DEVELOPMENT OF A METHOD FOR THE COPPER-CATALYZED ASYMMETRIC PROPARGYLATION OF OXIME ESTERS

Thesis by

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In Partial Fulfillment of the Requirements

for the Degree of

Master of Science

CALIFORNIA INSTITUTE OF TECHNOLOGY

Pasadena, California

2018

(Submitted January 15th, 2018)

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ACKNOWLEDGEMENTS

I would like to thank my research advisor, Professor Sarah Reisman. Sarah provided me with a fantastic opportunity to learn and study exciting new fields of chemistry. It was a privilege to conduct research under her mentorship. With her help I was able to grow and become a knowledgeable organic chemist in addition to a chemical biologist. Sarah's advice and input have been invaluable to my development as a scientist and what I learned from her and my experiences in her lab have set the stage to propel me forward in my career as a chemist.

I would like to thank my undergraduate research advisor, Professor Jared Shaw at University of California, Davis. After taking his organic synthesis class, I asked to conduct organic chemistry research in his laboratory the following quarter. It was in his class and lab that I initially developed my passion for organic chemistry and chemical biology. I'm so grateful to Jared for helping me to realize my love of organic chemistry and for giving me such a strong foundation in research.

There are many other people at Caltech who contributed to the successful completion of my Master's degree. I would like to thank Professor Brian Stoltz for his support and encouragement. His door is always open to students and the close relationship between our two groups was one of the special aspects of my experience at Caltech. I would like to thank Dr. Scott Virgil for taking great care of the catalysis center and for always being available and willing to help students. He goes above and beyond to help any student who asks, and I am so grateful for his help in separation of my racemic compounds. I would like to thank Dr. David VanderVelde for maintaining a great NMR facility.

I would also be remiss if I didn't mention some of the wonderful friends and labmates who helped make this journey possible. First, thanks to my mentor and project partner, Nick Cowper, who helped fine-tune my hands in lab and was always ready with helpful advice and ideas. I would also like to thank my yearmates Jordan Beck, Julie Hofstra, Kelsey Poremba, and Alice Wong, who are both inspiring colleagues and great friends. Many, many thanks go to Matt Hesse and Jared Moore, without whose advice and experience I would have been lost. Thanks also to Denise Grünenfelder, whose wonderful friendship and support made life at Caltech a little easier and a lot more fun.

It is a rare and precious thing to be able to collaborate without any sense of competition. That feeling is something that Caltech gives us – no matter whom you ask, any person is willing to offer help or ideas. That sense of community is something I will fondly remember.

Lastly, I would like to thank my parents, John and Barbara Chan, for their endless love and support. No matter what life has thrown at me, they have always been there with advice and encouragement to help me keep going. They have urged me to pursue my dreams and I could not have gotten to where I am today without them.

ABSTRACT

Alkynes represent a significant motif in natural products and pharmaceutical drugs, and the wide variety of reactions they can undergo makes them a handy tool in total synthesis. They can be introduced readily in various manners, including via propargylations of ketones and aldehydes. However, one reaction that remains to be examined is the propargylation of oximes to give a propargyl hydroxylamine. Current enantioselective propargylations of oximes typically require a chiral auxiliary and/or rare metals such as palladium or indium. Having an enantioselective propargylation of oximes which could use an external ligand and more commonly available metals would facilitate use of the product in total synthesis, as well as potentially as an unnatural amino acid. Unusual amino acids including alkynes are desirable for their use in copper(I)-catalyzed azide-alkyne [3+2] dipolar cycloadditions, a common bioorthogonal reaction.

Herein, the development of a copper-catalyzed propargylation of oxime esters is described. Initial efforts to induce enantioselectivity using a zinc nucleophile-based system proved fruitless. Although some Lewis acids could raise the yield, the enantioselectivity remained very low. Therefore, new reaction conditions using a boronate nucleophile were investigated. The use of a copper catalyst with a diphosphine ligand gave the desired product in high enantioselectivity, albeit low yield.

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LIST OF ABBREVIATIONS

Ac	acetyl
acac	acetylacetonate
app	apparent
aq	aqueous
Ar	aryl group
BBD	borabicyclodecane
BIBOP	(2*R*,2'*R*,3*R*,3'*R*)-3,3'-di-*tert*-butyl-2,2',3,3'-tetrahydro-2,2'-**bib**enzo[*d*][1,3]**o**xa**p**hosphole
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthalene
BINOL	1,1'-bi-2-naphthol
BiOX	bi-oxazoline
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Box	bis(oxazoline)
BPE	1,2-bis(phospholano)ethane
br	broad
BTFM	bis(3,5-trifluoromethylphenyl)
Bu	butyl
^{i}Bu	*iso*-butyl
^{n}Bu	butyl or *norm*-butyl
^{t}Bu	*tert*-butyl
Bz	benzoyl

^{13}C	carbon-13 isotope
/C	supported on activated carbon charcoal
°C	degrees Celcius
calc'd	calculated
CAM	ceric ammonium molybdate
Cbz	benzyloxycarbonyl
cm	centimeter(s)
cm^{-1}	wavenumber(s)
comp	complex
conc.	concentrated
conv.	conversion
Cy	cyclohexyl
d	doublet
d	dextrorotatory
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
de	diastereomeric excess
DIPEA	*N*,*N*-diisopropylethylamine (Hunig's base)
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMS	dimethylsulfide
dr	diastereomeric ratio

EDTA	ethylenediaminetetraacetic acid
ee	enantiomeric excess
E^+	electrophile
E	trans (entgegen) olefin geometry
e.g.	for example (Latin: *exempli gratia*)
EI	electron ionization
eq	equation
equiv	equivalence(s)
er	enantiomeric ratio
ESI	electrospray ionization
Et	ethyl
et al.	and others (Latin: *et alii*)
Fmoc	fluorenylmethyloxycarbonyl
g	gram(s)
h	hour(s)
^1H	proton
^2H	deuterium
HFIP	hexafluoroisopropanol
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IC_{50}	half maximal inhibitory concentration (50%)

IR	infrared spectroscopy
J	coupling constant
L	liter or neutral ligand
l	levorotatory
LA	Lewis acid
m	multiplet or meter(s)
M	molar or molecular ion or metal
m	meta
μ	micro
Me	methyl
MeCN	acetonitrile (CH_3CN)
MEK	methyl ethyl ketone
Mes	mesityl
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	milliliter(s)
mm	millimeter(s)
μM	micromolar
mol	mole(s)
MS	molecular sieves
m/z	mass-to-charge ratio
NMR	nuclear magnetic resonance

Nu^-	nucleophile
o	ortho
OTf	trifluoromethanesulfonate
p	para
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
ppm	parts per million
Pr	propyl
^{c}Pr	cyclopropyl
^{i}Pr	isopropyl
^{n}Pr	propyl or *norm*-propyl
py	pyridine
Pyox	pyridinyl oxazoline
pyr	pyridine
q	quartet
Quinox	quinolinyl oxazoline
R	alkyl group
R	rectus
ref	reference
R_f	retention factor
rt	room temperature
s	singlet or seconds
S	sinister

sat.	saturated
SFC	supercritical fluid chromatography
t	triplet
TADDOL	(−)-*trans*-α,α′-(2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis(diphenylmethanol)
TBS	*tert*-butyldimethylsilyl
temp	temperature
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
tol	tolyl
Ts	*para*-toluenesulfonyl (tosyl)
UAA	unnatural or unusual amino acid
UV	ultraviolet
W	watts
X	anionic ligand or halide
Xyl	xylyl
Z	cis (zusammen) olefin geometry

Chapter 1

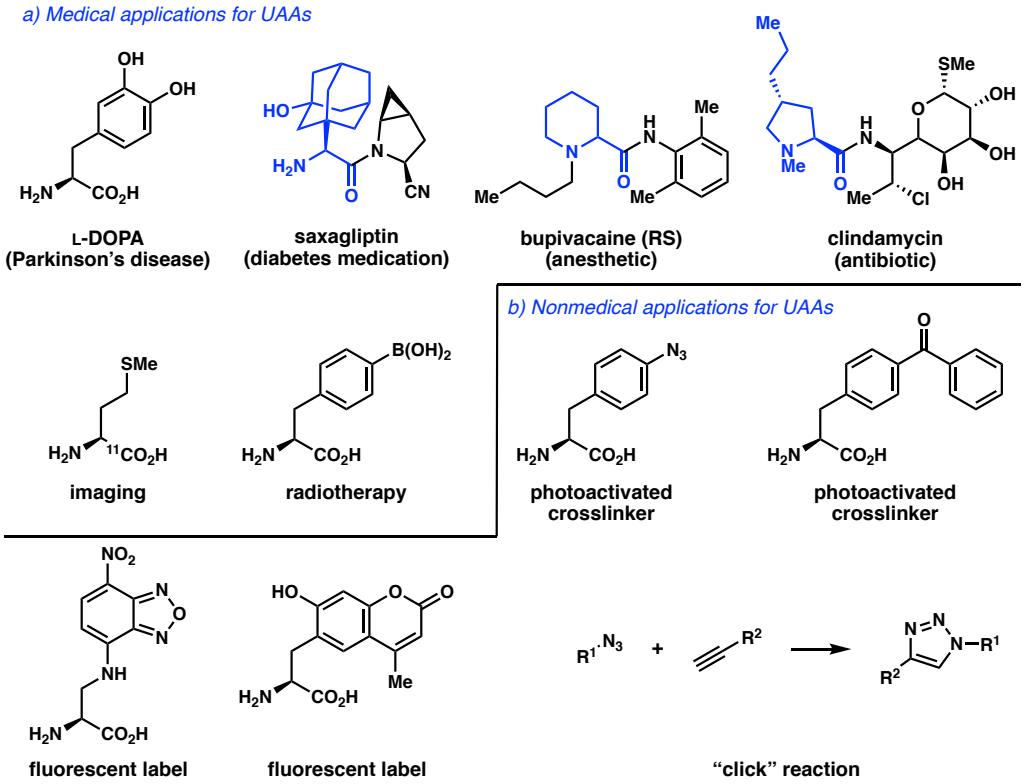
Nucleophilic Additions to Oximes, Ketones, and Aldehydes

1.1 INTRODUCTION

Unnatural or unusual amino acids (UAAs) are a commonly used tool in many fields, particularly medicinal chemistry, in which they embody potential drugs, building blocks for structure-activity relationship studies, and starting materials for syntheses of complex molecules.[1] These compounds comprise amino acids not included in the twenty most common amino acids found in proteins. They are not coded for in proteins and in most cases are lab-made for a variety of purposes. Medical uses include treatment for various conditions, anesthesia, imaging, and radiotherapy (Figure 1.1, a). Nonmedical uses for UAAs include biochemical research, where they can be used as fluorescent labels, photoactivated crosslinkers, or in bioorthogonal reactions. Often in these cases the amino acid is incorporated into a protein where it can be reacted with a marker to allow for later monitoring.[2,3] In these cases, the copper(I)-catalyzed azide-alkyne [3+2] dipolar cycloaddition or click reaction is a useful tool.[3] A UAA bearing either an azide

or alkyne can be incorporated into the desired protein, and the corresponding compound introduced in a click reaction. This allows for monitoring of protein activity or investigation of a particular enzyme active site. The flexibility of incorporating either azide or alkyne as the UAA allows for less disruption of natural enzymatic function.

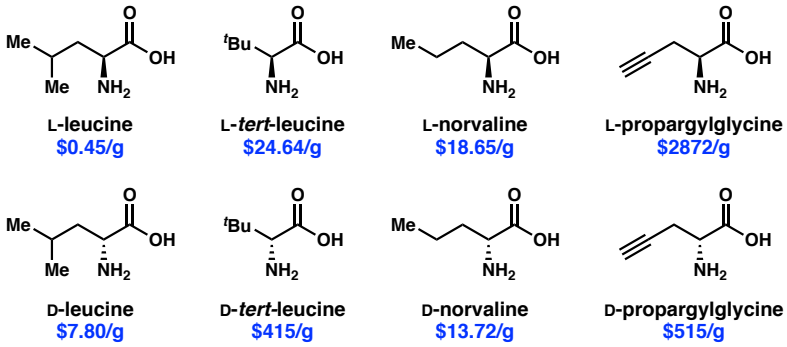
Figure 1.1. *Uses of unnatural amino acids.*[1-4]



However, UAAs are often very expensive or only available as racemates. D isomers are often even more expensive than L isomers due to the lack of existing starting materials that can be sourced from the chiral pool. This pattern is seen even in naturally occurring amino acids, such as leucine, as the L isomers are more common (Figure 1.2). In the case of racemic synthesis, separation is often difficult and time-consuming. For example, on a gram-for-gram basis, D-*tert*-leucine from Sigma-Aldrich is almost seventeen times the price of L-*tert*-leucine (Figure 1.2). Propargylated UAAs are also

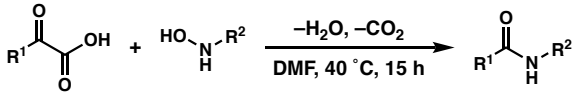
considerably more expensive than their alkyl counterparts. L- and D-propargylglycine are only available in 250 mg and 100 mg sizes, compared to the up to 10 g and 5 g sizes available for their saturated counterparts, L- and D-norvaline. When prices are normalized to per gram, L-propargylglycine costs $2872 per gram, compared to $18.65 per gram if L-norvaline is purchased in bulk or $54 per gram if not. It would therefore be useful to have a way to readily and cheaply access unnatural amino acids

Figure 1.2. *Price per gram comparison of select amino acids.*



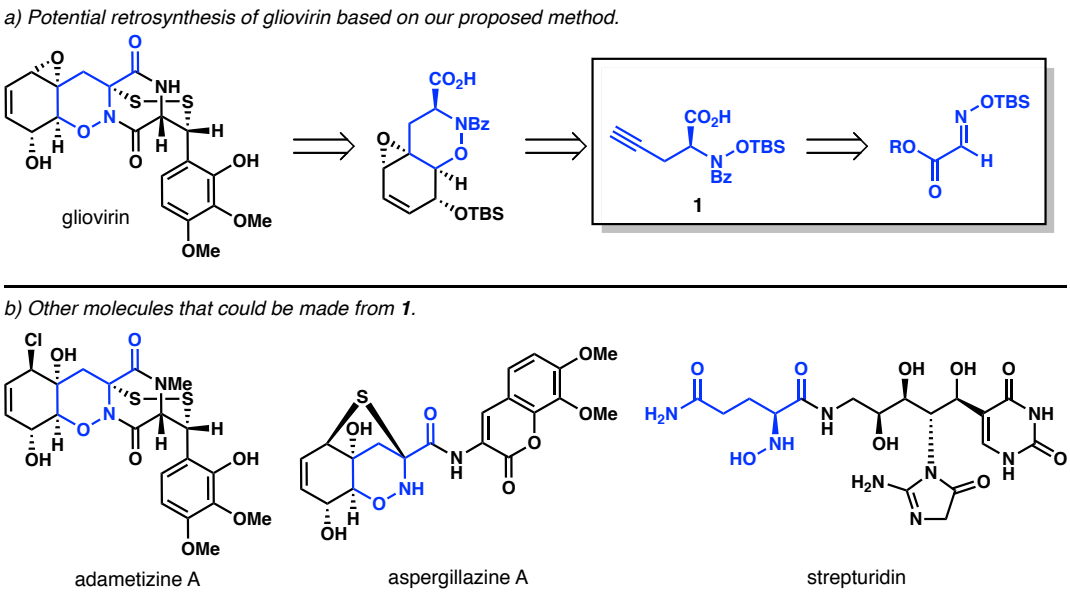
Bode *et al.* have shown that C-terminal α-keto carboxylic acids can be condensed with hydroxylamines to give peptide bonds, allowing quick use of a hydroxylamine as an unnatural amino acid (Scheme 1.1).[5] Similarly, the hydroxylamine could readily be reduced to the free amine, providing the same result. It was therefore desired to design a new reaction framework by which an oxime ester could be nucleophilically substituted with a propargyl group to form a propargylated hydroxylamine, which could be useful as a UAA as well as handles for "click" chemistry.[3]

Scheme 1.1. *Formation of peptide bonds via condensation of hydroxylamines with α-ketoacids.*



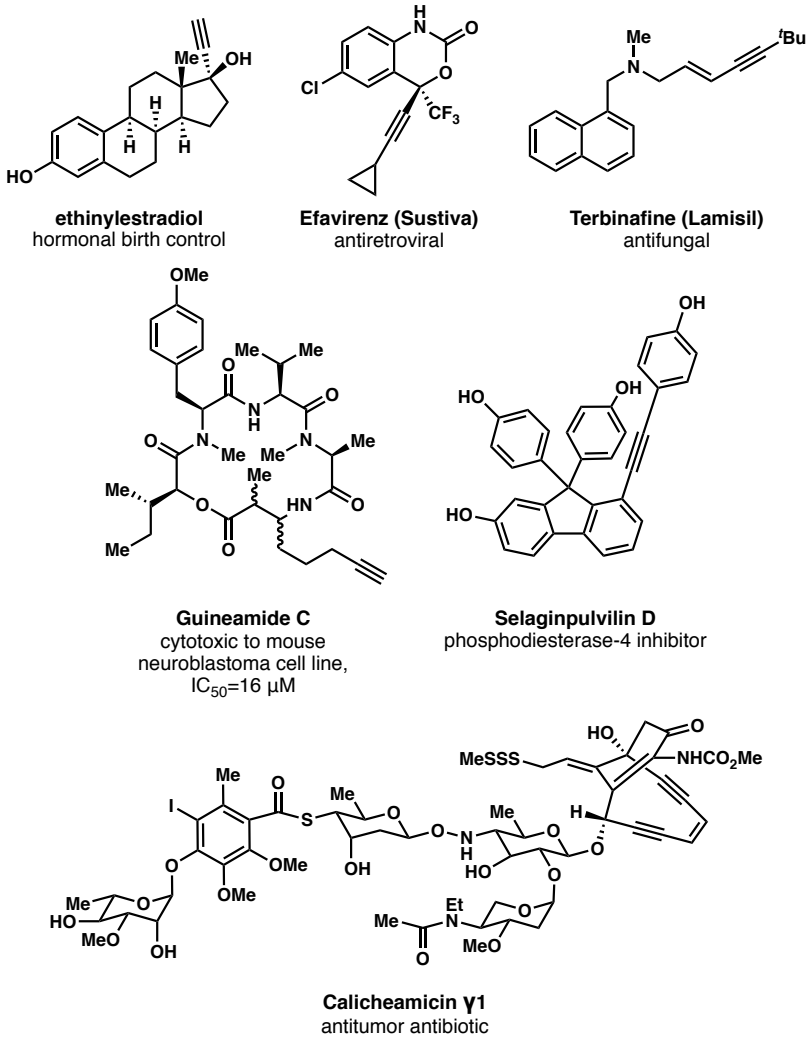
In addition to providing potential UAAs, the desired methodology could prove useful in synthesis. Our lab intended to use the product in the total synthesis of gliovirin, a natural product. A potential retrosynthesis can be seen in Figure 1.3, a. Other natural products that might be made from the desired product (**1**) include adametizine A, aspergillazine A, and strepturidin.

Figure 1.3. *Examples of natural products which could be made using the proposed method.*[6,7]



Alkyne **1** is useful in chemical synthesis where it provides a convenient source of acetylenic groups, which can then be used as a functional handle to access a wide variety of structural motifs. Additionally, alkynes are a significant motif in natural products and pharmaceutical design (Figure 1.4).

Figure 1.4. *Alkyne-containing drugs and natural products.*[8-10]

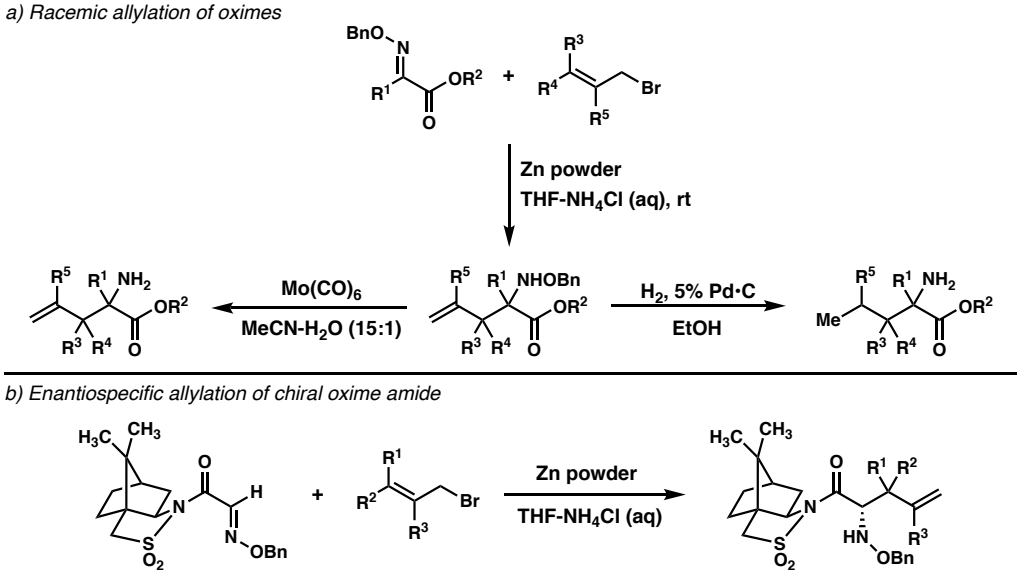


1.2 REACTIONS OF OXIMES

In 1996, Hanessian *et al.* designed the asymmetric allylation of oxime esters via a stoichiometric zinc nucleophile. Initially, they developed the racemic reaction using stoichiometric zinc powder, an allyl bromide, and a glyoxylic oxime ester to provide the corresponding allylated hydroxylamine, which could either be reduced to a homoallylic amine using $Mo(CO)_6$ or fully reduced to the alkyl amine using H_2/Pd-C (Scheme 1.2, a).[11] They then showed that by using Oppolzer's camphorsultam chiral auxiliary, the

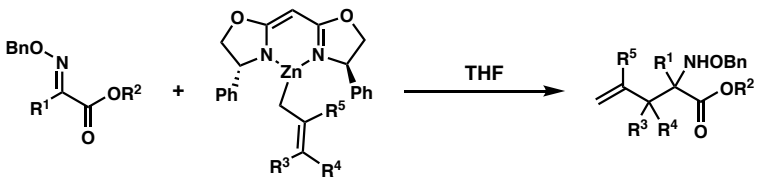
corresponding oxime amide could be reacted enantiospecifically with an allyl bromide, zinc powder, and THF-NH_4Cl to form an allylated hydroxylamine in excellent yield and moderate to good diastereoselectivity (Scheme 1.2, b).[11]

Scheme 1.2. *Racemic and enantiospecific allylation of oximes.*



Later that year, Hanessian *et al*. developed a second allylation that used an external ligand to form a chiral allylic zinc bromide and allylate α-ketoester oximes (Scheme 1.3). By using phenyl bis(oxazoline) (PhBOX), they achieved allylation of their oximes in good yield and high e.e. Additionally, the ligand could be recovered without loss of optical activity.[12]

Scheme 1.3. *Asymmetric allylation with an external ligand.*



Building from Hanessian's successful allylation of oximes, Ritson *et al.* developed a one-pot procedure for the allylation of various oximes.[13] They initially

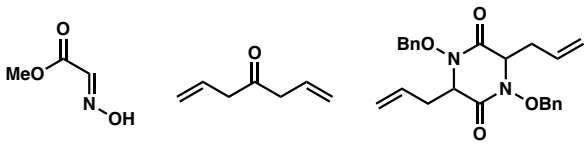
tested Hanessian's aqueous conditions against compounds **2** and **3** but found that while **2** gave the expected hydroxylamine **4** in 92% yield, the more electrophilic **3** only gave a 38% yield of **5** (Table 1.1, entries 1 and 2). They next found that **3** was unreactive toward allyltrimethylsilane in the presence of BF_3•OEt_2 (Table 1.1, entry 3).

Table 1.1. *Allylation of oximes using allylindium reagents.*

2 R = Bn
3 R = $COCH_2CH{=}CH_2$

4 R = Bn
5 R = $COCH_2CH{=}CH_2$

Entry	Oxime	Conditions	Product	Yield
1	2	$CH_2{=}CHCH_2Br$, Zn NH_4Cl (aq.)	4	92%
2	3	$CH_2{=}CHCH_2Br$, Zn NH_4Cl (aq.)	5	38%
3	3	$TMSCH_2CH{=}CH_2$ $BF_3{\cdot}OEt_2$, CH_2Cl_2	nr	nr
4	3	$CH_2{=}CHCH_2MgBr$, Et_2O	6, 7	—
5	3	In^0, $CH_2{=}CHCH_2Br$, DMF	5	56%
6	2	In^0, $CH_2{=}CHCH_2Br$, DMF	4	>80%
7	2	In^0, $CH_2{=}CHCH_2Br$ THF—DMF, 15 min	4, 8	24%



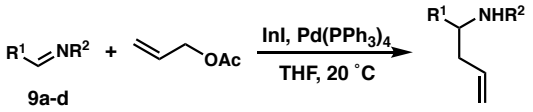
6 **7** **8**

Treatment of **3** with allylmagnesium bromide produced the deprotected oxime **6** and the bisallyl ketone **7** instead of the desired allylated compound (entry 4). Ritson *et al.* then "reasoned that the electron-withdrawn oxime glyoxylates such as [**3**] and [**2**] might react with allylindium reagents." Therefore, they added indium powder to allyl bromide and subsequently added **3**, which was converted to **5** in 56% yield (entry 5). Subjecting oxime **2** to the same conditions gave compound **4** in >80% yield (entry 6). In order to optimize the reaction, the authors increased the concentration of the reagents. Analysis of

the reaction mixture showed that, in fifteen minutes, **2** was converted to product **4** (24%), dimers such as **8** (19%) and polymers (entry 7). The authors added acetic anhydride in order to eliminate dimerization, and subsequently triethylamine to force full reaction with the acetic anhydride. They were able to expand the reaction to encompass substrates containing different esters, as well as both benzoyl- and benzyl-protected oximes. Additional viable substrates included crotyl bromide, one ketoxime, and one nitrile.

Miyabe *et al.* previously "reported the palladium-indium iodide-mediated regioselective allylation of glyoxylic oxime ether." They noted that in anhydrous THF α-adducts were selectively formed, whereas in the presence of water γ-adducts were formed.[14] Therefore, they next examined the reactivity of glyoxylic oximes and hydrazones toward an allylindium reagent and the effects of water on this reaction.[15] Initially, they tested the reactivity of different oximes and hydrazones toward allyl acetate in the presence of $Pd(PPh_3)_4$ and indium(I) iodide in THF. They found that **9a** could be allylated in one hour in 92% yield (Table 1.2, entry 1). However, **9b** did not react, and

Table 1.2. *Palladium- and indium-catalyzed allylation of oximes and hydrazones with allyl acetate.*



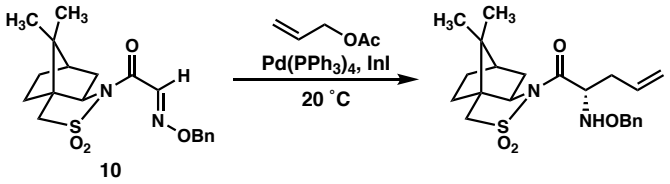
Entry	Imine	R^1	R^2	Time (h)	Yield (%)
1	9a	CO_2Me	OBn	1	92
2	9b	Ph	OBn	10	nr
3	9c	CO_2Me	NHBz	1	82
4	9d	CO_2Me	NPh_2	10	nr

they recovered 97% of the starting material (entry 2). **9c** also afforded the desired allylated product in 82% yield, whereas **9d** did not react (entries 3-4). They suggest that

the results are consistent with a six-membered ring transition state being important for successful allylation.

They next examined the reaction of **10**, which showed low diastereomer excess in anhydrous THF and marked improvement when running in 10:1 THF—H_2O (Table 1.3, entries 1 and 3). They suggest this effect would be due to the reversibility of the allylation reaction. Although in anhydrous THF longer reaction times led to lower diastereoselectivity (Table 1.3, entries 1-2), this was not found to be the case in 10:1 THF—H_2O (entries 3-4).

Table 1.3. *Effects of solvent on the allylation of oxime* ***10****.*

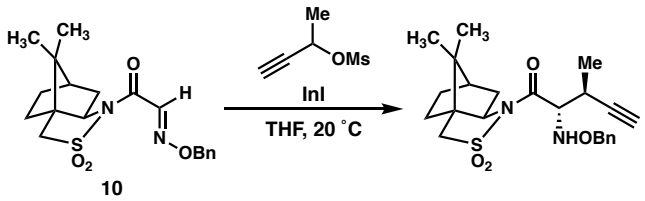


10

Entry	Solvent	Time (h)	Yield (%)	de (%)
1	THF	0.25	89	62
2	THF	3	91	20
3	THF—H_2O (10:1)	0.25	88	92
4	THF—H_2O (10:1)	20	95	91

Finally, they tested the propargylation of oxime **10** in anhydrous THF (Table 1.4). It was found that the reaction proceeded in good yield with LiBr or LiCl and a palladium catalyst (Table 1.4, entries 3-5). Although they could not determine the exact diastereoselectivity by ^{1}H NMR, they state that "the combined yields of other diastereoisomers were less than 7%."

Table 1.4. *Propargylation of* ***10*** *in anhydrous THF.*

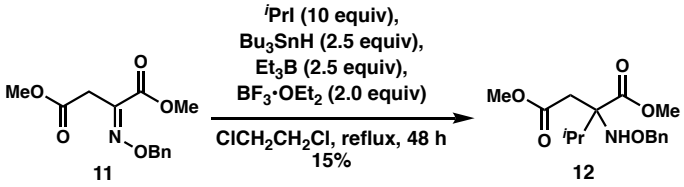


10

Entry	Catalyst	Additive	Time (h)	Yield (%)
1	none	none	20	nr
2	$Pd(PPh_3)_4$	none	50	67
3	$Pd(PPh_3)_4$	LiBr	25	75
4	$Pd(OAc)_2 \cdot PPh_3$	LiBr	15	78
5	$Pd(dppf)Cl_2$	LiCl	15	72

Mitani *et al.* developed a method for the preparation of α,α-disubstituted amino acid derivatives by the reaction of α-oxime esters with alkylzinc reagents.[16] Initially, they examined the radical alkylation of **11** using isopropyl iodide, Bu_3SnH, and Et_3B. After trying a variety of reaction conditions, the best result was formation of **12** in 15% yield (Scheme 1.4).

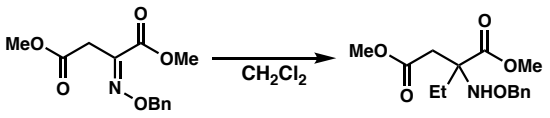
Scheme 1.4. *Alkylation of* ***11*** *via radical pathway.*



11 12

They next began examining reactivity of **11** with various alkylzinc reagents, finding 76% yield when **11** was reacted with two equivalences of diethylzinc in the presence of $BF_3 \cdot OEt_2$ in CH_2Cl_2 at reflux (Table 1.5, entry 2). Mitani *et al*. then attempted to enhance the nucleophilicity of the organozinc species by using the zincate complex (e.g. $Et_3Zn \cdot MgBr$) as well as by trying a different Lewis acid, $Ti(O\text{-}^iPr)_4$ (Table 1.5, entry 3). Using $BF_3 \cdot OEt_2$ and two equivalences of $Et_3Zn \cdot MgBr$, they were able to achieve a maximum yield of 82% (entry 4).

Table 1.5. *Optimization of the alkylation of* ***11****.*

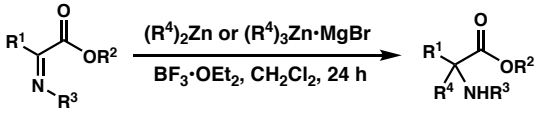


11 **13**

Entry	Alkylzinc (equiv)	Lewis acid	Temp	Yield (%)
1	Et_2Zn (1)	$BF_3{\cdot}OEt_2$	reflux	55
2	Et_3Zn (2)	$BF_3{\cdot}OEt_2$	reflux	76
3	$Et_3Zn{\cdot}MgBr$ (2)	$Ti(O\text{-}^iPr)_4$	0 ˚C	65
4	$Et_3Zn{\cdot}MgBr$ (2)	$BF_3{\cdot}OEt_2$	0 ˚C	82

With these conditions in hand, the authors set out to expand the scope of their reaction. They first tested the alkylation of methyl pyruvate oxime, **14a**. Unbranched alkylzincate reagents gave the corresponding product in good yield (Table 1.6, entry 1). Reaction with $^iPr_3Zn{\bullet}MgBr$ resulted in a low yield, which was improved by increasing the equivalence of alkylzinc (entries 2-3). Allylation of **14a** occurred in low yield (23-41% yield), but this was increased to 68% by increasing the reaction temperature to

Table 1.6. *Alkylation of glyoxyl oximes and imine with organozinc reagents.*



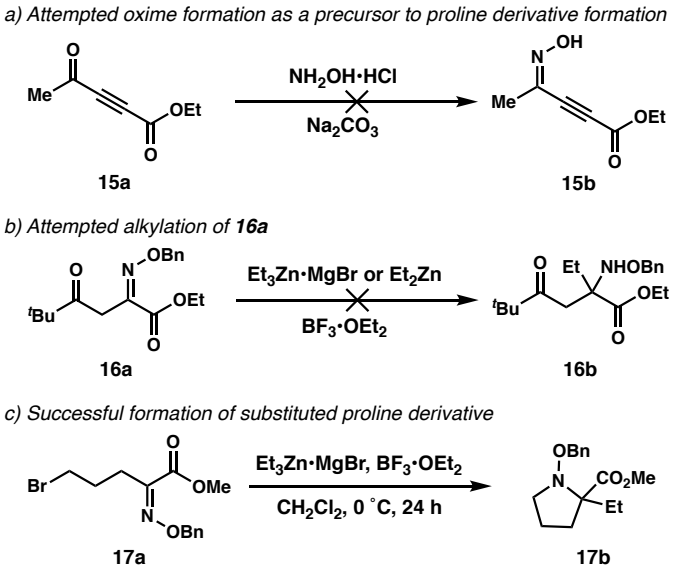
14a R^1 = Me, R^2 = Me, R^3 = OBn
14b R^1 = ^{n}Bu, R^2 = Et, R^3 = OBn
14c R^1 = ^{i}Pr, R^2 = Et, R^3 = OBn
14d R^1 = Me, R^2 = Me, R^3 = Bn

Entry	Starting Material	Conditions	Yield (%)
1	14a	Et_2Zn (2 equiv), 0 ˚C	85
2	14a	$^iPr_3Zn{\cdot}MgBr$ (2 equiv, 0 ˚C)	31
3	14a	$^iPr_3Zn{\cdot}MgBr$ (3 equiv, 0 ˚C)	64
4	14a	$(CH_2{=}CHCH_2)_3Zn{\cdot}MgBr$ (2 equiv), 0 ˚C	23
5	14a	$(CH_2{=}CHCH_2)_3Zn{\cdot}MgBr$ (2 equiv), reflux	68
6	14b	$Bu_3Zn{\cdot}MgBr$ (4 equiv), reflux	74
7	14b	$Et_3Zn{\cdot}MgBr$ (4 equiv), r.t.	67
8	14b	$^iPr_3Zn{\cdot}MgBr$ (4 equiv), r.t.	69
9	14b	$(CH_2{=}CHCH_2)_3Zn{\cdot}MgBr$ (2 equiv), r.t.	72
10	14c	$(CH_2{=}CHCH_2)_3Zn{\cdot}MgBr$ (2 equiv), r.t.	66
11	14d	$(CH_2{=}CHCH_2)_3Zn{\cdot}MgBr$, 0 ˚C	19
12	14d	$(CH_2{=}CHCH_2)_2Zn$, 0 ˚C	9

reflux (entries 4-5). Additionally, the authors tested their conditions against oximes **14b** and **14c**, with good yield (entries 6-10). They attempted the allylation of an imine (**14d**) using this reaction scaffold, which gave low yields (entries 11-12).

Finally, they turned their attention to synthesis of amino acid derivatives. However, they initially were unable to form the desired oxime ester **15b** (Scheme 1.5, a), and subsequently found that treatment of **16a** resulted in complete consumption of the starting material with no desired product formed (Scheme 1.5, b). Finally, they found that under their reaction conditions, **17a** could be used to form α-substituted proline derivatives (Scheme 1.5, c).

Scheme 1.5. *Attempted formation of α-substituted proline derivatives.*

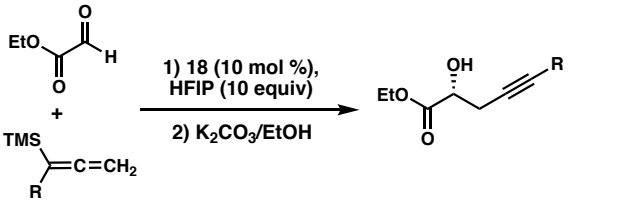


1.3 PROPARGYLATION REACTIONS

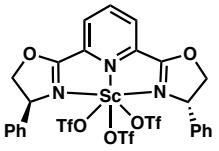
In 2001, Evans *et al.* showed the selective propargylation of ethyl glyoxylate using scandium triflate and TMS-allenyl compounds as the nucleophile.[17] They found that $Sc(OTf)_3$ and Ph-PyBOX (**18**) promoted the addition of 1-methyl-1-(trimethylsilyl)allene

to ethyl glyoxylate in high enantioselectivity and yield. Adding hexafluoro-2-propanol (HFIP) was found to slightly improve yields by suppressing formation of oligomeric byproducts. Ethyl glyoxylate was propargylated in good to excellent enantioselectivity and yield using allenyl silanes with both linear and branched alkyl substituents (Table 1.7). It was discovered that [3+2] cycloaddition products could be formed by increasing the steric bulk of the silane substituents.

Table 1.7. *Propargylation of ethyl glyoxylate.*



Entry	R	Yield (%)	ee (%)
1	Me	95	98
2	Cy	95	90
3	$(CH_2)_3OTBS$	75	93
4	^{i}Pr	96	93

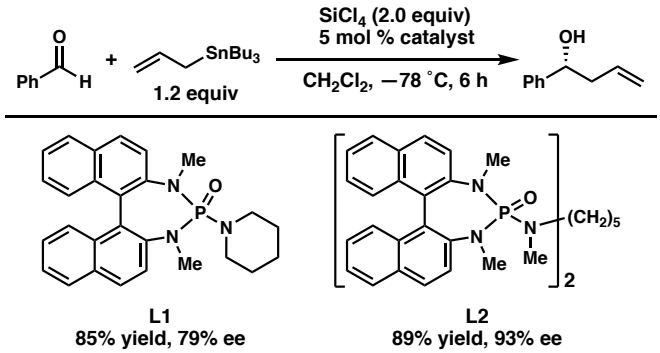


18

Denmark *et al.* utilized a Lewis base-activated Lewis acid to catalyze the enantioselective allylation and propargylation of aldehydes.[18] By activating a weak, achiral Lewis acid with a chiral Lewis base, they avoided some of the complications of Lewis acids including a competing achiral background reaction. Proof-of-concept studies showed that $SiCl_4$ and HMPA could promote the allylation of benzaldehyde with allyltributylstannane without background reactions. They next began developing the asymmetric reaction and found that a BINAP-based phosphoramide ligand **L1** could catalyze this reaction in high yield and enantioselectivity (Figure 1.5). Initial optimization showed that linked phosphoramide **L2** gave the highest enantioselectivity (Figure 1.5),

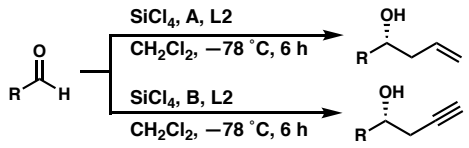
and further investigations showed that silicon tetrachloride was the optimal silicon source.

Figure 1.5. *Optimization of the phosphoramide ligand for allylation of benzaldehyde.*



Investigation into the reaction showed that it gave good yields for a variety of aldehydes but enantioselectivity was highly dependent on the structure of the substrate (Table 1.8, entries 1-5). The authors were also able to use allenyltributylstannane to propargylate compounds in high yield and enantioselectivity without detecting the isomeric allenyl compound (Table 1.8, entries 6-8).

Table 1.8. *Activated Lewis acid-catalyzed allylation and propargylation of aldehydes.*

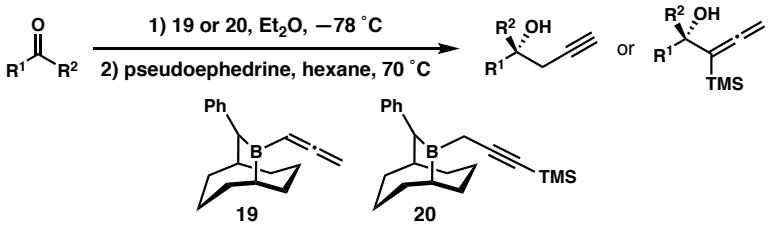


A = $(CH_2=CH-CH_2)SnBu_3$, B = $(CH_2=C=CH)SnBu_3$

Entry	Alkylstannane	R	Yield (%)	ee (%)
1	A	C_6H_5	91	94
2	A	4-$NO_2C_6H_4$	90	83
3	A	(E)-$C_6H_5CH=CH$	91	65
4	A	(E)-$C_6H_5CH=C(CH_3)$	75	11
5	A	$C_6H_5C\equiv C$	92	22
6	B	Ph	81	97
7	B	cinnamyl	90	87
8	B	2-naphthyl	95	93

Hernandez *et al.* reported the use of two borabicyclodecanes, *B*-allenyl-10-Ph-9-BBD (**19**) and γ-trimethylsilyl-propargyl-10-Ph-9-BBD (**20**) for propargylation and allenylation of ketones.[19] These reagents are air-stable and readily prepared in optically pure forms. Initially, the authors examined the asymmetric propargylation of various ketones using **19** (Table 1.9, entries 1-5). The resulting tertiary alcohols were obtained in good yield (62-85%) and good to high enantioselectivity (61-93%). They note that the addition to propiophenone was much slower, requiring two days at 25 ˚C (Table 1.9,

Table 1.9. *Propargylation and allenylation of ketones using borabicyclodecanes.*



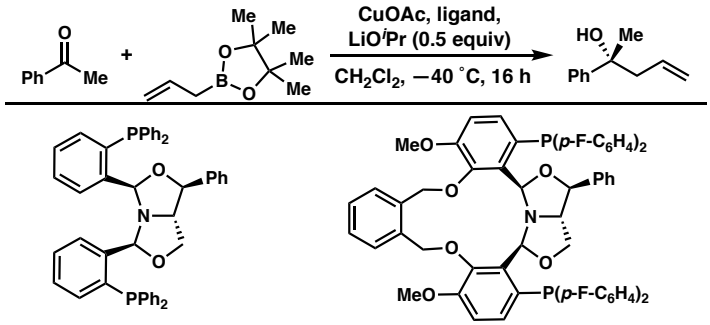
Entry	R^1	R^2	19 or 20	Yield (%)	% ee
1	Ph	Me	19	85	93
2	Ph	Et	19	65	76
3	Et	Me	19	71	74
4	TMS	Me	19	62	90
5	CH_2=CH	Me	19	64	61
6	Bu	Me	20	62	84
7	*p*-$MeOC_6H_4$	Me	20	95	92
8	*p*-BrC_6H_4	Me	20	80	98
9	2-C_4H_2S	Me	20	71	78
10	Ph	Et	20	63	64

entry 2). However, even this and other challenging substrates such as 2-butanone and methyl vinyl ketone were obtained with good selectivities (76%, 74%, and 61% respectively). Hernandez *et al.* found that the allenylation of various ketones using **20** proceeded in good to excellent yield (62-95%) and good to excellent enantioselectivity (78-98%) with the exception of propiophenone, which gave 64% ee (Table 1.9, entries 6-

10). The recyclable nature of the 9-BBD reagent and fairly wide variety of ketones make this a suitable addition to the propargylation toolbox.

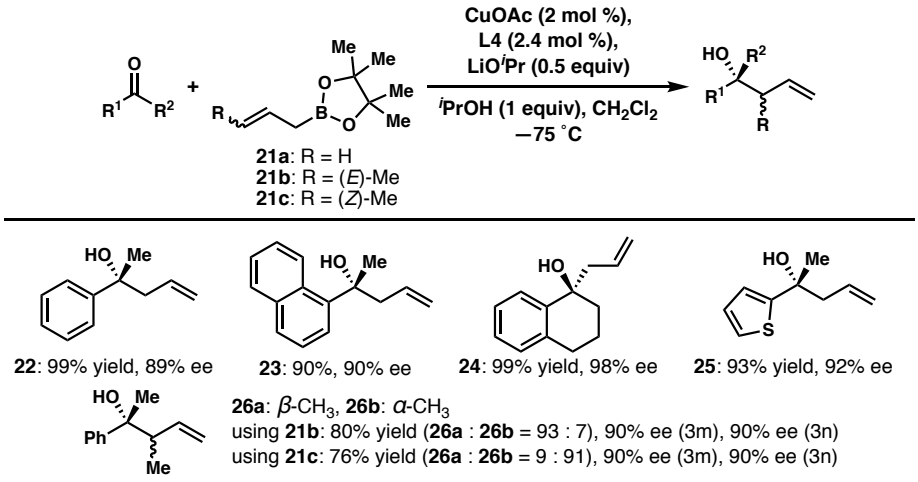
Shi *et al.* sought to develop a modular approach to chiral phosphine development, which they applied to discovery of a catalyst for the Cu(I)-catalyzed asymmetric allylation and propargylation of ketones.[20] They first examined diphosphine **L3** in the Cu-catalyzed asymmetric allylation of acetophenone (Figure 1.6). The product was obtained in quantitative yield and 41% ee. In order to improve the enantioselectivity of the reaction, they designed the next ligands with a constrained macrocycle, which eventually increased enantioselectivity to 89% ee using **L4** (Figure 1.6).

Figure 1.6. *Ligand optimization for the copper-catalyzed allylation of acetophenone.*



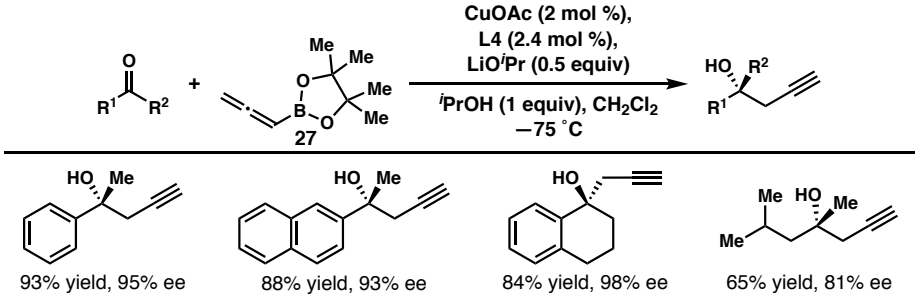
Using **L4** and the tetramethyl dioxaborolane **21a**, the authors were able to allylate a variety of ketones in good to excellent yield and enantioselectivity (Figure 1.7, **22**-**25**). They also found that crotylation using **L4** and **21a** or **21b** "also proceeded with improved diastereo- and enantioselectivity" relative to their previous reaction using ^{i}Pr-DuPHOS (Figure 1.7, **26a**-**26b**). However, they note that their enantio- and diastereoselectivity were slightly inferior to that reported by Schaus.[21]

Figure 1.7. *Copper-catalyzed allylation and crotylation using tetramethyl dioxaborolanes.*



They also were able to use this reaction with allenyl dioxaborolane **27** to propargylate a range of ketones in good to excellent yield and enantioselectivity (Figure 1.8).

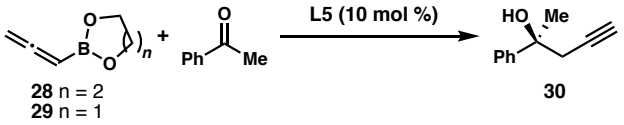
Figure 1.8. *Copper-catalyzed propargylation using allenyl tetramethyl dioxaborolane.*



Schaus and Barnett demonstrated the enantioselective propargylation of ketones using 1,3-dioxaborolanes with a BINOL catalyst.[22] They initially investigated the reactions of **28** with acetophenone with **L5** as the catalyst. They found that no reaction occurred at room temperature. However, with heating to 65 °C, they obtained alcohol **30** in 80% yield and an enantiomeric ratio of 93:7 after only 15 hours (Table 1.10, entry 1).

They were able to reduce the reaction time by the use of microwave irradiation (entry 2). Next, they investigated the use of allenyldioxaborolane **29**, hypothesizing that the greater ring strain in the boronate would result in a faster reaction. They found that this was the case, and in addition saw an increase in reactivity at room temperature (Table 1.10, entries 3-4). Ultimately it was determined that reaction with **29** under microwave conditions gave the greatest yield (85%) and enantioselectivity (97:3 er).

Table 1.10. *Chiral biphenol-catalyzed propargylation of acetophenone.*

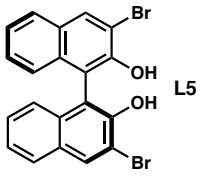


28 n = 2
29 n = 1

30

Entry	Boronate	Method[a]	Temp (°C)	Time (h)	Yield (%)	er
1	28	a	65	15	80	93:7
2	28	b	105	1	77	93:7
3	29	a	65	15	80	97:3
4	29	b	60	1	85	97:3

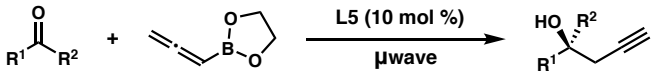
[a] Catalyst was dissolved in boronate and then ketone added. Heated using the following methods: (a) conventional heating (b) microwave reactor held at 10 W



L5

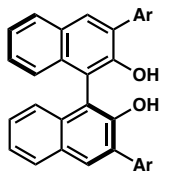
The substrate scope of the reaction was found to encompass ketones with varied steric and electronic properties, and the authors found that in the case of ketones with lowered steric hindrance they could use 3,3'-Mes_2-BINOL (**L6**) or 3,3'-anthracyl-BINOL to improve the selectivity (Table 1.11, entries 2 and 5).

Table 1.11. *Substrate scope of biphenol-catalyzed propargylation.*



Entry	R^1	R^2	Yield (%)	er
1	Ph	CH_3	85	97:3
2[a]	$Ph(CH_2)_2$	CH_3	86	79:21
3	Ph	CH_2Ph	98	98:2
4	naphthyl	CH_3	86	97:3
5[a]	PhCHCH	CH_3	91	95:5
6	1-cyclohexenyl	CH_3	68	96:4

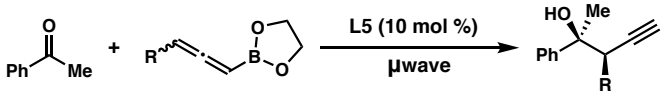
[a] Reaction run with 10 mol % **L6** instead of **L5**



L6
Ar = 2,4,6-$(CH_3)_3C_6H_2$

They also investigated whether the reaction could be used for diastereoselective propargylations using a racemic boronate. They found that the methyl allenyl borolane gave the *syn*-methylpropargyl product in 93% yield and in 86:14 diasteromeric ratio (Table 1.12, entry 1). By using allenes with larger substituents at the γ-position, the authors were able to improve the diastereoselectivity of the reaction even to the point of obtaining the product in >25:1 dr and 94:6 er from the isopropyl allenyl borolane (Table 1.12, entry 2).

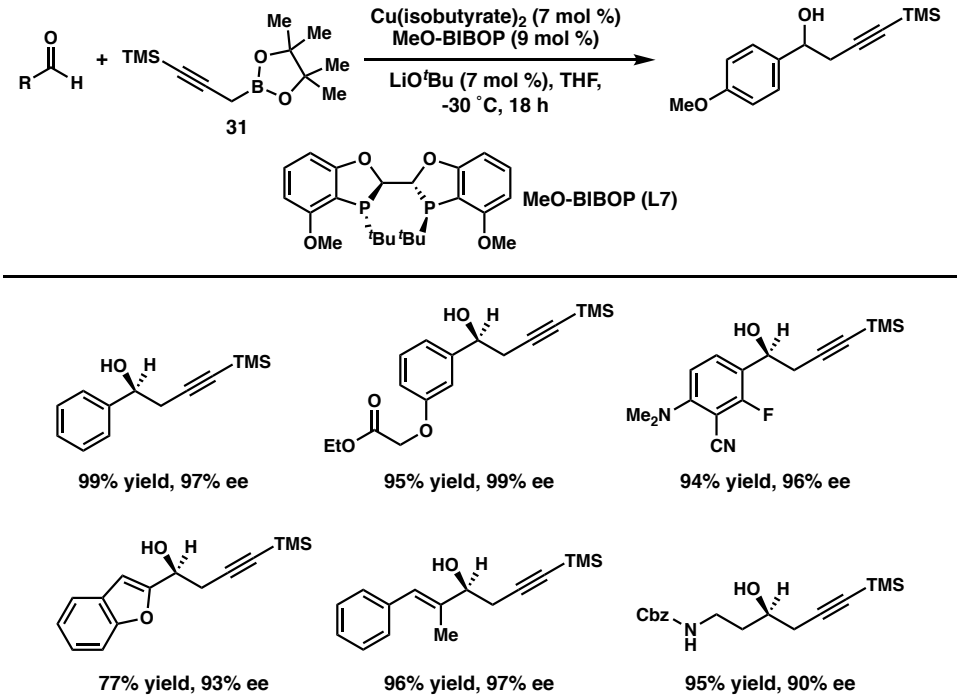
Table 1.12. *Diastereoselective biphenol-catalyzed propargylation.*



Entry	R	Yield (%)	er	dr
1	Me	93	92:8 (major) 98:2 (minor)	86:14
2	^{i}Pr	82	94:6 (major)	>25:1
3	Ph	98	94:6 (major) 96:4 (minor)	87:13

Similarly, in 2010 Fandrick *et al.* used a dioxaborolane compound (**31**) with a BIBOP catalyst to perform enantioselective propargylation of aldehydes.[23] During their initial optimization, they noted a slow background reaction with or without a copper catalyst. They found that phosphine ligands greatly increased the selectivity for the alkynyl product rather than the allene; the highest enantioselectivity came from the methoxy derivative of their parent BIBOP ligand (MeO-BIBOP, **L7**). Their reaction conditions gave high enantioselectivities and yields for a variety of aromatic substrates with a slight decrease in enantioselectivity for the one aliphatic substrate (Figure 1.9). Their conditions also allowed them, in at least one case, to selectively propargylate an aromatic ketone rather than an ester (Figure 1.9).

Figure 1.9. *Copper(II) isobutyrate-catalyzed propargylation substrate scope.*

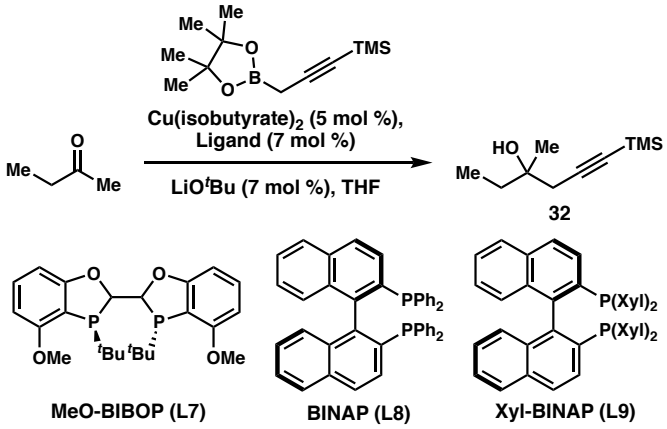


A 2011 study by Fandrick *et al.* focused on the copper-catalyzed, enantioselective propargylation of ketones.[24] They initially focused on methyl ethyl ketone (MEK) for the challenges it represents in enantiocontrol. Initial attempts employing their previous copper(II) isobutyrate—MeO-BIBOP system yielded the homopropargylated alcohol **32** with an ee of 69% (Table 1.13, entry 1). After "an intensive ligand, solvent, and catalyst survey," they found that using Xyl-BINAP (**L9**) raised the enantioselectivity to 83% and unsubstituted BINAP raised enantioselectivity to 90% (Table 1.13, entries 2-3). Decreasing the reaction temperature to –83 ˚C provided **32** in 83% yield and 95% ee (entry 4).

Subsequently, the authors investigated the scope of the reaction, finding it to be efficient over a variety of compounds with uniformly high enantioselectivity and good to excellent yield (Table 1.14). However, benzofuran methyl ketone required increased

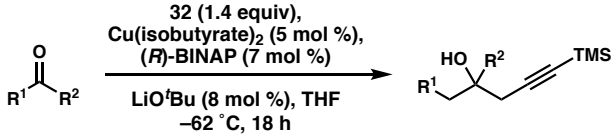
catalyst loading and 35 hours reaction time to go to completion and showed an ee of only 84% (Table 1.14, entry 5).

Table 1.13. *Ligand optimization for copper-catalyzed propargylation of ketones.*



Entry	Ligand	Temp (°C)	Conversion (Isolated Yield)	ee (%)
1	MeO-BIBOP	−25	99%	69%
2	Xyl-BINAP	−25	99%	83%
3	BINAP	−62	99% (81%)	90%
4	BINAP	−83	99% (83%)	95%

Table 1.14. *Substrate scope of the Cu-BINAP asymmetric propargylation.*



Entry	R^1	R^2	Yield (%)	ee (%)
1	Et	Me	81	90
2	^{c}Pr	Me	96	98
3	CH_2CH_2Ph	Me	77	90
4	*p*-NO_2-Ph	Me	85	93
5[a]	Benzofuran	Me	80	84

[a] 10 mol % catalyst, 35 h

1.4 CONCLUDING REMARKS

As this chapter encompasses, transition metal catalysis readily enables the allylation and propargylation of ketones and aldehydes, as well as the allylation of oximes in high yield and enantioselectivity. The propargylation of oximes, however, is a less explored field. Enantioselective reactions often require expensive metals such as palladium or indium, or a chiral auxiliary, which can increase steps in a synthesis and is often simply unwieldy. There remains to be seen a straightforward oxime propargylation which proceeds catalytically over a wide substrate scope. This would fill a gap in the synthetic toolbox as well as provide a method of access to various unnatural amino acids or synthetic precursors.

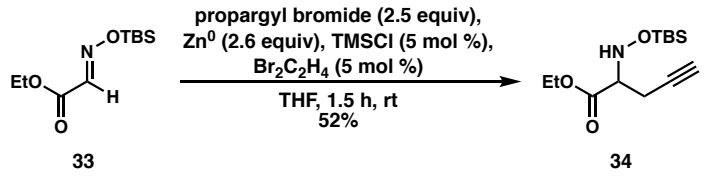
Chapter 2

Efforts in Our Laboratory[‡]

2.1 LEWIS ACID-CATALYZED ASYMMETRIC ADDITION TO OXIME ESTERS

Initial studies (performed by Nicholas Cowper) showed that the racemic propargylation could be carried out using propargyl bromide, and 2.6 equivalents of Zn^0 to achieve 52% yield. Initially the ethyl ester (**33**) was used (Scheme 2.1), but this was replaced by the phenethyl ester (**35**) in order to have a UV-active moiety for ease of detection.

Scheme 2.1. *Racemic propargylation of ethyl glyoxylate oxime.*



33 **34**

An initial ligand screen showed that most ligands gave almost no enantioselectivity in this reaction (Figure 2.1). The yields were reduced from greater than 50% to 6% and lower. The highest ee attained was from ^{t}BuCNBox (**L18**), which gave the desired product in 2% yield and 15% ee (Figure 2.1).

[‡] Work conducted in collaboration with Nicholas Cowper.

Figure 2.1. *Survey of ligands for zinc nucleophile propargylation.*

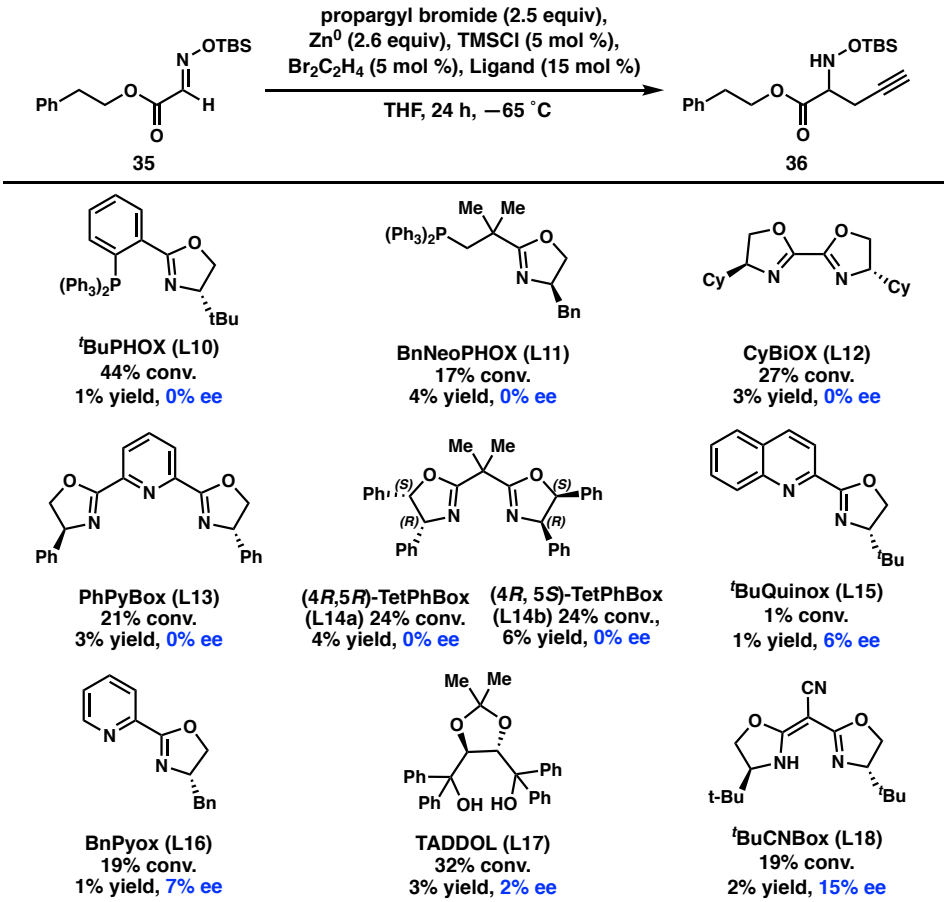
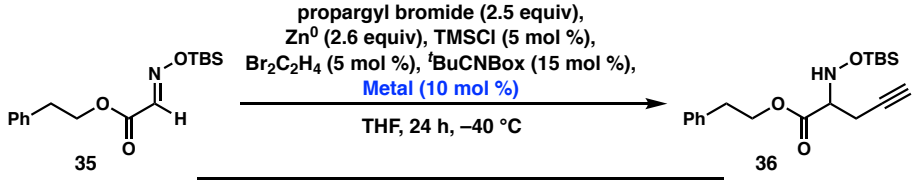


Table 2.1. *Effect of Lewis acids on the nucleophilic addition.*

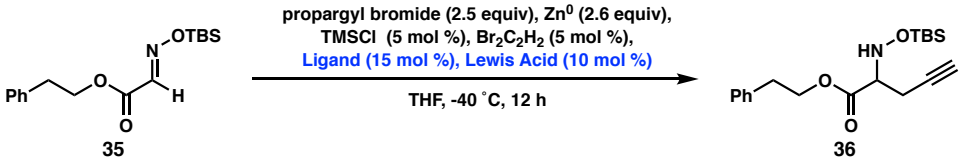


Entry	Metal	Conversion (%)	Yield (%)	ee (%)
1	none	30	10	0
2	$Yb(OTf)_3$	48	40	0
3	$In(OTf)_3$	59	42	1
4	$Sc(OTf)_3$	70	70	0
5	$NiCl_2$·dme	49	47	1
6	$(CuOTf)_2$·PhMe	60	48	0
7	$Cu(OTf)_2$	53	49	2
8	$MgBr_2$	70	57	0

Further investigation using **L18** and various Lewis acids showed that $Sc(OTf)_3$ gave the product (**36**) in 70% yield but with no enantioselectivity (Table 2.1, entry 4). This was also the most efficient reaction as all starting material consumed was converted to product. $In(OTf)_3$, NiCl•dme, and $Cu(OTf)_2$ all gave 1-2% ee but at far lower yields (Table 2.1, entries 3, 5, and 7). All other Lewis acids showed no enantiomeric excess.

At this point, we began investigating the effects of different ligands and Lewis acids on the reaction (Table 2.2). Three ligands (PhBOX, **L19**; ^{i}PrPyOx, **L20**; and ^{i}PrQuinox, **L21**; see Appendix 2) were investigated. PhBOX gave no enantioselectivity with any of the metals observed (Table 2.2, entries 1-7), although $MgBr_2$ did increase the yield to 77% (entry 5). **L20** showed lower yields and a similar lack of enantioselectivity (Table 2.2, entries 8-14). Although $Cu(OTf)_2$ gave 2% ee, the yield in this case was only 16% (entry 11). **L21** also showed considerably lower yields than the original reaction or the reaction with PhBOX, but all reactions had 1-3% ee (Table 2.2, entries 15-21).

Table 2.2. *Effects of Lewis Acids in conjunction with different ligands on the propargylation.*



	PhBox (L19)				^{i}PrPyOx (L20)				^{i}PrQuinox (L21)			
Metal	**Entry**	**Conv. (%)**	**Yield (%)**	**ee (%)**	**Entry**	**Conv (%)**	**Yield (%)**	**ee (%)**	**Entry**	**Conv (%)**	**Yield (%)**	**ee (%)**
$Yb(OTf)_3$	1	72	64	0	8	59	53	0	15	51	29	2
$In(OTf)_3$	2	47	47	0	9	53	33	0	16	89	6	1
$Sc(OTf)_3$	3	74	71	0	10	69	33	0	17	56	37	3
$Cu(OTf)_2$	4	73	72	0	11	84	16	2	18	53	33	1
$MgBr_2$	5	77	77	0	12	71	45	0	19	55	36	1
$NiCl_2$•dme	6	50	49	0	13	44	22	0	20	65	9	2
$(CuOTf)_2$•PhMe	7	74	18	0	14	62	34	0	21	46	46	1

A broad screen of 40 phosphoramidite and bis-phosphine ligands in conjunction with $(CuOTf)_2$•PhMe was carried out resulting in 0-3% ee. A second screen of eight N/O bidentate ligands with $Sc(OTf)_3$ resulted in 0-8% ee.

2.2 COPPER-CATALYZED ASYMMETRIC ADDITION TO OXIME ESTERS

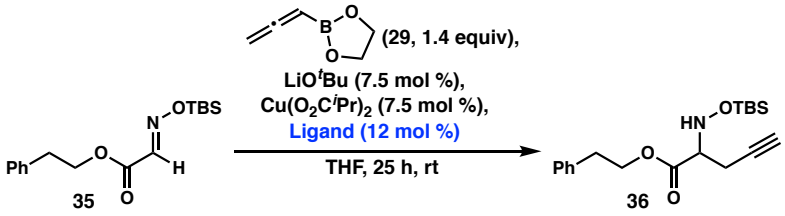
Due to the lack of improvement in the reaction, in particular the low enantioselectivity, we began searching for other reaction conditions. Inspired by Schaus' work on the enantionselective propargylation of ketones using 1,3-dioxaborolanes[21-22] and Fandrick's copper-catalyzed enantioselective propargylations of ketones[23-24], we began investigating 2-allenyl-1,3,2-dioxaborolane (**29**) as a nucleophile and subsequently copper as a catalyst.

We first attempted to replicate Schaus' microwave conditions (without copper) using neat **29** and a selection of diol catalysts, with and without alcohol additives. Yields were extremely low for all catalysts. Although 66% ee could be achieved using 15 mol % 3,3'-Br-BINOL and 3.3 equiv ^{t}BuOH, the yield was only 3%. Similarly, 3,3'-Br_2-BINOL and 4.5 equiv ^{i}PrOH gave 5% yield and 22% ee.

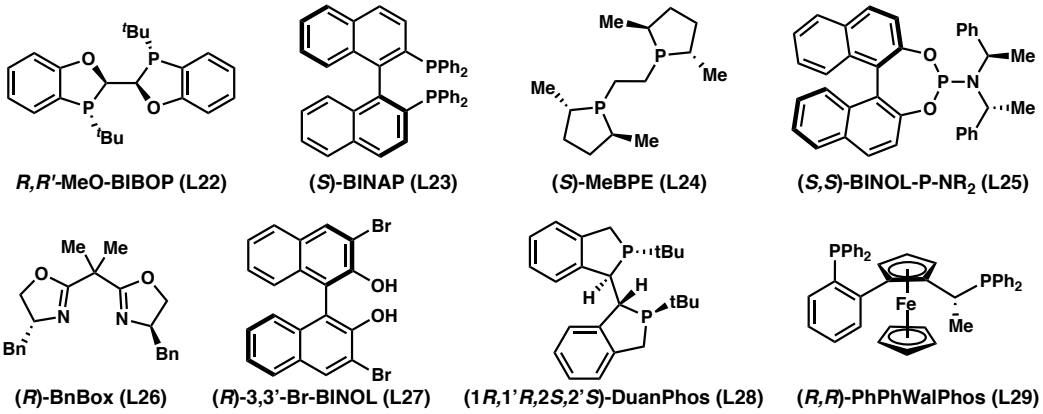
From there, we began to explore copper catalysis. We maintained use of Schaus' allenyl dioxaborolane (**29**) and began investigating Fandrick's conditions with lithium *tert*-butoxide and copper isobutyrate. An initial ligand screen under these conditions showed that Fandrick's optimal ligand,[23] MeO-BIBOP (**L22**) gave no product with our system (Table 2.3, entry 1). Fandrick's later optimal ligand, BINAP (**L23**) gave a 2% yield and 63% ee (entry 2). Further investigation showed MeBPE (**L24**) gave 40% yield but only 3% ee (entry 3). Aside from **L27**, which only gave trace yield, phosphoramidite

L25 gave the next highest ee (26%) to **L23** and 12% yield. Other ligands investigated gave low yields and enantioselectivities.

Table 2.3. *Effects of ligands on the copper(II) isobutyrate-catalyzed propargylation.*

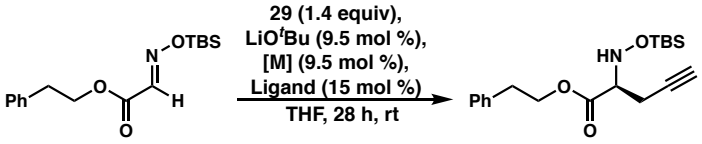


Entry	Ligand	Conversion (%)	Yield (%)	ee (%)
1	MeO-BIBOP	<10	—	—
2	BINAP	13	2	63
3	MeBPE	74	40	3
4	BINOL-P-NR$_2$	53	12	26
5	BnBox	46	26	7
6	3,3'-Br$_2$-BINOL	37	trace	32
7	DuanPhos	37	5	4
8	PhPhWalPhos	27	4	6

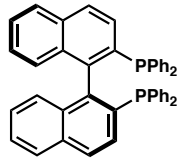


From there, copper sources were screened with both **L23** and **L25** (Table 2.4). It was determined that [Cu(MeCN)$_4$]BF$_4$ gave a low yield and high ee with **L23** as a ligand (Table 2.4, entry 5) and moderate yield and low-moderate ee with **L25** (entry 6). Cu(acac)$_2$ provided slightly higher yield with **L23** and similar results as [Cu(MeCN)$_4$]BF$_4$ with **L25** (entries 11-12).

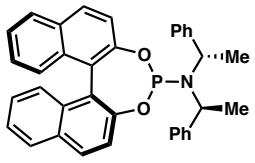
Table 2.4. *Survey of copper sources for the asymmetric propargylation.*[‡]



Entry	[M]	Ligand	Conversion (%)	Yield (%)	ee (%)
1	$(CuOTf)_2$·PhMe	A	23	6	70
2	$(CuOTf)_2$·PhMe	B	65	40	34
3	CuBr·DMS	A	35	9	0
4	CuBr·DMS	B	50	11	28
5	$[Cu(MeCN)_4]BF_4$	A	41	12	72
6	$[Cu(MeCN)_4]BF_4$	B	80	51	30
7	$[Cu(MeCN)_4]PF_6$	A	43	7	65
8	$[Cu(MeCN)_4]PF_6$	B	66	39	30
9	$[Cu(MeCN)_4]ClO_4$	A	47	11	70
10	$[Cu(MeCN)_4]ClO_4$	B	89	47	30
11	$Cu(acac)_2$	A	51	28	66
12	$Cu(acac)_2$	B	92	47	31



A: (*S*)-BINAP (L23)



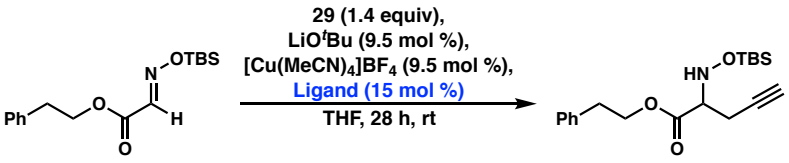
B: (*S,S*)-BINOL-P-N(CH(Me)Ph)$_2$ (L25)

With $[Cu(MeCN)_4]BF_4$ in hand as a copper source, a broad ligand screen was carried out across several classes of ligands. Based on availability in our ligand library, a total of 50 ligands were screened (8 BINAP ligands, 29 phosphoramidites, and 13 biaryl bisphosphines). Among BINAP ligands, (*R*)-DM-BINAP gave a low yield (8%) but moderate enantioselectivity (76% ee) (Table 2.5, entry 1), whereas (*S*)-QUINAP gave the highest yield (72%) with low enantioselectivity (30% ee) (entry 2). Standout phosphoramidite ligands included TADDOL-P-NMe_2 (entry 3, 70% yield, 34% ee), **L33** (entry 4, 25% yield, 41% ee), and **L34** (entry 5, 38% yield, 50% ee). Finally, biaryl bisphosphines included (*R*)-DiFluoroPhos (entry 6, 11% yield, 80% ee), (*R*)-P-Phos (entry 7, 12% yield, 80% ee), and (*R*)-BTFM-GarPhos (**L37**, entry 8, 24% yield, 82%

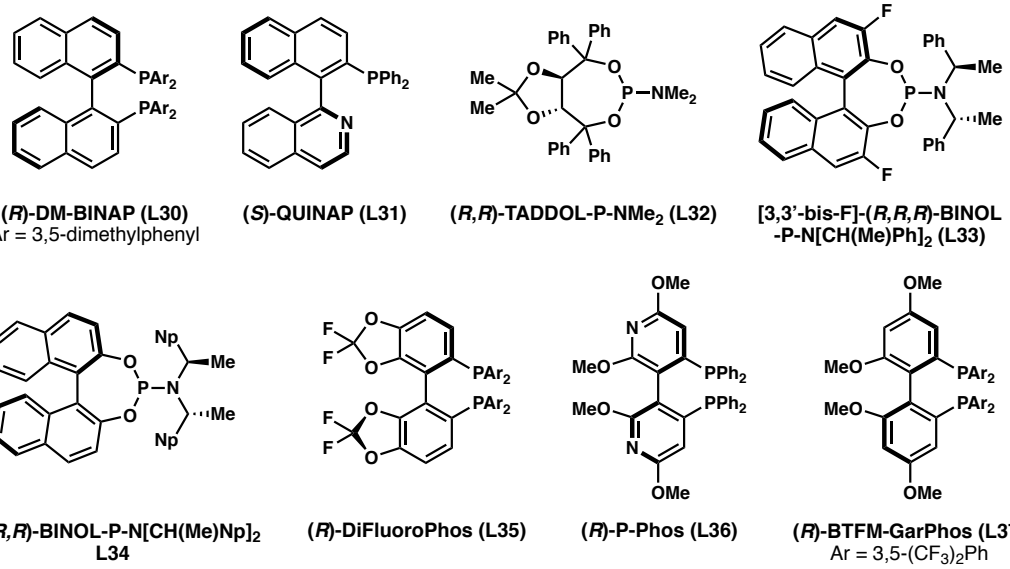
[‡] See Appendix 2.

ee). Of the three ligands with the highest ee, BTFM-GarPhos was chosen for subsequent reaction optimization due to its comparably high yield.

Table 2.5. *Standout ligands for [Cu(MeCN)$_4$]BF$_4$-catalyzed propargylation.*[‡]



Entry	Ligand	Conversion (%)	Yield (%)	ee (%)
1	(*R*)-DM-BINAP	45	8	76
2	(*S*)-QUINAP	85	72	30
3	TADDOL-P-NMe$_2$	97	70	34
4	[3,3'-bis-F]-(*R,R,R*)-BINOL-P-N[CH(Me)Ph]$_2$	69	25	41
5	(*R,R,R*)-BINOL-P-N[CH(Me)Np]$_2$	77	38	50
6	(*R*)-DiFluoroPhos	32	11	80
7	(*R*)-P-Phos	34	12	80
8	(*R*)-BTFM-GarPhos	60	24	82



(*R*)-DM-BINAP (L30)
Ar = 3,5-dimethylphenyl

(*S*)-QUINAP (L31)

(*R,R*)-TADDOL-P-NMe$_2$ (L32)

[3,3'-bis-F]-(*R,R,R*)-BINOL-P-N[CH(Me)Ph]$_2$ (L33)

(*R,R,R*)-BINOL-P-N[CH(Me)Np]$_2$ L34

(*R*)-DiFluoroPhos (L35)

(*R*)-P-Phos (L36)

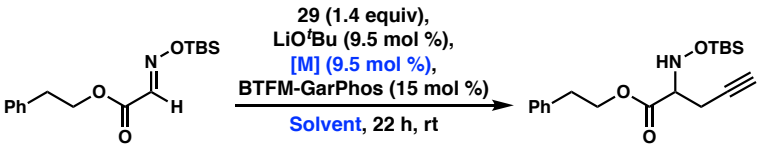
(*R*)-BTFM-GarPhos (L37)
Ar = 3,5-(CF$_3$)$_2$Ph

Using BTFM-GarPhos (**L37**), we then investigated the effects of solvent and copper source on the reaction. The reaction was screened with Cu(acac)$_2$ and [Cu(MeCN)$_4$]BF$_4$ in various solvents. The highest enantioselectivities were observed with [Cu(MeCN)$_4$]BF$_4$ with yields ranging from 16% to 33% (Table 2.6, entries 2, 4, 6,

[‡] See Appendix 2.

and 8). $Cu(acac)_2$ gave lower ee's (54-73%) with yields at times lower than the other metal (entries 1, 3) and occasionally higher (entries 5, 7). The highest yields observed with $[Cu(MeCN)_4]BF_4$ were 31% with THF (entry 2) and 33% with 2-MeTHF (entry 4). THF was chosen because it is more readily available.

Table 2.6. *Effects of solvents and comparison of copper sources on the Cu-catalyzed propargylation.*



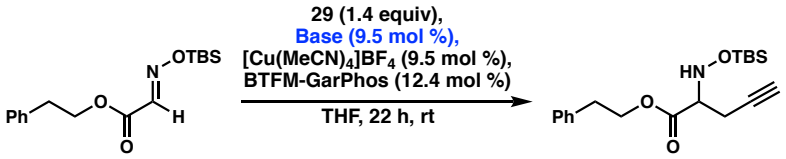
Entry	Solvent	Metal[a]	Conversion (%)	Yield (%)	ee (%)
1	THF	A	50	25	54
2	THF	B	51	31	94
3	2-MeTHF	A	45	22	58
4	2-MeTHF	B	63	33	>95
5	Et_2O	A	80	50	71
6	Et_2O	B	39	17	>95
7	Hexane	A	76	41	73
8	Hexane	B	59	16	>95

[a] A = $Cu(acac)_2$, B = $[Cu(MeCN)_4]BF_4$

At this point, we examined the base used. The previously used base, lithium *tert*-butoxide gave 33% yield and 80% ee (Table 2.7, entry 2). It was found that Cs_2CO_3 and no base gave similar yields to LiO^{t}Bu with higher enantioselectivity (Table 2.7, entries 1 and 7). It was therefore decided to examine new reactions under conditions of both Cs_2CO_3 and no base until the optimal conditions were achieved. (Some reactions later in this paper were carried out with LiO^{t}Bu simply due to being carried out at nearly the same time as the base screen.)

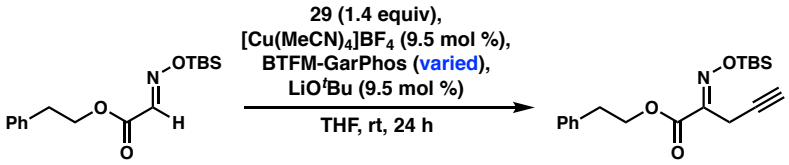
The effect of the stoichiometry of the metal and ligand was examined by varying the equivalence of BTFM-GarPhos. The highest enantioselectivity and yield were found using a 1:1.3 ratio of $[Cu(MeCN)_4]BF_4$ to BTFM-GarPhos (Table 2.8, entry 2).

Table 2.7. *Optimization of base in the Cu-catalyzed propargylation.*



Entry	Base	Conversion (%)	Yield (%)	ee (%)
1	none	73	30	95
2	LiO^{t}Bu	36	33	80
3	KOH	72	29	95
4	NaO^{t}Bu	58	26	90
5	KO^{t}Bu	40	11	68
6	Li_2CO_3	80	18	94
7	Cs_2CO_3	65	30	96
8	K_3PO_4	48	28	84
9	DBU	32	11	42
10	Et_3N	27	7	88

Table 2.8. *Metal-ligand stoichiometry.*

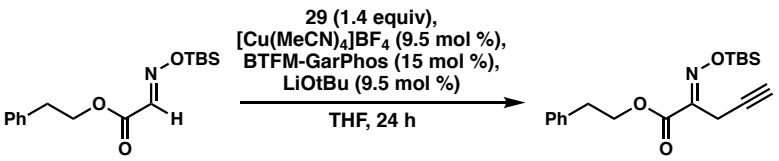


Entry	Metal:Ligand (Ligand mol %)	Conversion (%)	Yield (%)	ee(%)
1	1:2 (19 mol %)	78	16	90
2	1:1.3 (12.4 mol %)	80	26	94
3	1:1 (9.5 mol %)	63	11	74
4	1:0.8 (7.6 mol %)	78	16	90
5	1:0.67 (6.4 mol %)	74	13	88
6	1:0.5 (4.8 mol %)	62	8	72

The effects of temperature on the reaction were examined by testing the reaction at -20, 0, 20, 40, and 60 ˚C (Table 2.9, entries 1-5). However, this screen was determined to be contaminated as the reactions – including the control at room temperature – gave abnormally low yields (6-14%). The reaction was later tested with optimized conditions at room temperature and 40 ˚C (Table 2.9, entries 6-7). Increasing the temperature was found to improve the yield to 37%, compared to a control of 33%, and the

enantioselectivities were comparable. Since the increase in yield was minor, it was therefore decided to proceed at room temperature for ease of set-up.

Table 2.9. *Effects of temperature on the Cu-catalyzed propargylation.*

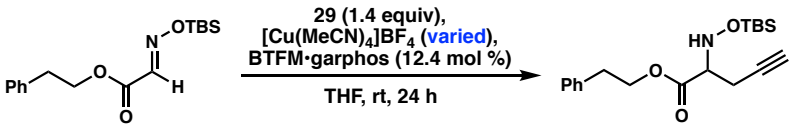


Entry	Temperature	Conversion (%)	Yield (%)	ee (%)
1	−20 ˚C	80	6	94
2	0 ˚C	67	9	88
3	r.t.	72	8	82
4	40 ˚C	87	14	88
5	60 ˚C	89	13	26
6[a]	r.t.	63	33	95
7[a]	40 ˚C	75	37	94

[a] Second screen; 12.4 mol % BTFM-GarPhos.

At this point, we investigated the effects of the equivalence of copper used in the reaction (Table 2.10). We also re-examined the effects of base on the reaction. This experiment was run in two series (with and without 0.095 equiv of Cs_2CO_3) of increasing $[Cu(MeCN)_4]BF_4$, from 0.095 equiv to 1.0 equiv, while maintaining the GarPhos ligand at 0.124 equiv. It was found that when the reaction included Cs_2CO_3 and 0.4 equiv copper, the yield was 24% and the ee was 95% (Table 2.10, entry 3). However, this was determined to be anomalous as later repetition of this experiment gave 14% yield and 68% ee. Using no base and 0.2 equiv copper gave a considerable increase in yield (37%) with a decrease in ee to 88% (Table 2.10, entry 6). The control experiment in this case (0.095 equiv copper, without base) showed 19% yield but 94% ee (Table 2.10, entry 5). It was determined that since the ee was greater in this case than with 0.2 equiv copper, and higher yield had been observed under these conditions, the optimal copper stoichiometry was 0.095 equiv and the best reaction conditions were without base.

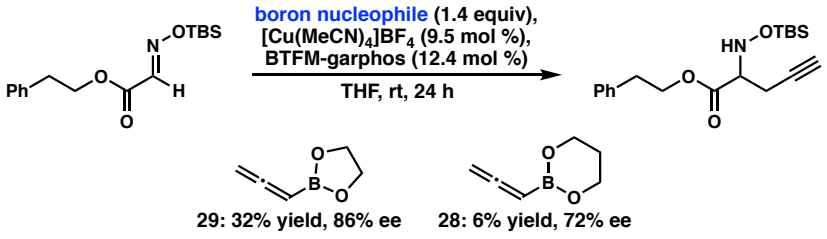
Table 2.10. *Effects of copper stoichiometry with and without base on the propargylation reaction.*



Entry	Conditions	Conversion (%)	Yield (%)	ee (%)
1	$[Cu(MeCN)_4]BF_4$ (0.095 equiv) Cs_2CO_3 (0.095 equiv)	71	21	90
2	$[Cu(MeCN)_4]BF_4$ (0.2 equiv) Cs_2CO_3 (0.095 equiv)	67	18	90
3	$[Cu(MeCN)_4]BF_4$ (0.4 equiv) Cs_2CO_3 (0.095 equiv)	73	24	95
4	$[Cu(MeCN)_4]BF_4$ (1 equiv) Cs_2CO_3 (0.095 equiv)	59	11	40
5	$[Cu(MeCN)_4]BF_4$ (0.095 equiv)	78	19	94
6	$[Cu(MeCN)_4]BF_4$ (0.2 equiv)	53	37	88
7	$[Cu(MeCN)_4]BF_4$ (0.4 equiv)	65	10	50
8	$[Cu(MeCN)_4]BF_4$ (1 equiv)	62	1	26

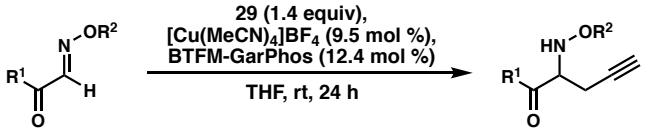
Schaus notes that the greater ring strain in the five-membered ring of borolane **29** is thought to cause it to exchange better with their BINOL-based catalyst.[22] It is also possible that a softer nucleophile with less ring strain such as borinane **28** could be more compatible with the oxime in our case. In order to test this with our own system, we synthesized **28** using 1,3-propanediol and a similar procedure as **29**. We discovered that our reactivity followed a similar pattern to Schaus', in that yield was greatly decreased from 32% in the control to 6% with the 6-membered boronate (Figure 2.2).

Figure 2.2. *Comparison of 5- and 6-member boron nucleophiles with the Cu-catalyzed propargylation.*



We also wondered what effect changing the parameters of the starting material would have on the reaction. We found that using a TIPS protecting group on the oxime rather than a TBS group effectively eliminated product formation, with or without added LiO^{t}Bu (Table 2.11, entries 1-2). A benzyl ester starting material showed similar results to the phenethyl (entry 3). Finally, using a benzyl amide instead of an ester decreased reactivity to 5% yield (entry 4).

Table 2.11. *Screen of different starting materials with the Cu-catalyzed propargylation.*

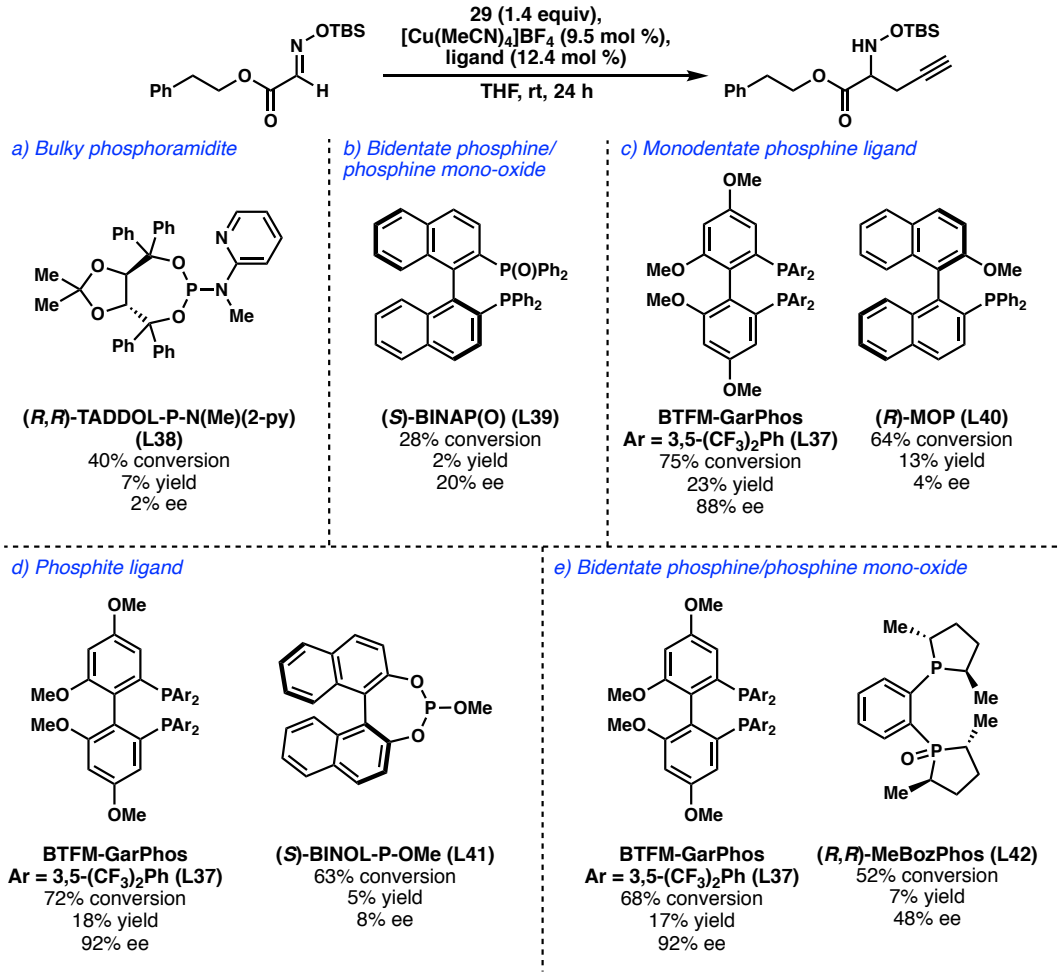


Entry	R^1	R^2	Conversion (%)	Yield (%)	ee (%)
1	OCH_2CH_2Ph	OTIPS	39	1	—
2[a]	OCH_2CH_2Ph	OTIPS	42	0	—
3	OCH_2Ph	OTBS	70	32	84
4	NCH_2Ph	OTBS	55	5	17

[a] LiO^{t}Bu (9.5 mol %) added.

We investigated whether different ligands, in particular those with different electronic configurations, could improve results on our propargylation. A bulky TADDOL-based phosphoramidite, **L38**, decreased yield to 7% and ee to 2% (Figure 2.3, a). BINAP ligands had previously shown low yield but promising ee, so we tried BINAP mono-oxide, hoping that the oxidation would be sufficient to improve our yield. However the yield was 2% and ee only 20% (Figure 2.3, b). We subsequently tried MOP (**L40**, a monodentate phosphine ligand), a BINOL-based phosphite (**L41**), and MeBozPhos (**L42**, a bidentate phosphine/phosphine mono-oxide with different bite angle), all of which showed severely decreased yield and enantioselectivity compared to the control, BTFM-GarPhos (Figure 2.3, c-e).

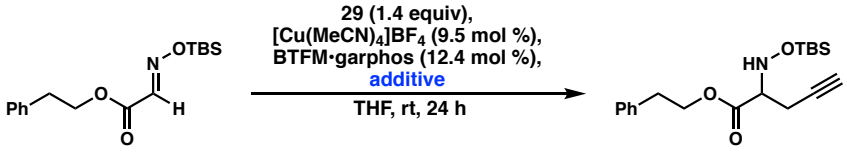
Figure 2.3. *Ligand screens for the Cu-catalyzed propargylation.*



Inspired by a surprising success by a colleague in our lab,[25] we screened 2,6-dibromophenol as a proton source in our reaction (Table 2.12). However, concentration of 2,6-dibromophenol was found to have an inverse effect on the yield of our reaction. At 0.4 equiv 2,6-dibromophenol, the reaction yield was only 15%, and the ee dropped to 88% (Table 2.12, entry 1). At 1.0 equiv, the yield was reduced to 2%, and the ee could not be measured (entry 2). *Tert*-butanol showed similar effects on reactivity. At 0.7 equiv ^{t}BuOH, the reaction yield decreased to 11% (Table 2.12, entry 8). At higher equivalences, no product was observed, although some starting material was consumed (entries 9-10).

Water was also investigated as a proton source. It was found that at low concentrations it neither hindered nor improved reactivity (Table 2.12, entries 3, 6), as yield stayed approximately the same as had been observed in previous reactions. However, the enantioselectivity was reduced to 82-84%. At higher concentrations, the yield decreased considerably (Table 2.12, entries 4-5, 7). This trend was the same for the reaction with and without 0.095 equiv Cs_2CO_3.

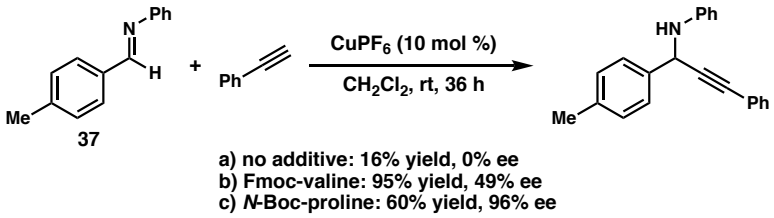
Table 2.12. *Effects of proton-bearing additives on the Cu-catalyzed propargylation.*



Entry	Additive	Conversion (%)	Yield (%)	ee (%)
1	2,6-dibromophenol (0.4 equiv)	75	15	88
2	2,6-dibromophenol (1.0 equiv)	64	2	—
3	H_2O (0.1 equiv)	45	27	84
4	H_2O (0.4 equiv)	47	13	78
5	H_2O (1.0 equiv)	9	6	52
6	H_2O (0.1 equiv) Cs_2CO_3 (0.095 equiv)	72	29	82
7	H_2O (1.0 equiv) Cs_2CO_3 (0.095 equiv)	76	1	20
8	^{t}BuOH (0.7 equiv)	45	11	81
9	^{t}BuOH (1.4 equiv)	31	0	—
10	^{t}BuOH (2.8 equiv)	27	0	—

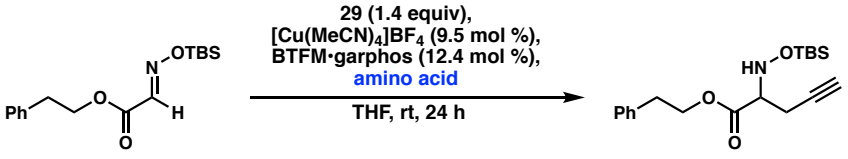
Arndtsen *et al.* demonstrated that amino acids could be used as a highly tunable additive to increase the enantioinduction of a reaction, in their case copper-catalyzed alkyne-imine coupling (Scheme 2.2).[26] They showed that their initial reaction, the coupling of imine **37** to phenylacetylene using $CuPF_6$, could be raised from 16% yield and 0% ee to 95% yield and 49% ee using Fmoc-valine. A quick screen determined *N*-Boc-proline could be used to raise the ee to 96% with a yield of 60%.

Scheme 2.2. *Use of amino acids to increase enantioenduction of copper-catalyzed alkyne-imine coupling.*[26]



Based on this, we hoped it might be possible to use amino acids as a tunable hydrogen bond donor in our reaction. We investigated both L-Boc-proline and D-Boc-proline in case of possible additive effects on enantioselectivity; however, both amino acids caused a decrease in reactivity – no product was observed and there was an additional decrease in consumption of starting material (Table 2.13, entries 2-3). It should be noted that the control (entry 1) showed an unusually low yield in this screen, but the complete lack of product with the addition of amino acids in the reaction was clear.

Table 2.13. *Amino acid additives in the Cu-catalyzed propargylation.*

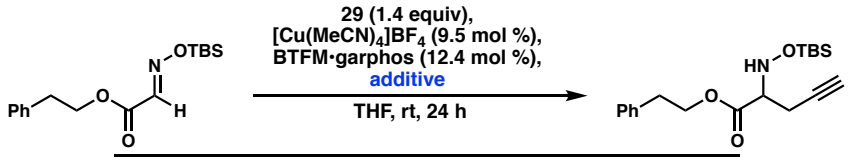


Entry	Amino acid	Conversion (%)	Yield (%)	ee (%)
1	none	87	7	90
2	Boc-L-proline (0.19 equiv)	59	0	—
3	Boc-D-proline (0.19 equiv)	63	0	—

Shibasaki *et al.* found they could use La(O^{i}Pr)$_3$ as a cocatalyst to greatly accelerate the copper-catalyzed enantioselective allylation of ketones and imines.[27-28] They also found it greatly improved their yield. We therefore hoped to be able to use the same effect to our advantage and screened La(O^{i}Pr)$_3$ in the same stoichiometry (1.5 times the amount of copper catalyst) as Shibasaki. We also revisited Sc(OTf)$_3$ to see if it would

give a higher yield with our new conditions. We found that both compounds greatly decreased the yield, to 12% and 11% respectively (Table 2.14, entries 1-2). The enantioselectivity was also considerably reduced.

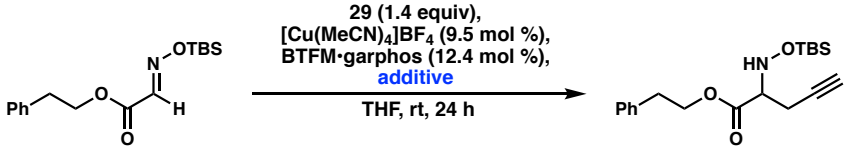
Table 2.14. *Lewis acid additives in the Cu-catalyzed propargylation.*



Entry	Additive	Conversion (%)	Yield (%)	ee (%)
1	$La(O^iPr)_3$ (14.3 mol %)	40	12	65
2	$Sc(OTf)_3$ (9.5 mol %)	54	11	40

As we noted previously (Table 2.12), water can slow or nearly halt the reaction. In order to test if trace water was holding back the reaction, we screened molecular sieves. However, these reduced the yield from 34% to 21% as well as decreasing the ee (Table 2.15, entry 2). Subsequently, we wondered if adding a fluoride source could improve catalyst turnover by taking up excess boronate. However, CsF reduced the yield to 13-18% (Table 2.15, entries 3-5). We screened pyridine, 2,6-lutidine, and proton

Table 2.15. *Additives in the Cu-catalyzed propargylation.*



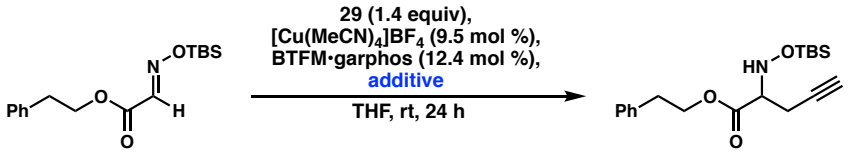
Entry	Additive	Conversion (%)	Yield (%)	ee (%)
1	none	71	34	92
2	mol sieves	74	21	84
3	CsF (0.095 equiv)	64	13	94
4	CsF (0.19 equiv)	70	18	93
5	CsF (1.0 equiv)	69	14	90
6	pyridine (0.095 equiv)	95	19	90
7	2,6-lutidine (0.95 equiv)	59	24	92
8	proton sponge[a] (0.095 equiv)	66	12	92
9	DMS (0.095 equiv)	74	13	94

[a] 1,8-Bis(dimethylamino)naphthalene

sponge to see if excess protons were stopping catalyst turnover; however, all three gave reduced yields (entries 6-8). Finally, we examined DMS to see if a reducing agent could improve catalyst turnover; this too reduced yield to 13% (entry 9).

We also wondered if copper-ligand electron transfer was playing a role in preventing catalyst turnover. We therefore screened electron scavengers such as nitrobenzene and metallic copper. Nitrobenzene showed little change in reactivity compared to control (Table 2.16, entry 2), but the copper reduced both yield and ee (entry 3). Finally, in order to see if the initial ligand on the copper had any effect, we screened both 0.095 and 1.0 equiv acetonitrile. The lower concentration had little effect (Table 2.16, entry 4) but the higher concentration (entry 5) raised the yield 6 percentage points compared to the control (entry 1).

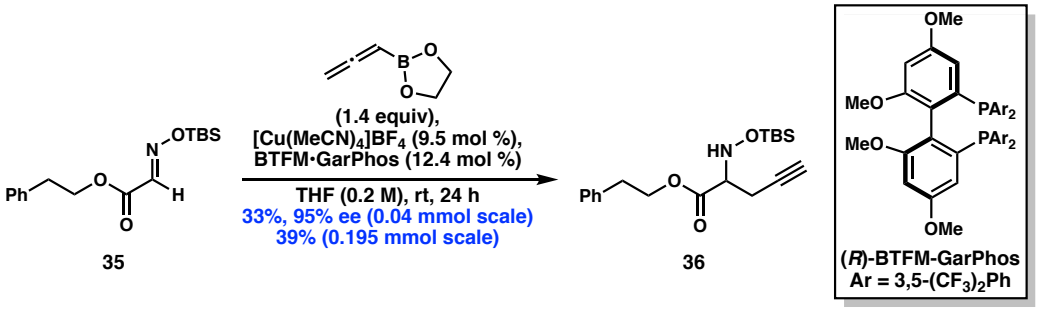
Table 2.16. *Electron scavengers and acetonitrile in the Cu-catalyzed propargylation.*



Entry	Additive	Conversion (%)	Yield (%)	ee (%)
1	none	79	19	93
2	nitrobenzene (0.095 equiv)	77	20	94
3	copper bead	82	15	88
4	acetonitrile (0.095 equiv)	95	21	95
5	acetonitrile (1.0 equiv)	79	25	92

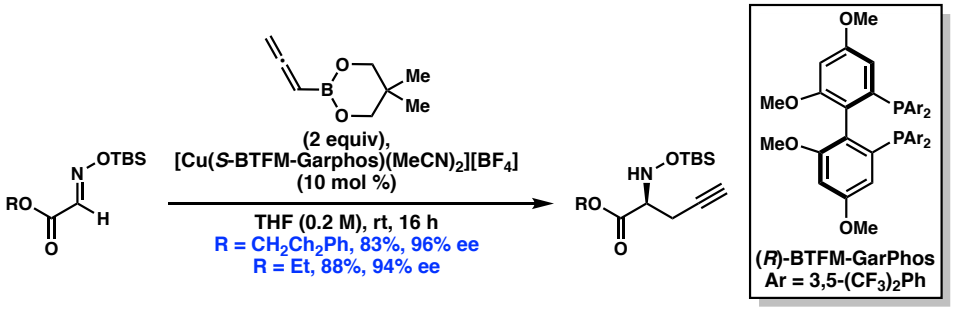
The highest yield of the propargylation reaction was found to be 39% upon scaleup (0.060 mg starting material). Enantiomeric excess found during screening was as high as 95%. The best conditions are shown in Scheme 2.3.

Scheme 2.3. *Optimized reaction conditions for the copper-catalyzed asymmetric propargylation.*



Later efforts by Nicholas Cowper and Matthew Hesse showed that by using 2 equivalences of 5,5-dimethyl-2-(allenyl)-1,3,2-dioxaborinane and a copper-BTFM-GarPhos complex the nucleophilic addition could be achieved in 83% yield and 96% ee for the phenethyl oxime ester, and 88% yield and 94% ee for the ethyl ester (Scheme 2.4).

Scheme 2.4. *Best conditions for the catalytic asymmetric propargylation of oxime esters.*



2.3 CONCLUDING REMARKS

In conclusion, a copper catalyzed asymmetric addition to oxime esters has been developed. The $[Cu(MeCN)_4]BF_4$–BTFM-GarPhos system gives the propargylated

hydroxylamine product with high enantioselectivity. Later work was able to raise the yield considerably. The product is potentially useful in total synthesis or in various biochemical or medical applications. Further work is needed to expand the reaction scope, at which point the reaction could be a useful tool in organic synthesis.

2.4 EXPERIMENTAL SECTION

2.4.1 Materials and Methods

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), acetonitrile (MeCN), dimethylformamide (DMF), and toluene (PhMe) were dried by passing through activated alumina columns. Unless otherwise stated, chemicals and reagents were used as received. Triethylamine (Et_3N) was distilled over calcium hydride prior to use. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm) and were visualized by UV, *p*-anisaldehyde, or CAM staining. Flash column chromatography was performed as described by Still et al.[29] using silica gel (particle size 0.032-0.063) purchased from Silicycle. Analytical SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system with Chiralcel AD-H, OD-H, AS-H, OB-H, and OJ-H columns (4.6 mm x 25 cm). ^1H and ^{13}C NMR spectra were recorded on a Varian 400 MR (at 400 MHz and 101 MHz, respectively), a Varian Inova 500 (at 500 MHz and 126 MHz, respectively), or a Varian Inova 600 (at 600 MHz and 150 MHz, respectively), and are reported relative to internal $CHCl_3$ (^1H, $\delta = 7.26$), and $CDCl_3$ (^{13}C, $\delta = 77.0$). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent.

2.4.2. Starting Materials Synthesis

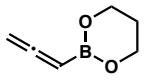
General Procedure for Synthesis of Boronates

According to the procedure of Schaus and coworkers,[22] $HgCl_2$ (0.17 mmol, 0.0017 equiv) and magnesium turnings (101 mmol, 1.01 equiv) were added to a 3-necked flask and flame dried under vacuum. To this were added dry Et_2O (15 mL) and 5% of the total propargyl bromide solution (80% wt in toluene, 5 mmol, 0.05 equiv). When the ether refluxed, the solution was cooled in an ice-salt bath. In a separate flame dried flask, the remainder of the propargyl bromide solution (95 mmol, 0.95 equiv) was dissolved in dry Et_2O (45 mL). The remainder of the propargyl bromide solution was added slowly to the flask with Mg^0. The ice bath was removed and the solution stirred 2 h at room temperature. The resulting allenyl Grignard reagent was titrated with 1,10-phenanthroline.

To a flame-dried flask were added $B(OMe)_3$ (100 mmol, 1.0 equiv) and Et_2O (100 mL). The solution was cooled to -78 ˚C and allenylmagnesium bromide solution added dropwise over 45 min. The reaction was allowed to warm to room temperature, then cooled to 0 ˚C, and 100 mL of 3M HCl were added slowly. The biphasic mixture was stirred until the solids dissolved, and then 20 min more. The mixture was poured into a separatory funnel and the organic layer removed. The aqueous layer was extracted with Et_2O (3 x 50 mL) and the organic layers combined, dried over $MgSO_4$, and concentrated to 200 mL. To this solution was added $MgSO_4$ (100 g) and ethylene glycol (8.4 mL, 150 mmol). An overhead mechanical stirrer was added and the reaction stirred overnight at room temperature. The mixture was filtered and the $MgSO_4$ washed with Et_2O (2 x 75 mL). Per Schaus, “Solvent was removed by rotary evaporation and the crude product then

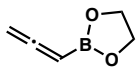
dissolved in 150 mL pentane and cooled to 0 ˚C. If necessary, excess diol is removed as the bottom layer. If a precipitate remains, the solution is filtered through a pad of oven-dried Celite®. The solvent was removed under reduced pressure and the resulting clear liquid was purified *via* Kugelrohr distillation".

_B_-(allenyl)-1,3,2-dioxaborinane (28)



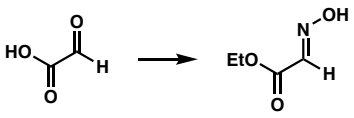
Prepared from 1,3-propanediol (10.8 mL, 150 mmol) following General Procedure for Synthesis of Boronates. The crude liquid was purified via Kugelrohr distillation to yield 3.228 g (17% yield) of **28** as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.80 (t, J = 7.0 Hz, 1H), 4.60 (d, J = 6.9 Hz, 2H), 4.06 (t, J = 4.5 Hz, 4H), 2.08 – 1.92 (m, 2H).

_B_-(allenyl)-1,3,2-dioxaborolane (29)



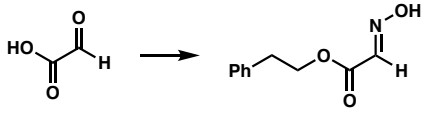
Prepared from ethylene glycol (8.4 mL, 150 mmol) following General Procedure for Synthesis of Boronates. The crude liquid was purified via fractional Kugelrohr distillation (40 ˚C, 10 mm Hg) to yield **29** as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.97 (t, J = 7.0 Hz, 1H), 4.68 (d, J = 7.1 Hz, 2H), 4.27 (d, J = 1.3 Hz, 4H); ^{11}B NMR (128 MHz, $CDCl_3$) δ 30.93.

ethyl 2-(hydroxyimino)acetate



A round bottom flask was charged with a stir bar, glyoxylic acid monohydrate (20.0 g, 217 mmol), NH_2OH•HCl (15.3 g, 220 mmol), *p*-TsOH•H_2O (3.12 g, 16 mmol), and EtOH (260 mL). It was then fitted with a Socklett extractor and condenser, and the reaction heated at 120 ˚C for 15 h. The reaction was cooled to room temperature and concentrated *in vacuo*. The resulting oil was diluted in Et_2O (400 mL) and sat. $NaHCO_3$ (240 mL). The biphasic mixture was added to a separatory funnel and the aqueous layer removed. The organic layer was washed with sat. NH_4Cl (100 mL) and pH 7 buffer (100 mL). The aqueous layer was tested for product and re-extracted with Et_2O (150 mL) if necessary. Combined organic layers were washed with brine (100 mL), then dried over Na_2SO_4, filtered, and concentrated in vacuo to yield the product (25.2 g, 99% yield) without need for further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (s, 1H), 4.32 (q, *J* = 7.1 Hz, 3H), 1.40 – 1.31 (t, *J* = 7.1 Hz, 2H).

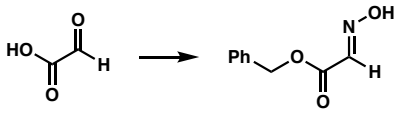
phenethyl 2-(hydroxyimino)acetate



A flask was charged with stir bar and the following reagents: glyoxylic acid monohydrate (1.50 g, 16.30 mmol), hydroxylamine hydrochloride (1.14 g, 16.46 mmol), 2-phenylethanol (5.87 mL, 48.9 mmol), *p*-TsOH•H_2O (0.233 g, 1.22 mmol). Toluene (50 mL) was added and a reflux condenser attached. The reaction was heated to 80 ˚C and stirred 15 min, then heated to 100 ˚C and stirred 1 h. Finally, the reaction was heated to 120 ˚C and stirred overnight. The reaction was then cooled to room temperature, diluted with 50 mL EtOAc, and added to a separatory funnel. The organic layer was washed with

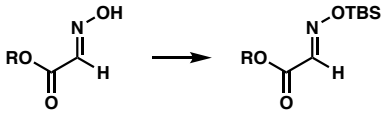
sat. $NaHCO_3$ (60 mL), sat. NH_4Cl (10 mL), pH 7 buffer (10 mL), and brine (20 mL). The organic layer was then dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (20 → 30% EtOAc/Hexanes) to yield 1.053 g (33% yield) of product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (s, 1H), 7.55 (s, 1H), 4.47 (t, J = 7.2 Hz, 2H), 3.02 (t, J = 7.2 Hz, 2H).

benzyl 2-(hydroxyimino)acetate



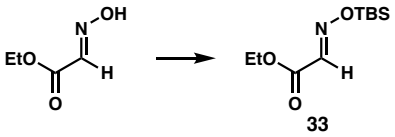
A flask was charged with stir bar and the following reagents: glyoxylic acid monohydrate (1.00 g, 10.9 mmol), hydroxylamine hydrochloride (0.764 g, 11.0 mmol), benzyl alcohol (3.39, 32.7 mmol), *p*-TsOH•H_2O (0.156 g, 0.818 mmol). Toluene (33 mL) was added and a reflux condenser attached. The reaction was heated to 80 ˚C and stirred 15 min, then heated to 100 ˚C and stirred 1 h. Finally, the reaction was heated to 120 ˚C and stirred overnight. The reaction was then cooled to room temperature, diluted with 33 mL EtOAc, and added to a separatory funnel. The organic layer was washed with sat. $NaHCO_3$ (40 mL), sat. NH_4Cl (7 mL), pH 7 buffer (7 mL), and brine (15 mL). The organic layer was then dried over Na_2SO_4 and concentrated in vacuo. BnOH was removed by vacuum distillation (265 mTorr, 68-70 ˚C). The product was subsequently purified by column chromatography (20 → 40% EtOAc/Hexanes). BnOH was still present so it was removed by a second vacuum distillation to furnish the product (0.443 g, 23% yield) with approximately 2% BnOH. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.86 (br s, 1H), 7.59 (s, 1H), 7.47 – 7.30 (m, 5H), 5.29 (s, 2H).

General Procedure for Silylation of Oxime Esters



A flask was charged with a stir bar, the unprotected oxime (5.45 mmol, 1.0 equiv), TBSCl (8.18 mmol, 1.5 equiv), imidazole (16.9 mmol, 3.1 equiv), and DMF (10 mL) and stirred 48-72 h under a nitrogen atmosphere. The mixture was poured into 6:1 deionized water:brine (45 mL) and extracted with Et_2O (30 mL). The organic layer was washed with brine (6 mL) and dried over Na_2SO_4, then filtered and concentrated in vacuo. The crude product was purified via column chromatography (5% Et_2O/Hexanes).

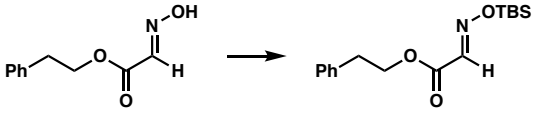
ethyl 2-(((*tert*-butyldimethylsilyl)oxy)imino)acetate (33)



33

Prepared from ethyl 2-(hydroxyimino)acetate (25.2 g, 215 mmol) following the General Procedure for Silylation of Oxime Esters. The crude product was purified via column chromatography (3.5 → 4.5% Et_2O/Hexanes) to yield **33** as a clear oil (28.787 g, 58% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (s, 1H), 4.30 (q, J = 7.1 Hz, 2H), 1.33 (t, J = 7.1 Hz, 3H), 0.94 (s, 9H), 0.23 (s, 6H).

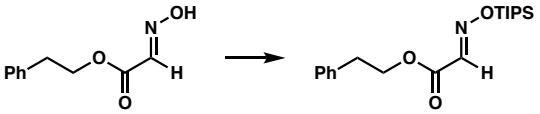
phenethyl 2-(((*tert*-butyldimethylsilyl)oxy)imino)acetate (35)



35

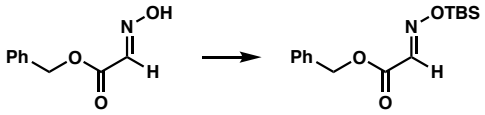
Prepared from phenethyl 2-(hydroxyimino)acetate (1.053 g, 5.45 mmol) following the General Procedure for Silylation of Oxime Esters. The crude product was purified via column chromatography (5% Et_2O/Hexanes) to yield **35** as a clear oil (1.032 g, 62% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.35 – 7.20 (m, 5H), 4.44 (t, *J* = 6.9 Hz, 2H), 3.01 (t, *J* = 6.9 Hz, 2H), 0.96 (s, 9H), 0.25 (s, 6H).

phenethyl 2-(((triisopropylsilyl)oxy)imino)acetate



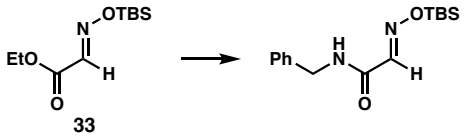
Prepared from phenethyl 2-(hydroxyimino)acetate (1.40 g, 7.2 mmol) and TIPSCl (2.31 mL, 10.8 mmol) following the General Procedure for Silylation of Oxime Esters. The crude product was purified via column chromatography to yield the product (1.647 g, 65% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.32 – 7.21 (m, 5H), 4.44 (t, *J* = 6.8 Hz, 2H), 3.01 (t, *J* = 6.8 Hz, 2H), 1.33 – 1.22 (m, 3H), 1.10 (d, *J* = 7.4 Hz, 18H).

benzyl 2-(((*tert*-butyldimethylsilyl)oxy)imino)acetate



Prepared from benzyl 2-(hydroxyimino)acetate (0.440 g, 2.46 mmol) following the General Procedure for Silylation of Oxime Esters. The crude product was purified via column chromatography (5% Et_2O/Hexanes) to yield the product (0.504 g, 70% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.42 – 7.32 (m, 5H), 5.28 (s, 2H), 0.94 (s, 9H), 0.23 (s, 6H).

_N_-benzyl-2-(((*tert*-butyldimethylsilyl)oxy)imino)acetamide



Oxime **33** (0.440 g, 1.90 mmol) was dissolved in $BnNH_2$ (4.0 mL, 36.6 mmol) in a microwave vial with a stir bar. The mixture was irradiated for 15 min at 100 ˚C. It was then tested for product via TLC (20% EtOAc/Hexanes). Since some starting material remained, the mixture was irradiated 5 min more at 100 ˚C. The reaction mixture was then dissolved in 4 mL CH_2Cl_2 and washed with 1 M HCl (3 x 12 mL). The organic layer was concentrated in vacuo. The crude product was purified by column chromatography (10 → 15 → 20 % EtOAc/Hexanes) to give 0.211 g (38% yield) of the desired amide product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.41 – 7.27 (m, 5H), 6.78 (br s, 1H), 4.55 (d, J = 6.1 Hz, 3H), 0.93 (s, 9H), 0.20 (s, 6H).

2.4.3. Ligand Synthesis

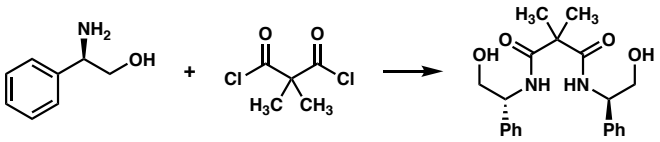
2,2-dimethylmalonyl chloride

2,2-dimethylmalonic acid (4.00 g, 30.3 mmol) and DMF (0.304 mL, 3.94 mmol) were dissolved in CH_2Cl_2 (30 mL) and the solution cooled to 0 ˚C. Oxalyl chloride (7.80 mL, 90.9 mmol) was added to the solution dropwise over 1 hour. The mixture was then warmed to room temperature, stirred 18 h, and concentrated in vacuo. The crude product was purified by distillation (77 ˚C, 60 Torr) to give 3.90 g (76% yield) of 2,2-dimethylmalonyl chloride as a yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.68 (s, 6H).

(*R*)-(–)- 2-phenylglycinol [(*R*)-2-amino-2-phenylethanol]

To a flame-dried flask were added R-phenylglycine (4.00 g, 26.4 mmol), $NaBH_4$ (2.50 g, 66 mmol), and THF (110 mL). In a separate flame-dried flask, I_2 (8.05 g, 31.7 mmol) was dissolved in THF (40 mL). The phenylglycine solution was cooled to 0 ˚C and the I_2 solution added slowly via cannula over 1 h, trying to maintain a white slurry. The reaction mixture was then heated to reflux (66 ˚C) under N_2 for 66 h. The mixture was then cooled to room temperature and MeOH was added until the solution became clear. The solvent was removed via rotary evaporation, leaving a thick white oil. To this oil was added 20% aq KOH (75 mL), and the resulting solution was stirred 4 h at room temperature. The solution was extracted with CH_2Cl_2 (4 x 75 mL) and the organic layers dried over Na_2SO_4 and concentrated in vacuo to give R-phenylglycinol as a white solid (3.00 g, 83% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.27 (m, 5H), 4.05 (dd, *J* = 8.3, 4.4 Hz, 1H), 3.75 (dd, *J* = 10.7, 4.4 Hz, 1H), 3.55 (dd, *J* = 10.7, 8.3 Hz, 1H), 2.08 (br s, 3H).

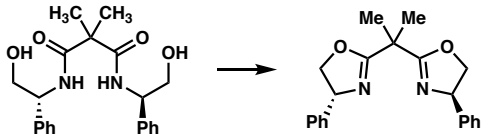
N^1,N^3-bis((*R*)-2-hydroxy-1-phenylethyl)-2,2-dimethylmalonamide



To a flame-dried flask were added phenylglycinol (2.508 g, 18.3 mmol) and CH_2Cl_2 (73.2 mL). The solution was cooled to 0 ˚C and freshly distilled Et_3N (5.8 mL, 41.6 mmol) was added dropwise, followed by dimethylmalonyl chloride (1.10 mL, 8.32

mmol) dropwise. The reaction was allowed to warm to room temperature and stirred 3 h under a nitrogen atmosphere. The reaction was then quenched with 1 M HCl to pH 0. (If precipitate is present, filter with several portions of water and concentrate in vacuo.) No precipitate was present, so the solution was extracted with CH_2Cl_2 and the organic layers concentrated in vacuo to give 2.866 g (93% yield) of product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.19 (m, 10H), 7.10 (d, *J* = 7.6 Hz, 2H), 5.12 (td, *J* = 7.0, 3.9 Hz, 2H), 3.94 (dd, *J* = 11.5, 4.0 Hz, 2H), 3.81 (dd, *J* = 11.4, 6.6 Hz, 2H), 1.53 (s, 6H), 1.41 (t, *J* = 7.3 Hz, 2H).

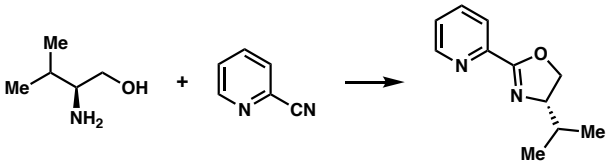
(4*R*,4'*R*)-2,2'-(propane-2,2-diyl)bis(4-phenyl-4,5-dihydrooxazole) (PhBOX, L19)



PhBox (**L19**)

To a flame-dried flask were added amide (2.428 g, 6.55 mmol), DMAP (0.120 g, 0.98 mmol), and CH_2Cl_2 (65 mL). The flask was placed in a water bath and freshly distilled Et_3N (4.01 mL, 28.8 mmol) added dropwise. TsCl (2.745 g, 14.4 mmol) was added in one portion and the reaction stirred at room temperature under a nitrogen atmosphere for 36 h. The reaction was quenched with NH_4Cl and water. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 x 50 mL). The organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography (15% acetone/hexanes) to give **L19** (1.113 g, 51% yield) as a viscous, pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.21 (m, 10H), 5.24 (dd, *J* = 10.1, 7.6 Hz, 2H), 4.68 (dd, *J* = 10.1, 8.3 Hz, 2H), 4.17 (dd, *J* = 8.3, 7.6 Hz, 2H), 1.69 (s, 6H).

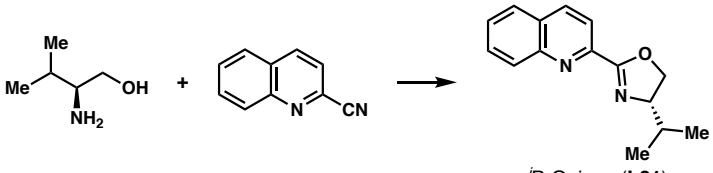
(*S*)-4-isopropyl-2-(pyridin-2-yl)-4,5-dihydrooxazole (^{i}PrPyOx, L20)



^{i}PrPyOx (**L20**)

According to the procedure of Hassine and coworkers,[30] 2-cyano-pyridine (0.050 g, 0.48 mmol) and L-valinol (0.06 mL, 0.53 mmol) were mixed and sealed in a microwave vial. The vial was irradiated at 150 ˚C for 90 min, then allowed to come to room temperature. The reaction was quenched with EtOAc, then filtered through silica, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by column chromatography (2% MeOH/CH_2Cl_2) to give **L20** (25 mg, 27% yield). ^{1}H NMR (500 MHz, $CDCL_3$) δ 8.70 (ddt, *J* = 4.8, 1.7, 0.8 Hz, 1H), 8.06 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.80 – 7.73 (m, 1H), 7.42 – 7.35 (m, 1H), 4.55 – 4.48 (m, 1H), 4.27 – 4.13 (m, 2H), 1.97 – 1.83 (m, *J* = 6.7 Hz, 1H), 1.06 (d, *J* = 6.7 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H).

(*S*)-4-isopropyl-2-(quinolin-2-yl)-4,5-dihydrooxazole (^{i}PrQuinox, L21)

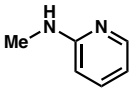


^{i}PrQuinox (**L21**)

According to the procedure of Hassine and coworkers,[30] L-valinol (0.04 mL, 0.35 mmol) and 2-quinolinecarbonitrile (50 mg, 0.32 mmol) were mixed and sealed in a microwave vial. The vial was irradiated at 150 ˚C for 60 min, then allowed to come to room temperature. The reaction was quenched with EtOAc, then filtered through silica, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by column

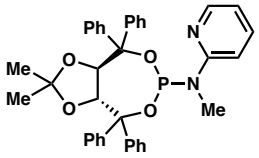
chromatography (35% EtOAc/Hexanes) to give **L21** (17.1 mg, 22% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 – 8.24 (m, 1H), 8.23 (s, 2H), 7.85 (ddd, *J* = 8.2, 1.6, 0.7 Hz, 1H), 7.75 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H), 7.60 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 4.66 – 4.54 (m, 1H), 4.35 – 4.17 (m, 2H), 2.01 – 1.87 (m, 1H), 1.08 (d, *J* = 6.7 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H).

_N_-methylpyridin-2-amine



According to the procedure of Singh and coworkers,[31] in a flame-dried flask, 2-aminopyridine (1.000 g, 10.6 mmol) was dissolved in dry THF (8.50 mL). The solution was cooled to 0 ˚C and ^{n}BuLi (4.24 mL, 10.6 mmol) was added dropwise. The reaction was allowed to come to room temperature and stirred 30 min. CH_3I (0.66 mL, 10.6 mmol) was added dropwise with cooling in an ice bath to prevent refluxing. The reaction was stirred 1 h at room temperature, then poured into 3 mL water. NH_4Cl (0.567 g, 10.6 mmol) was added and the organic layer separated. The aqueous layer was extracted with $CHCl_3$ (4 x 10 mL) and 10% ^{i}PrOH in $CHCl_3$ (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (5%/1%/94% → 25%/2%/73% EtOAC/Et_3N/Hexanes) to give the product as a yellow oil (0.346 g, 30% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (ddd, *J* = 5.0, 1.9, 0.9 Hz, 1H), 7.43 (ddd, *J* = 8.5, 7.1, 1.9 Hz, 1H), 6.57 (ddd, *J* = 7.1, 5.0, 0.9 Hz, 1H), 6.38 (dt, *J* = 8.3, 1.0 Hz, 1H), 4.55 (br s, 1H), 2.92 (d, *J* = 4.9 Hz, 3H).

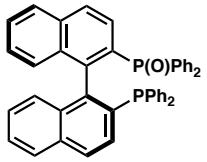
_N_-((3a_R_,8a_R_)-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-_e_][1,3,2]dioxaphosphepin-6-yl)-_N_-methylpyridin-2-amine (L38)



(_R_,_R_)-TADDOL-P-N(Me)(2-py) (L38)

According to the procedure of Kitamura and coworkers,[32] PCl_3 (0.08 mL, 0.925 mmol) was dissolved in THF (2.8 mL). To this solution was added *N*-methylpyridin-2-amine (0.100 g, 0.925 mmol) and the reaction was stirred 1.5 h at room temp. In a separate flask, Et_3N (0.41 mL, 2.94 mmol) and (-)-TADDOL (0.392 g, 0.841 mmol) were dissolved in THF (5.6 mL). The PCl_3 solution was cooled to 0 ˚C and the TADDOL solution added. The reaction was allowed to warm to room temperature and stirred 24 h. The solution was then filtered through Celite and washed with THF (15 mL), then concentrated in vacuo. The crude product was purified via column chromatography (5% EtOAc/Hex). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 – 8.19 (m, 1H), 7.86 – 7.77 (m, 2H), 7.59 (dd, *J* = 8.1, 1.5 Hz, 2H), 7.49 – 7.18 (m, 17H), 6.87 – 6.82 (m, 1H), 6.75 (ddd, *J* = 7.2, 5.0, 0.9 Hz, 1H), 5.31 (dd, *J* = 8.5, 3.0 Hz, 1H), 4.89 (d, *J* = 8.5 Hz, 1H), 3.38 (d, *J* = 2.6 Hz, 3H), 1.35 (s, 3H), 0.33 – 0.27 (s, 3H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 135.68.

(_S_)-(2'-(diphenylphosphaneyl)-[1,1'-binaphthalen]-2-yl)diphenylphosphine oxide ((_S_)-BINAP(O); L39)

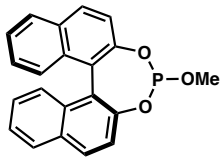


(S)-BINAP(O) was synthesized according to the procedure of Grushin.[33] (*S*)-BINAP (0.250 g, 0.40 mmol) and PdI_2 (0.0032 g, 0.009 mmol) were dissolved in CH_2Cl_2 (2.5 mL) in a flame-dried flask under nitrogen atmosphere. The solution was stirred 3 h at room temperature. NaOH (0.226 g, 5.64 mmol) was dissolved in water (1.5 mL) and added to the BINAP solution, followed by 1,2-dibromoethane (0.23 mL, 2.65 mmol). The biphasic solution was heated to 50 ˚C for 18 h. The reaction was cooled to room temperature and acidified to pH 3 using 20% aq H_3PO_4. Ethylenebis(diphenylphosphine) (dppe, 10 mg, 0.025 mmol) was added and the solids rinsed with CH_2Cl_2. The reaction was stirred 5 min, then the organic layer was separated, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified via column chromatography (100% CH_2Cl_2 → 10% EtOAc/CH_2Cl_2) to give the product (0.109 g , 43% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 – 7.89 (m, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.77 – 7.54 (m, 6H), 7.45 – 6.58 (m, 24H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 27.15, -15.33.

Dichloro(methoxy)phosphane

According to the procedure of Turhanen and coworkers,[34] PCl_3 (0.31 mL, 3.50 mmol) was dissolved in dry Et_2O (2.9 mL) and cooled to 0 ˚C under a nitrogen atmosphere. Methanol (0.16 mL, 3.85 mmol) was added dropwise with stirring. The reaction was allowed to warm to room temperature and stirred 4 h with monitoring by ^{31}P NMR. The product was used in solution without further purification. ^{31}P NMR (121 MHz, $CDCl_3$) δ 180.80.

(11b*S*)-4-methoxydinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine (BINOL-P-OMe, L41)



According to the procedure of Tanaka and coworkers,[35] (*S*)-BINOL (0.836 g, 2.92 mmol) and DIPEA (1.67 mL, 9.64 mmol) were dissolved in dry CH_2Cl_2 and cooled to 0 ˚C for 15 min. Dichloro(methoxy)phosphane solution was added via cannula and the reaction stirred 1 h at room temperature. The solvent was removed via rotary evaporation and the crude product purified by column chromatography (5% EtOAc/hexanes → 100 % EtOAc). The resulting residue was further purified by column chromatography using Florisil® (5% → 25% EtOAc/hexanes) to obtain the product phosphite (63 mg, 6% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 – 7.84 (m, 5H), 7.57 – 7.29 (m, 7H), 3.55 (d, J = 9.9 Hz, 3H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 139.98.

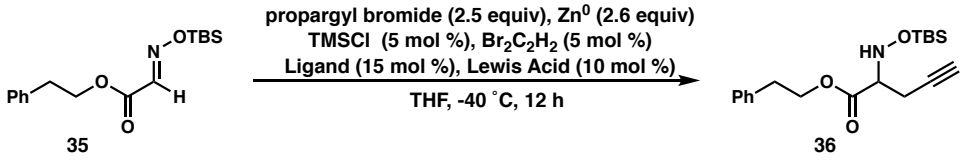
2.4.4. Propargylation Reactions

(±)-ethyl 2-(((*tert*-butyldimethylsilyl)oxy)amino)pent-4-ynoate (34)

Zn^0 (147.1 mg, 2.25 mmol) was added to a round bottom flask and flame dried under vacuum. Dry THF (8 mL) was added, followed by 1,2-dibromoethane (3 μL, 0.04 mmol) and TMSCl (5 μL, 0.04 mmol). The suspension was stirred 5 min and propargyl bromide (80% wt in toluene, 0.24 mL, 2.16 mmol) added. The mixture was heated gently until

reaction was observed, then stirred vigorously at room temperature until zinc was no longer consumed (10 min). In a separate flask, oxime **33** (0.200 g, 0.864 mmol) was dissolved in THF (8 mL). Organozinc solution was added to the solution of **33**, and the reaction stirred 1.5 h in a room temperature water bath. Upon disappearance of starting material, the reaction was quenched with sat. $NaHCO_3$ (4 mL). The salts were filtered off through a pad of Celite, and washed with Et_2O (2 x 12 mL). The organic layers were washed with brine (2 x 8 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified via column chromatography (3.5 → 5% EtOAc/Hexanes) to give **34** (0.121 g, 52% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.24 (q, *J* = 7.1 Hz, 2H), 3.63 (td, *J* = 6.4, 0.6 Hz, 1H), 2.67 – 2.48 (m, 2H), 2.02 (td, *J* = 2.7, 0.6 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H), 0.88 (s, 9H), 0.11 (s, 6H).

General Procedure for Organozinc Propargylation Screens



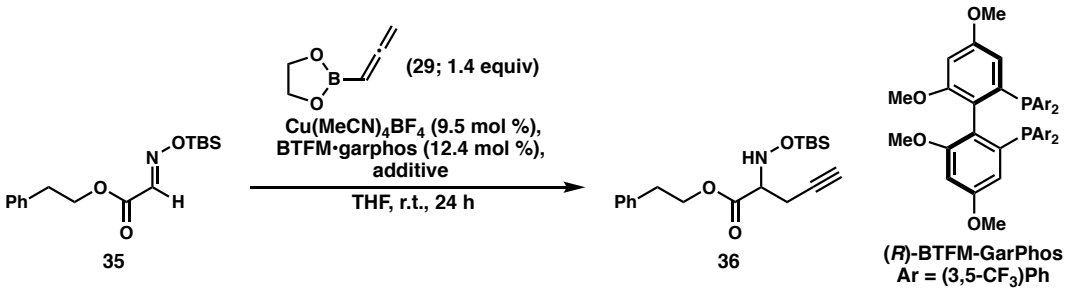
The Lewis acids (0.10 equiv, 5 μmol per reaction) were weighed into vials. The ligand (0.15 equiv, 7.5 μmol per reaction) was dissolved in THF (0.1 mL per reaction). Oxime **35** (1.0 equiv, 0.05 mmol per reaction) was dissolved in THF (0.5 mL per reaction). The ligand and oxime solutions were combined and stirred 20 min at room temperature, then added to the vials with the Lewis acids.

In a separate flask, Zn^0 (2.6 equiv, 0.125 mmol per reaction) was suspended in dry THF (0.5 mL per reaction) and 1,2-dibromoethane (0.05 equiv, 2.5 μmol per reaction) and TMSCl (0.05 equiv, 2.5 μmol per reaction) were added. Propargyl bromide (2.5

equiv, 0.125 mmol per reaction) was added and the solution stirred 30 min at room temperature.

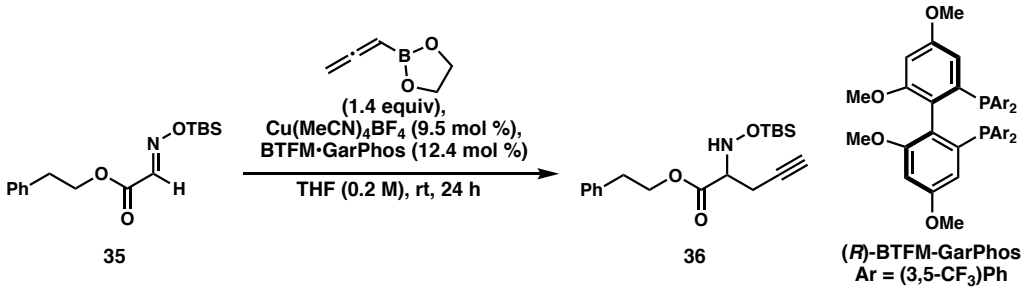
The oxime solutions were cooled to -40 ˚C. The organozinc solution was added and the reactions stirred at -40 ˚C overnight. The reactions were allowed to come to room temperature and quenched with sat. $NaHCO_3$ (0.2 mL per vial). Each reaction was filtered through $MgSO_4$ and Celite and washed with Et_2O (2 x 2 mL), then concentrated in vacuo. ^{1}H NMR and SFC analyses were done on the crude mixtures.

General Procedure for Copper-Catalyzed Asymmetric Addition Reaction Screens



In the glove box, oven-dried vials were charged with stir bars, $[Cu(MeCN)_4]BF_4$ (0.095 equiv, 0.0038 mmol per reaction), and any additives. Oxime **35** (1.0 equiv, 0.040 mmol per reaction) and borolane **29** (1.4 equiv, 0.056 mmol per reaction) were dissolved in THF (0.05 mL per reaction) to make a stock solution. BTFM-GarPhos (**L37**, 0.124 equiv, 0.0050 mmol per reaction) was dissolved in THF (0.15 mL per reaction). The BTFM-Garphos solution was added (0.15 mL to each vial) and the vials stirred 5 min. The oxime/borolane stock was then added (0.05 mL to each vial) and the reactions stirred 24 h at room temperature. The reactions were quenched with 20% EtOAc/Hexanes and filtered through a small silica plug. ^{1}H NMR and SFC analyses were done on the crude mixtures.

Copper-Catalyzed Asymmetric Addition Scale-Up



To an oven-dried 1-dram vial charged with a stir bar were added $[Cu(MeCN)_4]BF_4$ (0.0185 mmol, 0.0058 g) and BTFM-GarPhos (0.0242 mmol, 0.0287 g). Oxime **35** (0.195 mmol, 0.060 g) and borolane **29** (0.273 mmol, 0.040 g) were dissolved in THF (0.25 mL) in a separate vial. THF (0.75 mL) was added to the Cu and GarPhos, and both vials were pre-stirred 5 min at room temperature. The oxime/borolane solution was added to the Cu/GarPhos solution and the reaction stirred 24 h at room temperature. The reaction was quenched with 0.5 M EDTA in pH 8 NH_3/NH_4Cl buffer (1 mL). EtOAc (2 mL) was added and the layers separated. The aqueous layer was extracted with EtOAc (1 mL) and the combined organic layers washed with brine (4 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified via column chromatography (3% → 50 % EtOAc/Hexanes) to give **36** (26.5 mg, 39% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.17 (m, 5H), 5.59 (s, 1H), 4.40 (td, J = 7.1, 1.3 Hz, 2H), 3.63 (t, J = 6.4 Hz, 1H), 2.98 (t, J = 7.0 Hz, 2H), 2.65 – 2.43 (m, 2H), 1.99 (t, J = 2.7 Hz, 1H), 0.89 (s, 10H), 0.10 (d, J = 2.2 Hz, 6H).

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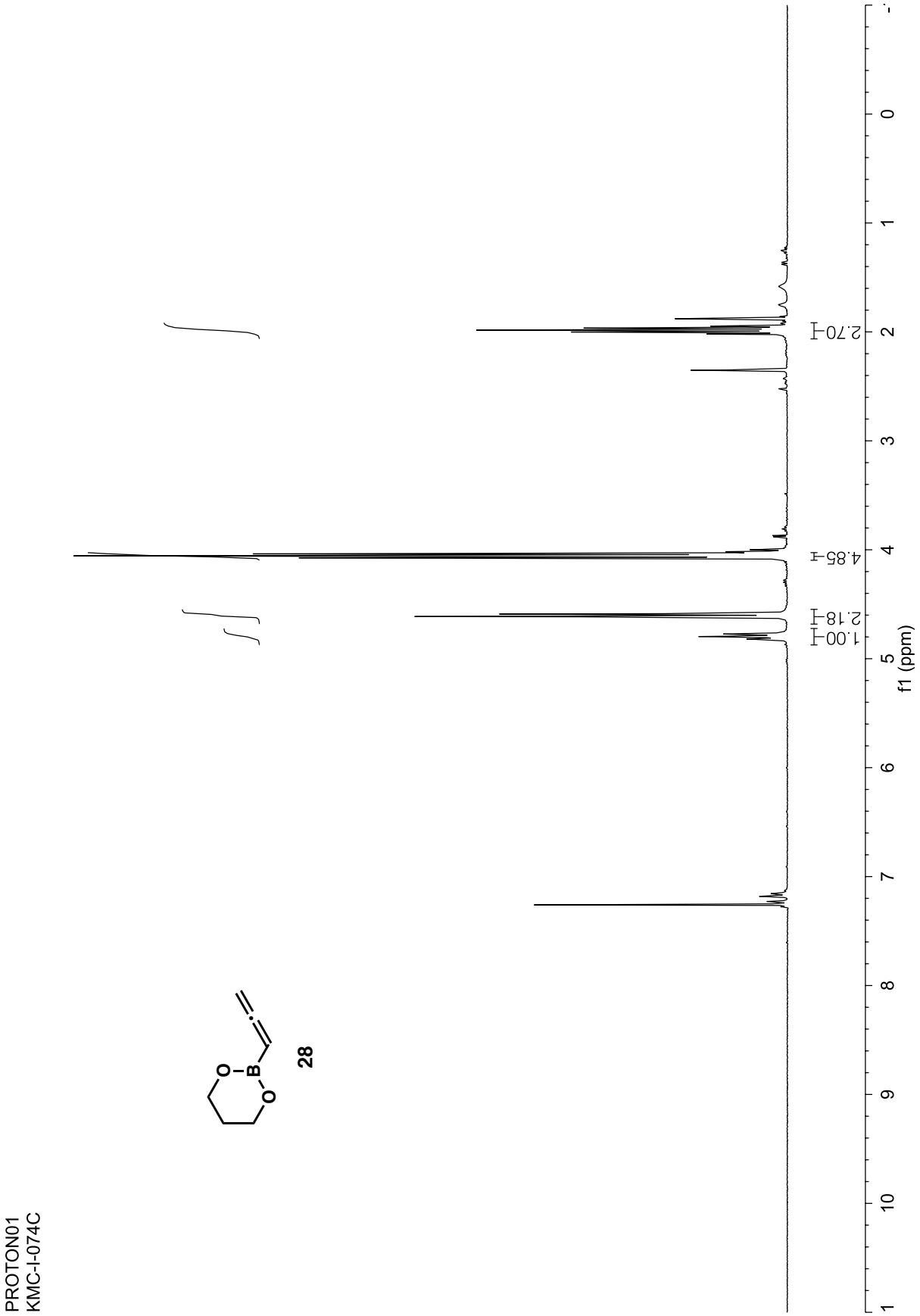
Appendix 1

Spectra Relevant to Chapter 2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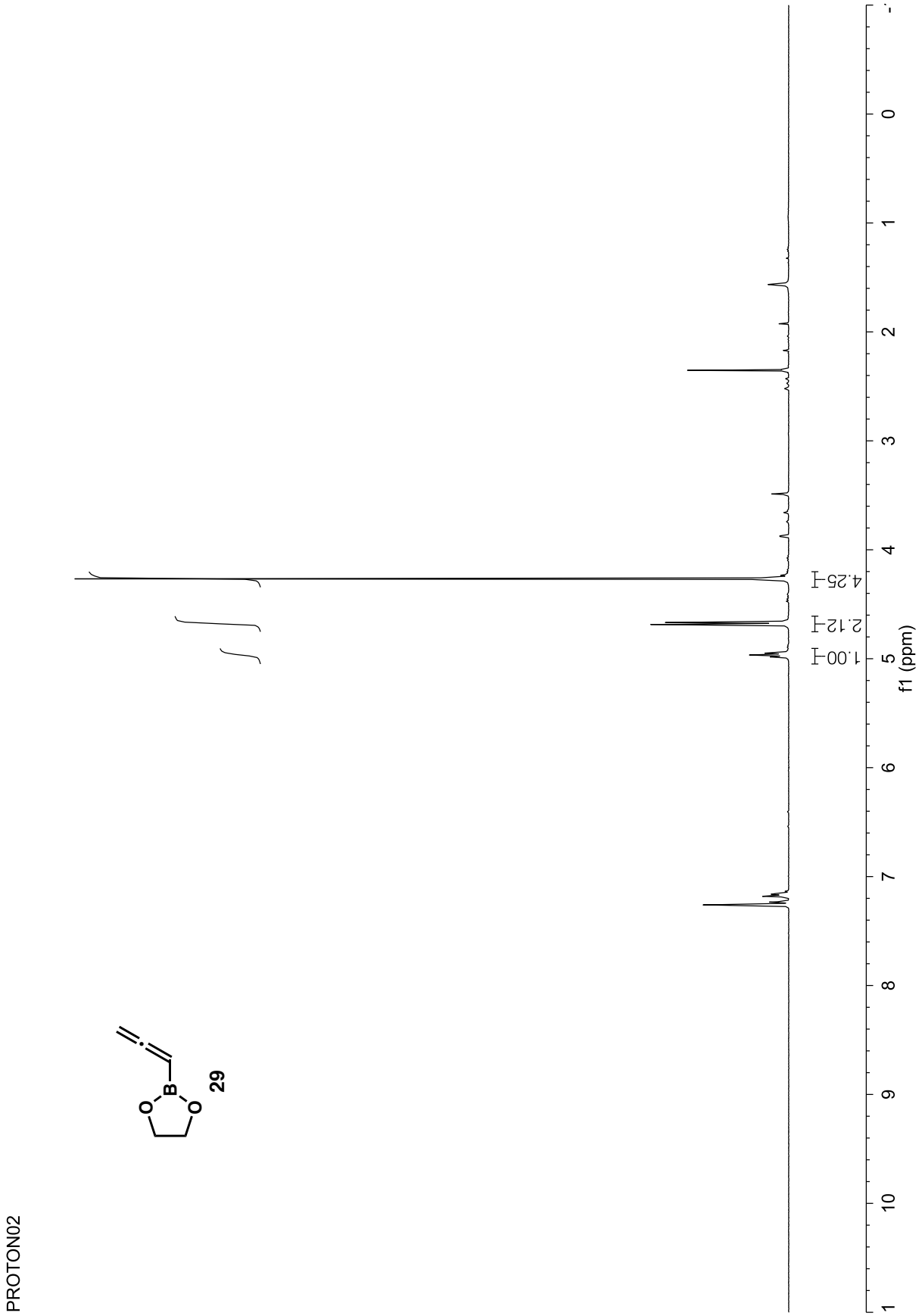
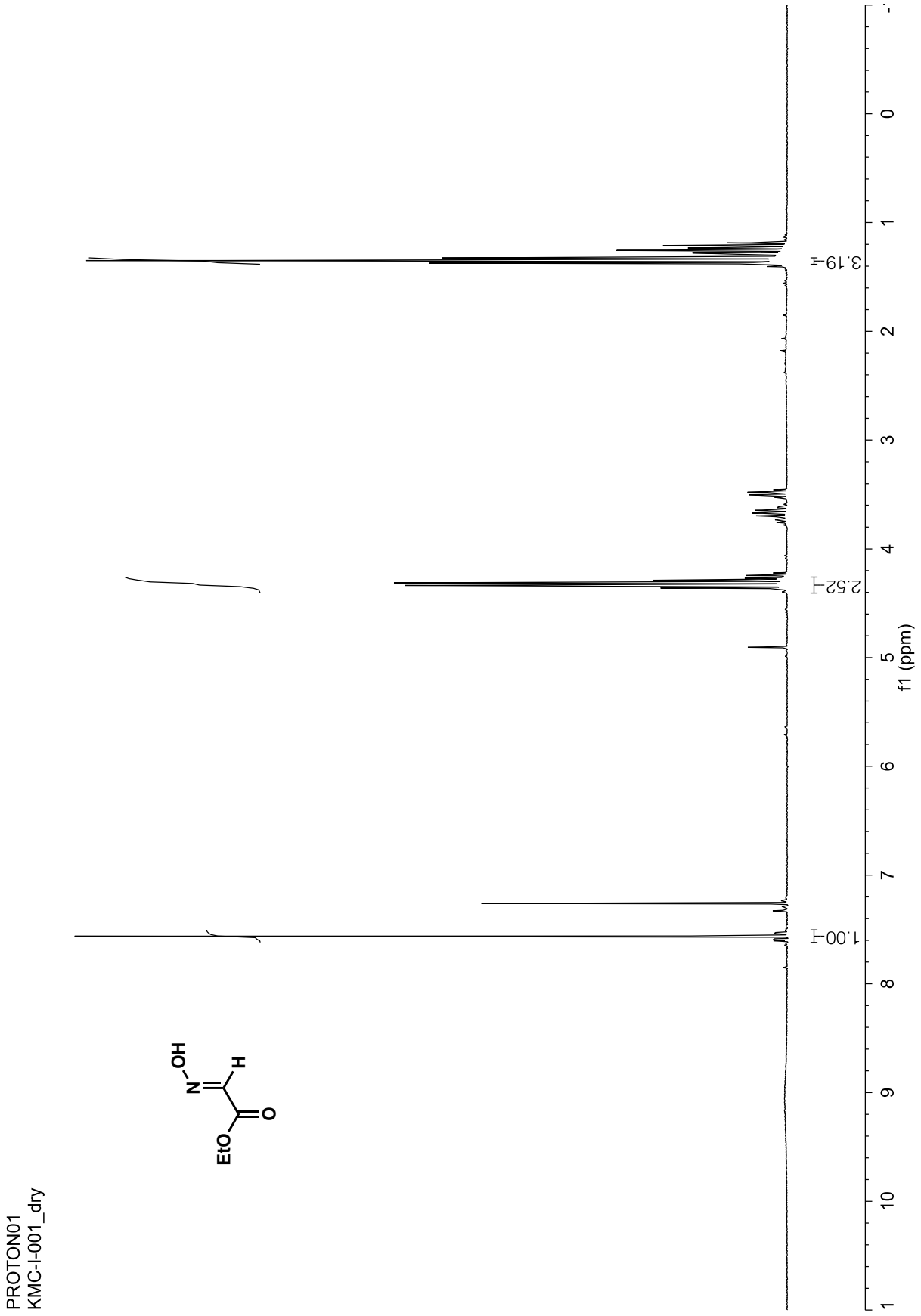
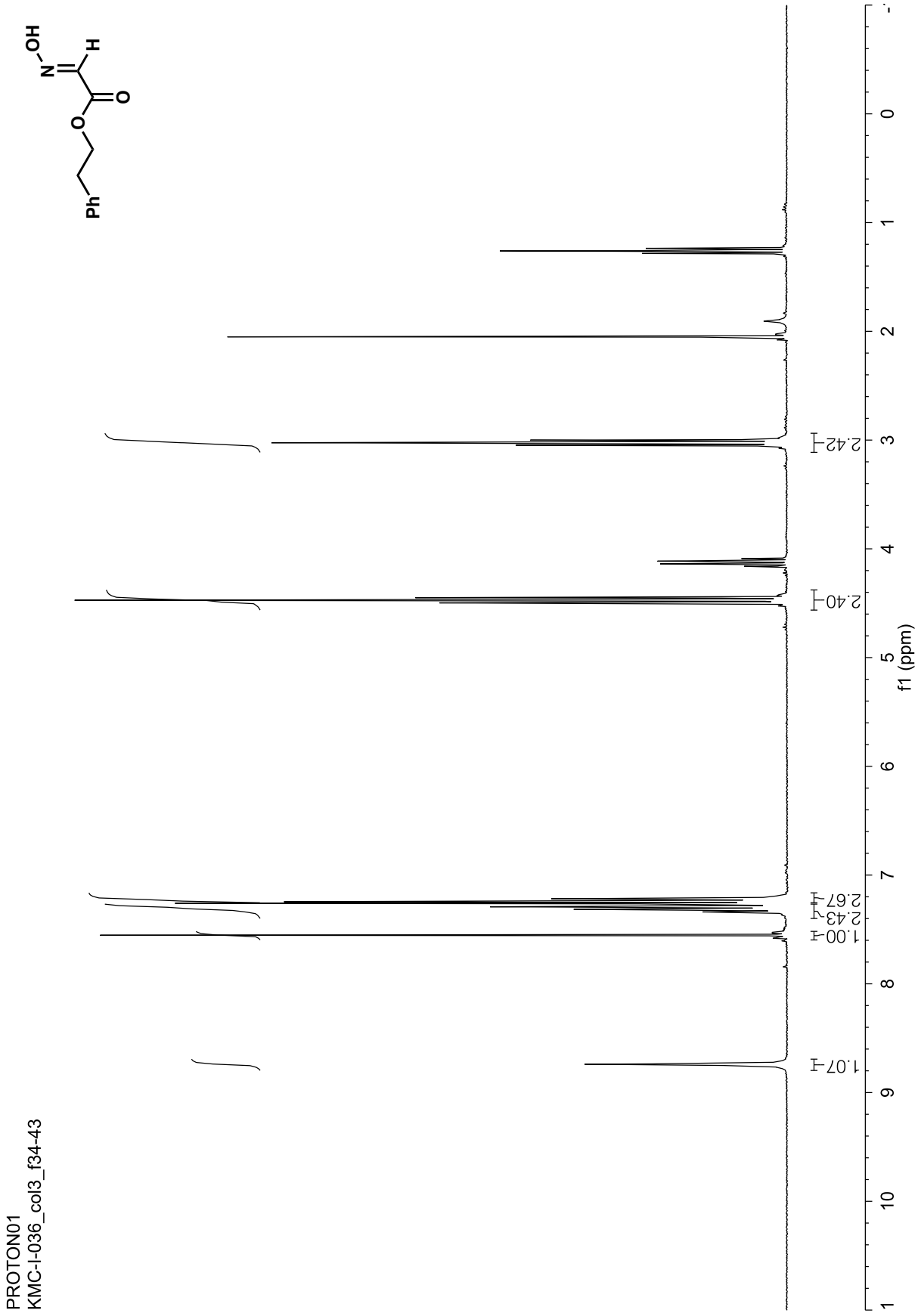
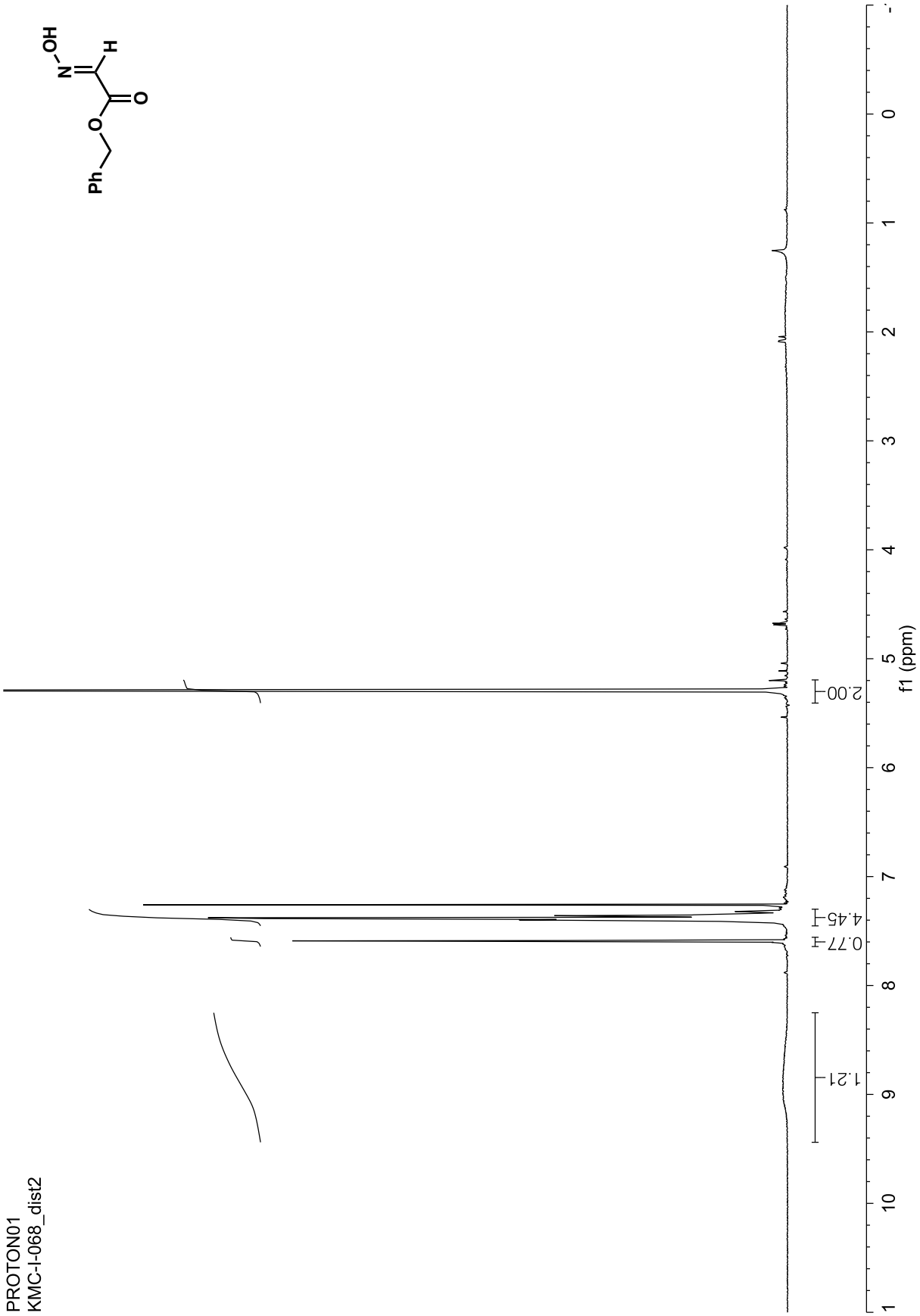
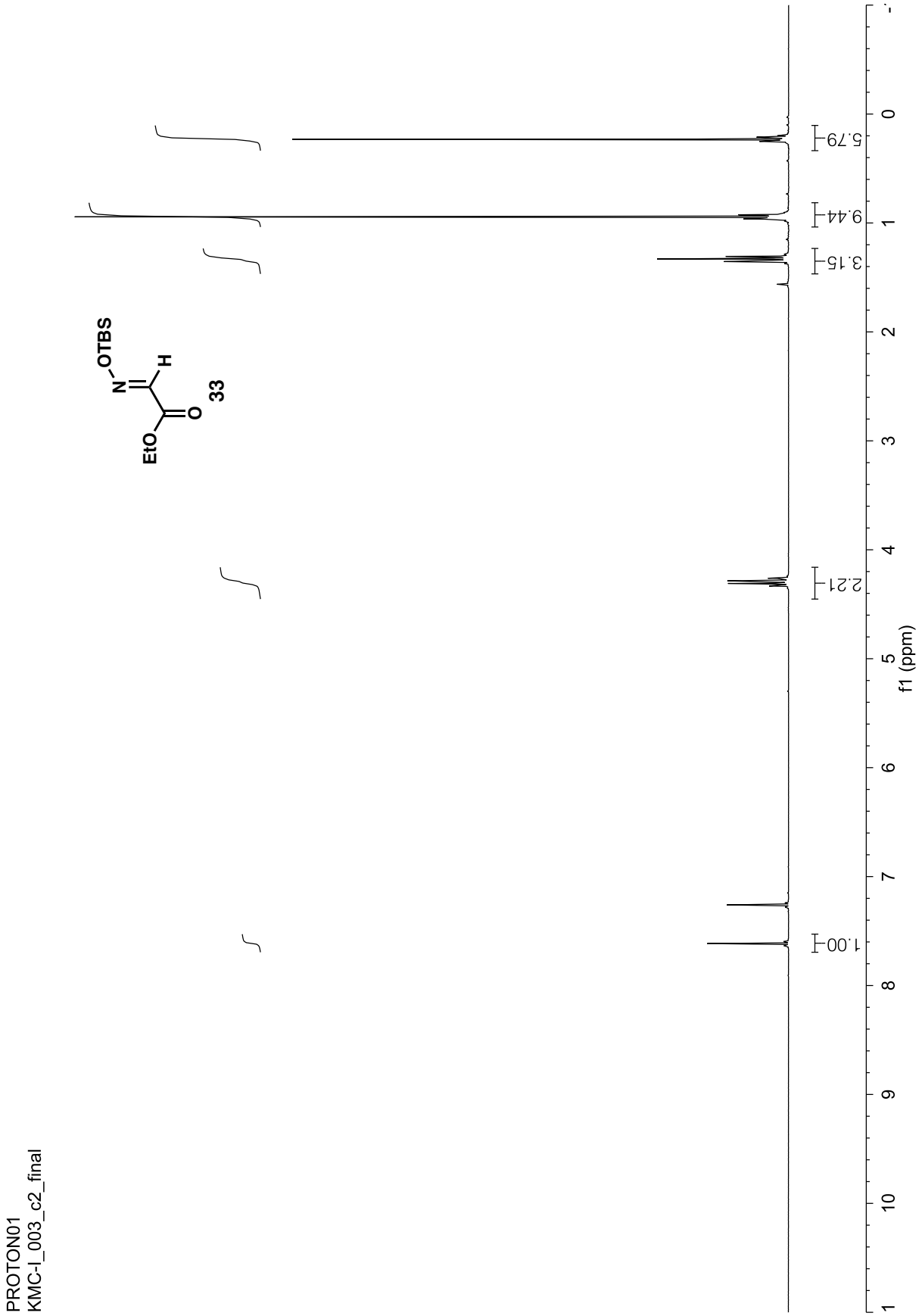
28
2.70
4.85
2.18
1.00
f1 (ppm)

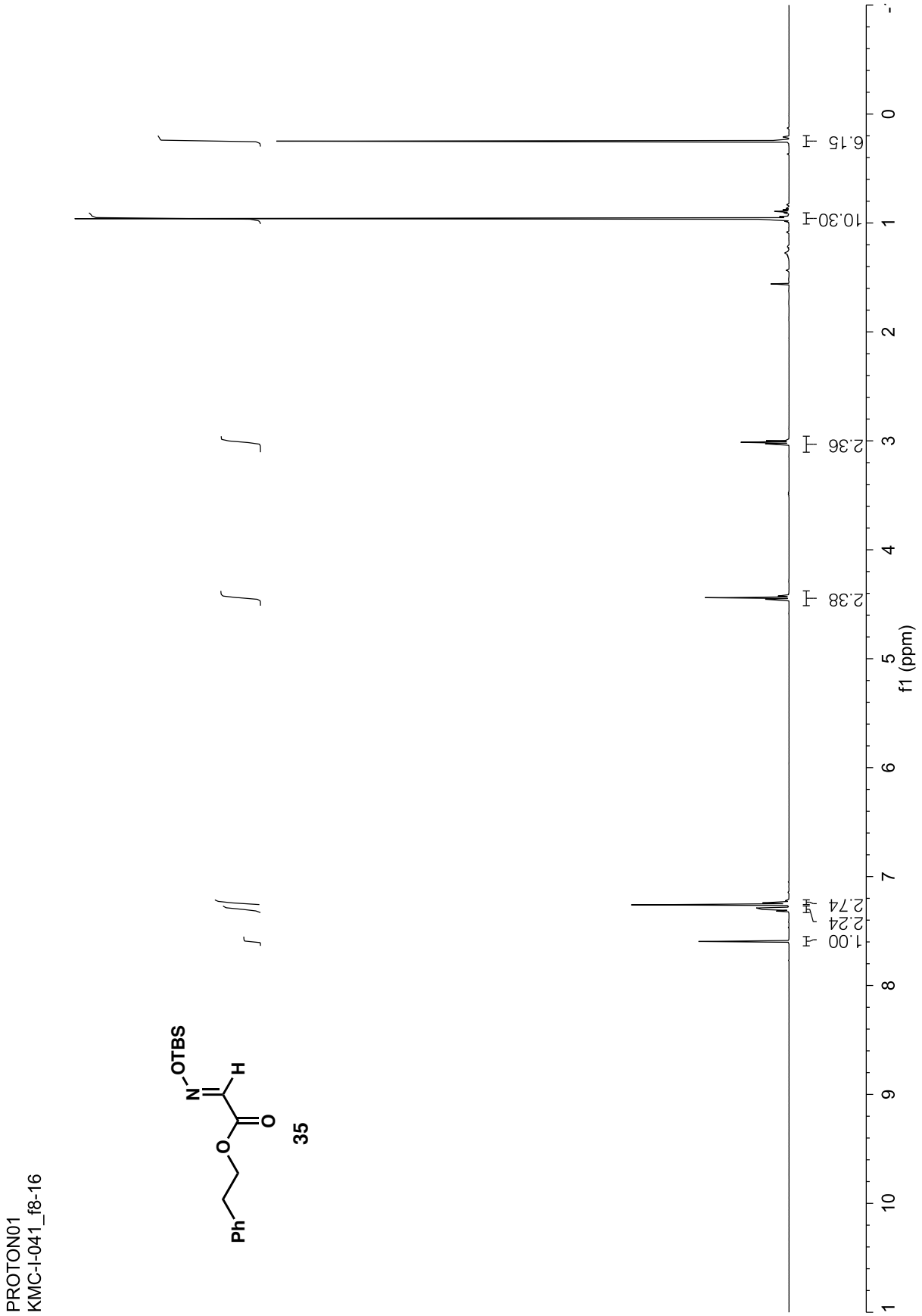

PROTON02
29
4.25
2.12
1.00
f1 (ppm)

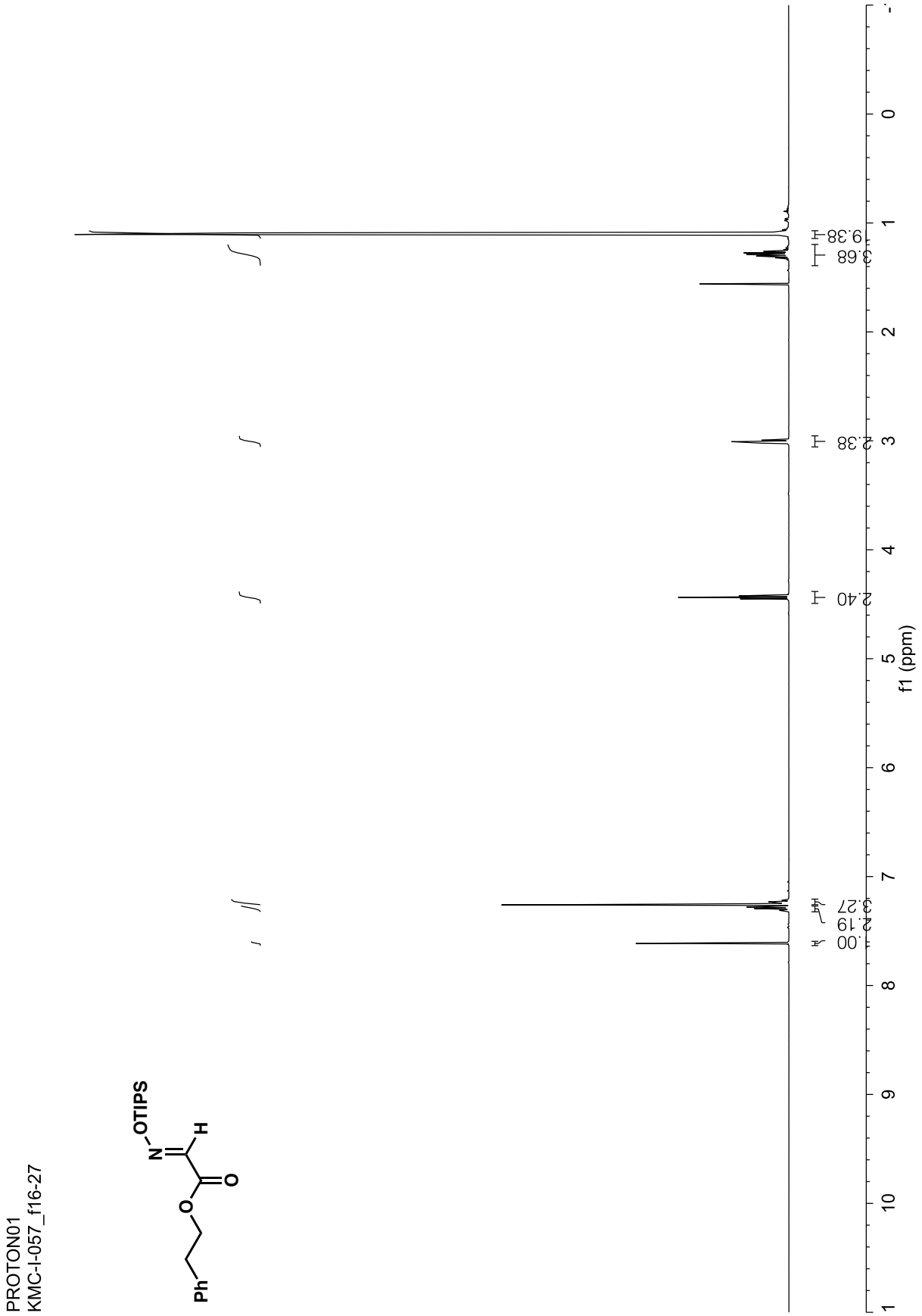

PROTON01
KMC-I-001_dry
OH
N
H
O
EtO
3.19
2.52
1.00
f1 (ppm)

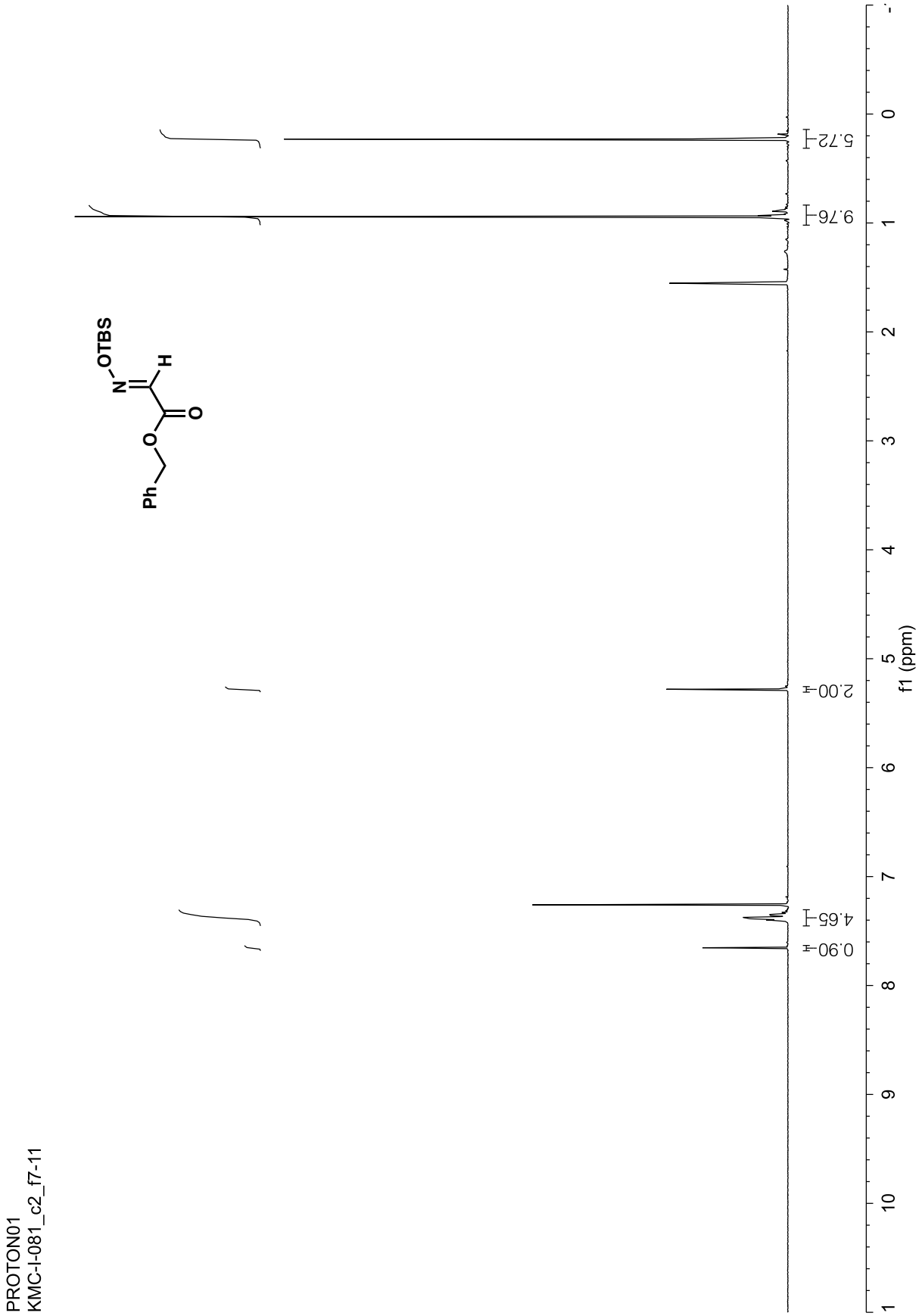

PROTON01
KMC-I-036_col3_f34-43
OH
N
H
O
O
Ph
2.42
2.40
2.67
2.43
1.00
1.07
f1 (ppm)

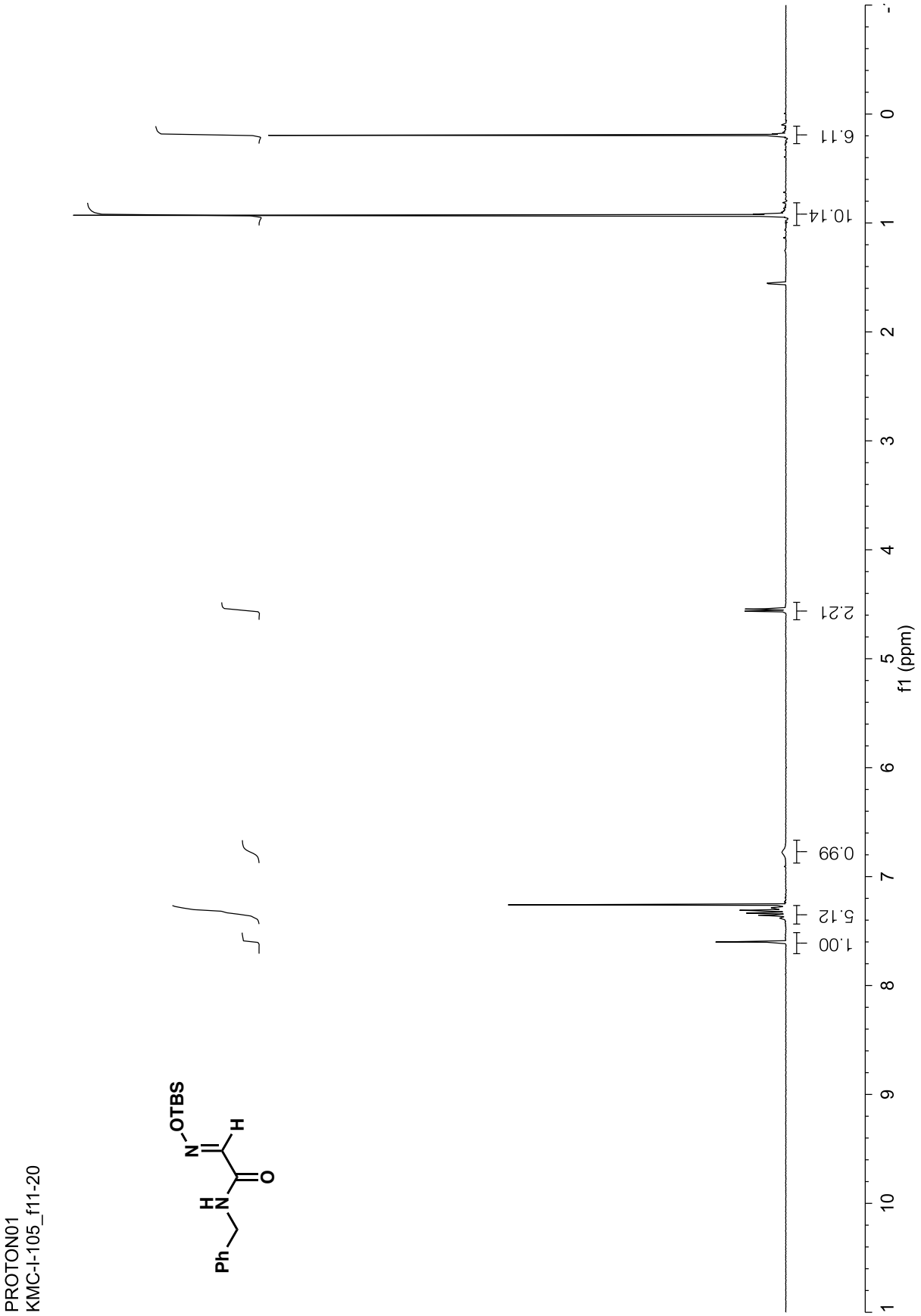

PROTON01
KMC-I-068_dist2
2.00
4.45
0.77
1.21
f1 (ppm)

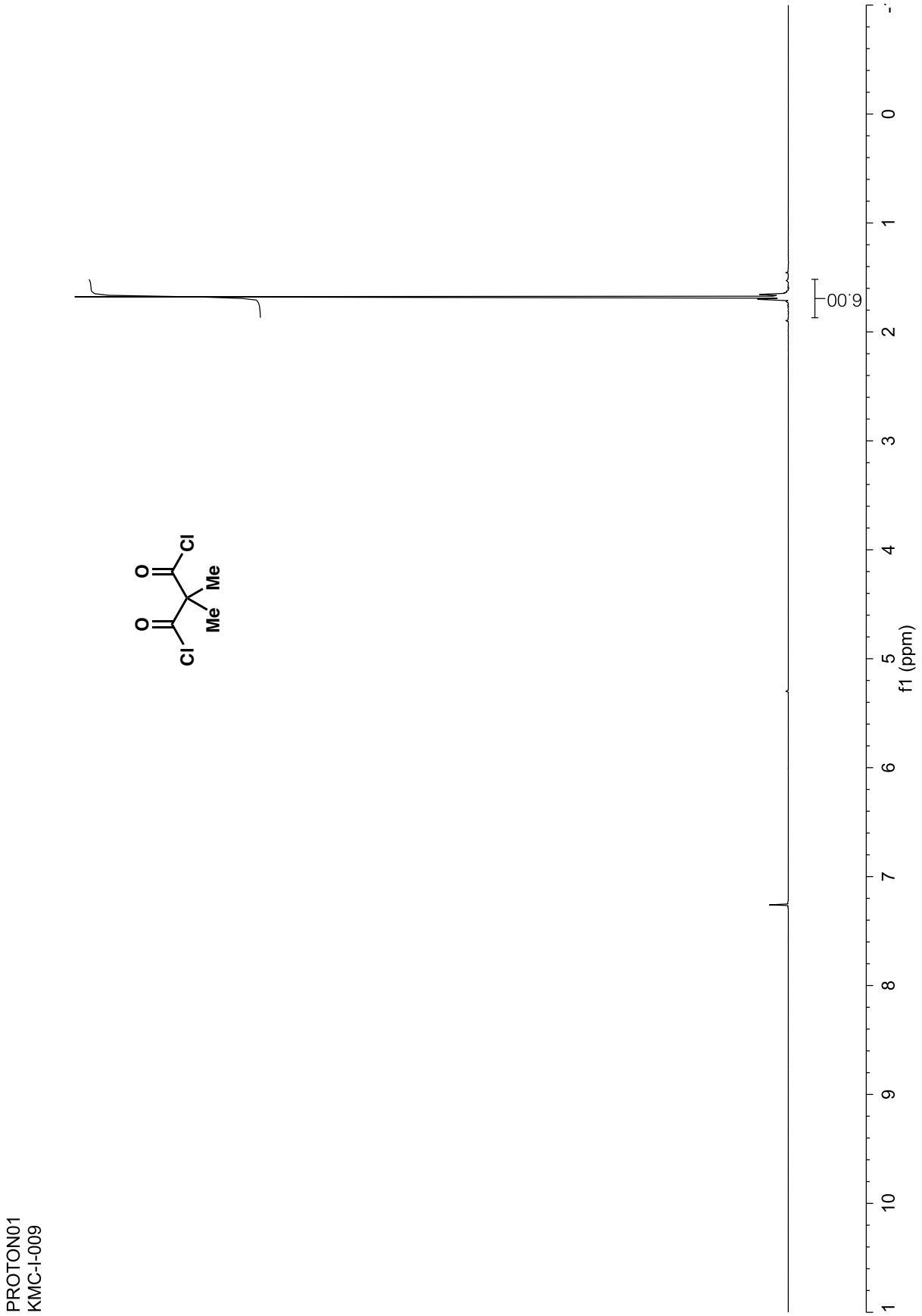

PROTON01
KMC-I_003_c2_final
OTBS
N
H
O
EtO
33
5.79
9.44
3.15
2.21
1.00
f1 (ppm)

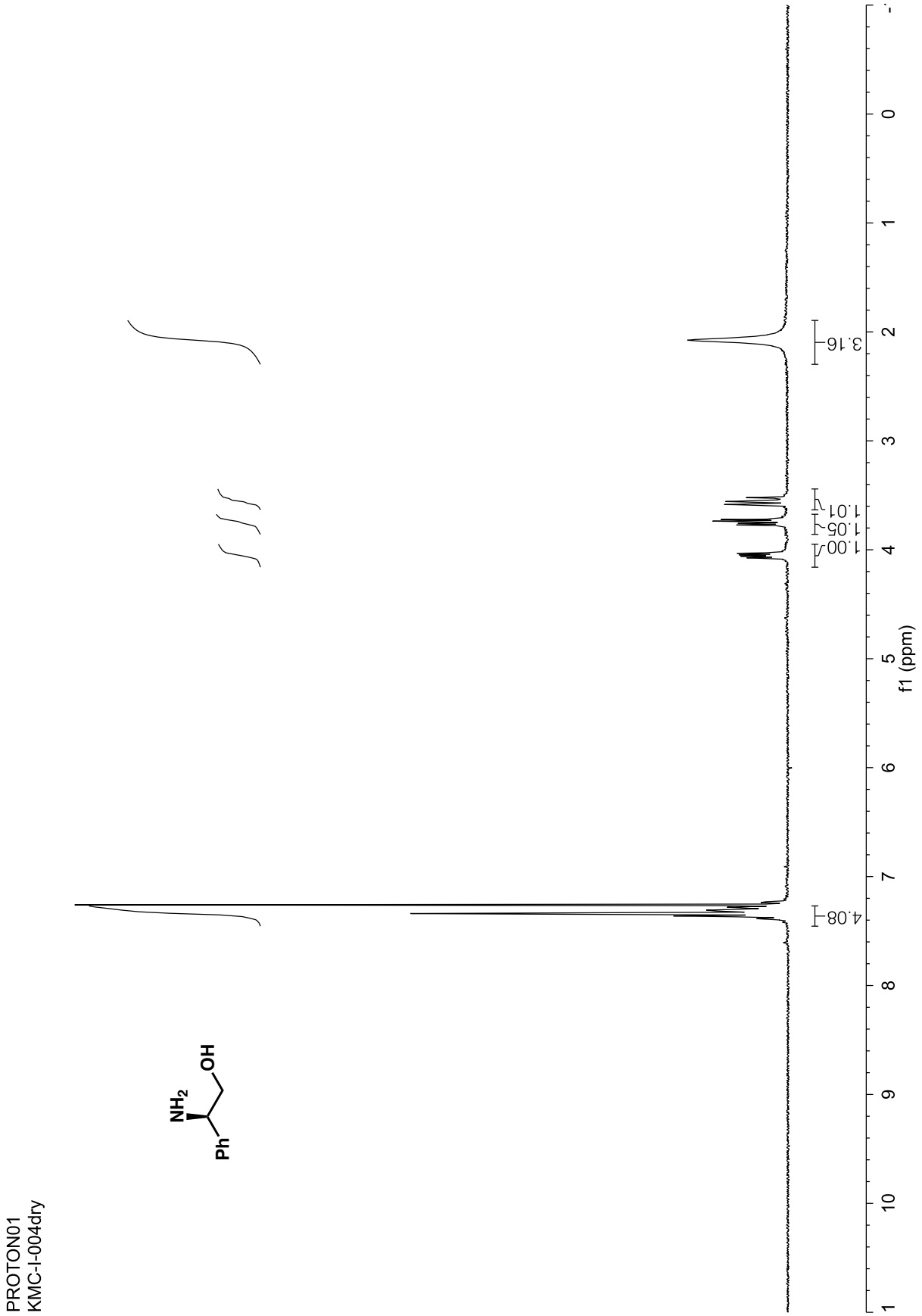

PROTON01
KMC-I-041_f8-16
OTBS
H
N
O
O
Ph
35
6.15
10.30
2.36
2.38
2.74
2.24
1.00
f1 (ppm)

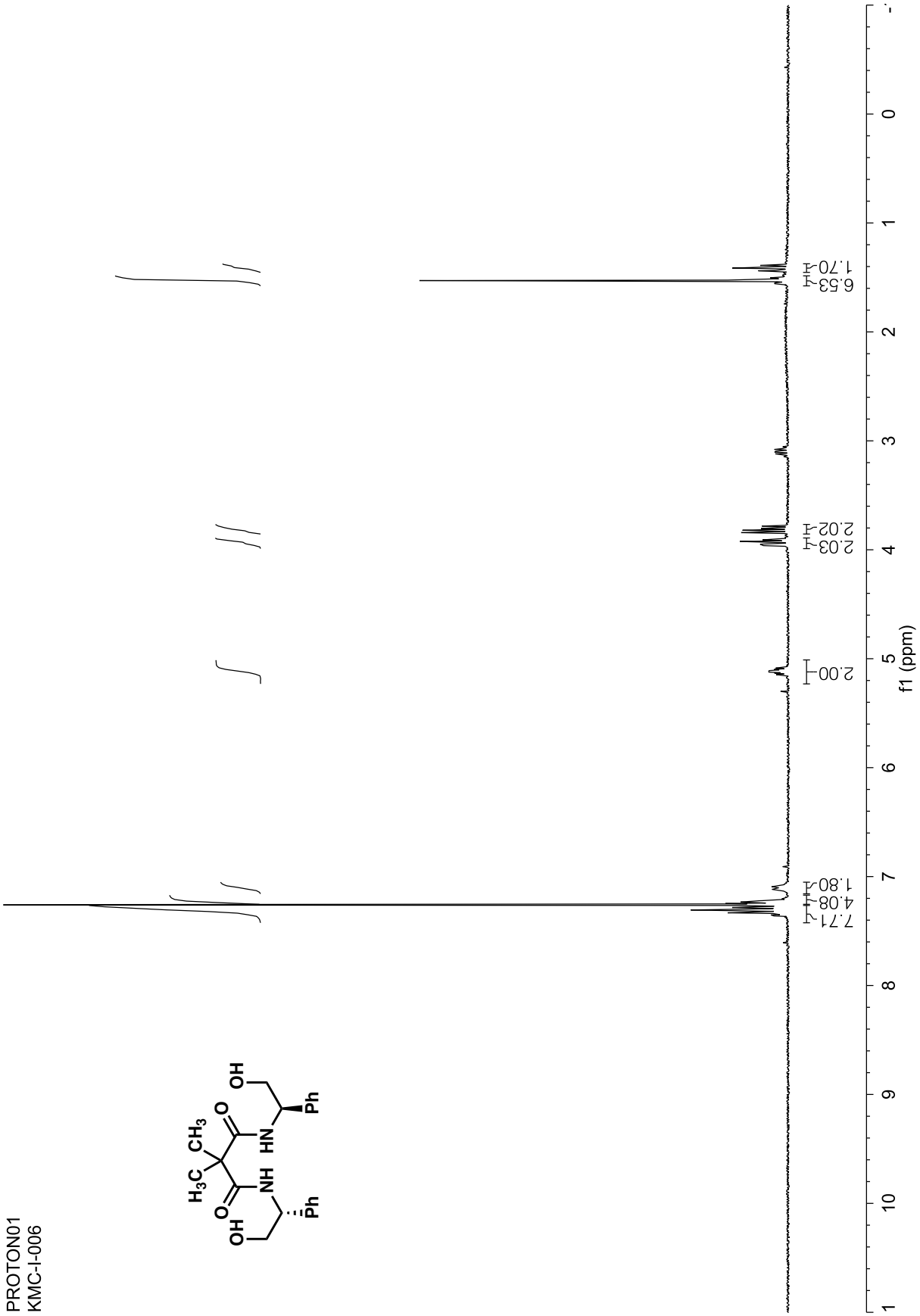

PROTON01
KMC-I-057_f16-27
OTIPS
H
N
O
O
Ph
9.38
3.68
2.38
2.40
2.27
2.19
1.00
f1 (ppm)


PROTON01
KMC-I-081_c2_f7-11
OTBS
H
N
O
O
Ph
5.72
9.76
2.00
4.65
0.90
f1 (ppm)


PROTON01
KMC-I-105_f11-20
OTBS
H
N
O
H
N
Ph
6.11
10.14
2.21
0.99
5.12
1.00
f1 (ppm)


PROTON01
KMC-I-009
6.00
f1 (ppm)
Cl
O
Me
Me
O
Cl


PROTON01
KMC-I-004dry
NH2
OH
Ph
4.08
3.16
1.01
1.05
1.00
f1 (ppm)


PROTON01
KMC-I-006
OH
O
CH3
H3C
HN
Ph
NH
O
OH
Ph
7.71
4.08
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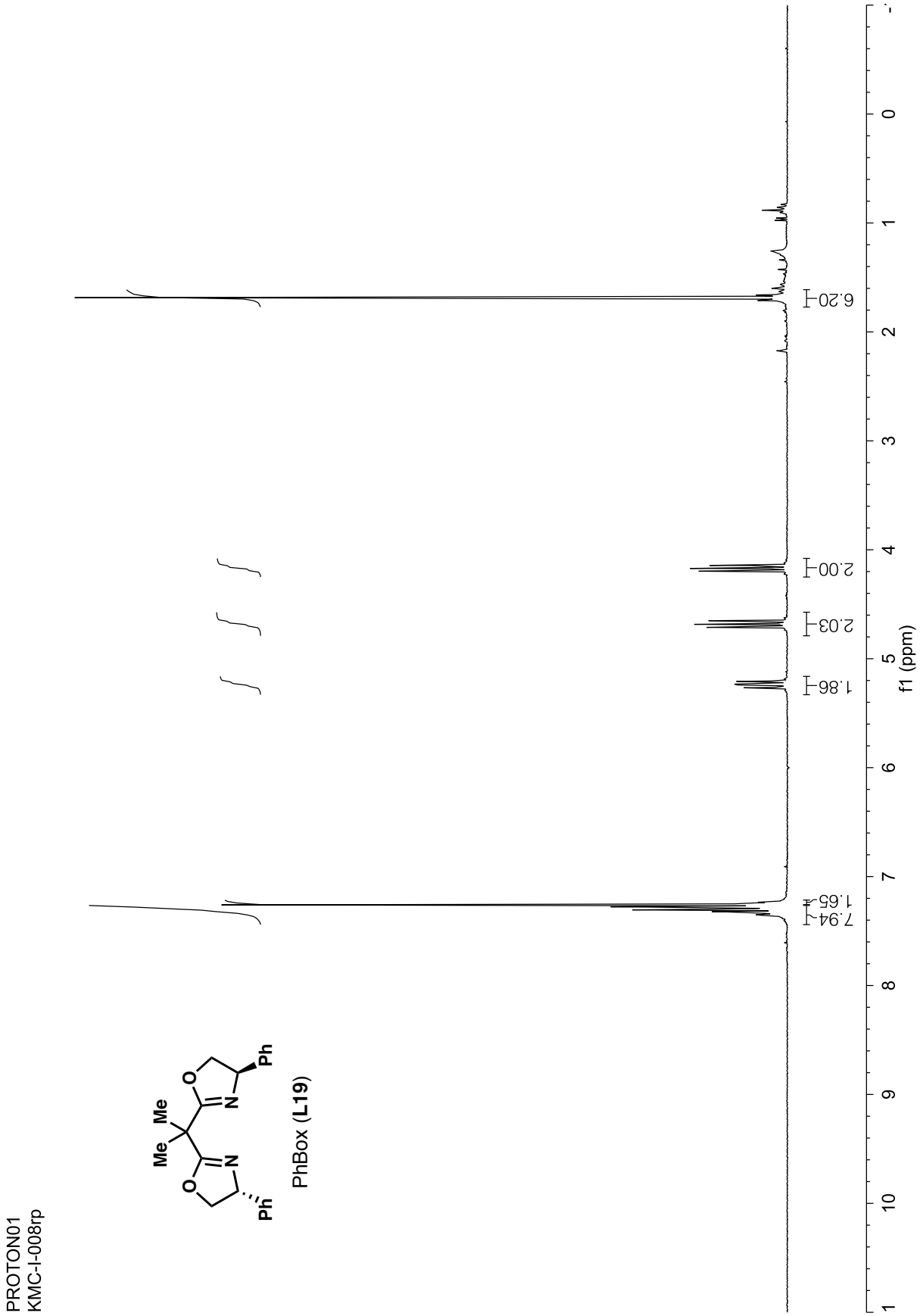
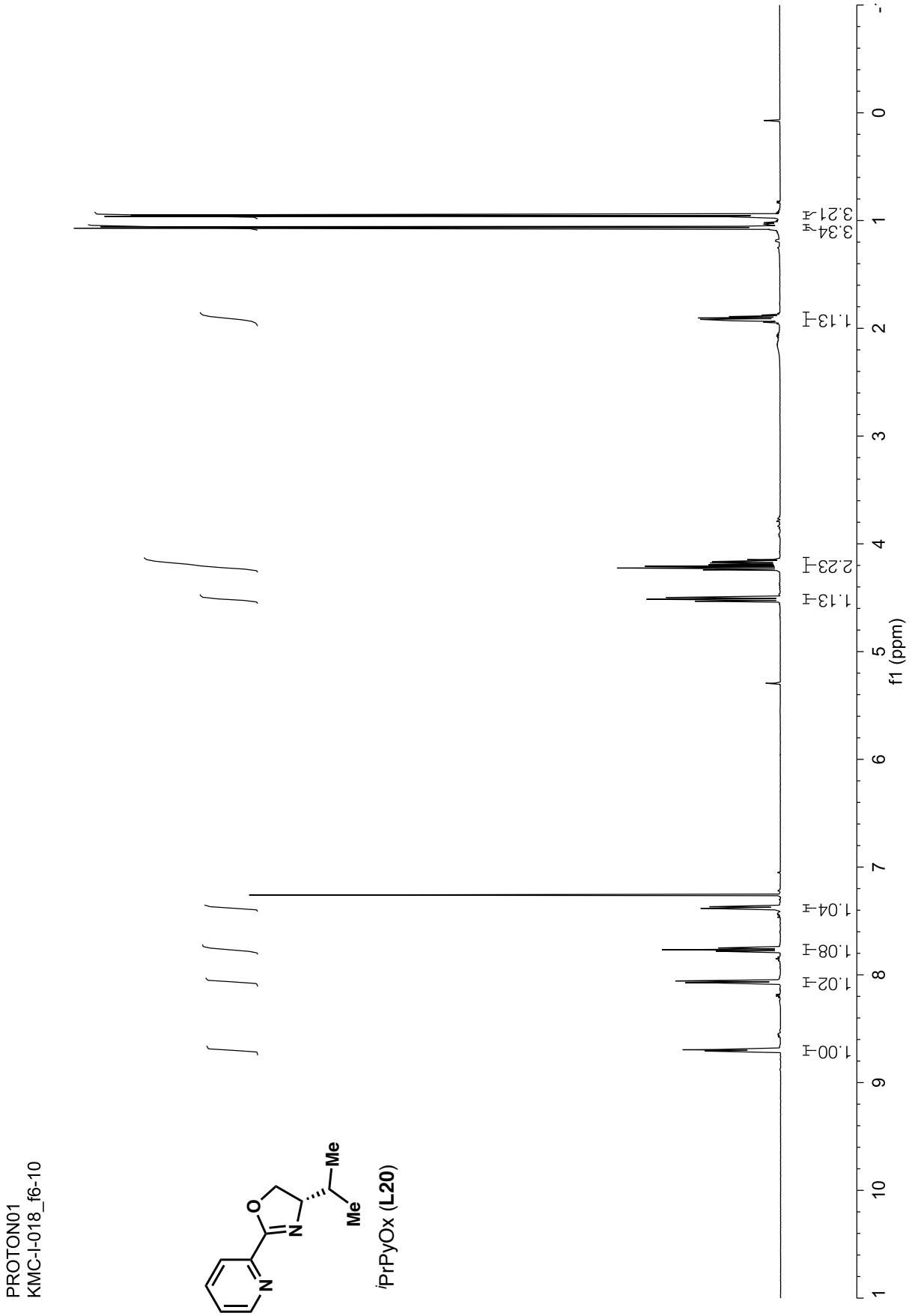
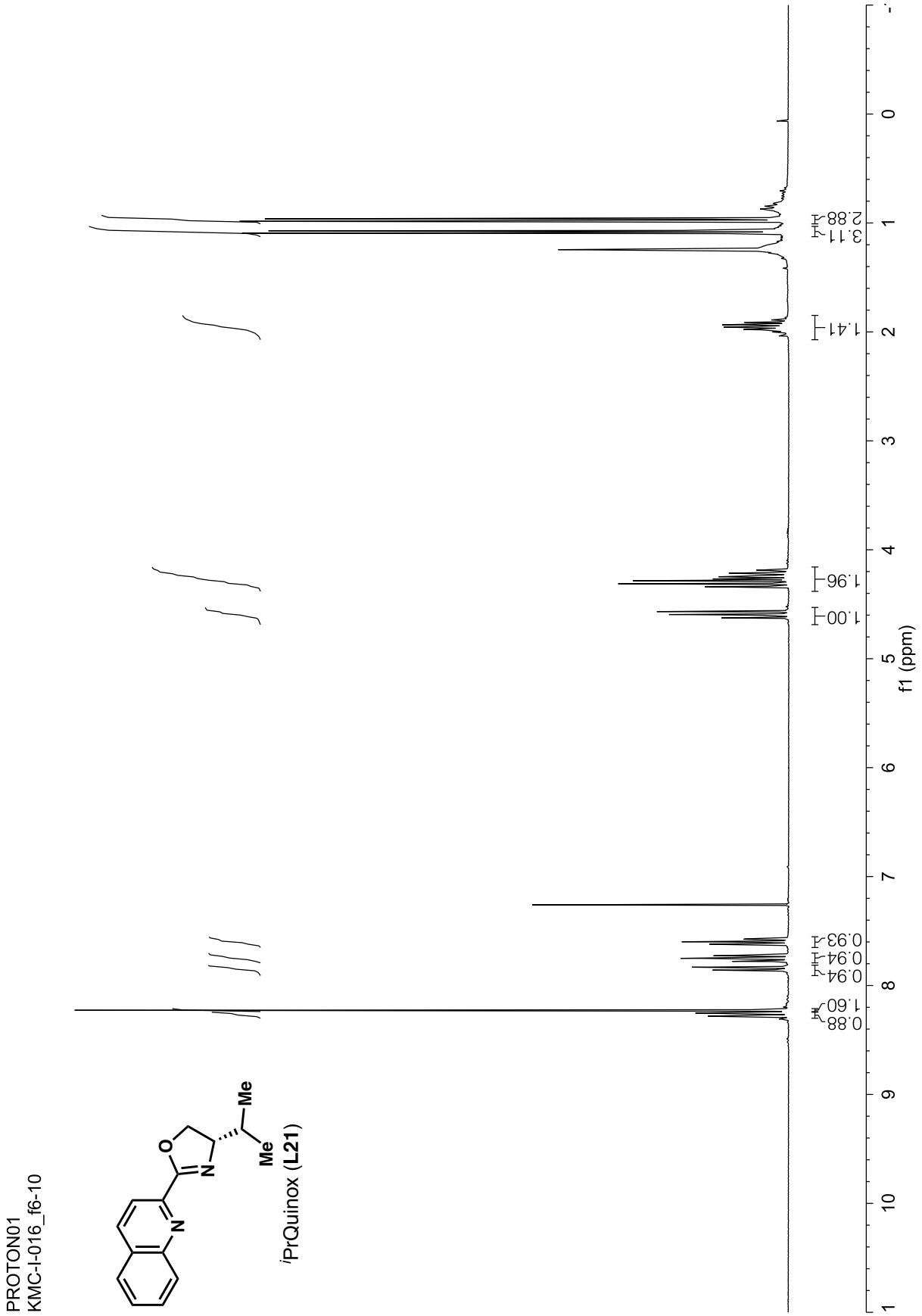
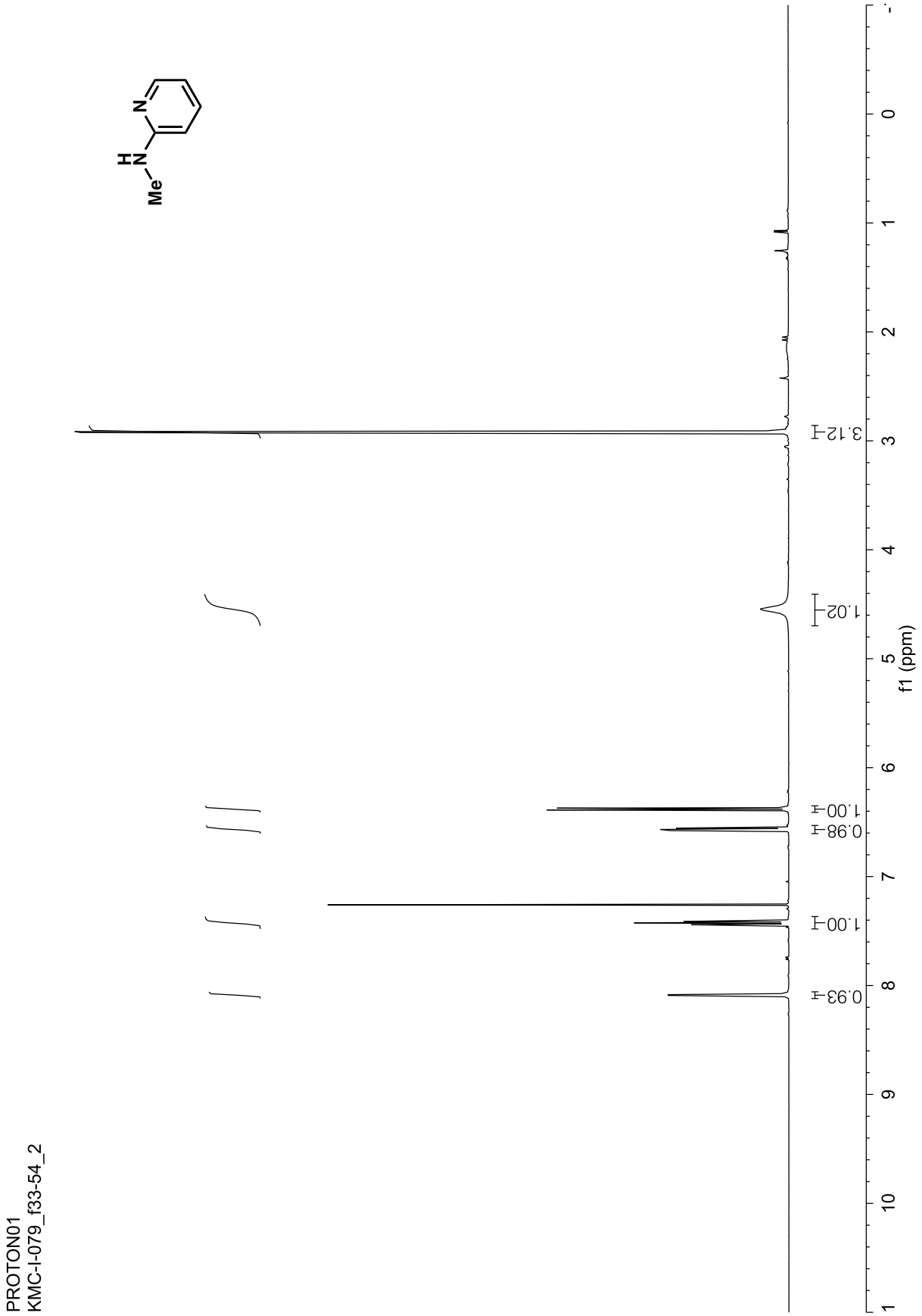
2.00
2.03
2.02
6.53
1.70
f1 (ppm)

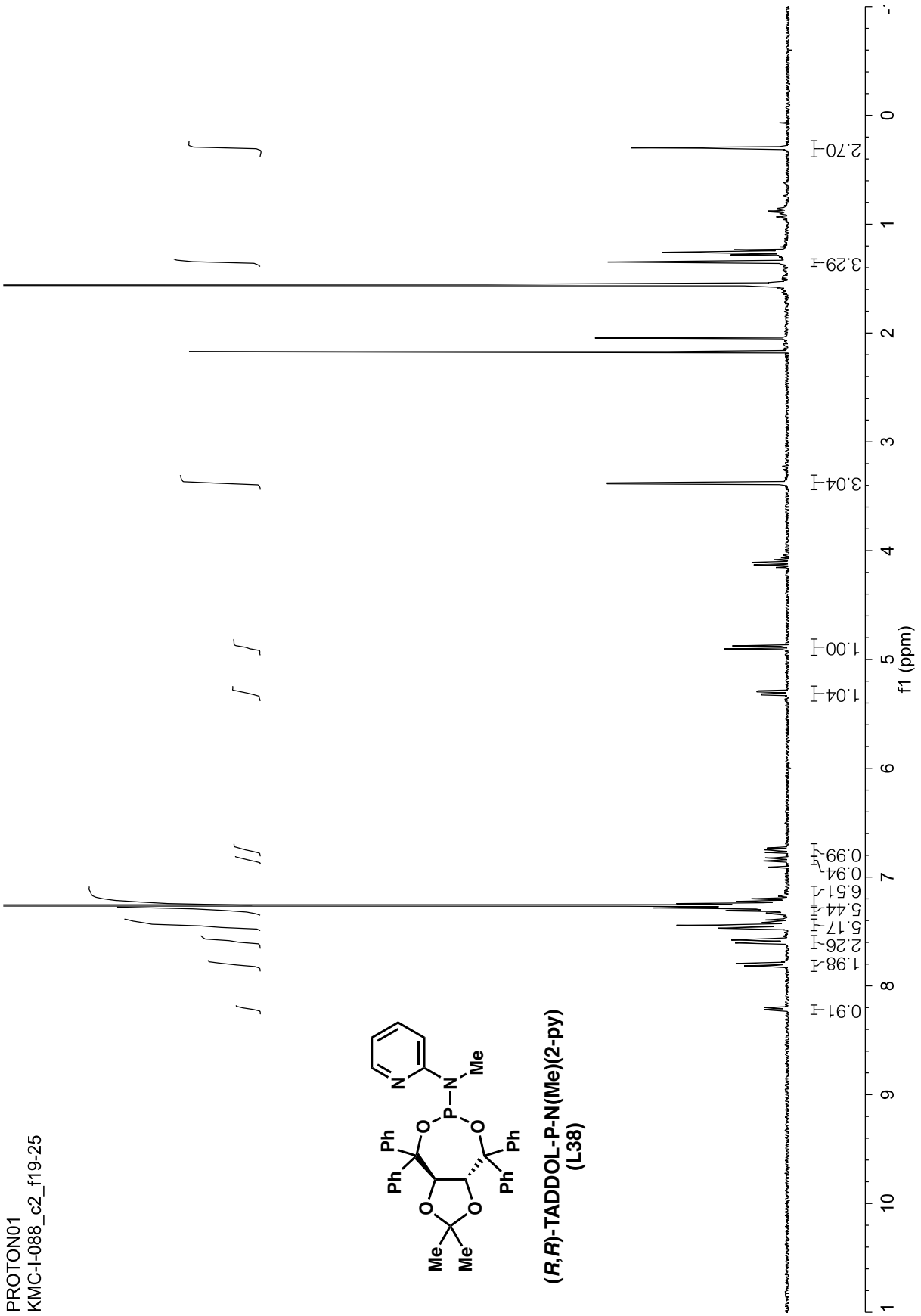

PROTON01
KMC-I-008rp
PhBox (L19)
Me
Me
Ph
Ph
O
N
N
O
6.20
2.00
2.03
1.86
7.94
1.65
f1 (ppm)

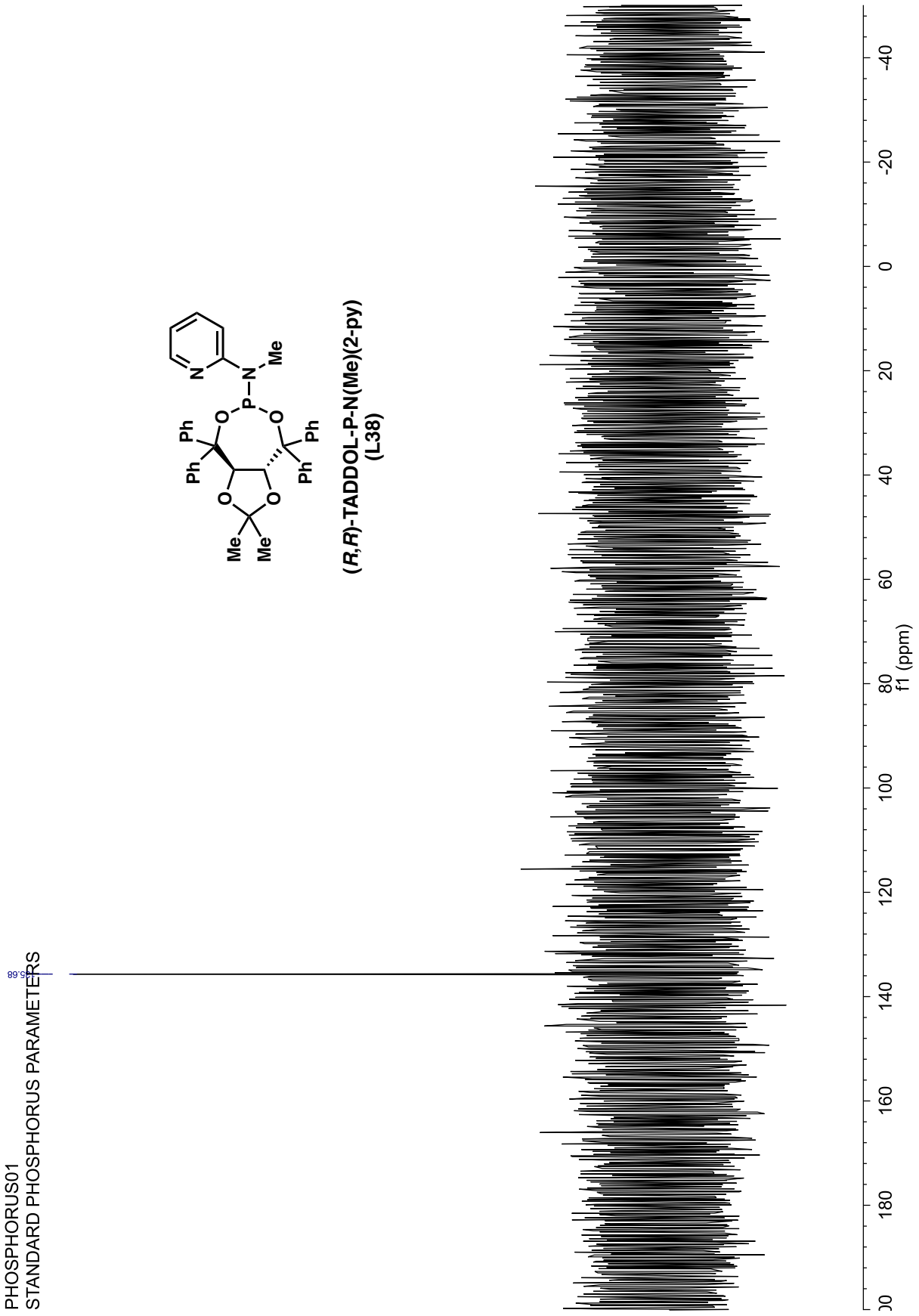

PROTON01
KMC-I-018_f6-10
3.21
3.34
1.13
2.23
1.13
1.04
1.08
1.02
1.00
f1 (ppm)
Me
Me
O
N
N

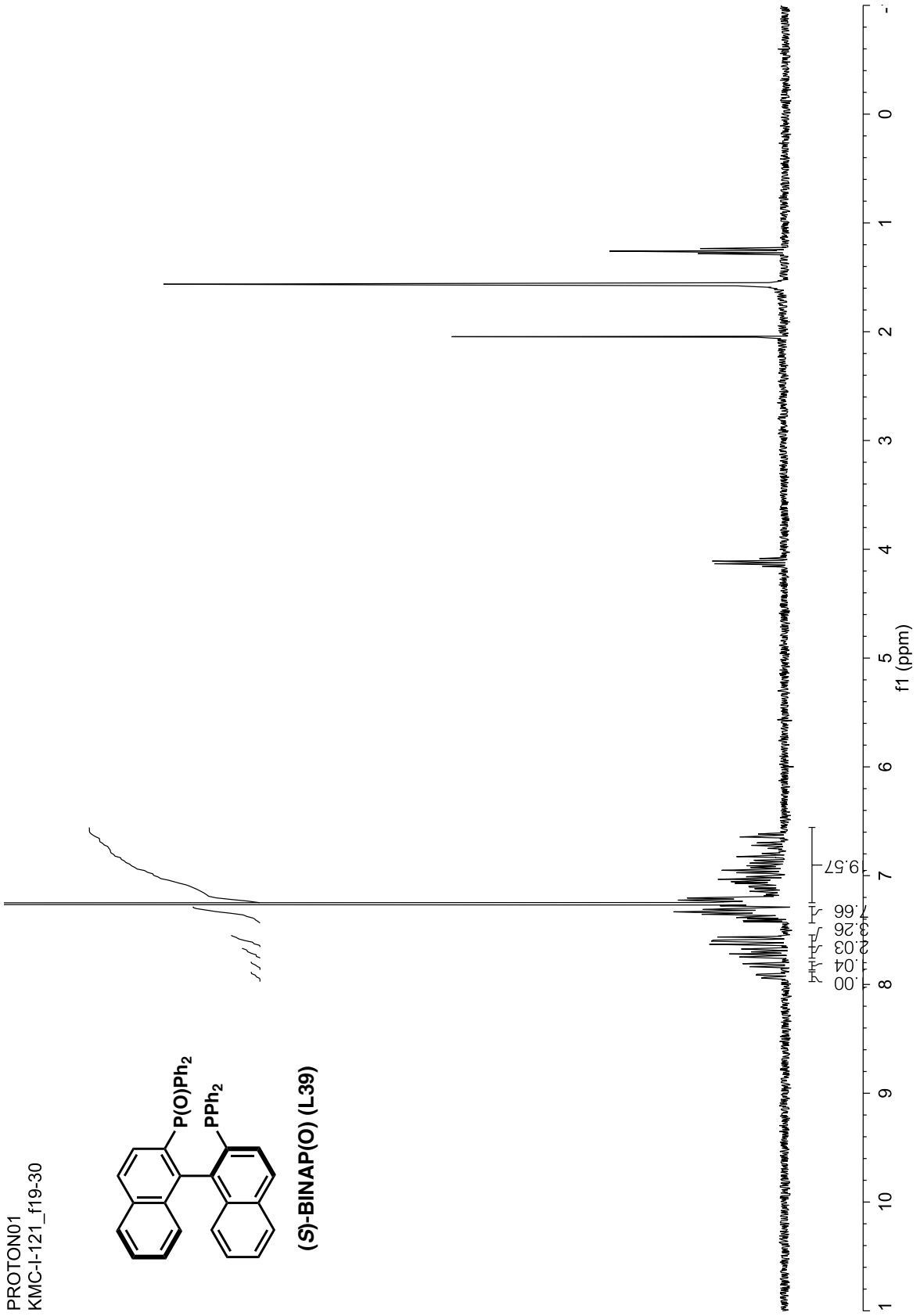
*i*PrPyOx (**L20**)

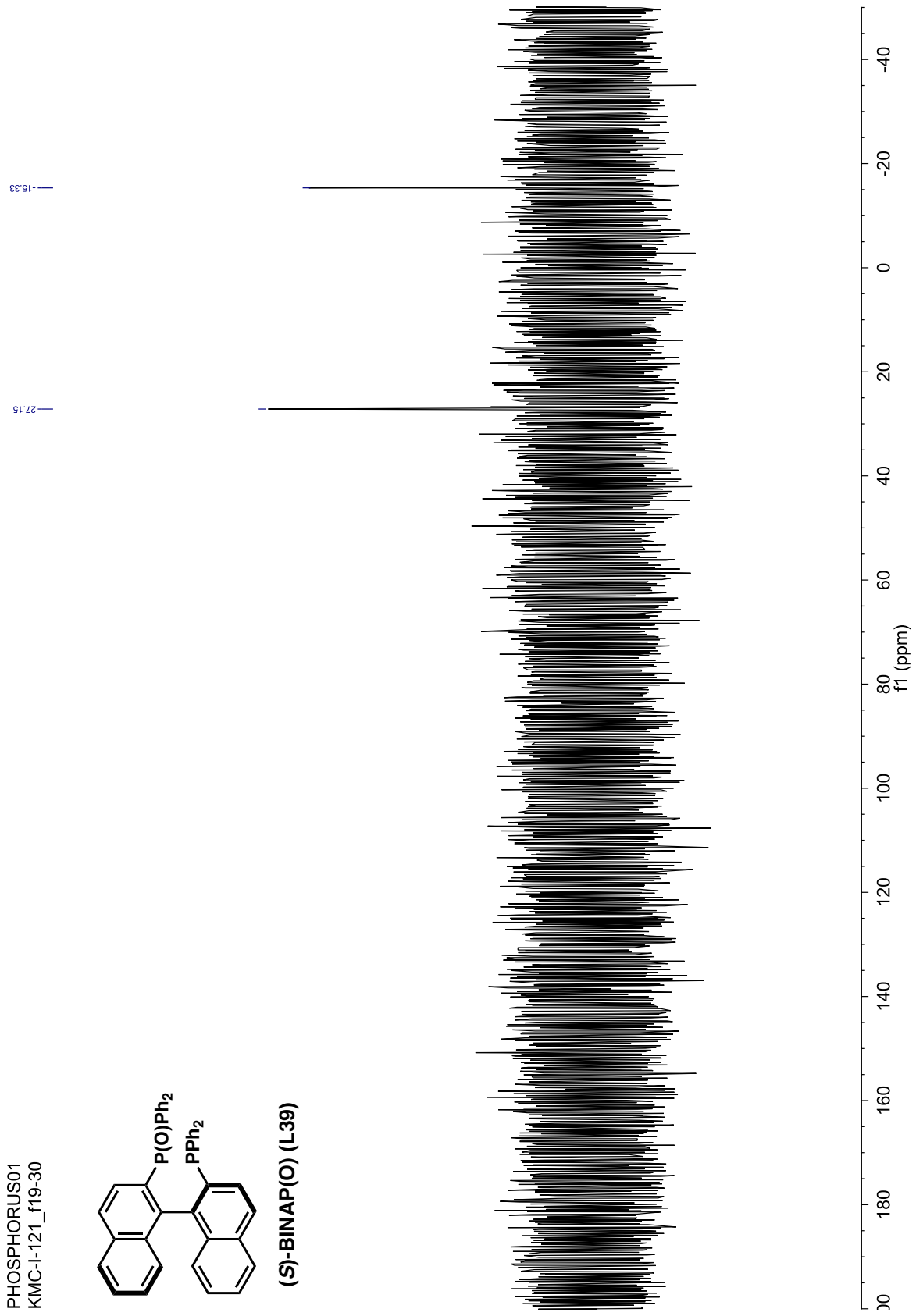

PROTON01
KMC-I-016_f6-10
Me
Me
O
N
N
*i*PrQuinox (**L21**)
0.88
1.60
0.94
0.94
0.93
1.00
1.96
1.41
3.11
2.88
f1 (ppm)

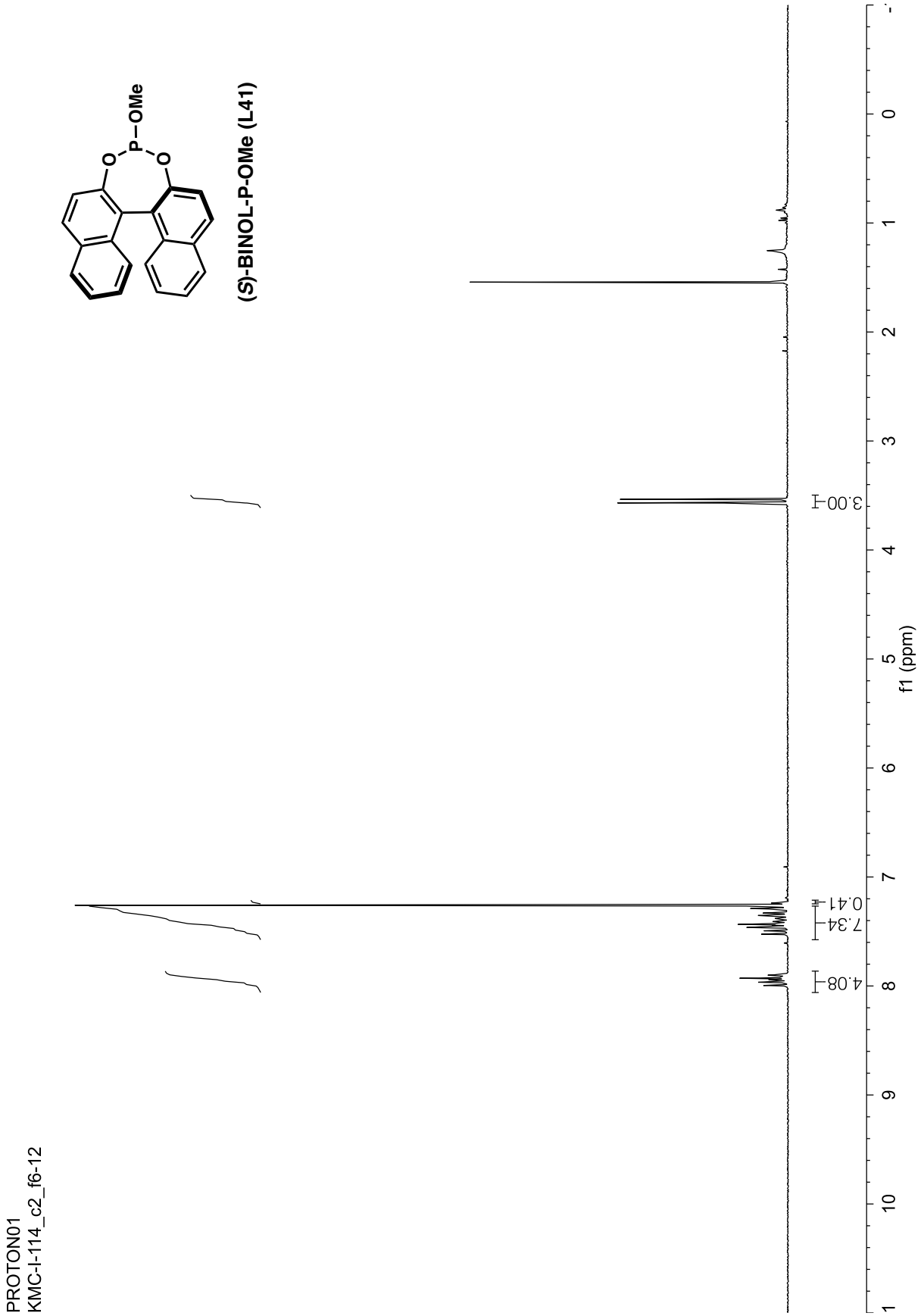

PROTON01
KMC-I-079_f33-54_2
3.12
1.02
1.00
0.98
1.00
0.93
f1 (ppm)

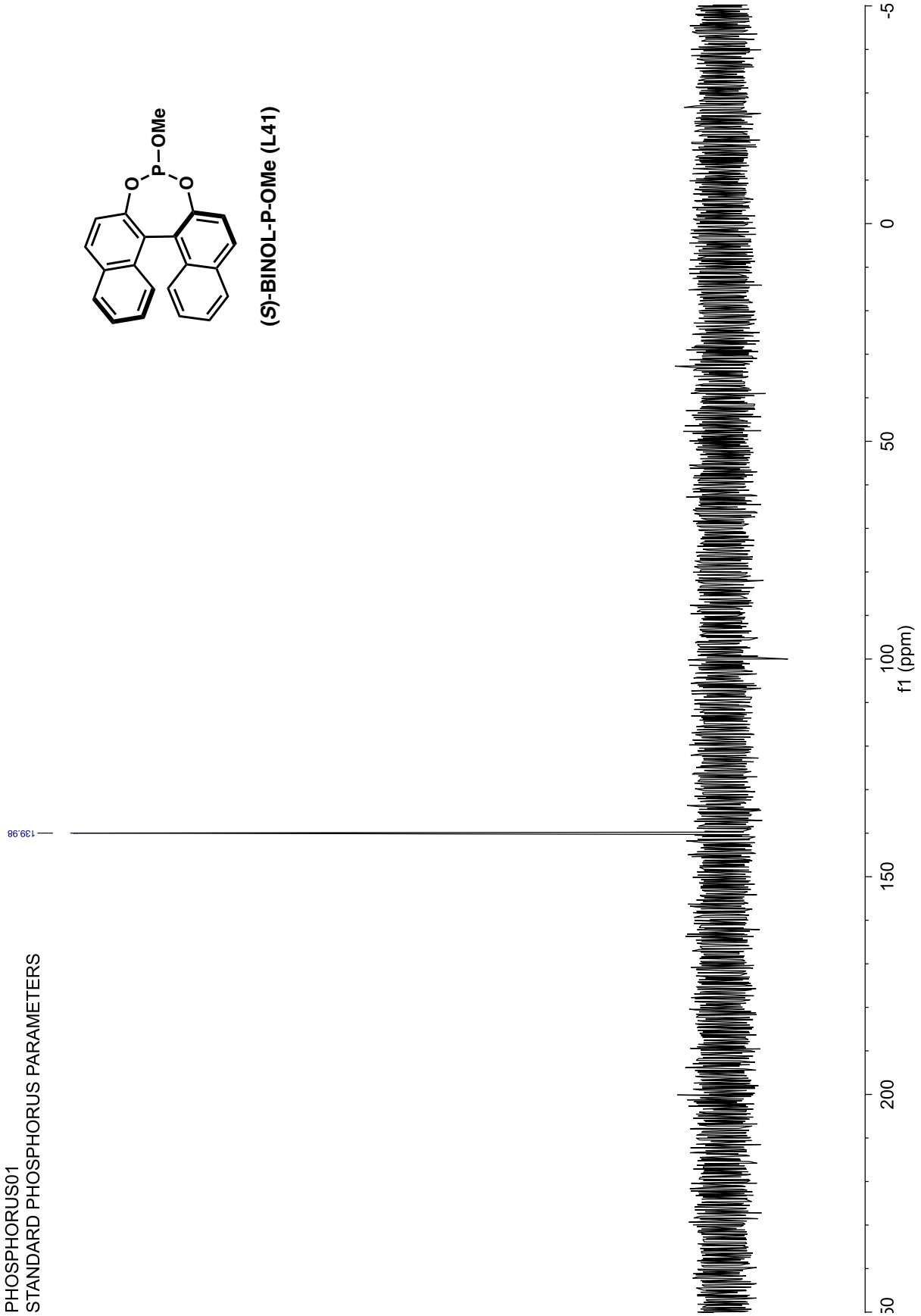

PROTON01
KMC-I-088_c2_f19-25
(*R*,*R*)-TADDOL-P-N(Me)(2-py)
(L38)
Me
Ph
O
P
N
f1 (ppm)
0.91
1.98
2.26
5.17
5.44
6.51
0.94
0.99
1.04
1.00
3.04
3.29
2.70

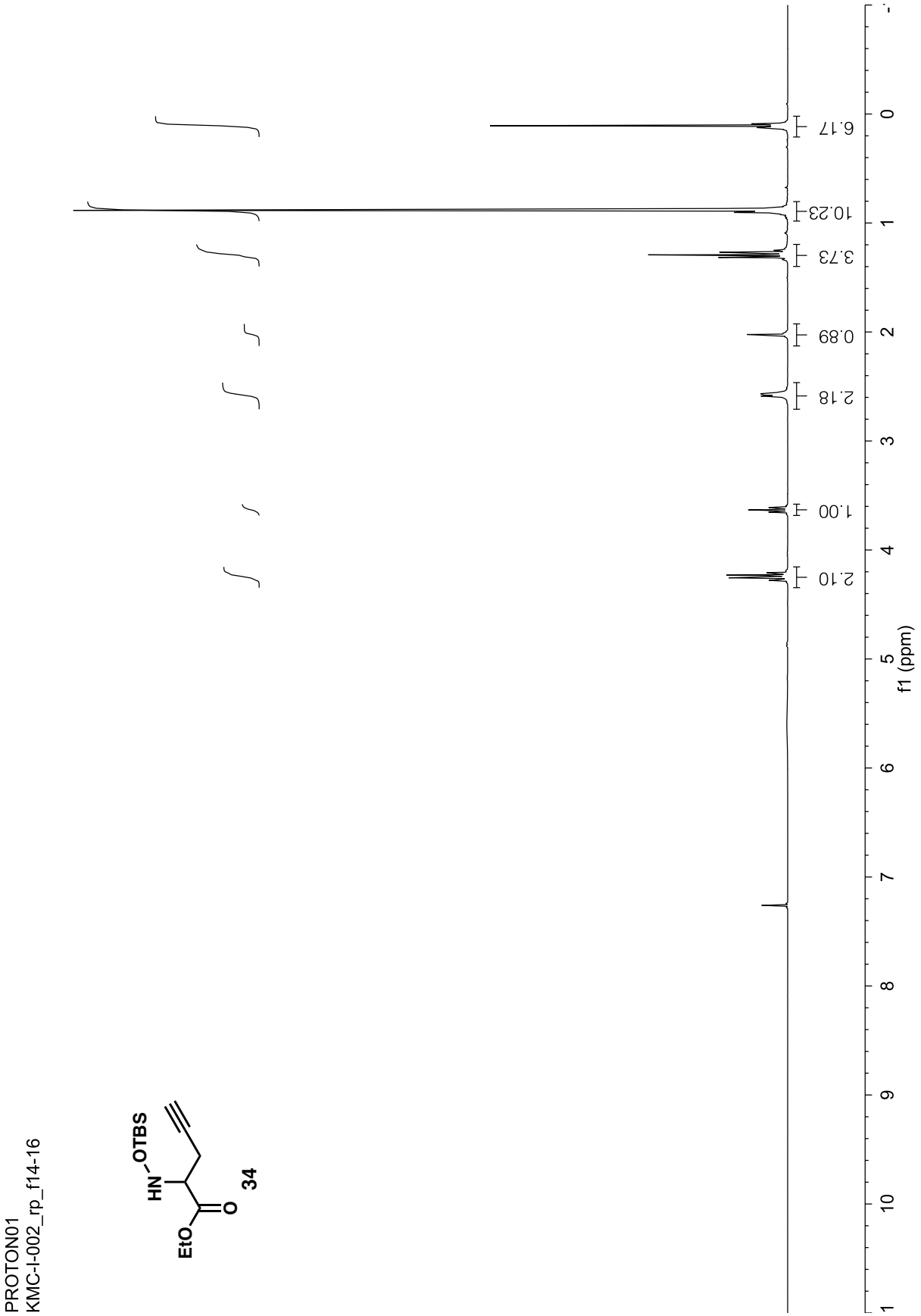

PHOSPHORUS01
STANDARD PHOSPHORUS PARAMETERS
(*R*,*R*)-TADDOL-P-N(Me)(2-py)
(L38)
f1 (ppm)

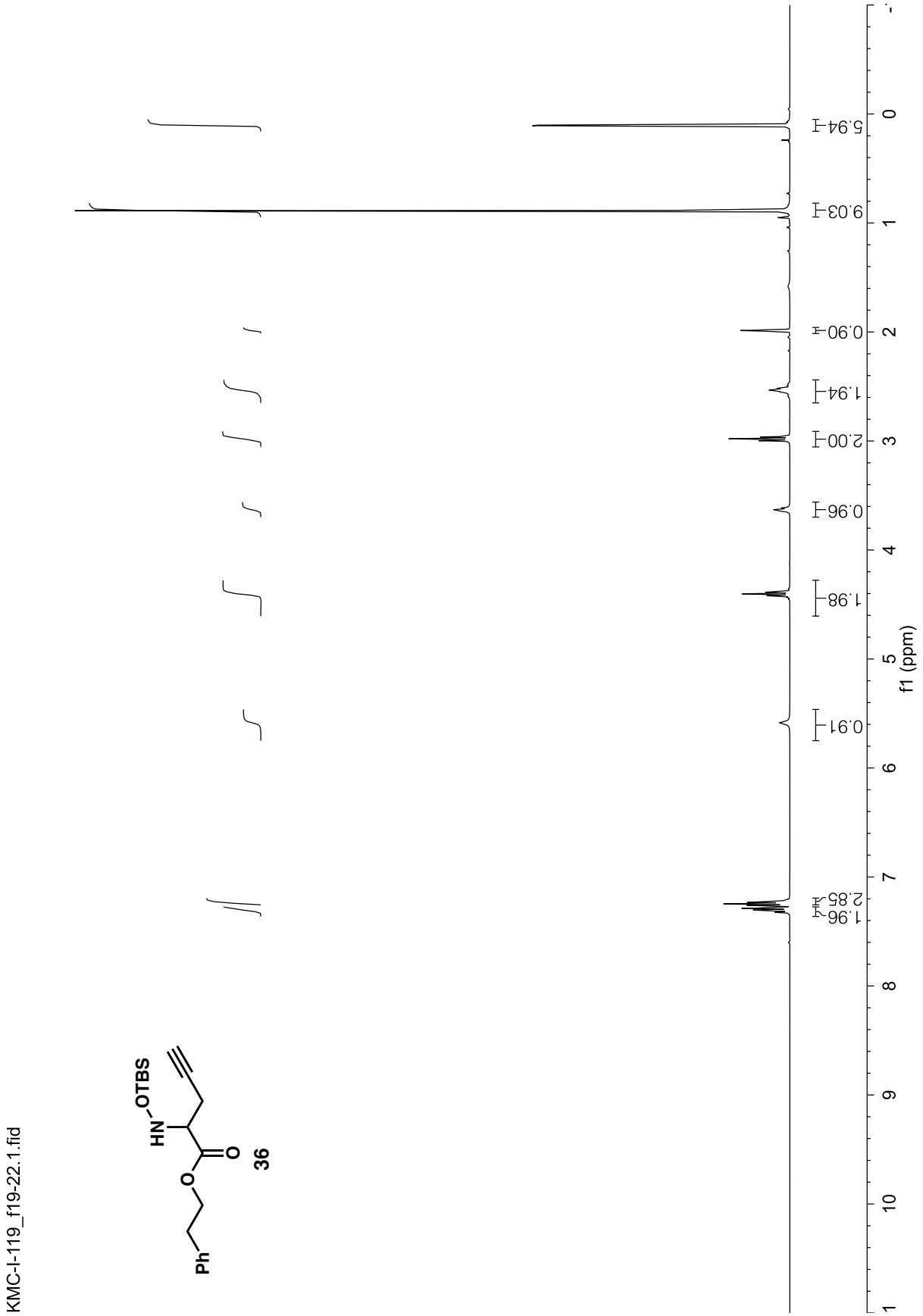

PROTON01
KMC-I-121_f19-30
P(O)Ph2
PPh2
(S)-BINAP(O) (L39)
9.57
7.66
3.26
3.03
1.04
1.00
f1 (ppm)


PHOSPHORUS01
KMC-I-121_f19-30
P(O)Ph2
PPh2
(S)-BINAP(O) (L39)
-15.33
27.15
f1 (ppm)


(S)-BINOL-P-OMe (L41)
P–OMe
O
O
PROTON01
KMC-I-114_c2_f6-12
3.00
0.41
7.34
4.08
f1 (ppm)


PHOSPHORUS01
STANDARD PHOSPHORUS PARAMETERS
139.98
P–OMe
O
O
(S)-BINOL-P-OMe (L41)
f1 (ppm)
-5
0
50
100
150
200
50

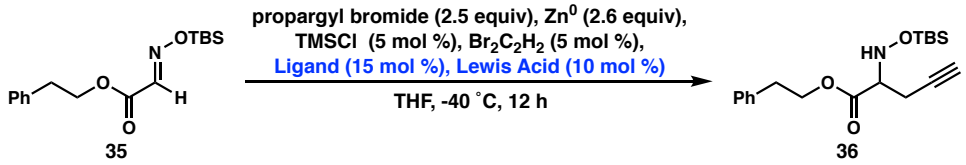

PROTON01
KMC-I-002_rp_f14-16
HN
OTBS
O
EtO
34
6.17
10.23
3.73
0.89
2.18
1.00
2.10
f1 (ppm)


KMC-I-119_f19-22.1.fid
HN
OTBS
O
O
Ph
36
5.94
9.03
0.90
1.94
2.00
0.96
1.98
0.91
1.96
2.85
f1 (ppm)

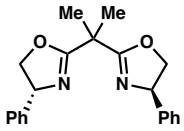
Appendix 2

Additional Tables Relevant to Chapter 2

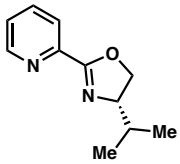
Table 2.2. *Effects of Lewis Acids in conjunction with different ligands on the propargylation.*



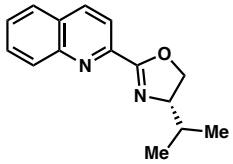
	PhBox (L19)				*i*PrPyOx (L20)				*i*PrQuinox (L21)			
Metal	**Entry**	**Conv. (%)**	**Yield (%)**	**ee (%)**	**Entry**	**Conv (%)**	**Yield (%)**	**ee (%)**	**Entry**	**Conv (%)**	**Yield (%)**	**ee (%)**
$Yb(OTf)_3$	1	72	64	0	8	59	53	0	15	51	29	2
$In(OTf)_3$	2	47	47	0	9	53	33	0	16	89	6	1
$Sc(OTf)_3$	3	74	71	0	10	69	33	0	17	56	37	3
$Cu(OTf)_2$	4	73	72	0	11	84	16	2	18	53	33	1
$MgBr_2$	5	77	77	0	12	71	45	0	19	55	36	1
$NiCl_2$·dme	6	50	49	0	13	44	22	0	20	65	9	2
$(CuOTf)_2$·PhMe	7	74	18	0	14	62	34	0	21	46	46	1



A: PhBox (**L19**)

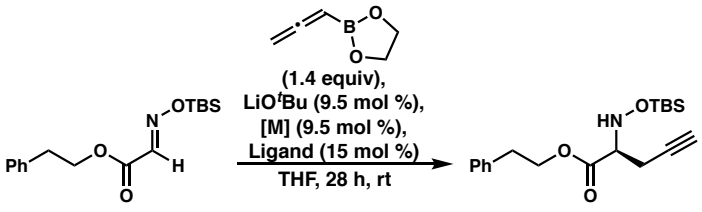


B: *i*PrPyOx (**L20**)

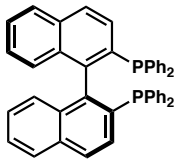


C: *i*PrQuinox (**L21**)

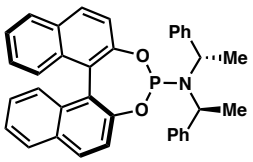
Table 2.4. *Survey of copper sources for the asymmetric propargylation.*



Entry	[M]	Ligand	Conversion (%)	Yield (%)	ee (%)
1	$(CuOTf)_2$·PhMe	A	23	6	70
2	$(CuOTf)_2$·PhMe	B	65	40	34
3	CuBr·DMS	A	35	9	0
4	CuBr·DMS	B	50	11	28
5	$[Cu(MeCN)_4]BF_4$	A	41	12	72
6	$[Cu(MeCN)_4]BF_4$	B	80	51	30
7	$[Cu(MeCN)_4]PF_6$	A	43	7	65
8	$[Cu(MeCN)_4]PF_6$	B	66	39	30
9	$[Cu(MeCN)_4]ClO_4$	A	47	11	70
10	$[Cu(MeCN)_4]ClO_4$	B	89	47	30
11	$Cu(acac)_2$	A	51	28	66
12	$Cu(acac)_2$	B	92	47	31
13	CuI	A	48	6	0
14	CuI	B	76	15	29
15	$Cu(OTf)_2$	A	16	0	—
16	$Cu(OTf)_2$	B	31	0	—
17	$Cu(OAc)_2$	A	29	1	—
18	$Cu(OAc)_2$	B	41	4	30
19	Cu(^{i}butyrate)$_2$	A	36	trace	—
20	Cu(ibutyrate)$_2$	B	45	4	28
21	Cu(2-pyrazinecarboxylate)	A	35	4	71
22	Cu(2-pyrazinecarboxylate)	B	70	36	34



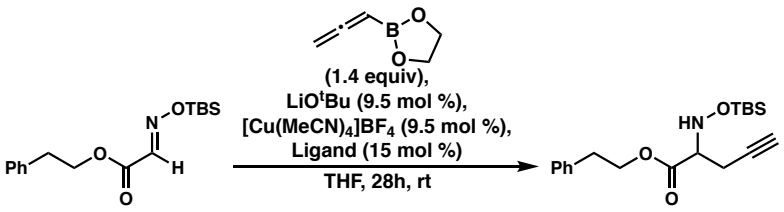
A: (*S*)-BINAP (L23)



B: (*S,S*)-BINOL-P-N(CH(Me)Ph)$_2$ (L25)

Table 2.5. *Standout ligands for $[Cu(MeCN)_4]BF_4$-catalyzed propargylation.*

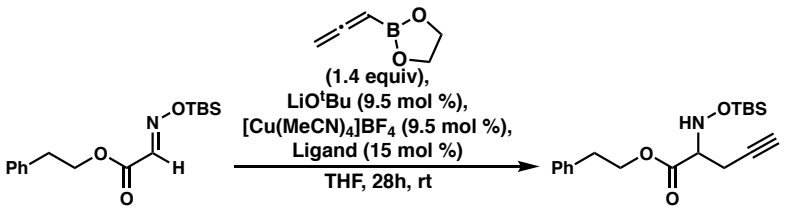
a) *BINAP ligands*



Ligand	Conversion (%)	Yield (%)	ee (%)
(*S*)-BINAP	36	12	65
(*S*)-T-BINAP	33	7	72
(*R*)-DM-BINAP	45	8	76
(*R*)-H8-BINAP	20	7	63
(*R*)-SDP	29	6	12
(*S*,*S*,*S*)-Ph-SKP	95	72	0
(*S*)-QUINAP	85	72	30
(*S*)-BINAPINE	25	trace	—

Table 2.5. *Standout ligands for $[Cu(MeCN)_4]BF_4$-catalyzed propargylation.*

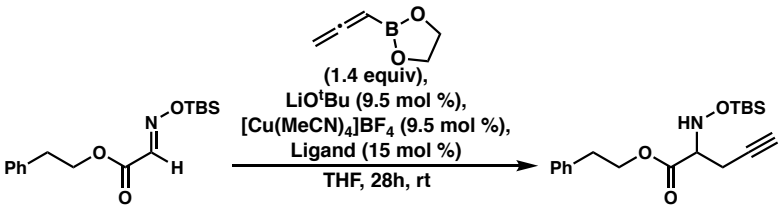
b) *Phosphoramidite ligands*



Ligand	Conversion (%)	Yield (%)	ee (%)	Ligand	Conversion (%)	Yield (%)	ee (%)
(*S*)-BINOL-P-NMe_2	88	60	24	(*R,R*)-Ph-TADDOL-P-morpholine	90	43	16
(*S*)-H8-BINOL-P-NMe_2	77	46	24	(*R,R,S,S*)-Ph-TADDOL-P-N*CH(CH_3)Ph)$_2$	52	15	9
(*R*)-SIPHOS	100	69	14	(*R,R,R,R*)-Ph-TADDOL-P-N*CH(CH_3)Ph)$_2$	46	15	6
[3,3'-bis'PPh_2]-(*R*)-BINOL-P-NMe_2	38	9	7	(*S*)-BINOL-P-(*R*)-NHCH(Me)Ph	58	26	19
(*R,R*)-TADDOl-P-NMe_2	97	70	34	(*S,S*)-BINOL-P-NBn(CH(Me)Np)	76	49	24
(*S*)-BINOL-P-morpholine	60	9	31	(*R,S*)-BINOL-P-NBn(CH(Me)Np)	87	56	10
(*S*)-BINOL-P-NMeBn	75	45	20	(*S,S,S*)-BINOL-P-N[CH(Me)Ph]$_2$	78	54	30
(*R*)-BINOL-P-NBn_2	76	41	2	(*S,R.R*)-BINOL-P-N[CH(Me)Ph]$_2$	48	8	16
(*R,R*)-Ph-TADDOL-P-NMe_2	100	45	32	[3,3'-bis-F]-(*R,R,R*)-BINOL-P-N[CH(Me)Ph]$_2$	69	25	41
(*R,R*)-Ph-TADDOL-P-NEt_2	90	43	32	(*R,R,R*)-BINOL-P-N(CH(Me)Ph)(CH(Me)Np)	59	36	30
(*R,R*)-Np-TADDOL-P-NEt_2	73	16	8	(*R,R,R*)-BINOL-P-N(CH(Me)Np)$_2$	77	38	50
(*R,R*)-Ph-TADDOL-P-NBn_2	82	40	26	(*R,R,R*)-BINOL-P-Ph2pyrrolidine	98	84	15
(*R,R*)-Ph-TADDOL-P-NMePh	75	22	32	(*R,R,R*)-BINOL-P-Np2pyrrolidine	61	32	16
(*R,R*)-Ph-TADDOL-P-pyrollidine	84	34	32				
(*R,R*)-Ph-TADDOL-P-piperidine	91	46	20	(*S,Sa*)-BOGERPhos	82	73	31

Table 2.5. *Standout ligands for [Cu(MeCN)$_4$]BF$_4$-catalyzed propargylation.*

c) *Biaryl bisphosphine ligands*



Ligand	Conversion(%)	Yield (%)	ee (%)
(*R*)-SEGPHOS	39	10	54
(*R*)-DM-SEGPHOS	34	4	48
(*R*)-DTBM-SEGPHOS	28	2	54
(*R*)-DiFluoroPhos	32	11	80
(*R*)-SynPhos	50	9	34
SolPhos	61	45	4
(*S*)-Xyl-MeOBIPHEP	31	2	68
(*S*)-3,5-^{t}Bu-MeOBIPHEP	35	1	48
(*S*)-3,5-^{t}Bu-4-MeO-MeOBIPHEP	26	trace	--
(*S*)-3,5-^{i}Pr-4-Me$_2$N-MeOBIPHEP	20	trace	--
(*S*)-C3-TunePhos	25	3	45
(*R*)-P-Phos	34	12	80
(*R*)-BTFM-GarPhos	60	24	82