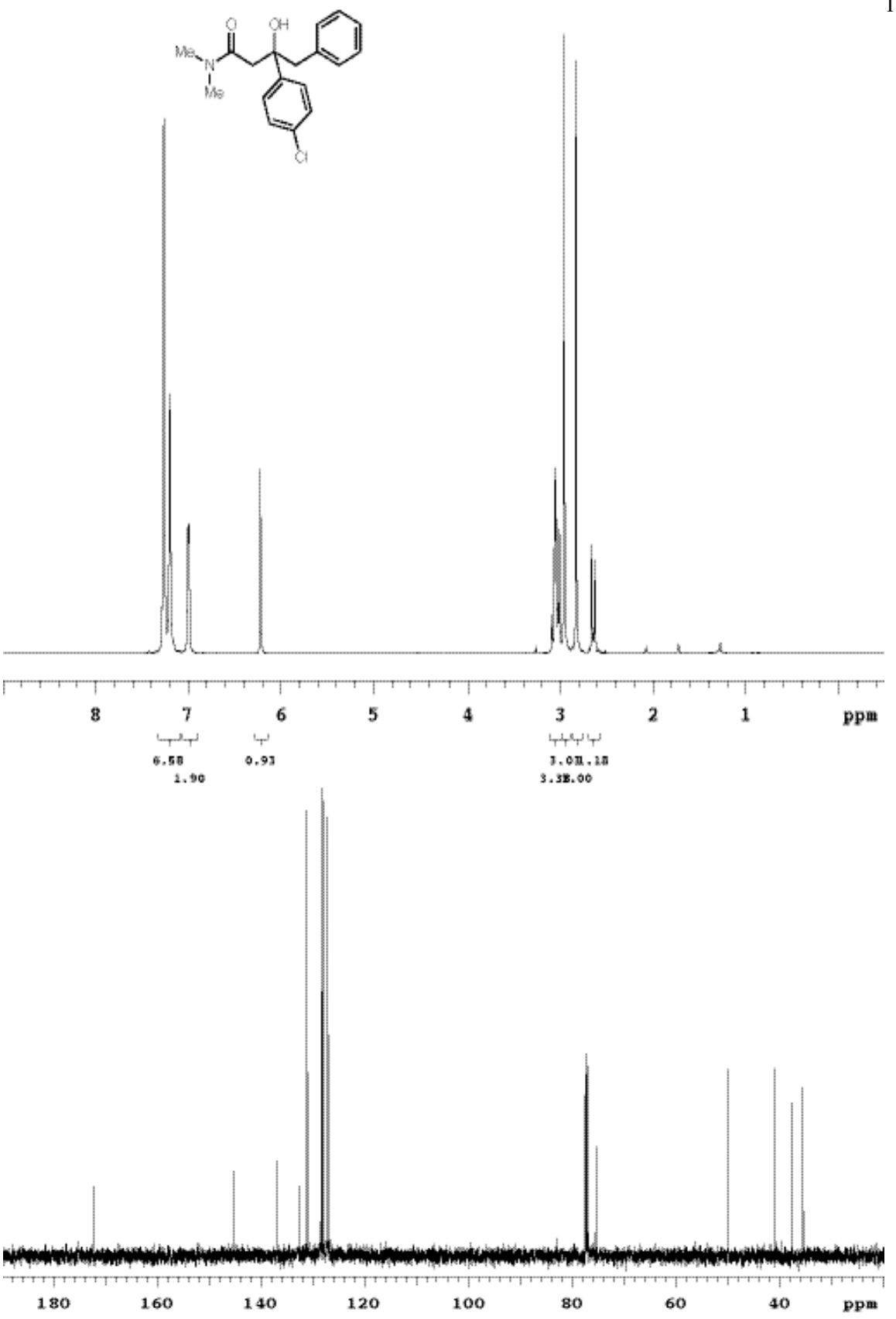
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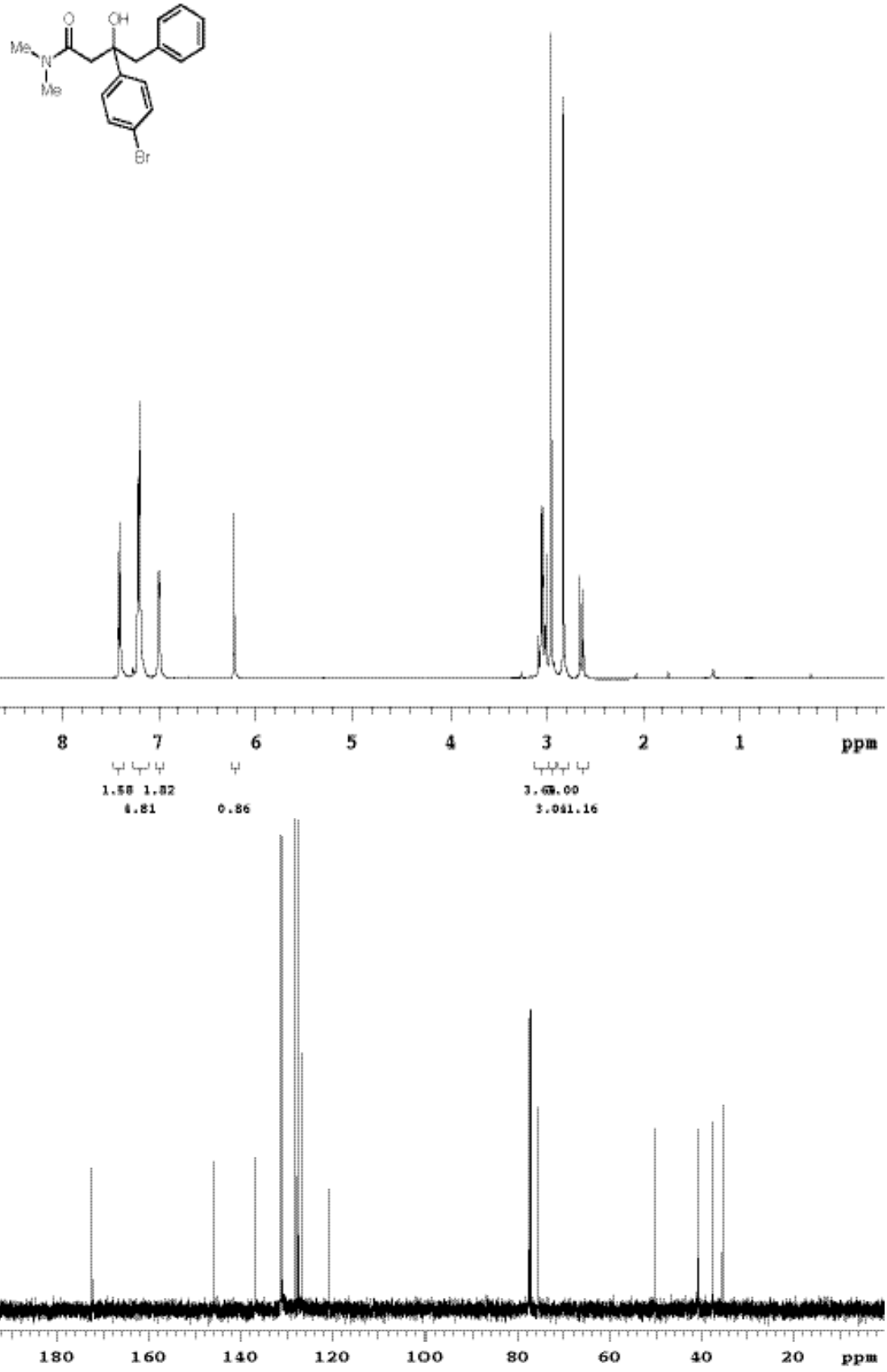
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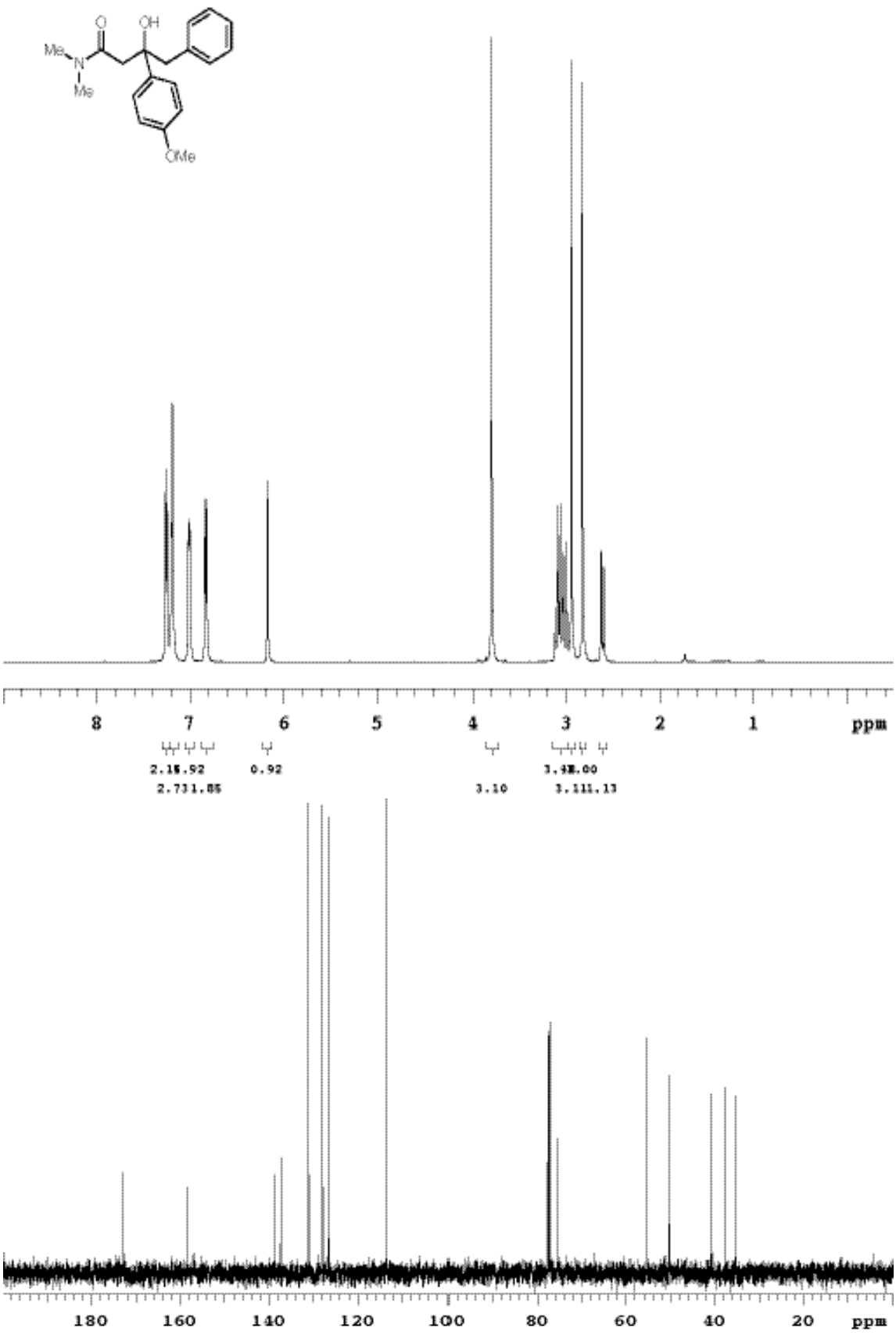
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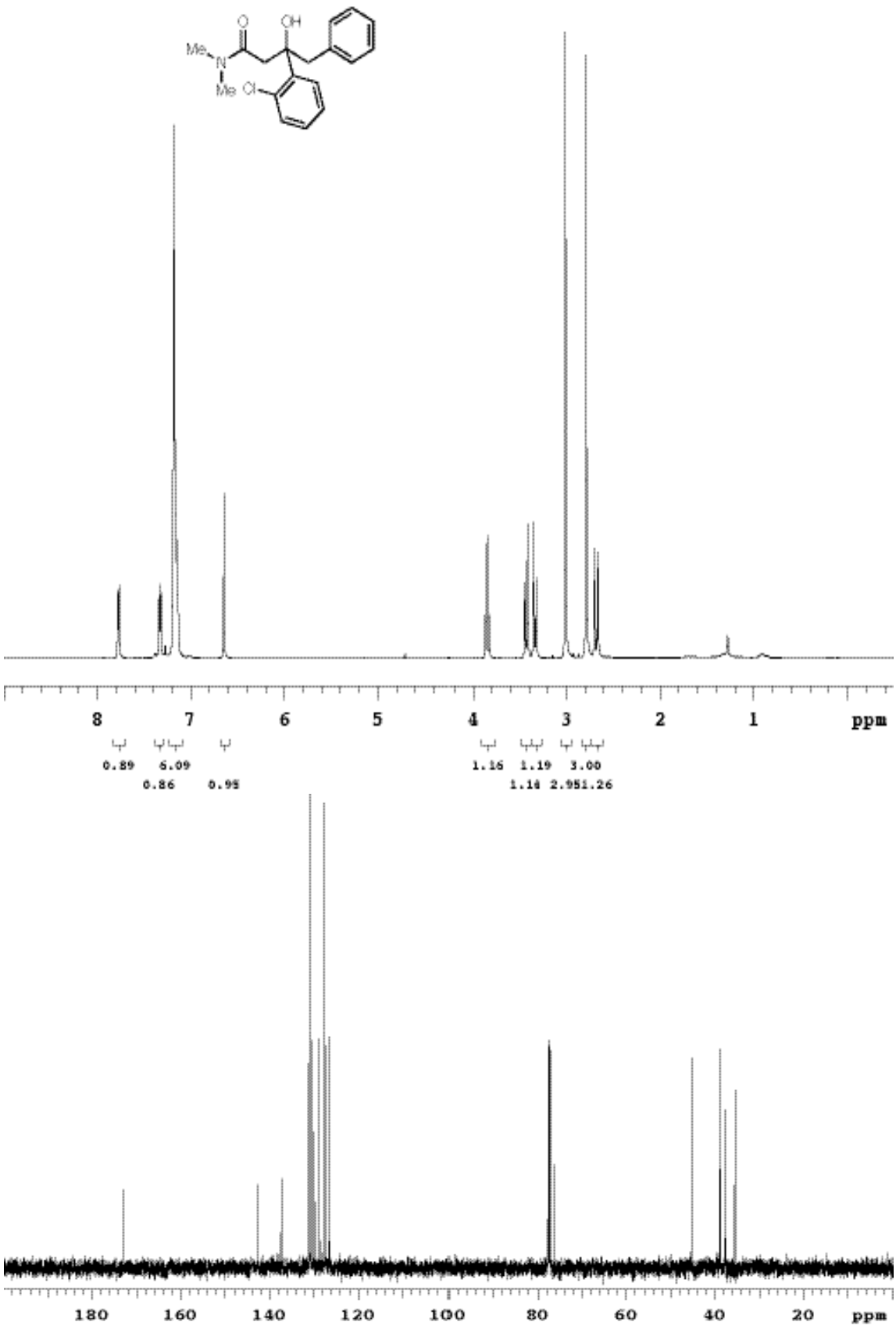
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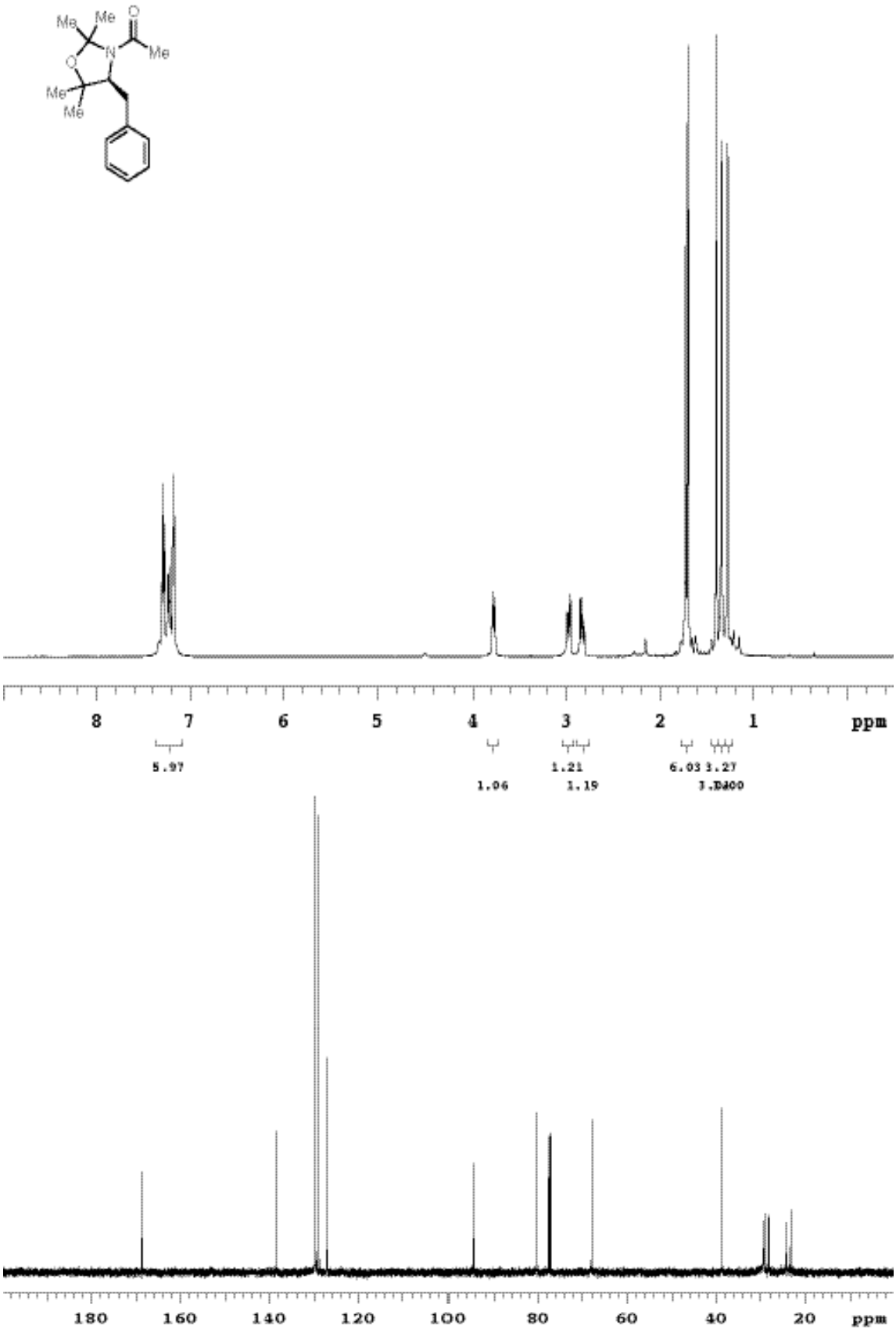
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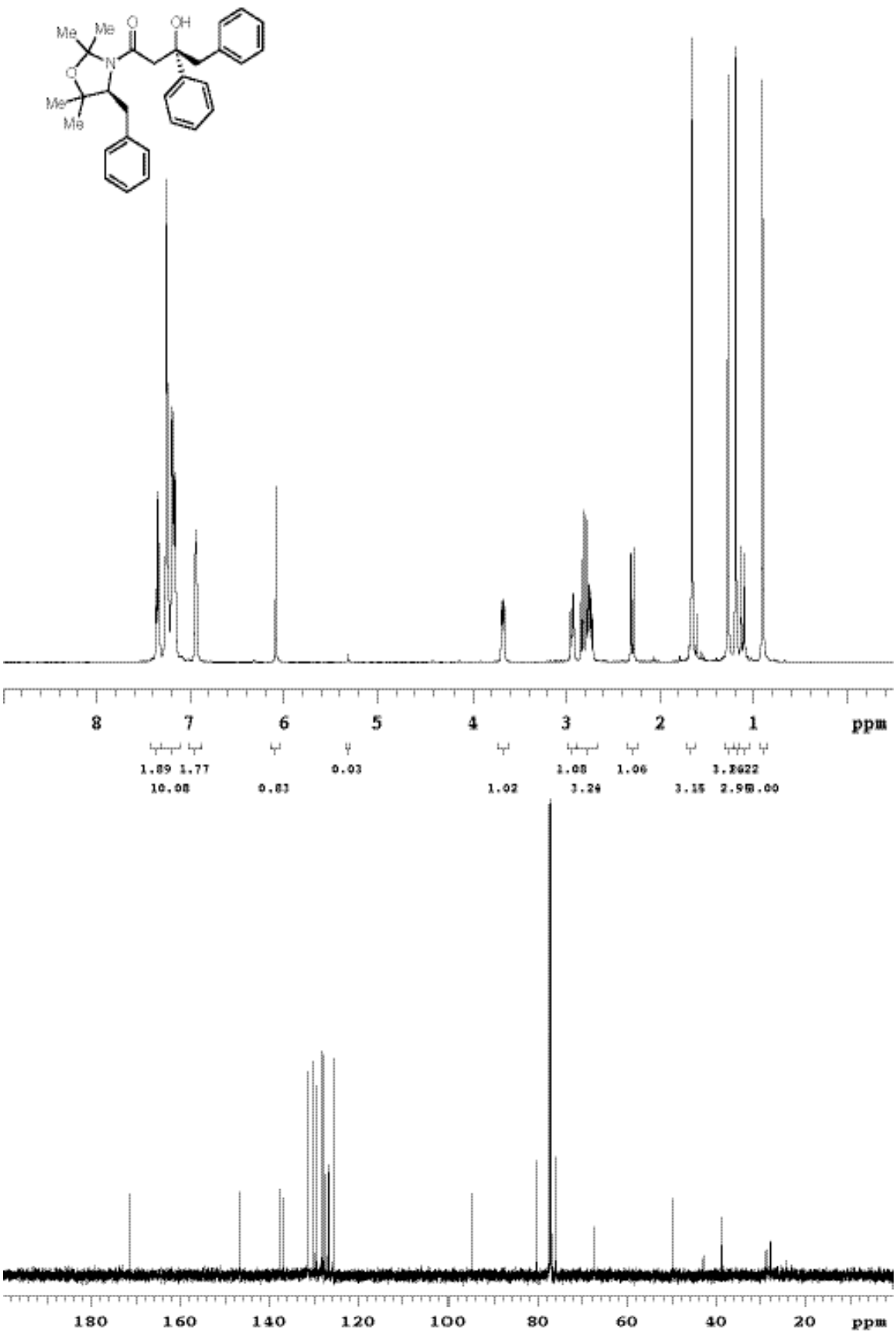
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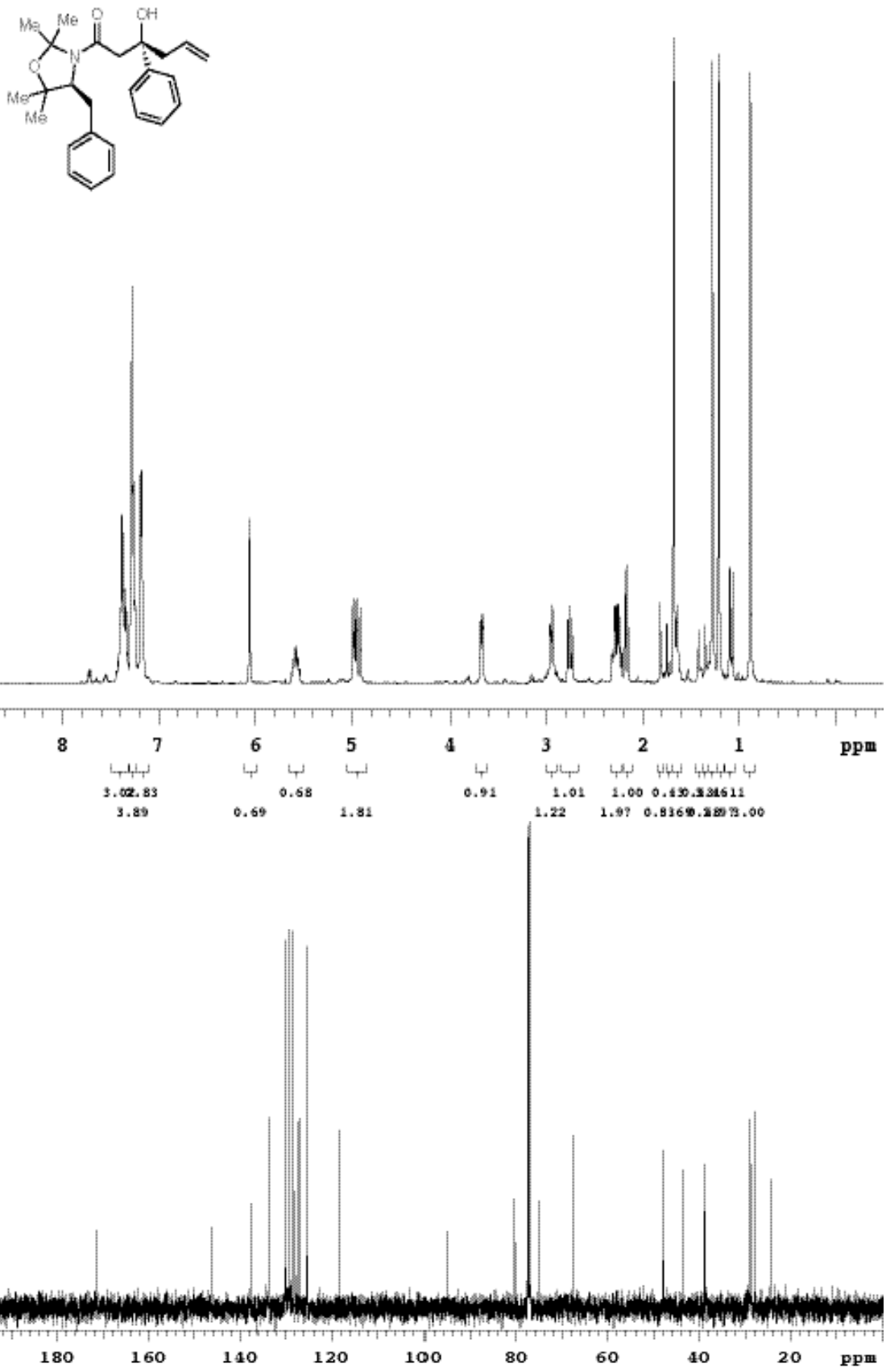
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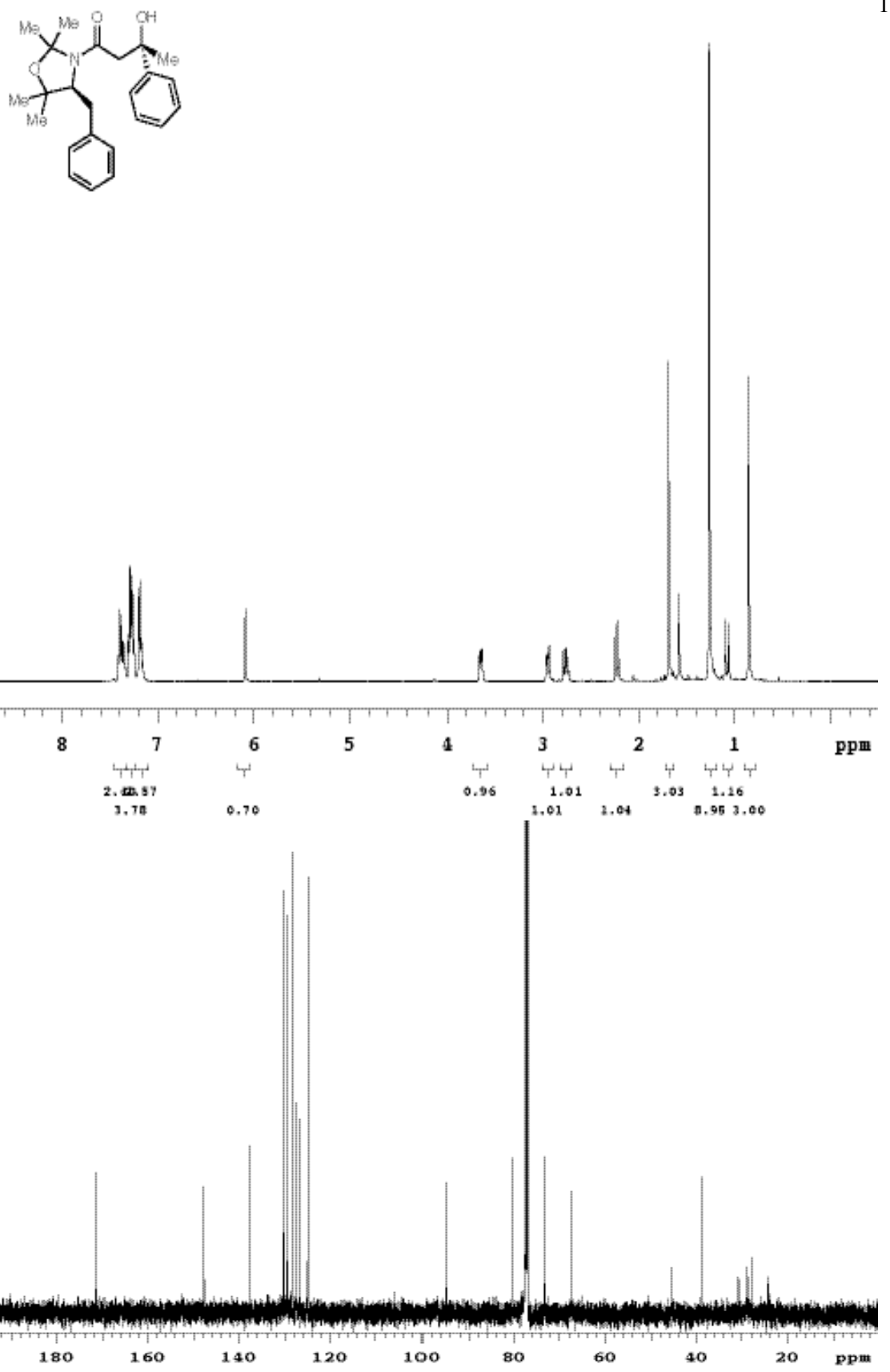
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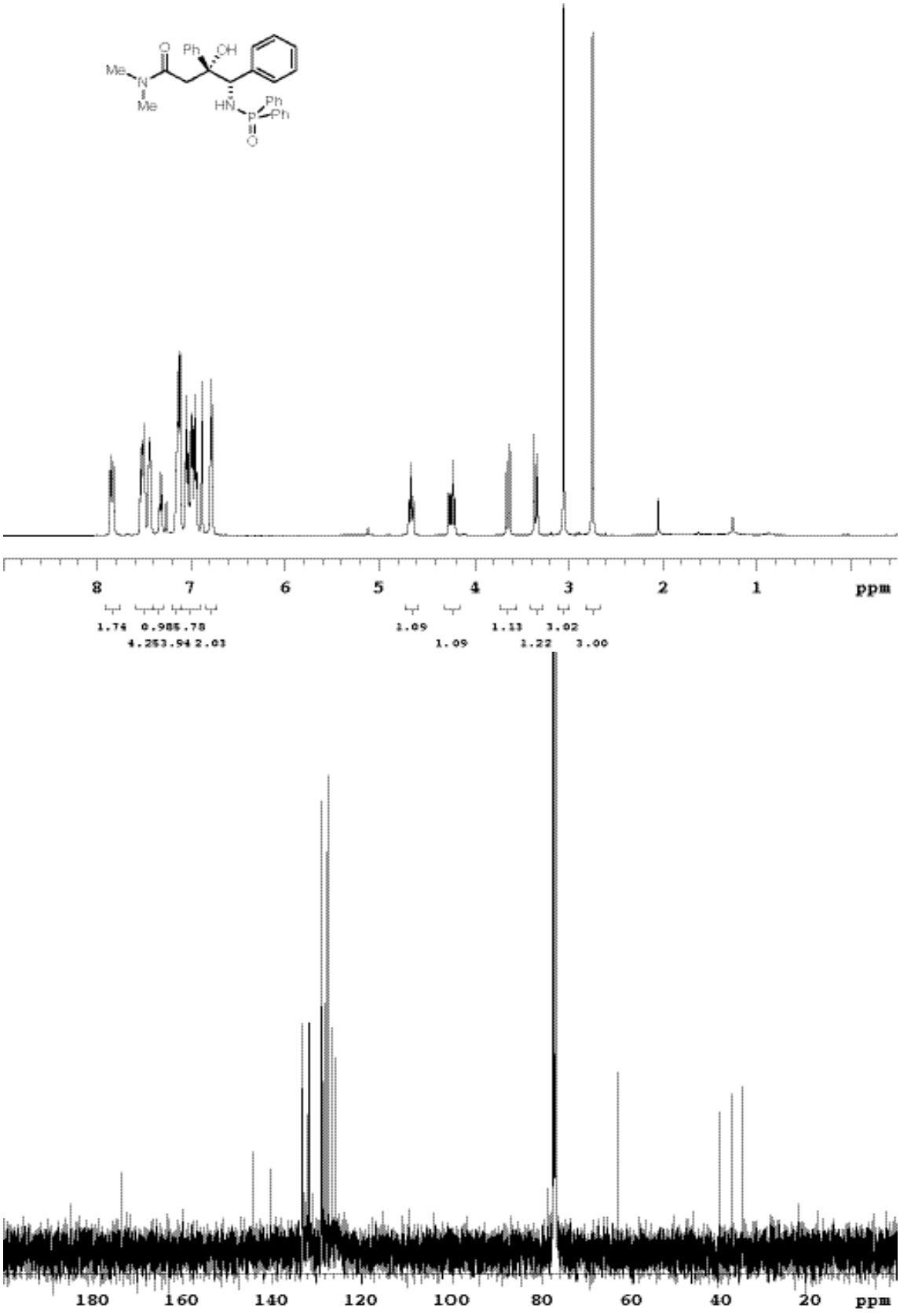
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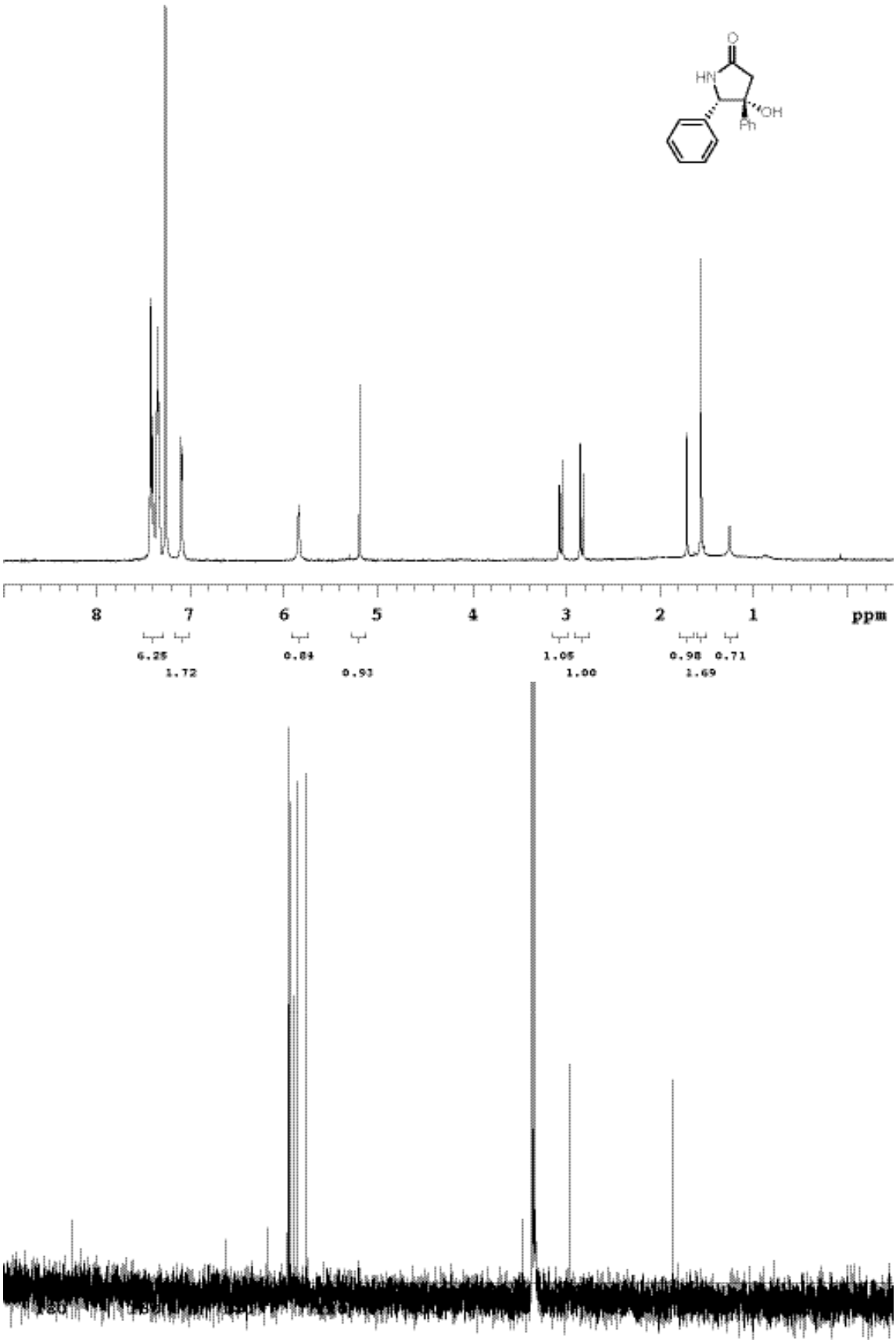
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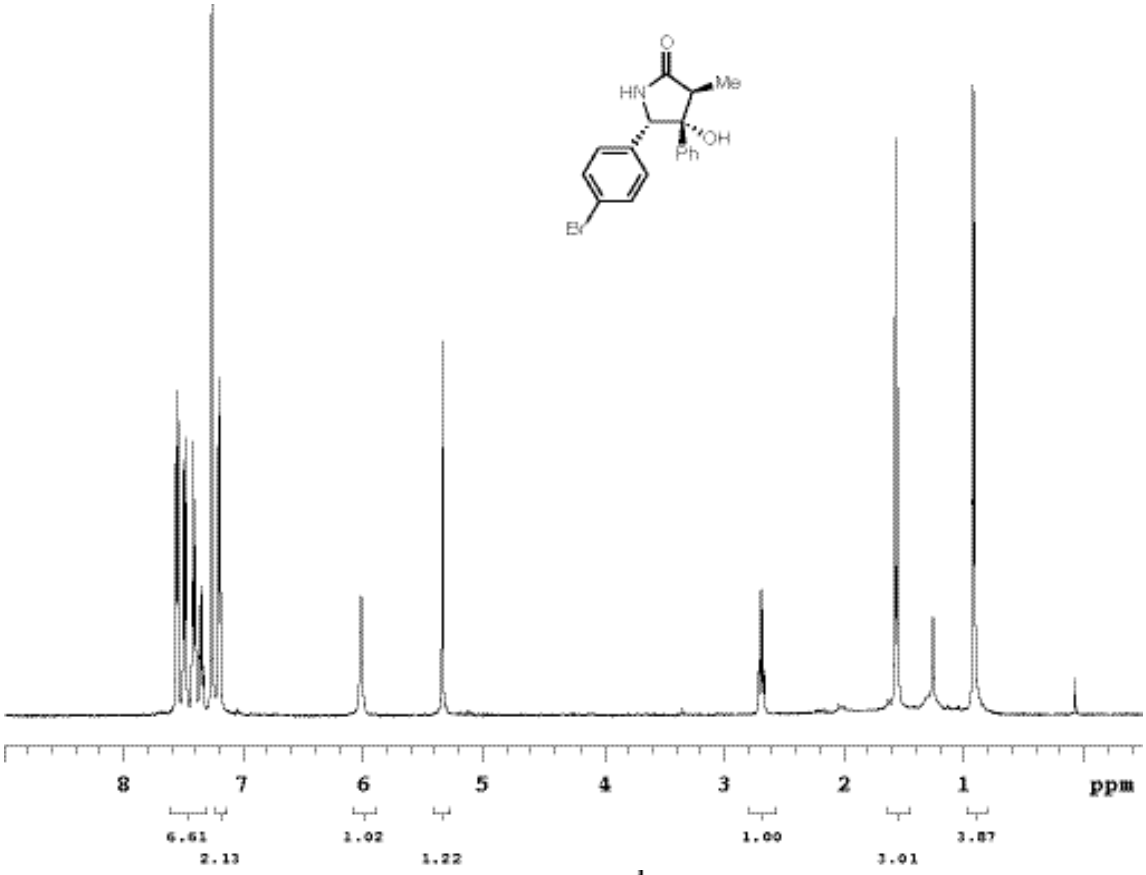
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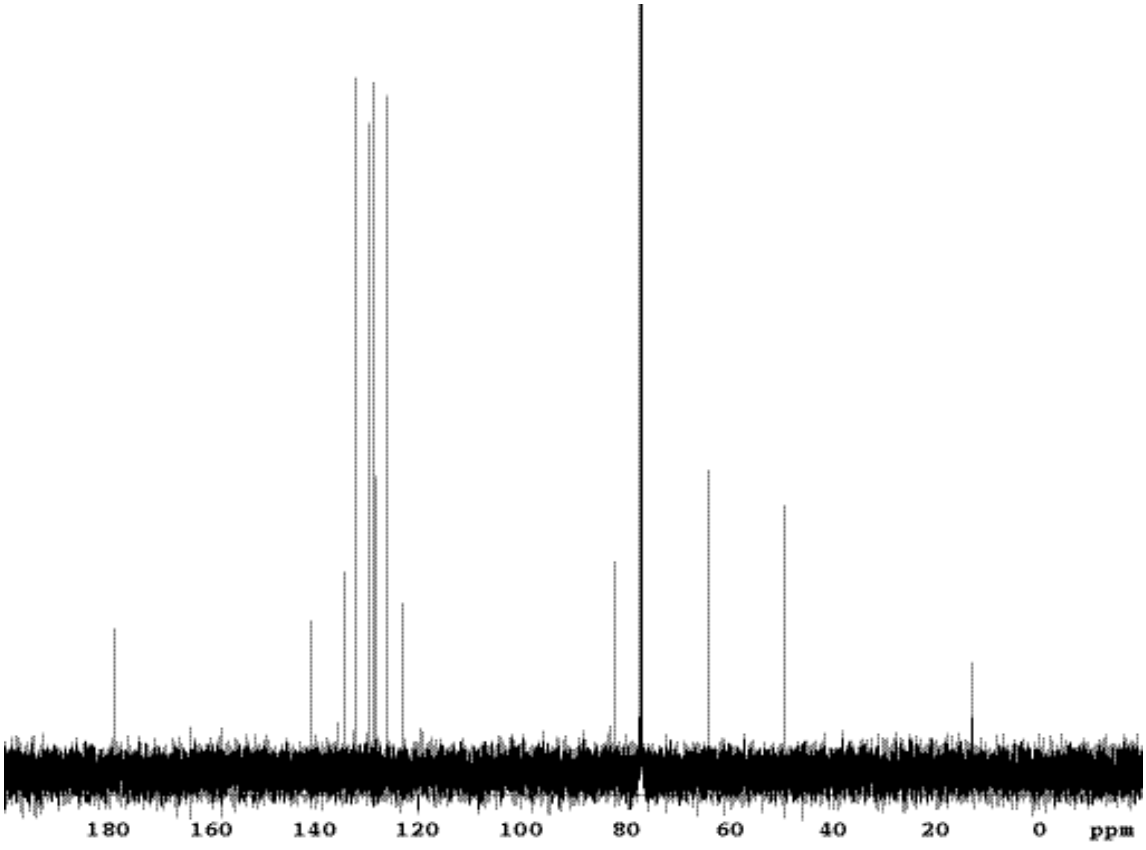
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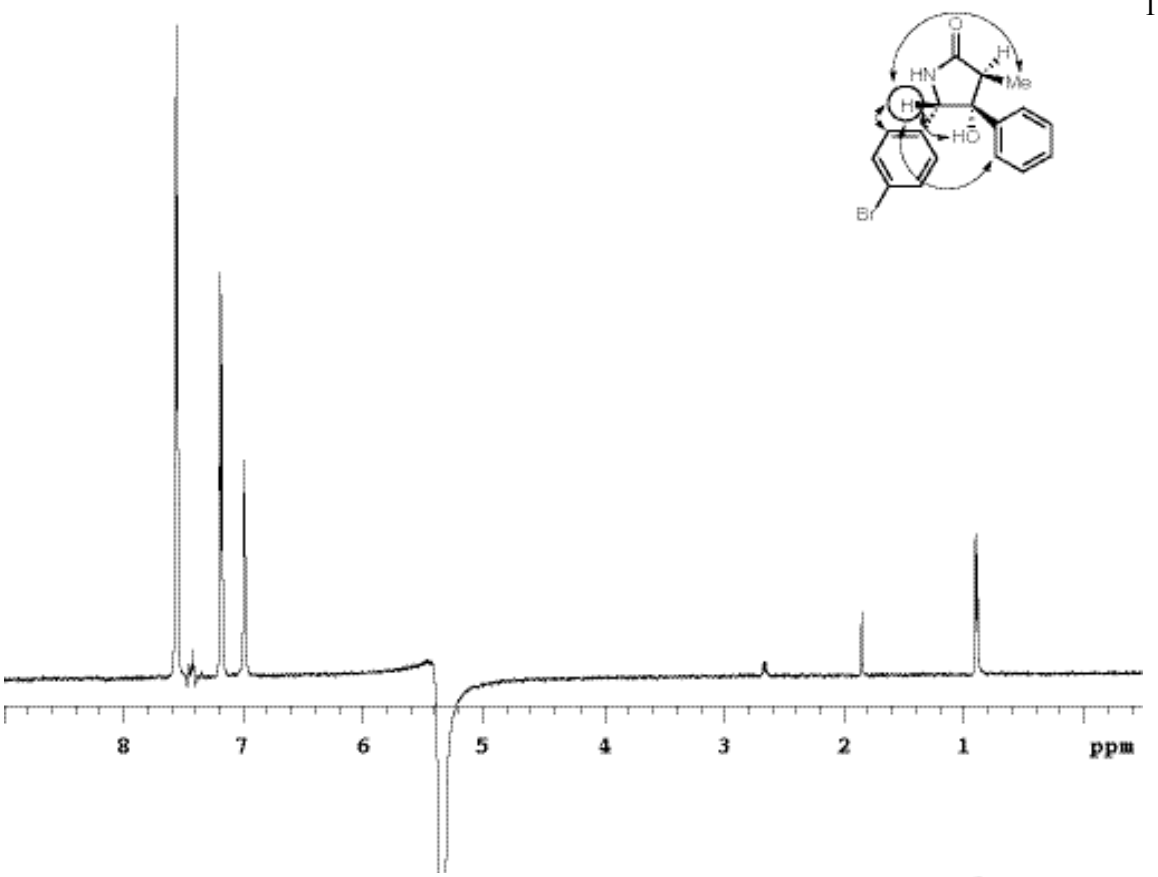
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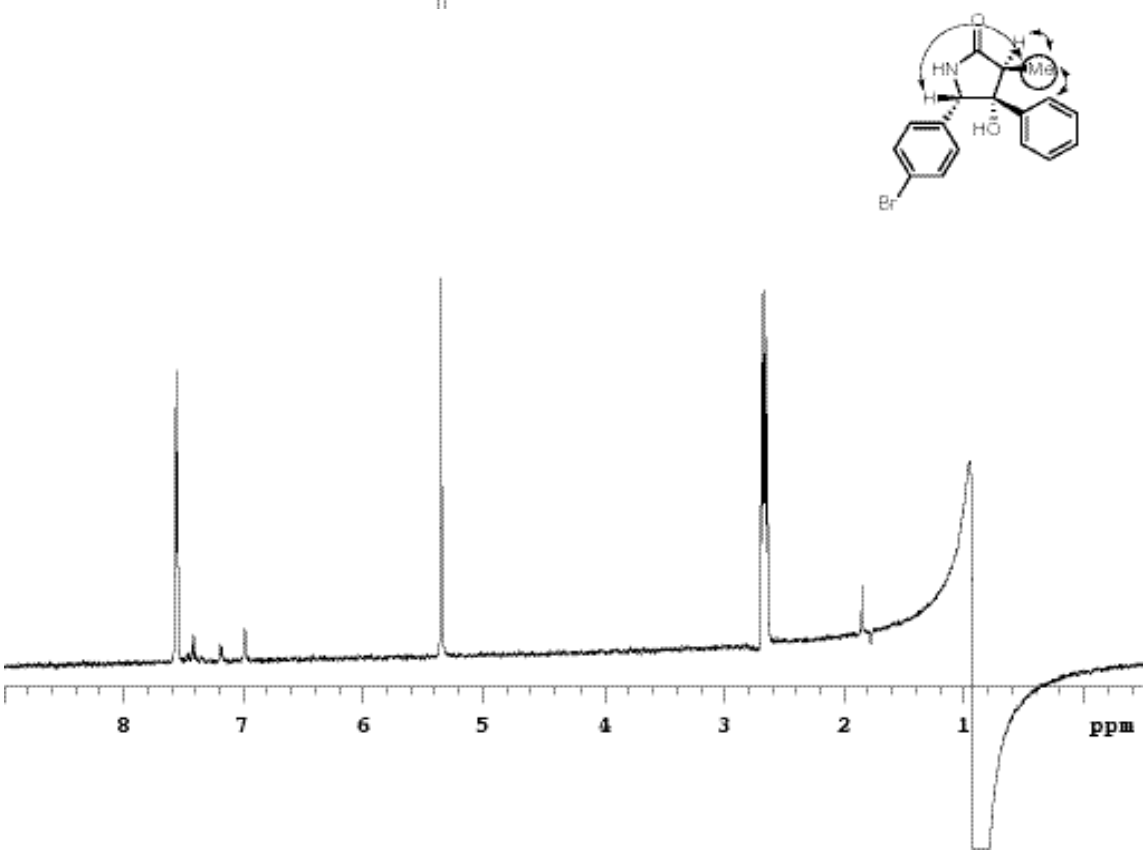
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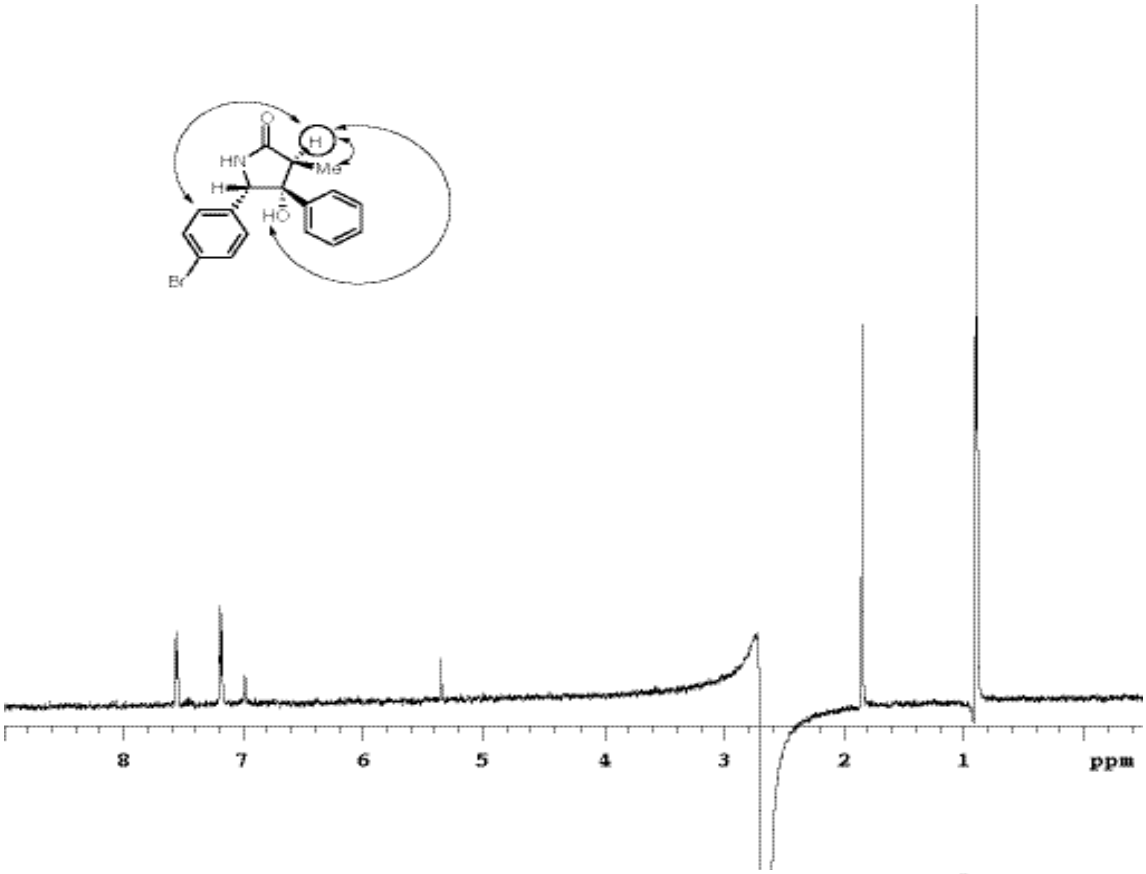
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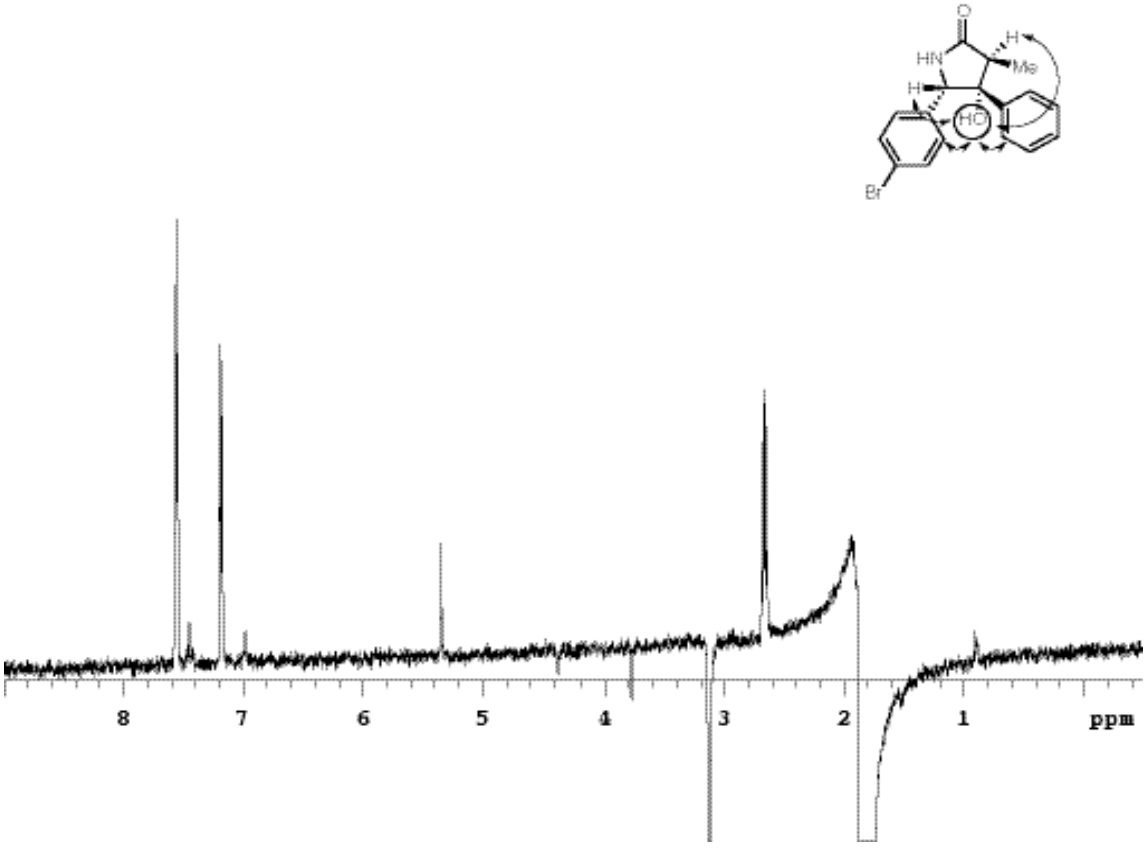
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Appendix 1

Structure Refinement Data, Atomic Coordinates, Bond Lengths, and Bond Angle Data for the Crystal Structure of II-85

Crystal structure data provided by Dr. Charlotte Stern (Northwestern University, c-stern@northwestern.edu) and solved by Troy Reynolds (Northwestern University, t-reynolds2@northwestern.edu)

X-ray Crystal Structure Analysis for II-85

The absolute stereochemistry of **II-85** was determined by X-ray crystallography. Amide **II-85** was crystallized from methylene chloride.

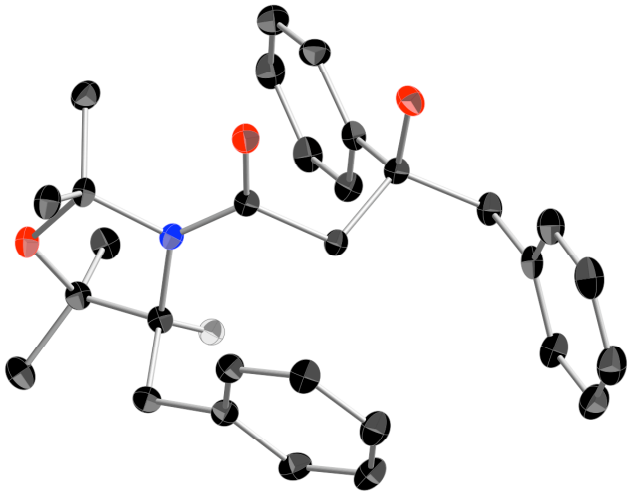


Table 1. Crystal data and structure refinement for **II-85**.

Identification code	S19T
Empirical formula	C30 H35 N1 O3
Formula weight	457.59
Temperature	153(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)
Unit cell dimensions	a = 11.3593(11) Å b = 9.6066(9) Å c = 12.1731(12) Å
Volume	1250.4(2) $Å^3$
Z	2
Density (calculated)	1.215 Mg/m^3
Absorption coefficient	0.077 mm^{-1}
F(000)	492
Crystal size	0.38 x 0.59 x 0.19 mm^3
Theta range for data collection	2.77 to 28.50°
Index ranges	-15≤h≤14, -12≤k≤12, -15≤l≤16
Reflections collected	11483

Independent reflections	5736 [R(int) = 0.0453]
Completeness to theta = 28.50°	99.4 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data/ restraints/ parameters	5736 / 1 / 447
Goodness-of-fit on F^2	1.038
Final R indices [I>2sigma(I)]	R1 = 0.0394, wR2 = 0.1054
R indices (all data)	R1 = 0.0427, wR2 = 0.1090
Absolute structure parameter	-0.7(7)

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for **II-85**.

	x	y	z	U(eq)
C(30)	0.33270(15)	0.39534(18)	-0.11192(12)	0.0326(3)
O(1)	0.47646(10)	0.00046(11)	0.27230(10)	0.0311(2)
O(3)	0.19507(9)	0.50765(11)	-0.02966(8)	0.0284(2)
O(2)	0.42436(10)	0.16250(11)	0.08278(8)	0.0300(2)
N	0.34814(10)	0.37578(12)	0.09921(9)	0.0229(2)
C(16)	0.41851(12)	0.26320(14)	0.14465(11)	0.0235(3)
C(15)	0.49017(12)	0.25482(14)	0.27556(11)	0.0235(3)
C(17)	0.34577(12)	0.51037(14)	0.15597(11)	0.0240(3)
C(1)	0.45097(12)	0.12227(14)	0.32706(11)	0.0245(3)
C(9)	0.31085(12)	0.13198(14)	0.31011(11)	0.0261(3)
C(3)	0.66845(13)	0.12684(16)	0.49131(12)	0.0291(3)
C(28)	0.26279(12)	0.38064(15)	-0.02531(11)	0.0258(3)
C(29)	0.17306(15)	0.25689(17)	-0.05664(14)	0.0338(3)
C(10)	0.22523(14)	0.05048(16)	0.22629(14)	0.0335(3)
C(20)	0.63403(14)	0.46453(16)	0.14193(13)	0.0293(3)
C(2)	0.52878(13)	0.10800(16)	0.45834(12)	0.0295(3)
C(24)	0.64439(14)	0.57551(17)	0.32157(13)	0.0328(3)
C(14)	0.26549(13)	0.22692(16)	0.37309(13)	0.0300(3)
C(23)	0.75908(15)	0.5129(2)	0.37733(13)	0.0379(4)
C(19)	0.57901(12)	0.55026(15)	0.20372(12)	0.0270(3)
C(26)	0.11735(14)	0.48936(18)	0.13530(15)	0.0324(3)
C(21)	0.74951(14)	0.40251(18)	0.19789(14)	0.0342(3)
C(4)	0.74135(15)	0.04037(18)	0.44686(14)	0.0355(3)
C(13)	0.13769(15)	0.23585(19)	0.35482(14)	0.0362(3)
C(11)	0.09726(15)	0.06113(19)	0.20712(15)	0.0392(4)
C(7)	0.85693(16)	0.2520(2)	0.60086(15)	0.0425(4)
C(18)	0.44943(13)	0.60997(15)	0.14715(13)	0.0282(3)
C(6)	0.92738(16)	0.1667(2)	0.55624(16)	0.0436(4)
C(8)	0.72766(15)	0.23255(19)	0.56778(13)	0.0367(3)
C(25)	0.21077(13)	0.55746(15)	0.08663(12)	0.0265(3)
C(5)	0.86976(16)	0.0622(2)	0.47853(15)	0.0420(4)
C(12)	0.05359(15)	0.1526(2)	0.27201(15)	0.0392(4)

C(22)	0.81160(15)	0.42549(19)	0.31563(15)	0.0383(4)
C(27)	0.19042(16)	0.71358(16)	0.07756(15)	0.0349(3)

Table 3. Bond lengths (Å) and angles (°) for **II-85**.

C(30)-C(28)	1.526(2)
O(1)-C(1)	1.4241(17)
O(3)-C(28)	1.4338(17)
O(3)-C(25)	1.4472(17)
O(2)-C(16)	1.2414(17)
N-C(16)	1.3477(17)
N-C(17)	1.4704(17)
N-C(28)	1.4992(16)
C(16)-C(15)	1.5273(17)
C(15)-C(1)	1.5496(18)
C(17)-C(25)	1.5475(18)
C(17)-C(18)	1.5488(19)
C(1)-C(9)	1.5371(18)
C(1)-C(2)	1.5493(18)
C(9)-C(10)	1.389(2)
C(9)-C(14)	1.397(2)
C(3)-C(8)	1.388(2)
C(3)-C(4)	1.404(2)
C(3)-C(2)	1.5104(19)
C(28)-C(29)	1.528(2)
C(10)-C(11)	1.396(2)
C(20)-C(21)	1.392(2)
C(20)-C(19)	1.397(2)
C(24)-C(23)	1.387(2)
C(24)-C(19)	1.3961(19)
C(14)-C(13)	1.395(2)
C(23)-C(22)	1.388(2)
C(19)-C(18)	1.512(2)
C(26)-C(25)	1.526(2)
C(21)-C(22)	1.385(2)
C(4)-C(5)	1.393(2)
C(13)-C(12)	1.385(3)
C(11)-C(12)	1.381(3)
C(7)-C(6)	1.378(3)
C(7)-C(8)	1.398(2)
C(6)-C(5)	1.383(3)
C(25)-C(27)	1.516(2)

Table 4. Anisotropic displacement parameters ($Å^2$) for **II-85**.

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(30)	0.0347(7)	0.0422(8)	0.0229(6)	0.0015(6)	0.0123(6)	0.0060(6)
O(1)	0.0374(5)	0.0259(5)	0.0324(5)	0.0020(4)	0.0148(4)	0.0051(4)
O(3)	0.0274(5)	0.0328(5)	0.0243(5)	0.0036(4)	0.0076(4)	0.0075(4)
O(2)	0.0350(5)	0.0298(5)	0.0254(5)	-0.0017(4)	0.0105(4)	0.0054(4)
N	0.0216(5)	0.0267(6)	0.0207(5)	-0.0004(4)	0.0073(4)	0.0009(4)
C(16)	0.0221(6)	0.0271(6)	0.0230(6)	0.0013(5)	0.0100(5)	0.0012(5)
C(15)	0.0223(6)	0.0274(6)	0.0206(6)	0.0011(5)	0.0071(5)	0.0004(5)
C(17)	0.0258(6)	0.0245(6)	0.0238(6)	0.0005(5)	0.0112(5)	0.0024(5)
C(1)	0.0239(6)	0.0269(6)	0.0241(6)	0.0020(5)	0.0098(5)	0.0016(5)
C(9)	0.0251(6)	0.0276(6)	0.0265(6)	0.0050(5)	0.0100(5)	-0.0001(5)
C(3)	0.0272(6)	0.0379(7)	0.0228(6)	0.0091(5)	0.0092(5)	0.0070(6)
C(28)	0.0240(6)	0.0311(7)	0.0209(6)	0.0019(5)	0.0056(5)	0.0043(5)
C(29)	0.0280(7)	0.0360(8)	0.0329(7)	-0.0036(6)	0.0046(6)	-0.0008(6)
C(10)	0.0327(7)	0.0312(7)	0.0365(7)	-0.0016(6)	0.0114(6)	-0.0069(6)
C(20)	0.0277(7)	0.0359(7)	0.0262(6)	0.0026(5)	0.0115(6)	-0.0025(5)
C(2)	0.0276(6)	0.0379(8)	0.0255(6)	0.0073(6)	0.0123(5)	0.0053(6)
C(24)	0.0303(7)	0.0406(8)	0.0309(7)	-0.0063(6)	0.0148(6)	-0.0076(6)
C(14)	0.0265(7)	0.0351(7)	0.0292(6)	0.0001(6)	0.0103(5)	0.0004(6)
C(23)	0.0308(7)	0.0526(10)	0.0280(7)	-0.0049(7)	0.0069(6)	-0.0079(7)
C(19)	0.0255(6)	0.0292(6)	0.0274(6)	0.0017(5)	0.0103(5)	-0.0058(5)
C(26)	0.0272(7)	0.0365(8)	0.0371(8)	0.0037(6)	0.0157(6)	0.0026(6)
C(21)	0.0306(7)	0.0430(8)	0.0325(7)	0.0008(6)	0.0152(6)	0.0030(6)
C(4)	0.0335(7)	0.0420(8)	0.0327(7)	0.0058(6)	0.0133(6)	0.0095(6)
C(13)	0.0295(7)	0.0444(9)	0.0383(8)	0.0070(7)	0.0163(6)	0.0050(6)
C(11)	0.0322(8)	0.0396(8)	0.0422(8)	0.0031(7)	0.0078(6)	-0.0085(6)
C(7)	0.0341(8)	0.0522(10)	0.0356(8)	0.0050(7)	0.0044(7)	0.0002(7)
C(18)	0.0294(7)	0.0254(7)	0.0310(7)	0.0009(5)	0.0120(5)	-0.0011(5)
C(6)	0.0268(8)	0.0591(11)	0.0432(9)	0.0130(8)	0.0096(7)	0.0033(7)
C(8)	0.0312(7)	0.0481(9)	0.0285(7)	0.0024(6)	0.0072(6)	0.0042(7)
C(25)	0.0267(6)	0.0274(6)	0.0270(6)	0.0010(5)	0.0110(5)	0.0029(5)
C(5)	0.0345(8)	0.0539(10)	0.0421(8)	0.0118(8)	0.0190(7)	0.0147(7)
C(12)	0.0255(7)	0.0480(9)	0.0441(9)	0.0120(7)	0.0119(6)	-0.0006(6)
C(22)	0.0260(7)	0.0504(9)	0.0365(8)	0.0015(7)	0.0080(6)	0.0018(6)
C(27)	0.0381(8)	0.0282(7)	0.0416(8)	0.0040(6)	0.0176(7)	0.0083(6)

Table 5. Hydrogen coordinates and isotropic displacement parameters ($Å^2$) for **II-85**.

	x	y	z	U(eq)
H(7)	0.896(2)	0.330(3)	0.652(2)	0.058(7)
H(10)	0.2513(19)	-0.013(2)	0.1788(18)	0.038(5)
H(24)	0.607(2)	0.643(2)	0.3649(18)	0.039(5)
H(20)	0.5886(17)	0.4480(19)	0.0628(16)	0.026(4)
H(14)	0.3225(17)	0.2947(19)	0.4255(16)	0.025(4)
H(181)	0.4428(16)	0.689(2)	0.1832(15)	0.021(4)
H(4)	0.700(2)	-0.031(2)	0.3908(18)	0.038(5)
H(182)	0.4336(16)	0.626(2)	0.0634(16)	0.030(4)
H(21)	0.788(2)	0.339(3)	0.156(2)	0.048(6)
H(5)	0.919(2)	0.005(2)	0.4466(18)	0.039(5)
H(1)	0.462(2)	0.032(3)	0.195(2)	0.055(6)
H(222)	0.5080(16)	0.0195(19)	0.4799(15)	0.023(4)
H(152)	0.5831(18)	0.249(2)	0.2848(16)	0.031(4)
H(151)	0.4801(16)	0.3396(18)	0.3195(15)	0.023(4)
H(17)	0.3565(16)	0.4977(19)	0.2392(15)	0.025(4)
H(211)	0.4959(17)	0.1795(18)	0.5041(16)	0.023(4)
H(12)	-0.036(2)	0.164(3)	0.261(2)	0.056(6)
H(23)	0.803(2)	0.530(3)	0.464(2)	0.054(6)
H(6)	1.011(2)	0.180(3)	0.574(2)	0.055(6)
H(22)	0.895(2)	0.389(2)	0.3579(18)	0.043(5)
H(11)	0.039(2)	0.005(2)	0.1485(19)	0.044(5)
H(8)	0.678(2)	0.299(2)	0.602(2)	0.047(6)
H(13)	0.113(2)	0.304(2)	0.400(2)	0.045(6)
H(262)	0.1330(18)	0.392(2)	0.1459(16)	0.034(5)
H(303)	0.387(2)	0.485(3)	-0.0981(19)	0.047(6)
H(273)	0.105(2)	0.733(2)	0.0259(18)	0.039(5)
H(292)	0.2133(19)	0.171(2)	-0.0645(18)	0.038(5)
H(261)	0.036(2)	0.498(2)	0.0815(19)	0.041(5)
H(302)	0.2749(19)	0.402(2)	-0.1884(18)	0.038(5)
H(263)	0.1233(18)	0.535(2)	0.2077(18)	0.033(5)
H(271)	0.2530(19)	0.758(2)	0.0518(17)	0.035(5)
H(301)	0.383(2)	0.313(2)	-0.1098(18)	0.037(5)
H(293)	0.1346(18)	0.245(2)	0.0029(17)	0.034(4)
H(272)	0.208(2)	0.752(2)	0.161(2)	0.050(6)
H(291)	0.105(2)	0.282(2)	-0.128(2)	0.053(6)

Table 6. Torsion angles (°) for **II-85**.

C(28)-O(3)-C(25)	110.96(10)
C(16)-N-C(17)	127.97(11)
C(16)-N-C(28)	122.11(11)
C(17)-N-C(28)	109.85(10)
O(2)-C(16)-N	121.48(12)
O(2)-C(16)-C(15)	118.23(12)
N-C(16)-C(15)	120.26(11)
C(16)-C(15)-C(1)	109.92(11)
N-C(17)-C(25)	99.95(10)
N-C(17)-C(18)	112.07(11)
C(25)-C(17)-C(18)	114.72(11)
O(1)-C(1)-C(9)	110.61(11)
O(1)-C(1)-C(2)	105.95(11)
C(9)-C(1)-C(2)	110.37(10)
O(1)-C(1)-C(15)	110.75(10)
C(9)-C(1)-C(15)	108.77(10)
C(2)-C(1)-C(15)	110.38(11)
C(10)-C(9)-C(14)	118.33(13)
C(10)-C(9)-C(1)	120.06(13)
C(14)-C(9)-C(1)	121.53(12)
C(8)-C(3)-C(4)	118.42(14)
C(8)-C(3)-C(2)	119.57(13)
C(4)-C(3)-C(2)	122.01(14)
O(3)-C(28)-N	102.69(10)
O(3)-C(28)-C(30)	107.07(11)
N-C(28)-C(30)	113.07(11)
O(3)-C(28)-C(29)	110.40(11)
N-C(28)-C(29)	112.17(11)
C(30)-C(28)-C(29)	111.01(12)
C(9)-C(10)-C(11)	120.84(15)
C(21)-C(20)-C(19)	120.52(13)
C(3)-C(2)-C(1)	116.48(11)
C(23)-C(24)-C(19)	120.90(14)
C(13)-C(14)-C(9)	120.62(14)
C(24)-C(23)-C(22)	120.12(14)
C(24)-C(19)-C20	118.43(13)
C(24)-C(19)-C(18)	120.04(13)
C(20)-C(19)-C(18)	121.47(12)
C(22)-C(21)-C(20)	120.33(15)
C(5)-C(4)-C(3)	120.20(16)

C(12)-C(13)-C(14)	120.37(16)
C(12)-C(11)-C(10)	120.39(15)
C(6)-C(7)-C(8)	120.02(18)
C(19)-C(18)-C(17)	112.34(11)
C(7)-C(6)-C(5)	119.82(16)
C(3)-C(8)-C(7)	120.99(16)
O(3)-C(25)-C(27)	106.88(12)
O(3)-C(25)-C(26)	111.45(12)
C(27)-C(25)-C(26)	110.09(13)
O(3)-C(25)-C(17)	102.07(10)
C(27)-C(25)-C(17)	115.32(13)
C(26)-C(25)-C(17)	110.72(12)
C(6)-C(5)-C(4)	120.53(16)
C(11)-C(12)-C(13)	119.41(15)
C(21)-C(22)-C(23)	119.64(15)

Appendix 2

Structure Refinement Data, Atomic Coordinates, Bond Lengths, and Bond Angle Data for the Crystal Structure of (±)-II-114

Crystal structure data provided by Dr. Charlotte Stern (Northwestern University, c-stern@northwestern.edu) and solved by Troy Reynolds (Northwestern University, t-reynolds2@northwestern.edu)

X-ray Crystal Structure Analysis for (±)-II-114

The absolute stereochemistry of **(±)-II-114** was determined by X-ray crystallography. Amide **(±)-II-114** was crystallized from slow-diffusion of hexanes into methylene chloride.

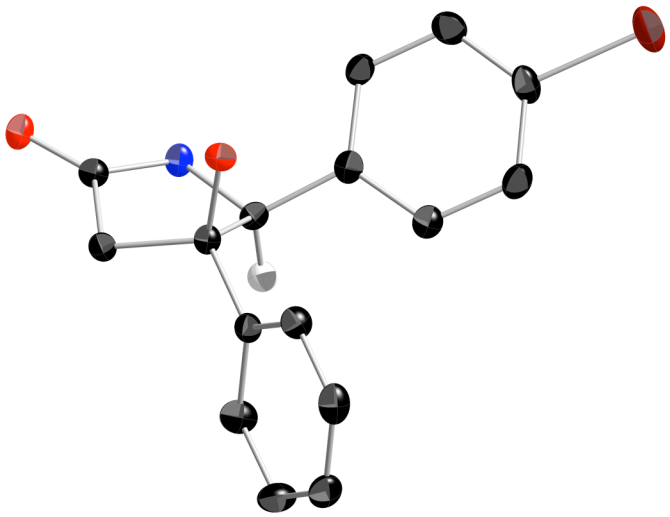


Table 1. Crystal data and structure refinement for **(±)-II-114**.

Identification code	s59vm
Empirical formula	$C_{17}H_{14}BrCl_2NO_2$
Formula weight	417.11
Temperature	153(2) K
Wavelength	0.71073 Å
Crystal system, space group	triclinic, P-1
Unit cell dimensions	a = 7.4375(5) Å; α = 93.6070(10) °
	b = 8.8670(6) Å; β = 97.4310(10) °
	c = 14.4876(10) Å; γ = 113.7950(10) °
Volume	859.87(10) $Å^3$
Z, Calculated density	2, 1.466 Mg/m^3
Absorption coefficient	2.551 mm^{-1}
F(000)	382
Crystal size	0.36 x 0.24 x 0.10 mm
Theta range for data collection	1.43 to 28.48 °
Limiting indices	-9≤h≤9, -11≤k≤11, -19≤l≤18
Reflections collected / unique	7903 / 3902 [R(int) = 0.0750]
Completeness to theta = 28.48	90.1 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3902 / 0 / 216
Goodness-of-fit on F^2	0.974
Final R indices [I>2sigma(I)]	R1 = 0.0354, wR2 = 0.0916

R indices (all data)	R1 = 0.0433, wR2 = 0.0970
Largest diff. peak and hole	0.932 and -0.509 e.A^{-3}

Table 2. Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2x10^3$) for **(±)-II-114**.

	x	y	z	U(eq)
Br	11981(1)	3014(1)	10586(1)	39(1)
C(1)	8108(3)	1120(2)	4964(1)	17(1)
C(2)	6840(3)	2092(2)	5018(1)	16(1)
C(3)	7220(3)	2691(2)	6072(1)	15(1)
C(4)	9456(3)	2986(2)	6351(1)	15(1)
C(5)	6849(3)	4221(2)	6312(1)	17(1)
C(6)	7739(3)	5656(2)	5890(2)	23(1)
C(7)	7437(3)	7067(3)	6115(2)	27(1)
C(8)	6226(3)	7073(3)	6771(2)	25(1)
C(9)	5321(3)	5657(3)	7186(2)	24(1)
C(10)	5634(3)	4243(2)	6964(2)	20(1)
C(11)	10075(3)	2933(2)	7375(1)	18(1)
C(12)	10272(3)	1561(2)	7713(2)	21(1)
C(13)	10826(3)	1574(3)	8670(2)	25(1)
C(14)	11184(3)	2962(3)	9279(2)	24(1)
C(15)	11010(3)	4347(3)	8965(2)	24(1)
C(16)	10447(3)	4314(2)	8007(2)	21(1)
C(17)	5645(4)	207(3)	8601(2)	35(1)
Cl(1)	3211(1)	-1150(1)	8036(1)	46(1)
Cl(2)	5648(1)	1895(1)	9307(1)	44(1)
N(1)	9564(2)	1695(2)	5707(1)	18(1)
O(1)	7834(2)	-7(2)	4339(1)	19(1)
O(2)	6128(2)	1344(2)	6542(1)	17(1)

Table 3. Bond lengths [Å] and angles [°] for **(±)-II-114**.

Br-C(14)	1.901(2)
C(1)-O(1)	1.238(2)
C(1)-N(1)	1.333(2)
C(1)-C(2)	1.518(3)
C(2)-C(3)	1.535(3)
C(3)-O(2)	1.419(2)
C(3)-C(5)	1.518(3)
C(3)-C(4)	1.569(2)
C(4)-N(1)	1.465(2)
C(4)-C(11)	1.505(3)
C(5)-C(10)	1.393(3)
C(5)-C(6)	1.398(3)
C(6)-C(7)	1.385(3)
C(7)-C(8)	1.391(3)
C(8)-C(9)	1.382(3)
C(9)-C(10)	1.391(3)
C(11)-C(16)	1.391(3)
C(11)-C(12)	1.393(3)
C(12)-C(13)	1.393(3)
C(13)-C(14)	1.379(3)
C(14)-C(15)	1.384(3)
C(15)-C(16)	1.391(3)
C(17)-Cl(2)	1.758(3)
C(17)-Cl(1)	1.770(3)

Table 4. Anisotropic displacement parameters ($Å^2$ x 10^3) for **(±)-II-114**.

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br	55(1)	55(1)	18(1)	0(1)	-1(1)	37(1)
C(1)	15(1)	19(1)	18(1)	3(1)	6(1)	8(1)
C(2)	16(1)	19(1)	16(1)	2(1)	3(1)	10(1)
C(3)	13(1)	18(1)	16(1)	1(1)	3(1)	8(1)
C(4)	13(1)	16(1)	19(1)	1(1)	4(1)	8(1)
C(5)	16(1)	20(1)	16(1)	1(1)	1(1)	9(1)
C(6)	26(1)	24(1)	26(1)	6(1)	13(1)	14(1)
C(7)	32(1)	21(1)	31(1)	7(1)	10(1)	4(1)
C(8)	28(1)	26(1)	26(1)	-2(1)	2(1)	19(1)
C(9)	22(1)	33(1)	22(1)	-3(1)	4(1)	17(1)
C(10)	20(1)	24(1)	20(1)	3(1)	5(1)	10(1)
C(11)	11(1)	21(1)	20(1)	0(1)	2(1)	7(1)
C(12)	21(1)	21(1)	20(1)	-3(1)	1(1)	11(1)
C(13)	26(1)	28(1)	25(1)	5(1)	3(1)	16(1)
C(14)	22(1)	37(1)	16(1)	-3(1)	-2(1)	16(1)
C(15)	26(1)	26(1)	22(1)	-4(1)	3(1)	13(1)
C(16)	20(1)	22(1)	22(1)	0(1)	3(1)	9(1)
C(17)	32(1)	51(1)	32(1)	13(1)	13(1)	26(1)
Cl(1)	40(1)	36(1)	62(1)	-7(1)	16(1)	13(1)
Cl(2)	35(1)	47(1)	44(1)	-5(1)	3(1)	13(1)
N(1)	15(1)	23(1)	18(1)	-1(1)	2(1)	12(1)
O(1)	18(1)	22(1)	19(1)	-4(1)	2(1)	10(1)
O(2)	14(1)	18(1)	21(1)	4(1)	3(1)	7(1)

Table 5. Hydrogen coordinates (x10^4) and isotropic displacement parameters ($Å^2$x10^3) for **(±)-II-114**.

	x	y	z	U(eq)
H(2A)	5412	1373	4790	19
H(2B)	7273	3041	4649	19
H(4)	10320(30)	4100(30)	6185(17)	19
H(6)	8565	5663	5440	28
H(7)	8056	8032	5822	32
H(8)	6024	8042	6931	30
H(9)	4478	5650	7627	29
H(10)	5012	3282	7259	25
H(12)	10029	612	7288	25
H(13)	10955	637	8901	30
H(15)	11269	5297	9392	29
H(16)	10315	5253	7781	25
H(17A)	6219	-416	8995	41
H(17B)	6498	630	8121	41

H(1)	10450(40)	1380(30)	5760(19)	28(7)
H(2)	4907	989	6326	26

Table 6. Torsion angles (°) for **(±)-II-114**.

O(1)-C(1)-N(1)	126.18(18)
O(1)-C(1)-C(2)	125.96(17)
N(1)-C(1)-C(2)	107.86(16)
C(1)-C(2)-C(3)	102.74(15)
O(2)-C(3)-C(5)	112.35(16)
O(2)-C(3)-C(2)	109.10(14)
C(5)-C(3)-C(2)	114.85(16)
O(2)-C(3)-C(4)	105.22(14)
C(5)-C(3)-C(4)	113.39(15)
C(2)-C(3)-C(4)	100.96(15)
N(1)-C(4)-C(11)	115.08(15)
N(1)-C(4)-C(3)	101.50(14)
C(11)-C(4)-C(3)	114.26(16)
C(10)-C(5)-C(6)	118.16(18)
C(10)-C(5)-C(3)	121.20(18)
C(6)-C(5)-C(3)	120.64(18)
C(7)-C(6)-C(5)	121.1(2)
C(6)-C(7)-C(8)	120.0(2)
C(9)-C(8)-C(7)	119.40(19)
C(8)-C(9)-C(10)	120.6(2)
C(9)-C(10)-C(5)	120.7(2)
C(16)-C(11)-C(12)	119.06(19)
C(16)-C(11)-C(4)	118.13(17)
C(12)-C(11)-C(4)	122.80(18)
C(13)-C(12)-C(11)	120.29(19)
C(14)-C(13)-C(12)	119.27(19)
C(13)-C(14)-C(15)	121.8(2)
C(13)-C(14)-Br	119.82(16)
C(15)-C(14)-Br	118.39(16)
C(14)-C(15)-C(16)	118.35(19)
C(11)-C(16)-C(15)	121.25(19)
Cl(2)-C(17)-Cl(1)	111.78(13)
C(1)-N(1)-C(4)	113.86(16)

Appendix 3

Structure Refinement Data, Atomic Coordinates, Bond Lengths, and Bond Angle Data for the Crystal Structure of II-121

Crystal structure data provided by Dr. Charlotte Stern (Northwestern University, c-stern@northwestern.edu) and solved by Troy Reynolds (Northwestern University, t-reynolds2@northwestern.edu)

X-ray Crystal Structure Analysis for II-121

The absolute stereochemistry of **II-121** was determined by X-ray crystallography. Imide **II-121** was crystallized from slow-diffusion of hexanes into methylene chloride.

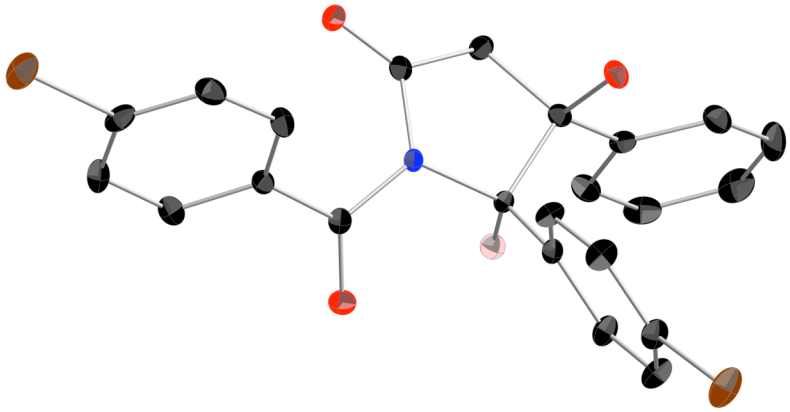


Table 1. Crystal data and structure refinement for **II-121**.

Identification code	s23w_1_0m
Empirical formula	$C_{23}H_{17}Br_2NO_3$
Formula weight	515.20
Temperature	296(2) K
Wavelength	0.71073 Å
Crystal system, space group	monoclinic, P21
Unit cell dimensions	a = 14.0078(3) Å; α = 90.00 ° b = 5.54060(10) Å; β = 117.0080(10) ° c = 14.8626(3) Å; g = 90.00 °
Volume	102.71(4) $Å^3$
Z, Calculated density	2, 1.665 Mg/m^3
Absorption coefficient	3.968 mm^{-1}
F(000)	512
Crystal size	0.509 x 0.108 x 0.020 mm
Theta range for data collection	1.54 to 30.33 °
Limiting indices	-19≤h≤19, -7≤k≤7, -20≤l≤21
Reflections collected / unique	5027 / 4166 [R(int) = 0.0596]
Completeness to theta = 30.33	90.1 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5027 / 1 / 266
Goodness-of-fit on F^2	1.047
Final R indices [I>2sigma(I)]	R1 = 0.0323, wR2 = 0.0712

R indices (all data)	R1 = 0.0437, wR2 = 0.1045
Largest diff. peak and hole	3.593 (max) and 0.028 (min) A^{-3}

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for **II-121**.

	x	y	z	U(eq)
O(1)	0.4215(2)	-0.0724(5)	0.9126(2)	0.0151(6)
Br(1)	0.67975(3)	0.05678(10)	0.47016(3)	0.02517(13)
Br(2)	-0.03876(3)	0.10801(8)	0.59249(3)	0.02565(13)
O(3)	0.4757(2)	0.5253(5)	0.7831(2)	0.0152(6)
C(7)	0.2557(3)	0.4433(8)	0.7486(3)	0.0159(9)
C(11)	0.2877(3)	0.0539(8)	0.6952(3)	0.0165(8)
C(22)	0.9274(4)	0.2864(8)	1.1345(3)	0.0207(10)
C(15)	0.6627(3)	0.1022(8)	0.5890(3)	0.0168(8)
C(23)	0.8234(3)	0.2286(8)	1.0656(3)	0.0174(9)
C(5)	0.4423(3)	0.3278(7)	0.7904(3)	0.0127(8)
O(2)	0.6898(2)	-0.2566(5)	0.8808(2)	0.0160(6)
C(1)	0.5046(3)	-0.0168(7)	0.9107(3)	0.0121(8)
C(2)	0.6277(3)	0.1661(7)	0.8588(3)	0.0116(8)
C(6)	0.3268(3)	0.2710(7)	0.7460(3)	0.0123(8)
C(3)	0.6871(3)	-0.0459(7)	0.9334(3)	0.0117(8)
C(14)	0.7262(4)	0.2647(8)	0.6625(3)	0.0198(9)
C(9)	0.1100(3)	0.1785(8)	0.6538(3)	0.0184(9)
C(12)	0.6354(3)	0.1531(7)	0.7609(3)	0.0121(8)
C(10)	0.1786(3)	0.0085(7)	0.6472(3)	0.0193(9)
C(17)	0.5708(3)	-0.0052(7)	0.6847(3)	0.0154(8)
C(13)	0.7118(3)	0.2881(8)	0.7486(3)	0.0159(8)
C(18)	0.8015(3)	0.0198(8)	1.0065(3)	0.0134(8)
N(1)	0.5148(2)	0.1409(6)	0.8411(2)	0.0106(6)
C(19)	0.8866(3)	-0.1274(8)	1.0183(3)	0.0193(9)
C(4)	0.6158(3)	-0.0879(8)	0.9855(3)	0.0151(9)
C(16)	0.5842(3)	-0.0342(8)	0.5984(3)	0.0183(9)
C(21)	1.0105(3)	0.1339(10)	1.1454(3)	0.0251(10)
C(20)	0.9904(4)	-0.0689(9)	1.0876(4)	0.0270(11)
C(8)	0.1458(3)	0.3932(8)	0.7044(3)	0.0189(9)

Table 3. Bond lengths [Å] for **II-121**.

O(1)-C(1)	1.217(5)
Br(1)-C(15)	1.904(4)
Br(2)-C(9)	1.897(4)
O(3)-C(5)	1.215(5)
C(7)-C(6)	1.392(5)
C(7)-C(8)	1.400(6)
C(11)-C(10)	1.385(5)
C(11)-C(6)	1.393(6)
C(22)-C(23)	1.385(6)
C(22)-C(21)	1.387(7)
C(15)-C(14)	1.383(6)
C(15)-C(16)	1.392(6)
C(23)-C(18)	1.400(7)
C(5)-N(1)	1.405(5)
C(5)-C(6)	1.478(6)
O(2)-C(3)	1.415(5)
C(1)-N(1)	1.409(5)
C(1)-C(4)	1.498(5)
C(2)-N(1)	1.488(5)
C(2)-C(12)	1.508(5)
C(2)-C(3)	1.570(5)
C(3)-C(18)	1.516(5)
C(3)-C(4)	1.533(6)
C(14)-C(13)	1.389(6)
C(9)-C(8)	1.374(6)
C(9)-C(10)	1.381(6)
C(12)-C(13)	1.384(5)
C(12)-C(17)	1.393(5)
C(17)-C(16)	1.387(6)
C(18)-C(19)	1.389(6)
C(19)-C(20)	1.385(6)
C(21)-C(20)	1.364(7)

Table 4. Anisotropic displacement parameters ($Å^2$ x 10^3) for **II-121**.

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	14.7(15)	15.3(15)	18.3(16)	-0.4(11)	10.0(13)	0.1(11)
Br(1)	21.4(2)	42.9(3)	14.6(2)	-4.42(17)	11.08(17)	-4.23(18)
Br(2)	10.91(19)	3.95(3)	2.17(2)	3.9(2)	3.18(16)	-2.49(19)
O(3)	15.5(14)	14.0(14)	15.1(14)	0.1(11)	6.1(12)	-1.3(11)
C(7)	17(2)	16(2)	11(2)	0.0 (15)	4.3(17)	2.9(16)
C(11)	12.9(18)	16(2)	18(2)	-1.1(16)	5.1(16)	2.3(16)
C(22)	19(2)	20(2)	16(2)	-3.2(17)	1.8(19)	-9.7(18)
C(15)	16.7(18)	25(2)	10.5(18)	2.7(17)	7.4(15)	2.3(18)
C(23)	17(2)	17(2)	14(2)	0.9(17)	4.2(17)	1.9(17)
C(5)	12(2)	16(2)	9(2)	0.6(14)	4.4(16)	1.6(15)
O(2)	13.6(14)	12.2(14)	20.0(16)	-2.4(11)	5.8(13)	0.4(11)
C(1)	16(2)	10.7(19)	12(2)	-3.1(14)	8.3(16)	0.7(15)
C(2)	7.4(16)	11.3(19)	16(2)	1.1(15)	4.8(15)	-0.9(14)
C(6)	10.9(19)	13.8(19)	1.1(2)	3.2(15)	3.8(16)	2.6(15)
C(3)	14(2)	10.1(19)	12(2)	-0.8(15)	6.2(17)	0.5(15)
C(14)	17(2)	27(2)	17(2)	0.0(17)	9.8(18)	-3.7(18)
C(9)	10.2(18)	2.8(2)	14(2)	6.1(17)	2.7(16)	-3.0(16)
C(12)	10.0(17)	14.1(19)	12.3(19)	0.4(15)	5.2(15)	1.0(15)
C(10)	17(2)	15(2)	20(2)	1.1(16)	3.9(18)	-0.8(16)
C(17)	16(2)	17(2)	14(2)	-1.0(15)	8.0(17)	-4.3(15)
C(13)	10.3(19)	22(2)	14(2)	-2.6(16)	4.7(17)	-2.7(16)
C(18)	11.3(19)	15(2)	11.8(19)	3.5(15)	3.3(15)	-0.3(15)
N(1)	9.1(14)	11.1(16)	12.1(16)	-0.1(13)	5.3(12)	0.9(13)
C(19)	17(2)	14(2)	24(2)	-0.4(17)	7.1(19)	0.4(17)
C(4)	14(2)	16(2)	16(2)	5.9(16)	7.6(18)	2.1(16)
C(16)	17(2)	23(2)	13(2)	-4.5(16)	5.5(17)	-4.1(17)
C(21)	12(19)	34(3)	21(2)	2(2)	-0.2(17)	-6(2)
C(20)	10(2)	32(3)	34(3)	2(2)	6(2)	4.4(19)
C(8)	13(2)	24(2)	19(2)	-0.1(17)	7.5(18)	4.0(17)

Table 5. Hydrogen coordinates ($x10^4$) and isotropic displacement parameters ($Å^2$) for **II-121**.

	x	y	z	U(eq)
H(7)	0.2812	0.5915	0.7796	0.019
H(11)	0.3352	-0.0613	0.6936	0.020
H(22)	0.9413	0.4263	1.1730	0.025
H(23)	0.7674	0.3297	1.0586	0.021
H(2)	0.6297	-0.3162	0.8529	0.024
H(2A)	0.657(4)	0.321(8)	0.892(3)	0.014
H(14)	0.7775	0.3563	0.6545	0.024
H(10)	0.1521	-0.1337	0.6111	0.023
H(17)	0.5179	-0.0927	0.6918	0.019
H(13)	0.7542	0.3961	0.7988	0.019
H(19)	0.8739	-0.2664	0.9794	0.023
H(4A)	0.6177	-0.2563	1.0041	0.018
H(4B)	0.6400	0.0099	1.0460	0.018
H(16)	0.5418	-0.1420	0.5481	0.022
H(21)	1.0803	0.1702	1.1925	0.030
H(20)	1.0468	-0.1687	1.0948	0.032
H(8)	0.0981	0.5029	0.7091	0.023

Table 6. Torsion angles (°) for **31**.

C(6)-C(7)-C(8)	119.9(4)
C(10)-C(11)-C(6)	120.4(4)
C(23)-C(22)-C(21)	119.4(4)
C(14)-C(15)-C(16)	121.9(4)
C(14)-C(15)-Br(1)	120.8(3)
C(16)-C(15)-Br(1)	117.3(3)
C(22)-C(23)-C(18)	120.8(4)
O(3)-C(5)-N(1)	119.9(4)
O(3)-C(5)-C(6)	122.7(4)
N(1)-C(5)-C(6)	117.4(3)
O(1)-C(1)-N(1)	126.2(4)
O(1)-C(1)-C(4)	126.8(4)
N(1)-C(1)-C(4)	106.9(3)
N(1)-C(2)-C(12)	111.2(3)
N(1)-C(2)-C(3)	103.5(3)
C(12)-C(2)-C(3)	113.5(3)
C(7)-C(6)-C(11)	119.8(4)
C(7)-C(6)-C(5)	119.6(4)
C(11)-C(6)-C(5)	120.5(4)

O(2)-C(3)-C(18)	108.0(3)
O(2)-C(3)-C(4)	109.9(3)
C(18)-C(3)-C(4)	113.2(3)
O(2)-C(3)-C(2)	111.4(3)
C(18)-C(3)-C(2)	112.0(3)
C(4)-C(3)-C(2)	102.3(3)
C(15)-C(14)-C(13)	118.5(4)
C(8)-C(9)-C(10)	122.4(4)
C(8)-C(9)-Br(2)	119.3(3)
C(10)-C(9)-Br(2)	118.3(3)
C(13)-C(12)-C(17)	119.3(4)
C(13)-C(12)-C(2)	120.0(3)
C(17)-C(12)-C(2)	120.6(3)
C(9)-C(10)-C(11)	118.7(4)
C(16)-C(17)-C(12)	120.9(4)
C(12)-C(13)-C(14)	121.0(4)
C(19)-C(18)-C(23)	118.4(4)
C(19)-C(18)-C(3)	121.1(4)
C(23)-C(18)-C(3)	120.5(4)
C(5)-N(1)-C(1)	124.1(3)
C(5)-N(1)-C(2)	118.5(3)
C(1)-N(1)-C(2)	112.5(3)
C(20)-C(19)-C(18)	120.5(4)
C(1)-C(4)-C(3)	106.3(3)
C(17)-C(16)-C(15)	118.3(4)
C(20)-C(21)-C(22)	120.4(4)
C(21)-C(20)-C(19)	120.5(4)
C(9)-C(8)-C(7)	118.6(4)

Appendix 4

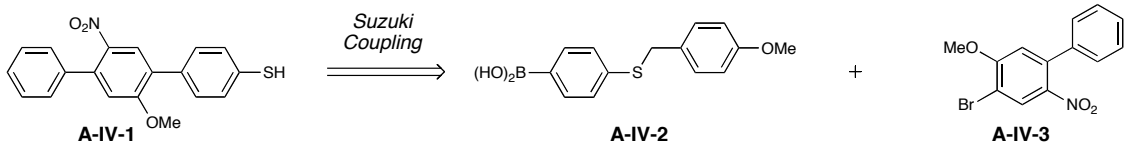
Synthesis of 4-Nitro-5-phenyl-2-(*p*-thiophenol) anisole

The following molecule was synthesized for the study of electron transport and function in collaboration with Professor Richard P. Van Duyne and David Andrews (Northwestern University).

Synthesis of 4-Nitro-5-phenyl-2-(p-thiophenol) anisole (A-IV-1)

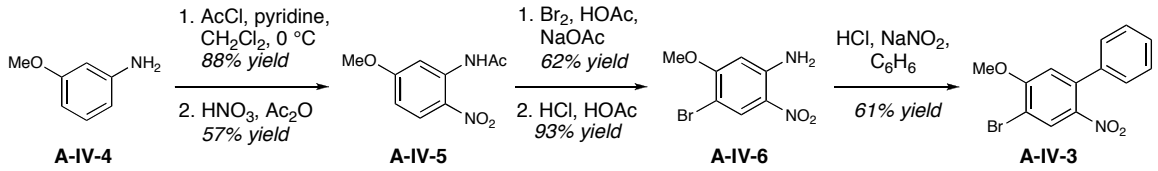
This work uses synthesis to address how molecular structure can control electron transport and function. Rationally designed 4-nitro-5-phenyl-2-(*p*-thiophenol) anisole (**A-IV-1**) contains conjugated electron donating (OMe) and electron withdrawing (NO_2) substituents in its molecular architecture (Scheme A4-1). Retrosynthetically, this molecule can be accessed through a Suzuki coupling of aryl boronate **A-IV-2** and aryl bromide **A-IV-3**. Appropriate installation of a thiol linker on this synthetically sophisticated electronic scaffold allows for appendage of the molecule to gold surfaces. In collaboration, the electronic properties of this molecule are in the process of being studied using a custom-built low temperature ultra high vacuum scanning tunneling microscope. Vibration information under current flow will be measured using surface enhanced Raman spectroscopy.

Scheme A4-1. Retrosynthesis of 4-nitro-5-phenyl-2-(*p*-thiophenol) anisole **(A-IV-1)**



The synthesis of aryl bromide **A-IV-3** was accomplished using a modified procedure reported by Kauffman, Litak, and Boyko (Scheme A4-2).[1] Acetate protection of the primary amine of *m*-anisidine (**A-IV-4**)[2] followed by nitration,[3] provided trisubstituted benzene **A-IV-5**. Bromination of nitrobenzene **A-IV-5**, followed by *N*-acetyl deprotection gave tetrasubstituted bromobenzene **A-IV-6**. Sandmeyer arylation of the diazonium salt of **A-IV-6** generated key biaryl bromide fragment **A-IV-3**.[4]

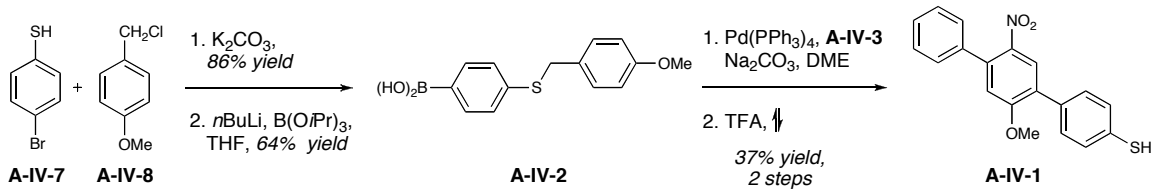
Scheme A4-2. Synthesis of aryl bromide **A-IV-3**



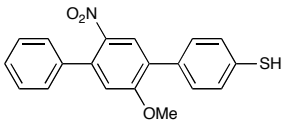
A-IV-4 **A-IV-5** **A-IV-6** **A-IV-3**

The problematic portion of the synthesis of 4-nitro-5-phenyl-2-(*p*-thiophenol) anisole (**A-IV-1**) was the incorporation of an appropriately protected thiophenol that would be robust enough for the Suzuki coupling, but also labile for removal in the presence of the methoxy substituent (from **A-IV-3**), following the coupling reaction. In the literature, most reported Suzuki coupling events with thiophenol functionality mask the thiol using an alkyl-protecting group (e.g. methyl or *tert*-butyl). Both of these compounds were utilized for this reaction sequence, but selective removal of these functional groups in the presence of the aryl methoxy group was either unsuccessful (methyl) or resulted in very low and irreproducible yields of the desired **A-IV-1** (*tert*-butyl). Gratifyingly, utilization of *p*-methoxy benzyl protected *p*-thiophenol boronate **A-IV-2** permitted the formation of 4-nitro-5-phenyl-2-(*p*-thiophenol) anisole (**A-IV-1**) in usable yield (Scheme A4-3). Protection of *p*-bromothiophenol (**A-IV-7**) with *p*-methoxybenzyl chloride (**A-IV-8**),[5] followed by nucleophilic boronation,[6] afforded aryl boronate **A-IV-2**. Suzuki coupling of *p*-thiophenol boronate **A-IV-2** with biaryl bromide **A-IV-3**,[7] and subsequent thiol deprotection with refluxing trifluoroacetic acid (TFA),[8] generated the desired 4-nitro-5-phenyl-2-(*p*-thiophenol) anisole (**A-IV-1**) in moderate yield, following purification.

Scheme A4-3. Synthesis of 4-nitro-5-phenyl-2-(*p*-thiophenol) anisole (**A-IV-1**)



Characterization of 4-Nitro-5-phenyl-2-(p-thiophenol) anisole (A-IV-1)



4-nitro-5-phenyl-2-(*p*-thiophenol) anisole (A-IV-1): Purified with 50% dichloromethane/hexanes, yielding 87 mg (76%) of **A-IV-1** as a white solid; R_f = 0.34 (50:50 dichloromethane/hexanes); mp = 164-166 °C; IR (film) 3058, 3024, 2939, 2850, 2569, 1597, 1558, 1510, 1481, 1386, 1341, 1292, 1224, 1107, 1016, 908, 827, 758, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.46-7.45 (m, 5H), 7.37-7.35 (m, 4H), 6.90 (s, 1H), 3.91 (s, 3H), 2.36 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 142.1, 138.6, 138.4, 133.4, 131.4, 130.3, 129.7, 129.4, 128.9, 128.5, 128.1, 127.4, 114.3, 56.5; LRMS (ESI): Mass calculated for $C_{19}H_{15}NO_3S$ $[M-H]^-$, 336.1. Found $[M-H]^-$, 336.1.

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Mentor to three undergraduate students during my graduate career
Otterbein College: (1998-2002)
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Nursing Chemistry Lab (1 year): Professor Charles Fulton

Activities

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American Chemical Society Member (2001-present)
American Chemical Society Student Affiliates – Vice President, Otterbein College (2001-2002)
Phi Eta Sigma National Honorary – President and Member, Otterbein College (1999-2002)
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The Chancellor's List, Northwestern University (2005-2006)
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Research Accomplishments to Date

- Investigated the Lewis base activation of triethoxysilylalkynes for the synthesis of propargyl alcohols and amines.
- Developed a large-scale preparation of aliphatic acylsilanes from the silyllithium addition to morpholine amides.
- Discovered a multi-component strategy for the synthesis of enantiomerically enriched tertiary propargyl alcohols using acysilanes and chiral amide enolates as homoenolate equivalents.
- Applied multi-component homoenolate methodology towards the stereoselective synthesis of β-hydroxy-γ-lactams.
- Designed and synthesized atmospherically relevant small molecules and attached to glass surfaces for use in laser studies in collaboration with Professor Franz M. Geiger, Northwestern University.
- Designed and Synthesized novel organic electron transport materials for studies in collaboration with Professor Richard P. Van Duyne, Northwestern University.

Publications

8. Lettan, R. B., II; Galliford, C. V.; Woodward, C. C.; Reynolds, T. E.; Scheidt, K. A. "Synthetic Applications of Enolate Additions to Acylsilanes as Homoenolate Equivalents." *J. Am. Chem. Soc.* **2007**, manuscript in preparation.

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5. Lettan, R. B., II; Milgram, B. C.; Clark, C. T.; Scheidt, K. A. "Synthesis of Acylsilanes from Morpholine Amides. Synthesis of 1-(Dimethyl(phenyl)silyl)propan-1-one." *Org. Syn.* **2007**, *84*, 22-31.

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3. Lettan, R. B., II; Reynolds, T. E.; Galliford, C. V.; Scheidt, K. A. "Multicomponent Reaction of Acylsilanes, Enolates, and Alkyl Halides: Stereoselective Synthesis of Tertiary-β-hydroxy Amides." *J. Am. Chem. Soc.* **2006**, *128*, 15566-15567.

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1. Lettan, R. B., II; Scheidt, K. A. "Lewis Base-Catalyzed Additions of Alkynes Using Triethoxysilylalkynes." *Org. Lett.* **2005**, *7*, 3227-3230.

Presentations

5. *Synthesis of Tertiary β-Hydroxy Amides by Enolate Additions to Acylsilanes*
   Robert B. Lettan II, Chase C. Woodward, Troy E. Reynolds, Chris V. Galliford and Karl A. Scheidt*
   American Chemical Society National Meeting, Presentation, Chicago, IL, March 2007.

4. *Silicon Lewis Base Activation, Acylsilane Synthesis, and Acylsilane Enolate Additions*
   Robert B. Lettan II and Karl A. Scheidt*
   Gelewitz Award Application, Presentation, Northwestern University, Evanston, Illinois, April 2006.

3. *Lewis Base Promoted Alkyne Additions Utilizing Triethoxysilylalkynes*
   Robert B. Lettan II and Karl A. Scheidt*
   American Chemical Society National Meeting, Presentation, Washington D.C., August 2005.

2. *Lewis Base-Catalyzed Additions of Alkynes Using Triethoxysilylalkynes*
   Robert B. Lettan II and Karl A. Scheidt*
   National Organic Symposium, Poster, Salt Lake City, Utah, June 2005.

1. *Lewis Base Promoted Alkyne Additions Utilizing Activated Silicon Species*
   Robert B. Lettan II and Karl A. Scheidt*
   Otterbein College Visiting Speaker, Presentation, Columbus, Ohio, May 2005.