2,1-BENZOTHIAZINES

PREPARATION AND REACTIVITY

A Dissertation presented to the Faculty of the Graduate School

University of Missouri-Columbia

In Partial Fulfillment

Of the Requirements for the Degree

Doctor of Philosophy

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by

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MAY 2010

The undersigned, appointed by the dean of the Graduate School, have examined the dissertation entitled:

2,1-BENZOTHIAZINES

PREPARATION AND REACTIVITY

Presented by Nathan L. Calkins

A candidate for the degree of Doctor of Philosophy

And hereby certify that in their opinion it is worthy of acceptance.

Professor Michael Harmata

Professor Kent S. Gates

Professor Timothy E. Glass

Professor Paul R. Sharp

Professor Michael Lewis

For Nora, Lainey, Evonelle, and Maggie.

ACKNOWLEDGEMENTS

I would like to extend my gratitude to Professor Michael Harmata for his mentoring, his friendship, and his direction in my research and dissertation. Special thanks for his insight, encouragement, knowledge, and understanding of life's complications to make my graduate experience rewarding. I would like to thank those that have had me as a student and served on my committee: Professor Kent S. Gates, Professor Paul R. Sharp, Professor Timothy E. Glass, and Professor Michael Lewis for their advice, patience, and support.

I would like to extend my thanks to Dr. Charles Barnes and Dr. Wei Wycoff for their help in elucidating x-ray crystal structures and NMR support, respectively, during my time at MU as a graduate student. Special thanks to Bill Vellema for technical support and Jerry Brightwell for all the administrative help he has given since my first days as a Summer Fellow in the Steven Summer Program. Also, special thanks to my fellow Harmata group members, past and present, and the MU Chemistry department.

I would like to extend a special thanks to the many teachers, instructors, and professors that have molded my foundation in chemistry. Two in particular I am very thankful for having been a student of are: Professor Anne E. Moody, Truman State University, Organic Chemistry 1 and 2; and Ty Abel, Owensville High School, Chemistry 1 and 2; for their enthusiasm toward organic chemistry and guidance to pursue chemistry.

Lastly and most importantly, I thank God for the gifts, talents, and abilities I enjoy on a daily basis. Special thanks to my wife Nora and my children, Lainey, Evonelle, and Maggie for their love, support, and past, present, and future memories. Thanks to my parents and family for their love and financial support. Special thanks to my best friend Peter Kelsey. And lastly I thank all those that believed in me and those that didn't, for those are people who made me try even harder.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF SCHEMES

LIST OF TABLES

2,1-BENZOTHIAZINES

PREPARATION AND REACTIVITY

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Dr. Michael Harmata, Dissertation Supervisor

ABSTRACT

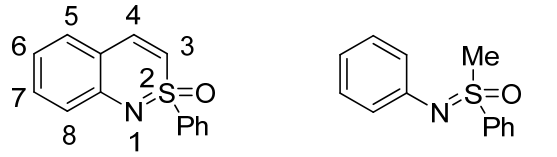
The synthesis of chiral ligands to tune the reactivity and stereoselectivity of many catalytic asymmetric reactions has been given considerable attention in synthetic organic chemistry over the past decade. This report will show the results of efforts toward the syntheses of several families of enantiomerically pure 2,1-benzothiazine ligands. These ligands are unique in that they contain a chiral sulfoximine.

Several 2,1-benzothiazine ligands were prepared in single one-pot syntheses and others in as many as five or more steps for larger heterocycles. An optimized synthetic route will be shown for a very well known Buchwald Hartwig *N*-arylation of sulfoximines and haloarenes. The synthetic procedure for the *N*-arylation of sulfoximines synthetic procedure has virtually been unchanged since its introduction in 1998. The new synthesis herein has dramatically improved reaction time and scope for the *N*-arylation of aryl bromides and aryl chlorides. Until now, aryl chloride based *N*-arylations gave extremely poor conversions when attempted thermally. Lastly, unsubstituted and 4-phenyl substituted 2,1-benzothiazine lithiation reactivity will be discussed for the sulfoximine stabilized lithium vinyl carbanions. Mono- and di-substitutions are now synthetically possible. New synthetic strategies for accessing the *ortho*-*S*-phenyl ring as a viable carbanion will also be shown.

CHAPTER 1

Introduction and Syntheses of Enantiopure Sulfoximine Ligands

When thinking of sulfoximines as ligands, two categories of compounds have been utilized.[1] "Fixed" sulfoximine **1**, an unsubstituted 2,1-benzothiazine, was the focus of the research performed. "Free" sulfoximine **2**, an *N*-substituted sulfoximine, is also described herein and its synthesis re-optimized in Chapter 3. Generic structures for both types of sulfoximine-containing compounds are displayed in Figure 1. The numbering system of 2,1-benzothiazine **1** carbon skeleton is also illustrated in Figure 1.



1: "Fixed" sulfoximine **2**: "Free" sulfoximine

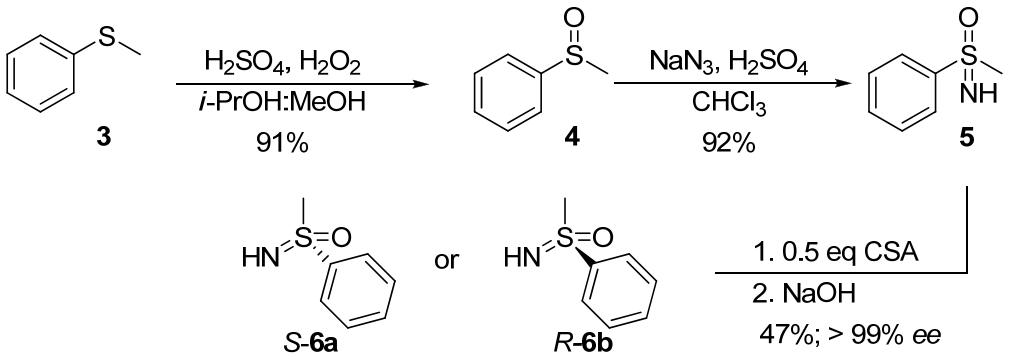
Figure 1. "Fixed" and "Free" Sulfoximines

1.1 Discovery and Preparation of Chiral *S*-Methyl-*S*-Phenylsulfoximine

1.1.1 Introduction and Discovery of Sulfoximine

Discovered in 1949,[2] sulfoximines are the key component and source of chirality for the ligands prepared and studied herein. The synthesis of sulfoximines is well known and straightforward, and some are commercially available (Scheme 1). The synthesis of the "parent" sulfoximine **6** begins with commercially available methyl phenyl sulfide **3**, which is first oxidized by hydrogen peroxide under acidic conditions, resulting in racemic methyl phenyl sulfoxide **4**. Racemic sulfoxide **5** undergoes subsequent imination with sodium azide, also under acidic conditions, to afford racemic methyl phenyl sulfoximine **6**. Enantiomerically pure sulfoximine **6** can be obtained by resolution with the appropriate chiral camphorsulfonic acid (CSA) in which (+)-CSA gives *S*-sulfoximine **6a**

and (-)-CSA gives *R*-sulfoximine **6b** after sodium hydroxide mediated hydrolysis of the diastereomerically pure crystals.[3] All of the previously described reactions are possible on a multigram scale, making sulfoximine **6** readily accessible.

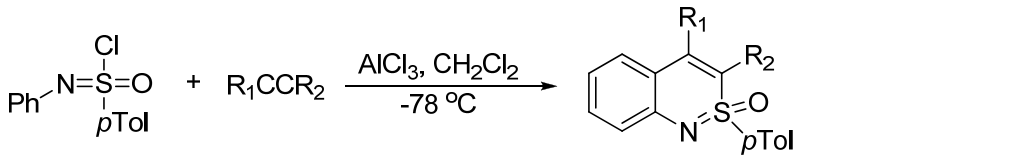


Scheme 1. Synthesis of Chiral *S*-Methyl-*S*-Phenylsulfoximine

1.2 Preparation of "Fixed" Sulfoximines or 2,1-Benzothiazines

1.2.1 Synthesis of "Fixed" Sulfoximines via Cycloadditions

The utilization of sulfoximine-containing compounds in the Harmata group began first with *N*-phenyl-(4-methylphenyl)-sulfonimidoyl chloride **7** and various symmetrical and unsymmetrical alkynes generically represented by **8a-c** to give "fixed" sulfoximines **9a-c**, called simply benzothiazines from this point on. A variety of Lewis acids promoted the cyclization in a range of yields. With $AlCl_3$, the yields ranged from 90% with electron rich phenyl acetylene **8a** to 14% with acetylene (**8c**) itself (Scheme 2).[4]



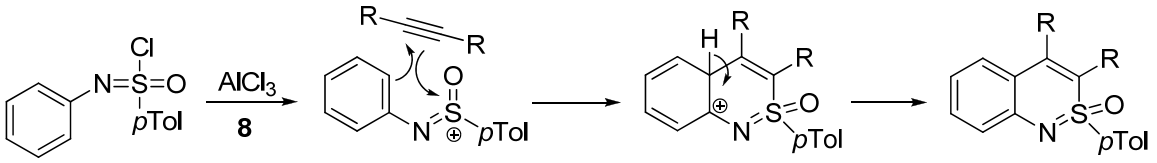
7

8a R_1=H; R_2=Ph
8b R_1=*n*-propyl; R_2=*n*-propyl
8c R_1=H; R_2=H

9a R_1=H; R_2=Ph; 90%
9b R_1=*n*-propyl; R_2=*n*-propyl; 30%
9c R_1=H; R_2=H; 14%

Scheme 2. Early Synthesis of Benzothiazines

The proposed mechanism is straightforward. First the sulfonimidoyl chloride **7** forms reactive intermediate **10** in the presence of the Lewis acid, $AlCl_3$. Alkyne **8** cyclizes with the electron-deficient intermediate **10** to yield benzothiazine intermediate **11**. Loss of proton to regenerate aromaticity gives the final product, benzothiazine **9** (Scheme 3). The problem with this synthesis is the inability to obtain enantiomerically pure products.[4]

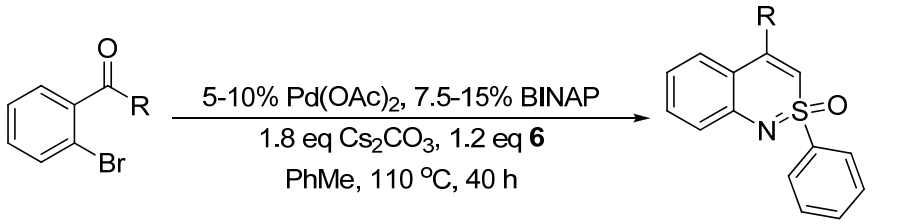


7 **10** **11** **9**

Scheme 3. Mechanism of Lewis Acid-Catalyzed Benzothiazine Formation

1.2.2. **Synthesis of Benzothiazines via *N*-Arylation of Aryl Bromides**

Another way to make benzothiazines is in a one pot fashion discovered previously by Harmata and coworkers. This one-pot synthesis utilizes a Buchwald-Hartwig type *N*-arylation reaction between sulfoximines and an aryl halide followed by intramolecular condensation with 2-bromobenzaldehyde **12** or 2-bromoacetophenone **13** to give benzothiazines **1** and **14**, respectively (Scheme 4). The mechanism of the Buchwald Hartwig *N*-arylation reaction is shown in Figure 2.[5]



12 R = H
13 R = Me

1 R = H, 78%
14 R = Me, < 10%

Scheme 4. *N*-Arylation of 2-Bromobenzaldehyde **12** and 2-Bromoacetophenone **13**

The mechanism begins by Pd(II) acetate being reduced to Pd(0)-BINAP species **16** via **15**. This reduction of Pd(II) to Pd(0) likely occurs from the oxidation of one of two phosphines of the bidentate BINAP ligand (Figure 2). The structure of *R*-BINAP is shown in Figure 3. Complex **16**, absolute structure unknown, can undergo oxidative addition to the C-Br bond of bromobenzene **17** to give the palladium species **18**. Ligand substitution of the bromide anion by sulfoximine **6** affords one mole of HBr that is consumed by cesium carbonate in the reaction mixture to give palladium species **19**. This compound undergoes reductive elimination to regenerate Pd(0)-BINAP complex **16** and *N*-phenyl substituted sulfoximine **2**.

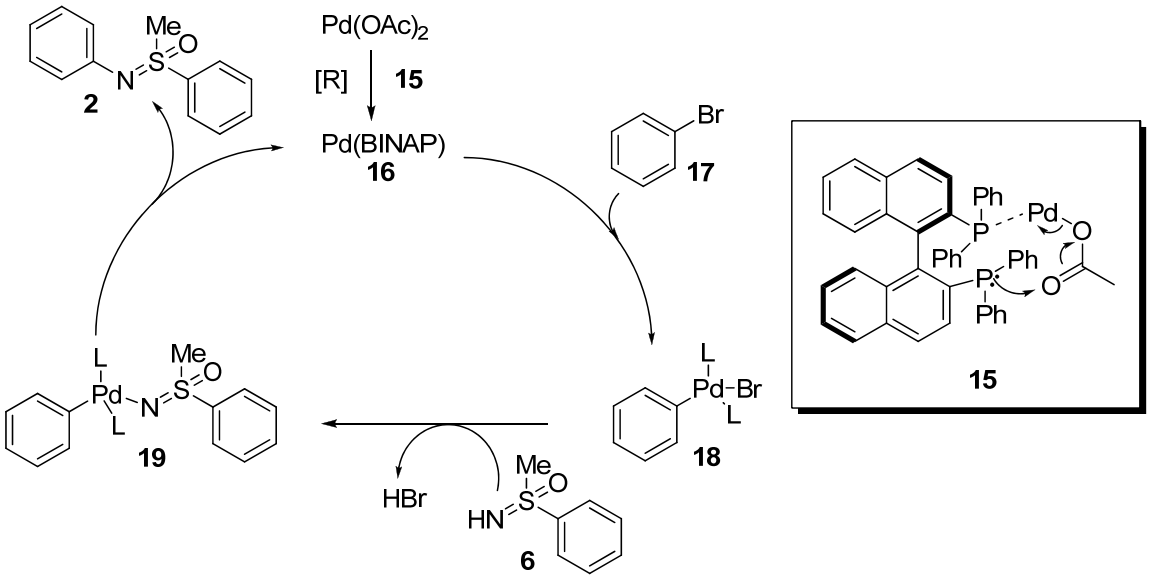


Figure 2. Mechanism of the Buchwald Hartwig *N*-Arylation

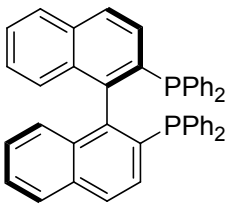
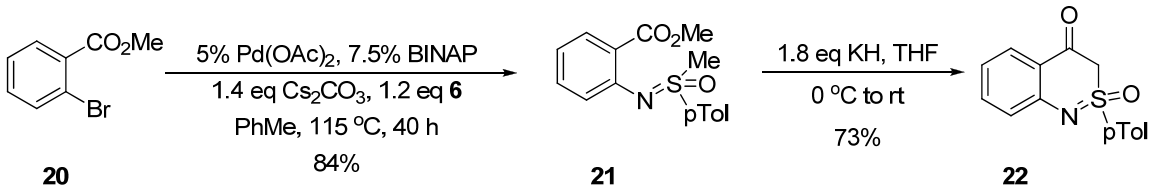


Figure 3. Structure of (*R*)-2,2'-Bis(diphenylphosphino)-1,1'-Binaphthyl, or *R*-BINAP

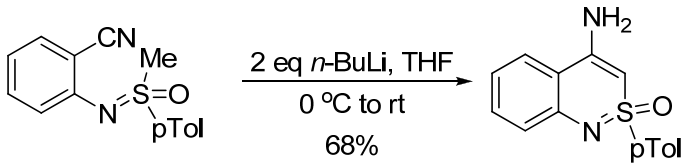
It should be noted that under these mildly basic conditions, coupling of enolizable ketone **13** gave a very poor yield of the desired benzothiazine. Refluxing toluene and weak base likely generates some enolate, albeit in small amounts. This enolate must be an incompatible substrate for the *N*-arylation and subsequent condensation provided the low yield < 10%. Efforts to address this significant flaw in the scope of this reaction have yet to be investigated. Some substrates *N*-arylated successfully but did not condense in the presence of the weak base, Cs_2CO_3. With methyl 2-bromobenzoate **20**, only *N*-arylation was observed under conditions used previously to give **21**. So it is not surprising that the electrophilicity of the carbonyl determines the rate at which condensation occurs. A second addition of a much stronger base, KH, was needed for the condensation of **21** to form **22**, which tautomerized rapidly to the corresponding enol (Scheme 5).[5]



20 **21** **22**

Scheme 5. Synthesis of Benzothiazine **22**

Another similar example has been shown by Bolm with 2-bromobenzonitrile where again only *N*-arylation occurs to form **23**.[6] Harmata and coworkers demonstrated that with *n*-BuLi the condensation occurs in good yield to form 4-amino-2,1-benzothiazine **24** (Scheme 6). So it has been shown that very electrophilic carbonyl compounds will rapidly condense to form benzothiazines whereas less electrophilic carbonyl compounds such as nitriles and esters take much stronger bases but still condense in good yields and under general conditions.[5]

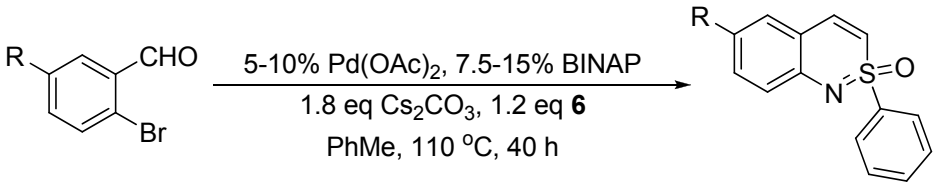


23 **24**

Scheme 6. Synthesis of 4-Amino-2,1-Benzothiazine

Utilizing the formation of 2,1-benzothiazines via *N*-arylation is the key reaction that will be discussed at length in this report. This method is the most efficient way to prepare functionalized benzothiazines. One important note is that this reaction is applicable on a multigram scale, making this class of compounds viable synthetic targets as typical yields approach quantitative conversion for aryl bromides, but is lower for aryl chlorides. Both electron-donating and electron-withdrawing were tolerated in good yields (Table 1).[5]

Table 1. Scope of *N*-Arylation of Aryl Bromides



12 **1a-d**

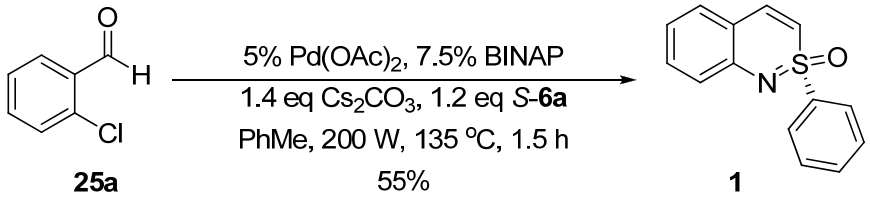
Entry	R	Yield (%)	Compound
1	H	78	**1a**
2	OMe	81	**1b**
3	OBn	75	**1c**
4	NO_2	73	**1d**

Strong electron donating groups *para* (Table 1, entries 2,3) to the site of oxidative addition allowed for similar yields to that of bromobenzene **17** (Table 1, entry 1).

Electron withdrawing groups show the same pattern, but more needs to be done to establish definitive trends. Overall, the change in yield was not significantly affected by substituent changes in the *para* position with respect to the carbon that undergoes oxidative addition.[5]

1.2.3. **Synthesis of Benzothiazines via *N*-Arylation of Aryl Chlorides**

Less expensive and typically less reactive aryl chlorides required longer reaction times and gave lower yields than with the standard *N*-arylation conditions presented previously. More recently, microwave irradiation has been shown to drastically increase yields of *N*-arylation of aryl chlorides and dramatically reduce reaction times from 44 hours to 1.5 hours for many substrates. Harmata and coworkers were able to greatly improve the yield of very sluggish aryl chlorides to moderate and excellent yields in this way. In previous attempts, thermal *N*-arylation of aryl chlorides gave trace products with extended reaction times. 2-Chlorobenzaldehyde **25a** was reacted in a microwave reactor and irradiated at 200W for 1.5 h to yield 55% of **1a** (Scheme 7).[7]

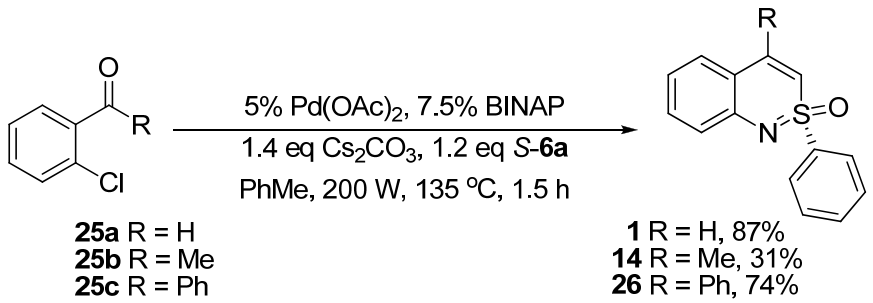


25a **1**

Scheme 7. Synthesis of Benzothiazines by Microwave Irradition

Again a variety of functional groups were tolerated under microwave irradiation. Overall, Harmata and coworkers observed excellent yields with aryl chlorides bearing electron withdrawing groups. This observation expanded the types of benzothiazines that can be prepared and expanded the library of benzothiazines and *N*-arylated sulfoximines to date significantly. A comparative selection of aryl chlorides subjected to irradiation

and yielding benzothiazines is summarized in Scheme 8. It is worth mentioning that many examples gave *N*-arylated products and others gave benzothiazines depending on the substrate and the presence or absence of an electron withdrawing group *ortho* to the site of *N*-arylation.[7]



Scheme 8. Synthesis of Benzothiazines from a Variety of Aryl Chlorides

2-Chlorobenzophenone **25c** shows that non-enolizable ketones undergo *N*-arylation smoothly and condense much like 2-chlorobenzaldehyde **25a**. Benzothiazine **14** was isolated in a meager 31%, much improved from the previous < 10% from the corresponding bromide.[7] The improvement in conversion is likely due to the reduced reaction time possible with microwave irradiation, minimizing side reactions that occur via enolization.

This work demonstrates that both aryl chlorides and aryl bromides successfully *N*-arylate under palladium catalysis. Typically cheaper than aryl bromides, aryl chlorides readily undergo *N*-arylation with the assistance of microwave irradiation. One important note is that this reaction and previous reactions reported are applicable on a multi-gram scale, making this class of compounds viable synthetic targets.

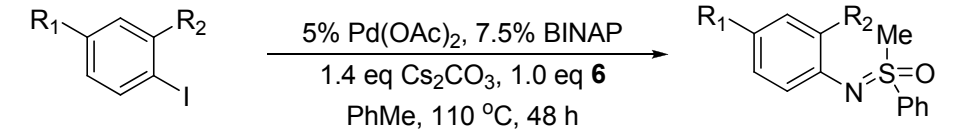
1.2.4 **Synthesis of *N*-arylated Sulfoximines from Aryl Iodides**

Aryl iodides are also suitable candidates for sulfoximine coupling. However, aryl iodides are not good candidates for palladium catalysis and aryl bromides are the

substrate of choice for palladium-catalyzed processes involving sulfoximine coupling partners. Bolm and coworkers have established two additional metal-catalyzed processes in which aryl iodide coupling to sulfoximines proceeds in good to excellent yields.

Palladium-mediated Buchwald-Hartwig coupling of aryl iodides and sulfoximines was reported by Bolm and coworkers in 2000. Typical reactions conditions seen previously were not successful in the *N*-arylation of aryl iodides with sulfoximine when identical aryl bromide substrates afforded respectable to excellent yields. Additional additives on a substrate specific basis were employed for a few aryl iodides for which poor to moderate yields were observed. The use of a specific additive was not general and in some examples no coupling was observed. A summary of selected examples is shown in Table 2.[8]

Table 2. *N*-Arylation of Aryl Iodides with Additives



27a R_1 = H, R_2 = CO_2Me
27b R_1 = H, R_2 = OMe
27c R_1 = NO_2, R_2 = H

28a R_1 = H, R_2 = CO_2Me
28b R_1 = H, R_2 = OMe
28c R_1 = NO_2, R_2 = H

Entry	Substrate	Product	Additive	Yield (%)
1	**27a**	**28a**	LiBr	56
2	**27a**	**28a**	LiCl	22
3	**27a**	**28a**	AgOTf	7
4	**27b**	**28b**	LiBr	< 2
5	**27b**	**28b**	LiCl	< 2
6	**27b**	**28b**	AgOTf	< 2

7	**27c**	**28c**	LiBr	31[a]
8	**27c**	**28c**	LiCl	17[a]
9	**27c**	**28c**	AgOTf	79[a]

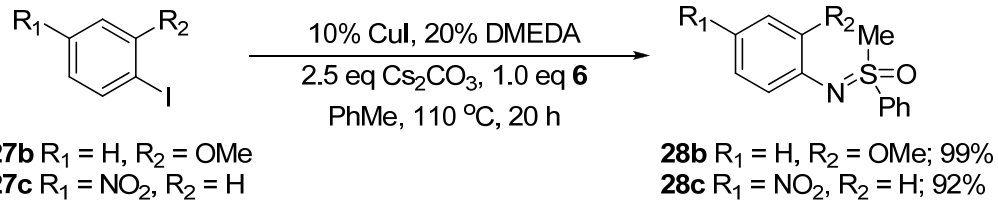
[a] *p*Tol-Me sulfoximine was used instead of Ph-Me sulfoximine

The inactivity of aryl iodides was deemed by Bolm and coworkers to be a change in the rate determining step of the catalytic cycle. It is their belief that with aryl bromides and likely chlorides, the oxidative addition of the metal to the C-halide bond is the slow step. With a much longer, weaker C—I bond, oxidative addition was deemed faster than the ligand exchange of the weakly nucleophilic sulfoximine to the palladium-BINAP complex **16**. Consequently, the rate of reductive elimination in the catalytic cycle is either halted or at least slowed extensively.[8]

Electron rich substrates did not successfully *N*-arylate, as seen with 2-iodoanisole **27b** (Table 2, entries 4-6). Electron deficient systems worked best, as seen with 2-iodo-1-nitrobenzene **27c** (Table 2, entries 1-3) and methyl 2-iodobenzoate **27a** (Table 2, entries 7, 8). In an independent study, Bolm reported that aryl triflates act identically to iodo species and proposed that oxidative addition into C-I and C-OTf bonds give similar intermediates.[8]

More recently, the problems associated with palladium-based coupling were addressed with the use of copper salts, as also shown by Bolm and coworkers. Stoichiometric amounts of copper salts were used initially in 2004.[9] In 2005, a catalytic amount of copper salt gave respectable yields of *N*-arylated products. A summary is shown in Scheme 9 with substrates identical to those used with palladium. Excellent

yields were observed in half the reaction time with this system even for the seemingly problematic anisole derivative **29b**.[10]

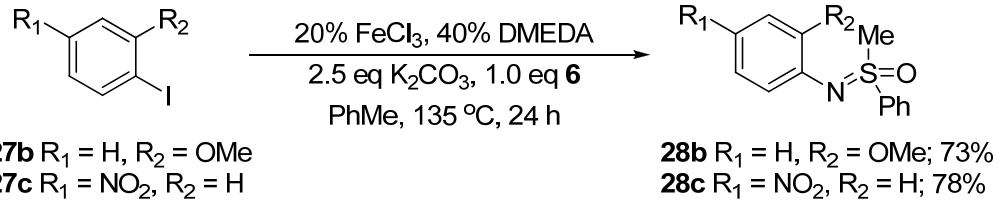


27b R_1 = H, R_2 = OMe
27c R_1 = NO_2, R_2 = H

28b R_1 = H, R_2 = OMe; 99%
28c R_1 = NO_2, R_2 = H; 92%

Scheme 9. Catalytic Copper *N*-Arylation of Aryl Iodides

Very recent was the use of iron (III) chloride in the *N*-arylation of aryl iodides by Bolm and coworkers.[11] This is a simple, inexpensive, and environmentally friendly method for preparing *N*-substituted sulfoximines that complements the variety of metals that can *N*-arylate weakly nucleophilic sulfoximines readily with a variety of aryl halides. The pitfall for this synthesis is the inability to *N*-arylate aryl bromides or aryl chlorides, much like palladium's problem in the *N*-arylation of aryl iodides. Each synthesis is unique and the characteristics of each metal different. Thus, preferences for specific substrates is by no means unreasonable.[11]



27b R_1 = H, R_2 = OMe
27c R_1 = NO_2, R_2 = H

28b R_1 = H, R_2 = OMe; 73%
28c R_1 = NO_2, R_2 = H; 78%

Scheme 10. Catalytic Iron *N*-Arylation of Aryl Iodides

To date, no successful palladium-catalyzed benzothiazine formation of aryl iodides has been published. The substrate of choice for palladium-catalyzed benzothiazine formations continues to be a one-pot *N*-arylation of aryl bromides thermally or with the assistance of microwave irradiation for aryl chlorides. If aryl iodides were to be used, a two step approach of first *N*-arylation then successive

condensation with a stronger base might be needed for benzothiazine formation. The inclusion of iron- and copper-catalyzed syntheses provides evidence that sulfoximines can be coupled with a variety of aryl iodides. Tolerance of a variety of functional groups in a variety of similar catalytic cycles involving different transition metal catalysts has been shown.

1.3 Preparation of "Free" Sulfoximines or *N*-Substituted Sulfoximines

1.3.1 Synthesis of "Free" Sulfoximines via Buchwald Hartwig *N*-Arylation

As mentioned briefly, *N*-arylation of sulfoximines began in 1998 with the Bolm group.[6] Shortly after, in 1999, the Harmata group expanded this reaction to prepare the first benzothiazine via *N*-arylation.[5] It is important to lead into the syntheses of sulfoximine based ligands by also introducing the Bolm group's methods to prepare *N*-arylated sulfoximines in their research group's path toward ligands for asymmetric catalysis. The very first and the simplest *N*-arylation of bromobenzene **17** was optimized affording *N*-phenylsulfoximine **2** in good yield (Scheme 11).[6]

Scheme 11. Optimized *N*-Arylation Procedure for Aryl Bromides

In short, $Pd(OAc)_2$ outperformed Pd_2dba_3 and $PdCl_2$. Of the ligands examined, *p*-tol-BINAP slightly improved upon BINAP and significantly enhanced reaction conversion compared to both P(*o*-tol)$_3$ and dppf, 1,1'-bis(diphenylphosphino)ferrocene. The structures of the ligands are provided in Figure 4. Two bases were studied and of the

two, Cs_2CO_3 outperformed NaO^tBu slightly. This optimized procedure is still used widely today with little change.[6]

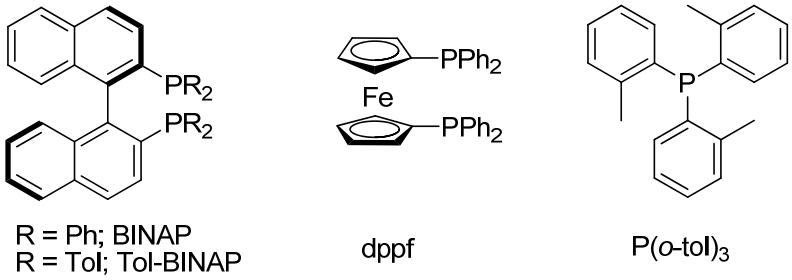
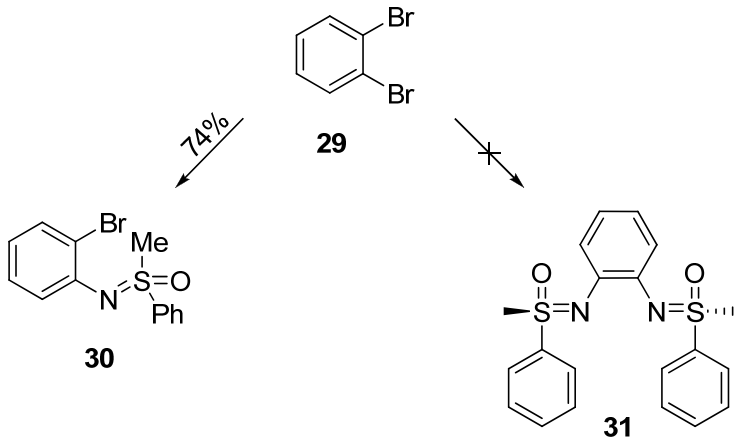


Figure 4. Structures of Ligands Used in the *N*-Arylation of Aryl Bromides

A temporary setback for the Bolm group involved the formation of bissulfoximine **31**. As mentioned before, coupling of mono-substituted aryl chlorides, bromides and iodides to some extent have been well established and the conditions have been optimized, albeit not extensively. However, when dibromobenzene **29** was used with large excesses of sulfoximine, base, ligand, and metal, only single amination to **30** was observed. This was thought to be due to deactivation of the second carbon-bromine bond toward oxidative addition by the newly introduced *ortho*-sulfoximine. Steric hindrance of the sulfoximine group was likely not an issue; since 1,3-dibromobenzene also displayed similar problems where only single amination product was observed in 51% yield. Therefore, the discerning issue of bisamination must be an electronic effect of the oxidative addition capability of the metal catalyst system. Different ligands failed to change the outcome of the reaction. One important observation is that dehalogenation was not seen; thus, palladium insertion likely does not occur under the applied reaction conditions to the remaining C—Br bond after the first *N*-arylation.[8]



Scheme 12. Initial Attempts at the *N*-Arylation of Aryl Dibromides

1.3.2 Synthesis of "Free" Bissulfoximines via Buchwald Hartwig *N*-Arylation

Further studies into this problem revealed that a different source of palladium and a change in the reaction conditions could effectively solve the problem. The Bolm group led the way to another family of bissulfoximines via *N*-arylation a year later in 2001.[8] Keep in mind, the first bissulfoximine ligand to be prepared by the Bolm group was in 1996 (Figure 5).[12]

However, bissulfoximine **31** was this first example of a double Buchwald Hartwig *N*-arylation of two sulfoximines from a dibromoarene to be reported. A change in base from Cs_2CO_3 to NaO^tBu was necessary and 8% Pd(0) (4% Pd_2dba_3), 8% *rac*-BINAP, and a large 5 equivalent excess of sulfoximine was required. A 75% yield of **31** was isolated (Scheme 13).[8] This synthesis led way to a plethora of asymmetric ligands based on a single or double sulfoximine based moiety, all of which were synthesized via Buchwald-Hartwig *N*-arylations using haloarenes and *S*-methyl-*S*-phenylsulfoximine **6** as coupling partners. A review of the ligands derived from this method will be presented in the next section. The ligands presented will be shown in order of their discovery over the past decade.

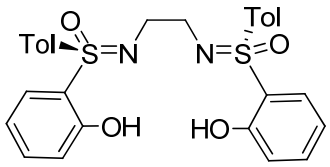
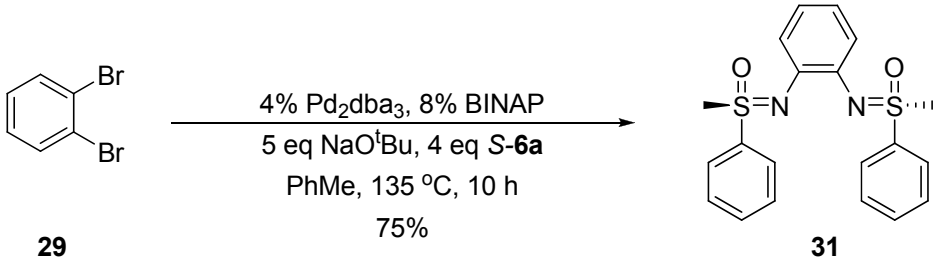


Figure 5. The First Bissulfoximine Ligand



29 **31**

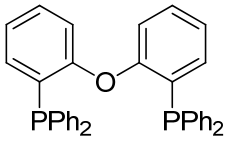
Scheme 13. The First Synthesis of Bissulfoximine **31** via *N*-Arylation

1.4 Chiral Sulfoximine-Based Ligands in Asymmetric Reactions

1.4.1 Preparation of an Oxazoline-Based Sulfoximine Ligand

Retention of configuration at the sulfur of sulfoximines makes the syntheses of many enantiomerically pure ligands very accessible. It was found by Buchwald and coworkers that racemization of chiral amines was a problem due to β-H elimination in the formation of imines. They found that the use of chelating ligands like BINAP, dppf, and DPEphos (Figure 6) minimized racemization.[13]

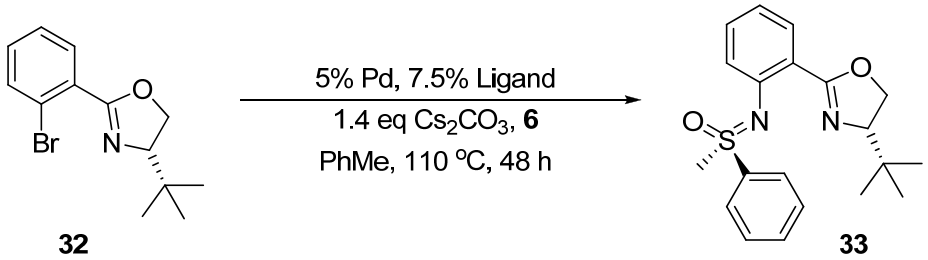
Under this methodology, Bolm and coworkers reasoned that since the sulfoximine's chirality was centered at the chiral sulfur atom, it would proceed with retention of configuration. Upon reaction with chiral oxazoline **32** and racemic sulfoximine **6**, the Bolm group observed only one diastereomer signifying retention of configuration at sulfur. This was the first example of a Buchwald Hartwig *N*-arylation of an aryl bromide and sulfoximine to produce a chiral ligand capable of being employed in asymmetric catalytic reactions. A summary of this synthesis is shown in Table 3.[8]



DPEphos

Figure 6. Structure of Bis(2-diphenylphosphinophenyl)ether, DPEphos

Table 3. Synthesis of a Chiral Sulfoximine-Oxazoline Ligand **33**



32 **33**

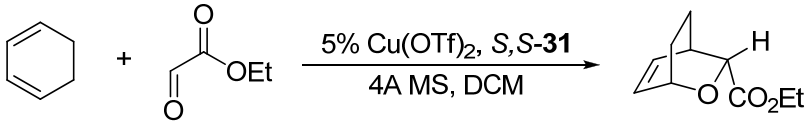
Entry	Pd/Ligand	6:32	Yield (%)
1	$Pd(OAc)_2$/BINAP	1:2	54
2	$Pd(OAc)_2$/BINAP	2:1	61
3	$Pd(OAc)_2$/BINAP	1:1	82
4	$PdCl_2$(dppf)/dppf	1:1	75
5	$Pd(OAc)_2$/DPEphos	1:1	86

As shown in Table 3, an excess of **6** or **32** did not promote coupling. Of the ligands tested, BINAP and DPEphos gave the highest yields with a 1:1 stoichiometric mixture of aryl bromide and sulfoximine (Table 3, entries 3, 5). Dppf with $PdCl_2$ was moderately successful as well (Table 3, entry 4). Ligand **33** was not examined in any asymmetric reactions in this investigation.[8] This *N*-arylation based upon a sulfoximine will be the key reaction in the syntheses of all ligands presented herein.

1.4.2 **Use of Bissulfoximine 31 in Asymmetric Hetero-Diels Alder Reactions**

As shown previously in Scheme 13, bissulfoximine **31** was isolated in 75% yield from a modified Buchwald Hartwig *N*-arylation employing Pd_2dba_3 instead of $Pd(OAc)_2$, NaO^tBu instead of Cs_2CO_3, and a large excess of sulfoximine **6**. In 2001, Bolm successfully tested bissulfoximine **31** in enantioselective hetero-Diels Alder reactions. The results of this study are summarized in Table 4 for the reaction of 1,3-cyclohexadiene **34** and ethyl glyoxalate **35** affording **36**. One important feature shown in Table 4 is that even as little as 0.5 mol % of **31** (Table 4, entry 5) gave 96% yield and 98% *ee* and an *endo/exo* selectivity of 99:1.[14]

Table 4. Ligand **31** in an Asymmetric Hetero-Diels Alder Reaction



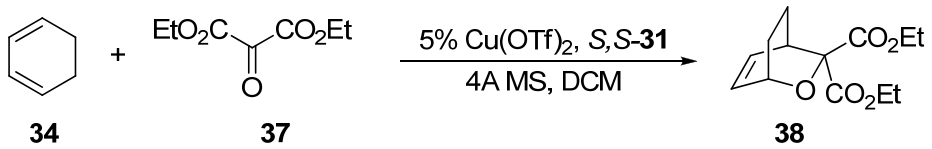
34 **35** **36**

Entry	*S,S*-31 (mol %)	Temp. (^oC)	Time (h)	Yield (%)	*ee* (%)	*endo/exo* ratio
1	10	rt	6	62	99	99:1
2	5	rt	6	61	98	99:1
3	5	-5	10	61	99	99:1
4	1	-5	10	98	98	99:1
5	0.5	rt	6	96	98	99:1

Table 5 shows a summary of the hetero-Diels Alder reaction of 1,3-cyclohexadiene **34** and diethylketomalonate **37** affording **38**. Typically, lower reaction temperatures corresponded to better enantioselectivities (Table 4, entries 3, 4; Table 5,

entries 2-4) without lowering yield, but extending reaction time significantly. Overall, excellent yields and enantioselectives were seen for the reaction in Table 5.[14]

Table 5. Ligand **31** in Another Asymmetric Hetero-Diels Alder Reaction



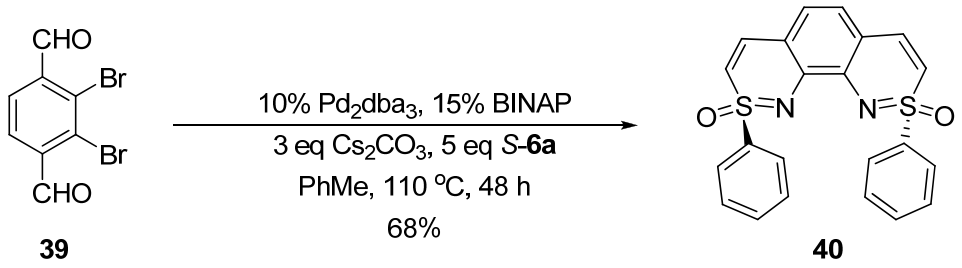
34 **37** **38**

Entry	*S,S*-31 (mol %)	Temp. (^{o}C)	Time (h)	Yield (%)	*ee* (%)
1	5	rt	8	95	92
2	10	-5	12	98	94
3	10	-20	18	93	96
4	5	-40	30	92	98

This ligand is the first enantiopure sulfoximine based ligand derived from the *N*-arylation of an aryl halide, in this case an aryl dibromide, which was successfully used in an asymmetric reaction. The ligand system shows respectable turnover ability with low catalyst loadings. Excellent enantioselectivities are accompanied by high yields. This chemistry led way to many more similar ligand systems in different asymmetric reactions.

1.4.3 **Use of Bisbenzothiazine in an Asymmetric Allylic Alkylation**

With new accessibility to bissulfoximines, new sulfoximine-containing bisbenzothiazines became possible. In 2001, Harmata and coworkers reported the efficient conversion of dibromodibenzaldehyde **39** to the corresponding *S,S*-bisbenzothiazine **40** in 68% yield (Scheme 14). Noteworthy is that Cs_2CO_3 could be used in this case.[15]

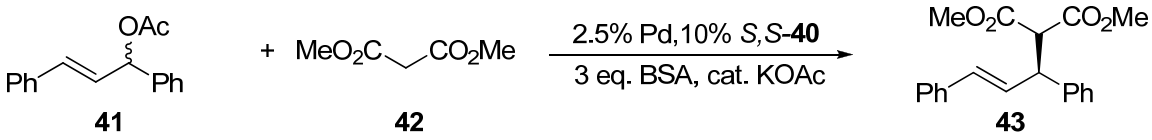


39 40

Scheme 14. Synthesis of Bisbenzothiazine **40**

This new bisbenzothiazine **40** is the first example of a cyclic "fixed" sulfoximine, or benzothiazine, used as a ligand in an asymmetric allylic alkylation reaction. The reaction of racemic 1,3-diphenylallyl acetate **41** with dimethyl malonate **42** under palladium catalysis in the presence of **40** gave enantioenriched **43** in good yield and enantioselectivity (Table 6). The best enantiomeric excess seen was 86% *ee* (Table 6, entry 4).[15]

Table 6. Bisbenzothiazine **40** in a Pd-Catalyzed Allylic Alkylation

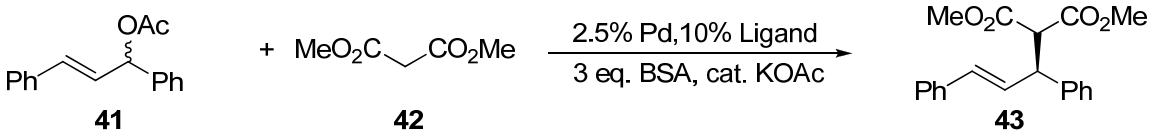


41 42 43

Entry	Pd Source	Solvent	Time (h)	Yield (%)	*ee* (%)
1	$[Pd(allyl)Cl]_2$	THF	3.5	90	80
2	$[Pd(allyl)Cl]_2$	PhH	3	85	82
3	$[Pd(allyl)Cl]_2$	PhMe	3.5	70	78
4	Pd_2dba_3	THF	3.5	69	86
5	$Pd(OAc)_2$	THF	7.5	67	73
6	$Pd(PPh_3)_4$	THF	5	90	16

Interestingly, bissulfoximine **31** failed to give any enantioselectivity in the same reaction. The reaction also was very sluggish and isolated yields were 30% and 31% for Pd_2dba_3 and $[Pd(allyl)Cl]_2$, respectively (Table 7, entries 1,2). Remarkably, 4-phenyl-2,1-benzothiazine **28** gave a 15% yield and 28% *ee* of alkylated product **43 (**Table 7, entry 3).[15]

Table 7. Bissulfoximine **31** and Benzothiazine **26** in an Allylic Alkylation



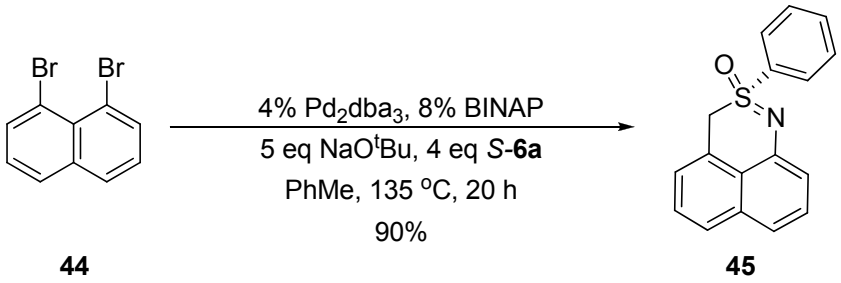
Entry	Pd Source	Ligand	Solvent	Time (h)	Yield (%)	*ee* (%)
1	Pd_2dba_3	**31**	THF	4	30	0
2	$[Pd(allyl)Cl]_2$	**31**	THF	5	31	0
3	$[Pd(allyl)Cl]_2$	**26**	THF	6	15	28

1.4.4 **Preparation of Benzothiazine-like Compounds**

In search of similar families of compounds, Bolm and coworkers explored other dibromoarene-type compounds in 2002. Expanding upon the synthesis of **31**, they sought to expand the reaction scope to that of the naphthalene and biphenyl type dibromide systems. First was coupling of 1,8-dibromonaphthalene **44** with sulfoximine **6** in 90% yield over 20 hours to give 6-membered heterocycle **45** (Scheme 15). This process required a five equivalent excess of sulfoximine **6a**. Noteworthy is that $Pd(OAc)_2$ or Pd_2bda_3 could be used to afford product in respectable yields. The use of Cs_2CO_3, as base, was not reported, and only NaO^tBu was used in this study. Isolation of the product showed that dual *N*-arylation did not occur but that instead a different cyclization had

occurred. The absence of palladium resulted in absence of the cyclization and coupling. Bolm and coworkers expanded the scope to biphenyl and biphenyl ether type compounds to make both 7- and 8-membered heterocycles. The proposed base-induced aryne mechanism is shown in Figure 7 for **46**.[16] This mechanism mirrors that shown by Hartwig and coworkers for the palladium-catalyzed conversion of bromoanilides to oxindoles to make 5-membered heterocycles.[17]

2,2'-Dibromobiphenyl **46** gave 7-membered heterocycle **47** in 98% yield and 2,2'-oxybis(bromobenzene) **48** gave 8-membered heterocycle **49** in 69% yield (Scheme 16).[16] The reduction in yield of the larger 8-membered heterocycle is likely due to larger entropic effects involved in the cyclization of the larger ring system as compared to the slightly smaller 7-membered heterocycle.



Scheme 15. Synthesis of a Sulfoximine Based 6-Membered Heterocycle **45**

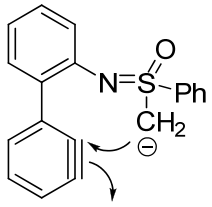
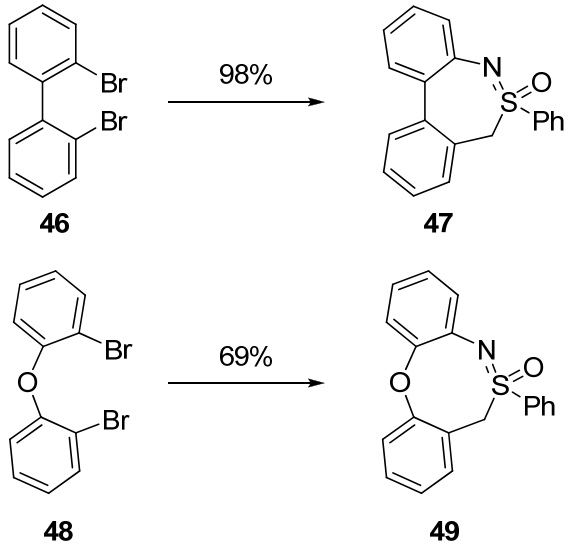


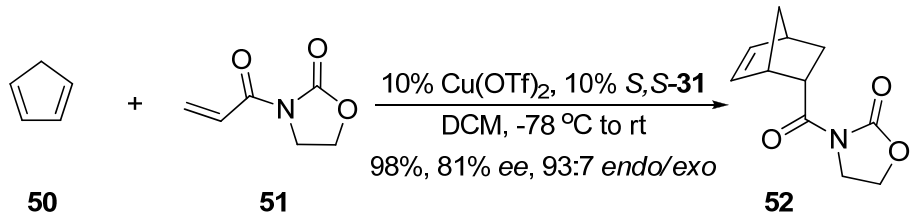
Figure 7. Proposed Base Induced Benzyne Mechanism



Scheme 16. Syntheses of 7- and 8-Membered Heterocycles

1.4.5 Use of Bissulfoximine 31 in Asymmetric Diels Alder Reactions

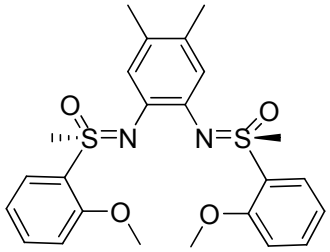
Bissulfoximine **31** was shown earlier to be successful in copper-catalyzed hetero-Diels Alder reactions that proceeded in high yield and enantioselectivity. [14] Bolm and coworkers expanded the scope of the chemistry of bissulfoximine **31** and used it as a ligand in normal Diels Alder reactions in 2003. Cyclopentadiene **50** and 3-acryloyloxazolidin-2-one **51** afforded Diels Alder adduct **52** in 98% yield, 81% *ee*, and a 93:7 *endo/exo* ratio. Only bissulfoximine **31**, in this specific study, was prepared by *N*-arylation and its use as a ligand is shown in Scheme 17. [18]



Scheme 17. Bissulfoximine **31** in an Enantioselective Diels Alder Reaction

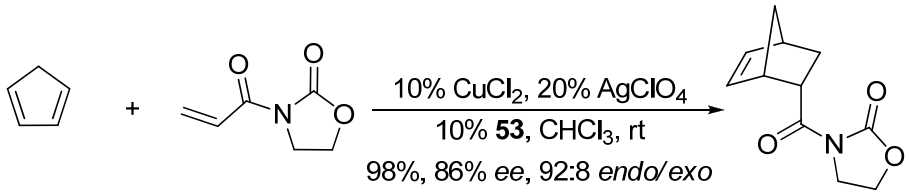
Other ligands tested were those similar to the bissulfoximine ligand **37**. Of these ligands, bissulfoximine ligand **53**, shown in Figure 8, slightly outperformed all others

including bissulfoximine **31** (Scheme 18). After reaction optimization, the Bolm group deduced several things: $Cu(ClO_4)_2$ was the best copper(II) source; chloroform was the best solvent; and the ideal ligand contained both an electron rich arene bridge and *ortho*-bound methoxy substituents about the sulfoximine aryl groups.[18] However, **31** can be made in a single step, and it would likely be the ligand of choice as its performance was respectable.



53

Figure 8. Bissulfoximine Ligand **53**



50 **51** **52**

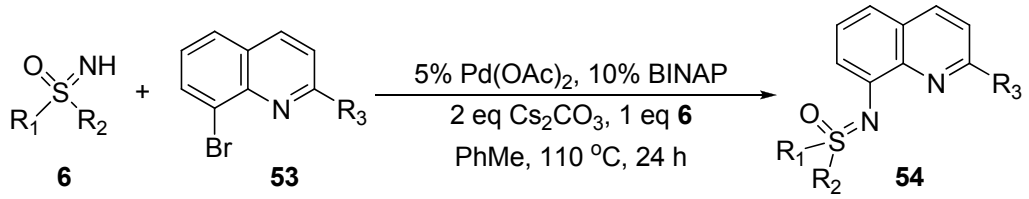
Scheme 18. The Use of **53** in an Optimized Diels Alder Reaction

1.4.6 Use of *N*-Quinolinesulfoximines in Asymmetric Hetero-Diels Alder Reactions

Later in 2003, another class of sulfoximine-based ligands was reported by Bolm and coworkers. A variety of substrates were prepared and tested. Overall, the best ligands for this reaction contain a sulfoximine bearing a small alkyl group and an aryl group with bulky *ortho*-substituents. Syntheses of these quinoline-based ligands model those previously shown with the *N*-arylation of sulfoximine **6** and quinoline derivatives **53** to yield a variety of *N*-quinolinesulfoximines **54** (Table 8). Reduced yields were

observed for bulky alkyl bearing sulfoximines, especially in the case of the *t*-butyl group, which gave a 55% isolated yield of product (Table 8, entry 11). Larger arenes like acridine gave only 68% isolated yield (Table 8, entry 3). Most yields were good to excellent, providing further evidence that the Buchwald Hartwig *N*-arylation works well with a variety of sulfoximines in the presence of quinoline-type substrates. [19]

Table 8. Syntheses of Quinolinesulfoximines by *N*-Arylation

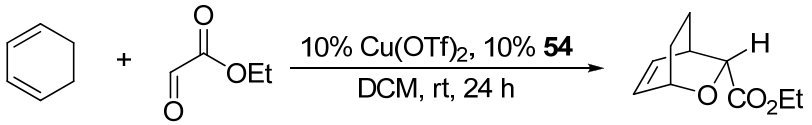


6 **53** **54**

Entry	Sulfoximine	R_1	R_2	R_3	Yield (%)
1	**54a**	Me	Ph	H	90
2	**54b**	Me	Ph	*n*-Bu	75
3	**54c**	Me	Ph	$-C_4H_4$	68
4	**54d**	*i*-Pr	Ph	H	75
5	**54e**	*t*-Bu	Ph	H	72
6	**54f**	Me	biphenyl	H	84
7	**54g**	Me	3,5-di-*t*-Bu-Ph	H	81
8	**54h**	Me	2-MeO-Ph	H	87
9	**54i**	*n*-pentyl	2-MeO-Ph	H	85
10	**54j**	phenethyl	2-MeO-Ph	H	73
11	**54k**	*t*-Bu	2-MeO-Ph	H	55
12	**54l**	Me	2-MeO-Naph	H	81

Many of these ligands were tested in the same hetero-Diels Alder reaction presented previously in Tables 4 and 5. Results for these different sulfoximines are collected in Table 9. Ligands with small alkyl and bulky *ortho*-aryl groups on the sulfoximine gave better enantioselectivities than those with larger alkyl and less bulky aryl groups.[19]

Table 9. *N*-Quinolinesulfoximines in an Asymmetric Hetero-Diels Alder Reaction



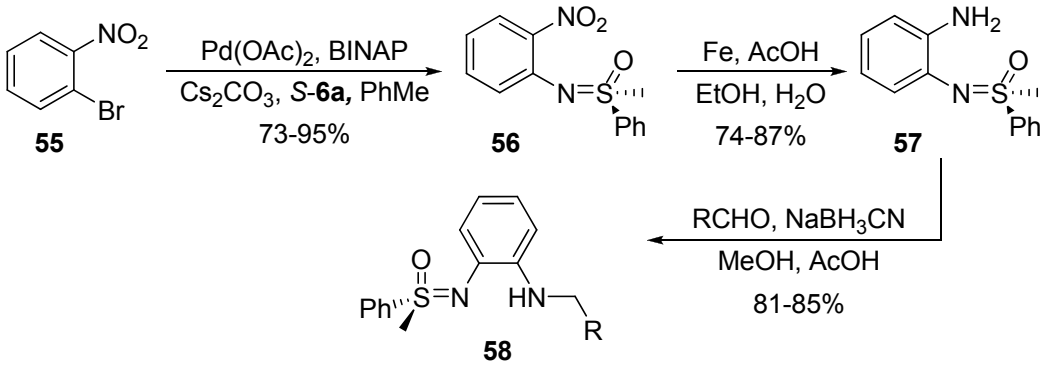
34 **35** **36**

Entry	Sulfoximine	Yield (%)	*ee* (%)	*endo/exo* ratio
1	**54a**	97	75	97:3
2	**54b**	93	63	99:1
3	**54c**	95	56	99:1
4	**54d**	22	38	96:4
5	**54e**	18	0	88:12
6	**54f**	92	73	98:2
7	**54g**	81	73	97:3
8	**54h**	98	91	98:2
9	**54i**	92	90	98:2
10	**54j**	93	86	97:3
11	**54k**	41	0	92:8
12	**54l**	88	91	98:2

A few interesting features are displayed in Table 9. First, yields suffered in many cases. When the alkyl group on the sulfoximine was bulky or very bulky the reaction progress was extremely limited and the yields were quite low (Table 9, entries 4, 5, and 11). Enantioselectivity suffered in these cases as well. So it is logical to believe that larger alkyl groups are a strong contributing factor to how well defined the asymmetric cavity around the metal sphere is and that they therefore dictate to some extent yield and enantioselectivity of the hetero-Diels-Alder reaction. In all other cases substituent changes about the aryl sulfoximine group and the quinoline group had little effect on yield or enantioselectivity.[19]

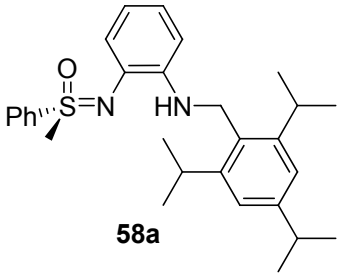
1.4.7 Use of Aminosulfoximines in Asymmetric Mukaiyama-Type Aldol Reactions

In 2004, the attention of the Bolm group was directed toward the synthesis of aminosulfoximines. The synthesis began with 2-bromonitrobenzene **55** and sulfoximine *S*-**6a** as coupling partners in a Buchwald Hartwig *N*-arylation to give *N*-substituted sulfoximine **56** in 73-95% yield. Compound **56** was reduced to the aniline *N*-substituted sulfoximine **57** in 74-87% yield. Reductive amination of **57** gave aminosulfoximine **58** in 81-85% yield (Scheme 19).[20]



Scheme 19. Generic Synthesis of Aminosulfoximine **58**

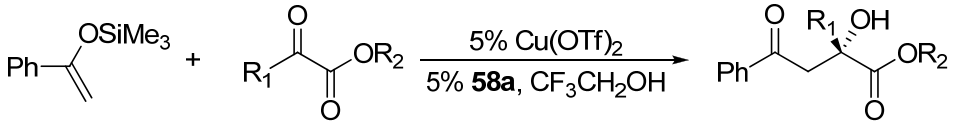
Many *N*-substituents were tested and of those, the very bulky *N*-2,4,6-triisopropylphenyl aminosulfoximine **58a** (Figure 9) was found to outperform other substituents such as phenyl, naphthyl, 2-anisyl, and mesityl. The test reaction was between silyl enol ether **59** and ketoester **60** to yield Mukaiyama aldol product **61**. The results are shown in Table 10. In all examples, good yields and enantioselectivities were observed when aminosulfoximine **58a** was employed as the ligand.[20]



58a

Figure 9. Aminosulfoximine Ligand **58a**

Table 10. Aminosulfoximine **58a** as a Ligand in Mukaiyama-Type Aldol Reactions

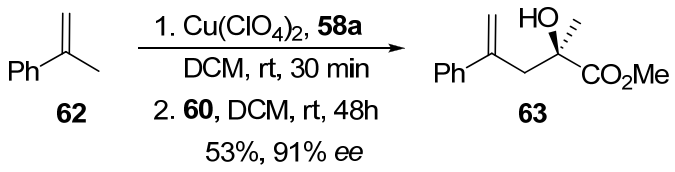


59 **60** **61**

Entry	R_1	R_2	Temp. (^{0}C)	Time (h)	Yield (%)	*ee* (%)
1	Me	Me	-30	15	89	98
2	Me	Bn	-50	47	86	98
3	Me	*i*-Pr	-40	28	90	99
4	Et	Me	rt	24	78	89
5	CH_2Bn	Et	-20	40	86	96

1.4.8 **Use of Aminosulfoximines in Asymmetric Carbonyl-ene Reactions**

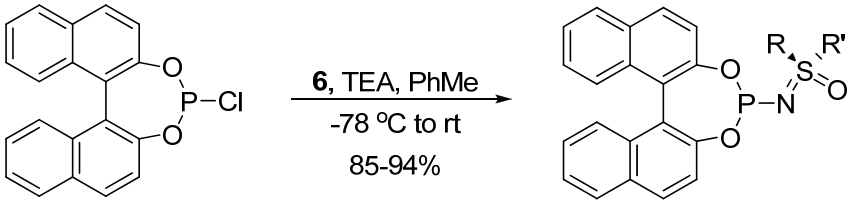
Aminosulfoximines were again tested in various copper-catalyzed carbonyl-ene reactions in 2005. Similar to those tested above in Mukaiyama-type aldol reactions, several aminosulfoximines prepared by *N*-arylation were tested and acceptable yields and good enantioselectivities were found. Ligand **58a** was also the best ligand for this reaction. In this case, α-methylstyrene **62** was reacted under copper catalysis with methyl pyruvate **60** to give hydroxyl ester **63** in 53% yield and 91% *ee* (Scheme 20). Notice the enantioselectivities were not quite as high as before, but it shows that sulfoximine type ligands are applicable to more than one reaction type.[21]



Scheme 20. Aminosulfoximine **58a** in an Asymmetric Carbonyl-Ene Reaction

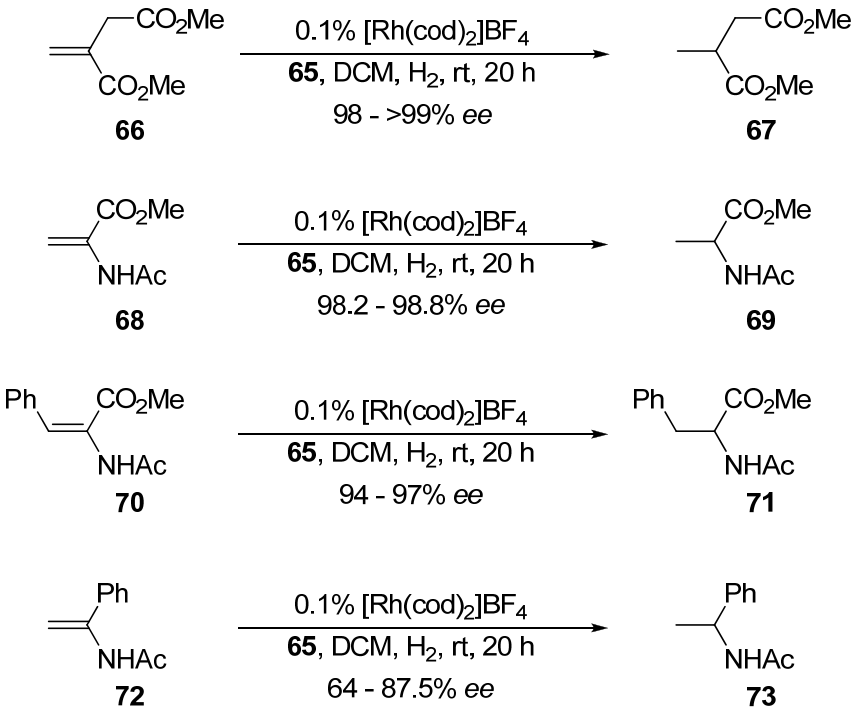
1.4.9 **BINOL-Based *N*-Phosphino Sulfoximines in Asymmetric Reactions**

Soon after in 2005, Bolm and coworkers reported a BINOL-based *N*-phosphino sulfoximine based ligand system. This ligand was not prepared via Buchwald Hartwig *N*-arylation but provides yet another very simple synthesis of a sulfoximine based-ligand. Chlorophosphite **64** was added to sulfoximine **6** in the presence of triethylamine in toluene. The reaction was warmed from -78 ^{o}C to room temperature to afford *N*-phosphino sulfoximine **65** in excellent yields (Scheme 21). This ligand system was investigated in two asymmetric reactions. First, it was tested in asymmetric rhodium-catalyzed hydrogenations (Scheme 22) and palladium-catalyzed asymmetric allylic alkylations (Scheme 23). In both cases high yields and high enantioselectivities were observed.[22]



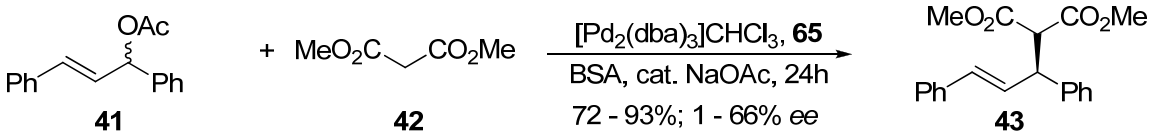
Scheme 21. Preparation of BINOL-Based *N*-Phosphino Sulfoximines

In all examples, quantitative conversion was observed. In all cases, good to excellent enantioselectivities were seen. As little as 0.1% Rh-**65** catalyst was used. The extremely low catalyst loading displays how well the catalyst was able to turnover in a period of 20 hours to allow for the excellent conversions. It was found that a matched ligand, *R*-BINOL/*S*-**6** gave higher enantioselectivity than the mismatched case *S*-BINOL/*S*-**6** where as much as a 12% *ee* difference was observed.[22]



Scheme 22. BINOL *N*-Phosphino Sulfoximines in Asymmetric Hydrogenations

Typically monodentate BINOL-based ligands are not used in Pd-catalyzed allylic substitution reactions as they provide poor enantioselectivities. This was also the case, for ligands like **65**. The highest enantioselectivity observed was 66% *ee* where the methyl group was substituted with an *t*-butyl group to improve steric demand. Increasing the amount of ligand to palladium available also reduced the enantioselectivity by a noticeable amount, in some cases as much as 50% *ee*. However, yields slightly improved with more ligand present, albeit by only a few percent.[22]



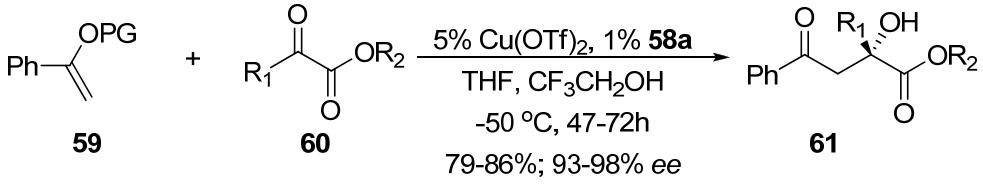
Scheme 23. BINOL *N*-phosphino Sulfoximines in Asymmetric Allylic Alkylations

1.4.10 **Optimization of Aminosulfoximines in Asymmetric Aldol Reactions**

As shown in 2004, aminosulfoximines as ligands worked well in Mukaiyama-type aldol reactions.[20] Bolm and coworkers expanded this methodology and optimized the reaction conditions to improve the yield, enantioselectivity, and substrate scope. As previous results suggested and confirmed again here, ligand **58a** provided the highest *ee* and the highest yield. A bulky *ortho*-substituent remains the largest determining factor to attain high enantiomeric excess. Both configurations of **61** could be prepared by switching to the opposite ligand chirality. Here (*R*)-**58a** gave (*S*)-**61** and (*S*)-**58a** gave (*R*)-**61**. Modifying the substituents on the bridging arene had little to no effect on yield or enantioselectivity.[23]

Solvent effects were explored and typically THF outperformed all others in terms of enantioselectivity. Ether, dioxane, and toluene gave similar enantioselectivity but much lower yields than THF. The reaction did not proceed in propionitrile. Chloroform

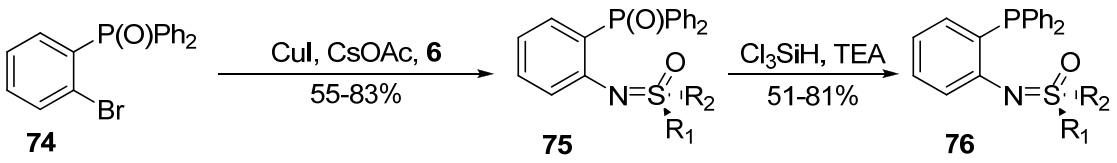
and dichloromethane gave lower enantioselectivity as well. Copper(II) salts were examined and the $^{-}$OTf salt outperformed PF_6^-, BF_4^-, and SbF_6^- salts in both with regards to yield and enantioselectivity. The perchlorate counterion, however, provided the best yield of all salts tested but suffered reduced enantioselectivity relative to that of the $^{-}$OTf salt. Catalyst loadings of less than 1% resulted in diminished enantioselectivity. Lowering temperatures of the reaction allowed for better enantioselectivity but significantly lengthened reaction times to as much as 10 days. The best temperature was found to be -50 ^{o}C with the assistance of trifluoroethanol as an accelerant. Temperatures near -78 ^{o}C or lower inhibited catalysis completely. The overall optimized reaction is shown in Scheme 24.[23]



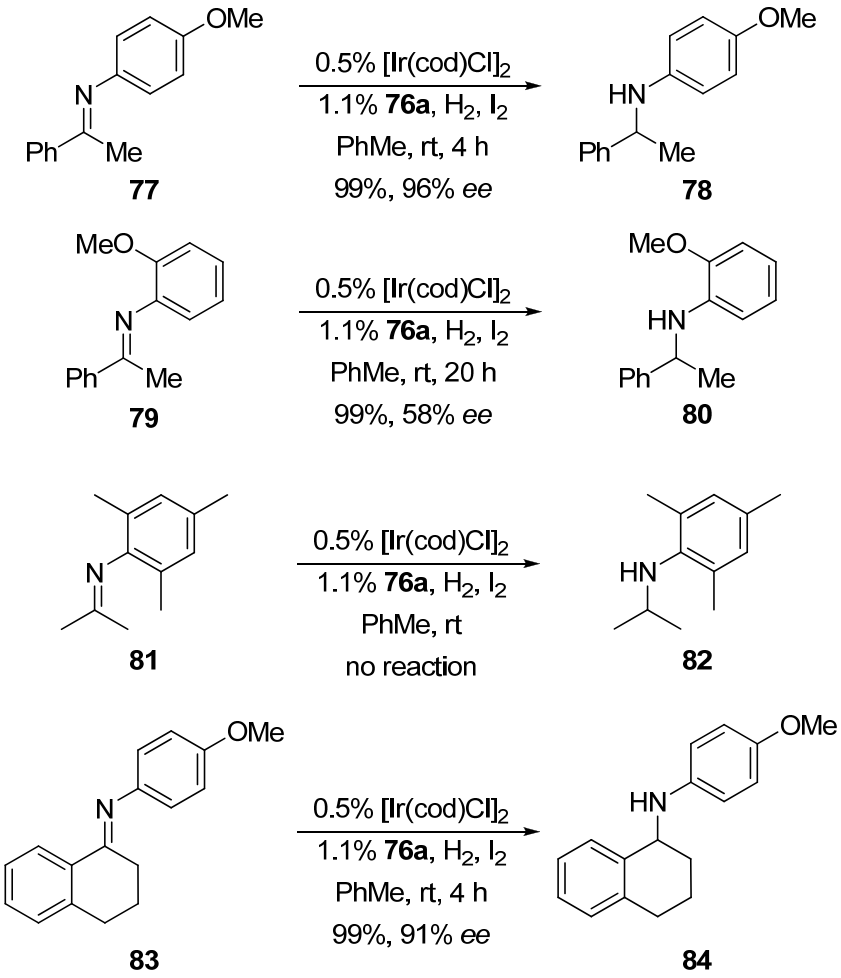
Scheme 24. Optimized Asymmetric Mukaiyama-Type Aldol Reaction

1.4.11 **Diphenylphosphanylsulfoximines in Asymmetric Imine Hydrogenations**

A new ligand system was prepared and tested in asymmetric imine hydrogenations by the Bolm group in 2005. This *P,N*-ligand was prepared by coupling of aryl bromide **74** with sulfoximine **6** via copper mediated *N*-arylation in moderate to good yields (55-83%). The resulting *N*-substituted sulfoximine **75** was reductively deoxygenated with trichlorosilane to give the free phosphorous *P,N*-ligand **76** in yields of 51-81% (Scheme 25).



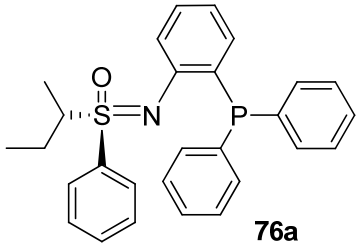
Scheme 25. Synthesis of *P,N*-Ligands Containing a Sulfoximine



Scheme 26. *P,N*-Sulfoximine Ligands in Imine Hydrogenation

A summary of selected imine reductions is shown in Scheme 26. Ligand **76a** (Figure 10) provided the best yield (99%) and *ee* (96%) for the hydrogenation of imine **77** into chiral amine **78**. *Ortho*-substituents on the *N*-aryl group of the imine reduced the enantioselectivity drastically as shown in conversion of imine **79** to amine **80**, which occurred in 99% yield but with only 58% *ee*. An *N*-mesityl group shut down the reaction

completely. The tetralone derivative **83** gave an excellent yield (99%) of amine **84** in as little as 4 hours with an enantiomeric excess of 91%.[24]

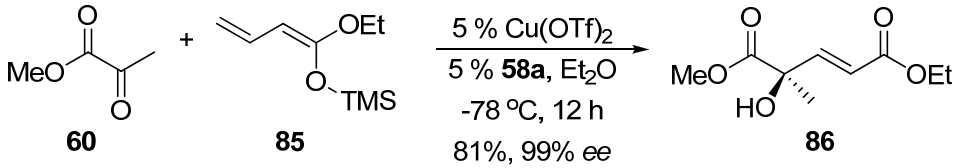


76a

Figure 10. Optimized *P,N*-Ligand **76a**

1.4.12 Aminosulfoximines in Asymmetric Vinylogous Aldol Reactions

Expanding the scope of previous asymmetric Mukaiyama-type aldol reactions, Bolm and coworkers tested aminosulfoximines in vinylogous aldol reactions in 2006. The very bulky tri-*iso*-propyl based aminosulfoximine **58a** again proved to outperform all other aminosulfoximines. A representative reaction is shown in Scheme 27.[25]



60 **85** **86**

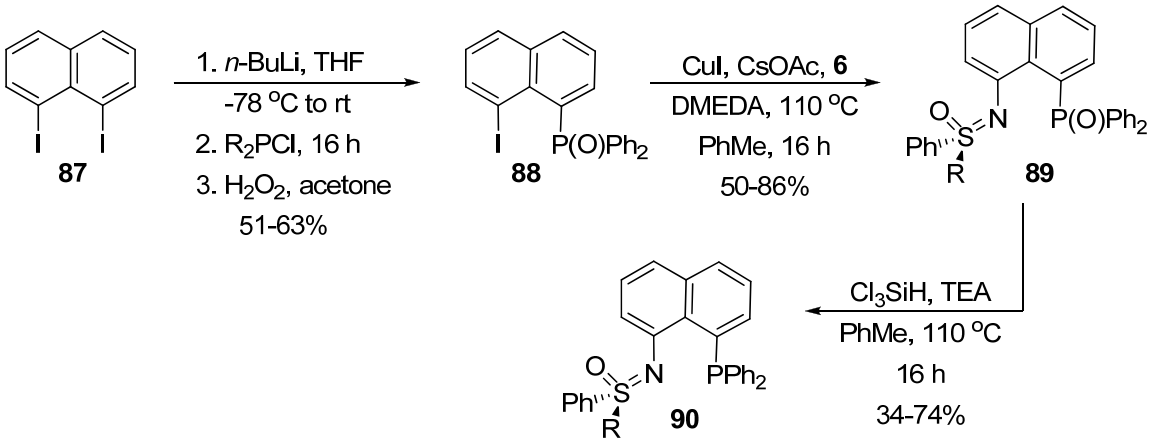
Scheme 27. Aminosulfoximine **58a** in an Asymmetric Vinylogous Aldol Reaction

Here methyl pyruvate **60** reacted with vinylogous TMS ester **85** in 12h to give aldol product **86** in 81% yield and 99% *ee*. This is yet another example of where a single sulfoximine ligand family can be applied to a wide variety of reactions.[25]

1.4.13 Naphthalene Based Sulfoximines in Asymmetric Quinoline Hydrogenations

In 2008, Bolm and coworkers devised another family of sulfoximine-containing compounds with the creation of naphthalene-based *P,N*-ligands for asymmetric catalysis. The synthesis began with halogen metal exchange of diiodo naphthalene **87** with *n*-BuLi followed by trapping with an aryl phosphine chloride. Subsequent oxidation gave

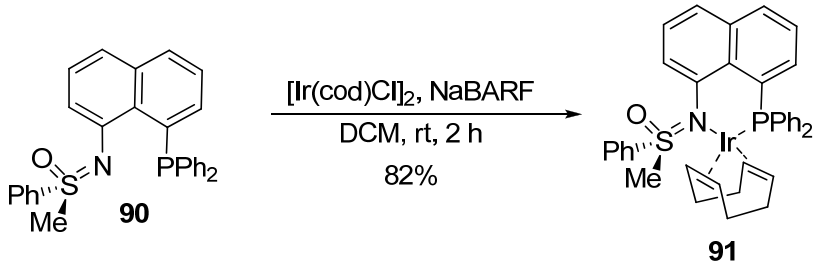
compound **88**. Similar to **74**, copper-mediated *N*-arylation of **88** with sulfoximine **6** gave *N*-arylated sulfoximine **89**. Reductive deoxygenation gave free phosphino *P,N*-ligand **90** in a wide range of yields (Scheme 28). A variety of quinolines were hydrogenated with precatalyst **91** which were prepared *in situ* with an Ir salt (Scheme 29). This is the first example of a sulfoximine-based ligand system being trapped successfully and isolated as a metal-ligand bound catalyst. [26]



Scheme 28. Synthesis of Naphthalene-Based Sulfoximine *P,N*-Ligands

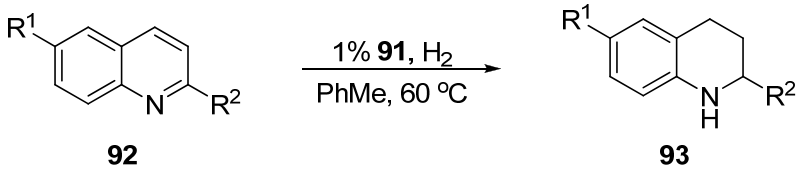
It was found that for the hydrogenation of quinolines, sulfoximine bulk reduced the enantioselectivity of the hydrogenation. Substitution on the aryl phosphorous groups had little or no effect. Several 1-, 5-, and 1,5-disubstituted quinolines were hydrogenated. The results are summarized in Table 11. Here quinoline **92** was hydrogenated to cyclic amine **93**. Conversions were typically fair to good. Longer reaction times gave better yields and poorer enantioselectivity (Table 11, entries 3, 5, and 7). Shorter reaction times gave lower yields but better enantioselectivity (Table 11, entries 1, 2, 4, 6, 8, and 10). The lowest yield was observed with 2-fluoroquinoline **93i** for which the reaction proceeded to the extent of only 43%, the *ee* of the product being 64% (Table 11, entry 9).

Overall enantioselectivity was moderate to good and conversions also moderate to good.[26]



Scheme 29. Preparation of Ir Precatalyst **91**

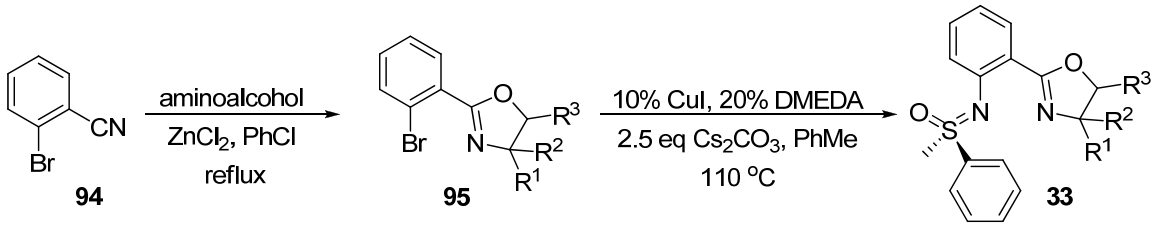
Table 11. Summary of Quinoline Hydrogenation via Precatalyst **91**



Entry	R^1	R^2	Compound	Time (h)	Conversion (%)	*ee* (%)
1	H	Me	**93a**	20	>95	87
2	H	Et	**93b**	24	62	77
3	H	Et	**93c**	48	69	70
4	H	*i*-Bu	**93d**	24	53	75
5	H	*i*-Bu	**93e**	48	71	55
6	H	Pr	**93f**	24	62	80
7	H	Pentyl	**93g**	48	90	65
8	Me	Me	**93h**	24	>95	75
9	F	Me	**93i**	24	43	64
10	OMe	Me	**93j**	24	>95	78

1.4.14 **Oxazolinyl Sulfoximines in Asymmetric Mukaiyama-type Aldol Reactions**

The last example to be discussed from the current literature involves the use of a oxazolinyl sulfoximine ligand. This ligand mentioned previously as oxazoline **33** or any derivative thereof had not been investigated as a chiral ligand until late 2008 by the Bolm group. A newer two step synthesis was reported to make this type of ligand in a more expedient manner (Scheme 30).



Scheme 30. Second Generation Synthesis of Oxazolinyl Sulfoximine Ligands

The synthesis began with 2-bromobenzonitrile **94** and zinc chloride to give oxazoline **95**. Copper mediated *N*-arylation afforded **33** from **95** and **6**. The ligand that gave the best enantioselectivity was **33a** (Figure 11). An example of **33a** used in asymmetric Mukaiyama-type aldol reactions is shown in Scheme 31.[27]

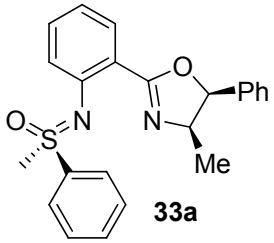
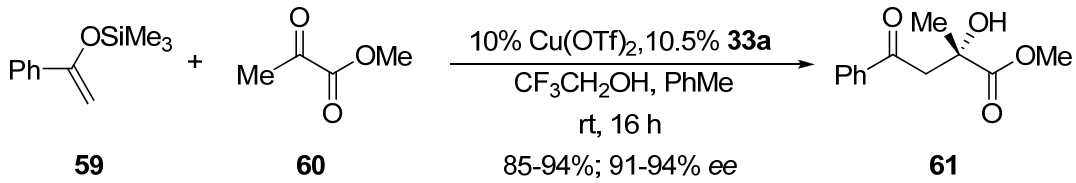


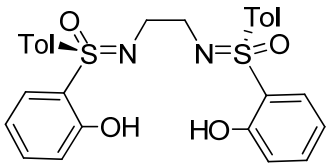
Figure 11. Optimized Oxazolinyl Sulfoximine Ligand **33a**



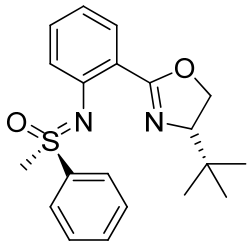
Scheme 31. Oxazolinyl Sulfoximine **33a** in Asymmetric Mukaiyama Aldol Reaction

1.4.15 **Summary of Sulfoximine Based Ligands Over the Past Decade**

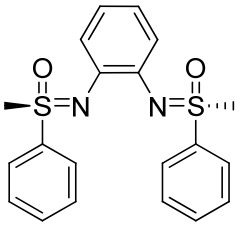
An in depth review of sulfoximines ligands over the past 10 years has been presented. Shown below in Figure 12 are a list of sulfoximine-based ligands and the years they were reported. The scope of ligands, reactions, and substrates makes sulfoximine ligands attractive to the synthetic world. High yields and enantioselectivities with low catalyst loading are common. Relatively short syntheses make sulfoximine ligands very accessible. These features are important to notice when thinking of a catalyst's performance. Many of the ligands introduced previously have made a significant impact on asymmetric reactions by giving a high enantiomeric excess of products formed in a variety of reactions with a variety of metals. The ever expanding scope of sulfoximine-based chiral ligands provides justification for further development of related systems that may also have the potential for the development of reactions that proceed in high enantioselectivity.



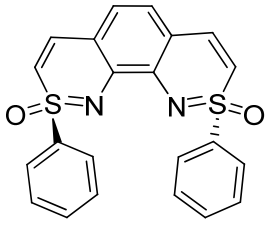
1996



33, 2000



31, 2001



40, 2001

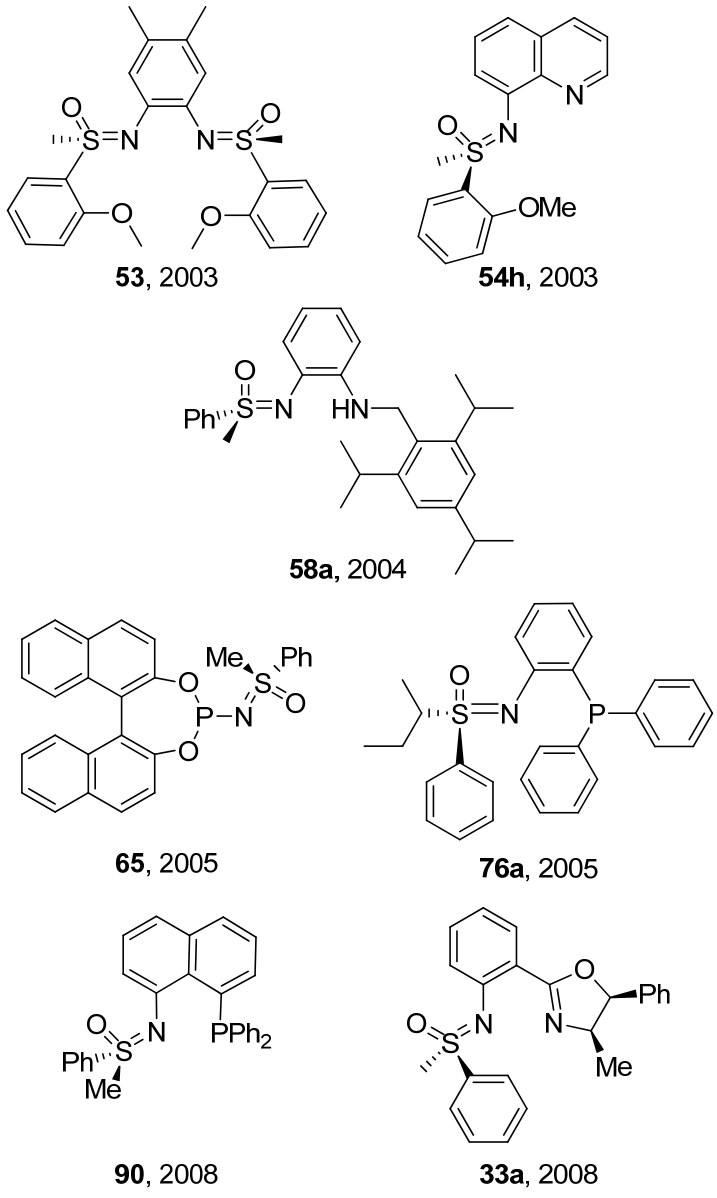


Figure 12. Chiral Sulfoximine Ligands over the Past Decade

CHAPTER 2

Syntheses of Potential Hydroxy-Based Benzothiazine Ligands

The development of hydroxy-based benzothiazine ligands was undertaken in order to create enantiopure molecular scaffolds. This scaffold would be the initial building block used to design more interesting and more complicated molecules. The syntheses of many related compounds will be presented herein. Many synthetic steps were optimized in order to provide respectable syntheses and those details are also presented herein. The key step in all syntheses is the palladium-catalyzed *N*-arylation of haloarenes with sulfoximines that has been examined in depth in the previous chapter.

2.1 Synthesis of a Hydroxy Benzothiazine

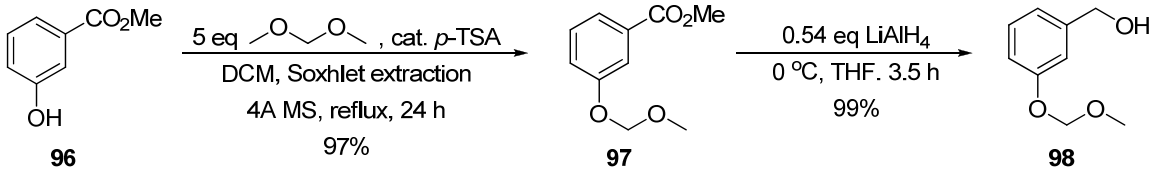
2.1.1 First Generation Synthesis of a Hydroxy Benzothiazine

Aside from bisbenzothiazine **40** and very briefly 4-phenyl-2,1-benzothiazine **28**, no other benzothiazines have been studied as ligands in asymmetric reactions to date. Little is known about their chemistry under different reaction conditions compared to the comprehensively studied various *N*-substituted sulfoximines presented previously. The optimized synthesis of a hydroxy benzothiazine scaffold will be presented. The preparation of this "fixed" sulfoximine building block provided a direct comparison of the benzothiazine's rigid structure to "free" sulfoximines with regards to reactivity. The synthesis of the hydroxy benzothiazine was published in 2006.[28]

The first generation synthesis began with commercially available methyl 3-hydroxybenzoate **96**. In the presence of 5 equiv. of dimethoxymethane and a catalytic amount of *para*-toluenesulfonic acid, the reaction mixture was refluxed in dichloromethane over 24 hours under Soxhlet extraction with freshly activated 4Å

molecular sieves to give MOM-protected phenol **97** (Scheme 32). Yields without molecular sieves or with weakly active molecular sieves ranged anywhere from 39% to 48%. Workup with 10% NaOH allowed for a chromatography-free separation from the starting materials.

The second step was a lithium aluminum hydride reduction of an ester to an alcohol. Less than one equivalent of the reagent could be used to obtain 100% reduction to primary benzyl alcohol **98** in near quantitative yield (Scheme 32). To avoid difficulties in isolation due to the resultant aluminum hydroxides, the widely known Fieser workup was used and as shown the isolated yields approached 100% yield on a multigram scale.



Scheme 32. First Generation Synthesis: MOM-Protection and LAH Reduction

The next step in the first generation synthesis was the selective *ortho*-bromination of benzyl alcohol **98** to give (2-bromo-3-(methoxymethoxy)phenyl)methanol **99**. The challenge that exists is getting single bromination and with complete regioselectivity (Figure 13). The difficulty arises from having three sites of bromination based upon the *ortho- para-* directing abilities of the protected phenol. The protected phenol, a strong electron pair donor, and the methanol substituent, as a weaker inductive electron donor, allow for multiple sites of reactivity about the aromatic ring. The three possible locations of bromination are shown in Figure 13.

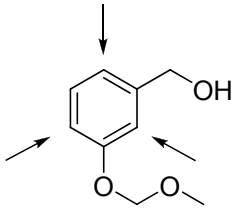


Figure 13. Possible Sites of Bromination

Many attempts to optimize this synthetic step were investigated. First, benzyl alcohol **98** was deprotonated with 2.5 equivalents of *n*-BuLi in various solvents, at various temperatures and for various reaction times. The hope was to take advantage of the two possible *ortho*-directing groups to gain regioselectivity at the most hindered *ortho*-hydrogen. A summary is shown in Table 12.

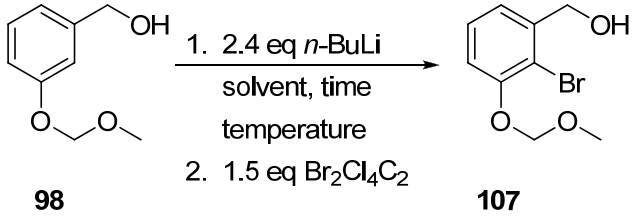
Initial reactions in toluene showed that at low temperatures the reaction progress was slow, giving clean conversion in very modest yields (Table 12, entries 1-2). Extended reaction times at lower temperatures seemed to have a negative effect on yield (Table 12, entry 3). Warming to room temperature and changing solvents increased yields to a respectable 89% (Table 12, entries 4, 5, 8-10, and 14). Both the THF and ether reactions had many baseline impurities that required silica chromatography to remove and attention was drawn to toluene as the solvent of choice (Table 12, entry 10).

Heating the reaction mixture in *n*-BuLi gave exclusive lithiation at the sterically more hindered position. Here the lithium cation could be dually stabilized by both the alkoxide anion and the MOM-substituent (Figure 14). Even if other sites were deprotonated, the resulting anion could act as a strong base such that only the desired dually stabilized anion remained over a period of several hours. Under the previously described reaction conditions, the highest yields and cleanest reactions were observed

(Table 12, entries 11, 14-18). The reaction was found to be reproducible up to ten or more gram scale.

Note that switching to stronger bases like *s*-BuLi and *t*-BuLi decomposed the starting materials and no product was observed (Table 12, entries 6, 7, and 13). When tetramethylethylenediamine, TMEDA, was employed to enhance the reactivity of *n*-BuLi, only 54% of **107** was obtained along with no recovered starting material (Table 12, entry 12).

Table 12. First Generation Synthesis: Bromination



98 **107**

Entry	Solvent	Temp. (°C)	Time (h)	Ratio (98 : 107)	Yield (%)
1	PhMe	-10	1.5	---	64
2	PhMe	-10	1.5	---	56
3	PhMe	-10	3.5	2.8 : 1	---
4	ether	rt	2	---	78
5	ether	rt	4	1 : 8.3	89
6	THF[a]	-78	1	0 : 0	---
7	ether[a]	rt	3	0 : 0	---
8	ether	rt	4	1 : 8.3	87
9	THF	rt	4	1 : 7.3	80
10	PhMe	rt	4	1 : 3.5	70

11	PhMe	80	5	1 : 12.5	87
12	PhMe[b]	rt	5	1 : 2.9	54
13	PhMe[c]	rt	24	0 : 0	---
14	PhMe	rt	24	1 : 5.2	84
15	PhMe	70	19	1 : 8.9	89
16	PhMe	70	6	1 : 15.7	96
17	PhMe	70	6	1 : 13.3	95
18	PhMe	70	8	1 : 11.1	95

[a] *t*-BuLi used
[b] 2.5eq TMEDA used
[c] *s*-BuLi used

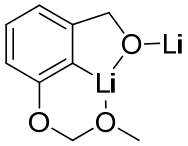
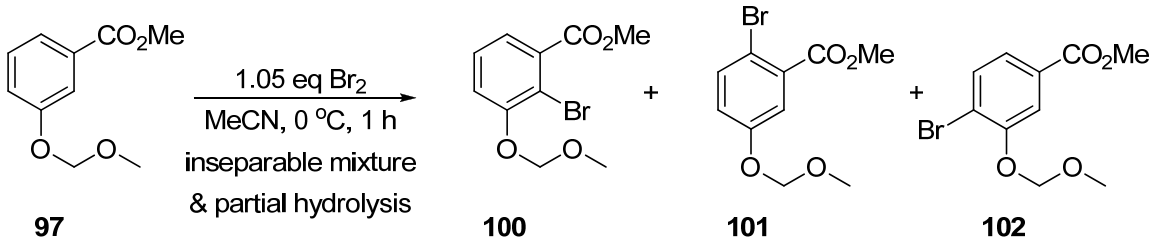


Figure 14. Possible Model for Lithium Cation Stabilization

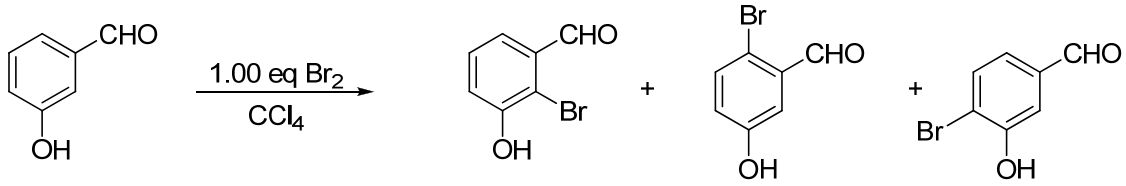
A normal bromination attempt of the commercially available ester **97** was made (Scheme 33). This procedure was based on one for a very different substrate.[29] Here methyl ester **97** was transformed into bromides **100**, **101**, and **103** as an inseparable mixture. Hydrolysis of the MOM-group was also observed due to the HBr formed *in situ*. This bromination route was abandoned due to previous success of the *ortho*-lithiation procedure.



Scheme 33. First Generation Phenol Synthesis: Failed Bromination Attempt 1

The de Koning group claimed in 2004 that only the desired regioisomer **104** was isolated from their optimized bromination procedure using aldehyde **103**. It seems that regioisomer **104** is in slight excess relative to the other two regioisomers **105** and **106**. However, in the report by de Koning, they were able to filter off the desired regioisomer cleanly and in as much as 50% isolated yield. [30] This was not the case in any of our attempts and **104** could not be separated from **105** and **106** as shown in Table 13.

Table 13. First Generation Synthesis: Failed Bromination Attempt 2

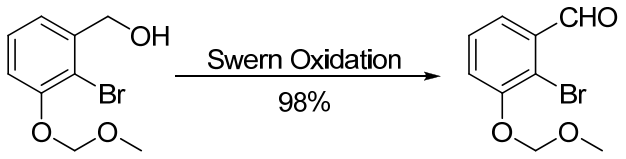


103 **104** **105** **106**

Entry	Solvent	Temp. (°C)	Time (h)	Ratio 103 : 104 : 105 : 106
1	CCl_4	25	2	2.0 : 3.2 : 1 : 2.0
2	CCl_4	25	16	*decomposition*[a]
3	CCl_4	25	72	5.3 : 2.6 : 1.5 : 1
4	CCl_4 : DCM[b]	25	4	1.4 : 1.7 : 1 : 0

[a] No products were observed in the crude NMR
[b] 10:1 mixture

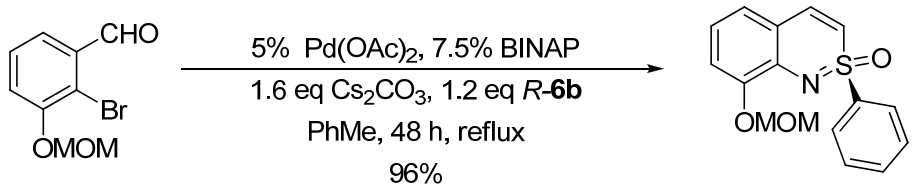
The next step to get to the bromoaldehyde precursor needed for the Buchwald Hartwig *N*-arylation step was the oxidation of benzyl alcohol **107** to benzaldehyde **108**. The oxidation method selected was the Swern oxidation, which afforded **108** in 98% yield (Scheme 34). A clean mixture of brominated alcohol and unbrominated alcohol could be oxidized and carried forward since the benzothiazine and unbrominated aldehyde have distinctly different polarities and could be separated by chromatography.



107 **108**

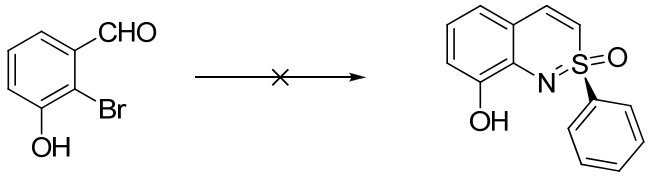
Scheme 34. First Generation Phenol Synthesis: Swern Oxidation of **107** to **108**

The key step, the Buchwald Hartwig *N*-arylation, was the next step in the synthesis. Using standard conditions, the reaction proceeded smoothly in 96% yield (Scheme 35). The reaction failed if the MOM-protecting group was not present even when excess base employed (Scheme 36).



108 **109**

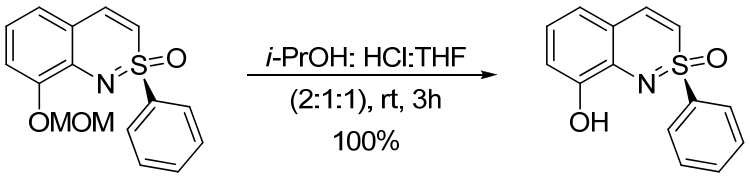
Scheme 35. First Generation Phenol Synthesis: *N*-Arylation of MOM-Protected Phenol



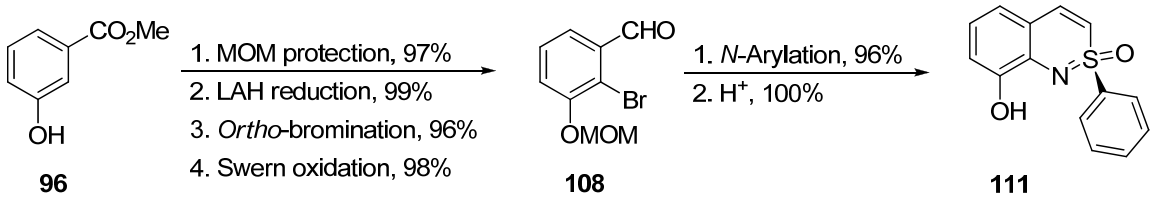
110 **111**

Scheme 36. First Generation Phenol Synthesis: Failed *N*-Arylation of Phenol

Completion of the synthesis was achieved by deprotecting the MOM-acetal protecting group under very acidic conditions to give the free phenol benzothiazine **111** in quantitative yield (Scheme 37). This completed the first generation synthesis of desired enantiomerically pure 8-hydroxy-2-*S*-oxa-2-*S*-phenyl-2,1-benzothiazine **111**. A summary of the first generation synthesis is shown in Scheme 38.



Scheme 37. First Generation Synthesis: MOM-Group Deprotection



Scheme 38. First Generation Synthesis: Summary

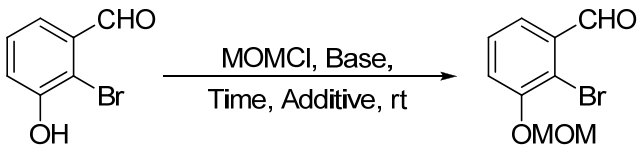
2.1.2 **Second Generation Synthesis of a Hydroxy Benzothiazine**

Soon after the completion of the first synthesis, compound **103** was commercially synthesized. Many grams of **103** were donated for research purposes to our group by Frontier Scientific. With this commercially available intermediate, a second generation synthesis was undertaken, reducing the step count to **109** by three. Since the free phenol would not take part in the *N*-arylation, it was important to protect the phenol without modifying the aldehyde and adding more synthetic steps. Thus MOM-protection seemed logical. A summary of results is provided in Table 14.

Only two bases were examined, NaH was tested first. In DMF, the reaction was very poor (Table 14, entry 1). By switching to THF and adding NaI, the reaction improved greatly. In 3 hours, **108** was isolated in 96% yield (Table 14, entry 2). This reaction was very exothermic on a large scale. Thus attention was drawn to TEA as base. Five equivalents of this weaker amine base were needed to obtain a near quantitative conversion in less than 3 hours with a twofold excess of MOMCl in THF (Table 14,

entries 3-5). The best synthesis included 5% NaI in THF in addition to TEA, affording **108** in 99% yield (Table 14, entry 6).

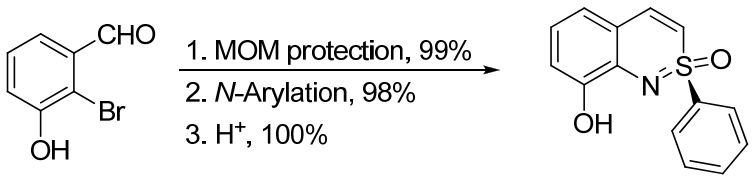
Table 14. Second Generation Synthesis: MOM-Group Protection



110 **108**

Entry	MOMCl (equiv.)	Base (equiv.)	Solvent	Additive (equiv.)	Time (h)	Yield (%)
1	1.1	NaH; 1.2	DMF	---	1	38
2	2	NaH; 2.5	THF	NaI; 0.5	3	96
3	2	TEA; 5.0	PhMe:THF	NaI; 0.5	1	92
4	2	TEA; 5.0	THF	NaI; 0.5	1.5	94
5	2	TEA; 5.0	THF	NaI; 0.05	2	93
6	2	TEA; 5.0	THF	NaI; 0.05	3	99

With a new more expedient synthesis to the key bromide **108**, the ease of preparing phenol **111** in a faster 3 step route makes it much more attractive as an attainable enantiopure ligand for asymmetric catalysis. This improved synthesis is now more economical and very direct. The second generation synthesis is summarized in Scheme 39.



110 **111**

Scheme 39. Second Generation Synthesis: Summary

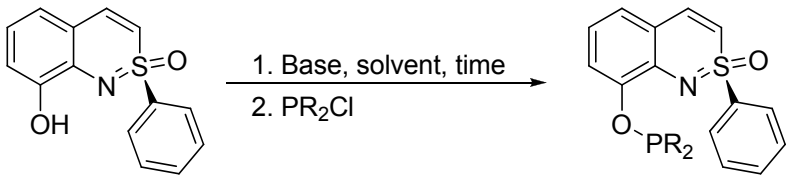
2.2 Preparation of Benzothiazine-Based Ligands

2.2.1 Attempts to Synthesize a *P,N*-Benzothiazine Ligand

With the phenol functional group now unprotected, it could be utilized as a nucleophile in the presence of base. The phenoxide could be trapped by various phosphine chlorides to produce *P,N*-benzothiazine based ligands (Table 15). In short, all attempts to react the phenolic nucleophile with a phosphine chloride gave excellent and often quantitative conversion to crude product. In all cases, the use of degassed solvents, oxygen-free silica gel, and oxygen-free alumina gave only recovered phenol **111** in excellent recoveries (Table 15, entries 1-6, 13-18).

Various phosphorus trapping reagents were used to determine if the structure of the phosphorus group could prevent product decomposition, but there was no observable difference (Structures of A and B are provided in Figure 15). Bulkier substituents on phosphorus afforded poor conversions (Table 15 entries 17, 18). To date there has been no successful attempt to isolate the free phosphino *P,N*-benzothiazine ligand from this series. Attempts to trap the crude material with transition metal salts gave no isolable product (Table 15, entries 7-12, 15-18).

Table 15. Attempts Toward *P,N*-Benzothiazine Ligands



111 **112**

Entry	Base (eq)	Solvent	Temp. (^{o}C)	Time (h)	R	Conv. (%)	Isolated Yield (%)
1	TEA (2.1)	THF	0	3	Ph (2.0)	---	>95 rsm

2	TEA (2.2)	PhMe	115	18	Ph (2.0)	34	>95 rsm
3	pyr (1.1)	ether	0	18	OPh (1.0)	28	>95 rsm
4	pyr (1.1)	DCM	25	72	OPh (1.0)	78	>95 rsm
5	*n*-BuLi (1.1)	THF	-78	18	A (1.05)	>95	>95 rsm
6	*n*-BuLi (1.1)	THF	-78	18	Ph (1.05)	>95	>95 rsm
7	*n*-BuLi (1.1)	THF	-78	18	Ph, Pd[a] (1.05)	black ppt	---
8	*n*-BuLi (1.1)	THF	-78	18	A, Pd[a] (1.05)	black ppt	---
9	*n*-BuLi (1.1)	THF	-78	18	Ph, Pd[b] (1.05)	black ppt	---
10	*n*-BuLi (1.1)	THF	-78	18	Ph, Pd[b] (1.05)	black ppt	---
11	*n*-BuLi (1.1)	THF	-78	18	Ph, Ir[c] (1.05)	black ppt	---
12	*n*-BuLi (1.1)	THF	-78	18	A, Ir[c] (1.05)	black ppt	---
13	TEA (5.0)	PhMe	80	48	*t*-Bu (1.0)	---	>95 rsm
14	TEA(5.0)	PhMe	80	48	*i*-Pr (1.0)	---	90 rsm
15	*n*-BuLi (1.1)	THF	-78	18	*t*-Bu, Ir[c] (1.0)	---	96 rsm
16	*n*-BuLi (1.1)	THF	-78	18	*i*-Pr, Ir[c] (1.0)	---	92 rsm
17	*n*-BuLi (1.1)	THF	-78	18	B[d] (1.0)	---	61 rsm
18	pyr (5.0)	PhMe	115	24	B[d] (1.0)	---	94 rsm

[a] Crude material trapped with $Pd(OAc)_2$
[b] Crude material trapped with $[Pd(allyl)Cl]_2$
[c] Crude material trapped with $[Ir(cod)Cl]_2$
[d] Crude material trapped with $[Pd(allyl)Cl]_2$; $[Ir(cod)Cl]_2$; $NiCl_2$; $CuCl_2$; $ZnCl_2$

Hydrolysis was deemed responsible for the decomposition of products to very clean recovered starting material. It seems the sulfoximine nitrogen may act as a weak base and provide a catalyst for hydrolysis during chromatography or workup. A proposed mechanism of decomposition is provided in Figure 16.

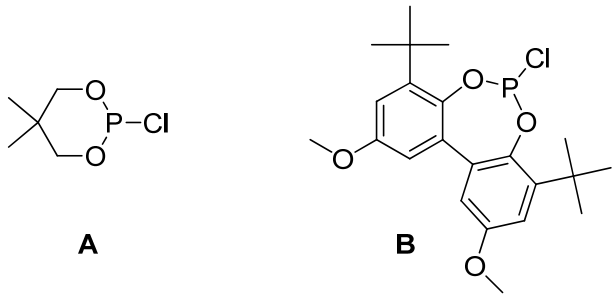


Figure 15. Phosphites Used In Attempts to Synthesize *P,N*-Benzothiazine Ligands

To test the validity of this hypothesis, it was necessary to do a model reaction to see if hydrolysis was partly due to imperfect techniques or if it was, indeed, a benzothiazine specific substrate problem. Therefore, a somewhat bulky phenol was selected that lacked an adjacent nitrogen. Phenol **113** was reacted with phosphite A to give **114** in excellent yield. This compound was subjected to the same workup and silica gel chromatography techniques as used in the previous study (Scheme 40). Partial oxidation of the product prevented clean isolation; however, hydrolysis was not seen. This provides some evidence that the benzothiazine structure is likely the problem, not the chemistry being investigated.

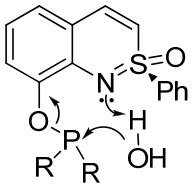
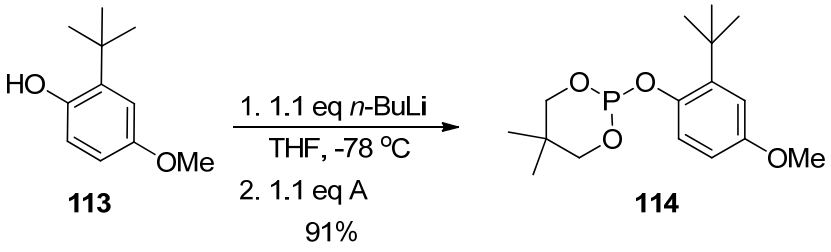
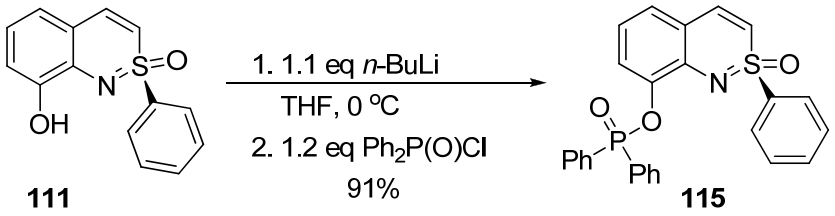


Figure 16. Possible Mechanism of Hydrolysis



Scheme 40. Model Reaction to Test Phosphite Hydrolysis

With the hope that P(V) compounds would be virtually inert towards both oxidation and hydrolysis, P(V) compound was prepared to see if this P(V) compound would be stable under the same conditions and methods as the previous P(III) compounds. Rather than trapping with a phosphine chloride, diphenylphosphinic chloride was used as the electrophilic trap. Thus, phenol **111** was treated with *n*-BuLi and the resultant phenoxide was trapped by a P(V) chloride (Scheme 41). The product was isolated cleanly and in excellent yield using the same workup and chromatrographic techniques used previously on P(III) compounds. No attempts to reduce the P(V) to P(III) were made; instead a synthesis of a benzyl alcohol analog was undertaken and this is presented in the next section.



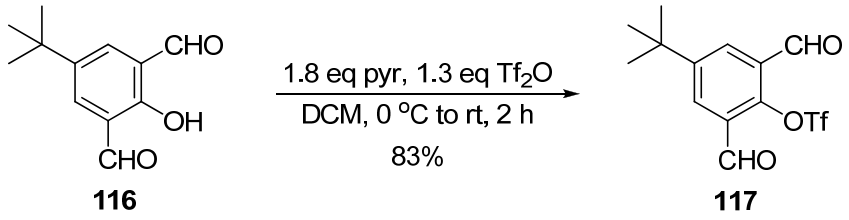
Scheme 41. Synthesis of a *P*(V),*N*-Benzothiazine

2.2.2 **Synthesis of a Benzyl Alcohol Benzothiazine**

One method that could slow the rate of hydrolysis of these phosphorous compounds would be to change the leaving group. Rather than have a phenoxide leaving group (pK_a of 8-10) a benzyl alcohol would allow for an alkoxide leaving group (pK_a of 16-18). With a benzyl alkoxide as the possible leaving group, the rate of hydrolysis should in principle be slowed if not stopped altogether.

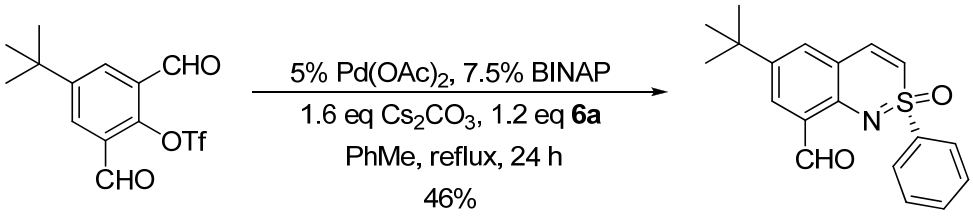
The synthesis began with commercially available dialdehyde **116**. This was treated with triflic anhydride in the presence of pyridine to give an 83% yield of triflate **117** (Scheme 42). Triflate **117** was treated under normal Buchwald-Hartwig coupling

conditions to give benzothiazine **118** in only 46% yield (Scheme 43). Aryl triflates act much like aryl iodides in that they are both relatively sluggish in palladium-catalyzed *N*-arylations, as demonstrated by Bolm and coworkers.[8] Keep in mind also that the condensation that takes place produces a molecule of water per molecule of benzothiazine formed. Triflates are sensitive to hydrolysis and no attempts to remove water via molecular sieves or drying reagents were employed in this model study. Subsequent reduction of aldehyde **118** with DIBAL gave benzyl alcohol **119** in near quantitative yield (Scheme 44). This completed the synthesis of **119**.



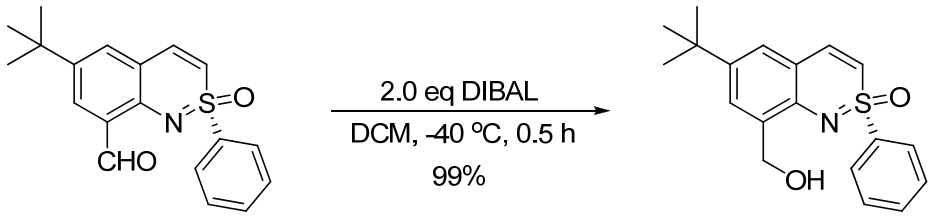
116 **117**

Scheme 42. Synthesis of Triflate *N*-Arylation Partner **117**



117 **118**

Scheme 43. Synthesis of Benzyl Alcohol Benzothiazine Precursor **118**



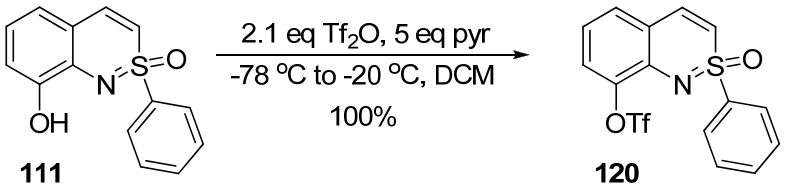
118 **119**

Scheme 44. Synthesis of Benzyl Alcohol Benzothiazine **119**

This synthesis was not taken further, and the synthesis, namely, the coupling step was not optimized. This will be a starting point for future investigations into the stability of phosphorous-based benzothiazine compounds of this nature. All in all, this is a quick route to another potentially useful and unique benzothiazine scaffold. This benzothiazine parent could be highly functionalized before and after reduction of aldehyde **118**. This feature gives tunability to the ligand structure if needed to enhance enantioselectivity in asymmetric reactions.

2.2.3 **Synthesis of a Triflate-Substituted Benzothiazine Coupling Partner**

In order to utilize the phenol functional group of benzothiazine **111**, triflate **120** was prepared. Phenol **111** was reacted with triflic anhydride in the presence of excess pyridine to give triflate **120** in quantitative yield (Scheme 45). This provides an expedient route to utilize the hydroxy benzothiazine scaffold as a coupling partner. Due to the sluggish reactivity of triflates presented earlier, very few attempts to expand upon this coupling partner have been investigated to date. As a result, a chloride analog was prepared and is the topic of the next section.



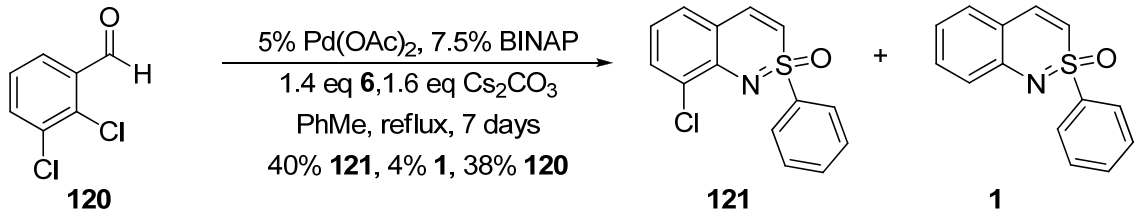
111 **120**

Scheme 45. Synthesis of Triflate **120**

2.2.4 **Synthesis of a Chloro-Substituted Benzothiazine Coupling Partner**

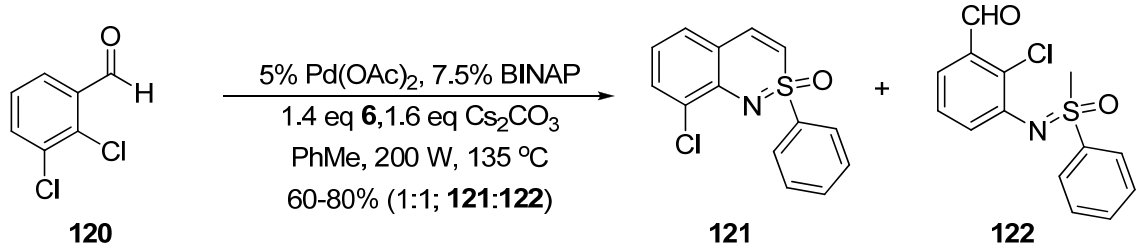
A one-step, one-pot procedure to prepare a similar coupling partner would be more efficient than the multistep synthesis of the previous triflate. However, commercially available 2,3-dichlorobenzaldehyde **121** reacted sluggishly in the

palladium-catalyzed *N*-arylation (Scheme 46). A very modest 40% yield of **121** was isolated alongside 38% of recovered starting material **120**. A small amount of dechlorinated product was observed (4% of **1**).

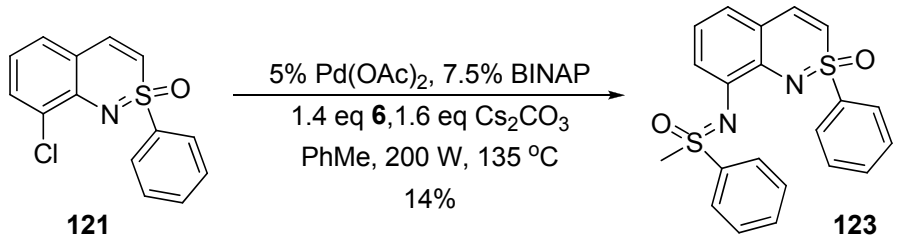


Scheme 46. Synthesis of 8-chlorobenzothiazine **121**

Attempts have also been made to obtain reasonable yields of **121** via microwave irradiation of dichlorides by the Harmata group in 2007. Under these conditions, a 1:1 mixture of **121** and **122** was observed (Scheme 47). Expanding upon this methodology, Harmata and coworkers coupled chloride **121** with sulfoximine **6** under the conditions of microwave irradiation to afford benzothiazine **123** albeit in only 14% yield (Scheme 48).



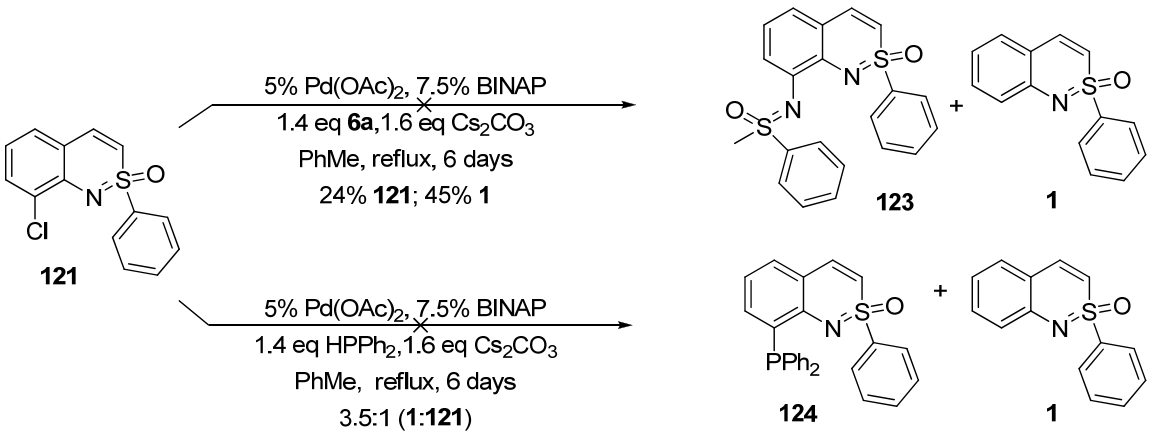
Scheme 47. Microwave Irradiation of 2,3-Dichlorobenzaldehyde



Scheme 48. Microwave Irradiation of Chloride **121**

Benzothiazine **123** was prepared from chloride **120** as described later in Chapter 3. The problem, in this example, arises in the coupling of an additional sulfoximine once the benzothiazine scaffold is intact.[31] This mirrors the problem that Bolm and coworkers experienced in the synthesis of bissulfoximine **31**.[14] Many improvements in the synthesis of **123** were the focus of the research presented next in Chapter 3.

An attempt to prepare **123** in a thermal process was not successful; dehalogenation was observed (45%) along with recovered starting material (24%) over a period of 6 days in refluxing toluene. An attempt to couple **121** with diphenylphosphine in the presence of base also failed and *P,N*-ligand **124** was not observed. Dehalogenation was seen and **1** and **121** were observed in a ratio of 3.5:1. In both cases, the desired product was not seen even in trace amounts (Scheme 49).

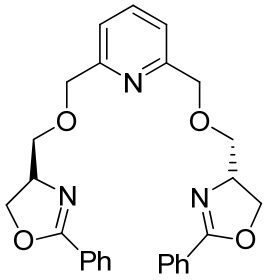


Scheme 49. Attempts to Couple Benzothiazine **121**

2.2.5 **Synthesis of Pyrido-Bridged Benzothiazine Heterocycles**

Our attention was drawn toward making larger heterocycles containing one or more benzothiazines. This would be a methodology toward potential *N,N*-benzothiazine-based ligands or multidentate heterocyclic ligands. This investigation was inspired by the interesting helical nonracemic structure of pentadentate bis(oxazoline) ligand **125** by the Reiser and coworkers (Figure 17). A similar synthesis was then undertaken in order to

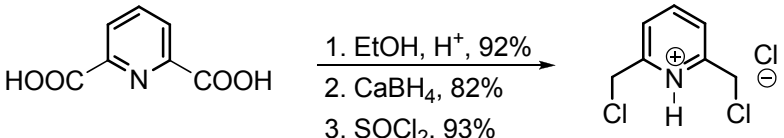
see if benzothiazine heterocycles of this type would give similar chiral helices in the crystal structure of the resultant metal complexes.[32]



125

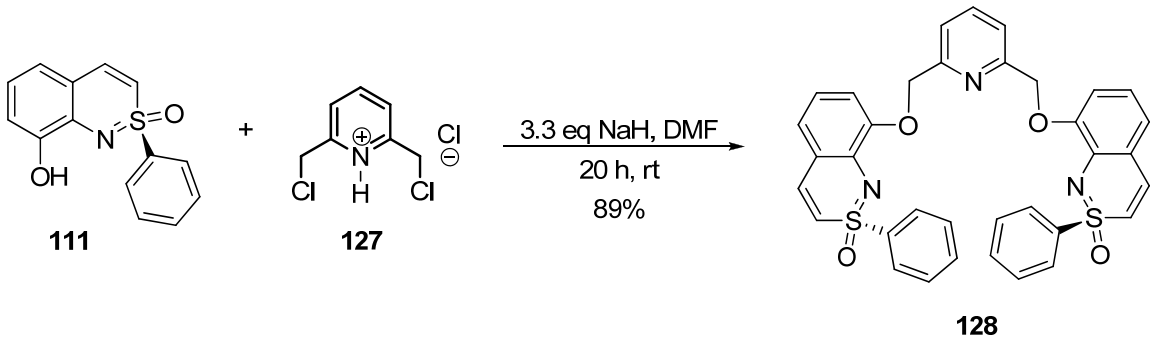
Figure 17. Pentadentate Bis(oxazoline) Ligand by Reiser and Coworkers

The synthesis began with the preparation of the pyridine bridge starting with dicarboxylic acid **126**. First, Fischer esterification of diacid **126** to the corresponding dimethyl diester proceeded in 92% yield.[33] Subsequent reduction of both ester functional groups with $CaBH_4$ gave the corresponding diol in 82% yield.[34] The diol was taken further to give the pyridyl dihydrochloride salt **127** in 93% yield using $SOCl_2$ (Scheme 50).[35] With this fragment in hand, the pentadentate heterocycle bisbenzothiazine **128** was prepared in 89% yield when NaH was used as base in DMF at room temperature (Scheme 51). This ligand was tested against a variety of metals in order to observe its conformation in a crystal lattice structure (Table 16).



126 **127**

Scheme 50. Synthesis of Pyridyl Dihyrochloride Salt **127**

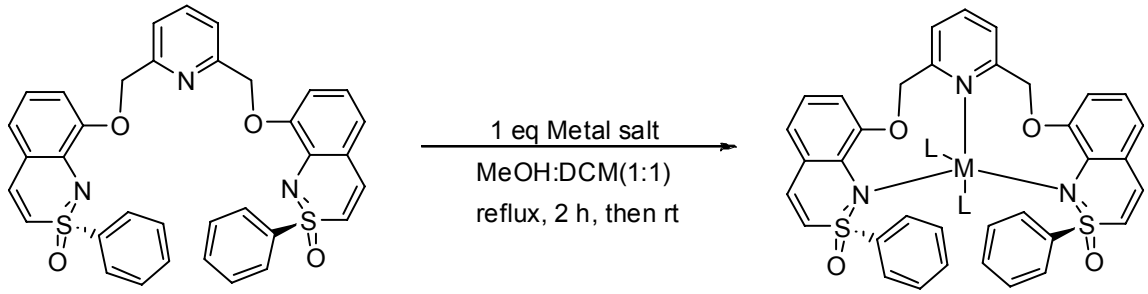


111 127 128

Scheme 51. Synthesis of Pentadentate Bisbenzothiazine **128**

Of all the metals tested, only a CdI_2 X-ray quality crystal was isolated and analyzed by X-ray crystallography. Although not entirely unexpected, the metal bound in a bidentate fashion. The steric environment of both benzothiazines, bound to a metal requires nearly an overlap of the sulfoximine oxygen from each of both benzothiazines which may be the reason why the solids that were prepared did not readily form crystals. The entropy associated with the freely floating "arm" of the heterocycle did not allow for a tightly packed crystal lattice resulting in insoluble precipitates in nearly all cases. The X-ray crystal structure of **129a** is shown below in Figure 18.

Table 16. Metal Ligand Study of Pentadentate Bisbenzothiazine **128**



128 129

Metal	Result[a]
$CdCl_2$	Brown solid
CdI_2	Yellow needles, 84%

CuI	Off-white solid
$ZnCl_2$	Light-yellow solid
$CuCl_2$	Yellow-green solid
$Cu(ClO_4)_2$	Off-white solid[c]
$ZnSO_4$	Transparent solid
$CuSO_4$	Transparent solid
$AlCl_3$	No reaction
$CuSO_4$	Blue-green solid
$Co(OAc)_2$	Pink solid
$FeCl_3$	No reaction
$PdCl_2$	Yellow-green solid
$Pd(OAc)_2$	Black solid
ZnI_2	White solid
$Ni(acac)_2$	White solid
$[Pd(allyl)Cl]_2$	No reaction
$Hg(OAc)_2$	Brown solid
$Pb(ClO_4)_2$	Dark brown solid[b]
$HgCl_2$	Brown solid
$CeCl_3$	Brown oil
$AuCl_3$	Black oil

[a] Appearance when cooled to rt under N_2.
[b] Reaction was not heated.

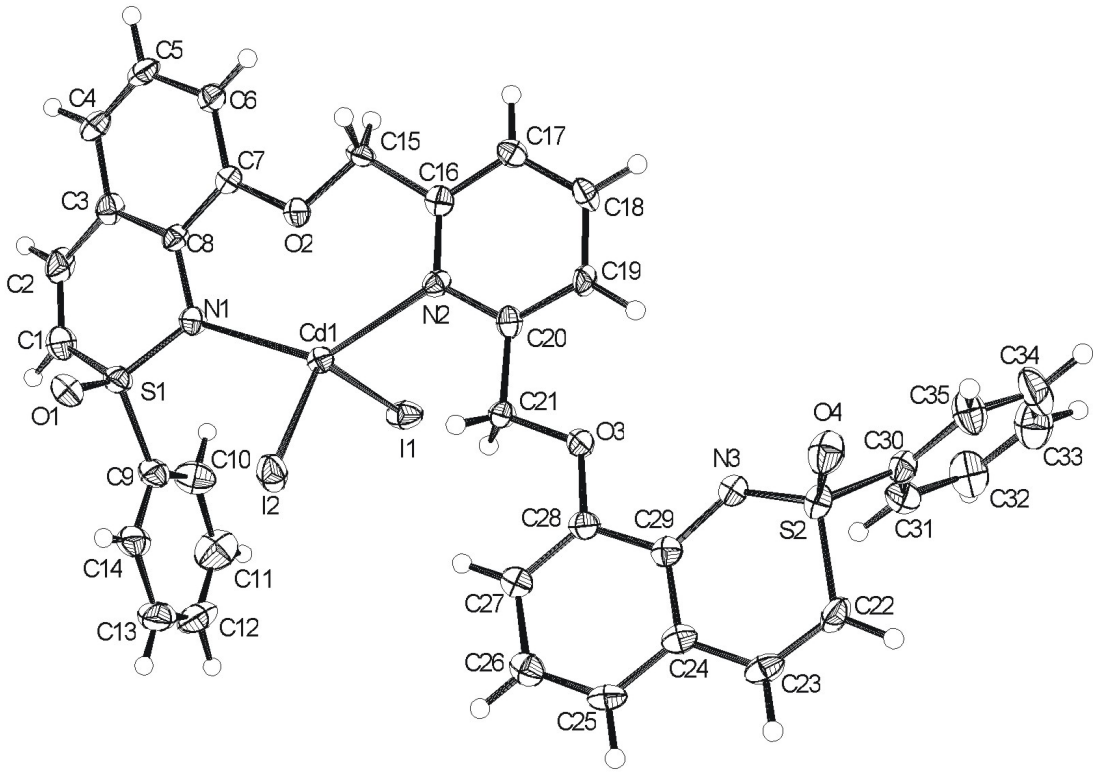
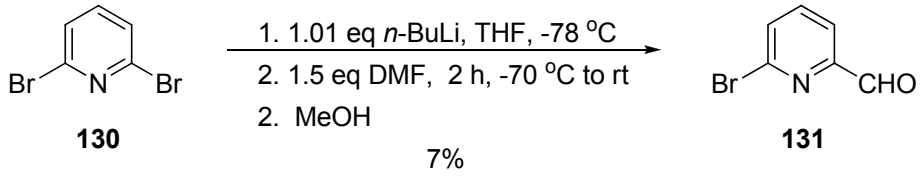


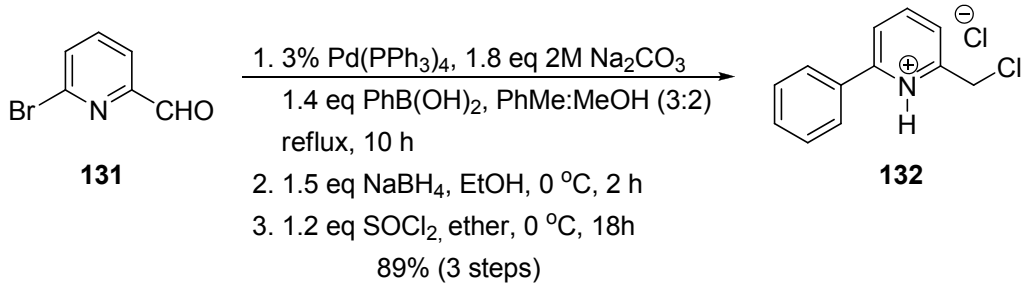
Figure 18. Crystal Structure of Tridentate Cd Complex **129a**

As a result, our attention was directed to a similar version of the same ligand but now with a phenyl group in place of one of the two benzothiazine ether bound arms. The synthesis of such a molecule required a new pyridyl fragment containing a phenyl substituent in the 6-position rather than the symmetrical 2,6-dimethylchloride **127**. This synthesis began with commercially available 2,6-dibromopyridine **130**, which upon treatment of *n*-BuLi gave a monolithio species. The resulting lithium species was trapped with dimethylformamide to give bromoaldehyde **131** upon acidic workup. This reaction proceeded in only 7% yield (Scheme 52).[36] The next three steps could be conducted with a single purification step at the end of the sequence that allowed isolation of **133** in 89% yield over 3 steps. The second synthetic step, first step of this three step sequence, was the known Suzuki coupling.[37] The resultant aldehyde was reduced by $NaBH_4$ to give the

corresponding primary alcohol. The final step was conversion of the primary alcohol into the chloromethylpyridine hydrochloride salt **132** (Scheme 53).[38]

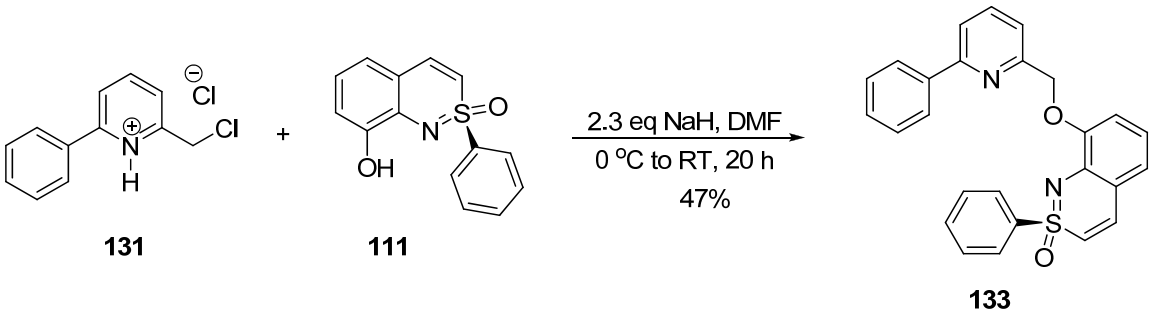


Scheme 52. Synthesis of Bromoaldehyde **131**



Scheme 53. Three-step Synthesis of Methylchloropyridine Hydrochloride **132**

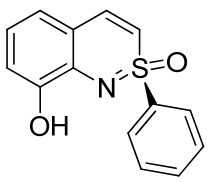
This synthesis of **133** was not extensively optimized. The best isolated yield on a relatively small scale was a modest 47% yield of **133** (Scheme 54). Neither TEA nor KH promoted any reaction. NaH at cold and room temperatures allowed for the best observed yields. At 60 °C or at temperatures of >140 °C yields reduced dramatically. No metal studies have been investigated with this ligand to date due.



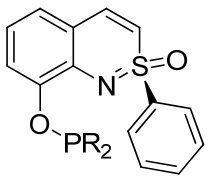
Scheme 54. Synthesis of Bidentate *N,N*-benzothiazine Ligand **133**

2.2.6 **Summary of Benzothiazine Based Ligands Prepared**

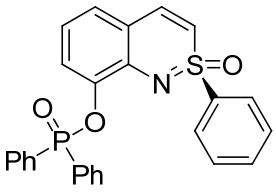
A variety of 2,1-benzothiazines have been prepared. In many cases, the synthesis shown has been optimized to provide excellent yields of the desired ligand. A summary of the benzothiazine-based ligands are shown below in Figure 19. The *N,O*-benzothiazine ligand **111** was prepared in 97% overall yield over three steps via its optimized second generation synthesis. Previously, **111** was prepared in 6 steps in 87% overall yield in its first generation synthesis. Derivatives of **111** of generic structure **112** were prepared. These ligands would need to be used without purification, as they appear to be unstable. *P(V),N*-benzothiazine ligand **115** can be made in 4 steps in 88% overall yield and stable. *N,O*-benzothiazine ligand **119** can be made in 3 steps in 38% overall yield. Optimization of the triflate coupling step (46%) would greatly improve the overall yield of **119**. *N,N*-benzothiazine ligand **123** can be produced in 2 steps in only 11% overall yield. Lastly, multi-dentate heterocycles **128** and **133** were prepared in a convergent fashion in 86% and 46% overall yields, respectively. With a quick route to these ligands available, a large stock of material can be prepared in an expedient manner. The ligands presented herein can be surveyed in many asymmetric reactions.



Linear Synthesis
111, 3 steps, 97% overall



Linear Synthesis
112, 4 steps, 92% crude



Linear Synthesis
115, 4 steps, 88% overall

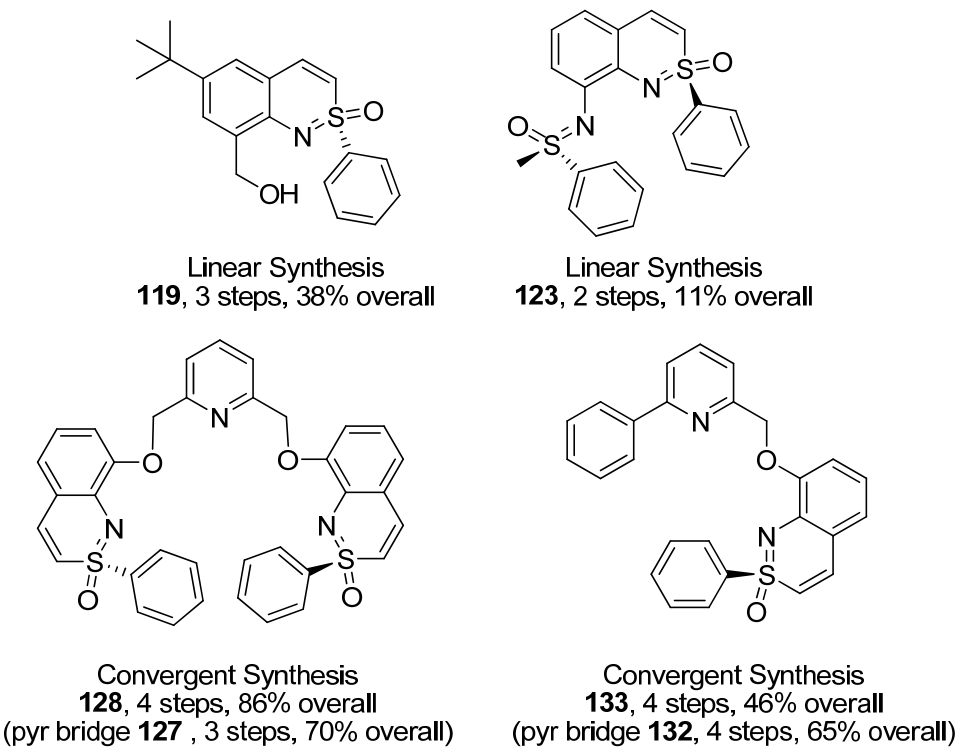


Figure 19. Summary of Benzothiazine Ligand Syntheses

CHAPTER 3

Syntheses and Optimization of Sulfoximine-Containing Ligands

In order to further synthetic developments of sulfoximine *N*-arylation, a new optimization of the very well known palladium-catalyzed system was undertaken. The goal of the following optimization was to improve the previously known method. This procedure was found to tolerate air and be robust for a variety of substrates. The optimized synthesis considerably improved the thermal synthesis of **123** from 2,3-dichlorobenzaldehyde **120**.

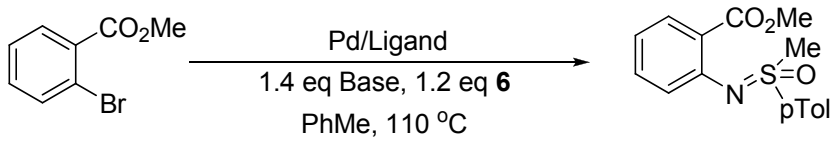
3.1 Previous Palladium Catalyzed *N*-Arylation Developments

3.1.1 Initial Optimization in 1998 by Bolm

As described previously, the first *N*-arylation of a sulfoximine with various aryl bromides was reported in 1998 by the Bolm Group.[6] The use of chelating bisphosphines was deemed crucial in order to obtain products in acceptable yields. The optimization began from methyl 2-bromobenzoate **20** and *S*-methyl-*S*-phenylsulfoximine **6** (Table 17). Four ligands were examined: P(*o*-tolyl)$_3$, a bulky monodentate phosphine; BINAP and Tol-BINAP, chelating binapthyl based bisphosphines; and dppf, a ferrocenyl based chelating bisphosphine (structures provided previously in Chapter 1). The ferrocenyl ligand dppf, with either Pd_2dba_3 or $Pd(OAc)_2$, failed to produce more than trace amounts of product (Table 17, entries 1 and 2). The use of $PdCl_2$(dppf)/dppf gave 87% yield of the desired product in 48 hours (Table 17, entry 7). The best results occurred with the use of BINAP and Tol-BINAP which gave 92% and 96% yield, respectively, over 48 hours (Table 17, entries 5 and 6). Only 2 bases were examined, cesium carbonate and

sodium *tert*-butoxide. Of those bases, the weaker cesium base gave rise to slightly higher yields (Table 17, entries 3 and 4).[6]

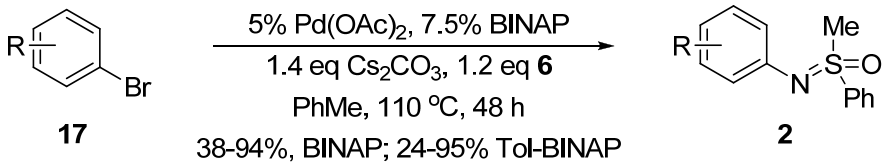
Table 17. 1998 Optimization of Pd-catalyzed *N*-Arylation



16 **17**

Entry	Pd/Ligand	Pd (%)	Ligand (%)	Time (h)	Base	Yield (%)
1	$Pd(OAc)_2/P(o\text{-}tol)_3$	4	6	36	Cs_2CO_3	< 4
2	$Pd_2dba_3/P(o\text{-}tol)_3$	4	6	36	Cs_2CO_3	< 4
3	$Pd(OAc)_2$/BINAP	4	6	36	Cs_2CO_3	82
4	$Pd(OAc)_2$/BINAP	4	6	36	NaO^tBu	76
5	$Pd(OAc)_2$/BINAP	5	7.5	48	Cs_2CO_3	92
6	$Pd(OAc)_2$/Tol-BINAP	5	7.5	48	Cs_2CO_3	96
7	$PdCl_2(dppf)$/dppf	5	20	48	Cs_2CO_3	87

The reaction scope was expanded with BINAP and with Tol-BINAP (Scheme 55). R groups examined were: 2-CN, 4-CO_2Me, 4-*t*-Bu, and H. All yields were above 72% for all cases except when R = 4-*tert*-Bu and the yields fell considerably to 24% for Tol-BINAP and 36% for BINAP.[6]



17 **2**

Scheme 55. Generalized Summary of Aryl Bromides Investigated in 1998

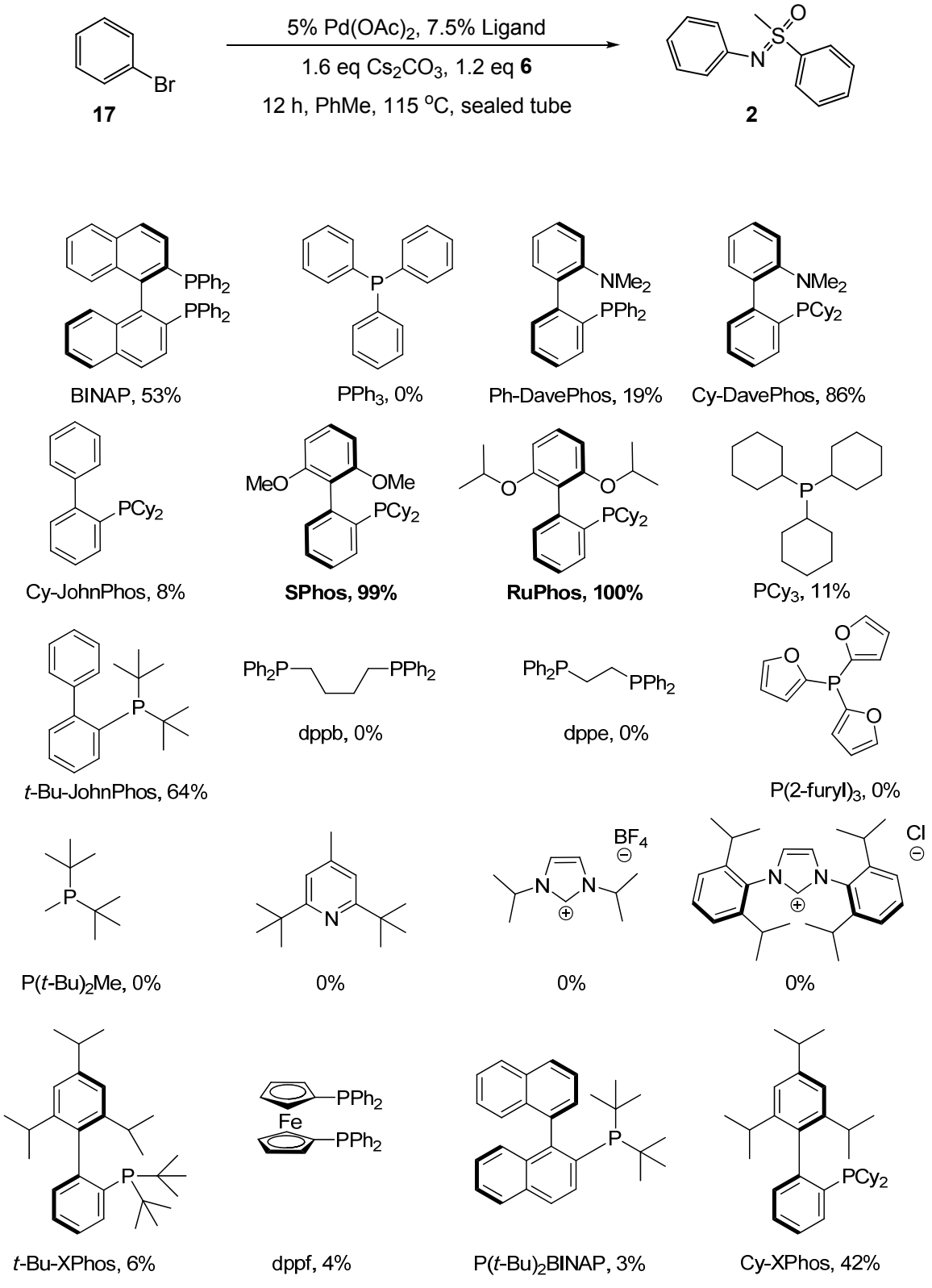
3.1.2 **1998 to Present *N*-arylation Overview**

Since 1998, a few attempts to improve or modify this synthesis have been reported. Namely, the use of Pd_2dba_3 and NaO^tBu in the synthesis of bissulfoximines **31** by the Bolm group[8] and microwave irradiation by the Harmata group, as discussed previously in Chapter 1, were reported.[7,31] The optimization results shown above are by no means comprehensive. However, newer syntheses have been reported using metals other than palladium including copper-based[9,10] and iron-based[11] *N*-arylations that have been described in some detail in Chapter 1. A more comprehensive evaluation of the palladium catalyzed *N*-arylation will be described in the remainder of this chapter.

3.2 Optimization of the Pd-based *N*-arylation of Sulfoximine and Bromobenzene 17

3.2.1 **Ligand Study**

The optimization began with the purchase of Sigma-Aldrich biphenyl phosphine ligand kits alongside a variety of in house ligands. The goal was to survey which ligand or ligand family would give the highest yield of *N*-arylated product in the course of 12 hours. Investigating many ligand types would either prove or disprove the idea that chelating bisphosphines were truly the only ligands able to achieve acceptable yields. We were curious if modern advances in ligand design over the past decade could reduce reaction time while increasing yield and catalyst turnover. The expansion of substrate scope was also of concern. Many ligand families were pursued: various mono- and bisphosphines, various binapthyl mono- and bisphosphines, various biphenyl phosphines, carbenes, and a bulky pyridine ligand. A summary of ligands examined with their structures and corresponding yields isolated are shown below in Scheme 56.



Scheme 56. Summary of Commercial Ligands Investigated

For referencing purposes, the trademark name is also given when available. The reaction was modeled initially on Bolm's 1998 procedure[6] except for a reduced time of 12 hours; all reactions performed were done so in sealed tubes at 115 ^{o}C unless otherwise noted. All the ligands were assumed to be of "commercial grade" and were not purified further nor checked for purity via NMR. This ligand study was pursued to give the most robust ligand, qualitatively, that could be extremely tolerable of an oxygen or "air" type environment. All reactants were weighed and added together in a one-pot fashion in an open sealed tube. Freshly distilled, oxygen-free toluene was used and also added in an open air environment. The reaction vessel was then capped, refluxed, and then stopped by a power outlet timer such that the same heating and cooling curves were used for all reactions.

All monodentate phosphines (PPh_3, P(2-furyl)$_3$, P(*t*-Bu)$_2$BINAP, and P(*t*-Bu)$_2$Me) failed to give any conversion of products according to crude NMR. Interestingly, electron rich PCy_3 did give some product, albeit only 11%. Bulky 2,6-di-*t*-butyl-4-methylpyridine and both *N*-heterocyclic carbene ligands failed to give any conversion of desired products. Alkyl bisphosphines (dppb and dppe) gave no product, and ferrocenyl based dppf gave only a trace amount of product (4%). Bulky biphenyl-based phosphine ligands did work, some better than others. The order of their reactivity is summarized by the following listed from best to worst: RuPhos > SPhos >> Cy-DavePhos > *t*-Bu-JohnPhos > BINAP > Cy-XPhos >> Ph-DavePhos > Cy-JohnPhos > *t*-Bu-X-Phos. A few assumptions can be made from the following study. Biphenyl ligands gave a large range in yield some excellent, some very poor. Thus, it appears that chelating bisphosphines may not be required in order to achieve excellent yields.

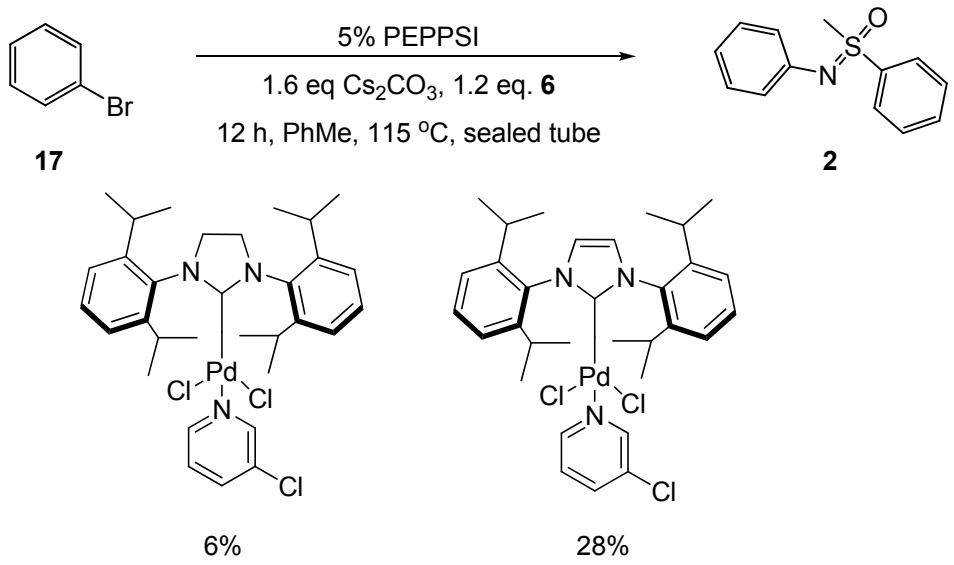
The presence of a nearby chelating N or O did greatly improve yields dramatically as shown with RuPhos. *P,N* bidentate ligands such as the DavePhos family also gave good yields up to 86% for Cy-DavePhos. Interestingly, a biphenyl monodentate ligand Cy-Xphos performed similarly to that of BINAP for this specific reaction.

Alkyl phosphines, being more electron rich than aryl phosphines, seemed to give substantially better yields. Once the phosphine becomes too electron rich, however, it can easily be oxidized by the oxygen in air and fail to catalyze the reaction. This is likely the reason why many of the electron rich phosphines did not perform well in the presence of air inside the sealed tube environment. All in all, this simplified approach gave way to a very robust and air friendly ligand metal system that performs very well for the *N*-arylation of bromobenzene **17** and sulfoximine **6** to give *N*-substituted sulfoximine **2**. Thus, a 100% yield of *N*-arylated product **2** was observed with RuPhos as the ligand in as little as 12 hours. In the 1998 synthesis reported by Bolm, 48 hours was required to afford a 74% yield with BINAP.[6] In all further optimization studies, RuPhos is typically used exclusively unless otherwise noted.

3.2.2 **PEPPSI Family Study**

Also tested were some precatalysts that the current literature cites as particularly favorable for *N*-arylation. The first example is the PEPPSI-carbene family. This ligand family was introduced in 2007 by the Organ group. Organ and coworkers found that metal complexes with PEPPSI ligands underwent facile oxidative addition due to the electron-rich nature of the ligand. They claimed the steric bulk of the adjacent substituents allowed for fast reductive elimination. Lastly, the very strong Pd-NHC bond

makes for an extremely stable species in a variety of conditions. The model reaction above was carried out with two version of the PEPPSI family donated by the Organ Group.[39] The reaction is summarized in Scheme 57.



Scheme 57. PEPPSI NHC Ligand Study

This ligand family displayed slow conversion to *N*-substituted sulfoximine **2**. The reaction never proceeded to completion as evidence by thin layer chromatography. Compared to biphenyl phosphine systems, the PEPPSI family provided a very poor yield of desired product **2** in the 12 hour reaction time length. Both saturated and unsaturated NHC were used and the yield of the unsaturated NHC was nearly 4 times the yield of the saturated version. No carbene ligands were pursued beyond this point.

3.2.3 **Bippyphos Ligand Study**

Recent attention has also been drawn to a pyrazole family of ligand first developed by Pfizer Global Research and Development in 2006. These ligands were known for the Pd-catalyzed coupling of primary and secondary amines to aromatic bromides. The optimized ligand was named bippyphos.[40] Later in 2009, the same ligand

was studied in the context of the substrate scope of Pd-catalyzed aminations using various ureas in the C-N amidation.[41] Several ligands of this family are shown in order of their development below in Figure 20.

With a generous donation of bippyphos from Abbot Laboratories, the same model reaction was examined in a 6 hour period and compared to that of a similar reaction with the best ligand shown above, RuPhos. This would allow a direct comparison of both ligand families for this particular reaction. The Pd source of choice for bippyphos reactions was Pd_2dba_3. A comparison of both ligands in the presence of Pd_2dba_3 in a period of 6 hours is shown in Scheme 58.

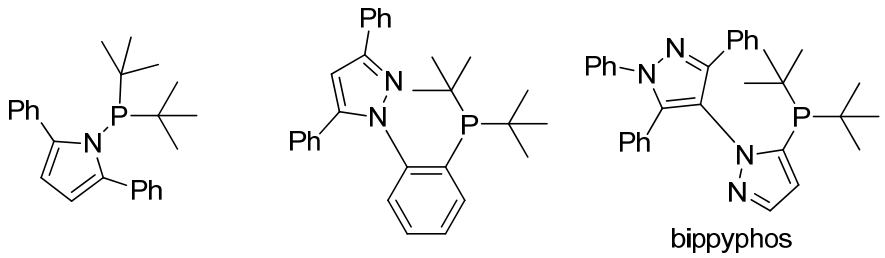
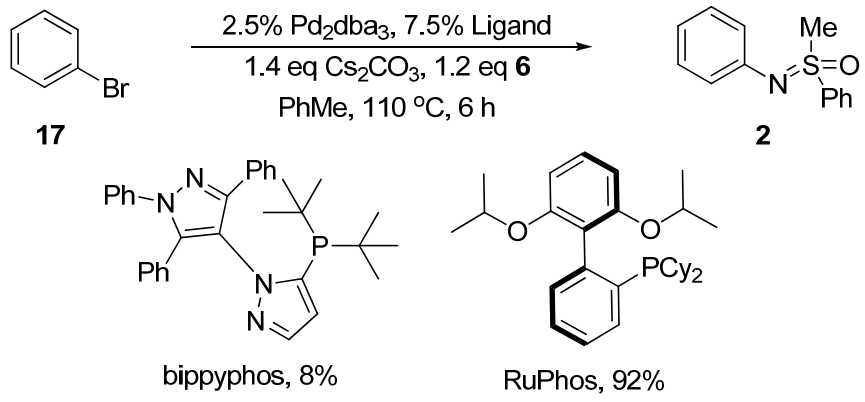


Figure 20. Nonproprietary Pyrrole, Pyrazole, and Bipyrazole Ligands



Scheme 58. Comparison of Bippyphos and RuPhos in an *N*-Arylation

As shown, the rate of *N*-arylation in 6 hours was much faster for RuPhos, a biphenyl phosphine ligand, compared to that of bippyphos, a bispyrazole phosphine, for C—N coupling of bromobenzene **17** and sulfoximine **6**. The isolated yield of **2** using

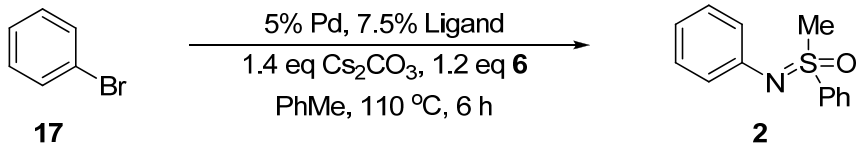
RuPhos was 92% with Pd_2dba_3 as the Pd source. This compares well with the procedure in which RuPhos was used with $Pd(OAc)_2$ to give **2** in 100% yield in twice the time as shown previously in Scheme 56. The next step in the optimization of this Buchwald Hartwig *N*-arylation reaction was finding the best Pd-source. Previously, a Pd(0) source improved the reaction rate to that of a Pd(II) source; this observation was explored.

3.2.4 **Pd Source Study**

Many palladium metal sources were tested in order to contrast their rate of reaction by comparison of their yields in a reduced time of 6 hours. Originally, Bolm prepared precatalysts of the ligand and metal sources. These precatalysts were prepared inside an anhydrous, oxygen free glove box.[6] In all the cases presented herein, all materials were added in one-pot with air. The hope was to find a robust oxygen tolerable system. A summary of the Pd sources examined are illustrated below in Table 18.

A few trends were apparent. Pd(0) sources tended to work better than Pd(II) sources. With $PdCl_2$, the cross coupling reaction went very smoothly in an acceptable yield of 71% (Table 18, entry 2). However, when the Cl^- anion was sequestered by precipitation of a scavenger such as $AgSbF_6$ the reaction yield dropped by 15% (Table 18, entry 3). This provides some evidence that the free Cl^- anion may be important in the reaction mechanism and or the palladium catalytic cycle; since the yield dropped noticeably when the Cl^- was precipitated out of the toluene solution as $AgCl_{(s)}$. No attempt to "spike" any reaction with a Cl^- source has been attempted to date. Interestingly, tetrakis $Pd(PPh_3)_4$ gave 61% yield (Table 18, entry 4). This suggests that RuPhos likely participated in ligand substitution to some extent as the PPh_3 ligand was shown earlier to not facilitate the formation of any product in 12 hours.

Table 18. Pd Source Summary



17 2

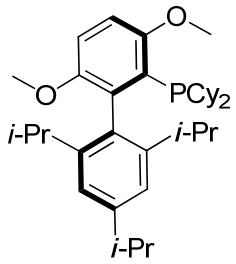
Entry	Pd Source	Ligand	Yield (%)
1	$Pd(OAc)_2$	RuPhos	55
2	$PdCl_2$	RuPhos	71
3	$PdCl_2$	RuPhos	56[a]
4	$Pd(PPh_3)_4$	RuPhos	61
5	Pd_2dba_3	RuPhos	92[b]
6	Pd_2dba_3	BrettPhos	57[b]

[a] 10% $AgSbF_6$ added
[b] 2.5% of Pd_2dba_3 added

BrettPhos (Figure 21) was shown by Buchwald and coworkers to outperform other biphenyl ligands such as RuPhos, SPhos, and XPhos as the most highly active amination cross coupling catalyst they have prepared to date for the Buchwald Hartwig *N*-arylation.[42] In this instance, RuPhos nearly doubled the product yield (92%) relative to that of BrettPhos (56%) (Table 18, entries 5 and 6).

Overall, this optimization of palladium sources provides some insight into the catalytic cycle that warrants further investigation. It appears that the presence of a chloride anion plays a role in the mechanism of *N*-arylation. This study reaffirms that Pd(0) does perform noticeably better than Pd(II) sources. This optimization was by no means comprehensive. In order to better understand the catalytic cycle, expanding the scope of palladium sources would be necessary. At this point in time, however, RuPhos

remained the best ligand of those tested when Pd_2dba_3 was used as the Pd source. A study of different bases was the next step in the *N*-arylation optimization.



BrettPhos

Figure 21. Structure of BrettPhos

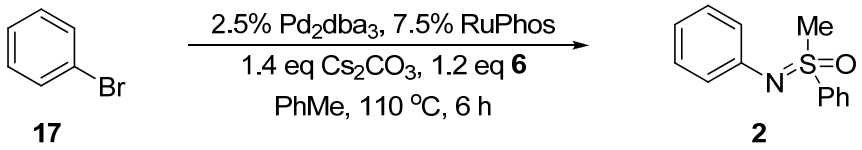
3.2.5 **Base Study**

The use of some bases in this study was somewhat counter productive. Most bases needed in amination reactions are anhydrous bases. So allowing the reaction to be run in high humidity and in the presence of oxygen will ultimately disqualify air sensitive bases and ligands. In order to be thorough, a variety of bases were examined and in a period of 6 hours, these bases were examined. The purpose of this study was to evaluate bases other than Cs_2CO_3. The results are summarized in Table 19.

Carbonate bases (pK_a = ~10) were the first to be investigated. Changing to a potassium or sodium cation resulted in drastically diminished yields (Table 19, entries 2 and 3). A similar trend was seen for anhydrous acetates (pK_a = ~5). The poor yield with CsOAc was likely due to its hygroscopic nature compared to less hygroscopic KOAc and NaOAc; in all cases the yields were poor (Table 19, entries 4-6). In Chapter 1, the use of a stronger base, NaO^tBu, circumvented reactivity issues. Thus it was not surprising that a base with a higher pK_a could help to afford a higher yield as in the case of bissulfoximines for the Bolm group.[8] As a result, higher pK_a bases are typically used in anhydrous conditions to minimize air and moisture sensitivity that can be detrimental to

their efficiency and lifetime in solution. Because no attempts to avoid oxygen or moisture were made, except for distilled toluene, higher pK_a bases would be expected to have diminishing results. Thus, as predicted, yields of K_3PO_4 (pK_a = ~12) and NaO^tBu (pK_a = ~20) were 47% and 79%, respectively (Table 19, entries 7 and 8).

Table 19. Optimization of Base Summary



17 **2**

Entry	Base	Yield (%)
1	Cs_2CO_3	92
2	K_2CO_3	11
3	Na_2CO_3	7
4	CsOAc	23
5	KOAc	28
6	NaOAc	2
7	K_3PO_4	47
8	NaO^tBu	79

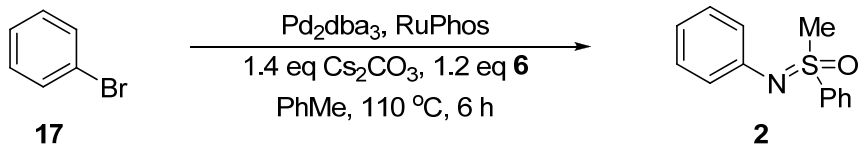
Overall, the mismatch in size of larger cations, Cs^+ to smaller oxygen based anions seems to allow for more efficient deprotonation as the base is likely more "naked" than if it were in the presence of smaller cations such as K^+ or Na^+. As shown earlier, the removal of the Cl^- anion seemed to hinder amination rate, albeit in a small amount; thus, it is possible that the use of a larger cation that has weak interactions with smaller resultant anions provides a mechanistic pathway that enhances rate to a small degree. In

the end, no improvements could be made with the bases studied and Cs_2CO_3 remains the base of choice having acceptable moisture and oxygen sensitivity that allows for excellent yields in the desired reaction.

3.2.6 **Catalyst Loading Study**

To ensure that ligand/and or palladium were not being wasted, a brief catalyst loading study was pursued. This would ensure that the same yields could be reached with lower catalyst loadings, thus saving money. The model reaction was examined at various catalyst loadings over a 6 hour reaction time. The results are summarized in Table 20.

Table 20. Catalyst Loading Study



17 **2**

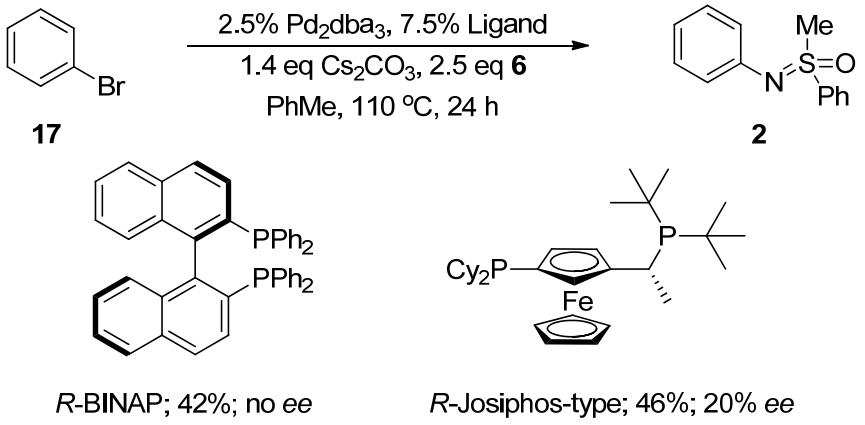
Entry	Pd_2dba_3 (%)	RuPhos (%)	Yield (%)
1	2.5	7.5	92
2	2.5	5.0	53
3	1.25	2.5	22

The results show that ligand/Pd source loading could not be reduced. By reducing the ligand concentration by 2.5%, the yield decreased by nearly half (Table 20, entry 2). A severe reduction in yield to 22% was also seen when the palladium and ligand concentration were halved (Table 20, entry 3). The reactions were not examined at extended reaction times to see if completion could be achieved as this was not the goal of the study. Simply put, a loading scheme of 2.5% Pd_2dba_3 (5% Pd) and 7.5% RuPhos

allows for excellent yields in as little as 6 hours for the model reaction in which **2** was prepared from bromobenzene **17**.

3.2.7 **Chiral Ligand Study**

The last study was carried out to see whether a racemic sulfoximine could be resolved if a chiral ligand were used in the reaction. Only two chiral commercial ligands were examined. No attempt to purchase any other ligands was made. The results of the two ligands, *R*-BINAP and *R*-Josiphos-type ligand, are shown in Scheme 59. In this reaction an excess of sulfoximine was used in order to make sure enough of the matched enantiomer was available to acquire acceptable conversion. Since neither ligand was of the biphenyl family, the reaction length was extended to 24 hours to ensure that an observable amount of product could be isolated.



Scheme 59. Kinetic Resolution of a Racemic Sulfoximine with a Chiral Ligand

The chiral binapthyl system failed to produce enantioenriched product. However, *R*-Josiphos did lead to enantioenrichment of the product, but the *ee* was low (20%). This is the first example of a chiral ligand being used in an *N*-arylation of a racemic sulfoximine to afford a non-racemic product. A better ligand might be similar to that of RuPhos as generically shown in Figure 22. Here X would be a chiral auxiliary

substituent that could be easily modified to maximize or minimize steric influence as deemed necessary.

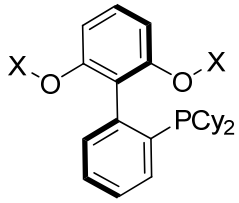


Figure 22. Possible Chiral Ligand Target for Racemic Sulfoximine Resolution

3.2.8 **Optimization Summary**

The goal of this optimization was to provide an improved synthesis that allows for a robust, air tolerable, bench top, one-pot, palladium-catalyzed *N*-arylation. The features deemed important were to provide desired the amination products in short reaction times with minimal catalyst loading under user friendly conditions. Many ligands were studied; biphenyl phosphine ligands with chelating P, N, or O bidentate possibilities gave the best results. RuPhos, a *P,O*-biphenyl ligand, was selected over all other ligands investigated. Commercially popular ligands such as the PEPPSI family, bippyphos, and BrettPhos ligands were also tested and they did not outperform RuPhos for the formation of **2** from **17**. Pd sources were next optimized. Pd(0) sources were in general better than Pd(II) sources and Pd_2dba_3 was found to outperform all others for the test reaction. No bases that were examined outperformed the originally selected Cs_2CO_3. Catalyst loading was briefly investigated at as well. No improvements could be made to increase yields in a 6 hour reaction time length. Kinetic resolution was examined with two chiral bisphosphine ligands with an excess of racemic sulfoximine. Of the two tested, *R*-Josiphos did allow for a meager 20% *ee* in the *N*-arylated product. Overall, a very robust process was developed.

3.3 Applications of the Optimized *N*-Arylation Synthesis

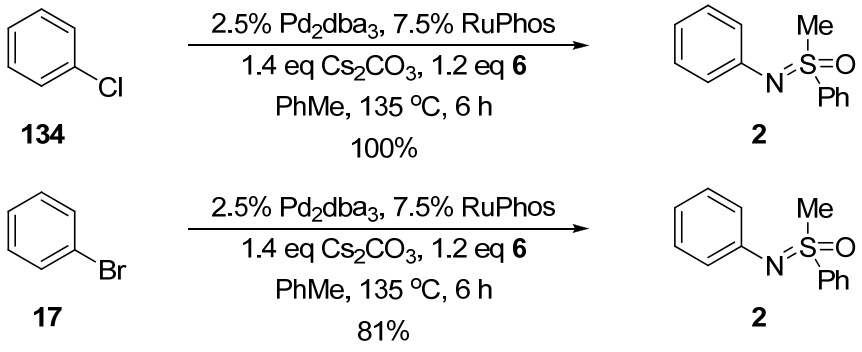
3.3.1 *N*-Substituted Sulfoximine Synthesis: Comparison of C—Cl and C—Br

With a new robust synthetic procedure in hand, it was logical to try other aryl halides in the coupling process. The purpose was to see if the scope and performance of this new ligand metal combination of Pd_2dba_3/RuPhos (versus the previous $Pd(OAc)_2$/BINAP synthesis) was general. Our second generation synthesis provides a different approach with a very electron rich "Pd" catalyst with a stronger sigma donating alkyl phosphine, in contrast to the previous "Pd" catalyst, consisting of a rather electron poor metal with an aryl bis-phosphine, a weaker sigma donor.

The first substrate examined was the thermal reaction of chlorobenzene **134**. It was compared directly to bromobenzene **12** both on a larger 250 mg scale (Scheme 60). Remarkably, the chloride outperformed the bromide in a period of 6 hours at 135 ^{o}C. The temperature was increased slightly to help stir the larger batch reactions by making the toluene boil more vigorously in the sealed tube. This modification kept the heterogenous mixture well mixed. Bromide **17**, on the larger scale, had a slightly reduced yield than seen on the smaller scale; however, leaving the reaction longer did allow for completion as monitored by TLC.

The increased reactivity could be due to the electron rich Pd/RuPhos catalyst enhancing the rate of oxidative addition of the very electropositive C—Cl bond. This effect appears to be less pronounced when the same electron rich Pd/RuPhos catalyst is in the presence of a more polarizable but less electropositive C—Br bond. This reaction was quite surprising; in previous attempts, microwave irradiation was needed to acquire products in respectable yields as shown by Harmata and coworkers.[7,31] The thermal

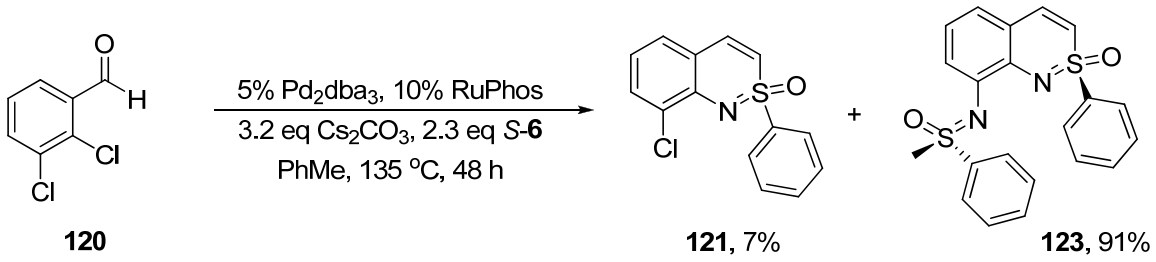
reaction of 2,3-dichlorobenzaldehyde **120** shown previously took 7 days to produce a modest 40% yield of benzothiazine **123**. So the fact that any chloride could be converted in 100% yield in as little as 6 hours thermally was an impressive achievement.



Scheme 60. *N*-Arylation of Aryl Halides with Pd/RuPhos Catalyst

3.3.2 **Improved Synthesis of Benzothiazine Ligand 123**

In order to probe aryl chloride reactivity, 2,3-dichlorobenzaldehyde **120** was subjected to the Pd/RuPhos system on a similar 250 mg scale. With two C—Cl bonds available for oxidative addition, only 2.3 equivalents of enantiopure sulfoximine was used. The reaction was closely monitored by TLC. Within a few hours, 8-chlorobenzothiazine **121** appeared as a major long UV spot and starting material became absent after 24 hours. During the first 24 hours a very polar baseline long UV spot appeared and continued to become more prominent. Another addition of 2.5% Pd_2dba_3, 2.5% RuPhos, and 1.6 equivalents of Cs_2CO_3 were required to diminish the long UV 8-chloro-2,1-benzothiazine **121** spot and enhance the baseline UV spot representing benzothiazine **123**. In 48 hours total reaction time, the reaction appeared to be complete (Scheme 61).



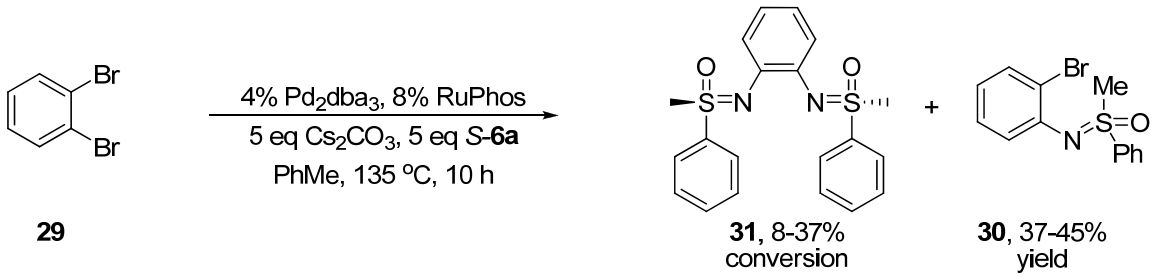
Scheme 61. Breakthrough Synthesis of **123**

The new conditions produced 91% of ligand **123** with 7% of benzothiazine **121** remaining. This reaction required as little as 2.3 equivalents of sulfoximine, (Bolm and coworkers needed 5 or more equivalents of sulfoximine to get bissulfoximines[14]). Overall, 5% of Pd_2dba_3, 10% RuPhos, and 3.2 equivalents of Cs_2CO_3 were required to achieve excellent yields of **123** thermally. Remember yields previously for **123** yields seen previously were very poor (14%) via microwave irradiation over two separate irradiation steps.[31] Thermal reactions previously with Pd/BINAP did not produce any doubly coupled product whatsoever; only **121** was isolated in 7 days in 40% yield.

This one-pot, one-step synthesis allowed a direct pathway to the desired missing link of the sulfoximine family. Bolm and coworkers have demonstrated the utility of bissulfoximines in many asymmetric reactions. Harmata and coworkers have shown the utility of a bisbenzothiazine in an asymmetric alkylation reaction. The only ligand of this *N,N*-sulfoximine based family missing was benzothiazine **123**. Now with an efficient synthesis of **123** in hand, its utility in asymmetric reactions can be investigated. This will be a topic of further investigations. This also introduces a practical approach to the *N*-arylation of sulfoximines and aryl chlorides that before now seemed unlikely to be successful thermally in a practical period of time.

3.3.3 **Examination of Multi-bromoarenes**

In an attempt to further expand the scope of this new generation synthesis, the reaction of dibromobenzene **29** to make bissulfoximine **31** was examined. Previously, Bolm reported that using Pd_2dba_3/BINAP/NaO^{t}Bu gave **31** in 75% yield using an excess of five equivalents of sulfoximine.[16] With our new system of Pd_2dba_3/RuPhos/Cs_2CO_3, the same reaction was attempted (Scheme 62).



29 **31**, 8-37% conversion **30**, 37-45% yield

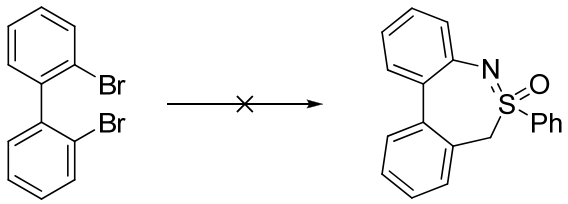
Scheme 62. New Synthesis of Bissulfoximine **31**

At best 87% of dibromide **29** underwent single *N*-arylation to yield *N*-substituted sulfoximine **30**. Of that 87%, only 37% converted to doubly coupled bissulfoximine **31**. This was far inferior to the previous synthesis for this substrate. As a result, this synthesis would not be the preferred synthesis of bissulfoximine **31**.

In a similar fashion, dibromide **46** also failed to convert to benzothiazine **47** and only sulfoximine was isolated after chromatography (Scheme 63). This reaction is another example of the poor compatibility of dibromides and the more electron rich ligand-metal system used. Previous examples by Bolm shown earlier allow for nearly quantitative yields of benzothiazine **47** when BINAP was used as the ligand instead of RuPhos and NaO^{t}Bu was in place of Cs_2CO_3.[16]

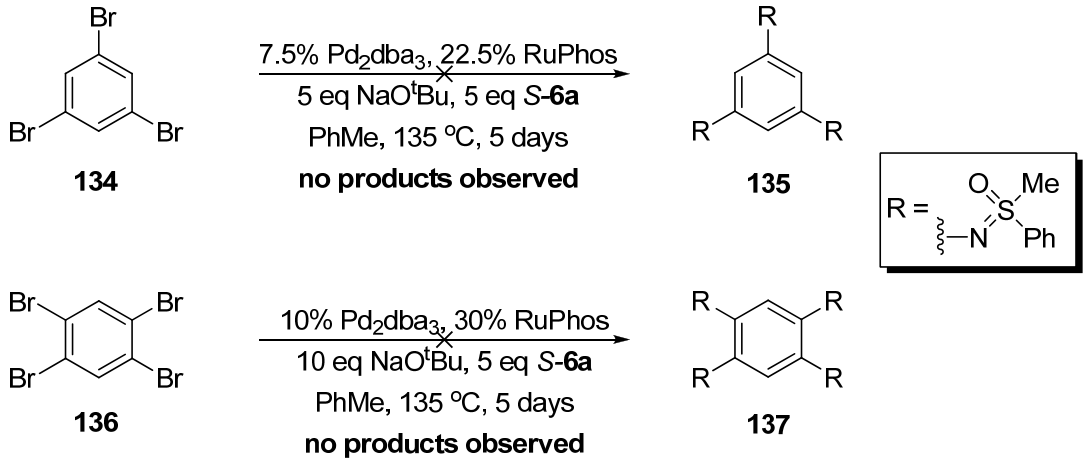
Not surprising given the result of dibromobenzene **32**, tribromobenzene **134** did not convert to trissulfoximine **135** nor did tetrabromobenzene **135** give any

tetrasulfoximine **136** (Scheme 64). In both cases, only sulfoximines was recovered after chromatography. Extended reaction lengths did not promote conversion nor did excess reagents (Pd_2dba_3, RuPhos, or Cs_2CO_3).



46 **47**

Scheme 63. Failed Reaction of Dibromobiphenyl **46**



134 **135** **136** **137**

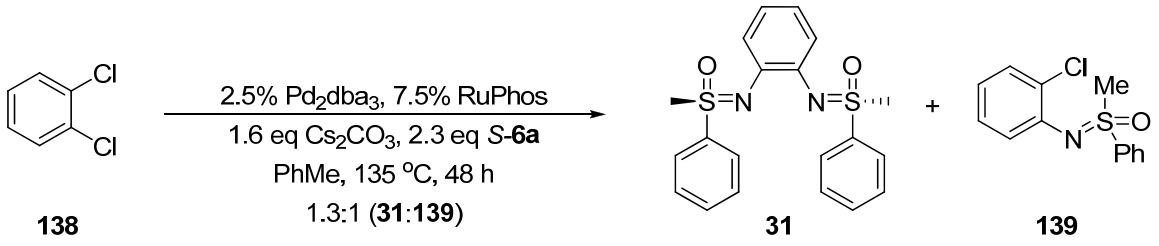
Scheme 64. Failed Attempts to Synthesize Multi-Substituted Sulfoximines

This investigation suggests that the electron rich catalyst combination Pd_2dba_3 and RuPhos has reactivity issues with di-, tri-, and tetrabromoarenes as little to no conversion of desired products was observed. This also suggests that this chemistry has problems with the successive oxidative addition to the second C—Br bond, much like Bolm had noticed in his studies.[18] It seems that bromides may not be the best substrates for the newly optimized synthesis. This is likely due to electronic effect with the overall electron richness of our catalyst combination versus that of Bolm's more electron poor

catalyst combination. Base strength may also play a small role; however, switching bases from Cs_2CO_3 to NaO^tBu had little to no effect in conversion for either process.

3.3.4 **Examination of a Dichlorobenzene**

Before abandoning the synthesis of bissulfoximine **31**, dichlorobenzene **138** was investigated. To elaborate on the idea of this system preferring C—Cl to C—Br substrates, it is expected that dichlorobenzene **138** should provide better conversion to bissulfoximine **31** than dibromobenzene **29**. With a reaction time extended to 48 hours, the crude NMR ratio revealed no starting material remained and a ratio of 1.3 to 1 of bissulfoximine **31** to *N*-substituted sulfoximine **139** was observed (Scheme 65). Notice as little as 2.3 equiv. of sulfoximine could be employed to get respectable conversions, allowing the use of less base. This compensates somewhat for the extended reaction time. It is worth mentioning that several attempts to reproduce the Bolm procedure failed for a variety of substrates. The Bolm procedure was found to be sensitive to air and moisture such that many attempts resulted in no reaction whatsoever. Our reaction was created such that it could tolerate air and moisture and still be reproducible.



138 **31** **139**

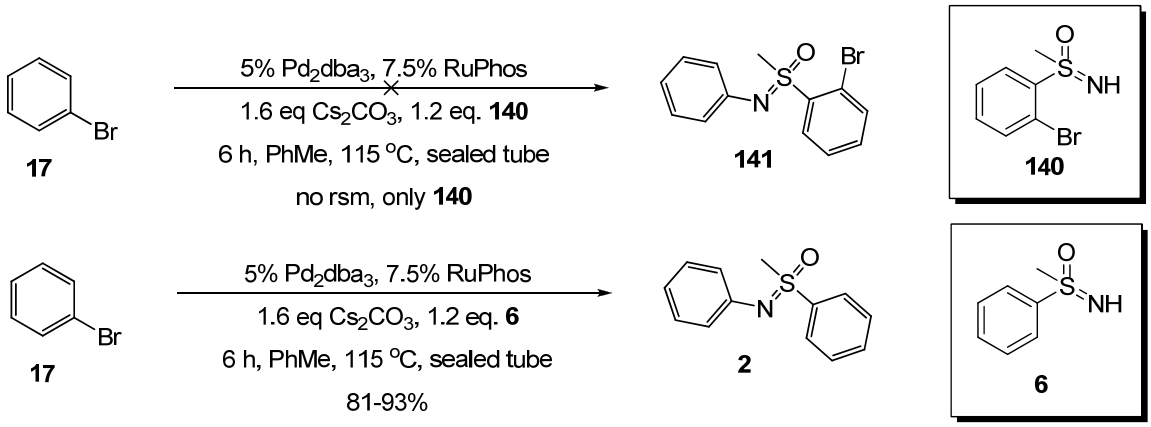
Scheme 65. Synthesis of Bissulfoximine **31** via Dichlorobenzene **138**

Interestingly, all previous investigations suggest that thermal reactions of aryl chlorides and sulfoximines are sluggish, if they occur at all. It seems that we may have found an important way to circumvent old problems associated with the use of aryl chlorides in reactions of this type. At present, our promising examples include the

syntheses of *N*-substituted sulfoximine **2**, bissulfoximine **31**, and benzothiazine **123** from aryl chlorides.

3.3.5 **Examination of a Bromosulfoximine 140**

We were curious as to the behavior of a brominated analog of **6**. Therefore, bromobenzene was reacted with sulfoximine **140** to afford no product in a period of 6 hours (Scheme 66). It was unclear if oxidative addition occurred at all with nearly a quantitative amount of bromosulfoximine **140** recovered. Remember in similar reactions presented earlier, yields greater than 81% were seen with sulfoximine **6** in the same reaction time length. This suggests that the presence of *ortho*-brominated sulfoximine **140** in the reaction mixture halts or severely slows *N*-arylation.

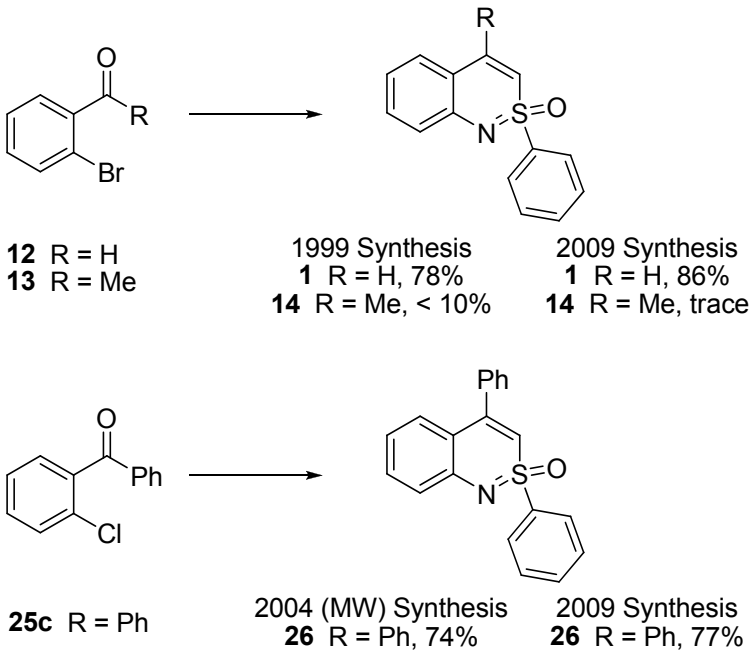


Scheme 66. Comparison of Bromosulfoximine **140** to Sulfoximine **6**

3.3.6 **New Syntheses of Previously Prepared Benzothiazines**

A final comparison was done for the three benzothiazines prepared initially by Harmata and coworkers in 1999[5] and 2004[7] using $Pd(OAc)_2$/BINAP, Cs_2CO_3. The previous synthesis of **1** was carried out in 78% yield under the standard conditions. The new Pd-RuPhos system allowed for an 86% yield in as little as 12 hours in "air" friendly conditions (Scheme 66). In both cases, the *N*-arylation of an enolizable acetophenone

was extremely poor. With microwave irradiation, 74% of benzothiazine **26** was isolated in 1.5 hours in comparison to the thermal reaction with the new Pd-RuPhos system which gave a 77% yield of benzothiazine **26** in 12 hours from 2-chlorobenzophenone **25c** (Scheme 67). With 2-bromoaldehyde **12** and 2-chlorobenzophenone **26**, the yields of benzothiazine products were improved with reduced reaction time and using less rigorous conditions.



Scheme 67. Comparison of Benzothiazine Syntheses

3.3.7 **Summary of 2009 Pd-RuPhos Synthetic Results**

Several substrates were re-examined in order to justify the new optimization of a well established procedure. The results suggest the new ligand metal system of Pd_2dba_3/RuPhos with Cs_2CO_3 is best suited with monobromo-, monochloro-, and dichloroarenes versus the previously established metal ligand system of $Pd(OAc)_2$/BINAP with Cs_2CO_3, which tends to be limited to various bromoarenes. For dibromoarenes, Pd_2dba_3/BINAP with NaO^tBu remains the best reagent set to date. The

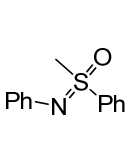
most interesting of these reactions was the increased reactivity of the aryl chlorides and dichlorides. Until now, successful C—Cl *N*-arylation required microwave irradiation. This is no longer the case. A summary of the synthetic developments for the substrates of interest, past and present, are itemized below in Table 21.

In all but one case, product yields increased, reaction time decreased, air sensitivity was of little concern, and in several cases the cheaper chloro- versions of the substrates were successful thermally and without microwave irradiation (Table 21, entries 1-4, and 7-12). With 2-bromoacetophenone **13**, no improvements could be made (Table 21, entries 5 and 6). Formation of bissulfoximine **31** was similar with dichlorobenzene **138** as it was with dibromobenzene **29** (Table 21, entries 9 and 10). Lastly, a significant improvement was made in the formation of benzothiazine **123** such that it could be made in one step in 91% yield as compared to the previous 2 step synthesis in 7.6% overall yield (Table 21, entries 11 and 12). By changing $Pd(OAc)_2$/BINAP to Pd_2dba_3/RuPhos, an overall more robust reaction was achieved.

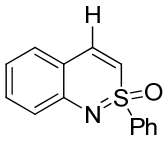
This enhancement in Pd-RuPhos reactivity may be due to the electropositive carbon of the C—Cl bond being more attractive toward oxidative addition. This electron rich palladium bearing an alkyl phosphine ligand has quite different reactivity to the electron poor palladium bearing electron poor bisarylphosphines. This ligand tuning of palladium has led to a reactivity that seems to be of the appropriate electronic character for thermal *N*-arylation of several aryl chlorides and dichlorides previously characterized as thermally "unreactive". This new combination seems to accelerate mono-bromide *N*-arylation as well. Dibromoarenes are also reactive but do not perform near as well, in a timely fashion, to the previously reported methods. In the end, a more facile, robust

reaction was optimized that allows access to substrates previously thought "unreactive" without microwave irradiation.

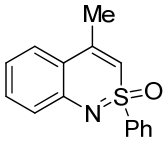
Table 21. Synthetic Improvements in *N*-Arylation of Sulfoximines and Haloarenes



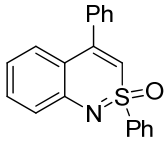
2



1



14



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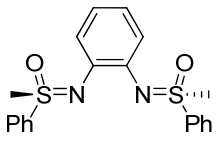
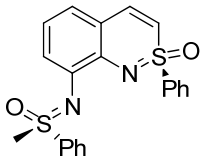


31



122

Entry	Year Group	Starting Material	Reaction Conditions	Product	Yield (%)
1	1998 Bolm[6]	**17**	5% $Pd(OAc)_2$, 7.5% BINAP 1.4 eq Cs_2CO_3, 1.2 eq **6** PhMe, 110 ^oC, 48 h, N_2	**2**	72
2	2009	**17**	2.5% Pd_2dba_3, 7.5% RuPhos 1.4 eq Cs_2CO_3, 1.2 eq **6** PhMe, 135 ^oC, 6 h, *air*	**2**	81
3	2009	**134**	2.5% Pd_2dba_3, 7.5% RuPhos 1.4 eq Cs_2CO_3, 1.2 eq **6** PhMe, 135 ^oC, 6 h, *air*	**2**	100
4	1999 Harmata[5]	**12**	10% $Pd(OAc)_2$, 15% BINAP 1.8 eq Cs_2CO_3, 1.2 eq **6** PhMe, 110 ^oC, 40 h, N_2	**1**	78
5	2009	**12**	2.5% Pd_2dba_3, 7.5% RuPhos 1.4 eq Cs_2CO_3, 1.2 eq **6** PhMe, 135 ^oC, 12 h, *air*	**1**	86
6	1999 Harmata[5]	**13**	10% $Pd(OAc)_2$, 15% BINAP 1.8 eq Cs_2CO_3, 1.2 eq **6** PhMe, 110 ^oC, 40 h, N_2	**14**	<10

7	2009	**13**	2.5% Pd_2dba_3, 7.5% RuPhos 1.4 eq Cs_2CO_3, 1.2 eq **6** PhMe, 135 ^oC, 12 h, *air*	**14**	*trace*
8	2004 Harmata[7]	**25c**	5% $Pd(OAc)_2$, 7.5% BINAP 1.4 eq Cs_2CO_3, 1.2 eq **6** PhMe, 200W, 135 ^oC, 1.5 h, N_2	**26**	74
9	2009	**25c**	2.5% Pd_2dba_3, 7.5% RuPhos 1.4 eq Cs_2CO_3, 1.2 eq **6** PhMe, 135 ^oC, 12 h, *air*	**26**	77
10	2002 Bolm[16]	**29**	4% Pd_2dba_3, 8% BINAP 5 eq NaO^tBu, 4 eq *S*-**6a** PhMe, 135 ^oC, 10 h, N_2	**31**	75
11	2009	**138**	2.5% Pd_2dba_3, 7.5% RuPhos 1.6 eq NaO^tBu, 2.3 eq *S*-**6a** PhMe, 135 ^oC, 48 h, *air*	**31:139**	1.3:1
12	2007 Harmata[31]	**121**	5% $Pd(OAc)_2$, 7.5% BINAP 1.4 eq Cs_2CO_3, 1.2 eq 6 PhMe, 200W, 135 ^oC, 1.5 h, N_2	**123**	14
13	2009	**120**	5% Pd_2dba_3, 10% RuPhos 3.2 eq Cs_2CO_3, 2.3 eq *S*-**6a** PhMe, 135 ^oC, 48 h, *air*	**123**	91

CHAPTER 4

Lithiation Reactivity of 2,1-Benzothiazines

Discovering and controlling benzothiazine reactivity is just as useful as creating and optimizing new syntheses to make benzothiazines. Understanding and investigating benzothiazine chemistry allows the discovery of new structures that could be useful in taking full advantage of the benzothiazine chirality. Benzothiazines represent a class of molecules that can be highly functionalized. Presented herein are several benzothiazines that were studied as part of a program directed toward the synthesis of new chiral ligands. These ligands can provide variable steric and electronic properties to tune reactivity and hopefully with high enantioselectivity in asymmetric reactions.

4.1 Previous Studies of Sulfoximine and Benzothiazine Reactivity

4.1.1 Benzothiazine Syntheses

The 4-position of benzothiazines can be functionalized using haloarenes that contain electrophilic groups *ortho* to the halogen on the aryl ring. In previous chapters, the intramolecular condensation of sulfoximines with various electrophilic groups was described under basic conditions. A variety of bases were used to cyclize *N*-substituted sulfoximines into substituted benzothiazines. A brief summary of the types of electron withdrawing groups that have been shown to condense are shown in Figure 23.[5]

Ortho-haloaldehydes react in a one-pot fashion under N-arylation conditions with[7,31] or without[5] microwave irradiation to produce benzothiazine **1**. Non-enolizable *ortho*-haloketones also condense in a one pot fashion[5] and thermally with microwave irradiation to give 4-phenyl-2,1-benzothiazines like **26**.[7,31] *Ortho*-bromobenzonitriles give 4-amino-2,1-benzothiazines in a two step process involving *N*-arylation followed by

n-BuLi-induced condensation.[5,6] Lastly, *ortho*-halobenzoate esters react in a two step sequence of *N*-arylation followed by KH-induced condensation to produce ketones like **20**.[5]

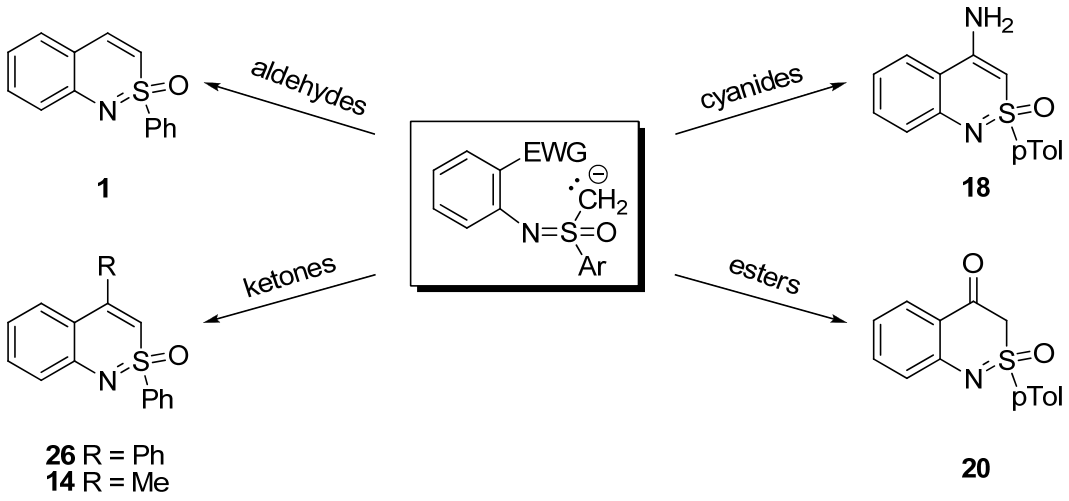


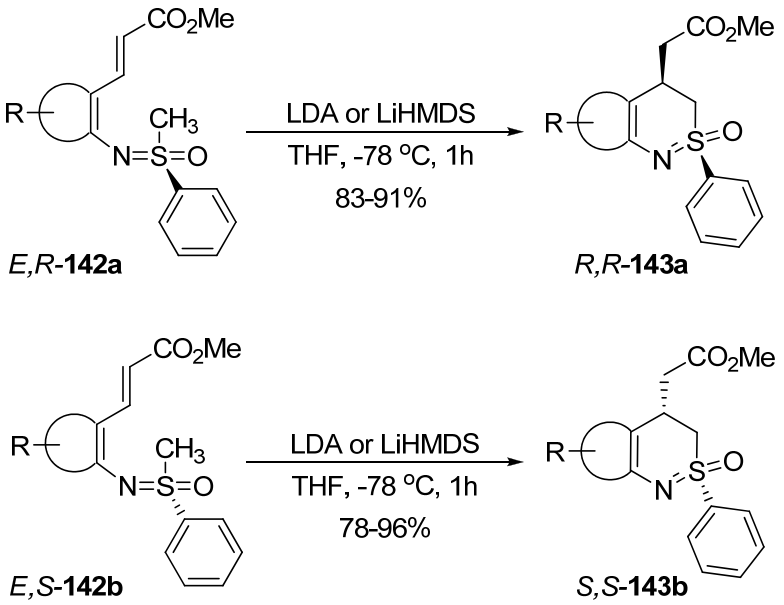
Figure 23. Summary of Sulfoximine Anion Condensations

4.1.2 **Sulfoximine Anion Michael Additions to α,β-Unsaturated Esters**

Another reaction of sulfoximine carbanions is the stereospecific intermolecular Michael addition to α,β-unsaturated esters. Precursors are prepared by *N*-arylation of *ortho*-bromocinnamates followed in many cases by a separate intramolecular, stereoselective Michael addition of a sulfoximine carbanion to the β position of an *α,β*-unsaturated ester. This allows for the 4-position of a benzothiazine to be stereoselectively modified.[43]

The first example of a stereoselective Michael addition of a chiral sulfoximine carbanion was reported by Harmata and coworkers in 2003. The reaction involved *α,β*-unsaturated methyl ester **142** with either lithium di-*iso*-propyl amide, LDA, or lithium hexamethyldisilazide, LHMDS, in THF to give 2,1-benzothiazine **143** (Scheme 68). The types of substrates examined were aromatic: phenyl, thiophenyl, furyl, and pyridyl

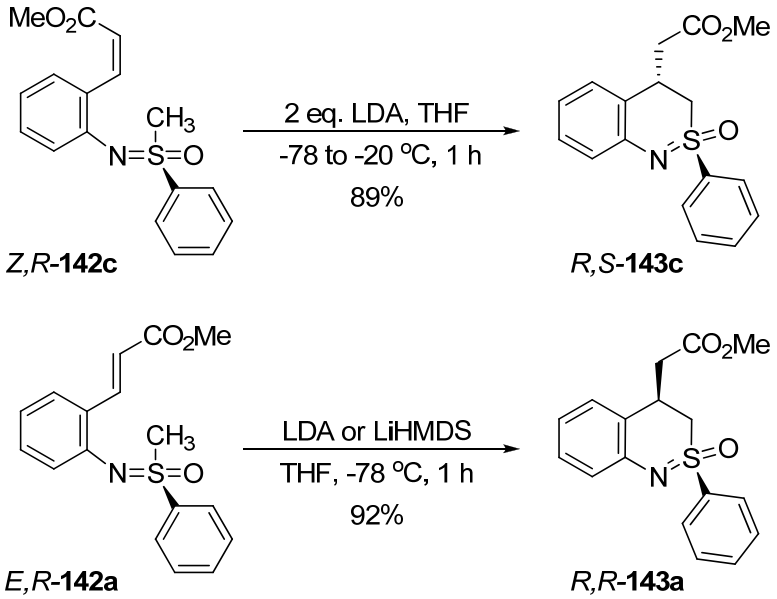
heterocycles. The reaction was also stereospecific. *E,R*-**142a** gave the *R,R*-**143a** diastereomer exclusively and *E,S*-**142b** gave the *S,S*-**143b** diastereomer exclusively. Thus, *trans*-alkenes bearing a *R*-sulfoximino group give *R,R*-benzothiazines and *cis*-alkenes bearing a *R*-sulfoximine group give the opposite diastereomer *R,S*-benzothiazines (Scheme 69).[43]



Scheme 68. Stereoselective 1,4-additions of Sulfoximine Carbanions

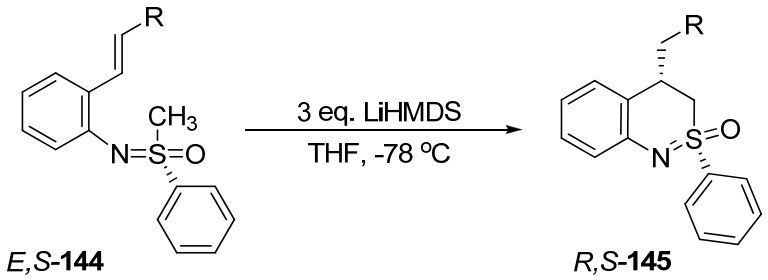
The scope of this reaction was very recently expanded by Harmata and coworkers in 2009 by the addition of a variety of electron withdrawing groups. Many substrates underwent intramolecular, stereoselective 1,4-addition in good to excellent yields. Various *α,β*-unsaturated functional groups were examined as well as the first example of a γ,δ-unsaturated system (Table 22). Not all groups facilitated the addition reaction. For example, –SPh, -Ph, and -Ph*p*CN did not react (Table 22, entries 2,3 and 6). Sulfones and phosphonates worked in excellent yields (Table 22, entries 1, 5, and 15). Cyclic and acyclic amides gave products in excellent yields as well (Table 22, entries 4 and 8). Some ketones were examined and isolated yields ranged from 53 to 82% yield (Table 22,

entries 9 – 14). Cyanide was another suitable withdrawing group giving desired benzothiazine in as much as 88% yield (Table 22, entry 16). Lastly, γ,δ-unsaturated ester gave a modest 42% yield of cyclized product (Table 22, entry 7).[44]



Scheme 69. Stereospecific, Stereoselective 1,4-Additions of Sulfoximine Carbanions

Table 22. Stereoselective 1,4-Additions with Different Electron Withdrawing Groups



Entry	R	Product	Yield (%)
1	SO_2Ph	**145a**	88
2	Ph	**145b**	*no reaction*
3	SPh	**145c**	*no reaction*
4	$CONMe_2$	**145d**	85

5	$PO(OMe)_2$	**145e**	83
6	Ph*p*CN	**145f**	*no reaction*
7	(*E*)-$CH{=}CHCO_2Me$	**145g**	42
8	$CON(CH_2)_5$	**145h**	88
9	COPh*o*OMe	**145i**	66
10	COPh*p*Me	**145j**	63
11	COPh*p*Cl	**145k**	65
12	CO*t*Bu	**145l**	82
13	COPh	**145m**	81
14	CO(2-furyl)	**145n**	53
15	$POPh_2$	**145o**	75
16	CN	**145p**	88

4.1.3 **Stereoselective Sulfoximine Michael Additions in Natural Product Syntheses**

The previous chemistry was exploited and used in recent natural product syntheses by the Harmata group. The first example of using the stereoselective, intramolecular Michael addition reaction of sulfoximines was in the formal syntheses of (+)-curcumene and (+)-curcuphenol in 2003.[45] The second synthesis was followed shortly after with the partial synthesis of psuedopteroxazole in 2004.[46] The total synthesis of psuedopteroxazole was later completed in 2005[47] and its synthesis improved in 2009.[48] In the same year, the formal synthesis of erogorgiaene was reported as well.[49] All total syntheses involving sulfoximines were investigated and completed by Harmata and coworkers. This displays the ever expanding role of benzothiazines in synthesis,

primarily of marine natural products. The structures of the natural products are shown below in Figure 24.

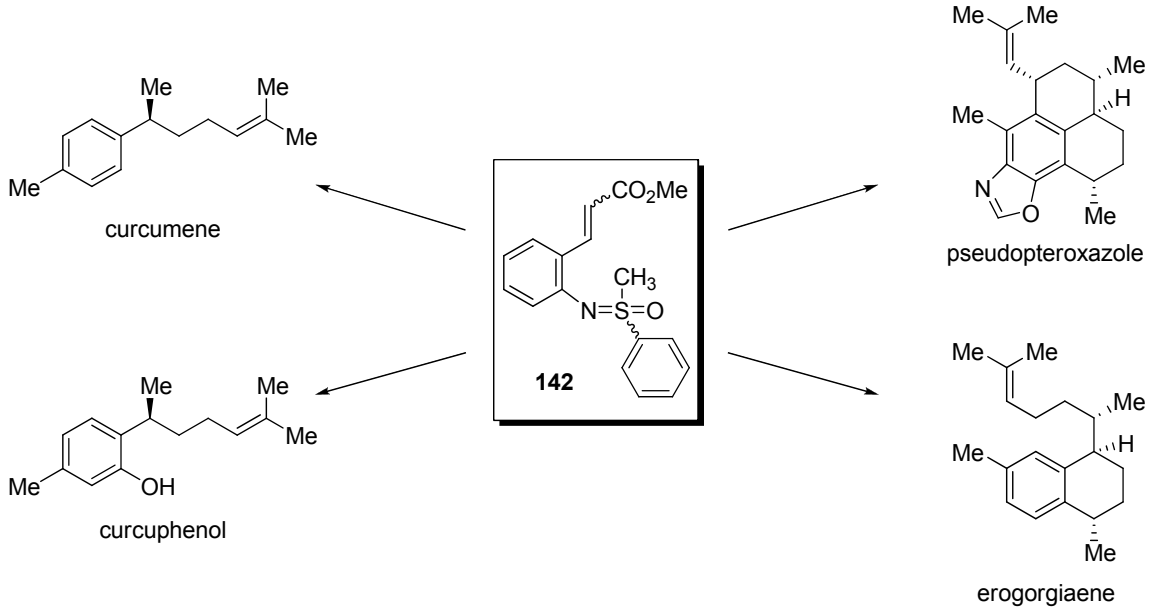
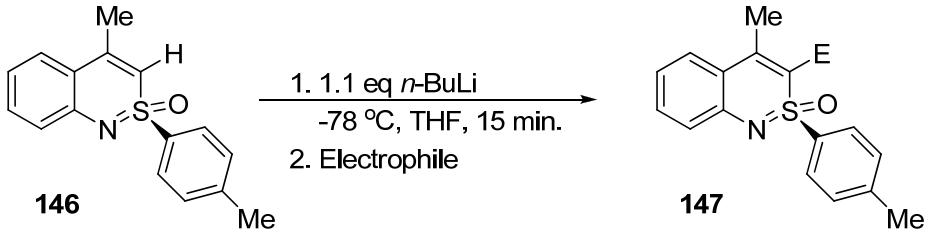


Figure 24. Benzothiazines in Natural Product Syntheses

4.1.4 **Sulfoximine Stabilized Vinyl Carbanions**

The first study of benzothiazine lithiation reactivity was carried out by Harmata in 1988. Harmata found that sulfoximine-stabilized vinyl carbanions can be trapped with various electrophiles at the 3-position of benzothiazine **146** in good to excellent yields. Benzothiazines were prepared for this study with the general regioselective cyclization reaction shown in early Chapter 1; at the time of this work, no metal-catalyzed *N*-arylation processes were available. Hence, the sulfoximine in **146** contains an *S*-*p*Tol ring rather than the *S*-phenyl ring seen in more recent *N*-arylation applications. A summary of the electrophiles investigated are provided in Table 23.[50]

Table 23. Sulfoximine Carbanion Study of 4-Methyl-2,1-Benzothiazine **146**

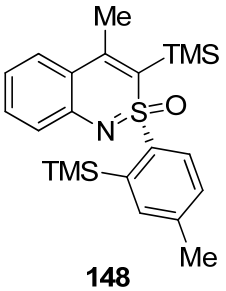


Entry	Electrophile	E	Product	Yield (%)
1	TMSCl	TMS	**147a**	89
2	CH_3I	CH_3	**147b**	79
3	$C_2Br_2Cl_4$	Br	**147c**	98
4	$ClCO_2CH_2CH{=}CH_2$	$CO_2CH_2CH{=}CH_2$	**147d**	76
5	Ph_2CO	$Ph_2C(OH)$	**147e**	65
6	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	**147f**	0
7	Et_2CO	$Et_2C(OH)$	**147g**	0
8	EtCHO	*rac*-EtCH(OH)	**147h**	83[a]
9	*t*BuCHO	*rac*-*t*BuCH(OH)	**147i**	76[b]
10	PhCHO	*rac*-PhCH(OH)	**147j**	84[c]

[a] Isomeric ratio, 1.9:1
[b] Isomeric ratio, 2.4-2.8:1
[c] Isomeric ratio, 1.2:1

Respectable to excellent yields were seen with all electrophiles reported except enolizable ketones, which likely quenched the benzothiazine during enolate formation (Table 23, entries 6 and 7). Trimethylsilyl chloride gave 89% of the TMS-benzothiazine **147a** (Table 23, entry 1); this product provides a removable protecting group to allow for further deprotonation of the *S*-*p*Tol ring. Larger excesses of *n*-BuLi allowed for minor

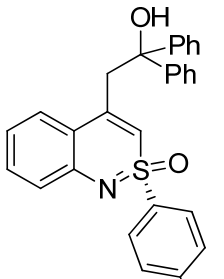
amounts of dilithiation, in only one example of trapping was dilithiation seen affording di-TMS product **148** in very minor amounts (Figure 25).



148

Figure 25. Evidence of Benzothiazine Dilithiation

Aldehydes and unsymmetrical ketones are prochiral; they have two enantiotopic faces that a sulfoximine stabilized vinyl carbanion can approach, providing a mixture of isomeric products. No unsymmetrical ketones were studied. Of the aldehydes studied, ratios ranged from 2.8 -1.2:1 for products in yields above 75% for **147h-j** (Table 23, entries 8-10). In the presence of a chloroformate, smooth transformation to **147d** was seen (Table 23, entry 4). Finally, benzophenone as an electrophile provided for the lowest isolated yield of 65% (Table 23, entry 65). The low yield may have been due to steric hindrance in the approach of the nucleophile to the electrophile. Side product **149** was observed in trace amounts when benzophenone was used as an electrophile (Figure 26). These products demonstrate the unique reactivity of benzothiazine **146**.



149

Figure 26. Benzophenone Side Product

This chemistry inspired the lithiation work reported later in this chapter. It is important to visualize the charge based reactivity pattern of 2,1-benzothiazines as shown below in Figure 27. Notice that the predicted reactivity matches that seen for 2- and 4-methyl- positions; however, the reactivity pattern of the *S*-*p*Tol ring is opposite to the theoretical reactivity based on alternating charges.

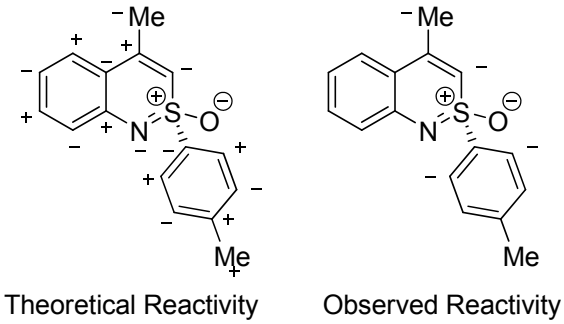


Figure 27. Reactivity Patterns of 2,1-Benzothiazine **146**

4.1.5 **Sulfoximine Stabilized Vinyl Lithiocarbanions**

Nine years later in 1997, a crystal structure was elucidated for a tetrameric *rac*-*S*-ethyl-*N*-methyl-*S*-phenylsulfoximine cluster with *N,N,N',N'*-tetramethylethylenediamine, TMEDA. This cluster (Figure 28) was prepared by treating a racemic sulfoximine with 2 equiv. of *n*-BuLi in TMEDA and in the presence of Li_2O to theoretically create a lithiodicarbanion. Within the entire cluster, a pair of *S*-sulfoximine monoanions and a pair of *R*-sulfoximine dianions are present with eight TMEDA molecules. The cluster is centrosymmetric meaning an internal chiral resolution took place. At the cluster center an octahedral Li_6O O(22) is present. Each side of the symmetrical cluster contains one mono- and one dianion pair. The dianion consists of an *ortho*-C(36) anion interacting with Li(2) and Li(4) cations which chelate to the adjacent *R*-sulfoximine O(21) and N(21)

in five-membered chelates. Interestingly, no Li—C bond was observed with the α-ethyl C(21) anion of the *R*-sulfoximine dianion.[51]

The *S*-sulfoximine α-ethyl C(1) monoanion interacts with the Li(2) cation bridging *R*-sulfoximine *ortho*-C(36) anion. Keep in mind only the α-ethyl C(1) is deprotonated suggesting that a significant amount of *n*-BuLi "lingers" in the reaction. This unique reactivity and structure appears to be partly driven by the presence of an organolithium contaminant, lithium oxide, which in turn suggests that the organolithium reactivity with sulfoximines could change from bottle to bottle.[51]

The oxygen and nitrogen heteroatoms of the sulfoximine help coordinate the lithium cations in an extremely complex network. The sulfoximine oxygen, sulfoximine nitrogen, sulfoximine α-ethyl carbanion, and sulfoximine *ortho*-phenyl carbanion all participate in various chelating interactions to further increase the complexity of this highly compact cluster. Therefore, with many sites available for stabilization and deprotonation, the multi-lithiation of our sulfoximine containing benzothiazines merits more investigation to understand the intricacies of their chemistry.[51]

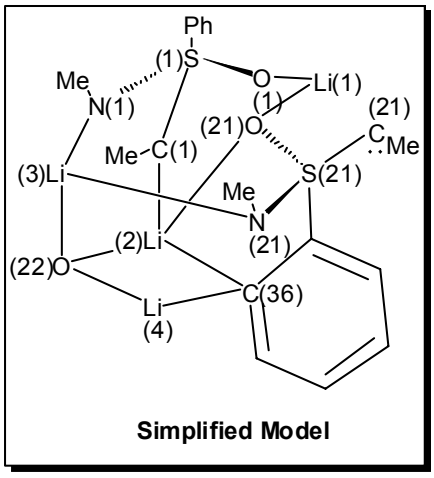
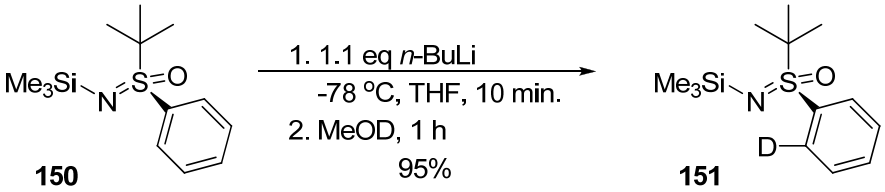


Figure 28. Tetrameric Structure of a Sulfoximine Dilithiocarbanion

4.1.6 *Ortho*-Lithiation of Sulfoximines

Levacher, Dupas and coworkers examined the reactivity of *S*-*t*-butyl-*S*-phenylsulfoximines in 1999 and observed them to be an *ortho*-director for lithiation reactions. The reaction was optimized and found to be general. The bases tried for the *ortho*-lithiation of sulfoximines were LDA, *n*-BuLi, and *s*-BuLi. Deprotonation of LDA took place exclusively at elevated temperatures. In the end, both lithium alkyl bases were preferred because of higher yields over shorter periods of time at reduced temperatures. Yields did not increase with an increase in temperature. Under the optimized conditions, deprotonation of the *ortho*-H about the *S*-phenyl ring of **150** took only 10 minutes at -78 ^{o}C in THF to allow for 95% deuterium incorporation as shown in Scheme 70.[52]

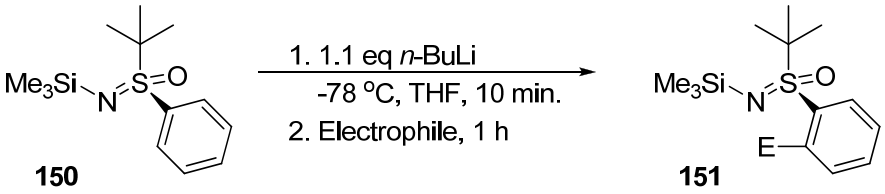


150 **151**

Scheme 70. Optimized *Ortho*-Lithiation Procedure of *S*-*tert*-Butyl Sulfoximine

With an optimized procedure for metalation in hand, the reaction was examined with several electrophiles to determine reaction scope. The summary of electrophiles examined is shown in Table 24. Only four electrophiles were tested. The best electrophile was shown to be dimethyl disulfide, affording a 95% yield of product (Table 24, entry 3). Benzaldehyde was tested and the corresponding diastereomeric alcohols were isolated in 60% yield with only a 25% diastereomeric excess (Table 24, entry 4). With a change in base to *s*-BuLi/TMEDA in toluene, the diastereomeric excess increased to as much as 50%.[52]

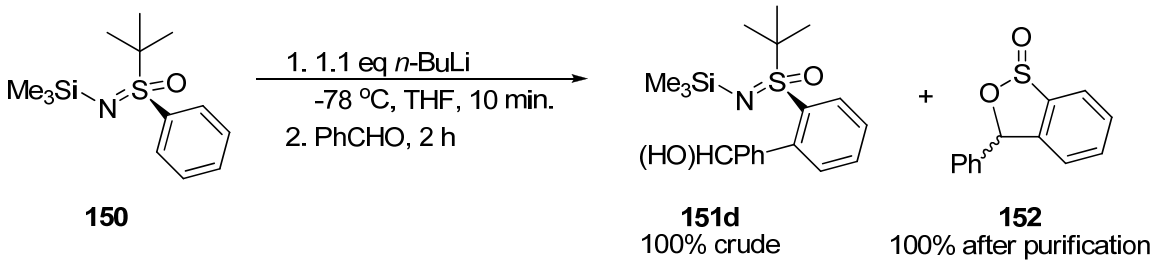
Table 24. *Ortho*-Lithiation of *S*-*tert*-Butyl Sulfoximine and Various Electrophiles



150 **151**

Entry	Electrophile	E	Product	Yield (%)
1	C_2Cl_6	Cl	**151a**	76
2	I_2	I	**151b**	75
3	MeSSMe	SMe	**151c**	95
4	PhCHO	*rac*-PhCH(OH)	**151d**	60

An interesting side reaction was observed during further investigations of sulfoximine *ortho*-lithiations in 2005. With different aldehydes, a de-*tert*-butylation was observed. The reaction was general for three aldehydes and *S*-*tert*-butyl-*S*-phenyl sulfoximine **150**. First, acetaldehyde as an electrophile gave no desired product and only sulfinic ester before chromatography in quantitative yield and with 13% *de*. Then benzaldehyde was used as the electrophile affording a quantitative yield of **151d** with 10% *de* in the crude NMR; however, when subjected to silica gel chromatography, all of sulfoximine **151d** was converted to sulfinic ester **152** in 100% yield maintaining the 10% *de* (Scheme 71). This suggests the mechanism of de-*tert*-butylation occurs with retention of configuration. Similarly, with pivaldehyde as the electrophile a sulfinic ester was also isolated in 50% yield as a 1:1 mixture of sulfoximine to sulfinic ester in 95% *de*. The scope of this decomposition reaction is currently under investigation by Dupas and coworkers.[53]



Scheme 71. Benzaldehyde Side Product: New Sulfinic Ester Formation

4.1.7 **Summary of Sulfoximine Lithiation**

The reactivity of several sulfoximine stabilized vinyl, methyl, and *ortho*-phenyl lithiocarbanions and dilithiocarbanions has been reported. Only 4-methyl-2-*S*-oxa-2-*S*-phenyl-2,1-benzothiazine **146** has been examined in the benzothiazine family of compounds. A summary of the selected lithiated sulfoximine containing compounds are summarized in Figure 29.

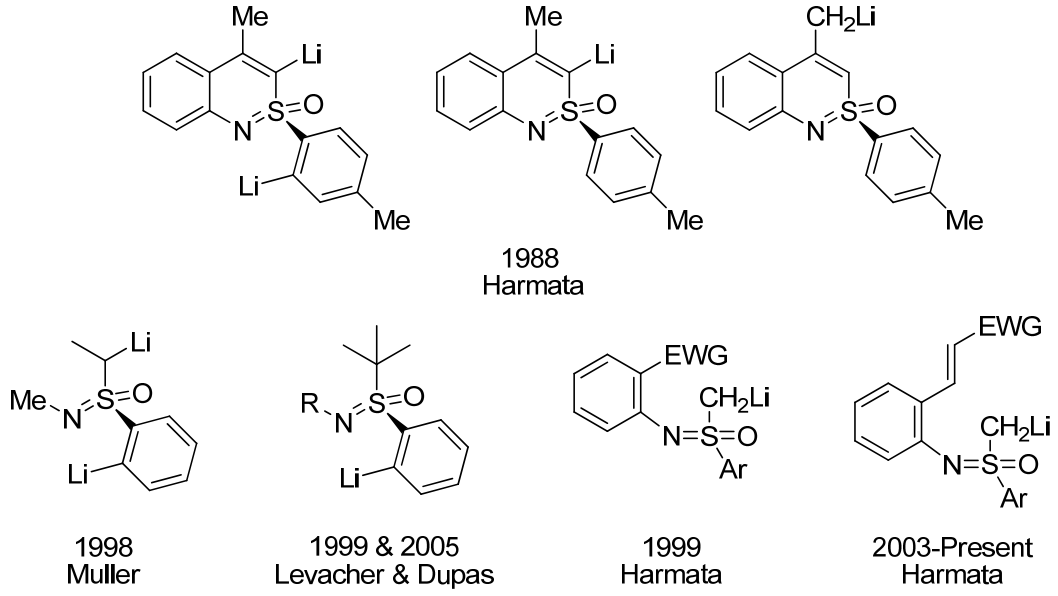


Figure 29. Summary of Lithiated Sulfoximine Containing Compounds

In other cases, metalation takes place with strong alkyl lithium bases at low temperature in THF solvent. In one example, the solid state structure of a multi-lithiated

sulfoximine cluster was very complex. Both the mono- and the dilithiation of sulfoximine-containing compounds have been reported. Overall, the study of benzothiazine compounds to date has been somewhat limited. Therefore, the goals of the research conducted in the sections that follow were to examine benzothiazine metalation and examine the reaction scope in order to advance our chiral benzothiazine-based ligand program.

4.2 Lithiation of Benzothiazines

4.2.1 α-Lithiation of Benzothiazine 1

Initial attention was drawn toward preparing a *P,N*-ligand using the previous methodology presented by Harmata in 1988.[50] The goal was to first protect the most acidic 3-position of **1** with a removable silyl group. Once protected, access to the less acidic *ortho*-*S*-phenyl site would allow trapping of a phosphine chloride to prepare a new family of *P,N*-ligands for use in asymmetric reactions. The retrosynthesis is shown in Figure 30.

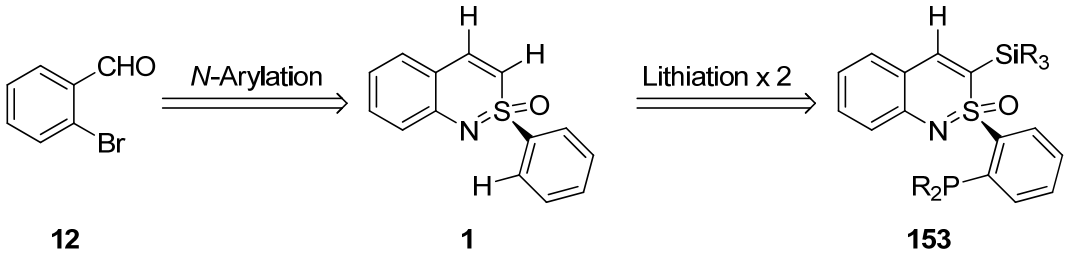
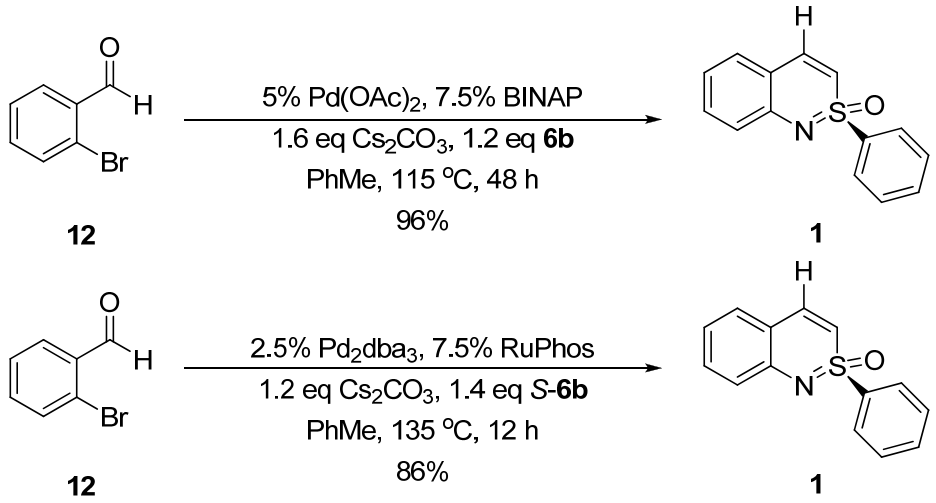


Figure 30. Retrosynthesis of 2,1-Benzothiazine *P,N*-Ligand **153**

N-Arylation of 2-bromobenzaldehyde **12** is well known and highly reproducible in multigram scales and affording an 87% yield of **1** (Scheme 72). The lithiation of **1** should be similar to that of **146**. The final step, accessing the *ortho*-*S*-phenyl ring hydrogen via lithiation was observed only in minor amounts and was trapped by TMSCl

only. Lithiation of the *ortho*-*S*-phenyl ring of the benzothiazine sulfoximine was the emphasis of the research conducted.

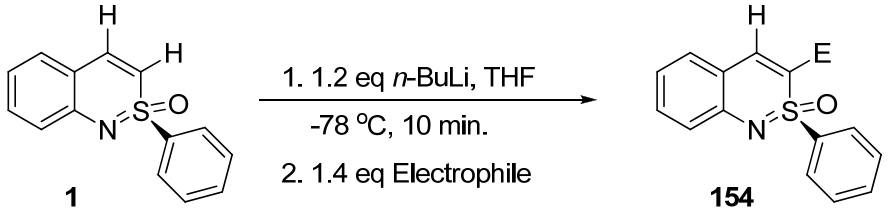


Scheme 72. Thermal *N*-Arylation of 2-Bromobenzaldehyde **12**

A large selection of electrophiles were studied in order to probe reactivity and provide the best protecting group to complete the synthesis of *P,N*-ligand **153**. Examining a large range of electrophiles provides detailed information on the nucleophilicity of the sulfoximine stabilized vinyl carbanion and provides a direct comparison to benzothiazine **146** in many examples (Table 25).

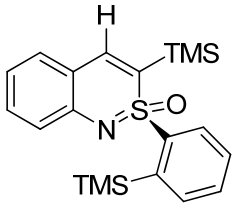
Silyl chlorides were chosen for their ease of removal once attached. Several silyl chlorides of various bulk were used to trap the lithiocarbanion. Yield slightly decreased as steric bulk of the silyl alkyl groups increased but all yields remained above 80% (Table 25, entries 1-4). Very near stoichiometric amounts of TMSCl were needed to prevent formation of di-TMS product **154** (Figure 31) as seen previously with 4-methyl-2,1-benzothiazine **146**. Bulkier silyl groups did not have issues with either hydrolysis or multiple trapping.

Table 25. α-Lithiation Summary of Benzothiazine **1**



Entry	Electrophile	E	Product	Yield (%)
1	TMSCl	TMS	**154a**	98
2	TESCl	TES	**154b**	94
3	TIPSCl	TIPS	**154c**	94
4	TBSCl	TBS	**154d**	85
5	PhSSPh	PhS	**154e**	38-92
6	Ph_2CO	$Ph_2C(OH)$	**154f**	91
7	2-Br(C_6H_4)CHO	*rac*-2-Br(C_6H_4)CH(OH)	**154g**	94[a]
8	$C_2Br_2Cl_4$	Br	**154h**	81
9	I_2	I	**154i**	96
10	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	**154j**	97
11	$ClCO_2CH_2CH(CH_3)_2$	$CO_2CH_2CH(CH_3)_2$	**154k**	11-51
12	DMF	CHO	**154l**	92
13	Et_2CO	$Et_2C(OH)$	**154m**	85
14	$(CH_2O)_n$	CH_2OH	**154n**	76
15	$(CH_2)_2O$	CH_2CH_2OH	**154o**	91
16	$BrCH_2CO_2C_4H_9$	$CH_2CO_2C_4H_9$	**154p**	0
17	Me_2CO	$Me_2C(OH)$	**154q**	85

[a] Diastereomeric ratio of 1.4:1 observed.



155

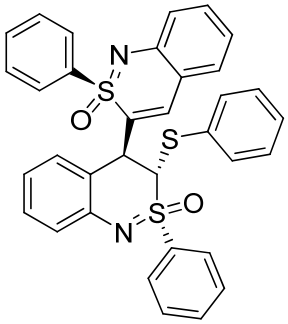
Figure 31. Lithiation Side Product **155**

An aromatic aldehyde reacted very smoothly in 94% yield to give a 1.4:1 mixture of diastereomers (Table 25, entry 7). Both cyclic and acyclic symmetrical ketones trapped smoothly to give yields greater than 85% for both examples (Table 25, entries 6, 10, 13, and 19). Propylene oxide reacted smoothly to give **154o** in 91% yield (Table 25, entry 15). Polymeric paraformaldehyde provided alcohol **154n** in 76% yield from freshly cracked paraformaldehyde; the reaction was very exothermic and could not be reproduced on larger scales. Other electrophiles such as $C_2Br_2Cl_4$, I_2, and DMF gave very clean reactions in respectable to excellent yields (Table 24, entries 8, 9, and 12).

Two electrophiles failed to provide any products. First, *t*-butyl bromoacetate did not alkylate in a S_n2 fashion nor did it react at the ester functional group. The second failed electrophile was diphenylphosphinic chloride, which provided no recovered starting material or product. It appeared that many new very polar products were formed but none could be isolated and identified.

Two other electrophiles gave particularly large ranges in yield. Both diphenyl disulfide and isobutyl chloroformate were problematic in achieving respectable yields consistently. During the isolation of sulfide **154e**, the baseline material was flushed off the column and collected in an additional vial; a single crystal grew out of the remaining brown residue. The x-ray quality crystal was analyzed, and evidence for new

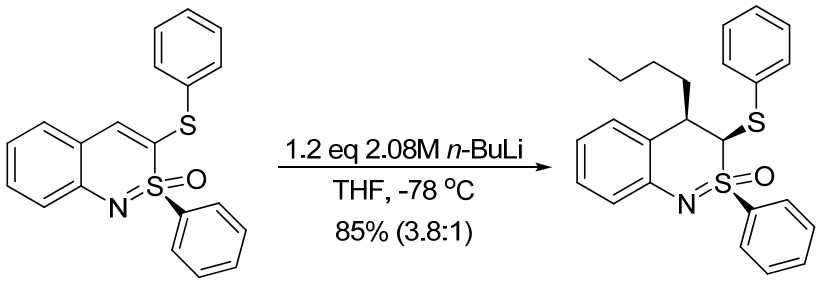
benzothiazine reactivity was seen. Remarkably, the lithiocarbanion attacked product **154e** to generate a dimeric benzothiazine **156** (Figure 32).



156

Figure 32. Lithiation Side Product **156**

To further investigate this unforeseen reactivity. The sulfide **154e** was simply treated with *n*-BuLi and allowed to warm to room temperature. This gave butylated product **157** in 85% yield in a 3.8:1 diasteromeric ratio (Scheme 73). This new Michael reaction of a 2,1-benzothiazine suggests that the sulfoximine and other polarizable or electron withdrawing groups will consume excess base and prevent further deprotonation. If *n*-BuLi acts as a nucleophile rather than a base, the protecting group scope becomes an issue.



154e **157**

Scheme 73. 1,4-Addition of *n*-BuLi to **154e**

This provides evidence for the reason that *iso*-butyl formate **154k** had a range of yields. It is possible that once the product began forming that the remaining

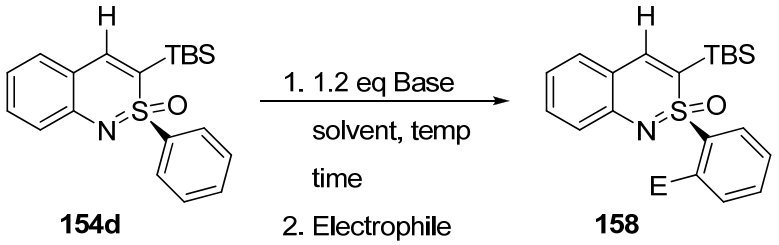
lithiocarbanion began attacking the product in a similar fashion to the sulfide **154e** to give dimeric product **156**. In the end, a new synthetic method for creating chiral benzylic centers has been shown. The ability to remove both the sulfide and sulfoximine via reductive desulfurization allows for highly functionalized benzothiazine precursors that could be applied to natural product syntheses. Further explorations into this Michael addition need to be examined for generality.

4.2.2 *Ortho-S*-phenyl Lithiation of α-Silyl Protected Benzothiazines

Initial studies began by using TBS-protected benzothiazine **154d**. This was deemed the most logical protecting group as it could be easily removed with TBAF later. Many attempts were made to *ortho*-lithiate the *S*-phenyl sulfoximino ring (Table 26). Shown previously to be general for sulfoximines, benzothiazine reactivity appeared quite different. All efforts to *ortho*-lithiate failed except for deuterium trapping (Table 26, entries 13-15).

Various lithium bases were tried with or without TMEDA, of which none were successful with any electrophile other than MeOD used for deuterium exchange (Table 26, entries 12-15). A recent addition to the unique variety of commercial main group metal bases, *i*-PrMgCl-LiCl/TMPH developed by Knochel and coworkers was also employed that helped in the *ortho*-lithiation of 2-phenylpyridine systems;[54] however, only recovered starting material was seen (Table 26, entries 8-10). Deprotonation with *n*-BuLi/THF/-78 ^{o}C/MeOD reactions gave 81-83% deuterium incorporation seen in 2-6 hours respectively (Table 26, entries 13-15). Other attempts were made with trimethylsilyl, TMS-benzothiazine **154a** and the results are summarized in Table 27.

Table 26. *Ortho*-Lithiation Study of α-TBS-Protected Benzothiazine **154d**

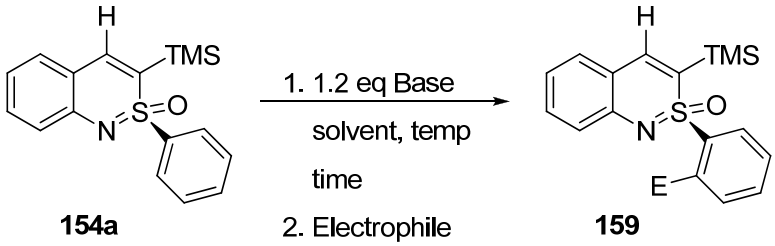


154d **158**

Entry	Base	Additive	Solvent	Temp. (°C)	Time (h)	E	Yield (%)
1	*s*-BuLi	---	ether	-78	1	$Ph_2C(OH)$	*n.r.*
2	*s*-BuLi	---	PhMe	-78	0.5	$Ph_2C(OH)$	*n.r.*
3	*s*-BuLi	TMEDA	PhMe	-78	2	$Ph_2C(OH)$	*dec.*
4	*s*-BuLi	---	PhMe	0	2	$Ph_2C(OH)$	*dec.*
5	*s*-BuLi	---	PhMe	35	2	$Ph_2C(OH)$	*dec.*
6	*n*-BuLi	---	THF	-78	3	A[a]	*dec.*
7	*n*-BuLi	TMEDA	PhMe	115	3	A[a]	*dec.*
8	*i*-PrMgCl-LiCl	TMPH	THF	-78	2	PCy_2	*n.r.*
9	*i*-PrMgCl-LiCl	TMPH	THF	35	20	I	*n.r.*
10	*i*-PrMgCl-LiCl	TMPH	THF	55	24	I	*n.r.*
11	*n*-BuLi	---	THF	-78	1	PPh_2	*n.r.*
12	*t*-BuLi	---	THF	-78	0.2	D	14
13	*n*-BuLi	---	THF	-78	2	D	81
14	*n*-BuLi	---	THF	-78	4	D	83
15	*n*-BuLi	---	THF	-78	6	D	83

[a] E = A (Figure 15, p. 50)

Table 27. *Ortho*-Lithiation Study of α-TMS-Protected Benzothiazine **154a**



154a **159**

Entry	Base	Additive	Solvent	Temp (^{o}C)	Time (h)	E	Yield (%)
1	*n*-BuLi	---	THF	-78	1	TMS	*mixture*[a]
2	*n*-BuLi	TMEDA	PhMe	-78	2	TMS	*mixture*[a]
3	*s*-BuLi	---	PhMe	0	2	Br	*mixture*[a]

[a] >85% conversions by crude NMR but partial hydrolysis on silica gel gave inseparable mixtures

It appears from the Table 26 that in 2 hours *n*-BuLi deprotonates the *ortho-S*-phenyl hydrogen to the extent of at least 80%. The acidity of the silica gel gave partial cleavage of the α-TMS group as well as the *ortho*-TMS group yielding a mixture of numerous adducts that could not be individually separated. This suggested at the time that the only compatible electrophile was MeOD for *ortho-S*-phenyl trapping of **154d**. The next section describes another attempted path to metalate the *ortho-S*-phenyl ring.

4.2.3 ***Ortho-S*-phenyl Lithiation of a Hydroxy Substituted Benzothiazine**

The *iso*-propanol appendage was investigated to determine if the lithium base could be directed. The hope was that the lithium base aggregate would position itself in such a way to allow for a more reactive species. Another equivalent of base was required to deprotonate the hydroxy group first; the second equivalent of base, would deprotonate the *ortho-S*-phenyl sulfoximine hydrogen. A neighboring group participation effect

could allow the alkoxide to assist in deprotonation of the *S*-phenyl ring (Figure 33). In the end, the few deprotonation sequences that were tried were unsuccessful (Table 28).

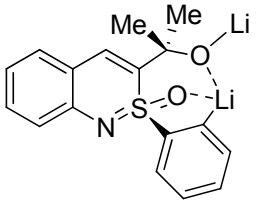
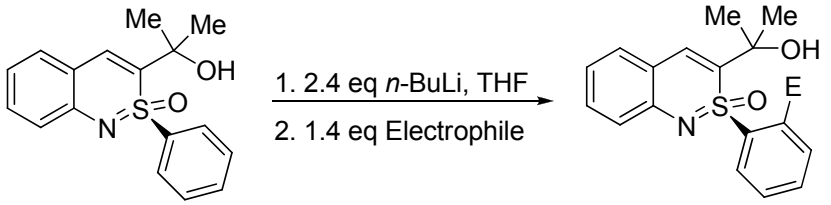


Figure 33. Possible Stabilization Model for *S*-phenyl Lithiation

Table 28. *Ortho*-Lithiation Study of Benzothiazine **154s**



154s **160**

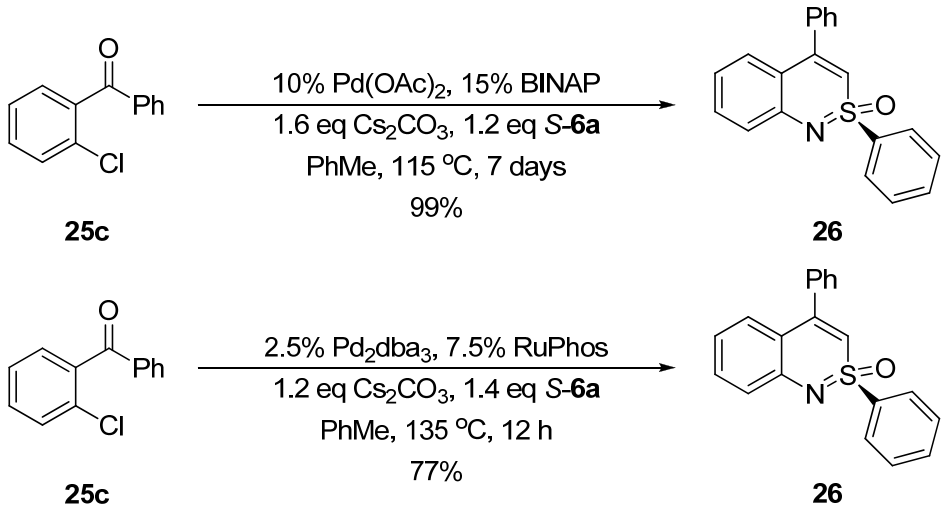
Entry	Additive	Solvent	Temp. (°C)	Time (h)	E	Yield (%)
1	---	THF	-78	3	$Ph_2C(OH)$	*n.r.*
2	---	THF	35	3	Br	*n.r.*
3	TMEDA	THF	-78	4	A[a]	*dec.*

[a] E = A (Figure 15, p. 50)

This concludes the description of our studies on the protection-deprotonation sequence in order to achieve *P,N*-ligand **153**. Only two electrophiles were able to shed any light on dilithiation reactivity of **1**. Both TMSCl and MeOD are very small, reactive electrophiles for our metalated benzothiazine nucleophiles. Increasing bulk at the 4-position of the benzothiazine is likely required to avoid unwanted Michael additions. This is the topic for the following section.

4.2.4 **α-Lithiation of Benzothiazine 26**

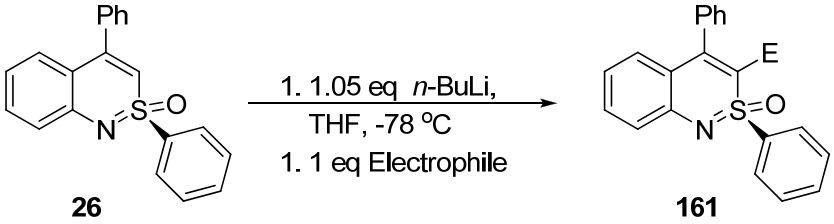
Due to the difficulty in preparing benzothiazine **14** or **146** in enantiopure form via sulfoximine *N*-arylation of bromo- or chloroacetophenone, we directed our attention to the non-enolizable ketone 2-chlorobenzophenone. Initially, the thermal reaction ($Pd(OAc)_2$/BINAP, Cs_2CO_3, **6**, PhMe, 7 days) afforded quantitative conversion, albeit in nearly a week. The new procedure (Pd_2dba_3/RuPhos, Cs_2CO_3, **6**, PhMe, 12 h) afforded an acceptable yield (77%) in as little as 12 hours. Both reactions are shown below in Scheme 74.



Scheme 74. Thermal *N*-Arylation of 2-Chlorobenzophenone **25c**

A similar monolithiation approach was investigated **26** as for the less bulky benzothiazine **1** shown previously. The goal was to expand the scope of the metalation reaction of benzothiazines. Several electrophiles were examined as shown below (Table 29).

Table 29. α-Lithiation Summary of Benzothiazine **26**



26 **161**

Entry	Electrophile	E	Product	Yield (%)
1	TIPSCl	TIPS	**161a**	0
2	Me_2CO	$Me_2C(OH)$	**161b**	0
3	Ph_2CO	$Ph_2C(OH)$	**161c**	0
4	I_2	I	**161d**	74
5	$C_2Br_2Cl_4$	Br	**161e**	95
6	PhCHO	*rac*-PhCH(OH)	**161f**	75[a]
7	MeSSMe	SMe	**161g**	98[b]
8	PhSSPh	SPh	**161h**	94[b]
9	EtSSEt	Set	**161i**	88[b]
10	CySSCy	SCy	**161j**	98[b]
11	*t*BuSS*t*Bu	S*t*Bu	**161k**	19

[a] Diasteromeric ratio of 2.4:1 observed.
[b] Dilithiocarbanion was trapped in minor amounts.

The reactivity pattern of **26** was quite different from that of **1**. TIPSCl did not react with the sulfoximine stabilized vinyl carbanion of benzothiazine **26**, most likely due to steric effects (Table 29, entry 1). Both the enolizable acetone and non-enolizable benzophenone were unreactive with the organolithium derived from **26** although they appeared very reactive with **1** (Table 29, entries 2 and 3). Remember, benzothiazine **146**

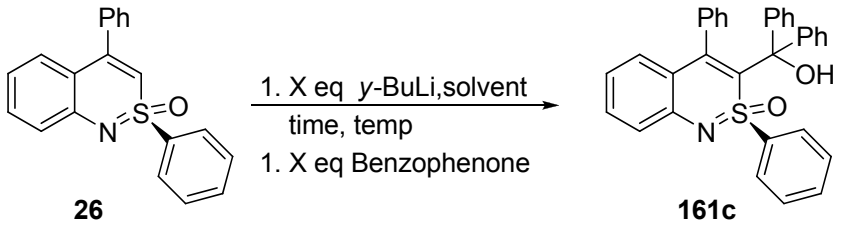
was reported by Harmata to react with benzophenone as an electrophile in 65% yield[50] suggesting that steric hindrance plays at least a minor role in the metalation studies presented herein. Note that benzaldehyde reacted smoothly in 75% yield to give **161f** with slightly improved diastereoselectivity as compared to both **1.** This increase in diastereomeric ratio is likely due to steric crowding near the adjacent 4-phenyl substituent.

The reaction of disulfides gave a remarkable breakthrough in benzothiazine dilithiation chemistry. Previously, benzothiazine **1** gave butylated product **157** when trapped with diphenyl disulfide. Now with the 4-position crowded with the phenyl group, numerous disulfides reacted smoothly without butylation in yields ranging from 98-88% yield (**161g-j,** Table 29, entries 7-10). Only a 19% yield of **161k** was obtained using di-*t*-butyl disulfide, the bulkiest disulfide electrophile tested (Table 29, entry 11). In the crude NMR, doubly substituted benzothiazines were observed in all cases except for very bulky di-*t*-butyl disulfide.

Based on the fact that benzothiazine **146** reacts with benzophenone in 65% yield to form **147e**[50] and benzothiazine **1** reacts with benzophenone in 91% yield, but that benzothiazine **26** did not react, an investigation probing lithiation was carried out to see if changes in reaction conditions would allow for an observable reaction of benzophenone with benzothiazine **26**. The results are shown in Table 30. In the best examples, less than <5% conversion was observed with extremely dirty crude reactions. Thus, it appears that benzophenone is too bulky to be trapped by the conjugate base of **26** in observable amounts. Significant differences in reactivity are shown by both

unsubstituted benzothiazine **1**, methyl-substituted benzothiazine **146**, and phenyl-substituted benzothiazine **26**.

Table 30. α-Lithiation Summary of Benzothiazine **26** with Benzophenone



26 **161c**

Entry	X (eq)	*y*-BuLi	Additive	Solvent	Temp. (^{o}C)	Time (h)	Ratio (26:161c)
1	1.2	*n*	---	THF	-78	0.25	*no reaction*
2	2.2	*t*	---	ether	-78	0.20	*trace*
3	2.2	*t*	---	ether	-78	1	*trace*
4	2.2	*t*	---	ether	0	2	*trace*
5	2.2	*t*	---	ether	0	0.20	*trace*
6	2.2	*t*	---	ether	-78	2	*trace*
7	2.1	*t*	---	THF	-78	0.20	*no reaction*
8	2.1	*t*	---	THF	-78	1	36 : 1
9	2.1	*s*	TMEDA	THF	-78	0.75	*no reaction*
10	2.1	*s*	TMEDA	THF	-78	4	*no reaction*
11	2.1	*s*	TMEDA	THF	-78	8	*no reaction*
12	2.1	*s*	TMEDA	THF	0	0.33	34:1
13	2.1	*s*	TMEDA	THF	0	4	*no reaction*
14	2.1	*n*	TMEDA	THF	0	0.33	*no reaction*
15	2.1	*n*	TMEDA	THF	0	3	*no reaction*

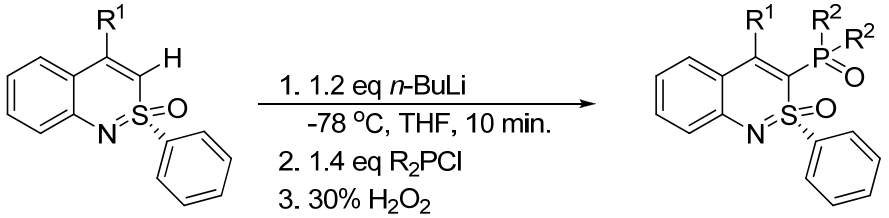
16	2.1	*n*	TMEDA	THF	0	0.33	*no reaction*
17	2.1	*n*	TMEDA	THF	0	3	*no reaction*
18	2.1	*n*	TMEDA	THF	-78	1	*no reaction*
19	2.1	*n*	TMEDA	THF	-78	4	30:1
20	2.1	*n*	TMEDA	THF	-78	22	37:1
21	2.1	*n*	TMEDA	THF	-78	0.25	*no reaction*

4.2.5 ***P*-Ligand Syntheses**

Up to this point, we experienced limited success trapping larger electrophiles with the lithiocarbanion of 4-phenyl substituted benzothiazine **26**. The steric bulk of the 4-phenyl ring of **26** introduced a different challenge than seen before with benzothiazine **1**, namely, trapping of bulkier electrophiles. To our delight, monolithiation of both benzothiazine **26** and benzothiazine **1** and their subsequent trapping with phosphine chlorides was general (Table 31).

Overall, the difference in yield between benzothiazines **1** and **26** was minimal, except with di-*t*-phosphine chloride (Table 31, entries 4 and 8). All of the phosphines prepared were sensitive to oxidation during their isolation and purification. Thus, we oxidized the products with hydrogen peroxide in the hope that the corresponding phosphine oxides could be isolated. However, baseline impurities prevented these extremely polar compounds from being isolated cleanly. As a result, reaction conversion is shown instead of reaction yield because upon isolation, some minor impurities remained. Therefore, if these potential ligands were to be used in asymmetric reaction, the crude products would be better utilized if trapped *in situ* by the appropriate metal and used as a metal-bound catalyst.

Table 31. α-Lithiation Summary of Benzothiazine**s 1** and **26** with Phosphines



R^1 = H; **1**
R^1 = Ph; **26**

162

Entry	R^1	R^2	Product	Conversion (%)
1	Ph	phenyl	**162a**	85
2	Ph	cyclohexyl	**162b**	84
3	Ph	piperidyl	**162c**	89
4	Ph	*t*-butyl	**162d**	0
5	H	phenyl	**162e**	88
6	H	cyclohexyl	**162f**	88
7	H	piperidyl	**162g**	90
8	H	*t*-butyl	**162h**	60
9	H	*i*-propyl	**162i**	59
10	H	A[a]	**162j**	51

[a] E = A (Figure 15, p. 50)

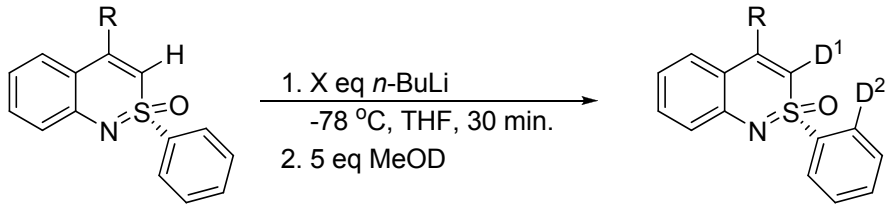
4.3 Dilithiation of Benzothiazines

4.3.1 Multilithiation Deuterium Study

With some data for the α-lithiation of some benzothiazines we concluded that benzothiazine **26** appeared to have the most promise and would allow for the fewest side reactions. For that reason, **26** was studied for dimetalation reactivity as it appeared that dilithiation had occurred to a small extent in previous metalation studies. For

comparison, benzothiazine **1** was also screened with MeOD to see if deuterium incorporation was general. The results are shown in Table 32. The reactions were run in THF at -78 ^{o}C with *n*-BuLi as base. The base was allowed to stir for 30 minutes before it was quenched with 5 equiv. of MeOD and the ratio was determined by the disappearance of the respective protons from the crude ^{1}H NMR spectra.

Table 32. Deuterium Study of 2,1-Benzothiazines **26** and **1**



R = H, **1**
R = Ph, **26**

R = H, **163**
R = Ph, **164**

Entry	R	X (eq)	D^1 (%)	D^2 (%)
1	**1**	3.0	95	109
2	**26**	3.0	82	108
3	**1**	2.5	93	62
4	**26**	2.5	92	76
5	**1**	2.0	70	19
6	**26**	2.0	95	72
7	**1**	1.5	99	38
8	**26**	1.5	90	17
9	**1**	1.0	96	16
10	**26**	1.0	83	19
11	**1**	3.0	98	100

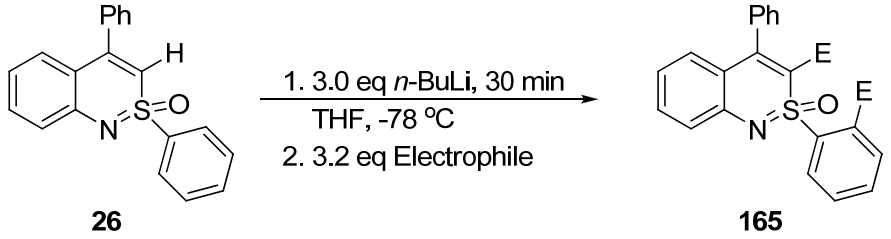
12	**26**	3.0	100	107
13	**1**	1.0/TMPH	81	40
14	**1**	1.5/TMPH	77	25
15	**1**	2.0/TMPH	92	52
16	**1**	2.5/TMPH	94	46
17	**1**	3.0/TMPH	95	50
18	**1**	3.5/TMPH	95	81

One equivalent of base gave primarily monolithiation with an observable amount of dilithiation (Table 32, entries 9 and 10). It was not until 3 equivalents of base were added that complete deprotonation of the *ortho*-*S*-hydrogen was seen along with a trace amount of trilithiation (Table 32, entries 1 and 2). Since excess *n*-BuLi is an incompatible base for benzothiazine **1**, TMPH was evaluated. As a result, 80% D-incorporation of the *ortho*-*S*-position was observed when 3.5 equiv. of LiTMP was added. In general, deprotonation of both benzothiazines **1** and **26** were very similar. This confirmed the hypothesis that differences in electrophile trapping were due to steric hindrance. Sulfoximine-stabilized dilithiocarbanions were examined in the next section.

4.3.2 **Dilithiation of Benzothiazine 26**

Using the previous methods, several electrophiles were employed to see if, indeed, double electrophilic trapping was a general process as shown earlier with the D incorporation. Due to visibility of di-sulfido products in the crude NMR of previous monometallations, disulfides were the central focus (Table 33). This reaction was carried out under similar conditions as reported above in Table 32 using excess *n*-BuLi and an even a slightly larger excess of electrophile.

Table 33. Dilithiation Study of Benzothiazine **26**



26 **165**

Entry	Electrophile	E	Product	Yield (%) (Double)	Yield (%) (Single)
1	MeSSMe	SMe	**165a**	98	trace
2	PhSSPh	SPh	**165b**	94	2
3	EtSSEt	SEt	**165c**	89	3
4	CySSCy	SCy	**165d**	98	0
5	*t*BuSS*t*Bu	S*t*Bu	**165e**	0	19
6	Ph_2CO	$Ph_2C(OH)$	**165f**	0	0
7	TMSCl	TMS	**165g**	*mixture*	*mixture*
8	I_2	I	**165h**	91	0
9	$Br_2Cl_4C_2$	Br	**165i**	95	0
10	$ClPCy_2$	PCy_2	**165j**	0	70[a]
11	$ClP(piperidyl)_2$	$P(piperidyl)_2$	**165k**	0	54[a]
12	$ClP(t\text{-}Bu)_2$	$P(t\text{-}Bu)_2$	**165l**	0	0

[a] Conversion is reported as the product could not be isolated cleanly.

Most disulfides examined trapped extremely well (Table 33, entries 1-4). Only di-*t*-butyl disulfide provided a monosubstituted adduct in poor yield (Table 33, entry 5). Halide trapping sources worked well giving di-iodo **165h** and di-bromo **165i** (Table 33, entries 8 and 9). Phosphines that were investigated also gave only monosubstituted

products in either no yield or moderate conversions (Table 33, entries 10-12). Thus, *P,N*-ligands of this type seem unattainable at this time by metalation and, as a result, were not investigated further.

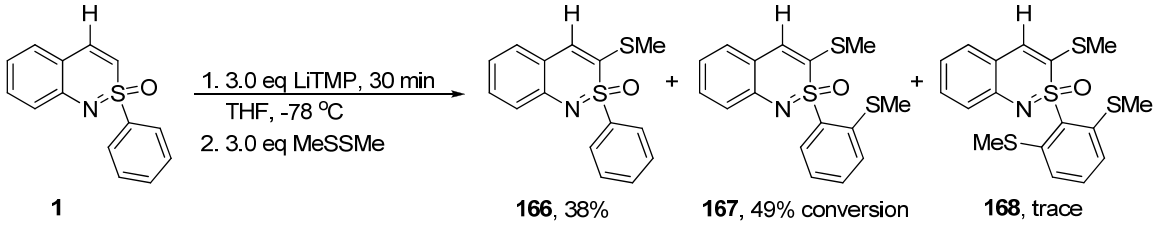
Overall, this provides evidence that dilithiation occurs and the resulting dianion can be trapped by several electrophilic classes. Bulky substrates did not trap efficiently in a disubstituted fashion and only the α-3-position was trapped. The remaining *ortho*-*S*-phenyl lithiocarbanion must have a relatively long lifetime because deuterium studies reported earlier provided evidence that dimetalation was complete under this procedure. Thus the anion must have been quenched in the workup with ammonium chloride. The investigation above is the first example of a successful dilithiation of a 2,1-benzothiazine. Many examples gave excellent yields with numerous electrophiles.

4.3.3 **Dilithiation of Benzothiazine 1**

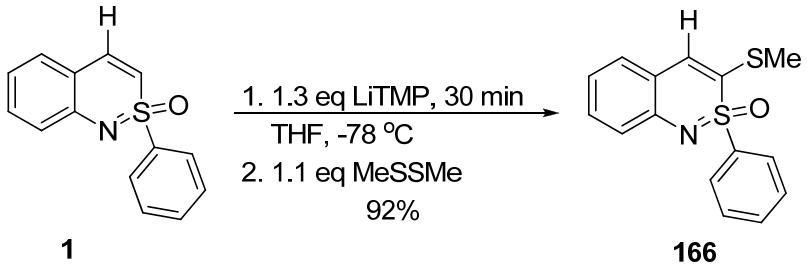
Due to the dilithiation success of benzothiazine **26**, we examined dilithiation of benzothiazine **1** taking into consideration the limitations of the bare 4-postion when using an excess of alkyl lithium base. It was shown previously that moderate amounts of deprotonation were observed with LiTMP amine base in the deuterium incorporation study. Thus, we reacted **1** with LiTMP, stirred for 30 minutes, and quenched with excess disulfide. To our surprise, we observed three products. One product was identified by X-ray crystallography as a trisubstituted benzothiazine found in trace amounts. The following scheme shows identities of all three products (Scheme 75).

Since this provided an alternate route by which problematic electrophiles could be trapped via monometallation 1.3 equiv. of LiTMP were added and the resulting anion was trapped with dimethyl disulfide. Previously butylation was observed with phenyl

sulfide products generated *in situ*, but, in this example, successful monometallation and trapping of dimethyl disulfide was seen with no side products (Scheme 76).



Scheme 75. Dilithiation of Benzothiazine **1** with Dimethyl Disulfide



Scheme 76. Monolithiation of Benzothiazine **1** with Dimethyl Disulfide

4.3.4 **Attempts Toward Electrophile "Dancing"**

The deuterium study discussed earlier provided evidence that multiple anions exist of differing character. We were interested in exploiting the pK_a difference between the two metalation sites. We wanted to "dance" an electrophile from the α-position of our benzothiazine by an intermolecular electrophile exchange to the *ortho*-*S*-phenyl position. Theoretically, the *ortho*-*S*-phenyl position would have a much higher pK_a than the sulfoximine stabilized vinyl carbanion site. To test this hypothesis, various monosubstituted products containing softer electrophiles were subjected to various basic conditions to see if, indeed, the *ortho*-*S*-phenyl lithiocarbanion would attack the electrophile and generate the more stable anion, which could be quenched by a proton in the workup. A possible mechanism of this mode of "electrophile dancing" is shown generically below in Figure 34. This is not a new concept as halogen dancing has been

studied in depth as shown in a review by Stanetty and coworkers.[55] A summary of our investigation is shown in Table 34. In short, we found no significant exchange from the α-position to the *ortho*-*S*-phenyl position of any of the substrates we investigated. It appeared that –SMe was slightly more favorable and led to trace exchanges as observed in the crude NMR compared to the –SPh substrate. Overall, there is not enough evidence in this study to suggest that significant "dancing" occurred.

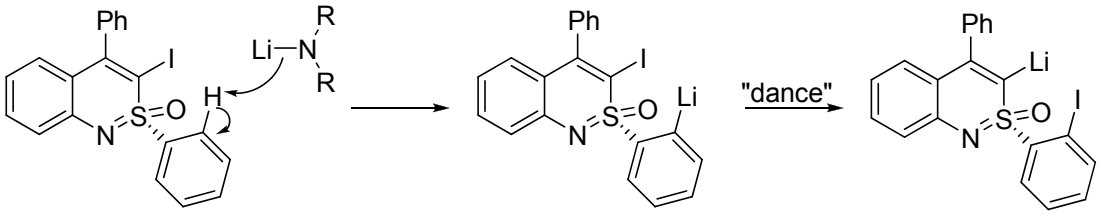
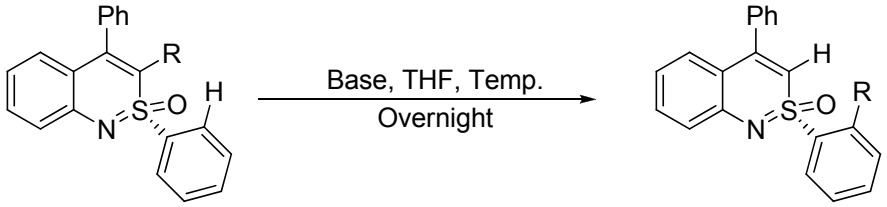


Figure 34. Mechanism of an Electrophile "Dance"

Table 34. Attempts Toward an Electrophile "Dance"



154 **169**

Entry	Base (eq)	R	Temp.[a] (^{o}C)	Result
1	LiTMP (1.1)	Br	-78	*no reaction*
2	LiTMP (1.1)	I	-78	*no reaction*
3	*n*-BuLi (1.05)	SMe	-78	*decomposition*
4	*n*-BuLi (1.05)	SPh	-78	*decomposition*
5	LiTMP (1.05)	Br	35	*decomposition*
6	LiTMP (1.05)	I	35	*decomposition*
7	LiTMP (1.05)	SMe	-40	*trace*

8	LiTMP (1.05)	SPh	-40	*trace*
9	LHMDS (1.05)	SMe	-78	*no reaction*
10	LHMDS (1.05)	SPh	-78	*no reaction*
11	*s*-BuLi (1.05)	SMe	-78	*decomposition*
12	*s*-BuLi (1.05)	SPh	-78	*decomposition*
13	PhLi (1.05)	SMe	-78	*trace*
14	PhLi (1.05)	SPh	-78	*no reaction*
15	LDA (1.05)	SMe	-78	*trace*
16	LDA (1.05)	SPh	-78	*no reaction*
17	LDEA (1.05)	SMe	-78	*trace*
18	LDEA (1.05)	SPh	-78	*no reaction*
19	PhLi (2.0)	SMe	-78	*no reaction*
20	PhLi (3.0)	SMe	-78	*no reaction*
21	PhLi (1.0)	SMe	0	*trace*
22	PhLi (2.0)	SMe	0	*decomposition*
23	LiTMP (1.25)	SMe	-78	*no reaction*
24	LiTMP/LiBr (1.25)	SMe	-78	*no reaction*

[a] All reactions were warmed to room temperature overnight.

4.3.5 **Lithiation Summary**

Numerous investigations of both benzothiazine **1** and benzothiazine **26** led to the same conclusion. Lithiation of these benzothiazine were quite different than their less rigid *N*-substituted sulfoximine analogs. The *N*-substituted sulfoximines presented in the beginning of this chapter had limited functionality outside the acidic α-methyl carbon and

the acidic *ortho*-*S*-phenyl hydrogen. Our study began by extensively trapping benzothiazine **1** with a variety of electrophiles exclusively at the 3-position. Butylation of benzothiazine **1** with *n*-BuLi gave 1,4 addition products *in lieu* of the desired dilithiation. Several polarizing and electron withdrawing substituents at the 3-position provided for a wide range of isolated yields likely due to the similar 1,4-addition processes. These side reactions were circumvented by switching to benzothiazine **26**.

Benzothiazine **26** was trapped by a variety of electrophiles at the 4-position as well. Several electrophiles provided poor yields due to steric interactions of the 4-phenyl group. Once a more efficient procedure was devised several electrophiles were trapped at both the α-3-position and *ortho*-*S*-phenyl position of benzothiazine **26** in good yields. The electrophiles were limited, however, to disulfides and halogenating electrophiles. Larger less reactive electrophiles, such as benzophenone, failed to trap at either position. In the same manner, seemingly large phosphine chlorides did trap in good yield with benzothiazine **26**.

The dilithiation of benzothiazine **26** was found to be general, and the dilithiation of benzothiazine **1** was found to not be general. A deuterium study expressed no difference in the rate at which deprotonation occurred with *n*-BuLi. Differences in reactivity were determined to be driven by electrophile reactivity and electrophile size compared to the metalated benzothiazine. All routes to *P,N*-ligands via benzothiazine **1** or **26** failed. Several mono *P*-ligands were prepared from benzothiazine **26** but required oxidative trapping due to their inherent sensitivity to oxidation. All of the research reported herein describes the novel but unique nature of benzothiazines. The potential of benzothiazines was expanded and we increased the applications of benzothiazines in

synthetic organic chemistry. A list of all lithiation reactions reported herein is illustrated below in Figure 35.

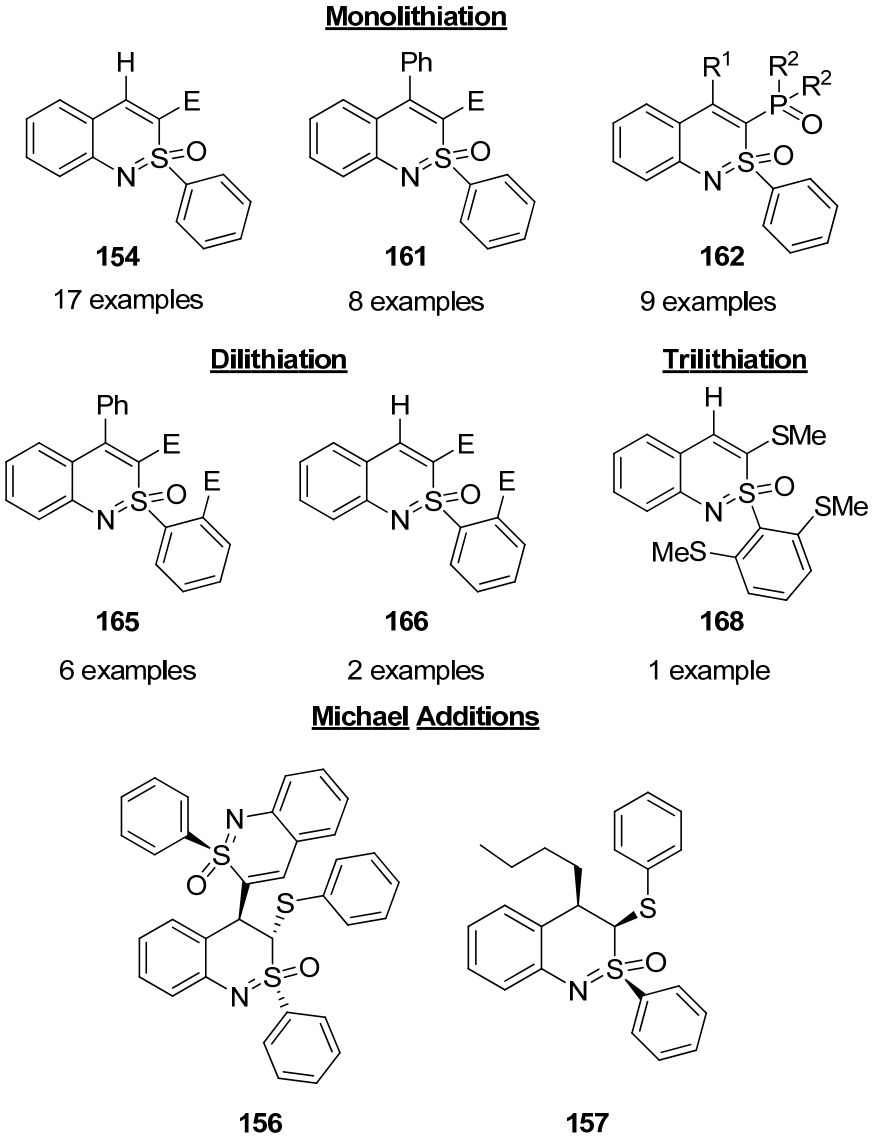


Figure 35. Lithiation Reactivity Summary

CHAPTER 5

Experimental Results

5.1 General Information

All reactions performed were carried out under anhydrous conditions involving either nitrogen or argon gas, except the metal ligand reactions of Chapter 2. The reaction design of Chapter 2 experiments involved "air". Glassware was oven dried (125 ^{o}C) and cooled by a continuous flow of dry nitrogen. Solvents were distilled under anhydrous and oxygen free conditions. Ether, toluene, and THF were dried over sodium metal and oxygen was removed by generation of a benzophenone ketyl. Dichloromethane was dried over calcium hydride in a dry nitrogen atmosphere. In most cases, reagents were distilled prior to use if liquid; solids reagents were crystallized or used directly from a newly purchased commercial container.

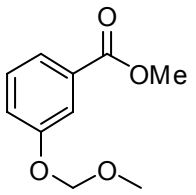
Handling of pyrophoric reagents, namely organometallic reagents, was done so with glass gas tight syringes, rubber septa, and argon balloons. Air and moisture sensitive reagents were handled with a dry nitrogen filled plastic glove bag. Molecular sieves used were freshly activated by heating to 200 ^{o}C under full vacuum (< 2 mm Hg) for several hours. Reaction mixtures were concentrated using rotary evaporators with both water aspiration and pneumatic vacuum pump sources depending on the boiling point of the solvent being removed. Residual solvent was removed by full vacuum when necessary. Silica gel used in chromatographic separations was purchased from Silicycle (230 – 400 mesh). Reactions were monitored by glass backed silica gel TLC plates purchased from Sigma Aldrich; all highly conjugated compounds were recognized by a UV irradiation lamp.

Melting points taken of new compounds were done so by a Fisher-Johns melting point apparatus. IR spectra were recorded via a liquid NaCl chamber on a Perkin Elmer 1600 series FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR were taken on one of three Bruker ARX-250, ARX-300, or ARX-500 Ultrashield spectrometers. Chemical shifts reported were in ppm with an internal TMS standard (TMS; $\delta = 0.0$). Spectra were taken with $CDCl_3$ solution containing TMS. NMR data is reported as follows: chemical shift, ppm; splitting pattern (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, etc.); coupling constant, Hz; and integration. ^{13}C NMR spectra taken were ^{1}H decoupled and contained a $CDCl_3$ ($CDCl_3$; $\delta = 77.0$) internal standard. HRMS were analyzed by a Bruker 12 Tesla Apex-Qe FTICR-MS with an Apollo II ion source.

5.2 Experimental Methods

5.2.1 Synthetic Procedures and Compound Characterization: Chapter 2

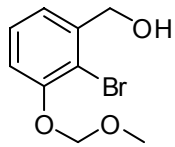
Methyl 3-(methoxymethoxy)benzoate (97): Commercially available, methyl 3-hydroxybenzoate **96** (5.27 g, 34.6 mmol) was dissolved in dry dichloromethane (70 mL), dimethoxymethane (15.27 mL, 173 mmol) and *p*-TSA (0.1319 g, 0.694 mmol) were mixed together. A Soxhlet extractor (filled with activated 4Å molecular sieves) with reflux condenser was flushed with dry nitrogen and attached. The mixture was brought to reflux for 24 hours or until the completion was observed by TLC. ($R_f = 0.75$ in 50% EtOAc/hexanes; short UV dark spot). The reaction was taken up in 10% NaOH (30 mL). Keep in mind hydrolysis of the methyl benzoate to the benzoic acid is possible and the workup stage should be carried out quickly. The resultant organic layer is washed first by water (2 x 20mL) then brine



(20mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was pure by TLC and NMR which yielded 6.619g **97** in 97% as a clear oily semi-solid with matching ^1H and ^{13}C NMR spectra as reported in the literature.[56] ^1H NMR: (250 MHz, $CDCl_3$) δ 3.45 (s, 3H), 3.88 (s, 3H), 5.18 (s, 2H), 7.19 (d, *J* = 8.2 Hz, 1H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.66 (d, *J* = 8.3 Hz, 1H), 7.69 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 51.8, 55.7, 94.1, 116.7, 120.8, 122.8, 129.2, 131.3, 157.0, 166.4.

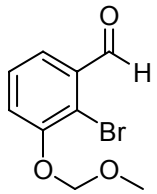
(3-(methoxymethoxy)phenyl)methanol (98): The MOM ester **97** (19.0 g, 96.9 mmol) in THF (17 mL) was added dropwise to a solution containing lithium aluminum hydride, LAH, (5.88 g, 193.8 mmol) in THF (100 mL) over 30 minutes at 0 °C. The reaction was allowed to stir further at 0 °C until TLC showed completion (3.5 hours), (R_f = 0.23 in 50% EtOAc/hexanes; short UV dark spot). The reaction was taken up in water (5.88 mL) then 15% NaOH (5.88 mL), then water (17.64 mL) to form a gray granular precipitate which was filtered off and washed by ether (20 mL). The organic layer was collected and the aqueous layer was extracted with ether (2 x 20 mL). The collected organic layers were washed by brine, dried ($MgSO_4$), and concentrated in vacuo. The crude residue was pure by TLC and NMR which yielded 14.75g **98** in 92% as a clear oil with matching ^1H and ^{13}C NMR spectra as reported in the literature.[57] ^1H NMR: (250 MHz, $CDCl_3$) δ 2.32 (s, 1H, broad), 3.45 (s, 3H), 4.61 (s, 2H), 5.15 (s, 2H), 6.96 (t, *J* = 7.1, 2H), 7.03 (s, 1H), 7.25 (t, *J* = 7.9, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 55.9, 64.9, 94.3, 114.6, 115.4, 120.3, 129.5, 142.6, 157.3.

(2-bromo-3-(methoxymethoxy)phenyl)methanol (107): A dry flask was flushed with



argon and the MOM protected benzalcohol **98** (5.05 g, 30.3 mmol) was dissolved in toluene (60 mL). At room temperature *n*-BuLi (72.9 mL, 2.20M in hexane, freshly titrated by diphenylacetic acid) was added to give a white suspension. This slurry was heated to 65 ^{o}C for 6 hours with vigorous stirring turning the heterogeneous mixture to a dark red-orange slurry. Upon cooling to room temperature, 1,1,2,2-tetrachloro-1,2-dibromoethane (11.84 g, 36.3 mmol) was added in toluene (50 mL) dropwise and stirred further for 2 hours at room temperature. The reaction was quenched by saturated NH_4Cl (20 mL). The organic layer was collected; the aqueous layer was extracted by dichloromethane (2 x 15 mL); the combined extracts were dried ($MgSO_4$) and concentrated in vacuo. (R_f = 0.58 in 50% EtOAc/hexanes; short UV dark spot). Purification by flash chromatography (silica gel) with 15% EtOAc/hexanes to afford 7.18 g **107** in 96% as a yellow oil with matching ^{1}H and ^{13}C NMR spectra as reported in the literature.[57] ^{1}H NMR: (250 MHz, $CDCl_3$) δ 2.46 (s, 1H, broad), 3.51 (s, 3H), 4.73 (s, 2H), 5.24 (s, 2H), 7.05 (d, *J* = 8.0, 1H), 7.12 (d, *J* = 6.7, 1H), 7.25 (t, *J* = 7.8, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 56.3, 65.1, 95.1, 112.9, 115.0, 121.8, 128.1, 141.5, 153.6.

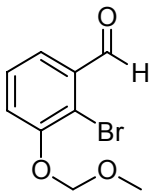
2-bromo-3-(methoxymethoxy)benzaldehyde (108): Procedure A: A dry flask was



flushed with nitrogen and oxalyl chloride (3.03 mL, 34.7 mmol) and dichloromethane (100mL) was cooled to –78 ^{o}C via a dry ice/acetone bath and was stirred for 10 minutes. Then anhydrous DMSO (4.94 mL, 69.4 mmol) was added dropwise over 10 minutes. Next, the MOM protected bromo-benzalcohol **107** (1.0 g, 4.97 mmol) was dissolved in dichloromethane (190 mL) and

added via cannula over 1 hour at –78 °C. The reaction was stirred further for one hour and then triethylamine, TEA, (20.1 mL, 144.5 mmol) was added and warmed to room temperature over 1 hour, stirred further for one additional hour. Water (50 mL) was then added; the organic layer was collected and washed again with 1N HCl until no longer basic. The organic layer was again washed by water and brine, and then dried ($MgSO_4$) and concentrated in vacuo. (R_f = 0.44 in 50% EtOAc/hexanes; short UV dark spot). Kugelrorh distillation at 2.0 mm Hg at 110 °C yielded 5.95 g **108** in 84% as a yellow-orange semi-solid at room temperature with matching ^1H and ^{13}C NMR spectra as reported in the literature.[29] ^1H NMR: (250 MHz, $CDCl_3$) δ 3.54 (s, 3H), 5.29 (s, 2H), 7.31-7.41 (m, 2H), 7.57 (dd, *J* = 6.7 Hz, *J* = 2.5 Hz, 1H), 10.43 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 56.5, 95.3, 118.0, 121.2, 122.8, 128.3, 134.9, 154.2, 192.1.

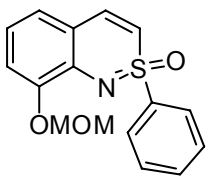
2-bromo-3-(methoxymethoxy)benzaldehyde (108): Procedure B: Commercially



available, 2-bromo-3-hydroxybenzaldehyde **110** (1.0 g, 4.97 mmol) was dissolved in THF (10 mL) along with triethylamine, TEA (3.4 mL, 24.8 mmol), NaI (0.372 g, 2.48 mmol) and stirbar. The resulting dark orange solution was then flushed with dry N_2 gas and MOMCl (0.751 mL, 9.94 mmol) was added drop-wise forming a white TEA•HCl salt. The reaction was allowed to stir further until TLC showed completion (1 hour), (R_f = 0.72 in 50% EtOAc/hexanes; short UV dark spot). The reaction was taken up in water (10 mL) and extracted with ethyl acetate (3 x 10 mL). Next the combined organic layers were washed by brine, dried ($MgSO_4$), and concentrated in vacuo. Purification by flash chromatography (silica gel) with 25% EtOAc/hexanes yielded 1.13g **108** in 93% as a yellow-orange semi-solid with matching ^1H and ^{13}C NMR spectra as reported in the literature.[29] ^1H NMR: (250 MHz, $CDCl_3$) δ

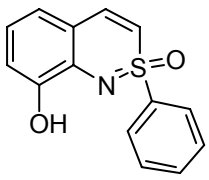
3.54 (s, 3H), 5.29 (s, 2H), 7.31-7.41 (m, 2H), 7.57 (dd, J = 6.7 Hz, J = 2.5 Hz, 1H), 10.43 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 56.5, 95.3, 118.0, 121.2, 122.8, 128.3, 134.9, 154.2, 192.1.

8-(methoxymethoxy)-2-*S*-oxa-2-*S*-phenyl-2,1-benzothiazine (109): (*N*-Arylation



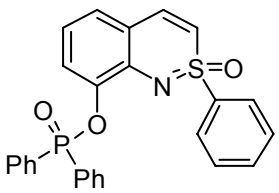
Procedure A) The protected bromoaldehyde, **108** (1.00 g, 4.08 mmol), $Pd(OAc)_2$ (45% Pd, 0.046 g, 0.204 mmol), *rac*-BINAP (0.191 g, 0.306 mmol), methyl phenyl sulfoximine **6** (0.759 g, 4.89 mmol), Cs_2CO_3 (2.12 g, 6.51 mmol) in toluene (80 mL) was flushed with dry N_2 for several minutes. A reflux condenser was added as well as a N_2 balloon. The mixture was stirred at reflux temperature (120 ^{o}C) for 48 hours. The solution was then cooled to room temperature, diluted in dichloromethane (25 mL), and filtered through a plug of celite. After being concentrated in vacuo, the dark brown semi-solid was purified by flash chromatography (silica gel) with 40% EtOAc/hexanes (R_f = 0.60 in 50% EtOAc/hexanes; long UV yellow spot) to afford 1.17g **109** in 89% as a yellow-orange solid.[28] Mp. 140 ^{o}C. ^{1}H NMR: (300 MHz, $CDCl_3$) δ 3.53 (s, 3H), 5.33 (q, J = 5.6 Hz, 2H), 6.38 (d, J = 9.8 Hz, 1H), 6.96 (t, J = 7.8 Hz, 1H), 7.07 (dd, J = 7.8 Hz, J = 1.2 Hz, 1H); 7.34 (dd, J = 7.8 Hz, J = 1.2 Hz, 1H); 7.50-7.62 (m, 3H); 7.63 (d, J = 9.8 Hz, 1H); 7.89 (d, J = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.1, 95.5, 110.4, 117.1, 118.4, 119.7, 123.4, 128.8, 129.1, 133.2, 136.4, 138.5, 141.6, 149.6; IR (NaCl, cm^{-1}) 3020, 1605, 1547, 1434, 1284, 1250, 1153, 1104, 1044, 992, 669; HRMS calculated for $C_{16}H_{15}NO_3SNa$ $[M+Na]^+$ 324.0664; Found 324.0661.

8-hydroxy-2-*S*-oxa-2-*S*-phenyl-2,1-benzothiazine (111): MOM-benzothiazine **109**



(2.43 g, 8.06 mmol) was added a solution of *iso*-propanol (32.1 mL, 419 mmol), HCl (12.1N, 16.6 mL, 201 mmol), THF (17.05 mL, 209 mmol), and stirbar. The mixture was stirred at room temperature until completion was observed by TLC (3 hours). Diluted in water (20 mL), extracted by ether (3 x 20 mL), washed by 5% (w/w) $NaHCO_3$, brine, dried ($MgSO_4$), and concentrated in vacuo. The remaining yellow-orange solid afforded 2.06 g of phenol **111** which was pure by NMR and TLC (R_f = 0.68 in 50% EtOAc/hexanes; brown/orange long UV spot) in >99% yield.[28] The solid can be purified by flash chromatography (silica gel) with 50% EtOAc/hexanes. Mp. 147 ^oC. ^1H NMR: (250 MHz, $CDCl_3$) δ 6.37 (d, J = 9.7 Hz, 1H), 6.7 (s, 1H), 6.95 (d, J = 4.7 Hz, 2H), 7.10 (p, J = 4.6 Hz, 1H), 7.54-7.67 (m, 3H), 7.67 (d, J = 9.7 Hz, 1H), 7.88 (d, J = 6.8 Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 110.2, 114.9, 115.7, 120.2, 120.4, 128.8, 129.1, 133.2, 133.6, 138.7, 141.3, 148.5; IR (NaCl, cm^{-1}) 3460, 3022, 1620, 1592, 1550, 1440, 1278, 1223, 1244, 1206, 1190, 1101, 992, 792, 729, 588, 426; HRMS calculated for $C_{14}H_{11}NO_2SNa$ $[M+Na]^+$ 280.0402; Found 280.0399.

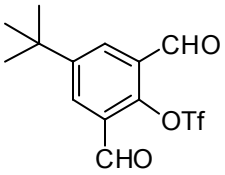
8-(*P*-oxa-*P*-diphenyl)-2-*S*-oxa-2-*S*-phenyl-2,1-benzothiazine (115): Benzothiazine **111**



(0.0587 g, 0.228 mmol) and stirbar were flushed by dry argon. THF (1.5 mL) was added to dissolve the solid resulting in a yellow solution. This solution was cooled to –78 ^oC via a dry ice/acetone bath and argon balloon. Then *n*-BuLi (2.20M in hexanes, 0.114 mL, 0.250 mmol, freshly titrated by diphenylacetic acid) was added dropwise resulting in dark brown solution. This solution was stirred further for 5 minutes at –78 ^oC and then diphenylphosphinic chloride (0.522 mL, 0.273 mmol) was added and warmed to room

temperature and further stirred overnight at room temperature resulting in a yellow-orange solution. MeOH (2 mL) was used to quench the reaction and the solvent was removed in vacuo to reveal a yellow oil which. Purification by flash chromatography (silica gel) with 50% EtOAc/hexanes and flushed with 100% EtOAc (R_f = 0.23 in 50% EtOAc/hexanes; yellow-green long UV spot) to afford 0.0953 g of **115** in 91% yield as a yellow semi-solid with matching ^{1}H and ^{13}C NMR spectra as reported in the literature.[28] ^{1}H NMR: (250 MHz, $CDCl_3$) δ 6.37 (d, *J* = 9.8 Hz, 1H), 6.86 (t, *J* = 7.9 Hz, 1H), 7.08 (d, *J* = 7.8 Hz, 1H), 7.23-7.25 (m, 2H), 7.30-7.50 (m, 4H), 7.54-7.65 (m, 4H), 7.71 (d, *J* = 7.9 Hz, 1H), 7.88 (d, *J* = 6.6 Hz, 2H), 8.02 (d, *J* = 7.5 Hz, 2H), 8.07 (d, *J* = 7.3 Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 110.6, 117.5, 119.5, 123.9, 123.9, 125.9, 128.0, 128.2, 128.5, 128.7, 129.0, 129.8, 130.5, 131.9, 132.0, 132.1, 132.8, 133.3, 138.3, 138.3, 141.6, 143.3; ^{31}P NMR (101 MHz, $CDCl_3$) δ 32.1.

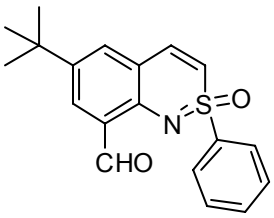
4-*tert*-butyl-2,6-diformylphenyl trifluoromethanesulfonate (117): Commercially



available phenol **116** (1.741 g, 8.44 mmol) and stirbar were treated with pyridine (1.229 mL, 15.1 mmol) at 0 °C in dichloromethane (50 mL) under a dry N_2 balloon. Triflic anhydride (1.845 mL, 10.9 mmol) was added by syringe pump (0.2 mL/min) dropwise over 10 minutes. The reaction mixture was warmed to room temperature and was stirred for an additional 30 minutes when reaction completion was observed by TLC. (R_f = 0.55 in 25% EtOAc/hexanes; dark short UV spot). The reaction was cooled to 0 °C and quenched by 1.5N HCl (5 mL) and extracted by dichloromethane (30 mL x 2). The organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The resulting organic layer was filtered by silica gel and washed by dichloromethane (100 mL). Once concentrated by vacuum,

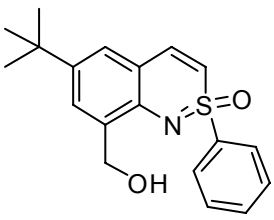
2.38 g crude triflate **117** was recovered in 83% yield as a bright yellow solid. Mp. 51 ^{o}C. ^{1}H NMR: (300 MHz, $CDCl_3$) δ 1.41 (s, 9H), 8.27 (s, 2H), 10.30 (s, 2H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.9, 35.3, 129.4, 132.6, 147.2, 153.4, 185.7; ^{19}F NMR: (235 MHz, $CDCl_3$) δ -72.3; IR (NaCl, cm^{-1}) 2970, 2878, 1700, 1595, 1479, 1464, 1436, 1410, 1368, 1217, 1156, 1136, 1103, 1087, 864, 614, 407; HRMS calculated for $C_{13}H_{13}F_3O_5SNa$ $[M+Na]^+$ 361.0328; Found 361.0335.

6-*tert*-butyl-8-formyl-2-*S*-oxa-2-*S*-phenyl-2,1-benzothiazine (118): Dialdehyde **117**



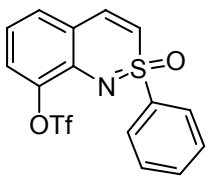
(0.215 g, 0.636 mmol), $Pd(OAc)_2$ (45% Pd, 0.0072 g, 0.0318 mmol), *rac*-BINAP (0.0297 g, 0.0477 mmol), methyl phenyl sulfoximine **6** (0.118 g, 0.763 mmol), Cs_2CO_3 (0.332 g, 1.01 mmol) in toluene (7 mL) was flushed with dry N_2 for several minutes. A reflux condenser was added as well as a N_2 balloon. The mixture was stirred at reflux temperature (120 ^{o}C) for 20 hours. The solution was then cooled to room temperature, diluted in dichloromethane (10 mL), and filtered through a plug of celite. After being concentrated in vacuo, the dark residue was purified by flash chromatography (silica gel) with 25% EtOAc/hexanes (R_f = 0.16 in 25% EtOAc/hexanes; long UV light blue spot) to afford 0.095 g **118** in 46% as an orange solid. Mp. 131 ^{o}C. ^{1}H NMR: (300 MHz, $CDCl_3$) δ 1.37 (s, 9H), 6.46 (d, *J* = 9.9 Hz, 1H), 7.59-7.68 (m, 4H), 7.69 (d, *J* = 8.1 Hz, 1H), 7.88 (d, *J* = 6.96 Hz, 2H), 8.15 (d, *J* = 2.50 Hz, 1H), 10.87 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.2, 34.2, 111.0, 116.7, 127.6, 128.6, 128.7, 129.0, 129.1, 132.5, 133.6, 138.6, 141.1, 142.7, 145.3, 191.5; IR (NaCl, cm^{-1}) 2965, 2868, 1678, 1614, 1543, 1448, 1310, 1299, 1280, 1242, 1221, 1120, 1097, 607, 573, 499; HRMS calculated for $C_{19}H_{19}NO_2SNa$ $[M+Na]^+$ 348.1029; Found 348.1028.

(6-*tert*-butyl-2-*S*-oxa-2-*S*-phenyl-2,1-benzothiazin-8-yl)methanol (119): Aldehyde



118 (0.210 g, 0.645 mmol) was dissolved in DCM (6.5 mL) with a magnetic stirbar and cooled to -40 ^{o}C. Next, DIBALH (1.29 mL, 1M solution, 1.29 mmol) was added dropwise to aldehyde **118** over 30 minutes and then warmed to room temperature. Reaction completion was found by TLC. (R_f = 0.55 in 50% EtOAc/hexanes; orange long UV spot). The reaction was quenched with water (5 mL) and extracted by dichloromethane (3 x 5 mL). The organic extracts were again washed by water (5 mL), dried ($MgSO_4$), and concentrated in vacuo. The remaining crude oil was pure by ^{1}H NMR affording 0.208 g of benzothiazine **119** in 99% yield as an orange oil. ^{1}H NMR: (250 MHz, $CDCl_3$) δ 1.35 (s, 9H), 3.83 (s, 1H, broad), 4.79 (d, *J* = 12.7 Hz, 1H), 4.99 (d, *J* = 12.7 Hz, 1H), 6.36 (d, *J* = 9.8 Hz, 1H), 7.29 (d, *J* = 2.3 Hz, 1H), 7.51–7.65 (m, 4H), 7.68 (d, *J* = 9.8 Hz, 1 H), 7.87 (d, *J* = 6.7 Hz, 2 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 31.2, 34.1, 64.0, 109.6, 115.2, 124.9, 128.5, 128.9, 129.1, 132.9, 133.3, 139.2, 141.4, 141.5, 142.6; IR (NaCl, cm^{-1}) 3445, 3070, 2966, 2246, 1616, 1588, 1551, 1448, 1296, 1269, 1250, 1118, 1098, 1005, 989, 736, 577, 511; HRMS calculated for $C_{19}H_{21}NO_2SNa$ $[M+Na]^+$ 350.1185; Found 350.1183.

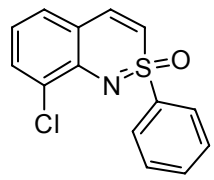
(2-*S*-oxa-2-*S*-phenyl-2,1-benzothiazine-8-yl) trifluoromethylsulfonate (120): Phenol



111 (0.196 g, 0.763 mmol) and stirbar were treated with pyridine (0.309 mL, 3.81 mmol) at 0 ^{o}C in dichloromethane (50 mL) under a dry N_2 balloon. Triflic anhydride (0.270 mL, 1.60 mmol) was added by syringe pump (0.2 mL/min) dropwise over 10 minutes. The reaction mixture was warmed to room temperature and was stirred for an additional 30 minutes when reaction

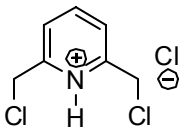
completion was observed by TLC. (R_f = 0.09 in 25% EtOAc/hexanes; blue green long UV spot). The reaction was cooled to 0 ^oC and quenched by 1.5N HCl (5 mL) and extracted by dichloromethane (30 mL x 2). The organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The resulting organic layer was filtered by silica gel and washed by dichloromethane (100 mL). Once concentrated by vacuum, a thick yellow-orange semi-solid afforded 0.297 g crude triflate **120** in 100% yield. Mp. 48 ^oC. ^1H NMR: (250 MHz, $CDCl_3$) δ 6.47 (d, *J* = 9.8 Hz, 1H), 6.99 (t, *J* = 7.9 Hz, 1H), 7.30–7.39 (m, 2H), 7.51–7.64 (m, 3H), 7.64 (d, *J* = 8.1 Hz, 1H), 7.88 (d, *J* = 6.7 Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 112.2, 116.2, 118.2, 119.1, 121.3, 124.0, 126.4, 128.6, 129.1, 129.4, 133.6, 136.9, 137.3, 138.4, 140.5, 142.0, 148.8; ^{19}F NMR: (235 MHz, $CDCl_3$) δ -73.9; IR (NaCl, cm^{-1}) 3069, 2928, 1617, 1540, 1436, 1423, 1294, 1249, 1216, 1159, 1141, 1102, 1002, 992, 864, 803, 589, 499; HRMS calculated for $C_{15}H_{10}F_3NO_4S_2Na$ $[M+Na]^+$ 411.9896; Found 411.9898.

8-chloro-2-*S*-oxa-2-*S*-phenyl-2,1-benzothiazine (121): (*N*-Arylation Procedure A)



This reaction required an extended reaction time of 6 days of refluxing toluene for observable amounts of product by TLC (R_f = 0.73 in 50% EtOAc/hexanes; light green long UV spot) with matching ^1H and ^{13}C NMR spectra as reported in the literature[31] in 40% yield as a white solid. Mp. 189 ^oC. ^1H NMR: (250 MHz, $CDCl_3$) δ 7.44 (d, *J* = 9.8 Hz, 1H), 7.0 (t, *J* = 7.8 Hz, 1H), 7.30 (dd, J_1 = 7.8 Hz, J_2 = 1.4 Hz, 1H), 7.53–7.67 (m, 5H), 7.92 (d, *J* = 6.7 Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 111.2, 117.4, 120.0, 127.5, 128.3, 128.9, 129.0, 132.2, 133.5, 138.2, 141.1, 142.0.

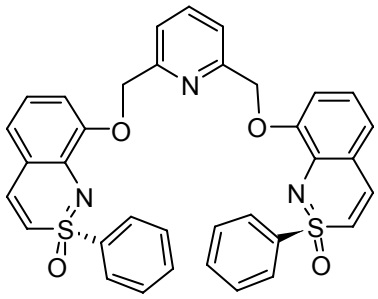
2,6-bis(chloromethyl)pyridinium chloride (127): *(Step 1 of 3)* Commercially available



dicarboxylic acid **126** (2.57 g, 15.4 mmol) was suspended in absolute ethanol (80 mL). Six drops of concentrated sulfuric acid was then added and the mixture was brought to reflux (85 ^{o}C) for 20 hours. The solvent was removed under full vacuum and the product was not purified further affording 3.17 g of diethyl pyridine-2,6-dicarboxylate in 92% yield as a white semi-solid with matching ^{1}H and ^{13}C NMR spectra as reported in the literature.[33] (R_f = 0.15 in 50% EtOAc/hexanes; yellow-orange long UV spot). Mp. 29 ^{o}C. ^{1}H NMR: (250 MHz, $CDCl_3$) δ 1.46 (t, J = 7.3 Hz, 6H), 4.49 (q, J_1 = 7.2 Hz, 4H), 8.02 (t, J = 7.3 Hz, 1H), 8.29 (d, J = 6.3 Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 14.1, 62.2, 126.6, 127.7, 128.6, 138.1, 148.6, 164.5. *(Step 2 of 3)* Then diethyl pyridine-2,6-dicarboxylate (3.17 g, 14.1 mmol) was dissolved in absolute ethanol (75 mL). $NaBH_4$ (1.07 g, 17.0 mmol) was added in portions in air and then $CaCl_2$ (2.15 g, 17.0 mmol) was added in portions evolving hydrogen gas at room temperature. The reaction mixture was stirred further for 4 hours at which time no starting material remained by TLC and a dark baseline spot appears (R_f = 0.0 in 25% EtOAc/hexanes; dark short UV spot). The solvent was evaporated under vacuum and saturated potassium carbonate solution was added (30 mL) and left overnight. Dichloromethane was then added (50 mL) which was extracted by EtOAc (3 x 25 mL) and dried ($MgSO_4$) and the solvent was again removed resulting in an off white solid that was recrystallized in absolute ethanol to afford 1.63 g of pyridine-2,6-diyldimethanol in 82% yield with matching ^{1}H and ^{13}C NMR spectra as reported in the literature.[34] Mp. 131 ^{o}C. ^{1}H NMR: (300 MHz, $CDCl_3$) δ 3.35 (s, 2H, broad), 4.78 (s, 4H), 7.19 (d, J = 7.5 Hz, 2H), 7.69 (t, J = 7.8 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 63.9, 128.4, 129.6,

139.3. *(Step 3 of 3)* A portion of the pyridine-2,6-diyldimethanol (0.269 g, 1.93 mmol) was suspended in diethyl ether (10 mL) and cooled to 0 ^{o}C. Then $SOCl_2$ (0.170 mL, 2.32 mmol) was added in diethyl ether (5 mL) over 15 minutes. The reaction mixture was warmed to room temperature and stirred overnight. The white hydrochloride salt was filtered to afford 0.382 g of **127** in 93% with matching ^{1}H and ^{13}C NMR spectra as reported in the literature.[35] Mp. 117 ^{o}C. ^{1}H NMR: (250 MHz, $CDCl_3$) δ 2.17 (s, H), 5.22 (s, 4H), 7.98 (d, *J* = 8.0 Hz, 2H), 8.38 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 50.8, 123.4, 146.5, 150.9.

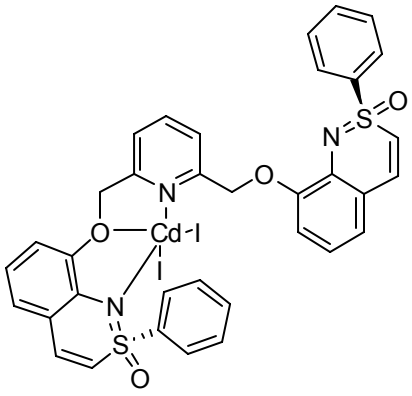
***R,R*-2,6-bis(dimethyl-8-*O*-2-*S*-oxa-2-*S*-phenyl-2,1-benzothiazine)pyridine (128):**



Phenol **111** (0.106 g, 0.414 mmol) and stirbar were treated with NaH (60% in mineral oil, 0.026 g, 0.6587 mmol) at 0 ^{o}C in DMF (10 mL) under a dry N_2 balloon resulting in a dark red solution. After 5 minutes, the 2,6-bis(chloromethyl)pyridinium chloride (0.040 g, 0.188 mmol) was added as a solid, allowed to warm to room temperature and stirred until completion by TLC (20 hours) (R_f = 0.15 in 50% EtOAc/hexanes; yellow-orange long UV spot). The reaction was quenched with water (5 mL) and extracted by dichloromethane (3 x 5 mL). The organic extracts were again washed by water (5 mL), dried ($MgSO_4$), and concentrated in vacuo. The remaining crude oil was purified by flash chromatography (silica gel) with 50% EtOAc/hexanes and flushed by 80% EtOAc/hexanes to afford 0.073 g of heterocycle **128** in 89% as an off-white solid. Mp. 124 ^{o}C. ^{1}H NMR: (250 MHz, $CDCl_3$) δ 5.42 (s, 4H), 6.35 (d, *J* = 9.8 Hz, 2H), 6.6 (t, *J* = 7.6 Hz, 2H), 6.95 (d, *J* = 7.6 Hz, 4H), 7.47-7.66 (m, 11H), 7.89 (d, *J* = 6.6 Hz, 4H); ^{13}C

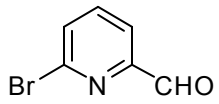
NMR (63 MHz, $CDCl_3$) δ 71.6, 110.3, 115.3, 117.0, 119.6, 120.0, 122.3, 128.8, 129.05, 133.2, 136.1, 137.6, 138.5, 141.7, 150.8, 157.0; IR (NaCl, cm^{-1}) 3015, 1605, 1546, 1464, 1449, 1432, 1284, 1256, 1223, 1206, 1105, 1090, 993, 792, 729, 426; HRMS calculated for $C_{35}H_{27}N_3O_4S_2Na$ $[M+Na]^+$ 640.1335; Found 680.1362.

Cd-complex (129a): The heterocycle **128** (0.0244 g, 0.00394 mmol) was dissolved in



dichloromethane (1 mL) and CdI_2 (0.0217 g, 0.00592 mmol) was added in methanol (1 mL) with a stirbar, then flushed with dry N_2. The solution was heated to reflux (40 ^oC) for 3 hours and then cooled to room temperature. The flask was capped and allowed to stand for 48 hours from which off-white spikes formed, the crystals were filtered to afford 0.0354 g of Cd-complex **129a** in 84% as off-white needles. Mp: 192 ^oC. The absolute structure was identified by x-ray crystal analysis. Due to the insolubility of this complex in many commercially available deuterated solvents, no NMR or IR data was taken.

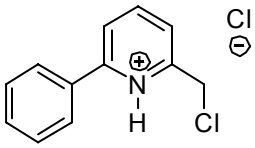
6-bromopicolinaldehyde (131): The commercially available dibromide **130** (10.0 g,



42.3 mmol) dissolved in THF (35 mL) and was added to a diluted solution of *n*-BuLi (18.4 mL, 2.3M, 42.3 mmol) in THF (50 mL) at -78 ^oC dropwise over 1.5 hours such that -75 ^oC was maintained throughout the duration. The reaction mixture was stirred an additional 30 minutes. DMF (4.92 mL, 63.5 mmol) was added to the dark green solution and warmed to 0 ^oC and then room temperature. The solvent was quenched by saturated ammonium chloride solution (10 mL), extracted by DCM (3 x 25 mL), concentrated and purified by flash chromatography (silica gel)

with 100% DCM (R_f = 0.28 in 100% DCM; dark short UV spot) to afford 1.11 g of **131** in 7% isolated yield as a orange to brown solid with matching ^{1}H and ^{13}C NMR spectra as reported in the literature.[36] Mp. 74 ^{o}C. ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.73–7.81 (m, 1H), 7.94 (d, *J* = 6.9 Hz, 2H), 10.0 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 120.3, 132.6, 139.3, 142.5, 153.3, 191.5.

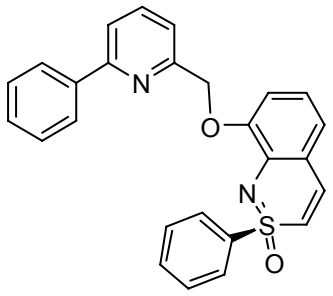
2-(chloromethyl)-6-phenylpyridinium chloride (132): *(Step 1 of 3)* Aldehyde **131**



(0.227 g, 1.22 mmol), $Pd(PPh_3)_4$ (0.0423g, 0.0366 mmol), Na_2CO_3 (1.10 mL, 2.0M, 2.20 mmol), diphenyl boronic acid (0.208 g, 1.71 mmol) and a stirbar were added to PhMe (10 mL). The mixture was refluxed overnight and diluted with DCM (20 mL). The aqueous layer was extracted by DCM (3 x 10 mL), dried ($MgSO_4$) which corresponded to >95% conversion of crude 6-phenylpicolinaldehyde as a white semi-solid with matching ^{1}H NMR as reported in the literature.[37] ^{1}H NMR: (250 MHz, $CDCl_3$) δ 7.67–7.72 (m, 3H), 7.87–7.97 (m, 3H), 7.94 (d, *J* = 5.8 Hz, 2H), 10.17 (s, 1H); *(Step 2 of 3)* The crude residue of 6-phenylpicolinaldehyde (0.224 g, 1.22 mmol) was dissolved in absolute ethanol (25 mL). $NaBH_4$ (0.0693 g, 1.83 mmol) was added at 0^o C. The reaction mixture was stirred further for 2 hours at which time no starting material remained by TLC (R_f = 0.46 in 50% EtOAc/hexanes; light blue long UV spot). The solvent was evaporated under vacuum. Then EtOAc (10 mL) was added with 1N HCl (1 mL) and further extracted by EtOAc (3 x 5 mL) and dried ($MgSO_4$) and the solvent was again removed and the remaining clear semi-solid gave quantitative crude conversion of (6-phenylpyridin-2-yl)methanol with the same ^{1}H NMR spectra as reported in the literature.[38] ^{1}H NMR: (300 MHz, $CDCl_3$) δ 4.20 (s, 1H, broad), 4.78 (s, 2H), 7.14 (d, *J* = 7.5 Hz, 1H), 7.36–7.46 (m, 4H), 7.57 (d, *J*

= 7.8 Hz, 1H), 7.67 (t, *J* = 7.8 Hz, 1H), 7.98 (d, *J* = 8.4 Hz, 1H); *(Step 3 of 3)* The residue of (6-phenylpyridin-2-yl)methanol (0.328 g, 1.77 mmol) was suspended in diethyl ether (10 mL) and cooled to 0 ^{o}C. Then $SOCl_2$ (0.155 mL, 2.13 mmol) was added in diethyl ether (5 mL) over 15 minutes. The reaction mixture was warmed to room temperature and stirred overnight. The tan hydrochloride salt was filtered to afford 0.417 g of **132** in 98% yield over 3 steps with matching ^{1}H and ^{13}C NMR spectra as reported in the literature.[38] Mp. 132 ^{o}C. ^{1}H NMR: (250 MHz, $CDCl_3$) δ 2.17 (s, 1H), 4.91 (s, 2H), 7.38–7.53 (m, 4H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.78 (t, *J* = 7.8 Hz, 1H), 8.00 (d, *J* = 6.9 Hz, 2H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 42.6, 127.3, 127.8, 130.2, 130.8, 132.0, 133.5, 149.3, 153.1, 155.2.

***R*-2-(methyl-8-*O*-2-*S*-oxa-2-*S*-phenyl-2,1-benzothiazine)-6-phenylpyridine (133):**

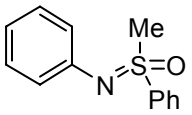


Phenol **111** (0.0922 g, 0.358 mmol) and stirbar were treated with NaH (60% in mineral oil, 0.034 g, 0.854 mmol) at 0 ^{o}C in DMF (7 mL) under a dry N_2 balloon resulting in a dark red solution. After 5 minutes, **132** (0.082 g, 0.341 mmol) was added as a solid, allowed to warm to room temperature and stirred until completion by TLC (20 hours) (R_f = 0.41 in 50% EtOAc/hexanes; yellow long UV spot). The reaction was quenched with water (5 mL) and extracted by dichloromethane (3 x 5 mL). The organic extracts were again washed by water (5 mL), dried ($MgSO_4$), and concentrated in vacuo. The remaining crude oil was purified by flash chromatography (silica gel) in 25% EtOAc/hexanes to afford 0.0684 g of heterocycle **133** in 47% as an orange semi-solid. ^{1}H NMR: (250 MHz, $CDCl_3$) δ 5.50 (s, 2H), 6.41 (d, *J* = 9.8 Hz, 1H), 6.87 (t, *J* = 7.9 Hz, 1H), 7.01 (t, *J* = 8.6

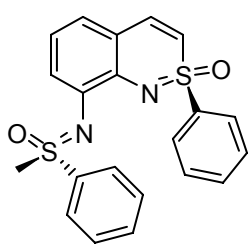
Hz, 2H), 7.37-7.70 (m, 10H), 7.94 (d, J = 6.8 Hz, 2H), 8.00 (d, J = 6.9 Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 71.8, 110.3, 115.1, 116.9, 119.1, 119.5, 119.6, 122.2, 126.9, 128.7, 128.9, 129.1, 133.2, 136.0, 137.4, 138.4, 139.3, 141.6, 150.7, 156.6, 157.7; IR (NaCl, cm^{-1}) 3064, 2927, 2232, 1605, 1595, 1544, 1448, 1433, 1285, 1218, 1106, 992, 763, 686, 590, 501, 459; HRMS calculated for $C_{26}H_{20}N_2O_2SNa$ $[M+Na]^+$ 447.1138; Found 447.1136.

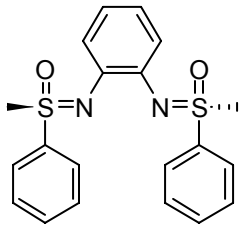
5.2.2 Synthetic Procedures and Compound Characterization: Chapter 3

***N*-phenyl-*S*-oxa-*S*-phenyl-*S*-methyl sulfoximine (2):** (*N*-Arylation Procedure B)

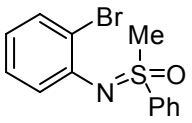


Chloro benzene **134** (0.250 g, 2.22 mmol), sulfoximine **6** (0.413, 2.66 mmol), Pd_2dba_3 (0.0508 g, 0.0555 mmol), Cs_2CO_3 (1.157 g, 3.55 mmol), and RuPhos (0.0776 g, 0.166 mmol) were added together in a sealed tube in air with toluene (22 mL). The sealed tube was capped in air and refluxed to 135 ^{o}C. The reaction was stopped after 6 hours by a power outlet timer. Once at room temperature, the reaction was diluted in dichloromethane (10 mL) and filtered through a plug of celite. After being concentrated in vacuo, the brownish semi-solid was purified by flash chromatography (silica gel) with 25% EtOAc/hexanes (R_f = 0.23 in 25% EtOAc/hexanes; dark short UV spot) to afford 0.513 g **2** in 100% as a orange solid with matching ^{1}H and ^{13}C NMR spectra as reported in the literature.[6] Mp. 75 ^{o}C. ^{1}H NMR: (300 MHz, $CDCl_3$) δ 3.20 (s, 3H), 6.84 (t, J = 7.1 Hz, 1H), 7.01 (d, J = 7.1 Hz, 2H), 7.09 (t, J = 8.3 Hz, 2H), 7.44-7.57 (m, 3H), 7.96 (d, J = 8.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.8, 121.5, 123.1, 128.4, 128.8, 129.4, 133.1, 139.2, 144.8.

***R,R*-*N*-(2-*S*-oxa-2-*S*-phenyl-2,1-benzothiazine-8-yl)-*S*-oxa-*S*-phenyl-*S*-methyl sulfoximine (123):**  (N-Arylation Procedure B) Another addition of Pd_2dba_3, RuPhos, sulfoximine **6** and Cs_2CO_3 was added after 24 hours and an additional 24 hours reaction time was added. Orange oil in 91% yield. (R_f = 0.17 in 50% EtOAc/hexanes; yellow long UV spot) This compound had matching ^1H and ^{13}C NMR spectra as reported in the literature.[31] ^1H NMR: (300 MHz, $CDCl_3$) δ 3.18 (s, 3H), 6.32 (d, *J* = 9.7 Hz, 1H), 6.74 (t, *J* = 7.7 Hz, 1H), 6.92 (d, *J* = 7.8 Hz, 1H), 7.27-7.63 (m, 10H), 7.85 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.0, 109.5, 116.8, 120.0, 124.1, 128.0, 128.5, 128.6, 128.7, 128.9, 132.7, 133.1, 137.4, 139.3, 140.2, 141.2, 142.3.

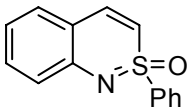
***S,S*-1*N*,2*N*-bis(*S*-oxa-*S*-phenyl-*S*-methyl sulfoximine)benzene (31):**  (N-Arylation Procedure B) Another addition of Pd_2dba_3, RuPhos, sulfoximine **6** and Cs_2CO_3 was added after 24 hours and an additional 24 hours reaction time was added. This compound could not be separated from sulfoximine **6** and was calculated in 8-37% conversions from an orange oily reaction mixture (R_f = 0.02 in 50% EtOAc/hexanes; dark short UV spot). For that reason ^1H and ^{13}C NMR spectra reported in the literature is listed herein for reference. ^1H NMR: (400 MHz, $CDCl_3$) δ 3.37 (s, 6H), 6.70 (d, *J* = 3.6 Hz, 2H), 7.04 (d, *J* = 3.6 Hz, 2H), 7.49-7.59 (m, 6H), 8.12-8.15 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 45.8, 122.5, 124.1, 128.6, 129.2, 132.8, 129.2, 132.8, 138.3, 140.2.[14]

***N*-(2-bromophenyl)-*S*-oxa-*S*-phenyl-*S*-methyl sulfoximine (30):** (N-Arylation



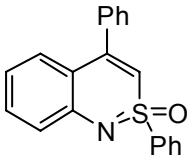
Procedure B) Orange oil in 37-45% yield. This compound (R_f = 0.43 in 25% EtOAc/hexanes; dark short UV spot) matched ^{1}H and ^{13}C NMR spectra reported in the literature.[14] ^{1}H NMR: (250 MHz, $CDCl_3$) δ 3.25 (s, 3H), 6.76 (t, *J* = 7.9 Hz, 1H), 7.03 (t, *J* = 7.9 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 1H), 7.48-7.60 (m, 4H), 8.08 (d, *J* = 6.6 Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 45.4, 119.3, 123.1, 123.6, 127.9, 128.6, 129.5, 132.9, 133.4, 139.0, 143.4.

2-*S*-oxa-2-*S*-phenyl-2,1-benzothiazine (1): (N-Arylation Procedure B) Yellow solid in



86% yield. This compound (R_f = 0.32 in 25% EtOAc/hexanes; yellow long UV spot) matched ^{1}H and ^{13}C NMR spectra reported in the literature.[5,7] Mp. 163 °C. ^{1}H NMR: (250 MHz, $CDCl_3$) δ 6.38 (d, *J* = 9.8 Hz, 1H), 7.03 (t, *J* = 8.0 Hz, 1H), 7.31 (t, *J* = 11.0 Hz, 2H), 7.46 (t, *J* = 6.8 Hz, 1H), 7.51-7.62 (m, 3H), 7.66 (d, *J* = 9.8 Hz, 1H), 7.90 (d, *J* = 6.5 Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 109.9, 116.1, 120.2, 124.2, 128.7, 129.0, 129.6, 132.1, 133.2, 138.8, 141.6, 145.1.

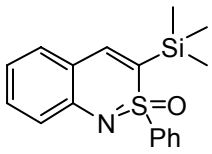
4-phenyl-2-*S*-oxa-2-*S*-phenyl-2,1-benzothiazine (26): (N-Arylation Procedure B)



Yellow solid in 77% yield. This compound (R_f = 0.58 in 25% EtOAc/hexanes; green long UV spot) matched ^{1}H and ^{13}C NMR spectra reported in the literature.[5,7] Mp. 140 °C. ^{1}H NMR: (250 MHz, $CDCl_3$) δ 6.32 (s, 1H), 7.03 (m, 1H), 7.35 (d, *J* = 8.6 Hz, 1H), 7.44-7.59 (m, 10H), 7.98 (d, *J* = 7.7 Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 108.4, 116.9, 119.9, 124.7, 128.0, 128.4, 128.8, 128.9, 129.0, 131.8, 133.2, 137.2, 141.3, 145.8, 150.8.

5.2.3 Synthetic Procedures and Compound Characterization: Chapter 4

3-(trimethylsilyl)-2-*S*-oxa-2-*S*-phenyl-2,1-benzothiazine (154a): Lithiation Procedure

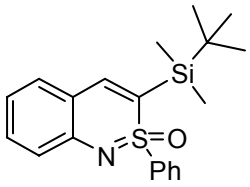


A: To an oven dried, N_2 cooled flask with stirbar, benzothiazine **1** (0.107 g, 0.443 mmol) was added and covered with a rubber septum. The flask was charged with argon, and freshly distilled THF (4 mL) was added via syringe. The reaction was then cooled to –78 ^{o}C via a dry ice/acetone bath. Then *n*-BuLi (0.256 mL, 2.08M, 0.532 mmol) was added drop-wise to the cooled solution resulting in a dark orange solution. After 5 minutes, TMSCl (0.0793 mL, 0.621 mmol) was added thru the rubber septum by syringe. The reaction mixture was stirred further for up to 3 hours (or until completion was observed by TLC). The mixture was quenched with saturated ammonium chloride (2 mL) and extracted with dichloromethane (3 x 5 mL), concentrated in by vacuum, and dried ($MgSO_4$). Purification (R_f = 0.40 in 25% EtOAc/hexanes; yellow long UV spot) by flash chromatography (silica gel) with 25% EtOAc/ hexane afforded 136.5 g **154a** as a yellow solid in 98% yield. Mp. 183 ^{o}C. ^{1}H NMR: (250 MHz, $CDCl_3$) δ 0.05 (s, 9H), 6.99 (t, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.43 (t, *J* = 6.9 Hz, 1H), 7.49–7.63 (m, 3H), 7.74 (s, 1H), 7.87 (d, *J* = 7.0 Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ -0.7, 116.3, 119.7, 121.4, 123.7, 128.7, 129.3, 129.7, 132.3, 133.2, 142.5, 145.6, 146.0; IR (NaCl, cm^{-1}) 3015, 2964, 1605, 1577, 1531, 1308, 1289, 1254, 1206, 990, 845, 729, 426; HRMS calculated for $C_{17}H_{19}NOSSiNa$ $[M+Na]^+$ 336.0849; Found 336.0851.

3-(triethylsilyl)-2-*S*-oxa-2-*S*-phenyl-2,1-benzothiazine (154b): (Lithiation Procedure A) Yellow solid in 94% yield. (R_f = 0.57 in 25% EtOAc/hexanes; yellow long UV spot) Mp. 60 °C. ^{1}H NMR: (250 MHz, $CDCl_3$) δ 0.37 (sextet, *J* = 8.0 Hz, 3H), 0.63 (sextet, *J* = 8.2 Hz, 3H), 0.84 (t, *J* = 7.7 Hz, 9H), 6.98 (t, *J* = 6.8 Hz, 1H), 7.24 (d, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.42 (t, *J* = 8.4 Hz, 1H), 7.47–7.62 (m, 3H), 7.71 (s, 1H), 7.87 (d, *J* = 6.9 Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 3.1, 6.8, 116.1, 118.4, 119.5, 123.5, 128.4, 129.0, 129.6, 132.1, 133.1, 142.7, 145.5, 147.0; IR (NaCl, cm^{-1}) 2959, 2912, 2878, 1605, 1576, 1529, 1308, 1289, 1308, 1224, 1127, 1004, 848, 787, 723, 667, 580, 438; HRMS calculated for $C_{20}H_{25}NOSSiNa$ $[M+Na]^+$ 378.1318; Found 378.1313.

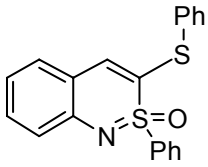
3-(tri-*iso*-propylsilyl)-2-*S*-oxa-2-*S*-phenyl-2,1-benzothiazine (154c): (Lithiation Procedure A) Orange solid in 94% yield. (R_f = 0.55 in 25% EtOAc/hexanes; yellow long UV spot) Mp. 115 °C. ^{1}H NMR: (250 MHz, $CDCl_3$) δ 0.75 (d, *J* = 6.6 Hz, 9H), 0.95-1.11 (m, 12H), 6.88 (t, *J* = 7.5 Hz, 1H), 7.12 (d, *J* = 8.3 Hz, 1H), 7.25 (d, *J* = 7.7 Hz, 1H), 7.32 (t, *J* = 8.5 Hz, 1H), 7.34–7.50 (m, 3H), 7.69 (s, 1H), 7.75 (d, *J* = 6.7 Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 11.7, 17.6, 18.2, 18.5, 115.8, 117.2, 119.4, 123.3, 128.4, 128.8, 129.7, 132.3, 133.0, 144.1, 145.4, 148.7; IR (NaCl, cm^{-1}) 3013, 2949, 2869, 1605, 1527, 1467, 1448, 1313, 1206, 1127, 1097, 988, 883, 844, 787, 727, 684, 643, 478; HRMS calculated for $C_{23}H_{31}NOSSiNa$ $[M+Na]^+$ 420.1788; Found 420.1791.

3-(dimethyl-*tert*-butylsilyl)-2-*S*-oxa-2-*S*-phenyl-2,1-benzothiazine (154d): (Lithiation



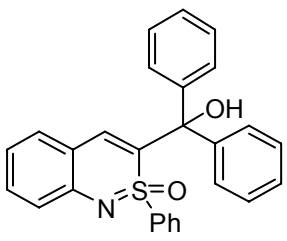
Procedure A) Yellow solid in 85% yield. (R_f = 0.44 in 25% EtOAc/hexanes; yellow long UV spot) Mp. 117 ^oC. ^1H NMR: (300 MHz, $CDCl_3$) δ -0.20 (s, 3H), 0.17 (s, 3H), 0.87 (s, 9H), 6.97 (t, *J* = 8.1 Hz, 1H), 7.21 (d, *J* = 8.3 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.41 (t, *J* = 8.3 Hz, 1H), 7.48–7.60 (m, 3H), 7.80-7.84 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.1, -4.8, 17.7, 26.5, 115.8, 119.0, 119.6, 123.5, 128.5, 128.9, 129.7, 132.4, 132.9, 143.7, 145.4, 148.3; IR (NaCl, cm^{-1}) 3067, 3015, 1605, 1579, 1531, 1286, 1224, 1206, 1097, 991, 728, 685, 438; HRMS calculated for $C_{20}H_{25}NOSSiNa$ $[M+Na]^+$ 378.1318; Found 378.1315.

3-(phenylsulfanyl)-2-*S*-oxa-2-*S*-phenyl-2,1-benzothiazine (154e): (Lithiation



Procedure A) Yellow solid in 38-92% yield. (R_f = 0.41 in 25% EtOAc/hexanes; yellow long UV spot) Mp. 104 ^oC. ^1H NMR: (250 MHz, $CDCl_3$) δ 7.05 (t, *J* = 8.0 Hz, 1H), 7.11 (s, 5H), 7.32-7.54 (m, 7H), 7.80 (d, *J* = 7.2 Hz, 1H), 7.98 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 116.0, 118.5, 120.4, 124.0, 127.2, 128.5, 128.9, 129.2, 129.7, 130.1, 132.8, 133.4, 134.6, 138.5, 145.4, 147.9; IR (NaCl, cm^{-1}) 3015, 2960, 2860, 1605, 1575, 1529, 1468, 1310, 1257, 1205, 1097, 988, 844, 811, 728, 667; HRMS calculated for $C_{20}H_{15}NOS_2Na$ $[M+Na]^+$ 372.0487; Found 372.0470.

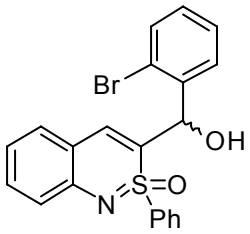
3-(hydroxydiphenylmethyl)-2-*S*-oxa-2-*S*-phenyl-2,1-benzothiazine (154f): (Lithiation



Procedure A) Tan solid in 91 % yield. (R_f = 0.26 in 25% EtOAc/hexanes; orange long UV spot) Mp. 176 ^oC. ^1H NMR: (250 MHz, $CDCl_3$) δ 3.86 (s, 1H, broad), 6.97-7.10 (m, 6H), 7.15-7.47 (m, 12H), 7.59 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (63

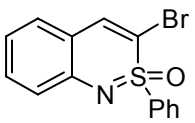
MHz, $CDCl_3$) δ 81.6, 116.6, 120.3, 123.5, 126.6, 127.1, 127.6, 127.9, 128.0, 128.3, 128.4, 130.0, 130.3, 131.9, 132.6, 138.3, 139.5, 141.3, 144.4, 145.8; IR (NaCl, cm^{-1}) 3579, 3064, 3018, 1608, 1447, 1292, 1223, 1206, 1188, 729, 702, 471, 445; HRMS calculated for $C_{27}H_{21}NO_2SNa$ $[M+Na]^+$ 446.1185; Found 446.1185.

3-(2-bromophenyl(hydroxy)methyl)-2-*S*-oxa-2-*S*-phenyl-2,1-benzothiazine (154g):



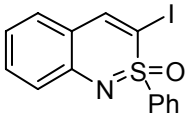
(Lithiation Procedure A) A racemic mixture of two diastereomers (1.4:1) was made as off-white solids in 94% overall yield. (R_f = 0.46 in 25% EtOAc/hexanes; yellow long UV spot) Major diastereomer: Mp. 204 °C. ^{1}H NMR: (300 MHz, $CDCl_3$) δ 3.49 (d, *J* = 2.3 Hz, 1H), 5.57 (d, *J* = 1.6 Hz, 1H), 6.94 (s, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 7.15-7.21 (m, 2H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.39-7.46 (m, 3H), 7.53-7.58 (m, 2H), 7.65 (t, *J* = 7.3 Hz, 1H), 7.78 (d, *J* = 7.7 Hz, 1H), 8.00 (d, *J* = 7.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.4, 116.8, 120.5, 122.2, 123.4, 123.6, 127.7, 128.9, 129.0, 129.7, 130.1, 130.3, 132.2, 132.7, 133.7, 137.0, 137.5, 138.0, 144.7; IR (NaCl, cm^{-1}) 3540, 3068, 3015, 1612, 1446, 1288, 1217, 1185, 1129, 1096, 1014, 991, 831, 771, 534; HRMS calculated for $C_{21}H_{16}BrNO_2SNa$ $[M+Na]^+$ 447.9977; Found 447.9979. Minor diastereomer: Mp. 193 °C. ^{1}H NMR: (300 MHz, $CDCl_3$) δ 2.62 (d, *J* = 5.7 Hz, 1H), 5.90 (d, *J* = 5.6 Hz, 1H), 7.03 (t, *J* = 8.1 Hz, 1H), 7.08 (t, *J* = 7.7 Hz, 1H), 7.22-7.28 (m, 2H), 7.33 (m, 7H), 7.65 (s, 1H), 7.70 (d, *J* = 7.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 72.3, 116.7, 120.3, 121.8, 122.6, 123.4, 127.6, 128.7, 129.1, 129.1, 129.9, 130.0, 132.2, 132.2, 132.9, 133.2, 138.6, 139.3, 140.5, 144.7; IR (NaCl, cm^{-1}) 3592, 3067, 3014, 1612, 1545, 1446, 1343, 1292, 1227, 1194, 1097, 991, 775, 765, 521; HRMS calculated for $C_{21}H_{16}BrNO_2SNa$ $[M+Na]^+$ 447.9977; Found 448.0019.

3-bromo-2-*S*-oxa-2-*S*-phenyl-2,1-benzothiazine (154h): (Lithiation Procedure A)



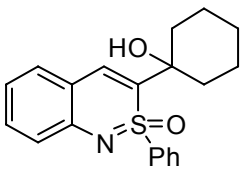
Yellow solid in 81% yield. (R_f = 0.54 in 50% EtOAc/hexanes; yellow-green long UV spot) Mp. 105 °C. ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.06 (t, *J* = 7.4 Hz, 1H), 7.32 (d, *J* = 8.3 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.56–7.70 (m, 3H), 7.82 (s, 1H), 7.93 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 103.2, 118.6, 120.8, 123.8, 128.8, 128.9, 130.1, 132.1, 133.9, 138.4, 141.3, 143.5; IR (NaCl, cm^{-1}) 3069, 3014, 2930, 1604, 1535, 1444, 1342, 1288, 1225, 1206, 1098, 995, 918, 786, 728, 569, 534; HRMS calculated for $C_{14}H_{10}BrNOSNa$ $[M+Na]^+$ 341.9559; Found 341.9570.

3-iodo-2-*S*-oxa-2-*S*-phenyl-2,1-benzothiazine (154i): (Lithiation Procedure A) Orange



solid in 96% yield. (R_f = 0.68 in 50% EtOAc/hexanes; dark short UV spot) Mp. 103 °C. ^{1}H NMR: (250 MHz, $CDCl_3$) δ 7.04 (t, *J* = 7.3 Hz, 1H), 7.26–7.35 (m, 2H), 7.46 (t, *J* = 7.2 Hz, 1H), 7.55–7.70 (m, 3H), 7.91 (d, *J* = 6.9 Hz, 2H), 8.03 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 74.2, 118.9, 120.5, 123.9, 128.7, 128.8, 130.0, 132.3, 133.8, 139.5, 144.2, 148.6; IR (NaCl, cm^{-1}) 3069, 3014, 1604, 1528, 1342, 1288, 1207, 1097, 992, 787, 729, 434, 426; HRMS calculated for $C_{14}H_{10}INOSNa$ $[M+Na]^+$ 389.9420; Found 389.9421.

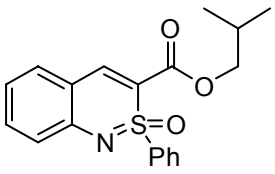
3-(1-hydroxycyclohexyl)-2-*S*-oxa-2-*S*-phenyl-2,1-benzothiazine (154j): (Lithiation



Procedure A) Yellow-tan solid in 97% yield. (R_f = 0.71 in 50% EtOAc/hexanes; light green long UV spot) Mp. 135 °C. ^{1}H NMR: (300 MHz, $CDCl_3$) δ 1.08-1.22 (m, 1H), 1.38-1.92 (m, 9H), 2.07 (s, 1H), 7.01 (t, *J* = 8.0 Hz, 1H), 7.23 (d, *J* = 7.9 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.40 (t, *J* = 7.2 Hz, 1H), 7.48-7.60 (m, 3H), 7.61 (s, 1H), 7.83 (d, *J* = 6.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 21.5, 25.0, 38.3, 40.5, 74.0, 116.4, 120.0, 123.1, 128.5, 128.9,

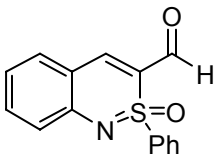
129.4, 130.1, 131.6, 132.8, 135.6, 143.8, 143.9; IR (NaCl, cm^{-1}) 3574, 3016, 2939, 2861, 1608, 1447, 1343, 1295, 1224, 1206, 1096, 993, 787, 728, 523, 467, 430; HRMS calculated for $C_{20}H_{21}NO_2SNa$ $[M+Na]^+$ 362.1185; Found 362.1178.

2-methylpropyl 2-*S*-oxa-2-*S*-phenyl-2,1-benzothiazine-3-carboxylate (154k):

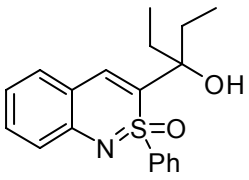


(Lithiation Procedure A) Yellow solid in 11-51% yield. (R_f = 0.45 in 25% EtOAc/hexanes; yellow long UV spot) Mp. 93 °C. ^{1}H NMR: (250 MHz, $CDCl_3$) δ 0.74 (d, *J* = 6.7 Hz, 3H), 0.80 (d, *J* = 6.7 Hz, 3H), 1.75 (septet, *J* = 6.7 Hz, 1H), 1.38-1.92 (dd, J_1 =6.7 Hz, J_2 = 3.8 Hz, 2H), 7.07 (t, *J* = 7.1 Hz, 1H), 7.31 (d, *J* = 8.2 Hz, 1H), 7.49-7.65 (m, 5H), 7.92 (d, *J* = 6.7 Hz, 2H), 8.56 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 18.9, 18.9, 27.5, 72.0, 111.8, 116.3, 120.7, 124.0, 128.5, 129.3, 131.3, 133.2, 134.8, 141.5, 145.7, 147.3, 161.9; IR (NaCl, cm^{-1}) 3027, 2963, 2875, 1712, 1609, 1533, 1448, 1287, 1206, 1152, 1098, 986, 469; HRMS calculated for $C_{19}H_{19}NO_3SNa$ $[M+Na]^+$ 364.0978; Found 364.0968.

2-*S*-oxa-2-*S*-phenyl-2,1-benzothiazine-3-carbaldehyde (154l): (Lithiation Procedure A) Yellow solid in 92% yield. (R_f = 0.14 in 25% EtOAc/hexanes; orange long UV spot) Mp. 119 °C. ^{1}H NMR: (250 MHz, $CDCl_3$) δ 7.10 (t, *J* = 7.0 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.50-7.68 (m, 5H), 7.96 (d, *J* = 7.2 Hz, 2H), 8.23 (s, 1H), 9.57 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 116.4, 119.1, 121.2, 124.6, 128.8, 129.9, 131.5, 133.8, 135.9, 139.5, 147.2, 148.6, 184.7; IR (NaCl, cm^{-1}) 3022, 2928, 2855, 1688, 1609, 1586, 1531, 1291, 1223, 1206, 1153, 729, 426; HRMS calculated for $C_{15}H_{11}NO_2SNa$ $[M+Na]^+$ 292.0403; Found 292.0345.

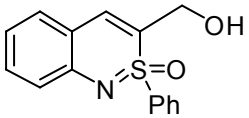


3-(3-hydroxypentan-3yl)-2-*S*-oxa-2-*S*-phenyl-2,1-benzothiazine (154m): (Lithiation



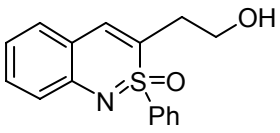
Procedure A) Tan solid in 85% yield. (R_f = 0.47 in 25% EtOAc/hexanes; purple long UV spot) Mp. 156 °C. ^{1}H NMR: (300 MHz, $CDCl_3$) δ 0.63 (t, *J* = 7.4 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 3H), 1.38 (sextet, *J* = 6.9 Hz, 1H), 1.64 (sextet, *J* = 7.3 Hz, 1H), 1.77 (q, *J* = 7.4 Hz, 2H), 2.50 (s, 1H), 7.02 (t, *J* = 7.0 Hz, 1H), 7.27 (d, *J* = 7.3 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.37 (s, 1H), 7.42 (t, *J* = 8.4 Hz, 1H), 7.48-7.60 (m, 3H), 7.85 (d, *J* = 7.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.5, 7.9, 33.3, 34.9, 78.2, 116.4, 120.1, 123.2, 126.5, 128.4, 129.5, 131.6, 133.0, 136.2 143.0, 144.1; IR (NaCl, cm^{-1}) 3574, 3018, 2975, 1608, 1446, 1344, 1296, 1224, 1206, 1094, 989, 792, 668, 528; HRMS calculated for $C_{19}H_{21}NO_2SNa$ $[M+Na]^+$ 350.1185; Found 350.1179.

3-(hydroxymethyl)-2-*S*-oxa-2-*S*-phenyl-2,1-benzothiazine (154n): (Lithiation



Procedure A) Orange solid in 76% yield. (R_f = 0.03 in 25% EtOAc/hexanes; green long UV spot) Mp. 134 °C. ^{1}H NMR: (300 MHz, $CDCl_3$) δ 2.05 (s, 1H, broad), 4.36 (s, 2H), 7.05 (t, *J* = 8.1 Hz, 1H), 7.31 (d, *J* = 8.2 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.46 (t, *J* = 6.9 Hz, 1H), 7.54-7.70 (m, 4H), 7.90 (d, *J* = 6.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 60.7, 116.9, 120.5, 121.6, 123.7, 129.1, 129.4, 129.7, 132.0, 133.6, 137.4, 139.3, 144.7; IR (NaCl, cm^{-1}) 3601, 3465, 3067, 3014, 2874, 1616, 1447, 1340, 1287, 1224, 1205, 1097, 991, 728, 686, 666, 532; HRMS calculated for $C_{15}H_{13}NO_2SNa$ $[M+Na]^+$ 294.0559; Found 294.0573.

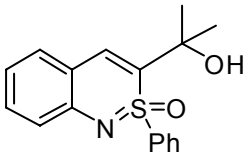
3-(2-hydroxyethyl)-2-*S*-oxa-2-*S*-phenyl-2,1-benzothiazine (154o): (Lithiation



Procedure A) Yellow solid in 91% yield. (R_f = 0.13 in 50% EtOAc/hexanes; light green long UV spot) Mp. 74 °C. ^{1}H NMR:

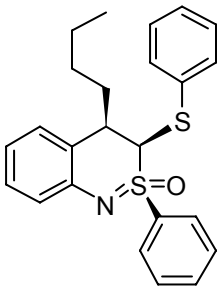
(250 MHz, $CDCl_3$) δ 2.37-2.46 (m, 1H), 2.58-2.67 (m, 1H), 3.66-3.85 (m, 2H), 7.02 (t, *J* = 7.1 Hz, 1H), 7.27-7.35 (m, 2H), 7.42 (t, *J* = 8.1 Hz, 1H), 7.48 (s, 1H), 7.51-7.67 (m, 4H), 7.89 (d, *J* = 6.7 Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 34.1, 62.0, 117.3, 120.1, 120.4, 123.5, 129.1, 129.1, 129.5, 131.4, 133.5, 138.1, 138.9, 143.8; IR (NaCl, cm^{-1}) 3620, 3487, 3067, 3016, 1613, 1447, 1289, 1223, 1206, 1099, 993, 729, 470, 426; HRMS calculated for $C_{16}H_{15}NO_2SNa$ $[M+Na]^+$ 308.0716; Found 308.0726.

3-(2-hydroxypropan-2-yl)-2-*S*-oxa-2-*S*-phenyl-2,1-benzothiazine (154q): (Lithiation



Procedure A) Green-tan solid in 85% yield. (R_f = 0.12 in 25% EtOAc/hexanes; light green long UV spot) Mp. 175 °C. ^1H NMR: (250 MHz, $CDCl_3$) δ 1.28 (s, 3H), 1.50 (s, 3H), 2.58 (s, 1H, broad), 7.00 (t, *J* = 7.5 Hz, 1H), 7.24 (d, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 5.9 Hz, 1H), 7.41 (t, *J* = 8.5 Hz, 1H), 7.46-7.61 (m, 3H), 7.63 (s, 1H), 7.85 (d, *J* =6.7 Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 30.9, 32.6, 72.6, 116.5, 120.1, 123.0, 128.6, 129.3, 129.4, 129.5, 131.6, 133.0, 135.4, 142.8, 143.8; IR (NaCl, cm^{-1}) 3534, 2975, 2361, 1608, 1546, 1447, 1345, 1322, 1296, 1202, 990, 910, 521, 507, 502, 408; HRMS calculated for $C_{17}H_{17}NO_2SNa$ $[M+Na]^+$ 322.0872; Found 322.0869.

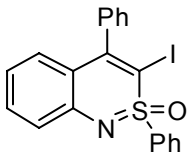
***R*-(3*S*,4*R*)-4-butyl-2-phenyl-3-(phenylsulfanyl)-3,4-dihydro-2-*S*-oxa-2-*S*-phenyl-2,1-**



benzothiazine (157): (Lithiation Procedure A) No electrophile was used and the reaction was stirred for 4 hours at -78 °C before it was stopped and quenched. Orange semi-solid in 85% yield in a 3.8:1 diastereomeric mixture. (R_f = 0.57 in 25% EtOAc/hexanes; green long UV spot) Major diastereomer (all *cis* product shown): ^1H NMR: (250 MHz, $CDCl_3$) δ 1.00 (t, *J* = 7.2 Hz, 3H), 1.48-1.61 (m, 4H), 2.06-2.21 (m, 1H), 2.35-2.45 (m, 1H), 3.91

(m, 1H), 4.56 (d, *J* = 3.1 Hz, 1H), 6.65 (d, *J* = 8.4 Hz, 2H), 6.14-6.95 (m, 4H), 7.19 (d, *J* = 7.3, 1H), 7.25-7.32 (m, 2H), 7.38-7.44 (m, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 8.04 (d, *J* = 7.1 Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 14.1, 22.7, 28.3, 29.3, 120.7, 123.0, 125.8, 127.6, 128.5, 128.6, 130.0, 131.5, 131.6, 133.9 135.1; IR (NaCl, cm^{-1}) 3478, 3012, 2959, 2931, 2859, 2361, 1732, 1582, 1477, 1444, 1374, 1251, 1146, 1090, 1023, 787, 689, 471; HRMS calculated for $C_{24}H_{25}NOS_2Na$ $[M+Na]^+$ 430.1270; Found 430.1275.

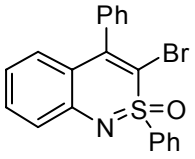
3-iodo-2-*S*-oxa-2-*S*,4-diphenyl-2,1-benzothiazine (161d): Lithiation Procedure B: To



an oven dried, N_2 cooled flask with stirbar, benzothiazine **26** (0.052 g, 0.164 mmol) was added and covered with a rubber septum. The flask was charged with argon, and freshly distilled THF (2 mL) was added via syringe. The reaction was then cooled to –78 ^{o}C via a dry ice/acetone bath. Then *n*-BuLi (0.0936 mL, 2.10M, 0.196 mmol) was added drop-wise to the cooled solution resulting in a dark orange solution. After 15 minutes, I_2 (0.0582 g, 0.229 mmol) was added in THF (1 mL) thru the rubber septum by syringe. The reaction mixture was stirred further for up to 3 hours (or until completion was observed by TLC). The mixture was quenched with saturated ammonium chloride (2 mL) and extracted with dichloromethane (3 x 5 mL), concentrated in by vacuum, and dried ($MgSO_4$). Purification (R_f = 0.24 in 25% EtOAc/hexanes; green long UV spot) by flash chromatography (silica gel) with 25% EtOAc/ hexane afforded 0.537 g **161e** in 74% yield as an orange solid. Mp. 83 ^{o}C. ^{1}H NMR: (250 MHz, $CDCl_3$) δ 6.84 (t, *J* = 8.2 Hz, 1H), 6.94 (d, *J* = 8.2 Hz, 1H), 7.07–7.11 (m, 1H), 7.24–7.68 (m, 9H), 7.99 (d, *J* = 7.0 Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 80.9, 119.2, 120.3, 124.0, 128.0, 128.6, 128.7, 129.0, 130.1, 131.9, 133.7, 140.1, 140.9, 144.6, 156.3; IR (NaCl, cm^{-1}) 3064, 2928, 2855, 2252, 1600, 1566, 1515, 1490, 1326,

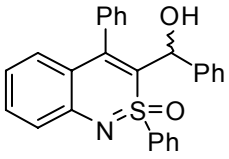
1249, 1218, 1098, 996, 959, 699, 650, 589, 545, 508, 499, 473; HRMS calculated for $C_{20}H_{14}INOSNa$ $[M+Na]^+$ 465.9733; Found 465.9728.

3-bromo-2-*S*-oxa-2-*S*,4-diphenyl-2,1-benzothiazine (161e): (Lithiation Procedure B)



Yellow solid in 95% yield. (R_f = 0.47 in 25% EtOAc/hexanes; green long UV spot) Mp. 174 °C. ^{1}H NMR: (250 MHz, $CDCl_3$) δ 6.88–7.01 (m, 2H), 7.16–7.18 (m, 1H), 7.39–7.71 (m, 9H), 8.05 (d, *J* = 7.1 Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 104.1, 119.7, 120.5, 124.1, 128.4, 128.5, 128.7, 128.9, 130.1, 131.6, 131.9, 133.8, 136.9, 138.7, 143.8, 150.8; IR (NaCl, cm^{-1}) 3065, 2927, 2855, 1600, 1567, 1523, 1492, 1330, 1252, 1222, 1098, 970, 605, 589, 545, 495, 476, 447, 408; HRMS calculated for $C_{20}H_{14}BrNOSNa$ $[M+Na]^+$ 417.9872; Found 417.9866.

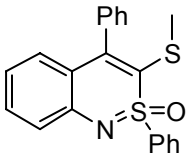
3-(phenyl(hydroxy)methyl)-2-*S*-oxa-2-*S*,4-diphenyl-2,1-benzothiazine (161f):



(Lithiation Procedure B) A 2.4:1 diastereomeric mixture could not be separated by flash chromatography and was identified by its mixture as a tan solid in 75% yield. (R_f = 0.20 in 25% EtOAc/hexanes; yellow long UV spot) A 2.4:1 diastereomeric mixture: Mp. 103 °C. ^{1}H NMR: (250 MHz, $CDCl_3$) δ *Major diastereomer*: 3.60 (d, *J* = 5.2 Hz, 1H), 5.78 (d, *J* = 5.2 Hz, 1H), 2.59 (s, 1H), 7.64 (d, *J* = 7.4 Hz, 2H); *Minor diastereomer*: 2.59 (s, 0.4H), 5.60 (s, 0.4H), 7.96 (d, *J* = 6.7 Hz, 0.8H); 6.68–7.42 (m, 27H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 70.6, 70.9, 118.7, 102.1, 124.1, 124.8, 125.4, 126.3, 127.5, 127.6, 127.8, 128.1, 128.3, 128.5, 128.6, 128.8, 129.2, 129.6, 130.4, 131.5, 132.9, 135.5, 139.8, 140.7, 144.6, 148.6; IR (NaCl, cm^{-1}) 3468, 3064, 2924, 2854, 1601, 1572, 1530, 1336, 1248, 1248,

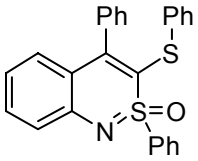
1208, 1190, 1153, 1127, 1039, 541, 538; HRMS calculated for $C_{27}H_{21}NO_2SNa$ $[M+Na]^+$ 446.1185; Found 446.1183.

3-(methylsulfanyl)-2-*S*-oxa-2-*S*,4-diphenyl-2,1-benzothiazine (161g): (Lithiation



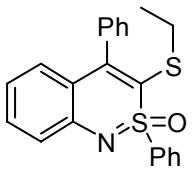
Procedure B) Yellow solid in 98% yield. (R_f = 0.47 in 25% EtOAc/hexanes; yellow long UV spot) Mp. 137 °C. ^{1}H NMR: (300 MHz, $CDCl_3$) δ 1.93 (s, 3H), 6.81-6.86 (m, 1H), 6.91 (d, *J* = 7.8 Hz, 1H), 7.12-7.15 (m, 1H), 7.37–7.63 (m, 9H), 8.03 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 116.1, 119.2, 119.8, 124.2, 128.2, 128.3, 128.6, 129.0, 130.0, 132.0, 133.3, 136.4, 139.7, 145.2, 157.6; IR (NaCl, cm^{-1}) 3065, 3045, 2925, 1601, 1562, 1515, 1490, 1448, 1332, 1245, 1210, 1153, 1097, 996, 971, 821, 590, 550, 491, 463, 431, 428; HRMS calculated for $C_{21}H_{17}NOS_2Na$ $[M+Na]^+$ 386.0644; Found 386.0640.

3-(phenylsulfanyl)-2-*S*-oxa-2-*S*,4-diphenyl-2,1-benzothiazine (161h): (Lithiation



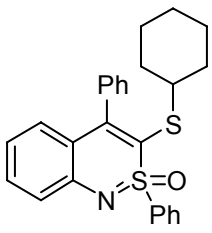
Procedure B) Yellow solid in 94% yield. (R_f = 0.46 in 25% EtOAc/hexanes; yellow long UV spot) Mp. 120 °C. ^{1}H NMR: (300 MHz, $CDCl_3$) δ 6.81-6.89 (m, 3H), 6.95-6.98 (m, 4H), 7.07-7.11 (m, 1H), 7.21-7.48 (m, 9H), 7.93 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 113.7, 119.6, 119.9, 124.3, 126.3, 127.9, 128.2, 128.3, 128.3, 128.4, 128.7, 128.8, 129.3, 129.7, 130.3, 132.3, 133.2, 135.2, 135.8, 138.3, 145.7, 158.3; IR (NaCl, cm^{-1}) 3065, 3042, 2926, 1601, 1560, 1512, 1490, 1331, 1244, 1213, 1153, 1097, 995, 972, 819, 684, 590, 553, 474, 444 441; HRMS calculated for $C_{26}H_{19}NOS_2Na$ $[M+Na]^+$ 448.0800; Found 448.0797.

3-(ethylsulfanyl)-2-*S*-oxa-2-*S*,4-diphenyl-2,1-benzothiazine (161i): (Lithiation



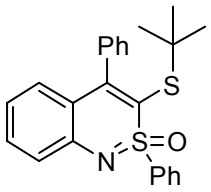
Procedure B) Yellow solid in 88% yield. (R_f = 0.41 in 25% EtOAc/hexanes; yellow long UV spot) Mp. 164 ^oC. ^1H NMR: (300 MHz, $CDCl_3$) δ 0.87 (t, *J* = 7.4 Hz, 3H), 2.33-2.43 (m, 2H), 6.81-6.87 (m, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 7.10-7.13 (m, 1H), 7.35-7.44 (m, 5H), 7.45-7.64 (m, 4H), 8.02 (d, *J* = 6.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 32.2, 115.0, 119.2, 119.7, 124.1, 128.0, 128.1, 128.1, 128.4, 128.6, 129.0, 129.1, 129.9, 131.8, 133.2, 136.4, 139.5, 145.1, 157.0; IR (NaCl, cm^{-1}) 3066, 3048, 2929, 1601, 1561, 1514, 1490, 1448, 1331, 1245, 1210, 1154, 1097, 996, 971, 821, 685, 590, 550, 467, 403; HRMS calculated for $C_{22}H_{19}NOS_2Na$ $[M+Na]^+$ 400.0800; Found 400.0797.

3-(cyclohexylsulfanyl)-2-*S*-oxa-2-*S*,4-diphenyl-2,1-benzothiazine (161j): (Lithiation

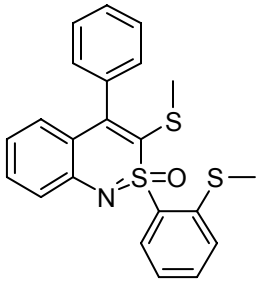


Procedure B) Yellow solid in 98% yield. (R_f = 0.53 in 25% EtOAc/hexanes; yellow long UV spot) Mp. 56 ^oC. ^1H NMR: (300 MHz, $CDCl_3$) δ 0.71-0.82 (m, 1H), 0.91-0.98 (m, 4H), 1.39-1.58 (m, 5H), 2.45-2.52 (m, 1H), 6.79-6.88 (m, 1H), 6.95 (d, *J* = 8.2 Hz, 1H), 7.09-7.14 (m, 1H), 7.36-7.45 (m, 5H), 7.47-7.64 (m, 4H), 8.03 (d, *J* = 6.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.2, 25.6, 25.7, 32.5, 32.8, 49.8, 115.1, 119.2, 119.7, 124.1, 127.9, 128.0, 128.4, 128.9, 129.0, 129.6, 130.1, 133.1, 136.3, 139.5, 145.1, 156.3; IR (NaCl, cm^{-1}) 3023, 2932, 2854, 1600, 1560, 1512, 1490, 1449, 1331, 1245, 1213, 1153, 1096, 970, 820, 618, 590, 479, 473, 403; HRMS calculated for $C_{26}H_{25}NOS_2Na$ $[M+Na]^+$ 454.1270; Found 454.1270.

3-(*tert*-butylsulfanyl)-2-*S*-oxa-2-*S*,4-diphenyl-2,1-benzothiazine (161k): (Lithiation Procedure B) Orange semi-solid in 19% yield. (R_f = 0.45 in 25% EtOAc/hexanes; yellow-orange long UV spot) ^{1}H NMR: (250 MHz, $CDCl_3$) δ 0.99 (s, 9H), 6.86 (t, *J* = 8.2 Hz, 1H), 7.04 (d, *J* = 8.4 Hz, 1H), 7.13-7.62 (m, 20H), 7.97 (d, *J* = 6.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.4, 50.1, 119.3, 119.7, 124.3, 127.6, 127.9, 128.2, 128.4, 129.6, 129.9, 130.4, 130.6, 132.1, 133.1, 136.8, 140.1, 145.7; IR (NaCl, cm^{-1}) 3463, 3061, 2925, 1601, 1571, 1529, 1448, 1321, 1247, 1193, 1154, 1097, 991, 699, 682, 603, 523, 504, 499, 439; HRMS calculated for $C_{24}H_{23}NOS_2Na$ $[M+Na]^+$ 428.1113; Found 428.1115.

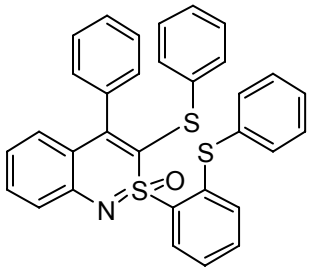


3-(methylsulfanyl)-2-*S*-oxa-2-*S*-[2-(methylsulfanyl)phenyl]-4-phenyl-2,1-benzothiazine (165a): Lithiation Procedure C: To an oven dried, N_2 cooled flask with stirbar, benzothiazine **26** (0.107 g, 0.338 mmol) was added and covered with a rubber septum. The flask was charged with argon, and freshly distilled THF (4 mL) was added via syringe. The reaction was then cooled to –78 ^{o}C via a dry ice/acetone bath. Then *n*-BuLi (0.467 mL, 2.17M, 1.02 mmol) was added drop-wise to the cooled solution resulting in a dark red solution. After 30 minutes, dimethyl disulfide (0.122 mL, 1.35 mmol) was added thru the rubber septum by syringe. The reaction mixture was stirred further overnight (or until completion was observed by TLC). The mixture was quenched with saturated ammonium chloride (2 mL) and extracted with dichloromethane (3 x 5 mL), concentrated in by vacuum, and dried ($MgSO_4$). Purification (R_f = 0.45 in 25% EtOAc/hexanes; green long UV spot) by flash chromatography (silica gel) with 25% EtOAc/ hexane afforded 0.131 g **165a** in 95%

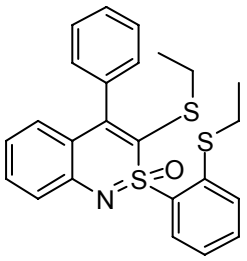


yield as a yellow solid. Mp. 193 °C. ^{1}H NMR: (300 MHz, $CDCl_3$) δ 2.05 (s, 3H), 2.36 (s, 3H), 6.86-6.96 (m, 2H), 7.20-7.31-7.60 (m, 10H), 8.40 (d, *J* = 8.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.9, 21.1, 119.7, 119.9, 124.0, 124.4, 125.9, 127.9, 128.2, 128.3, 128.9, 129.1, 131.1, 131.8, 133.6, 134.4, 137.0, 143.5, 145.4, 159.1; IR (NaCl, cm^{-1}) 3049, 2927, 2855, 1601, 1563, 1517, 1488, 1437, 1332, 1245, 1208, 1154, 701, 590, 556, 500, 497, 444, 402; HRMS calculated for $C_{22}H_{19}NOS_3Na$ $[M+Na]^+$ 432.0521; Found 432.0517.

3-(phenylsulfanyl)-2-*S*-oxa-2-*S*-[2-(phenylsulfanyl)phenyl]-4-phenyl-2,1-benzothiazine (165b): (Lithiation Procedure C) Yellow solid in 94% yield. (R_f = 0.56 in 25% EtOAc/hexanes; green long UV spot) Mp. 136 °C. ^{1}H NMR: (300 MHz, $CDCl_3$) δ 6.82-6.86 (m, 1H), 6.90-6.97 (m, 2H), 7.08-7.12 (m, 7H), 7.20-7.50 (m, 12H), 8.24 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 111.1, 120.0, 120.2, 124.4, 124.8, 126.8, 127.8, 127.9, 128.1, 128.5, 128.8, 129.0, 129.2, 129.6, 129.8, 129.9, 131.0, 132.2, 133.5, 134.6, 134.8, 136.3, 143.7, 145.4, 160.6; IR (NaCl, cm^{-1}) 3023, 2927, 2855, 1601, 1581, 1561, 1514, 1490, 1441, 1332, 1213, 1153, 820, 590, 558, 499, 469, 445; HRMS calculated for $C_{32}H_{23}NOS_3Na$ $[M+Na]^+$ 556.0834; Found 556.0830.

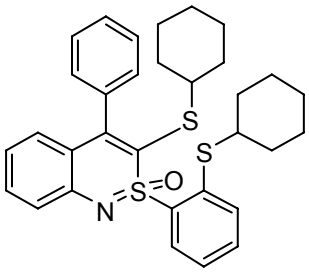


3-(ethylsulfanyl)-2-*S*-oxa-2-*S*-[2-(ethylsulfanyl)phenyl]-4-phenyl-2,1-benzothiazine (165c): (Lithiation Procedure C) Yellow solid in 89% yield. (R_f = 0.63 in 25% EtOAc/hexanes; yellow long UV spot) Mp. 184 °C. ^{1}H NMR: (300 MHz, $CDCl_3$) δ 0.97 (t, *J* = 7.4 Hz, 3H), 1.70 (t, *J* = 7.3 Hz, 3H), 2.46-2.56 (m, 1H), 2.59-2.70 (m, 1H), 2.78-2.91 (m, 2H), 6.83 (t, *J* = 6.7 Hz, 1H), 6.94 (d, *J* = 8.1 Hz, 1H), 7.16-7.20 (m, 1H), 7.27-7.56 (m, 9H),

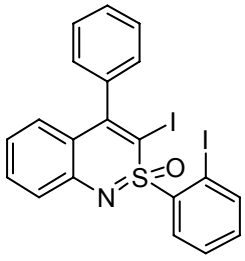


8.38 (d, J = 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.5, 14.3, 27.0, 32.2, 112.6, 119.6, 119.7, 124.2, 124.2, 127.6, 128.0, 128.2, 129.0, 130.9, 131.5, 133.4, 135.4, 137.1, 142.1, 145.2, 158.4; IR (NaCl, cm^{-1}) 2967, 2929, 2855, 1601, 1562, 1516, 1488, 1450, 1332, 1245, 1206, 734, 701, 590, 555, 409, 402; HRMS calculated for $C_{24}H_{23}NOS_3Na$ $[M+Na]^+$ 460.0834; Found 460.0837.

3-(cyclohexylsulfanyl)-2-*S*-oxa-2-*S*-[2-(cyclohexylsulfanyl)phenyl]-4-phenyl-2,1-benzothiazine (165d): (Lithiation Procedure C) Yellow solid in 98% yield. (R_f = 0.53 in 25% EtOAc/hexanes; yellow long UV spot) Mp. 117 °C. ^{1}H NMR: (300 MHz, $CDCl_3$) δ 0.85-1.26 (m, 10H), 1.34-1.89 (m, 10H), 2.96-2.97 (m, 1H), 2.21-2.23 (m, 1H), 6.80 (t, J = 8.2 Hz, 1H), 6.92 (d, J = 8.1 Hz, 1H), 7.23-7.59 (m, 9H), 8.38 (d, J = 8.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.4, 25.5, 25.6, 25.6, 25.7, 25.9, 32.4, 32.6, 33.0, 33.6, 45.5, 50.4, 113.1, 119.3, 119.8, 124.0, 124.9, 127.8, 128.0, 128.4, 129.0, 129.3, 130.1, 130.7, 130.9, 131.3, 133.0, 137.1, 137.7, 140.5, 145.3, 157.9; IR (NaCl, cm^{-1}) 3032, 2934, 2855, 1600, 1562, 1514, 1489, 1449, 1332, 1244, 1211, 1154, 1050, 997, 971, 820, 590, 556, 456, 452; HRMS calculated for $C_{32}H_{35}NOS_3Na$ $[M+Na]^+$ 568.1773; Found 568.1771.

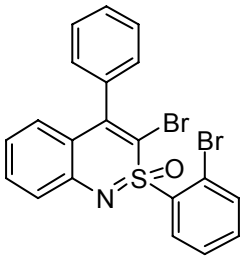


3-iodo-2-*S*-oxa-2-*S*-(2-iodophenyl)-4-phenyl-2,1-benzothiazine (165h): (Lithiation Procedure C) Brown solid in 91% yield. (R_f = 0.64 in 25% EtOAc/hexanes; short dark UV spot) Mp. 174 °C. ^{1}H NMR: (250 MHz, $CDCl_3$) δ 6.86 (t, J = 8.2 Hz, 1H), 7.00 (d, J = 8.2 Hz, 1H), 7.23–7.36 (m, 4H), 7.41–7.55 (m, 4H), 7.63 (t, J = 7.9 Hz, 1H), 8.13 (d, J = 7.8 Hz, 1H), 8.60 (d, J = 8.0 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 98.0,



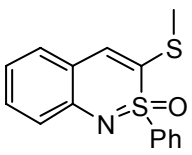
120.0, 120.4, 124.1, 127.6, 128.4, 128.7, 128.7, 128.8, 129.0, 131.9, 132.2, 134.4, 139.7, 141.0, 142.9, 145.4, 159.1; IR (NaCl, cm^{-1}) 3065, 3044, 2928, 1599, 1566, 1515, 1491, 1342, 1328, 1248, 1218, 1154, 998, 959, 599, 587, 548, 489, 424; HRMS calculated for $C_{20}H_{13}I_2NOSNa$ $[M+Na]^+$ 591.8699; Found 591.8696.

3-bromo-2-*S*-oxa-2-*S*-(2-bromophenyl)-4-phenyl-2,1-benzothiazine (165i):



(Lithiation Procedure C) Brown solid in 95% yield. (R_f = 0.73 in 25% EtOAc/hexanes; dark short UV spot) Mp. 172 °C. ^{1}H NMR: (250 MHz, $CDCl_3$) δ 6.86–6.98 (m, 2H), 7.20–7.24 (m, 2H), 7.28 (t, *J* = 8.2 Hz, 2H), 7.36–7.63 (m, 5H), 7.79 (d, *J* = 7.8 Hz, 1H), 8.51 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 100.9, 119.8, 120.5, 124.0, 124.8, 127.7, 128.1, 128.2, 128.7, 128.7, 131.9, 132.2, 134.9, 135.8, 136.5, 137.0, 144.3, 153.9; IR (NaCl, cm^{-1}) 3068, 3033, 2931, 1600,1567, 1523, 1443, 1343, 1333, 1250, 1224, 1155, 1043, 971, 605, 587, 551, 483, 464, 412; HRMS calculated for $C_{20}H_{13}Br_2NOSNa$ $[M+Na]^+$ 495.8977; Found 495.8975.

3-(methylsulfanyl)-2-*S*-oxa-2-*S*-[2-(methylsulfanyl)phenyl]-4-phenyl-2,1-



benzothiazine (166): Lithiation Procedure D: To an oven dried, N_2 cooled flask with stirbar, benzothiazine **1** (0.515 g, 2.13 mmol) was added and covered with a rubber septum. The flask was charged with argon, and freshly distilled THF (21 mL) was added via syringe. The reaction was then cooled to –78 °C via a dry ice/acetone bath. Then LiTMP (4.55 mL, 0.68M in THF, 2.87 mmol) was added drop-wise to the cooled solution resulting in a dark red solution. After 30 minutes, dimethyl disulfide (0.211 mL, 2.34 mmol) was added thru the rubber septum by syringe. The reaction mixture was stirred further overnight (or until completion was

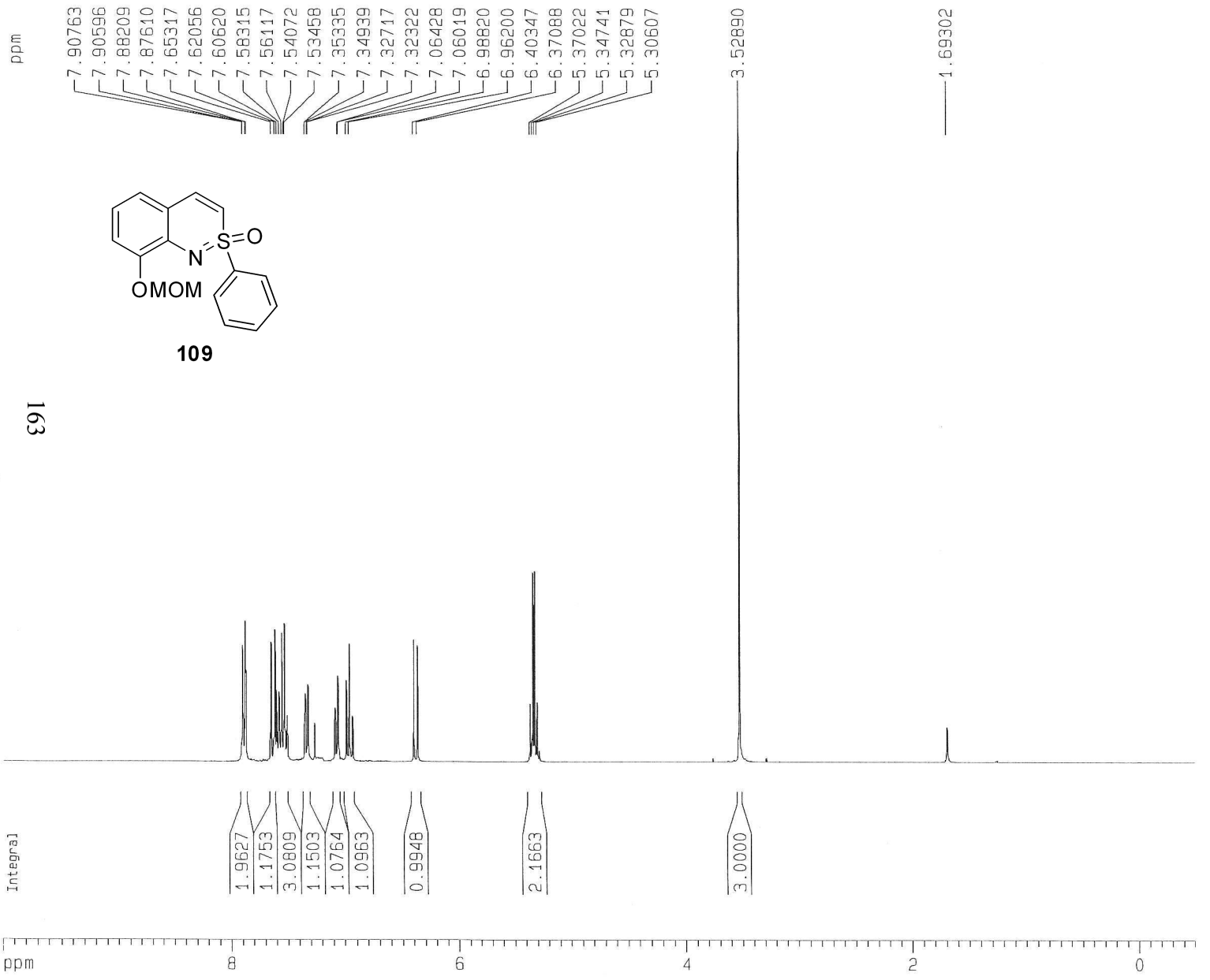
observed by TLC). The mixture was quenched with saturated ammonium chloride (5 mL) and extracted with dichloromethane (3 x 10 mL), concentrated in by vacuum, and dried ($MgSO_4$). Purification (R_f = 0.49 in 25% EtOAc/hexanes; yellow long UV spot) by flash chromatography (silica gel) with 25% EtOAc/ hexane afforded 0.565 g **166** in 92% yield as a very viscous orange oil. ^{1}H NMR: (250 MHz, $CDCl_3$) δ 2.21 (s, 3H), 6.94 (t, *J* = 6.9 Hz, 1H), 7.26-7.30 (m, 2H), 7.36 (t, *J* = 7.1 Hz, 1H), 7.43-7.57 (m, 3H), 7.76 (s, 1H), 7.86 (d, *J* = 7.0 Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 20.7, 117.7, 118.5, 119.9, 123.0, 128.3, 128.9, 129.2, 131.7, 133.1, 138.7, 143.8, 144.1; IR (NaCl, cm^{-1}) 3071, 2927, 1604, 1579, 1534, 1286, 1210, 1127, 993, 909, 583, 495, 454, 439; HRMS calculated for $C_{15}H_{13}NOS_2Na$ $[M+Na]^+$ 310.0331; Found 310.0328.

CHAPTER 6

APPENDIX

Selected ^{1}H and ^{13}C NMR and X-ray Structures for New Compounds

1H NMR



109

Current Data Parameters

NAME	NC-I-18A
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20041103
Time	13.06
INSTRUM	drx300
PROBHD	5 mm Multinucl
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	6172.839 Hz
FIDRES	0.188380 Hz
AQ	2.6542580 sec
RG	203.2
DW	81.000 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec
D31	0.00000000 sec

======== CHANNEL f1 ========

NUC1	1H
P1	7.05 usec
PL1	0.00 dB
SFO1	300.1318534 MHz

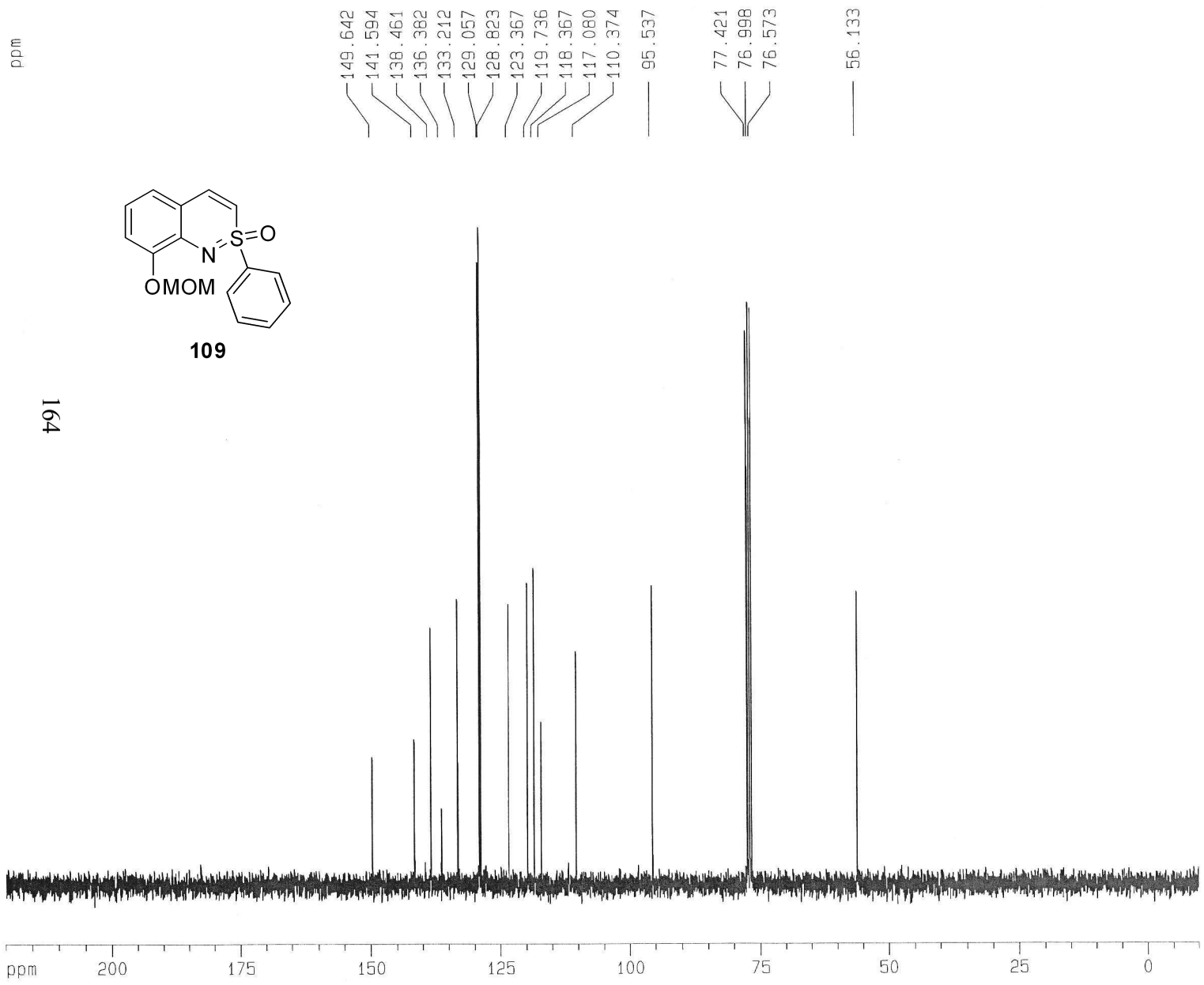
F2 - Processing parameters

SI	32768
SF	300.1300052 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.30

1D NMR plot parameters

CX	20.00 cm
CY	12.50 cm
F1P	10.000 ppm
F1	3001.30 Hz
F2P	-0.500 ppm
F2	-150.06 Hz
PPMCM	0.52500 ppm/cm
HZCM	157.56825 Hz/cm

13C NMR



Current Data Parameters

NAME	NC-I-18A
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20041103
Time	13.13
INSTRUM	drx300
PROBHD	5 mm Multinucl
PULPROG	zgdc30
TD	65536
SOLVENT	CDCl3
NS	141
DS	4
SWH	18832.393 Hz
FIDRES	0.287360 Hz
AQ	1.7400308 sec
RG	22528
DW	26.550 usec
DE	6.00 usec
TE	297.1 K
D1	1.29999995 sec
d11	0.03000000 sec
D31	0.00000000 sec

======== CHANNEL f1 ========

NUC1	13C
P1	8.50 usec
PL1	5.00 dB
SFO1	75.4760107 MHz

======== CHANNEL f2 ========

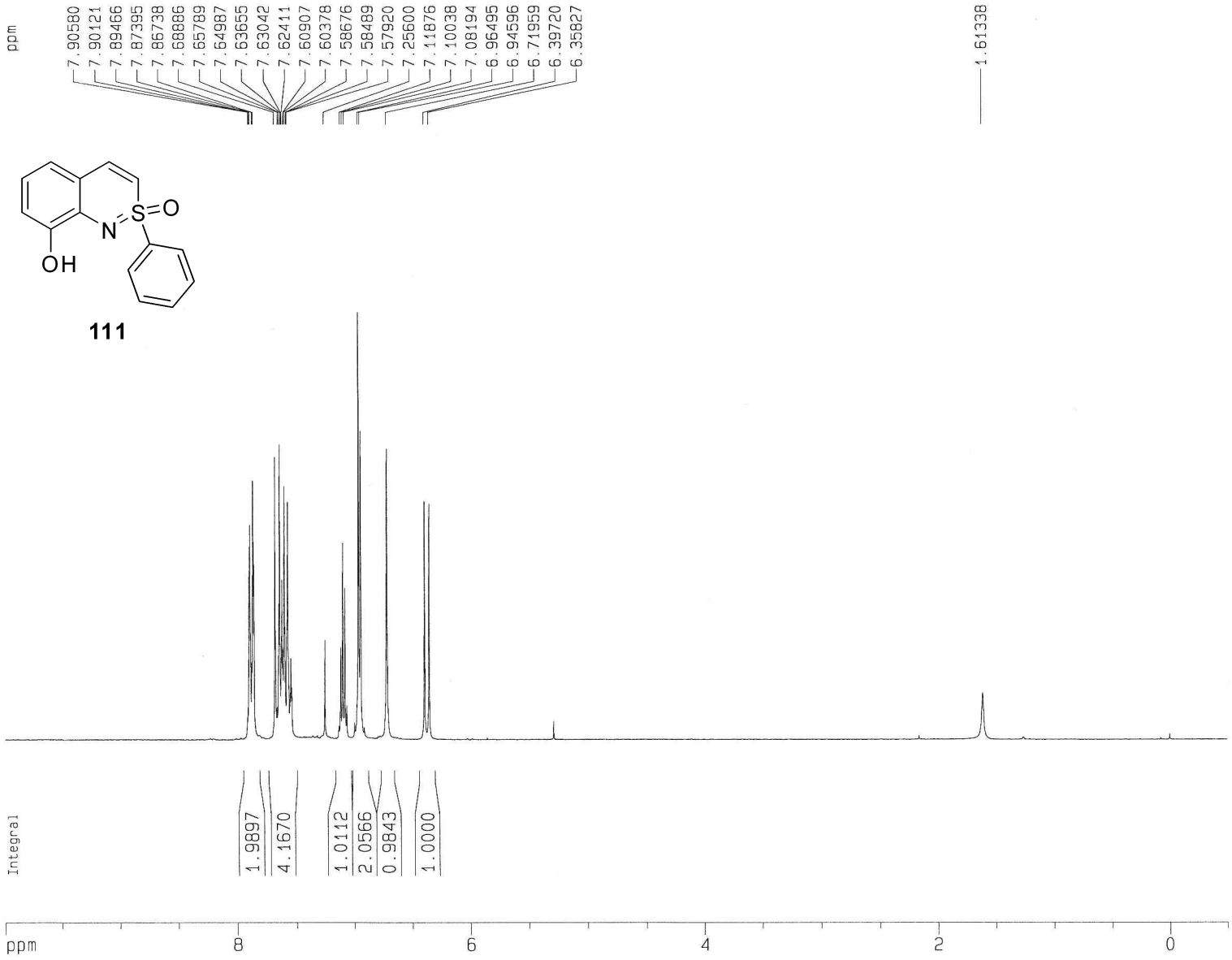
CPDPRG2	waltz16
NUC2	1H
PCPD2	100.00 usec
PL2	120.00 dB
PL12	25.60 dB
SFO2	300.1312005 MHz

F2 - Processing parameters

SI	32768
SF	75.4677548 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
CY	11.00 cm
F1P	220.000 ppm
F1	16602.91 Hz
F2P	-10.000 ppm
F2	-754.68 Hz
PPMCM	11.50000 ppm/cm
HZCM	867.87921 Hz/cm



Current Data Parameters

NAME	NC-I-16A
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

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Time	15.25
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PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	5208.333 Hz
FIDRES	0.158946 Hz
AQ	3.1457779 sec
RG	1430
DW	96.000 use
DE	137.14 use
TE	300.0 K
D1	1.00000000 sec
P1	8.70 use
SFO1	250.1315321 MHz
NUCLEUS	1H

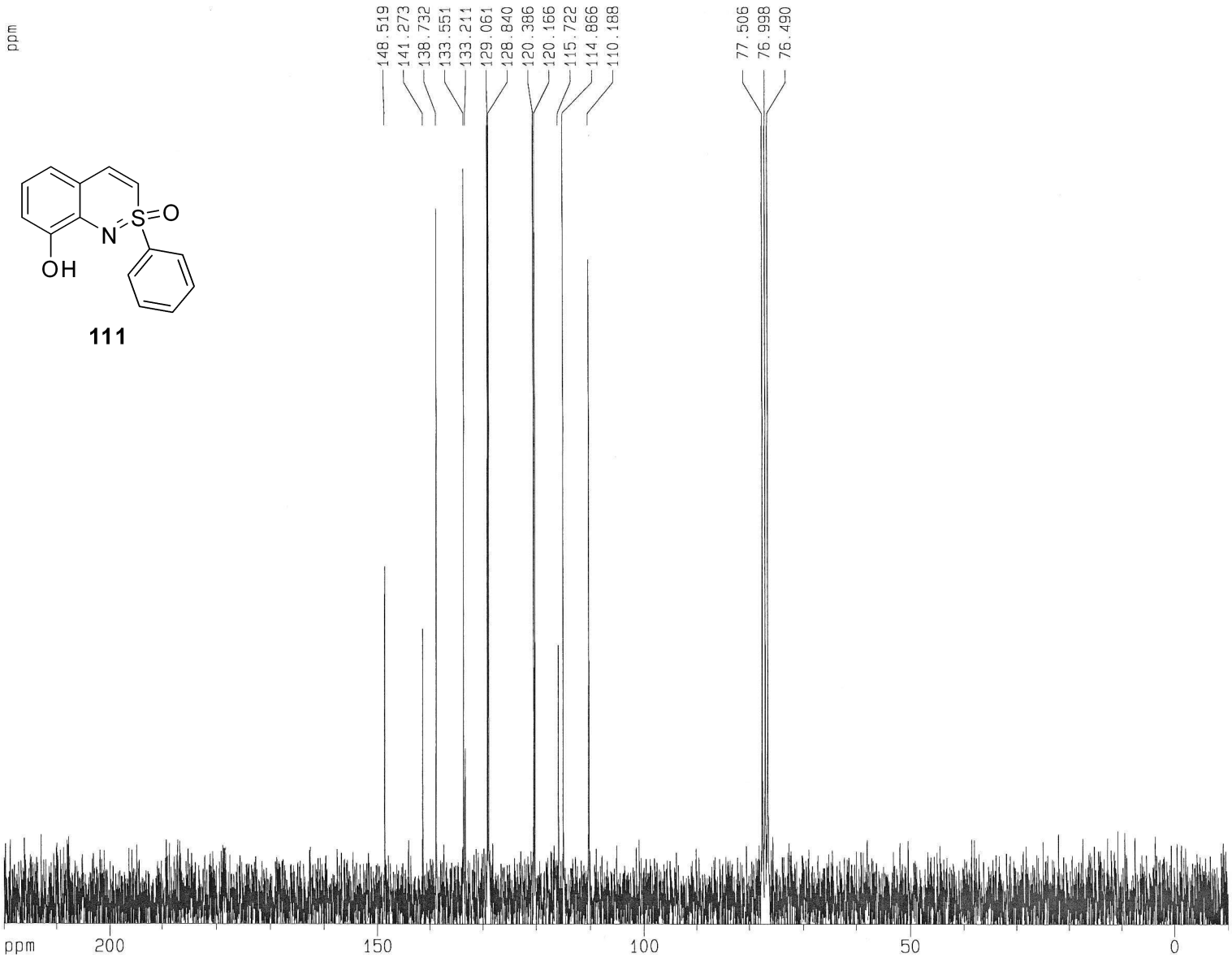
F2 - Processing parameters

SI	16384
SF	250.1300084 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.50

1D NMR plot parameters

CX	20.00 cm
CY	7.00 cm
F1P	10.000 ppm
F1	2501.30 Hz
F2P	-0.500 ppm
F2	-125.07 Hz
PPMCM	0.52500 ppm
HZCM	131.31825 Hz/

13C NMR



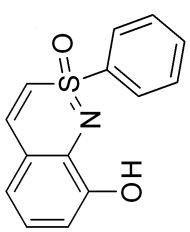
111

Current Data Parameters	
NAME	NC-I-16A
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters	
Date_	20041028
Time	15.32
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zgdc30
TD	36864
SOLVENT	CDCl3
NS	335
DS	4
SWH	17241.379 Hz
FIDRES	0.467702 Hz
AQ	1.0691060 sec
RG	22800
DW	29.000 use
DE	41.43 use
TE	300.0 K
D12	0.00002000 sec
DL5	23.00 dB
CPDPRG	waltz16
P31	103.00 use
D1	1.00000000 sec
P1	6.00 use
SFO1	62.9023694 MHz
NUCLEUS	13C
D11	0.03000000 sec

F2 - Processing parameters	
SI	32768
SF	62.8952424 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters	
CX	20.00 cm
CY	25.00 cm
F1P	220.000 ppm
F1	13836.95 Hz
F2P	-10.000 ppm
F2	-628.95 Hz
PPMCM	11.50000 ppm
HZCM	723.29529 Hz/



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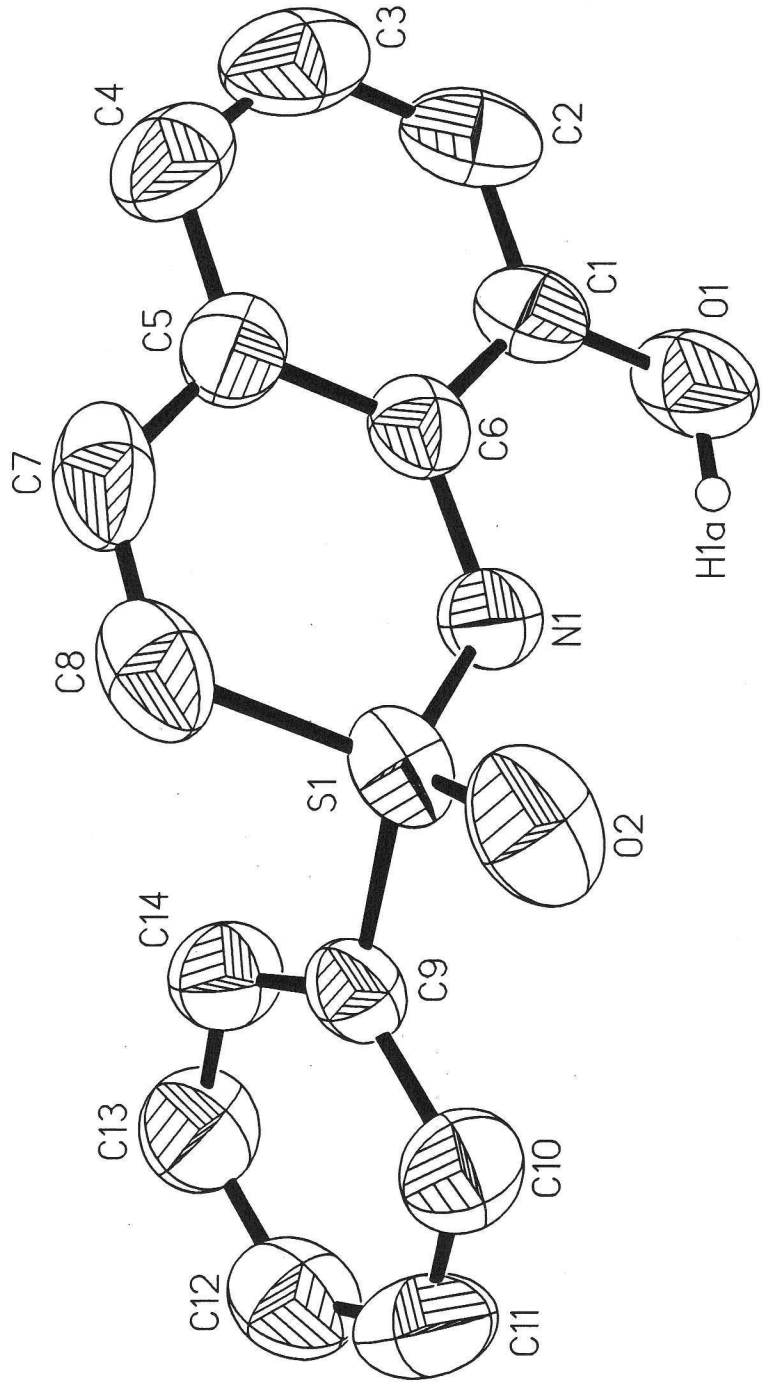
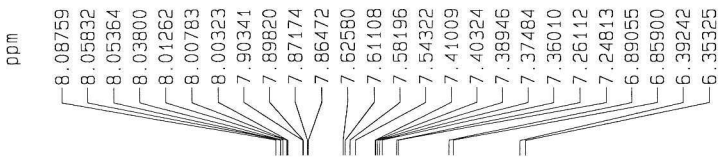
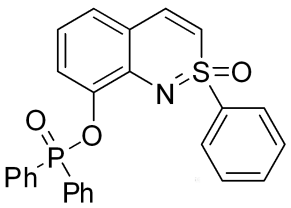
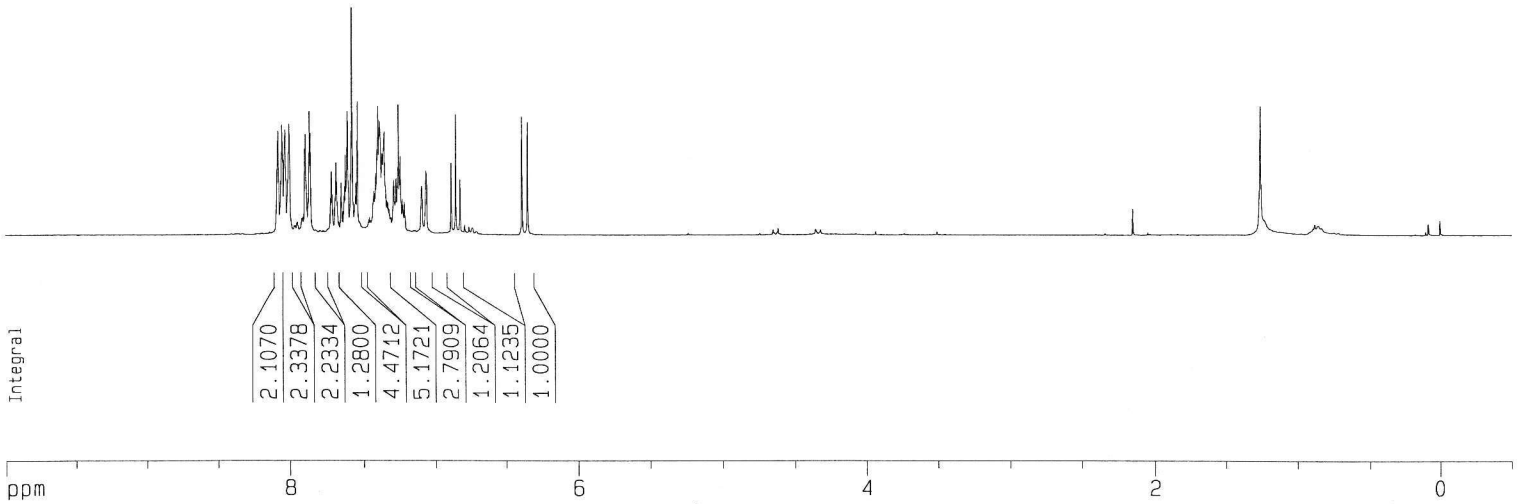


1H NMR





115



Current Data Parameters

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EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

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Time	13.39
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	5208.333 Hz
FIDRES	0.158946 Hz
AQ	3.1457779 sec
RG	715
DW	96.000 use
DE	137.14 use
TE	300.0 K
D1	1.00000000 sec
P1	9.50 use
SFO1	250.1315321 MHz
NUCLEUS	1H

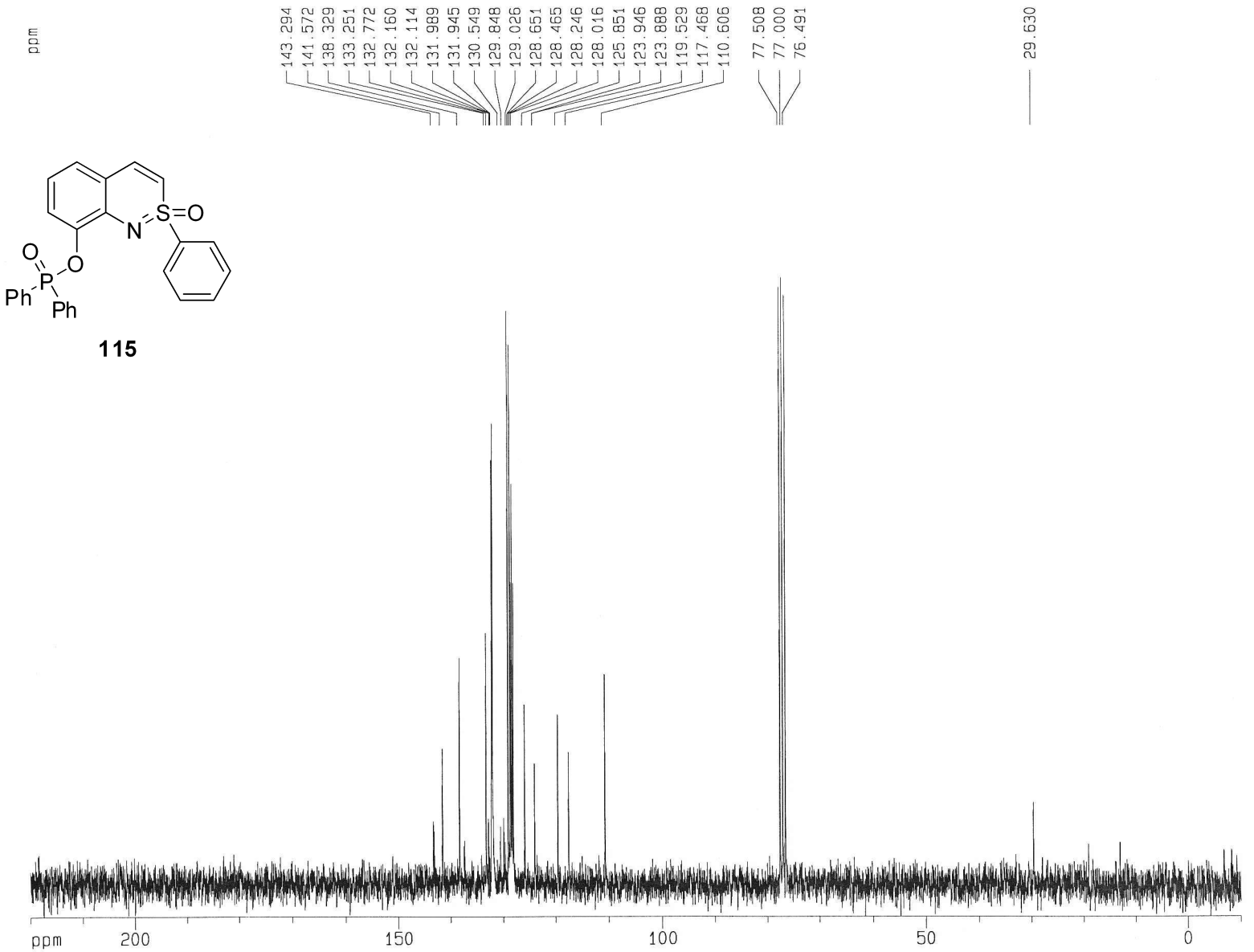
F2 - Processing parameters

SI	16384
SF	250.1300072 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.50

1D NMR plot parameters

CX	20.00 cm
CY	3.00 cm
F1P	10.000 ppm
F1	2501.30 Hz
F2P	-0.500 ppm
F2	-125.07 Hz
PPMCM	0.52500 ppm
HZCM	131.31825 Hz/

13C NMR



115

Current Data Parameters

NAME	XH-VI-15
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20051220
Time	13.45
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zgdc30
TD	36864
SOLVENT	CDCl3
NS	231
DS	4
SWH	17241.379 Hz
FIDRES	0.467702 Hz
AQ	1.0691060 sec
RG	22800
DW	29.000 use
DE	41.43 use
TE	300.0 K
D12	0.00002000 sec
DL5	23.00 dB
CPDPRG	waltz16
P31	103.00 use
D1	2.00000000 sec
P1	8.00 use
SFO1	62.9023694 MHz
NUCLEUS	13C
D11	0.03000000 sec

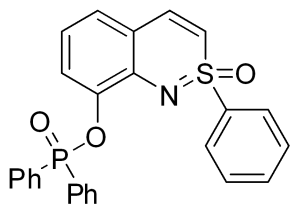
F2 - Processing parameters

SI	32768
SF	62.8952440 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	220.000 ppm
F1	13836.95 Hz
F2P	-10.000 ppm
F2	-628.95 Hz
PPMCM	11.50000 ppm
HZCM	723.29529 Hz/

31P NMR



115

Current Data Parameters

NAME	XH-VI-15
EXPNO	3
PROCNO	1

F2 - Acquisition Parameters

Date_	20051220
Time	13.55
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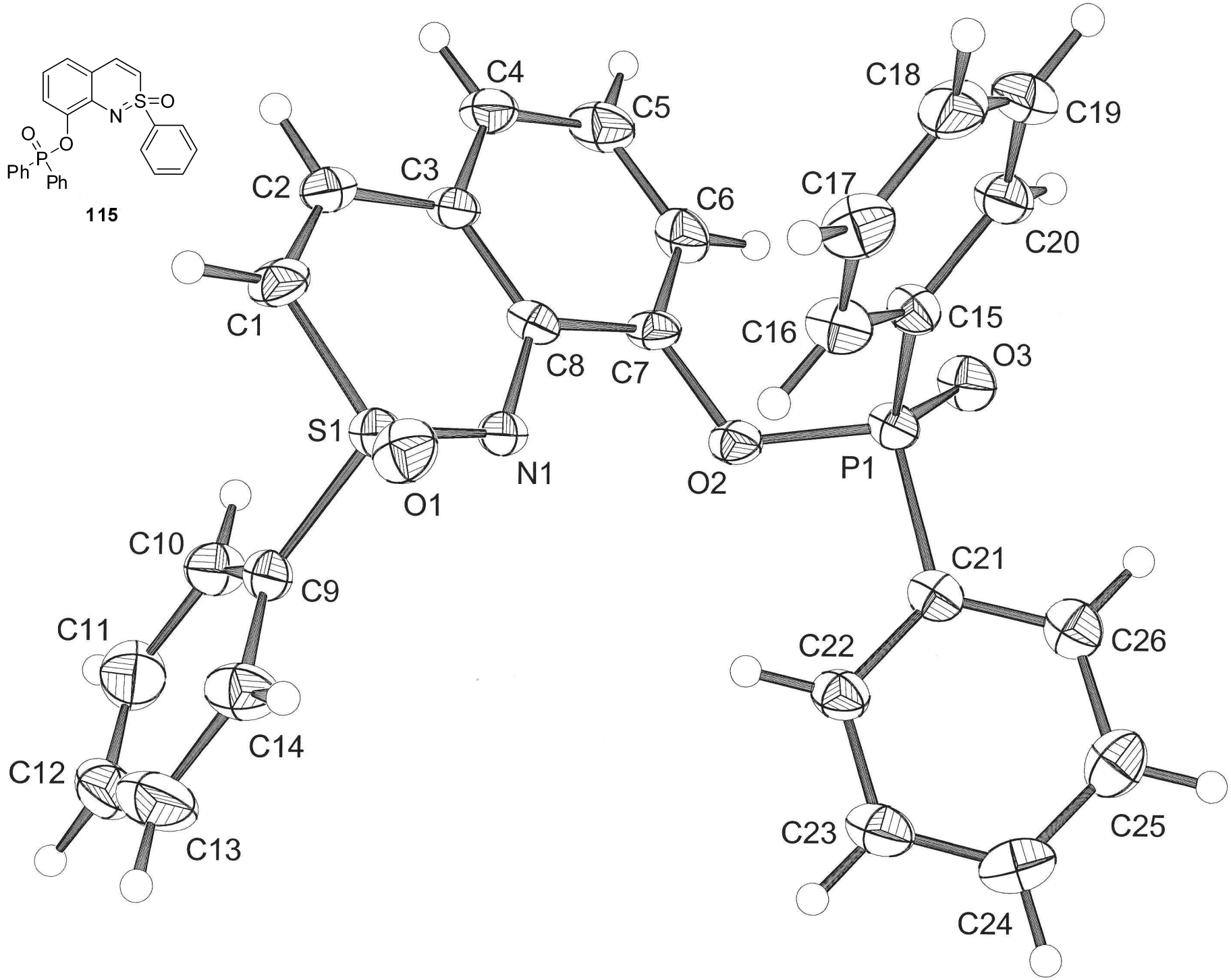
PROBHD	5 mm QNP 1H
PULPROG	zgdc30
TD	61440
SOLVENT	CDCl3
NS	85
DS	4
SWH	41667.047 Hz
FIDRES	0.678175 Hz
AQ	0.7373300 sec
RG	16384
DW	12.000 use
DE	17.14 use
TE	300.0 K
D12	0.00002000 sec
DL5	23.00 dB
CPDPRG	garp
P31	103.00 use
D1	1.50000000 sec
P1	8.00 use
SFO1	101.2548342 MHz
NUCLEUS	31P
D11	0.03000000 sec

F2 - Processing parameters

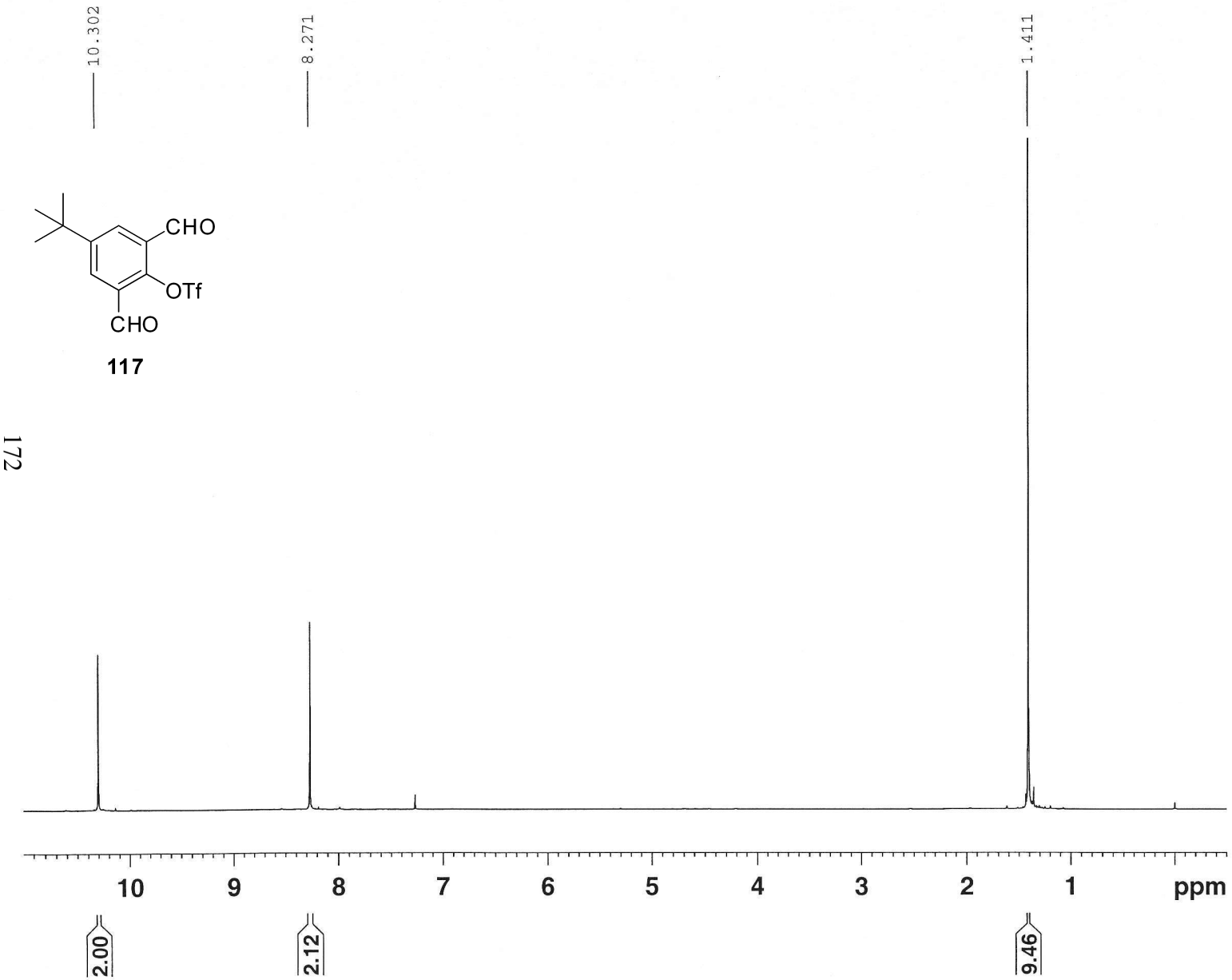
SI	32768
SF	101.2544133 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
CY	9.00 cm
F1P	200.000 ppm
F1	20250.88 Hz
F2P	-200.000 ppm
F2	-20250.88 Hz
PPMCM	20.00000 ppm
HZCM	2025.08813 Hz/


115
C4
C5
C18
C19
C2
C3
C6
C17
C20
C1
C8
C7
C16
C15
O3
S1
N1
O2
P1
O1
C10
C9
C21
C11
C22
C26
C14
C12
C25
C13
C23
C24

H NMR



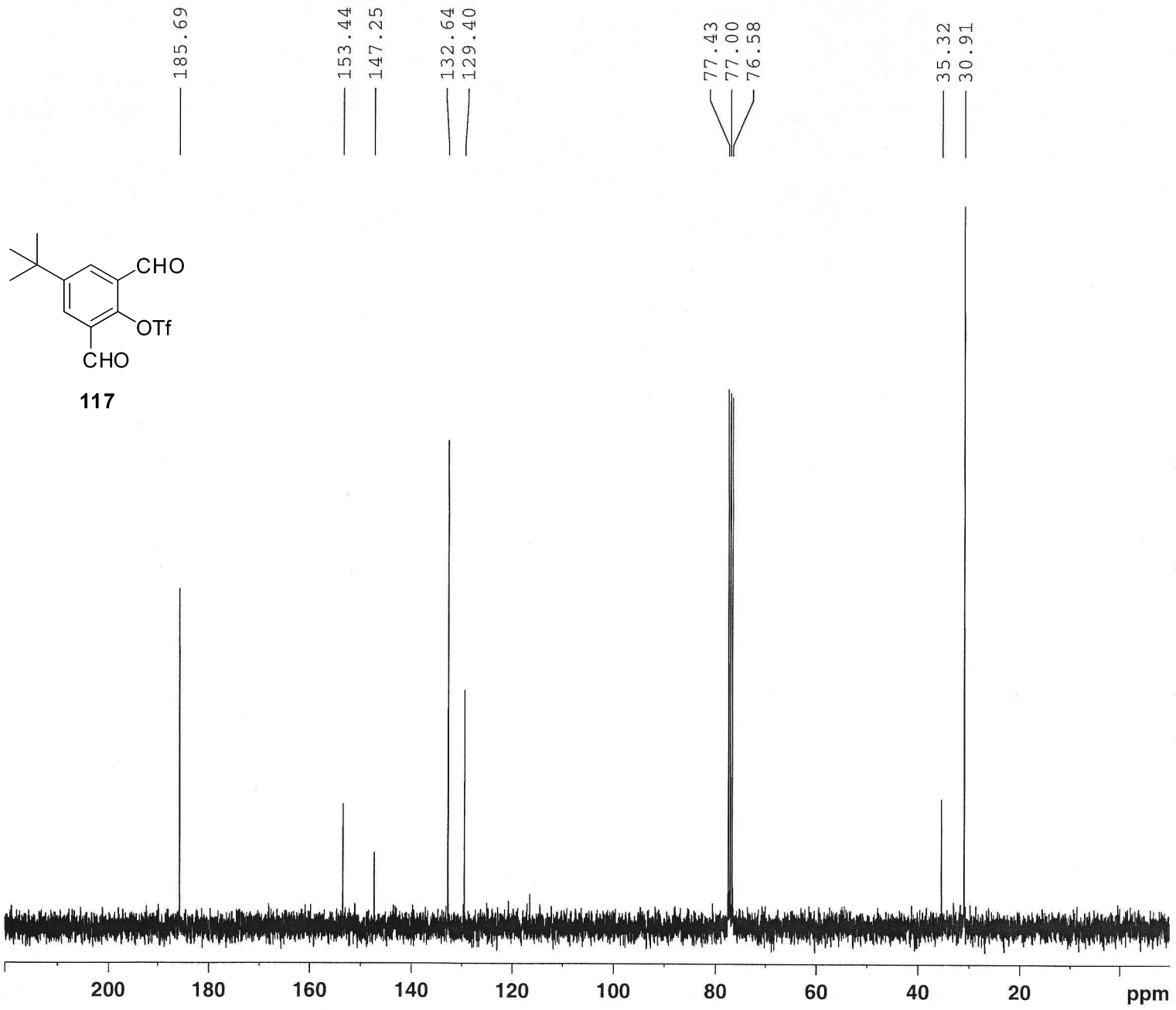

```
Current Data Parameters
NAME                 NC-IV-69
EXPNO                       1
PROCNO                      1

F2 - Acquisition Parameters
Date_               20070104
Time                   11.18
INSTRUM                DRX300
PROBHD   5 mm Multinucl
PULPROG              zg30pad
TD                     32768
SOLVENT                CDCl3
NS                        16
DS                         2
SWH                 6172.839 Hz
FIDRES              0.188380 Hz
AQ                  2.6542580 sec
RG                     228.1
DW                    81.000 usec
DE                     6.00 usec
TE                     300.0 K
D1                 1.00000000 sec
D31                0.00000000 sec

======== CHANNEL f1 ========
NUC1                       1H
P1                       7.05 usec
PL1                      0.00 dB
SFO1              300.1318534 MHz

F2 - Processing parameters
SI                     32768
SF                300.1300022 MHz
WDW                       EM
SSB                        0
LB                      0.30 Hz
GB                         0
PC                      1.30
```

13C NMR




```
Current Data Parameters
NAME                 NC-IV-69
EXPNO                       2
PROCNO                      1

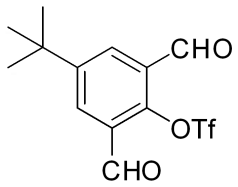
F2 - Acquisition Parameters
Date_               20070104
Time                   11.22
INSTRUM                DRX300
PROBHD   5 mm Multinucl
PULPROG             zgdc30pad
TD                      65536
SOLVENT                 CDCl3
NS                         57
DS                          4
SWH                18832.393 Hz
FIDRES             0.287360 Hz
AQ                 1.7400308 sec
RG                      22528
DW                     26.550 usec
DE                      6.00 usec
TE                     300.0 K
D1                2.00000000 sec
D11               0.03000000 sec
D31               0.00000000 sec

======== CHANNEL f1 ========
NUC1                      13C
P1                       9.00 usec
PL1                      5.00 dB
SFO1              75.4760107 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                       1H
PCPD2                  100.00 usec
PL2                    120.00 dB
PL12                    21.41 dB
SFO2             300.1312005 MHz

F2 - Processing parameters
SI                         32768
SF                75.4677502 MHz
WDW                           EM
SSB                            0
LB                      1.00 Hz
GB                             0
PC                          1.30
```

19F NMR



117

Current Data Parameters

NAME	NC-IV-69
EXPNO	3
PROCNO	1

F2 - Acquisition Parameters

Date_	20070104
Time	12.21
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	f19qnp
TD	65536
SOLVENT	CDCl3
NS	45
DS	2
SWH	71428.570 Hz
FIDRES	1.089913 Hz
AQ	0.4588020 sec
RG	1024
DW	7.000 usec
DE	10.00 usec
TE	300.0 K
D12	1.00000000 sec
D1	1.00000000 sec
P1	12.25 usec
SFO1	235.3521028 MHz
NUCLEUS	19F

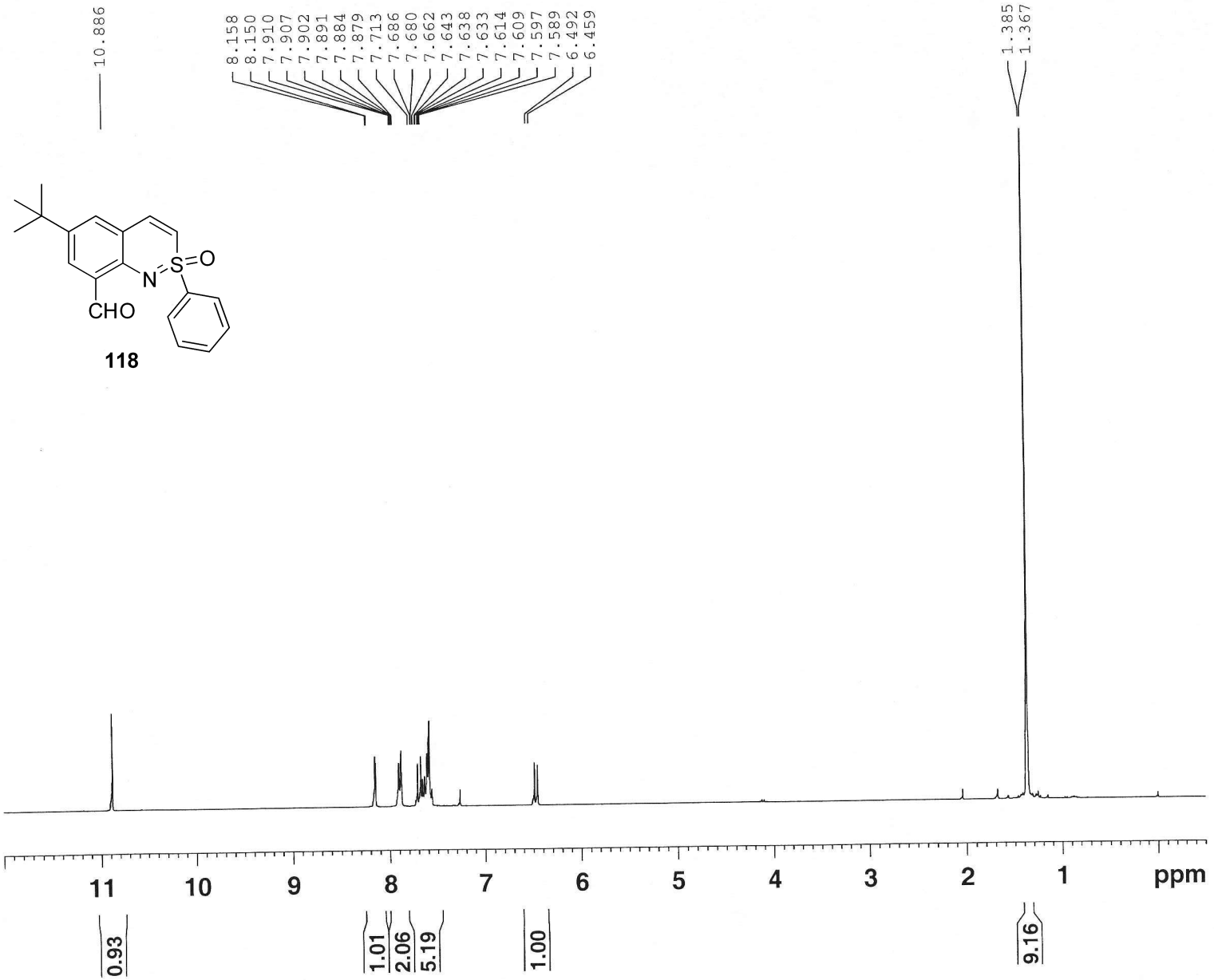
F2 - Processing parameters

SI	65536
SF	235.3574619 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	150.000 ppm
F1	35303.62 Hz
F2P	-150.000 ppm
F2	-35303.62 Hz
PPMCM	15.00000 ppm/cm
HZCM	3530.36157 Hz/cm

H NMR



118

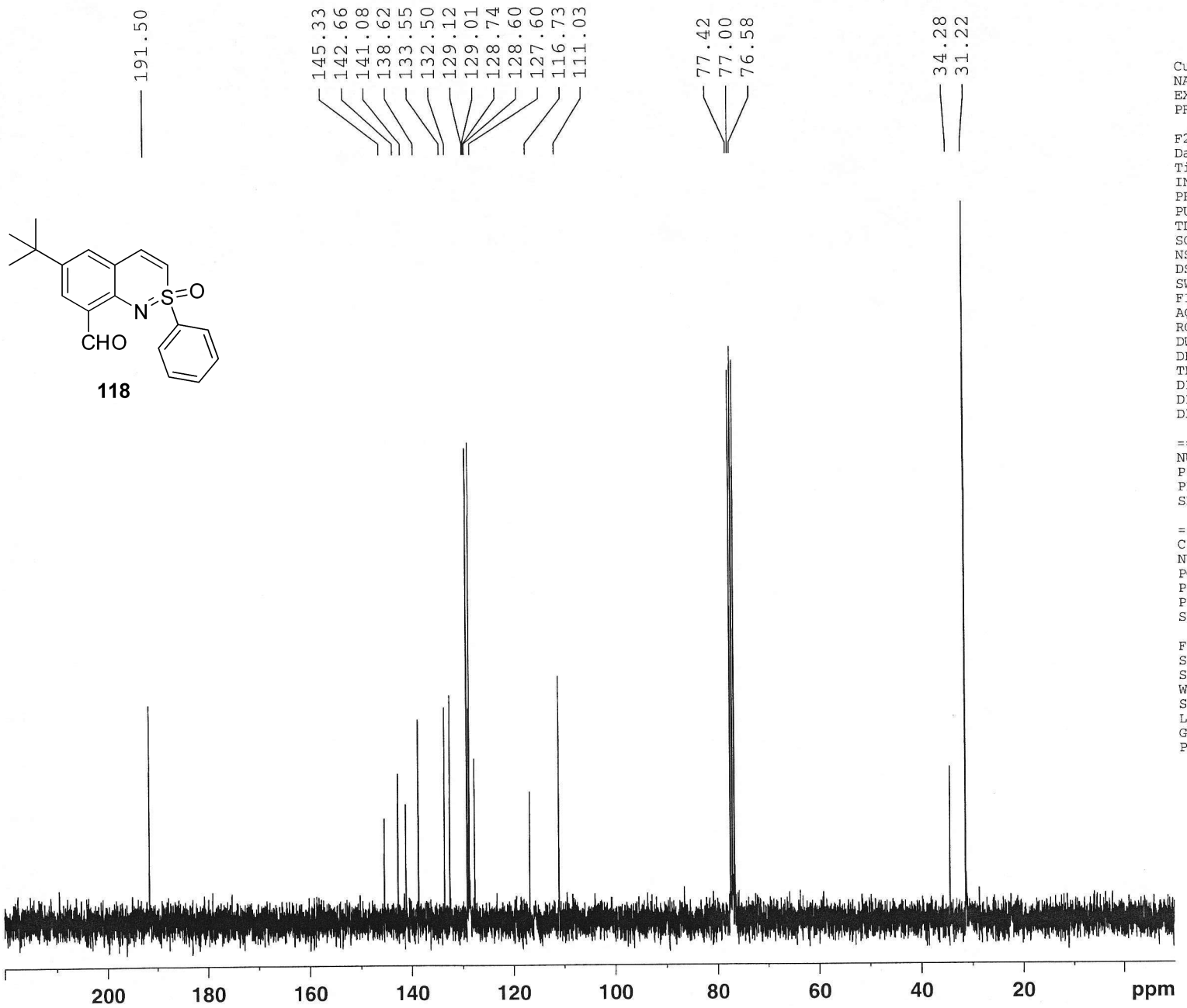
Current Data Parameters	
NAME	NC-IV-71B
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters	
Date_	20070110
Time	15.32
INSTRUM	DRX300
PROBHD	5 mm Multinucl
PULPROG	zg30pad
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	6172.839 Hz
FIDRES	0.188380 Hz
AQ	2.6542580 sec
RG	181
DW	81.000 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec
D31	0.00000000 sec

======== CHANNEL f1 ========	
NUC1	1H
P1	7.05 usec
PL1	0.00 dB
SFO1	300.1318534 MHz

F2 - Processing parameters	
SI	32768
SF	300.1300041 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.30

13C NMR




```
Current Data Parameters
NAME                  NC-IV-71B
EXPNO                         2
PROCNO                        1

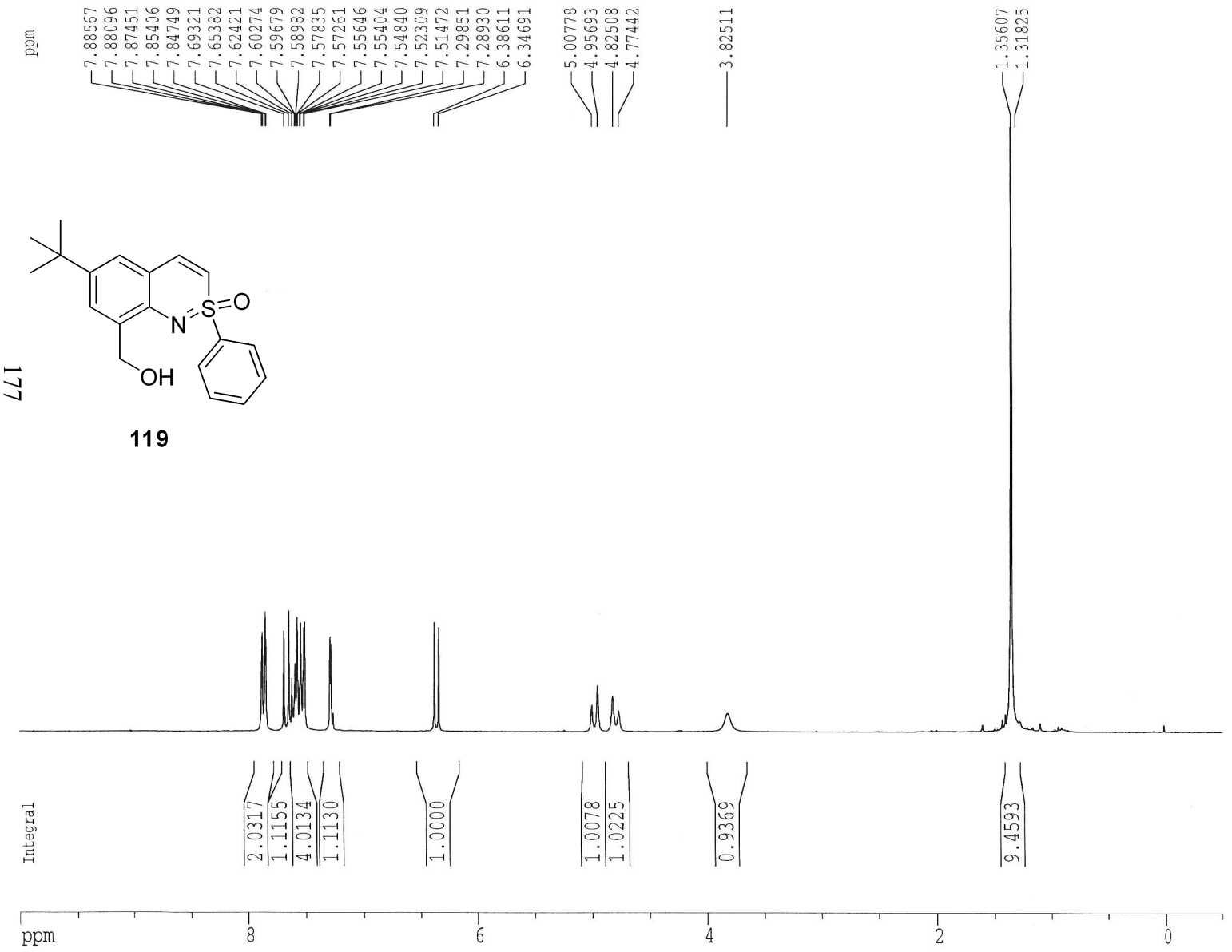
F2 - Acquisition Parameters
Date_                  20070110
Time                      15.36
INSTRUM                  DRX300
PROBHD    5 mm Multinucl
PULPROG               zgdc30pad
TD                        65536
SOLVENT                   CDCl3
NS                           57
DS                            4
SWH                  18832.393 Hz
FIDRES                0.287360 Hz
AQ                    1.7400308 sec
RG                        22528
DW                       26.550 usec
DE                        6.00 usec
TE                       300.0 K
D1                   2.00000000 sec
D11                  0.03000000 sec
D31                  0.00000000 sec

======== CHANNEL f1 ========
NUC1                        13C
P1                         9.00 usec
PL1                        5.00 dB
SFO1                75.4760107 MHz

======== CHANNEL f2 ========
CPDPRG2                 waltz16
NUC2                        1H
PCPD2                    100.00 usec
PL2                      120.00 dB
PL12                      21.41 dB
SFO2               300.1312005 MHz

F2 - Processing parameters
SI                        32768
SF                 75.4677537 MHz
WDW                          EM
SSB                           0
LB                         1.00 Hz
GB                            0
PC                         1.30
```

1H NMR



177

119

Current Data Parameters

NAME	NC-IV-83
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20091222
Time	9.20
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	5208.333 Hz
FIDRES	0.158946 Hz
AQ	3.1457779 sec
RG	256
DW	96.000 usec
DE	137.14 usec
TE	300.0 K
D1	1.00000000 sec
P1	8.50 usec
SFO1	250.1315321 MHz
NUCLEUS	1H

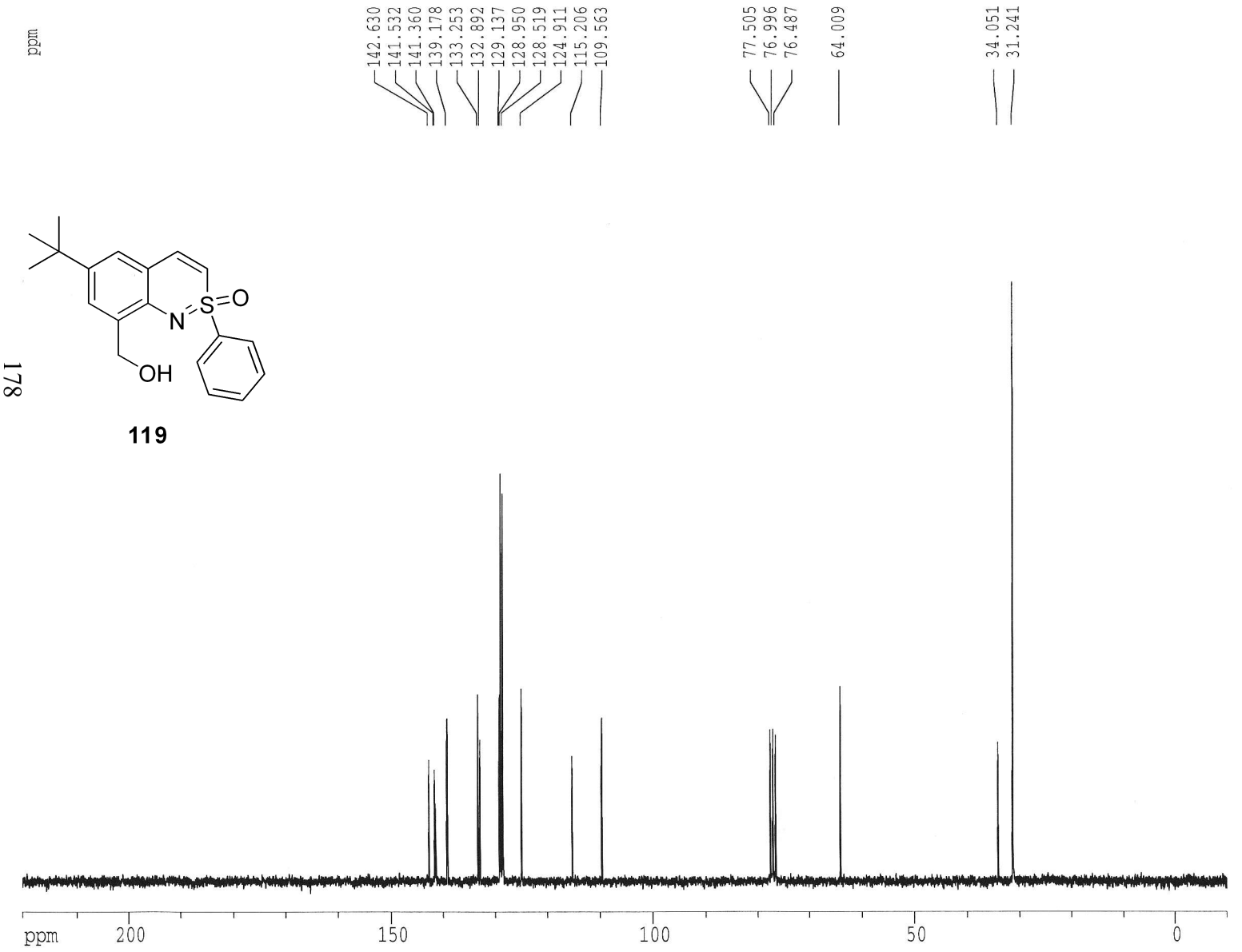
F2 - Processing parameters

SI	16384
SF	250.1300049 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.50

1D NMR plot parameters

CX	20.00 cm
CY	30.00 cm
F1P	10.000 ppm
F1	2501.30 Hz
F2P	-0.500 ppm
F2	-125.07 Hz
PPMCM	0.52500 ppm/cm
HZCM	131.31825 Hz/cm

13C NMR



Current Data Parameters

NAME	NC-IV-83
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

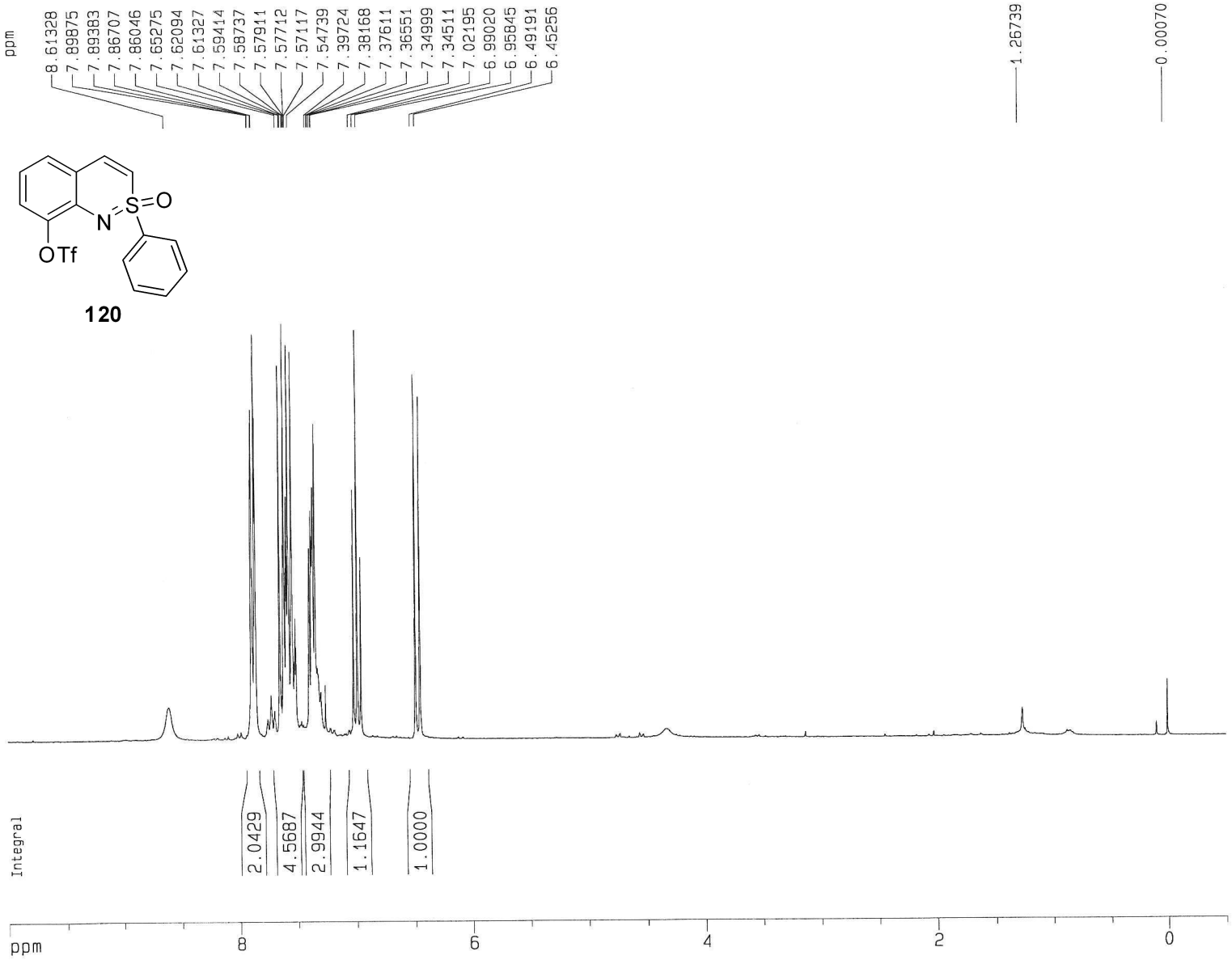
Date_	20091222
Time	9.27
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zgdc30
TD	36864
SOLVENT	CDCl3
NS	126
DS	4
SWH	17241.379 Hz
FIDRES	0.467702 Hz
AQ	1.0691060 sec
RG	22800
DW	29.000 usec
DE	41.43 usec
TE	300.0 K
D12	0.00002000 sec
DL5	23.00 dB
CPDPRG	waltz16
P31	103.00 usec
D1	2.00000000 sec
P1	6.25 usec
SFO1	62.9023694 MHz
NUCLEUS	13C
D11	0.03000000 sec

F2 - Processing parameters

SI	32768
SF	62.8952497 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	220.000 ppm
F1	13836.95 Hz
F2P	-10.000 ppm
F2	-628.95 Hz
PPMCM	11.50000 ppm/cm
HZCM	723.29535 Hz/cm



120

Current Data Parameters

NAME	NC-III-57
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20060308
Time	14.47
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	5208.333 Hz
FIDRES	0.158946 Hz
AQ	3.1457779 sec
RG	512
DW	96.000 use
DE	137.14 use
TE	300.0 K
D1	1.00000000 sec
P1	9.50 use
SFO1	250.1315321 MHz
NUCLEUS	1H

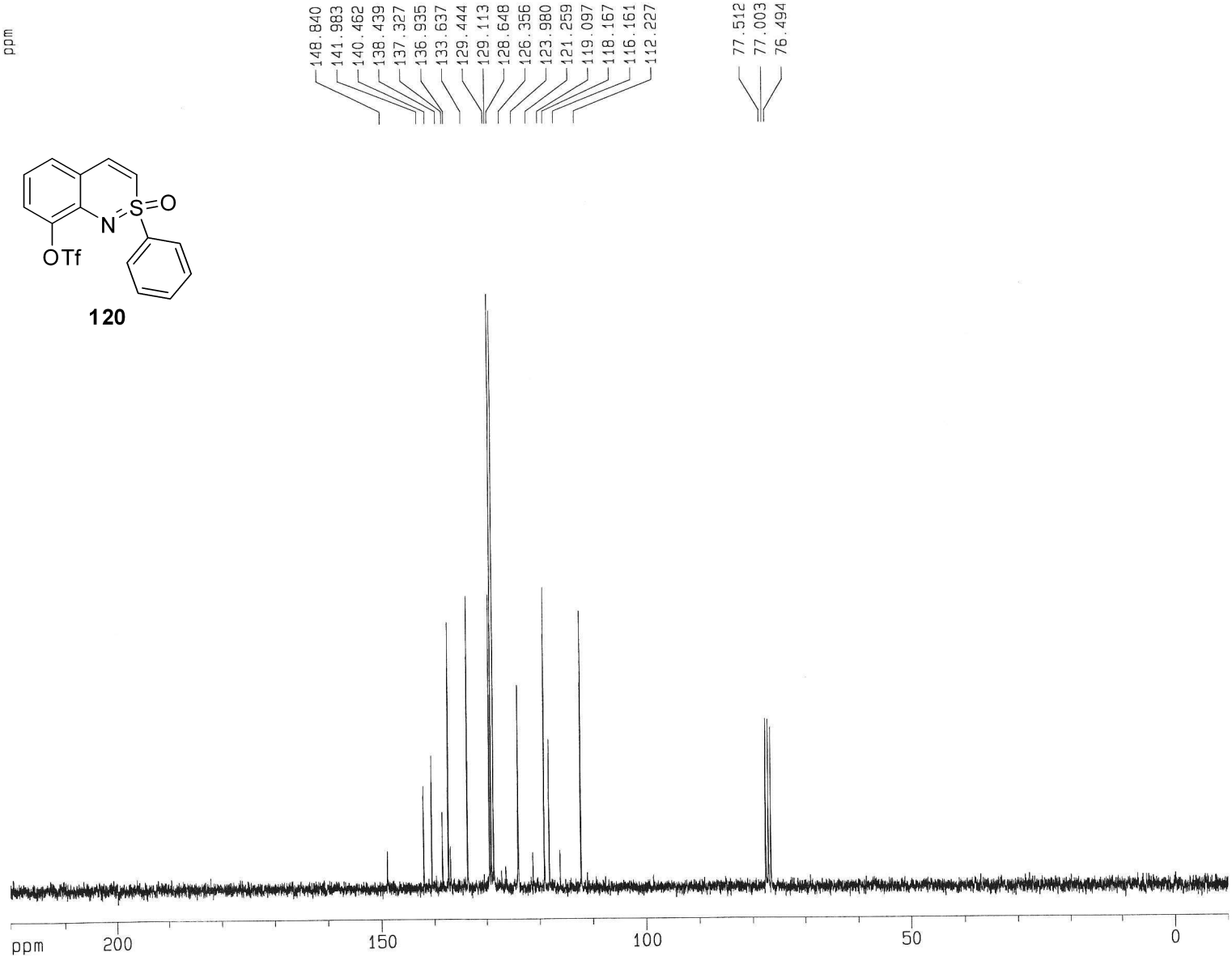
F2 - Processing parameters

SI	16384
SF	250.1300068 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.50

1D NMR plot parameters

CX	20.00 cm
CY	7.00 cm
F1P	10.000 ppm
F1	2501.30 Hz
F2P	-0.500 ppm
F2	-125.07 Hz
PPMCM	0.52500 ppm
HZCM	131.31825 Hz/

13C NMR



120

Current Data Parameters

NAME	NC-III-57
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20060308
Time	14.50
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zgdc30
TD	36864
SOLVENT	CDCl3
NS	120
DS	4
SWH	17241.379 Hz
FIDRES	0.467702 Hz
AQ	1.0691060 sec
RG	22800
DW	29.000 use
DE	41.43 use
TE	300.0 K
D12	0.00002000 sec
DL5	23.00 dB
CPDPRG	waltz16
P31	103.00 use
D1	2.00000000 sec
P1	8.00 use
SFO1	62.9023694 MHz
NUCLEUS	13C
D11	0.03000000 sec

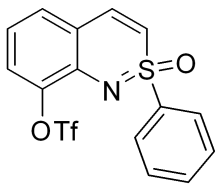
F2 - Processing parameters

SI	32768
SF	62.8952466 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	220.000 ppm
F1	13836.95 Hz
F2P	-10.000 ppm
F2	-628.95 Hz
PPMCM	11.50000 ppm
HZCM	723.29535 Hz/

19F NMR



120

Current Data Parameters

NAME	NC-III-57
EXPNO	3
PROCNO	1

F2 - Acquisition Parameters

Date_	20060308
Time	14.59
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	f19qnp
TD	65536
SOLVENT	CDCl3
NS	59
DS	2
SWH	71428.570 Hz
FIDRES	1.089913 Hz
AQ	0.4588020 sec
RG	1024
DW	7.000 use
DE	10.00 use
TE	300.0 K
D12	1.00000000 sec
D1	1.00000000 sec
P1	12.25 use
SFO1	235.3521028 MHz
NUCLEUS	19F

F2 - Processing parameters

SI	65536
SF	235.3573954 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

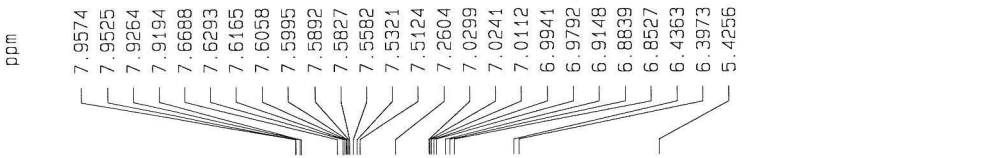
1D NMR plot parameters

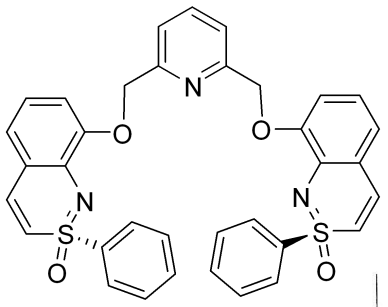
CX	20.00 cm
CY	10.00 cm
F1P	150.000 ppm
F1	35303.61 Hz
F2P	-150.000 ppm
F2	-35303.61 Hz
PPMCM	15.00000 ppm
HZCM	3530.36060 Hz/

1H NMR

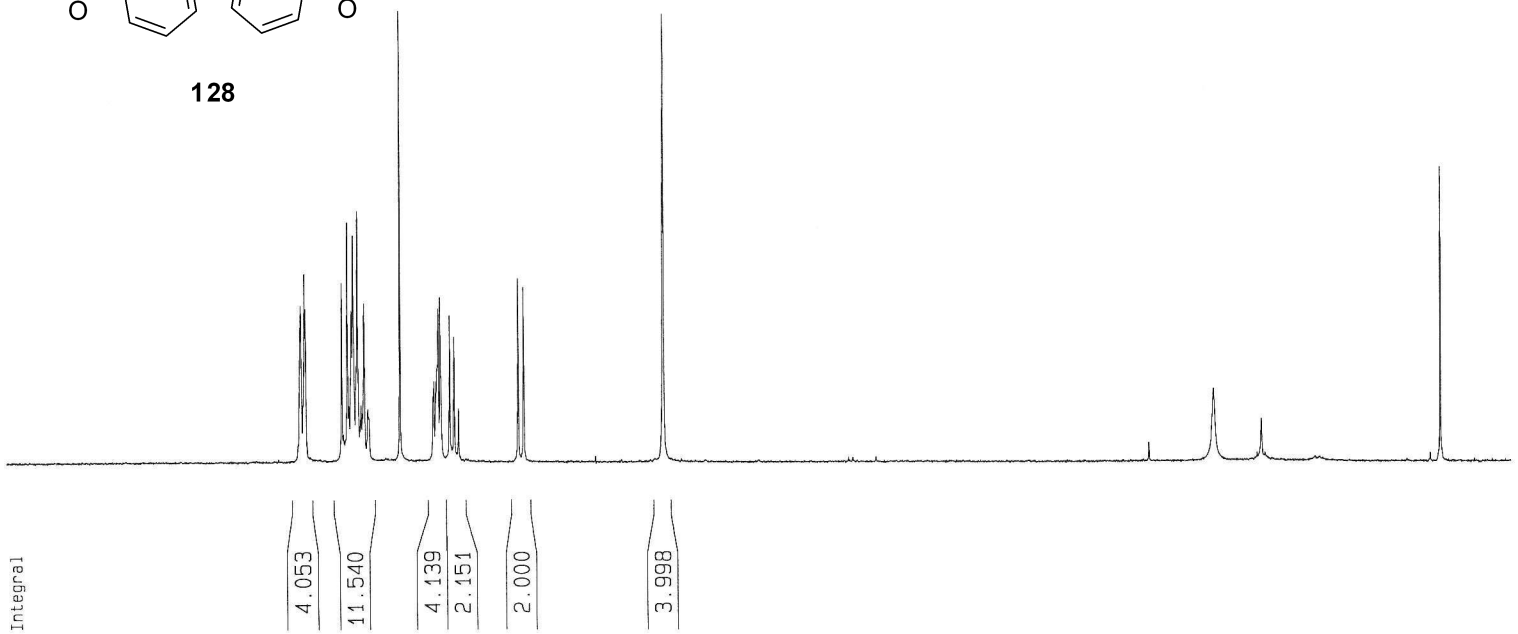
2, 6-bis (O-8- (2, 1-benzothiazine)) pyridine

12/22/05





128



Current Data Parameters

NAME	NC-I-78D
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20051222
Time	13.31
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	5208.333 Hz
FIDRES	0.158946 Hz
AQ	3.1457779 sec
RG	4096
DW	96.000 use
DE	137.14 use
TE	300.0 K
D1	1.00000000 sec
P1	9.50 use
SF01	250.1315321 MHz
NUCLEUS	1H

F2 - Processing parameters

SI	16384
SF	250.1300072 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.50

1D NMR plot parameters

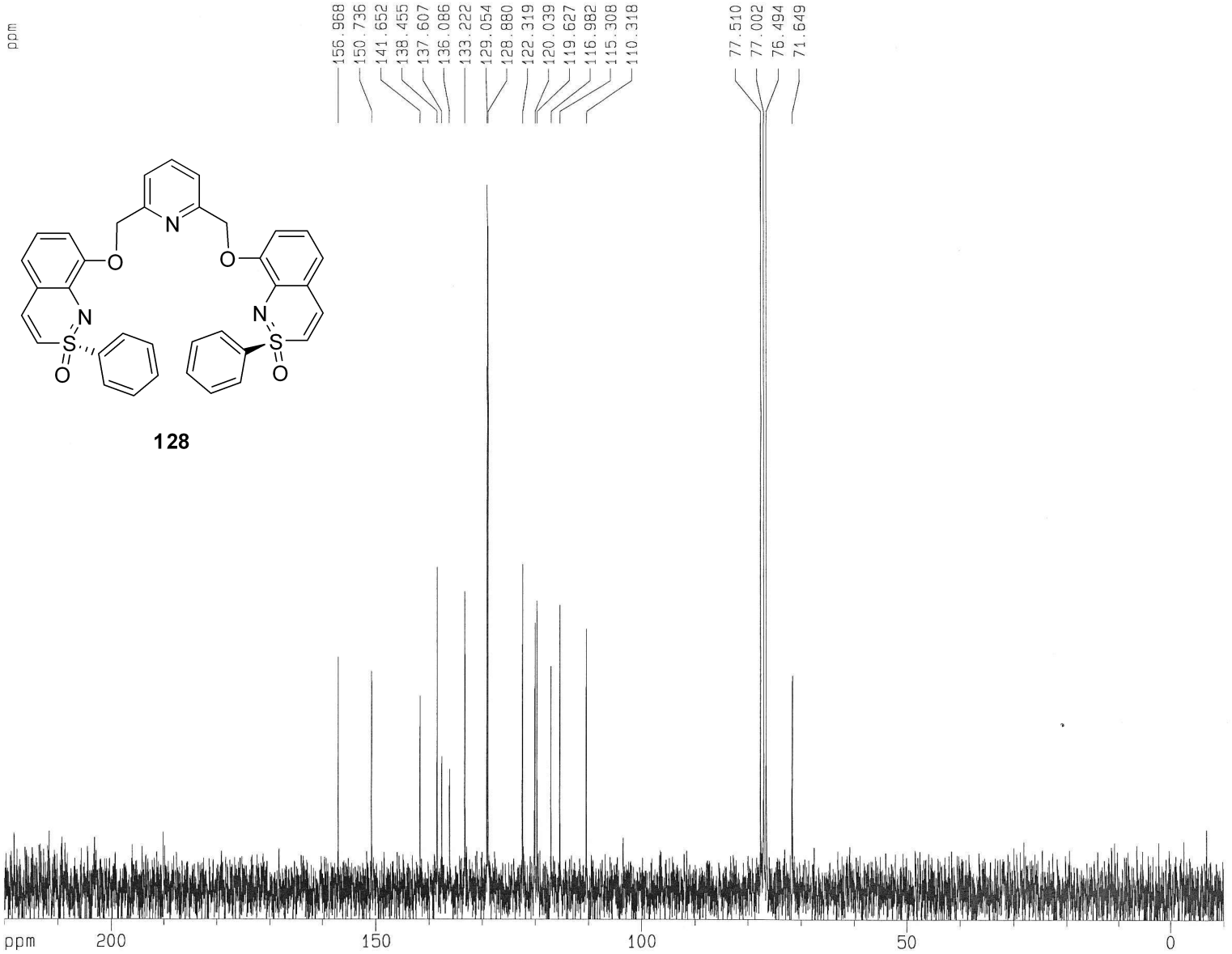
CX	20.00 cm
CY	6.00 cm
F1P	10.000 ppm
F1	2501.30 Hz
F2P	-0.500 ppm
F2	-125.07 Hz
PPMCM	0.52500 ppm
HZCM	131.31825 Hz/

13C NMR

NC-I-78D

2, 6-dimethyl (8-oxobenzothiazine) pyridine

1/18/05



128

Current Data Parameters

NAME	NC-I-78D
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

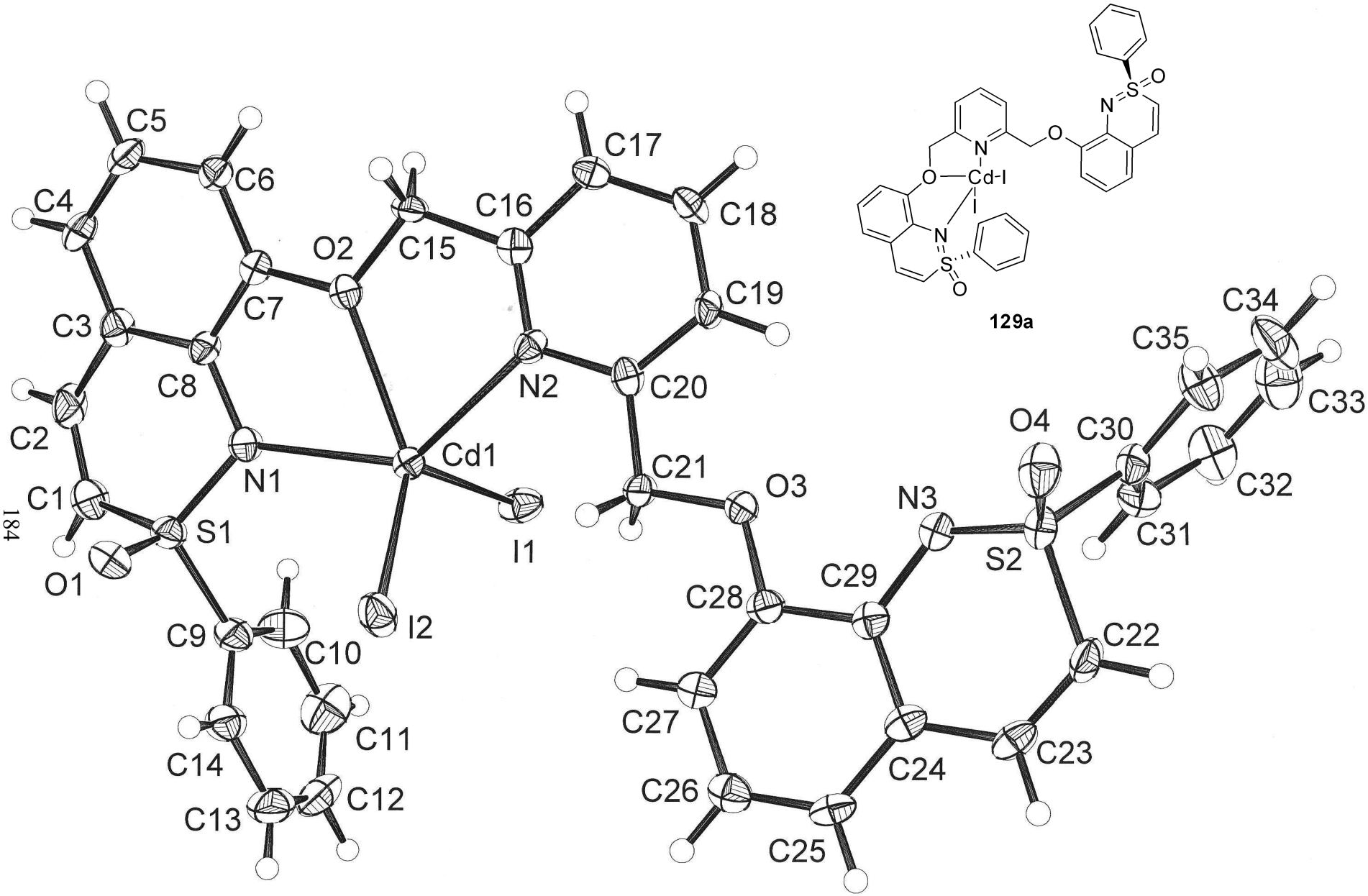
Date_	20050118
Time	15.18
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zgdc30
TD	36864
SOLVENT	CDCl3
NS	193
DS	4
SWH	17241.379 Hz
FIDRES	0.467702 Hz
AQ	1.0691060 sec
RG	22800
DW	29.000 use
DE	41.43 use
TE	300.0 K
D12	0.00002000 sec
DL5	23.00 dB
CPDPRG	waltz16
P31	103.00 use
D1	1.00000000 sec
P1	6.00 use
SFO1	62.9023694 MHz
NUCLEUS	13C
D11	0.03000000 sec

F2 - Processing parameters

SI	32768
SF	62.8952424 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

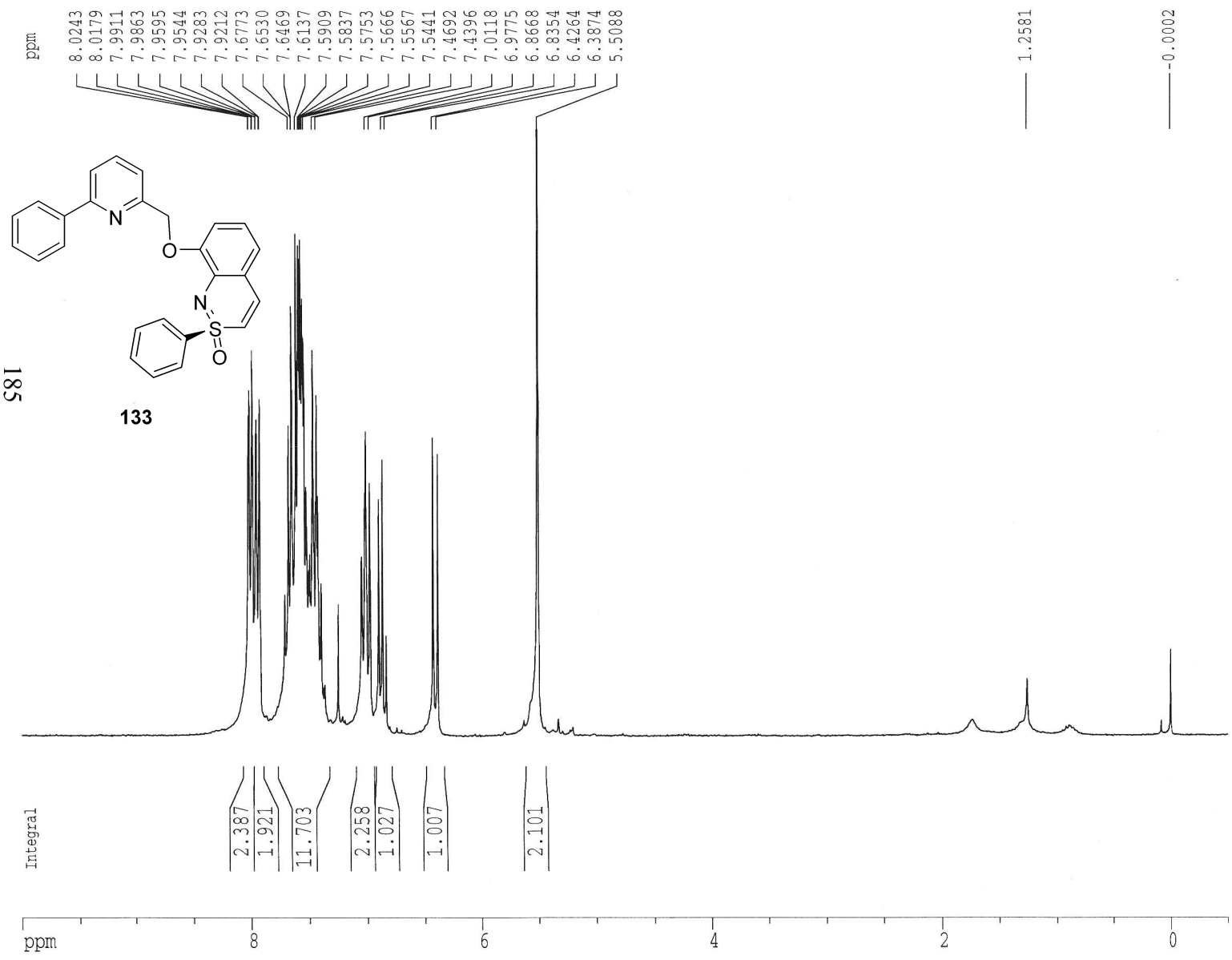
1D NMR plot parameters

CX	20.00 cm
CY	15.00 cm
F1P	220.000 ppm
F1	13836.95 Hz
F2P	-10.000 ppm
F2	-628.95 Hz
PPMCM	11.50000 ppm
HZCM	723.29529 Hz/


C5
C6
C4
C17
C16
C18
O2
C15
C7
C19
C3
C8
N2
C20
C2
N1
Cd1
C21
C1
O3
N3
O4
C30
C34
C35
C33
C32
S1
I1
C31
S2
O1
C29
C28
I2
C9
C10
C22
C27
C11
C14
C23
C24
C12
C26
C13
C25
O
N
S
Cd-I
I

129a

1H NMR



185

Current Data Parameters

NAME	NC-II-44D
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20091222
Time	8.59
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	5208.333 Hz
FIDRES	0.158946 Hz
AQ	3.1457779 sec
RG	715
DW	96.000 usec
DE	137.14 usec
TE	300.0 K
D1	1.00000000 sec
P1	8.50 usec
SFO1	250.1315321 MHz
NUCLEUS	1H

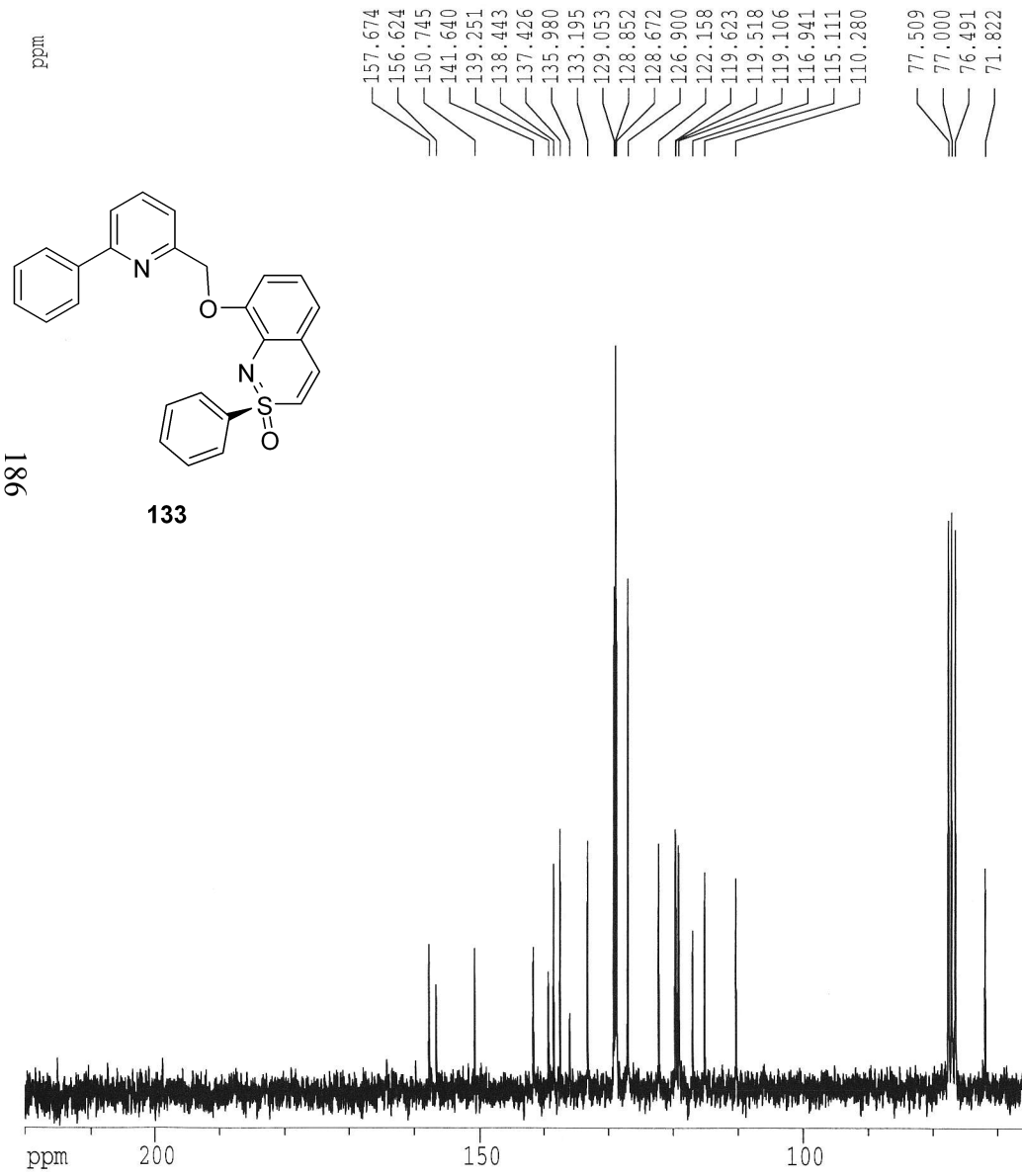
F2 - Processing parameters

SI	16384
SF	250.1300097 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.50

1D NMR plot parameters

CX	20.00 cm
CY	12.50 cm
F1P	10.000 ppm
F1	2501.30 Hz
F2P	-0.500 ppm
F2	-125.07 Hz
PPMCM	0.52500 ppm/cm
HZCM	131.31825 Hz/cm

13C NMR



Current Data Parameters

NAME	NC-II-44D
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20091222
Time	9.03
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zgdc30
TD	36864
SOLVENT	CDCl3
NS	252
DS	4
SWH	17241.379 Hz
FIDRES	0.467702 Hz
AQ	1.0691060 sec
RG	22800
DW	29.000 usec
DE	41.43 usec
TE	300.0 K
D12	0.00002000 sec
DL5	23.00 dB
CPDPRG	waltz16
P31	103.00 usec
D1	2.00000000 sec
P1	6.25 usec
SFO1	62.9023694 MHz
NUCLEUS	13C
D11	0.03000000 sec

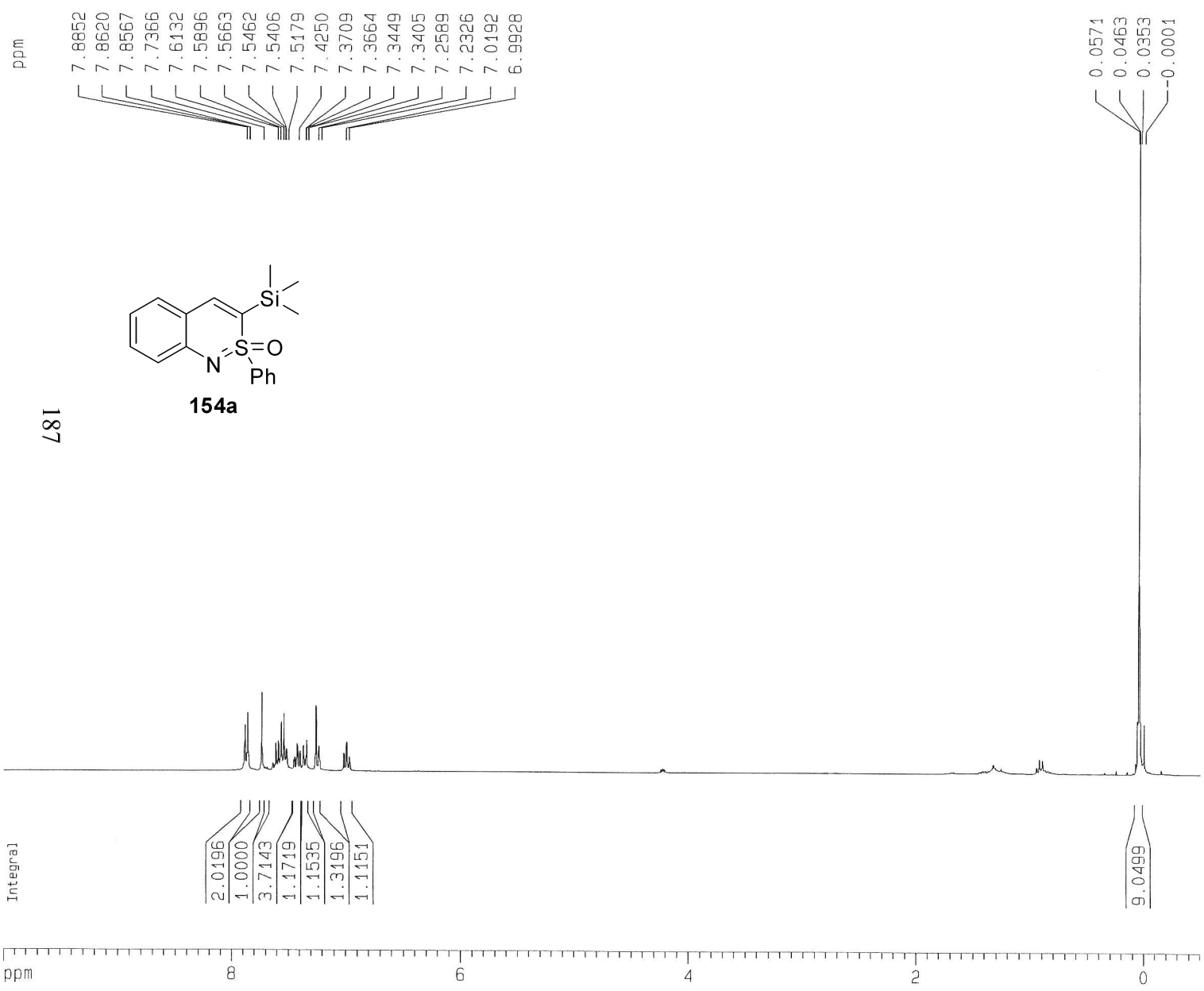
F2 - Processing parameters

SI	32768
SF	62.8952450 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	220.000 ppm
F1	13836.95 Hz
F2P	-10.000 ppm
F2	-628.95 Hz
PPMCM	11.50000 ppm/cm
HZCM	723.29529 Hz/cm

1H NMR



154a

187

Current Data Parameters

NAME	NC-I-26A
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20041104
Time	17.26
INSTRUM	drx300
PROBHD	5 mm Multinucl
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	6172.839 Hz
FIDRES	0.188380 Hz
AQ	2.6542580 sec
RG	256
DW	81.000 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec
D31	0.00000000 sec

======== CHANNEL f1 ========

NUC1	1H
P1	7.05 usec
PL1	0.00 dB
SFO1	300.1318534 MHz

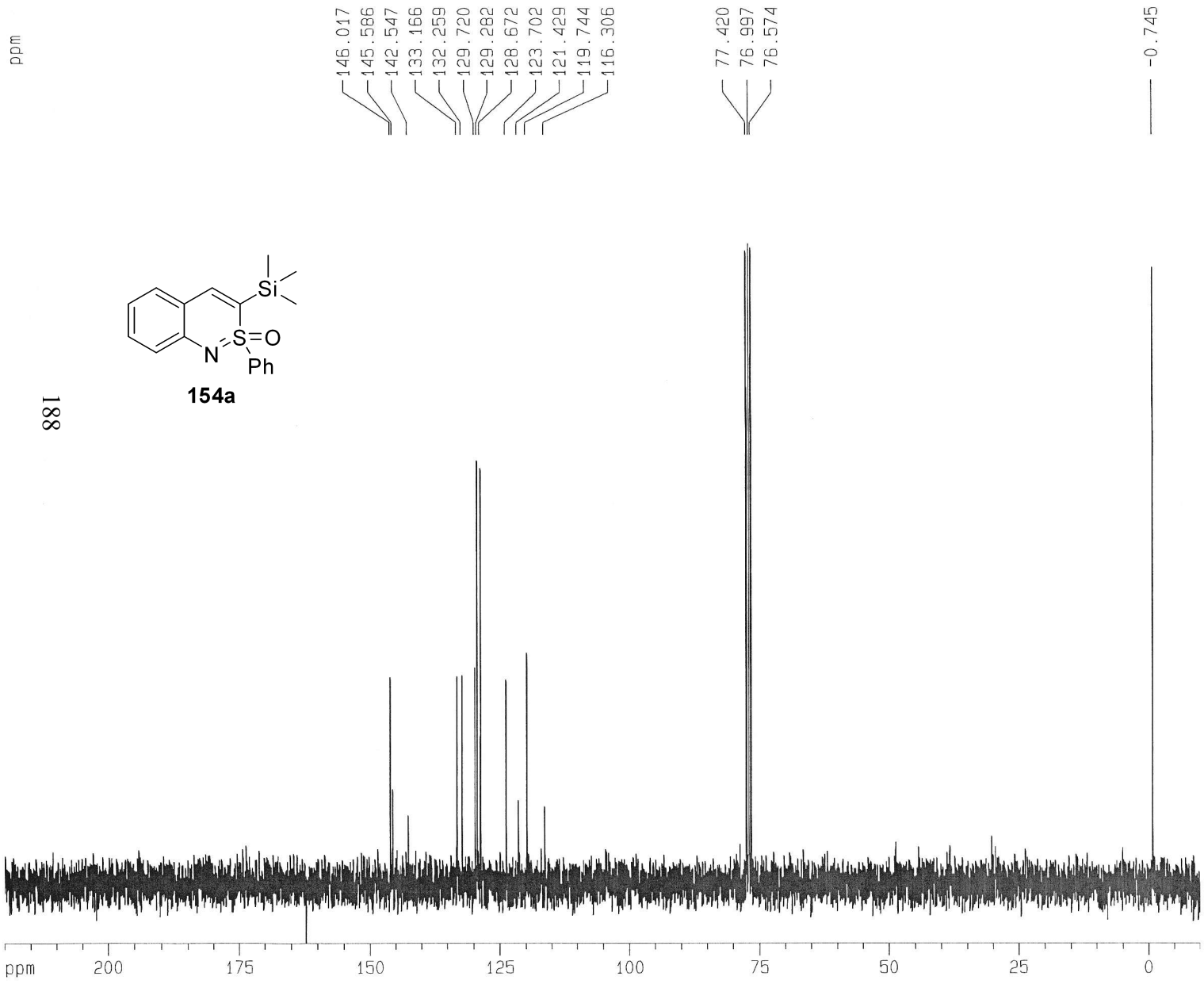
F2 - Processing parameters

SI	32768
SF	300.1300067 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.30

1D NMR plot parameters

CX	20.00 cm
CY	15.00 cm
F1P	10.000 ppm
F1	3001.30 Hz
F2P	-0.500 ppm
F2	-150.06 Hz
PPMCM	0.52500 ppm/cm
HZCM	157.56825 Hz/cm

13C NMR



Current Data Parameters

NAME	NC-I-26A
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20041104
Time	17.31
INSTRUM	drx300
PROBHD	5 mm Multinucl
PULPROG	zgdc30
TD	65536
SOLVENT	CDCl3
NS	66
DS	4
SWH	18832.393 Hz
FIDRES	0.287360 Hz
AQ	1.7400308 sec
RG	22528
DW	26.550 usec
DE	6.00 usec
TE	297.1 K
D1	1.29999995 sec
d11	0.03000000 sec
D31	0.00000000 sec

======== CHANNEL f1 ========

NUC1	13C
P1	8.50 usec
PL1	5.00 dB
SFO1	75.4760107 MHz

======== CHANNEL f2 ========

CPDPRG2	waltz16
NUC2	1H
PCPD2	100.00 usec
PL2	120.00 dB
PL12	25.60 dB
SFO2	300.1312005 MHz

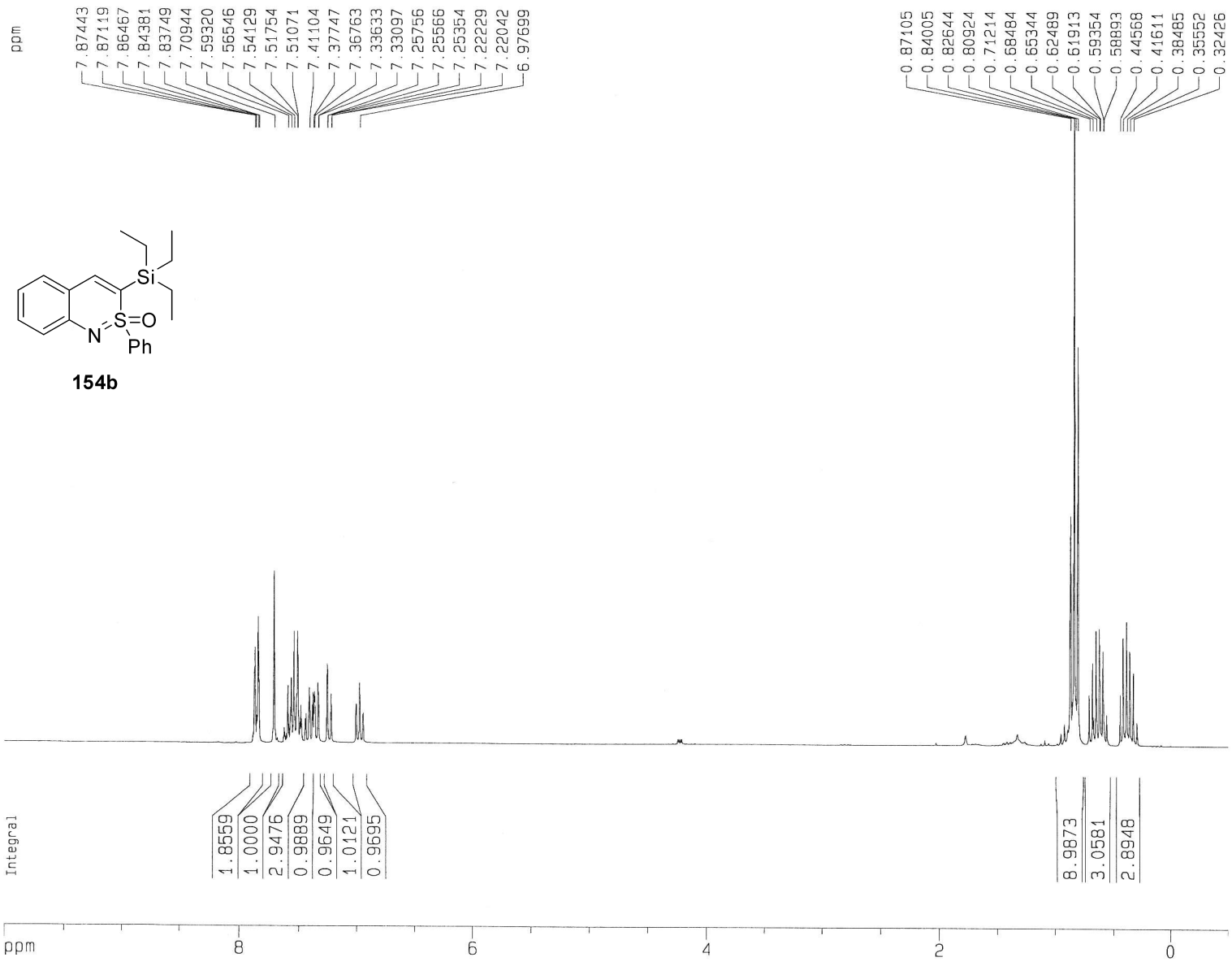
F2 - Processing parameters

SI	32768
SF	75.4677525 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
CY	11.00 cm
F1P	220.000 ppm
F1	16602.90 Hz
F2P	-10.000 ppm
F2	-754.68 Hz
PPMCM	11.50000 ppm/cm
HZCM	867.87909 Hz/cm

1H NMR



154b

Current Data Parameters

NAME	NC-I-52A
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20041028
Time	15.43
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	5208.333 Hz
FIDRES	0.158946 Hz
AQ	3.1457779 sec
RG	256
DW	96.000 use
DE	137.14 use
TE	300.0 K
D1	1.00000000 sec
P1	8.70 use
SFO1	250.1315321 MHz
NUCLEUS	1H

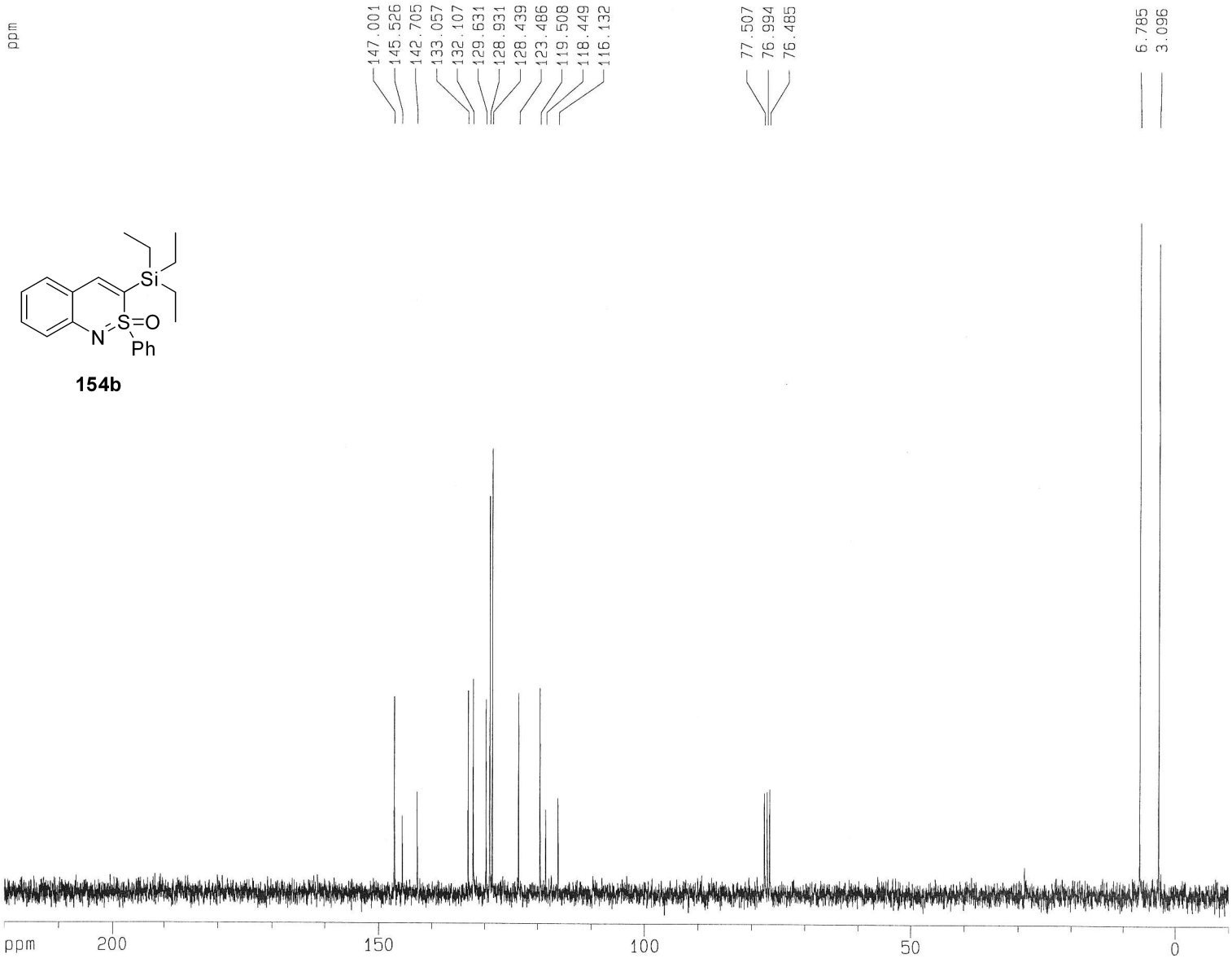
F2 - Processing parameters

SI	16384
SF	250.1300081 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.50

1D NMR plot parameters

CX	20.00 cm
CY	12.50 cm
F1P	10.000 ppm
F1	2501.30 Hz
F2P	-0.500 ppm
F2	-125.07 Hz
PPMCM	0.52500 ppm
HZCM	131.31825 Hz/

13C NMR



154b

Current Data Parameters

NAME	NC-I-52A
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

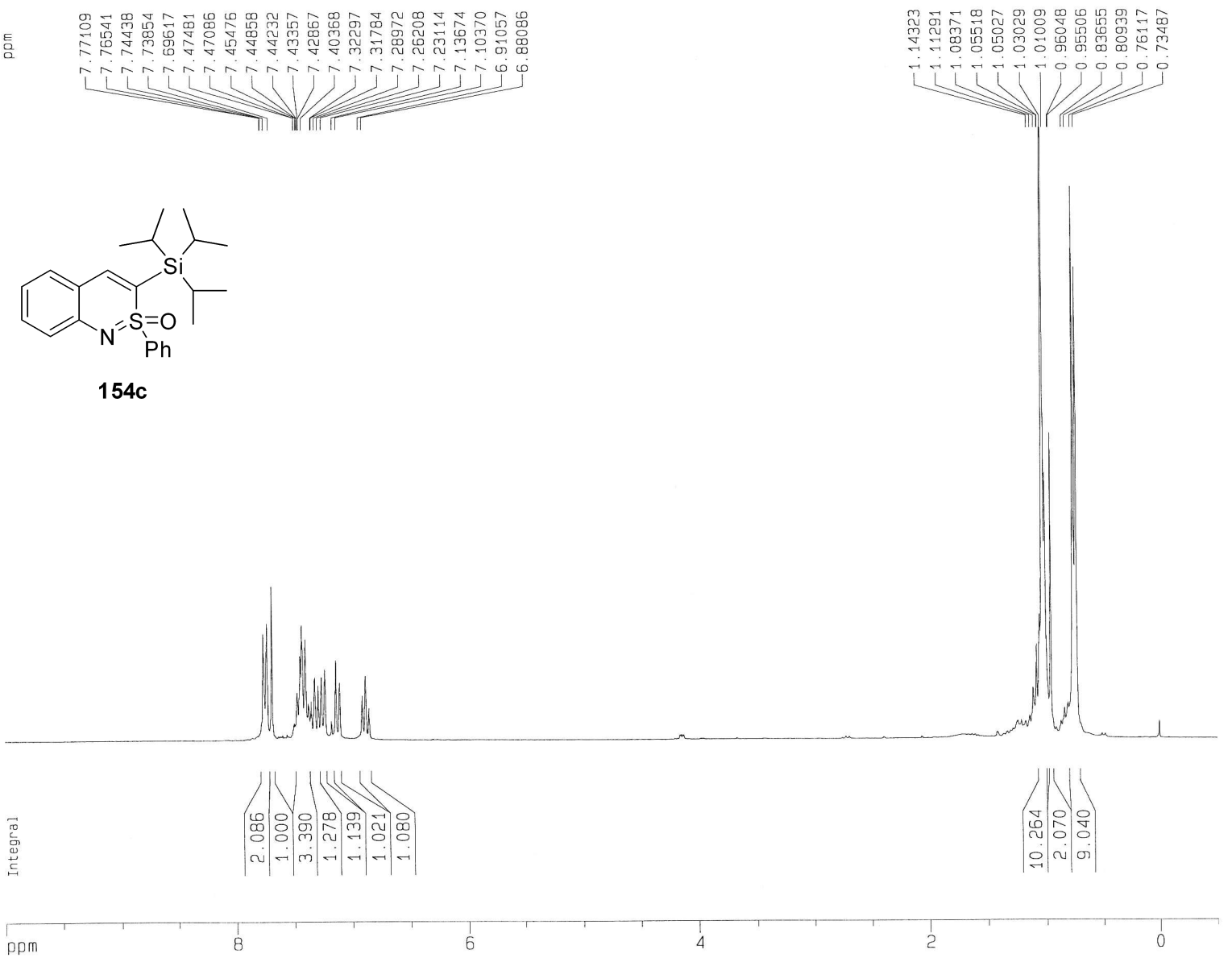
Date_	20041103
Time	12.32
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zgdc30
TD	36864
SOLVENT	CDCl3
NS	45
DS	4
SWH	17241.379 Hz
FIDRES	0.467702 Hz
AQ	1.0691060 sec
RG	22800
DW	29.000 use
DE	41.43 use
TE	300.0 K
D12	0.00002000 sec
DL5	23.00 dB
CPDPRG	waltz16
P31	103.00 use
D1	1.00000000 sec
P1	6.00 use
SFO1	62.9023694 MHz
NUCLEUS	13C
D11	0.03000000 sec

F2 - Processing parameters

SI	32768
SF	62.8952508 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
CY	11.00 cm
F1P	220.000 ppm
F1	13836.95 Hz
F2P	-10.000 ppm
F2	-628.95 Hz
PPMCM	11.50000 ppm
HZCM	723.29541 Hz/



154c

Current Data Parameters

NAME	NC-I-54A
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20041103
Time	12.43
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	5208.333 Hz
FIDRES	0.158946 Hz
AQ	3.1457779 sec
RG	256
DW	96.000 use
DE	137.14 use
TE	300.0 K
D1	1.00000000 sec
P1	8.70 use
SFO1	250.1315321 MHz
NUCLEUS	1H

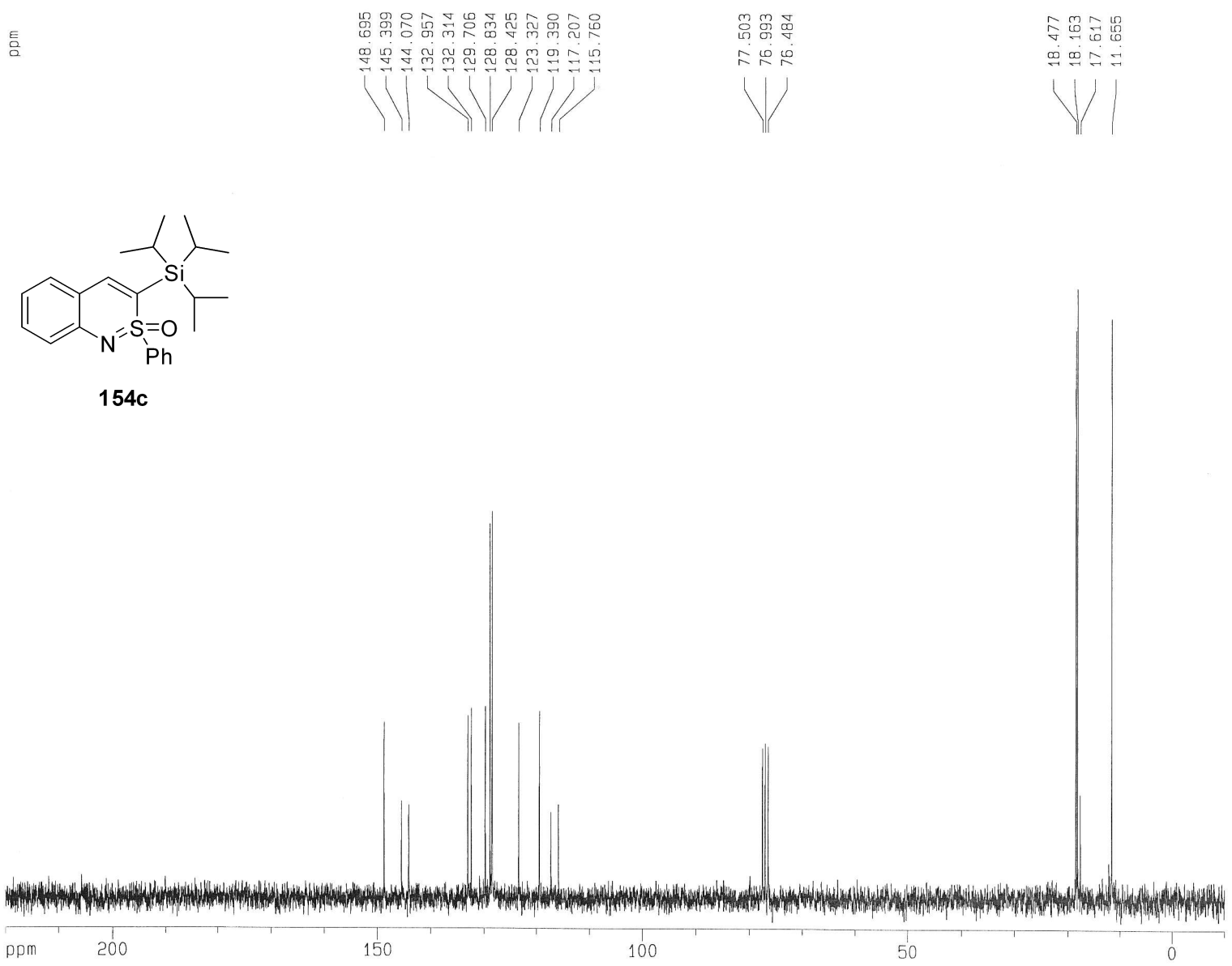
F2 - Processing parameters

SI	16384
SF	250.1300288 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.50

1D NMR plot parameters

CX	20.00 cm
CY	12.50 cm
F1P	10.000 ppm
F1	2501.30 Hz
F2P	-0.500 ppm
F2	-125.07 Hz
PPMCM	0.52500 ppm
HZCM	131.31827 Hz/

13C NMR



154c

Current Data Parameters

NAME	NC-I-54A
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20041103
Time	12.55
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zgdc30
TD	36864
SOLVENT	CDCl3
NS	40
DS	4
SWH	17241.379 Hz
FIDRES	0.467702 Hz
AQ	1.0691060 sec
RG	22800
DW	29.000 use
DE	41.43 use
TE	300.0 K
D12	0.00002000 sec
DL5	23.00 dB
CPDPRG	waltz16
P31	103.00 use
D1	1.00000000 sec
P1	6.00 use
SFO1	62.9023694 MHz
NUCLEUS	13C
D11	0.03000000 sec

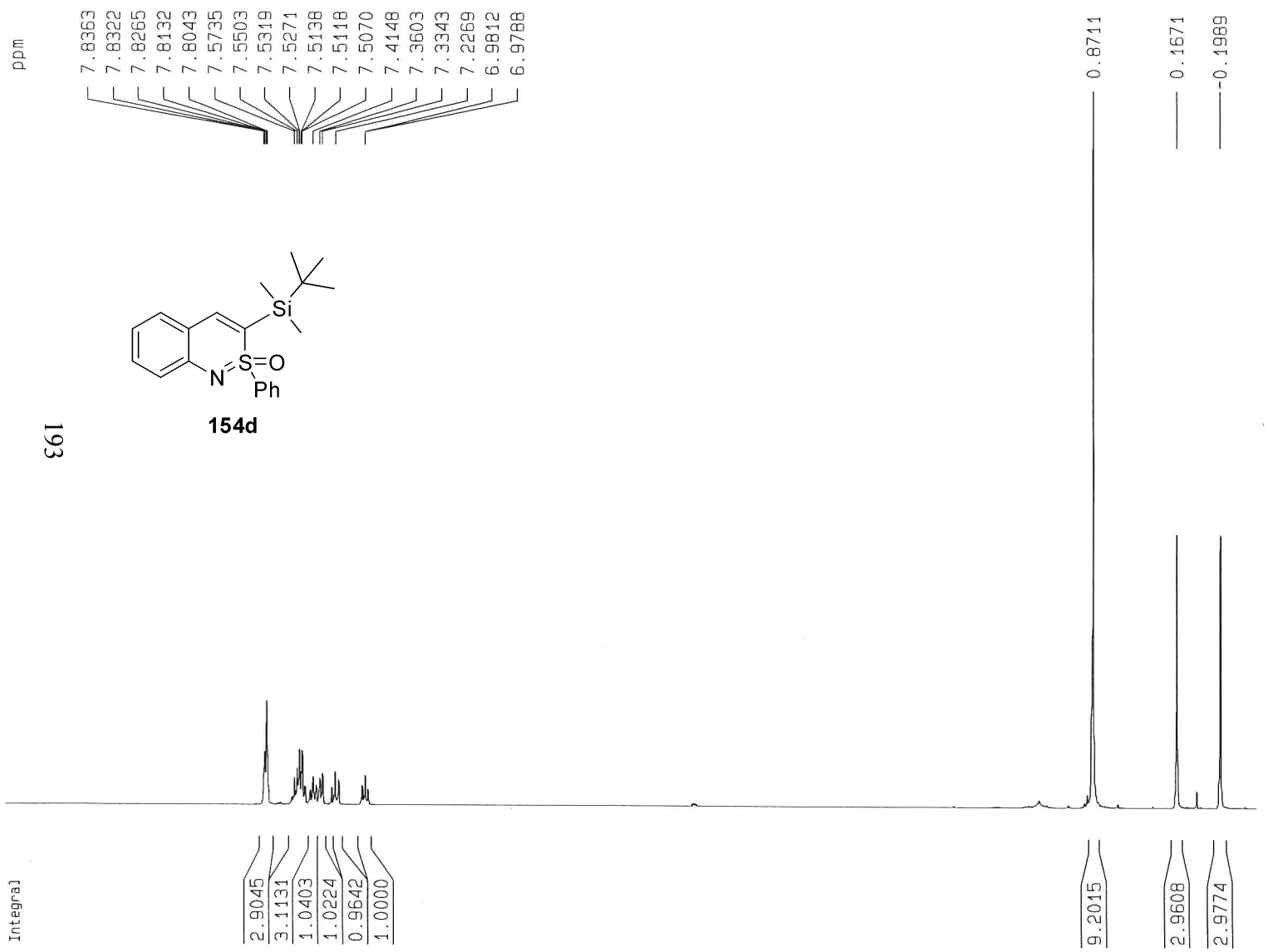
F2 - Processing parameters

SI	32768
SF	62.8952471 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	220.000 ppm
F1	13836.95 Hz
F2P	-10.000 ppm
F2	-628.95 Hz
PPMCM	11.50000 ppm
HZCM	723.29535 Hz/

1H NMR



154d

Current Data Parameters

NAME	NC-I-55A
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20041202
Time	15.16
INSTRUM	drx300
PROBHD	5 mm Multinucl
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	6172.839 Hz
FIDRES	0.188380 Hz
AQ	2.6542580 sec
RG	114
DW	81.000 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec
D31	0.00000000 sec

======== CHANNEL f1 ========

NUC1	1H
P1	7.05 usec
PL1	0.00 dB
SFO1	300.1318534 MHz

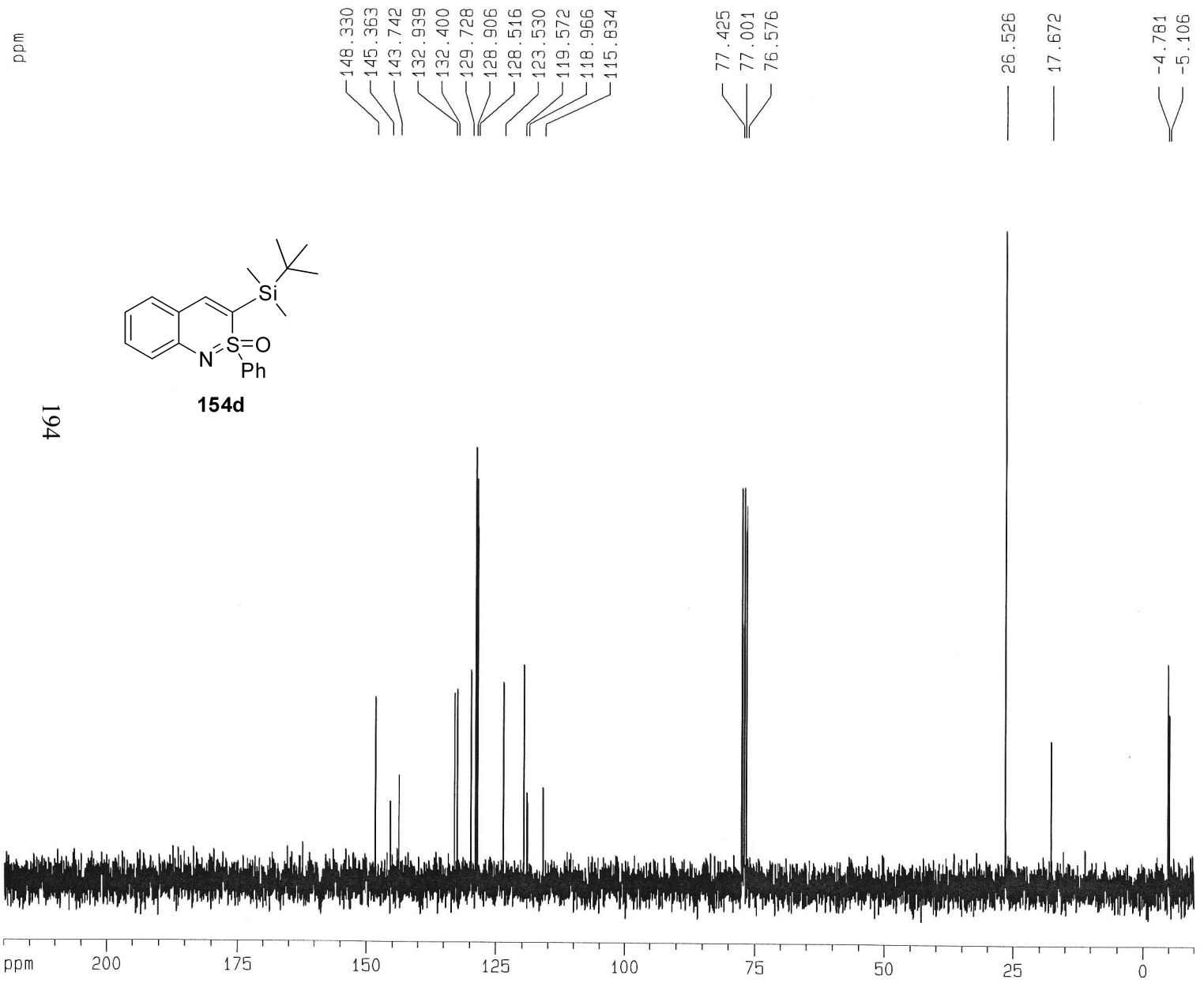
F2 - Processing parameters

SI	32768
SF	300.1300071 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.30

1D NMR plot parameters

CX	20.00 cm
CY	12.50 cm
F1P	10.000 ppm
F1	3001.30 Hz
F2P	-0.500 ppm
F2	-150.06 Hz
PPMCM	0.52500 ppm/cm
HZCM	157.56825 Hz/cm

13C NMR



154d

Current Data Parameters

NAME	NC-I-55A
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20041202
Time	15.24
INSTRUM	drx300
PROBHD	5 mm Multinucl
PULPROG	zgdc30
TD	65536
SOLVENT	CDCl3
NS	18
DS	4
SWH	18832.393 Hz
FIDRES	0.287360 Hz
AQ	1.7400308 sec
RG	22528
DW	26.550 usec
DE	6.00 usec
TE	297.1 K
D1	1.29999995 sec
d11	0.03000000 sec
D31	0.00000000 sec

======== CHANNEL f1 ========

NUC1	13C
P1	8.50 usec
PL1	5.00 dB
SFO1	75.4760107 MHz

======== CHANNEL f2 ========

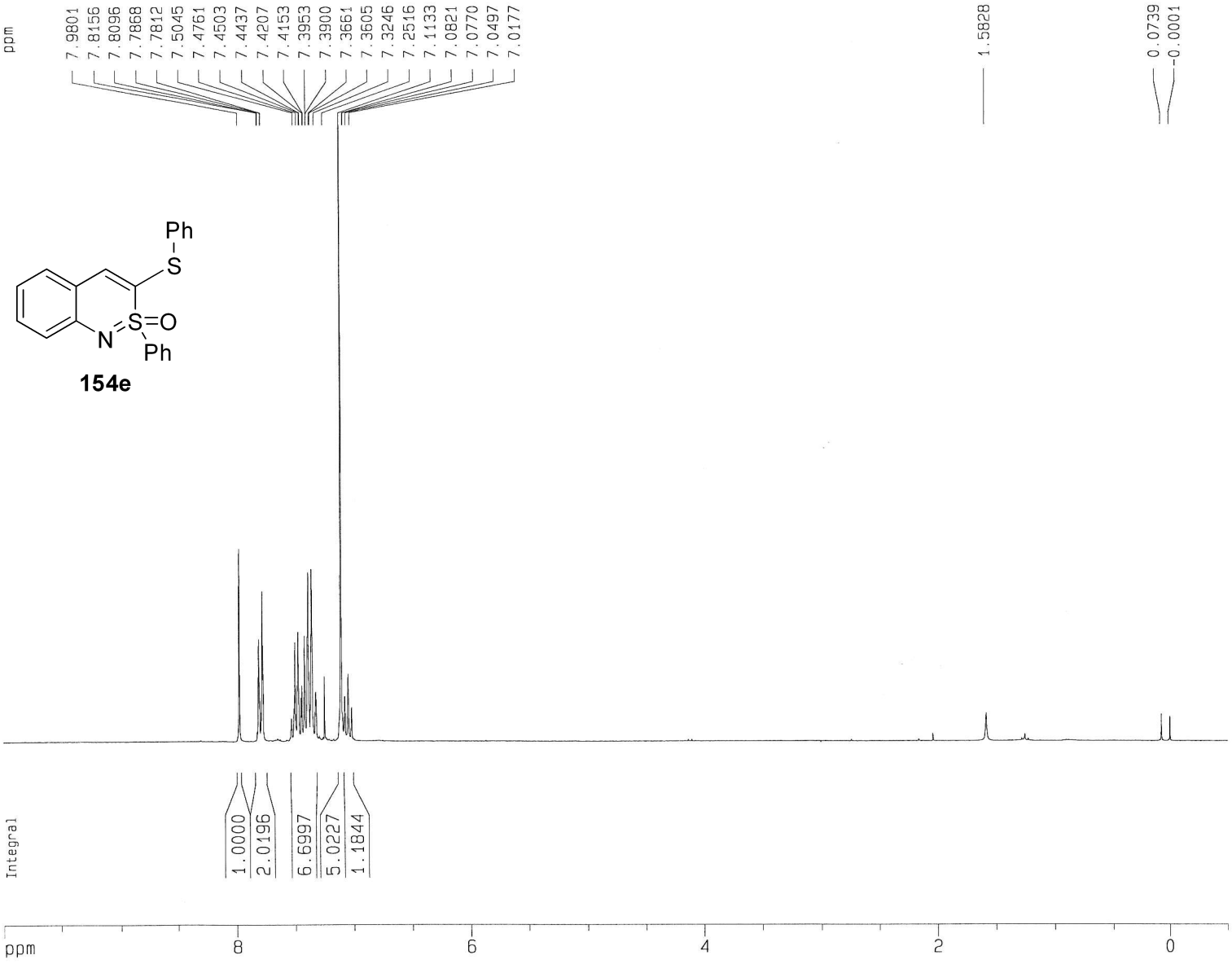
CPDPRG2	waltz16
NUC2	1H
PCPD2	100.00 usec
PL2	120.00 dB
PL12	25.60 dB
SFO2	300.1312005 MHz

F2 - Processing parameters

SI	32768
SF	75.4677542 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
CY	11.00 cm
F1P	220.000 ppm
F1	16602.90 Hz
F2P	-10.000 ppm
F2	-754.68 Hz
PPMCM	11.50000 ppm/cm
HZCM	867.87909 Hz/cm



154e

Current Data Parameters

NAME	NC-I-56A
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

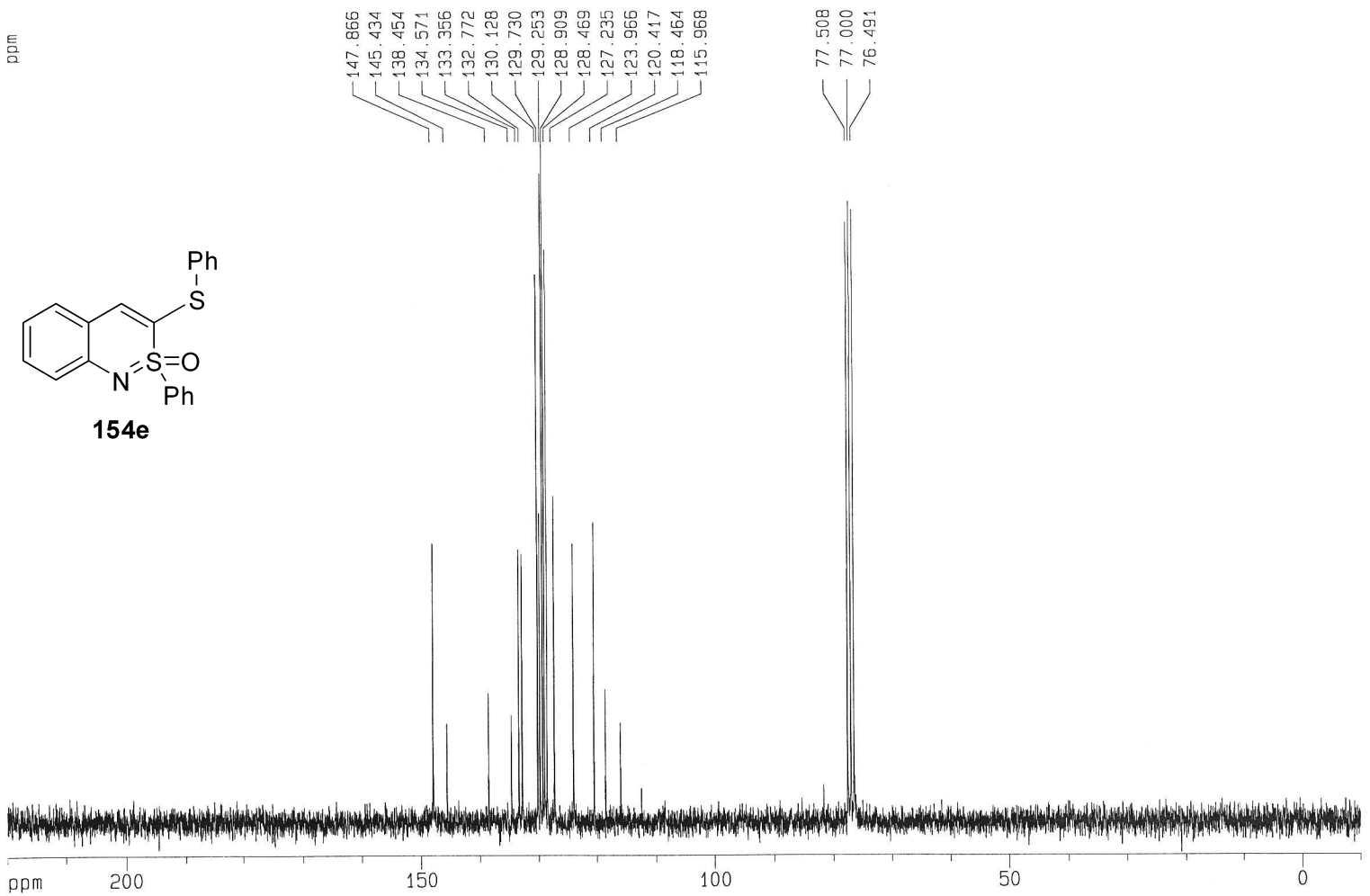
Date_	20041006
Time	18.18
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	5208.333 Hz
FIDRES	0.158946 Hz
AQ	3.1457779 sec
RG	1024
DW	96.000 use
DE	137.14 use
TE	300.0 K
D1	1.00000000 sec
P1	8.70 use
SFO1	250.1315321 MHz
NUCLEUS	1H

F2 - Processing parameters

SI	16384
SF	250.1300097 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.50

1D NMR plot parameters

CX	20.00 cm
CY	20.00 cm
F1P	10.000 ppm
F1	2501.30 Hz
F2P	-0.500 ppm
F2	-125.07 Hz
PPMCM	0.52500 ppm
HZCM	131.31825 Hz/



154e

Current Data Parameters

NAME	NC-I-56A
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

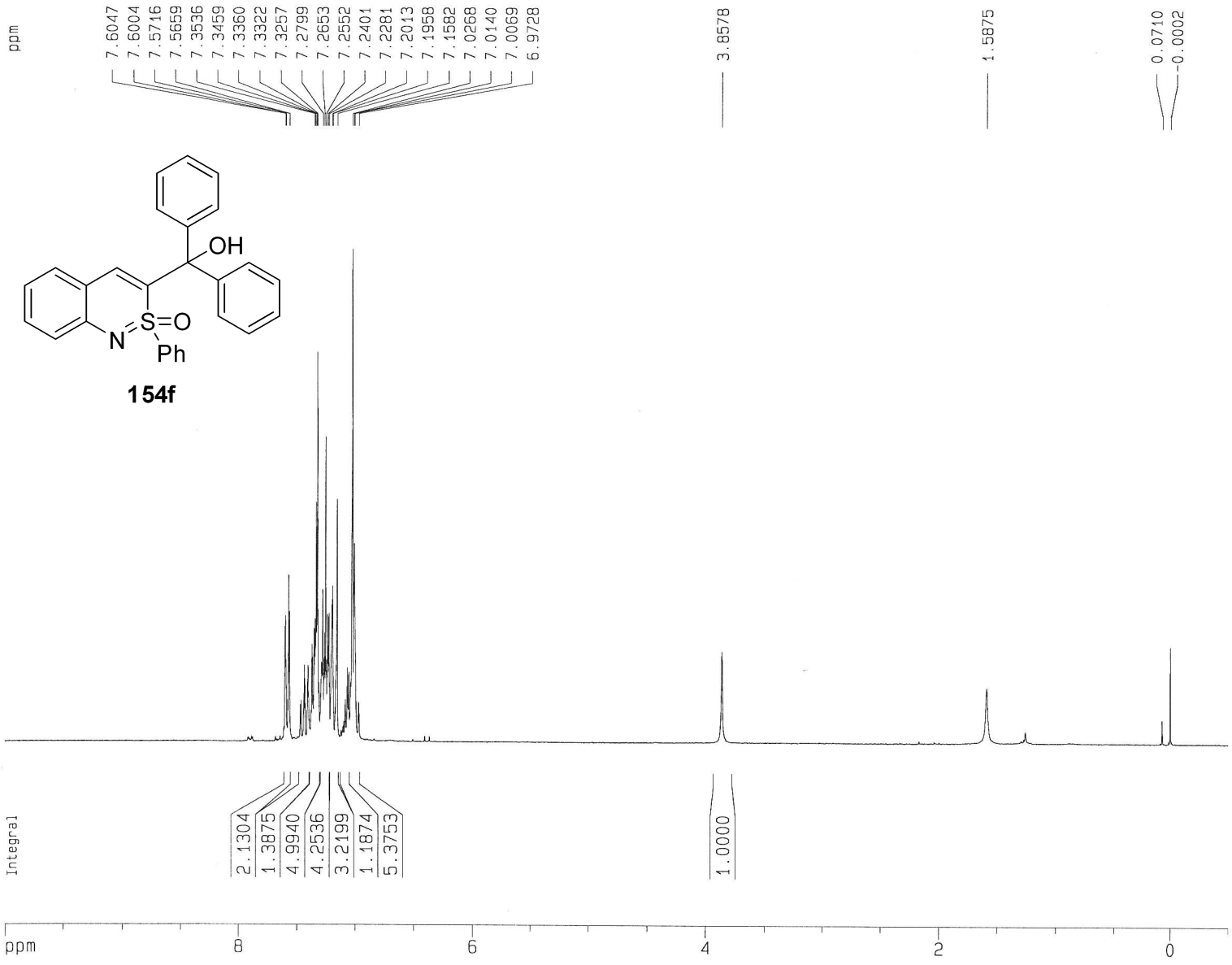
Date_	20041006
Time	18.27
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zgdc30
TD	36864
SOLVENT	CDCl3
NS	496
DS	4
SWH	17241.379 Hz
FIDRES	0.467702 Hz
AQ	1.0691060 sec
RG	22800
DW	29.000 use
DE	41.43 use
TE	300.0 K
D12	0.00002000 sec
DL5	23.00 dB
CPDPRG	waltz16
P31	103.00 use
D1	1.00000000 sec
P1	6.00 use
SFO1	62.9023694 MHz
NUCLEUS	13C
D11	0.03000000 sec

F2 - Processing parameters

SI	32768
SF	62.8952424 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	220.000 ppm
F1	13836.95 Hz
F2P	-10.000 ppm
F2	-628.95 Hz
PPMCM	11.50000 ppm
HZCM	723.29529 Hz/



154f

Current Data Parameters

NAME	NC-I-57A
EXPNO	3
PROCNO	1

F2 - Acquisition Parameters

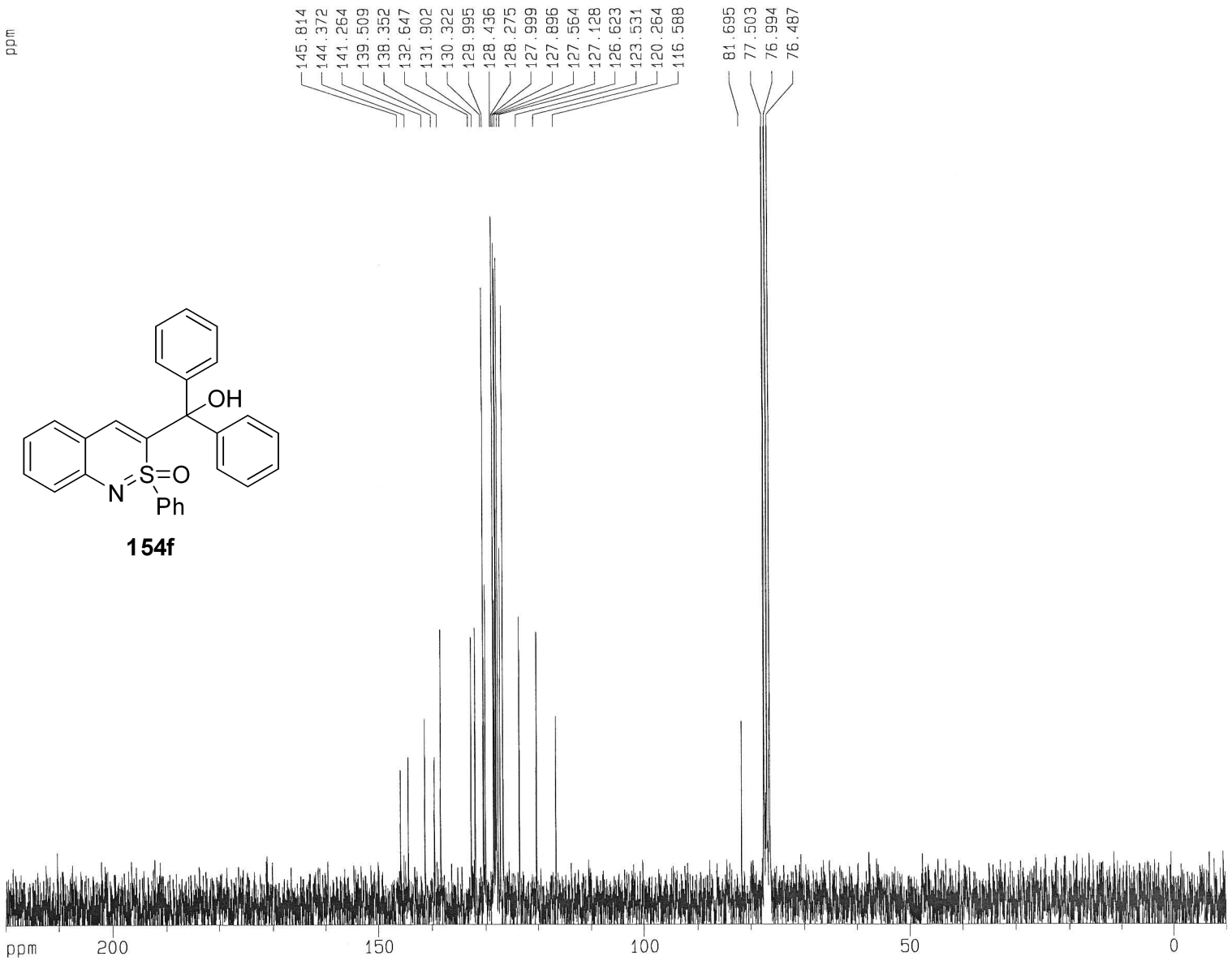
Date_	20041013
Time	14.28
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	5208.333 Hz
FIDRES	0.158946 Hz
AQ	3.1457779 sec
RG	2048
DW	96.000 use
DE	137.14 use
TE	300.0 K
D1	1.00000000 sec
P1	8.70 use
SFO1	250.1315321 MHz
NUCLEUS	1H

F2 - Processing parameters

SI	16384
SF	250.1300087 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.50

1D NMR plot parameters

CX	20.00 cm
CY	8.00 cm
F1P	10.000 ppm
F1	2501.30 Hz
F2P	-0.500 ppm
F2	-125.07 Hz
PPMCM	0.52500 ppm
HZCM	131.31825 Hz/



154f

Current Data Parameters

NAME	NC-I-57A
EXPNO	4
PROCNO	1

F2 - Acquisition Parameters

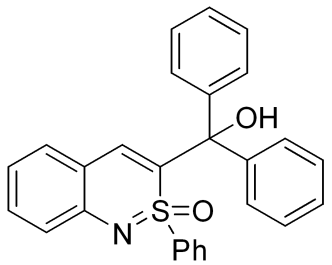
Date_	20041013
Time	14.40
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zgdc30
TD	36864
SOLVENT	CDCl3
NS	812
DS	4
SWH	17241.379 Hz
FIDRES	0.467702 Hz
AQ	1.0691060 sec
RG	22800
DW	29.000 use
DE	41.43 use
TE	300.0 K
D12	0.00002000 sec
DL5	23.00 dB
CPDPRG	waltz16
P31	103.00 use
D1	1.00000000 sec
P1	6.00 use
SFO1	62.9023694 MHz
NUCLEUS	13C
D11	0.03000000 sec

F2 - Processing parameters

SI	32768
SF	62.8952413 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

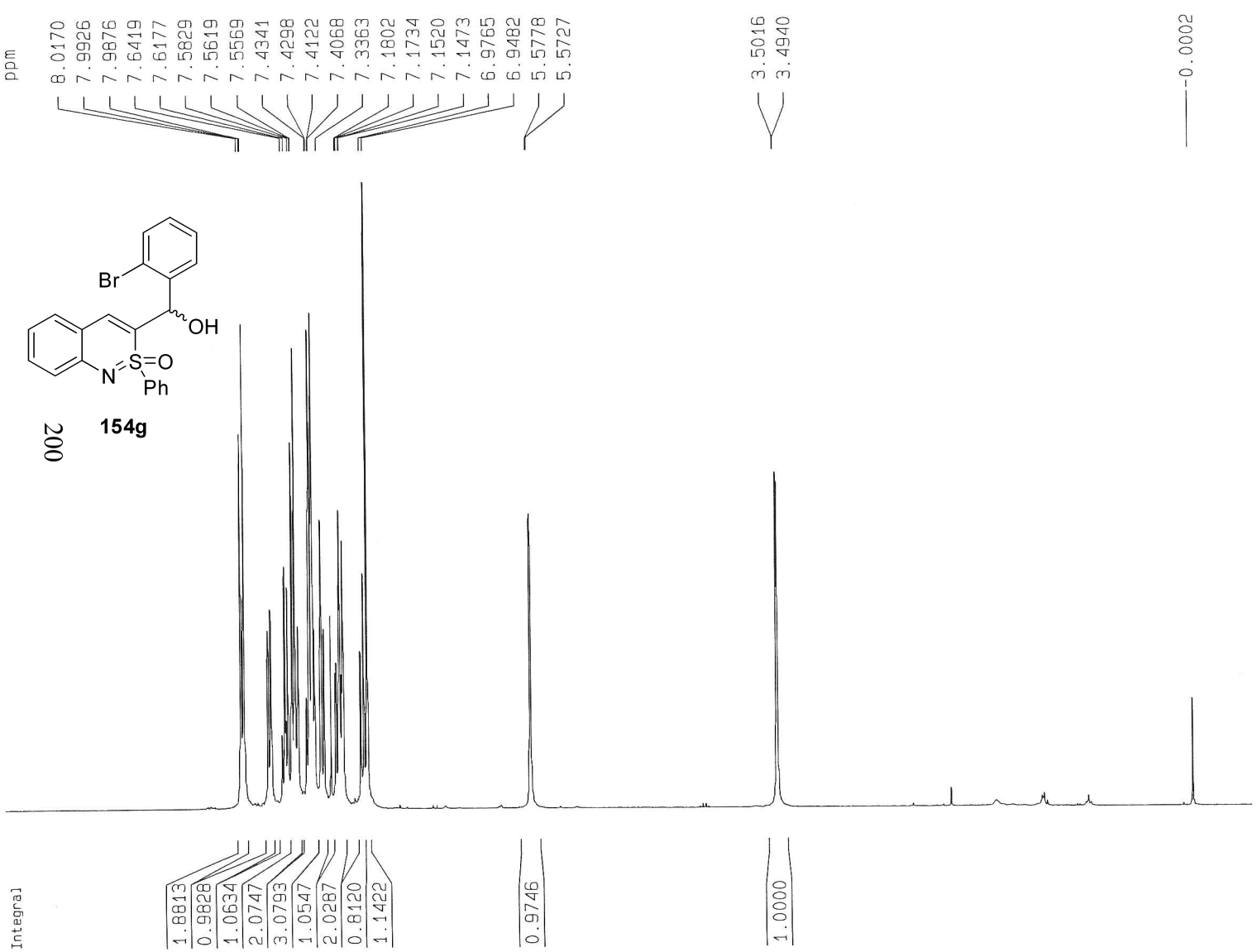
CX	20.00 cm
CY	30.00 cm
F1P	220.000 ppm
F1	13836.95 Hz
F2P	-10.000 ppm
F2	-628.95 Hz
PPMCM	11.50000 ppm
HZCM	723.29529 Hz/


OH
N
S=O
Ph

154f

C25
C26
C24
C27
C18
C23
C22
C17
C19
C20
C4
C2
C5
C3
C1
C15
C16
C21
O2
C6
C10
S1
C11
C8
C12
C7
N1
C9
O1
C14
C13

1H NMR



Current Data Parameters

NAME	NC-I-73B
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20050208
Time	15.02
INSTRUM	drx300
PROBHD	5 mm Multinucl
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	6172.839 Hz
FIDRES	0.188380 Hz
AQ	2.6542580 sec
RG	256
DW	81.000 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec
D31	0.00000000 sec

======== CHANNEL f1 ========

NUC1	1H
P1	7.05 usec
PL1	0.00 dB
SFO1	300.1318534 MHz

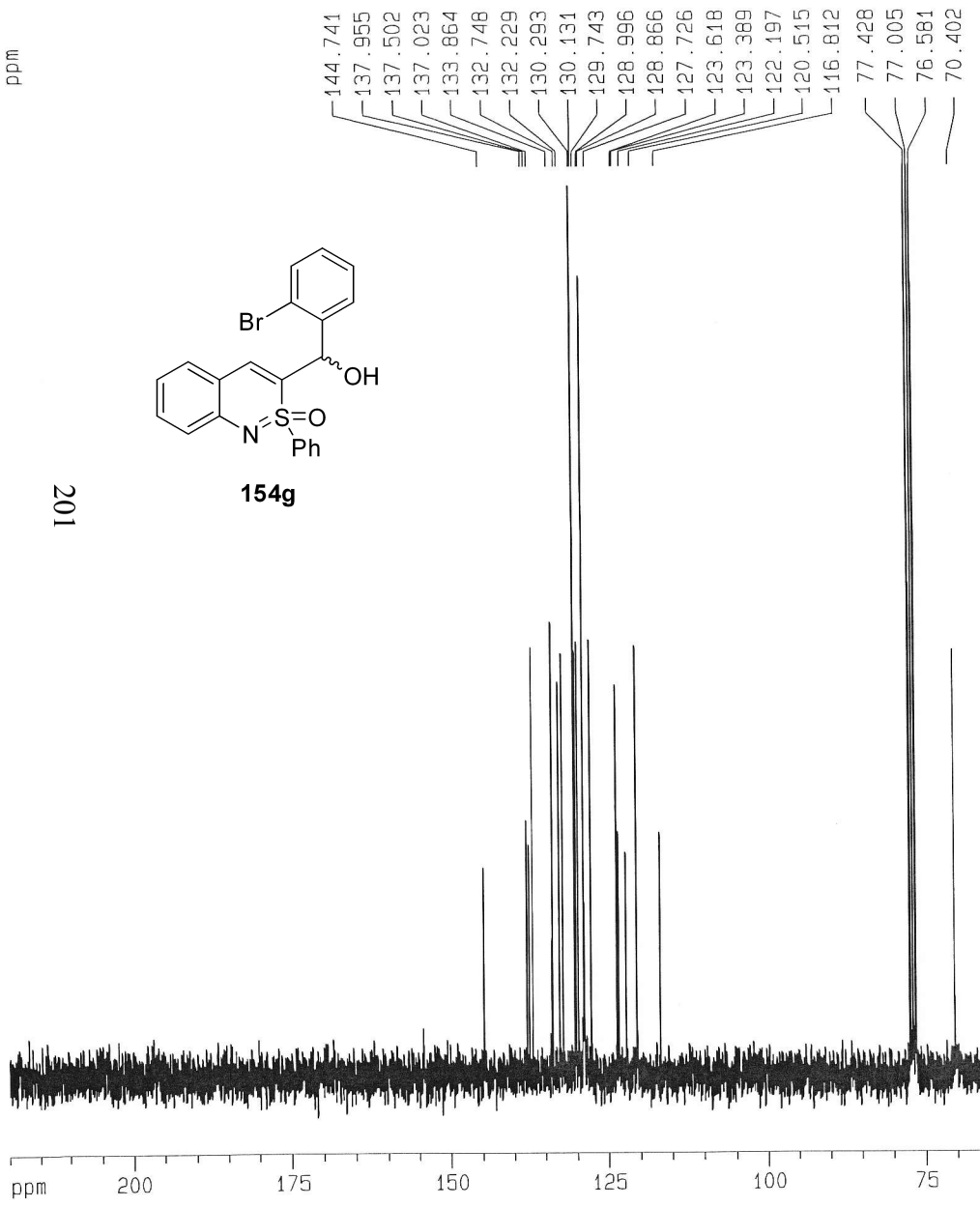
F2 - Processing parameters

SI	32768
SF	300.1300084 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.30

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	10.000 ppm
F1	3001.30 Hz
F2P	-0.500 ppm
F2	-150.06 Hz
PPMCM	0.52500 ppm/cm
HZCM	157.56825 Hz/cm

13C NMR



Current Data Parameters

NAME	NC-I-73B
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20050208
Time	15.07
INSTRUM	drx300
PROBHD	5 mm Multinucl
PULPROG	zgdc30
TD	65536
SOLVENT	CDCl3
NS	121
DS	4
SWH	18832.393 Hz
FIDRES	0.287360 Hz
AQ	1.7400308 sec
RG	22528
DW	26.550 usec
DE	6.00 usec
TE	297.1 K
D1	1.29999995 sec
d11	0.03000000 sec
D31	0.00000000 sec

======== CHANNEL f1 ========

NUC1	13C
P1	8.50 usec
PL1	5.00 dB
SFO1	75.4760107 MHz

======== CHANNEL f2 ========

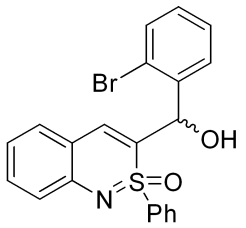
CPDPRG2	waltz16
NUC2	1H
PCPD2	100.00 usec
PL2	120.00 dB
PL12	25.60 dB
SFO2	300.1312005 MHz

F2 - Processing parameters

SI	32768
SF	75.4677531 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
CY	13.50 cm
F1P	220.000 ppm
F1	16602.90 Hz
F2P	-10.000 ppm
F2	-754.68 Hz
PPMCM	11.50000 ppm/cm
HZCM	867.87909 Hz/cm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N
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Ph

154g

O2a
Br1a
C15a
C16a
C17a
C2a
C1a
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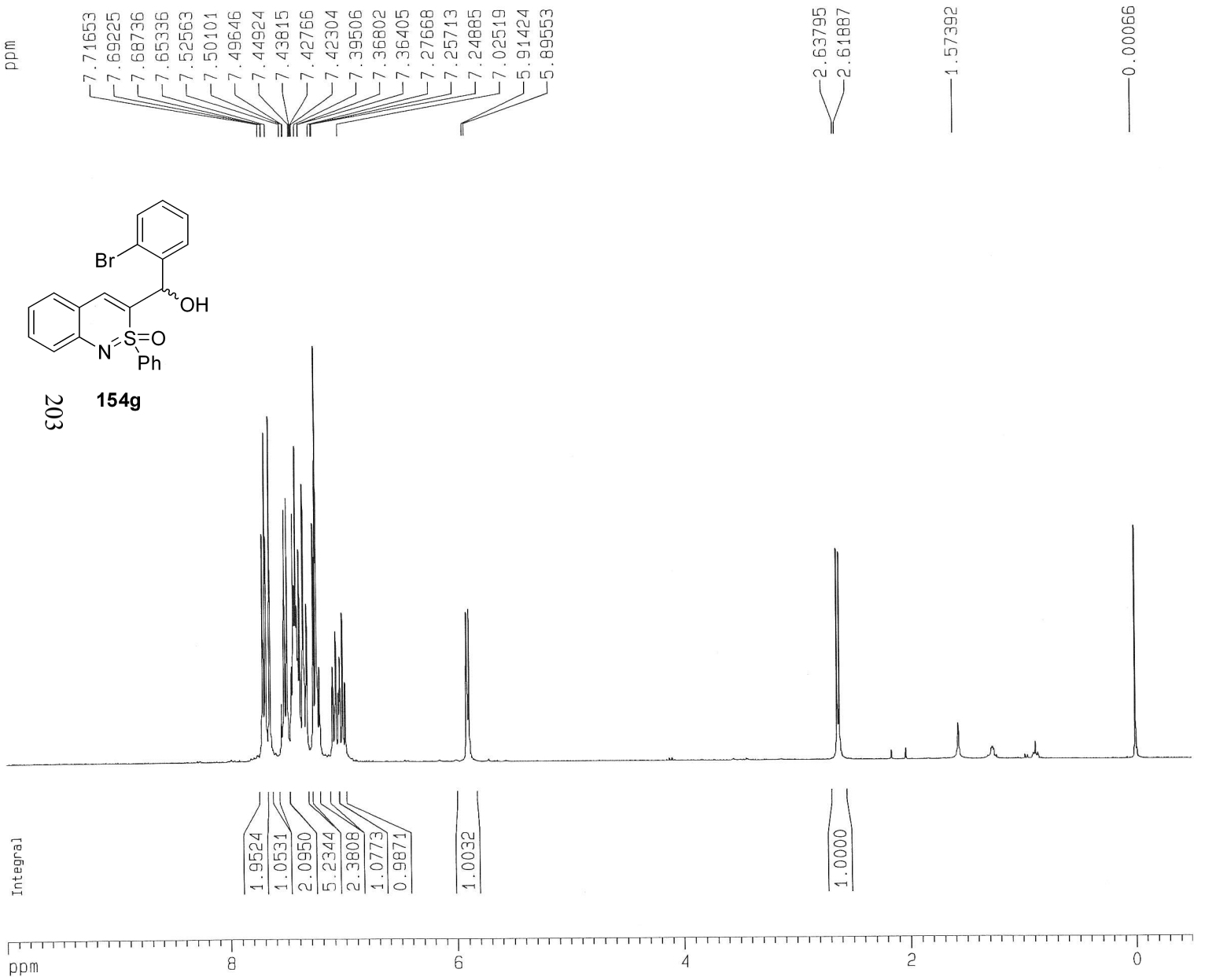
C3a
C21a
O1a
C20a
C19a
C5a
S1a
C9a
C10a
C8a
N1a
C6a
C7a
C11a
C14a
C13a
C12a

1H NMR



Current Data Parameters

NAME	NC-I-73C
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20050208
Time	15.17
INSTRUM	drx300
PROBHD	5 mm Multinucl
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	6172.839 Hz
FIDRES	0.188380 Hz
AQ	2.6542580 sec
RG	574.7
DW	81.000 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec
D31	0.00000000 sec

======== CHANNEL f1 ========

NUC1	1H
P1	7.05 usec
PL1	0.00 dB
SF01	300.1318534 MHz

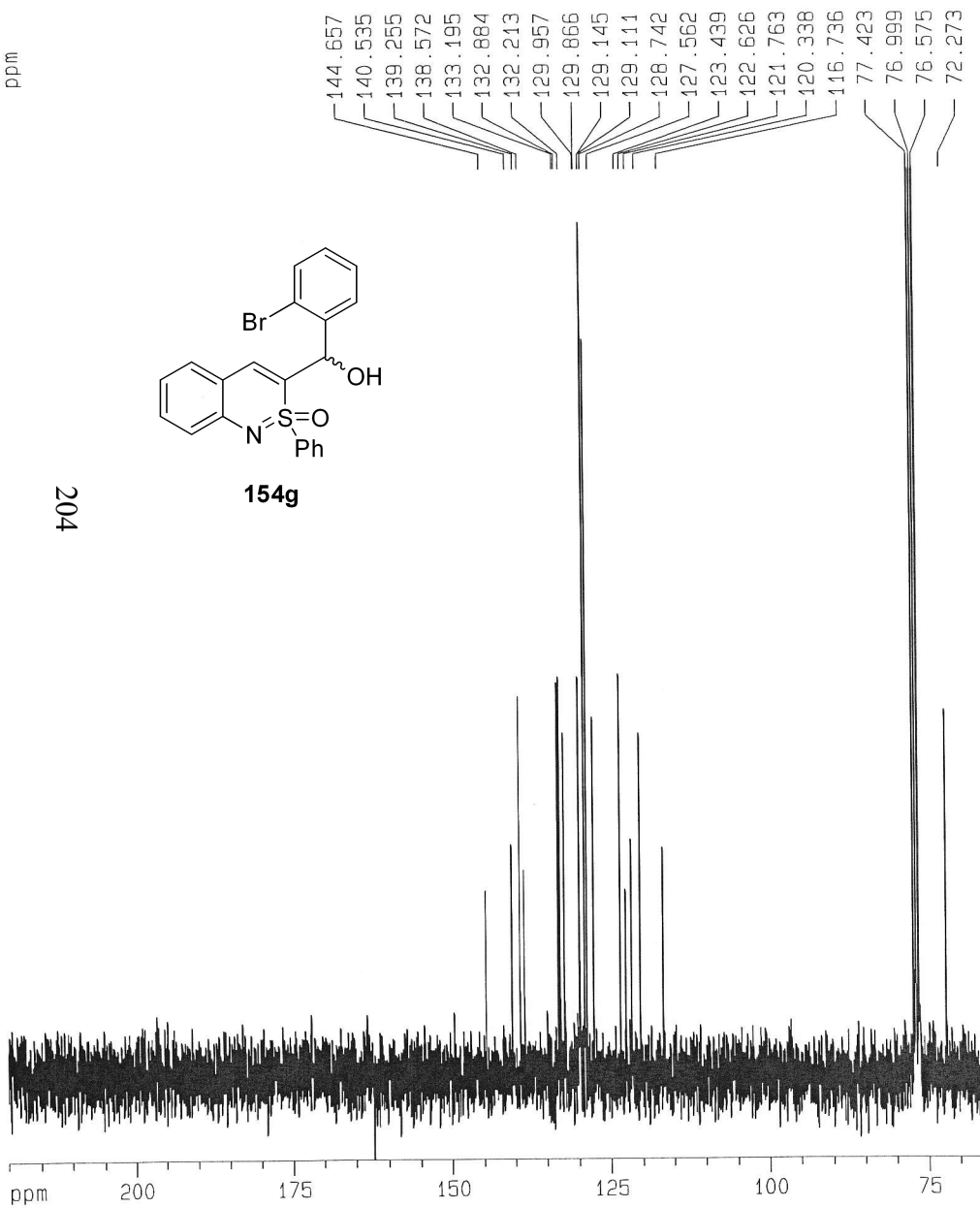
F2 - Processing parameters

SI	32768
SF	300.1300071 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.30

1D NMR plot parameters

CX	20.00 cm
CY	7.00 cm
F1P	10.000 ppm
F1	3001.30 Hz
F2P	-0.500 ppm
F2	-150.06 Hz
PPMCM	0.52500 ppm/cm
HZCM	157.56825 Hz/cm

13C NMR



Current Data Parameters

NAME	NC-I-73C
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20050208
Time	15.24
INSTRUM	drx300
PROBHD	5 mm Multinucl
PULPROG	zgdc30
TD	65536
SOLVENT	CDCl3
NS	230
DS	4
SWH	18832.393 Hz
FIDRES	0.287360 Hz
AQ	1.7400308 sec
RG	22528
DW	26.550 usec
DE	6.00 usec
TE	297.1 K
D1	1.29999995 sec
d11	0.03000000 sec
D31	0.00000000 sec

======== CHANNEL f1 ========

NUC1	13C
P1	8.50 usec
PL1	5.00 dB
SFO1	75.4760107 MHz

======== CHANNEL f2 ========

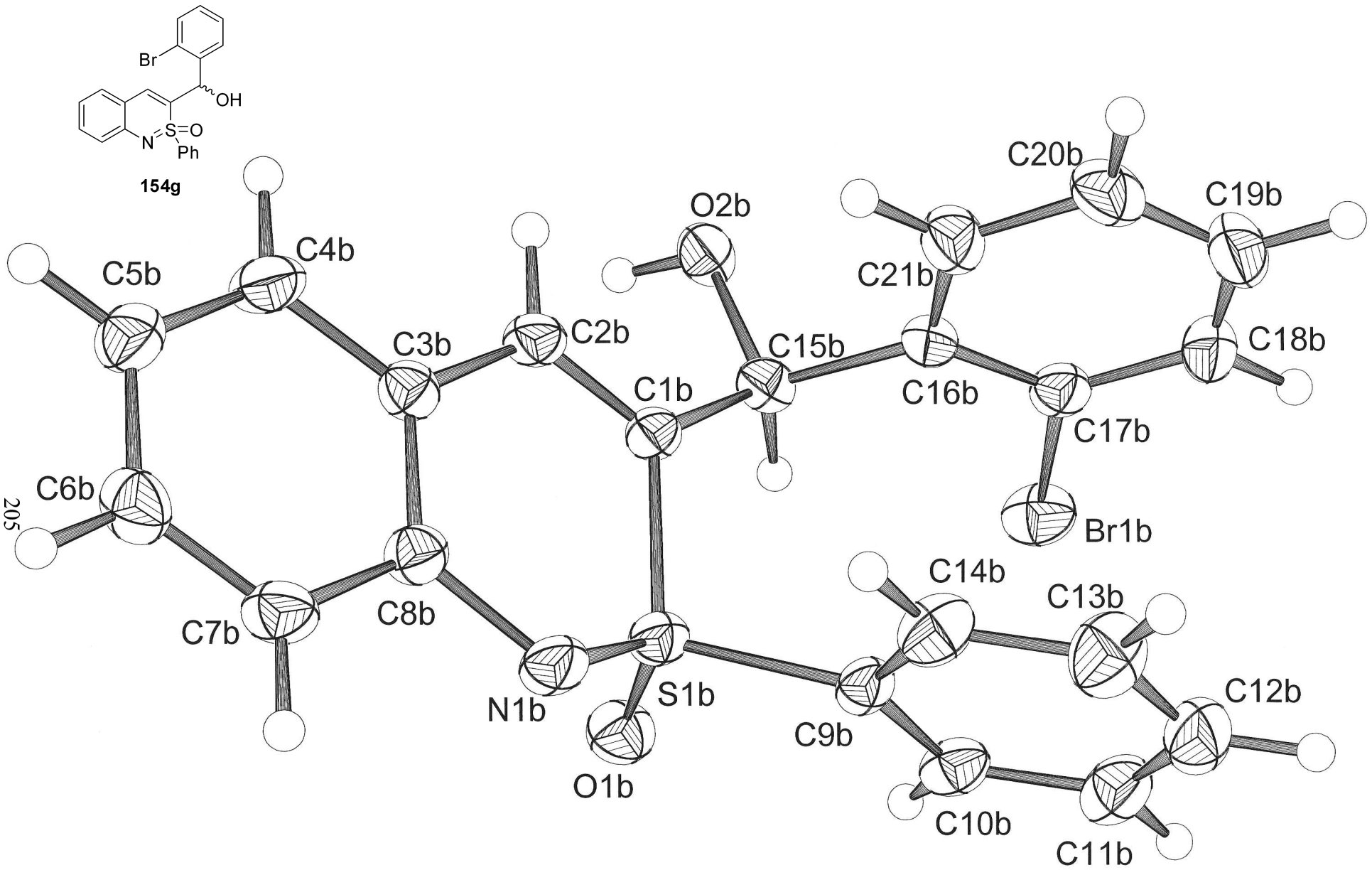
CPDPRG2	waltz16
NUC2	1H
PCPD2	100.00 usec
PL2	120.00 dB
PL12	25.60 dB
SFO2	300.1312005 MHz

F2 - Processing parameters

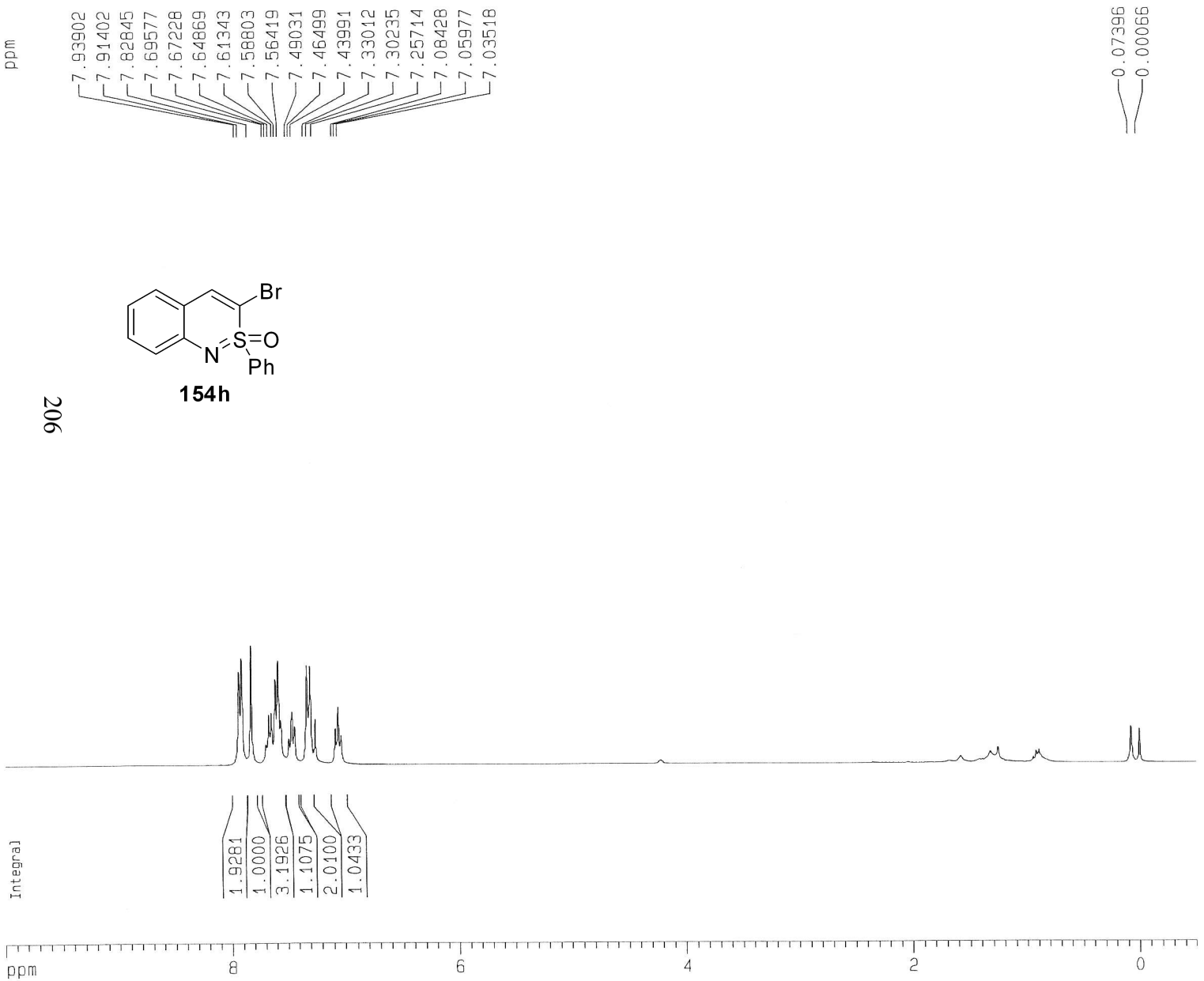
SI	32768
SF	75.4677514 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
CY	30.00 cm
F1P	220.000 ppm
F1	16602.90 Hz
F2P	-10.000 ppm
F2	-754.68 Hz
PPMCM	11.50000 ppm/cm
HZCM	867.87909 Hz/cm


Br
OH
N
S=O
Ph
154g
C20b
C19b
O2b
C4b
C5b
C21b
C3b
C2b
C15b
C18b
C1b
C16b
C17b
C6b
Br1b
C14b
C13b
C7b
C8b
C12b
N1b
S1b
C9b
O1b
C10b
C11b

1H NMR



154h

206

Current Data Parameters

NAME	NC-I-59A
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20041104
Time	17.48
INSTRUM	drx300
PROBHD	5 mm Multinucl
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	6172.839 Hz
FIDRES	0.188380 Hz
AQ	2.6542580 sec
RG	362
DW	81.000 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec
D31	0.00000000 sec

======== CHANNEL f1 ========

NUC1	1H
P1	7.05 usec
PL1	0.00 dB
SFO1	300.1318534 MHz

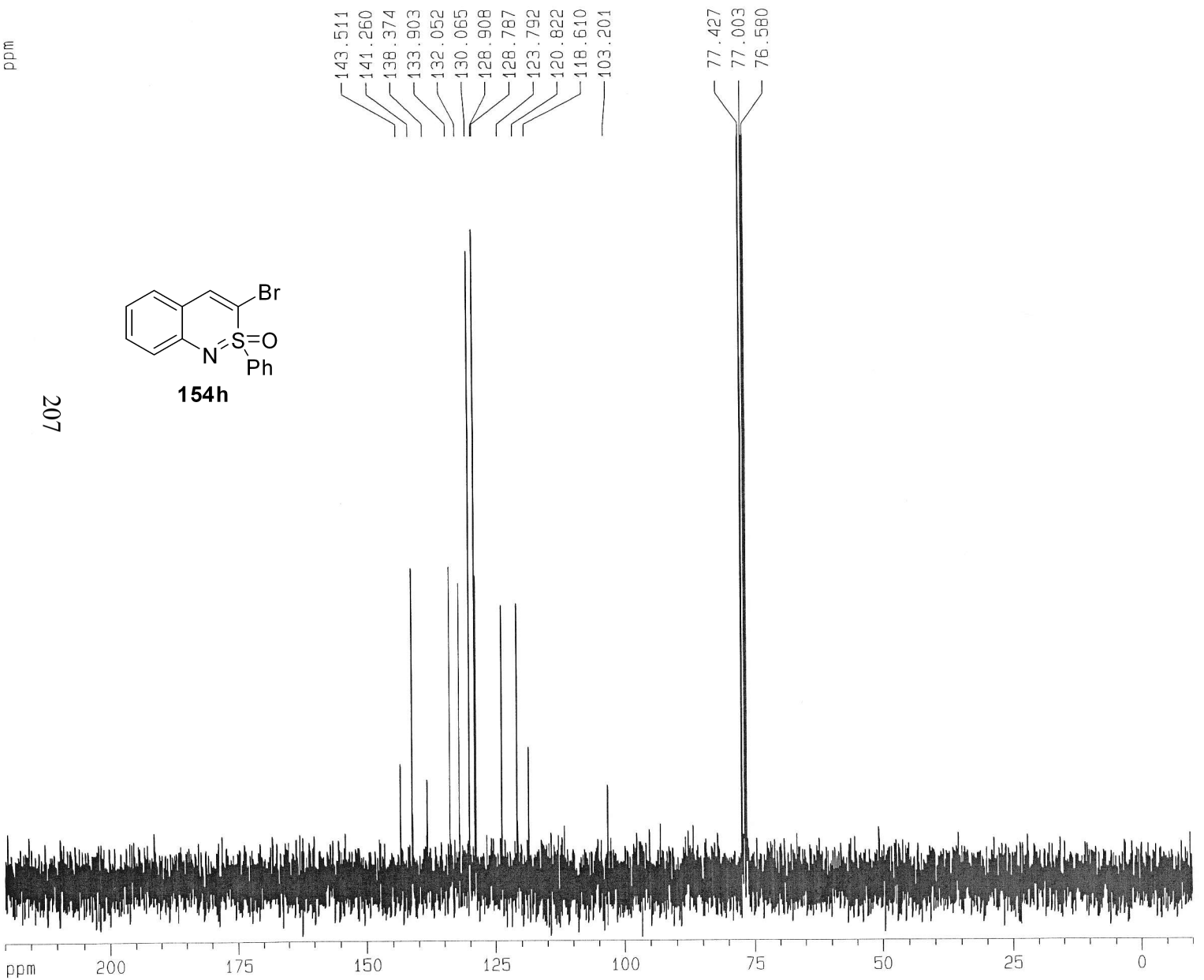
F2 - Processing parameters

SI	32768
SF	300.1300073 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.30

1D NMR plot parameters

CX	20.00 cm
CY	2.00 cm
F1P	10.000 ppm
F1	3001.30 Hz
F2P	-0.500 ppm
F2	-150.06 Hz
PPMCM	0.52500 ppm/cm
HZCM	157.56825 Hz/cm

13C NMR



Current Data Parameters

NAME	NC-I-59A
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20041104
Time	17.50
INSTRUM	drx300
PROBHD	5 mm Multinucl
PULPROG	zgdc30
TD	65536
SOLVENT	CDCl3
NS	64
DS	4
SWH	18832.393 Hz
FIDRES	0.287360 Hz
AQ	1.7400308 sec
RG	22528
DW	26.550 usec
DE	6.00 usec
TE	297.1 K
D1	1.29999995 sec
d11	0.03000000 sec
D31	0.00000000 sec

======== CHANNEL f1 ========

NUC1	13C
P1	8.50 usec
PL1	5.00 dB
SFO1	75.4760107 MHz

======== CHANNEL f2 ========

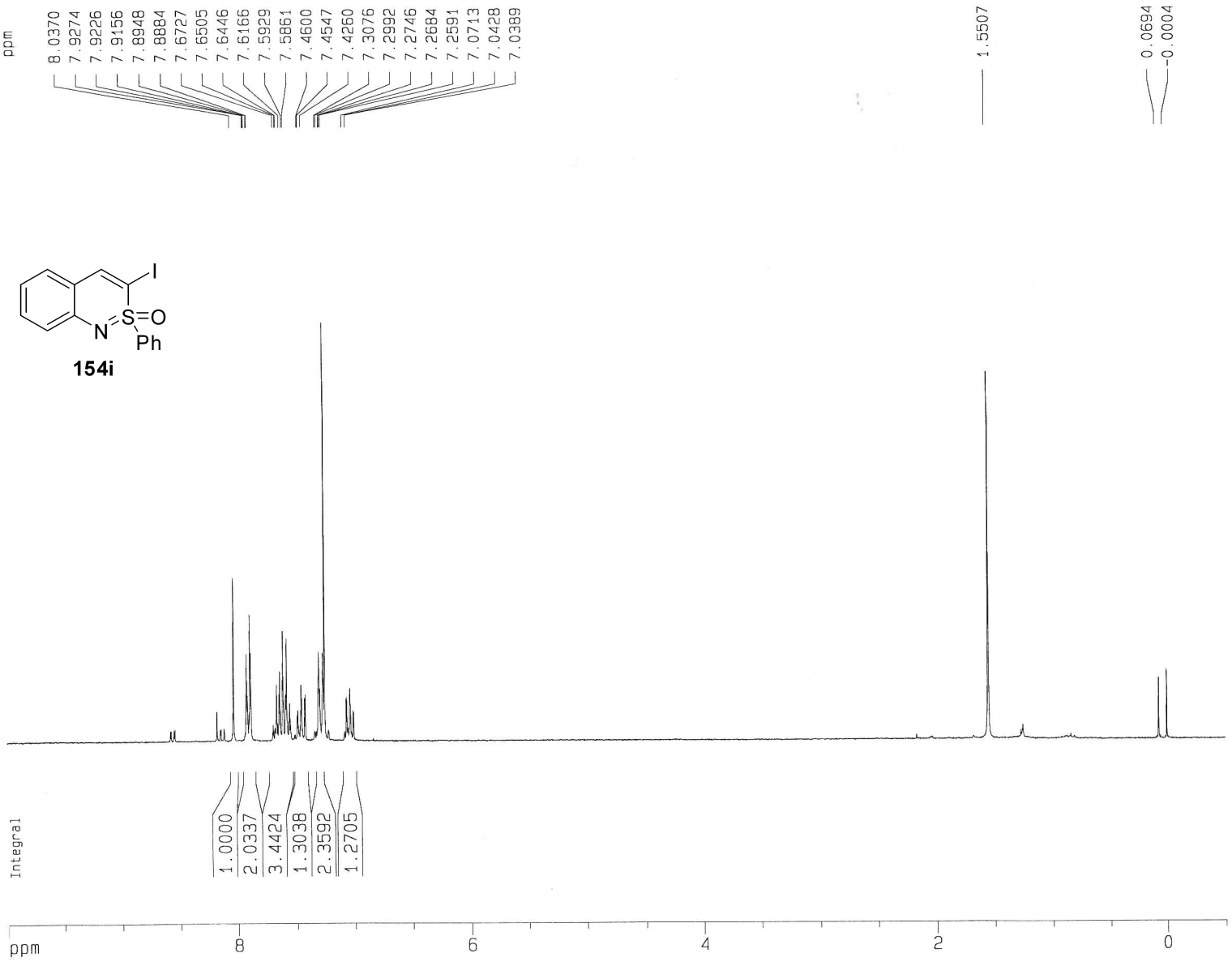
CPDPRG2	waltz16
NUC2	1H
PCPD2	100.00 usec
PL2	120.00 dB
PL12	25.60 dB
SFO2	300.1312005 MHz

F2 - Processing parameters

SI	32768
SF	75.4677520 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
CY	15.00 cm
F1P	220.000 ppm
F1	16602.90 Hz
F2P	-10.000 ppm
F2	-754.68 Hz
PPMCM	11.50000 ppm/cm
HZCM	867.87909 Hz/cm



Current Data Parameters

NAME	NC-I-60B
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

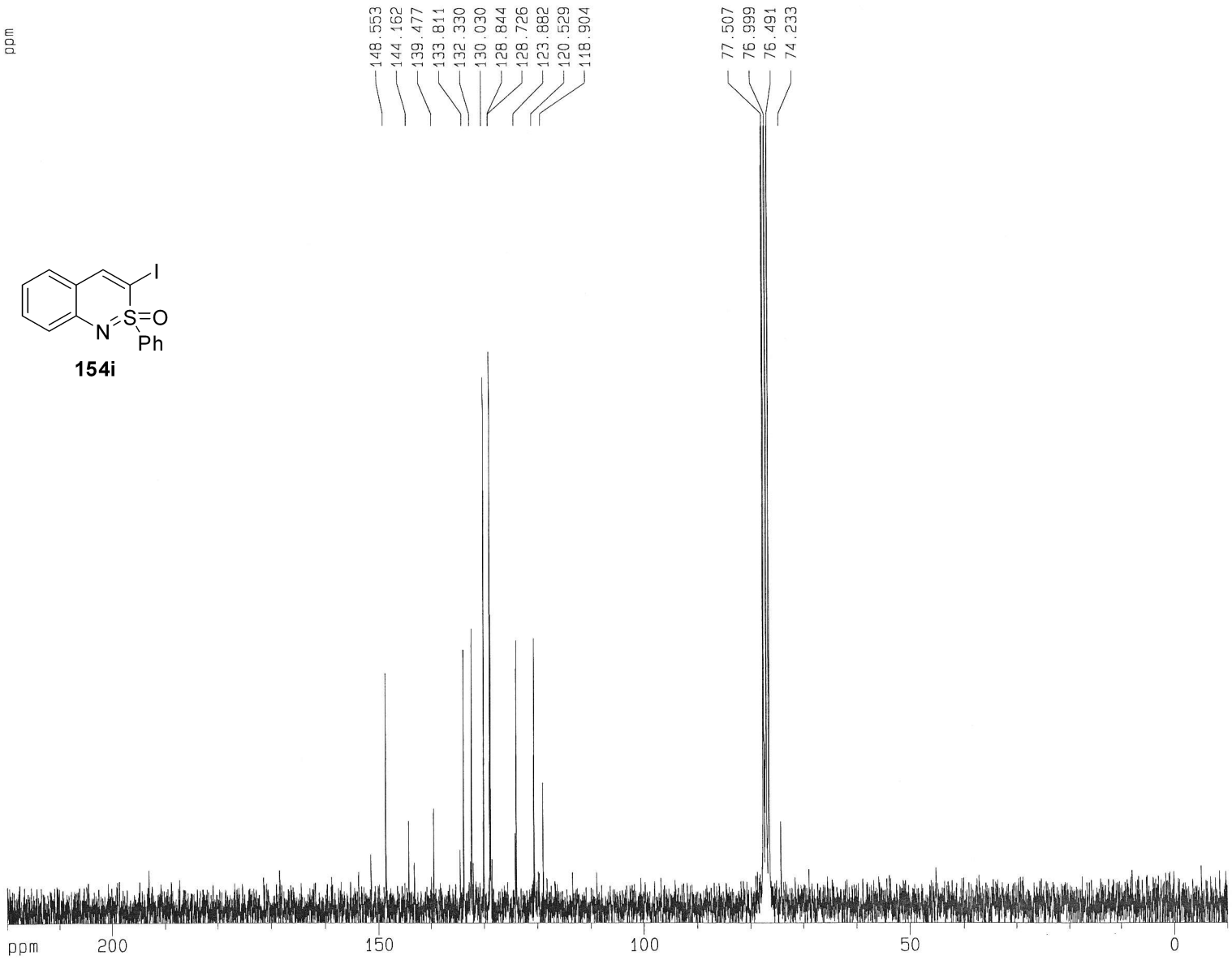
Date_	20041026
Time	17.33
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	5208.333 Hz
FIDRES	0.158946 Hz
AQ	3.1457779 sec
RG	5700
DW	96.000 use
DE	137.14 use
TE	300.0 K
D1	1.00000000 sec
P1	8.70 use
SFO1	250.1315321 MHz
NUCLEUS	1H

F2 - Processing parameters

SI	16384
SF	250.1300078 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.50

1D NMR plot parameters

CX	20.00 cm
CY	7.00 cm
F1P	10.000 ppm
F1	2501.30 Hz
F2P	-0.500 ppm
F2	-125.07 Hz
PPMCM	0.52500 ppm
HZCM	131.31825 Hz/



Current Data Parameters

NAME	NC-I-60B
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20041026
Time	17.41
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zgdc30
TD	36864
SOLVENT	CDCl3
NS	5532
DS	4
SWH	17241.379 Hz
FIDRES	0.467702 Hz
AQ	1.0691060 sec
RG	22800
DW	29.000 use
DE	41.43 use
TE	300.0 K
D12	0.00002000 sec
DL5	23.00 dB
CPDPRG	waltz16
P31	103.00 use
D1	1.00000000 sec
P1	6.00 use
SFO1	62.9023694 MHz
NUCLEUS	13C
D11	0.03000000 sec

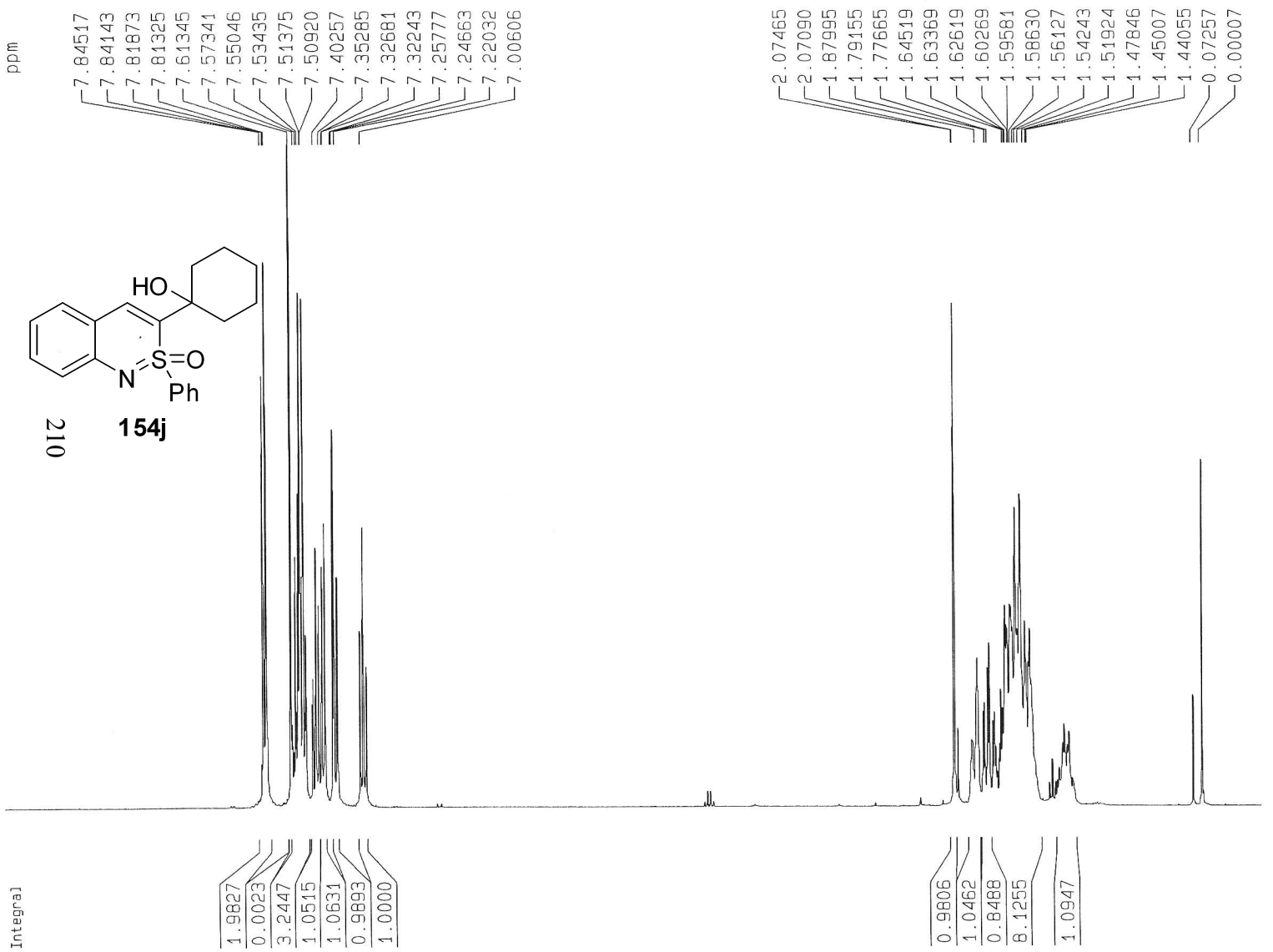
F2 - Processing parameters

SI	32768
SF	62.8952403 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
CY	50.00 cm
F1P	220.000 ppm
F1	13836.95 Hz
F2P	-10.000 ppm
F2	-628.95 Hz
PPMCM	11.50000 ppm
HZCM	723.29529 Hz/

1H NMR



Current Data Parameters

NAME	NC-I-61A
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20041104
Time	18.06
INSTRUM	drx300
PROBHD	5 mm Multinucl
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	6172.839 Hz
FIDRES	0.188380 Hz
AQ	2.6542580 sec
RG	256
DW	81.000 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec
D31	0.00000000 sec

======== CHANNEL f1 ========

NUC1	1H
P1	7.05 usec
PL1	0.00 dB
SFO1	300.1318534 MHz

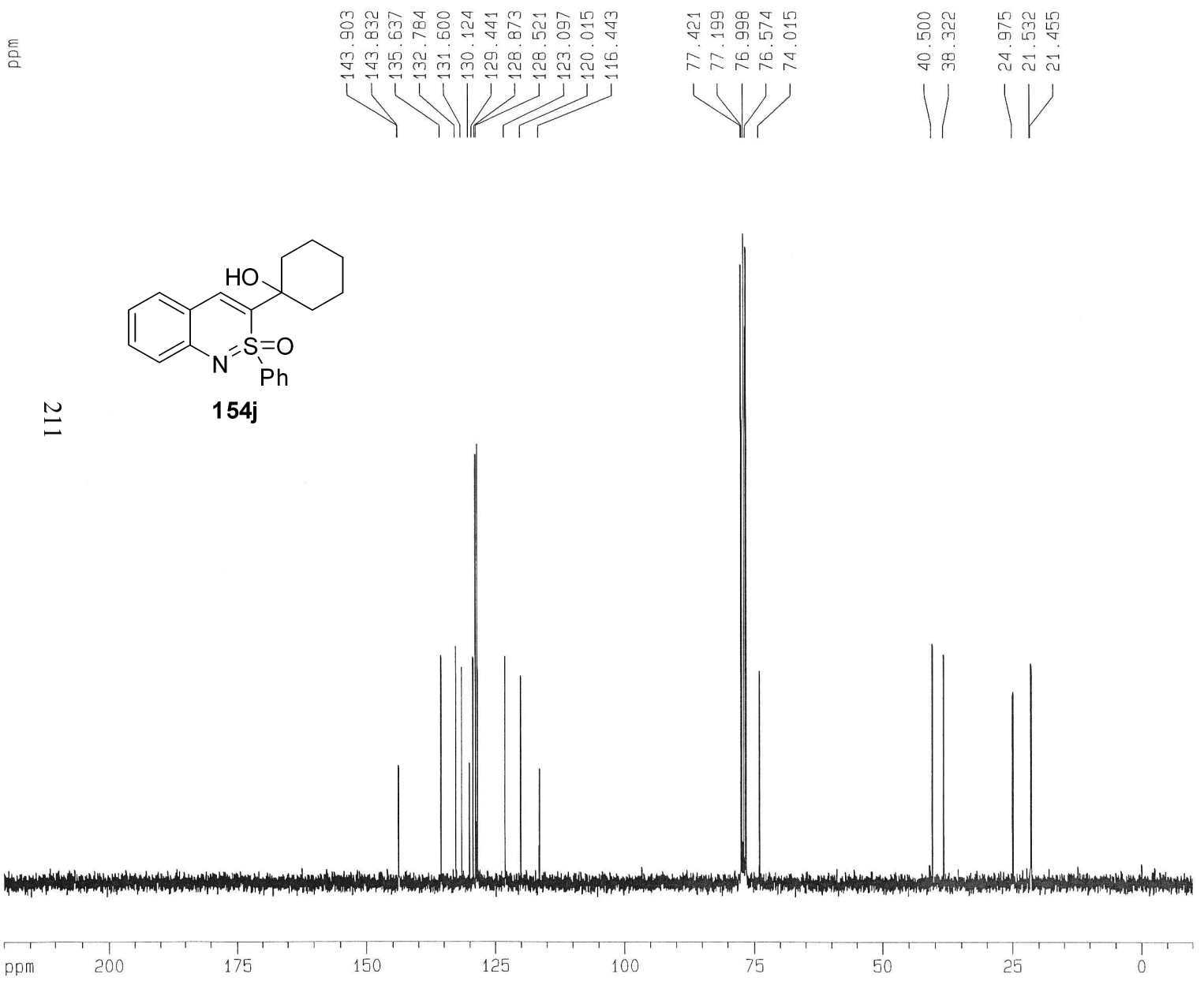
F2 - Processing parameters

SI	32768
SF	300.1300071 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.30

1D NMR plot parameters

CX	20.00 cm
CY	12.50 cm
F1P	10.000 ppm
F1	3001.30 Hz
F2P	-0.500 ppm
F2	-150.06 Hz
PPMCM	0.52500 ppm/cm
HZCM	157.56825 Hz/cm

13C NMR



Current Data Parameters

NAME	NC-I-61A
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20041104
Time	18.23
INSTRUM	drx300
PROBHD	5 mm Multinucl
PULPROG	zgdc30
TD	65536
SOLVENT	CDCl3
NS	392
DS	4
SWH	18832.393 Hz
FIDRES	0.287360 Hz
AQ	1.7400308 sec
RG	22528
DW	26.550 usec
DE	6.00 usec
TE	297.1 K
D1	1.29999995 sec
d11	0.03000000 sec
D31	0.00000000 sec

======== CHANNEL f1 ========

NUC1	13C
P1	8.50 usec
PL1	5.00 dB
SFO1	75.4760107 MHz

======== CHANNEL f2 ========

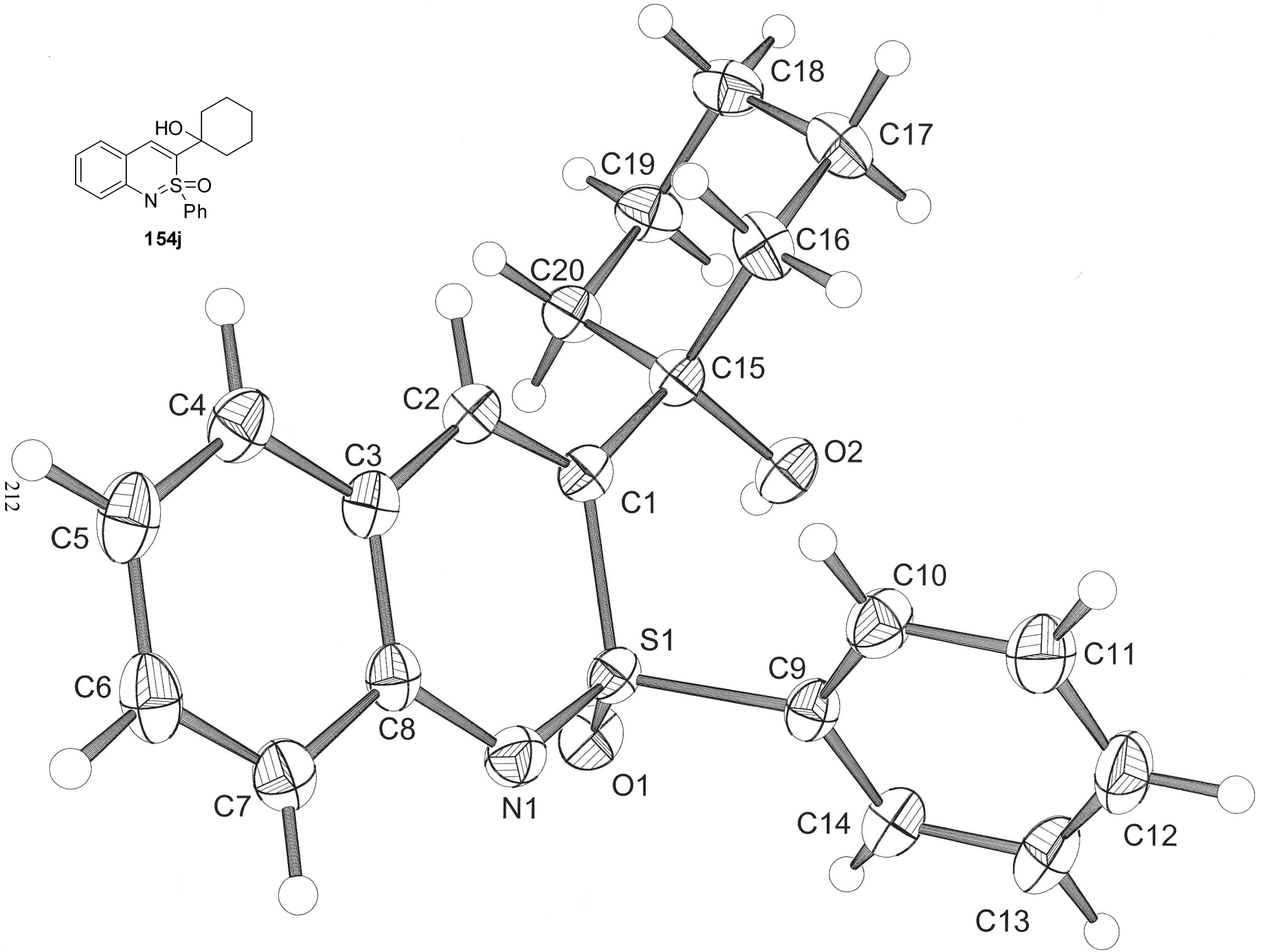
CPDPRG2	waltz16
NUC2	1H
PCPD2	100.00 usec
PL2	120.00 dB
PL12	25.60 dB
SFO2	300.1312005 MHz

F2 - Processing parameters

SI	32768
SF	75.4677525 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
CY	11.00 cm
F1P	220.000 ppm
F1	16602.90 Hz
F2P	-10.000 ppm
F2	-754.68 Hz
PPMCM	11.50000 ppm/cm
HZCM	867.87909 Hz/cm


HO
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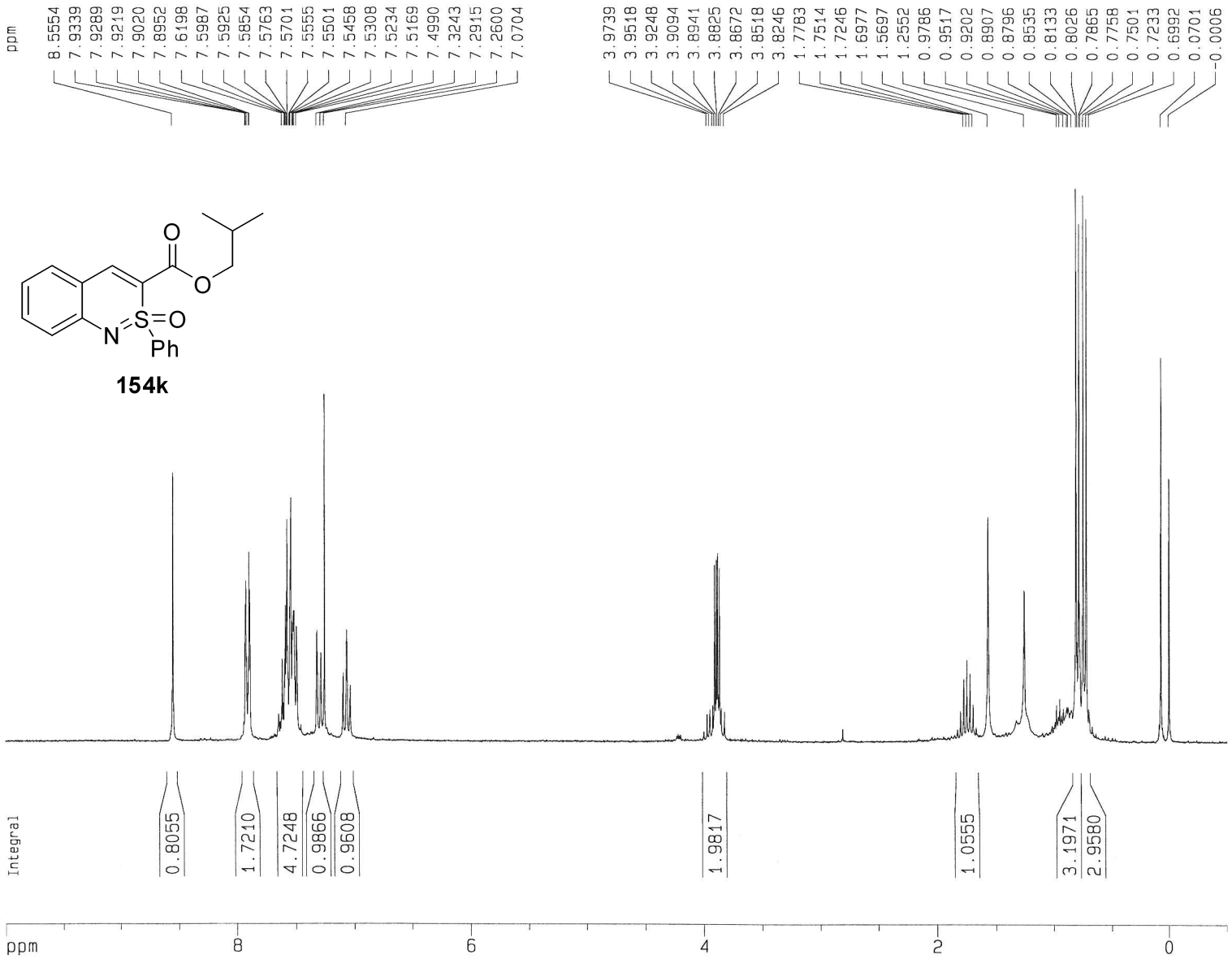
Ph
154j
C18
C17
C19
C16
C20
C15
C4
C2
O2
C3
C1
C5
C10
S1
C11
C6
C9
C8
O1
C7
N1
C14
C12
C13

1H NMR



Current Data Parameters

NAME	NC-I-67A
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

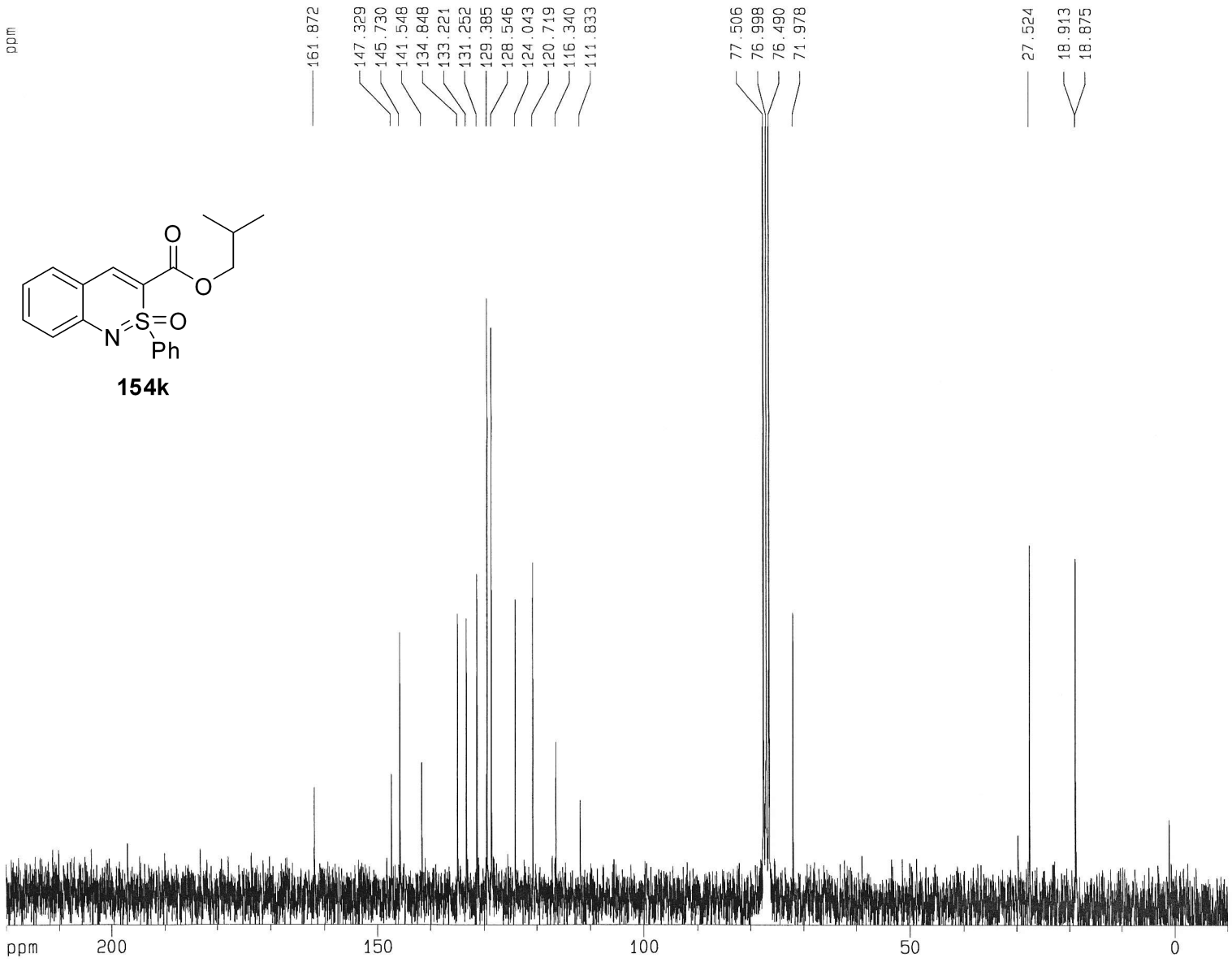
Date_	20041230
Time	22.06
INSTRUM	arx250
PROBHD	5 mm GNP 1H
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	5208.333 Hz
FIDRES	0.158946 Hz
AQ	3.1457779 sec
RG	2048
DW	96.000 use
DE	137.14 use
TE	300.0 K
D1	1.00000000 sec
P1	8.70 use
SFO1	250.1315321 MHz
NUCLEUS	1H

F2 - Processing parameters

SI	16384
SF	250.1300075 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.50

1D NMR plot parameters

CX	20.00 cm
CY	9.00 cm
F1P	10.000 ppm
F1	2501.30 Hz
F2P	-0.500 ppm
F2	-125.07 Hz
PPMCM	0.52500 ppm
HZCM	131.31825 Hz/



154k

Current Data Parameters

NAME	NC-I-67A
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20041230
Time	22.19
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zgdc30
TD	36864
SOLVENT	CDCl3
NS	1882
DS	4
SWH	17241.379 Hz
FIDRES	0.467702 Hz
AQ	1.0691060 sec
RG	22800
DW	29.000 use
DE	41.43 use
TE	300.0 K
D12	0.00002000 sec
DL5	23.00 dB
CPDPRG	waltz16
P31	103.00 use
D1	1.00000000 sec
P1	6.00 use
SFO1	62.9023694 MHz
NUCLEUS	13C
D11	0.03000000 sec

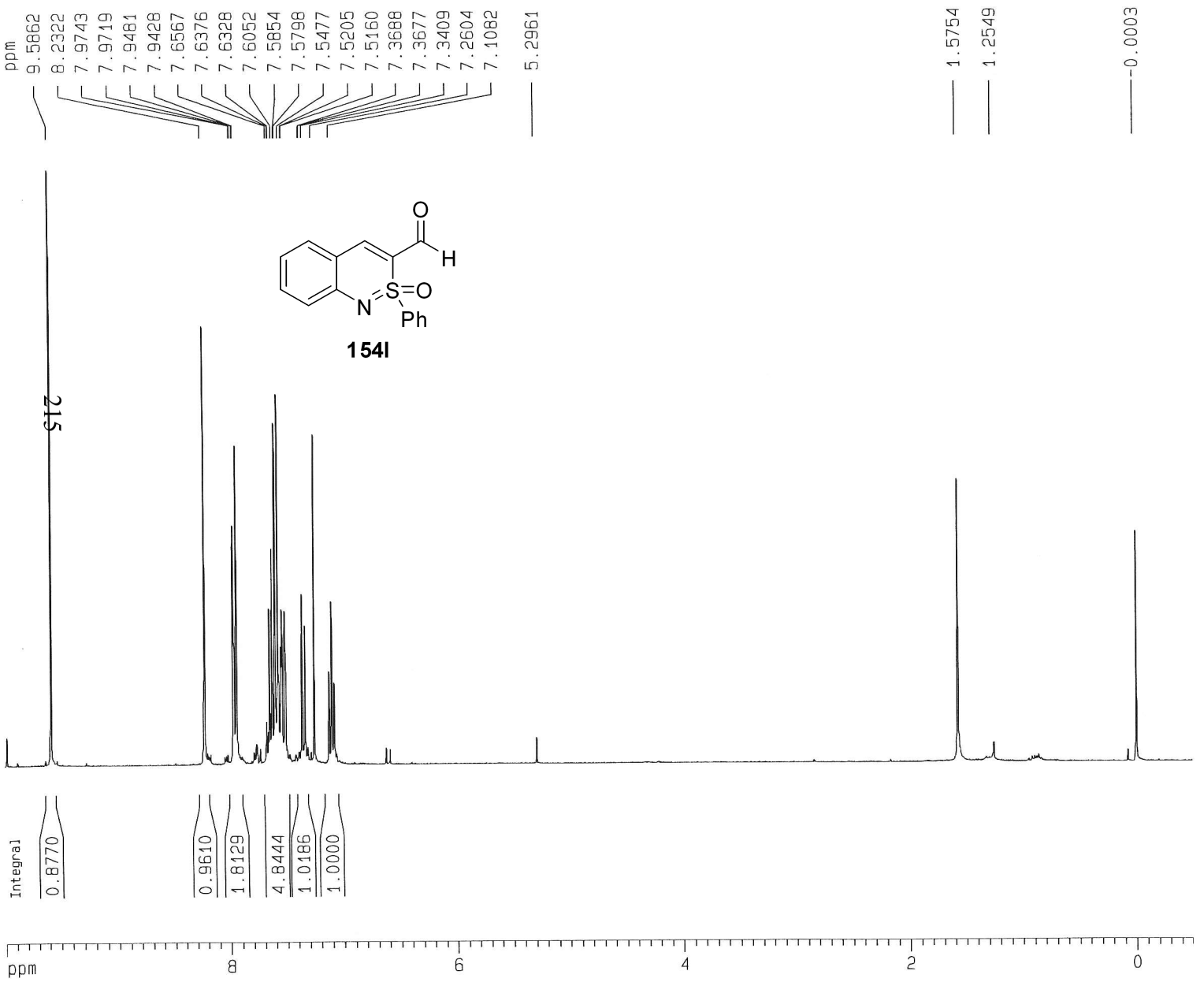
F2 - Processing parameters

SI	32768
SF	62.8952408 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
CY	40.00 cm
F1P	220.000 ppm
F1	13836.95 Hz
F2P	-10.000 ppm
F2	-628.95 Hz
PPMCM	11.50000 ppm
HZCM	723.29529 Hz/

1H NMR



154l

Current Data Parameters

NAME	NC-I-69A
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20041230
Time	22.57
INSTRUM	drx300
PROBHD	5 mm Multinucl
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	6172.839 Hz
FIDRES	0.188380 Hz
AQ	2.6542580 sec
RG	912.3
DW	81.000 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec
D31	0.00000000 sec

======== CHANNEL f1 ========

NUC1	1H
P1	7.05 usec
PL1	0.00 dB
SF01	300.1318534 MHz

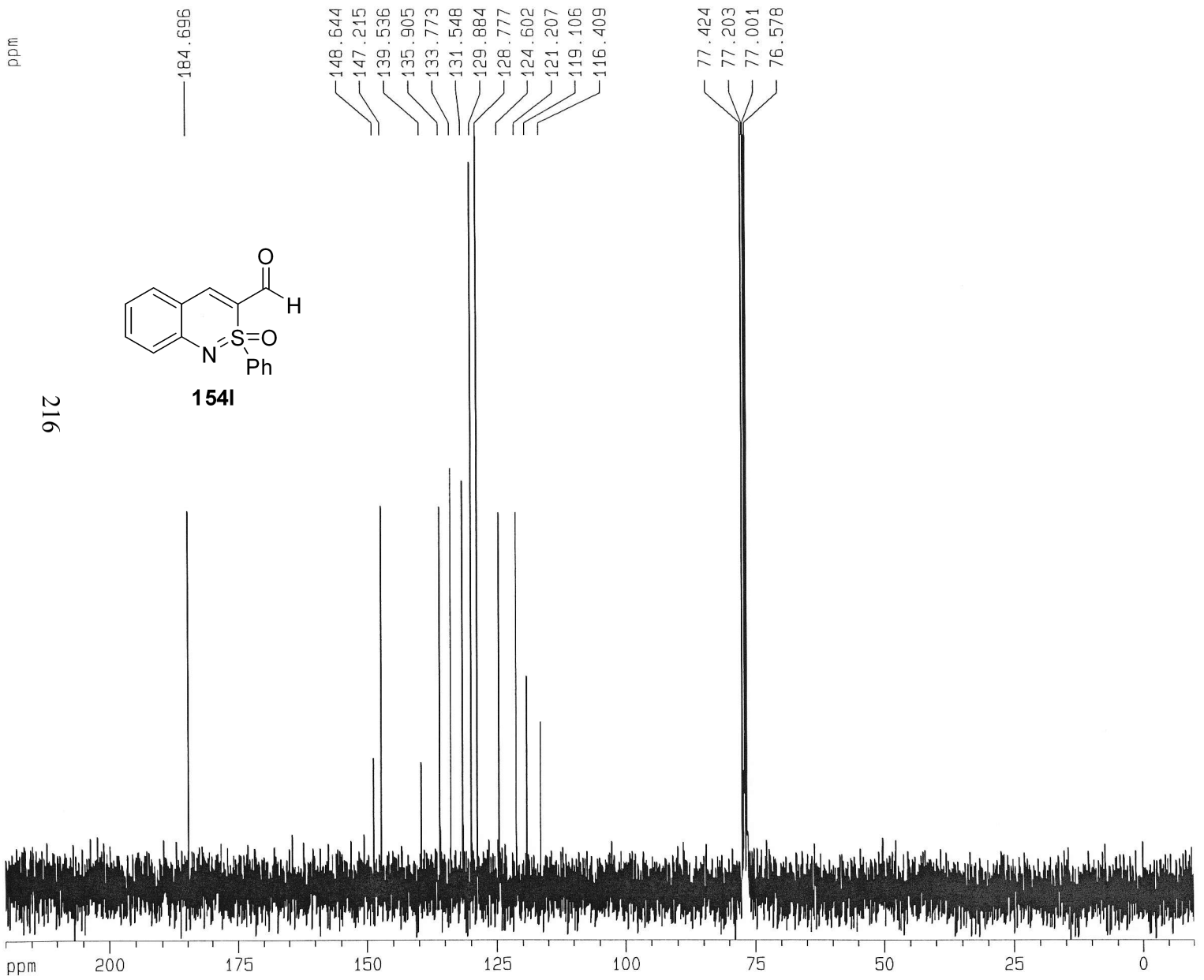
F2 - Processing parameters

SI	32768
SF	300.1300064 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.30

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	10.000 ppm
F1	3001.30 Hz
F2P	-0.500 ppm
F2	-150.06 Hz
PPMCM	0.52500 ppm/cm
HZCM	157.56825 Hz/cm

13C NMR



Current Data Parameters

NAME	NC-I-69A
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20041230
Time	23.04
INSTRUM	drx300
PROBHD	5 mm Multinucl
PULPROG	zgdc30
TD	65536
SOLVENT	CDCl3
NS	386
DS	4
SWH	18832.393 Hz
FIDRES	0.287360 Hz
AQ	1.7400308 sec
RG	22528
DW	26.550 usec
DE	6.00 usec
TE	297.1 K
D1	1.29999995 sec
d11	0.03000000 sec
D31	0.00000000 sec

======== CHANNEL f1 ========

NUC1	13C
P1	8.50 usec
PL1	5.00 dB
SFO1	75.4760107 MHz

======== CHANNEL f2 ========

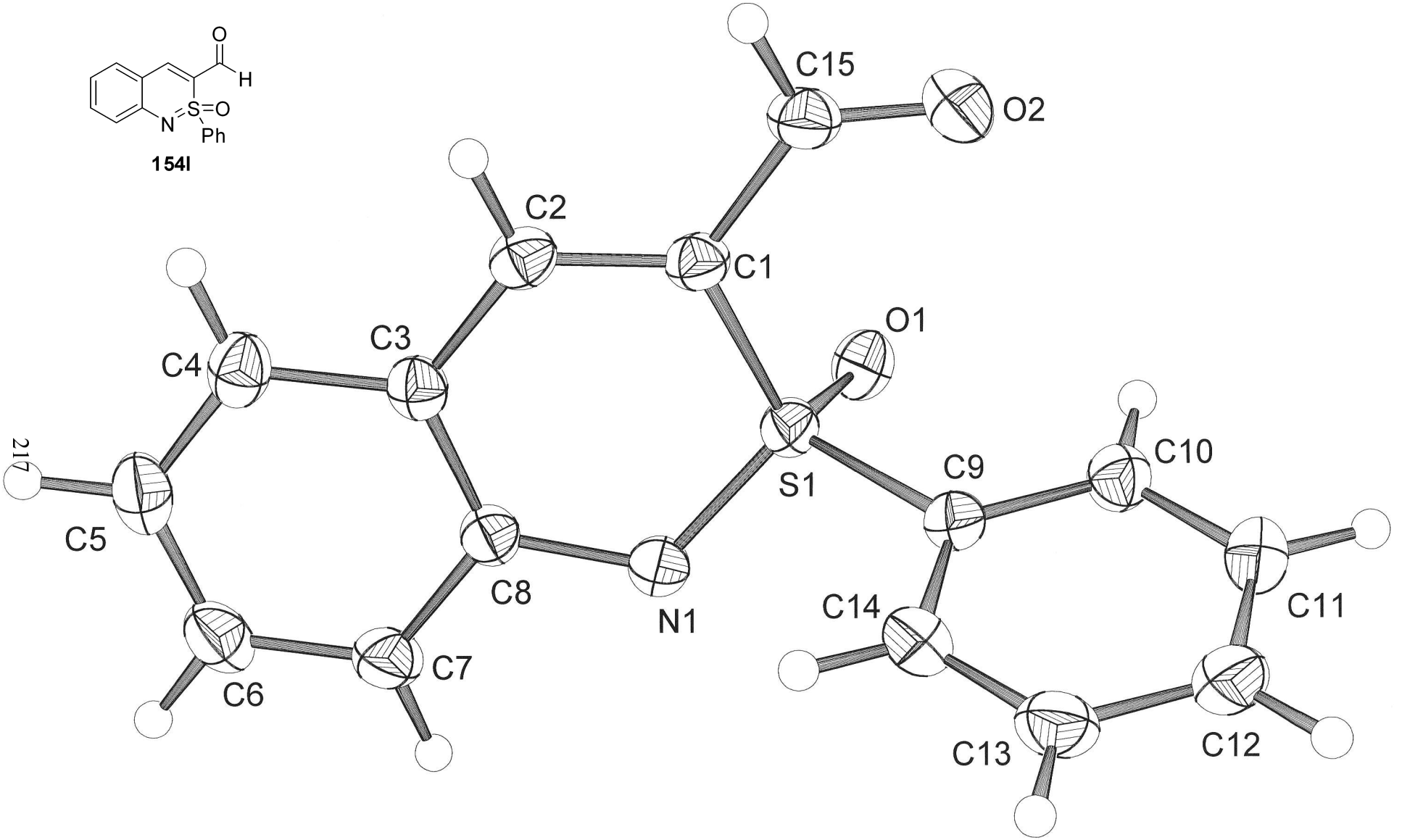
CPDPRG2	waltz16
NUC2	1H
PCPD2	100.00 usec
PL2	120.00 dB
PL12	25.60 dB
SFO2	300.1312005 MHz

F2 - Processing parameters

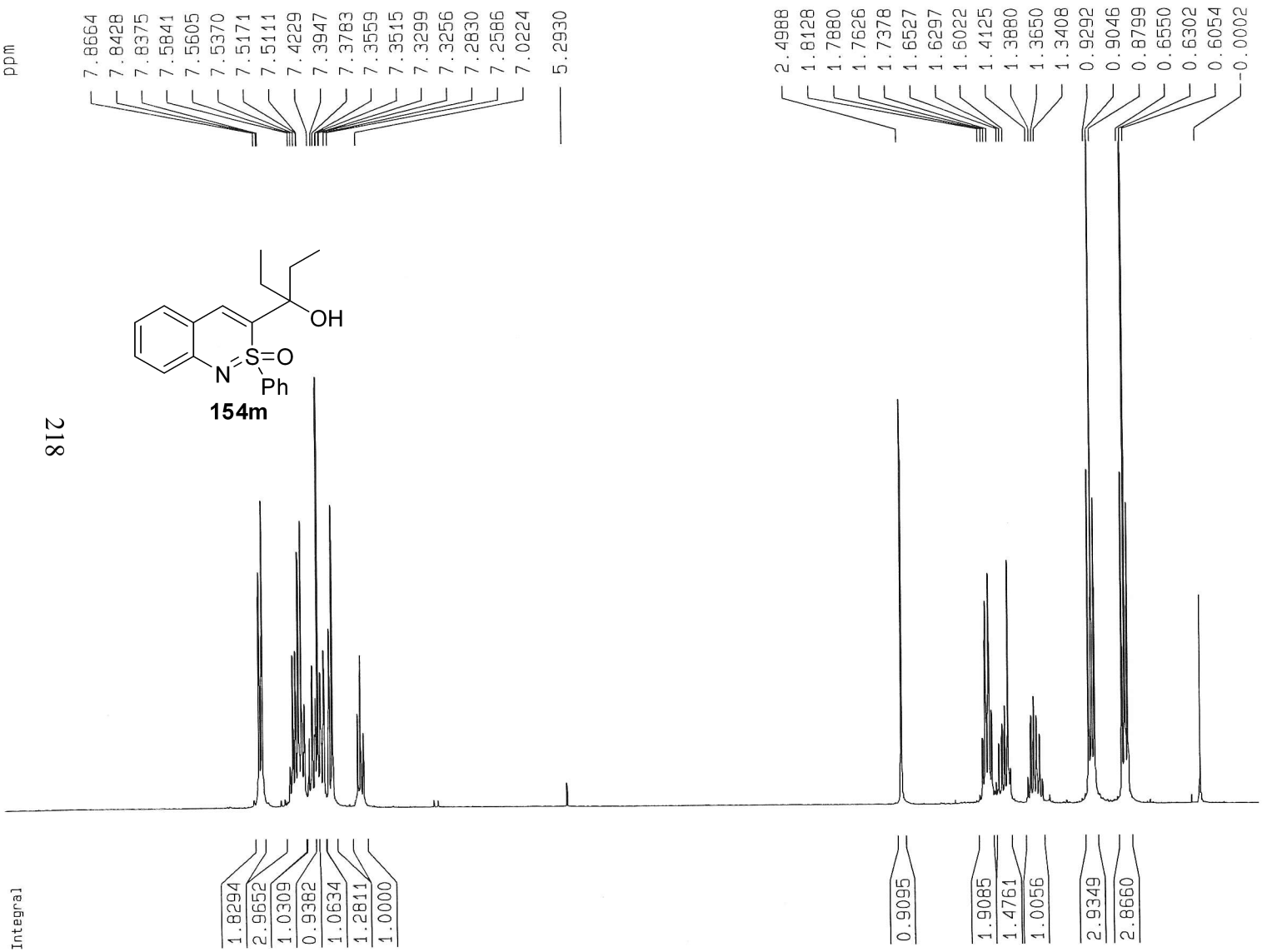
SI	32768
SF	75.4677508 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
CY	40.00 cm
F1P	220.000 ppm
F1	16602.90 Hz
F2P	-10.000 ppm
F2	-754.68 Hz
PPMCM	11.50000 ppm/cm
HZCM	867.87909 Hz/cm


O
H
S
O
N
Ph
154l
C15
O2
C2
C1
O1
C3
C4
C5
S1
C9
C10
C8
N1
C14
C11
C6
C7
C13
C12

1H NMR



Current Data Parameters

NAME	NC-I-68B
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20041230
Time	22.33
INSTRUM	drx300
PROBHD	5 mm Multinucl
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	6172.839 Hz
FIDRES	0.188380 Hz
AQ	2.6542580 sec
RG	362
DW	81.000 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec
D31	0.00000000 sec

======== CHANNEL f1 ========

NUC1	1H
P1	7.05 usec
PL1	0.00 dB
SFO1	300.1318534 MHz

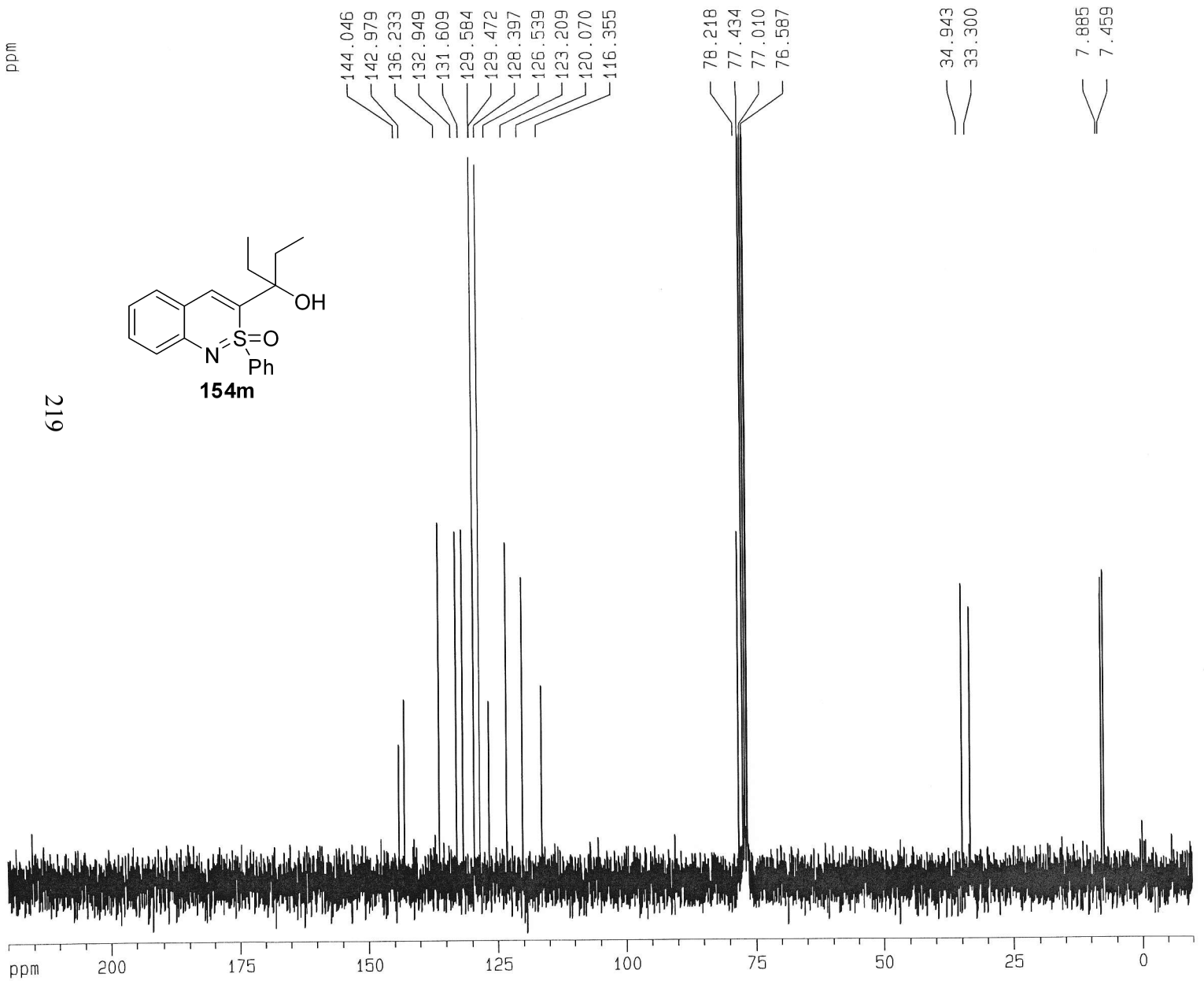
F2 - Processing parameters

SI	32768
SF	300.1300067 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.30

1D NMR plot parameters

CX	20.00 cm
CY	11.00 cm
F1P	10.000 ppm
F1	3001.30 Hz
F2P	-0.500 ppm
F2	-150.06 Hz
PPMCM	0.52500 ppm/cm
HZCM	157.56825 Hz/cm

13C NMR



Current Data Parameters

NAME	NC-I-68B
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20041230
Time	22.45
INSTRUM	drx300
PROBHD	5 mm Multinucl
PULPROG	zgdc30
TD	65536
SOLVENT	CDCl3
NS	201
DS	4
SWH	18832.393 Hz
FIDRES	0.287360 Hz
AQ	1.7400308 sec
RG	22528
DW	26.550 usec
DE	6.00 usec
TE	297.1 K
D1	1.29999995 sec
d11	0.03000000 sec
D31	0.00000000 sec

======== CHANNEL f1 ========

NUC1	13C
P1	8.50 usec
PL1	5.00 dB
SFO1	75.4760107 MHz

======== CHANNEL f2 ========

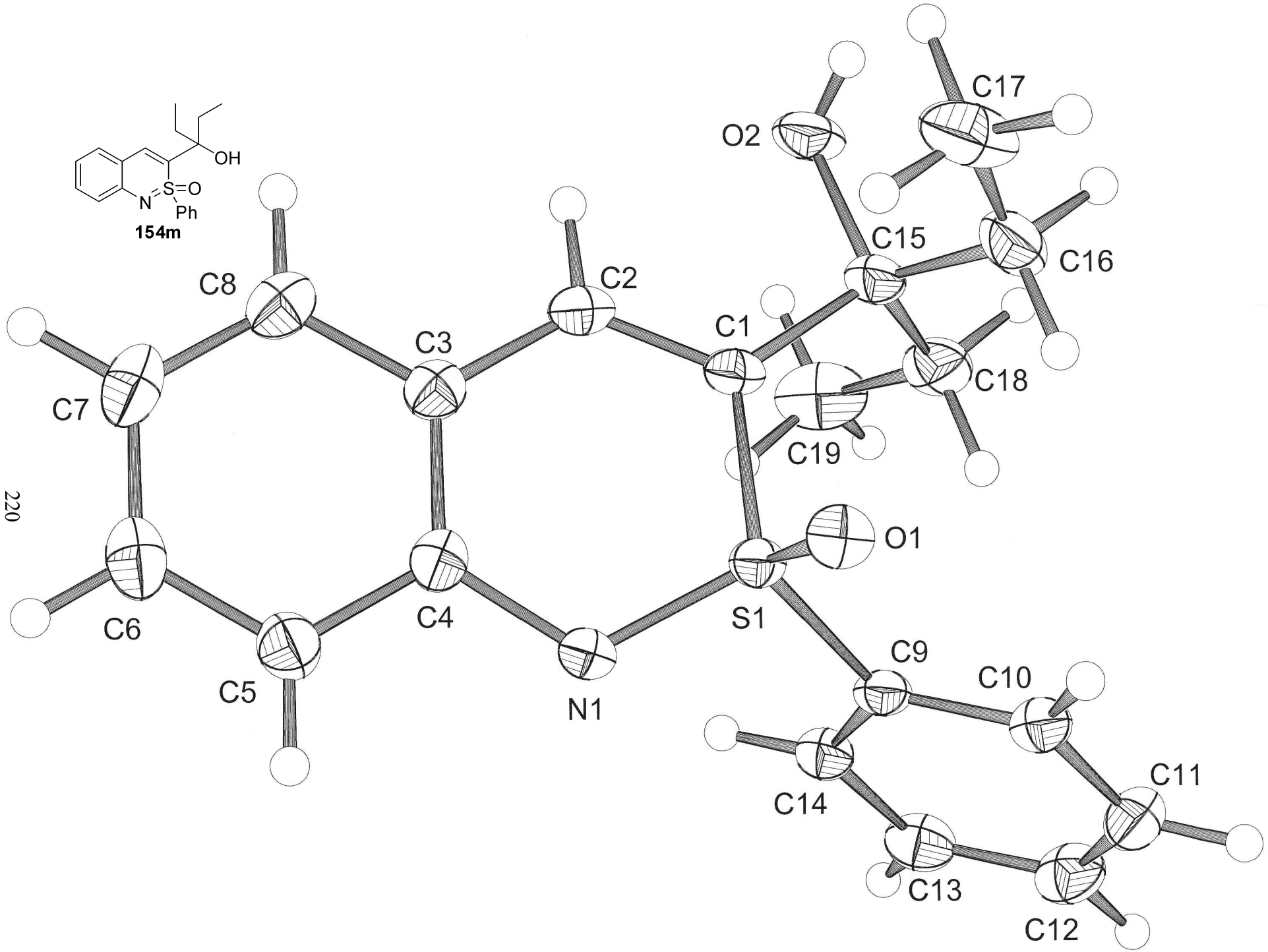
CPDPRG2	waltz16
NUC2	1H
PCPD2	100.00 usec
PL2	120.00 dB
PL12	25.60 dB
SFO2	300.1312005 MHz

F2 - Processing parameters

SI	32768
SF	75.4677508 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
CY	25.00 cm
F1P	220.000 ppm
F1	16602.90 Hz
F2P	-10.000 ppm
F2	-754.68 Hz
PPMCM	11.50000 ppm/cm
HZCM	867.87909 Hz/cm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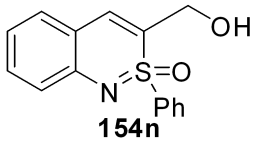
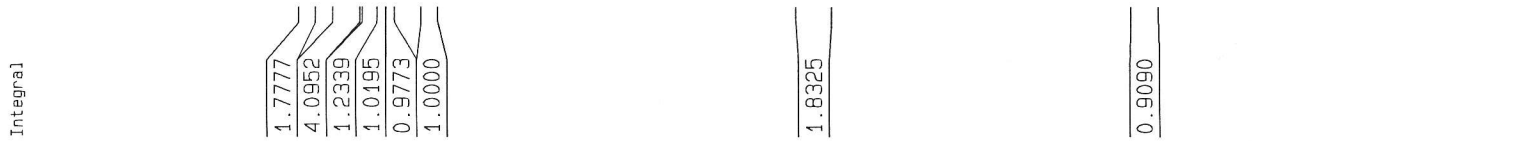
N
Ph
154m
C8
C2
C17
O2
C15
C16
C1
C3
C18
C7
C19
O1
C6
C4
S1
C9
C10
C5
N1
C11
C14
C13
C12

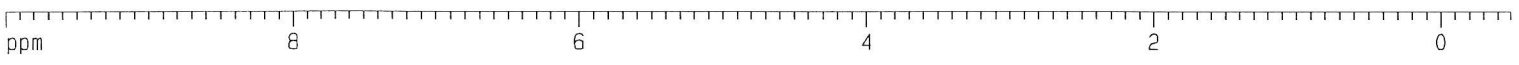
1H NMR



154n

221





Current Data Parameters

NAME	NC-I-77B
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20050112
Time	10.40
INSTRUM	drx300
PROBHD	5 mm Multinucl
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	6172.839 Hz
FIDRES	0.188380 Hz
AQ	2.6542580 sec
RG	912.3
DW	81.000 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec
D31	0.00000000 sec

======== CHANNEL f1 ========

NUC1	1H
P1	7.05 usec
PL1	0.00 dB
SFO1	300.1318534 MHz

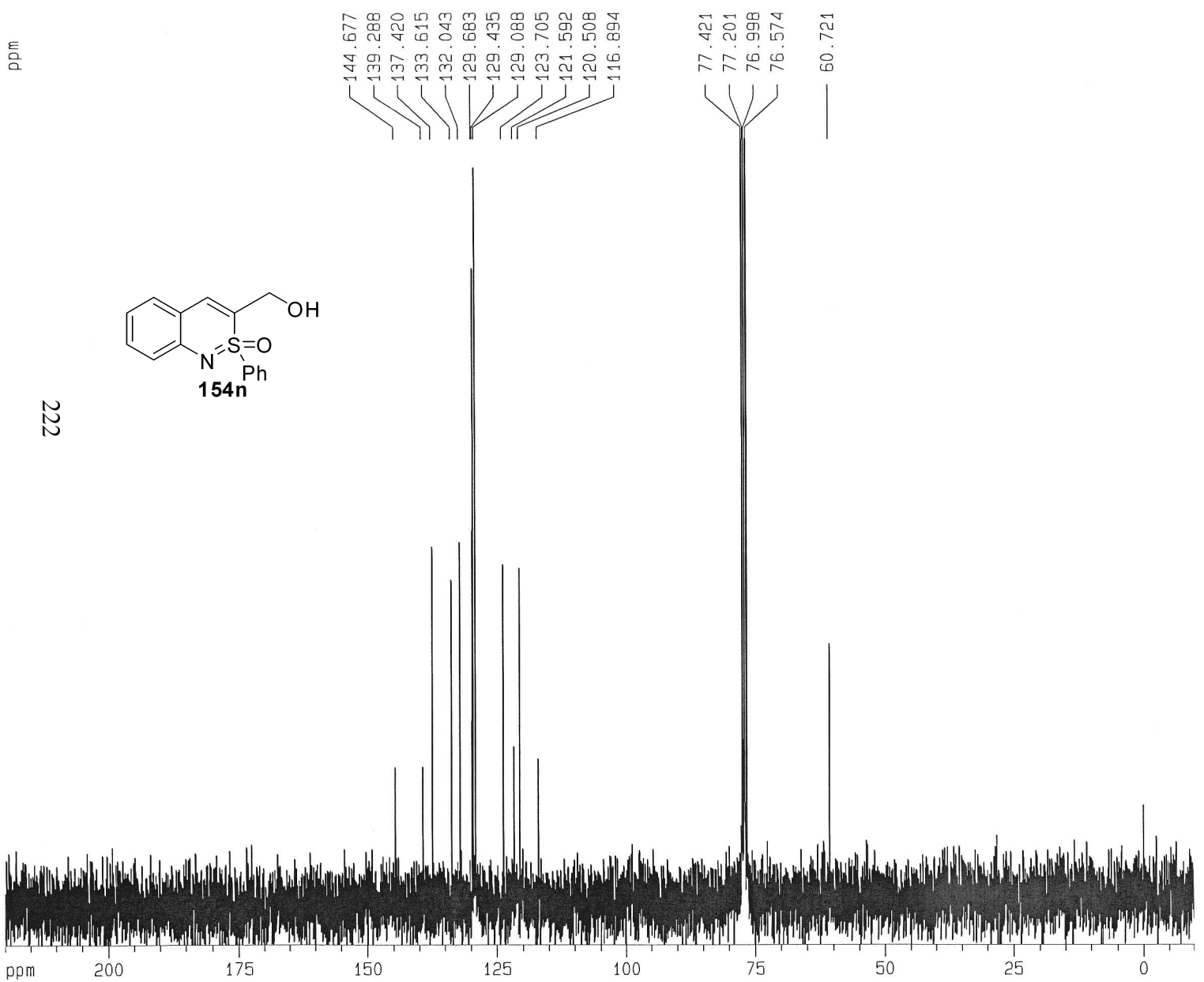
F2 - Processing parameters

SI	32768
SF	300.1300064 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.30

1D NMR plot parameters

CX	20.00 cm
CY	9.00 cm
F1P	10.000 ppm
F1	3001.30 Hz
F2P	-0.500 ppm
F2	-150.06 Hz
PPMCM	0.52500 ppm/cm
HZCM	157.56825 Hz/cm

13C NMR



Current Data Parameters

NAME	NC-I-77B
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20050112
Time	10.46
INSTRUM	drx300
PROBHD	5 mm Multinucl
PULPROG	zgdc30
TD	65536
SOLVENT	CDCl3
NS	500
DS	4
SWH	18832.393 Hz
FIDRES	0.287360 Hz
AQ	1.7400308 sec
RG	22528
DW	26.550 usec
DE	6.00 usec
TE	297.1 K
D1	1.29999995 sec
d11	0.03000000 sec
D31	0.00000000 sec

======== CHANNEL f1 ========

NUC1	13C
P1	8.50 usec
PL1	5.00 dB
SFO1	75.4760107 MHz

======== CHANNEL f2 ========

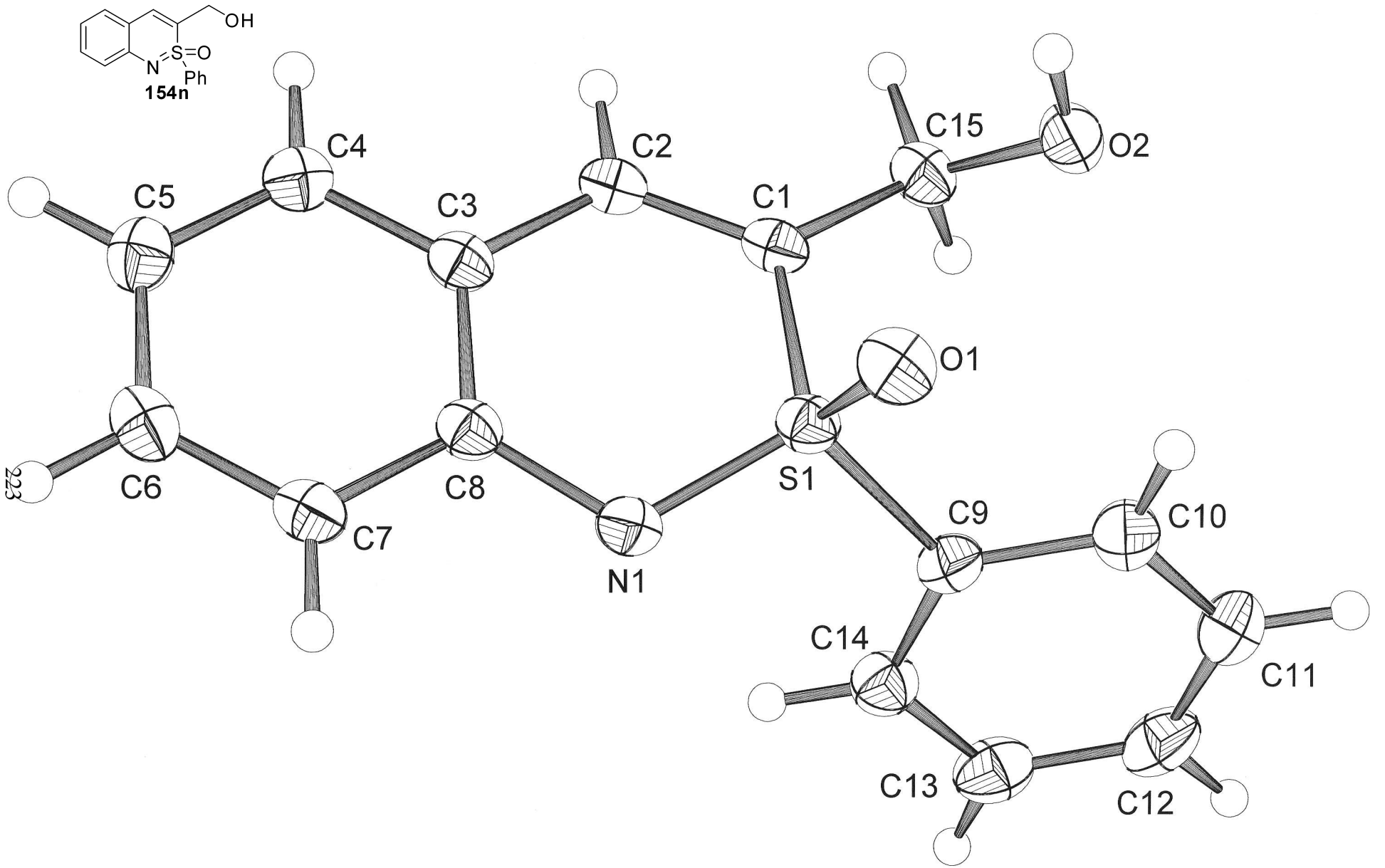
CPDPRG2	waltz16
NUC2	1H
PCPD2	100.00 usec
PL2	120.00 dB
PL12	25.60 dB
SFO2	300.1312005 MHz

F2 - Processing parameters

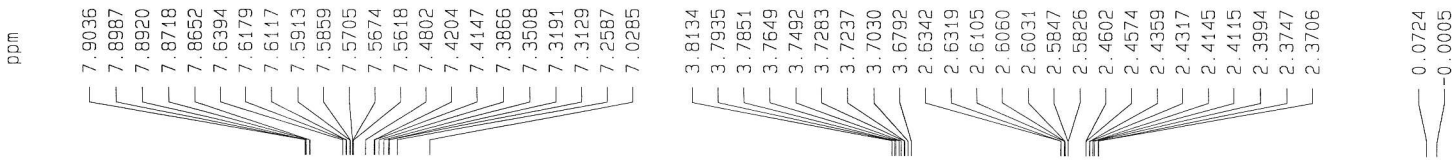
SI	32768
SF	75.4677502 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

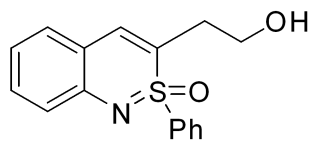
1D NMR plot parameters

CX	20.00 cm
CY	50.00 cm
F1P	220.000 ppm
F1	16602.90 Hz
F2P	-10.000 ppm
F2	-754.68 Hz
PPMCM	11.50000 ppm/cm
HZCM	867.87909 Hz/cm

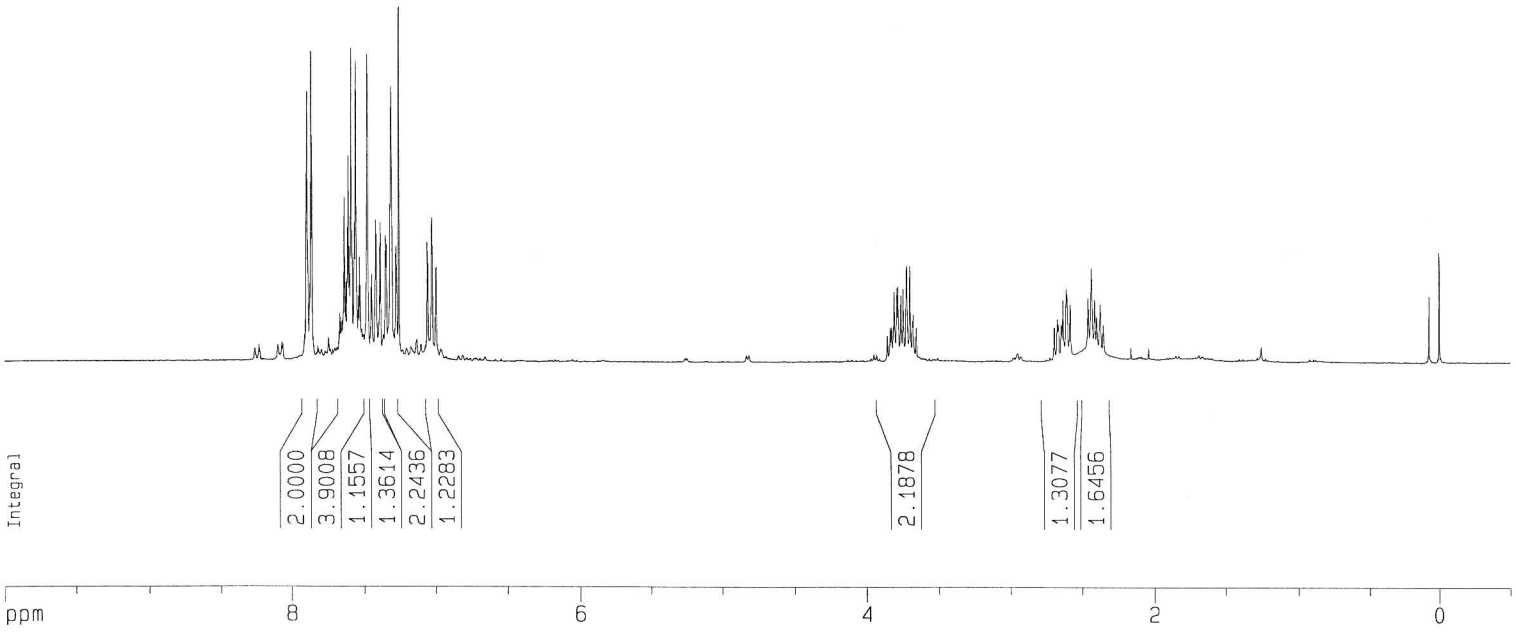

OH
S=O
N
Ph
154n
C4
C2
C15
O2
C5
C3
C1
O1
C6
C8
S1
C9
C10
C7
N1
C14
C11
C13
C12

1H NMR





154o



Current Data Parameters

NAME	NC-I-86A
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20050216
Time	10.33
INSTRUM	arx250
PROBHD	5 mm GNP 1H
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	5208.333 Hz
FIDRES	0.158946 Hz
AQ	3.1457779 sec
RG	1430
DW	96.000 use
DE	137.14 use
TE	300.0 K
D1	1.00000000 sec
P1	8.70 use
SFO1	250.1315321 MHz
NUCLEUS	1H

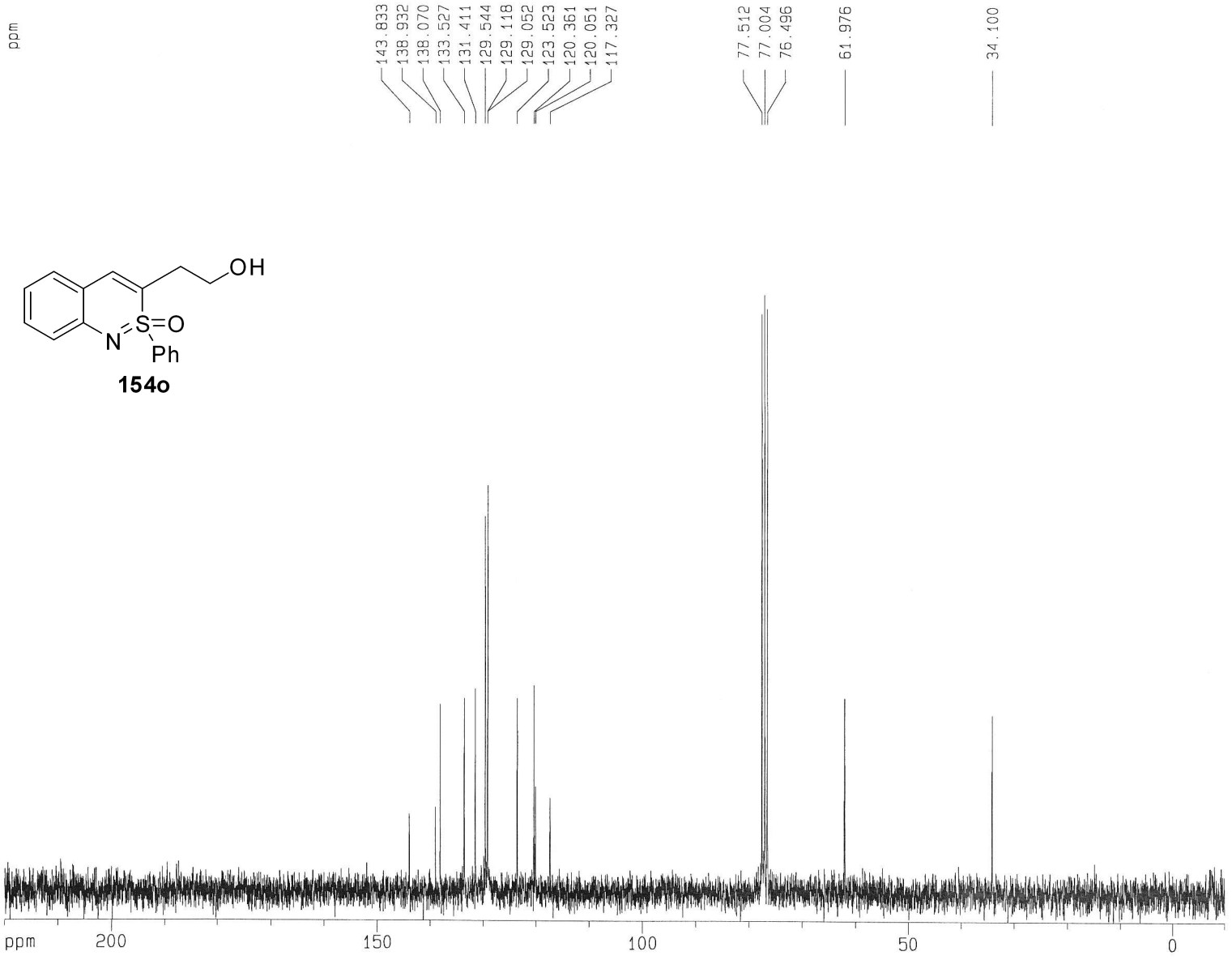
F2 - Processing parameters

SI	16384
SF	250.1300078 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.50

1D NMR plot parameters

CX	20.00 cm
CY	5.00 cm
F1P	10.000 ppm
F1	2501.30 Hz
F2P	-0.500 ppm
F2	-125.07 Hz
PPMCM	0.52500 ppm
HZCM	131.31825 Hz/

13C NMR



Current Data Parameters

NAME	NC-I-86A
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20050216
Time	10.43
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zgdc30
TD	36864
SOLVENT	CDCl3
NS	283
DS	4
SWH	17241.379 Hz
FIDRES	0.467702 Hz
AQ	1.0691060 sec
RG	22800
DW	29.000 use
DE	41.43 use
TE	300.0 K
D12	0.00002000 sec
DL5	23.00 dB
CPDPRG	waltz16
P31	103.00 use
D1	1.00000000 sec
P1	6.00 use
SFO1	62.9023694 MHz
NUCLEUS	13C
D11	0.03000000 sec

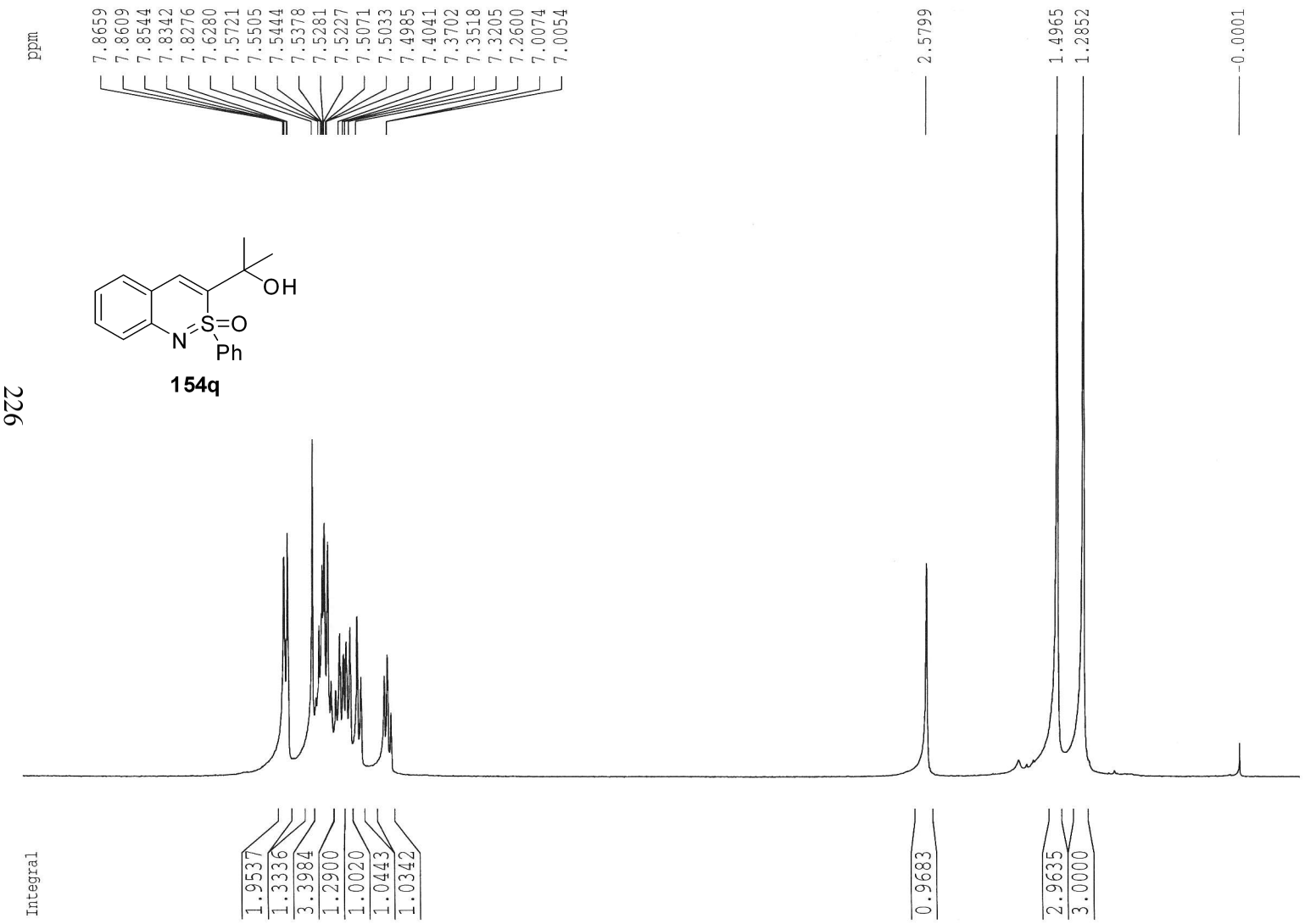
F2 - Processing parameters

SI	32768
SF	62.8952419 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	220.000 ppm
F1	13836.95 Hz
F2P	-10.000 ppm
F2	-628.95 Hz
PPMCM	11.50000 ppm
HZCM	723.29529 Hz/

1H NMR



Current Data Parameters

NAME	NC-II-99
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20091222
Time	8.47
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	5208.333 Hz
FIDRES	0.158946 Hz
AQ	3.1457779 sec
RG	512
DW	96.000 usec
DE	137.14 usec
TE	300.0 K
D1	1.00000000 sec
P1	8.50 usec
SFO1	250.1315321 MHz
NUCLEUS	1H

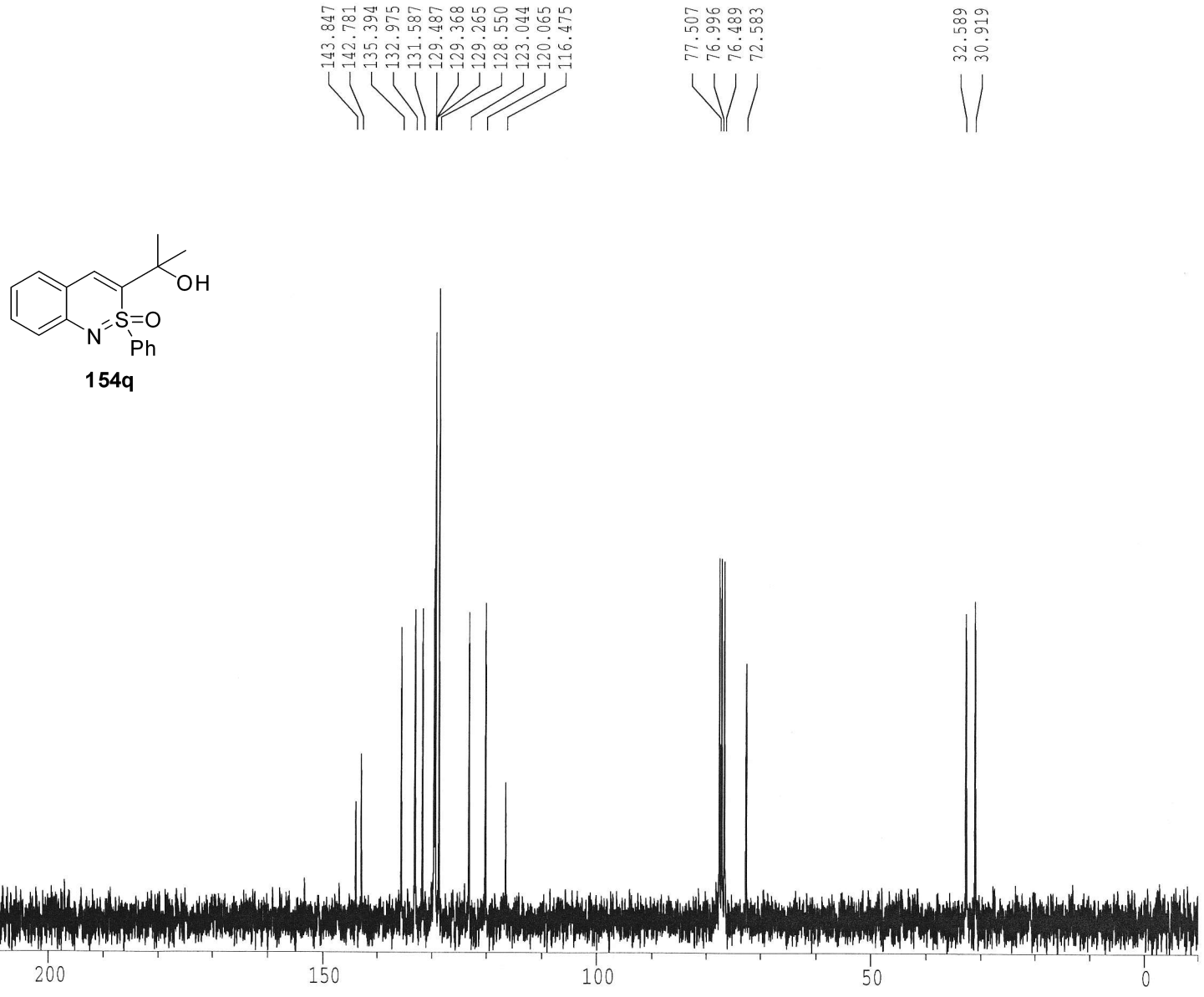
F2 - Processing parameters

SI	16384
SF	250.1300081 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.50

1D NMR plot parameters

CX	20.00 cm
CY	12.50 cm
F1P	10.000 ppm
F1	2501.30 Hz
F2P	-0.500 ppm
F2	-125.07 Hz
PPMCM	0.52500 ppm/cm
HZCM	131.31825 Hz/cm

13C NMR



Current Data Parameters

NAME	NC-II-99
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

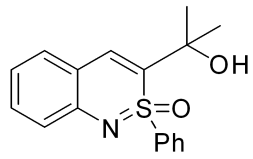
Date_	20091222
Time	8.51
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zgdc30
TD	36864
SOLVENT	CDCl3
NS	97
DS	4
SWH	17241.379 Hz
FIDRES	0.467702 Hz
AQ	1.0691060 sec
RG	22800
DW	29.000 usec
DE	41.43 usec
TE	300.0 K
D12	0.00002000 sec
DL5	23.00 dB
CPDPRG	waltz16
P31	103.00 usec
D1	2.00000000 sec
P1	6.25 usec
SFO1	62.9023694 MHz
NUCLEUS	13C
D11	0.03000000 sec

F2 - Processing parameters

SI	32768
SF	62.8952466 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

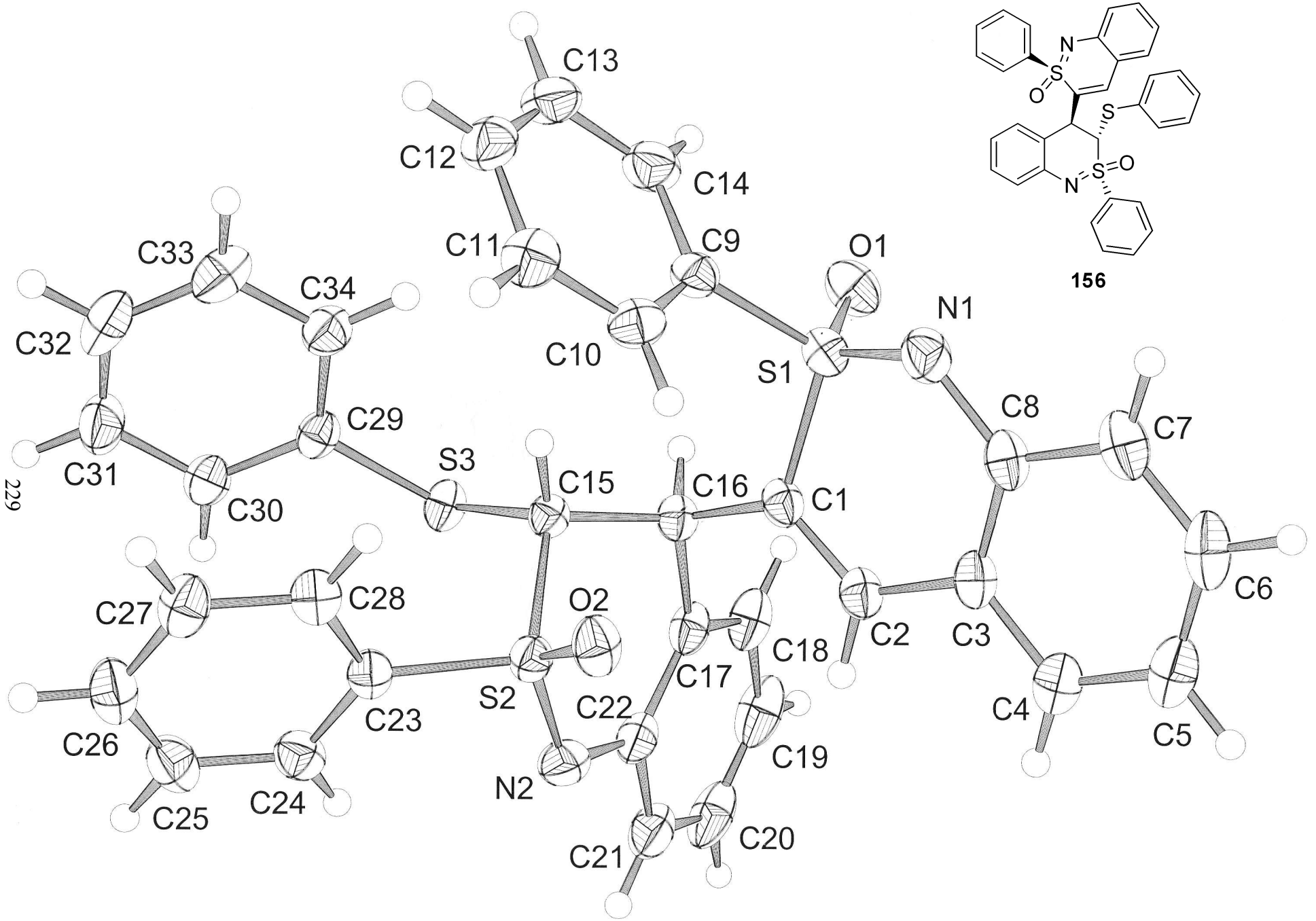
1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	220.000 ppm
F1	13836.95 Hz
F2P	-10.000 ppm
F2	-628.95 Hz
PPMCM	11.50000 ppm/cm
HZCM	723.29535 Hz/cm


OH
S=O
N
Ph

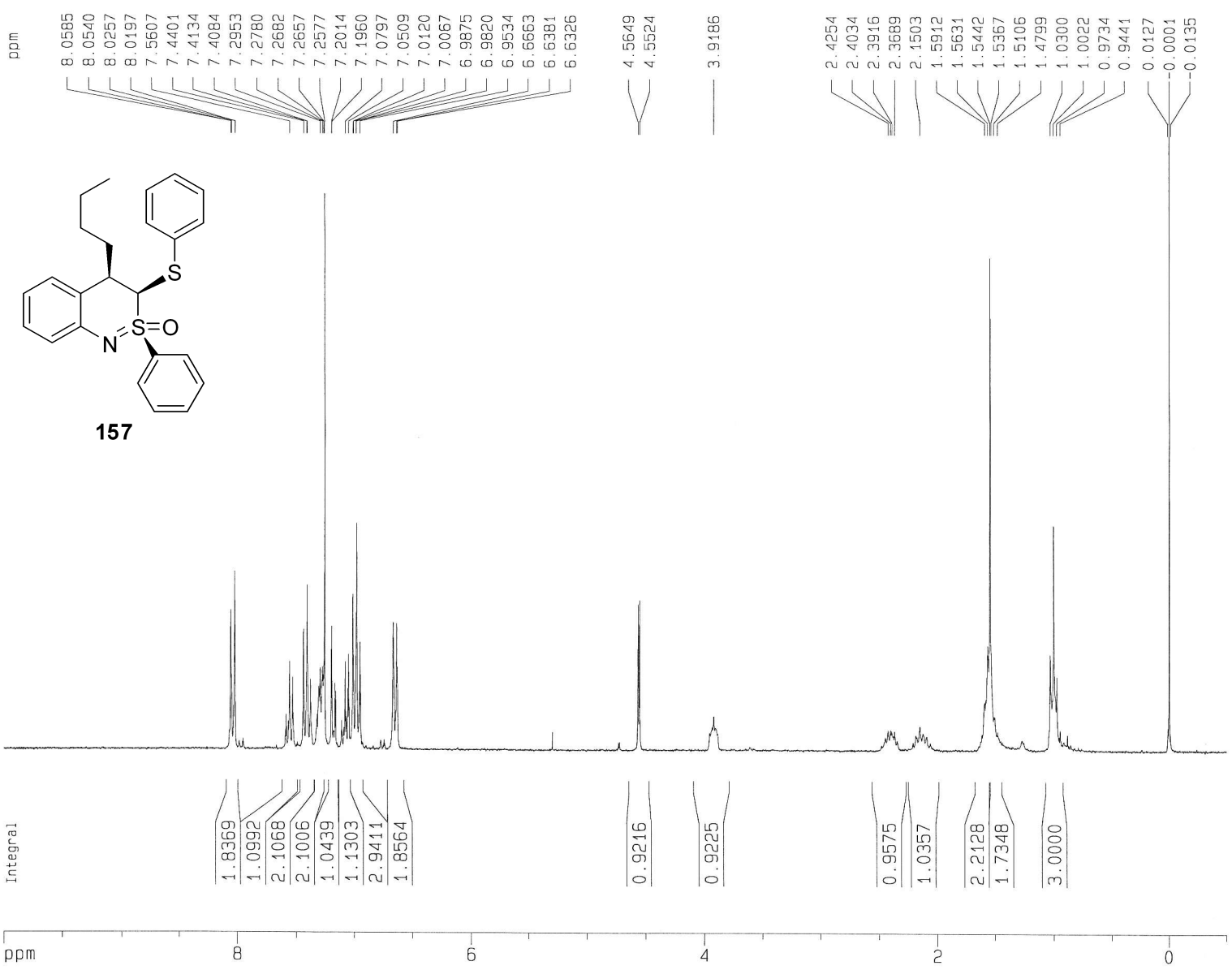
154q

C16
C17
C15
C2
C8
C3
O2
C1
C7
S1
C14
C13
C4
C6
C5
N1
O1
C9
C12
C10
C11


C13
C12
C14
C11
C9
O1
C33
C34
N1
C32
C10
S1
C29
C8
C7
S3
C31
C15
C16
C1
C30
C6
C27
C28
O2
C2
C3
C18
C17
S2
C22
C23
C4
C5
C26
C19
N2
C24
C25
C20
C21

156

1H NMR



Current Data Parameters

NAME	NC-I-88
EXPNO	3
PROCNO	1

F2 - Acquisition Parameters

Date_	20050210
Time	10.08
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	5208.333 Hz
FIDRES	0.158946 Hz
AQ	3.1457779 sec
RG	4096
DW	96.000 use
DE	137.14 use
TE	300.0 K
D1	1.00000000 sec
P1	8.70 use
SFO1	250.1315321 MHz
NUCLEUS	1H

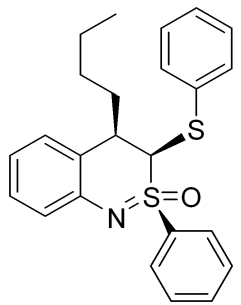
F2 - Processing parameters

SI	16384
SF	250.1300081 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.50

1D NMR plot parameters

CX	20.00 cm
CY	12.00 cm
F1P	10.000 ppm
F1	2501.30 Hz
F2P	-0.500 ppm
F2	-125.07 Hz
PPMCM	0.52500 ppm
HZCM	131.31825 Hz/

13C NMR



157

Current Data Parameters

NAME	NC-I-88
EXPNO	4
PROCNO	1

F2 - Acquisition Parameters

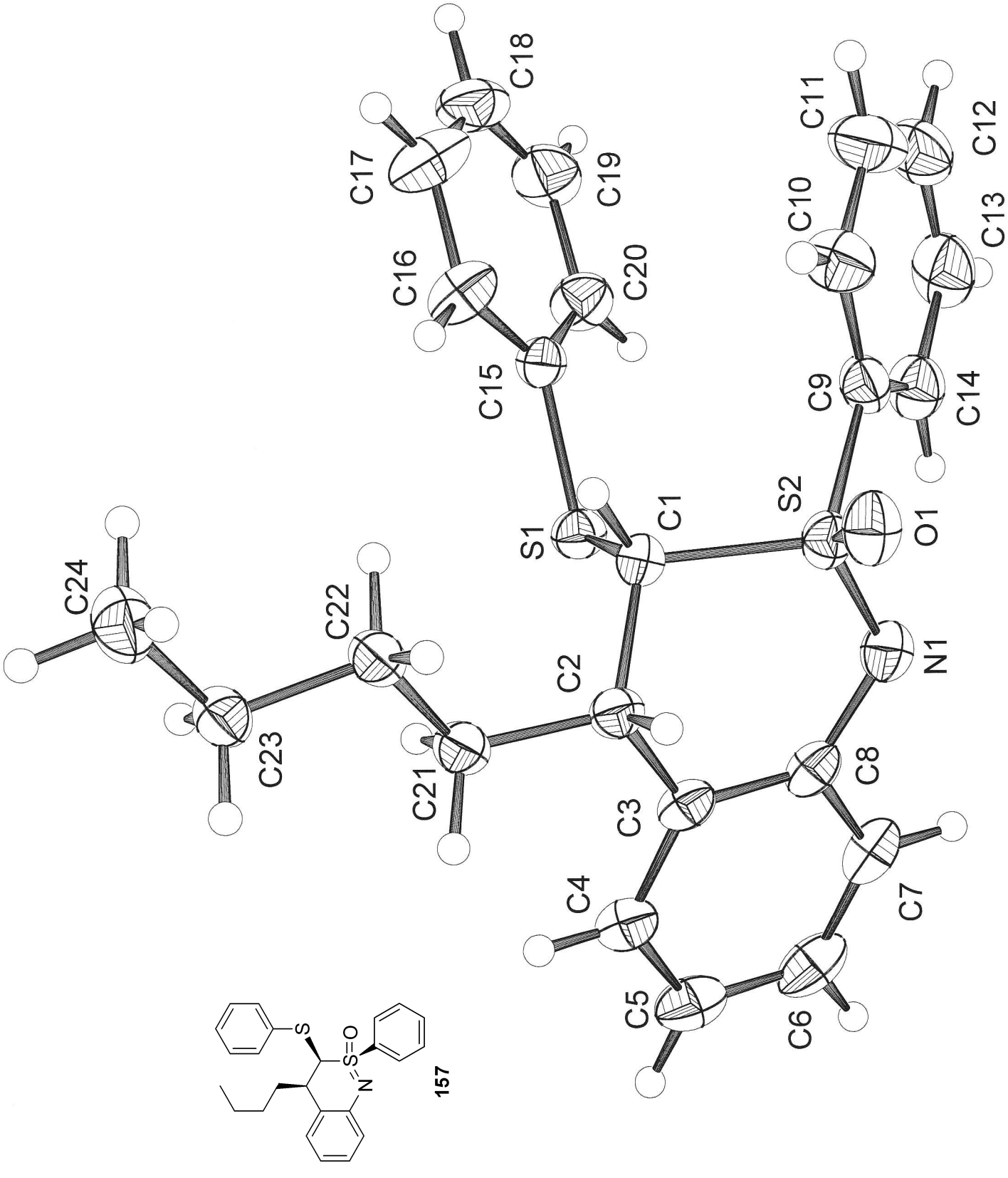
Date_	20050210
Time	10.21
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zgdc30
TD	36864
SOLVENT	CDCl3
NS	1320
DS	4
SWH	17241.379 Hz
FIDRES	0.467702 Hz
AQ	1.0691060 sec
RG	22800
DW	29.000 use
DE	41.43 use
TE	300.0 K
D12	0.00002000 sec
DL5	23.00 dB
CPDPRG	waltz16
P31	103.00 use
D1	1.00000000 sec
P1	6.00 use
SF01	62.9023694 MHz
NUCLEUS	13C
D11	0.03000000 sec

F2 - Processing parameters

SI	32768
SF	62.8952403 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

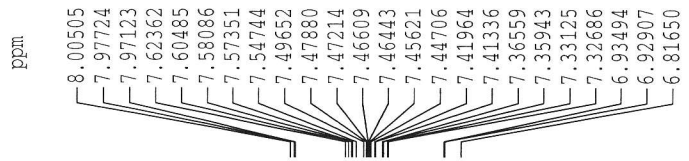
CX	20.00 cm
CY	30.00 cm
F1P	220.000 ppm
F1	13836.95 Hz
F2P	-10.000 ppm
F2	-628.95 Hz
PPMCM	11.50000 ppm
HZCM	723.29529 Hz/

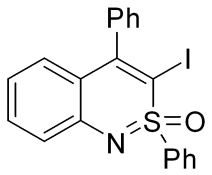

C24
C22
C23
C21
C2
C3
C4
C5
C6
C7
C8
N1
S1
C1
S2
O1
C9
C10
C11
C12
C13
C14
C15
C16
C17
C18
C19
C20

S
S=O
N

157

1H NMR





161d

Current Data Parameters

NAME	NC-VI-16A
EXPNO	6
PROCNO	1

F2 - Acquisition Parameters

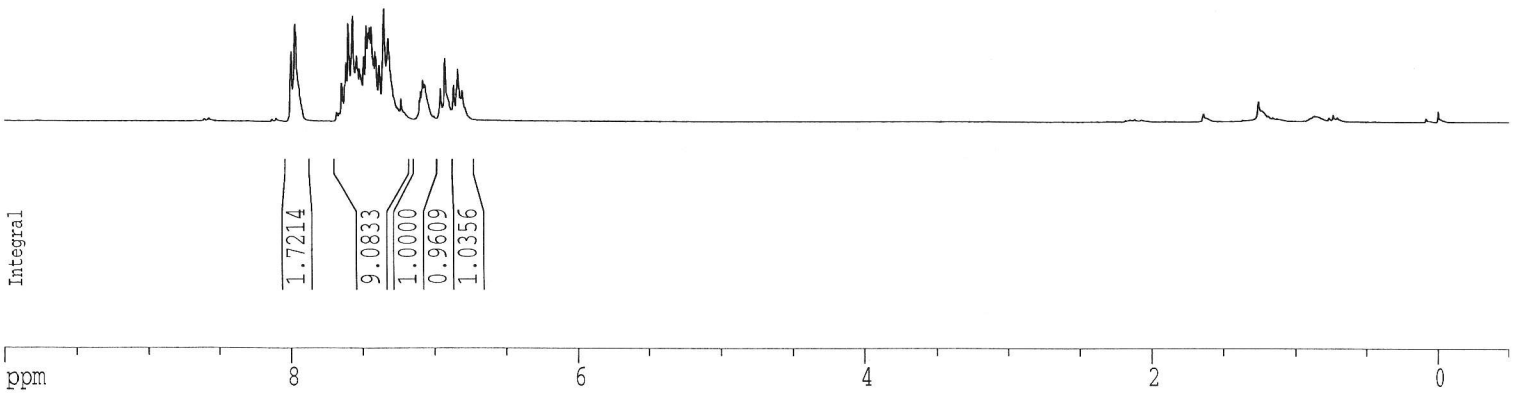
Date_	20091231
Time	2.04
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	5208.333 Hz
FIDRES	0.158946 Hz
AQ	3.1457779 sec
RG	512
DW	96.000 usec
DE	137.14 usec
TE	300.0 K
D1	1.00000000 sec
P1	8.50 usec
SFO1	250.1315321 MHz
NUCLEUS	1H

F2 - Processing parameters

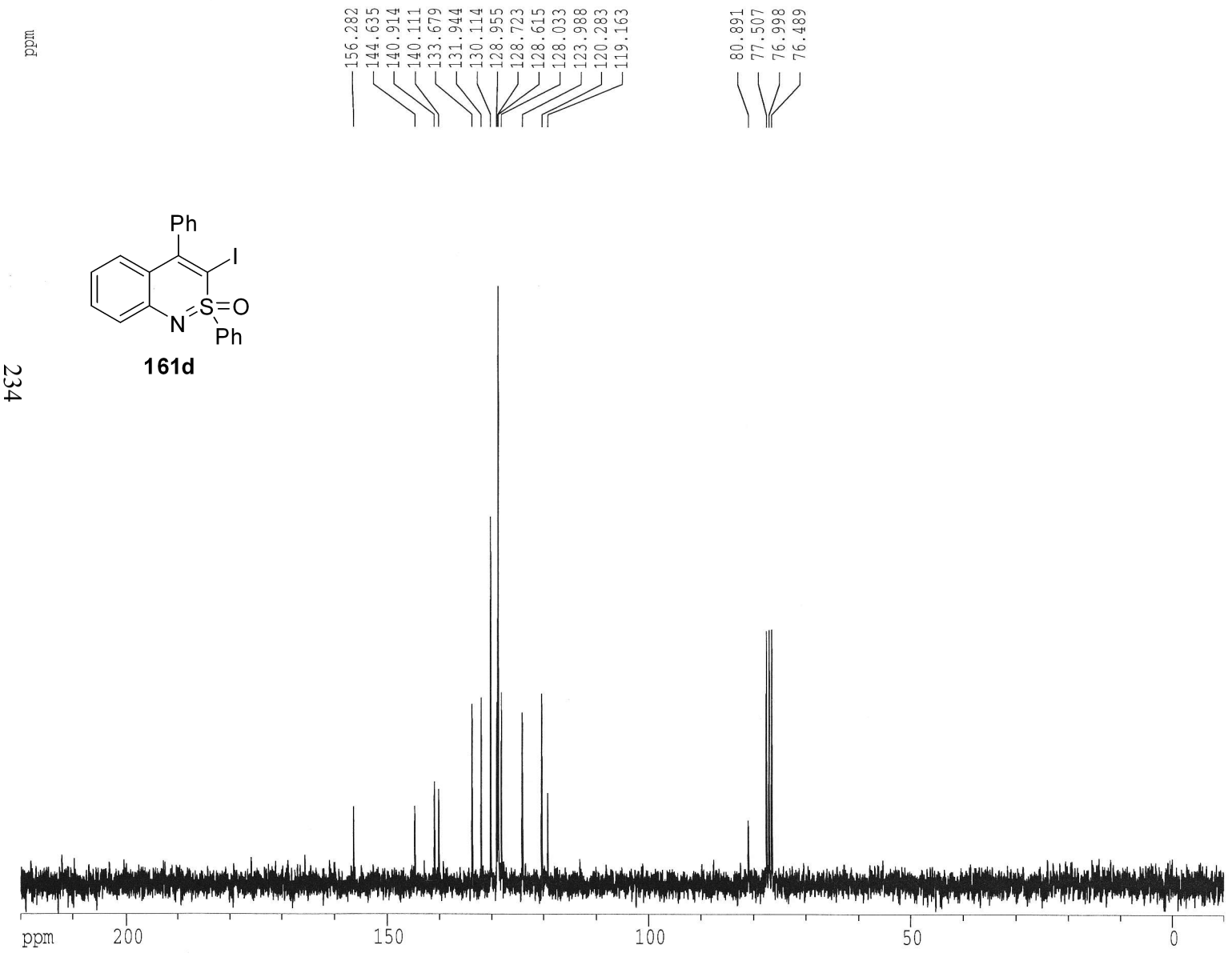
SI	16384
SF	250.1300122 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.50

1D NMR plot parameters

CX	20.00 cm
CY	1.50 cm
F1P	10.000 ppm
F1	2501.30 Hz
F2P	-0.500 ppm
F2	-125.07 Hz
PPMCM	0.52500 ppm/cm
HZCM	131.31825 Hz/cm



13C NMR



Current Data Parameters

NAME	NC-VI-16A
EXPNO	7
PROCNO	1

F2 - Acquisition Parameters

Date_	20091231
Time	2.09
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zgdc30
TD	36864
SOLVENT	CDCl3
NS	72
DS	4
SWH	17241.379 Hz
FIDRES	0.467702 Hz
AQ	1.0691060 sec
RG	22800
DW	29.000 usec
DE	41.43 usec
TE	300.0 K
D12	0.00002000 sec
DL5	23.00 dB
CPDPRG	waltz16
P31	103.00 usec
D1	2.00000000 sec
P1	6.25 usec
SFO1	62.9023694 MHz
NUCLEUS	13C
D11	0.03000000 sec

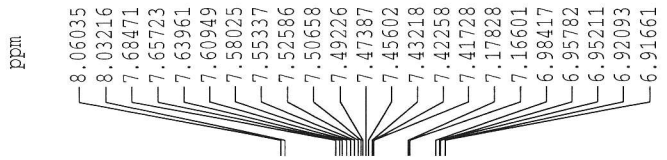
F2 - Processing parameters

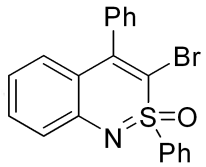
SI	32768
SF	62.8952466 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

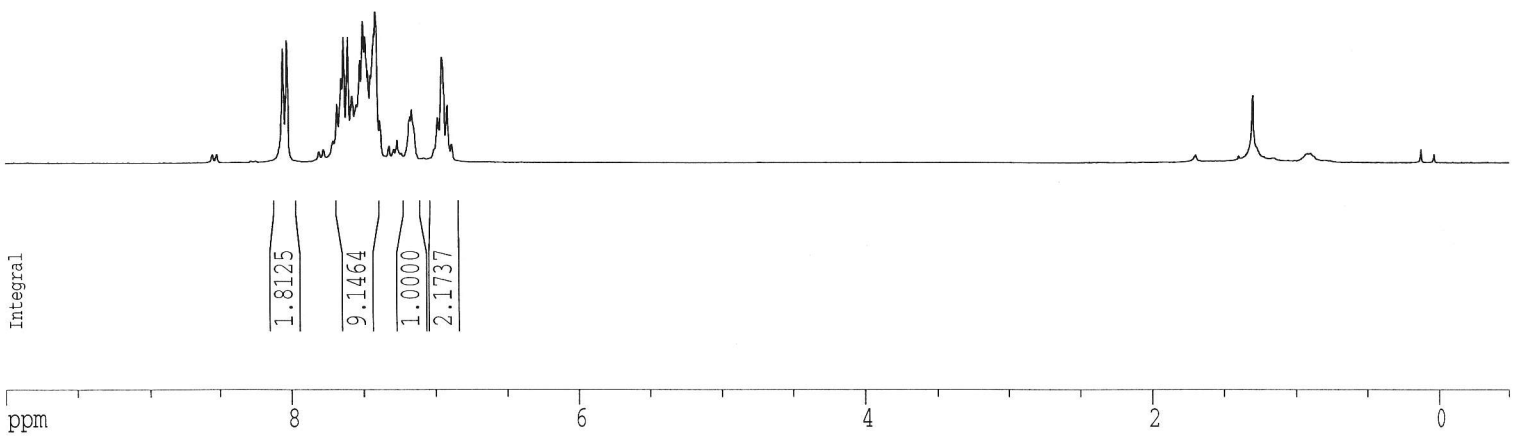
CX	20.00 cm
CY	10.00 cm
F1P	220.000 ppm
F1	13836.95 Hz
F2P	-10.000 ppm
F2	-628.95 Hz
PPMCM	11.50000 ppm/cm
HZCM	723.29535 Hz/cm

1H NMR





161e



Current Data Parameters

NAME	NC-VI-36A
EXPNO	6
PROCNO	1

F2 - Acquisition Parameters

Date_	20091231
Time	2.15
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	5208.333 Hz
FIDRES	0.158946 Hz
AQ	3.1457779 sec
RG	512
DW	96.000 usec
DE	137.14 usec
TE	300.0 K
D1	1.00000000 sec
P1	8.50 usec
SFO1	250.1315321 MHz
NUCLEUS	1H

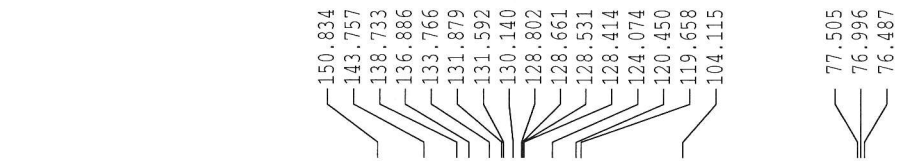
F2 - Processing parameters

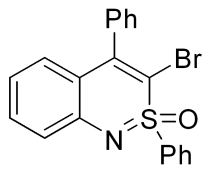
SI	16384
SF	250.1300049 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.50

1D NMR plot parameters

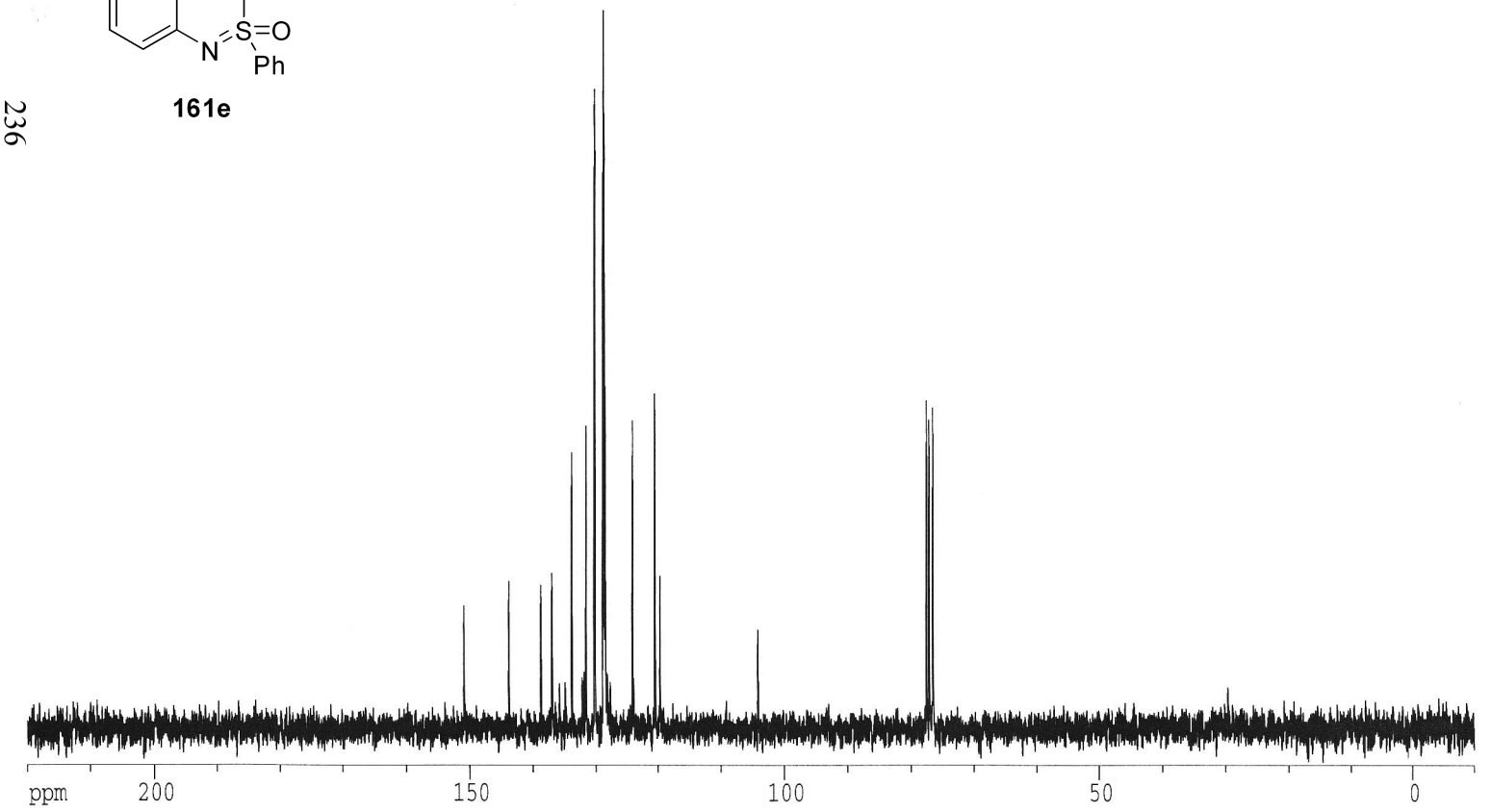
CX	20.00 cm
CY	2.00 cm
F1P	10.000 ppm
F1	2501.30 Hz
F2P	-0.500 ppm
F2	-125.07 Hz
PPMCM	0.52500 ppm/cm
HZCM	131.31825 Hz/cm

13C NMR





161e



Current Data Parameters

NAME	NC-VI-36A
EXPNO	7
PROCNO	1

F2 - Acquisition Parameters

Date_	20091231
Time	2.19
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zgdc30
TD	36864
SOLVENT	CDCl3
NS	76
DS	4
SWH	17241.379 Hz
FIDRES	0.467702 Hz
AQ	1.0691060 sec
RG	22800
DW	29.000 usec
DE	41.43 usec
TE	300.0 K
D12	0.00002000 sec
DL5	23.00 dB
CPDPRG	waltz16
P31	103.00 usec
D1	2.00000000 sec
P1	6.25 usec
SFO1	62.9023694 MHz
NUCLEUS	13C
D11	0.03000000 sec

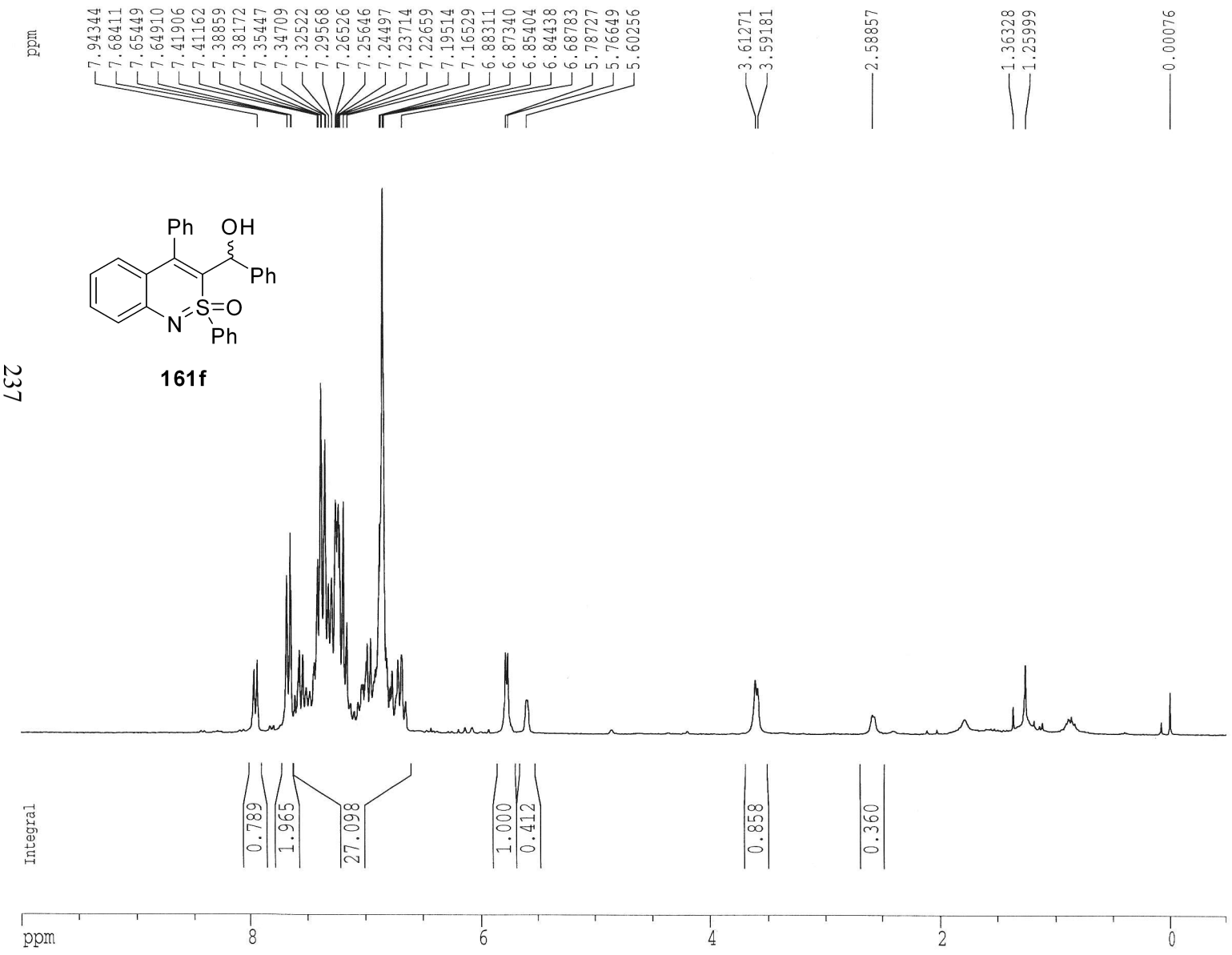
F2 - Processing parameters

SI	32768
SF	62.8952487 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	220.000 ppm
F1	13836.95 Hz
F2P	-10.000 ppm
F2	-628.95 Hz
PPMCM	11.50000 ppm/cm
HZCM	723.29535 Hz/cm

1H NMR



Current Data Parameters

NAME	NC-IV-49B
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20091223
Time	10.45
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	5208.333 Hz
FIDRES	0.158946 Hz
AQ	3.1457779 sec
RG	512
DW	96.000 usec
DE	137.14 usec
TE	300.0 K
D1	1.00000000 sec
P1	8.50 usec
SFO1	250.1315321 MHz
NUCLEUS	1H

F2 - Processing parameters

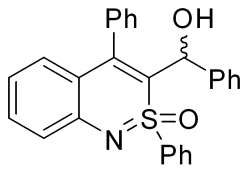
SI	16384
SF	250.1300132 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.50

1D NMR plot parameters

CX	20.00 cm
CY	9.00 cm
F1P	10.000 ppm
F1	2501.30 Hz
F2P	-0.500 ppm
F2	-125.07 Hz
PPMCM	0.52500 ppm/cm
HZCM	131.31827 Hz/cm

13C NMR

148.560
144.566
140.708
139.785
135.457
132.943
131.488
130.365
129.636
129.169
128.825
128.573
128.471
128.398
128.320
128.129
127.811
127.571
127.528
126.347
125.443
124.799
124.140
120.095
118.738
77.509
77.001
76.492
70.852
70.642



161f

Current Data Parameters

NAME	NC-IV-49B
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

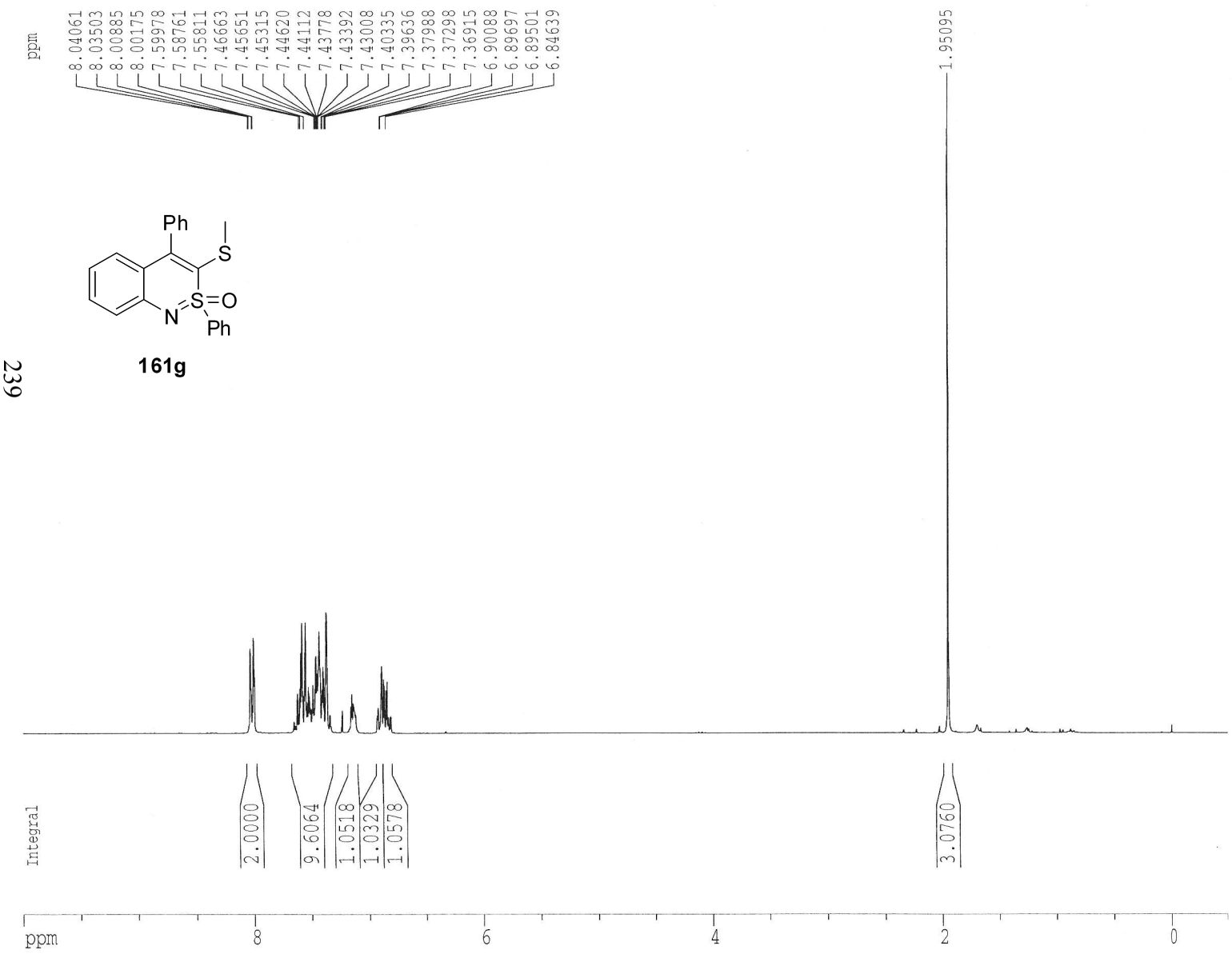
Date_	20091223
Time	10.56
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zgdc30
TD	36864
SOLVENT	CDCl3
NS	203
DS	4
SWH	17241.379 Hz
FIDRES	0.467702 Hz
AQ	1.0691060 sec
RG	22800
DW	29.000 usec
DE	41.43 usec
TE	300.0 K
D12	0.00002000 sec
DL5	23.00 dB
CPDPRG	waltz16
P31	103.00 usec
D1	2.00000000 sec
P1	6.25 usec
SFO1	62.9023694 MHz
NUCLEUS	13C
D11	0.03000000 sec

F2 - Processing parameters

SI	32768
SF	62.8952455 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	220.000 ppm
F1	13836.95 Hz
F2P	-10.000 ppm
F2	-628.95 Hz
PPMCM	11.50000 ppm/cm
HZCM	723.29529 Hz/cm



161g

239

Current Data Parameters

NAME	NC-VI-37A
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20070801
Time	12.36
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	5208.333 Hz
FIDRES	0.158946 Hz
AQ	3.1457779 sec
RG	360
DW	96.000 usec
DE	137.14 usec
TE	300.0 K
D1	1.00000000 sec
P1	9.50 usec
SFO1	250.1315321 MHz
NUCLEUS	1H

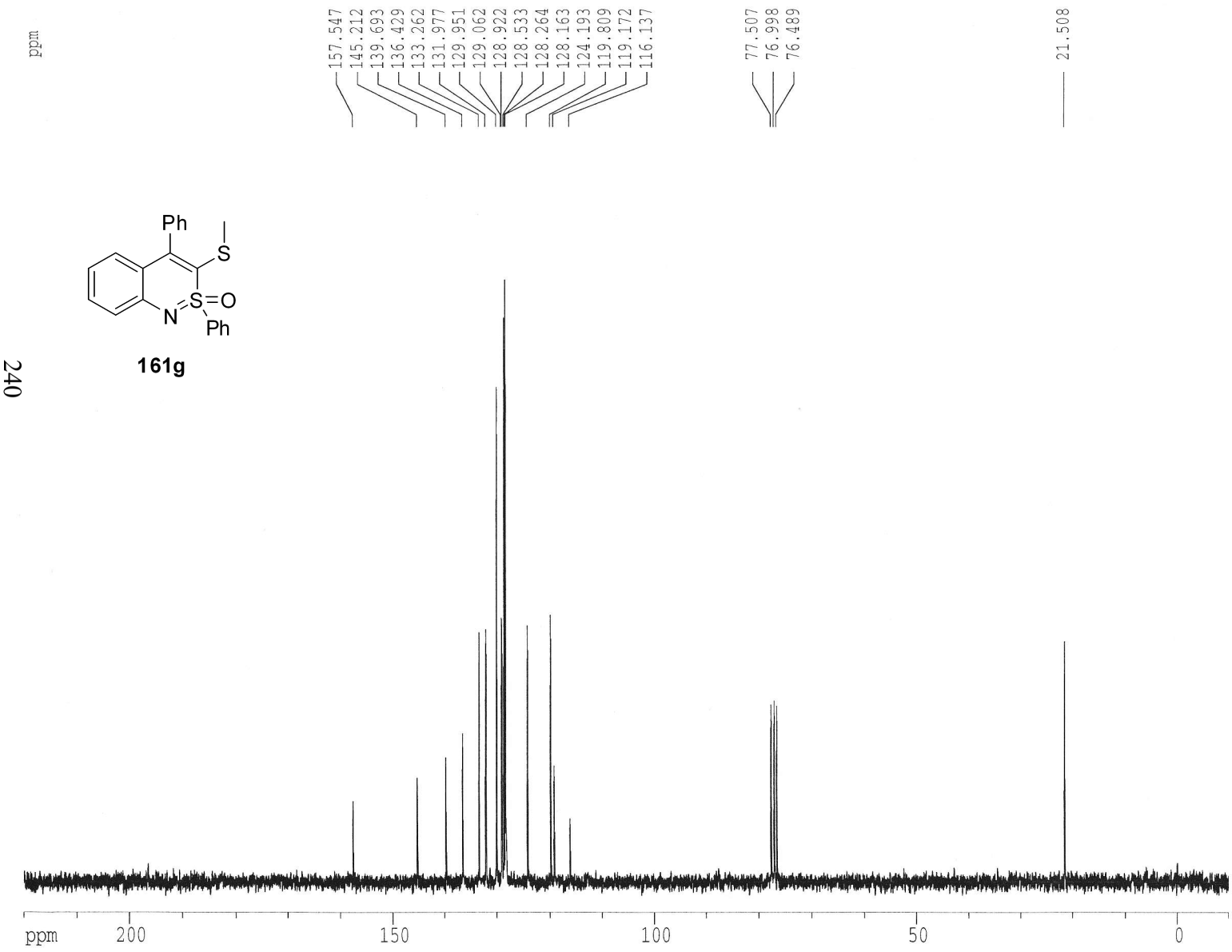
F2 - Processing parameters

SI	16384
SF	250.1300129 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.50

1D NMR plot parameters

CX	20.00 cm
CY	12.50 cm
F1P	10.000 ppm
F1	2501.30 Hz
F2P	-0.500 ppm
F2	-125.07 Hz
PPMCM	0.52500 ppm/cm
HZCM	131.31827 Hz/cm

13C NMR



Current Data Parameters

NAME	NC-VI-37A
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20070801	
Time	12.41	
INSTRUM	arx250	
PROBHD	5 mm QNP 1H	
PULPROG	zgdc30	
TD	36864	
SOLVENT	CDCl3	
NS	88	
DS	4	
SWH	17241.379	Hz
FIDRES	0.467702	Hz
AQ	1.0691060	sec
RG	22800	
DW	29.000	usec
DE	41.43	usec
TE	300.0	K
D12	0.00002000	sec
DL5	23.00	dB
CPDPRG	waltz16	
P31	103.00	usec
D1	2.00000000	sec
P1	8.00	usec
SFO1	62.9023694	MHz
NUCLEUS	13C	
D11	0.03000000	sec

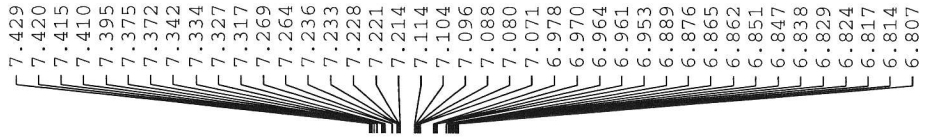
F2 - Processing parameters

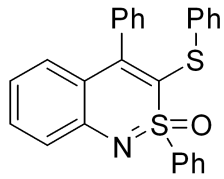
SI	32768	
SF	62.8952482	MHz
WDW	EM	
SSB	0	
LB	1.00	Hz
GB	0	
PC	1.40	

1D NMR plot parameters

CX	20.00	cm
CY	10.00	cm
F1P	220.000	ppm
F1	13836.95	Hz
F2P	-10.000	ppm
F2	-628.95	Hz
PPMCM	11.50000	ppm/cm
HZCM	723.29535	Hz/cm

1H NMR





161h

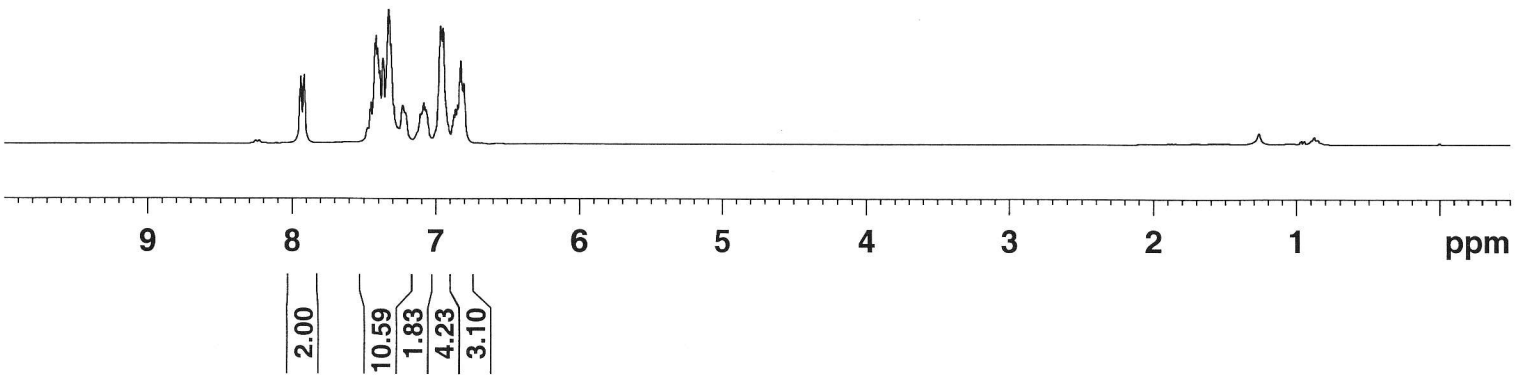
241

Current Data Parameters
NAME NC-VI-33B
EXPNO 1
PROCNO 1

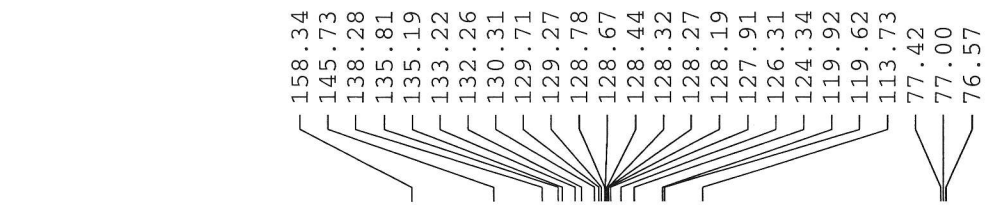
F2 - Acquisition Parameters
Date_ 20071018
Time 11.18
INSTRUM DRX300
PROBHD 5 mm Multinucl
PULPROG zg30pad
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 6172.839 Hz
FIDRES 0.188380 Hz
AQ 2.6542580 sec
RG 57
DW 81.000 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
D31 0.00000000 sec

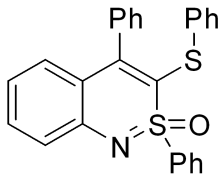
======== CHANNEL f1 ========
NUC1 1H
P1 7.05 usec
PL1 0.00 dB
SFO1 300.1318534 MHz

F2 - Processing parameters
SI 32768
SF 300.1300216 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.30



13C NMR





161h


```
Current Data Parameters
NAME                 NC-VI-33B
EXPNO                        2
PROCNO                       1

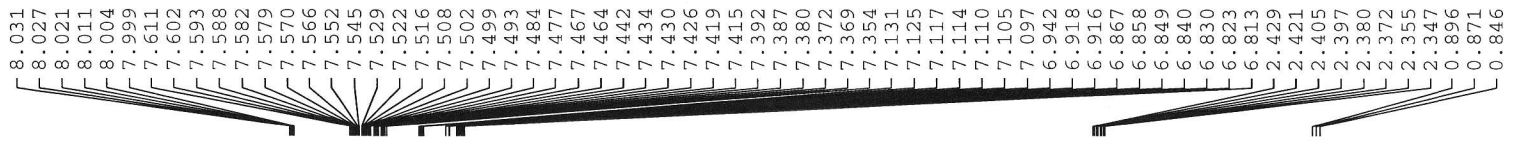
F2 - Acquisition Parameters
Date_                 20071018
Time                     11.28
INSTRUM                DRX300
PROBHD   5 mm Multinucl
PULPROG              zgdc30pad
TD                       65536
SOLVENT                  CDCl3
NS                          17
DS                           4
SWH                  18832.393 Hz
FIDRES                0.287360 Hz
AQ                    1.7400308 sec
RG                       22528
DW                      26.550 usec
DE                       6.00 usec
TE                      300.0 K
D1                   2.00000000 sec
D11                  0.03000000 sec
D31                  0.00000000 sec

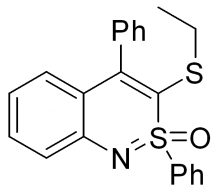
======== CHANNEL f1 ========
NUC1                       13C
P1                        9.00 usec
PL1                       5.00 dB
SFO1                75.4760107 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                       1H
PCPD2                   100.00 usec
PL2                     120.00 dB
PL12                     21.41 dB
SFO2               300.1312005 MHz

F2 - Processing parameters
SI                         32768
SF                  75.4677686 MHz
WDW                           EM
SSB                            0
LB                        1.00 Hz
GB                             0
PC                         1.40
```

1H NMR





161i

243

Current Data Parameters

NAME	NC-VI-50B
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

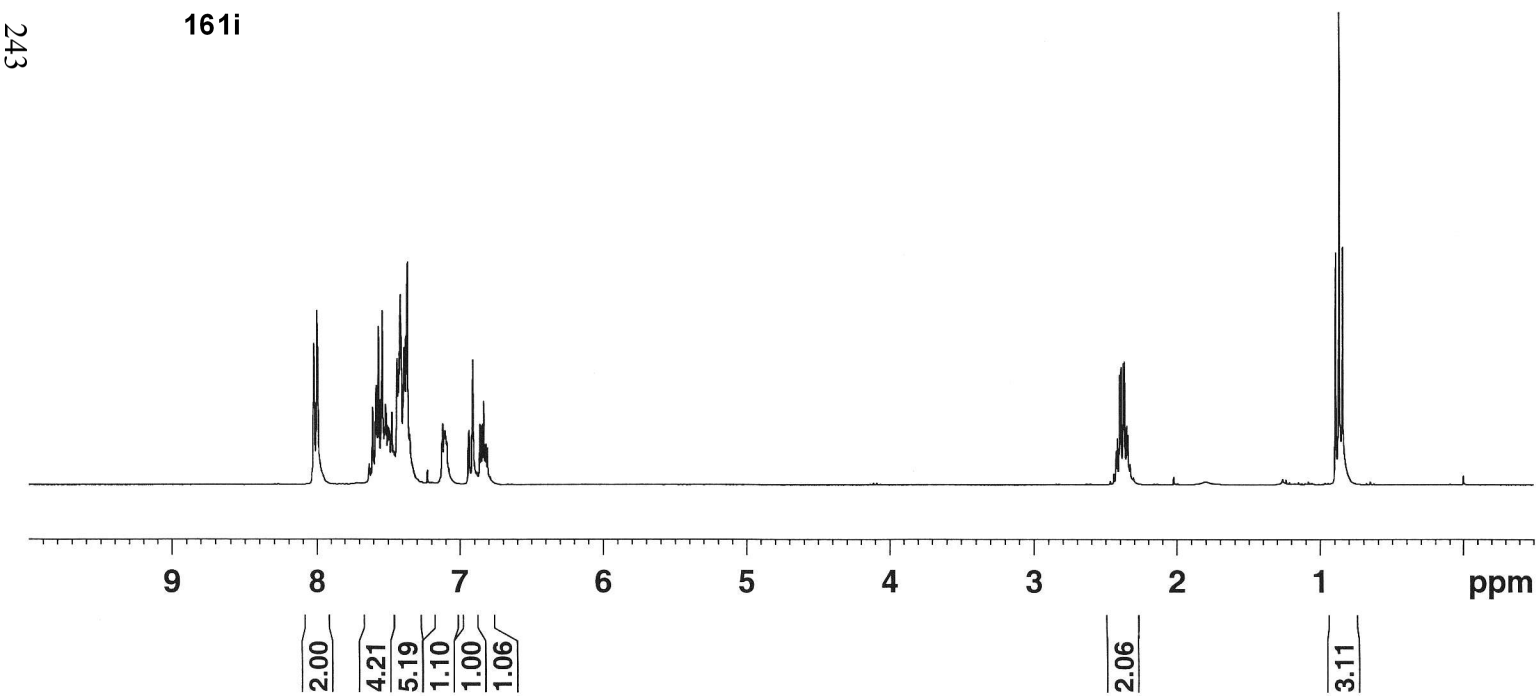
Date_	20071018
Time	11.45
INSTRUM	DRX300
PROBHD	5 mm Multinucl
PULPROG	zg30pad
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	6172.839 Hz
FIDRES	0.188380 Hz
AQ	2.6542580 sec
RG	64
DW	81.000 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec
D31	0.00000000 sec

======== CHANNEL f1 ========

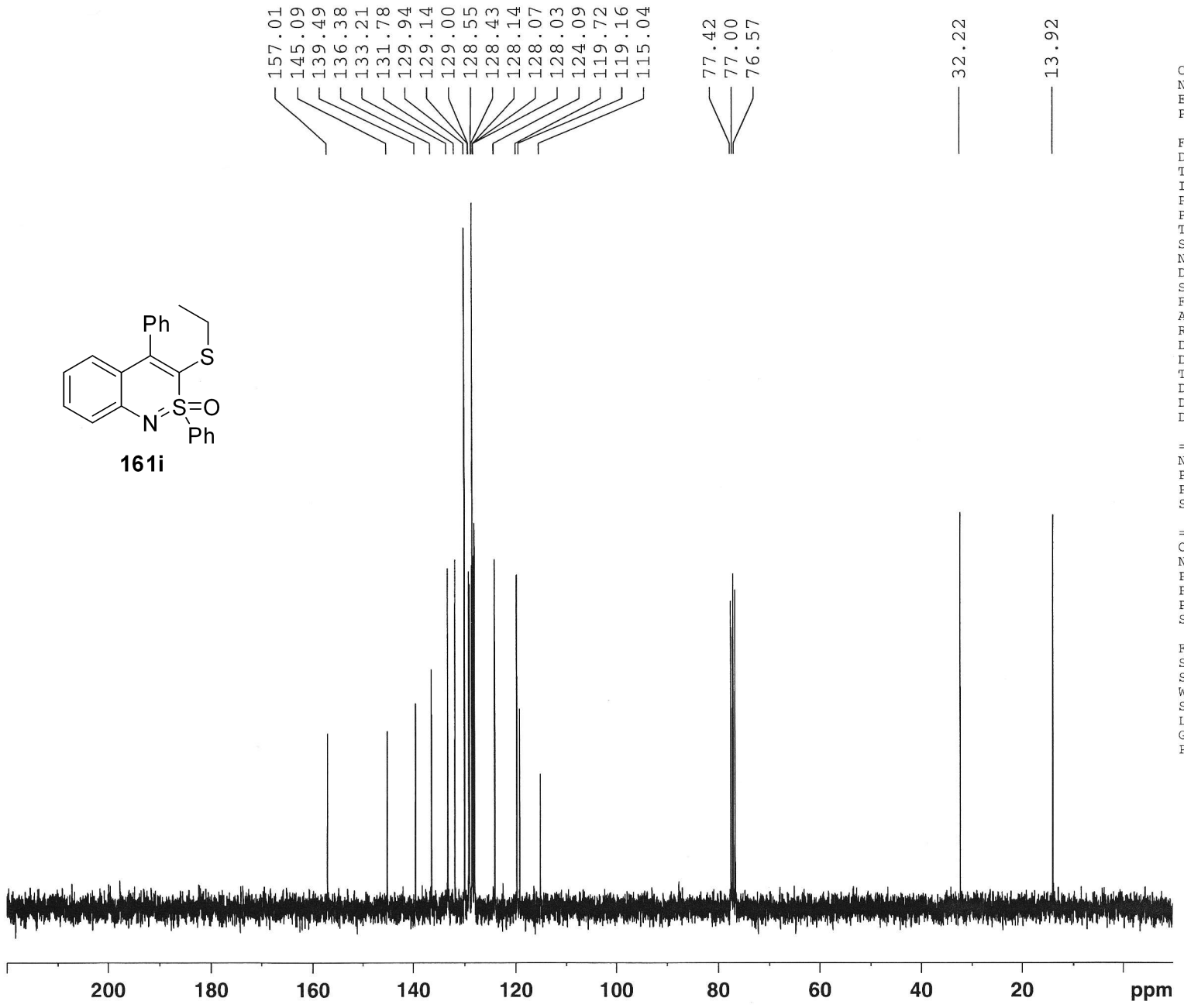
NUC1	1H
P1	7.05 usec
PL1	0.00 dB
SFO1	300.1318534 MHz

F2 - Processing parameters

SI	32768
SF	300.1300148 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.30



13C NMR



Current Data Parameters

NAME	NC-VI-50B
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20071018
Time	11.52
INSTRUM	DRX300
PROBHD	5 mm Multinucl
PULPROG	zgdc30pad
TD	65536
SOLVENT	CDCl3
NS	20
DS	4
SWH	18832.393 Hz
FIDRES	0.287360 Hz
AQ	1.7400308 sec
RG	22528
DW	26.550 usec
DE	6.00 usec
TE	300.0 K
D1	2.00000000 sec
D11	0.03000000 sec
D31	0.00000000 sec

======== CHANNEL f1 ========

NUC1	13C
P1	9.00 usec
PL1	5.00 dB
SFO1	75.4760107 MHz

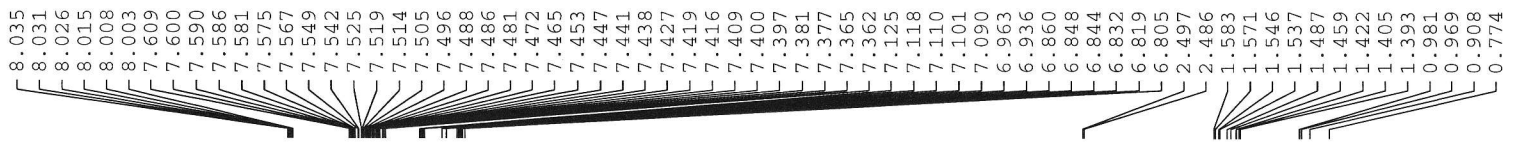
======== CHANNEL f2 ========

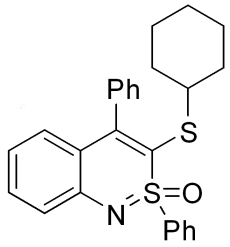
CPDPRG2	waltz16
NUC2	1H
PCPD2	100.00 usec
PL2	120.00 dB
PL12	21.41 dB
SFO2	300.1312005 MHz

F2 - Processing parameters

SI	32768
SF	75.4677657 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.30

1H NMR





161j

245

Current Data Parameters

NAME	NC-VI-52B
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

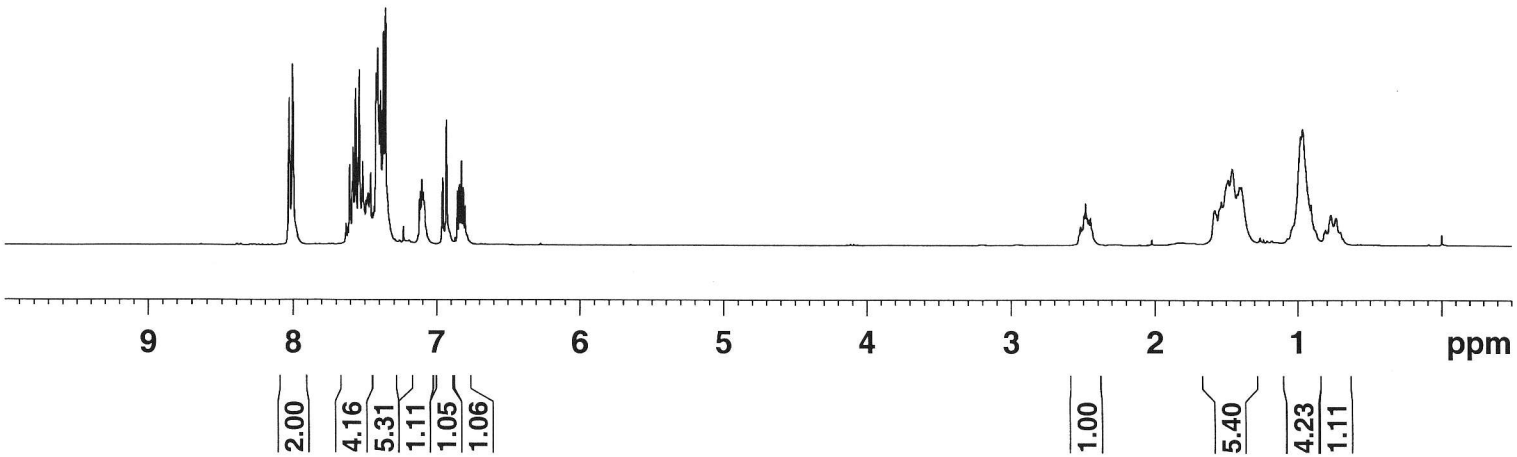
Date_	20071018
Time	12.11
INSTRUM	DRX300
PROBHD	5 mm Multinucl
PULPROG	zg30pad
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	6172.839 Hz
FIDRES	0.188380 Hz
AQ	2.6542580 sec
RG	50.8
DW	81.000 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec
D31	0.00000000 sec

======== CHANNEL f1 ========

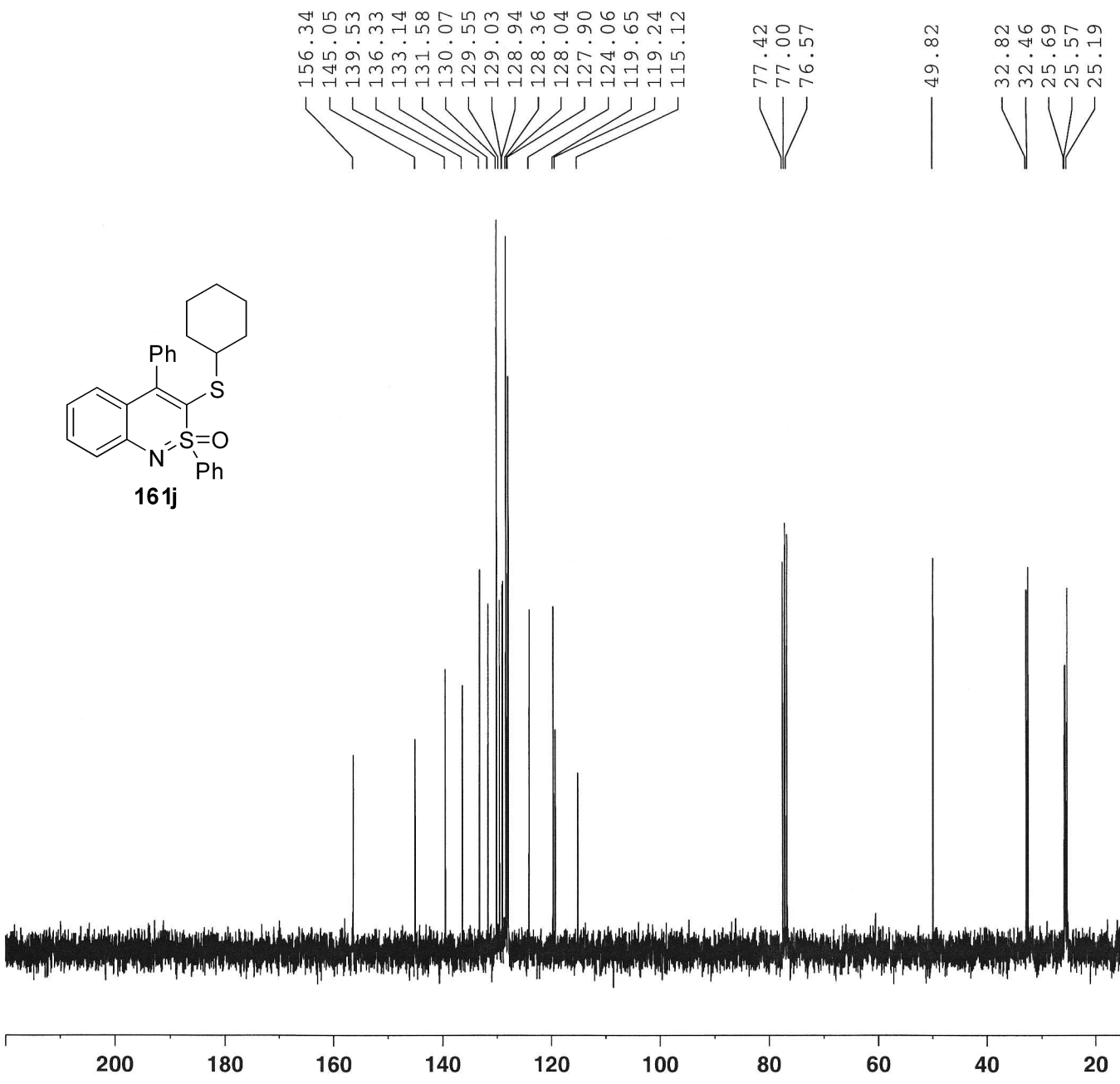
NUC1	1H
P1	7.05 usec
PL1	0.00 dB
SFO1	300.1318534 MHz

F2 - Processing parameters

SI	32768
SF	300.1300128 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.40



13C NMR

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Current Data Parameters
NAME                 NC-VI-52B
EXPNO                        2
PROCNO                       1

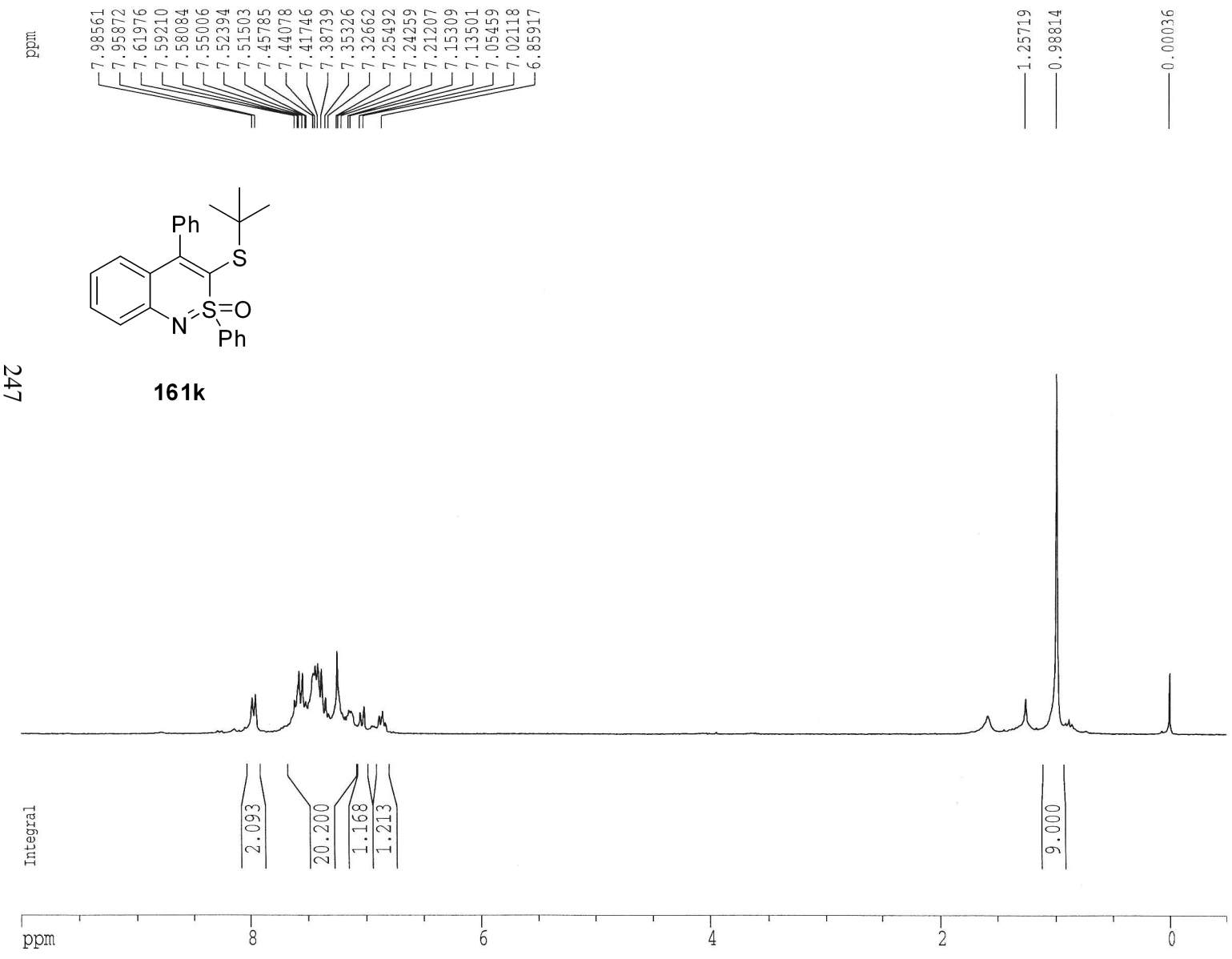
F2 - Acquisition Parameters
Date_                 20071018
Time                     12.16
INSTRUM                DRX300
PROBHD   5 mm Multinucl
PULPROG              zgdc30pad
TD                       65536
SOLVENT                  CDCl3
NS                          15
DS                           4
SWH                  18832.393 Hz
FIDRES                0.287360 Hz
AQ                    1.7400308 sec
RG                       22528
DW                      26.550 usec
DE                       6.00 usec
TE                      300.0 K
D1                    2.00000000 sec
D11                   0.03000000 sec
D31                   0.00000000 sec

======== CHANNEL f1 ========
NUC1                       13C
P1                        9.00 usec
PL1                       5.00 dB
SFO1                75.4760107 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                       1H
PCPD2                   100.00 usec
PL2                     120.00 dB
PL12                     21.41 dB
SFO2               300.1312005 MHz

F2 - Processing parameters
SI                       32768
SF                  75.4677657 MHz
WDW                         EM
SSB                          0
LB                        1.00 Hz
GB                           0
PC                        1.30
```

1H NMR



Current Data Parameters

NAME	NC-IV-17B
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20091223
Time	11.08
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	5208.333 Hz
FIDRES	0.158946 Hz
AQ	3.1457779 sec
RG	1430
DW	96.000 usec
DE	137.14 usec
TE	300.0 K
D1	1.00000000 sec
P1	8.50 usec
SFO1	250.1315321 MHz
NUCLEUS	1H

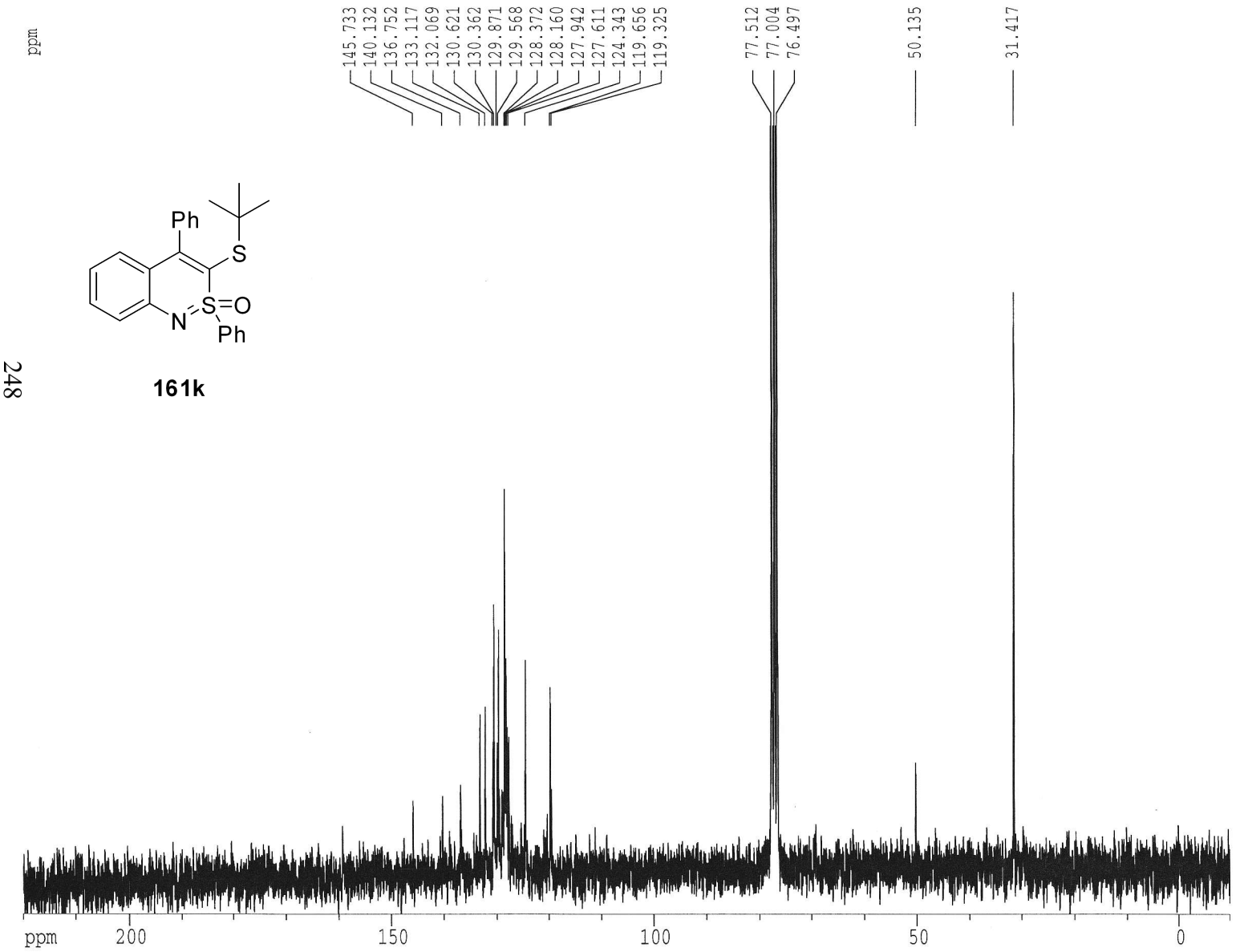
F2 - Processing parameters

SI	16384
SF	250.1300084 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.50

1D NMR plot parameters

CX	20.00 cm
CY	6.00 cm
F1P	10.000 ppm
F1	2501.30 Hz
F2P	-0.500 ppm
F2	-125.07 Hz
PPMCM	0.52500 ppm/cm
HZCM	131.31825 Hz/cm

13C NMR



161k

248

Current Data Parameters

NAME	NC-IV-17B
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

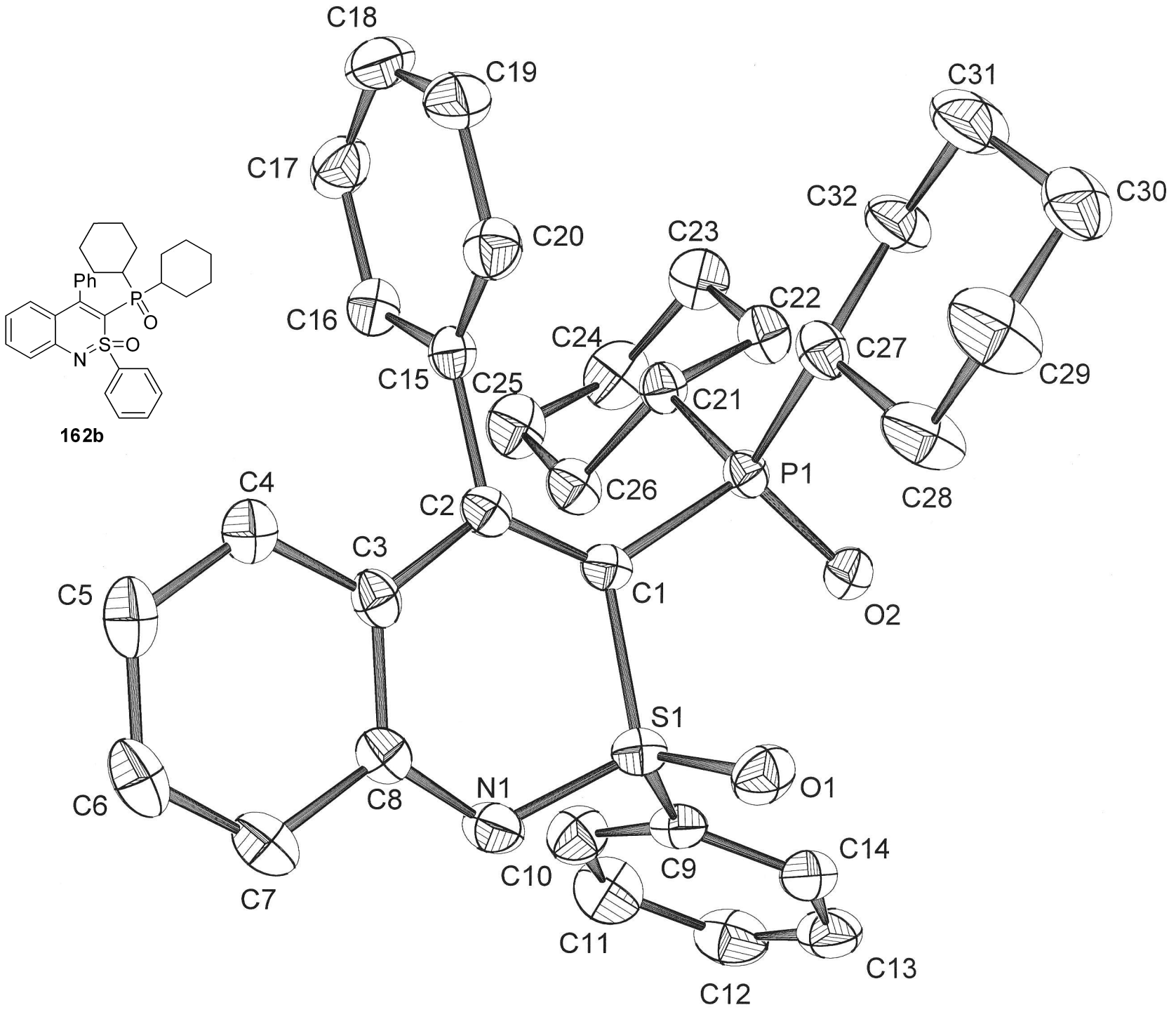
Date_	20091223
Time	11.49
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zgdc30
TD	36864
SOLVENT	CDCl3
NS	2039
DS	4
SWH	17241.379 Hz
FIDRES	0.467702 Hz
AQ	1.0691060 sec
RG	22800
DW	29.000 usec
DE	41.43 usec
TE	300.0 K
D12	0.00002000 sec
DL5	23.00 dB
CPDPRG	waltz16
P31	103.00 usec
D1	2.00000000 sec
P1	6.25 usec
SFO1	62.9023694 MHz
NUCLEUS	13C
D11	0.03000000 sec

F2 - Processing parameters

SI	32768
SF	62.8952408 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
CY	30.00 cm
F1P	220.000 ppm
F1	13836.95 Hz
F2P	-10.000 ppm
F2	-628.95 Hz
PPMCM	11.50000 ppm/cm
HZCM	723.29529 Hz/cm


C18
C19
C31
C17
C32
C30
C20
C23
C16
C22
C24
C27
C29
C15
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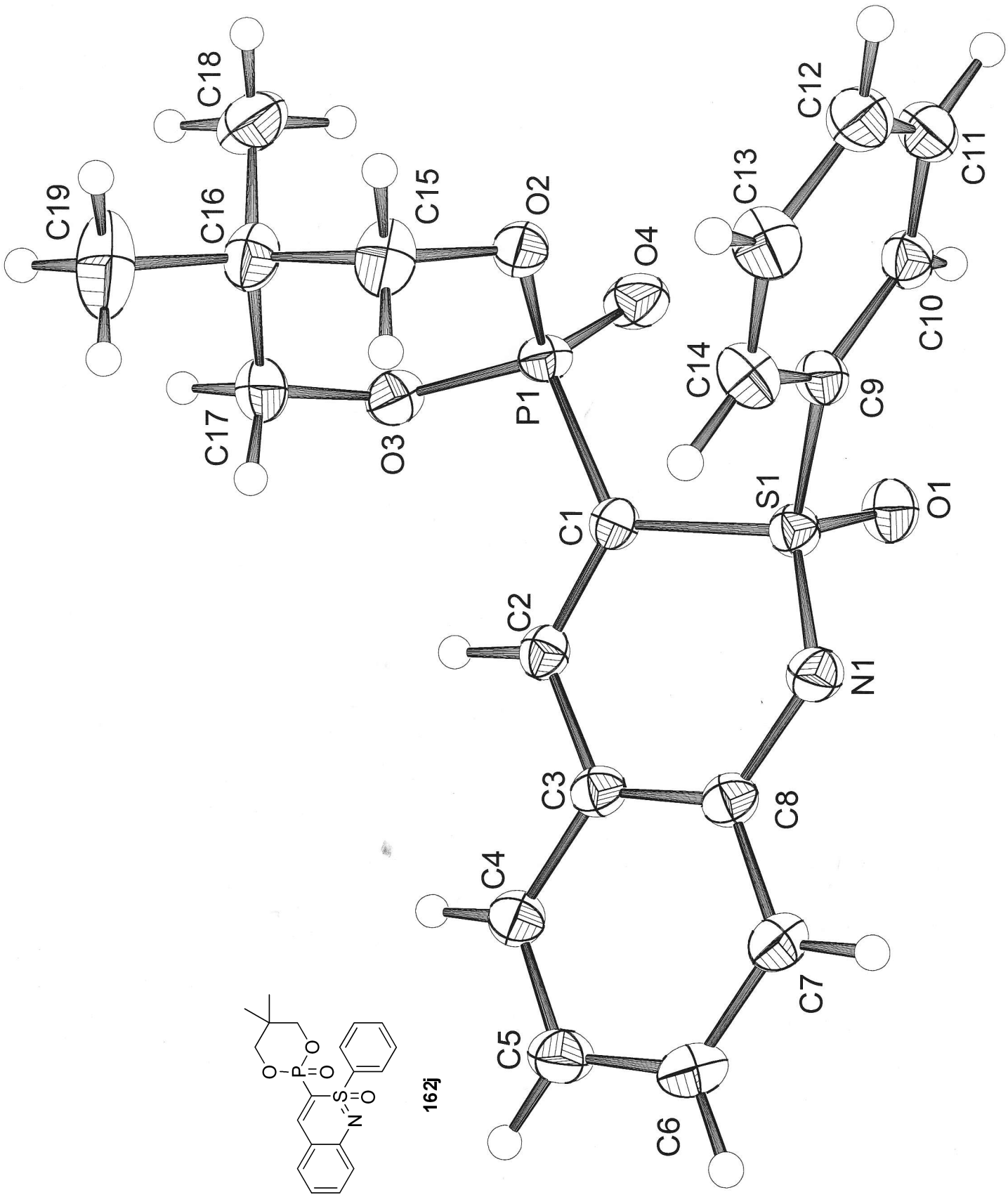
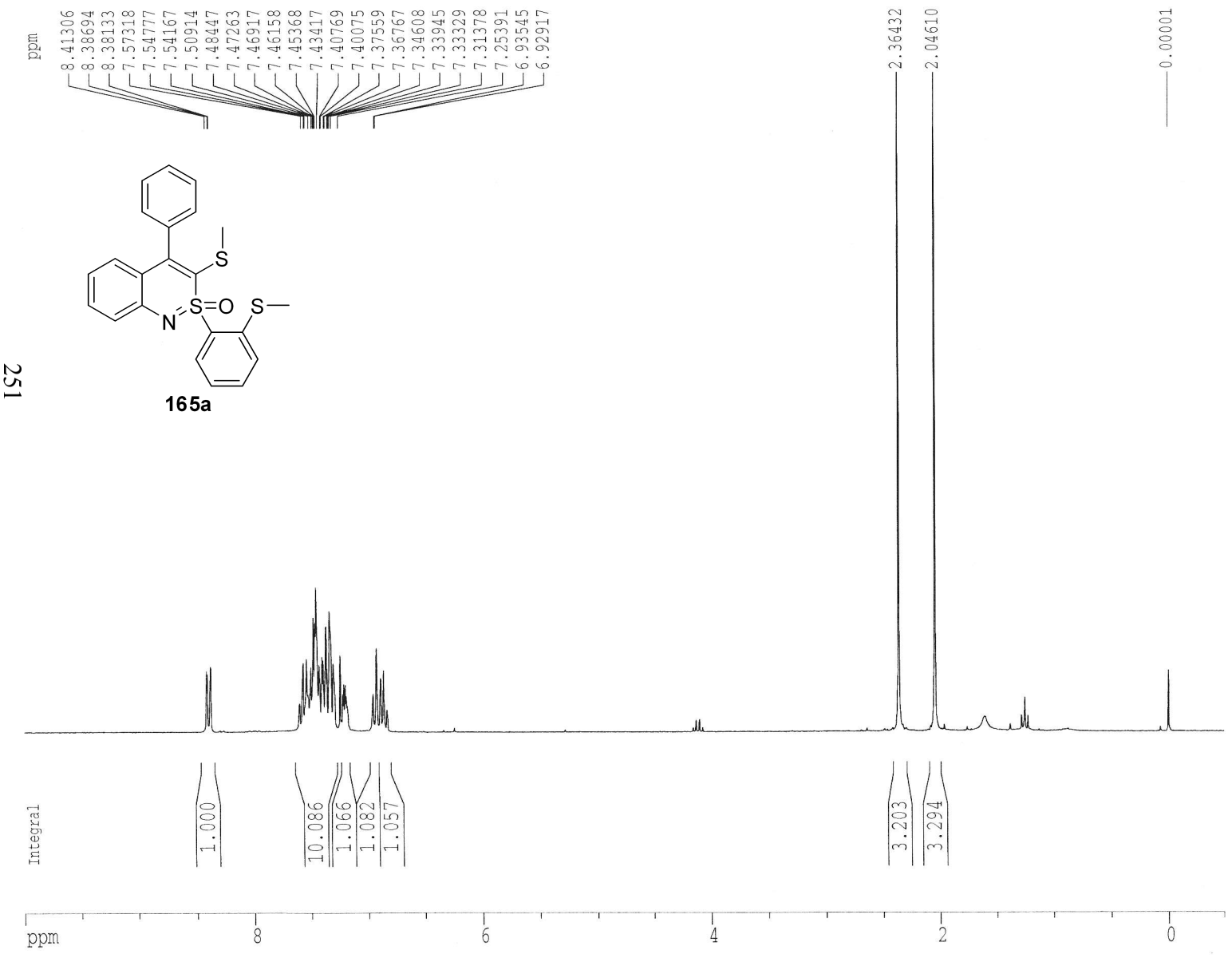
C21
C26
P1
C28
C4
C2
C3
C1
C5
O2
S1
O1
C6
C8
N1
C14
C10
C9
C7
C11
C13
C12
Ph
P
O
S=O
N
162b


C19
C16
C18
C15
O2
O4
C17
O3
P1
C1
S1
O1
C2
N1
C3
C8
C4
C7
C5
C6
C14
C9
C13
C12
C10
C11

162j

1H NMR



165a

251

Current Data Parameters

NAME	NC-VI-SMeB
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20070803
Time	11.27
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	5208.333 Hz
FIDRES	0.158946 Hz
AQ	3.1457779 sec
RG	715
DW	96.000 usec
DE	137.14 usec
TE	300.0 K
D1	1.00000000 sec
P1	9.50 usec
SFO1	250.1315321 MHz
NUCLEUS	1H

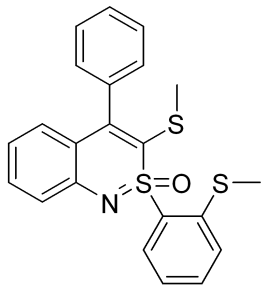
F2 - Processing parameters

SI	16384
SF	250.1300091 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.50

1D NMR plot parameters

CX	20.00 cm
CY	12.50 cm
F1P	10.000 ppm
F1	2501.30 Hz
F2P	-0.500 ppm
F2	-125.07 Hz
PPMCM	0.52500 ppm/cm
HZCM	131.31825 Hz/cm

13C NMR



165a

Current Data Parameters

NAME	NC-VI-SMeB
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

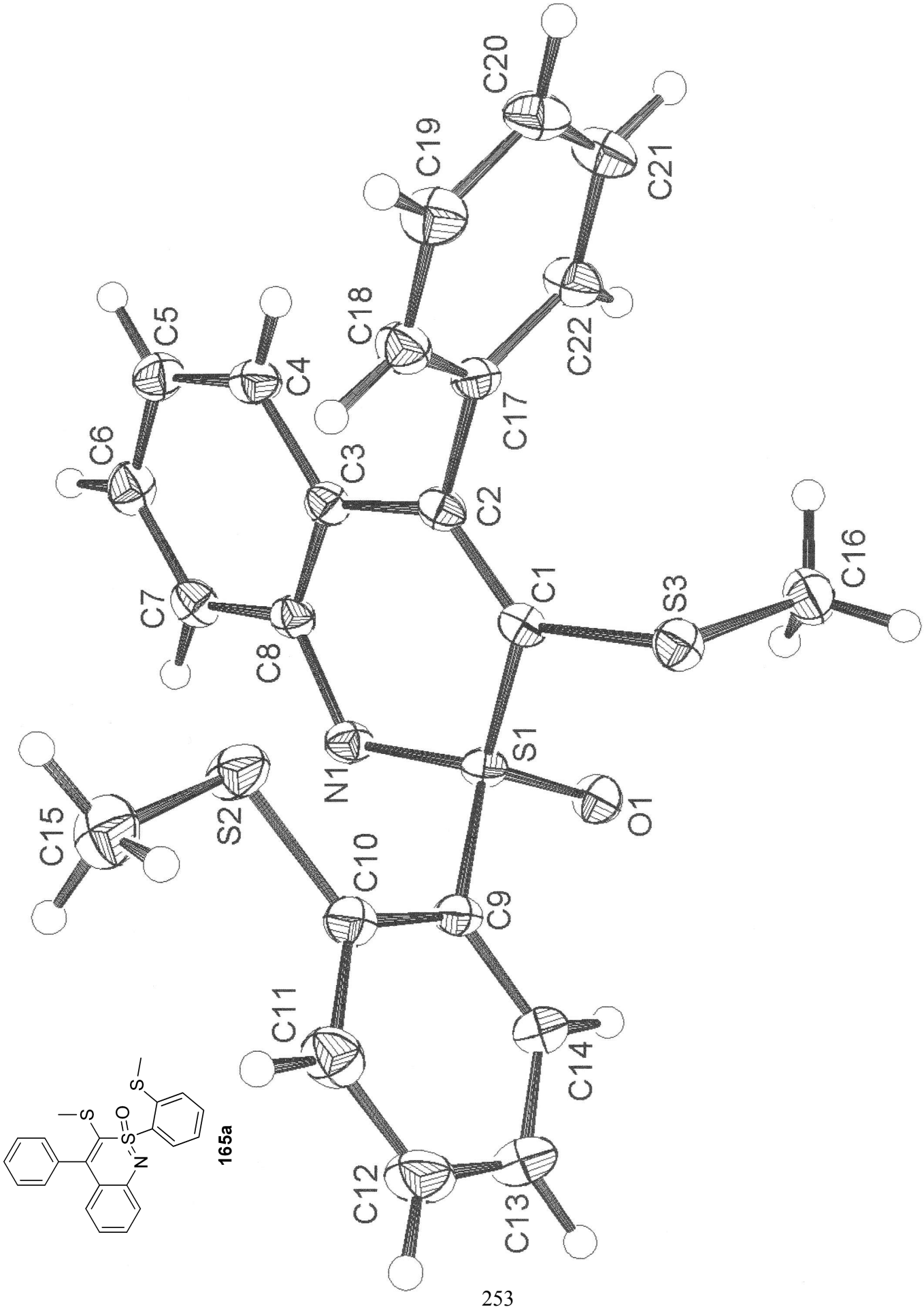
Date_	20070803
Time	11.32
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zgdc30
TD	36864
SOLVENT	CDCl3
NS	105
DS	4
SWH	17241.379 Hz
FIDRES	0.467702 Hz
AQ	1.0691060 sec
RG	22800
DW	29.000 usec
DE	41.43 usec
TE	300.0 K
D12	0.00002000 sec
DL5	23.00 dB
CPDPRG	waltz16
P31	103.00 usec
D1	2.00000000 sec
P1	8.00 usec
SFO1	62.9023694 MHz
NUCLEUS	13C
D11	0.03000000 sec

F2 - Processing parameters

SI	32768
SF	62.8952429 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

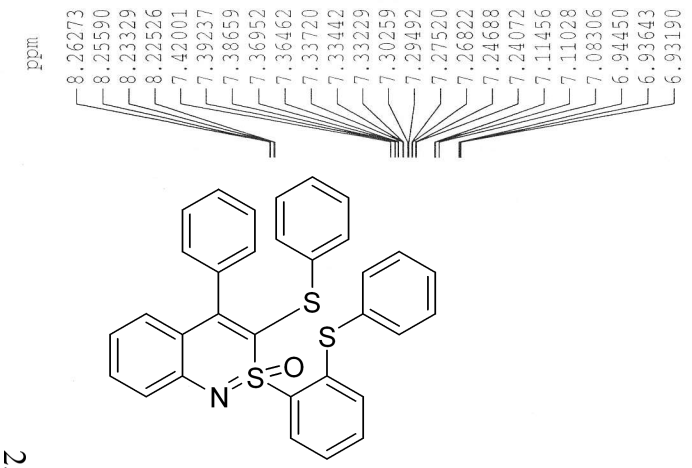
1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	220.000 ppm
F1	13836.95 Hz
F2P	-10.000 ppm
F2	-628.95 Hz
PPMCM	11.50000 ppm/cm
HZCM	723.29529 Hz/cm

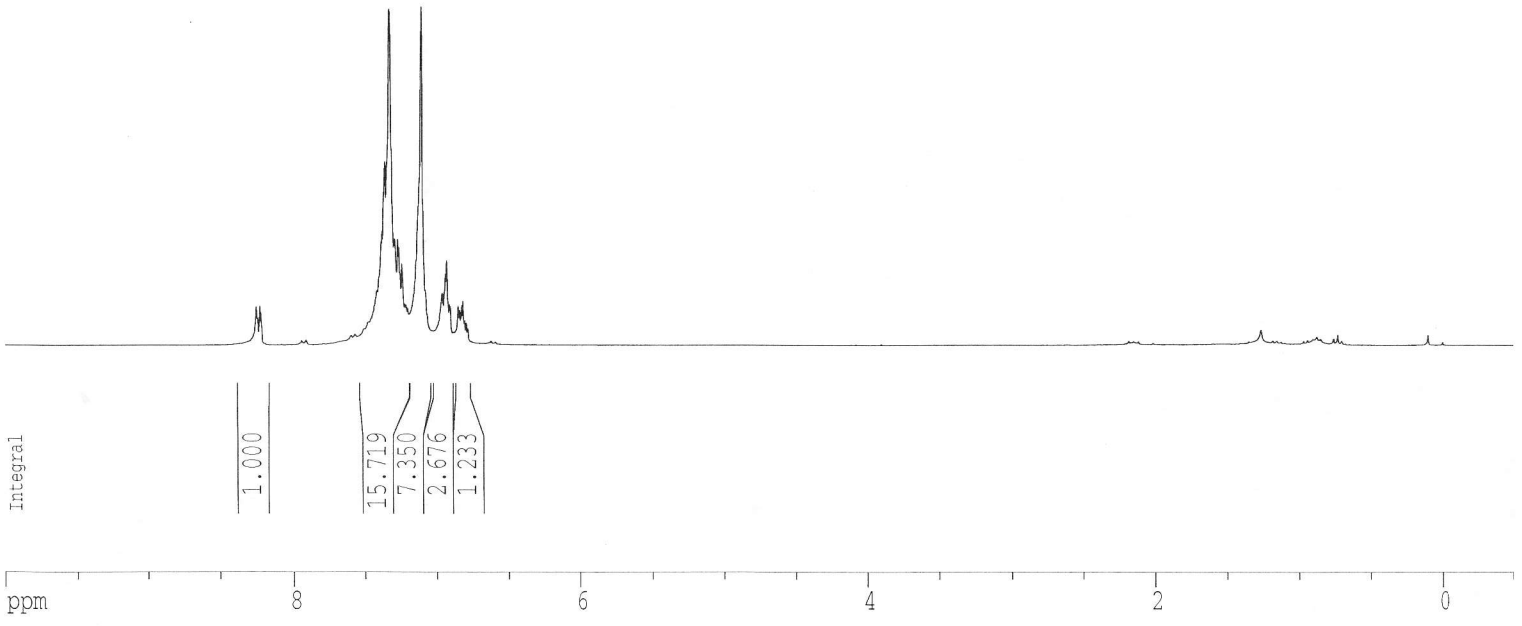

C20
C19
C21
C18
C22
C5
C4
C17
C6
C3
C2
C7
C1
S3
C16
C8
N1
S1
O1
C15
S2
C10
C9
C11
C14
C12
C13

165a

1H NMR



165b



Current Data Parameters

NAME	NC-VI-66B
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20071023
Time	15.28
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	5208.333 Hz
FIDRES	0.158946 Hz
AQ	3.1457779 sec
RG	256
DW	96.000 usec
DE	137.14 usec
TE	300.0 K
D1	1.00000000 sec
P1	9.50 usec
SFO1	250.1315321 MHz
NUCLEUS	1H

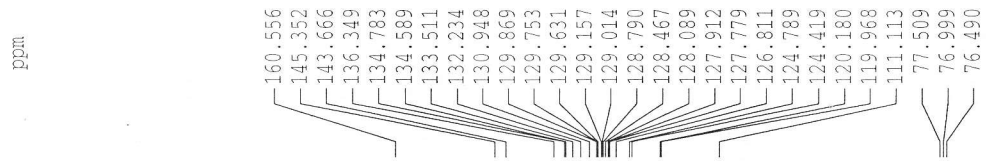
F2 - Processing parameters

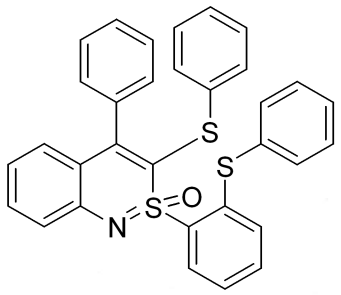
SI	16384
SF	250.1300208 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.50

1D NMR plot parameters

CX	20.00 cm
CY	4.50 cm
F1P	10.000 ppm
F1	2501.30 Hz
F2P	-0.500 ppm
F2	-125.07 Hz
PPMCM	0.52500 ppm/cm
HZCM	131.31827 Hz/cm

13C NMR





165b

Current Data Parameters

NAME	NC-VI-66B
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20071023
Time	15.34
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zgdc30
TD	36864
SOLVENT	CDCl3
NS	110
DS	4
SWH	17241.379 Hz
FIDRES	0.467702 Hz
AQ	1.0691060 sec
RG	22800
DW	29.000 usec
DE	41.43 usec
TE	300.0 K
D12	0.00002000 sec
DL5	23.00 dB
CPDPRG	waltz16
P31	103.00 usec
D1	2.00000000 sec
P1	8.00 usec
SFO1	62.9023694 MHz
NUCLEUS	13C
D11	0.03000000 sec

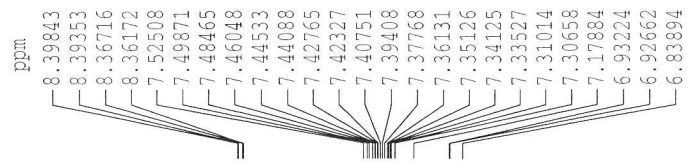
F2 - Processing parameters

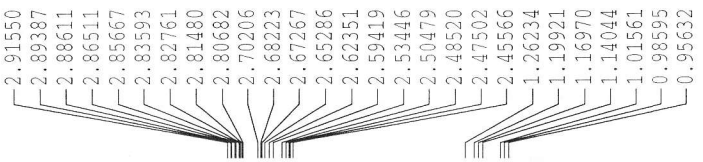
SI	32768
SF	62.8952529 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

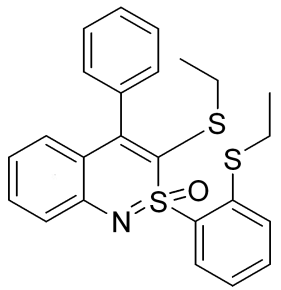
1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	220.000 ppm
F1	13836.95 Hz
F2P	-10.000 ppm
F2	-628.95 Hz
PPMCM	11.50000 ppm/cm
HZCM	723.29541 Hz/cm

1H NMR







165c

Current Data Parameters

NAME	NC-VI-68B
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20071023
Time	15.42
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	5208.333 Hz
FIDRES	0.158946 Hz
AQ	3.1457779 sec
RG	256
DW	96.000 usec
DE	137.14 usec
TE	300.0 K
D1	1.00000000 sec
P1	9.50 usec
SFO1	250.1315321 MHz
NUCLEUS	1H

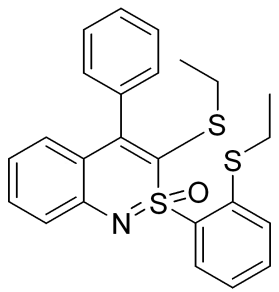
F2 - Processing parameters

SI	16384
SF	250.1300119 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.50

1D NMR plot parameters

CX	20.00 cm
CY	8.00 cm
F1P	10.000 ppm
F1	2501.30 Hz
F2P	-0.500 ppm
F2	-125.07 Hz
PPMCM	0.52500 ppm/cm
HZCM	131.31825 Hz/cm

13C NMR



165c

Current Data Parameters

NAME	NC-VI-68B
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20071023
Time	15.47
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zgdc30
TD	36864
SOLVENT	CDCl3
NS	49
DS	4
SWH	17241.379 Hz
FIDRES	0.467702 Hz
AQ	1.0691060 sec
RG	22800
DW	29.000 usec
DE	41.43 usec
TE	300.0 K
D12	0.00002000 sec
DL5	23.00 dB
CPDPRG	waltz16
P31	103.00 usec
D1	2.00000000 sec
P1	8.00 usec
SFO1	62.9023694 MHz
NUCLEUS	13C
D11	0.03000000 sec

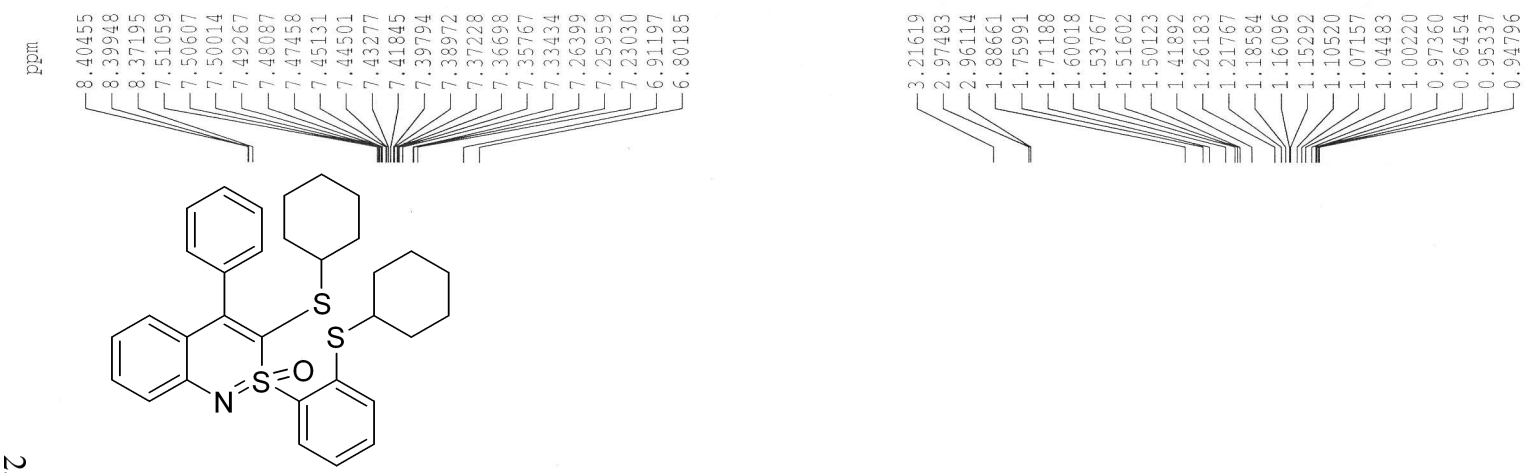
F2 - Processing parameters

SI	32768
SF	62.8952497 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

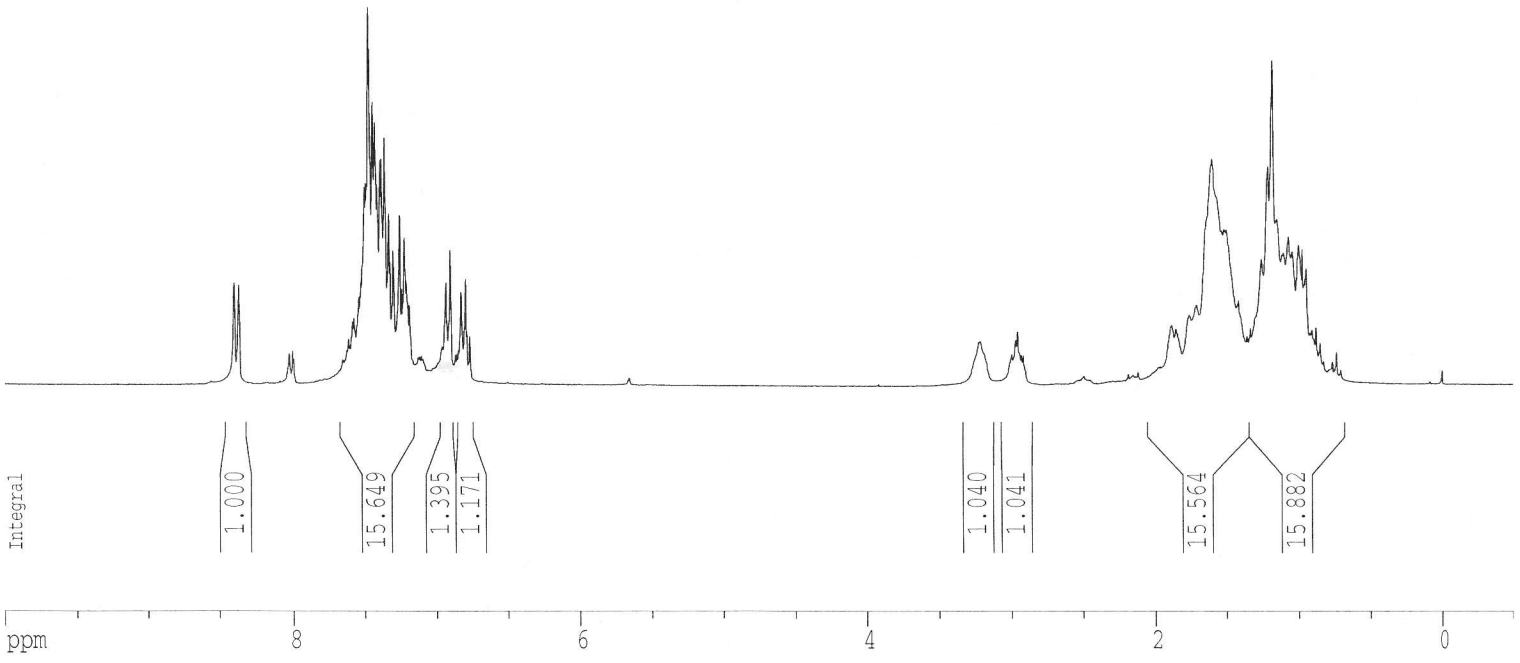
1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	220.000 ppm
F1	13836.95 Hz
F2P	-10.000 ppm
F2	-628.95 Hz
PPMCM	11.50000 ppm/cm
HZCM	723.29535 Hz/cm

1H NMR



165d



Current Data Parameters

NAME	NC-VI-85B
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20071023
Time	15.55
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	5208.333 Hz
FIDRES	0.158946 Hz
AQ	3.1457779 sec
RG	256
DW	96.000 usec
DE	137.14 usec
TE	300.0 K
D1	1.00000000 sec
P1	9.50 usec
SFO1	250.1315321 MHz
NUCLEUS	1H

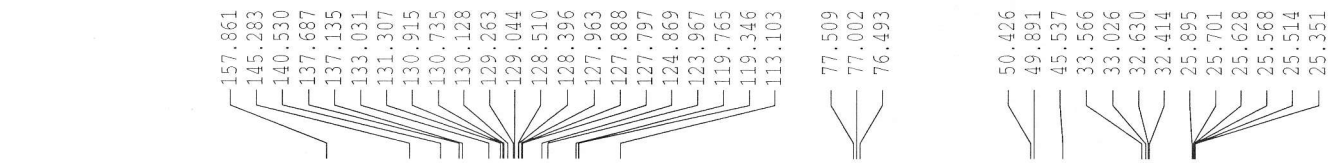
F2 - Processing parameters

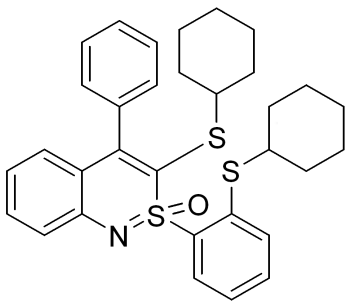
SI	16384
SF	250.1300100 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.50

1D NMR plot parameters

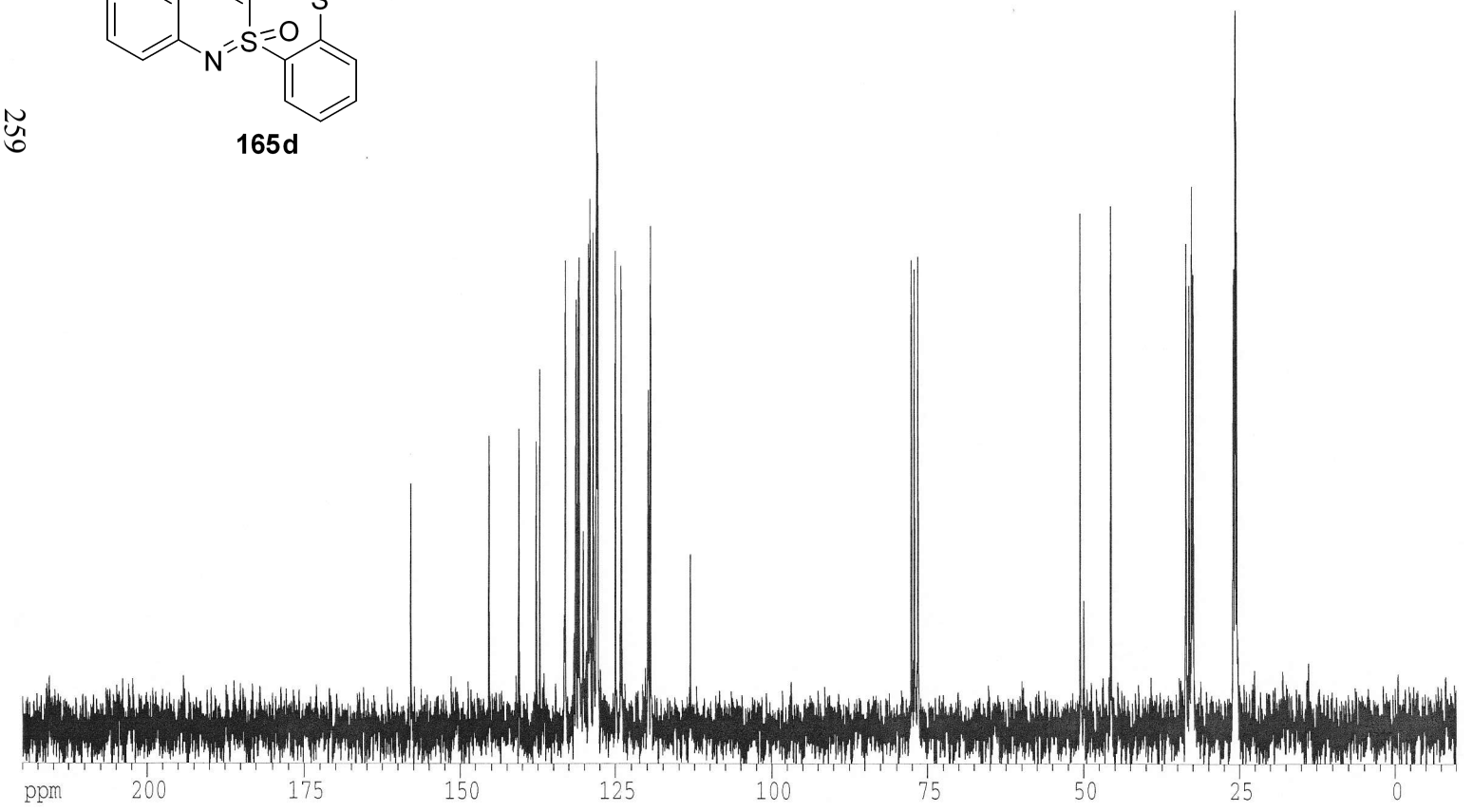
CX	20.00 cm
CY	5.00 cm
F1P	10.000 ppm
F1	2501.30 Hz
F2P	-0.500 ppm
F2	-125.07 Hz
PPMCM	0.52500 ppm/cm
HZCM	131.31825 Hz/cm

13C NMR





165d



Current Data Parameters

NAME	NC-VI-85B
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20071023
Time	16.00
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zgdc30
TD	36864
SOLVENT	CDCl3
NS	99
DS	4
SWH	17241.379 Hz
FIDRES	0.467702 Hz
AQ	1.0691060 sec
RG	22800
DW	29.000 usec
DE	41.43 usec
TE	300.0 K
D12	0.00002000 sec
DL5	23.00 dB
CPDPRG	waltz16
P31	103.00 usec
D1	2.00000000 sec
P1	8.00 usec
SFO1	62.9023694 MHz
NUCLEUS	13C
D11	0.03000000 sec

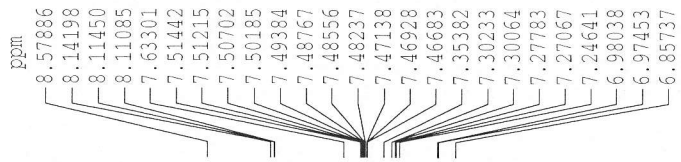
F2 - Processing parameters

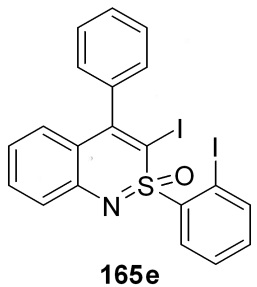
SI	32768
SF	62.8952487 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	220.000 ppm
F1	13836.95 Hz
F2P	-10.000 ppm
F2	-628.95 Hz
PPMCM	11.50000 ppm/cm
HZCM	723.29535 Hz/cm

1H NMR





165e

260

Current Data Parameters

NAME	NC-VI-101B
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

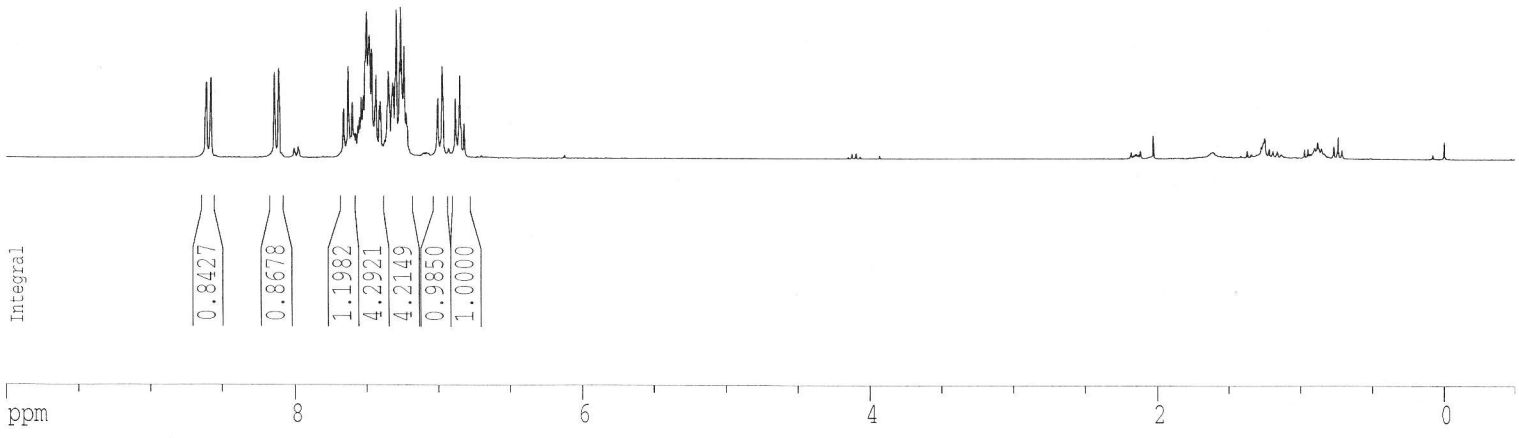
Date_	20071129
Time	11.58
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	5208.333 Hz
FIDRES	0.158946 Hz
AQ	3.1457779 sec
RG	715
DW	96.000 usec
DE	137.14 usec
TE	300.0 K
D1	1.00000000 sec
P1	9.50 usec
SFO1	250.1315321 MHz
NUCLEUS	1H

F2 - Processing parameters

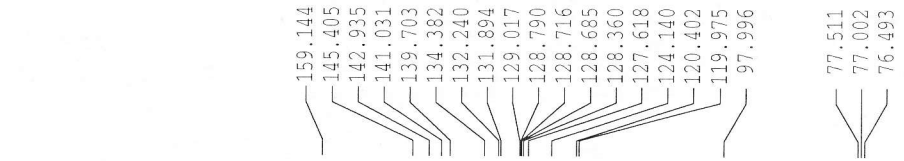
SI	16384
SF	250.1300107 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.50

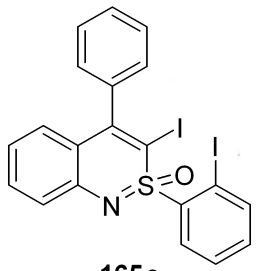
1D NMR plot parameters

CX	20.00 cm
CY	2.00 cm
F1P	10.000 ppm
F1	2501.30 Hz
F2P	-0.500 ppm
F2	-125.07 Hz
PPMCM	0.52500 ppm/cm
HZCM	131.31825 Hz/cm



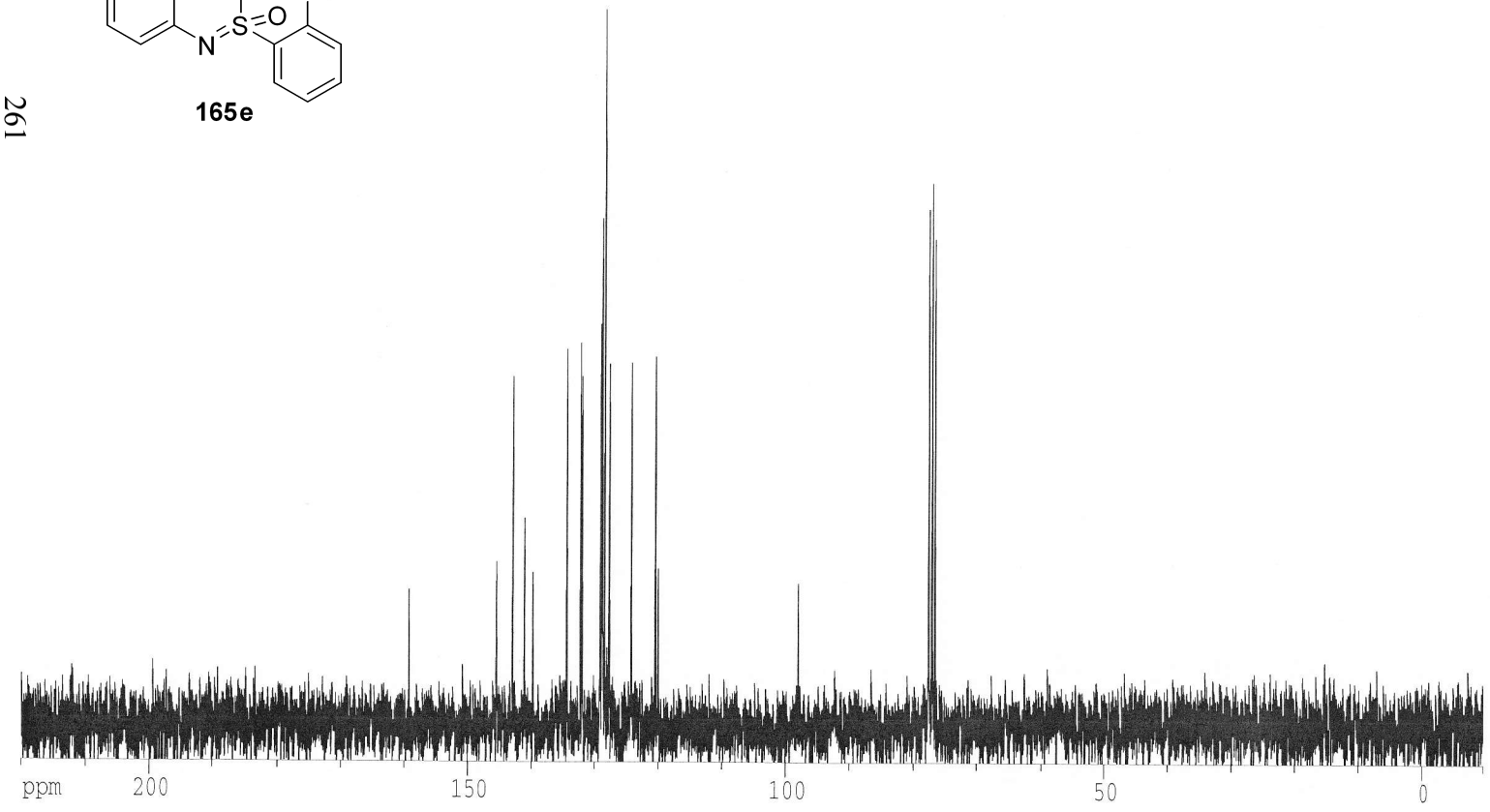
13C NMR





165e

261



Current Data Parameters

NAME	NC-VI-101B
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

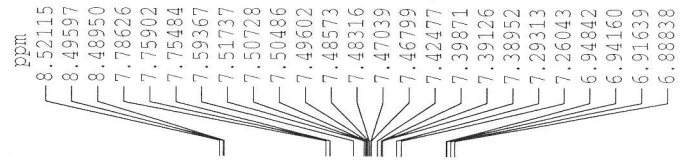
Date_	20071129	
Time	12.02	
INSTRUM	arx250	
PROBHD	5 mm QNP 1H	
PULPROG	zgdc30	
TD	36864	
SOLVENT	CDCl3	
NS	28	
DS	4	
SWH	17241.379	Hz
FIDRES	0.467702	Hz
AQ	1.0691060	sec
RG	22800	
DW	29.000	usec
DE	41.43	usec
TE	300.0	K
D12	0.00002000	sec
DL5	23.00	dB
CPDPRG	waltz16	
P31	103.00	usec
D1	2.00000000	sec
P1	8.00	usec
SFO1	62.9023694	MHz
NUCLEUS	13C	
D11	0.03000000	sec

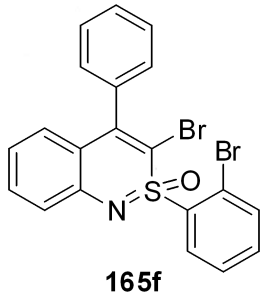
F2 - Processing parameters

SI	32768	
SF	62.8952461	MHz
WDW	EM	
SSB	0	
LB	1.00	Hz
GB	0	
PC	1.40	

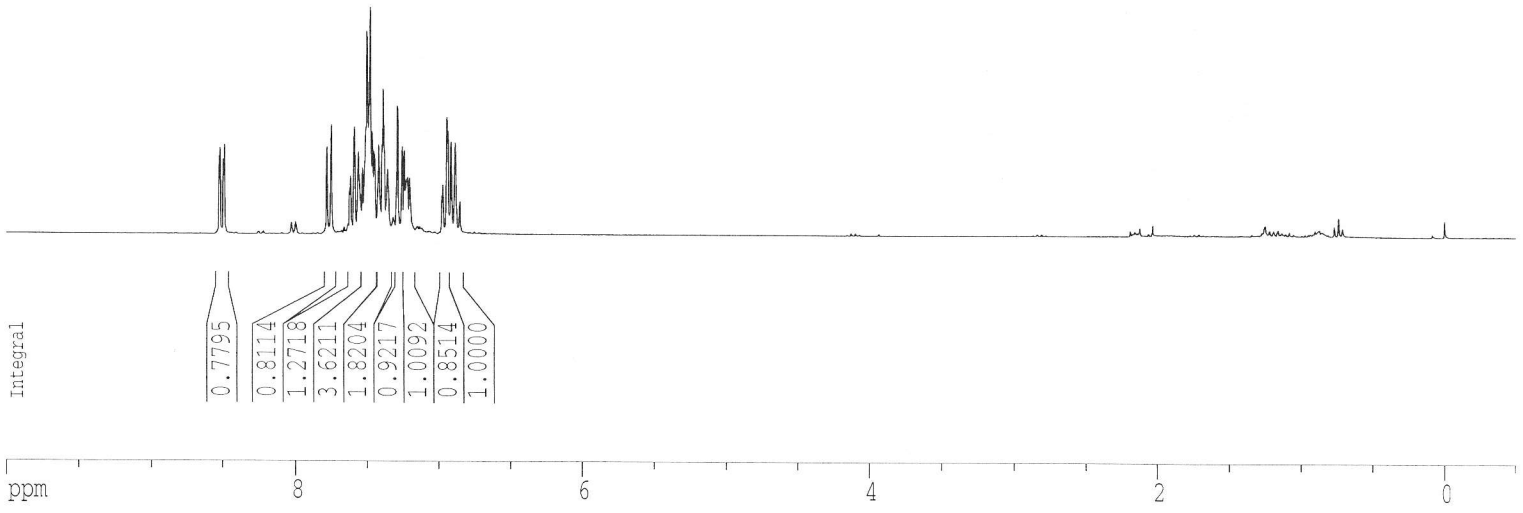
1D NMR plot parameters

CX	20.00	cm
CY	10.00	cm
F1P	220.000	ppm
F1	13836.95	Hz
F2P	-10.000	ppm
F2	-628.95	Hz
PPMCM	11.50000	ppm/cm
HZCM	723.29529	Hz/cm





165f



Current Data Parameters

NAME	NC-VI-100A
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20071129
Time	11.42
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	5208.333 Hz
FIDRES	0.158946 Hz
AQ	3.1457779 sec
RG	715
DW	96.000 usec
DE	137.14 usec
TE	300.0 K
D1	1.00000000 sec
P1	9.50 usec
SFO1	250.1315321 MHz
NUCLEUS	1H

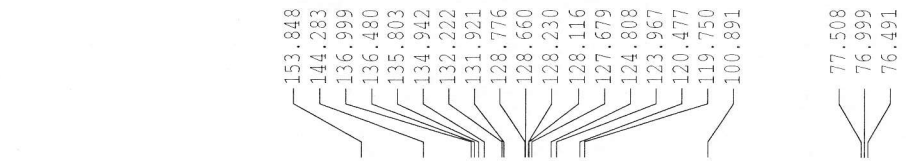
F2 - Processing parameters

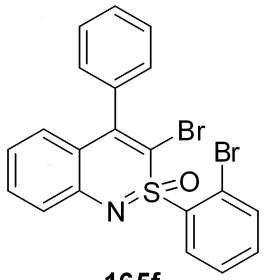
SI	16384
SF	250.1300110 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.50

1D NMR plot parameters

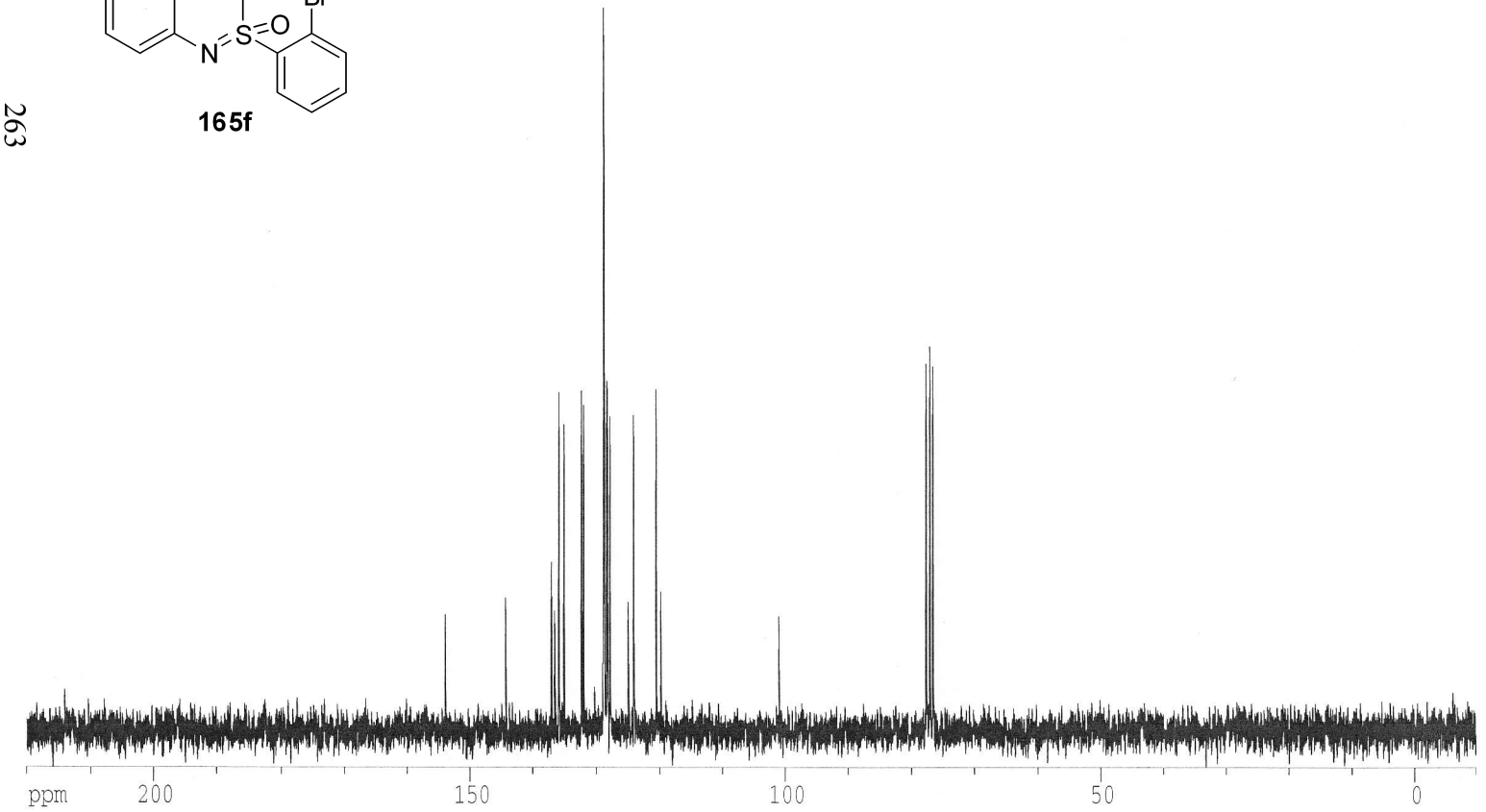
CX	20.00 cm
CY	3.00 cm
F1P	10.000 ppm
F1	2501.30 Hz
F2P	-0.500 ppm
F2	-125.07 Hz
PPMCM	0.52500 ppm/cm
HZCM	131.31825 Hz/cm

13C NMR





165f



Current Data Parameters

NAME	NC-VI-100A
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PROCNO	1

F2 - Acquisition Parameters

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PULPROG	zgdc30	
TD	36864	
SOLVENT	CDCl3	
NS	55	
DS	4	
SWH	17241.379	Hz
FIDRES	0.467702	Hz
AQ	1.0691060	sec
RG	22800	
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TE	300.0	K
D12	0.00002000	sec
DL5	23.00	dB
CPDPRG	waltz16	
P31	103.00	usec
D1	2.00000000	sec
P1	8.00	usec
SFO1	62.9023694	MHz
NUCLEUS	13C	
D11	0.03000000	sec

F2 - Processing parameters

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SF	62.8952461	MHz
WDW	EM	
SSB	0	
LB	1.00	Hz
GB	0	
PC	1.40	

1D NMR plot parameters

CX	20.00	cm
CY	10.00	cm
F1P	220.000	ppm
F1	13836.95	Hz
F2P	-10.000	ppm
F2	-628.95	Hz
PPMCM	11.50000	ppm/cm
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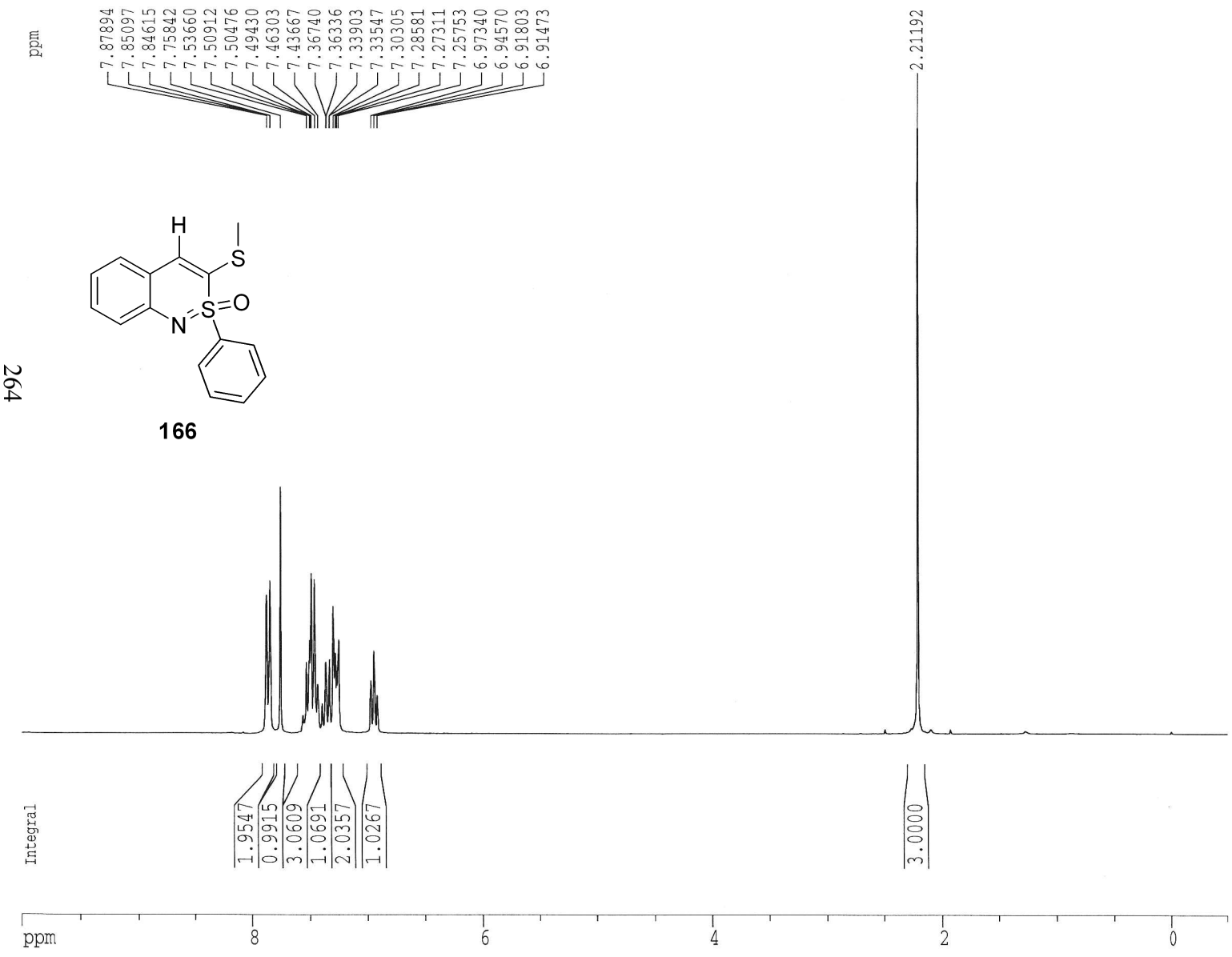
1H NMR



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166

Current Data Parameters

NAME	NC-VI-84a
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PROCNO	1

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DS	2
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NUCLEUS	1H

F2 - Processing parameters

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SF	250.1300065 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.50

1D NMR plot parameters

CX	20.00 cm
CY	12.50 cm
F1P	10.000 ppm
F1	2501.30 Hz
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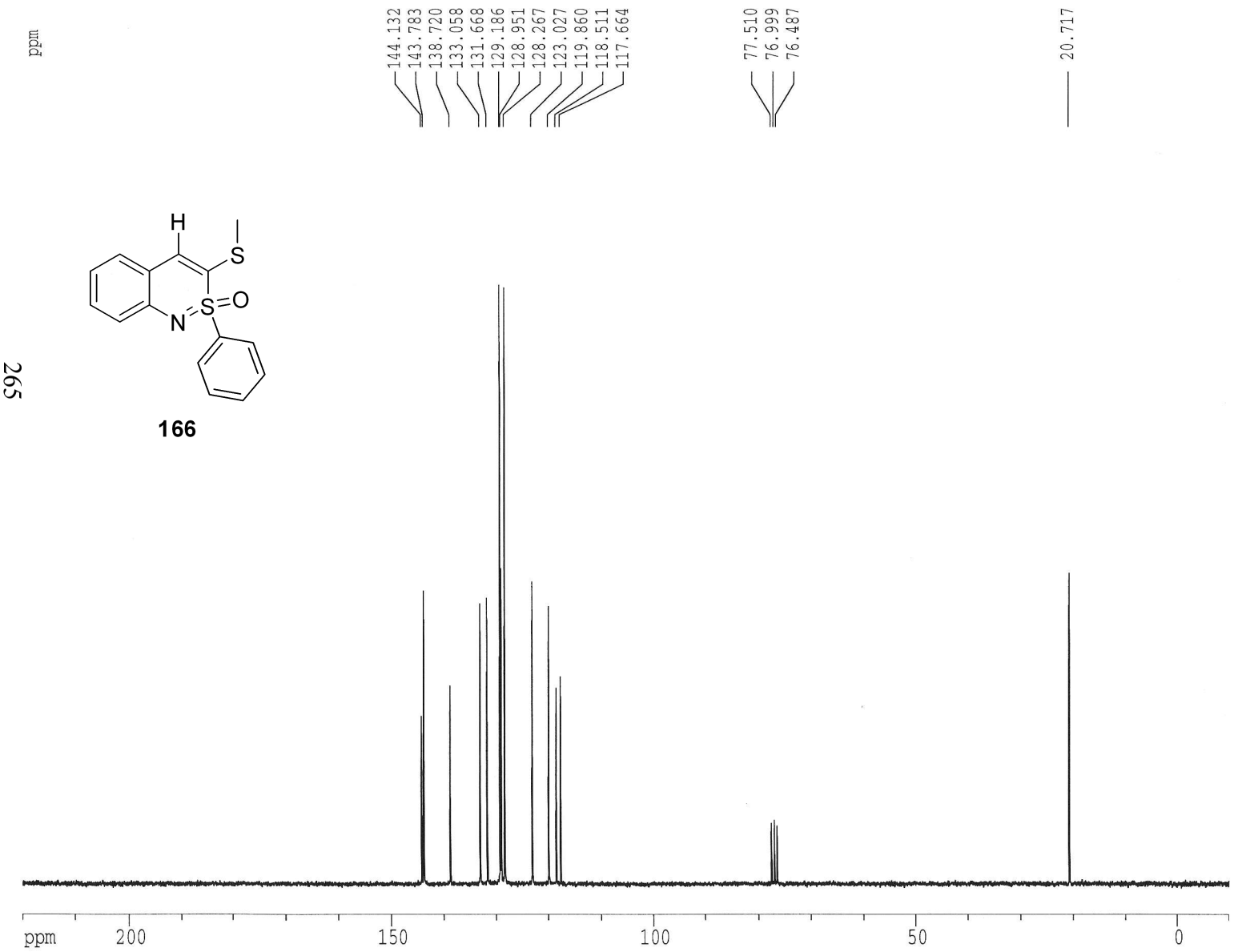
13C NMR



Current Data Parameters

NAME	NC-VI-84a
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

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SOLVENT	CDCl3
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SWH	17241.379 Hz
FIDRES	0.467702 Hz
AQ	1.0691060 sec
RG	22800
DW	29.000 usec
DE	41.43 usec
TE	300.0 K
D12	0.00002000 sec
DL5	23.00 dB
CPDPRG	waltz16
P31	103.00 usec
D1	2.00000000 sec
P1	6.25 usec
SFO1	62.9023694 MHz
NUCLEUS	13C
D11	0.03000000 sec

F2 - Processing parameters

SI	32768
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WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	220.000 ppm
F1	13836.96 Hz
F2P	-10.000 ppm
F2	-628.95 Hz
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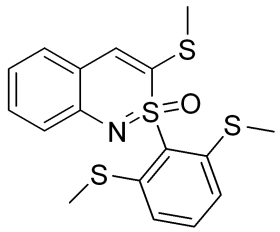
HZCM	723.29565 Hz/cm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C2
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C10
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C15

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VITA

Nathan L. Calkins was born on September 16th of 1982 in Washington, Missouri. He graduated valedictorian of the Gasconade County R-2 High School in Owensville, Missouri in May of 2000. Later that fall, he began his undergraduate education at Truman State University in Kirksville, MO. He graduated in May of 2004 with an American Chemical Society certified bachelors of science degree in chemistry. He participated in the Stevens' Summer Fellowship with Norman Rabjohn Distinguished Professor of Chemistry, Michael Harmata, in the summer of 2003. He then joined Dr. Harmata's research group at the University of Missouri-Columbia after his undergraduate commencement in May of 2004. He took part in a variety of research funded by the Petroleum Research Fund of the American Chemical Society, National Institute of Health, and the United States Air Force. He graduated from the University of Missouri-Columbia in May of 2010 under Dr. Harmata's guidance. He served briefly as an adjunct Chemistry Instructor at Westminster College and is currently an Assistant Professor in Chemistry at Mineral Area College in Park Hills, MO. He currently resides in Bonne Terre, MO with his wife Nora Calkins and his three children Lainey, Evonelle, and Maggie Calkins.