SELECTIVE FORMATION OF SECONDARY AMIDES VIA THE COPPER-CATALYZED CROSS-COUPLING OF PRIMARY AMIDES WITH ALKYLBORONIC ESTERS

by

Steven A. Rossi

A thesis submitted to the Faculty of the University of Delaware in partial fulfillment of the requirements for the degree of Master of Science in Chemistry and Biochemistry

Summer 2013

© 2013 Steven A. Rossi
All Rights Reserved

Selective Formation of Secondary Amides via the

Copper-Catalyzed Cross-Coupling of

Primary Amides with Alkylboronic Esters

by

Steven A. Rossi

Approved: _____

Donald A. Watson, Ph.D
Professor in charge of thesis on behalf of the Advisory Committee

Approved: _____

Murray V. Johnston, Ph.D
Chair of the Department of Chemistry and Biochemistry

Approved: _____

George H. Watson, Ph.D
Dean of the College of Arts and Sciences

Approved: _____

James G. Richards, Ph.D.
Vice Provost for Graduate and Professional Education

This thesis is dedicated to the three most important people in my life.

First to my mother, Barbara, for without her courage to start over, I would not be here.

Second to my father, Perry, for being my father, even when he didn't have to be.

Finally, to my soon-to-be wife, Theresa, for more than I could ever write. Thank you.

ACKNOWLEDGMENTS

There are many people who have contributed to this thesis being possible and to whom, I am deeply grateful.

First, I would like to thank my advisor, Professor Don Watson, for giving me this opportunity to work for him, even though I am not actually an "organic" chemist. Without his guidance and "keep pushing" attitude, I would not be the chemist I am today.

To the entire organic and inorganic faculty at UDel for their dedication and encouragement throughout my entire career here. Thank you for not only teaching, but for caring about the subject and pressing your passion upon all of the students.

To my undergraduate advisor and friend, Dr. Nathan "Ned" West, for giving me my start in inorganic chemistry and for teaching me how to be an excellent chemist. You were a great chemist, and a better friend.

I would also like to thank the dedicated reviewers of this thesis. I know that it is an extremely tedious job that is anything but easy, but I am very grateful for the time and effort you put into this. Thank you Sara Martin, Luis Mori-Quiroz, and Kirk Shimkin.

A special thank you to Dr. Shi "Steve" Bai for maintaining the NMR facilities. With your training, help, and dedication to keeping the instruments running, there is no way anybody (including me) could ever get anything done. Also, to the MS lab staff, Dr. Stephen Chan and Jesse McAtee, for running samples and helping me "fix" the ESI multiple times.

To the wonderful staff in our department shops, Jim Draper and John Famiglietti (instrucment shop), Derrick Allen (machine shop), and Doug Nixon (glass shop). You

four are truly amazing and talented, and I have been extremely fortunate to have worked with you. Thank you for fixing our glove boxes, pumps, and building/rebuilding our manifolds more times than I can count.

Susan Cheadle, I am pretty sure the entire graduate community would self-implode with you weren't here to keep us all on track. When in doubt, "go talk with Susan" seemed to be everybody's motto, and you have never disappointed. You have helped me since day one. Thank you very much for all your time and help.

Also a very special thank you to Pat McMahon for teaching me how to use Windows 8. This thesis could not have been written without your tutorial.

I would also like to thank the entire D. Watson group. I have worked with all of you 6 days a week for the past few years, and I can honestly say, this experience would not have been the same without you. Everybody has taught me something and/or helped me along the way, and I believe I am better for it. Thank you.

To Dr. Qun Xu, for originating this project and teaching me everything I would need to know about it. Also, thank you Kirk Shimkin for working on this project with me. The Kirkapedia Encyclopedia has been a great source of knowledge and more reliable than Scifinder.

A special thanks to Peter Gildner for his mentorship and guidance throughout my career at UDel. You really made my time here more enjoyable and were always a great source of information and encouragement. Thank you for doing everything you possibly could for me. I will not forget it.

Thank you to Andrew "Cindy" "Pocahontas" "Pokey" Cinderella for sharing a hood with me. You were a great hood mate, and are a better friend.

And of course, most importantly, I need to thank my family from the very bottom of my heart. Mom and Dad (Barbara and Perry in case you needed clarification), thank you for supporting me, not only throughout this interesting ride, but for my entire life. I would not be where I am and who I am without your teaching, love, and unconditional support. I can never thank you enough for what you two have done me.

And of course, thank you Theresa Ann D'Addio-(soon-to-be Rossi). I said that words cannot express how thankful I am for you, but I'll still try. Your support has been unwavering, your help unconditional, and your dedication immeasurable. I have known you since I was a sophomore in high school, and I know that nobody has had a more interesting 9 years than us. I also know that they haven't had a better 9 years. Every day you help me be a better person, and I cannot imagine doing this without you. You are the force behind this thesis. I know this isn't "thank you," but it's more fitting. ARRIVEDERCI! And grazie di tutto, thanks for everything.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

ABSTRACT

Chapter 1 begins with an abbreviated introduction into traditional formation of amides as published in the chemical literature. Previous examples for this transformation, including Buchwald-Hartwig type couplings and the copper catalyzed Ullmann and Lam-Chan cross-couplings, are reviewed, followed by a short, but detailed summary of the alkyl Lam-Chan protocols and available methods to date. The limitations of the known procedures are also examined.

Chapter 2 describes the first ever report of exclusive mono-alkylation of a primary amide via a copper-catalyzed cross-coupling with an alkylboronic acid. In order to demonstrate generality of the method, a multitude of substrates with varying functional groups were synthesized. After optimization from standard Lam-Chan reaction conditions using a model system, the optimal conditions were tested on a variety of commercially available and on-site synthesized substrates. Variations to both the primary amide and the alkylboronic acid were tested and analyzed thoroughly. A detailed discussion on the suitable coupling partners, in addition to the examination of intolerant functional groups, is also presented.

Chapter 3 describes the next step in the formation of new C-N bonds using alkyl boronates. Further investigation has shown successful alkylation with alkylboronic acid pinacol esters, which are of great interest due to their abundance and ease of synthesis, temperature and air stability, and commercial availability. Preliminary optimization and investigation into the generality of this reaction, in addition to the synthesis of novel alkyl boronates, is reported.

Chapter 1

INTRODUCTION AND BACKGROUND

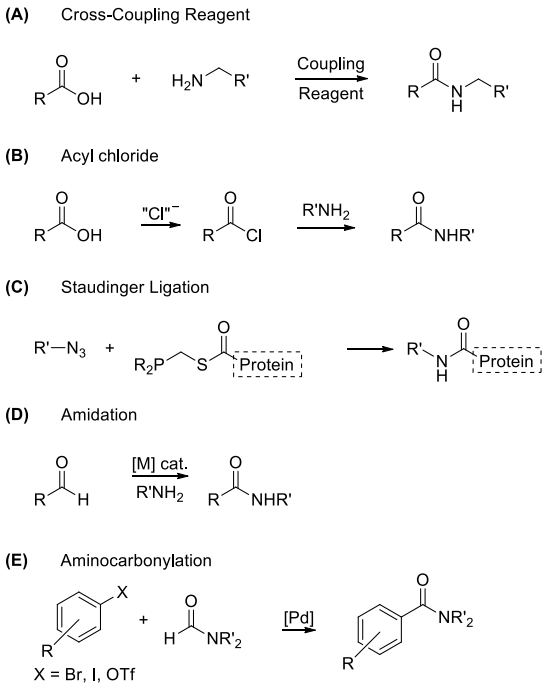
1.1 Introduction

Amides are an extremely common and crucial motif in natural products, polymers, and pharmaceutical compounds.[1,2] In addition to being the backbone of all natural peptides and proteins, 25% of available pharmaceuticals contain amides in their structure.[3,4] The synthesis of amides is well established, with traditional methods utilizing the coupling of a carboxylic acid group with an amine. Common conversions involve the use of a coupling reagent to activate the carboxylic acid or the preformation of a carboxylic acid derivative, i.e. acyl chloride (Scheme 1-1).[5,6] Multiple other procedures have been developed that are functional group tolerant and highly scalable, including the Staudinger ligation, oxidative amidation of aldehydes, and aminocarbonylation of aryl halides.[7-10] However, many of these procedures require a large excess of one of the starting materials to successfully produce the amide. Furthermore, in addition to requiring a stoichiometric to super-stoichiometric amounts of coupling reagents, a large amount of waste is generated, resulting in poor atom economy.[11,12]

Recently, a substantial amount of effort has been put forth to develop catalytic systems that would generate the same products, but require significantly less reagents, thus reducing the amount of consequential side products.[10] However, many of these reactions have multiple drawbacks, especially on an industrial scale, requiring specialized starting materials, expensive pre-catalysts and ligands, and harsh reaction conditions.[13,14] Therefore, a new synthetic system is needed that meets a wide range of synthetic and economic requirements, including, but not limited to, high atom economy,

inexpensive starting materials, high functional group tolerance, and high scalability to prepare carbon-nitrogen (C-N) bond containing compounds.

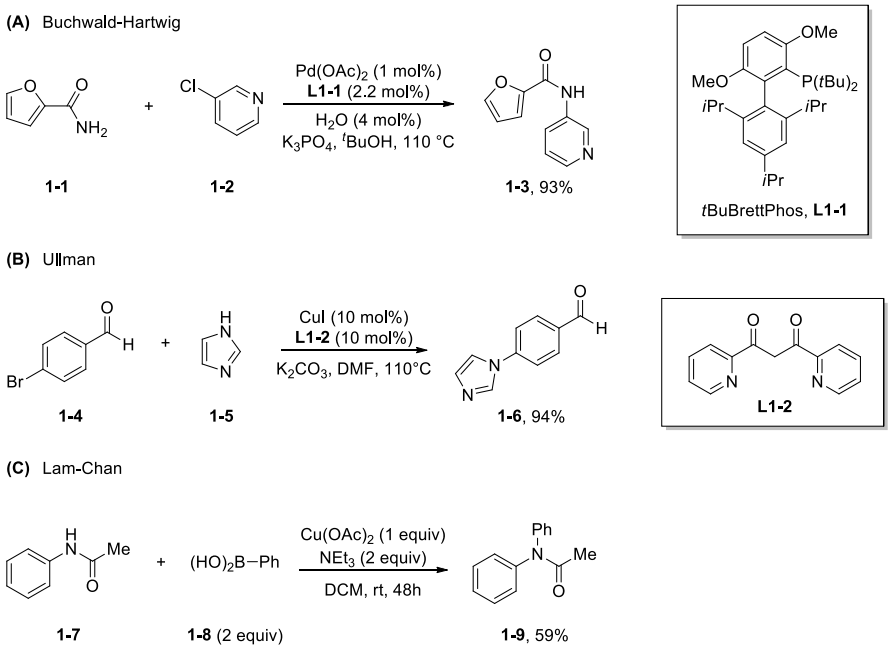
Scheme 1-1. Traditional Transformations for Amide Synthesis.



Multiple potential solutions have been developed to advance the synthesis of these nitrogen containing compounds. Many of these methods involve transition metal-assisted or catalyzed systems. However, the vast majority of advances in this area have been via cross-coupling of heteroatoms with aryl groups. Various protocols have been developed, mainly utilizing late transition metals to couple aryl halides with amines or alcohols. Of these procedures, a few have revolutionized the field, including palladium- and nickel-catalyzed Buchwald-Hartwig cross-couplings,[15,16] copper-catalyzed Ullman-Type reactions,[17] and copper-assisted and copper-catalyzed Lam-Chan coupling

reactions[18,19] (Scheme 1-2).[20-22] These procedures have been used extensively in the production of biologically active and pharmaceutical compounds due to their vast generality, high scalability, and extremely high functional group tolerance. Cross-coupling is now possible between aryl halides (Cl, Br, I) and pseudo-halides (OMs, OTs, ONf, OTf) and multiple heteroatom functionalities (amides, amines, alcohols, imides, ureas, carbonates). Even with this wide range of methods, the scope has been limited to the formation of C_{sp}^2-N bonds due to cross-coupling compatibility with only aryl systems (aryl halides/ aryl boronic acids).

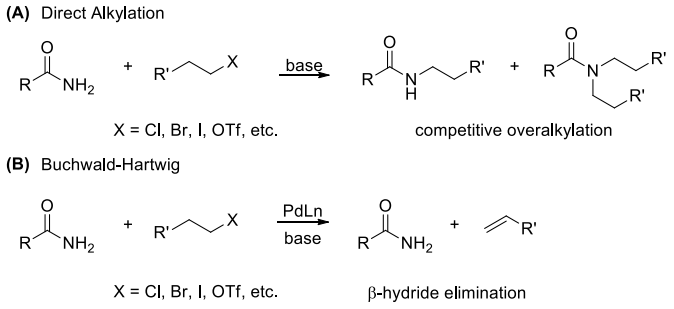
Scheme 1-2. Transition Metal Cross-Couplings of Heteroatoms.



Expanding this field to include alkyl cross-coupling partners would greatly improve the overall utility for the formation of C_{sp}^3-N bonds. The reaction pathways

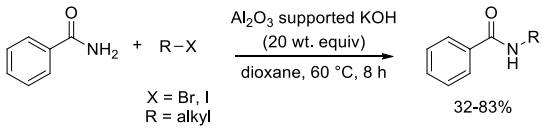
previously discussed would not be suitable for this transformation due to the general lack of reactivity of alkyl halides and alkyboronate reagents. In general, alkyl halides undergo slow oxidative addition, while alkylboronates are slow to transmetallate. In the case of direct alkylation, the amide nucleophile has been known to undergo competitive overalkylation (Scheme 1-3A), while alkyl-metal intermediates are inclined toward β-hydride elimination, especially in the presence of late transition metal catalysts, such as those used in Buchwald-Hartwig type reactions (Scheme 1-3B).

Scheme 1-3. Strategies for Alkylation of Amides.



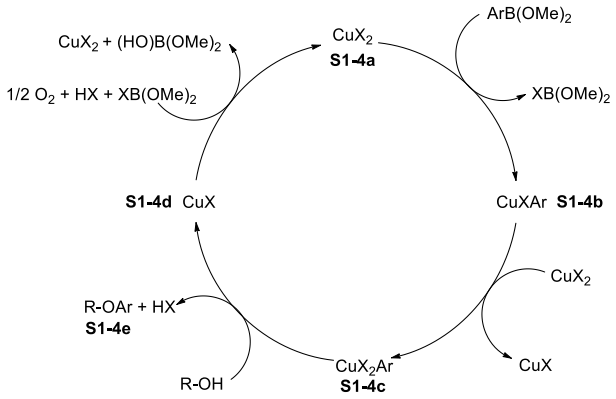
It is important to note that a method for the successful mono-alkylation of primary amides with alkyl halides has been reported (Figure 1-1).[23] However, this protocol relies on a large excess (20 weight equivalents) of a specialized Alumina/KOH reagent and is completely intolerant of all functionality. Di-alkylation was also reported albeit in minimal amounts. Despite the high selectively for mono-alkylation, the excessive amount of specialized reagents and subsequent work-up make this procedure inadequate for laboratory and industrial scale synthesis.

Figure 1-1. Direct Mono-Alkylation with Alkyl Halides.



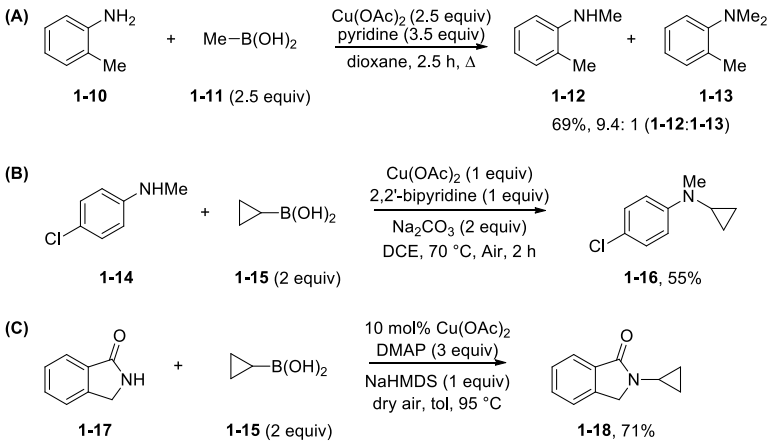
A few protocols have been developed which focus on the conversion of carbon-boron (C-B) bonds to C-N bonds, but all require highly electrophilic boronate sources.[24-26] By switching to a less electrophilic boron coupling partner (alkylboronic acid, alkylboronic acid pinacol ester, etc.), a copper-catalyzed alkyl variant of the Lam-Chan reaction could be a potential solution for the mono-alkylation of primary amides.[27] While traditional Lam-Chan-type reactions require stoichiometric amounts of copper, catalytic variants have been established, primarily with arylboronic acids.[27,28] A detailed investigation into the mechanism of the Lam-Chan-Evans (oxygen as heteroatom) reaction was recently conducted (Scheme 1-4). In this case, the heteroatom is an oxygen atom, but the general principles established by King et al. still apply to nitrogen containing compounds (amines, amides, imides).[29] The study suggests that the resting state for this reaction is the initial copper salt (**S1-4a**). First, the copper salt **S1-4a** undergoes a transmetalation with the arylboronic acid to provide copper (II) species **S1-4b**. This copper (II) species undergoes an oxidation with another equivalent of the copper pre-catalyst **S1-4a** to give the copper (III) species **S1-4c**. Once the copper intermediate reaches this electron deficient state, the substrate undergoes rapid carbon-oxygen (C-O) bond formation to provide the arylated product **S1-4e** and the copper (I) salt **S1-4d**. The copper (I) salt then undergoes aerobic oxidation to regenerate the starting pre-catalyst **S1-4a**.

Scheme 1-4. Proposed Catalytic Cycle for Lam-Chan-Evans Type Reactions.



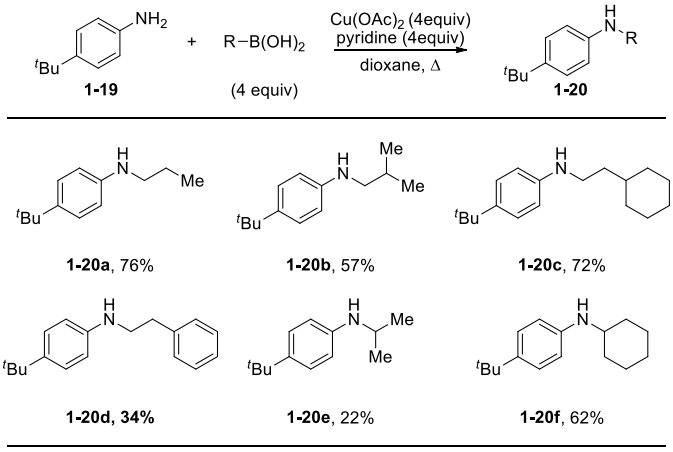
Lam-Chan and Lam-Chan-Evans reactions have been well investigated in the context of aryl coupling partners, but studies of alkyl variants are significantly lacking.[30,31] A few protocols employing alkyl boron reagents have been developed[32-38], but most are limited in scope to cyclopropyl and methylboronates (Scheme 1-5).[32,34,37] Both of these boronate substrates are unable to undergo competitive β-hydride elimination and also lack additional functionality.[39] In addition, stoichiometric and super stoichiometric amounts of copper are needed to facilitate these reactions, and competitive overalkylation is a prominent problem (Scheme 1-5A).[32,34] To date, only a single example of a catalytic alkylboronic acid variant for the conversion of C-B to C-N bonds is known (Scheme 1-5C). In this report, the catalytic copper systems were compared to the stoichiometric experiments, with the latter being significantly higher yielding, ranging as high as 85%.[37] More recently, a new catalytic protocol using alkylboronic acid pinacol esters was reported to successfully cross-couple with amines and phenol derivatives.[38]

Scheme 1-5. Known Alkyl Variants for Lam-Chan Reactions.



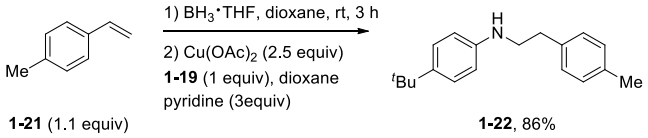
While the aforementioned boronate substrates have been developed extensively, the Cruces group has produced multiple general protocols for the alkylation of amines.[35,36] Using a range of alkylboronic acids as coupling partners with aniline derivatives, several different C-B bonds were converted to C-N bonds using copper (II) acetate as transition metal pre-catalyst (Scheme 1-6). While there is little functionality reported (mostly un-substituted alkylboronates are used), all of the reported compounds possessed hydrogens available for β-hydride elimination, which is a significant improvement in scope over previous reports.

Scheme 1-6. Anilines Cross-Coupled with Alkylboronic Acids.



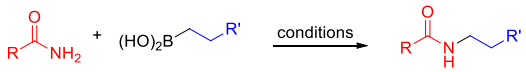
Another protocol published by the Cruces group combines two previously well-established areas of boron chemistry to generate mono-alkylated aniline derivatives. Using the well-developed Brown Hydroboration[40,41], the Crucues method starts by generating a terminal borane *in situ* from an alkene (Figure 1-2). The freshly formed borane is then reacted under typical Lam-Chan conditions to generate the alkylated product. However, in both of these reports (Scheme 1-6 and Figure 1-2), large amount of excess copper and boronic acid are needed to generate products in high yields.

Figure 1-2. Lam-Chan Type Cross-Coupling with *in situ* Generated Alkylboranes.



The selective formation of secondary amides is of great interest due to their prevalent nature, both in naturally occurring peptides and in proteins.[3] As illustrated in this chapter, this area of alkyl Lam-Chan reactions remains tremendously underdeveloped. While there are several general protocols for the formation of C_{sp}^2-N bonds, few procedures can efficiently form new C_{sp}^3-N bonds from C-B bonds without using an excessive amount of copper and/or alkylboronate. In addition, amide synthesis is often atom inefficient and costly. A method that could address both of these areas would positively affect organic synthesis. Therefore, a novel, catalytic route for the exclusive mono-alkylation of primary amides with alkylboronates is a vital research objective (Figure 1-3).

Figure 1-3. Exclusive Mono-Alkylation of Primary Amides.



1.2 Conclusions

Despite the vast amount of literature on Lam-Chan and Lam-Chan-Evans reactions, few examples contain primary amides and little effort has been dedicated towards developing a general alkyl variant. A copper-catalyzed alkyl variant Lam-Chan type protocol would greatly improve and expand the current methods used for the synthesis of secondary amides. Not only would this novel method constitute a rare example of catalytic C-N bond formation, but it would also expand the area of C-B to C-N bond transformation, which is a notably difficult process. This orthogonal method for secondary amide synthesis would fulfill an underdeveloped area of chemistry while

expanding the overall generality of heteroatom-alkyl halide/pseudo-halide cross-coupling reactions. This reaction would also help satisfy laboratory and industrial needs, i.e. inexpensive staring materials and catalyst, high atom economy, high functional group tolerance, and high scalability.

In summary, the alkyl Lam-Chan reaction appears to be a viable solution to the formation of new C-N bonds without competitive over alkylation or β-hydride elimination. Investigation into this transformation will expand and broaden the area of C-B to C-N bond formation, while fulfilling multidisciplinary objectives.

1.3 References

(1) Humphrey, J. M.; Chamberlin, A. R. *Chemical Reviews* **1997**, *97*, 2243.
(2) Zabicky, J. *Amides*; Wiley: Weinheim, 1970.
(3) *Bioorganic Chemistry: Peptides and Proteins*; Hecht, S. M., Ed.; Oxford Univeristy Press New York, 1998.
(4) Ghose, A. K.; Viswanadhan, V. N.; Wendoloski, J. J. *Journal of Combinatorial Chemistry* **1998**, *1*, 55.
(5) Han, S.-Y.; Kim, Y.-A. *Tetrahedron* **2004**, *60*, 2447.
(6) Montalbetti, C. A. G. N.; Falque, V. *Tetrahedron* **2005**, *61*, 10827.
(7) Köhn, M.; Breinbauer, R. *Angewandte Chemie International Edition* **2004**, *43*, 3106.
(8) Martinelli, J. R.; Clark, T. P.; Watson, D. A.; Munday, R. H.; Buchwald, S. L. *Angewandte Chemie International Edition* **2007**, *46*, 8460.
(9) Yoo, W.-J.; Li, C.-J. *Journal of the American Chemical Society* **2006**, *128*, 13064.
(10) Allen, C. L.; Williams, J. M. J. *Chemical Society Reviews* **2011**, *40*, 3405.
(11) Nordstrøm, L. U.; Vogt, H.; Madsen, R. *Journal of the American Chemical Society* **2008**, *130*, 17672.
(12) Shimizu, K.-i.; Ohshima, K.; Satsuma, A. *Chemistry – A European Journal* **2009**, *15*, 9977.
(13) Orito, K.; Horibata, A.; Nakamura, T.; Ushito, H.; Nagasaki, H.; Yuguchi, M.; Yamashita, S.; Tokuda, M. *Journal of the American Chemical Society* **2004**, *126*, 14342.
(14) Matteoli, U.; Scrivanti, A.; Beghetto, V. *Journal of Molecular Catalysis A: Chemical* **2004**, *213*, 183.
(15) Hartwig, J. F. *Accounts of Chemical Research* **2008**, *41*, 1534.
(16) Surry, D. S.; Buchwald, S. L. *Angewandte Chemie International Edition* **2008**, *47*, 6338.
(17) Monnier, F.; Taillefer, M. *Angewandte Chemie International Edition* **2009**, *48*, 6954.
(18) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Letters* **1998**, *39*, 2941.
(19) Evans, D. A.; Katz, J. L.; West, T. R. *Tetrahedron Letters* **1998**, *39*, 2937.
(20) Surry, D. S.; Buchwald, S. L. *Chemical Science* **2011**, *2*, 27.
(21) Xi, Z.; Liu, F.; Zhou, Y.; Chen, W. *Tetrahedron* **2008**, *64*, 4254.
(22) Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Letters* **1998**, *39*, 2933.
(23) Sukata, K. *Bulletin of the Chemical Society of Japan* **1985**, *58*, 838.
(24) Brown, H. C.; Heydkamp, W. R.; Breuer, E.; Murphy, W. S. *Journal of the American Chemical Society* **1964**, *86*, 3565.
(25) Brown, H. C.; Kim, K.-W.; Srebnik, M.; Bakthan, S. *Tetrahedron* **1987**, *43*, 4071.
(26) Matteson, D. S.; Kim, G. Y. *Organic Letters* **2002**, *4*, 2153.
(27) Qiao, J. X.; Lam, P. Y. S. *Synthesis* **2011**, *2011*, 829.

(28) Sreedhar, B.; Venkanna, G. T.; Shiva Kumar, K. B.; Balasubrahmanyam, V. *Synthesis* **2008**, *2008*, 795.
(29) King, A. E.; Brunold, T. C.; Stahl, S. S. *Journal of the American Chemical Society* **2009**, *131*, 5044.
(30) Ley, S. V.; Thomas, A. W. *Angewandte Chemie International Edition* **2003**, *42*, 5400.
(31) Sanjeeva Rao, K.; Wu, T.-S. *Tetrahedron* **2012**, *68*, 7735.
(32) Benard, S.; Neuville, L.; Zhu, J. *Chemical Communications* **2010**, *46*, 3393.
(33) Bénard, S. b.; Neuville, L.; Zhu, J. *The Journal of Organic Chemistry* **2008**, *73*, 6441.
(34) González, I.; Mosquera, J. s.; Guerrero, C. s.; Rodríguez, R. n.; Cruces, J. *Organic Letters* **2009**, *11*, 1677.
(35) Larrosa, M.; Guerrero, C.; Rodríguez, R.; Cruces, J. *Synlett* **2010**, *2010*, 2101.
(36) Naya, L.; Larrosa, M.; Rodríguez, R.; Cruces, J. *Tetrahedron Letters* **2012**, *53*, 769.
(37) Tsuritani, T.; Strotman, N. A.; Yamamoto, Y.; Kawasaki, M.; Yasuda, N.; Mase, T. *Organic Letters* **2008**, *10*, 1653.
(38) Sueki, S.; Kuninobu, Y. *Organic Letters* **2013**, *15*, 1544.
(39) Nuzzo, R. G.; McCarthy, T. J.; Whitesides, G. M. *Journal of the American Chemical Society* **1981**, *103*, 3404.
(40) Beller, M. B. C. *Transition metals for organic synthesis : building blocks and fine chemicals*; Wiley-VCH: Weinheim; New York, 1998.
(41) Brown, H. C. *Hydroboration*; W.A. Benjamin: New York, 1962.

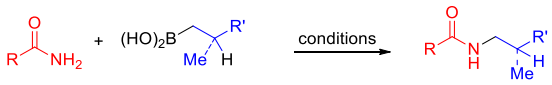
Chapter 2

EXAMINATION OF THE CROSS-COUPLING REACTION OF PRIMARY AMIDES WITH ALKYLBORONIC ACIDS

2.1 Introduction

Given the limitations and drawbacks of known alkylboronic acid systems (Chapter 1), we began our preliminary investigation with isobutylboronic acid and benzamide. Isobutylboronic acid provides insight into two key structural characteristics. First, the substrate possesses one hydrogen available for β-hydride elimination. Second, the substrate exhibits β-branching which will ensure that bulkier groups are tolerated. In addition, several other boronic acids were synthesized with various functionality, including secondary boronic acid systems. Consequently, functional group tolerance was also tested on the primary amide substituent, and several analogs were synthesized to gauge the generality of the transformation. These substrates were designed to test both steric and electronic effects through utilization of electron donating and withdrawing groups, and steric effects through use of sterically encumbered amides and boronic acids.

Figure 2-1. Model System for Cross-Coupling.



This chapter is separated into several sections. The first section is a compilation of the modified protocols and procedures used for the synthesis of all the boronic acids and several primary amides. Next, optimization of the cross-coupling reaction and

expansion of the scope is presented. To conclude, a discussion on the functional group tolerance and generality of the reaction, in addition to the limitations and disadvantages are reviewed. Experimental details are included at the end of the chapter. Supporting spectral data can be found in Appendix 1.

2.2 Substrate Synthesis

A variety of boronic acids and amides were prepared to test this transformation. Various modifications to known procedures were applied to the synthesis of the boronic acid substrates. Significant challenges were seen in the isolation of the alkylboronic acids. Since this class of compound is incompatible with common column chromatography, recrystallization and precipitation are the only means for purification. In addition, careful monitoring of temperature, primarily below 25 °C, was needed to prevent decomposition. Decomposition was also observed under vacuum (ca. 100 mtorr) due to formation of water and boroxines.

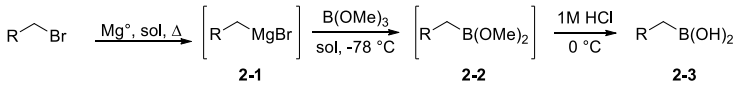
Syntheses of novel primary amides were relatively straightforward and readily performed with small modifications of known procedures and/or simple functional group manipulation. All new amide compounds were air, temperature, and vacuum stable.

2.2.1 Boronic Acid Synthesis

Synthesis of primary alkylboronic acids was done primarily through a modified Grignard reaction (Scheme 2-1).[1] Synthesis began with formation of a Grignard by reaction of an alkyl bromide and magnesium turnings under nitrogen to form **2-1**. The freshly formed Grignard reagent was added at -78 °C to a solution of trimethylborate in

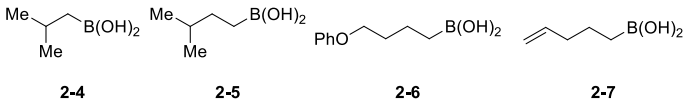
ethereal solvent to give the alkylboronic ester **2-2**. Addition of 1M HCl at 0 °C, followed by extraction and precipitation with cold hexanes gave the resulting primary alkylboronic acid **2-3**.

Scheme 2-1. Synthesis of Primary Boronic Acids via Grignard Reaction.



Careful consideration was given to the choice of ethereal solvent for the aforementioned Grignard reactions. Diethyl ether was used for the preparation of isobutylboronic acid (**2-4**), isopentylboronic acid (**2-5**), and 4-phenoxybutylboronic acid (**2-6**). Tetrahydrofuran (THF) was used for the preparation of pent-4-enylboronic acid (**2-7**, Figure 2-2). No desired product was observed when deviating from the stated solvent.

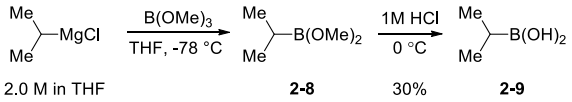
Figure 2-2. Synthesized Primary Alkyboronic Acids.



Isopropylboronic acid was prepared according to a modified literature procedure from a commercially available Grignard.[2] Isopropylmagnesium chloride (2.0 M, THF) was added at -78 °C to a solution of trimethylborate and THF. After coming to room temperature slowly, 1M HCl was added at 0 °C. The resulting solution was extracted

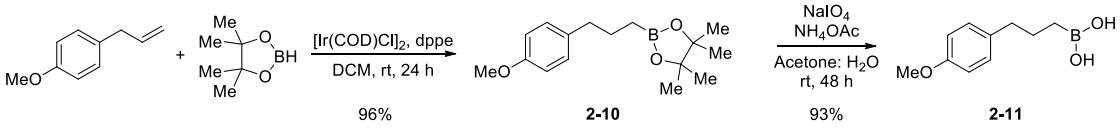
and precipitated out with cold hexanes to give the corresponding secondary alkylboronic acid **2-9** in 30% yield over 2 steps.

Scheme 2-2. Synthesis of **2-9**.



3-(4-methoxyphenyl)propylboronic acid was synthesized in 2 steps following the general protocols from 4-allylanisole.[3,4] Using an iridium catalyst, 4-allyanisole was reacted with pinacolborane through hydroboration to give the resulting pinacol ester **2-10**. Hydrolysis of the boronic ester with sodium periodate, ammonium acetate, water, and acetone produced the boronic acid **2-11** in 93% yield (Scheme 2-3).

Scheme 2-3. Synthesis of **2-11**.

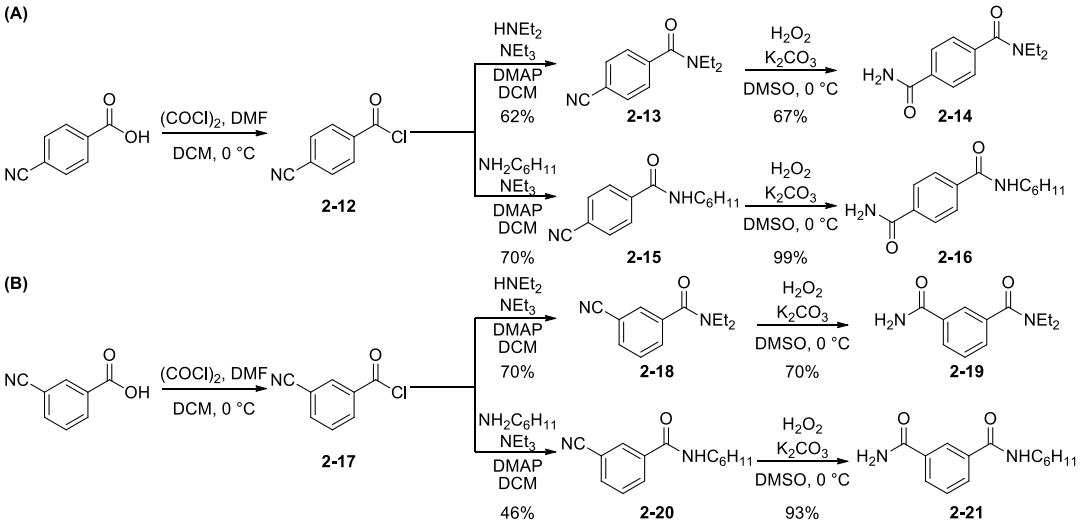


2.2.2 Amide Synthesis

For substituent modification of the primary amide, a series of compounds were prepared to test for compatibility with strong to mild electron withdrawing groups. To probe electronic effects on the reaction, two sets of amides were made. One with the secondary and tertiary amides in the *para* position (**2-14**, **2-16**) to test for strong electron withdrawing effects. A second set of amides were made with the same amide

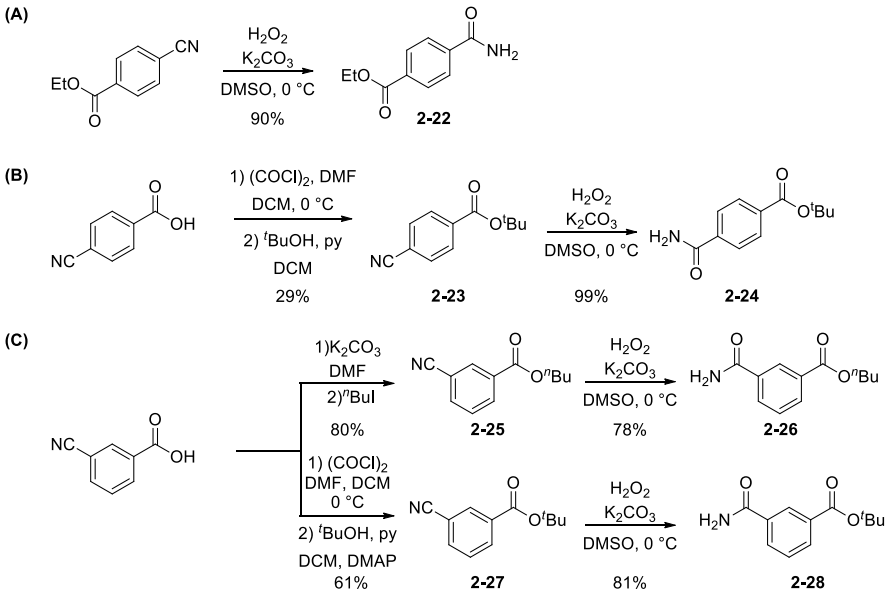
substituents in the *meta* position (**2-19**, **2-21**) to test for inductive electron donating effects. Synthesis was similar for all of these compounds (Scheme 2-4). Starting from 4-cyanobenzoic acid (Scheme 2-4A), the corresponding acyl chloride **2-12** was generated *in situ*, before addition of diethylamine or hexylamine to give the proper tertiary amide **2-13** or secondary amide **2-15**, respectively. The nitrile functionalities were then hydrolized to the primary amides **2-14** and **2-16** in good yield following the general protocol reported by Katritzky.[5] Similarly, 3-cyanobenzoic acid (Scheme 2-4B) was transformed into amides **2-18** and **2-20** through *in situ* generation of the acyl chloride **2-17**, and then addition of the proper amine. Isolated compounds **2-18** and **2-20**, were then converted to final products **2-19** and **2-20** respectively, with excess 30% hydrogen peroxide and catalytic potassium carbonate.[5]

Scheme 2-4. Synthesis of Amides **2-14**, **2-16**, **2-19**, and **2-21**.



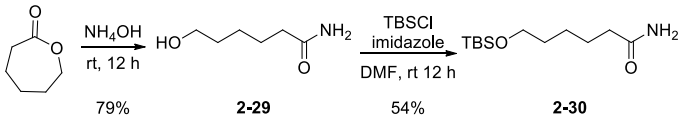
Another series of compounds bearing electron withdrawing ester groups was prepared (Scheme 2-5). Compound **2-22** was synthesized in one step from commercially available ethyl 4-cyanobenzoate in 90% yield (Scheme 2-5A).[5] A *para*-*tert*-butyl ester benzamide was prepared in 2 steps from 4-cyanobenzoic acid (Scheme 2-5B). The requisite acyl chloride was generated *in situ* from a reaction of 4-cyanobenzoic acid with oxalyl chloride, in the presence of catalytic dimethylformamide (DMF) in dichloromethane (DCM), followed by addition of *tert*-butanol and pyridine to generate the sterically hindered ester **2-23**. Using the method established by Katritzky, the nitrile group of ester **2-23** was converted to primary amide **2-24** in nearly quantitative yield. A corresponding set of benzamides bearing esters in the *meta*-position were prepared in 2 steps from 3-cyanobenzoic acid (Scheme 2-5C). Ester **2-25** was prepared through deprotonation of 3-cyanobenzoic acid with potassium carbonate, followed by addition of butyl iodide in excess. The ester was then converted to amide **2-26** in 78% yield. The sterically hindered ester **2-28** was prepared from 3-cyanobenzoic acid in identical fashion as ester **2-24**.

Scheme 2-5. Synthesis of *Para* and *Meta*-Ester Amides.



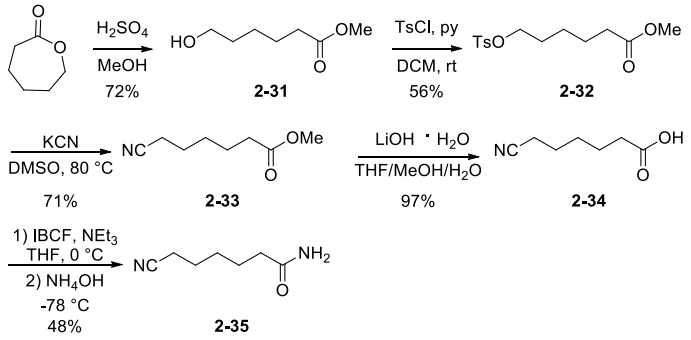
In addition to the substrates bearing electron withdrawing groups, several substrates with alkyl amide substituents with terminal functionality were synthesized. Protected alcohol **2-30** was prepared in 2 steps from commercially available ε-caprolactone (Scheme 2-6). ε-Caprolactone was first reacted with aqueous ammonia to afford 6-hydroxyhexanoamide.[6] The terminal alcohol was then protected with *tert*-butyldimethylsilyl chloride (TBSCl) according to the classic literature protocol.[7]

Scheme 2-6. Synthesis of 6-(tert-butyldimethylsilyloxy)hexanamide.



The synthesis of 6-cyanohexanamide (**2-35**) proved to be a more challenging target and required significantly more effort to generate moderate yields for each individual step (Scheme 2-7). However, through simple functional group manipulation **2-35** was successfully synthesized in 5 steps. First the ε-caprolactone ring was reacted with sulfuric acid in methanol to afford the ester **2-31**.[8] Compound **2-31** was then treated with 4-toluenesulfonyl chloride (TsCl), and subsequent substitution of the tosyl alcohol with potassium cyanide provided nitrile **2-33**. Hydrolysis of the methyl ester, followed by *in situ* generation of the acyl chloride and successive addition of aqueous ammonia provided amide **2-35**.

Scheme 2-7. Synthesis of 6-Cyanohexanamide.



2.3 Cross-Coupling of Substrates

Early development of this reaction began with the cross-coupling of benzamide and isobutylboronic acid (**2-4**). To begin, typical Lam-Chan reaction conditions were chosen for the initial investigation.[9] Since the desired optimal reaction conditions would only require catalytic copper, 10 mol% of the copper precatalyst was employed, along with slight excess of boronic acid (1.5 equiv), base (2.2 equiv), and oxidant (3 equiv).

The reactions were conducted in a variety of solvents at 75 °C for 24 hours to ensure complete conversion of the starting material. All the reactions were run a minimum of two times and the yields reported are the average of those runs. Any exceptions to these conditions are noted.

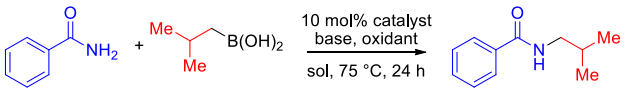
The fundamental key for successful mono-alkylation is the unique mixture of the mild oxidant di-*tert*-butyl peroxide (DTBP), a mild base (sodium trimethylsilanolate, NaOTMS, pK_a' = 12.7)[10], and an alcohol solvent (*tert*-butanol, ^{t}BuOH). Examination of the reaction conditions across a broad scope of compounds revealed remarkable functional group tolerance, as well as successful cross-coupling for both primary and secondary alkylboronic acids.

2.3.1 Optimization

Examination of the cross-coupling between benzamide and isobutylboronic acid (**2-4**) began with typical Lam-Chan reaction conditions in the halogenated solvent 1,2-dichloroethane (DCE) and the copper salt $Cu(OAc)_2$ (Table 2-1, entry 1), which gave trace amounts of desired secondary amide **2-36**. Various oxidants were tested including dry O_2, (diacetoxyiodo)benzene, benzoquinone, 30% hydrogen peroxide solution, *meta*-chloroperbenzoic acid, and *tert*-butyl hydrogen peroxide, all of which yielded >99% starting material by NMR (entries 2-7). By switching to the milder oxidant DTBP, a small, but noticeable yield was seen by NMR (5%, entry 8) of **2-36**. A significant increase in yield was observed after switching to a stronger base, sodium tert-butoxide (Na*O*^{t}Bu, entry 9). An assortment of non-polar and polar solvents were surveyed, including benzene (PhH), acetonitrile (MeCN), THF, ethanol (EtOH), and ^{t}BuOH (entries 10-14). Mono-alkylated amide **2-36** was generated in 36% yield when ^{t}BuOH

was employed (entry 14). Yields were further improved by switching to the mild base NaOTMS, in coordination with ^{t}BuOH as the solvent (entry 15). Product was generated in 87% yield under these conditions. In the presence of this weaker base, the concentration of deprotonated amide is expected to be lower, which would result in lowering the competitive ligation to the copper catalyst. After further optimization of the copper pre-catalyst (entries 16-20), including both copper (I) and copper (II) salts, CuBr emerged as the optimal copper source with 92% assay yield (entry 19). Ligand additives, such as 2,2'-bipyridine (entry 16) did not positively affect the reaction. Finally, other silanolate salts were investigated (entries 21-22), but both resulted in lower yields. All of the reactions reported produced only mono-alkylated secondary amides with no observation of di-alkylation.

Table 2-1. Optimization of Reaction Conditions.



2-4 **2-36**

entry	catalyst	base	oxidant	solvent	yield[a]
1	$Cu(OAc)_2$	Na_2CO_3	Air	DCE	trace
2	$Cu(OAc)_2$	Na_2CO_3	O_2	DCE	trace
3	$Cu(OAc)_2$	Na_2CO_3	$PhI(OAc)_2$	DCE	0%
4	$Cu(OAc)_2$	Na_2CO_3	BQ	DCE	0%
5	$Cu(OAc)_2$	Na_2CO_3	H_2O_2	DCE	0%
6	$Cu(OAc)_2$	Na_2CO_3	*m*-CPBA	DCE	0%
7	$Cu(OAc)_2$	Na_2CO_3	TBHP	DCE	0%
8	$Cu(OAc)_2$	Na_2CO_3	DTBP	DCE	5%
9	$Cu(OAc)_2$	NaO^tBu	DTBP	DCE	31%
10	$Cu(OAc)_2$	NaO^tBu	DTBP	PhH	16%
11	$Cu(OAc)_2$	NaO^tBu	DTBP	MeCN	8%
12	$Cu(OAc)_2$	NaO^tBu	DTBP	THF	16%
13	$Cu(OAc)_2$	NaO^tBu	DTBP	EtOH	0%
14	$Cu(OAc)_2$	NaO^tBu	DTBP	^{t}BuOH	36%
15	$Cu(OAc)_2$	NaOTMS	DTBP	^{t}BuOH	87%
16	$Cu(OAc)_2$[b]	NaOTMS	DTBP	^{t}BuOH	60%
17	Cu(OAc)	NaOTMS	DTBP	^{t}BuOH	71%
18	CuCl	NaOTMS	DTBP	^{t}BuOH	70%
19	CuBr	NaOTMS	DTBP	^{t}BuOH	92%
20	CuI	NaOTMS	DTBP	^{t}BuOH	88%
21	CuBr	NaOTBS	DTBP	^{t}BuOH	87%
22	CuBr	NaOTIPS	DTBP	^{t}BuOH	50%

[a] Yield determined using NMR. [b] 10 mol% 2-2'-bipyridine DCE = 1,2-dichloroethane; BQ = Benzoquinone; *m*-CPBA = *meta*-chloroperbenzoic acid; TBHP = *tert*-butyl hydrogen peroxide; DTBP = di-tert-butyl peroxide.

2.3.2 Scope

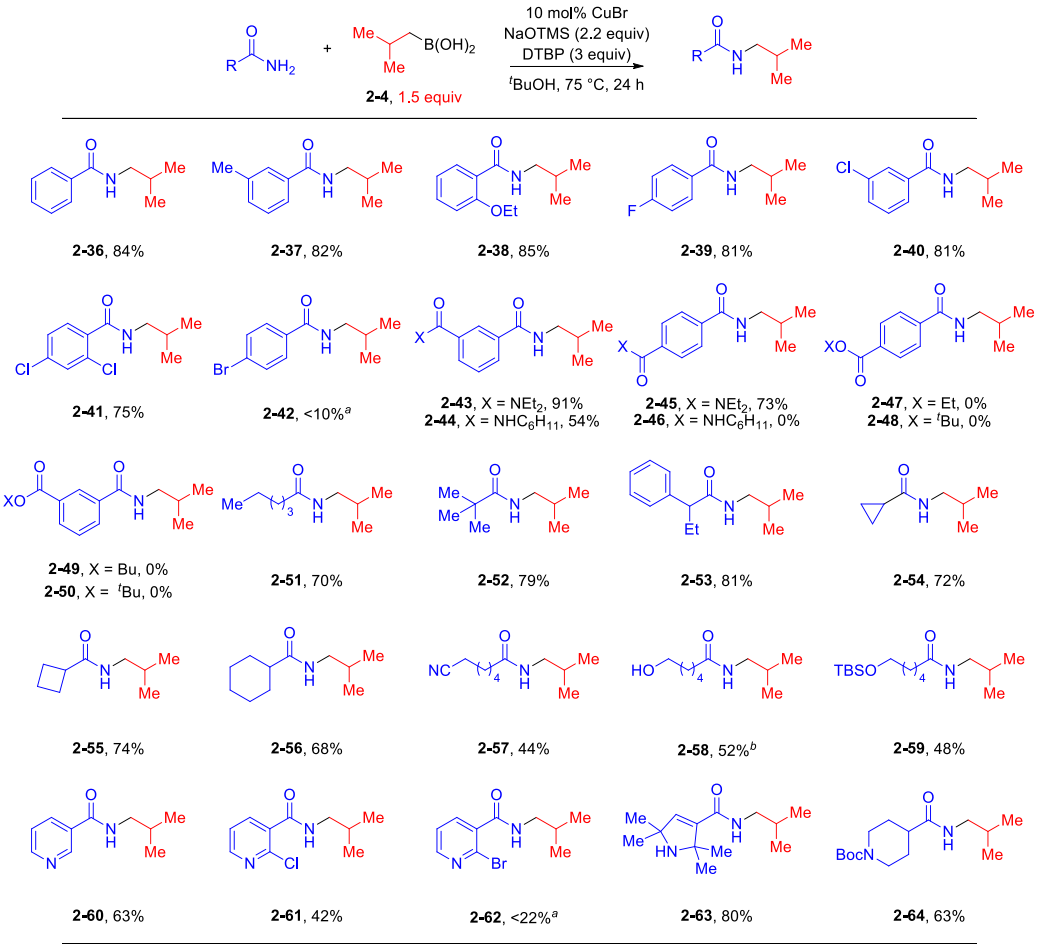
With optimal reaction conditions identified, a great deal of effort was put forth to demonstrate that this transformation is a more general, orthogonal method for the synthesis of secondary amides. The conversion of the carbon-boron (C-B) bond to the carbon-nitrogen (C-N) bond proved to not only be highly universal and tolerant of functionality on both the amide and alkylboronic acid coupling partners, but it is also highly scalable (ca. 19 mmol).

Under optimal conditions, amide **2-36** was isolated in 84% yield on a 1.0 mmol scale (Scheme 2-8). Modification of the aromatic ring did not hinder the reaction, including the alkyl variant **2-37,** which was isolated in 82% yield. Changes in the electronic nature of the ring via the electron donating *ortho*-ethoxy group (**2-38**) proved to increase the yield slightly when compared to the model substrate. Halogenated aromatic systems were also well tolerated, including mildly electron withdrawing fluorine amide **2-39**, *meta*-chlorinated amide **2-40,** and di-halogenated compound **2-41**. Amide **2-40** was synthesized on a both a 1 mmol and 19 mmol scale resulting in identical yields, proving the scalability of this method. However, aromatic bromides (**2-42**) failed to react, resulting in low yields of desired product.

While electron-rich (**2-38**) and mildly electron-deficient systems (**2-39**) were well tolerated, benzamides containing highly electron-withdrawing groups failed to react. Tertiary and secondary amides (**2-43** and **2-44**) resulted in high (91%) and moderate (54%) yields when placed in the moderately electron-withdrawing *meta* position. However, when switching to the strongly electron-withdrawing *para* position, the yield of the diethyl tertiary amide **2-45** dropped in yield while the secondary amide **2-46** failed to react at all, resulting only in isolation of starting material. All synthesized

esters, both alkyl and aromatic (**2-47** *to* **2-50**) were completely incompatible under preparative conditions.

Scheme 2-8. Scope with Respect to Primary Amides.



[a] Yield determined using NMR, [b] 20 mol% CuBr, 2 equiv boronic acid.

Aliphatic amide systems were well tolerated, including an un-substituted aliphatic chain (**2-51**, 70%). Steric hindrance was also tolerated alpha to the carbonyl group. Substrates **2-52** and **2-53** were generated in 79% and 81%, respectively. Amides

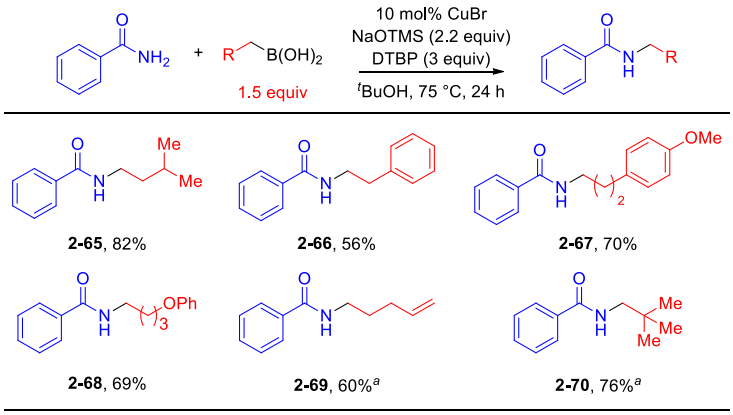
containing carbocyclic rings gave good yields (**2-56**, 68%), including those with high ring strain, such as cyclopropyl (**2-54**, 72%) and cyclobutyl (**2-55**, 74%). In addition to the tolerance for steric hindrance and ring strain, functional group tolerance of the aliphatic amides was also high. Nitrile containing amide **2-35** was mono-alkylated to afford amide **2-57** in 44% yield. Terminal alcohol **2-29** and protected alcohol **2-30** were also successfully cross-coupled with isobutylboronic acid in 52% and 46% yield, respectively.

Heterocyclic amides also proved to be competent cross-coupling partners under these conditions. Commercially available heteroaromatic amide nicotinamide was alkylated in 63% yield (**2-60**). The addition of an *ortho*-chlorine was also a suitable substrate (**2-61**). As with the halogenated benzamide derivatives, bromides were not tolerated under these reaction conditions, and exhibited significant isolation problems. Nonaromatic heterocycles, including free amine **2-63** and Boc-protected amine **2-64** were tolerated under optimum conditions, resulting in 80% and 63% yields, respectively.

The catalytic cross-coupling reaction was not limited to only isobutylboronic acid (**2-4**). Several alkylboronic acids bearing various functional groups were prepared and utilized as alkylating reagents (Scheme 2-9). Amides **2-65** and **2-66** were prepared in 82% and 56% yield when isopentyl- and phenethylboronic acids, respectively, were cross-coupled with benzamide. Ether containing alkylboronic acids were also well tolerated under the catalytic conditions, resulting in amides **2-67** and **2-68** in 70% and 69% yields, respectively. Using a slightly higher catalyst loading (20 mol%) and an excess of pent-4-enylboronic acid (2 equiv, **2-7**), amide **2-69** was synthesized in 60%

yield. Even the more sterically demanding neopentylboronic acid was tolerated in good yield (**2-70**, 70%).

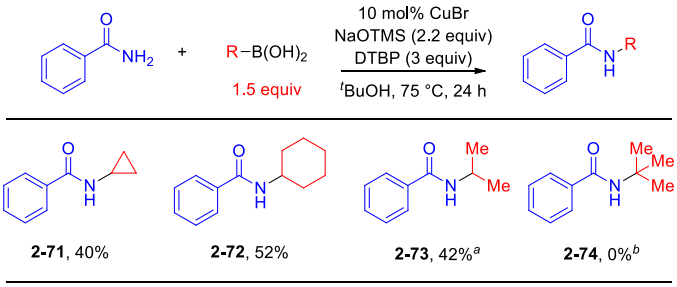
Scheme 2-9. Scope with Respect to Primary Alkylboronic Acids.



[a] 20 mol% CuBr, 2 equiv boronic acid.

A brief investigation into cross-coupling with secondary and tertiary alkylboronic acids was also conducted (Scheme 2-10). Secondary alkylbronic acids showed successful alkylation in regards to two types of systems. Amides **2-71** and **2-72** were prepared from secondary cyclopropyl- and cyclohexylboronic acids in moderate yields. The non-cyclic aliphatic isopropylboronic acid was used as an alkylating reagent in 42% yield (**2-73**). Tertiary alkylboronic acids were not suitable alkylating reagents under these conditions (**2-74**).

Scheme 2-10. Scope with Respect to Secondary and Tertiary Alkylboronic Acids.



[a] 20 mol% CuBr, 2 equiv boronic acid, [b] Yield determined using NMR.

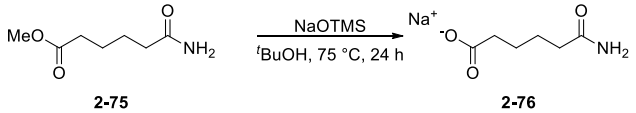
2.4 Discussion

The results reported in this chapter illustrate the extent and generality of this novel transformation. The conversion of a C-B bond to a C-N bond, while known for a relatively long period of time, has remained under-developed. Various attempts have been made to achieve this conversion, however, these have been limited primarily to the synthesis of amines and usually require highly electrophilic boronate reagents.[11-13] Additionally, the scope in alkyl-boronates is limited with most existing methods utilizing only methyl and cyclopropylboroantes.[14,15] Notably, both of these boronate sytems do not possess hydrogen atoms suitable for β–hydride elimination.[16] The synthesis of amides via C-B to C-N conversion has recently been investigated, but requires extremely harsh reaction conditions and excessive amounts of dangerous and hazardous chemicals.[17] The reaction reported herein is a mild, orthogonal, and general protocol for the formation of C-N bonds from alkyl C-B bonds using a copper catalyst. The reaction is highly functional group tolerant; only a select group of functionalities are incompatible with this transformation.

While some halogenated aromatic species are tolerated under the mildly basic conditions, the reaction remains intolerant to aromatic bromides, which generates only a minimal amount of desired product. A possible cause for the low yields of desired amide **2-42** and **2-62** could be due to competitive oxidative addition of the copper catalyst into the aryl-bromide. A recent study has shown that under basic conditions, copper (I) salts can oxidatively add to an aryl-bromine bond to form a copper (III) complex.[18] Aryl-iodide containing species were not tested due to the low yields obtained in cross-coupling with the aforementioned bromide systems.

Unfortunately, esters proved to be completely incompatible under these reaction conditions. Both aromatic (**2-47** *to* **2-50**) and alkyl amides with pendant esters provided 0% of the desired coupling product due to competitive hydrolysis. We believe that the Lewis acidic catalyst and the mildly basic conditions promote the hydrolysis of the ester functionality. Several control experiments were run and showed decomposition of the esters when only NaOTMS and CuBr were present. Furthermore, in the presence of NaOTMS, esters have been known to form the sodium carboxylate.[19] This theory was tested and proven correct through analysis with Atmospheric Pressure Chemical Ionization, negative mode (Figure 2-3).

Figure 2-3. Formation of Sodium Carboxylate **2-76**.

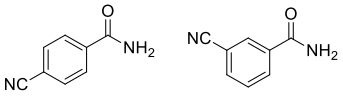


2-75 **2-76**

Alkyl nitrile (**2-35**) proved to be a suitable coupling partner, but aromatic nitrile substituents proved to be poor reactants (Figure 2-4, **2-77** and **2-78**). Similar to the

strongly electron-withdrawing secondary amide **2-16**, the electron withdrawing nature of the nitriles proved to hinder the alkylation of the amide.

Figure 2-4. Aryl Nitriles **2-77** and **2-78.**



2-77 **2-78**

While not extensive, the relative scope for the mono-alkylation of primary amides has been improved. A significant challenge of this chemistry is the synthesis of the boronic acid starting materials. While arylboronic acids are well established and available commercially with a wide range of functional groups, known alkylboronic acids remain limited to basic hydrocarbon functionality. The resulting small scope in Schemes 2-9 and 2-10 are a result of the lack of synthetic methods to readily produce functional group containing alkylboronic acids. Finally, alkylboronic acids are extremely temperature unstable, and have to be stored well below room temperature (ca. 5-10 °C). If allowed to warm to room temperature, formation of the trimeric boroxines occurs resulting in decomposition of the boronic acid.

2.5 Conclusions

In summary, a novel, mild, and efficient, functional group tolerant protocol for the catalytic cross-coupling of primary amides with alkylboronic acids was developed, proceeding exclusively with mono-alkylation. In addition to the inexpensive, commercially available copper pre-catalyst, this reaction proceeds without the aid of

any expensive ligand, typical of many cross-coupling reactions. The key to success was the identification of the mild base NaOTMS and the use of DTBP as an effective oxidant for this catalytic process. Not only is this a significant improvement over previously published protocols for the conversion of C-B bonds to C-N bonds to make secondary amides, but it also considerably expands the scope of Lam-Chan type reactions in organometallic synthesis.

2.6 Experimental Procedures & Data

2.6.1 General Experimental Details

THF and toluene were dried on alumina according to published procedures.[20] 1,2-dichloroethane (DCE), acetonitrile, and ethanol were purchased in an anhydrous septa sealed bottle. *Tert*-Butanol (^{t}BuOH) was distilled from calcium hydride and sparged with nitrogen prior to use, and stored under nitrogen in a sealed vessel. Copper bromide and sodium trimethylsilanolate (95%, Sigma-Aldrich) were purchased commercially and used as received. The bulk of these materials were stored in a nitrogen filled glove box, with samples being removed from the glovebox and stored in a desiccator under air for up to one week prior to use. All hot glassware was oven dried for a minimum of two hours or flame-dried under vacuum prior to use. Cyclobutanecarboxamide and 6-cyanohexanamide were prepared using a general protocol from cyclobutanecarboxcylic acid and 6-cyanohexanoic acid, respectively.[21 2] N,N-diethylterephthalamide, N3,N3-diethylbenzene-1,3-dicarboxamide, and N3-hexylbenzene-1,3-dicarboxamide were prepared in 2 steps using a literature protocol from 4-cyano-benzoic acid and 3-cyano-benzoic acid, respectively.[5,22] 6-

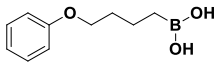
hydroxyhexanamide was synthesized directly from ε-Caprolactone according to the literature procedure.[6] 6-hydroxyhexanamide was protected to afford 6-(tert-butyldimethylsilyloxy)hexanamide.[7] Tert-butyl 4-carbamoylpiperidine-1-carboxamide was prepared according to the literature procedure.[23] All other substrates and reagents were purchased in highest analytical purity from commercial suppliers and used as received. Optimization of the reaction conditions in Table 1 were performed using standard Schlenk technique on a 0.3 mmol scale in 16 mm x 100 mm threaded test tubes sealed with septum caps, and heated and stirred in temperature controlled oil baths. Product yields in Table 2-1 obtained by NMR. All other reactions, unless otherwise noted, were carried out using standard Schlenk technique on a 1.0 mmol scale in a 10 mL recovery flask fitted with a 14/20 septum. "Double manifold" refers to a standard Schlenk-line gas manifold equipped with nitrogen and vacuum (ca. 100 mtorr).

All yields reported in tables of main text reflect the average of isolated yields of at least two independent runs. Any deviation between these yields and those reported in this supporting information reflect the difference between individual and average yields.

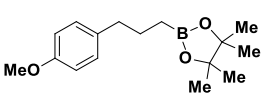
400 MHz ^{1}H, 101 MHz ^{13}C, 128 MHz ^{11}B, and 376 MHz ^{19}F spectra were obtained on a 400 MHz FT-NMR spectrometer equipped with a Bruker CryoPlatform. 600 MHz ^{1}H and 151 MHz ^{13}C spectra were obtained on a 600 MHz FT-NMR spectrometer equipped with a Bruker SMART probe. All samples were analyzed in the indicated deutero-solvent and were recorded at ambient temperatures. Chemical shifts are reported in ppm. ^{1}H NMR spectra were calibrated using the residual protio-signal in deutero-solvents as a standard. ^{13}C NMR spectra were calibrated using the deutero-solvent as a standard. IR spectra were recorded on an FT-IR spectrometer as thin films. Column chromatography was performed with 40-63 μm silica gel with the eluent

reported in parentheses. Analytical thin-layer chromatography (TLC) was performed on precoated glass plates and visualized by UV or by staining with $KMnO_4$. All NMR yields are reported using 1,3,5-trimethoxybenzene as an internal standard. GCMS data was collected using an Agilent 6850 series GC and 5973 MS detector. Low resolution ESI data was collected on a Thermo LCQ Advantage running in positive ion mode. High resolution mass spectrometry data was obtained at the University of Illinois at Urbana-Champaign or at the University of Delaware, Newark on a Waters GCT Premier.

2.6.2 Novel Alkylboronic Acids

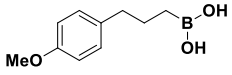


4-phenoxybutylboronic acid (**2-6**) was prepared according to the modification of the literature procedure[1] from 4-phenoxy-1-butylbromide (2.5 g, 10.9 mmol), magnesium turnings (292 mg, 12.0 mmol), 1,2-dibromoethane (5 drops), anhydrous diethyl ether, and trimethylborate (1.09 mL, 9.8 mmol) to afford the alkyl boronic acid (1.25 g, 66%) as a white solid: mp = 85-88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.33 – 7.27 (m, 2H), 7.02 – 6.83 (m, 3H), 4.44 (s, 2H), 3.97 (dt, *J* = 9.7, 6.2 Hz, 2H), 1.94 – 1.70 (m, 2H), 1.63 (dd, *J* = 9.5, 6.2 Hz, 2H), 0.93 (dt, *J* = 19.1, 7.7 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 159.0, 129.6, 120.8, 114.6, 67.7, 31.6, 20.9, 20.2; ^{11}B NMR (128 MHz, $CDCl_3$) ∂ 33.0.; FTIR (cm^{-1}): 3278, 2940, 2870, 1601, 1586, 1493, 1475, 1457, 1380, 1239, 1138, 1035, 753. HRMS (EI) m/z, calculated for $[C_{10}H_{13}O_3B]^+$: 192.0958; found: 192.0950.



3-(3-(4-methoxyphenyl)propyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**2-10**) was prepared according to the modification

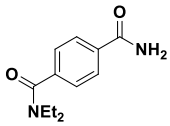
of the literature procedure[3] from 4-allylanisole (1.56 mL, 10.12 mmol), pinacolborane (1.577 mL, 12.15 mmol), bis(1,5-cyclooctadiene) diiridium(I) dichloride (68 mg, 0.101 mmol), 1,2-bisdiphenylphosphinoethane (80.65 mg, 0.202 mmol), and anhydrous DCM (15 mL) and purified by flash silica gel chromatography (hexanes → 50:1 hexanes: diethyl ether) to afford the pinacol ester (2.69 g, 96%) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) ∂ 7.09 (d, *J* = 8.4 Hz, 2H), 6.81 (d, *J* = 8.5 Hz, 2H), 3.78 (s, 3H), 2.55 (t, *J* = 7.7 Hz, 2H), 1.69 (p, *J* = 7.8 Hz, 2H), 1.24 (s, 12H), 0.81 (t, *J* = 7.9 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 157.7, 135.0, 129.6, 113.7, 83.1, 55.4, 53.6, 37.8, 26.5, 25.0; ^{11}B NMR (128 MHz, $CDCl_3$) ∂ 34.1.; FTIR (cm^{-1}): 2978, 2932, 2863, 2835, 1612, 1513, 1372, 1320, 1246, 1145, 1038, 968, 849. HRMS (EI) m/z, calculated for $[C_{16}H_{25}O_3B]^+$: 276.1897; found: 276.1892.



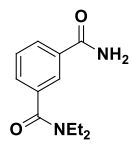
3-(4-methoxyphenyl)propylboronic acid (**2-**11) was prepared according to the modification of the literature procedure[4] from 2-(3-(4-methoxyphenyl)propyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.5 g, 5.43 mmol), sodium periodate (3.48 g, 16.29 mmol), ammonium acetate (1.26 g, 16.29 mmol), water (34 mL), and reagent grade acetone (68 mL) to afford the alkyl boronic acid (980 mg, 93%) as a white solid: mp = 98-102 °C; ^{1}H NMR (600 MHz, $CDCl_3$) ∂ 7.09 (t, *J* = 8.3 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 1H), 6.78 (d, *J* = 8.6 Hz, 1H), 4.08 (d, *J* = 13.8 Hz, 2H), 3.77 (d, *J* = 15.4 Hz, 3H), 2.56 (dt, *J* = 16.2, 7.5 Hz, 2H), 1.72 (dp, *J* = 23.0, 7.7 Hz, 2H), 0.88 (t, *J* = 7.6 Hz, 1H), 0.83 (t, *J* = 7.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 157.8, 134.5, 129.5, 113.7, 55.4, 37.6, 26.6, 25.7; ^{11}B NMR (128 MHz, $CDCl_3$) ∂ 33.0; FTIR (cm^{-1}): 3252, 2921, 2868, 1612, 1515, 1360, 1301, 1274, 1244,

1179, 1099, 814. HRMS (EI) m/z, calculated for $[C_{10}H_{13}O_3B]^+$: 192.0958; found: 192.0964.

2.6.3 Novel Amide Starting Reagents

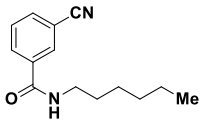


N,N-diethylterephthalamide (**2-14**) was prepared according to the modification of the literature procedure[5] from 4-cyano-N,N-diethylbenzamide (1.0 g, 4.9 mmol), 30% hydrogen peroxide (1.0 mL), potassium carbonate (68 mg, 0.5 mmol), and DMSO (3 mL) to afford the primary amide (722 mg, 67%) as an off-white solid: mp = 122-125 °C; ^{1}H NMR (600 MHz, $CDCl_3$) 7.82 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 8.1 Hz, 2H), 6.38 (s, 1H), 5.76 (s, 1H), 3.55 (d, *J* = 7.1 Hz, 2H), 3.20 (d, *J* = 7.0 Hz, 2H), 1.25 (t, *J* = 7.0 Hz, 3H), 1.09 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) ∂ 170.4, 168.7, 140.8, 134.1, 127.8, 126.7, 43.4, 39.5, 14.4, 13.1; FTIR (cm^{-1}): 3366, 3200, 3016, 2975, 2933, 1670, 1616, 1407, 1291, 1136, 935, 860. HRMS (EI) m/z, calculated for $[C_{12}H_{16}N_2O_2]^+$: 220.1212; found: 220.1211.

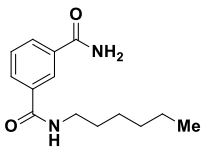


N3,N3-diethylbenzene-1,3-dicarboxamide (**2-19**) was prepared according to the modification of the literature procedure[5] from 3-cyano-N,N-diethylbenzamide (800 mg, 4.0 mmol), 30% hydrogen peroxide (1.2 mL), potassium carbonate (55 mg, 0.5 mmol), and DMSO (3 mL) to afford the primary amide (778 mg, 70%) as a white solid: mp = 139-142 °C; ^{1}H NMR (600 MHz, $CDCl_3$) ∂ 7.85 (d, *J* = 7.7 Hz, 1H), 7.81 (s, 1H), 7.63 – 7.39 (m, 2H), 6.42 (s, 1H), 5.81 (s, 1H), 3.54 (s, 2H), 3.24 (s, 2H), 1.25 (s, 3H), 1.11 (s, 3H).; ^{13}C NMR (151 MHz, $CDCl_3$) ∂

170.5, 168.8, 137.6, 134.0, 129.7, 129.0, 128.4, 125.5, 43.6, 39.6, 14.4, 13.0; FTIR (cm^{-1}): 3365, 3201, 2975, 2936, 1670, 1617, 1430, 1383, 1291, 1097. HRMS (EI) m/z, calculated for $[C_{12}H_{16}N_2O_2]^+$: 220.1212; found: 220.1211.

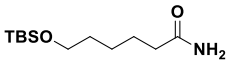


3-cyano-N-hexylbenzamide (**2-20**) was prepared according to the modification of the literature procedure[22] from 3-cyanobenzoic acid (2.0 g, 13.6 mmol), oxalyl chloride (1.7 mL, 20.4 mmol), DMF (0.09 mL, 1.36 mmol), anhydrous DCM (20 mL), hexylamine (2.2 mL, 16.32 mmol), triethylamine (2.27 mL, 16.32 mmol), and DMAP (250 mg, 2.1 mmol to afford the secondary amide (1.43 g, 46%) as an off-white solid: mp = 58-61 °C; ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 8.05 (s, 1H), 8.00 (dt, J = 7.9, 1.4 Hz, 2H), 7.77 (dt, J = 7.7, 1.4 Hz, 2H), 7.57 (t, J = 7.8 Hz, 2H), 6.17 (s, 1H), 3.46 (q, 2H), 1.79 – 1.53 (m, 2H), 1.51 – 1.19 (m, 6H), 0.90 (d, J = 6.2 Hz, 3H).; ^{13}C NMR (151 MHz, $CDCl_3$) ∂ 165.4, 136.3, 134.7, 131.3, 130.7, 129.7, 118.1, 113.2, 40.6, 31.6, 29.7, 26.8, 22.7, 14.2; FTIR (cm^{-1}): 3317, 3071, 2956, 2929, 2857, 2232, 1723, 1641, 1546, 1298, 1204, 814. HRMS (EI) m/z, calculated for $[C_{14}H_{18}N_2O]^+$: 230.1419; found: 230.1422.

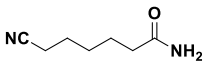


N3-hexylbenzene-1,3-dicarboxamide (**2-21**) was prepared according to the modification of the literature procedure[5] from 3-cyano-N-hexylbenzamide (700 mg, 3.0 mmol), 30% hydrogen peroxide (1.0 mL), potassium carbonate (42 mg, 0.3 mmol), and DMSO (2.5 mL) to afford the primary amide (702 mg, 93%) as a white solid: mp = 148-150 °C; ^{1}H NMR (400 MHz, d_6-DMSO) ∂ 8.54 (t, J = 5.7 Hz, 1H), 8.32 (s, 1H), 8.06 (s, 1H), 8.02 – 7.89 (m, 2H), 7.53 (t, J = 7.7 Hz, 1H), 7.48 (s, 1H), 3.25 (d, J = 6.0 Hz, 2H), 1.65 – 1.46 (m, 2H), 1.41

– 1.20 (m, 6H), 1.03 – 0.77 (m, 3H); ^{13}C NMR (101 MHz, d_6-DMSO) ∂ 167.5, 165.7, 134.9, 134.4, 129.8, 129.8, 128.3, 126.5, 39.9, 31.1, 29.1, 26.2, 22.1, 13.99, 13.96; FTIR (cm^{-1}): 3383, 3318, 3174, 2953, 2924, 2859, 1727, 1660, 1631, 1531, 1275, 1135. HRMS (EI) m/z, calculated for $[C_{14}H_{20}N_2O_2]^+$: 248.1525; found: 248.1520.



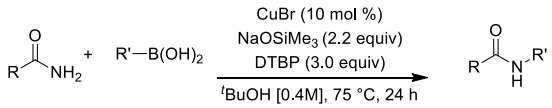
6-(tert-butyldimethylsilyloxy)hexanamide (**2-30**) was prepared according to the modification of the literature procedure[7] from 6-hydroxyhexanamide (3.30 g, 25 mmol), TBSCl (4.80 g, 32 mmol), imidazole (2.20 g, 32 mmol), and DMF (35 mL) and purified by flash silica gel chromatography (1:1 hexanes: ethyl acetate) to afford the protected alcohol (3.30 g, 54%) as a white solid; mp = 47-50 °C; ^{1}H NMR (600 MHz, $CDCl_3$) ∂ 5.41 (s, 1H), 3.61 (t, J = 6.5 Hz, 2H), 2.23 (d, J = 7.7 Hz, 2H), 1.66 (p, J = 7.6 Hz, 2H), 1.56 – 1.49 (m, 2H), 1.43 – 1.35 (m, 2H), 0.89 (s, 9H), 0.04 (s, 6H);^{13}C NMR (151 MHz, $CDCl_3$) ∂ 175.3, 63.0, 35.9, 32.5, 26.0, 25.5, 25.3, 18.4, -5.3; FTIR (cm^{-1}): 3367, 3189, 2930, 2886, 2857, 1653, 1635, 1462, 1417, 1255, 1104, 836, 775. HRMS (EI) m/z, calculated for $[C_{11}H_{24}NO_2Si]^+$: 230.1576; found: 230.1573.



6-cyanohexanamide (**2-35**) was prepared according to the modification of the literature procedure[21] from 6-cyanohexanoic acid (1.00g, 7.2 mmol), isobutyl chloroformate (1.04 mL, 8.0 mmol), triethylamine (1.25 mL, 9.0 mmol), anhydrous THF (6 mL), and ammonium hydroxide (5 mL) to afford the primary amide (484 mg, 48%) as a white solid; mp = 96-98 °C; ^{1}H NMR (600 MHz, $CDCl_3$) ∂ 5.37 (s, 1H), 2.36 (t, J = 7.1 Hz, 2H), 2.25 (t, J = 7.4 Hz, 2H), 1.70 (p, J = 7.4 Hz, 4H), 1.56 – 1.46 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) ∂ 174.7, 119.6, 35.3,

28.2, 25.1, 24.4, 17.0; FTIR (cm^{-1}): 3347, 3185, 2949, 2876, 1668, 1635, 1466, 1420. HRMS (EI) m/z, calculated for $[C_7H_{12}N_2O]^+$: 140.0950; found: 140.0956.

2.6.4 Copper-Catalyzed Alkylation of Primary Amides



General Protocol A.

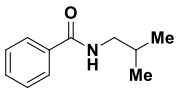
A hot 10 mL recovery flask equipped with a magnetic stir bar was attached to a double manifold and cooled under vacuum. Once cooled, the flask was backfilled with nitrogen and removed from the manifold. The flask was then charged with CuBr (0.1 equiv), primary amide (1.0 equiv), boronic acid (1.5 equiv), sodium trimethylsilanolate (2.2 equiv), and fitted with a rubber septum. The flask was then evacuated and backfilled three times with nitrogen. Under nitrogen, 2.5 mL of anhydrous ^{t}BuOH, followed by di-*tert*-butyl peroxide (3.0 equiv) were added via syringe. The flask was then placed in a temperature controlled oil bath at 75 °C and stirred for 24 hours. The flask was cooled to room temperature, and diluted with CH_2Cl_2, and filtered through celite. The celite was washed with 30ml of CH_2Cl_2. The filtrate was washed with saturated aqueous sodium thiosulfate (1x), brine (1x), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The product was purified by flash chromatography on silica gel using the indicated eluent mixture.

General Protocol B.

A hot 10 mL recovery flask equipped with a magnetic stir bar was attached to a double manifold and cooled under vacuum. Once cooled, the flask was backfilled with nitrogen

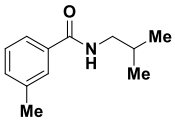
and removed from the manifold. The flask was then charged with CuBr (0.1 equiv), boronic acid (1.5 equiv), sodium trimethylsilanolate (2.2 equiv), and fitted with a rubber septum. The flask was then evacuated and backfilled three times with nitrogen. A second hot 10 mL recovery flask was attached to a double manifold and cooled under vacuum. Once cooled, the flask was backfilled with nitrogen and removed from the manifold. The flask was then charged with the primary amide (1.0 equiv) and fitted with a rubber septum. The flask was then evacuated and backfilled three times with nitrogen. Under nitrogen, 2.5 mL of anhydrous ^{t}BuOH was added via syringe to the amide containing recovery flask. The ^{t}BuOH/amide solution was then cannula transferred to the CuBr/ boronic acid/ sodium trimethylsilanolate containing recovery flask. Under nitrogen, di-*tert*-butyl peroxide (3.0 equiv) was added via syringe. The flask was then placed in a temperature controlled oil bath at 75 °C and stirred for 24 hours. The flask was cooled to room temperature, and diluted with CH_2Cl_2, and filtered through celite. The celite was washed with 30ml of CH_2Cl_2. The filtrate was washed with saturated aqueous sodium thiosulfate (1x), brine (1x), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The product was purified by flash chromatography on silica gel using the indicated eluent mixture.

2.6.5 Cross-Coupling of Primary Amides

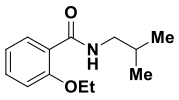


(**2-36**). According to general protocol A: CuBr (14.4 mg, 0.1 mmol), benzamide (121 mg, 1.0 mmol), isobutylboronic acid (153 mg, 1.5 mmol), sodium trimethylsilanolate (246 mg, 2.2 mmol), anhydrous ^{t}BuOH (2.5 mL), and di-*tert*-butyl peroxide (0.55 mL, 3.0 mmol) were combined under nitrogen and

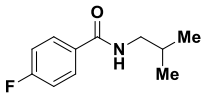
heated at 75 °C for 24 h. The reaction was worked up according to general protocol A and purified by flash silica gel chromatography (5:1 hexanes: ethyl acetate) to afford secondary amide 1 (150 mg, 85%) as a yellow solid: mp = 59-62 °C; ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.76 (dd, *J* = 7.1, 1.8 Hz, 2H), 7.54 – 7.39 (m, 3H), 3.30 (t, *J* = 6.5 Hz, 2H), 1.91 (dt, *J* = 13.4, 6.7 Hz, 1H), 1.55 (s, 1H), 1.25 (s, 1H), 0.99 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) ∂ 167.7, 135.1, 131.4, 128.7, 126.9, 47.5, 28.8, 20.3; FTIR (cm^{-1}): 3309, 2960,2929, 2870, 1636, 1540, 1291, 696. HRMS (EI) m/z, calculated for $[C_{11}H_{15}NO]^{+}$: 177.1154; found: 177.1156.



(**2-37**). According to general protocol A: CuBr (14.4 mg, 0.1 mmol), m-toluamide (135 mg, 1.0 mmol), isobutylboronic acid (153 mg, 1.5 mmol), sodium trimethylsilanolate (246 mg, 2.2 mmol), anhydrous ^{t}BuOH (2.5 mL), and di-*tert*-butyl peroxide (0.55 mL, 3.0 mmol) were combined under nitrogen and heated at 75 °C for 24 h. The reaction was worked up according to general protocol A and purified by flash silica gel chromatography (3:1 hexanes: ethyl acetate) to afford secondary amide 2 (154 mg, 81%) as a yellow solid: mp = 44-46 °C; ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.59 (s, 1H), 7.56 – 7.48 (m, 1H), 7.39 – 7.28 (m, 2H), 6.13 (s, 1H), 3.29 (t, *J* = 6.4 Hz, 2H), 2.40 (s, 3H), 1.90 (hept, *J* = 6.8 Hz, 1H), 0.98 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 167.9, 138.6, 135.0, 132.2, 128.6, 127.7, 123.8, 47.4, 28.8, 21.5, 20.3; FTIR (cm^{-1}): 3314, 3063, 2959, 2925, 2870, 1639, 1586, 1543, 1466, 1319, 1292, 1156, 693. HRMS (EI) m/z, calculated for $[C_{12}H_{17}NO]^{+}$: 191.1310; found: 191.1314.

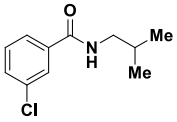


(**2-38**). According to general protocol A: CuBr (14.4 mg, 0.1 mmol), 2-ethoxybenzamide (165 mg, 1.0 mmol), isobutylboronic acid (153 mg, 1.5 mmol), sodium trimethylsilanolate (246 mg, 2.2 mmol), anhydrous ^{t}BuOH (2.5 mL), and di-*tert*-butyl peroxide (0.55 mL, 3.0 mmol) were combined under nitrogen and heated at 75 °C for 24 h. The reaction was worked up according to general protocol A and purified by flash silica gel chromatography (3:1 hexanes: ethyl acetate) to afford secondary amide 3 (180 mg, 81%) as a white solid: mp = 56-59 °C; ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 8.23 (dd, J = 7.8, 1.8 Hz, 1H), 8.10 (s, 1H), 7.46 – 7.37 (m, 1H), 7.07 (t, J = 7.8 Hz, 1H), 6.95 (d, J = 8.2 Hz, 1H), 4.20 (q, J = 7.0 Hz, 2H), 3.32 (t, J = 6.5 Hz, 2H), 1.96 – 1.82 (m, 1H), 1.52 (t, J = 7.0 Hz, 3H), 1.00 (d, J = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 165.3, 156.9, 132.5, 132.4, 121.7, 121.2, 112.1, 64.6, 28.5, 20.4, 15.0; FTIR (cm^{-1}): 3407, 2959, 2871, 1656, 1600, 1536, 1474, 1390, 1232, 1162, 1027, 755. HRMS (EI) m/z, calculated for $[C_{13}H_{19}NO_2]^{+}$: 221.1416; found: 221.1424.

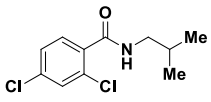


(**2-39**). According to general protocol A: CuBr (14.4 mg, 0.1 mmol), 4-flurobenzamide (140 mg, 1.0 mmol), isobutylboronic acid (153 mg, 1.5 mmol), sodium trimethylsilanolate (246 mg, 2.2 mmol), anhydrous ^{t}BuOH (2.5 mL), and di-*tert*-butyl peroxide (0.55 mL, 3.0 mmol) were combined under nitrogen and heated at 75 °C for 24 h. The reaction was worked up according to general protocol A and purified by flash silica gel chromatography (3:1 hexanes: ethyl acetate) to afford secondary amide 4 (157 mg, 80%) as a light yellow solid: mp = 82-85 °C; ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.88 – 7.70 (m, 2H), 7.17 – 7.06 (m, 2H), 6.06 (s, 1H), 3.29 (t, J = 6.5 Hz, 2H), 1.97 – 1.84 (m, 1H), 0.98 (d, J = 6.7 Hz, 6H).; ^{13}C NMR (151 MHz, $CDCl_3$) 164.61 (d, J = 251.5 Hz), 131.09 (d, J = 3.1 Hz), 129.12 (d, J = 8.9 Hz), 115.55 (d, J =

21.9 Hz) 47.4, 28.6, 20.2.; ^{19}F NMR (376 MHz, $CDCl_3$) ∂ -108.5; FTIR (cm^{-1}): 3296, 3079, 2958, 2925, 2871, 1634, 1546, 1504, 1468, 1234, 1158, 848. HRMS (EI) m/z, calculated for $[C_{11}H_{14}NOF]^+$: 195.1059; found: 195.1056.

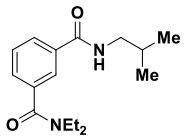


(**2-40**). Using a modification of general protocol A: CuBr (276 mg, 1.93 mmol), 3-chlorobenzamide (3.00 g, 19.3 mmol), isobutylboronic acid (2.94 g, 28.3 mmol), sodium trimethylsilanolate (4.75 g, 42.4 mmol), anhydrous ^{t}BuOH (48.2 mL), and di-*tert*-butyl peroxide (10.6 mL, 57.9 mmol) were combined under nitrogen in a 100mL Schlenk flask and heated at 75 °C for 24 h. The reaction was worked up according to general protocol A and purified by flash silica gel chromatography (3:1 hexanes: ethyl acetate) to afford secondary amide 5 (3.23 g, 79%) as a white solid: mp = 101-102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.74 (t, J = 1.8 Hz, 1H), 7.63 (d, J = 7.7 Hz, 1H), 7.47 (d, J = 7.0 Hz, 0H), 7.38 (t, J = 7.9 Hz, 1H), 6.10 (s, 0H), 3.29 (t, 1H), 1.97 – 1.84 (m, 1H), 0.98 (d, J = 6.7 Hz, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 166.2, 136.7, 134.7, 131.4, 129.9, 127.2, 124.9, 47.5, 28.6, 20.2; FTIR (cm^{-1}): 3302, 3071, 2954. 2928, 2869, 1633, 1596, 1545, 1466, 1164, 1084, 804. HRMS (EI) m/z, calculated for $[C_{11}H_{14}NOCl]^+$: 211.0764; found: 211.0771.

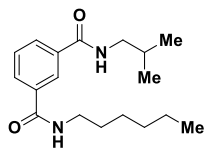


(**2-41**). According to general protocol A: CuBr (14.4 mg, 0.1 mmol), 2,4-dichlorobenzamide (190 mg, 1.0 mmol), isobutylboronic acid (153 mg, 1.5 mmol), sodium trimethylsilanolate (246 mg, 2.2 mmol), anhydrous ^{t}BuOH (2.5 mL), and di-*tert*-butyl peroxide (0.55 mL, 3.0 mmol) were combined under nitrogen and heated at 75 °C for 24 h. The reaction was worked up according to general protocol A and purified by flash silica gel chromatography (3:1 hexanes: ethyl acetate) to afford

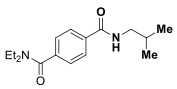
secondary amide 6 (174 mg, 71%) as a white solid: mp = 115-117 °C; ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.65 (d, *J* = 8.3 Hz, 1H), 7.42 (d, *J* = 2.0 Hz, 1H), 7.32 (dd, *J* = 7.9, 1.8 Hz, 0H), 6.23 (s, 1H), 3.30 (t, *J* = 6.4 Hz, 2H), 1.99 – 1.85 (m, 1H), 1.00 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 165.4, 136.7, 133.6, 131.4, 131.3, 130.0, 127.6, 47.6, 28.5, 20.2; FTIR (cm^{-1}): 3272, 3075, 2956, 2926, 2870, 1641, 1590, 1546, 1467, 1370, 1156, 1060, 832. HRMS (EI) m/z, calculated for $[C_{11}H_{13}NOCl_2]^+$: 245.0374; found: 245.0368.



(**2-43**). According to general protocol A: CuBr (14.4 mg, 0.1 mmol), N3,N3-diethylbenzene-1,3-dicarboxamide (220 mg, 1.0 mmol), isobutylboronic acid (153 mg, 1.5 mmol), sodium trimethylsilanolate (246 mg, 2.2 mmol), anhydrous ^{t}BuOH (2.5 mL), and di-*tert*-butyl peroxide (0.55 mL, 3.0 mmol) were combined under nitrogen and heated at 75 °C for 24 h. The reaction was worked up according to general protocol A and purified by flash silica gel chromatography (1:2 hexanes: ethyl acetate) to afford secondary amide 7 (249 mg, 90%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) ∂ ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.91 – 7.77 (m, 1H), 7.73 (s, 1H), 7.53 – 7.46 (m, 2H), 6.25 (s, 1H), 3.56 (d, *J* = 6.4 Hz, 2H), 3.28 (t, *J* = 5.9 Hz, 2H), 3.24 (d, *J* = 6.5 Hz, 2H), 2.03 – 1.79 (m, 1H), 1.25 (s, 3H), 1.11 (s, 3H), 0.97 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) ∂ 170.6, 167.1, 137.6, 135.6, 129.0, 128.9, 128.0, 124.9, 47.6, 43.5, 39.6, 28.7, 20.3, 14.4, 13.0; FTIR (cm^{-1}): 3334.28, 3066.02, 2962.51, 2934.10, 2871.59, 1636.20, 1617.70, 1540.83, 1457.78, 1436.14, 1273.11, 1100.08. HRMS (EI) m/z, calculated for $[C_{16}H_{24}N_2O_2]^+$: 276.1838; found: 276.1828.

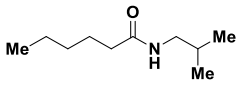


(**2-44**). According to general protocol A: CuBr (14.4 mg, 0.1 mmol), N3-hexylbenzene-1,3-dicarboxamide (248 mg, 1.0 mmol), isobutylboronic acid (153 mg, 1.5 mmol), sodium trimethylsilanolate (246 mg, 2.2 mmol), anhydrous ^{t}BuOH (2.5 mL), and di-*tert*-butyl peroxide (0.55 mL, 3.0 mmol) were combined under nitrogen and heated at 75 °C for 24 h. The reaction was worked up according to general protocol A and purified by flash silica gel chromatography (1:1 hexanes: ethyl acetate) to afford secondary amide 8 (162 mg, 53%) as an off-white solid: mp = 126-129 °C; ^{1}H NMR (600 MHz, $CDCl_3$) ∂ ^{1}H NMR (600 MHz, $CDCl_3$) ∂ 8.16 (s, 1H), 7.90 (dd, *J* = 7.7, 1.7 Hz, 2H), 7.51 (t, *J* = 7.7 Hz, 1H), 6.25 (d, *J* = 26.7 Hz, 2H), 3.46 (q, *J* = 7.1, 6.7 Hz, 2H), 3.30 (t, *J* = 6.4 Hz, 2H), 2.06 – 1.80 (m, 1H), 1.62 (p, *J* = 7.4 Hz, 2H), 1.49 – 1.35 (m, 2H), 1.32 (dd, *J* = 7.0, 3.2 Hz, 4H), 0.99 (d, *J* = 6.7 Hz, 6H), 0.90 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) ∂ 166.8, 166.7, 135.31, 135.30, 129.81, 129.76, 129.1, 125.4, 47.7, 40.4, 31.6, 29.7, 28.8, 26.8, 22.7, 20.4, 14.2; FTIR (cm^{-1}): 3338, 3292, 3074, 2958, 2930, 2871, 1653, 1541, 1275. HRMS (EI) m/z, calculated for $[C_{18}H_{28}N_2O_2]^+$: 304.2151; found: 304.2144.

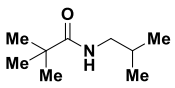


(**2-45**). According to general protocol A: CuBr (14.4 mg, 0.1 mmol), N,N-diethylterephthalamide (220 mg, 1.0 mmol), isobutylboronic acid (153 mg, 1.5 mmol), sodium trimethylsilanolate (246 mg, 2.2 mmol), anhydrous ^{t}BuOH (2.5 mL), and di-*tert*-butyl peroxide (0.55 mL, 3.0 mmol) were combined under nitrogen and heated at 75 °C for 24 h. The reaction was worked up according to general protocol A and purified by flash silica gel chromatography (1:2 hexanes: ethyl acetate) to afford secondary amide 9 (217 mg, 79%) as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) ∂ ^{1}H NMR (600 MHz, $CDCl_3$) ∂ 7.78 (d, *J* = 7.9 Hz, 2H), 7.45 – 7.37 (m, 2H), 6.28 (s, 1H),

3.55 (s, 2H), 3.29 (t, *J* = 6.4 Hz, 2H), 3.21 (s, 2H), 1.99 – 1.85 (m, 1H), 1.26 (s, 3H), 1.09 (s, 3H), 0.99 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) ∂ 170.5, 167.2, 140.2, 135.7, 127.2, 126.6, 47.6, 43.4, 39.5, 28.8, 20.3, 14.4, 13.0; FTIR (cm^{-1}): 3324, 3067, 2962, 2934, 2871, 1620, 1546, 1461, 1433, 1318, 1287, 1098, 857. HRMS (EI) m/z, calculated for $[C_{16}H_{24}N_2O_2]^+$: 276.1828; found: 276.1842.

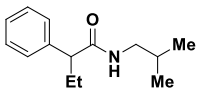


(**2-51**). According to general protocol A: CuBr (14.4 mg, 0.1 mmol), hexanoamide (101 mg, 1.0 mmol), isobutylboronic acid (153 mg, 1.5 mmol), sodium trimethylsilanolate (246 mg, 2.2 mmol), anhydrous ^{t}BuOH (2.5 mL), and di-*tert*-butyl peroxide (0.55 mL, 3.0 mmol) were combined under nitrogen and heated at 75 °C for 24 h. The reaction was worked up according to general protocol A and purified by flash silica gel chromatography (3:1 hexanes: ethyl acetate) to afford secondary amide 10 (123 mg, 72%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 5.44 (s, 1H), 3.07 (t, *J* = 6.6 Hz, 2H), 2.16 (t, *J* = 7.6 Hz, 2H), 1.76 (hept, *J* = 6.7 Hz, 1H), 1.63 (dt, *J* = 14.9, 13.4, 7.8, 7.1 Hz, 2H), 1.44 – 1.15 (m, 4H), 0.96 – 0.88 (m, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 173.3, 46.9, 37.1, 31.6, 28.7, 25.7, 22.6, 20.2, 14.1; FTIR (cm^{-1}): 3293, 2958, 2929, 2871, 1642, 1631, 1549. HRMS (EI) m/z, calculated for $[C_{10}H_{22}NO]^+$: 172.1701; found: 172.1701.

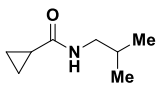


(**2-52**). According to general protocol A: CuBr (14.4 mg, 0.1 mmol), trimethylacetamide (115 mg, 1.0 mmol), isobutylboronic acid (153 mg, 1.5 mmol), sodium trimethylsilanolate (246 mg, 2.2 mmol), anhydrous ^{t}BuOH (2.5 mL), and di-*tert*-butyl peroxide (0.55 mL, 3.0 mmol) were combined under nitrogen and heated at 75 °C for 24 h. The reaction was worked up according to general protocol A

and purified by flash silica gel chromatography (3:1 hexanes: ethyl acetate) to afford secondary amide 11 (122 mg, 78%) as a off-white solid: mp = 85-87 °C; ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 5.66 (s, 1H), 3.07 (t, *J* = 6.4 Hz, 2H), 1.77 (hept, *J* = 6.7 Hz, 1H), 1.20 (s, 9H), 0.90 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 178.4, 46.9, 38.8, 28.7, 27.8, 20.2; FTIR (cm^{-1}): 3338, 2957, 2929, 2870, 1638, 1537, 1467, 1367, 1294, 1214, 1156. HRMS (EI) m/z, calculated for $[C_9H_{20}NO]^+$: 158.1545; found: 158.1548.

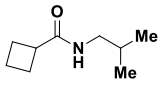


(**2-53**). According to general protocol A: CuBr (14.4 mg, 0.1 mmol), 2-phenylbutyramide (164 mg, 1.0 mmol), isobutylboronic acid (153 mg, 1.5 mmol), sodium trimethylsilanolate (246 mg, 2.2 mmol), anhydrous ^{t}BuOH (2.5 mL), and di-*tert*-butyl peroxide (0.55 mL, 3.0 mmol) were combined under nitrogen and heated at 75 °C for 24 h. The reaction was worked up according to general protocol A and purified by flash silica gel chromatography (3:1 hexanes: ethyl acetate) to afford secondary amide 12 (182 mg, 83%) as a yellow solid: mp = 59-62 °C; ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.38 – 7.27 (m, 5H), 5.37 (s, 1H), 3.22 (t, *J* = 7.6 Hz, 1H), 3.02 (t, *J* = 6.4 Hz, 2H), 2.21 (hept, *J* = 7.3 Hz, 1H), 1.73 (dtt, *J* = 46.3, 13.5, 7.1 Hz, 2H), 0.88 (t, *J* = 7.4 Hz, 3H), 0.80 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 173.6, 140.3, 128.9, 128.2, 127.3, 55.6, 46.9, 28.6, 26.4, 20.1, 12.6; FTIR (cm^{-1}): 3297, 3064, 2961, 2930, 2872, 1643, 1551, 1453, 1370, 1271, 1228, 1159, 697. HRMS (EI) m/z, calculated for $[C_{14}H_{21}N]^+$: 219.1623; found: 219.1620.

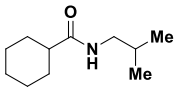


(**2-54**). According to general protocol A: CuBr (14.4 mg, 0.1 mmol), cyclopropanecarboxamide (85 mg, 1.0 mmol), isobutylboronic acid (153 mg, 1.5 mmol), sodium trimethylsilanolate (246 mg, 2.2 mmol), anhydrous ^{t}BuOH

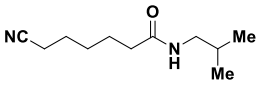
(2.5 mL), and di-*tert*-butyl peroxide (0.55 mL, 3.0 mmol) were combined under nitrogen and heated at 75 °C for 24 h. The reaction was worked up according to general protocol A and purified by flash silica gel chromatography (2:1 hexanes: ethyl acetate) to afford secondary amide 13 (105 mg, 74%) as a white solid: mp = 68-71 °C; ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 5.62 (s, 1H), 3.10 (t, J = 7.3 Hz, 2H), 1.77 (hept, J = 6.7 Hz, 1H), 1.32 (tt, J = 7.9, 4.6 Hz, 1H), 1.01 – 0.94 (m, 2H), 0.92 (d, J = 6.7 Hz, 6H), 0.77 – 0.68 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 173.6, 47.2, 28.8, 20.3, 15.0, 7.2; FTIR (cm^{-1}): 3291, 3093, 2958, 2927, 2871, 1642, 1563, 1468, 1404, 1247, 703. HRMS (EI) m/z, calculated for $[C_8H_{15}N]^+$: 141.1154; found: 141.1146.



(**2-55**). According to general protocol A: CuBr (14.4 mg, 0.1 mmol), cyclobutanecarboxamide (99 mg, 1.0 mmol), isobutylboronic acid (153 mg, 1.5 mmol), sodium trimethylsilanolate (246 mg, 2.2 mmol), anhydrous ^{t}BuOH (2.5 mL), and di-*tert*-butyl peroxide (0.55 mL, 3.0 mmol) were combined under nitrogen and heated at 75 °C for 24 h. The reaction was worked up according to general protocol A and purified by flash silica gel chromatography (20:1 DCM:MeOH) to afford secondary amide 14 (114 mg, 75%) as a yellow solid: mp = 69-73 °C; ^{1}H NMR (600 MHz, $CDCl_3$) ∂ 5.35 (s, 1H), 3.07 (dd, J = 6.3, 0.5 Hz, 2H), 2.98 (p, J = 8.6 Hz, 1H), 2.33 – 2.21 (m, 2H), 2.19 – 2.08 (m, 2H), 2.00 – 1.90 (m, 1H), 1.90 – 1.81 (m, 1H), 1.80 – 1.70 (m, 1H), 0.90 (d, J = 6.7 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) ∂ 175.0, 46.8, 40.2, 28.7, 25.6, 20.2, 18.3; FTIR (cm^{-1}): 3301, 3089, 2956, 2869, 1640, 1556, 1502, 1260, 1159, 752. HRMS (EI) m/z, calculated for $[C_9H_{17}NO]^+$: 155.1310; found: 155.1313.

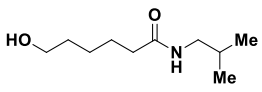


(**2-56**). According to general protocol A: CuBr (14.4 mg, 0.1 mmol), cyclohexanecarboxamide (127 mg, 1.0 mmol), isobutylboronic acid (153 mg, 1.5 mmol), sodium trimethylsilanolate (246 mg, 2.2 mmol), anhydrous ^{t}BuOH (2.5 mL), and di-*tert*-butyl peroxide (0.55 mL, 3.0 mmol) were combined under nitrogen and heated at 75 °C for 24 h. The reaction was worked up according to general protocol A and purified by flash silica gel chromatography (20:1 DCM:MeOH) to afford secondary amide 15 (119 mg, 65%) as a yellow solid: mp = 70-75 °C; ^{1}H NMR (600 MHz, $CDCl_3$) ∂ 5.42 (s, 1H), 3.07 (t, *J* = 6.4 Hz, 2H), 2.07 (tt, *J* = 11.8, 3.5 Hz, 1H), 1.93 – 1.83 (m, 2H), 1.83 – 1.77 (m, 2H), 1.77 – 1.71 (m, 1H), 1.71 – 1.61 (m, 1H), 1.44 (qd, *J* = 12.3, 3.1 Hz, 2H), 1.34 – 1.16 (m, 3H), 0.90 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 176.2, 46.7, 45.9, 30.0, 28.7, 25.91, 25.90, 20.2; FTIR (cm^{-1}): 3299, 3087, 2929, 2854, 1641, 1552, 1444. HRMS (EI) m/z, calculated for $[C_{11}H_{22}NO]^{+}$: 184.1701; found: 184.1701.

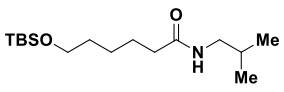


(**2-57**). According to general protocol A: CuBr (14.4 mg, 0.1 mmol), 6-cyanohexanamide (140 mg, 1.0 mmol),), isobutylboronic acid (153 mg, 1.5 mmol), sodium trimethylsilanolate (246 mg, 2.2 mmol), anhydrous ^{t}BuOH (2.5 mL), and di-*tert*-butyl peroxide (0.55 mL, 3.0 mmol) were combined under nitrogen and heated at 75 °C for 24 h. The reaction was worked up according to general protocol A and purified by flash silica gel chromatography (1:3 hexanes: ethyl acetate) to afford secondary amide 16 (89 mg, 45%) as a yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) ∂ ^{1}H NMR (600 MHz, $CDCl_3$) ∂ 5.44 (s, 1H), 3.08 (t, *J* = 6.4 Hz, 2H), 2.35 (t, *J* = 7.1 Hz, 2H), 2.19 (t, *J* = 7.4 Hz, 2H), 1.76 (hept, *J* = 13.5, 6.7 Hz, 1H), 1.69 (p, *J* = 7.2 Hz, 4H), 1.54 – 1.45 (m, 2H), 0.91 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR

(151 MHz, $CDCl_3$) ∂ 1172.4, 119.8, 47.0, 36.5, 28.7, 28.4, 25.3, 24.9, 20.2, 17.1; FTIR (cm^{-1}): 3305, 3082, 2957, 2870, 2245, 1644, 1548, 1467, 1370, 1271, 1160. HRMS (EI) m/z, calculated for $[C_{11}H_{20}N_2O]^+$: 196.1576; found: 196.1578.

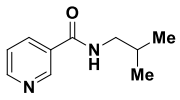


(**2-58**). According to general protocol A: CuBr (28.7 mg, 0.2 mmol), 6-hydroxyhexanamide (131 mg, 1.0 mmol), isobutylboronic acid (202 mg, 2.0 mmol), sodium trimethylsilanolate (246 mg, 2.2 mmol), anhydrous ^{t}BuOH (2.5 mL), and di-*tert*-butyl peroxide (0.55 mL, 3.0 mmol) were combined under nitrogen and heated at 75 °C for 24 h. The reaction was worked up according to general protocol A and purified by flash silica gel chromatography (50:1 ethyl acetate: methanol) to afford secondary amide 17 (92 mg, 49%) as a yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) ∂ ^{1}H NMR (600 MHz, $CDCl_3$) ∂ 5.42 (s, 1H), 3.66 (q, *J* = 6.3 Hz, 2H), 3.09 (t, *J* = 6.4 Hz, 2H), 2.61 (s, 1H), 2.19 (t, *J* = 7.5 Hz, 2H), 1.82 – 1.72 (m, 1H), 1.68 (p, *J* = 7.6 Hz, 2H), 1.60 (p, *J* = 14.4, 6.7 Hz, 2H), 1.46 – 1.37 (m, 2H), 0.91 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) ∂ 166 13C NMR (151 MHz, CDCl3) ∂ 172.9, 62.6, 46.8, 36.7, 32.3, 28.5, 25.4, 20.1;FTIR (cm^{-1}): 3296, 2956, 2932, 2869, 1653, 1559, 1541, 1465, 1271, 1057. HRMS (EI) m/z, calculated for $[C_{10}H_{21}NO_2]^+$: 187.1572; found: 187.1579.

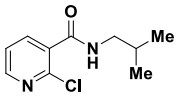


(**2-59**). According to general protocol B: CuBr (14.4 mg, 0.1 mmol), 6-(tert-butyldimethylsilyloxy)hexanamide (245 mg, 1.0 mmol), isobutylboronic acid (153 mg, 1.5 mmol), sodium trimethylsilanolate (246 mg, 2.2 mmol), anhydrous ^{t}BuOH (2.5 mL), and di-*tert*-butyl peroxide (0.55 mL, 3.0 mmol) were combined under nitrogen and heated at 75 °C for 24 h. The reaction was

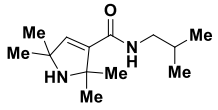
worked up according to general protocol A and purified by flash silica gel chromatography 3:1 hexanes: ethyl acetate to afford secondary amide 18 (166 mg, 55%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 1H NMR (400 MHz, CDCl3) ∂ 5.43 (s, 1H), 3.60 (t, J = 6.5 Hz, 2H), 3.08 (t, J = 6.5 Hz, 2H), 2.18 (t, J = 7.7 Hz, 2H), 1.82 – 1.70 (m, 1H), 1.65 (p, J = 7.6 Hz, 2H), 1.56 – 1.47 (m, 2H), 1.41 – 1.31 (m, 2H), 0.91 (d, J = 6.7 Hz, 6H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 166 ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 172.9, 63.1, 46.8, 37.0, 32.6, 28.5, 26.0, 25.6, 20.1, 18.4, -5.3; FTIR (cm^{-1}): 3294, 3085, 2930, 2858, 1644, 1553, 1464, 1388, 1255, 1102, 836, 775. HRMS (EI) m/z, calculated for $[C_{16}H_{35}NO_2Si]^+$: 301.2437; found: 301.2428.



(**2-60**). According to general protocol A: CuBr (14.4 mg, 0.1 mmol), nicotinamide (122 mg, 1.0 mmol), isobutylboronic acid (153 mg, 1.5 mmol), sodium trimethylsilanolate (246 mg, 2.2 mmol), anhydrous ^{t}BuOH (2.5 mL), and di-*tert*-butyl peroxide (0.55 mL, 3.0 mmol) were combined under nitrogen and heated at 75 °C for 24 h. The reaction was worked up according to general protocol A and purified by flash silica gel chromatography (3:1:0.04 hexanes: ethyl acetate: triethylamine→ 3:1 hexanes: ethyl acetate) to afford secondary amide 19 (108 mg, 61%) as a yellow solid: mp = 49-52 °C; ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 8.96 (s, 1H), 8.73 (d, *J* = 3.8 Hz, 1H), 8.12 (dt, *J* = 7.9, 2.0 Hz, 1H), 7.40 (dd, *J* = 7.8, 4.8 Hz, 1H), 6.18 (s, 1H), 3.32 (t, *J* = 6.3 Hz, 2H), 1.92 (hept, *J* = 6.7 Hz, 1H), 0.99 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 165.8, 152.3, 147.8, 135.2, 130.7, 123.7, 47.6, 28.7, 20.3; FTIR (cm^{-1}): 3292, 3064, 2959, 2928, 2871, 1642, 1592, 1545, 1468, 1316, 1156, 1028, 707. HRMS (EI) m/z, calculated for $[C_{10}H_{14}N_2O]^+$: 178.1106; found: 178.1105.

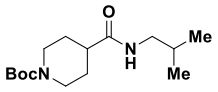


(**2-61**). According to general protocol A: CuBr (14.4 mg, 0.1 mmol), 2-chloronicotinamide (157 mg, 1.0 mmol), isobutylboronic acid (153 mg, 1.5 mmol), sodium trimethylsilanolate (246 mg, 2.2 mmol), anhydrous ^{t}BuOH (2.5 mL), and di-*tert*-butyl peroxide (0.55 mL, 3.0 mmol) were combined under nitrogen and heated at 75 °C for 24 h. The reaction was worked up according to general protocol A and purified by flash silica gel chromatography (1:1:0.04 hexanes: ethyl acetate: triethylamine→ 1:1 hexanes: ethyl acetate to afford secondary amide 20 (93 mg, 44%) as a yellow solid: mp = 62-65 °C; [1] ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 8.46 (dd, *J* = 4.8, 2.0 Hz, 1H), 8.14 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.36 (dd, *J* = 7.6, 4.8 Hz, 1H), 6.52 (s, 1H), 3.33 (t, *J* = 6.4 Hz, 2H), 1.94 (hept, *J* = 6.7 Hz, 1H), 1.01 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 164.7, 151.1, 147.1, 140.2, 131.5, 123.0, 47.8, 28.6, 20.4; FTIR (cm^{-1}): 3271, 3077, 2960, 2927, 2871, 1646, 1583, 1557, 1470, 1399, 1319, 1169, 1079. HRMS (EI) m/z, calculated for $[C_{10}H_{13}N_2OCl]^+$: 212.0717; found: 212.0717.

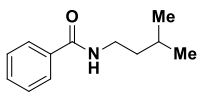


(**2-63**). According to general protocol A: CuBr (14.4 mg, 0.1 mmol), 2,2,5,5-Tetramethyl-3-pyrroline-3-carboxamide (168 mg, 1.0 mmol), isobutylboronic acid (153 mg, 1.5 mmol), sodium trimethylsilanolate (246 mg, 2.2 mmol), anhydrous ^{t}BuOH (2.5 mL), and di-*tert*-butyl peroxide (0.55 mL, 3.0 mmol) were combined under nitrogen and heated at 75 °C for 24 h. The reaction was worked up according to general protocol A and purified by flash silica gel chromatography (10:1 DCM:MeOH) to afford secondary amide 21 (180 mg, 80%) as an off-white solid: mp = 108-111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 6.03 (s, 1H), 5.78 (s, 1H), 3.12 (t, *J* = 6.4 Hz, 2H), 1.82 (hept, *J* = 6.8 Hz, 1H), 1.45 (s, 6H), 1.30 (s, 6H), 0.94 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 165.3, 143.8, 139.5, 67.3, 63.7, 46.8, 30.3, 30.2, 28.8,

20.3; FTIR (cm^{-1}): 3282, 3068, 2959, 2924, 2869, 1649, 1608, 1540, 1467, 1369, 1283, 1155. HRMS (EI) m/z, calculated for $[C_{13}H_{25}N_2O]^+$: 225.1967; found: 225.1968.

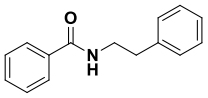


(**2-64**). According to general protocol A: CuBr (14.4 mg, 0.1 mmol), Tert-butyl 4-carbamoylpiperidine-1-carboxamide (153 mg, 1.0 mmol), isobutylboronic acid (153 mg, 1.5 mmol), sodium trimethylsilanolate (246 mg, 2.2 mmol), anhydrous ^{t}BuOH (2.5 mL), and di-*tert*-butyl peroxide (0.55 mL, 3.0 mmol) were combined under nitrogen and heated at 75 °C for 24 h. The reaction was worked up according to general protocol A and purified by flash silica gel chromatography (1:1 hexanes: ethyl acetate) to afford secondary amide 22 (200 mg, 71%) as a yellow solid: mp = 117-121 °C; ^{1}H NMR (600 MHz, $CDCl_3$) ∂ 5.45 (s, 1H), 4.14 (s, 2H), 3.09 (t, J = 6.4 Hz, 2H), 2.74 (s, 2H), 2.22 (tt, J = 11.6, 3.6 Hz, 1H), 1.81 (d, J = 12.9 Hz, 2H), 1.75 (dq, J = 13.5, 6.8 Hz, 1H), 1.63 (qd, J = 12.3, 4.3 Hz, 2H), 1.45 (s, 9H), 0.91 (d, J = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 174.4, 154.8, 79.7, 46.8, 43.7, 28.9, 28.7, 28.6, 28.5, 20.2; FTIR (cm^{-1}): 3306, 2958, 2928, 2870, 1696, 1648, 1548, 1425, 1220, 1169, 1130. HRMS (EI) m/z, calculated for $[C_{15}H_{29}N_2O_3]^+$: 285.2178; found: 285.2187.

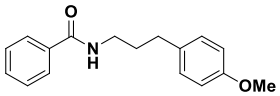


(**2-65**). According to general protocol A: CuBr (14.4 mg, 0.1 mmol), benzamide (121 mg, 1.0 mmol), isopentylboronic acid (174 mg, 1.5 mmol), sodium trimethylsilanolate (246 mg, 2.2 mmol), anhydrous ^{t}BuOH (2.5 mL), and di-*tert*-butyl peroxide (0.55 mL, 3.0 mmol) were combined under nitrogen and heated at 75 °C for 24 h. The reaction was worked up according to general protocol A and purified by flash silica gel chromatography (5:1 hexanes: ethyl acetate) to afford secondary amide 23 (171 mg, 89%) as a yellow solid: mp = 42-45 °C; ^{1}H NMR (400

MHz, $CDCl_3$) ∂ 7.79 – 7.72 (m, 2H), 7.54 – 7.45 (m, 1H), 7.47 – 7.40 (m, 2H), 6.06 (s, 1H), 3.48 (dd, *J* = 14.8, 5.8 Hz, 2H), 1.69 (hept, *J* = 6.7 Hz, 1H), 1.51 (td, *J* = 7.9, 7.3 Hz, 2H), 0.96 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 167.6, 135.0, 131.5, 128.7, 126.9, 38.7, 38.5, 26.1, 22.7; FTIR (cm^{-1}): 3306, 2956, 2929, 2870, 1639, 1547, 1310. HRMS (EI) m/z, calculated for $[C_{12}H_{18}NO]^+$: 192.1388; found: 192.1390.

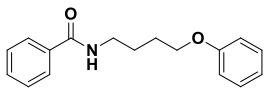


(**2-66**). According to general protocol A: CuBr (14.4 mg, 0.1 mmol), benzamide (121 mg, 1.0 mmol), phenethylboronic acid (225 mg, 1.5 mmol), sodium trimethylsilanolate (246 mg, 2.2 mmol), anhydrous ^{t}BuOH (2.5 mL), and di-*tert*-butyl peroxide (0.55 mL, 3.0 mmol) were combined under nitrogen and heated at 75 °C for 24 h. The reaction was worked up according to general protocol A and purified by flash silica gel chromatography (3:1 hexanes: ethyl acetate) to afford secondary amide 24 (127 mg, 56%) as a yellow solid: mp = 113-119 °C; ^{1}H NMR (400 MHz, d_6-DMSO) ∂ 8.58 (t, *J* = 5.5 Hz, 1H), 7.95 – 7.70 (m, 2H), 7.64 – 7.49 (m, 1H), 7.48 – 7.39 (m, 2H), 7.37 – 7.11 (m, 5H), 3.58 – 3.41 (m, 2H), 2.84 (t, *J* = 7.4 Hz, 2H).; ^{13}C NMR (101 MHz, d_6-DMSO) ∂ 166.1, 139.6, 134.6, 131.1, 128.7, 128.4, 128.3, 127.1, 126.1, 40.9, 35.1.; FTIR (cm^{-1}): 3342, 2922, 1640, 1632, 1547. HRMS (EI) m/z, calculated for $[C_{15}H_{16}N_x]^+$: 226.1232; found: 226.1233.

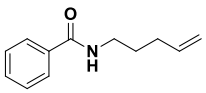


(**2-67**). According to general protocol A: CuBr (14.4 mg, 0.1 mmol), benzamide (121 mg, 1.0 mmol), 3-(4-methoxyphenyl)propylboronic acid (291 mg, 1.5 mmol), sodium trimethylsilanolate (246 mg, 2.2 mmol), anhydrous ^{t}BuOH (2.5 mL), and di-*tert*-butyl peroxide (0.55 mL, 3.0 mmol) were combined under nitrogen and heated at 75 °C for 24 h. The reaction

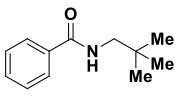
was worked up according to general protocol A and purified by flash silica gel chromatography (3:1 hexanes: ethyl acetate) to afford secondary amide 25 (186 mg, 69%) as a yellow solid: mp = 77-80 °C; ^{1}H NMR (600 MHz, $CDCl_3$) ∂ 7.66 (d, J = 7.3 Hz, 2H), 7.48 (t, J = 7.4 Hz, 1H), 7.40 (t, J = 7.6 Hz, 2H), 7.13 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 6.02 (s, 1H), 3.79 (s, 3H), 3.50 (q, J = 6.7 Hz, 2H), 2.69 (t, J = 7.4 Hz, 2H), 1.94 (p, J = 7.2 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) ∂ 167.5, 158.1, 134.9, 133.6, 131.4, 129.4, 128.6, 126.9, 114.1, 55.4, 40.0, 32.8, 31.5; FTIR (cm^{-1}): 3320, 2933, 2857, 2834, 1639, 1512, 1545, 1301, 1246, 1178, 1036, 828, 696. HRMS (EI) m/z, calculated for $[C_{17}H_{20}NO_2]^+$: 270.1494; found: 270.1492.



(**2-68**). According to general protocol A: CuBr (14.4 mg, 0.1 mmol), benzamide (121 mg, 1.0 mmol), 4-phenoxybutylboronic acid (291 mg, 1.5 mmol), sodium trimethylsilanolate (246 mg, 2.2 mmol), anhydrous ^{t}BuOH (2.5 mL), and di-*tert*-butyl peroxide (0.55 mL, 3.0 mmol) were combined under nitrogen and heated at 75 °C for 24 h. The reaction was worked up according to general protocol A and purified by flash silica gel chromatography (5:1 hexanes: ethyl acetate) to afford secondary amide 26 (187 mg, 70%) as a yellow solid: mp = 67-70 °C; ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.85 – 7.67 (m, 2H), 7.56 – 7.45 (m, 1H), 7.45 – 7.36 (m, 2H), 7.36 – 7.27 (m, 2H), 6.95 (t, J = 7.4 Hz, 1H), 6.90 (d, J = 8.7 Hz, 2H), 6.27 (s, 1H), 4.03 (t, J = 5.9 Hz, 2H), 3.56 (q, J = 6.7 Hz, 2H), 2.07 – 1.72 (m, 4H); ^{13}C NMR (151 MHz, $CDCl_3$) ∂ 167.7, 158.9, 134.9, 131.5, 129.6, 128.8, 126.7, 120.9, 114.6, 67.5, 39.8, 26.9, 26.7; FTIR (cm^{-1}): 3306, 3063, 2934, 2871, 1640, 1600, 1546, 1493, 1302, 1245, 754. HRMS (EI) m/z, calculated for $[C_{17}H_{20}NO_2]^+$: 270.1494; found: 270.1491.

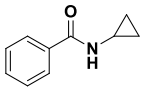


(**2-69**). According to general protocol A: CuBr (28.7 mg, 0.2 mmol), benzamide (121 mg, 1.0 mmol), pent-4-enylboronic acid (228 mg, 2.0 mmol), sodium trimethylsilanolate (246 mg, 2.2 mmol), anhydrous ^{t}BuOH (2.5 mL), and di-*tert*-butyl peroxide (0.55 mL, 3.0 mmol) were combined under nitrogen and heated at 75 °C for 24 h. The reaction was worked up according to general protocol A and purified by flash silica gel chromatography (5:1 hexanes: ethyl acetate) to afford secondary amide 27 (114 mg, 60%) as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) ∂ 7.75 (d, J = 7.3 Hz, 2H), 7.49 (t, J = 7.3 Hz, 1H), 7.43 (t, J = 7.5 Hz, 2H), 6.16 (s, 1H), 5.84 (dt, J = 16.9, 8.5 Hz, 1H), 5.07 (d, J = 17.1 Hz, 1H), 5.01 (d, J = 10.1 Hz, 1H), 3.48 (q, J = 6.7 Hz, 2H), 2.17 (q, J = 6.8 Hz, 2H), 1.74 (p, J = 7.2 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) ∂ 167.6, 138.0, 134.9, 131.5, 128.7, 127.0, 115.5, 39.8, 31.4, 28.9; FTIR (cm^{-1}): 3316, 3076, 2928, 2858, 1640, 1579, 1546, 1491, 1440, 1309, 992, 912, 695. HRMS (EI) m/z, calculated for $[C_{12}H_{16}NO]^{+}$: 190.1232; found: 190.1237.

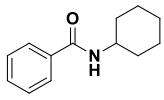


(**2-70**). According to general protocol A: CuBr (28.7 mg, 0.2 mmol), benzamide (121 mg, 1.0 mmol), neopentylboronic acid (230 mg, 2.0 mmol), sodium trimethylsilanolate (246 mg, 2.2 mmol), anhydrous ^{t}BuOH (2.5 mL), and di-*tert*-butyl peroxide (0.55 mL, 3.0 mmol) were combined under nitrogen and heated at 75 °C for 24 h. The reaction was worked up according to general protocol A and purified by flash silica gel chromatography (5:1 hexanes: ethyl acetate) to afford secondary amide 28 (147 mg, 76%) as a white solid: mp = 117-120 °C; ^{1}H NMR (600 MHz, $CDCl_3$) ∂ 7.77 (d, J = 7.4 Hz, 2H), 7.50 (t, J = 6.8 Hz, 1H), 7.44 (t, J = 7.3 Hz, 2H), 6.13 (s, 1H), 3.29 (d, J = 6.2 Hz, 2H), 0.99 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) ∂ 167.8, 135.3, 131.5, 128.8, 126.9, 51.1, 32.3, 27.5; FTIR (cm^{-1}): 3374, 2920, 2864,

1640, 1545, 1492, 1310, 1208. HRMS (EI) m/z, calculated for $[C_{12}H_{18}NO]^+$: 192.1388; found: 192.1390.

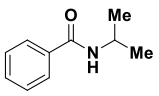


(**2-71**). According to general protocol A: CuBr (14.4 mg, 0.1 mmol), benzamide (121 mg, 1.0 mmol), cyclopropylboronic acid (128 mg, 1.5 mmol), sodium trimethylsilanolate (246 mg, 2.2 mmol), anhydrous ^{t}BuOH (2.5 mL), and di-*tert*-butyl peroxide (0.55 mL, 3.0 mmol) were combined under nitrogen and heated at 75 °C for 24 h. The reaction wlas worked up according to general protocol A and purified by flash silica gel chromatography (2:1 hexanes: ethyl acetate) to afford secondary amide 29 (73 mg, 45%) as a light yellow solid: mp = 89-92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.80 – 7.70 (m, 2H), 7.54 – 7.38 (m, 1H), 7.46 – 7.37 (m, 2H), 6.23 (s, 1H), 2.91 (tq, *J* = 7.0, 3.6 Hz, 1H), 1.00 – 0.74 (m, 2H), 0.74 – 0.52 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 169.0, 134.5, 131.6, 128.7, 127.0, 23.3, 7.0; FTIR (cm^{-1}): 3291, 3063, 2920, 1640, 1546, 1531, 1487, 1306. HRMS (EI) m/z, calculated for $[C_{10}H_{11}NO]^+$: 162.0919; found: 162.0927.



(**2-72**). According to general protocol A: CuBr (14.4 mg, 0.1 mmol), benzamide (121 mg, 1.0 mmol), cyclohexylboronic acid (192 mg, 1.5 mmol), sodium trimethylsilanolate (246 mg, 2.2 mmol), anhydrous ^{t}BuOH (2.5 mL), and di-*tert*-butyl peroxide (0.55 mL, 3.0 mmol) were combined under nitrogen and heated at 75 °C for 24 h. The reaction was worked up according to general protocol A and purified by flash silica gel chromatography (10:1 hexanes: ethyl acetate) to afford secondary amide 30 (101 mg, 50%) as a white solid: mp = 150-152 °C; ^{1}H NMR (600 MHz, $CDCl_3$) ∂ 7.75 (d, *J* = 7.7 Hz, 2H), 7.48 (t, *J* = 7.3 Hz, 1H), 7.43 (t, *J* = 7.5 Hz,

2H), 5.93 (s, 1H), 3.99 (qd, *J* = 11.0, 5.9 Hz, 1H), 2.04 (d, *J* = 12.5 Hz, 2H), 1.76 (d, *J* = 9.7 Hz, 2H), 1.66 (d, *J* = 13.1 Hz, 1H), 1.44 (q, *J* = 12.3 Hz, 2H), 1.32 – 1.15 (m, 3H); ^{113}C NMR (151 MHz, $CDCl_3$) ∂ 166.7, 135.3, 131.4, 128.7, 127.0, 48.8, 33.4, 25.8, 25.1; FTIR (cm^{-1}): 3305, 2929, 2853, 1631, 1536, 1329, 1580. HRMS (EI) m/z, calculated for $[C_{13}H_{18}NO]^+$: 204.1388; found: 204.1391.



(**2-73**). According to general protocol A: CuBr (28.7 mg, 0.2 mmol), benzamide (121 mg, 1.0 mmol), isopropylboronic acid (176 mg, 2.0 mmol), sodium trimethylsilanolate (246 mg, 2.2 mmol), anhydrous ^{t}BuOH (2.5 mL), and di-*tert*-butyl peroxide (0.55 mL, 3.0 mmol) were combined under nitrogen and heated at 75 °C for 24 h. The reaction was worked up according to general protocol A and purified by flash silica gel chromatography (5:1 hexanes: ethyl acetate) to afford secondary amide 31 (70 mg,43%) as a light yellow solid: mp = 88-92 °C; ^{1}H NMR (600 MHz, $CDCl_3$) ∂ 7.78 – 7.71 (m, 2H), 7.52 – 7.46 (m, 1H), 7.42 (td, *J* = 6.9, 1.5 Hz, 2H), 5.90 (s, 1H), 4.30 (dq, *J* = 13.1, 6.6 Hz, 1H), 1.27 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) ∂ 166.8, 135.2, 131.4, 128.7, 126.9, 42.0, 23.0; FTIR (cm^{-1}): 3853, 2970, 2918, 2361, 2339, 1653, 1559. HRMS (EI) m/z, calculated for $[C_{10}H_{14}NO]^+$: 164.1075; found: 164.1081.

2.7 References

(1) Beauchard, A.; Phillips, V. A.; Lloyd, M. D.; Threadgill, M. D. *Tetrahedron* **2009**, *65*, 8176.
(2) Pintaric, C.; Olivero, S.; Gimbert, Y.; Chavant, P. Y.; Duñach, E. *Journal of the American Chemical Society* **2010**, *132*, 11825.
(3) Reichle, M. A.; Breit, B. *Angewandte Chemie International Edition* **2012**, *51*, 5730.
(4) Kozhushkov, S. I.; Wagner-Gillen, K.; Khlebnikov, A. F.; de Meijere, A. *Synthesis* **2010**, *2010*, 3967.
(5) Nakamura, M.; Hara, K.; Hatakeyama, T.; Nakamura, E. *Organic Letters* **2001**, *3*, 3137.
(6) Bull, J. A.; Charette, A. B. *Journal of the American Chemical Society* **2010**, *132*, 1895.
(7) Corey, E. J.; Venkateswarlu, A. *Journal of the American Chemical Society* **1972**, *94*, 6190.
(8) Nielsen, L.; Skrydstrup, T. *Journal of the American Chemical Society* **2008**, *130*, 13145.
(9) Sorin, G.; Martinez Mallorquin, R.; Contie, Y.; Baralle, A.; Malacria, M.; Goddard, J.-P.; Fensterbank, L. *Angewandte Chemie* **2010**, *122*, 8903.
(10) Zhang, L.; Peng, D.; Leng, X.; Huang, Z. *Angewandte Chemie International Edition* **2013**, *52*, 3676.
(11) Brown, H. C.; Kim, K.-W.; Srebnik, M.; Bakthan, S. *Tetrahedron* **1987**, *43*, 4071.
(12) Kabalka, G. W.; Sastry, K. A. R.; McCollum, G. W.; Yoshioka, H. *The Journal of Organic Chemistry* **1981**, *46*, 4296.
(13) Brown, H. C.; Heydkamp, W. R.; Breuer, E.; Murphy, W. S. *Journal of the American Chemical Society* **1964**, *86*, 3565.
(14) Benard, S.; Neuville, L.; Zhu, J. *Chemical Communications* **2010**, *46*, 3393.
(15) González, I.; Mosquera, J. s.; Guerrero, C. s.; Rodríguez, R. n.; Cruces, J. *Organic Letters* **2009**, *11*, 1677.
(16) Nuzzo, R. G.; McCarthy, T. J.; Whitesides, G. M. *Journal of the American Chemical Society* **1981**, *103*, 3404.
(17) Mlynarski, S. N.; Karns, A. S.; Morken, J. P. *Journal of the American Chemical Society* **2012**, *134*, 16449.
(18) Zhang, S.; Ding, Y. *Organometallics* **2011**, *30*, 633.
(19) Ortiz, A.; Young, I. S.; Sawyer, J. R.; Hsiao, Y.; Singh, A.; Sugiyama, M.; Corbett, R. M.; Chau, M.; Shi, Z.; Conlon, D. A. *Organic & Biomolecular Chemistry* **2012**, *10*, 5253.
(20) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.
(21) Jacobi, P. A.; Brielmann, H. L.; Hauck, S. I. *The Journal of Organic Chemistry* **1996**, *61*, 5013.
(22) Dothager, R. S.; Putt, K. S.; Allen, B. J.; Leslie, B. J.; Nesterenko, V.; Hergenrother, P. J. *Journal of the American Chemical Society* **2005**, *127*, 8686.

(23) Davies, J. R.; Kane, P. D.; Moody, C. J. *Tetrahedron* **2004**, *60*, 3967.

Chapter 3

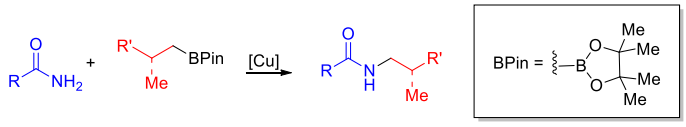
FUTURE DIRECTIONS

3.1 Introduction

With our disclosure of a successful general protocol for the mono-alkylation of primary amides with alkylboronic acids, we noted a few limitations (Chapter 2.4). The biggest limitation of the previously reported method was the use of alkylboronic acids, which are highly temperature sensitive (ca. 5-10 °C) and high vacuum intolerant (decomposition). Additionally, the protocols for the synthesis of these compounds have extremely limited functional group tolerance. While the limits of the boron cross-coupling partner hindered the scope of the first transformation, a change to alkylboronic acid pinacol esters (alkyl-BPins) would greatly increase the generality of the copper-catalyzed alkylation method. Alkyl-BPins are of great interest due to their abundant synthetic protocols, temperature and air stability, and commercial availability.[1-4]

In order to make this new transformation general, we sought to develop this transformation for use with alkyl-BPins. However, instead of starting from general Lam-Chan reaction conditions, we began with the optimized conditions that we developed in Chapter 2 for the alkylboronic acids. The selection of stating materials remained the same, with benzamide as the primary amide, and isobutylboronic acid pinacol ester (isobutyl-BPin) as its coupling partner (Scheme 3-1). As before, isobutyl-BPin was selected to test for β-hydride elimination and for mild steric tolerance.

Figure 3-1. Model System for Cross-Coupling with Alkyl-BPins.



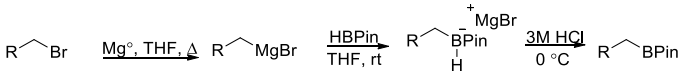
This chapter is divided into multiple sections. The first section is a collection of the modified procedures and protocols used for the synthesis of all alkyl-BPins. No new amides were synthesized. Next, optimization of the copper-catalyzed reaction is presented, followed by presentation of the initial scope. The chapter concludes with a concise discussion on the development of the new method to date, followed by full characterization of all novel alkyl-BPins. Experimental details are included at the end of the chapter. Supporting spectral data can be found in Appendix 2.

3.2 Synthesis of Boronate Esters

Since the synthesis of alkyl-BPins is well established, several methods were used and modified to synthesize the boronate cross-coupling partners. Similar to the alkylboronic acids, a modified Grignard reaction was one of the primary protocols used to synthesize the boronate starting materials (Scheme 3-1).[5] First the alkyl bromide was reacted under nitrogen with magnesium turnings in THF. The newly formed Grignard reagent was then added at room temperature to a solution of pinacolborane in THF. After stirring overnight, the mixture was cooled to 0 °C, and 3M HCl was added drop-wise. After stirring for 30 minutes at 0 °C, the reaction mixture was allowed to come to room temperature and then was extracted with diethyl ether three times. After

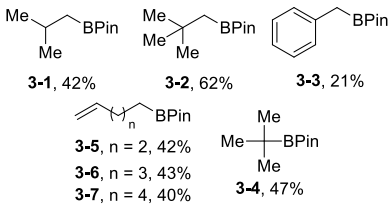
combining the organic layers, the resulting solution was concentrated *in vacuo* and purified through column chromatography to afford the alkyl-Bpin.

Scheme 3-1. Synthesis of Alkyl-BPins via Grignard Reaction.



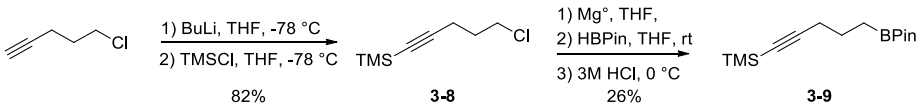
A number of alkyl-BPins were synthesized using this general reaction scheme, including the model substrate isobutyl-BPin (Figure 3-2, **3-1**). Using this method, the neopentyl alkyl-BPin (**3-2**) was successfully synthesized for the first time in 62% yield. However, not all of the synthesized boronate esters were synthesized using a freshly formed Grignard. Alkyl-BPins **3-3** and **3-4** were produced via addition of a commercial Grignard solution (2.0 M in THF and 1.7 M in Et_2O, respectively) to a mixture of pinacolborane and THF at room temperature. The subsequent addition of 3M HCl and workup were identical to that in the synthesis of the model substrate. A series of alkyl-BPins with terminal alkenes were synthesized with varying alkyl chain lengths (**3-5** *to* **3-7**).

Figure 3-2. Synthesized Alkyl-BPins**.**



While these boronate esters would readily showcase moderate to high steric tolerance, benzylic systems, and modest functional group tolerance, the substrates are exclusive to alkyl groups. In order to increase the functionality of this reaction, a series of compounds were synthesized to showcase heteroatom tolerance. First, compound **3-9** was synthesized through TMS protection of the terminal alkyne of 1-chloro-4-pentyne (Scheme 3-2) according to a literature procedure.[6] The alkyne was cooled to -78 °C in THF, followed by slow addition of *n*-butyl-lithium (BuLi). After the addition was complete, the solution was stirred at -78 °C for 30 minutes. Then TMSCl was added drop-wise at -78 °C, and the mixture was allowed to warm to room temperature overnight. Protected alkyne **3-8** was then isolated following simple extraction and column chromatography. Next, **3-8** was subjected to the previously stated modified Grignard reaction, and after workup, alkyl-Bpin **3-9** was isolated.

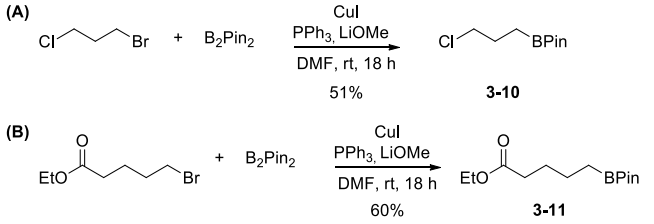
Scheme 3-2. Synthesis of **3-9.**



Another efficient, one step process for the direct synthesis of alkyl-BPins is through a copper-catalyzed cross-coupling reaction between an alkyl bromide and bis(pinacolato)diboron (B_2Pin_2).[7] Using a simple copper salt, an extremely inexpensive ligand, and a commercially available base, a number of alkyl-BPins containing a large variety of functional groups were synthesized using this method. Since this method primarily works with alkyl bromides, 1-bromo-3-chloro-propane was a suitable starting material to afford the mono boronated compound **3-10** in 51% yield (Scheme 3-3A).

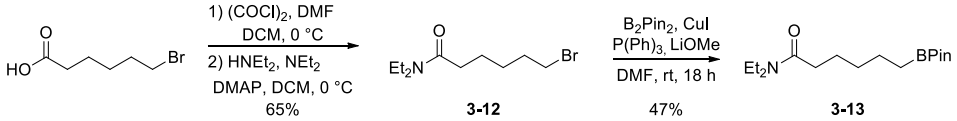
Using this same method, the ester containing alkyl bromide was added to a solution of B_2Pin_2, CuI, triphenylphosphine, and lithium methoxide in DMF at room temperature for 18 hours (Scheme 3-3B). The resulting heterogeneous solution was then diluted with ethyl acetate and filtered through a pad of silica gel. The resulting filtrate was then concentrated and purified via column chromatography to give the alkyl-BPin **3-11** in good yield.

Scheme 3-3. Synthesis of Alky-BPins **3-10** and **3-11.**



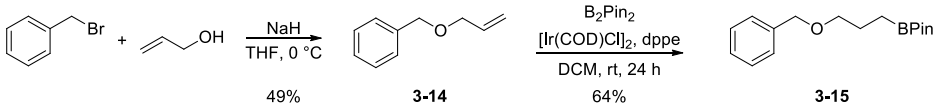
Alkylboronic ester **3-13** was synthesized in 2 steps from the commercially available carboxylic acid (Scheme 3-4). Starting from the carboxylic acid, the acyl chloride was generated *in situ,* followed by addition of diethylamine to give the tertiary amide **3-12**. The amide was then converted to boronate **3-13** using a modification of the method by Yang *et al*. in 47% yield.[7]

Scheme 3-4. Synthesis of Alkyl-BPin **3-13.**



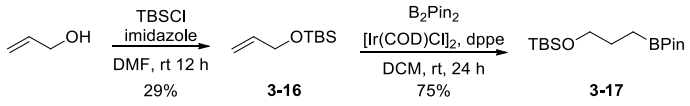
Another efficient method for the synthesis of alkylboronic esters is hydroboration. Alkyl-BPin **2-10** was synthesized in one step using a modified iridium-catalyzed hydroboration protocol.[8] Using a similar method, **3-15** was synthesized in 2 steps from allyl alcohol (Scheme 3-5). First, allyl alcohol was benzyl protected using benzyl bromide and sodium hydride to afford benzyl ether **3-14** in 44% yield. The terminal alkene was then hydroborated with pinacolborane to give the pinacol ester **3-15** in 64% yield.

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



Boronate **3-17** was synthesized in 2 steps from allyl alcohol (Scheme 3-6). The allylic alcohol was first protected following the general protocol with TBSCl.[9] The resulting silyl-protected alcohol **3-16** was then hydroborated to afford the alkyl-BPin **3-17** in 75% yield.

Scheme 3-6. Synthesis of **3-17.**



3.3 Preliminary Investigation

Initial development of this reaction began with the cross-coupling of the benzamide and isobutyl-BPin (**3-1**). Initial reaction conditions were identical to the

previously optimized copper-catalyzed reaction (Chapter 2.3.1). Using the same 10 mol% catalyst loading, excess of boronate ester and base, and 3 equivalents of DTBP, we investigated the reaction thoroughly. A multitude of copper pre-catalysts, ligands, bases, and solvents were tested. The reactions were run for 24 hours to ensure maximum conversion of the starting material. All the reactions were run on 0.3 mmol scale and the yields reported are NMR yields, using 1,3,5-trimethoxybenzene as an internal standard.

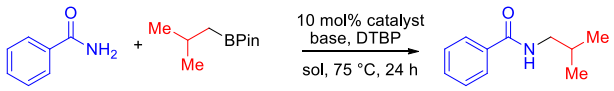
Two key reaction parameters were vital for a successful, high yielding cross-coupling. First, identification of a more reactive copper pre-catalyst, (Copper (II) Hexafluoroacetylacetonate hydrate) proved to be essential. Second, the addition of a desiccant additive (4Å Molecular Sieves, 4Å MS) proved to be the crucial reagent to obtain a near quantitative yield. Preliminary examination of the reaction conditions across a broad scope of compounds revealed moderate functional group tolerance. However, the results reported herein could lead to a whole new realm of C-N bond formation, including those with high functional group utility.

3.3.1 Optimization

Preliminary investigation began with the cross-coupling of isobutyl-BPin (**3-1**) and benzamide, using the previously established reaction conditions, 10 mol% CuBr, 2.2 equiv NaOTMS, and 3 equiv of DTBP in ^{t}BuOH. Under these conditions, desired amide **2-**36 was generated in 47% yield (Table 3-1, entry 1). Changing the copper salt pre-catalyst showed an increase in yield (54%, entry 2), but when changing to Copper (I) Acetate (entry 3), an increase of over 20% of amide **2-36** was observed by NMR. A range of solvents with varying degrees of polarity, including MeCN, toluene, THF,

DCE, and DMF, were found to be ineffective for this reaction (entries 4-8). A multitude of bases were tested (ca. 30, not shown) but NaOTMS was the only effective base. Further investigation showed that copper (II) salts proved to be mostly comparable in yields (entries 9 and 10). However, switching to the more reactive copper (II) pre-catalyst, Copper (II) Hexafluoroacetylacetonate hydrate, a 75% yield was observed by NMR. Various temperatures were surveyed, and a slight increase in yield occurred at 70 °C (entry 12). Additives also had a positive and negative effect on the yield. The addition of 1 equiv of water decreased the yield (entry 13), while 1 weight equiv of freshly dried 4Å MS increased the observed yield of **2-36** to 96% yield. Under these conditions, other silanolate bases were tested and were inferior to NaOTMS (entries 15 and 16). The reaction was exclusive to mono-alkylation, with no double-alkylation being observed.

Table 3-1. Optimization of Cross-Coupling Reaction with Alkyl-BPins.



3-1 2-36

entry	catalyst	base	solvent	yield[a]
1	CuBr	NaOTMS	^{t}BuOH	47%
2	CuI	NaOTMS	^{t}BuOH	54%
3	CuOAc	NaOTMS	^{t}BuOH	69%
4	CuOAc	NaOTMS	MeCN	17%
5	CuOAc	NaOTMS	PhMe	0%
6	CuOAc	NaOTMS	THF	15%
7	CuOAc	NaOTMS	DCE	17%
8	CuOAc	NaOTMS	DMF	0%
9	$Cu(OAc)_2$	NaOTMS	^{t}BuOH	58%
10	$Cu(AcAc)_2$	NaOTMS	^{t}BuOH	66%
11	$Cu(HexFAcAc)_2$	NaOTMS	^{t}BuOH	75%
12	$Cu(HexFAcAc)_2$	NaOTMS	^{t}BuOH	79%[b]
13	$Cu(HexFAcAc)_2$	NaOTMS	^{t}BuOH	65%[b,c]
14	$Cu(HexFAcAc)_2$	NaOTMS	^{t}BuOH	96%[b,d]
15	$Cu(HexFAcAc)_2$	NaOTBS	^{t}BuOH	81%[b,d]
16	$Cu(HexFAcAc)_2$	NaOTIPS	^{t}BuOH	65%[b,d]

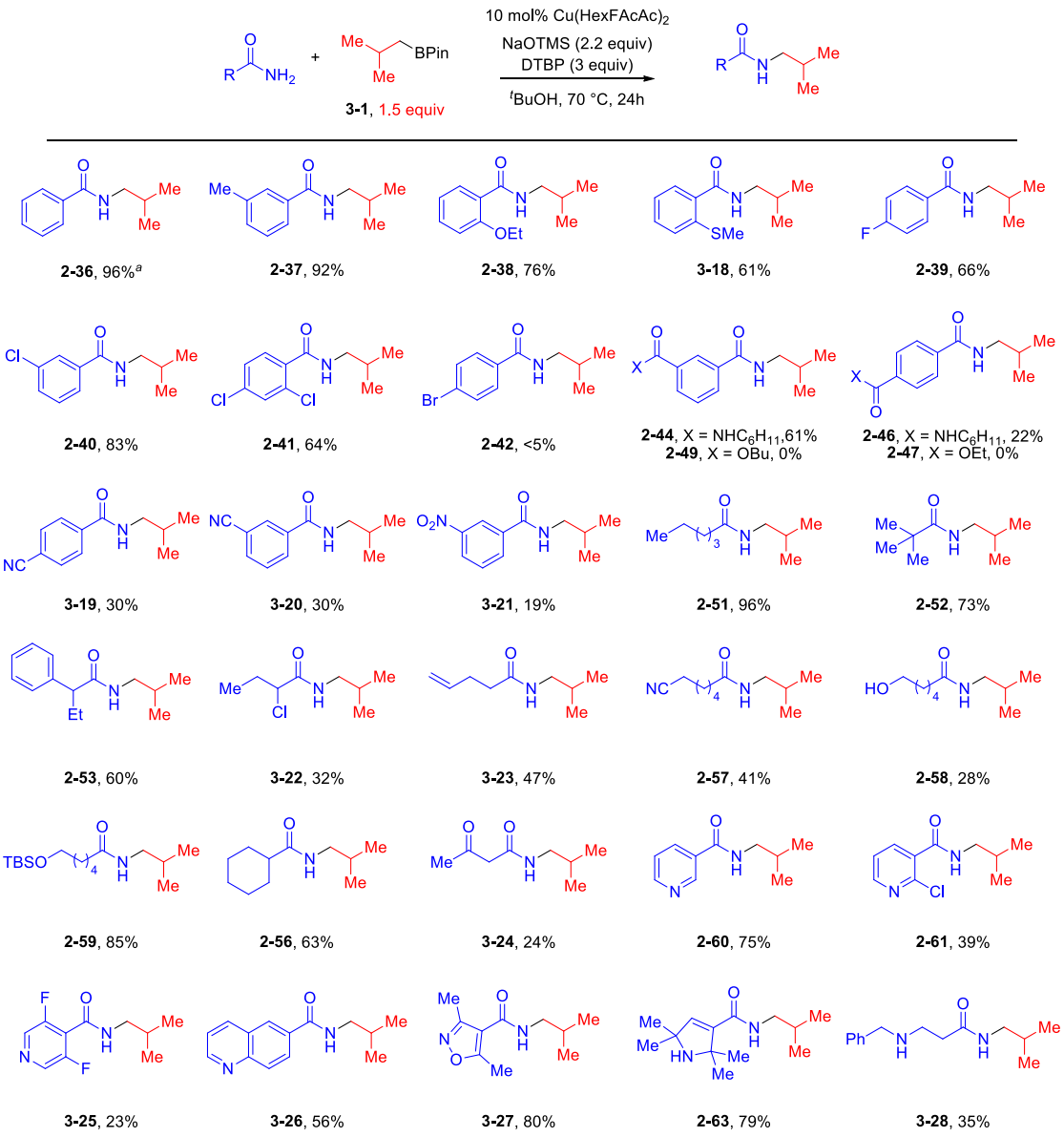
[a] Yield determined using NMR, [b] Exp. run at 70 °C, [c] 1 equiv H_2O, [d] 1 wt/equiv 4Å Mol. Sieves.
$Cu(HexFAcAc)_2$ = Copper (II) Hexafluoroacetylacetonate hydrate

In addition to the optimization shown above, additional screening was conducted. A large variety of ligands, including monodentate and bidentate phosphines, pincer-type phosphines, N-heterocyclic carbenes, β-diketimidate ligands, and acetonylacetonate ligands were tested and shown to have no effect on the reaction. An extensive investigation into solvents and co-solvents was also undertaken, with 100% ^{t}BuOH proving to be the optimal solvent.

3.3.2 Initial Scope

Under the optimized conditions, amide **2-36** was isolated in 96% yield (Table 3-1, entry 14). We then investigated the overall utility and generality of the reaction. All of the reactions were conducted on a 0.3 mmol scale, and all of the yields reported are NMR yields, unless otherwise noted. A large range of functionality was tested on both the primary amide and alkyl-BPin substituents, and modest yields and functional group tolerance were achieved (Scheme 3-7). Several of the same products were synthesized in Chapter 2.3.2 and the numbering of the compounds is directly correlated, however all of the products discussed below were synthesized according to the reaction conditions discussed in Chapter 3.3.1. All of the yields and compounds discussed in this chapter are based on the data in Scheme 3-7 unless otherwise noted.

Scheme 3-7. Preliminary Scope with Respect to Primary Amides.



[a] Isolated yield, 1 mmol scale

An extensive set of benzamide derivatives were tested, including alkyl variants, those bearing electron donating and withdrawing functional groups, and halogenated

compounds. *Meta*-toluamide (**2-37**) was mono-alkylated in 92% yield. Electron donating aryl ether (**2-38**) and aryl thioether (**3-18**) were both suitable coupling partners, generating products in 76% and 61% respectively. Halogenated compounds were also successfully alkylated, including the moderately electron withdrawing fluorine containing amide **2-39**. Both mono- and di-halogenated chlorine derivatives (**2-40**, **2-41**) were cross-coupled with the boronic ester in 83% and 64% yield. However, similar to the boronic acid cross-coupling reaction, amides containing a bromide atom remained intolerant under these conditions, resulting in less than a 5% yield. A large range of electron withdrawing groups were tested, including amides, esters, aryl nitriles, and nitro groups. Similar to the original reaction, *meta* secondary amides (**2-44**) were successfully reacted. However, under these reaction conditions, the *para* secondary amide (**2-46**) was also a suitable coupling partner with **3-1** in a modest 22% yield. Esters (**2-47** and **2-49**) remained unreactive due to the formation of the sodium carboxylate under mildly basic conditions.[10] Aryl nitriles in both *para* (**3-19**) and *meta* (**3-20**) positions were alkylated in 30% yield, while the *meta*-nitro benzamide (**3-21**) was only produced in 19% yield.

Aliphatic substrates were extensively tested, including those with high steric demand and varied functionality. The purely aliphatic chain **2-51** reacted with isobutyl-BPin in 96% yield, while α-branching amide **2-52** produced a 73% yield when coupled with **3-1**. Benzylic system **2-53** was also alkylated in a modest yield (60%), while haloketone **3-22** reacted in 47% yield. Terminal functional groups were also tested, including alkene **3-23**, nitrile **2-57**, free alcohol **2-58**, and silyl ether **2-59**. The protection of the alcohol with a sterically bulky TBS group increased the yield over by

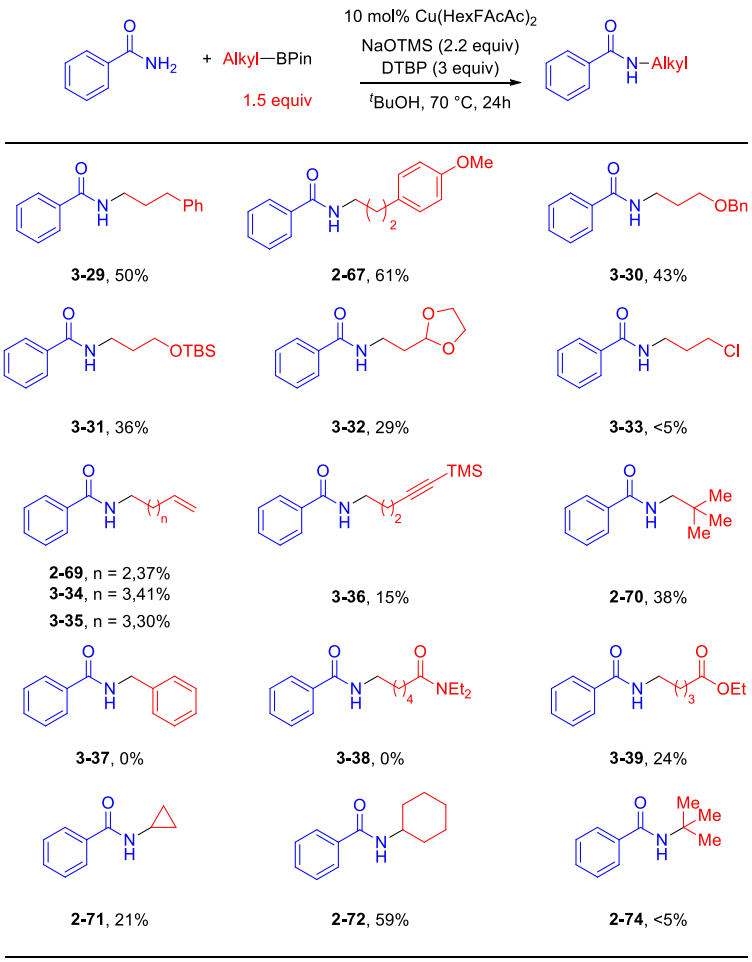
over 50% when compared to the free alcohol. Carbocyclic systems are also tolerated (**2-56**, 63%). Ketones were ineffective coupling partners (**3-24**, 24%).

A number of different heterocyles and secondary amines were cross-coupled with **3-1**, including nicotinamide (**2-60**, 75%). Halogenated nicotinamide derivatives, including mono-chlorinated amide **2-61** and di-fluorinated amide **3-25**, were exclusively mono-alkylated in low yield (39% and 23% respectively). The quinolone derivative **3-26** was alkylated in 56% yield by NMR, while the oxazole amide **3-27** was alkylated in remarkably high yield (80%). Benzylated amines are also tolerated (**2-63** and **3-28**), with the sterically hindered amine reacting in a much higher yield.

As discussed in Chapter 3.2, a wide range of alkyl-BPins were successfully synthesized. All of these boronate esters were tested under the optimized conditions, resulting in only modest yields (Scheme 3-8). Secondary and tertiary pinacol esters were also tested for compatibility.

The secondary amide **3-29** was synthesized through the cross coupling of benzamide and 3-phenyl-1-propylboronic acid pinacol ester in 50% yield. Aromatic ether (**2-67**) was synthesized in moderate yield from previously synthesized boronate ester **2-10**, which is comparable to the yield reported when benzamide was cross-coupled with the alkylboronic acid variant. Two types of protected alcohols, benzyl ether **3-30** and silyl ether **3-31**, alkylated the primary amide in 43% and 36% yield, respectively. The acetal amide **3-32** was formed in a low yield, but remains an important substrate due to the easy removal of the protecting group to the aldehyde. Primary halogens, such as **3-33**, are unreactive under these reaction conditions.

Scheme 3-8. Scope with Respect to Alkyl-BPins.



The secondary amide **3-29** was synthesized through the cross coupling of benzamide and 3-phenyl-1-propylboronic acid pinacol ester in 50% yield. Aromatic ether (**2-67**) was synthesized in moderate yield from previously synthesized boronate ester **2-10**. Ether **2-67** was formed in a comparable yield to that reported when benzamide was cross-coupled with the corresponding alkylboronic acid variant

A previously successful cross-coupling reaction was conducted with a boronate bearing a terminal alkene. However, under these conditions, the alkyl-BPin **3-5** resulted in only a 37% yield of **2-69**. A possible cause of the low yield was the coordination of the alkene to the electron poor copper catalyst. Longer chain alkyl-BPins **3-6** and **3-7** were synthesized to try and increase the yield in hopes of pushing the alkene out of proximity of the copper catalyst, but to no avail. **3-34** and **3-35** were formed in the same yield as **2-69**. TMS protected alkyne (**3-36**) was also not a suitable reaction partner for benzamide, due to de-protection of the alkyne under basic conditions.[10] Sterically encumbered substituent **2-70** was synthesized in moderate yield. The pure benzyl system **3-37** remained unreactive. Alkyl-BPins with terminal amide (**3-38**) functionality did not generate any alkylated product, while the terminal ester boronate **3-39** generated a slight amount of desired product.

Secondary and tertiary alkyl-BPins were investigated briefly, with only cyclohexyl-BPin (**2-72**) coupling in decent yield. The reactivity of cyclopropyl-Bpin **2-71** was minimal, while tertiary pinacol boranes **2-74** was an inert coupling partner.

3.4 Discussion

The preliminary results reported in this chapter highlight many positive features of this reaction, as well as a few solvable problems. First, the system succeeds in being completely tolerant of β-hydrogens, i.e. no β-hydride elimination is observed, and second, the system generates exclusively mono-alkylated products. Throughout all of the optimization and scope investigation, no over-alkylation was detected. However, the primary benefit of using alkyl-BPins in place of alkylboronic acids is their ease of synthesis, commercial availability, and stability. Thus far, modification of this system

for use with alkyl-BPin substituents as cross-coupling partners has generated products in modest yields at best. Additional investigation into the cross-coupling reaction will need to be conducted to improve the generality of the reaction.

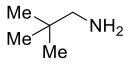
Overall the reaction did show significant functional group tolerance, and in some cases, better reactivity than the original reaction. The model substrate **2-36** was synthesized in 96% yield, which was more than a 10% increase from the original system. However, this phenomenon is infrequent, and only applies to simple systems (**2-37, 2-51,** and **2-60**). In general, the yields tended to be either comparable or inferior to the previously reported products. The more reactive copper-catalyst and hygroscopic additive did have a positive effect on previously unreactive systems. *Para*-secondary amide **2-16** yielded no product when cross-coupled with an alkylboronic acid, but did produce a low yielding alkylated product with isobutyl-BPin (**2-46**, 22%). Strongly electron-withdrawing systems also did not seem to have as profound of an effect on the reaction, giving 30% yields from both *para* and *meta*-nitrile containing systems (**3-19** and **3-20**). The *meta*-nitro amide **3-21** was also alkylated, but in nearly half the yield as the nitriles (19%). Additionally, esters continue to be problematic in the presence of the mild base. Other new functional groups include terminal alkenes (**3-22**), α-chloro amides (**3-23**), complex heterocycles (**3-25** and **3-27**), and non-sterically hindered free secondary amines (**3-28**). A ketone was also tested, but yielded only 24% yield (**3-24**). This could be due to the presence of the acidic protons in acetoacetamide.[11]

Newly synthesized alkyl-BPins were tested, but yielded only low to modest yields (Scheme 3-8). In most cases, analysis of the crude reaction mixture by ^{11}B NMR shows a significant amount of boronate starting material. This, however, comes as no surprise since one of the significant advantages to alkyl-BPins is their stability.[12]

Improvement in the yields for this reaction will require more stringent conditions, i.e. higher temperatures, longer reaction times, additional activating reagents, and/or more equiv of boronate ester.

While the chemistry is extremely novel, and showcases rare C-B to C-N bond conversion, the products could be produced in various ways. There are multiple reported protocols for the synthesis of secondary amides, including acylation, DCC-coupling and various catalytic methods.[13-15] Therefore, isobutyl secondary amides in themselves (Scheme 3-7) are not interesting products. However, by modifying the cross-coupling boronate partner to a substrate that is not accessible by traditional methods, the utility of the reaction would increase. For example, the neopentyl amide **2-70** could not be made reasonably using the common methods due to low availability and hard synthesis of 2,2-dimethyl-1-propylamine (**3-40**, Figure 3-8).[16] Using the easily synthesized boronate ester **3-2**, our method is the only route available to make secondary amides like **2-70**.

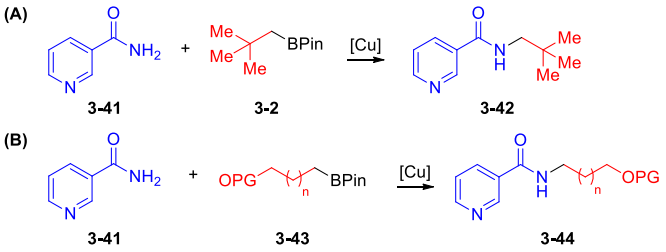
Figure 3-3. Structure of Amine **3-40.**



A change in the model system would also increase the generality of the reaction. Isobutyl-BPin tests for β-hydride elimination and possesses some steric bulk, but pinacol borane **3-2** is bulkier and previous results have shown no β-hydride elimination. Therefore, optimization on two different types of systems will be investigated (Scheme 3-9). First, a switch in primary amide source to a slightly more complicated system,

such as nicotinamide (**3-41**), would allow for the synthesis of complex secondary amide heterocyclic products. Another option would be to change the boronate coupling partner to a substrate that would provide unique, original products. Boronates **3-2** and **3-43** are unique boronic esters that have shown promise for mono-alkylation of an amide (Scheme 3-9, **3-31** and **2-70**), and they are easily synthesized. Their amine counterparts are hard to synthesize and expensive. After optimization and with using these reagents, the scope, utility, practicality, and generality of this transformation would revolutionize C-B to C-N bond formation.

Scheme 3-9. Proposed Complex Model Systems.



3.5 Conclusions

By switching the boronate cross-coupling partner from a boronic acid to a pinacol ester, the scope of the reaction should expand substantially. The identification of a more reactive copper source (Copper (II) Hexafluoroacetylacetonate hydrate) and a hydroscopic additive (4Å MS) appeared to be the key reaction changes needed to successfully mono-alkylate the primary amide using these substrates. The initial optimization of the reaction produced a high yield of the model substrate, but has failed as yet to translate to other substrates, especially to modified alkyl-BPins. A reinvestigation into the reaction using a more complex primary amide and a functional

group-bearing alkyl boronate is a necessity for this reaction. Because alkyl-BPins are extremely stable, a more reactive, possibly ligand-containing, catalytic system may have to be employed. However, even with the low yields, this constitutes another mild method for the conversion of C-B to C-N bonds, once again establishing an orthogonal method for the synthesis of secondary amides. Further investigation into this reaction will expand upon its utility, and once successful, will greatly influence the synthetic organic community in respect to amide synthesis.

3.6 Experimental Procedures & Data

3.6.1 General Experimental Details

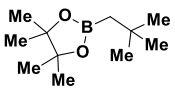
THF, toluene, acetonitrile, and DMF were dried on alumina according to published procedures.[17] DCE was purchased in an anhydrous septa sealed bottle. *Tert*-Butanol (^{t}BuOH) was distilled from calcium hydride and sparged with nitrogen prior to use, and stored under nitrogen in a sealed vessel. Copper (II) Hexafluoroacetylacetonate hydrate and NaOTMS (95%, Sigma-Aldrich) were purchased commercially and used as received. The bulk of these materials were stored in a nitrogen filled glove box, with samples being removed from the glove box and stored in a desiccator under air for up to one week prior to use. All hot glassware was oven dried for a minimum of two hours or flame-dried under vacuum prior to use. 4,4,5,5-tetramethyl-2-(3-phenylpropyl)-1,3,2-dioxaborolane was synthesized using a modified procedure from 1-bromo-3-phenyl-propane, matching previously published data.[5,18] 2-(3-(benzyloxy)propyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was synthesized in 2 steps from allyl alcohol via a benzyl protection, followed by hydroboration with pinacolborane.[19,20] *Tert*-

butyldimethyl (3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propoxy)silane was prepared in 2 steps from allyl alcohol and TBSCl according to the classic procedure, followed by hydroboration.[9,21] 2-(2-(1,3-dioxolan-2-yl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was prepared according to the procedure published by Yang et al.[7] The previously characterized 4,4,5,5-tetramethyl-2-(pent-4-en-1-yl)-1,3,2-dioxaborolane was synthesized using the general protocol reported by Clary et al.[5,22] 1-chloro-5-(trimethylsilyl)-4-pentyne was prepared using the general protocol from 1-chloro-5-hexyne.[23] Benzylboronic acid pinacolate ester was prepared from a commercially available Grignard solution (Sigma-Aldrich, 2.0 M in THF) and pinacolborane.[5,24] Ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborol-2-yl)-pentanoate was prepared using the general protocol from ethyl 5-bromopentanoate, matching previously published data.[7,17] *Tert*-butylboronic acid pinacolester was prepared according the known literature procedure from *tert*-butylbromide.[5] All other substrates and reagents were purchased in high analytical purity from commercial suppliers and used as received. Optimization of reaction conditions in Table 3-1 and all product yields in Schemes 3-7 and 3-8 were performed using standard Schlenk technique on a 0.3 mmol scale in 16 mm x 100 mm threaded test tubes sealed with septum caps, and heated and stirred in temperature controlled oil baths. All product yields were obtained by NMR unless otherwise noted.

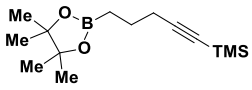
400 MHz ^{1}H, 101 MHz ^{13}C, and 128 MHz ^{11}B spectra were obtained on a 400 MHz FT-NMR spectrometer equipped with a Bruker CryoPlatform. 600 MHz ^{1}H and 151 MHz ^{13}C spectra were obtained on a 600 MHz FT-NMR spectrometer equipped with a Bruker SMART probe. All samples were analyzed in the indicated deutero-solvent and were recorded at ambient temperatures. Chemical shifts are reported in ppm.

^{1}H NMR spectra were calibrated using the residual protio-signal in deutero-solvents as a standard. 13C NMR spectra were calibrated using the deutero-solvent as a standard. IR spectra were recorded on an FT-IR spectrometer as thin films. Column chromatography was performed with 40-63 μm silica gel with the eluent reported in parentheses. Analytical thin-layer chromatography (TLC) was performed on precoated glass plates and visualized by UV or by staining with $KMnO_4$ and CAM. All NMR yields are reported using 1,3,5-trimethoxybenzene as an internal standard. GCMS data was collected using an Agilent 6850 series GC and 5973 MS detector. Low resolution ESI data was collected on a Thermo LCQ Advantage running in positive ion mode. High resolution mass spectrometry data was obtained at the University of Delaware, Newark on a Waters GCT Premier.

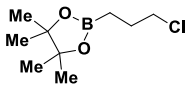
3.6.2 Novel Boronate Esters



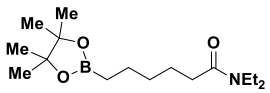
4,4,5,5-tetramethyl-2-neopentyl-1,3,2-dioxaborolane (**3-2**) was prepared according to the modification of the literature procedure[5] from 1-bromo-2,2-dimethylpropane (6.3 mL, 49.65 mmol), magnesium turnings (1.33 g, 54.62 mmol), pinacolborane (7 mL, 74.12 mmol), and anhydrous THF (50 mL) and purified by silica gel chromatography (25:1 hexanes: ethyl acetate) to afford the pinacol ester (5.45 g, 62%) as a colorless oil: : ^{1}H NMR (600 MHz, $CDCl_{3)}$ ∂ 1.24 (s, 12H), 0.99 (s, 9H), 0.80 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 82.9, 32.1, 29.9, 29.5, 25.0; ^{11}B NMR (193 MHz, $CDCl_3$) ∂ 33.4; FTIR (cm^{-1}): 2953, 1357, 1320, 1145. HRMS (EI) m/z, calculated for $[C_{11}H_{23}BO_2]^+$: 198.1797 found: 198.1807.



Trimethyl(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-1-yn-1-yl)silane (**3-9**) was prepared according to the modification of the literature procedure[5] from (6-chlorohex-1-yn-1-yl)trimethylsilane (1.35 g, 7.7 mmol), magnesium turnings (206 mg, 8.5 mmol), pinacolborane (1.1 mL, 6.93 mmol), and anhydrous THF (15 mL) and purified by silica gel chromatography (20:1 hexanes: ethyl acetate) to afford the pinacol ester 526 mg, 26%) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) ∂ 2.23 (t, J = 7.3 Hz, 2H), 1.71 – 1.57 (m, 2H), 1.24 (s, 12H), 0.87 (t, J = 8.0 Hz, 2H), 0.14 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) ∂ 107.7, 84.5, 83.1, 25.00, 24.96, 23.5, 22.4, 0.4; ^{11}B NMR (193 MHz, $CDCl_3$) ∂ 33.9; FTIR (cm^{-1}): 2979, 2174, 1379, 1319, 1146. HRMS (EI) m/z, calculated for $[C_{14}H_{27}O_2SiB]^+$: 266.1873; found: 266.1892.



2-(3-chloropropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**3-10**) was prepared according to the modification of the literature procedure[7] from 1-bromo-3-chloropropane (1.25 mL, 12.7 mmol), bis(pinacolato)diboron (4.85 g, 19.05 mmol), CuI (241 mg, 1.27 mmol), triphenylphospine (441 mg, 1.68 mmol), lithium methoxide (965 mg, 25.4 mmol), and anhydrous DMF (20 mL) and purified by silica gel chromatography (20:1 hexanes: ethyl acetate) to afford the pinacol ester (1.32 g, 51%) as a colorless oil: ^{1}H NMR (600 MHz, CDCl3) ∂ 3.53 (t, J = 6.8 Hz, 2H), 1.99 – 1.79 (m, 2H), 1.24 (s, 12H), 0.91 (t, J = 7.8 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) ∂ 83.3, 47.3, 31.1, 27.5, 25.0; ^{11}B NMR (193 MHz, $CDCl_3$) ∂ 33.7; FTIR (cm^{-1}): 2979, 1380, 1226, 1146. HRMS (EI) m/z, calculated for $[C_9H_{18}O_2BCl]^+$: 204.1088; found: 204.1088.



N,N-diethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexanamide (**3-13**) was prepared according to the modification of the literature procedure[7] from 6-bromo-N,N-diethylhexanamide (7.75 g, 6.7 mmol), bis(pinacolato)diboron (2.56 g, 10.1 mmol), CuI (127 mg, 0.67 mmol), triphenylphospine (211 mg, 0.80 mmol), lithium methoxide (510 mg, 13.4 mmol), and anhydrous DMF (12 mL) and purified by silica gel chromatography (3:1 hexanes: ethyl acetate) to afford the pinacol ester (930 mg, 47%) as a colorless oil: ^{1}H NMR (600 MHz, CDCl3) ∂ 3.55 (t, *J* = 6.7 Hz, 2H), 3.37 (q, *J* = 7.1 Hz, 2H), 3.30 (q, *J* = 7.2 Hz, 2H), 2.31 (d, *J* = 7.4 Hz, 2H), 1.85 – 1.78 (m, 2H), 1.68 (p, *J* = 7.6 Hz, 2H), 1.53 – 1.46 (m, 2H), 1.24 (s, 12H), 1.17 (t, *J* = 7.1 Hz, 3H), 1.11 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) ∂ 171.9, 75.2, 45.1, 42.1, 40.3, 33.0, 32.6, 26.9, 25.0, 24.8, 14.5, 13.3; ^{11}B NMR (193 MHz, $CDCl_3$) ∂ 22.4; FTIR (cm^{-1}): 3435, 2977, 1626, 1459, 1146. HRMS (ESI) m/z, calculated for $[C_{16}H_{33}BNO_3]^+$: 298.2553; found: 298.2556.

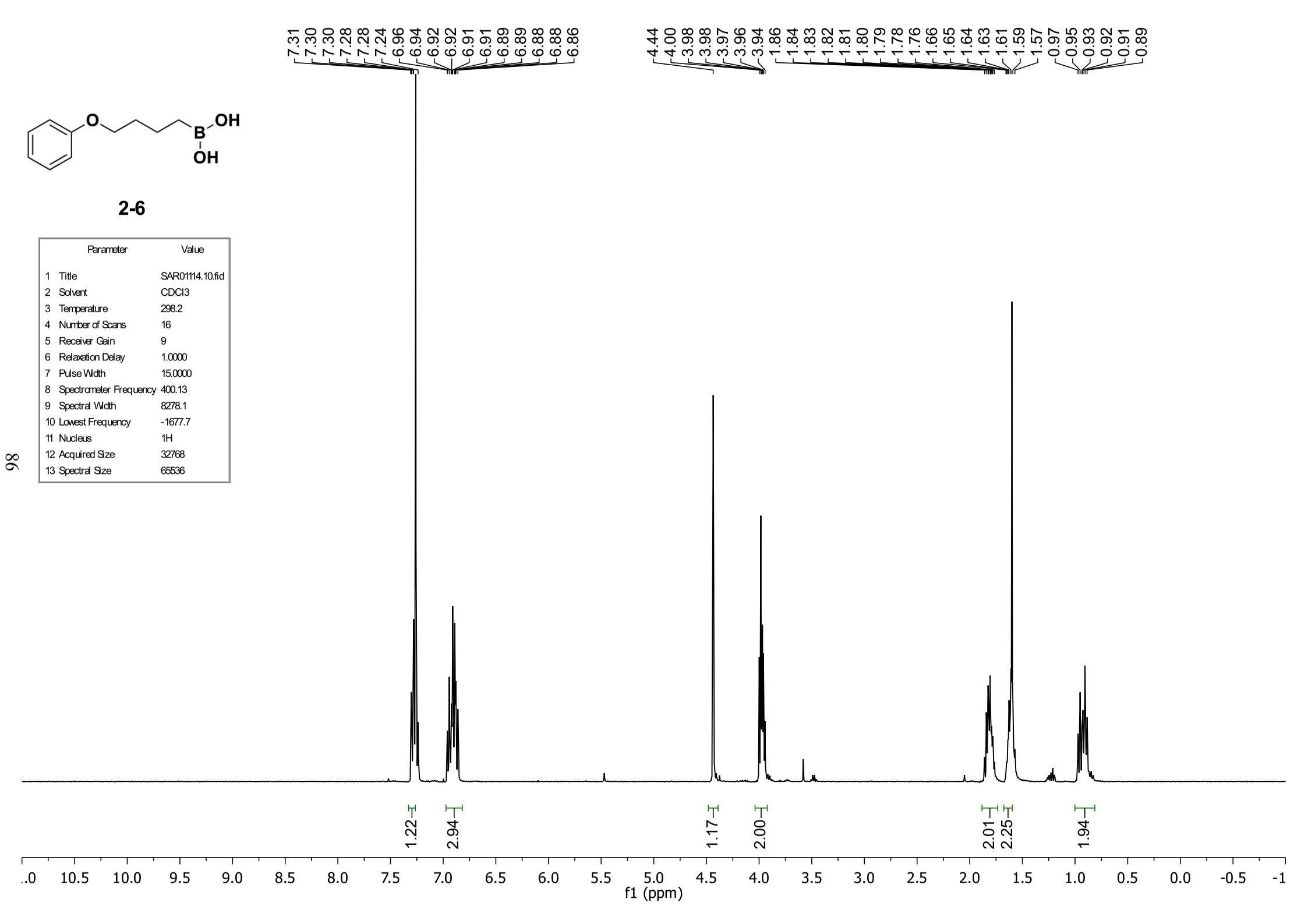
3.7 References

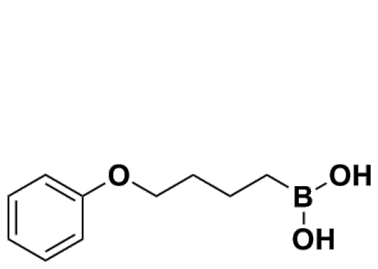
(1) Brown, H. C.; Bhat, N. G.; Somayaji, V. *Organometallics* **1983**, *2*, 1311.
(2) Corberán, R.; Mszar, N. W.; Hoveyda, A. H. *Angewandte Chemie International Edition* **2011**, *50*, 7079.
(3) Crudden, C. M.; Hleba, Y. B.; Chen, A. C. *Journal of the American Chemical Society* **2004**, *126*, 9200.
(4) Lee, Y.; Hoveyda, A. H. *Journal of the American Chemical Society* **2009**, *131*, 3160.
(5) Clary, J. W.; Rettenmaier, T. J.; Snelling, R.; Bryks, W.; Banwell, J.; Wipke, W. T.; Singaram, B. *The Journal of Organic Chemistry* **2011**, *76*, 9602.
(6) Das, I.; Chowdhury, S.; Ravikumar, K.; Roy, S.; Gupta, B. D. *Journal of Organometallic Chemistry* **1997**, *532*, 101.
(7) Yang, C.-T.; Zhang, Z.-Q.; Tajuddin, H.; Wu, C.-C.; Liang, J.; Liu, J.-H.; Fu, Y.; Czyzewska, M.; Steel, P. G.; Marder, T. B.; Liu, L. *Angewandte Chemie International Edition* **2012**, *51*, 528.
(8) Reichle, M. A.; Breit, B. *Angewandte Chemie International Edition* **2012**, *51*, 5730.
(9) Corey, E. J.; Venkateswarlu, A. *Journal of the American Chemical Society* **1972**, *94*, 6190.
(10) Xiong, H.; Hsung, R. P.; Wei, L.-L.; Berry, C. R.; Mulder, J. A.; Stockwell, B. *Organic Letters* **2000**, *2*, 2869.
(11) Kim, M.-h.; Choi, S.-h.; Lee, Y.-J.; Lee, J.; Nahm, K.; Jeong, B.-S.; Park, H.-g.; Jew, S.-s. *Chemical Communications* **2009**, *0*, 782.
(12) Tucker, C. E.; Davidson, J.; Knochel, P. *The Journal of Organic Chemistry* **1992**, *57*, 3482.
(13) Hardee, D. J.; Kovalchuke, L.; Lambert, T. H. *Journal of the American Chemical Society* **2010**, *132*, 5002.
(14) Singh, C.; Kumar, V.; Sharma, U.; Kumar, N.; Singh, B. *Curr. Org. Synth.* **2013**, *10*, 241.
(15) Montalbetti, C. A. G. N.; Falque, V. *Tetrahedron* **2005**, *61*, 10827.
(16) Shapiro, S. L.; Parrino, V. A.; Rogow, E.; Freedman, L. *Journal of the American Chemical Society* **1959**, *81*, 3725.
(17) Beauchard, A.; Phillips, V. A.; Lloyd, M. D.; Threadgill, M. D. *Tetrahedron* **2009**, *65*, 8176.
(18) Zhang, L.; Peng, D.; Leng, X.; Huang, Z. *Angewandte Chemie International Edition* **2013**, *52*, 3676.
(19) Nielsen, L.; Skrydstrup, T. *Journal of the American Chemical Society* **2008**, *130*, 13145.
(20) Sorin, G.; Martinez Mallorquin, R.; Contie, Y.; Baralle, A.; Malacria, M.; Goddard, J.-P.; Fensterbank, L. *Angewandte Chemie* **2010**, *122*, 8903.
(21) Bull, J. A.; Charette, A. B. *Journal of the American Chemical Society* **2010**, *132*, 1895.

(22) Nakamura, M.; Hara, K.; Hatakeyama, T.; Nakamura, E. *Organic Letters* **2001**, *3*, 3137.
(23) Kozhushkov, S. I.; Wagner-Gillen, K.; Khlebnikov, A. F.; de Meijere, A. *Synthesis* **2010**, *2010*, 3967.
(24) Pintaric, C.; Olivero, S.; Gimbert, Y.; Chavant, P. Y.; Duñach, E. *Journal of the American Chemical Society* **2010**, *132*, 11825.

Appendix A

SPECTRAL DATA FOR CHAPTER 2


7.31
7.30
7.30
7.28
7.28
7.24
6.96
6.94
6.92
6.92
6.91
6.91
6.89
6.89
6.88
6.88
6.86
4.44
4.00
3.98
3.98
3.97
3.96
3.94
1.86
1.84
1.83
1.82
1.81
1.80
1.79
1.78
1.76
1.66
1.65
1.64
1.63
1.61
1.59
1.57
0.97
0.95
0.93
0.92
0.91
0.89
O
B
OH
OH
2-6
Parameter Value
1 Title SAR01114.10.fid
2 Solvent CDCl3
3 Temperature 298.2
4 Number of Scans 16
5 Receiver Gain 9
6 Relaxation Delay 1.0000
7 Pulse Width 15.0000
8 Spectrometer Frequency 400.13
9 Spectral Width 8278.1
10 Lowest Frequency -1677.7
11 Nucleus 1H
12 Acquired Size 32768
13 Spectral Size 65536
98
1.22
2.94
1.17
2.00
2.01
2.25
1.94
f1 (ppm)

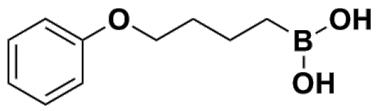


2-6

	Parameter	Value
1	Title	SAR01114.11.fid
2	Solvent	CDCl3
3	Temperature	298.2
4	Number of Scans	1024
5	Receiver Gain	512
6	Relaxation Delay	2.0000
7	Pulse Width	9.2500
8	Spectrometer Frequency	100.62
9	Spectral Width	23980.8
10	Lowest Frequency	-1916.9
11	Nucleus	13C
12	Acquired Size	32768
13	Spectral Size	65536

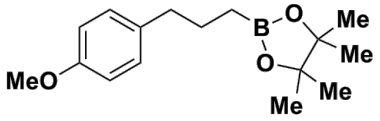
158.96
129.59
120.82
114.57
77.48
67.71
31.60
20.93
20.24

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



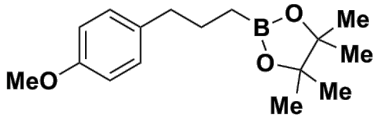
2-6

	Parameter	Value
1	Title	SAR01114.1.fid
2	Solvent	CDCl3
3	Temperature	298.3
4	Number of Scans	128
5	Receiver Gain	203
6	Relaxation Delay	1.0000
7	Pulse Width	8.3000
8	Spectrometer Frequency	128.38
9	Spectral Width	25510.2
10	Lowest Frequency	-12755.1
11	Nucleus	11B
12	Acquired Size	32768
13	Spectral Size	65536



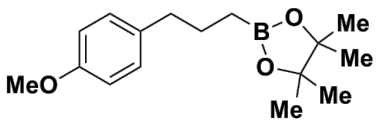
2-10

	Parameter	Value
1	Title	SAR01125.10.fid
2	Solvent	CDCl3
3	Temperature	300.0
4	Number of Scans	8
5	Receiver Gain	144
6	Relaxation Delay	1.0000
7	Pulse Width	10.7700
8	Spectrometer Frequency	600.32
9	Spectral Width	8403.4
10	Lowest Frequency	-915.7
11	Nucleus	1H
12	Acquired Size	32768
13	Spectral Size	65536



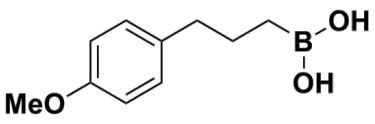
2-10

	Parameter	Value
1	Title	SAR01125_2.10.fid
2	Solvent	CDCl3
3	Temperature	298.1
4	Number of Scans	1024
5	Receiver Gain	512
6	Relaxation Delay	2.0000
7	Pulse Width	9.2500
8	Spectrometer Frequency	100.62
9	Spectral Width	23980.8
10	Lowest Frequency	-1916.6
11	Nucleus	13C
12	Acquired Size	32768
13	Spectral Size	65536



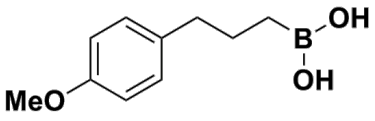
2-10

	Parameter	Value
1	Title	SAR01125.1.fid
2	Solvent	CDCl3
3	Temperature	298.3
4	Number of Scans	128
5	Receiver Gain	203
6	Relaxation Delay	1.0000
7	Pulse Width	8.3000
8	Spectrometer Frequency	128.38
9	Spectral Width	25510.2
10	Lowest Frequency	-12755.1
11	Nucleus	11B
12	Acquired Size	32768
13	Spectral Size	65536



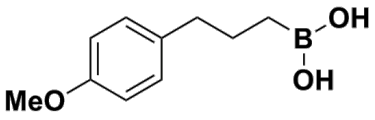
2-11

	Parameter	Value
1	Title	SAR01131.1.fid
2	Solvent	CDCl3
3	Temperature	300.0
4	Number of Scans	8
5	Receiver Gain	161
6	Relaxation Delay	1.0000
7	Pulse Width	10.7700
8	Spectrometer Frequency	600.32
9	Spectral Width	8403.4
10	Lowest Frequency	-915.7
11	Nucleus	1H
12	Acquired Size	32768
13	Spectral Size	65536



2-11

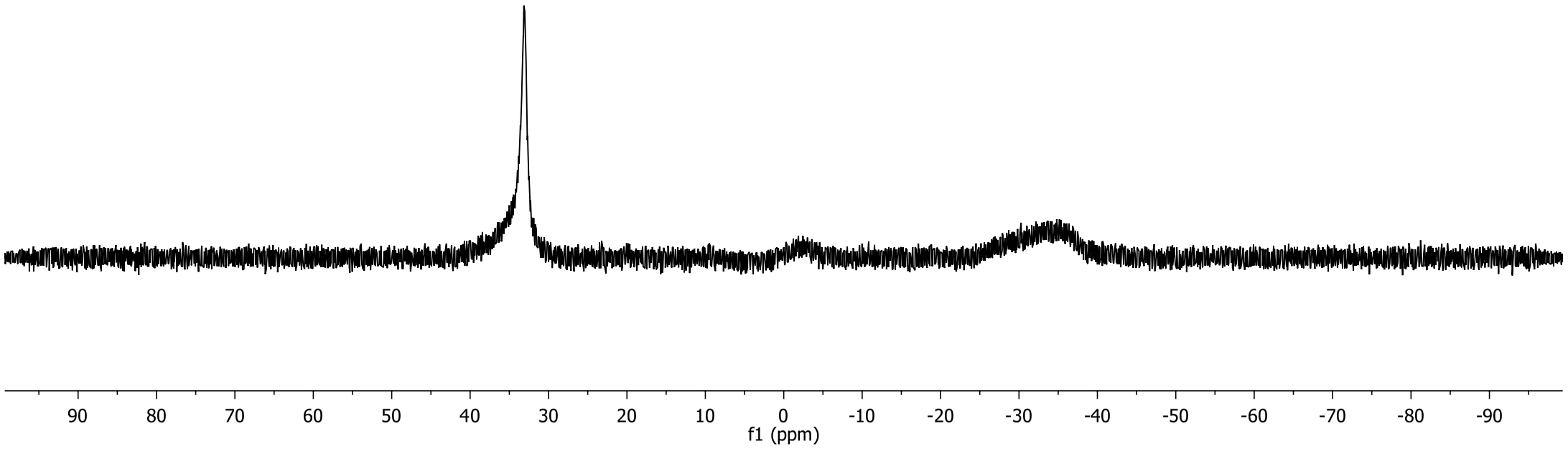
	Parameter	Value
1	Title	SAR01131.10.fid
2	Solvent	CDCl3
3	Temperature	298.1
4	Number of Scans	1024
5	Receiver Gain	512
6	Relaxation Delay	2.0000
7	Pulse Width	9.2500
8	Spectrometer Frequency	100.62
9	Spectral Width	23980.8
10	Lowest Frequency	-1916.6
11	Nucleus	13C
12	Acquired Size	32768
13	Spectral Size	65536

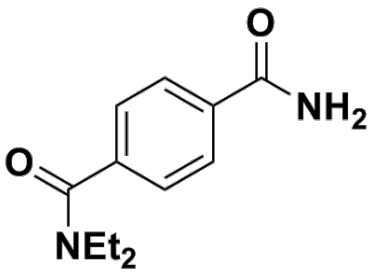


33.02

2-11

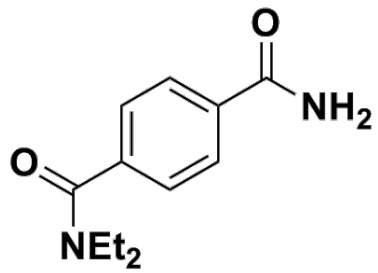
	Parameter	Value
1	Title	SAR01131.1.fid
2	Solvent	CDCl3
3	Temperature	298.3
4	Number of Scans	128
5	Receiver Gain	203
6	Relaxation Delay	1.0000
7	Pulse Width	8.3000
8	Spectrometer Frequency	128.38
9	Spectral Width	25510.2
10	Lowest Frequency	-12755.1
11	Nucleus	11B
12	Acquired Size	32768
13	Spectral Size	65536





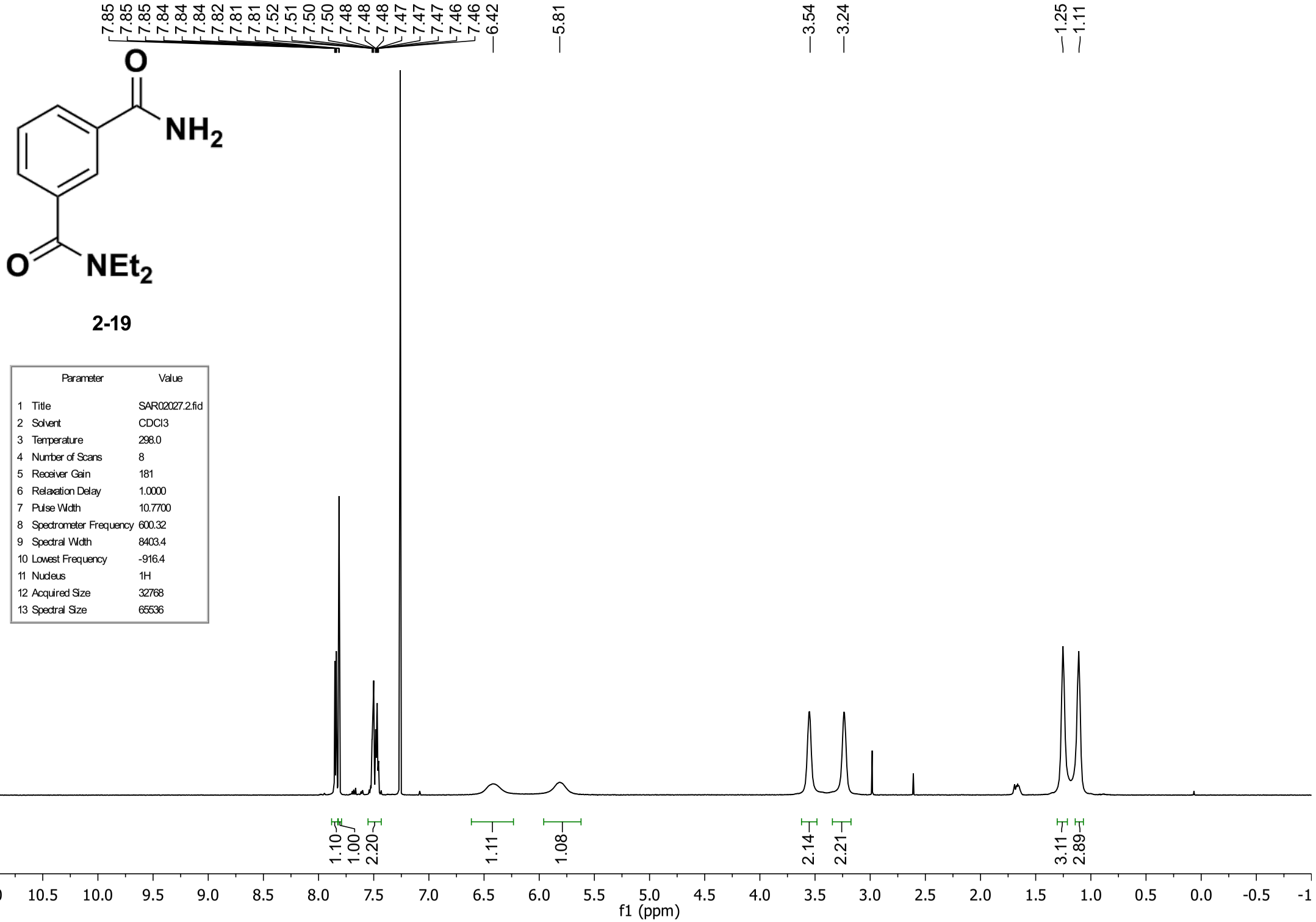
2-14

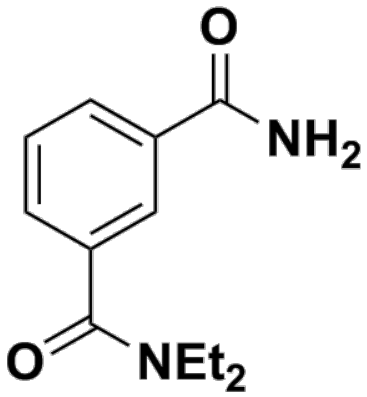
	Parameter	Value
1	Title	SAR02011.20.fid
2	Solvent	CDCl3
3	Temperature	298.1
4	Number of Scans	8
5	Receiver Gain	161
6	Relaxation Delay	1.0000
7	Pulse Width	10.7700
8	Spectrometer Frequency	600.32
9	Spectral Width	8403.4
10	Lowest Frequency	-916.4
11	Nucleus	1H
12	Acquired Size	32768
13	Spectral Size	65536



2-14

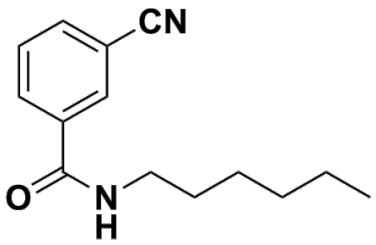
	Parameter	Value
1	Title	SAR02011.2.fid
2	Solvent	CDCl3
3	Temperature	298.1
4	Number of Scans	2048
5	Receiver Gain	2050
6	Relaxation Delay	1.1000
7	Pulse Width	10.6300
8	Spectrometer Frequency	150.97
9	Spectral Width	34722.2
10	Lowest Frequency	-2245.4
11	Nucleus	13C
12	Acquired Size	32768
13	Spectral Size	65536


7.85
7.85
7.85
7.84
7.84
7.84
7.82
7.81
7.81
7.52
7.51
7.50
7.50
7.48
7.48
7.48
7.47
7.47
7.47
7.46
7.46
6.42
5.81
3.54
3.24
1.25
1.11
O
NH2
O
NEt2
2-19
Parameter Value
1 Title SAR02027.2.fid
2 Solvent CDCl3
3 Temperature 298.0
4 Number of Scans 8
5 Receiver Gain 181
6 Relaxation Delay 1.0000
7 Pulse Width 10.7700
8 Spectrometer Frequency 600.32
9 Spectral Width 8403.4
10 Lowest Frequency -916.4
11 Nucleus 1H
12 Acquired Size 32768
13 Spectral Size 65536
1.10
1.00
2.20
1.11
1.08
2.14
2.21
3.11
2.89
f1 (ppm)



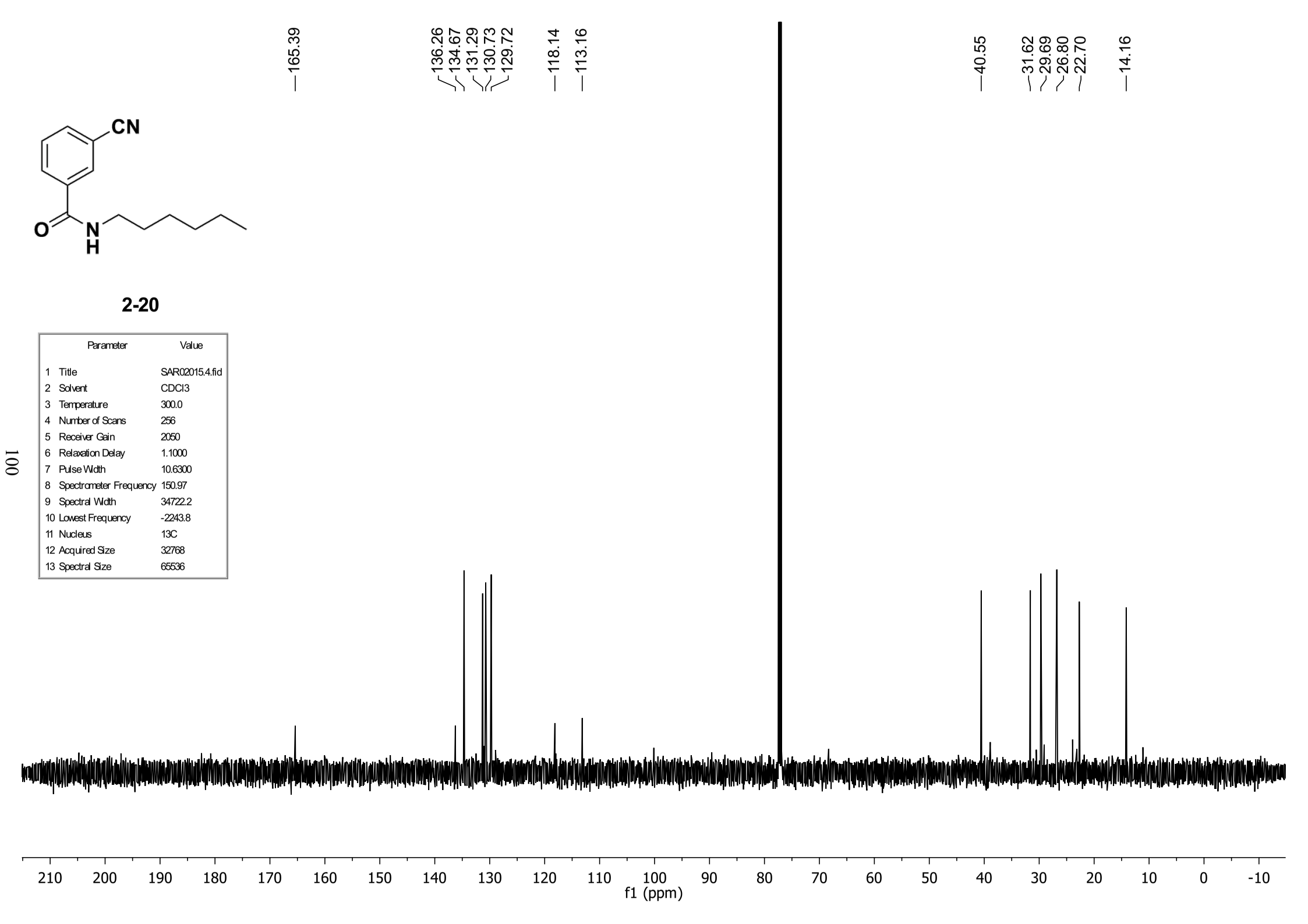
2-19

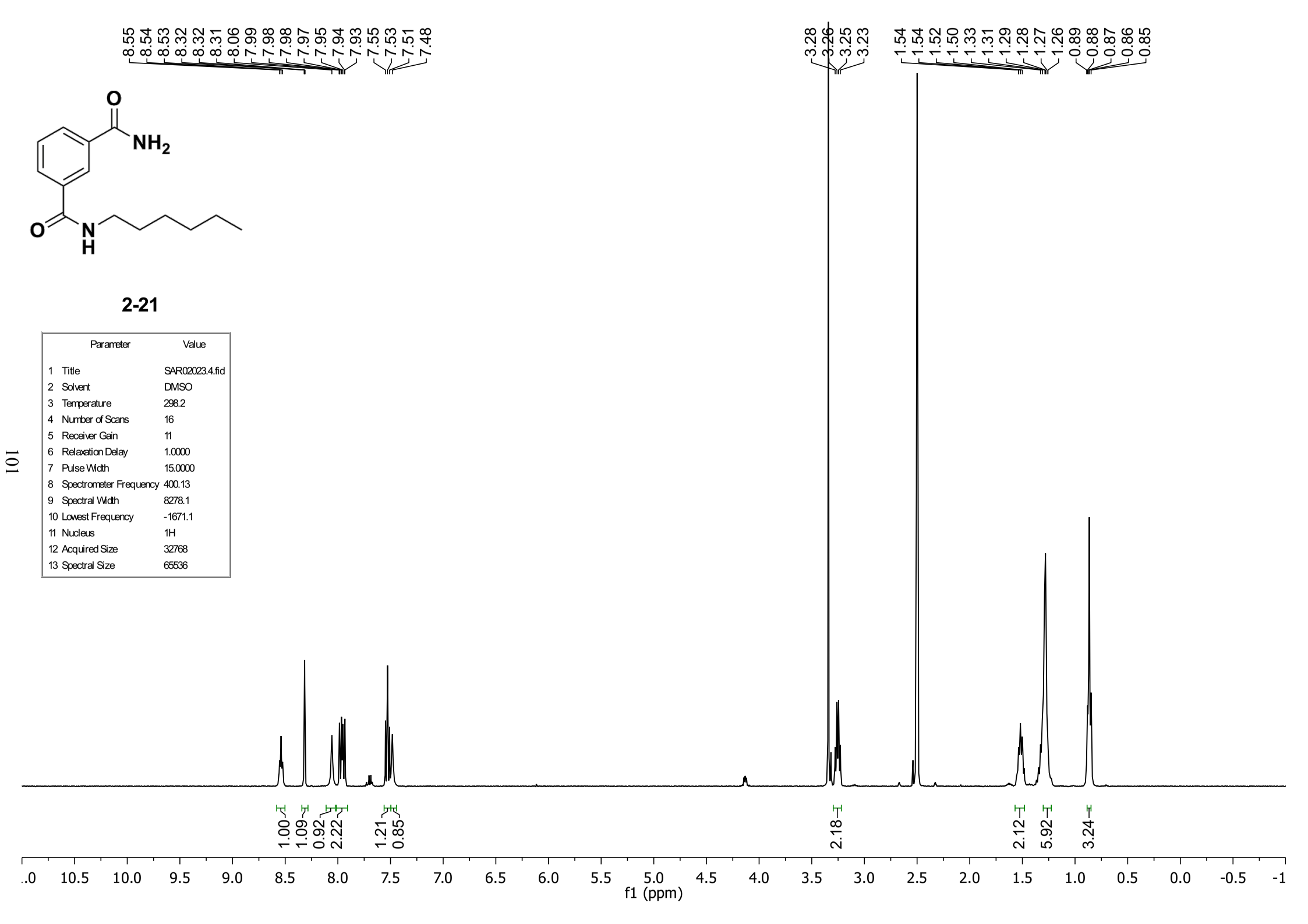
	Parameter	Value
1	Title	SAR02027.3.fid
2	Solvent	CDCl3
3	Temperature	298.0
4	Number of Scans	2048
5	Receiver Gain	2050
6	Relaxation Delay	1.1000
7	Pulse Width	10.6300
8	Spectrometer Frequency	150.97
9	Spectral Width	34722.2
10	Lowest Frequency	-2246.8
11	Nucleus	13C
12	Acquired Size	32768
13	Spectral Size	65536

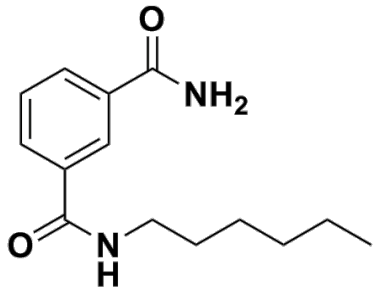


2-20

	Parameter	Value
1	Title	SAR02015.10.fid
2	Solvent	CDCl3
3	Temperature	295.8
4	Number of Scans	16
5	Receiver Gain	256
6	Relaxation Delay	1.0000
7	Pulse Width	11.0000
8	Spectrometer Frequency	400.13
9	Spectral Width	8278.1
10	Lowest Frequency	-1677.5
11	Nucleus	1H
12	Acquired Size	32768
13	Spectral Size	65536

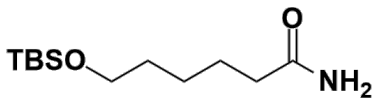

165.39
136.26
134.67
131.29
130.73
129.72
118.14
113.16
40.55
31.62
29.69
26.80
22.70
14.16
CN
O
N
H
2-20
Parameter Value
1 Title SAR02015.4.fid
2 Solvent CDCl3
3 Temperature 300.0
4 Number of Scans 256
5 Receiver Gain 2050
6 Relaxation Delay 1.1000
7 Pulse Width 10.6300
8 Spectrometer Frequency 150.97
9 Spectral Width 34722.2
10 Lowest Frequency -2243.8
11 Nucleus 13C
12 Acquired Size 32768
13 Spectral Size 65536
100
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


8.55
8.54
8.53
8.32
8.32
8.31
8.06
7.99
7.98
7.98
7.97
7.95
7.94
7.93
7.55
7.53
7.51
7.48
3.28
3.26
3.25
3.23
1.54
1.54
1.52
1.50
1.33
1.31
1.29
1.28
1.27
1.26
0.89
0.88
0.87
0.86
0.85
O
NH2
O
N
H
2-21
Parameter Value
1 Title SAR02023.4.fid
2 Solvent DMSO
3 Temperature 298.2
4 Number of Scans 16
5 Receiver Gain 11
6 Relaxation Delay 1.0000
7 Pulse Width 15.0000
8 Spectrometer Frequency 400.13
9 Spectral Width 8278.1
10 Lowest Frequency -1671.1
11 Nucleus 1H
12 Acquired Size 32768
13 Spectral Size 65536
101
1.00
1.09
0.92
2.22
1.21
0.85
2.18
2.12
5.92
3.24
f1 (ppm)



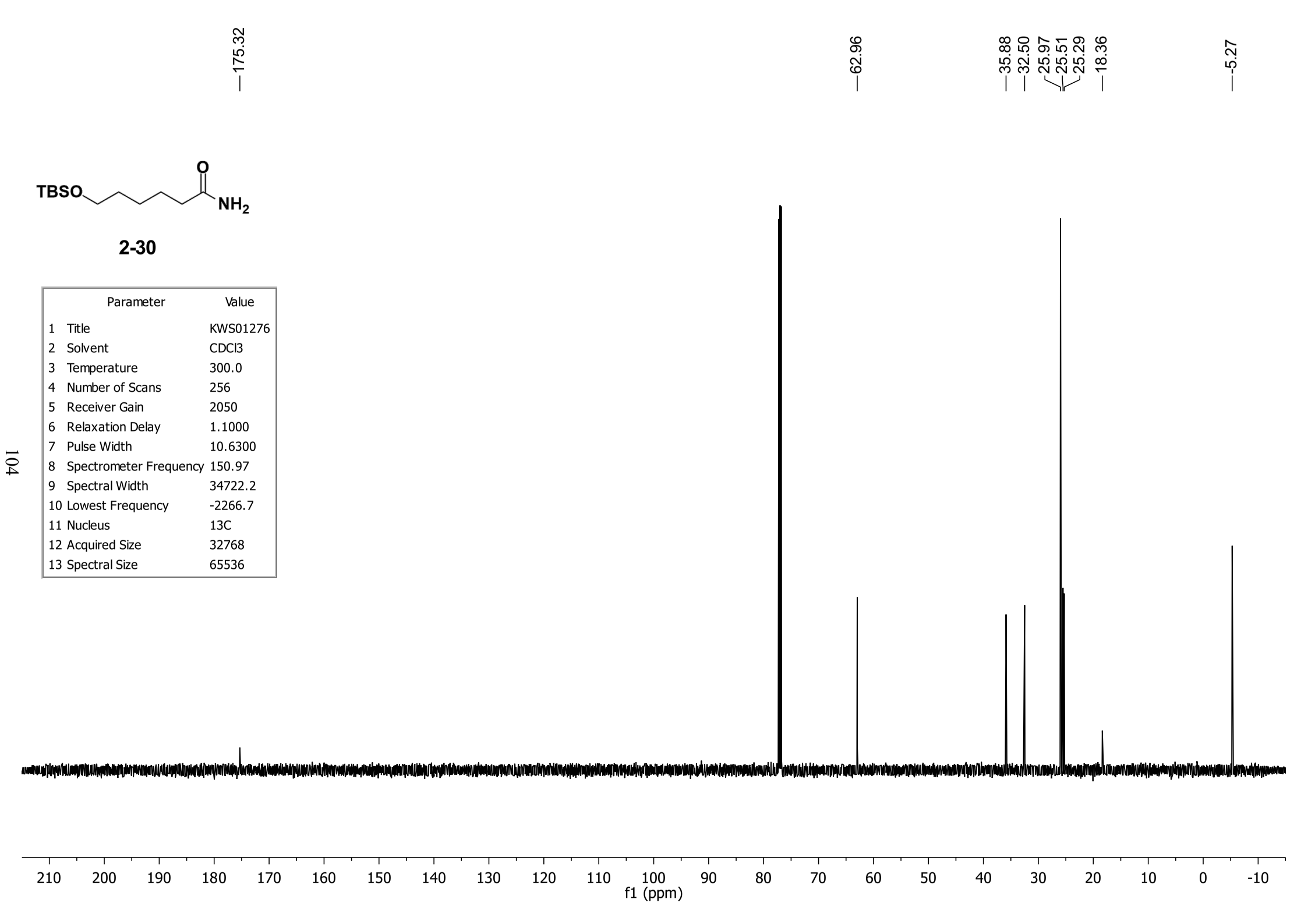
2-21

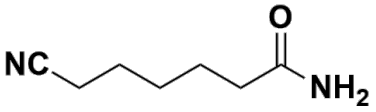
	Parameter	Value
1	Title	SAR02023.5.fid
2	Solvent	DMSO
3	Temperature	298.1
4	Number of Scans	1024
5	Receiver Gain	512
6	Relaxation Delay	2.0000
7	Pulse Width	9.2500
8	Spectrometer Frequency	100.62
9	Spectral Width	23980.8
10	Lowest Frequency	-1973.6
11	Nucleus	13C
12	Acquired Size	32768
13	Spectral Size	65536



2-30

	Parameter	Value
1	Title	KWS01276
2	Solvent	CDCl3
3	Temperature	300.0
4	Number of Scans	8
5	Receiver Gain	144
6	Relaxation Delay	1.0000
7	Pulse Width	10.7700
8	Spectrometer Frequency	600.32
9	Spectral Width	8403.4
10	Lowest Frequency	-915.8
11	Nucleus	1H
12	Acquired Size	32768
13	Spectral Size	65536

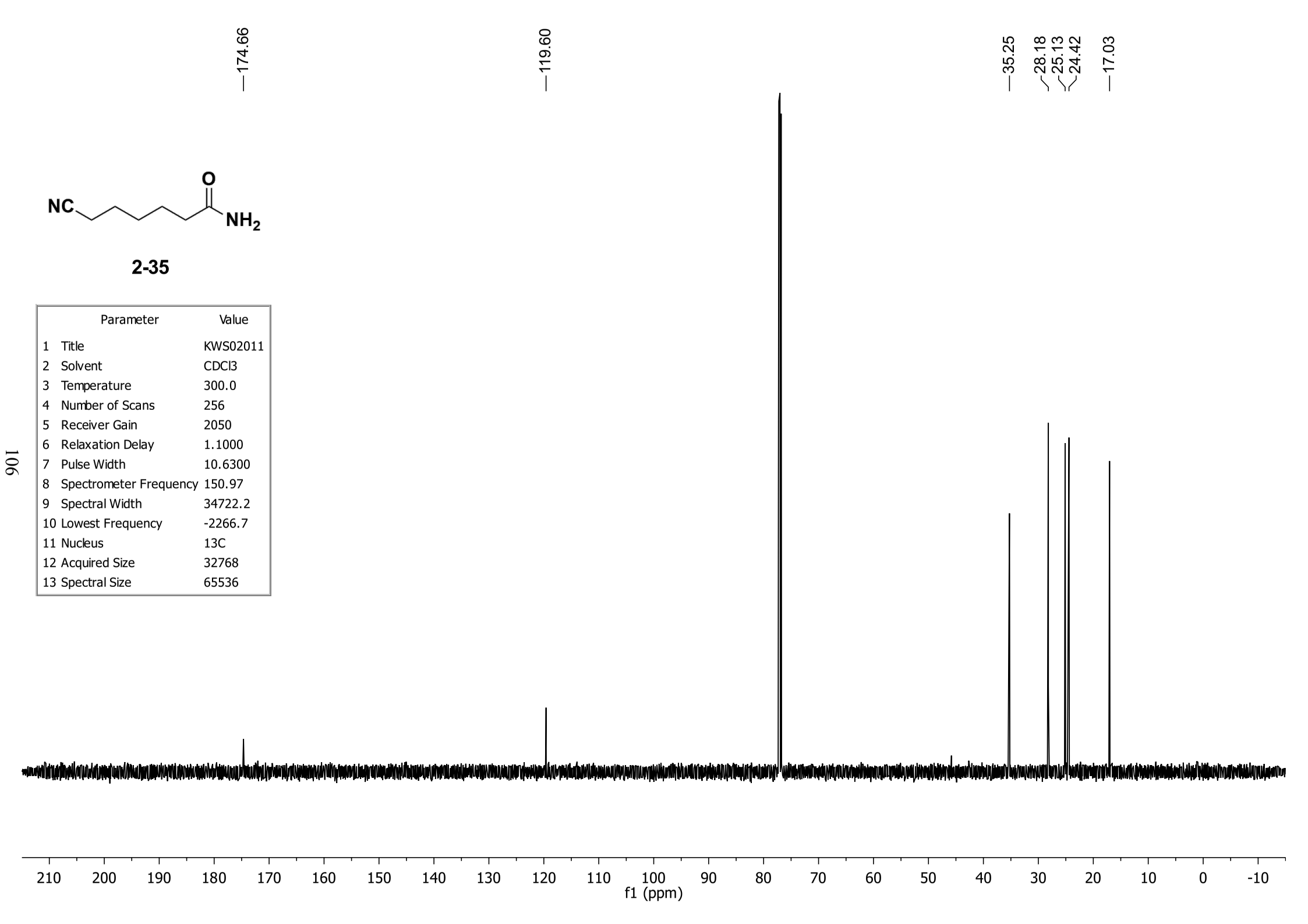

175.32
62.96
35.88
32.50
25.97
25.51
25.29
18.36
-5.27
TBSO
O
NH2
2-30
Parameter Value
1 Title KWS01276
2 Solvent CDCl3
3 Temperature 300.0
4 Number of Scans 256
5 Receiver Gain 2050
6 Relaxation Delay 1.1000
7 Pulse Width 10.6300
8 Spectrometer Frequency 150.97
9 Spectral Width 34722.2
10 Lowest Frequency -2266.7
11 Nucleus 13C
12 Acquired Size 32768
13 Spectral Size 65536
104
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

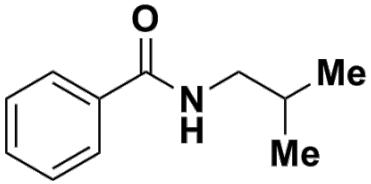


2-35

	Parameter	Value
1	Title	KWS02011
2	Solvent	CDCl3
3	Temperature	300.0
4	Number of Scans	8
5	Receiver Gain	228
6	Relaxation Delay	1.0000
7	Pulse Width	10.7700
8	Spectrometer Frequency	600.32
9	Spectral Width	8403.4
10	Lowest Frequency	-915.8
11	Nucleus	1H
12	Acquired Size	32768
13	Spectral Size	65536

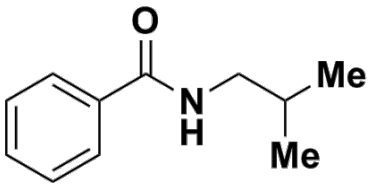
105


174.66
119.60
35.25
28.18
25.13
24.42
17.03
NC
O
NH2
2-35
Parameter Value
1 Title KWS02011
2 Solvent CDCl3
3 Temperature 300.0
4 Number of Scans 256
5 Receiver Gain 2050
6 Relaxation Delay 1.1000
7 Pulse Width 10.6300
8 Spectrometer Frequency 150.97
9 Spectral Width 34722.2
10 Lowest Frequency -2266.7
11 Nucleus 13C
12 Acquired Size 32768
13 Spectral Size 65536
106
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



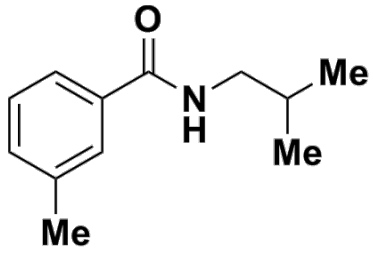
2-36

	Parameter	Value
1	Title	KWS01071.1.fid
2	Solvent	CDCl3
3	Temperature	298.2
4	Number of Scans	16
5	Receiver Gain	13
6	Relaxation Delay	1.0000
7	Pulse Width	15.0000
8	Spectrometer Frequency	400.13
9	Spectral Width	8278.1
10	Lowest Frequency	-1677.9
11	Nucleus	1H
12	Acquired Size	32768
13	Spectral Size	65536



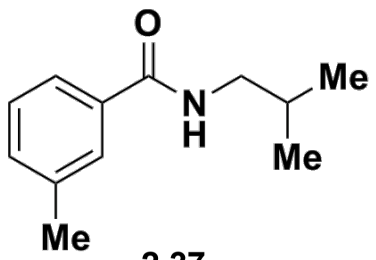
2-36

	Parameter	Value
1	Title	KWS01071C13.1.fid
2	Solvent	CDCl3
3	Temperature	298.0
4	Number of Scans	256
5	Receiver Gain	2050
6	Relaxation Delay	1.1000
7	Pulse Width	10.6300
8	Spectrometer Frequency	150.97
9	Spectral Width	34722.2
10	Lowest Frequency	-2266.7
11	Nucleus	13C
12	Acquired Size	32768
13	Spectral Size	65536



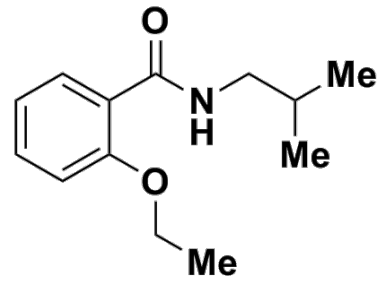
2-37

	Parameter	Value
1	Title	SAR01092.1.fid
2	Solvent	CDCl3
3	Temperature	298.1
4	Number of Scans	16
5	Receiver Gain	14
6	Relaxation Delay	1.0000
7	Pulse Width	15.0000
8	Spectrometer Frequency	400.13
9	Spectral Width	8278.1
10	Lowest Frequency	-1677.0
11	Nucleus	1H
12	Acquired Size	32768
13	Spectral Size	65536



2-37

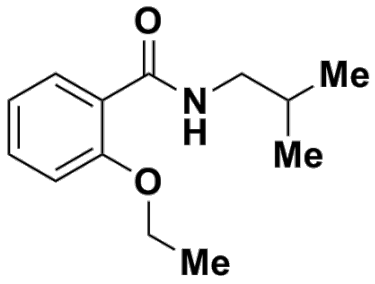
	Parameter	Value
1	Title	SAR01092.2.fid
2	Solvent	CDCl3
3	Temperature	298.2
4	Number of Scans	256
5	Receiver Gain	512
6	Relaxation Delay	2.0000
7	Pulse Width	9.2500
8	Spectrometer Frequency	100.62
9	Spectral Width	23980.8
10	Lowest Frequency	-1917.3
11	Nucleus	13C
12	Acquired Size	32768
13	Spectral Size	65536



2-38

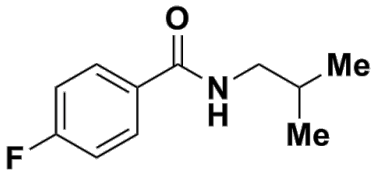
	Parameter	Value
1	Title	KWS01076H.1.fid
2	Solvent	CDCl3
3	Temperature	298.2
4	Number of Scans	16
5	Receiver Gain	14
6	Relaxation Delay	1.0000
7	Pulse Width	15.0000
8	Spectrometer Frequency	400.13
9	Spectral Width	8278.1
10	Lowest Frequency	-1678.2
11	Nucleus	1H
12	Acquired Size	32768
13	Spectral Size	65536

111



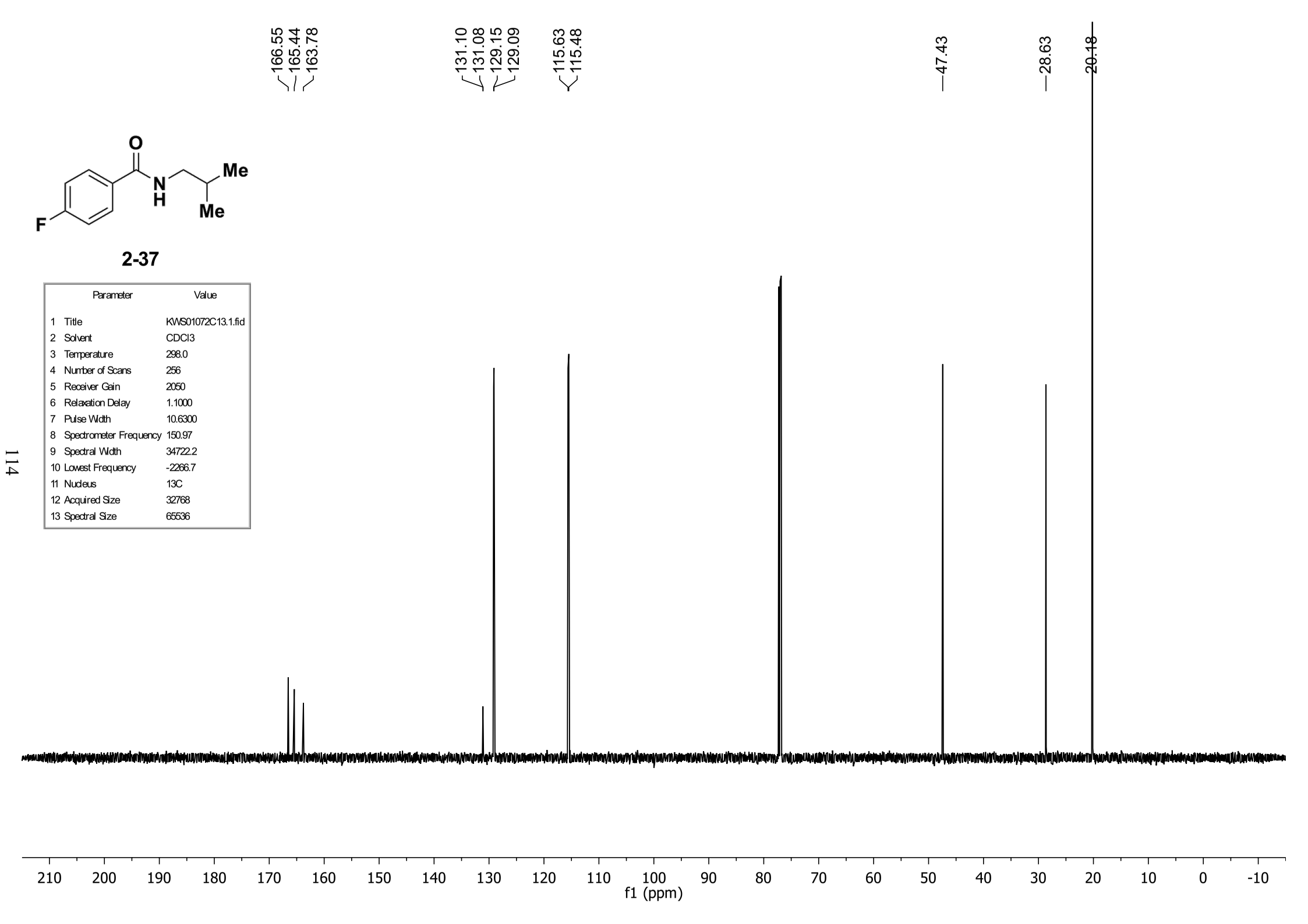
2-38

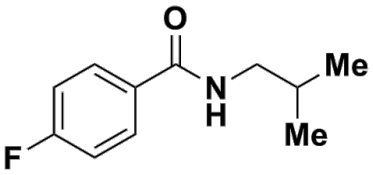
	Parameter	Value
1	Title	KWS01076C13.1.fid
2	Solvent	CDCl3
3	Temperature	298.2
4	Number of Scans	256
5	Receiver Gain	512
6	Relaxation Delay	2.0000
7	Pulse Width	9.2500
8	Spectrometer Frequency	100.62
9	Spectral Width	23980.8
10	Lowest Frequency	-1929.6
11	Nucleus	13C
12	Acquired Size	32768
13	Spectral Size	65536



2-37

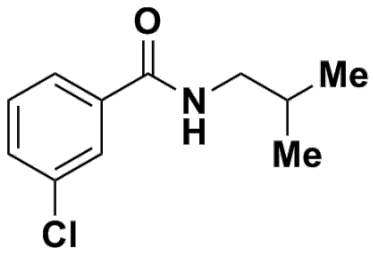
	Parameter	Value
1	Title	KWS01072.1.fid
2	Solvent	CDCl3
3	Temperature	298.2
4	Number of Scans	16
5	Receiver Gain	13
6	Relaxation Delay	1.0000
7	Pulse Width	15.0000
8	Spectrometer Frequency	400.13
9	Spectral Width	8278.1
10	Lowest Frequency	-1677.8
11	Nucleus	1H
12	Acquired Size	32768
13	Spectral Size	65536


166.55
165.44
163.78
131.10
131.08
129.15
129.09
115.63
115.48
47.43
28.63
20.18
O
N
H
Me
Me
F
2-37
Parameter Value
1 Title KWS01072C13.1.fid
2 Solvent CDCl3
3 Temperature 298.0
4 Number of Scans 256
5 Receiver Gain 2050
6 Relaxation Delay 1.1000
7 Pulse Width 10.6300
8 Spectrometer Frequency 150.97
9 Spectral Width 34722.2
10 Lowest Frequency -2266.7
11 Nucleus 13C
12 Acquired Size 32768
13 Spectral Size 65536
114
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



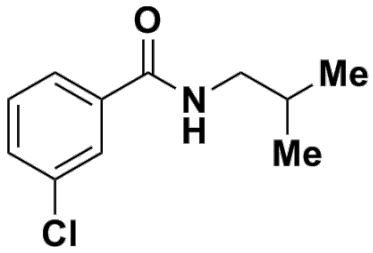
2-37

	Parameter	Value
1	Title	KWS01072.3.fid
2	Solvent	CDCl3
3	Temperature	298.1
4	Number of Scans	16
5	Receiver Gain	1626
6	Relaxation Delay	2.0000
7	Pulse Width	15.0300
8	Spectrometer Frequency	376.46
9	Spectral Width	75188.0
10	Lowest Frequency	-75243.6
11	Nucleus	19F
12	Acquired Size	65536
13	Spectral Size	131072



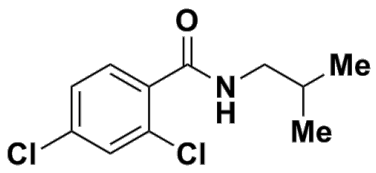
2-40

	Parameter	Value
1	Title	KWS01129H.1
2	Solvent	CDCl3
3	Temperature	298.1
4	Number of Scans	16
5	Receiver Gain	6
6	Relaxation Delay	1.0000
7	Pulse Width	15.0000
8	Spectrometer Frequency	400.13
9	Spectral Width	8278.1
10	Lowest Frequency	-1678.5
11	Nucleus	1H
12	Acquired Size	32768
13	Spectral Size	65536



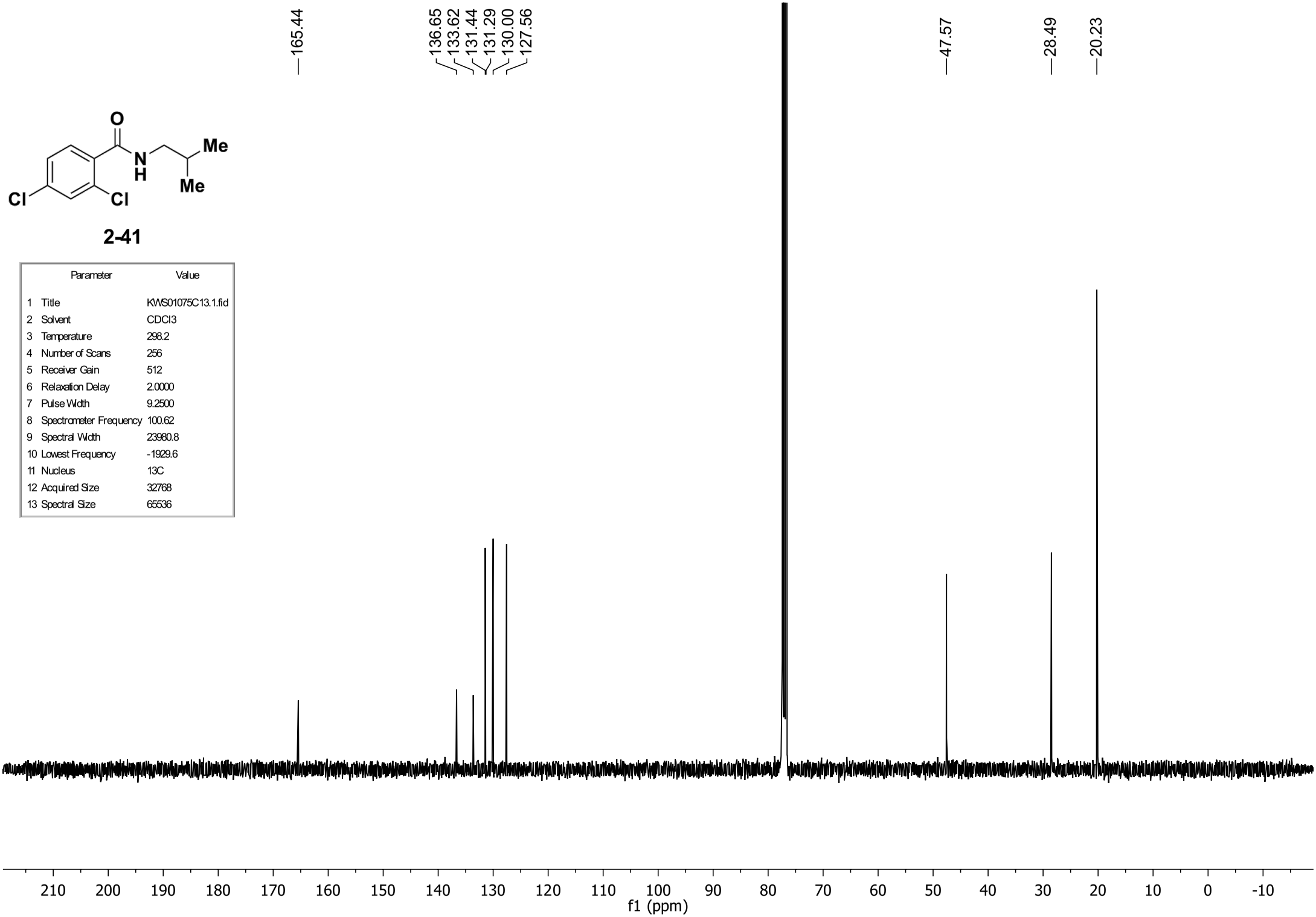
2-40

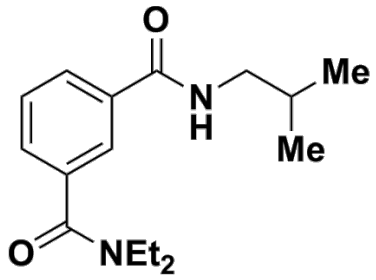
	Parameter	Value
1	Title	KWS01129C13.
2	Solvent	CDCl3
3	Temperature	298.2
4	Number of Scans	256
5	Receiver Gain	512
6	Relaxation Delay	2.0000
7	Pulse Width	9.2500
8	Spectrometer Frequency	100.62
9	Spectral Width	23980.8
10	Lowest Frequency	-1929.6
11	Nucleus	13C
12	Acquired Size	32768
13	Spectral Size	65536



2-41

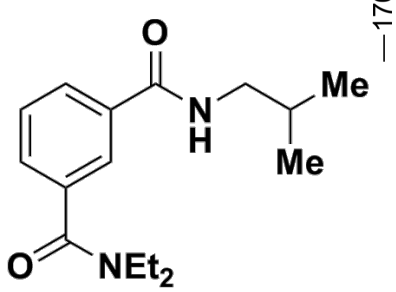
	Parameter	Value
1	Title	KWS01075H.1.fid
2	Solvent	CDCl3
3	Temperature	298.2
4	Number of Scans	16
5	Receiver Gain	11
6	Relaxation Delay	1.0000
7	Pulse Width	15.0000
8	Spectrometer Frequency	400.13
9	Spectral Width	8278.1
10	Lowest Frequency	-1677.9
11	Nucleus	1H
12	Acquired Size	32768
13	Spectral Size	65536


165.44
136.65
133.62
131.44
131.29
130.00
127.56
47.57
28.49
20.23
O
N
H
Me
Me
Cl
Cl
2-41
Parameter Value
1 Title KWS01075C13.1.fid
2 Solvent CDCl3
3 Temperature 298.2
4 Number of Scans 256
5 Receiver Gain 512
6 Relaxation Delay 2.0000
7 Pulse Width 9.2500
8 Spectrometer Frequency 100.62
9 Spectral Width 23980.8
10 Lowest Frequency -1929.6
11 Nucleus 13C
12 Acquired Size 32768
13 Spectral Size 65536
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



2-43

	Parameter	Value
1	Title	SAR02039
2	Solvent	CDCl3
3	Temperature	298.2
4	Number of Scans	16
5	Receiver Gain	4
6	Relaxation Delay	1.0000
7	Pulse Width	15.0000
8	Spectrometer Frequency	400.13
9	Spectral Width	8278.1
10	Lowest Frequency	-1678.4
11	Nucleus	1H
12	Acquired Size	32768
13	Spectral Size	65536

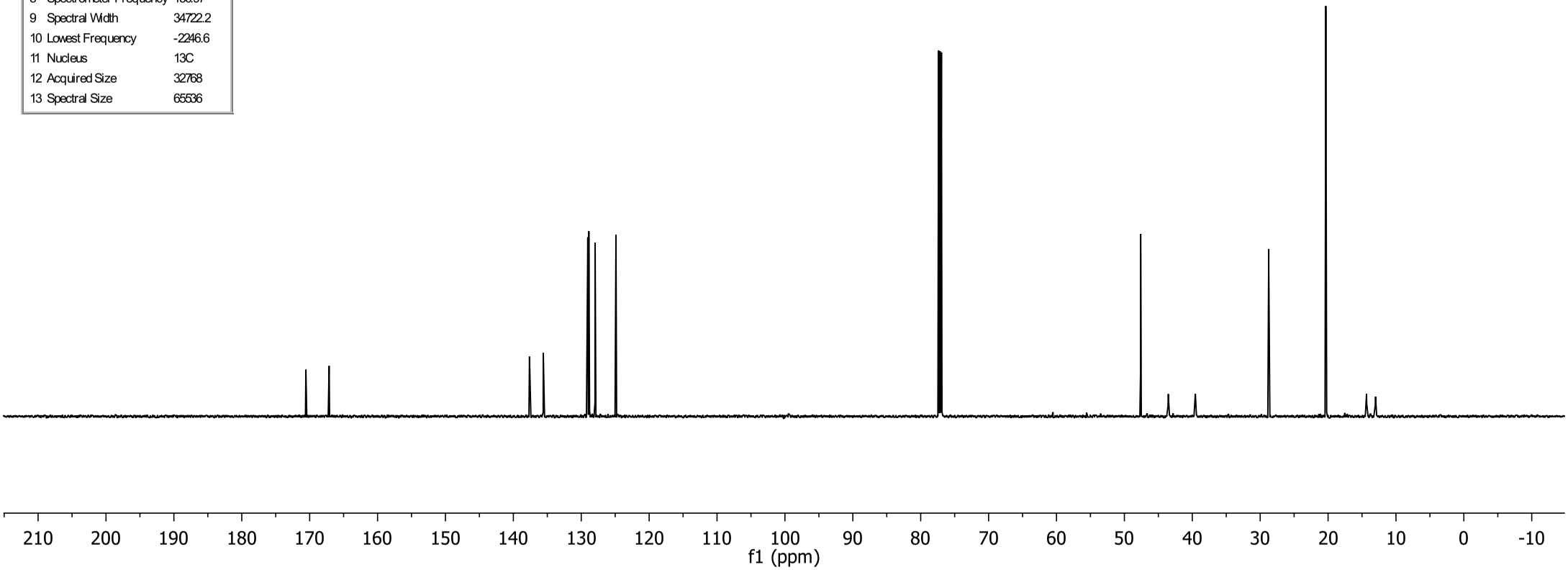


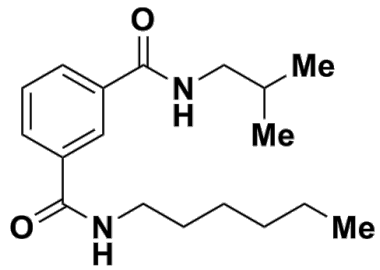
170.56
167.14
137.62
135.59
129.03
128.88
127.96
124.89
47.60
43.53
39.55
28.74
20.33
14.35
13.01

2-43

	Parameter	Value
1	Title	SAR02039
2	Solvent	CDCl3
3	Temperature	300.0
4	Number of Scans	2048
5	Receiver Gain	2050
6	Relaxation Delay	1.1000
7	Pulse Width	10.6300
8	Spectrometer Frequency	150.97
9	Spectral Width	34722.2
10	Lowest Frequency	-2246.6
11	Nucleus	13C
12	Acquired Size	32768
13	Spectral Size	65536

121

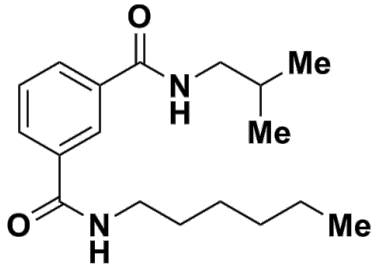




2-44

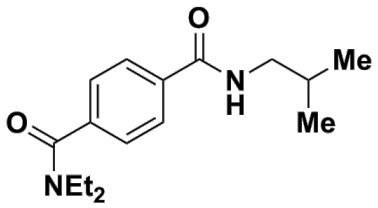
	Parameter	Value
1	Title	SAR02036
2	Solvent	CDCl3
3	Temperature	298.0
4	Number of Scans	8
5	Receiver Gain	203
6	Relaxation Delay	1.0000
7	Pulse Width	10.7700
8	Spectrometer Frequency	600.32
9	Spectral Width	8403.4
10	Lowest Frequency	-916.6
11	Nucleus	1H
12	Acquired Size	32768
13	Spectral Size	65536

122



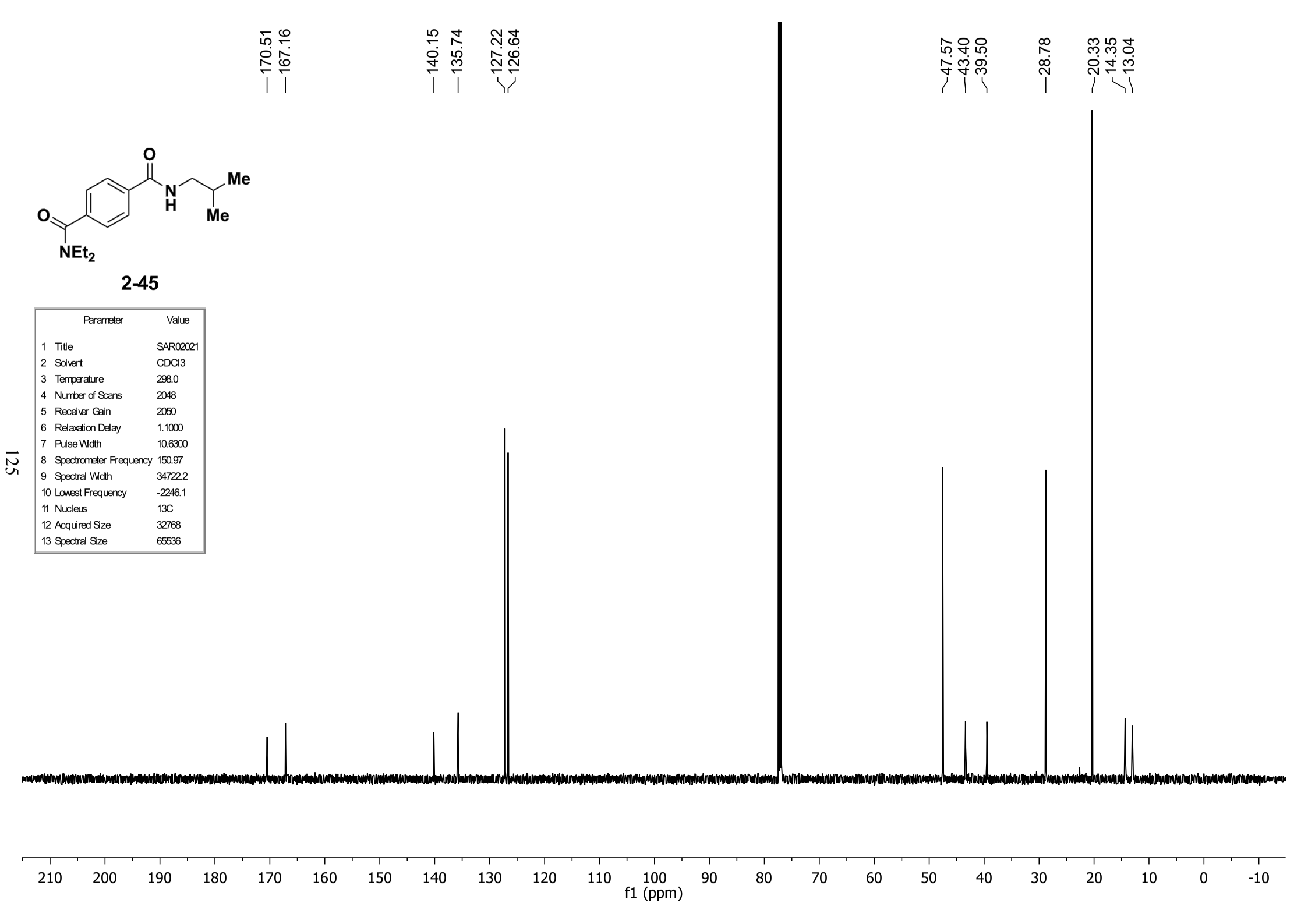
2-44

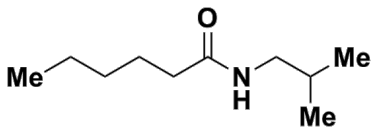
	Parameter	Value
1	Title	SAR02036
2	Solvent	CDCl3
3	Temperature	298.0
4	Number of Scans	2048
5	Receiver Gain	2050
6	Relaxation Delay	1.1000
7	Pulse Width	10.6300
8	Spectrometer Frequency	150.97
9	Spectral Width	34722.2
10	Lowest Frequency	-2245.2
11	Nucleus	13C
12	Acquired Size	32768
13	Spectral Size	65536



2-45

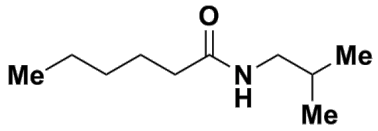
	Parameter	Value
1	Title	SAR02021
2	Solvent	CDCl3
3	Temperature	298.0
4	Number of Scans	8
5	Receiver Gain	161
6	Relaxation Delay	1.0000
7	Pulse Width	10.7700
8	Spectrometer Frequency	600.32
9	Spectral Width	8403.4
10	Lowest Frequency	-916.4
11	Nucleus	1H
12	Acquired Size	32768
13	Spectral Size	65536


170.51
167.16
140.15
135.74
127.22
126.64
47.57
43.40
39.50
28.78
20.33
14.35
13.04
O
N
H
Me
Me
O
NEt2
2-45
Parameter Value
1 Title SAR02021
2 Solvent CDCl3
3 Temperature 298.0
4 Number of Scans 2048
5 Receiver Gain 2050
6 Relaxation Delay 1.1000
7 Pulse Width 10.6300
8 Spectrometer Frequency 150.97
9 Spectral Width 34722.2
10 Lowest Frequency -2246.1
11 Nucleus 13C
12 Acquired Size 32768
13 Spectral Size 65536
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



2-51

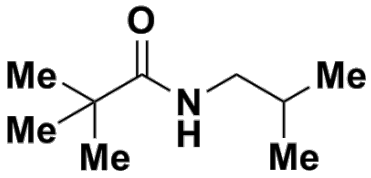
	Parameter	Value
1	Title	SAR01088.1.fid
2	Solvent	CDCl3
3	Temperature	298.2
4	Number of Scans	16
5	Receiver Gain	13
6	Relaxation Delay	1.0000
7	Pulse Width	15.0000
8	Spectrometer Frequency	400.13
9	Spectral Width	8278.1
10	Lowest Frequency	-1677.2
11	Nucleus	1H
12	Acquired Size	32768
13	Spectral Size	65536



2-51

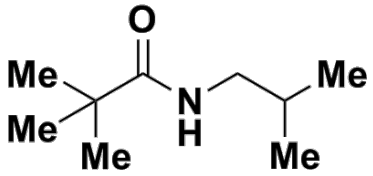
	Parameter	Value
1	Title	SAR01088.2.fid
2	Solvent	CDCl3
3	Temperature	298.2
4	Number of Scans	256
5	Receiver Gain	512
6	Relaxation Delay	2.0000
7	Pulse Width	9.2500
8	Spectrometer Frequency	100.62
9	Spectral Width	23980.8
10	Lowest Frequency	-1917.3
11	Nucleus	13C
12	Acquired Size	32768
13	Spectral Size	65536

127



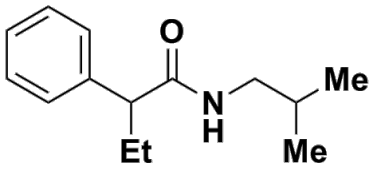
2-52

	Parameter	Value
1	Title	SAR01079.1.fid
2	Solvent	CDCl3
3	Temperature	298.2
4	Number of Scans	16
5	Receiver Gain	13
6	Relaxation Delay	1.0000
7	Pulse Width	15.0000
8	Spectrometer Frequency	400.13
9	Spectral Width	8278.1
10	Lowest Frequency	-1678.1
11	Nucleus	1H
12	Acquired Size	32768
13	Spectral Size	65536



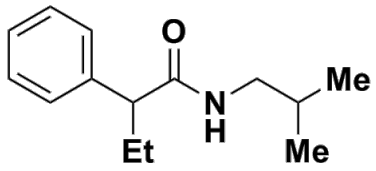
2-52

	Parameter	Value
1	Title	SAR01079.2.fid
2	Solvent	CDCl3
3	Temperature	298.2
4	Number of Scans	256
5	Receiver Gain	512
6	Relaxation Delay	2.0000
7	Pulse Width	9.2500
8	Spectrometer Frequency	100.62
9	Spectral Width	23980.8
10	Lowest Frequency	-1917.0
11	Nucleus	13C
12	Acquired Size	32768
13	Spectral Size	65536



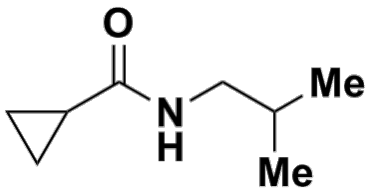
2-53

	Parameter	Value
1	Title	SAR01086.3.fid
2	Solvent	CDCl3
3	Temperature	298.2
4	Number of Scans	16
5	Receiver Gain	13
6	Relaxation Delay	1.0000
7	Pulse Width	15.0000
8	Spectrometer Frequency	400.13
9	Spectral Width	8278.1
10	Lowest Frequency	-1677.4
11	Nucleus	1H
12	Acquired Size	32768
13	Spectral Size	65536



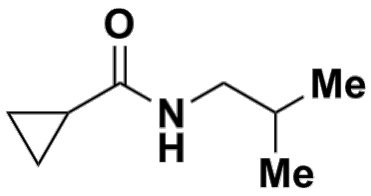
2-53

	Parameter	Value
1	Title	SAR01086.4.fid
2	Solvent	CDCl3
3	Temperature	298.1
4	Number of Scans	256
5	Receiver Gain	512
6	Relaxation Delay	2.0000
7	Pulse Width	9.2500
8	Spectrometer Frequency	100.62
9	Spectral Width	23980.8
10	Lowest Frequency	-1916.3
11	Nucleus	13C
12	Acquired Size	32768
13	Spectral Size	65536



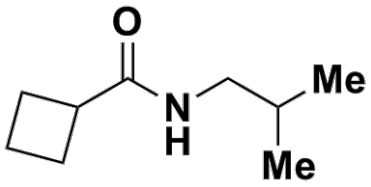
2-54

	Parameter	Value
1	Title	SAR01089.3.fid
2	Solvent	CDCl3
3	Temperature	298.2
4	Number of Scans	16
5	Receiver Gain	20
6	Relaxation Delay	1.0000
7	Pulse Width	15.0000
8	Spectrometer Frequency	400.13
9	Spectral Width	8278.1
10	Lowest Frequency	-1677.0
11	Nucleus	1H
12	Acquired Size	32768
13	Spectral Size	65536



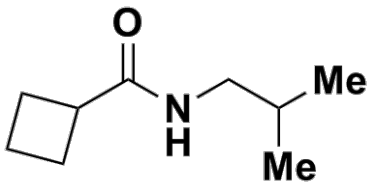
2-54

	Parameter	Value
1	Title	SAR01089.4.fid
2	Solvent	CDCl3
3	Temperature	298.2
4	Number of Scans	256
5	Receiver Gain	512
6	Relaxation Delay	2.0000
7	Pulse Width	9.2500
8	Spectrometer Frequency	100.62
9	Spectral Width	23980.8
10	Lowest Frequency	-1916.6
11	Nucleus	13C
12	Acquired Size	32768
13	Spectral Size	65536



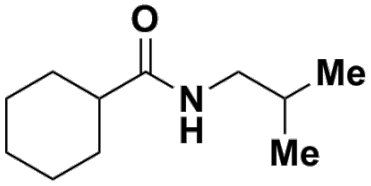
2-55

	Parameter	Value
1	Title	KWS01083
2	Solvent	CDCl3
3	Temperature	298.1
4	Number of Scans	8
5	Receiver Gain	256
6	Relaxation Delay	1.0000
7	Pulse Width	14.8000
8	Spectrometer Frequency	600.32
9	Spectral Width	8403.4
10	Lowest Frequency	-915.7
11	Nucleus	1H
12	Acquired Size	32768
13	Spectral Size	65536



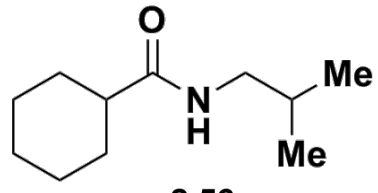
2-55

	Parameter	Value
1	Title	KWS01083
2	Solvent	CDCl3
3	Temperature	298.1
4	Number of Scans	256
5	Receiver Gain	2050
6	Relaxation Delay	1.1000
7	Pulse Width	9.0000
8	Spectrometer Frequency	150.97
9	Spectral Width	34722.2
10	Lowest Frequency	-2245.7
11	Nucleus	13C
12	Acquired Size	32768
13	Spectral Size	65536



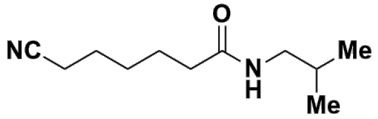
2-56

	Parameter	Value
1	Title	SAR01121.3.fid
2	Solvent	CDCl3
3	Temperature	300.0
4	Number of Scans	16
5	Receiver Gain	64
6	Relaxation Delay	10.0000
7	Pulse Width	10.7700
8	Spectrometer Frequency	600.32
9	Spectral Width	12335.5
10	Lowest Frequency	-2477.0
11	Nucleus	1H
12	Acquired Size	32768
13	Spectral Size	65536



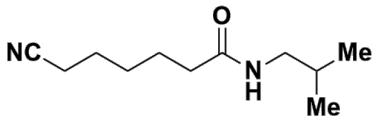
2-56

	Parameter	Value
1	Title	SAR01121.5.fid
2	Solvent	CDCl3
3	Temperature	298.1
4	Number of Scans	256
5	Receiver Gain	512
6	Relaxation Delay	2.0000
7	Pulse Width	9.2500
8	Spectrometer Frequency	100.62
9	Spectral Width	23980.8
10	Lowest Frequency	-1917.1
11	Nucleus	13C
12	Acquired Size	32768
13	Spectral Size	65536



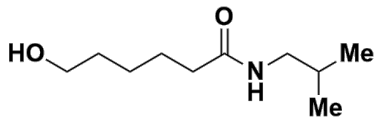
2-57

	Parameter	Value
1	Title	SAR02075
2	Solvent	CDCl3
3	Temperature	300.0
4	Number of Scans	16
5	Receiver Gain	64
6	Relaxation Delay	10.0000
7	Pulse Width	10.7700
8	Spectrometer Frequency	600.32
9	Spectral Width	12335.5
10	Lowest Frequency	-2476.3
11	Nucleus	1H
12	Acquired Size	32768
13	Spectral Size	65536



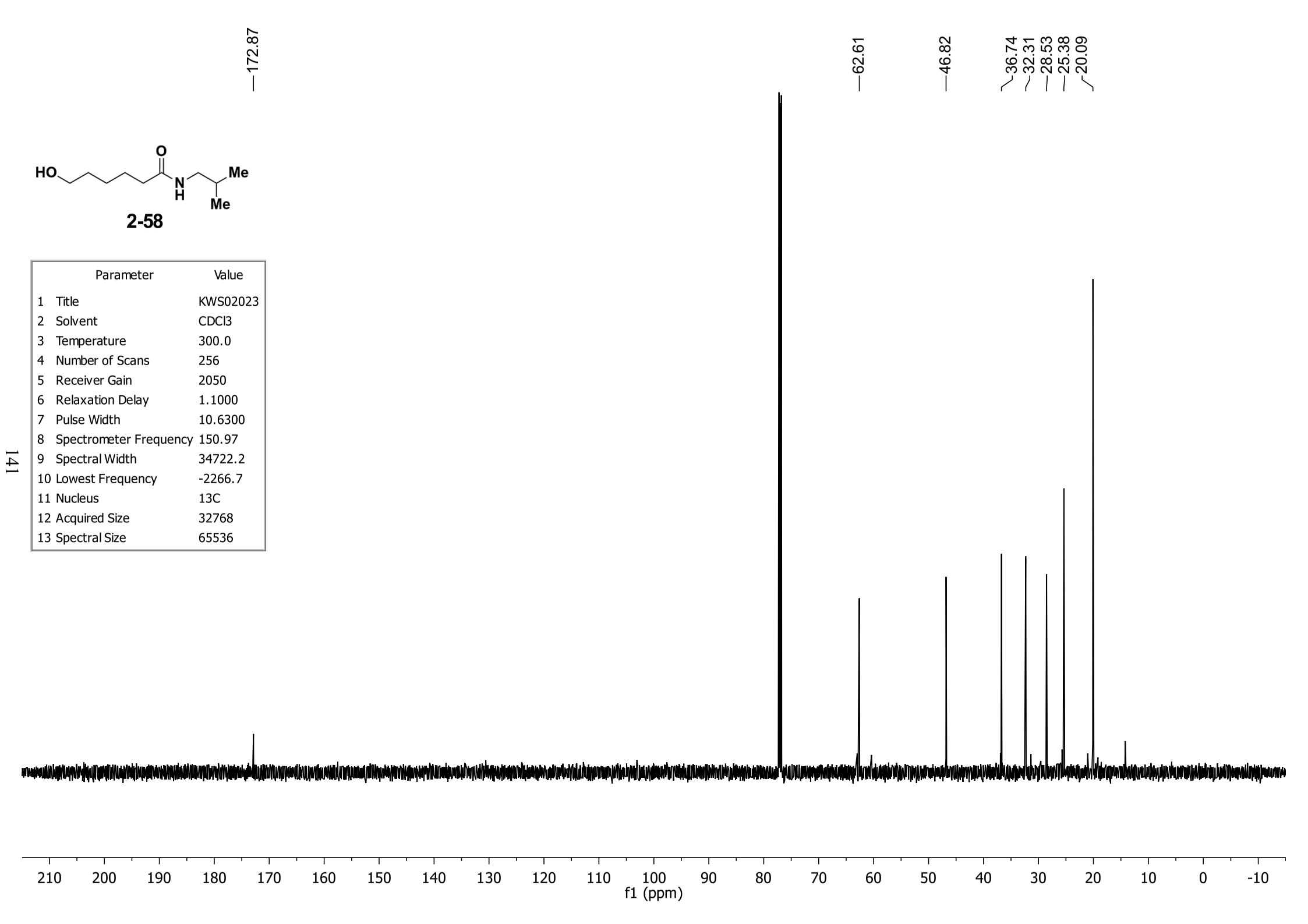
2-57

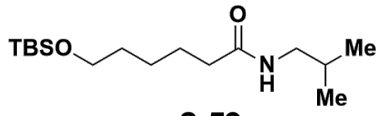
	Parameter	Value
1	Title	SAR02075
2	Solvent	CDCl3
3	Temperature	300.0
4	Number of Scans	2048
5	Receiver Gain	2050
6	Relaxation Delay	1.1000
7	Pulse Width	10.6300
8	Spectrometer Frequency	150.97
9	Spectral Width	34722.2
10	Lowest Frequency	-2244.5
11	Nucleus	13C
12	Acquired Size	32768
13	Spectral Size	65536



2-58

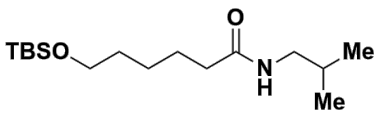
	Parameter	Value
1	Title	KWS02023
2	Solvent	CDCl3
3	Temperature	300.0
4	Number of Scans	64
5	Receiver Gain	256
6	Relaxation Delay	1.0000
7	Pulse Width	10.7700
8	Spectrometer Frequency	600.32
9	Spectral Width	8403.4
10	Lowest Frequency	-915.3
11	Nucleus	1H
12	Acquired Size	32768
13	Spectral Size	65536


172.87
62.61
46.82
36.74
32.31
28.53
25.38
20.09
HO
O
N
H
Me
Me
2-58
Parameter Value
1 Title KWS02023
2 Solvent CDCl3
3 Temperature 300.0
4 Number of Scans 256
5 Receiver Gain 2050
6 Relaxation Delay 1.1000
7 Pulse Width 10.6300
8 Spectrometer Frequency 150.97
9 Spectral Width 34722.2
10 Lowest Frequency -2266.7
11 Nucleus 13C
12 Acquired Size 32768
13 Spectral Size 65536
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



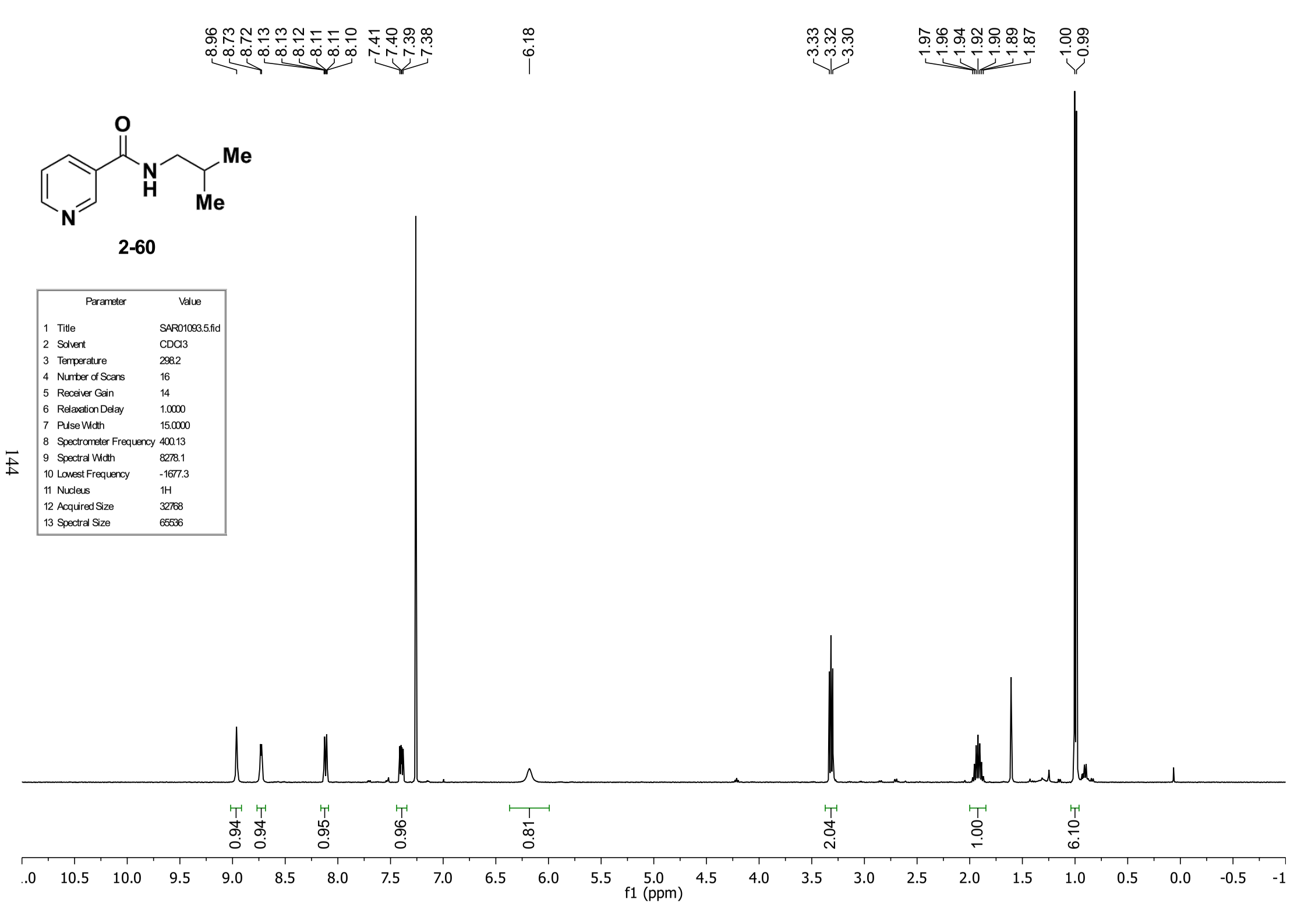
2-59

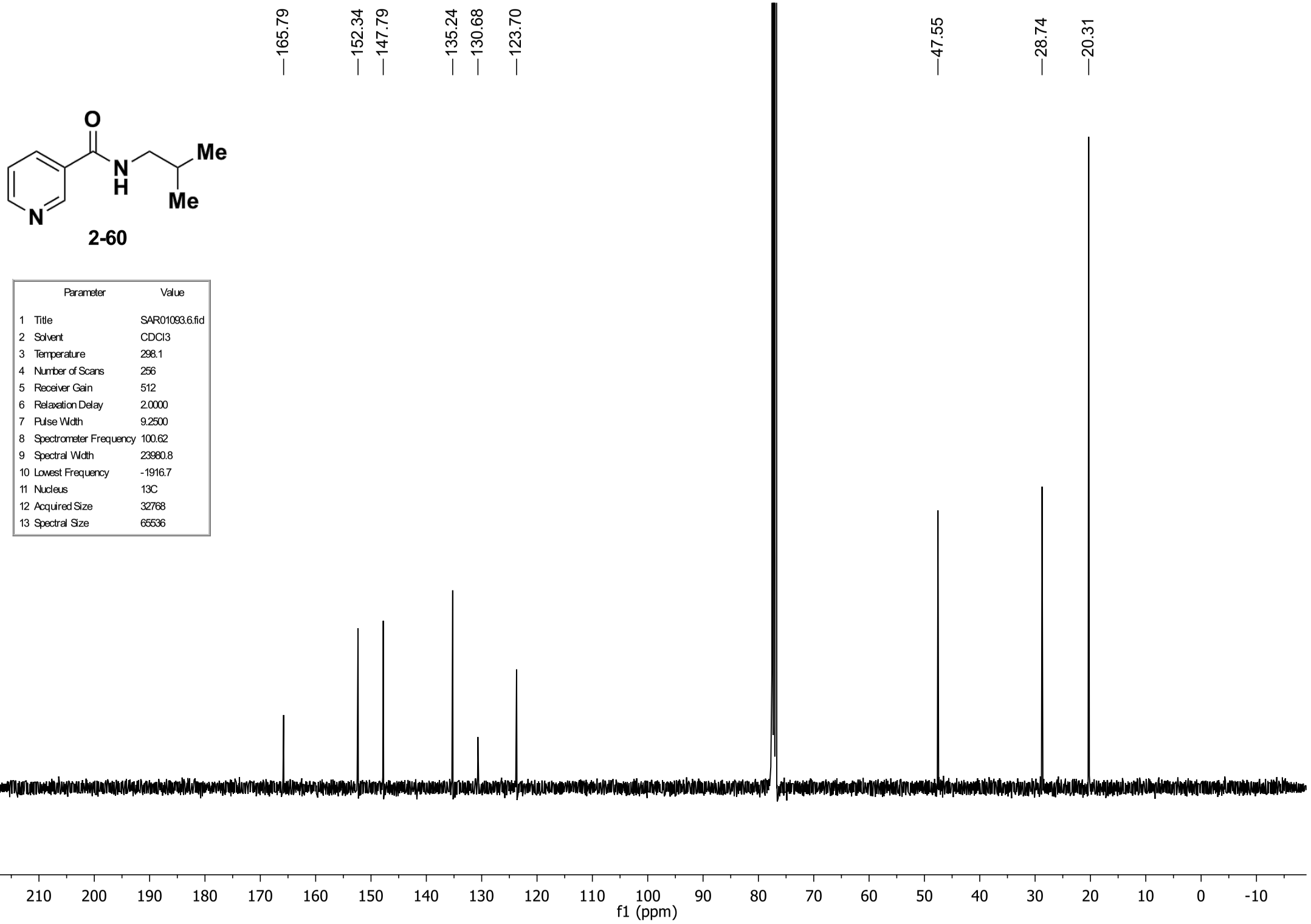
	Parameter	Value
1	Title	KWS02028
2	Solvent	CDCl3
3	Temperature	298.2
4	Number of Scans	16
5	Receiver Gain	4
6	Relaxation Delay	1.0000
7	Pulse Width	15.0000
8	Spectrometer Frequency	400.13
9	Spectral Width	8278.1
10	Lowest Frequency	-1677.8
11	Nucleus	1H
12	Acquired Size	32768
13	Spectral Size	65536

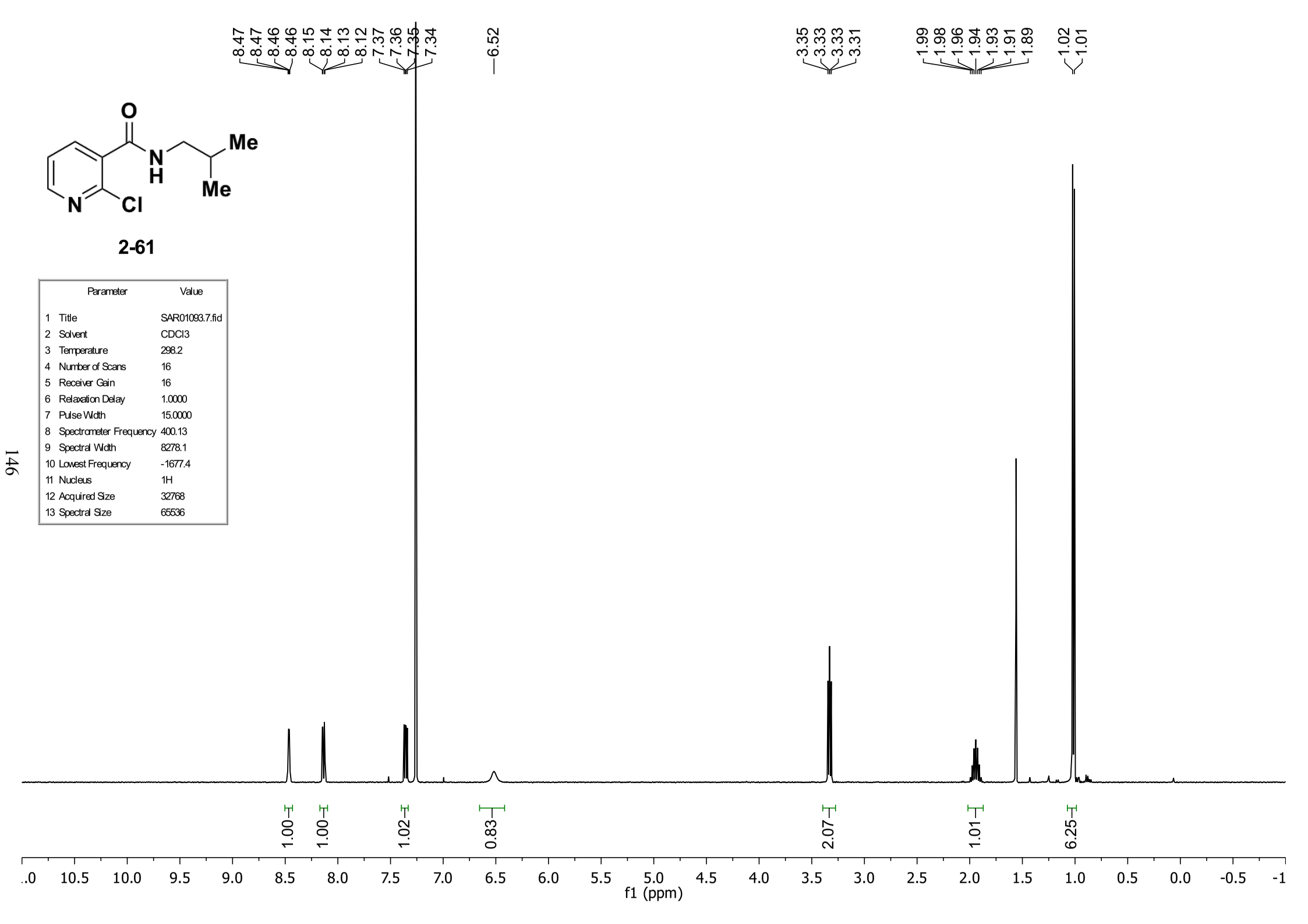


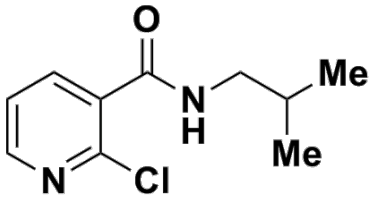
2-59

	Parameter	Value
1	Title	KWS02028
2	Solvent	CDCl3
3	Temperature	298.2
4	Number of Scans	1024
5	Receiver Gain	512
6	Relaxation Delay	2.0000
7	Pulse Width	9.2500
8	Spectrometer Frequency	100.62
9	Spectral Width	23980.8
10	Lowest Frequency	-1929.6
11	Nucleus	13C
12	Acquired Size	32768
13	Spectral Size	65536


8.96
8.73
8.72
8.13
8.13
8.12
8.11
8.11
8.10
7.41
7.40
7.39
7.38
6.18
3.33
3.32
3.30
1.97
1.96
1.94
1.92
1.90
1.89
1.87
1.00
0.99
O
N
H
Me
Me
N
2-60
Parameter Value
1 Title SAR01093.5.fid
2 Solvent CDCl3
3 Temperature 298.2
4 Number of Scans 16
5 Receiver Gain 14
6 Relaxation Delay 1.0000
7 Pulse Width 15.0000
8 Spectrometer Frequency 400.13
9 Spectral Width 8278.1
10 Lowest Frequency -1677.3
11 Nucleus 1H
12 Acquired Size 32768
13 Spectral Size 65536
0.94
0.94
0.95
0.96
0.81
2.04
1.00
6.10
f1 (ppm)

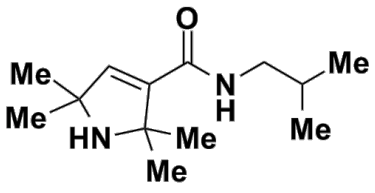

165.79
152.34
147.79
135.24
130.68
123.70
47.55
28.74
20.31
O
N
H
Me
Me
N
2-60
Parameter Value
1 Title SAR01093.6.fid
2 Solvent CDCl3
3 Temperature 298.1
4 Number of Scans 256
5 Receiver Gain 512
6 Relaxation Delay 2.0000
7 Pulse Width 9.2500
8 Spectrometer Frequency 100.62
9 Spectral Width 23980.8
10 Lowest Frequency -1916.7
11 Nucleus 13C
12 Acquired Size 32768
13 Spectral Size 65536
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


8.47
8.47
8.46
8.46
8.15
8.14
8.13
8.12
7.37
7.36
7.35
7.34
6.52
3.35
3.33
3.33
3.31
1.99
1.98
1.96
1.94
1.93
1.91
1.89
1.02
1.01
O
N
H
Me
Me
N
Cl
2-61
Parameter Value
1 Title SAR01093.7.fid
2 Solvent CDCl3
3 Temperature 298.2
4 Number of Scans 16
5 Receiver Gain 16
6 Relaxation Delay 1.0000
7 Pulse Width 15.0000
8 Spectrometer Frequency 400.13
9 Spectral Width 8278.1
10 Lowest Frequency -1677.4
11 Nucleus 1H
12 Acquired Size 32768
13 Spectral Size 65536
1.00
1.00
1.02
0.83
2.07
1.01
6.25
f1 (ppm)



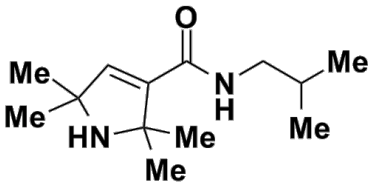
2-61

	Parameter	Value
1	Title	SAR01093.8.fid
2	Solvent	CDCl3
3	Temperature	298.2
4	Number of Scans	256
5	Receiver Gain	512
6	Relaxation Delay	2.0000
7	Pulse Width	9.2500
8	Spectrometer Frequency	100.62
9	Spectral Width	23980.8
10	Lowest Frequency	-1916.4
11	Nucleus	13C
12	Acquired Size	32768
13	Spectral Size	65536



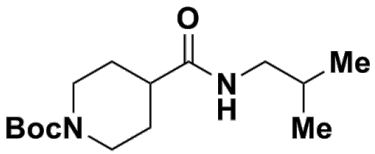
2-63

	Parameter	Value
1	Title	SAR01087.2.fid
2	Solvent	CDCl3
3	Temperature	298.1
4	Number of Scans	16
5	Receiver Gain	13
6	Relaxation Delay	1.0000
7	Pulse Width	15.0000
8	Spectrometer Frequency	400.13
9	Spectral Width	8278.1
10	Lowest Frequency	-1677.2
11	Nucleus	1H
12	Acquired Size	32768
13	Spectral Size	65536



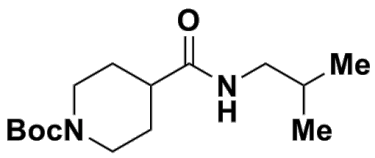
2-63

	Parameter	Value
1	Title	SAR01087.3.fid
2	Solvent	CDCl3
3	Temperature	298.2
4	Number of Scans	256
5	Receiver Gain	512
6	Relaxation Delay	2.0000
7	Pulse Width	9.2500
8	Spectrometer Frequency	100.62
9	Spectral Width	23980.8
10	Lowest Frequency	-1916.7
11	Nucleus	13C
12	Acquired Size	32768
13	Spectral Size	65536



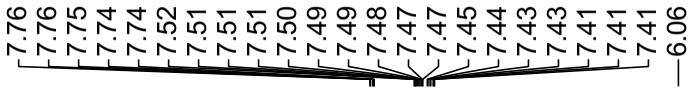
2-64

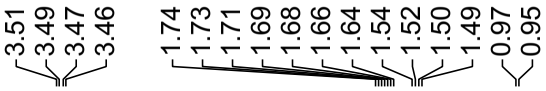
	Parameter	Value
1	Title	SAR01135.1.fid
2	Solvent	CDCl3
3	Temperature	300.0
4	Number of Scans	8
5	Receiver Gain	161
6	Relaxation Delay	1.0000
7	Pulse Width	10.7700
8	Spectrometer Frequency	600.32
9	Spectral Width	8403.4
10	Lowest Frequency	-915.9
11	Nucleus	1H
12	Acquired Size	32768
13	Spectral Size	65536

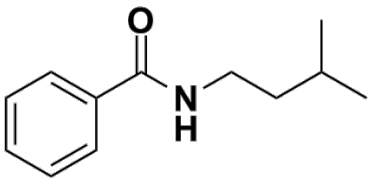


2-64

	Parameter	Value
1	Title	SAR01135.10.fid
2	Solvent	CDCl3
3	Temperature	298.1
4	Number of Scans	1024
5	Receiver Gain	512
6	Relaxation Delay	2.0000
7	Pulse Width	9.2500
8	Spectrometer Frequency	100.62
9	Spectral Width	23980.8
10	Lowest Frequency	-1917.3
11	Nucleus	13C
12	Acquired Size	32768
13	Spectral Size	65536

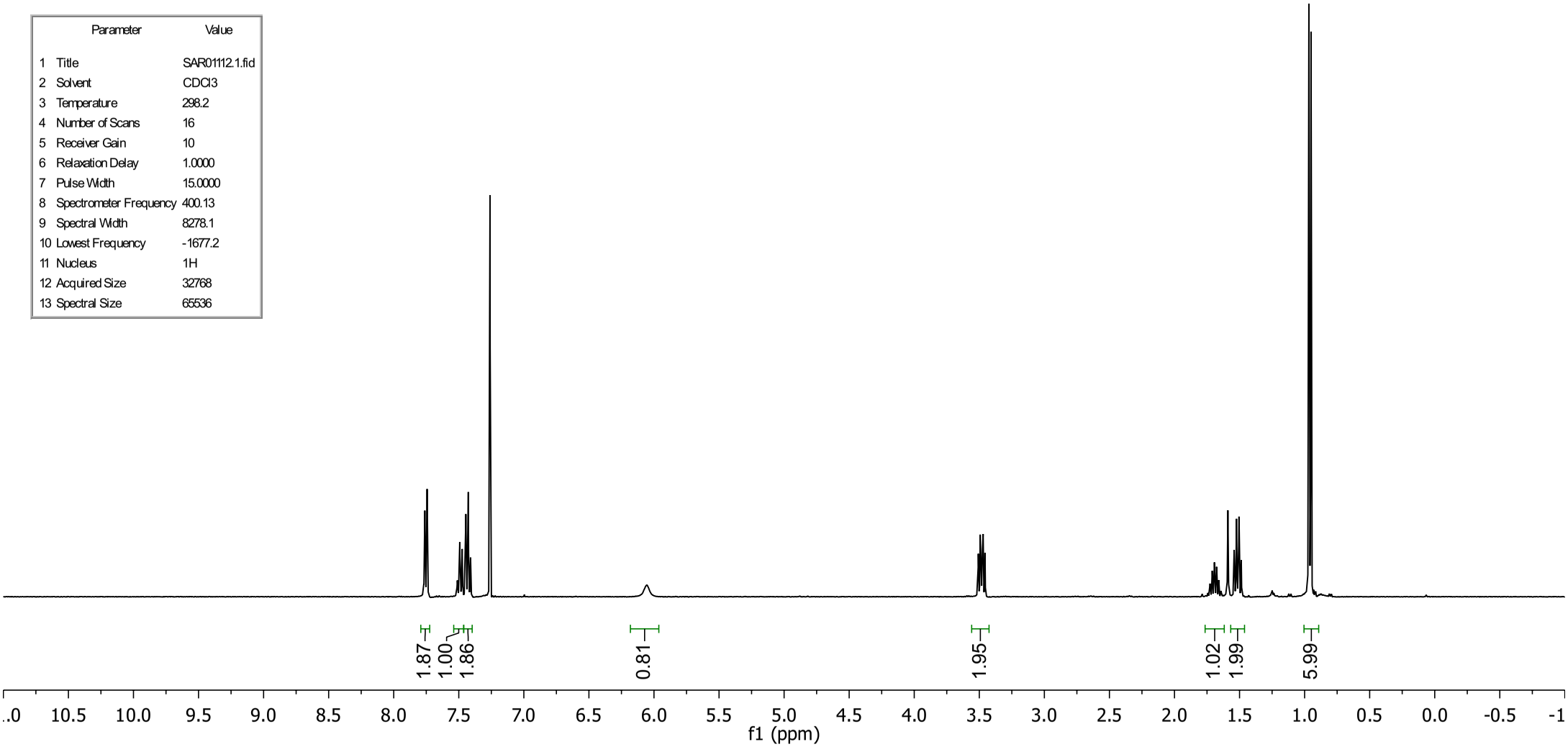


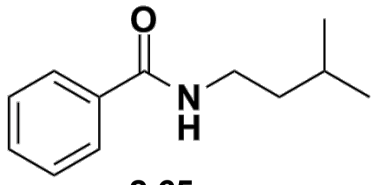




2-65

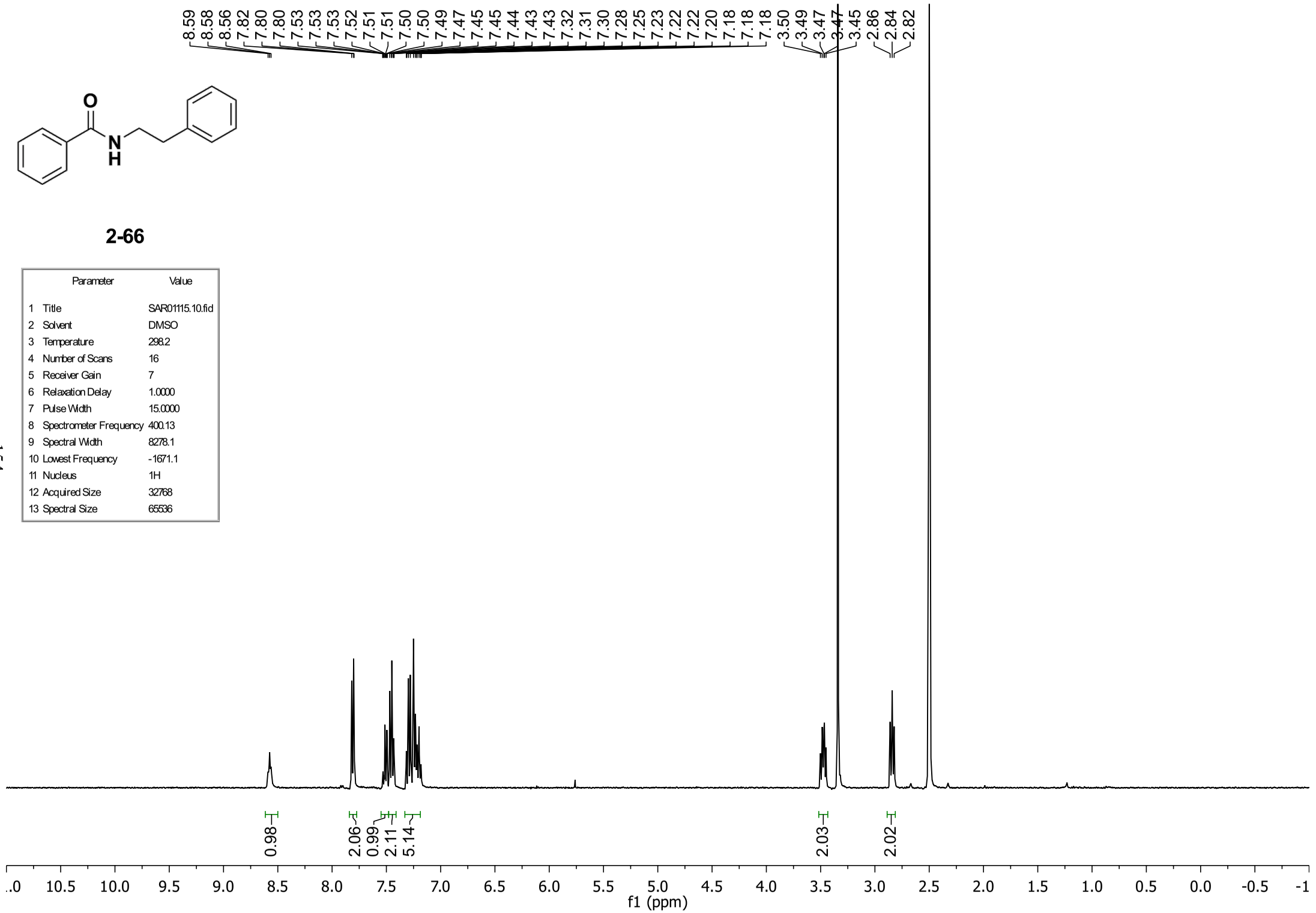
	Parameter	Value
1	Title	SAR01112.1.fid
2	Solvent	CDCl3
3	Temperature	298.2
4	Number of Scans	16
5	Receiver Gain	10
6	Relaxation Delay	1.0000
7	Pulse Width	15.0000
8	Spectrometer Frequency	400.13
9	Spectral Width	8278.1
10	Lowest Frequency	-1677.2
11	Nucleus	1H
12	Acquired Size	32768
13	Spectral Size	65536

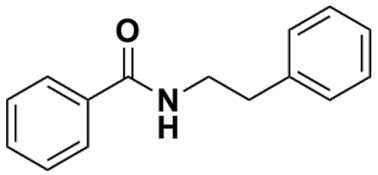




2-65

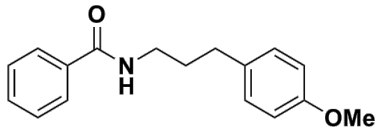
	Parameter	Value
1	Title	SAR01112.2.fid
2	Solvent	CDCl3
3	Temperature	298.2
4	Number of Scans	256
5	Receiver Gain	512
6	Relaxation Delay	2.0000
7	Pulse Width	9.2500
8	Spectrometer Frequency	100.62
9	Spectral Width	23980.8
10	Lowest Frequency	-1917.1
11	Nucleus	13C
12	Acquired Size	32768
13	Spectral Size	65536


8.59
8.58
8.56
7.82
7.80
7.80
7.53
7.53
7.53
7.52
7.51
7.51
7.50
7.50
7.49
7.47
7.45
7.45
7.44
7.43
7.43
7.32
7.31
7.30
7.28
7.25
7.23
7.22
7.22
7.20
7.18
7.18
3.50
3.49
3.47
3.47
3.45
2.86
2.84
2.82
O
N
H
2-66
Parameter Value
1 Title SAR01115.10.fid
2 Solvent DMSO
3 Temperature 298.2
4 Number of Scans 16
5 Receiver Gain 7
6 Relaxation Delay 1.0000
7 Pulse Width 15.0000
8 Spectrometer Frequency 400.13
9 Spectral Width 8278.1
10 Lowest Frequency -1671.1
11 Nucleus 1H
12 Acquired Size 32768
13 Spectral Size 65536
0.98
2.06
0.99
2.11
5.14
2.03
2.02
f1 (ppm)



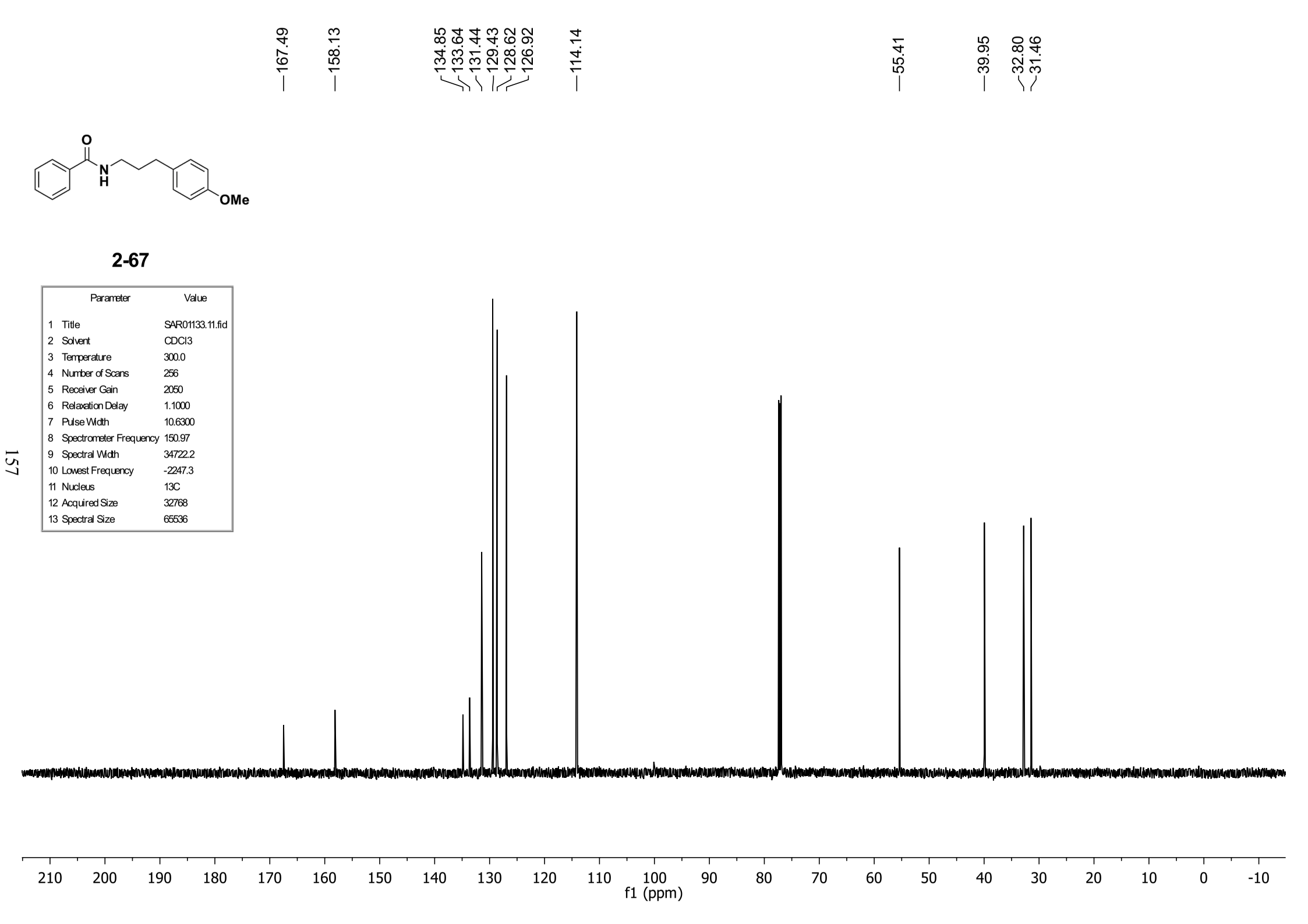
2-66

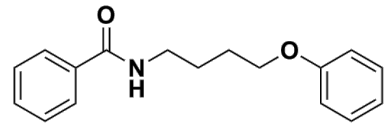
	Parameter	Value
1	Title	SAR01115.11.fid
2	Solvent	DMSO
3	Temperature	298.1
4	Number of Scans	1024
5	Receiver Gain	512
6	Relaxation Delay	2.0000
7	Pulse Width	9.2500
8	Spectrometer Frequency	100.62
9	Spectral Width	23980.8
10	Lowest Frequency	-1972.6
11	Nucleus	13C
12	Acquired Size	32768
13	Spectral Size	65536



2-67

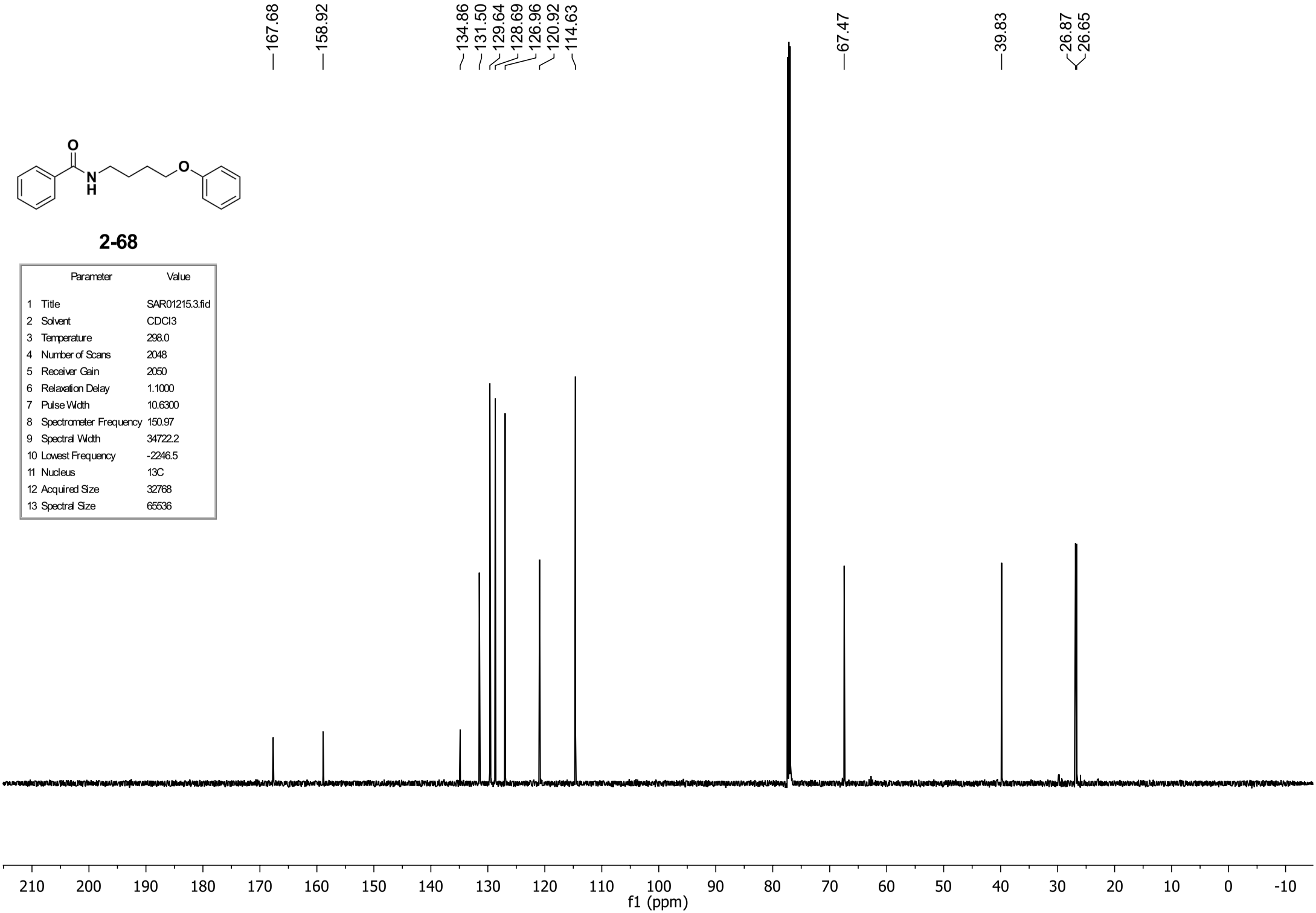
	Parameter	Value
1	Title	SAR01133.10.fid
2	Solvent	CDCl3
3	Temperature	300.0
4	Number of Scans	8
5	Receiver Gain	144
6	Relaxation Delay	1.0000
7	Pulse Width	10.7700
8	Spectrometer Frequency	600.32
9	Spectral Width	8403.4
10	Lowest Frequency	-915.4
11	Nucleus	1H
12	Acquired Size	32768
13	Spectral Size	65536

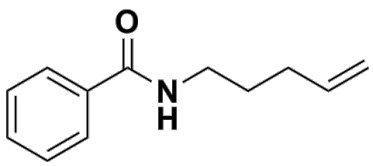

167.49
158.13
134.85
133.64
131.44
129.43
128.62
126.92
114.14
55.41
39.95
32.80
31.46
O
N
H
OMe
2-67
Parameter Value
1 Title SAR01133.11.fid
2 Solvent CDCl3
3 Temperature 300.0
4 Number of Scans 256
5 Receiver Gain 2050
6 Relaxation Delay 1.1000
7 Pulse Width 10.6300
8 Spectrometer Frequency 150.97
9 Spectral Width 34722.2
10 Lowest Frequency -2247.3
11 Nucleus 13C
12 Acquired Size 32768
13 Spectral Size 65536
157
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



2-68

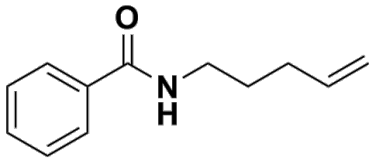
	Parameter	Value
1	Title	SAR01215.10.fid
2	Solvent	CDCl3
3	Temperature	298.2
4	Number of Scans	16
5	Receiver Gain	9
6	Relaxation Delay	1.0000
7	Pulse Width	15.0000
8	Spectrometer Frequency	400.13
9	Spectral Width	8278.1
10	Lowest Frequency	-1677.7
11	Nucleus	1H
12	Acquired Size	32768
13	Spectral Size	65536


167.68
158.92
134.86
131.50
129.64
128.69
126.96
120.92
114.63
67.47
39.83
26.87
26.65
O
N
H
O
2-68
Parameter Value
1 Title SAR01215.3.fid
2 Solvent CDCl3
3 Temperature 298.0
4 Number of Scans 2048
5 Receiver Gain 2050
6 Relaxation Delay 1.1000
7 Pulse Width 10.6300
8 Spectrometer Frequency 150.97
9 Spectral Width 34722.2
10 Lowest Frequency -2246.5
11 Nucleus 13C
12 Acquired Size 32768
13 Spectral Size 65536
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



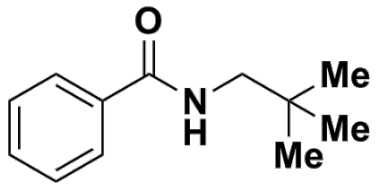
2-69

	Parameter	Value
1	Title	SAR01234.1.fid
2	Solvent	CDCl3
3	Temperature	298.0
4	Number of Scans	8
5	Receiver Gain	181
6	Relaxation Delay	1.0000
7	Pulse Width	10.7700
8	Spectrometer Frequency	600.32
9	Spectral Width	8403.4
10	Lowest Frequency	-916.2
11	Nucleus	1H
12	Acquired Size	32768
13	Spectral Size	65536



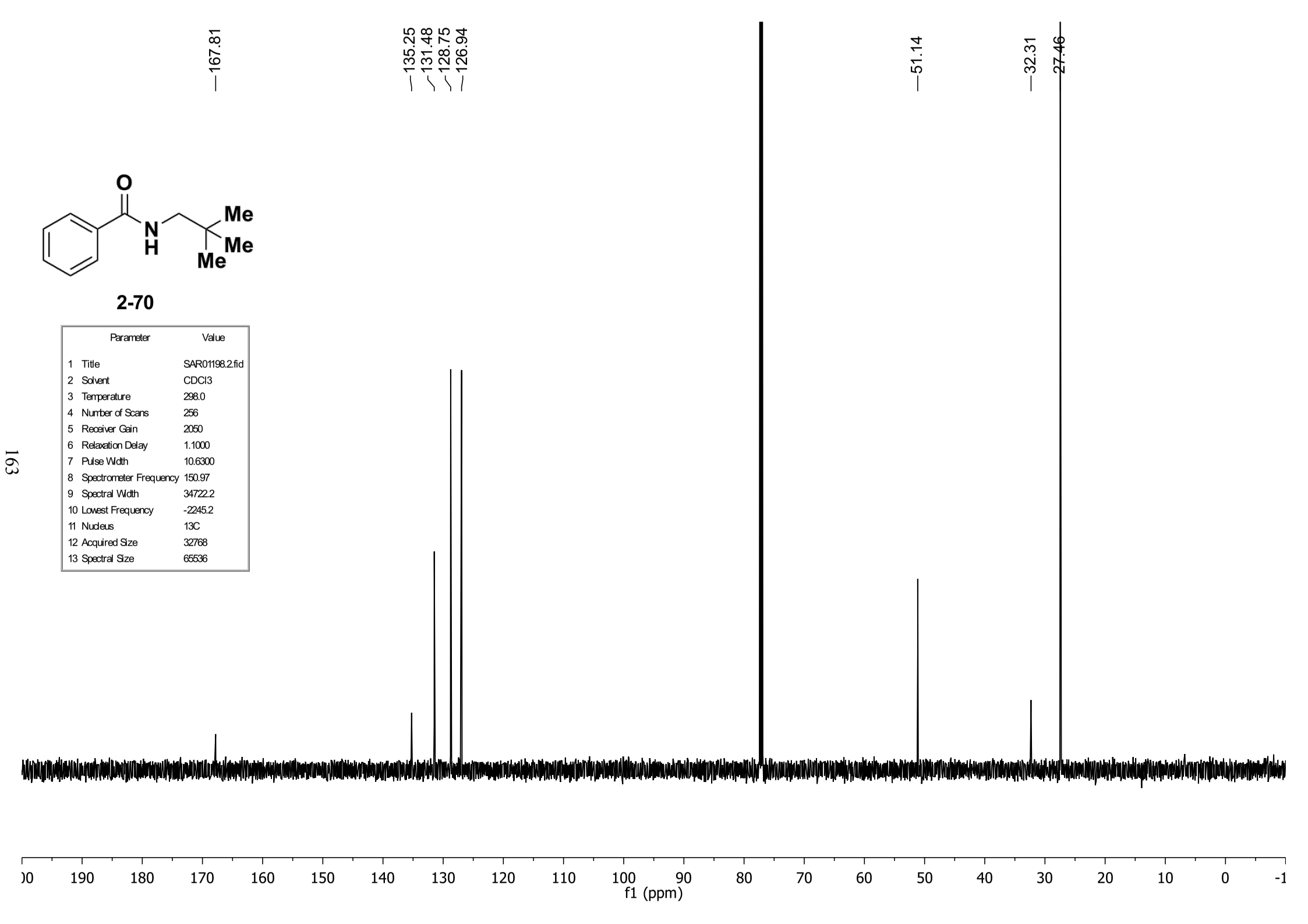
2-69

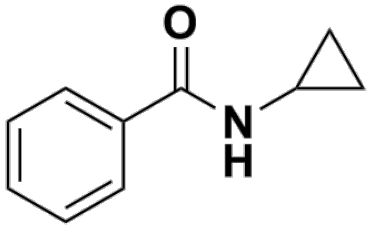
	Parameter	Value
1	Title	SAR01234.2.fid
2	Solvent	CDCl3
3	Temperature	298.0
4	Number of Scans	256
5	Receiver Gain	2050
6	Relaxation Delay	1.1000
7	Pulse Width	10.6300
8	Spectrometer Frequency	150.97
9	Spectral Width	34722.2
10	Lowest Frequency	-2245.9
11	Nucleus	13C
12	Acquired Size	32768
13	Spectral Size	65536



2-70

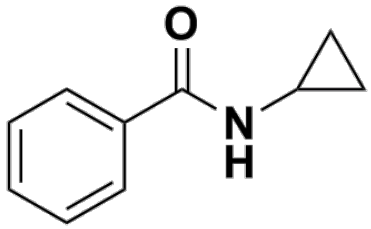
	Parameter	Value
1	Title	SAR01198.1.fid
2	Solvent	CDCl3
3	Temperature	298.0
4	Number of Scans	8
5	Receiver Gain	203
6	Relaxation Delay	1.0000
7	Pulse Width	10.7700
8	Spectrometer Frequency	600.32
9	Spectral Width	8403.4
10	Lowest Frequency	-916.6
11	Nucleus	1H
12	Acquired Size	32768
13	Spectral Size	65536


167.81
135.25
131.48
128.75
126.94
51.14
32.31
27.46
O
N
H
Me
Me
Me
2-70
Parameter Value
1 Title SAR01198.2.fid
2 Solvent CDCl3
3 Temperature 298.0
4 Number of Scans 256
5 Receiver Gain 2050
6 Relaxation Delay 1.1000
7 Pulse Width 10.6300
8 Spectrometer Frequency 150.97
9 Spectral Width 34722.2
10 Lowest Frequency -2245.2
11 Nucleus 13C
12 Acquired Size 32768
13 Spectral Size 65536
f1 (ppm)



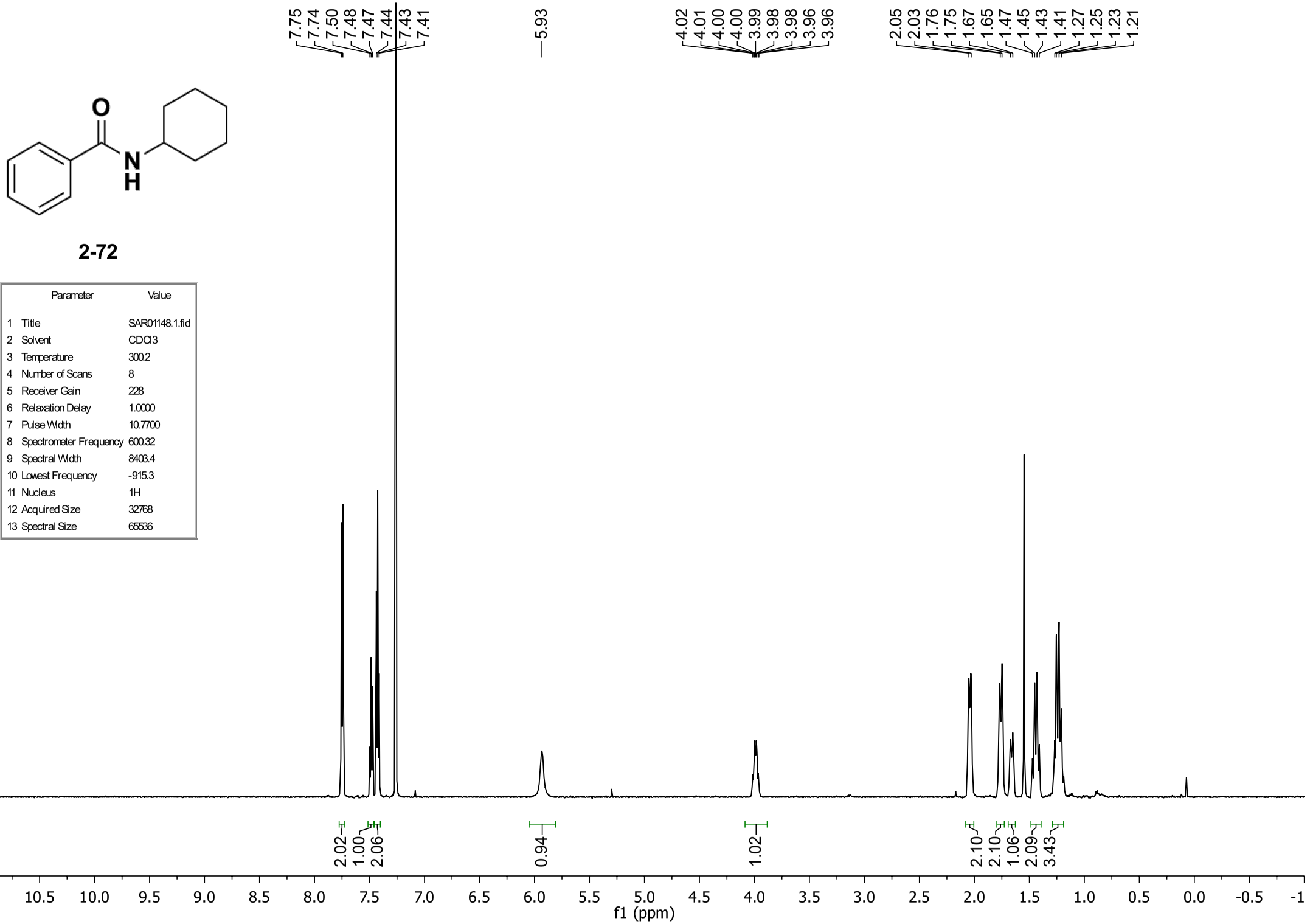
2-71

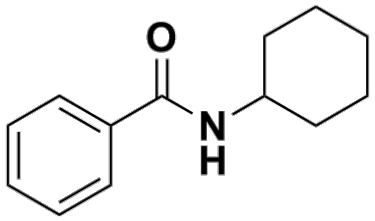
	Parameter	Value
1	Title	SAR01110.10.fid
2	Solvent	CDCl3
3	Temperature	298.2
4	Number of Scans	16
5	Receiver Gain	4
6	Relaxation Delay	1.0000
7	Pulse Width	15.0000
8	Spectrometer Frequency	400.13
9	Spectral Width	8278.1
10	Lowest Frequency	-1677.6
11	Nucleus	1H
12	Acquired Size	32768
13	Spectral Size	65536



2-71

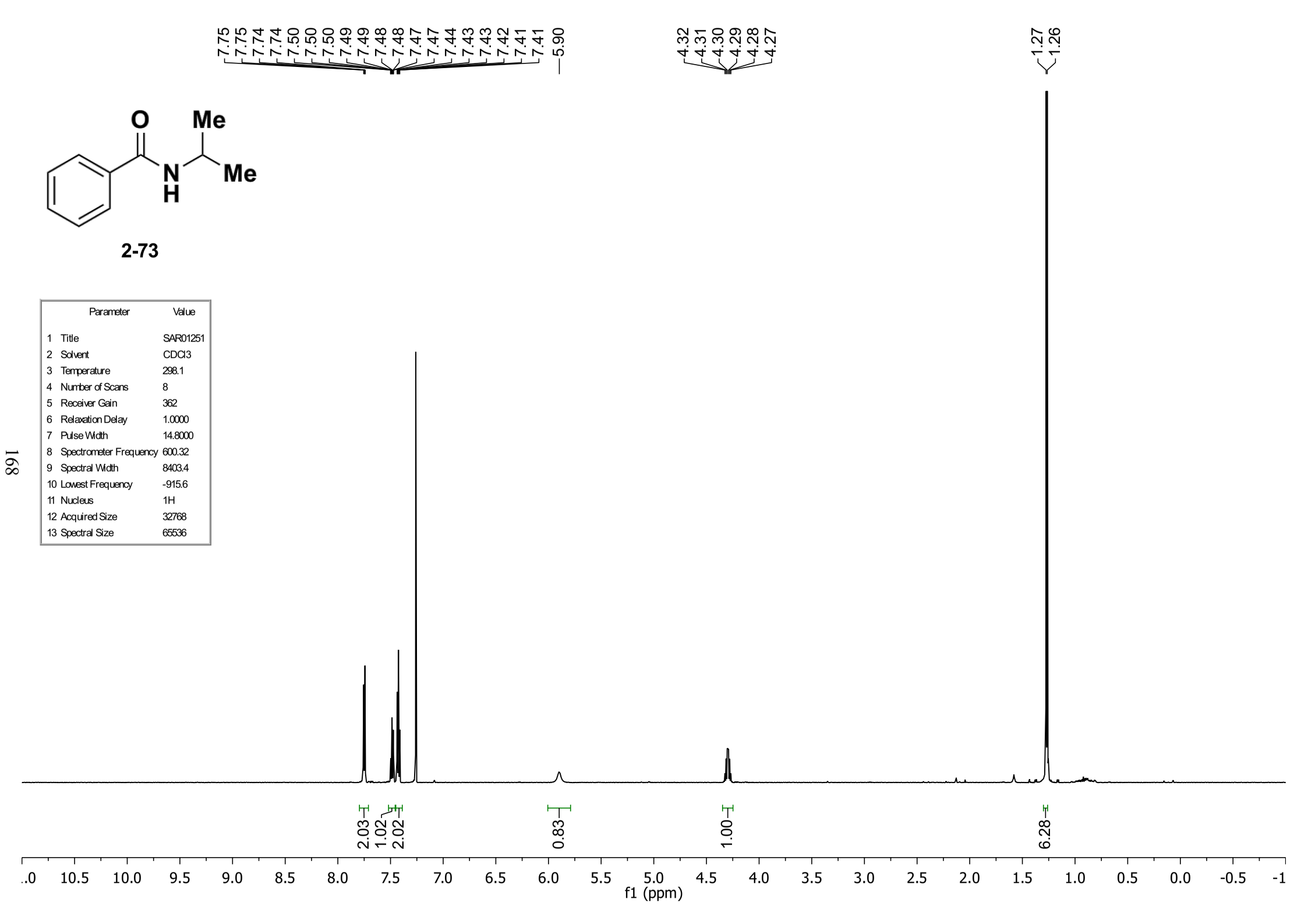
	Parameter	Value
1	Title	SAR01110.11.fid
2	Solvent	CDCl3
3	Temperature	298.2
4	Number of Scans	1024
5	Receiver Gain	512
6	Relaxation Delay	2.0000
7	Pulse Width	9.2500
8	Spectrometer Frequency	100.62
9	Spectral Width	23980.8
10	Lowest Frequency	-1916.7
11	Nucleus	13C
12	Acquired Size	32768
13	Spectral Size	65536

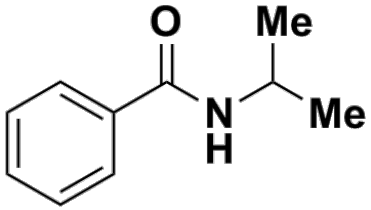

7.75
7.74
7.50
7.48
7.47
7.44
7.43
7.41
5.93
4.02
4.01
4.00
4.00
3.99
3.98
3.98
3.96
3.96
2.05
2.03
1.76
1.75
1.67
1.65
1.47
1.45
1.43
1.41
1.27
1.25
1.23
1.21
O
N
H
2-72
Parameter Value
1 Title SAR01148.1.fid
2 Solvent CDCl3
3 Temperature 300.2
4 Number of Scans 8
5 Receiver Gain 228
6 Relaxation Delay 1.0000
7 Pulse Width 10.7700
8 Spectrometer Frequency 600.32
9 Spectral Width 8403.4
10 Lowest Frequency -915.3
11 Nucleus 1H
12 Acquired Size 32768
13 Spectral Size 65536
2.02
1.00
2.06
0.94
1.02
2.10
2.10
1.06
2.09
3.43
f1 (ppm)



2-72

	Parameter	Value
1	Title	SAR01148.2.fid
2	Solvent	CDCl3
3	Temperature	300.2
4	Number of Scans	256
5	Receiver Gain	2050
6	Relaxation Delay	1.1000
7	Pulse Width	10.6300
8	Spectrometer Frequency	150.97
9	Spectral Width	34722.2
10	Lowest Frequency	-2244.1
11	Nucleus	13C
12	Acquired Size	32768
13	Spectral Size	65536


7.75
7.75
7.74
7.74
7.50
7.50
7.50
7.49
7.49
7.48
7.48
7.47
7.47
7.44
7.43
7.43
7.42
7.41
7.41
5.90
4.32
4.31
4.30
4.29
4.28
4.27
1.27
1.26
O
Me
N
H
Me
2-73
Parameter Value
1 Title SAR01251
2 Solvent CDCl3
3 Temperature 298.1
4 Number of Scans 8
5 Receiver Gain 362
6 Relaxation Delay 1.0000
7 Pulse Width 14.8000
8 Spectrometer Frequency 600.32
9 Spectral Width 8403.4
10 Lowest Frequency -915.6
11 Nucleus 1H
12 Acquired Size 32768
13 Spectral Size 65536
2.03
1.02
2.02
0.83
1.00
6.28
f1 (ppm)

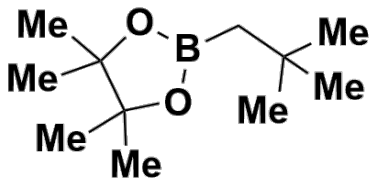


2-73

	Parameter	Value
1	Title	SAR01251
2	Solvent	CDCl3
3	Temperature	298.1
4	Number of Scans	2048
5	Receiver Gain	2050
6	Relaxation Delay	1.1000
7	Pulse Width	9.0000
8	Spectrometer Frequency	150.97
9	Spectral Width	34722.2
10	Lowest Frequency	-2245.3
11	Nucleus	13C
12	Acquired Size	32768
13	Spectral Size	65536

Appendix B

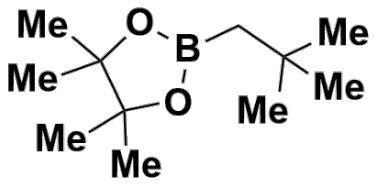
SPECTRAL DATA FOR CHAPTER 3



3-2

	Parameter	Value
1	Title	SAR02092
2	Solvent	CDCl3
3	Temperature	298.0
4	Number of Scans	8
5	Receiver Gain	128
6	Relaxation Delay	1.0000
7	Pulse Width	10.7700
8	Spectrometer Frequency	600.32
9	Spectral Width	8403.4
10	Lowest Frequency	-916.1
11	Nucleus	1H
12	Acquired Size	32768
13	Spectral Size	65536

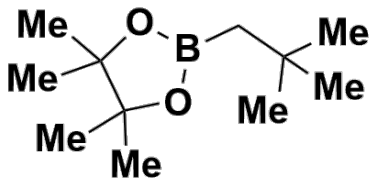
171



3-2

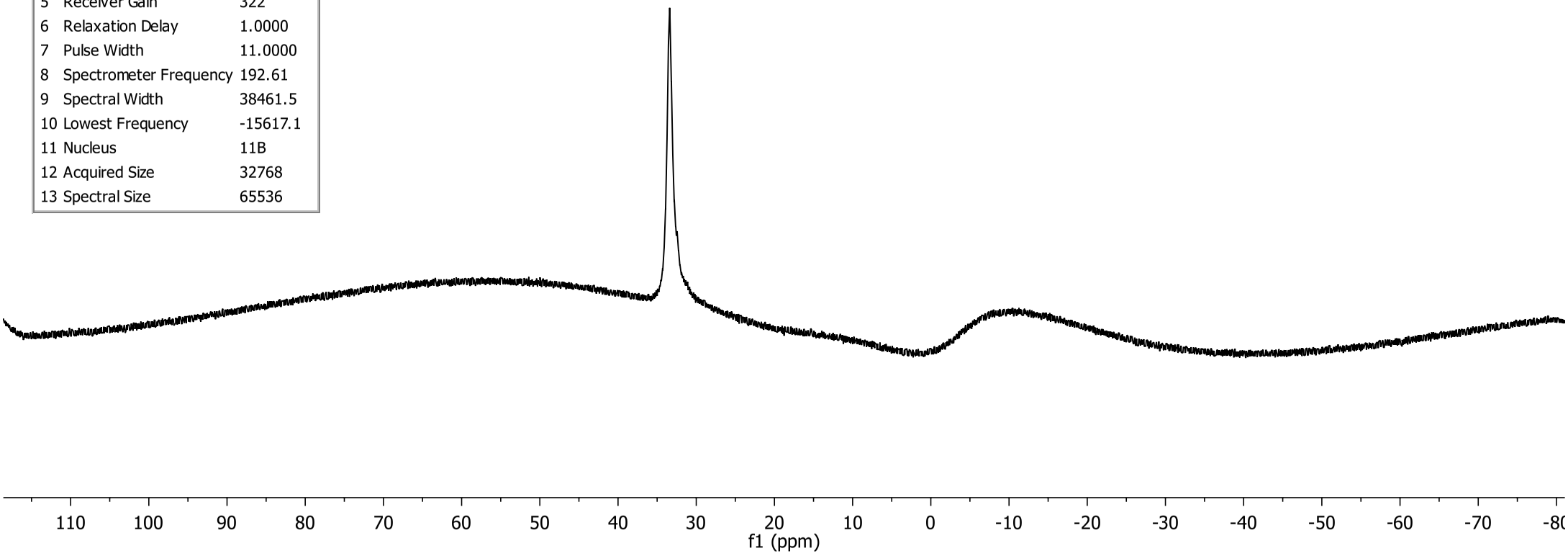
	Parameter	Value
1	Title	SAR02092
2	Solvent	CDCl3
3	Temperature	298.2
4	Number of Scans	32
5	Receiver Gain	512
6	Relaxation Delay	2.0000
7	Pulse Width	9.2500
8	Spectrometer Frequency	100.62
9	Spectral Width	23980.8
10	Lowest Frequency	-1916.3
11	Nucleus	13C
12	Acquired Size	32768
13	Spectral Size	65536

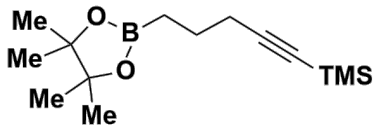
33.42



3-2

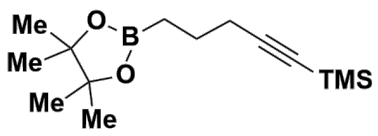
	Parameter	Value
1	Title	SAR02092
2	Solvent	CDCl3
3	Temperature	298.0
4	Number of Scans	32
5	Receiver Gain	322
6	Relaxation Delay	1.0000
7	Pulse Width	11.0000
8	Spectrometer Frequency	192.61
9	Spectral Width	38461.5
10	Lowest Frequency	-15617.1
11	Nucleus	11B
12	Acquired Size	32768
13	Spectral Size	65536





3-9

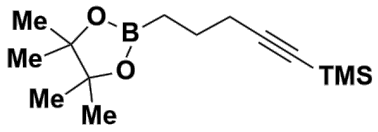
	Parameter	Value
1	Title	SAR02111
2	Solvent	CDCl3
3	Temperature	298.0
4	Number of Scans	8
5	Receiver Gain	203
6	Relaxation Delay	1.0000
7	Pulse Width	10.7700
8	Spectrometer Frequency	600.32
9	Spectral Width	8403.4
10	Lowest Frequency	-915.5
11	Nucleus	1H
12	Acquired Size	32768
13	Spectral Size	65536



3-9

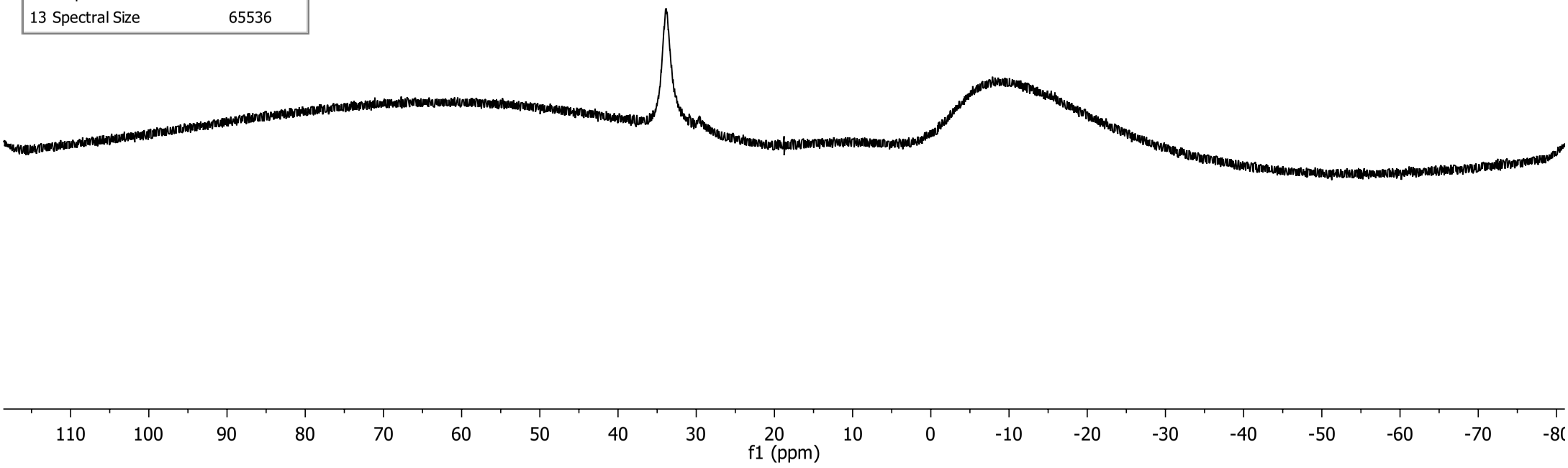
	Parameter	Value
1	Title	SAR02111
2	Solvent	CDCl3
3	Temperature	298.0
4	Number of Scans	2048
5	Receiver Gain	2050
6	Relaxation Delay	1.1000
7	Pulse Width	10.6300
8	Spectrometer Frequency	150.97
9	Spectral Width	34722.2
10	Lowest Frequency	-2245.0
11	Nucleus	13C
12	Acquired Size	32768
13	Spectral Size	65536

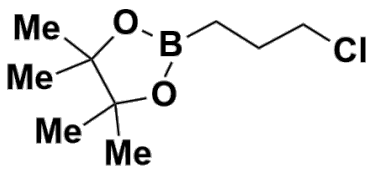
33.84



3-9

	Parameter	Value
1	Title	SAR02111
2	Solvent	CDCl3
3	Temperature	298.0
4	Number of Scans	32
5	Receiver Gain	322
6	Relaxation Delay	1.0000
7	Pulse Width	11.0000
8	Spectrometer Frequency	192.61
9	Spectral Width	38461.5
10	Lowest Frequency	-15617.1
11	Nucleus	11B
12	Acquired Size	32768
13	Spectral Size	65536

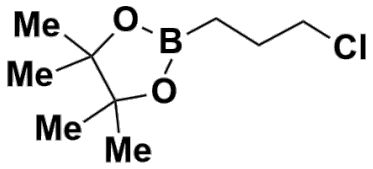




3-10

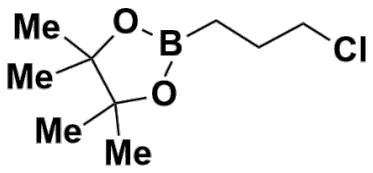
	Parameter	Value
1	Title	SAR01270
2	Solvent	CDCl3
3	Temperature	298.1
4	Number of Scans	8
5	Receiver Gain	287
6	Relaxation Delay	1.0000
7	Pulse Width	14.8000
8	Spectrometer Frequency	600.32
9	Spectral Width	8403.4
10	Lowest Frequency	-915.9
11	Nucleus	1H
12	Acquired Size	32768
13	Spectral Size	65536

177



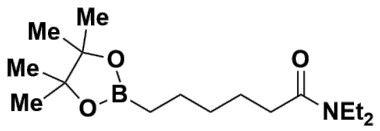
3-10

	Parameter	Value
1	Title	SAR01270
2	Solvent	CDCl3
3	Temperature	298.0
4	Number of Scans	2048
5	Receiver Gain	2050
6	Relaxation Delay	1.1000
7	Pulse Width	10.6300
8	Spectrometer Frequency	150.97
9	Spectral Width	34722.2
10	Lowest Frequency	-2245.2
11	Nucleus	13C
12	Acquired Size	32768
13	Spectral Size	65536



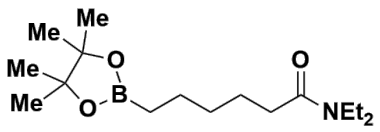
3-10

	Parameter	Value
1	Title	SAR01270
2	Solvent	CDCl3
3	Temperature	298.0
4	Number of Scans	32
5	Receiver Gain	322
6	Relaxation Delay	1.0000
7	Pulse Width	11.0000
8	Spectrometer Frequency	192.61
9	Spectral Width	38461.5
10	Lowest Frequency	-15617.1
11	Nucleus	11B
12	Acquired Size	32768
13	Spectral Size	65536



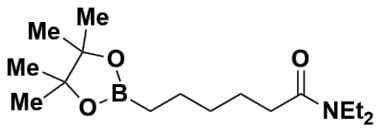
3-13

	Parameter	Value
1	Title	SAR02110
2	Solvent	CDCl3
3	Temperature	298.0
4	Number of Scans	8
5	Receiver Gain	181
6	Relaxation Delay	1.0000
7	Pulse Width	10.7700
8	Spectrometer Frequency	600.32
9	Spectral Width	8403.4
10	Lowest Frequency	-915.5
11	Nucleus	1H
12	Acquired Size	32768
13	Spectral Size	65536



3-13

	Parameter	Value
1	Title	SAR02110
2	Solvent	CDCl3
3	Temperature	298.0
4	Number of Scans	2048
5	Receiver Gain	2050
6	Relaxation Delay	1.1000
7	Pulse Width	10.6300
8	Spectrometer Frequency	150.97
9	Spectral Width	34722.2
10	Lowest Frequency	-2246.0
11	Nucleus	13C
12	Acquired Size	32768
13	Spectral Size	65536



3-13

	Parameter	Value
1	Title	SAR02110
2	Solvent	CDCl3
3	Temperature	298.0
4	Number of Scans	32
5	Receiver Gain	322
6	Relaxation Delay	1.0000
7	Pulse Width	11.0000
8	Spectrometer Frequency	192.61
9	Spectral Width	38461.5
10	Lowest Frequency	-15617.1
11	Nucleus	11B
12	Acquired Size	32768
13	Spectral Size	65536

22.44

182

110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80

f1 (ppm)