Summer 2015

The radical-polar crossover annulation approach to chiral substituted pyrrolidines and piperidines

Kara Anne Slater
University of Iowa

THE RADICAL-POLAR CROSSOVER ANNULATION APPROACH TO CHIRAL SUBSTITUTED PYRROLIDINES AND PIPERIDINES

by

Kara Anne Slater

A thesis submitted in partial fulfillment of
the requirements for the Doctor of Philosophy
degree in Chemistry
in the Graduate College of
The University of Iowa

August 2015

Thesis Supervisor: Associate Professor Gregory K. Friestad

Graduate College
The University of Iowa
Iowa City, Iowa

CERTIFICATE OF APPROVAL

PH.D. THESIS

This is to certify that the Ph.D. thesis of

Kara Anne Slater

has been approved by the Examining Committee
for the thesis requirement for the Doctor of Philosophy
degree in Chemistry at the August 2015 graduation.

Thesis Committee:

Gregory K. Friestad, Thesis Supervisor

F. Christopher Pigge

Hien M. Nguyen

Lou Messerle

Horacio F. Olivo

To: Derek, my soulmate, my rock, the one who inspires me to achieve success in all areas of life.

Do not be wise in your own conceits.

Paul, Romans 12:16
Holy Bible (KJV)

ACKNOWLEDGMENTS

There are so many people to thank for supporting me throughout my life and helping me to become the person and scientist I am today. I have been blessed by God from the beginning with a loving, supporting, God-fearing family who taught me that you can achieve great feats if you only trust in God and put your whole heart into everything you do. Mom, thank you for always building up my confidence and never judging me. Dad, thank you for teaching me integrity and work ethic. Jon, thank you for teaching me how to live a little.

All of my teachers throughout the years have fostered my love of learning, and I would especially like to thank Tobey Hauter, Dr. Brad Andersh and Dr. Gregory Friestad. Tobey Hauter, my high school chemistry teacher, is the one who inspired my first true interest in science and I will be forever indebted to her for her engaging lectures and interesting choice of laboratory experiments. Dr. Brad Andersh invited me to join his research group at Bradley University and so sparked my love of laboratory research. He was a huge support during my undergraduate studies, and offered numerous opportunities for me to become familiar with the art of presenting my research. Dr. Gregory Friestad has always challenged me intellectually and for that I am a better scientist and person. Performing graduate research under his direction has provided me with the knowledge I need to become a successful research chemist.

I have also been blessed with wonderful fellow researchers throughout my time in graduate school. Koushik Banerjee took me under his wing when I joined the Friestad research group and I will always appreciate his willingness to teach me and kindness in his approach. Gopeekrishnan Sreenilayam and Luke Slominski provided a very enjoyable work environment in our laboratory and I still miss them in the laboratory today. An Ji and I were lunch buddies and I truly enjoyed and miss our conversations. Sherif Ibrahim has been a great friend and I especially enjoy his modesty and his appreciation of the

differences in people. Ryan Friedrich has also been a great friend, and I have enjoyed our conversations and his support throughout classes and group research. I only knew Andrew Cox for a short time, but he is a very kind person and I enjoyed our interactions. Manshu Li joined our research group this year, and I am glad that I have been able to get to know him, he is a very sweet young man. I have had the pleasure of working with numerous undergraduate students; Ellie Keuter, Michelle Kroc, Callie Eyman-Casey, Maxwell Court, Levi Goff, Jay Bell, Alfredo Garcia and Garrett Obenauf. They all provided me with the opportunity to foster young scientific minds, and also with a bit of levity in the laboratory.

Last, but by all means not least, I would like to thank my best friend, my husband, the father of my children. Without him, I know with all of my heart, I would not have made it through graduate school. His understanding, love and support has been what fuels me each day, especially during the tough times in school. He has made me a better person in so many ways and has been a wonderful father to our children. I am so proud to say I am his wife, and I can hardly wait to experience all that the future has to offer us with him.

ABSTRACT

Chiral amine functionality is abundant in the world of natural products. In the past, many research groups have made use of the addition of carbanions to imine derivatives in order to achieve such functionality. Nucleophilic addition, however, can prove to be difficult when utilizing complex starting materials since many functional groups are not orthogonal to this approach. Radical addition to imine derivatives is an alternative strategy. There is a broader range of functional group tolerance with this method due to the mild nature and chemoselectivity of radical reactions. Further, secondary functionality may be included in either the radical precursor or acceptor, leading to subsequent formation of nitrogen heterocycles through a radical-polar crossover reaction.

We have found that photolysis of alkyl iodides in the presence of $Mn_2(CO)_{10}$ leads to chemoselective iodine atom abstraction and radical addition to *N*-acylhydrazones without affecting alkyl chloride functionality. Using radical precursors or acceptors bearing a suitably positioned alkyl chloride, the radical addition is followed by further bond construction enabled by radical-polar crossover. After the alkyl radical adds to the imine bond, the resulting *N*-nucleophile displaces the alkyl chloride leaving group via 5-*exo*-*tet* or 6-*exo*-*tet* cyclizations, furnishing either pyrrolidine or piperidine functionality, respectively. When both 5-*exo*-*tet* and 6-*exo*-*tet* pathways are available, the 5-*exo*-*tet* cyclization is preferred. Isolation of the intermediate radical adduct, still bearing the alkyl chloride functionality, confirms the order of events in this radical-polar crossover annulation. A chiral oxazolidinone stereocontrol element in the *N*-acylhydrazones provides excellent stereocontol in these reactions.

In the past, the Mn-mediated radical addition to *N*-acylhydrazones methodology was applied to the synthesis of γ-amino esters and synthetic studies of the tubulysin family of natural products. Throughout this work, it became apparent that there exists a need for a versatile, general approach to the installation of *N,O*-acetal functionality at peptide bonds.

Initial results suggest that such a structure can be synthesized in a latent form, and then oxidized to reveal the *N,O*-acetal moiety.

PUBLIC ABSTRACT

Numerous pharmaceuticals currently in use find their origins in nature. Biologically active compounds found in plants and insects are known as natural products. It is important to be able to synthesize such compounds in a laboratory setting in order to decrease the destruction of nature, and often in order to gain a significant amount of the compound for use in industry.

Chiral amines, specifically chiral pyrrolidines and piperidines, are substructures that occur often in natural products. Throughout my studies in graduate school, I have developed a new method for the synthesis of these substructures. The methodology, termed a Radical-Polar Crossover approach, incorporates two types of intermediates in one reaction, and so facilitates a wide scope of application. Compounds are traditionally constructed one bond at a time, but with the use of Radical-Polar Crossover reactions, the construction of multiple bonds can be achieved in one reaction. The omission of reactions in a synthetic scheme eliminates time consuming workup and purification steps, and this saves time, money, and offers a more “green” approach to synthesis. This methodology will add to the field of medicinal chemistry, hopefully allowing for numerous discoveries in natural product research.

TABLE OF CONTENTS

LIST OF TABLES

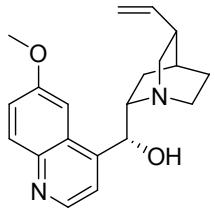
LIST OF FIGURES

CHAPTER 1

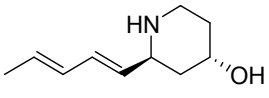
INTRODUCTION

Chiral amine functionality is a common motif in biologically active natural products. It is often desirable to synthesize such natural products in a laboratory setting rather than to isolate them from the natural source since the active compound is often present in the natural source in only trace amounts. In the past, many research groups have made use of the addition of carbanions to imine derivatives in order to achieve such functionality. Nucleophilic addition, however, can prove to be difficult when complex starting materials are used since many functional groups are not orthogonal to this approach. Radical addition to imine derivatives is an alternative strategy. There is a broader range of functional group tolerance with this method due to the mild nature and chemoselectivity of radical reactions. Further, secondary functionality may be included in either the incoming carbon radical or in the imine derivative, leading to subsequent formation of nitrogen-containing rings, specifically pyrrolidine and piperidine rings, through a radical-polar crossover reaction.

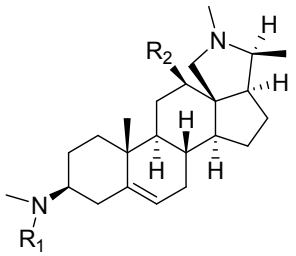
Chiral pyrrolidine and piperidine structures are present in a variety of natural products. Selected examples of such compounds (Figure 1) illustrate a wide range of biological activity. Quinine (**1**) may be the most well-known piperidine natural product, and has been synthesized in a variety of different ways. The antimalarial activity of quinine has been exploited as early as the 1600's, prior to the knowledge that it was the key component in cinchona bark responsible for healing effects in malaria patients.[1] Another chiral piperidine natural product, **2**, depicted below, has a restrictive action upon the digestive system.[2] The less known steroidal alkaloids **3-8** depicted in Figure 1 were isolated from the stem bark of *Funtumia elastica*, and showed antiplasmodial activity.[3] (+)-Preussin (**9**), the antifungal agent isolated from fermentations of *Aspergillus ochraceus*, showed a broad range of activity against filamentous fungi and yeast species.[4, 5] Finally, cytotoxic activity against a skin cancer cell line was demonstrated by two alkaloids, gelsedine (**10**) and gelsemicine (**11**), isolated from *Gelsemium elegans* and *G. sempervirens*, respectively.[6]



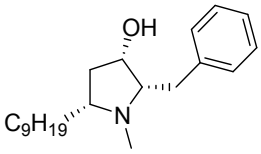
1 quinine



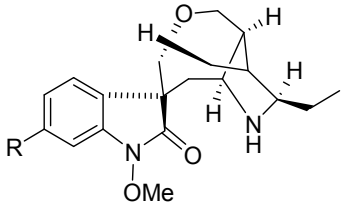
2 SS 20 846A



3 R_1=CH_3,
4 R_2=$(CH_3)_2C{=}CHCH_2COO$ holarrhetine
5 R_1=CH_3, R_2=H conessine
6 R_1=H,
7 R_2=$(CH_3)_2C{=}CHCH_2COO$ holarrhesine
8 R_1, R_2=H isoconessimine



9 (+)-preussin



10 R=H gelsedine
11 R=OMe gelsemicine

Figure 1. Biologically Active Pyrrolidine/Piperidine Natural Products

CHAPTER 2

BACKGROUND

Chiral Amines via Carbanion Addition to Imines

A commonly used strategy for the synthesis of chiral amines involves the addition of carbanion reagents to imine derivatives. There are numerous examples of this strategy in the literature, and Charette did a nice job of reviewing them in 2010.[7] Included in this review are the addition of simple alkyls via organometallic reagents, the addition of allyl groups, and the addition of sp^2 and sp hybridized carbanions. Authors have built on these types of addition reactions since 2010 in order to make them amenable to the synthesis of useful biologically active organic compounds.

Grignard and organolithium reagents are among the most well-known carbanion sources for carbon-carbon bond (C-C) formation reactions. There are many examples in the literature of their use in the presence of imines, and Ellman developed the *N-tert*-butanesulfinyl chiral auxiliary shown as part of imine **12** in Figure 2. When attached to the nitrogen atom of an aromatic or aliphatic imine such as **12**, this group can allow for the addition of sp^3 or sp^2 hybridized Grignard reagents, as well as sp hybridized organolithium reagents, resulting in diastereomer ratios (dr) exceeding 93:7 in most cases.[8] This method differs from others employing Grignard and organolithium reagents in that the imine can be derived from an enolizable aldehyde. It appears the *N-tert*-butanesulfinyl chiral auxiliary somehow hinders aza-enolization from occurring (Figure 2).

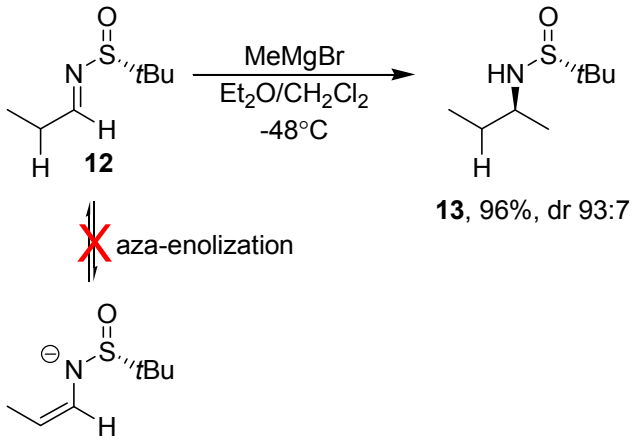


Figure 2. Addition of Grignard Reagent to *N-t*-Butanesulfinyl Imine

Since 2010, Ellman has made advances with the use of his *N-tert*-butanesulfinyl chiral auxiliary. He found that it is possible to add benzyl zinc reagents such as **15**

asymmetrically to aromatic imines such as **14** (Figure 3) in moderate to good yields (42-98%) with high dr ranging from 90:10 to exceeding 99:1.[9] Selectivity decreased when most aliphatic imines were used, however, addition of benzylzinc to a glyceraldehyde-derived imine gave a dr of >99:1. This reaction type could potentially be used in the synthesis of hydroxyethylamine-based aspartyl protease inhibitors.[9]

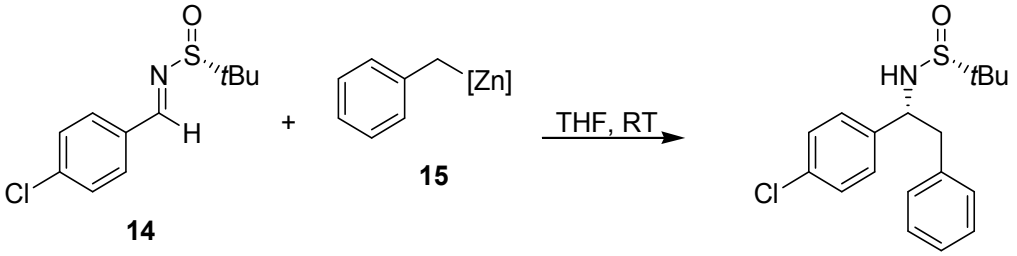
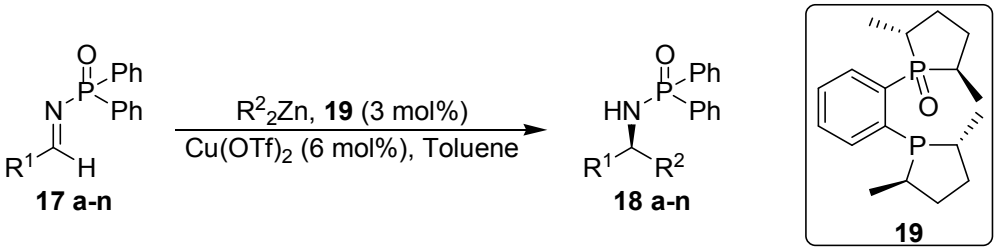


Figure 3. Addition of Benzylzinc to *N*-*t*-Butanesulfinyl Aromatic Imine

Dialkyl zinc reagents are also used for the organometallic addition of carbanions to imines. These reagents are often used in conjunction with a catalyst (Cu, Zr, Hf, Ti, or Zn-alkoxide) and a ligand for stereocontrol. Charette, for example, discovered that chiral α-branched amines **18 a-n** could be generated from nonenolizable *N*-phosphinoyl imines **17 a-n** in copper-catalyzed additions of simple alkyls in the presence of the Me-DuPHOS monoxide ligand **19** (Figure 4). Yields ranged from 73-98% with enantiomeric excess (ee) percentages of 94-98%.



R^1 = Ph, *p*-MePh, *m*-MePh, *p*-MeOPh, 1-Naphthyl, 2-Naphthyl, 2-Furyl, cyclopropyl, *o*-MeOPh; R^2 = Et

R^1 = Ph; R^2 = Me, Et, *i*-Pr, *n*Bu, $nC_{10}H_{21}$

Figure 4. Addition of Dialkylzinc Reagents to *N*-Phosphinoyl Imines

The addition of an allyl group to imines has been studied, and usually employs an imine derived from a nonenolizable aldehyde. Schaus, however, found that enolizable imines **20 a-p** could be used in the 3,3'-diphenyl-BINOL **22** catalyzed addition of allyldiisopropoxyborane (Figure 5).[12] In this method, imines incorporating a double bond, phenethyl group, or benzyl ether were tolerated.

Yields of amines **21 a-p** ranged from 75-94% with enantiomeric excesses between 90-99%.

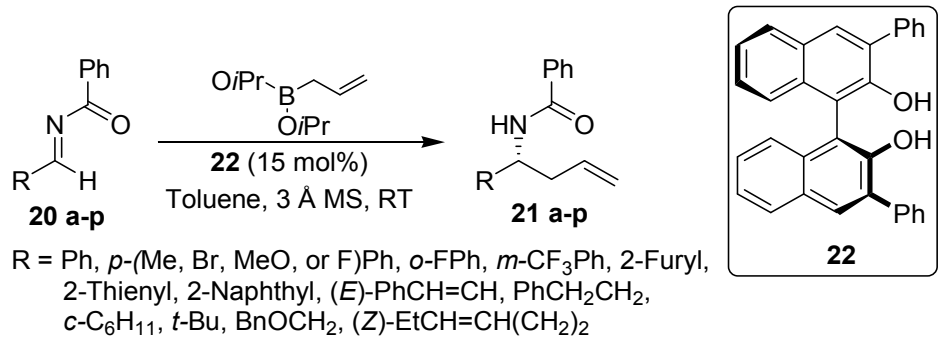


Figure 5. Addition of Allyl Functionality to *N*-Acyl Imines

Fernandes, et. al., were able to apply a new method of imine allylation to the synthesis of a DMP 777 fragment **27** (Figure 6), and also (*R*)-pipecolic acid.[13] (DMP 777 is a human leukocyte elastase inhibitor.) In this method, a β-pinene based chiral π-allylpalladium complex (**25**) was used to guide the stereochemical outcome of the addition of allyltributyl stannane **24** to various aromatic *N*-PMB- and *N*-Bn-imines. Yields of 48-88% with ee values ranging from 40-98% were achieved during reaction times of 48-90 hours.

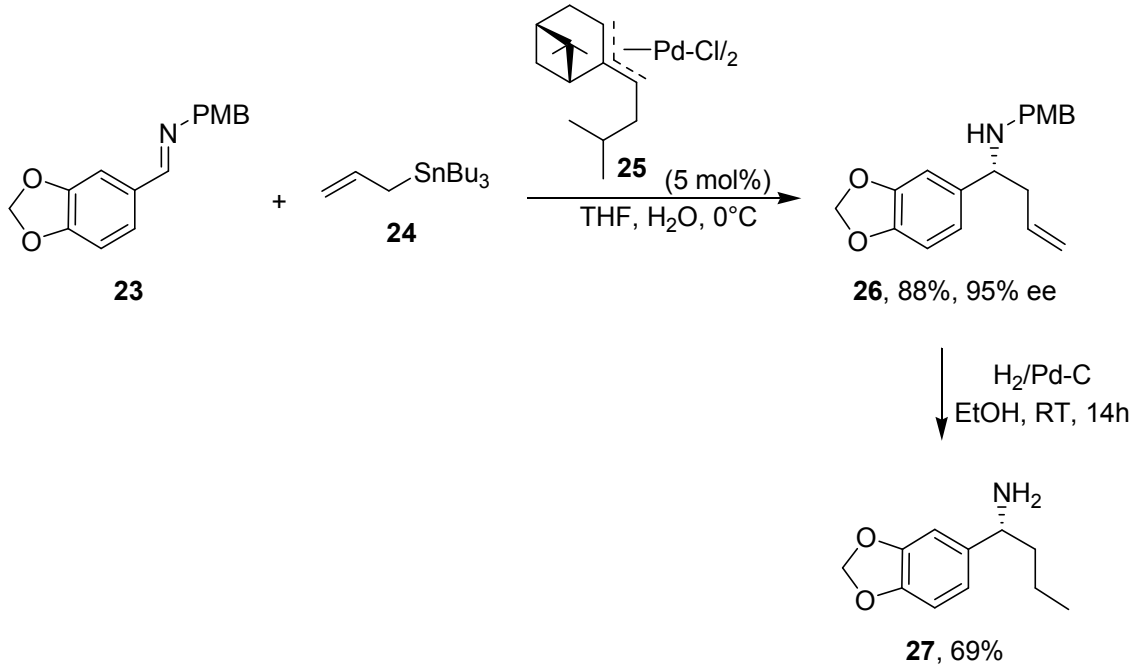


Figure 6. Addition of Allyl to *N*-Alkylimine Toward Synthesis of DMP 777 Fragment **27**

The production of chiral β,γ-unsaturated amines can be achieved via the addition of sp^2 hybridized carbanions to imines. Such reactions usually employ a catalyst/ligand system that binds an alkyne and assists in the asymmetric addition of the subsequent alkene to an imine. One example method by Krische made use of aromatic and aliphatic *N*-arylsulfonyl imines such as **28** (Figure 7) for the addition of simple symmetrical (2-butyne) and unsymmetrical alkynes such as **29**.[14] Carbon-carbon bond formation occurs at the more substituted position when unsymmetrical alkynes are used. Moderate yields between 66-81% are possible with excellent values of ee ranging from 94-99%. The remaining sp^2 functionality on the amine product **30** could potentially be used to further functionalize the molecule in a natural product synthesis, for example.

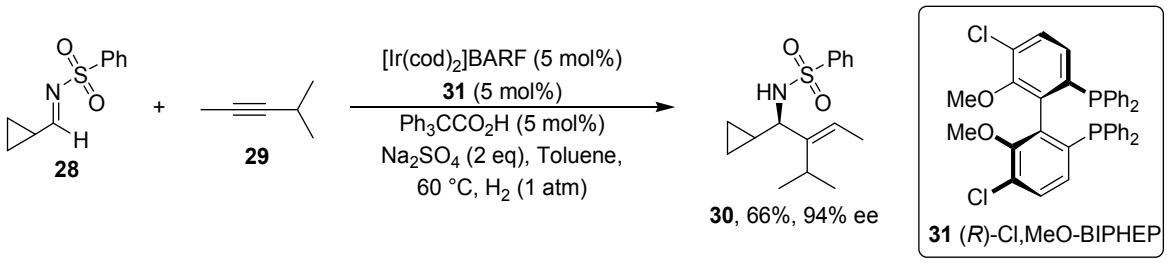


Figure 7. Addition of sp^2 Hybridized Carbanion to *N*-Arylsulfonyl Imine

The asymmetric addition of sp hybridized carbanions to imines is less developed than other additions, but some advances have been made in this area. Copper/ligand or zirconium/ligand catalyst systems are often used. Knochel, for example, developed a method that involves the *in situ* formation of an imine from aldehydes such as **33** and bis(phenallyl)-protected amine components such as **32**, with subsequent addition of trimethylsilylacetylene **34** (Figure 8).[15] The yields of these reactions are moderate, ranging from 58-86%. The ee greatly depends on the steric demand of the aldehyde used, with a direct relationship between enantioselectivity and steric hindrance (ee 34-96%). It was also possible to use phenyl- and *n*-butylacetylene as the addition species.

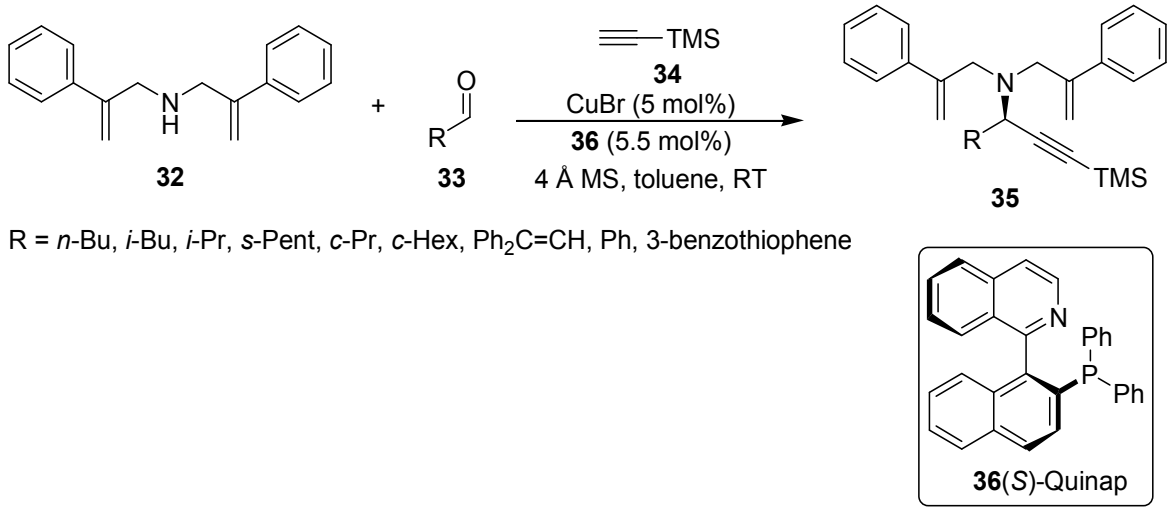


Figure 8. Addition of Trimethylsilylacetylene to Protected Amine

There is a need for a more generalized approach to addition reactions to imines incorporating a broader tolerance of functional groups both on the imine and as part of the addition species. In most cases, imines derived only from nonenolizable aldehydes may be used with carbanion reagents, and with dialkylzinc reagents, only simple alkyls (mainly ethyl) can be used as the addition species. Another disadvantage in the addition of allyl, sp^2 and sp functionality lies in the need for expensive catalysts and ligands that are not typically commercially available.

Chiral Amines via Radical Addition to Imines

The synthesis of chiral amines via carbon-centered radical addition to imine derivatives is underdeveloped to date, although it appears work in this area is growing. The inherently mild reaction conditions necessary to generate radicals makes this method advantageous over carbanion additions to imines in the areas of functional group tolerance and avoidance of aza-enolization. Recently, several functionalized imine derivatives have been used for the addition of simple alkyl, as well as functionalized carbon radicals.

Radical reactions start with an initiation step in which a weak chemical bond is homolytically cleaved, resulting in a radical(s) (**Error! Reference source not ound.**).[16] The bond cleavage is usually initiated by heat or light. The next step(s) are known as propagation step(s), in which radicals react with non-radicals, creating a chemical bond, and also more radicals as shown. In radical chain reactions, the radical created in the last propagation step has the same identity as the radical starting material of the first propagation step, thereby creating a chain

process as shown in **Error! Reference source not found.**. Finally, every radical eaction ends with a termination step, in which radicals combine with each other to form a product(s) with a full octet of electrons.

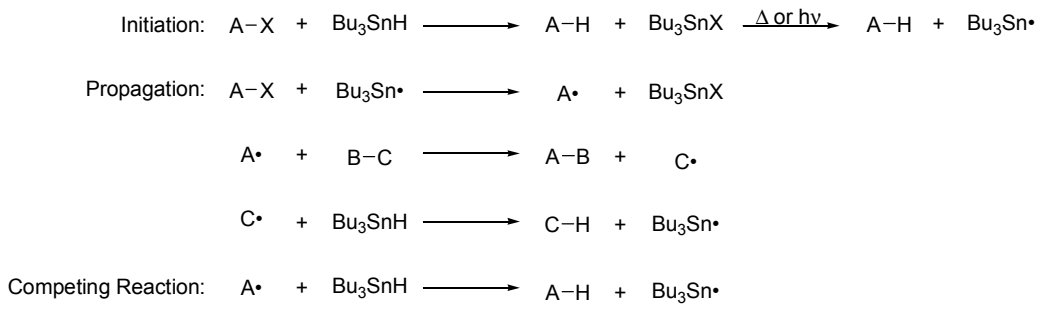


Figure 9. Radical Chain Mechanism

When considering the mechanism of a radical reaction (**Error! Reference source not found.**), one may note that chemoselectivity plays a very important role. If, for example, radical A were to react with tributyltin hydride (Bu_3SnH) instead of molecule B-C as shown, a different product would result and subsequent reactions would be affected. Therefore, as Giese tells us in his book on radicals in organic synthesis, one must consider thermodynamic laws when planning a radical reaction.[17] For example, it is not thermodynamically favorable to break an oxygen-hydrogen bond (O-H) in order to form a weaker carbon-hydrogen bond (C-H), therefore carbon centered radicals will not abstract a hydrogen atom from an alcohol. This further demonstrates an advantage to using radical reactions in a synthetic scheme; alcoholic functional groups do not need to be protected prior to a radical reaction.

As Giese also pointed out, kinetic laws need to be considered when designing a radical reaction.[17] The Frontier Molecular Orbital Theory can be used to discuss this concept. Radicals with a high energy, singly occupied molecular orbital (SOMO), known as nucleophilic radicals, should be paired with radical acceptors that have a low energy, lowest unoccupied molecular orbital (LUMO). Likewise, radicals with a low energy SOMO, known as electrophilic radicals, should be paired with radical acceptors that have a high energy, highest occupied molecular orbital (HOMO). Examples of high energy SOMO radicals include alkyl, alkoxyalkyl, and aminoalkyl radicals (due to the electron donating nature of C, N, and O substituents). Such radicals should be paired with radical acceptors that have electron withdrawing substituents attached since such acceptors will have a low energy LUMO. Of the high energy SOMO radicals mentioned, tertiary radicals (3°) react faster than secondary radicals (2°), which react faster than primary radicals (1°) when low energy LUMO acceptors are used since the relative order of the SOMO energies for these radicals is 3°>2°>1°.

This chapter will focus on the intermolecular asymmetric addition of carbon-centered radicals to the carbon-nitrogen double bond (C=N) of imine derivatives. One might consider that it is not thermodynamically favorable to break a C=N in order to form a C-C or C-N bond, and this is why nucleophilic radicals (high SOMO energy) and activated C=N (low SOMO energy) are a common motif in such reactions. Activation of the C=N is most commonly done through the linkage of an oxygen- or nitrogen-containing substituent onto the nitrogen atom of the C=N, creating an oxime ether in the former case and a hydrazone in the latter.[18] An excellent review by Friestad discusses the many forms of stereocontrol that are used with such acceptors.[18]

Initial work on carbon-centered radical addition to imine derivatives was done by the Friestad research group and made use of chiral *N*-acylhydrazones such as **37** as radical acceptors (Figure 10).[19] Hydrazones derived from aliphatic and aromatic aldehydes were successfully used in the tin-mediated radical addition of 2° (**38**) and 3° alkyl iodides. A Lewis acid was used and presumably increased the yield and stereoselectivity through the formation of a chelate with the hydrazones. Yields of products such as **39** ranged from 28-83% with good diastereomer ratios (dr) from 93:7 to 99:1. This work was expanded in 2005, and the group found that lower yields were obtained when 1° alkyl iodides and hydrazones with α–branching were used.[20] This method demonstrated that with the use of nucleophilic carbon radicals in place of carbanions, aza-enolization side products can be avoided.

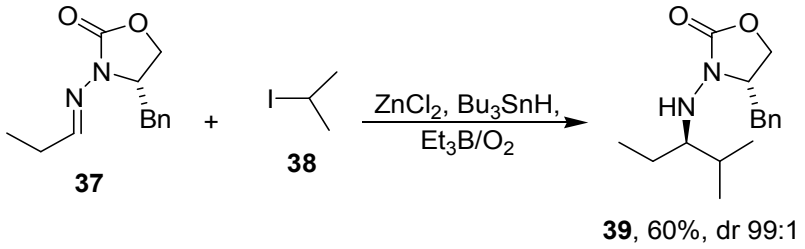


Figure 10. Addition of 2° Alkyl Halide to *N*-Acylhydrazone

The first asymmetric catalytic radical addition to imine derivatives was achieved by Friestad, et. al.[21] They used a copper triflate bisoxazoline aquo complex incorporating chiral ligand **42** in the triethylborane/oxygen generated radical addition of 1° and 2° alkyl halides to aromatic *N*-acylhydrazones such as **40 a-e** (Figure 11). Moderate to high yields (44-88%) and enantiomeric excesses (83-95%) were achieved with stoichiometric amounts of copper catalyst loading. Selectivity decreased (46-81%) when substoichiometric amounts of catalyst were used.

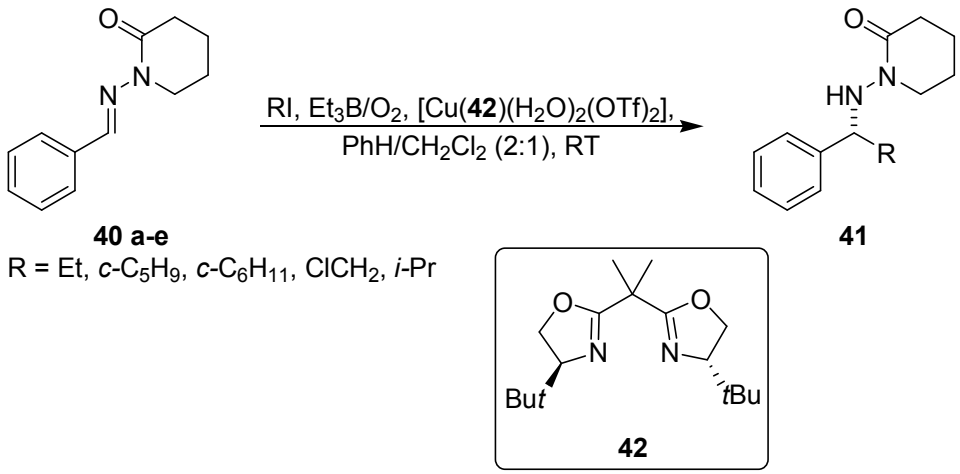


Figure 11. Addition of 1° and 2° Alkyl Halides to Aromatic *N*-Acylhydrazones

More recently, a binaphthol-derived chiral phosphoric acid catalyst was used in the asymmetric radical addition of alkyl halides to various *N,N*-diarylimines (Figure 12a).[22] Reactions incorporating a substoichiometric amount of chiral catalyst **46** provided yields of 31-56% and enantiomeric excesses of 74-81% in the addition of *iso*-propyl or *tert*-butyl radicals to phenyl imine derivatives such as **43 a-f** and **47**. Since a triethylborane/oxygen system was used to initiate the radical process, formation of an ethyl radical addition byproduct such as **45 a-f** and **49** decreased the yield of the desired addition products **44 a-f** and **48**. Efforts to decrease the byproduct yield by the use of a polarity-reversal catalyst, *tert*-butyl mercaptan, were met with an increased ratio of desired product to ethyl addition product, but at the cost of lower selectivity (69% ee, Figure 12b).

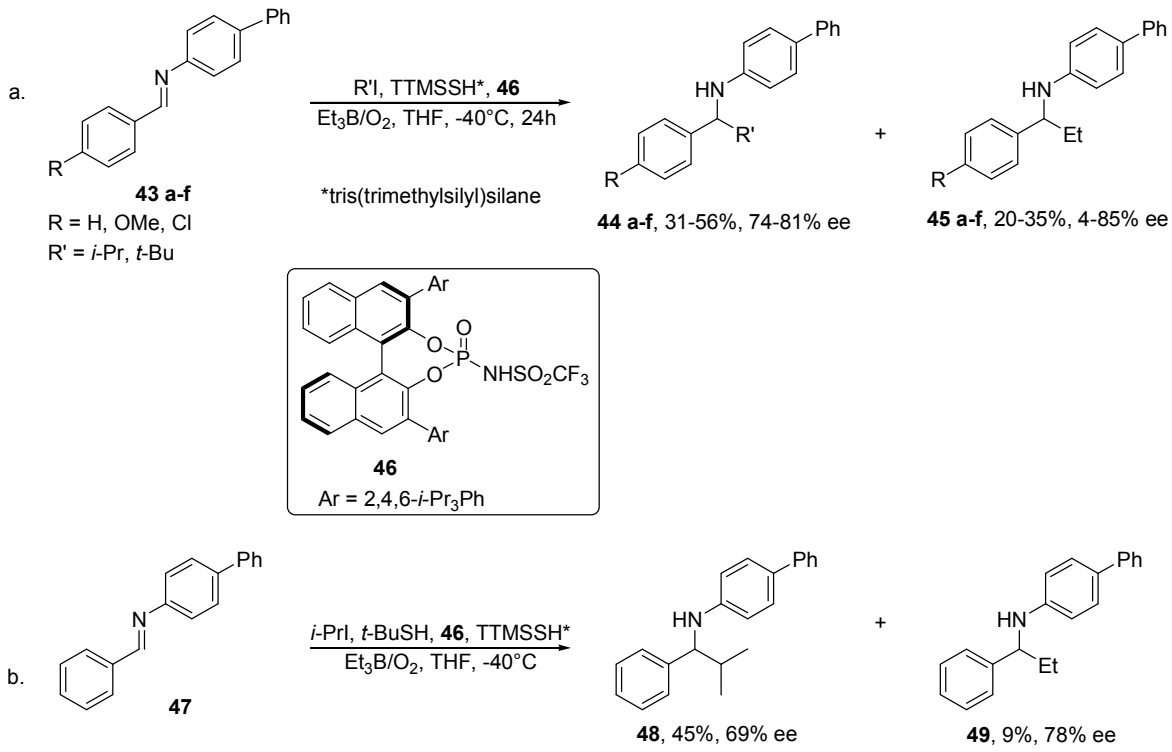
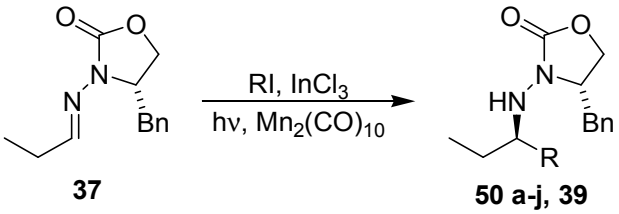


Figure 12. Addition of 2° and 3° Alkyl Halides to *N,N*-Diarylimines

The Friestad group replaced the triethylborane/oxygen system for radical initiation in alkyl halide additions to chiral *N*-acylhydrazones with UV-active dimanganese decacarbonyl (Mn_2CO_{10}, 300 nm) for the same purpose (Figure 13).[23] Yields of products **50 a-j** and **39** ranged from 38-85% with diastereomer ratios from 93:7-98:2 in the addition of various 1° and 2° alkyl iodides to propionaldehyde-derived hydrazone **37**.

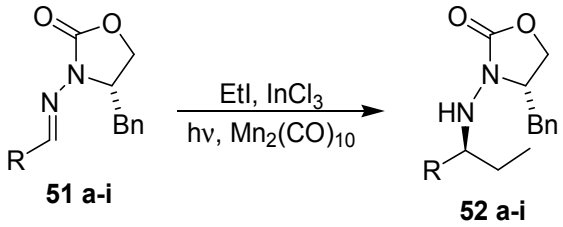


R = Me, Et, Pr, Bu, pentyl, *i*Bu, *i*Pr, $ClCH_2$, $Cl(CH_2)_3$, $Cl(CH_2)_4$, Cl_2CHBr

Figure 13. Addition of 1° and 2° Alkyl Halides to *N*-Acylhydrazone

Versatility of the method was demonstrated when ethyl iodide was used for the addition to various aliphatic hydrazones **51 a-i** (Figure 14). The products of these reactions, **52 a-i**, were the diastereomeric equivalent of the previously mentioned products (Figure 13), showing the ease of obtaining the desired stereocenter in a

synthetic route. It should be mentioned that the diastereomeric equivalent products could also potentially be synthesized through the use of the opposite enantiomer of the chiral auxiliary. The group later published a related article which explored the mechanism of the reaction.[24] One advantage to the use of this method of chiral amine synthesis over the use of carbanion additions to imines lies in the fact that the hydrazone can include halogen functionality, which could be used to further functionalize the molecule in a synthetic scheme.



51 a-i **52 a-i**

R = Me, Pr, Bu, pentyl, *i*Bu, $ClCH_2$, $Cl(CH_2)_3$, $Cl(CH_2)_4$, Cl_2CH

Figure 14. Addition of Iodoethane to *N*-Acylhydrazones

The scope of the manganese-mediated radical addition approach was next expanded to include more complex hydrazones such as **53** and alkyl iodides such as **54** (Figure 15). Yields of 26-93% were obtained when hydrazones and alkyl iodides containing ester, ether, halogen, alkene, and protected and unprotected alcohol functionality were used (further support of functional group tolerance in radical addition reactions).[25] The diastereomer ratio exceeded 95:5 in all cases except one, where it was 94:6. The reaction was used in a synthetic scheme toward the formal synthesis of the antimalarial compound, quinine **1**, to demonstrate synthetic utility.[26]

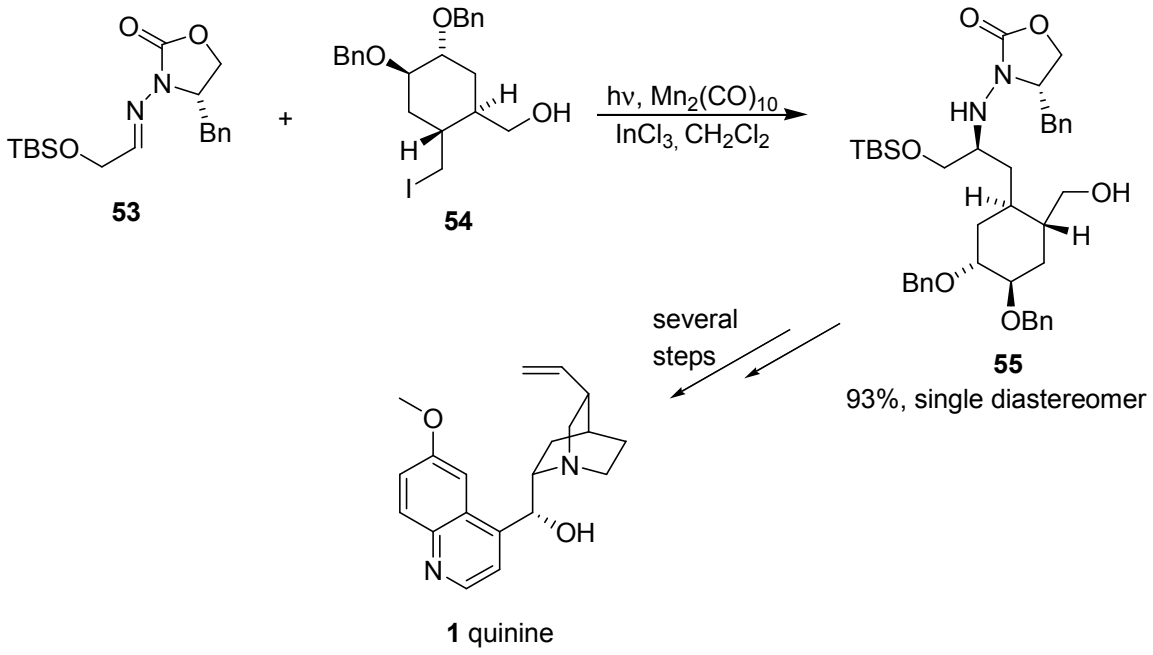
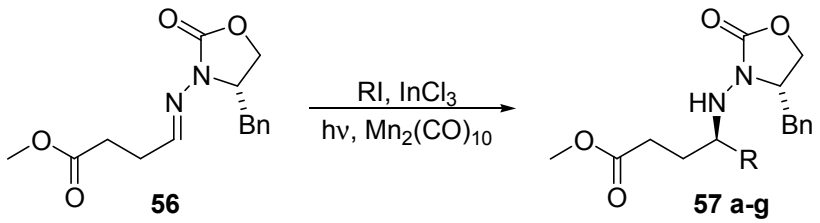


Figure 15. Addition of Complex Alkyl Iodide to *N*-Acylhydrazone: Formal Quinine Synthesis

The synthesis of γ-amino esters was also accomplished with the manganese-mediated radical addition method (Figure 16).[27] Starting with a γ-hydrazonoester **56**, and adding functionalized 1° and 2° alkyl iodides, yields of 33- >99% were observed with diastereomer ratios ranging from 85:15 to 97:3 in products **57 a-g**. γ-Hydrazonoesters with substituents at the position α to the ester gave excellent yields when isopropyl iodide was added as well (96- >99% yield, dr 90:10-99:1).



R = *i*Pr, *s*Bu, $(CH_2)_4CH_3$, $(CH_2)_3OTBS$, $(CH_2)_3OH$, $(CH_2)_2OH$, $(CH_2)_3Cl$

Figure 16. Addition of Alkyl Iodides to γ-Hydrazonoester

Tomioka, et. al., found a method for the radical addition of acetals such as **59** to chiral aromatic *N*-sulfinyl imines **58 a-g** (Figure 17).[28] Radicals were generated by dimethylzinc in air, and a Lewis acid was used to activate the imines. Moderate to high yields of 50-92% were obtained with 80-82% enantiomer excesses. Ethers successfully added to a benzaldehyde derived *N*-sulfinyl imine, albeit with lower yield and ee.

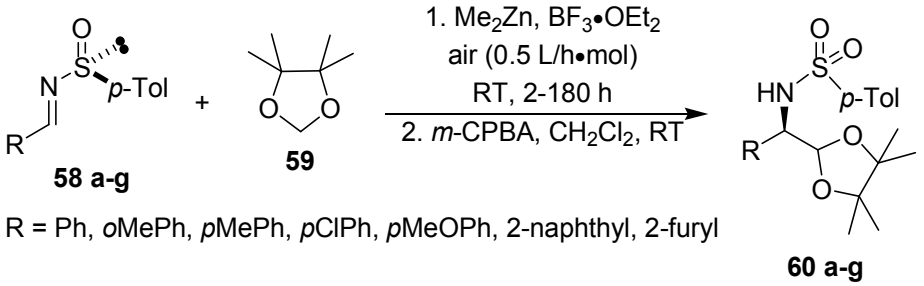


Figure 17. Addition of Acetal to Aromatic *N*-Sulfinyl Imines

A three-component radical addition to an *in situ* generated *N*-arylimine was developed by Muñoz, et. al.(Figure 18).[29] Various aldehydes and 1° amines were used to create 2° amines through a radical pathway, but only one product was obtained asymmetrically. Upon reaction of tetrahydro-2-furancarbaldehyde **62** with *para*-methoxyaniline **61** in the presence of triethylborane, 1,2-stereoinduction was observed with the formation of an 87:13 mixture of amine **64**. This reaction proceeded more quickly than the rest (20 minutes versus 2-6 days), and they attributed the higher reactivity and 1,2-stereoinduction to the formation of a chelate **63**, presumably between the oxygen atom of the tetrahydrofuran ring, the nitrogen atom of the imine, and the boron atom of the triethylborane as shown.

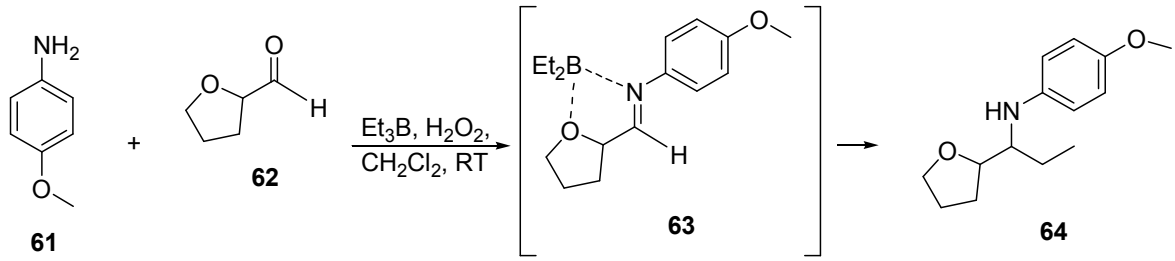


Figure 18. Addition of Triethylborane to *in situ* generated *N*-Arylimine

Ellman's *N-tert*-butanesulfinyl chiral auxiliary, used in carbanion additions to imine derivatives as discussed earlier (Figure 2), has recently been used in radical approaches as well. Fernàndez, et. al., developed a tin-mediated radical addition of 1°, 2°, and 3° alkyl iodides to aromatic *N-tert*-butanesulfinyl imines (Figure 19).[30] A wide range of functionality could be incorporated into the alkyl iodide including ether, ester, and additional halide as shown. These iodides gave yields of products **66 a-g** ranging from 40-91% when added to benzaldehyde derived imines **65 a-g**, with the dr exceeding 98:2 in all cases. Aryl, heteroaryl, benzyl, and alkynyl imines were also used in the addition of isopropyl iodide to give yields from 60-98% with the dr exceeding 98:2 in all cases except one (dr 95:5).

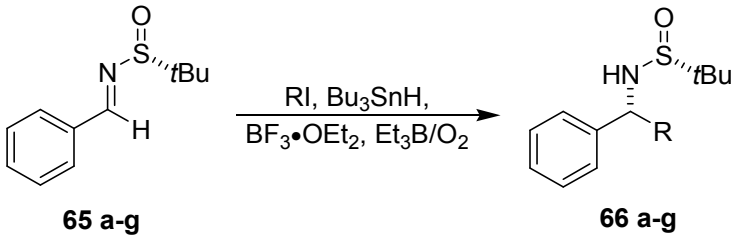


Figure 19. Addition of Alkyl Iodides to Aromatic *N-t*-Butanesulfinyl Imine

A tin-free radical approach that also uses Ellman's auxiliary has recently been used to create *tert*-leucine derivatives such as **69** (Figure 20).[31] A number of substituted benzylzinc bromides such as **68** successfully added benzyl radicals to the *N-tert*-sulfinyl imine derivative of glycine ethyl ester **67**, giving migration-addition products where the *tert*-butyl group of the chiral auxiliary migrated to the imine carbon atom, and the alkyl group added to the sulfur of the auxiliary. Yields of 41-75% were obtained with excellent diastereomer ratios exceeding 95:5 in most cases.

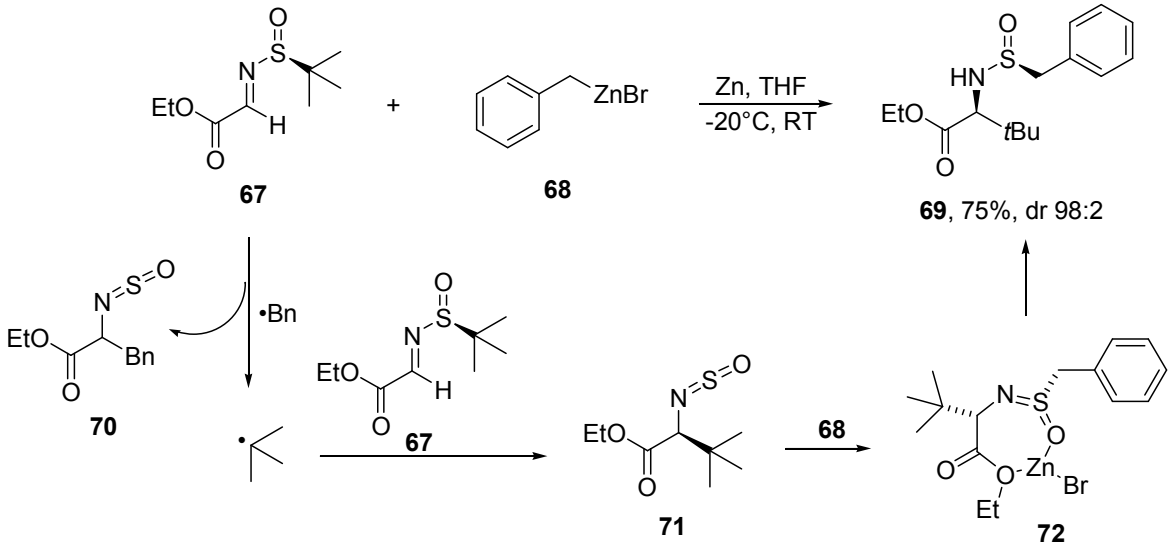


Figure 20. Mechanism of Addition of Benzylzinc Bromides to *N-t*-Butanesulfinyl Imine

Although a fairly new idea, the practicality of the asymmetric synthesis of chiral amines through the addition of carbon centered radicals to imine derivatives is evident even in the few examples we see in literature today. Yields and selectivities mirror those found in carbanion addition methods, but the radical approach has proven to be more versatile in nature. Aza-enolization of the imine is avoided, there is a broader tolerance of functional groups both in the imine derivative and addition species, and obtaining the desired stereocenter in the

amine product can be achieved in more ways than by changing the stereocenter of the stereo-control element (see discussion of manganese-mediated method above).

Radical-Polar Crossover Reactions

The synthesis of molecules one bond at a time is a very time consuming process. Most reactions require a workup procedure, followed by purification and characterization steps. Radical-polar crossover (RPC) reactions, however, allow for the construction of multiple bonds in one pot, saving both time and money spent on workup/purification materials. In 2009, Landais and Godineau composed a review article introducing three classifications of radical-ionic reactions.[32] Class A were classified as radical-anionic reactions, Class B were radical-cationic reactions, and Class C were sequential radical-polar crossover reactions (

Figure 21). Examples of all three classifications have since been referred to simply as RPC reactions.

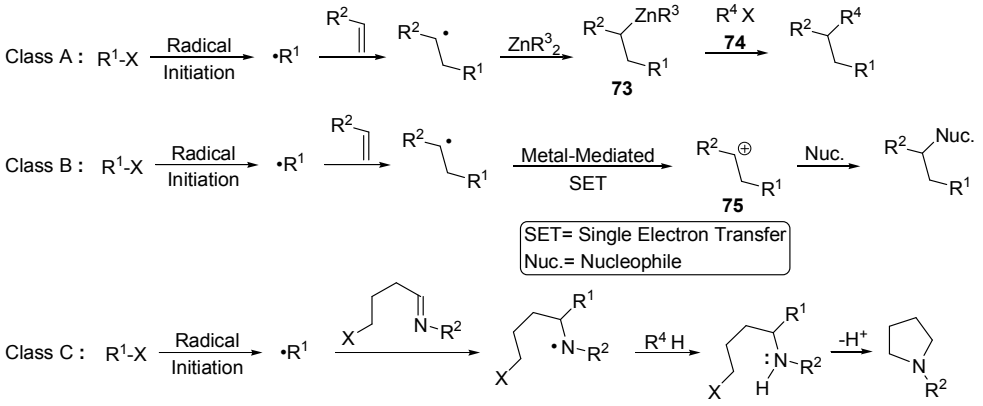


Figure 21. Three Classifications of Radical-Polar Crossover Reactions

All RPC reactions begin with a radical process, and sequential radical reactions often occur. In Class A RPC reactions, a metal-mediated process follows the radical step(s), creating a carbanion (**73**) which reacts with an electrophile (**74**). The electrophile is often internal, leading to a cyclized product, but intermolecular nucleophilic transformations can also occur. In Class B RPC reactions, transition metals are used to induce single electron transfers (SETs) which create a cationic intermediate (**75**) following the initial radical process. The reaction is then terminated by action of a nucleophile. Class C RPC reactions involve neutral reactive intermediates, and often a radical quenching step, followed by a nucleophilic step which is often intramolecular leading to heterocycle production as shown. Jahn has presented a fourth type of RPC reaction, where the polar step

precedes the radical step(s). These reactions are mediated by ferrocenium salts and will be presented later in this section as well.

When designing an RPC reaction, one must consider chemoselectivity, and apply the thermodynamic and kinetic principles that were discussed earlier in the introduction to the section on radical additions to imine derivatives (**Error! Reference source not found.**). For example, if an RPC reaction is to begin with a radical cascade, the initiation step must produce a radical donor exclusively from one radical precursor. This radical donor must exclusively add to one acceptor, and the resulting radical in turn must exclusively add to one other acceptor. Radical donors, therefore, usually originate from alkyl halides since the carbon-halogen bond of such species are easily cleaved homolytically under radical initiation conditions. If the initial radical donor is nucleophilic in nature, the radical acceptor that it is to be paired with must have electron withdrawing substituents attached, making it electrophilic. The resulting radical of this pairing would be electron deficient in nature, so it would need to be paired with a high energy acceptor. The reader should keep these concepts in mind while reviewing the various RPC reactions presented within in order to recognize the beauty of the transformations that are possible in one pot with functional group compatibilities that are not possible in other types of reaction sequences.

Class B RPC Reactions: Cationic Intermediate

The first RPC reactions were published by John A. Murphy in 1993 and were of the Class B classification mediated by tetrathiafulvalene (TTF).[33] In 2001, Murphy wrote a review article entitled The Radical-Polar Crossover Reaction, and it detailed the mechanism and scope of TTF-mediated reactions.[34] Few other examples of RPC reactions existed before 2001, and those that did exist had not yet come to be classified as RPC reactions, so they were not included in Murphy's review.

An example of a TTF-mediated RPC reaction is shown below (Figure 22). The reactions employ arenediazonium salts such as **76** which are excellent electron acceptors to which TTF (**78**) can donate. After donation of a single electron, gaseous nitrogen is lost, an aryl radical **79** is formed, and also the radical-cation of TTF. **79** then reacts with an internal double bond, creating a heterocyclic ring **80** (containing oxygen[33] or nitrogen[35]), and also another carbon-centered radical. The TTF radical-cation momentarily combines with the carbon-centered radical, but then an SN_1 reaction quickly takes place through intermediate **81** in the presence of a nucleophile. The SN_1 reaction is often that of solvolysis with water giving alcohols, methanol giving methyl ethers or with acetonitrile giving amides (shown).

Amide **77** was formed in 57% yield. Murphy used this strategy in his total synthesis of the natural product (±)-aspidospermidine.[36]

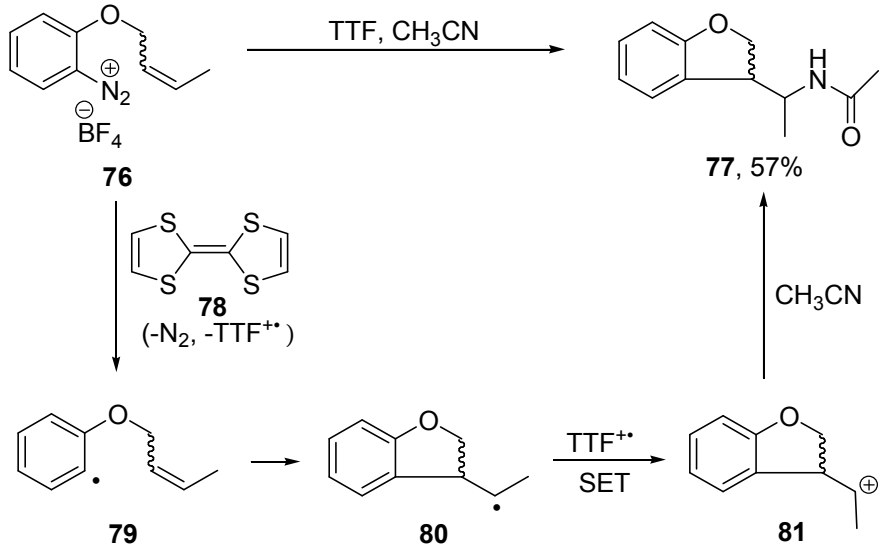


Figure 22. Mechanism of TTF-Mediated RPC Reaction

Another well-developed Class B RPC strategy has been reviewed by Andrew J. Clark and is characterized as having an iminium ion intermediate **84** (Figure 23).[37] Much of Clark's work involves catalysis by copper complexes, in solution[37,38] or on solid-support,[39] but he has also presented a ceric ammonium nitrate (CAN)-mediated approach.[40] The reaction is initiated by homolytic cleavage of a C_α-halogen bond in an *N*-allyl-α-halo-amide such as **82**. The carbon-centered radical cyclizes onto an internal double bond, and the resulting radical **83** is oxidized in a SET by a Cu(II) complex, giving an iminium ion intermediate **84**. The intermediate is quickly quenched by action of α-proton elimination as shown, or by solvolysis.[40]

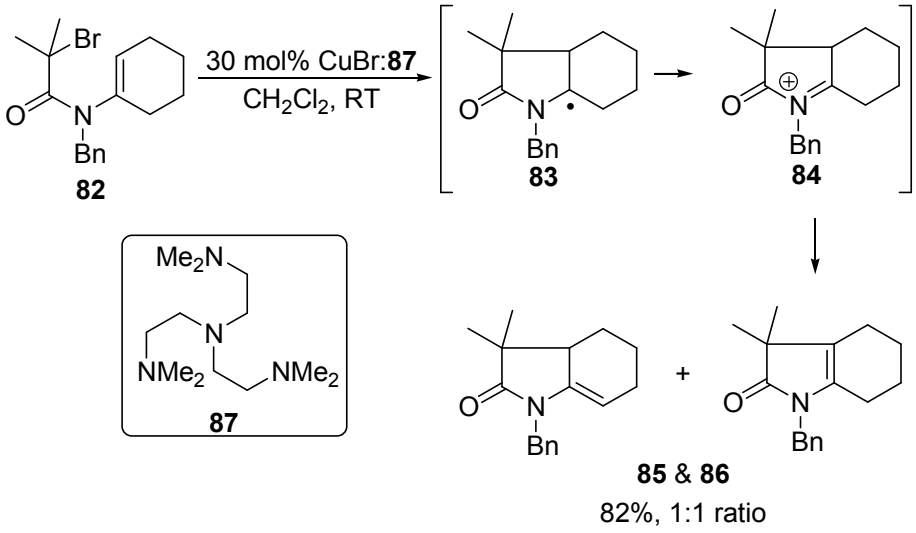


Figure 23. Mechanism of Copper-Catalyzed RPC Reaction Towards Pyrrolone Derivatives

Ghelfi, et.al. extended this method to the synthesis of the maleimide nucleus or precursors of this for the ultimate formation of disubstituted maleic anhydrides (Figure 24).[41] The reaction begins the same way with homolytic cleavage of a carbon-halogen bond and subsequent intramolecular cyclization to give a radical of type **89** which undergoes a SET with copper (II) chloride to give an *N*-acyliminium ion **90**. Hydrochloric acid is lost from **90**, and then a chloride ion is eliminated from the resulting ketene-*N,S*-acetal **93**, giving a second *N*-acyliminium ion **94**. Two products are formed from **94**, the first resulting from hydrolysis to give a maleimide of type **95**. This maleimide either acts as a nucleophile on **94** to give a sulfide dimer **96**, or it undergoes oxidation by Cu(II) yielding a disulfide dimer of type **97**. Both dimers can be carried through an oxidation and hydrolysis process and the disubstituted maleic anhydride **98** was obtained in 52% yield over 4 steps for the example depicted below.

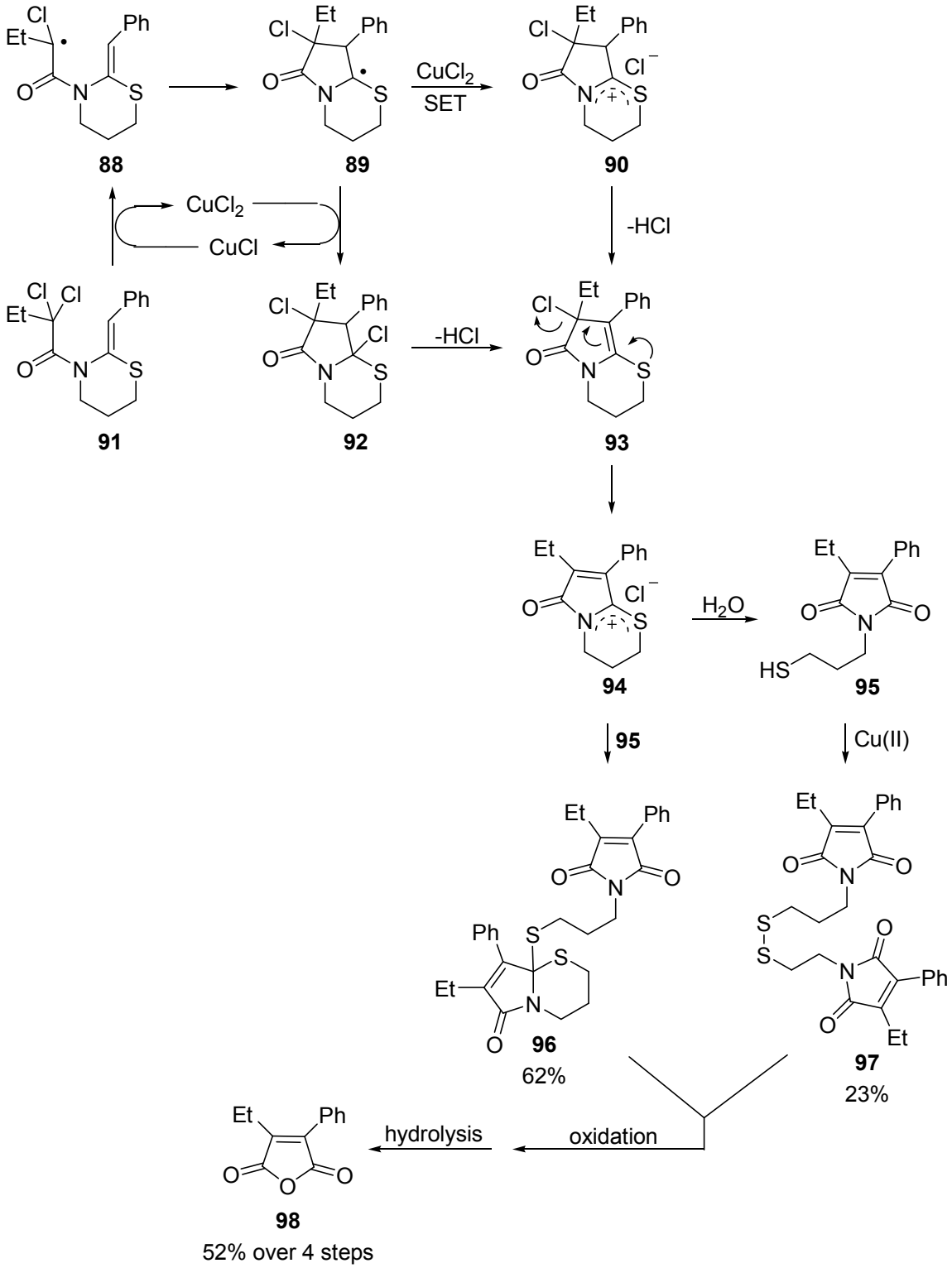


Figure 24. Mechanism of Copper-Catalyzed RPC Reaction Towards Maleic Anhydride

An unrelated reaction which also proceeds through an iminium ion was presented by Friestad (Figure 25).[42] Here we see a tin-mediated nonreductive alkylation of

enamides. Various oxazolidinones reacted with ethyl iodoacetate (68-76% yield) and iodoacetonitrile (66-67% yield) to give the *E*-enamides. Primary and secondary α-bromoesters gave good yields as well (58-65%). In the example below, the initial ethoxycarbonylmethyl radical generated from ethyl iodoacetate adds to enamide **99**, giving an α-amido radical **101**. An iminium ion is then generated either indirectly by an atom transfer reaction between **101** and ethyl iodoacetate followed by loss of an iodide anion, or directly by a SET with ethyl iodoacetate. Either process regenerates the ethoxycarbonylmethyl radical to propagate the radical chain. The final product is realized after reduction by triethylamine.

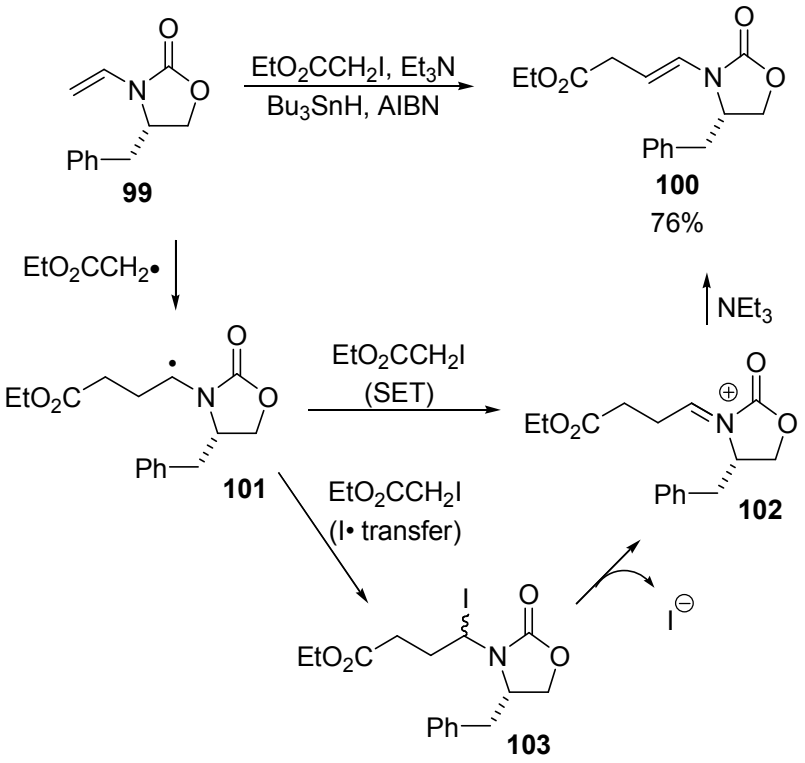


Figure 25. Tin-Mediated RPC Reaction Towards *E*-Enamides

Francisco has made use of anomeric alkoxyl radical fragmentation (ARF) promoted by hypervalent iodine(III) for the synthesis of carbohydrates **109**,[43] alduronic acid lactones **108**,[44] polyhydroxylated *N*-heterocycles **111**,[45,46] and iminoketoses **110**[47] based on the identity of R (Figure 26). This reaction proceeds through an oxonium ion intermediate and gives moderate to excellent yields in most cases for the various product types: 36-94% for carbohydrates, 25-70% for alduronic acid lactones, and 15-80% for polyhydroxylated *N*-heterocycles. Initially, the hypervalent iodine (III) reagent, acetylhypoiodite (CH_3COOI), is generated *in situ* from iodosylbenzene and iodine. This acts on the alcohol of the starting

heterocycle **104** to give an anomeric alkoxyl radical which undergoes an ARF at the C1-C2 bond. The resulting radical is then oxidized by a SET with excess acetylhypoiodite to yield the oxonium ion **107**, and this is can be trapped intra- or intermolecularly by various nucleophiles as shown.

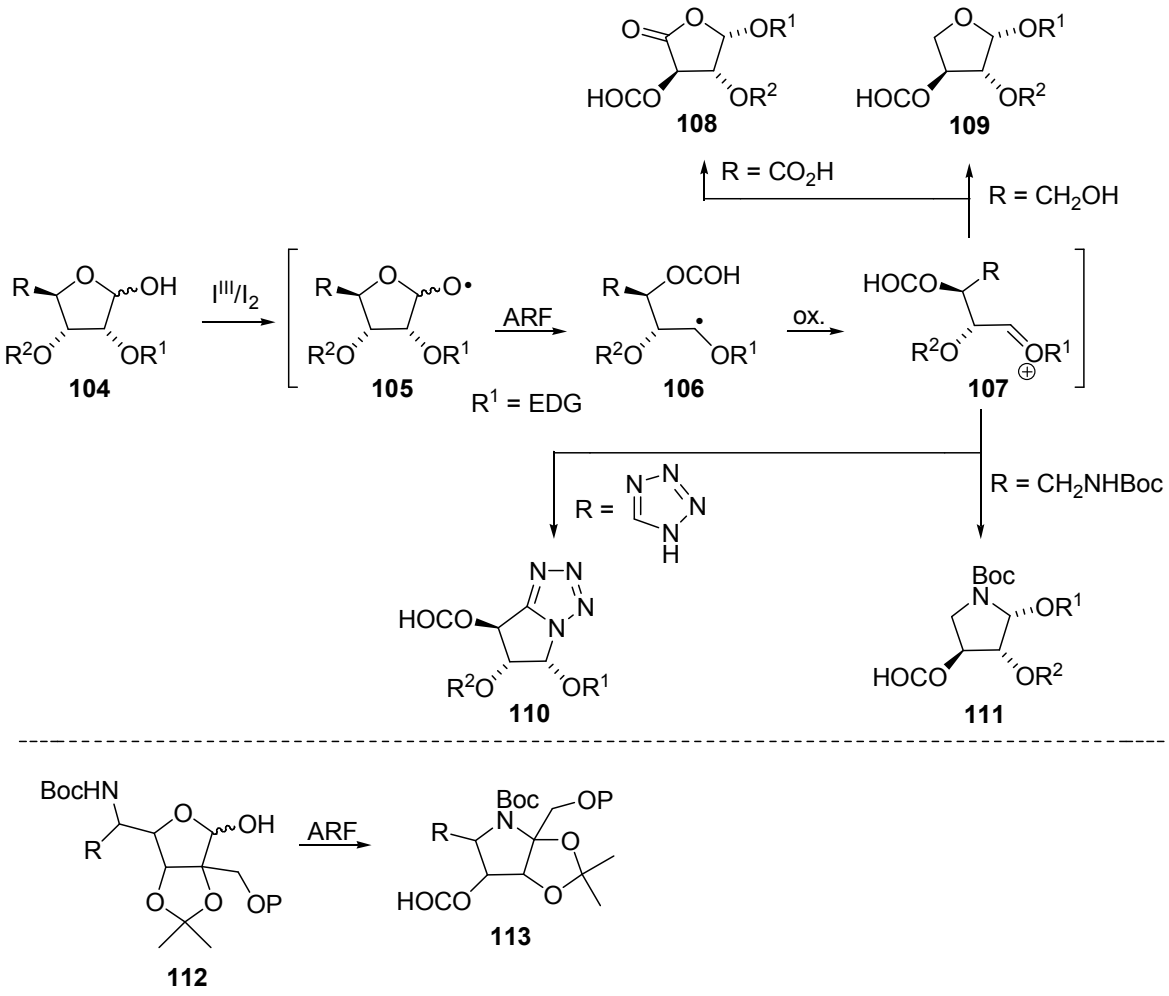


Figure 26. Mechanism of Hypervalent Iodine(III)-Mediated RPC Reaction

An enantioselective RPC reaction was developed by MacMillan and produces chiral substituted pyrrolidines[48] or cyclohexanes.[49] As can be seen in Figure 27, an imidazolidinone catalyst **116** is used along with an oxidant to invoke SOMO-activation of an aldehyde starting material such as **114**. The resulting radical cation **118** then reacts intermolecularly with an olefinic species to generate alky radical **119**, with the stereochemistry of the newly formed carbon-carbon bond being directed by the attached imidazolidinone. A SET then occurs yielding a carbocation **120** which undergoes a nucleophilic addition reaction. When n=1 in the aldehyde side chain, the nucleophilic species is a protected amine, and the pyrrolidine products are formed in 50-85% yield with dr ratios of 2:1 to greater than

20:1. The cyclohexane products are formed by using various aromatic species as the terminal nucleophile in the aldehyde starting material. The yields range from 69-90% with dr ratios of 4:1 to greater than 20:1.

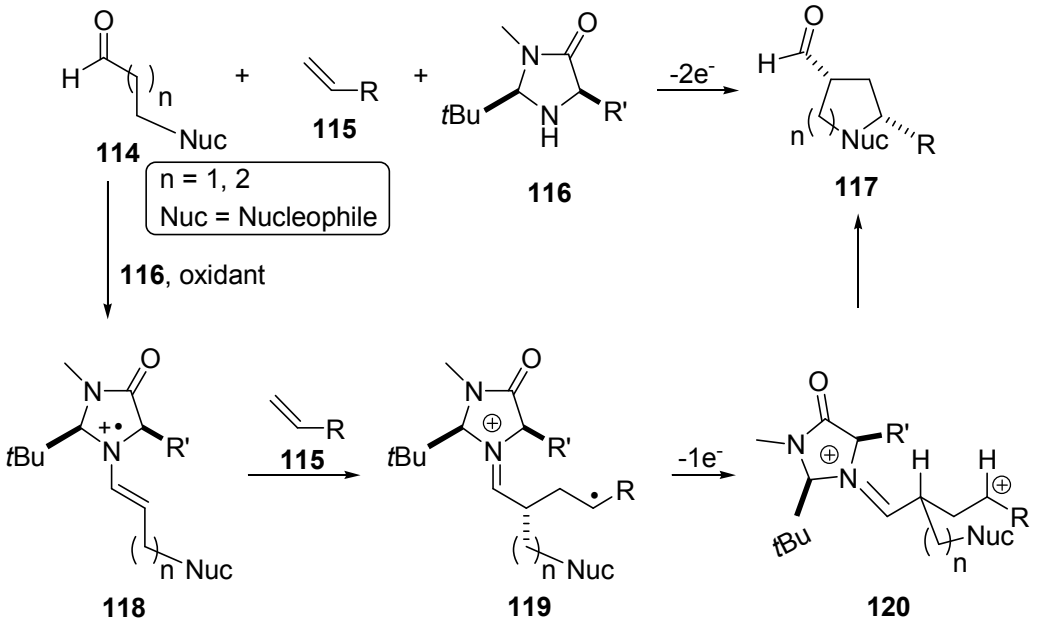


Figure 27. Mechanism of Enantioselective Organo-SOMO Cycloaddition RPC Reactions

Various chiral 5-membered rings can be synthesized using organic photoredox chemistry. Nicewicz developed a route catalyzed by an acridinium photooxidant/redox-active hydrogen atom donor system (Figure 28). The positively charged intermediate here is also a radical-cation, and the mechanism can be seen below. A SET from an olefin **121** generates the radical-cation **124**, which is then attacked by a terminal nucleophile of an allylic alcohol, carboxylic acid, allylic amine, or protected amide. The alkyl radical **125** which results then undergoes an intramolecular cyclization, and the final radical **126** is then reduced by a hydrogen atom donor in solution. When the starting material consists of an allylic alcohol, the yields range from 42-95% with dr ratios of 1.1:1 to greater than 20:1.[50] Carboxylic acid starting materials yield dihydrofuranones in 41-85% yield with dr ratios of 1.3:1 to greater than 25:1.[51] Pyrrolidines are formed with the use of allylic amine starting materials in yields of 38-65% with dr ratios ranging from 2.5:1 to 3:1. Finally, protected amide starting materials are used to create pyrrolidinones in 35-74% yield with dr ratios of 1:1-10:1.[52]

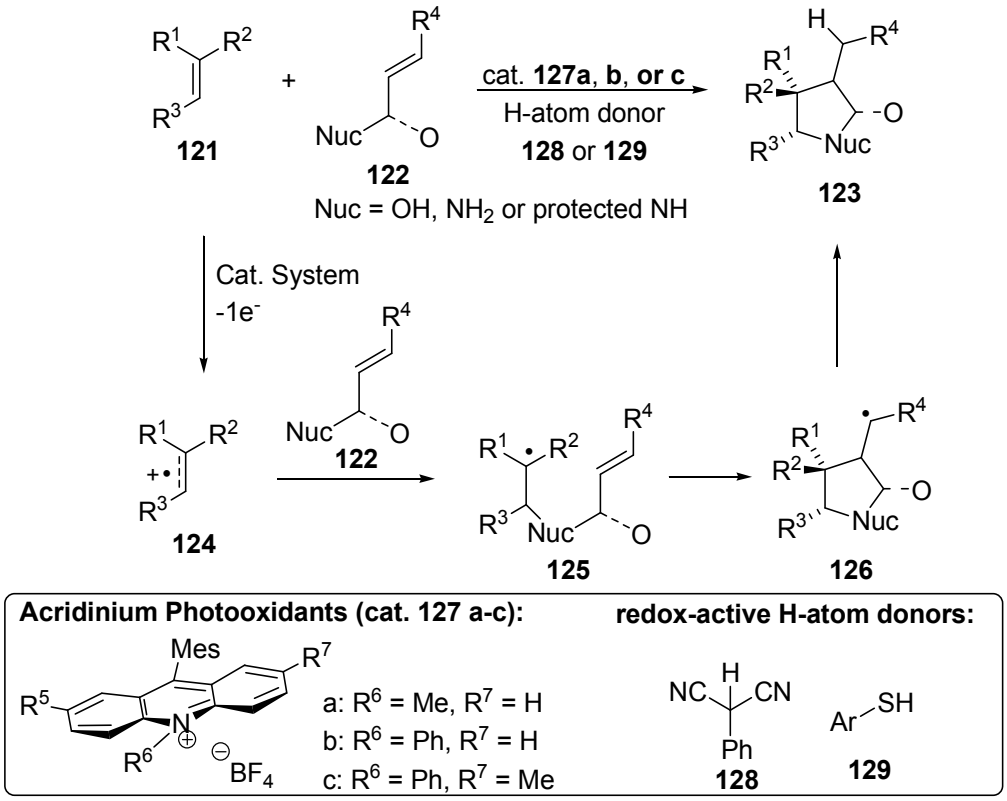


Figure 28. Mechanism of Organic Photoredox Cycloaddition RPC Reactions

Crich has developed an enantioselective RPC reaction with alkene radical cations as the positively charged intermediates paired with either a phosphonoyl or sulfonoyl counter anion (Figure 29). The radical step is initiated by trialkyltin hydride/AIBN reagents to ultimately generate alkyl radicals **132** from nitro compounds **131**. A phosphonoyl or sulfonoyl anion is then eliminated to form a radical-cation **133** which tends to adopt a pseudo-envelope orientation as depicted. This orientation lends to the enantioselectivity in the carbon-nitrogen bond which is subsequently formed through an intramolecular nucleophilic cyclization. In the example below, an intramolecular radical cyclization then occurs, and the resulting terminal radical **135** is then reduced by trialkyltin hydride. Pyrrolidines, piperidines,[53,54] and various other cyclic products including fused and bicyclic nitrogen heterocycles[55] can be synthesized with this reaction. Yields range from 25-90% with ee values of 0-62%.

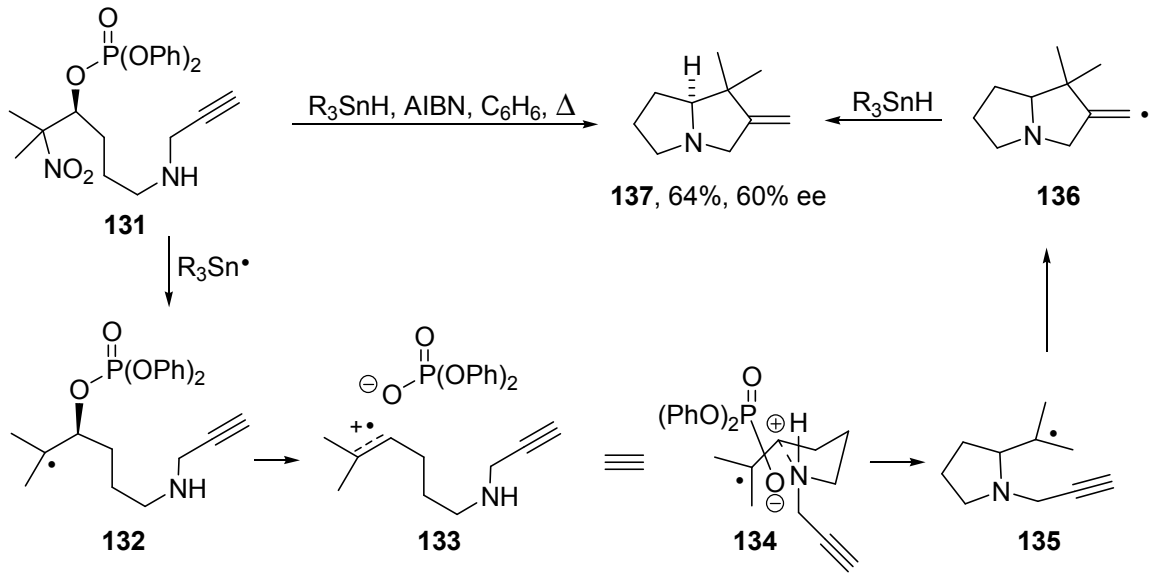


Figure 29. Mechanism of Enantioselective RPC Reaction Towards Nitrogen Heterocycles

A similar phosphonoyl radical-cation intermediate appears in the total synthesis of cephalosporolide E (Figure 30).[56] Here the carbon-centered radical is obtained from a phthalimido derivative **138**, which first gives an oxygen-centered radical upon initiation by the triphenyltin hydride/AIBN system. Elimination of the phosphonyl group in radical **140** gives the radical-cation intermediate **141**. An intramolecular nucleophilic cyclization then occurs, followed by hydrogen atom donation from the tin hydride reagent to give cephalosporolide F. The diphenylphosphoric acid which is generated *in situ* finally promotes the stereocontrolled spiroketal isomerization of cephalosporolide F to cephalosporolide E. This synthesis represents the first direct diastereoselective total synthesis of cephalosporolide E; previous syntheses produced the natural product admixed with the F stereoisomer.

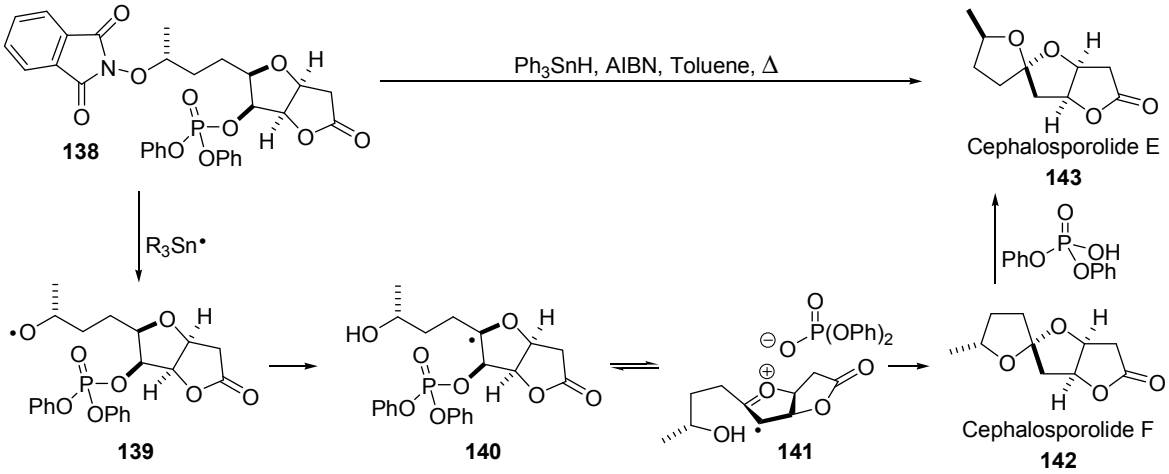


Figure 30. Total Synthesis of Cephalosporolide E (**143**)

One method towards aminoalcohol synthesis goes through two cycles of radical and polar processes (Figure 31).[57] First, an aldehyde **144** is formed from a primary alcohol through α-hydrogen atom abstraction by a *t*-butoxy radical, followed by oxidation to a carbocation by titanium (IV) chloride ($TiCl_4$). Once the aldehyde is formed, it condenses with an amine in solution to form an imine which is then activated by $TiCl_4$ to give an iminium ion **145**. A second equivalent of α-alcohol radical attacks the iminium carbon, leaving a radical cation **146** which is finally reduced to the aminoalcohol **147** by Ti(III). Yields observed were 36-96%, and an identical range of yields was obtained when the alcohol starting material was replaced by various cyclic ethers.

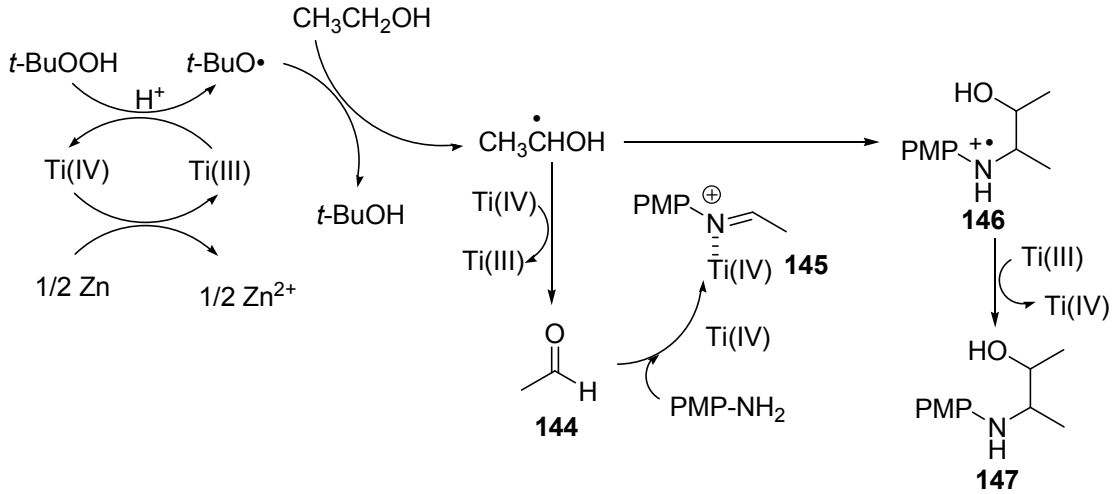


Figure 31. Ti-Mediated RPC Reaction Towards Aminoalcohols

Class A RPC Reactions: Anionic Intermediate

Perez-Luna has developed a synthesis of chiral substituted pyrrolidines[58] and dihydrofurans[59,60] through the use of dialkylzinc or alkyl-, vinyl- or arylcopper-zinc reagents in RPC domino 1,4-addition-carbocyclization reactions (Figure 32). The zinc reagent first adds an alkyl or aryl substituent radically to the double bond of an α,β-unsaturated ester such as **148**. The resulting radical **150** adopts a pseudo-envelope orientation as shown, and a 5-*exo*-cyclization then occurs stereoselectively. The reaction proceeds through an organozinc intermediate **153** which acts as a pseudo carbanion on electrophilic species such as acids, iodine, and allyl bromide. Yields of 42-87% are obtained with a wide range of dr, sometimes exceeding 95:5.

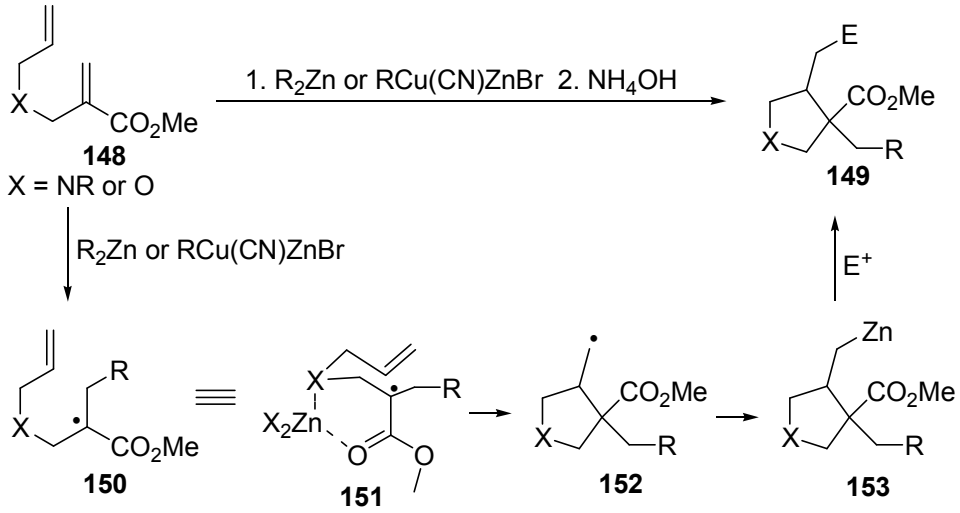


Figure 32. Mechanism of Zn-Mediated RPC Reaction Towards Heterocylces

Zinc enolates are used in aldol condensations by Bertrand, and the method has been expanded to include a subsequent lactonization step (Figure 33). Diethylzinc in the presence of oxygen is used to create a carbon-centered radical from an alkyl halide in solution (*tert*-butyl iodide in the example shown). After addition of the radical to chiral *N*-enoyloxazolidinones, a zinc enolate forms which is free to attack an internal[61] or external carbonyl.[62] A second nucleophilic step then occurs where organo-zinc species **159** undergoes an intramolecular cyclization to give a mixture of isomers of **155**. Surprisingly, upon removal of the auxiliary in use, lactone **156** was obtained as a single isomer.

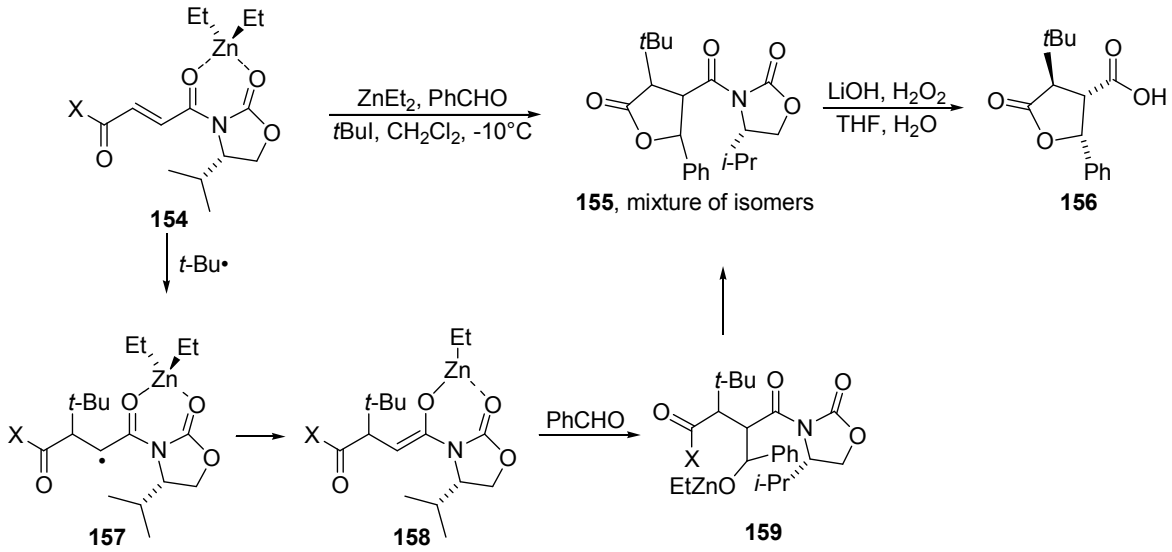


Figure 33. Zn-Mediated Aldol Condensation RPC Reaction

Bicyclo[3.3.0]octan-1-ols and bicyclo[3.2.1]octan-1-ols can be synthesized through a zinc-mediated RPC dual annulation reaction (Figure 34).[63] The starting iodides are transformed through a one-electron reduction by zinc and subsequent attack of carbon monoxide. The resulting acyl radical **163** cyclizes onto an internal alkene, leaving a radical **164** which adds to acrylonitrile. An α-cyano anion is produced after reduction of the α-cyano radical by zinc, and this adds to an internal carbonyl group to give alcohol **161**. Acrylonitrile can be replaced by an α,β-unsaturated ester as well. Yields obtained ranged from 43-71% with *exo*/*endo* ratios of 50:50 to 61:39.

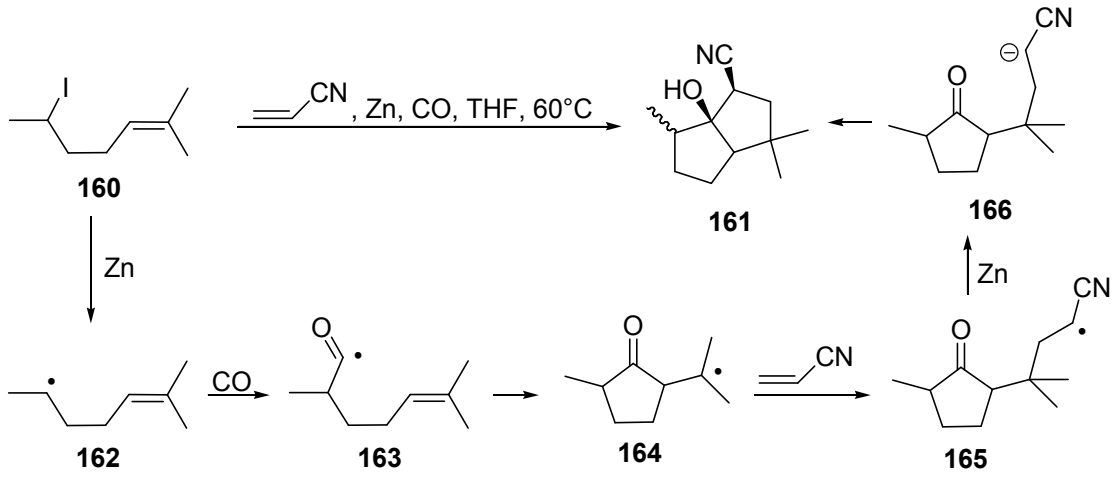
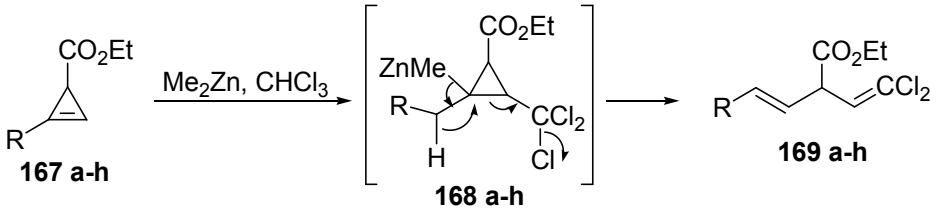


Figure 34. Mechanism of Zn-Mediated RPC Dual Annulation Reaction

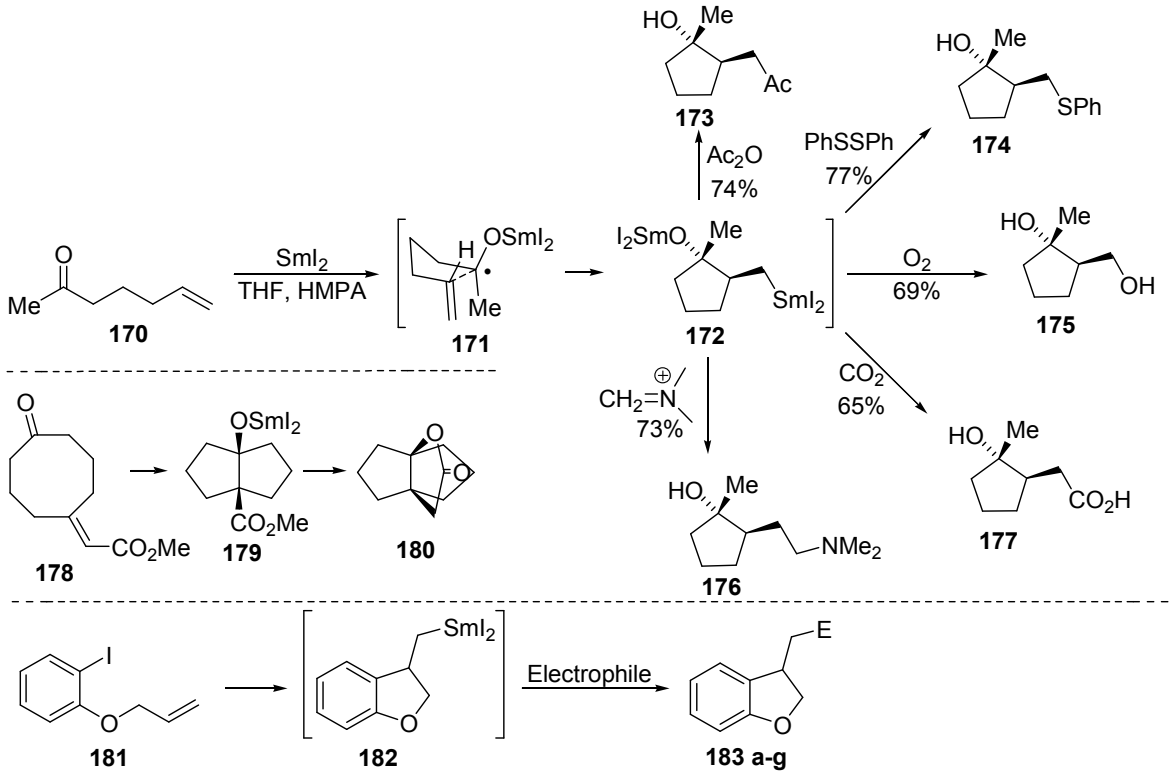
Masafumi recently published a Zn-mediated RPC reaction to produce unconjugated dienes **169 a-h** (Figure 35).[64] The method is initiated by dimethylzinc to create a trichloromethane radical from chloroform. This is a more economical generation of the radical than halogen abstraction from carbon tetrachloride or bromotrichloromethane. The trichloromethane radical adds to the double bond of a cyclopropene ring in compounds **167 a-h**, and zinc combines with the resulting radical to create a carbanion such as **168 a-h** which participates in a rearrangement and ring opening to give an unconjugated diene **169 a-h**. Yields range from 54-74% with various R groups on the starting cyclopropene ring.



R = *n*Pr,*n*-heptyl, Bn,*i*-Pr, *t*Bu, *c*C_5H_9, *c*C_4H_7, *c*C_6H_{11}

Figure 35. Zn-Mediated RPC Reaction Towards Unconjugated Dienes

Molander composed a review of sequenced reactions mediated by samarium (II) iodide, SmI_2, and although they are not referred to as such, many constitute RPC reactions.[65] The top half of Figure 36 illustrates the SmI_2-mediated formation of a ketyl **171**, which undergoes intramolecular cyclization onto an olefin, leaving an external radical which is reduced by SmI_2 (**172**) and can be trapped by various electrophilic species to give products such as **173-177**. Stereoselectivity arises from the ketyl adopting a pseudo-envelope orientation with the olefin and ketyl oxygen in *trans* orientation as shown, presumably to avoid electronic repulsion.[66] When a cyclic ketone is used, bicyclic products can be produced. A tricyclic lactone **180** has also been produced starting from an eight-membered lactone with an external ester group. The bottom half of Figure 36 involves an initial aryl radical formation from an aryl halide **181**, which likewise cyclizes to give a radical which can be trapped by electrophiles. Curran has used this approach for the synthesis of the BCD ring system of the penitrem family of natural products.[67]



E = (*i*PrCO)$_2$O, I_2, PhSeSePh, $CH_3CO(CH_2)_3NEt_2$, PhSSPh, Bu_3SnI, PhNCO

Figure 36. SmI_2-Mediated RPC Reactions Towards Various Cyclized Products

A three-component coupling of alkyl iodides, olefins, and carbonyl compounds can be carried out under a manganese-lead(II) chloride catalytic system (Figure 37).[68] A carbon-centered radical is generated from an alkyl iodide such as **184 a-c**, and this adds to an electron deficient olefin such as **185 a** and **b**, leaving a radical which is quickly reduced to an anion of type **186** by the catalytic system and subsequently adds to a carbonyl. Yields of 61-96% with diastereomeric ratios of 41:59-68:32 were obtained with various substituents on each component of the three-component system. Takai has also applied this method to sequential 1,4-addition and Ireland-Claisen Rearrangement reactions of acrylate compounds **190**.[69] Good to excellent yields were obtained with *E/Z* ratios of the rearrangement products exceeding 99:1 in most cases.

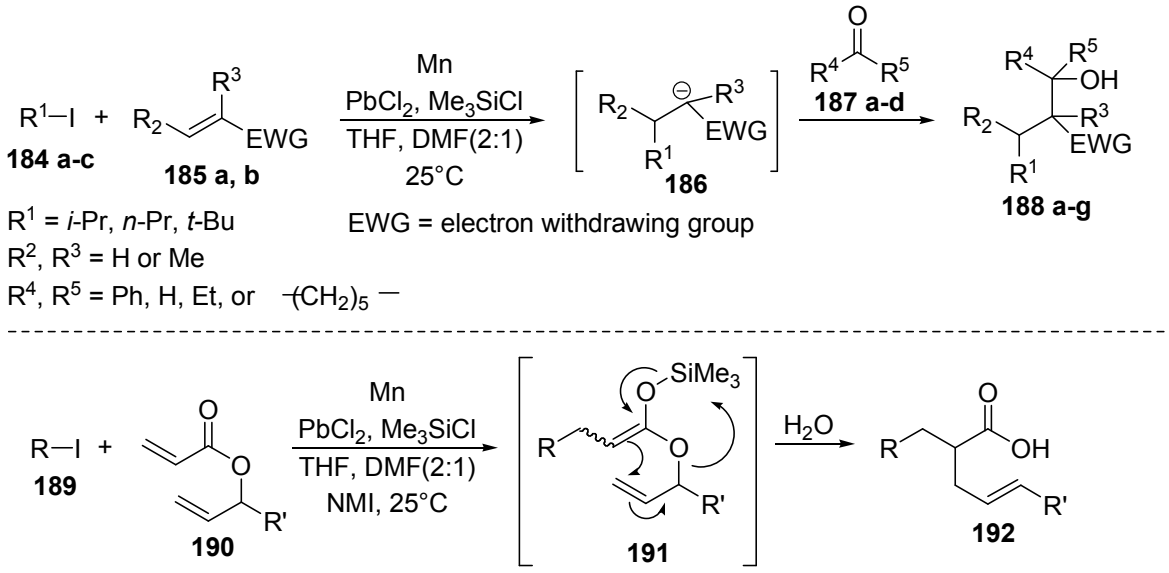


Figure 37. Mn-Pb(II)-Mediated RPC Multicomponent Reactions

Another three component reaction can be seen below (Figure 38). This RPC reaction is mediated by triethylborane (Et_3B), and brings together *O,Te*-acetals such as **193**, α,β-unsaturated cyclic ketones such as **194 a-c**, and either aldehydes or ketones **195 a-d**.[70] Three stereocenters are set in this one-pot reaction that has been applied to the synthesis of the complex substructures of the terpenoid natural products. Yields range from 22-99%, and the stereoselectivity can be explained by the chair-like transition state. The initial bridgehead radical of the acetal adds to the double bond of the α,β-unsaturated ketone, leaving a radical intermediate which is quickly reduced to the boron enolate of type **196 a-g**. When the electrophilic aldehyde or ketone **195 a-d** approaches the enolate, a chelate is formed on the face of the enolate opposite the bulky trioxadamantane group, and this leads to a *trans*-relationship between the trioxadamantane and the resulting alcohol in the product.

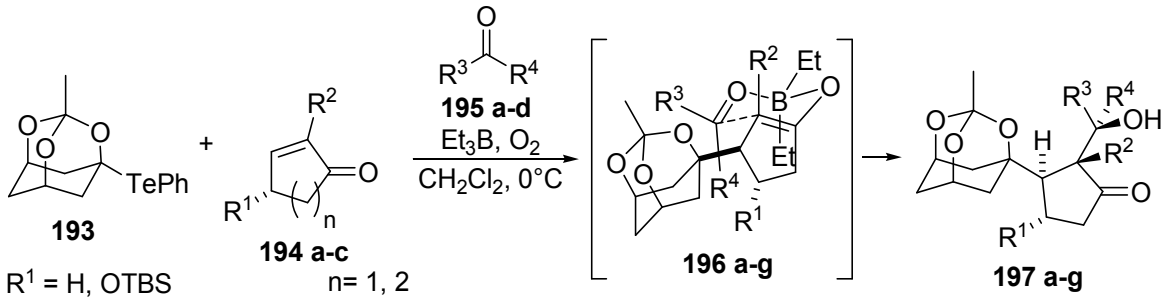


Figure 38. Et_3B-Mediated RPC Reaction Towards β-Trioxatricyclodecyl-β'-hydroxyketones

Naito used Et_3B in combination with the Lewis acid BF_3•Et_2O for the synthesis of substituted pyrrolidines and piperidines (Figure 39).[71] Radical addition of an alkyl halide to *N*-oxime ethers **198** is followed by formation of nucleophilic borylamine functionality shown in **199**, which cyclizes onto an internal electrophilic tosylate group. Yields of 13-80% were obtained with the use of various alkyl halides. Pyrrolidinone and piperidinone rings were formed when the internal electrophile consisted of an ester group instead of a tosylate. Higher yields were obtained in these cases (65-95%). The method was also applied to the formal synthesis of indolizidine alkaloids which have potent biological activity in neuroscience.

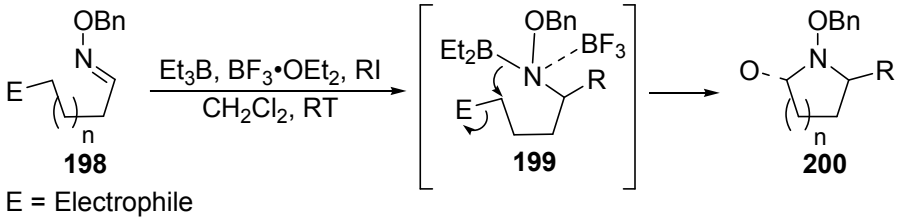


Figure 39. Et_3B-Mediated RPC Reaction Towards Nitrogen Heterocycles

A similar reaction, starting with aryl hydrazones such as **201**, yields isoindolinone formation shown in **202** in 30-90% when various alkyl halides and aromatic substituents are incorporated (Figure 40).[72] With the use of a chiral auxiliary, dr ranged from 53:47-90:10.

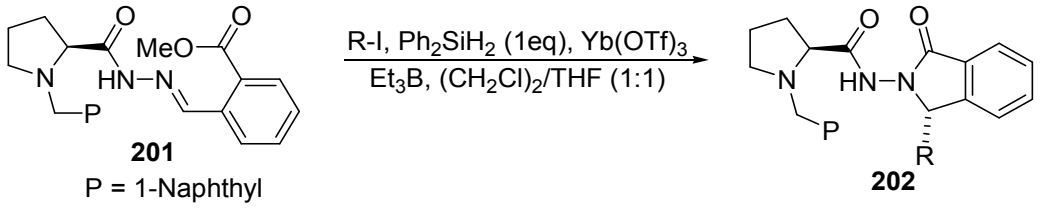


Figure 40. Et_3B-Mediated RPC Reaction Towards Isoindolinones

Godineau published three- and four component Et_3B-mediated RPC reactions towards substituted piperidinones (Figure 41).[73] An initial carbonyl-substituted radical adds to an olefin, generating a second radical **209** which adds to a sulfonyl oxime **205** in solution. Since the second radical addition step is followed by β-fragmentation of the sulfonyl group, a neutral oxime **210** is left which is subsequently attacked either radically through the addition of an alkyl halide to the reaction mixture, or ionically with the use of an organometallic species **206**. A nucleophilic amine moiety such as shown in **211** is left after either addition type (in the form of a borylamine in the case of radical addition), and this cyclizes onto an internal ester to give the final product. Yields range from 43-58% with various olefin starting materials, and diastereomeric ratios of 60:40-98:2 were obtained.

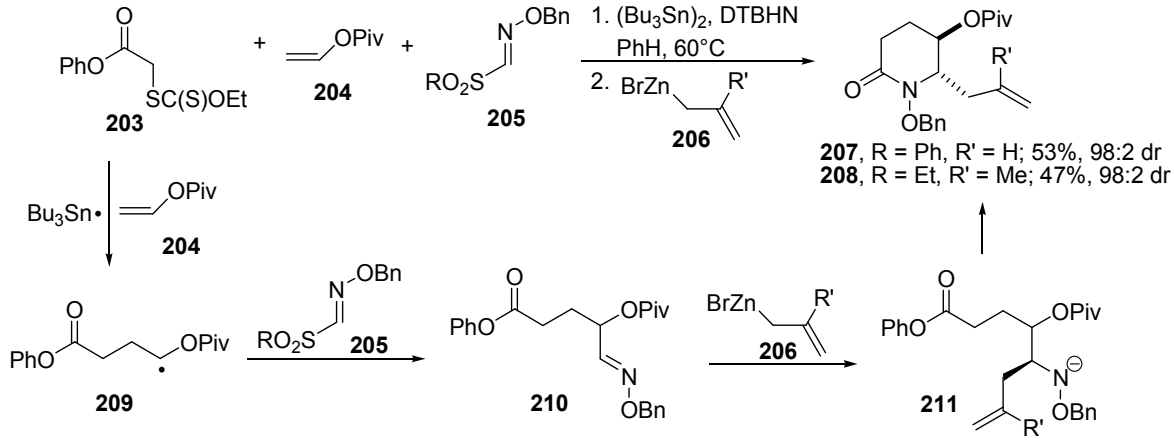


Figure 41. Piperidinone Synthesis via Radical-Polar Crossover Reaction

Pyrrolidinone-fused dihydrobenzofurans have been synthesized using a Et_3B-mediated RPC reaction (Figure 42).[74] The first step involves radical addition of an ethyl group from Et_3B or *t*-butyl group from *t*-butyl iodide to an α,β-unsaturated *O*-aryl oxime ether such as **212**. The resulting aminyl radical is reduced to an *N*-boryl enamine **215**, which undergoes a [3,3]-sigmatropic rearrangement and subsequent cyclization to give a dihydrobenzofuran ring shown in **216**. The sigmatropic rearrangement proceeds through a six-membered transition state that minimizes the steric repulsion between the *t*-butyl and phenyl groups. The nucleophilic *N*-

boryl enamine is left intact in **216** after this transformation, and it attacks an internal ester to give a pyrrolidinone moiety as shown in *cis*-**213**. The transition state for the initial cyclization which gives the dihydrobenzofuran moiety in **216** exists in equilibrium between the *cis* and *trans* forms. The equilibrium is pushed toward the *cis* form as shown by the irreversible lactamization that follows since the *cis* form leads to the sterically favored *cis*-fused tricyclic product. Yields of 22-98% were obtained when substituents on the aromatic ring were varied. Oppolzer's camphorsultam chiral auxiliary was shown to direct the stereochemistry of the initial radical addition step in one case, leading to an ee of 93%.

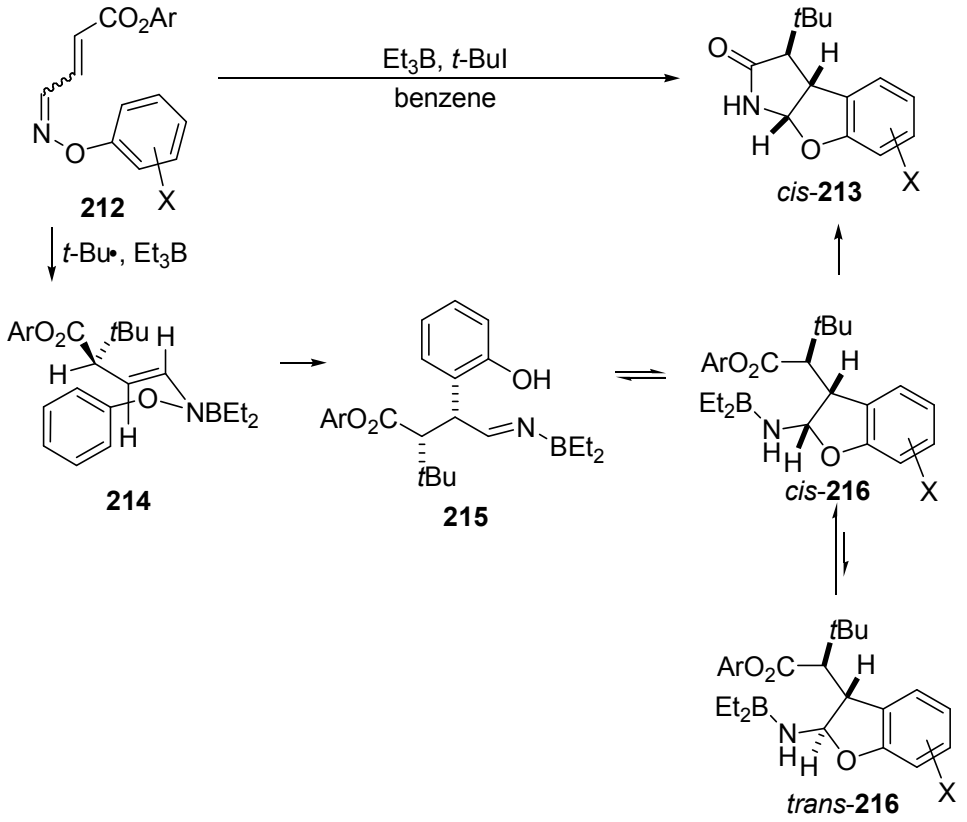


Figure 42. Et_3B-Mediated RPC Reaction Towards Dihydrobenzofuran Derivatives

An *N*-borylaminoallene intermediate is formed in Miyata's synthesis of furanone rings (Figure 43).[75] Radical addition of an alkyl halide to an alkynyl oxime forms the reactive intermediate which is used in a subsequent aldol-type reaction. When secondary and tertiary alkyl halides are used, transition state **221** is favored in the aldol-type reaction, leading to a borate **222** which cyclizes to give furanone products (borate **220** was undetected in reaction mixtures). Yields ranged from 63-93% with varying alkyl halide and aldehyde starting materials. A related synthesis produces dihydrofuranones.[76]

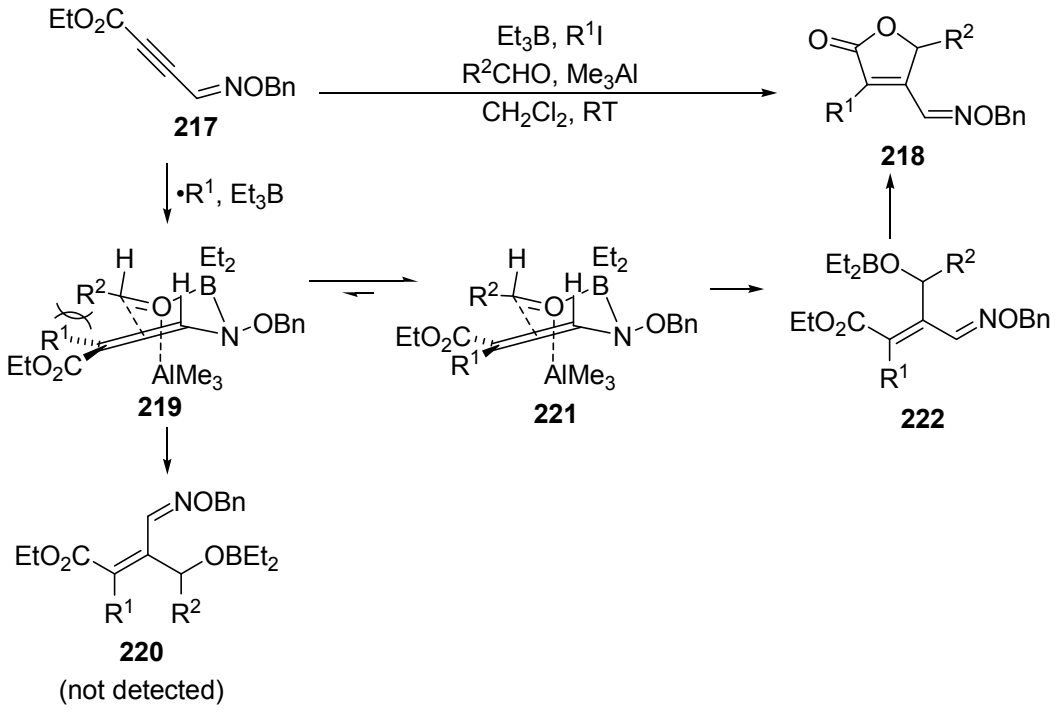


Figure 43. Et_3B-Mediated RPC Reaction Towards Furanones

A triethylaluminum-mediated (Et_3Al) RPC reaction was used in the total synthesis of (-)-acutumine by Castle (Figure 44).[77] Hexabutylditin was used in place of tributyltin hydride for the initiation of an aromatic radical from **223** to avoid reduction of the radical. After the aromatic radical adds to the internal olefin on the face opposite of the α protected alcohol, an aluminum enolate forms, and this is trapped by oxaziridine to give an alcohol on the enolate carbon. The oxaziridine molecule approaches the spirocyclic enolate on the face opposite of the bulky aromatic group to give **225** as a single diastereomer in 62% yield.

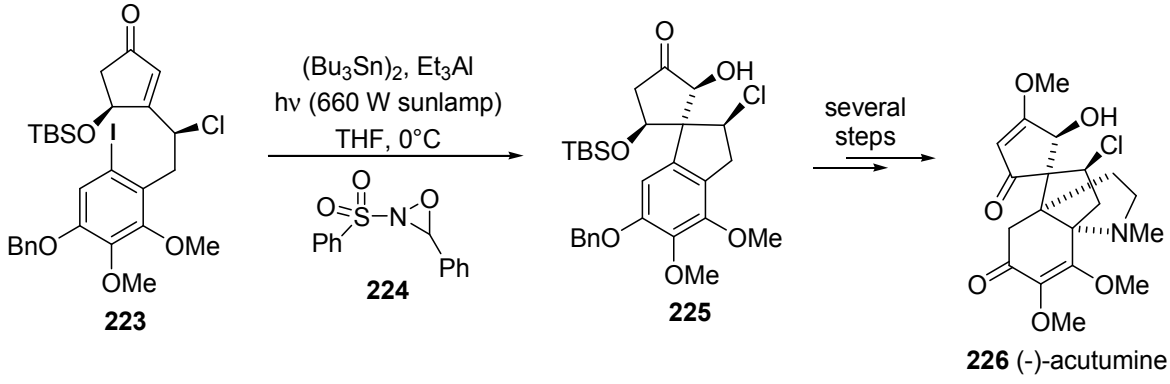


Figure 44. Et_3Al-Mediated RPC Reaction Towards (-)-Acutumine

Class C RPC Reactions: Neutral Intermediate

Ryu has developed an RPC reaction which involves free-radical carbonylation of terminal alkynylamines (Figure 45).[78] In the initial method, two products (α-methylene lactams and α-stannylmethylene lactams) were always formed in differing amounts, but with the addition of a protodestannylation step at the end of the sequence, α-methylene lactams formed exclusively in 59-71%. Initially, α-ketenyl radicals **228** are formed through the addition of a tributyltin radical to the terminal alkyne of an amine starting material, followed by incorporation of carbon monoxide. The amino group then cyclizes intramolecularly onto the ketene carbonyl. This step leaves the radical **229** intact, and this is quenched by a 1,4-H shift followed by β-elimination of tributyltin radical giving an α-methylene lactam **230**.

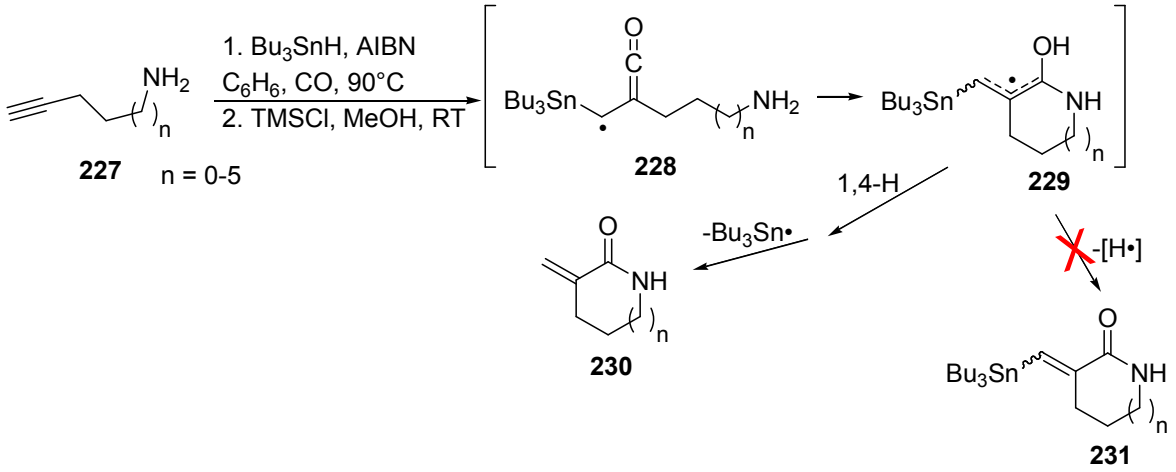


Figure 45. Tin-Mediated RPC Reaction towards Lactams

A Kornblum-DeLaMare rearrangement occurs as the polar step of an RPC reaction mediated by a cobalt-TBHP catalytic system (Figure 46).[79] This is a three component reaction which starts with the radical addition of a cyclic ether **232** to an electron-deficient olefin **233**. The resulting radical **237** adds to an electron-rich vinylarene **234**, and the benzyl radical product of this is trapped by a *t*-butyl peroxide radical as shown (originating from TBHP). After base-catalyzed rearrangement, a polyfunctionalized carbonyl compound **235** is formed. The scope of all three components of the reaction was investigated, and yields of 33-83% were obtained.

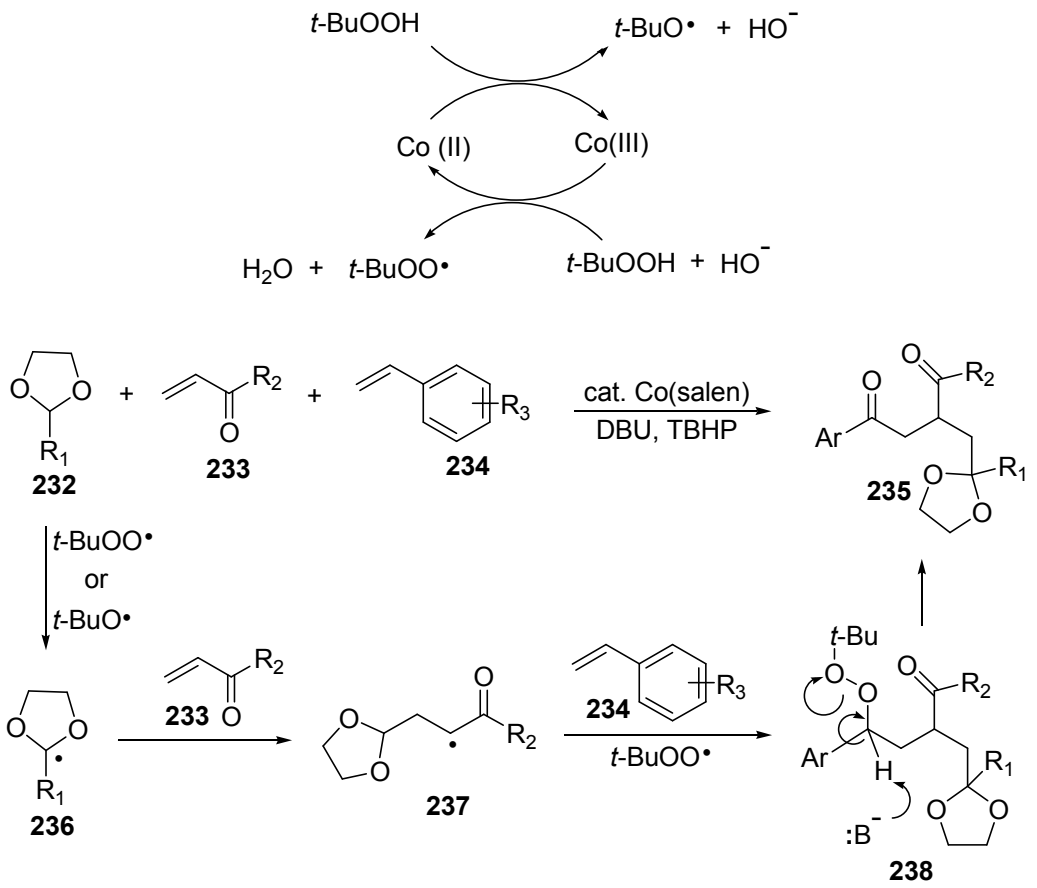


Figure 46. Co-Catalyzed RPC Reaction towards Polyfunctionalized Carbonyl Compounds

Polar-Radical Crossover Reactions

Jahn has developed RPC reactions mediated by ferrocenium salts wherein the polar step precedes the radical step. The polar step consists of generating an enolate **242** from a malonate or ester starting material such as **239** with the use of a strong base (Figure 47). **242** is then oxidized to an α-carbonyl radical **245** through a SET to a ferrocenium salt, usually ferrocenium hexafluorophosphate **243**. An intramolecular radical cyclization then occurs to create a cyclic product **246** which can usually be further derivatized to useful organic molecules. In this manner, mono-[80] and more highly substituted[81] cyclo-dicarboxylates have been generated by the RPC method and further reacted to produce bicyclic lactones. Likewise, N,3,4-trisubstituted[82] and N,2,3,4-substituted[83] pyrrolidines created by the RPC method were used to yield bicyclic lactones. Disubstituted cyclopentane-dicarboxylates were produced and taken on to dihydronepetalactone structures.[84] Finally, the RPC reaction was used to generate trisubstituted cyclopentane

carboxylates which were transformed into the cyclic core of prostanes.[85] This methodology was applied to the synthesis of 15-F_{2t}-isoprostane, which is a cyclic derivative of arachidonic acid and diastereomeric to the enzymatically formed prostaglandins.[86] It was also used in a study toward the elucidation of the metabolism of 15-E_2-isoprostane by synthesis of a methyl ester of a potential metabolite of the natural product.[87] Recently, this type of transformation was made more efficient through the use of ferrocenium salts with electron withdrawing substituents attached to increase their oxidation potential.[88]

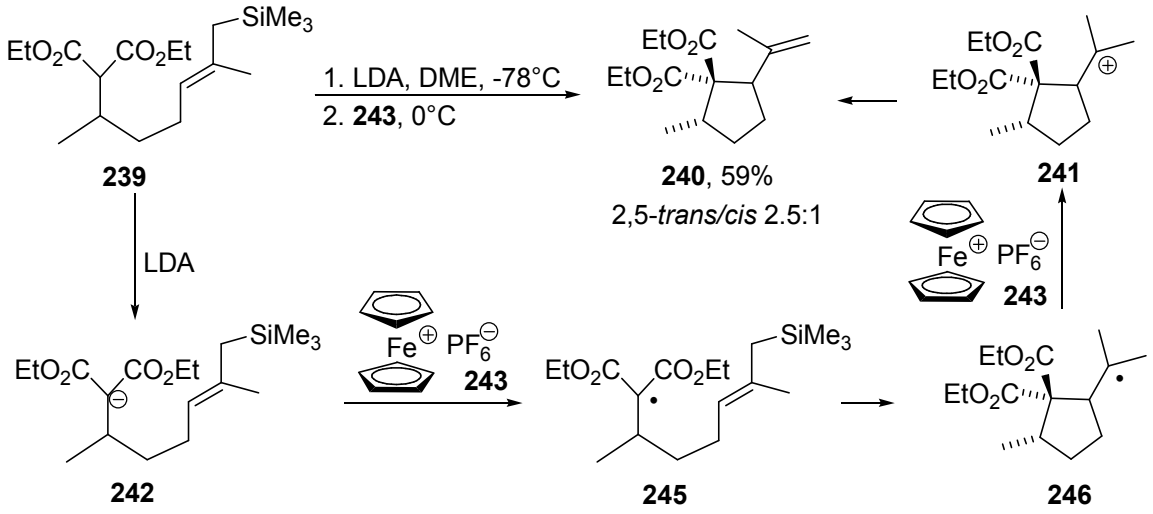


Figure 47. Ferrocenium Salt Mediated RPC Reaction towards Substituted Cyclopentane

The Molander review on SmI_2 mentioned earlier also features RPC reactions where the polar step precedes the radical step.[65] These reactions begin with a nucleophilic acyl substitution mediated by SmI_2 as shown, and then subsequent radical transformations occur to ultimately create five- and six-membered carbon or oxygen containing polycyclic ring systems such as **255**-**259** (Figure 48).

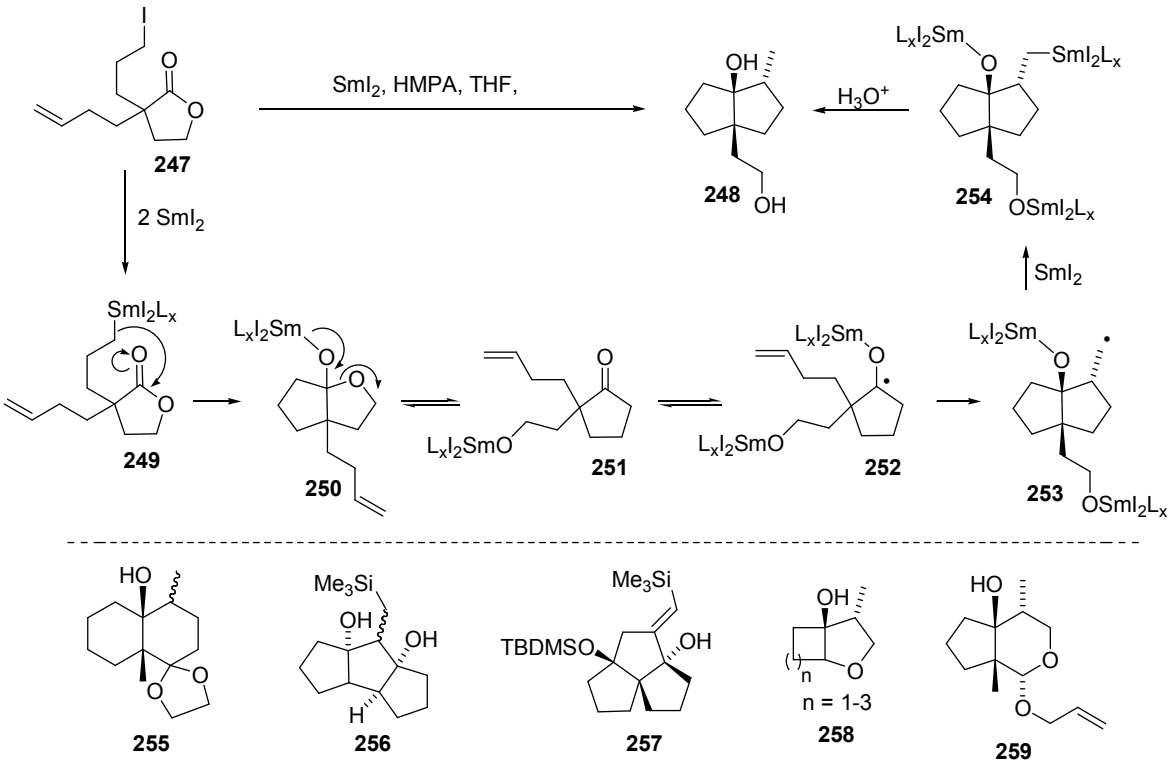


Figure 48. SmI_2 Mediated RPC Reaction Towards Polycyclic Ring Systems

Recently, Ragains has developed a polar-radical crossover reaction which proceeds through a radical translocation and ultimately accomplishes a remote hydroxylation or methoxylation of unactivated sp^3-hydridized C-H bonds (Figure 49).[89] The reaction begins with the acid-catalyzed generation of an arenediazonium salt from a Tzº sulfonate ester or Tzº sulfonamide. A subsequent SET from an iridium photocatalyst in its excited state furnishes an electron-poor aryl radical which is translocated to an alkyl radical through 1,6- or 1,7-hydrogen atom transfer. This radical then transfers an electron to either the iridium photocatalyst which is now in its oxidized state, or to another equivalent of the arenediazonium salt to create a carbocation intermediate. The latter transfer would give rise to a chain reaction as shown. The carbocation finally undergoes solvolysis with water or methanol to create 2º or 3º alcohols or ethers in 27-63% yield.

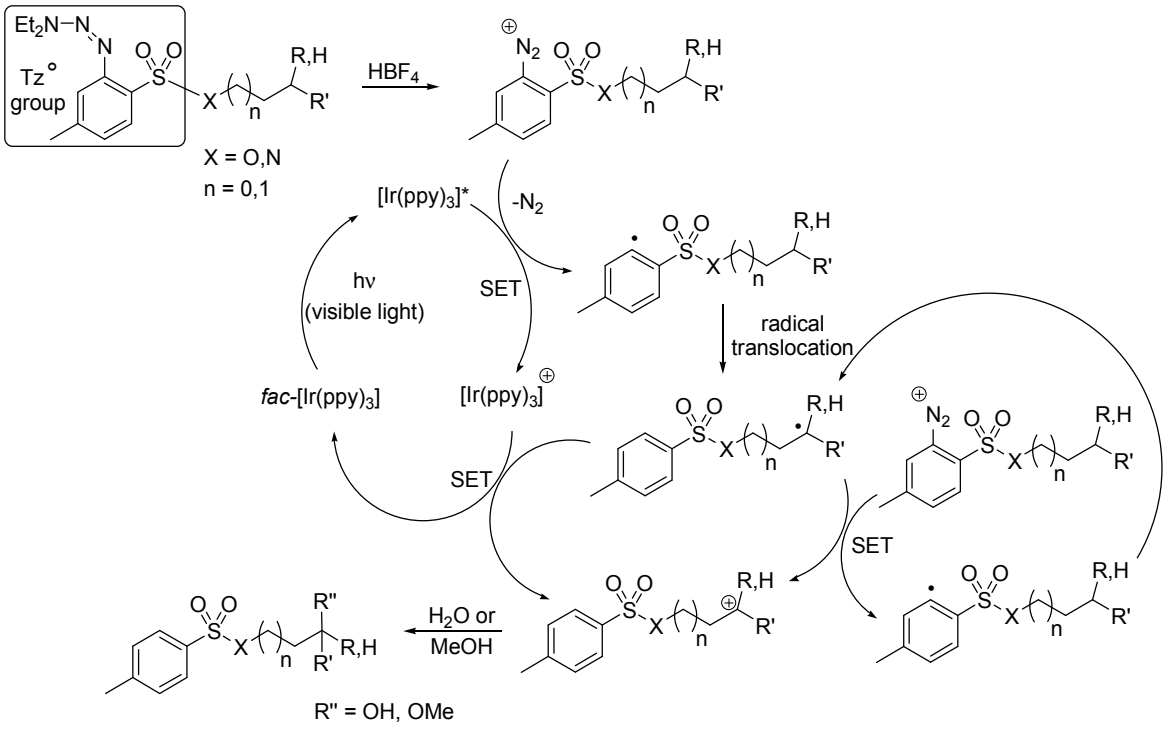


Figure 49. Irridium-Mediated RPC Reaction Towards Remote Hydroxylation

Synthesis of Five and Six Membered Nitrogen Heterocycles

Numerous strategies for the asymmetric synthesis of nitrogen heterocycles can be found in the literature today. Syntheses of five- and six-membered nitrogen containing rings, specifically pyrrolidines and piperidines, are of particular interest for comparison to the Mn-mediated RPC annulation that will be described in the subsequent chapter. Several reviews have been compiled in recent years which summarize methods towards the asymmetric synthesis of pyrrolidine and piperidine moieties, and many newer examples have since been added to the literature.[90-95]

Nitrogen Heterocycles by Carbon-Nitrogen Bond Formation

Many synthetic methods involve nucleophilic attack of an electrophilic group by a nucleophilic nitrogen to close the ring, creating either a pyrrolidine or piperidine structure depending on the number of carbon atoms in the chain connecting the reactive termini. One such strategy is shown below (Figure 50) and makes use of a nucleophilic nitrogen in compounds such as **260** and **261** for intramolecular

attack of a carbon-carbon double bond (C=C).[96] A lanthanide lithium ate complex **263** is used in this hydroamination to provide moderate stereocontrol. When additional lanthanide complexes were used, lower values of ee were obtained (the absolute stereochemistry of the major enantiomer of the products were not determined).

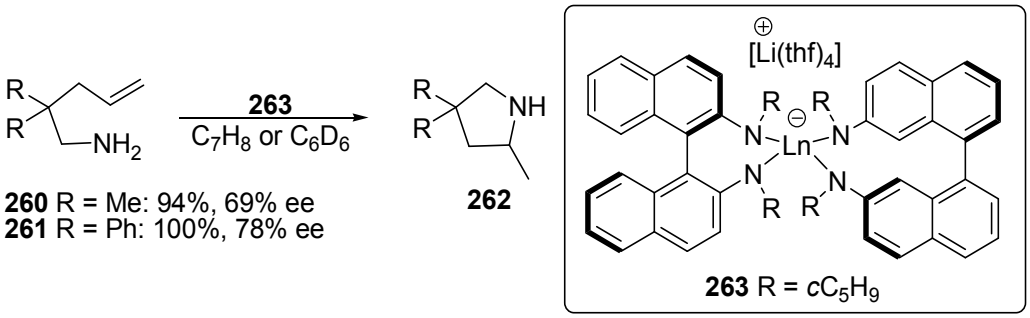


Figure 50. Pyrrolidine Synthesis by Nucleophilic Attack of Olefin (Hydroamination)

A similar strategy for the synthesis of nitrogen heterocycles such as **265** from bis-allylic carbonates such as **264** makes use of an iridium complex with ligand **266** to direct the stereochemical outcome (Figure 51).[97] Several pyrrolidines and piperidines were prepared in this manner with excellent yield and ee. Nucleophilic attack occurred first intermolecularly, followed by an intramolecular nucleophilic cyclization. Figure 50 and Figure 51 are two examples of many that use transition metal/chiral ligand complexes to create pyrrolidine and piperidine moieties through nucleophilic attack of an olefin.[98-103]

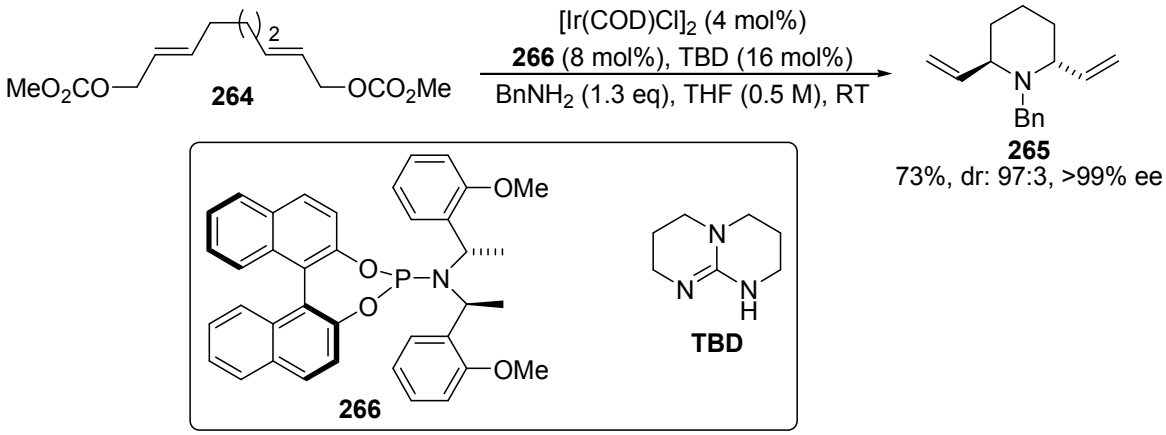


Figure 51. Piperidine Synthesis by Nucleophilic Attack of Olefin

Intramolecular epoxide opening by a nucleophilic nitrogen is shown below (Figure 52).[104] In this example, inversion during the SN_2 epoxide opening of the chiral starting material **267** sets the stereochemistry of the newly formed carbon-nitrogen

bond, and the epoxide is opened at the more substituted position as expected. Palladium on carbon is used catalytically to give a yield of 90% for **268**.

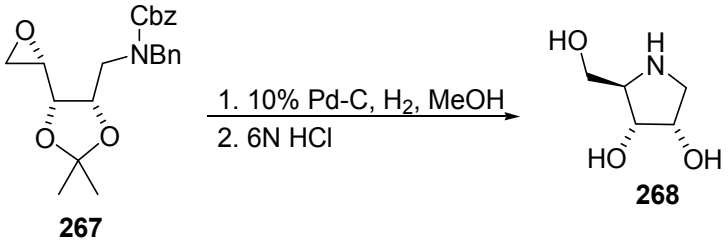
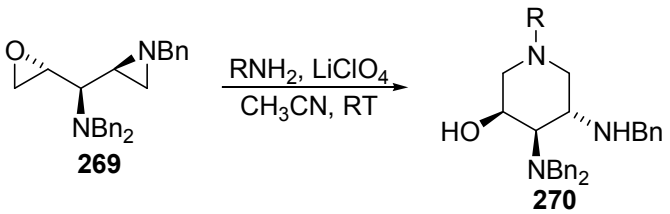


Figure 52. Pyrrolidine Synthesis by Nucleophilic Epoxide Opening

Another method which demonstrates epoxide opening to create a carbon-nitrogen bond is shown in Figure 53.[93] In this case, the first carbon-nitrogen bond is formed intermolecularly between starting material **269** and the primary amine in solution. An intramolecular carbon-nitrogen bond is next formed through an aziridine opening to give a chiral piperidine **270**. Yields ranging from 60-78% were achieved with various groups attached to the nucleophilic nitrogen.



R = *n*Pr, $CH_2CH{=}CH_2$, Bn, *c*C_6H_{11}, (*S*)-Ph(Me)CH

Figure 53. Piperidine Synthesis by Sequential Nucleophilic Epoxide and Aziridine Opening

Pyrrolidine formation by an SN_1 mechanism is seen in the total synthesis of the antibiotic (-)-codonopsinine **273** (Figure 54).[93] A prochiral carbocation is formed through an acid-catalyzed process and is stabilized by the neighboring aromatic group in **271**. Nucleophilic attack occurs intramolecularly in the *trans* orientation exclusively to give an 81% yield of **272**. A simple reduction reveals the final natural product structure.

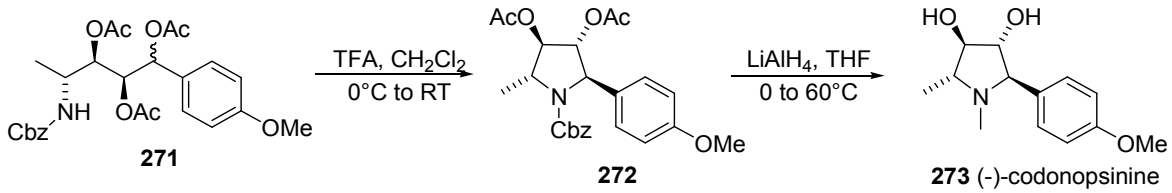


Figure 54. Pyrrolidine Synthesis by Nucleophilic Substitution (SN_1)

Several piperidine alkaloid natural products can be synthesized using double SN_2 attack on the meso diol building block **274** shown in Figure 55.[93] Here, an intermolecular attack by nitrogen is followed by an identical intramolecular attack to give the meso piperidine building block shown in **275**. This can be further derivatized to give alkaloids such as (-)-solenopsin A **276** and (-)-porantheridine **277**.

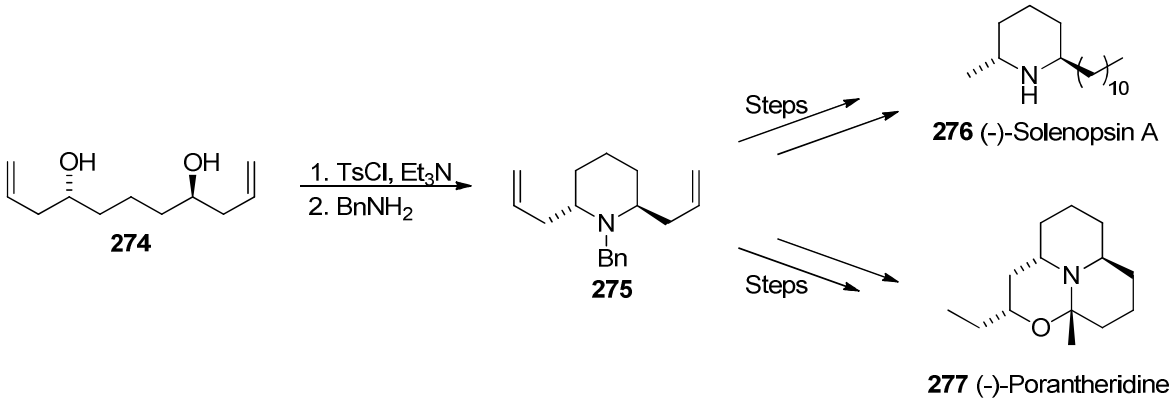


Figure 55. Piperidine Synthesis by Nucleophilic Substitution (SN_2)

Carbonyls are great electrophiles, and have been utilized as such for nucleophilic attack by nitrogen to create pyrrolidine and piperidine rings.[93] One example is shown below in the synthesis of pyrrolidine **279** (Figure 56). A remarkable 99% yield was achieved in this Lewis acid-catalyzed cyclization which proceeds through an *N*-acyliminium ion intermediate.

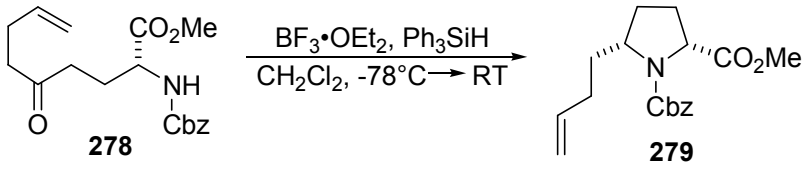


Figure 56. Pyrrolidine Synthesis by Reductive Amination

Piperidine synthesis by reductive amination can be seen below (Figure 57).[105] Palladium hydroxide in methanol was used to catalyze the process, and a yield of 78% was achieved in the substrate-controlled stereocontrol outcome shown. Piperidine **281** was converted to (+)-carpamic acid **282** after several subsequent steps.

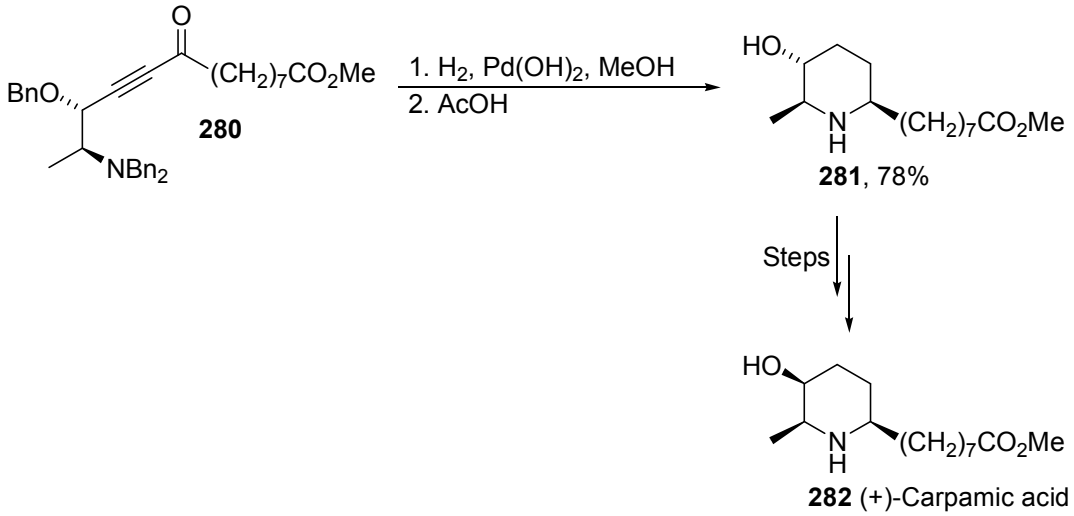


Figure 57. Piperidine Synthesis by Reductive Amination

Nitrogen Heterocycles by α-Carbon-Carbon Bond Formation

Expanding the synthesis of pyrrolidine and piperidine rings beyond nucleophilic attack by nitrogen to create a carbon-nitrogen bond, we see strategies in the literature which create the α-carbon-carbon bond of such ring systems. Shown below is the asymmetric synthesis of highly substituted piperidines such as **285** through the use of a Mannich-type reaction.[106,107] As seen in Figure 58, an imine **284** is formed *in situ*, followed by the formation of a pseudo-enolate by an acid-catalyzed process. The pseudo-enolate then attacks the imine carbon, creating the piperidine ring in **285**. The substituents in the 2nd and 6th positions of the ring are always in the *cis* orientation. The stereochemistry of the other positions can be set later on after the conversion of the piperidines to piperidones, followed by selective reduction to **286**.

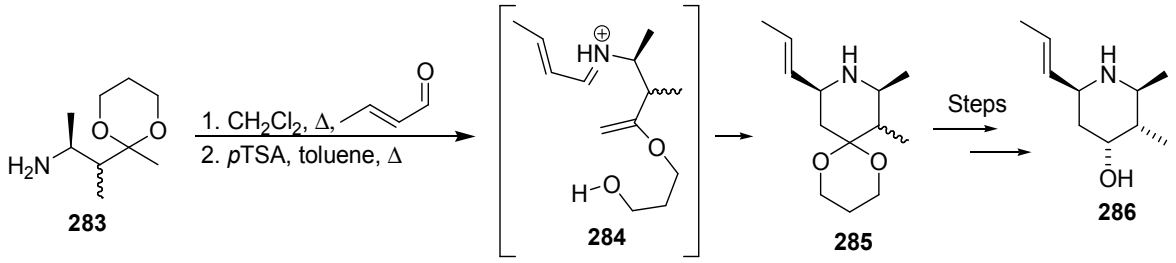


Figure 58. Piperidine Synthesis by Mannich-Type Reaction

Many pyrrolidine and piperidine natural products have been synthesized by the use of iminium ion cyclization strategies.[108] The Overman reaction, also known as an aza-Cope-Mannich reaction, is used in the synthesis of the antifungal agent (+)-preussin **9** (Figure 59).[109] Oxazolidine **287** was first synthesized from *N*-Cbz-(*S*)-phenylalanine in four steps, and then subjected to reaction with camphorsulfonic acid (CSA) to induce the aza-Cope-Mannich rearrangement which proceeds through an iminium ion intermediate **288** as shown. After three additional steps, (+)-preussin was obtained in 11% overall yield with approximately 83% optical purity.

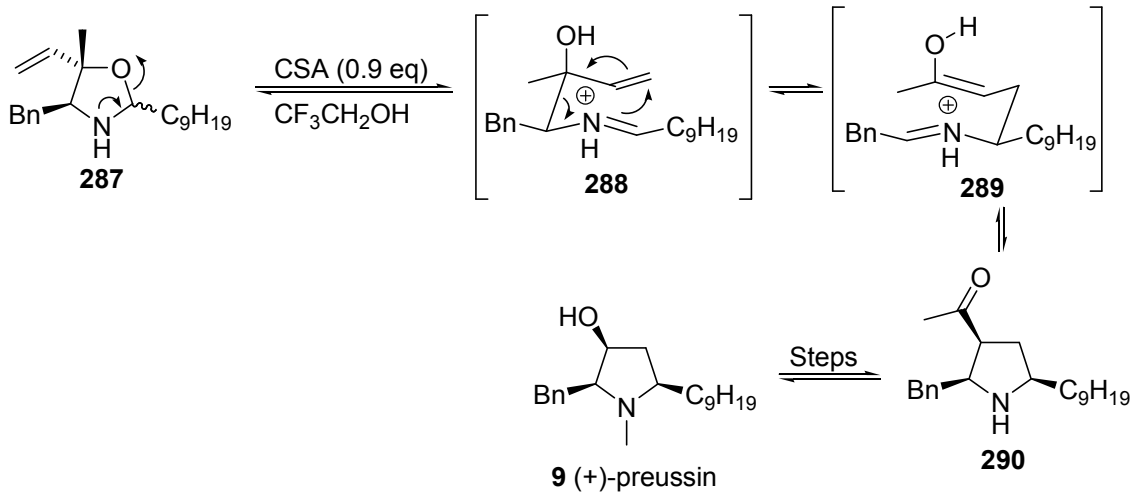


Figure 59. Pyrrolidine Natural Product Synthesis by Iminium Ion Cyclization

Charette has expanded on his dialkylzinc addition methodology to include a cyclization resulting in pyrrolidine and piperidine derivatives such as **294** and **295** (Figure 60).[110] In this example, an *N*-phosphinoyl imine is generated *in situ* upon addition of diethylzinc to sulfinic acid adducts of *N*-phosphinoyl imines such as **292**. After addition of a second equivalent of diethylzinc to the carbon atom of the imine bond, the nucleophilic nitrogen of the former imine bond intramolecularly cyclizes onto an electrophilic carbon atom either four or five bonds away. Stereocontrol is brought about by the use of a copper catalyst with an attached chiral ligand. An ester was also successfully used as the intramolecular electrophile for cyclization.

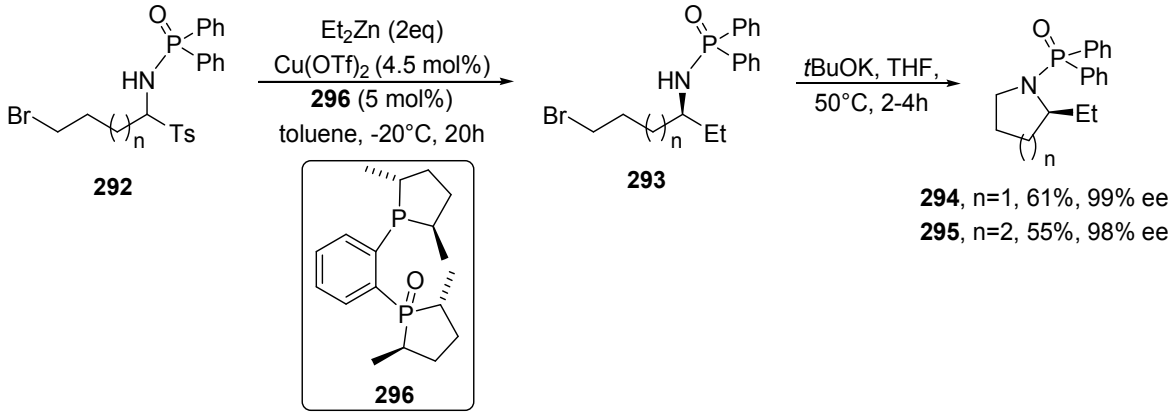


Figure 60. Pyrrolidine/Piperidine Synthesis by Carbanion Addition/Nucleophilic Cyclization

Highly substituted pyrrolidines such as **300** can be synthesized through 1,3-dipolar cycloaddition reactions (Figure 61).[111] This versatile approach exhibits moderate to high yields with a high ratio of endo to exo product and excellent ee. Many have contributed to the scope of this methodology resulting in the successful use of beta-substituted α,β-unsaturated esters, enones, nitroalkenes, α,β-unsaturated sulfones and fullerenes as dipolarophiles; and α -iminoesters, azlactones, α-iminophosphonates, α-iminonitriles, and *N*-(2-pyridylmethyl)imines as dipole precursors. In all cases, a metal catalyst with an attached chiral ligand chelates to the imino nitrogen of the dipole precursor **297** and the heteroatom three bonds away to create a rigid five-membered complex as shown in **298**. This makes the α-position of the dipole precursor more acidic and also allows for the excellent stereocontrol.

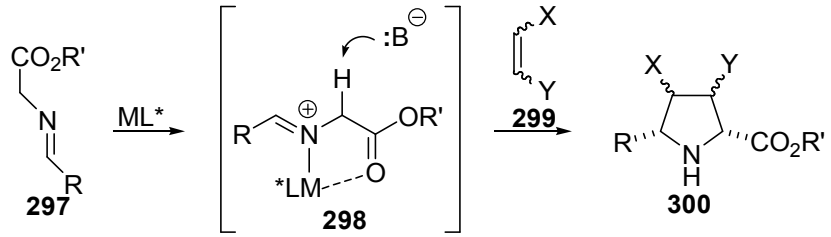


Figure 61. Pyrrolidine Synthesis by 1,3-Dipolar Cycloaddition

A titanium(III)-mediated radical cyclization was reported by Chakraborty, et. al., yielding substituted pyrrolidine and piperidine rings (Figure 62).[112] The piperidine **302** was obtained in 40% yield when the starting material consisted of an unprotected alcohol and the identity of R was a methyl group. The absolute stereochemistry of **302** was established by single-crystal X-ray analysis. Only a 20% yield was achieved in the case of pyrrolidine **303** from the starting material

consisting of a protected alcohol with the identity of R being a hydrogen atom. The acyclic byproduct **304** that was formed alongside **303** in 70% yield, however, could fortunately be converted to **303** in 70% yield by treatment with potassium carbonate in methanol. The pyrrolidine obtained from both methods showed a 4:1 ratio of isomers at the C3 position.

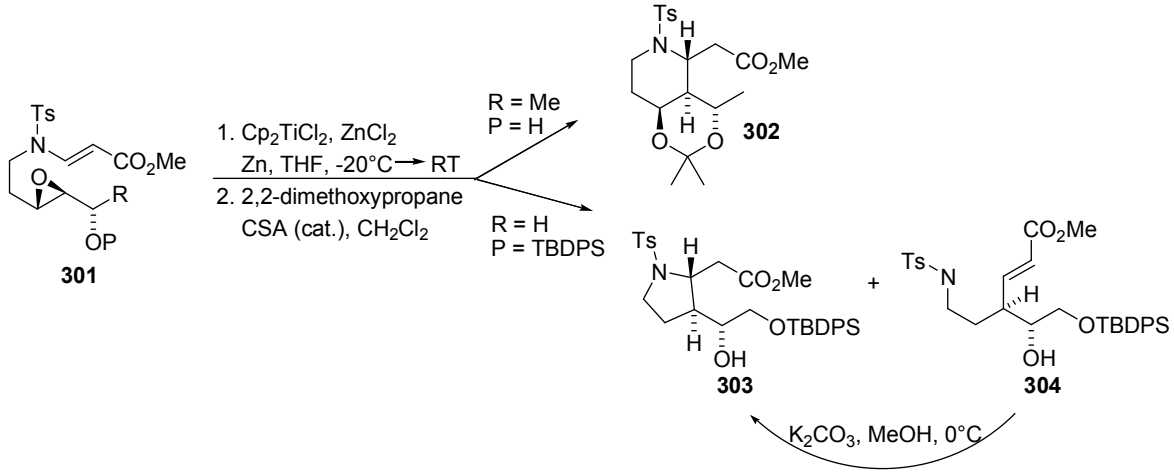


Figure 62. Pyrrolidine/Piperidine Synthesis by Ti-Mediated Radical Cyclization

The final strategy that should be presented as an example of current asymmetric syntheses of nitrogen heterocycles is the imino Diels-Alder reaction developed by Weinreb (

Figure 63).[113,114] Here, two bonds are constructed in one pot and a highly substituted piperidine ring is obtained after two subsequent steps. The diene shown started as a 4:1 mixture of *Z* and *E* isomers, and enone **307** was obtained in 60% yield as a 22:1 mixture of *cis* and *trans* isomers. The dienophile **306** can exist in *E* and *Z* isomers, and it is believed that the *cis* enone product resulted from reaction of the *Z* dienophile isomer. The major *cis* enone isomer was isolated and then subjected to reaction with vinylmagnesium bromide followed by reduction with L-selectride to give the piperidine **308** as a single stereoisomer. This approach was used in the total synthesis of the freshwater cyanobacterial heptatotoxin cylindrospermopsin.[115]

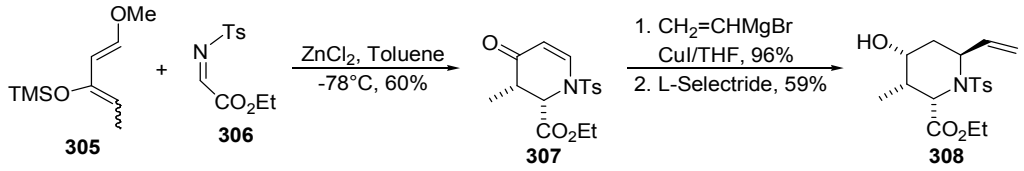


Figure 63. Piperidine Synthesis by Imino Diels-Alder Reaction

CHAPTER 3

A MANGANESE-MEDIATED RADICAL-POLAR CROSSOVER ROUTE TO CHIRAL SUBSTITUTED PYRROLIDINE AND PIPERIDINE RINGS

Introduction

The many representative examples of chiral amine, pyrrolidine, and piperidine synthesis in Chapter 2 give insight to understanding the limitations and advantages of the current synthetic methods toward these moieties, how they complement each other, and what is lacking in the literature. Our group has contributed much to the area of chiral amine synthesis through Mn-mediated radical additions to *N*-acylhydrazones, and we recognized the need for further development of this method[23-27,115,116] Towards this goal, research was completed on the topic of further testing the scope of the radical addition including optimization of an *in situ* subsequent cyclization which was discovered in the past[23] and which contributes to the field of RPC chemistry.

Background

As stated earlier, the synthesis of chiral amines through the addition of carbon centered radicals to imine derivatives has the advantages over carbanion addition methods of functional group tolerance and avoidance of aza-enolization of the imine starting material. Taking this further, the *Mn-mediated* radical addition of alkyl iodides (**RI**) to chiral *N*-acylhydrazones (Figure 64) has the additional advantages of avoiding the use of toxic and difficult to remove tin reagents commonly used in radical chemistry, and also the successful selective addition of complex primary radicals to the carbon of the imine bond. In this method, Mn_2CO_{10} is used stoichiometrically to initiate and carry the radical process to completion.

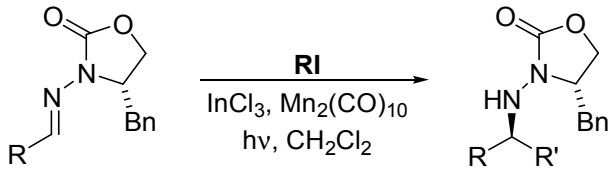
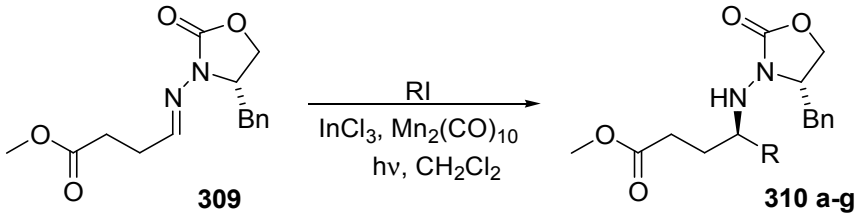


Figure 64. Chiral Amine Synthesis via Mn-Mediated Radical Addition to *N*-Acylhydrazones

Scope

Many alkyl iodides and *N*-acylhydrazones have been shown to give chiral amines in good yield and excellent selectivity through this approach. Hydrazones with R groups (Figure 64) consisting of hydrocarbon chains of multiple lengths (with or without α or β-branching),[23] or with ester, [27,116] halogen,[23,24,116] aromatic,[26,117] substituted cyclohexene,[116] and protected or free alcohol[116,117] functionality have been used. Likewise, alkyl iodides with R' groups consisting of hydrocarbon chains of multiple lengths (with or without α or β-branching),[23,27] or with halogen,[23,27,116] protected or free alcohol,[24,26,27,116,117] substituted cyclohexene,[116] or substituted cyclohexane[116] have successfully added to the imine carbon. This methodology has been applied to complex targets **310 a-g**, in synthetic studies of tubulysins[117] (Figure 65) and in a formal synthesis of quinine (Figure 67, later in text).[25,26,116]



R = *i*Pr, *s*Bu, $(CH_2)_4CH_3$, $(CH_2)_3OTBS$, $(CH_2)_3OH$, $(CH_2)_2OH$, $(CH_2)_3Cl$

Figure 65. Mn-Mediated Radical Addition in Synthetic Studies of Tubulysins

Stereocontrol

Diastereomer ratios exceed 95:5 in most cases due to the use of a chiral oxazolidinone auxiliary and the Lewis acid, indium (III) chloride, $InCl_3$ (Figure 66). A chelate is formed between the carbonyl oxygen of the oxazolidinone ring, the imine nitrogen, and the indium of $InCl_3$ as shown. This restricts rotation about the nitrogen-nitrogen bond of the hydrazone, creating a clear Si and Re face to the molecule. The Re face is blocked from nucleophilic radical attack due to the benzyl group of the oxazolidinone ring, and attack occurs primarily on the Si face. When bulky alkyl iodides are used, attack happens exclusively on the Si face (Figure 67).[116]

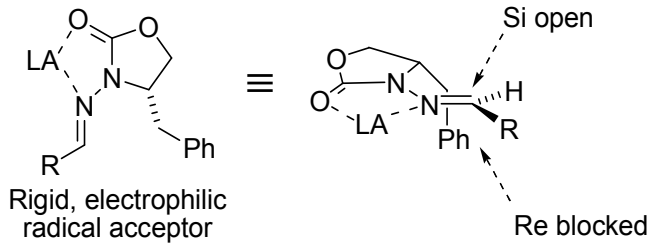


Figure 66. Stereocontrol Model for Radical Addition to *N*-Acylhydrazone

Yield and Use of Primary Radicals

In addition to directing stereocontrol, the auxiliary and $InCl_3$ also activate the imine bond towards nucleophilic radical attack at the carbon atom. Yields range from 30 to greater than 99%, with an average of 60% with the use of primary and secondary alkyl halides. It is remarkable to note that complex primary radicals are generated and successfully add to the imine carbon before being quenched by the reaction medium in this method. As seen in Chapter 2, most radical reactions only support the addition of simple primary radicals, mainly ethyl radicals from the use of Et_3B/O_2 as a radical initiator. An example of the complexity that is supported by this method can be seen below (Figure 67) in a reaction used toward the formal synthesis of the antimalarial natural product, quinine.[25] For this example, it is also important to note that only 1.25 equivalents of the iodide **54** were needed to achieve a 93% yield of desired product **55**. This shows one aspect of the synthetic utility of this approach to chiral amine synthesis, as starting materials in total synthesis schemes can be very valuable once they have been built upon by multiple transformations, and the need for a large excess late in a scheme is undesirable.

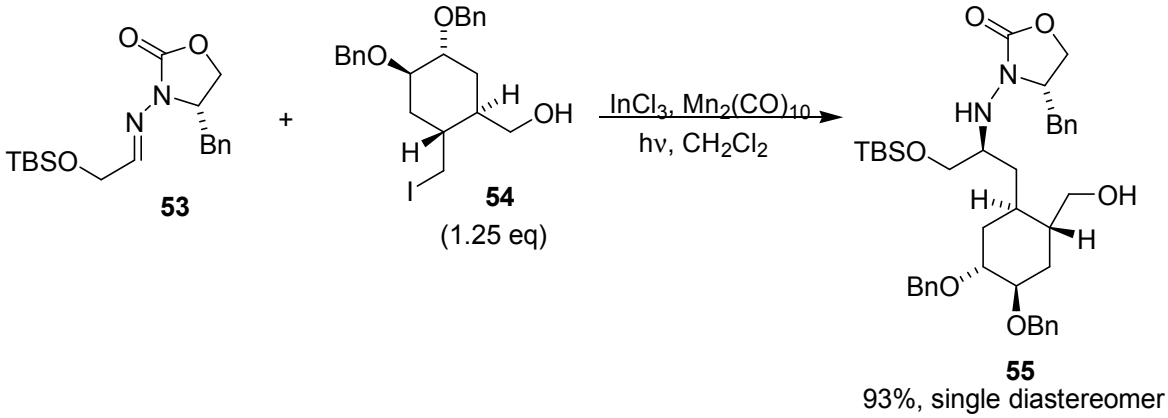


Figure 67. Complex Primary Radical Addition to *N*-Acylhydrazone

Mechanism

The Mn-Mn bond in $Mn_2(CO)_{10}$ can be homolytically cleaved under thermal or photochemical conditions.[118-121] The manganese pentacarbonyl radicals ($\cdot Mn(CO)_5$) that result have been shown to abstract hydrogen[122-124] and halogen atoms[125-129] from compounds in solution. In our method (Figure 68), $\cdot Mn(CO)_5$ are generated by 300nm light with the use of a Rayonet photoreactor. These radicals abstract an iodine atom from an alkyl iodide in solution, and the resulting carbon-centered radical ($R\cdot$) adds to the carbon atom of the imine bond in an *N*-acylhydrazone such as **37**. Finally, the resulting aminyl radical **311** is reduced to yield the desired chiral amine product. An organometallic addition route, labeled as path B below, is feasible, but has been ruled out by control experiments wherein organometallic species **312** and **313** replaced $Mn_2(CO)_{10}$ under the usual reaction conditions using propionaldehyde derived *N*-acylhydrazone **37**, and no reaction took place.[24]

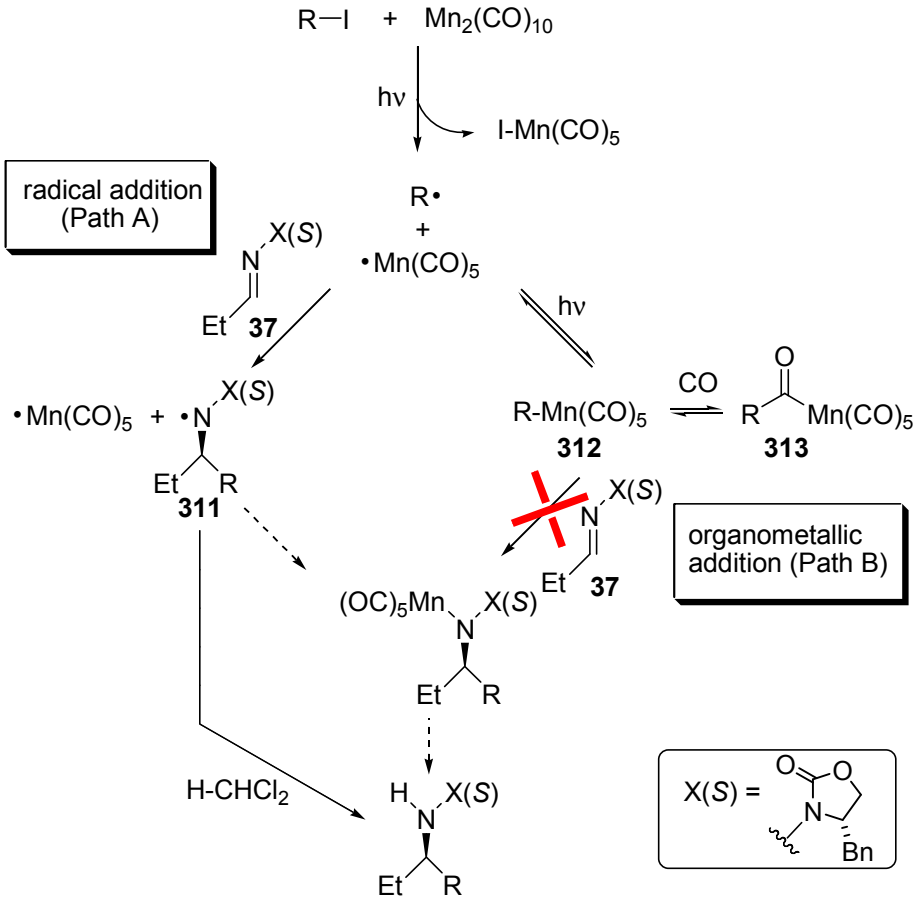


Figure 68. Mechanism of Mn-Mediated Radical Addition to *N*-Acylhydrazones

With the addition of a chloropropyl radical (derived from 3-chloropropyl iodide) to the propionaldehyde derived *N*-acylhydrazone **37**, a cyclized product **315** was obtained through an assumed RPC annulation (Figure 69).[23] As mentioned in Chapter 2, RPC reactions are valuable synthetic operations since they allow for the increase of complexity through multiple bond constructions (carbon-carbon and/or carbon-heteroatom) in one pot. This saves both time and money spent on workup, purification, and characterization steps compared to step-wise synthesis of bonds. Unlike other multi-component reactions, RPC reactions utilize two different types of reactive intermediates, radical and polar, which leads to a wider scope of application as can be seen in the earlier presented examples. Therefore, it became desirable to further develop this methodology leading to substituted chiral pyrrolidines such as **315**. Towards this goal, optimization studies were conducted, and the scope, versatility, and synthetic utility of the RPC annulation were investigated.

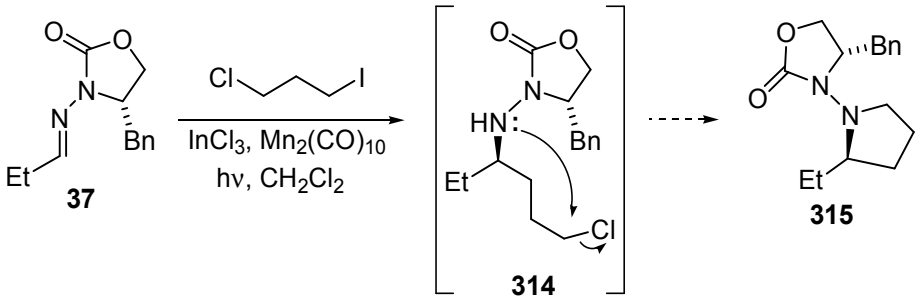


Figure 69. Discovery of RPC Annulation Towards Chiral Pyrrolidines

Further Test of Scope of Radical Addition to *N*-Acylhydrazones

Towards the goal of further testing the scope of the radical addition of alkyl iodides to chiral *N*-acylhydrazones mediated by $Mn_2(CO)_{10}$, hydrazones with α-methyl,[19] α-silyl ether, and α,β-unsaturation were prepared by condensation of amino oxazolidinone **319** with the appropriate aldehydes (Figure 70). The amino oxazolidinone **319** was prepared by initial reduction of L-phenylalanine **316**,[130] followed by condensation with diethylcarbonate[131] and final reaction with freshly prepared amine chloride. The *N*-acylhydrazones such as **320**, **321**, and **322** exclusively adopted the *E* geometry as shown.

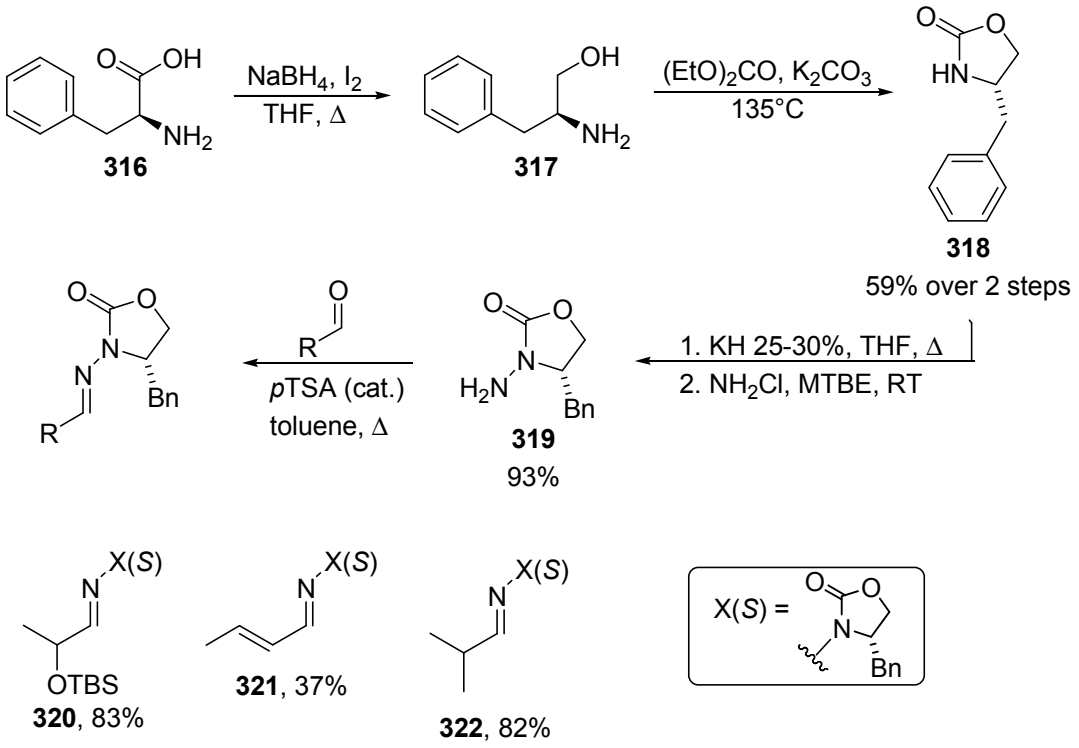


Figure 70. Preparation of *N*-Acylhydrazones

Isopropyl addition to α-branched hydrazones **323 a** and **b** gave modest yields (Figure 71), and it appeared they may be potential starting materials for the RPC annulation methodology.

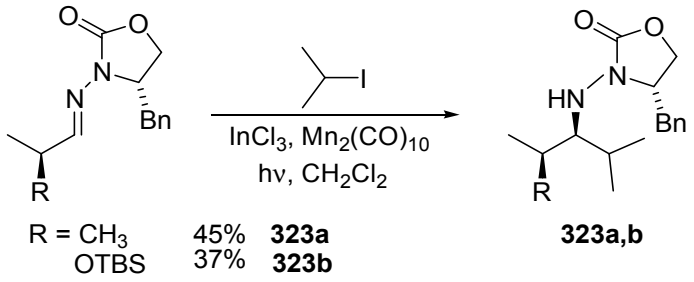


Figure 71. Isopropyl Addition to α-Branched *N*-Acylhydrazones

Isopropyl addition to the α,β-unsaturated hydrazone **321**, however, gave a complex mixture of products that were mainly inseparable by chromatographic efforts (Figure 72). ^{1}H NMR of product mixtures obtained after attempted chromatographic separation revealed no peaks in the expected region for olefin functionality. GC-MS characterization of two separate samples obtained from attempted chromatographic separation revealed that there were three compounds with the same molecular ion peak in one sample, and two compounds with the

same molecular ion peak in the second sample. The molecular weight of the compounds in the first sample corresponded to compounds **324-326**, which could be envisioned being produced by mono-addition of isopropyl radical to the three potential sites in the hydrazone starting material, the imine carbon, and each carbon of the unsaturation. The molecular weight of the compounds in the second sample corresponded to compounds **327** and **328**, and these could arise from double-addition of isopropyl radical to the imine carbon and one of the two unsaturation sites. It appeared, then, that although unsaturation was tolerated in the hydrazone starting material further out from the α-position, α,β-unsaturation would not be tolerated under the current conditions. Since there is conjugation with the imine bond when the unsaturation is at the α,β-position, it seems logical that this location would be susceptible to attack by a high SOMO energy radical since conjugation lowers the LUMO energy of the olefin carbon atoms.

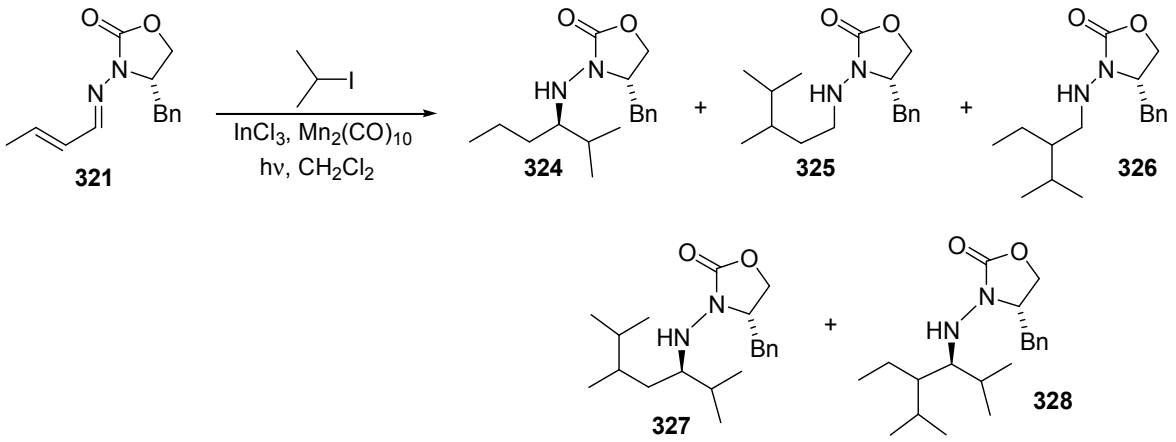


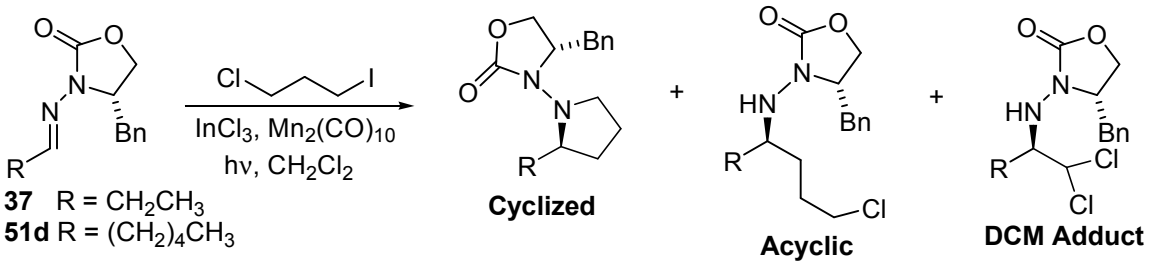
Figure 72. Isopropyl Addition to α,β-Unsaturated *N*-Acylhydrazone

Optimization of Conditions for Annulation in RPC Reaction

Below is a table which summarizes the optimization efforts towards the RPC annulation methodology (Table 1). Portions of this table will be displayed separately when discussion of various conditions are presented, however it may be useful to have a full table for comparison of variables as a whole. Note that two different *N*-acylhydrazones were used in these studies. The “Ar Flow” column describes whether or not there was a constant flow of argon (Ar) pumped into the reaction tube during irradiation. The $InCl_3$ column notes whether or not the Lewis acid, $InCl_3$, was used in each reaction. The “Time” column refers to the amount of time the reaction mixture was irradiated. The “Δ” column states whether or not the reaction mixture was refluxed after irradiation. The three possible products from the reactions are described in the scheme above the table, and their yields are

listed in their respective table columns. The “% Addn” column refers to the total addition of chloropropyl radical to the *N*-acylhydrazone used.

Table 1. Optimization of Conditions for Mn-Mediated RPC Annulation[a]



37 R = CH_2CH_3
51d R = $(CH_2)_4CH_3$

Entry	s.m.[b]	Solvent	Ar Flow	$InCl_3$	Time	% Evap.	Δ	% Cyclized	% Acyclic	%[c] Addn	% DCM Adduct	dr[d]
1	**37**	CH_2Cl_2	Y	Y	45 h	~99	N	49	0	49	0	>95:5
2	**37**	CH_2Cl_2	Y	Y	44 h	66	N	43	14	57	7	>95:5
3	**37**	CH_2Cl_2	N	N	42 h	8	N	<3	<8	<11	<14	72:28
4	**37**	CH_2Cl_2	N	Y	43 h	0	N	52	<19	<71	<12	>95:5
5	**37**	CH_2Cl_2	N	Y	65 h	65	N	35	<16	<51	<30	>95:5
6	**37**	C_6H_6/ CH_3CN	N	Y	42 h	0	N	<29	<14%	<43	N/A	>95:5
7	**51d**	CH_2Cl_2	N	N	44 h	25	Y	10	0	10	12	83:17
8	**51d**	CH_2Cl_2	N	Y	45 h	25	Y	70	<7	<77	trace	>95:5
9	**51d**	CH_2Cl_2	Y	Y	16 h	0	N	18	57	75	23	>95:5
10	**51d**	CH_2Cl_2	N	Y	42 h	26	N	39	54	93	0	>95:5

a. Conditions: hydrazone (0.1-0.3 mmol) in CH_2Cl_2 & $InCl_3$ (0 eq or 2.3 eq as indicated) stirred 3 h. Iodide (10eq) & $Mn_2(CO)_{10}$ (2.0 eq) added, irradiation for specified time

b. s.m. refers to reactant **37** or **51d**

c. % Addn refers to the sum of Cyclized and Acyclic product yields

d. diastereomer ratio, measured by integration of ^1H NMR spectra

Effect of Solvent Evaporation

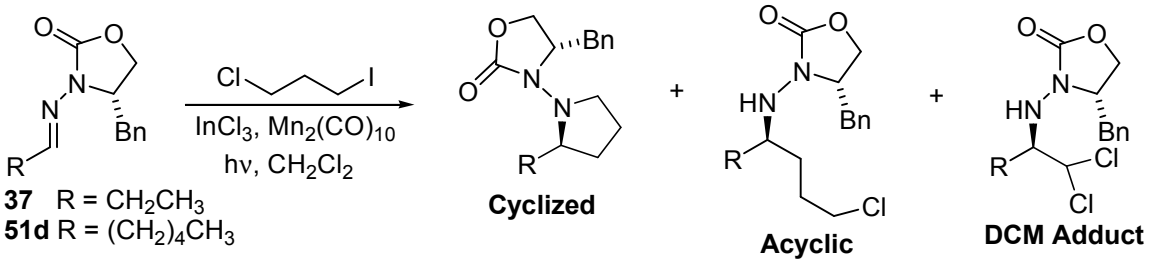
At the beginning of the optimization efforts, there was an issue with solvent evaporation, creating a concern for reproducibility issues (see “% Evap.” Column for entries 1 and 2,

Table 1). (Percent evaporation was estimated by measuring the volume in the reaction vessel before and after irradiation.) The reactions were run in a Rayonet

photoreactor in a Pyrex tube sealed with a septum which had an inlet of argon gas (Ar) through a needle. It was hypothesized that sealing the reaction tube under Ar using a teflon-coated glass stopper instead of allowing a constant flow of Ar to be pumped into the reaction tube would circumvent the evaporation issue. When comparing entries 3 and 4 with entries 1 and 2, it can be seen that the hypothesis was correct, and subsequent reactions were therefore sealed under inert gas. Later on, the issue of solvent evaporation surfaced again. For this reason, an exhaust fan was added to the top of the Rayonet photoreactor to pull hot air out of the reactor, and this eliminated solvent evaporation (reactions during the investigation of the scope of the methodology showed no solvent evaporation with the use of the exhaust fan).

During the course of purification of reaction mixtures, a byproduct was isolated and characterized. The byproduct appeared to have originated from the addition of a dichloromethyl radical to the hydrazone starting material (see scheme above Table 2). The dichloromethyl radical would originate from a hydrogen atom abstraction from the solvent, dichloromethane (DCM). The yield of this byproduct for each table entry is displayed in the % DCM Adduct column. Upon further comparison of entries 1-4 (Table 2), one can see that as the concentration increased due to solvent evaporation, the percentage of DCM adduct decreased. Therefore, reactions performed during the investigation of the scope of the methodology were run at a higher concentration in dichloromethane (0.17M vs. 0.057M).

Table 2. Effect of Solvent Evaporation on Yield of DCM Adduct [a]



Entry	s.m.[b]	Solvent	Ar Flow	$InCl_3$	Time	% Evap.	Δ	% Cyclized	% Acyclic	%[c] Addn	% DCM Adduct	dr[d]
1	**37**	CH_2Cl_2	Y	Y	45 h	~99	N	49	0	49	0	>95:5
2	**37**	CH_2Cl_2	Y	Y	44 h	66	N	43	14	57	7	>95:5
3	**37**	CH_2Cl_2	N	N	42 h	8	N	<3	<8	<11	<14	72:28
4	**37**	CH_2Cl_2	N	Y	43 h	0	N	52	<19	<71	<12	>95:5

a. Conditions: hydrazone (0.1-0.3 mmol) in CH_2Cl_2 & $InCl_3$ (0 eq or 2.3 eq as indicated) stirred 3 h. Iodide (10eq) & $Mn_2(CO)_{10}$ (2.0 eq) added, irradiation for specified time

b. s.m. refers to reactant **37** or **51d**

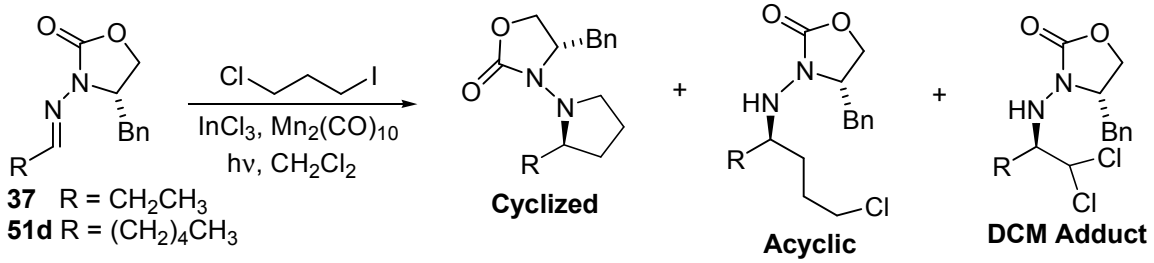
c. % Addn refers to the sum of Cyclized and Acyclic product yields

d. diastereomer ratio, measured by integration of ^1H NMR spectra

Effect of Lewis Acid

The effect of Lewis acid (L.A.) presence was next investigated for each hydrazone used (Table 3). Upon exclusion of the L.A., $InCl_3$, from the reaction medium, product yield decreased dramatically, and the dr of the cyclized product was lowered as well. It appeared then, as expected based on previous group results, that the L.A. plays a role in activation of the carbon of the imine bond of the hydrazone towards attack by radicals, as well as in the stereocontrol of the radical addition as explained earlier by the chelate model. Subsequent runs, accordingly, included $InCl_3$.

Table 3. Effect of Lewis Acid (L.A.) on Yield and Selectivity [a]



Entry	s.m.[b]	Solvent	Ar Flow	$InCl_3$	Time	% Evap.	Δ	% Cyclized	% Acyclic	%[c] Addn	% DCM Adduct	dr[d]
3	**37**	CH_2Cl_2	N	N	42 h	8	N	<3	<8	<11	<14	72:28
4	**37**	CH_2Cl_2	N	Y	43 h	0	N	52	<19	<71	<12	>95:5
7	**51d**	CH_2Cl_2	N	N	44 h	25	Y	10	0	10	12	83:17
8	**51d**	CH_2Cl_2	N	Y	45 h	25	Y	70	<7	<77	trace	>95:5

a. Conditions: hydrazone (0.1-0.3 mmol) in CH_2Cl_2 & $InCl_3$ (0 eq or 2.3 eq as indicated) stirred 3 h. Iodide (10eq) & $Mn_2(CO)_{10}$ (2.0 eq) added, irradiation for specified time

b. s.m. refers to reactant **37** or **51d**

c. % Addn refers to the sum of Cyclized and Acyclic product yields

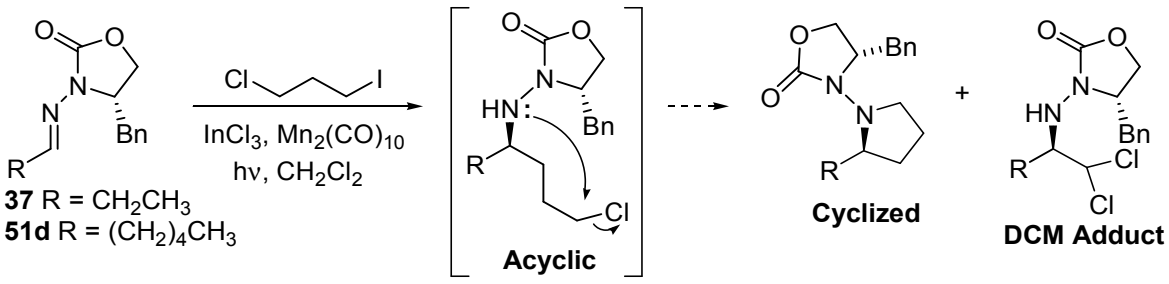
d. diastereomer ratio, measured by integration of ^1H NMR spectra

Effect of Irradiation Time

A power outage occurred in the building during one trial of optimization, and the reaction only ran for a total of 16 hours compared to the usual average of 43 hours (

Table 4). Upon isolation of products from this shorter reaction, it was discovered that the percentage of undesired acyclic product far outweighed the percentage of desired cyclized product. It was hypothesized that the acyclic product forms through chloropropyl radical addition to hydrazone starting material, and then is slowly converted to the cyclized product through nucleophilic substitution of the alkyl chloride by the basic former imine nitrogen as shown. For this reason, the reaction was purposely run for a longer reaction time of 65 hours in hopes that the yield of desired cyclized product would increase due to the allowance of more time for cyclization to occur. A longer reaction time, however, did not give an increased yield of cyclized product. In fact, it appeared that the longer reaction time may have caused decomposition of addition products since the overall addition of the chloropropyl radical to hydrazone is lower than in other entries which included L.A.[a] Therefore, an average reaction time of 43 hours was adopted as the optimized duration.

Table 4. Effect of Irradiation Time on Yield of Cyclized Product



Entry	s.m.[b]	Solvent	Ar Flow	$InCl_3$	Time	% Evap.	Δ	% Cyclized	% Acyclic	%[c] Addn	% DCM Adduct	dr[d]
4	**37**	CH_2Cl_2	N	Y	43 h	0	N	52	<19	<71	<12	>95:5
5	**37**	CH_2Cl_2	N	Y	65 h	65	N	35	<16	<51	<30	>95:5
9	**51d**	CH_2Cl_2	Y	Y	16 h	0	N	18	57	75	23	>95:5

a. Conditions: hydrazone (0.1-0.3 mmol) in CH_2Cl_2 & $InCl_3$ (0 eq or 2.3 eq as indicated) stirred 3 h. Iodide (10eq) & $Mn_2(CO)_{10}$ (2.0 eq) added, irradiation for specified time

b. s.m. refers to reactant **37** or **51d**

c. % Addn refers to the sum of Cyclized and Acyclic product yields

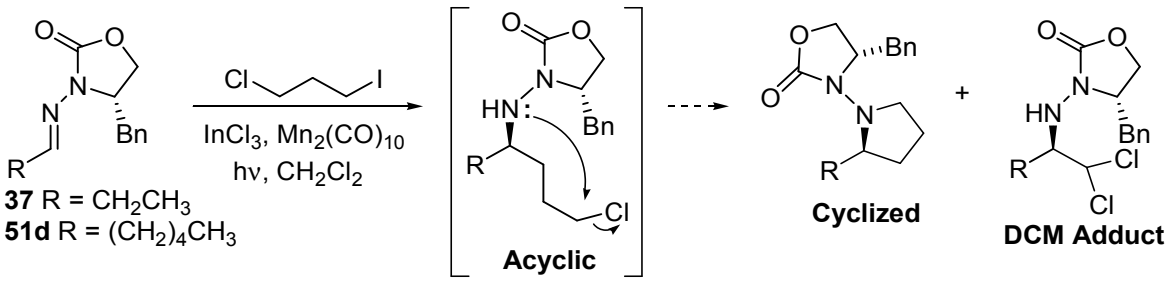
d. diastereomer ratio, measured by integration of ^1H NMR spectra

Effect of Higher Temperature

Since a longer reaction time did not increase the yield of desired cyclized product at the expense of undesired acyclic product yield, it was hypothesized that a higher temperature may. It was assumed that the temperature of the reaction medium during irradiation reached 40 ºC, the boiling point of DCM, because of the issue of solvent evaporation early on. This was attributed to heat generated by the UV lights in the photoreactor. A trial was therefore run with an extra step in the workup procedure. After irradiation for 45 hours, the DCM was evaporated *in vacuo*, and then acetonitrile (0.02M with respect to hydrazone starting material) was added, and the mixture was subjected to reflux overnight. This, to our delight, resulted in the highest yield of cyclized product yet obtained (entry 8,

Table 5).

Table 5. Effect of Higher Temperature on Yield of Cyclized Product



Entry	s.m.[b]	Solvent	Ar Flow	$InCl_3$	Time	% Evap.	Δ	% Cyclized	% Acyclic	%[c] Addn	% DCM Adduct	dr[d]
8	**51d**	CH_2Cl_2	N	Y	45 h	25	Y	70	<7	<77	trace	>95:5
10	**51d**	CH_2Cl_2	N	Y	42 h	26	N	39	54	93	0	>95:5
4	**37**	CH_2Cl_2	N	Y	43 h	0	N	52	<19	<71	<12	>95:5
6	**37**	C_6H_6/ CH_3CN	N	Y	42 h	0	N	<29	<14%	<43	N/A	>95:5

a. Conditions: hydrazone (0.1-0.3 mmol) in CH_2Cl_2 & $InCl_3$ (0 eq or 2.3 eq as indicated) stirred 3 h. Iodide (10eq) & $Mn_2(CO)_{10}$ (2.0 eq) added, irradiation for specified time

b. s.m. refers to reactant **37** or **51d**

c. % Addn refers to the sum of Cyclized and Acyclic product yields

d. diastereomer ratio, measured by integration of ^1H NMR spectra

Although this result was positive, it inherently added an extra step to the methodology, which was undesirable. Therefore, in hopes of achieving a higher temperature during the reaction, although the internal reaction temperature could not be monitored, benzene, with a higher boiling point of 80 ºC, was chosen as the solvent for a subsequent trial run. (There was also hope that the use of an aprotic solvent would increase addition product yield since there would be no solvent radical present to compete for addition to the hydrazone.) The starting materials, however, were not soluble in benzene alone, and so a 10:1 mixture of benzene:acetonitrile was instead used. Unfortunately, the cyclized product yield decreased in this solvent system. DCM was, thus, kept as the solvent for all future runs.

Effect of Alkyl Iodide

The final parameter which was investigated was the identity of the alkyl iodide radical precursor. It was hypothesized that the rate of cyclization would increase with the replacement of chlorine for a better leaving group (LG). An iodide atom should serve as a better LG because a carbon-iodine bond is weaker than a carbon-chlorine bond due to less defined overlap of sigma orbitals because of size difference. Upon the use of 1,3-diiodopropane as the radical precursor, however,

cyclized product yield decreased dramatically (Figure 73). A byproduct was isolated, characterized, and identified as the acyclic *n*-propyl radical adduct **330**. This adduct presumably resulted from reductive dehalogenation following addition of an iodopropane radical to the hydrazone starting material. It was decided, after the attainment of these results, that 3-chloropropyl iodide would remain as the radical precursor.

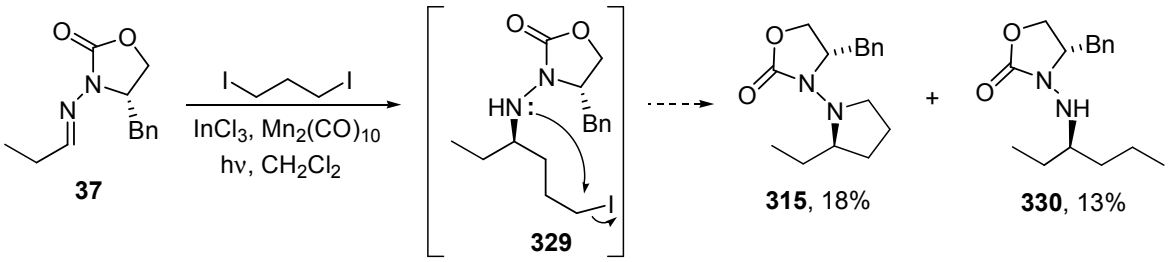


Figure 73. Effect of Better LG in Radical Precursor on Yield of Cyclized Product

In summary, the optimized conditions became to run the reaction in a tube sealed with a Teflon-coated glass stopper under inert gas (Ar or N_2) at a concentration of 0.17M in DCM for an average of 43 hours using $InCl_3$ as a Lewis acid and 3-chloropropyl iodide as the radical precursor.

Examining the Mechanism of the RPC Annulation

We next began to focus on the order of events in the RPC annulation reaction. A nucleophilic substitution on the alkyl halide could occur first, giving charged intermediate **331a**, followed by an intramolecular radical cyclization as shown (Path A in Figure 74). This would classify the reaction as a Class B RPC annulation. The alternative route (Path B in Figure 74) would begin with a radical addition of the alkyl halide to the imine carbon to give the neutral intermediate **331b**, followed by an intramolecular nucleophilic cyclization. This would classify the reaction as a Class C RPC annulation.

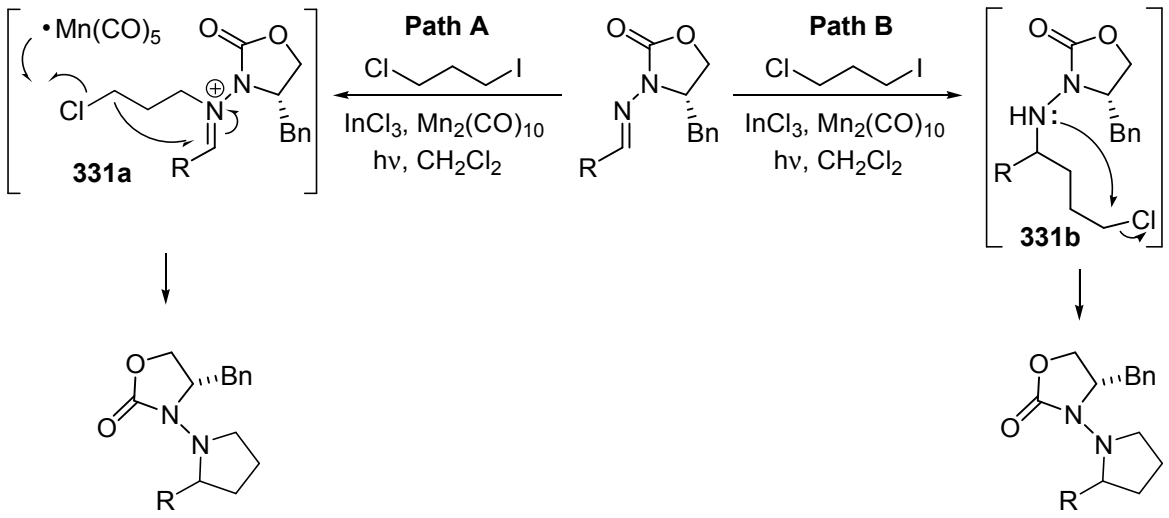
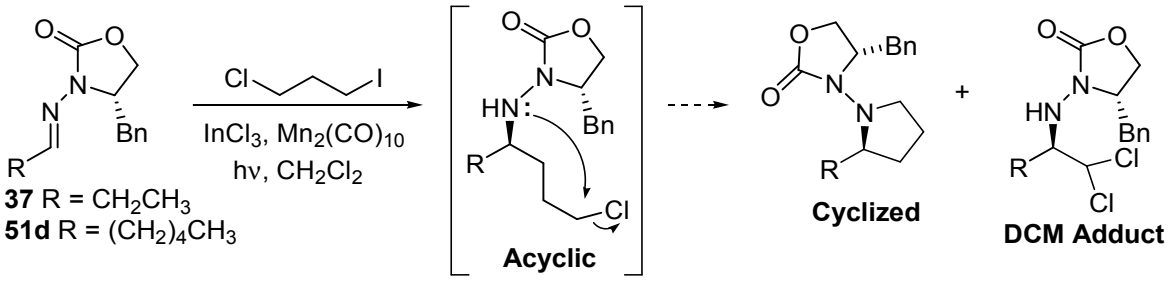


Figure 74. Two Possible Mechanisms for the RPC Annulation

Mechanistic insight was gained upon further reflection on the data obtained during the optimization reactions. It was mentioned earlier that a shorter reaction time yielded significantly more acyclic than cyclized product (entry 9 vs. 10 below, Table 6), and the assumption was made that the acyclic product forms through radical addition, and then undergoes intramolecular nucleophilic substitution to yield cyclized product. The assumption was supported by an experiment which included a reflux step after irradiation wherein the highest yield of cyclized product was obtained, with only a very low acyclic product yield (entry 8 vs. 10 below). In order to affirm the identity of the acyclic product, it was isolated from the reaction mixture which was obtained by a shorter irradiation period (entry 9). Attempts were made to fully characterize this sample, however the intermediate proved to be too reactive, and partial cyclization occurred at room temperature during data collection. The most convincing piece of data to support the acyclic structure, though, came from electrospray ionization mass spectrometry (ESI-MS) of the isolated sample. The molecular ion peaks ($[M+Na]^+$ and $[M+H]^+$) matching the molecular weight of the proposed acyclic structure showed chlorine isotope peaks as expected. In the ^{13}C NMR spectrum, all but one carbon peak (due to the terminal methyl group) for the acyclic product resolved from the known cyclized product peaks. The ^{1}H NMR showed mostly an overlap of cyclized and acyclic peaks, however two separate peaks for the acyclic product were resolved (peaks due to one of the benzylic protons, and the protons neighboring the chlorine atom). This sample was subjected to an overnight reflux in acetonitrile (0.023 M), and the acyclic product was cleanly converted to the cyclized product as judged by ^{1}H and ^{13}C NMR spectra (Figure 75).

Table 6. Optimization Results Leading to Mechanistic Insight of RPC Annulation[a]



Entry	s.m.[b]	Solvent	Ar Flow	$InCl_3$	Time	% Evap.	Δ	% Cyclized	% Acyclic	%[c] Addn	% DCM Adduct	dr[d]
7	**51d**	CH_2Cl_2	N	N	44 h	25	Y	10	0	10	12	83:17
8	**51d**	CH_2Cl_2	N	Y	45 h	25	Y	70	<7	<77	trace	>95:5
9	**51d**	CH_2Cl_2	Y	Y	16 h	0	N	18	57	75	23	>95:5
10	**51d**	CH_2Cl_2	N	Y	42 h	26	N	39	54	93	0	>95:5

a. Conditions: hydrazone (0.1-0.3 mmol) in CH_2Cl_2 & $InCl_3$ (0 eq or 2.3 eq as indicated) stirred 3 h. Iodide (10eq) & $Mn_2(CO)_{10}$ (2.0 eq) added, irradiation for specified time

b. s.m. refers to reactant **37** or **51d**

c. % Addn refers to the sum of Cyclized and Acyclic product yields

d. diastereomer ratio, measured by integration of ^1H NMR spectra

After gathering this evidence, it became very convincing that radical addition to the imine carbon occurs prior to nucleophilic substitution on the alkyl halide by the imine nitrogen, characterizing the reaction as a Class C [3+2] RPC annulation. One further piece of evidence of this mechanism, though, lies in the dr of >95:5 of the cyclized product obtained after the overnight reflux of acyclic product, which matches the dr of the cyclized product isolated from the original reaction mixture. If nucleophilic substitution of the imine nitrogen onto 3-chloropropyl iodide occurred prior to chloropropyl radical addition to the imine carbon, the imine would become an iminium ion **331** and would be incapable of forming a chelate with the Lewis acid due to a lack of open valancies (Figure 75). The dr, then, would be expected to be lower, as in the experiment lacking Lewis acid where a dr of 83:17 was obtained (entry 7, Table 6). This is because without the formation of the rigid chelate, the only stereocontrol lies in the use of the chiral auxiliary. In fact, a previous publication shows an example where nucleophilic substitution was presumed to occur prior to radical addition, and the dr of cyclized product **334** in this example was a mere 3:1 (Figure 75).[24] Therefore, since a high dr was observed in the cyclized product obtained by the acyclic reflux experiment, we are convinced of the proposed identity of the acyclic product and the order of addition and substitution steps.

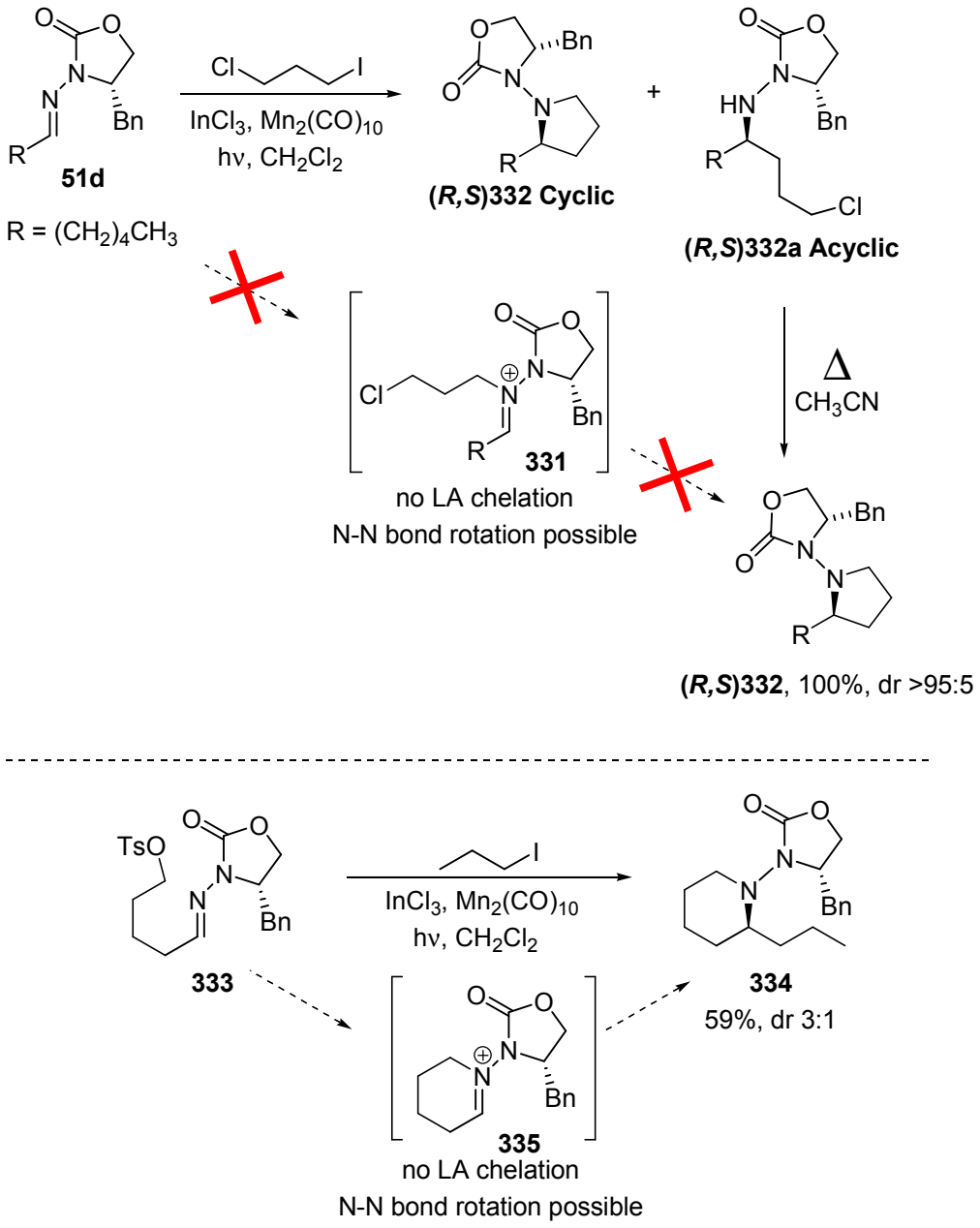


Figure 75. Mechanistic Evidence of RPC Annulation

The mechanistic picture was further sharpened when our attention was drawn to the varying amounts of dichloromethyl adduct mentioned earlier. This indicates that a hydrogen atom abstraction event produces •$CHCl_2$, which then competes for the radical acceptor. Thus it appears that hydrogen atom abstraction by the alkyl radical adduct **337**, a *N*-centered aminyl radical, intervenes between radical addition and cyclization. The full mechanistic route is presented below (Figure 76). Irradiation of $Mn_2(CO)_{10}$ produces two ·$Mn(CO)_5$, one of which abstracts an iodide atom from 3-chloropropyl iodide, resulting in the carbon-centered chloropropyl

radical shown. After addition of the radical to the Si face of the hydrazone-LA chelate **336**, the resulting aminyl radical, **337**, abstracts a hydrogen atom from DCM. This gives both the acyclic product which is transformed to cyclized product by an intramolecular nucleophilic cyclization, and also the ·$CHCl_2$, which competes for addition to another equivalent of chelate **336**, producing the DCM adduct.

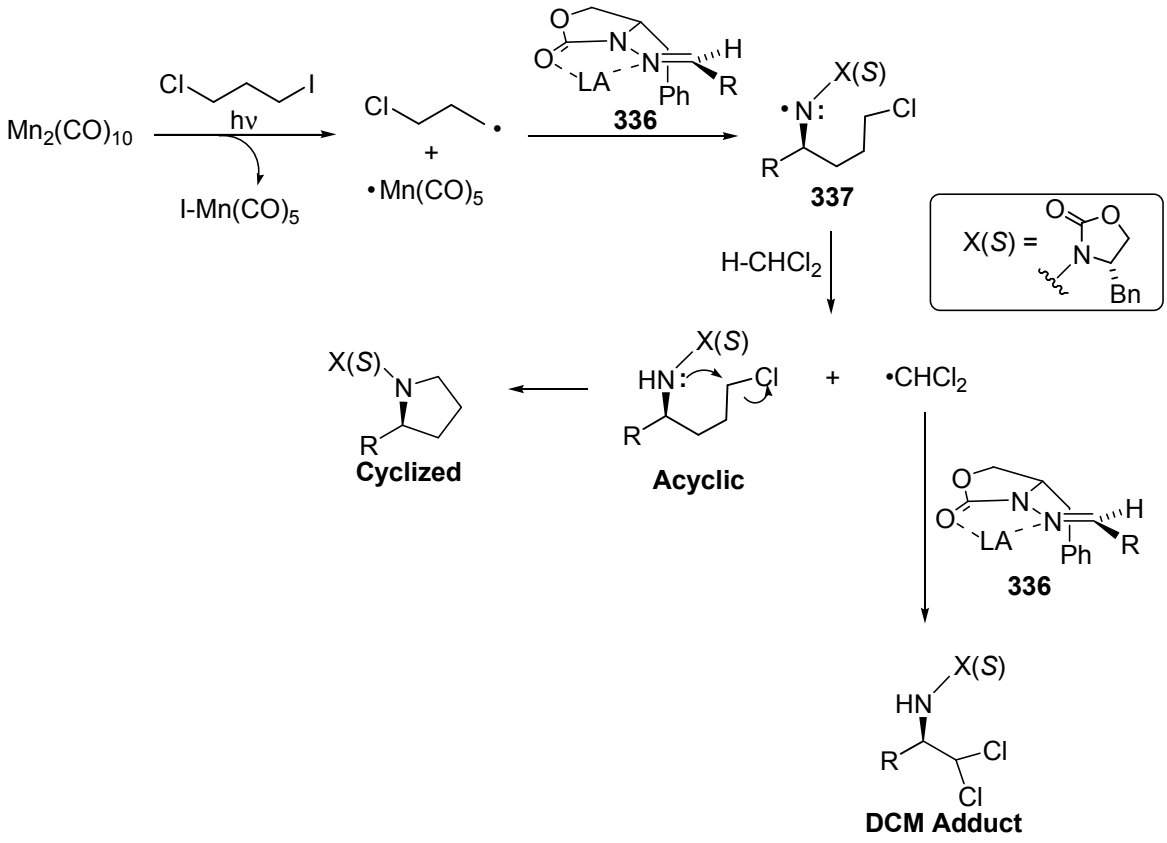


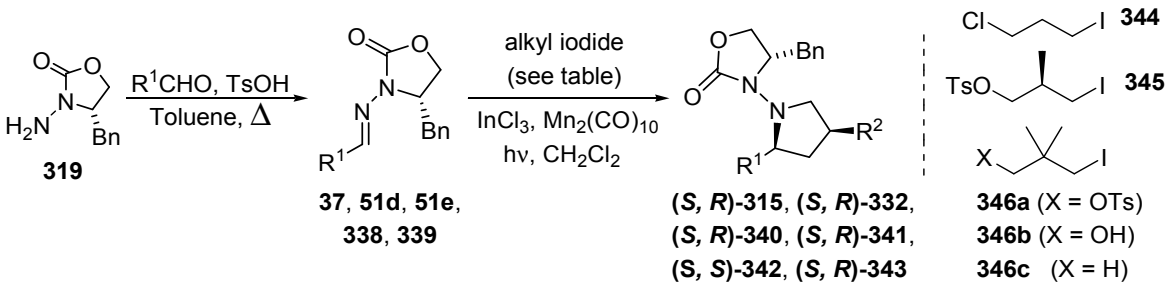
Figure 76. Mechanism of RPC Annulation

Test of Scope of the RPC Annulation

With a clear mechanistic picture in hand, our attention turned toward the scope of the [3+2] RPC annulation reaction to produce pyrrolidine structures. Known chiral *N*-acyl hydrazones **37**, **51d**, **51e** and new hydrazones **338** and **339** (Table 7) were prepared according to the established methods[19,132] and subjected to annulations using the optimized conditions presented earlier. Hydrazones of varying aliphatic chain lengths gave annulation products in yields ranging from 52–70% (Table 7, entries 1, 2 and 4). The phenyl group in hydrocinnamaldehyde hydrazone **339** was well tolerated, giving an annulation product yield of 60% (entry 5). Isovaleraldehyde hydrazone **51e**, bearing branching at the β-position, worked

especially well, yielding 86% of the annulation product (entry 6). Mass balances in these annulations were quite good; combined yields of chloroalkyl adducts and annulation products based on conversion range from 63–100%.

Table 7. Scope of [3+2] RPC Annulation of Chiral *N*-Acylhydrazones[a]



319

37, **51d**, **51e**, **338**, **339**

(*S, R*)-315, **(*S, R*)-332**, **(*S, R*)-340**, **(*S, R*)-341**, **(S, *S*)-342**, **(*S, R*)-343**

344

345

346a (X = OTs)
346b (X = OH)
346c (X = H)

Entry	R^1	Hydrazone, Yield[b]	Alkyl Iodide	Total Addition[c]	Annulation Product, Yield[b]	Hydrazone Recovered	dr[d]
1	CH_3CH_2	**37**, 73%[e]	**344**	70%	**(*S,R*)-315**, 52%[e]	~7%[g]	96:4
2	$CH_3(CH_2)_3CH_2$	**51d**, 41%[e]	**344**	76%	**(*S,R*)-332**, 70%	~11%[g]	>95:5
3	$CH_3(CH_2)_8CH_2$	**338**, 74%	**344**	59%	**(*S,R*)-340**, 54%	~6%[g]	>95:5
4	$PhCH_2CH_2$	**339**, 70%	**344**	70%	**(*S,R*)-341**, 60%	~30%[g]	>95:5
5	$(CH_3)_2CHCH_2$	**51e**, 67%[e]	**344**	96%	**(S,*S*)-342**, 86%	0%	>95:5
6	CH_3CH_2	**37**	**345**	42%	**(*S,R*)-343**, 42%	5%	>95:5
7	CH_3CH_2	**37**	**346a**	18%[f]	0%	61%	nd[h]
8	CH_3CH_2	**37**	**346b**	0%	N/A[i]	53%	N/A[i]
9	CH_3CH_2	**37**	**346c**	12%	N/A[i]	50%	nd[h]

a. Conditions: hydrazone (0.1-0.3 mmol) in CH_2Cl_2 (0.17 M) & $InCl_3$ (2.2-2.3 eq) stirred 3 h. Iodide (10 eq) & $Mn_2(CO)_{10}$ (2.0 eq) added, irradiation 40-45 h.

b. Isolated yield

c. Combined yields of isolated acyclic and cyclized products

d. Ratio determined by NMR

e. Previously reported compound

f. Yield of DCM adduct

g. approximate due to slight impurities in isolated sample

h. not determined

i. not applicable

Diastereoselectivity in the annulation reactions is consistent with Mn-mediated radical additions reported previously. All cases exhibited diastereomer ratios >95:5 with minor diastereomer peaks undetected in ^{1}H NMR (500 MHz), ^{13}C NMR, or HPLC. In order to confirm that minor diastereomer peaks could be detected if present, the ^{1}H NMR (500 MHz) and ^{13}C NMR of the annulation product in entry 2 (**(*S,R*)332**, Table 7) were collected with enough scans to produce a clean baseline and compared with the ^{1}H NMR (500 MHz) and ^{13}C NMR of the same product obtained in the reaction lacking $InCl_3$ Lewis acid which was presented earlier

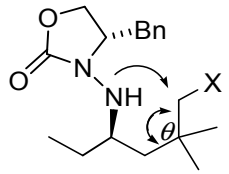
during the discussion of the optimization experiments (Table 1, entry 7). In the case lacking Lewis acid, the minor diastereomer (present in 13%) peaks were identifiable, however none of these peaks were present in the spectra of the product in entry 2 (Table 7).

Variations of the alkyl iodide component were examined. The synthesis of 3-chloro-2-methylpropyl iodide was attempted starting from 3-bromo-2-methylpropanol (Figure 77). The bromine was successfully substituted for iodine using a literature procedure[133] (the enantiomer of this alcohol was previously reported, and NMR spectra matched the literature report[134]). The transformation from alcohol to chloride using the Appel Reaction, however, was unsuccessful.

347 **348,** 90% **349**

Figure 77. Attempted Synthesis of Substituted Chloride

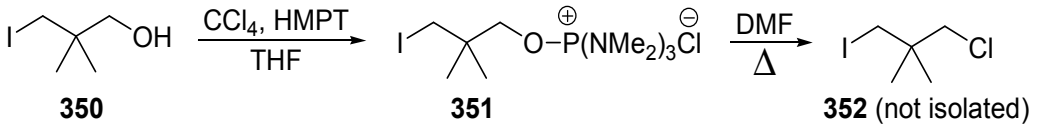
The alcohol was instead changed to a tosylate leaving group (**345**, entry 6), and the annulation reaction with this iodide was moderately successful, furnishing disubstituted pyrrolidine **(*S,R*)-343** in 42% yield. This was somewhat unexpected, given the previously described behavior of the tosylate shown in Figure 75. Annulation with 3-iodo-2,2-dimethylpropyl *p*-toluenesulfonate (**346a**, entry 7), bearing *gem*-dimethyl substitution, was completely unsuccessful. It was originally hypothesized that the *gem*-dimethyl substitution of this iodide would increase the rate of cyclization compared to entry 6 due to the Thorpe-Ingold Effect (Figure 78).[135] This precedent, simply stated, highlights the idea that *geminal* substituents cause an angle compression due to steric hindrance, and this angle compression pushes reactive termini closer together, causing an increased rate of cyclization. Since this effect was not observed in the case of iodide **346a**, we wondered whether the bulky tosylate leaving group was inhibiting cyclization. For this reason, iodide **346b** (entry 8), with a smaller hydroxyl group, was reacted with hydrazone **37**, however, none of the expected addition product was produced.



Angle (θ) compression pushes reactive termini closer together increasing rate of cyclization

Figure 78. The Thorpe-Ingold Effect

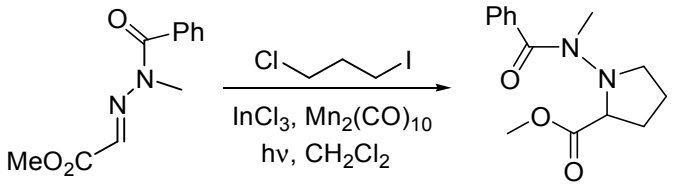
We initially planned to use 3-chloro-2,2-dimethylpropyl iodide as the radical precursor for the synthesis of a 2,4,4-trisubstituted pyrrolidine (Figure 79). This is a previously reported iodide, however it is not commercially available. Synthesis through the phosphonium salt intermediate **351** was unsuccessful.[136] Instead of using this iodide, an iodide with a simple hydrogen atom in place of the chlorine (iodide **346c**, entry 9) was purchased, and when subjected to the RPC conditions, only 12% of addition product was obtained (no annulation was possible in this case). It appears that further changes to the method will need to be made in order to enable the use of iodides bearing *gem*-dimethyl substitution.



350 **351** **352** (not isolated)

Figure 79. Attempted Synthesis of Chloride with *Gem*-Dimethyl Substitution

Hydrazones prepared from chloroacetaldehyde and *O-tert*-butyldimethylsilylglycolaldehyde did not perform well in these annulations, despite their success in earlier Mn-mediated radical additions (albeit with shorter irradiation times).[23,25,116] In both cases, crude mixtures showed evidence of the expected annulation product, but it apparently decomposed during chromatographic purification. On the other hand, ester functionality at the α-position was compatible with the conditions; annulation of *N*-benzoylhydrazone **353** with 3-chloropropyl iodide (Figure 80) afforded a 56% yield of **354**, a hydrazine analog of proline. Thus, the scope of other iodides for [3+2] annulations of this type may have broader potential for further application to multifunctional compounds.



353 **354**, 56%

Figure 80. RPC Annulation in the Presence of Ester Functionality

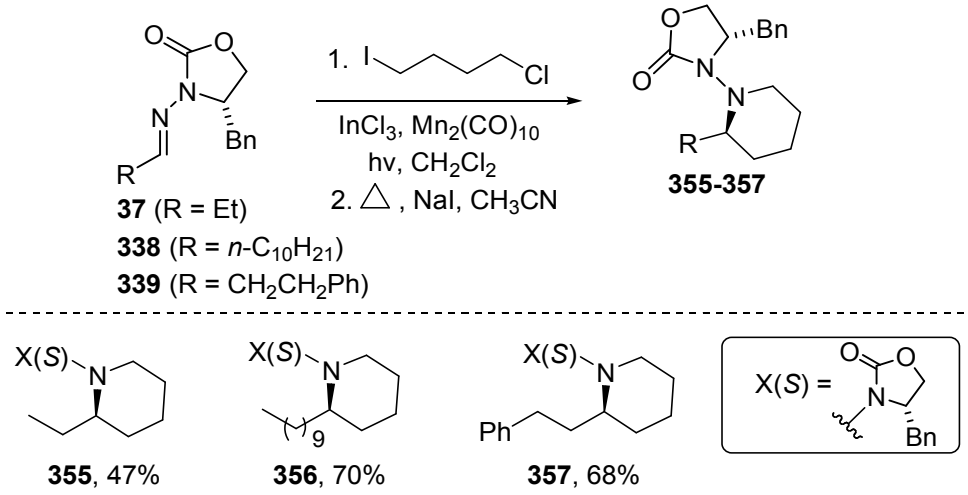
We next envisioned the synthesis of piperidine structures through a [4+2] RPC annulation. As mentioned earlier, the first attempt at piperidine synthesis through

Mn-mediated radical addition to a hydrazone bearing a tosylate leaving group resulted in poor diastereoselectivity (Figure 75). We attributed this anomalously poor selectivity to a change in mechanism; premature cyclization to form an iminium ion would disrupt the stereocontrol of radical addition. From this we hypothesized that moderating the reactivity of the leaving group would potentially delay cyclization until after the radical addition, avoiding stereocontrol problems. We previously encountered a 4-chlorobutyl adduct which did not readily cyclize; this adduct was stable during isolation, storage, and transport for combustion analysis.[23]

Supported by the above reasoning, 4-chlorobutyl iodide was chosen for further examination for a [4+2] annulation of a series of hydrazones (

Table 8). By adjustments to the conditions, using a solvent change to accelerate the polar cyclization, efficient and general annulations indeed provided the desired piperidines **355-357** in 47-70% yield with high selectivity (dr >95:5). Selectivity, again, was judged by ^{1}H NMR (500 MHz) and ^{13}C NMR, collecting enough scans in each case to produce a very clean baseline (see appendix). The improved method entailed addition of 4-chlorobutyl iodide under routine Mn-mediated radical addition conditions with a shorter irradiation time of around 24 hours, followed by separation of Mn-containing byproducts (filtration through silica gel), then heating with NaI in refluxing acetonitrile. No acyclic products were isolated from the reaction mixtures. Presumably, the more polar medium and higher reflux temperature both contributed to the improvement in the polar component of this annulation.

Table 8. Scope of [4+2] RPC Annulation of Chiral N-Acylhydrazones[a]



37 (R = Et)
338 (R = *n*-$C_{10}H_{21}$)
339 (R = CH_2CH_2Ph)

355-357

355, 47% **356**, 70% **357**, 68%

a. Conditions: hydrazone (0.09-0.12 mmol) in CH_2Cl_2 (0.17M) & $InCl_3$ (2.3 eq) stirred 3 h. Iodide (10 eq) & $Mn_2(CO)_{10}$ (2.0 eq) added, irradiation 23-24 h.
b. Diasteromer ratios were >95:5 in all cases, as judged by ^1H and ^{13}C NMR

It should be noted that these reactions are not technically classifiable as RPC annulations since there is a slight workup step between the radical and polar aspects. They could presumably be of the RPC type, however, if the entire reaction mixture was refluxed following irradiation as in entry 8 of Table 1. We chose to include the filtration for removal of Mn-containing byproducts for ease of glassware cleanup following reflux (the Mn-containing byproducts tend to stick to the glassware more stubbornly after they have been refluxed in the glassware.)

Demonstration of Versatility of the RPC Annulation

From a retrosynthetic standpoint, the RPC annulation disconnection could be envisioned in two modes that differ by which component carries the electrophilic reactivity (Figure 81): Type I annulation was presented above, where the nucleofuge and radical are in the same component, while Type II annulation entails linking the nucleofuge to the imino compound. The Type II annulation approach to pyrrolidines was next explored.

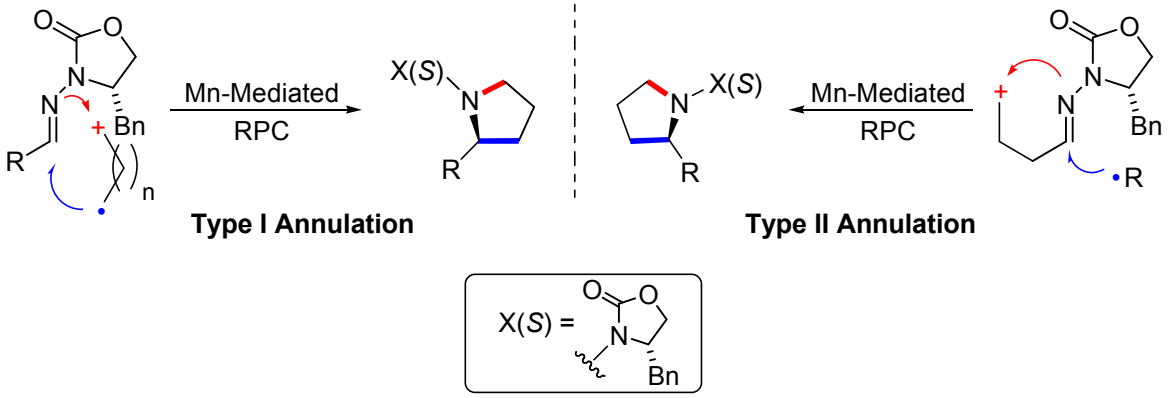
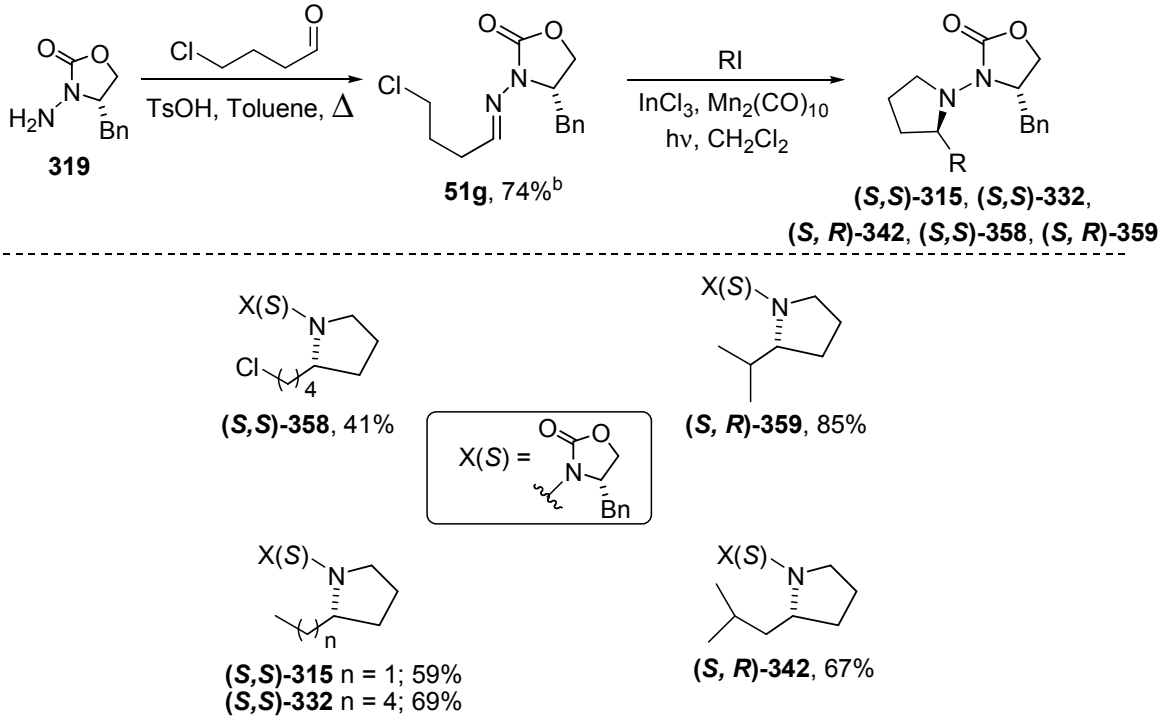


Figure 81. Type I and Type II Annulation in RPC Reaction

Additions of 4-chlorobutyl, isopropyl, ethyl, pentyl, and isobutyl iodides to hydrazone **51g** resulted in pyrrolidines **(*S,S*)315**, **(*S,S*)332**, **(*S,R*)342**, **(*S,S*)358**, **(*S,R*)359** (

Table 9). Unsurprisingly, isopropyl iodide gave the highest yield (**(*S,R*)359**, 85%), consistent with its ease of conversion to the secondary radical. It is noteworthy that the simple primary alkyl iodides are also successful (41-69% yield); primary radicals perform inefficiently in most intermolecular additions, but are handled smoothly by the Mn-mediated conditions. Another advantage to our approach lies in the fact that both Type I and Type II annulations can be performed. In a total synthesis scheme, it is very valuable to have this type of versatility so that if, for example, Type I annulation does not work, simple changes to the starting materials can be made to attempt a Type II annulation instead.

Table 9. Scope of [3+2] RPC Type II Annulation of Chiral *N*-Acylhydrazones[a]



a. Conditions: hydrazone (0.09-0.14 mmol) in CH_2Cl_2 (0.17M) & $InCl_3$ (2.2-2.3 eq) stirred 3 h. Iodide (10 eq) & $Mn_2(CO)_{10}$ (2.0 eq) added, irradiation 40-45 h.

b. Previously reported compound

c. Diasteromer ratios were >95:5, unless otherwise noted, as judged by ^1H and ^{13}C NMR

Data from x-ray crystallography confirmed the assigned structure of isopropyl-substituted pyrrolidine **(*S,R*)-359**, (Figure 82, see Apendix also). The absolute stereochemistry of the newly formed stereocenter of all other products in Table 9, as well as the products in Tables 7 and 8, was assigned based on analogy to this crystallographic data, and also based on the results of previous group members' chemical correlation studies conducted on chiral amine products gained through the use of the oxazolidinone auxiliary.[20,24,25,137]

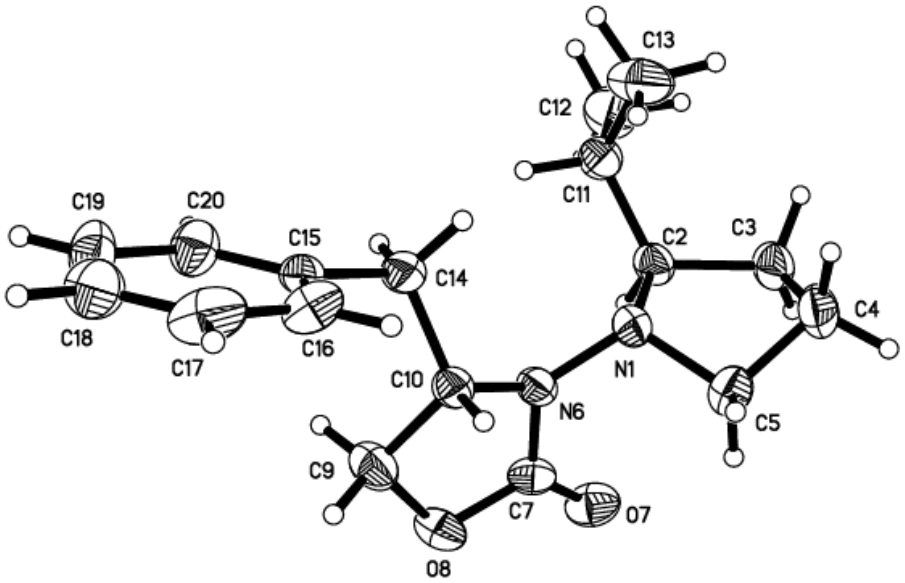


Figure 82. X-Ray Crystollography Structure of Pyrrolidine **(*S,R*)-359**

Addition of 4-chlorobutyl iodide to hydrazone **51g** would be expected to give intermediate **360** (Figure 83, a), setting up a direct internal competition between cyclization of two ω-chloroalkyl groups of different length, either 5-*exo-tet* or 6-*exo-tet* (using Baldwin's designations).[138] Although some compounds closely related to **360** such as **362** have been reported, mainly in the literature of indolizidine alkaloid synthesis,[139,140] these were employed for bis-cyclizations without discussion of group-selectivity. Therefore the annulation affording **(*S,S*)-358**, was of some further interest. In the event, group-selective cyclization occurred, providing only the pyrrolidine **(*S,S*)358**. This selectivity was consistent with reports of related 5-

exo-tet cyclizations to afford bis-pyrrolidines **363** wherein no products of 6-*exo-tet* cyclization were observed (Figure 83, b).[141,142]

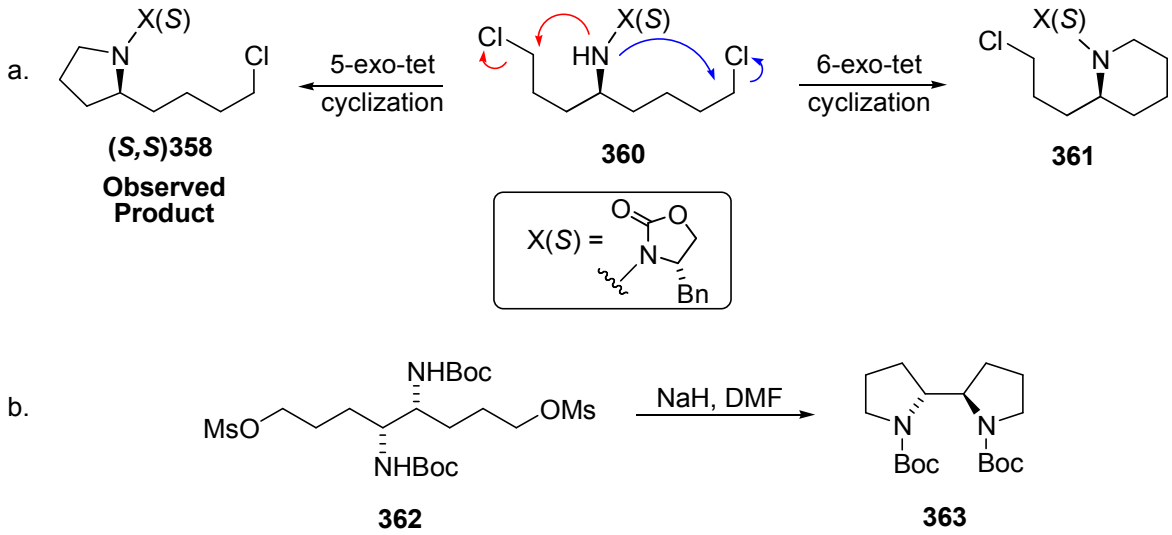


Figure 83. 5-*Exo-Tet* vs. 6-*Exo-Tet* Cyclization

In comparison with the products in Table 7, pyrrolidines **(*S,S*)-315**, **(*S,S*)-332**, **(*S,R*)-342**, **(*S,S*)-358**, and **(*S,R*)-359** in

Table 9 are formed with opposite configuration at the new stereogenic center. This outcome follows from the fact that the roles of the reactant partners are interchanged in Type I vs Type II annulations. Considering that the enantiomeric auxiliary stereocontrol element is also available, there are four complementary

routes to access the two pyrrolidine C2 epimers, highlighting the synthetic design flexibility of radical addition to *N*-acylhydrazones (Figure 84).

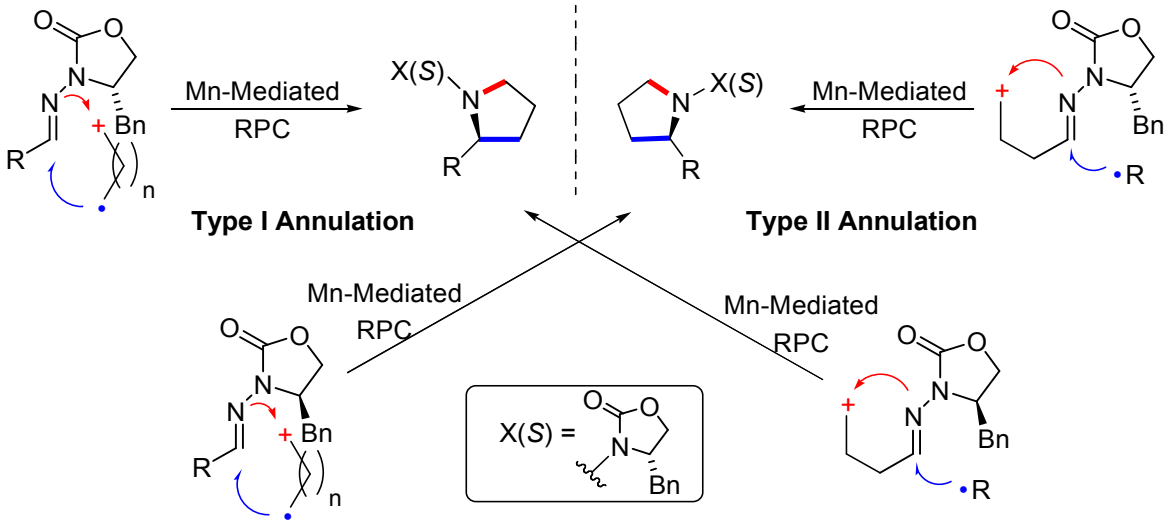
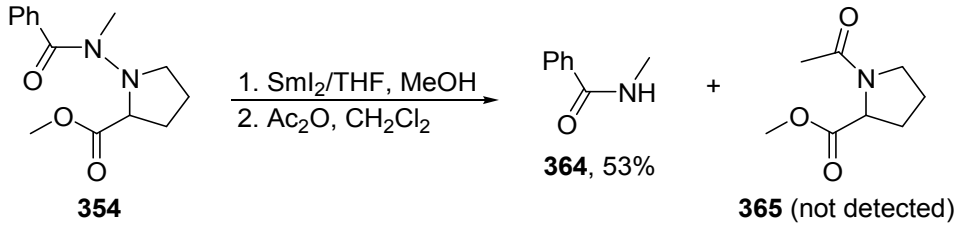


Figure 84. Versatility of [3+2] RPC Annulation

Demonstration of Synthetic Utility of the RPC Annulation

Lastly, to establish synthetic utility, it was necessary to demonstrate the removal of the chiral auxiliary without alteration of the pyrrolidine ring. Initial N-N bond reduction experiments began with pyrrolidine **354**, which contains the *N,N*-methylbenzoyl group in place of the chiral auxiliary (Figure 85). The reduction was successfully carried out using samarium (II) iodide (SmI_2, freshly prepared according to the literature[143]) as judged by the isolation of *N*-methylbenzamide in 53% yield. For the reduction, SmI_2 was added to a solution of the starting pyrrolidine in degassed methanol until the characteristic blue color persisted for 30 minutes. We attempted to cleave the bond and then perform an acylation in dichloromethane on the free pyrrolidine as shown for ease of purification, however neither the free pyrrolidine nor the acylated derivative were found in any of the column fractions.



354

364, 53%

365 (not detected)

Figure 85. Reductive Cleavage of N-N Bond Using SmI_2

We next attempted to cleave the N-N bond in pyrrolidine **(*S,*R)-315** containing the chiral auxiliary. Initially, we endeavored to precipitate the chloride salt of the pyrrolidine following reduction by BH_3•THF complex (Figure 86 a), however we believe the salt was only obtained in trace amount and no starting material was left over. We attempted the experiment again using titanium (III) chloride ($TiCl_3$) as the reducing agent, however similar results were obtained. Borane reduction of **(*S,R*)-341** with a 1M solution of BH_3•THF followed by workup with acetic anhydride, however, fortunately resulted in clean and complete reductive cleavage of the N–N bond to afford the acylated amine **368** in 86% yield (Figure 86 b).

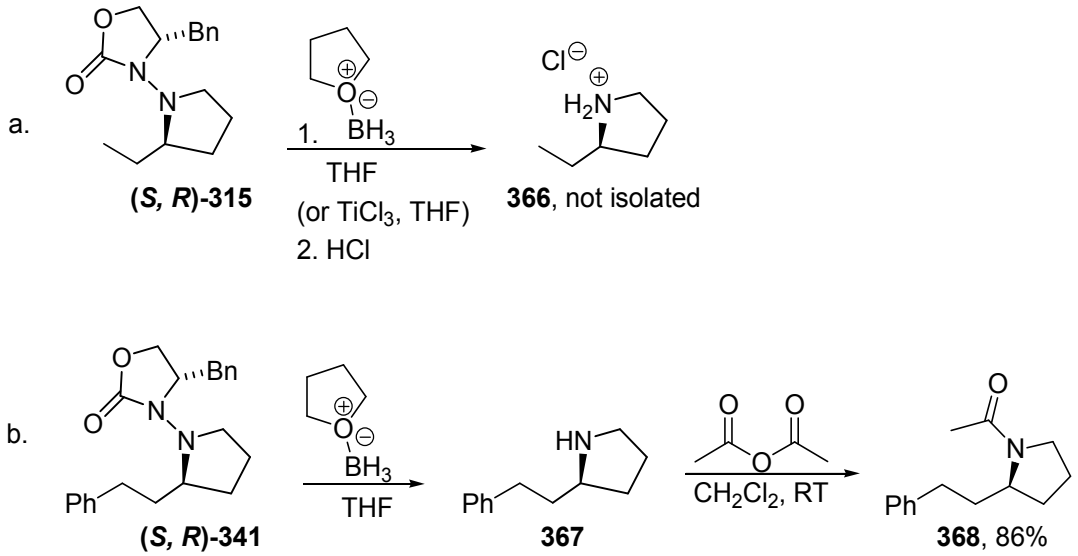


Figure 86. Reductive Cleavage of Chiral Auxiliary

Summary

The RPC annulation offers a non-basic C–C bond construction approach with excellent stereocontrol in order to make pyrrolidines and piperidines, which are ubiquitous substructures in compounds of importance to medicinal and biological chemistry. Avoiding the use of toxic tin reagents, the Mn-mediated radical conditions permit the presence of additional electrophilic functionality, which is often a limitation that plagues carbanion-based bond constructions. Either configuration of the heterocyclic product may be synthesized by switching the roles of the precursors (Type I or Type II annulations) or by using the enantiomeric chiral auxiliary. Compared with previously reported RPC annulations of imino

compounds, these conditions provide three additional elements of versatility, enabling (a) use of a variety of primary alkyl radicals, (b) generation of both five- and six-membered heterocycles, and (c) availability of two alternate routes with placement of the polar cyclization functionality in either precursor. The data reported herein lay the groundwork for further studies of Mn-mediated RPC reactions by future group members.

CHAPTER 4

N,O-ACETAL INSTALLATION ON DIPEPTIDE TOWARDS USE AS TRACELESS LINKER IN BIOCONJUGATE CHEMISTRY

Background

The Mn-mediated radical addition methodology developed by our group was applied to the synthesis of γ-amino acid building blocks for the natural product tubulysin D (Figure 87),[117] and during this work, it became apparent that there is no versatile and general method for the installation of *N,O*-acetals at peptide bonds. If such a method were developed, it could not only be used in the total synthesis of tubulysins A-F (Figure 87), which possess high cytotoxic activity,[144] but it would also contribute greatly to the area of bioconjugate chemistry, as *N,O*-acetals have been used to alter the transport properties of drugs bearing carboxylate functionality, and the *N,O*-acetal has potential application as a traceless linker for peptide drugs.

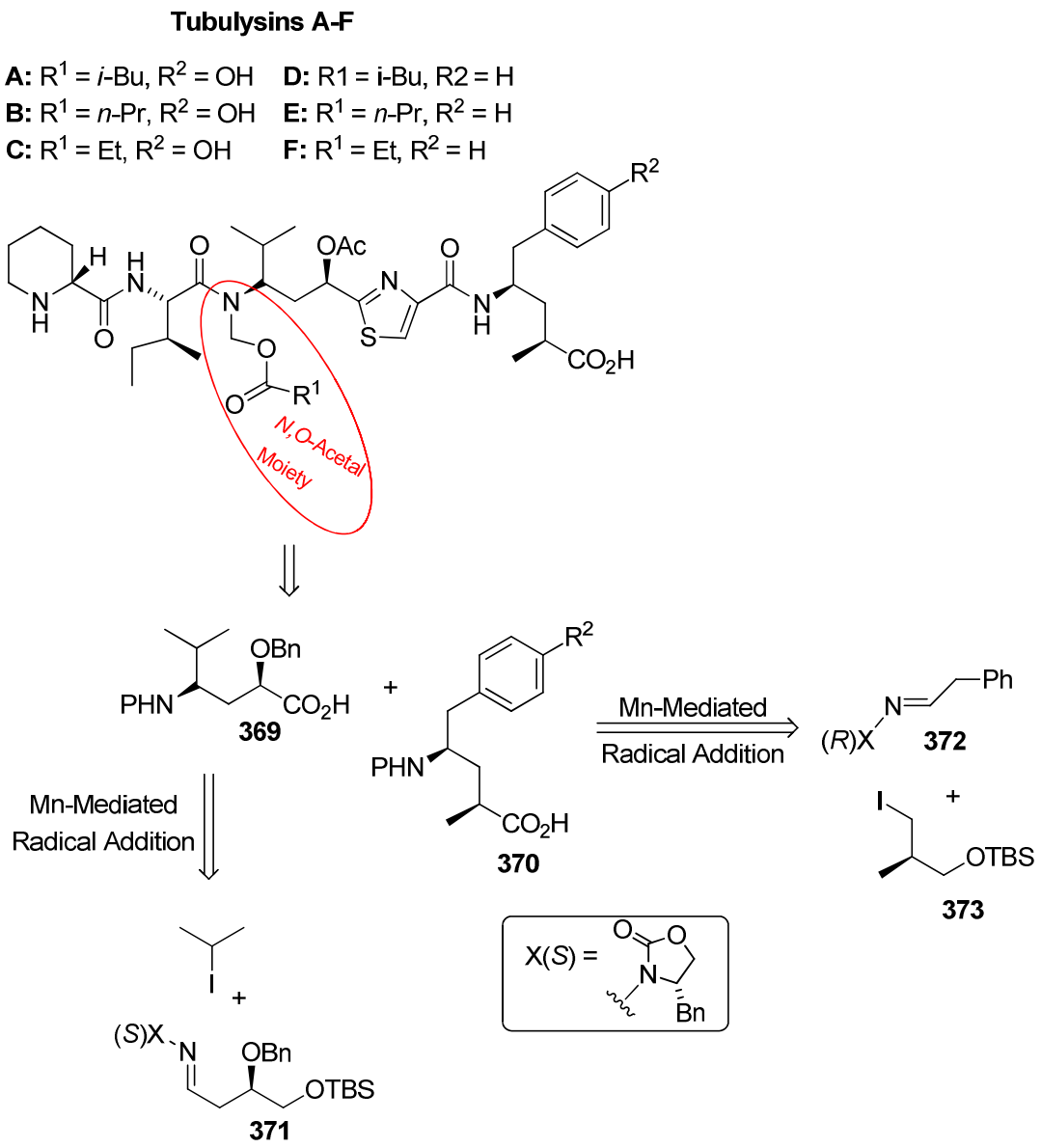


Figure 87. Retrosynthetic Analysis of the Tubulysins

Methods Towards N,O-Acetal Synthesis

Previous syntheses of the *N,O*-acetal moiety have either proven limited in scope, or rely on conditions that would not be useful for installation onto long peptide chains. The latter case is exhibited in a synthetic route to tubulysin D (

Figure 88).[145] As shown, it was necessary to incorporate an azide masking group on the *N*-terminus of a portion of the tubulysin framework to afford the availability of a single nucleophilic nitrogen which could attack the chloromethyl ester in

solution to yield the *N,O*-acetal moiety. The installation of an alcoholic protecting group prior to exposure to the chloromethyl ester was also required. This would obviously be an inconvenient route to *N,O*-acetal installation on complex peptides with multiple free NH groups.

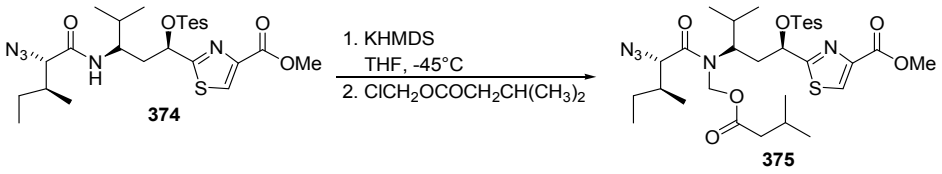
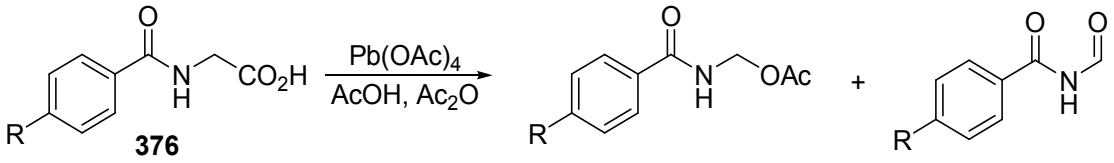


Figure 88. N,O-Acetal Installation During Synthesis of Tubulysin D

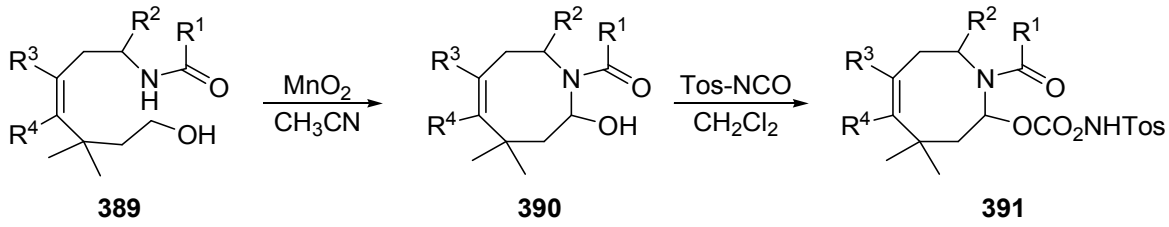
Oxidative decarboxylation of *N*-aroylamino acids (Figure 89) has been used to synthesize the *N,O*-acetal moiety.[146] This transformation of the carboxylic acid to an *O*-acylated *N,O*-acetal moiety is plagued trifold: the reaction is prone to *N*-formyl overoxidation to yield a byproduct, the yield of desired oxidation product is highly dependent on the identity of the aryl R group, and no desired product is obtained when the starting *N*-aroylamino acid is more sterically hindered. With either a methyl group on the amide nitrogen or in the α-position, the reaction fails.



R = H, 10% **379**, 22% **380**
R = Cl, 39% **381**, 28% **382**
R = Me, 2.5% **383**, 11% **384**
R = NO_2, 72% **385**, 0% **386**
R = OMe, 21% **387**, 12% **388**

Figure 89. Decarboxylation of *N*-Aroylamino Acids Yielding *N,O*-Acetals

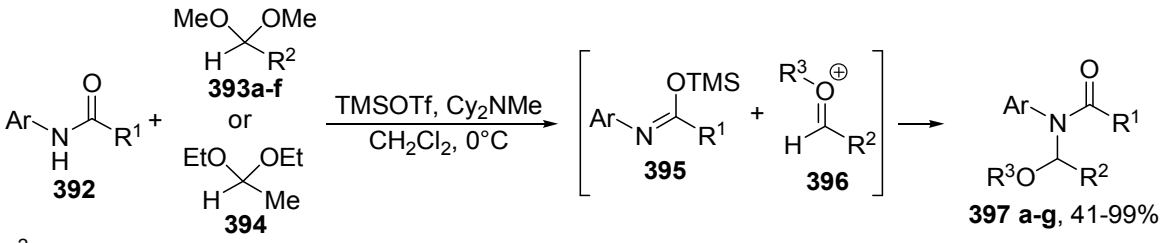
An *O*-acylated *N,O*-acetal moiety was installed during the course of the total synthesis of dl-austamide, a toxic metabolite of *Aspergillus ustus*.[147] As shown (Figure 90), a hemiacetal was first formed through the oxidation of an alcohol to an aldehyde, followed by *in situ* intramolecular cyclization by a nucleophilic nitrogen. The resulting alcoholic functional group was then acylated. An intermolecular version of this approach would not be useful for *N,O*-acetal synthesis on a long peptide chain, as there would be numerous nucleophilic NH sites which would compete for attack on an external aldehyde, giving a hemiacetal moiety at numerous undesired sites on the chain.



389 **390** **391**

Figure 90. *N,O*-Acetal Installation During Synthesis of *dl*-Austamide

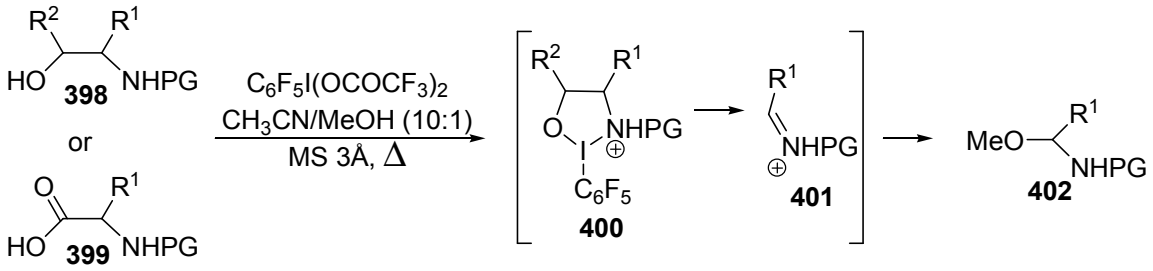
Another synthetic method with the same limitation, is shown below (Figure 91). Here, *N*-aryl amides are converted to silyl imidates in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf), and then used to attack an *in situ* generated oxycarbenium electrophile (originating from an acetal).[148] Besides the fact that this methodology would not be easily amenable to *N,O*-acetal installation on a long peptide chain, it is also limited to the use of *N*-aryl amides, and synthesis of only methyl or ethyl *N,O*-acetals with substituents between the nitrogen and oxygen atoms. *O*-alkylated *N,O*-acetals do not have the potential for direct application as traceless linkers like *O*-acylated *N,O*-acetals.



R^2 = Me, Et, Ph, *p*-Br-Ph, *p*-OMe-Ph, furan
R^3 = Me, Et

Figure 91. Reaction of *N*-Aryl Amides with Acetals Yielding *N,O*-Acetals

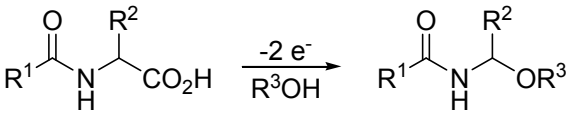
Kita found that oxidative fragmentation reactions of α-amino acids or β-amino alcohols could be induced by using a hypervalent iodine (III) reagent to yield methyl *N,O*-acetals (Figure 92).[149] It is believed that the hypervalent iodine atom binds to the amino nitrogen and alcoholic oxygen, forming a five membered ring which undergoes fragmentation to an iminium ion. Solvolysis with methanol yields the methyl *N,O*-acetals in 46-100% yield.



PG = protecting group

Figure 92. Oxidative Fragmentation Yielding *N,O*-Acetals

An electrochemical approach to methyl, ethyl, and isopropyl *N,O*-acetals can be applied to *N*-acylglycines and DL-α-alanines (Figure 93).[150] Electrolysis of the amino acids can be done in methanol, ethanol, or isopropanol to yield the *O*-alkylated *N,O*-acetals in 56-91% yield. This is yet another case that would not be easily applied to *N,O*-acetal installation on a peptide chain.



R^1 = Me, Ph, OBn
R^2 = H, Me
R^3 = Me, Et, *i*-Pr

Figure 93. Electrochemical Synthesis of *N,O*-Acetals

Pyrrolidine hemiacetals and *O*-alkylated *N,O*-acetals can be synthesized from pyrrolidine-2-aminols[151] or proline derivatives[152] through an oxidative radical reaction (Figure 94). When exposed to (diacetoxy-iodo)benzene (DIB) and iodine, a carbon-centered radical forms α to the nitrogen through loss of carbon monoxide or carbon dioxide depending on the starting material used. A single electron transfer (SET) then yields an iminium ion which can be quenched by either water or methanol. It appears this method could possibly be used for the installation of an *N,O*-acetal moiety located at a proline linkage in a peptide chain, provided the presence of a single terminal proline unit in the peptide chain.

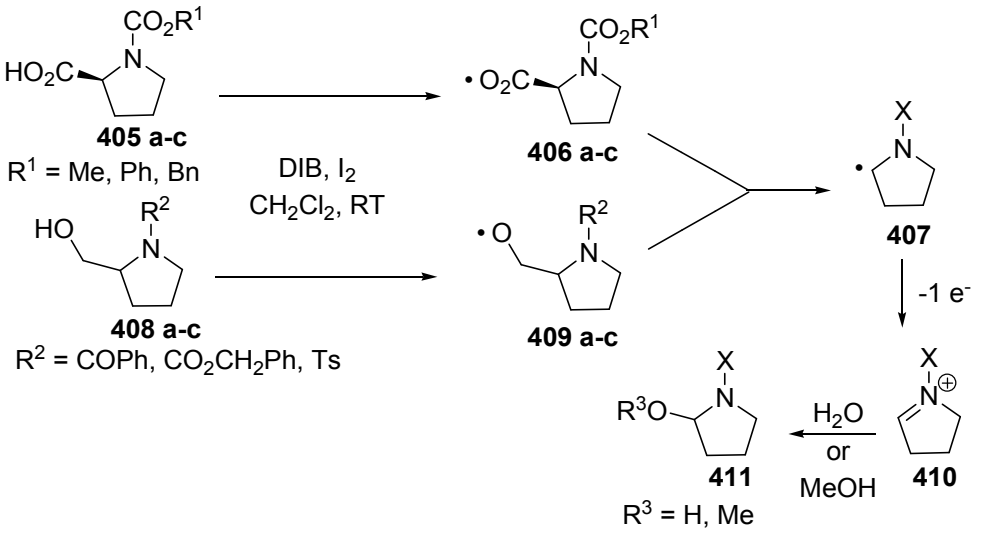


Figure 94. Oxidative Radical Reaction Yielding *N,O*-Acetals

Potential Applications

As mentioned before, if a convenient and general route toward installation of an *O*-acylated *N,O*-acetal moiety on peptide chains were available, there would be potential application of such modified peptides in biological chemistry (Figure 95). The electrophilic ester, for example, could be used to attach a fluorescent dye to a peptide drug. This could enable tracking of the drug through a biological system to provide insight on mode of action. If these modified peptides were used in bioconjugation applications instead, hydrolysis would release both the native peptide and its conjugate in traceless fashion.[153-155] *N,O*-acetals have proven useful in prodrug studies[156] for alteration of the lipophilicity,[157] transport properties,[157,158] and efficacy of drugs;[155] this could potentially be applied to peptide drugs or drugs containing a peptide bond as well.

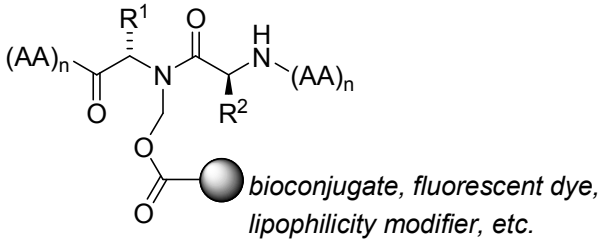


Figure 95. Potential Applications of *N,O*-Acetal Installed on Peptide Chain

Majumdar installed an *N*-acylated *N,O*-acetal onto acetaminophen in order to alter its lipophilicity and transport properties (Figure 96).[157] The effect of the length of

the ester chain was studied, and it was found, as expected, that the lipid solubilities measured in isopropyl myristate (IPM) increased as chain length increased. With a chain length of 6 carbon atoms, the lipophilicity was improved 69-fold compared to the parent drug. The solubilities of the prodrugs in water and pH 4 buffer were lower than the parent drug, which could help in the prevention of premature metabolism of phenolic drugs during oral delivery. When the prodrugs were administered to mice topically, there was an increased flux of drug delivery through the mouse skin compared to acetaminophen alone. A similar study was done with similar prodrugs of theophylline.[159]

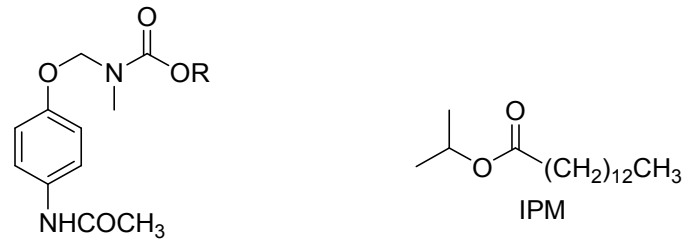


Figure 96. N-acylated *N,O*-acetal in Acetaminophen Prodrug Studies

Majumdar also studied the mechanism of hydrolysis of an *N,O*-acetal installed on naproxen.[153] The proposed mechanism is displayed below (Figure 97). It was hypothesized that aryl electron withdrawing groups would stabilize the SN_1 transition state more than aryl electron donating groups. The hypothesis was confirmed when a slower hydrolysis rate was observed for a prodrug bearing a *para*-ethyl ester aryl group verses one with a *para*-methoxy aryl group. The former prodrug exhibited the same hydrolysis rate in the pH range of 4-8.25, while the latter prodrug exhibited the fastest hydrolysis rate in pH 7.1 at 39 ºC.

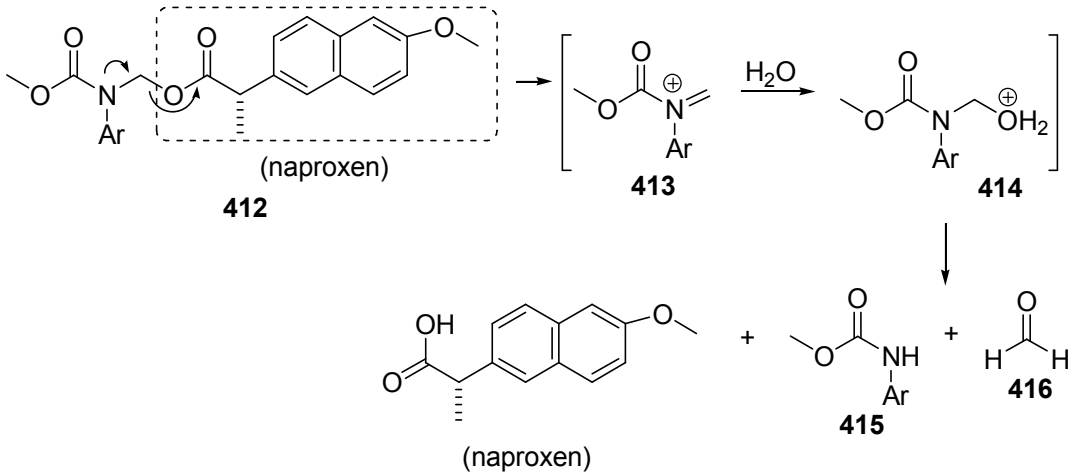


Figure 97. Mechanism of Hydrolysis of *N,O*-Acetal-Containing Prodrug

The mechanism of hydrolysis, or degradation, of the *N,O*-acetal moiety in peptide-like model prodrug compounds was studied by Bundgaard, et. al (Figure 98).[154] Here, compounds of type **417** were separately decomposed in acidic and neutral solutions, and the reaction mixtures were monitored by HPLC. It was found that each *O*-acylated *N,O*-acetal was quantitatively converted to the *N*-hydroxymethyl derivative, which was subsequently quantitatively converted to the parent peptide-like model compound **418**. This demonstrates the potential of the *N,O*-acetal moiety to be used as a traceless linker on peptide-drugs. The parent peptide-like model compound was obtained unaltered, while leaving behind only a simple carboxylic acid and aldehyde.

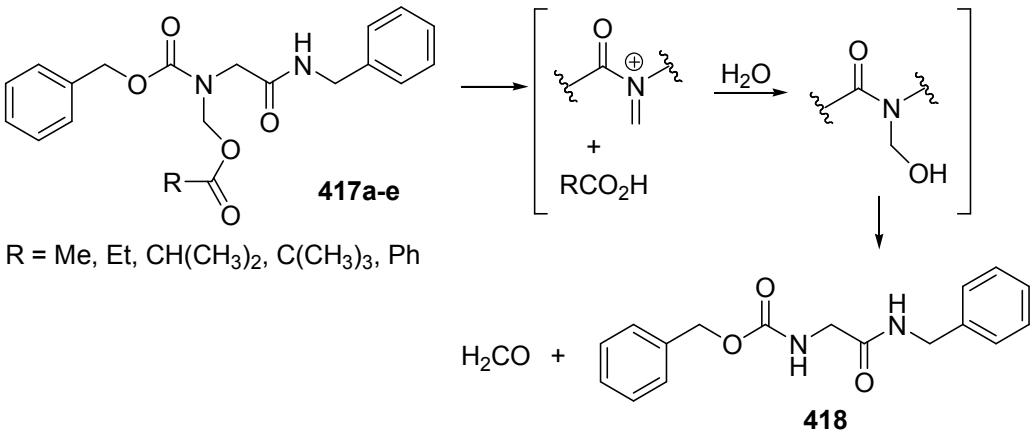


Figure 98. Degradation of the N,O-Acetal Moiety in Peptide-Like Model Prodrugs

The quinazoline structure **419a** (Figure 99) containing an *N,O*-acetal moiety was designed to be a prodrug of multiple inhibitors of the epidermal growth factor receptor (EGFR).[155] The overexpression of EGFR in cancerous cells leads to the

progression of many types of cancers. Support for the proposed physiological degradation pathway of **419a** was gathered by Jean-Claude, et. al., and is shown below (note the similarity to the degradation pathway depicted in Figure 97). When tested separately, quinazoline **419a** and its proposed metabolites **423**, **421**, and **422** all inhibited EGFR at lower IC_{50} values than the structurally similar control quinazoline **419b**, with amine **423** showing a 5-fold increase of inhibition. **419b** is known to degrade under physiological conditions into the EGFR inhibitor, 6-amino-4-anilinoquinazoline, and a cytotoxic DNA alkylating agent (methyldiazonium ion), and also lacks the *N,O*-acetal moiety. **423**, **421** and **419a** all inhibited the growth of NIH3T3 at lower IC_{50} values than control **419b**, with a 9.8-fold decrease of IC_{50} value for hydroxymethyltriazine **421**. (3T3 cell lines are highly susceptible to murine leukemia virus.[160]) The inhibition of related cell lines, NIH3T3/HER14 and NIH3T3/neu, was also higher for compounds **423**, **421**, **419a** and **422** than control **419b**, with a 13.8-fold increase of activity towards NIH3T3/HER14 for triazine **421** and a 183-fold increase of activity towards NIH3T3/neu for compounds **421** and **422.** Temozolomide (TEM) was used as a control cytotoxic DNA alkylating agent, and compounds **423**, **421**, **419a** and **422** all exhibited higher DNA-alkylating activity than TEM (and also higher activity than control **419b**). In fact, amine **423** showed a 226-fold increase of alkylating activity versus TEM. These last results support the proposed formation of the methyldiazonium ion from quinazoline **419a**.

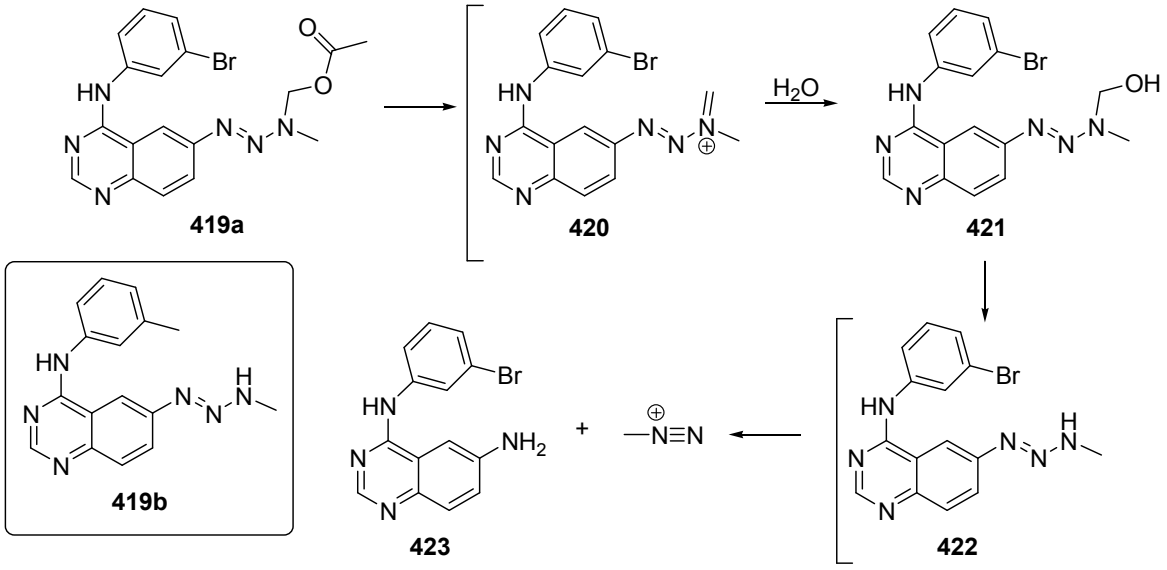
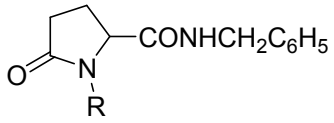


Figure 99. Proposed Physiological Degradation of Potential Inhibitor of EGFR

A study more closely related to peptide prodrugs demonstrated the effect of the installation of an *N,O*-acetal on the model peptide, L-pyroglutamyl benzylamide, **424** (Figure 100).[158] Peptide drugs are often plagued by rapid metabolism through proteolysis at the site of administration. **424** is readily hydrolyzed by pyroglutamyl

aminopeptidase, making it a useful control compound for studies with the goal of protection of the *N*-terminal pyroglutamyl residue in peptides from enzymatic cleavage. The half-life of **424** is a mere 10 minutes in an enzymatic solution of pyroglutamyl aminopeptidase. With the addition of an *N,O*-acetal moiety, however, the half-life of compounds **425** and **426** in an identical solution are 143 hours, and 61 minutes, respectively. Further, compound **426** was stable in a buffered solution at pH 7.4 for 64 minutes, but was readily hydrolyzed in an 80% human plasma solution to the parent pyroglutamyl benzylamide in 12 minutes, which shows the potential for this type of *N,O*-acetal-containing compound to be used as an orally administered prodrug.



424, R = H (*L*-pyroglutamyl benzylamide)
425, R = $CH(CO_2H)OAc$
426, R = $CH(CO_2Bn)OAc$

Figure 100. *L*-Pyroglutamyl Benzylamide and Derivatives

N,O-Acetal Installation on Dipeptides

Introduction

Towards the goal of incorporating *O*-acylated *N,O*-acetal functionality on long-chain peptides, we envisioned a synthetic route which makes use of an *N*-silylmethyl group (Figure 101). The *N*-silylmethyl group is stable under a plethora of peptide bond-constructing transformations, and can be easily oxidized and acylated after the completion of the desired peptide bonds. Moeller has presented an electrochemical oxidation of the *N*-silylmethyl group incorporated in dipeptides (Figure 101).[161] This method results in a methoxymethyl peptide **431** which can only be manipulated further under harshly acidic conditions. In our approach, however, a Tamao-Fleming oxidation gives the *N*-hydroxymethyl derivative **432**, which can be transformed to various esters under conditions that are compatible with a wider range of complex peptide systems.

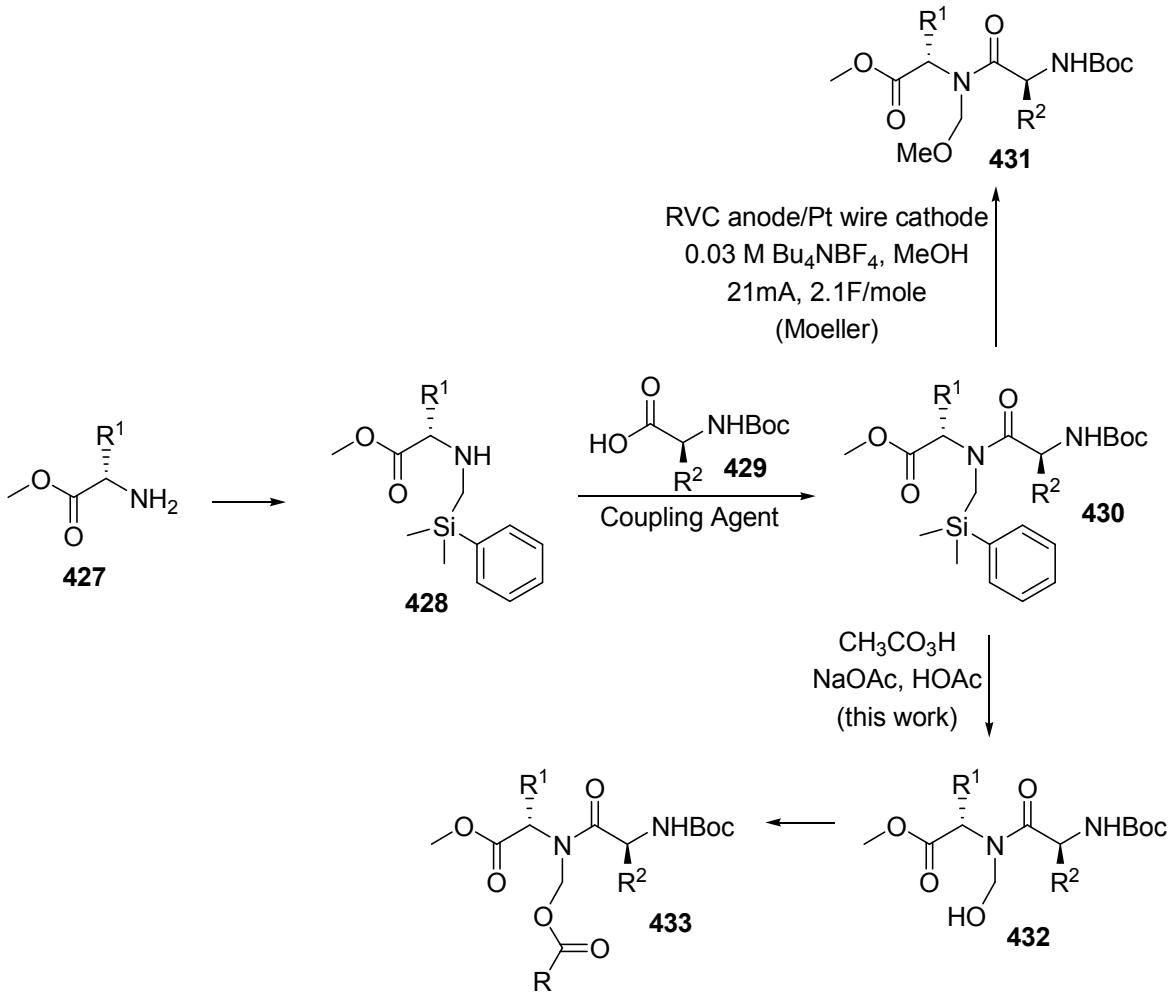


Figure 101. Methods of *N,O*-Acetal Installation on Dipeptides

Coupling N-*Silylmethyl Amino Acid Ester to* N-*Protected Amino Acids*

The initial *N*-silylmethyl amino acid was prepared according to a literature procedure by adding L-phenylalanine methyl ester hydrochloride **437** to (chloromethyl)dimethylphenylsilane, which gave the known product **436** in 60% yield (Figure 102).[162] This was then coupled with *N-tert*-butoxycarbonyl-protected glycine **434** according to the literature, and the known dipeptide derivative **438** was obtained in 72% yield.

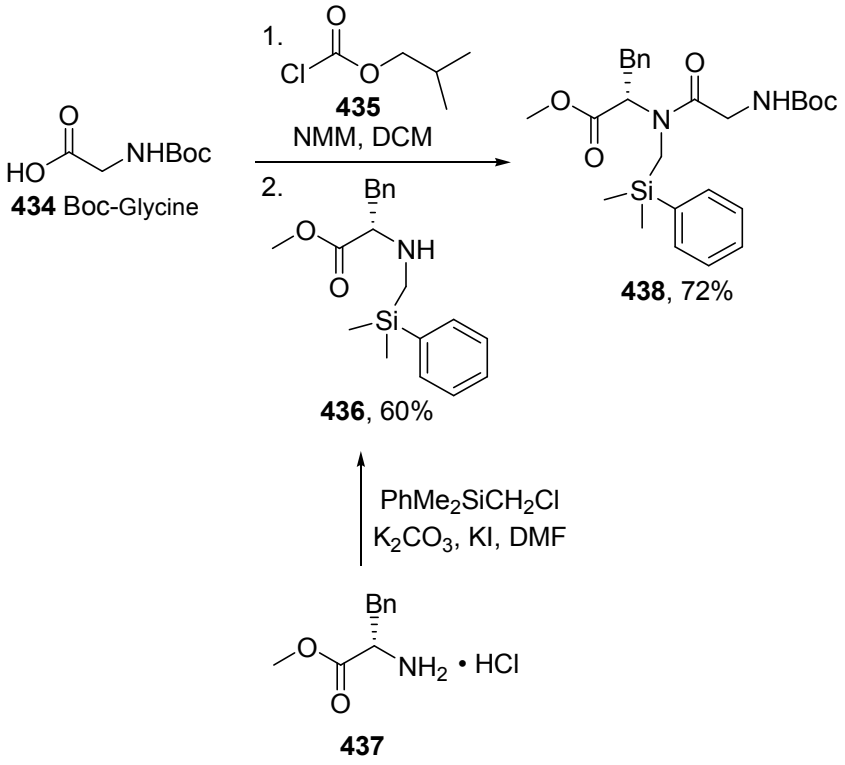


Figure 102. Synthesis and Coupling of *N*-Silylmethyl L-Phenylalanine

With this successful coupling method in hand, we sought to produce several additional *N*-silylmethyl dipeptide derivatives by coupling the *N*-silylmethyl L-phenylalanine **436** with more complex Boc-protected amino acids. With Boc-L-alanine, the expected coupling product was obtained, although in an unexpectedly low yield of 29% (Figure 103). An isobutylcarbamate byproduct, **442**, was isolated in 29% yield as well. This byproduct could have resulted either from compound **436** attacking the isobutylchloroformate reagent, or from **436** attacking at the wrong carbonyl of the activated Boc-alanine mixed anhydride intermediate **440** as shown.

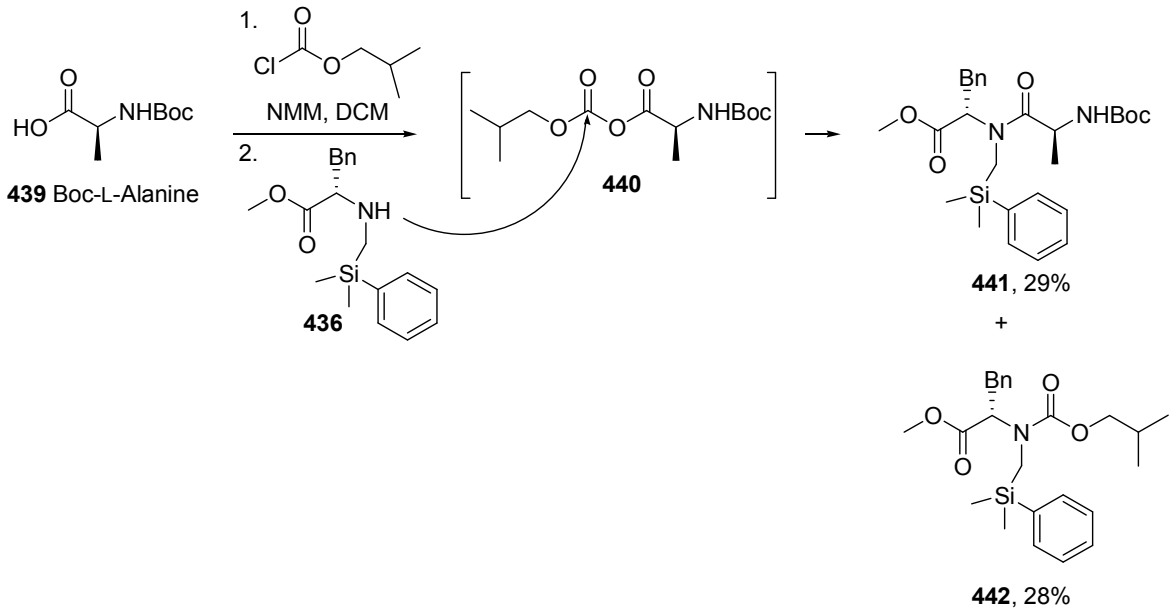


Figure 103. Isobutychloroformate Coupling With Boc-L-Alanine

In an attempt to ensure the complete formation of the activated Boc-L-alanine intermediate **440**, the initial step in the sequence was run at an elevated temperature (0ºC vs. -15 ºC) with a higher equivalence of isobutylchloroformate (2.2 eq vs. 1.1 eq) at a more concentrated level (0.27 M vs. 0.065M). To our delight, this reaction resulted in the desired coupling product **441** (Figure 103) in 50% yield. Subsequent experiments conducted with a lower equivalence of *N*-silylmethyl L-phenylalanine **436**, or with a higher temperature for the initial step (RT vs. 0 ºC) did not result in a higher yield of desired product.

The procedure with the modified initial step leading to a 50% yield of alanine-coupled product **441** was next applied to a coupling using Boc-L-phenylalanine, however none of the desired dipeptide derivative was obtained. In this experiment, the isobutylcarbamate byproduct **442** was isolated in 55% yield, and 46% of the *N*-silylmethyl **436** was recovered.

These last results lead us to consider using a method which would generate a mixed anhydride intermediate with more steric hindrance at the site where attack by **436** is not desired. For this purpose, Boc-L-phenylalanine was reacted with 2,4,6-trichlorobenzoylchloride **444** to generate the mixed anhydride intermediate **445** (Figure 104). The desired dipeptide derivative **446** was obtained from this method, however in a low yield of 18%.

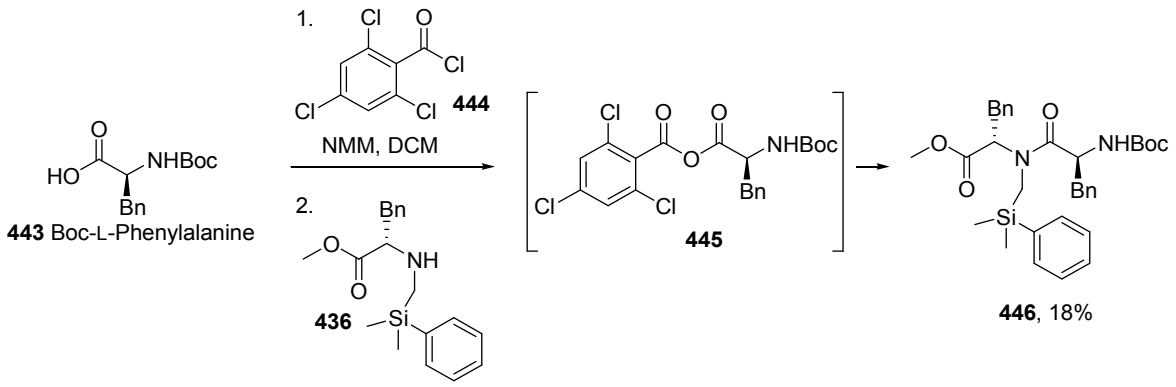


Figure 104. Coupling with Boc-L-Phenylalanine

It appeared from these results that the Boc-protected amino acid would need to be activated toward attack by means other than the generation of a mixed anhydride derivative. Therefore, we next investigated activation by generation of the acid chloride of the Boc-protected amino acids. Boc-glycine was chosen as a test case, and was reacted with oxalyl chloride under refluxing conditions according to the literature (Figure 105).[163] The reaction mixture from this initial step was next added to a solution of the *N*-silylmethyl **436** and triethylamine in dichloromethane (DCM) at 0 ºC, and this was stirred at room temperature overnight. Unfortunately, the *N*-silylmethyl starting material was recovered nearly quantitatively from this method.

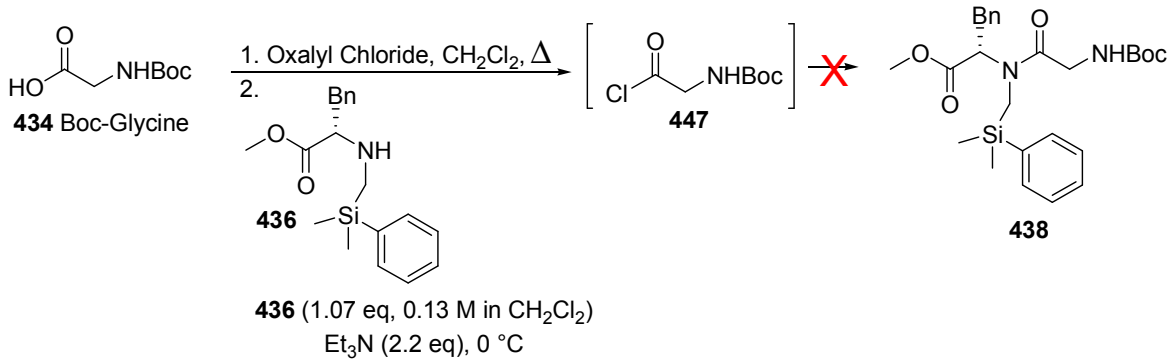


Figure 105. Attempted Coupling with Boc-Glycine Acid Chloride

A second attempt was made with a slight modification to the first step; one drop of dimethylformamide (DMF) was added along with the usual solvent, DCM. IR analysis of the reaction mixture of the first step versus a pure sample of Boc-glycine indicated a carbonyl shift from 1711 cm^{-1} to 1744 cm^{-1}. This shift could potentially result from the formation of the desired Boc-glycine acid chloride, however, no desired product was obtained after the second step, and the *N*-silylmethyl starting material was again recovered.

The Vilsmeier reagent (Figure 106), generated *in situ* from oxalyl chloride and DMF, is often used to generate acid chlorides when oxalyl chloride alone will not give the desired acid chloride.[164] Several modified reactions with Boc-glycine, and one with Boc-L-isoleucine, were conducted using a microwave reactor in the presence of Vilsmeier reagent, however, no desired coupling was observed and no clear evidence was gathered for the formation of the acid chloride of the Boc-protected amino acid. In the case of reaction with Boc-L-isoleucine, it appeared that a trace amount of cyclized amino acid may have been present in the crude reaction mixture.

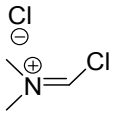


Figure 106. Vilsmeier Reagent

Since it appeared that Boc-L-isoleucine may have cyclized on itself to produce the known *N*-carboxy-α-amino acid anhydride **450** (NCA) derivative in the last method described (Figure 107), a literature procedure was followed to purposely bring about this cyclization in higher yield.[165] It was shown in the literature that NCA's can act as activated intermediates in amino acid coupling reactions,[166] however when the attempt was made using the NCA of L-isoleucine, no desired product was obtained, and only the *N*-silylmethyl starting material was recovered.

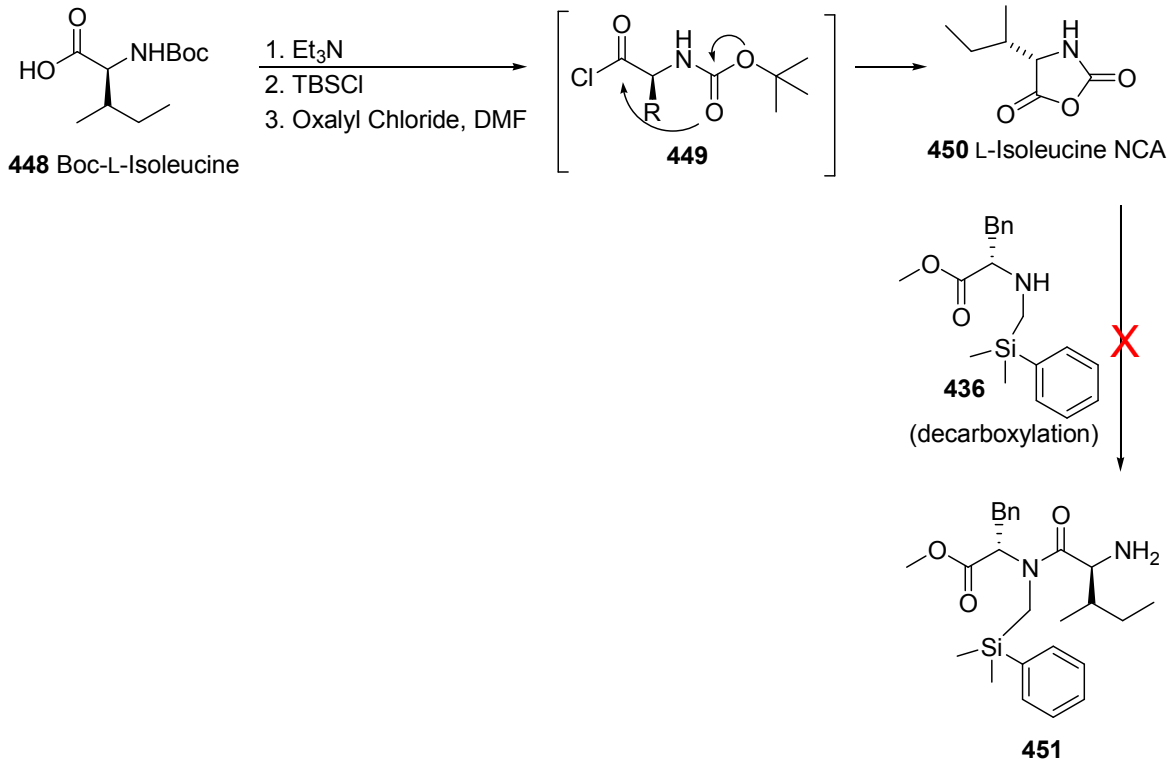


Figure 107. Attempted Coupling with L-Isoleucine NCA

The more traditional amino acid coupling reagent, dicyclohexylcarbodiimide (DCC), was next used along with additive *N*-hydroxybenzotriazole (HOBt) in an attempt to couple the *N*-silylmethyl **436** to Boc-L-alanine according to a literature procedure.[167] None of the desired coupling product was obtained, and 85% of **436** was recovered from the reaction mixture. A higher temperature version of the procedure (50 ºC vs. -5 ºC) using Boc-glycine instead was subsequently attempted according to a different literature procedure, however the desired coupling product was obtained in less than 2% yield (Figure 108).[168]

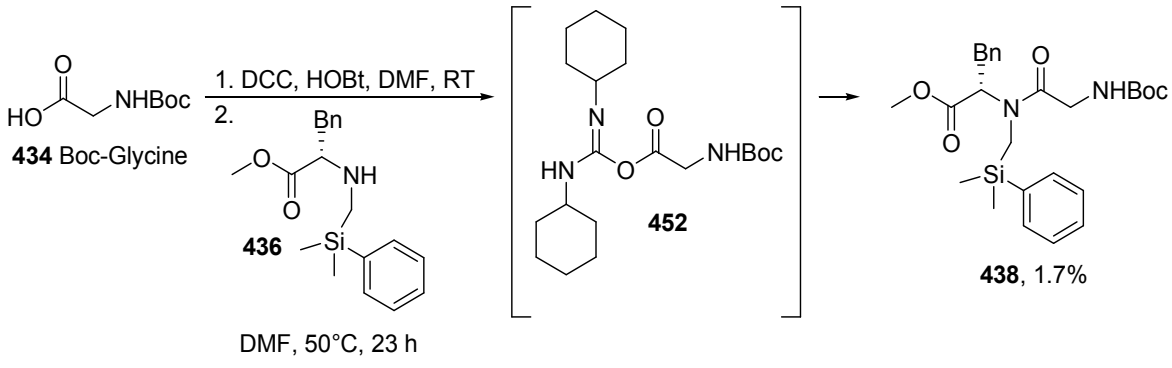


Figure 108. DCC Coupling with Boc-Glycine

A similar coupling approach was attempted using *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide (EDCI, Figure 109). Unlike DCC, the urea byproduct from EDCI is water soluble and easily removed from reaction mixtures through liquid-liquid extraction. A literature procedure was followed initially for a coupling with Boc-glycine (1-hydroxy-7-azabenzotriazole, HOAt, was replaced with HOBt).[169] In this reaction, EDCI and HOBt were added to a mixture of *N*-silylmethyl **436** and Boc-glycine at -10 ºC. The reaction was allowed to warm to room temperature and stir overnight. The expected product was isolated in only 4% yield. A slight change was made to the procedure in a second attempt; Boc-glycine was allowed to react with the EDCI/HOBt mixture for 30 minutes at room temperature prior to addition of the *N*-silylmethyl **436**. A slightly higher yield of 6% was obtained from this reaction.

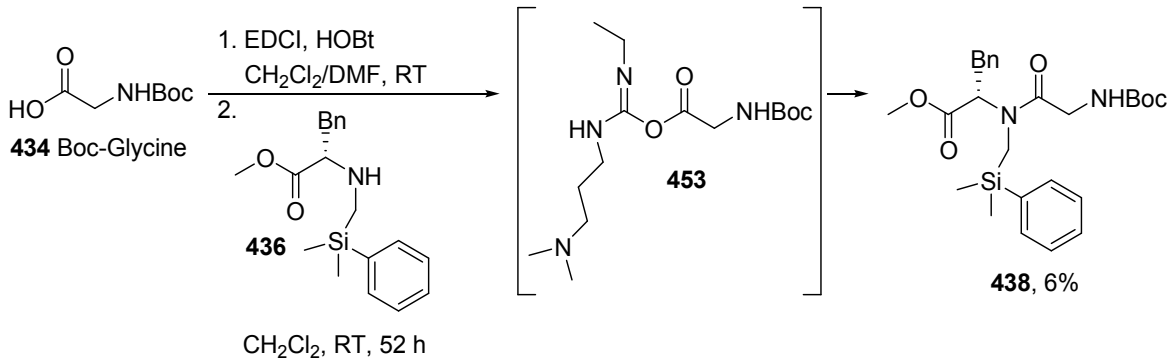


Figure 109. EDCI Coupling with Boc-Glycine

In an attempt to decrease reaction times, a microwave reactor was utilized in subsequent experiments with the EDCI/HOBt mixture. All reagents were added to a microwave reactor tube under inert gas and subjected to microwave reaction at 40 ºC for 20 minutes with the maximum power and pressure settings at 250 W and 300 PSI, respectively. A control experiment with Boc-glycine resulted in the appearance of expected product peaks in the crude NMR. When the same conditions were applied to a coupling with Boc-L-isoleucine, however, none of the expected product was obtained. This led us to consider the fact that the extra steric hindrance brought about by the *sec*-butyl group in Boc-L-isoleucine may be the cause of failed couplings in EDCI activation reactions.

A vast array of peptide coupling reagents and procedures appear in the literature, and many involve the coupling of secondary amines to activated, hindered *N*-protected amino acids. At this point in the project, it was unclear as to which coupling methods should be attempted. It was suggested to us that we try the reagent known as T3P (*n*-propanephosphonic acid anhydride) for our hindered coupling.[170] A literature procedure was first attempted using Boc-L-alanine, however this resulted in a complex reaction mixture, that when purified did not

contain the expected product (Figure 110).[171] A second attempt was made with a higher reaction temperature (room temperature vs. 0 ºC), however this gave the same results. When *N*-silylmethyl **436** was added after the addition of T3P in a third attempt, the results were also the same, even after a longer reaction time of 48 hours compared with the original duration of 21 hours.

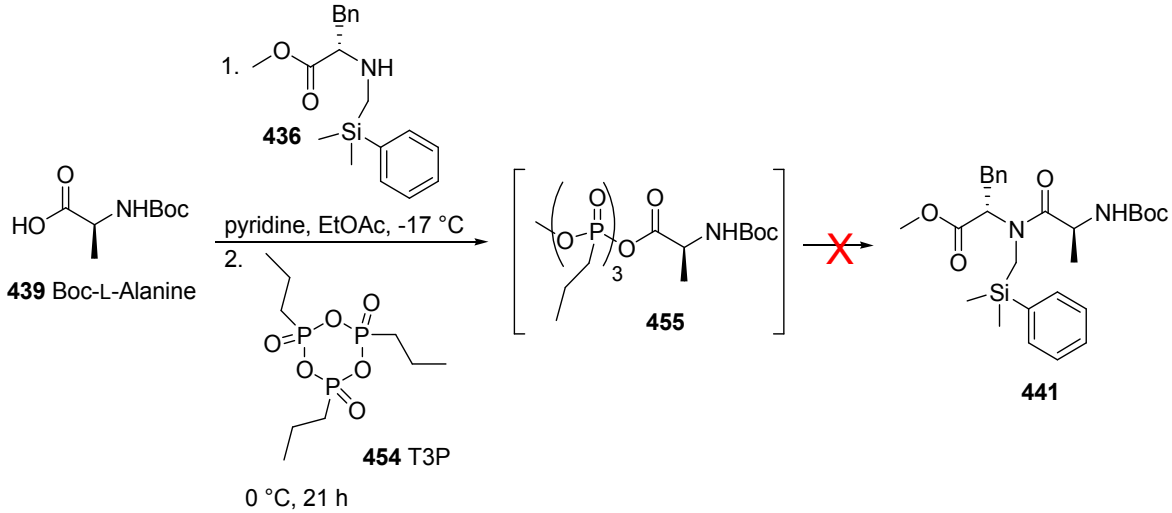


Figure 110. Attempted T3P Coupling with Boc-L-Alanine

We decided to try a different phosphate coupling reagent next, diphenylphosphinic chloride. Boc-glycine was chosen for a control experiment according to the literature, and ^{1}H NMR analysis revealed the expected product peaks (Figure 111).[172] When the method was applied to a coupling using Boc-L-isoleucine, however, none of the expected product was obtained, even after an extended reaction period of 26 hours compared with the initial 30 minute reaction duration. The same procedure was followed using Boc-L-isoleucine, but with stirring in a microwave apparatus for 30 minutes at 35 ºC rather than the original room temperature stir. This did not result in the expected product formation, and when this method was applied a third time to a more concentrated reaction mixture (0.34 M vs. 0.21 M with respect to *N*-silylmethyl **436**) at a higher temperature of 40 ºC for 40 minutes, the same results were obtained. Additionally, a second literature procedure was followed using Boc-L-Proline, however none of the expected product was obtained with this method either.[173]

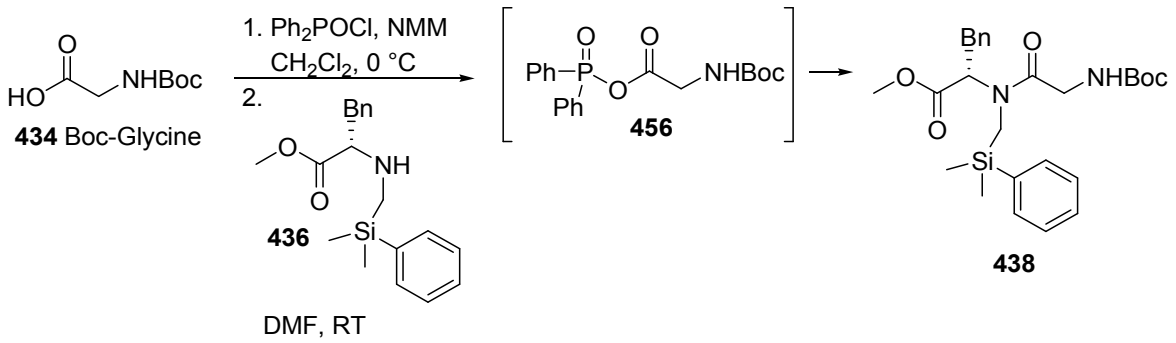


Figure 111. Diphenylphosphinic Chloride Coupling with Boc-Glycine

The last coupling reagent that was investigated was 2-bromo-1-ethyl pyridinium tetrafluoroborate (BEP, Figure 112). This reagent activates amino acids through the formation of the acid bromide derivative, which is expected to be more reactive than the acid chloride derivative based on carbon-halogen bond strength. BEP was synthesized and allowed to react in solution phase with Boc-L-isoleucine according to the literature,[174] however none of the expected product was obtained (24 hour reaction). A control experiment with Boc-glycine resulted in product formation as judged by ^{1}H NMR analysis of the crude reaction mixture. It, therefore, appeared again that the failure of the initial reaction utilizing Boc-L-isoleucine was due to steric hindrance at the desired site of attack.

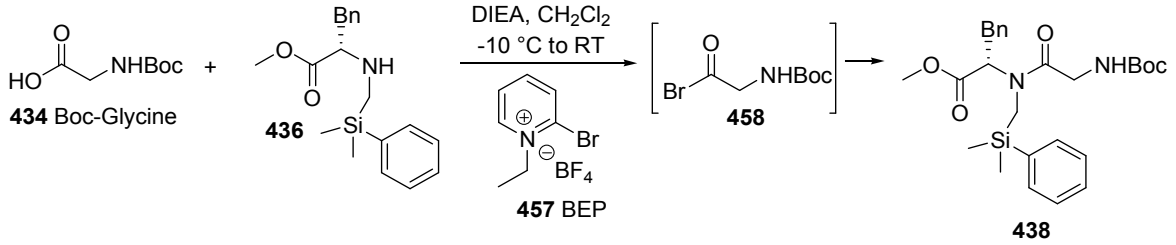


Figure 112. BEP Coupling with Boc-Glycine

We again attempted a microwave procedure for the reaction of *N*-silylmethyl **436** with Boc-L-isoleucine in the presence of BEP. In this experiment, BEP, Boc-L-isoleucine, and *N*-methylmorpholine (NMM) were all added to *N*-silylmethyl **436** in DCM under inert gas. After a 20 minute stir at 40 ºC with the maximum power and pressure set to 250W and 300 PSI, respectively, ^{1}H NMR analysis of the crude reaction mixture revealed the presence of all of the starting materials and none of the expected product. When this experiment was conducted in dichloroethane (DCE) at a higher temperature of 85 ºC, the ^{1}H NMR of the crude reaction mixture showed the presence of the BEP byproduct, 1-ethyl-2(1H)-pyridinone (Figure 113).

This byproduct could result either from the desired reaction of BEP with Boc-L-

isoleucine, or simply from reaction with water.

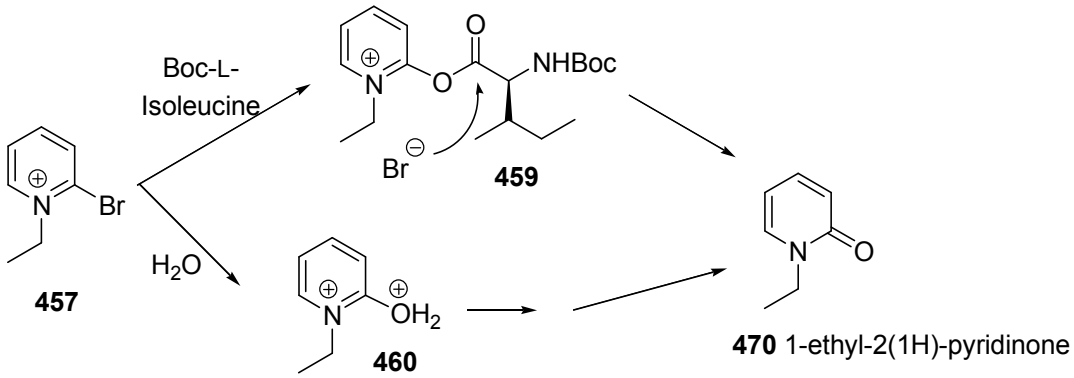


Figure 113. Formation of BEP Byproduct

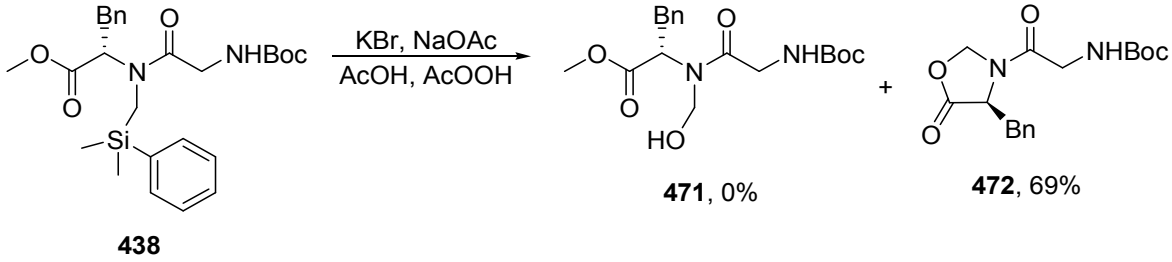
A control microwave experiment with only BEP in DCE at 95 ºC resulted in no reaction, indicating that the byproduct in the last experiment likely resulted from the desired reaction of BEP with the protected amino acid. If this were true, it would lend further support of the idea that the coupling reactions using various coupling reagents are unsuccessful with protected amino acids other than Boc-glycine due to the steric hindrance brought about by substituents in the α-position of the *C*-terminus of such amino acids. In a test case, the DCE microwave reaction mentioned above was attempted with Boc-L-isoleucine for a short reaction time of one minute. The ^{1}H NMR of the crude reaction mixture did contain the BEP byproduct peaks, so it appeared that the activated amino acid may have formed immediately upon exposure to BEP. The microwave reaction was conducted with Boc-L-proline in DMF rather than DCE at 100 ºC for 40 minutes, however this did not result in the desired product formation either.

With all of these results in hand, it appears that the initial synthetic scheme may need to be altered, perhaps incorporating a less hindered *N*-silylmethyl group on the amino acid ester component. Numerous publications present couplings of *N*-methylated amino acid esters with complex amino acid acceptors, however we have not found any examples with higher steric hindrance other than a methyl group at the *N*-terminus.

Tamao-Fleming Oxidation of N-Silylmethyl Functionality

With the Boc-glycine **438** and Boc-L-alanine **441** dipeptide products in hand, we set out to investigate the Tamao-Fleming Oxidation of these compounds. One of Fleming's publications was consulted for the initial procedure that we attempted

with **438**.[175] A product in high yield was isolated, and the ^{1}H NMR was evaluated. All of the expected product peaks were present except for the methoxy peak from the ester functional group. We suspected that the *N*-silylmethyl group had in fact been oxidized, and the resulting hydroxyl group subsequently cyclized onto the ester of the *C*-terminus, yielding a cyclized product **472** that would look similar by ^{1}H NMR to the expected oxidation product (Figure 114). Upon full characterization of the product, our assumption was confirmed. We next consulted an earlier Fleming publication utilizing the same reagents, but with a slightly different procedure, however this did not result in the formation of the expected product, the cyclized product, or the recovery of starting material.[176]



438

471, 0%

472, 69%

Figure 114. Tamao-Fleming Oxidation of Boc-Glycine Dipeptide

We briefly explored two different oxidation approaches next using Boc-glycine dipeptide **438**. The first approach utilized hydrogen peroxide as the oxidizing agent. A Tamao article was consulted for this approach, however none of the expected product was obtained, and 72% of the starting material was recovered.[177] The second approach, involving a method taken from Fleming, made use of fluoroboric acid diethyl ether complex along with peracetic acid, and was unsuccessful as well.[178]

At this point, we revisited the results from the oxidation leading to cyclic product **472**. The original route for the revelation of the *N,O*-acetal moiety from the *N*-silylmethyl group called for a two-pot process where the silylmethyl would first be oxidized to a hydroxyl group, and this would then participate in an intermolecular acylation reaction acting as a nucleophile (Figure 115). It occurred to us that the formation of the cyclic product **472** must have resulted from an initial oxidation of the silylmethyl group, followed by intramolecular acylation with the hydroxyl group acting as a nucleophile on the terminal ester group. We decided to try the Tamao-Fleming oxidation again, but with the addition of acetic anhydride in hopes that the hydroxyl group would participate in an intermolecular acylation reaction rather than the intramolecular cyclization. To our delight, when Boc-L-alanine dipeptide **441** was exposed to the original oxidation conditions in the presence of acetic anhydride, the desired *N,O*-acetal product **473** was obtained in 89% yield (Figure

115). The method was next applied to the Boc-glycine dipeptide **438** using two equivalents of acetic anhydride, however the cyclized product was again obtained. It appears that a higher equivalents of acetic anhydride will need to be used in future oxidation/acylation routes.

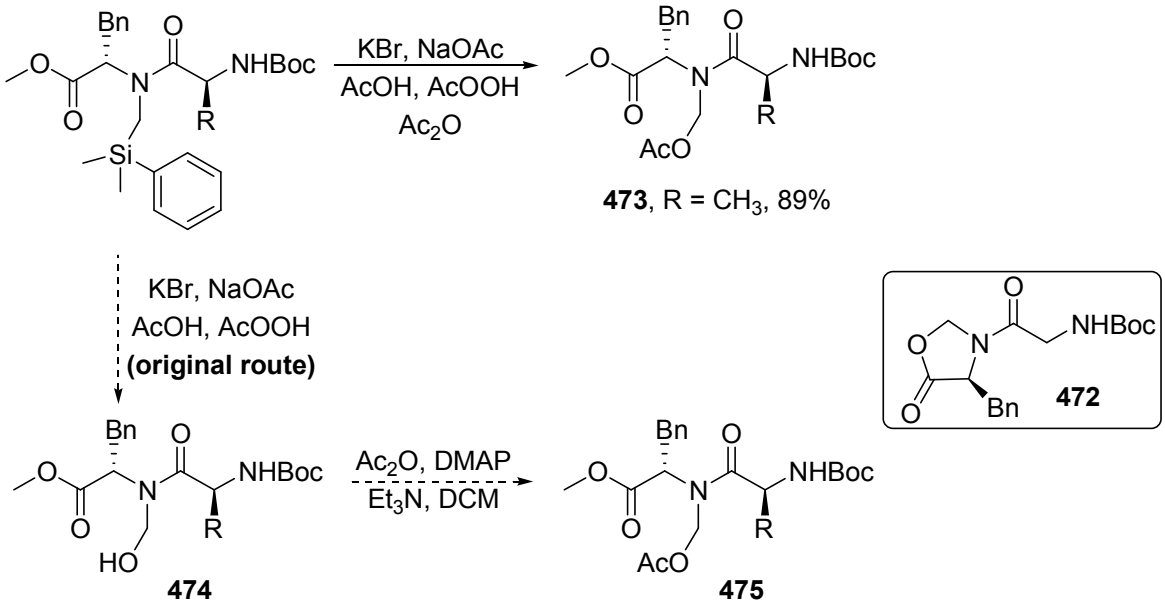


Figure 115. Oxidation/Acylation of *N*-Silylmethyl Group

Conclusion

The initial successful results for the installation of the *N,O*-acetal moiety on a dipeptide lay the groundwork for future group members to develop a general and versatile route for the incorporation of *N,O*-acetal functionality on long-chain peptides. Future group members will have the challenge of finding a suitable amino acid coupling method that will allow for a higher amount of steric hindrance in the α-position of the *N*-terminus beyond methyl functionality. When all work has been completed, this method should prove useful in various biochemical applications including the synthesis of biologically active natural products, fluorescent labeling studies and bioconjugation for the alteration of the lipophilicity, transport properties, and efficacy of countless pharmaceuticals.

CHAPTER 5

EXPERIMENTAL

Materials and Methods. Reactions employed oven- or flame-dried glassware under nitrogen unless otherwise noted. Toluene and CH_2Cl_2 were purchased inhibitor-free, sparged with argon, and passed through columns of activated alumina under argon atmosphere prior to use. Nitrogen was passed successively through columns of anhydrous $CaSO_4$ and R3-11 catalyst for removal of water and oxygen, respectively. All other materials were used as received from commercial sources unless otherwise noted. Thin layer chromatography (TLC) employed glass 0.25 mm silica gel plates with UV indicator. Flash chromatography columns were packed with 230–400 mesh silica gel as a slurry in the initial elution solvent. Gradient flash chromatography was conducted by adsorption of product mixtures on silica gel, packing over a short pad of clean silica gel as a slurry in hexane, and eluting with a continuous gradient as indicated. Radial chromatography refers to centrifugally accelerated thin-layer chromatography performed using commercially supplied rotors. Nuclear magnetic resonance (NMR) data were obtained at operating frequencies indicated in the text and are reported in units of ppm relative to TMS (internal standard in deuterated solvents in use). Infrared spectra were recorded using a single beam FT-IR spectrophotometer by standard transmission method. Optical rotations were determined using a digital polarimeter operating at ambient temperature. Low and high resolution mass spectra (TOF) were obtained from local instrumentation facilities services.

(*R*)-3-Iodo-2-methylpropyl 4-methylbenzenesulfonate (345). To (*R*)-(–)-3-bromo-2-methyl-1-propanol (0.34 mL, 3.25 mmol) in acetone (0.42 M) was added sodium iodide (1.22 g, 8.12 mmol) portionwise. The mixture was heated at reflux for 16 h, then concentrated and partitioned between H_2O with Et_2O. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated to afford (*R*)-3-iodo-2-methyl-1-propanol (479.7 mg, 74%) as a colorless oil which was used without further purification. To a solution of (*R*)-3-iodo-2-methyl-1-propanol (28 mg, 0.14 mmol) in CH_2Cl_2 (0.08 M) was added 4-(dimethylamino)pyridine (<1 mg), *p*-toluenesulfonyl chloride (29 mg, 0.15 mmol), and triethylamine (0.02 mL, 0.15 mmol). The mixture was stirred at RT for 20 h. Flash chromatography (1:1 hexane/CH_2Cl_2, Et_2O) furnished **345** (35.9 mg, 72%) as a yellow oil. $[\alpha]_D^{25}$ –8.0 (*c* 1.80, $CHCl_3$); IR (film from $CDCl_3$) 2970, 2917, 1593, 1454, 1262 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, 8.5 Hz, 2H), 7.37 (d, 8.4 Hz, 2H), 3.96 (dd, *J* = 5.1, 9.8 Hz, 1H), 3.86 (dd, *J* = 6.9, 9.7 Hz, 1H), 3.17 (d, *J* = 5.1 Hz, 2H), 2.45 (s, 3H), 1.92-1.78 (m, 1H), 0.98 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.9,

132.6, 129.9, 128.0, 73.2, 34.4, 21.6, 17.1, 10.5; HRMS (ESI) *m/z* calcd. for $C_{11}H_{15}O_3SNaI$ 376.9684 ([M+Na$^+$]), found 376.9707.

(*S*)-3-Amino-4-phenylmethyl-2-oxazolidinone (319). To a solution of **318**[19] (1.0005 g, 5.7 mmol) in THF (56 mL) was added KH (30 wt % in oil, 1.0895 g, 8.15 mmol) and solution was left to stir at RT for 0.5 h. Reaction was subsequently refluxed 1 h, allowed to cool to RT, then monochloramine[179] (85 mL of 0.52M solution in methyl *tert*-butyl ether) was added via cannula. After stirring at RT overnight, reaction was quenched with sat'd aq. $Na_2S_2O_3$ and allowed to stir 0.5 h. Solution was next transferred to a separatory funnel and organic layer separated and set aside. Aqueous layer was extracted with EtOAc 3x, and the combined ether and EtOAc layers were washed with brine, dried (an. Na_2SO_4), filtered and concentrated *in vacuo* to give **319** (1.0236g, 93%) as a white solid. Characterization of **319** has been previously reported.[19]

Preparation of *N*-Acylhydrazones. *N*-Acylhydrazones **320**, **321**, **338**, **339**, and **353**, were prepared as described below. Preparation and characterization of *N*-acylhydrazones **322**,[24] **37**,[19] **51d**,[23] **51e**,[23] and **51g**[23] have been previously reported.

(*S*)-3-(2-*tert*-Butyldimethylsilyloxypropylideneamino)-4-benzyloxazolidin-2-one (320). To a solution of ethyl (*S*)-(-)-2-(*tert*-butyldimethylsilyloxy)propionate (1 g, 4.3 mmol) in freshly distilled hexane (5.2 ml) at -78ºC was added DIBAL-H (5.2 ml, 5.2 mmol) dropwise over 0.5 h. After stirring an additional 1 h at -78ºC, reaction was quenched with water, allowed to warm to RT, then filtered through a plug of Celite with hexane. Filtrate was washed with brine, dried (an. Na_2SO_4), filtered and concentrated *in vacuo* to yield (2*S*)-2-[[(1,1-dimethylethyl)dimethylsilyl]oxy] propanal. To a solution of **319** (463.7 mg, 2.41 mmol) in toluene (2.4 ml) with approximately 30 mg 4Å molecular sieves was added (2*S*)-2-[[(1,1-dimethylethyl) dimethylsilyl]oxy]propanal in hexane (5.4 ml) dropwise over 10 min. Reaction was refluxed 3 h then filtered through Celite plug with EtOAc. Concentration and gradient flash chromatography (30:1 hexane/EtOAc to 3:1 hexane/EtOAc) furnished **320** (654.9 mg, 42% over 2 steps) as a white solid. mp 70 – 72°C; [α]$_D$ –8.99° (*c* 2.37, $CHCl_3$); IR (film) 2954, 2929, 2857, 1760, 1410, 1400, 1246, 1217, 1080 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95-7.91 (d, *J* = 5.29 Hz, 1H), 7.35-7.30, (m, 2H), 7.29-7.24 (m, 1H), 7.17-7.14 (m, 2H), 4.58-4.51 (m, 1H), 4.38-4.32 (m, 1H), 4.26-4.21 (dd, *J* = 8.67, 8.15 Hz, 1H), 4.14-4.09 (dd, *J* = 4.78, 8.88 Hz, 1H), 3.24-3.18 (dd, *J* = 3.36, 13.87 Hz, 1H), 2.83–2.77 (dd, *J* = 8.88, 13.87 Hz, 1H), 1.38-1.34 (d, *J* = 6.45, 3H), 0.91 (s, 9H), 0.11 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.1, 153.8, 135.1, 129.2, 128.9, 127.2, 69.2, 65.5, 57.1, 36.6, 25.7, 22.2, 18.1; MS (CI) *m*/*z* (relative intensity) 363 ([M+H]$^+$, 1%), 231 (100%), 128 (44%); Anal.

Calcd. for $C_{19}H_{30}N_2O_3Si$: C, 62.95; H, 8.34; N, 7.73. Found: C, 63.04; H, 8.31; N, 7.62.

(*S*)-3-((*E*)-But-2-enylideneamino)-4-benzyloxazolidin-2-one (321). To a mixture of (*S*)-3-amino-4-phenylmethyl-2-oxazolidinone (**319**, 639 mg, 3.32 mmol) in toluene (1 M), 4 Å molecular sieves (ca. 60 mg) and *p*-TsOH (ca. 10 mg) was added a solution of crotonaldehyde (2.72 mL, 33.2 mmol) in toluene (1.3 M) over 30 min. The reaction was stirred at RT for 28.5 h, then filtered through Celite, washing the cake with EtOAc. Concentration and flash chromatography (hexane/EtOAc) furnished *N*-acylhydrazone **321** (675 mg, 83%) as a colorless oil. $[\alpha]_D^{23}$ -24.3 (*c* 9.06, $CHCl_3$); IR (film from $CDCl_3$) 3056, 2913, 2843, 1761, 1287, 1095 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.5 Hz, 1H), 7.28-7.08 (m, 5H), 6.29-6.09 (m, 2H), 4.30 (dddd, *J* = 12.3, 8.6, 5.0, 3.6 Hz, 1H), 4.18 (dd, *J* = 8.8, 8.8 Hz, 1H), 4.04 (dd, *J* = 8.8, 5.1 Hz, 1H), 3.15 (dd, *J* = 3.5, 13.8 Hz, 1H), 2.75 (dd, *J* = 8.7, 13.8 Hz, 1H), 1.85 (d, *J* = 5.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9, 153.2, 139.7, 135.2, 129.2, 129.1, 128.8, 127.2, 65.6, 57.7, 37.2, 18.6; HRMS (ESI) *m/z* calcd. for $C_{14}H_{16}N_2O_2Na$ 267.1109 ($[M+Na]^+$), found 267.1116; calcd. for $C_{14}H_{17}N_2O_2$ 245.1290 ($[M+H]^+$), found 245.1300. Minor *Z* isomer ^1H NMR (300 MHz, $CDCl_3$) δ 8.67 (d, *J* = 9.7 Hz, 1H), 6.05-5.96 (m, 2H), 4.19 (dd, *J* = 8.8, 8.8 Hz, 1H), 1.91 (d, *J* = 5.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.5, 135.7, 128.3, 126.6, 65.7, 57.8, 37.3, 14.1; several *Z* isomer resonances were unresolved from those of the major *E* isomer.

(*S*)-*E*-4-Benzyl-3-(undecylideneamino)oxazolidin-2-one (338). To a mixture of (*S*)-3-amino-4-phenylmethyl-2-oxazolidinone (**319**, 246 mg, 1.28 mmol) in toluene (1 M), 4 Å molecular sieves (ca. 30 mg) and *p*-TsOH (ca. 0.1 mg) was added a solution of undecanal (1.30 mL, 6.30 mmol) in toluene (1.3 M) over 25–40 min. The reaction was heated at reflux for 2 h, then filtered through Celite, washing the cake with EtOAc. Concentration and flash chromatography (hexane/EtOAc) furnished *N*-acylhydrazone **338** (324 mg, 74%) as a colorless oil. $[\alpha]_D^{26}$ –1.2 (*c* 0.505, $CHCl_3$); IR (film from CH_2Cl_2) 3026, 2928, 1763, 1207, 1087 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (t, *J* = 5.6 Hz, 1H), 7.36-7.15 (m, 5H), 4.38-4.30 (m, 1H), 4.23 (dd, *J* = 8.4, 8.4 Hz, 1H), 4.07 (dd, *J* = 5.7, 8.7 Hz, 1H), 3.21 (dd, *J* = 3.6, 13.8 Hz, 1H), 2.79 (dd, *J* = 8.8, 13.8 Hz, 1H), 2.41-2.34 (m, 2H), 1.62-1.52 (m, 2H), 1.40-1.26 (m, 14H), 0.87 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4, 154.5, 135.3, 129.2, 128.9, 127.2, 65.7, 57.9, 37.3, 33.3, 31.9, 29.5, 29.4, 29.3, 29.2, 29.1, 26.4, 22.6, 14.1; HRMS (ESI) *m/z* calcd. for $C_{21}H_{32}N_2O_2Na$ 367.2361 ($[M+Na]^+$), found 367.2362.

(*S*)-*E*-4-Benzyl-3-((3-phenylpropylidene)amino)oxazolidin-2-one (339). A solution of **319** (512 mg, 2.66 mmol) in toluene (1 M) was added over 30 min to a mixture of 4 Å molecular sieves (ca. 30 mg), *p*-TsOH (ca. 0.1 mg) and

hydrocinnamaldehyde (1.75 mL, 13.3 mmol) in toluene (1.3 M). The reaction mixture was heated at reflux for 100 min, then filtered through Celite, washing the cake with EtOAc. Concentration and flash chromatography (hexane/EtOAc) furnished **339** (571 mg, 70%) as a yellow oil. $[\alpha]_D^{26}$ +0.99 (*c* 0.505, $CHCl_3$); IR (film from CH_2Cl_2) 3023, 2925, 1757, 1205, 1082 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.01 (t, *J* = 5.3 Hz, 1H), 7.34-7.08 (m, 10H), 4.36-4.27 (m, 1H), 4.23 (dd, *J* = 8.4, 8.4 Hz, 1H), 4.07 (dd, *J* = 5.2, 8.6 Hz, 1H), 3.15 (dd, *J* = 3.4, 13.8 Hz, 1H), 2.95-2.90 (m, 2H), 2.77-2.72 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 154.4, 140.6, 135.2, 129.3, 128.9, 128.5, 128.4, 127.2, 126.2, 65.7, 57.6, 37.0, 34.8, 32.6; HRMS (ESI) *m/z* calcd. for $C_{19}H_{20}N_2O_2Na$ 331.1422 ($[M+Na]^+$), found 331.1426; calcd. for $C_{19}H_{21}N_2O_2$ 309.1603 ($[M+H]^+$), found 309.1613.

Methyl *E*-2-(2-benzoyl-2-methylhydrazono)acetate (353). To methyl glyoxylate (1.24 g, 14.1 mmol) in toluene (30 mL) was added *N*-benzoyl-*N*-methyl hydrazine (1.90 g, 13.0 mmol), and the mixture was heated at reflux for 1 h under a Dean-Stark trap. Concentration and cooling afforded crystalline **353** as colorless plates, mp 127–129 °C. Concentration of the mother liquor and recrystallization afforded two additional crops, first from $CHCl_3/Et_2O$, second from $CHCl_3/Et_2O$/hexane for a total of 2.5 g (87%). IR (film from $CDCl_3$) 3064, 2958, 1712, 1675, 1569, 1446; ^1H (300 MHz, $CDCl_3$) δ 7.79-7.75 (m, 2H), 7.51-7.39 (m, 3H), 7.11 (s, 1H), 3.80 (s, 3H), 3.48 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 163.6, 133.0, 131.3, 130.6, 128.6, 127.6, 52.4, 29.5; HRMS (ESI) *m/z* calcd. for $C_{11}H_{12}N_2O_3Na$ 243.0746 ($[M+Na]^+$), found 243.0749; calcd. for $C_{11}H_{13}N_2O_3$ 221.0927 ($[M+H]^+$), found 221.0928.

Radical-Polar Crossover Annulation of *N*-Acylhydrazones (General Procedure A). To the *N*-acylhydrazone (0.1–0.3 mmol) in CH_2Cl_2 (0.17 M) in a Pyrex reaction tube was added $InCl_3$ (2.2–2.3 equiv), and this mixture was stirred for 3 h. To this mixture was added 1-chloro-3-iodopropane (or other iodide as specified in Table 1, 10.0 equiv) and $Mn_2(CO)_{10}$ (2.0 equiv). After briefly heating the flask to reflux, the N_2 inlet was quickly replaced with a teflon-coated glass stopper. The reaction mixture was irradiated (300 nm, Rayonet photoreactor) for 40–45 h, during which time the temperature was ca. 35°C. The reaction was diluted with an equal volume of hexane and NEt_3 (10 equiv) was added. After stirring for 1 h, the mixture was filtered through a pad of silica gel, eluting sequentially with 13:1 hexane/Et_2O, 5.5:1 hexane/Et_2O, and a more polar eluent (either 0.8:1 hexane/Et_2O or EtOAc). Concentration of the fraction eluted with the more polar eluent, followed by gradient flash chromatography (20:1 hexane/EtOAc to EtOAc) furnished adducts **323a**, **323b**, (***S,R*** and ***S,S)*****315**, (***S,R*** and ***S,S)*****332**, (***S,R*****)340**, (***S,R*****)341**, (***S,S*** and ***S,R)*****342**, (***S,R*****)343**, **354, (*S,S*)358, (*S,R*)359**.

(*S*)-3-(2,4-Dimethylpentan-3-ylamino)-4-benzyloxazolidin-2-one (323a). From **322** (77.4 mg, 0.314 mmol) by General Procedure A (2.3 eq $InCl_3$) was obtained **323a** (47.8 mg, 46%) as a yellow oil. IR (film from $CDCl_3$) 3023, 2954, 2868, 1757, 1242, 1086 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28-7.08 (m, 5H), 4.04-3.93 (m, 2H), 3.87-3.79 (m, apparent dddd, *J* = 3.7, 7.3, 10.2, 10.2 Hz, 1H), 3.29 (dd, *J* = 3.3, 13.2 Hz, 1H), 2.59- 2.49 (m, 2H), 1.89-1.78 (m, 2H), 0.99-0.91 (m, 12H); ^{13}C NMR (75MHz, $CDCl_3$) δ 158.1, 135.9, 129.0, 128.7, 126.8, 68.9, 65.0, 59.2, 36.2, 28.5, 28.1, 20.4, 19.8, 18.9, 18.8; HRMS (ESI) *m/z* calcd. for $C_{17}H_{26}N_2O_2Na$ 313.1892 ($[M+Na]^+$), found 313.1902; calcd. for $C_{17}H_{27}N_2O_2N$ 291.2073 ($[M+H]^+$), found 291.2082.

(*S*)-3-(2-*tert*-Butyldimethylsilyloxy,4-methylpentan-3-ylamino)-4-benzyloxazolidin-2-one (323b). From **320** (102.1 mg, 0.282 mmol) by General Procedure A (shorter reaction time of 18 h) (2.3 eq $InCl_3$) was obtained **323b** (42.1 mg, 37%) as a yellow oil. $[\alpha]_D^{21.4}$ 22.6 (*c* 2.01, $CHCl_3$); IR (film from $CDCl_3$) 2958, 2929, 2856, 1761, 1250, 1091 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35-7.14 (m, 5H), 4.3 (br d, *J* = 3.9 Hz, 1H), 4.07 (dd, *J* = 9.0, 16.5 Hz, 1H), 4.07-4.00 (m, 2H), 3.95-3.87 (m, 1H), 3.33 (dd, *J* = 3.3, 13.2 Hz, 1H), 2.71 (m, apparent dd, *J* = 4.5, 9.3 Hz, 1H), 2.6 (dd, *J* = 10.2, 13.4 Hz, 1H), 1.97 (m, 1H), 1.28 (d, *J* = 6.4 Hz, 3H), 1.08 (d, *J* = 1.8 Hz, 3H), 1.06 (d, *J* = 1.6 Hz, 3H), 0.90 (m, apparent br s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 158.1, 135.7, 129.0, 128.9, 127.1, 68.8, 68.2, 65.6, 58.5, 36.8, 29.7, 27.3, 25.8, 20.0, 19.9, 19.4, 18.0; HRMS (ESI) *m/z* calcd. for $C_{22}H_{38}N_2O_3SiNa$ 430.2628 ($[M+Na]^+$), found 430.2606; calcd. for $C_{22}H_{39}N_2O_3Si$ 407.2722 ($[M+H]^+$), found 430.2730.

(*S*)-4-Benzyl-3-((*R*)-2-ethylpyrrolidin-1-yl)oxazolidin-2-one ((*S,R*)315). From **37** (79.8 mg, 0.344 mmol) by General Procedure A (2.3 eq $InCl_3$) was obtained **(*S,R*)315**[23] (49.7 mg, 52%) as a colorless oil.

(*S*)-3-(1-Chlorononan-4-ylamino)-4-benzyloxazolidin-2-one (332a). From **51d** (52.5 mg, 0.19 mmol) by a modification of General Procedure A (shorter reaction time of 16 h) was obtained **332a** (24.7 mg, 37%) as a yellow oil which gradually transformed to a mixture of **332a** and **332**. Data for **332a**: ^1H NMR (400 MHz, $CDCl_3$) δ 3.29 (dd, *J* = 3.4, 13.3 Hz, 1H), 3.17-3.12 (ddd, *J* = 4.4, 8.0, 8.0, Hz 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 135.9, 129.04, 128.9, 127.1, 65.9, 59.6, 58.5, 45.3, 37.1, 32.2, 32.1, 29.3, 28.4, 24.8, 22.6, several resonances of **332a** were unresolved from those of **332**; MS (ESI) *m/z* (relative intensity) 377 ($[M+Na]^+$, ^{37}Cl, 26%), 375 ($[M+Na]^+$, ^{35}Cl, 70%), 355 ($[M+H]^+$, ^{37}Cl, 22%), 353 ($[M+H]^+$, ^{35}Cl, 63%),

317 ([M-Cl]$^+$, 100%). Optical rotation and high resolution mass spectra were not obtained because samples of **332a** transformed into **332**.

(*S*)-4-Benzyl-3-((*R*)-2-pentylpyrrolidin-1-yl)oxazolidin-2-one ((*S,R*)332). From **51d** (49.4 mg, 0.180 mmol) by General Procedure A (2.3 eq $InCl_3$) was obtained **(*S,R*)332** (39.6 mg, 70%) as a colorless oil. $[\alpha]_D^{26}$ +7.1 (*c* 0.525, $CHCl_3$); IR (film from $CDCl_3$) 2958, 2925, 2864, 1752, 1242, 1107 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.16 (m, 5H), 4.14 (dd, *J* = 8.5, 8.5 Hz, 1H), 3.99 (dd, *J* = 5.6, 8.8 Hz, 1H), 3.95-3.89 (m, 1H), 3.62-3.57 (m, 1H), 3.53 (ddd, *J* = 8.3, 8.3, 8.3 Hz, 1H), 3.41 (dd, *J* = 3.5, 13.3 Hz, 1H), 3.12 (ddd, *J* = 8.2, 8.2, 4.3 Hz, 1H), 2.60 (dd, *J* = 10.6, 13.3 Hz, 1H), 2.04-1.96 (m, 1H), 1.92-1.84 (m, 1H), 1.82-1.72 (m, 1H), 1.62-1.57 (m, 1H), 1.46-1.38 (m, 1H), 1.36-1.25 (m, 7H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 154.7, 136.1, 129.0, 128.8, 126.9, 66.3, 61.3, 60.3, 51.9, 38.9, 34.6, 32.3, 29.0, 25.9, 22.7, 21.7, 14.0; HRMS (ESI) *m/z* calcd. for $C_{19}H_{28}N_2O_2Na$ 339.2048 ([M+Na]$^+$), found 339.2064; calcd. for $C_{19}H_{29}N_2O_2$ 317.2229 ([M+H]$^+$), found 317.2225. Minor diastereomer ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.27 (ddd, *J* = 8.2, 8.2, 8.2 Hz, 1H), 2.52 (dd, *J* = 10.3, 13.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 136.3, 129.6, 128.77, 128.3, 67.4, 60.4, 57.9, 48.5, 39.5, 34.5, 29.7, 28.99, 26.1, 21.5; several minor diastereomer resonances were unresolved from those of **(*S,R*)332**.

Chemical Correlation of 332a and (*S,R*)332. A solution of chloropropyl adduct **332a** (24.7 mg, 0.07 mmol) in CH_3CN (0.023 M) was heated at reflux for 19 hr, then concentrated to afford **(*S,R*)332** (24.7 mg, 100%). Spectroscopic data (^{1}H and ^{13}C NMR) matched data for the sample of **(*S,R*)332** obtained from the radical–ionic annulation using General Procedure A, as described above.

(*S*)-4-Benzyl-3-(((*R*)-1,1-dichlorobutan-2-yl)amino)oxazolidin-2-one (DCM Adduct) From **37** (76 mg, 0.33 mmol) by the General Procedure A (except operating at a lower concentration of 0.057M in CH_2Cl_2) were obtained **(*S,R*)315** (39.4 mg, 44%) and DCM Adduct[23] (18.6 mg, 14%) as a yellow oil.

(*S*)-4-Benzyl-3-((*R*)-hexan-3-ylamino)oxazolidin-2-one (330) From **37** (31.2 mg, 0.13 mmol) and 1,3-diiodopropane (0.15 mL, 1.34 mmol) by the General Procedure A (2.2 eq $InCl_3$) was obtained **330**[23] (4.9 mg, 13%) as a yellow oil.

(*S*)-4-Benzyl-3-((*R*)-2-decylpyrrolidin-1-yl)oxazolidin-2-one ((*S,R*)340). From **338** (42.5 mg, 0.123 mmol) by General Procedure A (2.2 eq $InCl_3$) was obtained **(*S,R*)340** (25.6 mg, 54%) as a yellow oil. $[\alpha]_D^{23}$ 1.3 (*c* 0.08, $CHCl_3$); IR (film from CH_2Cl_2) 3019, 2921, 1753, 1234, 1095, 1025 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.16 (m, 5H), 4.15 (dd, *J* = 8.6, 8.6 Hz, 1H), 4.00 (dd, *J* = 5.6, 8.9 Hz, 1H), 3.96-3.90 (m, 1H), 3.60-3.56 (m, 1H), 3.53 (ddd, *J* = 8.4, 8.4, 8.4 Hz, 1H), 3.42 (dd,

J = 3.6, 13.4 Hz, 1H), 3.12 (ddd, *J* = 4.3, 8.2, 8.2 Hz, 1H), 2.61 (dd, *J* = 10.7, 13.3 Hz, 1H), 2.04-1.97 (m, 1H), 1.94-1.85 (m, 1H), 1.81-1.73 (m, 1H), 1.59-1.56 (m, 2H), 1.45-1.38 (m, 1H), 1.30-1.25 (m, 16H), 0.88 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8, 136.2, 129.0, 128.8, 126.9, 66.3, 61.3, 60.3, 51.9, 38.9, 34.7, 31.9, 30.1, 29.73, 29.69, 29.63, 29.3, 29.0, 26.2, 22.7, 21.7, 14.1; HRMS (ESI) *m/z* calcd. for $C_{24}H_{38}N_2O_2Na$ ($[M+Na]^+$) 409.2831, found 409.2823; calcd. for $C_{24}H_{39}N_2O_2$ ($[M+H]^+$) 387.3012, found 387.3036.

(*S*)-4-Benzyl-3-((*R*)-2-phenethylpyrrolidin-1-yl)oxazolidin-2-one ((*S,R*)341). From **339** (31.0 mg, 0.101 mmol) by General Procedure A (2.2 eq $InCl_3$) was obtained **(*S,R*)341** (21.2 mg, 60%) as off-white crystals. $[\alpha]_D^{25}$ –2.4 (*c* 0.805, $CHCl_3$); IR (film from $CDCl_3$) 3027, 2932, 1757, 1599, 1245, 1036 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.20 (m, 10H), 4.19 (dd, *J* = 8.6, 8.6 Hz, 1H), 4.06 (dd, *J* = 5.5, 8.9 Hz, 1H), 4.02-3.97 (m, 1H), 3.80-3.74 (m, 1H), 3.62 (ddd, *J* = 8.4, 8.4, 8.4 Hz, 1H), 3.46 (dd, *J* = 3.6, 13.3 Hz, 1H), 3.23 (ddd, *J* = 4.3, 8.2, 8.2 Hz, 1H), 2.76-2.64 (m, 3H), 2.18-2.10 (m, 1H), 2.05-1.96 (m, 2H), 1.93-1.85 (m, 1H), 1.76-1.68 (m, 1H), 1.61-1.54 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8, 142.3, 136.0, 129.0, 128.8, 128.4, 128.3, 127.0, 125.9, 66.2, 61.3, 60.1, 51.9, 38.9, 36.7, 32.6, 29.1, 21.8; HRMS (ESI) *m/z* calcd. for $C_{22}H_{27}N_2O_2$ 351.2073 ($[M+H]^+$), found 351.2101; calcd. for $C_{22}H_{26}N_2O_2Na$ 373.1892 ($[M+Na]^+$), found 373.1895.

(*S*)-4-Benzyl-3-((*S*)-2-isobutylpyrrolidin-1-yl)oxazolidin-2-one ((*S,S*)342). From **51e** (26.3 mg, 0.101 mmol) by General Procedure A (2.2 eq $InCl_3$) was obtained **(*S,S*)342** (26.4 mg, 86%) as yellow oil. $[\alpha]_D^{26}$ +2.9 (*c* 0.735, $CHCl_3$); IR (film from $CDCl_3$) 3027, 2950, 1748, 1233, 1098 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.17 (m, 5H), 4.15 (dd, *J* = 8.6, 8.6 Hz, 1H), 3.99 (dd, *J* = 5.4, 8.9 Hz, 1H), 3.96-3.90 (m, 1H), 3.70-3.64 (m, 1H), 3.50 (ddd, *J* = 8.5, 8.5, 8.5 Hz, 1H), 3.40 (dd, *J* = 3.5, 13.3 Hz, 1H), 3.11 (ddd, *J* = 4.3, 8.2, 8.2 Hz, 1H), 2.59 (dd, *J* = 10.6, 13.2 Hz, 1H), 2.07-2.00 (m, 1H), 1.94-1.86 (m, 1H), 1.82-1.74 (m, 1H), 1.67-1.57 (m, 1H), 1.46-1.35 (m, 2H), 1.29-1.24 (m, 1H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 154.7, 136.1, 129.0, 128.8, 126.9, 66.2, 60.3, 59.8, 51.7, 44.2, 38.8, 29.5, 26.0, 23.9, 22.4, 21.7; HRMS (ESI) *m/z* calcd. for $C_{18}H_{27}N_2O_2$ 303.2073 ($[M+H^+]$), found 303.2085.

(*S*)-4-Benzyl-3-((2*R*,4*S*)-2-ethyl-4-methylpyrrolidin-1-yl)oxazolidin-2-one (*(S,R*)343) From **37** (23.2 mg, 0.10 mmol) and **345** by General Procedure A (2.2 eq $InCl_3$) was obtained **(*S,R*)343** (12 mg, 42%) as a yellow oil. $[\alpha]_D^{23}$ +0.4 (*c* 0.26, $CHCl_3$); IR (film from $CDCl_3$) 2958, 2868, 1757, 1454, 1233, 1099; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.16 (m, 5H), 4.14 (dd, J = 8.6, 8.6 Hz, 1H), 3.99 (dd, *J* = 5.3, 8.9 Hz, 1H), 3.94-3.90 (m, 1H), 3.66-3.65 (m, 1H), 3.62 (dd, *J* = 9.0, 9.0 Hz, 1H), 3.41 (dd, *J* = 3.6, 13.9 Hz, 1H), 2.81 (dd, *J* = 6.6, 8.7 Hz, 1H), 2.59 (dd, *J* = 10.7,

13.3 Hz, 1H), 2.46-2.41 (m, 1H), 2.13-2.08 (m, 1H), 1.70-1.65 (m, 1H), 1.37-1.32 (m, 1H), 1.07-1.02 (m, 1H), 1.04 (d, *J* = 7.3 Hz, 3H), 0.91 (t, *J* = 7.3 Hz, 3H);^{13}CNMR (125 MHz, $CDCl_3$) δ 154.8, 136.2, 129.0, 128.8, 126.9, 66.1, 64.0, 60.4, 60.2, 38.8, 38.2, 30.2, 26.9, 20.3, 10.2; HRMS (ESI) *m/z* calcd. for $C_{17}H_{25}N_2O_2$ 289.1916 ([M+H$^+$]), found 289.1915; calcd. for $C_{17}H_{24}N_2O_2Na$ 311.1735 ([M+Na$^+$]), found 311.1732.

(S)-3-((R)-5,5-Dimethylhexan-3-ylamino)-4-benzyloxazolidin-2-one (A1). From **37** (30.9 mg, 0.133 mmol) by General Procedure A (shorter reaction time of 19.5 h) was obtained **A1** (4.7 mg, 12%) as a dark yellow oil. $[\alpha]_D^{23.5}$ 14 (*c* 0.24, $CDCl_3$); IR (film from $CDCl_3$) 3030, 2932, 2867, 1759, 1240, 1029 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.17 (m, 5H), 4.14 (dd, *J* = 8.7, 8.7 Hz, 1H), 4.04 (dd, *J* = 3.7, 8.9 Hz, 1H), 3.92-3.87 (m, 1H), 3.35 (dd, *J* = 2.9, 13.4 Hz, 1H), 3.18-3.13 (m, 1H), 2.62 (dd, *J* = 10.4, 13.3 Hz, 1H), 2.06-2.01 (m, 1H), 1.60-1.44 (m, 1H), 1.39 (dd, *J* = 2.9, 15.0 Hz, 1H), 1.30-1.22 (m, 1H), 1.02 (s, 9H), 0.97 (t, *J* = 7.3 Hz; 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.4, 136.1, 129.2, 128.9, 127.0, 65.6, 60.2, 57.6, 45.9, 36.9, 30.4, 30.0, 26.9, 9.1; HRMS (ESI) *m/z* calcd. for $C_{18}H_{28}N_2O_2Na$ 327.2048 ([M+Na]$^+$), found 327.2062. Minor Diastereomer ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.50 (dd, *J* = 4.6, 4.6 Hz, 1H), 3.98 (dd, *J* = 8.4, 8.4 Hz, 1H), 3.46 (dd, *J* = 3.2, 13.4 Hz, 1H), 2.56 (dd, *J* = 13.0, 13.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.3, 128.8, 67.3, 59.4, 39.1, 29.7, 21.5, 11.7; several minor diastereomer resonances were unresolved from those of **A1**.

Methyl 1-(*N*-methylbenzamido)pyrrolidine-2-carboxylate (*rac*-354). From **353** (22.0 mg, 0.100 mmol) by General Procedure A (2.2 eq $InCl_3$) was obtained racemic **354** (14.7 mg, 56%) as a yellow oil. IR (film from $CDCl_3$) 2929, 1736, 1638, 1442, 1262 cm^{-1}; ^{1}H NMR (400 MHz, DMSO, 80°C) δ 7.44-7.42 (m, 2H), 7.36-7.30 (m, 3H), 3.76-3.72 (m, 1H), 3.11-3.07 (m, 2H), 3.42 (s, 3H), 3.00 (s, 3H), 2.03-1.94 (m, 1H), 1.83-1.76 (m, 2H), 1.73-1.65 (m, 1H); ^{13}C NMR (100 MHz, DMSO) δ 171.3, 171.0, 136.4, 128.5, 126.8, 126.7, 60.3, 50.8, 50.2, 28.4, 26.5, 21.5; HRMS (ESI) *m/z* calcd. for $C_{14}H_{18}N_2O_3Na$ 285.1215 ([M+Na$^+$]), found 285.1221; calcd. for $C_{14}H_{19}N_2O_3$ 263.1400 ([M+H$^+$]), found 263.1405.

Modified Radical–Ionic Annulation of *N*-Acylhydrazones (General Procedure B). General Procedure A was employed, with the following modification: The reaction mixture was irradiated (300 nm, Rayonet photoreactor) 23–24 h. After filtration of the crude product through silica gel, the fraction eluting with 0.8:1 hexane/Et_2O was concentrated in vacuo, then heated with NaI (2.5 eq) in refluxing CH_3CN (0.3 M) for 1–2 d. After concentration, the residue was partitioned

between Et_2O and H_2O. The organic phase was dried (Na_2SO_4), concentrated, and purified by radial chromatography (hexane/Et_2O).

(*S*)-4-Benzyl-3-((*R*)-2-ethylpiperidin-1-yl)oxazolidin-2-one (355). From hydrazone **37** (28.0 mg, 0.12 mmol) and 1-chloro-4-iodobutane (0.15 mL, 1.23 mmol) by General Procedure B (2.3 eq $InCl_3$, omitting the NEt_3 step from the workup) was obtained **355** (16.4 mg, 47%) as a yellow oil. $[\alpha]_D^{24}$ +13.3 (*c* 0.77, $CHCl_3$); IR (film from $CDCl_3$) 3032, 2938, 2848, 1757, 1397, 1230, 1082, 1025 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33-7.15 (m, 5H), 4.16 (dd, *J* = 8.7, 8.7 Hz, 1H), 4.00 (dd, *J* = 6.7, 8.9 Hz, 1H), 3.92-3.86 (m, 1H), 3.58-3.54 (m, apparent t, *J* = 11.5 Hz, 1H), 3.45 (dd, *J* = 3.7, 13.3 Hz, 1H), 3.35-3.31 (m, 1H), 2.98-2.95 (m, 1H), 2.58 (dd, *J* = 10.8, 13.2 Hz, 1H), 1.84-1.81 (m, 1H), 1.70-1.63 (m, 3H), 1.60-1.52 (m, 1H), 1.34-1.25 (m, 2H), 1.22-1.08 (m, apparent qd, *J* = 3.2, 13.2 Hz, 1H), 0.91 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2, 136.2, 128.9, 128.8, 126.9, 66.8, 61.5, 60.5, 54.6, 38.7, 30.8, 26.5, 25.6, 23.8, 9.5; HRMS (ESI) *m/z* calcd. for calcd. for $C_{17}H_{24}N_2O_2Na$ ($[M+Na]^+$) 311.1735, found 311.1728; calcd. for $C_{17}H_{25}N_2O_2$ ($[M+H]^+$) 289.1916, found 289.1912.

(*S*)-4-Benzyl-3-((*R*)-2-decylpiperidin-1-yl)oxazolidin-2-one (356). From hydrazone **338** (30.5 mg, 0.089 mmol) and 1-chloro-4-iodobutane (0.11 mL, 0.89 mmol) by General Procedure B (2.3 eq $InCl_3$, omitting the NEt_3 step from the workup) was obtained **356** (24.9 mg, 70%) as a colorless oil. $[\alpha]_D^{23.9}$ +4.02 (*c* 0.82, $CHCl_3$); IR (film from $CDCl_3$) 3026, 2925, 2852, 1755, 1396, 1225, 1084, 1022 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33-7.16 (m, 5H), 4.17 (dd, *J* = 8.7, 8.7 Hz, 1H), 4.00 (dd, *J* = 6.6, 9.0 Hz, 1H), 3.89-3.83 (m, 1H), 3.58-3.54 (m, apparent t, 11.1 Hz, 1H), 3.44 (dd, *J* = 3.6, 13.2 Hz, 1H), 3.41-3.35 (m, 1H), 2.97-2.95 (m, apparent d, *J* = 10.7 Hz, 1H), 2.57 (dd, *J* = 10.8, 13.2 Hz, 1H), 1.84-1.80 (m, 1H), 1.69-1.65 (m, 2H), 1.61-1.55 (m, 2H), 1.36-1.13 (m, 19H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3, 136.4, 129.1, 129.0, 127.1, 67.0, 60.8, 60.7, 54.8, 38.9, 33.3, 32.0, 31.7, 30.3, 29.9, 29.76, 29.75, 29.5, 26.7, 25.4, 24.0, 22.8, 14.2; HRMS (ESI) *m/z* calcd. for $C_{25}H_{40}N_2O_2Na$ ($[M+Na]^+$) 423.2987, found 423.2988; calcd. for $C_{25}H_{41}N_2O_2$ ($[M+H]^+$) 401.3168, found 401.3176.

(*S*)-4-Benzyl-3-((*R*)-2-phenethylpiperidin-1-yl)oxazolidin-2-one (357). From hydrazone **339** (32.0 mg, 0.10 mmol) and 1-chloro-4-iodobutane (0.13 mL, 1.04 mmol) by modified general procedure B (2.3 eq $InCl_3$) was obtained **357** (25.9 mg, 68%) as a yellow solid. mp 78–81 °C; $[\alpha]_D^{23}$ +15.0 (*c* 1.19, $CHCl_3$); IR (film from $CDCl_3$) 3027, 2938, 2856, 1757, 1397, 1225, 1078, 1021 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30-7.12 (m, 10H), 4.10 (dd, *J* = 8.9, 8.9 Hz, 1H), 3.97 (dd, *J* = 6.4, 9.0 Hz, 1H), 3.88-3.82 (m, 1H), 3.60-3.56 (m, 1H), 3.52-3.48 (m, 1H), 3.42 (dd, *J* = 3.6, 13.2 Hz, 1H), 2.99-2.97 (m, 1H), 2.71 (ddd, *J* = 5.0, 12.2, 13.5 Hz, 1H), 2.59-2.54

(m, 2H), 1.97-1.90 (m, 2H), 1.71-1.66 (m, 2H), 1.63-1.56 (m, 2H), 1.37-1.24 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.1, 142.2, 136.0, 128.9, 128.8, 128.4, 128.2, 126.9, 125.8, 66.7, 60.5 (2C), 54.6, 38.7, 35.0, 31.7, 31.6, 26.4, 23.8; HRMS (ESI) *m/z* calcd. for $C_{23}H_{28}N_2O_2Na$ ($[M+Na]^+$) 387.2048, found 387.2046; calcd. for $C_{23}H_{29}N_2O_2$ ($[M+H]^+$) 365.2229, found 365.2221.

(*S*)-4-Benzyl-3-((*S*)-2-ethylpyrrolidin-1-yl)oxazolidin-2-one ((*S,S*)315) From hydrazone **51g** (32.9 mg, 0.12 mmol) and iodoethane (0.09 mL, 1.17 mmol) by General Procedure A (2.3 eq $InCl_3$) was obtained **(*S,S*)315**[23] (19.0 mg, 59%) as a colorless oil.

(*S*)-4-Benzyl-3-((*R*)-2-isopropylpyrrolidin-1-yl)oxazolidin-2-one ((*S,R*)359). From hydrazone **51g** (31.8 mg, 0.11 mmol) and 2-iodopropane (0.11 mL, 1.13 mmol) by General Procedure A (2.2 eq $InCl_3$) was obtained **(*S,R*)359** (27.7 mg, 85%) as colorless crystals. mp 59–62 °C; $[\alpha]_D^{23}$ +79.3 (*c* 0.595, $CHCl_3$); IR (film from $CDCl_3$) 3032, 2950, 2872, 1753, 1213, 1103, 1029 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.15 (m, 5H), 4.12-4.06 (m, 1H), 4.00-3.92 (m, 2H), 3.67 (ddd, *J* = 3.3, 6.9, 9.2 Hz, 1H), 3.45 (dd, *J* = 2.7, 13.0 Hz, 1H), 3.27 (ddd, *J* = 8.1, 8.1, 8.1 Hz, 1H), 3.18 (ddd, *J* = 3.3, 7.5, 10.9 Hz, 1H), 2.53 (dd, *J* = 10.3, 13.2 Hz, 1H), 1.96-1.81 (m, 3H), 1.75-1.66 (m, 1H), 1.58-1.52 (m, 1H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.3, 136.2, 128.9, 128.7, 127.0, 67.4, 65.1, 58.1, 49.3, 39.3, 28.8, 23.0, 22.8, 20.2, 15.2; HRMS (ESI) *m/z* calcd. for $C_{17}H_{25}N_2O_2$ ($[M+H]^+$) 289.1916, found 289.1916. The structural assignment was confirmed by x-ray crystallography.

(*S*)-4-Benzyl-3-((*R*)-2-isobutylpyrrolidin-1-yl)oxazolidin-2-one ((*S,R*)342). From hydrazone **51g** (26.4 mg, 0.094 mmol) and 1-iodo-2-methylpropane (0.11 mL, 0.94 mmol) by General Procedure A (2.3 eq $InCl_3$) was obtained **(*S,R*)342)** (19.0 mg, 67%) as a white solid. $[\alpha]_D^{25}$ +80.3 (*c* 0.63, $CHCl_3$); IR (film from $CDCl_3$) 3023, 2957, 2863, 1752, 1392, 1225, 1102, 1033 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.16 (m, 5H), 4.13 (dd, *J* = 8.3, 8.3 Hz, 1H), 3.98 (dd, *J* = 9.1, 9.1 Hz, 1H), 3.94-3.88 (m, 1H), 3.73-3.67 (m, 1H), 3.45 (dd, *J* = 3.3, 13.4 Hz, 1H), 3.27 (ddd, *J* = 8.2, 8.2, 8.2 Hz, 1H), 3.17 (ddd, *J* = 4.1, 8.4, 8.4 Hz, 1H), 2.53 (dd, *J* = 10.8, 13.2 Hz, 1H), 2.08-2.02 (m, 1H), 1.95-1.87 (m, 1H), 1.84-1.77 (m, 1H), 1.64-1.58 (m, 1H), 1.53-1.50 (m, 1H), 1.41-1.33 (m, 1H), 1.24-1.18 (m, 1H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.4, 136.5, 129.0, 129.0, 127.1, 67.6, 58.9, 58.1, 48.4, 44.1, 39.7, 29.5, 26.2, 24.5, 22.2, 21.5; HRMS (ESI) *m/z* calcd. for $C_{18}H_{26}N_2O_2Na$ ($[M+Na]^+$) 325.1892, found 325.1887; calcd. for $C_{18}H_{27}N_2O_2$ ($[M+H]^+$) 303.2073, found 303.2065.

(*S*)-4-Benzyl-3-((*S*)-2-pentylpyrrolidin-1-yl)oxazolidin-2-one ((*S,S*)332). From hydrazone **51g** (30.9 mg, 0.11 mmol) and iodopentane (0.14 mL, 1.07 mmol) by

General Procedure A (2.2 eq $InCl_3$) was obtained **(*S,S*)332** (19.0 mg, 67%) as a colorless oil. $[\alpha]_D^{23}$ +79.0 (*c* 0.765, $CHCl_3$); IR (film from $CDCl_3$) 3027, 2954, 2925, 2856, 1753, 1397, 1217, 1099, 1025 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26-7.09 (m, 5H), 4.08 (dd, *J* = 8.0, 8.0 Hz, 1H), 3.93 (dd, *J* = 9.1, 9.1 Hz, 1H), 3.88-3.82 (m, 1H), 3.58-3.52 (m, 1H), 3.36 (dd, *J* = 3.5, 13.5 Hz, 1H), 3.22 (ddd, *J* = 8.2, 8.2, 8.2 Hz, 1H), 3.08 (ddd, *J* = 4.1, 8.0, 8.0 Hz, 1H), 2.46 (dd, *J* = 10.5, 13.3 Hz, 1H), 2.00-1.94 (m, 1H), 1.88-1.80 (m, 1H), 1.76-1.67 (m, 1H), 1.66-1.61 (m, 1H), 1.36-1.30 (m, 1H), 1.28-1.13 (m, 7H), 0.82 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 136.3, 128.8, 128.77, 126.9, 67.4, 60.4, 57.9, 48.5, 39.5, 34.5, 32.3, 28.98, 26.1, 22.7, 21.5, 14.0; HRMS (ESI) *m/z* calcd. for $C_{19}H_{28}N_2O_2Na$ ($[M+Na]^+$) 339.2048, found 339.2039; calcd. for $C_{19}H_{29}N_2O_2$ ($[M+H]^+$) 317.2229, found 317.2224.

(*S*)-4-Benzyl-3-((*S*)-2-(4-chlorobutyl)pyrrolidin-1-yl)oxazolidin-2-one ((*S,S*)358). From hydrazone **51g** (39.7 mg, 0.14 mmol) and 1-chloro-4-iodobutane (0.17 mL, 1.41 mmol) by General Procedure A (2.2 eq $InCl_3$) was obtained **(*S,S*)358** (19.5 mg, 41%) as a yellow oil. $[\alpha]_D^{24}$ +70.2 (*c* 0.50, $CHCl_3$); IR (film from $CDCl_3$) 3021, 2938, 2868, 1757, 1221, 1086, 1029 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33-7.16 (m, 5H), 4.13 (dd, *J* = 8.1, 8.1 Hz, 1H), 3.98 (dd, *J* = 8.5, 8.5 Hz, 1H), 3.95-3.89 (m, 1H), 3.69-3.63 (m, 1H), 3.55 (m, apparent t, *J* = 6.6 Hz, 2H), 3.44 (dd, *J* = 3.5, 13.4 Hz, 1H), 3.24 (ddd, *J* = 8.2, 8.2, 8.2 Hz, 1H), 3.18 (ddd, *J* = 4.1, 8.1, 8.1 Hz, 1H), 2.53 (dd, *J* = 10.5, 13.3 Hz, 1H), 2.09-2.02 (m, 1H), 1.96-1.88 (m, 1H), 1.85-1.70 (m, 4H), 1.56-1.37 (m, 3H), 1.31-1.19 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 136.1, 128.9, 128.8, 127.0, 67.4, 60.1, 57.9, 48.5, 45.0, 39.4, 33.7, 32.8, 28.9, 23.7, 21.5; HRMS (ESI) *m/z* (relative intensity) calcd. for $C_{18}H_{25}N_2O_2ClNa$ ($[M+Na]^+$, ^{37}Cl) 361.1473, found 361.1477 (5%); calcd. for $C_{18}H_{25}N_2O_2ClNa$ ($[M+Na]^+$, ^{35}Cl) 359.1502, found 359.1500 (17%); calcd. for $C_{18}H_{26}N_2O_2Cl$ ($[M+H]^+$, ^{37}Cl) 339.1654, found 339.1646 (33%); calcd. for $C_{18}H_{26}N_2O_2Cl$ ($[M+H]^+$, ^{35}Cl) 337.1683, found 337.1685 (100%).

(*R*)-1-(2-Phenethylpyrrolidin-1-yl)ethanone (368). A mixture of **341** (110.9 mg, 0.316 mmol) and BH_3•THF (1M solution in THF, 9.49 mL, 9.49 mmol) was heated to reflux and sealed under a cold finger condenser. After heating at reflux for 48 h, additional BH_3•THF (6.3 mL, 6.3 mmol) was added and heating was continued for 72 h. After cooling to RT, 2M HCl was cautiously added until gas evolution ceased. The mixture was then made basic by addition of aqueous 1.25 M KOH, concentrated, and the aqueous residue was extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4) and concentrated. After azeotropic removal of moisture by concentration from benzene solution, CH_2Cl_2 (1.46 mL) and acetic anhydride (1.86 mL, 19.65 mmol) were added, and the mixture was heated at reflux. After 24 h, the reaction mixture was partitioned between water and CH_2Cl_2, and the organic

phase was dried (Na_2SO_4), filtered, and concentrated. Filtration through a plug of silica gel, eluting first with 85:15 mixture of hexane/(5:1 CH_2Cl_2/MeOH), then with 60:40 hexane/(5:1 CH_2Cl_2/MeOH), afforded crude **368** in the more polar fraction. Radial chromatography (1 mm plate, eluted with EtOAc) provided **368** (56 mg, 86%) as a yellow oil. $[\alpha]_D^{24}$ –71.75 (*c* 2.21, $CHCl_3$); IR (film from $CDCl_3$) 3023, 2954, 1646, 1450, 1197 cm^{-1}; ^1H NMR (400 MHz, DMSO, 115°C) δ 7.28-7.14 (m, 5H), 4.00-3.90 (br s, 1H), 3.49-3.42 (m, 1H), 3.42-3.30 (br s, 1H), 2.64-2.58 (m, 2H), 1.92 (s, 3H), 1.87-1.80 (m, 2H), 1.78-1.75 (m, 2H), 1.71-1.66 (m, 2H); ^{13}C NMR (100 MHz, DMSO, 115°C) δ 167.2, 141.2, 129.61, 129.59 (detected by DEPT), 124.9, 56.0, 46.0, 34.4, 31.3, 28.9, 22.4, 21.4; HRMS (ESI) *m/z* calcd. for $C_{14}H_{20}NO$ 218.1545 ($[M+H^+]$), found 218.1548.

(*S*)-Methyl 2-((dimethyl(phenyl)silyl)methylamino)-3-phenylpropanoate (436). From L-phenylalanine methyl ester hydrochloride (3.2 g, 14.8 mmol) was obtained **436** (2.9073 g, 60%). Preparation and characterization of **436** have been previously reported.[162]

2-{(2-*tert*-Butoxycarbonylaminoacetyl)-[(dimethylphenylsilanyl)methyl]amino}-3-phenyl-propionic acid methyl ester (438). From *N*-(*tert*-butoxycarbonyl)glycine (23.9 mg, 0.136 mmol) was obtained **438** (43.4 mg, 72%). Preparation and characterization of **438** have been previously reported.[162]

2-{(2-*tert*-Butoxycarbonylamino-(*S*)-methyl-acetyl)-[(dimethylphenylsilanyl)methyl]amino}-3-phenyl-propionic acid methyl ester (441). From **436** (43.9 mg, 0.134 mmol) by the literature procedure for the preparation of **438** was obtained **441** (18.5 mg, 29%) as a clear oil. $[\alpha]_D^{24.5}$ -118 (*c* 1.48, $CDCl_3$); IR (film from $CDCl_3$) 3428, 3027, 2974, 1740, 1708, 1638, 1503, 1176 cm^{-1}; ^1H NMR (400 MHz, DMSO, 120ºC) (one resonance was unresolved from the residual H_2O peak at 2.86) δ 7.53-7.18 (m, 10H), 5.96 (br s, 1H), 4.32 (dd, J = 7.6 Hz, 1H), 3.62 (br s, 3H), 3.16 (ABX, Δv = 91.6, J_{AB} = 14.3, J_{AX} = 5.6, J_{BX} = 8.8 Hz, 2H), 2.73 (br s, 1H), 1.40 (s, 9H), 0.90 (br s, 3H), 0.34 (s, 3H), 0.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, two main rotamers present) δ 172.8, 171.4, 170.2, 169.9, 154.7, 154.6, 139.6, 137.7, 136.5, 136.1, 133.8, 133.6, 129.7, 129.2, 129.1, 128.8, 128.7, 128.4, 127.9, 127.5, 127.0, 126.7, 79.4, 79.2, 64.1, 62.1, 52.4, 51.9, 46.5, 44.9, 41.7, 35.72, 35.66, 34.2, 28.24, 28.18, 19.1, 18.1, -2.0, -2.6, -4.0, -4.9; HRMS (ESI) *m/z* calcd. for $C_{27}H_{38}N_2O_5NaSi$ 521.2447 ($[M+Na]^+$), found 521.2458; calcd. $C_{27}H_{39}N_2O_5Si$ 499.2628 ($[M+H]^+$), found 499.2637.

Isobutyl (*S*)-1-(methoxycarbonyl)-2-phenylethyl(dimethyl(phenyl)silyl)methylcarbamate (442). From **436** (43.9 mg, 0.134 mmol) by the literature procedure for the preparation of **438** were obtained

441 (18.5 mg, 29%) and **442** (15.8 mg, 28%) as a clear oil. $[\alpha]_D^{23.9}$ -78.7 (*c* 1.38, $CDCl_3$); IR (film from $CDCl_3$) 3070, 2954, 2870, 1752, 1697, 1453, 1105 cm^{-1}; ^1H NMR (400 MHz, DMSO, 140 ºC) δ 7.49-7.16 (m, 10H), 4.56 (dd, *J* = 6.1, 9.0 Hz, 1H), 3.75 (ddd, *J* = 6.4, 10.5, 16.9 Hz, 2H), 3.64 (s, 3H), 3.15 (ABX, Δv = 75.2, J_{AB} = 14.3, J_{AX} = 6.0, J_{BX} = 9.0 Hz, 2H), 2.91 (d, *J* = 15.4 Hz, 1H), 2.66 (d, *J* = 15.4 Hz, 1H), 1.86-1.76 (m, 1H), 0.87 (s, 3H), 0.85 (s, 3H), 0.29 (s, 3H), 0.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 156.2, 156.18, 139.3, 138.3, 137.8, 137.6, 133.7, 133.6, 129.6, 129.3, 129.2, 129.0, 128.6, 128.5, 127.7, 126.7, 126.6, 72.1, 71.5, 62.9, 62.5, 52.1, 38.6, 38.2, 35.9, 35.2, 29.7, 28.4, 28.0, 19.1, 19.05, -2.8, -3.2, -3.3, -3.7; HRMS (ESI) *m/z* calcd. for $C_{24}H_{34}NO_4Na$ 450.2077 ($[M+Na]^+$), found 450.2075.

2-{(2-*tert*-Butoxycarbonylamino-(*S*)-benzyl-acetyl)-[(dimethylphenylsilanyl)methyl]amino}-3-phenyl-propionic acid methyl ester (446). From **436** (45.0 mg, 0.137 mmol) by the literature procedure for the preparation of **438** was obtained **446** (13.8 mg, 18%) as a clear oil. $[\alpha]_D^{23.3}$ -94.3 (*c* 0.715, $CDCl_3$); IR (film from $CDCl_3$) 3306, 3019, 2968, 1748, 1705, 1639, 1494, 1109 cm^{-1}; ^1H NMR (400 MHz, DMSO, 140ºC) (several resonances were unresolved from the residual H_2O peak at 2.73) δ 7.54-6.91 (m, 15H), 5.96 (br d, *J* = 10.3 Hz, 1H), 4.52 (br dd, *J* = 8.7, 13.2 Hz, 1H), 3.61 (s, 3H), 3.12 (ABX, Δv = 119.1, J_{AB} = 14.3, J_{AX} = 6.0, J_{BX} = 8.4 Hz, 2H), 1.30 (s, 9H, rotameric peak present at 1.42), 1.41 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, two main rotamers present) δ 172.1, 170.5, 170.4, 170.0, 154.8, 154.7, 139.8, 138.1, 137.0, 136.9, 136.7, 136.6, 134.1, 134.0, 133.7, 129.7, 129.3, 129.2, 128.9, 128.9, 128.49, 128.46, 128.2, 128.0, 127.6, 127.2, 126.8, 126.6, 126.4, 79.6, 79.5, 64.0, 62.2, 52.4, 52.0, 51.9, 50.2, 41.1, 40.0, 38.4, 36.0, 35.8, 34.6, 28.3, 28.2, -1.8, -2.4, -3.8, -4.9 (one resonance was not resolved from its rotameric counterpart); HRMS (ESI) *m/z* calcd. for $C_{33}H_{42}N_2O_5NaSi$ 597.2761 ($[M+Na]^+$), found 597.2761; calcd. for $C_{33}H_{43}N_2O_5Si$ 575.2942 ($[M+H]^+$), found 575.2951.

(*S*)-4-(2-*tert*-Butoxycarbonylaminoacetyl)-3-benzyloxazolidin-2-one (472). 472 was prepared by a similar procedure to the literature:[175] To **438** (55.3 mg, 0.114 mmol) was added KBr (16.3 mg, 0.137 mmol) and NaOAc (29 mg, 0.353 mmol) and solution was cooled to 0ºC. To this was added g. AcOH (0.3 mL, 5.31 mmol) and 2nd portion of NaOAc (179.4 mg, 2.18 mmol), followed by dropwise addition of AcOOH (0.29 mL, 1.37 mmol). Solution stirred 15 min at 0 ºC and then 2nd portion of AcOOH (0.86 mL, 4.11 mmol) was added slowly and solution was allowed to warm to RT and stir 1.5 h. Reaction was quenched at 0ºC with sat'd aq. $Na_2S_2O_3$ which was added until yellow color dissipated. To this was added solid $NaHCO_3$ slowly until effervescence ceased. Aqueous mixture was partitioned with CH_2Cl_2 and extracted five times. Combined organic layers were washed with brine, dried (an. Na_2SO_4) and filtered. Concentration and purification by gradient flash

chromatography (3:1 hexane/EtOAc to EtOAc) furnished **472** (26.3 mg, 69%) as a light yellow oil. $[\alpha]_D^{24.5}$ 129 (*c* 1.35, $CDCl_3$); IR (film from $CDCl_3$) 3350, 3030, 2979, 1799, 1712, 1679, 1501, 1163 cm^{-1}; ^1H NMR (400 MHz, DMSO, 140ºC) δ 7.33-7.19 (m, 5H), 6.32 (br s, 1H), 5.52 (d, *J* = 5.2 Hz, 1H), 4.77 (dd, *J* = 4.1, 5.9 Hz, 1H), 4.67 (d, *J* = 4.6 Hz, 1H), 3.74 (dd, *J* = 5.7, 5.7 Hz, 2H, rotamer peaks buried but apparent at this shift), 3.22 (ABX, Δv = 72.5, J_{AB} = 14.1, J_{AX} = 6.2, J_{BX} = 4.3 Hz, 2H), 1.44 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, two main rotamers present) δ 171.3, 167.3, 165.9, 155.8, 134.6, 133.5, 134.5, 133.5, 129.6, 129.5, 129.2, 129.0, 128.11, 127.8, 80.4, 78.1, 56.4, 56.2, 42.6, 37.3, 34.7,30.6, 29.7, 28.4, 19.1, 13.7; HRMS (ESI) *m/z* calcd. for $C_{17}H_{22}N_2O_5Na$ 357.1426 ($[M+Na]^+$), found 357.1445.

2-[(2-*tert*-Butoxycarbonylamino-(*S*)-methyl-acetyl)acetoxymethylamino]-3-phenyl-propionic acid methyl ester (473). To **441** (55 mg, 0.12 mmol) was added Ac_2O (20 µL, 0.23 mmol), KBr (16.7 mg, 0.14 mmol) and NaOAc (29.7 mg, 0.36 mmol). Reaction was cooled to 0ºC and glacial AcOH (0.31 ml, 5.4 mmol), 2nd portion of NaOAc (89.1 mg, 1.1 mmol) and AcOOH (32 wt % in dilute AcOH, 0.29 ml, 1.4 mmol) were added. Solution stirred 15 min at 0ºC and then 2nd portion of AcOOH (0.88 ml, 4.2 mmol) was added dropwise. Solution was allowed to warm to RT and stir 1 h. Reaction was quenched at 0ºC with sat'd aq. $Na_2S_2O_3$ which was added until yellow color dissipated. To this was added solid $NaHCO_3$ slowly until effervescence ceased. Aqueous mixture was partitioned with CH_2Cl_2 and extracted five times. Combined organic layers were dried (an. Na_2SO_4) and filtered. Concentration under high vacuum overnight furnished **473** (31.1 mg, 89%) as a clear oil. $[\alpha]_D^{22.8}$ -67.6 (*c* 1.53, $CDCl_3$); IR (film from $CDCl_3$) 3358, 3063, 2983, 1737, 1712, 1683, 1654, 1247, 1029, 858 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31-7.15 (m, 5H), 5.15 (d, *J* = 9.0 Hz, 1H), 4.90 (d, *J* = 12.5 Hz, 1H), 4.86 (X of ABX, *J* = 5.0, 10.1 Hz, 1H), 4.63 (m, apparent quint, *J* = 7.3 Hz, 1H), 4.39 (d, *J* = 12.2 Hz, 1H), 3.73 (s, 3H), 3.37 (A of ABX, *J* = 5.2, 14.2 Hz, 1H), 3.21 (B of ABX, *J* = 10.2, 14.0 Hz, 1H), 2.19 (s, 3H), 1.42 (s, 9H), 1.31 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 171.9, 166.1, 155.8, 137.4, 129.1, 128.6, 126.9, 80.4, 71.9, 60.3, 52.5, 45.8, 35.8, 28.3, 18.4, 16.6; HRMS (ESI) *m/z* calcd. for $C_{21}H_{30}N_2O_7Na$ 445.1951 ($[M+Na]^+$), found 445.1959.

REFERENCES

(1) Kaufman, T. S.; Ruveda, E. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 854-885.

(2) Grabley, S.; Hammann, P.; Kluge, H.; Wink, J.; Kricke, P.; Zeeck, A. *J. Antibiot.* **1991**, *44*, 797-800.

(3) Zirihi, G. N.; Grellier, P.; Guede-Guina, F.; Bodo, B.; Mambu, L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2637-2640.

(4) Schwartz, R. E.; Liesch, J.; Hensens, O.; Zitano, L.; Honeycutt, S.; Garrity, G.; Fromtling, R. A.; Onishi, J.; Monaghan, R. *J. Antibiot.* **1988**, *41*, 1774-1779.

(5) Johnson, J. H.; Phillipson, D. W.; Kahle, A. D. *J. Antibiot.* **1989**, *42*, 1184-1185.

(6) Kitajima, M.; Nakamura, T.; Kogure, N.; Ogawa, M.; Mitsuno, Y.; Ono, K.; Yano, S.; Aimi, N.; Takayama, H. *J. Nat. Prod.* **2006**, *69*, 715-718.

(7) Charette, A. B. *Chiral Amine Synth.* **2010**, 1-49.

(8) Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913-9914.

(9) Buesking, A. W.; Baguley, T. D.; Ellman, J. A. *Org. Lett.* **2011**, *13*, 964-967.

(10) Desrosiers, J.-N.; Cote, A.; Charette, A. B. *Tetrahedron* **2005**, *61*, 6186-6192.

(11) Cote, A.; Boezio, A. A.; Charette, A. B. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5405-5410.

(12) Lou, S.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc.* **2007**, *129*, 15398-15404.

(13) Fernandes, R. A.; Nallasivam, J. L. *Org. Biomol. Chem.* **2012**, *10*, 7789-7800.

(14) Ngai, M.-Y.; Barchuk, A.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 12644-12645.

(15) Gommermann, N.; Knochel, P. *Chem. Commun. (Cambridge, U. K.)* **2005**, 4175-4177.

(16) Curran, D. P.; Porter, N. A.; Giese, B.; Editors *Stereochemistry of Radical Reactions: Concepts, Guidelines, and Synthetic Applications*, 1996.

(17) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*, 1986.

(18) Friestad, G. K. *Tetrahedron* **2001**, *57*, 5461-5496.

(19) Friestad, G. K.; Qin, J. *J. Am. Chem. Soc.* **2000**, *122*, 8329-8330.

(20) Friestad, G. K.; Draghici, C.; Soukri, M.; Qin, J. *J. Org. Chem.* **2005**, *70*, 6330-6338.

(21) Friestad, G. K.; Shen, Y.; Ruggles, E. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 5061-5063.

(22) Lee, S.; Kim, S. *Tetrahedron Lett.* **2009**, *50*, 3345-3348.

(23) Friestad, G. K.; Qin, J. *J. Am. Chem. Soc.* **2001**, *123*, 9922-9923.

(24) Friestad, G. K.; Marie, J.-C.; Suh, Y.; Qin, J. *J. Org. Chem.* **2006**, *71*, 7016-7027.

(25) Friestad, G. K.; Ji, A.; Baltrusaitis, J.; Korapala, C. S.; Qin, J. *J. Org. Chem.* **2012**, *77*, 3159-3180.

(26) Friestad, G. K.; Ji, A.; Korapala, C. S.; Qin, J. *Org. Biomol. Chem.* **2011**, *9*, 4039-4043.

(27) Friestad, G. K.; Banerjee, K. *Org. Lett.* **2009**, *11*, 1095-1098.

(28) Akindele, T.; Yamamoto, Y.; Maekawa, M.; Umeki, H.; Yamada, K.-I.; Tomioka, K. *Org. Lett.* **2006**, *8*, 5729-5732.

(29) Valpuesta, M.; Munoz, C.; Diaz, A.; Torres, G.; Suau, R. *Eur. J. Org. Chem.* **2010**, 1934-1942, S1934/1931-S1934/1936.

(30) Fernandez-Salas, J. A.; Maestro, M. C.; Rodriguez-Fernandez, M. M.; Garcia-Ruano, J. L.; Alonso, I. *Org. Lett.* **2013**, *15*, 1658-1661.

(31) Huang, W.; Ye, J.-L.; Zheng, W.; Dong, H.-Q.; Wei, B.-G. *J. Org. Chem.* **2013**, *78*, 11229-11237.

(32) Godineau, E.; Landais, Y. *Chemistry - A European Journal* **2009**, *15*, 3044-3055.

(33) Lampard, C.; Murphy, J. A.; Lewis, N. *J. Chem. Soc., Chem. Commun.* **1993**, 295-297.

(34) Murphy, J. A. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH Verlag GmbH: Weinheim, 2001; Vol. 1.

(35) Lampard, C.; Murphy, J. A.; Rasheed, F.; Lewis, N.; Hursthouse, M. B.; Hibbs, D. E. *Tetrahedron Lett.* **1994**, *35*, 8675-8678.

(36) Callaghan, O.; Lampard, C.; Kennedy, A. R.; Murphy, J. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 995-1002.

(37) Clark, A. J. *Chem. Soc. Rev.* **2002**, *31*, 1-11.

(38) Clark, A. J.; Collis, A. E. C.; Fox, D. J.; Halliwell, L. L.; James, N.; O'Reilly, R. K.; Parekh, H.; Ross, A.; Sellars, A. B.; Willcock, H.; Wilson, P. *J. Org. Chem.* **2012**, *77*, 6778-6788.

(39) Clark, A. J.; Geden, J. V.; Thom, S. *J. Org. Chem.* **2006**, *71*, 1471-1479.

(40) Clark, A. J.; Dell, C. P.; McDonagh, J. M.; Geden, J.; Mawdsley, P. *Org. Lett.* **2003**, *5*, 2063-2066.

(41) Cornia, A.; Felluga, F.; Frenna, V.; Ghelfi, F.; Parsons, A. F.; Pattarozzi, M.; Roncaglia, F.; Spinelli, D. *Tetrahedron* **2012**, *68*, 5863-5881.

(42) Friestad, G. K.; Wu, Y. *Org. Lett.* **2009**, *11*, 819-822.

(43) de Armas, P.; Francisco, C. G.; Suarez, E. *J. Am. Chem. Soc.* **1993**, *115*, 8865-8866.

(44) Francisco, C. G.; Gonzalez Martin, C.; Suarez, E. *J. Org. Chem.* **1998**, *63*, 2099-2109.

(45) Francisco, C. G.; Freire, R.; Gonzalez, C. C.; Leon, E. I.; Riesco-Fagundo, C.; Suarez, E. *J. Org. Chem.* **2001**, *66*, 1861-1866.

(46) Paz, N. R.; Santana, A. G.; Francisco, C. G.; Suarez, E.; Gonzalez, C. C. *Org. Lett.* **2012**, *14*, 3388-3391.

(47) Santana, A. G.; Paz, N. R.; Francisco, C. G.; Suarez, E.; Gonzalez, C. C. *J. Org. Chem.* **2013**, *78*, 7527-7543.

(48) Jui, N. T.; Garber, J. A. O.; Finelli, F. G.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2012**, *134*, 11400-11403.

(49) Jui, N. T.; Lee, E. C. Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 10015-10017.

(50) Grandjean, J.-M. M.; Nicewicz, D. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 3967-3971.

(51) Zeller, M. A.; Riener, M.; Nicewicz, D. A. *Org. Lett.* **2014**, *16*, 4810-4813.

(52) Gesmundo, N. J.; Grandjean, J.-M. M.; Nicewicz, D. A. *Org. Lett.* **2015**, *17*, 1316-1319.

(53) Crich, D.; Shirai, M.; Rumthao, S. *Org. Lett.* **2003**, *5*, 3767-3769.

(54) Crich, D.; Shirai, M.; Brebion, F.; Rumthao, S. *Tetrahedron* **2006**, *62*, 6501-6518.

(55) Crich, D.; Ranganathan, K.; Neelamkavil, S.; Huang, X. *J. Am. Chem. Soc.* **2003**, *125*, 7942-7947.

(56) Cortezano-Arellano, O.; Quintero, L.; Sartillo-Piscil, F. *J. Org. Chem.* **2015**, *80*, 2601-2608.

(57) Prosperini, S.; Pastori, N.; Ghilardi, A.; Clerici, A.; Punta, C. *Org. Biomol. Chem.* **2011**, *9*, 3759-3767.

(58) Perez-Luna, A.; Botuha, C.; Ferreira, F.; Chemla, F. *New J. Chem.* **2008**, *32*, 594-606.

(59) Perez-Luna, A.; Botuha, C.; Ferreira, F.; Chemla, F. *Chemistry - A European Journal* **2008**, *14*, 8784-8788.

(60) Giboulot, S.; Perez-Luna, A.; Botuha, C.; Ferreira, F.; Chemla, F. *Tetrahedron Lett.* **2008**, *49*, 3963-3966.

(61) Bazin, S.; Feray, L.; Vanthuyne, N.; Bertrand, M. P. *Tetrahedron* **2005**, *61*, 4261-4274.

(62) Bazin, S.; Feray, L.; Siri, D.; Naubron, J. V.; Bertrand, M. P. *Chem. Commun. (Cambridge, U. K.)* **2002**, 2506-2507.

(63) Tsunoi, S.; Ryu, I.; Yamasaki, S.; Tanaka, M.; Sonoda, N.; Komatsu, M. *Chem. Commun. (Cambridge)* **1997**, 1889-1890.

(64) Ueda, M.; Doi, N.; Miyagawa, H.; Sugita, S.; Takeda, N.; Shinada, T.; Miyata, O. *Chem. Commun. (Cambridge, U. K.)* **2015**, *51*, 4204-4207.

(65) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321-3354.

(66) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1995**, *60*, 872-882.

(67) Rivkin, A.; Nagashima, T.; Curran, D. P. *Org. Lett.* **2003**, *5*, 419-422.

(68) Takai, K.; Ueda, T.; Ikeda, N.; Moriwake, T. *J. Org. Chem.* **1996**, *61*, 7990-7991.

(69) Takai, K.; Ueda, T.; Kaihara, H.; Sunami, Y.; Moriwake, T. *J. Org. Chem.* **1996**, *61*, 8728-8729.

(70) Kamimura, D.; Urabe, D.; Nagatomo, M.; Inoue, M. *Org. Lett.* **2013**, *15*, 5122-5125.

(71) Miyata, O.; Takahashi, S.; Tamura, A.; Ueda, M.; Naito, T. *Tetrahedron* **2008**, *64*, 1270-1284.

(72) Zhang, L.; Kim, J. B.; Jang, D. O. *Tetrahedron Lett.* **2014**, *55*, 2654-2658.

(73) Godineau, E.; Landais, Y. *J. Am. Chem. Soc.* **2007**, *129*, 12662-12663.

(74) Ueda, M.; Ito, Y.; Ichii, Y.; Kakiuchi, M.; Shono, H.; Miyata, O. *Chemistry - A European Journal* **2014**, *20*, 6763-6770.

(75) Ueda, M.; Matsubara, H.; Yoshida, K.-i.; Sato, A.; Naito, T.; Miyata, O. *Chemistry - A European Journal* **2011**, *17*, 1789-1792, S1789/1781-S1789/1759.

(76) Ueda, M.; Miyabe, H.; Sugino, H.; Miyata, O.; Naito, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 6190-6193.

(77) Castle, S. L. *Chem. Rec.* **2014**, *14*, 580-591.

(78) Tojino, M.; Uenoyama, Y.; Fukuyama, T.; Ryu, I. *Chem. Commun. (Cambridge, U. K.)* **2004**, 2482-2483.

(79) Du, P.; Li, H.; Wang, Y.; Cheng, J.; Wan, X. *Org. Lett.* **2014**, *16*, 6350-6353.

(80) Jahn, U.; Hartmann, P.; Dix, I.; Jones, P. G. *Eur. J. Org. Chem.* **2001**, 3333-3355.

(81) Jahn, U. *Chem. Commun. (Cambridge, U. K.)* **2001**, 1600-1601.

(82) Jahn, U.; Kafka, F.; Pohl, R.; Jones, P. G. *Tetrahedron* **2009**, *65*, 10917-10929.

(83) Jahn, U.; Mueller, M.; Aussieker, S. *J. Am. Chem. Soc.* **2000**, *122*, 5212-5213.

(84) Jahn, U.; Hartmann, P.; Kaasalainen, E. *Org. Lett.* **2004**, *6*, 257-260.

(85) Jahn, U.; Hartmann, P.; Dix, I.; Jones, P. G. *Eur. J. Org. Chem.* **2002**, 718-735.

(86) Jahn, U.; Dinca, E. *Chemistry - A European Journal* **2009**, *15*, 58-62.

(87) Jahn, U.; Dinca, E. *J. Org. Chem.* **2010**, *75*, 4480-4491.

(88) Khobragade, D. A.; Mahamulkar, S. G.; Pospisil, L.; Cisarova, I.; Rulisek, L.; Jahn, U. *Chem. - Eur. J.* **2012**, *18*, 12267-12277, S12267/12261-S12267/12271.

(89) Hollister, K. A.; Conner, E. S.; Spell, M. L.; Deveaux, K.; Maneval, L.; Beal, M. W.; Ragains, J. R. *Angew. Chem., Int. Ed.* **2015**, *54*, 7837-7841.

(90) Mitchinson, A.; Nadin, A. *Perkin 1* **2000**, 2862-2892.

(91) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701-1729.

(92) Cossy, J. *Chem. Rec.* **2005**, *5*, 70-80.

(93) Royer, J.; Editor *Asymmetric Synthesis of Nitrogen Heterocycles*, 2009.

(94) Wijdeven, M. A.; Willemsen, J.; Rutjes, F. P. J. T. *Eur. J. Org. Chem.* **2010**, 2831-2844.

(95) Vo, C.-V. T.; Bode, J. W. *J. Org. Chem.* **2014**, *79*, 2809-2815.

(96) Aillaud, I.; Collin, J.; Duhayon, C.; Guillot, R.; Lyubov, D.; Schulz, E.; Trifonov, A. *Chemistry - A European Journal* **2008**, *14*, 2189-2200.

(97) Welter, C.; Dahnz, A.; Brunner, B.; Streiff, S.; Duebon, P.; Helmchen, G. *Org. Lett.* **2005**, *7*, 1239-1242.

(98) Guerinot, A.; Serra-Muns, A.; Gnamm, C.; Bensoussan, C.; Reymond, S.; Cossy, J. *Org. Lett.* **2010**, *12*, 1808-1811.

(99) Singh, S.; Singh, O. V.; Han, H. *Tetrahedron Lett.* **2007**, *48*, 8270-8273.

(100) Chen, F.; Tan, C. K.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2013**, *135*, 1232-1235.

(101) Ackermann, L.; Althammer, A. *Synlett* **2008**, 995-998.

(102) Montoro, R.; Marquez, F.; Llebaria, A.; Delgado, A. *Eur. J. Org. Chem.* **2003**, 217-223.

(103) Hirai, Y.; Watanabe, J.; Nozaki, T.; Yokoyama, H.; Yamaguchi, S. *J. Org. Chem.* **1997**, *62*, 776-777.

(104) Chirke, S. S.; Rajender, A.; Rao, B. V. *Tetrahedron* **2014**, *70*, 103-109.

(105) Masuda, Y.; Tashiro, T.; Mori, K. *Tetrahedron Asymmetry* **2007**, *17*, 3380-3385.

(106) Rougnon Glasson, S.; Canet, J. L.; Troin, Y. *Tetrahedron Lett.* **2000**, *41*, 9797-9802.

(107) Wenkert, E.; Dave, K. G.; Stevens, R. V. *J. Amer. Chem. Soc.* **1968**, *90*, 6177-6182.

(108) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev. (Washington, DC, U. S.)* **2004**, *104*, 2311-2352.

(109) Deng, W.; Overman, L. E. *J. Am. Chem. Soc.* **1994**, *116*, 11241-11250.

(110) Bonnaventure, I.; Charette, A. B. *Tetrahedron* **2009**, *65*, 4968-4976.

(111) Adrio, J.; Carretero, J. C. *Chem. Commun. (Cambridge, U. K.)* **2011**, *47*, 6784-6794.

(112) Chakraborty, T. K.; Samanta, R.; Roy, S.; Sridhar, B. *Tetrahedron Lett.* **2009**, *50*, 3306-3310.

(113) Heintzelman, G. R.; Weinreb, S. M.; Parvez, M. *J. Org. Chem.* **1996**, *61*, 4594-4599.

(114) Heintzelman, G. R.; Meigh, I. R.; Mahajan, Y. R.; Weinreb, S. M. *Org. React. (N. Y.)* **2005**, *65*, 141-599.

(115) Heintzelman, G. R.; Fang, W.-K.; Keen, S. P.; Wallace, G. A.; Weinreb, S. M. *J. Am. Chem. Soc.* **2002**, *124*, 3939-3945.

(116) Korapala, C. S.; Qin, J.; Friestad, G. K. *Org. Lett.* **2007**, *9*, 4243-4246.

(117) Friestad, G. K.; Marie, J.-C.; Deveau, A. M. *Org. Lett.* **2004**, *6*, 3249-3252.

(118) Geoffroy, G. L.; Wrighton, M. S. *Organometallic photochemistry*; Academic Press: New York :, 1979.

(119) Pauson, P. L. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995; Vol. 2.

(120) Meyer, T. J.; Caspar, J. V. *Chem. Rev.* **1985**, *85*, 187-218.

(121) Gilbert, B. C.; Parsons, A. F. *J. Chem. Soc., Perkin Trans. 2* **2002**, 367-387.

(122) McCullen, S. B.; Brown, T. L. *J. Am. Chem. Soc.* **1982**, *104*, 7496-7500.

(123) Freidlina, R. K.; Terent'ev, A. B.; Petrova, R. G.; Churkina, T. D.; Moskalenko, M. A. *Dokl. Akad. Nauk SSSR* **1986**, *288*, 1436-1439 [Phys Chem].

(124) Chukovskaya, E. T.; Kuz'mina, N. A.; Blinova, N. V.; Freidlina, R. K. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1984**, 2061-2064.

(125) Connor, J. A.; Zafarani-Moattar, M. T.; Bickerton, J.; El Saied, N. I.; Suradi, S.; Carson, R.; Al Takhin, G.; Skinner, H. A. *Organometallics* **1982**, *1*, 1166-1174.

(126) Herrick, R. S.; Herrinton, T. R.; Walker, H. W.; Brown, T. L. *Organometallics* **1985**, *4*, 42-45.

(127) Biddulph, M. A.; Davis, R.; Wilson, F. I. C. *J. Organomet. Chem.* **1990**, *387*, 277-293.

(128) Chukovskaya, E. T.; Rozhkova, M. A.; Kuz'mina, N. A.; Freidlina, R. K. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1982**, 354-359.

(129) Gasanov, R. G.; Freidlina, R. K. *Dokl. Akad. Nauk SSSR* **1979**, *246*, 111-114 [Chem].

(130) McKennon, M. J.; Meyers, A. I.; Drauz, K.; Schwarm, M. *J. Org. Chem.* **1993**, *58*, 3568-3571.

(131) Organ, M. G.; Bilokin, Y. V.; Bratovanov, S. *J. Org. Chem.* **2002**, *67*, 5176-5183.

(132) Shen, Y.; Friestad, G. K. *J. Org. Chem.* **2002**, *67*, 6236-6239.

(133) Chesis, P. L.; Hwang, D. R.; Welch, M. J. *J. Med. Chem.* **1990**, *33*, 1482-1490.

(134) Xu, S.; Oda, A.; Negishi, E.-I. *Chemistry - A European Journal* **2014**, *20*, 16060 - 16064.

(135) Ingold, C. K.; Sako, S.; Thorpe, J. F. *J. Chem. Soc., Trans.* **1922**, *121*, 1177-1198.

(136) Castro, B.; Selve, C. *Bull. Soc. Chim. Fr.* **1974**, 3004-3008.

(137) Friestad, G. K.; Ji, A. *Org. Lett.* **2008**, *10*, 2311-2313.

(138) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734-736.

(139) Prelog, V.; Balenovic, K. *Ber. Dtsch. Chem. Ges. B* **1941**, *74B*, 1510-1512.

(140) Cutter, A. C.; Miller, I. R.; Keily, J. F.; Bellingham, R. K.; Light, M. E.; Brown, R. C. D. *Org. Lett.* **2011**, *13*, 3988-3991.

(141) Gresser, M. J.; Keller, P. A.; Wales, S. M. *Tetrahedron Lett.* **2009**, *50*, 4899-4902.

(142) Kotsuki, H.; Kuzume, H.; Gohda, T.; Fukuhara, M.; Ochi, M.; Oishi, T.; Hirama, M.; Shiro, M. *Tetrahedron Asymmetry* **1995**, *6*, 2227-2236.

(143) Molander, G. A.; Kenny, C. *J. Org. Chem.* **1991**, *56*, 1439-1445.

(144) Steinmetz, H.; Glaser, N.; Herdtweck, E.; Sasse, F.; Reichenbach, H.; Hoefle, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 4888-4892, S4888/4881-S4888/4886.

(145) Peltier, H. M.; McMahon, J. P.; Patterson, A. W.; Ellman, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 16018-16019.

(146) Gledhill, A. P.; McCall, C. J.; Threadgill, M. D. *J. Org. Chem.* **1986**, *51*, 3196-3201.

(147) Hutchison, A. J.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 6786-6788.

(148) Downey, C. W.; Fleisher, A. S.; Rague, J. T.; Safran, C. L.; Venable, M. E.; Pike, R. D. *Tetrahedron Lett.* **2011**, *52*, 4756-4759.

(149) Harayama, Y.; Yoshida, M.; Kamimura, D.; Wada, Y.; Kita, Y. *Chemistry - A European Journal* **2006**, *12*, 4893-4899.

(150) Linstead, R. P.; Shephard, B. R.; Weedon, B. C. L. *J. Chem. Soc.* **1951**, 2854-2858.

(151) Boto, A.; Hernandez, R.; Montoya, A.; Suarez, E. *Tetrahedron Lett.* **2004**, *45*, 1559-1563.

(152) Boto, A.; Hernandez, R.; Suarez, E. *J. Org. Chem.* **2000**, *65*, 4930-4937.

(153) Majumdar, S.; Sloan, K. B. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1447-1450.

(154) Bundgaard, H.; Rasmussen, G. J. *Pharm. Res.* **1991**, *8*, 1238-1242.

(155) Banerjee, R.; Rachid, Z.; McNamee, J.; Jean-Claude, B. J. *J. Med. Chem.* **2003**, *46*, 5546-5551.

(156) Hamman, J. H.; Steenekamp, J. H. *Pept. Drug Discovery Dev.* **2011**, 71-90.

(157) Majumdar, S.; Sloan, K. B. *Int. J. Pharm.* **2007**, *337*, 48-55.

(158) Moess, J.; Bundgaard, H. *Int. J. Pharm.* **1989**, *52*, 255-263.

(159) Majumdar, S.; Sloan, K. B. *Int. J. Pharm.* **2007**, *332*, 64-71.

(160) NIH/3T3 ATCC. http://www.atcc.org/Products/All/CRL-1658.aspx#characteristics (accessed 05/29/2015).

(161) Sun, H.; Moeller, K. D. *Org. Lett.* **2002**, *4*, 1547-1550.

(162) Sun, H.; Martin, C.; Kesselring, D.; Keller, R.; Moeller, K. D. *J. Am. Chem. Soc.* **2006**, *128*, 13761-13771.

(163) Ihara, M.; Yasui, K.; Taniguchi, N.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1469-1476.

(164) Salmon, R. *e-EROS Encycl. Reagents Org. Synth.* **2001**, 1-2.

(165) Mobashery, S.; Johnston, M. *J. Org. Chem.* **1985**, *50*, 2200-2202.

(166) Bailey, J. L.; J. Chem. Soc., **1950**.

(167) Davies, J. S.; Mohammed, A. K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2982-2990.

(168) Wang, D.; Lu, M.; Arora, P. S. *Angew. Chem., Int. Ed.* **2008**, *47*, 1879-1882.

(169) Chen, Y.; Bilban, M.; Foster, C. A.; Boger, D. L. *J. Am. Chem. Soc.* **2002**, *124*, 5431-5440.

(170) Ready, J., Department of Biochemistry, UT Southwestern Medical Center, Dallas, TX. Personal Communication, 2013.

(171) Dunetz, J. R.; Xiang, Y.; Baldwin, A.; Ringling, J. *Org. Lett.* **2011**, *13*, 5048-5051.

(172) Ramage, R.; Hopton, D.; Parrott, M. J.; Richardon, R. S.; Kenner, G. W.; Moore, G. A. *J. Chem. Soc., Perkin Trans. 1* **1985**, 461-470.

(173) Ookawa, A.; Soai, K. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1465-1471.

(174) Li, P.; Xu, J. C. *J. Org. Chem.* **2000**, *65*, 2951-2958.

(175) Fleming, I.; Henning, R.; Parker, D. C.; Plaut, H. E.; Sanderson, P. E. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 317-337.

(176) Fleming, I.; Lawrence, N. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3309-3326.

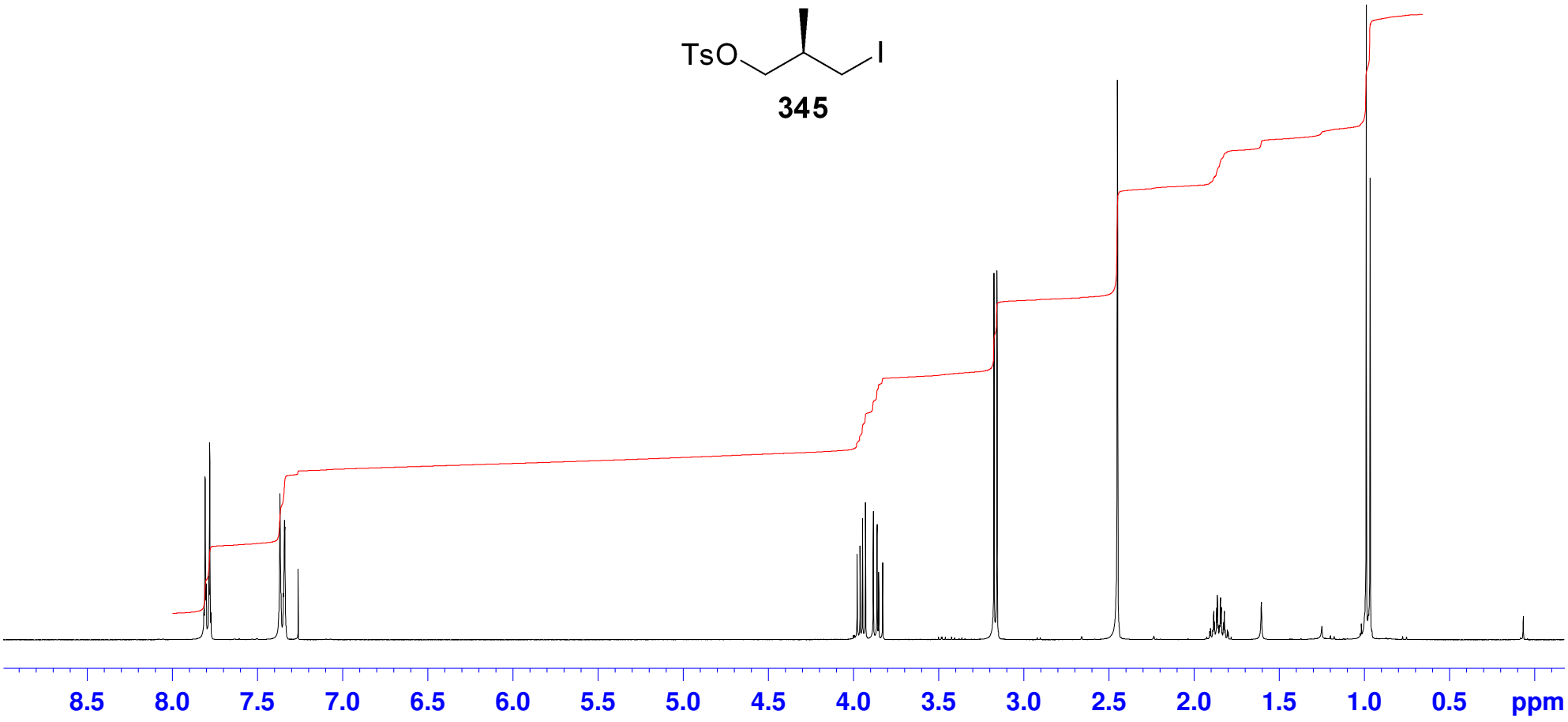
(177) Tamao, K.; Ishida, N.; Kumada, M. *J. Org. Chem.* **1983**, *48*, 2120-2122.

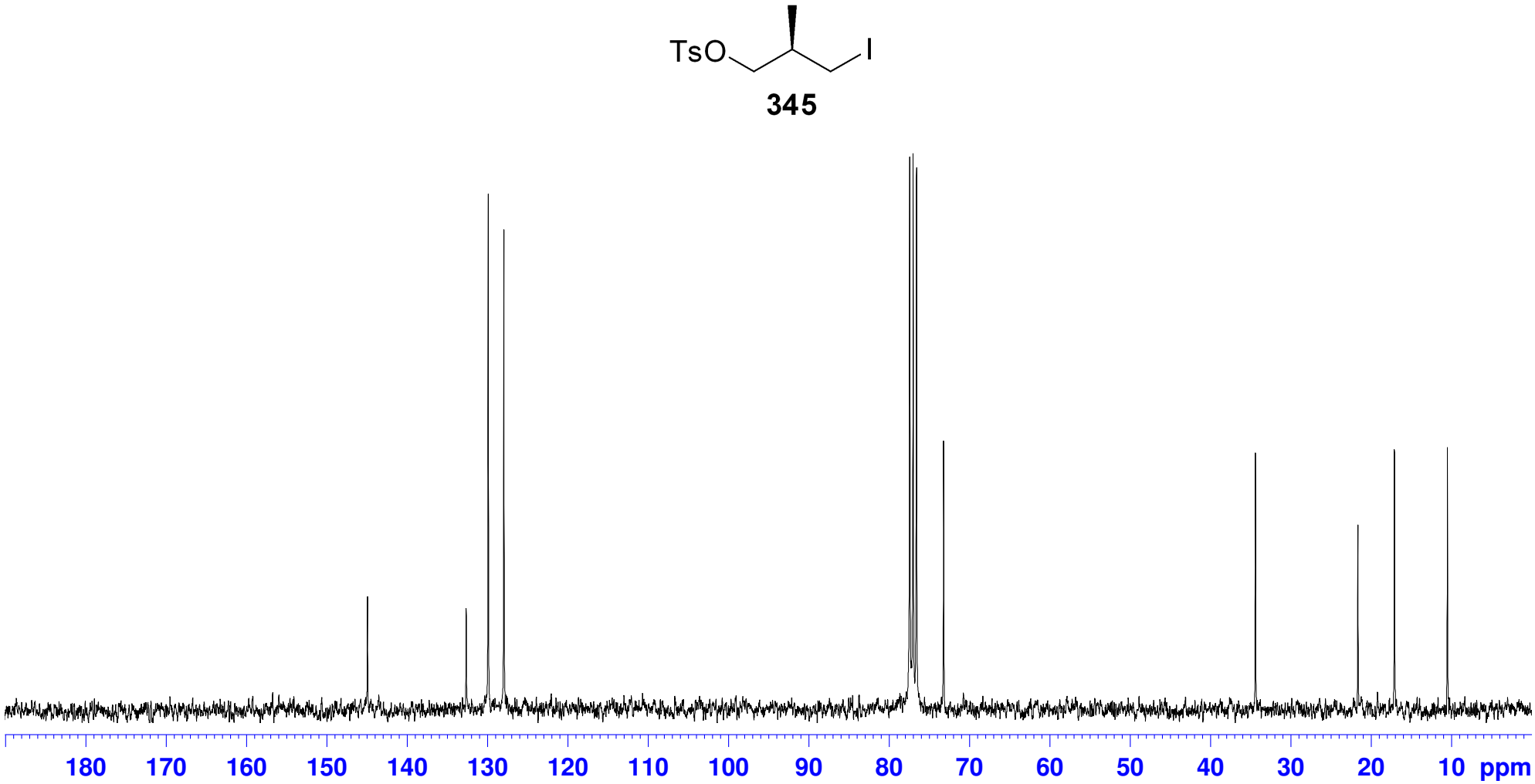
(178) Palomo, C.; Aizpurua, J. M.; Urchegui, R.; Iturburu, M. *J. Org. Chem.* **1992**, *57*, 1571-1579.

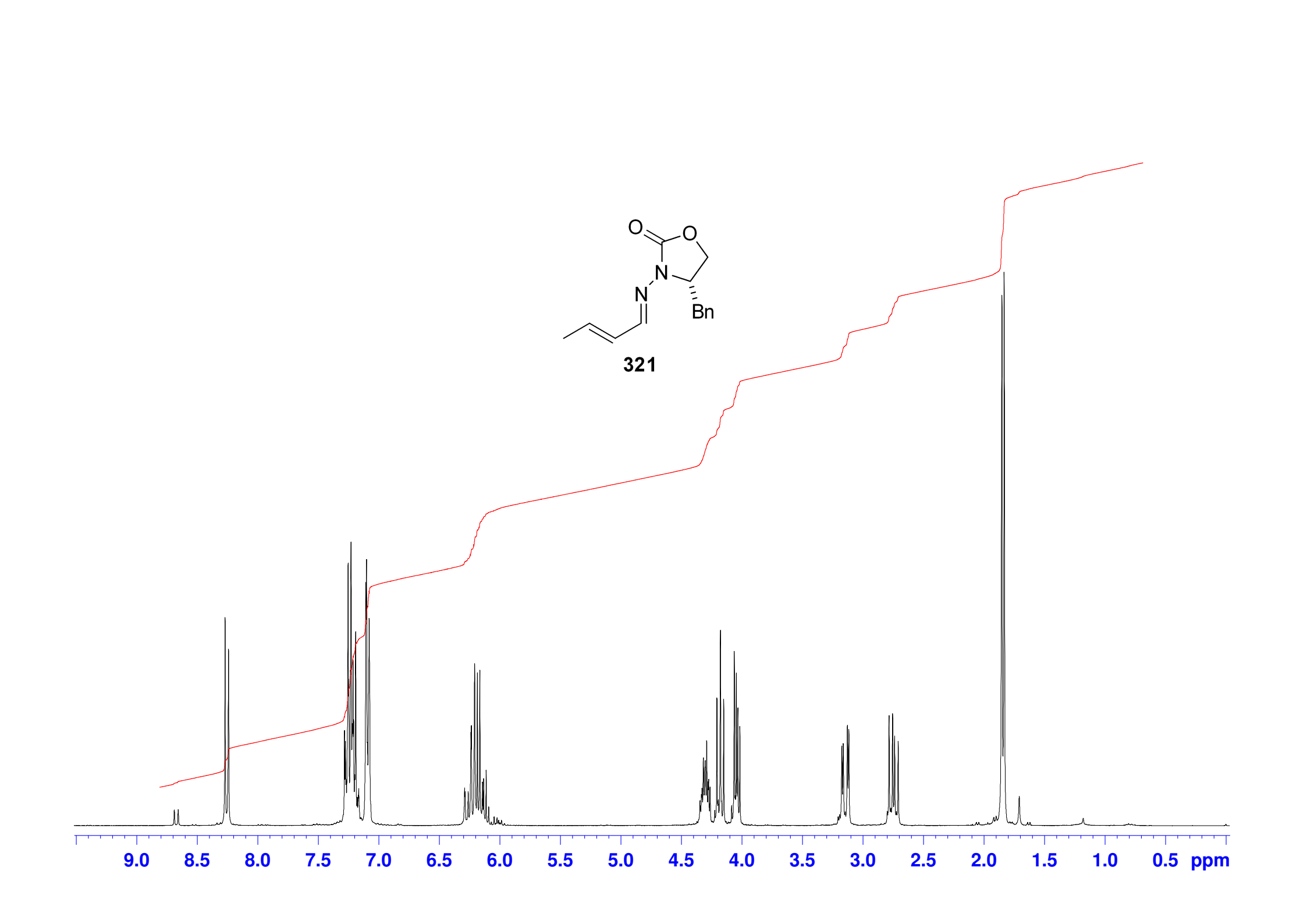
(179) Hynes, J., Jr.; Doubleday, W. W.; Dyckman, A. J.; Godfrey, J. D., Jr.; Grosso, J. A.; Kiau, S.; Leftheris, K. *J. Org. Chem.* **2004**, *69*, 1368-1371.

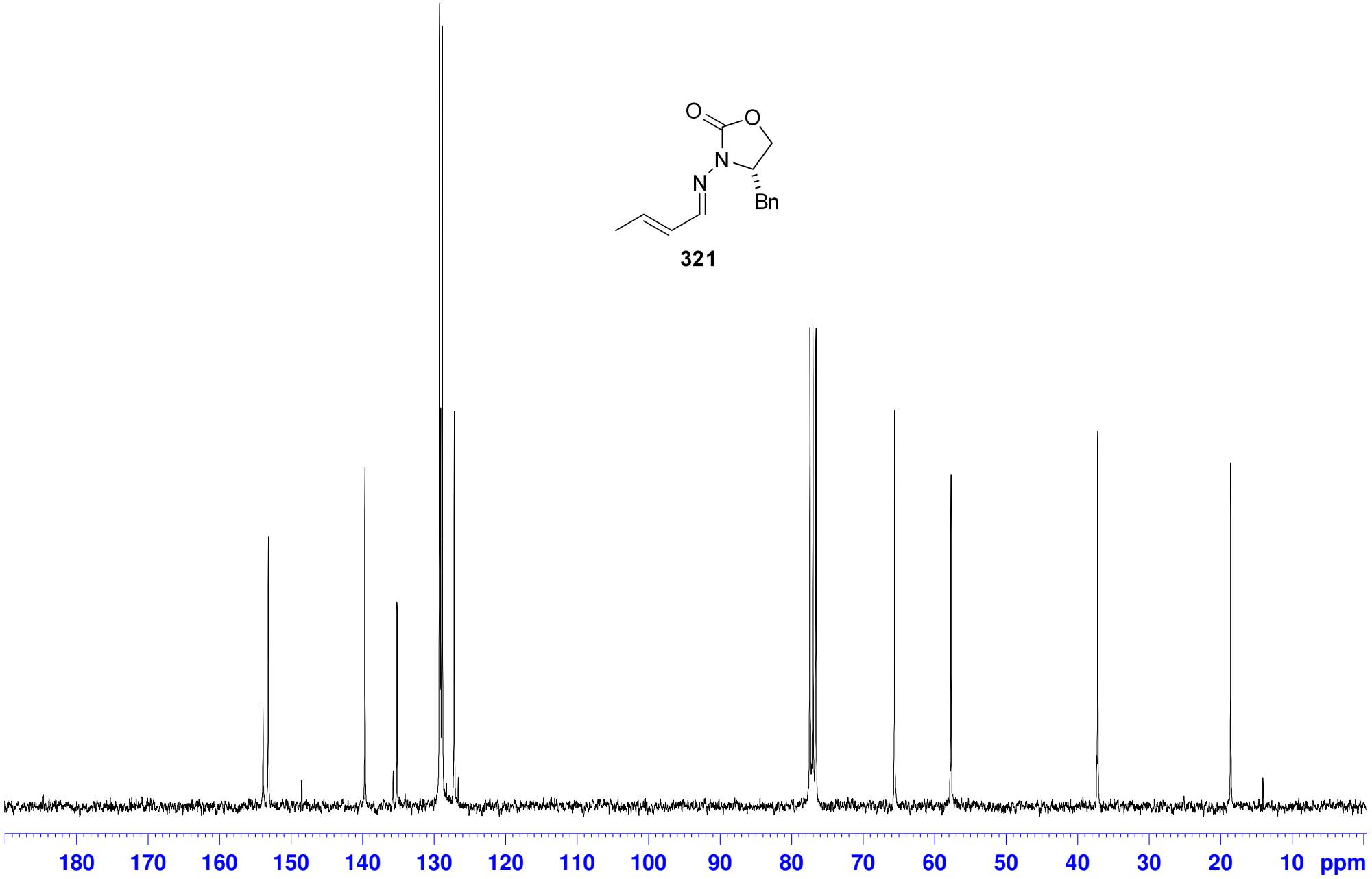
APPENDIX

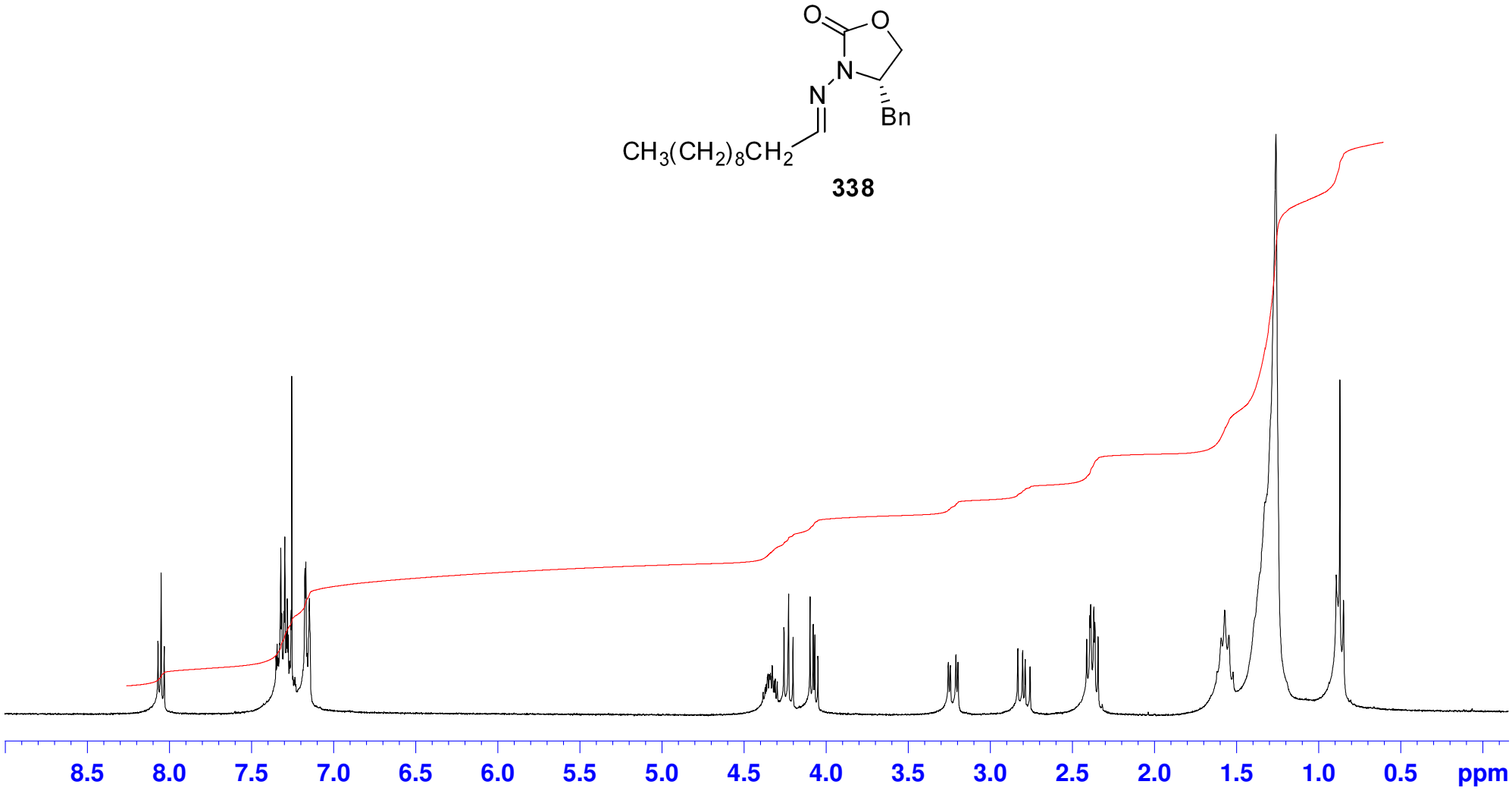
Selected NMR Spectra


TsO
I
345
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

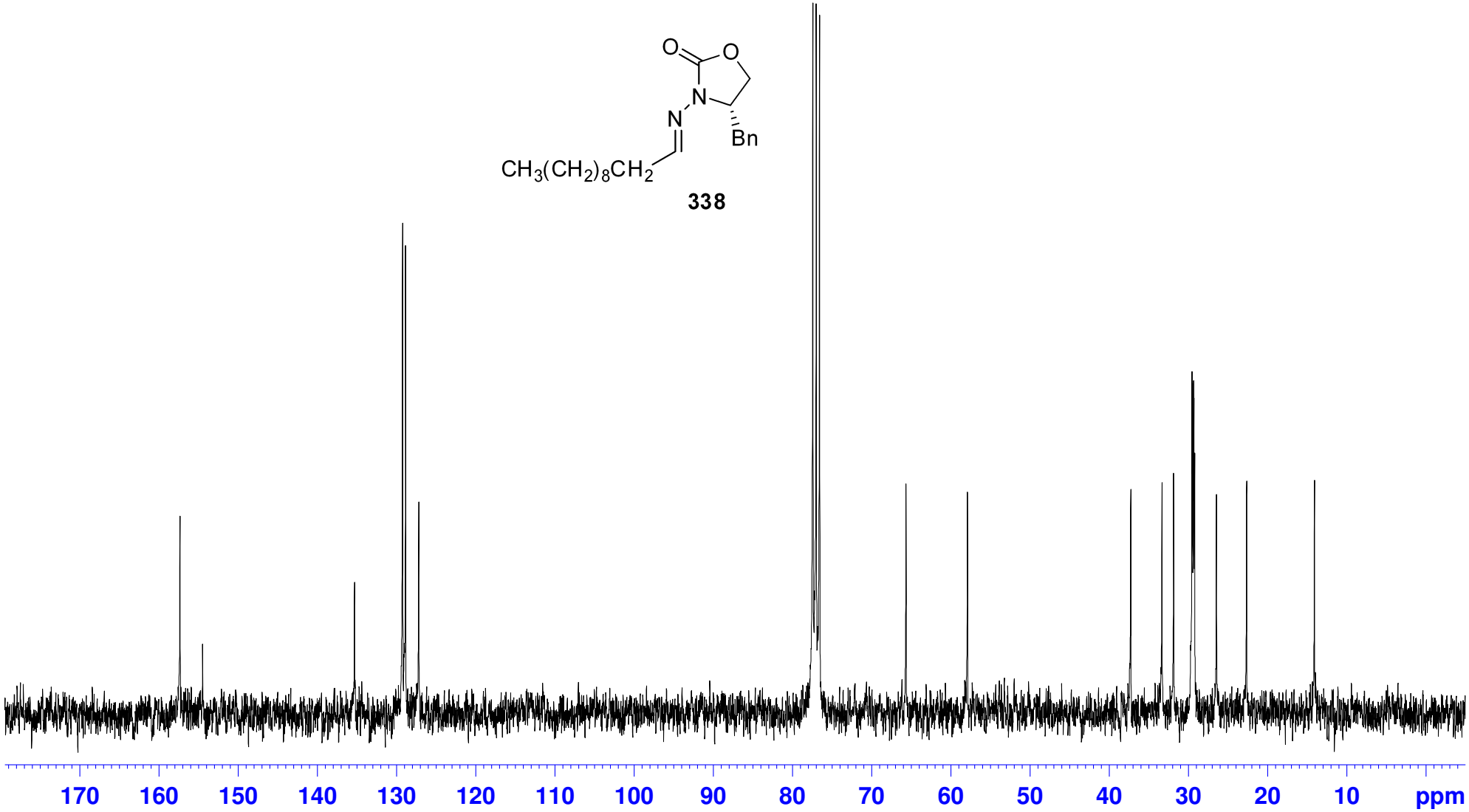

TsO
I
345
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

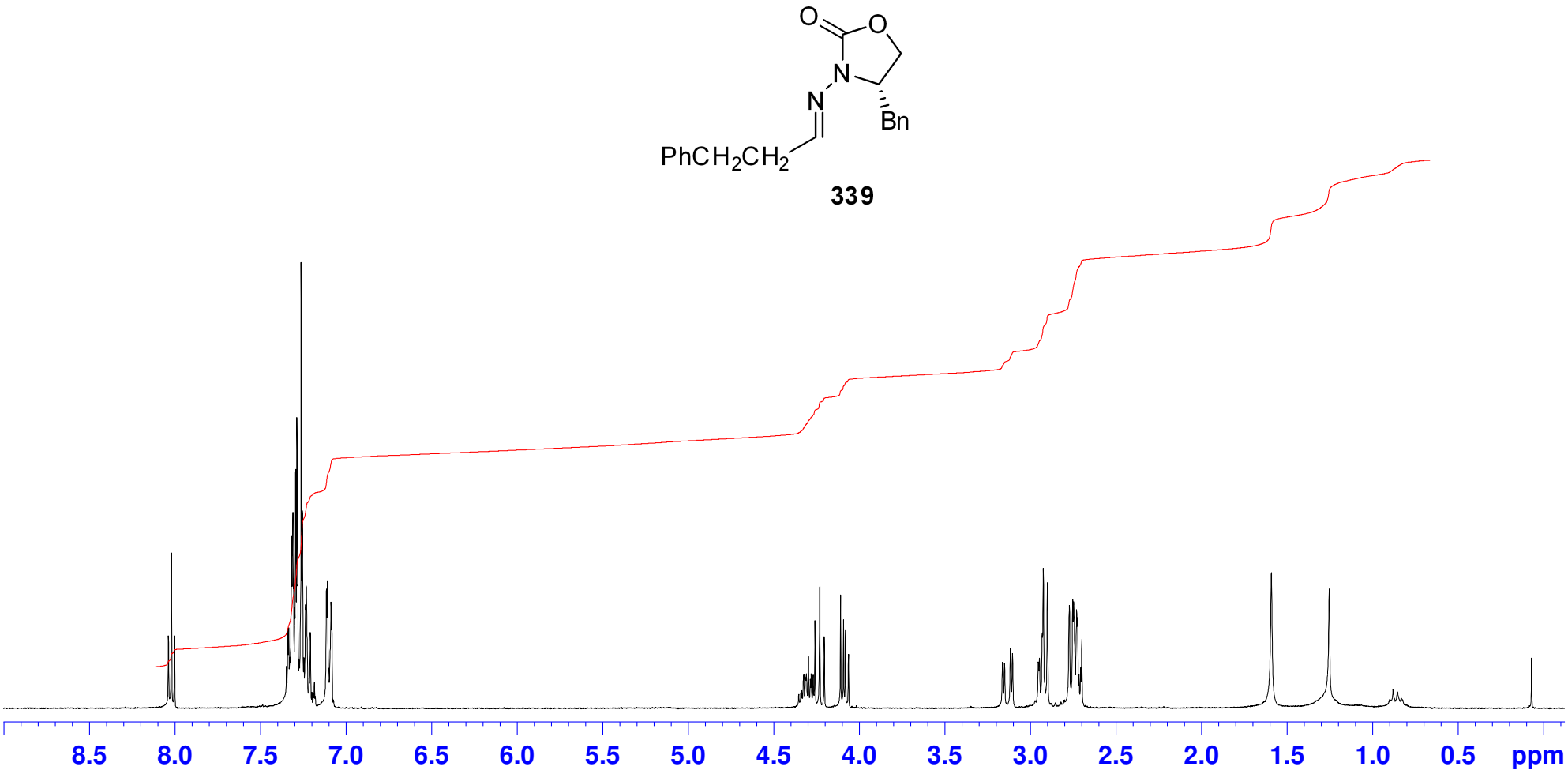

O
O
N
N
Bn
321
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


O
O
N
N
Bn
321
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

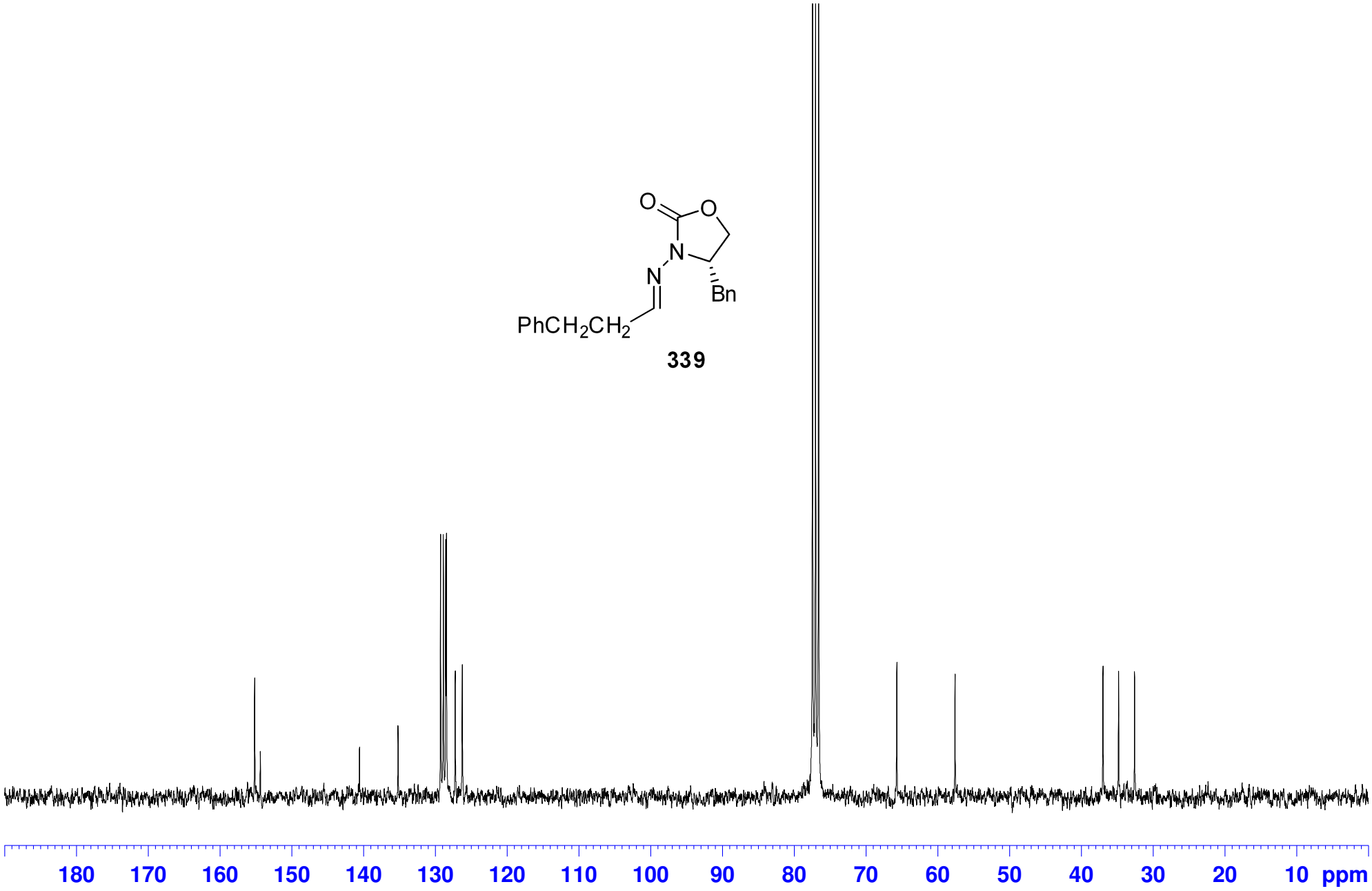

O
O
N
N
Bn
CH3(CH2)8CH2
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

338

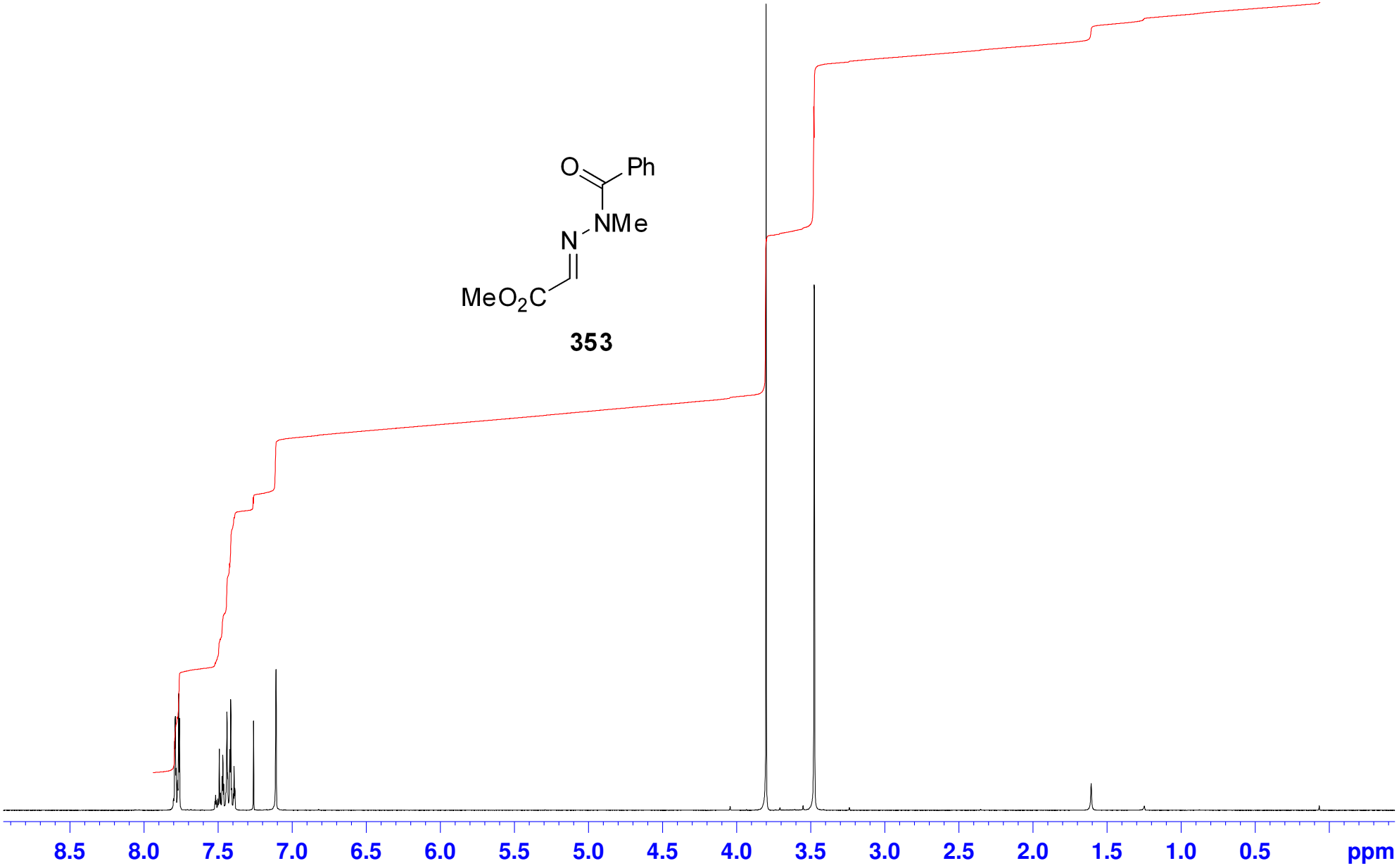

O
O
N
N
Bn
CH3(CH2)8CH2
338
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

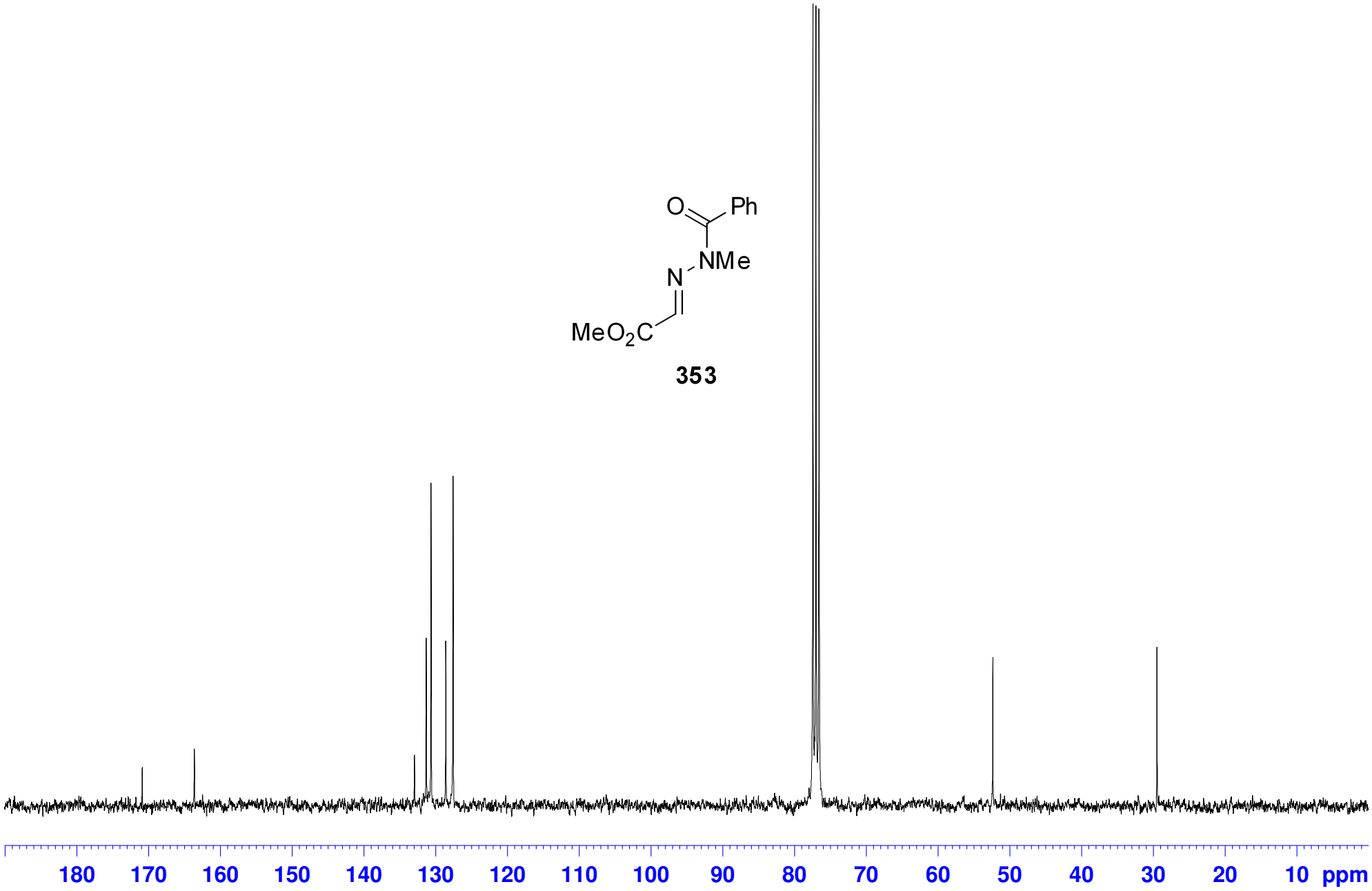

O
O
N
N
Bn
PhCH2CH2
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

339

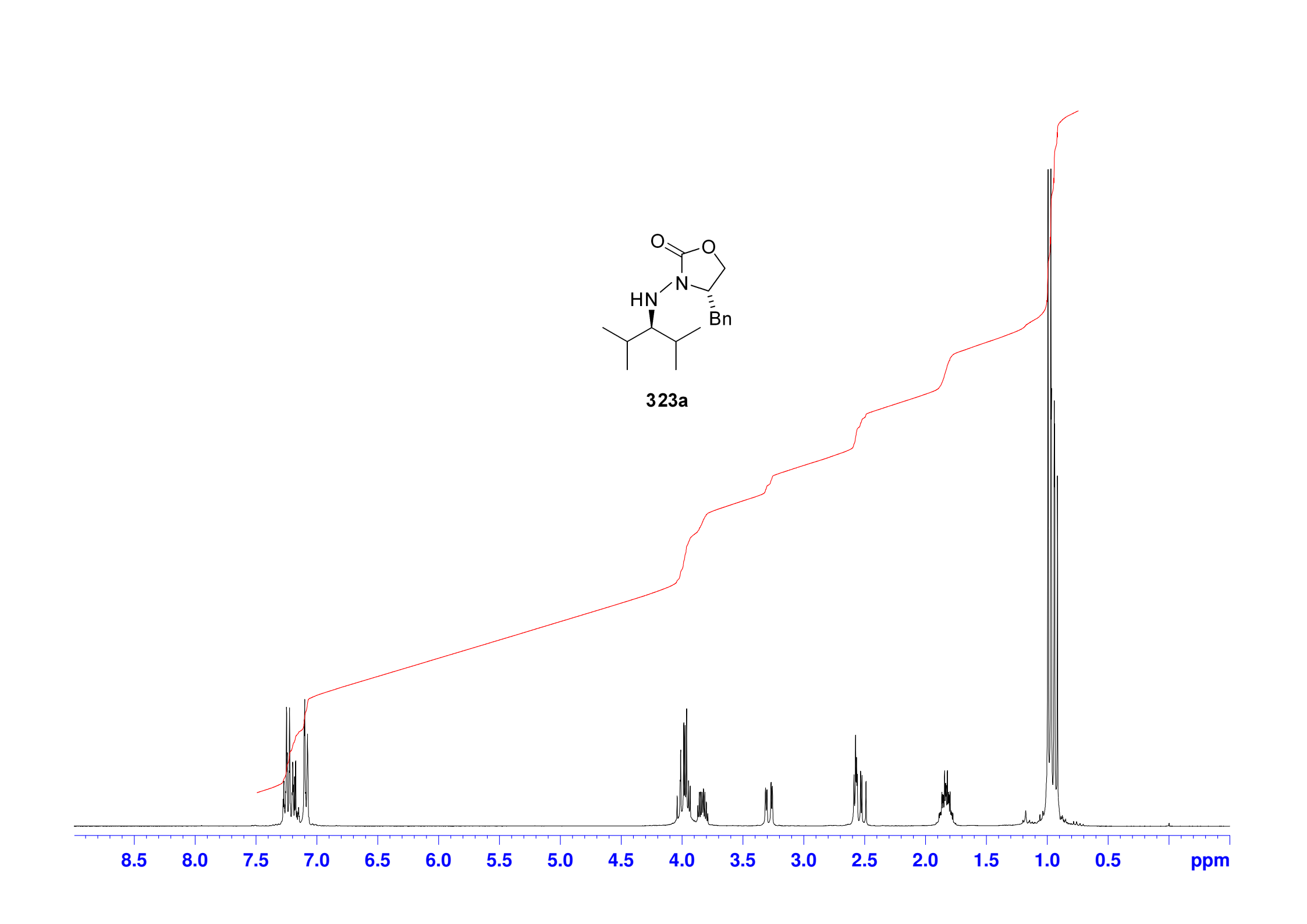

O
O
N
N
Bn
PhCH2CH2
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

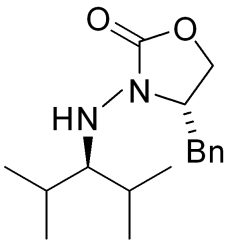
339


O
Ph
NMe
N
MeO2C
353
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
Ph
NMe
N
MeO2C
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

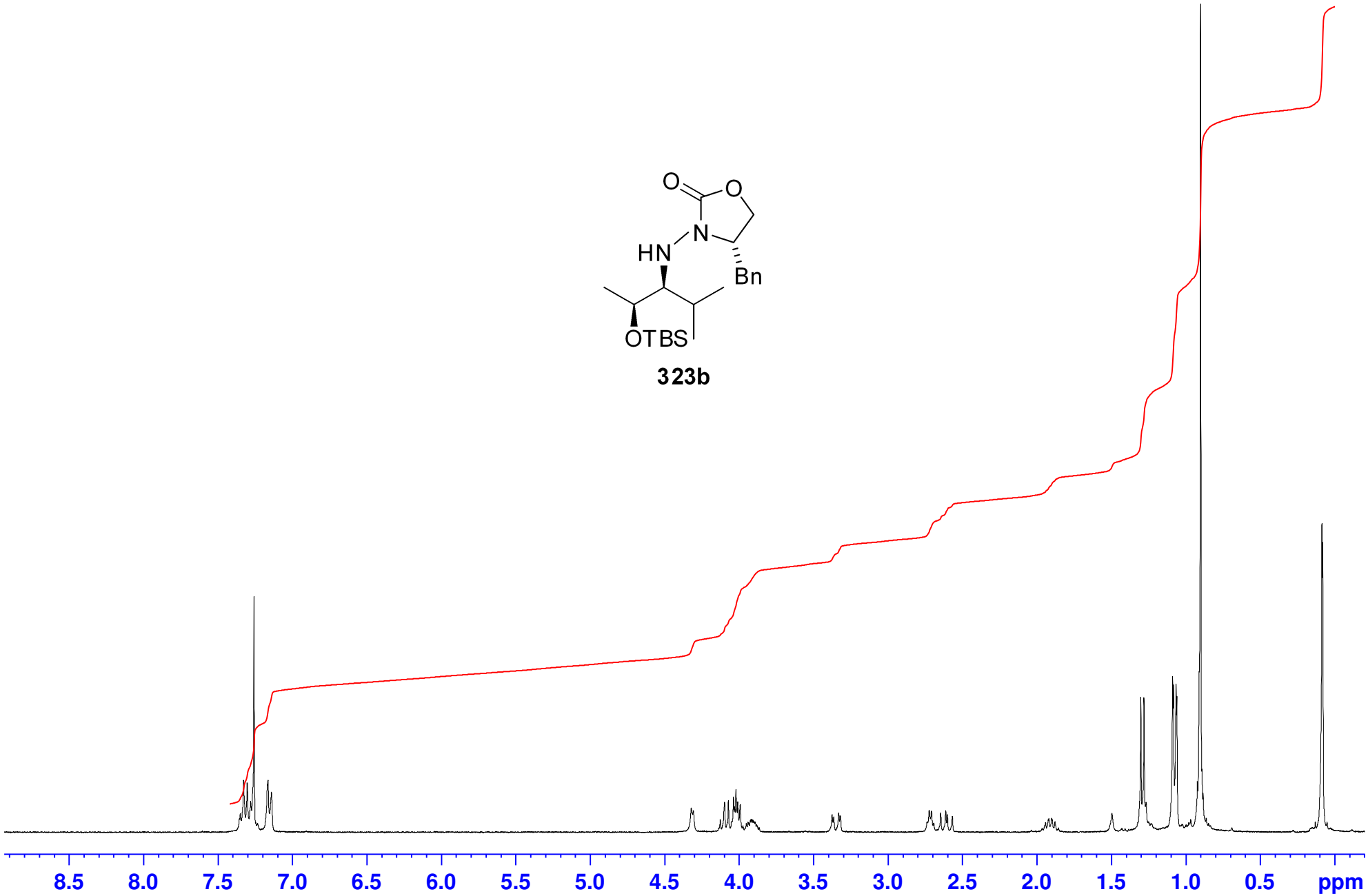
353


O
O
N
HN
Bn
323a
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

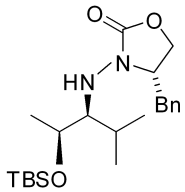

O
O
N
HN
Bn

323a

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

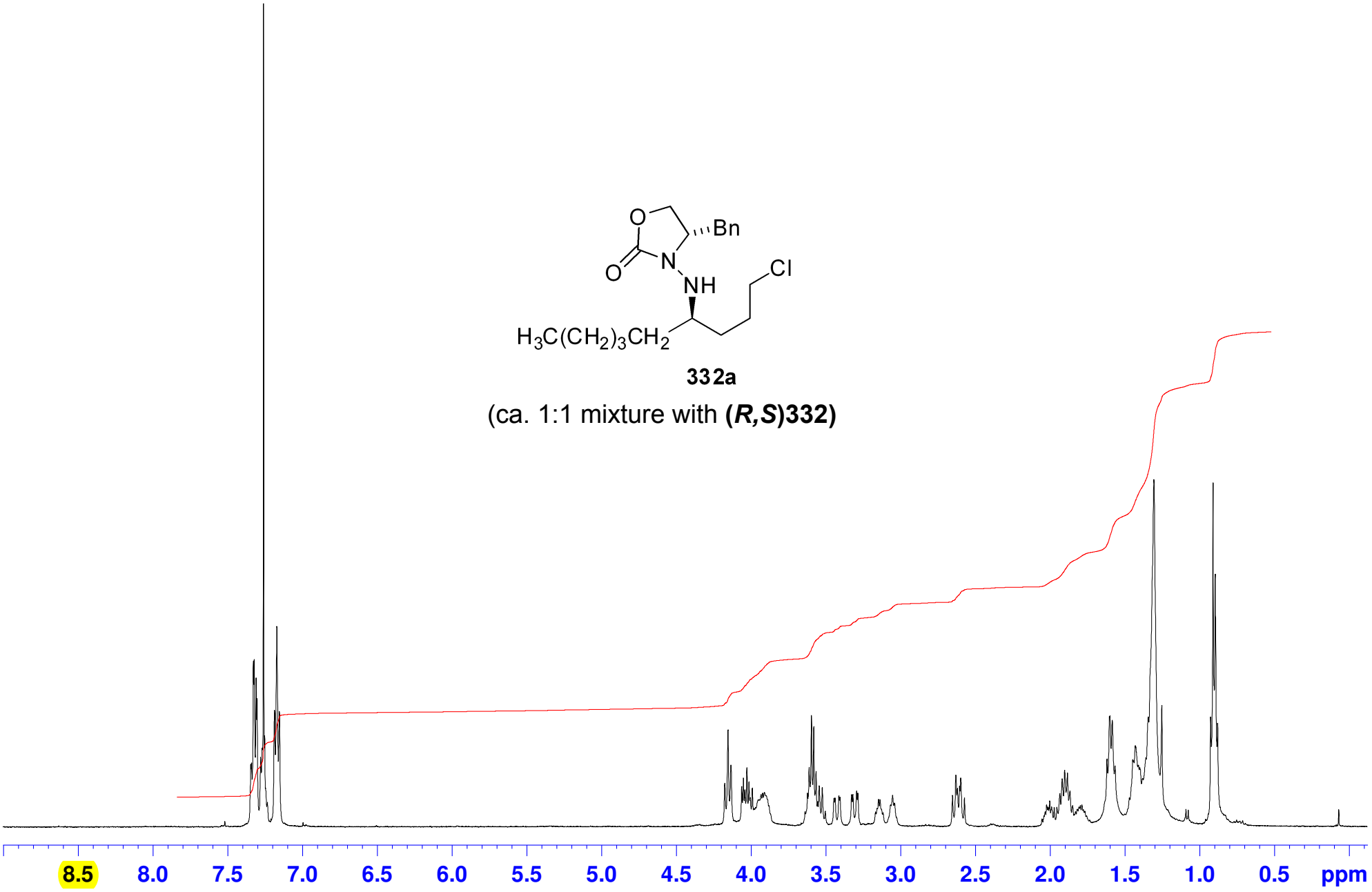


323b


O
O
N
HN
Bn
TBSO

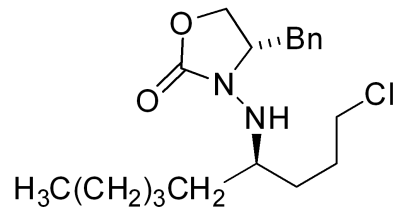
323b

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



332a

(ca. 1:1 mixture with ***(R,S)*332)**

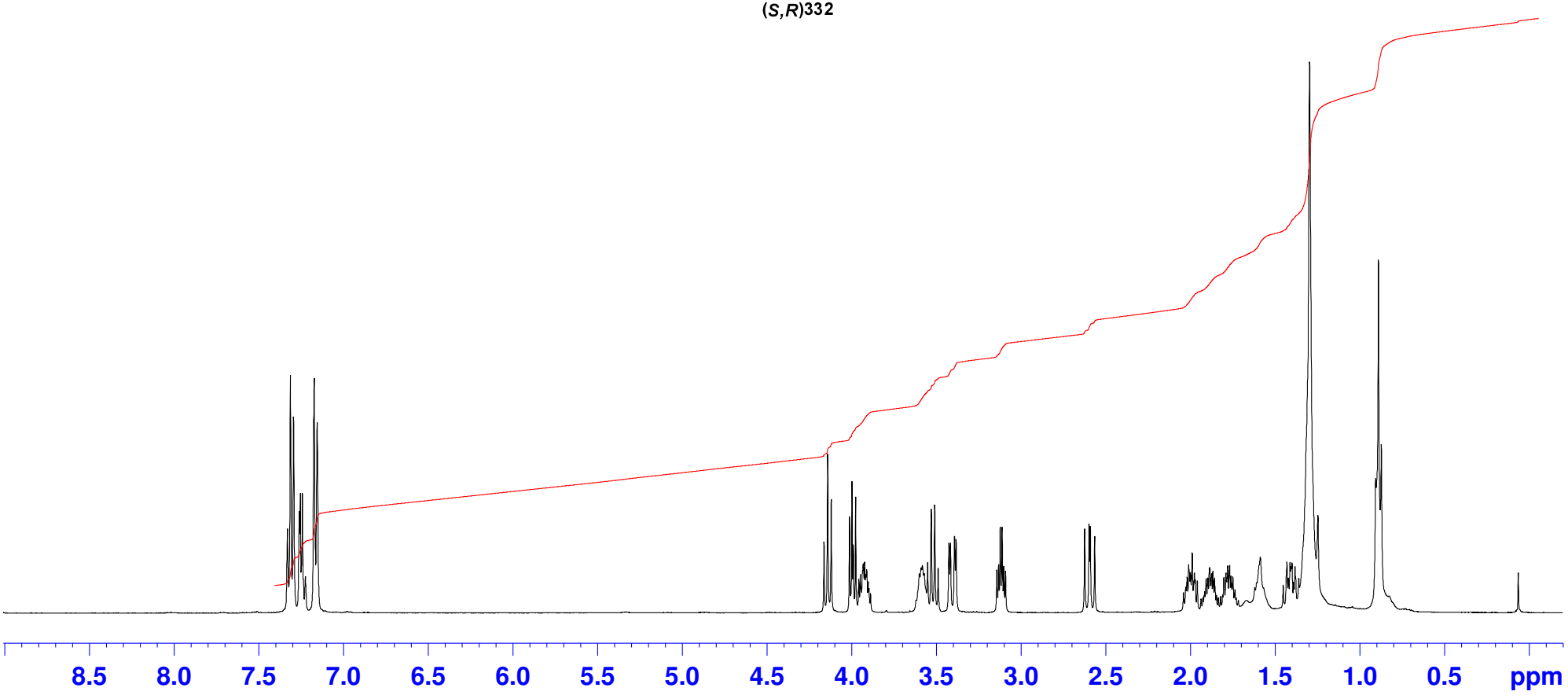


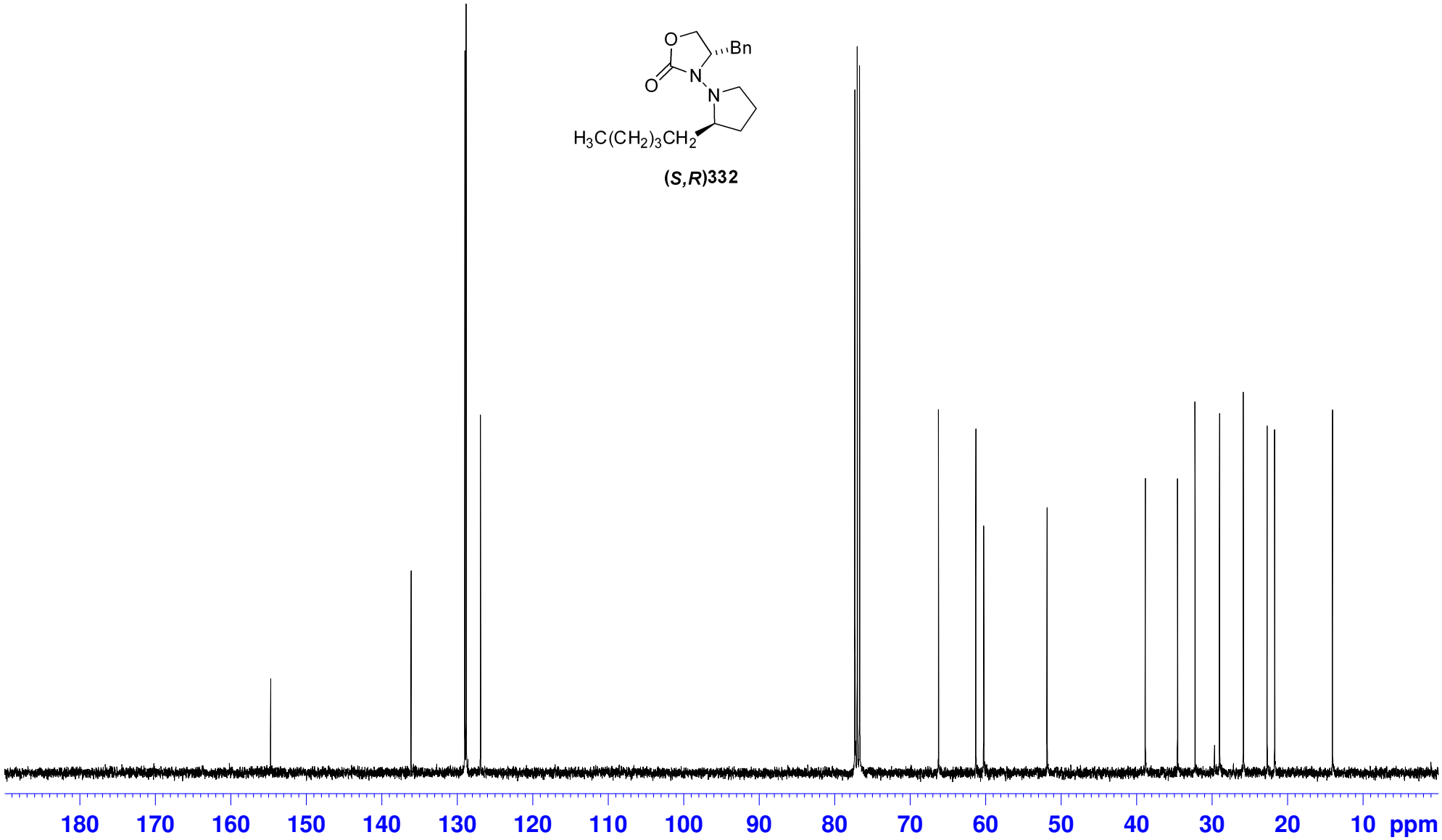
332a

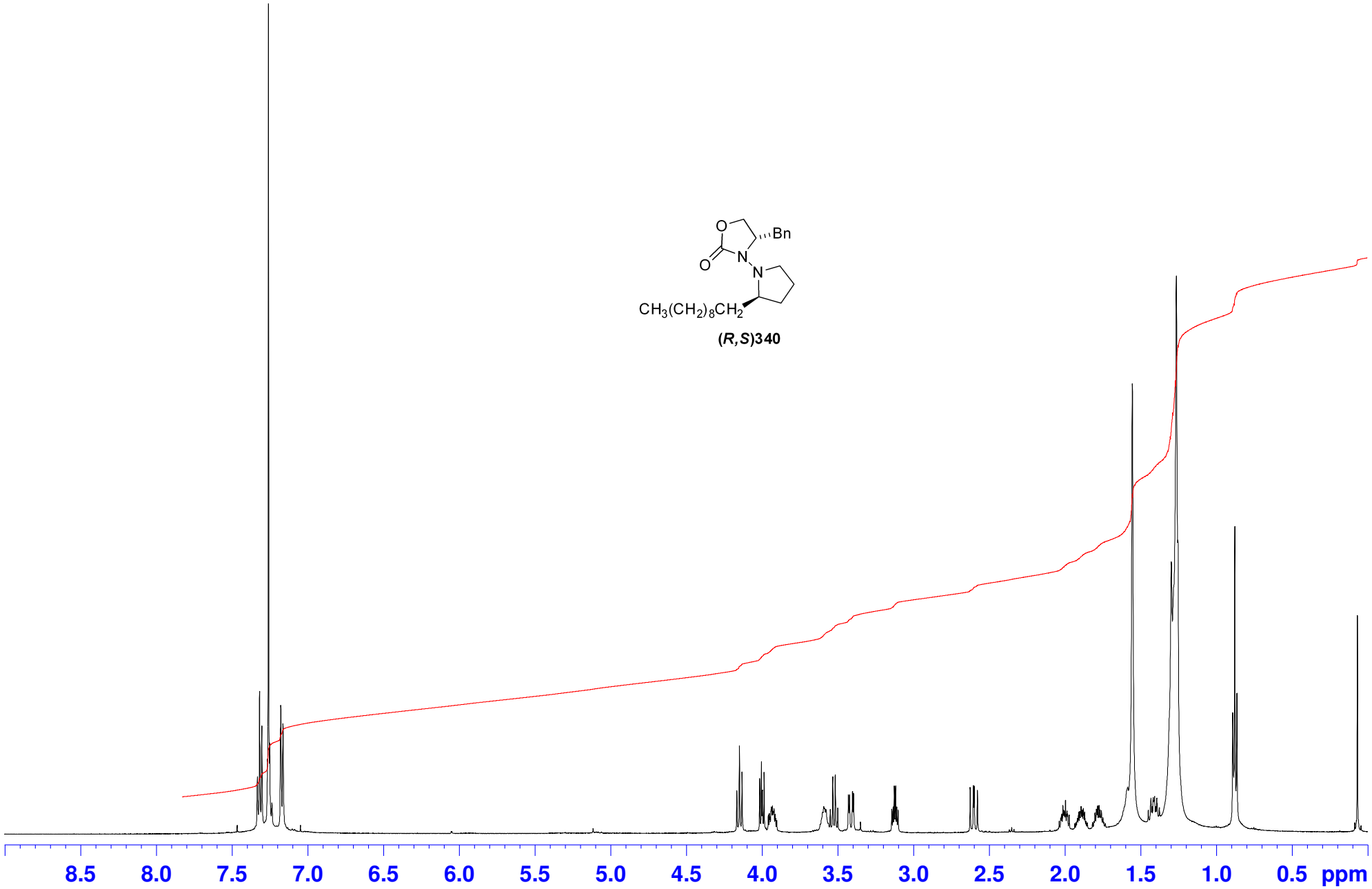
(ca. 1:1 mixture with **(*R,S*)332**)

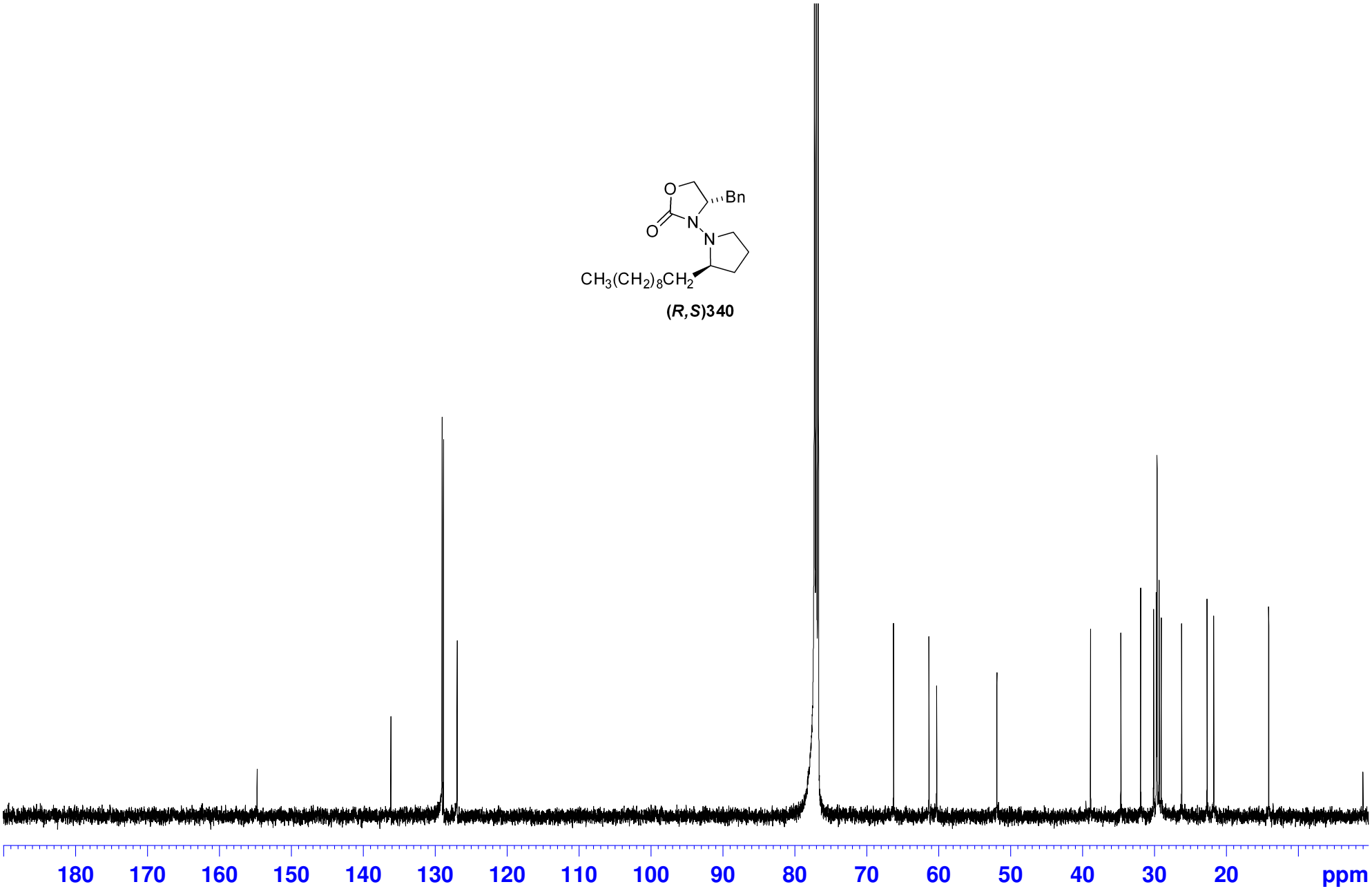

O
Bn
O
N
N
H3C(CH2)3CH2

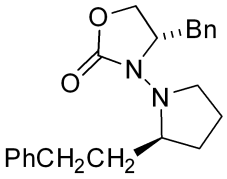
(*S*,*R*)332


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
Bn
O
N
N
H3C(CH2)3CH2
(S,R)332
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

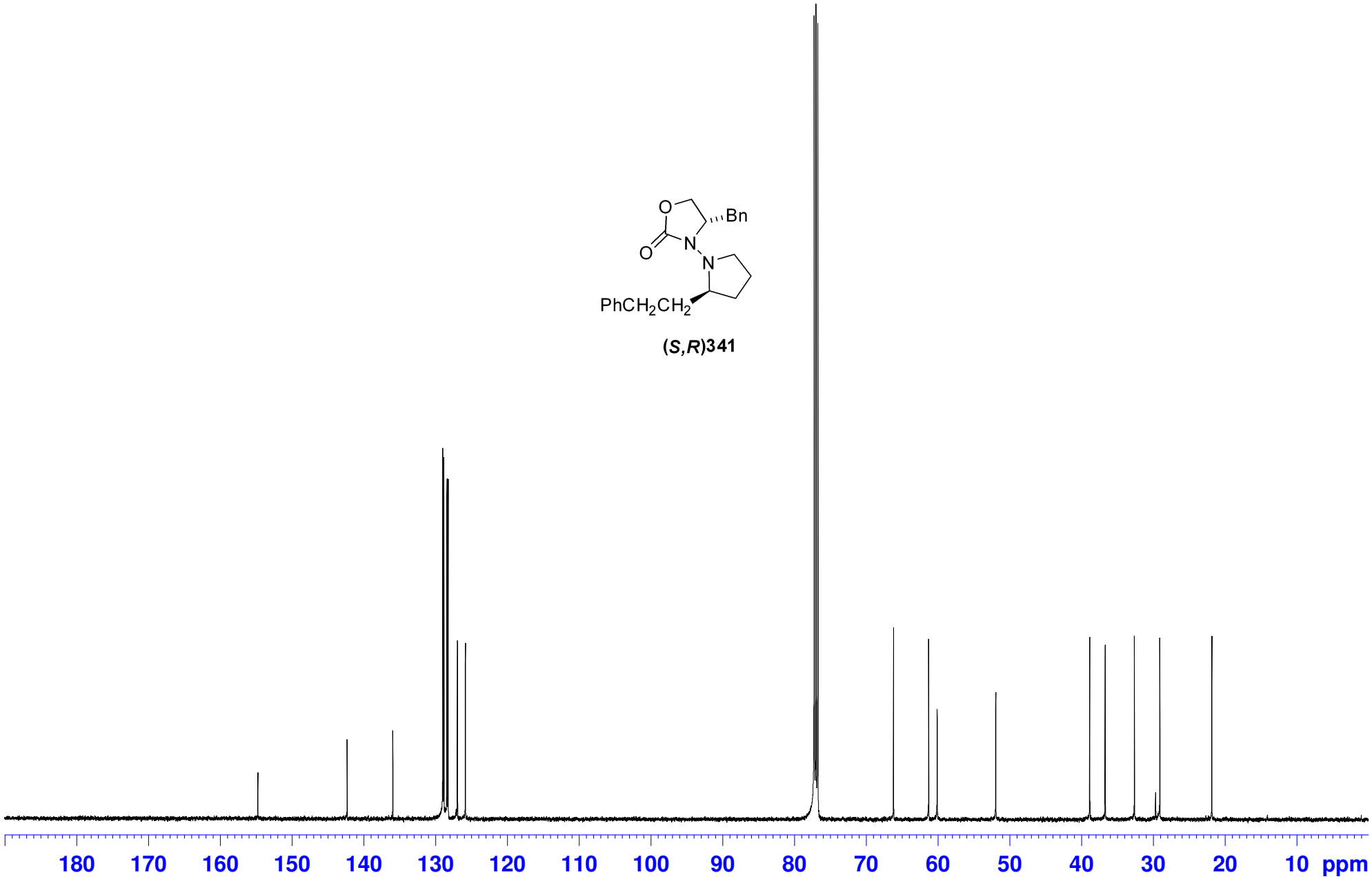

O
O
N
N
Bn
CH3(CH2)8CH2
(R,S)340
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


O
Bn
O
N
N
CH3(CH2)8CH2
(R,S)340
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

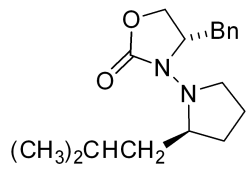

O
Bn
O
N
N
PhCH2CH2

(*S*,*R*)341

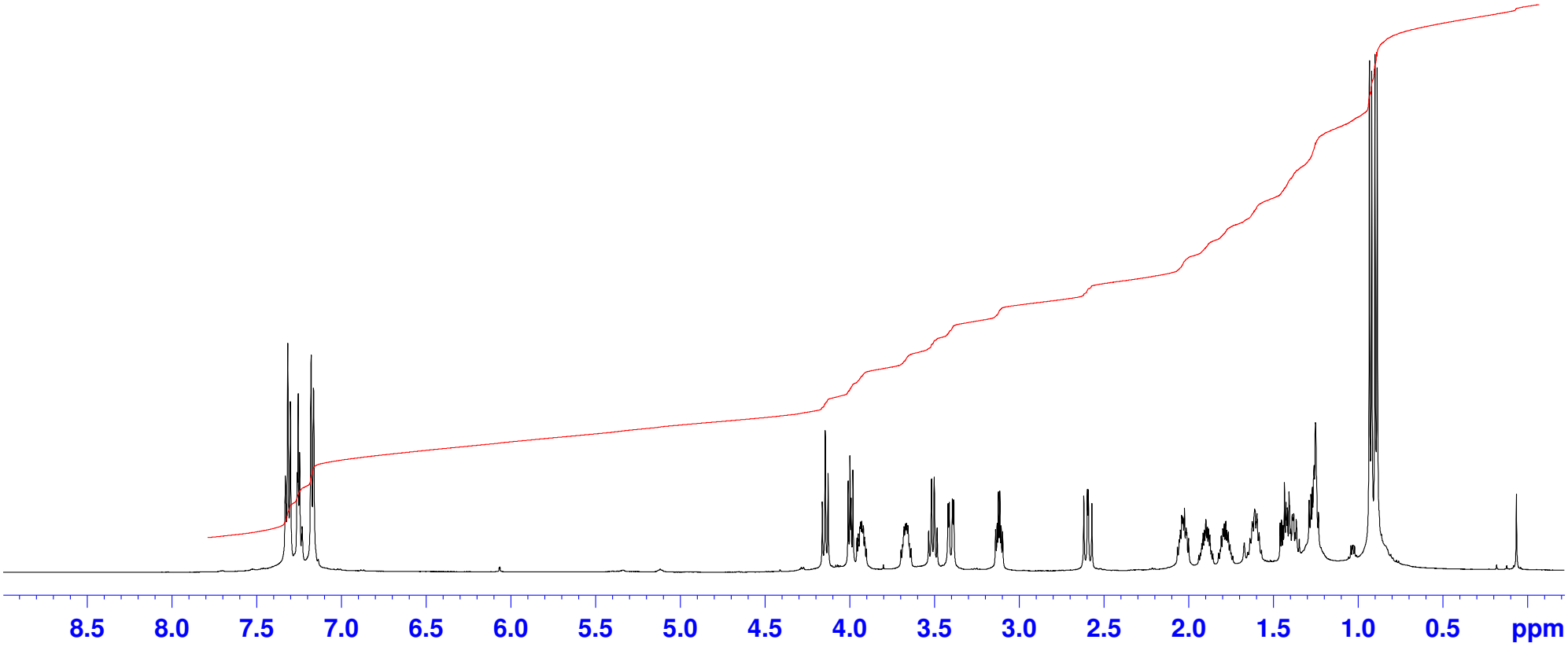
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

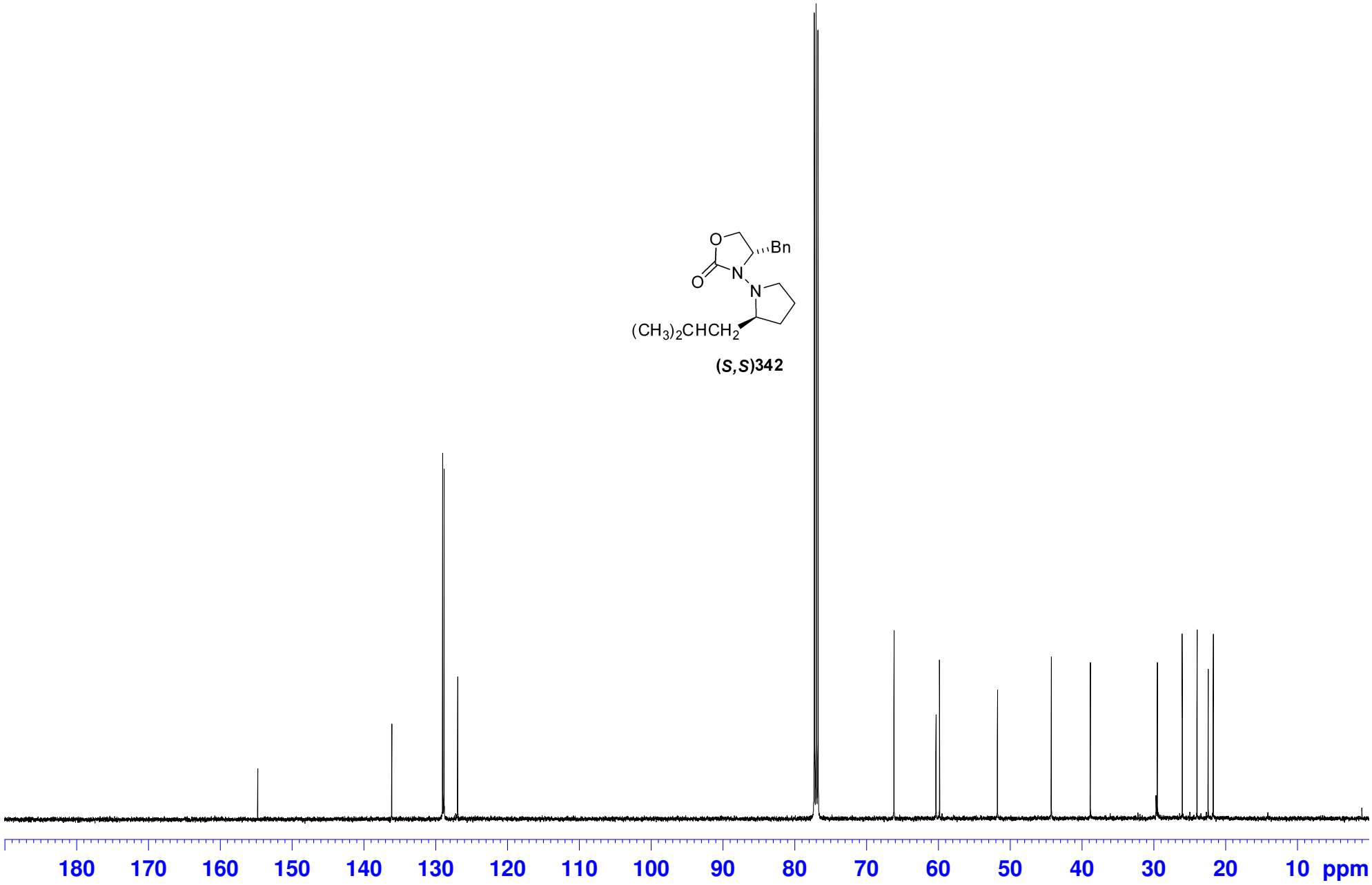

O
Bn
O
N
N
PhCH2CH2
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

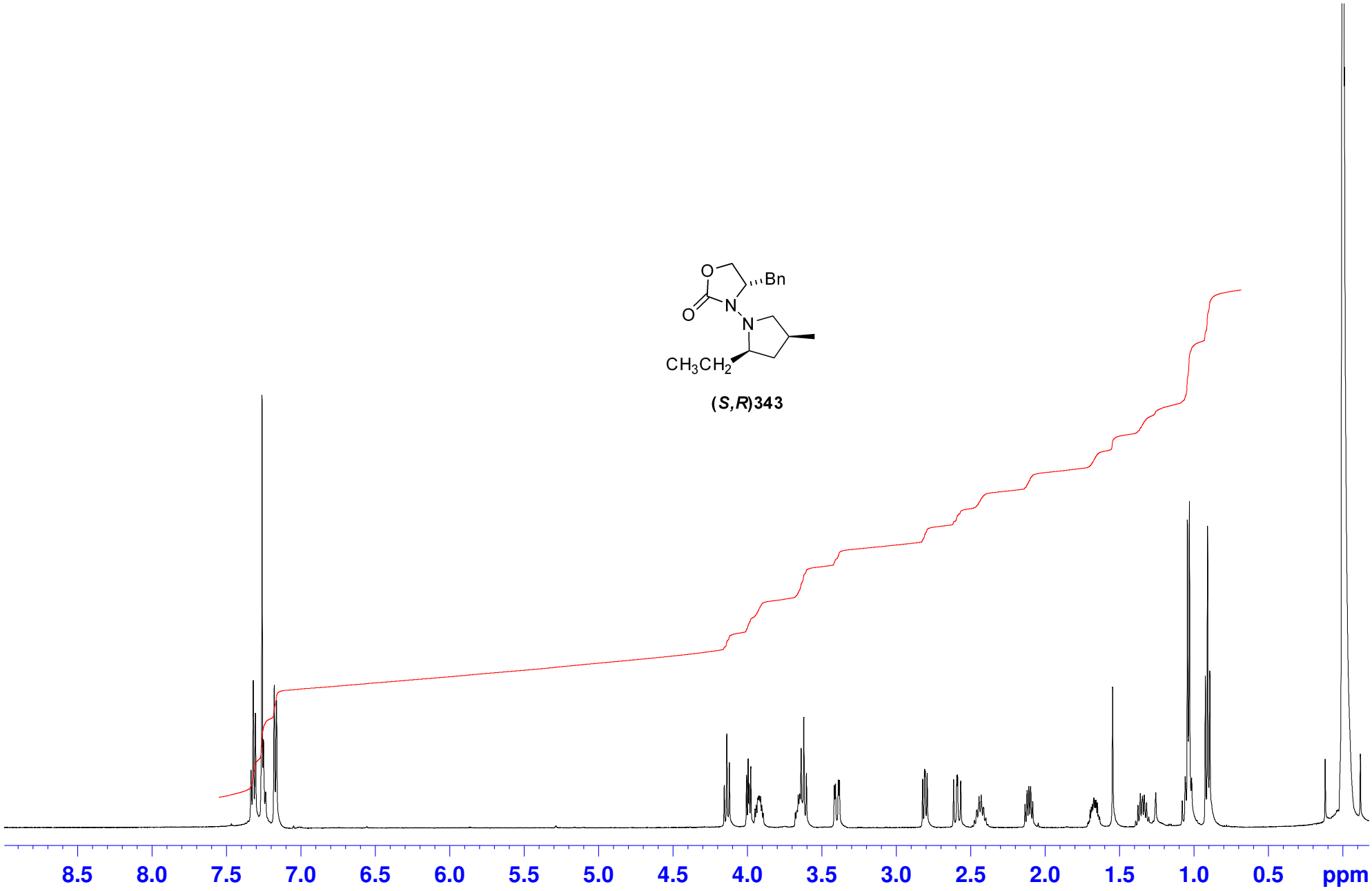
(*S*,*R*)341


O
Bn
O
N
N
(CH3)2CHCH2

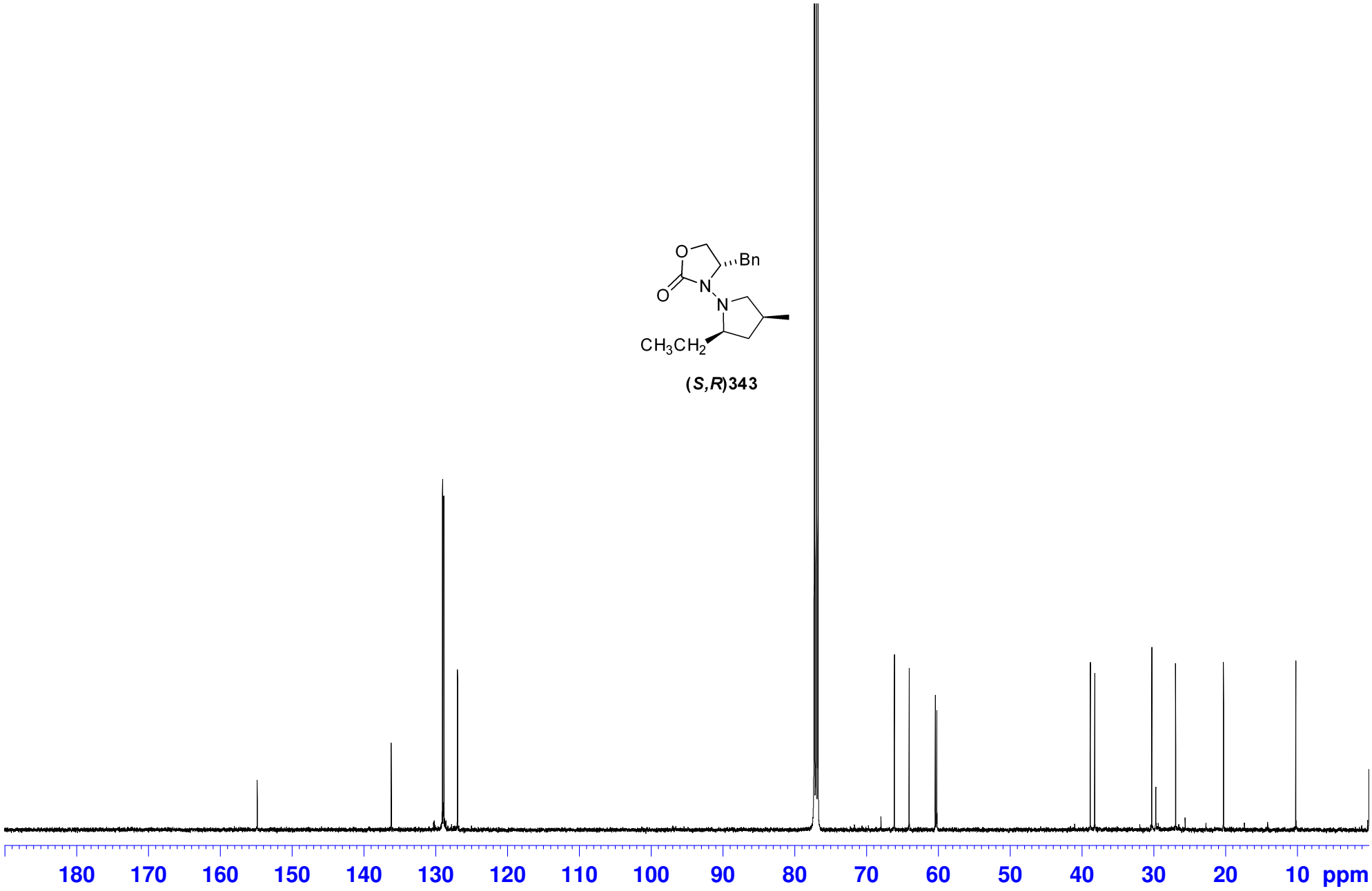
(*S*,*S*)342


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

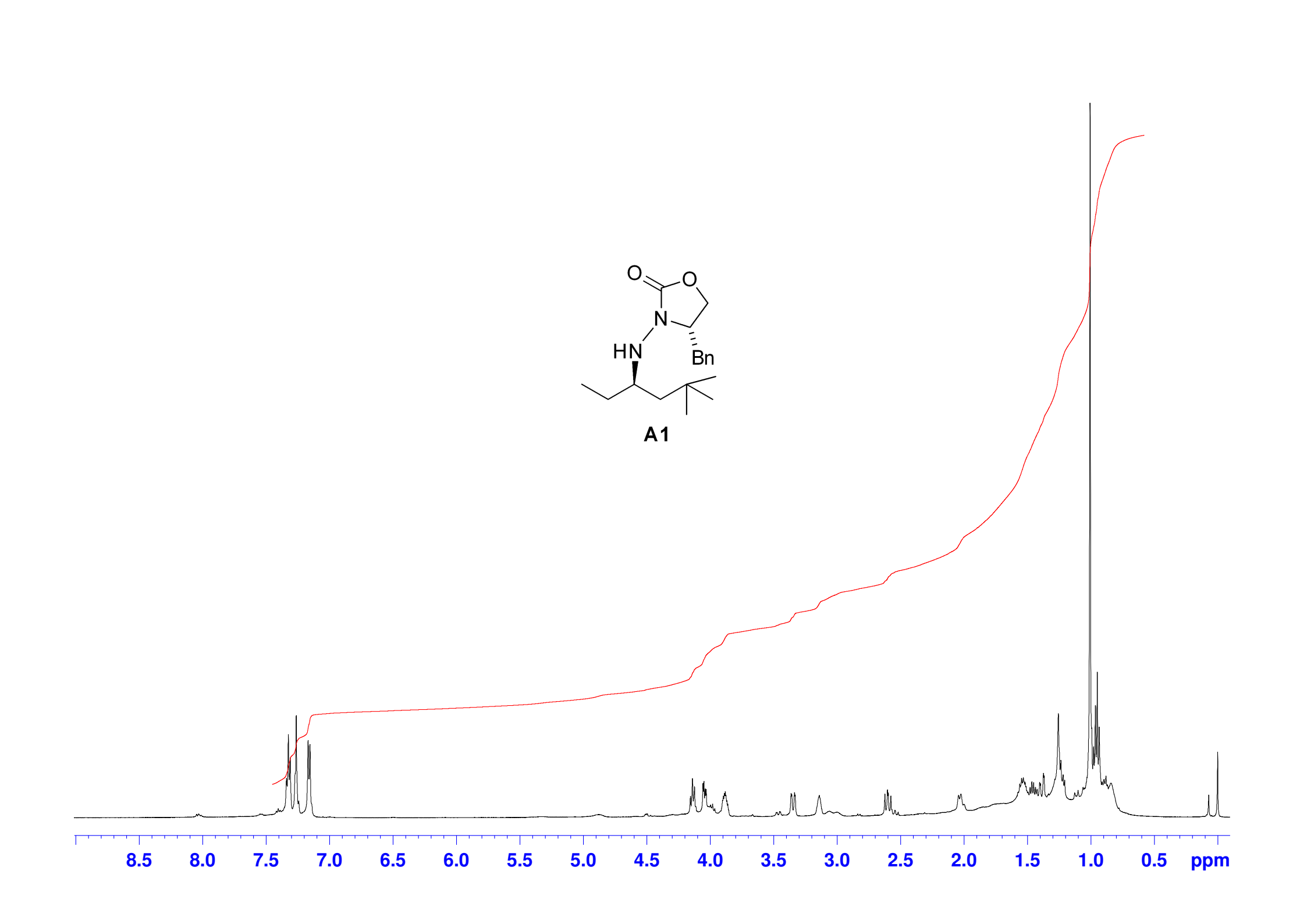

O
Bn
O
N
N
(CH3)2CHCH2
(S,S)342
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

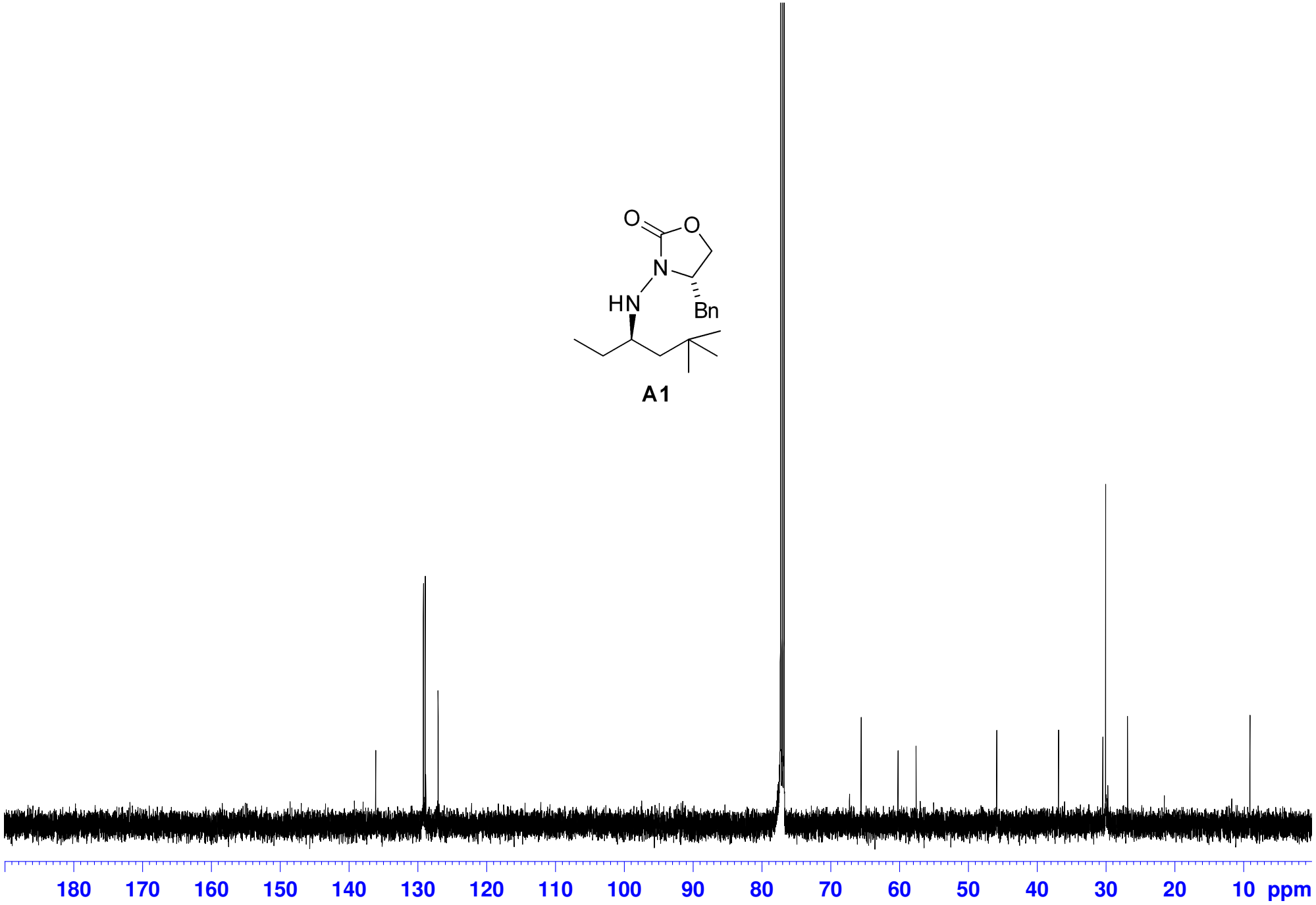


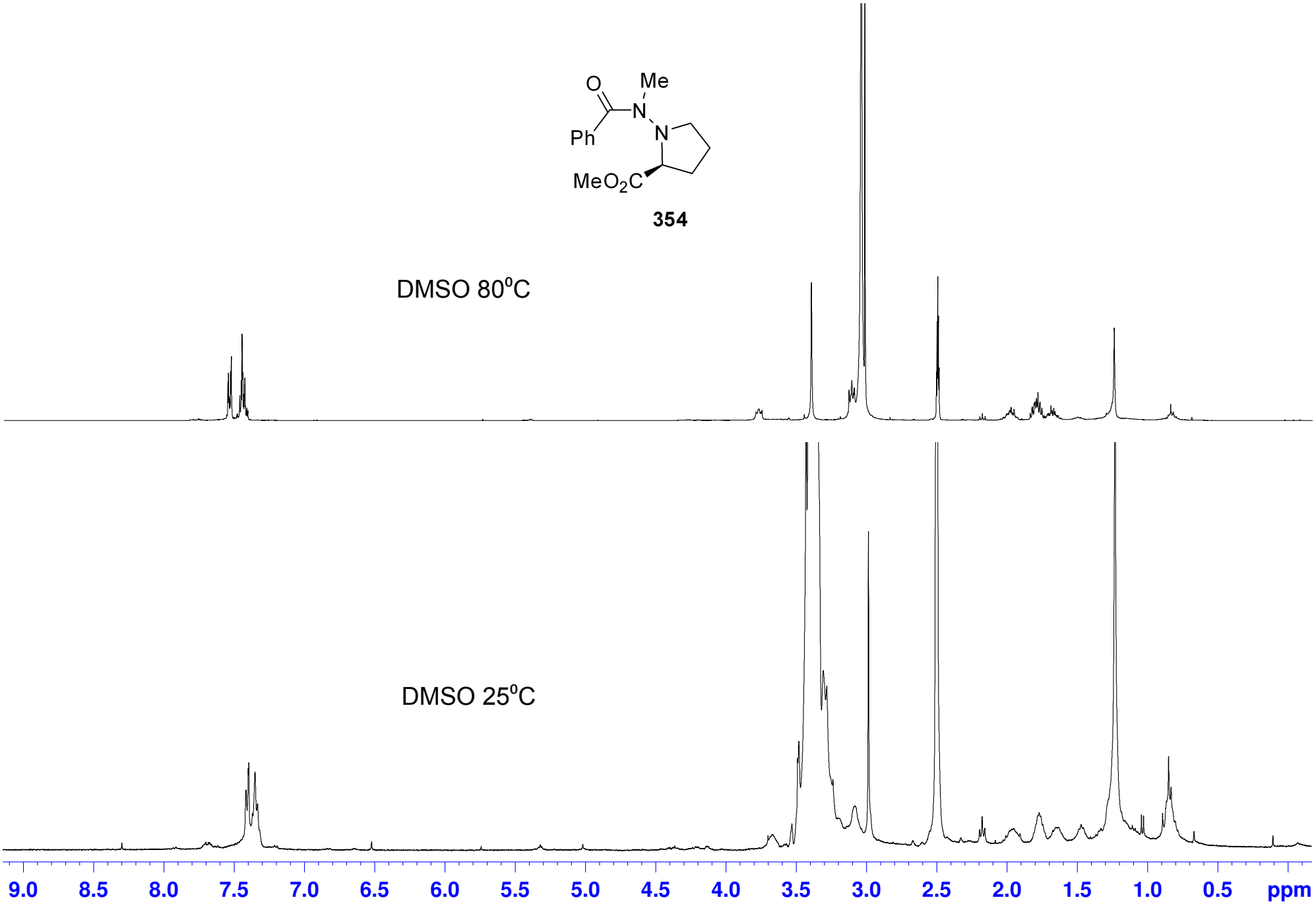
(*S*,*R*)**343**

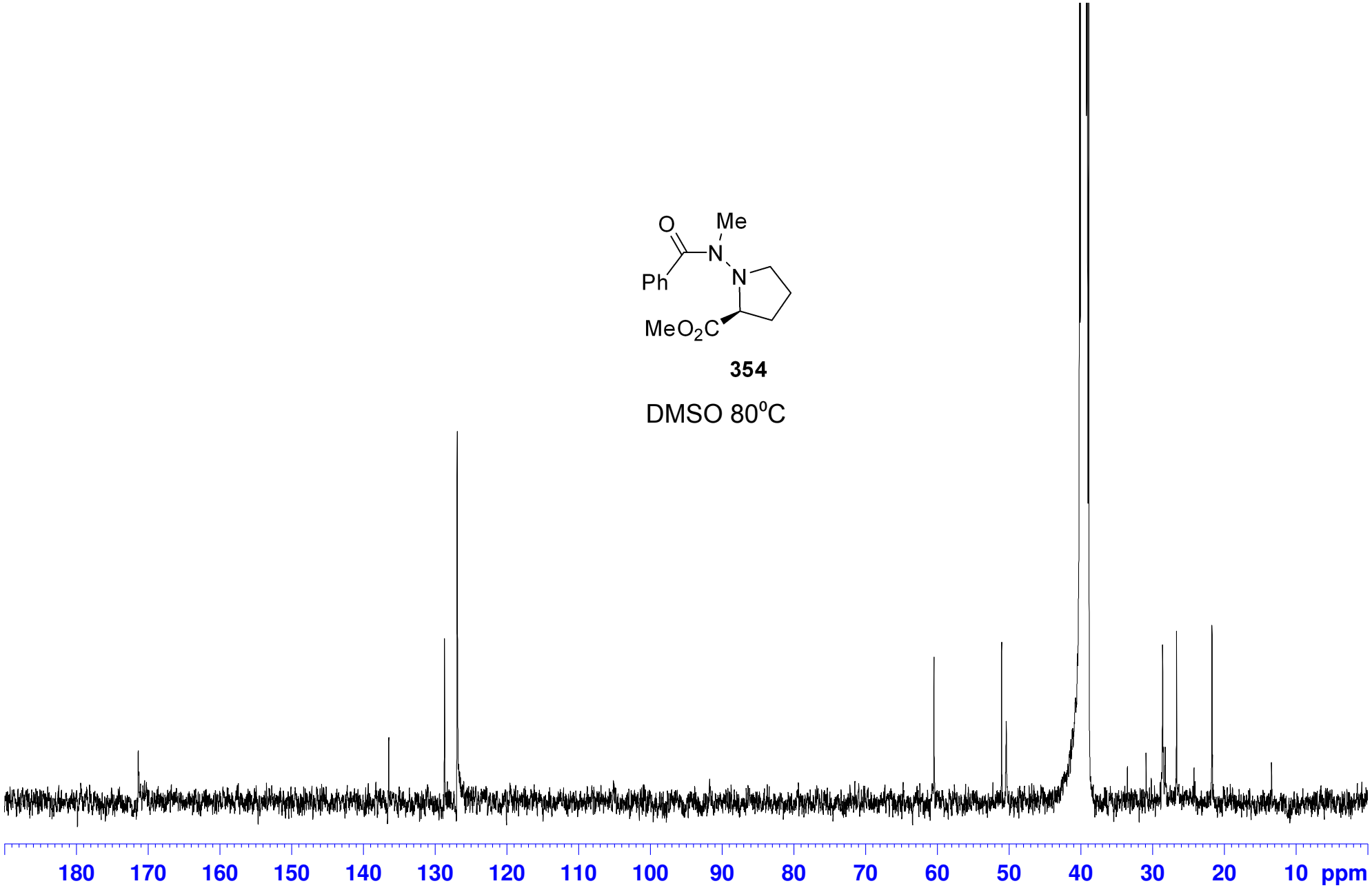

O
Bn
O
N
N
CH3CH2
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

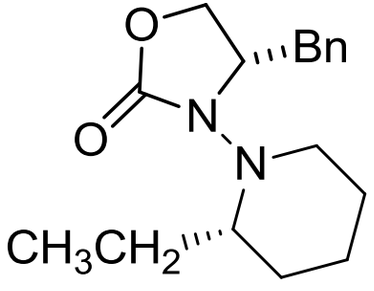
(*S*,*R*)**343**


O
O
N
HN
Bn
A1
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

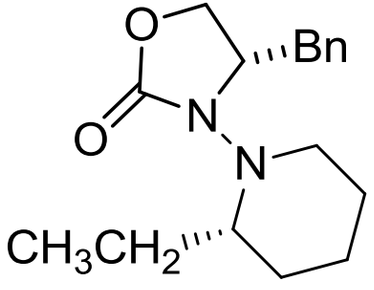

O
O
N
HN
Bn
A1
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


O
Me
N
N
Ph
MeO2C
354
DMSO 80°C
DMSO 25°C
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

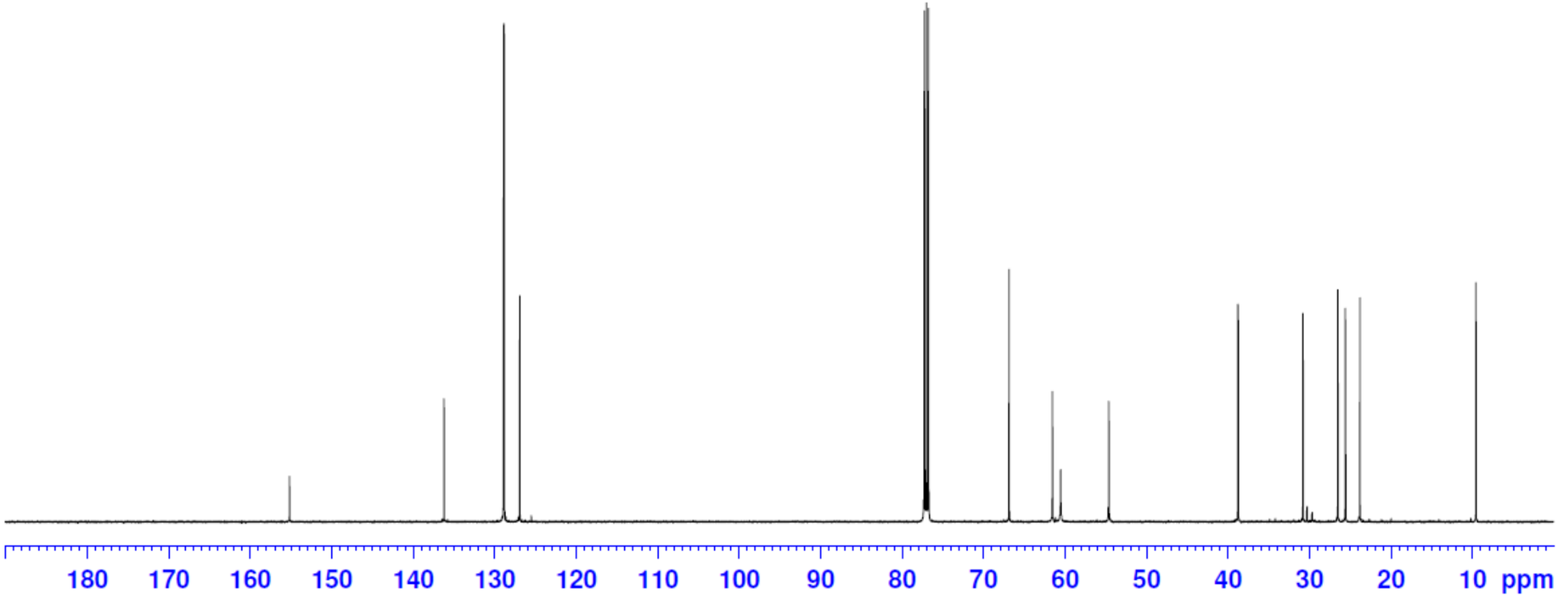

O
Me
N
N
Ph
MeO2C
354
DMSO 80°C
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

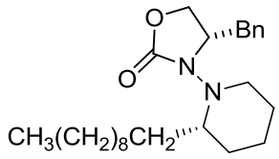


355

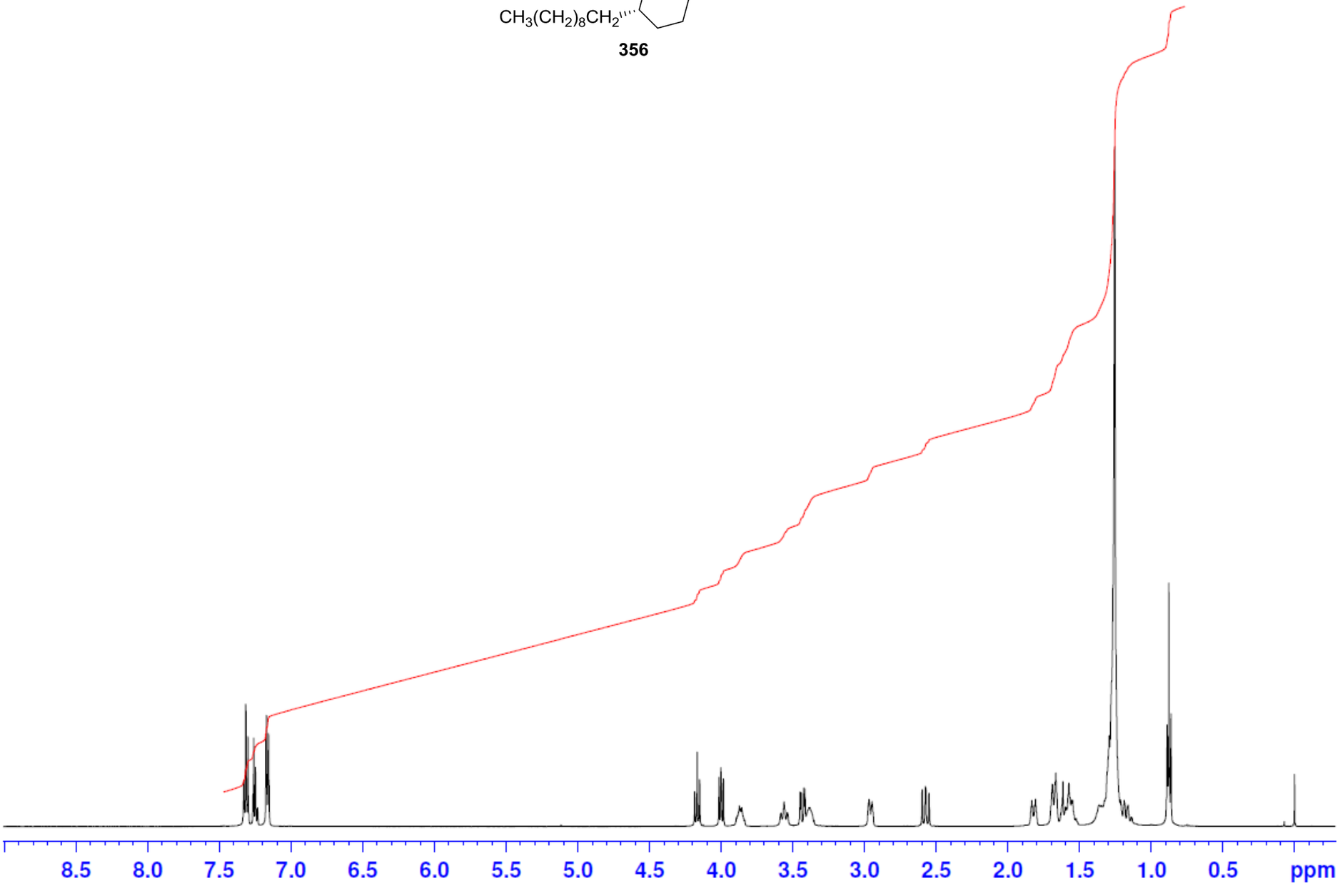

O
Bn
N
O
N
CH3CH2

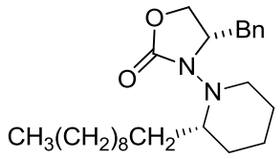
355


180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

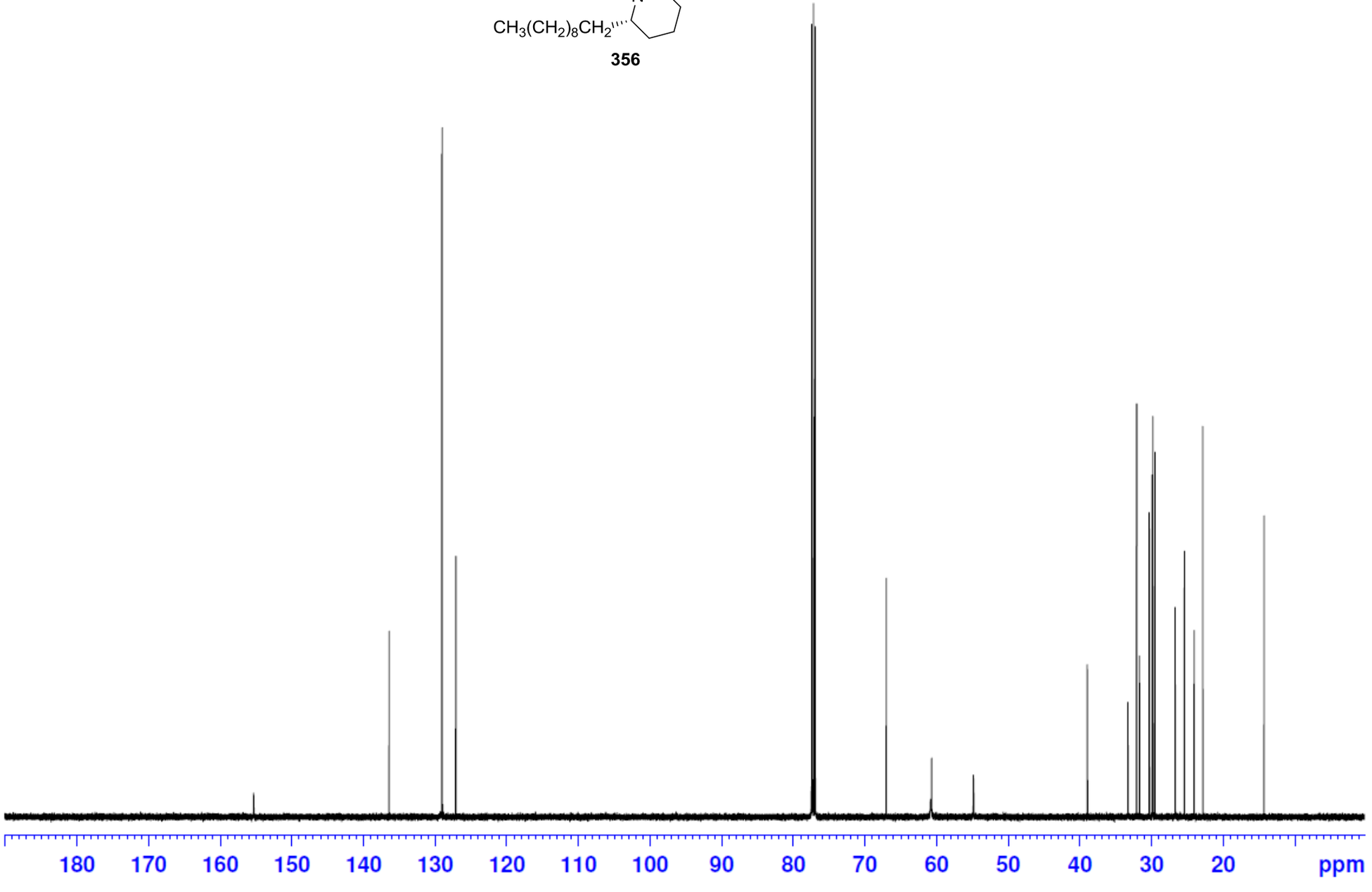

O
Bn
O
N
N
CH3(CH2)8CH2

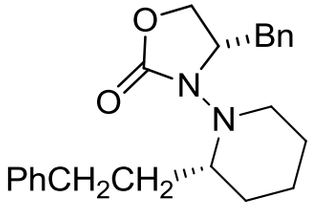
356


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
Bn
O
N
N
CH3(CH2)8CH2

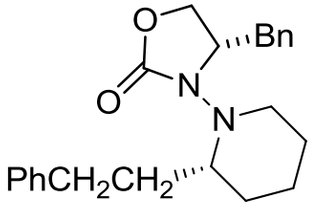
356


180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

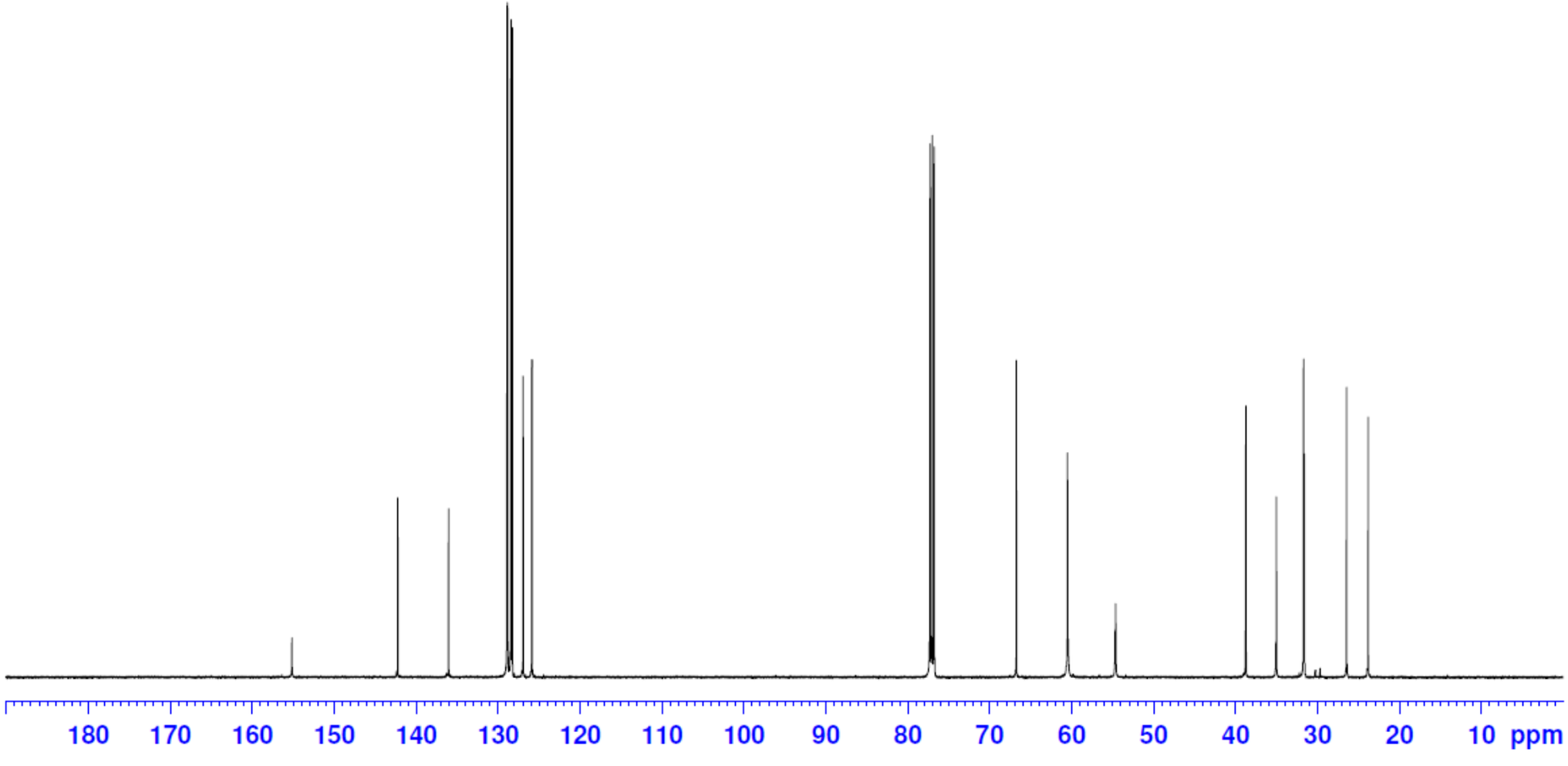

O
Bn
O
N
N
PhCH2CH2

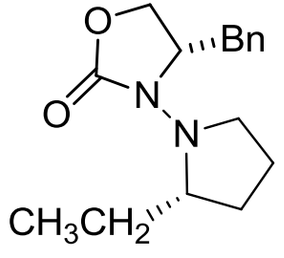
357

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

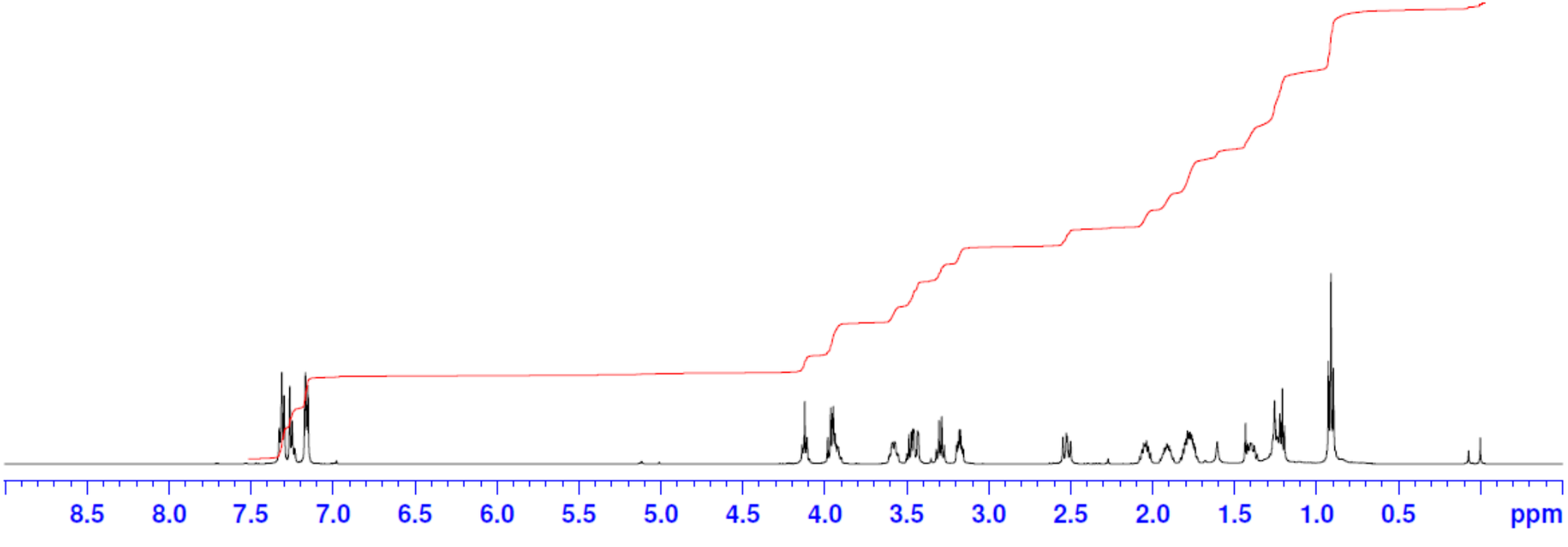

O
Bn
O
N
N
PhCH2CH2

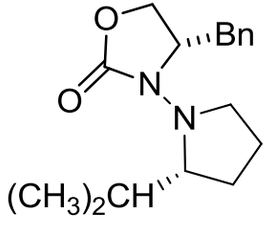
357


180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

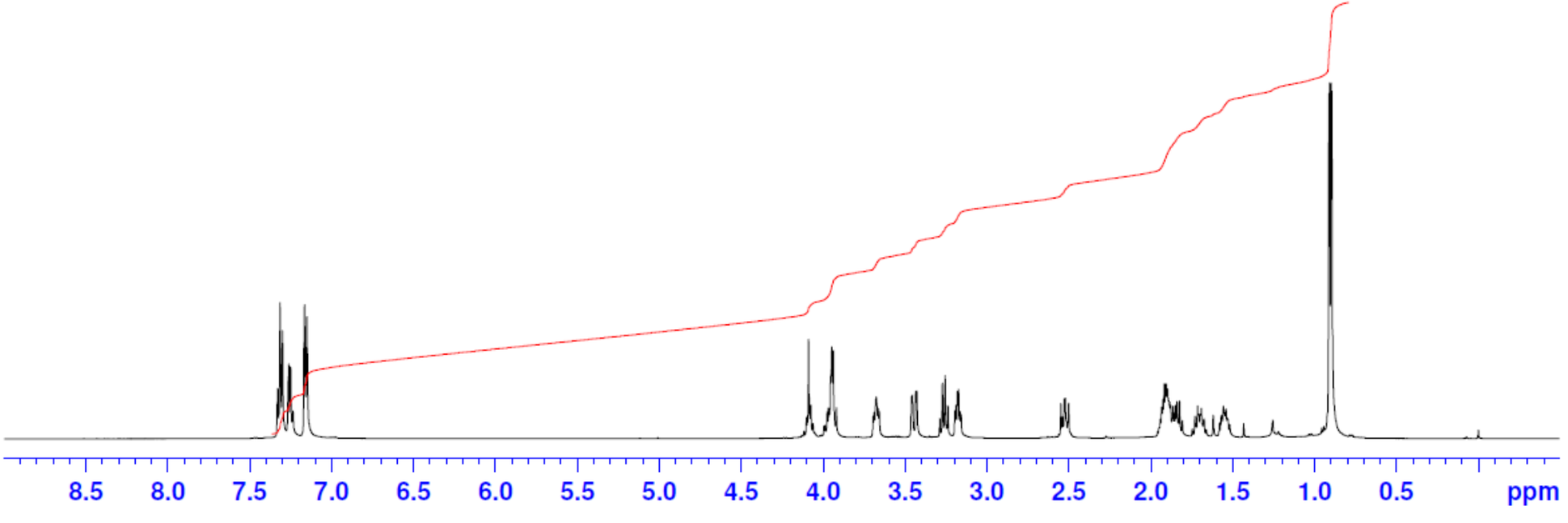


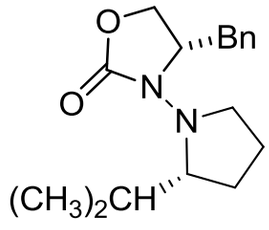
(*S*,*S*)315





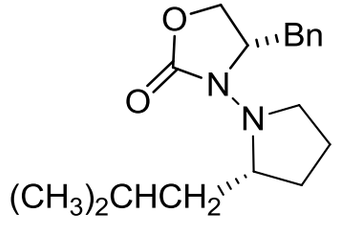
(*S*,*S*)359



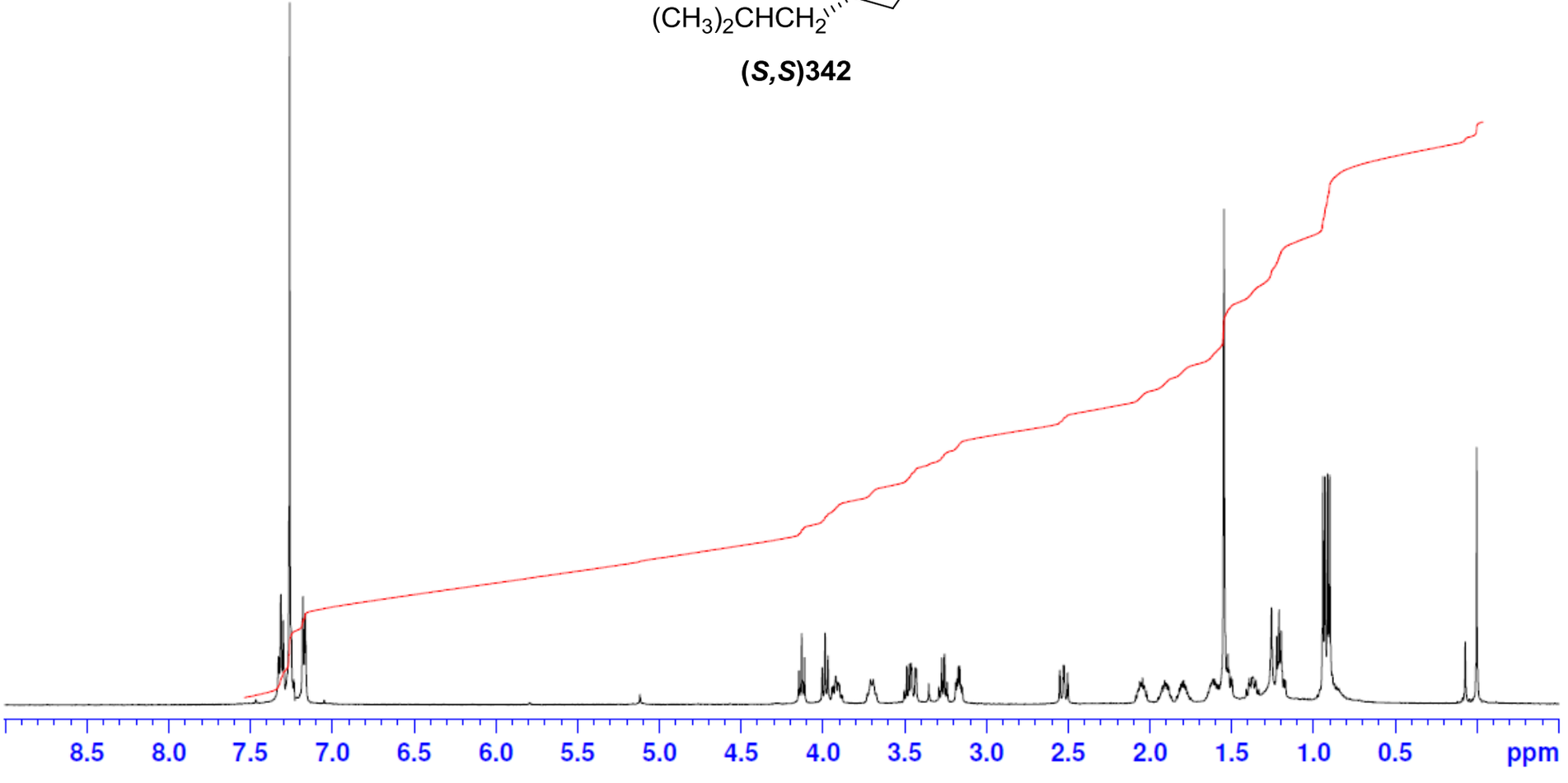

O
Bn
O
N
N
(CH3)2CH

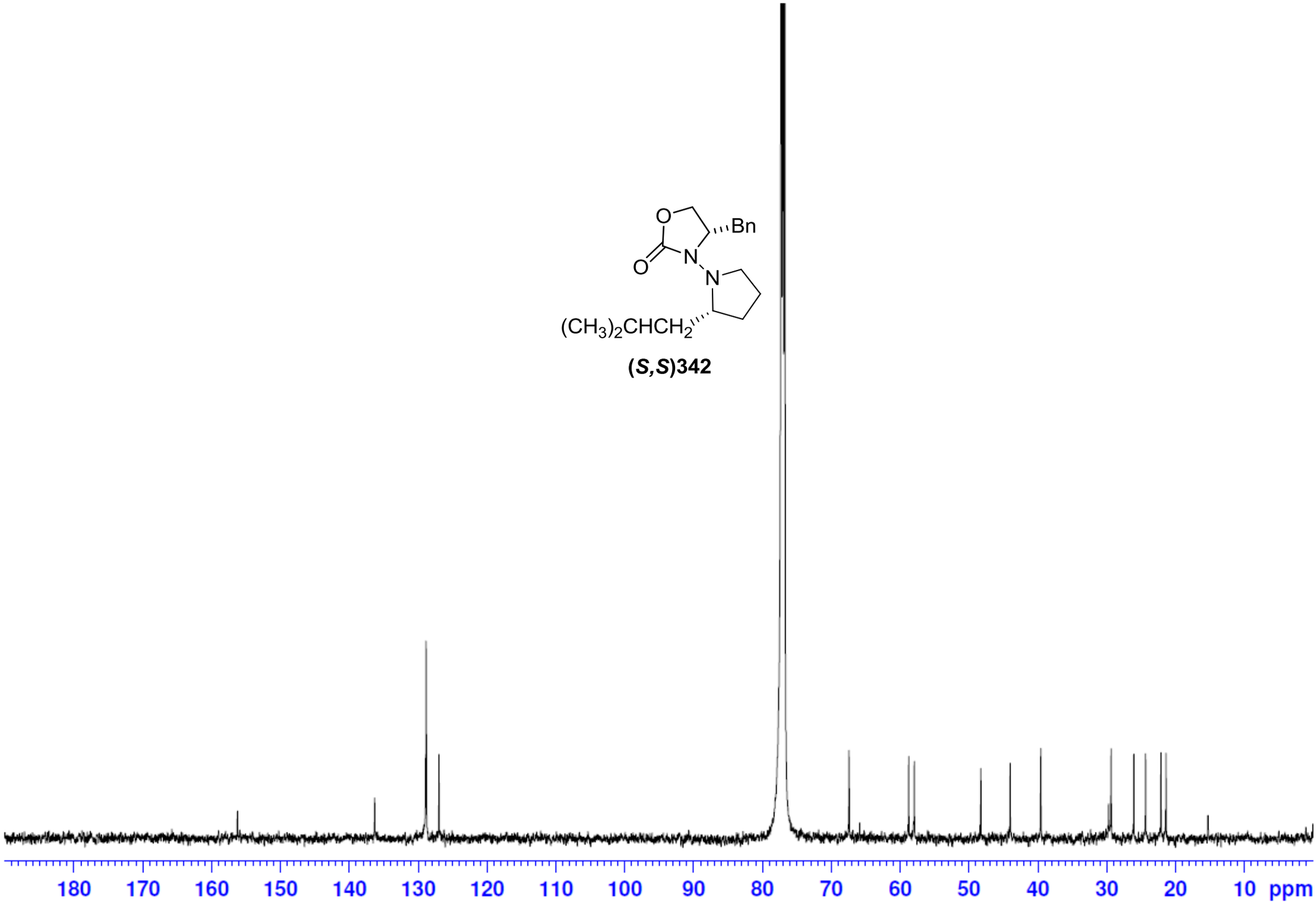
(*S*,*S*)359

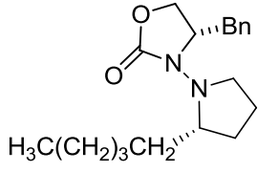
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


O
Bn
O
N
N
(CH3)2CHCH2

(*S*,*S*)342

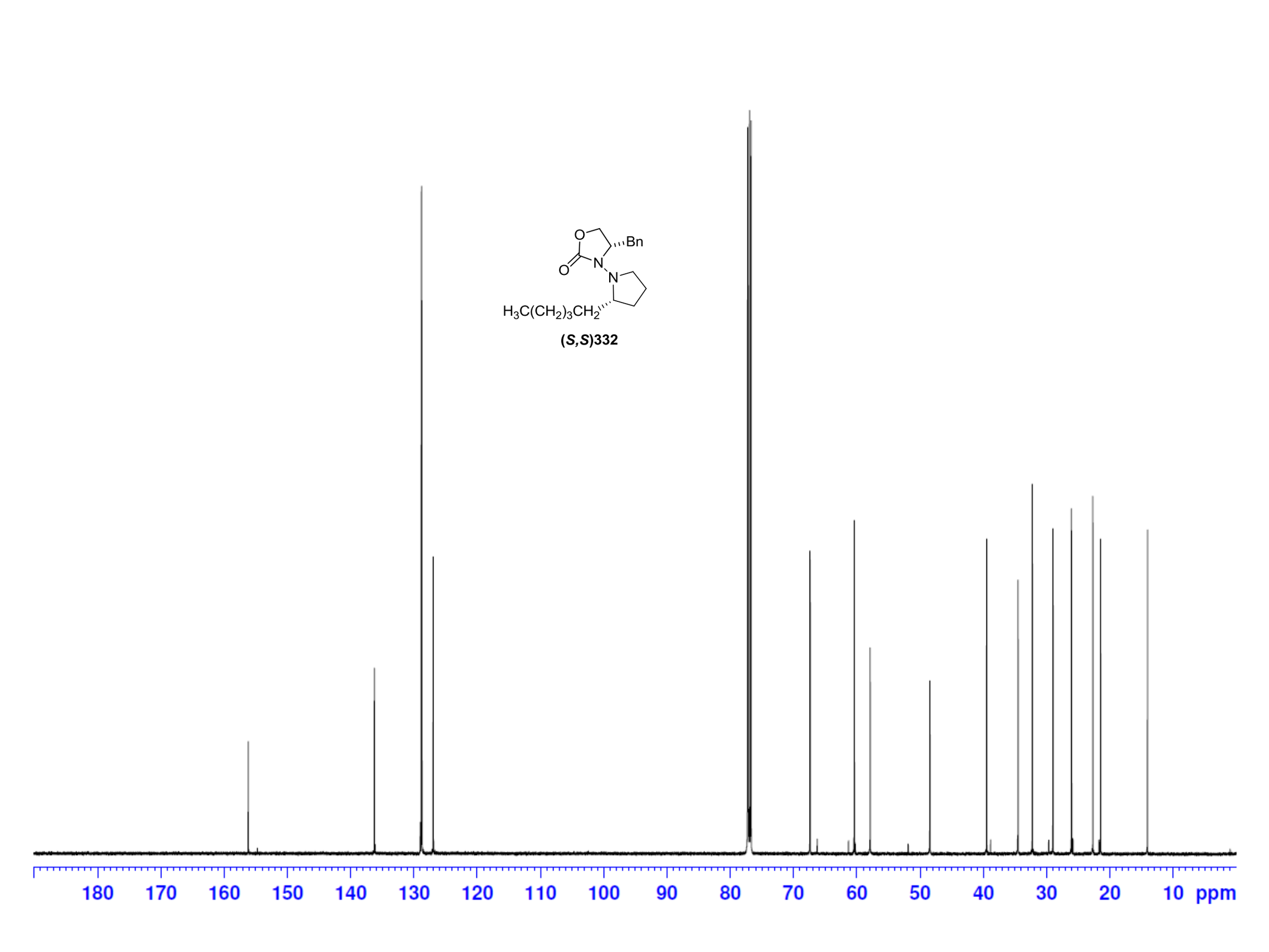

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

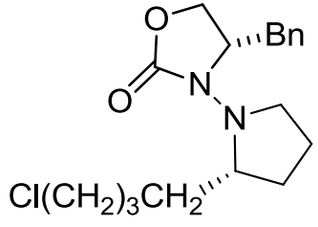

O
Bn
O
N
N
(CH3)2CHCH2
(S,S)342
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


O
Bn
O
N
N
H3C(CH2)3CH2

(*S*,*S*)332

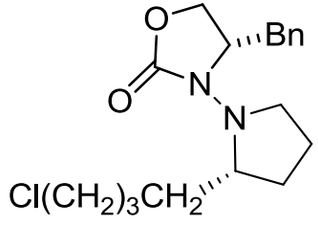
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


O
Bn
O
N
N
H3C(CH2)3CH2
(S,S)332
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


O
Bn
O
N
N
Cl(CH2)3CH2

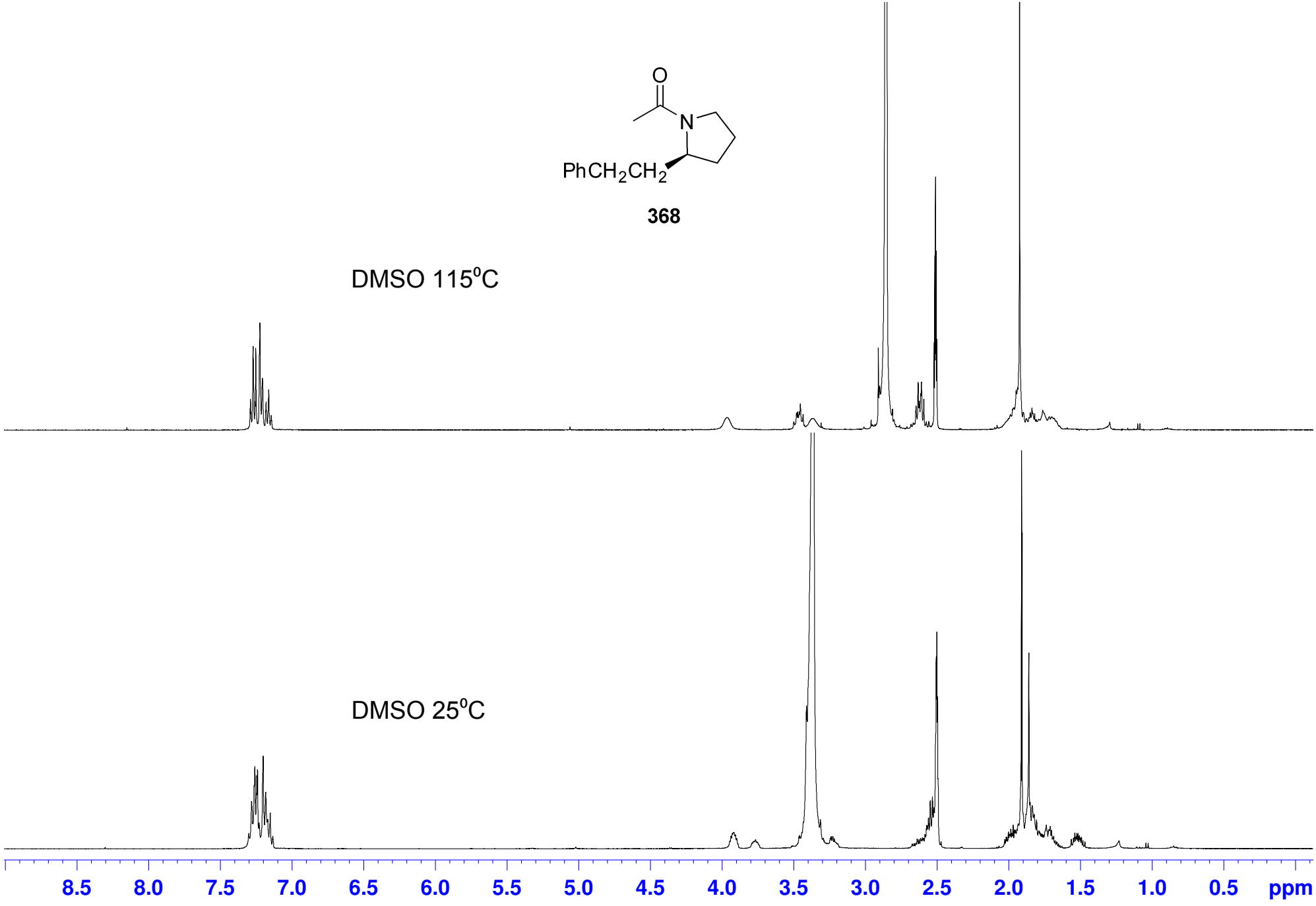
(*S*,*S*)358

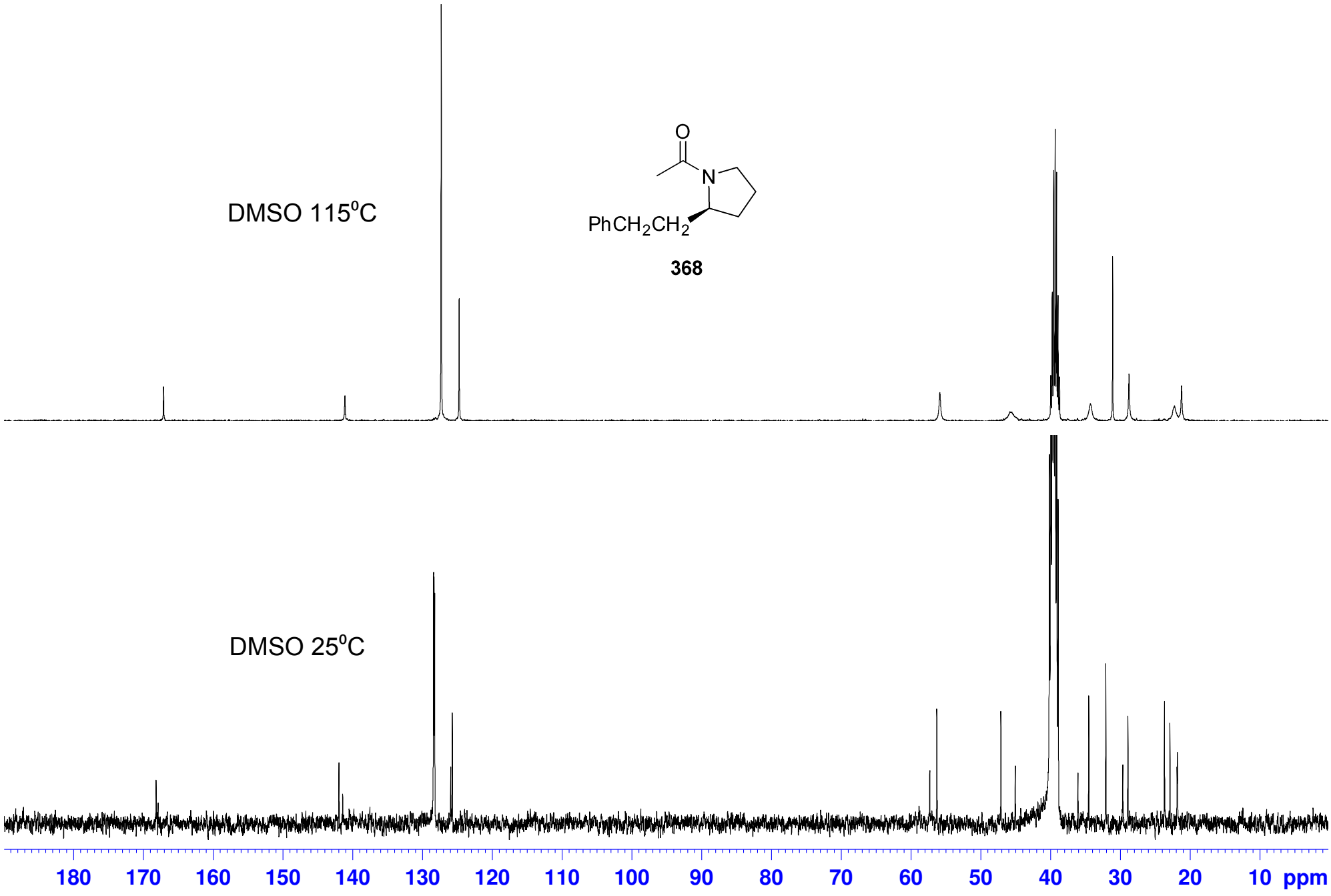
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

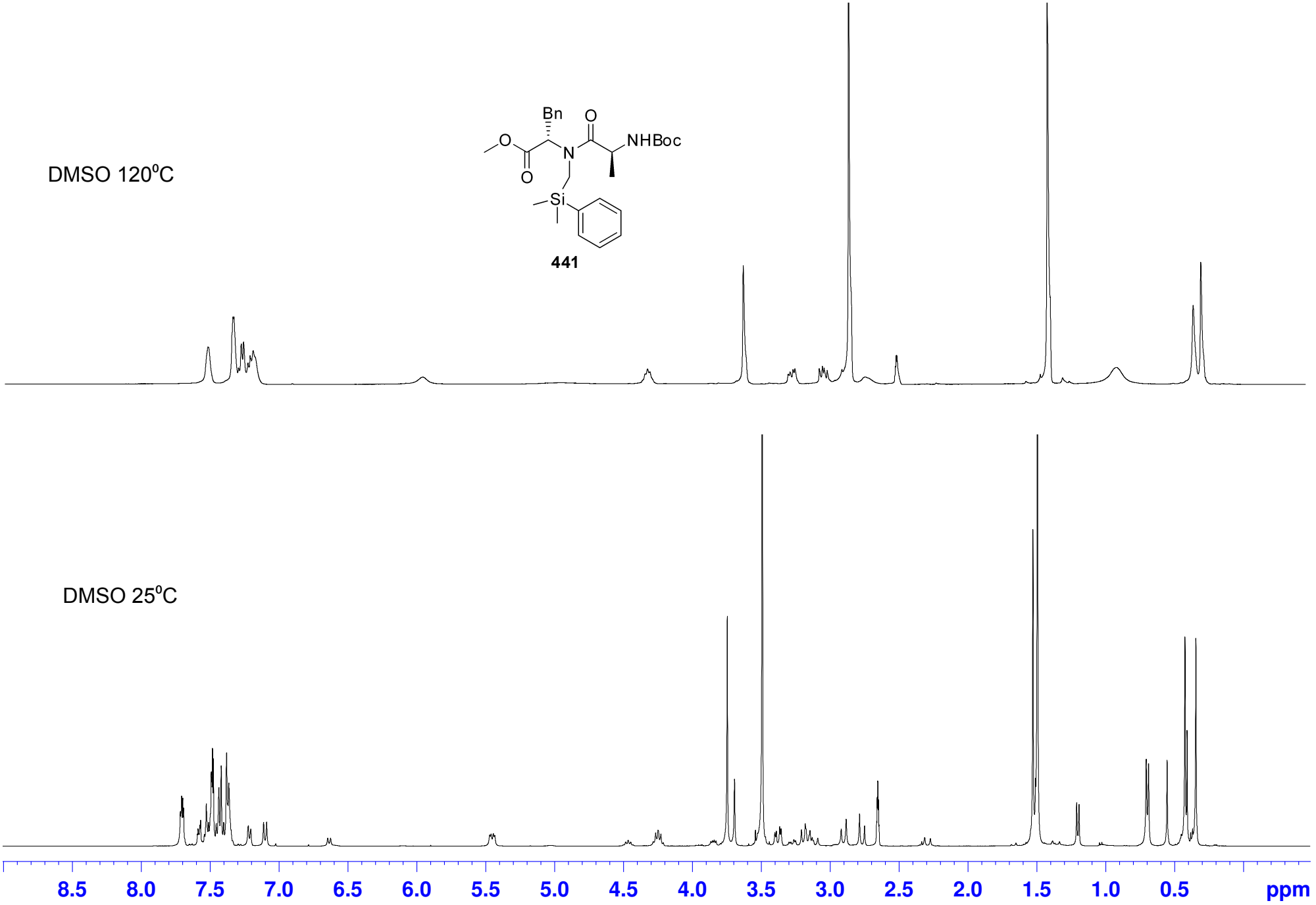

O
Bn
O
N
N
Cl(CH2)3CH2

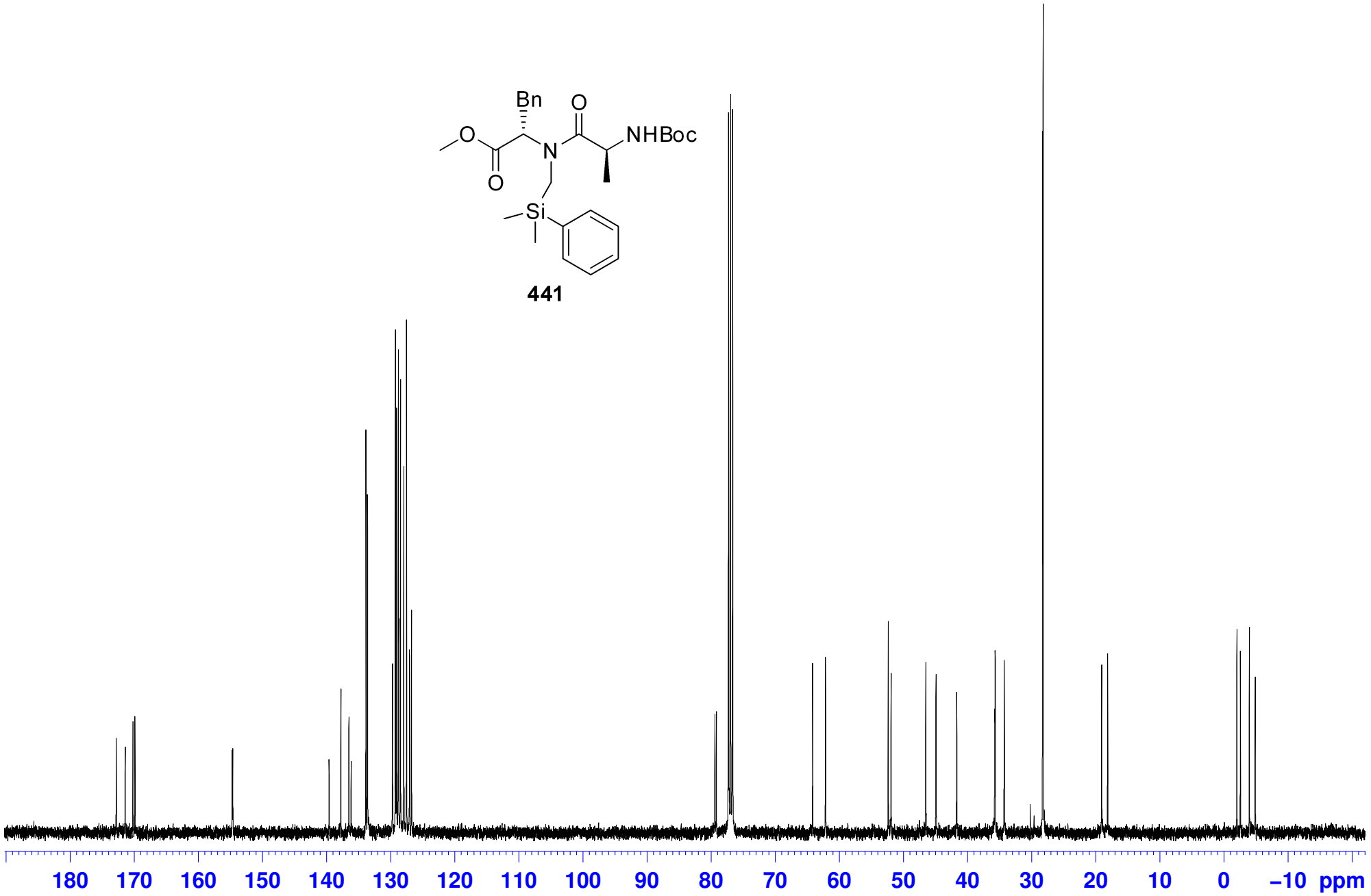
(*S*,*S*)358

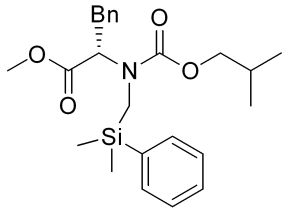
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


O
N
PhCH2CH2
368
DMSO 115°C
DMSO 25°C
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


DMSO 115°C
O
N
PhCH2CH2
368
DMSO 25°C
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


DMSO 120°C
Bn
O
O
N
NHBoc
O
Si
441
DMSO 25°C
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

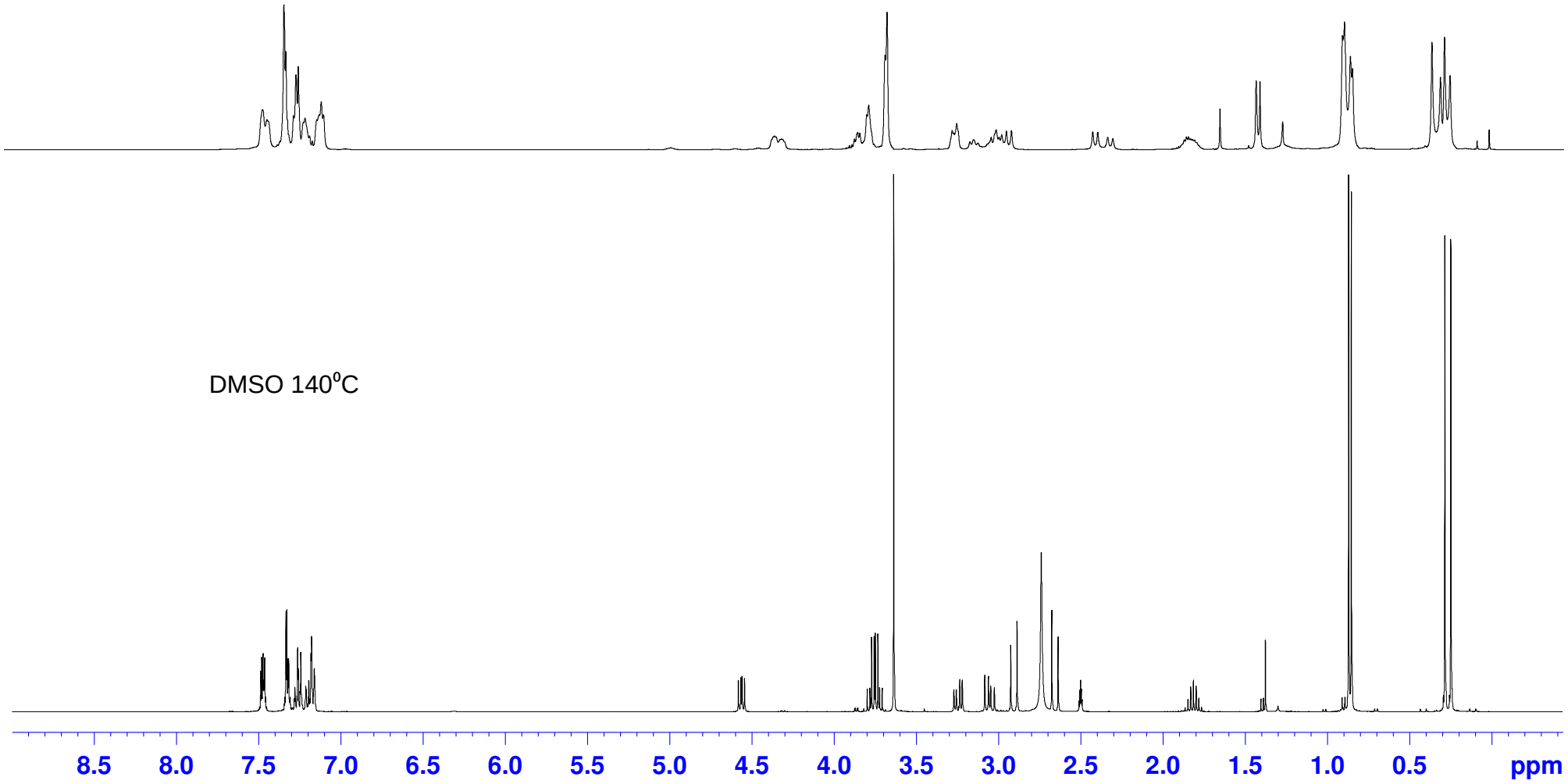

Bn
O
O
N
NHBoc
O
Si
441
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
–10
ppm

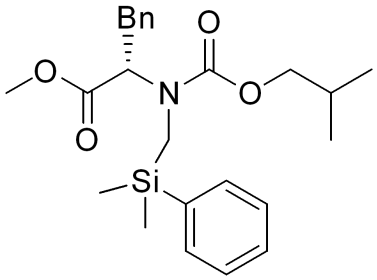


442

CDCl3 25^{o}C

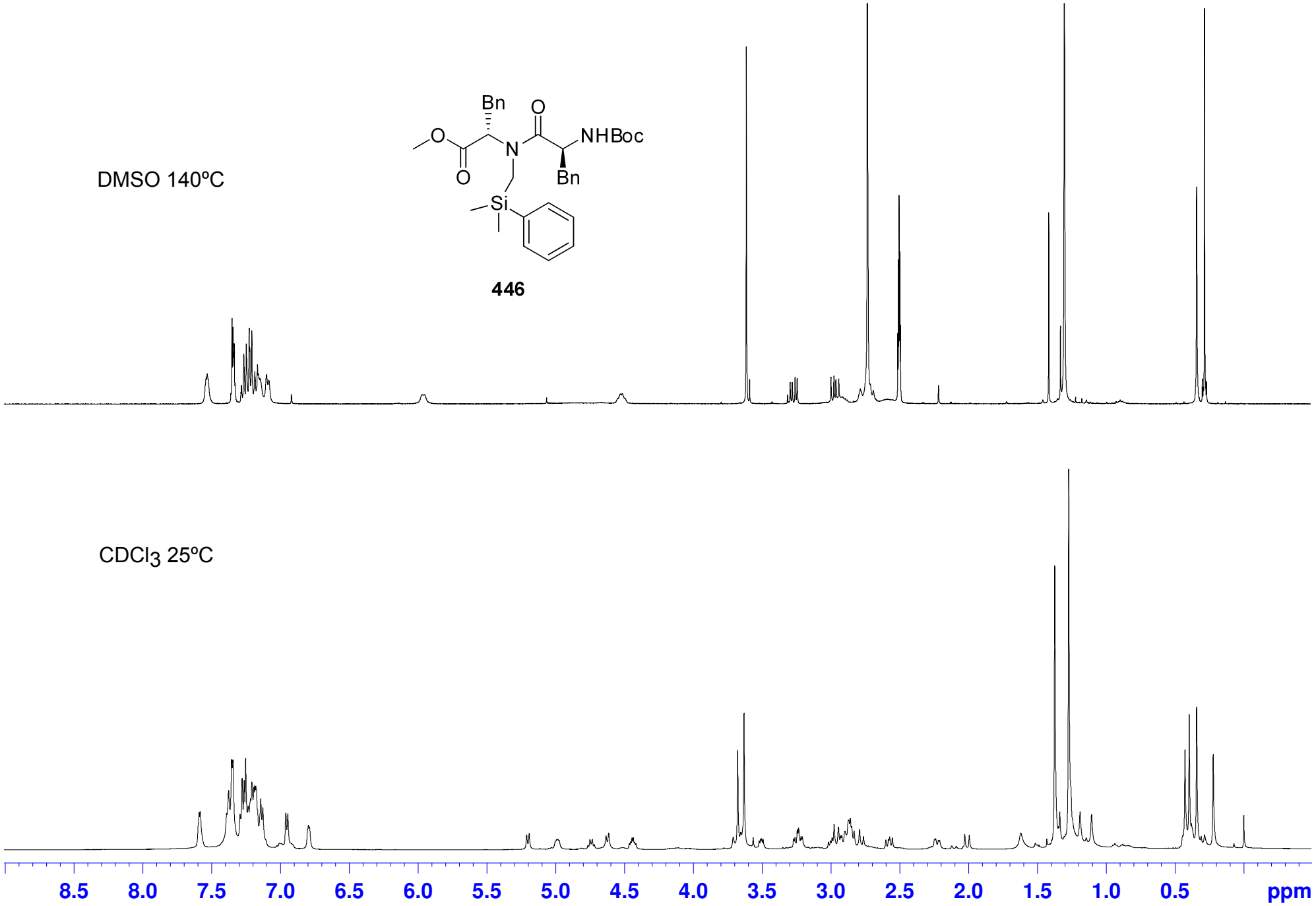
DMSO 140^{o}C

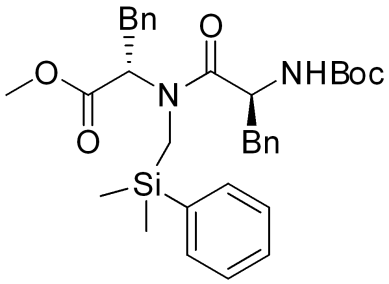



Bn
O
O
N
O
O
Si

442

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

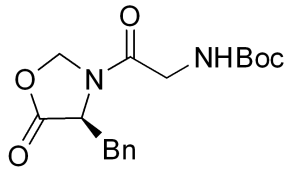

DMSO 140ºC
Bn
O
O
N
NHBoc
O
Bn
Si
446
CDCl3 25ºC
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


Bn
O
O
NHBoc
N
O
Bn
Si

446

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

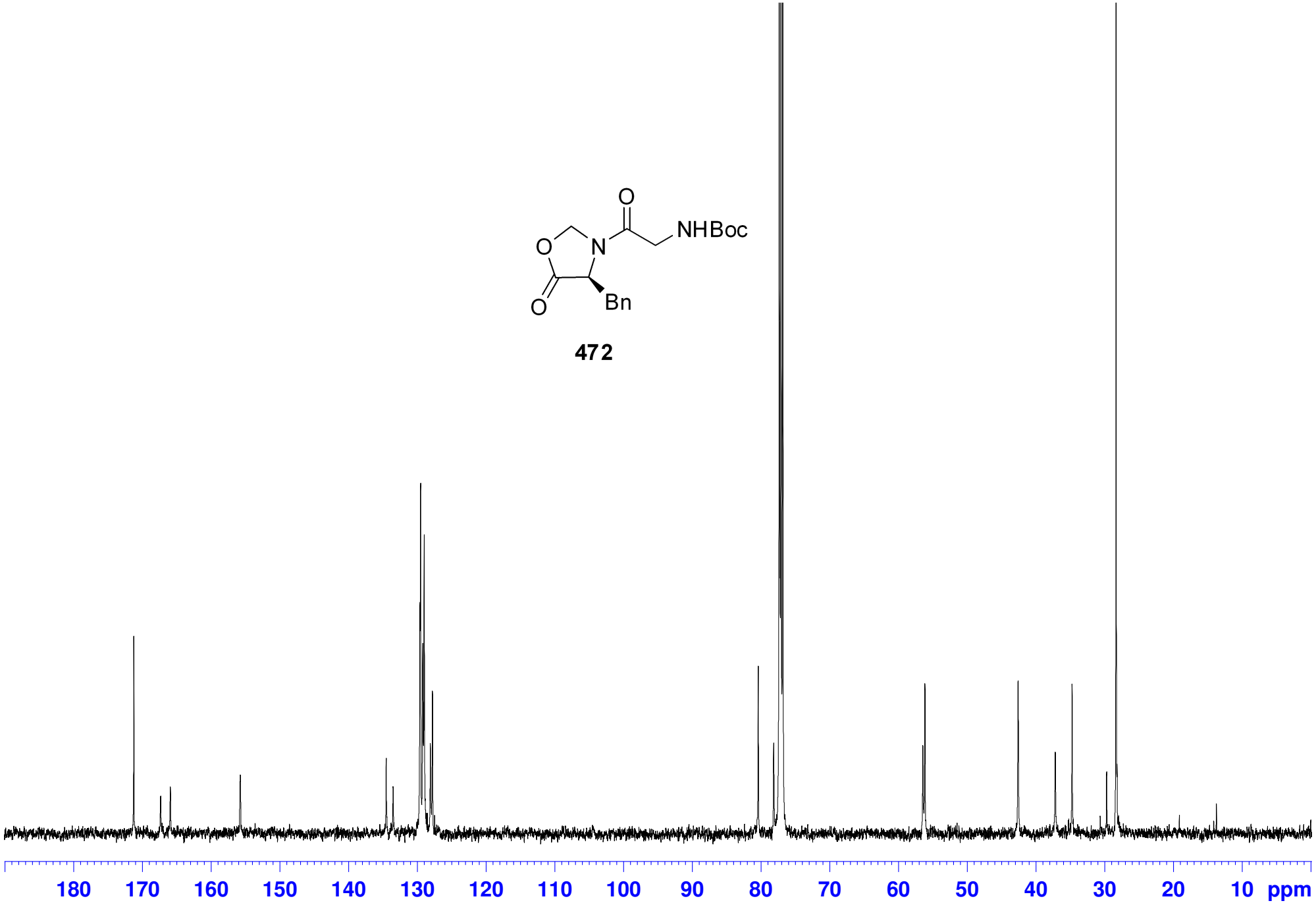
DMSO 140ºC

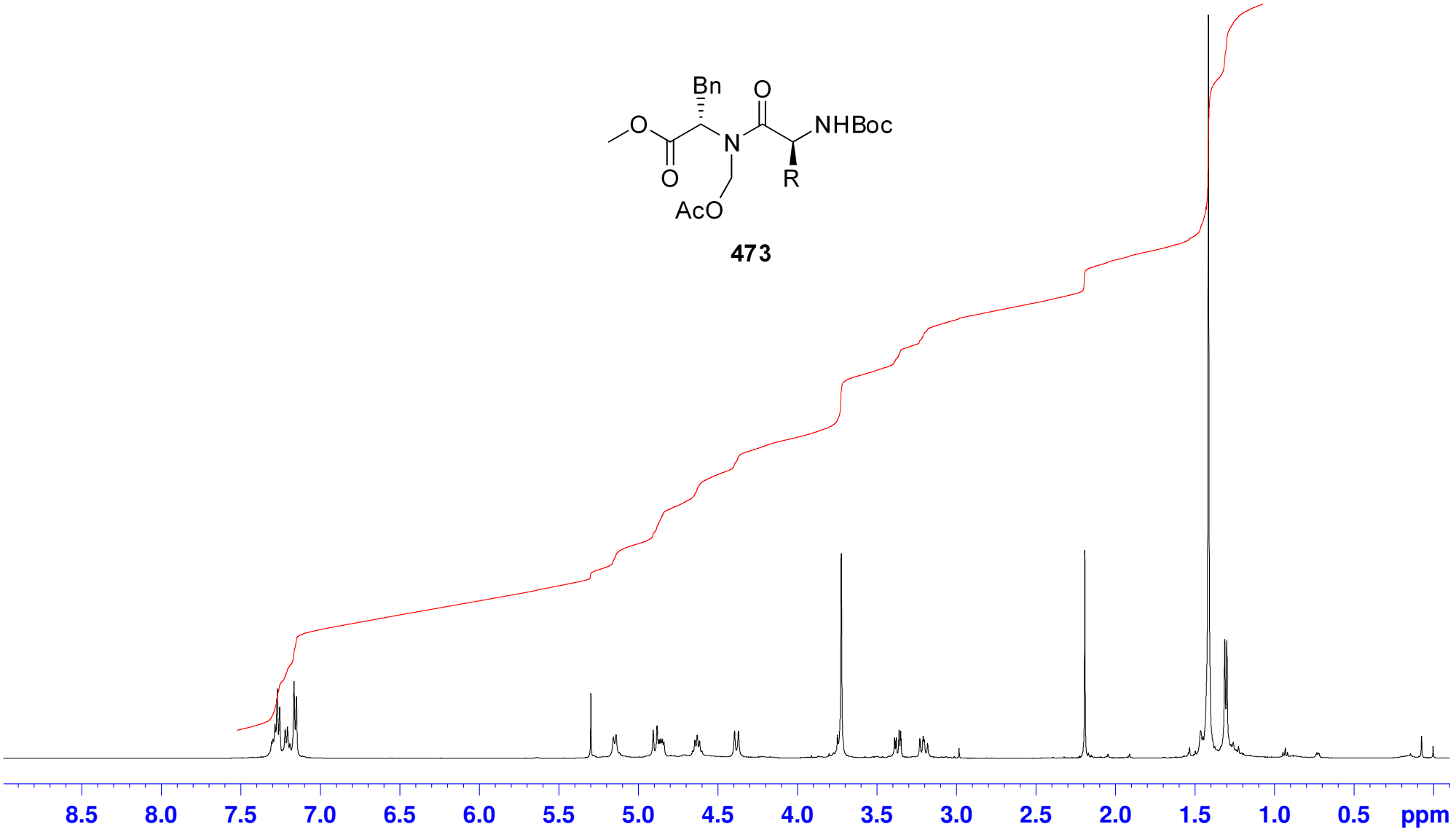


472

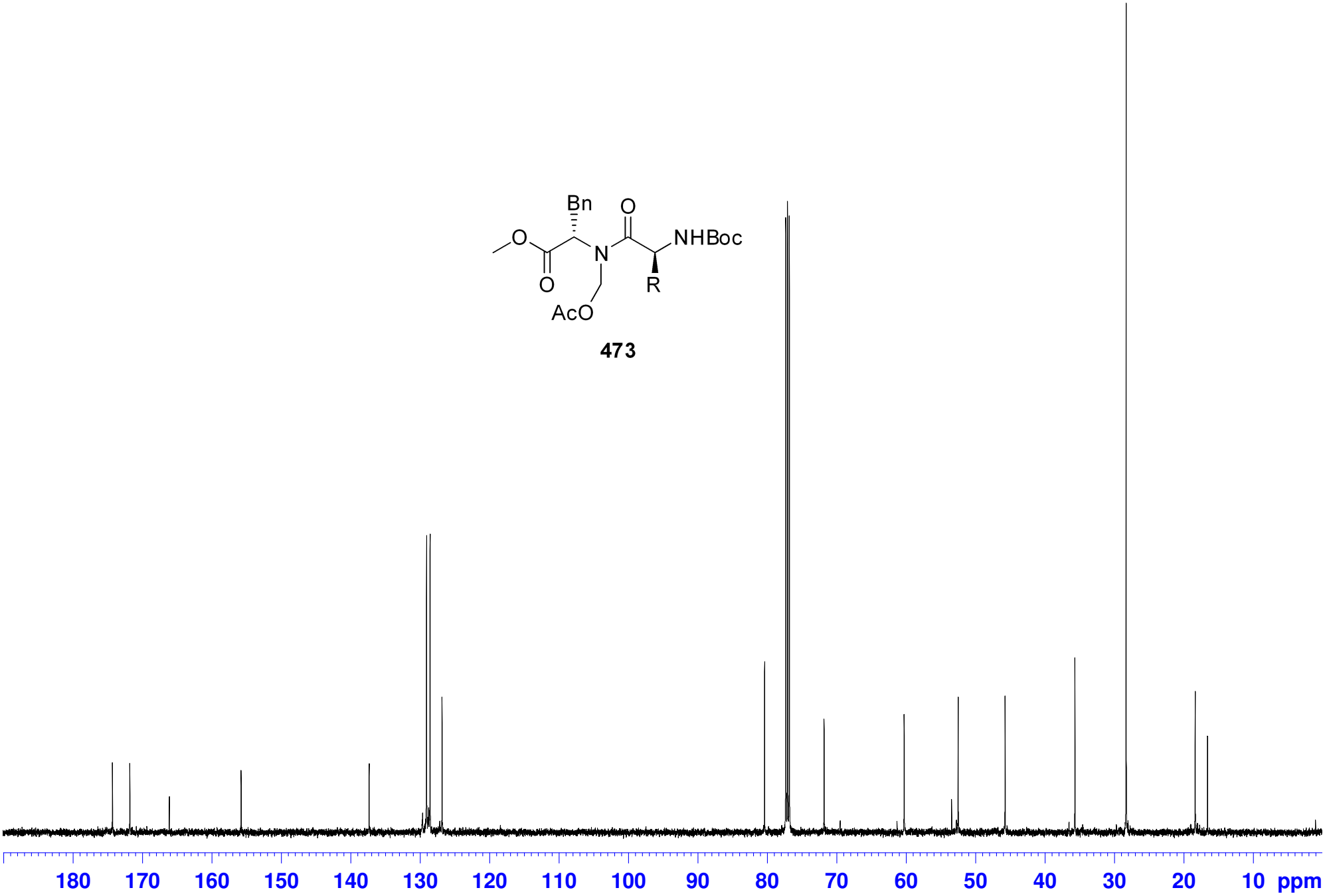
$CDCl_3$ 25ºC

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
NHBoc
O
N
O
Bn
472
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

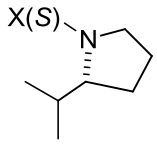

Bn
O
O
NHBoc
N
O
R
AcO
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

473

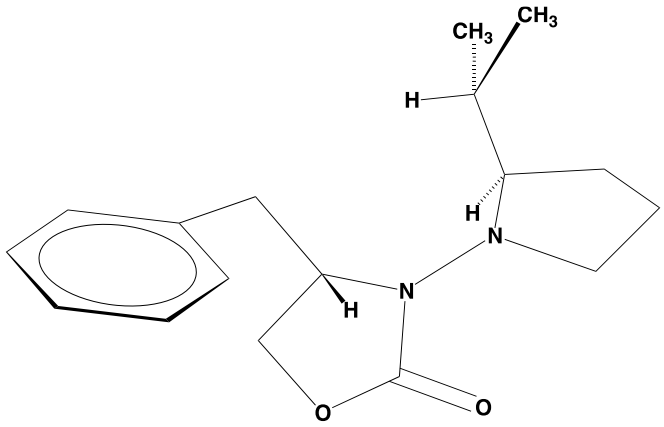

Bn
O
O
N
NHBoc
O
R
AcO
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

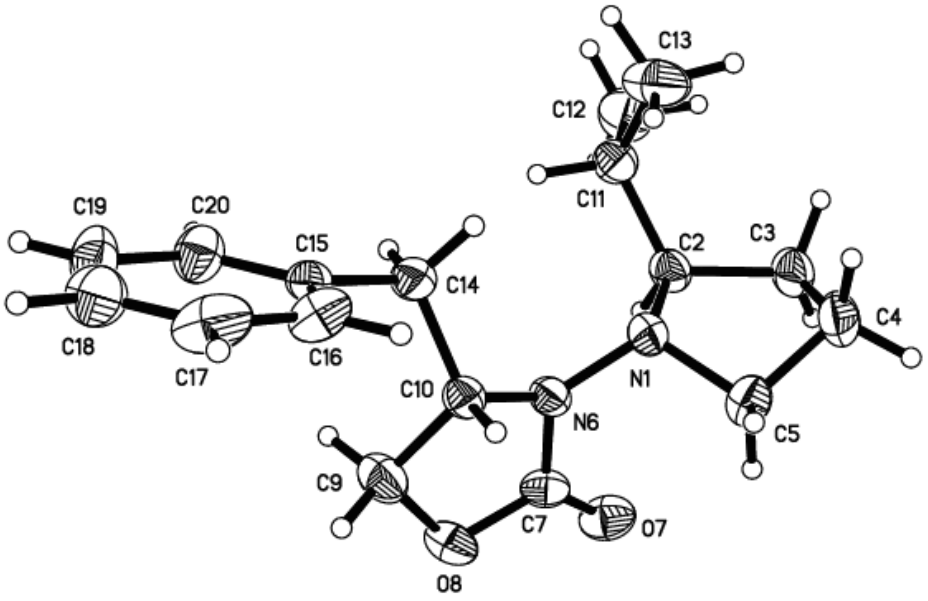
473

Crystallographic Data For Compound (*S*,*R*)-359



(*S, R*)-359





The N1-C2-C3-C4-C5 ring showed disorder in the final cycles of refinement. The final model included two conformations: N1-C2-C3-C4-C5 (occ=0.784(8)), a C5-envelope conformation and N1-C2-C3'-C4'-C5' (occ=0.216(8)), a C3'-envelope conformation. The two ring distances were restrained to be the same (esd=0.005) and the C3 and C3' and C5 and C5' anisotropic displacement parameters were constrained to be the same due to close proximity (<0.4A) and the C4' site was refined with an isotropic displacement parameter. The structure is shown at 50% ellipsoid contour probability level.