Stony Brook University

Development of Enantiopure Biphenol-Based Phosphorus Ligand Libraries and Their Applications to Palladium-Catalyzed Asymmetric Transformations

A Dissertation Presented

by

Chi-Feng Lin

to

The Graduate School

In partial fulfillment of the

requirements

for the Degree of

Doctor of Philosophy

in

Chemistry

Stony Brook University

August 2012

Stony Brook University

The Graduate School

Chi-Feng Lin

We, the dissertation committee for the above candidate for the

Doctor of Philosophy degree, hereby recommend

acceptance of this thesis

Professor Iwao Ojima
Dissertation Advisor
Department of Chemistry

Professor Robert C. Kerber
Chairman
Department of Chemistry

Professor Nancy S. Goroff
Third Member
Department of Chemistry

Dr. Ramesh C. Gupta
Outside Member
Vice President, Chem-Master International

This dissertation is accepted by the Graduate School

Charles Taber
Interim Dean of the Graduate School

Abstract of the Dissertation

Development of Enantiopure Biphenol-Based Phosphorus Ligand Libraries and Their Applications to Palladium-Catalyzed Asymmetric Transformations

Chi-Feng Lin

Doctor of Philosophy

in

Chemistry

Stony Brook University

2012

Among methods of asymmetric synthesis, transition-metal catalyzed asymmetric transformation has proven to be a highly efficient and enabling methodology to induce desired chirality. In our laboratory, libraries of novel biphenol-based monodentate phosphoramidite and bidentate diphosphonite ligands have been developed, which are very effective in asymmetric allylic transformations. We present here the application of Pd-catalyzed intramolecular asymmetric allylic amination to the synthesis of enantiopure key intermediates, 1-vinyltetrahydroisoquinolines in the total synthesis of Schulzeines A-C using our diphosphonite ligands. Schulzeines A-C, isolated from a marine sponge, *Penares Schulzei*, have been identified as a new class of marine natural products, which exhibit potent α-glucosidase inhibitory activity making them promising leads for drug development for cancer, diabetes, viral infections and other diseases.

We also studied a highly efficient Pd-catalyzed asymmetric tandem allylic alkylation process for the synthesis of an advanced key intermediate to (-)-Huperzine A with excellent enantioseletivity using our phosphoramidite ligands. (-)-Huperzine A, isolated from the plant firmoss, *Huperzia serrata*, is an acetylcholinesterase (AChE) inhibitor and shows promise in the treatment of Alzheimer's disease and enhance memory.

Besides, Pd-catalyzed asymmetric Heck reaction, chiral biphenol-based phosphoric acid mediated asymmetric organocatalysis and Rh-catalyzed [2+2+2+1] cycloaddition of enediynes were investigated and highlighted in the dissertation as well.

Dedicated to my entire family

TABLE OF CONTENTS

CHAPTER 2
Palladium-Catalyzed Asymmetric Allylic Amination with Bidentate Diphosphonite Ligands

CHAPTER 3
Formal Enantioselective Total Synthesis of Schulzeines A-C *via* Pd-Catalyzed Intramolecular Asymmetric Allylic Amination

CHAPTER 4
Enantioselective Synthesis of Huperzine-A Key Intermediate via Tandem Pd-Catalyzed Intermolecular Allylic Alkylations

CHAPTER 5

Palladium-Catalyzed Asymmetric Heck Reactions with Monophosphoramidite and Bidentate Phosphite-Oxazoline Ligands

CHAPTER 6

Synthesis of Chiral Biphenol-based Phosphoric Acids and their Applications to Asymmetric Organocatalysis

CHAPTER 7

Formation of 5-7-5 Fused Tricyclic γ-Lactams via Rh(I)-Catalyzed [2+2+2+1] Cycloaddition and CO-SiCaT Reaction of Enediynes with Carbon Monoxide

BIBLIOGRAPHY

APPENDICES

LIST OF FIGURES

CHAPTER 1

CHAPTER 2

CHAPTER 3

CHAPTER 4

CHAPTER 5

CHAPTER 6

LIST OF SCHEMES

CHAPTER 1

CHAPTER 2

CHAPTER 3

CHAPTER 4

CHAPTER 5

CHAPTER 6

CHAPTER 7

LIST OF TABLES

CHAPTER 2

CHAPTER 4

CHAPTER 5

CHAPTER 6

CHAPTER 7

LIST OF ABBREVIATIONS

Ac	-	acetyl
AChE	-	acetylcholine esterase
atm	-	atmosphere
BINAP	-	2,2'-bis(diphenylphosphino)-1-1'-binapthyl
BINOL	-	1,1'-bi-2-naphthol
Bn	-	benzyl
Boc	-	*tert*-butyl carbonate
BOP	-	biphenol-based diphosphonite
Bu	-	butyl
*t*Bu	-	*tert*-butyl
bp	-	boiling point
bs	-	broad singlet
bt	-	broad triplet
calcd.	-	calculated
CAMP	-	methylcyclohexyl-o-anisylphosphine
Celite®	-	diatomaceous earth filter reagent, ®Celite Corp.
*c*Hex	-	cyclohexyl
COD	-	1,5-cyclooctadiene
CO	-	carbon monoxide
d	-	doublet
DCE	-	1,2-dichloroethane
DCM	-	dichloromethane
de	-	diastereomeric excess
DIOP	-	(+)-2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
dd	-	doublet of doublets
DMAP	-	4-dimethylaminopyridine
DME	-	ethylene glycol dimethyl ether
DMF	-	dimethylformamide
DMSO	-	dimethylsulfoxide
dppp	-	diphenylphosphino propane
DuPHOS	-	(+)-1,2-Bis[(2S,5S)-2,5-dimethylphospholano]benzene
ee	-	enantiomeric excess
EI	-	electron impact (MS)
ESI	-	electrospray ionization
Et	-	ethyl
Et_2O	-	ethyl ether
EtOAc	-	ethyl acetate
FIA	-	flow-injection analysis
g	-	gram
GC- MS	-	gas chromatography mass spectrometry
h	-	hour
HMPT	-	hexamethylphosphorus triamide
HPLC	-	high performance liquid chromatography
HR-MS	-	high resolution mass spectrometry

Hz	-	hertz
IR	-	infrared spectroscopy
J	-	coupling constant
K	-	Kelvin
L	-	liter
LAH	-	lithium aluminum hydride
LC-MS	-	liquid chromatography mass spectrometry
LiHMDS	-	lithium hexamethyldisilizane
m	-	multiplet
Me	-	methyl
MeCN	-	acetonitrile
MeOH	-	methanol
min	-	minute
mmol	-	millimole
mol	-	mole
M	-	molarity
mg	-	milligram
MHz	-	mega hertz
mL	-	milliliters
mp	-	melting point
MPN	-	biphenol-based phosphoramidite
MS	-	mass spectrometry
Ms	-	mesylate
MW	-	molecular weight
μW	-	microwave
NIS	-	*N*-iodosuccinimide
NMR	-	nuclear magnetic resonance
o.n.	-	overnight
PA	-	biphenol-based phosphoric acid
PCC	-	pyridinium chlorochromate
Ph	-	phenyl
PMB	-	*p*-methoxy benzyl
PN	-	biphenol-based phosphite-oxazoline ligand
ppm	-	parts per million
prep HPLC	-	preparative high performance liquid chromatography
q	-	quartet
quint.	-	quintet
RCM	-	ring-closing metathesis
Red-Al®	-	sodium bis(2-methoxyethoxy)aluminumhydride
rt	-	room temperature
s	-	singlet
t	-	triplet
TADDOL	-	α,α,α',α'-tetraphenyl-2,2'-dimethyl-1,3-dioxolane-4,5-dimethanol
TBAI	-	tetrabutylammonium iodide
TEA	-	triethylamine
TFA	-	trifluroacetic acid

TFE	-	2,2,2-trifluoroethanol
THF	-	tetrahydrofuran
TLC	-	thin layer chromatography
TMG	-	tetramethylguanidine
TMS	-	trimethylsilyl
Ts	-	tosylate
p-TSA	-	*p*-toluenesulfonic acid

ACKNOWLEDGEMENTS

I would like to first give my sincere gratitude to my dissertation advisor, Prof. Iwao Ojima, for offering me an excellent opportunity to do research in his laboratory. His guidance, patience, support and encouragement on my research fulfill my entire graduate career. I gratefully appreciate his mentorship. I wish to thank my ACC committee members: Prof. Robert C. Kerber and Prof. Nancy S. Goroff for their brilliant discussion with me and giving me different thinking of my research in all my committee meetings. I benefited greatly from their insightful advice. Also, I especially would like to express my thankfulness to Dr. Ramesh Gupta for taking his time to serve as my Outside Member of my dissertation committee. I also wish to thank Prof. Tadashi Honda for giving me advice in all my presentations. A special and wholehearted thanks to Mrs. Patricia Marinaccio "the Ojima Group Mom" for taking care of all group members on everything. I have to say everything because she really helped me this "fresh farther" to solve lots of tough baby issues. I wish to also thank Mrs. Yoko Ojima for her wonderful hospitality and kindness on many different occassions.

I would like to thank Ojima Group and ICB&DD alumni, Dr. Gary Yu-Han Teng, Dr. Joseph Kaloko, Dr. Xianrui "Ray" Zhao, Dr. Stephen J. Chaterpaul, Dr. Liang Sun, Dr. Ce Shi, Dr. Shuyi Chen, Dr. Jin Chen, Dr. Olivier Marrec, Dr. Seung-Yub Lee, Dr. Hengguang Li and Ms. Ilaria Zanadi for giving me many advice, encouragement and discussions on my research projects. I wish to thank all the current members of the Ojima Lab; Dr. Edison Zuniga, Chih-Wei Chien, William Berger, Alexandra Athan, Joshua D. Seitz, Tao Wang, Yang Zang, Bora Park, Jacob G. Vineberg and the current members of ICBⅅ Dr. Kunal Kumar, Dr. Suqing Zheng, Dr. Motohiro Takahashi, Dr. Eduard H. Melief, Dr. Anushree Kamath, Dr. Wei Li for their support and help with every aspect of research. A special gratitude is given to Tolga Sevinc and Robert Robinson for being my mentee and helping me on my research projects. I truly appreciate to have worked with all of you in the Ojima group. A heartfelt thank to Dr. Edison Zuniga, Dr. Kunal Kumar, Dr. Anushree Kamath, Dr. Joseph Kaloko, and Alexandra Athan for spending time proofreading my dissertation. Because of your efforts, a dissertation with good quality can be performed to everyone.

I wish to thank all faculty members of the Chemistry Department, especially Prof. Iwao Ojima, Prof. Nancy S. Goroff, Prof. Jin Wang, Prof. Clare P. Grey, Prof. Kathlyn A. Parker and

Prof. Andreas Mayr for teaching me abundant knowledge of chemistry during my first-year course work. A special thank to Dr. James Marecek for operating various NMR experiments and solving numerous problems related to NMR. I also wish to thank Dr. Béla Ruzsicska for helping me to run lots of LC-MS and solving problems related to mass spectrometry. For Dr. Alvin Silverstein and Mr. Micheal Teta, thank you for keeping the chemistry building in good condition so I can work here freely. Moreover, thankfulness for the entire staff of the chemistry department's main office can not be forgotten. Ms. Carol Brekke, Ms. Charmaine Yapchin, Ms. Heidi Ciolfi, Ms. Lizandia Perez, Ms. Barbara Schimmenti and especially Ms. Katherine Hughes, with your presence, everything related to my academic status in Stony Brook University goes smoothly. A thank is also given to the National Science Foundation for funding my research.

I would like to give my appreciation to all my friends in long island and Taiwan for their support, encouragement and their friendships. Finally, I would like to express my deepest gratitude to my entire family. For my parents, thank you for continuous mental and materially supports in my life. For my lovely wife, Chia-Yen Claire Wu, thank you for believing in me, encouraging me all the time and giving us the most precious present, our cutest daughter Amelia Pin-Chieh Lin. Her smile always makes me forget those unpleasant things bothering my life. For all my family members who always stood by me, the accomplishment I achieved belongs to you as well.

Chapter 1

Introduction and Synthesis of Phosphorus Ligands for Catalytic Asymmetric Reactions

Table of Contents

§ 1.1 History of asymmetric organometallic catalysis

By the 1960s, asymmetric organometallic catalysis started to attract the attention of many synthetic organic chemists. In 1961, Natta polymerized benzofurane using an $AlCl_3$/phenylalanine catalyst to produce optically active polymer.[1] In 1966, Nozaki, Noyori et al. introduced the first example of organometallic asymmetric catalysis through the cyclopropanation of different alkenes using chiral salen-copper complex catalyst.[2] In the same year, Wilkinson discovered a rhodium catalyst ($[RhCl(PPh_3)_3]$) which was used to catalyze the homogenous hydrogenation of alkenes.[3] Two years later, Knowles and Horner individually modified Wilkinson's catalyst with a chiral monodentate phosphine **1-1** for asymmetric catalytic hydrogenation (**Figure 1-1**).[4] Although the best enantioselectivity was only 15%, this study showed that an achiral catalyst can be converted into a chiral catalyst simply by ligand exchange using chiral ligands. Based on this successful achievement, further ligand modification of chiral monodentate phosphine **1-1** was done and more efficient ligands were synthesized. Among them, methylcyclohexyl-*o*-anisylphosphine (**CAMP**) gave impressive results in many cases and was used as the first chiral ligand in the industrial production of L-DOPA, an anti-Parkinson's drug.[5]

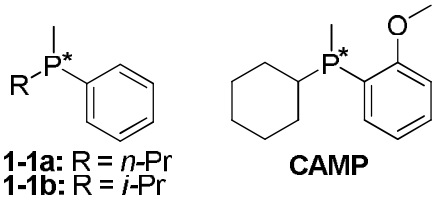
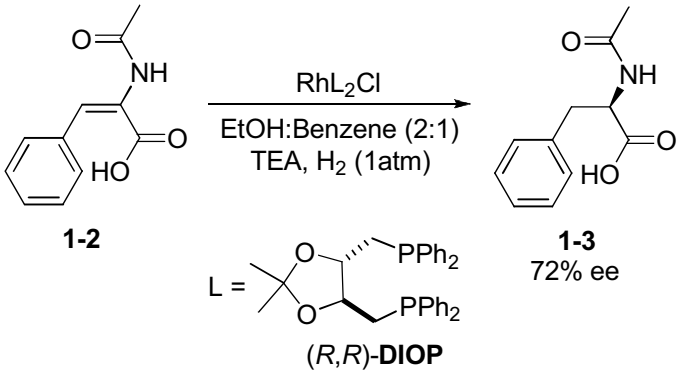


Figure 1-1. Chiral monodentate phosphine ligands

In 1971, Kagan developed a chiral bidentate phosphine ligand, diphenylphosphino(dimethyl))dioxolane (**DIOP**) for the asymmetric hydrogenation of the α-acetoamidocinnamic acid **1-2**, affording the (*R*)-*N*-acetylphenylalanine in 72% ee (**Scheme 1-1**).[6] The good enantioselectivity induced by (*R*,*R*)-**DIOP** demonstrated that the chirality of a chiral catalyst is not necessary to be on the chelating atom (eg. phosphorus) to give the product in good enantiomeric excess.



Scheme 1-1. Asymmetric hydrogenation of the α-acetoamidocinnamic acid **1-2** using (*R*,*R*)-**DIOP**

Inspired by the impressive results accomplished by using **DIOP** ligand, chemists started to switch their attention from monodentate ligands to bidentate ligands. Thus, a variety of diphosphane ligands, especially C_2-symmetric ones, such as **DIPAMP**[7], **BINAP**[8] and **DuPHOS**[9] were developed to afford excellent enantioselectivity for asymmetric hydrogenation of different types of prochiral substrates. These ligands dominated the field of asymmetric catalysis for several decades (**Figure 1-2**).[10]

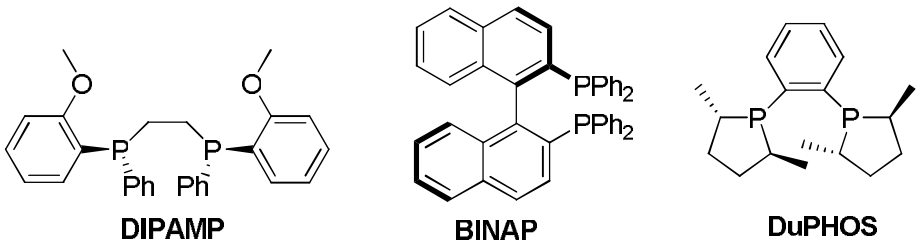


Figure 1-2. Chiral bidentate phosphine ligands

In 1980, two dramatic breakthroughs in asymmetric catalysis were published. One was the asymmetric epoxidation of allylic alcohols using diethyl tartrate-titanium complex catalyst discovered by Katsuki and Sharpless,[11] and the other was the application of asymmetric hydrogenation using **BINAP**-rhodium complexes by Noyori.[8] To date, both catalytic reactions are still very useful in asymmetric synthesis because of their wide application and high enantioselectivity. In 2001, Knowles, Noyori, and Sharpless received a Nobel Prize in recognition of their contributions to asymmetric synthesis.

§ 1.2 Development of a library of fine-tunable chiral biphenol-based, monodentate phosphorus ligands and their applications to asymmetric catalysis

Although bidentate phosphine ligands have shown excellent efficacy in some asymmetric transformations, the diversity of the ligands was limited due to the tedious synthetic route and difficult modification of the bidentate ligand. With these drawbacks, the application of bidentate ligands in different types of asymmetric reactions is difficult. Therefore, to investigate the asymmetric synthesis more efficient, the most efficient way is to develop a ligand library which is easy to synthesize and finely tunable to a certain reaction. Along this line, many monodentate phosphorus ligand libraries have been developed, due to their straightforward syntheses and fine-tunable capability. For example, in 1998, Alexakis and co-workers used commercially available TADDOL to synthesize monodentate phosphorus ligands **(Figure 1-3)**, and utilized them with copper (II) triflate to catalyze asymmetric conjugate addition of diethyl zinc to enones, achieving a 96 % ee.[12]

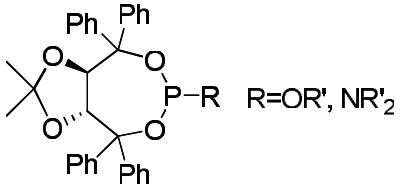


Figure 1-3. Monophosphorus Ligands based on (-)-**TADDOL**

Futhermore, Reetz and Feringa used monodentate ligands derived from commercially available, enantiopure BINOL **(Figure 1-4)** with a rhodium (I) complex to catalyze the hydrogenation of methyl-2-acetamido acrylate with 99 % ee.[13]

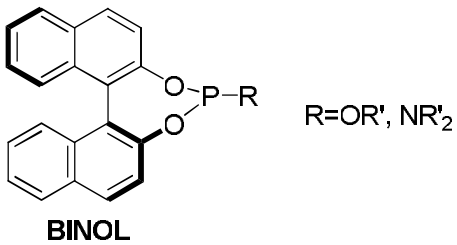


Figure 1-4. Monophosphorus Ligands based on (*S*)-**BINOL**

Based on the successful examples mentioned above, new classes of monodentate phosphorous ligands based on the biphenol backbone have been developed in the Ojima group from 2003 (**Figure 1-5**). The biphenol-based monophosphorous ligands have three adjustable positions which play different roles in asymmetric synthesis. The 6 and 6'-dimethyl groups make biphenol-based ligands more configurationally stable compared to the corresponding chiral BINOLs because of steric-restricted rotation.[14] The 3 and 3' substituents of biphenol-based ligands may substantially affect the catalytic activity and enantioselectivity, depending on their steric or electronic properties.[14-15] Finally, the 5 and 5' substituents of biphenol-based ligands can be modified for recovery and recycling of catalyst.[16] Those modifiable positions have led us to explore many specific asymmetric reactions utilizing the biphenol-based monophosphorous ligands.

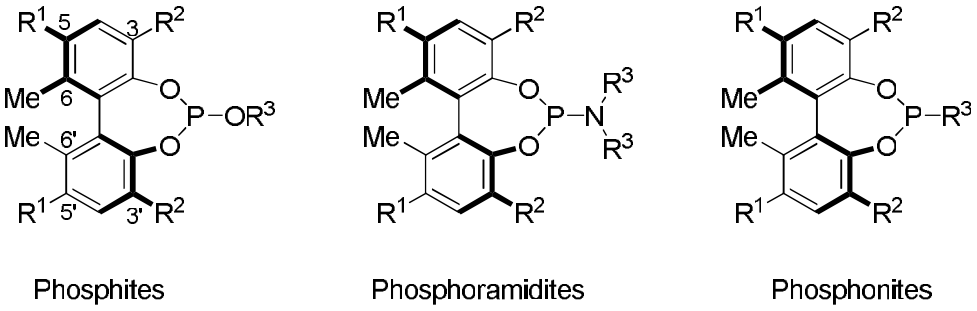


Figure 1-5. Biphenol-based monodentate phosphorus ligand libraries

In 2003, Ojima and co-workers described the development of a new class of readily accessible biphenol-based chiral monophosphite ligands (**Figure 1-6**) and their application to the Rh(I)-catalyzed asymmetric hydrogenation of dimethyl itaconate **1-4** (**Scheme 1-2**).[14]

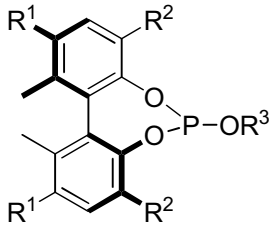
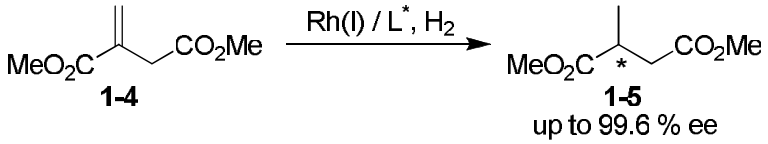


Figure 1-6. (*S*)-Biphenol-based Monophosphite Ligands

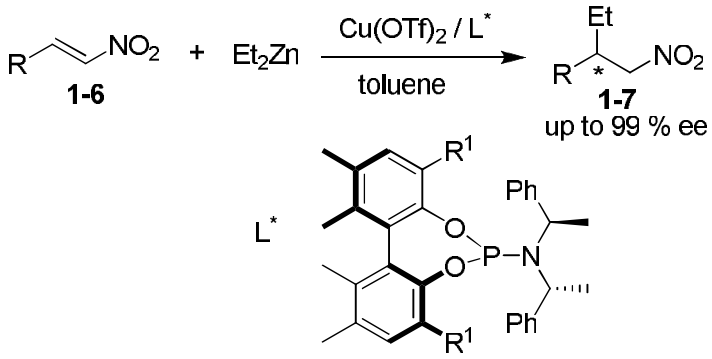


1-4 **1-5**

up to 99.6 % ee

Scheme 1-2. Rh(I)-catalyzed asymmetric hydrogenation of dimethyl itaconate **1-4**

Furthermore, in 2004, Ojima et al. used biphenol-based chiral monophosphoramidite ligands with copper (II) precatalyst to catalyze the asymmetric conjugate addition of diethyl zinc to nitroalkenes **1-6** with enantioselectivity up to 99 % (**Scheme 1-3**).[15a]



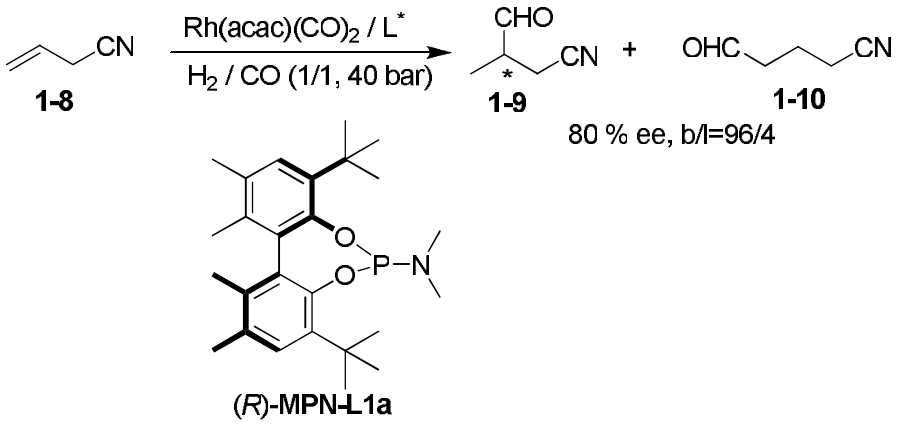
1-6 **1-7**

up to 99 % ee

Scheme 1-3. Asymmetric conjugate addition of diethyl zinc to nitroalkenes **1-6**

Also, in the same year, the Ojima group utilized a family of biphenol-based chiral monophosphoramidite ligands with Rh (I) complex to catalyze asymmetric hydroformylation of allyl cyanide **1-8** under hydrogen and carbon monoxide gases. Among our novel phosphoramidite ligands with the facile fine-tuning capability, biphenol-based monophosphoramidite with *tert*-butyl substitutes at the 3,3' positions of biphenol gave good regioselectivity and enantioselectivity (**Scheme 1-4**).[15b]

Moreover, Ojima et al. also synthesized a family of biphenol-based chiral monophosphoramidite ligands and the one with unsymmetrical chiral amine on the phosphorus atom of monophosphoramidite (**Figure 1-7**) was used in the Pd-catalyzed asymmetric allylic alkylation towards the preparation of (+)-γ-lycorane to afford (+)-γ-lycorane with > 99 % ee (**Scheme 1-5**).[15c]



Scheme 1-4. Asymmetric hydroformylation of allyl cyanide **1-8**

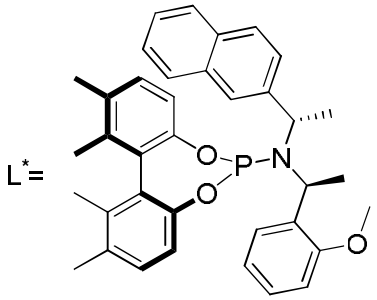
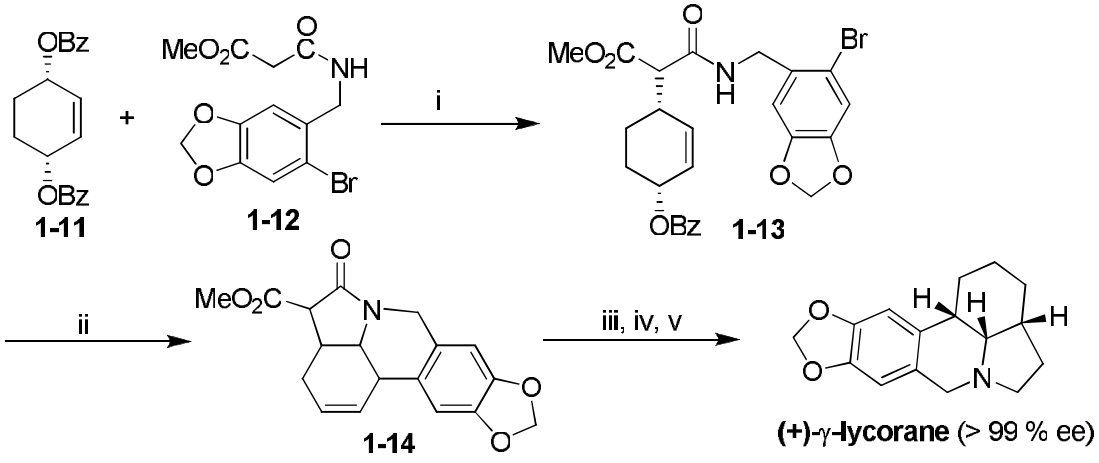


Figure 1-7. Biphenol-based chiral monophosphoramidite ligand

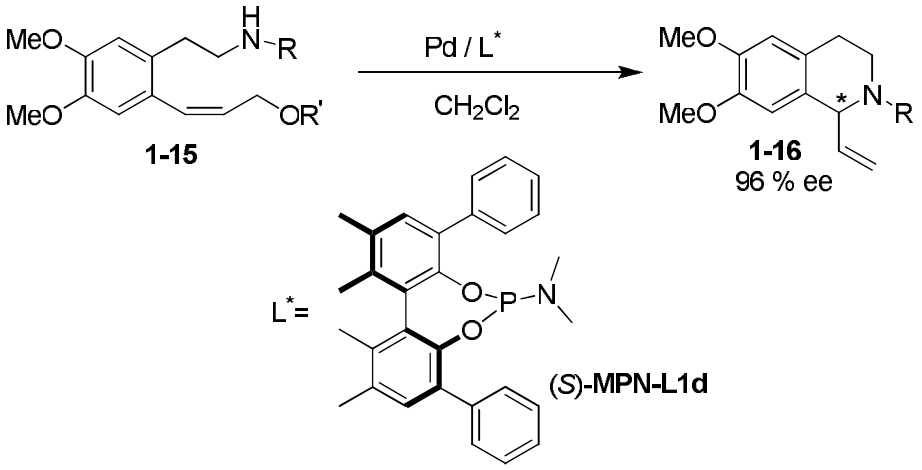


(i) $Pd(OAc)_2$, L*, LDA, THF/CH_3CN; (ii) $Pd(OAc)_2$-dppb, NaH, DMF, then $Et(i\text{-}Pr)_2N$,

(iii) NaCl, $DMSO/H_2O$; (iv) Pd/C, H_2, MeOH; (v) $LiAlH_4$

Scheme 1-5. Total synthesis of (+)-γ-lycorane via asymmetric allylic alkylation

The asymmetric synthesis of 6,7-dimethoxy-1-vinyltetrahroisoquinoline through Pd-catatalyzed intramolecular allylic amination of 3-(amidoethylphenyl)prop-2-enyl carbonates **1-15** was also studied by Ojima et al. using a library of fine-tunable monophosphoramidite ligands in 2007. Excellent enantiopurity (up to 96 %) and 100 % product selectivity were achieved (**Scheme 1-6**).[17]



Scheme 1-6. Pd-catatalyzed intramolecular asymmetric allylic amination

§ 1.3 Development of a library of fine-tunable chiral biphenol-based, bidentate phosphorus ligands and their applications to asymmetric catalysis

During the development of monodentate chiral phosphorus ligands, a number of biaryl atropisomeric ligands have also been explored as effective bidentate ligand system. The ligands have proved to be useful for asymmetric transformations such as hydrogenation and allylic substitution reactions.[18] **BINAP** possessing a binaphthalene skeleton is the most useful bidentate phosphorus ligand which can form a 7-membered ring with a transition metal (**Figure 1-10**). **BINAPO**, another common bidentate ligand that has an addition oxygen atom between the C-P bonds compared to **BINAP**, forms a 9-membered ring with a transition metal (**Figure 1-10**). The formation of the large ring has advantages and disadvantages in asymmetric catalysis. For example, due to its conformational flexibility, **BINAPO** is not as effective as **BINAP** for certain asymmetric hydrogenation reactions. However, taking advantage of the large bite angle (P-M-P) in the 9-membered chelating ring with a transition metal,[19] **BINAPO** has proven to be efficient in asymmetric allylic substitutions.[20]

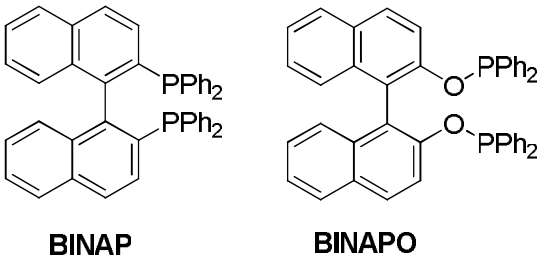


Figure 1-8. Biaryl atropisomeric ligands

In 2008, Ojima et al. developed of a new class of easily accessible biphenol-based chiral diphosphonite ligands (**BOP**) based on the concept of the **BINAPO** ligand (**Figure 1-11**). We expected that the modification of the 3, 3' positions of the biphenol scaffold can help to increase the enantioselectivity. Indeed, this **BOP** ligand library can be applied to Pd-catalyzed intermolecular asymmetric allylic amination to give up to 96% ee for the key intermediate of *Strychnos* indole alkaloids for which Mori et al. were only able to achieve 84% ee using **BINAPO** in 2003 (**Scheme 1-7**).[22]

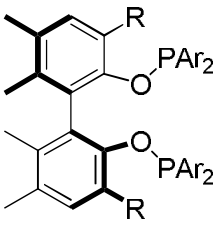
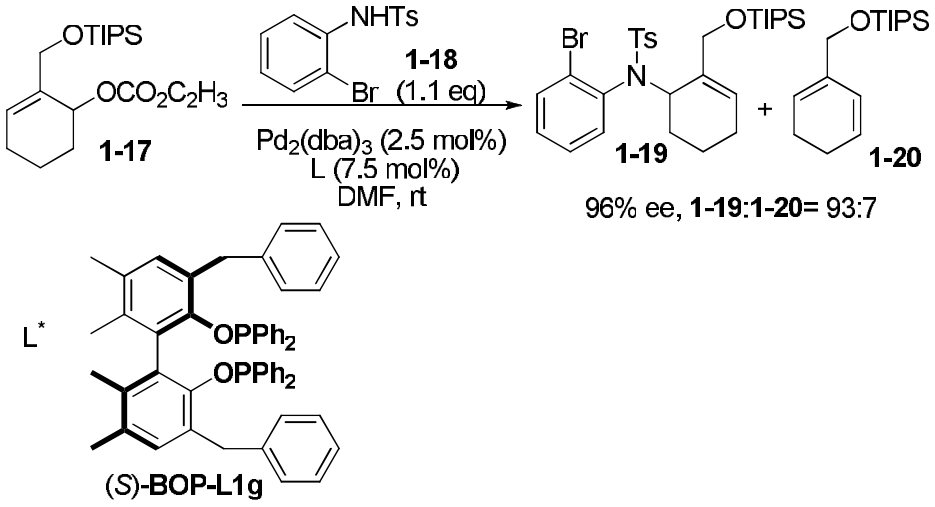


Figure 1-9. Biphenol-based bidentate phosphorus (**BOP**) ligand library



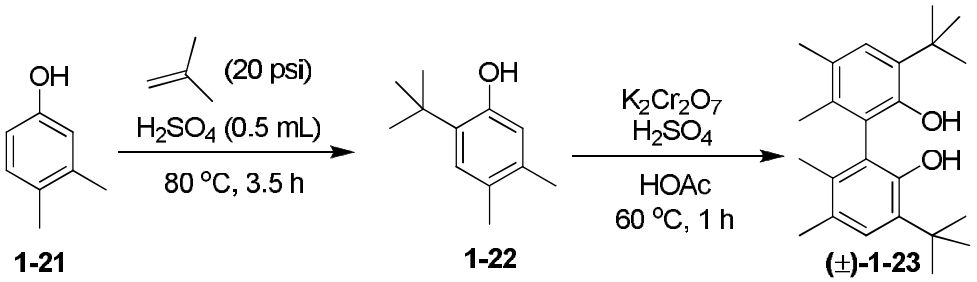
Scheme 1-7. Pd-catalyzed intermolecular asymmetric allylic amination

§ 1.4 Results and discussion

§ 1.4.1 Synthesis of enantiopure biphenol derivatives

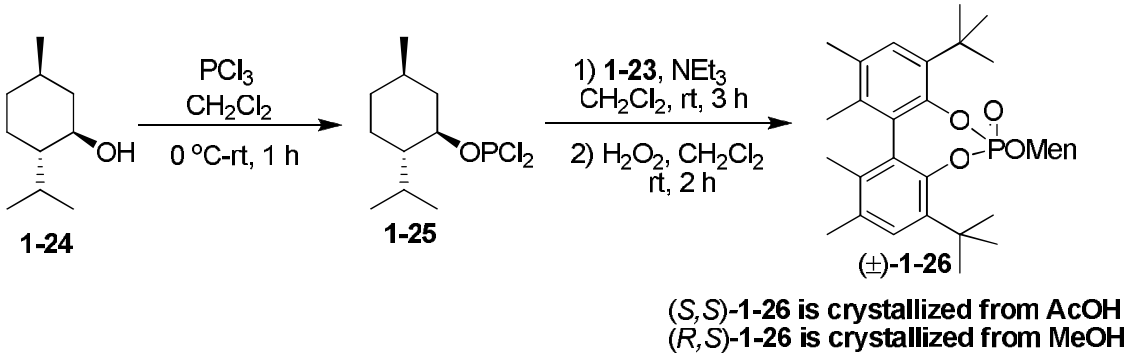
§ 1.4.1.1 (*S*)- and (*R*)-3,3'-Di-*tert*-butyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol

To prepare enantiopure biphenols and monophosphoramidites with fine-tunable capability, racemic 3,3'-di-*tert*-butyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol (±)-**1-23** was first synthesized.[23] Friedal-Craft alkylation of 3,4-dimethyl phenol **1-21** with isobutene under acidic condition gave 2-*tert*-butyl-4,5-dimethyl-phenol **1-22;** followed by oxidative coupling in the presence of potassium dichromate to afford methyl and *tert*-butyl substituted biphenol (±)-**1-23** in 60 % isolated yield after two steps (**Scheme 1-8**).



Scheme 1-8. Synthesis of racemic biphenols (±)-**1-23**

To obtain enantiomerically pure biphenols, diastereomers **1-26** were synthesized (**Scheme 1-9**). (-)-menthol **1-24** was treated with phosphorus trichloride in dichloromethane to give dichlorophosphite **1-25**. The addition of racemic biphenols **1-23** in the presence of triethylamine to **1-25** gave the corresponding diastereomeric phosphates **1-26**.

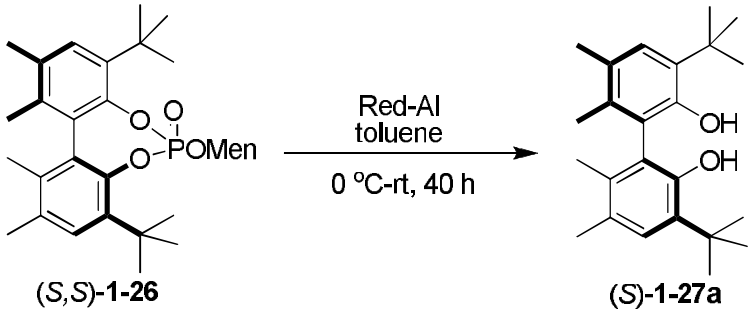


Scheme 1-9. Synthesis of diastereomers (*S,S*)-**1-26** and (*R,S*)-**1-26**

(*S,S*)-based and (*R,S*)-based diastereomers **1-26** were recrystallized from acetic acid and methanol respectively. ^{31}P NMR was utilized to determine diastereomeric purity; only one single

peak was shown in each spectrum [δ -4.87 ppm for (*R,S*)-**1-26** and -4.34 ppm for (*S,S*)-**1-26**] indicating both compounds are diastereomerically pure.[23]

The reduction of either isomer [(*S,S*)-**1-26** or (*R,S*)-**1-26**] using Red-Al gave enantiomerically pure 3,3'-di-*tert*-butyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*S*)-**1-27a** or (*R*)-**1-27a**) in 80 % and 88 % yield respectively (**Scheme 1-10**).[14]

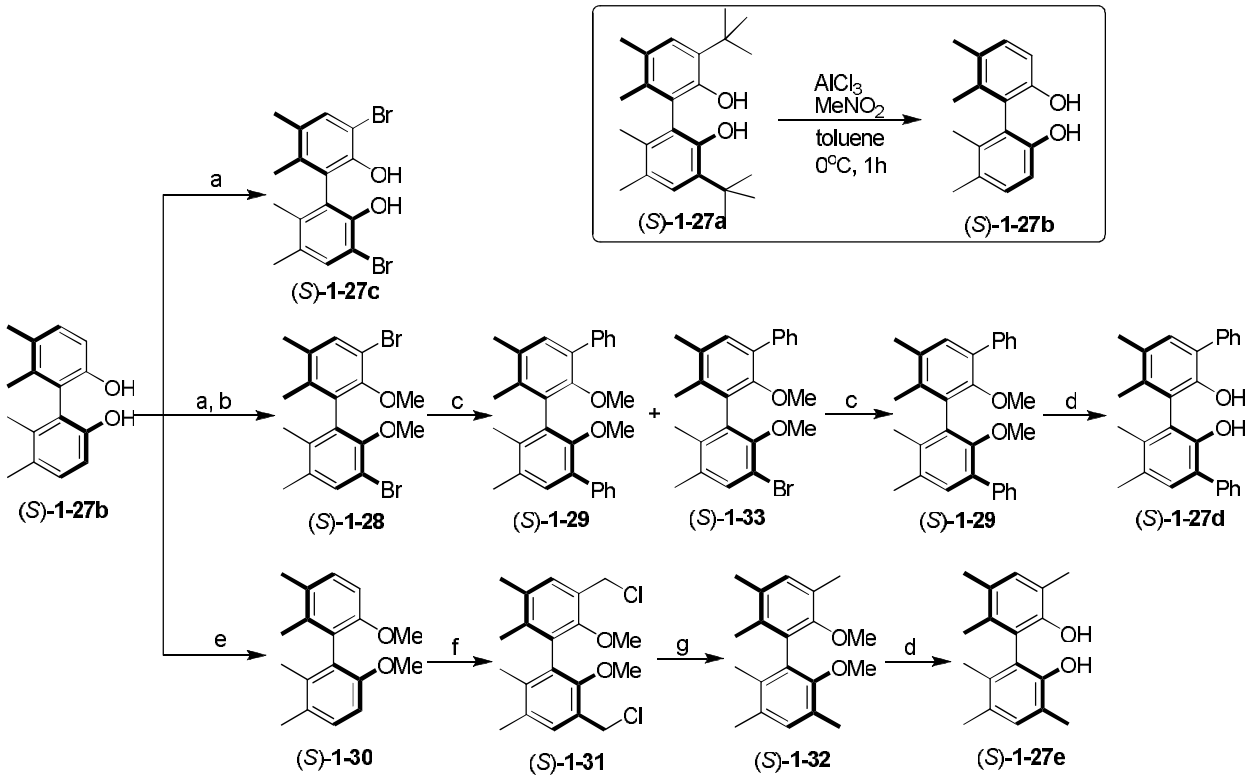


Scheme 1-10. Synthesis of enantiopure biphenol (*S*)-**1-27a**

§ 1.4.1.2 (*S*)- and (*R*)-5,5',6,6'-Tetramethyl-1,1'-biphenyl-2,2'-diol and modification of enantiopure biphenols at 3 and 3' positions

After enantiopure biphenols (*S*)-**1-27a** and (*R*)-**1-27a** were obtained, many chemical modifications were achieved using different reaction conditions (**Scheme 1-11**). The *tert*-butyl groups at 3 and 3' positions of (*S*)- or (*R*)-**1-27a** were replaced by treating with aluminum trichloride in the presence of nitromethane and toluene via Friedel-Crafts transformation at 0 °C for 1 hour to produce (*S*)- or (*R*)-**1-27b** in 95 % and 88 % isolated yield respectively.[14]

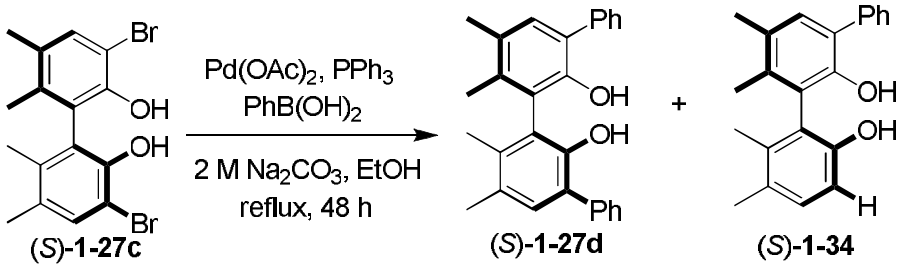
Dibromo substituted biphenols, (*S*)- and (*R*)-**1-27c**, were obtained by the bromination of (*S*)- and (*R*)-**1-27b** in almost quantitative yield. Methyl protection of (*S*)- and (*R*)-**1-27c** provided diether adducts (*S*)- and (*R*)-**1-28**, respectively, for Suzuki coupling.[14] In the Suzuki coupling reaction, the reported catalytic condition[14] could not catalyze this reaction to completion. The ^{1}H NMR showed two sets of peaks; one set corresponds to the desired products (*S*)- and (*R*)-**1-29**, and the other set corresponds to unreacted, mono-phenyl and mono-bromo biphenol (*S*)- and (*R*)-**1-33**. For this reason, another portion of catalyst had to be added to complete the reaction to gave (*S*)- and (*R*)-**1-29** in 90-95 % isolated yield. The phenyl substituted biphenols (*S*)- and (*R*)-**1-27d** were synthesized from deprotection of (*S*)- and (*R*)-**1-29**, respectively, by treating with tribromoborane in dichloromethane at 0 °C for 2 hours. Both reactions gave 80-85 % isolated yield.[14]



(a) Br_2, $CHCl_3$, rt, 1.5h; (b) Me_2SO_4, Bu_4HSO_4, KOH, CH_2Cl_2-H_2O (1:1), rt, o.n; (c) $Pd(PPh_3)_4$, $PhB(OH)_2$, $NaHCO_3$, DME-H_2O, 95 °C, 16 h; (d) BBr_3, CH_2Cl_2, 0 °C, 2 h; (e) Me_2SO_4, $(Bu_4N)I$, KOH, CH_2Cl_2-H_2O (1:1) rt, o.n.; (f) H_3PO_4, HCl, AcOH, CH_2O, 90°C, 42h; (g) $LiAlH_4$, THF, reflux, 3.5h.

Scheme 1-11. Synthesis of enantiopure biphenols (*S*)-**1-27b** to (*S*)-**1-27e**

In addition to the above method to synthesize phenyl-substituted biphenol (*S*)-**1-27d**, an alternative route was also used to afford this compound in fewer synthetic steps (**Scheme 1-12**). In this synthesis, direct Suzuki coupling proceeded without the protection of biphenol.[24] However, this one-step synthesis gave only 42 % of (*S*)-**1-27d** which is a much lower yield compared to the previous synthetic method (65 % in three steps) and 15 % of byproduct (*S*)-**1-34** from possible reductive elimination of phenyl moiety and hydrogen. Furthermore, the reaction time of this method was 48 hours which was almost equal to the total reaction time of previous method. For this reason, steps shown in **Scheme 1-11** are still the best route to afford (*S*)-**1-27d**.

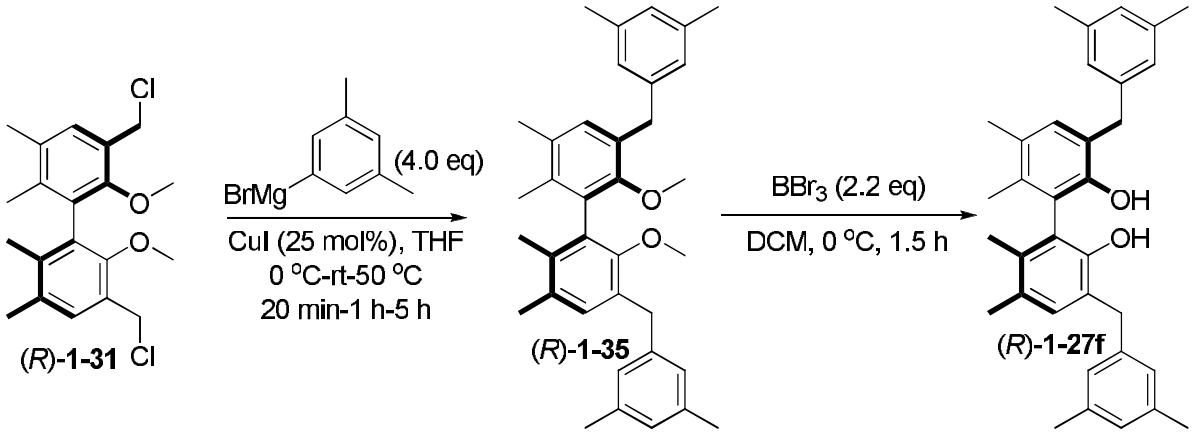


Scheme 1-12. Alternative route towards the synthesis of enantiopure biphenol (*S*)-**1-27d**

Finally, enantiopure biphenols with methyl-substitutents at 3,3' positions, (*S*)- and (*R*)-**1-27e**, were synthesized in four steps respectively. Methyl-protection of enantiopure biphenols (*S*)- and (*R*)-**1-27a** were first employed to give ether adducts (*S*)- and (*R*)-**1-30**, respectively, in up to 85 % yield followed by chloromethylation to provide (*S*)- and (*R*)-**1-31** in 90 % isolated yield. This chloromethyl substituted biphenol was then treated with $LiAlH_4$ to afford reduced product (*S*)- and (*R*)-**1-32** followed by deprotection with tribromoborane to achieve enantiopure, methyl-substituted biphenol (*S*)- and (*R*)-**1-33**.[14]

§ 1.4.1.3 Synthesis of (*R*)-3,3'-bis(substituted-benzyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diols

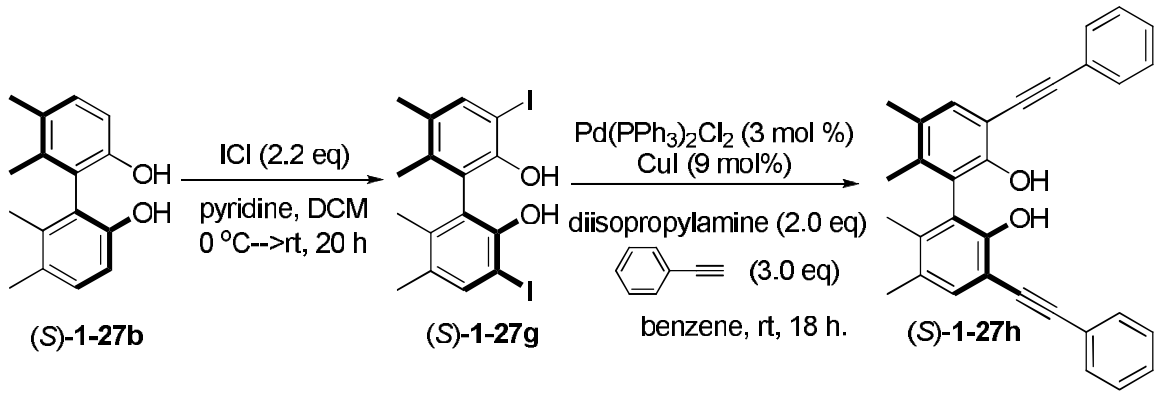
This series of biphenols was prepared from the chloromethyl substituted and methyl protected biphenol, (*R*)-**1-31,** coupling with corresponding aryl Grignard reagents generated *in situ* using CuI as the coupling reagent and followed by the subsequent removal of the methyl group with boron tribromide (**Scheme 1-13**). Both reactions went smoothly and excellent yields were obtained in each step.



Scheme 1-13. Synthesis of enantiopure biphenol (*R*)-**1-27f**

§ 1.4.1.4 Synthesis of (*S*)-3,3'-diiodo-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol and (*R*)-5,5',6,6'-tetramethyl-3,3'-bis(phenylethynyl)-1,1'-biphenyl-2,2'-diol

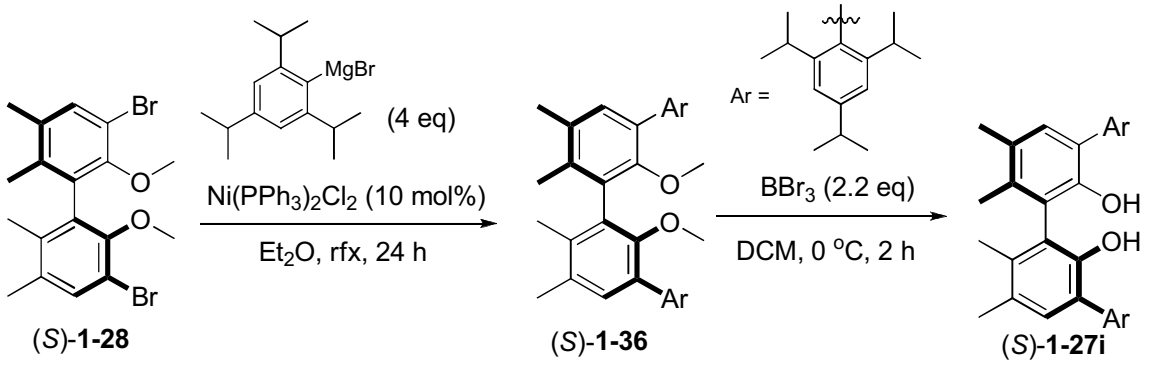
The enantiopure (*S*)-3,3'-diiodo-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*S*)-**1-27g**) was synthesized from (*S*)-**1-27b** using ICl as the iodination agent in 73% isolated yield. Next, the synthesis of (*S*)-**1-27h** via Sonogashira coupling of unprotected (*S*)-**1-27g** with phenyl acetylene using diisopropylamine as the base gave the desired product (*S*)-**1-27h** in 54% isolated yield (**Scheme 1-14**).



Scheme 1-14. Synthesis of enantiopure biphenols (*S*)-**1-27g** and (*S*)-**1-27h**

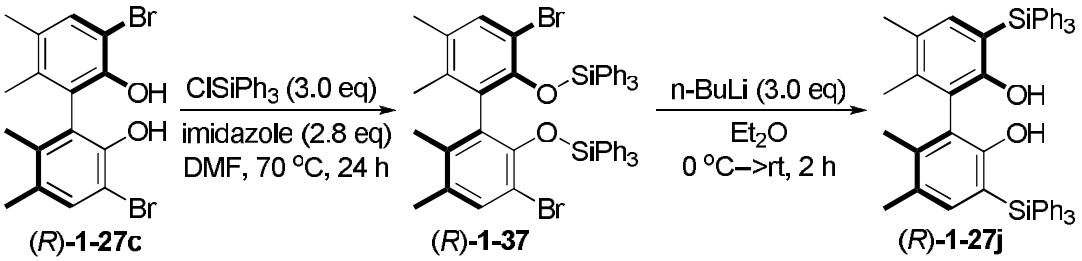
§ 1.4.1.5 Synthesis of (*S*)-3,3'-di(2,4,6-triisopropyl phenyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol and (*R*)- 3,3'-di(triphenyl silyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol

For the synthesis of (*S*)-**1-27i**, (*S*)-**1-28** was first coupled with the corresponding aryl Grignard reagent using 10 mol% of $Ni(PPh_3)_2Cl_2$ to introduce triisopropyl phenyl substituted diether adduct (*S*)-**1-36** and followed by the subsequent removal of the methyl group with boron tribromide gave the desired biphenol (*S*)-**1-27i** in moderate yield after two steps (**Scheme 1-15**).



Scheme 1-15. Synthesis of enantiopure biphenols (*S*)-**1-27i**

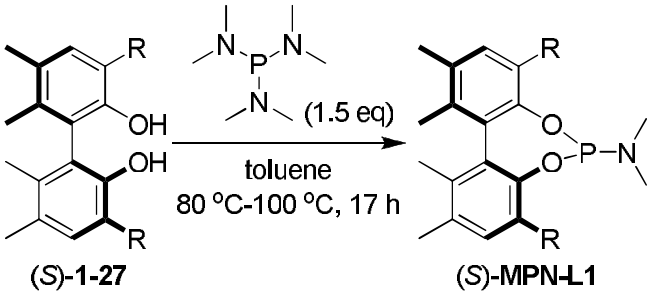
For the synthesis of (*R*)-**1-27j**, (*R*)-**1-27c** was first protected with chlorotriphenylsilane in the presence of imidazole to give triphenyl silyl substituted diether adduct (*R*)-**1-37**, followed by silane rearrangement to give desired the biphenol (*R*)-**1-27j** in good yield after two steps (**Scheme 1-16**).



Scheme 1-16. Synthesis of enantiopure biphenols (*S*)-**1-27j**

§ 1.4.2 Synthesis of enantiopure biphenol-based monophosphoramidite ligands

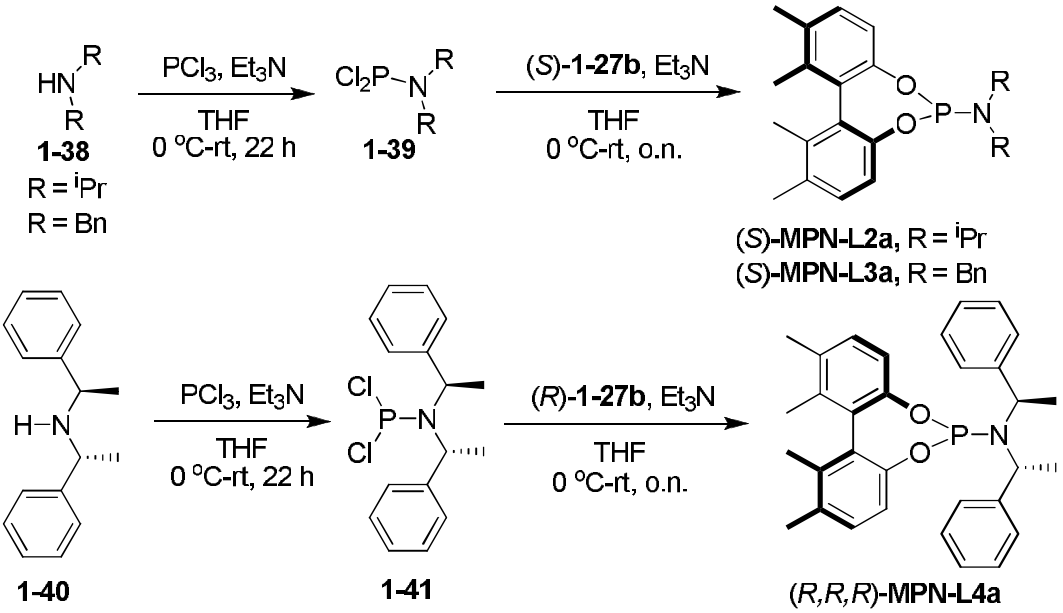
A large enantiopure biphenol-based monophosphoramidite ligand library was previously developed in our laboratory. In general, two methods are used to synthesize those ligands (**Schemes 1-17** and **1-18**). When the amine moiety is dimethyl amino group, commercially available hexamethylphosphorustriamide (HMPT) is used to react with enantiopure biphenols **1-7** to easily give the desired monophosphoramidite ligands in good to excellent yields (**Scheme 1-17**).[15b]



Scheme 1-17. Synthesis of **MPN** ligands with dimethyl amine moiety

When other amines are chosen as the amine moieties of the monophosphoramidite ligands, a more complicated synthetic method is used. In this method, secondary amine is treated with phosphorus trichloride to produce a dichlorophosphinoamine which is characterized by ^{31}P NMR. Then the resulting dichlorophosphinoamine reacts with enantiopure biphenol to afford

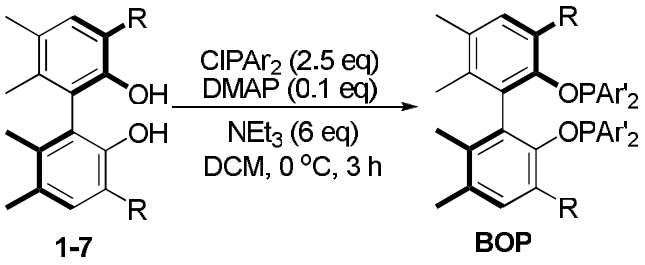
biphenol-based monophosphoramidite ligand in reasonable yield (**Scheme 1-18**).[15a, b]



Scheme 1-18. Synthesis of MPN ligands with other amine moieties (only the synthesis of (*S*)-**MPN-L2a**, (*S*)-**MPN-L3a** and (*R*,*R*,*R*)-**MPN-L4a** shown in the Scheme)

§ 1.4.3 Synthesis of enantiopure biphenol-based diphosphonite ligands

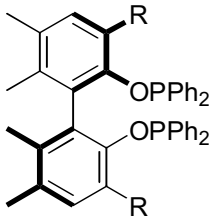
The 3,3'-disustituted-biphenol-based diphosphonite ligands (**BOP**) were synthesized following the synthetic protocol described for the BINAPO ligand (**Scheme 1-19**).[25] In the scheme, we have designed the **BOP** ligands to have fine-tuning capability at the 3,3' positions of the biphenol moiety and Ar groups on the phosphorus moieties.



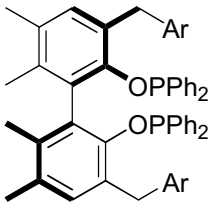
Scheme 1-19. General procedure of **BOP** ligand synthesis

The coupling reaction between biphenol and chlorodiarylphosphine ($ClPAr_2$) proceeded smoothly, affording the desired products in good to excellent yields after column chromatography on neutral/basic alumina or silica gel pretreated with NEt_3. The synthesized ligands are shown in **Figure 1-12**. Of these ligands, **BOP-L1a~i** and **L3a~b** have been

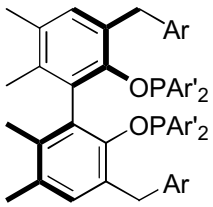
synthesized previously in the Ojima laboratory. Only **BOP-L2a~c** were newly synthesized by the author following the above procedure.



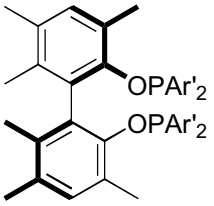
(*R*)-**BOP-L1a**: R= H
(*S*)-**BOP-L1b**: R= Me
(*R*)-**BOP-L1c**: R= Br
(*R*)-**BOP-L1d**: R= Ph



(*R*)-**BOP-L1e**: Ar = Ph
(*R*)-**BOP-L1f**: Ar = 4-MeC_6H_4
(*R*)-**BOP-L1g**: Ar = 3,5-$Me_2C_6H_3$
(*R*)-**BOP-L1h**: Ar = 4-*t*-BuC_6H_4
(*R*)-**BOP-L1i**: Ar = 1-Np



(*R*)-**BOP-L2a**: Ar' = 4-MeC_6H_4
(*S*)-**BOP-L2a**: Ar' = 4-MeC_6H_4
(*R*)-**BOP-L2b**: Ar' = 4-$MeOC_6H_4$
(*R*)-**BOP-L2c**: Ar' = 4-$CF_3C_6H_4$
Ar = 3,5-$Me_2C_6H_3$



(*R*)-**BOP-L3a**: Ar' = 4-MeC_6H_4
(*R*)-**BOP-L3b**: Ar' = 3,5-$Me_2C_6H_3$

Figure 1-10. BOP ligand library

§ 1.5 Conclusions

Enantiopure biphenol derivatives and their related monophosphoramidite, bidentate diphosphonite ligands were successfully synthesized in satisfied isolated yield. Those biphenol-based chiral ligands will be screened for a number of asymmetric transformations as described in later chapters to evaluate their efficacy in enantiopurity and reactivity.

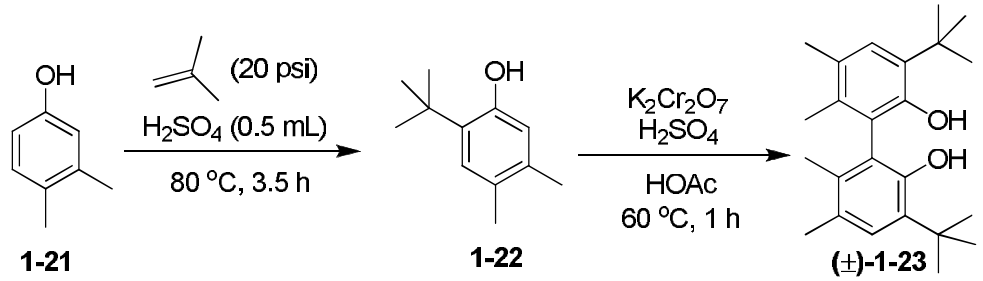
§ 1.6 Experimental section

General Methods: ^{1}H and ^{13}C and ^{31}P NMR were measured on a Varian Inova-500 NMR (500 MHz ^{1}H, and 125 MHz ^{13}C), a Varian Inova-400 NMR (400 MHz ^{1}H; 100 MHz ^{13}C; 162 MHz ^{31}P) or a Varian Gemini-2300 (300 MHz ^{1}H; 75 MHz ^{13}C; 121.5 MHz ^{31}P) spectrometer in a deuterated solvent using residual protons ($CHCl_3$: ^{1}H, 7.26 ppm; ^{13}C, 77.0 ppm. C_6H_6: ^{1}H, 7.15 ppm) as the internal standard or phosphoric acid as the external reference (^{31}P 0.00 ppm).

Analytical HPLC in reverse phase was carried out with a Shimadzu LC-2010A HPLC system using a Chiralpak AD-RH analytical column. Melting points were measured on a Thomas Hoover Capillary melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Helmer Model 241 polarimeter. TLC analyses were performed using Merck DC Alufolien 60F254 aluminum pre-coated silica gel plates. Flash column chromatography was carried out using Silicyle Silia*Flash*P60® silica gel (particle size 40–63 μm). High-resolution mass spectrometric analyses were carried out by Mass Spectrometry Laboratories, University of Illinois Urbana-Champaign, Urbana, IL or by ICB&DD at Stony Brook University. Unless otherwise noted, all reactions were carried out under argon or nitrogen atmosphere in oven-dried glassware using standard Schlenck techniques.

Materials: Solvents were reagents grade and freshly distilled before use. Tetrahydrofuran (THF) and dichloromethane (DCM) were dried and degassed using an Innovative Technology PureSolvTM solvent purification system. Acetonitrile was distilled from calcium hydride. Anhydrous *N,N*-dimethylformamide (DMF) was purchased from Acros and used without further purification. Other solvents were used without purification. Other chemicals and reagents were purchased from Sigma-Aldrich or Fisher Scientific and used without further purification unless otherwise noted.

Synthesis of 3,3'-di-*tert*-butyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol[14, 23]



1-21 **1-22** **(±)-1-23**

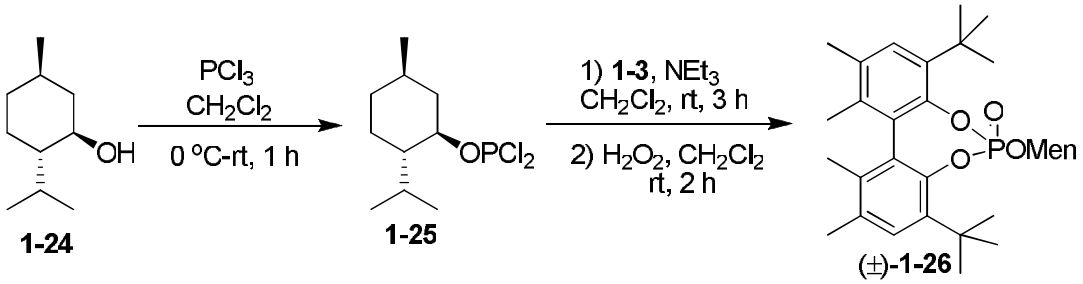
2-*tert*-Butyl-4,5-dimethylphenol (1-22)[23]

3,4-Dimethylphenol **1-21** (81.3 g, 0.66 mol) and concentrated sulfuric acid (0.5 mL) were added into a 300 mL autoclave with a glass liner and stirring bar. This autoclave was then pressurized with 2-methylpropene (20 psi) and heated to 80 °C for 3.5 h. The autoclave was opened and the mixture was analyzed by GC-MS (m/z = 178). This resulting crude was used in next step without any purification.

3,3'-Di-*tert*-butyl-5,5'-6,6'-tetramethyl-1,1'-diphenyl-2,2'-diol ((±)-1-23)[23]

Potassium dichromate (60 g, 0.204mol) dissolved in the solution of sulfuric acid (120 mL) and water (400 mL) was carefully added to an acetic acid (650 mL) solution of the crude **1-22** from the previous step. It was an exothermic reaction, and thus the reaction temperature reached around 60 °C. The reaction mixture was then stirred for an additional 45 min at 60 °C and cooled down to room temperature. The brown solid was filtrated and washed with water (250 mL x2) and MeOH (200 mL x3). The remaining solid was then stirred with methanol at 0 °C for 15 min and filtered again. The purified solid was dried *in vacuo* to give pure diol (±)-**1-23** as a white solid (71.8 g, 60 % for two steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (s, 18 H), 1.84 (s, 6 H), 2.27 (s, 6 H), 4.82 (s, 2 H), 7.15 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.9, 20.0, 29.6, 34.5, 121.0, 128.0, 128.7, 133.4, 134.1, 150.4. All data are in agreement with the literature values.[23]

Preparation and Resolution of (*R*)-1-26 and (*S*)-1-26[23]



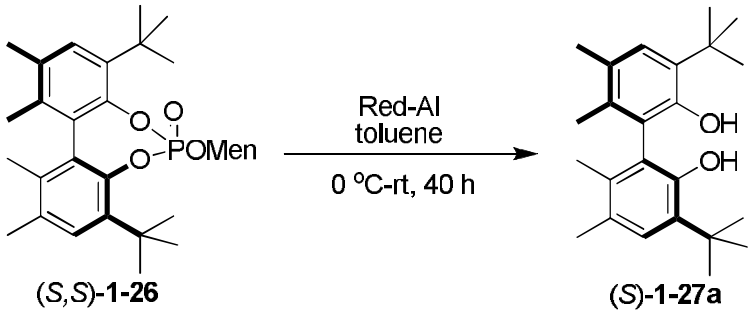
(*S,S*)-1-26 was crystallized from AcOH
(*R,S*)-1-26 was crystallized from MeOH

A solution of (*1R,2S,5R*)-(-)-menthol **1-24** (31.8 g, 202 mmol) in DCM (72 mL) was carefully added to a solution of phosphorus trichloride (41.6 g, 303 mmol, 1.5 eq) in DCM (144 mL) over 30 min at 0 °C. After this period of time, the ice bath was removed and the reaction mixture was kept at room temperature for another hour. The solvent and other volatile liquids were removed *in vacuo* to give the remaining oil **1-25**. This oil was then redissolved in DCM (108 mL) and a DCM (216 mL) solution of triethylamine (84.6 mL, 06 mmol, 3.0 eq) and (±)-**1-23** (71.8 g, 202 mmol) was slowly added over 50 min. After an additional 2 h, the solution was filtered and H_2O_2 (35 %, 123 mL) was added slowly with stirring. This biphasic mixture was vigorously stirred overnight. The organic layer was separated, washed with water (200 mLx2) and brine (200 mL), and dried over $MgSO_4$. The solution was filtered to remove $MgSO_4$ and then concentrated by rotary evaporation to give a white solid. The solid was further dried *in vacuo* to

give (±)-**1-26**: ^{31}P NMR (121.5 MHz, $CDCl_3$) -4.87 for (*R*,*S*)-**1-26** , -4.34 for (*S*,*S*)-**1-26**.

The diastereomeric mixture of phosphate was dissolved in a minimum amount of hot acetic acid (~ 160 mL) and white crystals were formed after 24 h at room temperature. These crystals were collected by filtration and washed with cold acetic acid (50 mL x2). The isolated crystals were then dried *in vacuo* to afford crude (*S*,*S*)-**1-26**. It was further recrystallized twice from hot acetic acid to give pure (*S*,*S*)-**1-26** (29.8 g, >99 % de, corresponding to 57 % of (*S*,*S*)-diastereomer). The remaining liquid from the first crystallization was concentrated *in vacuo* to give (*R*,*S*)-**1-26**. The crude (*R*,*S*)-**1-26** was recrystallized from hot MeOH (~200 mL). White crystals formed on cooling to 0 °C with ice bath. These crystals were recrystallized again from hot MeOH to afford pure (*R*,*S*)-**1-26** (25.1 g, >99 % de, corresponding to 48 % of (*R*,*S*)-diastereomer). All data are in agreement with the literature values.[23]

(*S*)-3,3'-Di-*tert*-butyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*S*)-1-27)[23]



(*S*,*S*)-**1-26** (*S*)-**1-27a**

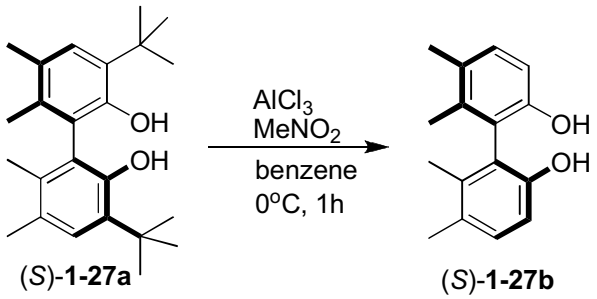
Resolved (*S*,*S*)-**1-26** (29.8 g, 53.8 mmol) was dissolved in toluene (250 mL) in a 2 L round bottomed flask equipped with an addition funnel. Red-Al® (65.0 mL, 65 % wt. in toluene) was added to an addition funnel and then added dropwise to (*S*)-**1-26** solution with continuous gas evolution at 0 °C. After this step, the reaction mixture was stirred at room temperature for 40 h and then quenched with water (90 mL) followed by bleach (6 %, 90 mL). The slurry was filtered through Celite and washed with toluene (250 mL). The remaining bi-layer solution was separated by extraction funnel. The toluene layer was washed with bleach (6 %, 200 mL) and brine (200 mL) and then dried over $MgSO_4$. Magnesium sulfate was removed by filtration and toluene by vacuum distillation to give a white solid. The side product menthol was removed by washing with cold MeOH several times until no minty odor remained. Biphenol (*S*)-**1-27a** was collected by filtration and dried *in vacuo* to give a white solid (15.2 g, 80 %). The optical purity of (*S*)-**1-27a** was examined by ^{31}P NMR of the (*S*)-biphenPMen* derivative (Phophite): mp

165.0-167.0 °C (lit.[23] mp 165.0-167.0 °C); $[\alpha]_D^{23}$ -76.9 (*c* 0.91, DCM) [lit. $[\alpha]_D^{22}$ -72.8 (*c* 1.25, DCM)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (s, 18 H), 1.83 (s, 6 H), 2.26 (s, 6 H), 4.81 (s, 2 H), 7.14 (s, 2 H). All data were in agreement with the literature values.[23] The reduction of (*R*,*S*)-**1-26** to (*R*)-**1-27** followed the same procedure.

(*R*)-3,3'-Di-*tert*-butyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*R*)-1-27a)[23]

(*R*)-**1-27a** was obtained as a white solid (13.4 g, 83 %): $[\alpha]_D^{23}$ +66.3 (*c* 0.92, DCM) [lit.[23] $[\alpha]_D^{22}$ +74.0 (CH_2Cl_2, 1.69)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (s, 18 H), 1.83 (s, 6 H), 2.25 (s, 6 H), 4.81 (s, 2 H), 7.15 (s, 2 H). All data are in agreement with the literature values.[23]

(*S*)-5,5',6,6'-Tetramethyl-1,1'-biphenyl-2,2'-diol ((*S*)-1-27b)[14]



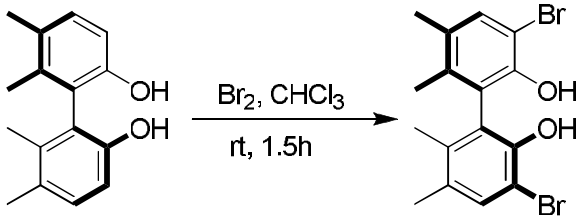
(*S*)-**1-27a** (*S*)-**1-27b**

A solution of $AlCl_3$ (6.67 g, 50.0 mmol) in benzene (40 mL) and nitromethane was added dropwise to a solution of (*S*)-**1-27a** (10.6 g, 29.8 mmol) in toluene (120 mL) at 0 °C over a period of 30 min. After this step, the reaction mixture was stirred another 30 min at 0 °C. The reaction was then quenched with water (50 mL). The aqueous layer was extracted with Et_2O (30 mL x3). The collected organic layers were washed with brine (50 mL) and then dried over Na_2SO_4. The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure to give crude (*S*)-**1-27b**. This crude product was then recrystallized from hexanes-CH_2Cl_2 to give pure (*S*)-**1-27b** as a cotton-like white solid (6.90 g, 95 %): mp 199.0-200.5 °C (lit.[14] mp 198.5-200.0 °C); $[\alpha]_D^{23}$ -53.8 (*c* 0.90, DCM) [lit.[14] $[\alpha]_D^{22}$ -53.3 (*c* 0.90 , DCM)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.90 (s, 6 H), 2.26 (s, 6 H), 4.56 (s, 2 H), 6.81 (d, 2 H, *J* = 8.1 Hz), 7.12 (d, 2 H, *J* = 8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.3, 19.8, 112.6, 120.2, 129.1, 131.2, 136.9, 151.8. All data are in agreement with the literature values.[14] The reaction of (*R*)-**1-27a** to (*R*)-**1-27b** followed the same procedure.

(*R*)-**5,5',6,6'-Tetramethyl-1,1'-biphenyl-2,2'-diol ((*R*)-1-27b)**[14]

(*R*)-**1-27b** was obtained as a cotton-like white solid (2.54 g, 88 %): mp 199.0-200.5 °C (lit.[14] mp 198.5-200.0 °C); $[\alpha]_D^{23}$ +54.4 (*c* 1.25, DCM) [lit.[14] $[\alpha]_D^{22}$ +54.0 (*c* 1.16, DCM)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.90 (s, 6 H), 2.26 (s, 6 H), 4.51 (s, 2 H), 6.82 (d, 2 H, *J* = 8.1 Hz), 7.13 (d, 2 H, *J* = 8.1 Hz). All data are in agreement with the literature value.[14]

(*S*)-**3,3'-Dibromo-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*S*)-1-27c)**[14]



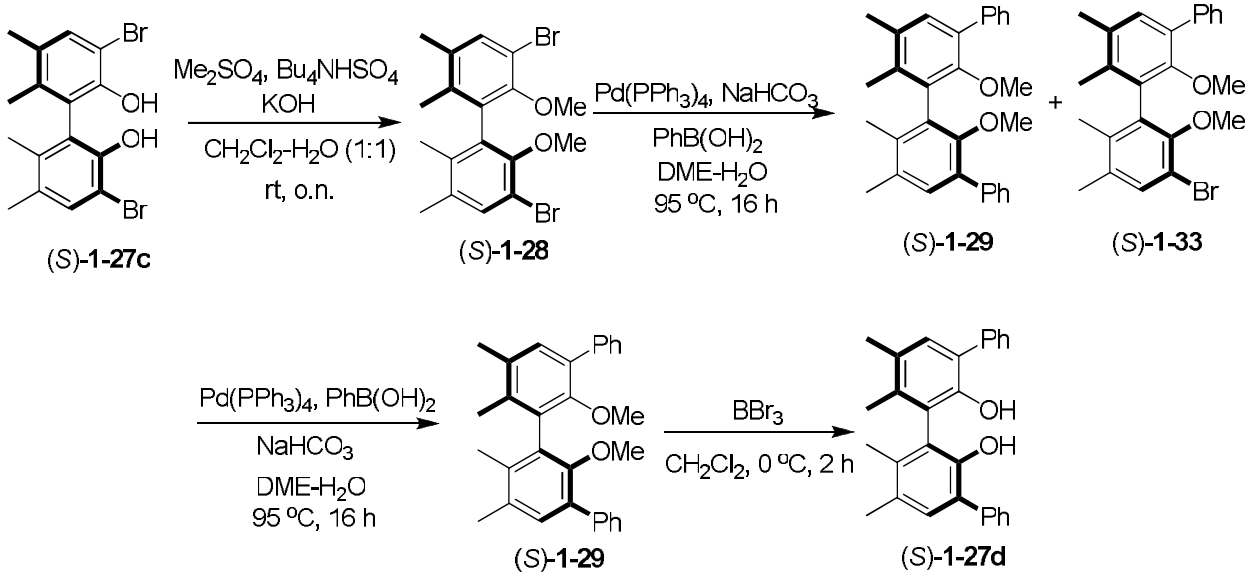
(*S*)-**1-27b** (*S*)-**1-27c**

A solution of bromine (1.62 mL, 30.8 mmol) in $CHCl_3$ (12 mL) was slowly added to a solution of (*S*)-**1-27b** (2.98 g, 12.3 mmol) in $CHCl_3$ (72 mL) over 30 min. Then the reaction mixture was stirred for another hour at room temperature. The reaction was quenched by adding saturated Na_2SO_3 solution (20 mL). The aqueous layer was extracted with Et_2O (20 mL x3). The organic layer was then washed with water (20 mL x2) and brine (30 mL), and dried over Na_2SO_4. The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure to give (*S*)-**1-27c** as an off-white solid (4.80g, 98 %): mp 169.5-171.0 °C (lit.[14] mp 171.0-172.5 °C); $[\alpha]_D^{23}$ +13.8 (*c* 0.80, DCM) [lit.[14] $[\alpha]_D^{22}$ +11.7 (*c* 0.77, DCM)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.87 (s, 6 H), 2.26 (s, 6 H), 5.12 (s, 2 H), 7.35 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.2, 19.6, 106.6, 123.5, 130.5, 132.7, 136.6, 147.7. All data are in agreement with the literature values.[14] The bromination of (*R*)-**1-27b** to (*R*)-**1-27c** followed the same procedure.

(*R*)-**3,3'-Dibromo-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*S*)-1-27c)**[14]

(*S*)-**1-7c** was obtained as a white solid (6.36 g, 99 %): mp 169.0-171.0 °C; $[\alpha]_D^{23}$ = -13.5 (*c* 0.85, DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.86 (s, 6 H), 2.25 (s, 6 H), 5.12 (s, 2 H), 7.35 (s, 2 H). All data are in agreement with the literature values.[14]

(*S*)-3,3'-Diphenyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*S*)-1-27d)[14]



Dimethyl sulfate (1.07 mL, 11.4 mmol) was added to the biphasic mixture of (*S*)-**1-27c** (1.52 g, 3.80 mmol), $(Bu_4N)HSO_4$ (148 mg, 0.38 mmol), and KOH (0.69 g, 11.4 mmol) in DCM-H_2O (1:1) (30 mL). The reaction mixture was then stirred overnight at room temperature. The organic and aqueous layers were separated by a separation funnel. The aqueous layer was extracted with DCM (15 mL x3). The combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$. The drying agent was removed by filtration and the remaining solution was concentrated *in vacuo* and triturated with cold MeOH to give (*S*)-**1-28** as a white solid (1.51 g, 93 %): mp 150.5-151.5 °C (lit.[14] mp 150.0-151.5 °C); $[\alpha]_D^{22}$ +39.1 (*c* 0.60, DCM) [lit.[14] $[\alpha]_D^{22}$ +11.7 (*c* 0.77, DCM)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.84 (s, 6 H), 2.26 (s, 6 H), 3.50 (s, 6 H), 7.39 (s, 2 H). All data are in agreement with the literature values.[14] The protection of (*R*)-**1-27c** to (*R*)-**1-28** followed the same procedure.

(*R*)-**1-28** was obtained as a white solid (2.78 g, 92 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.84 (s, 6 H), 2.26 (s, 6 H), 3.50 (s, 6 H), 7.39 (s, 2 H). All data are in agreement with the literature values.[14]

(*S*)-**1-28** (808 mg, 1.89 mmol) and 6 mol% of $Pd(PPh_3)_4$ (138 mg, 0.11 mmol) were suspended in DME (17 mL) and the suspension was stirred for 30 min at room temperature. Then, a solution of $PhB(OH)_2$ (515 mg, 4.22 mmol) and $NaHCO_3$ (0.95 g, 11.3 mmol) in water (13 mL) was added to the above suspension. The mixture was stirred and refluxed for 16 h. The reaction

mixture was then cooled down and diluted with Et_2O (40 mL). The organic layer was washed with brine (30 mL) and dried over $MgSO_4$. The drying agent was removed by filtration and the remaining solution was concentrated *in vacuo* to afford the crude compound. However, from ^1H NMR, only 75% of the desired product was obtained. The other 25% of the compound corresponds to mono-phenyl substituted product (*S*)-**1-33**. Therefore, the crude and 6 mol% of $Pd(PPh_3)_4$ based on the mole of unreacted aryl bromide were redissolved into DME (5 mL) and stirred for 30 min at room temperature. Then, a solution of $PhB(OH)_2$ (31 mg, 0.25 mmol) and $NaHCO_3$ (125 mg, 1.49 mmol) in water (3 mL) was added to above suspension. The mixture was stirred and refluxed for another 18 h. This crude product was purified by the same procedures shown above and further purified by column chromatography on silica gel (hexanes:EtOAc = 20:1) to give pure (*S*)-**1-29** as a white solid (730 mg, 92 %): mp 57.0-58.5 ^oC (lit.[14] mp 56.5-58.5 ^oC); $[\alpha]_D^{22}$ +139.3 (*c* 0.43, DCM) [lit.[14] $[\alpha]_D^{22}$ +143.6 (*c* 0.55, DCM)]; ^1H NMR (300 MHz, $CDCl_3$) δ 1.99 (s, 6 H), 2.33 (s, 6 H), 3.19 (s, 3 H), 7.23-7.62 (m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.4, 19.8, 121.6, 125.6, 127.0, 128.4, 129.1, 129.2, 132.1, 136.3, 137.9, 148.4. All data are in agreement with the literature values.[14] The Suzuki coupling of (*R*)-**1-28** to (*R*)-**1-29** followed the same procedure.

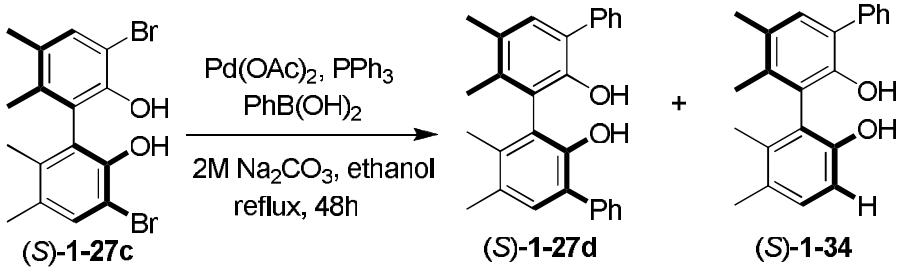
(*R*)-**1-29** was obtained as a white solid (189 mg, 93 %): ^1H NMR (300 MHz, $CDCl_3$) δ 1.98 (s, 6 H), 2.33 (s, 6 H), 3.19 (s, 3 H), 7.23-7.62 (m, 12 H). All data were in agreement with the literature values.[14]

To a stirring solution of (*S*)-**1-29** (730 mg, 1.73 mmol) in DCM (16 mL) at 0 ^oC, BBr_3 solution (5.3 mL, 1M in DCM) was added over 5 min. The reaction mixture was then stirred at 0 ^oC for 2 h. Next, the reaction was quenched by adding water (40 mL). The aqueous layer was extracted with DCM (30 mL x2). The combined organic layers were washed with brine (25 mL) and dried over $MgSO_4$. The drying agent was removed by filtration and the remaining solution was concentrated *in vacuo* to afford crude (*S*)-**1-27d**. This crude product was further purified by column chromatography on silica gel (hexanes:EtOAc = 30:1, 25:1, 20:1, 15:1, then 10:1) to give pure (*S*)-**1-27d** as a white solid (555 mg, 82 %): mp 152.5-154.5 ^oC (lit.[14] mp 153.0-154.0 ^oC); $[\alpha]_D^{23}$ +96.2 (*c* 0.52, DCM) [lit.[14] $[\alpha]_D^{22}$ +86.3(*c* 0.53, DCM)]; ^1H NMR (300 MHz, $CDCl_3$) δ 1.99 (s, 6 H), 2.32 (s, 6 H), 4.88 (s, 2 H), 7.23-7.61 (m, 12 H). All data are in agreement with the literature values.[14] The deprotection of (*R*)-**1-29** to (*R*)-**1-27d** followed the same procedure.

(*R*)-3,3'-Diphenyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*R*)-1-27d)[14]

(*R*)-**1-27d** was obtained as a white solid (400 mg, 84 %): mp 153.0-154.5 °C (lit.[14] mp 153.0-154.0 °C); $[\alpha]_D^{23}$ -124.8 (*c* 0.42, DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.99 (s, 6 H), 2.32 (s, 6 H), 4.88 (s, 2 H), 7.23-7.61 (m, 12 H). All data are in agreement with the literature values.[14]

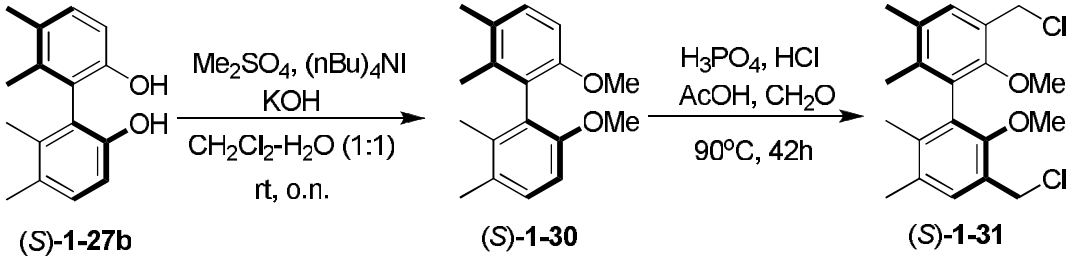
Alternative route toward the synthesis of (*S*)-1-27d[14]



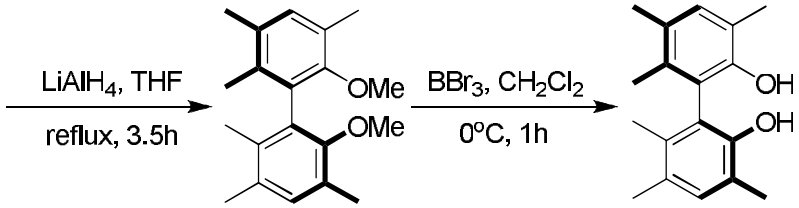
(*S*)-**1-27c** (*S*)-**1-27d** (*S*)-**1-34**

$Pd(OAc)_2$ and PPh_3 were dissolved in EtOH and the solution was stirred at room temperature for 30 min. To this solution, (*S*)-**1-27c** (1.00 g, mmol) in EtOH and $PhB(OH)_2$ in 2 M $Na_2CO_{3(aq)}$ were added. The reaction mixture was refluxed for 27 h with stirring. The reaction mixture was then cooled down and monitored by TLC. From TLC monitoring, the reaction did not go to completion. Therefore, the reaction mixture was transferred to another flask with *in situ* generated $Pd(PPh_3)_4$ solution. The reaction mixture was refluxed for another 21 h with stirring. The reaction mixture was then cooled down and diluted with Et_2O (40 mL). The organic layer was washed with brine (30 mL) and dried over $MgSO_4$. The drying agent was removed by filtration and the remaining solution was concentrated *in vacuo* to afford crude product (*S*)-**1-27d** and byproduct (*S*)-**1-34**. This crude product was further purified by column chromatography on silica gel (hexanes:EtOAc = 30:1, 25:1, 20:1, then 15:1) to give pure (*S*)-**1-27d** as a white solid (410 mg, 42 %) and (*S*)-**1-34** as a yellow solid (120 mg, 15 %): ^{1}H NMR (300 MHz, $CDCl_3$) of (*S*)-**1-34** δ 1.95 (s, 3 H), 1.97 (s, 3 H), 2.28 (s, 3 H), 2.33 (s, 3 H), 4.62 (s, 1 H), 4.84 (s, 1 H), 6.84 (d, 1 H, *J* = 8.1 Hz), 7.15 (d, 1 H, *J* = 8.1 Hz), 7.24 (s, 1 H), 7.31-7.62 (m, 5 H). All data are in agreement with the literature values.[14]

(*S*)-3,3'-Dimethyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*S*)-1-27e)[14]



(*S*)-1-27b (*S*)-1-30 (*S*)-1-31



(*S*)-1-32 (*S*)-1-27e

Dimethyl sulfate (1.75 mL, 18.7 mmol) was added to the biphasic mixture of (*S*)-**1-27b** (2.52 g, 6.25 mmol), $(nBu)_4NI$ (231 mg, 0.63 mmol), and KOH (1.07 g, 18.7 mmol) in DCM-H_2-O (1:1) (40 mL). The reaction mixture was then stirred overnight at room temperature. The organic and aqueous layers were separated by an extraction funnel. The aqueous layer was extracted with DCM (25 mL x3). The combined organic layers were washed with water (30 mL), followed by NH_4OH (30 mL), and brine (30 mL), and dried over $MgSO_4$. The drying agent was removed by filtration and the remaining solution was concentrated *in vacuo* and triturated with MeOH to give (*S*)-**1-30** as a white solid (2.41 g, 86 %): mp 110.5-112.0 °C (lit.[14] mp 110.0-112.0 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.87 (s, 6 H), 2.30 (s, 6 H), 3.69 (s, 6 H), 6.77 (d, 2 H, J = 8.1 Hz), 7.15 (d, 2 H, J = 8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.3, 19.9, 55.9, 108.1, 126.8, 128.5, 128.9, 136.5, 155.3. All data are in agreement with the literature values.[14] The protection of (*R*)-**1-27b** to (*R*)-**1-30** followed the same procedure.

(*R*)-**1-30** was obtained as a white solid (1.14 g, 83 %): mp 110.0-112.0 °C (lit.[14] mp 110.0-112.0 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.87 (s, 6 H), 2.30 (s, 6 H), 3.69 (s, 6 H), 6.77 (d, 2 H, J = 8.1 Hz), 7.15 (d, 2 H, J = 8.1 Hz). All data are in agreement with the literature values.[14]

Next, concentrated HCl (16 mL), AcOH (16 mL) H_3PO_4 (85 %, 16 mL) and paraformaldehyde (4.25 g) were added to a round-bottomed flask with (*S*)-**1-30** (1.50 g, 5.55 mmol). The mixture was then stirred at 90 °C for 42 h. After that step, the solution was cooled down and extracted with toluene (50 mL x3). The combined organic layers were washed with

water (50 mL), saturated Na_2CO_3 solution (50 mL), brine (50 mL), and dried over $MgSO_4$. The drying agent was removed by filtration and the remaining solution was concentrated *in vacuo* to give crude (*S*)-**1-31**. This crude product was further purified by column chromatography on silica gel (hexane:EtOAc = 10:1) to give pure (*S*)-**1-31** as a white solid (1.84 g, 90 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.94 (s, 6 H), 2.30 (s, 6 H), 3.38 (s, 6 H), 4.60 (d, 2 H, *J* = 13.0 Hz), 4.79 (d, 2 H, *J* = 13.0 Hz), 7.25 (s, 2H). All data are in agreement with the literature values.[14] The chloro-methylation of (*R*)-**1-30** to (*R*)-**1-31** followed the same procedure.

(*R*)-**1-31** was obtained as a white solid (1.22 g, 89 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.94 (s, 6 H), 2.30 (s, 6 H), 3.37 (s, 6 H), 4.57 (d, 2 H, *J* = 14.4 Hz), 4.80 (d, 2 H, *J* = 14.4 Hz), 7.25 (s, 2H). All data are in agreement with the literature values.[14]

A solution of (*S*)-**1-31** (1.84 g, 5.01 mmol) in THF (15 mL) was added dropwise to the suspension of $LiAlH_4$ (0.66 g, 17.0 mmol) in THF (8 mL). The mixture was refluxed for 3.5 h. The reaction was then slowly quenched with THF/water (1:1, 10 mL) at 0 ^{o}C. The aqueous layer was extracted with ether (20 mL x3). The combined organic layers were washed with water (50 mL) and dried over $MgSO_4$. The drying agent was removed by filtration and the remaining solution was concentrated *in vacuo* to give crude (*S*)-**1-32**. This crude product was further purified by column chromatography on silica gel (hexane:EtOAc = 20:1) to give pure (*S*)-**1-32** as a white solid (1.19 g, 90 %): mp 76.0-77.5 ^{o}C (lit.[14] mp 74.0-75.0 ^{o}C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.87 (s, 6 H), 2.25 (s, 6 H), 2.28 (s, 6H), 3.38 (s, 6 H), 7.00 (s, 2H). All data are in agreement with the literature values.[14] The reduction of (*R*)-**1-31** to (*R*)-**1-32** followed the same procedure.

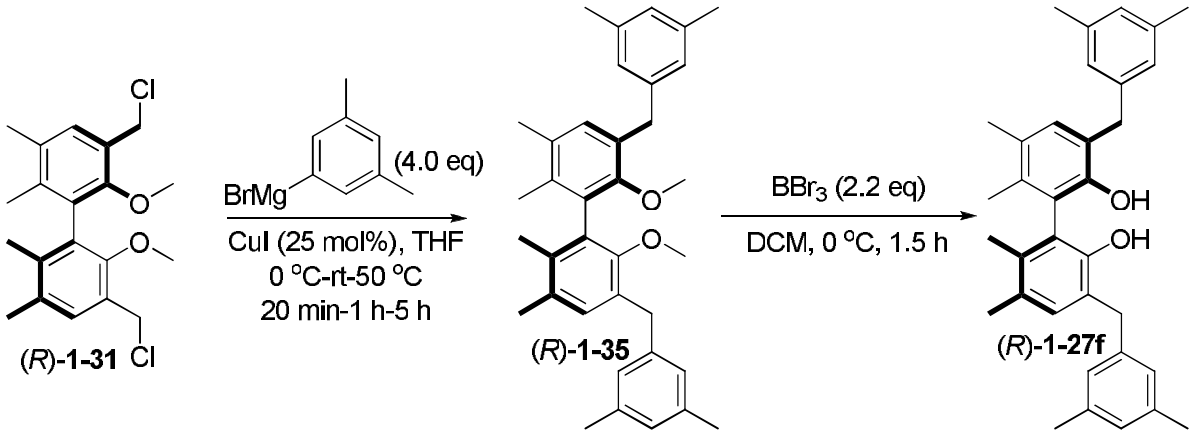
(*R*)-**1-32** was obtained as a white solid (0.80 g, 96 %): mp 75.0-76.0 ^{o}C (lit.[14] mp 74.0-75.0 ^{o}C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.87 (s, 6 H), 2.25 (s, 6 H), 2.28 (s, 6H), 3.34 (s, 6 H), 7.00 (s, 2H). All data are in agreement with the literature values.[14]

To a stirring solution of (*S*)-**1-32** (1.19 g, 3.99 mmol) in DCM (5 mL) at 0 ^{o}C , BBr_3 solution (11 mL, 1M in DCM) was added slowly. The reaction mixture was then stirred at 0 ^{o}C for 1 h. Next, the reaction was quenched by adding water (40 mL). The aqueous layer was extracted with DCM (30 mL x2). The combined organic layers were washed with water (50 mL), brine (50 mL), and dried over $MgSO_4$. The drying agent was removed by filtration and the remaining solution was concentrated *in vacuo* to afford crude (*S*)-**1-27e**. This crude product was further purified by column chromatography on silica gel (hexanes:EtOAc = 10:1) to give pure (*S*)-**1-27e** as a white

solid (0.97 g, 80 %): mp 135.0-137.0 °C (lit.[14] mp 136.0-137.5 °C); $[\alpha]_D^{23}$ -47.4 (*c* 0.76, DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.85 (s, 6 H), 2.23 (s, 12 H), 4.54 (s, 2H), 7.00 (s, 2H). All data are in agreement with the reported literature.[14] The deprotection of (*R*)-**1-32** to (*R*)-**1-27e** followed the same procedure.

(*R*)-**1-27e** was obtained as a white solid (0.70 g, 97 %): mp 136.0-137.5 °C (lit.[14] mp 136.0-137.5 °C); $[\alpha]_D^{23}$ +46.8 (*c* 0.62, DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.86 (s, 6 H), 2.24 (s, 12 H), 4.56 (s, 2H), 7.01 (s, 2H). All data are in agreement with the literature values.[14]

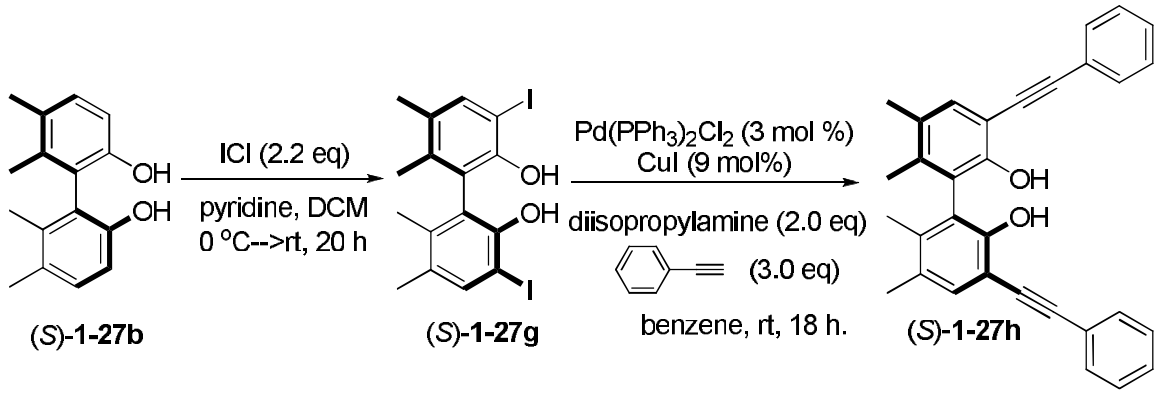
(*R*)-3,3'-Bis(3,5-dimethylbenzyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diols ((*R*)-1-27f)[26]



To a suspension of Mg (69 mg, 2.9 mmol) and a catalytic amount of I_2 in THF (6 mL) was added 5-bromo-*m*-xylene (473 mg, 2.56 mmol). The mixture was stirred at room temperature for 30 min. To a solution of (*R*)-**1-31** (234 mg, 0.638 mmol) and CuI (31 mg, 0.20 mmol) in THF (6 mL) was added dropwise the above mixture at 0 °C. The reaction mixture was warmed up to room temperature and stirred for 1 h at the same temperature and then at 50 °C for 5 h. The reaction was then quenched with aqueous NH_4Cl solution (10 mL) and the aqueous layer was separated and extracted with DCM (10 mL x3). The combined organic layer was washed with water (20 mL), brine (20 mL), and then dried over $MgSO_4$. The drying agent was removed by filtration and the solvent was concentrated *in vacuo* to afford the crude product as a yellow oil. Further purification by flash column chromatography on silica gel (hexanes/EtOAc =30:1-25:1) afforded pure (*R*)-**1-35** as a colorless oil (305 mg, 94% yield). $[\alpha]_D^{22}$ +14.1 (*c* 1.0, DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.98 (s, 6H), 2.29 (s, 6H), 2.34 (s, 12H), 3.35 (s, 6H), 4.02 (S, 4H), 6.89 (s, 2H), 6.92 (s, 2H), 6.99 (s, 2H). All data are in agreement with the literature values.[26]

To a stirred solution of (*R*)-**1-35** (300 mg, 0.592 mmol) in DCM (10 mL) was added BBr_3 (1.3 mL, 1.0 M solution in DCM) dropwise at 0 °C over 30 min. The mixture was stirred at 0 °C for 1.5 h. The reaction was quenched by water (3 mL). The aqueous layer was separated and extracted with Et_2O (15 mL x3). The combined organic layer was washed with brine (20 mL) and dried over anhydrous Na_2SO_4. The drying agent was removed by filtration and the solvent was concentrated *in vacuo* to afford the crude product as light yellow oil. Further purification by flash column chromatography on silica gel (hexanes/EtOAc =50:1-20:1) afforded pure (*R*)-**1-27f** as a white foam (277 mg, 98% yield): mp 48-50 °C; $[\alpha]_D^{22}$ -13.0 (*c* 1.0, DCM); ^{1}H NMR (300 MHz, CDCl3) δ 1.93 (s, 6H), 2.27 (s, 6H), 2.33 (s, 12H), 3.97 (q, *J*= 8.4 Hz, 4H), 4.69 (s, 2H), 6.88 (s, 2H), 6.92 (s, 4H), 7.00 (s, 2H). All data are in agreement with the literature values.[26]

Synthesis of (*S*)-5,5',6,6'-Tetramethyl-3,3'-bis(phenylethynyl)-1,1'-biphenyl-2,2'-diols ((*S*)-1-27h)[26]



(*S*)-3,3'-Diiodo-5,5',6,6'-tetramethylbiphenyl-2,2'-diol ((*S*)-1-27g)[26]

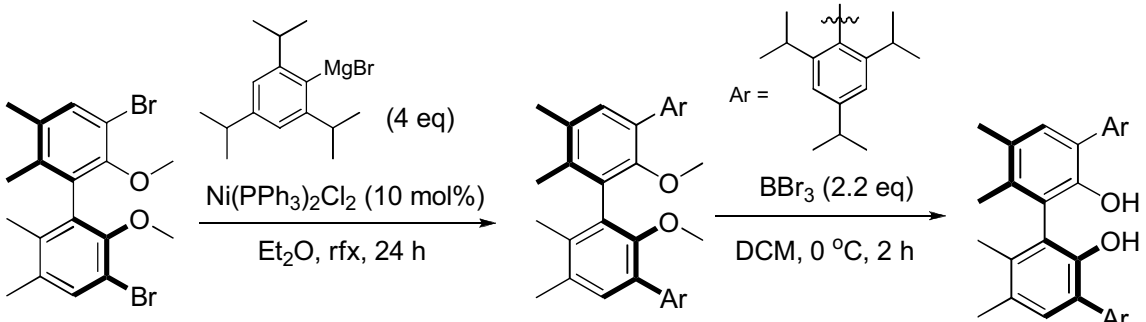
To a solution of (*S*)-**1-27b** (972 mg, 4.01 mmol) and pyridine (5 mL) in 8 mL DCM was added a solution of ICl (9 mL, 1M in DCM) dropwise at 0 °C over 30 min. The mixture was warmed to room temperature and stirred for 20 h. The reaction was quenched by saturated $Na_2SO_{3(aq)}$ (25 mL) and the aqueous layer was separated and extracted with DCM (15 mL x3). The combined organic layer was washed with water (30 mL), brine (30 mL), and dried over $MgSO_4$. The drying agent was removed by filtration and the solvent was concentrated in *vacuo* to afford the crude product as an off-white solid. Further purification by flash column chromatography on silica gel (hexanes/EtOAc =20:1-10:1) afforded pure (*S*)-**1-27g** as a white solid (1.43 g, 73% yield): mp 213-214 °C; $[\alpha]_D^{22}$ -57.5 (*c* 1.0, DCM); ^{1}H NMR (300 MHz,

$CDCl_3$) δ 1.86 (s, 6H), 2.22 (s, 6H), 2.23 (s, 6H), 4.95 (S, 2H), 7.56 (s, 2H). All data are in agreement with the literature values.[26]

(*S*)-5,5',6,6'-Tetramethyl-3,3'-bis(phenylethynyl)-1,1'-biphenyl-2,2'-diols ((*S*)-1-27h)[26]

To a suspension of $PdCl_2(PPh_3)_2$ (21 mg, 0.030 mmol), CuI (17 mg, 0.090 mmol), and (*S*)-**1-27g** (247 mg, 0.5 mmol) in benzene (5 mL) was added phenylacetylene (0.17 mL, 1.5 mmol) at room temperature under nitrogen. To this reaction mixture was added diisopropylamine (0.14 mL, 1.0 mmol) and the reaction mixture was stirred at room temperature for 18 h. The aqueous layer was separated and extracted with Et_2O (15 mL x3). The combined organic layer was washed with water (20 mL), brine (20 mL), and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the solvent was concentrated *in vacuo* to afford the crude product as a light yellow solid. Further purification by flash column chromatography on silica gel (hexanes/EtOAc =10:1-4:1) afforded pure (*S*)-**1-27h** as a light yellow solid (119 mg, 54% yield): mp 73-75 °C; $[\alpha]_D^{22}$ -132.8 (*c* 1.0, DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.97 (s, 6H), 2.29 (s, 6H), 5.53 (s, 2H), 7.35 (m, 8H), 7.52 (m, 4H). All data are in agreement with the literature values.[26]

(*S*)-3,3'-Di(2,4,6-triisopropyl phenyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*S*)-1-27i)



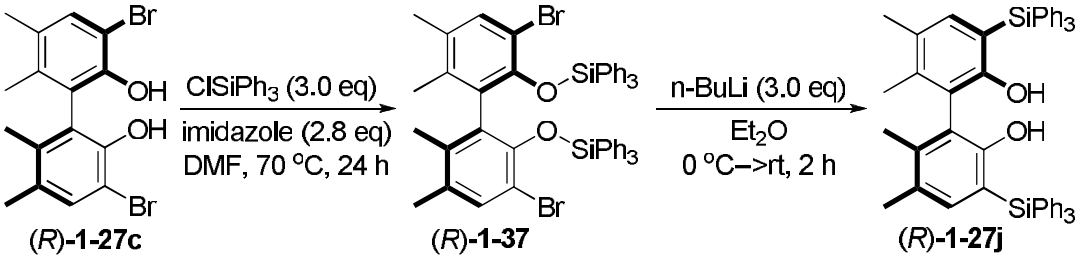
(*S*)-**1-28** (*S*)-**1-36** (*S*)-**1-27i**

To a suspension of Mg (825 mg, 34.4 mmol) and a catalytic amount of dibromoethane in Et_2O (6 mL) was added 3mL of 2-bromo-1,3,5-triisopropylbenzene (4.72 mL, 18.8 mmol) in Et_2O (15 mL) at room temperature. Once the solution began to reflux, the rest of aryl bromide was added to the reaction mixture over 1 h and the resulting mixture was refluxed for 18 h. To a suspension of (*S*)-**1-28** (2.01 g, 4.71 mmol) and $Ni(PPh_3)_2Cl_2$ (330 mg, 0.471 mmol) in THF (40 mL) was added dropwise the Grignard reagent solution prepared above at room temperature. The

reaction mixture was refluxed for 24 h. The reaction was then quenched with 1M HCl (30 mL) at 0 ^{o}C and the aqueous layer was separated and extracted with Et_2O (35 mL x 3). The combined organic layer was washed with brine (50 mL) and dried over $MgSO_4$. The drying agent was removed by filtration and the solvent was concentrated in *vacuo* to afford the crude product as yellow oil. Further purification by flash column chromatography on silica gel (hexanes/EtOAc =30:1-20:1) afforded pure (*S*)**-1-36** as colorless oil (2.11 g, 66% yield): $[\alpha]_D^{20}$ +43.2 (*c* 0.81, DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (t, *J* = 6.8 Hz, 18H), 1.23 (d, *J* = 6.8 Hz, 6H), 1.34 (d, *J* = 6.8 Hz, 12H), 2.01 (s, 6H), 2.33 (s, 6H), 2.85 (quint., *J* = 6.8 Hz, 4H), 2.97 (quint., *J* = 6.8 Hz, 2H), 3.13 (s, 6H), 6.93 (s, 2H), 7.08 (d, *J* = 4.0 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.5, 20.2, 23.3, 23.4, 24.1, 25.3, 25.5, 30.5, 30.6, 34.2, 59.1, 120.4, 120.5, 129.7, 130.7, 131.8, 131.9, 133.8, 135.1, 146.7, 147.5, 153.4; HRMS (ESI+) calcd. For $C_{48}H_{70}NO_2$ $[M+NH_4]^+$ 692.5401, found 692.5400 (Δ = -0.1 ppm).

To a stirred solution of (*S*)**-1-36** (505 mg, 0.748 mmol) in DCM (11 mL) was added BBr_3 (1.9 mL, 1.0 M solution in CH_2Cl_2) dropwise at 0 ^{o}C over 30 min. The reaction mixture was stirred at 0 ^{o}C for 2 h. The reaction was quenched by water (10 mL). The aqueous layer was separated and extracted with DCM (15 mL x3). The combined organic layer was washed with brine (20 mL) and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the solvent was concentrated *in vacuo* to afford the crude product as light yellow oil. Further purification by flash column chromatography on silica gel (hexanes/EtOAc =30:1-20:1) afforded pure (*S*)**-1-27i** as colorless oil (402 mg, 83% yield): $[\alpha]_D^{20}$ +49.5 (*c* 1.07, DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (d, *J* = 6.8 Hz, 6H), 1.11 (d, *J* = 6.8 Hz, 6H), 1.15 (d, *J* = 6.8 Hz, 6H), 1.20 (d, *J* = 6.8 Hz, 6H), 1.33 (s, 6H), 1.35 (s, 6H), 2.06 (s, 6H), 2.34 (s, 6H), 2.70 (quint., *J* = 6.8 Hz, 2H), 2.83 (quint., *J* = 6.8 Hz, 2H), 2.98 (quint., 2H), 4.45 (br, 2H), 6.96 (s, 2H), 7.11 (d, *J* = 1.6 Hz, 2H), 7.13 (d, *J* = 1.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1, 19.9, 23.8, 23.9, 24.0, 24.1, 24.2, 30.6, 34.3, 120.9, 121.0, 122.0, 123.6, 128.2, 131.1, 131.7, 135.6, 147.6, 147.7, 148.5, 148.9; HRMS (ESI-) calcd. For $C_{46}H_{61}O_2$ $[M-H]^-$ 645.4677, found 645.4673 (Δ = -0.6 ppm).

(*R*)- **3,3'-Di(triphenylsilyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol** ((*S*)-**1-27j**)

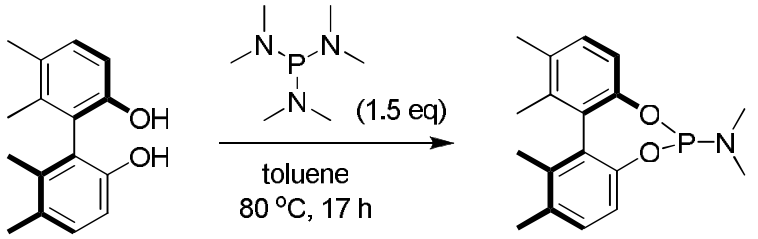


(*R*)-**1-27c** (*R*)-**1-37** (*R*)-**1-27j**

To a stirred solution of (*R*)-**1-27c** (800 mg, 2.00 mmol) and imidazole (381 mg, 5.60 mmol) in DMF (20 mL) was added chlorotriphenylsilane (1.82 g, 6.00 mmol) at room temperature. The reaction mixture was stirred at 70 °C for 24 h. The reaction was quenched by water (30 mL). The aqueous layer was separated and extracted with DCM (35 mL x3). The combined organic layer was washed with brine (30 mL) and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the solvent was concentrated *in vacuo* to afford the crude product as light yellow oil. Further purification by flash column chromatography on silica gel (hexanes/DCM=4:1-2:1) afforded pure (*R*)-**1-37** as colorless oil (1.48 g, 81% yield): $[\alpha]_D^{20}$ -83.0 (*c* 0.94, DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60 (s, 6H), 1.90 (s, 6H), 6.96 (s, 2H), 7.20 (t, *J* = 7.6 Hz, 12H), 7.34 (t, *J* = 7.6 Hz, 6H), 7.40 (d, *J* = 7.6 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.7, 19.6, 111.6, 127.3, 129.5, 131.2, 131.4, 133.6, 134.6, 135.4, 135.8, 147.9; HRMS (ESI+) calcd. For $C_{52}H_{48}Br_2NO_2Si_2$ $[M+NH_4]^+$ 932.1585, found 932.1579 (Δ = -0.6 ppm).

To a stirred solution of (*R*)-**1-37** (917 mg, 1.00 mmol) in Et_2O (10 mL) was added dropwise n-BuLi (1.2 mL, 2.5 M solution in hexanes) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. The reaction was quenched by saturated $NH_4Cl_{(aq)}$ (10 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (20 mL x3). The combined organic layer was washed with brine (20 mL) and dried over anhydrous Na_2SO_4. The drying agent was removed by filtration and the solvent was concentrated *in vacuo* to afford the crude product as colorless oil. Further purification by flash column chromatography on silica gel (hexanes/DCM=4:1-2:1) afforded pure (*R*)-**1-27j** as a white foam (594 mg, 78% yield): $[\alpha]_D^{20}$ -16.4 (*c* 0.61, Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.05 (s, 6H), 2.18 (s, 6H), 4.92 (s, 2H), 7.06 (s, 2H), 7.38 (t, *J* = 7.2 Hz, 12H), 7.45 (t, *J* = 7.2 Hz, 6H), 7.64 (d, *J* = 7.2 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.5, 19.8, 116.6, 120.4, 127.7, 129.0, 129.3, 134.5, 136.2, 139.6, 139.7, 156.7; HRMS (ESI-) calcd. For $C_{52}H_{45}O_2Si_2$ $[M-H]^-$ 757.2964, found 757.2954 (Δ = -1.3 ppm).

General procedure for the synthesis of monophosphoramidite ligands[14,15a]



(*R*)-**1-7b** (*R*)-**MPN-L1b**

***O,O′*-*(R)*-(5,5′,6,6′-Tetramethyl-1,1′-biphenyl-2,2′-diyl)-*N,N*-dimethylphosphor amidite ((*R*)-MPN-L1b)**[15a]

To a mixture of (*R*)-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol (*R*)-**1-7b** (242 mg, 1.00 mmol) in toluene (5 ml), hexamethylphosphorous triamide (HMPT) (248 mg, 1.50 mmol) was added under nitrogen. The resulting mixture was stirred at 80 °C for 17 h. The solvent was evaporated under reduced pressure to afford a gel-like liquid, which was further purified by column chromatography [silica gel (neutralized by 1 % TEA in hexanes) /hexanes : EtOAc = 10:1] to give (*R*)-**MPN-L1b** as a white solid (256 mg, 81 % yield): mp 157.0-159.0 °C (lit.[14] mp 161.0-163.5 °C); $[\alpha]_D^{23}$ -142.9 (*c* 0.56, DCM) (lit.[14] $[\alpha]_D^{22}$ -167.1 (*c* 1.55, DCM)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.99 (s, 3H), 2.04 (s, 3H), 2.28 (s, 3H), 2.29 (s, 3H), 2.48 (s, 3H), 2.51 (s, 3H), 6.83 (d, *J* = 8.1 Hz, 1H), 6.98 (d, *J* = 8.1 Hz, 1H), 7.03 (d, *J* = 8.1 Hz, 1H), 7.13 (d, *J* = 8.1 Hz, 1H); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 143.0. All data are in agreement with the literature values.[14]

Other monophosphoramidite ligands were obtained in the same manner as that described for the synthesis of (*R*)-**MPN-L1b** with some variations.

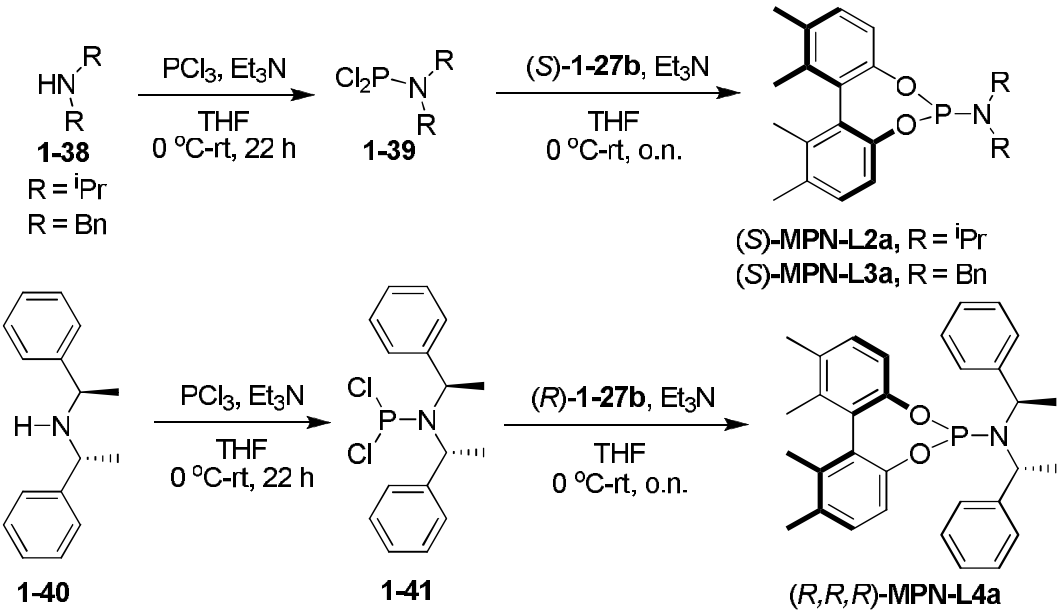
***O,O′*-(*S*)-(3,3′,5,5′,6,6′-Hexamethyl-1,1′-biphenyl-2,2′-diyl)-*N,N*-dimethylphosphoramidite ((*S*)-MPN-L1c)**[14] Purified by column chromatography on silica gel [(neutralized by 1 % TEA in hexanes) /hexanes:EtOAc = 10:1] to give pure (*S*)-**MPN-L1c** as a white solid (302mg, 88 % yield); mp 119.0-120.0 °C (lit.[14] mp 121.0-121.5 °C); $[\alpha]_D^{22}$ +417.3 (*c* 0.30, DCM) (lit.[14] $[\alpha]_D^{22}$ +488.0 (*c* 0.50, DCM)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.92 (s, 3H), 1.99 (s, 3H), 2.21 (s, 3H), 2.24 (s, 3H), 2.25 (s, 3H), 2.32 (s, 3H), 2.45 (s, 3H), 2.48 (s, 3H), 6.95 (s, 1H), 7.01 (s, 1H); ^{31}P NMR (161.9 MHz, C_6D_6) δ 138.8. All data are in agreement with the literature values.[14]

***O,O′*-(*S*)-(3,3′-Diphenyl-5,5′,6,6′-tetramethyl-1,1′-biphenyl-2,2′-diyl)-*N,N*-dimethylphospho ramidite ((*S*)-MPN-L1d)**[14]

Purified by column chromatography on silica gel [(neutralized by 1 % TEA in hexanes) /hexanes:EtOAc = 10:1] to give pure (*S*)-**MPN-L1d** as a foam-like white solid (338 mg, 95 % yield): mp 98-100 °C (lit.[14] mp 109.5-112.5 °C); $[\alpha]_D^{23}$ +502.1 (*c* 0.48, DCM) (lit.[14] $[\alpha]_D^{22}$ +466.7 (*c* 0.45, DCM)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.87 (s, 3H), 1.90 (s, 3H), 2.09 (s, 3H), 2.11 (s, 3H), 2.35 (s, 3H), 2.36 (s, 3H), 7.21-7.66 (m, 12H); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 140.5. All data are in agreement with the literature values.[14]

***O,O′*-*(R)*-(3,3′-Di-*tert*-butyl-5,5′,6,6′-tetramethyl-1,1′-biphenyl-2,2′-diyl)-*N,N*-dimethylphos phoramidite ((*R*)-MPN-L1e)**[14]

Purified by column chromatography on silica gel [(neutralized by 1 % TEA in hexanes) /hexanes:EtOAc = 10:1] to give pure (*R*)-**MPN-L1e** as a white solid (293 mg, 69 % yield): mp 189.0-191.0 °C (lit.[14] mp 191.5-193.0 °C); $[\alpha]_D^{22}$ -367.7 (*c* 0.62, DCM) (lit.[14] $[\alpha]_D^{22}$ -380.8 (*c* 0.43, DCM)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (s, 9H), 1.44 (s, 9H), 1.76 (s, 3H), 1.88 (s, 3H), 2.24 (s, 3H), 2.25 (s, 3H), 2.40 (br, 6H), 7.08 (s, 1H), 7.12 (s, 1H); ^{31}P NMR (161.9 MHz, C_6D_6) δ 141.1. All data are in agreement with the literature values.[14]



***O,O′*-(*S*)-(5,5′,6,6′-Tetramethyl-1,1′-biphenyl-2,2′-diyl)-*N,N*-diisopropylphosphoramidite ((*S*)-MPN-L2a)[14]**

A solution of bis(*i*-propyl)amine **1-38a** (0.15 mL, 1.03 mmol) in THF (2 mL) was added to a mixture of PCl_3 (0.09 ml, 1.03 mmol) and Et_3N (0.70 mL, 5.00 mmol) in THF (5 mL) at 0 °C. The mixture was stirred under room temperature and monitored by ^{31}P NMR until intermediate **1-39** formed completely. Then to this reaction mixture was added a solution of (*S*)-**1-27b** (242 mg, 1.00 mmol) in THF (3 mL) at 0 °C. The solution was then stirred overnight at room temperature. The reaction mixture was diluted with toluene (10 mL) and filtered through neutral alumina. The remaining solution was concentrated under reduced pressure and purified by column chromatography on silica gel [(neutralized by 1 % TEA in hexanes) /hexanes:EtOAc = 10:1] to give pure (*S*)-**MPN-L2a** as a white and foam-like solid (190 mg, 50 % yield): mp 78.0-79.5 °C (lit.[14] mp 79.0-81.0 °C); $[\alpha]_D^{23}$ +244.1 (*c* 0.68, DCM) (lit.[14] $[\alpha]_D^{22}$ +236.0 (*c* 0.75, DCM)); ^1H NMR (400 MHz, $CDCl_3$) δ 1.16 (m, 12H), 1.97 (s, 3H), 2.03 (s, 3H), 2.27 (s, 3H), 2.28 (s, 3H), 3.30 (m, 2H), 6.89 (d, 1H, *J* = 8.0 Hz), 6.98 (d, 1H, *J* = 8.0 Hz), 7.06 (d, 1H, *J* = 8.0 Hz), 7.12 (d, 1H, *J* = 8.0 Hz); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 148.2. All data are in agreement with the literature values.[14]

Other monophosphoramidite ligands were obtained in the same manner as that described for the synthesis of (*S*)-**MPN-L2a** with some variations.

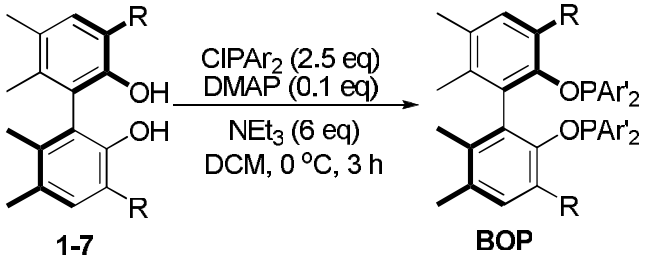
***O,O′*-(*S*)-(5,5′,6,6′-Tetramethyl-1,1′-biphenyl-2,2′-diyl)-*N,N*-dibenzylphosphoramidite ((*S*)-MPN-L3a)[14]**

Purified by column chromatography on silica gel [(neutralized by 1 % TEA in hexanes) /hexanes:EtOAc = 10:1] to give pure (*S*)-**MPN-L3a** as a white and foam-like solid (370 mg, 79 % yield): ^1H NMR (400 MHz, $CDCl_3$) δ 1.97 (s, 3H), 1.99 (s, 3H), 2.19 (s, 3H), 2.30 (s, 3H), 3.37 (m, 2H), 4.14 (m, 2H), 6.57 (d, 1H, *J* = 8.0 Hz), 6.91 (d, 1H, *J* = 8.0 Hz), 7.11 (d, 1H, *J* = 8.0 Hz), 7.18 (d, 1H, *J* = 8.0 Hz), 7.04-7.17 (m, 12H); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 147.7. All data are in agreement with the literature values.[14]

***O,O′*-(*R*)-(5,5′,6,6′-Tetramethyl-1,1′-biphenyl-2,2′-diyl)-*N,N*-bis[(*R*)-methylbenzyl] phosphoramidite ((*R,R,R*)-MPN-L4a)**[14]

Purified by column chromatography on silica gel [(neutralized by 1 % TEA in hexanes) /hexanes:EtOAc = 50:1] to give pure (*R,R,R*)-**MPN-L4a** as a white and foam-like solid (327 mg, 66 % yield): $[\alpha]_D^{23}$ +171.4 (*c* 0.56, DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62 (s, 3H), 1.64 (s, 3H), 1.94 (s, 3H), 2.00 (s, 3H), 2.19 (s, 3H), 2.27 (s, 3H), 3.30 (m, 2H), 6.76 (d, 1H, *J* = 8.0 Hz), 6.89 (d, 1H, *J* = 8.0 Hz), 7.06 (d, 1H, *J* = 8.0 Hz), 7.12 (d, 1H, *J* = 8.0 Hz); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 148.2 ppm. All data are in agreement with the literature values.[14]

General procedure for the synthesis of chiral diphosphonite ligands



1-7 **BOP**

To a solution of a chiral biphenol[12] (1 mmol), DMAP (10 mol%) and Et_3N (0.8 mL, 6 mmol) in DCM (10 mL) at 0 °C was added a solution of a chlorodiarylphosphine (2.5 mmol) in DCM (5 mL) over the period of 20 min via a syringe. The mixture was stirred at the same temperature for additional 3 h, and concentrated *in vacuo*. The residue was dissolved in dry ether (20 mL) and filtered through a pad of Celite. The filtrate was concentrated *in vacuo* and the crude product was purified on a silica gel column pretreated with Et_3N using (hexanes: NEt_3 = 99:1) as the eluent.

(*R*)-2,2'-Bis[bis(4-methylphenyl)phosphinoxy]-3,3'-bis(3,5-dimethylbenzyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl, (*R*)-**BOP-L2a**

Colorless oil; 50% yield; $[\alpha]_D^{21}$ -72.5 (*c* 0.69, DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.68 (s, 6H), 1.81 (s, 6H), 2.22 (s, 18H), 2.27 (s, 6H), 3.45 (d, *J* =15.6 Hz, 2H), 3.57 (d, *J* =15.6 Hz, 2H), 6.34 (s, 2H), 6.63 (s, 4H), 6.81 (t, *J* =8.1 Hz, 6H), 7.01 (d, *J* =7.8 Hz, 4H), 7.15 (t, *J* =7.8 Hz, 4H), 7.31 (t, *J* =7.8 Hz, 4H); ^{31}P NMR (121.5 Hz, $CDCl_3$) δ 111.0; HRMS (EI) calcd $C_{62}H_{64}O_4P_2$ $[M+O2]^+$ 934.4280, found 934.4267 (Δ = -1.3 ppm).

(*S*)-**2,2'-Bis[bis(4-methylphenyl)phosphinyloxy]-3,3'-bis(3,5-dimethylbenzyl)-5,5',6,6'-tetra methyl-1,1'-biphenyl,** (*S*)-**BOP-L2a**

Colorless oil; 45% yield; $[\alpha]_D^{21}$ +74.4 (*c* 0.73, DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.68 (s, 6H), 1.81 (s, 6H), 2.22 (s, 18H), 2.27 (s, 6H), 3.45 (d, *J* =15.6 Hz, 2H), 3.57 (d, *J* =15.6 Hz, 2H), 6.34 (s, 2H), 6.63 (s, 4H), 6.81 (t, *J* =8.1 Hz, 6H), 7.01 (d, *J* =7.8 Hz, 4H), 7.15 (t, *J* =7.8 Hz, 4H), 7.31 (t, *J* =7.8 Hz, 4H); ^{31}P NMR (121.5 Hz, $CDCl_3$) δ 110.9; HRMS (EI) calcd $C_{62}H_{64}O_2P_2$ $[M]^+$ 902.4382, found 902.4399 (Δ = 1.7 ppm).

(*R*)-**2,2'-Bis[bis(4-methoxyphenyl)phosphinyloxy]-3,3'-bis(3,5-dimethylbenzyl)-5,5',6,6'-tetr amethyl-1,1'-biphenyl**, (*R*)-**BOP-L2b**

Colorless oil; 62% yield; $[\alpha]_D^{21}$ -31.4 (*c* 0.51, DCM); ^{1}H NMR (300 MHz, CD_2Cl_2) δ 1.67 (s, 6H), 1.84 (s, 6H), 2.22 (s, 12H), 3.44 (d, *J* =15.3 Hz, 2H), 3.60 (d, *J* =15.3 Hz, 2H), 3.69 (s, 6H), 3.75 (s, 6H), 6.39 (s, 2H), 6.64 (s, 4H), 6.53 (d, *J* =8.4 Hz, 4H), 6.66 (s, 4H), 6.76-6.79 (m, 4H), 7.16-7.21 (m, 4H), 7.33-7.38 (m, 4H); ^{31}P NMR (121.5 Hz, CD_2Cl_2) δ 112.7; HRMS (EI) calcd $C_{62}H_{84}O_8P_2$ $[M+O2]^+$ 998.4076, found 998.4059 (Δ = -1.4 ppm).

(*R*)-**2,2'-Bis[bis(4-trifluoromethylphenyl)phosphinyloxy]-3,3'-bis(3,5-dimethylbenzyl)-5,5',6 ,6'-tetramethyl-1,1'-biphenyl**, (*R*)-**BOP-L2c**

Colorless oil; 35% yield; $[\alpha]_D^{23}$ -115.8 (*c* 1.2, DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.77 (s, 6H), 1.86 (s, 6H), 2.19 (s, 12H), 3.40 (d, *J* =15.6 Hz, 2H), 3.62 (d, *J* =15.6 Hz, 2H), 6.42 (s, 2H), 6.49 (s, 4H), 6.77 (s, 2H), 7.30-7.44 (m, 14H) ^{31}P NMR (121.5 Hz, CDCl3) δ 103.5; HRMS (EI) calcd $C_{62}H_{52}O_2F_{12}P_2$ $[M]^+$ 1118.3251, found 1118.3233 (Δ = -1.8 ppm).

§ 1.7 References

1. Natta, G.; Porri, L.; Valenti, S., Synthesis of optically active cis-1,4 poly(1,3-pentadiene) by asymmetric induction, kurzmitteilung. *Die Makromolekulare Chemie* **1963,** *67* (1), 225-228.
2. Nozaki, H.; Moriuti, S.; Takaya, H.; Noyori, R., Asymmetric induction in carbenoid reaction by means of a dissymmetric copper chelate. *Tetrahedron Lett.* **1966,** *7* (43), 5239-5244.
3. (a) Osborn, J. A.; Jardine, F. H.; Young, J. F.; Wilkinson, G., The preparation and properties of tris(triphenylphosphine)halogenorhodium(I) and some reactions thereof including catalytic homogeneous hydrogenation of olefins and acetylenes and their derivatives. *J. Chem. Soc. A* **1966**, 1711-1732; (b) Baird, M. C.; Lawson, D. N.; Mague, J. T.; Osborn, J. A.; Wilkinson, G., Novel Addition Reactions of Chlorotris(triphenyl phosphine)rhodium(I).

Chem. Commun. **1966**, 129-130; (c) Mague, J. T.; Wilkinson, G., Tris(triphenylarsine)- and tris(triphenylstibine)-chlororhodium(I) complexes and their reactions with hydrogen, olefins, and other reagents. *J. Chem. Soc. A* **1966**, 1736-1740.

4. (a) Horner, L.; Siegel, H.; Büthe, H., Asymmetric Catalytic Hydrogenation with an Optically Active Phosphinerhodium Complex in Homogeneous Solution. *Angew. Chem., Int. Ed.* **1968,** *7* (12), 942; (b) Knowles, W. S.; Sabacky, M. J., Catalytic asymmetric hydrogenation employing a soluble, optically active, rhodium complex. *Chem. Commun.* **1968,** (22), 1445-1446.
5. Knowles, W. S., Asymmetric hydrogenation. *Acc. Chem. Res.* **1983,** *16* (3), 106-112.
6. Dang, T. P.; Kagan, H. B., The asymmetric synthesis of hydratropic acid and amino-acids by homogeneous catalytic hydrogenation. *J. Chem. Soc. D, Chem. Commun.* **1971,** (10), 481.
7. Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, D. J., Asymmetric hydrogenation. Rhodium chiral bisphosphine catalyst. *J. Am. Chem. Soc.* **1977,** *99* (18), 5946-5952.
8. Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R., Synthesis of 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), an atropisomeric chiral bis(triaryl)phosphine, and its use in the rhodium(I)-catalyzed asymmetric hydrogenation of .alpha.-(acylamino)acrylic acids. *J. Am. Chem. Soc.* **1980,** *102* (27), 7932-7934.
9. Burk, M. J., C2-symmetric bis(phospholanes) and their use in highly enantioselective hydrogenation reactions. *J. Am. Chem. Soc.* **1991,** *113* (22), 8518-8519.
10. (a) Noyori, R., *Asymmetric Catalysis in Organic Synthesis*. Wiley: New York, 1994; (b) Ojima, I., *Catalytic Asymmetric Synthesis*. Wiley: New York, 2000; p 1-110; (c) Tang, W.; Zhang, X., New Chiral Phosphorus Ligands for Enantioselective Hydrogenation. *Chem. Rev.* **2003,** *103* (8), 3029-3070.
11. Katsuki, T.; Sharpless, K. B., The first practical method for asymmetric epoxidation. *J. Am. Chem. Soc.* **1980,** *102* (18), 5974-5976.
12. Alexakis, A.; Vastra, J.; Burton, J.; Benhaim, C.; Mangeney, P., Asymmetric conjugate addition of diethyl zinc to enones with chiral phosphorus ligands derived from TADDOL. *Tetrahedron Lett.* **1998,** *39* (43), 7869-7872.
13. (a) Reetz, M. T.; Sell, T., Rhodium-catalyzed enantioselective hydrogenation using chiral monophosphonite ligands. *Tetrahedron Lett.* **2000,** *41* (33), 6333-6336; (b) van den Berg, M.; Minnaard, A. J.; Schudde, E. P.; van Esch, J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L., Highly Enantioselective Rhodium-Catalyzed Hydrogenation with Monodentate Ligands. *J. Am. Chem. Soc.* **2000,** *122* (46), 11539-11540.
14. Hua, Z.; Vassar, V. C.; Ojima, I., Synthesis of New Chiral Monodentate Phosphite Ligands and Their Use in Catalytic Asymmetric Hydrogenation. *Org. Lett.* **2003,** *5* (21), 3831-3834.
15. (a) Choi, H.; Hua, Z.; Ojima, I., Highly Enantioselective Copper-Catalyzed Conjugate Addition of Diethylzinc to Nitroalkenes. *Org. Lett.* **2004,** *6* (16), 2689-2691; (b) Hua, Z.; Vassar, V. C.; Choi, H.; Ojima, I., New biphenol-based, fine-tunable monodentate phosphoramidite ligands for catalytic asymmetric transformations. *Proc. Natl. Acad. Sci. U. S. A.* **2004,** *101* (15), 5411-5416; (c) Chapsal, B. D.; Ojima, I., Total Synthesis of

Enantiopure (+)-γ-Lycorane Using Highly Efficient Pd-Catalyzed Asymmetric Allylic Alkylation. *Org. Lett.* **2006,** *8* (7), 1395-1398.

16. (a) Bonafoux, D.; Hua, Z.; Wang, B.; Ojima, I., Design and synthesis of new fluorinated ligands for the rhodium-catalyzed hydroformylation of alkenes in supercritical CO2 and fluorous solvents. *J. Fluorine Chem.* **2001,** *112* (1), 101-108; (b) Hultzsch, K. C.; Jernelius, J. A.; Hoveyda, A. H.; Schrock, R. R., The First Polymer-Supported and Recyclable Chiral Catalyst for Enantioselective Olefin Metathesis. *Angew. Chem., Int. Ed.* **2002,** *41* (4), 589-593.
17. Shi, C.; Ojima, I., Asymmetric synthesis of 1-vinyltetrahydroisoquinoline through Pd-catalyzed intramolecular allylic amination. *Tetrahedron* **2007,** *63* (35), 8563-8570.
18. Pu, L., 1,1‘-Binaphthyl Dimers, Oligomers, and Polymers: Molecular Recognition, Asymmetric Catalysis, and New Materials†. *Chem. Rev.* **1998,** *98* (7), 2405-2494.
19. van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P., Ligand Bite Angle Effects in Metal-catalyzed C−C Bond Formation. *Chem. Rev.* **2000,** *100* (8), 2741-2770.
20. Trost, B. M.; Murphy, D. J., A model for metal-templated catalytic asymmetric induction via .pi.-allyl fragments. *Organometallics* **1985,** *4* (6), 1143-1145.
21. Kaloko, J. J.; Teng, Y.-H.; Ojima, I., One-step formation of fused tetracyclic skeletons from cyclohexene-diynes and carbon monoxide through Rh(I)-catalyzed [2+2+2+1] cycloaddition reaction. *Chemical Communications* **2009,** (30), 4569-4571.
22. Mori, M.; Nakanishi, M.; Kajishima, D.; Sato, Y., A Novel and General Synthetic Pathway to Strychnos Indole Alkaloids: Total Syntheses of (−)-Tubifoline, (−)-Dehydrotubifoline, and (−)-Strychnine Using Palladium-Catalyzed Asymmetric Allylic Substitution. *J. Am. Chem. Soc.* **2003,** *125* (32), 9801-9807.
23. Alexander, J. B.; Schrock, R. R.; Davis, W. M.; Hultzsch, K. C.; Hoveyda, A. H.; Houser, J. H., Synthesis of Molybdenum Imido Alkylidene Complexes That Contain 3,3‘-Dialkyl-5,5‘,6,6‘-tetramethyl-1,1‘-biphenyl-2,2‘-diolates (Alkyl = t-Bu, Adamantyl). Catalysts for Enantioselective Olefin Metathesis Reactions. *Organometallics* **2000,** *19* (18), 3700-3715.
24. (a) Freundlich, J. S.; Landis, H. E., An expeditious aqueous Suzuki–Miyaura method for the arylation of bromophenols. *Tetrahedron Lett.* **2006,** *47* (25), 4275-4279; (b) Chouteau, F.; Ramanitrahasimbola, D.; Rasoanaivo, P.; Chibale, K., Exploiting a basic chemosensitizing pharmacophore hypothesis. Part 1: Synthesis and biological evaluation of novel arylbromide and bicyclic chemosensitizers against drug-resistant malaria parasites. *Bioorg. Med. Chem. Lett.* **2005,** *15* (12), 3024-3028.
25. Yoshizaki, H.; Satoh, H.; Sato, Y.; Nukui, S.; Shibasaki, M.; Mori, M., Palladium-Mediated Asymmetric Synthesis of Cis-3,6-Disubstituted Cyclohexenes. A Short Total Synthesis of Optically Active (+)-.gamma.-Lycorane. *J. Org. Chem.* **1995,** *60* (7), 2016-2021.
26. Shi, C.; Chien, C.-W.; Ojima, I., Synthesis of Chiral Biphenol-Based Diphosphonite Ligands and Their Application in Palladium-Catalyzed Intermolecular Asymmetric Allylic Amination Reactions. *Chem. Asian J.* **2011,** *6* (2), 674-680.

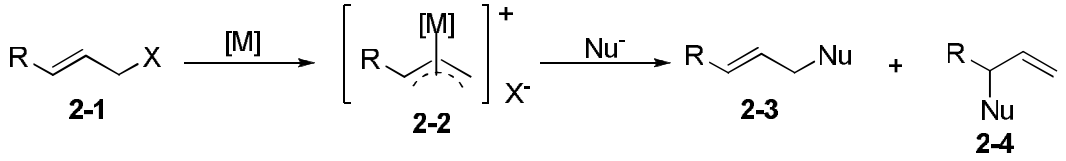
Chapter 2

Palladium-Catalyzed Asymmetric Allylic Amination with Bidentate Diphosphonite Ligands

Table of Contents

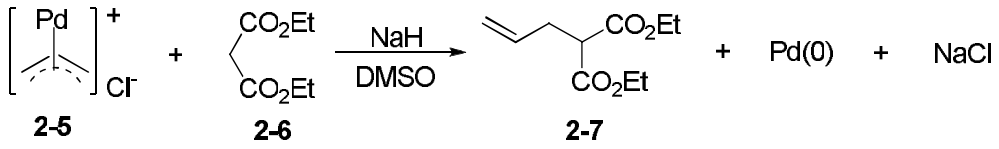
§ 2.1 Transition metal-catalyzed asymmetric allylic alkylation

Transition-metal catalyzed allylic alkylation has proven to be one of the most powerful methods for asymmetric synthesis, due to the ability to form multiple types of bonds such as C-C, C-O, C-S, C-N and C-H. Instead of acting as the nucleophile, the formation of the key η-allyl metal complex intermediate makes the allyl moiety become an electrophile, resulting in nucleophilic substitution on the allylic substrate (**Scheme 2-1**).



Scheme 2-1. Allylic alkylation

The first example of C-C bond formation by allylic alkylation was carried out by Tsuji and coworkers in 1965 (**Scheme 2-2**).[1] In 1977, the first example of an asymmetric version of allylic alkylation was published by Trost et al.[2] Since then, many research groups intended to extend the asymmetric potential of allylic alkylations, but have been unsuccessful until it was realized that chiral ligands have to be designed to reach across the plane of the allyl moiety to create a proper chiral environment for the enantiodiscrimination. Although most of accomplished efforts were done by palladium catalysts, this process can also be catalyzed by other transition metal complexes including cobalt, platinum, rhodium, ruthenium, iridium, molybdenum, tungsten, and copper to complement the patterns of reactivity.[3]

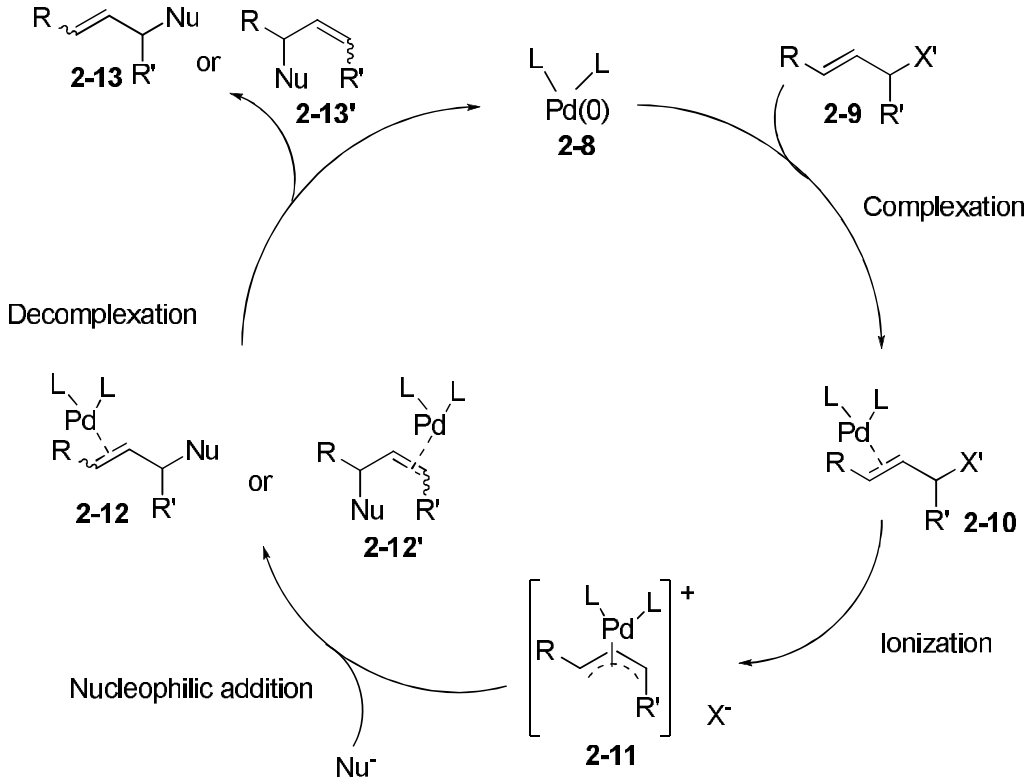


Scheme 2-2. First example of allylic substitution reaction

The general mechanism for the palladium-catalyzed allylic substitution is illustrated below (**Scheme 2-3**).[3-4] As shown in the scheme, the catalytic cycle begins with the complexation of the olefin moiety of the allylic substrate **2-9** to $Pd(0)L_2$ **2-8**, followed by the ionization step where X' is cleaved from the allyl moiety, leading to the formation of a Pd(II)-allyl intermediate **2-11**. It is generally observed that the ionization step occurs with the leaving group at a position *anti* to the metal. The third step is the nucleophilic addition to the Pd(II)-allyl complex **2-11** to form the

corresponding Pd(0)-olefin complexes (**2-12** or **2-12'**). In the case of soft nucleophiles (pKa < 25), which generally refer to stabilized nucleophiles, the attack occurs on the π-allyl group *anti* to the metal. In contrast, hard nucleophiles (pKa > 25), such as alkylmetals, bind to the palladium metal first, thus leading to a *syn*-attack on the allylic substrate. The final step is the decomplexation to release the newly formed compounds and regenerate $Pd(0)L_2$ **2-8** to complete the cycle.

From the mechanism, each step offers the chance for enantiodiscrimination, depending on the structure of the substrate, except for the decomplexation step, which is the step after the bond formation. Thus, the recognition of the step in the catalytic cycle that determines the enantiopurity, followed by the design of proper chiral ligands based on the above judgment becomes crucial to obtain high enantioselectivity.[3]



Scheme 2-3. General mechanism of Pd(0) catalyzed allylic substitution reaction

When compared to monodentate ligands, bidentate ligands are the better ligand system in this field. Among numerous bidentate ligands, the Trost ligands, the DPPBA ligand and its derivatives, are the most efficient ligands in various asymmetric allylic alkylations due to the extension of the chiral induction caused by their large bite angle (P-M-P) (**Figure 2-1**).[5]

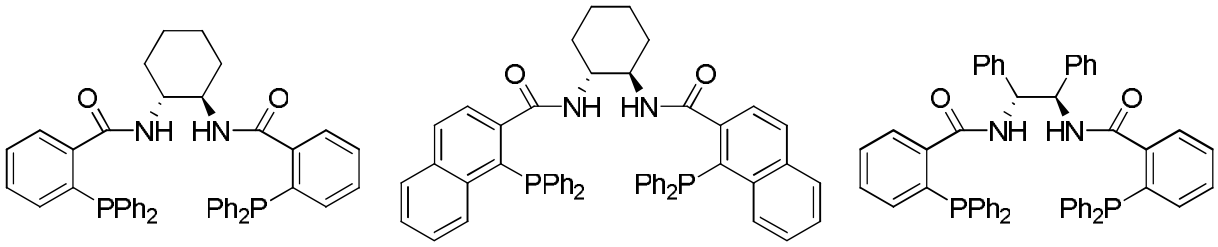


Figure 2-1. Trost ligands (DPPBA ligand series)

In the Ojima laboratory, our monodentate phosphoramidite ligands gave excellent enantioselectivity in Pd-catalyzed allylic alkylation reaction for the total synthesis of (+)-lycorane and allylic amination of 3-(amidoethylphenyl)prop-2-enyl carbonates for the synthesis of 1-vinyltetrahydroisoquinoline. Moreover, diphosphonite ligands also achieved excellent % ee in Pd-catalyzed intermolecular asymmetric allylic amination for the key intermediate of *Strychnos* indole alkaloids. As a result, both our ligand libraries have the potential for other types of palladium-catalyzed allylic substitutions.

§ 2.2 Asymmetric synthesis of 1-vinyltetrahydroisoquinoline through Pd-catalyzed intramolecular allylic amination

§ 2.2.1 Asymmetric synthesis of natural products bearing C1-substituted tetrahydroisoquinolines

The development of efficient methods for the synthesis of C1-substituted tetrahydroisoquinolines has attracted much interest among synthetic organic chemists, mainly due to the interesting pharmacological properties these alkaloids possess.[6] Members of this family (**Figure 2-2**) have shown diverse activities,[7] such as anti-inflammatory properties,[8] neuromuscular transmission blocking,[9] antiplatelet aggregation activity,[10] and enzyme inhibitory activities for acetylcholinesterase (AChE)[11] and α-glucosidase.[12] Thus, in order to study the biological and pharmacological activities of this class of compounds, the efficient synthesis of these alkaloids in enantiomerically pure form is of great importance.

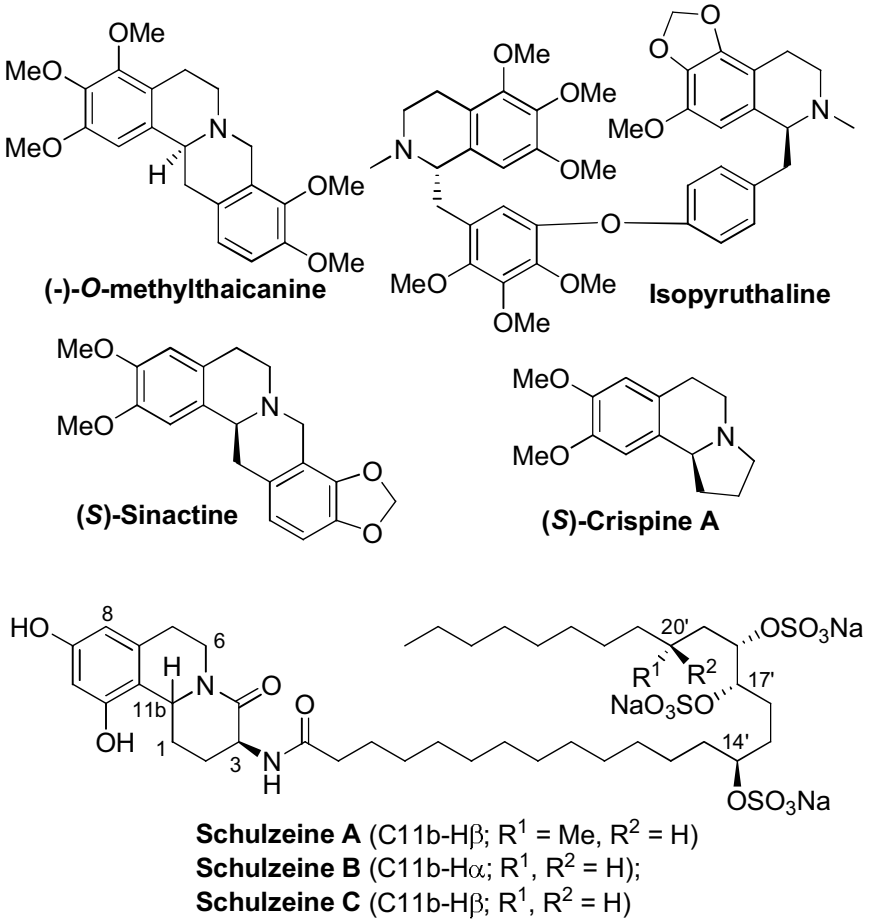
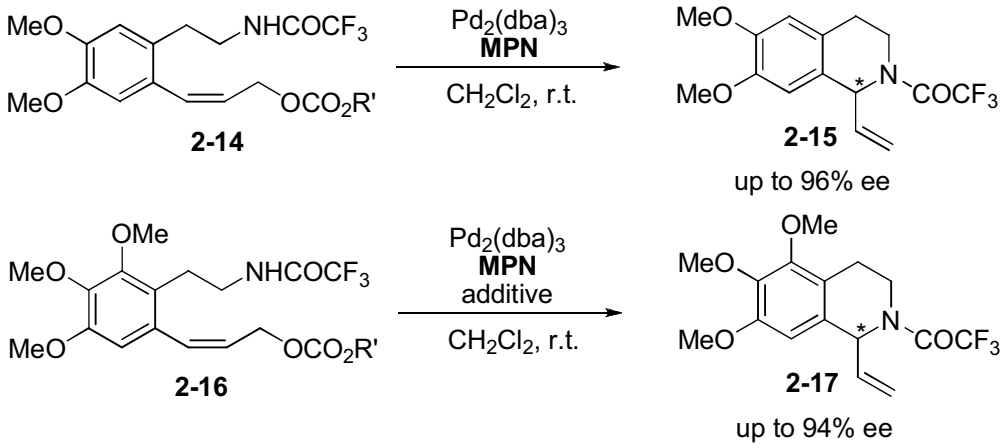


Figure 2-2. Selected naturally occurring C1-substituted tetrahydroisoquinolines

Optically active C1-substituted tetrahydroisoquinolines have been prepared through diastereoselective reactions for the introduction of chirality at the C1 position. Other methods utilizing enantioselective reactions to introduce the chirality at the C1 position have been developed in the past decade, these include enantioselective Pictet-Spengler reaction,[13] alkylation, vinylation or cyanation of 3,4-dihydroisoquinolines,[14] asymmetric hydrogenation of 3,4-dihydroisoquinolines[15] as well as 1- alkylidenetetrahydroisoquinolines,[16] and other transformations.[17] In 2003, a Pd-catalyzed intramolecular asymmetric allylic amination (AAA) catalyzed by a Pd catalyst with a chiral P,N ligand in the presence of a strong base was reported, giving 6,7-dimethoxy-1-vinyltetrahydroisoquinoline in a single step and introducing chirality at the C-1 position.[18] Although high enantioselectivity (82-88% ee) was realized under optimized conditions, the catalytic activity of this system was insufficient since it required 12-23 days to reach synthetically meaningful conversions.

In order to achieve excellent efficiency and enantioselectivity, the selection of suitable chiral ligands for this process is essential. We have been developing a library of novel enantiopure monodentate phosphite,[19] and phosphoramidite (MPN)[20] ligands based on axially chiral biphenols. These ligands can be readily prepared as described in Chapter 1 and are fine-tunable for a variety of catalytic asymmetric reactions. For example, asymmetric hydrogenation,[19] asymmetric hydroformylation,[20b] asymmetric conjugate additions to cycloalkenones and nitroalkeness,[20a,b] and asymmetric allylic alkylation, as well as its application to the total synthesis of (+)-γ-lycorane.[20c]

Since several of these chiral MPN ligands were found to be extremely effective (up to 99.7% ee) in the Pd-catalyzed asymmetric allylic alkylation mentioned above,[20c] we anticipated that this type of ligands would be effective for the AAA process. Thus, we employed chiral MPN ligands to the intramolecuar AAA reaction of compounds **2-14** and **2-16**, which indeed gave compounds **2-15** and **2-17** with excellent enantioselectivity (up to 96% ee for **2-15** and 91% ee for **2-17**) and high catalyst activity under neutral conditions (**Scheme 2-4**).[21]



Scheme 2-4. Highly efficient AAA reaction of **2-14** and **2-16**

We have also developed a library of novel chiral bidentate bisphosphonite (BOP) ligands based on axially chiral biphenols and successfully applied it to the intermolecular AAA reaction.[22] Building upon the successful application of our MPN ligands to the enantioselective synthesis of compounds **2-15** and **2-17** through Pd-catalyzed AAA reaction (**Scheme 2-5**), we have expanded the scope of the AAA reaction to the enantioselective synthesis of 6,8-dimethoxy-1-vinyltetrahydroisoquinoline **2-19A**, using MPN and BOP ligands (**Figure 2-3**), which serve as versatile intermediates for the synthesis of naturally occurring alkaloids

exemplified in **Figure 2-2**.

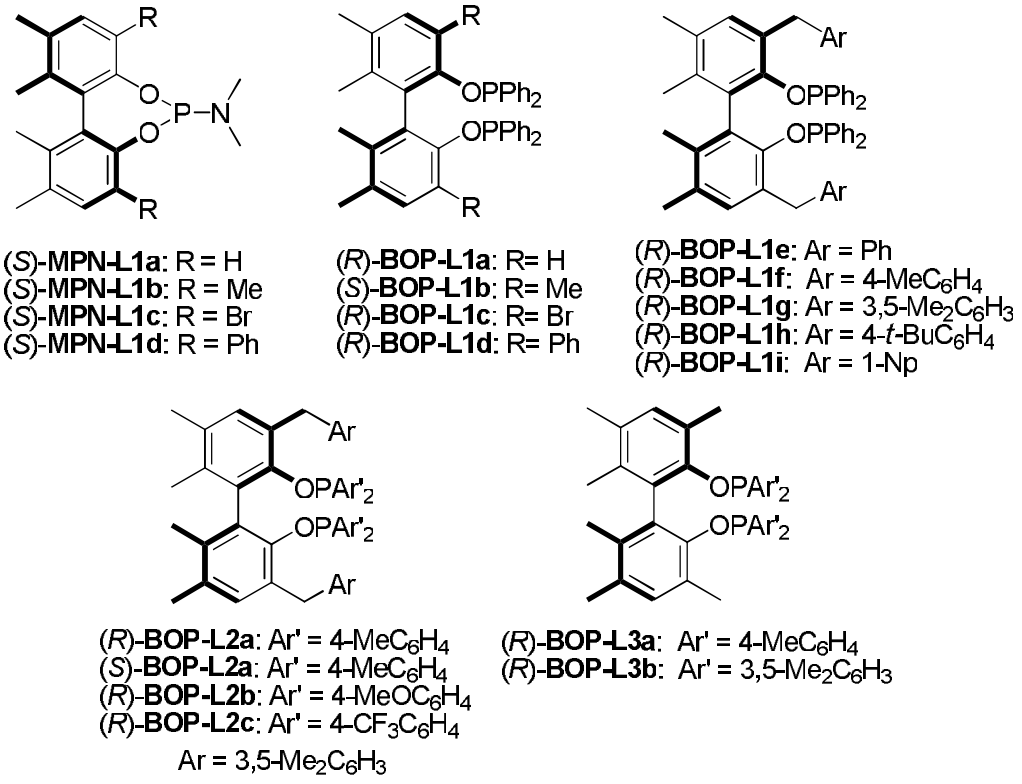
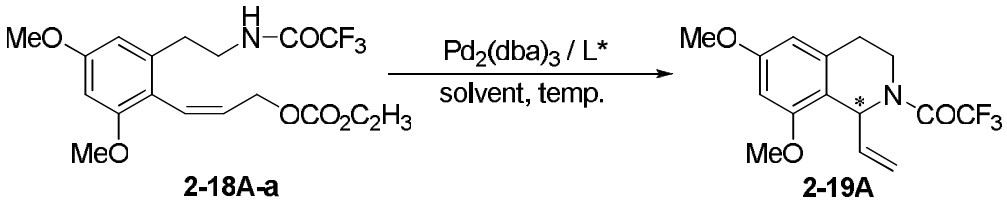


Figure 2-3. MPN and **BOP** ligand libraries



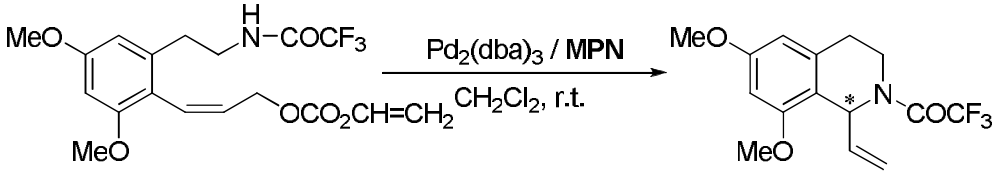
Scheme 2-5. AAA reactions for the formation of **2-19A**

§ 2.2.2 Preliminary results of intramolecular asymmetric allylic amination of 2-18A-a

The Pd-catalyzed AAA reaction of 2,4-dimethoxyphenylallyl carbonate **2-18A-a** was first carried out by Dr. Ce Shi using MPN ligands under the same conditions as those employed in the reaction of 3,4-dimethoxyphenylallyl carbonate **2-14**,[21] which gave excellent results (**Scheme 2-4**). The reaction proceeded smoothly to give (*S*)-(+)-tetrahydroisoquinoline **2-19A** in excellent yield (Table 2-1). To our surprise, however, the reactions using (*S*)-**MPN-L1a~1d** did not give the same high level of enantioselectivity as that observed in the reactions of **2-14**.[21] As Table 2-1

shows, the best result was 47% ee (entry 3) when (*S*)-**MPN-L1c** (R = Br) was used as the chiral ligand. (*S*)-**MPN-L1d** (R = Ph), which achieved 95-96% ee in the AAA reaction of **2-14**,[21] gave only 29% ee (entry 4). (*S*)-**MPN-L1a** (R = H) afforded (*R*)-(+)-**2-19A** with 26% ee (entry 1), which has the opposite configuration to that induced by all other MPN ligands examined. The results appear to indicate that the methoxy group at the C6 position of **2-18A-a**, which is *ortho* to the allyl carbonate moiety, is responsible for the observed marked difference in enantioselectivity for the AAA reaction of **2-14** and that of **2-18A-a**.[23]

Table 2-1. Efficacy of **MPN** ligands in the Pd-catalyzed AAA reaction of **2-18A-a**[23]



2-18A-a **2-19A**

Entry[a]	Ligand	Time (h)	Conv. (%)[b]	**2-19A** % *ee*[c]
1	(*S*)-**MPN-L1a**	10	>95	26 (*R*)
2	(*S*)-**MPN-L1b**	16	>95	19 (*S*)
3	(*S*)-**MPN-L1c**	22	>95	47 (*S*)
4	(*S*)-**MPN-L1d**	48	>95	29 (*S*)

[a] Reaction was run with **2-18** (0.05 mmol), $Pd_2(dba)_3$ (1.25×10^{-3} mmol) and **MPN-L** (3.75×10^{-3} mmol) in DCM at room temperature.
[b] Determined by ^1H NMR.
[c] Determined by chiral HPLC analysis (OD-H column, isopropanol /hexanes = 0.5/99.5, flow rate: 0.5 mL/min.

Since none of the simple MPN ligands gave encouraging result, we examined the efficacy of BOP ligands, (*R*)-**BOP-L1a~1g** and (*R*)-**BOP-L3a~3b**, in this AAA reaction. Results are summarized in Table 2-2. The reactions proceeded very smoothly in DMF at room temperature and completed in 1.5~8 h. Among the first four BOP ligands employed (**BOP-L1a~1d**), which bears H, Me, Br, and Ph groups at the 3, 3' positions, **BOP-L1c** (R = Br) gave the best result, i.e., 72% ee (entry 3). However, **BOP-L1e** (Ar = Ph) achieved even better result, giving (*S*)-(+)-**2-19A** with 79% ee (entry 5). Enantioselectivity was further increased to 84% ee and

88% ee by introducing 4-methylbenzyl (**BOP-L1f**) and 3,5-dimethylbenzyl (**BOP-L1g**) groups, respectively, in place of benzyl group (entries 6 and 9). Introduction of p-tolyl (**BOP-L3a**) and 3,5-xylyl (**BOP-L3b**) groups as Ar moiety, keeping methyl groups as the 3, 3' substituents, also improved the enantioselectivity to 72% ee and 80% ee, respectively (entries 12 and 13), as compared to 68% ee achieved by the parent ligand, **BOP-L1b** (entry 2).[23]

Table 2-2. The Pd-catalyzed AAA reaction of **2-18A-a** with **BOP** ligands[23]

Entry[a]	Ligand	Temp (^{o}C)	Time (h)	Conv. (%)[b]	**2-19A** (*S*) % ee[c]
1	(*R*)-**BOP-L1a**	r.t.	1.5	>95	35
2	(*R*)-**BOP-L1b**	r.t.	4	>95	68
3	(*R*)-**BOP-L1c**	r.t.	8	>95	72
4	(*R*)-**BOP-L1d**	r.t.	8	>95	68
5	(*R*)-**BOP-L1e**	r.t.	6	>95	79
6	(*R*)-**BOP-L1f**	r.t.	8	>95	84
7	(*R*)-**BOP-L1f**	0	24	>95	88
8	(*R*)-**BOP-L1f**	-25	48	<5	nd
9	(*R*)-**BOP-L1g**	r.t.	8	>95	88
10	(*R*)-**BOP-L1g**	0	24	>95	90
11	(*R*)-**BOP-L1g**	-25	48	<5	nd
12	(*R*)-**BOP-L3a**	r.t.	8	>95	72
13	(*R*)-**BOP-L3b**	r.t.	12	>95	80

[a] Reaction was run with **2-18A-a** (0.05 mmol), $Pd_2(dba)_3$ (1.1 x 10^{-3} mmol) and **BOP-L** (3.3 x 10^{-3} mmol) in DMF (0.5 mL)
[b, c, d] See the captions in **Table 2-1**.

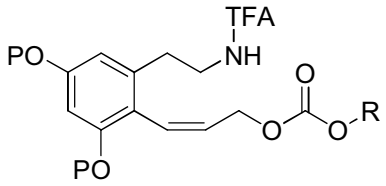
Lowering the reaction temperature from room temperature to 0 ^{o}C improved enantioselectivity to 88% ee (from 84% ee, entry 7) for **BOP-L1f** and to 90% ee (from 88% ee,

entry 9) for **BOP-L1g**. However, at -25 °C, the reaction was basically shut down (entries 8 and 11).[23]

According to the data reported above, so far, the best ee achieved is 90% using **(*R*)-BOP-L1g** at 0 °C for 24 h. (**Table 2-2**, entry 10). Therefore, further optimization on the structure of both the ligand and substrate are still necessary to improve the enantioselectivity of above AAA reaction.

§ 2.3 Results and discussion

Here, the main strategy for the substrate modifications was to change the substituents bearing on the resorcinol moiety from Me to Bn and PMB because we believe that the alkoxy group at C-6 position of the phenyl ring might have some steric effect to the allylic moiety and thus affect the chiral ligand orientation on the Pd catalyst to provide either a decrease or increase of enantioselectivity during the catalytic process (**Figure 2-4**). Furthermore, if these substituents need to be cleaved at the end of the synthesis, Bn and PMB are more appropriate protecting groups than Me due to the milder deprotection conditions. In addition to the modification of alkoxy groups, the R group of the carbonate moiety was also investigated because it acts as counterion to the Pd-η-allyl complex which can also have potential to affect the enantioselectivity during the catalytic process (**Figure 2-4**).



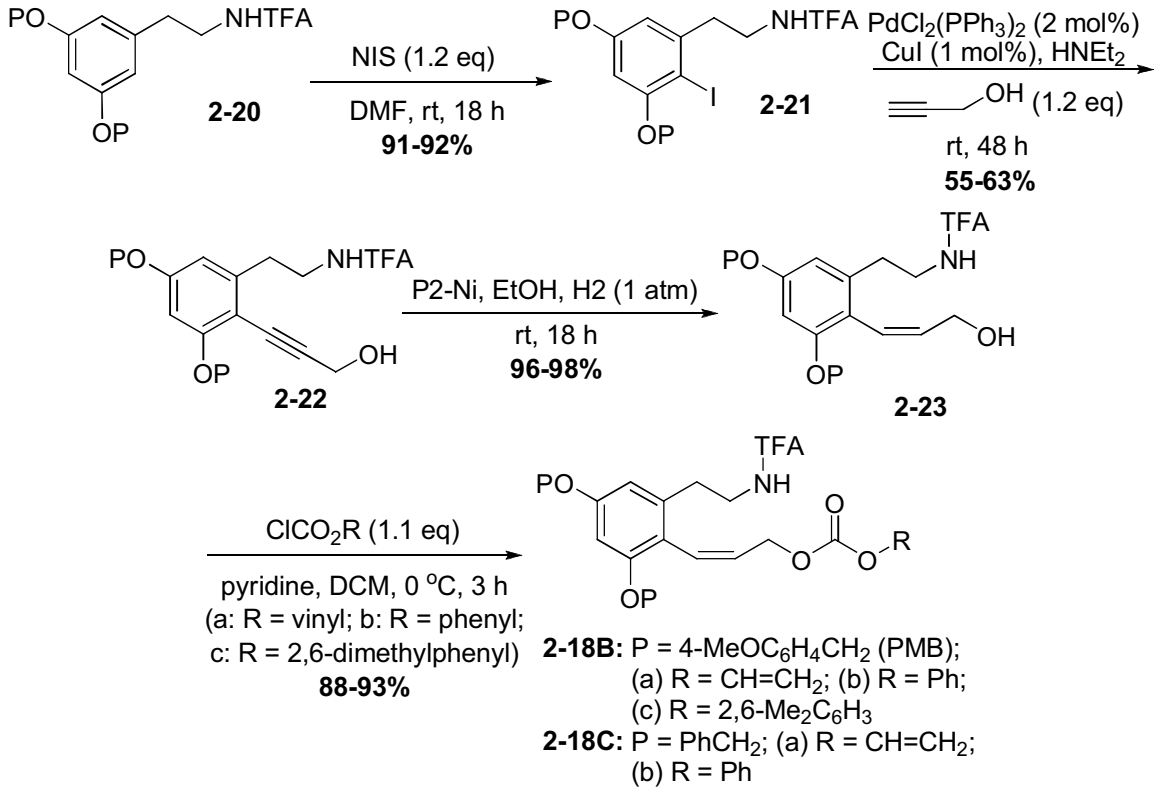
P = $PhCH_2$ (Bn), 4-$MeOC_6H_4CH_2$ (PMB)
R = $CH{=}CH_2$, Ph, 2,6-$Me_2C_6H_3$

Figure 2-4. Substrate modifications

§ 2.3.1 Synthesis of substrates 2-18B-a~c and 2-18C-a~b

The AAA substrate **2-18B** (P = 4-methoxybenzyl (PMB), R' = CF_3) was prepared from the *N*-trifluoroacetyl-*O,O*-bis-PMB-resorcinolamine (**2-20B**)[25] as shown in **Scheme 2-6**. The iodination of **2-20B** (TFA = trifluoroacetyl) with *N*-iodosuccinimide (NIS)[26] proceeded smoothly to give **2-21B**. No bis-iodinated product was detected by TLC. The Sonogashira coupling of **2-21B** with propargyl alcohol gave compound **2-22B** in fairly good yield (60-65%), wherein

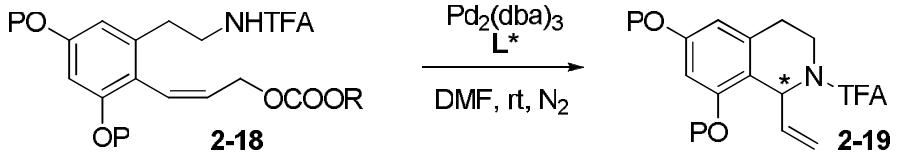
conversion was 80-85% after 48 h (15-20% **2-21B** was recovered). Selective hydrogenation of **2-22B** over P2-Ni catalyst under ambient conditions gave cis-allylic alcohol **2-23B** cleanly. The subsequent acylation of the alcohol moiety with chloroformates gave the corresponding allylic carbonates, i.e., AAA substrates **2-18B-a~c** in excellent yields. In the same manner, AAA substrates **2-18C-a,b** were prepared from *N*-trifluoroacetyl-*O,O*-dibenzylresorcinolamine (**2-20C**) in similar yield.



Scheme 2-6. Preparation of AAA substrate **2-18B-a~c** and **2-18C-a~b**

§ 2.3.2 Pd-Catalyzed intramolecular asymmetric allylic amination

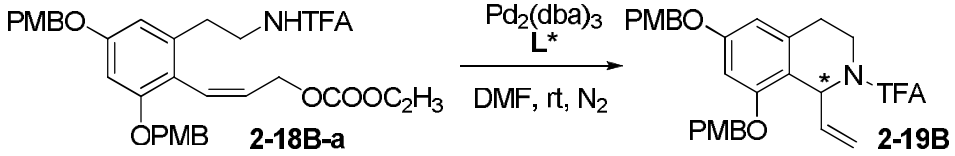
Since BOP ligands gave better ee than MPN ligands did in this type of reaction, the previously reported **BOP** ligands (**L1a~1i**) and some new **BOP** ligands (**L2a~2c**) were synthesized (**Figure 2-3**) and examined for efficacy in the AAA reaction of **2-18**.



Scheme 2-7. Pd-catalyzed AAA reaction of **2-18**

First, **BOP-L1a~d** were screened for the AAA reaction of **2-18B-a** to give **2-19B** using $Pd_2(dba)_3$ (dba = dibenzylideneacetone) as the catalyst precursor in DMF at room temperature under nitrogen (**Scheme 2-7**). As shown in **Table 2-3**, all reactions gave >95% conversion in less than 6 h. There was a dramatic increase in enantioselectivity when the 3,3'-substituents were changed from hydrogen (entry 1) to methyl and other groups (entries 2-4). Among the four BOP ligands examined, (*S*)-**BOP-L1b** (R = Me), gave (-)-**2-19B** with 80% ee (entry 2). Accordingly, we also carried out the reaction of **2-18C-a** (P = $PhCH_2$, R = vinyl) to see if there was a difference in enantioselectivity, depending on the protecting group of the phenolic hydroxyl groups (**Scheme 2-7**). The reactions of **2-18C-a** and **2-18C-b** under the same conditions as those for **2-18B-a** completed in 2 h and 6h, respectively, to afford (-)-**2-19C** (P = $PhCH_2$) in quantitative yield with 75% ee and 76% ee, respectively. Thus, **2-18B-a** appeared to be a better substrate than **2-18C-a** and **2-18C-b**. Also, it was found that there was a difficulty in separating (-)-**2-19C** from a small amount of dba by flash chromatography on silica gel, due to their very small difference in polarity. In contrast, the separation of (-)-**2-19B** from dba did not have any problem. Therefore, **2-18B** series substrates (P = PMB) were selected for optimization.

Table 2-3. Screening of **BOP** ligands **L1a~d** for the AAA reaction of **2-18B-a**[a]



Entry	Ligand (L*)	Time (h)	Conv. (%)[b]	**2-19B** % ee[c]
1	(*R*)-**BOP-L1a**	1.5	>95	4 (+)
2	(*S*)-**BOP-L1b**	2	>95	80 (-)
3	(*R*)-**BOP-L1c**	5	>95	79 (+)
4	(*R*)-**BOP-L1d**	5	>95	74 (+)

[a]All reactions were run using $Pd_2(dba)_3$ (2.5 mol%) with a BOP ligand (7.5 mol%) in DMF at room temperature under N_2.
[b]Determined by 1H NMR.
[c]Determined by HPLC using Chralpak AD-RH, CH3CN/H2O = 50/50.

BOP ligands bearing benzyl or substituted benzyl group at the 3,3'-positions were examined, as well. Results are shown in **Table 2-4**. Among those **BOP** ligands screened,

(*R*)-**BOP-L1g** (R = 3,5-dimethylbenzyl) gave the best result so far (entry 3). Thus, this **BOP** ligand was selected as the ligand of choice for further optimization.

Table 2-4. Screening of new **BOP** ligands for the AAA reaction of **2-18B-a**[a]

Entry	Ligand (L*)	Time (h)	Conv. (%)[b]	**2-19B** % ee[c]
1	(*R*)-**BOP-L1e**	4	>95	83 (+)
2	(*R*)-**BOP-L1f**	4	>95	83 (+)
3	(*R*)-**BOP-L1g**	6	>95	84 (+)
4	(*R*)-**BOP-L1h**	4	>95	80 (+)
5	(*R*)-**BOP-L1i**	4	>95	80 (+)

[a,b,c] See the footnote of **Table 2-3**.

Next, the effects of the concentration of the reaction mixture as well as the chiral ligand/Pd ratio on enantioselectivity were examined using (*R*)-**BOP-L1g**. As shown in **Table 2-5**, higher concentrations gave better results (entries 3 and 4) than the lower concentration (entry 1) that was employed in the screening described above. At concentrations higher than 0.5 M, Pd species precipitated out, resulting in low reactivity. Thus, we chose 0.5 M concentration for further optimization, although 0.25 M concentration afforded a slightly higher enantioselectivity, by taking into account the economical and environmental merit of using less solvent.

Table 2-5. Effect of concentration and L*/Pd ratio on the AAA reaction of **2-18B-a**[a]

Entry	conc. (M)	L*/Pd	Time (h)	Conv. (%)[b]	**2-19B** % ee[c]
1	0.05	1.5	6.0	>95	84.0 (+)
2	0.10	1.5	5.5	>95	87.5 (+)
3	0.25	1.5	5.0	>95	90.3 (+)
4	0.50	1.5	5.0	>95	90.1 (+)
5	0.50	1.0	4.5	>95	91.1 (+)

[a]Reactions were run using $Pd_2(dba)_3$ (2.5 mol%) with (*R*)-**BOP-L1g** ligand (L*) in DMF at room temperature under N_2.
[b,c] See the footnote of **Table 2-3**.

For the optimal ligand/Pd ratio, just the use of 1 equivalent of **BOP-L1g** to Pd metal gave a bit better enantioselectivity than that achieved by using 1.5 equivalents of the ligand to the metal (entry 5). Thus, the stoichiometric use of the ligand was employed for further optimization.

At this point, we examined the possible electronic effect of the diphenylphosphinyl moiety of **BOP-L1g** on enantioselectivity as a further optimization process. Thus, (*R*)-**BOP-L2a~c** ligands were prepared (see Experimental Section), and their efficacy evaluated in the AAA of **2-18B-a** under the optimized conditions described above. As shown in **Table 2-6**, the introduction of electron-releasing substituents, i.e. Me (**BOP-L2a**) and MeO (**BOP-L2b**) groups, at the para-position of the diphenylphosphinyl moiety of **BOP-L1g** improved the efficacy (entries 2-4), while that of electron-withdrawing CF_3 group (**BOP-L2c**) considerably decreased enantioselectivity (entry 5). Accordingly, (*R*)-**BOP-L2a**, which gave 94.0% ee (entry 2), was selected as the best **BOP** ligand for this reaction.

Table 2-6. Electronic effect on the efficacy of new **BOP** ligands

Entry	Ligand (L*)	Time (h)	Conv. (%)[b]	**2-19B** % ee[c]
1	(*R*)-**BOP-L1g**	4.5	>95	91.1 (+)
2	(*R*)-**BOP-L2a**	7	>95	94.0 (+)
3	(*S*)-**BOP-L2a**	7	>95	96.1 (-)
4	(*R*)-**BOP-L2b**	7	>95	93.3 (+)
5	(*R*)-**BOP-L2c**	7	>95	81.5 (+)

[a]Reactions were run using Pd2(dba)3 (2.5 mol%) with a BOP ligand (5.0 mol%) in DMF at room temperature.
[b,c] See the footnote of **Table 2-3**.

We also examined the effect of the allylic carbonate substituents on this AAA reaction. As shown in **Table 2-7**, the vinyl carbonate (**2-18B-a**) gave slightly better result (94.0% ee) (entry 1) than other two carbonates (**2-18B-b** and **2-18B-c**; entries 2 and 3). Effect of the reaction temperature on enantioselectivity and reaction rate was also examined. The reaction at 10 and 0 ^{o}C gave higher enantioselectivity (95.0 and 95.6% ee, respectively), but at 0 ^{o}C the reaction rate was substantially decreased as compared to that at 10 or 25 ^{o}C (entries 4 and 5).

Table 2-7. Effects of the substrate structure and reaction temperature on the AAA reaction

Entry	Substrate	Temp(°C)	Time (h)	Conv. (%)[b]	**2-19B** % ee[c]
1	2-18B-a	25	7	>95	94.0 (+)
2	2-18B-b	25	7	>95	93.6 (+)
3	2-18B-c	25	7	>95	92.0 (+)
4	2-18B-a	10	48	>95	95.0 (+)
5	2-18B-a	0	96	76	95.6 (+)

[a]Reactions were run using $Pd_2(dba)_3$ (2.5 mol%) with (*R*)-**BOP-L2a** (5.0 mol%) in DMF at room temperature.
[b,c] See the footnote of **Table 2-3**.

§ 2.4 Conclusions

We have successfully synthesized 1-vinyl-6,8-di(4-methoxybenzyl)tetrahydroisoquinoline **2-19B** with >95% ee by means of Pd-catalyzed intramolecular AAA reactions using the BOP ligand library, developed in our laboratory. The 1-vinlyltetrahydroisoquinolines thus obtained can be served as the key intermediate for the synthesis of Schulzeines A-C which was described in chapter 3.

§ 2.5 Experimental section

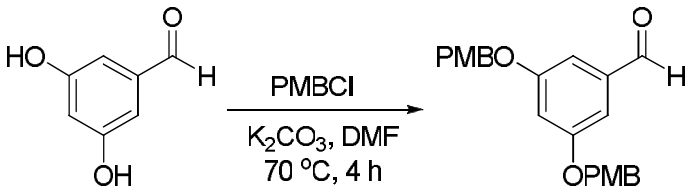
General Methods: ^{1}H and ^{13}C and ^{31}P NMR were measured on a Varian Inova-500 NMR (500 MHz ^{1}H, and 125 MHz ^{13}C), a Varian Inova-400 NMR (400 MHz ^{1}H; 100 MHz ^{13}C; 162 MHz ^{31}P) or a Varian Gemini-2300 (300 MHz ^{1}H; 75 MHz ^{13}C; 121.5 MHz ^{31}P) spectrometer in a deuterated solvent using residual protons ($CHCl_3$: ^{1}H, 7.26 ppm; ^{13}C, 77.0 ppm. C_6H_6: ^{1}H, 7.15 ppm) as the internal standard or phosphoric acid as the external reference (^{31}P 0.00 ppm). Analytical HPLC in reverse phase was carried out with a Shimadzu LC-2010A HPLC system using a Chiralpak AD-RH analytical column. Melting points were measured on a Thomas Hoover Capillary melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Helmer Model 241 polarimeter. TLC analyses were performed using Merck DC Alufolien 60F254 aluminum pre-coated silica gel plates. Flash column chromatography was carried out using Silicyle Silia*Flash*P60® silica gel (particle size 40–63 μm). High-resolution mass spectrometric analyses were carried out at Mass Spectrometry Laboratories, University of

Illinois Urbana-Champaign, Urbana, IL and ICB&DD at Stony Brook University. Unless otherwise noted all reactions were carried out under argon or nitrogen atmosphere in oven-dried glassware using standard Schlenck techniques.

Materials: Solvents were reagents grade and freshly distilled before use. Tetrahydrofuran (THF) and dichloromethane (DCM) were dried and degassed using an Innovative Technology PureSolvTM solvent purification system. Acetonitrile was distilled from calcium hydride. Anhydrous *N,N*-dimethylformamide (DMF) was purchased from Acros and used without further purification. Other solvents were used without purification. Other chemicals and reagents were purchased from Sigma-Aldrich or Fisher Scientific and used without further purification unless otherwise noted. Chiral biphenols and chiral **BOP** ligands, **L1a-L1i** were prepared according to the procedure previously reported by our laboratory.[22]

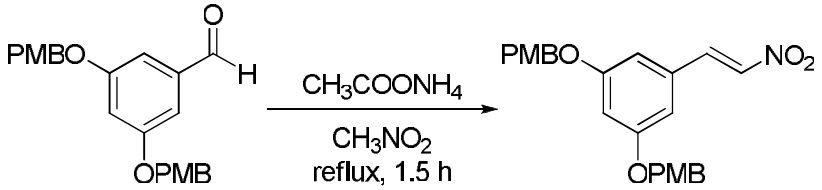
Synthesis of substrates 2-18B-a~c and 2-18C-a~b

3,5-Bis(4-methoxybenzyloxy)benzaldehyde



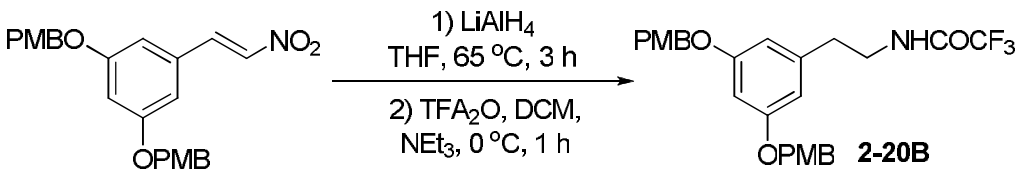
To a stirred solution of 3,5-dihydroxybenzaldehyde (4.50 g, 32.6 mmol) and K_2CO_3 (6 equiv) in DMF (150 mL) was added 4-methoxybenzyl chloride (9.60 mL, 71.7 mmol) at room temperature. Then, the mixture was stirred at 70 ^oC for 4 h. The reaction mixture was cooled to room temperature and diluted with EtOAc (75 mL) and water (75 mL). The organic layer was separated and washed with water (100 mL x3). The organic layer was then washed with brine and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the solvent evaporated *in vacuo* to afford crude yellow solid. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc = 10:1→4:1) afforded 3,5-bis(4-methoxybenzyloxy)benzaldehyde as a white solid (9.48 g, 77% yield): mp 70-71 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 6H), 5.01 (s, 4H), 6.84 (t, J = 2.1 Hz, 1H), 6.92 (d, J = 8.4 Hz, 4H), 7.09 (d, J = 2.1 Hz, 2H), 7.35 (d, J = 8.4 Hz, 4H), 9.89 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 70.4, 106.1, 108.5, 108.9, 114.3, 128.5, 129.5, 138.6, 159.9, 160.6, 192.0; HRMS (ESI+) calcd. For $C_{23}H_{22}O_5Na$ $[M+Na]^+$ 401.1365, found 401.1366 (Δ = 0.2 ppm).

1,3-Bis(4-methoxybenzyloxy)-5-[(*E*)-2-nitroethenyl]benzene



A mixture of 3,5-bis(4-methoxybenzyloxy)benzaldehyde (7.62 g, 20.2 mmol), $CH_3CO_2NH_4$ (1.56 g, 20.2 mmol) and CH_3NO_2 (106 mL) was placed in a 250 mL round-bottomed flask. Then, the mixture was heated to reflux (about 110 ^oC) for 1.5 h. The reaction mixture was cooled to room temperature and diluted with Et_2O (100 mL) and water (100 mL). The aqueous layer was separated and extracted with Et_2O (100 mL x2). The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the solvent evaporated *in vacuo* to afford crude yellow solid, which was washed with EtOH to afford 1,3-bis(4-methoxybenzyloxy)-5-[(*E*)-2-nitroethenyl]benzene as a yellow solid (7.21 g, 85% yield): mp 128-130 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 3.83 (s, 6H), 4.99 (s, 4H), 6.73 (m, 3H), 6.93 (d, J = 8.7 Hz, 4H), 7.34 (d, J = 8.7 Hz, 4H), 7.51 (d, J = 13.5 Hz, 1H), 7.90 (d, J = 13.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 70.4, 106.1, 108.4, 114.3, 128.4, 129.5, 131.9, 137.7, 139.3, 159.9, 160.6; HRMS (ESI+) calcd. For $C_{24}H_{23}NO_6Na$ $[M+Na]^+$ 444.1423, found 444.1422 (Δ = -0.2 ppm).

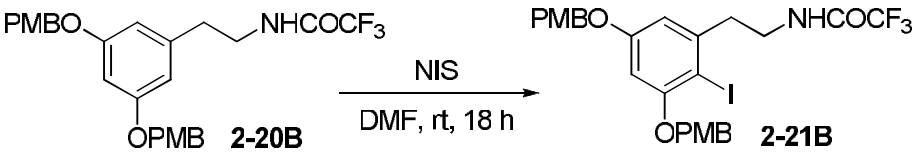
1,3-Bis(4-methoxybenzyloxy)-5-[2-(*N*-trifluoroacetylamino)ethyl]benzene (2-20B)



To a suspension of $LiAlH_4$ (2.54 g, 66.4 mmol) in THF (50 mL) was added dropwise a solution of 1,3-bis(4-methoxybenzyloxy)-5-[(*E*)-2-nitroethenyl]benzene (6.98 g, 16.6 mmol) in THF (120 mL) at 0 ^oC under nitrogen. Then, the mixture was heated to 65 ^oC for 3 h. The reaction mixture was cooled to room temperature, diluted with Et_2O (30 mL), and quenched with 20% KOH (50 mL) at 0 ^oC. The resulting precipitate was removed by filtration, and the aqueous layer was separated and extracted with Et_2O (50 mL x3). The combined organic layer was washed with brine and dried over anhydrous K_2CO_3. The drying agent was removed by filtration and the solvent was concentrated in *vacuo* to afford the crude product as brown oil. The brown

oil was dissolved in DCM (120 mL) and NEt_3 (5.77 mL, 41.5 mmol) was added. To this mixture was added slowly $(CF_3CO)_2O$ (3.04 mL, 21.6 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, and distilled water (10 mL) was added to quench the reaction. The aqueous layer was separated and extracted with DCM (50 mL x3). The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the solvent evaporated *in vacuo* to afford the crude product as a brown solid. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc = 20:1→5:1) afforded **2-20B** as a white solid (4.68 g, 58% yield for two steps): mp 116-117 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.81 (t, *J* = 6.6 Hz, 2H), 3.60 (q, *J* = 6.6 Hz, 2H), 3.82 (s, 6H), 4.94 (s, 4H), 6.26 (br, 1H), 6.41 (d, *J* = 2.4 Hz, 2H), 6.51 (t, *J* = 2.4 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 4H), 7.34 (d, *J* = 8.4 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.3, 40.9, 55.5, 70.1, 100.8, 107.9, 114.3, 116.0 (q, *J* = 286 Hz), 128.9, 129.5, 139.9, 157.3 (q, *J* = 37 Hz), 159.7, 160.6; HRMS (ESI+) calcd. For $C_{26}H_{27}NO_5F_3$ $[M+H]^+$ 490.1841, found 490.1840 (Δ = -0.2 ppm).

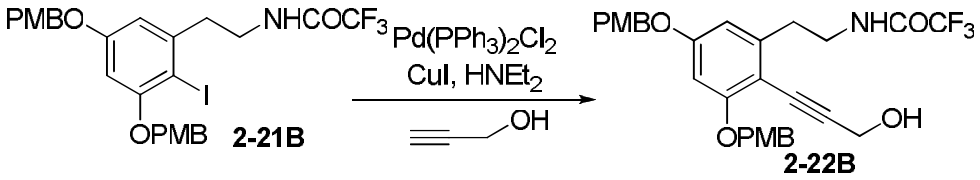
2,4-Bis(4-methoxybenzyloxy)-1-iodo-6-[2-(trifluoroacetamido)ethyl)]benzene (2-21B)



To a solution of **2-20B** (3.26 g, 6.65 mmol) in anhydrous DMF (12 mL) was added *N*-iodosuccinimide (NIS) (1.87 g, 8.31 mmol) all at once at room temperature. The mixture was stirred at room temperature until TLC indicated the completion of the reaction (18 h). The reaction mixture was then diluted with EtOAc (50 mL) and filtered through a pad of Celite. The filtrate was washed with distilled water (50 mL), and the aqueous layer was extracted with EtOAc (50 mL x2). The combined organic layer was washed with saturated Na_2SO_3 (50 mL x2) and brine, and died over anhydrous $MgSO_4$. The drying agent was removed by filtration and the solvent evaporated *in vacuo* to afford the crude product as a yellow solid. Recrystallization of the crude product from hexanes/EtOAc (4/1) afforded **2-21B** as white solid (3.71 g, 91% yield): mp 134-135 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.07 (t, *J* = 6.9 Hz, 2H), 3.64 (q, *J* = 6.9 Hz, 2H), 3.82 (s, 6H), 4.93 (s, 2H), 5.03 (s, 2H), 6.34 (br, 1H), 6.45 (d, *J* = 2.7 Hz, 1H), 6.51 (d, *J* = 2.7 Hz, 1H), 6.92 (d, *J* = 8.7 Hz, 4H), 7.32 (d, *J* = 8.7 Hz, 2H), 7.40 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.9, 40.0, 55.4, 55.5, 70.3, 71.2, 82.9, 100.2, 108.6, 114.2, 114.3, 116.0 (q,

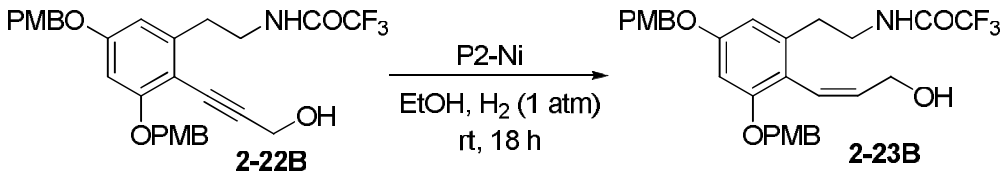
J = 287 Hz), 128.5, 128.6, 128.9, 129.5, 142.6, 157.5 (q, J = 37 Hz), 158.6, 159.6, 159.9, 160.5; HRMS (ESI+) calcd. For $C_{26}H_{25}NO_5F_3NaI$ $[M+Na]^+$ 638.0627, found 638.0626 (Δ = -0.2 ppm).

1,3-Bis(4-methoxybenzyloxy)-6-(3-hydroxyprop-1-ynyl)-5-[2-(trifluoroacetamido)ethyl]benzene (2-22B)



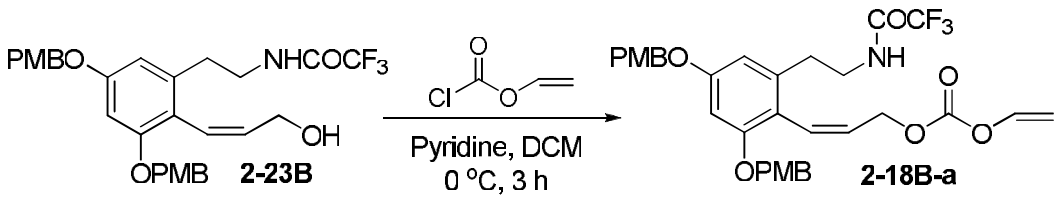
A mixture of **2-21B** (1.52 g, 2.47 mmol), $Pd(PPh_3)_2Cl_2$ (86.7 mg, 0.124 mmol), and CuI (47.0 mg, 0.247 mmol) was placed in a 50 mL round-bottomed flask. After purging the flask with nitrogen, Et_2NH (30 mL) was added to the mixture, and the solution was stirred for 20 min at 30 ^oC to dissolve **2-21B**. Propargyl alcohol (0.29 mL, 4.94 mmol) was added to this mixture via a syringe under at the same temperature. The reaction mixture was heated to reflux until TLC indicated the completion of the reaction (48 h). Then, saturated NH_4Cl solution (25 mL) was added to quench the reaction. The aqueous layer was extracted with EtOAc (30 mL x3). The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the solvent evaporated *in vacuo* to afford the crude product as brown oil. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc = 5:1→1:1) afforded **2-22B** as an off-white solid (851 mg, 63% yield): mp 123-124 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 2.44 (t, J = 6.3 Hz, 1H), 3.03 (t, J = 7.2 Hz, 2H), 3.64 (q, J = 7.2 Hz, 2H), 3.82 (s, 3H), 3.83 (s, 3H), 4.53 (d, J = 6.3 Hz, 2H), 4.93 (s, 2H), 4.93 (s, 2H), 5.05 (s, 2H), 6.42 (d, J = 2.1 Hz, 1H), 6.45 (d, J = 2.1 Hz, 1H), 6.63 (br, 1H), 6.90 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 7.32 (d, J = 8.7 Hz, 2H), 7.35 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.5, 40.7, 52.0, 55.5, 55.6, 70.2, 70.7, 80.2, 95.2, 99.8, 105.6, 107.9, 114.2, 114.3, 116.0 (q, J = 286 Hz), 128.5, 128.8, 128.9, 129.5, 142.9, 157.6 (q, J = 37 Hz), 159.6, 159.9, 160.1, 161.1; HRMS (ESI+) calcd. For $C_{29}H_{29}NO_6F_3$ $[M+H]^+$ 544.1947, found 544.1947 (Δ = 0.0 ppm).

1,3-Bis(4-methoxybenzyloxy)-6-[(*Z*)-3-hydroxyprop-1-enyl]-5-[2-(trifluoroacetamido)ethyl] benzene (2-23B)



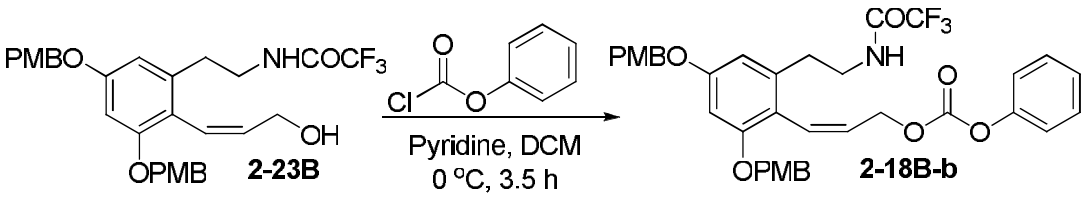
P2-Ni catalyst was generated *in situ* by adding $NaBH_4$ (85.9 mg, 1.70 mmol) to a suspension of $Ni(OAc)_2$ (271.3 mg, 0.893 mmol) in EtOH (7 mL) at room temperature under nitrogen with stirring. After 30 min, neat ethylenediamine (140 μL, 2.05 mmol) was added to the reaction mixture via a syringe. After stirring the catalyst solution for another 10 min, **2-22B** (790 mg, 1.45 mmol) in EtOH (50 mL) was added. The nitrogen atmosphere was then replaced by hydrogen (1 atm). The reaction mixture was stirred until TLC indicated the completion of the reaction (18 h). The reaction was quenched by addition of water (20 mL), and the aqueous layer was extracted with EtOAc (25 mL x3). The combined organic layer was washed with saturated $NaHCO_3$ solution and brine, and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the solvent evaporated *in vacuo* to afford the crude product as an off-white solid. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc = 7:3→1:1) afforded **2-23B** as a white solid (759 mg, 96% yield): mp 74-76 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.73 (m, 1H), 2.83 (t, *J* = 6.9 Hz, 2H), 3.54 (q, *J* = 6.9 Hz, 2H), 3.81 (s, 3H), 3.82 (s, 3H), 3.92 (dd, *J* = 0.9, 7.2 Hz, 2H), 4.91 (s, 2H), 4.95 (s, 2H), 6.01 (dt, *J* = 7.2, 10.8 Hz, 1H), 6.31 (d, *J* = 10.8 Hz, 1H), 6.44 (d, *J* = 2.4 Hz, 1H), 6.47 (br, 1H), 6.56 (d, *J* = 2.4 Hz, 1H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 7.30 (d, *J* = 8.7 Hz, 2H), 7.35 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.2, 40.0, 55.5, 55.6, 60.5, 70.2, 70.9, 100.0, 107.8, 114.3, 114.4, 116.0 (q, *J* = 287 Hz), 118.4, 124.8, 128.6, 128.9, 129.4, 129.5, 133.5, 138.3, 157.2, 157.4 (q, *J* = 38 Hz), 159.4, 159.8; HRMS (ESI+) calcd. For $C_{29}H_{30}NO_6F_3Na$ $[M+Na]^+$ 568.1923, found 568.1918 (Δ = -0.9 ppm).

1,3-Bis(4-methoxybenzyloxy)-6-(3-ethenyloxycarbonyloxyprop-1-enyl)-[2-(trifluoroacetamido) ethyl]benzene (2-18B-a)



To a solution of **2-23B** (221 mg, 0.404 mmol) and pyridine (0.8 mL) in DCM (8 mL) was added slowly vinyl chloroformate (0.050 mL, 0.48 mmol) in DCM (2.4 mL) at 0 ºC. After stirring the mixture at 0 °C for 3 h, the reaction was quenched by saturated $CuSO_4$ (10 mL). The aqueous layer was separated and extracted with Et_2O (15 mL x4). Combined organic layer was washed with distilled water and brine, and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the solvent evaporated *in vacuo* to afford the crude product as an off-white solid. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc = 5:1→7:3) afforded **2-18B-a** as a white solid (231 mg, 93% yield): mp 109-110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.89 (t, *J* = 6.6 Hz, 2H), 3.54 (q, *J* = 6.6 Hz, 2H), 3.82 (s, 3H), 3.83 (s, 3H), 4.51 (dd, *J* = 1.2, 6.3 Hz, 2H), 4.55 (dd, *J* = 2.1, 6.3 Hz, 1H), 4.88 (dd, *J* = 2.1, 13.8 Hz, 1H), 4.91 (s, 2H), 4.94 (s, 2H), 5.90 (dt, *J* = 6.3, 11.1 Hz, 1H), 6.42 (d, *J* = 2.1 Hz, 1H), 6.46 (dt, *J* = 2.1, 11.1 Hz, 1H), 6.55 (d, *J* = 2.1 Hz, 1H), 6.68 (br, 1H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 6.88-6.95 (m, 1H), 7.30 (d, *J* = 8.7 Hz, 2H), 7.33 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.9, 39.5, 55.5, 55.6, 66.9, 70.2, 70.6, 98.3, 99.8, 107.9, 114.2, 114.3, 116.0 (q, *J* = 287 Hz), 117.0, 127.0, 127.4, 128.8, 128.9, 129.3, 129.6, 138.5, 142.6, 153.1, 157.4, 157.5 (q, *J* = 38 Hz), 159.7, 159.8; HRMS (ESI+) calcd. For $C_{32}H_{32}NO_8F_3Na$ $[M+Na]^+$ 638.1978, found 638.1979 (Δ = 0.2 ppm).

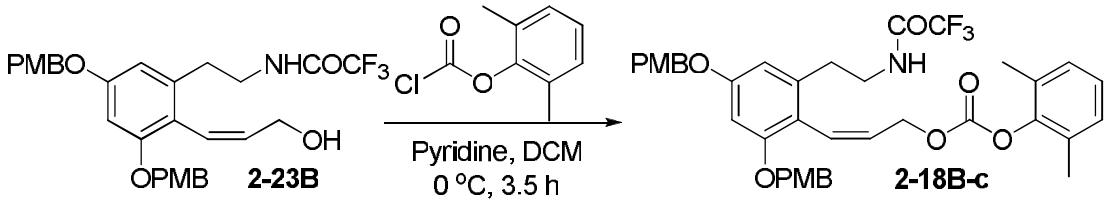
1,3-Bis(4-methoxybenzyloxy)-6-(3-phenoxycarbonyloxyprop-1-enyl)-[2-(trifluoroacetylamino)ethyl]benzene (2-18B-b)



The carbonate **2-18B-b** was synthesized in the same manner as that described for **2-18B-a**:

White solid (88% yield); mp 109-110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.88 (t, *J* = 6.6 Hz, 2H), 3.51 (q, *J* = 6.6 Hz, 2H), 4.60 (d, *J* = 6.6 Hz, 2H), 4.90 (s, 2H), 4.92 (s, 2H), 5.92 (dt, *J* = 6.6, 11.1 Hz, 1H), 6.39 (d, *J* = 2.1 Hz, 1H), 6.48 (d, *J* = 11.1 Hz, 1H), 6.55 (d, *J* = 2.1 Hz, 1H), 6.66 (br, 1H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 7.04-7.37 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.9, 39.4, 55.5, 55.6, 67.0, 70.1, 70.6, 99.8, 107.9, 114.2, 114.3, 115.9 (q, *J* = 286 Hz), 117.1, 121.1, 126.3, 127.1, 127.4, 128.8, 128.9, 129.3, 129.5, 129.6, 138.5, 151.2, 154.1, 157.3, 157.4 (q, *J* = 37 Hz), 159.6, 159.7, 159.8; HRMS (ESI+) calcd. For $C_{36}H_{34}NO_8F_3Na$ $[M+Na]^+$ 688.2134, found 688.2131 (Δ = -0.4 ppm).

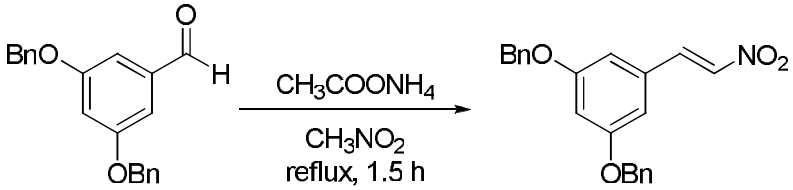
1,3-Bis(4-methoxybenzyloxy)-6-[3-(2,6-dimethylphen-1-oxy)carbonyloxyprop-1-enyl]-[2-(trifluoroacetylamino)ethyl]benzene (2-17A-c)



The carbonate **2-18B-c** was synthesized in the same manner as that described for **2-18B-a**: Colorless oil (92% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.12 (s, 6H), 2.88 (t, *J* = 6.8 Hz, 2H), 3.49 (q, *J* = 6.8 Hz, 2H), 3.82 (s, 6H), 4.57 (dd, *J* = 1.2 and 6.8 Hz, 2H), 4.90 (s, 2H), 4.92 (s, 2H), 5.91 (dt, *J* = 6.8, 10.8 Hz, 1H), 6.39 (d, *J* = 2.0 Hz, 1H), 6.48 (d, *J* = 10.8 Hz, 1H), 6.55 (d, *J* = 2.0 Hz, 1H), 6.67 (t, *J* = 6.8 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 2H), 7.02 (s, 3H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.8, 15.9, 32.7, 39.1, 55.3, 66.8, 69.9, 70.3, 99.6, 107.7, 113.9, 114.0, 115.7 (q, *J* = 282 Hz), 116.8, 126.1, 126.9, 127.2, 128.5, 128.6, 129.1, 129.3, 129.9, 138.3, 148.2, 153.3, 157.0, 157.3 (q, *J* = 36 Hz), 159.4, 159.5, 159.6; HRMS (ESI+) calcd. For $C_{38}H_{38}NO_8F_3Na$ $[M+Na]^+$ 716.2447, found 716.2451 (Δ = 0.6 ppm).

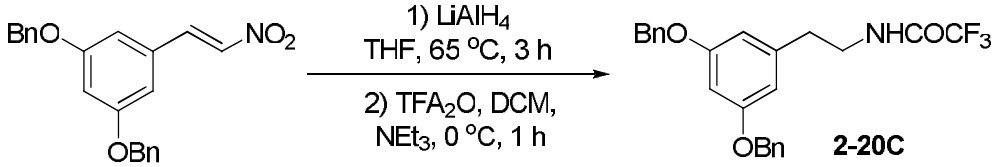
In the same manner as that described for **2-18B-a~c**, **2-18C-a,b** were prepared. Characterization data are shown below:

1,3-Dibenzyloxy-5-[(*E*)-2-nitroethenyl]benzene



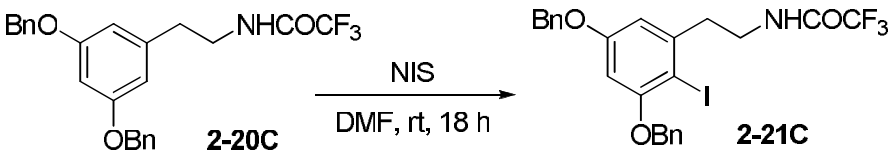
Yellow solid; 65% yield; mp 110-112 °C; ^{1}H NMR (300 MHz, CDC1$_3$) δ 5.06 (s, 4H), 6.75 (br, 3H), 7.35-7.42 (m, 10H), 7.50 (d, *J* = 13.5 Hz, 1H), 7.90 (d, *J* = 13.5 Hz, 1H); ^{13}C NMR (100 MHz, CDC1$_3$) δ 70.5, 106.0, 108.4, 127.7, 128.4, 128.9, 132.0, 136.4, 137.7, 139.2, 160.6; HRMS (ESI+) calcd. For $C_{22}H_{20}NO_4$ $[M+H]^+$ 362.1392, found 362.1396 (Δ = 1.1 ppm). All data are in agreement with the literature values.

1,3-Dibenzyloxy-5-[2-(*N*-trifluoroacetylamino)ethyl]benzene (2-20C)



White crystal; 55% yield for two steps from 1,3-dibenzyloxy-5-[(*E*)-nitroethenyl]benzene: mp 85-87 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.82 (t, *J* = 6.8 Hz, 2H), 3.61 (q, *J* = 6.8 Hz, 2H), 5.03 (s, 4H), 6.26 (br, 1H), 6.43 (d, *J* = 2.4 Hz, 2H), 6.54 (t, *J* = 2.4 Hz, 1H), 7.32-7.43 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.4, 40.9, 70.3, 100.8, 108.1, 116.0 (q, *J* = 286 Hz), 127.7, 128.3, 128.8, 136.9, 140.1, 157.3 (q, *J* = 36 Hz), 160.6; HRMS (ESI+) calcd. For $C_{24}H_{23}NO_3F_3$ $[M+H]^+$ 430.1630, found 430.1629 (Δ = -0.2 ppm).

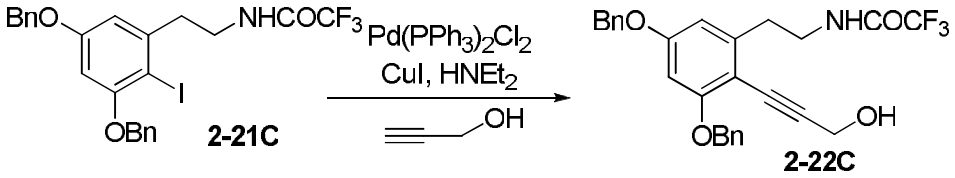
2,4-Dibenzyloxy-1-iodo-6-[2-(trifluoroacetamido)ethyl)]benzene (2-21C)



White solid; 92% yield; mp 139-141 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.08 (t, *J* = 6.9 Hz, 2H), 3.61 (q, *J* = 6.9 Hz, 2H), 5.00 (s, 2H), 5.10 (s, 2H), 6.37 (br, 1H), 6.46 (d, *J* = 2.4 Hz, 1H), 6.52 (d, *J* = 2.4 Hz, 1H), 7.31-7.50 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.9, 40.0, 70.6, 71.3, 82.9, 100.1, 108.6, 116.0 (q, *J* = 286 Hz), 127.3, 127.7, 128.2, 128.5, 128.8, 128.9, 136.4,

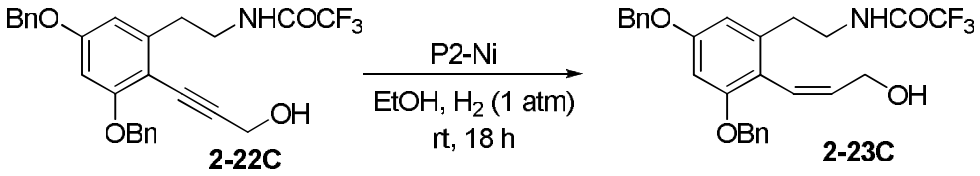
136.5, 142.7, 157.5 (q, J = 36 Hz), 158.5, 160.5. HRMS (ESI+) calcd. For $C_{24}H_{21}NO_3F_3NaI$ $[M+Na]^+$ 578.0416, found 578.0415 (Δ = -0.2 ppm).

1,3-Dibenzyloxy-6-(3-hydroxyprop-1-ynyl)-5-[2-(trifluoroacetamido)ethyl]benzene (2-22C)



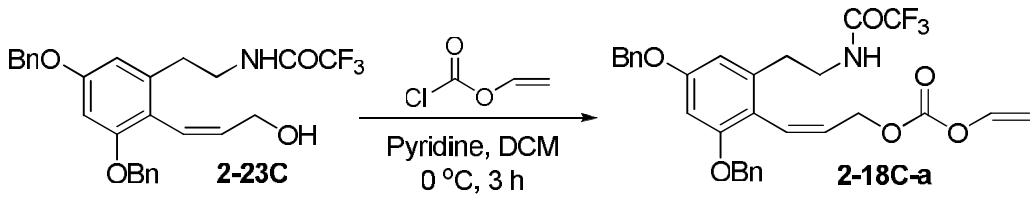
Off-white solid; 55% yield; mp 121-123 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 2.50 (t, J = 6.0 Hz, 1H), 3.03 (t, J = 7.2 Hz, 2H), 3.64 (q, J = 7.2 Hz, 2H), 5.00 (s, 2H), 5.12 (s, 2H), 6.43 (d, J = 2.4 Hz, 1H), 6.46 (d, J = 2.4 Hz, 1H), 6.68 (br, 1H), 7.31-7.45 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.5, 40.7, 51.9, 70.4, 70.8, 80.1, 95.3, 99.8, 105.7, 107.9, 116.0 (q, J = 287 Hz), 127.1, 127.8, 128.1, 128.4, 128.8, 128.9, 136.5, 136.8, 142.9, 157.7 (q, J = 37 Hz), 160.0, 161.0. HRMS (ESI+) calcd. For $C_{27}H_{24}NO_4F_3Na$ $[M+Na]^+$ 506.1555, found 506.1551 (Δ = -0.8 ppm).

1,3-Dibenzyloxy-6-[(*Z*)-3-hydroxyprop-1-enyl]-5-[2-(trifluoroacetamido)ethyl]benzene (2-23C)



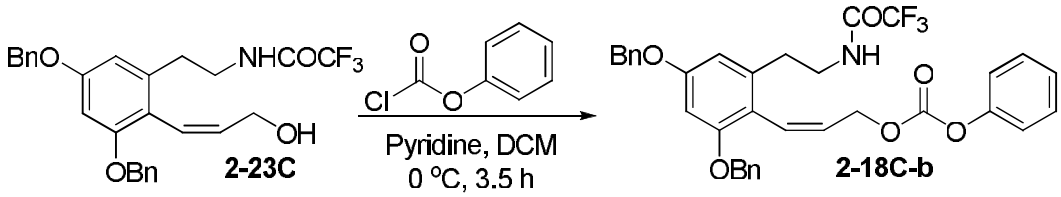
White solid; 98% yield; mp 138-140 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 2.84 (t, J = 6.9 Hz, 2H), 3.55 (q, J = 6.9 Hz, 2H), 3.94 (d, J = 7.2 Hz, 2H), 5.00 (s, 2H), 5.02 (s, 2H), 6.03 (dt, J = 7.2, 11.1 Hz, 1H), 6.34 (d, J = 11.1 Hz, 1H), 6.44 (d, J = 2.4 Hz, 1H), 6.50 (br, 1H), 6.56 (d, J = 2.4 Hz, 1H), 7.32-7.42 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.1, 39.9, 60.4, 70.4, 71.0, 99.9, 107.8, 116.0 (q, J = 286 Hz), 118.4, 124.8, 127.6, 127.8, 128.3, 128.4, 128.8, 128.9, 133.5, 136.7, 136.8, 138.3, 157.2, 157.5 (q, J = 36 Hz), 159.3; HRMS (ESI+) calcd. For $C_{27}H_{26}NO_4F_3Na$ $[M+Na]^+$ 508.1712, found 508.1714 (Δ = 0.4 ppm).

1,3-Dibenzyloxy-6-(3-ethenyloxycarbonyloxyprop-1-enyl)-[2-(trifluoroacetamido) ethyl]benzene (2-18C-a)



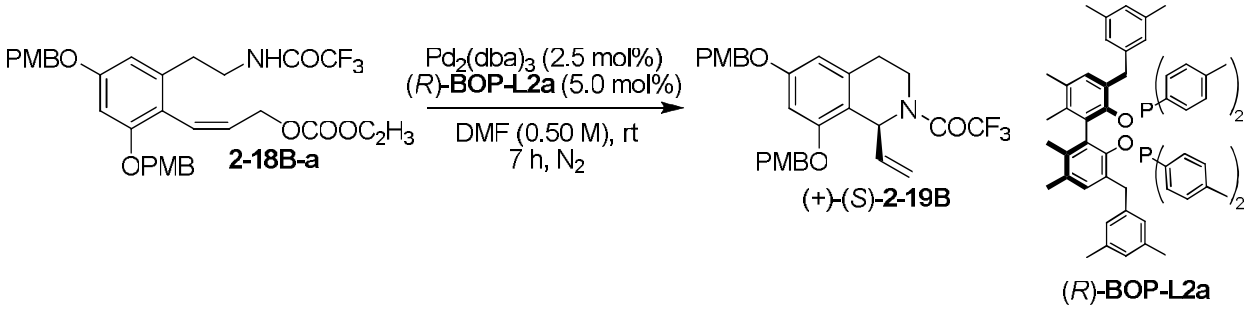
White sticky solid; 89% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.89 (t, *J* = 6.9 Hz, 2H), 3.55 (q, *J* = 6.9 Hz, 2H), 4.55 (m, 3H), 4.88 (dd, *J* = 2.1, 13.8 Hz, 2H), 4.98 (s, 2H), 5.01 (s, 2H), 5.90 (dt, *J* = 7.2, 11.1 Hz, 1H), 6.44 (d, *J* = 2.1 Hz, 1H), 6.48 (d, *J* = 11.1 Hz, 1H), 6.56 (d, *J* = 2.1 Hz, 1H), 6.73 (br, 1H), 6.95 (dd, *J* = 7.2, 13.8 Hz, 1H), 7.32-7.44 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.7, 39.3, 66.6, 70.2, 70.6, 98.1, 99.6, 107.8, 115.8 (q, *J* = 286 Hz), 117.0, 126.9, 127.3, 127.6, 128.0, 128.1, 128.6, 136.5, 136.6, 138.4, 142.4, 152.9, 157.1, 157.5 (q, *J* = 37 Hz), 159.4; HRMS (ESI+) calcd. For $C_{30}H_{28}NO_6F_3Na$ $[M+Na]^+$ 578.1766, found 578.1762 (Δ = -0.7 ppm).

1,3-Dibenzyloxy-6-(3-phenoxycarbonyloxyprop-1-enyl)-[2-(trifluoroacetylamino)ethyl]benz ene (2-18C-b)



White solid; 91% yield; mp 112-114 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.89 (t, *J* = 6.6 Hz, 2H), 3.52 (q, *J* = 6.6 Hz, 2H), 4.60 (d, *J* = 6.6 Hz, 2H), 4.99 (s, 4H), 5.95 (dt, *J* = 6.3, 11.1 Hz, 1H), 6.40 (d, *J* = 2.1 Hz, 1H), 6.50 (d, *J* = 11.1 Hz, 1H), 6.56 (d, *J* = 2.1 Hz, 1H), 6.67 (br, 1H), 7.04-7.25 (m, 5H), 7.32-7.44 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.9, 39.4, 67.0, 70.4, 70.8, 99.8, 108.0, 116.3 (q, *J* = 287 Hz), 117.2, 121.1, 126.3, 127.1, 127.4, 127.5, 127.8, 128.2, 128.3, 128.8, 128.9, 129.6, 136.8, 138.6, 151.1, 154.1, 157.2, 157.5 (q, *J* = 37 Hz), 159.6; HRMS (ESI+) calcd. For $C_{34}H_{30}NO_6F_3Na$ $[M+Na]^+$ 628.1923, found 628.1917 (Δ = -1.0 ppm).

General procedure for intramolecular asymmetric allylic amination

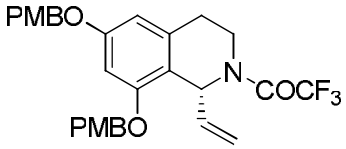


Typical procedure is described for the reaction of **2-18B-a** to afford (+)-6,8-bis-(4-methoxybenzyloxy)-1-ethenyl-2-trifluroacetyl-3,4-dihydro-1*H*-isoquinoline, (+)-(*S*)-**2-19B**: A solution of **BOP** ligand (*R*)-**L2a** (28.5 mg, 0.0319 mmol) and $Pd_2(dba)_3$ (14.8 mg, 0.0159 mmol) in DMF (1.3 mL) was added to a reaction tube with a stirring bar under nitrogen. The solution was stirred at room temperature until the color of the solution turned to light yellow from purple. Then, **2-18B-a** (400 mg, 0.638 mmol) was added to the catalyst solution via a syringe. The mixture was stirred at room temperature until TLC indicated completion of the reaction. The resulting solution was diluted with water (20 mL). The aqueous layer was separated and extracted with Et_2O (25 mL x3). The combined organic layer was washed with water (20 mL x5) and brine, and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the solvent evaporated *in vacuo* to afford the crude product as orange oil. The conversion of the reaction was checked by ^1H NMR, which indicated over 95% conversion and 100% product selectivity. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc = 10:1→5:1) afforded (+)-(*S*)-**2-19B** as colorless oil (285 mg, 85% yield). The pure product was then subjected to chiral HPLC analysis, using a Chiralcel AD-RH column (CH_3CN/H_2O = 50/50, 0.7 mL/min), which indicated that the enantiopurity of the product (+)-(*S*)-**2-19B** was 94.0% ee. The *S* configuration was tentatively assigned by comparison of the sign of the optical rotation of (+)-(*S*)-**2-19B** with that of structurally close (+)-(*S*)-1-ethenyl-2-trifluoroacetyl-6,7-dimethoxy- 1,2,3,4-tetrahydroisoquinoline1 and further confirmed by converting (+)-(*S*)-**2-19B** to literature known (-)-(*S*,*S*)-**3-12** (see chapter 3 for the detail).

(+)-(*S*)-**2-19B:** $[\alpha]_D^{21}$ +66.0 (*c* 1.5, DCM); ^1H NMR (300 MHz, $CDCl_3$) (a mixture of two rotamers) δ 2.76-2.82 (m, 1H), 2.88-3.05 (m, 1H), [3.30-3.40 (m, 0.33H), 3.58-3.66 (m, 0.67H)], 3.81 (s, 3H), 3.82 (s, 3H), [3.92-4.00 (m, 0.67H), 4.35-4.42 (m, 0.33H)], 4.93-4.99 (m, 5H),

5.19-5.24 (m, 1H), 5.87-6.00 (m, 1H), [5.80-5.84 (m, 0.33H), 6.20-6.24 (m, 0.67H)], [6.35 (d, *J* = 2.1 Hz, 0.67H), 6.38 (d, *J* = 2.1 Hz, 0.33H)], 6.48 (d, *J* = 2.1 Hz, 1H), 6.89 (d, *J* = 7.5 Hz, 2H), 6.92 (d, *J* = 7.5 Hz, 2H), 7.31 (d, *J* = 7.5 Hz, 2H), 7.33 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) (a mixture of two rotamers) (major) δ 29.5, 39.9, 51.6, 55.5, 70.0 70.1, 99.1, 105.6, 114.2, 114.3, 115.4, 116.7, 116.8 (q, *J* = 287 Hz), 128.8, 128.9, 129.0, 129.4, 135.1, 135.4, 155.9 (q, *J* = 36 Hz), 156.0, 159.1, 159.6, 159.8; (minor) δ 28.0, 38.0, 53.4, 55.5, 70.0, 70.1, 99.0, 105.9, 114.2, 114.3, 115.4, 116.8 (q, *J* = 287 Hz), 117.1, 128.8, 128.9, 129.0, 129.5, 135.8, 136.2, 155.8 (q, *J* = 36 Hz), 156.6, 159.4, 159.6, 159.8; HRMS (ESI+) calcd. For $C_{29}H_{28}NO_5F_3Na$ $[M+Na]^+$ 550.1817, found 550.1818 (Δ = 0.2 ppm).

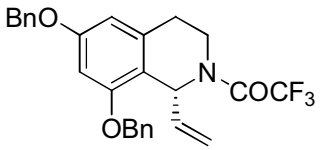
(-)-6,8-Bis(4-methoxybenzyloxy)-1-ethenyl-2-trifluroacetyl-3,4-dihydro-1*H*-isoquinoline,(-)-(*R*)-**2-19B.**



(-)-(*R*)-**2-19B**

The compound (-)-(*R*)-**2-19B** was obtained in the same manner as that described for the synthesis of (+)-(*S*)-**2-19B** except for using (*S*)-**BOP-L2a** as the chiral ligand: 85% yield; 96.1% ee. All characterization data were identical to those of (+)-(*S*)-**2-19B** except for $[\alpha]_D^{21}$ -67.1 (*c* 1.5, DCM). HRMS (ESI+) calcd. For $C_{29}H_{29}NO_5F_3$ $[M+H]^+$ 528.1998, found 528.1996 (Δ = -0.4 ppm).

(-)-6,8-Dibenzyloxy-1-ethenyl-2-trifluroacetyl-3,4-dihydro-1*H*-isoquinoline [(-)-(*R*)-**2-19C].**



(-)-(*R*)-**2-19C**

Colorless oil; 83% yield; 75% ee; ^{1}H NMR (400 MHz, $CDCl_3$) (a mixture of two rotamers) δ 2.73-2.85 (m, 1H), 2.90-3.06 (m, 1H), [3.32-3.42 (m, 0.36H), 3.58-3.69 (m, 0.64H)], [3.90-4.00 (m, 0.64H), 4.35-4.44 (m, 0.36H)], 4.93-5.10 (m, 5H), 5.19-5.27 (m, 1H), 5.99 (ddd, *J* = 4.4, 10.4, 17.2 Hz, 1H), [5.85-5.90 (m, 0.36H), 6.25-6.30 (m, 0.64H)], [6.37 (d, *J* = 2.0 Hz,

0.64H), 6.39 (d, J = 2.0 Hz, 0.36H)], 6.48 (d, J = 2.0 Hz, 1H), 7.35-7.42 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) (a mixture of two rotamers) (major) δ 29.5, 39.8, 51.6, 70.3 70.5, 99.1, 105.8, 115.6, 116.8 (q, J = 287 Hz), 116.9, 117.0, 117.2, 127.3, 128.3, 128.8, 135.1, 135.9, 136.8, 137.0, 155.8 (q, J = 36 Hz), 156.6, 159.1; (minor) δ 28.0, 38.0, 53.4, 70.2, 70.4, 99.0, 106.1, 115.5, 116.7, 116.8 (q, J = 287 Hz), 117.1, 117.3, 127.1, 127.7, 128.1, 135.0, 135.8, 136.3, 136.9, 155.9, 156.2 (q, J = 36 Hz), 159.1; HRMS (ESI+) calcd. For $C_{27}H_{25}NO_3F_3$ $[M+H]^+$ 468.1787, found 468.1786 (Δ = -0.2 ppm).

§ 2.6 References

1. Tsuji, J.; Takahashi, H.; Morikawa, M., Organic syntheses by means of noble metal compounds XVII. Reaction of π-allylpalladium chloride with nucleophiles. *Tetrahedron Letters* **1965,** *6* (49), 4387-4388.
2. Trost, B. M.; Strege, P. E., Asymmetric induction in catalytic allylic alkylation. *Journal of the American Chemical Society* **1977,** *99* (5), 1649-1651.
3. Trost, B. M.; Lee, C., *Catalytic Asymmetric Synthesis, ed. Ojima, I. (Wiley-VCH, New. York)*. 2nd ed.; 2000; p 593-649.
4. Tsuji, J., *Palladium reagents and catalyst; Wiley: New york*. 1995; p 290.
5. Trost, B. M.; Crawley, M. L., Asymmetric Transition-Metal-Catalyzed Allylic Alkylations: Applications in Total Synthesis. *Chemical Reviews* **2003,** *103* (8), 2921-2944.
6. Scott, J. D.; Williams, R. M., Chemistry and Biology of the Tetrahydroisoquinoline Antitumor Antibiotics. *Chem. Rev.* **2002,** *102* (5), 1669-1730.
7. Bentley, K. W., The Isoquinoline Alkaloids. In *Chemistry and Biochemistry of Organic Natural Products*, Ravindranath, B., Ed. Harwood Academic Publishers: Amsterdam, 1998.
8. Ivanovska, N.; Nikolova, P.; Hristova, M.; Philipov, S.; Istatkova, R., Complement modulatory activity of bisbenzylisoquinoline alkaloids isolated from Isopyrum thalictroides--I: Influence on classical pathway in human serum. *International Journal of Immunopharmacology* **1999,** *21* (5), 325-336.
9. Banning, J. W.; Salman, K. N.; Patil, P. N., A Pharmacological Study of Two Bisbenzylisoquinoline Alkaloids, Thalistyline and Obamegine. *Journal of Natural Products* **1982,** *45* (2), 168-177.
10. Pingaew, R.; Ruchirawat, S., Application of the Hypervalent Iodine Reagent to the Synthesis of Some Pentasubstituted Aporphine Alkaloids. *Synlett* **2007,** *2007* (EFirst), 2363,2366.
11. Markmee, S.; Ruchirawat, S.; Prachyawarakorn, V.; Ingkaninan, K.; Khorana, N., Isoquinoline derivatives as potential acetylcholinesterase inhibitors. *Bioorganic & Medicinal Chemistry Letters* **2006,** *16* (8), 2170-2172.
12. Takada, K.; Uehara, T.; Nakao, Y.; Matsunaga, S.; van Soest, R. W. M.; Fusetani, N.,

Schulzeines A−C, New α-Glucosidase Inhibitors from the Marine Sponge Penares schulzei1. *Journal of the American Chemical Society* **2004,** *126* (1), 187-193.

13. Taylor, M. S.; Jacobsen, E. N., Highly Enantioselective Catalytic Acyl-Pictet−Spengler Reactions. *Journal of the American Chemical Society* **2004,** *126* (34), 10558-10559.
14. (a) Ukaji, Y.; Shimizu, Y.; Kenmoku, Y.; Ahmed, A.; Inomata, K., Catalytic Asymmetric Addition of Dialkylzinc to 3,4-Dihydroisoquinoline N-Oxides Utilizing Tartaric Acid Ester as a Chiral Auxiliary. *Bulletin of the Chemical Society of Japan* **2000,** *73* (2), 447-452; (b) Kanemitsu, T.; Yamashita, Y.; Nagata, K.; Itoh, T., Catalytic Asymmetric Synthesis of (R)-(-)-Calycotomine, (S)-(-)-Salsolidine and (S)-(-)-Carnegine. *Synlett* **2006,** *2006* (10), 1595,1597; (c) Wang, S.; Seto, C. T., Enantioselective Addition of Vinylzinc Reagents to 3,4-Dihydroisoquinoline N-Oxide. *Organic Letters* **2006,** *8* (18), 3979-3982.
15. (a) Morimoto, T.; Suzuki, N.; Achiwa, K., Enantioselective synthesis of (S)-calycotomine employing catalytic asymmetric hydrogenation with an iridium(I)-(R)-BINAP-phthalimide complex. *Tetrahedron: Asymmetry* **1998,** *9* (2), 183-187; (b) Mujahidin, D.; Doye, S., Enantioselective Synthesis of (+)-(S)-Laudanosine and (–)-(S)-Xylopinine. *European Journal of Organic Chemistry* **2005,** *2005* (13), 2689-2693.
16. Ohkuma, T.; Kitamura, M.; Noyori, R., Asymmetric Hydrogenation. In *Catalytic Asymmetric Synthesis (2nd Edition)*, Ojima, I., Ed. Wiley-VCH: New York, 2000; pp 1-110.
17. Chrzanowska, M.; Rozwadowska, M. D., Asymmetric Synthesis of Isoquinoline Alkaloids. *Chem. Rev.* **2004,** *104* (7), 3341-3370.
18. Ito, K.; Akashi, S.; Saito, B.; Katsuki, T., Asymmetric Intramolecular Allylic Amination: Straightforward Approach to Chiral C1-Substituted Tetrahydroisoquinolines. *Synlett* **2003**, 1809-1812.
19. Hua, Z.; Vassar, V.; Ojima, I., Synthesis of new chiral monodentate phosphite ligands and their use in catalytic asymmetric hydrogenation. *Organic Letters* **2003,** *5*, 3831-3834.
20. (a) Choi, H.; Hua, Z.; Ojima, I., Highly Enantioselective Copper-Catalyzed Conjugate Addition of Diethylzinc to Nitroalkenes. *Organic Letters* **2004,** *6* (16), 2689-2691; (b) Hua, Z.; Vassar, V. C.; Choi, H.; Ojima, I., New biphenol-based, fine-tunable monodentate phosphoramidite ligands for catalytic asymmetric transformations. *Proc. Nat. Acad. Sci., U. S. A.* **2004,** *101* (15), 5411-5416; (c) Chapsal, B. D.; Ojima, I., Total Synthesis of Enantiopure (+)-γ-Lycorane Using Highly Efficient Pd-Catalyzed Asymmetric Allylic Alkylation. *Organic Letters* **2006,** *8* (7), 1395-1398.
21. Shi, C.; Ojima, I., Asymmetric synthesis of 1-vinyltetrahydroisoquinoline through Pd-catalyzed intramolecular allylic amination. *Tetrahedron* **2007,** *63* (35), 8563-8570.
22. Shi, C.; Chien, C. W.; Ojima, I., Synthesis of chiral biphenol-based diphosphonite ligands and their application to Pd-catalyzed intermolecular asymmetric allylic amination. *Chem. Asian J.* **2011,** *6*, 674.
23. Shi, C. Development and Applications of Chiral Phosphorus Ligands to Transition-Metal Catalyzed Asymmetric Reactions. Doctor of Philosophy in Chemistry, Stony Brook University, Stony Brook, NY, August 2008.
24. (a) Lesch, B.; Toräng, J.; Nieger, M.; Bräse, S., The Diels-Alder Approach towards

Cannabinoids. *Synthesis* **2005,** (11), 1888-1900; (b) Sawant, D.; Kumar, R.; Maulik, P. R.; Kundu, B., Unprecedented SnCl2-Mediated Cyclization of Nitro Arenes via N−N Bond Formation†. *Organic Letters* **2006,** *8* (8), 1525-1528.

25. Compound 8 (A or B) can be prepared in two steps from commercially available resorcinolamine. Alternatively, 8 (A or B) can also be prepared from commercially available 3,5-dihydroxybenzaldehyde through PMB or benzyl protection and nitro-aldol reaction, followed by reduction and trifluoroacetylation. See Experimental Section.

26. Denmark, S. E.; Regens, C. S.; Kobayashi, T., Total Synthesis of Papulacandin D. *Journal of the American Chemical Society* **2007,** *129* (10), 2774-2776.

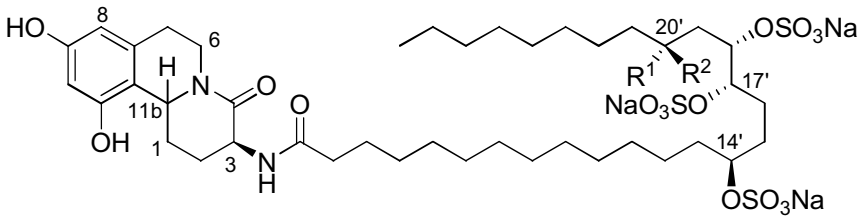
Chapter 3

Formal Enantioselective Total Synthesis of Schulzeines A-C *via* Pd-Catalyzed Intramolecular Asymmetric Allylic Amination

Table of Contents

§ 3.1 Asymmetric synthesis of Schulzeines A-C

Schulzeines A-C, isolated from the marine sponge, *Penares Schulzei*, have been identified as a new class of marine natural products (**Figure 3-1**).[1] These new alkaloids were found to exhibit potent α-glucosidase inhibitory activity, which made them promising leads in drug development for the treatment of cancer, diabetes and viral infections.[2] Therefore, it is important to develop efficient synthesis for these natural products to provide sufficient amounts for biological studies as well as structure-activity relationship studies for discovery of more potent analogs.



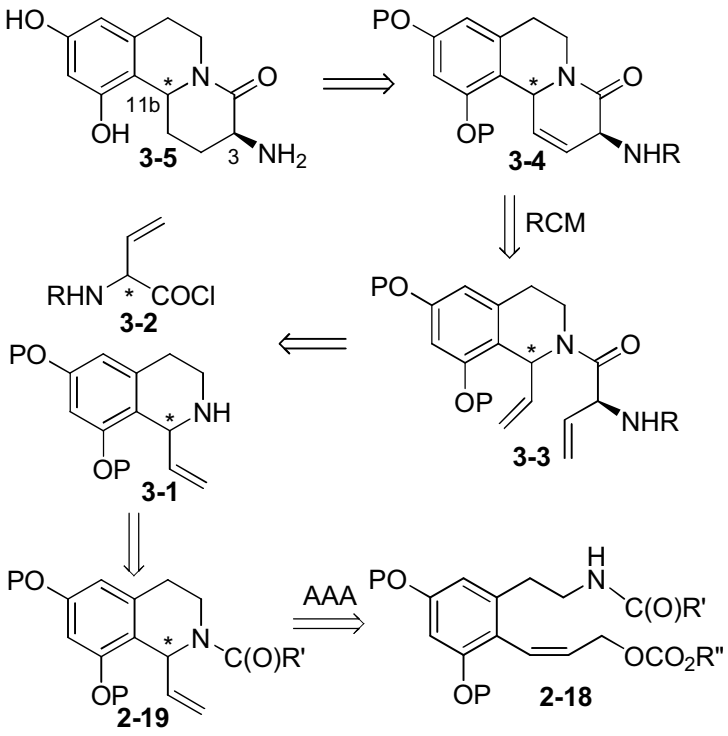
Schulzeine A (C11b-Hβ; R^1 = Me, R^2 = H)
Schulzeine B (C11b-Hα; R^1, R^2 = H);
Schulzeine C (C11b-Hβ; R^1, R^2 = H)

Figure 3-1. Schulzeines A-C

Five research groups have reported the synthesis of Schulzeines A-C tricyclic core to date.[3] All but one of these syntheses employed Pictet-Spengler-type cyclization to form the tricyclic core, and the introduction of the critical stereocenter at C-11b was either totally nonselective or gave only low to moderate diastereoselectivity, wherein the separation of two diastereomers was difficult in some cases. Furthermore, the diastereoselectivity at C-11b of those reported results favors the *cis* configuration (C1-C11b bond is *cis* to C3-N bond) which required for Schulzeine B tricyclic core. The efficacy for the synthesis of Schulzeines A and C which possess *trans* configuration (C1-C11b bond is *trans* to C3-N bond) was greatly disfavored (**Figure 3-1**). Thus, it is apparent that a more efficient construction of the tricyclic core needs to be developed. We envisioned that an intramolecular asymmetric allylic amination (AAA) could serve as the key reaction in the construction of required stereochemistry at C11b. We describe here a new and efficient synthesis of the tricyclic core of Schulzeines A-C based on the AAA approach.

Our retrosynthetic analysis is illustrated in **Scheme 3-1**. The *S* configuration to the C3 position of the tricyclic core **3-5** can be introduced by coupling (*S*)-vinylglycine derivative **3-2** to the amine moiety of 1-vinyltetrahydroisoquinoline **3-1** (for representative approaches to the

construction of 1-vinyltetrahydroisoquinolines, see References 10-15),[4] followed by ring-closing metathesis (RCM) of **3-3**[5] and hydrogenation of the resulting didehydropiperidinone ring of **3-4**. Then, **3-1** can be derived from **2-19** by *N*-deprotection, and **2-19** with excellent enantiopurity can be obtained through the intramolecular AAA of **2-18**, which should introduce the chiral center at C11b of **3-5**.



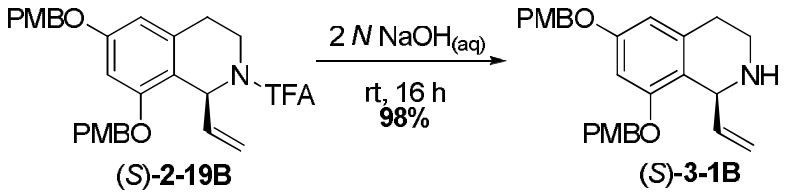
Scheme 3-1. Retrosynthetic analysis of the tricyclic core of Schulzeines A-C

§ 3.2 Results and discussion

§ 3.2.1 Formal total synthesis of Schulzeine B

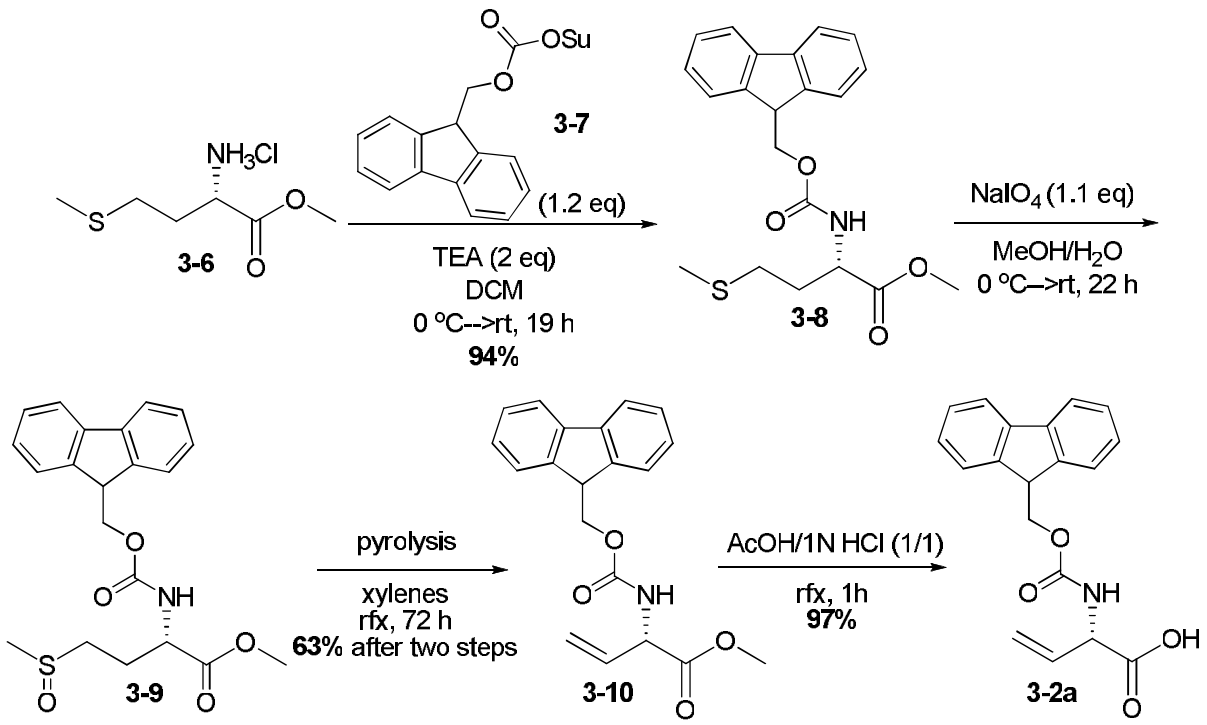
With the optimized conditions for the AAA reaction of compound **2-18B** reported in the chapter 2, we prepared (+)-(*S*)-**2-19B**[6] with excellent enantiopurity (94-95% ee) in a larger quantity, and set out to complete the synthesis of the Schulzeine B tricyclic core in accordance with the planned synthetic route based on the retrosynthetic analysis (Scheme 3-1) described above. The synthesis is divided into two parts. One part is to introduce 1-vinyltetrahydronisoquinoline (+)-(*S*)-**3-1B** which can be generated from the amide deprotection of TFA-substituted 1-vinyltetrahydronisoquinoline (+)-(*S*)-**2-19B** using 2 *N* NaOH and EtOH at room temperature for 16 h, with 98% isolated yield after purification (**Scheme**

3-2).[7]



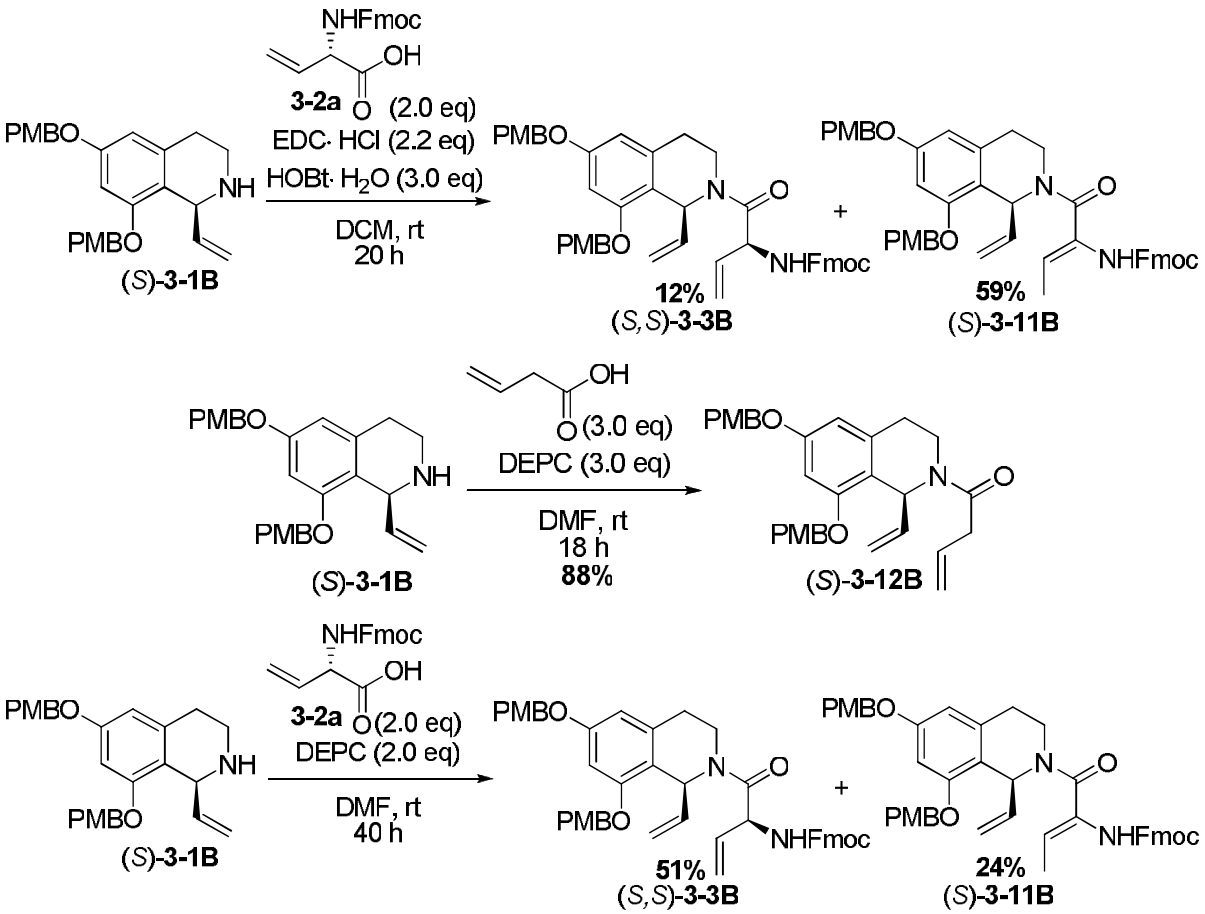
Scheme 3-2. Synthesis of (+)-(*S*)-**3-1B**

With the secondary amine (+)-(*S*)-**3-1B** for the formal synthesis of tricyclic core of Schulzeines B in hand, the other part is to synthesize the corresponding vinylglycine derivative for the amide coupling reaction with compound (*S*)-(+)-**3-1B**. **Scheme 3-3** shows the synthesis of Fmoc-N-protected vinylglycine **3-2a**.[8] Because basic conditions are not compatible for vinylglycine synthesis due to the fast isomerization of the double bond of vinylglycine, only neutral or acidic conditions can be used in the synthesis of vinylglycine. Therefore, we herein chose the Fmoc group as the protecting group because it can tolerate acidic conditions during the synthesis and can be cleaved under mild basic conditions or hydrogenolysis at the end of the synthesis. Starting with L-Methionine methyl ester hydrochloride **3-6** treated with Fmoc-OSu **3-7** in the presence of triethylamine and methylene chloride, [*N*-(9-fluorenylmethoxycarbonyloxy)]-L-methionine methyl ester **3-8** was prepared with 94% isolated yield.[8a] Next, compound **3-8** was converted into the corresponding sulfoxide **3-9** using sodium periodate in MeOH/H_2O cosolvent. After the work-up and simple purification, **3-9** can be used for the next step without further purification. To synthesize [*N*-(9-fluorenylmethoxycarbonyloxy)]-L-vinyl glycine methyl ester **3-10**, the pyrolysis of **3-9** was employed using xylenes as the solvent under reflux condition for 72 h. Because of these harsh reaction conditions, compound **3-10** and its regioisomers were generated. After careful flash column chromatography on silica gel twice, **3-10** was obtained in 63% isolated yield after two steps and 15% of regioisomers were also isolated.[8a] The desired Fmoc-N-protected vinylglycine **3-2a** was simply produced by the acid hydrolysis of methyl ester **3-10** in the presence of acetic acid and hydrochloric acid with 97% isolated yield.[8b]



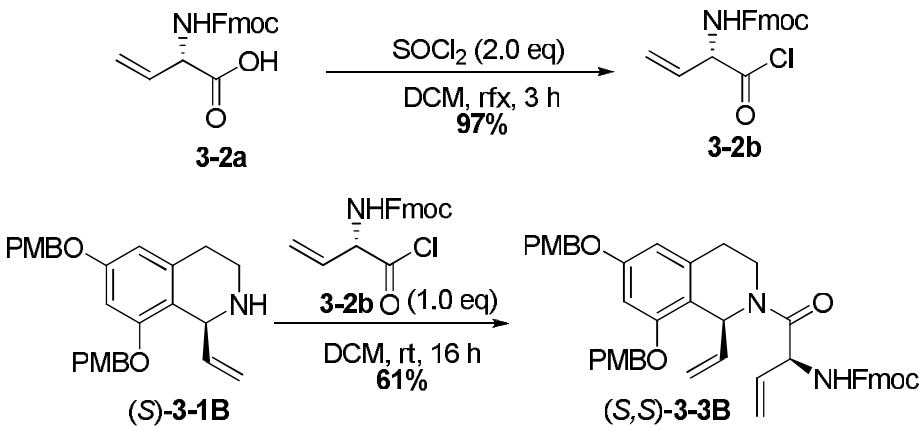
Scheme 3-3. Synthesis of vinylglycine derivative **3-2a**

With 1-vinyltetrahydronisoquinoline (+)-(*S*)-**3-1B** and Fmoc-N-protected vinylglycine **3-2a** in hands, we first investigated the amide coupling reaction of (+)-(*S*)-**3-1B** and **3-2a** using EDC.HCl and HOBt as the coupling reagents. After 20 h at room temperature, only 12% of desired diene product (*S,S*)-**3-3B** was obtained and the major product was the diene with the double bond isomerization of vinyl glycine moiety which can be attributed to the basicity of HOBt (**Scheme 3-4**). As a result, to avoid the use of basic reagents, DEPC (diethyl cyanophosphonate), which is a relatively neutral amide coupling reagent, was employed. Before dealing directly with the vinylglycine derivative, a model reaction using butenoic acid was investigated first to check the efficacy of the above coupling reagent. The reaction went smoothly using 3 equivalent of DEPC in DMF at room temperature and 88% of desired product (*S*)-**3-12B** was obtained after 18 h. With this encouraging result, (*S*)-**3-1B** and **3-2a** were coupled under the similar reaction conditions mentioned above. However, this reaction is not as fast as the model reaction and took 40 h to be completed. Comparing to the result using EDC·HCl and HOBt as the coupling reagents, the yield of desired product (*S,S*)-**3-3B** was indeed much higher here (51%) although 24% of byproduct (*S*)-**3-11B** was still obtained (**Scheme 3-4**).



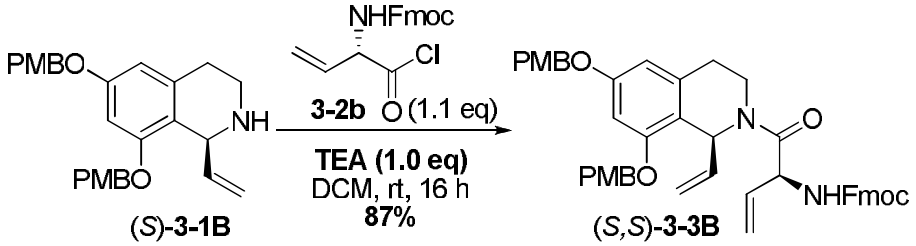
Scheme 3-4. Investigation of amidation of (*S*)-**3-1B and 3-2a**

To further optimize this reaction, we tried to run the reaction without adding any coupling reagent and under neutral or even acidic condition. Therefore, carboxylic acid **3-2a** was then converted into acyl chloride **3-2b**[8] using thionyl chloride, and compound **3-2b** was employed to couple with (*S*)-**3-1B** without adding any base to neutralize HCl formed from the reaction (**Scheme 3-5**). Indeed, as expected, none of the isomerized byproduct was found and only the desired product (*S,S*)-**3-3B** was observed. However, because no extra base was added in this reaction, almost half the starting material (*S*)-**3-1B** acts as the base to neutralize the generated HCl instead of reactant. As a result, the yield of (*S,S*)-**3-3B** should be 50% (61% yield may due to the measurement error in the small scale reaction) even though there is no isomerized byproduct was formed.



Scheme 3-5. Optimization of amidation of (*S*)-**3-1B and 3-2b**

Therefore, to increase the yield and minimize the formation of the isomer from above optimized reaction, we decided to add a minimal amount of triethylamine as base, i.e., one equivalent relative to the starting material (*S*)-**3-1B**, and use a slight excess of acyl chloride **3-2b** (1.1 eq relative to (*S*)-**3-1B**) for the further optimized conditions (**Scheme 3-6**). After 16 h under room temperature, (*S,S*)-**3-3B** was obtained in 87% yield, and no isomerized product was observed in the presence of 1 eq of triethylamine.

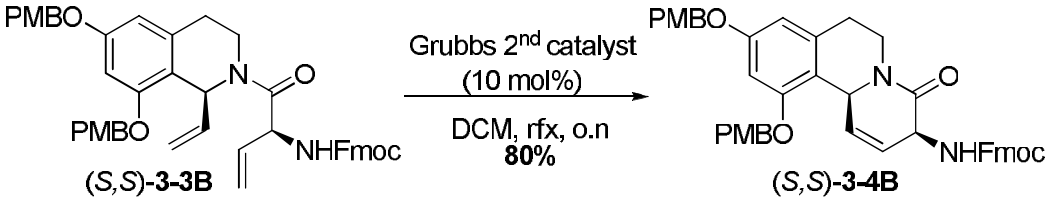


Scheme 3-6. Optimized condition for amidation of (*S*)-**3-1B** and **3-2b**

Before discussing the next step, one issue has to be clarified. Actually, to simplify the discussion of the optimization of amidation, we only focused on the product selectivity of (*S,S*)-**3-3B** and its isomerized byproduct but did not mention the diastereomeric ratio of (*S,S*)-**3-3B**. However, since (*S*)-**3-1B** is not an enantiopure compound (97:3 er), reaction with enantiopure **3-2b** could theoretically give (*S,S*)-**3-3B** with 97:3 dr. Indeed, from ^{1}H NMR analysis, over 20:1 dr value was observed in favor of (*S,S*)-**3-3B**. Unfortunately, these two diastereomers have the same R_f value on TLC and are inseparable by column chromatography. For that reason, the mixture was used for the next step without doing further separation.

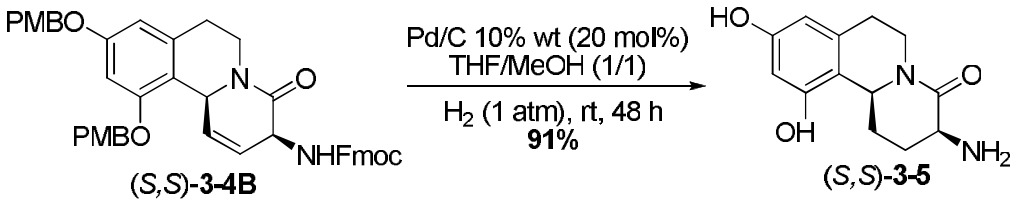
With (*S,S*)-**3-3B** (97:3 dr) in hand, ring-closing metathesis proceeded to form the third ring

of Schulzeine tricylic core. By using 10 mol% of 2nd generation Grubbs catalyst[9] in refluxing dichloromethane, the tricyclic RCM product (*S,S*)-**3-4B** was obtained as a single diastereomer in 80% yield after column chromatography (**Scheme 3-7**).



Scheme 3-7. Ring-closing metathesis (RCM) of (*S,S*)-**3-3B**

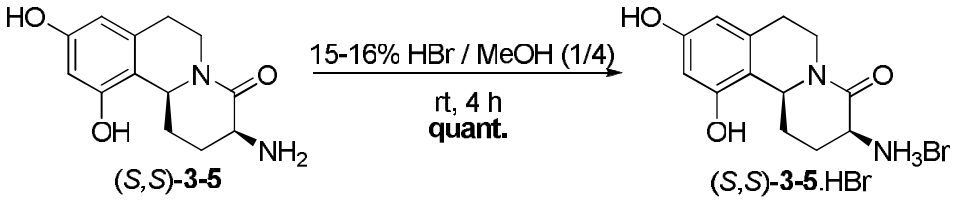
Next, we originally planned to convert compound (*S,S*)-**3-4B** to compound (*S,S*)-**3-5** through the hydrogenation of the olefin and hydrogenolysis of the PMB group using Pd/C under H_2, followed by the deprotection of Fmoc moiety using piperidine. To our surprise, while (*S,S*)-**3-4B** was treated with 10% Pd/C (20 mol%) in THF/MeOH cosolvent system under ambient pressure of H_2 for 48 h, all three reactions were done and the desired (*S,S*)-**3-5** was afforded in 91% yield (**Scheme 3-8**).



Scheme 3-8. Hydrogenation and hydrogenolysis of (*S,S*)-**3-4B**

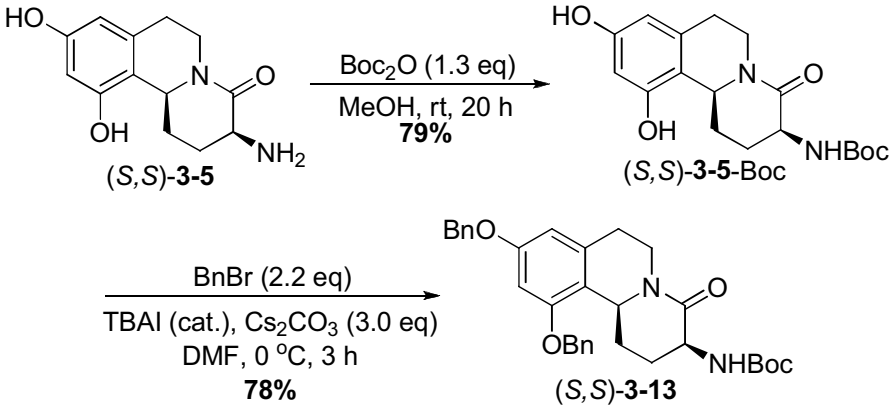
(*S,S*)-**3-5,** which has been made by Romo's group, can be used as a reference to assign the absolute configuration at C11b of the tricylic core. However, $[\alpha]_D$ value that we got is way higher than that they provided (the literature value for (*S,S*)-**3-5** (free amine form) from Ref. 7 is $[\alpha]_D^{23}$ -138.7 (*c* 0.73, MeOH) but (*S,S*)-**3-5**, in our hands, showed the specific rotation of $[\alpha]_D^{20}$ -252.3 (*c* 0.35, MeOH)). Therefore, we reevaluated our data and also checked their experimental procedure to see whose data has the mistake, and we found that they used BBr_3 for this reaction but they didn't use any base to quench and neutralize the product. As a result, (*S,S*)-**3-5** that they obtained should be its corresponding HBr salt. To confirm our finding, we prepared (*S,S*)-**3-5**.HBr salt by the treatment of (*S,S*)-**3-5** with 15-16% $HBr_{(aq)}$ in MeOH (Scheme 3-9). After simple purification, (*S,S*)-**3-5**.HBr was obtained and its $[\alpha]_D$ value ($[\alpha]_D^{20}$ -138.9 (*c* 0.72,

MeOH)) was found to be virtually identical to that of the literature value for (*S,S*)-**3-5** (free amine form) with $[\alpha]_D^{20}$ -138.9 (*c* 0.72, MeOH) and it appears that the data in Ref. 7 indeed made an error.

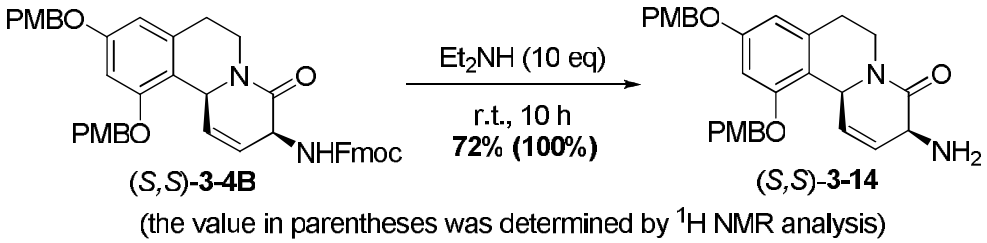


Scheme 3-9. Synthesis of (*S,S*)-**3-5.HBr**

To convert (*S,S*)-**3-5** to (*S,S*)-**3-13**, Boc protection was first introduced to mask the secondary amine at the C3 position to give (*S,S*)-**3-5**-Boc in 79% yield. Next, (*S,S*)-**3-5**-Boc was smoothly reacted with benzyl bromide in the presence of TBAI and Cs_2CO_3 to give (*S,S*)-**3-13** in 78% yield (**Scheme 3-10**). From (*S,S*)-**3-13**, three groups already reported the total synthesis of Schulzeine B.[3b-d] Thus, a formal total synthesis of this compound will be completed.



Scheme 3-10. Synthesis of the common advanced key intermediate (*S,S*)-**3-13**



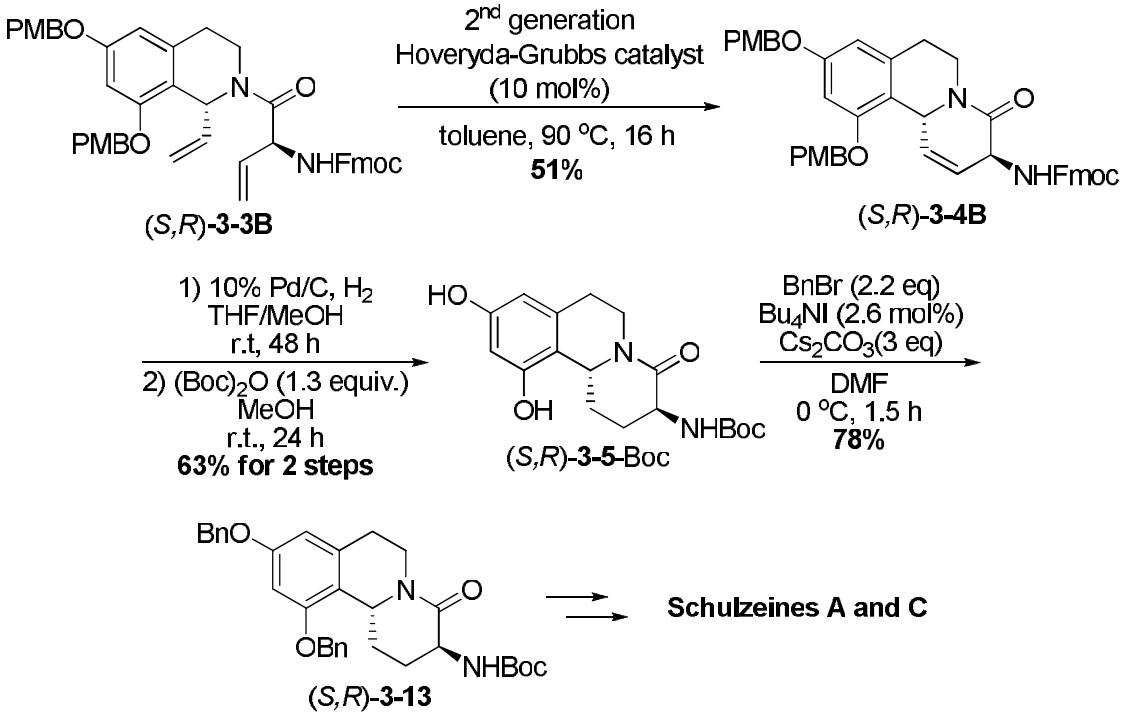
Scheme 3-11. Synthesis of an alternative key advanced intermediate (*S,S*)-**3-14**

Although *O,O'*-dibenzyl protection was used in the known total syntheses, *O,O'*-bis-PMB

protection should work equally well. Thus, (*S,S*)-**3-14** was also prepared as an alternative key advanced intermediate through Fmoc deprotection of (*S,S*)-**3-4B** with diethylamine in DCM at room temperature for 10 h (**Scheme 3-11**).

§ 3.2.2 Formal total synthesis of Schulzeine A and C

In the same manner, we carried out the asymmetric synthesis of (*S,R*)-**3-5,** **3-5**-Boc and **3-13**, starting from (*R*)-(-)-**2-19B**, which was obtained in 96.1% ee through the AAA reaction of **2-18B-a** using (*S*)-**BOP-L2a** (**Scheme 3-12**). Diene (*S,R*)-**3-3B** was prepared, and subjected to the RCM reaction in the same manner as that for (*S,S*)-**3-3B** to give the corresponding RCM product (*S.R*)-**3-4B**. However, unexpectedly, substantial epimerization occurred during the RCM reaction to give almost an equal amount of (*R,R*)-**3-4B**.[10] After screening of RCM catalysts and reaction variables, we found that the 2nd generation Hoveyda-Grubbs catalyst[11] gave the best results so far, favoring the formation of (*S.R*)-**3-4B** in 3:1 ratio. Thus, enantio- and diastereopure (*S.R*)-**3-4B** was isolated in 51% yield. From (*S.R*)-**3-4B**, (*S,R*)-**3-5**-Boc and (*S,R*)-**3-13** were synthesized in a similar manner to that illustrated before, and thus the formal total synthesis of Schulzeines A and C have also been completed.



Scheme 3-12. Formal total synthesis of Schulzeines A and C

§ 3.3 Conclusions

A new approach toward the total synthesis of Schulzeines A-C, featuring efficient asymmetric allylic amination and ring-closing metathesis as key steps, has been successfully developed. Every step in the synthesis gave good to excellent yield except for the formation of (*S,R*)-**3-4B.** Further optimizations of the whole process, especially the RCM step for (*S,R*)-**3-3B**, and mechanistic studies are actively underway in our laboratory.

§ 3.4 Experimental section

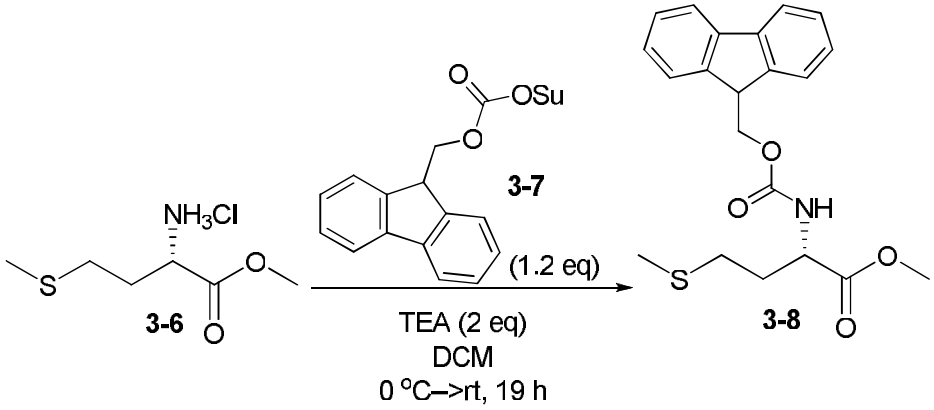
General Methods: ^{1}H and ^{13}C and ^{31}P NMR were measured on a Varian Inova-500 NMR (500 MHz ^{1}H, and 125 MHz ^{13}C), a Varian Inova-400 NMR (400 MHz ^{1}H; 100 MHz ^{13}C; 162 MHz ^{31}P) or a Varian Gemini-2300 (300 MHz ^{1}H; 75 MHz ^{13}C; 121.5 MHz ^{31}P) spectrometer in a deuterated solvent using residual protons ($CHCl_3$: ^{1}H, 7.26 ppm; ^{13}C, 77.0 ppm. C_6H_6: ^{1}H, 7.15 ppm) as the internal standard or phosphoric acid as the external reference (^{31}P 0.00 ppm). Analytical HPLC in reverse phase was carried out with a Shimadzu LC-2010A HPLC system using a Chiralpak AD-RH analytical column. Melting points were measured on a Thomas Hoover Capillary melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Helmer Model 241 polarimeter. TLC analyses were performed using Merck DC Alufolien 60F254 aluminum pre-coated silica gel plates. Flash column chromatography was carried out using Silicyle Silia*Flash*P60® silica gel (particle size 40–63 μm). High-resolution mass spectrometric analyses were carried out at the Mass Spectrometry Laboratories, University of Illinois Urbana-Champaign, Urbana, IL and ICB&DD at Stony Brook University. Unless otherwise noted all reactions were carried out under argon or nitrogen atmosphere in oven-dried glassware using standard Schlenck techniques.

Materials: Solvents were reagents grade and freshly distilled before use. Tetrahydrofuran (THF) and dichloromethane (DCM) were dried and degassed using an Innovative Technology PureSolvTM solvent purification system. Acetonitrile was distilled from calcium hydride. Anhydrous *N,N*-dimethylformamide (DMF) was purchased from Acros and used without further purification. Other solvents were used without purification. Benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine)ruthenium (2nd generation Grubbs catalyst), [1,3-bis(2,4,6-tri-methylphenyl)-2-Imidazoli-

dinylidene]dichloro(*o*-isopropoxyphenylmethylene)ruthenium (2nd generation Hoveyda-Grubbs catalyst), *N*-iodosuccinimide was obtained from Sigma-Aldrich and used as received. (*S*)-*N*-Fmoc-vinylglycinyl chloride was synthesized in five steps from commercial available L-methionine methyl ester hydrochloride.[8] Other chemicals and reagents were purchased from Sigma-Aldrich or Fisher Scientific and used without further purification unless otherwise noted. Chiral biphenols and chiral **BOP** ligands, **L1a**-**L1i** were prepared according to the procedure previously reported by our laboratory.[12]

Preparation of L-vinylglycine derivative[8a, 13]

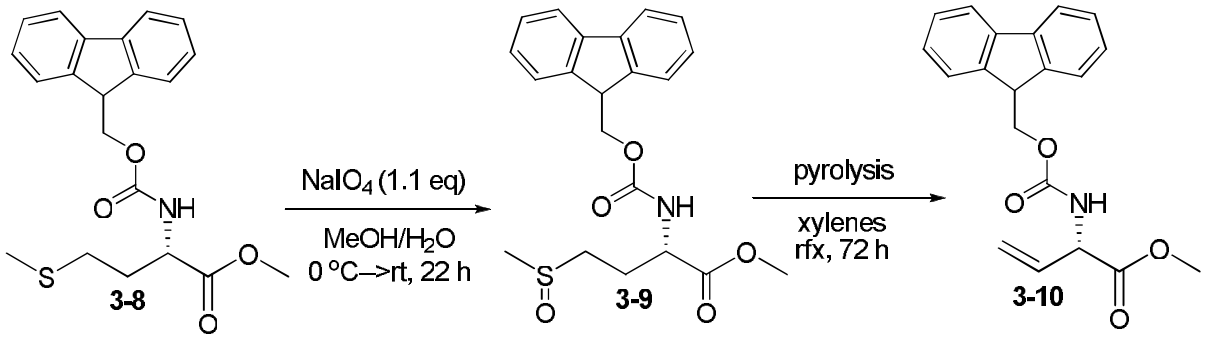
[*N*-(9-Fluorenylmethoxycarbonyloxy)]-L-methionine methyl ester (3-8)[8a]



To a stirred solution of L-methionine methyl ester hydrochloride **3-6** (2.01 g, 10.0 mmol) in distilled DCM (100 mL) was added triethylamine (2 eq) in an ice bath, followed by the slow addition of *N*-(9-fluorenylmethoxycarbonyloxy)succinimide **3-7** (1.2 eq) in methylene chloride via a syringe over the period of 20 min under the same temperature. After the addition was complete, the ice bath was removed and the mixture was stirred at room temperature for 19 h. The reaction mixture was diluted with DCM and water. The aqueous layer was separated and extracted with DCM (3x). The combined organic layer was washed with brine and dried over $MgSO_4$. The drying agent was removed by filtration and the solvent was concentrated *in vacuo* to afford crude off-white solid **3-8**. Further purification by flash column chromatography on silica gel (hexanes/EtOAc = 4:1-2:1) afforded pure **3-8** as a white solid (3.65 g, 94% yield): mp 80-82 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.94-2.21 (m, 2H), 2.10 (s, 3H), 2.53 (br, 2H), 3.77 (s, 3H), 4.23 (t, *J* = 6.9 Hz, 1H), 4.42 (d, *J* = 7.2 Hz, 2H), 4.52 (m, 1H), 5.42 (d, *J* = 8.1 Hz, 1H),

7.32 (dd, *J* = 6.9 and 7.5 Hz, 2H), 7.41 (dd, *J* = 6.9 and 7.5 Hz, 2H), 7.60 (d, *J* = 6.9 Hz, 2H), 7.76 (d, *J* = 7.5 Hz, 2H). All data are in good agreement with the literature values.[8a]

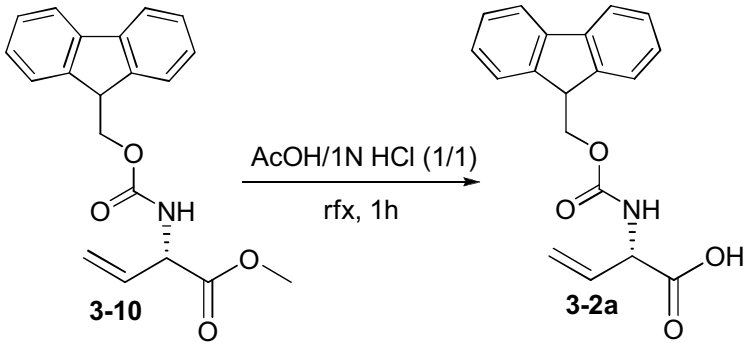
[*N*-(9-Fluorenylmethoxycarbonyloxy)]-L-vinyl glycine methyl ester (3-10)[8a]



To a stirred solution of [*N*-(9-fluorenylmethoxycarbonyloxy)]-L-methionine methyl ester **3-8** (3.65 g, 9.46 mmol) in distilled MeOH (120 mL) was added slowly aqueous sodium periodate (1.1 eq in 20 mL of H_2O) over 25 min in an ice bath. After the addition was complete, the ice bath was removed and the reaction mixture was stirred at room temperature for 22 h. The resulting solid was filtrated off and MeOH was removed under reduced pressure. The resulting colorless oil was diluted with $CHCl_3$ (30 mL). The aqueous layer was separated and extracted with $CHCl_3$ (3x). The combined organic layer was washed with water, brine and dried over $MgSO_4$. The drying agent was removed by filtration and the solvent was concentrated in *vacuo* to afford crude white solid **3-9**. This product was used in the next step without further purification. To the crude **3-9** was added xylenes (100 mL) and the mixture was heated to reflux (150 ^oC) for 72 h. The reaction mixture was cooled to room temperature and xylenes were evaporated under reduced pressure to give crude orange oil **3-10** and its isomers. Further purification by flash column chromatography on silica gel (hexanes/EtOAc = 10:1) afforded pure **3-10** as a white solid (2.07 g, 63% yield) and 15% isomers.

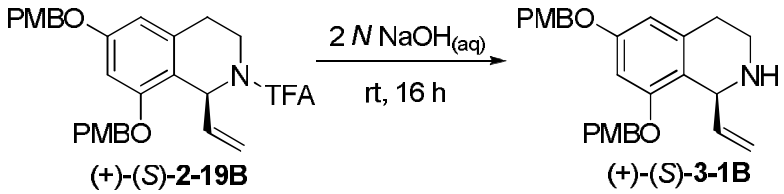
3-10: mp 107-109 ^oC; $[\alpha]_D^{21}$ -7.3 (*c* 4.1, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 3.79 (s, 3H), 4.24 (t, *J* = 7.2 Hz, 1H), 4.43 (d, *J* = 6.9 Hz, 2H), 4.95 (m, 1H), 5.29 (d, *J* = 10.5 Hz, 1H), 5.35 (d, *J* = 17.4 Hz, 1H), 5.49 (d, *J* = 6.9 Hz, 1H), 5.92 (m, 1H), 7.32 (dd, *J* = 6.9 and 7.5 Hz, 2H), 7.41 (dd, *J* = 6.9 and 7.5 Hz, 2H), 7.60 (d, *J* = 6.9 Hz, 2H), 7.77 (d, *J* = 7.5 Hz, 2H). All data are in good agreement with the literature values.[8a]

[*N*-(9-Fluorenylmethoxycarbonyloxy)]-L-vinyl glycine (3-2a)[13]



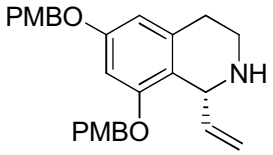
To [*N*-(9-fluorenylmethoxycarbonyloxy)]-L-methionine methyl ester **3-10** (502 mg, 1.49 mmol) placed in a 25 mL round-bottom flask were added acetic acid and water in 1:1 ratio (8 mL total) at room temperature. After the addition was complete, the mixture was heated to reflux for 1.5 h. The reaction mixture was cooled to room temperature and acetic acid was evaporated under reduced pressure. The resulting oil was diluted with DCM. The aqueous layer was separated and extracted with DCM (3x). The combined organic layer was washed with water, brine and dried over $MgSO_4$. The drying agent was removed by filtration and the solvent was concentrated *in vacuo* to afford **3-2a** as a white crystal (470 mg, 97% yield): mp 151-153 ^oC; $[\alpha]_D^{21}$ +1.39 (*c* 16.6, MeOH); (*note*: the product existed in the form of two distinguishable rotamers with 2:1 ratio); ^1H NMR (300 MHz, $CDCl_3$) δ 4.24 (t, *J* = 7.2 Hz, 1H), 4.47 (two d, *J* = 6.9 Hz, 2H), 4.63 and 5.00 (two m, 1H), 5.20 and 7.03 (two m, 1H), 5.35 and 5.41 (two m, 2H), 5.80 and 5.92 (two m, 1H), 7.34 (dd, *J* = 6.9 and 7.5 Hz, 2H), 7.41 (dd, *J* = 6.9 and 7.5 Hz, 2H), 7.55 and 7.60 (two d, *J* = 6.9 Hz, 2H), 7.77 (d, *J* = 7.5 Hz, 2H). All data are in good agreement with the literature values.

(+)-6,8-Bis(4-methoxybenzyloxy)-3,4-dihydro-1-ethenyl-1*H*-isoquinoline, (+)-(*S*)-**3-1B**



To a stirred solution of (+)-(*S*)-**2-19B** (280 mg, 0.531 mmol, 94.0% ee) in EtOH (5 mL) was added slowly 2 M NaOH solution (1 mL) at room temperature, and the mixture was stirred at room temperature for 16 h. Then, EtOH was evaporated under reduced pressure, and the resulting oil was diluted with Et_2O (20 mL) and water (20 mL). The aqueous layer was separated

and extracted with Et_2O (20 mL x3). The combined organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4. The drying agent was removed by filtration and the solvent evaporated *in vacuo* to afford (+)-(*S*)-**3-1B** (225 mg, 98% yield) as a light yellow solid: mp 83-85 ^oC; $[\alpha]_D^{21}$ +25.8 (*c* 0.62, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 2.61-2.66 (m, 1H), 2.78-2.90 (m, 1H), 2.97-3.04 (m, 1H), 3.09-3.20 (m, 1H), 3.80 (s, 3H), 3.81 (s, 3H), 4.70 (d, *J* = 5.2 Hz, 1H), 4.86-4.95 (m, 5H), 5.11 (dt, *J* = 10.0 and 1.2 Hz, 1H), 6.01-6.12 (m, 1H), 6.35 (d, *J* = 2.0 Hz, 1H), 6.42 (d, *J* = 2.0 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.4, 38.1, 52.6, 55.5, 69.8, 70.0, 98.5, 106.1, 114.1, 114.2, 116.2, 118.1, 128.9, 129.2, 129.3, 129.5, 136.9, 139.0, 156.8, 158.5, 159.5, 159.7; HRMS (ESI+) calcd. For $C_{27}H_{30}NO_4$ $[M+H]^+$ 432.2175, found 432.2163 (Δ = -2.8 ppm).

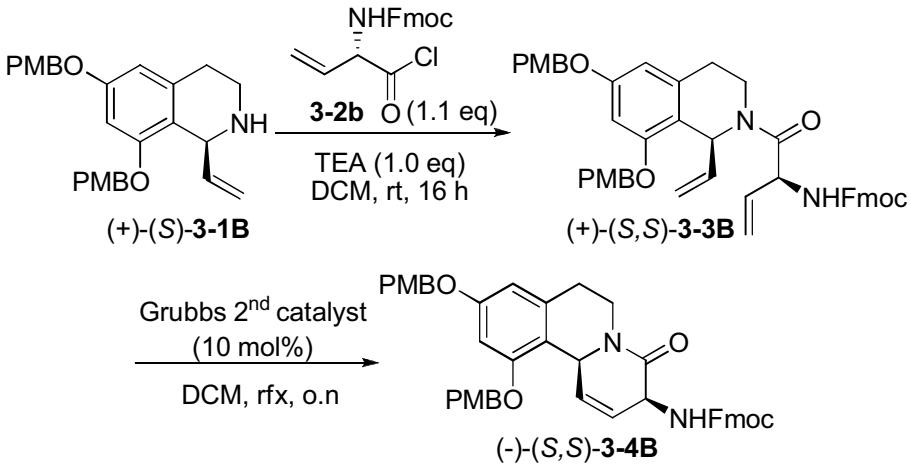


(-)-(*R*)-**3-1B**

(-)-6,8-Bis(4-methoxybenzyloxy)-3,4-dihydro-1-ethenyl-1*H*-isoquinoline, (-)-(*R*)-**3-1B.**

The compound (-)-(*R*)-**3-1A** was obtained in 98% yield in the same manner as that described for the synthesis of (+)-(*S*)-**3-1A**. All characterization data were identical to those of (+)-(*S*)-**3-1A** except for $[\alpha]_D^{21}$ -27.0 (*c* 0.62, $CHCl_3$); HRMS (ESI+) calcd. For $C_{27}H_{30}NO_4$ $[M+H]^+$ 432.2175, found 432.2172 (Δ = -0.7 ppm).

(3*S*,11b*S*)-9,11-Bis(4-methoxybenzyloxy)-3-(9H-fluoren-9-yl)methoxycarbonylamino-2,3,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-4(11bH)-one, (-)-(*S*,*S*)- **3-4B**

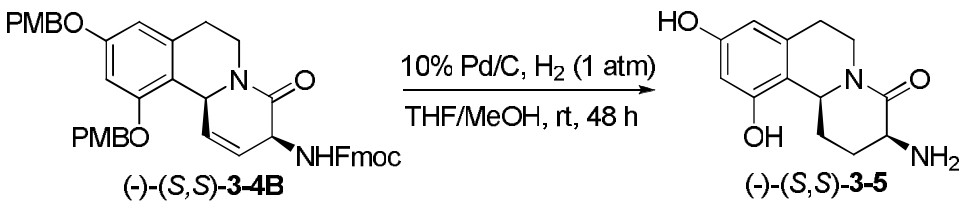


(+)-(*S*)-**3-1B** (+)-(*S,S*)-**3-3B** (-)-(*S,S*)-**3-4B**

To a stirred solution of (+)-(*S*)-**3-1B** (94% ee) (58.3 mg, 0.135 mmol) and Et_3N (18.8 μL, 0.135 mmol) in distilled DCM (0.8 mL) was added (*S*)-*N*-Fmoc-vinylglycinyl chloride **3-2b** (50.8 mg, 0.149 mmol) in distilled DCM (2 mL) at 0 °C under nitrogen. The mixture was then stirred at room temperature for 16 h, and the reaction was quenched by adding Et_2O (10 mL) and water (10 mL). The aqueous layer was separated and extracted with Et_2O (15 mL x2). The combined organic layer was washed with 1 M hydrochloric acid, water and brine, and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the solvent evaporated *in vacuo* to afford the crude product as yellow oil. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc = 5:1→2:1) afforded (+)-(*S*,*S*)-**3-3B** as colorless oil (83 mg, 84% yield): *cis/trans* > 20/1 by ^{1}H NMR); $[\alpha]_D^{21}$ +61.0 (*c* 1.0, CH_2Cl_2); HRMS (ESI+) calcd. For $C_{46}H_{45}N_2O_7$ $[M+H]^+$ 737.3227, found 737.3232 (Δ = 0.7 ppm).

To a stirred solution of (+)-(*S*,*S*)-**3-3B** (63 mg, 0.086 mmol) in distilled DCM (3.5 mL) was added the 2nd generation Grubbs catalyst (7.4 mg, 10 mol%) under nitrogen, and the mixture was heated to reflux for 16 h. The reaction mixture was cooled to room temperature and DCM was evaporated under reduced pressure to give the crude product as a brown solid. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc = 4:1→1:1) afforded (-)-(*S*,*S*)-**3-4B** as a white solid (48 mg, 80% yield): mp 125-127 °C (dec.); $[\alpha]_D^{21}$ -132 (*c* 0.5, CHCl3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.63-2.85 (m, 3H), 3.83 (s, 6H), 4.26 (t, *J* = 7.2 Hz, 1H), 4.41 (d, *J* = 7.2 Hz, 2H), 4.65-4.70 (m, 1H), 4.89-5.08 (m, 5H), 5.39 (d, *J* = 5.7 Hz, 1H), 5.95-6.08 (m, 2H), 6.39 (d, *J* = 2.4 Hz, 1H), 6.56 (d, *J* = 2.4 Hz, 1H), 6.90-6.95 (m, 4H), 7.26-7.40 (m, 8H), 7.62 (d, *J* = 6.6 Hz, 2H), 7.76 (d, *J* = 6.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.1, 40.4, 47.4, 51.5, 52.8, 55.5, 55.6, 67.4, 70.1, 70.2, 99.3, 106.1, 114.3, 114.4, 114.5, 115.8, 120.2, 125.4, 127.3, 127.9, 128.4, 128.5, 128.9, 129.0, 129.1, 129.5, 129.9, 137.9, 141.5, 144.1, 144.2, 156.4, 158.9, 159.7, 159.8, 167.5; HRMS (ESI+) calcd. For $C_{44}H_{41}N_2O_7$ $[M+H]^+$ 709.2914, found 709.2906 (Δ = -1.1 ppm).

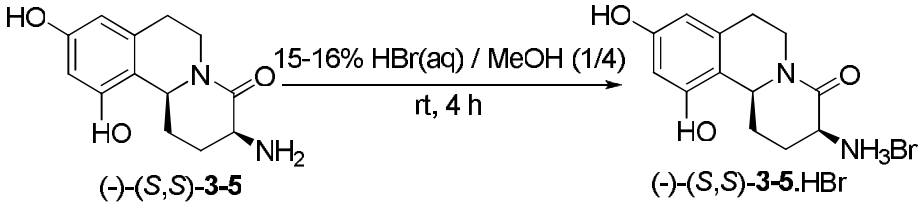
(3*S*,11b*S*)-3-Amino-9,11-dihydroxy-2,3,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-4(11bH)-one, (-)-(*S*,*S*)-**3-5**



(-)-(*S*,*S*)-**3-4B** (-)-(*S*,*S*)-**3-5**

To (-)-(*S*,*S*)-**3-4B** (40 mg, 0.055 mmol) and 10% Pd/C (12 mg, 0.011 mmol) placed in a 10 mL round-bottomed flask were added distilled MeOH (1.5 mL) and THF (1.5 mL) at room temperature. The nitrogen atmosphere was then replaced with hydrogen (1 atm), and the mixture was stirred for 48 h. The reaction mixture was filtered through Celite, washed with MeOH (30 mL), and the filtrate was concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel [CH_2Cl_2/(2 M NH_3 in MeOH) = 30:1→10:1) afforded (-)-(*S*,*S*)-**3-5** as a white paste (13 mg, 91% yield): $[\alpha]_D^{20}$ -252.3 (*c* 0.35, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ 1.28-1.52 (m, 3H), 2.22-2.31 (m, 1H), 2.47-2.74 (m, 4H), 3.58 (t, *J* = 8.1 Hz, 1H), 4.62-4.66 (m, 1H), 4.79 (dd, *J* = 3.6 and 14.4 Hz, 2H), 6.11 (d, *J* = 2.4 Hz, 1H), 6.18 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 28.1, 29.1, 30.6, 40.5, 50.8, 52.1, 102.1, 107.5, 115.5, 138.6, 156.4, 158.1, 175.2; HRMS (ESI+) calcd. For $C_{13}H_{17}N_2O_3$ $[M+H]^+$ 249.1239, found 249.1232 (Δ = -2.8 ppm).

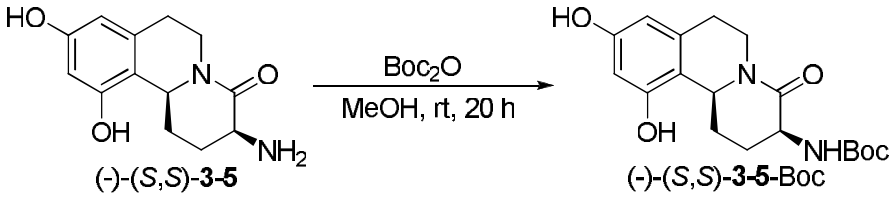
(3*S*,11b*S*)-3-Amino-9,11-dihydroxy-2,3,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-4(11bH)-one hydrobromide, (-)-(*S*,*S*)-**3-5**.HBr



(-)-(*S*,*S*)-**3-5** (-)-(*S*,*S*)-**3-5**.HBr

To (-)-(*S*,*S*)-**3-5** (5.5 mg, 0.022 mmol) in a 5 mL round-bottomed flask was added 16% hydrobromic acid (0.6 mL) and MeOH (2.4 mL) at room temperature, and the mixture was stirred for 4 h. All volatiles were removed under high vaccum to give (-)-(*S*,*S*)-**3-5**.HBr as a light yellow paste (7.3 mg, 100% yield): $[\alpha]_D^{20}$ -138.9 (*c* 0.73, MeOH); ^{1}H NMR (300 MHz, D_2O) δ 1.41-1.56 (m, 1H), 1.67-1.83 (m, 1H), 2.35-2.53 (m, 2H), 2.66-2.86 (m, 3H), 4.21 (dt, *J* = 7.8 and 11.7 Hz, 1H), 4.44-4.51 (m, 1H), 4.82-4.84 (m, 1H), 6.25-6.41 (m, 2H); ^{13}C NMR (125 MHz, D_2O): δ 22.3, 27.0, 28.4, 39.5, 48.8, 49.8, 101.3, 107.1, 114.4, 138.3, 153.9, 155.4, 168.3; LRMS (ESI-) calcd. For $C_{13}H_{17}N_2O_3Br$ $[M-H]^-$ 327.0, found 327; HRMS (ESI+) calcd. For $C_{13}H_{17}N_2O_3$ $[M-Br]^+$ 249.1239, found 249.1237 (Δ = -0.8 ppm).

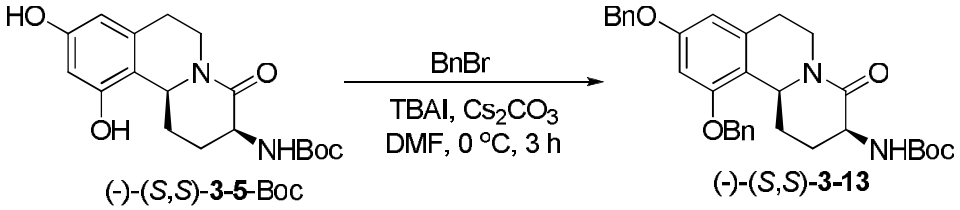
(3*S*,11b*S*)-3-(*tert*-Butoxycarbonylamino)-9,11-dihydroxy-2,3,6,7-tetrahydro-1H-pyrido-[2,1-a] isoquinolin-4(11bH)-one, (-)-(*S*,*S*)-**3-5**-Boc.[3b]



(-)-(*S*,*S*)-**3-5** (-)-(*S*,*S*)-**3-5**-Boc

To a stirred solution of (-)-(*S*,*S*)-**3-5** (5.8 mg, 0.023 mmol) in distilled MeOH (0.5 mL) was added Boc_2O (7.4 mg, 0.030 mmol) under nitrogen, and a mixture was stirred at room temperature for 20 h. The solvent was evaporated under reduced pressure to give the crude product as light yellow oil. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc = 4:1→1:1) afforded (-)-(*S*,*S*)-**3-5**-Boc as colorless oil (6.4 mg, 79% yield): $[\alpha]_D^{22}$ -176.6 (*c* 0.64, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 1.28-1.40 (m, 1H), 1.42 (s, 9H), 1.46-1.55 (m, 1H), 2.22-2.37 (m, 1H), 2.48-2.52 (m, 1H), 2.59-2.75 (m, 3H), 4.32 (t, *J* = 8.4 Hz, 1H), 4.59-4.62 (m, 1H), 4.80-4.81 (m, 1H), 6.11 (d, *J* = 2.4 Hz, 1H), 6.18 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 26.3, 28.7, 29.2, 30.3, 40.4, 50.8, 51.2, 80.5, 102.0, 107.3, 115.1, 138.4, 156.3, 158.0, 158.2, 172.4. All data were in agreement with the literature values except for the specific rotation. Gurjar et al.[3b] reported the specific rotation of this compounds to be $[\alpha]_D$ -49.1 (*c* 0.90, MeOH). However, the value was $[\alpha]_D^{22}$ -176.6 (*c* 0.64, MeOH) in our hands, as shown above. It appears that the reported value is either an error or their compound is not enantiomerically pure.

(3*S*,11b*S*)-3-(*tert*-Butoxycarbonylamino)-9,11-bis(benzyloxy)-2,3,6,7-tetrahydro-1Hpyrido[2,1-a]isoquinolin-4(11bH)-one, (-)-(*S*,*S*)-**3-13**.[3b, 3d]

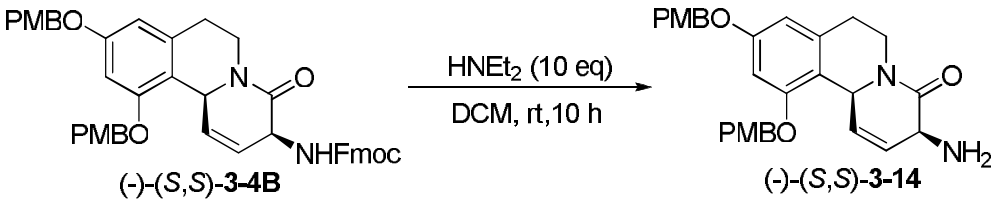


(-)-(*S*,*S*)-**3-5**-Boc (-)-(*S*,*S*)-**3-13**

To a stirred solution of (*S*,*S*)-**3-5**-Boc (6.4 mg, 0.019 mmol), tetrabutylammonium iodide (TBAI) (0.2 mg, 0.0005 mmol), and Cs_2CO_3 (18 mg, 0.057 mmol) in dry DMF (0.5 mL) was added benzyl bromide (0.026 mL, 0.042 mmol) at 0 °C under nitrogen, and the mixture was stirred under the same temperature for 3 h. The reaction was quenched with water (5 mL) and diluted with EtOAc (5 mL). The aqueous layer was separated and extracted with EtOAc (5 mL x2). The combined organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4. The drying agent was removed by filtration and the solvent evaporated *in vacuo* to

afford the crude product as light yellow oil. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc = 10:1→4:1) afforded (*S*,*S*)-**3-13** as colorless oil (7.6 mg, 78% yield): $[\alpha]_D^{19}$ -109.2 (*c* 0.76, $CHCl_3$) [lit.[3d] $[\alpha]_D^{24}$ -108.1 (*c* 1.97, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35-1.42 (m, 2H), 1.46 (s, 9H), 2.41-2.60 (m, 2H), 2.71-2.82 (m, 3H), 4.30-4.36 (m, 1H), 4.72-4.76 (m, 1H), 4.89-4.92 (m, 1H), 5.00 (s, 2H), 5.07 (s, 2H), 5.75 (d, *J* = 5.2 Hz, 1H), 6.39 (d, *J* = 2.1 Hz, 1H), 6.48 (d, *J* = 2.1 Hz, 1H), 7.30-7.42 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0, 28.6, 28.7, 29.9, 39.0, 49.0, 50.0, 70.4, 79.7, 99.2, 106.0, 117.6, 127.4, 127.7, 128.3, 128.4, 128.8, 129.0, 136.7, 136.9, 137.5, 155.9, 156.2, 158.7, 170.8. All data were in good agreement with those reported by Bowen and Wardrop.[3d] However, the specific rotaion reported by Gurjar et al.[3b] was $[\alpha]_D$ -102 (*c* 1.1, $CHCl_3$), which is considerably lower than our value as well as that of Bowen and Wardrop.

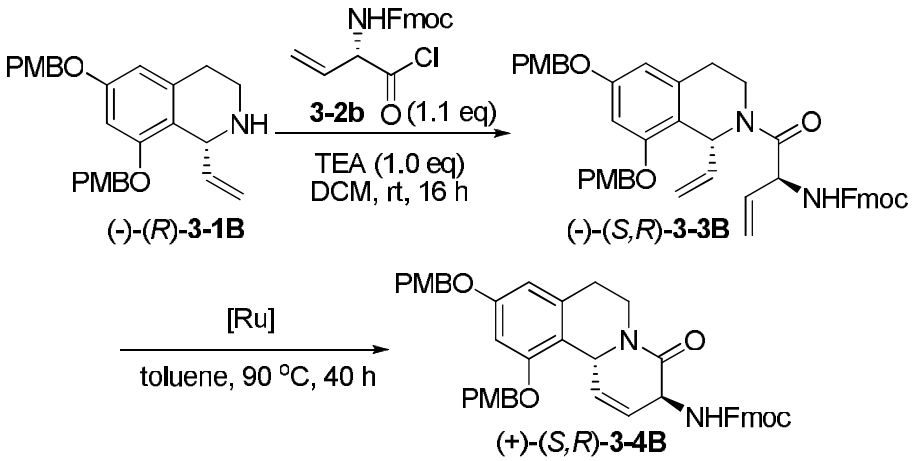
(3*S*,11b*S*)-3-Amino-9,11-bis(4-methoxybenzyloxy)-2,3,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-4(11bH)-one, (-)-(*S*,*S*)-**3-14.**



(-)-(*S*,*S*)-**3-4B** (-)-(*S*,*S*)-**3-14**

To a stirred solution of (-)-(*S*,*S*)-**3-4B** (25 mg, 0.036 mmol) in distilled DCM (4.0 mL) was added Et_2NH (37 μL, 0.36 mmol) at room temperature, and the mixture was stirred at room temperature for 10 h. Solvents were evaporated under reduced pressure to give the crude product as brown oil. ^{1}H NMR analysis of the crude product indicated a quantitative formation of the desired product, (-)-(*S*,*S*)-**3-14**. Purification of the crude product by flash column chromatography on silica gel (CH_2Cl_2/(2 M NH_3 in MeOH) = 99:1→98:2) afforded (-)-(*S*,*S*)-**3-14** as a light yellow oil (13 mg, 72% yield): $[\alpha]_D^{21}$ -197.8 (*c* 0.45, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ 2.60-2.80 (m, 3H), 3.78 (s, 6H), 3.84-3.87 (m, 1H), 4.77-4.80 (m, 1H), 4.91-5.04 (m, 4H), 5.35-5.37 (m, 1H), 5.81 (ddd, *J* = 2.0, 3.2, 9.6 Hz, 1H), 6.18 (ddd, *J* = 2.0, 3.2, 9.6 Hz, 1H), 6.41 (d, *J* = 2.0 Hz, 1H), 6.61 (d, *J* = 2.0 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 4H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 29.6, 40.0, 53.8, 54.5, 69.7, 69.9, 99.1, 106.5, 113.7, 113.8, 115.9, 127.6, 128.9, 129.1, 129.3, 137.6, 156.4, 158.9, 159.8, 159.9, 171.3; HRMS (ESI+) calcd. For $C_{29}H_{31}N_2O_5$ $[M+H]^+$ 487.2233, found 487.2220 (Δ = -2.7 ppm).

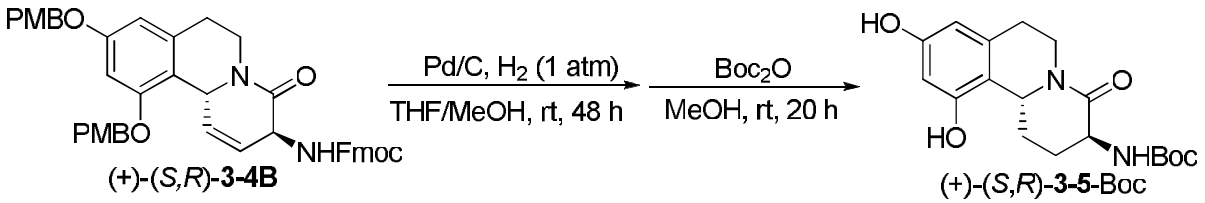
(3*S*,11*R*)-9,11-Bis(4-methoxybenzyloxy)-3-(9H-fluoren-9-yl)methoxycarbonylamino-2,3,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-4(11bH)-one, (+)-(*S*,*R*)-**3-4B.**



To a stirred solution of (-)-(*R*)-**3-1B** (96.1% ee) (76.5 mg, 0.177 mmol) and Et_3N (24.6 μL, 0.177 mmol) in distilled DCM (1 mL) was added **3-2b** (72.7 mg, 0.212 mmol) in distilled DCM (3 mL) at 0 °C under nitrogen, and the mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with Et_2O (10 mL) and water (10 mL). The aqueous layer was separated and extracted with Et_2O (15 mL x2). The combined organic layer was washed with 1 M hydrochloric acid, water and brine, and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the solvent evaporated *in vacuo* to afford the crude product as yellow oil. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc = 5:1→2:1) afforded (-)-(*S*,*R*)-**3-3B** as colorless oil (105 mg, 81% yield): *trans/cis* > 20/1 by ^{1}H NMR; $[\alpha]_D^{20}$ -36.8 (*c* 1.25, CH_2Cl_2); HRMS (ESI+) calcd. For $C_{46}H_{45}N_2O_7$ $[M+H]^+$ 737.3227, found 737.3218 (Δ = -1.2 ppm).

To a stirred solution of (-)-(*S*,*R*)-**3-3B** (41 mg, 0.055 mmol) in distilled toluene (5.5 mL) was added 2nd generation Hoveyda-Grubbs catalyst (7.0 mg, 20 mol%) under nitrogen, and the mixture was heated to 90 °C for 40 h. The reaction mixture was cooled to room temperature and toluene was evaporated under reduced pressure to give the crude product as a brown solid. The ^{1}H NMR analysis of the crude product indicated that (*S*,*R*)-**3-4B** and (*R*,*R*)-**3-4B** were formed in 3:1 ratio. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc = 2:1→1:1) afforded (*S*,*R*)-**3-4B** as an off-white solid (20 mg, 51% yield). Since (*S*,*R*)-**3-4B** was found to be rather unstable and prone to decompose, the purified compound was immediately used for the next step without further characterization.

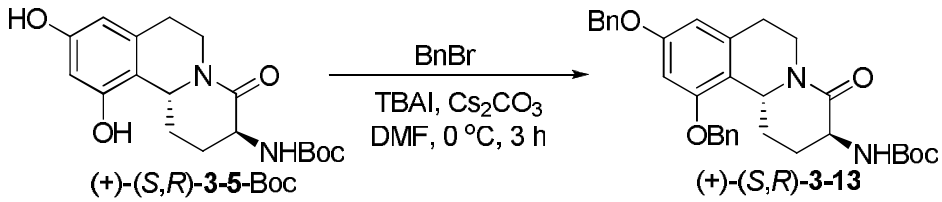
(3*S*,11b*R*)-3-(*tert*-Butoxycarbonylamino)-9,11-dihydroxy-2,3,6,7-tetrahydro-1H-pyrido-[2,1-a] isoquinolin-4(11bH)-one, (+)-(*S*,*R*)-**3-5**-Boc.[3b]



(+)-(*S*,*R*)-**3-4B** (+)-(*S*,*R*)-**3-5**-Boc

To (*S*,*R*)-**3-4B** (20 mg, 0.028 mmol), thus obtained, and 10% Pd/C (6.0 mg, 0.0056 mmol) placed in a 5 mL round-bottomed flask were added distilled MeOH (0.8 mL) and THF (0.8 mL) at room temperature. The nitrogen atmosphere was then replaced with hydrogen (1 atm). The mixture was stirred at room temperature for 48 h, and Boc_2O (9.0 mg, 0.036 mmol) in MeOH (0.2 mL) was added without removing Pd/C. The reaction mixture was stirred at room temperature for 20 h. The solid was then filtered out and the filtrate was evaporated under reduced pressure to give the crude product as light yellow oil. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc = 2:1→1:1) afforded (*S*,*R*)-**3-5**-Boc as colorless oil (6.1 mg, 63% yield for two steps): $[\alpha]_D^{20}$ +184.3 (*c* 0.51, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ 1.34-1.51 (m, 1H), 1.45 (s, 9H), 1.91-2.12 (m, 2H), 2.49-2.70 (m, 3H), 3.05-3.09 (m, 1H), 3.92-4.05 (m, 1H), 4.73-4.79 (m, 2H), 6.08 (d, *J* = 2.1 Hz, 1H), 6.16 (d, *J* = 2.1 Hz, 1H). ^{1}H NMR data were in agreement with the literature values. Gurjar et al.[3b] reported the specific rotation of this compounds to be $[\alpha]_D$ +122 (*c* 1.4, MeOH). However, the value was $[\alpha]_D^{20}$ +184.3 (*c* 0.51, MeOH) in our hands, as shown above. It appears that the reported value is either an error or their compound is enantiomerically not pure.

(3*S*,11b*R*)-3-(*tert*-Butoxycarbonylamino)-9,11-bis(benzyloxy)-2,3,6,7-tetrahydro-1Hpyrido[2,1-a]isoquinolin-4(11bH)-one, (+)-(*S*,*R*)-**3-13.**[3b, 3d]



(+)-(*S*,*R*)-**3-5**-Boc (+)-(*S*,*R*)-**3-13**

Compound (+)-(*S*,*R*)-**3-13** was obtained in 78% yield as color less oil in the same manner as that described for the synthesis of (-)-(*S*,*S*)-**3-13**: $[\alpha]_D^{19}$ +177.2 (*c* 0.57, $CHCl_3$) [lit.[8] $[\alpha]_D^{24}$ +182.2 (*c* 1.33, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40-1.53 (m, 1H), 1.45 (s, 9H), 1.69-1.75 (m, 1H), 2.41-2.49 (m, 1H), 2.57-2.66 (m, 2H), 2.83-2.90 (m, 1H), 3.04-3.08 (m, 1H),

3.99-4.06 (m, 1H), 4.78 (dd, J = 3.6, 11.2 Hz, 1H), 4.89-4.94 (m, 1H), 4.98-5.08 (m, 4H), 5.32 (br s, 1H), 6.36 (d, J = 2.4 Hz, 1H), 6.49 (d, J = 2.4 Hz, 1H), 7.32-7.42 (m, 10H). ^{1}H NMR data are in agreement with the literature values.[3d]

Gurjar et al.[3b] reported the specific rotation of this compounds to be $[\alpha]_D$ +116 (*c* 1.35, MeOH). However, the value was $[\alpha]_D^{19}$ +177.2 (*c* 0.57, $CHCl_3$) in our hands and $[\alpha]_D^{24}$ +182.2 (*c* 1.33, $CHCl_3$) by Bowen and Wardrop,[3d] as shown above. It appears that the reported value by Gurjar et al.[3b] is either an error or their compound is enantiomerically not pure. We believe that a small difference in our specific rotation and that by Bowen and Wardrop[3d] is due to the difference in concentration and temperature for the measurement.

§ 3.5 References

1. Takada, K.; Uehara, T.; Nakao, Y.; Matsunaga, S.; van Soest, R. W. M.; Fusetani, N., Schulzeines A-C, New α-Glucosidase Inhibitors from the Marine Sponge Penares schulzei. *J. Am. Chem. Soc.* **2004,** *126* (1), 187-193.
2. (a) Braun, C.; Brayer, G. D.; Withers, S. G., Mechanism-based Inhibition of Yeast alpha-Glucosidase and Human Pancreatic alpha-Amylase by a New Class of Inhibitors. *J. Biol. Chem.* **1995,** *270* (45), 26778-26781; (b) Mehta, A.; Zitzmann, N.; Rudd, P. M.; Block, T. M.; Dwek, R. A., α-Glucosidase inhibitors as potential broad based anti-viral agents. *FEBS Lett.* **1998,** *430* (1–2), 17-22; (c) Dwek, R. A.; Butters, T. D.; Platt, F. M.; Zitzmann, N., Targeting glycosylation as therapeutic approach. *Nat. Rev. Drug Discov.* **2002,** *1*, 65-75.
3. (a) Kuntiyong, P.; Akkarasamiyo, S.; Eksintkun, G., Short Synthetic Route toward the Tricyclic Core of Schulzeines. *Chem. Lett.* **2006,** *35*, 1008-1009; (b) Gurjar, M. K.; Pramanik, C.; Bhattasali, D.; Ramana, C. V.; Mohapatra, D. K., Total Syntheses of Schulzeines B and C. *J. Org. Chem.* **2007,** *72* (17), 6591-6594; (c) Liu, G.; Romo, D., Enantioselective Synthesis of Schulzeines B and C via a β-Lactone-Derived Surrogate for Bishomoserine Aldehyde. *Org. Lett.* **2009,** *11* (5), 1143-1146; (d) Bowen, E. G.; Wardrop, D. J., Total Synthesis of the α-Glucosidase Inhibitors Schulzeine A, B, and C and a Structural Revision of Schulzeine A. *J. Am. Chem. Soc.* **2009,** *131* (17), 6062-6063; (e) Miyazaki, M.; Ando, N.; Sugai, K.; Seito, Y.; Fukuoka, H.; Kanemitsu, T.; Nagata, K.; Odanaka, Y.; Nakamura, K. T.; Itoh, T., Catalytic Asymmetric Allylation of 3,4-Dihydroisoquinolines and Its Application to the Synthesis of Isoquinoline Alkaloids. *J. Org. Chem.* **2011,** *76* (2), 534-542.
4. (a) Vicario, J. L.; Badía, D.; Carrillo, L.; Etxebarria, J., α-Amino Acids and Derivatives in the Asymmetric Synthesis of Tetrahydroisoquinoline Alkaloids. *Curr. Org. Chem.* **2003,** *7* (18), 1775-1792; (b) Chrzanowska, M.; Rozwadowska, M. D., Asymmetric Synthesis of Isoquinoline Alkaloids. *Chem. Rev.* **2004,** *104* (7), 3341-3370; (c) Kaufman, T. S., Approaches to the Total Synthesis of Calycotomine, a Widespread 1-Hydroxymethyl-Substituted Simple Tetrahydroisoquinoline. *Synthesis* **2005,** (EFirst), 339,360; (d) Ito, K.; Akashi, S.; Saito, B.; Katsuki, T., Asymmetric Intramolecular Allylic

Amination: Straightforward Approach to Chiral C1-Substituted Tetrahydroisoquinolines. *Synlett* **2003**, 1809-1812; (e) Taylor, A. M.; Schreiber, S. L., Enantioselective Addition of Terminal Alkynes to Isolated Isoquinoline Iminiums. *Org. Lett.* **2006,** *8* (1), 143-146; (f) Teichert, J. F.; Fañanás-Mastral, M.; Feringa, B. L., Iridium-Catalyzed Asymmetric Intramolecular Allylic Amidation: Enantioselective Synthesis of Chiral Tetrahydroisoquinolines and Saturated Nitrogen Heterocycles. *Angew. Chem. Int. Ed.* **2011,** *50* (3), 688-691.

5. Kinderman, S. S.; Wekking, M. M. T.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T., Catalytic N-Sulfonyliminium Ion-Mediated Cyclizations to α-Vinyl-Substituted Isoquinolines and β-Carbolines and Applications in Metathesis. *J. Org. Chem.* **2005,** *70* (14), 5519-5527.
6. The absolute configuration of (+)-2 was tentatively assigned to S based on the sign of the specific rotation of close related (S)-(+)-1-vinyltetrahydroisoquinoline that we reported previously (Ref. 2-11), and confirmed by the known value of (S,S)-13 (See Experimental Section).
7. Capilla, A. S.; Romero, M.; Pujol, M. D.; Caignard, D. H.; Renard, P., Synthesis of isoquinolines and tetrahydroisoquinolines as potential antitumour agents. *Tetrahedron* **2001,** *57* (39), 8297-8303.
8. (a) Organ, M. G.; Xu, J.; N'Zemba, B., A modular, general and enantiospecific strategy for the synthesis of CVS 1778 analogs: inhibitors of factor Xa. *Tetrahedron Lett.* **2002,** *43* (45), 8177-8180; (b) Rajendra, G.; Miller, M. J., Intramolecular electrophilic additions to olefins in organic syntheses. Stereoselective synthesis of 3,4-substituted .beta.-lactams by bromine-induced oxidative cyclization of O-acyl .beta.,.gamma.-unsaturated hydroxamic acid derivatives. *J. Org. Chem.* **1987,** *52* (20), 4471-4477.
9. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H., Synthesis and Activity of a New Generation of Ruthenium-Based Olefin Metathesis Catalysts Coordinated with 1,3-Dimesityl-4,5-dihydroimidazol-2-ylidene Ligands§. *Org. Lett.* **1999,** *1* (6), 953-956.
10. The Spartan program indicates that cis-6 and trans-6 have almost same energy, and an attempted epimerization of trans-6 to cis-6 under the RCM conditions did not cause any epimerization. Thus, this epimerization should have taken place during the RCM reaction.
11. Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H., Efficient and Recyclable Monomeric and Dendritic Ru-Based Metathesis Catalysts. *J. Am. Chem. Soc.* **2000,** *122* (34), 8168-8179.
12. Shi, C.; Chien, C. W.; Ojima, I., Synthesis of chiral biphenol-based diphosphonite ligands and their application to Pd-catalyzed intermolecular asymmetric allylic amination. *Chem. Asian J.* **2011,** *6*, 674.
13. Rajendra, G.; Miller, M. J., Intramolecular electrophilic additions to olefins in organic syntheses. Stereoselective synthesis of 3,4-substituted .beta.-lactams by bromine-induced oxidative cyclization of O-acyl .beta.,.gamma.-unsaturated hydroxamic acid derivatives. *The Journal of Organic Chemistry* **1987,** *52* (20), 4471-4477.

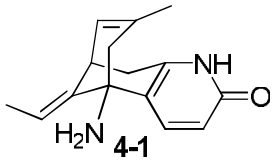
Chapter 4

Enantioselective Synthesis of Huperzine A Key Intermediate via Tandem Pd-Catalyzed Intermolecular Allylic Alkylations

Table of Contents

§ 4.1 Introduction of Huperzine A

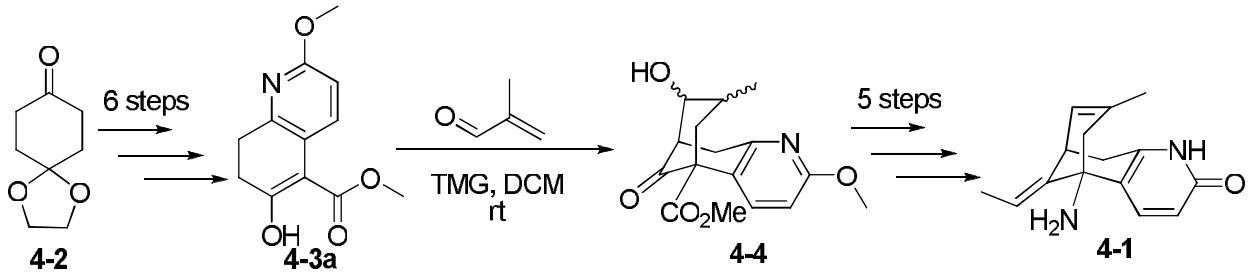
Huperzine A (**Figure 4-1**) is a naturally occurring sesquiterpene alkaloid that can be isolated from the Chinese lycopod *Huperzia serrata.*[1] Huperzine A is an acetylcholinesterase (AchE) inhibitor, which has a mechanism of action similar to donepezil, rivastigmine, and galantamine. In addition, it has also been shown to attenuate β-amyloid-induced apoptosis in cortical neurons along with several other neuroprotective effects.[2] In China, it has been used for the treatment of swelling, fever and blood disorders for many hundred years. In the US, Huperzine A is a dietary supplement for memory support. Clinical trials in China have shown it to be effective in the treatment of Alzheimer's disease[3] and enhancing memory in students. Given its promising medicinally benefits, the isolation of Huperzine A is in great demand. However, *Huperzia serrata* on average contains only 0.08 mg HupA/g dry weight. As a result of over harvesting, the population of *Huperzia serrata* is in rapid decline in China.[4] Therefore, alternative natural sources of Huperzine A are necessary. These natural sources include other *Huperzia* species such as *H. elmeri*, *H. carinat*, and *H. aqualupian*; some of these plants contain up to 1.01 mg HupA/g.[4]



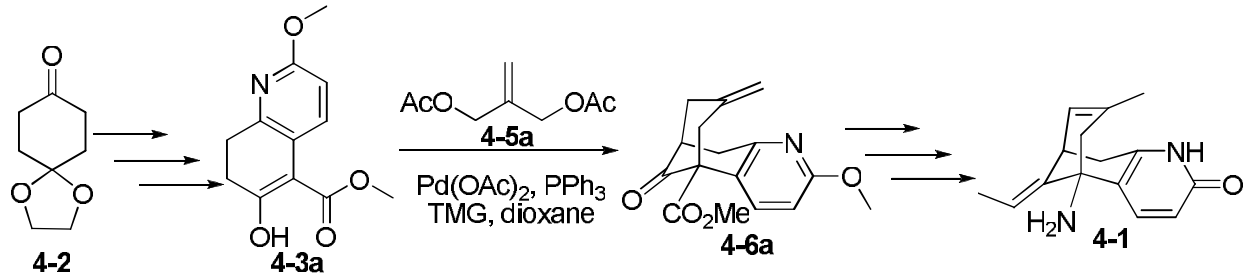
4-1

Figure 4-1. Structure of Huperzine A

With the rapid decline of natural sources of Huperzine A, synthetic organic chemists have to discover efficient ways to synthesize Huperzine A. The first total synthesis of the alkaloid Huperzine A was completed by Kozikowski in 1989 (**Scheme 4-1**).[5] Four years later, he modified the key step for the total synthesis of Huperzine A using tandem Pd-catalyzed allylic alkylations for the formation of the tricylic core of Huperzine A as shown in **Scheme 4-2**.[6]

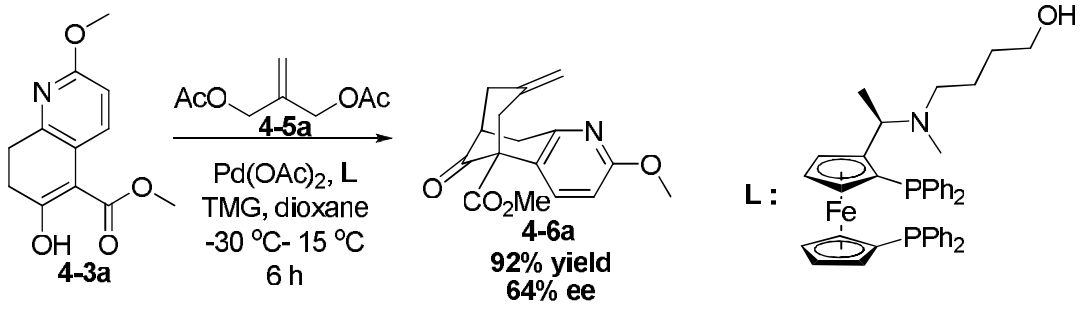


Scheme 4-1. The first total synthesis of the alkaloid Huperzine-A **4-1**



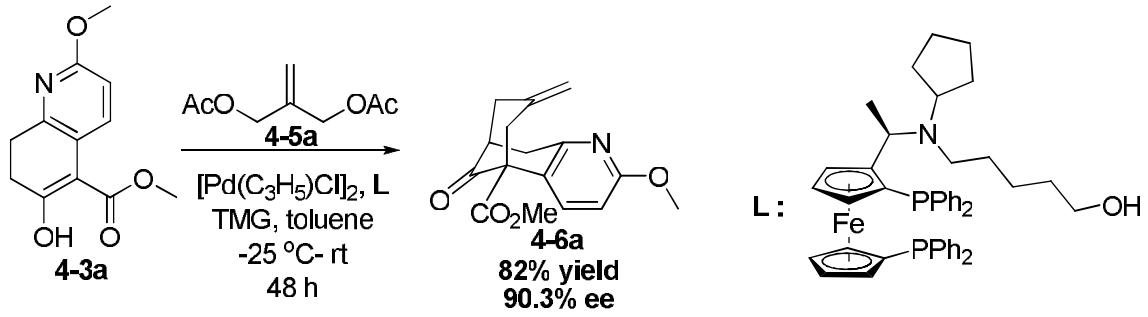
Scheme 4-2. The total synthesis of Huperzine-A via tandem Pd-catalyzed allylic alkylations

Inspired by Kozikowski's successful synthesis, Terashima and co-workers completed the first catalytic asymmetric synthesis of Huperzine A by using a bidentate ferrocene-based ligand, to affording the desired key intermediate **4-6a** in excellent yield and moderate enantioselectivity (92% yield and 64% ee) (**Scheme 4-3**).[7]



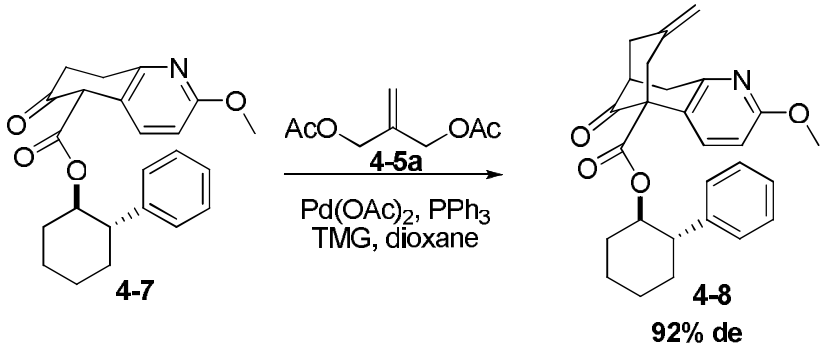
Scheme 4-3. The first catalytic asymmetric synthesis of Huperzine-A intermediate **4-6a**

In 2001, Bai and co-workers achieved 90% ee of **4-6a** by employing a slightly modified Terashima's bidentate ferrocenyl-based ligand (**Scheme 4-4**).[8]



Scheme 4-4. The modified catalytic asymmetric synthesis of Huperzine-A intermediate **4-6a**

In addition to the use of chiral ligand to obtain the enantioenriched Huperzine A intermediate **4-6a**, Langolis and co-workers adopted the diastereoselective synthesis using Whitesell's chiral auxiliary to afford the desired intermediate **4-8** in 92% d.r (**Scheme 4-5**).[9]



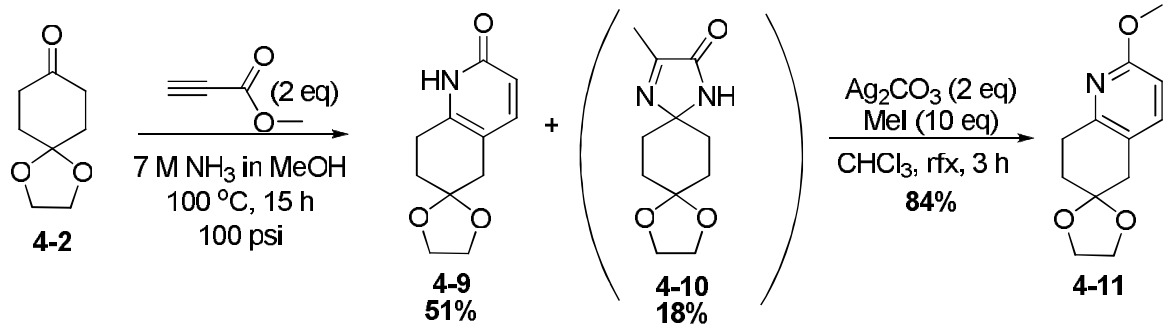
Scheme 4-5. The diastereoselective synthesis of Huperzine-A intermediate **4-8**

Based on the previously reported results, there is still need to improve the enantioselective synthesis of entiopure key intermediates of Huperzine A. Moreover, the use of monodentate chiral ligands for the tandem allylic alkylations has not been reported thus far. Therefore, building upon the successful application of our biphenol-based MPN ligands used for the total synthesis of (+)-lycorane through asymmetric allylic alkylation as the key step for the excellent enantioselectivity,[10] we would like to study the enantioselective efficacy of this ligand library on the same reaction investigated by the Kozikowski, Terashima and Bai's groups.

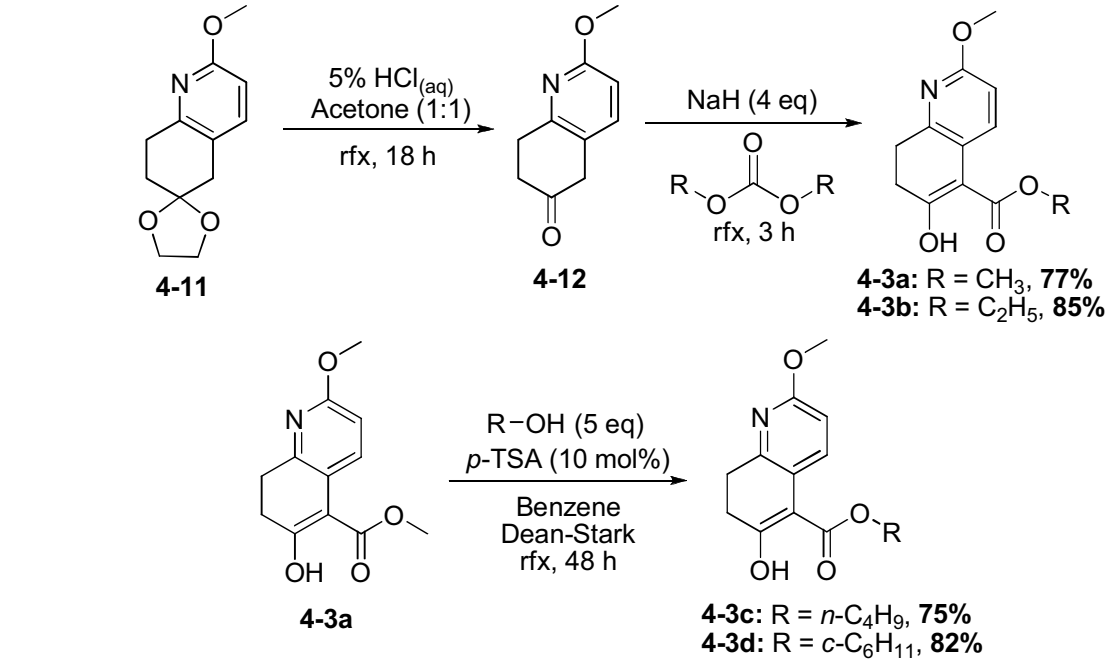
§ 4.2 Results and discussion

§ 4.2.1 Synthesis of key-step substrates

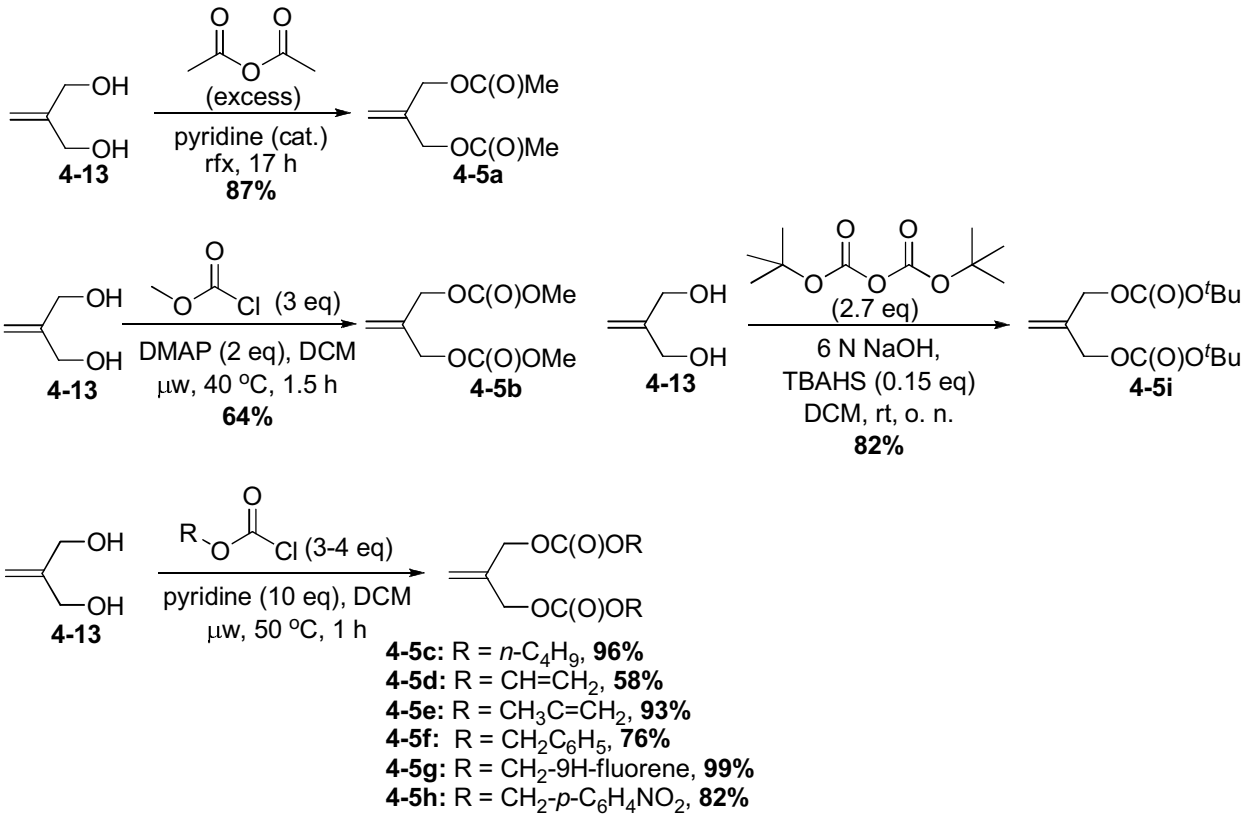
The synthesis of desired enol substrates **4-3a** to **4-3d** is outlined below. The commercially available mono-protected 1,4-cyclohexanedione (**4-2**) first underwent a modified Stork-enamine synthesis with methyl propiolate in the presence of 7 M NH_3 in MeOH at 100 ^oC to afford compound **4-9**.[11] However, the major side product **4-10** and other impurities were obtained in a significant amount according to TLC and flash column chromatography, thus lowering the yield of the desired product. The subsequent *O*-methylation promoted by silver carbonate afforded compound **4-11** in 84% yield (**Scheme 4-6**).[5] Next, the ketal group was deprotected under the acidic condition to afford compound **4-12**, followed by the carboxylation at the most acidic position to give the desired substrates **4-3a** and **4-3b**, in 77% and 85% yield, respectively over two steps (**Scheme 4-7**).[5] The synthesis of substrates containing *n*-butyl and cyclohexyl esters began with **4-**3a, which underwent ester exchange using *n*-butanol and cyclohexanol in the presence of a catalytic amount of *p*-TSA and benzene as the solvent to afford **4-3c** and **4-3d**, in 75% and 82% yields, respectively (**Scheme 4-7**). It is worthy of note that the enol-tautomer is a stable isomer due to an intramolecular hydrogen-bond between the ester carbonyl and the enol moiety, thus only the enoltautomers of **4-3a-d** were isolated.[6]



Scheme 4-6. Synthesis of 7',8'-Dihydro-2'-methoxyspiro[1,3-dioxolane-2,6'-(5'H)]quinoline **4-11**



Scheme 4-7. Synthesis of enol substrates **4-3a** to **4-3d**

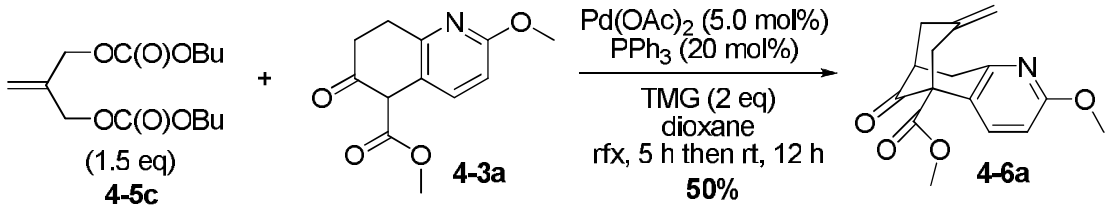


Scheme 4-8. Synthesis of allylic substrates **4-5a** to **4-5i**

The second substrate series containing an allylic group was synthesized from commercially available 2-methylene-1,3-propane-diol and the corresponding anhydride or chloformate to afford the desired allylic diacetate (**4-5a**)[6] and allylic dicarbonates (**4-5b** to **4-5i**)[12] in good to excellent yields under conventional or microwave-irradiated heating conditions (**Scheme 4-8**).

§ 4.2.2 Enantioselective synthesis of Huperzine-A key intermediate via tandem Pd-catalyzed intermolecular allylic alkylations

Although the reaction for the synthesis of the key intermediate **4-6a** has previously been reported by other groups, we were not able to find the detailed chiral HPLC condition for these two enantiomers in any literature. Therefore, a racemic allylic alkylation of **4-3a** and **4-5c** for the formation of tricyclic intermediate **4-6a** was used to set chiral HPLC condition for further study. By using the reaction conditions described by Kozikowski,[6] racemic product **4-6a** can be obtained in moderate yield and the two enantiomers can be separated very well with 5.2 minutes differential (t_R = 19.0 and 24.2 mins) using a Chiracel OD-H normal phase column with an eluent of 3% ispropanol in hexanes (**Figure 4-2**).



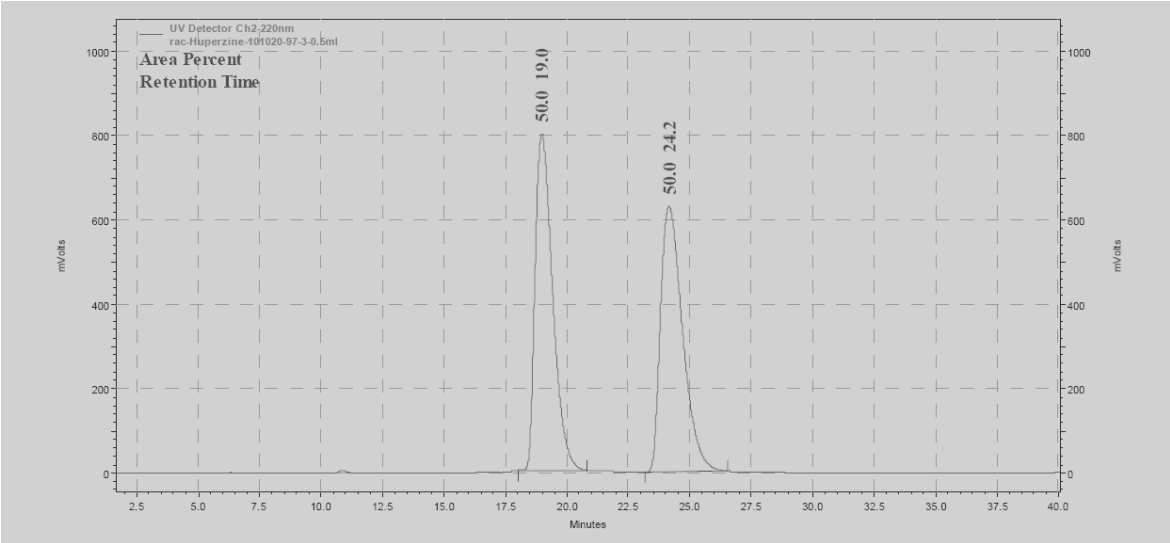
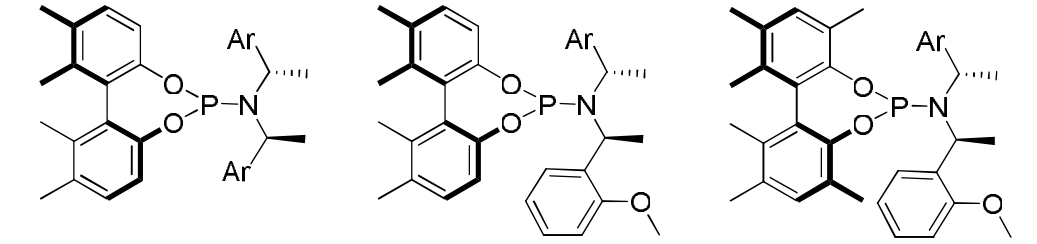


Figure 4-2. Chiral HPLC trace of racemic products **4-6a**

After setting the chiral HPLC conditions for racemic products **4-6a**, the ligand and substrate screenings for the intermolecular asymmetric allylic alkylation were performed to optimize the enantioselectivity of product **4-6a**. **Figure 4-3** shows a library of chiral MPN ligands that were used for the ligand screening. This ligand library demonstrated good to excellent chiral induction in the Pd-catalyzed asymmetric allylic alkylation of (+)-γ-lycorane.[10]



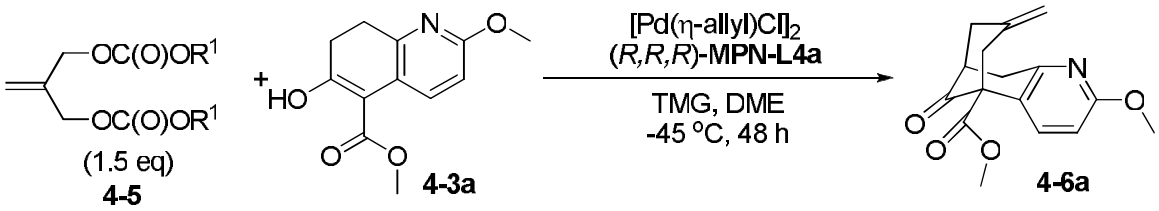
(*R,R,R*)-**MPN-L4a**: Ar = Ph
(*S,S,S*)-**MPN-L5a**: Ar = 2-Np

(*S,S,S*)-**MPN-L6a**: Ar = Ph
(*R,S,S*)-**MPN-L6a**: Ar = Ph
(*S,S,S*)-**MPN-L7a**: Ar = 2-Np
(*S,S,S*)-**MPN-L8a**: Ar = 1-Np

(*S,S,S*)-**MPN-L6b**: Ar = Ph

Figure 4-3. Chiral biphenol-based **MPN** ligand library

Table 4-1. Preliminary Study of the allyl substrate structure on the tandem asymmetric allylic alkylations with **4-3a**



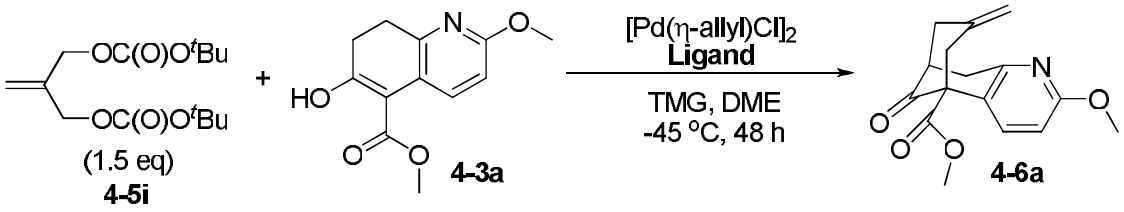
Entry[a]	Allyl substrate	Conv. %[b]	%ee[c]
1	**4-5a**	100	33 (-)
2	**4-5b**	100	38 (-)
3	**4-5c**	100	36 (-)
4	**4-5i**	100	40 (-)

[a]All reactions were run using $[Pd(\eta\text{-allyl})Cl]_2$ (2.5 mol%) with a MPN ligand (15 mol%) and TMG (2.5 eq) in DME [0.025] at -45 °C for 48 h under N_2.
[b]Determined by GC-MS.
[c]Determined by HPLC using Chiracel OD-H normal phase column with an eluent of 3% ispropanol in hexanes.

A small number of various allylic substrates using **4-3a** as the nucleophile and TMG as the base in the presence of $[Pd(\eta\text{-allyl})Cl]_2$ and (*R,R,R*)-**MPN-L4a** were investigated to determine the optimal substrate for the Pd-catalyzed intermolecular asymmetric allylic alkylation (**Table 4-1**). Among those results, more bulky R^1 groups tend to provide higher entioselectivity. It was observed that the allyl substrate **4-5i** which contain *t*-Bu groups gave the best enantioselectivity, thus was selected for the further optimization (entry 4).

Next, the **MPN** ligand library shown in **Figure 4-3** was screened for the Pd-catalyzed asymmetric allylic alkylation of **4-3a** and **4-5i** (**Table 4-2**). As shown in Table 4-2, all reactions achieved full conversion in 48 h except for entries 4 and 5 which gave less than 5% conversion indicated by GC-MS. Among the **MPN** ligands screened, each ligand containing the unsymmetric chiral amine on the phosphorus atom (entries 3,6 and 7) gave higher enantioselectivity than those possessing the symmetric chiral amine on the phosphorus atom did (entries 1 and 2).

Table 4-2. Screening of **MPN** ligands for tandem asymmetric allylic alkylations of **4-3a** and **4-5f**



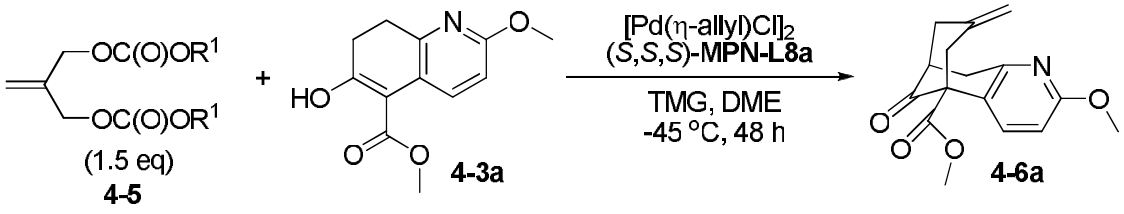
Entry[a]	Ligand (L*)	conv. %[b]	%ee[c]
1	(*R,R,R*)-**MPN-L4a**	100	40 (-)
2	(*S,S,S*)-**MPN-L5a**	100	2 (+)
3	(*S,S,S*)-**MPN-L6a**	100	49 (-)
4	(*R,S,S*)-**MPN-L6a**	<5	n.d.
5	(*S,S,S*)-**MPN-L6b**	<5	n.d.
6	(*S,S,S*)-**MPN-L7a**	100	61 (-)
7	(*S,S,S*)-**MPN-L8a**	100	76 (-)

[a,b,c] See the footnote of Table 4-1.

(*S,S,S*)-**MPN-L8a**, which contains a 1-naphthalenyl substituent as the Ar group, afforded 76% ee; the highest enantioselectivity among these three **MPN** ligands with an unsymmetric amine attached to the phosphorus atom. It is worthy of note that there were dramatic decreases in reactivity observed when the mismatched ligand pairings were used, i.e., ligands where the chirality of biphenol is opposite to that of the chiral amine moiety and the ligand bearing methyl group at the 3,3'-positions of the biphenol, were used (**Table 4-2**, entries 4-5). Thus, (*S,S,S*)-**MPN-L8a** was selected as the ligand of choice for further optimization studies.

Next, the effect of different allyl dicarbonates on the tandem asymmetric allylic alkylation using the optimized condition determined thus far were investigated (**Table 4-3**). As shown in **Table 4-3**, the allyl dicarbonate containing benzyl moieties **4-5f** gave a slightly better result (87% ee) (entry 3) compared to the other two allyl carbonates, which have vinyl-type moieties (**4-5d** and **4-5e**; entries 1 and 2). Moreover, the use of **4-5f** also afforded better enantioselectivity compared to that of **4-5i** which was the optimized allyl substrate shown in **Table 4-2** (76% ee, entry 7). Thus, substrate **4-5f** was carried for the next step of optimization.

Table 4-3. Further study of the allyl substrate structure on tandem asymmetric allylic alkylations with **4-3a**

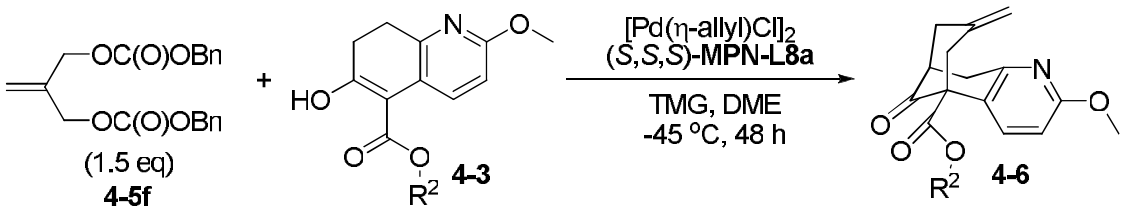


Entry[a]	Allyl substrate	Conv. %[b]	%ee[c]
1	**4-5d**	100	55 (-)
2	**4-5e**	100	54 (-)
3	**4-5f**	100	87 (-)

[a]All reactions were run using $[Pd(\eta\text{-allyl})Cl]_2$ (2.5 mol%) with a MPN ligand (15 mol%) and TMG (2.5 eq) in DME [0.025] at -45 °C for 48 h under N_2.
[b,c] See the footnote of **Table 4-1**.

With the further optimized allyl dicarbonate **4-5f** in hand, the effect of enol substrate structure was also studied to determine the best enol for this reaction (**Table 4-4**). Among the four substrates examined, **4-3a**, which has the smallest R group (Me), gave **4-6** with the highest %ee (87%ee, entry 1).

Table 4-4. Effect of enol substrate structure on tandem asymmetric allylic alkylations with **4-5f**

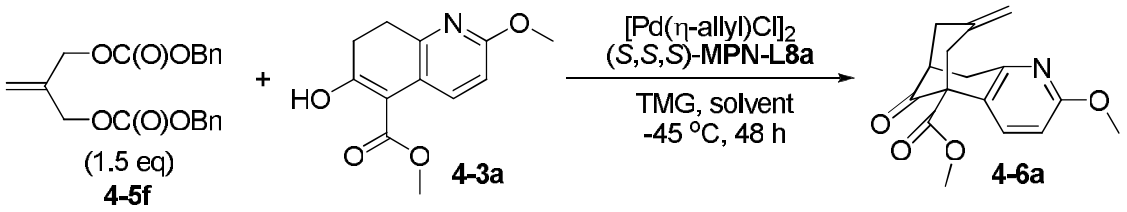


Entry[a]	Enol substrate	Conv. %[b]	%ee[c]
1	**4-3a**	100	87 (-)
2	**4-3b**	100	80 (-)
3	**4-3c**	100	82 (-)
4	**4-3d**	100	66 (-)

[a]All reactions were run using $[Pd(\eta\text{-allyl})Cl]_2$ (2.5 mol%) with a MPN ligand (15 mol%) and TMG (2.5 eq) in DME [0.025] at -45 °C for 48 h under N_2.
[b,c] See the footnote of **Table 4-1**.

As shown in **Table 4-5**, the solvent effect on the intermolecular asymmetric allylic alkylation of **4-3a** and **4-5f** was demonstrated. Among the solvents selected, DCM gave a slightly better result (89% ee, entry 2) compared to DME (87% ee, entry 1) and DMF, a polar solvent (88% ee, entry 3). When toluene, a nonpolar solvent, was used as solvent, a decrease in enantioselectivity (81% ee, entry 4) was observed compared to the results observed with polar solvents. Surprisingly, we expected the use of ether, which is similar to DME, to give at least comparable enantioselectivity, but gave the poorest result (71% ee, entry 5). Accordingly, DCM was employed as the optimized solvent for the further optimization process.

Table 4-5. Solvent effect on tandem asymmetric allylic alkylations of **4-3a** and **4-5f**



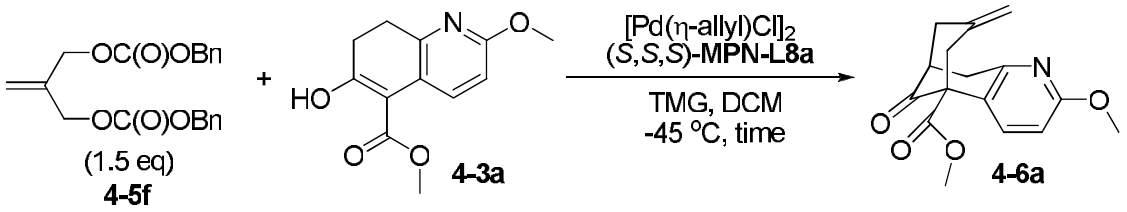
Entry[a]	Solvent	Conv. %[b]	%ee[c]
1	DME	100	87 (-)
2	DCM	100	89 (-)
3	DMF	100	88 (-)
4	Toluene	100	81 (-)
5	Ether	100	70 (-)

[a]All reactions were run using $[Pd(\eta\text{-allyl})Cl]_2$ (2.5 mol%) with a MPN ligand (15 mol%) and TMG (2.5 eq) in the solvent [0.025] at -45 °C for 48 h under N_2.
[b,c] See the footnote of Table 4-1.

At this point, the concentration effect on this reaction was investigated (**Table 4-6**). As shown in **Table 4-6**, More diluted concentration compared to the concentration in entry 2 gave both lower reactivity and enantioselectivity (72 h, 100% conv. and 67 %ee, entry 1). On the other hand, a higher concentration (0.05 M) afforded better reactivity (24 h, 100% conv., entry 3) but the enantioselectivity was lower compared to the % ee observed when the concentration was 0.025M (80% vs 89% ee, entries 1 and 2). Thus, a concentration of 0.025 M was used for the further optimization.

The effect of the reaction temperature on both enantioselectivity and reaction rate was also examined. In general, there is no obvious relationship between the reaction temperature and its corresponding %ee. The reaction at -45 °C still gave the best enantioselectivity among all temperatures we screened (89% ee, entry 3), although the reaction rate is the slowest compared to those observed at -25 and -35 °C (entries 1 and 2).

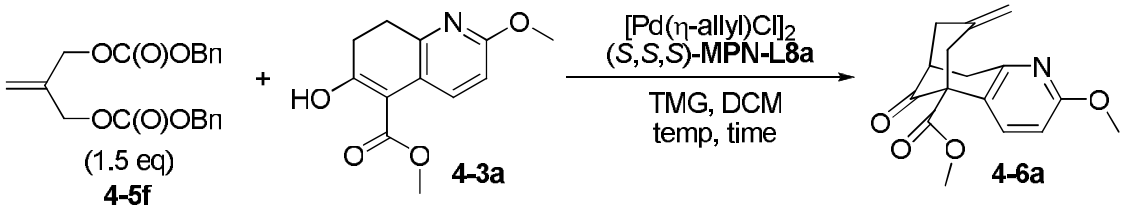
Table 4-6. Effect of concentration on tandem asymmetric allylic alkylations of **4-3a** and **4-5f**



Entry	Conc. (M)	Time (h)	conv. %	%ee
1	0.0125	72	100	67 (-)
2	0.025	48	100	89 (-)
3	0.05	24	100	80 (-)

[a]All reactions were run using $[Pd(\eta\text{-allyl})Cl]_2$ (2.5 mol%) with a MPN ligand (15 mol%) and TMG (2.5 eq) in the DCM at -45 °C under N_2.
[b,c] See the footnote of **Table 4-1**.

Table 4-7. Effect of temperature on tandem asymmetric allylic alkylations of **4-3a** and **4-5f**

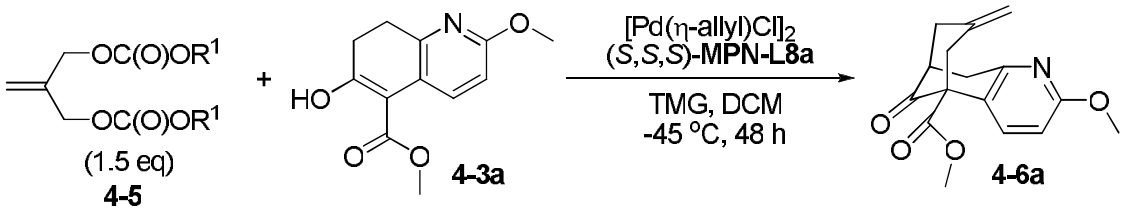


Entry	Temp (°C)	Time (h)	conv. %	%ee
1	-25	24	100	85 (-)
2	-35	24	100	81 (-)
3	-45	48	100	89 (-)
4	-55	48	100	86 (-)
5	-78	96	100	68 (-)

[a]All reactions were run using $[Pd(\eta\text{-allyl})Cl]_2$ (2.5 mol%) with a MPN ligand (15 mol%) and TMG (2.5 eq) in the DCM [0.025] under N_2.
[b,c] See the footnote of **Table 4-1**.

Since the benzyl substituted allyl dicarbonate **4-5f** gave the best enantioselectivity for this reaction thus far, additional benzyl-type substituted allyl dicarbonates were screened to determine if benzyl-type substrates can improve the %ee. As shown in **Table 4-8**, the allyl dicarbonate bearing (9H-fluoren-9-yl)methyl on the oxygen (**4-5g)** afforded a very similar result (89.0% ee, entries 2) compared to that obtained from the allyl substrate **4-5f** with the benzyl substituent (89.2% ee, entry 1). The introduction of the electron-withdrawing group, i.e. 4-nitrobenzyl, at the allyl dicarbobnate moiety (**4-5h**) gave slightly lower enantioselectivity than the allyl substrate without any electronic effect on the benzyl group (**4-5f**) (89.2% vs 87.4%, entries 2 and 3). If there is a correlation between the electronic effect and enantioselectivity, the improvement of %ee can be expected where an electron-donating group is attached to the benzyl moiety of the allyl substrate.

Table 4-8. Effects of the allylic substrates 4-5 on tandem asymmetric allylic alkylations with **4-3a**



Entry[a]	Allyl substrate	Conv. %[b]	%ee[c]
1	**4-5f**	100	89.2 (-)
2	**4-5g**	100	89.0 (-)
3	**4-5h**	100	87.4 (-)

[a]All reactions were run using $[Pd(\eta\text{-allyl})Cl]_2$ (2.5 mol%) with a MPN ligand (15 mol%) and TMG (2.5 eq) in DCM [0.025] at -45 °C for 48 h under N_2.
[b,c] See the footnote of Table 4-1.

§ 4.3 Conclusions

The key intermediate **4-6a** in the synthesis of (-)-Huperzine A has been prepared with 89.2% ee by means of Pd-catalyzed tandem intermolecular asymmetric allylic alkylations using our **MPN** ligand library and optimized substrates **4-3a** and **4-5f** in the presence of TMG as the base and DCM as the solvent at -45 °C for 48 h. Although the enantioselectivity is still lower

than that achieved by Bai's bidentate ferrocenyl-based ligand (90.3% ee)[8], this is the first time monodentate chiral ligand has been used for this asymmetric allylic alkylation to date. Further optimization on enantioselectivity is underway in our labrotatory.

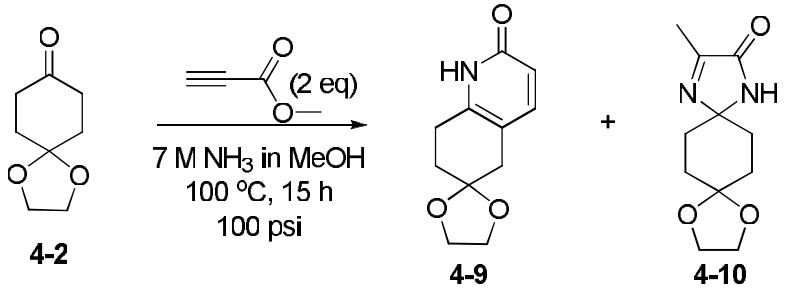
§ 4.4 Experimental section

General Methods: ^{1}H and ^{13}C and ^{31}P NMR were measured on a Varian Inova-500 NMR (500 MHz ^{1}H, and 125 MHz ^{13}C), a Varian Inova-400 NMR (400 MHz ^{1}H; 100 MHz ^{13}C; 162 MHz ^{31}P) or a Varian Gemini-2300 (300 MHz ^{1}H; 75 MHz ^{13}C; 121.5 MHz ^{31}P) spectrometer in a deuterated solvent using residual protons ($CHCl_3$: ^{1}H, 7.26 ppm; ^{13}C, 77.0 ppm. C_6H_6: ^{1}H, 7.15 ppm) as the internal standard or phosphoric acid as the external reference (^{31}P 0.00 ppm). Analytical HPLC in normal phase was carried out with a Shimadzu LC-2010A HPLC system using a Chiralpak OD-H analytical column. Melting points were measured on a Thomas Hoover Capillary melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Helmer Model 241 polarimeter. TLC analyses were performed using Merck DC Alufolien 60F254 aluminum pre-coated silica gel plates. Flash column chromatography was carried out using Silicyle Silia*Flash*P60® silica gel (particle size 40–63 μm). High-resolution mass spectrometric analyses were carried out at Mass Spectrometry Laboratories, University of Illinois Urbana-Champaign, Urbana, IL and ICB&DD at Stony Brook University. Unless otherwise noted all reactions were carried out under argon or nitrogen atmosphere in oven-dried glassware using standard Schlenck techniques.

Materials: Solvents were reagents grade and freshly distilled before use. Tetrahydrofuran (THF) and dichloromethane (DCM) were dried and degassed using an Innovative Technology PureSolvTM solvent purification system. Acetonitrile was distilled from calcium hydride. Anhydrous *N,N*-dimethylformamide (DMF) was purchased from Acros and used without further purification. Other solvents were used without purification. Other chemicals and reagents were purchased from Sigma-Aldrich or Fisher Scientific and used without further purification unless otherwise noted. Chiral biphenols were prepared according to the procedure previously reported by our laboratory.[10]

Synthesis of substrates 4-3a to **4-3d**[5, 11]

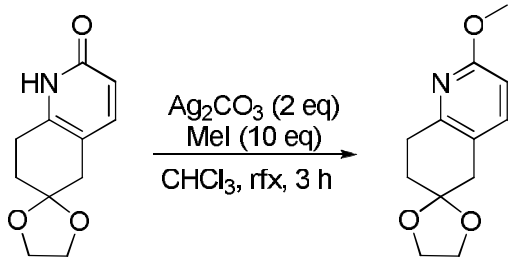
2',5',7',8'-Tetrahydro-1'H-spiro[1,3-dioxolane-2,6'-quinoline]-2'-one (4-9)[11]



4-2 4-9 4-10

1,4-Cyclohexanedione monoethylene ketal (**4-2**) (3.00 g, 19.20 mmol), methyl propiolate (3.229 g, 38.41 mmol) were placed into a 300 mL beaker. A 7 N solution of ammonia in methanol (60 mL) was added to the reaction beaker and the flask was then placed into a stainless steel Parr reaction vessel and heated to 100 °C for 15 h. The pressure can approximately reach 90-100 psi. The vessel was evacuated and the solvent was concentrated *in vacuo*. The resulting red-orange solid was adhered to silica gel and subjected to flash chromatography on silica gel (MeOH/DCM = 5:95), affording **4-9** as a light yellow solid (2.04 g, 51% yield): mp >220 °C dec, (lit.[11] mp dec >220 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.90 (t, J = 4.8 Hz, 2H,), 2.70 (s, 2H), 2.86 (s, 2H), 4.01 (s, 4H), 6.38 (d, J = 6.9 Hz, 1H), 7.12 (d, J = 6.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.1, 30.2, 36.4, 64.9, 107.5, 112.0, 117.9, 141.8, 143.6. All data are in agreement with the literature values.[11]

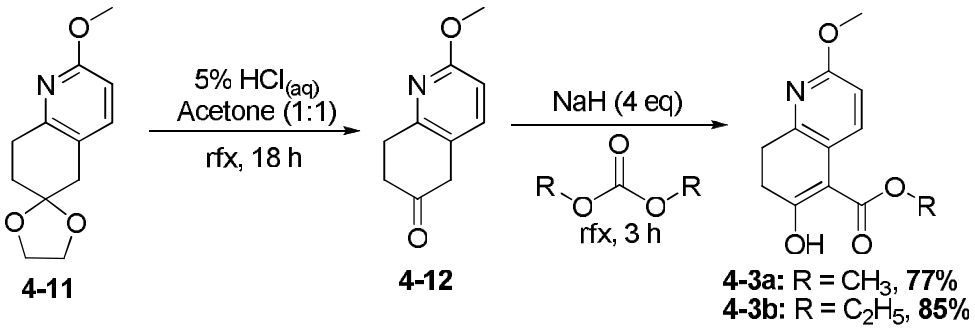
7', 8'-Dihydro-2'-methoxyspiro[1,3-dioxolane-2,6'-(5'H)]quinoline (4-11)[5]



4-9 4-11

To a solution of **4-9** (1.75 g, 8.44 mmol) and Ag_2CO_3 (4.66 g, 16.9 mmol, 2 eq) in $CHCl_3$ (50 mL) was added dropwise iodomethane (5.25 mL, 84.4 mmol, 10 eq). The reaction mixture was refluxed for 3 h. The resulting mixture was filtered through Celite and concentrated *in vacuo* to afford crude product as a yellow solid. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc = 10:1-4:1) afforded **4-11** as a white needle

crystals (1.56 g, 84% yield): mp 73-75 °C (lit.[5] mp 77.5-78.5 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.97 (t, *J* = 6.9 Hz, 2H,), 2.88 (s, 2H), 2.97 (t, *J* = 6.9 Hz, 2H,), 3.87 (s, 3H), 4.02 (s, 2H), 6.49 (d, *J* = 8.1 Hz, 1H), 7.20 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.0, 31.7, 53.5, 64.8, 108.1, 108.3, 121.7, 140.0, 152.9,162.5. All data are in agreement with the literature values.[5]



6-Oxo-2-methoxy-5,6,7,8-tetrahydroquinoline-5-methylcarbonyl (4-3a)[5]

Compound **4-11** (966 mg, 4.37 mmol) was dissolved in a 5% HCl solution in acetone (1:1) and refluxed overnight. All volatiles were evaporated *in vacuo*. The aqueous layer was then basified with sat. $NaHCO_{3(aq)}$ until no more gas evolution was noted. The resulting solution was then extracted with EtOAc (20 mL x3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the solvent evaporated *in vacuo* to afford the product as light yellow oil. The resulting product **4-12** was used without further purification.

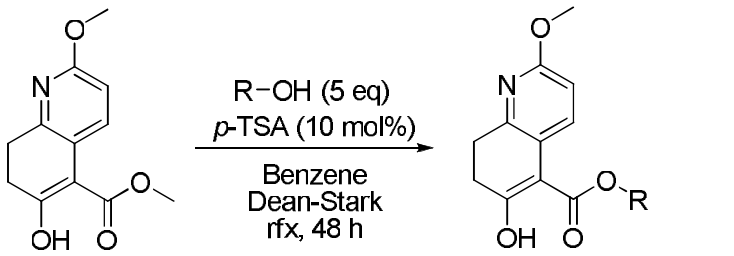
To a solution of **4-12** in dimethyl carbonate (25 mL) was added a solution of sodium hydride (60% w/v in mineral oil, 1.75 g, 43.7 mmol, 4 eq) in 10 mL of dimethyl carbonate. The reaction mixture was refluxed for 3 h and the reaction was quenched with MeOH (10 mL). All volatiles were removed *in vacuo* and the resulting solution was neutrualized with sat. $NH_4Cl_{(aq)}$ (10 mL). The resulting solution was then extracted with EtOAc (20 mL x3). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the solvent evaporated *in vacuo* to afford the product as a light yellow solid. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc = 30:1-20:1) afforded **4-3a** as a light yellow solid (788 mg, 77% yield for two steps): mp 73-74 °C (lit.[5] mp 71-72 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.06 (t, *J* = 6. 9 Hz, 2H), 2.91 (t, *J* = 8.1 Hz, 2H), 3.90 (s, 6H), 6.55 (d, *J* = 8.7 Hz, 1H) 7.89 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.3, 30.2, 52.0, 53.6, 98.5, 107.5, 120.0, 136.3, 151.3, 161.3, 172.2, 177.0.

All data are in agreement with the literature values.[5]

Ethyl 6-hydroxy-2-methoxy-7,8-dihydroquinoline-5-carboxylate (4-3b)

Compounds **4-3b** was obtained in the same manner as that described for the synthesis of **4-3a** with some variations.

Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc = 19:1-9:1) afforded pure **4-3b** as colorless oil (250 mg, 85% yield for two steps): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (t, *J* = 7.2 Hz, 3H), 2.62 (t, *J* = 7.6 Hz, 2H), 2.93 (t, *J* = 7.6 Hz, 2H), 3.90 (s, 3H), 4.37 (q, *J* = 7.2 Hz, 2H), 6.56 (d, *J* = 8.8 Hz, 1H), 7.93 (d, *J* = 8.8 Hz, 1H), 13.3 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 29.1, 30.0, 53.3, 61.0, 98.3, 107.2, 120.0, 136.1, 151.1, 161.0, 171.6, 176.7; HRMS (ESI+) calcd. For $C_{13}H_{16}NO_4$ $[M+H]^+$ 250.1079, found 250.1073 (Δ = -2.4 ppm).



Butyl 6-hydroxy-2-methoxy-7,8-dihydroquinoline-5-carboxylate (4-3c)

Methyl 6-hydroxy-2-methoxy-7,8-dihydroquinoline-5-carboxylate (**4-3a**) (122 mg, 0.519 mmol), *p*-TSA (10 mg, 0.052 mmol) and butanol (0.237 mL, 2.60 mmol) were dissolved in benzene (13 mL) and the solution was heated to reflux in a Dean-Stark apparatus. After the disappearance of **4-3a** indicated by TLC (ca. 48 h), the reaction mixture was concentrated *in vacuo* to afford the crude product as yellow oil. Further purification by flash column chromatography on silica gel (hexanes/EtOAc = 19:1-9:1) afforded pure **4-3c** as colorless oil (108 mg, 75% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, *J* = 7.2 Hz, 3H), 1.44 (q, *J* = 7.2 Hz, 2H), 1.73 (q, *J* = 7.2 Hz, 2H), 2.62 (t, *J* = 7.6 Hz, 2H), 2.93 (t, *J* = 7.6 Hz, 2H), 3.91 (s, 3H), 4.32 (q, *J* = 7.2 Hz, 2H), 6.56 (d, *J* = 8.8 Hz, 1H), 7.91 (d, *J* = 8.8 Hz, 1H), 13.3 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 19.3, 29.1, 30.0, 30.6, 53.3, 64.9, 98.3, 107.2, 120.0, 136.1, 151.1, 161.0, 171.7, 176.7; HRMS (ESI+) calcd. For $C_{15}H_{20}NO_4$ $[M+H]^+$ 278.1392, found 278.1386 (Δ

= -2.2 ppm).

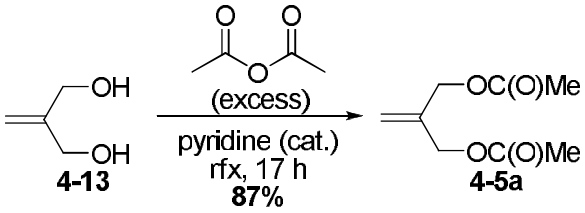
Cyclohexyl 6-hydroxy-2-methoxy-7,8-dihydroquinoline-5-carboxylate (4-3d)

Compounds **4-3d** was obtained in the same manner as that described for the synthesis of **4-3c** with some variations.

Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc = 19:1-9:1) afforded pure **4-3d** as light-yellow oil (247 mg, 82% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42-1.60 (m, 4H), 1.61-1.63 (m, 2H), 1.73-1.77 (m, 2H), 1.93-1.98 (m, 2H), 2.61 (t, *J* = 7.6 Hz, 2H), 2.93 (t, *J* = 7.6 Hz, 2H), 3.90 (s, 3H), 5.01-5.08 (m, 1H), 6.55 (d, *J* = 8.8 Hz, 1H), 7.96 (d, *J* = 8.8 Hz, 1H), 13.4 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 25.3, 29.1, 30.0, 31.6, 53.3, 73.7, 98.4, 107.1, 120.2, 136.1, 151.1, 161.0, 171.7, 176.6; HRMS (ESI+) calcd. For $C_{17}H_{22}NO_5$ $[M+H]^+$ 304.1549, found 304.1545 (Δ = -1.3 ppm).

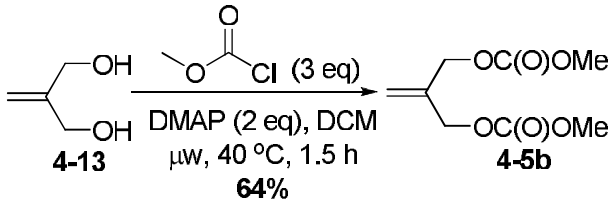
Synthesis of substrates 4-5a to **4-5i**[6, 12]

2-Methylenepropane-1,3-diyl diacetate (4-5a)[6]

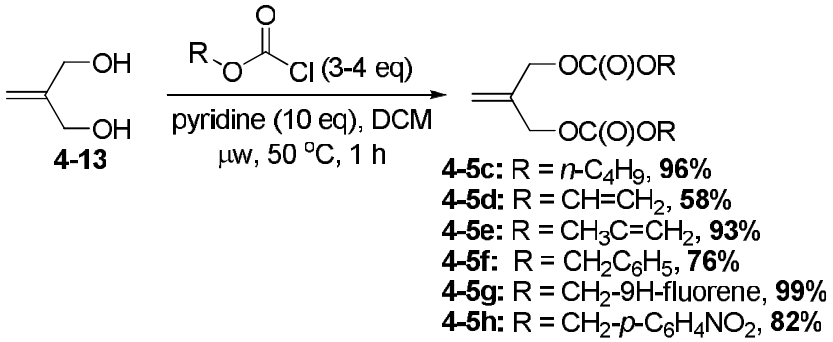


1,3-(2-Methylene)propandiol (**4-13**) (407 mg, 4.62 mmol,) and 0.033 mL of pyridine were placed in a 10 mL round-bottomed flask. To this solution 3 mL of acetic anhydride was added. The reaction mixture was then refluxed overnight. The excess acetic anhydride was concentrated in *vacuo* and ice water was added to the resulting solution. The aqueous layer was then basified with sat. $NaHCO_{3(aq)}$ until no more gas evolution was noted. The aqueous layer was separated and extracted with Et_2O (10 mL x3). The combined organic layer was washed with water (20 mL) and brine (20 mL), and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the solvent evaporated *in vacuo* to afford the product **4-5a** as colorless oil. (694 mg, 87% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.16 (s, 6H) 4.67 (s, 4H) 5.35 (s, 2H); 13C NMR ($CDCl_3$, 100 MHz) δ 21.1, 64.7, 116.9, 138.8, 170.1. All data are in agreement with the literature values.[6]

Dimethyl 2-methylenepropane-1,3-diyl dicarbonate (4-5b)[12a]



1,3-(2-Methylene)propandiol (**4-13**) (250 mg, 2.84 mmol) and DMAP (1.275 g, 5.68 mmol, 2 eq) were introduced to a 35 mL microwave reaction vessel, followed by DCM (15 mL) under nitrogen at room temperature. The mixture was then cooled to 0 °C and the methyl chloroformate (1.16 g, 8.52 mmol, 3 eq) was added dropwise with stirring. The reaction mixture was warmed to room temperate and placed in a microwave reactor for 90 min at 40 °C. The reaction was quenched by adding sat. $NaCl_{(aq)}$ (10 mL). The aqueous layer was separated and extracted with DCM (20 mL x3). The combined organic layer was washed with water (40 mL) and brine (40 mL), and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the solvent evaporated *in vacuo* to afford the crude product as yellow oil. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc = 10:1→4:1) afforded **4-5b** as colorless oil (367 mg, 64% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.80 (s, 6H), 4.67 (s, 4H) 5.35 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 54.7, 67.4, 117.8, 137.6, 155.2. All data are in agreement with the literature values.[12a]



Di-*n*-butyl 2-methylenepropane-1,3-diyl di-*n*-butyl dicarbonate (4-5c)[12b]

1,3-(2-Methylene)propandiol (**4-13**) (274 mg, 3.11 mmol) and pyridine (2.51 mL, 31.1 mmol, 10 eq) were introduced to a 35 mL microwave reaction vessel, followed by DCM (15 mL) under nitrogen at room temperature. The mixture was then cooled to 0 °C and the butyl chloroformate (1.60 mL, 12.4 mmol, 4 eq) was added dropwise with stirring. The reaction mixture was warmed to room temperate and placed in a microwave reactor for 60 min at 50 °C.

The reaction was quenched by adding sat. $CuSO_{4(aq)}$ (15 mL). The aqueous layer was separated and extracted with DCM (20 mL x3). The combined organic layer was washed with water (40 mL) and brine (40 mL), and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the solvent evaporated *in vacuo* to afford the crude product as yellow oil. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc = 10:1→4:1) afforded **4-5c** as colorless oil (858 mg, 96% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, *J* = 7.5 Hz, 6H) 1.33 (q, *J* = 7.8 Hz, 4H), 1.59 (q, *J* = 8.1 Hz, 4H), 4.09 (t, *J* = 6.9 Hz, 4H), 4.63 (s, 4H), 5.31 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.4, 18.7, 67.3, 67.9, 154.8. All data are in agreement with the literature values.[12b]

Compounds **4-5d** to **4-5h** were obtained in the same manner as that described for the synthesis of **4-5c** with some variations.

2-Methylenepropane-1,3-diyl divinyl dicarbonate (4-5d)[12b]

Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc = 10:1→4:1) afforded **4-5d** as colorless oil (58% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.58 (dd, *J* = 5.4, 1.2 Hz, 2H), 4.74 (s, 4H), 4.90 (dd, *J* = 3.0, 0.9 Hz, 2H), 5.41 (s, 2H), 7.03 (dd, *J* = 21, 6.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 68.0, 98.1, 119.4, 136.7, 142.5, 152.4. All data are in agreement with the literature values.[12b]

2-Methylenepropane-1,3-diyl diprop-1-en-2-yl dicarbonate (4-5e)

Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc = 10:1→4:1) afforded **4-5e** as light yellow oil (93% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.92 (s, 6H), 4.66 (s, 2H), 4.67 (s, 4H), 5.36 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.9, 67.7, 101.8, 118.6, 137.0, 152.4, 152.8; HRMS (ESI+) calcd. For $C_{12}H_{20}NO_6$ $[M+NH_4]^+$ 274.1291, found 274.1285 (Δ = -2.2 ppm).

2-Methylenepropane-1,3-diyl dibenzyl dicarbonate (4-5f)[12b]

Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc = 10:1→4:1) afforded **4-5f** as colorless oil (76% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.76 (s, 4H), 5.23 (s, 2H), 5.42 (s 2H), 7.41 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 60.3, 67.7, 69.7, 118.2, 128.3, 128.5, 128.5, 137.4, 154.7. All data are in agreement with the

literature values.[12b]

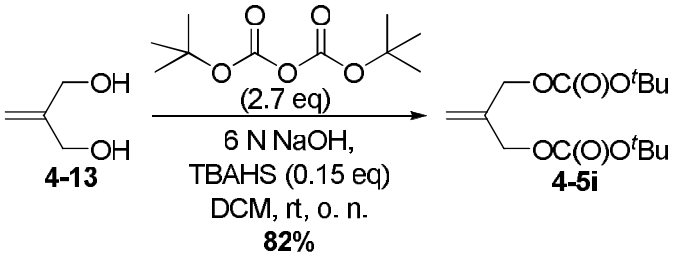
Bis((9H-fluoren-9-yl)methyl) 2-methylenepropane-1,3-diyl dicarbonate (4-5g)

Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc = 10:1→4:1) afforded **4-5g** as light yellow oil (99% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.30 (t, *J* = 7.2 Hz, 2H), 4.47 (d, *J* = 7.2 Hz, 4H), 4.79 (s, 4H), 5.44 (s, 2H), 7.36 (t, *J* = 7.6 Hz, 4H), 7.44 (t, *J* = 7.6 Hz, 4H), 7.66 (d, *J* = 7.6 Hz, 4H), 7.80 (d, *J* = 7.6 Hz, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 46.6, 67.7, 69.9, 118.3, 120.0, 125.1, 127.1, 127.8, 137.5, 141.2, 143.2, 154.8; HRMS (ESI+) calcd. For $C_{34}H_{32}NO_6$ $[M+NH_4]^+$ 550.2230, found 550.2224 (Δ = -1.1 ppm).

2-Methylenepropane-1,3-diyl 4-nitrobenzyl dicarbonate (4-5h)

Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc = 10:1→4:1) afforded **4-5h** as light yellow oil (82% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.70 (s, 4H), 5.23 (s, 4H), 5.37 (s, 2H), 7.51 (d, *J* = 8.8 Hz, 4H), 8.18 (d, *J* = 8.8 Hz, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 67.9, 68.0, 118.9, 123.7, 128.2, 136.9, 142.2, 147.7, 154.4; HRMS (ESI+) calcd. For $C_{20}H_{22}N_3O_{10}$ $[M+NH_4]^+$ 464.1300, found 464.1300 (Δ = 0.0 ppm).

***tert*-Butyl 2-methylenepropane-1,3-diyl dicarbonate (4-5i)**



To a solution of 1,3-(2-methylene)propandiol (**4-13**) (535 mg, 6.07 mmol), (*t*-Boc)$_2$O (3.58 g, 16.4 mmol, 2.7 eq) and tetrabutylammonium hydrogen sulfate (350 mg, 1.03 mmol, 0.17 eq) in DCM (15 mL) was added dropwise 6 N $NaOH_{(aq)}$ (7 mL) at 0 °C and the mixture was stirred overnight at room temperature. The reaction was quenched by adding water. The aqueous layer was separated and extracted with DCM (20 mL x3). The combined organic layer was washed with water (40 mL) and brine (40 mL), and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the solvent evaporated *in vacuo* to afford the crude product as yellow

oil. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc = 10:1→4:1) afforded **4-5i** as colorless oil (1.43 g, 82% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.37 (s, 18H), 4.45 (s, 4H), 5.16 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.4, 66.5, 81.7, 116.7, 138.2, 152.8; HRMS (ESI+) calcd. For $C_{14}H_{24}NaO_6$ $[M+Na]^+$ 311.1471, found 311.1464 (Δ = -2.2 ppm).

A typical procedure for tandem asymmetric allylic alkylations

A chiral ligand (15 mol%), and a catalyst $[Pd(\eta^3\text{-}C_3H_3)Cl]_2$ (1.2 mg, 2.5 mol %) and 2-methylene-1,3-propane diacetate (**4-5a**) (34 mg, 0.20 mmol, 1.5 eq) and **4-3a** (31 mg, 0.13 mmol) were dissolved in 8 mL of dry solvent in a 35 mL Schlenck tube. The mixture was then stirred at room temperature for 30 min and cooled to -45 ^{o}C for 30 min. Then tetramethylguanidine (TMG) (37.4 mg, 0.33 mmol) was slowly added to this solution and the reaction mixture was stirred at -45 ^{o}C for 48 h. The solvent was evaporated and the resulting yellow oil was submitted to normal phase chiral HPLC column (Chiracel OD-H) with an eluent of 3% ispropanol in hexanes (t_R = 19.0 and 24.2 mins) to determine the enantiopurity. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc = 20:1→10:1) afforded **4-6a** as a light yellow oil (26 mg, 70% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.53 (2H, m), 2.75 (1H, m), 2.92 (m, 1H), 3.06 (2H, m), 3.40 (1H, dd, *J* = 18.4, J= 6.8), 3.78 (3H, s), 3.86 (3H, s), 4.47 (1H, s), 4.80 (1H, s), 6.54 (1H, d, *J* = 8.4 Hz), 6.94 (1H, d, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 40.4, 43.9, 45.6, 47.8, 52.6, 53.4, 62.0, 109.5, 116.3, 124.7, 137.5, 138.9, 151.3, 162.9, 171.3, 208.3. All data are in agreement with the literature values.[6]

§ 4.5 References

1. Kozikowski, A. P.; Tückmantel, W., Chemistry, Pharmacology, and Clinical Efficacy of the Chinese Nootropic Agent Huperzine A. *Acc. Chem. Res.* **1999,** *32* (8), 641-650.
2. (a) Bai, D., Development of huperzine A and B for treatment of Alzheimer's disease. *Pure Appl. Chem.* **2007,** *79* (4), 469-479; (b) Xiao, X. Q.; Yang, J. W.; Tang, X. C., Huperzine A protects rat pheochromocytoma cells against hydrogen peroxide-induced injury. *Neurosci. Lett.* **1999,** *275* (2), 73-76; (c) Xiao, X. Q.; Zhang, H. Y.; Tang, X. C., Huperzine A attenuates amyloid β-peptide fragment 25-35-induced apoptosis in rat cortical neurons via inhibiting reactive oxygen species formation and caspase-3 activation. *J. Neurosci. Res.* **2002,** *67* (1), 30-36.
3. Wang, B.-s.; Wang, H.; Wei, Z.-h.; Song, Y.-y.; Zhang, L.; Chen, H.-z., Efficacy and safety of natural acetylcholinesterase inhibitor huperzine A in the treatment of Alzheimer's disease:

an updated meta-analysis. *Journal of Neural Transmission* **2009,** *116* (4), 457-465.

4. Lim, W.-H.; Goodger, J. Q. D.; Field, A. R.; Holtum, J. A. M.; Woodrow, I. E., Huperzine alkaloids from Australasian and southeast Asian Huperzia. *Pharm. Biol.* **2010,** *48* (9), 1073-1078.
5. Xia, Y.; Kozikowski, A. P., A practical synthesis of the Chinese "nootropic" agent huperzine A: a possible lead in the treatment of Alzheimer's disease. *J. Am. Chem. Soc.* **1989,** *111* (11), 4116-4117.
6. Campiani, G.; Sun, L. Q.; Kozikowski, A. P.; Aagaard, P.; McKinney, M., A palladium-catalyzed route to huperzine A and its analogs and their anticholinesterase activity. *J. Org. Chem.* **1993,** *58* (27), 7660-7669.
7. Kaneko, S.; Yoshino, T.; Katoh, T.; Terashima, S., A novel enantioselective synthesis of the key intermediate of (−)-huperzine a employing asymmetric palladium-catalyzed bicycloannulation. *Tetrahedron: Asymmetry* **1997,** *8* (6), 829-832.
8. He, X.-C.; Wang, B.; Yu, G.; Bai, D., Studies on the asymmetric synthesis of huperzine A. Part 2: Highly enantioselective palladium-catalyzed bicycloannulation of the β-keto-ester using new chiral ferrocenylphosphine ligands. *Tetrahedron: Asymmetry* **2001,** *12* (23), 3213-3216.
9. Chassaing, C.; Haudrechy, A.; Langlois, Y., Asymmetric palladium annulation: formal synthesis of (+)-huperzine A. *Tetrahedron Lett.* **1999,** *40* (50), 8805-8809.
10. Chapsal, B. D.; Ojima, I., Total Synthesis of Enantiopure (+)-γ-Lycorane Using Highly Efficient Pd-Catalyzed Asymmetric Allylic Alkylation. *Org. Lett.* **2006,** *8* (7), 1395-1398.
11. Kozikowski, A. P.; Reddy, E. R.; Miller, C. P., A simplified route to a key intermediate in the synthesis of the Chinese nootropic agent huperzine A. *J. Chem. Soc., Perkin Trans. 1* **1990,** (1), 195-197.
12. (a) Salamone, S. G.; Dudley, G. B., A Ring-Expansion Approach to Roseophilin. *Org. Lett.* **2005,** *7* (20), 4443-4445; (b) Chaterpaul, S. J. Application of Transition Metal-Catalyzed Reactions in the Synthesis of NHeterocyclic Natural Products. Doctor of Philosophy in Chemistry, Stony Brook University, Stony Brook, NY, August 2010.

Chapter 5

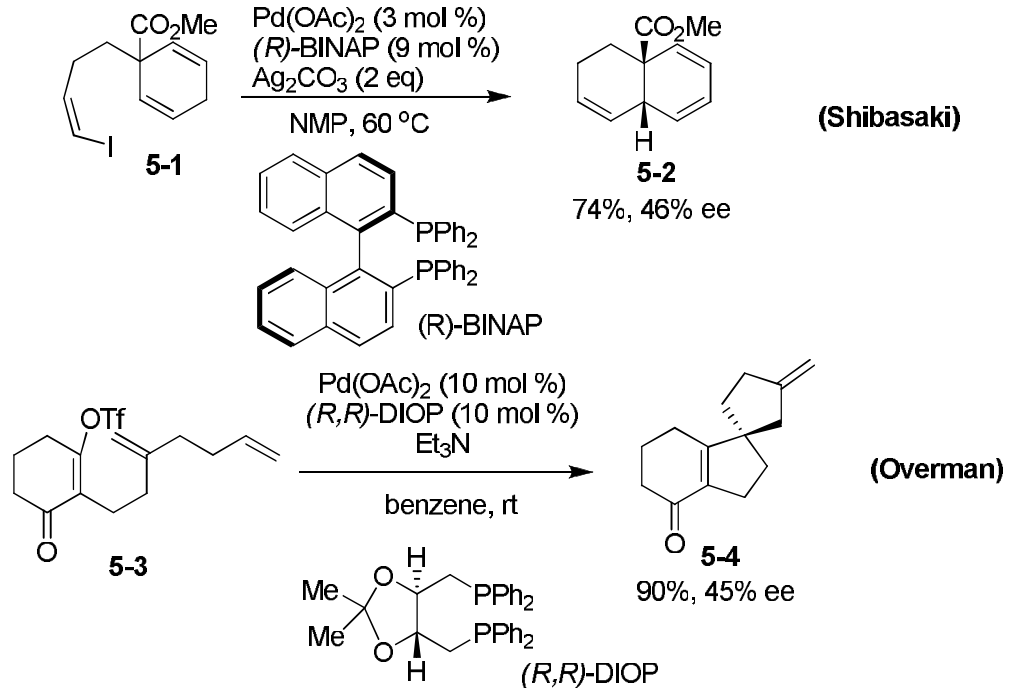
Palladium-Catalyzed Asymmetric Heck Reactions with Monophosphoramidite and Bidentate Phosphite-Oxazoline Ligands

Table of Contents

§ 5.1 Introduction to the asymmetric Heck reaction

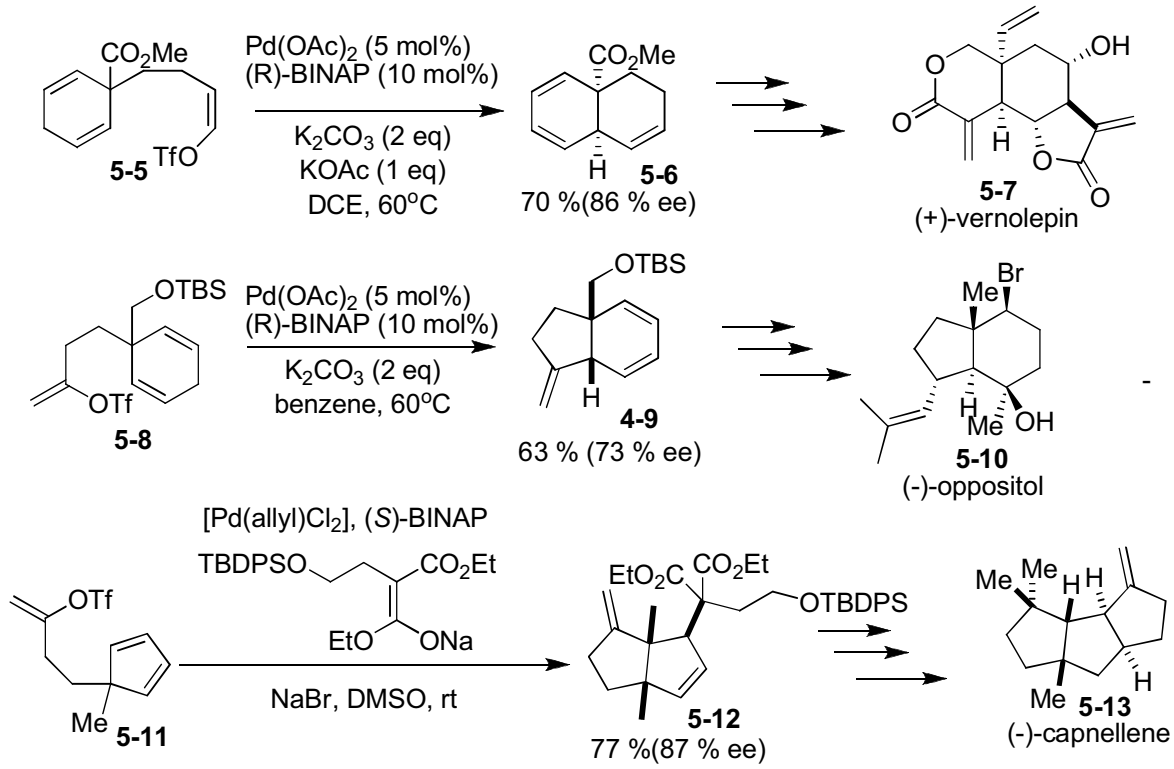
§ 5.1.1 The Heck reaction and its application to catalytic asymmetric synthesis

The Heck reaction (more accurately "Mizoroki–Heck reaction") is defined as a Pd(0)-catalyzed coupling reaction of aryl or alkenyl halides with alkenes in the presence of an appropriated base. This reaction was first discovered and developed by Mizoroki et al.[1] and Heck and Nolley[2] in the early 1970s. Since then, this coupling reaction has become one of the most widely used reactions in organic synthesis, and its popularity is mainly attributed to the fact that this reaction can construct tertiary and quaternary carbon centers through carbon–carbon bond formation. This feature has found numerous applications in the synthesis of complex natural products.[3] With the explosive development of chiral ligands for asymmetric catalysis over the past decades, the development of the asymmetric Heck reaction has attracted much attention.[4] The first successful examples of the intramolecular enantioselective reaction were reported independently by Shibasaki et al.[5] and Overman et al.[6] in 1989. In Shibasaki's process, a chiral tertiary carbon center was introduced (46% ee) by the catalysis of $Pd(OAc)_2$-*(R)*-BINAP in the presence of Ag_2CO_3 in *N*-methyl-2-pyrrolidinone (NMP), while in Overman's process, a chiral quaternary carbon center was created (45% ee) by using $Pd(OAc)_2$-(*R*)-DIOP as the catalyst in the presence of Et_3N in benzene (**Scheme 5-1**).



Scheme 5-1. The first successful examples of the intramolecular enantioselective reaction

After these reports, a variety of intra- and intermolecular asymmetric Heck reactions emerged quickly with improved enantioselectivities. For example, enantioselective intramolecular Heck reaction of *meso*-cycloalkadienes **5-5**, **5-8**, and **5-11**, bearing an enol triflate tether using Pd catalysts with (*R*)- or (*S*)-BINAP, gave key intermediates **5-6**, **5-9**, and **5-12** for the synthesis of various terpenoid natural products, including (+)-vernolepin **5-7**, (−)-oppositol **5-10**, and (−)-capnellene **5-13**, respectively (**Scheme 5-2**).[7] The reaction has also been applied to the total synthesis of natural polyketides such as halenaquinone, xestoquinone, and wortmannin.[3] Moreover, the reaction has been employed as the key step in the synthesis of various alkaloids, for example, physostigmine, quadrigemine C, spirotryprostatin B, and minfiensine.[3]

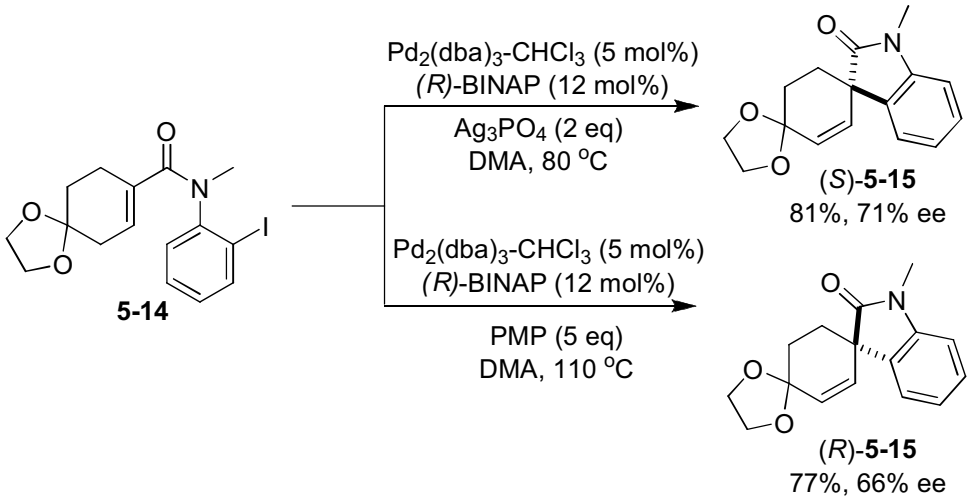


Scheme 5-2. The total synthesis of terpenoid natural products **5-7**, **5-10** and **5-13**

§ 5.1.2 Asymmetric intramolecular Heck reactions

The intramolecular asymmetric Heck reaction has found numerous applications in organic syntheses, as mentioned above. Among those applications, the synthesis of optically active oxindoles bearing a quaternary asymmetric center has been extensively studied, mainly because enantiopure oxindoles can serve as versatile intermediates or synthons in the total synthesis of a variety of natural products.[4, 8] The reaction of (*E*)-α,β-unsaturated-2-iodoanilide **5-14** was carried

out using $Pd_2(dba)_3$-(*R*)-BINAP as catalyst and Ag_3PO_4 or 1,2,2,6,6-pentamethylpiperidine (PMP) as HI scavenger in *N*,*N*dimethylacetamide (DMA), to give oxindoles (*S*)- or (*R*)-**5-15** in good yield and fairly good enantioselectivity under cationic or neutral conditions (**Scheme 5-3**). It should be noted that a dramatic switching in the direction of asymmetric induction was observed between these two conditions even though the same chiral ligand, (*R*)-BINAP, was used in both reactions. This was the first example that achieved fairly good enantioselectivity under neutral conditions.

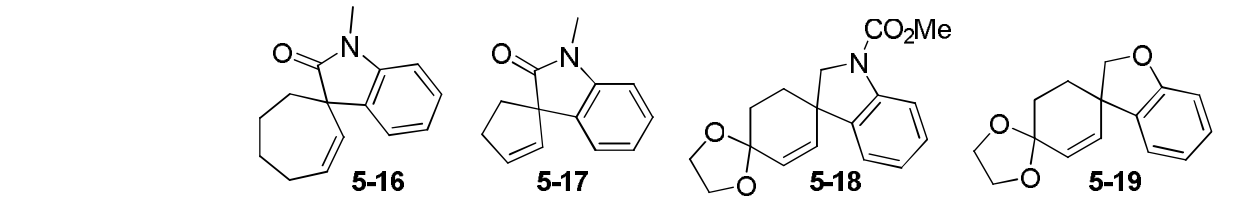


Scheme 5-3. Synthesis of enantioenriched oxidoles **5-15**

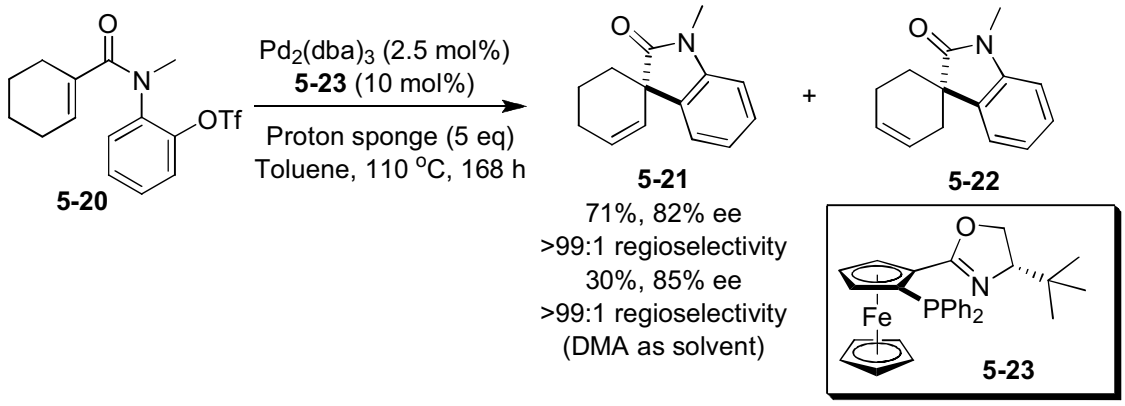
In the same manner, the reactions of a series of *N*-cycloalkenoyl-2-iodoanilides, *N*cycloalkenylmethyl-2-iodoaniline, and cycloalkenylmethyl 2-iodophenyl ether were investigated, and results are shown in **Scheme 5-4**.[8b] It is worthy of note that the cationic conditions with Ag_3PO_4 are detrimental to the enantioselectivity in the reactions of *N*-cycloalkenoyl-2-iodoanilides, while neutral conditions with PMP do not give appreciable asymmetric induction in the reaction of *N*-cycloalkenylmethyl-2-iodoaniline and cycloalkenylmethyl 2-iodophenyl ether. Thus, this reaction appears to be highly sensitive to the matching or mismatching of the functional groups in substrate and reaction conditions.

To optimize both enantioselectivity and regioselectivity of the reaction, new chiral ligands and modified substrates have been developed in the past 10 years. For example, Guiry and Kiely prepared aryl triflate **5-20** to investigate the regio- and enantioselectivity in the formation of oxindole **5-21** catalyzed by Pd(0) complex with oxazoline-based aminophosphine ligand **5-23** under cationic conditions (**Scheme 5-5**).[8c] Excellent regioselectivity (99:1) and high

enantioselectivity (up to 85% ee) were obtained using $Pd_2(dba)_3$, **5-23**, and proton sponge as TfOH scavenger in toluene or DMA.

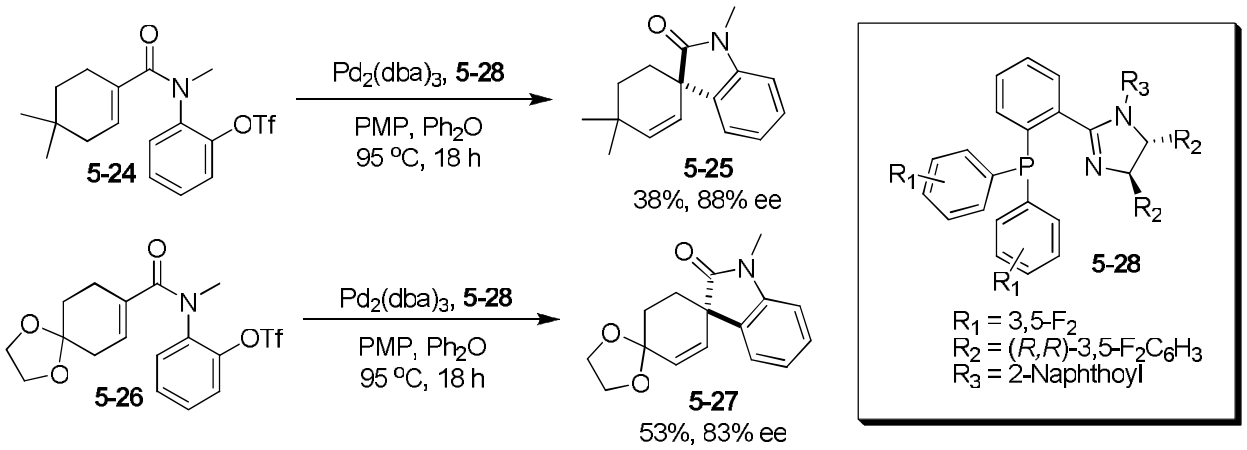


Scheme 5-4. Synthesis of enantioenriched oxidoles **5-16** to **5-19**

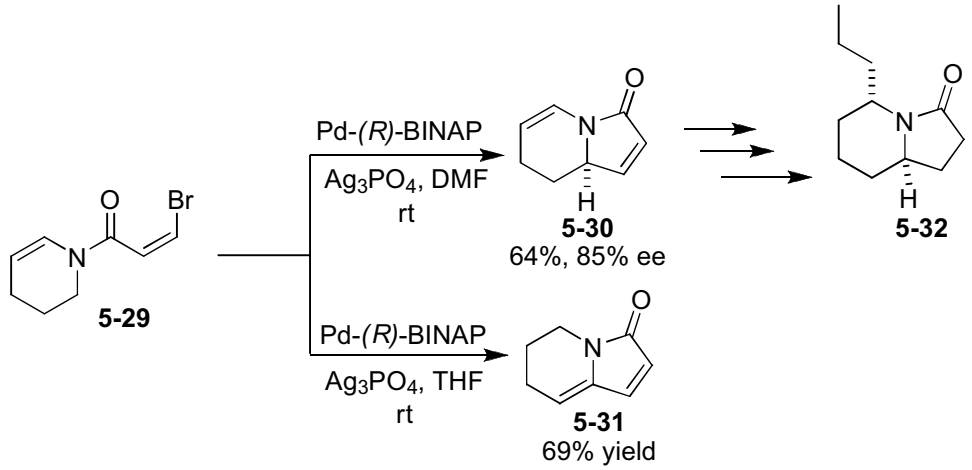


Scheme 5-5. Synthesis of enantioenriched oxidoles **5-21**

A library of phosphinoimidazoline (BIPI) ligands **5-28** was developed by Busacca et al. for asymmetric intramolecular Heck reactions.[9] Through electronic tuning of three substituents in a ligand, high enantioselectivity was achieved. Two examples are shown in **Scheme 5-6**. In addition to chiral oxindoles, other chiral nitrogen heterocycles have also been synthesized via intramolecular asymmetric Heck cyclization. For example, the reaction of endocyclic enamide **5-29** afforded indoloizidine **5-30** or its achiral isomer **5-31**, depending on the solvent used (**Scheme 5-7**).[10] The reaction of **5-29** catalyzed by Pd-*(R)*-BINAP in the presence of Ag_3PO_4 in DMF at room temperature gave **5-30** in 64% yield and 85% ee. However, when THF was employed as the solvent, **5-31** was formed exclusively (**Scheme 5-7**). Indolizidine **5-32**, a key intermediate for the synthesis of 5*E*,9*Z*-indolizidine 223AB[11] and (+)-5-epiindolizine 167B,[12] was obtained from **5-30** in four steps.[10]

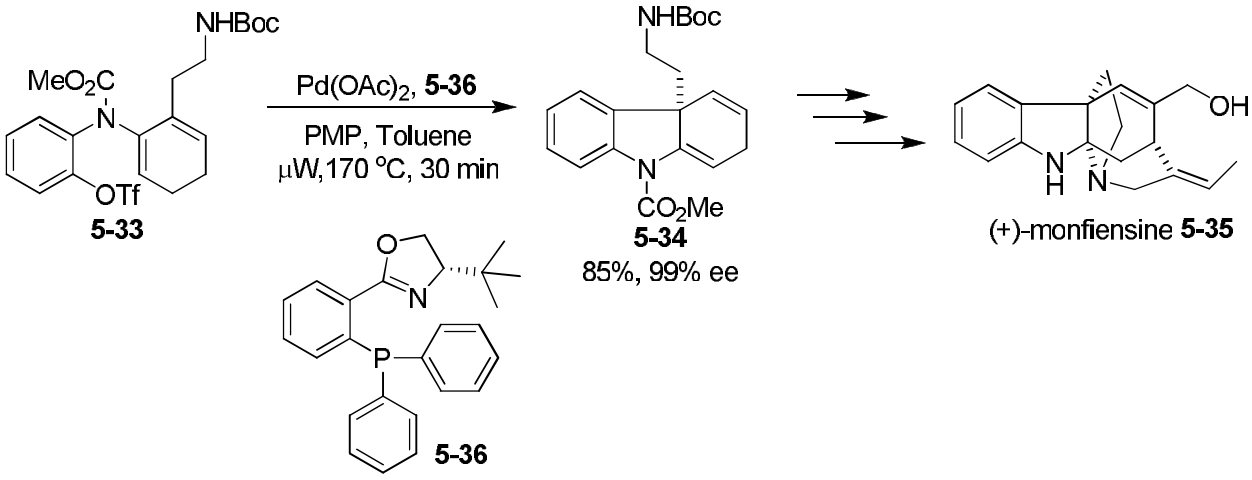


Scheme 5-6. Synthesis of enantioenriched oxidoles **5-25** and **5-27**

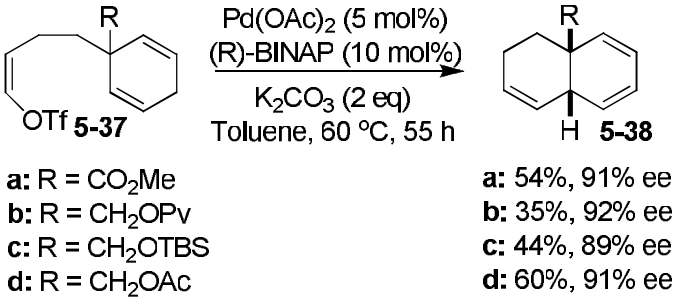


Scheme 5-7. Synthesis of Indolizidine **5-32**

A sequential catalytic asymmetric Heck–iminium ion cyclization was employed for the enantioselective total synthesis of minfiensine, a strychnos alkaloid.[13] In this synthesis, the reaction of **5-33** catalyzed by $Pd(OAc)_2$ with Pfaltz ligand **5-36** under microwave conditions gave tricyclic dienylcarbamate **5-34** in 85% yield and 99% ee (**Scheme 5-8**). The total synthesis of (+)-minfiensine **5-35** was completed with another 16 steps from key intermediate **5-34**. Desymmetrization of *meso*-1,4-cyclohexadienes with a vinyl iodide or triflate tether, forming the corresponding chiral bicyclic products can be achieved through intramolecular asymmetric Heck reaction. This methodology has proven to be powerful for the rapid and enantioselective construction of fused polycyclic compounds. The first example was reported by Shibasaki et al..[5] The reaction of **5-37** catalyzed by $Pd(OAc)_2$-(*R*)-BINAP gave *cis*-decalintrienes **5-38** in moderate yields and excellent enantioselectivity (up to 92% ee) (**Scheme 5-9**).

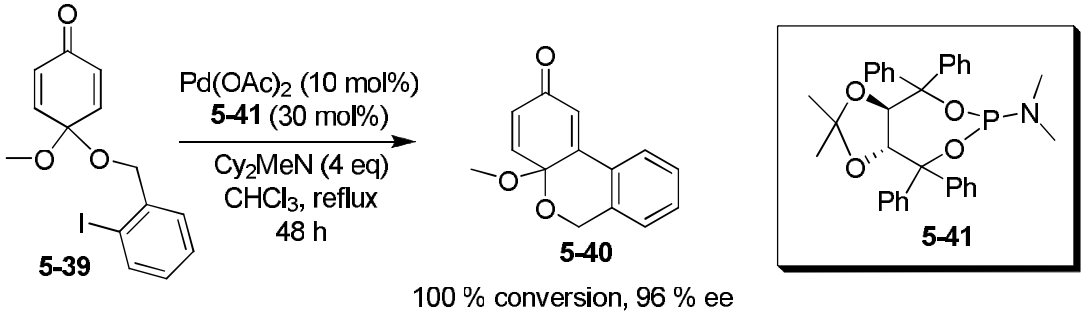


Scheme 5-8. The total synthesis of (+)-minfiensine **5-35**



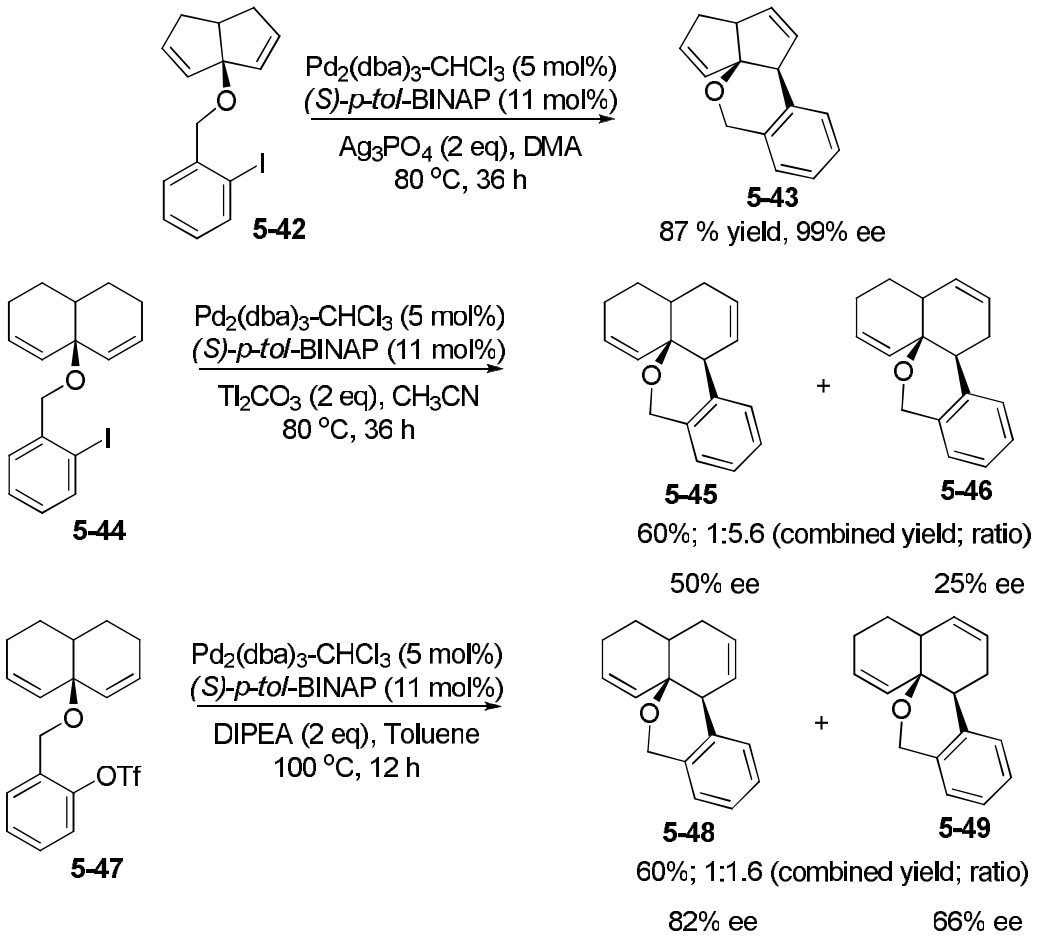
Scheme 5-9. Synthesis of enantioenriched cis-decalintrienes **5-38**

An efficient intramolecular Heck reaction of cyclohexadienone **5-39** gave **5-40** with high enantioselectivity (up to 96% ee) using a TADDOL-based monophosphoramidite ligand **5-41** instead of BINAP (**Scheme 5-10**).[14] It is noteworthy that excellent enantioselectivity can be achieved by a chiral monodentate phosphorus ligand in the absence of silver or thallium salt.

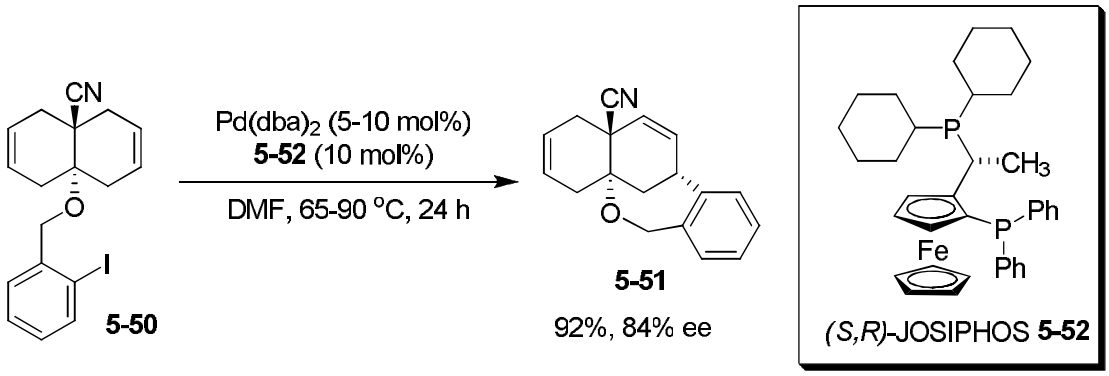


Scheme 5-10. Synthesis of enantioenriched tricyclic compound **5-40**

The intramolecular asymmetric Heck reaction through desymmetrization of bicyclo[3.3.0]octadiene **5-42** gave the corresponding fused polycyclic product **5-43** in high yield and excellent enantioselectivity using $Pd_2(dba)_3$–(*S*)-*p-tol*-BINAP as catalyst in the presence of Ag_3PO_4 (**Scheme 5-11**).[15] In contrast, the reaction of bicyclo[4.4.0] decadiene, **5-44** or **5-47**, with an aryl iodide or triflate tether under similar reaction conditions gave mixed results (Scheme 5-11).[15] The enantioselective desymmetrization of bicyclo[4.4.0]decadienes **5-50** catalyzed by Pd-(*S*,*R*)-JOSIPHOS complex **5-52** gave fused tetracyclic product **5-51** with three stereogenic centers in excellent yield and 84% ee (**Scheme 5-12**).[16]



Scheme 5-11. Synthesis of enantioenriched fused polycyclic products

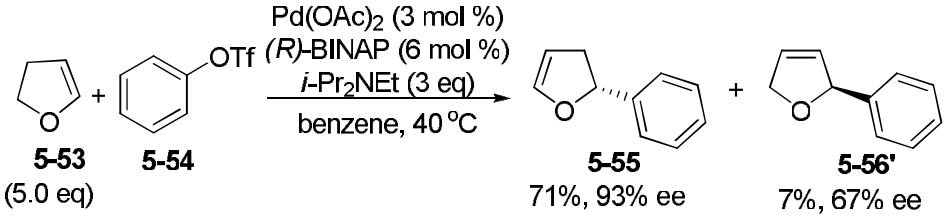


Scheme 5-12. Synthesis of enantioenriched fused tetracyclic product **5-51**

§ 5.1.3 Asymmetric intermolecular Heck reactions

§ 5.1.3.1 Dihyofurans

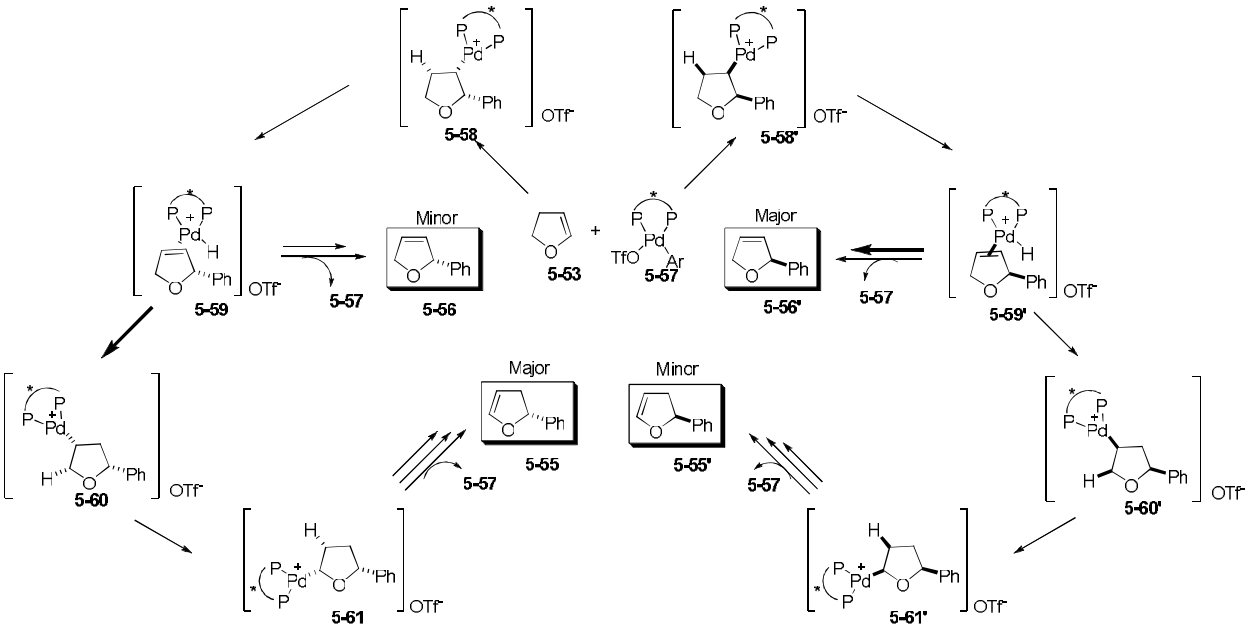
In 1991, Hayashi et al. reported the first example of the asymmetric intermolecular Heck reaction, wherein the asymmetric arylation of 2,3-dihydrofuran **5-53** with phenyl triflate **5-54** catalyzed by Pd-BINAP complex gave 2-phenyl-2,3-dihydrofuran **5-55'** (93% ee) as the predominant product accompanied by a small amount of 2-phenyl-2,5-dihydrofuran **5-56** (**Scheme 5-13**).[17]



Scheme 5-13. The first example of the asymmetric intermolecular Heck reaction

A plausible mechanism was proposed to explain the high enantiopurity of the major product **5-55** (*R*) and inversion of configuration in the formation of minor product **5-56'** (*S*). This mechanism was further refined by Brown et al. (**Scheme 5-14**).[17-18] As **Scheme 5-14** illustrates, the insertion of the double bond of **5-53** into the Ar–Pd bond of **5-57** yields two diastereomeric Pd complexes **5-58** (via *si*-face attack) and **5-58'** (via *re*-face attack). Next, β-hydride elimination takes place for both intermediates to form π-olefin-Pd-H complex **5-59** and its diastereomer **5-59'**. The π-complex **5-59** undergoes rapid hydropalladation to give **5-60**, followed by β-hydride elimination and reductive elimination to afford 2-phenyl-2,3-dihydrofuran **5-55**. Thus, for **5-59**, the hydropalladation is much faster than the dissociation of **5-56**. In contrast, the

π-complex **5-59'** rapidly dissociates 2-phenyl-2,5-dihydrofuran **5-56'** rather than undergoing hydropalladation. Accordingly, the proposed mechanism involves a kinetic resolution process that enhances enantioselectivity of **5-55** by selectively eliminating **5-58**' through the formation of **5-56**' as the minor product.



Scheme 5-14. Plausible mechanism of the asymmetric intermolecular Heck reaction

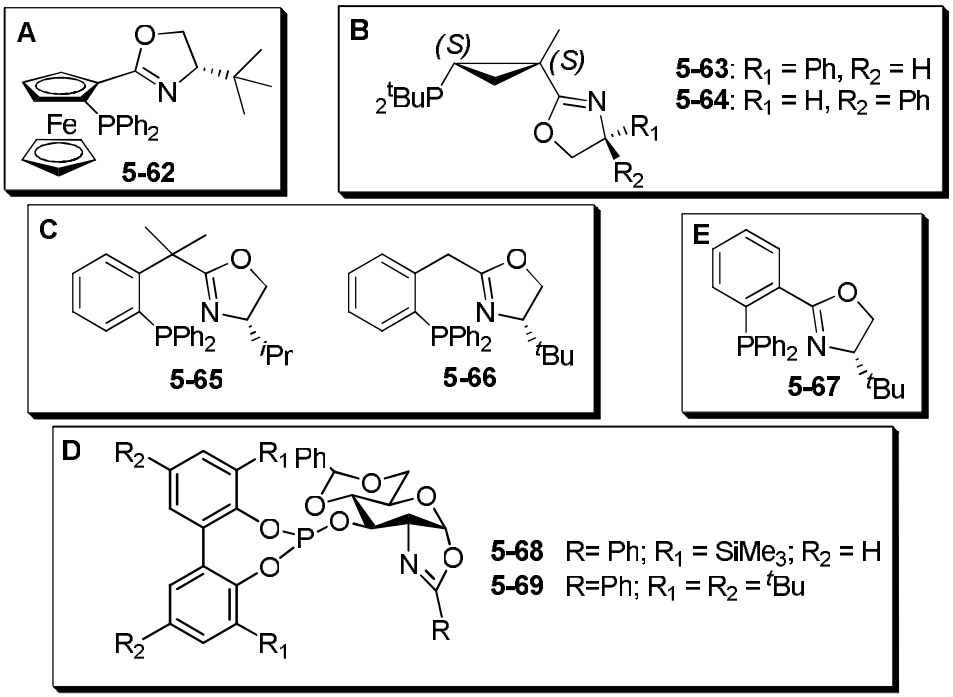
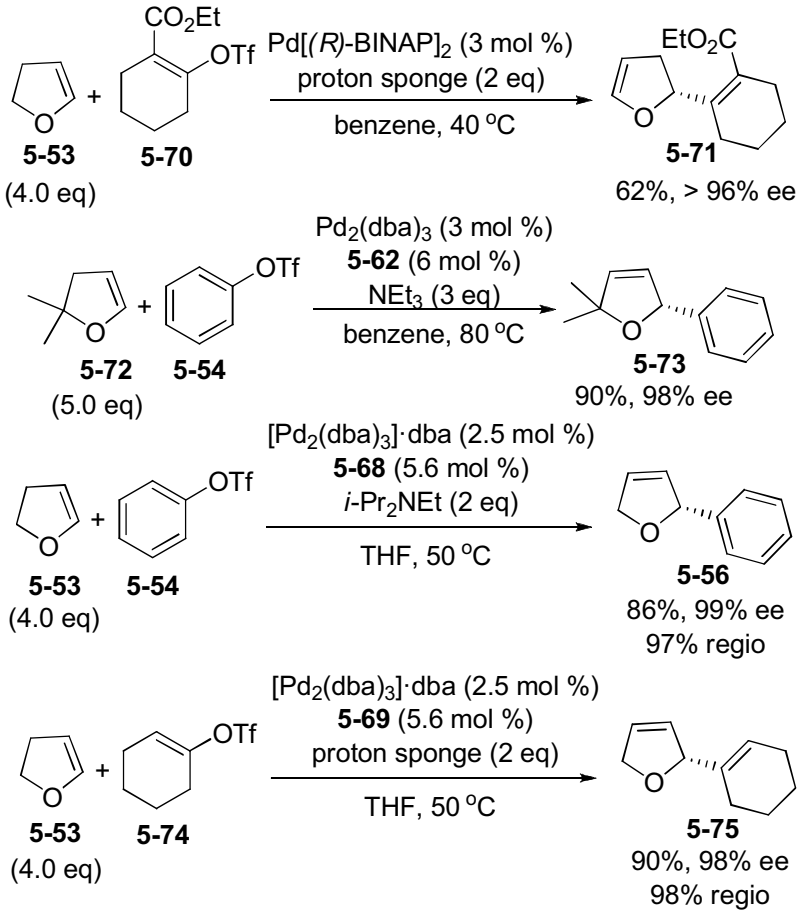


Figure 5-1. Various P-N type chiral ligands

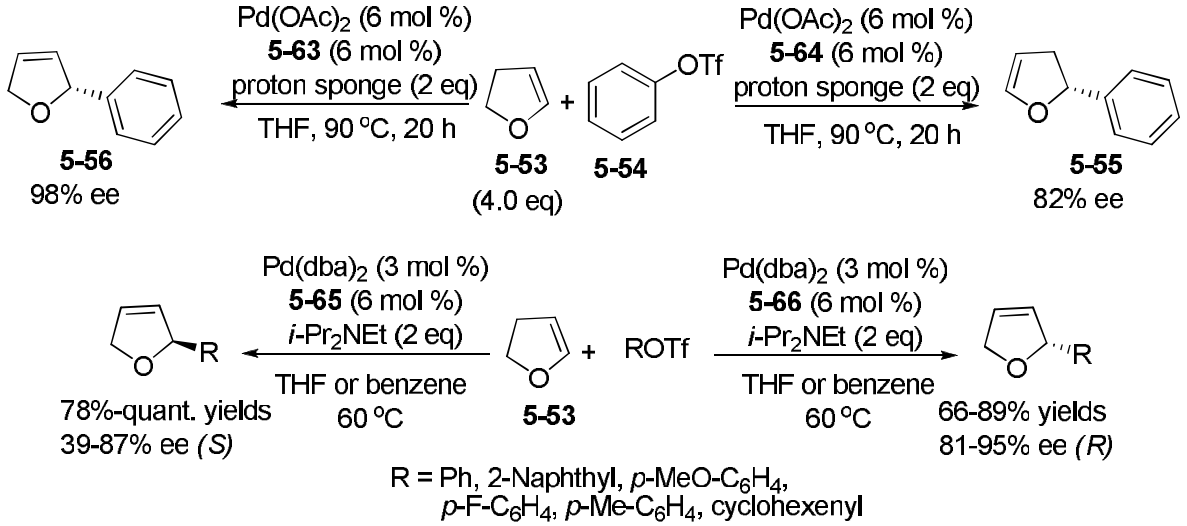
The asymmetric intermolecular Heck reaction, involving double-bond migration, has been extensively studied using various chiral P,N-ligands (**Figure 5-1**).

As **Scheme 5-15** exemplifies, the reaction of **5-53** with 2-carbethoxycyclhexenyl triflate **5-70** gave 5-cyclohexenyl-2,3-dihydrofuran **5-71** with 96% ee exclusively.[19] In contrast, the reaction of 2,2-dimethyl-2,3-dihydrofuran **5-72** with phenyl triflate **5-54** afforded 2-phenyl-2,5-dihydrofuran **5-73** with 98% ee, as the sole product.[20] The reaction of **5-53** with **5-54** catalyzed by a Pd complex with (D-glucosamine)phosphiteoxazoline ligand **5-68** gave **5-56** with 99% ee and 97% regioselectivity.[21] Also, the reaction of **5-53** with cyclohexenyl triflate **5-74** catalyzed by a Pd complex with **5-69** gave 2-cyclohexenyl-2,5-dihydrofuran **5-75** with 98% ee and 98% regioselectivity.[21] A series of PHOX ligands, for example, **5-63** and **5-64**, featuring a rigid chiral cyclopropyl backbone, were applied to the asymmetric Heck reaction of **5-53** with **5-54**. As Scheme 5-16 shows, the chirality in the oxazoline moiety of the PHOX ligands exerts a profound influence on the double-bond migration, forming either **5-55** or **5-56**, exclusively.[22]



Scheme 5-15. Synthesis of enantioenriched substituted dihydrofurans **5-71, 5-73**, **5-56** and **5-75**

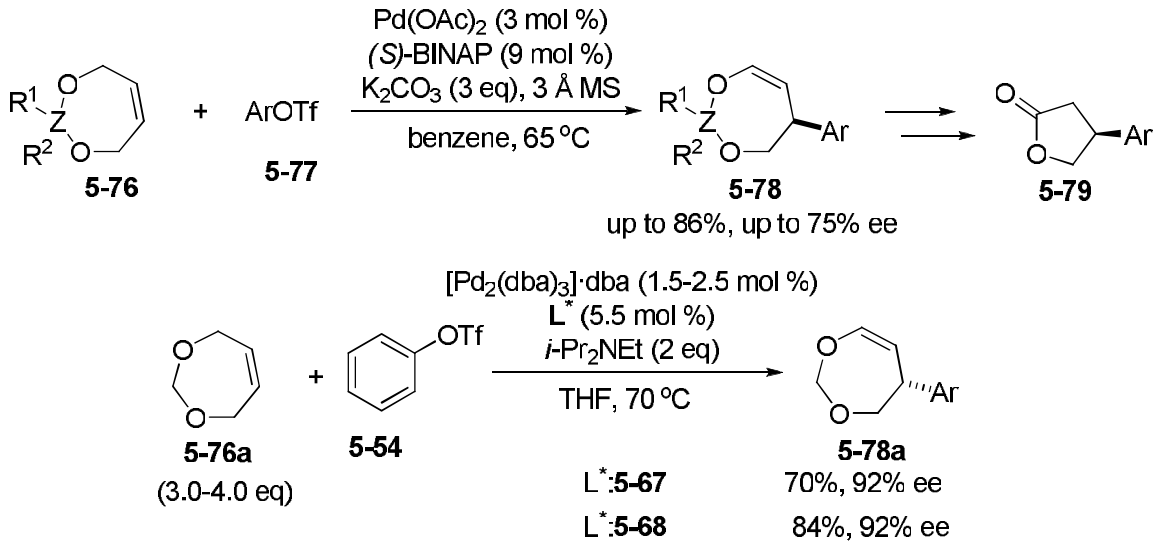
A dramatic change in enantioface selection was observed when closely related chiral P,N-ligands **5-65** and **5-66**, bearing chiral oxazolines with the same absolute configuration, were used in the reaction of **5-53** with aryl and cyclohexenyl triflates.[23] The ligand **5-66** led to the formation of (*R*)-2-substituted 2,5-dihydrofurans with up to 95% ee, while **5-65** bearing a *gem*-dimethyl group gave (*S*) products with up to 87% ee (**Scheme 5-16**).



Scheme 5-16. Synthesis of enantioenriched substituted dihydrofurans **5-55** and **5-56**

§ 5.1.3.2 Dihydrodioxepins

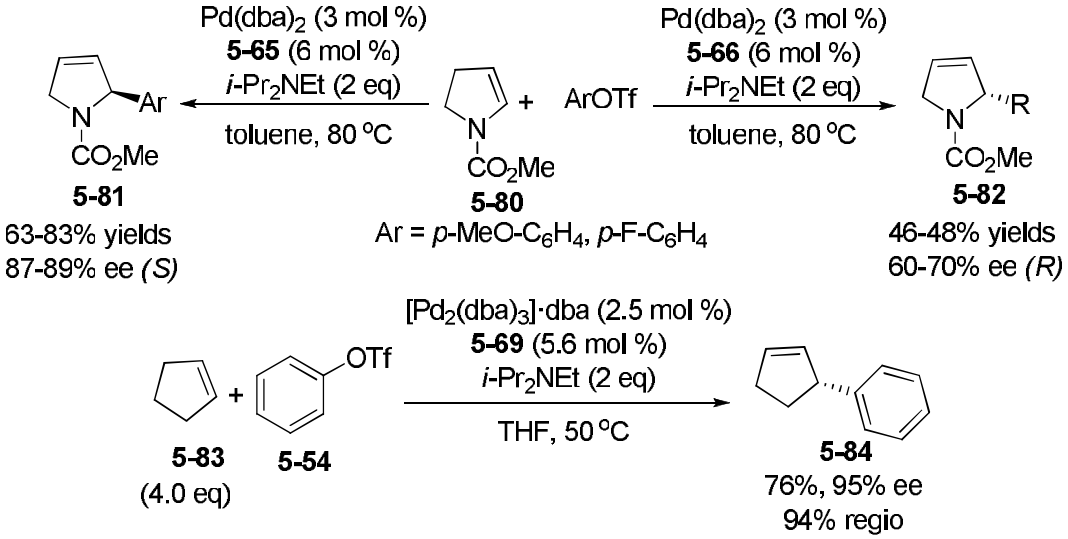
Asymmetric arylation reaction of 4,7-dihydro-1,3-dioxepins **5-76** through intermolecular Heck reaction has been studied in a similar manner as that for dihydrofurans. The resulting enol ether **5-78** can be readily transformed to chiral β-aryl-γ-butyrolactones **5-79**, which are useful chiral building blocks in natural product synthesis. Shibasaki et al. reported the first example in 1994, wherein products **5-78** were obtained in variable yields and enantioselectivities, using $Pd(OAc)_2$–(*S*)-BINAP as catalyst in the presence of potassium carbonate and 3 Å molecular sieves (**Scheme 5-17**).[24] The best results were obtained with **5-76a** ($R^1 = R^2 = H$), giving **5-78a** ($R^1 = R^2 = H$) in 48–86% yield and 60–75% ee.[24] The reaction of **5-76a** ($R^1 = R^2 = H$) with **5-54** catalyzed by a Pd complex with a chiral oxazoline-based P,N-ligand **5-67** gave **5-78a** ($R^1 = R^2 = H$, Ar = Ph) in 70% yield and 92% ee (**Scheme 5-17**).[25] The same reaction using P,N-ligand **5-68** also afforded **5-78a** in 84% yield and 92% ee (**Scheme 5-17**).[21]



Scheme 5-17. Synthesis of enantioenriched β-aryl-γ-butyrolactones **5-79**

§ 5.1.3.3 Other substrates for asymmetric intermolecular Heck reactions

In addition to dihydrofurans and dihydrodioxepins, dihydropyrroles and cyclopentene have been employed as substrates for asymmetric intermolecular Heck reaction. For example, the reaction of 2,3-dihydropyrrole **5-80** with aryl triflate catalyzed by Pd complex and chiral P,N-ligand **5-65** gave (*S*)-2-aryl-2,5-dihydropyrrole (*S*)-**5-81** in good yield and up to 89% ee, while the same reaction catalyzed by Pd-**5-66** afforded the enantiomeric (*R*)-**5-82** in moderate yield and 60–70% ee (**Scheme 5-18**).[23b]



Scheme 5-18. Synthesis of enantioenriched substituted dihydropyrrole **5-81**~**5-82** and cyclopentene **5-84**

The reaction of cyclopentene **5-83** with **5-54** using Pd-**5-69** as the chiral catalyst gave (*R*)-3-phenylcyclopent-1-ene **5-84** in good yield and 95% ee with 94% regioselectivity (**Scheme 5-18**).[21]

From the above introduction of asymmetric Heck reactions, it is apparently that the applications of mondentate ligands in palladium-catalyzed asymmetric Heck reactions are still very limited. However, this efficient intramolecular Heck reaction of cyclohexadienone **5-39** shown in **Scheme 5-10** inspired us to believe that monophosphoramidite ligands, including our tunable ligand system, still have potential to lead to high enantiomeric excess in some asymmetric Heck reactions.

§ 5.2 Results and discussion

In 2002, Feringa published the first and only successful asymmetric Heck reaction catalyzed by a phosphoramidite ligand, obtaining 100 % conversion and up to 96 % ee (**Scheme 5-10**).[14] However, this ligand provided only 33 % conversion and 32 % ee for one of Overman's substrate.[8b] These results clearly indicate the need for tunable ligands for each specific substrate type and substitution pattern. Accordingly, we plan to use these two substrates, **5-39** and **5-85**, for the evaluation of basic efficacy of our monodentate phosphorus ligands.

§ 5.2.1 Synthesis of substrates for asymmetric Heck reactions

In order to screen asymmetric Heck reactions by our monophosphoramidite ligand library (**MPN**), two substrates have to be synthesized as our starting materials. One is dienone **5-39** which was reported by Feringa,[14] and the other is carboxamide **5-85** which was published by Overman[8b] (**Figure 5-2**).

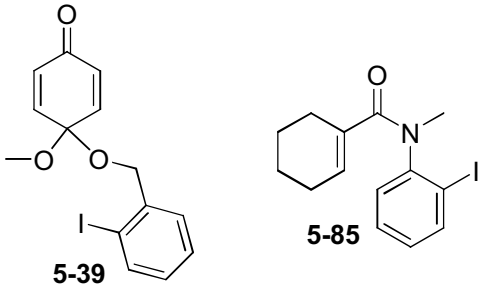
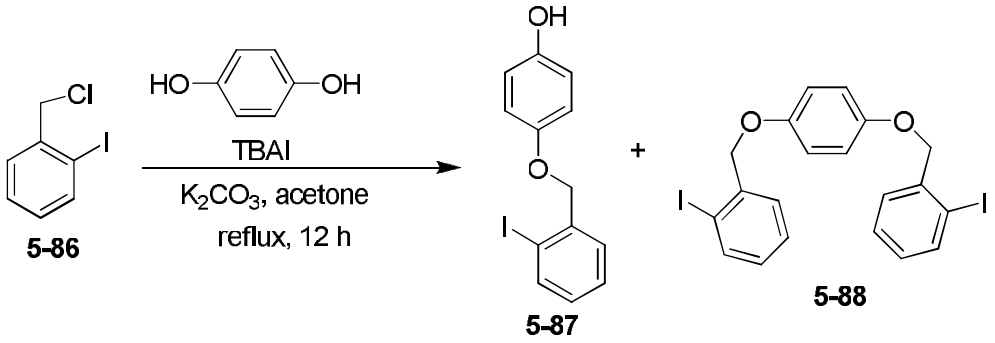


Figure 5-2. Two substrate candidates for asymmetric Heck reactions

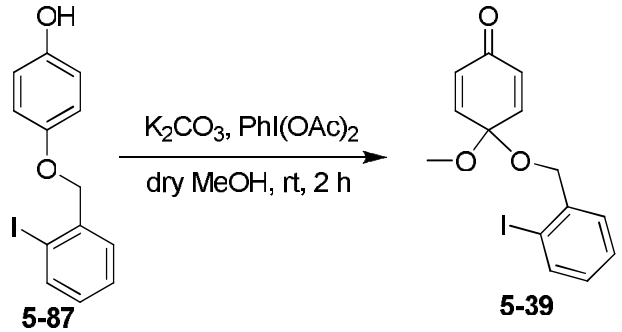
§ 5.2.1.1 Synthesis of 4-(2-iodo)benzyloxy-4-methoxycyclohexa-2,5-dien-2-one (5-39)

According to the reported literature,[14] 4-(2-iodo)benzyloxyphenol **5-87** was first synthesized from (2-iodo)-benzylchloride **5-86** and excess hydroquinone in the presence of K_2CO_3 and acetone under reflux condition overnight. Unfortunately, the starting material **5-86** was not able completely consumed until 40 h. For this reason, a catalytic amount of tetrabutylammonium iodide (TBAI) was added as an ion exchange reagent to increase reaction rate, and the reaction was finished after 12 h under reflux. In this ether-formation reaction, byproduct **5-88** was also formed and the ratio of product and byproduct was about 7 to 1 (74 % : 11 %). (**Scheme 5-19**)[14]



Scheme 5-19. Synthesis of 4-(2-iodo)benzyloxyphenol **5-87**

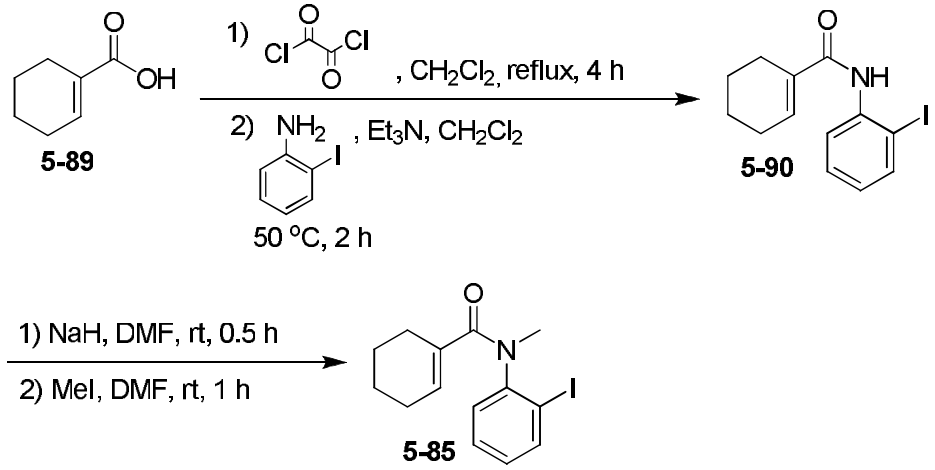
To achieve desired dienone substrate **5-39**, phenolic oxidation of 4-(2-iodo)benzyloxyphenol **5-87** with phenyliododiacetate (PIDA) and K_2CO_3 in dry MeOH was employed to afford dienenone **5-39** in 94 % isolated yield (**Scheme 5-20**).[14] In this reaction, K_2CO_3, which acts as base, was required. If no base is added in this reaction, several undesired products are obtained by TLC and the reaction does not go completion even after 2 days.



Scheme 5-20. Synthesis of 4-(2-Iodo)benzyloxy-4-methoxycyclohexa-2,5-dien-2-one **5-39**

§ 5.2.1.2 Synthesis of N-(2-Iodophenyl)-N-methyl-1-cyclohexene-1-carboxamide (5-85)

N-(2-Iodophenyl)-*N*-methyl-1-cyclohexene-1-carboxamide **5-85** was efficiently synthesized in four steps from commercially available 1-cyclohexenecarboxylic acid **5-89** which was treated with few drops of DMF and oxalyl chloride at reflux for 4 h followed by amidation with 2-iodoaniline and dry triethylamine to afford *N*-(2-Iodophenyl)-1-cyclohexene-1-carboxamide **5-90** in 51 % isolated yield. Next, methylation of NH-carboxamide **5-90** with sodium hydride and methyl iodide gave desired NMe- carboxamide **5-85** in 94 % isolated yield (**Scheme 5-21**).[8b]



Scheme 5-21. Synthesis of N-(2-Iodophenyl)-N-methyl-1-cyclohexene-1-carboxamide **5-85**

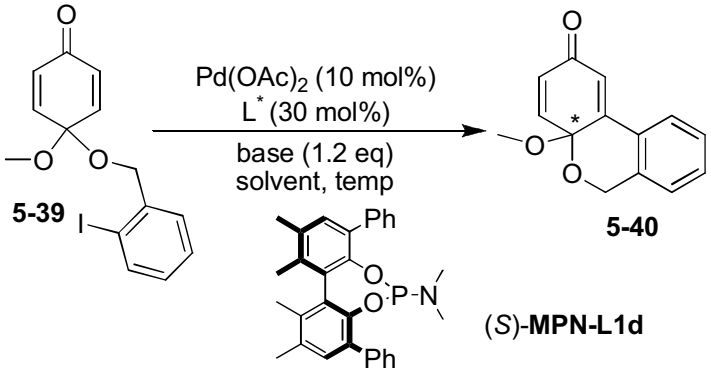
§ 5.2.2 Asymmetric Heck reactions with a library of biphenol-based monophosphoramidite ligands

§ 5.2.2.1 Pd-catalyzed asymmetric Heck reaction of dienone using chiral bipheol-based monophosphoramidite

In this study, phenyl-substituted monophosphoramidite (*S*)-**MPN-L1d** was first employed as the chiral ligand because it possesses the same substituted group as reported ligand which gave the best conversion and enantioselectivity in asymmetric Heck reaction of dienone **5-39**. Several conditions were attempted and all results were shown in **Table 5-1**. Entry 1 demonstrated the synthesis of racemic Heck product **5-40** to set up the chiral HPLC condition. In this reaction, dienone **5-39** was catalyzed by $Pd(OAc)_2$ and PPh_3 in the presence of Cy_2MeN and $CHCl_3$ under reflux for 48 h.[14] Product **5-40** was expected to be produced after 48 h; however, no desired product was formed, as determined by TLC, ^1H NMR and LC-MS characterization. At the same time, (*S*)-**MPN-L1d** was introduced and different reaction conditions were tested to evaluate this

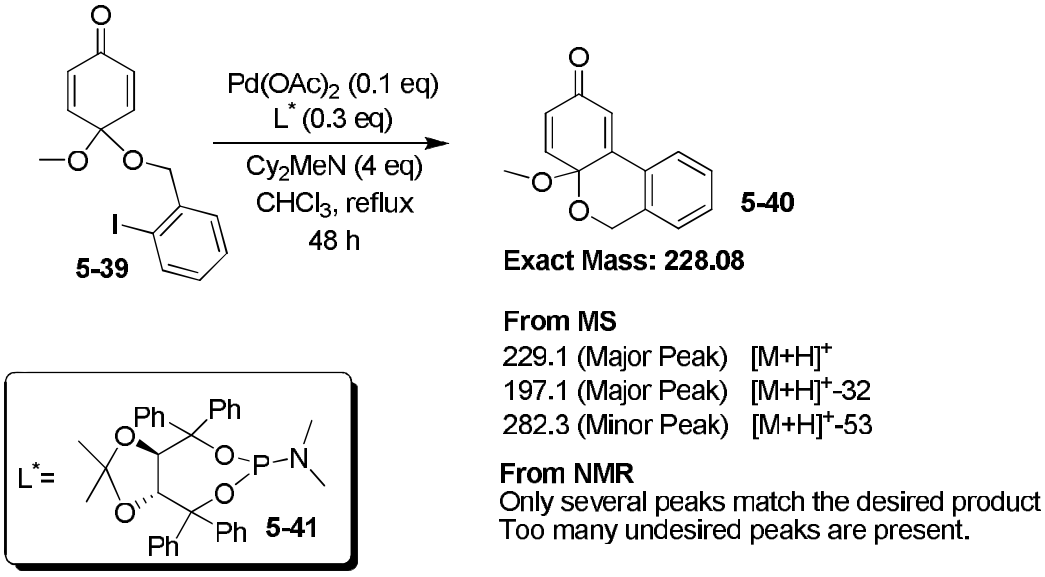
asymmetric Heck reaction (entries 2-5). Unfortunately, no matter which thermal or microwave condition was adopted, no product was found after reaction; even though solvent or base was changed, the same result was observed consistently. Due to these poor results, the reported ligand was synthesized to examine where the problem came from. Entry 6 and **Scheme 5-23** showed reaction details and the result using taddol-based monophosphoramidite ligand.[14] From MS determination, the peak of product was observed along with two other undesired peaks. Considering ^{1}H NMR, only few peaks match cyclisation product **5-40;** too many unexpected peaks appeared in the spectrum as well. Accordingly, this unanticipated problem was still not clear. A further study is necessary to solve this issue.

Table 5-1. Preliminary screening of MPN ligands for asymmetric Heck reaction of **5-39**



Entry[c]	Ligand	Base	Solvent	Temp(°C)	Time (h)	Condition	Results[e]
1[a]	PPh_3	Cy_2MeN	$CHCl_3$	reflux	48	Heating	Messy mixtures
2[a]	(*S*)-**MPN-L1d**	Cy_2MeN	$CHCl_3$	reflux	48	Heating	Only starting material
3[a]	(*S*)-**MPN-L1d**	Cy_2MeN	$CHCl_3$	80	3	MW	Messy mixtures
4[b]	(*S*)-**MPN-L1d**	Cy_2MeN	THF	80	3	MW	Messy mixtures
5[b]	(*S*)-**MPN-L1d**	K_2CO_3	THF	80	10	MW	Messy mixtures
6[a]	**5-41**	Cy_2MeN	$CHCl_3$	80	48	Heating	No desired product[f]

a. 40 mg of substrate and 2 mL of solvent were used.
b. 20 mg of substrate and 1 mL of solvent were used.
c. The conversion was determined by ^{1}H NMR.
d. Microwave condition: dynamic mode, 250 W, 100 psi.
e. Those results were characterized from TLC, ^{1}H NMR and LC-MS.
f. The result was shown in **Scheme 5-22**.



Scheme 5-22. Analysis of the tricyclic product **5-40** by MS and NMR

§ 5.2.2.2 Pd-catalyzed asymmetric Heck reaction of carboxamide using chiral bipheol-based monophosphoramidite

A library of our biphenol-based monophosphoramite ligands was intended to screen this known cyclisation substrate **5-85** in intramolecular asymmetric Heck reaction (**Figure 5-3**). The synthesis of racemic Heck cyclization products **5-21** and **5-22** was performed by using $Pd(OAc)_2$ as the precatalyst, Bu_3P and dppp as ligands in the presence of Ag_2CO_3 and DMF (**Table 5-**2, entry 1).[8b] As expected, isomers **5-21** and **5-22** were both obtained and were inseparable by column chromatography. Therefore, ^1H NMR was employed to determine the regioselectivity of isomers **5-21** and **5-22**. From ^1H NMR, two set of peaks are shown. However, only characteristic alkene peaks were able to be distinguished. Alkene peaks for isomer **5-21** were shown at 5.27 and 6.13 ppm and for isomer **5-22** were shown at 5.90 ppm.[8c] Besides, the conversion of the reaction was also obtained from ^1H NMR by comparing methyl group between starting material and products. These racemic products were then submitted to chiral HPLC (OD-H column) to determine their retention times. Unfortunately, racemic mixtures of isomer **5-22** were difficult to be separated in this column. However, based on previous literature,[8b] isomer **5-22** was the undesired product. For this reason, it is understandable if enantiomeric excess of **5-22** was ignored in the following data.

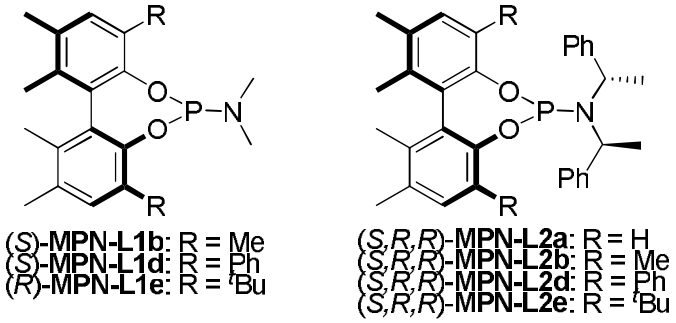
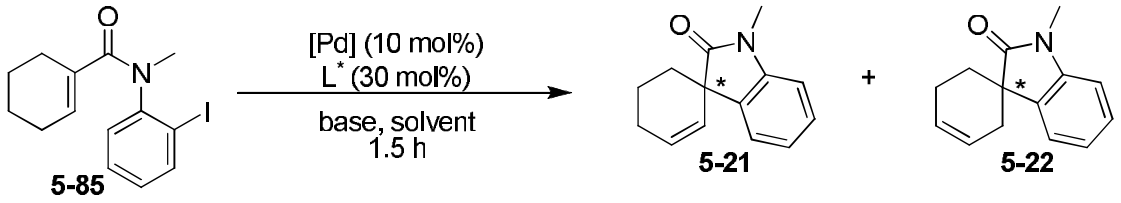


Figure 5-3. MPN ligands for asymmetric Heck reactions

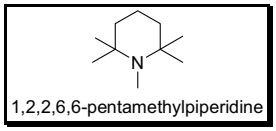
From **Table 5-2**, three enantiopure biphenol-based monophosphoramite ligands, (*S*)-**MPN-L1b**, (*S*)-**MPN-L1d** and (*R*)-**MPN-L1e**, were chosen to do some preliminary tests to decide which reaction condition was better for the future study. In entries 2-4, the reaction condition of neutral pathway reported by Overman was adopted.[8b] Each case gave about 95 % conversion after 1.5 h at 80 ^{o}C except entry 2 (60 %). No matter which ligand was used, regio ratio was almost 1 to 1 in each case which was similar to Overman's results. However, when considering enantiomeric excess, methyl-substitued monophosphoramite ligand (entry 2) gave nearly no enantioselectivity, and tert-butyl and phenyl-substituted monophosphoramite ligands (entries 3 and 4) only provided 27 % and 28 % ee which were poor enantiomeric excess compared to 89 % ee by chiral BINAP ligands. On the other hand, the reaction conditions for the cationic pathway was employed in entries 5-7. In this reaction conditions, $Pd(OAc)_2$ was used as precatalyst and Ag_2CO_3 acted as base and halide scavenger, favoring the cationic pathway.[8c] From entries 5-7, each reaction gave 100 % conversion after 1.5 h at 80 ^{o}C. The regioselectivity was pretty good when methyl- or tert-butyl-substitued monophosphoramite ligand was performed as the chiral ligand (entries 5 and 6). The ratio of **4-21** to **4-22** was poorer while phenyl-substituted monophosphoramite ligand was employed (entry 7). Regarding enantioselectivity, only tert-butyl-substitued monophosphoramite ligand provided significant result, 22 % ee (entry 6). Moreover, the comparison of the same ligand within these two sets of data indicated that the reaction condition of the cationic pathway gave comparable enantioselectivity but better reactivity and regioselectivity than the reaction conditions of the neutral pathway did (entries 2 and 5, entries 3 and 6). Therefore, the cationic reaction conditions were chosen as the standard conditions in the following study.

Table 5-2. Preliminary screening of MPN ligands for asymmetric Heck reaction of **5-85**



Entry[a]	Pd source	Ligand	Base (eq)	Solvent[b]	Temp(°C)	Conv. %[c]	**5-21**:**5-22**[d]	% ee[e] **5-21**[f]
1	$Pd(OAc)_2$	Bu_3P dppp	Ag_2CO_3 (2)	DMF	150	66	83:17	*rac*
2	$Pd_2(dba)_3$	(*S*)-**MPN-L1b**	PMP (5)	DMA	80	60	55:45	<5
3	$Pd_2(dba)_3$	(*R*)-**MPN-L1e**	PMP (5)	DMA	80	96	45:55	-28
4	$Pd_2(dba)_3$	(*S*)-**MPN-L1d**	PMP (5)	DMA	80	94	57:43	+27
5	$Pd(OAc)_2$	(*S*)-**MPN-L1b**	Ag_2CO_3 (2)	DMF	80	100	93:7	<5
6	$Pd(OAc)_2$	(*R*)-**MPN-L1e**	Ag_2CO_3 (2)	DMF	80	100	96:4	+22
7	$Pd(OAc)_2$	(*S*)-**MPN-L1d**	Ag_2CO_3 (2)	DMF	80	100	67:33	<5

a. 20 mg of substrate was used in each entry.
b. 0.75 mL of solvent was used.
c. The conversion was determined by ^{1}H NMR.
d. The regioselectivity was determined by ^{1}H NMR.
e. % ee was determined by chiral HPLC (OD-H column, eluent: Hexane:IPA=99.5:0.5).
f. % ee of **5-21** equals to the % area of first peak minus the % area of second peak.
* PMP=1,2,2,6,6-pentamethylpiperidine



Next, a variety of parameters were adjusted to optimize the regioselectivity and enantioselectivity using $Pd(OAc)_2$ as precatalyst, Ag_2CO_3 as base in DMF. First, temperature effect was investigated by tert-butyl-substitued monophosphoramite ligand which was the best ligand from the preliminary tests (**Table 5-3**, entries 1-4). The results suggested that lower temperature gave both poor regioselectivity and enantioselectivity. A valid explanation of those results was not clear so far because in principle, lower temperature should enhance

enantioselectivity due to less flexibility of the chiral monodentate ligand.

In addition to temperature effect, the loading of catalyst has also been discussed (entry 5). In this trial, the amount of $Pd(OAc)_2$ and chiral ligand was four times less than the amount in entry 1. After 3 h at 80 ^oC, the conversion was over 95 % and the regio- and enantioselectivity were only slightly unfavorable compared to the results in entry 1. It showed that lower catalytic loading had a chance to be applied to asymmetric Heck reaction in our ligand system. In entries 6-10, the amine moiety of ligands was replaced by *N,N*-bis(*(R)*-methyl benzyl) amine with C_2-symmetry to see whether bulky chiral amine moiety was capable of achieving higher enantioselectivity than small achiral amine moiety.

Table 5-3. Screening of MPN ligands for asymmetric Heck reaction of **5-85**

Entry[a]	Pd source	Ligand	Temp(^oC)	Time (h)	Conv. %[b]	**5-21**:**5-22**[c]	% ee[d] **5-21**[e]
1	$Pd(OAc)_2$	(*R*)-**MPN-L1e**	80	1.5	>95	96:4	+22
2	$Pd(OAc)_2$	(*R*)-**MPN-L1e**	60	2.5	93	56:44	<5
3	$Pd(OAc)_2$	(*R*)-**MPN-L1e**	40	3.5	82	56:44	<5
4	$Pd(OAc)_2$	(*R*)-**MPN-L1e**	rt	4.0	>95	57:43	<5
5[f]	$Pd(OAc)_2$	(*R*)-**MPN-L1e**	80	3.0	>95	85:15	+13
6	$Pd(OAc)_2$	(*S,R,R*)-**MPN-L2a**	80	1.5	76	77:23	<5
7	$Pd(OAc)_2$	(*S,R,R*)-**MPN-L2b**	80	1.5	83	85:15	-15
8	$Pd(OAc)_2$	(*S,R,R*)-**MPN-L2d**	80	1.5	41	76:24	-26
9	$Pd(OAc)_2$	(*S,R,R*)-**MPN-L2d**	80	48	77	78:22	-18
10	$Pd(OAc)_2$	(*S,R,R*)-**MPN-L2e**	80	48	83	76:24	<5

a,b,c,d,e, Please see the footnotes on **Table 5-2**.

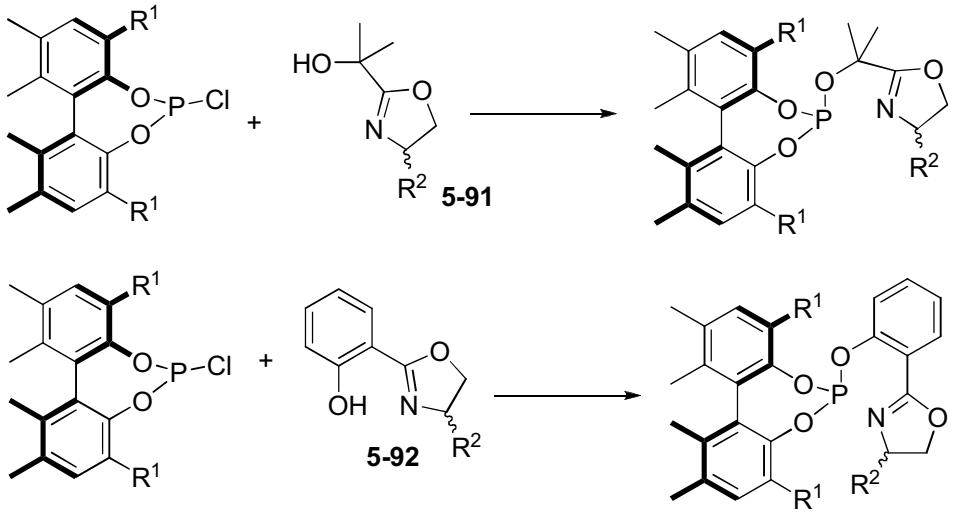
f. 2.5 mol% of $Pd(OAc)_2$ and 7.5 mol% **MPN-L1e** were used in the reaction.

From the data, entry 8, in which phenyl-substitued monophosphoramite ligand with chiral amine moiety (*S,R,R*)-**MPN-L2d** was used as a chiral ligand, performed the best enantiomeric

excess (26 % ee) but worst conversion (41 % after 1.5 h at 80 °C). Moreover, when comparing with (*S*)-**MPN-L1d** which possesses the same biphenol but different amine moiety in this asymmetric Heck reaction (**Table 5-2**, entry 7), the chiral amine moiety indeed affected the enantioselectivity but reduced the reactivity as well. Entries 6 and 7 gave higher conversion but lower enantiomeric excess and each case showed moderate regioselectivty (up to 85:15). In order to increase the conversion of entry 8, reaction time was prolonged to 48 h (entry 9). Although the conversion was really enhanced, enantiomeric excess slightly dropped to 18 % ee. According to above results, the chiral amine moiety does improve enantioselectivity but its steric effect decreases reactivity instead (**Table 5-2**, entries 5 and 7; **Table 5-3**, entries 7 and 8).

§ 5.2.3 Asymmetric Heck reactions with a library of chiral biphenol and oxazoline-based phosphite-oxazoline ligands

Because poor results were obtained by using chiral biphenol-based monophosphoramidite, the focus was shifted back onto bidentate P-N type ligands which achieved impressive results in both inter- and intramolecular asymmetric Heck reactions (**Figure 5-1**). Thus, new chiral biphenol and oxazoline-based phosphite-oxazoline ligands were designed and synthesized for asymmetric Heck reactions described in the chapter 5.2.



Scheme 5-23. General procedures for the synthesis of P-N type ligands

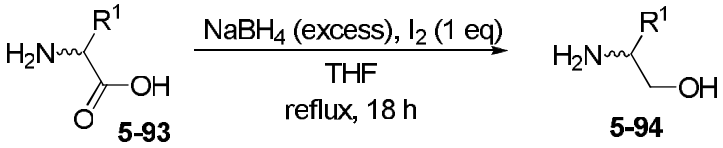
§ 5.2.3.1 Synthesis of chiral biphenol and oxazoline-based phosphite-oxazoline ligands

According to the synthetic route in **Scheme 5-23**, biphenyl chlorophosphite and hydroxy

substituted oxazoline are two mandatory components.Thus, two oxazoline derivatives were synthesized; one is α,α-dimethyl-2-ethanol substituted 4,5-dihydro-oxazole **5-91**, another is phenol substituted 4,5-dihydro-oxazole **5-92**.

To synthesize α,α-dimethyl-2-ethanol substituted 4,5-dihydro-oxazole moiety, the selected chiral amino acids **5-93** were reduced by $NaBH_4$ and I_2 in THF to introduce corresponding amino alcohols **5-94** in 57-70% isolated yields and the optical rotation for each amino alcohol is in agreement with the reported literature (**Table 5-4**).

Table 5-4. Synthesis of enantiopure **5-94a** to **5-94c**



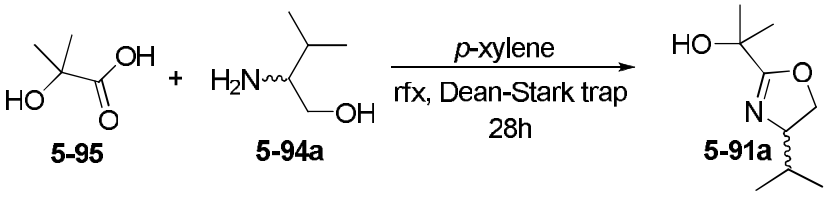
Entry	substrate	R^1	yield (%)	$[\alpha]_D^{22}$
1	*D*-Valine *(R)*	*i*-Pr	57	-17.3 (*c*=1.2 in EtOH)
2	*L*-Valine *(S)*	*i*-Pr	61	+14.6 (*c* 0.8, EtOH)
3	*L*-Phenylglycine *(S)*	Ph	70	+30.9 (*c* 1.4, 1N HCl)

Next, *D* or *L*-Valinol **5-94a** was reacted with 2-Hydroxy-2-methylpropanoic acid **5-95** in *p*-xylene under reflux condition using a Dean-Stark apparatus to generate desired (*R*) or (*S*)-4,5-Dihydro-α,α-dimethyl-4-isopropyloxazole-2-ethanol **5-91a**. However, even though water was removed by Dean-Stark trap to inhibit the reversed reaction, the reaction did not complete after 30 h. Therefore, only 15% and 18% yield of products were obtained (**Table 5-5**).[26]

On the other hand, because of the instability of chlorophosphite under moisture, each chiral chlorophosphite was formed *in situ*, followed by the condensation with chiral α,α-dimethyl-2-ethanol substituted 4,5-dihydro-oxazole moiety (*S*)-**5-91a** to introduce the corresponding chiral P,N ligand (**Tables 5-6** and **5-7**). According to the data, more bulky substituent on 3,3' positions of chiral biphenol results in lower yield of desired ligand (R^1=H, 62%, R^1=Me, 57%, R^1=Ph, 25%, R^1=Br, 34% in Table 4-6, R^1=Me, 50%, R^1=Ph, 46%, R^1=Br, 33% in **Table 5-7**). Biphenol bearing *tert*-butyl substituent on 3, 3' positions was also tried to

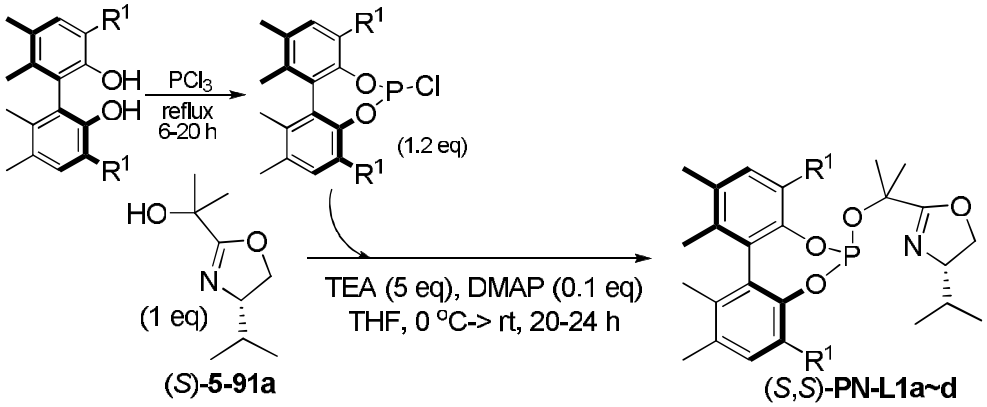
form its corresponding ligand using the same method. Unfortunately, none of desired ligand was observed after the reaction.

Table 5-5. Synthesis of (*S*)- and (*R*)-**5-91a**



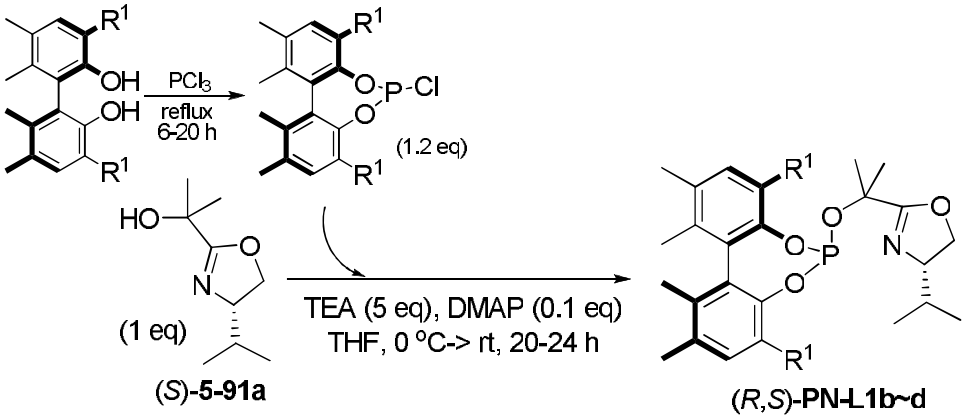
Entry	substrate	yield (%) **5-91a**	$[\alpha]_D^{22}$
1	*D*-Valinol *(R)*	15	+59.5 (*c* 0.4, CH_2Cl_2)
2	*L*-Valinol *(S)*	18	-69.1 (*c* 1.2, CH_2Cl_2)

Table 5-6. Synthesis of (*S*,*S*)-**PN-L1a** to **1d**



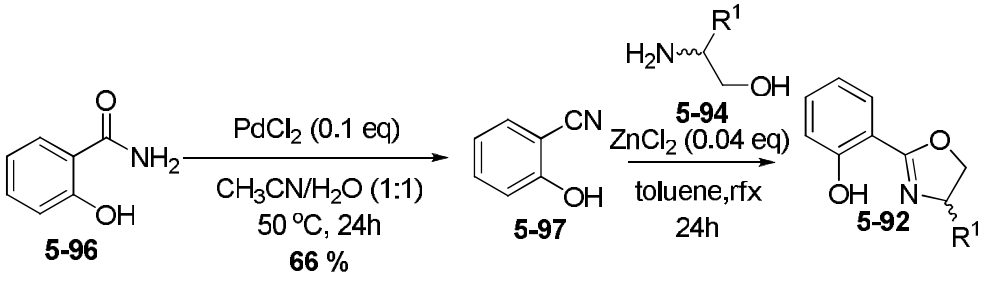
Entry	R^1	^{31}P NMR of chlorophosphite (ppm)	^{31}P NMR of P-N ligand (ppm)	Yield (%)	$[\alpha]_D^{23}$
(*S,S*)-**PN-L1a**	H	171.3	145.3	62	+92.3 (*c* 0.52, CH_2Cl_2)
(*S,S*)-**PN-L1b**	Me	166.4	140.9	57	+173.3 (*c* 0.45, CH_2Cl_2)
(*S,S*)-**PN-L1c**	Ph	167.5	142.5	25	+266.7 (*c* 0.30, $CHCl_3$)
(*S,S*)-**PN-L1d**	Br	172.2	143.9	34	+257.9 (*c* 0.40, $CHCl_3$)

Table 5-7. Synthesis of (*R*,*S*)-**PN-L1b** to **1d**



Entry	R^1	^{31}P NMR of chlorophosphite (ppm)	^{31}P NMR of P-N ligand (ppm)	yield (%)	$[\alpha]_D^{23}$
(*R,S*)-**PN-L1b**	Me	166.4	141.4	50	-237.5 (*c* 0.40, $CHCl_3$)
(*R,S*)-**PN-L1c**	Ph	167.5	142.8	46	-120.0 (*c* 0.45, $CHCl_3$)
(*R,S*)-**PN-L1d**	Br	172.2	143.9	33	-343.8 (*c* 0.30, $CHCl_3$)

Table 5-8. Synthesis of phenol substituted 4,5-dihydro-oxazoles **5-92**

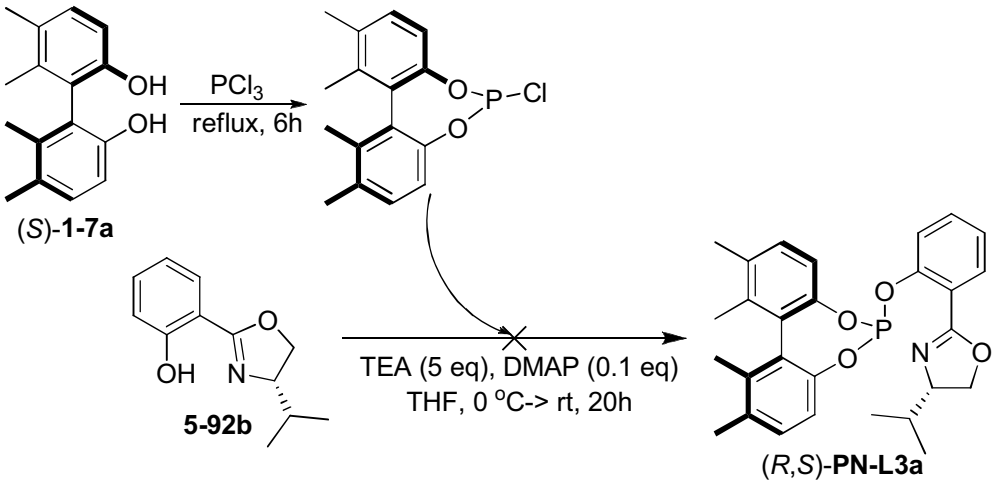


Entry	substrate	R^1	yield (%)	$[\alpha]_D^{22}$
1	*D*-Valinol *(R)*	*i*-Pr	81	+46.3 (*c* 1.6, $CHCl_3$)
2	*L*-Valinol *(S)*	*i*-Pr	83	-30.8 (*c* 2.3, $CHCl_3$)
3	*L*-Phenylglycinol *(S)*	Ph	63	+83.0 (*c*=1.1 in CHCl3)

To synthesize phenol substituted 4,5-dihydro-oxazoles **5-92**, 2-hydroxybenzamide **5-96** was converted into 2-hydroxybenzonitrile **5-97** in the presence of catalytic amount of $PdCl_2$ and 1:1 ratio of acetonitrille and water. After 24 h at 50 °C, 2-hydroxybenzonitrile **5-97** was obtained in

66% isolated yield.[21] The resulting substrate then reacted with chiral amino alcohols **5-94** which were described above to introduce corresponding phenol substituted 4,5-dihydro-oxazoles **5-92** in moderated yields (63-83% in **Table 5-8**).

Next, the same approach shown in **Tables 5-6** and **5-7** was employed to synthesize this type of P,N ligands. A chiral chlorophosphite was formed *in situ*, and then a solution of oxazole moiety was treated with it in the presence of NEt_3 and DMAP. After room temperature for 20 h, TLC and ^{31}P NMR indicated the presence of the desired ligand (*R*,*S*)-**PN-L3a**. However, no product was found after column chromatography on silical gel; only starting material **5-92b** was recovered (**Scheme 5-24**).



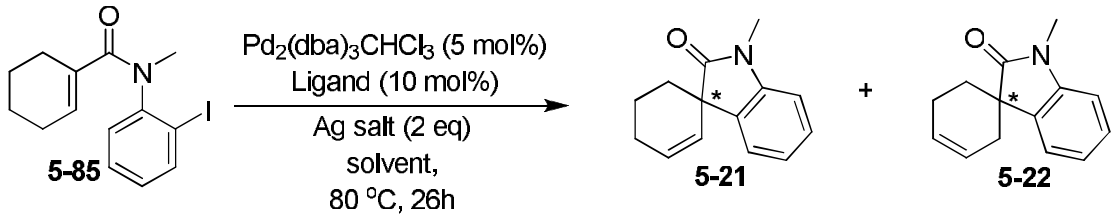
Scheme 5-24. Unsuccessful attempt toward the synthesis of (*R*,*S*)-**PN-L3a**

§ 5.2.3.2 Asymmetric Heck reaction of carboxamide with a library of chiral biphenol and oxazoline-based phosphite-oxazoline ligands

A small library of our chiral biphenol-based phosphite-oxazoline ligands in **Figure 5-3** was intended to screen this known cyclization substrate **5-85** in intramolecular asymmetric Heck reaction. The results are summarized in **Table 5-9**. The solvent effect was first studied in this reaction (entries 1-3). Among these three common solvents (DMA, NMP and toluene) for Heck reaction, NMP gave the best conversion, regio- and enantioselectivity (entry 2). Next, different silver source was used to investigate the reaction (entries 4 and 5). While AgOTf replaced Ag_3PO_4 as the HI scanvenger, the reactivity was enhanced a lot; however, both regio- and enantioselectivity dropped dramatically (entries 1 and 4). Therefore, according to above results, the ligand study will be performed in the presence of NMP as a solvent and Ag_3PO_4 as a HI

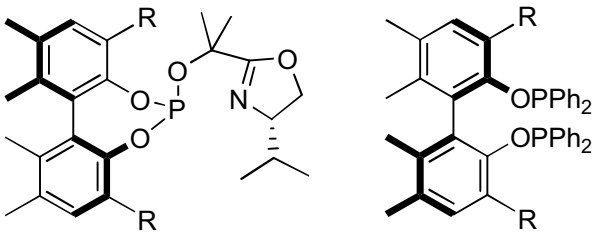
scanvenger. Here, three chiral biphenol-based phosphite-oxazoline ligands, (*S,S*)-**PN-L1a**, (*S,S*)-**PN-L1b**, (*R,S*)-**PN-L1c**, were used to screen the reaction (entries 2, 6, and 7). From those data, each of them gave 100% conversion after 26 h at 80 °C and more bulky substituent on 3, 3' positions of chiral biphenol results in higher regio- and enantioselectity. However, that's so called "higher regio- and enantioselectity" still not an encouraging outcome. Besides, two **BOP** ligands, (*R*)-**BOP-L1a** and (*S*)-**BOP-L1b** (Figure 4-3), were also employed in this reaction to test their efficacy. Unfortunately, the regioselectivity was improved but enantioselectivity became even worse; only racemic cyclization products were found for each isomer.

Table 5-9. Screening of **PN-L1a~c** and **BOP-L1a~b** for asymmetric Heck reaction of **5-85**



Entry[a]	Ligand	Ag salt	Solvent[b]	Conv. (%)[c]	Regioselectivity[d] **5-21**:**5-22**	% ee[e] **5-21**:**5-22**[f]
1	(*S,S*)-**PN-L1a**	Ag_3PO_4	DMA	40	50:50	25:rac *(R)*
2	(*S,S*)-**PN-L1a**	Ag_3PO_4	NMP	100	53:47	23:rac *(R)*
3	(*S,S*)-**PN-L1a**	Ag_3PO_4	Toluene	46	30:70	11:rac *(R)*
4	(*S,S*)-**PN-L1a**	AgOTf	DMA	100	36:64	Racemic
5	(*S,S*)-**PN-L1a**	AgOTf	NMP	100	38:62	Racemic
6	(*S,S*)-**PN-L1b**	Ag_3PO_4	NMP	100	53:47	21:rac *(R)*
7	(*R,S*)-**PN-L1c**	Ag_3PO_4	NMP	100	62:38	31:rac *(S)*
8	(*R*)-**BOP-L1a**	Ag_3PO_4	NMP	100	85:15	Racemic
9	(*S*)-**BOP-L1b**	Ag_3PO_4	NMP	100	87:13	Racemic

a,b,c,d,e,f Please see the footnotes on **Table 5-2**.



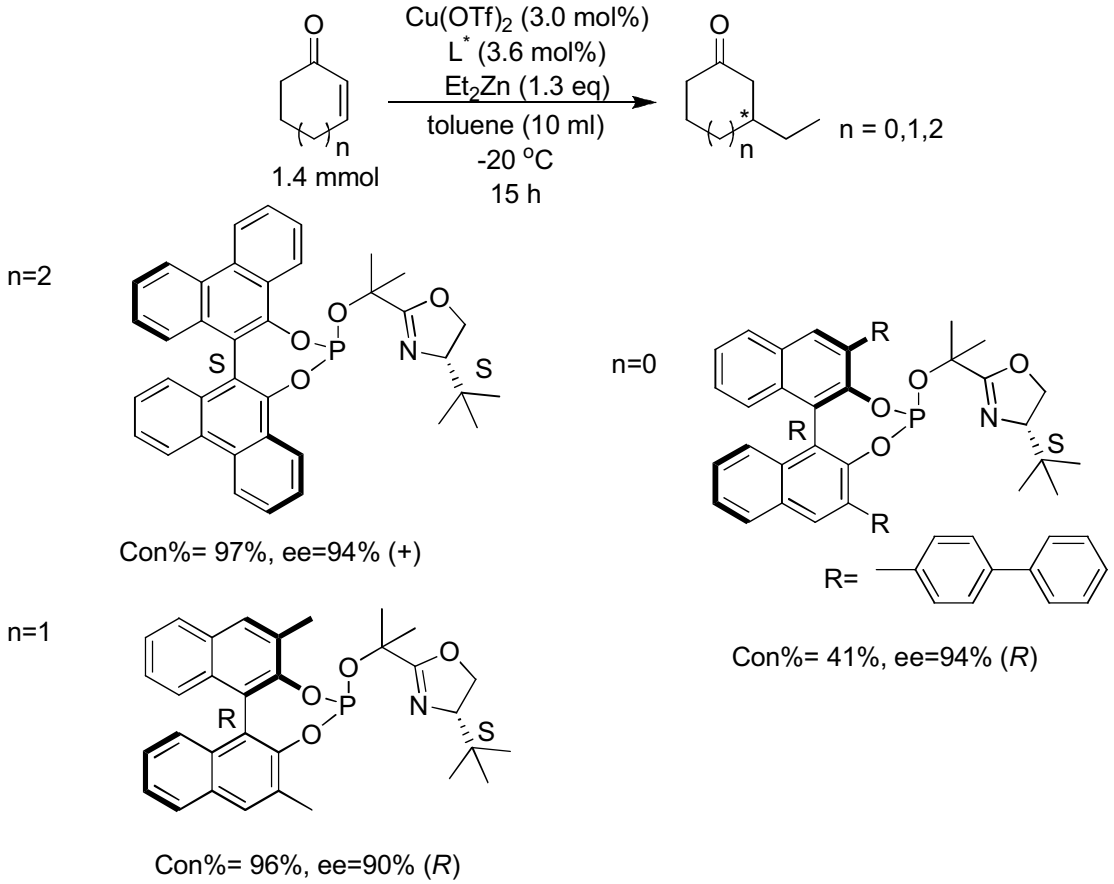
(*S*,*S*)-**PN-L1a:** R = H
(*S*,*S*)-**PN-L1b:** R = Me
(*R*,*S*)-**PN-L1c:** R = Ph

(*R*)-**BOP-L1a**: R = H
(*S*)-**BOP-L1b**: R = Me

Figure 5-4. PN and **BOP** ligands for asymmetric Heck reactions

§ 5.2.4 Asymmetric 1,4-conjugated addition with a library of chiral biphenol and oxazoline-based phosphite-oxazoline ligands

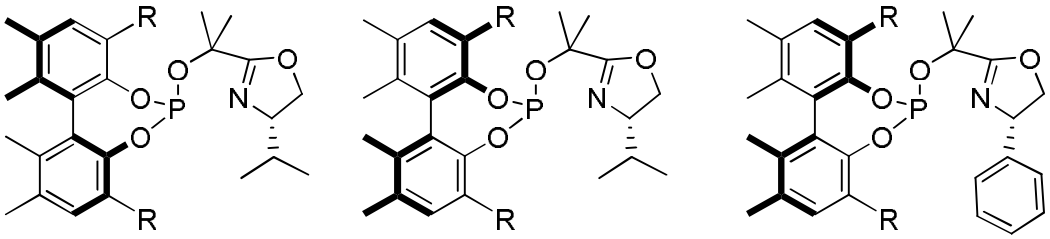
Although poor results for asymmetric Heck reaction were given by newly developed chiral phosphite-oxazoline ligands, other useful asymmetric reactions have to be tried without just sacrificing those ligands.



Scheme 5-25. Asymmetric 1,4-conjugate addition of diethyl zinc to enone systems

Here, asymmetric 1,4-conjugate addition was screened by those P,N ligands (**Figure 5-5**) since silimilar P,N type chiral ligands gave moderate to good enantioselectivity for this reaction (**Scheme 5-25**).[27]

In the asymmetric 1,4-conjugate addition, both cyclohepten-1-one and cyclohexen-1-one were used as substrates. The results are summarized in **Table 5-10** and **5-11**.



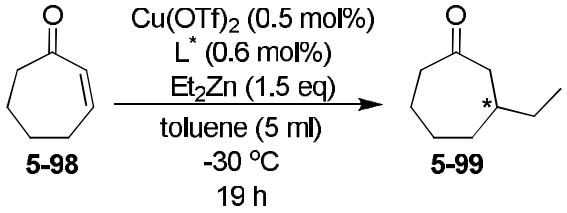
(*S,S*)-**PN-L1a:** R = H
(*S,S*)-**PN-L1b:** R = Me
(*S,S*)-**PN-L1c:** R = Ph
(*S,S*)-**PN-L1d:** R = Br

(*R,S*)-**PN-L1b:** R = Me
(*R,S*)-**PN-L1c:** R = Ph
(*R,S*)-**PN-L1d:** R = Br

(*R,S*)-**PN-L2c:** R = Ph

Figure 5-5. PN ligands for asymmetric 1,4-conjugate addition

Table 5-10. Screening of PN-L1a~d and L2c for asymmetric 1,4-conjugate addition of cycloheptenone **5-98**



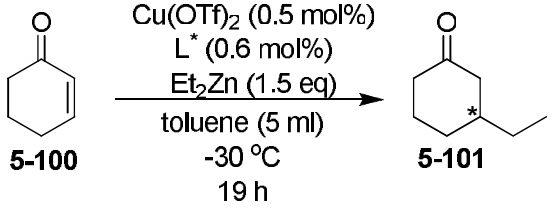
Entry[a,b]	Ligand	Conv. (%)[c]	% ee[d]	Entry[a,b]	Ligand	Conv. (%)[c]	% ee[d]
1	(*S,S*)-**PN-L1b**	89	7 (*S*)	4	(*R,S*)-**PN-L1b**	68	42 (*R*)
2	(*S,S*)-**PN-L1c**	97	75 (*S*)	5	(*R,S*)-**PN-L1c**	97	81 (*R*)
3	(*S,S*)-**PN-L1d**	79	42 (*S*)	6	(*R,S*)-**PN-L1d**	71	59 (*R*)
				7	(*R,S*)-**PN-L2c**	98	79 (*R*)

a. 1 mmol of substrate was used in each entry.
b. 5 mL of solvent was used.
c. The conversion was determined by 1H NMR and GC.
d. %ee was determined by chiral GC (β-Dex 225 column, t_R=12.0 min (*S*)-product, t_R=12.2 min (*R*)-product) for 2-cyclohepten-1-one).

In **Table 5-10**, (*R,S*)-**PN-L1c** gave very good conversion and the best ee among chiral P,N ligands (97% conv. and 81% ee in entry 5) for the asymmetric 1,4-conjugate addition of cyclohepten-1-one. While the substituent on the oxazolie moiety was changed from *i*Pr to Ph which is (*R,S*)-**PN-L2c**, the comparable result was observed (98% conv. and 79% ee in entry 7). Comparing ligands and their diastereomeric pairs (entries 1 and 4, 2 and 5, 3 and 6), (*S,S*) ligands seem to inhibit the ee of the product and (*R,S*) ligands enhance the ee. These results indicated that two moieties of the ligand possessing the same chiralty interfere with each other and the ee of the product decreases by this mismatch.

In **Table 5-11**, (*R,S*)-**PN-L1c** and (*R,S*)-**PN-L2c** gave the best results among chiral P,N ligands for the asymmetric 1,4-conjugate addition of cyclohexen-1-one (**Table 5-11**, entries 3 and 10); > 99% conv. and 68% ee were obtained. However, they are still not as good as the data reported in the literature. Moreover, the mismatch effect of two moieties of the ligand was not clearly found in this case.

Table 5-11. Screening of PN-L1a~d and L2c for asymmetric 1,4-conjugate addition of cyclohexenone **5-100**



Entry[a,b]	Ligand	Conv. (%)[c]	% ee[d]	Entry[a,b]	Ligand	Conv. (%)[c]	% ee[d]
1	(*S,S*)-**PN-L1a**	94	18 (*S*)	5	(*R,S*)-**PN-L1b**	89	10 (*R*)
2	(*S,S*)-**PN-L1b**	88	24 (*S*)	6	(*R,S*)-**PN-L1c**	62	50 (*R*)
3	(*S,S*)-**PN-L1c**	>99	64 (*S*)	7	(*R,S*)-**PN-L1d**	97	46 (*R*)
4	(*S,S*)-**PN-L1d**	87	37 (*S*)	8	(*R,S*)-**PN-L2c**	>99	68 (*R*)

a,b,c,d, Please see the footnotes on Table 5-10.

§ 5.3 Conclusions

So far, a small library of chiral biphenol-based phosphite-oxazoline ligands was successfully synthesized for asymmetric Heck reaction. For asymmetric Intramolecular Heck reactions of carboxamide substrate, these newly synthesized Phosphite-Oxazoline Ligands show good reactivity to catalyze this reaction (26 h, 100 % conversion). However, the regioselectivity and enantioselectivity of products are both unsatisfied so far. (About 2 :1 regio ratio and 31 % ee).

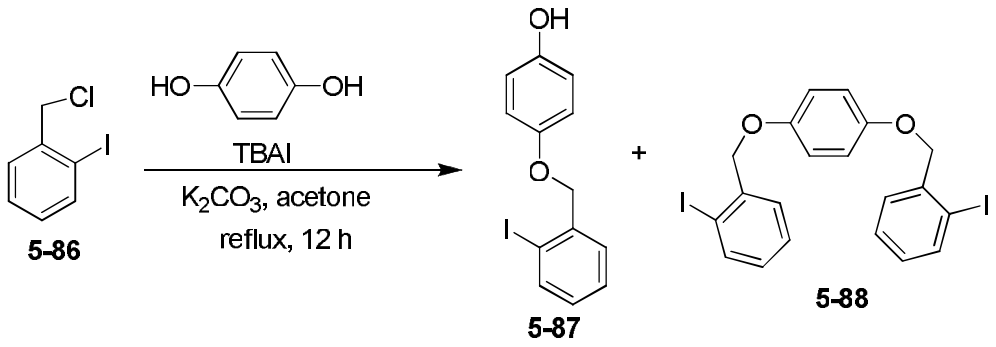
§ 5.4 Experimental section

General Methods: ^{1}H and ^{13}C and ^{31}P NMR were measured on a Varian Inova-500 NMR (500 MHz ^{1}H, and 125 MHz ^{13}C), a Varian Inova-400 NMR (400 MHz ^{1}H; 100 MHz ^{13}C; 162 MHz ^{31}P) or a Varian Gemini-2300 (300 MHz ^{1}H; 75 MHz ^{13}C; 121.5 MHz ^{31}P) spectrometer in a deuterated solvent using residual protons ($CHCl_3$: ^{1}H, 7.26 ppm; ^{13}C, 77.0 ppm. C_6H_6: ^{1}H, 7.15 ppm) as the internal standard or phosphoric acid as the external reference (^{31}P 0.00 ppm). Analytical HPLC in reverse phase was carried out with a Shimadzu LC-2010A HPLC system using a Chiralpak AD-RH analytical column. Melting points were measured on a Thomas Hoover Capillary melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Helmer Model 241 polarimeter. TLC analyses were performed using Merck DC Alufolien 60F254 aluminum pre-coated silica gel plates. Flash column chromatography was carried out using Silicyle Silia*Flash*P60® silica gel (particle size 40–63 μm). High-resolution mass spectrometric analyses were carried out at the Mass Spectrometry Laboratories, University of Illinois Urbana-Champaign, Urbana, IL and ICB&DD at Stony Brook University. Unless otherwise noted all reactions were carried out under argon or nitrogen atmosphere in oven-dried glassware using standard Schlenck techniques.

Materials: Solvents were reagents grade and freshly distilled before use. Tetrahydrofuran (THF) and dichloromethane (DCM) were dried and degassed using an Innovative Technology PureSolvTM solvent purification system. Acetonitrile was distilled from calcium hydride. Anhydrous *N,N*-dimethylformamide (DMF) was purchased from Acros and used without further purification. Other solvents were used without purification. All chemicals and reagents were purchased from Sigma-Aldrich or Fisher Scientific and used without further purification unless

otherwise noted.

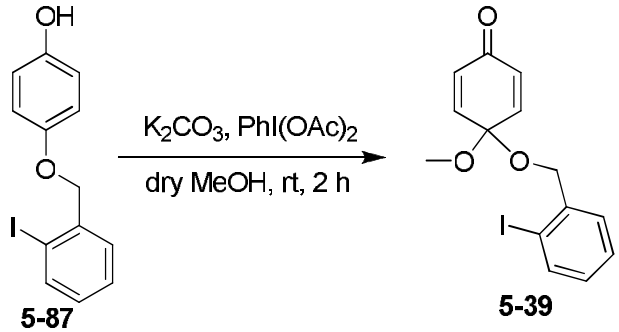
4-(2-Iodo)benzyloxyphenol (5-87)[14]



5-86 **5-87** **5-88**

To a solution of acetone (10 mL), 2-iodobenzyl chloride **5-86** (676 mg, 2.68 mmol), hydroquinone (1.49 g, 13.4 mol), tetrabutylammonium iodide (TBAI) (100 mg, 0.27 mmol) and K_2CO_3 (561 mg, 4.1 mmol) were added and stirred under reflux for 12 h. The reaction mixture was then cooled to room temperature and the salts were removed by filtration. The remaining solution was evaporated under reduced pressure and the residue was redissolved in $CHCl_3$. The insoluble hydroquinone was removed by filtration again. After evaporation of $CHCl_3$, methanol was added to the remaining oil and byproduct **5-88** was precipitated (155 mg, 11 %). After filtration and evaporation, the resulting orange oil was purified by column chromatography on silica gel (hexanes/EtOAc = 10:1-5:1) to give pure **5-87** as an off-white solid (650mg, 74 %): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.60 (s, 1 H), 4.98 (s, 2 H), 6.76-6.78 (m, 2 H), 6.86-6.88 (m, 2 H), 7.02 (td, 1 H, J = 7.5, 1.2 Hz), 7.38 (td, 1 H, J = 7.5, 1.2 Hz), 7.50 (dd, 1 H, J = 7.5, 1.2 Hz), 7.86 (dd, 1 H, J = 7.5, 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 74.7, 97.1, 116.0, 116.1, 128.3, 128.6, 129.4, 139.2, 139.3, 149.9, 152.7. All data are in agreement with the literature values.[14]

4-(2-Iodobenzyloxy)-4-methoxycyclohexa-2,5-dien-2-one (5-39)[14]

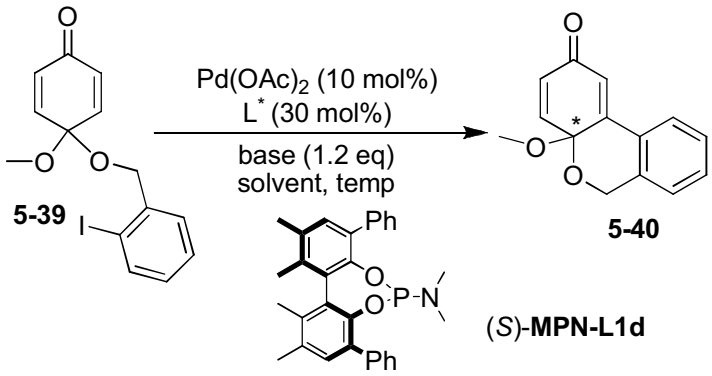


5-87 **5-39**

A mixture of $PhI(OAc)_2$ (500 mg, 1.53 mmol), K_2CO_3 (432 mg, 3.05 mmol) in dry MeOH

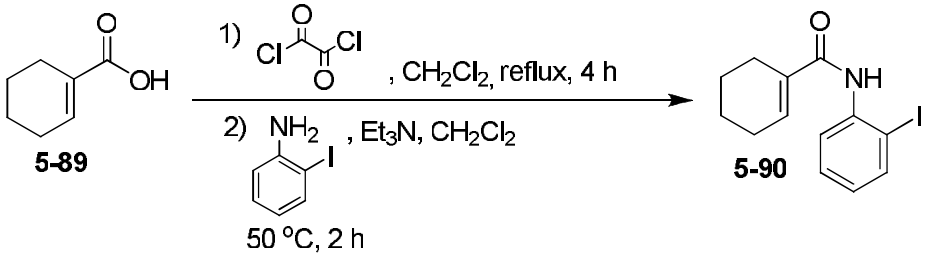
(18 mL) was placed in a flask and flushed with N_2. To this solution was added 4-(2-iodo)benzyloxyphenol **5-87** (400 mg, 1.22 mmol) in MeOH (15 mL) at 0 ^oC over 10 min. Stirring was continued for 2 h and the reaction was quenched with sat. $NaHCO_3$ (15 mL). The mixture was separated and the organic layer was diluted with ether and washed with water and brine, and dried over $MgSO_4$. The drying agent was removed by filtration and the remaining solution was concentrated *in vacuo* to afford crude **5-39**. This crude product was further purified by column chromatography on silica gel (hexanes/EtOAc = 5:1) to give pure **5-39** as a yellow solid (407 mg, 94 %): mp 37-38 ^oC (lit.[14] 35-37 ^oC); ^1H NMR (300 MHz, $CDCl_3$) δ 3.45 (s, 3 H), 4.65 (s, 2 H), 6.29-6.32 (m, 2 H), 6.90-6.94 (m, 2 H), 7.01 (td, 1 H, *J* = 7.5, 1.2 Hz), 7.35 (td, 1 H, *J* = 7.5, 1.2 Hz), 7.43 (dd, 1 H, *J* = 7.5, 1.2 Hz), 7.82 (dd, 1 H, *J* = 7.5, 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 50.8, 68.9, 92.8, 97.3, 128.3, 128.7, 129.4, 130.0, 139.2, 139.8, 143.2, 185.1. All data are in agreement with the reported literature.[14]

A typical procedure for asymmetric Heck reaction of 5-39[14]



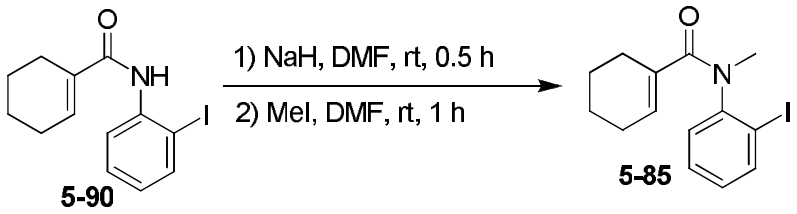
A mixture of $Pd(OAc)_2$ (0.011 mmol) and monophosphoramidite ligand (0.033 mmol) in dry solvent (1 mL) was heated to reflux for 1-2 h. After a clear yellow solution was obtained, a base (0.44 mmol) and dienone **5-39** (0.11 mmol) were added and the reaction mixture was refluxed for 48 h. The solvent was evaporated and the crude product was characterized by ^1H NMR, TLC and LC-MS. However, in every trial, each characterization showed several undesired products which are inconsistent with published results.[14]

***N*-(2-Iodophenyl)-1-cyclohexene-1-carboxamide (5-90)**[8b]



To a solution of 1-cyclohexenecarboxylic acid **5-89** (540 mg, 4.28 mmol) in dry DCM (10 mL) were added few drops of DMF and oxalyl chloride (0.81 mL, 8.63 mmol) in ice bath and the mixture was stirred at reflux for 4 h. The reaction mixture was concentrated to dryness under reduced pressure. To the remaining residue were added 2-iodoaniline (1.12 g, 5.13 mmol) in dry CH_2Cl_2 (6 mL) and dry Et_3N (0.81 mL, 5.82 mmol) ,and the solution was stirred at 50 °C for 2 h. The reaction mixture was diluted with DCM, and then washed with 1N HCl, 5 % NaOH and brine, and dried over $MgSO_4$. The drying agent was removed by filtration and the remaining solution was concentrated *in vacuo* to afford crude **5-90**. This crude product was further purified by column chromatography on silica gel (hexanes/EtOAc = 20:1, 15:1, then 10:1) to give pure **4-90** as a yellow solid (710 mg, 51 %): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.64-1.78 (m, 4 H), 2.24-2.28 (m, 2 H), 2.40-2.44 (m, 2 H), 6.82 (ddd, 1 H, *J* = 8.1, 8.1, 1.2 Hz), 6.89-6.91 (m, 1 H), 7.35 (ddd, 1 H, *J* = 8.1, 8.1, 1.2 Hz), 7.76 (dd, 1 H, *J* = 8.1, 1.2 Hz), 7.84 (br, 1 H), 8.36 (dd, 1 H, *J* = 8.1, 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 22.2, 24.4, 25.7, 89.9, 121.6, 125.6, 129.3, 133.5, 135.6, 138.4, 138.7, 166.2. All data are in agreement with the literature values.[8b]

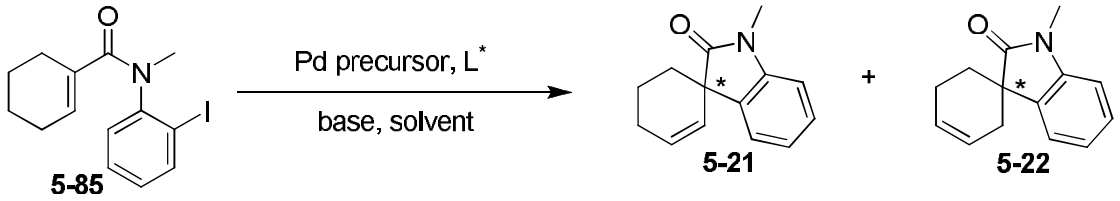
***N*-(2-Iodophenyl)-*N*-methyl-1-cyclohexene-1-carboxamide (5-85)**[8b]



A suspension of *N*-(2-iodophenyl)-1-cyclohexene-1-carboxamide **5-90** (607 mg, 1.85 mmol) and NaH (259 mg, 60 % dispersion in mineral oil, 6.48 mmol) in dry DMF (23 mL) was stirred at room temperature for 30 min. A solution of MeI (0.13 mL, 1.85 mmol) in dry DMF (13 mL) was added to the resulting mixture and the whole solution was stirred at room temperature for another 1 h. Then, the reaction mixture was diluted with ether and washed with brine, dried over

$MgSO_4$. The drying agent was removed by filtration and the remaining solution was concentrated *in vacuo* to afford crude **5-85**. This crude product was further purified by column chromatography on silica gel (hexanes/EtOAc = 5:1) to give pure **5-85** as a white solid (592 mg, 94 %): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36-1.50 (m, 4 H), 1.78-2.15 (m, 4 H), 3.22 (s, 3 H), 5.88 (br, 1 H), 6.97 (ddd, 1 H, *J* = 7.6, 7.6, 1.6 Hz), 7.14 (d, 1 H, *J* = 7.6 Hz), 7.33 (dd, 1 H, *J* = 7.6, 7.6 Hz), 7.86 (dd, 1 H, *J* = 7.6, 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 22.0, 24.9, 25.9, 36.9, 99.1, 128.9, 129.2, 129.3, 132.3, 134.1, 140.0, 172.4. All data are in agreement with the literature values.[8b]

General procedure for asymmetric Heck reaction of 5-85[8b]



Cationic Pathway:

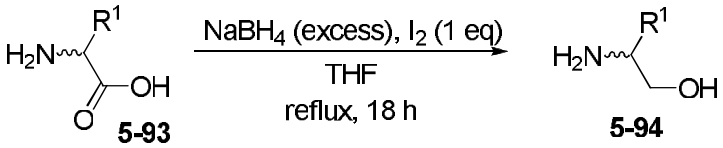
A mixture of $Pd(OAc)_2$ (0.006 mmol), monophosphoramidite ligand (0.018 mmol), and Ag_2CO_3 (0.12 mmol) in dry DMF (0.35 mL) was stirred at room temperature for 30 min. To this mixture was added carboxamide **5-85** (0.06 mmol) in dry DMF (0.40 mL) and the resulting mixture was heated to 80 ^{o}C for 1.5 h. The reaction mixture was diluted with ether and filtrated through Celite to remove salts and excess Ag_2CO_3. The solution was washed with sat. $NaHCO_3$ and brine, and dried over $MgSO_4$. The drying agent was removed by filtration and the remaining solution was concentrated *in vacuo* to afford crude cyclization products **5-21** and **5-22**. The conversion and regioselectivity of **5-21** and **5-22** were determined by ^{1}H NMR. The crude products were then passed through flash silical gel column and submitted to chiral HPLC analysis (OD-H or OJ column, eluent: Hexane:IPA=99.5:0.5) to give enantiopurity of both isomers.

Neutral Pathway:

A mixture of $Pd_2(dba)_3{\cdot}CHCl_3$ (0.003 mmol) and monophosphoramidite ligand (0.018 mmol) in dry DMF (0.35 mL) was stirred at room temperature until the color of solution turned red. To this mixture were added PMP (0.3 mmol) and carboxamide **9** (0.06 mmol) in dry DMF (0.40 mL)

and the resulting mixture was heated to 80 °C for 1.5 h. The reaction mixture was diluted with Et_2O and filtered through Celite to remove salts. The filtrate was washed with sat. $NaHCO_3$ and brine, and dried over $MgSO_4$. The drying agent was removed by filtration and the remaining solution was concentrated *in vacuo* to afford crude cyclization products **5-21** and **5-22**. The conversion and regioselectivity of **5-21** and **5-22** were determined by ^1H NMR. The crude products were then passed through flash silical gel column and submitted to chiral HPLC analysis (OD-H or OJ column, eluent: Hexane:IPA=99.5:0.5) to give enantiopurity of both isomers.

Synthesis of chiral biphenol and oxazoline-based phosphite-oxazoline ligands



***D*-Valinol [(*R*)-5-94a]**[28]

To a solution of *D*-Valine (*R*)-**5-93a** (4.95 g, 47.2 mmol) and $NaBH_4$ (3.89 g, 102.7 mmol) in THF (108 mL) was added slowly a solution of iodine (10.9 g, 47.2 mmol) in THF (40 mL) at 0 °C over 15 min. The reaction mixture was then heated to reflux for another 20 h. After cooling the reaction mixture to room temperature, THF was removed under reduced pressure and 20% KOH (100 mL) was added and stir for 4 h at room temperature. The aqueous mixture was extracted with DCM (100 mLx3). The combined organic layer was washed with brine and dried over $MgSO_4$. The drying agent was removed by filtration and the remaining solution was concentrated *in vacuo* to afford crude oil (*R*)-**5-94a**. This crude product was further purified by distillation (52 °C/0.5 mmHg) to give pure (*R*)-**5-94a** as a white solid (2.50 g, 64%): mp 31-32 °C (lit.[28] 31-32 °C); $[\alpha]_D^{23}$ -17.3 (EtOH, 1.2); ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (m, 6H), 1.57 (m, 1H), 2.00 (br, 3H), 2.55 (m, 1H), 3.29 (dd, *J* = 6.6, 8.1 Hz, 3H), 3.63 (dd, *J* = 3.0, 8.1 Hz, 2H). All data are in agreement with the literature values.[28]

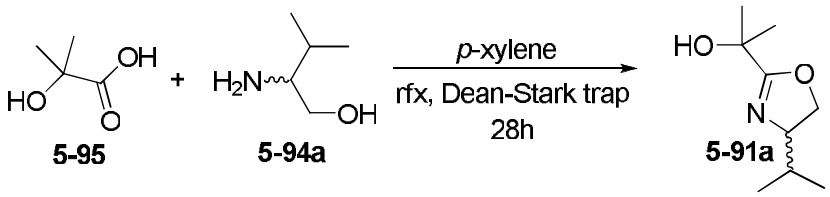
***L*-Valinol [(*S*)-5-94a]**[28]

The compound (*S*)-**5-94a** was synthesized in the same manner as that described for (*R*)-**5-94a**. White solid (61% yield); mp 31-32 °C (lit.[28] 31-32 °C); $[\alpha]_D^{23}$ +14.6 (EtOH, 0.8); ^1H

NMR (300 MHz, $CDCl_3$) δ 0.91 (m, 6H), 1.57 (m, 1H), 2.00 (br, 3H), 2.55 (m, 1H), 3.29 (dd, *J* = 6.6, 8.1 Hz, 3H), 3.63 (dd, *J* = 3.0, 8.1 Hz, 2H). All data are in agreement with the literature values.[28]

L-Phenylglycine [(*S*)-5-94b][28]

The compound (*S*)-**5-94b** was synthesized in the same manner as that described for (*R*)-**5-94a.** The crude oil (*S*)-**5-94b** was recrystallized from toluene to give a pure white solid (70% yield): mp 76-78 °C (lit.[28] 75-76 °C); $[\alpha]_D^{22}$ +30.9 (1N HCl, 1.4); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.79 (br, 3H), 3.52 (m, 1H), 3.68 (m, 1H), 3.99 (m, 1H). All data are in agreement with the literature values.[28]



5-95 **5-94a** **5-91a**

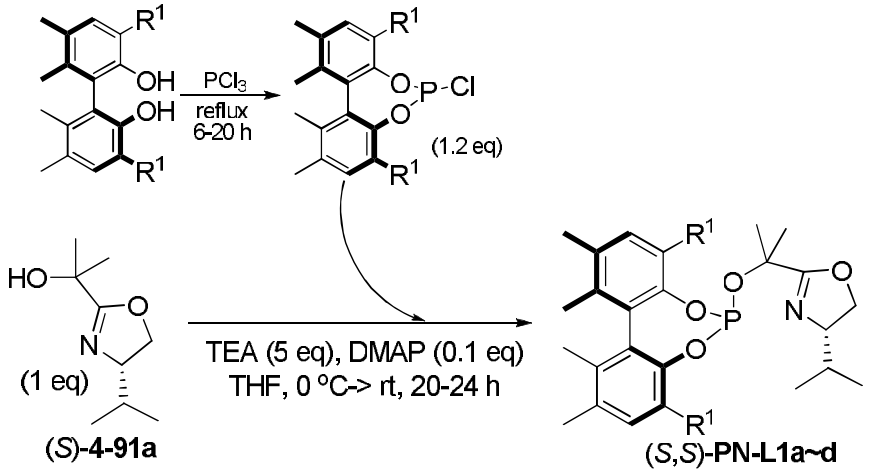
(*S*)-4,5-Dihydro-α,α-dimethyl-4-isopropyloxazole-2-ethanol [(*S*)-5-91a][26]

2-Hydroxy-2-methylpropanoic acid (**5-95**) (2.75 g, 26.4 mmol) and the *L*-valinol **[(*S*)-5-94a]** (2.75 g, 26.7 mmol) were dissolved in *p*-xylene (70 mL) (complete dissolution occurred during heating) and heated to reflux in a Dean-Stark apparatus (oil-bath temp. 180 °C). After water formation stopped (ca. 28-30 h). The mixture was cooled to room temperature and the solvent was removed under reduced pressure. The yellow crude liquid was further purified by flash column chromatography on silica gel (hexanes/EtOAc = 7:3) to afford pure (*S*)-**5-91a** as colorless oil at room temperature (white solid was formed in a refrigerator) (830 mg, 18% yield): $[\alpha]_D^{22}$ -69.1 (DCM, 1.2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 1.42 (s, 6H), 1.72-1.77 (m, 1H), 3.30 (br, 1H), 3.89-3.95 (m, 1H), 4.05-4.11 (m, 1H), 4.29-4.34 (m, 1H). All data are in agreement with the literature values.[26]

(*R*)-4,5-Dihydro-α,α-dimethyl-4-isopropyloxazole-2-ethanol [(*R*)-5-91a][26]

The compound (*R*)-**5-91a** was synthesized in the same manner as that described for (*S*)-**5-91a**. White solid (15% yield): mp 31-32 °C (lit.[26] 31-32 °C); $[\alpha]_D^{23}$ +59.5 (DCM, 0.4); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 1.42 (s, 6H),

1.72-1.77 (m, 1H), 3.30 (br, 1H), 3.89-3.95 (m, 1H), 4.05-4.11 (m, 1H), 4.29-4.34 (m, 1H). All data are in agreement with the literature values.[26]



(+)-{2-[(4'*S*)-(4'-Isopropyloxazolin-2'-yl)]-2-methylethyl[(*S*)-5,5',6,6'-tetramethylbiphenyl-2, 2'-diyl]phosphate [(*S,S*)-PN-L1a]

In a dry 5 mL Schlenk tube under nitrogen, (*S*)-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol (144 mg, 0.590 mmol) was dissolved in PCl_3 (1.0 mL). The mixture was heated to reflux for 6 h. Afterwards the reaction mixture was cooled to room temperature and excess PCl_3 and HCl were removed under reduced pressure. The crude product was characterized by ^{31}P NMR, which showed exclusively one peak at 171.3 ppm for the chlorophosphite; no peak at 210 ppm for PCl_3 was observed. In a second 10 mL round-bottomed flask, DMAP (7.2 mg, 0.052 mmol) and Et_3N (0.34 mL, 2.6 mmol) and (*S*)-4,5-dihydro-α,α-dimethyl-4-isopropyloxazole-2-ethanol [(*S*)-**5-91a**] (88 mg, 0.52 mmol) were dissolved in dry THF (2.5 mL). The chlorophosphite in THF (1 mL) was added slowly over 5 min by syringe at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 20 h. The salt was removed and then THF was evaporated under reduced pressure to give the crude oil (*S,S*)-**PN-L1a**. Further purification by flash column chromatography on silica gel [(Neutralized by 1% NEt_3) hexanes/EtOAc = 15:1-10:1] afforded pure (*S,S*)-**PN-L1a** as a sticky solid (140 mg, 62% yield): $[\alpha]_D^{23}$ +92.3 (DCM, 0.52); ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (d, *J* = 6.8Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H), 1.66 (s, 3H), 1.70 (s, 3H), 1.76-1.84 (m, 1H), 1.99 (s, 3H), 2.01 (s, 3H), 2.27 (s, 3H), 2.28 (s, 3H), 3.97-4.03 (m, 1H), 4.08-4.12 (m, 1H), 4.31-4.36 (m, 1H), 6.87 (d, *J* = 6.0 Hz, 1H), 6.99 (d, *J* = 6.0 Hz, 1H), 7.09 (d, *J* = 6.0 Hz, 1H), 7.12 (d, *J* = 6.0 Hz, 1H); ^{31}P NMR (162 MHz, $CDCl_3$): δ 145.3; HRMS (EI+)

calcd. For $C_{25}H_{32}NO_4P$ $[M]^+$ 441.2069, found 441.2068 (Δ = -0.1 ppm).

(+)-{2-[(4'*S*)-(4'-Isopropyloxazolin-2'-yl)]-2-methylethyl}[(*S*)-3,3'-dimethyl-5,5',6,6'-tetramethylbiphenyl-2,2'-diyl]phosphate [(*S,S*)-PN-L1b]

Compound (*S,S*)-**PN-L1b** was synthesized in the same manner as that described for (*S,S*)-**PN-L1a.** White, foam-like solid (57% yield): $[\alpha]_D^{23}$ +173.3 (DCM, 0.45); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (d, *J* = 6.6 Hz, 3H), 0.95 (d, *J* = 6.6 Hz, 3H), 1.66 (s, 3H), 1.69 (s, 3H), 1.76-1.84 (m, 1H), 1.93 (s, 3H), 1.96 (s, 3H), 2.23 (s, 3H), 2.24 (s, 3H), 2.31 (s, 3H), 2.32 (s, 3H), 3.97-4.12 (m, 2H), 4.28-4.36 (m, 1H), 6.99 (s, 1H), 7.01 (s, 1H); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 140.9; HRMS (EI+) calcd. For $C_{27}H_{36}NO_4P$ $[M]^+$ 469.2382, found 469.2382 (Δ = 0.0 ppm).

(+)-{2-[(4'*S*)-(4'-Isopropyloxazolin-2'-yl)]-2-methylethyl}[(*S*)-3,3'-diphenyl-5,5',6,6'-tetramethylbiphenyl-2,2'-diyl]phosphate [(*S,S*)-PN-L1c]

Compound (*S,S*)-**PN-L1c** was synthesized in the same manner as that described for (*S,S*)-**PN-L1a.** White, foam-like solid (25% yield): $[\alpha]_D^{23}$ +266.7 ($CHCl_3$, 0.3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.69 (d, *J* = 6.6 Hz, 3H), 0.78 (d, *J* = 6.6 Hz, 3H), 0.84 (s, 3H), 1.07 (s, 3H), 1.56-1.64 (m, 1H), 2.07 (s, 3H), 2.11 (s, 3H), 2.33 (s, 3H), 2.35 (s, 3H), 3.60-3.66 (m, 3H), 7.20-7.60 (m, 12H); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 142.4; HRMS (EI+) calcd. For $C_{37}H_{40}NO_4P$ $[M]^+$ 593.2695, found 593.2695 (Δ = 0.0 ppm).

(+)-{2-[(4'*S*)-(4'-Isopropyloxazolin-2'-yl)]-2-methylethyl}[(*S*)-3,3'-dibromo-5,5',6,6'-tetramethylbiphenyl-2,2'-diyl]phosphate [(*S,S*)-PN-L1d]

Compound (*S,S*)-**PN-L1d** was synthesized in the same manner as that described for (*S,S*)-**PN-L1a.** White, foam-like solid (34% yield): $[\alpha]_D^{22}$ +257.9 ($CHCl_3$, 0.4); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (d, *J* = 6.6 Hz, 3H), 0.96 (d, *J* = 6.6 Hz, 3H), 1.64 (s, 3H), 1.80-1.85 (m, 1H), 1.88 (s, 3H), 1.92 (s, 3H), 1.93 (s, 3H), 2.25 (s, 3H), 2.27 (s, 3H), 3.98-4.04 (m, 1H), 4.11-4.16 (m, 1H), 4.33-4.39 (m, 1H), 7.39 (s, 1H), 7.41 (s, 1H); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 143.9; HRMS (EI+) calcd. For $C_{25}H_{30}NO_4Br_2P$ $[M]^+$ 597.0279, found 597.0277 (Δ = -0.3 ppm).

(-)-{2-[(4'*S*)-(4'-Isopropyloxazolin-2'-yl)]-2-methylethyl}[(*R*)-3,3'-dimethyl-5,5',6,6'-tetrame

thylbiphenyl-2,2'-diyl]phosphate [(*R,S*)-PN-L1b]

Compound (*R,S*)-**PN-L1b** was synthesized in the same manner as that described for (*S,S*)-**PN-L1a.** White, foam-like solid (50% yield): $[\alpha]_D^{23}$ -237.5 ($CHCl_3$, 0.4); ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (d, *J* = 6.6 Hz, 3H), 0.95 (d, *J* = 6.6 Hz, 3H), 1.66 (s, 3H), 1.69 (s, 3H), 1.76-1.84 (m, 1H), 1.93 (s, 3H), 1.96 (s, 3H), 2.23 (s, 3H), 2.24 (s, 3H), 2.31 (s, 3H), 2.32 (s, 3H), 3.97-4.12 (m, 2H), 4.28-4.36 (m, 1H), 6.99 (s, 1H), 7.01 (s, 1H); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 141.4; HRMS (EI+) calcd. For $C_{27}H_{36}NO_4P$ $[M]^+$ 469.2382, found 469.2382 (Δ = 0.0 ppm).

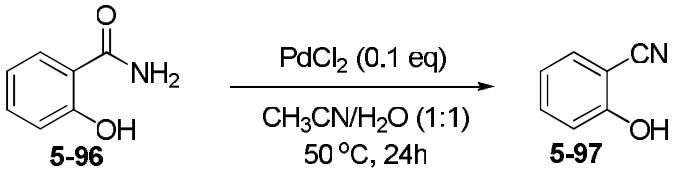
(-)-{2-[(4'*S*)-(4'-Isopropyloxazolin-2'-yl)]-2-methylethyl}[(*R*)-3,3'-diphenyl-5,5',6,6'-tetrame thylbiphenyl-2,2'-diyl]phosphate [(*R,S*)-PN-L1c]

Compound (*R,S*)-**PN-L1c** was synthesized in the same manner as that described for (*S,S*)-**PN-L1a.** White, foam-like solid (46% yield): $[\alpha]_D^{23}$ -120.0 ($CHCl_3$, 0.45); ^1H NMR (300 MHz, $CDCl_3$) δ 0.69 (d, *J* = 6.6 Hz, 3H), 0.78 (d, *J* = 6.6 Hz, 3H), 0.84 (s, 3H), 1.07 (s, 3H), 1.56-1.64 (m, 1H), 2.07 (s, 3H), 2.11 (s, 3H), 2.33 (s, 3H), 2.35 (s, 3H), 3.60-3.66 (m, 3H), 7.20-7.60 (m, 12H); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 142.8; HRMS (EI+) calcd. For $C_{37}H_{40}NO_4P$ $[M]^+$ 593.2695, found 593.2689 (Δ = -0.6 ppm).

(-)-{2-[(4'*S*)-(4'-Isopropyloxazolin-2'-yl)]-2-methylethyl}[(*R*)-3,3'-dibromo-5,5',6,6'-tetramet hylbiphenyl-2,2'-diyl]phosphate [(*R,S*)-PN-L1d]

Compound (*R,S*)-**PN-L1d** was synthesized in the same manner as that described for (*S,S*)-**PN-L1d.** White, foam-like solid (33% yield): $[\alpha]_D^{24}$ -343.8 (DCM, 0.3); ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (d, *J* = 6.6 Hz, 3H), 0.96 (d, *J* = 6.6 Hz, 3H), 1.64 (s, 3H), 1.80-1.85 (m, 1H), 1.88 (s, 3H), 1.92 (s, 3H), 1.93 (s, 3H), 2.25 (s, 3H), 2.27 (s, 3H), 3.98-4.04 (m, 1H), 4.11-4.16 (m, 1H), 4.33-4.39 (m, 1H), 7.39 (s, 1H), 7.41 (s, 1H); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 144.1; HRMS (EI+) calcd. For $C_{25}H_{30}NO_4Br_2P$ $[M]^+$ 597.0279, found 597.0281 (Δ = 0.2 ppm).

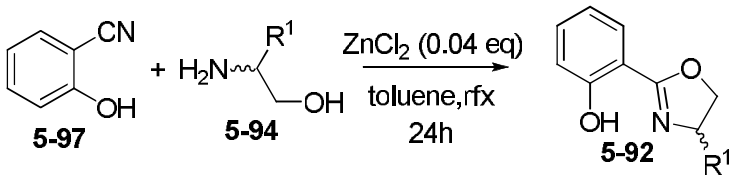
2-Hydroxybenzonitrile (5-97)[21]



5-96 **5-97**

To a suspension of 2-hydroxybenzamide **5-96** (3.01 g, 21.9 mmoli) in a mixture of

water:acetonitrile (1:1, 180 mL) was added $PdCl_2$ (383 mg, 2.19 mmol). The orange suspension was heated at 50°C for 24 h. Acetonitrile was evaporated under reduced pressure and aqueous layer was extracted with DCM (3x). The combined organic layer was washed with brine and dried over $MgSO_4$. The drying agent was removed by filtration and the remaining solution was concentrated *in vacuo* to afford crude solid **5-97**. The yellow crude solid was further purified by flash column chromatography on silica gel (hexanes/EtOAc = 9:1-1:1) to afford pure **5-97** as a white solid (1.72 g, 66% yield): mp 75-77 °C (lit.[21] 75-77 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60 (br, 1H), 6.96-7.03 (m, 2H), 7.45-7.52 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 99.4, 116.3, 116.6, 120.9, 132.9, 134.8, 158.6. All data are in agreement with the literature values.[21]



(*S*)-2-(4-Isopropyl-4,5-dihydrooxazol-2-yl)phenol [(*S*)-5-92a]

2-Hydroxybenzonitrile **5-97** (315 mg, 2.64 mmol), *L*-valinol [(*S*)-**5-94a**] (331 mg, 3.21 mmol), and $ZnCl_2$ (14.4 mg, 0.104 mmol) were placed in a 10 mL round-bottomed flask. Dry toluene (4 mL) was added in the flask. The reaction mixture was then heated to reflux for 24 h. After the reaction mixture was cooled to room temperature, Et_2O was added and the organic layer was washed with water (5x). The organic layer was washed with brine and dried over $MgSO_4$. The drying agent was removed by filtration and the remaining solution was concentrated *in vacuo* to afford crude (*S*)-**5-92a** as yellow oil. Further purification by flash column chromatography on silica gel (hexanes/EtOAc = 9:1) afforded pure (*S*)-**5-92a** as pale yellow oil (449 mg, 83%): $[\alpha]_D^{22}$ -30.8 ($CHCl_3$, 2.3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, *J* = 6.8 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 1.75-1.85 (m, 1H), 4.05-4.15 (m, 2H), 4.40-4.50 (m, 1H), 6.86 (t, *J* = 8.4 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 7.36 (t, *J* = 8.4 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 12.4 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.5, 18.6, 32.9, 69.8, 71.5, 110.6, 116.6, 118.5, 127.9, 133.2, 159.9, 165.0. All data are in agreement with the literature values.

(*R*)-2-(4-Isopropyl-4,5-dihydrooxazol-2-yl)phenol [(*R*)-5-92a]

Compound (*R*)-**5-92a** was synthesized in the same manner as that described for (*S*)-**5-92a.** Pale yellow oil (81% yield): $[\alpha]_D^{22}$ +46.3 ($CHCl_3$, 1.6); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, *J*

= 6.8 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 1.75-1.85 (m, 1H), 4.05-4.15 (m, 2H), 4.40-4.50 (m, 1H), 6.86 (t, *J* = 8.4 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 7.36 (t, *J* = 8.4 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 12.4 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.5, 18.6, 32.9, 69.8, 71.5, 110.6, 116.6, 118.5, 127.9, 133.2, 159.9, 165.0. All data are in agreement with the literature values.

(*S*)-2-(4-Phenyl-4,5-dihydrooxazol-2-yl)phenol [(*S*)-5-92b]

The compound (*S*)-**5-92b** was synthesized in the same manner as that described for (*S*)-**5-92a**. Pale yellow oil (63% yield): $[\alpha]_D^{22}$ +83.0 ($CHCl_3$, 1.1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.24 (t, *J* = 8.4 Hz, 1H), 4.80 (dd, *J* = 8.4, 10.0 Hz, 1H), 5.47 (dd, *J* = 8.4, 10.0 Hz, 1H), 6.91 (t, *J* = 8.0 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 7.29-7.40 (m, 5H), 7.73 (d, *J* = 8.0 Hz, 1H), 12.2 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.8, 73.9, 110.4, 116.8, 118.7, 126.5, 127.8, 128.2, 128.8, 133.6, 141.5, 160.0, 166.3. All data are in agreement with the literature values.

§ 5.5 References

1. Mizoroki, T.; Mori, K.; Ozaki, A., Arylation of Olefin with Aryl Iodide Catalyzed by Palladium. *Bull. Chem. Soc. Jpn.* 1971, *44* (2), 581-581.
2. Heck, R. F.; Nolley, J. P., Palladium-catalyzed vinylic hydrogen substitution reactions with aryl, benzyl, and styryl halides. *J. Org. Chem.* 1972, *37* (14), 2320-2322.
3. (a) Dounay, A. B.; Overman, L. E., The Asymmetric Intramolecular Heck Reaction in Natural Product Total Synthesis. *Chem. Rev.* 2003, *103* (8), 2945-2964; (b) Masakatsu Shibasaki, Erasmus M. V., Takashi Ohshima,, Asymmetric Heck Reaction. *Adv. Synth. Catal.* 2004, *346* (13-15), 1533-1552.
4. Ojima, I., *Catalytic asymmetric synthesis*. 2nd ed.; 2000.
5. Sato, Y.; Sodeoka, M.; Shibasaki, M., Catalytic asymmetric carbon-carbon bond formation: asymmetric synthesis of cis-decalin derivatives by palladium-catalyzed cyclization of prochiral alkenyl iodides. *J. Org. Chem.* 1989, *54* (20), 4738-4739.
6. Carpenter, N. E.; Kucera, D. J.; Overman, L. E., Palladium-catalyzed polyene cyclizations of trienyl triflates. *J. Org. Chem.* 1989, *54* (25), 5846-5848.
7. (a) Shibasaki, M.; Mase, T.; Ikegami, S., The first total syntheses of DELTA-9(12)-Capnellene-8-beta-10.alpha-diol and DELTA-9(12)-capnellene-3-beta-8-beta-10-alpha-triol. *J. Am. Chem. Soc.* 1986, *108* (8), 2090-2091; (b) Ohrai, K.; Kondo, K.; Sodeoka, M.; Shibasaki, M., Effects of Solvents and Additives in the Asymmetric Heck Reaction of Alkenyl Triflates: Catalytic Asymmetric Synthesis of Decalin Derivatives and Determination of the Absolute Stereochemistry of (+)-Vernolepin. *J. Am. Chem. Soc.* 1994, *116* (26), 11737-11748; (c) Sato, Y.; Mori, M.; Shibasaki, M., Asymmetric Heck reaction: A catalytic asymmetric synthesis of the key

intermediate of (−)-oppositol and (−)-prepinnaterpene. *Tetrahedron: Asymmetry* 1995, *6* (3), 757-766.

8. (a) Ashimori, A.; Overman, L. E., Catalytic asymmetric synthesis of quarternary carbon centers. Palladium-catalyzed formation of either enantiomer of spirooxindoles and related spirocyclics using a single enantiomer of a chiral diphosphine ligand. *The Journal of Organic Chemistry* 1992, *57* (17), 4571-4572; (b) Ashimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J., Catalytic Asymmetric Synthesis of Quaternary Carbon Centers. Exploratory Investigations of Intramolecular Heck Reactions of (E)-α,β-Unsaturated 2-Haloanilides and Analogues To Form Enantioenriched Spirocyclic Products. *J. Am. Chem. Soc.* 1998, *120* (26), 6477-6487; (c) Kiely, D.; Guiry, P. J., Palladium complexes of phosphinamine ligands in the intramolecular asymmetric Heck reaction. *J. Organomet. Chem.* 2003, *687* (2), 545-561.
9. Busacca, C. A.; Grossbach, D.; So, R. C.; O'Brie, E. M.; Spinelli, E. M., Probing Electronic Effects in the Asymmetric Heck Reaction with the BIPI Ligands. *Org. Lett.* 2003, *5* (4), 595-598.
10. Kiewel, K.; Tallant, M.; Sulikowski, G. A., Asymmetric Heck cyclization route to indolizidine and azaazulene alkaloids: synthesis of (+)-5-epiindolizidine 167B and indolizidine 223AB. *Tetrahedron Lett.* 2001, *42* (38), 6621-6623.
11. Hart, D. J.; Tsai, Y. M., Stereoselective indolizidine synthesis: preparation of stereoisomers of gephyrotoxin-223AB. *The Journal of Organic Chemistry* 1982, *47* (23), 4403-4409.
12. Yoda, H.; Katoh, H.; Ujihara, Y.; Takabe, K., SmI2-mediated hetero-coupling reaction of lactams with aldehydes; synthesis of indolizidine alkaloids, (−)-δ-coniceine, (+)-5-epiindolizidine 167B and (+)-lentiginosine. *Tetrahedron Lett.* 2001, *42* (13), 2509-2512.
13. Dounay, A. B.; Overman, L. E.; Wrobleski, A. D., Sequential Catalytic Asymmetric Heck−Iminium Ion Cyclization: Enantioselective Total Synthesis of the Strychnos Alkaloid Minfiensine. *J. Am. Chem. Soc.* 2005, *127* (29), 10186-10187.
14. Imbos, R.; Minnaard, A. J.; Feringa, B. L., A Highly Enantioselective Intramolecular Heck Reaction with a Monodentate Ligand. *J. Am. Chem. Soc.* 2001, *124* (2), 184-185.
15. Lautens, M.; Zunic, V., Sequential olefin metathesis-Intramolecular asymmetric Heck reactions in the synthesis of polycycles. *Can. J. Chem.* 2004, *82* (2), 399-407.
16. Lormann, M. E. P.; Nieger, M.; Brase, S., Desymmetrisation of bicyclo[4.4.0]decadienes: A planar-chiral complex proved to be most effective in an asymmetric Heck reaction. *J. Organomet. Chem.* 2006, *691* (10), 2159-2161.
17. Ozawa, F.; Kubo, A.; Hayashi, T., Catalytic asymmetric arylation of 2,3-dihydrofuran with aryl triflates. *J. Am. Chem. Soc.* 1991, *113* (4), 1417-1419.
18. K. K. Hii, Timothy D. W. C., John M. Brown, Andrew Smith, Robert J. Deeth,, The Intermolecular Asymmetric <I>Heck</I> Reaction: Mechanistic and Computational Studies13. *Helv. Chim. Acta* 2001, *84* (10), 3043-3056.
19. Ozawa, F.; Kobatake, Y.; Hayashi, T., Palladium-catalyzed asymmetric alkenylation of cyclic olefins. *Tetrahedron Lett.* 1993, *34* (15), 2505-2508.

20. (a) Hennessy, A. J.; Malone, Y. M.; Guiry, P. J., 2,2-Dimethyl-2,3-dihydrofuran, a new substrate for intermolecular asymmetric Heck reactions. *Tetrahedron Lett.* 1999, *40* (51), 9163-9166; (b) Hennessy, A. J.; Connolly, D. J.; Malone, Y. M.; Guiry, P. J., Intermolecular asymmetric Heck reactions with 2,2-diethyl-2,3-dihydrofuran. *Tetrahedron Lett.* 2000, *41* (40), 7757-7761.

21. Mata, Y.; Dieguez, M.; Pamies, O.; Claver, C., Chiral Phosphite-oxazolines: A New Class of Ligands for Asymmetric Heck Reactions. *Org. Lett.* 2005, *7* (25), 5597-5599.

22. Rubina, M.; Sherrill, W. M.; Rubin, M., Dramatic Stereo- and Enantiodivergency in the Intermolecular Asymmetric Heck Reaction Catalyzed by Palladium Complexes with Cyclopropane-Based PHOX Ligands. *Organometallics* 2008, *27* (24), 6393-6395.

23. (a) Hou, X.-L.; Dong, D. X.; Yuan, K., Synthesis of new chiral benzylically substituted P,N-ligands and their applications in the asymmetric Heck reaction. *Tetrahedron: Asymmetry* 2004, *15* (14), 2189-2191; (b) Wu, W.-Q.; Peng, Q.; Dong, D.-X.; Hou, X.-L.; Wu, Y.-D., A Dramatic Switch of Enantioselectivity in Asymmetric Heck Reaction by Benzylic Substituents of Ligands. *J. Am. Chem. Soc.* 2008, *130* (30), 9717-9725.

24. Koga, Y.; Sodeoka, M.; Shibasaki, M., Palladium-catalyzed asymmetric arylation of 4,7-dihydro-1,3-dioxepin. Catalytic asymmetric synthesis of γ-butyrolactone derivatives. *Tetrahedron Lett.* 1994, *35* (8), 1227-1230.

25. Loiseleur, O.; Hayashi, M.; Schmees, N.; Pfaltz, A., Enantioselective Heck Reactions Catalyzed by Chiral Phosphinooxazoline-Palladium Complexes. *Synthesis* 1997, *1997* (11), 1338-1345.

26. Dieter K. Heldmann, D. S., Catalytic Enantioselective Hydrosilylation of Ketones with Rhodium-Phosphite Complexes Containing a TADDOLate and a Dihydrooxazole Unit. *Helv. Chim. Acta* 1999, *82* (7), 1096-1110.

27. Escher, I. H.; Pfaltz, A., New Chiral Oxazoline-Phosphite Ligands for the Enantioselective Copper-Catalyzed 1,4-Addition of Organozinc Reagents to Enones. *Tetrahedron* 2000, *56* (18), 2879-2888.

28. McKennon, M. J.; Meyers, A. I.; Drauz, K.; Schwarm, M., A convenient reduction of amino acids and their derivatives. *J. Org. Chem.* 1993, *58* (13), 3568-3571.

Chapter 6

Synthesis of Chiral Biphenol-based Phosphoric Acids and their Applications to Asymmetric Organocatalysis

Table of Contents

§ 6.1 Introduction of chiral phosphoric acid for asymmetric organocatalysis

Chiral phosphoric acid derived from chiral BINOL has first been used as an organocatalyst by Akiyama,[1] Uraguchi, and Terada[2] groups independently in 2004. They developed a BINOL-based phosphoric acid library as a novel and easily accessible chiral Brønsted acid catalyst system. After this breakthrough, many groups have explored numerous asymmetric transformations such as Friedel-Crafts reactions,[3] Diels-Alder reactions,[4] and nucleophilic addition of imine[5] utilizing this catalyst system and found that phosphoric acids are actually bifunctional catalysts which possess a Brønsted acidic site and a Lewis basic site (**Figure 6-1**). Moreover, like BINOL or biphenol-based phosphoramidite and diphosphonite ligands that we mentioned in the previous chapters, 3, 3' substituents of BINOL for phosphoric acids are also crucial for controlling enantioselectivity and reactivity due to their steric and electronic properties.

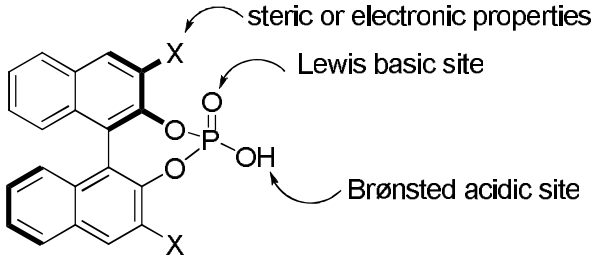


Figure 6-1. Chiral BINOL-based phosphoric acids

In addition to chiral BINOL-based phosphoric acids, several novel phosphoric acids with different backbones have also been reported and proven to be highly efficient for several asymmetric transformations such as Mannich-type reactions and transfer hydrogenations (**Figure 6-2**).[6]

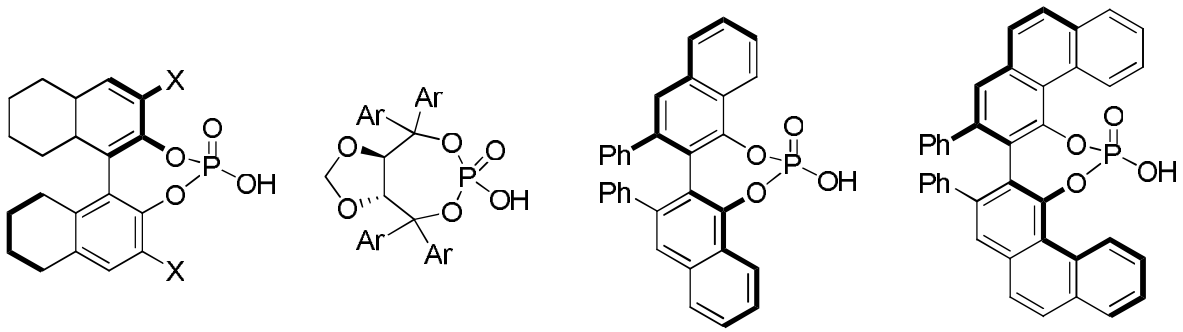


Figure 6-2. Other novel chiral phosphoric acids

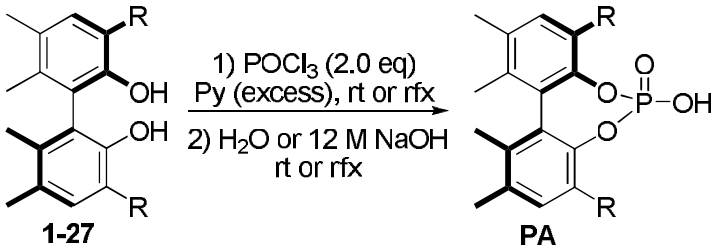
§ 6.2 Results and discussion

Several different biphenol-based phosphorus ligand libraries which gave comparable or even better enantioselectivities comparing to BINOL-based phosphorus ligands have been developed in the Ojima laboratory.[7] As a result, according to previously successful experiences and encouraging results reported by other research groups mentioned above, the development of novel enantiopure biphenol-based phosphoric acids has its significance and is worth to be done.

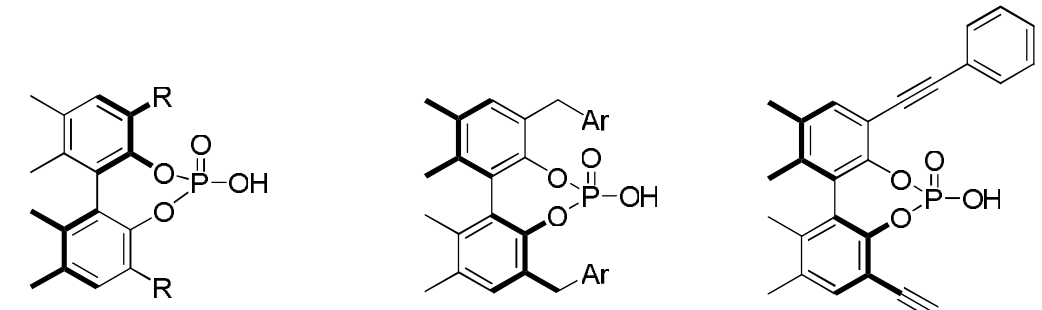
Described here is the synthesis of chiral biphenol-based phosphoric acids with various 3,3' substituents and the evaluation of asymmetric efficacy of these phosphoric acids through the desymmetrization of *meso*-1,3-diones for which BINOL-based phosphoric acids gave up to 92% ee.[8]

§ 6.2.1 Synthesis of chiral biphenol-based phosphoric acids

With various chiral biphenols in hand, a library of chiral bipenol-based phosphoric acids (**Figure 6-3**) can be synthesized according to literature procedures for the synthesis of BINOL-based phosphoric acids with some modifications (**Scheme 6-1**).[2, 9]



Scheme 6-1. General procedure for the synthesis of chiral bipenol-based phosphoric acids



(*R*)-**PA-1a**: R = H
(*R*)-**PA-1b**: R = Me
(*R*)-**PA-1c**: R = Ph
(*R*)-**PA-1d**: R = ^{t}Bu
(*S*)-**PA-1e**: R = 2,4,6-^{i}PrC$_6$H$_2$
(*R*)-**PA-1f**: R = SiPh$_3$

(*S*)-**PA-2a**: Ar = Ph
(*S*)-**PA-2b**: Ar = 3,5-Me$_2$C$_6$H$_3$

(*S*)-**PA-3a**

Figure 6-3. Chiral biphenol-based phosphoric acids

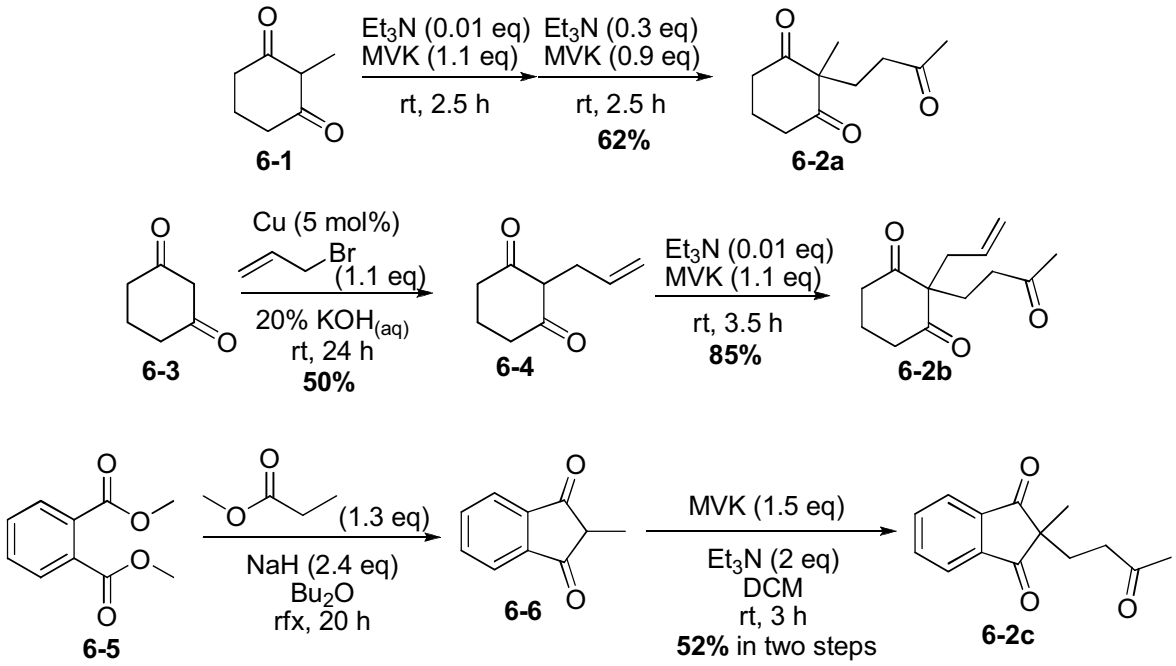
For the synthesis of chiral phosphoric acids bearing less bulky substituents on the 3, 3' positions of the biphenol, i.e. **PA-1a~1c**, **2a**, and **3a**, their corresponding biphenols were first treated with phosphoryl chloride in pyridine at room temperature for several hours and followed by the hydrolysis using water at room temperature to give desired phosphoric acids in 50 to 90% yields after recrystallization in DCM/hexanes. In the syntheses of **PA-1d~1f**, which possessing bulky groups on the 3, 3' positions of the biphenol, harsher conditions are necessary. Reflux temperature was mandatory in the first step to push the reaction to completion. In the hydrolysis step, phosphoric acids **PA-1d** and **1f** form in decent yield using water at 95 ^{o}C for 24 hours. However, the above conditions were not harsh enough to introduce **PA-1e**. In this case, 12 M $NaOH_{(aq)}$ was utilized as the hydrolysis reagent at 60 ^{o}C for 5 hours, and the desired phosphoric acid can be obtained in 80% yield after column chromatography.[2, 9]

§ 6.2.2 The Application of chiral biphenol-based phosphoric acids in the desymmetrization of meso-1,3-diones

§ 6.2.2.1 Synthesis of substrates 6-2a~c

Substrates **6-2a~c** were prepared following literature procedures[8, 10] to evaluate the efficacy of the chiral biphenol-based phosphoric acids (**Scheme 6-2**). According to literature procedure, compound **6-2a** can be obtained in excellent yield starting from 2-methylcyclohexane-1,3-dione **6-1** treated with methyl vinyl ketone in the presence of catalytic amount of triethylamine at room

temperature for 2 hours. However, due to the impurity which is most likely the oligomer of MVK in the original bottle, poor conversion was observed after 2.5 hours at room temperature. As a result, another 0.9 equivalent of distilled MVK and also 0.3 equivalent of triethylamine were added in the reaction mixture and **6-2a** can be obtained in decent yield. For the synthesis of **6-2b**, which is an allylic substituted triketone, cyclohexane-1,3-dione **6-3** was reacted with allyl bromide in the presence of 5 mol% copper powder and 20% $KOH_{(aq)}$ at room temperature for 24 hours to introduce 2-allylcyclohexane-1,3-dione **6-4** which is followed by 1,4 conjugate addition using the procedure described above to give **6-2b** in 85% isolated yield. To introduce **6-2c**, dimethyl phthalate **6-5** was first reacted with methyl propionate in the presence of sodium hydride and dibutyl ether to give desired diketone intermediate **6-6** and followed by 1,4 conjugate addition to give **6-1c** in good yield after two steps.



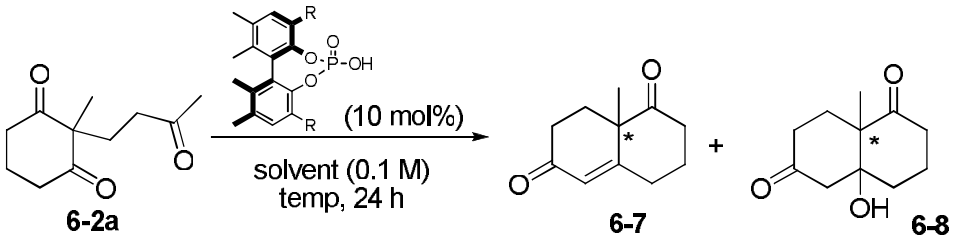
Scheme 6-2. Synthesis of substrates **6-2a** to **6-2c**[8, 10]

§ 6.2.2.2 Evaluation of the efficacy of chiral biphenol-based phosphoric acids in desymmetrization of *meso*-1,3-diones

With substrates **6-2a~c** in hand, the reaction using the library of chiral biphenol-based phosphoric acids were screened and results are summarized in **Table 6-1** to **6-3**. In **Table 6-1**, **PA-1a~e**, **2a** and **3a** were used to screen the desymmetrization of **6-2a**. No obvious trend for the increase of enantioselectivity was observed with the increase of bulkiness of the substituent on

the on the 3, 3' positions of the biphenol (entries 1-4). However, if the substituent of the 3, 3' positions of the biphenol becomes really bulky such as triphenyl silyl and 2,4,6-triisopropyl phenyl groups, the enantioselectivity did increase dramatically and was up to 82% which is comparable to the result from the literature using chiral binol-based phosphoric acid with 2,4,6-triisopropyl phenyl on the the 3, 3' positions of the binol (entries 5-7).[8] The use of benzyl or ethynyl phenyl group did not help much in enantioselectivity (entries 8 and 9). For the solvent screening, hexanes is better than toluene in enantioselectivity but poorer in reactivity (dehydration to non-dehydration product ratio) (entries 1, 5 and 6).

Table 6-1. Screening of **PA** catalysts **1a~f, 2a** and **3a** for the desymmetrization of **6-2a**



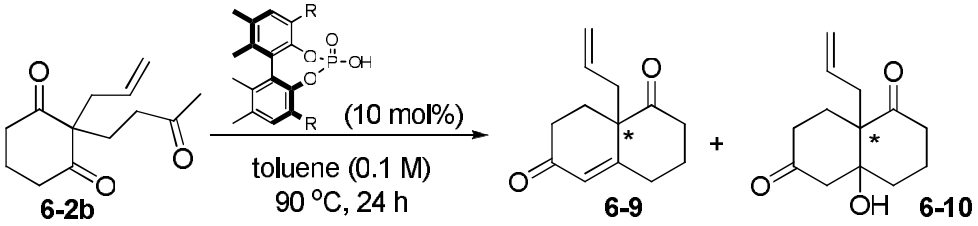
Entry	Catalyst	Temp (^{o}C)	Solvent	Conv. %[a]	**6-7** (%)[a]	%ee
1	(*R*)-**PA-1a**	70	Hexanes	100	80	12.2 (*R*)
2	(*R*)-**PA-1b**	90	Toluene	100	>95	22.4 (*R*)
3	(*R*)-**PA-1c**	90	Toluene	100	>95	*rac*
4	(*R*)-**PA-1d**	90	Toluene	100	>95	21.0 (*R*)
5	(*S*)-**PA-1e**	90	Toluene	100	>95	77.0 (*S*)
6	(*S*)-**PA-1e**	70	Hexanes	100	84	82.2 (*S*)
7	(*R*)-**PA-1f**	90	Toluene	100	>95	51.1 (*R*)
8	(*S*)-**PA-2a**	90	Toluene	100	>95	20.8 (*S*)
9	(*S*)-**PA-3a**	90	Toluene	100	>95	*rac*

[a]Determined by GC-MS.

As shown in **Table 6-2**, **PA-1e**, the best catalyst in **Table 6-1**, was employed for the

desymmetrization of **6-2b** and 77% ee was obtained which is comparable to the result of using **6-2a** as the starting substrate (**Table 6-1**, entry 5 and **Table 6-2**, entry 1). In the study of desymmetrization of **6-2c**, the combination of **PA-1e** and hexanes gave the best result which is also comparable to what they got in the literature (entry 2).[8]

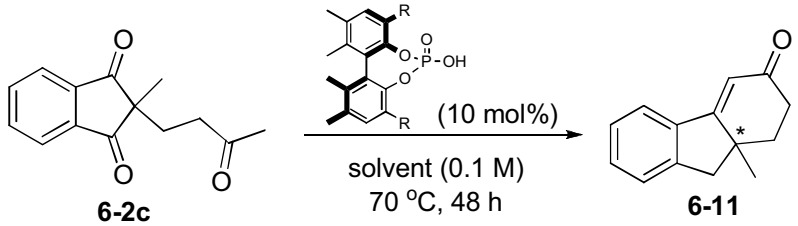
Table 6-2. Use of **PA-1e** for the desymmetrization of **6-2b**



Entry	Catalyst	Conv. %[a]	**6-9** (%)[a]	%ee
1	(*S*)-**PA-1e**	100	>95	77.1 (+)

[a]Determined by GC-MS.

Table 6-3. Screening of **PA** catalysts **1e** and **1f** for the desymmetrization of **6-2c**



Entry	Catalyst	Solvent	Conv. %[a]	**6-11** (%)[a]	%ee
1	(*S*)-**PA-1e**	Toluene	88	>95	90.6 (+)
2	(*S*)-**PA-1e**	Hexanes	100	>95	90.8 (+)
3	(*R*)-**PA-1f**	Toluene	100	>95	71.6 (-)

[a]Determined by GC-MS.

§ 6.3 Conclusions

A library of chiral biphenol-based phosphoric acids was successfully developed and its

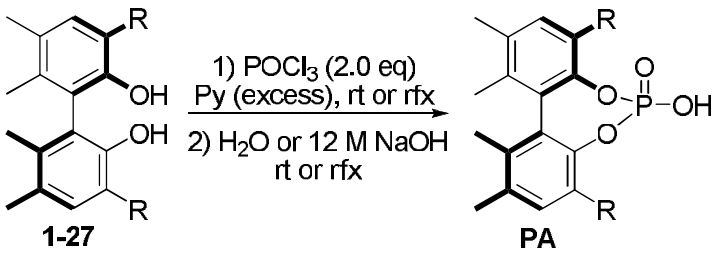
asymmetric efficacy was evaluated by desymmetrization of *meso*-1,3-diones. Among those chiral phosphoric acids, **PA-1e** bearing 2,4,6-triisopropyl phenyl group on the 3,3' positions of the biphenol gave the best ee in all three cases which is comparable to results from the literature using chiral binol-based phosphoric acid with 2,4,6-triisopropyl phenyl on the the 3,3' positions of the binol.[8] Further investigations in other asymmetric organocatalytic reactions catalyzed by our catalyst library are underway in our laboratory.

§ 6.4 Experimental section

General Methods: ^{1}H and ^{13}C and ^{31}P NMR were measured on a Varian Inova-500 NMR (500 MHz ^{1}H, and 125 MHz ^{13}C), a Varian Inova-400 NMR (400 MHz ^{1}H; 100 MHz ^{13}C; 162 MHz ^{31}P) or a Varian Gemini-2300 (300 MHz ^{1}H; 75 MHz ^{13}C; 121.5 MHz ^{31}P) spectrometer in a deuterated solvent using residual protons ($CHCl_3$: ^{1}H, 7.26 ppm; ^{13}C, 77.0 ppm. C_6H_6: ^{1}H, 7.15 ppm) as the internal standard or phosphoric acid as the external reference (^{31}P 0.00 ppm). Analytical HPLC in reverse phase was carried out with a Shimadzu LC-2010A HPLC system using a Chiralpak AD-RH analytical column. Melting points were measured on a Thomas Hoover Capillary melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Helmer Model 241 polarimeter. TLC analyses were performed using Merck DC Alufolien 60F254 aluminum pre-coated silica gel plates. Flash column chromatography was carried out using Silicyle Silia*Flash*P60® silica gel (particle size 40–63 μm). High-resolution mass spectrometric analyses were carried out at Mass Spectrometry Laboratories, University of Illinois Urbana-Champaign, Urbana, IL and ICB&DD at Stony Brook University. Unless otherwise noted all reactions were carried out under argon or nitrogen atmosphere in oven-dried glassware using standard Schlenck techniques.

Materials: Solvents were reagents grade and freshly distilled before use. Tetrahydrofuran (THF) and dichloromethane (DCM) were dried and degassed using an Innovative Technology PureSolvTM solvent purification system. Acetonitrile was distilled from calcium hydride. Anhydrous *N,N*-dimethylformamide (DMF) was purchased from Acros and used without further purification. Other solvents were used without purification. Other chemicals and reagents were purchased from Sigma-Aldrich or Fisher Scientific and used without further purification unless otherwise noted. Chiral biphenols were prepared according to the procedure previously reported by our laboratory.[7]

General procedure for the synthesis of chiral biphenol-based phosphoric acids[2, 9]



Synthesis of (*R*)-**PA-1a~1c**, (*S*)-**2a**, and (*S*)-**3a**

To a stirred solution of chiral biphenol **1-27** (1.00 mmol) in anhydrous pyridine (3 mL) was added $POCl_3$ (183 μL, 2.00 mmol) dropwise at 0 °C. The mixture was warmed up to room temperature and then stirred under room temperature until TLC indicated the completion of the reaction. To the reaction mixture was added water (2 mL) dropwise at room temperature and the reaction was stirred at the same temperature for 18 h. The reaction was quenched with 1 M HCl (10 mL) and the aqueous layer was separated and extracted with Et_2O (15 mL x4). The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the solvent was concentrated *in vacuo* to afford the crude product as a white foam. The recrystallizatoin of the white foam from DCM/hexanes gave pure chiral biphenol-based phosphoric acids as an off-white solid.

(*R*)-**PA-1a**: white solid (42% yield); $[\alpha]_D^{20}$ -96.5 (CH_2Cl_2, *c* 1.13); ^{1}H NMR (400 MHz, *d*-DMSO) δ 1.99 (s, 6H), 2.28 (s, 6H), 7.01 (d, *J* =8.0 Hz, 2H), 7.26 (d, *J* =8.0 Hz, 2H); ^{13}C NMR (100 MHz, *d*-DMSO) 17.2, 19.8, 118.2, 127.2, 130.1, 134.0, 136.9, 147.0; ^{31}P NMR (121.5 Hz, $CDCl_3$) δ 3.95; HRMS (ESI-) calcd. For $C_{16}H_{16}O_4P$ $[M-H]^-$ 303.0786, found 303.0790 (Δ = 1.3 ppm).

(*R*)-**PA-1b**: white solid (71% yield); $[\alpha]_D^{20}$ -173.6 (CH_2Cl_2, *c* 1.06); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93 (s, 6H), 2.20 (s, 6H), 2.31 (s, 6H), 6.95 (s, 2H), 7.61 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 16.2, 17.1, 20.0, 126.9, 127.8, 131.5, 133.1, 134.0, 145.9; ^{31}P NMR (121.5 Hz, $CDCl_3$) δ 3.57; HRMS (ESI-) calcd. For $C_{18}H_{20}O_4P$ $[M-H]^-$ 331.1099, found 331.1105 (Δ = 1.8 ppm).

(*R*)-**PA-1c**: white solid (75% yield); $[\alpha]_D^{20}$ -177.5 (CH_2Cl_2, *c* 1.02); ^{1}H NMR (400 MHz,

$CDCl_3$) δ 2.09 (s, 6H), 2.34 (s, 6H), 7.09-7.21 (m, 8H), 7.40-7.60 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) 17.4, 20.2, 126.9, 127.9, 128.2, 129.5, 131.5, 134.0, 136.5, 137.2, 143.7; ^{31}P NMR (121.5 Hz, $CDCl_3$) δ 1.52; HRMS (ESI-) calcd. For $C_{28}H_{24}O_4P$ $[M-H]^-$ 455.1412, found 455.1419 (Δ = 1.5 ppm).

(*S*)-**PA-2a**: white solid (97% yield); $[\alpha]_D^{20}$ +204.1 (CH_2Cl_2, *c* 1.45); ^1H NMR (400 MHz, $CDCl_3$) δ 1.94 (s, 6H), 2.17 (s, 6H), 3.95 (d, *J* = 12.8 Hz, 2H), 4.28 (d, *J* = 12.8 Hz, 2H), 6.84 (s, 2H), 7.10-7.20 (m, 10H), 7.40 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 17.2, 20.1, 35.4, 125.6, 128.0, 128.1, 129.3, 130.0, 130.9, 133.4, 140.7, 145.5; ^{31}P NMR (121.5 Hz, $CDCl_3$) δ 3.72; HRMS (ESI-) calcd. For $C_{30}H_{28}O_4P$ $[M-H]^-$ 483.1731, found 483.1731 (Δ = 0.0 ppm).

(*S*)-**PA-2b**: light yellow solid (97% yield); $[\alpha]_D^{20}$ +204.1 (CH_2Cl_2, *c* 1.45); ^1H NMR (400 MHz, $CDCl_3$) δ 1.91 (s, 6H), 2.09 (s, 12H), 2.14 (s, 6H), 3.72 (d, *J* = 13.2 Hz, 2H), 4.13 (d, *J* = 13.2 Hz, 2H), 6.52-6.75 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) 17.1, 20.1, 21.1, 34.8, 127.1, 127.2, 128.2, 130.4, 130.6, 132.9, 134.3, 137.3, 140.5, 145.8; ^{31}P NMR (121.5 Hz, $CDCl_3$) δ 2.70. HRMS (ESI-) calcd. For $C_{34}H_{36}O_4P$ $[M-H]^-$ 539.2351, found 539.2354 (Δ = 0.6 ppm).

(*S*)-**PA-3a**: light yellow solid (92% yield); $[\alpha]_D^{20}$ +321.1 (CH_2Cl_2, *c* 1.09); ^1H NMR (400 MHz, $CDCl_3$) δ 1.96 (s, 6H), 2.19 (s, 6H), 7.07-7.11 (m, 5H), 7.27 (s, 2H), 7.30-7.42 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) 17.5, 19.9, 85.6, 92.7, 113.8, 123.2, 126.1, 127.7, 127.9, 128.2, 131.5, 133.1, 133.3, 137.6, 141.0, 144.3, 148.3, 148.4; ^{31}P NMR (121.5 Hz, $CDCl_3$) δ 2.10; HRMS (ESI+) calcd. For $C_{32}H_{24}O_4P$ $[M-H]^-$ 503.1412, found 503.1419 (Δ = 1.4 ppm).

Synthesis of (*R*)-**PA-1d**[9a]

To a stirred solution of a chiral biphenol (354mg, 1.00 mmol) in anhydrous pyridine (3 mL) was added $POCl_3$ (183 μL, 2.00 mmol) dropwise at 0 °C. The mixture was refluxed until TLC indicated the completion of the reaction. To the reaction mixture was added water (2 mL) dropwise at room temperature and the resulting mixture was stirred at 95 °C for 24 h. The reaction was quenched with 1 M HCl (10 mL) and the aqueous layer was separated and extracted with Et_2O (15 mL x4). The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the solvent was concentrated

in vacuo to afford the crude product as a white solid. The recrystallizatoin of the white solid in hot acetic acid gave pure (*R*)-**PA-1d** as a white needle crystal (230 mg, 55%): $[\alpha]_D^{20}$ -87.7 (CH_2Cl_2, *c* 1.06); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 18H), 1.83 (s, 6H), 2.25 (s, 6H), 7.21 (s, 2H); ^{31}P NMR (121.5 Hz, $CDCl_3$) δ 0.84. All data are in agreement with the literature value.[9a]

Synthesis of (*S*)-**PA-1e**

To a stirred solution of chiral biphenol (328mg, 0.507 mmol) in anhydrous pyridine (3 mL) was added $POCl_3$ (140 μL, 1.52 mmol) dropwise at 0 ^{o}C. The mixture was refluxed until TLC indicated the completion of the reaction. To the reaction mixture was added 12M NaOH (0.5 mL) dropwise at room temperature and the resulting mixture was stirred at 60 ^{o}C for 5 h. The reaction was quenched with 1M HCl (20 mL) and the aqueous layer was separated and extracted with Et_2O (15 mL x4). The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the solvent was concentrated *in vacuo* to afford the crude product as a white solid. Further purification by flash column chromatography on silica gel (DCM/MeOH = 20:1-10:1) afforded pure (*S*)-**PA-1e** as a white solid (289 mg, 80% yield): $[\alpha]_D^{20}$ +53.2 (CH_2Cl_2, *c* 1.24); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79-0.85 (m, 12H), 0.97 (d, *J* = 6.6 Hz, 6H), 1.07 (d, *J* = 6.6 Hz, 2H), 1.08-1.25 (m, 12H), 2.10 (s, 6H), 2.32 (s, 6H), 2.48-2.58 (m, 4H), 2.76-2.85 (m, 2H), 6.88 (s, 2H), 6.93 (s, 2H), 7.01 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 17.3, 20.2, 22.8, 23.1, 23.9, 24.1, 24.8, 26.4, 30.4, 30.5, 34.2, 119.9, 120.8, 128.1, 128.4, 128.5, 129.1, 132.0, 132.1, 132.9, 136.3, 147.0, 147.6, 147.7; ^{31}P NMR (121.5 Hz, $CDCl_3$) δ 1.49; HRMS (ESI-) calcd. For $C_{46}H_{60}O_4P$ $[M-H]^-$ 707.4235, found 707.4236 (Δ = 0.1 ppm).

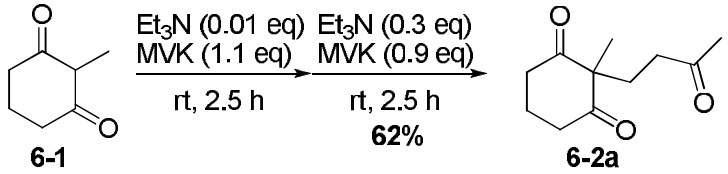
Synthesis of (*R*)-**PA-1f**

To a stirred solution of chiral biphenol (363mg, 0.48 mmol) in anhydrous pyridine (1.5 mL) and DMAP (117 mg, 0.96 mmol) was added $POCl_3$ (90 μL, 0.96 mmol) dropwise at 0 ^{o}C. The mixture was refluxed until TLC indicated the completion of the reaction. To the reaction mixture was added water (8 mL) dropwise at room temperature and the resulting mixture was refluxed for 24 h. The reaction was quenched with 1M HCl (10 mL) and the aqueous layer was separated and extracted with Et_2O (15 mL x4). The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the solvent was

concentrated *in vacuo* to afford the crude product as a white solid. The solid was washed with cold CH_2Cl_2 gave pure (*R*)-**PA-1f** as a white crystal (280 mg, 71%): $[\alpha]_D^{20}$ -162.2 (MeOH, *c* 0.37); ^{1}H NMR (300 MHz, *d*-DMSO) δ 1.97 (s, 18H), 2.16 (s, 6H), 5.75 (brs, 1H), 7.09 (s, 2H), 7.30-7.37 (m, 18H), 7.39-7.46 (m, 12H); ^{13}C NMR (100 MHz, *d*-DMSO) δ 17.1, 19.8, 121.5, 121.6, 127.6, 127.8, 129.4, 132.7, 134.2, 136.1, 138.5, 139.7, 152.2, 152.3; ^{31}P NMR (121.5 Hz, *d*-DMSO) δ 2.76. HRMS (ESI-) calcd. For $C_{52}H_{44}O_4PSi_2$ $[M-H]^-$ 819.2516, found 819.2520 (Δ = 0.5 ppm).

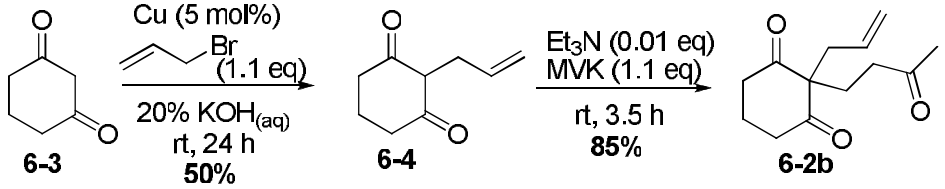
Synthesis of substrates 6-2a~2c[8, 10]

2-Methyl-2-(3-oxobutyl)cyclohexane-1,3-dione (6-2a)



To a stirred solution of 2-methylcyclohexane-1,3-dione **6-1** (3.80 g, 30.1 mmol) and methyl vinyl ketone (2.71 mL, 33.1 mmol) was added a catalytic amount of NEt_3 (1 mol%) at room temperature. The mixture was stirred under room temperature for 2.5 h. However, the reaction did not go well as indicated by TLC. Thus, another 0.3 equiv. of NEt_3 and 0.9 equiv. of distilled methyl vinyl ketone were added to the reaction mixture at room temperature. After stirring for another 2.5 h at room temperature, volatile components were removed under reduced pressure to give crude brown oil **6-2a**. Further purification by flash column chromatography on silica gel (hexanes/EtOAc = 3:1-1:1) afforded pure **6-2a** as colorless oil (3.64 g, 62% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (s, 3H), 1.87-2.09 (m, 4H), 2.09 (s, 3H), 2.31-2.36 (m, 2H), 2.57-2.77 (m, 4H). All data are in agreement with the literature values.[10]

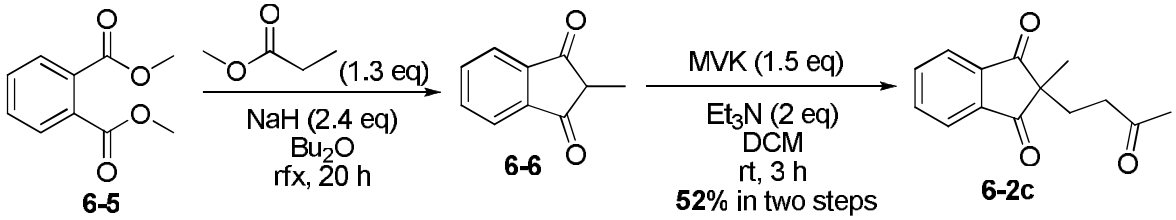
2-Allyl-2-(3-oxobutyl)cyclohexane-1,3-dione (6-2b)



To a stirred solution of cyclohexane-1,3-dione (**6-3**) (2.25 g, 20.1 mmol) and allyl bromide (1.55 g, 22.1 mmol) in 20% $KOH_{(aq)}$ was added a catalytic amount of copper powder (5 mol%) at room temperature. The mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with Et_2O (50 mL) and the resulting precipitate was removed by filtration. The aqueous layer was separated and extracted with Et_2O (50 mL x3). The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the solvent was concentrated *in vacuo* to afford the crude product as a brown solid. The recrystallization of the brown solid in toluene gave pure allyl substituted diketone **6-4** as an off-white solid (1.51 g, 50% yield).

To a solution of the off-white solid in distilled methyl vinyl ketone (1.1 equiv.) was added NEt_3 (1 mol%). The reaction mixture was stirred at room temperature for 3.5 h and then volatile components were removed under reduced pressure to give crude brown oil **6-2b**. Further purification by flash column chromatography on silica gel (hexanes/EtOAc=3:1-1:1) afforded pure **6-2b** as colorless oil (1.25 g, 85% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.97 (quint, J = 6.6 Hz, 2H), 2.05 (t, J = 7.2 Hz, 2H), 2.10 (s, 3H), 2.34 (t, J = 7.2 Hz, 2H), 2.49 (d, J = 7.5 Hz, 2H), 2.52-2.70 (m, 4H), 5.03 (m, 2H), 5.51-5.60 (m, 2H). All data are in agreement with the literature values.[10]

2-Methyl-2-(3-oxobutyl)-1H-indene-1,3(2H)-dione (6-2c)

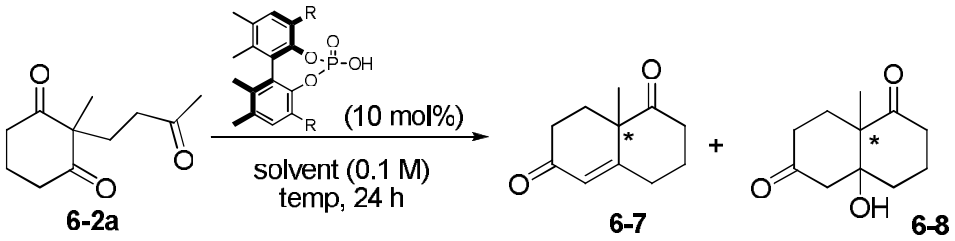


To a suspension of NaH (494 mg, 12.4 mmol) in Bu_2O (10 mL) were added dimethyl phthalate **6-5** (2.00 g, 10.3 mmol) and methyl propionate (1.18 g, 13.4 mmol) at room temperature. The mixture was refluxed for 2 h and then cooled to room temperature. To the

reaction mixture was added another 1.2 equiv. of NaH and the resulting mixture was refluxed for another 14 h. The reaction was quenched with 1M HCl (15 mL) and the aqueous layer was separated and extracted with Et_2O (15 mL x4). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The drying agent was removed by filtration and the solvent was concentrated *in vacuo* to afford the crude product **6-6** as yellow oil.

To a solution of crude **6-6** and distilled methyl vinyl ketone (1.5 equiv.) in DCM was added NEt_3 (2.0 equiv.). The reaction mixture was stirred at room temperature for 3 h and then volatile components were removed under reduced pressure to give crude yellow oil **6-2c**. Further purification by flash column chromatography on silica gel (hexanes/EtOAc = 10:1-4:1) afforded pure **6-2c** as yellow oil (1.23 g, 52% yield for two steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (s, 3H), 2.04-2.06 (m, 2H), 2.07 (s, 3H), 2.35-2.40 (m, 2H), 7.84-7.90 (m, 2H), 7.95-7.99 (m, 2H). All data are in agreement with the literature values.[8]

General procedure for the desymmetrization of *meso*-1,3-Diones.



Typical procedure is described for the reaction of **6-2a** to afford Wieland–Miescher ketone, (*S*)-**6-7**: A mixture of **6-2a** (19.6 mg, 0.100 mmol), and (*S*)-**PA-1e** (7.1 mg, 10 mol%) was placed in a 15 mL Schlenck tube. After purging the tube with nitrogen, toluene (1 mL) was added to the mixture, and the solution was stirred at 90 ^{o}C for 24 h. The conversion and the ratio of **6-7** to **6-8** were determined by GC-MS. The volatile solvent was removed under reduced pressure to give crude yellow oil (*S*)-**6-7**. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc = 10:1→5:1) afforded (*S*)-**6-7** as colorless oil (12 mg, 75% yield). The pure product was then subjected to chiral HPLC analysis, using a Chiralcel OD-H column (Hexanes/IPA = 96/4, 0.6 mL/min), which indicated that the enantiopurity of the product (*S*)-**5-2** was 77.0% ee. The *S* configuration was assigned by comparison of the HPLC trace in the literature.[8]

§ 6.5 References

1. Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K., Enantioselective Mannich-Type Reaction Catalyzed by a Chiral Brønsted Acid. *Angew. Chem., Int. Ed.* **2004,** *43* (12), 1566-1568.

2. Uraguchi, D.; Terada, M., Chiral Brønsted Acid-Catalyzed Direct Mannich Reactions via Electrophilic Activation. *J. Am. Chem. Soc.* **2004,** *126* (17), 5356-5357.

3. (a) Uraguchi, D.; Sorimachi, K.; Terada, M., Organocatalytic Asymmetric Aza-Friedel−Crafts Alkylation of Furan. *J. Am. Chem. Soc.* **2004,** *126* (38), 11804-11805; (b) Jia, Y.-X.; Zhong, J.; Zhu, S.-F.; Zhang, C.-M.; Zhou, Q.-L., Chiral Brønsted Acid Catalyzed Enantioselective Friedel–Crafts Reaction of Indoles and α-Aryl Enamides: Construction of Quaternary Carbon Atoms. *Angew. Chem., Int. Ed.* **2007,** *46* (29), 5565-5567; (c) Kang, Q.; Zhao, Z.-A.; You, S.-L., Highly Enantioselective Friedel−Crafts Reaction of Indoles with Imines by a Chiral Phosphoric Acid. *J. Am. Chem. Soc.* **2007,** *129* (6), 1484-1485; (d) Seayad, J.; Seayad, A. M.; List, B., Catalytic Asymmetric Pictet−Spengler Reaction. *J. Am. Chem. Soc.* **2006,** *128* (4), 1086-1087.

4. (a) Itoh, J.; Fuchibe, K.; Akiyama, T., Chiral Brønsted Acid Catalyzed Enantioselective Aza-Diels–Alder Reaction of Brassard's Diene with Imines. *Angew. Chem., Int. Ed.* **2006,** *45* (29), 4796-4798; (b) Akiyama, T.; Morita, H.; Fuchibe, K., Chiral Brønsted Acid-Catalyzed Inverse Electron-Demand Aza Diels−Alder Reaction. *J. Am. Chem. Soc.* **2006,** *128* (40), 13070-13071.

5. Guo, Q.-X.; Liu, H.; Guo, C.; Luo, S.-W.; Gu, Y.; Gong, L.-Z., Chiral Brønsted Acid-Catalyzed Direct Asymmetric Mannich Reaction. *J. Am. Chem. Soc.* **2007,** *129* (13), 3790-3791.

6. (a) Akiyama, T.; Saitoh, Y.; Morita, H.; Fuchibe, K., Enantioselective Mannich-Type Reaction Catalyzed by a Chiral Brønsted Acid Derived from TADDOL. *Adv. Synth. Catal.* **2005,** *347* (11-13), 1523-1526; (b) Rowland, G. B.; Zhang, H.; Rowland, E. B.; Chennamadhavuni, S.; Wang, Y.; Antilla, J. C., Brønsted Acid-Catalyzed Imine Amidation. *J. Am. Chem. Soc.* **2005,** *127* (45), 15696-15697.

7. (a) Mori, M.; Nakanishi, M.; Kajishima, D.; Sato, Y., A Novel and General Synthetic Pathway to Strychnos Indole Alkaloids: Total Syntheses of (−)-Tubifoline, (−)-Dehydrotubifoline, and (−)-Strychnine Using Palladium-Catalyzed Asymmetric Allylic Substitution. *J. Am. Chem. Soc.* **2003,** *125* (32), 9801-9807; (b) Choi, H.; Hua, Z.; Ojima, I., Highly Enantioselective Copper-Catalyzed Conjugate Addition of Diethylzinc to Nitroalkenes. *Org. Lett.* **2004,** *6* (16), 2689-2691.

8. Mori, K.; Katoh, T.; Suzuki, T.; Noji, T.; Yamanaka, M.; Akiyama, T., Chiral Phosphoric Acid Catalyzed Desymmetrization of meso-1,3-Diones: Asymmetric Synthesis of Chiral Cyclohexenones. *Angew. Chem., Int. Ed.* **2009,** *48* (51), 9652-9654.

9. (a) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C., Enantioselective Organocatalytic Reductive Amination. *J. Am. Chem. Soc.* **2005,** *128* (1), 84-86; (b) Alexander, J. B.; La, D. S.; Cefalo, D. R.; Hoveyda, A. H.; Schrock, R. R., Catalytic Enantioselective Ring-Closing Metathesis by a Chiral Biphen−Mo Complex. *J. Am. Chem. Soc.* **1998,** *120* (16), 4041-4042; (c) Liu, W.-J.; Chen, X.-H.; Gong, L.-Z., Direct Assembly of Aldehydes, Amino Esters, and Anilines into Chiral Imidazolidines via Brønsted Acid

Catalyzed Asymmetric 1,3-Dipolar Cycloadditions. *Org. Lett.* **2008,** *10* (23), 5357-5360.

10. Bradshaw, B.; Etxebarría-Jardi, G.; Bonjoch, J.; Viózquez, S. F.; Guillena, G.; Nájera, C., Efficient Solvent-Free Robinson Annulation Protocols for the Highly Enantioselective Synthesis of the Wieland–Miescher Ketone and Analogues. *Adv. Synth. Catal.* **2009,** *351* (14-15), 2482-2490.

Chapter 7

Formation of 5-7-5 Fused Tricyclic γ-Lactams via Rh(I)-Catalyzed [2+2+2+1] Cycloaddition and CO-SiCaT Reaction of Enediynes with Carbon Monoxide

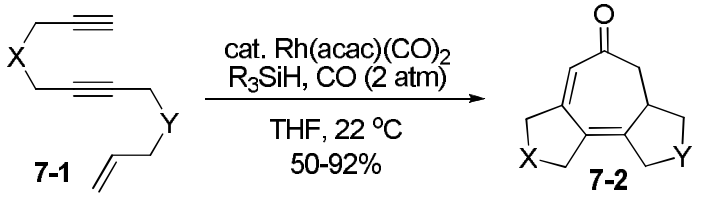
Table of Contents

§ 7.1. Introduction

Transition metal-catalyzed carbocyclization and cycloadditions are among the most efficient types of reactions to access complex polycyclic skeletons.[1] Recent advances of higher order cycloaddition reactions include [2+2+2+1][2], [4+2+2][3], [5+1+2+1][4], [3+3+1][5], [5+2+1][6], and [2+2+2+2][7] processes. Linear, unsaturated starting materials can be transformed into complex polycyclic systems *via* any of these higher order processes. This proves useful in rapid access to the cores of a number of natural products and natural product-like derivatives from acyclic precursors.[6c, 8]

In the Ojima laboratory, a series of Rh(I)-catalyzed, silicon initiated carbocyclizations and carbonylative carbocyclizations as well as the Rh(I)-catalyzed [2+2+2+1] cycloaddition for the formation of polycyclic compounds using linear eneynes, diynes, triynes and enediynes as substrates have been developed.[1a, 2, 9] Among them, enediyne type substrates have been the most extensively studied in recent years to give the desired tricyclic and tetracyclic products.[2, 9c]

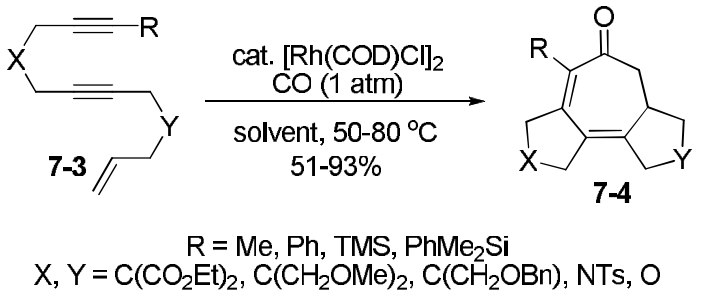
In 2000, the first example for the formation of 5-7-5 tricyclic products **7-2** using dodeca-1-en-6,11-diynes **7-1** was reported by the Ojima group *via* silylcarbocyclization (CO-SiCaT) (**Scheme 7-1**).[9c] However, these CO-SiCaT reactions only went smoothly with substrates having terminal alkyne moieties. None of the desired product was formed using enediyne substrates with substituted alkyne moieties under CO-SiCaT reaction condition.



X, Y = $C(CO_2Et)_2$, $C(CH_2OMe)_2$, $C(CH_2OBn)$, NTs, O

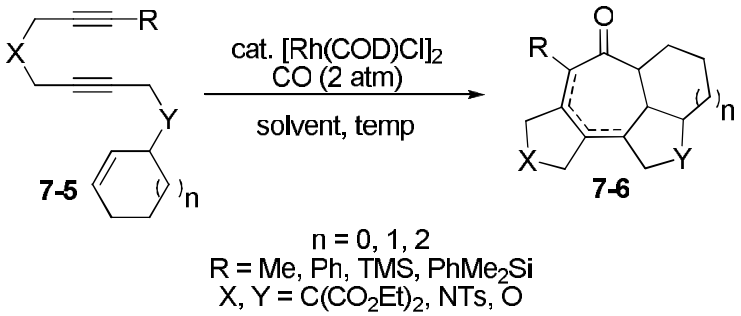
Scheme 7-1. Rh(I)-catalyzed CO-SiCaT reaction of dodeca-1-en-6,11-diynes **7-1**

After further study, the Ojima laboratory found that the 5-7-5 fused ring system can be easily introduced from enediyne substrates with substituted alkyne moieties through Rh(I)-catalyzed [2+2+2+1] cycloaddition without the addition of hydrosilane (**Scheme 7-2**).[2a, b]



Scheme 7-2. Rh(I)-catalyzed [2+2+2+1] cycloaddition reaction of 1-substituted dodec-11-ene-1,6-diynes **7-3**

Recently, the scope of the enediyne substrates has been extended for the formation of 5-7-n-5 tetracyclic fused ring systems *via* Rh(I)-catalyzed [2+2+2+1] cycloaddition. A number of 3-(nona-3,8-diynyl)-1-cycloalkene derivatives **7-5** were synthesized and subjected to the cycloaddition reaction to afford the corresponding tetracyclic fused products and their regioisomers in good to excellent yields (**Scheme 7-3**).[2c]

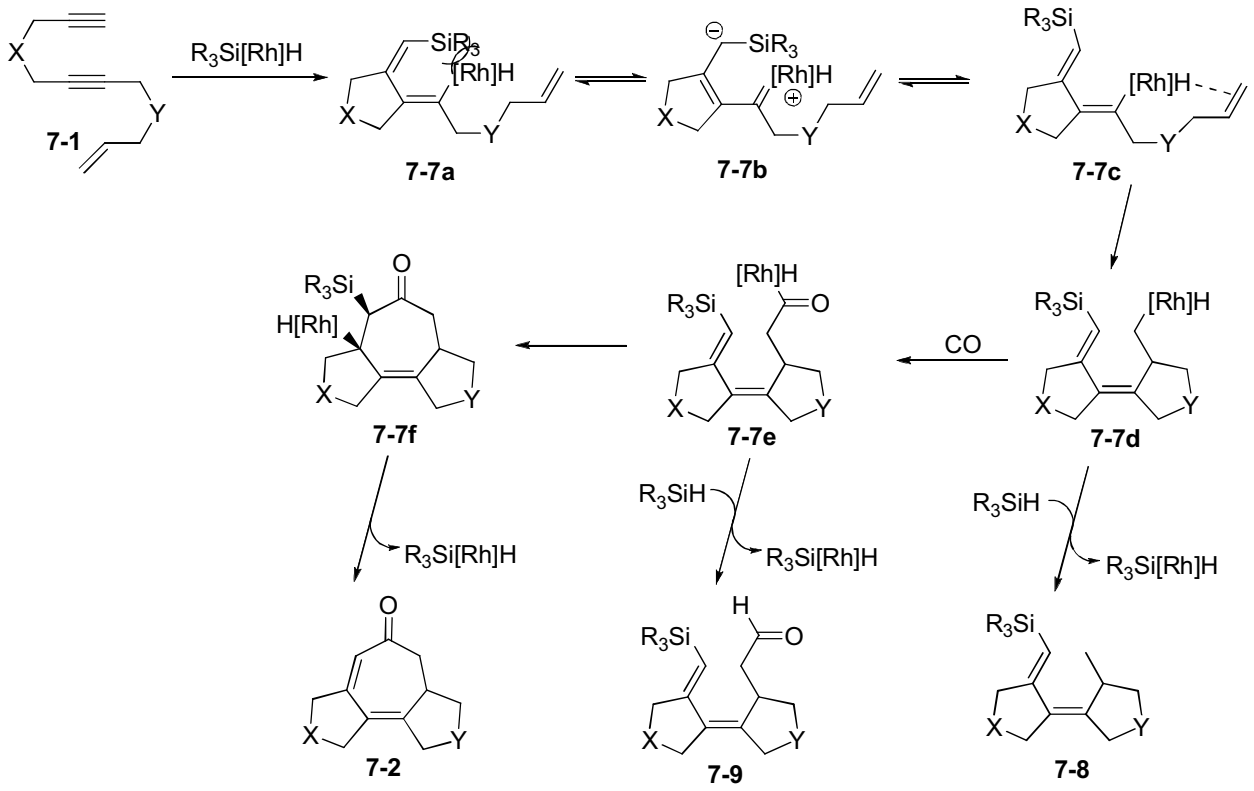


Scheme 7-3. Rh(I)-catalyzed [2+2+2+1] cycloaddition reaction of 3-(nona-3,8-diynyl)-1-cycloalkene derivatives **7-5**

Although the similar fused-ring products can be accessed *via* the CO-SiCaT and [2+2+2+1] cycloaddition reactions, their mechanisms are fundamentally different. The plausible mechanisms of two typical processes are illustrated in **Schemes 7-4** and **7-5**.[2b] The general mechanism of Rh(I)-catalyzed CO-SiCaT reaction of the enediyne begins with the insertion of the terminal alkyne moiety into the Si-Rh bond of the hydrosilane-Rh oxidative complex. Carbocyclization then takes place to give intermediate **7-7a** which isomerizes to **7-7c** *via* **7-7b** through the Ojima-Crabtree mechanism due to the steric hindrance between silane and [Rh]H. Intermediate **7-7c** can undergo the second carbocyclization to afford **7-7d**. At this stage, CO insertion to **7-7d** and reductive elimination of **7-7d** can compete to give different products. Reductive elimination of **7-7d** assisted by the hydrosilane gives **7-8** as the product and regenerate

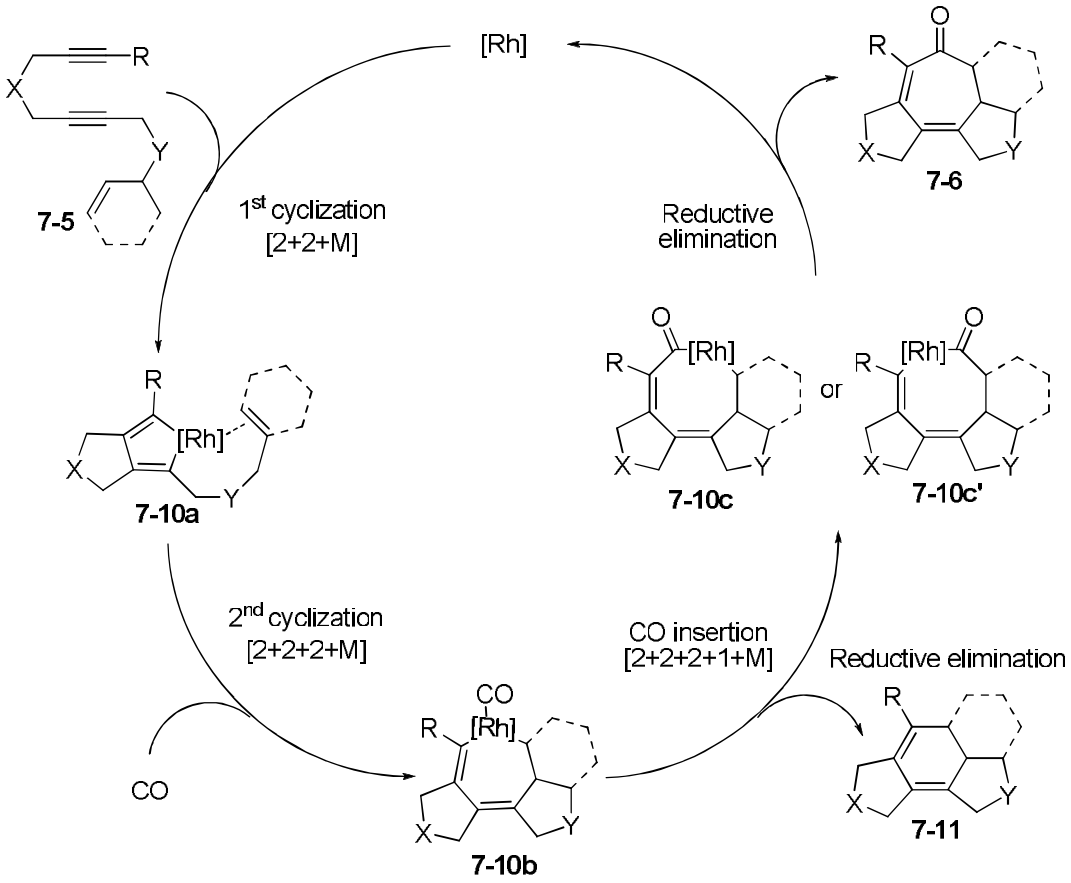
hydrosilane-Rh active species to complete the catalytic cycle. On the other hand, the insertion of CO into Rh-C bond introduces acyl-[Rh]H intermediate **7-7e**. The corresponding aldehyde **7-9** can be obtained by reductive elimination of **7-7e**. To afford the most desired 5-7-5 tricyclic fused product, the carbocyclization of **7-7e** should occur to give tricyclic intermediate **7-7f** which possesses the silane and rhodium species in syn positions. Because of the *syn* conformation, β-silyl elimination is able to happen to give the tricyclic product **7-2**.

It is worthy of note that the amount of hydrosilane and reaction concentration easily control the product selectivity. When stoichiometric or excess amount of hydrosilane and high reaction concentration are used, products **7-8** and **7-9** are obtained as major products due to the bimolecular process during the reductive elimination step (intermolecular reaction). On the other hand, tricyclic product **7-2** can be synthesized as the major product under the substoichiometric amount of hydrosilane and dilute concentration because the unimolecular process during the β-silyl elimination step (intramolecular reaction) is involved in the reaction mechanism. Furthermore, by using a catalytic amount of hydrosilane and high dilution conditions, product **7-2** can be obtained exclusively with excellent yield.[2b]



Scheme 7-4. The proposed mechanism Rh(I)-catalyzed CO-SiCaT reaction of enediyne

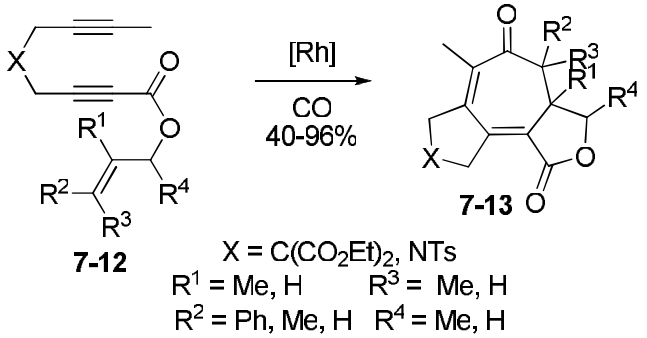
Scheme 7-5 shows the proposed mechanism of Rh(I)-catalyzed [2+2+2+1] cycloaddition reaction of enediynes. It includes; (i) the formation of metallacycle **7-10a** ([2+2+M]) by the oxidative cyclization of the diyne moiety into the active Rh catalyst species; (ii) the formation of fused 5-7-n-5 rhodacycle **7-10b** ([2+2+2+M]) by the insertion of the olefin moiety into the Rh-C bond followed by CO coordination to the metal; (iii) the formation of 5-8-n-5 rhodacycle **7-10c** or **7-10c'** ([2+2+2+1+M]) by the migratory insertion of CO into the Rh-C bond; and (iv) the production of the [2+2+2+1] cycloadduct **7-6** by reductive elimination and the regeneration of the active Rh catalyst species for the next catalytic cycle. If no CO insertion occurs at step (iii), the [2+2+2] cycloadduct **7-11** can be obtained by reductive elimination from the 5-7-n-5 rhodacycle **7-10b**.



Scheme 7-5. The proposed mechanism Rh(I)-catalyzed [2+2+2+1] cycloaddition reaction of enediyne

Very recently, 5-7-5 fused tricyclic γ-lactones were also obtained *via* the Rh(I)-catalyzed [2+2+2+1] cycloaddition from the corresponding enediyne substrates in good to excellent yields

(**Scheme 7-6**).[10] Because of these successful results, as part of the ongoing studies of the Rh(I)-catalyzed [2+2+2+1] cycloaddition, the synthesis of enediyne substrates with the incorporation of an amide moiety for the formation of 5-7-5 fused tricyclic γ-lactams has been explored. If this methodology can be applied to the γ-lactam synthesis as well, it will become a more powerful tool for the synthesis of natural products and natural product-like derivatives.

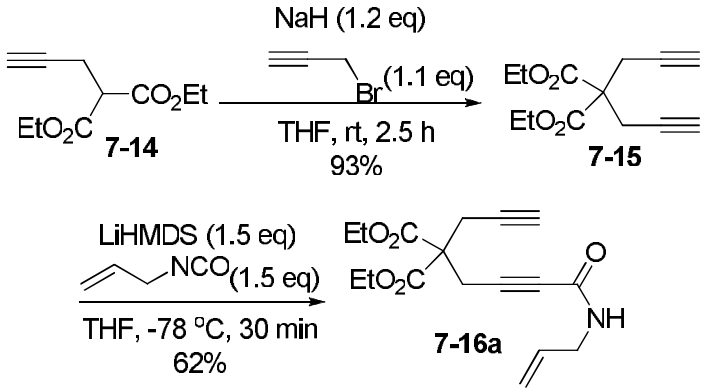


Scheme 7-6. [2+2+2+1] Cycloaddition of 1-substituted dodec-11-ene-8-oxo-1,6-diynes **7-12**

§ 7.2. Result and discussion

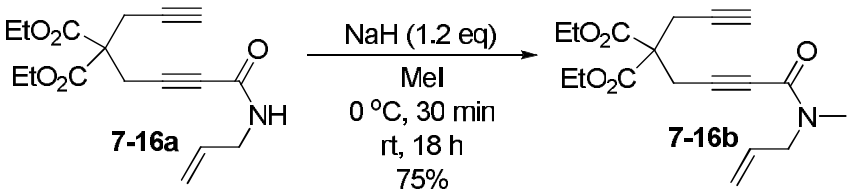
§ 7.2.1. Synthesis of 1,3-diethyl 2-{3-[(prop-2-en-1-yl)carbamoyl]prop-2-yn-1-yl}-2-(prop-2-yn-1-yl)propanedioate and its derivative

The synthesis of 1,3-diethyl 2-{3-[(prop-2-en-1-yl)carbamoyl]prop-2-yn-1-yl}-2-(prop-2-yn-1-yl)propanedioate **7-16a** first underwent the coupling of propynyl diethylmalonate **7-14** with propargyl bromide in the presence of NaH in THF to obtain the desired dipropynyl diethylmalonate **7-15** in 93% yield (**Scheme 7-7**).[10] Another coupling of **7-15** with allyl chloroformate in the presence of LiHMDS afforded the desired enediyne derivative **7-16a** in 62% isolated yield (**Scheme 7-7**).



Scheme 7-7. Synthesis of enediyne substrate **7-16a**

To extend the substrate scope, **7-16a** with *N*-methyl substituted group, **7-16b**, was also synthesized by using methyl iodide as the methylating reagent and solvent in the presence of NaH (**Scheme 7-8**).



Scheme 7-8. Synthesis of enediyne substrate **7-16b**

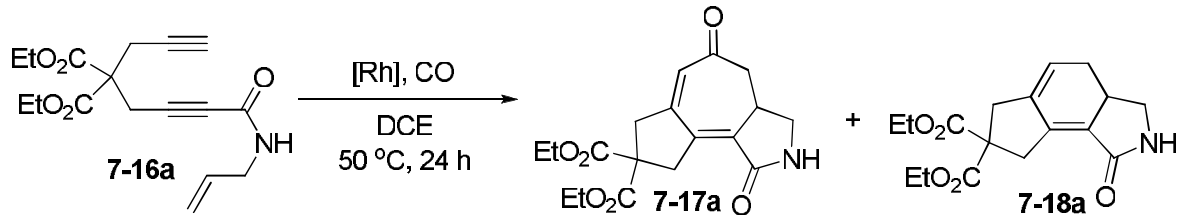
§ 7.2.2. Optimization of Rh(I)-catalyzed [2+2+2+1] cycloaddition reaction of enediyne 7-16a

With the enediyne substrates in hand, the Rh(I)-catalyzed [2+2+2+1] cycloaddition was investigated to find out the optimized condition (**Table 7-1**). First, enediyne **7-16a** was reacted with 5 mol% $[Rh(COD)Cl]_2$ and 2 atm of CO in DCE (0.05 M) at 50 ^oC to afford the desired [2+2+2+1] and [2+2+2] products. Analysis of the crude reaction mixture by HPLC indicated a clean reaction with two major peaks (**Table 7-1,** entry 1). Further analysis by LC-MS showed molecular masses consistent with the desired [2+2+2+1] product **7-17a** and [2+2+2] product **7-18a**. Since the two cycloaddition products have different absorption coefficients, each compound must be isolated to determine each coefficient which can be further used to determine the product selectivity by HPLC. However, both products have the same R_f value in any solvent combination and could not be separated by column chromatography. Fortunately, the products were able to be separated according to analytical HPLC analysis, and prep-HPLC enabled us to isolate each of them with excellent purity. In addition, to achieve the best accuracy in the determination of product selectivity by HPLC, the UV spectrum of each product is necessary to find out the most appropriate working wavelength for HPLC and 303 nm was found to be the best wavelength to give the most accurate estimation of product distribution.

After setting the method to determine the product ratio by HPLC, the optimization studies of concentration effect were investigated (**Table 7-1**). When the reaction was ran in DCE at a substrate concentration of 0.05 M and 2 atm CO at 50 ^oC for 24 h in the autoclave, 100% conversion and 81:19 product selectivity favoring the carbonylated product **7-17a** were obtained (entry 1). Decrease in selectivity for the carbonylated product **7-17a** was noted under more

concentrated condition (entry 2) due to the lower quantity of CO in the reaction mixture. Based on this logic, the reaction should be selective towards the carbonylated product **7-17a** under more dilute conditions and it indeed gave the result as expected but with some significant impurities based on HPLC analysis (entry 3). Thus, the reaction concentration at 0.05 M was selected for the further optimization.

Table 7-1. Effect of concentration on [2+2+2+1] cycloaddition of enediyne **7-16a** with CO



Entry[a]	Conc. (M)	Conv. (%)[b]	**7-17a**:**7-18a**[b]
1	0.05	100	81:19
2	0.1	100	66:34
3	0.025	100	Messy mixture

[a]All reactions were run using $[Rh(COD)Cl]_2$ (5.0 mol%) in DCE at 50 °C for 24 h under $CO_{(g)}$ (2 atm).
[b]Determined by HPLC using Proteo reverse phase column.

Next, a number of rhodium catalysts were screened for the [2+2+2+1] cycloaddition of enediyne **7-16a** with CO using the best reaction condition to date mentioned in **Table 7-1** (**Table 7-2**). When $[Rh(CO)_2Cl]_2$ was used as the catalyst, a decrease of the [2+2+2+1] product was observed, as determined by calibrated HPLC data (i.e. 81:19 vs. 73:27) (**Table 7-**2, entries 1 and 2). In addition to using rhodium dimer complex as the catalyst, catalysts with the mono rhodium, $Rh(acac)(CO)_2$, and the cationic rhodium complex, $[Rh(COD)_2]SbF_6$ were also employed for this reaction. Surprisingly, the [2+2+2+1] product **7-17a** was not obtained using $Rh(acac)(CO)_2$ as the catalyst, as the [2+2+2] product **7-18a** was obtained exclusively (entry 3). On the other hand, the reaction using $[Rh(COD)_2]SbF_6$ as the catalyst resulted in high selectivity towards the carbonylated product **7-17a**; however, the reaction mixture was very messy according to HPLC

analysis. To conclude, the effect of rhodium dimer precursor, $[Rh(COD)Cl]_2$, is still the most appropriate catalyst and was utilized for the further optimization.

Table 7-2. Screening of different Rh(I) species for the [2+2+2+1] cycloaddition of enediyne **7-16a** with CO

Entry[a]	Catalyst (mol%)	Conv. (%)[b]	**7-17a**:**7-18a**[b]
1	$[Rh(COD)Cl]_2$ (5)	100	81:19
2	$[Rh(CO)_2Cl]_2$ (5)	100	73:27
3	$Rh(acac)(CO)_2$ (10)	100	**7-18a** only
4	$[Rh(COD)_2]SbF_6$ (10)	100	Messy mixture

[a]All reactions were run using Rh catalyst (10.0 mol%) in DCE [0.05] at 50 °C for 24 h under $CO_{(g)}$ (2 atm).
[b]Determined by HPLC using Proteo reverse phase column.

Since the goal was to increase the selectivity towards the carbonylated product **7-17a**, the screening of different CO pressures was performed (**Table 7-3**). As shown in **Table 7-**3, increasing the pressure of CO from 2 atm to 3 atm gave the worse selectivity compared to that obtained when the CO pressure was 2 atm (entries 1 and 2). Also, higher CO pressure (6 atm) was explored in this reaction, but resulting in lower product ratio compared to the result at 3 atm of CO (entry 3). Based on above results, lower CO pressure gave better product selectivity. Therefore, 1 atm of CO was used to prove the proposed trend. Indeed, the reaction at 1 atm of CO afforded a bit better product selectivity than that at 2 atm of CO (entries 1 and 4). In addition, bubbling CO at ambient pressure has been shown to increase [2+2+2+1] product selectivity for [2+2+2+1] cycloaddition of other enediyne substrates. Thus, the reaction under CO bubbling was ran and gave the best result so far (i.e. 88:12) (entry 5).

The solvent effect was also studied to further optimize the product selectivity. When the reaction was run in toluene, at 1 atm of CO bubbling and 50 °C in 0.05 M substrate concentration, a significant decrease in product ratio of the [2+2+2+1] product **7-17a** to [2+2+2] product **7-18a** was noted by calibrated HPLC analysis (i.e. 88:12 vs. 70:30) (**Table 7-4**, entries 1 and 2). Because trifluoroethanol (TFE) has been shown to be an effective solvent in cyclocarbonylation reactions of other enediyne substrates,[2c] performing the reaction in TFE was done and afforded

very similar results to that in DCE (entries 1 and 3). With two good solvent candidates in hand, different co-solvent ratios of these two were investigated to evaluate their influence on the product selectivity. Thus far, only two co-solvent ratios were ran and a mixture of DCE and TFE (1 : 1) gave the best product selectivity (i.e. 94:6) favoring the [2+2+2+1] product **7-18** (entries 4 and 5).

Table 7-3. Effect of CO pressure on [2+2+2+1] cycloaddition of enediyne **7-16a** with CO

Entry[a]	CO (atm)	Conv. (%)[b]	**7-17a**:**7-18a**[b]
1	2	100	81:19
2	3	100	59:41
3	6	100	47:53
4	1	100	83:17
5	1 (bubble CO)	100	88:12

[a]All reactions were run using $[Rh(COD)Cl]_2$ (5.0 mol%) in DCE [0.05] at 50 °C for 24 h under $CO_{(g)}$.
[b]Determined by HPLC using Proteo reverse phase column.

Table 7-4. Solvent effect on [2+2+2+1] cycloaddition of enediyne **7-16** with CO

Entry[a]	Solvent	Conv. (%)[b]	**7-17a**:**7-18a**[b]
1	DCE	100	88:12
2	toluene	100	70:30
3	TFE	100	91:9
4	DCE/TFE 4/1	100	93:7
5	DCE/TFE 1/1	100	94:6

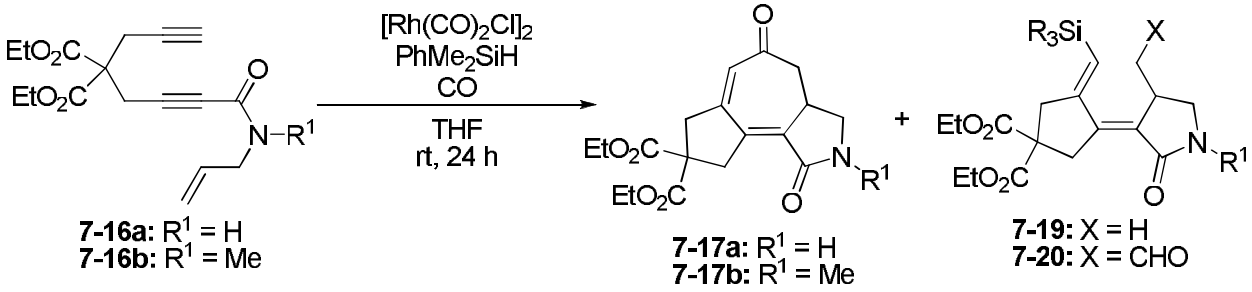
[a]All reactions were run using $[Rh(COD)Cl]_2$ (5.0 mol%) in the solvent [0.05] with $CO_{(g)}$ bubbling (1 atm) at 50 °C for 24 h.
[b]Determined by HPLC using Proteo reverse phase column.

§ 7.2.3. Rh(I)-catalyzed CO-SiCaT reaction of enediynes 7-16a and 7-16b

As mentioned above, because the reaction condition to obtain exclusive product selectivity was not found and the separation of two desired products was still impossible using column chromatography, the Rh(I)-catalyzed CO-SiCaT reaction of enediyne **7-16** with hydrosilane was studied as well to determine if the carbonylated product can be obtained exclusively or if multiple products can at least be separated using standard purification techiques.

Enediynes **7-16a** and **7-16b** were subnjected to the CO-SiCaT reaction (**Table 7-5**). When enediyne **7-16a** (R^1 = H) was used as the substrate, the reaction almost did not proceed after 24 h under the reaction condition described in **Table 7-5** (entry 1). Fortunately, enediyne **7-16b** (R^1 = Me) was able to give the desired 5-7-5 tricyclic carbonylated product **7-17b** in 71% isolated yield based on 70% conversion under the same CO-SiCaT reaction condition with no observation of other possible byproducts (**7-19** and **7-20**) by TLC (entry 2). The poor reactivity of enediyne **7-16a** may due to the formation of rhodium-imidate complex by rhodium catalyzed N-H activation prior to the formation of rhodium-silicon active species for CO-SiCaT reaction. This rhodium-imidate complex then traps the hydrosilane by strong Si-O bond and completely poisons the CO-SiCaT reaction.

Table 7-5. Rh(I)-catalyzed CO-SiCaT reaction of enediyne **7-16a** and **7-16b** with PhMe2SiH



7-16a: R^1 = H
7-16b: R^1 = Me

7-17a: R^1 = H
7-17b: R^1 = Me

7-19: X = H
7-20: X = CHO

Entry[a]	R^1	Conv. (%)[b]	Yield of **7-17**
1	H	<5	n.d.
2	Me	70	50 (71)[b]

[a]All reactions were run using $[Rh(CO)_2Cl]_2$ (1.0 mol%) in THF [0.015] at 22 °C for 24 h under $CO_{(g)}$ (2 atm).
[b]Determined by HPLC using Proteo reverse phase column.

§ 7.3. Conclusions

Enediynes containing amide moieties were successfully synthesized in moderate to good yields for the formation of 5-7-5 fused tricyclic γ-lactam products. Rh(I)-catalyzed [2+2+2+1] cycloaddition of **7-16a** has been applied and optimized to afford the desired 5-7-5 fused tricyclic γ-lactam **7-17a** and 5-6-5 fused tricyclic γ-lactam **7-18a** in 94:6 product selectivity. However, the separation of two desired products is impossible using flash column chromatography. Therefore, the Rh(I)-catalyzed CO-SiCaT reaction of enediyne with hydrosilane was studied and found to give the corresponding 5-7-5 fused tricyclic γ-lactam **7-17b** exclusively when enediyne **7-16b** was used as the substrate. Both methodologies are useful and promising to introduce desired fused tricyclic γ-lactams. Further studies on the synthesis of other enediyne derivatives for these methodologies are underway in our laboratory.

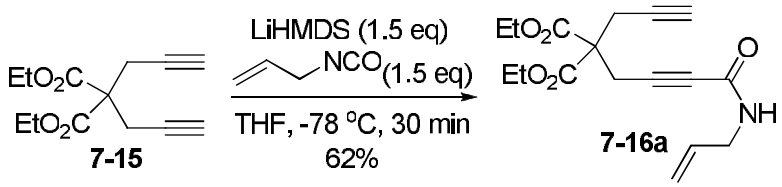
§ 7.4. Experimental section

General Methods: ^{1}H and ^{13}C and ^{31}P NMR were measured on a Varian Inova-500 NMR (500 MHz ^{1}H, and 125 MHz ^{13}C), a Varian Inova-400 NMR (400 MHz ^{1}H; 100 MHz ^{13}C; 162 MHz ^{31}P) or a Varian Gemini-2300 (300 MHz ^{1}H; 75 MHz ^{13}C; 121.5 MHz ^{31}P) spectrometer in a deuterated solvent using residual protons ($CHCl_3$: ^{1}H, 7.26 ppm; ^{13}C, 77.0 ppm. C_6H_6: ^{1}H, 7.15 ppm) as the internal standard or phosphoric acid as the external reference (^{31}P 0.00 ppm). Analytical HPLC in reverse phase was carried out with a Shimadzu LC-2010A HPLC system using a Chiralpak AD-RH analytical column. Melting points were measured on a Thomas Hoover Capillary melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Helmer Model 241 polarimeter. TLC analyses were performed using Merck DC Alufolien 60F254 aluminum pre-coated silica gel plates. Flash column chromatography was carried out using Silicyle Silia*Flash*P60® silica gel (particle size 40–63 μm). High-resolution mass spectrometric analyses were carried out at the Mass Spectrometry Laboratories, University of Illinois Urbana-Champaign, Urbana, IL and ICB&DD at Stony Brook University. Unless otherwise noted all reactions were carried out under argon or nitrogen atmosphere in oven-dried glassware using standard Schlenck techniques.

Materials: Solvents were reagents grade and freshly distilled before use. Tetrahydrofuran (THF), diethyl ether (Et_2O) and dichloromethane (DCM) were dried and degassed using an Innovative

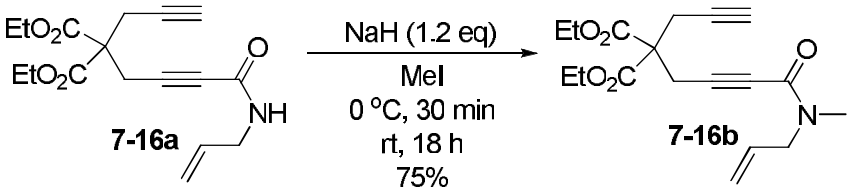
Technology PureSolvTM solvent purification system. Acetonitrile was distilled from calcium hydride. Anhydrous *N,N*-dimethylformamide (DMF) was purchased from Acros and used without further purification. Other solvents were used without purification. Other chemicals and reagents were purchased from Sigma-Aldrich or Fisher Scientific and used without further purification unless otherwise noted.

Synthesis of Diethyl 2-{3-[(prop-2-en-1-yl)carbamoyl]prop-2-yn-1-yl}-2-(prop-2-yn-1-yl)propanedioate (7-16a)



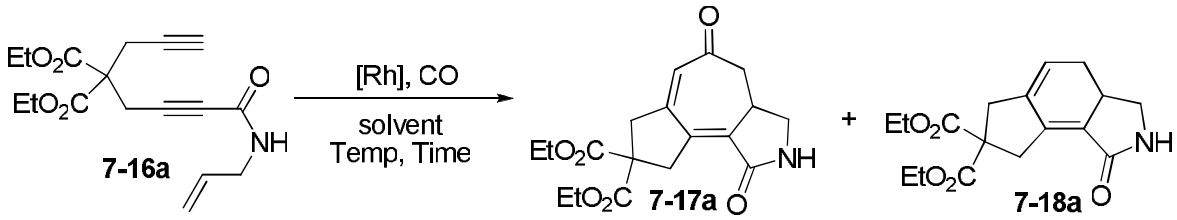
To a solution of dipropynyl diethylmalonate **7-15** (944 mg, 4.00 mmol) in THF (15 mL) was added dropwise 1 M LiHMDS (6.0 mL, 6.0 mmol) in THF at -78 ºC. After stirring the mixture at this temperature for 30 min, allyl isocyanate (498 mg, 6.00 mmol) was added to the reaction mixture and stirred for another 30 min at -78 ºC. The reaction was quenched by sat. $NH_4Cl_{(aq)}$. The aqueous layer was separated and extracted with EtOAc (50 mL x3). The combined organic layer was washed with distilled water, brine and dried over $MgSO_4$. The drying agent was removed by filtration and the solvent was concentrated *in vacuo* to afford the crude product as a light yellow oil. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc = 10:1-3:1) afforded **7-16a** as colorless oil (1.19 g, 62% yield): ^{1}H NMR (400 MHz, $CDCl_3$) [a mixture of two rotamers (6:1)] δ 1.23 (t, *J* = 7.2 Hz, 6H), 2.03 (t, *J* = 2.4 Hz, 1H), 2.93 (d, *J* = 2.4 Hz, 1H), [3.07 (s, 1.72H), 3.14 (s, 0.28H)], [3.85 (t, *J* = 5.6 Hz, 1.72H), 3.94 (t, *J* = 5.6 Hz, 0.28H)], 4.20 (q, *J* = 7.2 Hz, 4H), 5.11-5.22 (m, 2H), 5.73-5.84 (m, 1H), 6.00 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (a mixture of two rotamers) (major) δ 13.9, 22.6, 22.7, 42.0, 56.0, 62.3, 72.1, 77.9, 78.0, 81.0, 116.9, 133.1, 152.4, 168.2; (minor) δ 13.9, 22.8, 22.9, 45.4, 55.9, 62.3, 72.1, 77.9, 78.0, 81.0, 116.5, 133.8, 155.5, 168.1; HRMS (ESI+) calcd. For $C_{17}H_{22}NO_5$ $[M+H]^+$ 320.1498, found 320.1492 (Δ = -1.9 ppm).

Synthesis of Diethyl 2-{3-[methyl(prop-2-en-1-yl)carbamoyl]prop-2-yn-1-yl}-2-(prop-2-yn-1-yl)propanedioate (7-16b)



To a solution of enediyne **7-16a** (180 mg, 0.562 mmol) in MeI (1 mL) was added slowly NaH (60% oil dispersion, 27 mg, 0.67 mmol, 1.2 eq) at 0 ºC. After stirring the mixture at this temperature for 30 min, the reaction mixture was warmed up to room temperature and stirred for another 18 h. The reaction was then quenched by sat. $NH_4Cl_{(aq)}$. The aqueous layer was separated and extracted with Et_2O (10 mL x3). The combined organic layer was washed with distilled water, brine and dried over $MgSO_4$. The drying agent was removed by filtration and the solvent was concentrated *in vacuo* to afford the crude product as a light yellow oil. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc = 10:1-3:1) afforded **7-16b** as colorless oil (133 mg, 71% yield): ^{1}H NMR (400 MHz, $CDCl_3$) [a mixture of two rotamers (3:2)] δ [1.19 (t, *J* = 7.2 Hz, 2.4H), 1.20 (t, *J* = 7.2 Hz, 3.6H)], [1.99 (t, *J* = 2.4 Hz, 0.4 H), 2.00 (t, *J* = 2.4 Hz, 0.6H)], 2.03 (t, *J* = 2.4 Hz, 1H), 2.90 (s, 2H), [2.87 (d, *J* = 2.4 Hz, 1.2H), 2.90 (d, *J* = 2.4 Hz, 0.8H)], 3.02 (s, 1H), [3.09 (s, 1.2H), 3.11 (s, 0.8H)], [3.92 (d, *J* = 5.6 Hz, 0.8H), 4.04 (d, *J* = 5.6 Hz, 1.2H)], [4.15 (q, *J* = 7.2 Hz, 1.6H), 4.16 (q, *J* = 7.2 Hz, 2.4H)], 5.07-5.18 (m, 2H), 5.60-5.76 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (a mixture of two rotamers) (major) δ 13.8, 22.9, 23.0, 31.7, 35.5, 48.7, 53.2, 55.8, 62.1, 72.0, 76.6, 77.8, 86.0, 117.5, 132.3, 153.8, 168.1; (minor) δ 13.8, 22.7, 22.8, 31.7, 35.5, 48.7, 53.2, 55.8, 62.1, 72.0, 76.4, 77.8, 86.6, 117.8, 131.7, 153.5, 168.1; HRMS (ESI+) calcd. For $C_{18}H_{24}NO_5$ $[M+H]^+$ 334.1654, found 334.1648 (Δ = -1.8 ppm).

General procedure for the [2+2+2+1] cycloaddition reaction

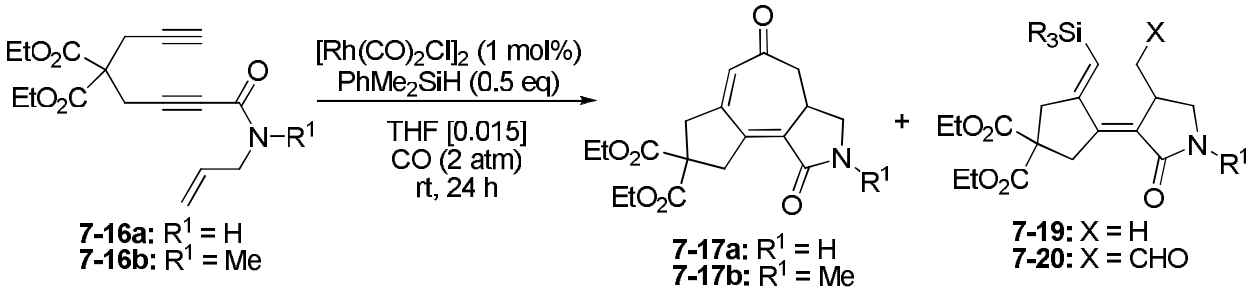


A typical procedure is described for the reaction of enediyne **7-16a**. All other reactions were run following the same procedure unless otherwise noted. Enediyne **7-16a** (32 mg, 0.10 mmol) was introduced to a 5 mL round-bottomed flask, followed by DCE (2 mL) under nitrogen, and

then CO was bubbled into the solution at room temperature. After 15 min, $[Rh(COD)Cl]_2$ (2.5 mg, 0.0050 mmol, 5 mol%) was added under CO and the resulting mixture was stirred at room temperature for an additional 5 min. Then, the reaction mixture was stirred at 50 ^oC for 16 h under CO (ambient pressure, bubbled into the solution). All volatiles were removed *in vacuo* to afford the crude product as yellow oil. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc = 1:1-2:8) afforded mixtures of **7-17a** and **7-18a** as light yellow oil. Two products were further separated by prep HPLC and **7-17a** was obtained as colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, J = 7.2 Hz, 6H), 2.60 (dt, J = 15.2, 2.0 Hz, 1H), 2.80 (t, J = 15.2 Hz, 1H), 3.06-3.14 (m, 2H), 3.24-3.33 (m, 2H), 3.61-3.72 (m, 2H), 3.83 (dd, J = 18.8, 3.6 Hz, 1H), 4.19 (qd, J = 7.2, 3.2 Hz, 4H), 6.23 (s, 1H), 6.61 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 33.8, 38.5, 42.7, 44.7, 45.1, 57.8, 61.9, 127.5, 140.7, 154.6, 170.0, 170.5, 170.6, 196.3; HRMS (ESI+) calcd. For $C_{18}H_{22}NO_6$ $[M+H]^+$ 348.1447, found 348.1441 (Δ = -1.7 ppm).

7-18a was obtained exclusively using $Rh(acac)CO_2$ as the catalyst. Light yellow oil. 75% yield: ^1H NMR (400 MHz, CD_3OD) δ 1.25 (t, J = 7.2 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H), 1.90-2.04 (m, 1H), 2.54-2.60 (m, 1H), 2.80-2.95 (m, 1H), 2.99-3.04 (m, 3H), 3.25-3.31 (m, 1H), 3.45 (dd, J = 18.4, 2.8 Hz, 1H), 3.72 (t, J = 8.8 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H), 4.22 (q, J = 7.2 Hz, 2H), 5.89-5.92 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 14.5, 29.9, 34.8, 37.6, 39.1, 49.2, 61.1, 62.9, 63.0, 122.6, 123.9, 140.3, 140.9, 172.5, 172.9; HRMS (ESI+) calcd. For $C_{17}H_{22}NO_5$ $[M+H]^+$ 320.1498, found 320.1491 (Δ = -2.2 ppm).

General procedure for the catalytic CO-SiCaT reaction



A typical procedure is described for the reaction of diethyl 2-(4-(allyl(methyl)amino)-4-oxobut-2-ynyl)-2-(prop-2-ynyl) malonate (**7-16b**). A reaction vessel equipped with a stirring bar and a CO inlet was charged with $[Rh(CO)_2Cl]_2$ (0.6 mg, 1 mol%). After purging the reaction

vessel with CO, THF (9 mL) was added to dissolve the catalyst. Dimethylphenylsilane (12 μL, 0.078 mmol, 0.5 eq) was then added, and the mixture was stirred at room temperature. After 1 min, a solution of substrate **7-16b** (52 mg, 0.16 mmol) in THF (2 mL) was added, and the reaction mixture was stirred under CO (1 atm) for 24 h. All volatiles were removed *in vacuo* to afford the crude product as yellow oil. Further purification by flash column chromatography on silica gel (hexanes/EtOAc = 8:2-7:3) afforded pure **7-17b** as light-yellow oil (26 mg, 71% yield based on 70% conversion): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.2 Hz, 6H), 2.60 (dt, *J* = 15.2, 2.0 Hz, 1H), 2.76 (t, *J* = 15.2 Hz, 1H), 3.04 (s, 1H), 2.90-3.28 (m, 4H), 3.64 (dt, *J* = 15.2, 4.4 Hz, 1H), 3.88 (dd, *J* = 18.4, 3.2 Hz, 1H), 4.19 (qd, *J* = 7.2, 2.4 Hz, 4H), 6.21 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 30.0, 31.3, 38.4, 42.7, 44.8, 52.1, 57.7, 61.8, 61.9, 127.1, 136.4, 139.6, 155.0, 167.1, 170.6, 170.7, 196.4; HRMS (ESI+) calcd. For $C_{19}H_{24}NO_6$ $[M+H]^+$ 362.1604, found 362.1599 (Δ = -1.4 ppm).

§ 7.5. References

1. (a) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J., Transition Metal-Catalyzed Carbocyclizations in Organic Synthesis. *Chem. Rev.* **1996,** *96* (2), 635-662; (b) Lautens, M.; Klute, W.; Tam, W., Transition Metal-Mediated Cycloaddition Reactions. *Chem. Comm.* **1996,** *96*, 49-92; (c) Lloyd-Jones, G. C., Mechanistic aspects of transition metal catalysed 1,6-diene and 1,6-enyne cycloisomerisation reactions. *Org. Biomol. Chem.* **2003,** *1*, 215-236; (d) Bauer, R. A.; DiBlasi, C. M.; Tan, D. S., The tert-Butylsulfinamide Lynchpin in Transition-Metal-Mediated Multiscaffold Library Synthesis. *Org. Lett.* **2010,** *12*, 2084-2087.
2. (a) Bennacer, B.; Fujiwara, M.; Ojima, I., Novel [2 + 2 + 2 + 1] Cycloaddition of Enediynes Catalyzed by Rhodium Complexes. *Org. Lett.* **2004,** *6* (20), 3589-3591; (b) Bennacer, B.; Fujiwara, M.; Lee, S.; Ojima, I., Silicon-Initiated Carbonylative Carbotricyclization and [2+2+2+1] Cycloaddition of Enediynes Catalyzed by Rhodium Complexes. *J. Am. Chem.Soc.* **2005,** *127* (50), 17756-17767; (c) Kaloko, J. J.; Teng, Y.-H.; Ojima, I., One-step formation of fused tetracyclic skeletons from cyclohexene-diynes and carbon monoxide through Rh(I)-catalyzed [2+2+2+1] cycloaddition reaction. *Chemical Communications* **2009,** (30), 4569-4571.
3. Evans, P. A.; Robinson, J. E.; Baum, E. W.; Fazal, A. N., Intermolecular transition metal-catalyzed [4+2+2] cycloaddition reactions: A new approach to the construction of eight-membered rings. *Journal of the American Chemical Society* **2002,** *124* (30), 8782-8783.
4. Wender, P. A.; Gamber, G. G.; Hubbard, R. D.; Pham, S. M.; Zhang, L., Multicomponent Cycloadditions: The Four-Component [5+1+2+1] Cycloaddition of Vinylcyclopropanes, Alkynes, and CO. *J. Am. Chem. Soc.* **2005,** *127*, 2836-2837.
5. Kim, S. Y.; Lee, S. I.; Choi, S. Y.; Chung, Y. K., Rhodium-Catalyzed Carbonylative [3+3+1] Cycloaddition of Biscyclopropanes with a Vinyl Substituent To Form Seven-Membered

Rings. *Angew. Chem. Int. Ed.* **2008,** *47*, 4914-4917.

6. (a) Wang, Y.; Wang, J.; Su, J.; Huang, F.; Jiao, L.; Liang, Y.; Yang, D.; Zhang, S.; Wender, P. A.; Yu, Z. X., A Computationally Designed Rh(I)-Catalyzed Two-Component [5+2+1] Cycloaddition of Ene-vinylcyclopropanes and CO for the Synthesis of Cyclooctenones. *J. Am. Chem. Soc.* **2007,** *129*, 10060-10061; (b) Yuana, C.; Jiaoa, L.; Yu, Z.-X., Formal total synthesis of (±)-hirsutic acid C using the tandem Rh(I)-catalyzed [(5+2)+1] cycloaddition/aldol reaction. *Tetrahedron Letters* **2010,** *51* (43), 5674-5676; (c) Liang, Y.; Jiang, X.; Yu, Z.-X., Enantioselective total synthesis of (+)-asteriscanolide via Rh(I)-catalyzed [(5+2)+1] reaction. *Chemical Communications* **2011,** *47*, 6659-6661.

7. (a) Wender, P. A.; Croatt, M. P.; Kühn, B., Rhodium(I)-Catalyzed [2+2], [2+2+2], and [2+2+2+2] Cycloadditions of Dienes or Alkynes with a Bis-ene. *Organometallics* **2009,** *28* (20), 5841-5844; (b) Wender, P. A.; Christy, J. P.; Lesser, A. B.; Gieseler, M. T., The Synthesis of Highly Substituted Cyclooctatetraene Scaffolds by Metal-Catalyzed [2+2+2+2] Cycloadditions: Studies on Regioselectivity, Dynamic Properties, and Metal Chelation. *Angew. Chem. Int. Ed.* **2009,** *48*, 7687-7690.

8. (a) Yu, R. T.; Friedman, R. K.; Rovis, T., Enantioselective Rhodium-Catalyzed [4+2+2] Cycloaddition of Dienyl Isocyanates for the Synthesis of Bicyclic Azocine Rings. *J. Am. Chem. Soc.* **2009,** *131* (13250-13251); (b) Krishna, U. M.; Patil, M. P.; Sunoj, R. B.; Trivedi, G. K., [5+3] cycloaddition of 3-oxidopyrylium: a novel route to functionalized cyclooctanoids from furans *Synthesis* **2010,** *2*, 320-328.

9. (a) Ojima, I.; McCullagh, J. V.; Shay, W. R., New Cascade Silylcarbocyclization (SiCaC) of Enediynes. *Journal of Organometallic Chemistry* **1996,** *521*, 421-423; (b) Ojima, I.; Vu, A. T.; McCullagh, J. V.; Kinoshita, A., Rhodium-Catalyzed Intramolecular Silylcarbotricyclization (SiCaT) of Triynes. *Journal of the American Chemical Society* **1999,** *121*, 3230-3231; (c) Ojima, I.; Lee, S.-Y., Rhodium-Catalyzed Novel Carbonylative Carbotricyclization of Enediynes. *J. Am. Chem. Soc.* **2000,** *122* (10), 2385-2386; (d) Ojima, I.; Vu, A. T.; Lee, S. Y.; McCullagh, J. V.; Moralee, A. C.; Fujiwara, M.; Hoang, T. H., Rhodium-Catalyzed Silylcarbocyclization (SiCaC) and Carbonylative Silylcarbocyclization (CO-SiCaC) Reactions of Enynes. *Journal of the American Chemical Society* **2002,** *124*, 9164-9174.

10. Kaloko, J. J. Synthesis of Novel Fused Tricyclic and Tetracyclic Skeletons Through Rh(I)-Catalyzed [2+2+2+1] Cycloaddition of Enediyne Derivatives with Carbon Monoxide. Doctor of Philosophy in Chemistry, Stony Brook University, Stony Brook, NY, August 2010.

Bibliography

Chapter 1

1. Natta, G.; Porri, L.; Valenti, S., Synthesis of optically active cis-1,4 poly(1,3-pentadiene) by asymmetric induction, kurzmitteilung. *Die Makromolekulare Chemie* **1963,** *67* (1), 225-228.
2. Nozaki, H.; Moriuti, S.; Takaya, H.; Noyori, R., Asymmetric induction in carbenoid reaction by means of a dissymmetric copper chelate. *Tetrahedron Lett.* **1966,** *7* (43), 5239-5244.
3. (a) Osborn, J. A.; Jardine, F. H.; Young, J. F.; Wilkinson, G., The preparation and properties of tris(triphenylphosphine)halogenorhodium(I) and some reactions thereof including catalytic homogeneous hydrogenation of olefins and acetylenes and their derivatives. *J. Chem. Soc. A* **1966**, 1711-1732; (b) Baird, M. C.; Lawson, D. N.; Mague, J. T.; Osborn, J. A.; Wilkinson, G., Novel Addition Reactions of Chlorotris(triphenyl phosphine)rhodium(I). *Chem. Commun.* **1966**, 129-130; (c) Mague, J. T.; Wilkinson, G., Tris(triphenylarsine)- and tris(triphenylstibine)-chlororhodium(I) complexes and their reactions with hydrogen, olefins, and other reagents. *J. Chem. Soc. A* **1966**, 1736-1740.
4. (a) Horner, L.; Siegel, H.; Büthe, H., Asymmetric Catalytic Hydrogenation with an Optically Active Phosphinerhodium Complex in Homogeneous Solution. *Angew. Chem., Int. Ed.* **1968,** *7* (12), 942; (b) Knowles, W. S.; Sabacky, M. J., Catalytic asymmetric hydrogenation employing a soluble, optically active, rhodium complex. *Chem. Commun.* **1968,** (22), 1445-1446.
5. Knowles, W. S., Asymmetric hydrogenation. *Acc. Chem. Res.* **1983,** *16* (3), 106-112.
6. Dang, T. P.; Kagan, H. B., The asymmetric synthesis of hydratropic acid and amino-acids by homogeneous catalytic hydrogenation. *J. Chem. Soc. D, Chem. Commun.* **1971,** (10), 481.
7. Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, D. J., Asymmetric hydrogenation. Rhodium chiral bisphosphine catalyst. *J. Am. Chem. Soc.* **1977,** *99* (18), 5946-5952.
8. Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R., Synthesis of 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), an atropisomeric chiral bis(triaryl)phosphine, and its use in the rhodium(I)-catalyzed asymmetric hydrogenation of .alpha.-(acylamino)acrylic acids. *J. Am. Chem. Soc.* **1980,** *102* (27), 7932-7934.
9. Burk, M. J., C2-symmetric bis(phospholanes) and their use in highly enantioselective hydrogenation reactions. *J. Am. Chem. Soc.* **1991,** *113* (22), 8518-8519.
10. (a) Noyori, R., *Asymmetric Catalysis in Organic Synthesis*. Wiley: New York, 1994; (b) Ojima, I., *Catalytic Asymmetric Synthesis*. Wiley: New York, 2000; p 1-110; (c) Tang, W.; Zhang, X., New Chiral Phosphorus Ligands for Enantioselective Hydrogenation. *Chem. Rev.* **2003,** *103* (8), 3029-3070.
11. Katsuki, T.; Sharpless, K. B., The first practical method for asymmetric epoxidation. *J. Am. Chem. Soc.* **1980,** *102* (18), 5974-5976.
12. Alexakis, A.; Vastra, J.; Burton, J.; Benhaim, C.; Mangeney, P., Asymmetric conjugate addition of diethyl zinc to enones with chiral phosphorus ligands derived from TADDOL.

Tetrahedron Lett. **1998,** *39* (43), 7869-7872.

13. (a) Reetz, M. T.; Sell, T., Rhodium-catalyzed enantioselective hydrogenation using chiral monophosphonite ligands. *Tetrahedron Lett.* **2000,** *41* (33), 6333-6336; (b) van den Berg, M.; Minnaard, A. J.; Schudde, E. P.; van Esch, J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L., Highly Enantioselective Rhodium-Catalyzed Hydrogenation with Monodentate Ligands. *J. Am. Chem. Soc.* **2000,** *122* (46), 11539-11540.

14. Hua, Z.; Vassar, V. C.; Ojima, I., Synthesis of New Chiral Monodentate Phosphite Ligands and Their Use in Catalytic Asymmetric Hydrogenation. *Org. Lett.* **2003,** *5* (21), 3831-3834.

15. (a) Choi, H.; Hua, Z.; Ojima, I., Highly Enantioselective Copper-Catalyzed Conjugate Addition of Diethylzinc to Nitroalkenes. *Org. Lett.* **2004,** *6* (16), 2689-2691; (b) Hua, Z.; Vassar, V. C.; Choi, H.; Ojima, I., New biphenol-based, fine-tunable monodentate phosphoramidite ligands for catalytic asymmetric transformations. *Proc. Natl. Acad. Sci. U. S. A.* **2004,** *101* (15), 5411-5416; (c) Chapsal, B. D.; Ojima, I., Total Synthesis of Enantiopure (+)-γ-Lycorane Using Highly Efficient Pd-Catalyzed Asymmetric Allylic Alkylation. *Org. Lett.* **2006,** *8* (7), 1395-1398.

16. (a) Bonafoux, D.; Hua, Z.; Wang, B.; Ojima, I., Design and synthesis of new fluorinated ligands for the rhodium-catalyzed hydroformylation of alkenes in supercritical CO2 and fluorous solvents. *J. Fluorine Chem.* **2001,** *112* (1), 101-108; (b) Hultzsch, K. C.; Jernelius, J. A.; Hoveyda, A. H.; Schrock, R. R., The First Polymer-Supported and Recyclable Chiral Catalyst for Enantioselective Olefin Metathesis. *Angew. Chem., Int. Ed.* **2002,** *41* (4), 589-593.

17. Shi, C.; Ojima, I., Asymmetric synthesis of 1-vinyltetrahydroisoquinoline through Pd-catalyzed intramolecular allylic amination. *Tetrahedron* **2007,** *63* (35), 8563-8570.

18. Pu, L., 1,1‘-Binaphthyl Dimers, Oligomers, and Polymers: Molecular Recognition, Asymmetric Catalysis, and New Materials†. *Chem. Rev.* **1998,** *98* (7), 2405-2494.

19. van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P., Ligand Bite Angle Effects in Metal-catalyzed C−C Bond Formation. *Chem. Rev.* **2000,** *100* (8), 2741-2770.

20. Trost, B. M.; Murphy, D. J., A model for metal-templated catalytic asymmetric induction via .pi.-allyl fragments. *Organometallics* **1985,** *4* (6), 1143-1145.

21. Mori, M.; Nakanishi, M.; Kajishima, D.; Sato, Y., A Novel and General Synthetic Pathway to Strychnos Indole Alkaloids: Total Syntheses of (−)-Tubifoline, (−)-Dehydrotubifoline, and (−)-Strychnine Using Palladium-Catalyzed Asymmetric Allylic Substitution. *J. Am. Chem. Soc.* **2003,** *125* (32), 9801-9807.

22. Alexander, J. B.; Schrock, R. R.; Davis, W. M.; Hultzsch, K. C.; Hoveyda, A. H.; Houser, J. H., Synthesis of Molybdenum Imido Alkylidene Complexes That Contain 3,3‘-Dialkyl-5,5‘,6,6‘-tetramethyl-1,1‘-biphenyl-2,2‘-diolates (Alkyl = t-Bu, Adamantyl). Catalysts for Enantioselective Olefin Metathesis Reactions. *Organometallics* **2000,** *19* (18), 3700-3715.

23. (a) Freundlich, J. S.; Landis, H. E., An expeditious aqueous Suzuki–Miyaura method for the arylation of bromophenols. *Tetrahedron Lett.* **2006,** *47* (25), 4275-4279; (b) Chouteau, F.; Ramanitrahasimbola, D.; Rasoanaivo, P.; Chibale, K., Exploiting a basic chemosensitizing pharmacophore hypothesis. Part 1: Synthesis and biological evaluation of novel arylbromide

and bicyclic chemosensitizers against drug-resistant malaria parasites. *Bioorg. Med. Chem. Lett.* **2005,** *15* (12), 3024-3028.

24. Yoshizaki, H.; Satoh, H.; Sato, Y.; Nukui, S.; Shibasaki, M.; Mori, M., Palladium-Mediated Asymmetric Synthesis of Cis-3,6-Disubstituted Cyclohexenes. A Short Total Synthesis of Optically Active (+)-.gamma.-Lycorane. *J. Org. Chem.* **1995,** *60* (7), 2016-2021.
25. Shi, C.; Chien, C.-W.; Ojima, I., Synthesis of Chiral Biphenol-Based Diphosphonite Ligands and Their Application in Palladium-Catalyzed Intermolecular Asymmetric Allylic Amination Reactions. *Chem. Asian J.* **2011,** *6* (2), 674-680.

Chapter 2

1. Tsuji, J.; Takahashi, H.; Morikawa, M., Organic syntheses by means of noble metal compounds XVII. Reaction of π-allylpalladium chloride with nucleophiles. *Tetrahedron Letters* **1965,** *6* (49), 4387-4388.
2. Trost, B. M.; Strege, P. E., Asymmetric induction in catalytic allylic alkylation. *Journal of the American Chemical Society* **1977,** *99* (5), 1649-1651.
3. Trost, B. M.; Lee, C., *Catalytic Asymmetric Synthesis, ed. Ojima, I. (Wiley-VCH, New. York)*. 2nd ed.; 2000; p 593-649.
4. Tsuji, J., *Palladium reagents and catalyst; Wiley: New york*. 1995; p 290.
5. Trost, B. M.; Crawley, M. L., Asymmetric Transition-Metal-Catalyzed Allylic Alkylations: Applications in Total Synthesis. *Chemical Reviews* **2003,** *103* (8), 2921-2944.
6. Scott, J. D.; Williams, R. M., Chemistry and Biology of the Tetrahydroisoquinoline Antitumor Antibiotics. *Chem. Rev.* **2002,** *102* (5), 1669-1730.
7. Bentley, K. W., The Isoquinoline Alkaloids. In *Chemistry and Biochemistry of Organic Natural Products*, Ravindranath, B., Ed. Harwood Academic Publishers: Amsterdam, 1998.
8. Ivanovska, N.; Nikolova, P.; Hristova, M.; Philipov, S.; Istatkova, R., Complement modulatory activity of bisbenzylisoquinoline alkaloids isolated from Isopyrum thalictroides--I: Influence on classical pathway in human serum. *International Journal of Immunopharmacology* **1999,** *21* (5), 325-336.
9. Banning, J. W.; Salman, K. N.; Patil, P. N., A Pharmacological Study of Two Bisbenzylisoquinoline Alkaloids, Thalistyline and Obamegine. *Journal of Natural Products* **1982,** *45* (2), 168-177.
10. Pingaew, R.; Ruchirawat, S., Application of the Hypervalent Iodine Reagent to the Synthesis of Some Pentasubstituted Aporphine Alkaloids. *Synlett* **2007,** *2007* (EFirst), 2363,2366.
11. Markmee, S.; Ruchirawat, S.; Prachyawarakorn, V.; Ingkaninan, K.; Khorana, N., Isoquinoline derivatives as potential acetylcholinesterase inhibitors. *Bioorganic & Medicinal Chemistry Letters* **2006,** *16* (8), 2170-2172.
12. Takada, K.; Uehara, T.; Nakao, Y.; Matsunaga, S.; van Soest, R. W. M.; Fusetani, N.,

Schulzeines A−C, New α-Glucosidase Inhibitors from the Marine Sponge Penares schulzei1. *Journal of the American Chemical Society* **2004,** *126* (1), 187-193.

13. Taylor, M. S.; Jacobsen, E. N., Highly Enantioselective Catalytic Acyl-Pictet−Spengler Reactions. *Journal of the American Chemical Society* **2004,** *126* (34), 10558-10559.
14. (a) Ukaji, Y.; Shimizu, Y.; Kenmoku, Y.; Ahmed, A.; Inomata, K., Catalytic Asymmetric Addition of Dialkylzinc to 3,4-Dihydroisoquinoline N-Oxides Utilizing Tartaric Acid Ester as a Chiral Auxiliary. *Bulletin of the Chemical Society of Japan* **2000,** *73* (2), 447-452; (b) Kanemitsu, T.; Yamashita, Y.; Nagata, K.; Itoh, T., Catalytic Asymmetric Synthesis of (R)-(-)-Calycotomine, (S)-(-)-Salsolidine and (S)-(-)-Carnegine. *Synlett* **2006,** *2006* (10), 1595,1597; (c) Wang, S.; Seto, C. T., Enantioselective Addition of Vinylzinc Reagents to 3,4-Dihydroisoquinoline N-Oxide. *Organic Letters* **2006,** *8* (18), 3979-3982.
15. (a) Morimoto, T.; Suzuki, N.; Achiwa, K., Enantioselective synthesis of (S)-calycotomine employing catalytic asymmetric hydrogenation with an iridium(I)-(R)-BINAP-phthalimide complex. *Tetrahedron: Asymmetry* **1998,** *9* (2), 183-187; (b) Mujahidin, D.; Doye, S., Enantioselective Synthesis of (+)-(S)-Laudanosine and (–)-(S)-Xylopinine. *European Journal of Organic Chemistry* **2005,** *2005* (13), 2689-2693.
16. Ohkuma, T.; Kitamura, M.; Noyori, R., Asymmetric Hydrogenation. In *Catalytic Asymmetric Synthesis (2nd Edition)*, Ojima, I., Ed. Wiley-VCH: New York, 2000; pp 1-110.
17. Chrzanowska, M.; Rozwadowska, M. D., Asymmetric Synthesis of Isoquinoline Alkaloids. *Chem. Rev.* **2004,** *104* (7), 3341-3370.
18. Ito, K.; Akashi, S.; Saito, B.; Katsuki, T., Asymmetric Intramolecular Allylic Amination: Straightforward Approach to Chiral C1-Substituted Tetrahydroisoquinolines. *Synlett* **2003**, 1809-1812.
19. Hua, Z.; Vassar, V.; Ojima, I., Synthesis of new chiral monodentate phosphite ligands and their use in catalytic asymmetric hydrogenation. *Organic Letters* **2003,** *5*, 3831-3834.
20. (a) Choi, H.; Hua, Z.; Ojima, I., Highly Enantioselective Copper-Catalyzed Conjugate Addition of Diethylzinc to Nitroalkenes. *Organic Letters* **2004,** *6* (16), 2689-2691; (b) Hua, Z.; Vassar, V. C.; Choi, H.; Ojima, I., New biphenol-based, fine-tunable monodentate phosphoramidite ligands for catalytic asymmetric transformations. *Proc. Nat. Acad. Sci., U. S. A.* **2004,** *101* (15), 5411-5416; (c) Chapsal, B. D.; Ojima, I., Total Synthesis of Enantiopure (+)-γ-Lycorane Using Highly Efficient Pd-Catalyzed Asymmetric Allylic Alkylation. *Organic Letters* **2006,** *8* (7), 1395-1398.
21. Shi, C.; Ojima, I., Asymmetric synthesis of 1-vinyltetrahydroisoquinoline through Pd-catalyzed intramolecular allylic amination. *Tetrahedron* **2007,** *63* (35), 8563-8570.
22. Shi, C.; Chien, C. W.; Ojima, I., Synthesis of chiral biphenol-based diphosphonite ligands and their application to Pd-catalyzed intermolecular asymmetric allylic amination. *Chem. Asian J.* **2011,** *6*, 674.
23. Shi, C. Development and Applications of Chiral Phosphorus Ligands to Transition-Metal Catalyzed Asymmetric Reactions. Doctor of Philosophy in Chemistry, Stony Brook University, Stony Brook, NY, August 2008.
24. (a) Lesch, B.; Toräng, J.; Nieger, M.; Bräse, S., The Diels-Alder Approach towards

Cannabinoids. *Synthesis* **2005,** (11), 1888-1900; (b) Sawant, D.; Kumar, R.; Maulik, P. R.; Kundu, B., Unprecedented SnCl2-Mediated Cyclization of Nitro Arenes via N−N Bond Formation†. *Organic Letters* **2006,** *8* (8), 1525-1528.

25. Compound 8 (A or B) can be prepared in two steps from commercially available resorcinolamine. Alternatively, 8 (A or B) can also be prepared from commercially available 3,5-dihydroxybenzaldehyde through PMB or benzyl protection and nitro-aldol reaction, followed by reduction and trifluoroacetylation. See Experimental Section.

26. Denmark, S. E.; Regens, C. S.; Kobayashi, T., Total Synthesis of Papulacandin D. *Journal of the American Chemical Society* **2007,** *129* (10), 2774-2776.

Chapter 3

1. Takada, K.; Uehara, T.; Nakao, Y.; Matsunaga, S.; van Soest, R. W. M.; Fusetani, N., Schulzeines A-C, New α-Glucosidase Inhibitors from the Marine Sponge Penares schulzei. *J. Am. Chem. Soc.* **2004,** *126* (1), 187-193.

2. (a) Braun, C.; Brayer, G. D.; Withers, S. G., Mechanism-based Inhibition of Yeast alpha-Glucosidase and Human Pancreatic alpha-Amylase by a New Class of Inhibitors. *J. Biol. Chem.* **1995,** *270* (45), 26778-26781; (b) Mehta, A.; Zitzmann, N.; Rudd, P. M.; Block, T. M.; Dwek, R. A., α-Glucosidase inhibitors as potential broad based anti-viral agents. *FEBS Lett.* **1998,** *430* (1–2), 17-22; (c) Dwek, R. A.; Butters, T. D.; Platt, F. M.; Zitzmann, N., Targeting glycosylation as therapeutic approach. *Nat. Rev. Drug Discov.* **2002,** *1*, 65-75.

3. (a) Kuntiyong, P.; Akkarasamiyo, S.; Eksintkun, G., Short Synthetic Route toward the Tricyclic Core of Schulzeines. *Chem. Lett.* **2006,** *35*, 1008-1009; (b) Gurjar, M. K.; Pramanik, C.; Bhattasali, D.; Ramana, C. V.; Mohapatra, D. K., Total Syntheses of Schulzeines B and C. *J. Org. Chem.* **2007,** *72* (17), 6591-6594; (c) Liu, G.; Romo, D., Enantioselective Synthesis of Schulzeines B and C via a β-Lactone-Derived Surrogate for Bishomoserine Aldehyde. *Org. Lett.* **2009,** *11* (5), 1143-1146; (d) Bowen, E. G.; Wardrop, D. J., Total Synthesis of the α-Glucosidase Inhibitors Schulzeine A, B, and C and a Structural Revision of Schulzeine A. *J. Am. Chem. Soc.* **2009,** *131* (17), 6062-6063; (e) Miyazaki, M.; Ando, N.; Sugai, K.; Seito, Y.; Fukuoka, H.; Kanemitsu, T.; Nagata, K.; Odanaka, Y.; Nakamura, K. T.; Itoh, T., Catalytic Asymmetric Allylation of 3,4-Dihydroisoquinolines and Its Application to the Synthesis of Isoquinoline Alkaloids. *J. Org. Chem.* **2011,** *76* (2), 534-542.

4. (a) Vicario, J. L.; Badía, D.; Carrillo, L.; Etxebarria, J., α-Amino Acids and Derivatives in the Asymmetric Synthesis of Tetrahydroisoquinoline Alkaloids. *Curr. Org. Chem.* **2003,** *7* (18), 1775-1792; (b) Chrzanowska, M.; Rozwadowska, M. D., Asymmetric Synthesis of Isoquinoline Alkaloids. *Chem. Rev.* **2004,** *104* (7), 3341-3370; (c) Kaufman, T. S., Approaches to the Total Synthesis of Calycotomine, a Widespread 1-Hydroxymethyl-Substituted Simple Tetrahydroisoquinoline. *Synthesis* **2005,** (EFirst), 339,360; (d) Ito, K.; Akashi, S.; Saito, B.; Katsuki, T., Asymmetric Intramolecular Allylic Amination: Straightforward Approach to Chiral C1-Substituted Tetrahydroisoquinolines. *Synlett* **2003**, 1809-1812; (e) Taylor, A. M.; Schreiber, S. L., Enantioselective Addition of

Terminal Alkynes to Isolated Isoquinoline Iminiums. *Org. Lett.* **2006,** *8* (1), 143-146; (f) Teichert, J. F.; Fañanás-Mastral, M.; Feringa, B. L., Iridium-Catalyzed Asymmetric Intramolecular Allylic Amidation: Enantioselective Synthesis of Chiral Tetrahydroisoquinolines and Saturated Nitrogen Heterocycles. *Angew. Chem. Int. Ed.* **2011,** *50* (3), 688-691.

5. Kinderman, S. S.; Wekking, M. M. T.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T., Catalytic N-Sulfonyliminium Ion-Mediated Cyclizations to α-Vinyl-Substituted Isoquinolines and β-Carbolines and Applications in Metathesis. *J. Org. Chem.* **2005,** *70* (14), 5519-5527.
6. The absolute configuration of (+)-2 was tentatively assigned to S based on the sign of the specific rotation of close related (S)-(+)-1-vinyltetrahydroisoquinoline that we reported previously (Ref. 2-11), and confirmed by the known value of (S,S)-13 (See Experimental Section).
7. Capilla, A. S.; Romero, M.; Pujol, M. D.; Caignard, D. H.; Renard, P., Synthesis of isoquinolines and tetrahydroisoquinolines as potential antitumour agents. *Tetrahedron* **2001,** *57* (39), 8297-8303.
8. (a) Organ, M. G.; Xu, J.; N'Zemba, B., A modular, general and enantiospecific strategy for the synthesis of CVS 1778 analogs: inhibitors of factor Xa. *Tetrahedron Lett.* **2002,** *43* (45), 8177-8180; (b) Rajendra, G.; Miller, M. J., Intramolecular electrophilic additions to olefins in organic syntheses. Stereoselective synthesis of 3,4-substituted .beta.-lactams by bromine-induced oxidative cyclization of O-acyl .beta.,.gamma.-unsaturated hydroxamic acid derivatives. *J. Org. Chem.* **1987,** *52* (20), 4471-4477.
9. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H., Synthesis and Activity of a New Generation of Ruthenium-Based Olefin Metathesis Catalysts Coordinated with 1,3-Dimesityl-4,5-dihydroimidazol-2-ylidene Ligands§. *Org. Lett.* **1999,** *1* (6), 953-956.
10. The Spartan program indicates that cis-6 and trans-6 have almost same energy, and an attempted epimerization of trans-6 to cis-6 under the RCM conditions did not cause any epimerization. Thus, this epimerization should have taken place during the RCM reaction.
11. Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H., Efficient and Recyclable Monomeric and Dendritic Ru-Based Metathesis Catalysts. *J. Am. Chem. Soc.* **2000,** *122* (34), 8168-8179.
12. Shi, C.; Chien, C. W.; Ojima, I., Synthesis of chiral biphenol-based diphosphonite ligands and their application to Pd-catalyzed intermolecular asymmetric allylic amination. *Chem. Asian J.* **2011,** *6*, 674.
13. Rajendra, G.; Miller, M. J., Intramolecular electrophilic additions to olefins in organic syntheses. Stereoselective synthesis of 3,4-substituted .beta.-lactams by bromine-induced oxidative cyclization of O-acyl .beta.,.gamma.-unsaturated hydroxamic acid derivatives. *The Journal of Organic Chemistry* **1987,** *52* (20), 4471-4477.

Chapter 4

1. Kozikowski, A. P.; Tückmantel, W., Chemistry, Pharmacology, and Clinical Efficacy of the Chinese Nootropic Agent Huperzine A. *Acc. Chem. Res.* **1999,** *32* (8), 641-650.
2. (a) Bai, D., Development of huperzine A and B for treatment of Alzheimer's disease. *Pure Appl. Chem.* **2007,** *79* (4), 469-479; (b) Xiao, X. Q.; Yang, J. W.; Tang, X. C., Huperzine A protects rat pheochromocytoma cells against hydrogen peroxide-induced injury. *Neurosci. Lett.* **1999,** *275* (2), 73-76; (c) Xiao, X. Q.; Zhang, H. Y.; Tang, X. C., Huperzine A attenuates amyloid β-peptide fragment 25-35-induced apoptosis in rat cortical neurons via inhibiting reactive oxygen species formation and caspase-3 activation. *J. Neurosci. Res.* **2002,** *67* (1), 30-36.
3. Wang, B.-s.; Wang, H.; Wei, Z.-h.; Song, Y.-y.; Zhang, L.; Chen, H.-z., Efficacy and safety of natural acetylcholinesterase inhibitor huperzine A in the treatment of Alzheimer's disease: an updated meta-analysis. *Journal of Neural Transmission* **2009,** *116* (4), 457-465.
4. Lim, W.-H.; Goodger, J. Q. D.; Field, A. R.; Holtum, J. A. M.; Woodrow, I. E., Huperzine alkaloids from Australasian and southeast Asian Huperzia. *Pharm. Biol.* **2010,** *48* (9), 1073-1078.
5. Xia, Y.; Kozikowski, A. P., A practical synthesis of the Chinese "nootropic" agent huperzine A: a possible lead in the treatment of Alzheimer's disease. *J. Am. Chem. Soc.* **1989,** *111* (11), 4116-4117.
6. Campiani, G.; Sun, L. Q.; Kozikowski, A. P.; Aagaard, P.; McKinney, M., A palladium-catalyzed route to huperzine A and its analogs and their anticholinesterase activity. *J. Org. Chem.* **1993,** *58* (27), 7660-7669.
7. Kaneko, S.; Yoshino, T.; Katoh, T.; Terashima, S., A novel enantioselective synthesis of the key intermediate of (−)-huperzine a employing asymmetric palladium-catalyzed bicycloannulation. *Tetrahedron: Asymmetry* **1997,** *8* (6), 829-832.
8. He, X.-C.; Wang, B.; Yu, G.; Bai, D., Studies on the asymmetric synthesis of huperzine A. Part 2: Highly enantioselective palladium-catalyzed bicycloannulation of the β-keto-ester using new chiral ferrocenylphosphine ligands. *Tetrahedron: Asymmetry* **2001,** *12* (23), 3213-3216.
9. Chassaing, C.; Haudrechy, A.; Langlois, Y., Asymmetric palladium annulation: formal synthesis of (+)-huperzine A. *Tetrahedron Lett.* **1999,** *40* (50), 8805-8809.
10. Chapsal, B. D.; Ojima, I., Total Synthesis of Enantiopure (+)-γ-Lycorane Using Highly Efficient Pd-Catalyzed Asymmetric Allylic Alkylation. *Org. Lett.* **2006,** *8* (7), 1395-1398.
11. Kozikowski, A. P.; Reddy, E. R.; Miller, C. P., A simplified route to a key intermediate in the synthesis of the Chinese nootropic agent huperzine A. *J. Chem. Soc., Perkin Trans. 1* **1990,** (1), 195-197.
12. (a) Salamone, S. G.; Dudley, G. B., A Ring-Expansion Approach to Roseophilin. *Org. Lett.* **2005,** *7* (20), 4443-4445; (b) Chaterpaul, S. J. Application of Transition Metal-Catalyzed Reactions in the Synthesis of NHeterocyclic Natural Products. Doctor of Philosophy in Chemistry, Stony Brook University, Stony Brook, NY, August 2010.

Chapter 5

1. Mizoroki, T.; Mori, K.; Ozaki, A., Arylation of Olefin with Aryl Iodide Catalyzed by Palladium. *Bull. Chem. Soc. Jpn.* 1971, *44* (2), 581-581.
2. Heck, R. F.; Nolley, J. P., Palladium-catalyzed vinylic hydrogen substitution reactions with aryl, benzyl, and styryl halides. *J. Org. Chem.* 1972, *37* (14), 2320-2322.
3. (a) Dounay, A. B.; Overman, L. E., The Asymmetric Intramolecular Heck Reaction in Natural Product Total Synthesis. *Chem. Rev.* 2003, *103* (8), 2945-2964; (b) Masakatsu Shibasaki, Erasmus M. V., Takashi Ohshima,, Asymmetric Heck Reaction. *Adv. Synth. Catal.* 2004, *346* (13-15), 1533-1552.
4. Ojima, I., *Catalytic asymmetric synthesis*. 2nd ed.; 2000.
5. Sato, Y.; Sodeoka, M.; Shibasaki, M., Catalytic asymmetric carbon-carbon bond formation: asymmetric synthesis of cis-decalin derivatives by palladium-catalyzed cyclization of prochiral alkenyl iodides. *J. Org. Chem.* 1989, *54* (20), 4738-4739.
6. Carpenter, N. E.; Kucera, D. J.; Overman, L. E., Palladium-catalyzed polyene cyclizations of trienyl triflates. *J. Org. Chem.* 1989, *54* (25), 5846-5848.
7. (a) Shibasaki, M.; Mase, T.; Ikegami, S., The first total syntheses of DELTA-9(12)-Capnellene-8-beta-10.alpha-diol and DELTA-9(12)-capnellene-3-beta-8-beta-10-alpha-triol. *J. Am. Chem. Soc.* 1986, *108* (8), 2090-2091; (b) Ohrai, K.; Kondo, K.; Sodeoka, M.; Shibasaki, M., Effects of Solvents and Additives in the Asymmetric Heck Reaction of Alkenyl Triflates: Catalytic Asymmetric Synthesis of Decalin Derivatives and Determination of the Absolute Stereochemistry of (+)-Vernolepin. *J. Am. Chem. Soc.* 1994, *116* (26), 11737-11748; (c) Sato, Y.; Mori, M.; Shibasaki, M., Asymmetric Heck reaction: A catalytic asymmetric synthesis of the key intermediate of (−)-oppositol and (−)-prepinnaterpene. *Tetrahedron: Asymmetry* 1995, *6* (3), 757-766.
8. (a) Ashimori, A.; Overman, L. E., Catalytic asymmetric synthesis of quarternary carbon centers. Palladium-catalyzed formation of either enantiomer of spirooxindoles and related spirocyclics using a single enantiomer of a chiral diphosphine ligand. *The Journal of Organic Chemistry* 1992, *57* (17), 4571-4572; (b) Ashimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J., Catalytic Asymmetric Synthesis of Quaternary Carbon Centers. Exploratory Investigations of Intramolecular Heck Reactions of (E)-α,β-Unsaturated 2-Haloanilides and Analogues To Form Enantioenriched Spirocyclic Products. *J. Am. Chem. Soc.* 1998, *120* (26), 6477-6487; (c) Kiely, D.; Guiry, P. J., Palladium complexes of phosphinamine ligands in the intramolecular asymmetric Heck reaction. *J. Organomet. Chem.* 2003, *687* (2), 545-561.
9. Busacca, C. A.; Grossbach, D.; So, R. C.; O'Brie, E. M.; Spinelli, E. M., Probing Electronic Effects in the Asymmetric Heck Reaction with the BIPI Ligands. *Org. Lett.* 2003, *5* (4), 595-598.
10. Kiewel, K.; Tallant, M.; Sulikowski, G. A., Asymmetric Heck cyclization route to indolizidine and azaazulene alkaloids: synthesis of (+)-5-epiindolizidine 167B and indolizidine 223AB. *Tetrahedron Lett.* 2001, *42* (38), 6621-6623.

11. Hart, D. J.; Tsai, Y. M., Stereoselective indolizidine synthesis: preparation of stereoisomers of gephyrotoxin-223AB. *The Journal of Organic Chemistry* 1982, *47* (23), 4403-4409.

12. Yoda, H.; Katoh, H.; Ujihara, Y.; Takabe, K., SmI2-mediated hetero-coupling reaction of lactams with aldehydes; synthesis of indolizidine alkaloids, (−)-δ-coniceine, (+)-5-epiindolizidine 167B and (+)-lentiginosine. *Tetrahedron Lett.* 2001, *42* (13), 2509-2512.

13. Dounay, A. B.; Overman, L. E.; Wrobleski, A. D., Sequential Catalytic Asymmetric Heck−Iminium Ion Cyclization: Enantioselective Total Synthesis of the Strychnos Alkaloid Minfiensine. *J. Am. Chem. Soc.* 2005, *127* (29), 10186-10187.

14. Imbos, R.; Minnaard, A. J.; Feringa, B. L., A Highly Enantioselective Intramolecular Heck Reaction with a Monodentate Ligand. *J. Am. Chem. Soc.* 2001, *124* (2), 184-185.

15. Lautens, M.; Zunic, V., Sequential olefin metathesis-Intramolecular asymmetric Heck reactions in the synthesis of polycycles. *Can. J. Chem.* 2004, *82* (2), 399-407.

16. Lormann, M. E. P.; Nieger, M.; Brase, S., Desymmetrisation of bicyclo[4.4.0]decadienes: A planar-chiral complex proved to be most effective in an asymmetric Heck reaction. *J. Organomet. Chem.* 2006, *691* (10), 2159-2161.

17. Ozawa, F.; Kubo, A.; Hayashi, T., Catalytic asymmetric arylation of 2,3-dihydrofuran with aryl triflates. *J. Am. Chem. Soc.* 1991, *113* (4), 1417-1419.

18. K. K. Hii, Timothy D. W. C., John M. Brown, Andrew Smith, Robert J. Deeth,, The Intermolecular Asymmetric Heck Reaction: Mechanistic and Computational Studies. *Helv. Chim. Acta* 2001, *84* (10), 3043-3056.

19. Ozawa, F.; Kobatake, Y.; Hayashi, T., Palladium-catalyzed asymmetric alkenylation of cyclic olefins. *Tetrahedron Lett.* 1993, *34* (15), 2505-2508.

20. (a) Hennessy, A. J.; Malone, Y. M.; Guiry, P. J., 2,2-Dimethyl-2,3-dihydrofuran, a new substrate for intermolecular asymmetric Heck reactions. *Tetrahedron Lett.* 1999, *40* (51), 9163-9166; (b) Hennessy, A. J.; Connolly, D. J.; Malone, Y. M.; Guiry, P. J., Intermolecular asymmetric Heck reactions with 2,2-diethyl-2,3-dihydrofuran. *Tetrahedron Lett.* 2000, *41* (40), 7757-7761.

21. Mata, Y.; Dieguez, M.; Pamies, O.; Claver, C., Chiral Phosphite-oxazolines: A New Class of Ligands for Asymmetric Heck Reactions. *Org. Lett.* 2005, *7* (25), 5597-5599.

22. Rubina, M.; Sherrill, W. M.; Rubin, M., Dramatic Stereo- and Enantiodivergency in the Intermolecular Asymmetric Heck Reaction Catalyzed by Palladium Complexes with Cyclopropane-Based PHOX Ligands. *Organometallics* 2008, *27* (24), 6393-6395.

23. (a) Hou, X.-L.; Dong, D. X.; Yuan, K., Synthesis of new chiral benzylically substituted P,N-ligands and their applications in the asymmetric Heck reaction. *Tetrahedron: Asymmetry* 2004, *15* (14), 2189-2191; (b) Wu, W.-Q.; Peng, Q.; Dong, D.-X.; Hou, X.-L.; Wu, Y.-D., A Dramatic Switch of Enantioselectivity in Asymmetric Heck Reaction by Benzylic Substituents of Ligands. *J. Am. Chem. Soc.* 2008, *130* (30), 9717-9725.

24. Koga, Y.; Sodeoka, M.; Shibasaki, M., Palladium-catalyzed asymmetric arylation of 4,7-dihydro-1,3-dioxepin. Catalytic asymmetric synthesis of γ-butyrolactone derivatives. *Tetrahedron Lett.* 1994, *35* (8), 1227-1230.

25. Loiseleur, O.; Hayashi, M.; Schmees, N.; Pfaltz, A., Enantioselective Heck Reactions Catalyzed by Chiral Phosphinooxazoline-Palladium Complexes. *Synthesis* 1997, *1997* (11), 1338-1345.

26. Dieter K. Heldmann, D. S., Catalytic Enantioselective Hydrosilylation of Ketones with Rhodium-Phosphite Complexes Containing a TADDOLate and a Dihydrooxazole Unit. *Helv. Chim. Acta* 1999, *82* (7), 1096-1110.

27. Escher, I. H.; Pfaltz, A., New Chiral Oxazoline-Phosphite Ligands for the Enantioselective Copper-Catalyzed 1,4-Addition of Organozinc Reagents to Enones. *Tetrahedron* 2000, *56* (18), 2879-2888.

28. McKennon, M. J.; Meyers, A. I.; Drauz, K.; Schwarm, M., A convenient reduction of amino acids and their derivatives. *J. Org. Chem.* 1993, *58* (13), 3568-3571.

Chapter 6

1. Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K., Enantioselective Mannich-Type Reaction Catalyzed by a Chiral Brønsted Acid. *Angew. Chem., Int. Ed.* **2004,** *43* (12), 1566-1568.

2. Uraguchi, D.; Terada, M., Chiral Brønsted Acid-Catalyzed Direct Mannich Reactions via Electrophilic Activation. *J. Am. Chem. Soc.* **2004,** *126* (17), 5356-5357.

3. (a) Uraguchi, D.; Sorimachi, K.; Terada, M., Organocatalytic Asymmetric Aza-Friedel−Crafts Alkylation of Furan. *J. Am. Chem. Soc.* **2004,** *126* (38), 11804-11805; (b) Jia, Y.-X.; Zhong, J.; Zhu, S.-F.; Zhang, C.-M.; Zhou, Q.-L., Chiral Brønsted Acid Catalyzed Enantioselective Friedel–Crafts Reaction of Indoles and α-Aryl Enamides: Construction of Quaternary Carbon Atoms. *Angew. Chem., Int. Ed.* **2007,** *46* (29), 5565-5567; (c) Kang, Q.; Zhao, Z.-A.; You, S.-L., Highly Enantioselective Friedel−Crafts Reaction of Indoles with Imines by a Chiral Phosphoric Acid. *J. Am. Chem. Soc.* **2007,** *129* (6), 1484-1485; (d) Seayad, J.; Seayad, A. M.; List, B., Catalytic Asymmetric Pictet−Spengler Reaction. *J. Am. Chem. Soc.* **2006,** *128* (4), 1086-1087.

4. (a) Itoh, J.; Fuchibe, K.; Akiyama, T., Chiral Brønsted Acid Catalyzed Enantioselective Aza-Diels–Alder Reaction of Brassard's Diene with Imines. *Angew. Chem., Int. Ed.* **2006,** *45* (29), 4796-4798; (b) Akiyama, T.; Morita, H.; Fuchibe, K., Chiral Brønsted Acid-Catalyzed Inverse Electron-Demand Aza Diels−Alder Reaction. *J. Am. Chem. Soc.* **2006,** *128* (40), 13070-13071.

5. Guo, Q.-X.; Liu, H.; Guo, C.; Luo, S.-W.; Gu, Y.; Gong, L.-Z., Chiral Brønsted Acid-Catalyzed Direct Asymmetric Mannich Reaction. *J. Am. Chem. Soc.* **2007,** *129* (13), 3790-3791.

6. (a) Akiyama, T.; Saitoh, Y.; Morita, H.; Fuchibe, K., Enantioselective Mannich-Type Reaction Catalyzed by a Chiral Brønsted Acid Derived from TADDOL. *Adv. Synth. Catal.* **2005,** *347* (11-13), 1523-1526; (b) Rowland, G. B.; Zhang, H.; Rowland, E. B.; Chennamadhavuni, S.; Wang, Y.; Antilla, J. C., Brønsted Acid-Catalyzed Imine Amidation. *J. Am. Chem. Soc.* **2005,** *127* (45), 15696-15697.

7. (a) Mori, M.; Nakanishi, M.; Kajishima, D.; Sato, Y., A Novel and General Synthetic

Pathway to Strychnos Indole Alkaloids: Total Syntheses of (−)-Tubifoline, (−)-Dehydrotubifoline, and (−)-Strychnine Using Palladium-Catalyzed Asymmetric Allylic Substitution. *J. Am. Chem. Soc.* **2003,** *125* (32), 9801-9807; (b) Choi, H.; Hua, Z.; Ojima, I., Highly Enantioselective Copper-Catalyzed Conjugate Addition of Diethylzinc to Nitroalkenes. *Org. Lett.* **2004,** *6* (16), 2689-2691.

8. Mori, K.; Katoh, T.; Suzuki, T.; Noji, T.; Yamanaka, M.; Akiyama, T., Chiral Phosphoric Acid Catalyzed Desymmetrization of meso-1,3-Diones: Asymmetric Synthesis of Chiral Cyclohexenones. *Angew. Chem., Int. Ed.* **2009,** *48* (51), 9652-9654.
9. (a) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C., Enantioselective Organocatalytic Reductive Amination. *J. Am. Chem. Soc.* **2005,** *128* (1), 84-86; (b) Alexander, J. B.; La, D. S.; Cefalo, D. R.; Hoveyda, A. H.; Schrock, R. R., Catalytic Enantioselective Ring-Closing Metathesis by a Chiral Biphen−Mo Complex. *J. Am. Chem. Soc.* **1998,** *120* (16), 4041-4042; (c) Liu, W.-J.; Chen, X.-H.; Gong, L.-Z., Direct Assembly of Aldehydes, Amino Esters, and Anilines into Chiral Imidazolidines via Brønsted Acid Catalyzed Asymmetric 1,3-Dipolar Cycloadditions. *Org. Lett.* **2008,** *10* (23), 5357-5360.
10. Bradshaw, B.; Etxebarría-Jardi, G.; Bonjoch, J.; Viózquez, S. F.; Guillena, G.; Nájera, C., Efficient Solvent-Free Robinson Annulation Protocols for the Highly Enantioselective Synthesis of the Wieland–Miescher Ketone and Analogues. *Adv. Synth. Catal.* **2009,** *351* (14-15), 2482-2490.

Chapter 7

1. (a) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J., Transition Metal-Catalyzed Carbocyclizations in Organic Synthesis. *Chem. Rev.* **1996,** *96* (2), 635-662; (b) Lautens, M.; Klute, W.; Tam, W., Transition Metal-Mediated Cycloaddition Reactions. *Chem. Comm.* **1996,** *96*, 49-92; (c) Lloyd-Jones, G. C., Mechanistic aspects of transition metal catalysed 1,6-diene and 1,6-enyne cycloisomerisation reactions. *Org. Biomol. Chem.* **2003,** *1*, 215-236; (d) Bauer, R. A.; DiBlasi, C. M.; Tan, D. S., The tert-Butylsulfinamide Lynchpin in Transition-Metal-Mediated Multiscaffold Library Synthesis. *Org. Lett.* **2010,** *12*, 2084-2087.
2. (a) Bennacer, B.; Fujiwara, M.; Ojima, I., Novel [2 + 2 + 2 + 1] Cycloaddition of Enediynes Catalyzed by Rhodium Complexes. *Org. Lett.* **2004,** *6* (20), 3589-3591; (b) Bennacer, B.; Fujiwara, M.; Lee, S.; Ojima, I., Silicon-Initiated Carbonylative Carbotricyclization and [2+2+2+1] Cycloaddition of Enediynes Catalyzed by Rhodium Complexes. *J. Am. Chem.Soc.* **2005,** *127* (50), 17756-17767; (c) Kaloko, J. J.; Teng, Y.-H.; Ojima, I., One-step formation of fused tetracyclic skeletons from cyclohexene-diynes and carbon monoxide through Rh(I)-catalyzed [2+2+2+1] cycloaddition reaction. *Chem. Commun.* **2009,** (30), 4569-4571.
3. Evans, P. A.; Robinson, J. E.; Baum, E. W.; Fazal, A. N., Intermolecular transition metal-catalyzed [4+2+2] cycloaddition reactions: A new approach to the construction of eight-membered rings. *J. Am. Chem. Soc.* **2002,** *124* (30), 8782-8783.
4. Wender, P. A.; Gamber, G. G.; Hubbard, R. D.; Pham, S. M.; Zhang, L., Multicomponent Cycloadditions: The Four-Component [5+1+2+1] Cycloaddition of Vinylcyclopropanes,

Alkynes, and CO. *J. Am. Chem. Soc.* **2005,** *127*, 2836-2837.

5. Kim, S. Y.; Lee, S. I.; Choi, S. Y.; Chung, Y. K., Rhodium-Catalyzed Carbonylative [3+3+1] Cycloaddition of Biscyclopropanes with a Vinyl Substituent To Form Seven-Membered Rings. *Angew. Chem. Int. Ed.* **2008,** *47*, 4914-4917.

6. (a) Wang, Y.; Wang, J.; Su, J.; Huang, F.; Jiao, L.; Liang, Y.; Yang, D.; Zhang, S.; Wender, P. A.; Yu, Z. X., A Computationally Designed Rh(I)-Catalyzed Two-Component [5+2+1] Cycloaddition of Ene-vinylcyclopropanes and CO for the Synthesis of Cyclooctenones. *J. Am. Chem. Soc.* **2007,** *129*, 10060-10061; (b) Yuana, C.; Jiaoa, L.; Yu, Z.-X., Formal total synthesis of (±)-hirsutic acid C using the tandem Rh(I)-catalyzed [(5+2)+1] cycloaddition/aldol reaction. *Tetrahedron Letters* **2010,** *51* (43), 5674-5676; (c) Liang, Y.; Jiang, X.; Yu, Z.-X., Enantioselective total synthesis of (+)-asteriscanolide via Rh(I)-catalyzed [(5+2)+1] reaction. *Chem. Commun.* **2011,** *47*, 6659-6661.

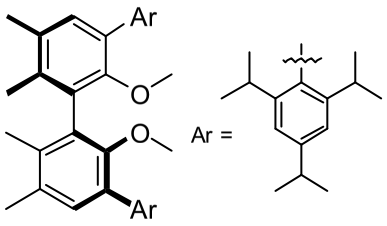
7. (a) Wender, P. A.; Croatt, M. P.; Kühn, B., Rhodium(I)-Catalyzed [2+2], [2+2+2], and [2+2+2+2] Cycloadditions of Dienes or Alkynes with a Bis-ene. *Organometallics* **2009,** *28* (20), 5841-5844; (b) Wender, P. A.; Christy, J. P.; Lesser, A. B.; Gieseler, M. T., The Synthesis of Highly Substituted Cyclooctatetraene Scaffolds by Metal-Catalyzed [2+2+2+2] Cycloadditions: Studies on Regioselectivity, Dynamic Properties, and Metal Chelation. *Angew. Chem. Int. Ed.* **2009,** *48*, 7687-7690.

8. (a) Yu, R. T.; Friedman, R. K.; Rovis, T., Enantioselective Rhodium-Catalyzed [4+2+2] Cycloaddition of Dienyl Isocyanates for the Synthesis of Bicyclic Azocine Rings. *J. Am. Chem. Soc.* **2009,** *131* (13250-13251); (b) Krishna, U. M.; Patil, M. P.; Sunoj, R. B.; Trivedi, G. K., [5+3] cycloaddition of 3-oxidopyrylium: a novel route to functionalized cyclooctanoids from furans *Synthesis* **2010,** *2*, 320-328.

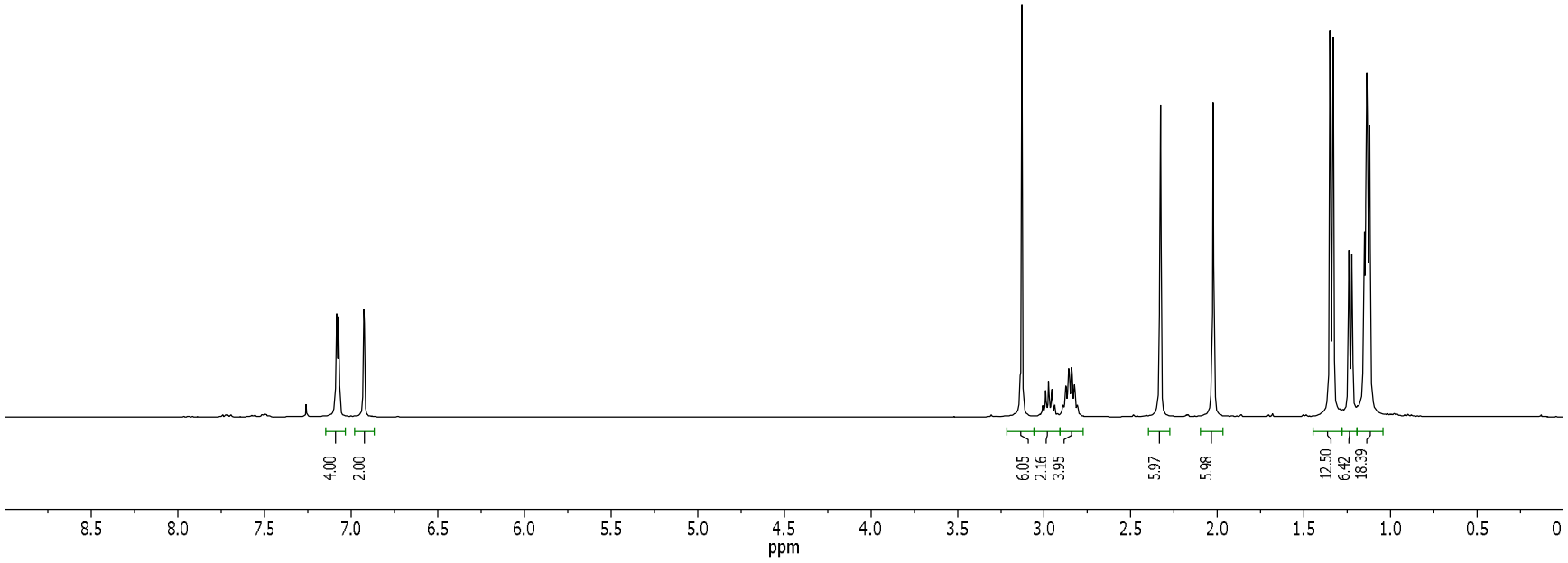
9. (a) Ojima, I.; McCullagh, J. V.; Shay, W. R., New Cascade Silylcarbocyclization (SiCaC) of Enediynes. *Journal of Organometallic Chemistry* **1996,** *521*, 421-423; (b) Ojima, I.; Vu, A. T.; McCullagh, J. V.; Kinoshita, A., Rhodium-Catalyzed Intramolecular Silylcarbotricyclization (SiCaT) of Triynes. *J. Am. Chem. Soc.* **1999,** *121*, 3230-3231; (c) Ojima, I.; Lee, S.-Y., Rhodium-Catalyzed Novel Carbonylative Carbotricyclization of Enediynes. *J. Am. Chem. Soc.* **2000,** *122* (10), 2385-2386; (d) Ojima, I.; Vu, A. T.; Lee, S. Y.; McCullagh, J. V.; Moralee, A. C.; Fujiwara, M.; Hoang, T. H., Rhodium-Catalyzed Silylcarbocyclization (SiCaC) and Carbonylative Silylcarbocyclization (CO-SiCaC) Reactions of Enynes. *J. Am. Chem. Soc.* **2002,** *124*, 9164-9174.

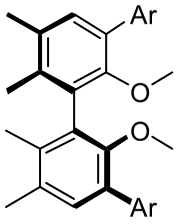
10. Kaloko, J. J. Synthesis of Novel Fused Tricyclic and Tetracyclic Skeletons Through Rh(I)-Catalyzed [2+2+2+1] Cycloaddition of Enediyne Derivatives with Carbon Monoxide. Doctor of Philosophy in Chemistry, Stony Brook University, Stony Brook, NY, August 2010.

APPENDIX

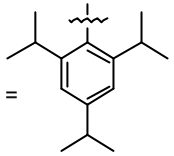

Ar
O
O
Ar
Ar =

(*S*)-**1-36**


4.00
2.00
6.05
2.16
3.95
5.97
5.98
12.50
6.42
18.39
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

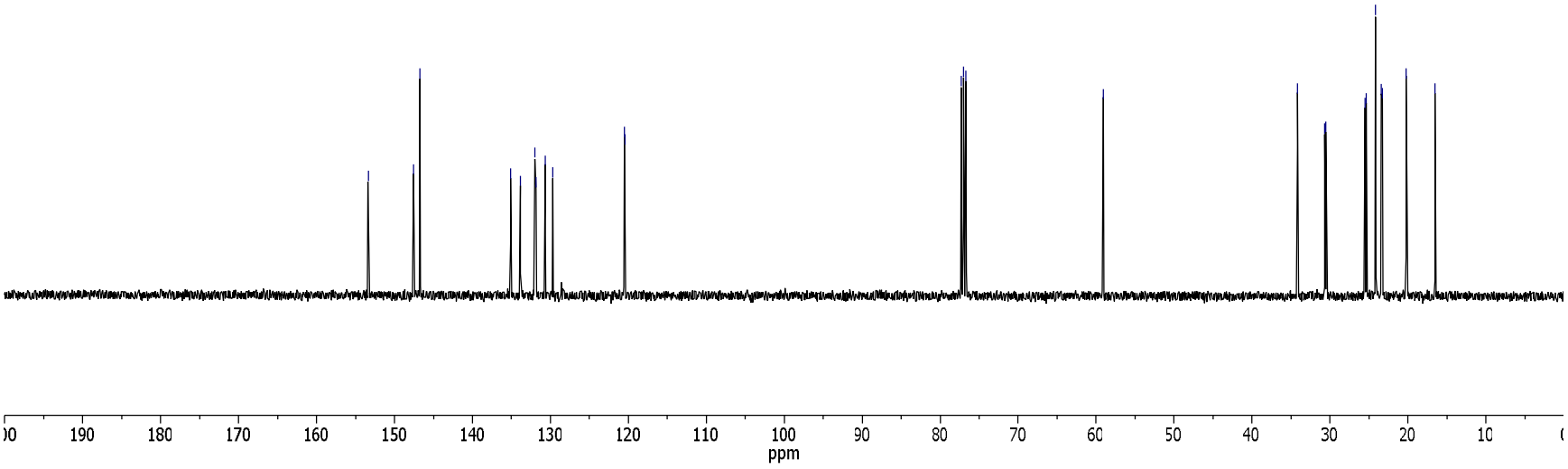


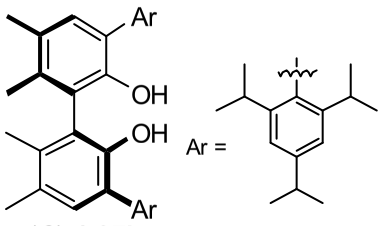
Ar =



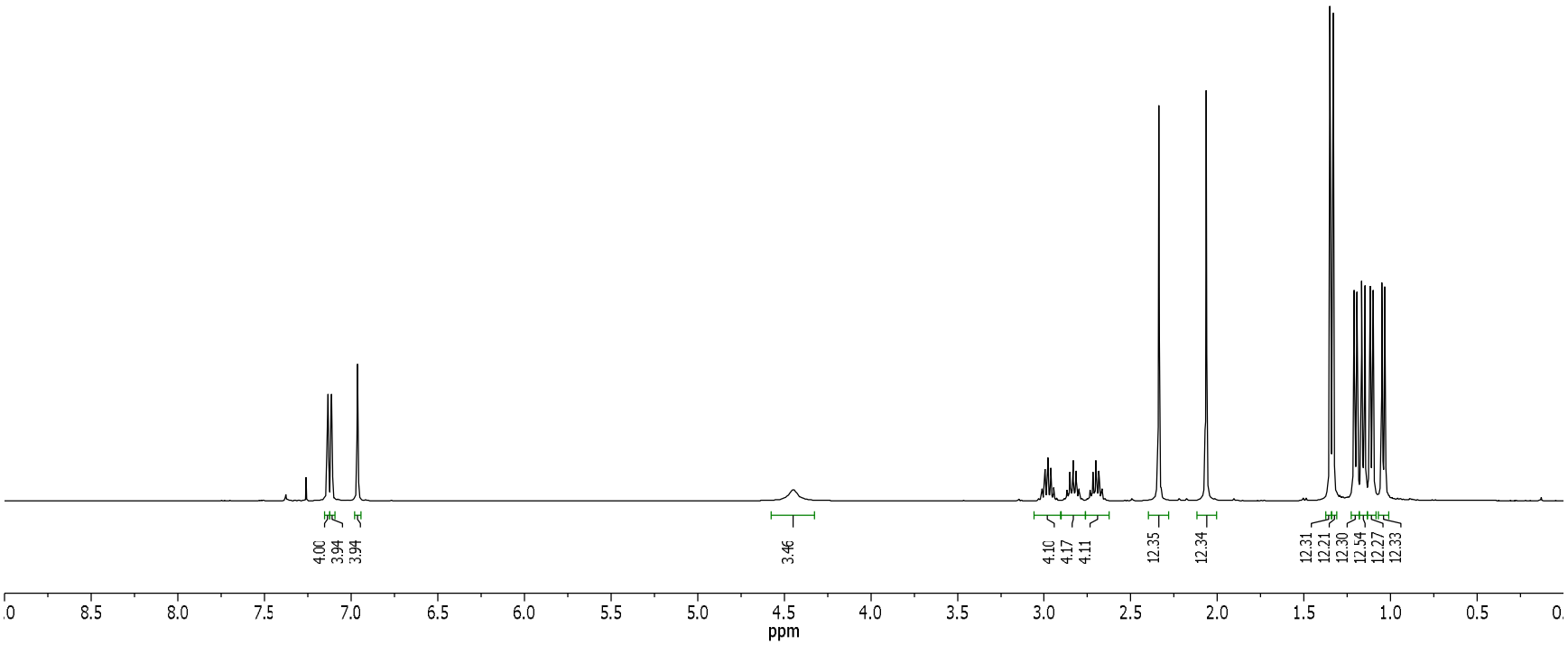
(*S*)-**1-36**

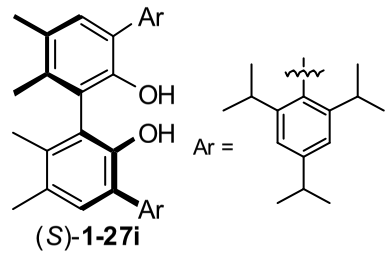
153.379
147.532
146.736
135.096
133.831
131.994
131.872
130.697
129.678
120.533
120.448
77.318
77.000
76.682
59.103
34.179
30.650
30.498
25.486
25.320
24.132
23.416
23.277
20.198
16.509




Ar
OH
OH
Ar
Ar =

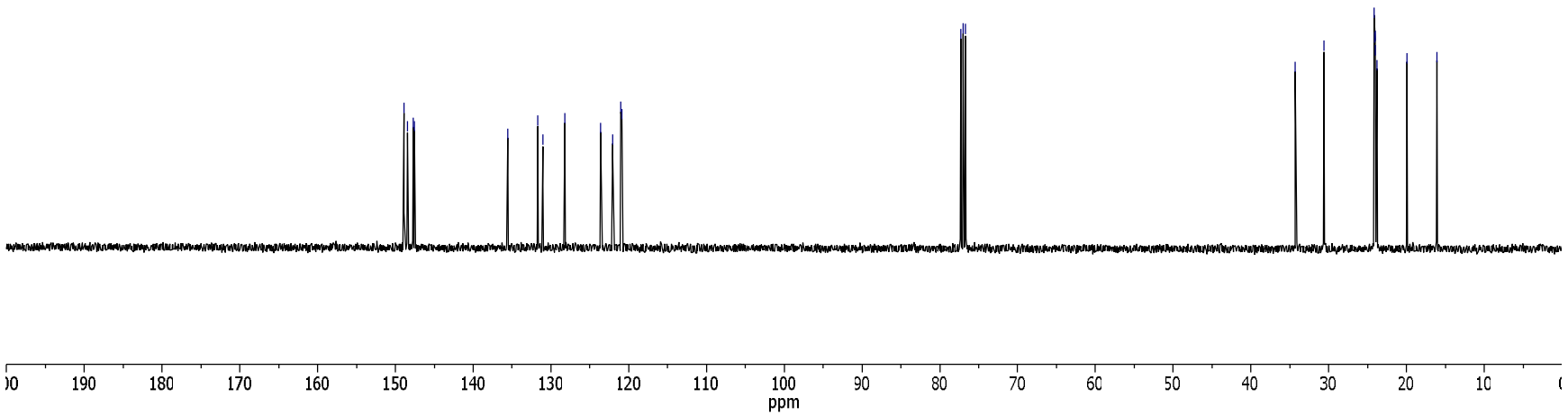
(*S*)-**1-27i**

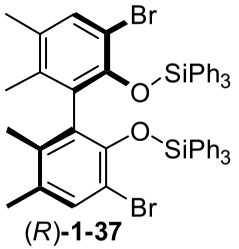

4.00
3.94
3.94
3.46
4.10
4.17
4.11
12.35
12.34
12.31
12.21
12.30
12.54
12.27
12.33
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm



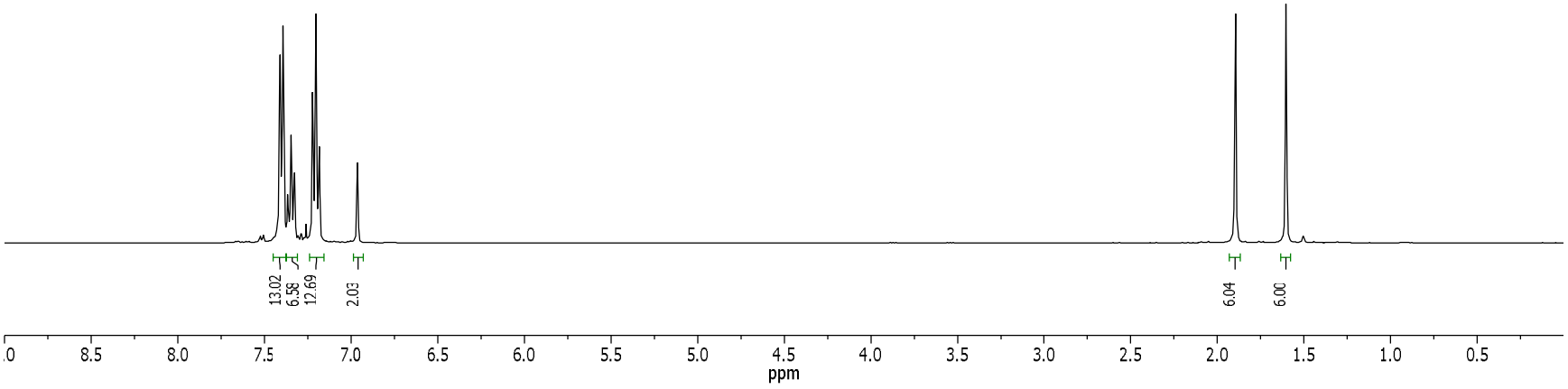
(*S*)-**1-27i**

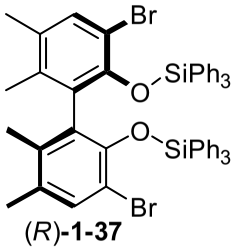
148.883
148.456
147.731
147.584
135.547
131.666
131.046
128.192
123.596
122.037
121.015
120.888
77.318
77.000
76.682
34.285
30.615
24.149
24.073
24.029
23.996
23.823
19.942
16.117




Br
O
SiPh3
O
SiPh3
Br

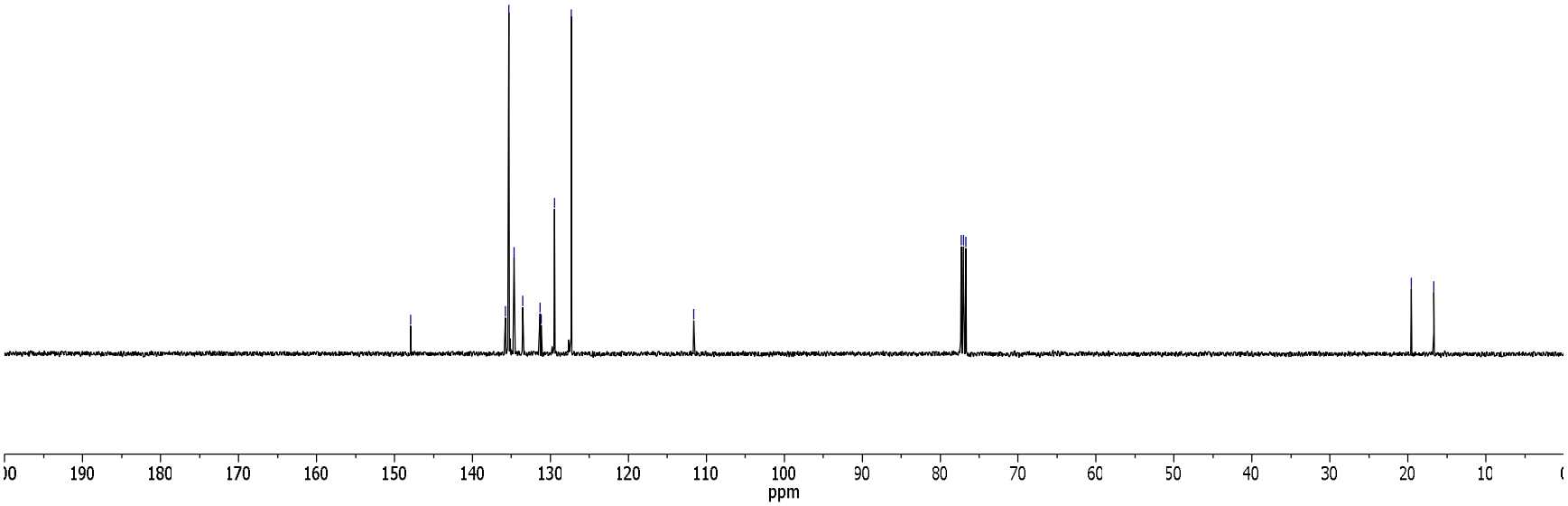
(*R*)-**1-37**

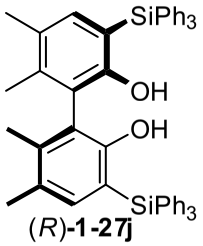

13.02
6.58
12.69
2.03
6.04
6.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

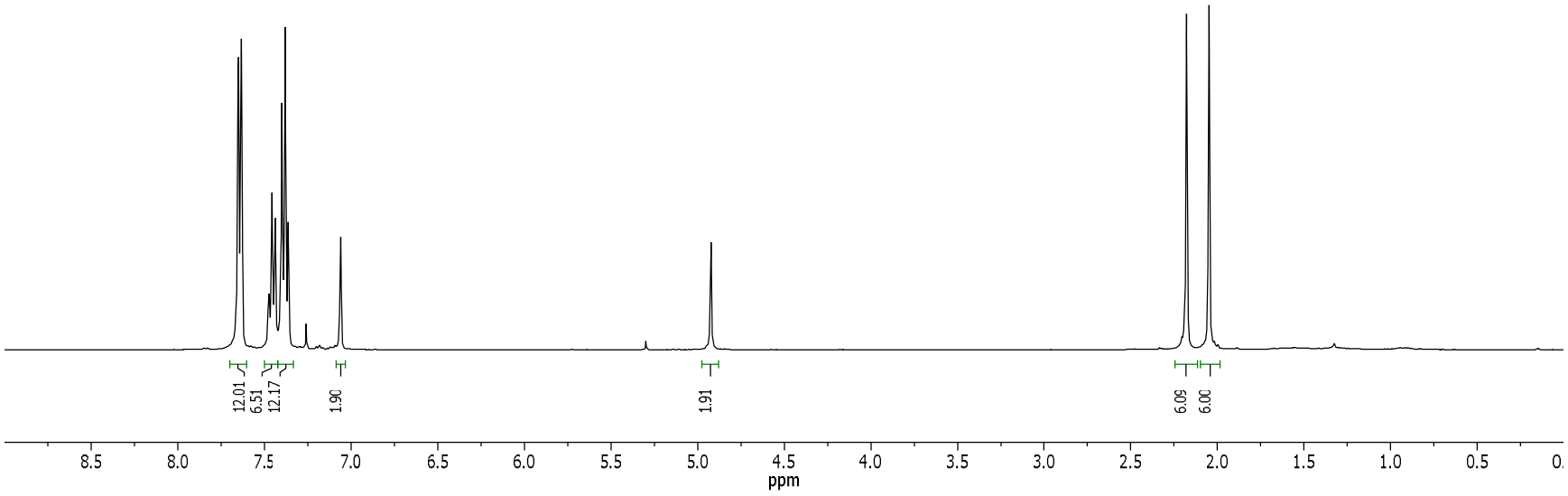


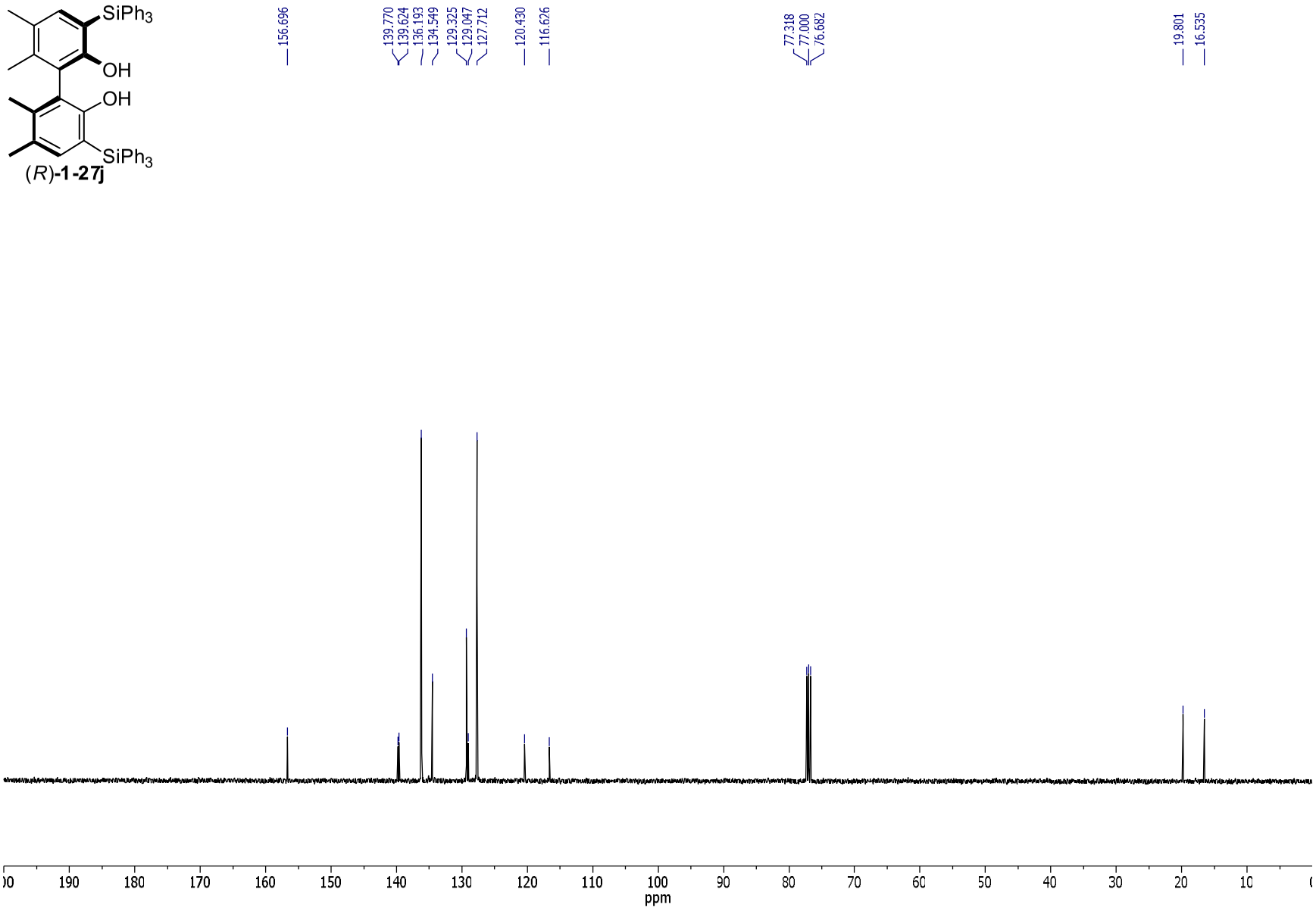
(*R*)-**1-37**

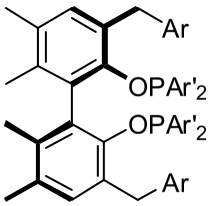
147.925
135.763
135.348
134.636
133.572
131.349
131.159
129.487
127.311
111.641
77.318
77.000
76.682
19.583
16.688



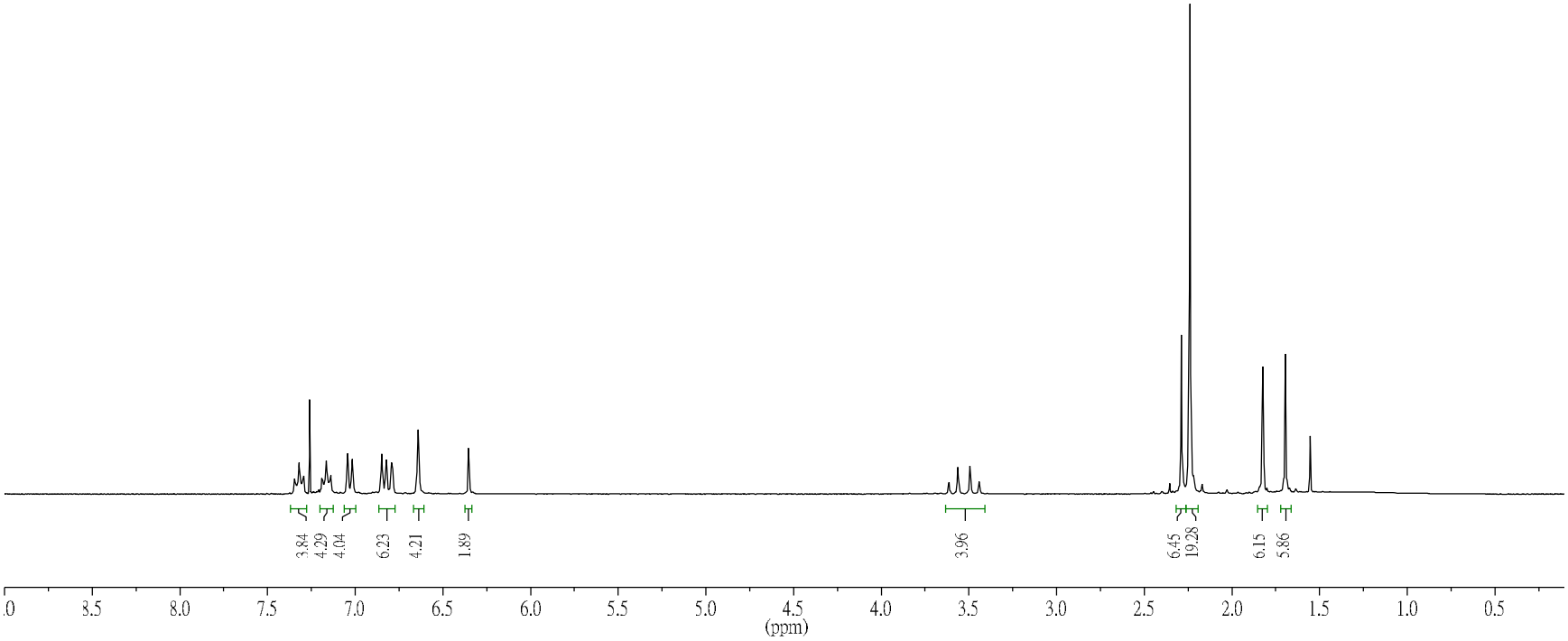

SiPh3
OH
OH
SiPh3
(*R*)-**1-27j**

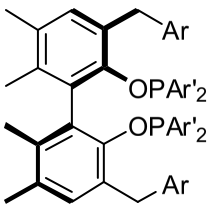

12.01
6.51
12.17
1.90
1.91
6.09
6.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


SiPh3
OH
OH
SiPh3
(R)-1-27j
156.696
139.770
139.624
136.193
134.549
129.325
129.047
127.712
120.430
116.626
77.318
77.000
76.682
19.801
16.535
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

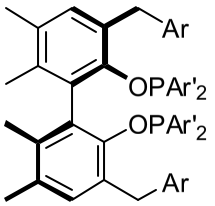


(*R*)-**BOP-L2a**: Ar' = 4-MeC_6H_4
Ar = 3,5-$Me_2C_6H_3$

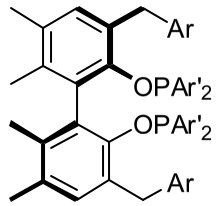




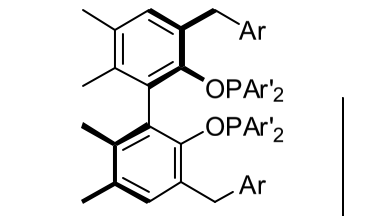
(*R*)-**BOP-L2a**: Ar' = 4-MeC_6H_4
Ar = 3,5-$Me_2C_6H_3$



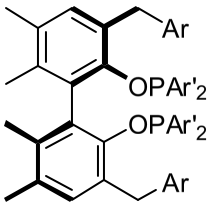
(*R*)-**BOP-L2b**: Ar' = 4-$MeOC_6H_4$
Ar = 3,5-$Me_2C_6H_3$



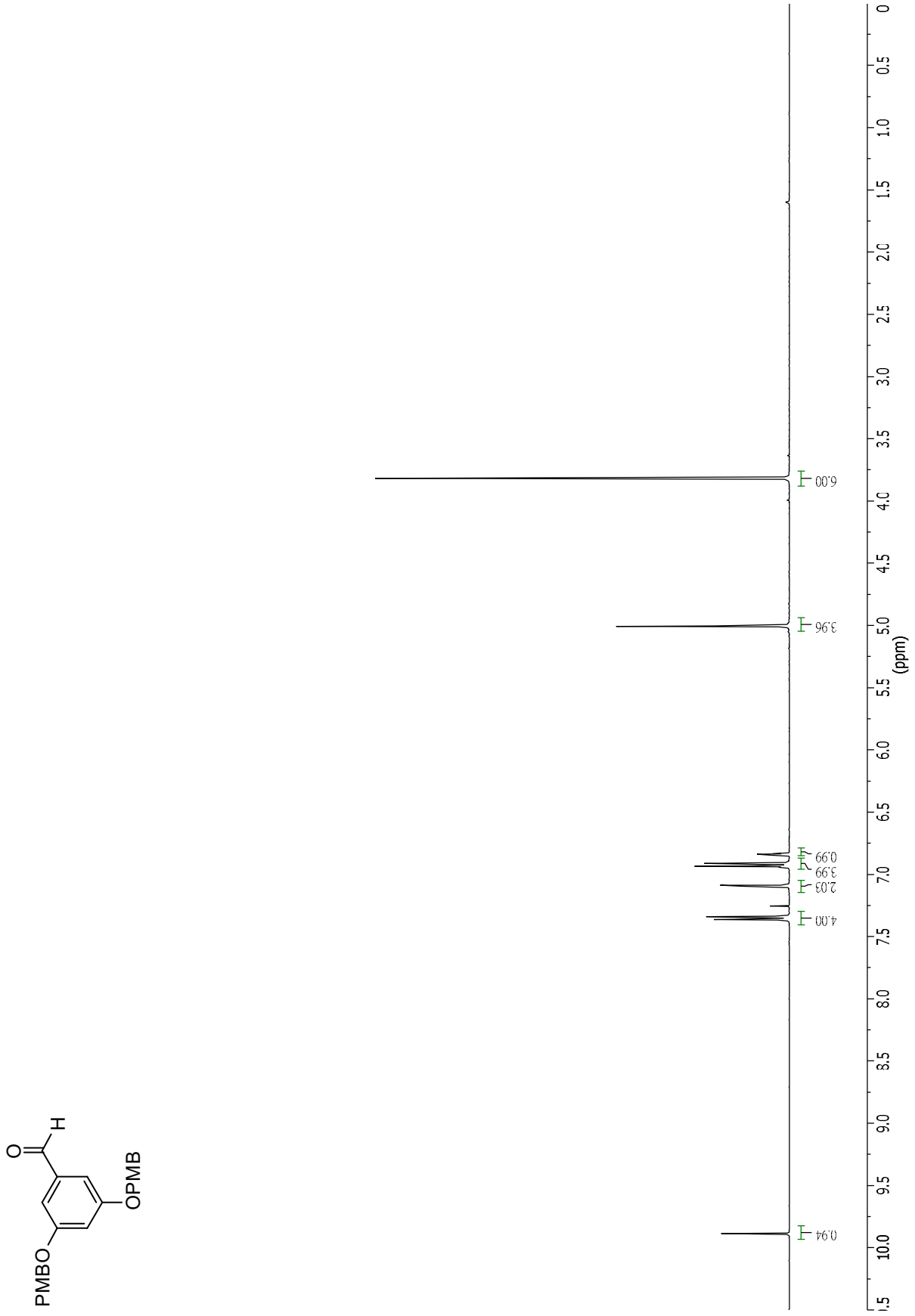
(*R*)-**BOP-L2b**: Ar' = 4-$MeOC_6H_4$
Ar = 3,5-$Me_2C_6H_3$

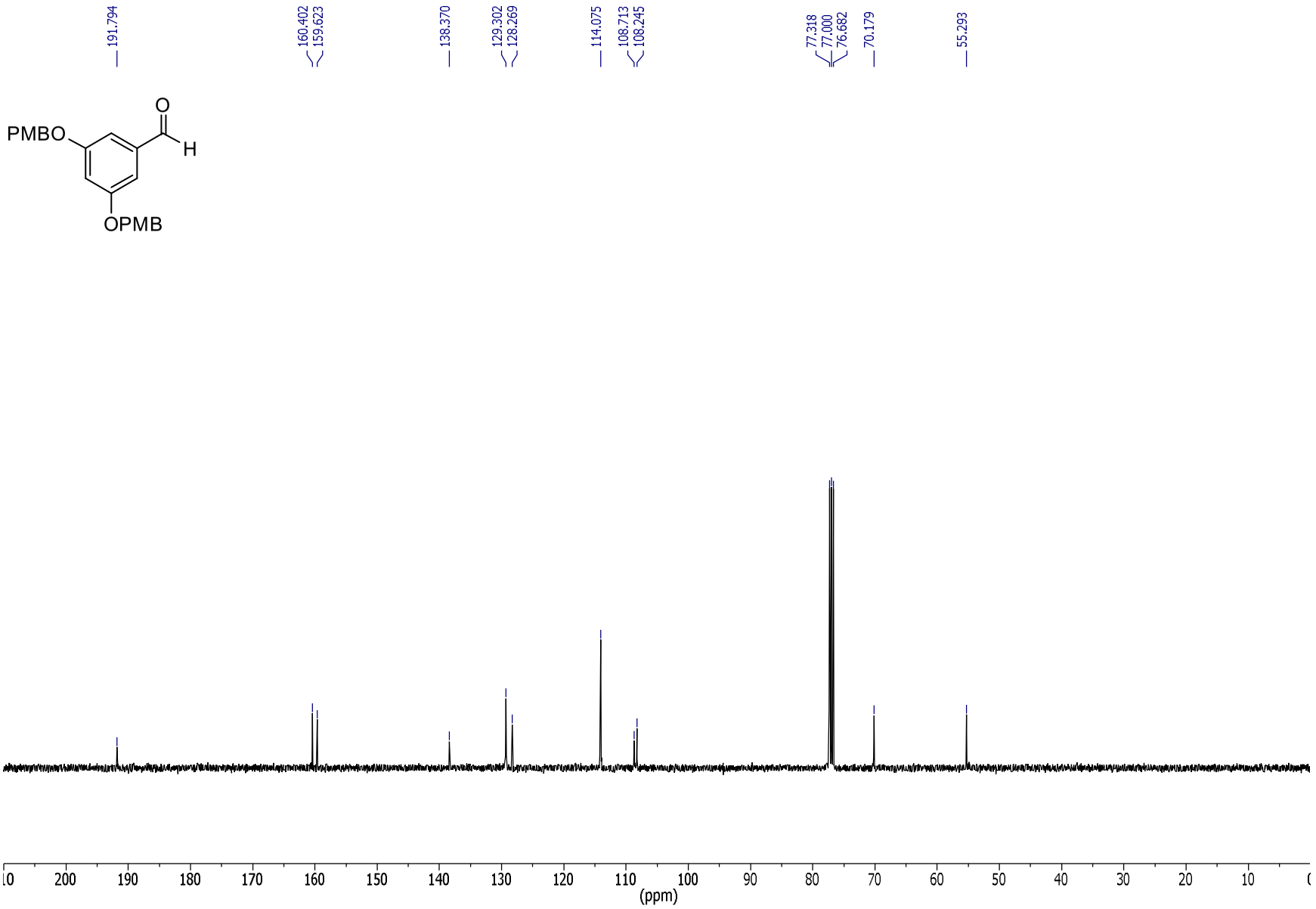


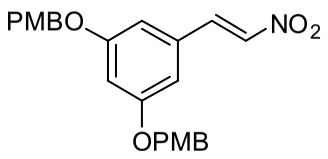
(*R*)-**BOP-L2c**: Ar' = 4-$CF_3C_6H_4$
Ar = 3,5-$Me_2C_6H_3$

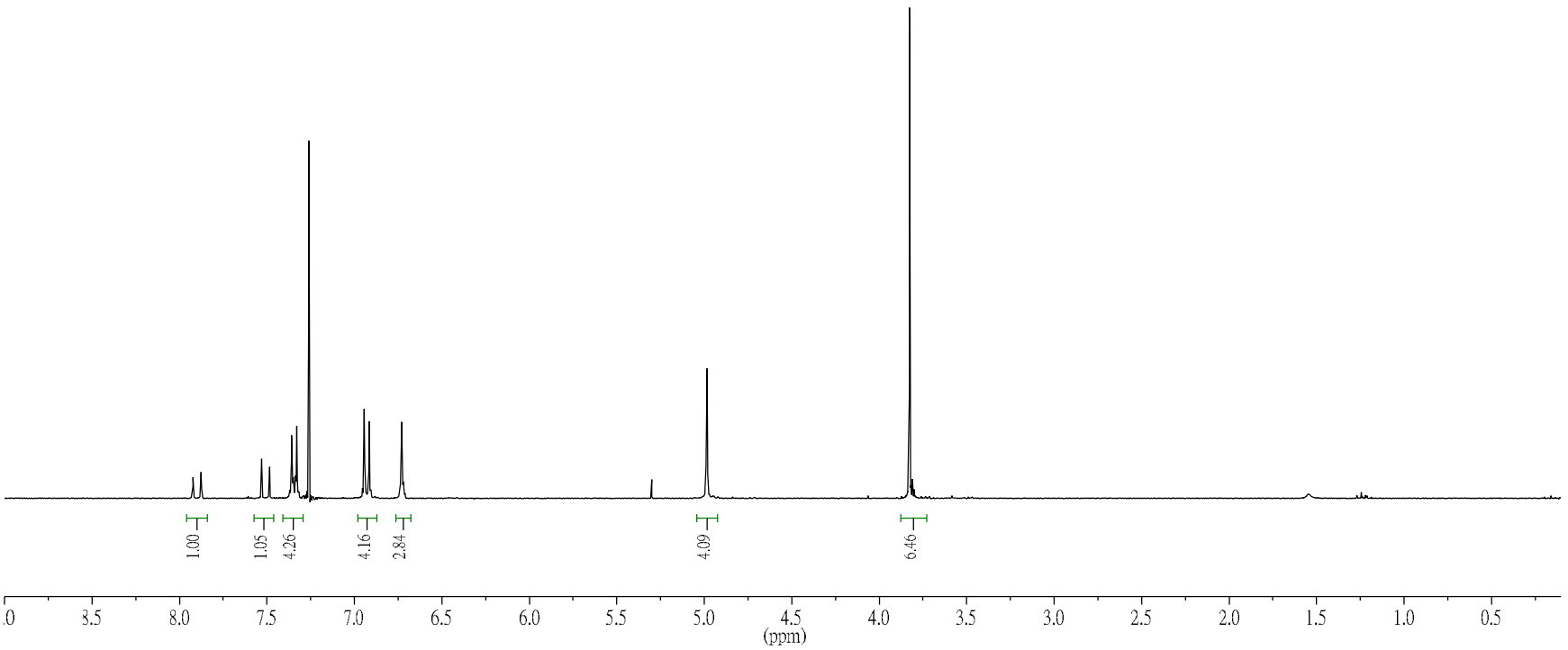


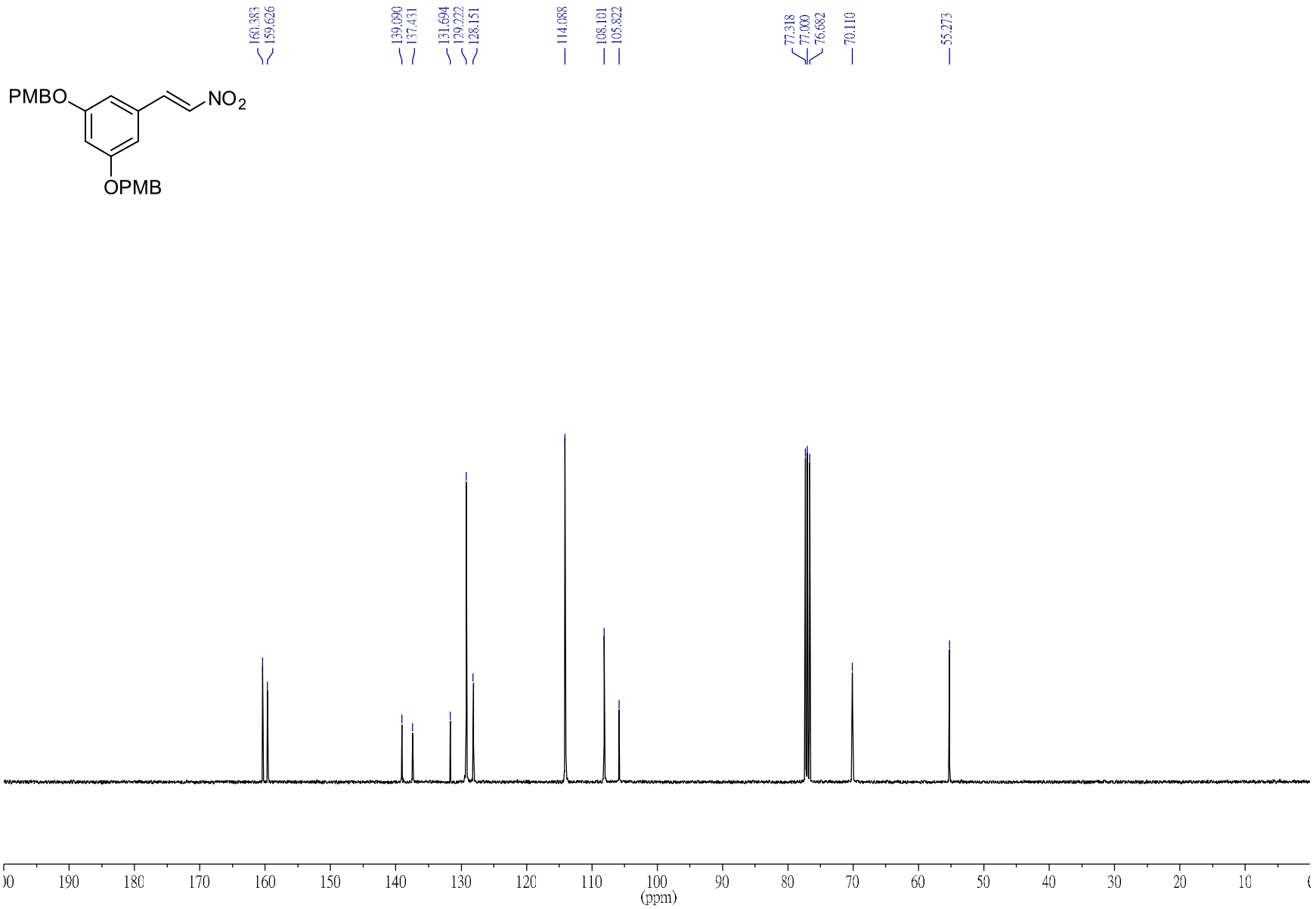
(*R*)-**BOP-L2c**: Ar' = 4-$CF_3C_6H_4$
Ar = 3,5-$Me_2C_6H_3$

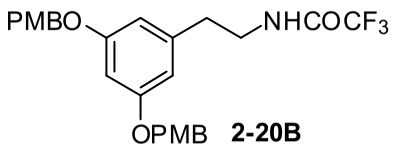

O
H
OPMB
PMBO
6.00
3.96
0.99
3.99
2.03
4.00
0.94
(ppm)


191.794
160.402
159.623
138.370
129.302
128.269
114.075
108.713
108.245
77.318
77.000
76.682
70.179
55.293
O
H
PMBO
OPMB
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

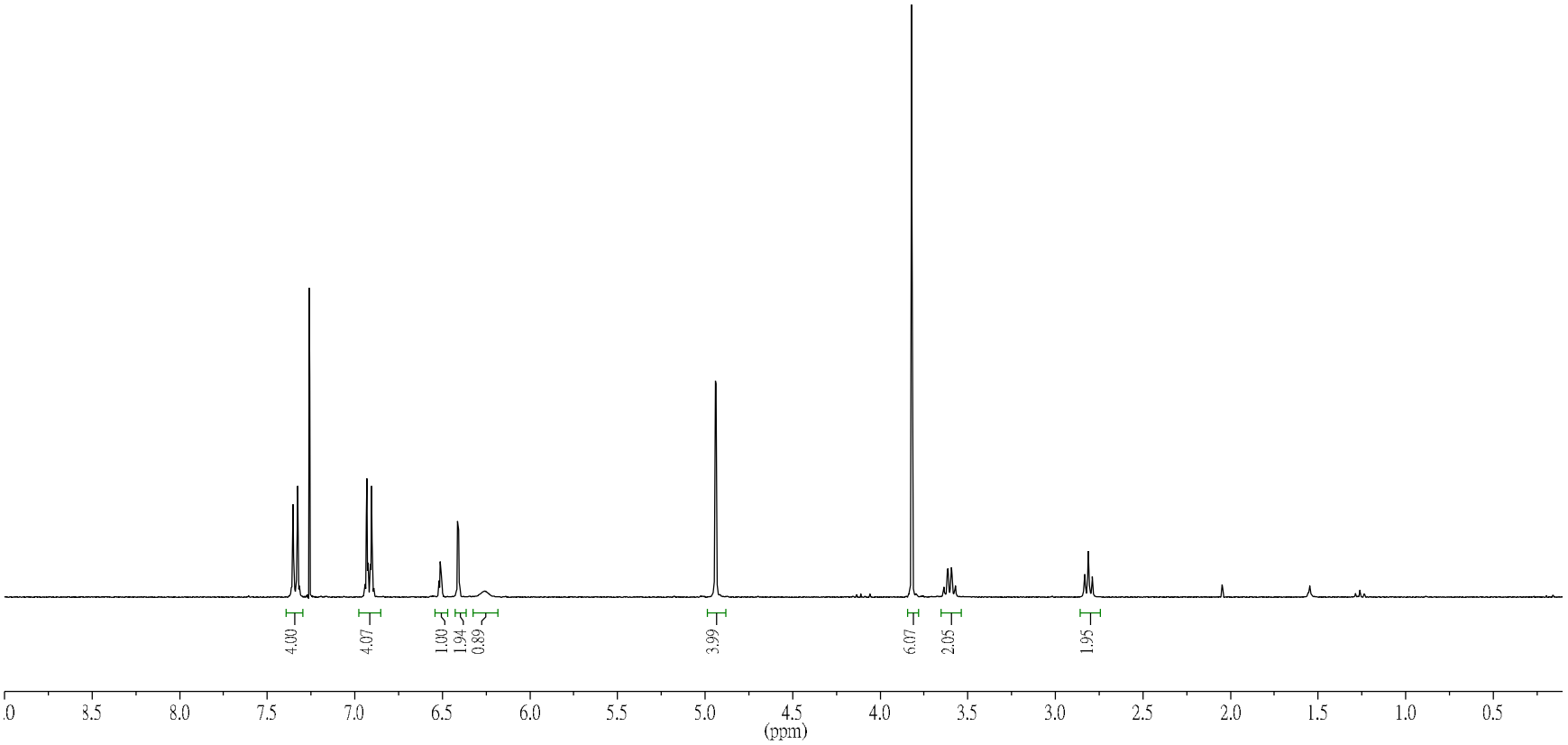

PMBO
NO2
OPMB


1.00
1.05
4.26
4.16
2.84
4.09
6.46
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

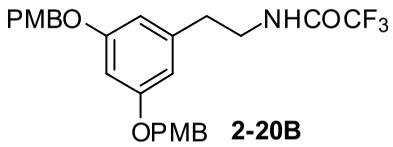

160.383
159.626
139.090
137.431
131.694
129.222
128.151
114.088
108.101
105.822
77.318
77.000
76.682
70.110
55.273
PMBO
NO2
OPMB
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)


PMBO
NHCOCF3
OPMB

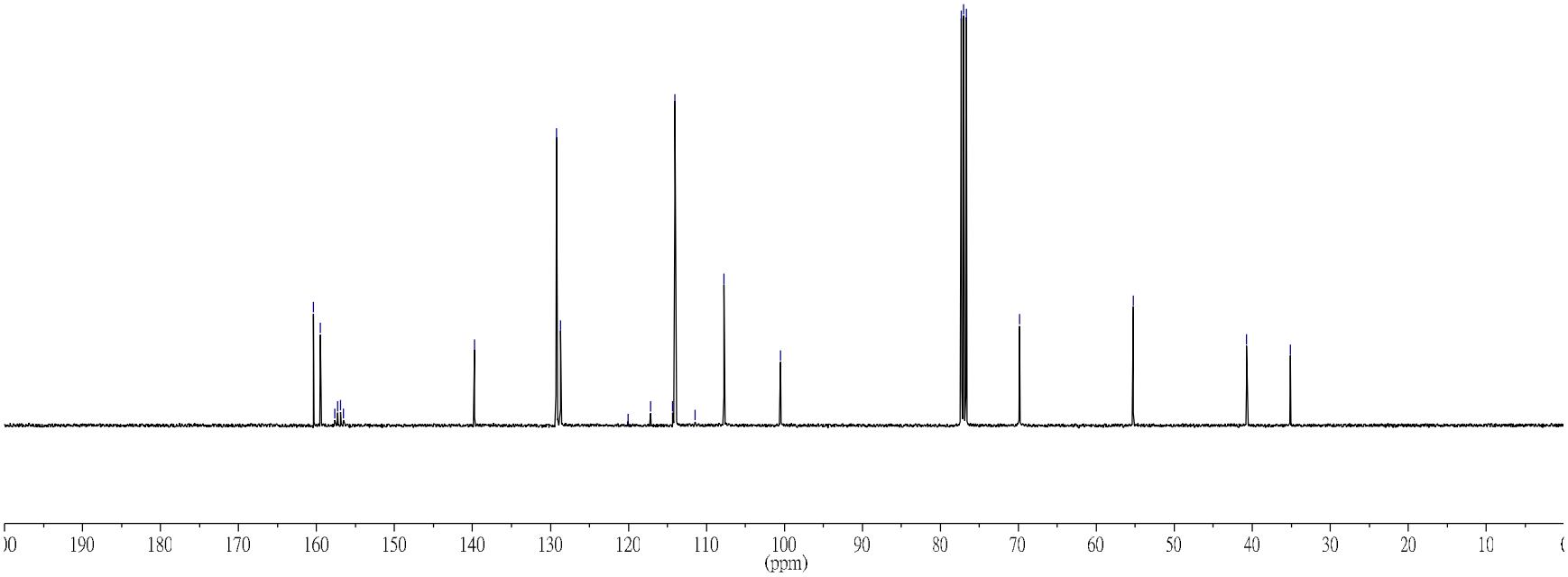
2-20B

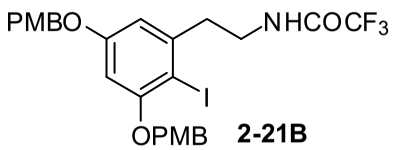

4.00
4.07
1.00
1.94
0.89
3.99
6.07
2.05
1.95
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

160.362
159.509
157.635
157.267
156.900
156.534
139.753
129.233
128.693
120.073
117.187
114.324
114.014
111.460
107.753
100.525
77.318
77.000
76.682
69.860
55.278
40.720
35.127

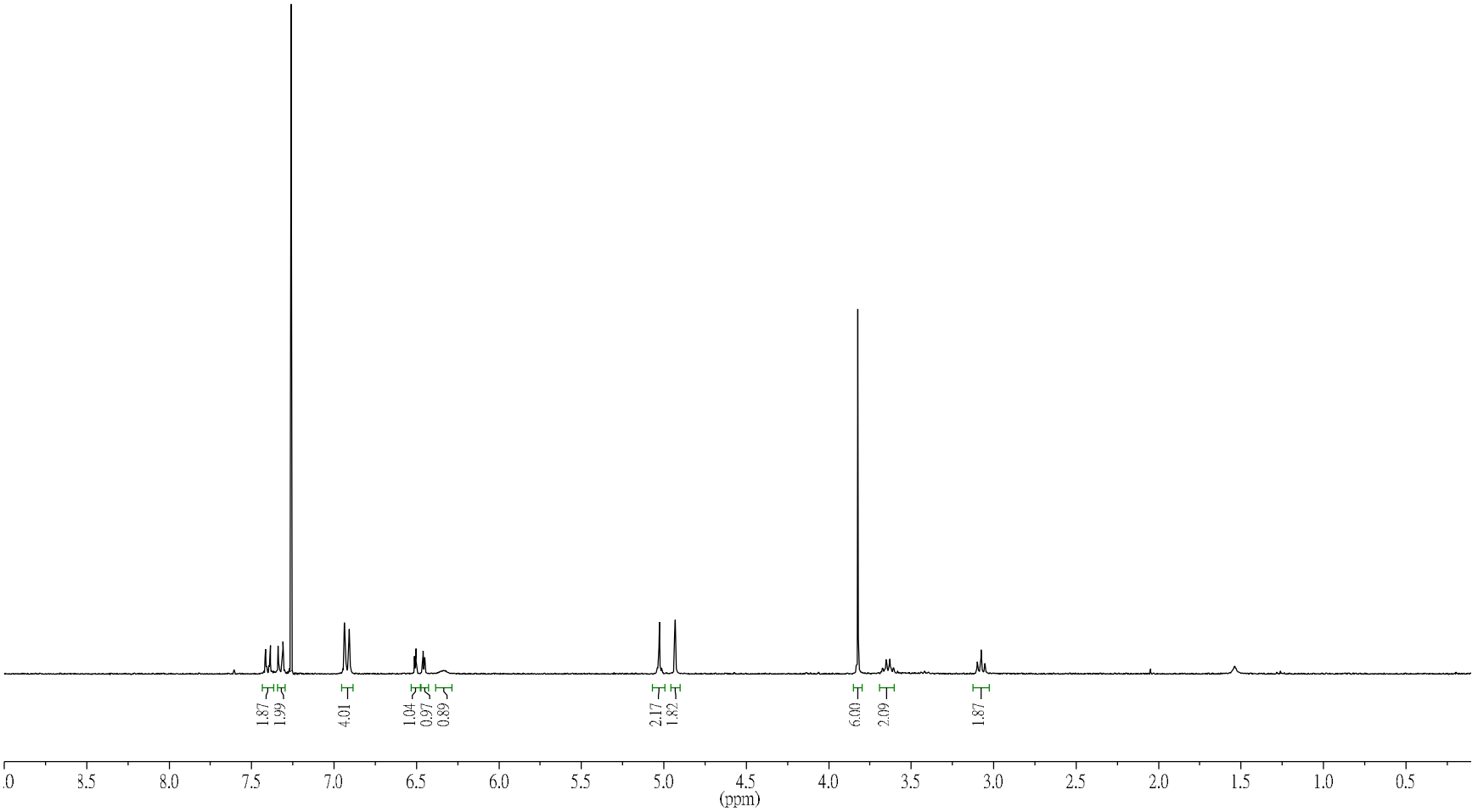


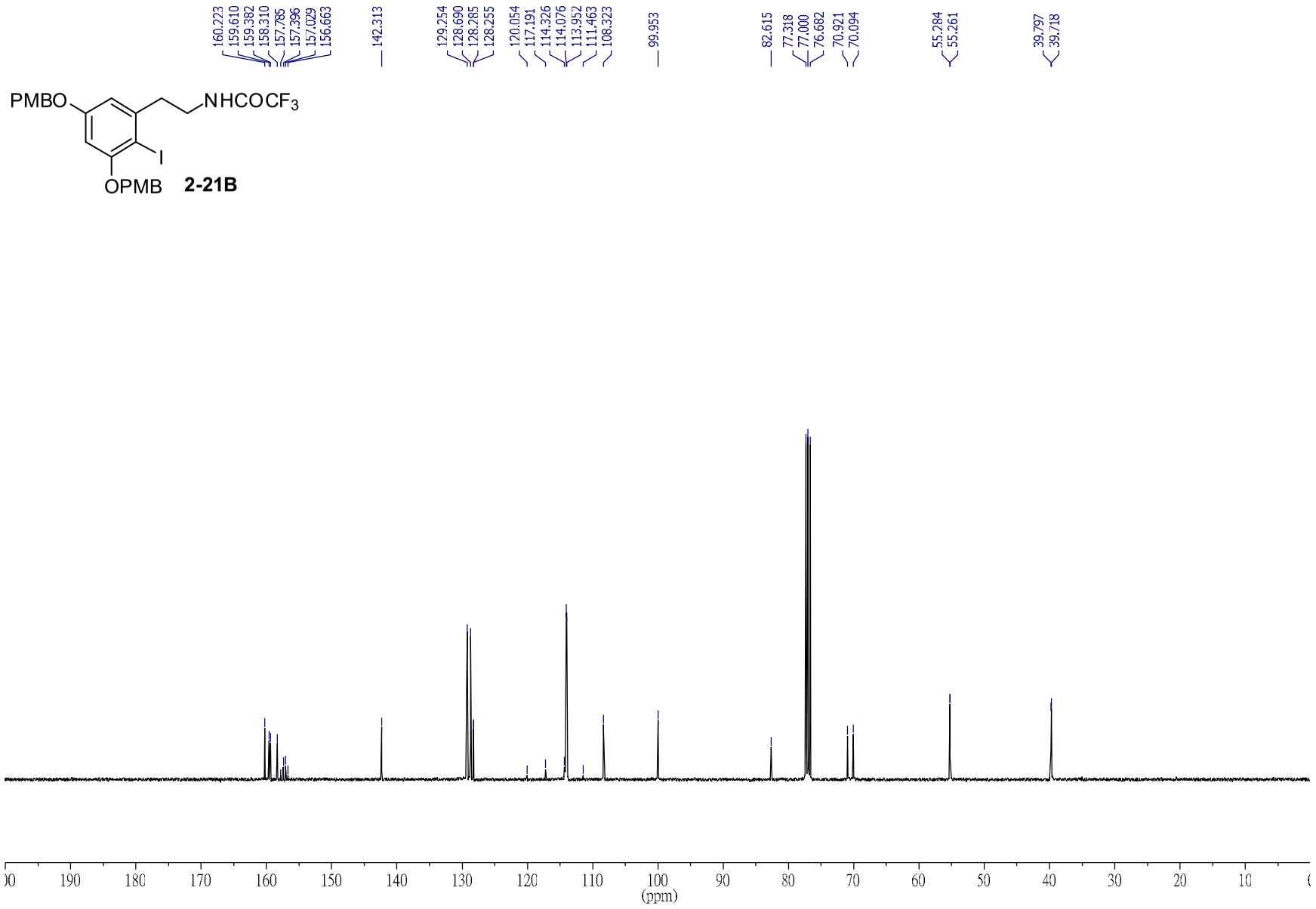
2-20B

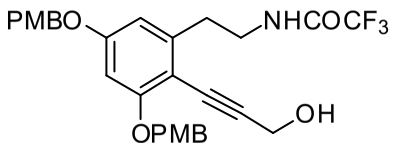



PMBO
NHCOCF3
I
OPMB

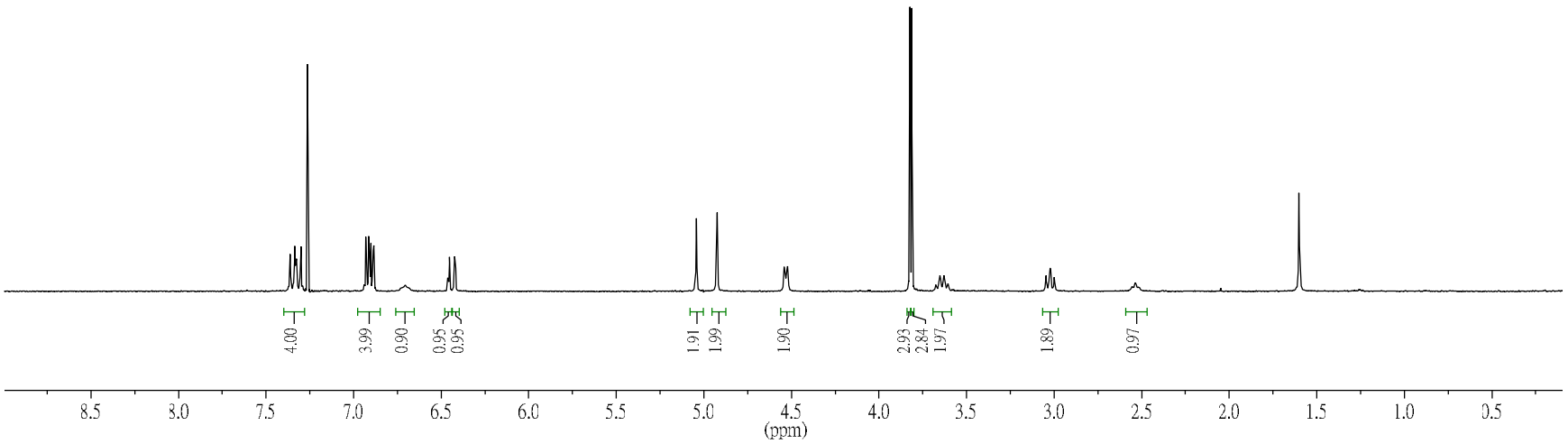
2-21B

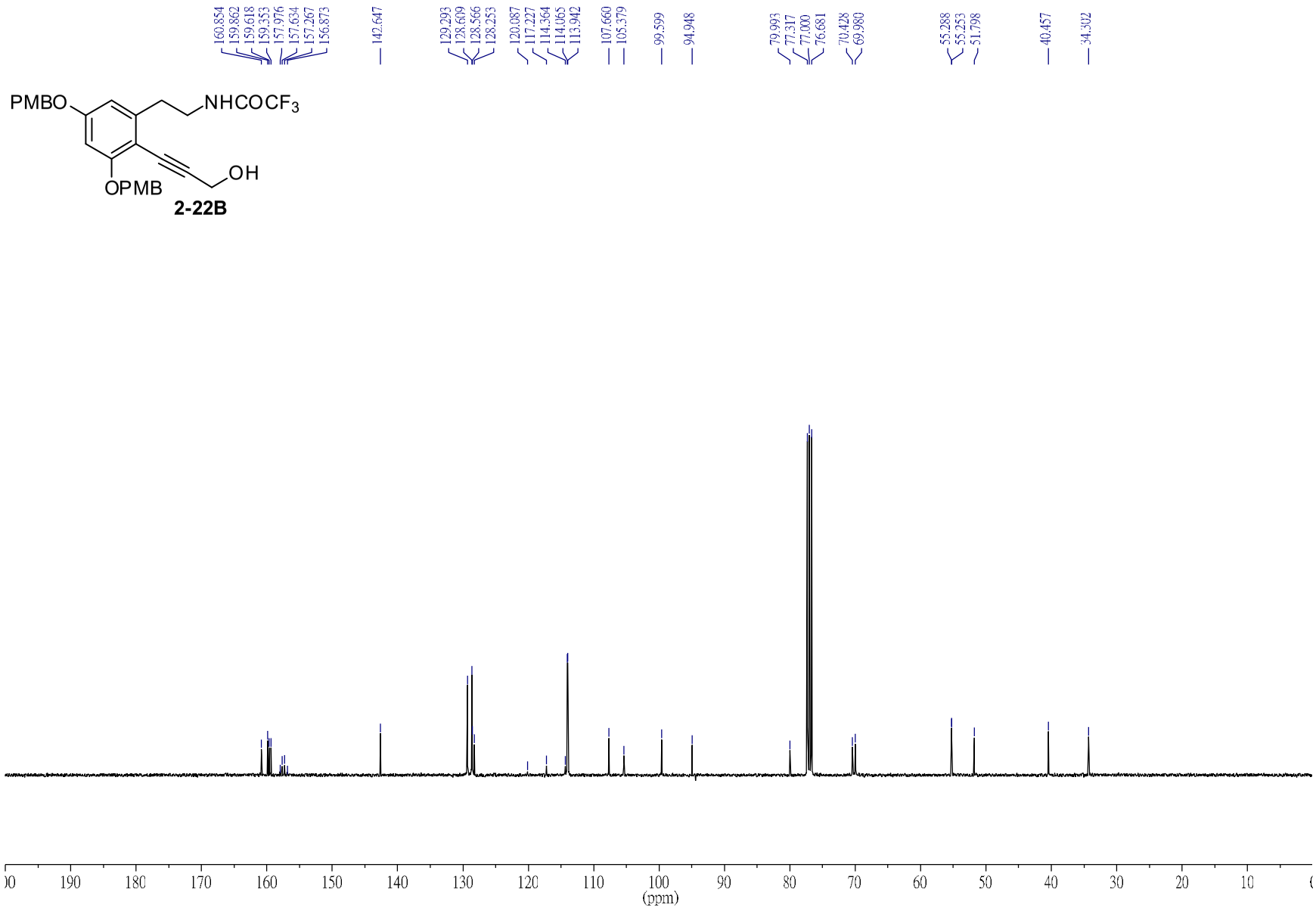

1.87
1.99
4.01
1.04
0.97
0.89
2.17
1.82
6.00
2.09
1.87
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

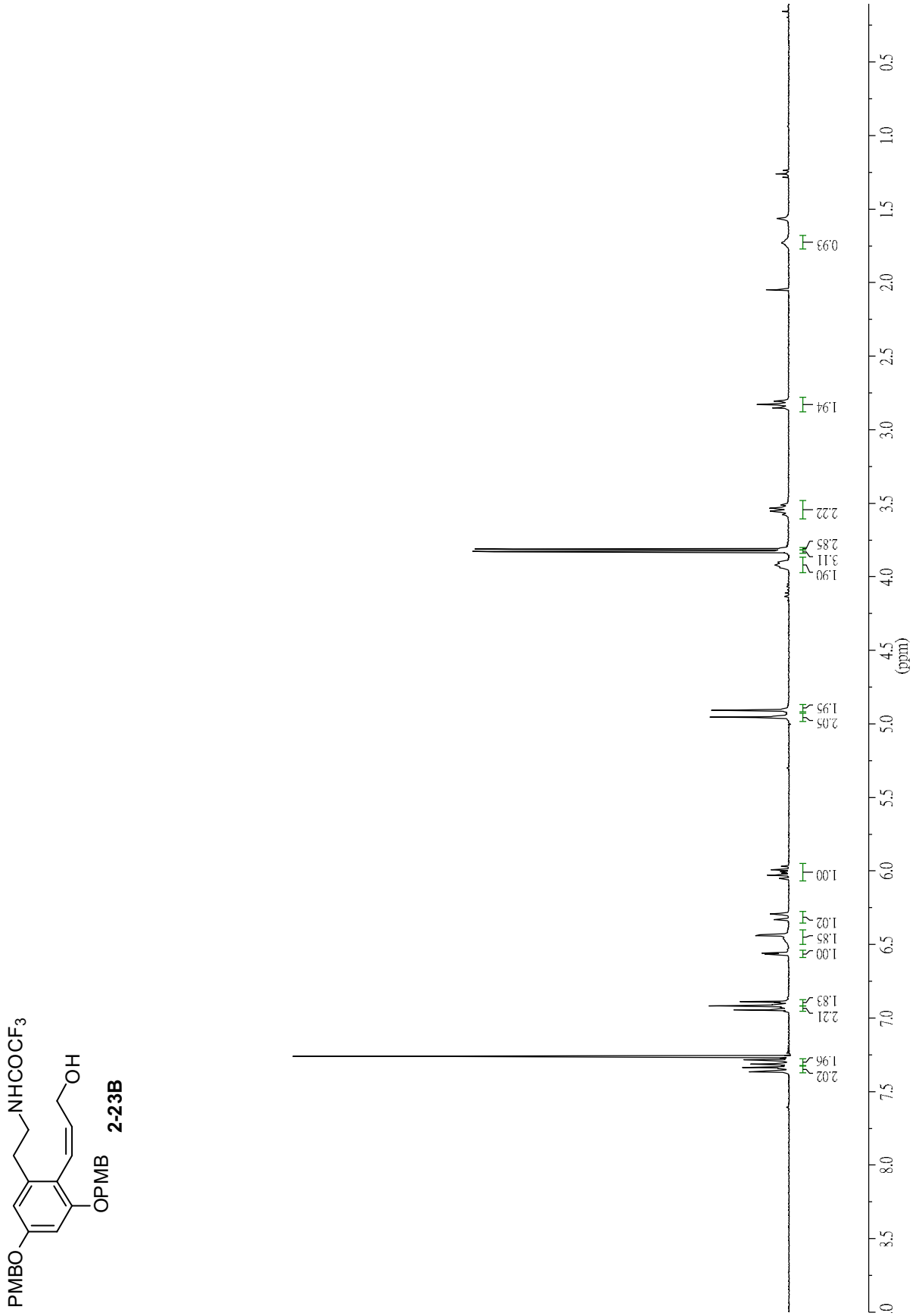

160.223
159.610
159.382
158.310
157.785
157.396
157.029
156.663
142.313
129.254
128.690
128.285
128.255
120.054
117.191
114.326
114.076
113.952
111.463
108.323
99.953
82.615
77.318
77.000
76.682
70.921
70.094
55.284
55.261
39.797
39.718
PMBO
NHCOCF3
I
OPMB
2-21B
(ppm)

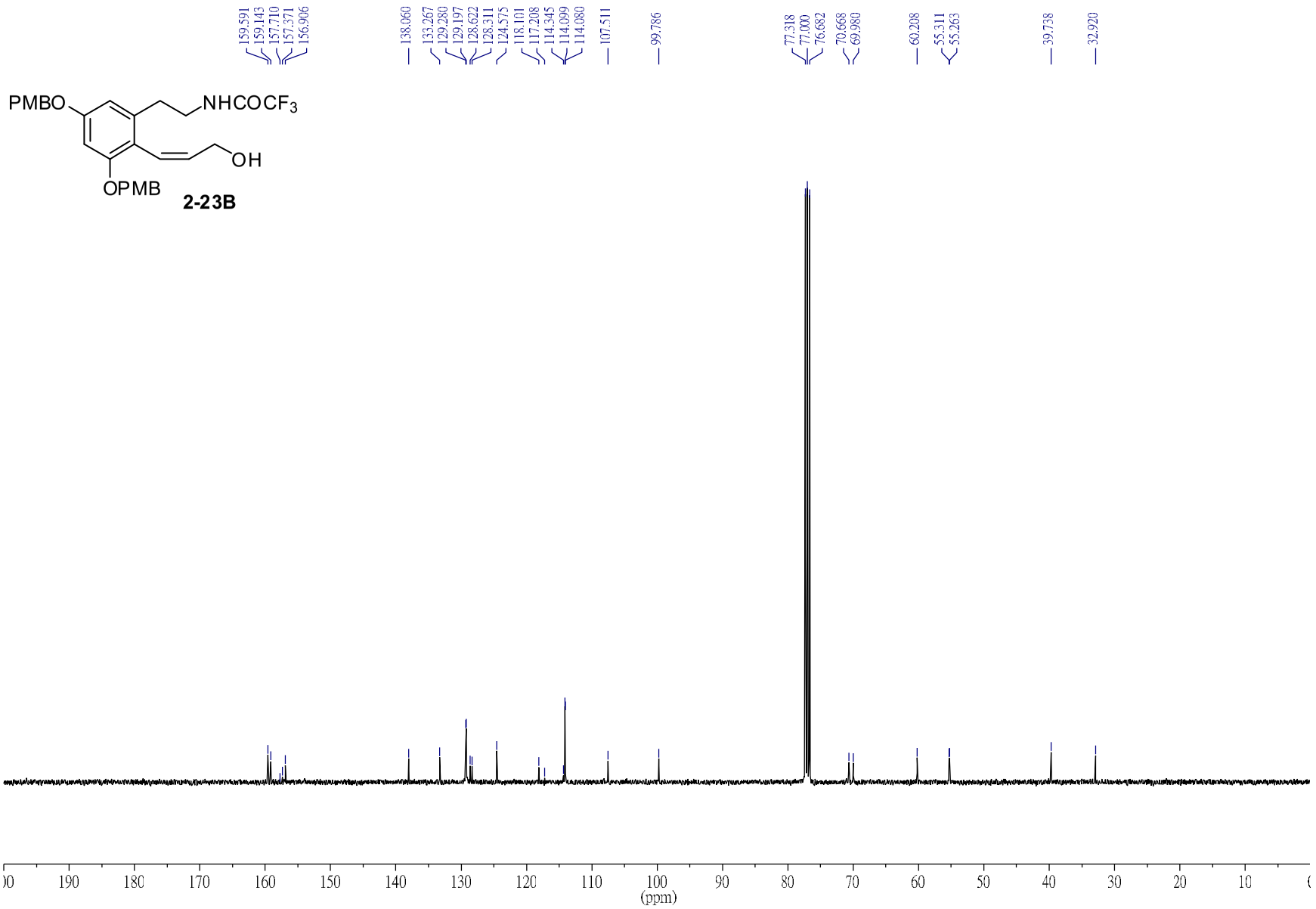

PMBO
NHCOCF3
OH
OPMB

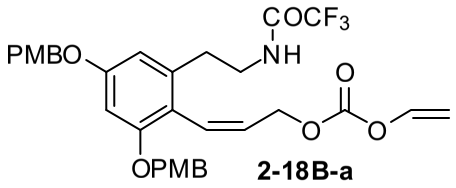
2-22B


4.00
3.99
0.90
0.95
0.95
1.91
1.99
1.90
2.93
2.84
1.97
1.89
0.97
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

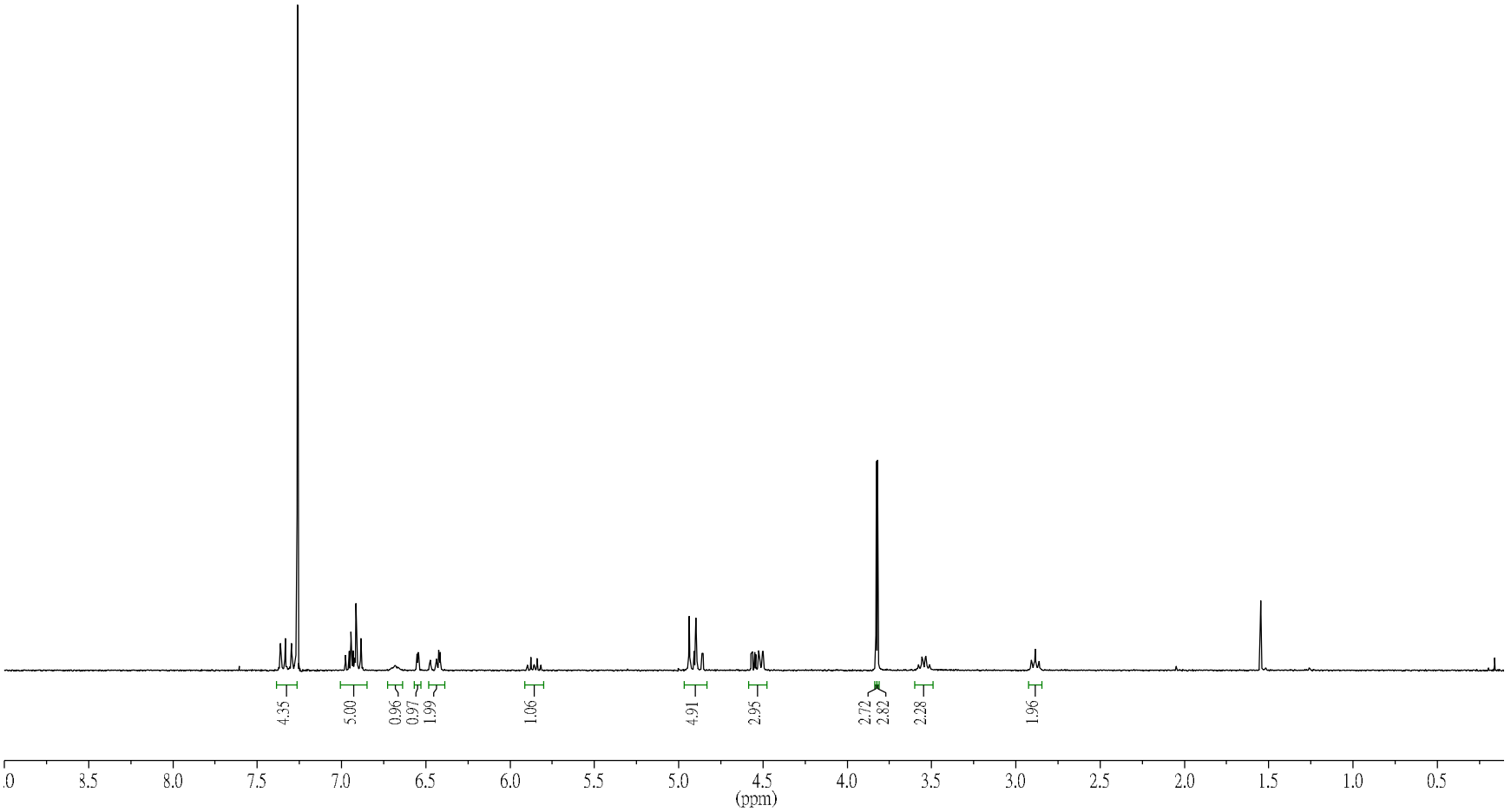

160.854
159.862
159.618
159.353
157.976
157.634
157.267
156.873
142.647
129.293
128.609
128.566
128.253
120.087
117.227
114.364
114.065
113.942
107.660
105.379
99.599
94.948
79.993
77.317
77.000
76.681
70.428
69.980
55.288
55.253
51.798
40.457
34.302
PMBO
NHCOCF3
OH
OPMB
2-22B
(ppm)

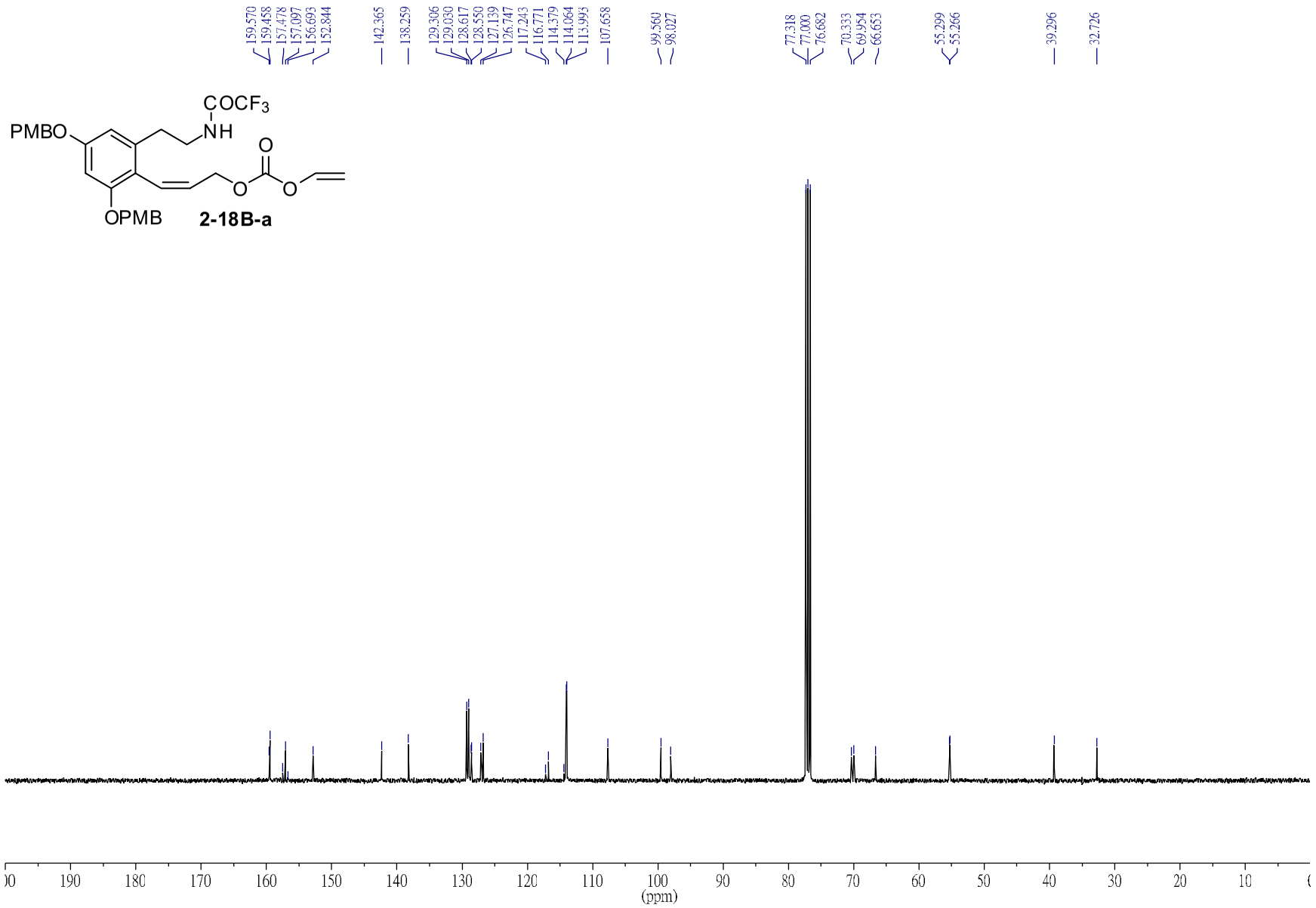

PMBO
OPMB
NHCOCF3
OH
2-23B
2.02
1.96
2.21
1.83
1.00
1.85
1.02
1.00
2.05
1.95
1.90
3.11
2.85
2.22
1.94
0.93
(ppm)

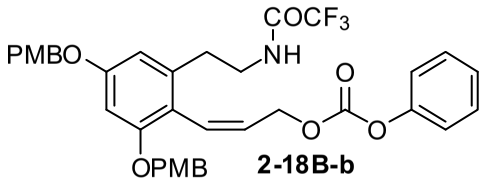

159.591
159.143
157.710
157.371
156.906
138.060
133.267
129.280
129.197
128.622
128.311
124.575
118.101
117.208
114.345
114.099
114.080
107.511
99.786
77.318
77.000
76.682
70.668
69.980
60.208
55.311
55.263
39.738
32.920
PMBO
NHCOCF3
OH
OPMB
2-23B
(ppm)


COCF3
NH
PMBO
O
O
O
OPMB

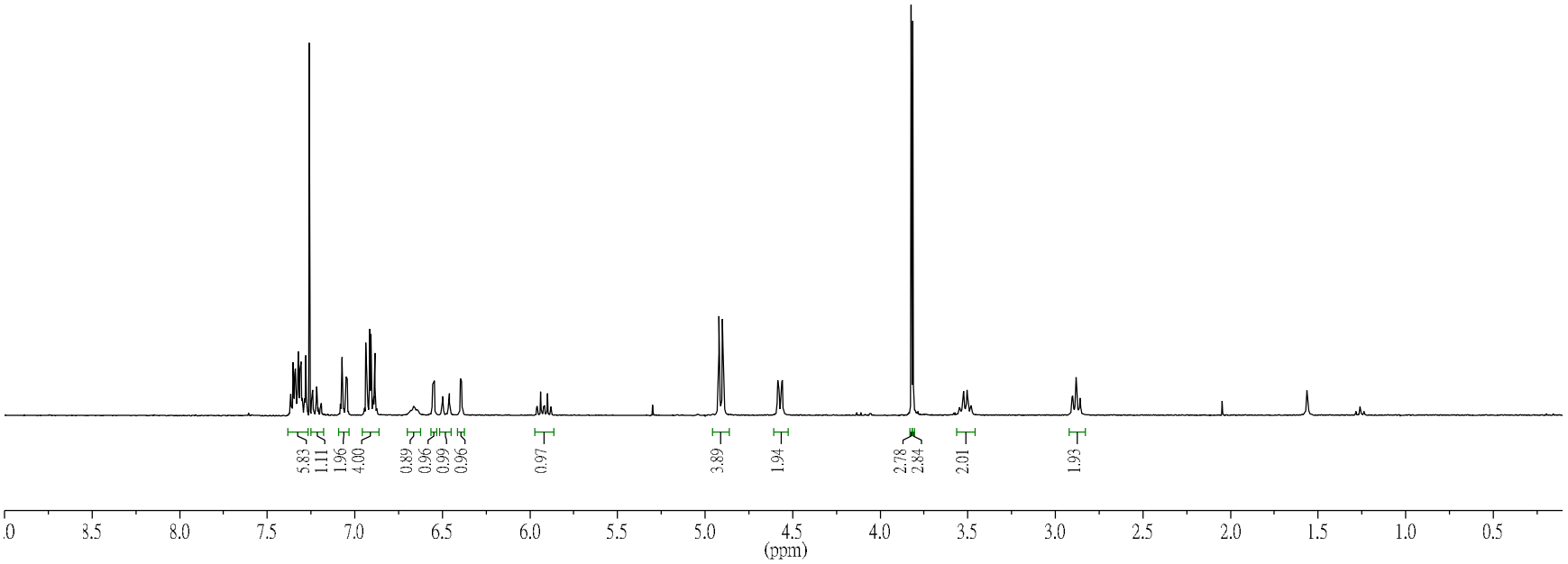
2-18B-a

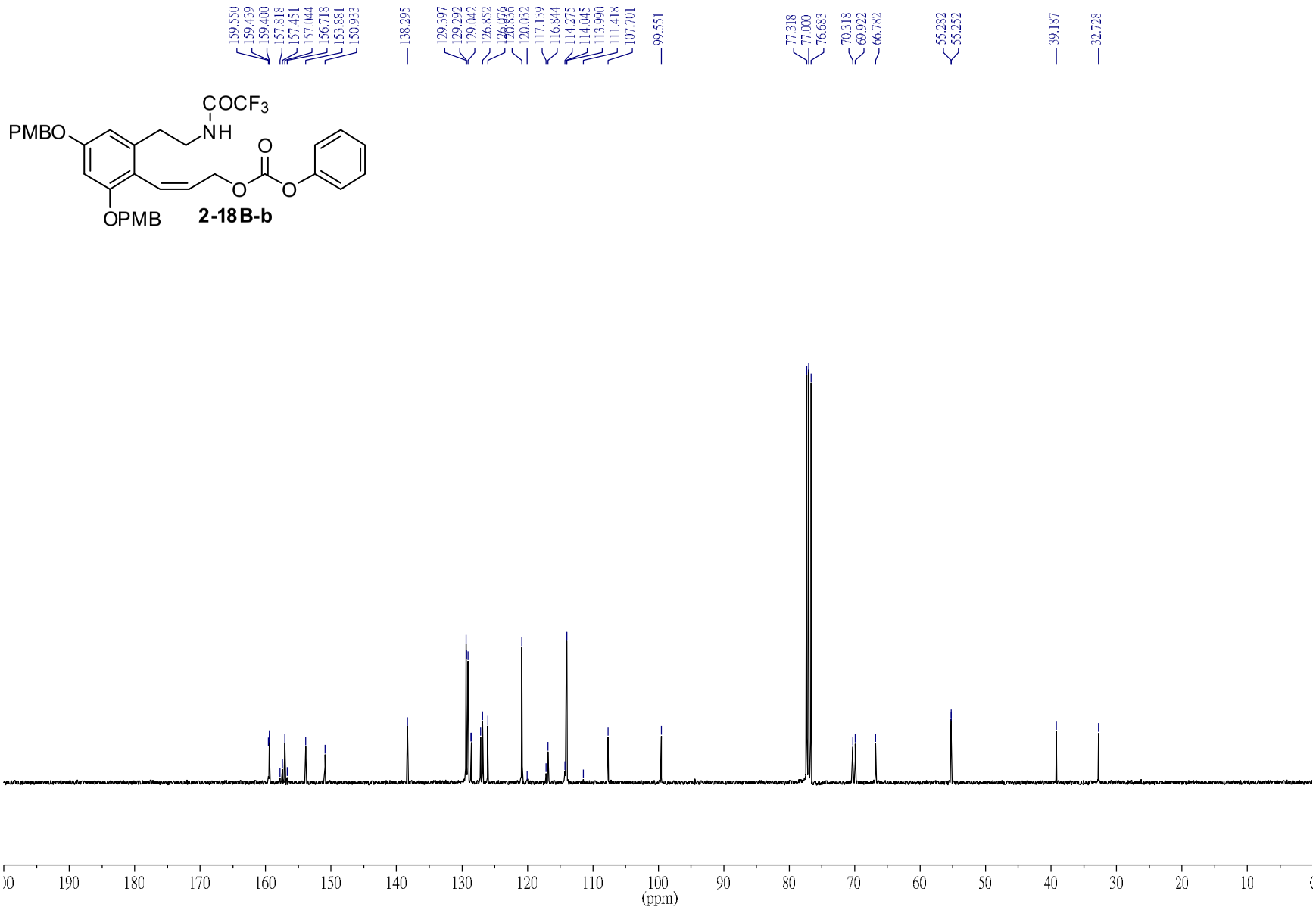

4.35
5.00
0.96
0.97
1.99
1.06
4.91
2.95
2.72
2.82
2.28
1.96
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

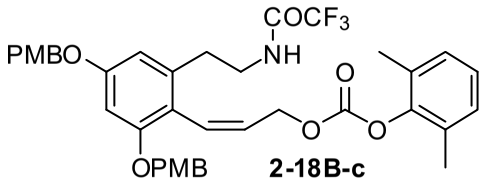

159.570
159.458
157.478
157.097
156.693
152.844
142.365
138.259
129.306
129.030
128.617
128.550
127.139
126.747
117.243
116.771
114.379
114.064
113.993
107.658
99.560
98.027
77.318
77.000
76.682
70.333
69.954
66.653
55.299
55.266
39.296
32.726
COCF3
NH
PMBO
O
O
O
OPMB
2-18B-a
(ppm)


COCF3
NH
PMBO
O
O
O
OPMB

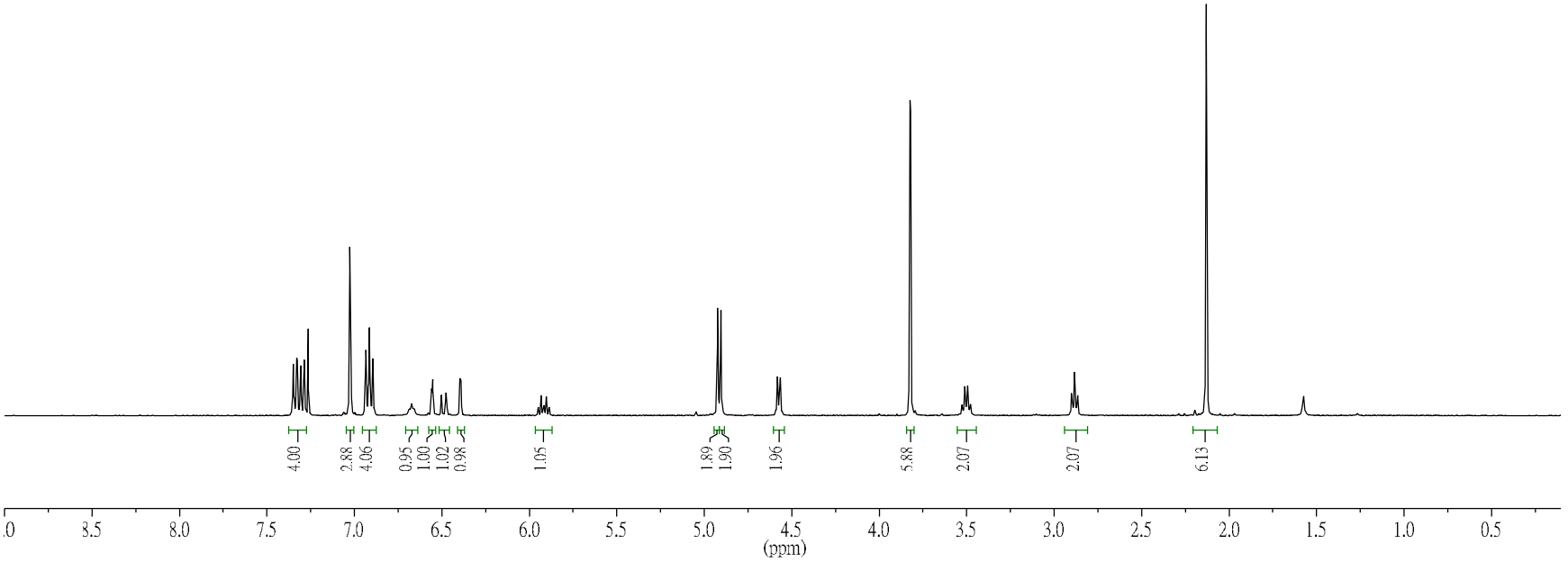
2-18B-b

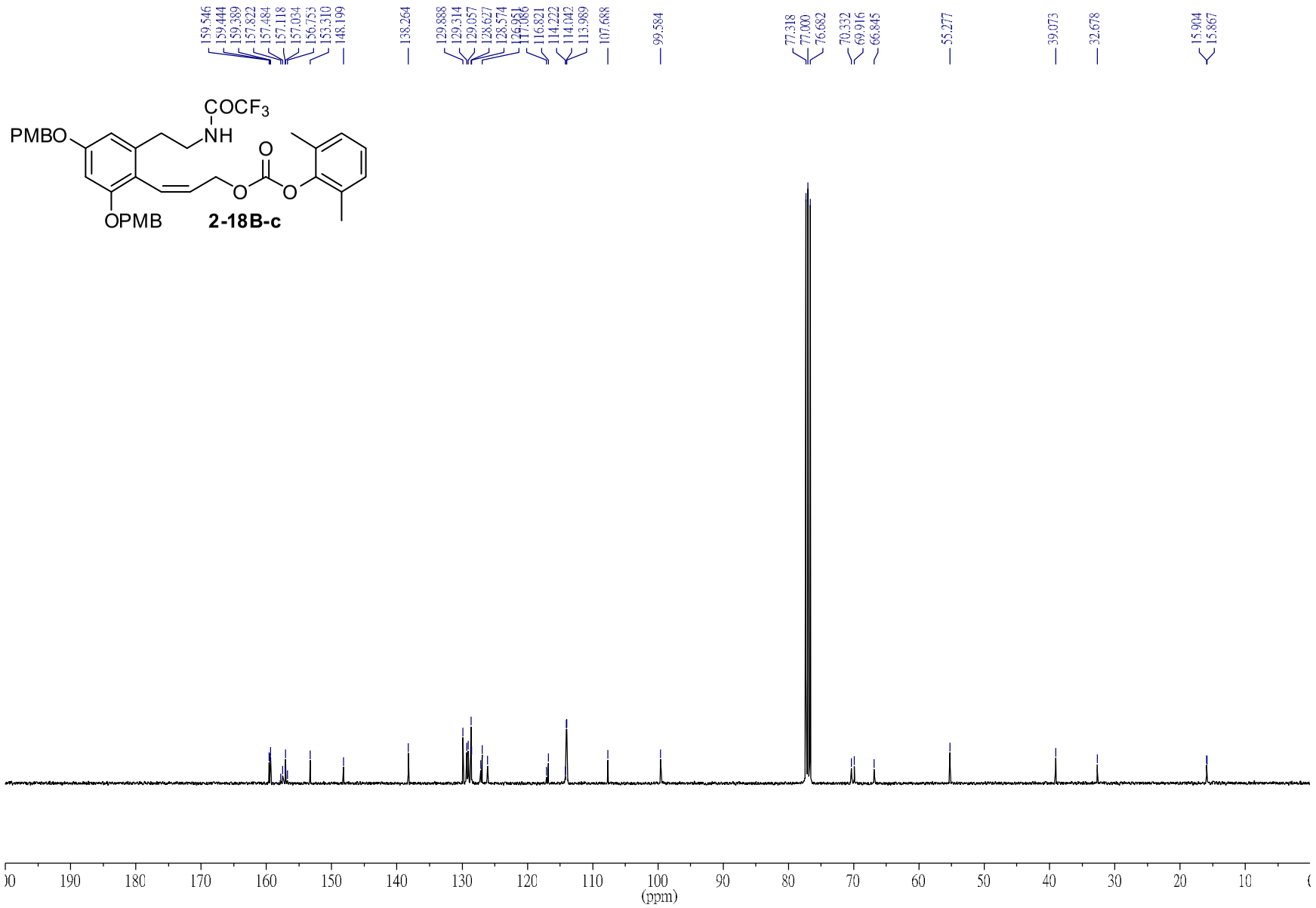

5.83
1.11
1.96
4.00
0.89
0.96
0.99
0.96
0.97
3.89
1.94
2.78
2.84
2.01
1.93
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

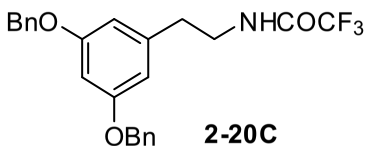

159.550
159.439
159.400
157.818
157.451
157.044
156.718
153.881
150.933
138.295
129.397
129.292
129.042
126.852
126.076
125.836
120.032
117.139
116.844
114.275
114.045
113.990
111.418
107.701
99.551
77.318
77.000
76.683
70.318
69.922
66.782
55.282
55.252
39.187
32.728
COCF3
NH
PMBO
O
O
O
OPMB
2-18B-b
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)


COCF3
NH
PMBO
O
O
O
OPMB

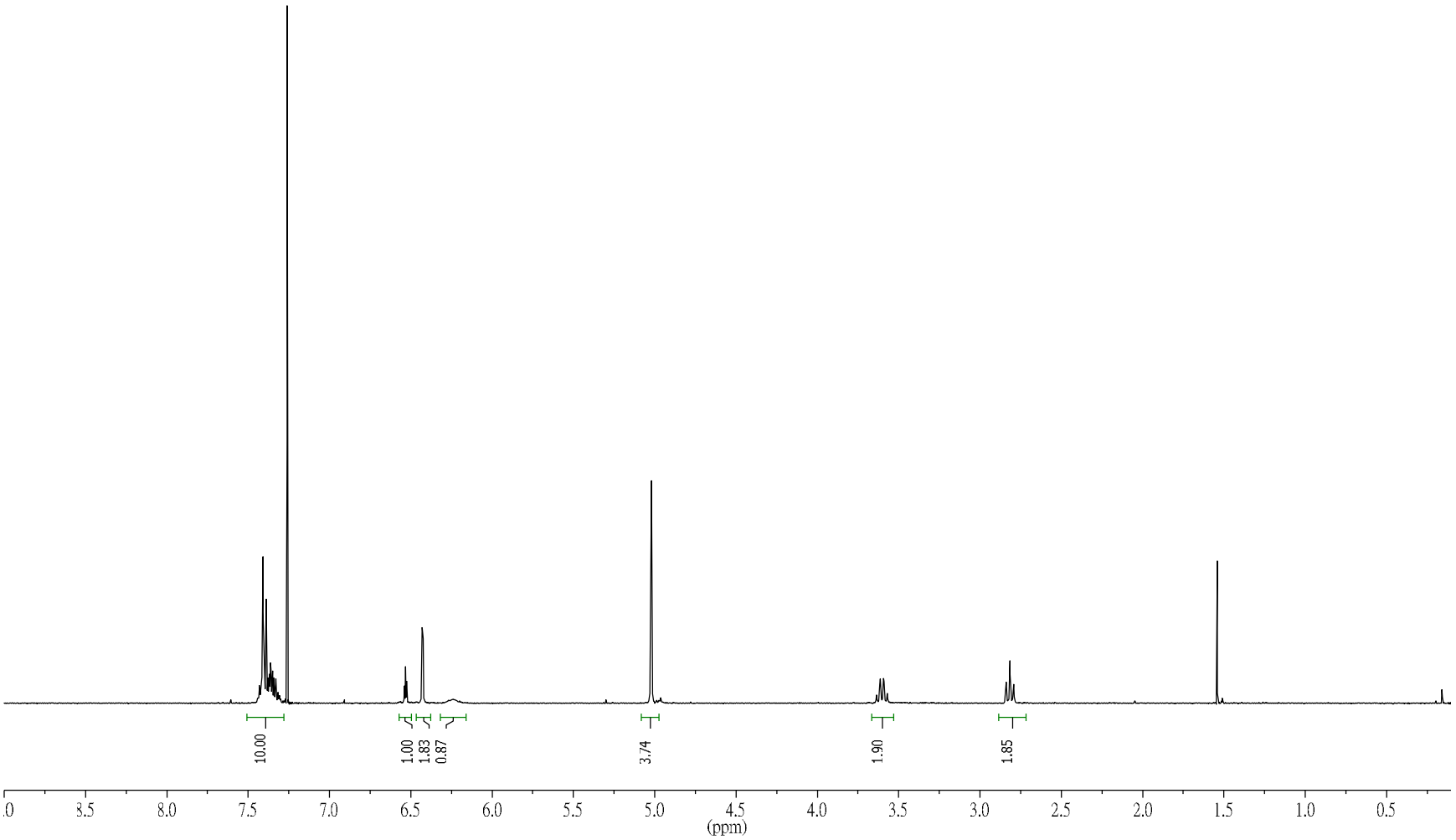
2-18B-c

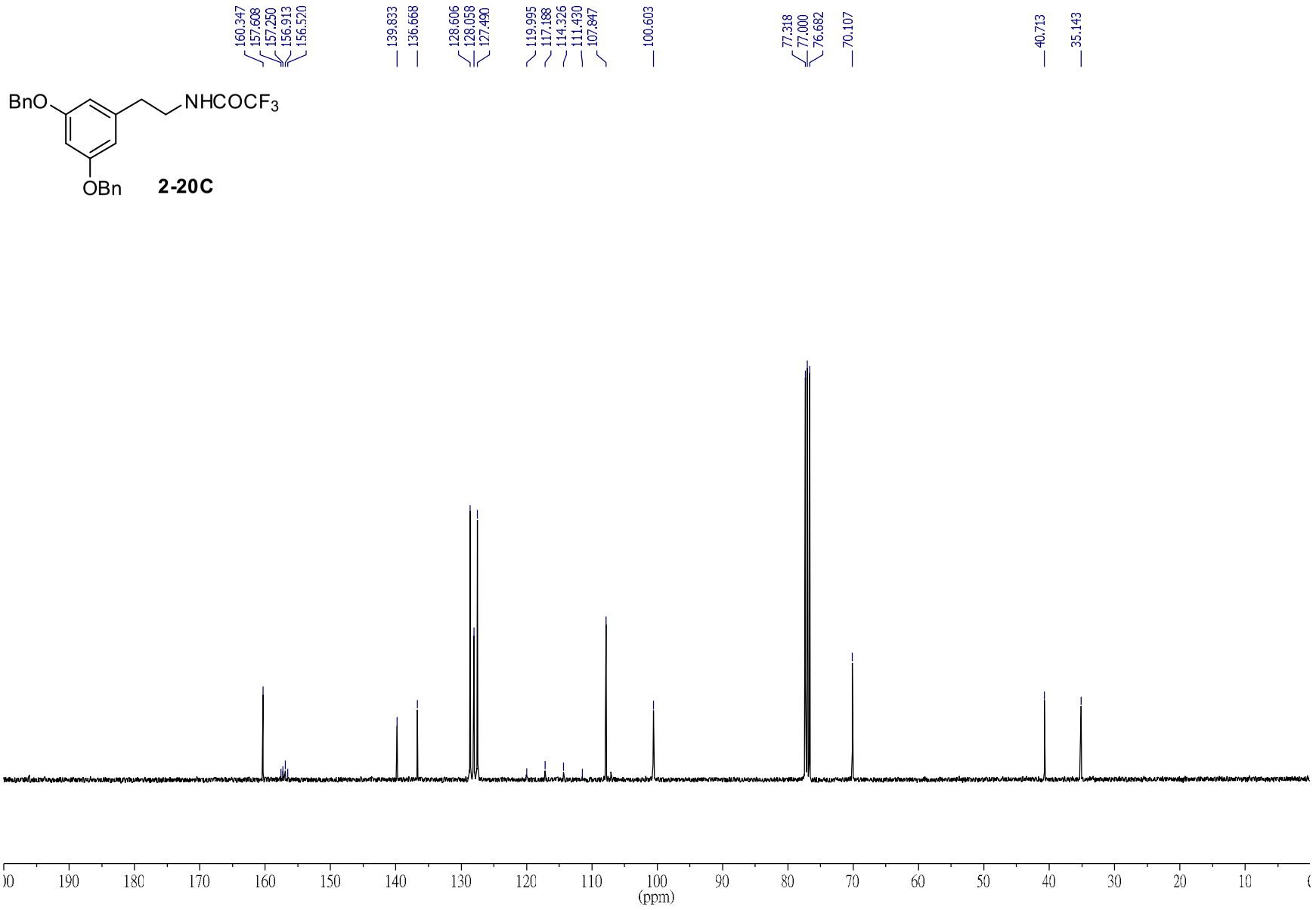

4.00
2.88
4.06
0.95
1.00
1.02
0.98
1.05
1.89
1.90
1.96
5.88
2.07
2.07
6.13
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

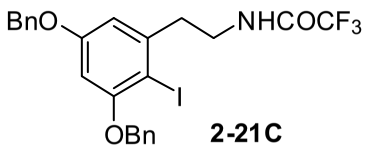

159.546
159.444
159.389
157.822
157.484
157.118
157.034
156.753
153.310
148.199
138.264
129.888
129.314
129.057
128.627
128.574
126.951
117.386
116.821
114.222
114.042
113.989
107.688
99.584
77.318
77.000
76.682
70.332
69.916
66.845
55.277
39.073
32.678
15.904
15.867
COCF3
NH
PMBO
O
O
O
OPMB
2-18B-c
(ppm)


BnO
NHCOCF3
OBn

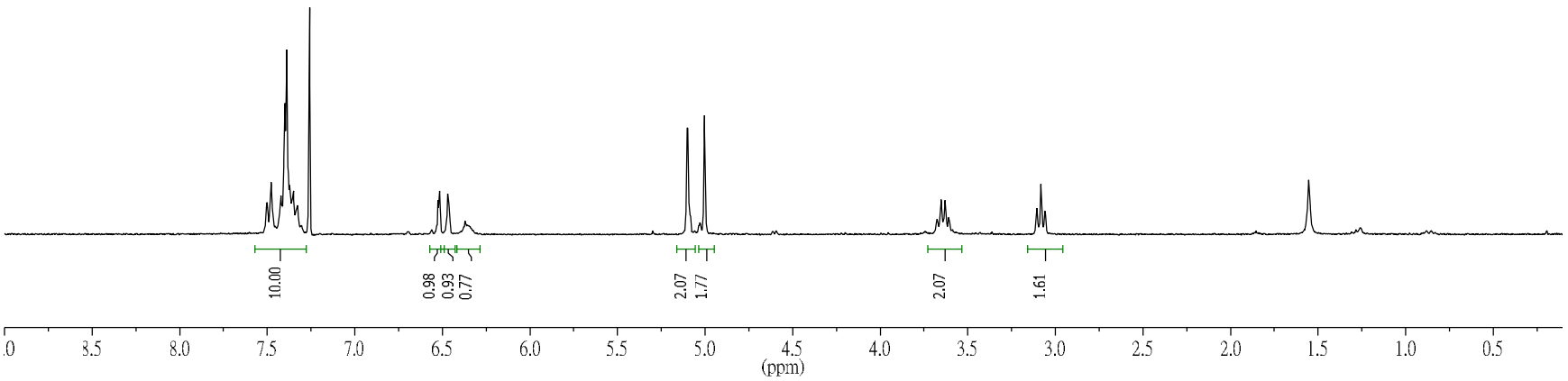
2-20C

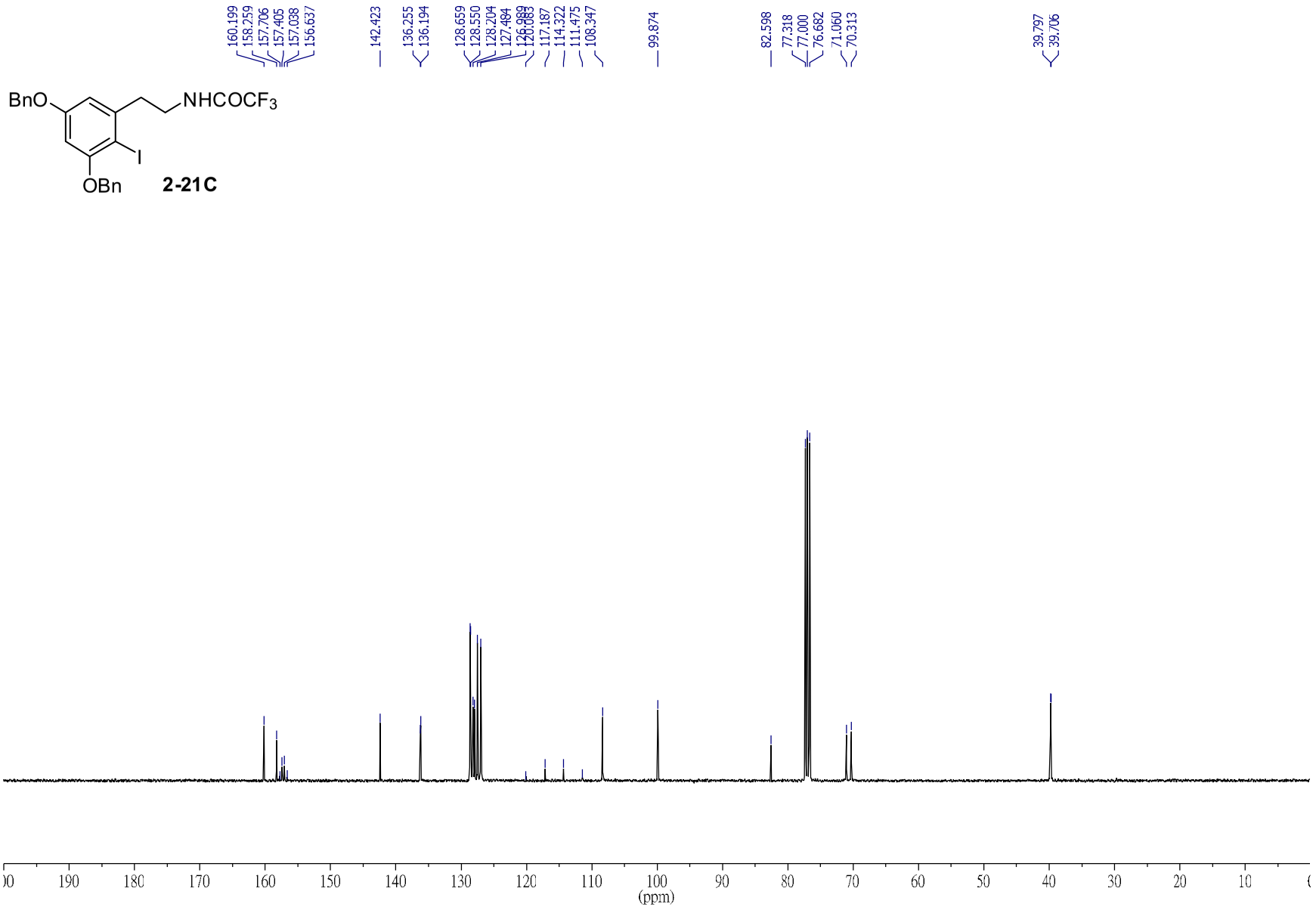

10.00
1.00
1.83
0.87
3.74
1.90
1.85
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

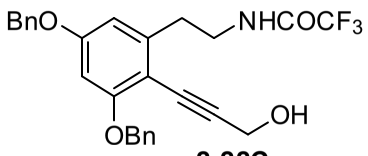

160.347
157.608
157.250
156.913
156.520
139.833
136.668
128.606
128.058
127.490
119.995
117.188
114.326
111.430
107.847
100.603
77.318
77.000
76.682
70.107
40.713
35.143
BnO
NHCOCF3
OBn
2-20C
(ppm)


BnO
NHCOCF3
I
OBn

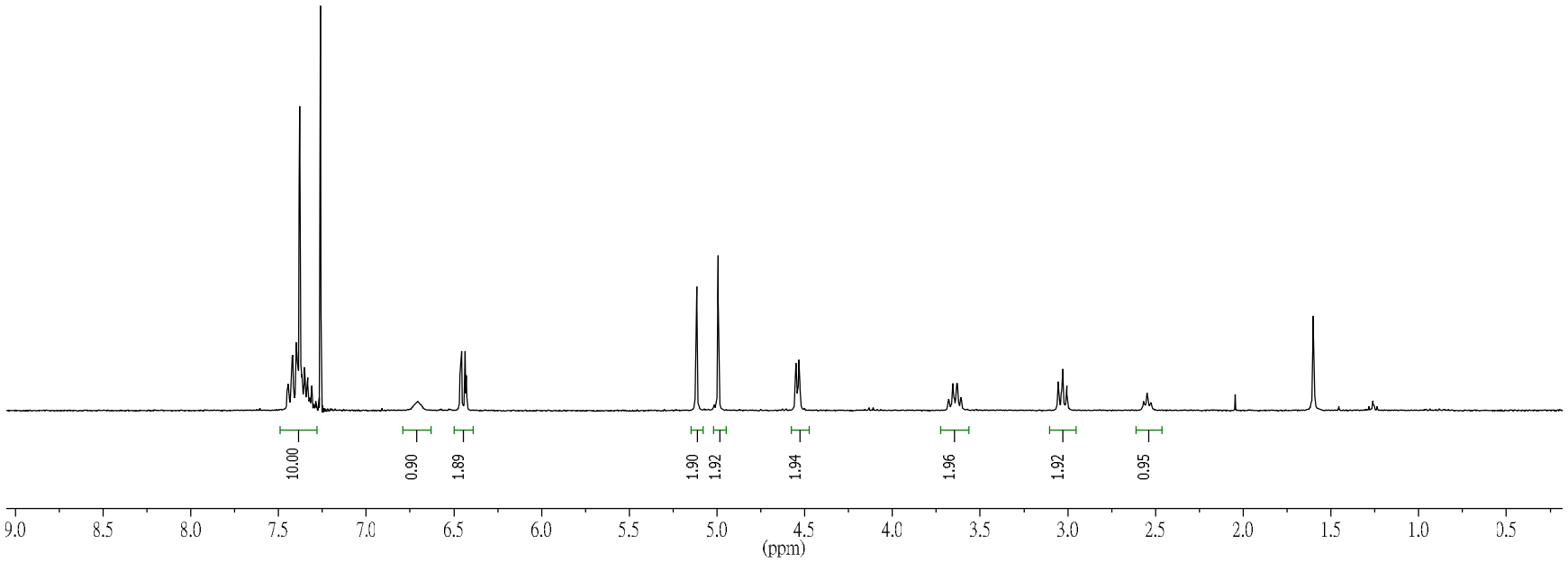
2-21C

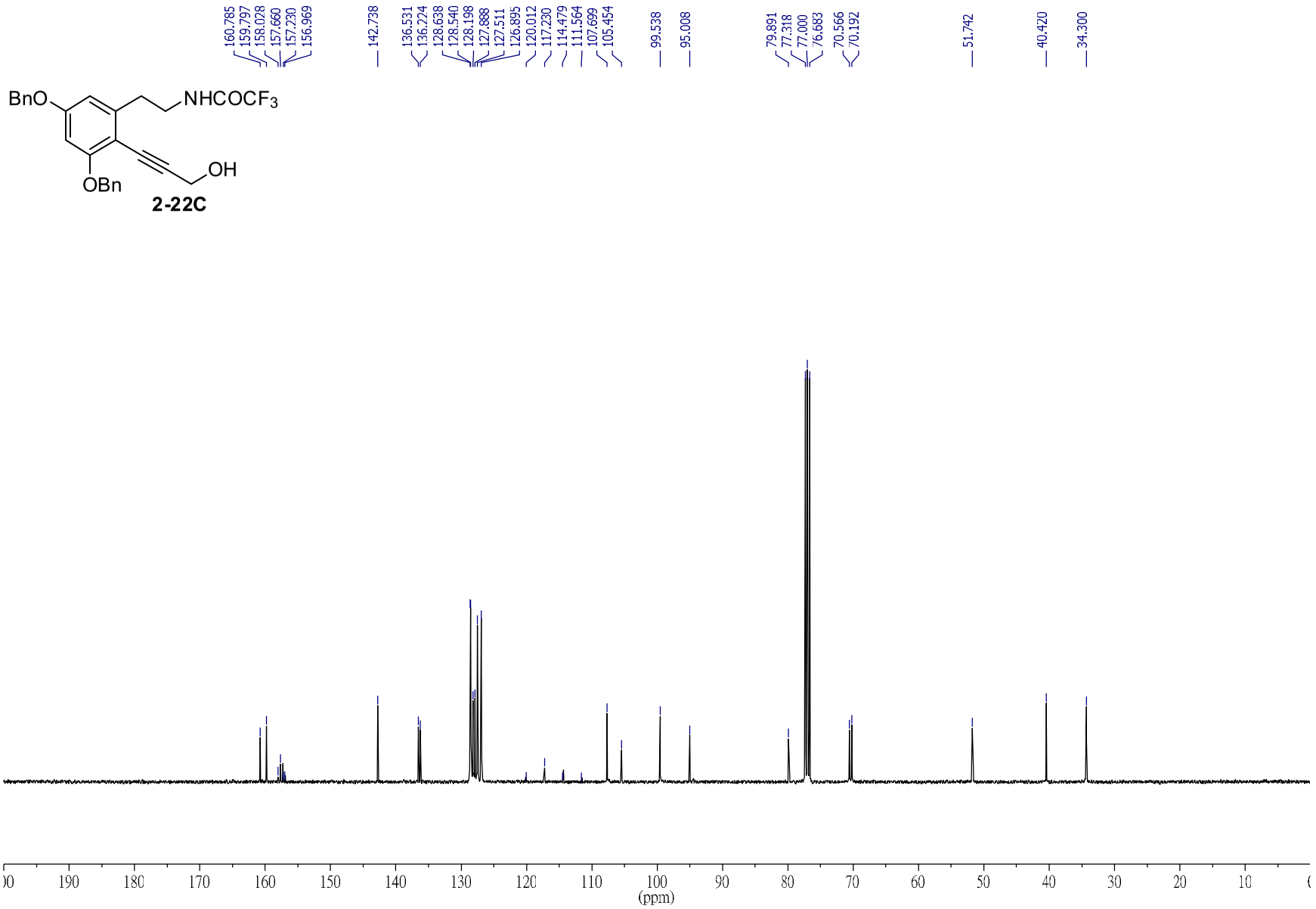

10.00
0.98
0.93
0.77
2.07
1.77
2.07
1.61
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

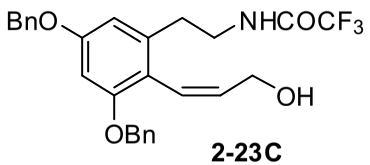

160.199
158.259
157.706
157.405
157.038
156.637
142.423
136.255
136.194
128.659
128.550
128.204
127.484
126.989
126.083
117.187
114.322
111.475
108.347
99.874
82.598
77.318
77.000
76.682
71.060
70.313
39.797
39.706
BnO
NHCOCF3
I
OBn
2-21C
(ppm)


BnO
NHCOCF3
OH
OBn

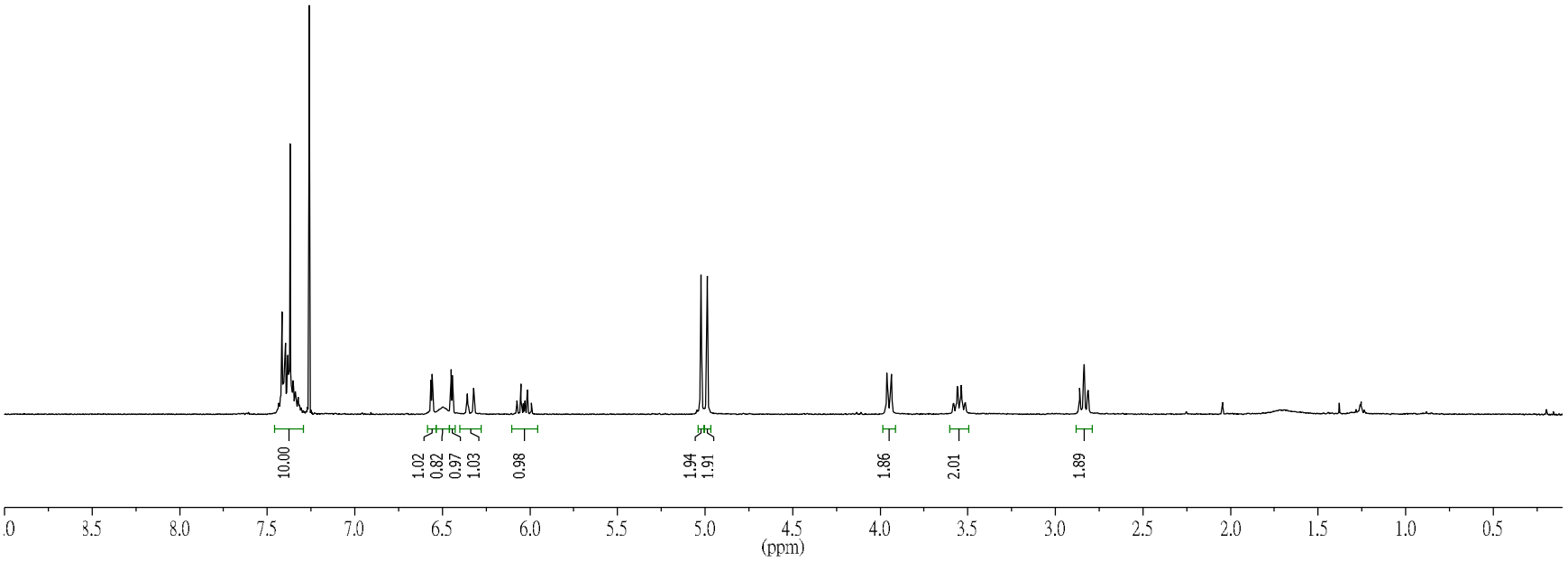
2-22C

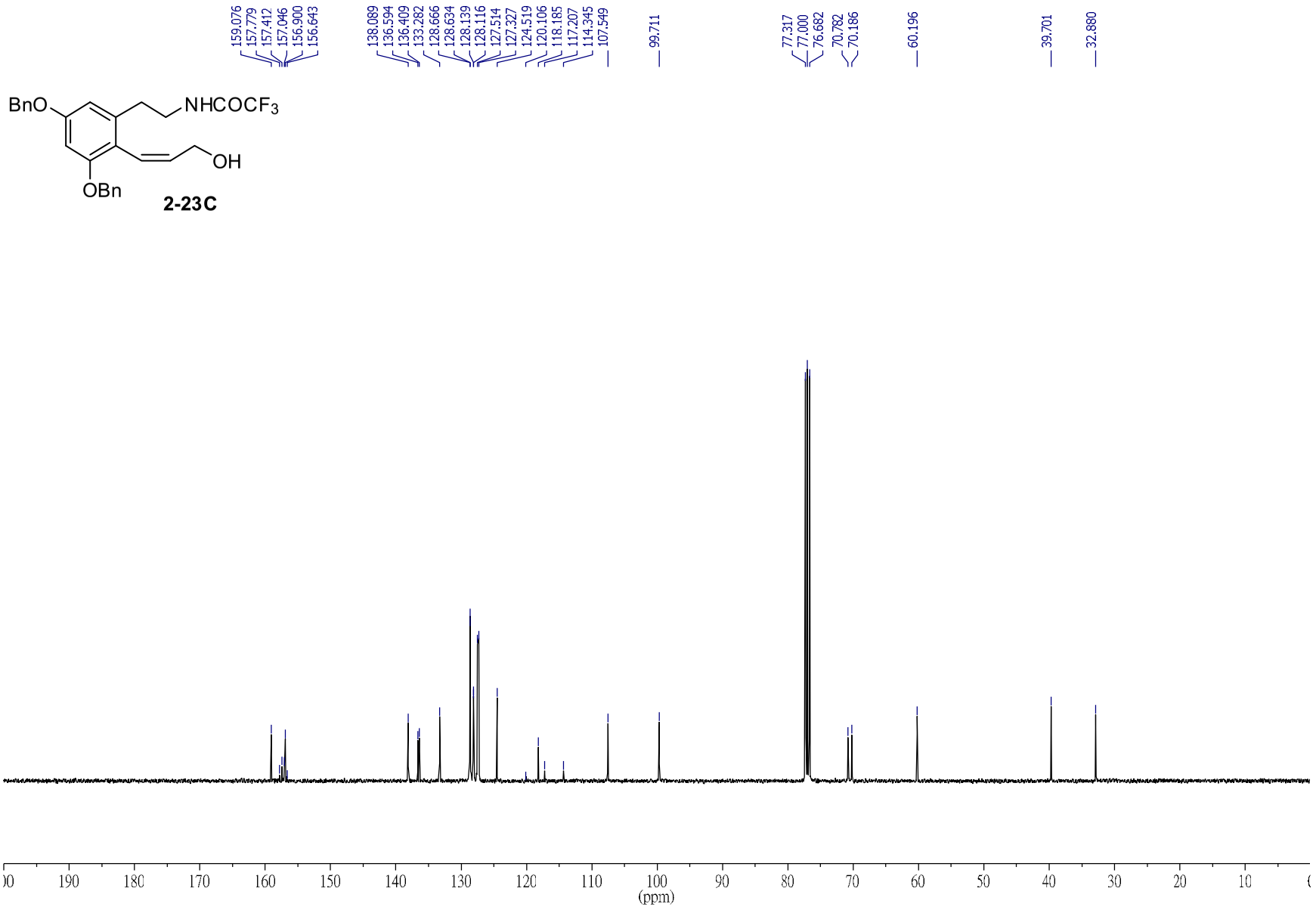

10.00
0.90
1.89
1.90
1.92
1.94
1.96
1.92
0.95
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

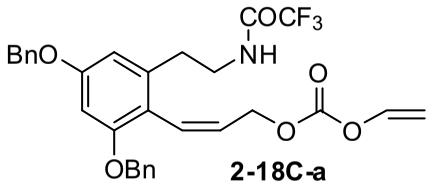

160.785
159.797
158.028
157.660
157.230
156.969
142.738
136.531
136.224
128.638
128.540
128.198
127.888
127.511
126.895
120.012
117.230
114.479
111.564
107.699
105.454
99.538
95.008
79.891
77.318
77.000
76.683
70.566
70.192
51.742
40.420
34.300
BnO
NHCOCF3
OH
OBn
2-22C
(ppm)


BnO
NHCOCF3
OH
OBn

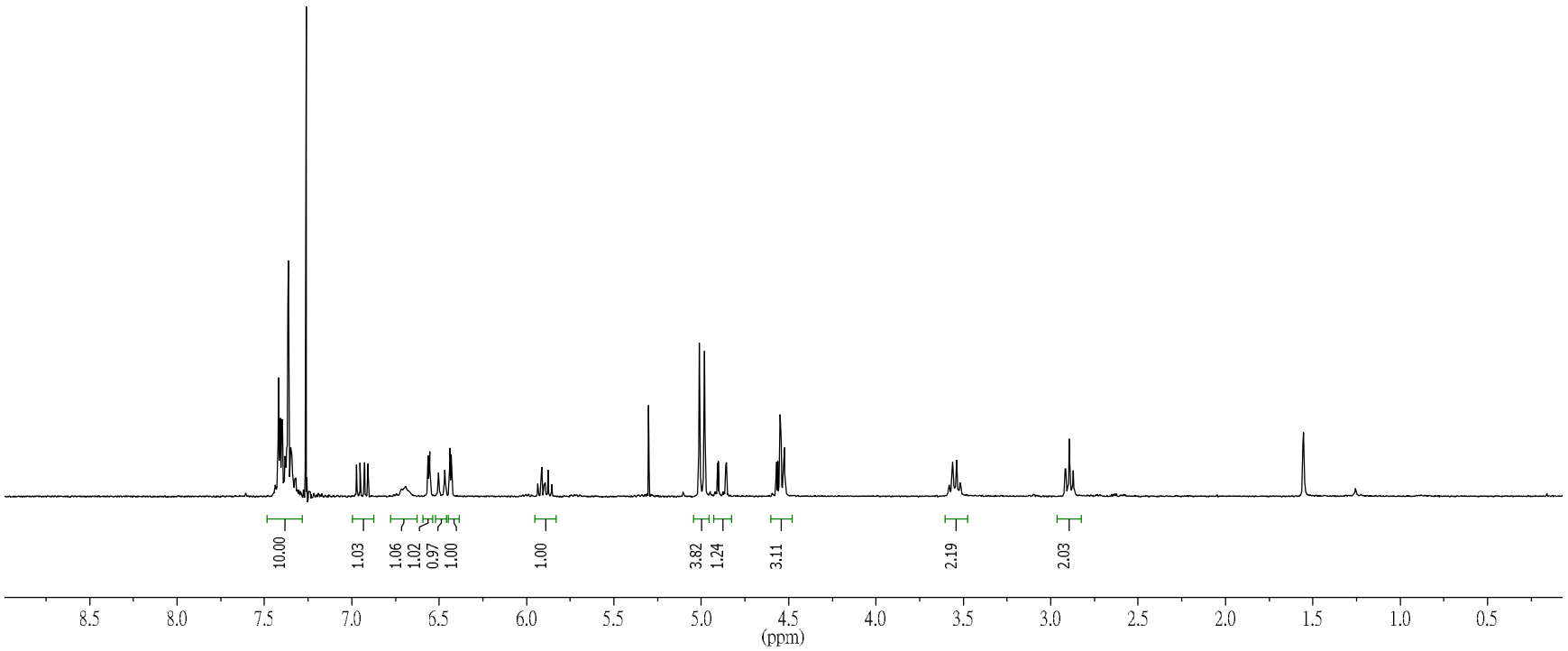
2-23C

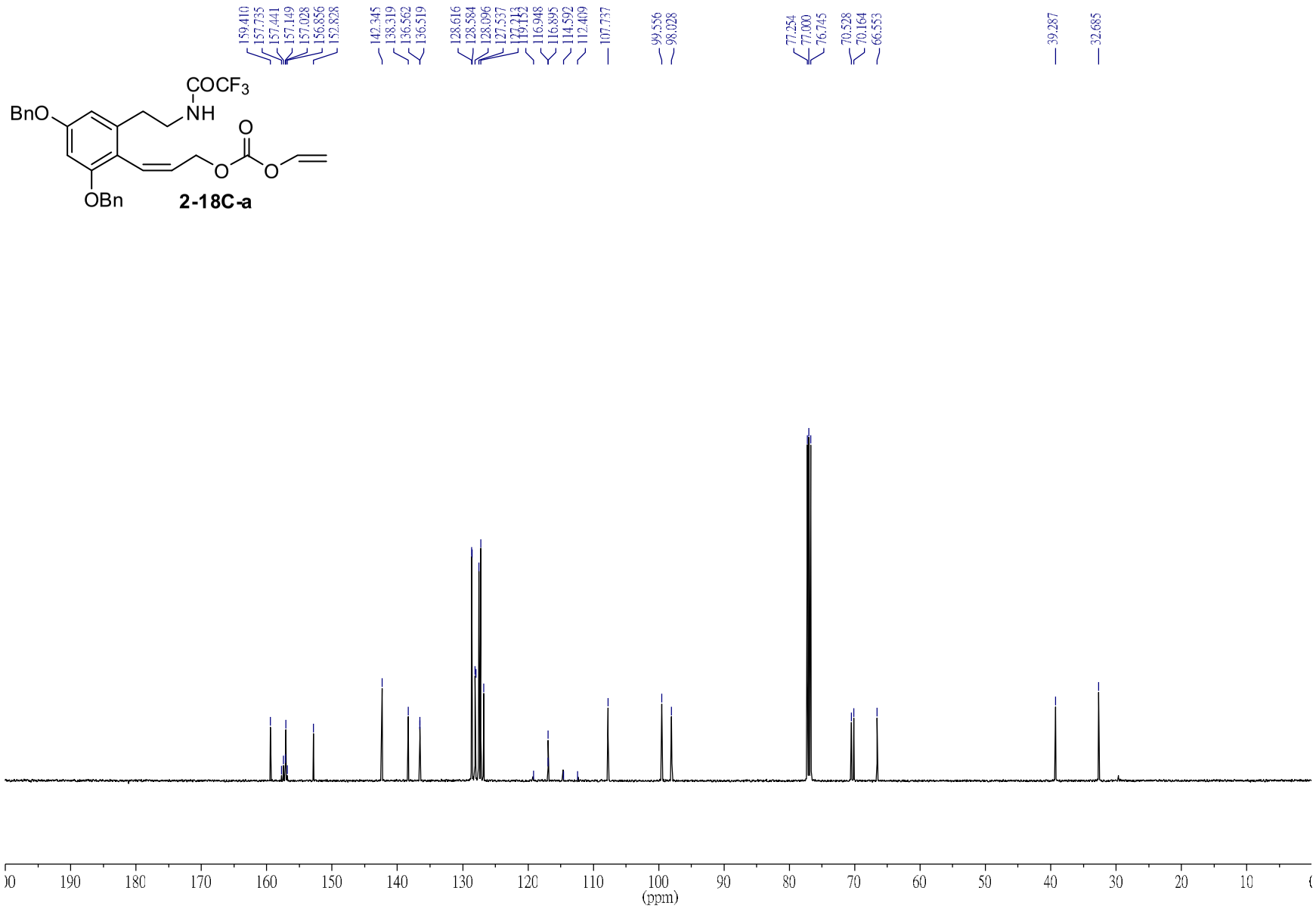

10.00
1.02
0.82
0.97
1.03
0.98
1.94
1.91
1.86
2.01
1.89
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

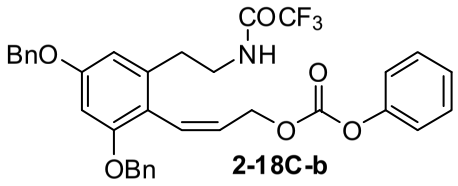

159.076
157.779
157.412
157.046
156.900
156.643
138.089
136.594
136.409
133.282
128.666
128.634
128.139
128.116
127.514
127.327
124.519
120.106
118.185
117.207
114.345
107.549
99.711
77.317
77.000
76.682
70.782
70.186
60.196
39.701
32.880
BnO
NHCOCF3
OH
OBn
2-23C
(ppm)


COCF3
NH
BnO
O
O
O
OBn

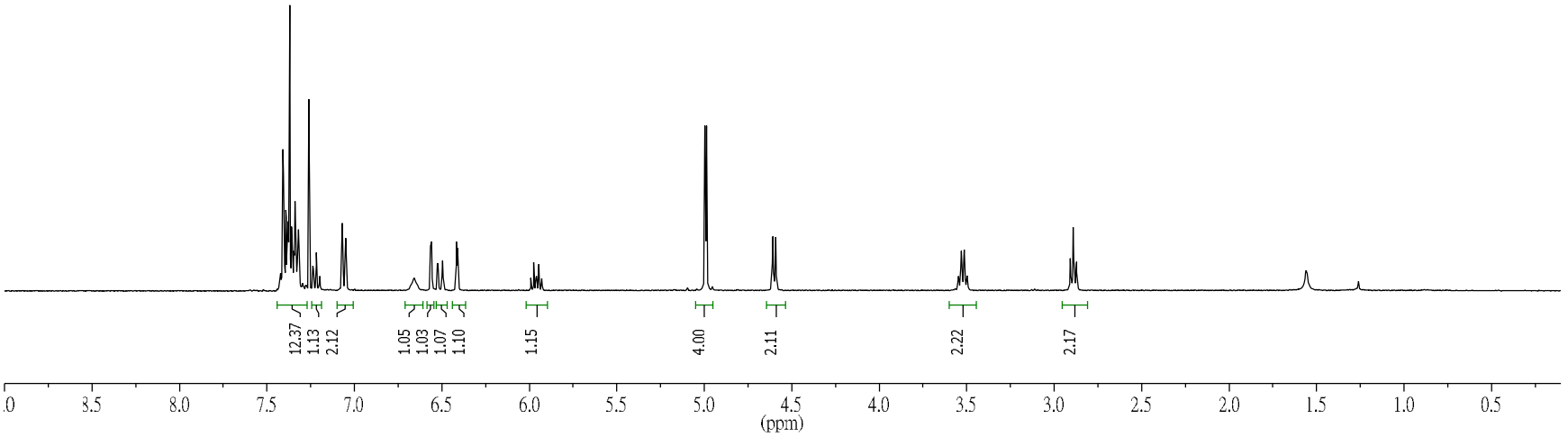
2-18C-a

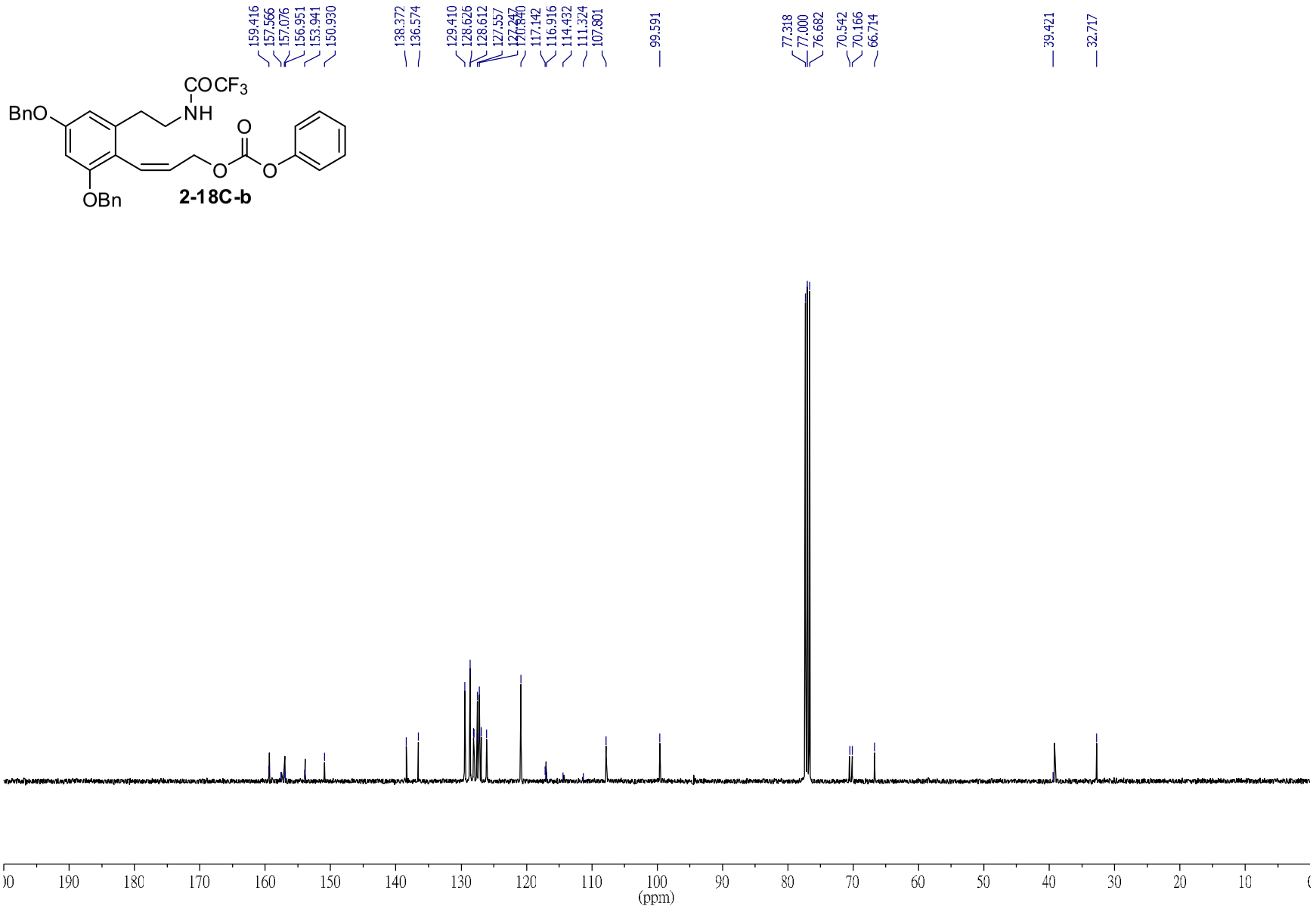

10.00
1.03
1.06
1.02
0.97
1.00
1.00
3.82
1.24
3.11
2.19
2.03
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

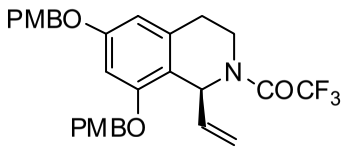

159.410
157.735
157.441
157.149
157.028
156.856
152.828
142.345
138.319
136.562
136.519
128.616
128.584
128.096
127.537
116.948
116.895
114.592
112.409
107.737
99.556
98.028
77.254
77.000
76.745
70.528
70.164
66.553
39.287
32.685
COCF3
NH
BnO
O
O
O
OBn
2-18C-a
(ppm)


COCF3
NH
BnO
O
O
O
OBn

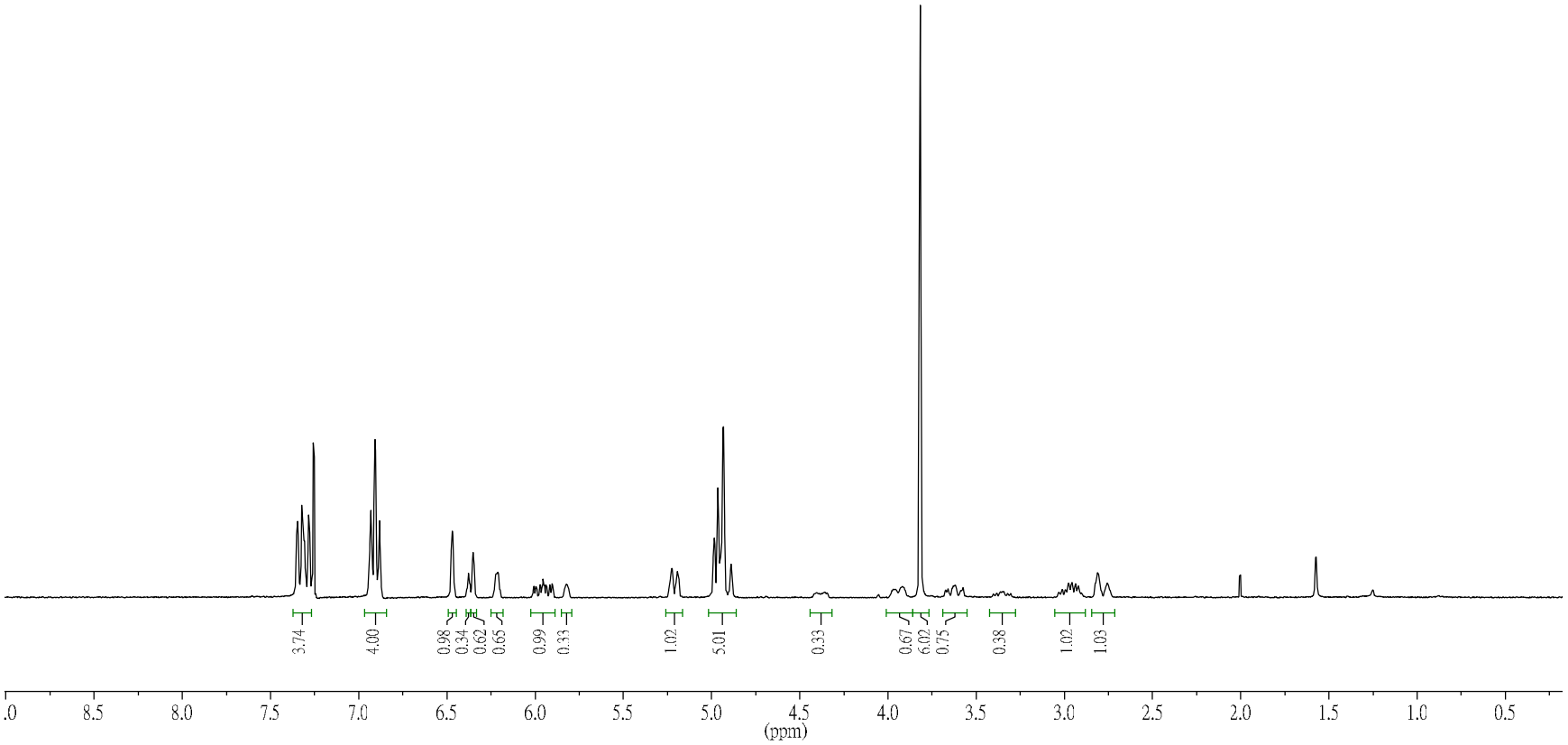
2-18C-b

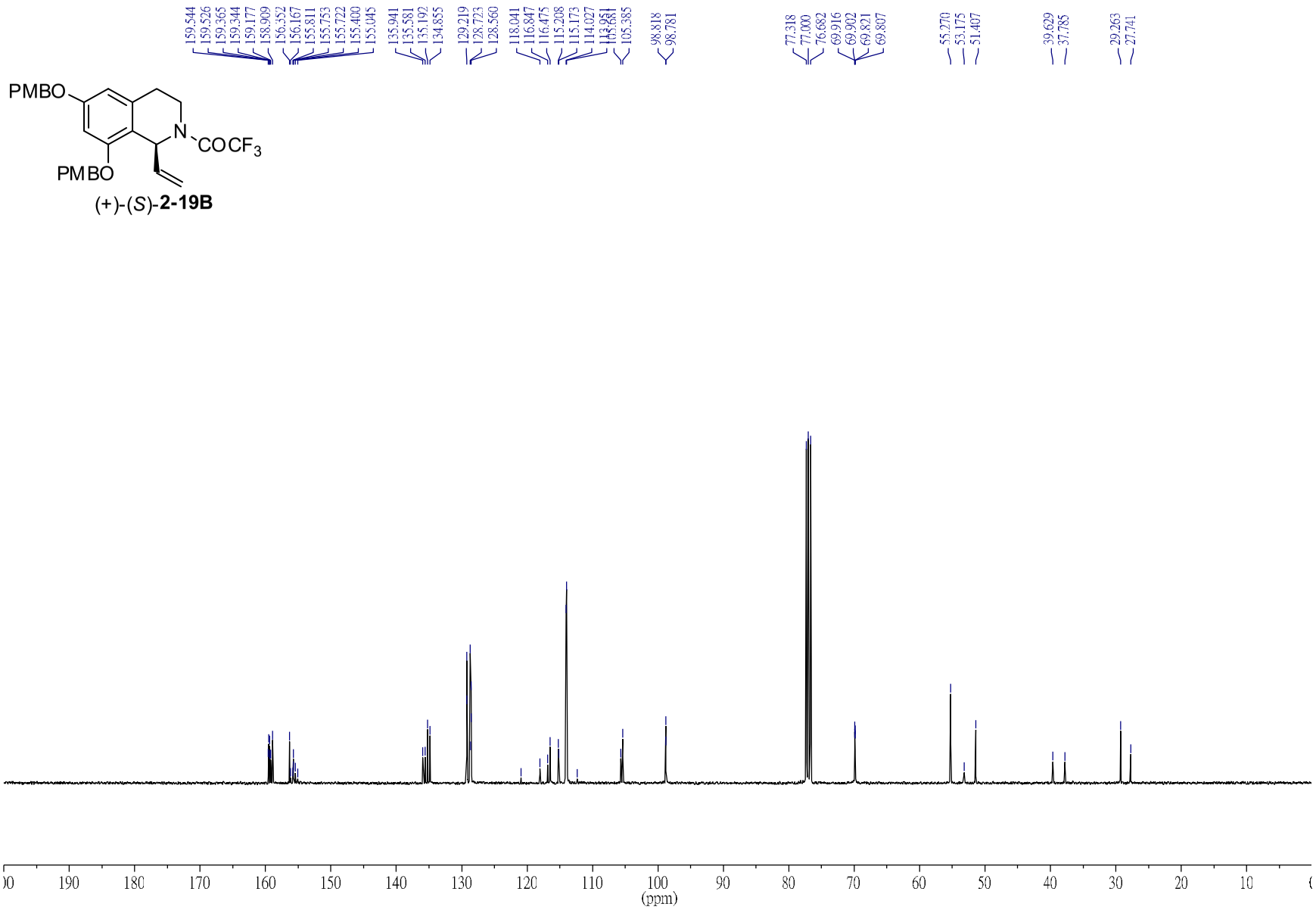

12.37
1.13
2.12
1.05
1.03
1.07
1.10
1.15
4.00
2.11
2.22
2.17
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

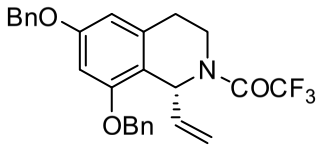

159.416
157.566
157.076
156.951
153.941
150.930
138.372
136.574
129.410
128.626
128.612
127.557
127.247
120.840
117.142
116.916
114.432
111.324
107.801
99.591
77.318
77.000
76.682
70.542
70.166
66.714
39.421
32.717
COCF3
NH
BnO
O
O
O
OBn
2-18C-b
(ppm)


PMBO
N
COCF3
PMBO

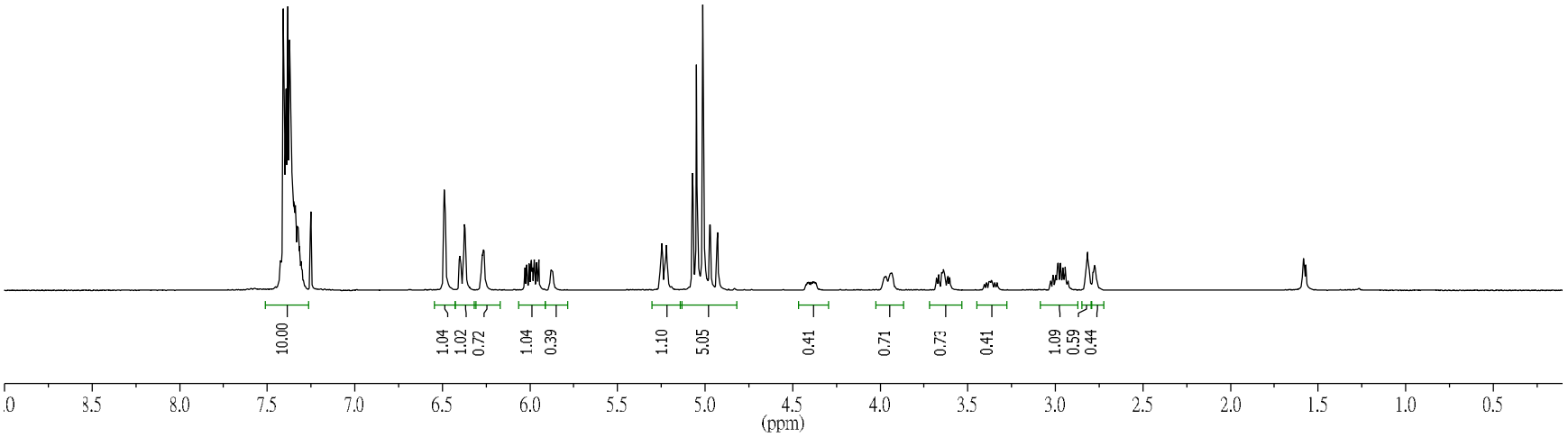
(+)-(*S*)-**2-19B**

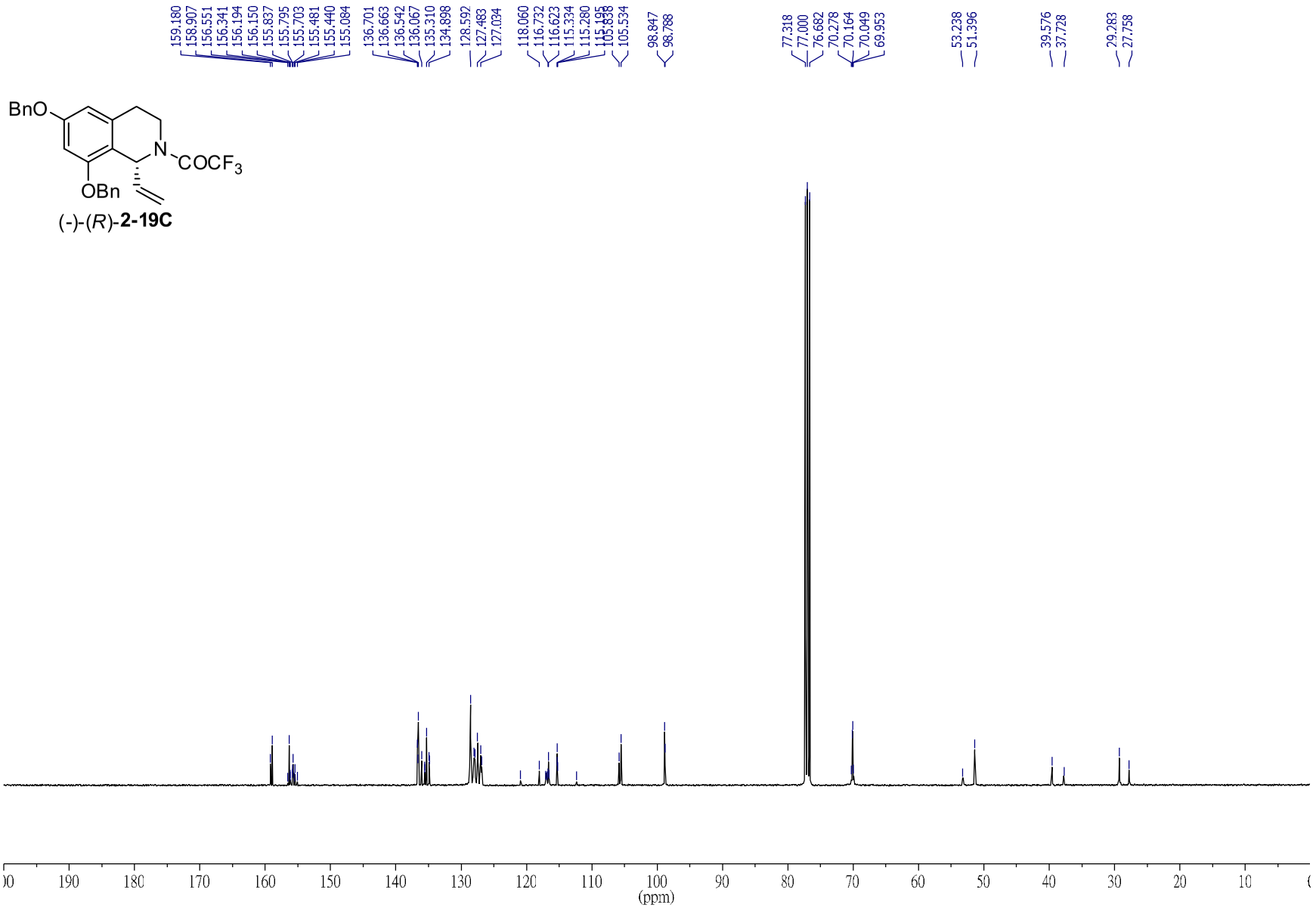

3.74
4.00
0.98
0.34
0.62
0.65
0.99
0.33
1.02
5.01
0.33
0.67
6.02
0.75
0.38
1.02
1.03
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

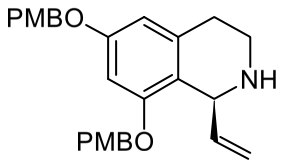

159.544
159.526
159.365
159.344
159.177
158.909
156.352
156.167
155.811
155.753
155.722
155.400
155.045
135.941
135.581
135.192
134.855
129.219
128.723
128.560
118.041
116.847
116.475
115.208
115.173
114.027
105.385
98.818
98.781
77.318
77.000
76.682
69.916
69.902
69.821
69.807
55.270
53.175
51.407
39.629
37.785
29.263
27.741
PMBO
N
COCF3
PMBO
(+)-(S)-2-19B
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)


BnO
N
COCF3
OBn

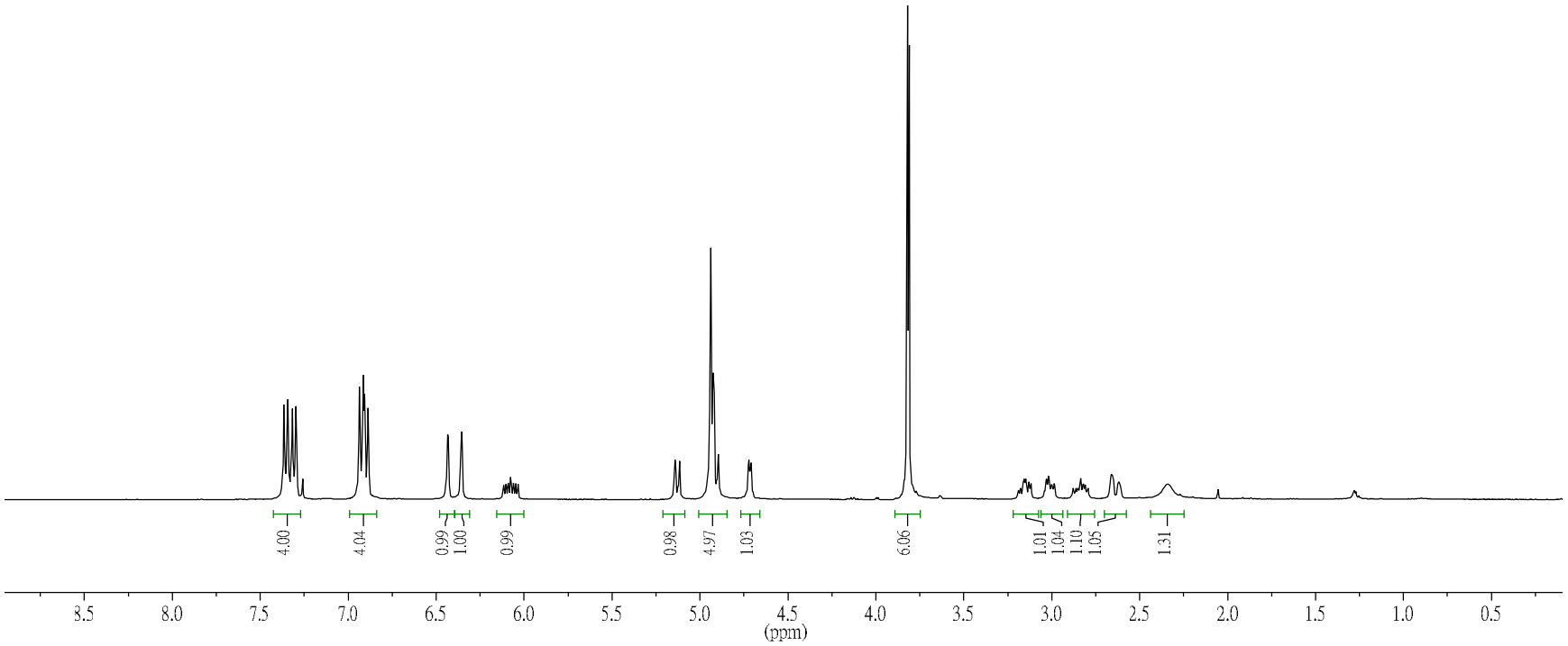
(-)-(*R*)-**2-19C**

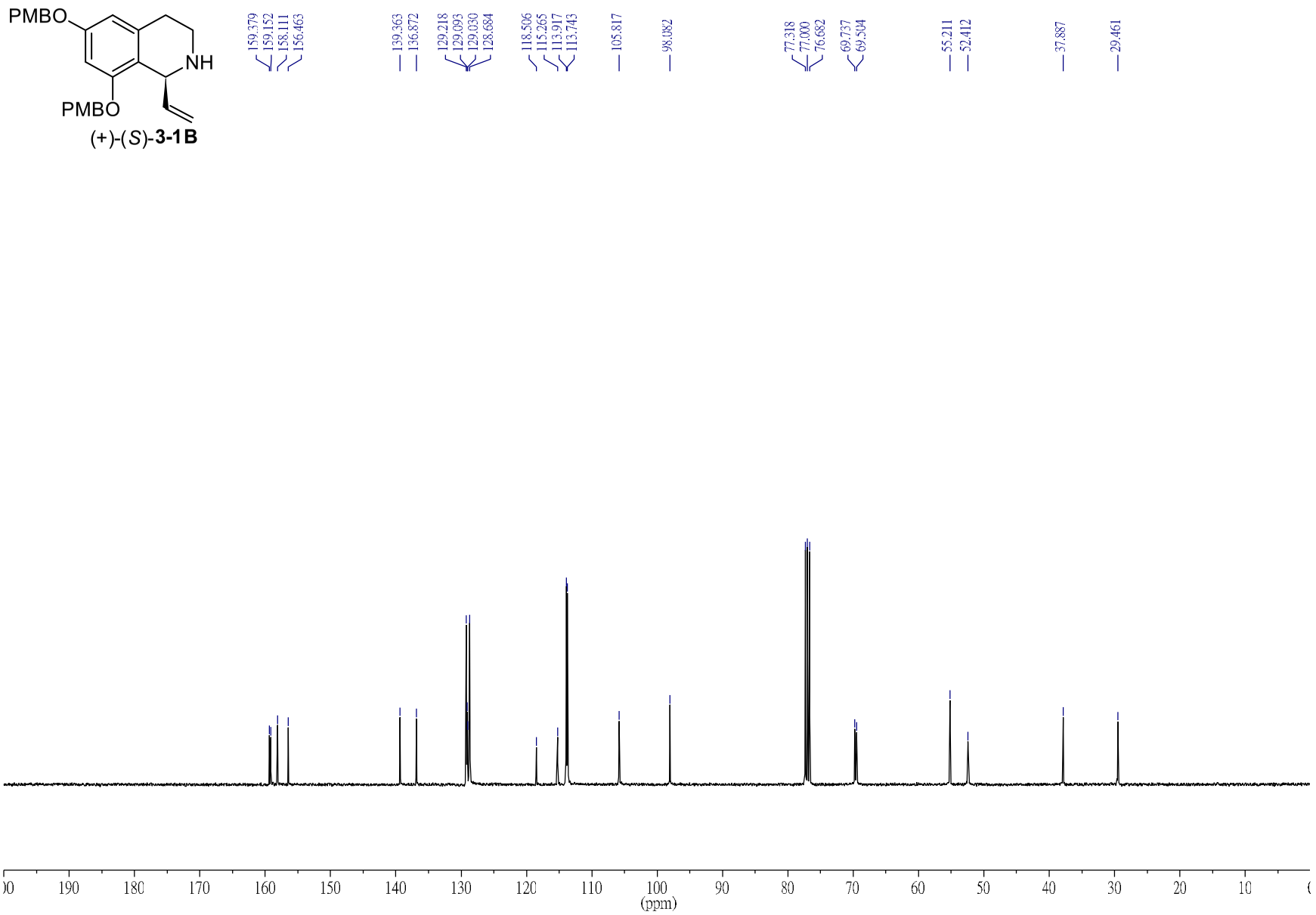

10.00
1.04
1.02
0.72
1.04
0.39
1.10
5.05
0.41
0.71
0.73
0.41
1.09
0.59
0.44
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

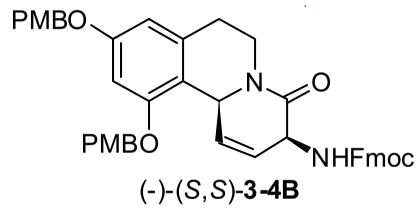

159.180
158.907
156.551
156.341
156.194
156.150
155.837
155.795
155.703
155.481
155.440
155.084
136.701
136.663
136.542
136.067
135.310
134.898
128.592
127.483
127.034
118.060
116.732
116.623
115.334
115.280
105.534
98.847
98.788
77.318
77.000
76.682
70.278
70.164
70.049
69.953
53.238
51.396
39.576
37.728
29.283
27.758
BnO
N
COCF3
OBn
(-)-(R)-2-19C
(ppm)


PMBO
NH
PMBO

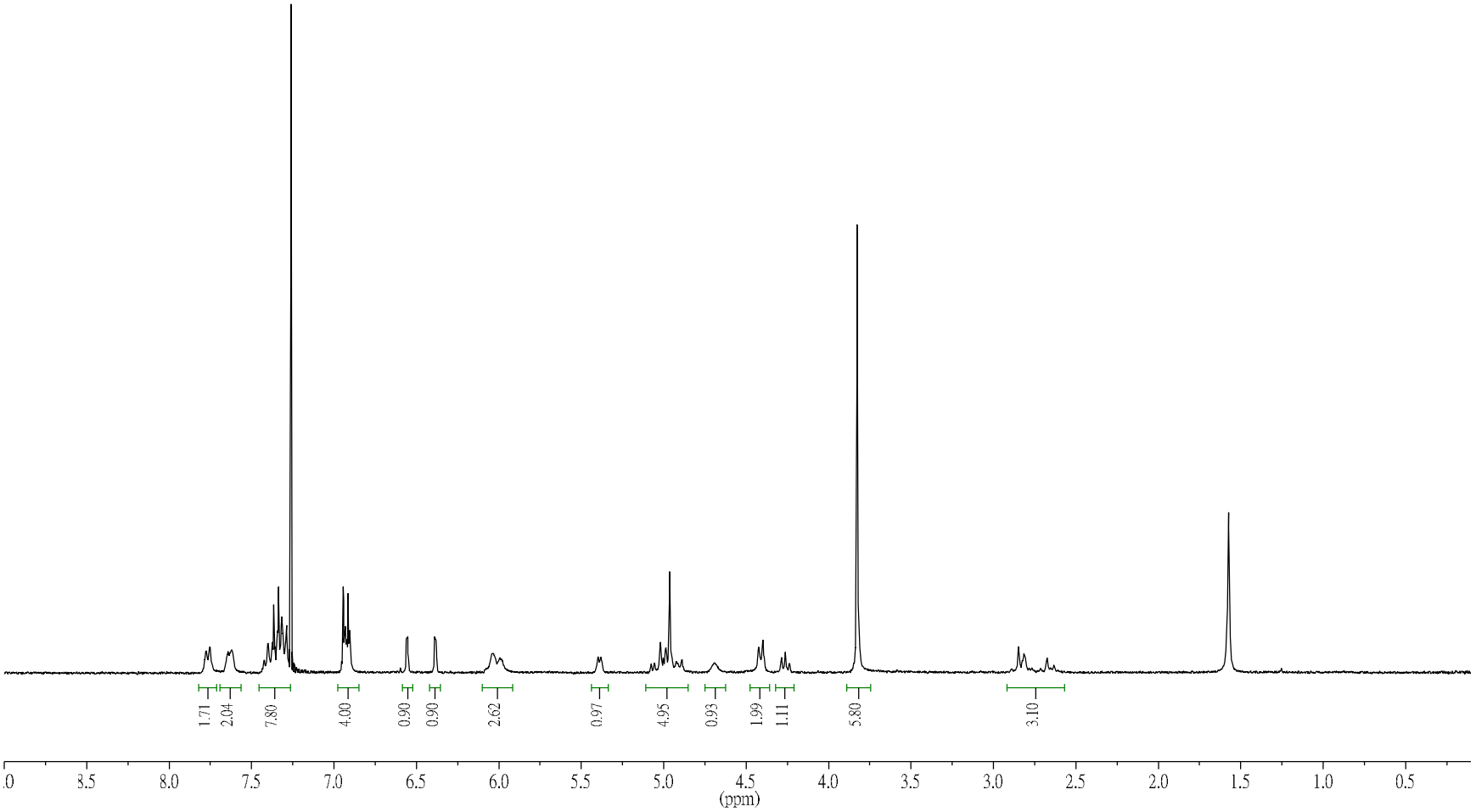
(+)-(*S*)-**3-1B**

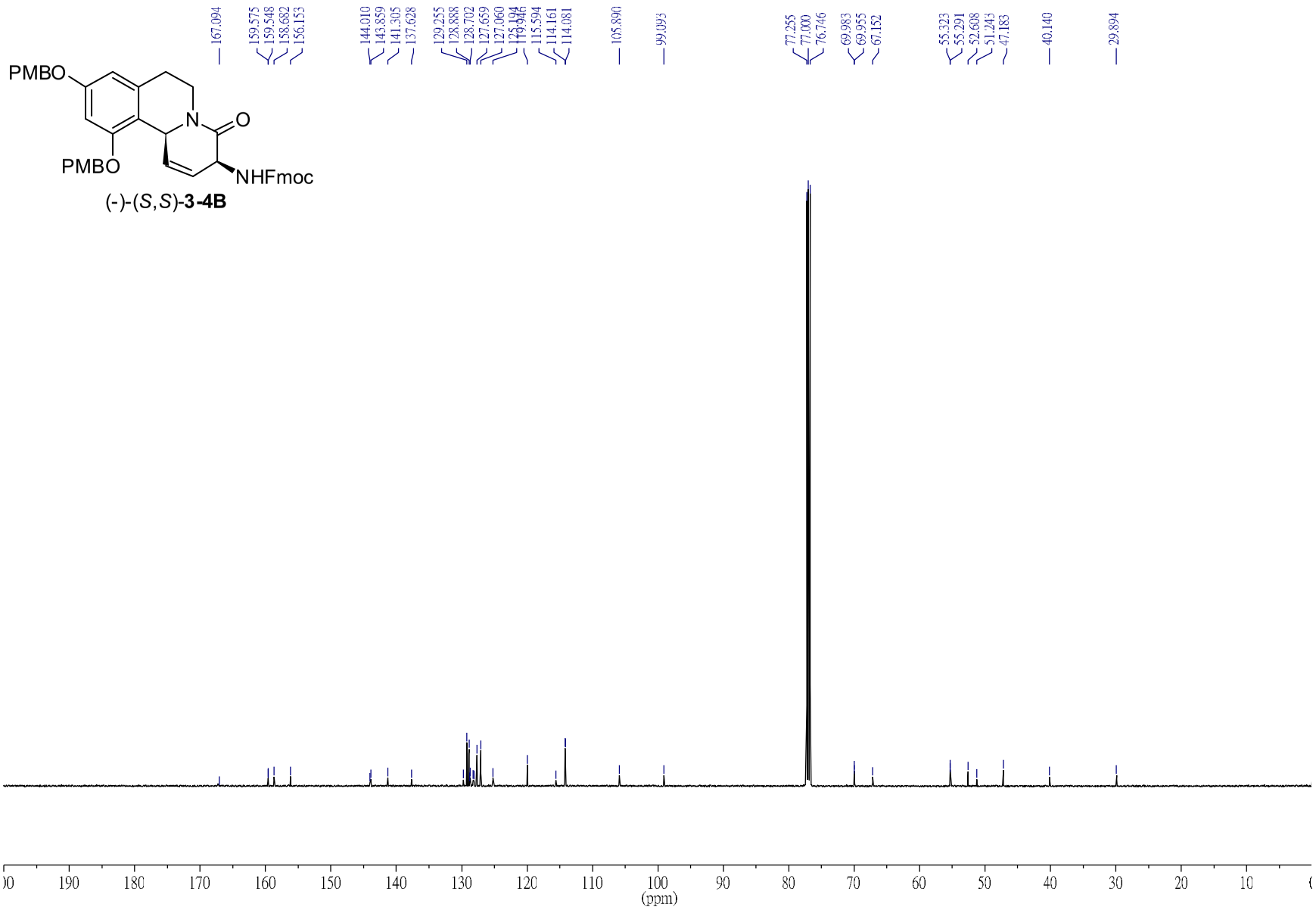

4.00
4.04
0.99
1.00
0.99
0.98
4.97
1.03
6.06
1.01
1.04
1.10
1.05
1.31
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

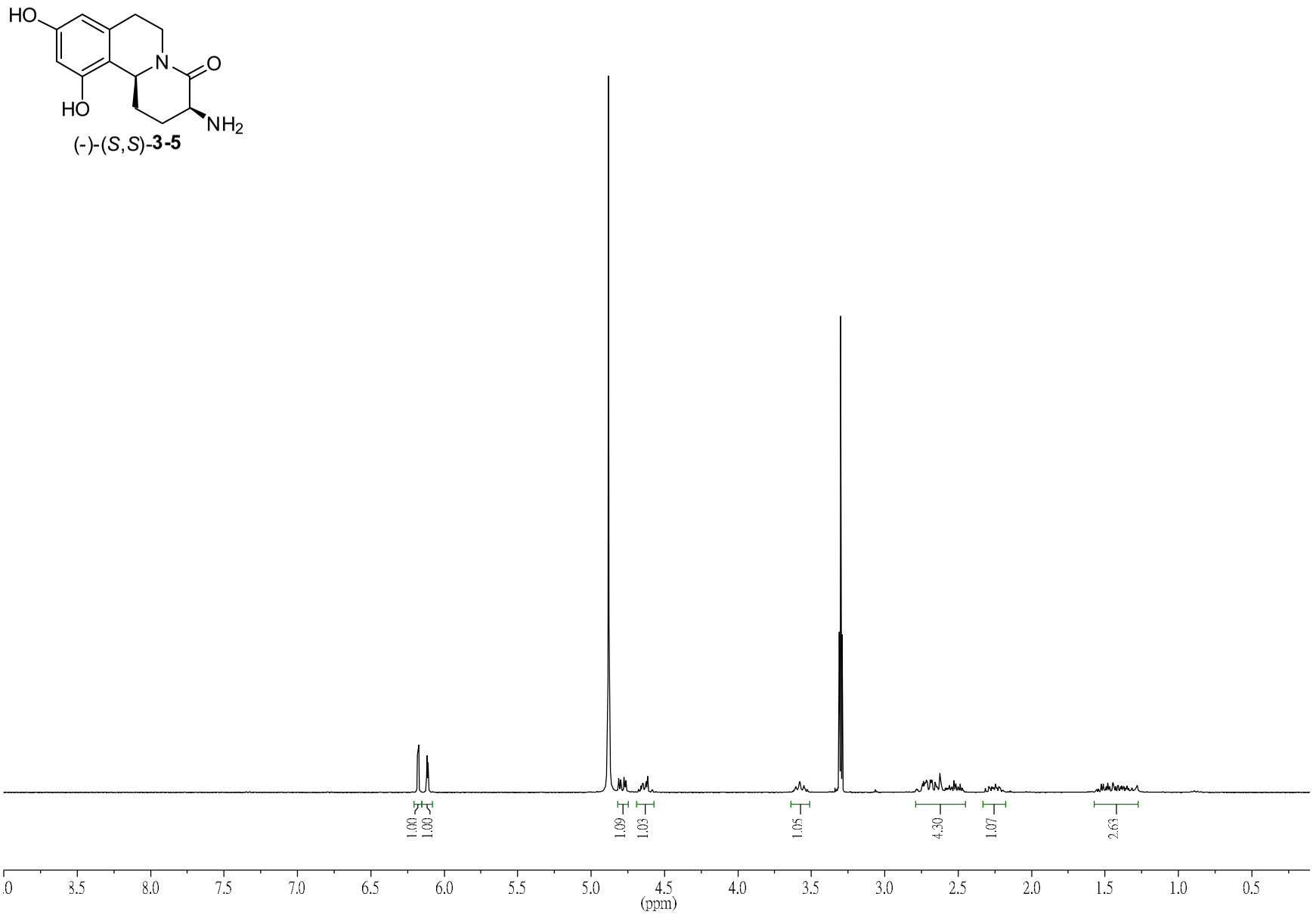

PMBO
NH
PMBO
(+)-(S)-3-1B
159.379
159.152
158.111
156.463
139.363
136.872
129.218
129.093
129.030
128.684
118.506
115.265
113.917
113.743
105.817
98.082
77.318
77.000
76.682
69.737
69.504
55.211
52.412
37.887
29.461
(ppm)

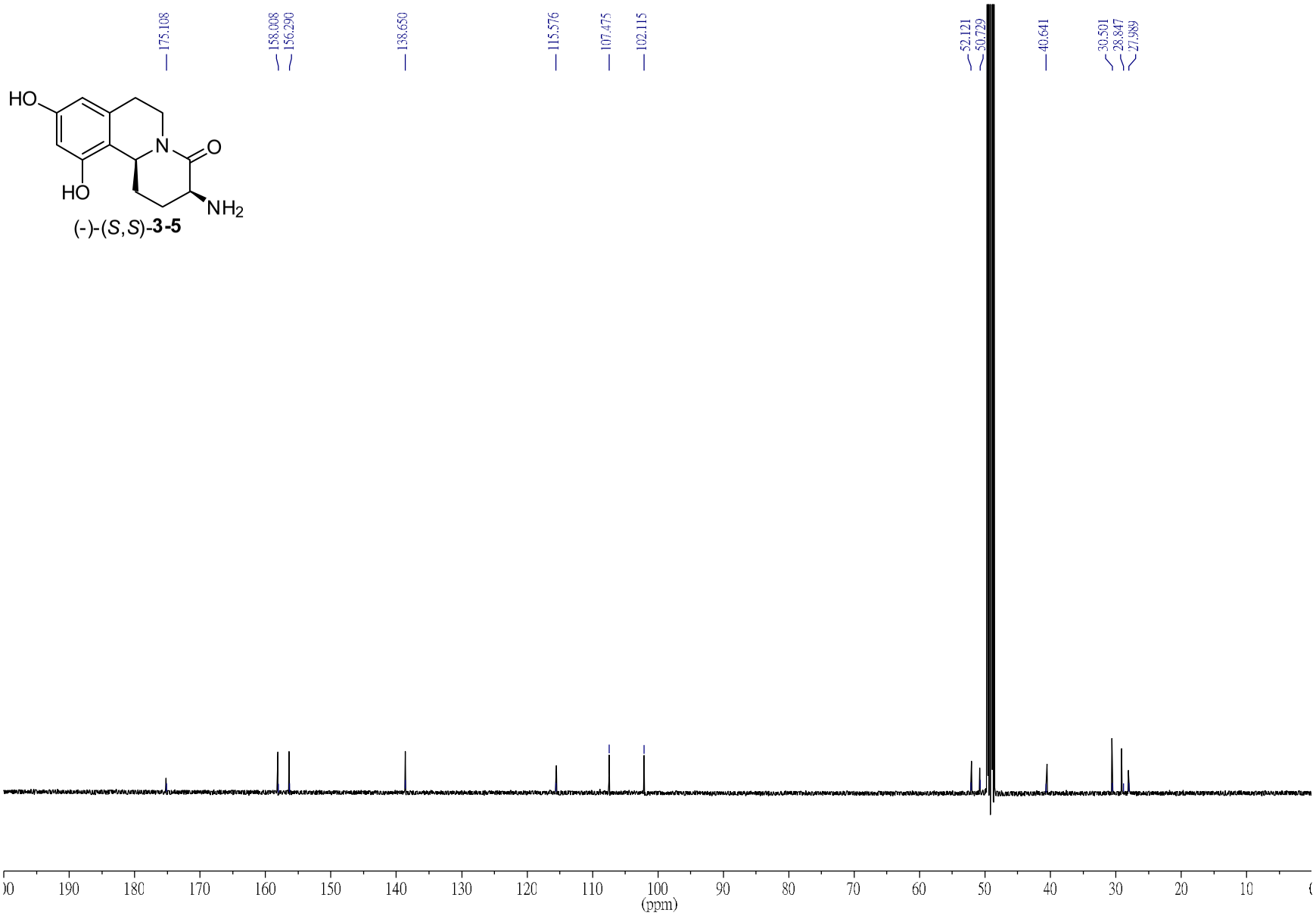

PMBO
N
O
PMBO
NHFmoc

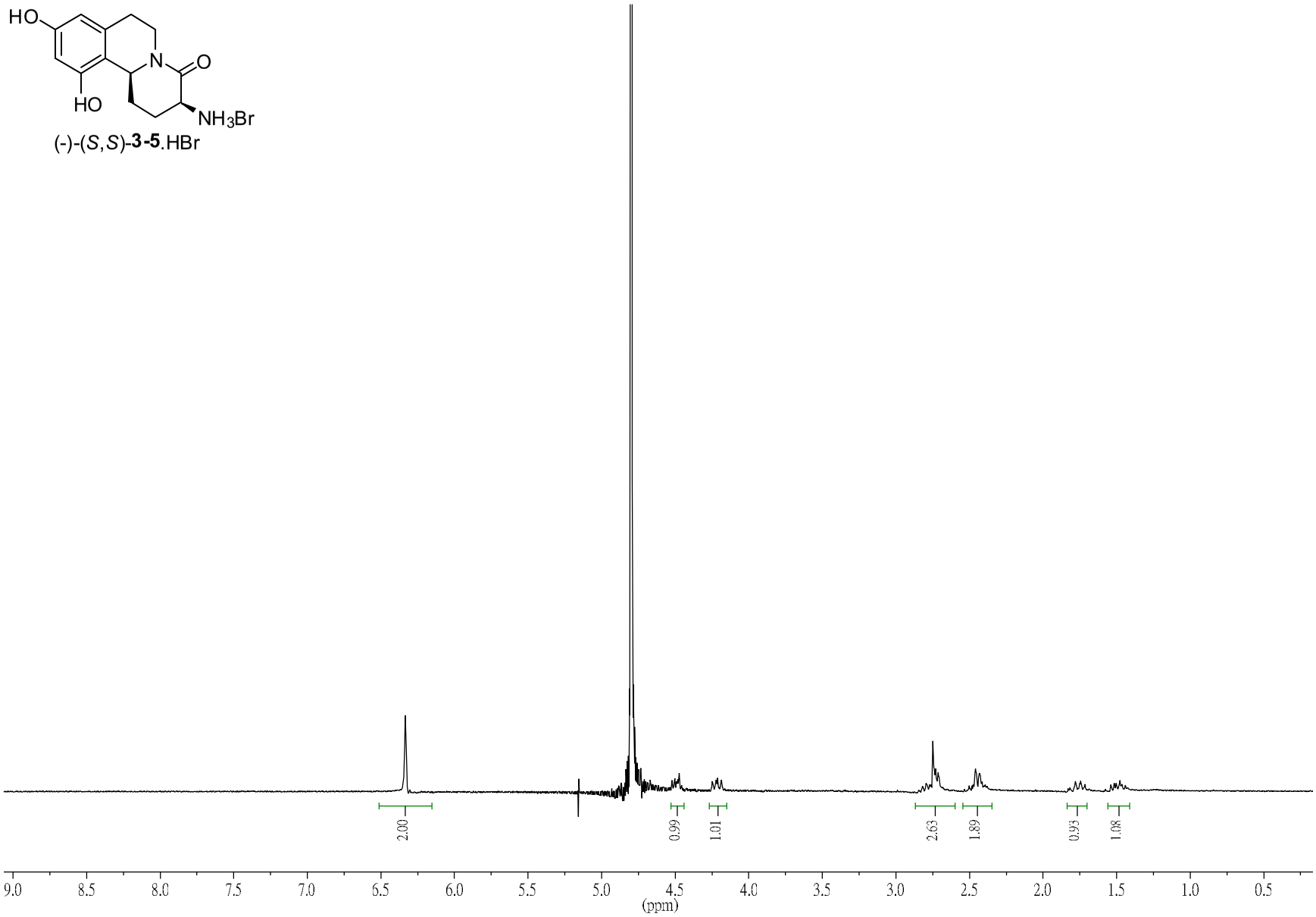
(-)-(*S*,*S*)-**3-4B**

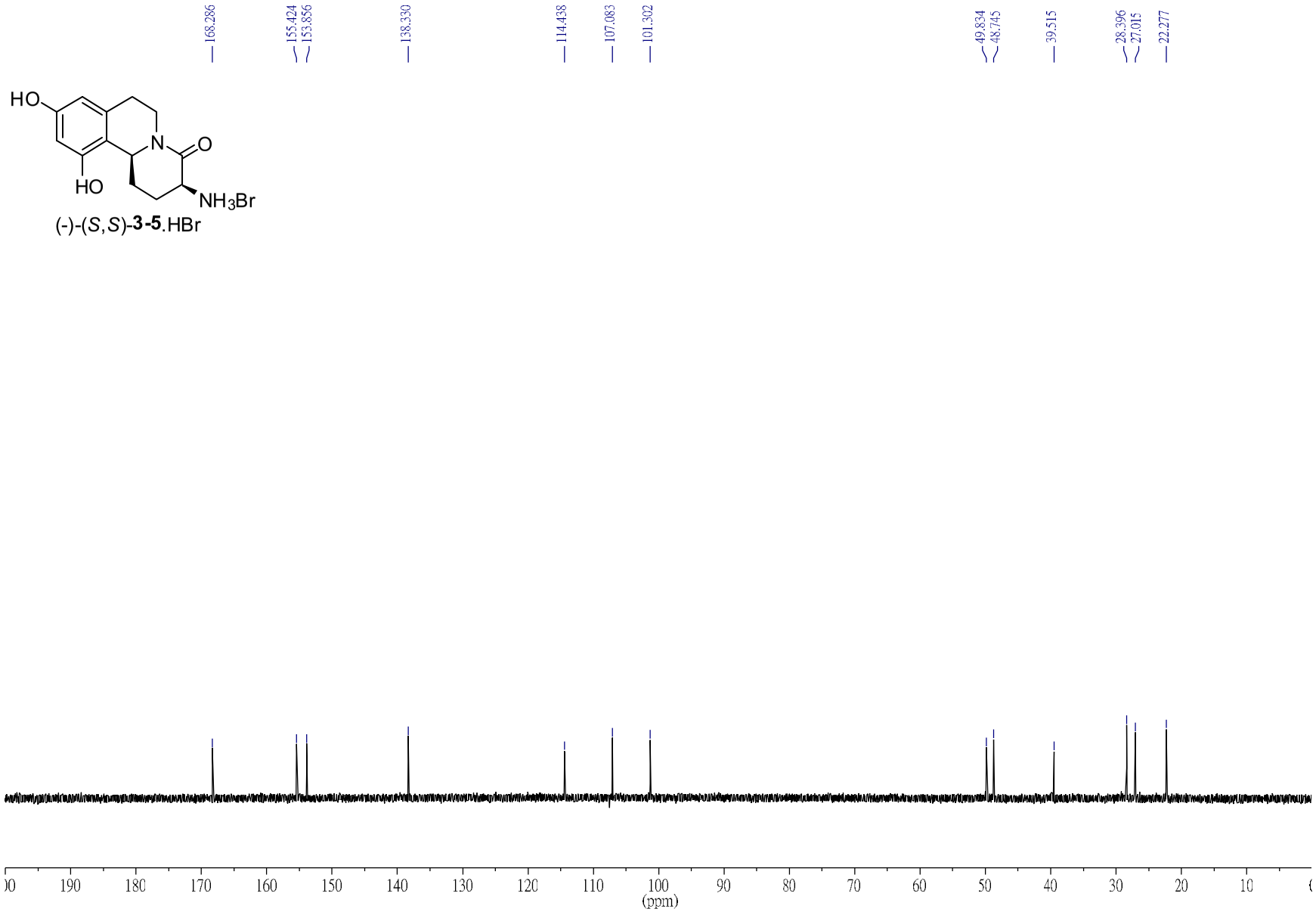

1.71
2.04
7.80
4.00
0.90
0.90
2.62
0.97
4.95
0.93
1.99
1.11
5.80
3.10
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

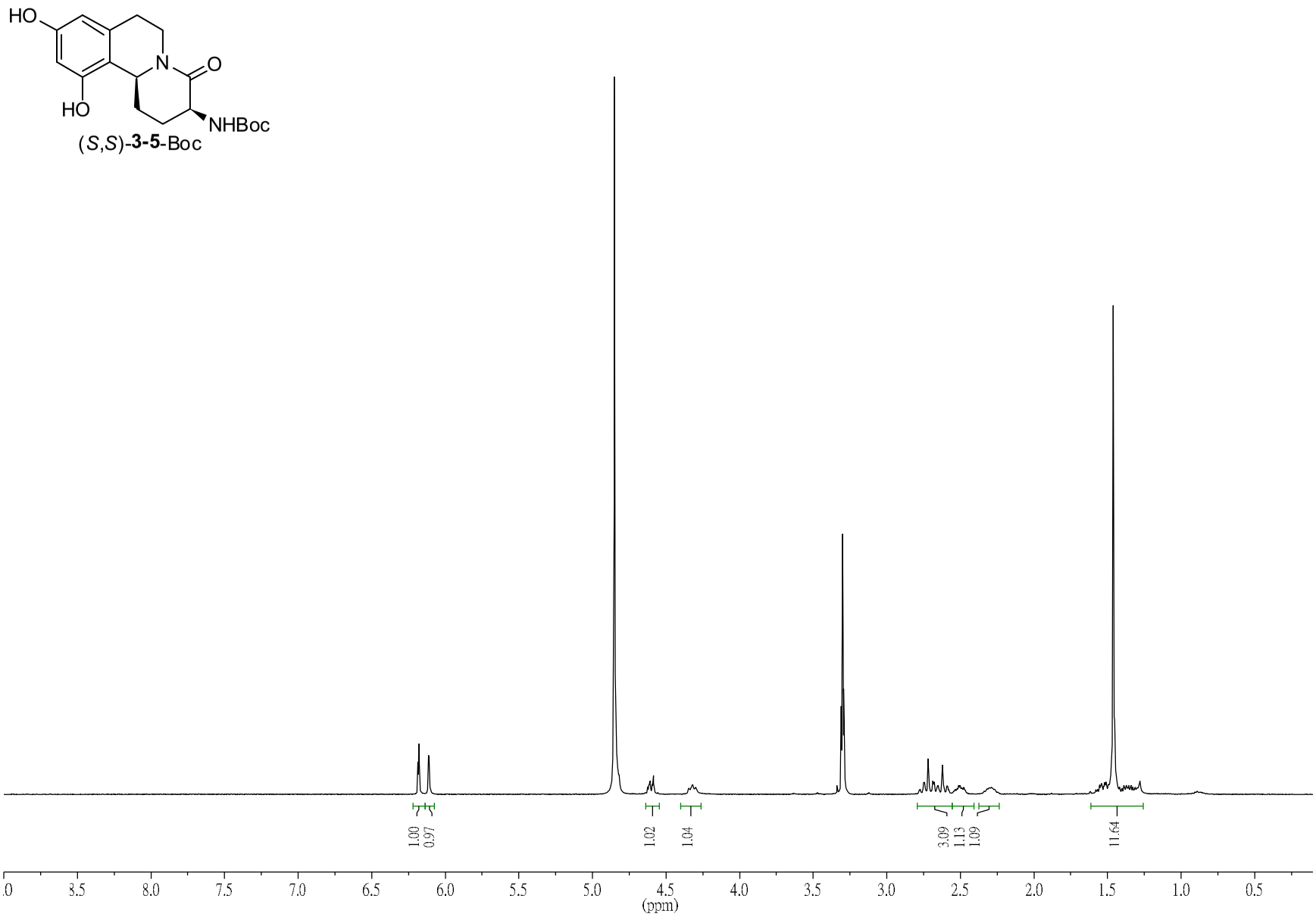

167.094
159.575
159.548
158.682
156.153
144.010
143.859
141.305
137.628
129.255
128.888
128.702
127.659
127.060
125.194
119.942
115.594
114.161
114.081
105.890
99.093
77.255
77.000
76.746
69.983
69.955
67.152
55.323
55.291
52.608
51.245
47.183
40.140
29.894
PMBO
PMBO
N
O
NHFmoc
(-)-(S,S)-3-4B
(ppm)

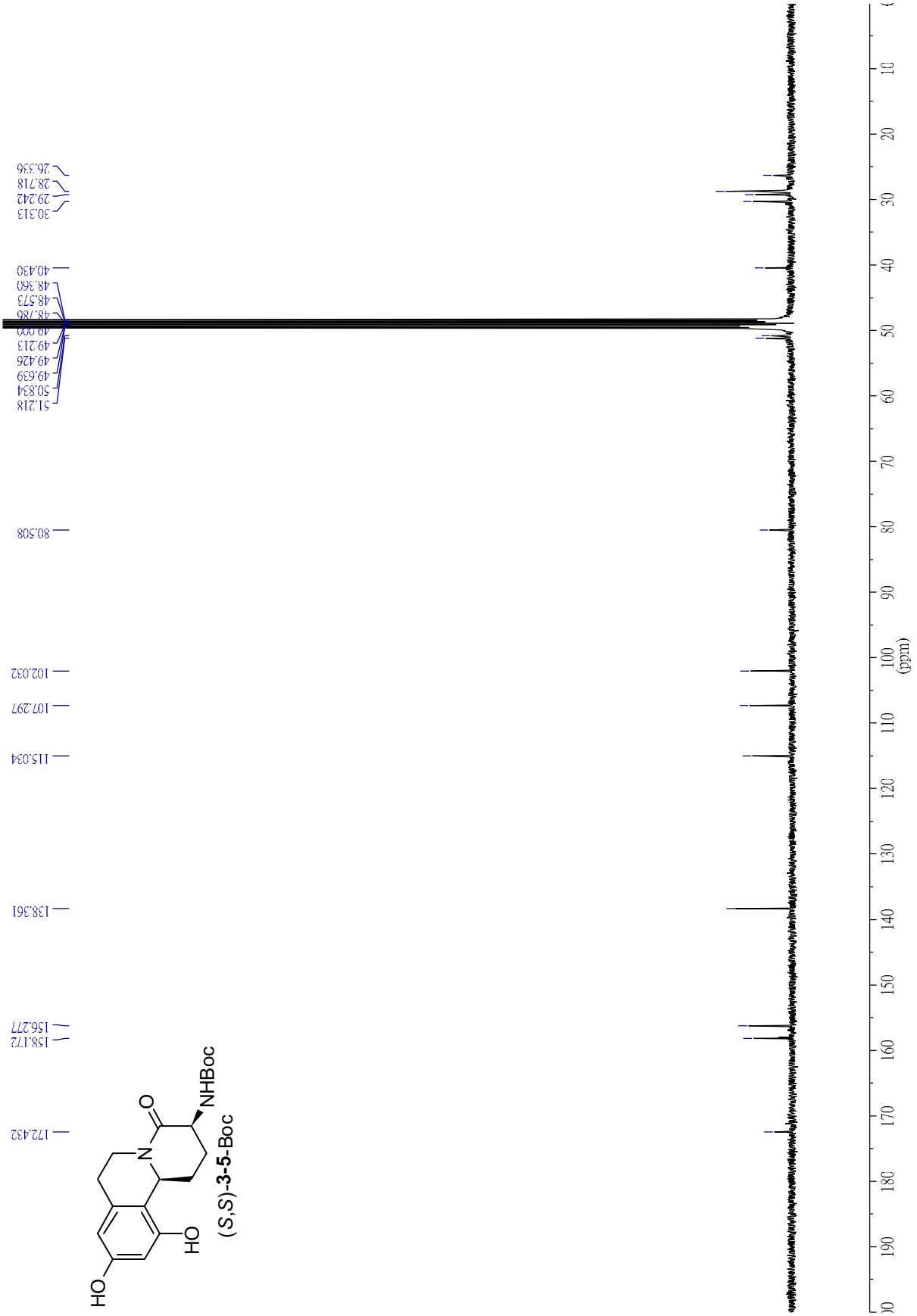

HO
HO
N
O
NH2
(-)-(S,S)-3-5
1.00
1.00
1.09
1.03
1.05
4.30
1.07
2.63
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

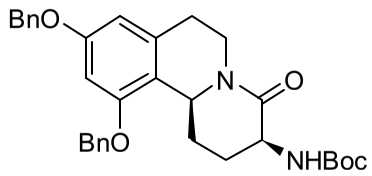

175.108
158.008
156.290
138.650
115.576
107.475
102.115
52.121
50.729
40.641
30.501
28.847
27.989
HO
HO
N
O
NH2
(-)-(S,S)-3-5
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)


HO
HO
N
O
NH3Br
(-)-(S,S)-3-5.HBr
2.00
0.99
1.01
2.63
1.89
0.93
1.08
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

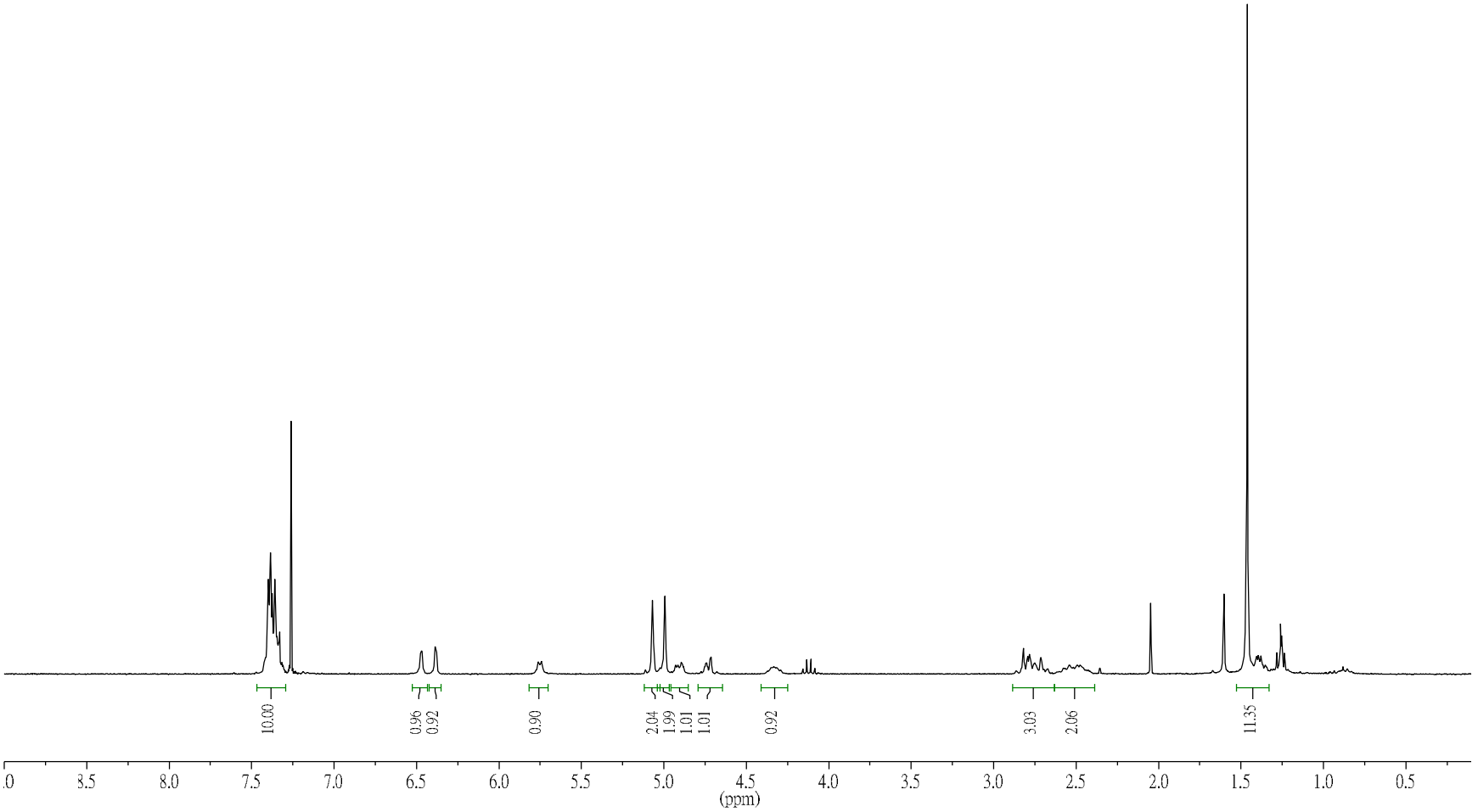

168.286
155.424
153.856
138.330
114.438
107.083
101.302
49.834
48.745
39.515
28.396
27.015
22.277
HO
HO
N
O
NH3Br
(-)-(S,S)-3-5.HBr
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

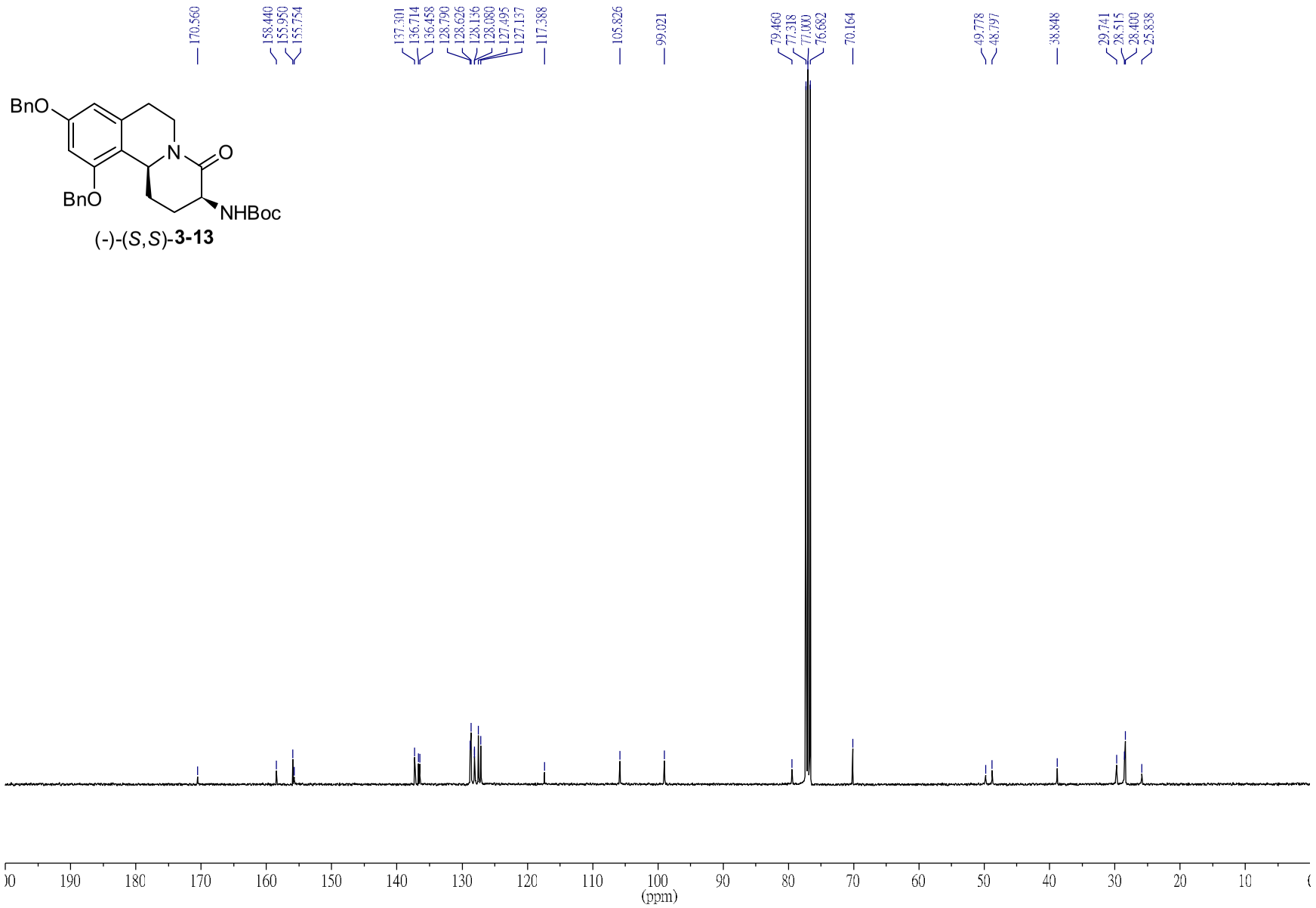

HO
HO
N
O
NHBoc
(S,S)-3-5-Boc
1.00
0.97
1.02
1.04
3.09
1.13
1.09
11.64
(ppm)

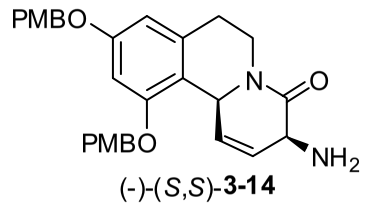

172.432
158.172
156.277
138.361
115.034
107.297
102.032
80.508
51.218
50.834
49.639
49.426
49.213
49.000
48.786
48.573
48.360
40.430
30.313
29.242
28.718
26.336
(S,S)-3-5-Boc
NHBoc
O
N
HO
HO
(ppm)


BnO
N
O
BnO
NHBoc

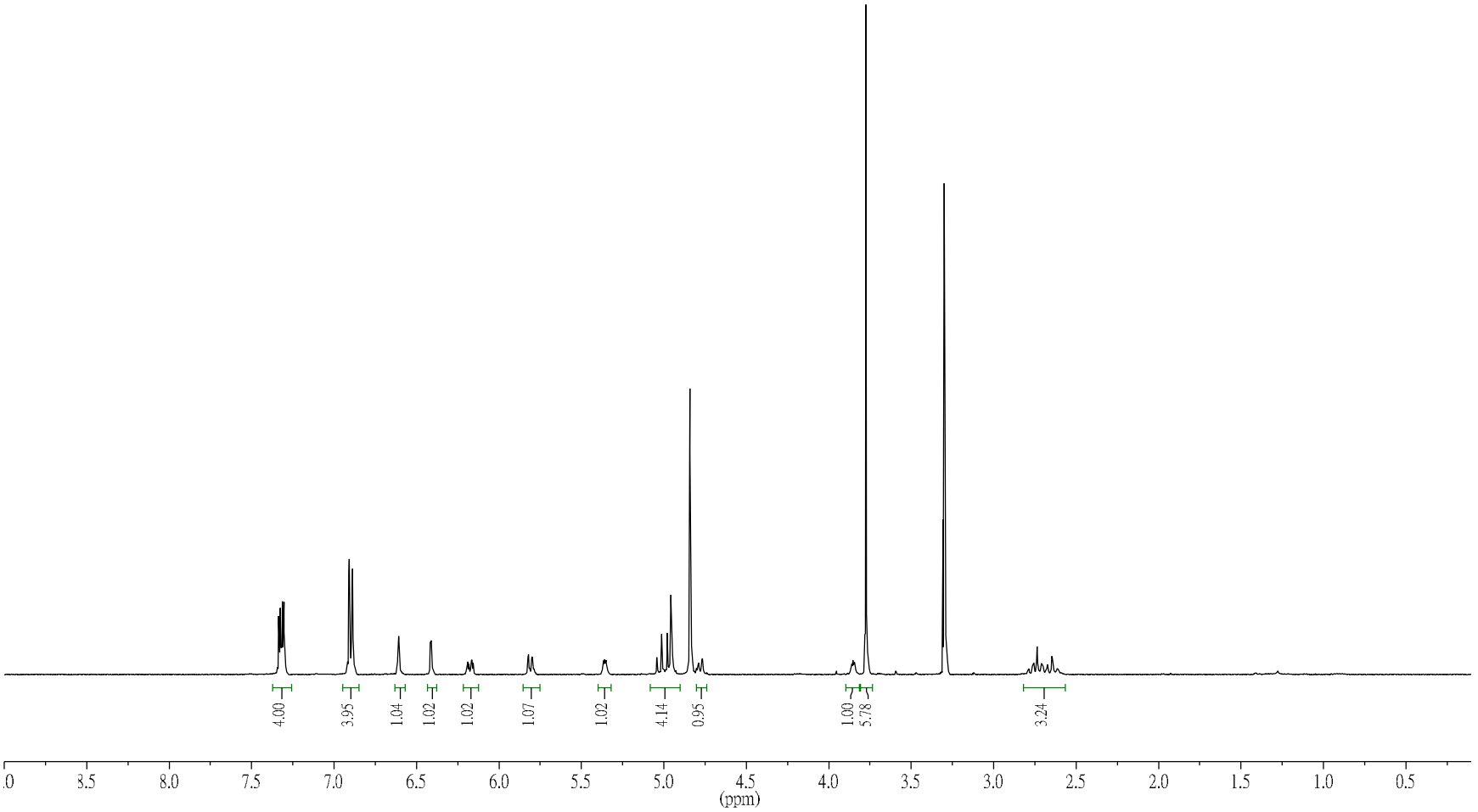
(-)-(*S*,*S*)-**3-13**

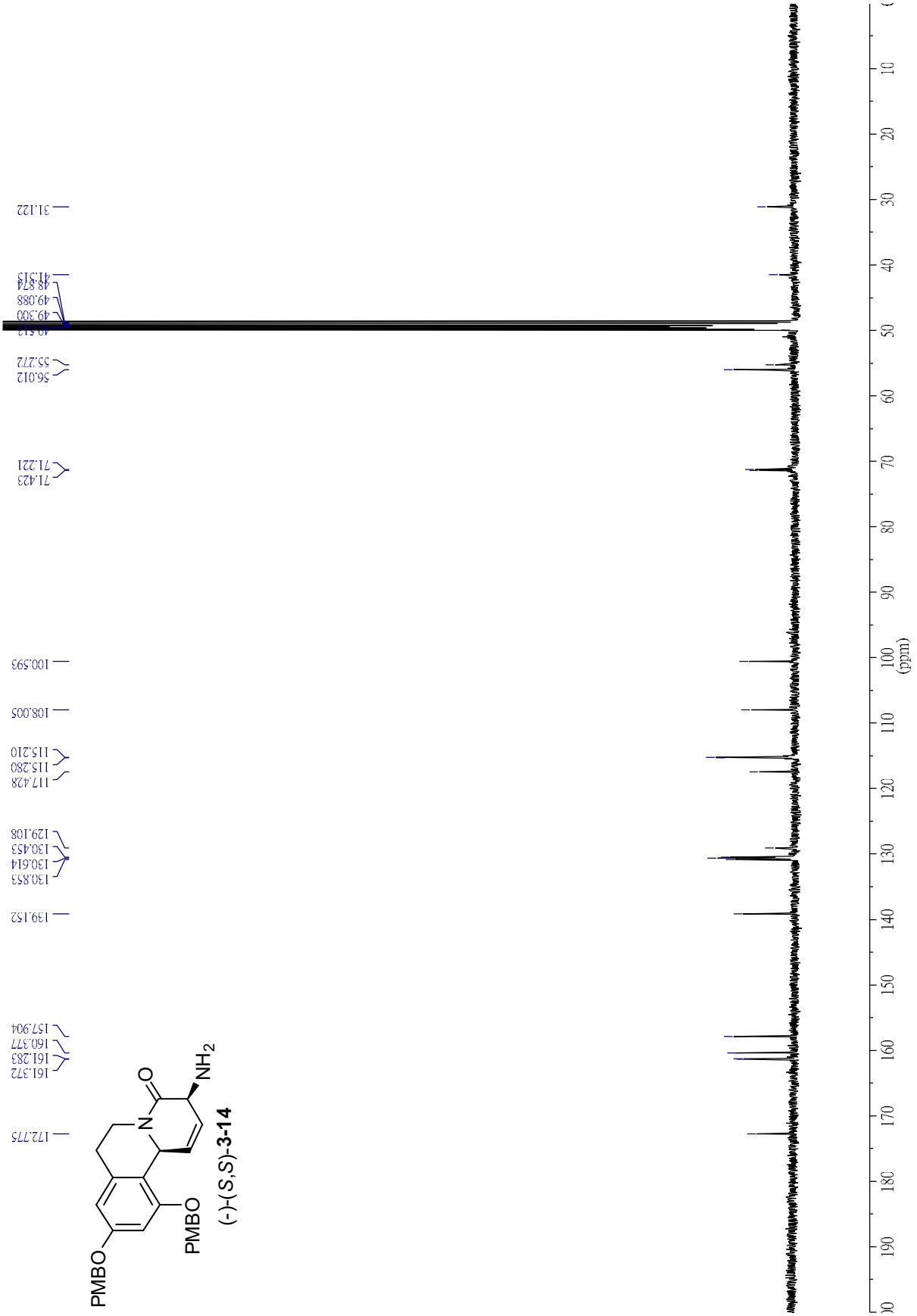

10.00
0.96
0.92
0.90
2.04
1.99
1.01
1.01
0.92
3.03
2.06
11.35
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

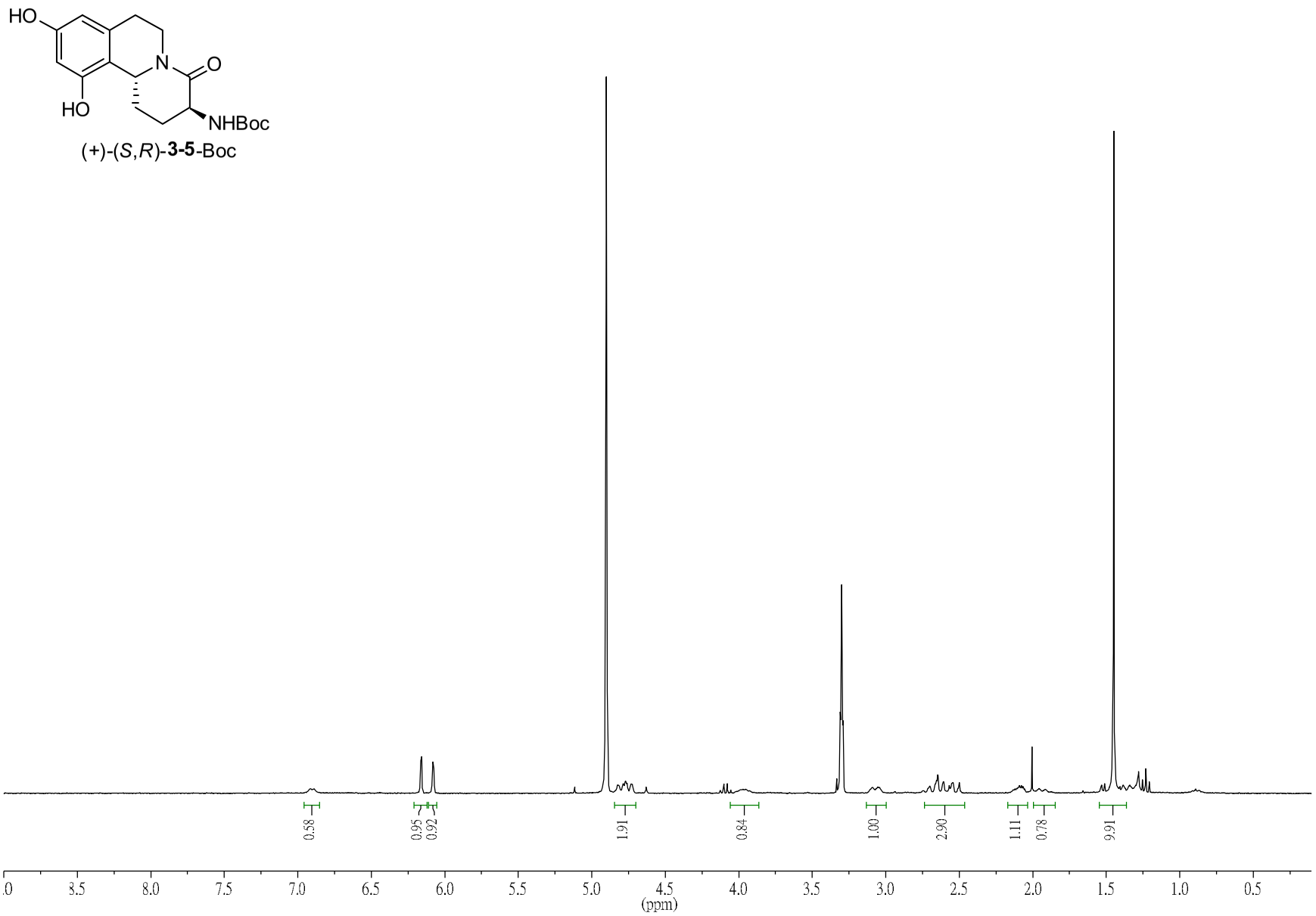

170.560
158.440
155.950
155.754
137.301
136.714
136.458
128.790
128.626
128.136
128.080
127.495
127.137
117.388
105.826
99.021
79.460
77.318
77.000
76.682
70.164
49.778
48.797
38.848
29.741
28.515
28.400
25.838
BnO
BnO
N
O
NHBoc
(-)-(S,S)-3-13
(ppm)

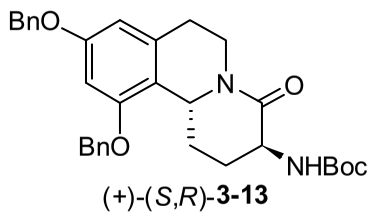

PMBO
N
O
PMBO
NH2

(-)-(*S*,*S*)-**3-14**


4.00
3.95
1.04
1.02
1.02
1.07
1.02
4.14
0.95
1.00
5.78
3.24
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

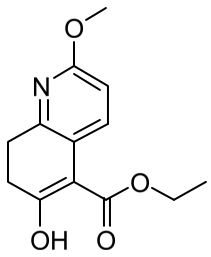

172.775
161.372
161.283
160.377
157.904
139.152
130.853
130.614
130.453
129.108
117.428
115.280
115.210
108.005
100.593
71.423
71.221
56.012
55.272
49.512
49.300
49.088
48.874
41.515
31.122
PMBO
PMBO
NH2
O
N
(-)-(S,S)-3-14
(ppm)


HO
HO
N
O
NHBoc
(+)-(S,R)-3-5-Boc
0.58
0.95
0.92
1.91
0.84
1.00
2.90
1.11
0.78
9.91
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

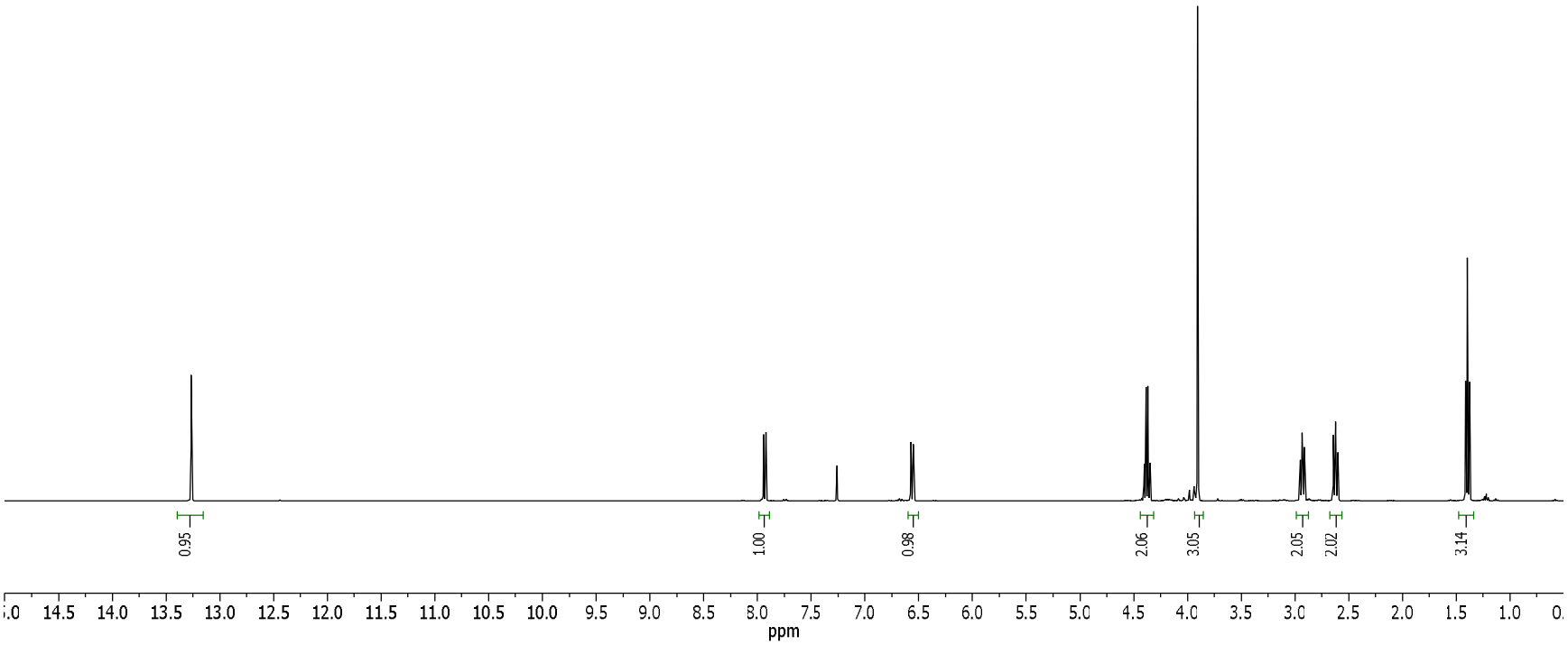

BnO
N
O
BnO
NHBoc

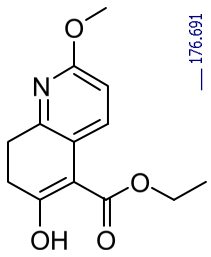
(+)-(*S*,*R*)-**3-13**

10.00
1.05
1.08
0.92
4.04
1.15
1.19
1.17
1.08
1.14
2.15
1.18
0.94
11.01
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)


O
N
O
O
OH
O

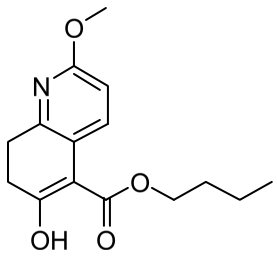
4-3b


0.95
1.00
0.98
2.06
3.05
2.05
2.02
3.14
14.5 14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm

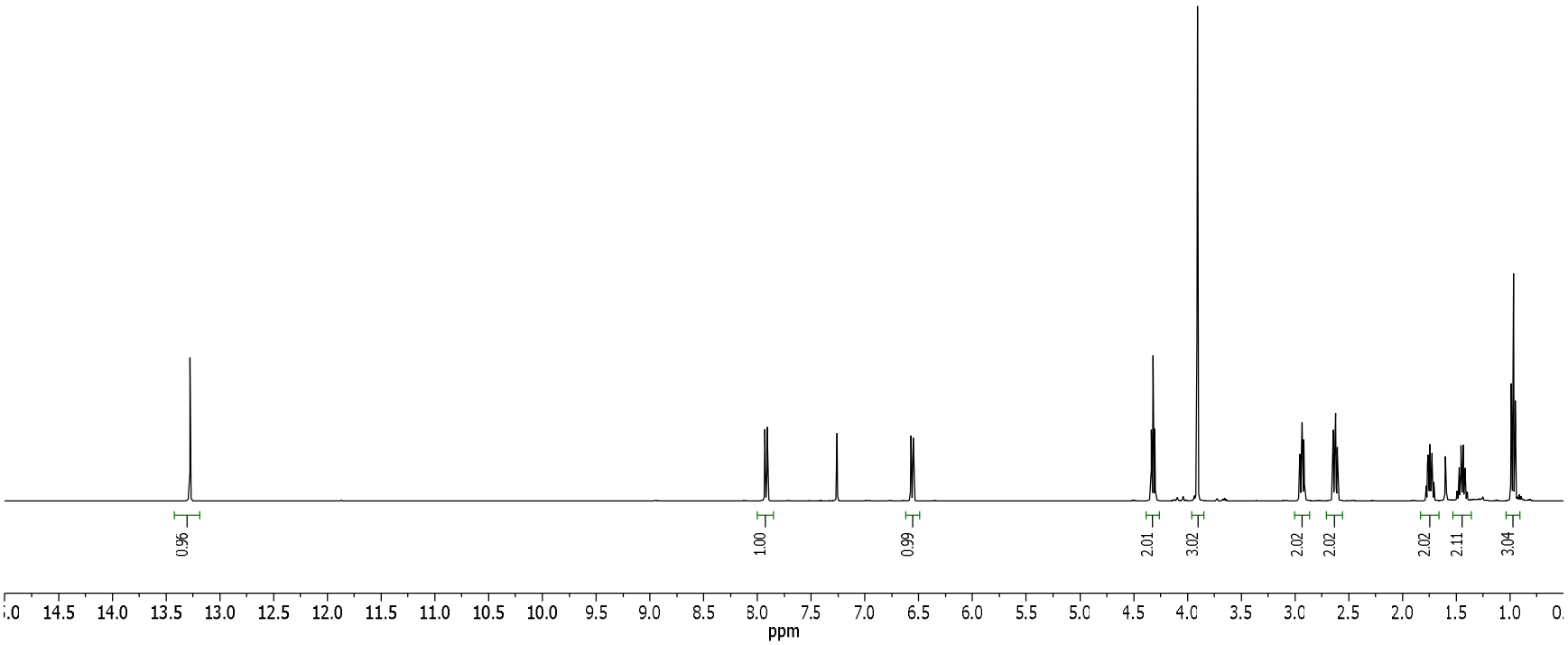

O
N
O
O
OH
O

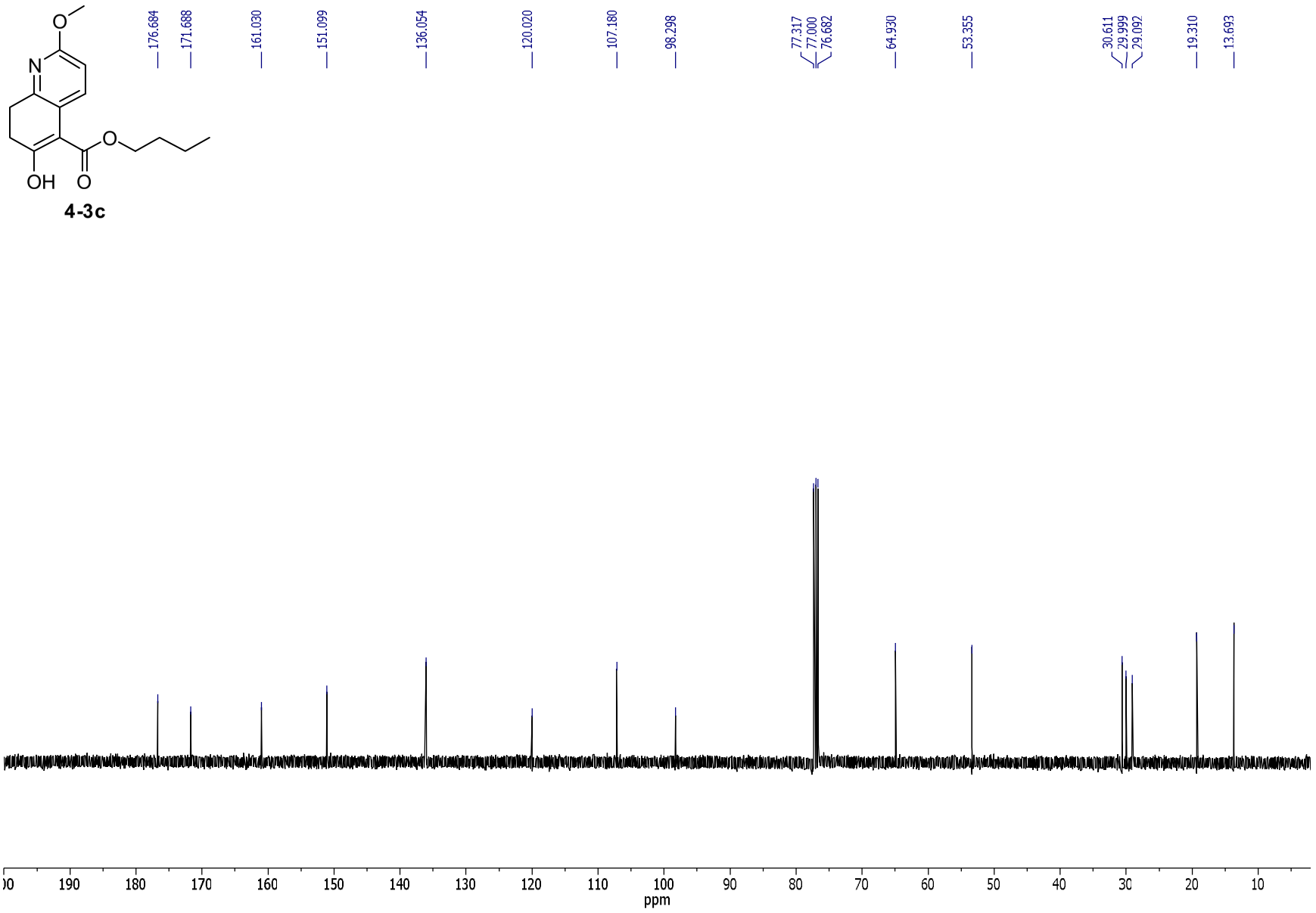
4-3b

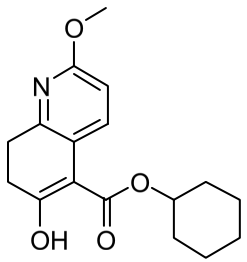
176.691
171.572
161.023
151.086
136.065
119.985
107.182
98.247
77.318
77.000
76.683
61.048
53.348
29.974
29.070
14.257
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


O
N
O
O
OH
O

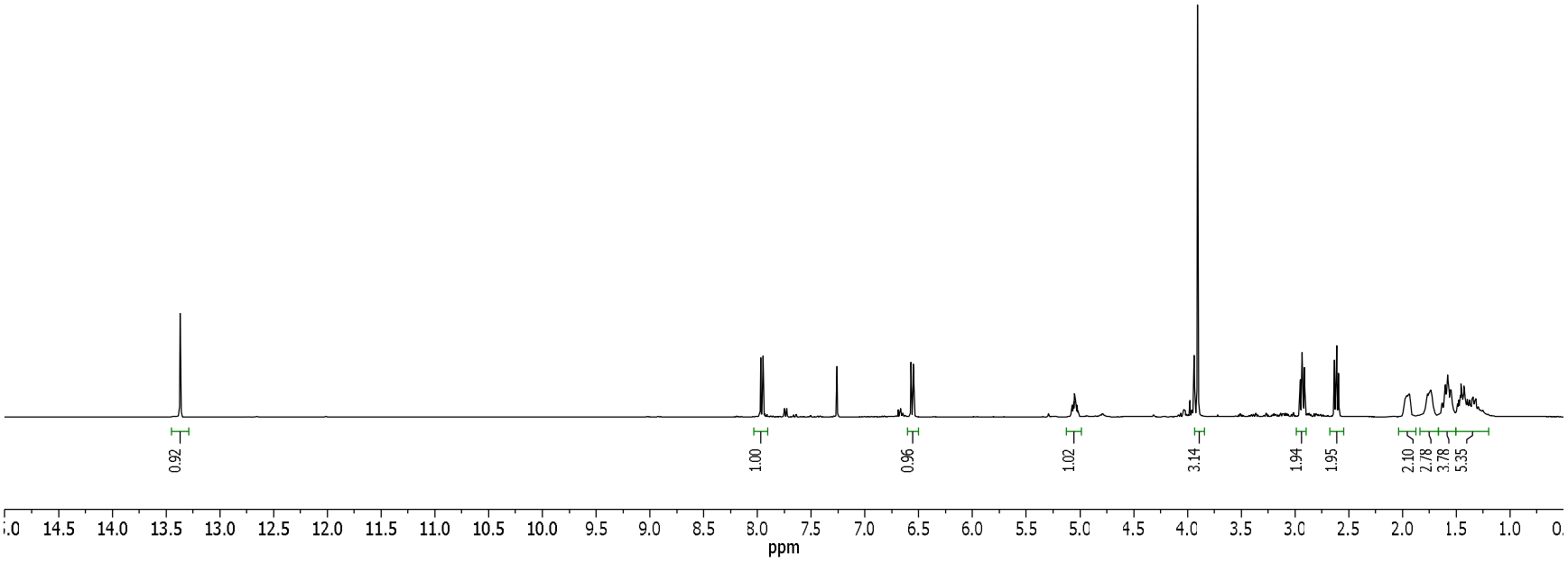
4-3c

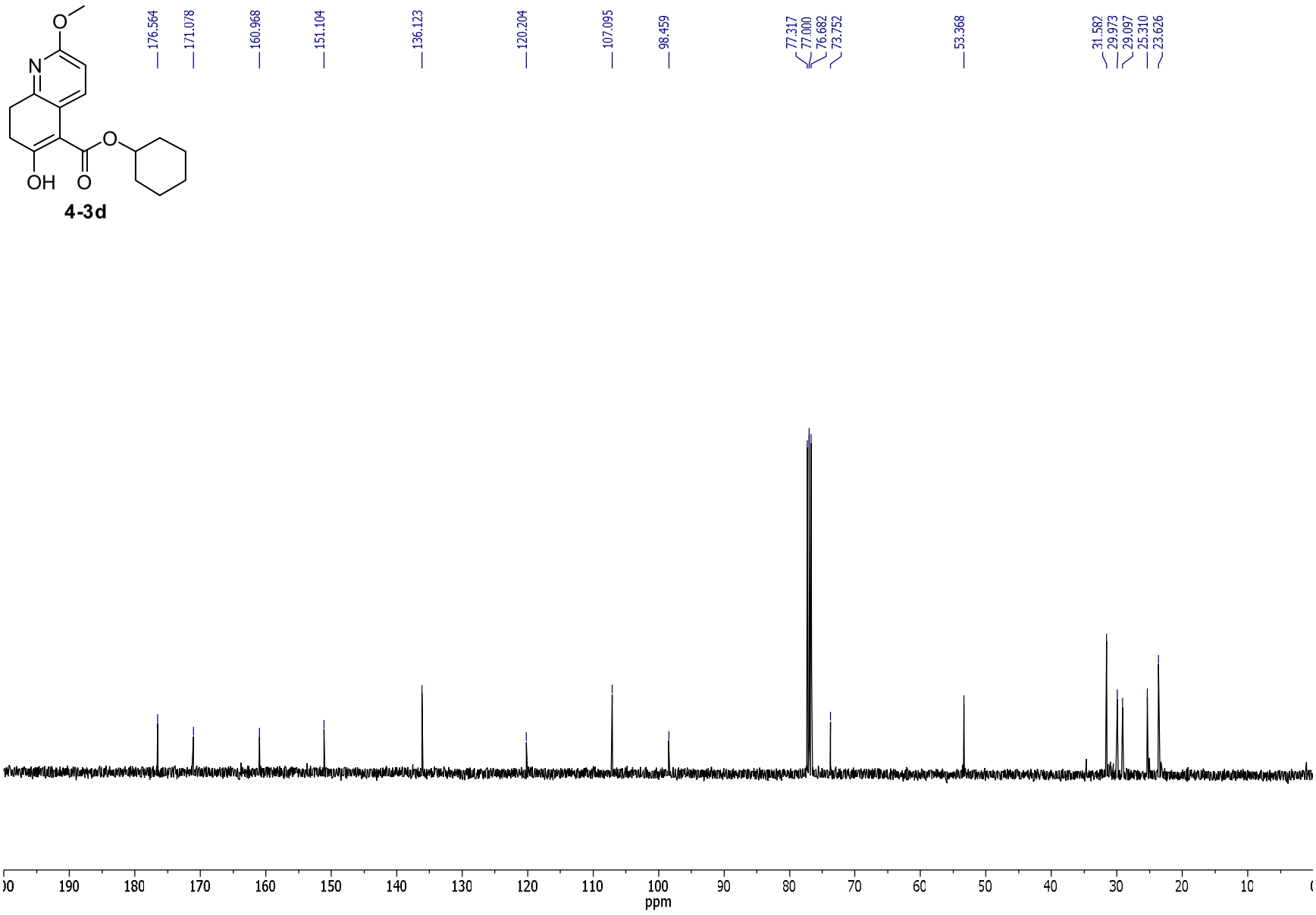

0.96
1.00
0.99
2.01
3.02
2.02
2.02
2.02
2.11
3.04
14.5
14.0
13.5
13.0
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

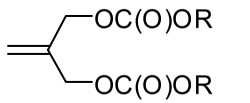

O
N
O
OH
O
4-3c
176.684
171.688
161.030
151.099
136.054
120.020
107.180
98.298
77.317
77.000
76.682
64.930
53.355
30.611
29.999
29.092
19.310
13.693
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


O
N
O
O
OH
O

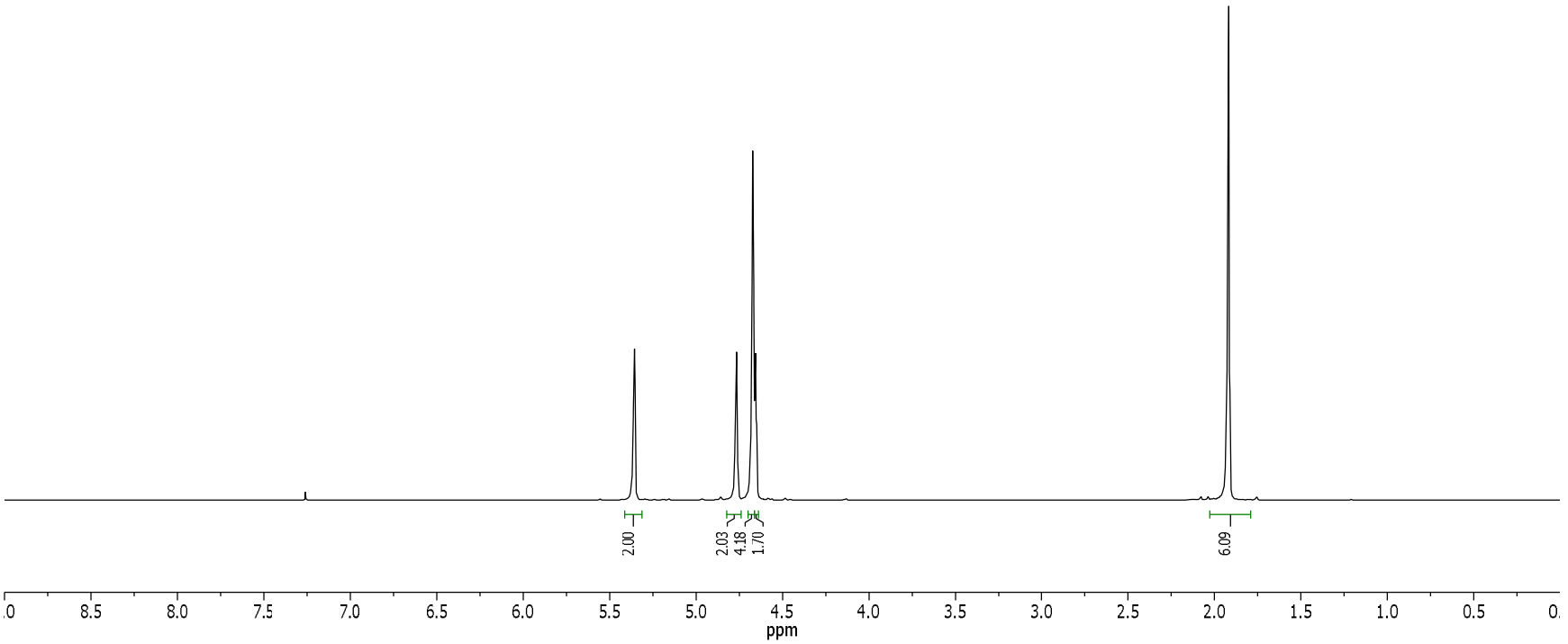
4-3d

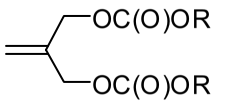

0.92
1.00
0.96
1.02
3.14
1.94
1.95
2.10
2.78
3.78
5.35
14.5
14.0
13.5
13.0
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


O
N
OH
O
O
4-3d
176.564
171.078
160.968
151.104
136.123
120.204
107.095
98.459
77.317
77.000
76.682
73.752
53.368
31.582
29.973
29.097
25.310
23.626
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

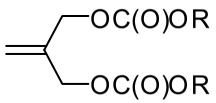


4-5e: R = $CH_3C{=}CH_2$

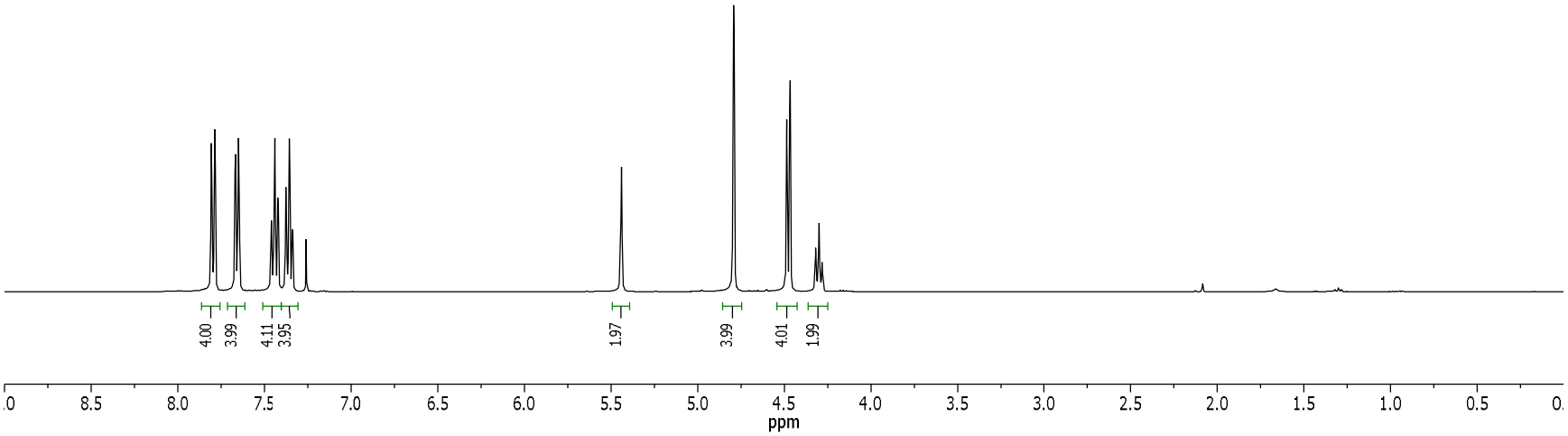


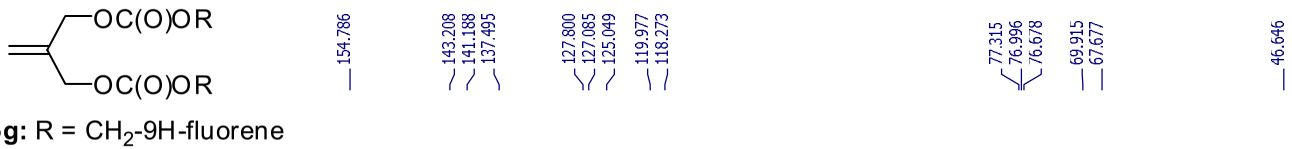


4-5e: R = $CH_3C{=}CH_2$

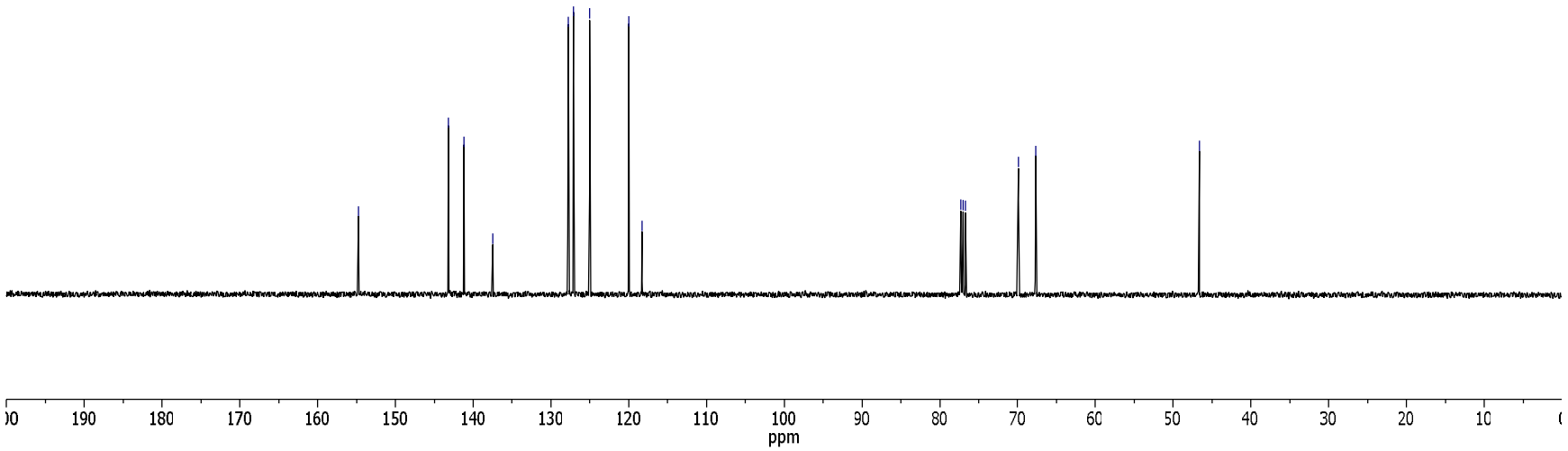


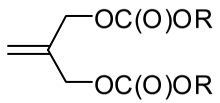
4-5g: R = CH_2-9H-fluorene



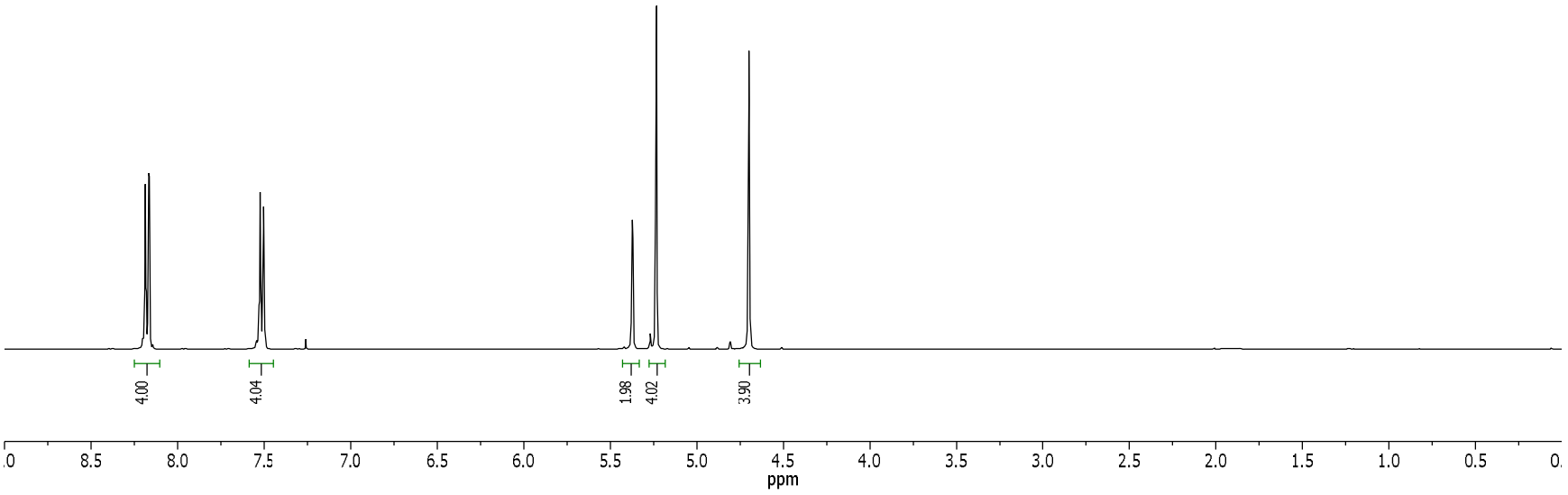


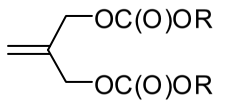
4-5g: R = CH_2-9H-fluorene





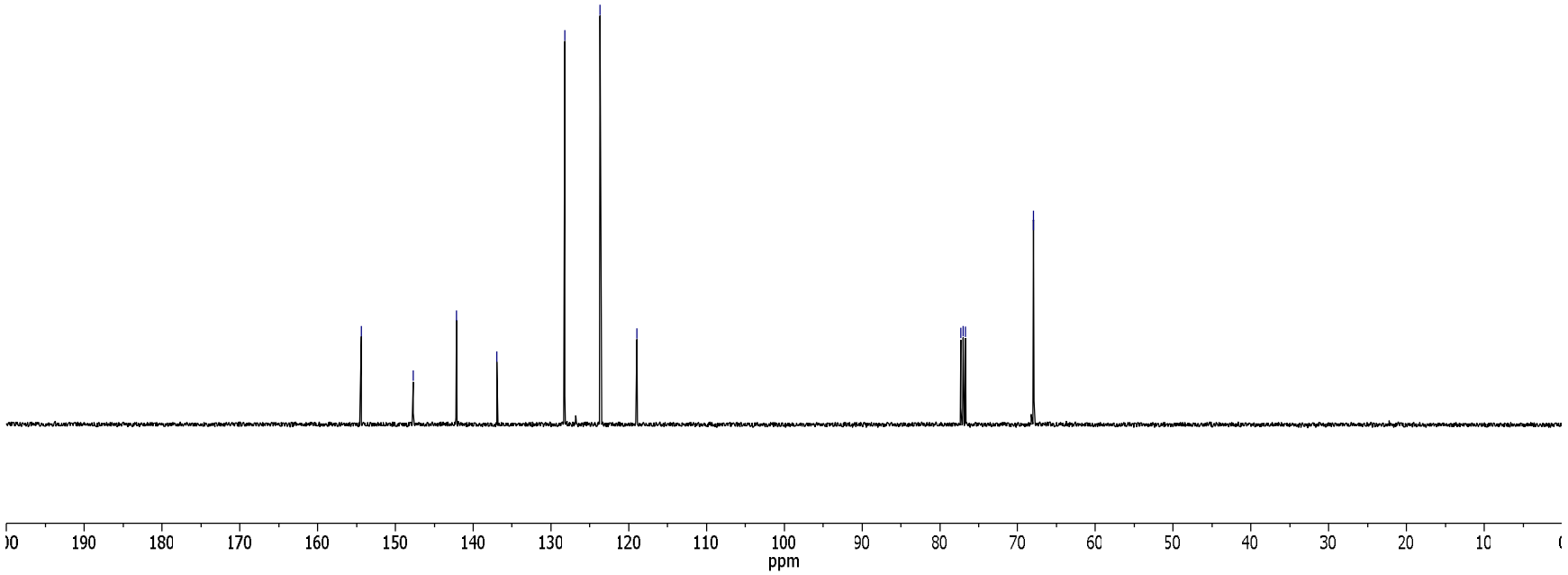
4-5h: R = CH_2-*p*-$C_6H_4NO_2$

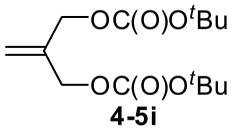




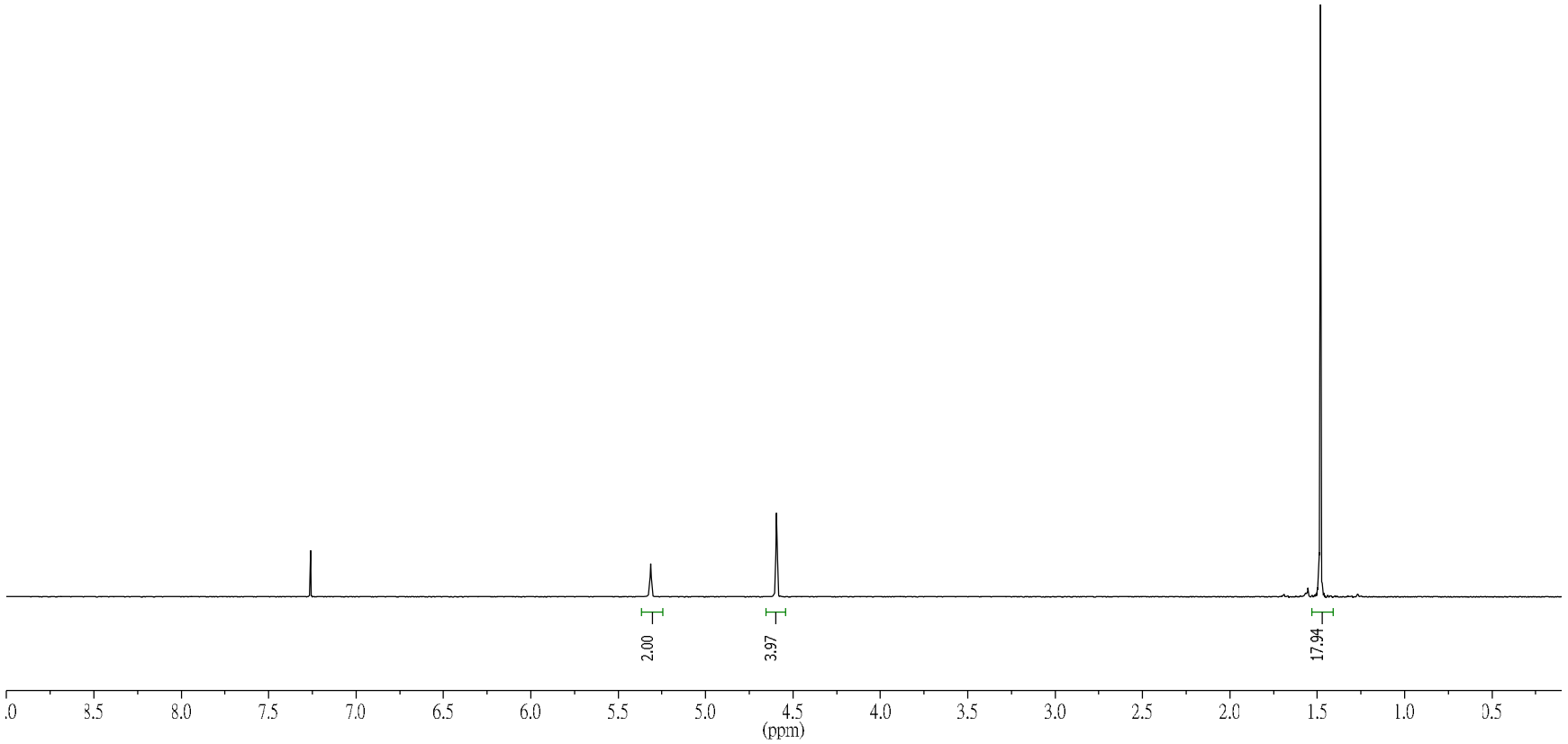
4-5h: R = CH_2-*p*-$C_6H_4NO_2$

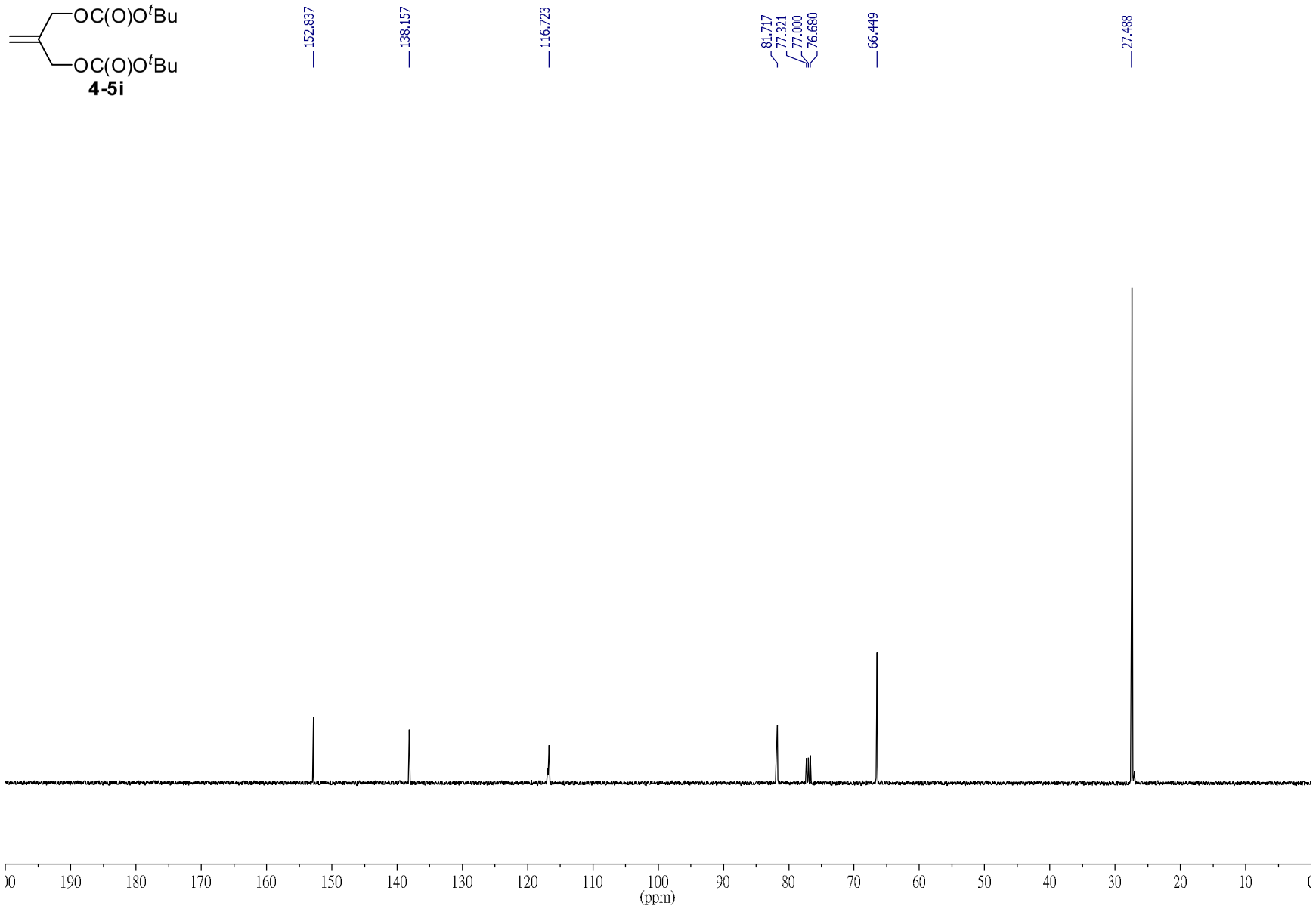
154.391
147.717
142.167
136.928
128.237
123.683
118.924
77.319
77.000
76.681
67.977
67.941

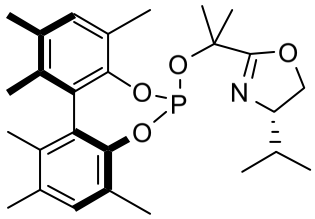



OC(O)O^{t}Bu
OC(O)O^{t}Bu

4-5i

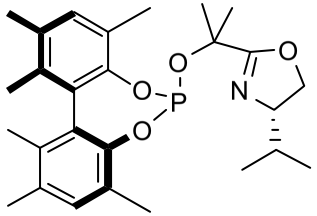

2.00
3.97
17.94
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)


OC(O)O^{t}Bu
OC(O)O^{t}Bu
4-5i
152.837
138.157
116.723
81.717
77.321
77.000
76.680
66.449
27.488
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)


O
O
P
O
N
O

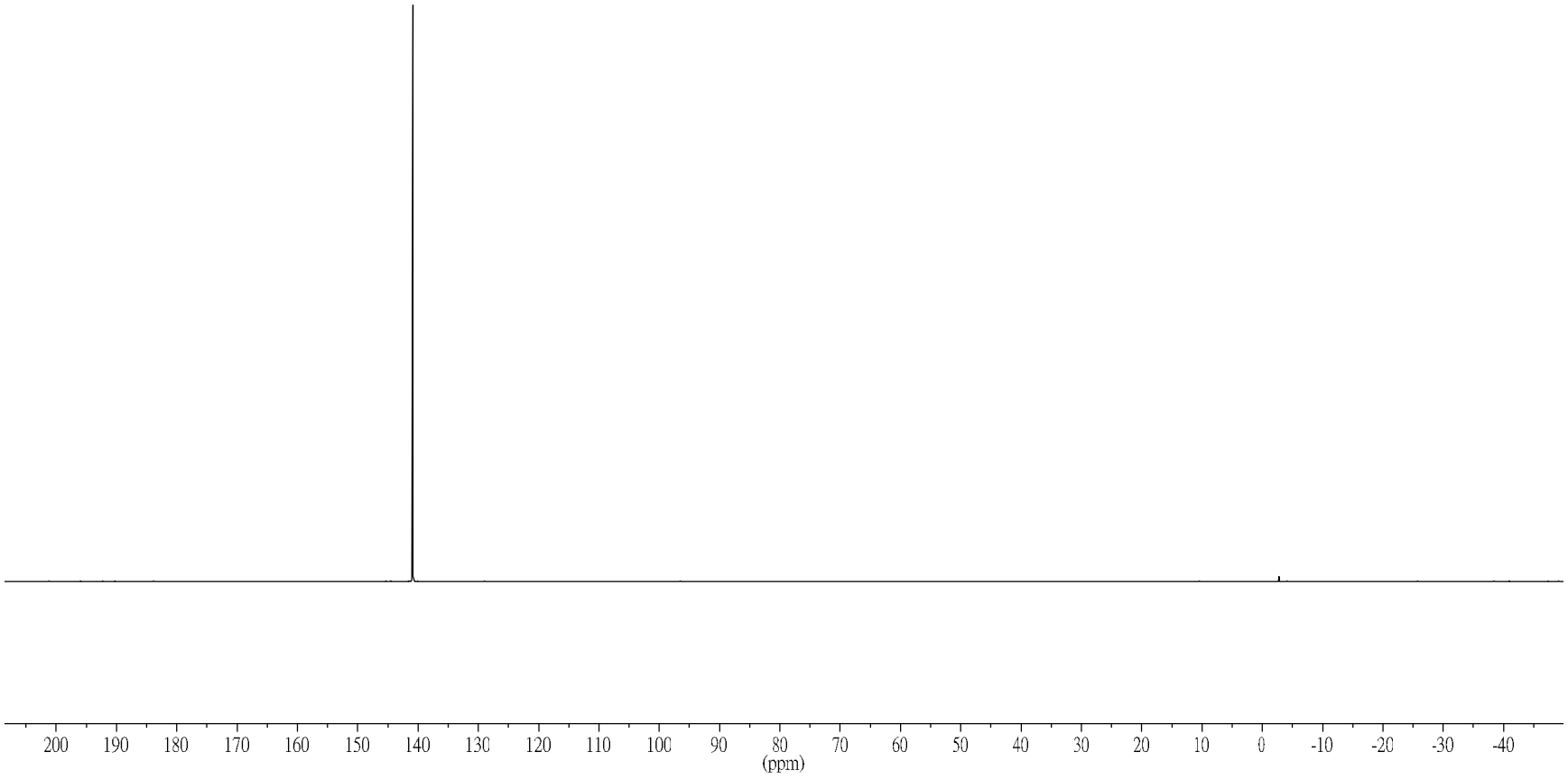
(*S*,*S*)-**PN-L1b**

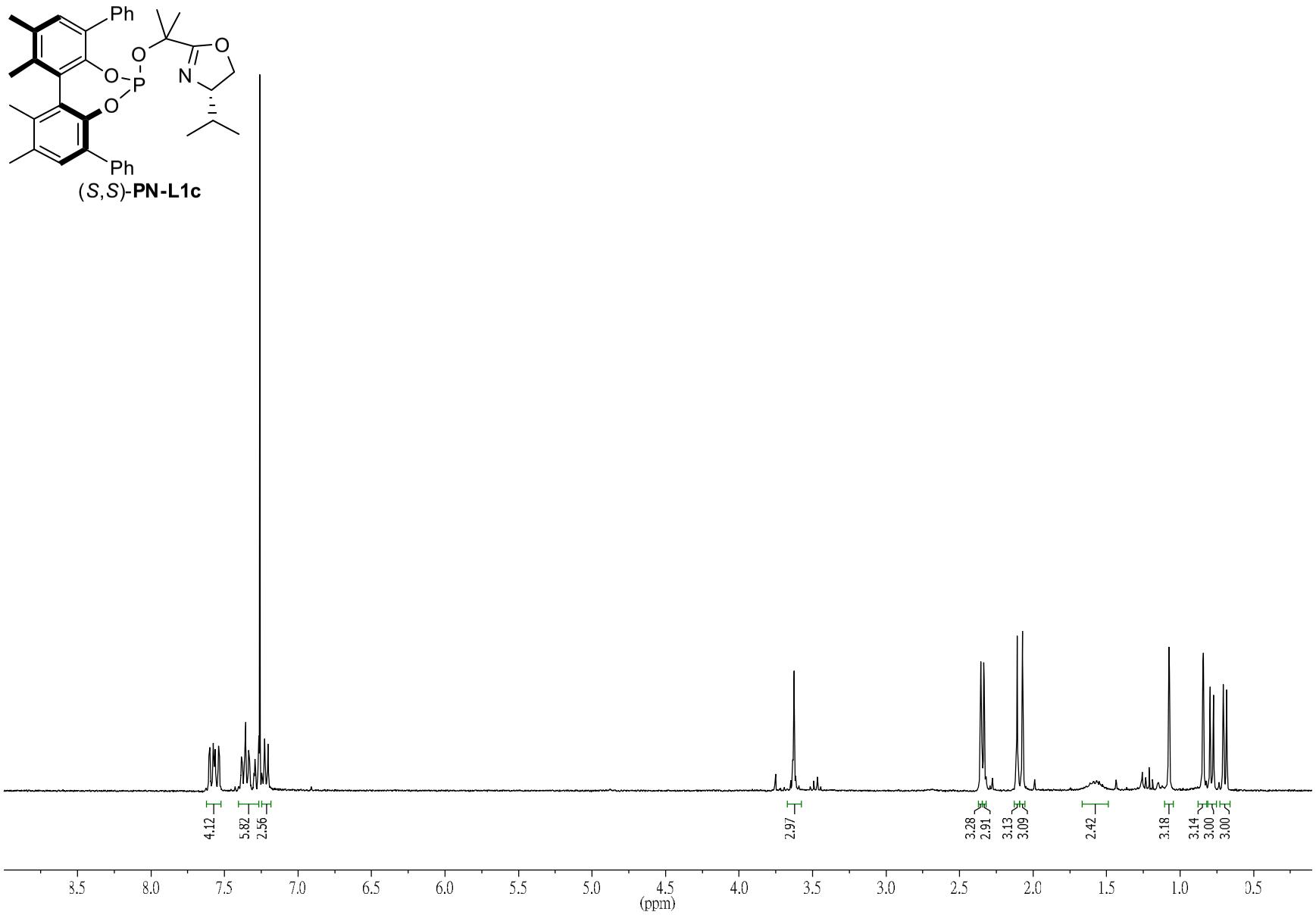
0.93
0.94
0.91
2.00
5.40
3.92
3.13
3.50
2.79
1.77
2.80
2.69
2.90
2.85
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

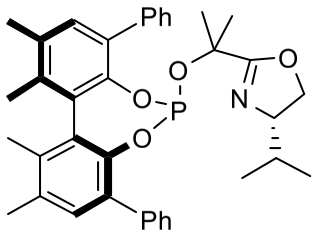


(*S*,*S*)-**PN-L1b**

140.9

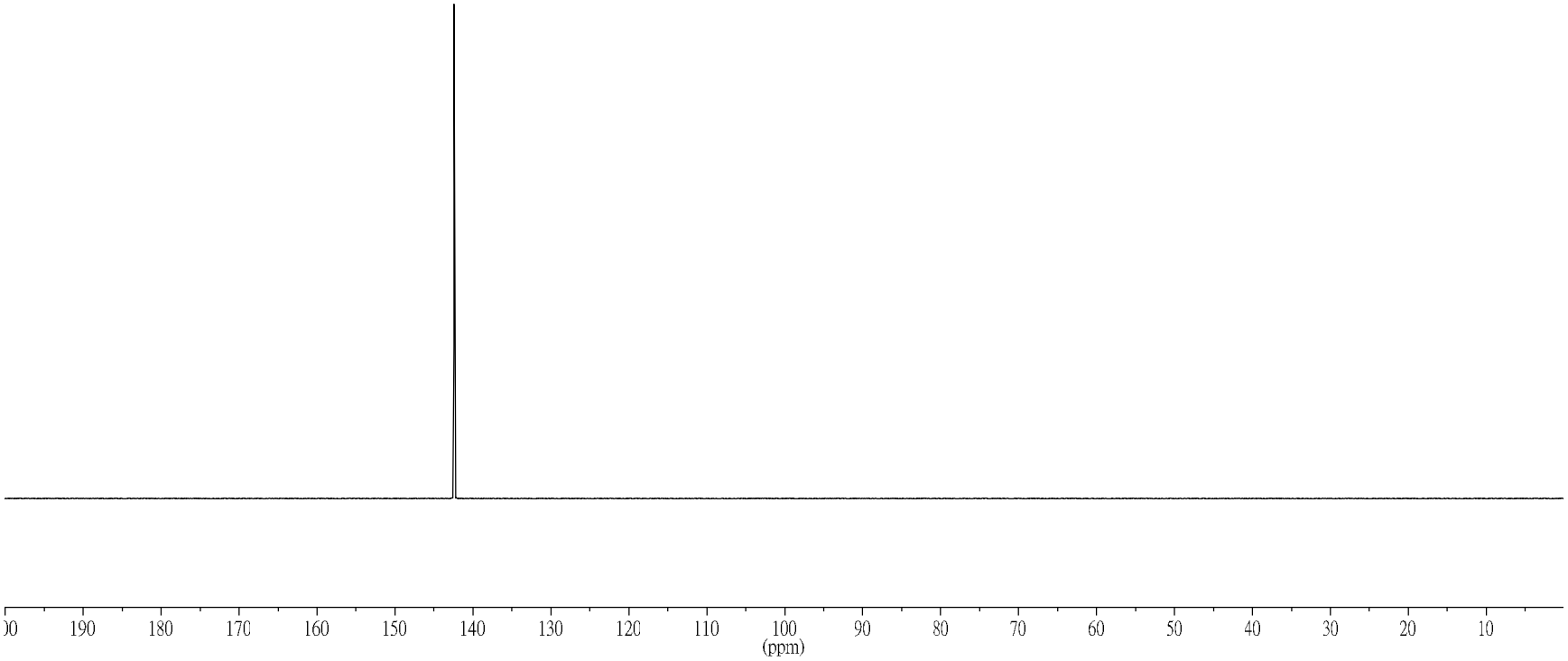


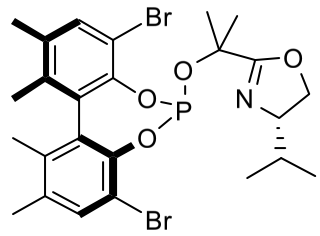

Ph
O
O
P
O
N
Ph
(S,S)-PN-L1c
4.12
5.82
2.56
2.97
3.28
2.91
3.13
3.09
2.42
3.18
3.14
3.00
3.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)



(*S*,*S*)-**PN-L1c**

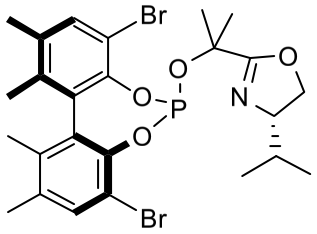
142.4




Br
O
O
P
O
N
O
Br

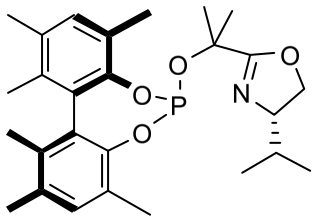
(*S*,*S*)-**PN-L1d**

1.00
0.97
1.02
1.25
0.92
2.96
3.01
2.77
2.81
4.22
3.04
3.14
3.23
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

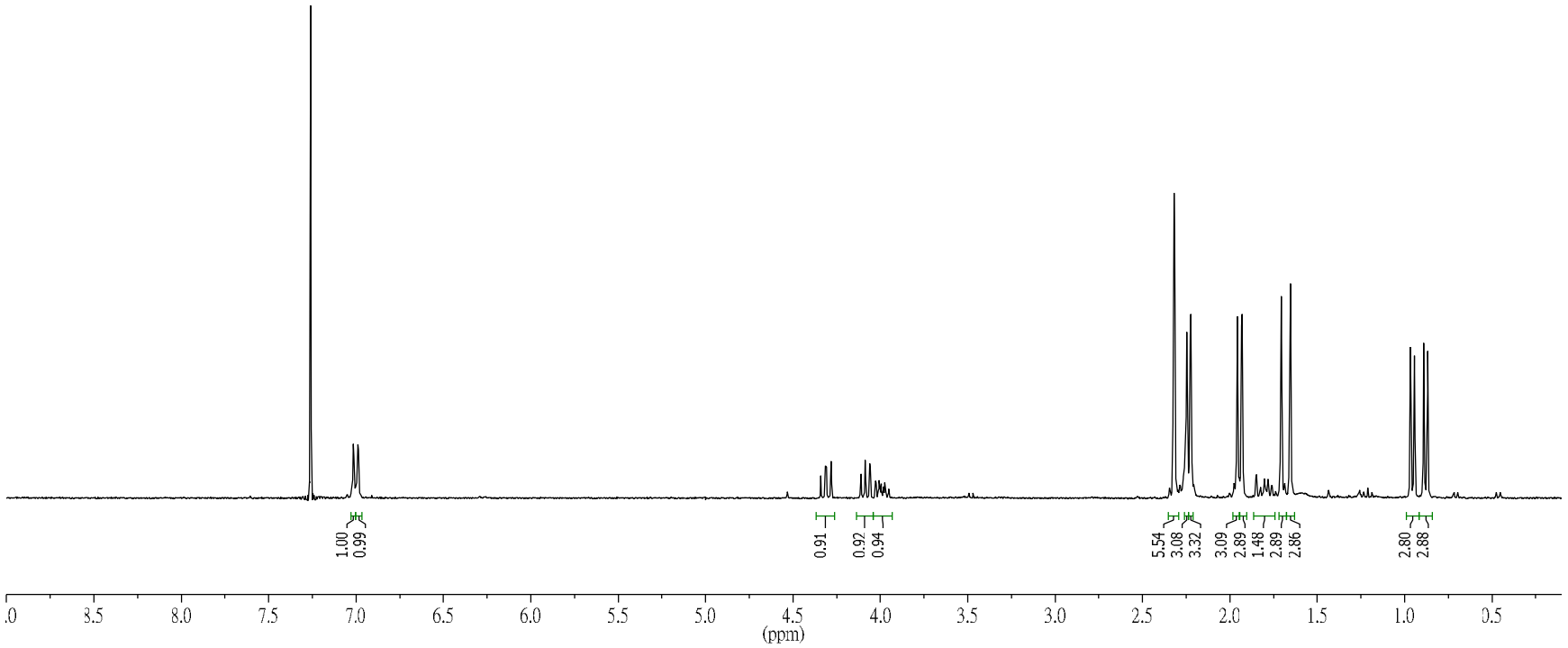

Br
O
O
P
O
N
O
Br

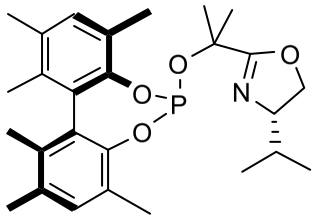
(*S*,*S*)-**PN-L1d**

143.9
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)



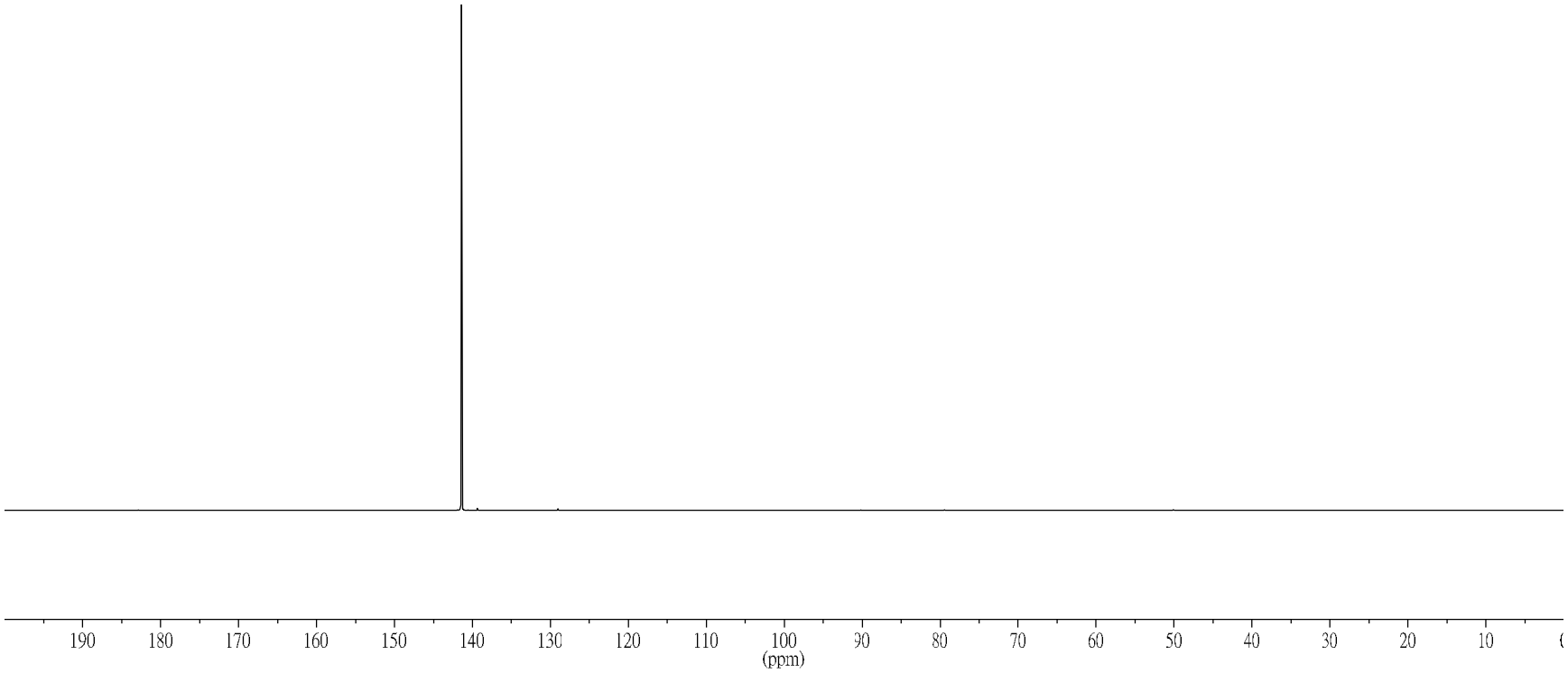
(*R*,*S*)-**PN-L1b**

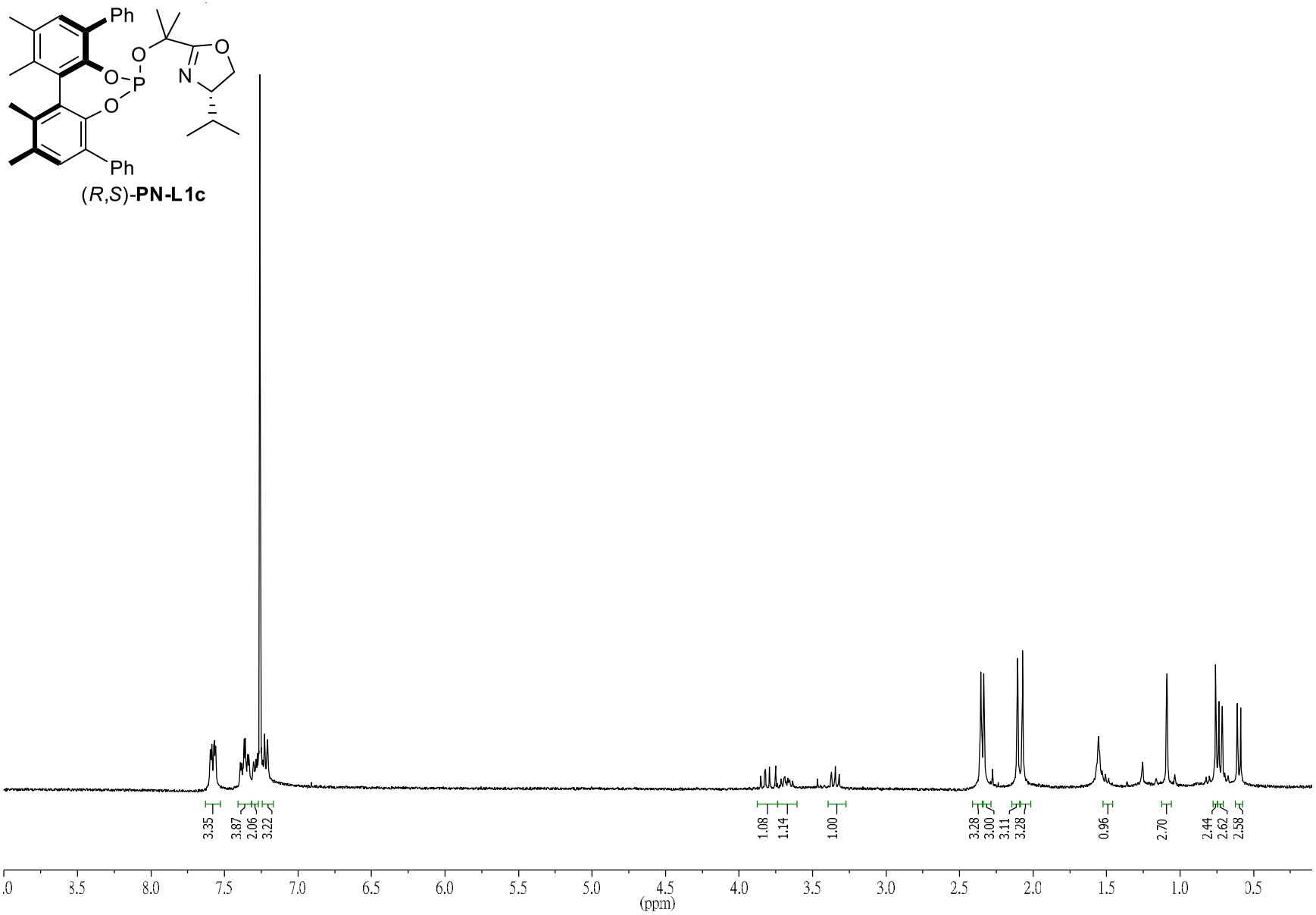

1.00
0.99
0.91
0.92
0.94
5.54
3.08
3.32
3.09
2.89
1.48
2.89
2.86
2.80
2.88
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

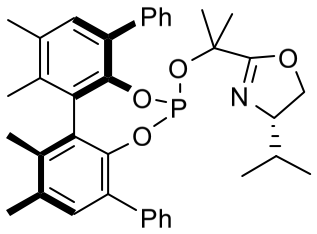


(*R*,*S*)-**PN-L1b**

141.4

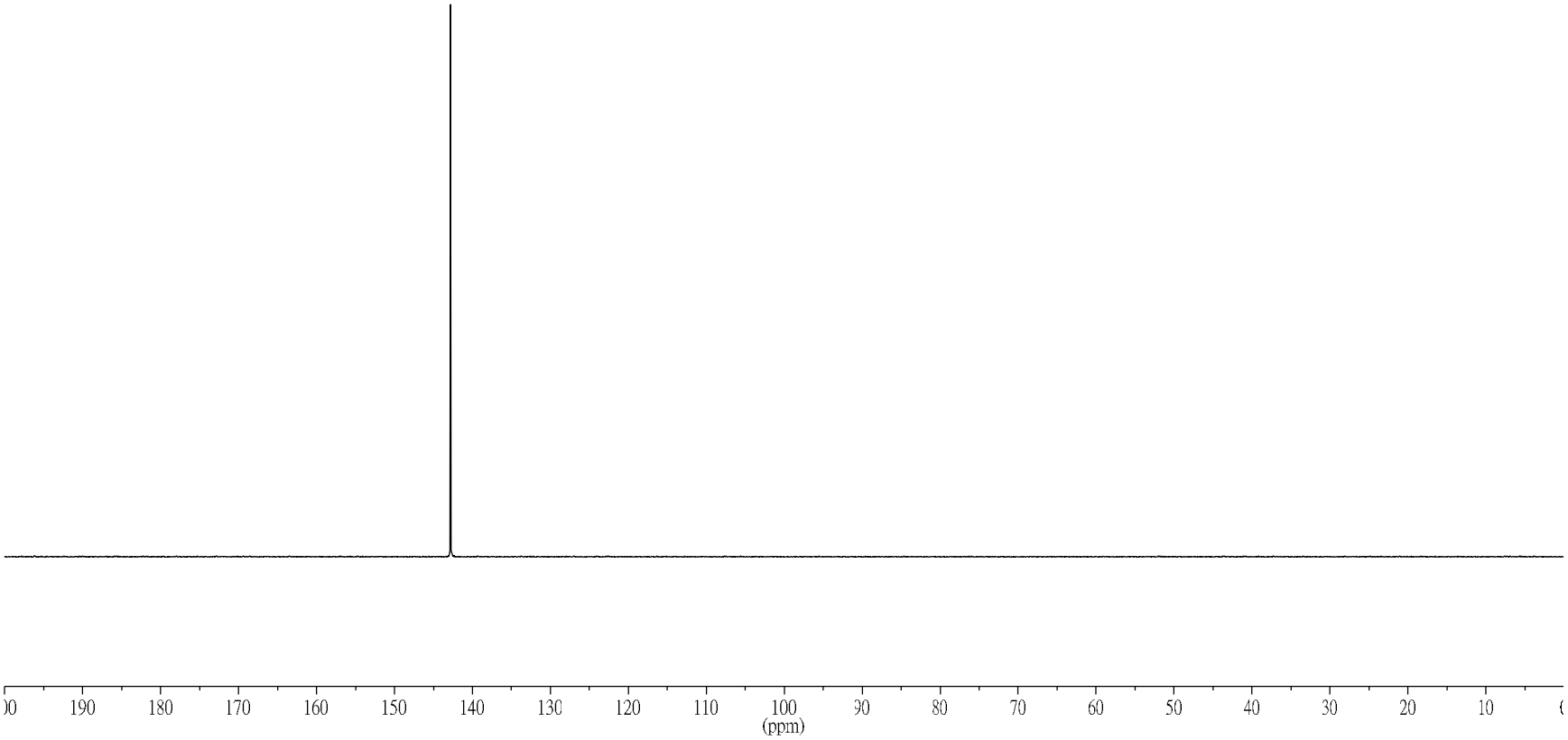


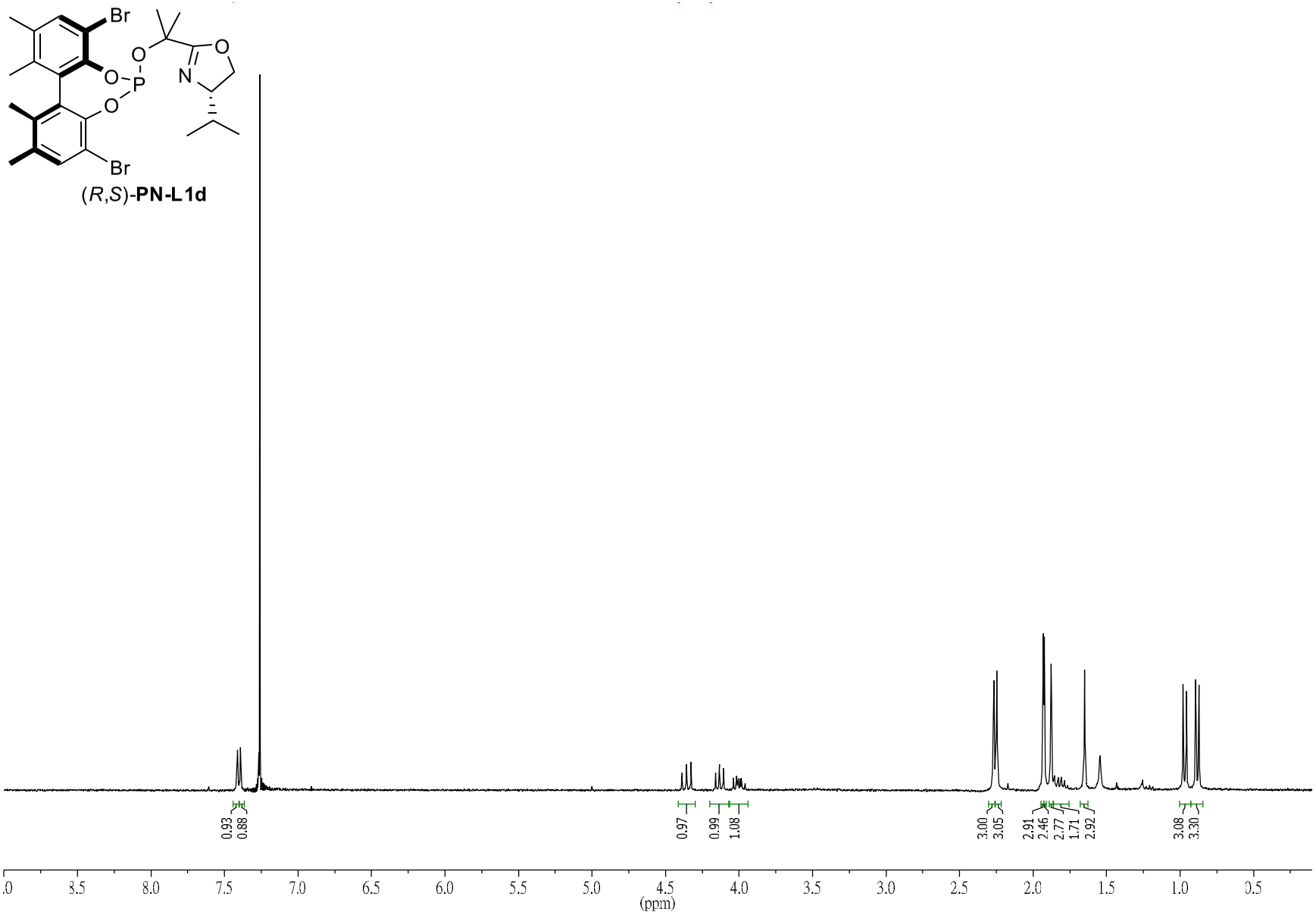

Ph
O
O
P
O
N
O
Ph
(R,S)-PN-L1c
3.35
3.87
2.06
3.22
1.08
1.14
1.00
3.28
3.00
3.11
3.28
0.96
2.70
2.44
2.62
2.58
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

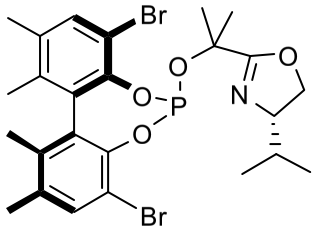


(*R*,*S*)-**PN-L1c**

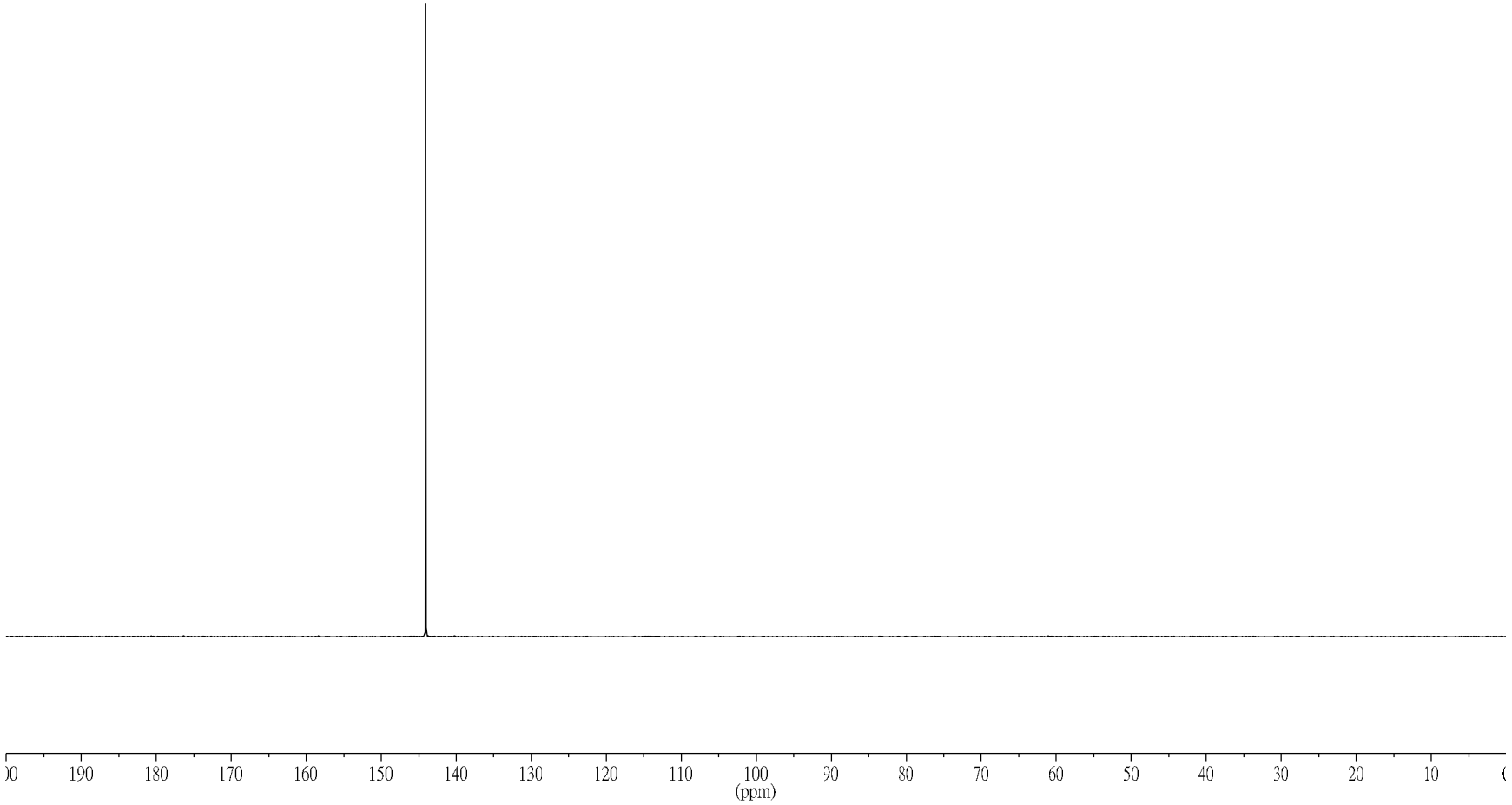
142.8

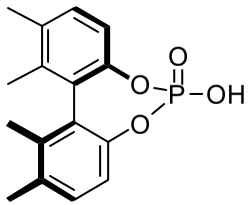



Br
O
O
P
O
N
O
Br
(R,S)-PN-L1d
0.93
0.88
0.97
0.99
1.08
3.00
3.05
2.91
2.46
2.77
1.71
2.92
3.08
3.30
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

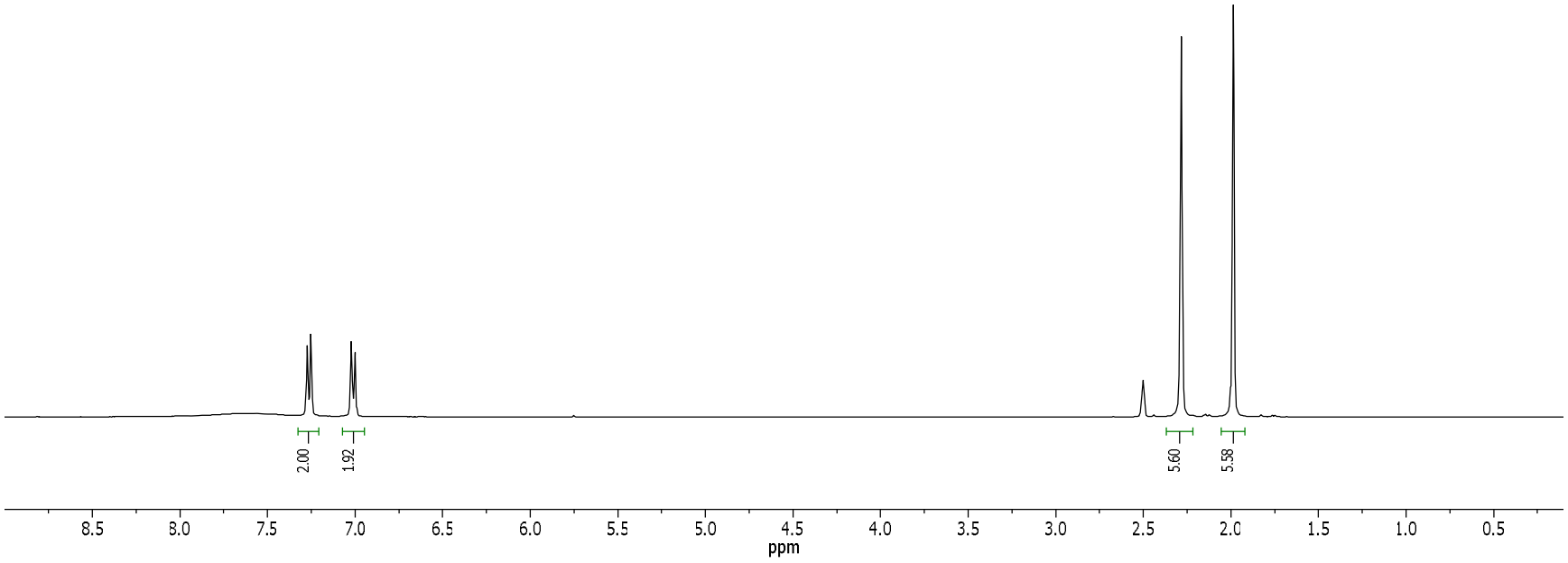

Br
O
O
P
O
N
O
Br

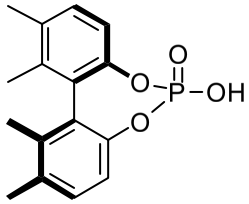
(*R*,*S*)-**PN-L1d**


190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)


O
O
P
OH
O

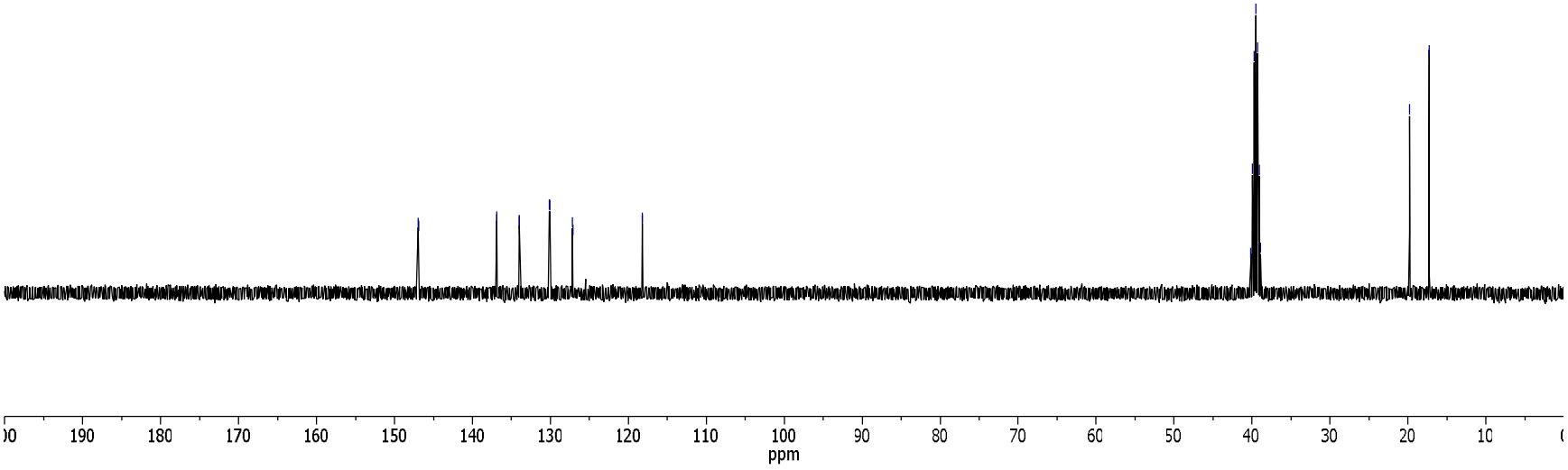
(*R*)-**PA-1a**

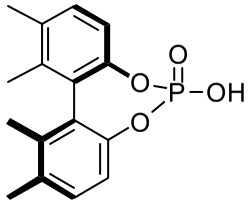

2.00
1.92
5.60
5.58
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm



(*R*)-**PA-1a**

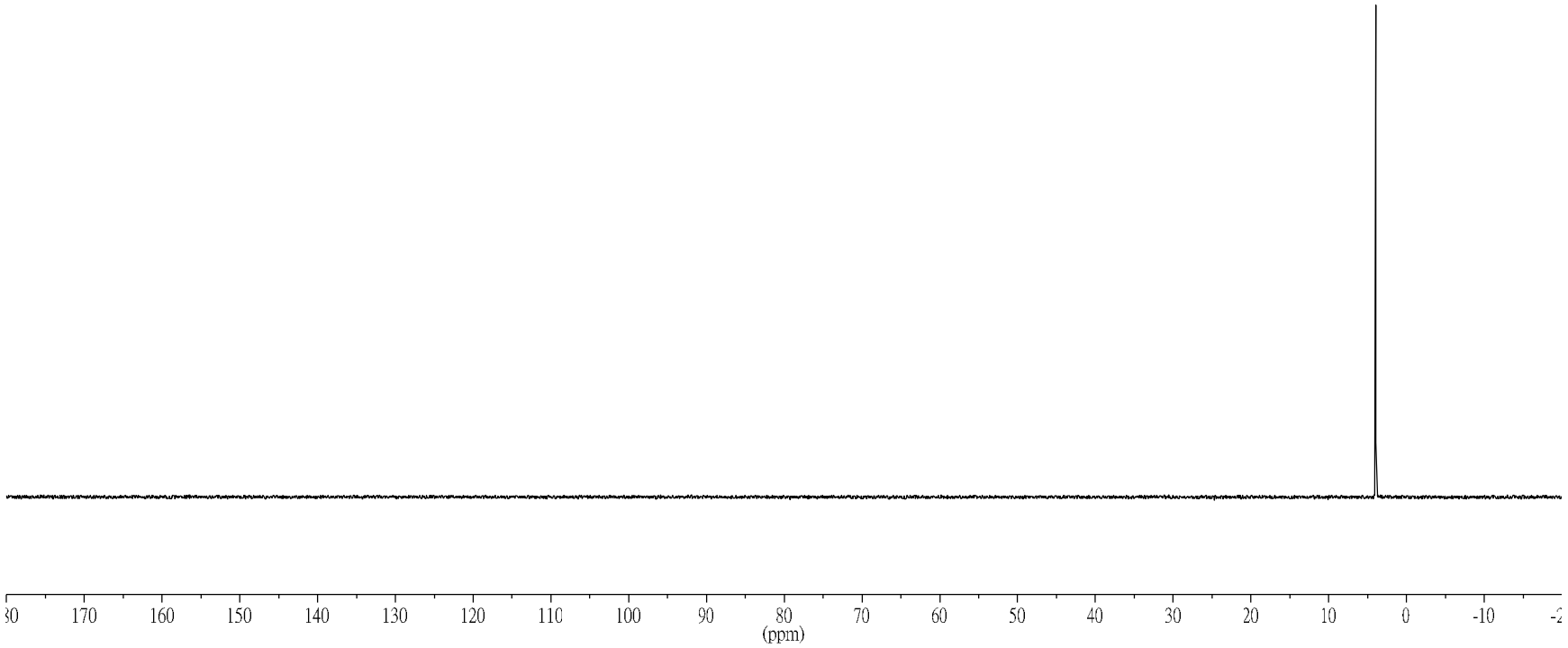
147.000
146.910
136.876
136.862
134.032
134.011
130.111
130.096
127.143
127.126
118.213
118.180
40.133
39.918
39.709
39.500
39.292
39.081
38.872
19.802
17.246

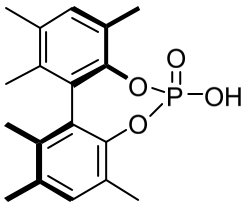



O
O
P
OH
O

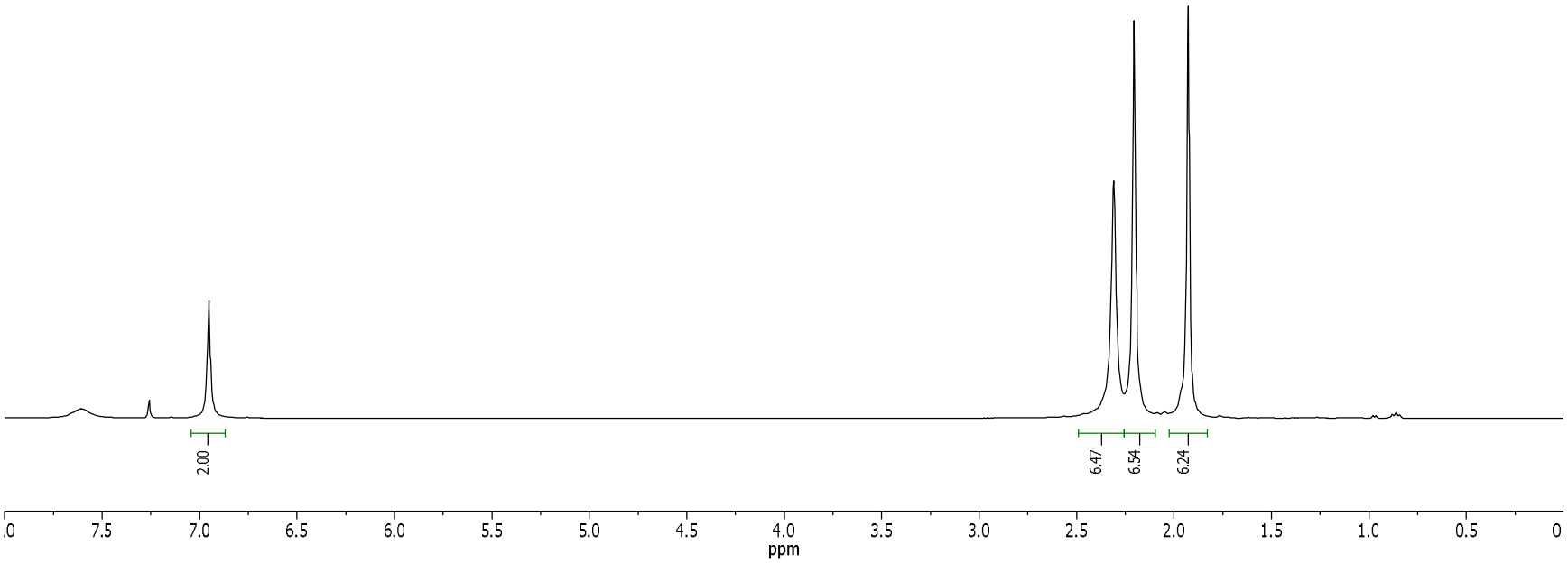
(*R*)-**PA-1a**

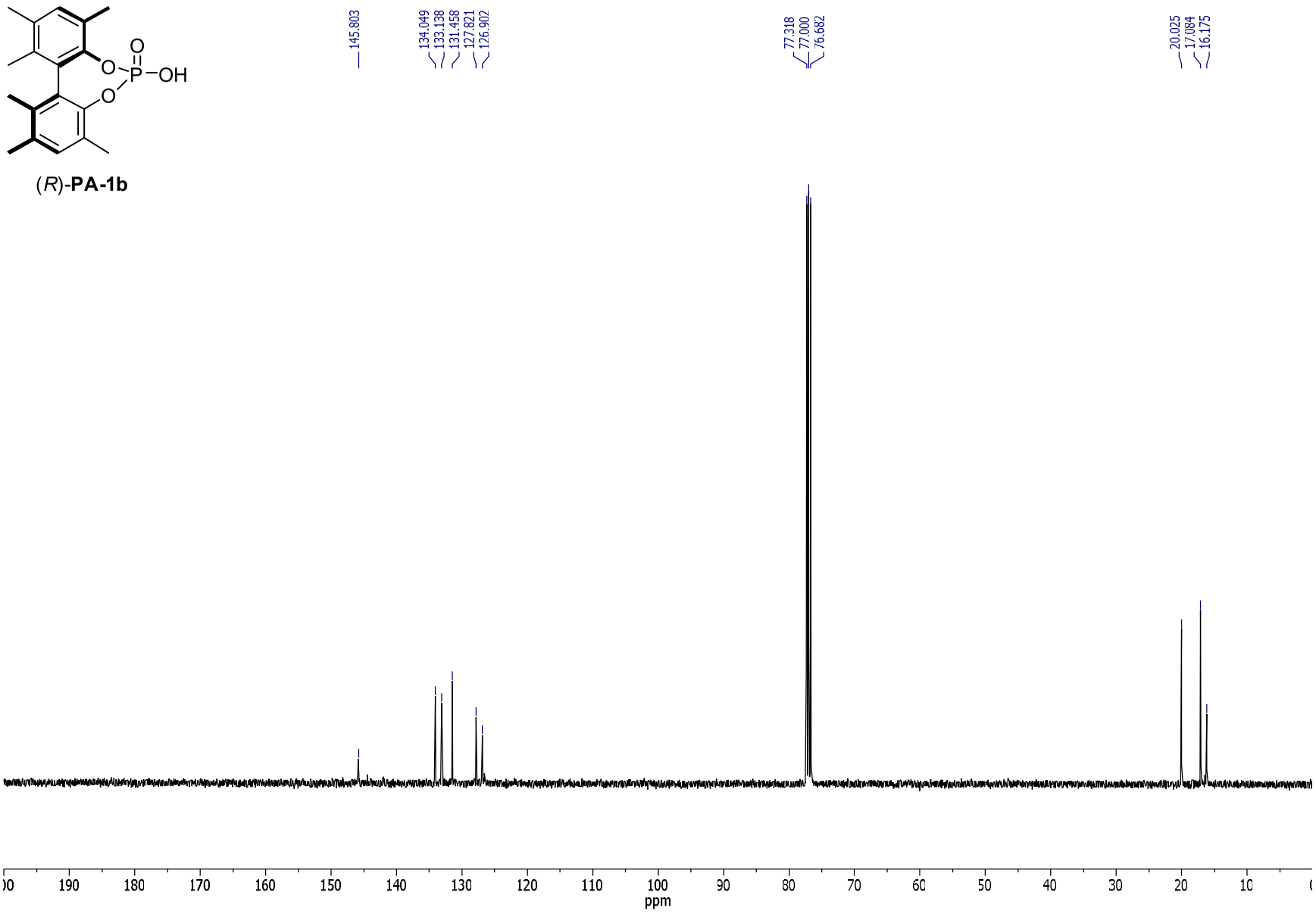
3.95

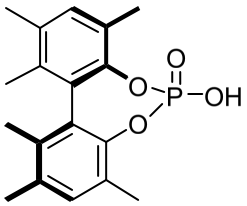

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
(ppm)


O
O
P
OH
O

(*R*)-**PA-1b**

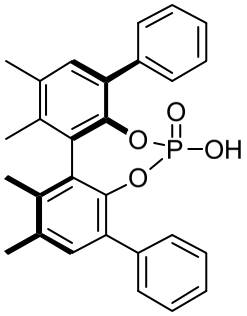

2.00
6.47
6.54
6.24
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


(R)-PA-1b
145.803
134.049
133.138
131.458
127.821
126.902
77.318
77.000
76.682
20.025
17.084
16.175
ppm

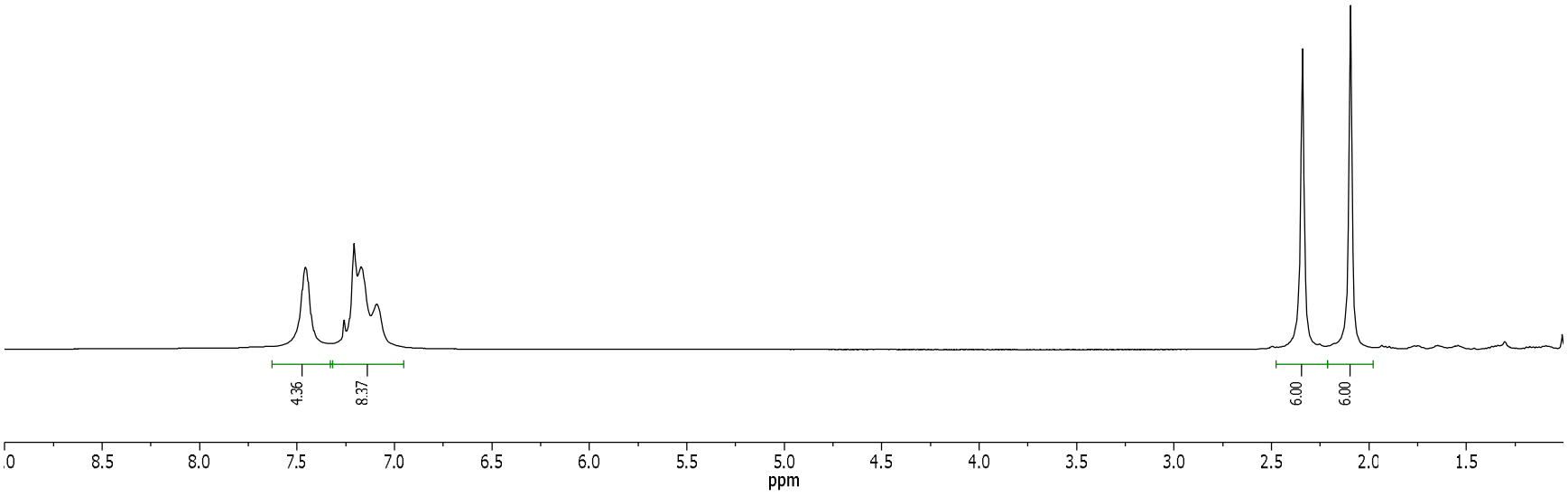

O
O
P
OH
O

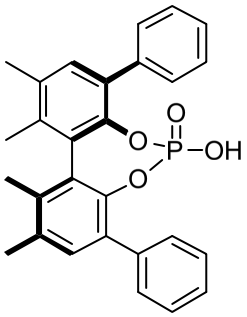
(*R*)-**PA-1b**

3.70
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
(ppm)


O
O
P
OH
O

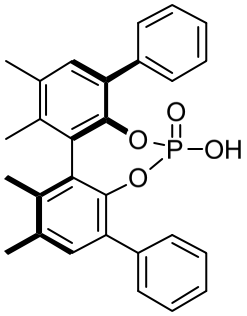
(*R*)-**PA-1c**


4.36
8.37
6.00
6.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

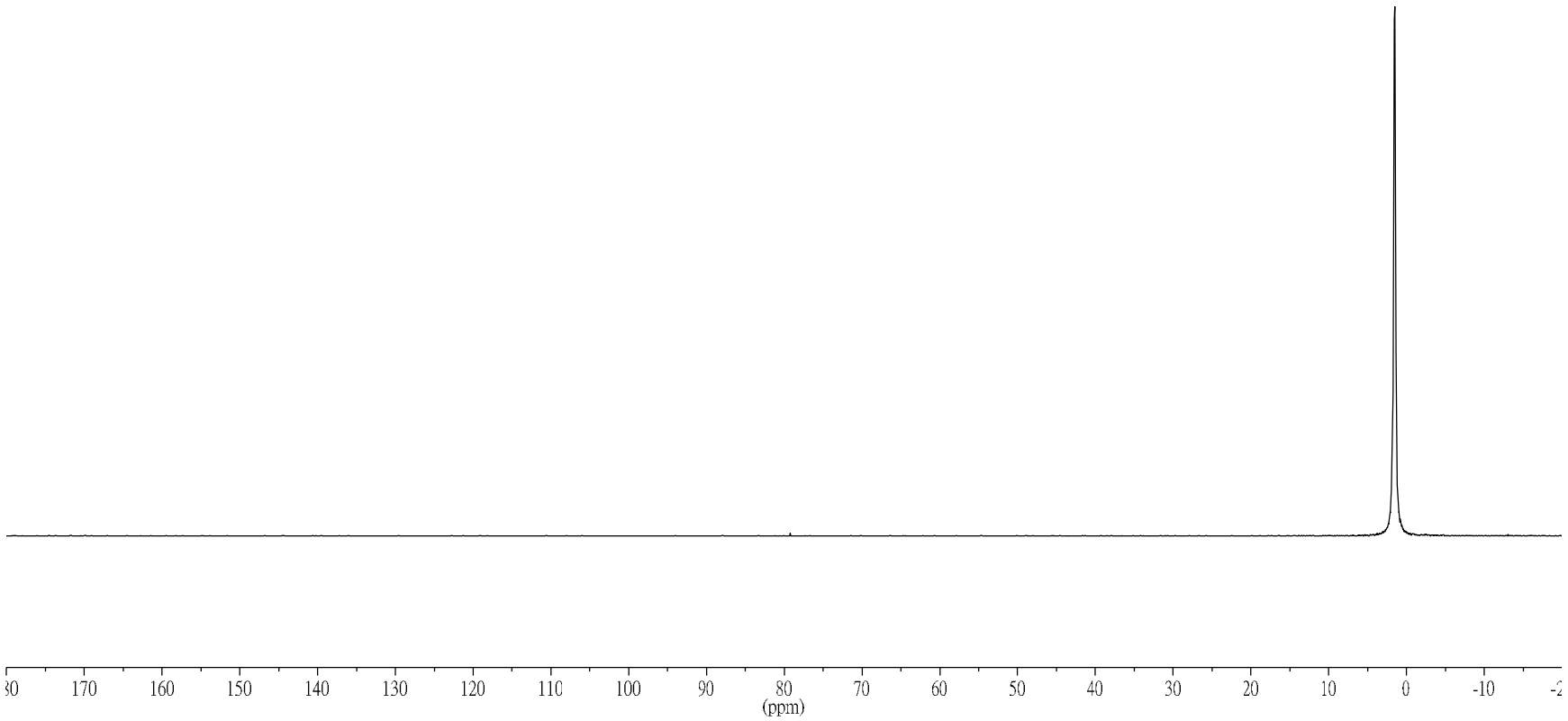

O
O
P
OH
O

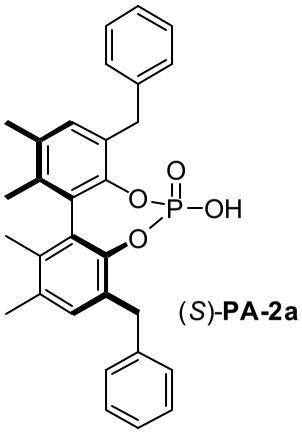
(*R*)-**PA-1c**

143.653
137.231
136.457
134.003
131.519
129.497
128.199
127.943
126.898
77.318
77.000
76.682
20.183
17.413
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

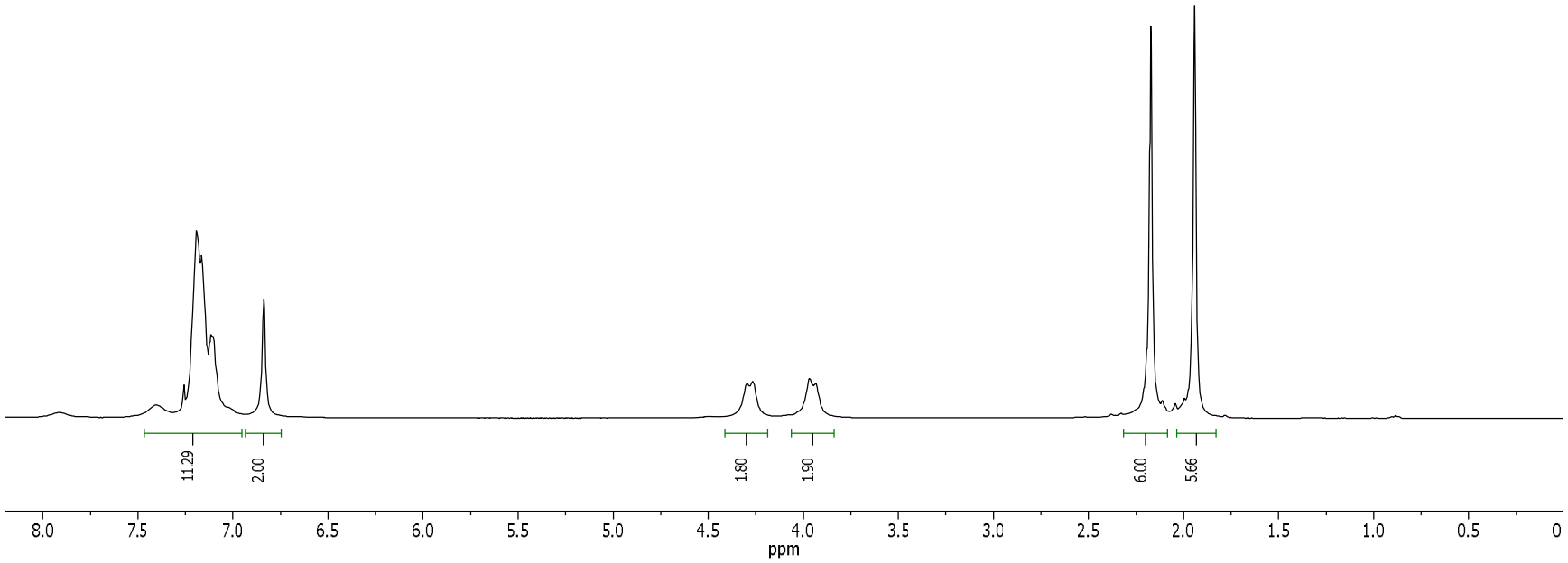

O
O
P
OH
O

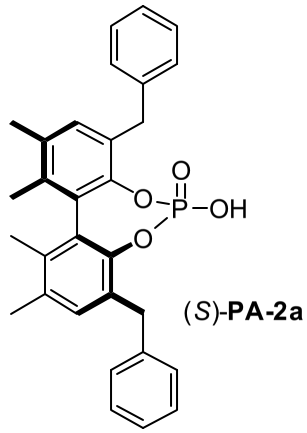
(*R*)-**PA-1c**


1.53
170
160
150
140
130
120
110
100
90
80
(ppm)
70
60
50
40
30
20
10
0
-10


O
O
P
OH
O

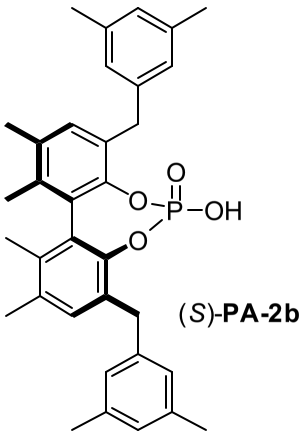
(*S*)-**PA-2a**


11.29
2.00
1.80
1.90
6.00
5.66
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

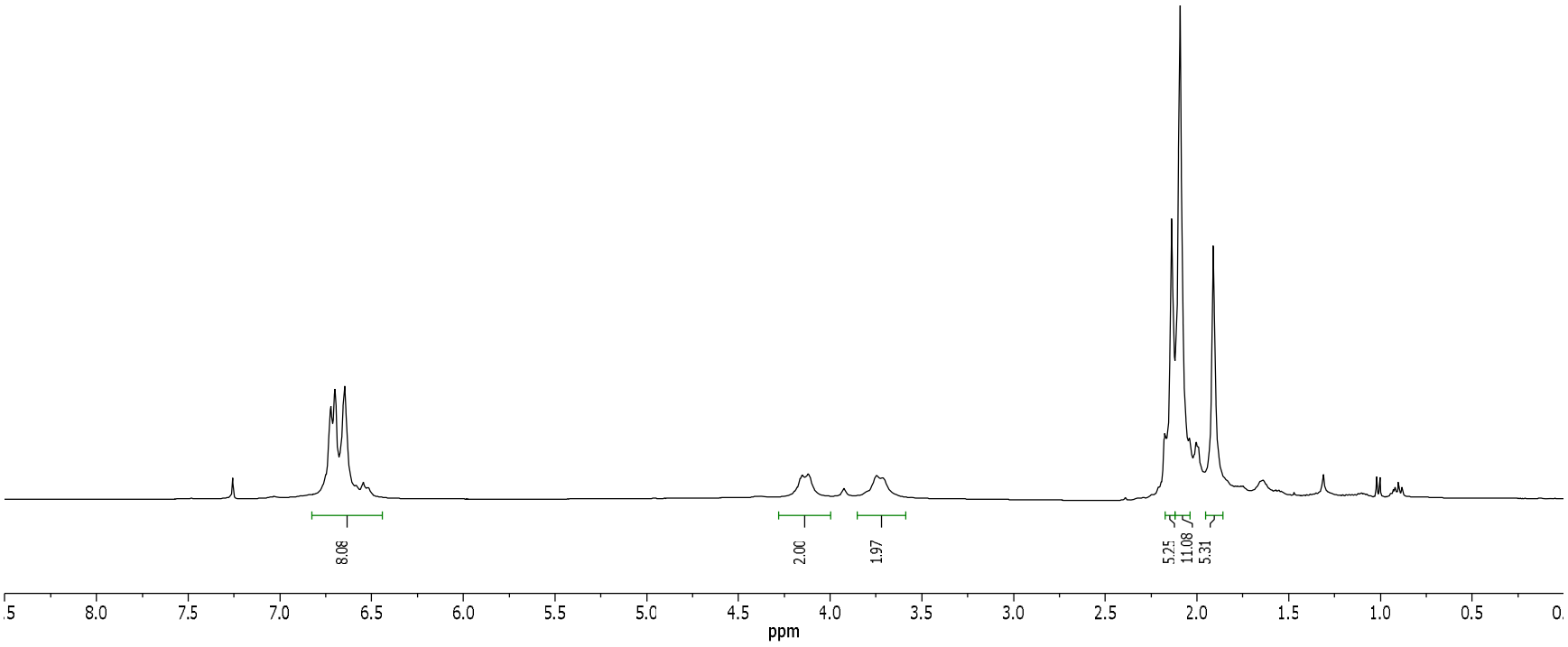

O
O
P
OH
O

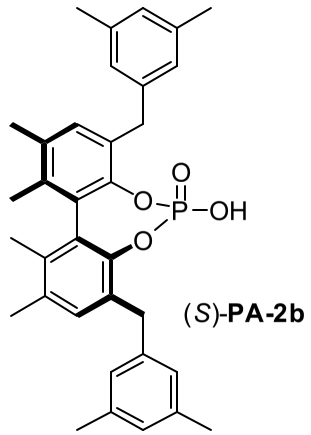
(*S*)-**PA-2a**

145.549
140.681
134.762
133.395
130.869
129.999
129.302
128.133
128.092
125.620
77.318
77.000
76.682
35.405
20.152
17.232
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm


O
O–P–OH
O

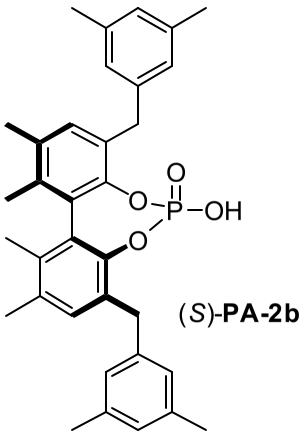
(*S*)-**PA-2b**


8.08
2.00
1.97
5.25
11.08
5.31
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


O
O
P
OH
O

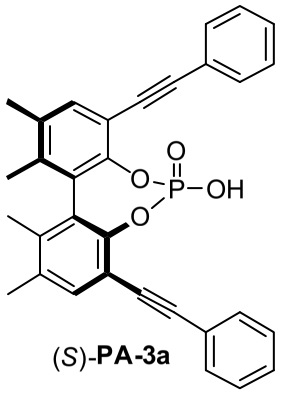
(*S*)-**PA-2b**

145.677
140.463
137.288
134.367
132.972
130.618
130.382
128.232
127.233
127.152
77.318
77.000
76.682
34.834
21.064
20.125
17.130
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm

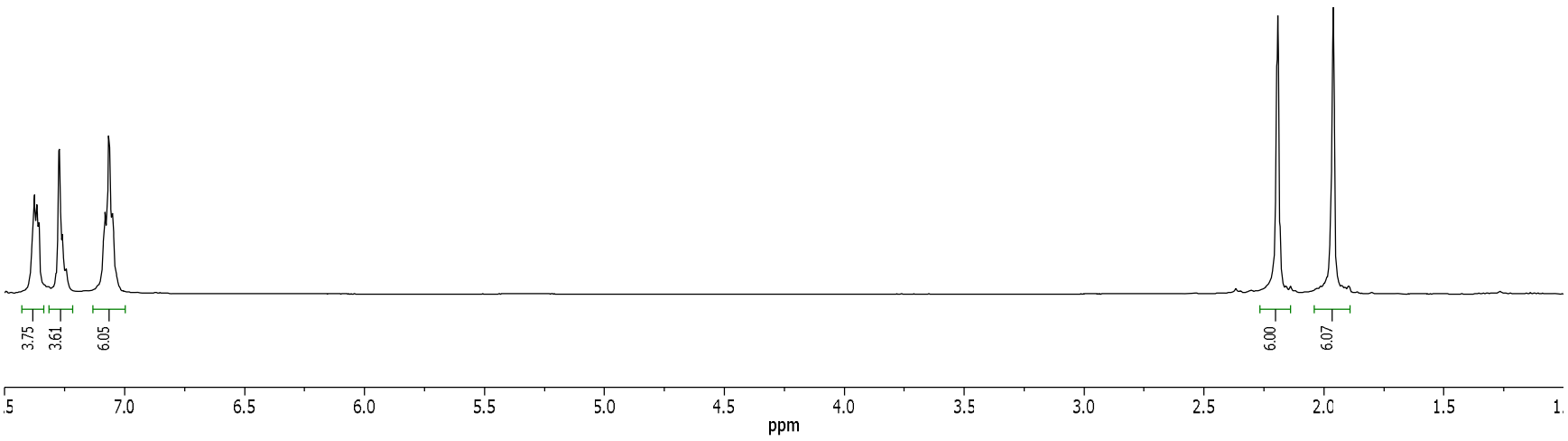

O
O
P
OH
O

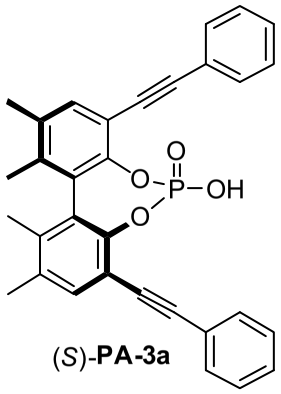
(*S*)-**PA-2b**

2.70
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
(ppm)



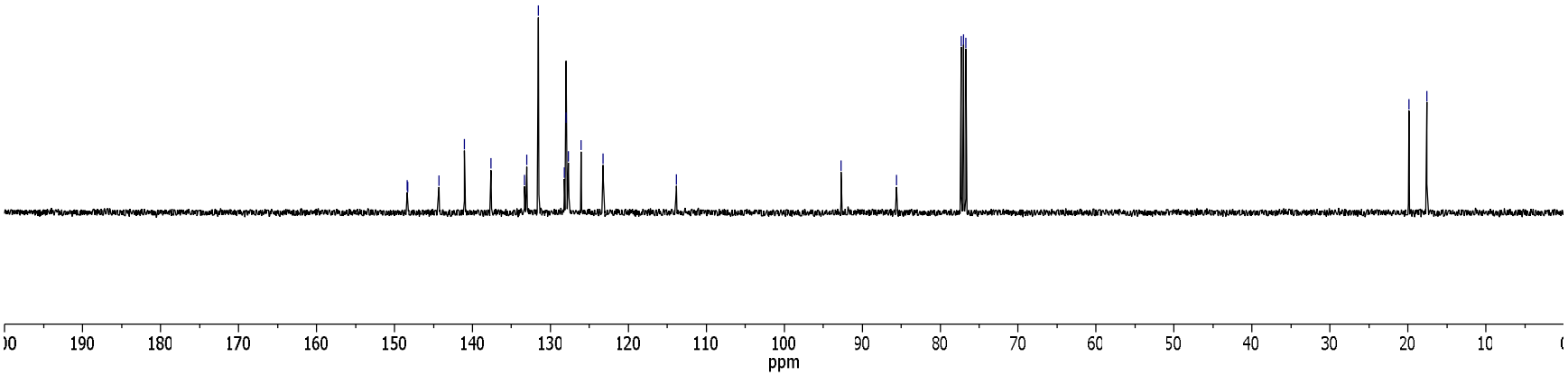
(*S*)-**PA-3a**

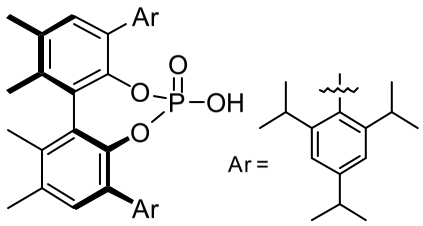




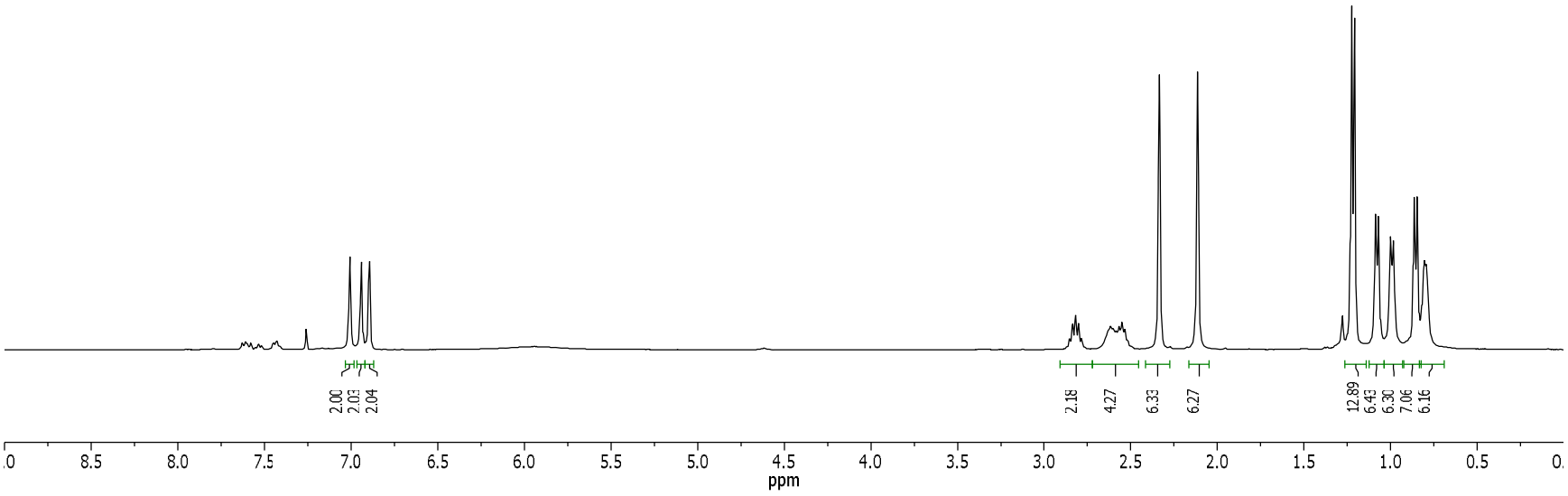
(*S*)-**PA-3a**

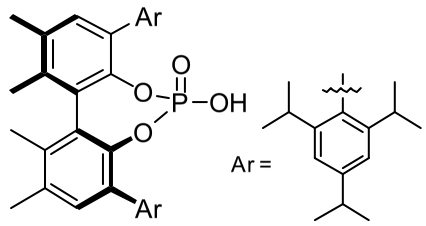
148.393
148.300
144.325
141.036
137.615
133.324
133.064
131.547
128.182
127.992
127.670
126.068
123.237
113.835
92.710
85.603
77.319
77.000
76.682
19.885
17.551




Ar
O
O
P
OH
O
Ar
Ar =

(*S*)-**PA-1e**


2.00
2.03
2.04
2.18
4.27
6.33
6.27
12.89
6.43
6.30
7.06
6.16
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

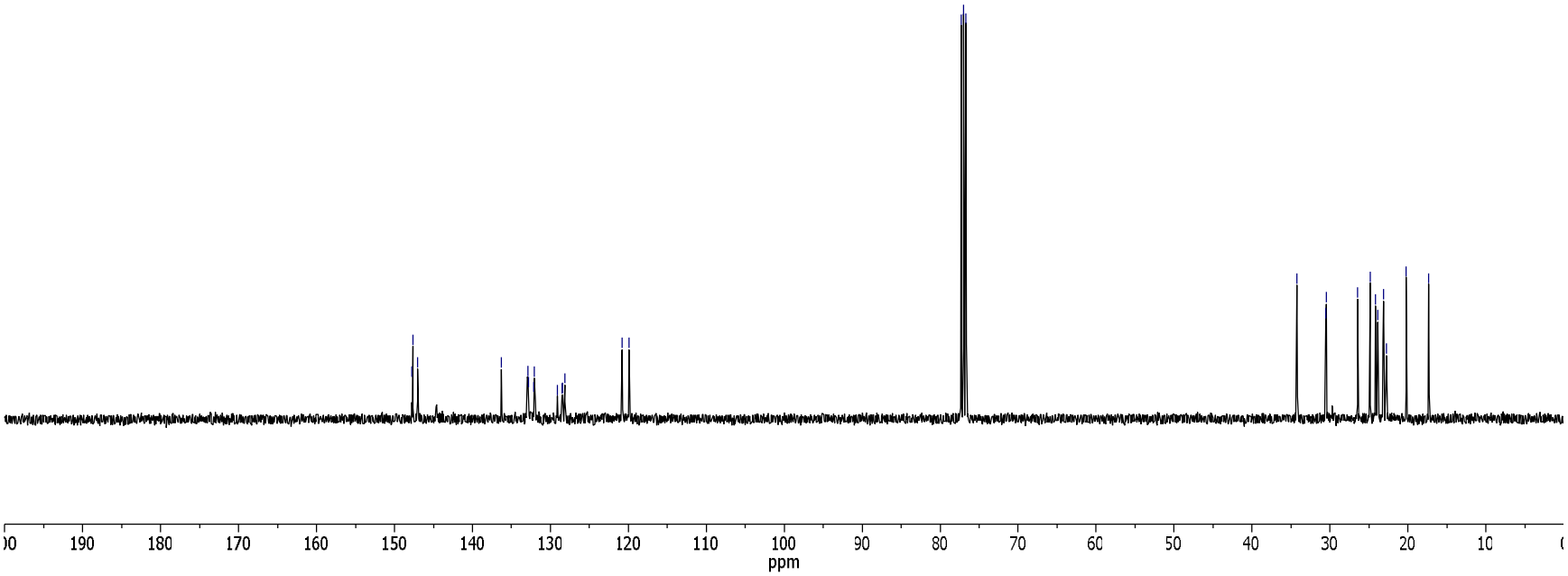


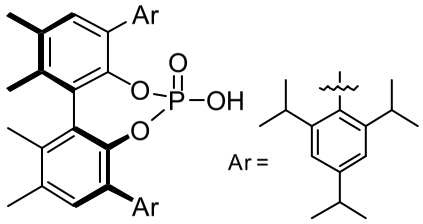
(*S*)-**PA-1e**

147.775
147.647
147.043
136.302
132.913
132.840
132.135
132.035
129.128
128.533
128.411
128.152
120.833
119.940

77.317
77.000
76.682

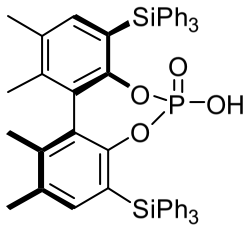
34.218
30.547
30.444
26.436
24.853
24.151
23.880
23.158
22.769
20.206
17.305



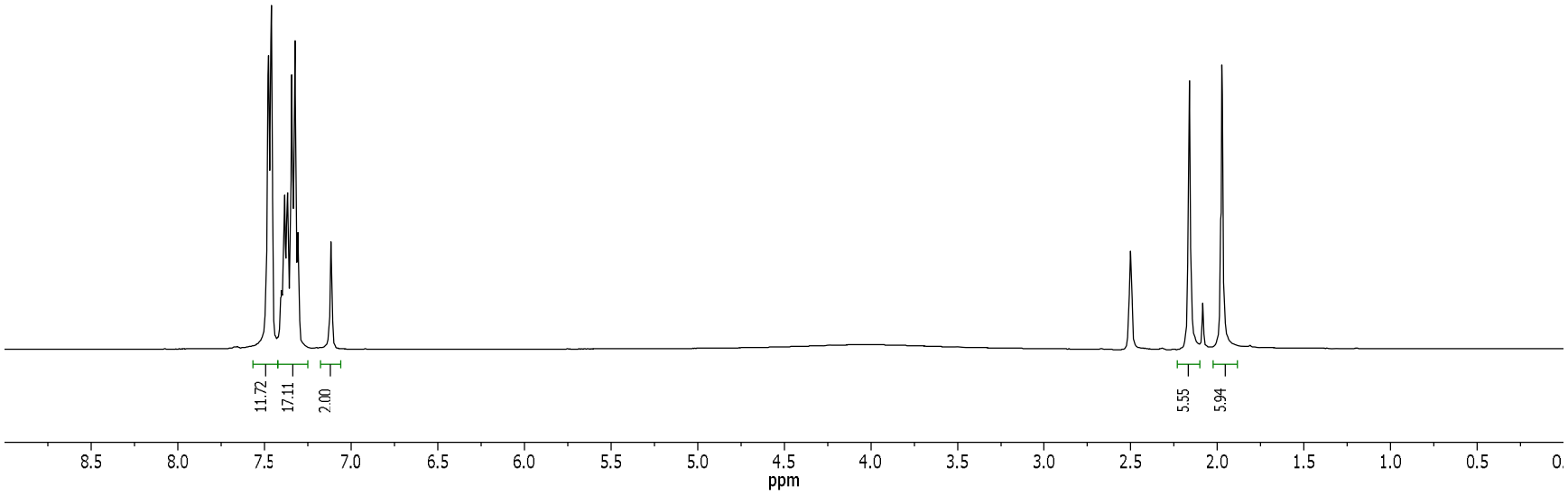

Ar
O
O
P
OH
O
Ar
Ar =

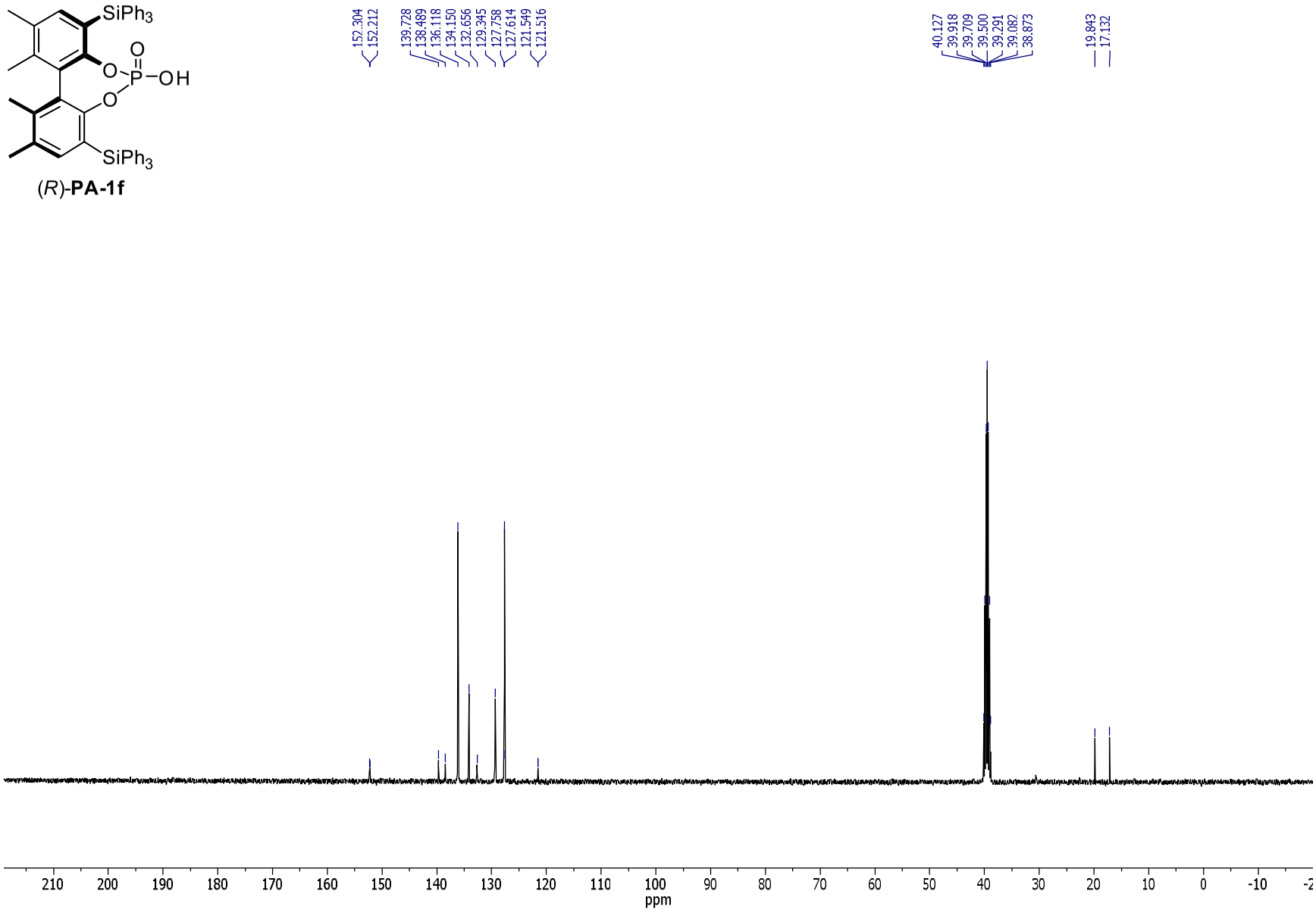
(*S*)-**PA-1e**

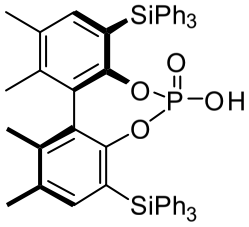
1.49
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
(ppm)


SiPh3
O
O
P
OH
O
SiPh3

(*R*)-**PA-1f**

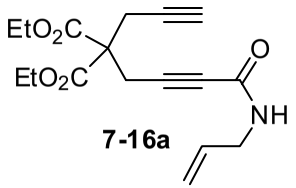

11.72
17.11
2.00
5.55
5.94
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


SiPh3
O
O
P
OH
O
SiPh3
(R)-PA-1f
152.304
152.212
139.728
138.489
136.118
134.150
132.656
129.345
127.758
127.614
121.549
121.516
40.127
39.918
39.709
39.500
39.291
39.082
38.873
19.843
17.132
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-2
ppm

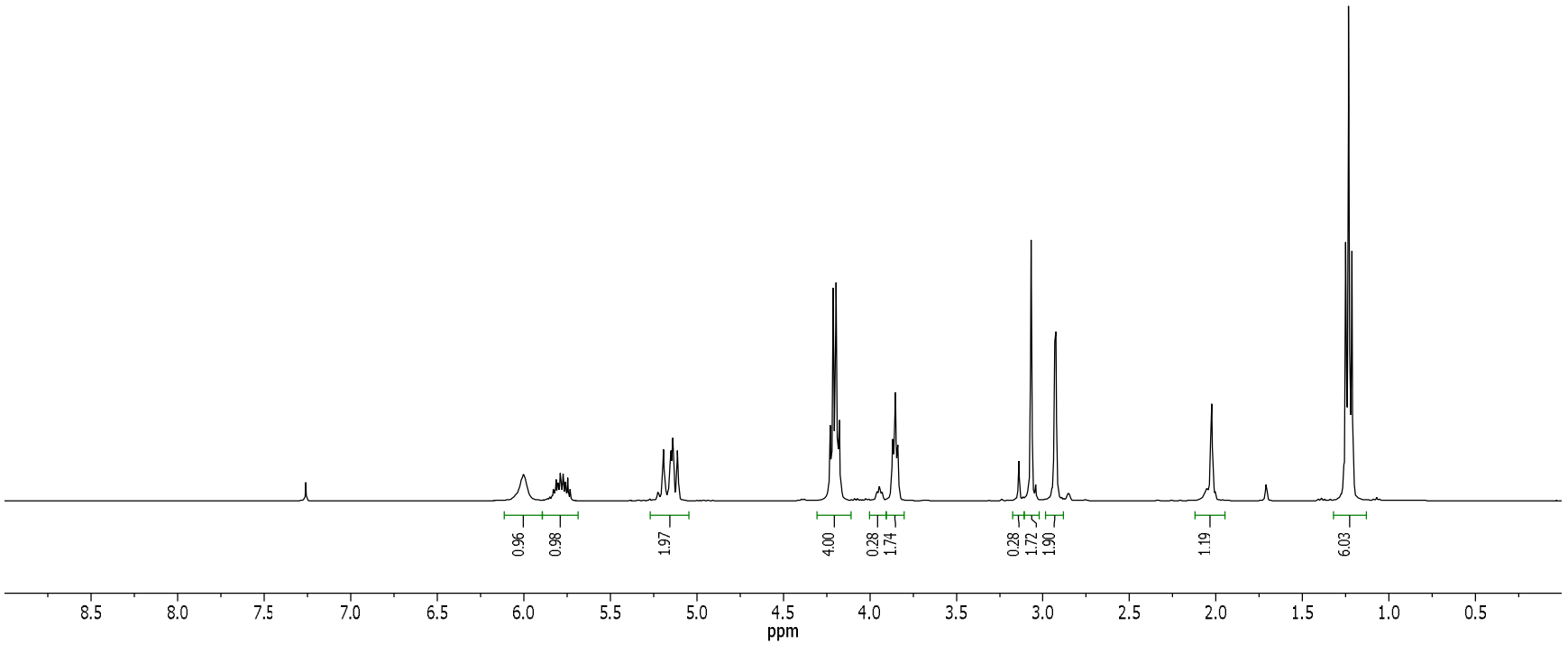

SiPh3
O
O
P
OH
O
SiPh3

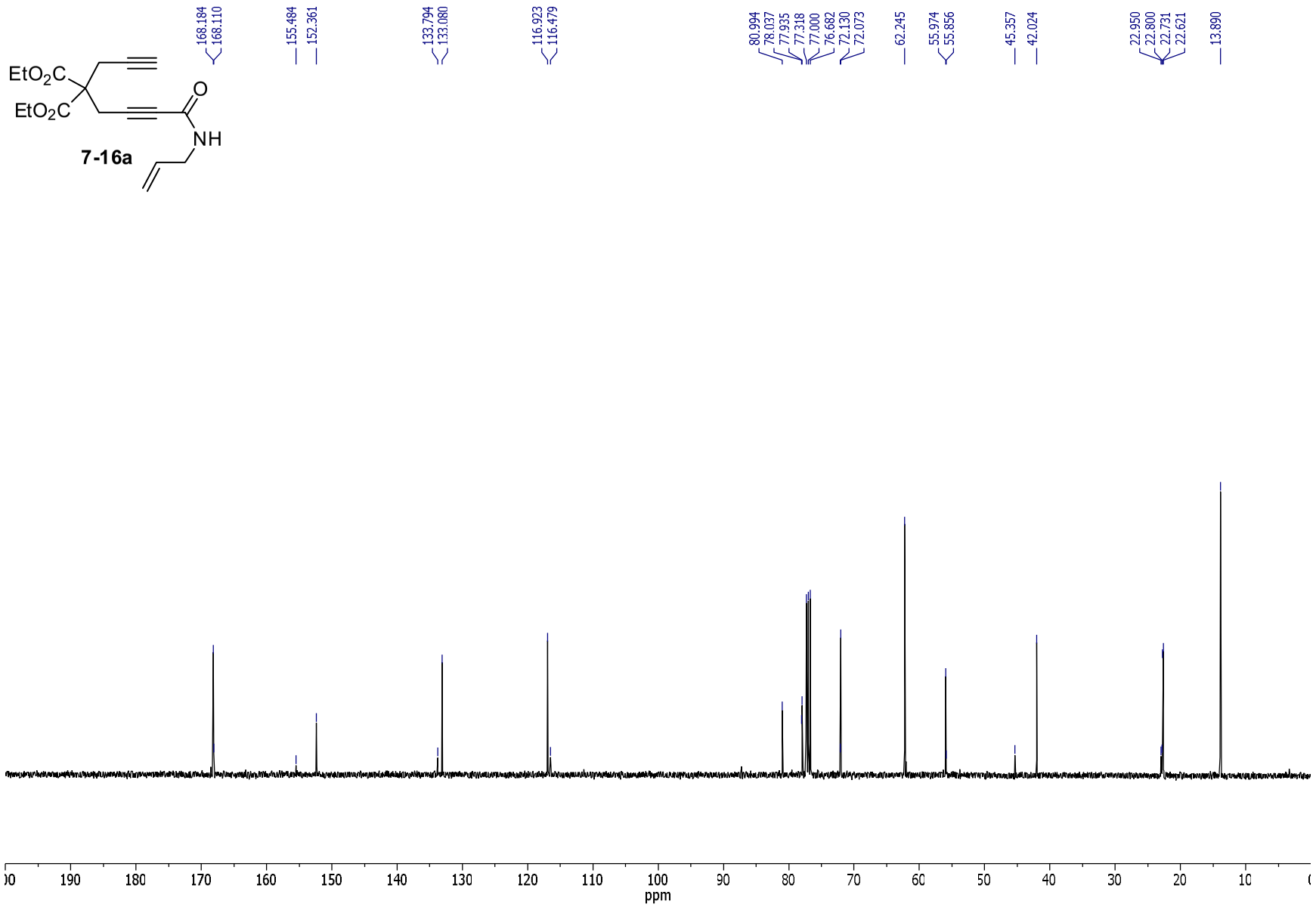
(*R*)-**PA-1f**

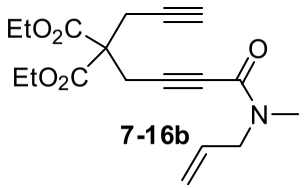
2.76
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
(ppm)

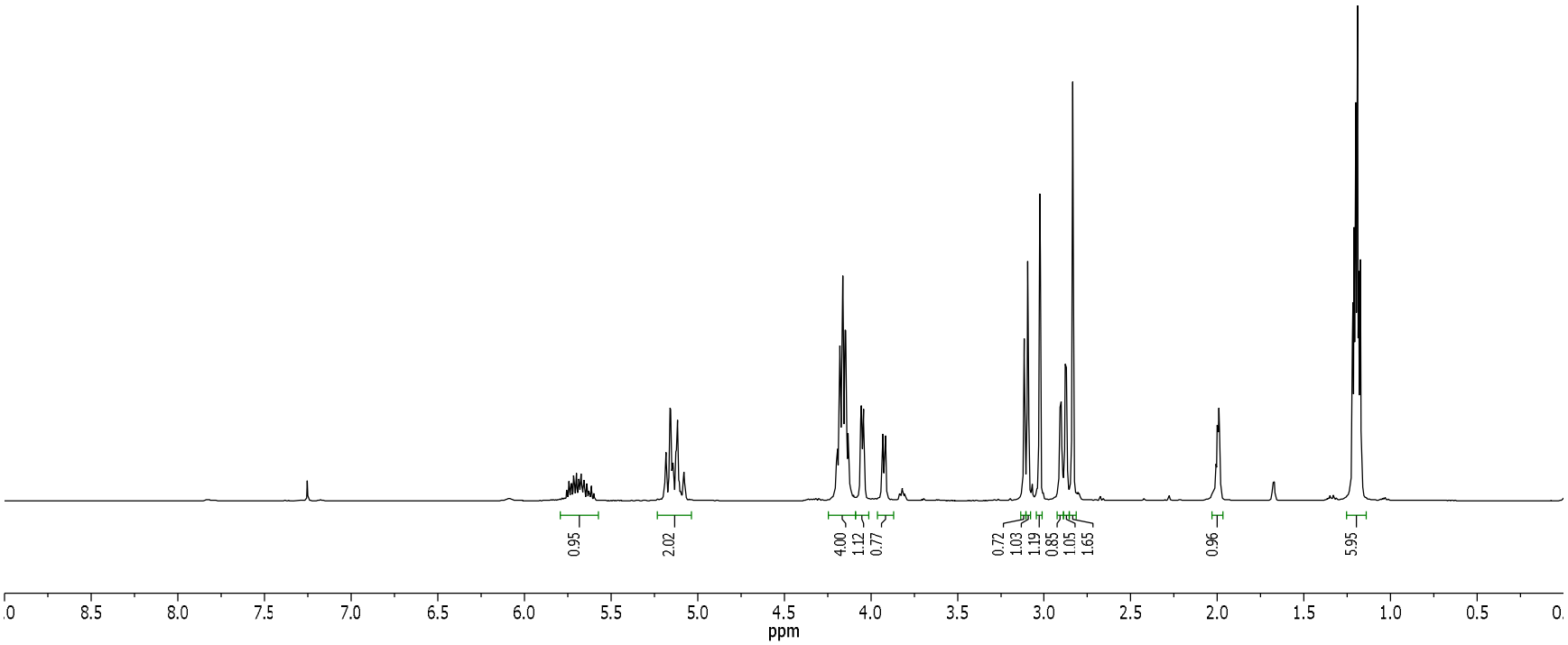

EtO2C
EtO2C
O
NH

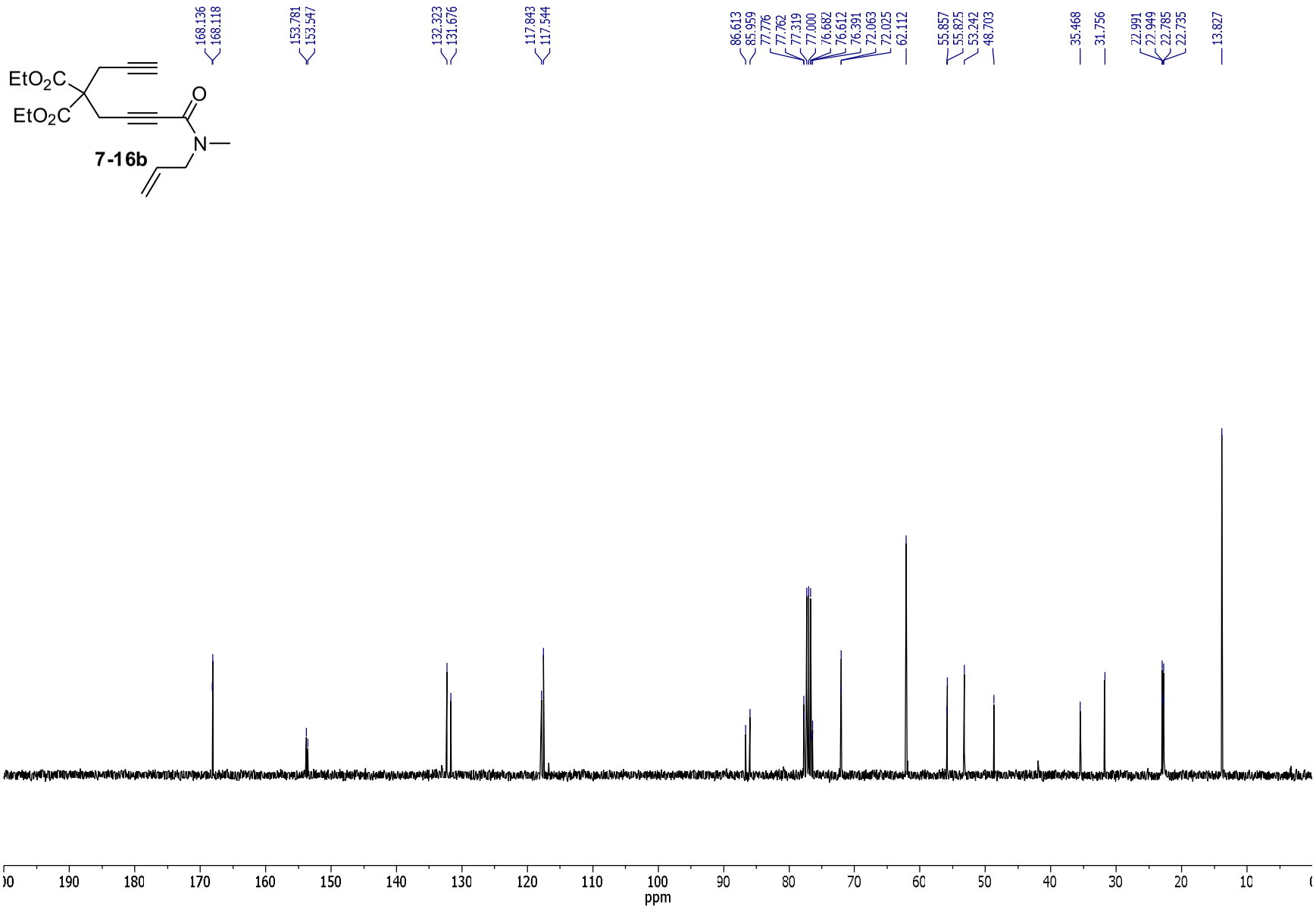
7-16a

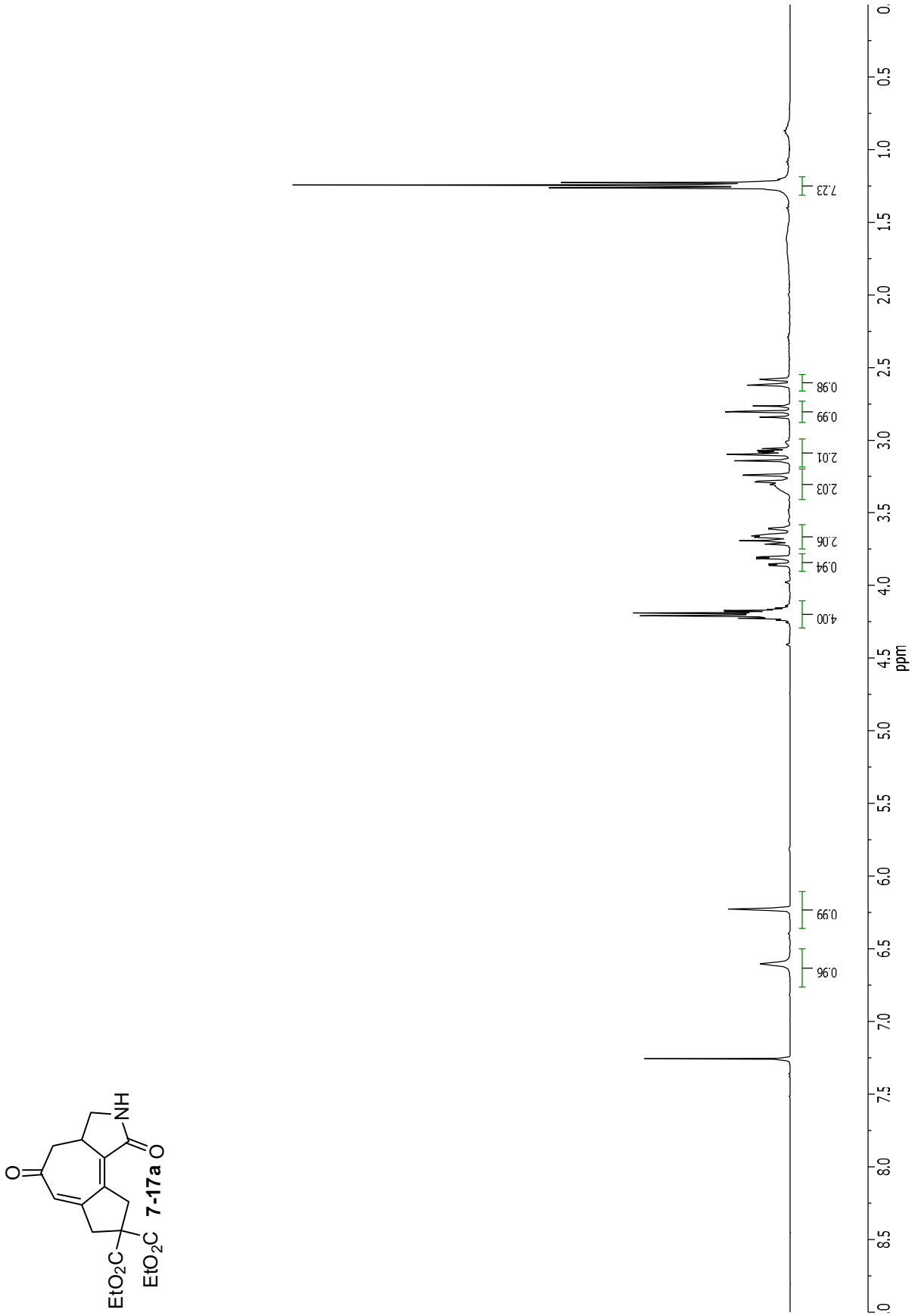

0.96
0.98
1.97
4.00
0.28
1.74
0.28
1.72
1.90
1.19
6.03
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

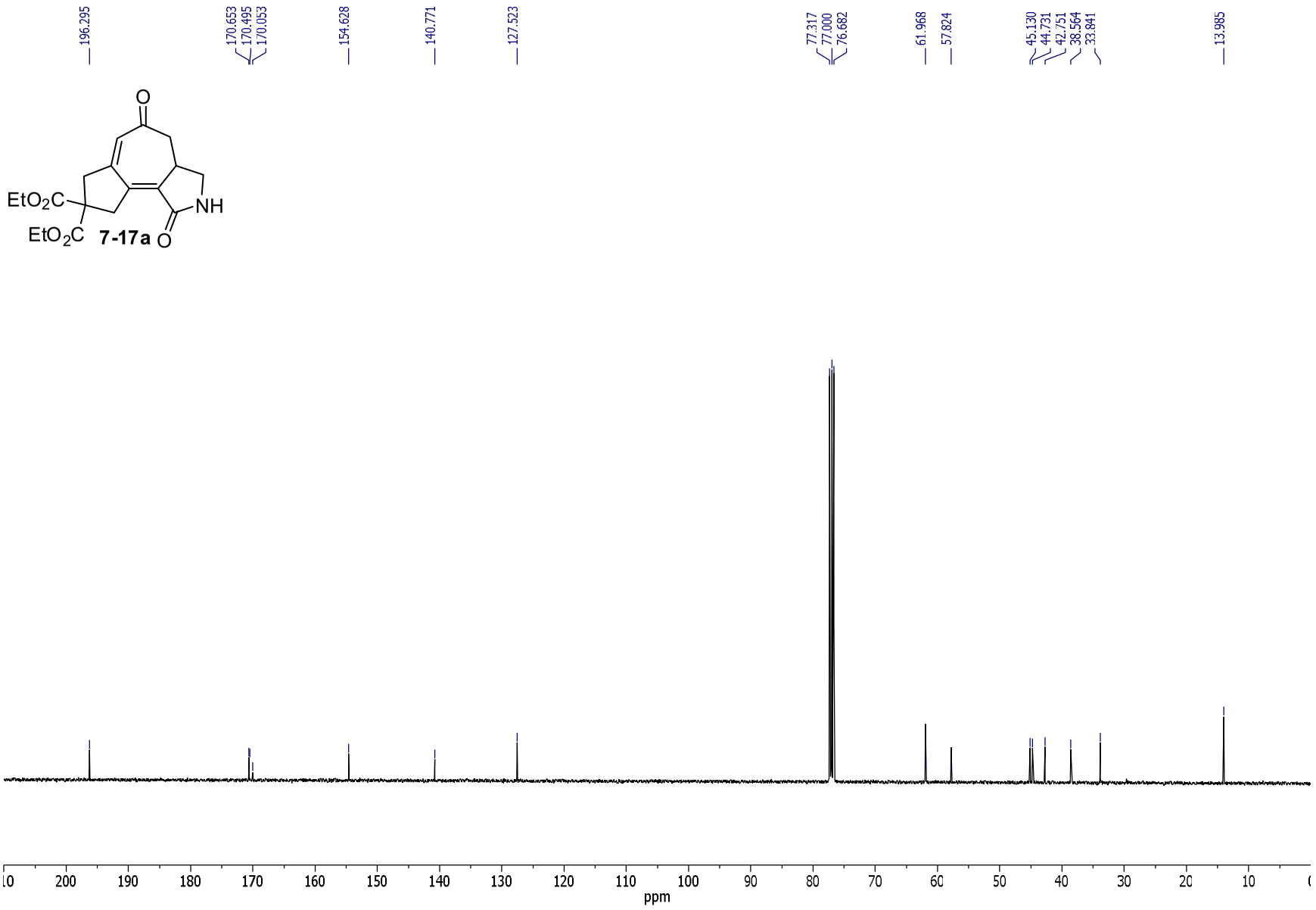

168.184
168.110
155.484
152.361
133.794
133.080
116.923
116.479
80.994
78.037
77.935
77.318
77.000
76.682
72.130
72.073
62.245
55.974
55.856
45.357
42.024
22.950
22.800
22.731
22.621
13.890
EtO2C
EtO2C
O
NH
7-16a
ppm

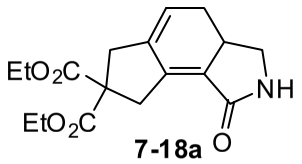

EtO2C
EtO2C
O
N
7-16b


0.95
2.02
4.00
1.12
0.77
0.72
1.03
1.19
0.85
1.05
1.65
0.96
5.95
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

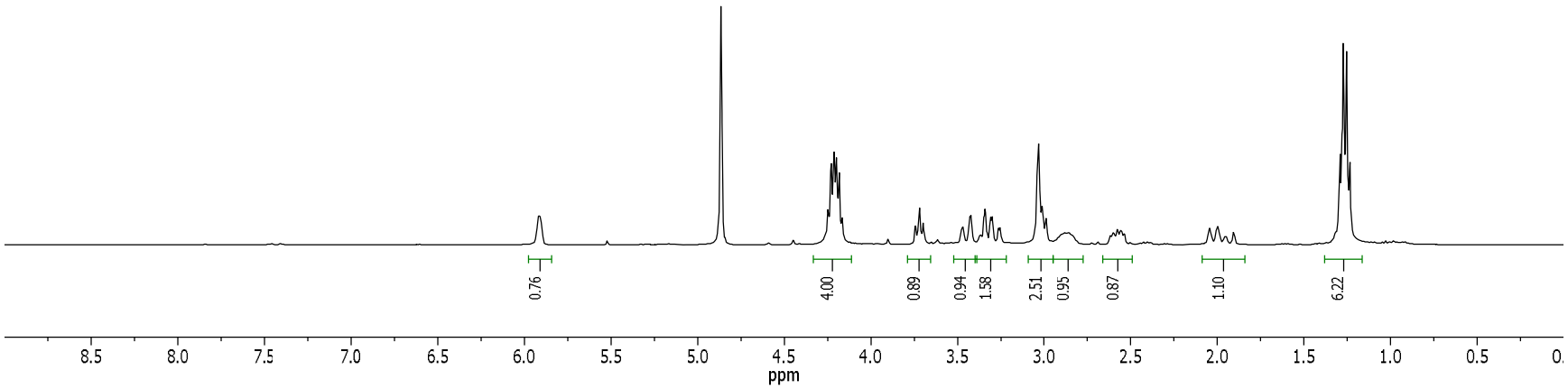

168.136
168.118
153.781
153.547
132.323
131.676
117.843
117.544
86.613
85.959
77.776
77.762
77.319
77.000
76.682
76.612
76.391
72.063
72.025
62.112
55.857
55.825
53.242
48.703
35.468
31.756
22.991
22.949
22.785
22.735
13.827
EtO2C
EtO2C
O
N
7-16b
ppm

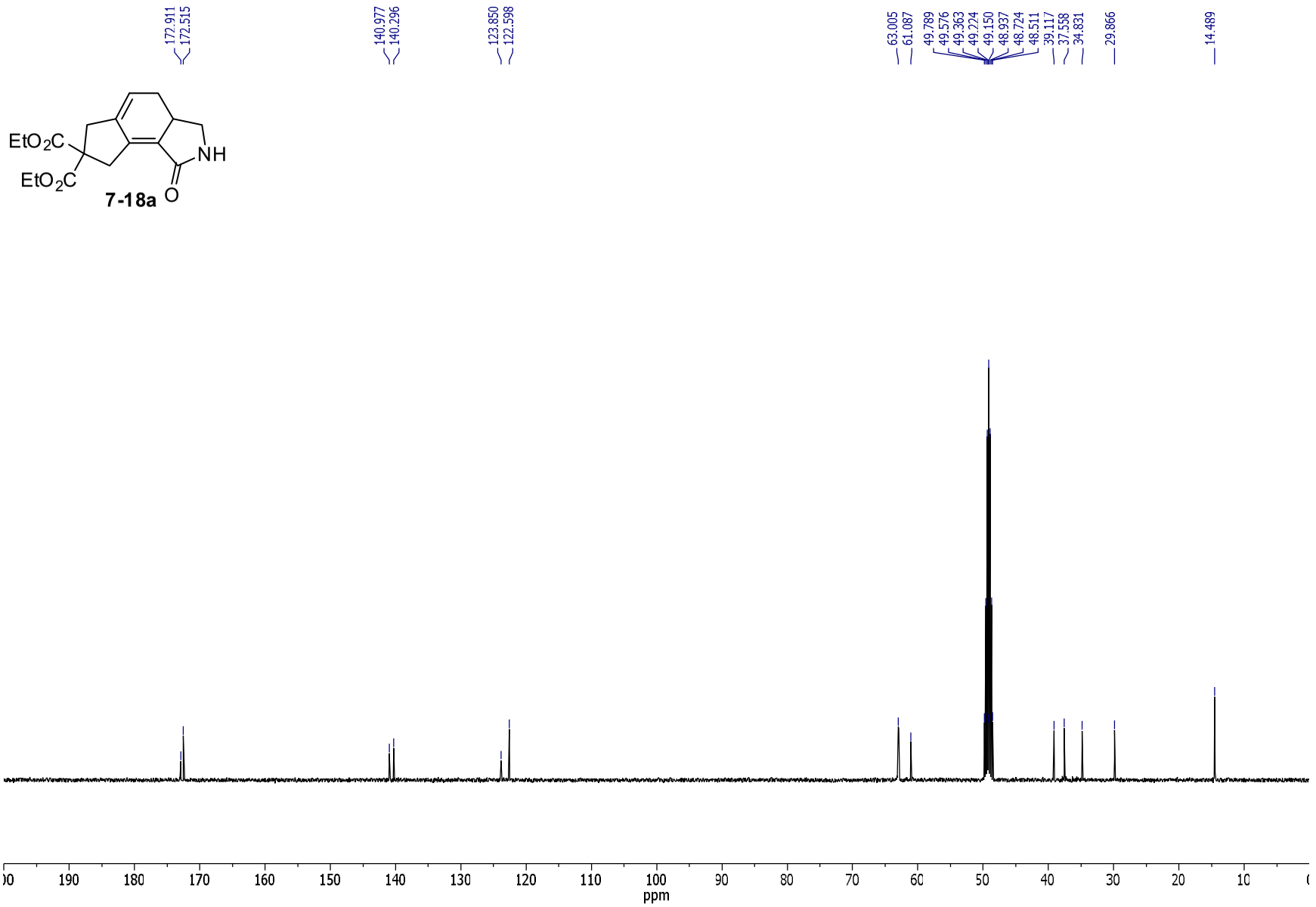

NH
O
O
O
EtO2C
EtO2C
7-17a
7.23
0.98
0.99
2.01
2.03
2.06
0.94
4.00
0.99
0.96
ppm

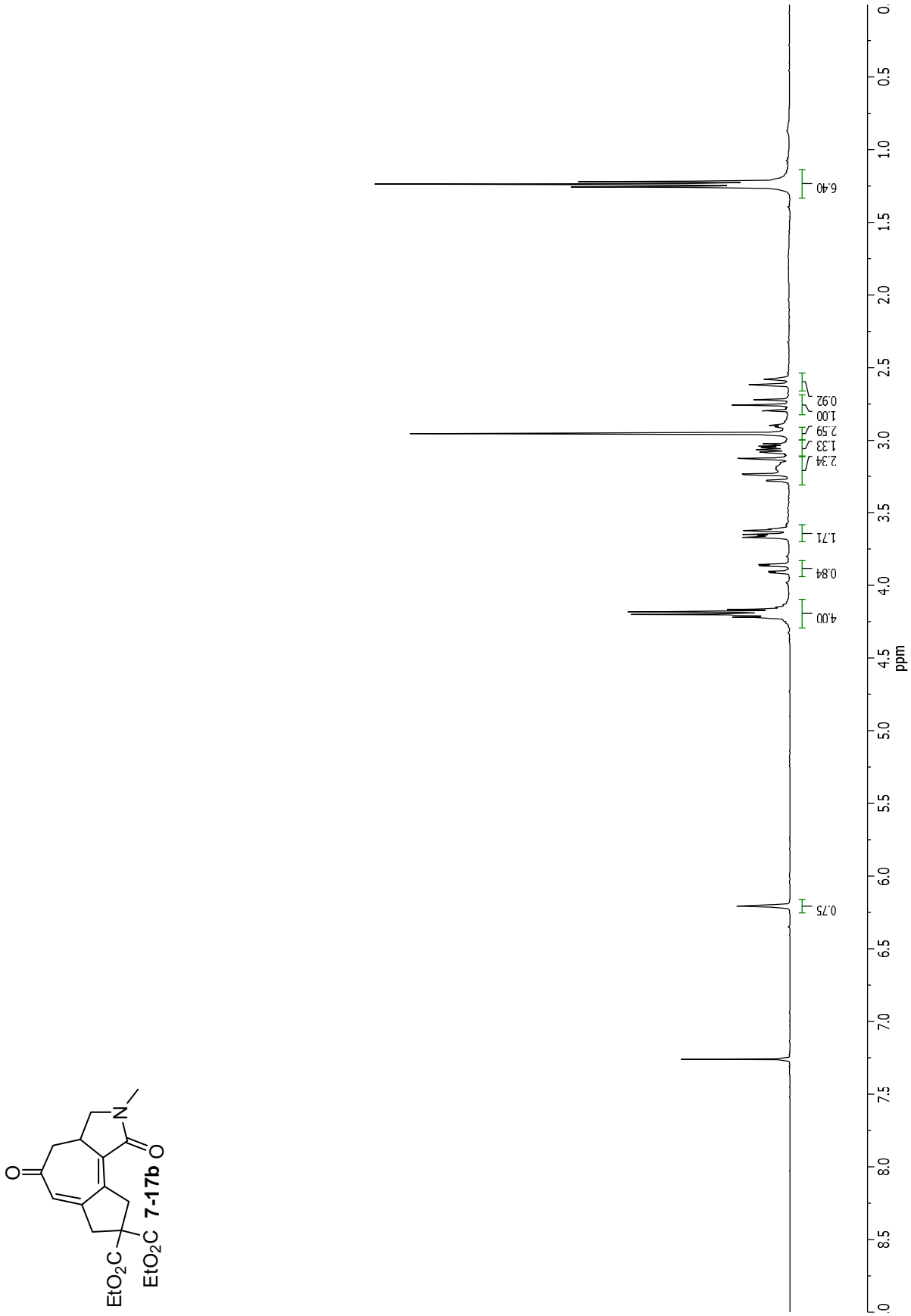

196.295
170.653
170.495
170.053
154.628
140.771
127.523
77.317
77.000
76.682
61.968
57.824
45.130
44.731
42.751
38.564
33.841
13.985
O
EtO2C
EtO2C
NH
O
7-17a
ppm

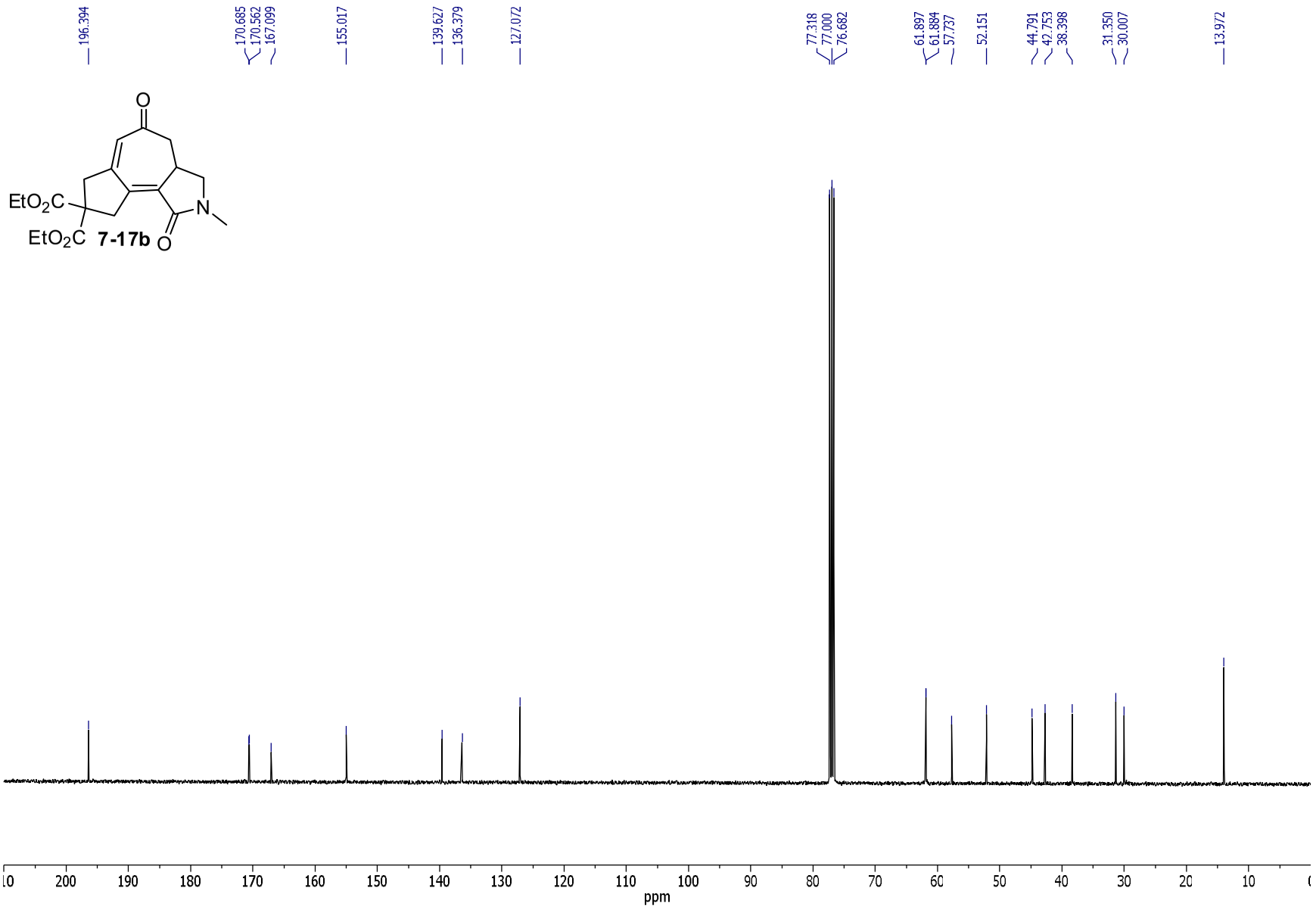

EtO2C
EtO2C
NH
O

7-18a


0.76
4.00
0.89
0.94
1.58
2.51
0.95
0.87
1.10
6.22
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


172.911
172.515
140.977
140.296
123.850
122.598
63.005
61.087
49.789
49.576
49.363
49.224
49.150
48.937
48.724
48.511
39.117
37.558
34.831
29.866
14.489
EtO2C
EtO2C
NH
O
7-18a
ppm


EtO2C
EtO2C
7-17b
O
O
N
6.40
0.92
1.00
2.59
1.33
2.34
1.71
0.84
4.00
0.75
ppm


196.394
170.685
170.562
167.099
155.017
139.627
136.379
127.072
77.318
77.000
76.682
61.897
61.884
57.737
52.151
44.791
42.753
38.398
31.350
30.007
13.972
EtO2C
EtO2C
7-17b
O
O
O
N
ppm